The Role of Vibrational Deactivation in Asymmetric Photochemistry

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Abstract

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In this thesis, vibrational deactivation of the singlet excited state of molecular oxygen is proposed as a previously unexplored stereodifferentiating mechanism in the reaction of singlet oxygen with the olefin bond in enecarbamates to form the corresponding dioxetane. Deuteration and analysis of the stereochemistry in the decomposition products of the dioxetane will be utilized to facilitate the assessment of this hypothesis. Additionally, the role of supramolecular achiral and chiral media in the stereochemical outcome of these photooxygenation reactions will be investigated.
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<table>
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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>$^1\text{O}_2$</td>
<td>Singlet Oxygen</td>
</tr>
<tr>
<td>$^1\text{Bu}$</td>
<td>tertButyl</td>
</tr>
<tr>
<td>C</td>
<td>Conversion</td>
</tr>
<tr>
<td>DPP</td>
<td>2,3-Diphenyl-3-pentanone</td>
</tr>
<tr>
<td>ee</td>
<td>Enantioselectivity</td>
</tr>
<tr>
<td>$k_Q$</td>
<td>Total Quenching Rate Constant</td>
</tr>
<tr>
<td>$k_{cQ}$</td>
<td>Chemical Quenching Rate Constant</td>
</tr>
<tr>
<td>$k_{pQ}$</td>
<td>Physical Quenching Rate Constant</td>
</tr>
<tr>
<td>MDB</td>
<td>Methyldesoxybenzoin</td>
</tr>
<tr>
<td>Me</td>
<td>Methyl</td>
</tr>
<tr>
<td>$^1\text{Pr}$</td>
<td>isoPropyl</td>
</tr>
<tr>
<td>Ph</td>
<td>Phenyl</td>
</tr>
<tr>
<td>s</td>
<td>Stereoselectivity (s) Factor</td>
</tr>
<tr>
<td>$T_0$</td>
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</tr>
<tr>
<td>$\Delta\Delta H^*$</td>
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</tr>
<tr>
<td>$\Delta\Delta S^*$</td>
<td>Differential Entropy</td>
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To my Mother, Berthlyn Jordan-Achorner,

Who I think took it as foregone that I would get to and beyond this point.

My Great-Grand Mother – Eurina Jordan who I continue to miss.

Every one of my Teachers

For their Patience.
1. Introduction and Background

1.1. Chiral Resolution and Enantiomers

Chirality is built into the human biology. From sugars to amino acids, enzymes to DNA, chirality is imprinted into our most basic structure. Often enough within the human body only one enantiomer is found to be biologically active and in cases where both enantiomers are biologically active, they both may affect the body in quite different ways, with one form sometimes being quite toxic. For example, D-glucose, an important component in carbohydrate and ATP synthesis, is biologically active but its counterpart, L-Glucose, is not metabolized by human cells in glycolysis. Furthermore, most of the amino acids found in human proteins are L-amino acids and they, rather than their D-amino acids counterparts, are subject to enzyme assisted polymerization to polypeptides and proteins.¹

The importance of chirality in biological systems extends to drugs as well. Both enantiomers of Promethazine (Figure 1-1, left) demonstrate the same antihistaminic biological properties while the S enantiomer of Propanolol (Figure 1-1, center) exhibits greater β-blocking activity than the (+)-(R)-Propranolol enantiomer.² The infamous Thalidomide can exist in one of the two forms pictured in Figure 1-1 (right). The R form is a drug for treatment of morning sickness while the S enantiomer is known to be teratogenic. Unfortunately, the racemization of the R form in vivo negates its beneficial use.³
Figure 1-1: Structures of Promethazine (left), Propranolol (center) and Thalimide (right).

It is sometimes the case what while one enantiomer is physiologically active, the other enantiomer is not known to have any harmful effects. Omeprazole (Figure 1-2), developed by AstraZeneca of London, is marketed as a racemate, Prilosec, in the US. In an attempt to maximize on the income from this drug, the company then patented the pharmacologically active (S)-enantiomer separately as esomeprazole (marketed as Nexium in the US). Evidently, the ability to resolve two enantiomers in such a case can be financially advantageous to a company. In fact, the use of single isomer chiral drugs was shown to increase from 31.1% to 34.2% in the years between 1982 and 1991. By 1997, about 50% of the top drugs and more than 80% of drugs in first phase trials were single isomer drugs.

Figure 1-2: Structure of Omeprazole.
At times, resolution is necessary not because one isomer is toxic and useless, but because there are benefits to obtaining both enantiomers separately. While L-Serine finds many uses in the body, D-Serine functions in neuronal signaling in the brain. The L-isomer of Methorphan, levomethorphan (Figure 1-3, left) is useful as an analgesic, while dextromethorphan (Figure 1-3, right) is a dissociative cough suppressant in high doses. Additionally, Cambridge Isotope Laboratories, and other companies specializing in the sale of enantiomers, often sell both D and L amino acids. However, owing to the purification process, one enantiomer (typically the D) is often more expensive because it is harder to generate. Therefore, obtaining both isomers in their enantiomerically pure forms is also highly advantageous.

Man’s innate homochirality and drug development are just the more outstanding reasons motivating the chiral resolution of compounds and, consequently, it is an area that has attracted much research and spawned many new fields.
1.2. Asymmetric Induction

Chiral resolution can be achieved through a variety of methods – chiral crystallization, chiral chromatography, diastereomereric salt derivatization and kinetic resolution. One major problem with chiral resolution (kinetic and diastereomerization, particularly) is that half of the material is often discarded and of the racemic mixture, at best generates only 50% useful product. For example, imagine a racemic mixture of amines that can be derivatized by salt formation with an enantiomerically pure, chiral acid (Scheme 1-1). Of the two diastereomers formed, generally only one mostly crystallizes out of the solution. The remaining mother liquor contains some of the first diastereomer (that crystallized) and all of the second (that did not crystallize). Therefore, only one enantiomer, the one that crystallized from the solution, is obtained with high purity from this procedure.

Scheme 1-1: Salt diastereomeric derivatization with enantiopure acid.

However, of the more popular alternative methods geared towards generating large amounts of enantiomerically pure material, asymmetric synthesis has invited much interest – particularly asymmetric induction and
asymmetric catalysis\textsuperscript{17-19}. Asymmetric induction, unlike chiral resolution, does not involve the separation of a racemic mixture into its enantiomerically pure compounds. Asymmetric induction, by definition, exploits some chiral feature present in a molecule in order to generate enantiomerically or diastereomerically pure products through diastereomeric intermediates. Since diastereomers behave and react differently then, by manipulating the environment, one can guide and control the stereochemical course of the reaction. The goal of asymmetric induction is to have the diastereomeric mixture of starting materials produce only one enantiomer, thereby bypassing the requirement to purify racemic mixtures and avoiding the waste of 50\% of the starting material.

For example, in the reaction outlined in \textbf{Scheme 1-2},\textsuperscript{20} alkylation of the N-acylated pseudoephedrine chiral auxiliary with the enantiopure alkyl halide exclusively generated one diastereomeric product. In both cases, it was postulated that the approach of the alkyl halide is directed by the methyl group. Clearly, the utilization of the pseudoephedrine chiral auxiliary generated diastereomerically pure products in a reaction that could plausibly generate two products.
Scheme 1-2: Alkylation of the N-acylated pseudoephedrine chiral auxiliary with the enantiopure alkyl halide to exclusively generate one diastereomeric product.\textsuperscript{20}

Asymmetric induction can be carried out in several ways. One can use chiral catalysts, a chiral auxiliary, a chiral reagent or a chiral environment. Of the variety of chiral catalysts – organocatalysts\textsuperscript{21}, metal-chiral ligand complexes\textsuperscript{19} and biocatalysts\textsuperscript{22-24} – biocatalysts such as enzymes, offer excellent chemo-, regio- and enantioselectivity under very mild conditions. Chiral auxiliaries such as the 2-oxazolidinones\textsuperscript{25, 26} and the pseudoephedrines\textsuperscript{20} (Figure 1-4) act as protecting groups that effectively block reaction from one trajectory, leaving the other open for the reaction to proceed. Chiral environments include chiral cavities such as cyclodextrins or chirally modified zeolites and promote the reaction of one enantiomer through favorable (or unfavorable) interactions with the reacting molecules.\textsuperscript{27, 28}
Each method has its own index of advantages and disadvantages. A major one exhibited by enzymes and thermal approaches (Scheme 1-2 for example) is that the reaction only generates one diastereomer/enantiomer. In the case of enzymatic catalysis, generation of the other isomer may not be viable utilizing the same enzyme. An isomeric starting material, because of the temperature and sometimes solvent requirements, is usually restricted to generating one diastereomeric product and, in thermal reactions, the other diastereomer may only be obtained by using the antipodal starting material.
1.3. **Photochirogenesis**

Photochemical asymmetric induction, aka photochirogenesis, is the control of stereochemistry during the course of a photoreaction. Traditionally, enzymatic and thermal approaches have been employed to achieve high enantioselectivities in asymmetric transformation. The narrow temperature range between which enzymes and these thermal reactions operate, as well as the solvent restrictions, prohibit the study of temperature and solvent effects on stereoselectivity.\textsuperscript{29, 30} Since the activating agent in photoreactions is light rather than heat and biological factors, the issue of temperature limitations are neatly avoided. Moreover, a wide array of different solvents – protic, aprotic, polar, non-polar- are available. Solvents limitations are dependent only on solvent transparency at the exciting wavelength and the solubility of the substrate, since there is a solvent dependent choice of sensitizers.

Asymmetric photochemistry bypasses these more traditional routes to product enantioselectivity, instead utilizing the absorption of light to generate an electronically excited state, during which the stereodifferentiating factors must operate in order to produce stereoselectivity in the product. The inherent difficulty of asymmetric photochemistry lies in the lifetime of these electronically excited states. These states are generally short-lived so that one must imprint the stereocontrol during this short lifetime (Scheme 1-3). The advantage of the photochemical approach over an enzymatic or thermal one lies in the ability to explore reactions over large temperature ranges and within a variety of solvent environments without affecting the reaction mechanism,\textsuperscript{31} options which are not available with the two more traditional approaches. Moreover, asymmetric
photochemistry allows us to exploit the properties of high-energy intermediates and transition states not accessible to us via thermal asymmetric induction. These intermediates provide a rich playground for imprinting stereocontrol and manipulating stereochemical outcomes.

\[
\begin{align*}
A & \xrightarrow{\text{hv}} A^* & \text{Photoexcitation of reagent } A. \\
A^* + S & \rightarrow [A\cdots S]^n & \text{Reaction with Substrate, } S, \text{ to form excited state complex during which stereocontrol is imprinted.}
\end{align*}
\]

**Scheme 1-3**: Schematic outline of asymmetric photochemical approach to imprinting stereocontrol in the excited state.

Within the realm of asymmetric photochemistry several excellent reviews\textsuperscript{30-32} elucidate the various approaches – circularly polarized light, asymmetric induction by chiral substituent, asymmetric induction by chiral complexing agent, and asymmetric photosensitizations. With circularly polarized light (cpl), one isomer is preferentially excited.\textsuperscript{31} Asymmetric induction by chiral substituent is a diastereodifferentiating process whereby, a chiral auxiliary is attached to a prochiral molecule in order to influence the trajectory of the reaction. Steric, electronic and hydrogen-bonding interactions in both the excited and ground state of the substrate direct the course of these reaction.\textsuperscript{31} Chiral complexing agents act similarly to chiral auxiliaries except that they are not required in stoichiometric amounts and they are not chemically bonded to the prochiral substrate. Only catalytic amounts of chiral (optically active) sensitizers are required in asymmetric photosensitizations and the enantiodifferentiation interactions take place in the electronically excited state.\textsuperscript{31, 33}
Photochemical asymmetric induction with chiral auxiliaries comprises many categories so far explored – photocyclization, \([2+2]\) and \([4+2]\) photocycloaddition, photopinacolization and the Paterno-Büchi, are just a few.\(^{31}\) An example follows (Table 1-1) for the photoisomerization utilizing a chiral sensitizer.\(^{34}\) The system exhibited both solvent and temperature dependent enantioselectivities and by merely changing the solvent and the temperature in some instances, isomer switching is induced. Herein lies a key argument for asymmetric photochemistry – by changing the reaction conditions, such as the temperature or solvent, the sense of the predominant isomer can be reversed. Solvent, temperature as well as pressure are entropy-related factors that substantially impact substrate conformation and it may be that minor differences in the conformation of two diastereomers induce considerable stereoselectivities. Entropical control emerges, consequently, as a powerful, photochemically accessible tool for obtaining a choice of isomers from the same starting materials.
Table 1-1: Enantioselectivity in the photoisomerization of \textbf{1Z} in the presence of a chiral sensitizer as a function of solvent and temperature.\textsuperscript{34}

\begin{align*}
\text{Exciplex} & \quad \xrightarrow{\text{Excipl ex}} \quad (R)(-)-1E \\
& \quad \quad \quad \quad \quad (S)(+)-1E
\end{align*}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>%ee\textsubscript{R-S}</th>
<th>25\textdegree C</th>
<th>-40\textdegree C</th>
<th>-78\textdegree C</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pentane</td>
<td>-5.5</td>
<td>-22.1</td>
<td>-40.4</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Heptane</td>
<td>-3.9</td>
<td>-13.5</td>
<td>-33.4</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Isopentane</td>
<td>-1.8</td>
<td>-20.2</td>
<td>-50.9</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Isooctane</td>
<td>-3.4</td>
<td>-21.4</td>
<td>-49.4</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Methylcyclohexane</td>
<td>-5.7</td>
<td></td>
<td>-57.2</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Ethylcyclohexane</td>
<td>-4.7</td>
<td>-11.7</td>
<td>-34.8</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Diisopropyl ether</td>
<td>3.8</td>
<td>24.3</td>
<td>43.8</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Diethyl Ether</td>
<td>-5.5</td>
<td>22.4</td>
<td>50.3</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Tetrahydrofuran</td>
<td>-0.2</td>
<td>31.8</td>
<td>47.6</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>1,2-Dimethoxyethane</td>
<td>-5.2</td>
<td>21.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Acetonitrile</td>
<td>11.3</td>
<td>34.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Methanol</td>
<td>3.4</td>
<td>16.2</td>
<td>24.3</td>
<td></td>
</tr>
</tbody>
</table>
1.4. **Singlet Oxygen - $^1\text{O}_2$**

One particularly interesting class of photochemical reactions is that of singlet oxygen ($^1\text{O}_2$) with the alkene double bond. $^1\text{O}_2$ is the first electronically excited state of ground state oxygen ($^3\text{O}_2$), lying 22.5 kcal/mole higher (**Figure 1-5**).\(^{35}\) It can be generated via two main methods – photochemical and chemical/thermal. Direct sensitization; triplet photosensitization; the decomposition of hydrogen peroxide; the thermal decomposition of organic ozonides, photoperoxides, endoperoxides; photolysis of ozone are just a few.\(^{35-37}\)

\[
\begin{align*}
^1\Sigma_g & \\
^1\Delta_g & \quad 37.5 \text{ kcal/mol} \\
^3\Sigma_g & \quad 22.5 \text{ kcal/mol} \\
S_0 & 
\end{align*}
\]

**Figure 1-5:** Electronic states of molecular oxygen: triplet ground state ($^3\Sigma_g$), first singlet excited state ($^1\Delta_g$) and second singlet excited state ($^1\Sigma_g$).

$^1\text{O}_2$ is a notable oxidant that reacts with olefins, aromatic and heterocyclic systems as well as playing a role in polymer degradation and in biological environments.\(^{35-37}\) In its reaction with an alkene double bond, $^1\text{O}_2$ may react via three possible modes:

i) The Ene reaction (**Scheme 1-4a**)

ii) [2+2] cycloaddition / Dioxetane formation (**Scheme 1-4b**)

iii) [4+2] cycloadditon / Endoperoxide formation (**Scheme 1-4c**).
In the Schenck-ene reaction, $^1\text{O}_2$ reacts with an alkene possessing an allylic hydrogen to form an allylic peroxide with a shifted double bond (Scheme 1-4a). The [2+2] cycloaddition reaction can alternatively be considered as a photooxidative cleavage reaction (Scheme 1-4b). The 1,2-dioxetane formed is often thermally unstable and decomposes into carbonyl fragments (Scheme 1-5)[36, 37]. [4+2] cycloaddition with dienes and aromatic systems produces endoperoxides (Scheme 1-4c), some of which are considered $^1\text{O}_2$ traps/storage since they can be thermally induced to release $^1\text{O}_2$ at a later date.

Scheme 1-5: Decomposition of dioxetane to carbonyl fragments.
1.5. Enecarbamates

The reaction of interest for us is the reaction of $^{1}\text{O}_2$ with the family of enecarbamate structures (Figure 1-6). The structure of the enecarbamate can be broken down into three sections. First, there is the Evans chiral auxiliary (shown boxed in the general structure in Figure 1-6). This chiral feature offers a handle with which to manipulate the stereochemical course of the reaction. Chirality on the Evans chiral auxiliary is introduced at the $C_4$ position. The Evans chiral auxiliary also possesses a carbonyl group and a nitrogen, both of which are believed to interact with and direct the incoming $^{1}\text{O}_2$.\textsuperscript{38-40} Second, there is the $C=C$ double bond which offers a possible docking and reaction site for the $^{1}\text{O}_2$. The $^{1}\text{O}_2$ can approach the double bond from either the top or the bottom face, and from either the left or right side (Figure 1-7). Third, there is the remainder of the molecule, the part of the molecule that houses the stereochemical compound of interest; that is, the compound that we wish to isolate enantiomerically pure. The presence of the chiral center in this part of the molecule together with the Evans chiral auxiliary produce diastereomerism in the enecarbamate.
O2 can theoretically react with enecarbamates in the three ways listed in the previous section. However, only two of the three reactions occur here in our enecarbamates E-1 and Z-1: the ene reaction to form the hydroperoxide and the [2+2] reaction to form the dioxetane and its subsequent decomposition products. It is the initial investigations on these two modes of reactivity that sets the background for this thesis.

1.5.a. Background\textsuperscript{38, 39, 41, 42}:

The role of the Evans chiral auxiliary as a means of controlling the mode selectivity in the reaction of O2 with olefins was first explored utilizing enecarbamates.\textsuperscript{38} With the enecarbamate i in Figure 1-8 all three modes are possible: the allylic proton allows for the ene reaction, the activated double bond allows for the [2+2] reaction and the styrene functionality permits [4+2] cycloaddition. In this case, there was evidence only of the first two modes for both the E-i and Z-i enecarbamates. It was observed, however, that while the E
diastereomers yielded mostly the ene hydroperoxide products, the Z enecarbamate afforded mostly the [2+2] cycloaddition product (Table 1-2).

The rationale for this lies in the interaction of the HOMO of the enecarbamate and the LUMO of the approaching O2 with the result that the O2 is steered on to the side of the bond bearing the nitrogen functionality of the oxazolidinone. For the E-i enecarbamate, the oxazolidinone auxiliary and the allylic protons of the C2' methyl group are on the same side. Therefore, the ene reaction is promoted. By contrast, in the Z-i enecarbamate, the oxazolidinone functionality and the phenyl group are on the same side and there are no allylic protons for abstraction on this side and consequently the ene reaction is suppressed in favor of the [2+2] cycloaddition.

Moreover, results showed that the diastereoselectivity in the products for both the ene reaction and the [2+2] reaction increased with increasing C4 substituent size (Table 1-2). In other words, the chiral auxiliary helped induce π-facial stereoselectivity via steric shielding of one face of the C=C double bond. This trend was more notable for the Z-i enecarbamate whose conformation imposed greater steric shielding on one face than the E-i counterpart. The results
presented in this publication showed, for the first time, the suppression of the ene reactivity in favor of the [2+2] reaction simply via the manipulation of the double bond geometry. Moreover, the effects of steric shielding by the C₄-X substituent were sufficient to induce high π-facial stereoselectivity. The authors believe that “judicious combination of the double bond geometry and the chiral auxiliary of the olefinic substrates [that] mode-selective photooxygenations with high stereoselectivity [might] be developed”.

Table 1-2: Mode selectivity and diastereoselectivity in the photooxygenation of enecarbamates

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>X</th>
<th>R₁</th>
<th>R₂</th>
<th>selectivity</th>
</tr>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>mode</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[2+2]:ene</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ii : iii</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>diastereo</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>ene</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>[2+]</td>
</tr>
<tr>
<td>1</td>
<td>E-ia</td>
<td>H</td>
<td>Me</td>
<td>Ph</td>
<td>15:85</td>
</tr>
<tr>
<td>2</td>
<td>Z-ia</td>
<td>H</td>
<td>Ph</td>
<td>Me</td>
<td>80:20</td>
</tr>
<tr>
<td>3</td>
<td>E-ib</td>
<td>(R)-Me</td>
<td>Me</td>
<td>Ph</td>
<td>16:84</td>
</tr>
<tr>
<td>4</td>
<td>E-ic</td>
<td>(R)-iPr</td>
<td>Me</td>
<td>Ph</td>
<td>36:64</td>
</tr>
<tr>
<td>5</td>
<td>E-id</td>
<td>(S)-Ph</td>
<td>Me</td>
<td>Ph</td>
<td>8:92</td>
</tr>
<tr>
<td>6</td>
<td>E-ie</td>
<td>(S)-tBu</td>
<td>Me</td>
<td>Ph</td>
<td>23:77</td>
</tr>
<tr>
<td>7</td>
<td>Z-ib</td>
<td>(R)-Me</td>
<td>Ph</td>
<td>Me</td>
<td>80:20</td>
</tr>
<tr>
<td>8</td>
<td>Z-ic</td>
<td>(R)-iPr</td>
<td>Ph</td>
<td>Me</td>
<td>75:25</td>
</tr>
<tr>
<td>9</td>
<td>Z-id</td>
<td>(S)-Ph</td>
<td>Ph</td>
<td>Me</td>
<td>87:13</td>
</tr>
<tr>
<td>10</td>
<td>Z-ie</td>
<td>(S)-tBu</td>
<td>Ph</td>
<td>Me</td>
<td>60:19</td>
</tr>
</tbody>
</table>
Utilizing enecarbamate Z-1, the consequence of steric interactions with the Evans chiral auxiliary and how that could guide the \( \pi \)-facial stereoselectivity in dioxetane formation was also investigated.\textsuperscript{39} Indeed, they found that the [2+2] photooxygenation reaction between \( ^1\text{O}_2 \) and enecarbamate Z-1 proceeded with complete diastereoselectivity (Figure 1-9). This complete diastereoselectivity was independent of the size of the \( C_4 \) substituent (\( \text{Me, } ^i\text{Pr, } ^t\text{Bu, Ph} \)), the \( R/S \) stereoconfiguration at \( C_3' \), solvent/solvent mixtures and therefore polarity.

\[ Z-1 \]

\[ ^1\text{O}_2 \]

Figure 1-9: Exclusive approach of \( ^1\text{O}_2 \) on to the top face of \( Z-1 \) to generate single dioxetane product. No product is observed for the approach of \( ^1\text{O}_2 \) on to the bottom face.

X-ray crystal structures of \( Z-1c \) indicate that the orientation of carbonyl functionality in these \( Z-1 \) enecarbamates could not engage in steric and/or electronic effects with the approaching \( ^1\text{O}_2 \). The chiral auxiliary was not guiding the approach of \( ^1\text{O}_2 \) and steric interactions induced by the chiral auxiliary were
most likely responsible for the observed complete diastereoselectivity. The conclusion, therefore, was that these “unprecedented results demonstrated that an appropriate choice of chiral auxiliary [enabled] complete diastereofacial control in the [2+2] cycloaddition with the smallest of all enophiles”.

These initial investigations into the role of the Evans chiral auxiliary in the mode selectivity and π-facial stereoselectivity of photooxygenation reaction of ¹O₂ with olefins, were not only unprecedented but opened the door to a better understanding of manipulating the stereochemical outcome in excited state reactions. However, the fact that the Me group can induce such extraordinary stereoselectivity in dioxetane formation with the smallest of all enophiles does provoke further questions as to whether steric interactions provide sufficient explanation or whether another factor may be contributing.

The possibility of vibrational deactivation as a plausible mechanism was first postulated after the Methyldeoxybenzoin (MDB) ketonic decomposition products (Figure 1-10) of the Z-1 and E-1 enecarbamates exhibited unexpected stereoselectivities. Starting with a 50/50 epimeric mixture at the C₃ stereogenic center, the enantiomeric excess of R-MDB and S-MDB products was not zero but rather strongly favoring the R-MDB for the C₄⁻R chiral configuration and the S-MDB for the C₄⁻S chiral configuration.
1.5.b. Summary

This thesis will explore the reaction of the enecarbamate 1 with $^1\text{O}_2$ and seek to understand whether or not vibrational deactivation plays a role in the observed stereoselectivities in both asymmetric chemistry and kinetic resolution. In chapter 2, the stereoselectivity of the enantiomeric ketone products is studied as a consequence of varying the size of the $C_4$ alkyl substituent (Scheme 1-6). In asymmetric induction with chiral auxiliaries, the steric contributions of the chiral auxiliary group may be the significant factor in producing the observed selectivity and varying the size of a key substituents often serves to increase stereoselectivity. By varying the size of the substituent here, the goal is to obtain a clearer picture about how $^1\text{O}_2$ interacts with the enecarbamate and how stereodifferentiation is induced.
Scheme 1-6: Reaction of Enecarbamate 1 with $^1$O$_2$ to form the dioxetane 2. The dioxetane decomposes to methyldesoxybenzoin (3) and carbaldehyde (4).

In chapters 3 and 4, deuteration of key groups will be one methodology for investigating vibrational deactivation. $^1$O$_2$ is vibrationally quenched about ten times faster by C-H bonds than C-D bonds.\textsuperscript{36} Therefore, by deuterating groups suspected of contributing to stereodifferentiation, we hope to observe changes in the product stereoselectivities and thereby validate vibrational deactivation as a contributing stereodifferentiation mechanism. Total ($k_Q$), chemical ($k_{cQ}$) and consequently, physical ($k_{pQ}$) rate constants are also determined (Equation 1-1). If two diastereomers physically quench $^1$O$_2$ to varying degrees, then we believe that this may be demonstrated by direct analysis of the physical quenching rate constants.

$$k_Q = k_{pQ} + k_{cQ}$$ \textbf{Equation 1-1}

In chapter 4, we transition from the first generation 1 to the second generation of enecarbamates I and investigate the stereoselectivity in the ketone products (Scheme 1-7). This second generation system has an additional chiral center at the $C_{2}$ position and the effect of this on stereoselectivity in the products is investigated. This work, we believe, will supplement any mechanistic information obtained with the first generation enecarbamates, 1.
Scheme 1-7: Structures of first generation 1 (far left) and second generation I (far right) enecarbamates.

Finally, in chapter 5, supramolecular assemblies such as cyclodextrins and zeolites provide chiral and achiral confined environments for the investigation of selectivity in these enecarbamates (Scheme 1-8).

Scheme 1-8: Transition from solution studies in chapters 2-5 to studies in supramolecular assemblies/confined media in chapter 6.
1.6. References


2. Alkyl Substituents, Conformations and Sterics.

2.1. Introduction:

The enecarbamate 1 provides a fertile scaffold for mechanistic investigations into stereoelectronic, steric, and conformational effects on stereoselectivity in $^1\text{O}_2$ [2+2] reactions. 1 reacts with $^1\text{O}_2$ to form the dioxetane 2 and this dioxetane then decomposes to form methyldesoxybenzoin (3) and the carbaldehyde 4 (Scheme 2-1).

![Scheme 2-1: Reaction of enecarbamate 1 with $^1\text{O}_2$ to form the dioxetane 2. The dioxetane decomposes to methyldesoxybenzoin (3) and carbaldehyde (4).]

Three notable features come together to form this rich investigative system: (i) The chiral 2-oxazolidinone functionality/auxiliary with alkyl substituent at C$_4$, (ii) the double bond at C$_1$-C$_2$, and (iii) the chiral center at C$_3'$. The oxazolidinone functionality contains a stereogenic center at the C$_4$ position when the X group is other than hydrogen. By varying the nature of the C$_4$-X group (Me vs. iPr), the stereogenic sense of the C$_4$ chiral center (R vs. S), the
alkene geometry (E vs. Z) or the chiral sense of the \( C_3' \) position (R vs. S) one can delve into the mechanistic intricacies and stereodifferentiating aspects of the reaction of \(^1\text{O}_2\) with 1 to form the methyldesoxybenzoin (MDB) product.

In early studies of the reaction outlined in Scheme 2-1, the enecarbamates \( Z\text{-}1\text{c} \) \((C_4\text{-}X=C_4\text{R}-i\text{Pr})\) and \( E\text{-}1\text{c} \) \((C_4\text{-}X=C_4\text{R}-i\text{Pr})\) were used with a 50-50 mixture of \( C_3'R \) and \( C_3'S \) (Scheme 2-2).\(^1\text{,}^2\) The photooxygenation reaction was undertaken in four different solvents at four different temperatures. The enantioselectivity (\( ee \)), conversion (C) and stereoselectivity factor (s)\(^3\text{–}^5\) were determined for each of these experiments. The \( s \) or stereoselectivity factor is a ratio of the rate constants for the formation of two enantiomers and is defined in Equation 2-1. Unlike the enantiomeric excess (\( ee \)), the \( s \) factor is independent of conversion and remains the same throughout the course of a reaction.

\[
s = \frac{k_R}{k_S}
\]

**Equation 2-1**

Where \( k_R \) is the rate constant for the formation of \( R\text{-}MDB \) and \( k_S \) is the rate constant for the formation of \( S\text{-}MDB \) and \( k_R > k_S \). The definition can be inverted when \( k_S > k_R \) so that values remain >1.
Scheme 2-2: 50-50 mixture of C$_3R$ and C$_3S$ enecarbamates 1b reacting with $^1$O$_2$ to produce a mixture of R-MDB and S-MDB.

The results clearly demonstrated that there was some selectivity in the MDB product for both the Z-1c and E-1c enecarbamates. Specifically, the results indicated that the s-factor for Z-1c remained firmly in the range of 1.7-2.6 despite solvent and temperature variations (Table 2-1).
Table 2-1: Stereoselectivity in the formation of MDB from Z-1c as a function of temperature and solvent.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>ee</th>
<th>C</th>
<th>s</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CDCl₃</td>
<td>25</td>
<td>27</td>
<td>49</td>
<td>2.2 (R)</td>
</tr>
<tr>
<td>2</td>
<td>CD₂Cl₂</td>
<td>20</td>
<td>22</td>
<td>29</td>
<td>1.7 (R)</td>
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<td>CD₂Cl₂</td>
<td>-20</td>
<td>22</td>
<td>59</td>
<td>2.1 (R)</td>
</tr>
<tr>
<td>4</td>
<td>CD₂Cl₂</td>
<td>-60</td>
<td>30</td>
<td>56</td>
<td>2.6 (R)</td>
</tr>
</tbody>
</table>

While the s-factor for Z-1c varies little with solvent or temperature, there was much greater variance with the E-1c enecarbamate over temperature and solvent (Table 2-2) such that exceptionally high stereoselectivities could be obtained with the latter. Figure 2-1 is an alternate presentation of the data in Table 2-2 and visually communicates the enantiomeric switching with varying solvent and temperature.
Table 2-2: Stereoselectivity in the formation of MDB from E-1c as a function of temperature and solvent.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>ee</th>
<th>C</th>
<th>s</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CDCl₃</td>
<td>50</td>
<td>8</td>
<td>5</td>
<td>1.2 (S)</td>
</tr>
<tr>
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<td></td>
<td>15</td>
<td>63</td>
<td>17</td>
<td>5.0 (R)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>-15</td>
<td>78</td>
<td>37</td>
<td>13 (R)</td>
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<tr>
<td>4</td>
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<td>-40</td>
<td>88</td>
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<td>CD₃CN</td>
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<td>15</td>
<td>30</td>
<td>34</td>
<td>2.1 (S)</td>
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<td>7</td>
<td></td>
<td>-15</td>
<td>0</td>
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<td>1.0</td>
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<tr>
<td>8</td>
<td></td>
<td>-40</td>
<td>58</td>
<td>37</td>
<td>5.2 (R)</td>
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<tr>
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<td>CD₃OD</td>
<td>50</td>
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<td>30</td>
<td>7.6 (R)</td>
</tr>
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<td></td>
<td>-40</td>
<td>94</td>
<td>12</td>
<td>37 (R)</td>
</tr>
</tbody>
</table>
Figure 2-1: Stereoselectivity in the formation of MDB from E-1c as a function of temperature and solvent.

By calculating the differential entropical ($\Delta \Delta S^*$) and enthalpic ($\Delta \Delta H^*$) activation parameters and using these numbers in conjunction with models and quantum mechanical calculations, the authors were able to speculate about the differences in the stereoselectivity trends between the $E$-1c and $Z$-1c enecarbamates. They hypothesized that conformational factors were key to the
observed trends and that the conformationally more flexible substrate/transition state of $E$-$1c$ was more subject to solvation/desolvation effects and enthalpic control than the more rigid $Z$-$1c$.\(^5\)

However, the isopropyl ($i$Pr) group is a sterically demanding substituent. In this chapter we will determine whether the sterically less demanding methyl (Me) group and the much greater steric bulk of the tertbutyl (tBu) group will impact the stereoselectivities we have seen thus far both for the $Z$-$1$ and the $E$-$1$ enecarbamates.
2.2. Results

Experiments were carried out on a 50-50 mixture of $C_3'$ diastereomers – that is, a 1:1 ratio of $C_3'R$ and $C_3'S$ diastereomers. For the series $C_4X - Me$, $iPr$, $tBu$, both $E$-1 and $Z$-1 enecarbamates were examined. The $C_4X$ chirality was also varied from $R$ to $S$. The enecarbamates investigated are presented in Table 2-3 for convenience. In the text, the $E$ variant of enecarbamate 1a may sometimes appear as $E$-1a(Me) where the $E$ refers to the alkene geometry and $Me$ refers to the $C_4X$ substituent.

Table 2-3: Structure matrix for enecarbamates 1.

<table>
<thead>
<tr>
<th></th>
<th>$C_4$</th>
<th>$X$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>R</td>
<td>Me</td>
</tr>
<tr>
<td>1b</td>
<td>S</td>
<td>Me</td>
</tr>
<tr>
<td>1c</td>
<td>R</td>
<td>$iPr$</td>
</tr>
<tr>
<td>1d</td>
<td>S</td>
<td>$iPr$</td>
</tr>
<tr>
<td>1e</td>
<td>R</td>
<td>$tBu$</td>
</tr>
<tr>
<td>1f</td>
<td>S</td>
<td>$tBu$</td>
</tr>
</tbody>
</table>

In Table 2-4 the results indicate that the same trend exists for the three different substituents - the $Me$-substituted enecarbamates $E$-1a and $E$-1b; the $iPr$-substituted enecarbamates $E$-1c and $E$-1d, and the $tBu$-substituted enecarbamates $E$-1f. With the $C_4(R)$ enecarbamates, $R$-MDB is increasingly favored as the temperature is lowered. Meanwhile, with the $C_4(S)$ enecarbamates,
S-MDB is favored with decreasing temperature. Within the experimental error of 10%, the stereoselectivity for the Me-substituted enecarbamates $E$-$1b$ is consistently higher than the stereoselectivity for the $t$Bu-substituted enecarbamates $E$-$1f$ (Entries 4, 8, 12, 16).
Table 2-4: Stereoselectivity factors for the reaction of $E$-1 enecarbamates with $^{1}O_{2}$ to form $R$- or $S$-MDB for the series of $X$ - Me, $^i$Pr, $^t$Bu as a function of temperature and solvent.$^5,^6$

![Reaction Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature $^\circ$C</th>
<th>$s$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$E$-1a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Me)</td>
</tr>
<tr>
<td>1</td>
<td>CD$_3$CN</td>
<td>50</td>
<td>5.6 (S)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>15</td>
<td>1.8 (S)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>-15</td>
<td>1.3 (R)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>-40</td>
<td>6.3 (R)</td>
</tr>
<tr>
<td>5</td>
<td>CDCl$_3$</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>15</td>
<td>4.7 (R)</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>-15</td>
<td>17 (R)</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>-40</td>
<td>41 (R)</td>
</tr>
<tr>
<td>9</td>
<td>CD$_3$OD</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>15</td>
<td>9.2 (S)</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>-15</td>
<td>19 (S)</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>-40</td>
<td>99 (S)</td>
</tr>
<tr>
<td>13</td>
<td></td>
<td>-98</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>CD$_2$Cl$_2$</td>
<td>20</td>
<td>1.6 (R)</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>-20</td>
<td>6.6 (R)</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>-60</td>
<td>50 (R)</td>
</tr>
</tbody>
</table>

Values are the average of two trials and experimental error is <10%.
Similarly for Table 2-5, the temperature trends are the same for all the Z-1 enecarbamates regardless of substituent size. There appears to be no notable temperature and solvent dependency. For all substituents, R-MDB is the predominant isomer when the C₄ chirality is R; S-MDB is favored when the C₄ chirality is S.

Table 2-5: Stereoselectivity factors for the reaction of Z-1 enecarbamates with ^1^O₂ to form MDB for the series of X - Me, i^Pr, t^Bu as a function of temperature and solvent.^5^-^6^  

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature °C</th>
<th>s</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Z-1a</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(Me)</td>
</tr>
<tr>
<td>1</td>
<td>CDCl₃</td>
<td>15</td>
<td>1.2  (R)</td>
</tr>
<tr>
<td>2</td>
<td>CD₃OD</td>
<td>15</td>
<td>1.4  (R)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>-15</td>
<td>1.5  (R)</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td>-40</td>
<td>1.7  (R)</td>
</tr>
<tr>
<td>5</td>
<td>CD₂Cl₂</td>
<td>20</td>
<td>1.5  (R)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>-20</td>
<td>1.4  (R)</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>-60</td>
<td>2.1  (R)</td>
</tr>
</tbody>
</table>

Values are the average of two trials and Experimental error is <10%.
Differential Activation parameters are presented in Tables 2-6 and 2-7. In the Eyring equation (Equation 2-2) there are two terms – the enthalpic term ($\Delta\Delta H^*_{R,S}/RT$) and the entropic term ($\Delta\Delta S^*_{R,S}/R$). $\Delta\Delta H^*_{R,S}$ describes the differential enthalpy of activation between the $C_3R$ and the $C_3S$ diastereomers (of the $C_4R$ enecarbamate) and can be rewritten as $\Delta H^*_R - \Delta H^*_S$ while $\Delta\Delta H^*_{R,S}$ can be rewritten as $\Delta S^*_R - \Delta S^*_S$.

\[
\ln(s) = \ln\left(\frac{k_R}{k_S}\right) = \frac{\Delta\Delta S^*_{R,S}}{R} - \frac{\Delta\Delta H^*_{R,S}}{RT} = \text{Equation 2-2}
\]

Where $s$ is the stereoselectivity factor, $k_R$ is the rate constant for formation of the $R$-MDB and $k_S$ the rate constant for formation of the $R$-MDB, $R$ is the gas constant and $T$ is temperature. Here, $k_R > k_S$ but the nomenclature of the ratio can be easily inverted when $k_R < k_S$ and the activation terms become $\Delta\Delta H^*_{S-R}$ and $\Delta\Delta S^*_{S-R}$.

When both activation terms, $\Delta\Delta H^*_{R,S}$ and $\Delta\Delta S^*_{R,S}$, have the same sign then there exists a temperature $T_0$, the equipodal temperature, when both terms ($\Delta\Delta H^*_{R,S}/RT$ and $\Delta\Delta S^*_{R,S}/R$) are equal thus giving rise to Equation 2-3. For there to be $T_0$, the $ee$ must be zero and therefore the $s$-factor must be 1. Below $T_0$ the enthalpic term dominates and above the entropic term dominates. In terms of stereoselectivity, at temperatures below $T_0$ the $ee$ increases with decreasing temperature (favoring one product isomer) and at temperatures above $T_0$, the $ee$ increases with increasing temperature (favoring the other isomeric product).
\[ T_0 = \frac{\Delta \Delta H^\dagger}{\Delta \Delta S^\dagger} \]

**Equation 2-3**

For the \textit{E-1} enecarbamates (Table 2-6), the notably large entropy term \((\Delta \Delta S_{R-S}^\dagger)\) and the enthalpy term \((\Delta \Delta H_{R-S}^\dagger)\) have the same sign indicating that above a certain temperature \(T_0\), one \textbf{MDB} isomer is predominantly formed and below \(T_0\), the opposite isomer dominates. In contrast, with the \textit{Z-1} enecarbamates (Table 2-7) both the differential entropy and differential enthalpy are significantly small. Even in this case when the differential entropy \(\Delta \Delta S_{R-S}^\dagger\) is so small and the signs of \(\Delta \Delta H_{R-S}^\dagger\) and \(\Delta \Delta S_{R-S}^\dagger\) are the same (and \(s\) can be 1), \(T_0\) is very high and no switching can occur within the range of the solvent so the stereoselectivity does not vary much. Additionally, when \(\Delta \Delta H_{R-S}^\dagger\) and \(\Delta \Delta S_{R-S}^\dagger\) have different signs, there is no temperature dependent stereoselectivity, since \(s\) is always >1 and one \textbf{MDB} isomer dominates regardless of temperature.

### Table 2-6: Differential activation parameters calculated for \textit{E-1} enecarbamates reaction with \textit{O}_2 to form \textbf{MDB} with \(X = Me, \textit{iPr}, \textit{tBu}\).\(^{5,6}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>(\Delta \Delta H_{R-S}^\dagger) (kJ/mol)</th>
<th>(\Delta \Delta S_{R-S}^\dagger) (J/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>(E-1a) (E-1b) (E-1c) (E-1f)</td>
<td>(E-1a) (E-1b) (E-1c) (E-1f)</td>
</tr>
<tr>
<td>1</td>
<td>CD(_3)CN</td>
<td>-25  10 -25  5</td>
<td>-90  20 -85  15</td>
</tr>
<tr>
<td>2</td>
<td>CDCl(_3)</td>
<td>-20  20 -25  15</td>
<td>-65  50 -75  50</td>
</tr>
<tr>
<td>3</td>
<td>CD(_3)OD</td>
<td>25   -10  15</td>
<td>65   -15  15</td>
</tr>
<tr>
<td>4</td>
<td>CD(_2)Cl(_2)</td>
<td>-20  25 -30  10</td>
<td>-75  75 -110  30</td>
</tr>
</tbody>
</table>

Values rounded off to nearest multiple of five to demonstrate trends (Error 20-30%).
Table 2-7: Differential activation parameters calculated for Z-1 enecarbamates reaction with \( ^{1}O_{2} \) to form MDB with X = Me, i\( ^{Pr} \), i\( ^{Bu} \).

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>( \Delta \Delta H_{R-S} ) (kJ/mol)</th>
<th>( \Delta \Delta S_{R-S} ) (J/mol)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Z-1a</td>
<td>Z-1b</td>
<td>Z-1c</td>
</tr>
<tr>
<td>1</td>
<td>CDCl(_3)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>CD(_2)Cl(_2)</td>
<td>0</td>
<td>5</td>
</tr>
</tbody>
</table>

Values rounded off to the nearest multiple of five to demonstrate trends (Error 20-30%).
2.3. Discussion

In previous studies, the \( E-1c \) enecarbamate showed high selectivities compared to the \( Z-1c \) enecarbamate. Additionally, while the stereoselectivity of the \( Z-1c \) enecarbamates did not change much with solvent or temperature, there was a clear solvent and temperature dependency of the stereoselectivity in the \( E-1c \) enecarbamate. Extraction of the differential activation parameters revealed the following:

1. \( \Delta \Delta H_{R-S}^{\dagger} \) and \( \Delta \Delta S_{R-S}^{\dagger} \) for the \( Z-1c \) compounds have opposite signs and their values are close to zero. \( \Delta \Delta G_{R-S}^{\dagger} \), \( (\Delta G_{R}^{\dagger} - \Delta G_{S}^{\dagger}) \) the differential free energy is >0, \( \Delta G_{R}^{\dagger} \) is more positive than \( \Delta G_{S}^{\dagger} \) and \( R-MDB \) is preferentially formed (Equation 2-4).

2. \( \Delta \Delta H_{R-S}^{\dagger} \) and \( \Delta \Delta S_{R-S}^{\dagger} \) for the \( E-1c \) compounds have the same sign and their values are non-negligible. That is, the \( E-1c \) diastereomers are subject to enthalpic and entropic controls.

\[
\ln(s) = \ln \left( \frac{k_R}{k_S} \right) = \frac{\Delta \Delta S_{R-S}^{\dagger}}{R} - \frac{\Delta \Delta H_{R-S}^{\dagger}}{RT}
\]

**Equation 2-2**

\[
\Delta \Delta G^{\dagger} = \frac{\Delta \Delta S^{\dagger}}{R} - \frac{\Delta \Delta H^{\dagger}}{RT}
\]

**Equation 2-4**

\( \Delta \Delta H_{R-S}^{\dagger} \) is the difference between the enthalpy of activation of the two diasteromers and since it was found to be negative for \( E-1a \) then the \( C_3'S \) diastereomer (Table 1-6) has a more negative enthalpy of activation (\( \Delta H' \)) than the \( C_3'R \) diastereomer. As the temperature decreases, the compound with the less
negative enthalpy of activation, the $C_3R$ isomer, is increasingly favored because the formation of its exciplex demands less kinetic energy. As the temperature decreases this is important because decreasing amounts of kinetic energy is available and the reaction requiring the smaller amount of kinetic energy has a better chance of occurring.

When the reagent $^1O_2$ come together with the substrate $E-1c$ or $Z-1c$ to form the exciplex the change in the activation entropy is negative. In fact, the formation of the dioxetane is generally considered to be the rate-limiting step. $^9$ $\Delta\Delta S^\dagger_{R-S}$ was determined to be negative for the $E-1c$ substrates, indicating that the $C_3R$ isomer has a more negative entropy of activation ($\Delta S^\dagger_R$) and therefore a greater entropic loss than the $C_3S$ isomer. The system with the smaller decrease in entropy is statistically more favored and therefore in an entropically driven environment, the reaction of the $C_3S$ diastereomer is increasingly promoted with increasing temperature. In summary therefore, the $C_3S$ diastereomer is entropy-favored and enthalpically disfavored while the $C_3R$ isomer is enthalpy favored and entropically disfavoured. $^{10}$ Thus, at higher temperatures, the $C_3S$ isomer prevails while at lower temperatures the $C_3R$ isomer prevails.

The solvent effect is notable. The equipodal temperature, $T_0$, changed with solvent for the reaction of $E-1c$ with $^1O_2$ to form the enantiomeric pair of MDB ketones. In methanol, the calculated equipodal temperature is quite high (above the boiling point of the solvent) while in acetonitrile and dichloromethane it occurs at near $0^\circ C$ and in trichloromethane it is close to $50^\circ C$. Acetonitrile is a polar, aprotic solvent (which may go some way to explaining its different
behavior) and both dichloromethane and trichloromethane are nonpolar, aprotic solvents. However, trichloromethane and dichloromethane do not behave in exactly the same way and in going from one solvent to the other at a particular temperature, notable changes in stereoselectivities are observed.

With temperature and solvent considerations explored to determine their impact on stereoselectivity values, attention can turn to the nature of the $C_4$-$X$ group. The $C_4$-isopropyl ($C_4$-$i$Pr) group is a standard for comparison. If it were to be replaced with the smaller methyl (Me) group or the sterically imposing tert-butyl ($t$Bu) group, what consequence would there be for the stereoselectivities? Since the Me group is smaller, would the $Z$-1a/$Z$-1b and $E$-1a/$E$-1b enecarbamates become more conformationally flexible and therefore more prone to stereodifferentiating factors?

In analyzing the results, it is evident that the general stereoselective trend with temperature and solvent seen with $Z$-1c and $E$-1c remains despite the changes in substituent size. Even with the smaller Me group, the $Z$-1a ($C_4$-$X$=$C_4$RMe) enecarbamate still has sufficient sterically-imposed rigidity so that the stereoselectively remains unvaried with changing solvent and temperature (Table 2-5). Likewise, in Table 2-4, the $E$-1a ($C_4$-$X$=$C_4$RMe) compound shows the same solvent and temperature dependencies as the $E$-1c compound ($C_4$-$X$=$C_4$R$i$Pr). The same isomer switching is evident in CD$_3$CN with the $E$-1a enecarbamates as with $E$-1c, and, as in all the solvents as the temperature is lowered the same isomer is increasingly favored.
What is notable, though, is that looking at the trends at -40°C, it is evident that as the size of the C₄-X substituent increases, the stereoselectivity decreases. For example, in CD₂Cl₂ (Table 2-4, Entry 16), the s-factor is 52, 45 and 9.5 for E-1b(Me), E-1d(iPr) and E-1f(tBu) respectively. One possible explanation for this is that as the C₄-X group increases in size, ΔΔH°S-R decreases. This smaller difference in ΔΔH°S-R may be the reason for the decreasing stereoselectivity.

Another hypothesis to explain the higher selectivities in the E-1a(Me) and E-1b(Me) compounds at lower temperatures may be due to solvent effects. There is clearly a solvent dependence for the E-1 enecarbamates. In methanol, higher selectivities are achieved at -40°C than for acetonitrile, for example. The different solvents, in solvating each substituted X-group differently, bring about differences in conformation between enecarbamates with different alkyl groups. These conformational differences, ultimately, may result in the equipodal temperature, T₀ increasing or decreasing on changing the X-group. For example, consider a situation where T₀ for the E-1b(Me) compound lies at a higher temperature than the E-1f(tBu) compound. Then, since stereoselectivities increase with decreasing temperature below T₀, the stereoselectivities for E-1b(Me) may be better enhanced at lower temperatures.

Either hypothesis may be borne out by examining the enthalpy-entropy plot. Examination of the data can indicate whether this difference in equipodal temperature or the decreasing ΔΔH° with increasing substituent size is the reason for the high Me (and lower tBu) stereoselectivities at lower temperatures. Or whether the reason may be a combination of both. An entropy-enthalpy plot was
constructed to compare the \textit{E-1b(Me)} and the \textit{E-1f(‘Bu)} substituted enecarbamates (\textbf{Figure 2-2}). The size difference between the \textit{Me} group and the \textit{tBu} group is extremely large and, in \textbf{Figure 2-2}, the \textit{E-1b(Me)} points generally appear to cluster further to the upper right than the \textit{E-1f(‘Bu)} points. While the differential enthalpy and entropy values are estimates (better values can be obtained with calorimetry experiments), the general trend does remain and \textit{E-1f(‘Bu)} has lower \(\Delta\Delta H^*\) and \(\Delta\Delta S^*\) values than \textit{E-1b(Me)} enecarbamate.

\textbf{Figure 2-2}: Enthalpy-Entropy Plot of \(\Delta\Delta S_{R,S}^*\) vs. \(\Delta\Delta H_{R,S}^*\) for \textit{E-1} enecarbamates with \(X – Me\) (triangles), \(tBu\) (squares) and \(C_4\) chirality – \(R, S\).

At the same time, \(T_0\), the equipodal temperature, can be easily calculated from the \(\Delta\Delta H^*\) and \(\Delta\Delta S^*\) values (\textbf{Equation 2-3}). Utilizing the values presented in \textbf{Table 2-6}, \(T_0\) for \textit{E-1f(‘Bu)} is determined to be lower than \(T_0\) for \textit{E-1b(Me)} ib
both acetonitrile (Me - 55°C; tBu - 142°C) and dichloromethane (Me - 33°C; tBu - 69°C). These two solvents have been previously found to induce quite similar stereoselectivity behavior.

\[ T_0 = \frac{\Delta \Delta H^\ddagger}{\Delta \Delta S^\ddagger} \]

**Equation 2-3**

It is important to note that enthalpy-entropy compensations plots (Figure 2-3) result in a straight line, indicating that the stereodifferentiating mechanism is the same regardless of solvent, \( C_4 \)-substituent (Me vs. \( iPr \)), alkene geometry (E vs. Z), or \( C_4 \) chirality (R vs. S). Consequently, it was suggested\(^5\)\(^,\)\(^6\) that the stereodifferentiating mechanism is tied to the \( C_3' \) configuration. Considering that these compounds differ only in spatial arrangement, it is not illogical to propose that that the same stereodifferentiating mechanism operates regardless of alkene geometry, \( C_4 \)-substituent and \( C_4 \) chirality. This aspect of the reaction will be explored in the next two chapters.
Figure 2-3: Enthalpy-entropy plot of $\Delta \Delta S_{R,S}^\dagger$ vs. $\Delta \Delta H_{R,S}^\dagger$ for $E$-1 and $Z$-1 enecarbamates with $X$ - Me, iPr, tBu and $C_4$ chirality – $R, S$.\textsuperscript{6}
2.4. Summary

Counterintuitive as it may seem, the smaller the $X$ group, the greater the obtained stereoselectivities as the temperature decreases below the equipodal temperature, and possibly as the temperature increases above the equipodal temperature. The behavior of the $iPr$-substituted enecarbamate is remarkably similar to the $Me$-substituted enecarbamate. High selectivities are obtained with both the $Me$- and $iPr$-substituted enecarbamates at high temperatures compared to the $tBu$-substituted enecarbamate. The stereoselectivity of the $Z$-$1$ enecarbamates demonstrate very little variation while the stereoselectivities of the $E$-$1$ enecarbamates vary greatly over a range of temperatures and solvents despite the size of the $C_4$-alkyl substituent, thus recommending the underpinnings of a single steredifferentiating framework.

2.4.a. Outlook

To summarize, in this chapter we varied the size of the $C_4$-alkyl substituent using the $iPr$ group as a size standard. The stereoselectivity trends with the smaller $C_4$-$Me$ and the larger $C_4$-$tBu$ substituted enecarbamates remained the same as with the $C_4$-$iPr$ enecarbamate. These unsurprising and consistent results therefore set the groundwork for the investigation into the hypothesized vibrational quenching mechanism.
2.5. References


3. Refer Section 7-12.


3. Asymmetric Induction and Vibrational Deactivation

3.1. Introduction

The enecarbamates $Z-1$ reacts with $^{1}\text{O}_2$ in the [2+2] addition reaction to form a dioxetane (Scheme 3-1). With a starting substrate that is enantiomerically pure, then $^{1}\text{O}_2$ can only react in two ways – on either face of the double bond (Figure 3-1). The bottom face of the double bond can be regarded as the face of the $\pi$ bond where the $C_4-X$ group resides.

Scheme 3-1: Photooxygenation of enecarbamate $Z-1$ with $^{1}\text{O}_2$ to form the dioxetane 2.

Figure 3-1: The approach of $^{1}\text{O}_2$ on the two faces of the $\pi$ bond of the enecarbamate 1.
Previous work\textsuperscript{1, 2} with the \textit{Z-1} enecarbamates varied the \textit{C$_4$} substituent (\textit{Me}, \textit{iPr}, \textit{Ph} and \textit{tBu}). In every case, \textgreater95\% of the reaction with \textit{1}O$_2$ proceeded from one face (the top face) of the molecule regardless of the chirality of the \textit{C$_3$}’ phenylethyl group (\textbf{Table 3-1}). The rationale for this was hypothesized that the result was due to steric hindrance provided to \textit{1}O$_2$ by the \textit{C$_4$}-\textit{X} group and the \textit{C$_2$}’ phenyl group.

\textbf{Table 3-1:} Diastereoselectivities in the photooxygenation of the enecarbamate \textit{Z-1}.\textsuperscript{1, 2}

\begin{tabular}{|c|c|c|c|}
\hline
Entry & \textit{X} & Chirality & Selectivity \\
\hline
& & \textit{C$_4$} & \textit{C$_3$}’ & (\textit{1’S,2’S}):\textit{(1‘R,2’R)} \\
\hline
1 & \textit{Me} & \textit{R} & \textit{S} & >95:5 \\
2 & \textit{Me} & \textit{R} & \textit{R} & >95:5 \\
3 & \textit{iPr} & \textit{R} & \textit{R} & >95:5 \\
4 & \textit{iPr} & \textit{R} & \textit{S} & >95:5 \\
5 & \textit{iPr} & \textit{S} & \textit{S} & <5:95 \\
6 & \textit{iPr} & \textit{R} & \textit{R} & >95:5 \\
7 & \textit{iPr} & \textit{R} & \textit{R} & >95:5 \\
8 & \textit{Ph} & \textit{S} & \textit{R} & <5:95 \\
9 & \textit{Ph} & \textit{S} & \textit{S} & <5:95 \\
10 & \textit{tBu} & \textit{S} & \textit{R} & <5:95 \\
11 & \textit{tBu} & \textit{S} & \textit{S} & <5:95 \\
\hline
\end{tabular}
The surprising and interesting aspect of these results is that the Me substituent is just as effective as the Ph and tBu substituents at blocking the approach of tO₂, quite a small enophile, on the bottom face of the molecule.

It was suggested in later papers³ that this remarkable diastereoselectivity might not be solely induced by steric shielding. In fact, considering that tO₂ can be quite effectively quenched by C-H bonds to 3O₂,⁴-⁷ the authors suggested that vibrational quenching of the tO₂ molecule be an additional rationale for the remarkable high diastereoselectivities observed.

C-D bonds are known to be much less inefficient than C-H bonds at quenching tO₂.⁴-⁷ If indeed vibrational quenching of tO₂ is a contributing agent to these high diastereoselectivities, then deuteration of the C₄-X carbon should result in a decrease in diastereoselectivity. The remaining diastereoselectivity should be the sterically induced diastereoselectivity.⁸ Upon deuteration of the C₄ substituents, the steric contributions of the Me and iPr groups are expected based on steric factors to block 75% and 82%, respectively, of the tO₂ approaching the bottom face, rather than <95%. In this chapter, we seek to demonstrate this by replacing the iPr-CH(CH₃)₂ substituent with the deuterated iPr-CD(CD₃)₂ moiety.

Understanding the reactive trajectory of tO₂ onto the enecarbamate double bond is important for understanding the mechanism of stereodifferentiation. It has been suggested that the oxazolidinone ring in the E-1 enecarbamate may factor into the approach of tO₂ and direct its trajectory towards the double bond. Crystal structures (Figure 3-2) indicate that the oxazolidinone ring is oriented
perpendicular to the plane of the double bond in the \( E-1 \) enecarbamates. If either the nitrogen or carbonyl functionalities do in fact steer the approach of \( ^1\text{O}_2 \), then one would expect to see diastereoselectivities reflecting this – that is, that more \( ^1\text{O}_2 \) reacts with the face of the double bond \textit{syn} to those oxazolidinone functionalities.

![Figure 3-2: Crystal structures and ChemDraw representations obtained for the \( 1'E4S-1b(\text{Me}) \) enecarbamate.][9]

In this work, we will investigate the diastereoselectivity of the \( E-1 \) enecarbamate and the \( C_4 \)-deuterated \( Z-1 \) in an attempt to gather information that will help to elucidate the stereodifferentiating mechanism in photooxygenation of the enecarbamate 1.\(^{10,11}\)
Determination of the approach of \(^1\)O\(_2\) is fundamentally a two-step process (Scheme 3-2). First, the substrate enecarbamate 1 is photooxygenated at low temperatures to minimize if not altogether prevent the decomposition of the dioxetane 2 intermediate. The progress of the conversion of 1 to 2 is followed by low temperature \(^1\)H-NMR. Second, the dioxetane is converted to the diol via oxidation of the dioxetane with OsO\(_4\) followed by cleavage of the molecule.\(^1,\)\(^2\) The diol obtained by this procedure is analyzed via HPLC on a chiral OD column and compared to the synthesized reference diols.\(^1,\)\(^2\)

**Scheme 3-2:** Experimental strategy for the analysis of the stereochemistry of \(^1\)O\(_2\) approach.
3.2. Vibrational Deactivation

In the electronic-vibrational deactivation of $^1\text{O}_2$, the electronic energy of $^1\text{O}_2$ is transferred to the vibrational modes of both ground state oxygen ($^3\text{O}_2$) and the quencher. It is consequently integral to understand to obtain an understanding of why $^1\text{O}_2$ persists longer in halogenated solvents than in deuterated solvents; and in deuterated solvents than in proteated solvents.

In comparing the vibrational modes of C-F versus C-D versus C-H, it is immediately apparent that the differences lie in the strength and therefore oscillation frequency of these bonds. The fluorine (F) atom is heavier than the deuterium (D) atom, which in its turn is heavier than its hydrogen (H) isotope. The heavier the atom, the more energy is required to get it to move at the same frequency as a lighter atom. The C-H bond, therefore, oscillates at a higher frequency than the C-D bond, and likewise, the C-D bond oscillates at a higher frequency than the C-F bond. This key difference determines the rate of deactivation of $^1\text{O}_2$ by these C-Y oscillators.

The Franck-Condon principle states that in transitioning between vibrational levels, the most likely transition that occurs is one where the wave functions of the two states more significantly overlap. This is why the $^1\text{O}_2$ ($v=0$) wants to return to $^3\text{O}_2$ ($v=0$), because the wave functions have better overlap. $^1\text{O}_2$ in its $v=0$ excited state vibrational level must dissipate 7882 cm$^{-1}$ of energy to return to the $v=0$ vibrational level of $^3\text{O}_2$ and transfer this energy to the C-Y vibrational energy level. The highest vibrational frequency of C-H is 3050 cm$^{-1}$, of C-D is 2240 cm$^{-1}$ and of C-F is $\sim$1200 cm$^{-1}$. Clearly, $^1\text{O}_2$ cannot transfer its quanta
of energy to one single vibrational mode and return to the \(v=0\) vibrational level of \(^{3}\text{O}_2\). This being the case, \(^1\text{O}_2\) shall have to return to a higher vibrational energy level of \(^{3}\text{O}_2\). In general, the lower the vibrational level, the better it’s overlap with the \(v=0\) level (Figure 3-3).

![Figure 3-3: Comparison of overlap in vibrational wave functions for \(v=0\) (blue), \(v=1\) (red), \(v=2\) (orange), and \(v=7\) (purple).](image)

This inability to transition to a vibrational state with great overlap and instead transition to a vibrational state with poorer overlap means that the transition takes longer. The better the overlap, the faster the deactivation; the poorer the overlap, the slower the deactivation.
In considering the vibrational energy levels of $^1\text{O}_2$ and the energy of the C-Y bonds (Figure 3-4), the change in energy ($\Delta E$) in going to the $v=3$ level of $^3\text{O}_2$ (3286 cm$^{-1}$) is close in energy to C-H bond (3050 cm$^{-1}$). Meanwhile, the closest $\Delta E$ to the C-D bond (2240 cm$^{-1}$) and the C-F bond ($\sim 1200$ cm$^{-1}$) is the $v=3$ level ($\Delta E = 3286$ cm$^{-1}$) and $v=4$ level ($\Delta E = 1903$ cm$^{-1}$), respectively.

\[ \text{\underline{v=0 of } } ^3\text{O}_2 \text{ standardized at } 0 \text{ cm}^{-1} \]

**Figure 3-4:** The first 6 vibrational energy levels of ground state oxygen, $^3\text{O}_2$ relative to the $v=0$ vibrational energy level of $^1\text{O}_2$.

In quantum mechanics, we know the transitions involve more or less precise quanta of energy. However, with these C-F and C-D bonds, the overlap between energy lost by $^1\text{O}_2$ and gained by the C-Y oscillator is poor. While there is much better overlap between the $v=0$ ($^3\text{O}_2$) to $v=3$ ($^3\text{O}_2$) transition and the C-H bond – The 3200 cm$^{-1}$ of energy lost by $^1\text{O}_2$ in going to the $v=3$ vibrational energy
level of $^3\text{O}_2$ can precisely go to the 3050 cm$^{-1}$ of energy required by the highest vibrational energy level of the C-H bond. Moreover, in considering the Franck-Condon factors, there is better overlap between the $v=0$ ($^1\text{O}_2$) wave function and the $v=3$ ($^3\text{O}_2$) wave function than with the $v=4$ ($^3\text{O}_2$) wave function. This is based on the previously mentioned fact that the lower vibrational level $v$ of $^3\text{O}_2$, the better its overlap with $v=0$ of $^1\text{O}_2$ (Figure 3-3). The difference between the overlap of $v=0$ ($^1\text{O}_2$) with $v=3$ ($^3\text{O}_2$) and with $v=4$ ($^3\text{O}_2$) may seem small, but in a transition where the overlap is not initially great and the lifetimes are long, the small difference is significant.

Additionally, since $^1\text{O}_2$ wants to get to the ground state $v=0$ level, it will have to transfer the entire 7882 cm$^{-1}$ of energy into the vibration of the solvent. To do so with C-F, it will have to dump the energy into more C-F bonds ($\sim 7$) or C-D bonds ($\sim 3$) than C-H bonds ($\sim 2$). There is better resonance and therefore probability associated with transferring energy to the fewer quanta of C-H bond than the greater quanta of C-D and C-H bonds, and therefore the greater likelihood means faster deactivation compared to C-D and C-F.
3.3. Results

The structural matrix outlining the compounds referred to in this chapter is presented in Table 3-2. The C₄ deuterated compounds are 1g and 1h and, as an example, are sometimes referred to as Z-1g (Me-D₃) where Z is the alkene geometry, and (Me-D₃) indicates the deuterated Me substituent. With 1'Z,4S,3'S-1f, for example, Z indicates the alkene geometry, 4S the chirality at the C₄ position and 3'S, the chirality at the C₃' position.

Table 3-2: Structure matrix for Z-1 and E-1 enecarbamates.

<table>
<thead>
<tr>
<th></th>
<th>C₄</th>
<th>X</th>
<th>X₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>Z-1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>R</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>1b</td>
<td>S</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>1c</td>
<td>R</td>
<td>¹Pr</td>
<td>H</td>
</tr>
<tr>
<td>1d</td>
<td>S</td>
<td>¹Pr</td>
<td>H</td>
</tr>
<tr>
<td>1e</td>
<td>R</td>
<td>¹Bu</td>
<td>H</td>
</tr>
<tr>
<td>1f</td>
<td>S</td>
<td>¹Bu</td>
<td>H</td>
</tr>
<tr>
<td>1g</td>
<td>S</td>
<td>Me-D₃</td>
<td>D</td>
</tr>
<tr>
<td>1h</td>
<td>S</td>
<td>¹Pr-D₇</td>
<td>D</td>
</tr>
</tbody>
</table>

E-1
The C₁ vinylic hydrogen in the ¹H-NMR spectra in Figure 3-5 is further upfield in the dioxetane than in the alkene. Moreover, examinations of these ¹H-NMR spectra provide evidence that the ₁Z₄S₃’₃₄S-1h enecarbamate gives rise to two dioxetanes – ¹O₂ reacts from both faces of the π bond. Integration of the peaks reveals that about 80% of the incoming ¹O₂ approach from one face and 20% from the other. This is further supported by the results of the HPLC traces (Figure 3-6). The SS diol correlates to the ₁’S,₃’S dioxetane and consequently to attack from the bottom face. Likewise, the RR diol correlates to the ₁’R,₃’R and attack from the top face of the molecule.

**Figure 3-5:** ¹H-NMR following the progress of the reaction from the enantiomerically pure enecarbamate ₁Z₄S₃’₃₄S-1h to the dioxetane Z-2h by monitoring the C₁ vinylic hydrogen.
Figure 3-6: HPLC traces on chiral GC column comparing standard diols with the diol obtained from oxidation and subsequent cleavage of the dioxetane Z-2h.\textsuperscript{10}

Stereoselectivity (s) factors obtained for the Z-1g enecarbamate, deuterated at the C\textsubscript{4} position, compare favorably with those obtained for the proteated Z-1b enecarbamate. Within the experimental error, the s values as a function of temperature and solvent did not change with deuteration.
Table 3-3: Stereoselectivity factors for \(Z-1b(\text{Me-H}_3)\) and \(Z-1g(\text{Me-D}_3)\) compounds as a function of solvent and temperature.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature °C</th>
<th>(s)</th>
<th>(Z-1b)</th>
<th>(Z-1f)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>((\text{Me-H}_3))</td>
<td>((\text{Me-D}_3))</td>
</tr>
<tr>
<td>1</td>
<td>CDCl(_3)</td>
<td>15</td>
<td>1.4</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>-15</td>
<td>1.6</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>-40</td>
<td>1.5</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>CD(_3)OD</td>
<td>15</td>
<td>2.0</td>
<td>1.8</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>-15</td>
<td>2.4</td>
<td>2.1</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>-40</td>
<td>2.8</td>
<td>2.6</td>
<td></td>
</tr>
</tbody>
</table>

Values are the average of two trials and experimental error is <10%.

Contrasting the deuterated \(Z-1h\) enecarbamate, \(^1\)H-NMR spectra for the photooxygenation of proteated \(1'E,4R,3'S-1c\) resulted in the formation of only one dioxetane (Figure 3-7). Additionally, the \(C_1\) vinylic hydrogen of the dioxetane occurs downfield of the starting substrates hydrogen whereas with the \(Z-1f\) substrate it was upfield of the starting substrate hydrogen. Confirmation of the single dioxetane was obtained via the HPLC results (Figure 3-8). Relating the diol obtained with the dioxetane and subsequently the starting substrate (Figure 3-9), revealed the \(^1\)O\(_2\) approach to be exclusively from the face of the \(\pi\) bond syn to the carbonyl of the oxazolidinone ring (the top face).
Figure 3-7: $^1$H-NMR following the progress of the reaction from the enantiomerically pure enecarbamate $1'E,4R,3'S$-1c to the dioxetane $E$-2c by monitoring the $C_1$-vynil hydrogen.10
Figure 3-8: HPLC traces on chiral GC column comparing standard diols with the diol obtained from oxidation and subsequent cleavage of the dioxetane $E$-2c.
**Figure 3-9:** Determination of the face of attack by $^3$O$_2$ on $E$-1c from the chirality of the diol observed in the HPLC.
3.4. **Discussion**\textsuperscript{10, 11}

As mentioned earlier, previous work performed with the Z-1 enecarbamates showed that >95% of the $^1\text{O}_2$ reacted almost exclusively with one face of the $\pi$ bond regardless of the size of the $C_4$-$X$ substituent (Figure 3-10).\textsuperscript{1, 2} However, on deuteration of the $C_4$ carbon, results showed that only 80% of the reactions occurred at the top face (Figure 3-11).

![Figure 3-10: Exclusive approach of $^1\text{O}_2$ on the top face of the $\pi$ bond to form the $1'S,2'SR$ dioxetane Z-$2c$($Pr$) from the Z-$1c$($Pr$) enecarbamate.](image)

Vibrational quenching or deactivation of $^1\text{O}_2$ occurs when the C-H vibrations couple with the electronic excited state of molecular $\text{O}_2$ leading to relaxation of the singlet excited state. That is, the electronically excited state is converted to vibration of the ground state $\text{O}_2$ and of the quencher/substrate.\textsuperscript{12} In fact, it is generally accepted that the most prominent deactivation pathway of $^1\text{O}_2$ in solution is quenching by oscillators of solvent molecules.\textsuperscript{13} Moreover, C-H bonds are much more efficient at quenching $^1\text{O}_2$ molecules than C-D bonds.\textsuperscript{4-7}
Deuteration of the \( C_4-X \) group does not noticeably affect the steric character of the group, only the vibrational character. Consequently, this difference between the deuterated and proteated molecule (Figure 3-8) can be attributed to vibrational quenching of \( ^1\text{O}_2 \) by the C-H bonds. Immediately, it becomes evident that the steric factors working synergistically with vibrational quenching produce the remarkably high diastereoselectivities observed in the \( Z-1 \) enecarbamates.

The \( Me \) group has a smaller steric contribution than the \( iPr, Ph \) and \( tBu \) groups. Yet >95% of all the reaction proceeds from the top face of the \( \pi \) bond. It follows then that <5% of the approaching \( ^1\text{O}_2 \) slips in through the bottom face regardless of the size of the \( C_4-X \) group (\( Me, iPr, Ph, tBu \)) extending across this bottom face. If the high stereoselectivity observed in the \( Z-1 \) enecarbamates is
solely the combination of steric and vibrational quenching by the terminal C-H bonds, then by this argument the Me group induces a greater vibrational quenching.

However, electronic-vibrational quenching is not the sole means of deactivating \(^{1}O_2\). Aside from transfer of its electronic energy to the molecule (vibrational or physical quenching), \(^{1}O_2\) can react with the substrate. Reaction with the substrate does not necessarily produce the dioxetane product (chemical quenching). The \(^{1}O_2\) is believed to form a charge transfer complex in the first stages of the reaction.\(^{14}\) Rather than continuing on to form the dioxetane, there can be intersystem crossing and the product can then dissociate back to the substrate and ground state O\(_2\) (\(^{3}O_2\)).\(^{15}\)

Consequently, even if the some \(^{1}O_2\) did get past the Me group, there would not only be more successful reactions with the double bond, but there might also be more quenching by the double bond via charge transfer quenching.

**Table 3-3** compares the stereoselectivities obtained for the proteated and deuterated methyl derivatives of the enecarbamate Z-1b. With the proteated compound, \(^{1}O_2\) approaches essentially only from the top face. With the deuteration, \(^{1}O_2\) can now react with the double bond from both faces. Yet, within the experimental error, the \(s\) factors for the proteated and deuterated compounds are the same in each solvent, at each temperature. Therefore, whether the \(C_4-Me\) substituent is proteated or deuterated, the same percentage of \(^{1}O_2\) molecules are chemically quenched on approaching the bottom face of the C=C double bond. So, whether proteated or deuterated, the incoming \(^{1}O_2\) has the same preference
for the top face of the C=C bond. Hence, the results of deuteration imply that the stereodifferentiation feature is quite likely present on the top face of the molecule.

One may entertain the possibility that the stereoselectivity may come about as a consequence of strain in the transition state of Z-1c. On reacting with ¹O₂, the substrate is forced to realign. In adopting these new tetrahedral conformations about the C₁' and C₂' carbons, the steric demands on the bottom face may translate to strain in the reversible exciplex transition state. If one diastereomeric exciplex (C₃'S) experiences more strain, its exciplex may more readily dissociate to yield the starting diastereomer. Meanwhile, the other diastereomeric exciplex (C₃'R) may continue on more readily to form the dioxetane intermediate. Consequently, the C₃'R diastereomer would react faster to give more R-MDB product.

On deuteration, ¹O₂ can now approach from the bottom face and the molecule is forced to align differently so that any steric demands of the top face may translate to strain in the transition state. In Figure 3-12 are the representations for crystal structures obtained for the Z-1c enecarbamate.¹,² If strain were integral to the stereodifferentiation mechanism, then one would theorize based on the structures in Figure 3-12 that the C₃'R diastereomer would experience more strain and therefore react more slowly, since the phenyl group is more sterically imposing than the methyl group. However, the results upon deuteration do not indicate that there is any decrease in the amount of R-MDB formed.
The approach of $^1\text{O}_2$ on to $C_3S$ diastereomer of the $E$-1 enecarbamate, as the results show, proceed almost exclusively from one face of the double bond, that is, the face that is syn (the top face) to the carbonyl and nitrogen functionalities of the oxazolidinone ring (Figure 3-13). This is consistent with the steering theory proposed in other publications.$^{2, 16}$ This result can be extrapolated to the $C_3R$ diastereomer.

**Figure 3-12:** ChemDraw representations of crystal structure obtained for $Z$-$\text{1c}, C_3R$ (left) and $Z$-$\text{1c}, C_3S$ (right) enecarbamates.$^{1, 2}$

**Figure 3-13:** Exclusive approach of $^1\text{O}_2$ syn to the carbonyl group of the oxazolidinone ring to form the $1'S,2'R$ dioxetane $E$-$\text{2c}(i\text{Pr})$ of the $E$-$\text{1c}(i\text{Pr})$ enecarbamate.
Once more, attention turns to the crystal structures. The two diastereomers of the $E$-$1b(Me)$ enecarbamate have quite similar crystal structures. The differences are as follows:

(i) the oxazolidinone ring is puckered in the $C_3'R$ isomer and planar in the $C_3'S$ isomer.

(ii) The orientation of the $C_4$-$X$ group in the $C_3'S$ isomer points towards the bottom face of the double bond, towards the $C_2'$ phenyl group while in the $C_3'R$ isomer it points away from the bottom face and towards the $C_3'$ phenylethyl group.

(iii) The $C_4$-$X$ group and the $C_3'$ methyl group are in closer proximity in the $C_3'R$ isomer.

The top faces of both structures are essentially the same. Both diastereomers adopt structures to minimize the steric interactions. Particularly, the puckered conformation in the $C_3'R$ isomer is meant to minimize the interaction of the oxazolidinone carbonyl with the $C_2'$ phenyl group, and the $C_4$-$Me$ group with the $C_3'$-$Me$ group.

At lower temperatures, there is little thermal motion in the molecule and it is plausible that the structures in the solvent approach the structures of the crystal structure representations. The carbonyl functionality steers the $^1O_2$ not only to the top face of the double bond, but towards its side of the molecule. On approaching the $C_3'R$ isomer, it encounters the $C_4$-$Me$ group pointing towards it. Contrastingly, in the $C_3'S$ diastereomer, the $C_4$-$Me$ group is pointing away from it,
towards the bottom face of the bond. The Me group is not very bulky, but there are C-H bonds and in approaching the $C_3R$ isomer, some $^1O_2$ molecules are deactivated by the Me group. This may explain, therefore, why the $C_3S$ isomer dominates at lower temperature for the $C_4(S)$ enecarbamate.

Collision theory states that a reaction occurs when two molecules collide with the appropriate energy and configuration. In Equation 3-1, these three considerations are taken into account –

(i) The need to collide – $Z$, the collision frequency.

(ii) The necessary minimal energy – $E_A$, the activation energy.

(iii) The appropriate configuration – $\rho$, the steric factor.

$$k(T) = Z\rho e^{-\frac{E_A}{RT}}$$ \hspace{1cm} \text{Equation 3-1}

This theory can be extended to the photooxygenation of the enecarbamates in analyzing the approach of $^1O_2$ on to the molecule. The steric factor, $\rho$, can also be described as the ratio of the cross-section of reactive collisions to the cross-section of total collisions. This term, in our photooxygenation reaction, accounts for both the steric demands and the vibrational quenching induced by the enecarbamate. Comparing and extending Equation 3-1 to the Eyring Equation, one obtains Equation 3-2 and 3-3.

$$\frac{k_R}{k_S} = \frac{Z\rho_R e^{\frac{E_A(R) - E_A(S)}{RT}}}{Z\rho_S}$$ \hspace{1cm} \text{Equation 3-2}
In the Z-1 enecarbamate the differential activation energy, $\Delta\Delta H^\dagger$, is negligible and the enthalpic exponential is essentially 1. The entropic term, though small, determines which diastereomer reacts faster. This term is temperature independent and the relative rates are expected to be insensitive to temperature changes. Since crystal structures reveal that the two Z-1 diastereomers have quite similar spatial orientations (Figure 3-12)$^{1,2}$ then they most likely experience the same total number of collisions and $Z$ is equivalent. The reason, then, why one isomeric product dominates must then be explained by the steric factor. That is, one diastereomer is experiencing more reactive collisions than the other diastereomer. This diastereomer, therefore, experiences less steric blocking and vibrational quenching.

The work above with the deuteration demonstrates the role that vibrational deactivation plays in dioxetane diastereoselectivity. Therefore, aside from the more familiar steric differentiation mechanism, vibrational quenching of $^1$O$_2$ may also be a key stereodifferentiating factor in the photooxygenation reaction.

Similar arguments can be extended to the E-1 enecarbamate and will be in the following chapter.
3.5. Summary

Studies on the diastereoselectivity of dioxetanes indicate that the approach of $^1\text{O}_2$ on to the double bond occurs almost exclusively on one face. Evidence obtained through deuteration suggests that *vibrational deactivation* plays a concerted role with steric shielding in order to exert diastereodifferentiating features on the approach of $^1\text{O}_2$ to form the dioxetane. Analysis of crystal structures offer the possibility of extending this vibrational deactivation theory to explaining the stereodifferentiating features of the photooxygenation reaction leading to preferential formation of one MDB enantiomer when starting from a $C_3'$ epimeric mixture of enecarbamates.

3.5.a. Outlook

An enantiopure enecarbamate diastereomer may react with $^1\text{O}_2$ to form two possible dioxetanes. In the proteated compound, photochemical asymmetric induction by the chiral auxiliary results in the formation of a single dioxetane. Deuteration of the $C_4$-$X$ substituent was sufficient to demonstrate the role of vibrational quenching in this highly selective photoreaction. Attention now turns to the role of vibrational quenching by C-H bonds in the kinetic resolution of a 50:50 mixture of diastereomeric enecarbamates to produce to $R/S$-MDB. That is, does one diastereomer preferentially deactivate (physically) $^1\text{O}_2$ leading to the preferential formation of one enantiomer of MDB?
3.6. References


6. Ogilby, P. R.; Foote, C. S., Chemistry of singlet oxygen. 42. Effect of solvent, solvent isotopic substitution, and temperature on the lifetime of singlet


4. Chemical and Physical Quenching

4.1. Introduction

In the previous chapter the idea of vibrational deactivation as a stereodifferentiating mechanism was introduced in the reaction of $^1\text{O}_2$ with the enecarbamate 1 to form the dioxetane 2 and eventually the ketone 3 through cleavage of the dioxetane (Scheme 4-1).

$$\text{Scheme 4-1: Reaction of enecarbamate 1 with } ^1\text{O}_2 \text{ to form the dioxetane 2. The dioxetane decomposes to methyldesoxybenzoin (3) and carbaldehyde (4).}$$

In approaching the enecarbamate 1 two things can happen to deactivate $^1\text{O}_2$: (i) $^1\text{O}_2$ can react with the double bond and (ii) $^1\text{O}_2$ can be physically deactivated to the ground state. Reaction of $^1\text{O}_2$ with the enecarbamate double bond to generate product is referred to as chemical quenching rate constant ($k_{cQ}$). However, $^1\text{O}_2$ may add to the double bond and then through intersystem crossing may generate ground state oxygen, $^3\text{O}_2$. This latter mechanism is considered under the heading of physical quenching since it does not follow through to product. The more familiar occurrence of physical or collisional deactivation ($k_{pQ}$) of $^1\text{O}_2$ occurs when it encounters and couples with terminal C-H bonds.
(electronic-vibrational coupling), thereby transferring its electronic energy to C-H and $^3$O$_2$ vibrations.

$$k_q = k_{pQ} + k_{cQ}$$

Equation 4-1

Together, the chemical quenching ($k_{cQ}$) and physical quenching ($k_{pQ}$) constitute the total quenching ($k_Q$) of $^1$O$_2$ (Equation 4-1; Scheme 4-2). To better understand the role of vibrational deactivation in the observed high stereoselectivities, we performed a systematic study of the rate constants for both chemical ($k_{cQ}$) and physical ($k_{pQ}$) quenching.$^{1-7}$

![Scheme 4-2: Quenching pathways for $^1$O$_2$ in the reaction with Enecarbamate 1.](image)

Another approach for investigating the possibility of vibrational quenching as a stereodifferentiation mechanism is by deuteration of the relevant features. This was an approach taken in the previous chapter and here it will be applied again to the $E$-1 enecarbamate in an attempt to validate or repudiate the vibrational quenching theory.
4.2. Results

Table 4-1: Structure matrix for compounds presented in this chapter.

<table>
<thead>
<tr>
<th></th>
<th>C₄</th>
<th>X</th>
<th>X₂</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>R</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>1b</td>
<td>S</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>1c</td>
<td>R</td>
<td>tPr</td>
<td>H</td>
</tr>
<tr>
<td>1d</td>
<td>S</td>
<td>tPr</td>
<td>H</td>
</tr>
<tr>
<td>1e</td>
<td>R</td>
<td>tBu</td>
<td>H</td>
</tr>
<tr>
<td>1f</td>
<td>S</td>
<td>tBu</td>
<td>H</td>
</tr>
<tr>
<td>1g</td>
<td>S</td>
<td>Me-D₃</td>
<td>D</td>
</tr>
<tr>
<td>1h</td>
<td>S</td>
<td>tPr-D₇</td>
<td>D</td>
</tr>
</tbody>
</table>

The chemical quenching rate constants (k_{cQ}) presented in Table 4-2 substantiate the stereoselectivities (s-factors) determined previously through the enantioselectivities (ee) of the R- and S-MDB enecarbamates.⁸ The s-factors obtained from k_{cQ} (calculated) and from the information compiled previously (theoretical)† are presented in the last column of the table and are in rough agreement with each other. The highest rate constants are found with the Z-1a Me substituted enecarbamates, with more molecules reacting per unit time than the corresponding tPr substituted enecarbamates (Entry 1 & 5, 2 & 6). The k_{cQ} values are uncommonly low, with values only on the order of 10⁻³. ¹⁸O₂ is an

† The theoretical values are calculated at 20°C and are extrapolations based on s-factor data obtained with MDB in the previous chapters.
enophile and reacts faster with electron rich C=C bonds. The C=C substituents in 1 exert negative inductive effects and the C=C bond is electron poor (compared to H substituents) and therefore not as reactive with \(^1\text{O}_2\).

Table 4-2: Chemical quenching rate constants calculated in CDCl\(_3\) at 20±1 °C using trans-4-octene as standard. Theoretical s-factors are calculated from extrapolation utilizing previously obtained values.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Configuration</th>
<th>(K_{cQ})</th>
<th>s-factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>(C_4)</td>
<td>(C_3)'</td>
</tr>
<tr>
<td>1</td>
<td>Z-1a(Me)</td>
<td>R</td>
<td>R</td>
<td>2.4</td>
</tr>
<tr>
<td>2</td>
<td>Z-1a(Me)</td>
<td>R</td>
<td>S</td>
<td>1.8</td>
</tr>
<tr>
<td>3</td>
<td>E-1a(Me)</td>
<td>R</td>
<td>R</td>
<td>1.9</td>
</tr>
<tr>
<td>4</td>
<td>E-1a(Me)</td>
<td>R</td>
<td>S</td>
<td>0.9</td>
</tr>
<tr>
<td>5</td>
<td>Z-1c(iPr)</td>
<td>R</td>
<td>R</td>
<td>1.6</td>
</tr>
<tr>
<td>6</td>
<td>Z-1c(iPr)</td>
<td>R</td>
<td>S</td>
<td>1.3</td>
</tr>
<tr>
<td>7</td>
<td>Z-1d(iPr)</td>
<td>S</td>
<td>S</td>
<td>1.6</td>
</tr>
<tr>
<td>8</td>
<td>Z-1d(iPr)</td>
<td>S</td>
<td>R</td>
<td>1.3</td>
</tr>
<tr>
<td>9</td>
<td>E-1c(iPr)</td>
<td>R</td>
<td>R</td>
<td>1.6</td>
</tr>
<tr>
<td>10</td>
<td>E-1c(iPr)</td>
<td>R</td>
<td>S</td>
<td>0.9</td>
</tr>
<tr>
<td>11</td>
<td>E-1d(iPr)</td>
<td>S</td>
<td>S</td>
<td>1.7</td>
</tr>
<tr>
<td>12</td>
<td>E-1d(iPr)</td>
<td>S</td>
<td>R</td>
<td>1.0</td>
</tr>
</tbody>
</table>

* Calculated (Theoretical)

Total quenching constants \((k_Q)\) of enantiopure enecarbamates 1 are shown in Table 4-3. Statistically, the Z-1(Me) enecarbamates appear to have \(k_Q\) values than the Z-1(iPr) enecarbamates. However, the results do not unequivocally
demonstrate that the $Z-1(iPr)$ enecarbamates have higher $k_Q$ values than the $E-1(iPr)$ counterparts.

**Table 4-3:** Total rate constants calculated in CDCl$_3$ at 22±1 °C using trans-4-octene and 1-methylcyclohexene as standards. Physical quenching rate constants also included.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Configuration</th>
<th>$k_Q$</th>
<th>$k_{pQ}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$C_4$</td>
<td>$C_3'$</td>
<td>$M^{-1}s^{-1} \times 10^{-3}$</td>
</tr>
<tr>
<td>1</td>
<td>$Z-1a(Me)$</td>
<td>$R$</td>
<td>$S$</td>
<td>56</td>
</tr>
<tr>
<td>2</td>
<td>$Z-1b(Me)$</td>
<td>$S$</td>
<td>$S$</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>$Z-1b(Me)$</td>
<td>$S$</td>
<td>$R$</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>$Z-1c(iPr)$</td>
<td>$R$</td>
<td>$R$</td>
<td>28</td>
</tr>
<tr>
<td>5</td>
<td>$Z-1c(iPr)$</td>
<td>$R$</td>
<td>$S$</td>
<td>24</td>
</tr>
<tr>
<td>6</td>
<td>$Z-1d(iPr)$</td>
<td>$S$</td>
<td>$S$</td>
<td>27</td>
</tr>
<tr>
<td>7</td>
<td>$E-1c(iPr)$</td>
<td>$R$</td>
<td>$S$</td>
<td>20</td>
</tr>
<tr>
<td>8</td>
<td>$E-1d(iPr)$</td>
<td>$S$</td>
<td>$S$</td>
<td>23</td>
</tr>
<tr>
<td>9</td>
<td>$Z-1h(iPr)$</td>
<td>$S$</td>
<td>$S$</td>
<td>54</td>
</tr>
<tr>
<td>10</td>
<td>$E-1b(Me)$</td>
<td>$S$</td>
<td>$R/S$</td>
<td>33</td>
</tr>
<tr>
<td>11</td>
<td>$E-1d(iPr)$</td>
<td>$S$</td>
<td>$R/S$</td>
<td>30</td>
</tr>
<tr>
<td>12</td>
<td>$Z-1c(iPr)$</td>
<td>$R$</td>
<td>$R/S$</td>
<td>26</td>
</tr>
</tbody>
</table>

The result of a single measurement.

**Calculated with equipode.**

The results in Table 4-4 are presented as $k_{pQ}/k_{cQ}$. This ratio represents the amount of $^1O_2$ that is physically deactivated to $^3O_2$ versus the amount of $^1O_2$ that reacts to form the dioxetane 2 (Scheme 4-1). The higher the ratio, the greater the physical quenching of $^1O_2$ by that molecule. The $k_Q$ values are an order
of magnitude higher than the $k_{cQ}$ values, however, these $k_Q$ values are still low and the inaccuracy associated with the $k_Q$ values are expected to be higher than the true values owing to possible contributions from impurities. Within the experimental error, the total quenching of the Me substituted compounds are higher than those for the iPr substituted compounds. However, the substantial nature of the errors result in a quite weak to non-existent correlation between the $C_3$ stereogenic center and the physical quenching rate constant ($k_{pQ}$) ergo vibrational/physical deactivation (Table 4-4).

**Table 4-4:** $k_{pQ}/k_{cQ}$ calculated and correlated as a function of stereogenic configuration.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Configuration</th>
<th>$k_{pQ}/k_{cQ}$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$C_4$</td>
<td>$C_3'$</td>
</tr>
<tr>
<td>1</td>
<td>Z-1a(Me)</td>
<td>$R$</td>
<td>$R$</td>
</tr>
<tr>
<td>2</td>
<td>Z-1a(Me)</td>
<td>$R$</td>
<td>$S$</td>
</tr>
<tr>
<td>3</td>
<td>Z-1c(iPr)</td>
<td>$R$</td>
<td>$R$</td>
</tr>
<tr>
<td>4</td>
<td>Z-1c(iPr)</td>
<td>$R$</td>
<td>$S$</td>
</tr>
<tr>
<td>5</td>
<td>Z-1d(iPr)</td>
<td>$S$</td>
<td>$S$</td>
</tr>
<tr>
<td>6</td>
<td>E-1c(iPr)</td>
<td>$R$</td>
<td>$R$</td>
</tr>
<tr>
<td>7</td>
<td>E-1c(iPr)</td>
<td>$R$</td>
<td>$S$</td>
</tr>
</tbody>
</table>

*Calculated utilizing equipode.

Deuteration of the $C_4$ substituent of the $E$-1b(Me) enecarbamate gives rise to the $E$-1g enecarbamate. Despite the 5-10% experimental error associated with generating the stereoselectivities, there does appear to be a decrease in
stereoselectivity with temperature for the deuterated compound compared to the proteated compound (Table 4-5) in CDCl₃. It is statistically possible, however, that the stereoselectivity at lower temperatures increases on deuteration in CD₃CN.

**Table 4-5:** Comparison of Stereoselectivities obtained for photooxygenation of proteated and deuterated Me substituted E-1 enecarbamates.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Substrate</th>
<th>Temperature</th>
<th>s-factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>°C</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>CDCl₃</td>
<td>E(Me)-1b</td>
<td>15</td>
<td>10 (S)  ± 0.5</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td>-15</td>
<td>44 (S)  ± 6.0</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td>-40</td>
<td>77 (S)  ± 0.3</td>
</tr>
<tr>
<td>4</td>
<td>CDCl₃</td>
<td>E(Me-D₃)-1g</td>
<td>15</td>
<td>11 (S)  ± 2.4</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td>-15</td>
<td>25 (S)  ± 4.3</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td>-40</td>
<td>41 (S)  ± 3.0</td>
</tr>
<tr>
<td>7</td>
<td>CD₃CN</td>
<td>E(Me)-1b</td>
<td>15</td>
<td>2.1     ± 0.4</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td>-15</td>
<td>2.5     ± 1.5</td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td>-40</td>
<td>4.3     ± 1.0</td>
</tr>
<tr>
<td>10</td>
<td>CD₃CN</td>
<td>E(Me-D₃)-1g</td>
<td>15</td>
<td>1.3     ± 0.3</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td>-15</td>
<td>3.5     ± 0.7</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
<td>-40</td>
<td>11      ± 0.4</td>
</tr>
</tbody>
</table>
4.3. Discussion

In the previous chapter we advanced the possibility of steric factors and vibrational quenching operating synergistically to effect stereodifferentiation. The goal of the experiments in this chapter were to elucidate the contribution of vibrational quenching between two enecarbamates that spatially differ only at the $C_3'$ center.

$$k_Q = k_{pQ} + k_{cQ}$$  \hspace{1cm} \text{Equation 4-1}

In calculating the physical quenching rate constant ($k_{pQ}$) via \textbf{Equation 4-1}, experiments were carried out to obtain chemical quenching ($k_{cQ}$) and total quenching ($k_Q$) rate constants. The chemical quenching rate constants were obtained and have been submitted in \textbf{Table 4-2}. The first notable feature is that the Me substituted enecarbamate $Z\text{-}1a$ has a higher chemical rate constant than its $i\text{Pr}$ counterpart $Z\text{-}1c$ (Entries 1 & 5). In the previous chapter we proposed that the Me group exerted smaller steric demand and vibrationally quenching relative to the $i\text{Pr}$ substituent. Furthermore, we suggested that the smaller size of the Me group allowed more $O_2$ to approach the double bond and as a consequence, both the chemical and physical quenching by the double bond would increase. The higher $k_{cQ}$ demonstrated in these results indicate that the smaller Me group allows $O_2$ more access to and reaction with the double bond. The higher physical quenching that therefore results from the greater accessibility of the double bond is also evident in \textbf{Table 4-3} where the Me substituted enecarbamates appear to display higher $k_Q$ (and $k_{pQ}$) values.
On inspection of Table 4-4, the $k_{pQ}/k_{cQ}$ values obtained for the $Z$-$1$(Me) compounds suggest that the $C_3'S$ diastereomer physically deactivates more $^1$O$_2$ than the $C_3'R$ diastereomer (Table 4-4; Entry 1 & 2). This supports results where the $C_4'R,C_3'R$ enecarbamate of $Z$-$1$a is formed in excess of the $C_4'R,C_3'S$ enecarbamate (Table 4-2; Entry 1,2). However, the $k_{cQ}$ values (Table 4-2) obtained are low and unsurprising considering the negative inductive effects of the alkene substituents. 9 The $k_{pQ}$ values (Table 4-3) are an order of magnitude greater. However, the $k_{pQ}$ values are still small and quite vulnerable to contributions by small impurities with comparative or larger quenching constants. These factors all taken into account diminish the accuracy of the results and consequently, within the experimental error, there is no convincing, stand-alone correlation between $C_3'$ configuration and the $k_{pQ}/k_{cQ}$ ratio (Table 4-4).

As an alternate approach to investigating the vibrational deactivation hypothesis, we deuterated the $C_4$ substituents and explored the stereoselectivity in the MDB product as a function of temperature and solvent. The results were compared to the proteated counterpart (Table 4-4). In both solvents the stereoselectivity still increases with decreased temperature for the deuterated compound. However in CDCl$_3$, the increase in stereoselectivity is smaller for the deuterated solvent than the proteated compound. In contrast, the stereoselectivity in the deuterated compound while comparable to the proteated compound at 15°C and -15°C in CD$_3$CN, is greater at -40°C.
The stereodifferentiating mechanism in the deuterated compound is quite likely steric in nature. The differences in stereoselectivities in going from the deuterated to the proteated compound in CDCl$_3$ can be attributed to the vibrational quenching, assuming that the only real difference in these two molecules is the higher deactivational character of the C-H bonds. The confluence in the stereoselectivities of the proteated and deuterated compounds on increasing the temperature is therefore owing to the decreasing impact of vibrational quenching as a stereodifferentiating mechanism with increasing temperature.

A possible explanation for temperature dependence of the vibrational quenching presumably may be linked to conformational changes in a molecule. Increased physical quenching at lower temperatures is insufficient to explain the stereodifferentiation ascribable to vibrational quenching if the two C$_3'$ diastereomers both deactivate $^1$O$_2$ to the same degree. Conformational changes and equilibrium in a molecule are temperature dependent. If the differences in conformations between the two C$_3'$ epimers are significant at lower temperatures then it is plausible that one diastereomer will be a more efficient physical quencher as the temperature decreases.

In CD$_3$CN, the contrasting results of increased selectivity in the deuterated compound can be rationalized in one of two ways. It may be that within the experimental error, the two values are really the same. Or it may be a solvent dependent nature in solvation, conformation and consequently vibrational quenching. Whereas in CDCl$_3$ one isomer exhibits greater vibrational
deactivation, in CD$_3$CN the other isomer may be the one with the greater physical quenching potential because it adopts a different conformation more able to deactivate $^1$O$_2$.

At 15°C, the proteated and deuterated stereoselectivities are more or less in agreement with each other. If the stereoselectivities in the deuterated compounds can be attributed to steric and the additional increase in stereoselectivity for the proteated compounds (compared to the deuterated) attributed to vibrational quenching, then the contribution of vibrational quenching at 15°C is nominal. It, therefore, is unsurprising that the physical quenching rate constants and $k_{pQ}/k_{cQ}$ values obtained in Table 4-4 show no definitive evidence of vibrational quenching. That is, since the difference in vibrational quenching appears to be insignificant near room temperatures then there should be no notable difference in $k_{pQ}$ values between two diastereomers differing only in their C$_3'$ configuration at room temperature.

In the first chapter we noted the solvent dependent nature of the stereoselectivities. We also noted that for the C$_4$S chiral configuration, the C$_3$S diastereomer (giving rise to S-MDB) is enthalpically favored and entropically favored while the reverse is true for the C$_3$R diastereomer (gives rise to R-MDB). Steric factors are entropic in nature because steric interactions influence molecular conformations and conformations are vulnerable to temperature and solvent effects. Therefore, the plausible reason for the entropic disfavoring of the C$_3$S diastereomer may be its greater intramolecular steric factors. In fact, on scrutinizing the crystal structures (Figures 4-1 bottom, 4-2 bottom) this can be
rationalized by the closer proximity of the $C_4$-$Me$ substituent and the $C_3$-$Me$ group in this molecule. As previously established in chapter 1, as the temperature increases therefore, the entropically favored isomer, the $C_3R$ isomer is favored reactively and $R$-MDB dominates the product distribution.

![Figure 4-1: Crystal structures and schematic representations of, for the $E$-$1b(Me)$ enecarbamates: (top) $C_3R$ diastereomer; (bottom) $C_3S$ diastereomer.](image-url)
The compound with the higher steric factors is not necessarily the compound exhibiting the higher vibrational deactivation. At lower temperatures, when the molecule has low vibrational, rotational and translational energy the differences in the vibrational quenching of the two diastereomers may be more distinct. However, much as the enthalpic control decreases with temperature, vibrational deactivation becomes less of a factor with the increasing temperature. However steric effects likely do increase with temperature since rotational and translational motions become more vigorous as more heat is introduced.
4.4. Summary

Steric and vibrational deactivation have been postulated and shown to be the stereodifferentiating mechanisms operating synergistically in the photooxygenation of $^1$O$_2$ with the enecarbamate 1 to form the dioxetane 2 and the MDB enantiomeric products.

4.4.a Outlook

The mechanism of vibrational quenching may offer a new excited state paradigm for explaining asymmetric induction in the photooxygenation reactions with $^1$O$_2$ (Figure 4-3)\textsuperscript{10}. In the ground state, Cram’s Rule and the Felkin and Felkin-Anh models offer explanations for the observed stereoselection in ground state asymmetric induction.

\begin{figure}
  \centering
  \includegraphics[width=\textwidth]{figure.png}
  \caption{Comparison of ground state and excited state paradigms.}
\end{figure}
Vibrational quenching is only operative in the excited state and is particularly effective in \(^1\)O\(_2\) because of its small size and absence of intramolecular vibrational dampening. Moreover, where the larger substituent exerts greater steric shielding than a smaller substituent in ground state models, the larger substituent is not necessarily the source of greater vibrational quenching in the excited state. The nature of the substituent also (C-H vs. C-D vs. C-F) dictates the degree of physical/vibrational quenching (Scheme 4-4).

**Figure 4-4**: Vibrational deactivation model to describe excited state stereoselection in asymmetric photoreactions.

Altogether, the concept of vibrational deactivation as a stereodifferentiating factor is original and, after further investigation, may serve as a powerful tool in the photochemist’s toolbox to manipulate stereochemistry within the transient lifetime of the excited state.
4.5. References


5. On to a Second Generation

5.1. Introduction

In the previous three chapters, research focused on the photooxygenation of enecarbamate 1 with $^{1}$O$_2$ by way of the [2+2] addition reaction to form dioxetane 2. Dioxetane 2 then decomposes to form the chiral ketone 3 and the aldehyde 4 (Scheme 5-1). Analogously, the “second generation” enecarbamate I was also synthesized. The symbol I is used to highlight the analogy of this new enecarbamate to 1. The difference between the two enecarbamates lies in the replacement of the phenyl group at the C$_{2'}$ position in 1 with the chiral phenylethyl group in I. Similarly, I undergoes the photooxygenation reaction with $^{1}$O$_2$, presumably through the dioxetane intermediate II, to ultimately produce the ketone III and the aldehyde 4 through cleavage of the dioxetane II (Scheme 5-2).

![Scheme 5-1: Photooxygenation of enecarbamate 1 to form dioxetane 2. Dioxetane 2 decomposes to the ketone 3 (MDB) and the aldehyde 4.](image-url)
Enecarbamate I has three stereogenic centers at the C₄, C₃' and C₃" positions. Consequently, there are 8 stereoisomers corresponding to the Lewis structure I. If the C₄ configuration is fixed as either R or S, then there are 4 diastereomers. On photooxygenation to form II and subsequent decomposition of these dioxetanes, potentially 3 structures of the ketone 2,4-diphenyl-3-pentanone (DPP) can be generated – a meso diastereomer RS-DPP and the two d and l enantiomers (RR-DPP and SS-DPP) as presented in Scheme 5-3. Therefore, in studying the stereoselectivities in the DPP products, this second-generation enecarbamate system allows both the diastereoselectivity (de) and enantioselectivity (ee) to be monitored as a function of solvent and temperature.

The C₂' carbon in enecarbamates I has two different substituents – phenyl and phenylethyl – that can be ranked according to Cahn-Ingold-Prelog rules to generate E and Z nomenclature. The E-1 enecarbamate was found to be flexible and the stereoselectivities were solvent and temperature dependent; the Z-1 enecarbamate was comparatively rigid and the stereoselectivities were independent of solvent and temperature variations.1-5 This second-generation

Scheme 5-2: Photooxygenation of enecarbamate I to form dioxetane II. Dioxetane II decomposes to the ketone III (DPP) and the aldehyde 4.
enecarbamate I contains no $E/Z$ geometry. That is, the $C_2'$ carbon in the C=C double bond is substituted with the same two groups - the phenylethyl groups. Therefore, neither phenylethyl substituent can be considered to be syn to the higher-ranking oxazolidinone functionality on the $C_1'$ carbon and therefore there can be no usual $E$ or $Z$ nomenclature. This absence of $E/Z$ geometry and based on the properties of 1, it may be that the enecarbamate I possesses flexibility and solvent/temperature dependent stereoselectivities lying between that of the $E$-1 and $Z$-1 substrates.

**Scheme 5-3:** Products obtained on photooxygenation of the four diastereomers of enecarbamate I.
Despite having no typical $E/Z$ assignment based on four different substituents about the C1’ carbon, $E/Z$ can be assigned based on the absolute stereochemistry of the phenylethyl stereocenters. For the SR-I and the RS-I second-generation enecarbamates, $Z$ is assigned to the structure where the $C_2'$ R-configured phenylethyl group is syn to the $C_1'$ oxazolidinone functionality (Figure 5-1).

![Figure 5-1: $E/Z$ assignment for the second-generation SR-I and RS-I enecarbamates.](image)

In this chapter, we seek to compare the stereoselectivities of the second-generation enecarbamates I with the first generation enecarbamates 1 in the reaction of $^1$O$_2$ (Scheme 5-1 and Scheme 5-2). Additionally the goal is to understand whether any stereoselective trends are more dependent on the $R/S$ configuration at the $C_3'$ or $C_3''$ stereocenter.
5.2. Results

The structure matrix for compounds utilized in this chapter is presented in Table 5-1. Nomenclature is such that RS-Ia refers to the enecarbamate I with the C₄ (Me) group with the C₄(R) configuration, C₃(R) configuration and the C₃(S) configuration. Experiments were carried out with a mixture of all four Ia diastereomers for a fixed C₄R configuration. The ratio of starting diastereomers was RS-Ia (1): SR-Ia (1.6): SS-Ia (0.7): RR-Ia (0.6) as determined by ¹H-NMR.

Table 5-1: Structure matrix for enecarbamates 1 and I.

<table>
<thead>
<tr>
<th></th>
<th>C₄</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>R</td>
<td>Me</td>
</tr>
<tr>
<td>1b</td>
<td>S</td>
<td>Me</td>
</tr>
<tr>
<td>Ia</td>
<td>R</td>
<td>Me</td>
</tr>
<tr>
<td>Ib</td>
<td>S</td>
<td>Me</td>
</tr>
</tbody>
</table>

The stereoselectivity factor (s-factor) in Equation 5-1, redefined as the enantioselectivity factor for the purposes of this chapter (e-factor), is defined in Equation 5-2 and the diastereoselectivity factor (d-factor) in Equation 5-3. In
the equations, $ee$ is the enantioselectivity calculated for the two $d, l$ DPP enantiomers, $de$ is the diastereoselectivity calculated for the meso and combined $d, l$-DPP diastereomers, $C$ is the total conversion while $C_{dl}$ is the conversion relative to the $d, l$ isomers. $k_{SS}$ is the reactive rate of the SS-I diastereomer and similarly for $k_{RR}$, $k_{meso}$ (the rate constant for the formation of both meso isomers) and $k_{dl}$ (the rate constant for the formation of both $d,l$ isomers).

\[
s = \frac{k_R}{k_S} = \frac{\ln[1 - C(1 + ee)]}{\ln[1 - C(1 - ee)]} \tag{Equation 5-1}
\]

\[
e = \frac{k_{SS}}{k_{RR}} = \frac{\ln[1 - C_{dl}(1 + ee)]}{\ln[1 - C_{dl}(1 - ee)]} \tag{Equation 5-2}
\]

\[
d = \frac{k_{meso}}{k_{dl}} = \frac{\ln[1 - C(1 + de)]}{\ln[1 - C(1 - de)]} \tag{Equation 5-3}
\]

In comparing the relative reaction rate constants for the first generation $Z$-$\textbf{1a}$ enecarbamates and the second generation $\textbf{1a}$ enecarbamates (Table 5-2), results indicate that the first generation enecarbamates react faster with $^1\text{O}_2$ than the second-generation enecarbamates. In chapter 3, we presented the relative rates for both $Me$ and $iPr$ substituted enecarbamates $Z$-$\textbf{1a}$ and $E$-$\textbf{1a}$ enecarbamates. The relative rates are reproduced in Table 5-3. It is evident, therefore, that both the $E$-$\textbf{1}$ and $Z$-$\textbf{1}$ enecarbamates of the first generation react substantially faster than the enecarbamates $\textbf{1a}$ from the second generation.
Table 5-2: Relative reactive rate constants determined for photooxygenation of $\text{Z-1a}$ and $\text{Ia}$ in CDCl$_3$ at 20°C after 7 minutes of irradiation with $^1\text{O}_2$.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>% Conversion</th>
<th>Relative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Z($C_3'R$)-1a</td>
<td>69</td>
<td>1.00</td>
</tr>
<tr>
<td>2</td>
<td>Z($C_3'S$)-1a</td>
<td>70</td>
<td>0.92</td>
</tr>
<tr>
<td>3</td>
<td>SR-Ia</td>
<td>18</td>
<td>0.09</td>
</tr>
<tr>
<td>4</td>
<td>RS-Ia</td>
<td>18</td>
<td>0.09</td>
</tr>
<tr>
<td>5</td>
<td>SS-Ia</td>
<td>17</td>
<td>0.12</td>
</tr>
<tr>
<td>6</td>
<td>RR-Ia</td>
<td>19</td>
<td>0.11</td>
</tr>
</tbody>
</table>

Table 5-3: Relative Reactive Rates for the reaction of enecarbamates 1 determined in CDCl$_3$ at 20°C.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Configuration</th>
<th>Relative Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>$C_4$</td>
<td>$C_3'$</td>
</tr>
<tr>
<td>1</td>
<td>Z(Me)-1a</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>Z(Me)-1a</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>3</td>
<td>Z(iPr)-1c</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>Z(iPr)-1c</td>
<td>R</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>E(iPr)-1c</td>
<td>R</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>E(iPr)-1c</td>
<td>R</td>
<td>S</td>
</tr>
</tbody>
</table>

The enantioselectivity factors obtained for the reaction of $\text{RR-Ia}$ and $\text{SS-Ia}$ to form $\text{RR-DPP}$ and $\text{SS-DPP}$, respectively, are presented in the last column of Table 5-4. There is evidence of some solvent dependence of the $e$-factors with the $\text{Ia}$ enecarbamates. $\text{SS-DPP}$ is the predominant enantiomer in all solvents except CD$_3$CN where $\text{RR-DPP}$ is the predominant enantiomer formed.
Considering the experimental error of 15%, there is a statistically real, but small temperature dependence of the e-factor exhibited as well in all solvents, with the most notable temperature dependence realized in CDCl₃. While the e-factors of the RR/SS-Ia enecarbamates do vary significantly with temperature as the E-Ia enecarbamates, the second-generation enecarbamates do not show the temperature and solvent independence of the Z-Ia enecarbamates.
Table 5-4: Stereoselectivity factors obtained for the photooxygenation of the C₄R configured E-1a, Z-1a and RR/SS-Ia enecarbamates to produce enantiomeric ketones for different solvents and temperatures.³

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature °C</th>
<th>s-factor</th>
<th>e-factor</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Z-1a</td>
<td>E-1a</td>
</tr>
<tr>
<td>1</td>
<td>CDCl₃</td>
<td>15</td>
<td>1.4 (R)</td>
<td>4.7 (R)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>-15</td>
<td>1.6 (R)</td>
<td>17 (R)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>-40</td>
<td>1.5 (R)</td>
<td>41 (R)</td>
</tr>
<tr>
<td>4</td>
<td>CD₃OD</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>15</td>
<td>2.0 (R)</td>
<td>9.0 (R)*</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>-15</td>
<td>2.4 (R)</td>
<td>19 (R)*</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>-40</td>
<td>2.8 (R)</td>
<td>97 (R)*</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>-78</td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>CD₃CN</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>15</td>
<td>2.2 (R)</td>
<td>1.8 (S)</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>-15</td>
<td>2.4 (R)</td>
<td>1.3 (R)</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>-40</td>
<td>3.4 (R)</td>
<td>6.3 (R)</td>
</tr>
<tr>
<td>13</td>
<td>CD₂Cl₂</td>
<td>20</td>
<td>1.8 (R)</td>
<td>1.6 (R)</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>-20</td>
<td>2.1 (R)</td>
<td>6.6 (R)</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>-40</td>
<td>3.6 (R)</td>
<td>50 (R)</td>
</tr>
</tbody>
</table>

* Obtained for C₄S equipode.

Experimental error is about 10-15%.

Activation parameters are shown for the photooxygenation of the RR-Ia and SS-Ia second-generation enecarbamates in the last column of Table 5-5.
Though the precise values ought to be viewed with some degree of skepticism (experimental error \( \sim 20-30\% \)), the data does suggest that the entropic and enthalpic are generally intermediate between the values obtained for the first generation \( E-1a \) and \( Z-1a \) enecarbamates.

One benefit of the second generation \( Ia \) system is the ability to monitor both enantioselective and diastereoselective changes as a function of temperature and solvent. This relationship is shown in Table 5-6, and the diastereoselectivity between the \textit{meso-DPP} and the sum \textit{d,l-DPP} exhibits no significant temperature or solvent dependence. This is despite the previously mentioned solvent and temperature dependence of the stereoselectivities within the \textit{d,l-DPP} enantiomers.

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|c|}
\hline
Entry & Solvent & \( \Delta \Delta H^\ddagger \) & \( \Delta \Delta S^\ddagger \) \\
& & \( R-S \) (kJ/mol) & \( R-S \) (J/mol) \\
\hline
1 & CDCl\(_3\) & 0 & -20 & -10 & 5 & -65 & -15 \\
2 & CD\(_3\)OD & 0 & -5 & 0 & 5 & \\
3 & CD\(_3\)CN & 0 & -25 & -5 & 0 & -90 & -25 \\
4 & CD\(_2\)Cl\(_2\) & 0 & -20 & -5 & -5 & -75 & -20 \\
\hline
\end{tabular}
\caption{Activation parameters, \( \Delta \Delta H^\ddagger \) and \( \Delta \Delta S^\ddagger \), calculated in the photooxygenation of the \( C_4R \) configured \( E-1a \), \( Z-1a \) and \( Ia \) enecarbamates to produce enantiomeric ketones for different solvents and temperatures.}
\end{table}

- Obtained for \( C_4S \) equipode.
- Values rounded to closest multiple of five to better show trend. Experimental Error 20-30\%.
Table 5-6: Enantioselectivity ($e$) and diastereoselectivity ($d$) factors obtained for the photooxygenation of $\text{Ia}$ to produce $\text{DPP}$ isomers as a function of solvent and temperature.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature</th>
<th>$e$-factor</th>
<th>$d$-factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CDCl$_3$</td>
<td>15</td>
<td>6.3 (SS)</td>
<td>1.2 (d,l)</td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>-15</td>
<td>14 (SS)</td>
<td>1.6 (d,l)</td>
</tr>
<tr>
<td>3</td>
<td></td>
<td>-40</td>
<td>16 (SS)</td>
<td>1.6 (d,l)</td>
</tr>
<tr>
<td>4</td>
<td>CD$_3$OD</td>
<td>50</td>
<td>6.2 (SS)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>15</td>
<td>4.8 (SS)</td>
<td>1.1 (d,l)</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>-15</td>
<td>4.2 (SS)</td>
<td>1.3 (d,l)</td>
</tr>
<tr>
<td>7</td>
<td></td>
<td>-40</td>
<td>6.9 (SS)</td>
<td>1.3 (d,l)</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td>-78</td>
<td>11 (SS)</td>
<td>1.4 (d,l)</td>
</tr>
<tr>
<td>9</td>
<td>CD$_3$CN</td>
<td>50</td>
<td>2.7 (RR)</td>
<td>1.1 (meso)</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td>15</td>
<td>1.8 (RR)</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>-15</td>
<td>1.8 (RR)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>-40</td>
<td>1.4 (RR)</td>
<td>1.1 (d,l)</td>
</tr>
<tr>
<td>13</td>
<td>CD$_2$Cl$_2$</td>
<td>20</td>
<td>1.2 (SS)</td>
<td>1.4 (meso)</td>
</tr>
<tr>
<td>14</td>
<td></td>
<td>-20</td>
<td>1.6 (SS)</td>
<td>1.3 (meso)</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>-40</td>
<td>2.9 (SS)</td>
<td>1.2 (meso)</td>
</tr>
</tbody>
</table>

Experimental Error is within 10-15%.
Further experiments were carried out with only three Ia enecarbamate diastereomers - the SR-Ia, SS-Ia and RR-Ia enecarbamates. The goal of these experiments was to determine if and whether the C$_{3'}$ or C$_{3''}$ stereogenic center played a more significant role in determining diastereoselectivity. There was no diastereoselectivity observed for the SR-Ia and SS-Ia diastereomeric substrates (Table 5-7) – that is, they gave rise to the same ratios of product (Column 5). These two diastereomers, in addition to having the same C$_4$R configuration, also have the same C$_3$S configuration. Moreover, the table also shows that the rates of these two diastereomers, relative to the RR-Ia diastereomer, are the same (Columns 4 and 6).

Table 5-7: DPP product ratios obtained in CDCl$_3$ for the photooxygenation of RR-Ia, RS-Ia and SS-Ia to meso-DPP and d,l-DPP.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Temperature °C</th>
<th>Conversion</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>SS:RR SS:SR SR:RR</td>
</tr>
<tr>
<td>1</td>
<td>-5</td>
<td>14</td>
<td>87:13 52:48 86:14</td>
</tr>
<tr>
<td>2</td>
<td>-40</td>
<td>34</td>
<td>88:12 51:49 87:13</td>
</tr>
</tbody>
</table>

A crystal structure was obtained for the RS-Ia (C$_4$R, C$_3$R, C$_3$S) second-generation enecarbamate (Figure 5-2) and compared to the crystal structures obtained for the E-1b enecarbamates (Figure 5-3). The oxazolidinone ring is oriented perpendicular to the plane of the double bond for both the RS-Ia and E-1b enecarbamates, with the carbonyl oxygen angled toward the molecule. Aside from the minor shift in the angling of the C$_{3'}$ phenyl group of the RS-Ia
enecarbamate, the orientation of the $C_{3'}$ phenylethyl substituent \textit{syn} to the oxazolidinone ring for all three structures are remarkably similar.

\textbf{Figure 5-2:} Crystal Structure Obtained for $C_4R.C_3R.C_3'S$-\textbf{Ia} second generation enecarbamate. Light Gray – C; Dark Gray – H, Blue – N, Red – O.

\textbf{Figure 5-3:} Crystal Structure Obtained for $C_3S.C_3'R$-\textbf{1b} (left) and $C_3S.C_3'S$-\textbf{1b} (right) first generation enecarbamates. Light Gray – C; Dark Gray – H, Blue – N, Red – O.
5.3. Discussion

In the preceding chapters, we presented stereoselectivity results for the photooxygenation of enecarbamate 1 with \(^1\text{O}_2\) (Scheme 5-1).\(^{1-9}\) The results were notable in that with the Z-1 enecarbamates, there was consistently a statistically valid absence of solvent and temperature effects on the rather inflexible stereoselectivity (Table 5-4). Whereas, with the E-1 enecarbamates, the stereoselectivity varied widely with changing solvent and temperature plausible owing to its conformational flexibility (Table 5-4).

The significant structural differences between the first generation E and Z enecarbamates is as follows:

i) the C\(_{3'}\) phenylethyl group was on the same side of the double as the oxazolidinone ring bond for the E enecarbamate;

ii) The C\(_{3'}\) phenylethyl group was on the opposite side for the Z enecarbamate meaning that the C\(_{2'}\) phenyl group is on the same side of the double bond as the oxazolidinone group.

For the second-generation Ia enecarbamates, the C\(_{2'}\) phenyl group has been replaced with a phenylethyl group. Now, therefore, there is both a phenylethyl on the same side and on the opposite side of the double bond from the oxazolidinone ring. One might hypothesize that the enantioselectivity of the RR-Ia and SS-Ia starting enecarbamates may lie somewhere between the stereoselectivities obtained for the Z-1(C\(_{3'}R/S\)) and E-1(C\(_{3'}R/S\)) enecarbamates.
This hypothesis is supported by the data in **Table 5-4**. There is indeed some variation in the enantioselectivity of the SS-DPP and RR-DPP second-generation product with solvent and temperature as would be expected if the compound reacted similarly to the first generation E-1 enecarbamate. However, the variation is quite small, not giving rise to large stereoselectivity differences. This decreased sensitivity to solvent and temperature can be attributed to a more increased rigidity. In fact, examination of the activation parameters in **Table 5-5** support this intermediary nature of Ia compared to E-1 and Z-1. While the $\Delta \Delta H^\alpha_{R,S}$ and $\Delta \Delta S^\alpha_{R,S}$ values for Ia are not as large as they were with E-1, they are not as close to zero as they were with Z-1.

As is also theorized from the increased substitution about the double bonds, the reaction rate of Ia relative to 1 decreases (**Table 5-2, Table 5-3**). The increased quenching potential as well as the increased electron-withdrawing nature of the phenylethyl group relative to the phenyl group possibly explains why the reaction of $^1$O$_2$ with Ia is slower than the reaction of $^1$O$_2$ with 1.

What is interesting is that as the enantioselectivity associated with the $d,l$-DPP enantiomers varies somewhat with temperature and solvent, the diastereoselectivity between the meso and $d,l$ DPP diastereomers remains constant (**Table 5-6**). This would imply that either the $C_3'$ or $C_3''$ stereo center has a more significant role in the observed selectivities.

In fact, the results of **Table 5-7** indicate that the $C_3'$ center (the same side as the oxazolidinone ring) apparently governs the selectivities. The fact that the $C_3'$ center is in a better position to sterically interact with the oxazolidinone ring...
may very well support this observation. The \textit{SS-}Ia and the \textit{SR-}Ia have similar reactivities and these two substrates have their \textit{C}_3S center common. Their reactivities are such that when comparing the DPP products that they give rise to, the resultant diastereoselectivity between the \textit{meso-DPP} and the \textit{SS-DPP} is more or less zero. Meanwhile, their selectivities with the \textit{RR-DPP} are the same in Entry 1 of Table 5-7 for example - 87:13 (\textit{SS-DPP:RR-DPP}) and 86:14 (\textit{meso-DPP:RR-DPP}).

If the Ia enecarbamates with the common \textit{C}_3'R configuration, \textit{RR-Ia} and \textit{RS-Ia}, have a similar relationship where their relative ratio remains roughly 1:1 over the course of the reaction, then one can very well understand how the constant diastereoselectivity results over the varying solvents and temperatures. That is the substrates with the \textit{C}_3R configuration (\textit{RR-Ia} and \textit{RS-Ia}) will have the same reactive rate constants and the substrates with the \textit{C}_3S configuration (\textit{SS-Ia} and \textit{SR-Ia}) will have the same reactive rate constants and the overall diastereoselectivity (\textit{meso – d,l DPP} isomers) will not change.

Imagine, for example, that the reactive rate constants for \textit{RR-Ia} and \textit{RS-Ia} are equivalent and equal to A. Imagine also that that the reactive rate constants for \textit{SS-Ia} and \textit{SR-Ia} are equivalent and equal to B. Then the diastereoselectivity (\textit{meso – d,l}) is now solved to be \((A_{RS}+B_{SR})-(A_{RR}+B_{SS})\) which is equal to zero and the \textit{d}-factor is 1. One might argue that the results in Table 5-6 bear out this theory. However, it is quite likely that with enecarbamates bearing a common \textit{C}_3'stereoconfiguration, the rates may not be quite equivalent, because the \textit{C}_3' center may have some influence on the observed stereoselectivities.
On examining the crystal structures in Figures 5-2 and 5-3, the oxazolidinone ring is perpendicular to the plane of the double bond for both the $E$-$\text{1b}$ and $RS$-$\text{Ia}$ enecarbamates. As results in chapter 2 indicated, this implies that the $\text{1}O_2$ will be steered to the top face of the double bond for the $RS$-$\text{Ia}$ enecarbamate as it was with the $E$-$\text{1b}$ enecarbamates. Based on the similarity of the crystal structures, that is between $RS$-$\text{Ia}$ and $E$-$\text{1b}(C_3R)$ (Figure 5-3, left) one can envisage that similar stereodifferentiating mechanisms exist between the $RS$-$\text{Ia}$ and $SR$-$\text{Ia}$ enecarbamates and therefore between the $SS$-$\text{Ia}$ and $RR$-$\text{Ia}$ enecarbamates. However, this hypothesis remains to be tested.
5.4. **Summary**

A study of the second generation Ia enecarbamates reveals a small solvent and temperature dependency of the enantioselectivities governed more by the $C_{3'}$ stereocenter than the $C_{3''}$ stereocenter. The behavior of the Ia enecarbamates appears to be intermediate between the $E$-1 and $Z$-1 enecarbamates, which is hypothesized to indicate a flexibility intermediate between the $E$-1 and $Z$-1 enecarbamates. The governing nature of the $C_{3''}$ center results in unchanging diastereoselectivities even as the enantioselectivities respond to the changing temperature and solvent environments.

5.4.a. **Outlook**

The study of the second-generation enecarbamate confirmed the role of the chiral auxiliary in effecting stereocontrol in the photooxygenation reaction with $^1O_2$. The $C_4$-substituent of the oxazolidinone auxiliary interacts strongly with the *syn* $C_{3'}$ substituent to exert steric and possibly vibrational control on the approaching $^1O_2$. Moreover, the results here support our initial hypothesis that greater conformational flexibility is intimately linked to greater entropic control. The more flexible the compound, the greater the temperature and solvent effect on the stereoselectivity. These insights can prove to be integral in understanding and designing systems to exploit entropic control and obtain remarkable stereocontrol.
References


6. Stereodifferentiation in Confined Media

6.1. Introduction

In addition to exploring the stereoselectivities for the photooxygenation of enecarbamate \textbf{1} with \(^1\text{O}_2\) to ultimately produce enantiomeric ketones \textbf{3} (Scheme 6-1) in a variety of solvents, the enantioselectivity in the MDB (3) products can be explored within confined media. As the phrase \textit{confined media} suggests, this approach imprints stereocontrol on the product by manipulating the spatial requirements of the excited states and reactive intermediates.\(^1\) For two diastereomers with different spatial demands, these differences may be compounded with confinement and stereoselectivities consequently enhanced.\(^2-8\)

![Scheme 6-1: Photooxygenation of enecarbamate 1 to form dioxetane 2. Dioxetane 2 decomposes to the chiral ketone 3 and aldehyde 4.](image)

Previous work compared the photooxygenation delineated in Scheme 6-1 in solution and within NaY faujasite zeolites.\(^1\) The results (Table 6-1)
found that although stereoselectivities were statistically unchanged upon confinement for the $E$-1c & $E$-1d enecarbamate, they were drastically enhanced for the $Z$-1c & $E$-1d enecarbamates. Moreover, photooxygenation of $Z$-1c and $Z$-1d in the NaY zeolite resulted in a change in the dominant MDB enantiomer. Whereas the $R$-MDB dominated in solution, the $S$-MDB became the predominant isomer formed within the zeolites. There was no enantiomeric switching in going from solution to zeolites for the $E$-1c and $E$-1d enecarbamates.

**Table 6-1:** Stereoselectivities obtained for photooxygenation of $E$-1 and $Z$-1 enecarbamates in solution and in NaY (methylene blue exchanged) zeolites at room temperature.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Medium</th>
<th>Substrate</th>
<th>s-factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CDCl₃</td>
<td>$Z(C₄R)-1c(iPr)$</td>
<td>2.2 ($R$)</td>
</tr>
<tr>
<td>2</td>
<td>NaY-MB</td>
<td>$Z(C₄R)-1c(iPr)$</td>
<td>12 ($S$)</td>
</tr>
<tr>
<td>3</td>
<td>CDCl₃</td>
<td>$Z(C₄S)-1d(iPr)$</td>
<td>1.4 ($S$)</td>
</tr>
<tr>
<td>4</td>
<td>NaY-MB</td>
<td>$Z(C₄S)-1d(iPr)$</td>
<td>16 ($R$)</td>
</tr>
<tr>
<td>5</td>
<td>CDCl₃</td>
<td>$E(C₄R)-1c(iPr)$</td>
<td>5.5 ($R$)</td>
</tr>
<tr>
<td>6</td>
<td>NaY-MB</td>
<td>$E(C₄R)-1c(iPr)$</td>
<td>5.9 ($R$)</td>
</tr>
<tr>
<td>7</td>
<td>CDCl₃</td>
<td>$E(C₄S)-1d(iPr)$</td>
<td>3.4 ($S$)</td>
</tr>
<tr>
<td>8</td>
<td>NaY-MB</td>
<td>$E(C₄S)-1d(iPr)$</td>
<td>5.6 ($S$)</td>
</tr>
</tbody>
</table>

The authors proposed that the superior behavior of the $Z$ enecarbamates within the zeolites came as a result of the better alignment of its more rigid structure within the zeolite supercages. Whereas the more inherent substrate–dependent features controlled stereoselectivity in solution, the
external cationic interaction of Na with specific groups in the molecules dictates stereocontrol in the zeolites. Consequently, the first part of the investigations in this chapter will explore the effect of changing the NaY cations on the observed stereoselectivities for both the first generation 1 (Scheme 6-1) and second generation 1 enecarbamates (Scheme 6-2).

Scheme 6-2: Photooxygenation of enecarbamate I to form dioxetane II. Dioxetane II decomposes to the chiral ketone II and aldehyde 4.

Aside from zeolites, cyclodextrins have also been utilized to effect stereocontrol.9 10 Whereas the zeolites utilized above were achiral, cyclodextrins possess an innate chirality that can be stereochemically exploited. Previous work in our group investigated the photoisomerization of the Z-1c to the E-1c enecarbamate within the hydrophobic γ-cyclodextrin (γ-CD) cavity.11 5-15% diastereoselectivities were obtained in the E-1c C3R and C3S diastereomers in CD3OD solution. In contrast, within γ-CD, diastereoselectivities of 41% were observed upon irradiation for 0.5 minutes of the E-1c:γ-CD complex in CD3OD/D2O. The de, however, decreased to 0% with
an increasing 4.5 minutes of irradiation. Additionally, upon solid-state irradiation of the complex diastereoselectivities of 36-40% *de* were observed after 15 minutes irradiation and decreased only to 30-36% *de* after a further 15 minutes of irradiation.

Clearly, the chiral hydrophobic γ-CD cavity can induce diastereoselectivities upon photoisomerization, with the Z-1c C₃S diastereomer isomerizing faster than the C₃R epimer. In fact, ¹H-NMR studies indicated that the C₃S epimer was more strongly complexed with γ-CD than the C₃R epimer of the solid Z-1c: γ-CD complex. Considering this, we also sought to investigate whether the utilization of cyclodextrin cavities could serve to enhance the diastereoselectivities in the photooxygenation reaction of Z-1c outlined in Scheme 6-1.

A third area of interest in this group has been controlling the stereoselectivity of geminate radical pair recombination within a zeolite. Often, a problem associated with this area is the introduction of a chiral co-guest into the same zeolite supercage as the molecule of interest, usually a chiral ketone. It is expected that when irradiated, the ketone would give rise to radical pairs, which would then recombine under the influence of the chiral co-guest. These investigations typically seek to determine whether the presence of the chiral inductor influence the radical pair recombination to yield a chiral ketone, thereby forming an excess of one enantiomer (Scheme 6-3). However, there is no guarantee that the chiral co-guest and a chiral ketone will occupy the same zeolite supercage.
**Scheme 6-3:** Photooxygenation of enecarbamate 1 and photolysis of **MDB** product 3 in MY zeolite.

The advantage of the enecarbamate @ zeolite approach is that upon photooxygenation of 1 and subsequent decomposition of the dioxetane intermediate to ketone 3, the chiral inductor and ketone must be generated in the same supercage. Here, we will explore whether the generation of the oxazolidinone chiral inductor and **MDB** in the same cage will affect the geminate radical pair recombination resulting from photolysis of **MDB** within the supercage.
6.2. Results

Table 6-2: Structure matrix of enecarbamates 1 and I.

![Structure matrix of enecarbamates 1 and I.]

<table>
<thead>
<tr>
<th></th>
<th>C</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>R</td>
<td>Me</td>
</tr>
<tr>
<td>1b</td>
<td>S</td>
<td>Me</td>
</tr>
<tr>
<td>1c</td>
<td>R</td>
<td>^Pr</td>
</tr>
<tr>
<td>1d</td>
<td>S</td>
<td>^Pr</td>
</tr>
</tbody>
</table>

\[
s = \frac{k_R}{k_S} = \frac{\ln[1 - C(1 + ee)]}{\ln[1 - C(1 - ee)]}
\]

Equation 6-1

\[
e = \frac{k_{SS}}{k_{RR}} = \frac{\ln[1 - C_{ll}(1 + ee)]}{\ln[1 - C_{ll}(1 - ee)]}
\]

Equation 6-2

\[
d = \frac{k_{MeMo}}{k_{ll}} = \frac{\ln[1 - C(1 + de)]}{\ln[1 - C(1 - de)]}
\]

Equation 6-3

The s-factors obtained for the photooxygenation of Me substituted enecarbamates 1 in MY faujasite zeolites for the periodic table group 1 (Li, Na,
K, Rb, Cs) series are presented in Table 6-3. The stereoselectivities for the Z-1(Me) enecarbamates increase with increasing cationic size (inversely, with decreasing supercage volume) and reaches a maximum in KY and thereafter the stereoselectivity decreases with increasing size of the cation. A similar trend is observed for the E-1(Me) enecarbamates except that the maximum stereoselectivity is observed with the RbY zeolites. In the Z enecarbamates, the C₄S configured enecarbamate generates an excess of the R-MDB and conversely for the C₄R enecarbamate. Alternatively, with the E enecarbamates, the C₄S configured enecarbamate generates an excess of the S-MDB and conversely for the C₄R enecarbamate.

Table 6-3: Enantioselectivity in the MDB product observed for the photooxygenation of enecarbamates 1 in the MY faujasite zeolites for the series of Group 1 cations for comparable conversions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Medium</th>
<th>Free Volume</th>
<th>%eeMDB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Å³</td>
<td>Z-1α</td>
</tr>
<tr>
<td>1</td>
<td>LiY-MB</td>
<td>843</td>
<td>5 (S)</td>
</tr>
<tr>
<td>2</td>
<td>NaY-MB</td>
<td>827</td>
<td>16 (S)</td>
</tr>
<tr>
<td>3</td>
<td>KY-MB</td>
<td>807</td>
<td>31 (S)</td>
</tr>
<tr>
<td>4</td>
<td>RbY-MB</td>
<td>796</td>
<td>17 (S)</td>
</tr>
<tr>
<td>5</td>
<td>CsY-MB</td>
<td>781</td>
<td>10 (S)</td>
</tr>
</tbody>
</table>

The e-factors and d-factors obtained for the photooxygenation of Me substituted enecarbamates I in MY faujasite zeolites are presented in Table 6-4. The difference between the NaY-MB (2.4) and NaY-MB (80) zeolites is that
in the former the Si/Al ratio is 2.4 and in the latter this ratio is 80. The NaY-MB (80) zeolites (aka dealuminated zeolites) therefore have a largely decreased Al content that leads to more space in the supercage. The e-factor indicates the prevalent formation of RR-DPP in both the LiY(80) and NaY(2.4) zeolites (Entries 1&2). While the RR-DPP is the enantiomer predominantly formed in the NaY(2.4) zeolites, SS-DPP is the predominant enantiomer in the NaY(80) zeolites. Moreover the d,l-DPP isomers are favored over the meso-DPP isomers for types of both NaY zeolites but on decreasing the Al content in the NaY zeolites, the diastereomeric selectivity in the DPP product d-factor decreases by an approximate factor of 10.

**Table 6-4:** Enantioselectivity and Diastereoselectivity factors (as defined by Equations 6-2 and 6-3) for the photooxygenation of enecarbamate I to RR-DPP, SS-DPP and meso-DPP in a selection of MY zeolites.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Medium</th>
<th>e-factor</th>
<th>d-factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiY-MB (80)</td>
<td>1.1 (RR)</td>
<td>10 (dl)</td>
</tr>
<tr>
<td>2</td>
<td>NaY-MB (2.4)</td>
<td>1.3 (RR)</td>
<td>17 (dl)</td>
</tr>
<tr>
<td>3</td>
<td>NaY-MB (80)</td>
<td>1.3 (SS)</td>
<td>1.7 (dl)</td>
</tr>
</tbody>
</table>

Experimental results with the γ-CD are presented in Table 6-5. The complexation of Z-1c with γ-CD does generate enhanced enantioselectivity. Unlike the zeolite results, R-MDB is predominantly formed both in solution and within the γ-CD hydrophobic cavity. These values were determined after
extraction of the **MDB** product from the cyclodextrin, neither $R$ nor $S$-MDB of which complexes preferentially with the $\gamma$-CD.

**Table 6.5:** Enantioselectivities obtained in the photooxygenation of $Z\text{-}1\text{c}:\gamma$-CD complex in solution.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate</th>
<th>Solvent</th>
<th>Temperature °C</th>
<th>%ee$_{\text{MDB}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$Z\text{-}1\text{a}$</td>
<td>CD$_3$OD</td>
<td>15</td>
<td>16 ($R$)</td>
</tr>
<tr>
<td>2</td>
<td>$Z\text{-}1\text{c}:\gamma$-CD</td>
<td>CD$_3$OD/D$_2$O</td>
<td>RT</td>
<td>52 ($R$)</td>
</tr>
<tr>
<td>3</td>
<td>$Z\text{-}1\text{c}:\gamma$-CD</td>
<td>CD$_3$OD/D$_2$O</td>
<td>RT</td>
<td>56 ($R$)</td>
</tr>
<tr>
<td>4</td>
<td>$Z\text{-}1\text{c}:\gamma$-CD</td>
<td>CD$_3$OD/D$_2$O</td>
<td>3</td>
<td>60 ($R$)</td>
</tr>
<tr>
<td>5</td>
<td>$Z\text{-}1\text{c}:\gamma$-CD</td>
<td>Hexanes</td>
<td>-30</td>
<td>66 ($R$)</td>
</tr>
</tbody>
</table>
Figure 6-1: 1H-NMR spectra obtained after extraction of unirradiated Z-1c (top) and Z-1d (bottom) enecarbamates from γ-CD.
After cleavage of the enecarbamate Z-1c with O₃, the system was irradiated at 254nm for a specific amount of time. Evident in Table 6-6 is the that with increased irradiation, there is a decrease in enantioselectivities with apparent epimerization of the C₃' chiral center.

Table 6-6: Enantioselectivities measured after ozonization of Z-1c in MY and subsequent irradiation at 254nm.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Experiment</th>
<th>ml O₃</th>
<th>Medium</th>
<th>Irradiation Time</th>
<th>%eeMDB</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>i</td>
<td>1</td>
<td>NaY</td>
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</tr>
<tr>
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<td></td>
<td></td>
<td>360</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
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<td>NaY</td>
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<td></td>
<td></td>
<td>180</td>
<td>0.1</td>
</tr>
<tr>
<td>7</td>
<td>iii</td>
<td>1</td>
<td>NaY</td>
<td>0</td>
<td>25</td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td>15</td>
<td>6</td>
</tr>
<tr>
<td>9</td>
<td>iv</td>
<td>0.1</td>
<td>LiY</td>
<td>0</td>
<td>15</td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>30</td>
<td>2</td>
</tr>
</tbody>
</table>
6.3. **Discussion**

Confined media have found widespread use in asymmetric chemistry\(^3\), and here they are found to enhance the stereoselectivities in the reactivity of the \(C_3\) epimers of enecarbamate 1 to form the enantiomeric MDB product. In inspecting **Table 6-3**, the volume of the supercage decreases as the size of the cation decreases and the extent of asymmetric induction for the \(Z\)-1\((Me)\) enecarbamates is clearly influenced by this. Considering this, it is plausible that the stereocontrol is exercised as a function of the enecarbamate fit within the cavity. That is, the more snug the fit, the higher the observed stereoselectivity. Hence the higher the enantioselectivity for \(Z\)-1\((Me)\) in KY and \(E\)-1\((Me)\) in RbY.

The rationale offered for this is schematically outlined in **Figure 6-2** for the \(Z\) enecarbamate.\(^5\) The interaction of the cation with one face of the molecule regulates the approach of \(^1\)O\(_2\), perhaps blocking out attack from one face of the molecule- the face that is coordinated with the zeolite surface. Moreover, the tighter the fit of the enecarbamate in the cavity, the stronger the interaction with the cation, the more rigidity imposed on the molecule and therefore the more pronounced the conformational differences between the two \(C_3\) epimers. Stereocontrol is then exercised via vibrational deactivation and steric through the differences in conformations of the exposed face. The decreased stereoselectivity after attainment of maximum enantioselectivity is presumably the consequence of further conformational changes whereby the two epimers are no longer as distinguishable.
In contrast, low enantioselectivities and diastereoselectivities are observed with the second generation I enecarbamates once confined to the zeolite supercage (Table 6-4). Plausibly, the replacement of the C2' phenyl group with a phenylethyl group results in diastereomers that are very similar to \(^1\)O\(_2\) when conformationally transformed by confinement.

In Table 6-5 is the data obtained on complexation of the Z-1c enecarbamate with \(\gamma\)-CD followed by photooxygenation to ultimately generate the enantiomeric MDB ketone (Scheme 6-1). Clearly, encapsulation within the chiral hydrophobic cavity enhances stereoselectivity (and allows photooxygenation within solvents in which the compound has limited solubility). The \(^1\)H-NMR in Figure 6-1 provide evidence that one epimer, the

Figure 6-2: Product Stereoselectivity of Enecarbamate Z-1c on Photooxygenation with \(^1\)O\(_2\) in Zeolite and Solution Zeolite \(^{15}\)
C₃S of Z-1c is preferentially complexed by the γ-CD. Moreover, earlier work indicated that this epimer also isomerizes faster to the E-1c enecarbamate than the C₃R epimer. Yet, results indicate that in the photooxygenation the C₃R epimer reacts faster thereby generating an excess of R-MDB in the product distribution. However the C₃S epimer is arranged within the cavity, its photooxygenation and decomposition to R-MDB is hindered compared to the C₃R epimer and this is likely a consequence of the influence of conformational differences.

Table 6-6 displays data acquired for the geminate radical pair recombination of MDB in the presence of the oxazolidinone chiral inductor in MY fajausite zeolites. Despite the initial excess of the R-MDB upon ozonization of the enecarbamate Z-1c, continued irradiation results in epimerization of the ketone product – that is, the stereoselectivity decreases to zero. Radical formation leads to a loss of chirality and on recombination, the inductive effect of the chiral roommate is nil because the radical pairs combine as you would expect them to in an achiral environment and there is no observed diastereoselectivity. Whether this is the consequence of a emigrated chiral inductor or its proximal inefficiency as an inductant will have to be explored in the future.
6.4. **Summary and Outlook**

In conclusion, the results reported in this chapter demonstrate the usefulness of zeolites and cyclodextrins as tools to effect stereocontrol in asymmetric chemistry. Varying the nature of the cation in MY zeolites, can serve to augment or decrement and even switch enantioselectivities obtained in solution by varying the fit of the molecule in the cavity. Consequently, an exploration of a single, stereochemically rich system has allowed us to show that the cooperation of spatial requirements, vibrational quenching and steric provide the photochemist with an initial arsenal in the quest to imprint stereocontrol within the fleeting lifetimes of the excited state.
6.5. References


5. Sivaguru, J.; Scheffer, J. R.; Chandarasekhar, J.; Ramamurthy, V., Confined space and cations enhance the power of a chiral auxiliary: photochemistry of 1,2-diphenylcyclopropane derivatives. *Chemical Communications (Cambridge, United Kingdom)* **2002**, (8), 830-831.


7. Experimental and Addendums

7.1. Chemicals

Chemicals and solvents were obtained and used as received through Sigma-Aldrich, Fisher Scientific, VWR and Cambridge Isotope Laboratories.
7.2. Instrumentation

- **NMR:** All NMR experiments were performed on Bruker DPX 300 MHZ, Bruker DRX 300 MHz (wide bore), Bruker 400 DRX MHz and Bruker 500 DMX MHz instruments.

- **GC:** All GC spectra were obtained on Varian 3900 instruments equipped with Varian CP-Chiral-Dex CB column as the chiral stationary phase and

- **HPLC:** HPLC analysis were performed on a Hewlett-Packard 1100 HPLC, equipped with a Chiralcel OD normal phase chiral column. The run program was - 90:10 Hexanes: 2-Propanol, Flow 0.5ml/min and with a Varian Factor-4 VF-1ms achiral column. Internal calibrations were carried out using 4,4′-di-tert-butylbiphenyl as internal standard.

- **Ozonolysis:** Ozone was generated from Ozone Lab OL100 Ozone Generator

- **Photolysis:** Irradiations were carried out with a Rayonet photochemical reactor with 300nm and 254nm light sources.

- **Irradiations:** Irradiations were performed with
  
  - A 500-W halogen lamp, attenuated with a variable voltage controller set to 80%. The lamp was housed in a jacketed condenser through which cold K₂CrO₄ (aq) filter solution was allowed to flow.¹ This condenser was in turn housed in a larger condenser that was
evacuated to $10^{-4}$ torr. A steady stream of air was also passed over the lamp for further cooling (**Figure 7-1**). This was the general setup for the production of enantiomeric **MDB** ketones 3 from the enecarbamate 1 starting material.

- A 300W lamp and <400 nm cutoff filter. This setup was general for formation of the dioxetane 2 product and $k_{cQ}$ determination.

**Figure 7-1**: Diagram of the halogen lamp and housing used in the photooxidation of the enecarbamates. The samples and the housing was inserted in a large Dewar filled with methanol (for ambient to low temperature irradiations) or water (for irradiations at 50 °C).

- **Chemiluminescence spectra** were recorded from 1200 to 1340nm at 22°C using a modified Fluorolog 2 spectrofluorimeter (Horiba Jobin-Yvon) in conjunction with a NIR sensitive photomultiplier detector (H9170-45, Hamamatsu)
7.3. Structure Matrix

<table>
<thead>
<tr>
<th>Structure</th>
<th>C&lt;sub&gt;4&lt;/sub&gt;</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Z-1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1a</td>
<td>R</td>
<td>Me</td>
</tr>
<tr>
<td>1b</td>
<td>S</td>
<td>Me</td>
</tr>
<tr>
<td>1c</td>
<td>R</td>
<td>iPr</td>
</tr>
<tr>
<td>1d</td>
<td>S</td>
<td>iPr</td>
</tr>
<tr>
<td>1e</td>
<td>R</td>
<td>iBu</td>
</tr>
<tr>
<td>1f</td>
<td>S</td>
<td>iBu</td>
</tr>
<tr>
<td><strong>E-1</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1g</td>
<td>S</td>
<td>Me-D&lt;sub&gt;4&lt;/sub&gt;</td>
</tr>
<tr>
<td>1h</td>
<td>S</td>
<td>iPr-D&lt;sub&gt;8&lt;/sub&gt;</td>
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<tr>
<td><strong>Z-2</strong></td>
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</tr>
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<td>iBu</td>
</tr>
<tr>
<td>2f</td>
<td>S</td>
<td>iBu</td>
</tr>
</tbody>
</table>
7.4. Synthesis of Enecarbamates 1

7.4.a. General Synthesis – A

![Scheme 7-1: Overall scheme for synthesis of aldehyde A, 2,3-diphenylbutanal.]

Methyl 2,3-diphenylbutanoate

A sample of 7.50 g (67.1 mmol) of potassium tert-butoxide were suspended in 100 mL of dry DMF at 0 ºC under an argon-gas atmosphere and methyl phenylacetate (10 g, 67.1 mmol) was added at once, followed by 8.25 g (67.1 mmol) of isopropyl bromide after 2 min. The reaction was allowed to warm up to room temperature (ca. 20 ºC) and magnetic stirring was continued for 1 h. Water (50 mL) was added and the solution was extracted with CH$_2$Cl$_2$ (2x40 mL). The organic layer was washed with 40 mL of a saturated, aqueous solution of NH$_4$Cl and 40 mL of water, and dried over MgSO$_4$. The solvent was evaporated (60 ºC, 15 torr) and the crude product (7.96 g, 62%) was used without purification. $^1$H-NMR (200 MHz, CDCl$_3$): $\delta$ = 0.70 (d, $J = 6.5$ Hz, 3 H), 1.03 (d, $J = 6.7$ Hz, 3 H), 2.15-2.45 (m, 1 H), 3.15 (d, $J = 10.5$ Hz, 1 H), 3.65 (s, 3 H), 7.12-7.39 (m, 5 H).

2,3-diphenyl-1-butanol
A sample of 2.60 g (67.5 mmol) of LiAlH₄ was suspended in 80 mL of dry ether and 10.7 g (56.0 mmol) of methyl 2,3-diphenylbutanoate in 40 mL ether were added slowly while stirring. The reaction was monitored by TLC and after complete consumption of the ester, the reaction was terminated by adding 40 mL of water. The layers were separated and the aqueous layer was extracted with CH₂Cl₂ (2x40 mL). The combined organic layers were dried over MgSO₄, the solvent was evaporated (20 °C, 15 torr) and the product (8.0 g, 87%) was obtained as colorless oil after column chromatography. ¹H-NMR (200 MHz, CDCl₃): δ = 0.85 (d, J = 7.0 Hz , 3 H), 1.10 (d, J = 7.0 Hz, 3 H), 1.95-2.15 (m, 1H), 2.00-2.10 (m, 1 H), 2.90-3.20 (br. s, 1 H), 3.80-3.95 (m, 2 H), 7.20-7.40 (m, 5 H); ¹³C NMR (60 MHz, CDCl₃): δ = 20.1 (q), 20.6 (q), 29.5(d), 55.2 (d), 64.1 (t), 126.0 (d), 127.8 (d), 128.3(d), 141.1 (s).

3-Methyl-2-phenyl-1-butanal

To a solution of 1.78 g (30.2 mmol) of oxalyl chloride in 130 mL of CH₂Cl₂ were added 4.27 g (65.8 mmol) of DMSO in 18 mL CH₂Cl₂ at -78 °C. The solution was stirred for 10 min and 4.50 g (27.4 mmol) of 2,3-diphenyl-1 butanol in 53 mL of CH₂Cl₂ were added. After 15 min, 20 mL of Et₃N were added and the solution was allowed to warm up to room temperature (ca. 20 °C) and stirred for 1 h. Water (150 mL) was added to terminate the reaction, the phases were separated, and the aqueous layer was extracted with CH₂Cl₂ (2x50 mL). The organic phase was washed with water (100 mL), dried over MgSO₄, and the solvent was evaporated (30 °C, 15 torr). The 2,3-diphenylbutanal (4.06 g, 91%) was obtained as colorless powder after silica-gel flash chromatography.
petroleum ether/ ethyl acetate (4:1)]. 1H-NMR (200 MHz, CDCl₃): δ = 0.77 (d, J = 6.7 Hz , 3 H), 1.45 (d, J = 6.7 Hz, 3 H), 2.25-2.59 (m, 1 H), 3.09-3.26 (m, 1 H), 6.94-7.48 (m, 5 H), 9.70 (d, J = 3.2 Hz , 1 H); 13C NMR (60 MHz, CDCl₃): δ = 19.5 (q), 20.7 (q), 28.3 (d), 66.6 (d), 127.6 (d), 129.1 (d), 129.5 (d), 135.7 (s), 201.8 (d).

4(R)-alkyl-2-oxazolidinone

(R)-(−)-2-Amino-1-alcohol (5.0 g, Aldrich), diethyl carbonate (10 mL, Aldrich), and 21 wt% solution of sodium ethoxide (0.43 mL, Aldrich) were added to a 100 mL 3-necked round-bottom flask equipped with a thermometer, a N₂ inlet, and a cooling column. The flask was heated up to 125 °C in an oil bath and ethanol was distilled from the reaction mixture for 10 h. After cooling the flask to ambient temperature, the residue was dissolved in 100 mL of diethyl ether and immersed into an acetone/dry ice bath kept at −78 °C. The white crystals were collected by filtration. 3.4 g, 90% yield.

Scheme 7-2: General scheme for synthesis of enecarbamate Z-1 via procedure A.
**General Procedure (A) for the Preparation of the Enecarbamates 1**

A solution of the aldehyde $A$ (1.0 equiv.), the particular oxazolidinone (0.9 equiv.), and a catalytic amount (ca. 10 mg) of $p$-toluenesulfonic acid in 50 mL of toluene was heated to reflux and the resulting water removed by azeotropic distillation during 12 h. After cooling the solution to ca. 20 °C, it was washed with a saturated, aqueous solution of NH$_4$Cl (50 mL) and water (50 mL), and the combined organic layers were dried over MgSO$_4$. After evaporation of the organic solvent (60 °C, 15 torr) and purification by silica-gel flash chromatography (petroleum ether/ethyl acetate 4:1), the encarbamates 1 were obtained in quantitative yield.

7.4.b. **General Synthesis – $B^3$**

**Peterson Olefination**

![Scheme 7-3: General scheme for synthesis of enecarbamate $Z-1$ via procedure $B$.](image)

Scheme 7-3: General scheme for synthesis of enecarbamate $Z-1$ via procedure $B$. 
**N-(Trimethylsilyl)methyl-4(R)-alkyl-2-oxazolidinone**

1.2 g of NaH (Aldrich) was suspended in dry DMF in a round-bottom flask and kept under a N₂ atmosphere. 4.0 g of 4(R)-alkyl-2-oxazolidinone (1a) was added and stirred vigorously for 90 min. 10 g of (iodomethyl)trimethylsilane (Aldrich) was added into the slurry solution and stirred overnight at ambient temperature. The reaction was quenched by adding 50 mL of water at 0 °C in an ice-cooled bath. The organic layer was extracted with ether (100 mL, 5 times) and concentrated by evaporation. The residue was purified by column chromatography using 300 g of aluminum oxide. 5.5 g of White crystals, 82% yield.

**Methyldesoxybenzoin (MDB) 3.**

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{Me} & \quad \text{N} \\
\text{Me} & \quad \text{O} \\
\end{align*}
\]

**Scheme 7-4:** Overall scheme for synthesis of MDB (3).

45 mL of PhMgBr (1.0 M, THF sol., Aldrich) was stirred under N₂ at 68 °C in a round-bottom flask (500 mL), followed by the addition of dry THF (10 mL)
and 8.3 g of N-methoxy-N-methyl-2-phenylpropanamide (Winereb amide, \(3'\)) diluted in THF (10 mL) drop by drop for 30 min, during reflux at 72 °C. After another 30 min, the reaction was quenched by adding NH\(_4\)Claq. 6.4 g of white crystals, 66% yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(d\) 1.68 (d, \(J = 6.81, 3\)H), 4.82 (q, \(J = 6.81, 1\)H), 7.24-7.60, 8.02-8.13 (m, \(10\)H); \(^{13}\)C NMR (75Hz, CDCl\(_3\)) \(d\) 20.0, 48.6, 127.3, 128.2, 128.9, 129.2, 129.4, 133.2, 136.9, 141.8, 200.7

**N-methoxy-N-methyl-2-phenylpropanamide \(3'\).**

\[\text{Ph} - \text{COOH} \xrightarrow{\text{Dichloromethane, N}_2, 0 \degree \text{C for 45 min}} \text{Ph} - \text{CO-N=NNMe} \xrightarrow{\text{Me,NHCl}^-} \text{Ph} - \text{CO-N=NNMe} \]

**Scheme 7-5:** Synthesis of N-methoxy-N-methyl-2-phenylpropanamide \(3'\).

8.0 g of 2-phenylpropionic acid (Aldrich) was suspended in dichloromethane (40 mL) under a N\(_2\) atmosphere at 0 °C, followed by the addition of 9.5 g of 1,1'-carbonyldiimidazole (Aldrich) into a round-bottom flask (250 mL). After stirring for 45 min, N,O-dimethylhydroxyamine hydrochloride was added to the reaction mixture and the stirring was kept overnight at ambient temperature. The reaction mixture was washed with 5% NaOHaq, 5% HCl, 5% NaHCO\(_3\), and water, successively, and then the organic layer was dried over MgSO\(_4\) and concentrated by evaporation. No further purification was needed. 9.6 g of colorless liquid, 94% yield. \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(d\) 1.54 (d, \(J = 7.05, 3\)H)
3H), 3.25 (s, 3H), 3.50 (s, 3H), 4.22 (q, J = 7.05, 1H), 7.26-7.39 (m, 5H); $^{13}$C NMR (75Hz, CDCl$_3$) d 20.3, 33.1, 42.7, 61.8, 122.3, 127.5, 128.3, 129.3, 142.6; EI-MS m/z (relative intensity) 194 (M$^+$, 100), 132 (21), 105 (15)

S- Methyldesoxybenzoin (S-MDB) was synthesized via published procedures. 4

**Peterson Olefination with 3.**

The silyl derivative the oxazolidinone was kept in a 3-neck round-bottom flask under a N$_2$ atmosphere, then the flask was immersed into an acetone/dry ice bath and kept at −78 °C. 10 mL of dry THF was added and stirred for 5 min, followed by addition of 1.1 equivalence of n-BuLi (2.5 M hexane sol., Aldrich). After the reaction mixture was stirred for 1 h at 25 °C, 1.1 equivalence of 3 dissolved in THF was added slowly and the reaction mixture was stirred for another 1h. The reaction was quenched by adding NH$_4$Cl aq. and the organic layer was extracted with diethyl ether (50 mL × 5 times) and concentrated by evaporation. The products were purified by preparative TLC (hexane : tert-butylmethyl ether = 2 : 1).
7.5. Synthesis and Characterization of Enecarbamates I

![Scheme 7-6: Outline for synthesis of methyl 3-phenylbutanoate.](image)

**3-Phenylbutyric Acid**

3-Phenylbutyraldehyde (135 mmol, 20g) dissolved in 74 ml CH₃CN. Flask cooled to 0°C and sodium phosphate dihydrate (NaH₂PO₄·H₂O; 32 mmol, 4.42g) dissolved in 31 ml water was added to flask followed by 13.9 ml Hydrogen peroxide (H₂O₂). Sodium Chlorite (NaClO₂; 197 mmol; 17.7g) dissolved in 74 ml water was slowly added to the solution over the course of three hours with the aid of an addition funnel. Allowed reaction to stir for an hour longer and then about 3 g Sodium Sulphate (Na₂SO₄) added to the solution. Sodium Bicarbonate (NaHCO₃) added until a PH of about 8-9 is achieved. Washed with CH₂Cl₂. Retained aqueous layer and acidified until pH 1-2, extracted product with CH₂Cl₂ and dried over dry MgSO₄ and the solvent evaporated off under reduced pressure. Yield (81%); ¹HNMR (300 Mhz, CDCl₃) δ 1.35 (3H, d, J=6.9 Hz), 2.65 (2H, octet, J=8.1 Hz), 3.30 (1H, sextet, J=6.9 Hz, 8.1 Hz), 7.24-7.36 (5H, m), 11.364 (1H, br).
Methyl 3-phenylbutanoate\textsuperscript{6}

3-Phenylbutyric acid (111 mmol, 18.27g) dissolved in CH\textsubscript{3}CN. DBU (111 mmol, 16.6 ml) added to flask followed by CH\textsubscript{3}I (145 mmol, 9.02ml). Reaction stirred and monitored by TLC until starting material disappears. Reaction extracted with CH\textsubscript{2}Cl\textsubscript{2} and washed with 5% KOH, 10% trifluoroacetic Acid (TFA) and 5% NaHCO\textsubscript{3} before drying over MgSO\textsubscript{4} and evaporating off solvent under reduced pressure. Crude yield (91%). Compound purified using column chromatography (silica, 0-20% EtOAc in Hexanes); \textsuperscript{1}HNMR (400 Mhz, CDCl\textsubscript{3}) $\delta$ 1.33 (3H, d, J=7.2 Hz), 2.62 (2H, octet), 3.31 (1H, sextet, J=7.2 Hz), 3.65 (3H, s), 7.21-7.35 (5H, m).

Scheme 7-7: Scheme for the synthesis of aldehyde B, 2,4-diphenyl-3-pentanal.

B was synthesized from Methyl 3-Phenylbutanoate as outlined for the synthesis of A from Methyl phenylacetate in section 7.4.a above after synthesis of the Methyl 2,4-dimethyl-3-pentanoate following alternative procedures\textsuperscript{7}. 
General Procedure for the Preparation of the Enecarbamates I

A solution of the aldehyde B (1.0 equiv.), the particular oxazolidinone (0.9 equiv.), and a catalytic amount (ca. 10 mg) of p-toluenesulfonic acid in 50 mL of toluene was heated to reflux and the resulting water removed by azeotropic distillation during 12 h. After cooling the solution to ca. 20 °C, it was washed with a saturated, aqueous solution of NH₄Cl (50 mL) and water (50 mL), and the combined organic layers were dried over MgSO₄. After evaporation of the organic solvent (60 °C, 15 torr) and purification by silica-gel flash chromatography (petroleum ether/ethyl acetate 4:1), the enecarbamates I were obtained in quantitative yield.

RR-Ia

determined from mixed spectra with SS-Ia. ¹H-NMR (500 MHz, CDCl₃) 1.183 (3H, d, J = 6.5 Hz), 1.526 (3H, d, J = 7 Hz), 1.60 (3H, d, J = 8 Hz), 3.529 (1H, q, J = 7.15 Hz), 3.609 (1H, q, 7.15 Hz), 3.868-3.904 (1H, m), 4.093 (1H, q, J = 7.15 Hz), 4.369 (1H, t, J = 8.25 Hz), 5.550 (1H, s), 6.880 (2H, d, J = 7.5 Hz), 7.074-7.239 (8H, m).

SS-Ia

was synthesized using optically pure starting materials following the procedure above. ¹H-NMR (500 MHz, CDCl₃) 1.238 (3H, d, J = 6Hz), 1.487 (3H, d, J = 7.5 Hz), 1.537 (3H, d, J = 7 Hz), 3.485 (1H, q, J = 7.15 Hz), 3.868-3.933 (2H,
m), 4.168 (1H, q, J = 7.15 Hz), 4.416 (1H, m), 5.670 (1H, s), 6.862 (2H, d, J = 7.5 Hz), 7.074-7.345 (8H, m).

**RR-Ia and SS-Ia**


**SR-Ia**

was separated via HPLC-MS using CD$_3$OD and H$_2$O and crystals obtained using hexanes and a crystal structure obtained. $^1$H-NMR (500 MHz, CDCl$_3$) 1.184 (3H, d, J = 7.5Hz), 1.248 (3H, d, J = 7Hz), 1.254 (3H, d, J = 6 Hz), 3.451 (1H, q, J = 7.15Hz), 3.841 (1H, m), 3.867 (1H, q, J = 7Hz), 4.178 (1H, q, J = 7.35 Hz), 4.364 (1H, t, J = 7.5 Hz), 5.710 (1H, s), 7.229-7.257 (2H, m), 7.298-7.347 (8H, m). $^{13}$C-NMR (500 MHz, CDCl$_3$) 17.738, 18.239, 23.452, 39.416, 40.739, 54.250, 69.215, 119.095, 126.249, 126.284, 127.495, 127.765, 128.253, 128.509, 143.210, 145.594, 151.651, 157.093.

**RS-Ia**
$^1$H-NMR (500 MHz, CDCl$_3$) 1.203 (3H, d, $J = 7.5$ Hz), 1.249 (3H, d, $J = 7$ Hz), 1.314 (3H, d, $J = 5.5$ Hz), 3.394 (1H, q, $J = 7.35$ Hz), 3.863-3.937 (2H, $m$), 4.126 (1H, q, $J = 7.15$ Hz), 4.412 (1H, t, $J = 7.5$ Hz), 5.900 (1H, s), 7.210-7.271 (4H, $m$), 7.296-7.353 (6H, $m$). $^{13}$C-NMR (500 MHz, CDCl$_3$) 16.849, 18.646, 23.236, 39.799, 40.666, 54.289, 69.158, 119.168, 126.246, 127.467, 127.488, 128.290, 128.516, 143.525, 145.805, 149.265, 157.157.
7.6. **Determination of Stereoselectivity Factors**

7.6.a. *General procedure for photooxidation of the enecarbamates by $^1$O$_2$:*

An aliquot of each enecarbamate pair from a standard solution in CH$_2$Cl$_2$ was added to a NMR tube. The solvent was removed by means of a stream of N$_2$ and the residual solvent was removed by placing the open NMR tube into a vacuum oven at room temperature for at least 2 h. To each NMR tube was added a 1.0-mL aliquot of methylene blue ($3.7 \times 10^{-4}$ M) in the desired solvent (enecarbamate $3.0 \times 10^{-3}$ M). Each tube was sealed with a rubber septum and fitted with a gas delivery needle and a vent needle. Samples were purged with O$_2$ for 20 min prior to and during irradiation.

Irradiations were performed with a 500-W halogen lamp, attenuated with a variable voltage controller set to 80%. The lamp was housed in a jacketed condenser through which cold K$_2$CrO$_4$ (aq) filter solution was allowed to flow. This condenser was in turn housed in a larger condenser that was evacuated to 10$^{-4}$ torr. A steady stream of air was also passed over the lamp for further cooling. A diagram of this apparatus is shown in **Figure 7-1**. Samples were inserted into uranium glass tubes (cutoff < 500 nm) and simultaneously irradiated for 30 min. After irradiation, samples were analyzed by NMR spectroscopy to obtain the conversion by integration of the signals of the aldehyde (decomposition product) and the unreacted enecarbamates. Samples were then analyzed by GC on a chiral stationary phase by using di-tertbiphenyl biphenyl as calibration standard.
7.7. Determination of $^1\text{O}_2$ approach with dioxetanes$^8$-$^9$

7.7.a. Chemicals

Spectrophotometric grade solvents were used as received from Aldrich. Methylene blue was used as received from Aldrich. Deuterated solvents and $L$-($d_8$)-Valine were obtained from Cambridge Isotope Labs. Chloroform-$d$, methylene chloride-$d_2$ and methanol-$d_4$ were used as received. The $Z$ and $E$ enecarbamates $Z$-$1d$-$H_8$ and $E$-$1d$-$H_8$ were synthesized as previously described. Synthesis of $L$-($d_8$)-Valinol precursor to the $Z$-$1h$-$D_8$ enecarbamate followed published procedures.$^{10}$

7.7.b. General Procedure for the Photooxygenation of Enecarbamates by $^1\text{O}_2$ to form the Dioxetane

The enecarbamate was dissolved in CD$_2$Cl$_2$ (kept over NaHCO$_3$) and 2 mg 5,10,15,20-Tetrakis-(Pentafluorophenyl)-Porphine (TFPP) added. The solution was irradiated at $-23^\circ$C (CCl$_4$/Dry Ice) and irradiated with a 300W lamp using <400 nm cutoff filter. The appearance of the $C_1'$-$H$ peak in the dioxetane and the disappearance of the $C_1'$-$H$ peak of the starting enecarbamate was monitored by low temperature $^1\text{H}$-NMR until >90% conversion. The resulting dioxetane was maintained at $-23^\circ$C and characterized by $^1\text{H}$-NMR.
7.7.c. Reduction of the Dioxetane 2 to 1,2-Dihydroxy-2,3-diphenylbutane:

![Scheme 7-8: Scheme for the reduction of dioxetane Z-2 to 2,3-diphenyl-1,2-butanol.]

The crude photooxygenation product was dissolved in 10 mL of a mixture of CH₃CN/water (5:1) at 0 °C, and an aqueous solution (5mL) of L-methionine (1 equiv.) was added, stirred for 15 min, followed by the addition of water (10 mL), and the two layers were separated. The aqueous layer was extracted with CH₂Cl₂ (2x20 mL), the combined organic layers were dried over MgSO₄, and the solvent was removed (20 °C, 15 torr). The residue was dissolved in 10 mL of a mixture of THF/water (4:1) and NaBH₄ (0.75 equiv.) and DBU (0.50 equiv.) were added consecutively at 0 °C while stirring; the oxazolidinone precipitated during the course of the reaction. The reaction mixture was stirred for 15 min, then 15 mL of a saturated, aqueous solution of NH₄Cl were added, and stirred for another 5 min. Ethyl ether (20 mL) was added and the organic layer was separated and dried over MgSO₄. The solvent was removed (20 °C, 15 torr) and the crude product (ca. 30% yield of the enantiomerically pure diol) was purified by silica-gel flash chromatography (8:1 mixture of petroleum ether/ethyl acetate).

The configuration of the diol obtained from the dioxetane was determined
by HPLC comparison with an authentic sample of 1,2-Dihydroxy-2,3-diphenylbutane (93 ee %) synthesized according to the literature procedure.²
7.8. Determination of Quenching Constants

7.8.a. Chemicals

*trans*-4-octene was obtained from Alfa Aesar and 1-methyl-1-cyclohexene from Aldrich. Both compounds were distilled before use. Hexamethyldisilane (HMDS) and 5,10,15,20-tetrakis(pentafluorophenyl)porphyrin (TFPP) were used as received from Aldrich. 1,4-Dimethylnapthalene endoperoxide was synthesized following established procedures.\textsuperscript{11} Deuterated solvents were obtained from Cambridge Isotope Laboratories and kept over dry NaHCO\textsubscript{3}. The Z and E enecarbamates were synthesized as previously described.

7.8.b. Exemplar procedure for competitive kinetics to determine $k_{cq}$:

Stock solution of HMDS [0.35ml to 25ml with CDCl\textsubscript{3}], TFPP [5.26mg to 10ml with CDCl\textsubscript{3}], *trans*-4-octene [**Stock 1**: 0.15ml to 5ml with CDCl\textsubscript{3}; **Stock 2**: 0.2ml Stock 1 dilute to 5ml with CDCl\textsubscript{3}] and enecarbamate [147.2mg to 25 ml with CDCl\textsubscript{3}] were made up. Using the stock solutions, 0.45 ml of the enecarbamate, 0.1ml *trans*-4-octene and 0.05ml TFPP were added to NMR tube. Oxygen was bubbled into samples and they were irradiated under ambient conditions using a 300W halogen lamp and a $<400$ nm cutoff filter. Low conversions (<20%) were maintained. After irradiation, 0.1ml of HMDS stock solution was added and the sample characterized using $^1$H-NMR. Chemical quenching rates were calculated based on the disappearance of enecarbamate
and trans-4-octene peaks and therefore the HMDS was used as a standard to
calculate the amount of enecarbamate remaining after irradiation.

In later experiments 1a was used as a standard in addition to trans-4-
octene.

7.8.c. General procedure for \(^1\)O\(_2\) chemiluminescence quenching experiment to
determine \(k_Q\)

All compounds were purified, dried and pumped for several days under
vacuum at ambient temperature. Stock solutions of enecarbamate quenchers, 1-
methyl-1-cyclohexene (0.05M), trans-4-octene (0.4M) and 1,4-
dimethylnaphthalene endoperoxide (10mM) were prepared. In a quartz cuvette
(1×1×4 cm) with 200µl of 1,4-dimethylnaphthalene endoperoxide solution in
2700µl CDCl\(_3\), aliquots of quencher (enecarbamate or standard) were added.
After the addition of each aliquot chemiluminescence spectra were recorded from
1200 to 1340nm at 22°C using a modified Fluorolog 2 spectrofluorimeter (Horiba
Jobin-Yvon) in conjunction with a NIR sensitive photomultiplier detector
(H9170-45, Hamamatsu). Stern-Volmer constants (\(K_{SV}\)) were determined from
the slope of the plot of the \(^1\)O\(_2\) phosphorescence intensity vs quencher
concentration. To convert \(K_{SV}\) into the total quenching rate constant (\(k_Q\)) using
Equation 7-1, the singlet oxygen lifetime in the absence of quencher (\(\tau_0\)) is
required. Because \(\tau_0\) under our experimental condition is expected to be shorter
than the published value in high purity CDCl₃, we determined τ₀ using trans-4-octene as standard (kₗ = 1.8 x 10⁴ M⁻¹s⁻¹).¹²

\[ K_{SV} = k_q \tau_0 \]
7.9. Determination of Stereoselectivities in Zeolites

7.9.a. General procedure for photooxidation of enecarbamates 1 inside methylene blue exchanged zeolite.

300 mg of zeolite loaded with the dye was dried in a vacuum oven at 60°C for 8 h. The dried dye-loaded zeolite was added to a test tube containing 12 mL of 2,2,4-trimethyl pentane (isooctane). The dye-zeolite slurry was purged with nitrogen for 15 min. followed by the addition of known amount of enecarbamate Z-1 or E-1 (2-3 mg) dissolved in 0.2 mL of methylene chloride and 1 mL isooctane. The dye-zeolite slurry was stirred in an oil bath kept at 70°C for 5-6 h. The zeolite slurry was then brought to room temperature and fitted with a gas delivery needle and a vent needle. Oxygen was purged through the sample for 20 min. prior to and during irradiation. Irradiations were performed using a 300 W halogen lamp with a <500 nm cutoff filter with stirring and continuous purging of oxygen for a given time interval. The slurry was then filtered and the filtrate (isooctane supernatant) was checked for the presence of the enecarbamate (enecarbamate was not observed in the supernatant). The zeolite residue was transferred to a test tube and extracted by stirring with acetonitrile in an oil bath at 70°C for 8 h. The acetonitrile slurry was filtered and the acetonitrile extract was transferred to a round bottom flask. The zeolite powder was further subjected to soxhlet extraction overnight with acetonitrile as solvent to confirm complete extraction. The soxhlet extract was combined with the previous acetonitrile extract and then concentrated. The concentrated extract was analyzed using a GC equipped with an achiral stationary phase to obtain the mass
balance (based on the unreacted enecarbamate and the amount of MDB formed after irradiation) and the conversion (based on the unreacted enecarbamate) using 4,4'-di-tert-butylbiphenyl as calibration standard. Samples were then analyzed for MDB enantioselectivity using GC equipped with a chiral stationary phase.
7.10. **Determination of Stereoselectivities in Cyclodextrin**

7.10.a. *Synthesis of Enecarbamate-Cyclodextrin complexes*

Complexation and Photooxygenation were carried out following literature procedure, with solvent variations. Methylene blue was adsorbed unto cyclodextrin surfaces after suspension of complex in desired solvent. Samples were irradiated with 300W lamp and afterward extracted from cyclodextrins with CH$_3$CN as above with zeolites. Extract was analyzed via $^1$H-NMR and GC.
7.11. **Photolysis**

7.11.a. *General procedure for oxidation of enecarbamates by ozone*\(^{15}\):

An aliquot of each enecarbamate pair from a standard solution in dichloromethane was added to an NMR tube. The solvent was removed by means of a stream of N\(_2\) and the residual solvent was removed by placing the open NMR tube into a vacuum oven at room temperature for at least 2 h. To each NMR tube was added 0.7-mL of the desired deuterated solvent (enecarbamate 2.3 \(\times\) 10\(^{-3}\) M). The NMR tube with the enecarbamate was kept in a cooling bath at the required temperature. A separate test tube with the deuterated solvent of interest, was placed into the cooling bath at the required temperature. Ozone (generated from Ozone Lab OL100 Ozone Generator) was bubbled through the desired deuterated solvent for a minimum of 15-20 min so that the solvent was saturated with ozone.

Known amounts of the ozone-saturated solution was added to the test tube. After addition of the ozone the samples were allowed to react at the desired temperature for a specific amount of time and then samples were then subjected to GC analysis on a chiral stationary phase or photolysis under N\(_2\) atmosphere.
7.12. **Stereoselectivity (s) factor**\textsuperscript{16}

The stereoselectivity (s) factor is a ratio of the relative reactive rate constants (chemical quenching) between two epimers that only differ in the R/S configuration at the C-3' center (Equation 7-2). While ee may change with conversion, the s-factor is conversion independent and is a way of comparing different compounds where the ee has been determined over different conversions.

\[
s = \frac{k_R}{k_S} = \frac{\ln[1 - C(1 + ee_{MDB})]}{\ln[1 - C(1 - ee_{MDB})]}
\]

7-2

### 7.12.a. Activation Parameters

Utilizing the Eyring Equation (Equation 7-3), the s-factor can be equated to the differential enthalpic and entropic activation parameters \(\Delta\Delta H^\ddagger_{R-S}\) and \(\Delta\Delta S^\ddagger_{R-S}\) (Equation 7-4).

\[
k = \frac{k_B T}{h} e^{\frac{\Delta S^\ddagger}{R}} e^{\frac{\Delta H^\ddagger}{RT}}
\]

7-3

\[
\ln \frac{k_R}{k_S} = \frac{\Delta\Delta S^\ddagger}{R} - \frac{\Delta\Delta H^\ddagger}{RT}
\]

7-4

Where \(\Delta\Delta H^\ddagger_{R-S}\) can be written \(\Delta H^\ddagger_{R} - \Delta H^\ddagger_{S}\) with the same analogy extending to the entropic factor.
7.13. References


