Chemistry 425b: Organic Reactions

Dr. Gregory O’Neil
Department of Chemistry
Western Washington University
Preface

This text/workbook was designed to accompany a one-quarter advanced undergraduate chemistry elective. Presentations of topics are by no means a complete treatise on the subject. Rather, these provide an entry point to core principles governing organic reactions. Selected examples are given to highlight these reactions in the context of complex molecule synthesis. An effort has been made to provide students with references that encourage further reading on a given topic.

The text is divided roughly into two halves (see Table of Contents), beginning with a more detailed analysis of reactions that should be familiar to students that have completed sophomore organic chemistry. Topics discussed include FMO- and conformational analysis. This then is followed by more synthesis-oriented subjects including fundamental reactions like oxidations and reductions plus more specialized topics like selectivity models for carbonyl additions and methods for alkene synthesis. It is the intention of the author to supplement this text with information on special topics that include protecting groups and palladium-catalyzed cross-coupling reactions.

Significant inspiration was gained from the following sources:


Table of Contents

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Principles of Organic Reactions</td>
<td>3</td>
</tr>
<tr>
<td>2. Conformational Analysis</td>
<td>18</td>
</tr>
<tr>
<td>3. Kinetics and Thermodynamics</td>
<td>24</td>
</tr>
<tr>
<td>4. Pericyclic Reactions</td>
<td>31</td>
</tr>
<tr>
<td>5. Oxidation Reactions</td>
<td>46</td>
</tr>
<tr>
<td>6. Reactions at the Carbonyl</td>
<td>56</td>
</tr>
<tr>
<td>7. Alkene Synthesis</td>
<td>71</td>
</tr>
<tr>
<td>8. Alkene Metathesis</td>
<td>77</td>
</tr>
</tbody>
</table>
Ch. 1 What do we need to know to understand, predict, and design organic reactions?

**Methodology:** An organic chemist’s toolkit.

**Retrosynthesis:** A strategy for analyzing complex problems.

**Mechanism:** A framework for predicting and understanding the products and stereochemistry of a reaction

### Classes of Mechanisms

Three general types:

a) **Polar**
   Movement of PAIRED electrons

\[
\text{aryl} - \text{Br} \quad \xrightarrow{\text{NaN}_3, \text{DMF}} \quad \text{aryl} - \text{N}_3
\]

b) **Free radical**
   Movement of UNPAIRED electrons

\[
\text{aryl} - \text{Br} \quad \xrightarrow{\text{Ph}_3\text{P}, \text{PhH}} \quad \text{aryl} - \text{N}_3
\]

### Mechanism Basics

**Notation:**

- **reaction arrow**

- **resonance arrow**

- **equilibria arrows**

- **electron movement**

- **1e**

- **2e**
c) Pericyclic
Movement of electrons within a closed ring (there are no intermediates, ions or radical species)

Pericyclic reactions can be subdivided into 4 categories:

i. Cycloadditions

\[ \text{Cycloaddition} \]

ii. Electro cyclic Reactions

\[ \text{Electro cyclic Reaction} \]

iii. Sigmatropic rearrangements

\[ \text{Sigmatropic rearrangement} \]

iv. Group Transfer reactions

\[ \text{Group Transfer reaction} \]

**Universal Effects Governing Chemical Reactions:**

- **Steric Effects** - Nonbonding interactions (Van Der Waals repulsion) between substituents within a molecule or between reacting molecules.

\[ \text{Steric Effects} \]

- **Electronic Effects (Inductive Effects)** - The effect of bond and through-space polarization by heteroatom substituents on reaction rates and selectivities.

\[ \text{Electronic Effects} \]

- **Stereoelectronic Effects** - Geometrical constraints placed upon ground and transition states by orbital overlap considerations.

\[ \text{Stereoelectronic Effects} \]
**Steric vs. Electronic Effects**: Case studies when steric and electronic effects lead to differing stereochemical outcomes:

Woerpel et al., J. Am. Chem. Soc. 1999, 121, 12208

Yakura et al., Tetrahedron 2000, 56, 7715

**MO Theory: The H₂ Molecule (revisited)**

Let’s combine two hydrogen atoms to form H₂.

- **Rule 1**: A linear combination of n atomic orbitals (AOs) will create n Molecular Orbitals (MOs).

What happens when you add two electrons to the MO diagram above? How about four electrons?

- **Rule 2**: Each MO is constructed by taking a linear combination of the individual atomic orbitals:

  Bonding MO \[ \sigma = C_1 \psi_1 + C_2 \psi_2 \]

  Antibonding MO \[ \sigma^* = (C_1^*) \psi_1 + (C_2^*) \psi_2 \]

The coefficients \( C_1 \) and \( C_2 \) represent the contribution of each AO.

The squares of the \( C \)-values are a measure of the electron density on the atoms in question.
• Rule 3: Both wave functions must contribute one net orbital.

Consider the C-O π-bond of acetone.

In the ground state, π C-O is polarized toward oxygen.

Note that the antibonding orbital is polarized in the opposite direction (Rule 3)

What does this mean in terms of reactivity?

**Chemical Bonding**

• Bond strengths (Bond Dissociation Energies) are composed of a covalent ($\delta E_{\text{cov}}$) and ionic contribution ($\langle \delta E_{\text{cov}} \rangle$).

• As two molecules collide:
  a) The occupied orbitals of one molecule repel the occupied orbitals of the other.
  b) Any positive charge on one attracts negative charge on the other.
  c) The occupied orbitals of each interact with the unoccupied orbitals of the other.

*Overlap between orbitals is most effective for orbitals of similar size and energy (Frontier Molecular Orbital Theory).*
Consider Group IV elements Carbon and Silicon:

- Weak bonds have corresponding low-lying antibonding orbitals.
- Orbital orientation greatly affects the strength of the interaction.

Case 1: Anti nonbonding electron pair and C-X bond.

Case 2: Two anti sigma bonds.
Donor Acceptor Properties

Consider the energy levels for both bonding and antibonding orbitals:

The greater electronegativity of oxygen lowers both the bonding and antibonding C-O states. Hence:

\[ \sigma^* \text{C-O} \text{ is a better acceptor orbital than } \sigma^* \text{C-C} \]

- **Hierarchy of Donor Acceptors:**

<table>
<thead>
<tr>
<th>C-X ( \sigma ) bonds</th>
<th>increasing donor capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(_2)C-CH(_3) ~ H(_2)C-H &gt; H(_3)C-NH(_2) &gt; H(_3)C-OH &gt; H(_3)C-F</td>
<td>best donor</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>C-X ( \sigma^* )</th>
<th>decreasing acceptor capacity</th>
</tr>
</thead>
<tbody>
<tr>
<td>H(_2)C-CH(_3) ~ H(_2)C-H &gt; H(_3)C-NH(_2) &gt; H(_3)C-OH &gt; H(_3)C-F</td>
<td>best acceptor</td>
</tr>
</tbody>
</table>

- The interaction of a vicinal bonding orbital with a p-orbital is referred to as hyperconjugation.

Stereoelectronic requirement: Syn-planar orientation between interacting orbitals.

The new occupied orbital is lower in energy. When you stabilize the electrons in a system, you stabilize the system as a whole.
- Consider the following X-ray structures of adamantine.

*Bonds participating in hyperconjugation (e.g. C-R) will be lengthened while the C(+)C bond will be shortened.*

Delocalization of nonbonding electrons into vicinal antibonding orbitals is also possible.

As the antibonding C-Y orbital energy *decreases*, the magnitude of this interaction will *increase*.

Note that $\sigma$ C-Y is slightly destabilized.

Since nonbonding electrons prefer hybrid orbitals, this orbital can adopt either a syn or anti to the vicinal C-Y bond.

**Syn Orientation**

**Anti Orientation**

Overlap is better in the anti orientation.

**Example: \( N_2F_2 \)**

This molecule can exist as either cis or trans. Which is preferred?

**Orbital Interactions:**

**M.O Description**

**Electrostatic Interactions (Dipole)?**
Anomeric Effect

A methoxy substituent on a cyclohexane ring prefers to adopt the equatorial conformation.

\[ \Delta G^0 = 0.6 \text{ kcal/mol} \]

Whereas the closely related 2-methoxytetrahydropyran prefers the axial conformation.

\[ \Delta G^0 = -0.6 \text{ kcal/mol} \]

The effect that provides the stabilization which overrides the inherent steric bias is referred to as the anomeric effect.

- Other electronegative atoms such as Cl, SR, etc. also participate in anomeric stabilization.

\[ 1.781 \text{ Å} \]

- There is also a rotational bias on the exocyclic C-OR bond.

\[ 1.819 \text{ Å} \]

Why is the axial C-Cl bond longer?

Principle HOMO-LUMO interaction:
Spectroscopic Evidence

Can you explain the following IR trends?

\[
\begin{array}{ccc}
\text{MeCH}_3 & \text{MeCBr}_3 & \text{MeCF}_3 \\
\text{C}=\text{O IR Frequency (cm}^{-1}\text{)} & 1720 & 1750 & 1780
\end{array}
\]

Compare the C-H stretching frequency for an aldehyde and related alkene.

\[
\begin{array}{cc}
\text{Aldehyde} & \text{Related Alkene} \\
\text{H} & \text{H} \\
v \text{C-H} = 2730 \text{ cm}^{-1} & v \text{C-H} = 3050 \text{ cm}^{-1}
\end{array}
\]

The N-H stretching frequency of cis-methyl diazene is 200 cm\(^{-1}\) lower than the trans isomer.

\[
\begin{array}{cc}
\text{cis-Me} & \text{trans-Me} \\
\text{N-H} & \text{N-H} \\
v \text{N-H} = 2188 \text{ cm}^{-1} & v \text{N-H} = 2317 \text{ cm}^{-1}
\end{array}
\]

Rationalize why B is more stable than A.

\[
\begin{array}{c}
\begin{array}{c}
\text{Me}_3\text{C-N} \text{N-CMe}_3 \\
\Delta G^0 = -0.35 \text{ kcal/mol}
\end{array}
\end{array}
\]


Carboxylic Acids and Esters

- **Conformations**: There are two planar conformations.

**Z** Conformer \[\text{R} \text{C}=\text{O} \text{R'} \leftrightarrow \text{E} \text{Conformer} \]

Specific Case: Methyl Formate.

\[
\begin{array}{c}
\begin{array}{c}
\text{H} \text{C}=\text{O} \text{Me} \\
\Delta G^0 = +4.8 \text{ kcal/mol}
\end{array}
\end{array}
\]

The (E) conformation of both acids and esters is less stable by 3-5 kcal/mol. Sterics would predict that the (E) conformer of methyl formate would be preferred (H smaller than O). Since this is not the case, **electronics must be considered**.
Conjugation and Hybridization

Note that the alkyl oxygen is sp² hybridized in order to allow for conjugation (resonance).

**Hyperconjugation**

(Z) Conformer:

(E) Conformer:

---

**Esters vs. Lactones**

Esters prefer to adopt the (Z) conformation while small ring lactones are constrained in the (E) conformation. Explain the following:

1. Lactone 2 is significantly more susceptible to nucleophilic attack at the carbonyl carbon than 1.
2. The pKa of 2 is 25 while ester 1 is 30.

**Reactions**

- Peracid epoxidation of alkenes.

Identify the important orbital interactions.
- Baeyer-Villiger reaction.

*Can you rationalize the rate data below? (Hint: Why is that the preferred intermediate?)*

\[
\begin{align*}
R & \quad \text{Me} \\
\text{O} & \quad + C F_3 CO_3 H \\
\text{O} & \quad \text{O} \\
\text{R} & \quad \text{C} \quad \text{Me} \\
\text{Me} & \quad \text{R} \\
\text{R} & \quad \text{C} \quad \text{O} \\
\text{Me} & \quad \text{O} \\
\text{R} & \quad \text{R} / \text{k Me} \\
\end{align*}
\]

\[
\begin{align*}
\text{CH}_3 \text{CH}_2 & \quad 72 \\
(\text{CH}_3)_2 \text{CH} & \quad 150 \\
(\text{CH}_3)_3 \text{C} & \quad 830 \\
\end{align*}
\]

\[\text{via}\]

\[
\begin{align*}
\text{R}_L & \quad \text{OH} \\
\text{R} & \quad \text{O} \quad \text{CF}_3 \\
\text{O} & \quad \text{O} \\
\end{align*}
\]

where \(R_L = \text{large substituent}\)
\(R_S = \text{small substituent}\)

---

**How important is the trajectory of approach for reacting molecules?**

- sp\(^3\) hybridized: \(S_n2\) displacement.

\[
\begin{align*}
\text{Nu}^- & \quad \text{C} \quad \text{Br} \\
\text{H}^- & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

\[
\begin{align*}
\text{Nu}^- & \quad \text{C} \quad \text{Br} \\
\text{H}^- & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\end{align*}
\]

**Inversion**

\[\text{HOMO}\]

\[\text{LUMO}\]

**Retention**

\[\text{Nu}\]

- Tether Nu and \(X\)

- **Endocyclic Restriction Test**

  \[
  \text{(CH}_3\text{)}_2\text{N} - \text{SO}_3\text{CH}_3 \rightarrow \text{(CH}_3\text{)}_3\text{N}^+ - \text{SO}_3^- \\
\]


- \text{sp}^2 \text{ Hybridized: } C=O \text{ and } C=C.

Some history:

1. Led to the idea of a partial *through-space bond* between Nitrogen and the carbonyl.
2. Later, Brent proposed that X-ray structures of donor-acceptor systems might represent the early stages of chemical reactions. (*Chem. Rev.* **1968**, 68, 587)

**Required Trajectories: Summary**


**Baldwin’s Rules: Stereoelectronic Considerations for Ring-Closure.**

Baldwin’s Rules provide a qualitative set of generalizations on the probability of a given ring-closure. They do not apply to non-first-row elements or electrocyclic processes.

- **Nomenclature:**
  
  A. **Exo-cyclization** - The bond that is breaking is exocyclic to the forming ring.

  ![Exo-cyclization Diagram](image)

  ![Exo-cyclization Example](image)

  B. **Endo-cyclization** - The bond that is breaking is endocyclic to the forming ring.

  ![Endo-cyclization Diagram](image)

  ![Endo-cyclization Example](image)

  C. Ring Closures are classified according to hybridization of the electrophilic component and size of the ring formed.

  ![Ring Closure Examples](image)
**Most exo cyclizations are allowed.**

Example: Formation of 3-membered rings:

\[ \text{H}_2C^{\text{X}} \leftarrow \text{H}_2C^{\text{Y}} \rightarrow \text{H}_2C^{\text{Y}} \]

\[ n \text{(HOMO)} \rightarrow \sigma^{\text{X}} \text{(LUMO)} \]

**Some endo cyclizations are disallowed.**

**Case 1:**

\[
\begin{align*}
\text{SO}_2\text{Ph} & \quad \text{NaH} \\
\text{CX}_3 & \quad 6\text{-endo-tet} \\
\text{SO}_2\text{Ph} & \quad \text{exclusively intermolecular}
\end{align*}
\]

**Case 2:**

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{CO}_2\text{Me} \\
\text{NH}_2 & \quad \text{X} \\
\text{MeO}_2\text{C} & \quad \text{NH} \quad \text{CO}_2\text{Me} \\
& \quad \text{100%}
\end{align*}
\]

**Case 3:**

\[
\begin{align*}
\text{Me} & \quad \text{Me} \quad \text{Br} \\
& \quad \text{X} \\
& \quad \text{100%}
\end{align*}
\]
Conclusions

<table>
<thead>
<tr>
<th></th>
<th>EXO</th>
<th>ENDO</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>4</td>
<td>√</td>
<td>X</td>
</tr>
<tr>
<td>5</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>6</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>7</td>
<td>√</td>
<td>√</td>
</tr>
</tbody>
</table>

Further reading:

Ch. 2  Conformational Analysis


Ethane and Propane

The eclipsed conformer may be broken down into its individual destabilizing interactions.

<table>
<thead>
<tr>
<th>Structure</th>
<th>Eclipsed Atoms</th>
<th>ΔE (kcal mol⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethane</td>
<td>H↔H</td>
<td>1.0</td>
</tr>
<tr>
<td>Propane</td>
<td>H↔H</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>H↔CH₃</td>
<td>1.4</td>
</tr>
</tbody>
</table>

FMO Analysis:

ΔE = 3 kcal/mol for ethane (R = H)
ΔE = 3.4 kcal/mol for propane (R = Me)
Butane

\[ \text{staggered} \quad \rightarrow \quad \text{eclipsed} \]
\[ \Delta E = ? \]

Torsional Energy Diagram

Pentane

\[ \text{anti } C_{2,3} \text{ anti } C_{3,4} \quad \leftrightarrow \quad \text{gauche } C_{2,3} \text{ anti } C_{3,4} \]
\[ G_{\text{ref}} = 0 \text{ kcal/mol} \quad \leftrightarrow \quad G_{\text{ref}} = 0.8 \text{ kcal/mol} \]

\[ \text{gauche } C_{2,3} \text{ gauche } C_{3,4} \quad \leftrightarrow \quad \text{gauche } C_{2,3} \text{ gauche } C_{3,4} \]
\[ G_{\text{ref}} = 1.6 \text{ kcal/mol} \quad \leftrightarrow \quad G_{\text{ref}} = 5.5 \text{ kcal/mol} \]

Heirarchy of Me - Me Interactions

\[ \text{ca 3.1} \quad \text{3.7} \quad \text{3.9} \quad \sim 7.6 \]

Can you calculate the magnitude of the Me - Me interaction?
Consider the conformation of zincophorin:

![Zincophorin diagram]

**Allylic Strain: Propane vs. Propene**

![Propene and Propane structures]

Hybridization changes the C-C-C bond angle.

**Propylene (Propene) Torsional Strain:**

![Propylene torsional strain diagram]

\[ \Delta E = -2.0 \text{ kcal mol}^{-1} \]

Can you identify the lowest/highest energy conformations?

3-methyl-1-butene

![3-methyl-1-butene structures]

2-Z-butene

![2-Z-butene structures]
Can the following selectivity:

\[
\text{Me} \quad \text{BH}_3\text{-THF} \quad \text{then H}_2\text{O}_2, \text{NaOH} \quad \text{Me}
\]

\[\text{d.r} \quad 8:1\]

_J. Am. Chem. Soc. 1979, 101, 259._

Allylic Strain: Definition

This has important consequences for the enolate chemistry of amides:

_A*\text{strains}_

Ketones and Aldehydes
Can you predict the stereochemical outcome of this reaction?

Cyclic Systems

Strain Energy and Ring Size

Cyclohexane

A chair ring-flip interconverts axial and equatorial substituents:

Substituted Cyclohexanes:

Methylcyclohexane
Typical A Values (kcal/mol):

<table>
<thead>
<tr>
<th>FG</th>
<th>A Value</th>
<th>FG</th>
<th>A Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>F</td>
<td>0.25</td>
<td>OEt</td>
<td>0.9</td>
</tr>
<tr>
<td>Cl</td>
<td>0.6</td>
<td>CO₂Et</td>
<td>1.15</td>
</tr>
<tr>
<td>Br</td>
<td>0.5</td>
<td>NH₂</td>
<td>1.4</td>
</tr>
<tr>
<td>I</td>
<td>0.5</td>
<td>CH₃</td>
<td>1.8</td>
</tr>
<tr>
<td>OH (in C₆H₆)</td>
<td>0.7</td>
<td>CH₂CH₃</td>
<td>1.9</td>
</tr>
<tr>
<td>OH (in i-PrOH)</td>
<td>0.9</td>
<td>CH(CH₃)₂</td>
<td>2.1</td>
</tr>
<tr>
<td>OCH₃</td>
<td>0.75</td>
<td>C(CH₃)₃</td>
<td>4.9</td>
</tr>
</tbody>
</table>

Note the difference between i-Pr and i-Bu A Values.

Consider 3-methylcyclohexanone:

\[\Delta G^0 = -1.36 \text{ kcal/mol}\]

Stereoselective Reductions:

\[
\text{Bu} \quad \overset{[\text{H}]}{\rightarrow} \quad \text{Bu}
\]

<table>
<thead>
<tr>
<th>Reagent</th>
<th>Ratio (Axial:Equatorial OH)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiAlH₄</td>
<td>93 : 7</td>
</tr>
<tr>
<td>NaBH₄</td>
<td>79 : 21</td>
</tr>
<tr>
<td>DIBAL-H</td>
<td>72 : 28</td>
</tr>
<tr>
<td>L-Selectride</td>
<td>8 : 92</td>
</tr>
</tbody>
</table>

Six-Membered Rings with Heteroatoms

Consider the following A-Values:

\[\Delta G^0 = -1.8 \text{ kcal/mol}\]

\[\Delta G^0 = -2.8 \text{ kcal/mol}\]

\[\Delta G^0 = -1.4 \text{ kcal/mol}\]
Note on axial vs. equatorial interconversion:

- A values are additive

- Even though Cl has a very small A value, the energy of activation ($E_a$) is high (it must go through a half-chair conformation).

Ch. 3 Kinetics and Thermodynamics of Organic Reactions

$$\Delta G = \Delta H - T \Delta S$$  Where $\Delta G$ = Free Energy  
$\Delta H$ = Enthalpy  
$\Delta S$ = Entropy

An equilibrium can be described by:

$$\ln K_{eq} = -\frac{\Delta G}{RT}$$

To achieve a high ratio of products in a thermodynamically controlled reaction, you need the following $\Delta G$'s (kcal/mol):

<table>
<thead>
<tr>
<th>$K$ (25 °C)</th>
<th>$\Delta G$</th>
<th>$K$ (0 °C)</th>
<th>$\Delta G$</th>
<th>$K$ (-78 °C)</th>
<th>$\Delta G$</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 (67:33)</td>
<td>0.41</td>
<td>2.1 (68:32)</td>
<td>0.41</td>
<td>2.9 (75:25)</td>
<td>0.41</td>
</tr>
<tr>
<td>5 (83:17)</td>
<td>0.95</td>
<td>5.7 (85:15)</td>
<td>0.95</td>
<td>11.6 (92:8)</td>
<td>0.95</td>
</tr>
<tr>
<td>9 (90:10)</td>
<td>1.30</td>
<td>10.9 (92:18)</td>
<td>1.30</td>
<td>28.5 (97:3)</td>
<td>1.30</td>
</tr>
<tr>
<td>20 (95:5)</td>
<td>1.74</td>
<td>27.5 (96:4)</td>
<td>1.80</td>
<td>103.3 (99:1)</td>
<td>1.80</td>
</tr>
</tbody>
</table>

Consider the following hydrogenation reaction:

$$H_2C=CH_2 + H_2 \rightarrow H_2C-CH_2$$

Bonds Broken:  
1 C=C 163 kcal/mol  
1 H-H 104 kcal/mol

Bonds Formed:  
1 C-C 88 kcal/mol  
2 C-H 98 kcal/mol

Total = 267 kcal/mol  
Total = 284 kcal/mol

Overall this reaction is exothermic ($\Delta G = -17$ kcal/mol), so the reaction is favorable or spontaneous.

- But experimentally this reaction is very slow, it takes about $2 \times 10^4$ years to hydrogenate one mole of ethylene (without a catalyst).
A transition state (TS) possesses a defined geometry and charge delocalization but has no finite existence.

Intra- versus Intermolecular Reactions

\[
\begin{align*}
\text{CH}_3\text{OH} + \text{HO-CH}_3 &\rightarrow \text{HO-CH}_3 \quad \Delta S^+_{1} \\
\text{HO} \quad \text{HO} &\rightarrow \text{HO} \quad \Delta S^+_{2}
\end{align*}
\]

\[\Delta S^+_{1} < \Delta S^+_{2}; \quad k_1 < k_2\]

Intramolecular reactions have a far more favorable entropy of activation.

Kinetic vs. Thermodynamic Control

If this is an irreversible reaction, the major product will be B. If the reaction is reversible, C will be major (more stable product).

Hammond Postulate

The transition state most closely resembles the side (i.e. reactant or product) to which it is closer in energy.

Consider the solvolysis of tert-butyl chloride:

Step 1:

Step 2:
The transition states will resemble the geometry of the carbocation intermediate and not the reactant or product.

Conformational Effects on Reactivity

- **Ester Hydrolysis**

- **Oxidation**

\[
\frac{k_{trans}}{k_{cis}} = 19.8
\]

\[
\frac{k_{trans}}{k_{cis}} = 0.25
\]
• Substitution Reactions

Which of the following Sn2 reactions is faster?

\[
\begin{align*}
\text{cis} & \quad \text{trans} \\
\begin{array}{c}
\text{Bu}^+ \quad \text{H} \\
\text{Bu}^+ \quad \text{H}
\end{array} & \quad \begin{array}{c}
\text{Bu}^+ \quad \text{H} \\
\text{Bu}^+ \quad \text{H}
\end{array}
\end{align*}
\]

\[
\begin{align*}
& \xrightarrow{\text{PhS}^-} \\
& \xrightarrow{\text{PhS}^-}
\end{align*}
\]

• Elimination Reactions

Can you explain the following ratio of elimination products?

\[
\begin{align*}
\text{H}_3\text{C} - \text{Br} & \quad \xrightarrow{\text{NaOEt}} \\
\text{H}_3\text{C} - \text{Et} & \quad 51% \\
\text{H}_3\text{C} - \text{Et} & \quad 18%
\end{align*}
\]

Consider the E2 Elimination of:

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{neomenthyl chloride} & \quad \text{menthyl chloride}
\end{align*}
\]
**Epoxide Opening**

*Under kinetically controlled conditions (irreversible), product ratios are dependent on $E_a (\Delta G^\ddagger)$.***

Consider the following:

Atom under attack *moves toward* the nucleophile.
Rearrangements

From the previous example, how does the rate of conformer interconversion affect the product distribution?

There are two limiting cases to consider:

a) The rate of reaction is much faster than interconversion
   i.e. \( k_3, k_4 \gg k_1, k_2 \)

b) The rate of reaction is much slower than interconversion
   i.e. \( k_3, k_4 \ll k_1, k_2 \)

Case A: The two conformers cannot equilibrate during the reaction. The product ratio thus depends solely on the initial ratios of the two conformers (aka “Kinetic Quench”).

Case B: The two conformers can equilibrate during the reaction. The product ratio depends on the difference in activation energies (\( E_a \)) leading to the respective products (“Curtin-Hammett conditions”).
Ch. 4 Pericyclic Reactions

- A pericyclic reaction is characterized as a change in bonding relationships that takes place as a continuous, concerted reorganization of electrons.

- The term "concerted" specifies that there is one single transition state and therefore no intermediates are involved in the process. To maintain continuous electron flow, pericyclic reactions occur through cyclic transition states.

- More precisely: The cyclic transition state must correspond to an arrangement of the participating orbitals which has to maintain a bonding interaction between the reaction components throughout the course of the reaction.

Is it possible to predict the stereochemical outcome of this reaction?

Huisgen Tet. Lett. 1964, 3381.

Some things to consider:

a. The number of electrons involved is important.

![Diagrams showing pericyclic reactions]

b. Pericyclic reactions are stereospecific

![Diagrams showing stereospecificity in pericyclic reactions]

c. Reactions behave differently under different conditions (i.e thermo- vs. photochemical)

![Diagrams showing differences under different conditions]
We can explain and predict the outcome of pericyclic reactions using Frontier Molecular Orbital (FMO) theory (HOMO and LUMO interactions) and orbital symmetry.

For further reading see:


Some Classes of Pericyclic Reactions

1. Electrocyclic Ring Closure/Opening

Ring closure (and hence opening) can occur in two distinct ways:

Conrotatory Closure:

Disrotatory Closure:

Some Observations

- butadienes undergo conrotatory closure under thermal conditions.

- hexatrienes undergo disrotatory closure under thermal conditions.
• Under photochemical conditions 4 electron systems undergo disrotatory motion.

\[ \text{Me-C=C-Me} \xleftrightarrow{\text{disrotation} \quad \text{hv}} \text{Me-C(Me)}\]

• While 6 electron systems undergo conrotatory motion.

\[ \text{Me-C=C-Me} \xleftrightarrow{\text{conrotation} \quad \text{hv}} \text{Me-C(Me)}\]

**FMO Analysis**

Butadiene \( \pi \) Molecular Orbital Diagram:

• 4 \( \pi \) electron thermal reaction

\[ \text{HOMO} \quad \xleftrightarrow{\text{conrotation} \quad \text{heat}} \quad \text{Me-C(Me)} \]

\( bonding \)
- 6 $\pi$ electron thermal reaction

Overall:

<table>
<thead>
<tr>
<th>No. $\pi$ electrons</th>
<th>Thermal</th>
<th>$h\nu$</th>
</tr>
</thead>
<tbody>
<tr>
<td>$4n$ ($n = 0,1...$)</td>
<td>conrotatory</td>
<td>disrotatory</td>
</tr>
<tr>
<td>$4n + 2$</td>
<td>disrotatory</td>
<td>conrotatory</td>
</tr>
</tbody>
</table>

Photochemical Activation:

When light is used to initiate an electrocyclic rxn, an electron is excited from $\Psi_2$ to $\Psi_3$. Treating $\Psi_3$ as the HOMO now shows that disrotatory closure is allowed and conrotatory closure is forbidden.

- 4 $\pi$ electron photochemical reaction

2. [1,3]-Sigmatropic Rearrangements

Consider the following H-Migration:
The hydrogen can move across the pi system in one of two ways. If hydrogen migrates on the same side of the system, it is said to migrate **suprafacially** with respect to that system. If hydrogen migrates from one side of the pi system to the other, it is said to migrate **antarafacially**.

**Suprafacial migration**: The group moves across the same face.

**Antarafacial migration**: The group moves from one face to another.

**FMO Analysis of Hydrogen Migration**: The bridging distance is too great for the antarafacial migration. Hence, [1,3] hydrogen migrations are not observed under thermal conditions. Under photochemical conditions, the [1,3] rearrangement is allowed suprafacially.

*How would you predict this using FMO?*

*What about a [1,5] Hydrogen Shift?*
3. [3,3]-Sigmatropic Rearrangements

The reaction can proceed via a chair or boat transition state.

Some examples of [3,3]-Sigmatropic Rearrangements:

a) Cope Rearrangement

The Cope rearrangement proceeds in a concerted manner via a chair transition state and requires no acid or base catalysis.

Consider the following:

Can you explain the following product distribution?

Doering Tetrahedron 1962, 18, 67.
Applications

Oxy-Cope

Evans and Golob showed that the oxy-Cope rearrangement could be greatly accelerated by deprotonation of the alcohol.

Mechanism:

b) Claisen Rearrangement


There are a number of important variants of this important reaction:

A general mechanism:

\[ \text{Olefins} \xrightarrow{150 - 200^\circ C} \text{Aromatic Claisen} \]

\[ \text{R-CH(OH)} \xrightarrow{150^\circ C, \text{MeO}} \text{Eschenmoser Claisen} \]

\[ \text{R-CH(OH)} \xrightarrow{\text{cat. } H^+, 130^\circ C} \text{Johnson Orthoester Claisen} \]

\[ \text{R-CH(OH)} \xrightarrow{\text{LDA, TMSCI}} \text{Ireland Claisen} \]

Applications

**Aromatic Claisen:**

\[ \text{MeO} \]

\[ \xrightarrow{\text{Et}_2\text{AlCl}, -78^\circ C} \text{82%} \]

\[ \text{Vyvyan et al., Tet. Lett. 2005, 46, 2457} \]
Johnson Claisen:

The stereochemical outcome can be controlled by careful control of the enolization conditions.

Ireland Claisen:

Ireland deprotonation model:

Compare the following to the previous related Johnson Claisen.
4. Cycloaddition Reactions

A cycloaddition reaction is the union of two smaller, independent pi systems. Sigma bonds are created at the expense of pi bonds.

Cycloaddition reactions are referred to as \([m + n]\) additions when a system of \(m\) conjugated atoms combines with a system of \(n\) conjugated atoms.

In a cycloaddition, a pi system may be attacked in one of two distinct ways. If the pi system is attacked from the same face, then the reaction is \textit{suprafacial} on that component. If the system is attacked from opposite faces, then the reaction is \textit{antarafacial} on that component.

\[\text{Diels-Alder} \quad \text{[4+2]} \]

\[\text{1,3-dipolar cycloaddition} \quad \text{[2+2]} \]
Role of FMO’s:

- HOMO-LUMO gap controls the rate of reaction. Smaller gap = faster reaction.
- Electron-withdrawing groups lower the energy of the HOMO and LUMO.
- Electron-donating groups raise the energy of the HOMO and LUMO.

Reactions between electron-rich dienes and electron-poor dienophiles are referred to as normal electron demand Diels-Alder reactions. The most significant orbital overlap is between the HOMO of diene and LUMO of dienophile.

For a normal electron demand process the most valuable feature of a good dienophile is a low-energy LUMO, usually achieved by conjugation to an electron withdrawing group.

Can you design suitable substrates for an inverse electron demand Diels-Alder reaction?

[2+2]-Cycloaddition

Two geometries of approach can be envisioned. Consider thermal activation:

The simplest approach (Supra/Supra) is forbidden under thermal activation. The less obvious approach (Antara/Supra) is allowed thermally but geometrically rather congested.
Photolytic [2+2]-cycloadditions are quite common.

\[
\begin{align*}
&\text{HOMO (diene)} \\
&\text{bonding interaction} \\
&\text{LUMO (dienophile)}
\end{align*}
\]

\[\text{Dauben, Tet. 1961, 15, 197.}\]

\[\text{JOC 2011 76, 5924}\]

**[4+2]-Cycloaddition**

Normal Diels-Alder reaction under thermal activation:

\[\text{a) Stereochemistry}\]

The Diels-Alder reaction is stereospecific (i.e., the relative stereochemistry in the diene and dienophile are preserved in the product).

Compare:

\[\begin{align*}
&\text{HOMO (diene)} \\
&\text{bonding interaction} \\
&\text{LUMO (dienophile)}
\end{align*}\]

- Suprafactial with respect to both reaction components.
- Reaction proceeds through a boat transition state.
Endo products are typically favored even though exo products are often more stable.

Because of the well-defined stereochemical and regiochemical behavior, the Diels-Alder reaction has been used extensively in complex molecule synthesis.


Some examples:
Enantioselective Diels-Alder Reactions.

One system of broad utility employs an oxazolidinone as a chiral auxiliary.

R = H, endoexo > 100:1; endoa:endoB = 93:7
R = Me, endoexo > 55:1; endoa:endoB = 93:7

Role of Lewis Acid:

Chiral Lewis Acid Catalyst:

Organocatalyst:

Macmillan JACS 2002, 122, 2458
Ch. 5 Oxidation Reactions.

**Alcohol Oxidations.**

\[
\begin{align*}
\text{R-OH} & \xrightarrow{[\text{O}]} \text{R-CO} \\
\text{X = H = aldehyde} & \quad \text{X = R = ketone}
\end{align*}
\]

General mechanism:

There are a number of reagents for this purpose, this is a survey of some of the most common reagents used in synthesis.

1. **Dess-Martin Periodinane**


Preparation: 

\[
\begin{align*}
\text{Ac}_2\text{O} & \xrightarrow{\text{cat. pTsOH}} \\
\text{AcOOAc} & \xrightarrow{\text{KBrO}_3, \text{H}_2\text{SO}_4} \\
\text{AcOOAc} & \xrightarrow{\text{cat. pTsOH}} \\
\text{AcOOAc} & \xrightarrow{\text{cat. pTsOH}}
\end{align*}
\]

Some examples:

- Good for small scale reactions.
- Tolerant of a wide range of functionality.
- Can buffer with pyridine or NaHCO₃(s).


*Synlett*, (4), 313-14; 1992
2. Swern

\[ R\text{OH} \xrightarrow{\text{DMSO, (COCl)}_2\text{, then Et}_3\text{N}} X\text{RCO} \]


**Mechanism:**

- Tolerant of a large range of functionality.
- Basic conditions can cause electrophilic additions α to the carbonyl or β-eliminations:

**Some Examples:**

\[ \text{C}_6\text{H}_{13}\text{OH} \xrightarrow{1. \text{DMSO, (COCl)}_2, \text{Et}_3\text{N}} \xrightarrow{2. \text{Ph}_3\text{P}\text{CO}_2\text{Et}} \text{C}_6\text{H}_{13}\text{CO}_2\text{Et} \]

*JOC 1993, 58, 7195*

\[ \text{HO} \circ \text{H} \circ \text{HO} \xrightarrow{\text{DMSO, (COCl)}_2, \text{Et}_3\text{N}} \text{94\%} \]

*OTBS*
3. Tetrapropylammonium Perruthenate (TPAP)

- Essentially neutral conditions.
- Ruthenium is expensive, used catalytically with NMO as the stoichiometric oxidant.
- Molecular sieves are used to prevent overoxidation of aldehydes to carboxylic acids.

**Selected Examples:**

4. TEMPO


- Good selectivity for 1° vs. 2° alcohols.
- Cheap, stoichiometric oxidant is bleach.

**Mechanism** (See *Tetrahedron* 1998, 54, 667.):
Examples:

![Chemical structures]

5. Chromium-Based Oxidations

a) Jones Reagent (J. Chem. Soc. 1953, 2548.)
- Simple Prep: 67 g. of chromium trioxide in 125 ml. of distilled water. To this solution is added 58 ml. of concentrated sulfuric acid and the salts which precipitate are dissolved by addition of a minimum quantity of distilled water; the total volume of the solution usually does not exceed 225 ml.
- Very acidic, good for the oxidation of simple primary alcohols to carboxylic acids or secondary alcohols to ketones.

b) PCC (Tet. Lett. 1975, 2647)
- Only slightly acidic.
- Workup and removal of chromium salts can be laborious.

Still widely used:

![Chemical structures]
6. Oxidation of primary alcohols to carboxylic acids.

a) TEMPO plus NaClO₂ (J. Org. Chem. 1999, 64, 2564.)
   - Two step cycle consisting of TEMPO oxidation to the aldehyde followed by NaClO₂ oxidation to the carboxylic acid.

   - Will also oxidize alkenes.

c) Two Step:

   ![Chemical structure](image)

   - There are many choices for step 1.
   - Step 2 can be achieved using NaClO₂ in the presence of a phosphate buffer and 2-methyl-2-butene as an acid scavenger.
Oxidation of Carbon-Carbon Double Bonds

1. Epoxidation Reactions.
   - Peroxyacids:
     \[
     \text{R} \overset{\text{O}}{\text{O}} \text{OH} + \text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{H} \rightarrow \text{R} \overset{\text{O}}{\text{O}} \text{OH} + \text{O} \text{O} \text{H}
     \]
     Rate increases: \( R = \text{CH}_3 < \text{C}_6\text{H}_5 < \text{mClC}_6\text{H}_4 (m\text{-CPBA}) \)

   **Stereochemistry**
   Consider the following:

\[
\begin{align*}
\text{R} & = \text{H} & \text{R} & = \text{CH}_3 \\
99\% & & 1\% & \\
10\% & & 90\%
\end{align*}
\]

**Mechanism:**

There is a small difference in the energies of the products, but a larger difference for reagent approach in the transition states.

- **Allylic Alcohols**

\[
\begin{align*}
\text{OR} & \quad \text{m-CPBA} \\
\text{OR} & \quad \text{OR} + \text{OR} \\
R = \text{COCH}_3 & \quad 43\% : 57\% \\
R = \text{H} & \quad 9\% : 91\%
\end{align*}
\]


Original proposal for selectivity:

Three of the following reactions are diastereoselective the fourth is not. Explain.
• **Enantioselective Epoxidation: Sharpless Asymmetric Epoxidation**


The original paper described the first truly general and useful asymmetric reaction.

![Reaction mechanism](image)

<table>
<thead>
<tr>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>R&lt;sup&gt;3&lt;/sup&gt;</th>
<th>yield (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>H</td>
<td>Me</td>
<td>15</td>
<td>73</td>
</tr>
<tr>
<td>H</td>
<td>Pr</td>
<td>H</td>
<td>80</td>
<td>89</td>
</tr>
<tr>
<td>H</td>
<td>n-decyl</td>
<td>H</td>
<td>82</td>
<td>90</td>
</tr>
<tr>
<td>Ph</td>
<td>H</td>
<td>H</td>
<td>87</td>
<td>95</td>
</tr>
<tr>
<td>n-decyl</td>
<td>H</td>
<td>Ph</td>
<td>79</td>
<td>95</td>
</tr>
</tbody>
</table>

The enantiofacial selectivity is determined by the choice of ligand. As drawn, (-)-DET would result in epoxidation from the top face while (+)-DET would give the epoxide on the bottom face.

3 Å or 4 Å molecular sieves are required to ensure both high conversion and ee. A typical reaction is run with 5 mol% Ti(i-PrO)<sub>4</sub>, and 6 mol% (+) or (-) tartrate ester.

**Some recent examples:**

![Reaction example](image)

*JOC* 2011, 76, 6525-6533.

![Reaction example](image)

*JOC* 2012, 77, 7364-7370.
Some useful patterns of reactivity for 2,3-epoxy alcohols:

Asymmetric Dihydroxylation: Sharpless


The catalytic variant of an old and powerful reaction:

\[
\begin{align*}
R^1\longrightarrow R^2 & \quad \xrightarrow{\text{OsO}_4} \quad R^1\longrightarrow R^2 \\
\text{OH} & \quad + \quad \text{OH}
\end{align*}
\]

Criegee noted that dihydroxylation could be accelerated in pyridine. Sharpless’ asymmetric variant builds upon this observation and chiral cinchona alkaloids ligands as the source of asymmetry.

Pthalazine (PHAL) and diphenylpyrimidine (PYR) derivatives of DHQ/DHQD give generally higher ee and allow for the formulation of AD-mix-α (contains (DHQ)₂PHAL) and AD-mix-β (contains (DHQD)₂PHAL). These commercially available systems contain:

(DHQ)₂PHAL or (DHQD)₂PHAL 0.0016 mole
Potassium carbonate, 0.4988 mole
Potassium ferricyanide 0.4988 mole (reoxidant)
Potassium osmate dihydrate 0.0007 mole (non-volatile Os(VIII))
The facial selectivity can be predicted by:

\[
\text{DHQD} \quad \downarrow \quad \text{DHQ}
\]

For mono-substituted alkenes, locate \( R_L \), then orient as shown.

**Some examples:**

\[ \begin{align*}
\text{TMS-} & \quad \text{MeO} \\
\longrightarrow & \quad \text{OPMB} \quad \text{(DHQ)2-} \quad \text{PYR, K3FeCN6} \\
\text{K2CO3, OsO4} & \quad t-\text{BuOH-H2O} \quad (85\%) \\
\text{AD-mix-β} & \quad \text{tBuOH-H2O, O Lub}
\end{align*} \]

\[ \text{C12H20} \quad \text{OH} \]

\[ \text{CH2} \quad \text{R} \quad \text{H} \]

\[ \text{OPMB} \]

\[ \text{R} \quad \text{OH} \]

\[ \text{OH} \quad \text{OH} \]

\[ \text{C12H20} \quad \text{OH} \quad \text{O} \]

\[ \text{JACS 1993, 115, 4891} \]

\[ \begin{align*}
\text{PMBO-} & \quad \text{Me} \\
\longrightarrow & \quad \text{OPMB} \quad \text{(DHQ)2-} \quad \text{PYR, K3FeCN6} \\
1. & \quad \text{K2CO3, OsO4} \quad t-\text{BuOH-H2O} \quad (85\%) \\
2. & \quad 1 \text{ eq. TsCl, pyr.} \\
3. & \quad \text{K2CO3, MeOH} \\
4. & \quad \text{TMS Li}
\end{align*} \]

\[ \text{PMBO} \quad \text{Me} \quad \text{OH} \quad \text{OH} \quad \text{TMS} \]

\[ \text{1,4-reduction} \]

\[ \text{1,2-reduction} \]

**Ch. 6 Reactions at the Carbonyl: Formation of C-H and C-C Bonds.**

\[ \begin{align*}
\text{R} \quad \text{OH} & \quad \text{NaBH4} \\
\text{OH} & \quad \text{M} \\
\text{R} \quad \text{H} & \quad \text{M-} \\
\text{R} \quad \text{H} & \quad \text{Ph3P=CH2}
\end{align*} \]
• Nucleophilic Hydride Reagents

a) Sodium Borohydride, NaBH₄: Most commonly used in MeOH to reduce ketones and aldehydes.

b) Lithium Borohydride, LiBH₄: In THF or Et₂O the increased Lewis acidity of Li⁺ vs. Na⁺ makes this a more powerful reductant that NaBH₄. Can reduce some esters and lactones, commonly used to cleave oxazolidinone auxiliaries.

c) Lithium Aluminum Hydride, LiAlH₄: Powerful hydride reagent that reduces essentially all carbonyl groups as well as other functional groups.

d) Lithium tri(sec-butyl)borohydride, Li(s-Bu)₃BH: Bulky hydride that is valued for increased stereoselectivity.

e) Sodium Cyanoborohydride, NaCNBH₃: Stable in acid (pH=3), primarily used to reduce imines (as part of the reductive amination process).

• Electrophilic Hydride Reagents

a) Borane, BH₃: Most commonly as the THF- or Me₂S-complex. Used to reduce amides and acids, but will also react with olefins and several other functional groups.

b) Diisobutylaluminum Hydride, DIBAL-H): The reagent of choice for the reduction of nitriles to aldehyde (via the imine), lactones to lactols, some esters to aldehydes, and α,β-unsaturated esters to allylic alcohols.

<table>
<thead>
<tr>
<th></th>
<th>NaBH₄</th>
<th>LiBH₄</th>
<th>LiAlH₄</th>
<th>BH₃</th>
<th>DIBAL-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>RCHO</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>R₂CO</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>RCO₂R</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>RCO₂H</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>RCONR’₂</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>RCN</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>alkene</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

Some Examples:

![Reductive Amination Reaction](image1)

**JACS 1995, 717, 11106**

![Reductive Reduction Reaction](image2)

**JACS 1995, 117, 558**

![Allylic Alcohol Reaction](image3)

**JACS 1998, 120, 6661**
Cyclic Ketones

AXIAL approach

EQUATORIAL approach

**Enantioselective Ketone Reductions**


- Chlorodiisopinocampheylborane, (-)-Ipc₂BCl, DIP-Cl

<table>
<thead>
<tr>
<th>reagent</th>
<th>axial</th>
<th>equitorial</th>
</tr>
</thead>
<tbody>
<tr>
<td>NaBH₄</td>
<td>14</td>
<td>86</td>
</tr>
<tr>
<td>LiAlH₄</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>L-Selectride</td>
<td>96.5</td>
<td>3.5</td>
</tr>
</tbody>
</table>

SMALL reagents prefer axial attack while LARGE reagents prefer equatorial attack.

These reactions are under kinetic control:

**Example:**

Oxazaborolidines: Itsuno-Corey System (“CBS” Reduction)


A broadly useful catalytic enantioselective reducing system.

Organolithium, Grignard, and Organocopper Reagents: Hard vs. Soft Nucleophiles

We saw previously that according to Frontier Molecular Orbital Theory, the most important interactions are between the HOMO of a nucleophile and the LUMO of an electrophile.

- **Hard nucleophiles** are characterized by a relatively low-energy HOMO. These react fastest with **hard electrophiles** which have high-energy LUMO’S. The large separation between the HOMO and LUMO makes these interactions more coulombic in nature and therefore typically involve charged species.

- **Soft nucleophiles** in contrast have a relatively high-energy HOMO. These react with **soft electrophiles** that have low-energy LUMO’s. Reactions of this type are therefore governed primarily by orbital overlap considerations.

Example:

The hydroxide ion is a **hard nucleophile**, because it has a charge, and because oxygen is a small, electronegative element. Accordingly, it reacts faster with a **hard electrophile** like a proton than with a soft electrophile like bromine. However, an alkene is a **soft nucleophile**, because it is uncharged and has a high-energy HOMO. Thus it reacts faster with a **soft electrophile** like bromine which has a low-energy LUMO.

\[
\text{HO}^- + \text{H}^+ \quad \text{is faster than} \quad \text{HO}^- + \text{Br}^-\text{Br}
\]

\[
\text{H}_2\text{C}=\text{CH}_2 + \text{H}^+ \quad \text{is slower than} \quad \text{H}_2\text{C}=\text{CH}_2 + \text{Br}^-\text{Br}
\]
**Hard vs. Soft (contd.)**

1,4-Addition Mechanism:

1. **Organolithium and Grignard Reagents**
   - Halide + Metal$^0$ (most common):
     \[ R-X + Mg^0 \rightarrow RMgX \]

   - Metal-Halogen Exchange:
     \[ R-I + ^3BuLi \rightarrow R-Li + ^3BuLi \rightarrow \text{RE} + ^3BuH + LiI \]

Reagent Synthesis

2. **Organocopper Reagents**
   - Organolithium + Copper(I) salt:
     \[ 2RLi + Cul \rightarrow R_2CuLi + LiI \]

If "R" is precious (note that only one R group gets transferred to the substrate) one can prepare "mixed" higher-order cuprates that utilize a non-transferable or "dummy" ligand (e.g. CN or 2-thiophenyl):

\[ RT-Li + CuCN \rightarrow RT-CuCN \]

where RT = transferable ligand

**Example:**

- **Organolithium and Grignard Reagents**
  - Haloide + Metal$^0$ (most common):
    \[ R-X + Mg^0 \rightarrow RMgX \]

  - Metal-Halogen Exchange:
    \[ R-I + ^3BuLi \rightarrow R-Li + ^3BuLi \rightarrow \text{RE} + ^3BuH + LiI \]

**Organ. Biomol. Chem. 2011, 9, 7671.**
Example:

\[
\begin{align*}
\text{Bu}_3\text{PCu} & \rightarrow \text{MeCO}_2\text{C}_8\text{H}_{11} \\
\text{then} & \\
\text{TBBSO} & \rightarrow \text{MeCO}_2\text{C}_8\text{H}_{11}
\end{align*}
\]

\[\text{JACS 1985, 107, 3348}\]

Some other organometallics to consider:

- Organochromium Reagents


\[\text{Enantioselective Organozinc Additions:}\]


Initial Report:

\[\text{PhCHO} + \text{Et}_2\text{Zn} \rightarrow \text{PhOH} 45\% \text{ee}\]

\[\text{TL 1984, 25, 2823}\]

Many examples in complex molecule synthesis:

See also Halichondrin: J. Am. Chem. Soc. 1992, 114, 3162.

- Organozinc Reagents
Alkyne Additions:

\[
\text{TMS-} + \text{CHO} \rightarrow \text{OH} \rightarrow \text{OH} \rightarrow \text{TMS}
\]

99% ee

(Carrera et al. JACS 2001 123, 9687)

Note: Carreira system reported to give no product.

How can you explain the result with no chiral ligand? And that the stereoselection is opposite for the following:

\[
\text{O} \rightarrow \text{OTBS} \rightarrow \text{Nu} \rightarrow \text{R}_S \rightarrow \text{R}_M
\]

95 : 5

L* = (R)-BINOL

10 : 90

L* = (S)-BINOL

60 : 40

L* = none


Diastereoselective Additions at CO.

- Cram proposed the earliest model to account for the diastereoselectivity obtained upon addition to a carbonyl group that contains a stereocenter at the \( \alpha \)-carbon.

- 90° approach of Nucleophile

- activated carbonyl is the largest group

- doesn’t consider torsional interactions between \( R \) and \( R_L \)


- Cornforth introduced a model to account for the stereochemistry observed with \( \alpha \)-chloroketones. Recently supported both experimentally and theoretically for additions of enolboranes to \( \alpha \)-alkoxy-aldehydes.

- 90° approach of Nucleophile

- activated carbonyl is the largest group

- net dipole is minimized

Cornforth, J.W.; Cornforth, R. H.; Mathew, K. K.; J. Chem. Soc. 1959, 112;

Evans, D. A.; Siska, S. J.; Cee, V. J. Angew. Chem. I. E. 2003, 42, 1761
Karabatsos introduced an alternative predictive model where the CO group eclipses either the C-R	extsubscript{L} bond or the C-R	extsubscript{M} bond

- 90° approach of Nucleophile
- activated carbonyl is the largest group
- product ratio is determined by the interaction of R	extsubscript{M} and O vs R	extsubscript{L} and O


- Felkin Noted that these models do not explain the effect of the R-group on selectivity

\[
\begin{align*}
\text{Ph} & \quad \text{R} \\
\text{LiAlH}_4 & \quad \text{Et}_2\text{O}
\end{align*}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{OH} \\
\text{R} & \quad \text{Ph} \\
R & = \text{Me} & 74:26 & \text{Et} & 76:24 & \text{i-Pr} & 83:17 & \text{i-Bu} & 98:2
\end{align*}
\]


- Felkin-Ahn Model:

- 90° approach of Nucleophile
- first model to consider torsional effects

Anh and Eisenstein computationally studied various conformation preferences and added:

- Burgi-Dunitz trajectory of attack
- places the best acceptor σ* (usually the large group) perpendicular to attack


The Felkin-Ahn Model does not accurately explain:

\[
\begin{align*}
\text{CHO} & \quad \text{O} \\
\text{Obn} & \quad \text{MeTiCl}_3 \\
\text{DCM}, -78 \degree \text{C} & \quad \text{92:8}
\end{align*}
\]

\[
\begin{align*}
\text{RO} & \quad \text{Ph} \\
\text{Me}_2\text{Mg} & \quad \text{THF}, -78 \degree \text{C} \\
R & = \text{Me} & >99:1 \\
R & = \text{TIPS} & 1:4
\end{align*}
\]
In 1959, Cram proposed a model to account for the addition of nucleophiles to α-hydroxy and α-amino compounds.

**Allyl Organometallic Additions**

Allyl organometallic reagents can react in one of two ways. Consider the following:

Most reagents give predominantly the γ-addition product via two different mechanisms:

a) For $M = B$, Ti, or Cr; The reaction proceeds via a “closed transition state”:

Cram, D. J.; Kopecky, K. R. *J. Am. Chem. Soc.* **1959** 81, 2748
b) For $M = \text{Si}$ or $\text{Sn}$, the reaction proceeds via an “open transition state” under Lewis acid (LA) catalysis:

\[
\text{RCHO} \xrightarrow{\text{LA}} \text{OLA} \xrightarrow{} \text{Si} \xrightarrow{} \text{OLA} \]

Reactions that proceed via a closed transition state are stereospecific, meaning that $E$-crotylation reagents give anti products while $Z$-crotylation products give syn.

\[
\text{E-Crotylborane reagents give anti-products via a closed T.S:}
\]

\[
\text{Z-Crotylborane reagents give syn-products via a closed T.S:}
\]
Reactions that proceed via an open transition state give predominantly syn products for both E and Z crotylation reagents.

**Chiral Reagents: Brown Allylation and Crotylation**


**Allylborane:**

\[
\begin{align*}
(+)-\text{Ipc}_2\text{BOMe} + \text{MgBr} & \rightarrow \text{B(Ipc)}_2 \\
(\text{Et}_2\text{O}, -78 \degree \text{C to rt.})
\end{align*}
\]

**E- and Z-crotylborane:**

\[
\begin{align*}
\text{E-} & : \text{n-BuLi, } t\text{-BuOK, THF} & \rightarrow & \text{B(Ipc)}_2 >97\% \text{E} \\
\text{Z-} & : \text{n-BuLi, } t\text{-BuOK, THF} & \rightarrow & \text{B(Ipc)}_2 >97\% \text{Z}
\end{align*}
\]
Some recent examples:

$$\text{BnO} \quad \text{O} \quad \text{CHO} \quad \text{BnO} \quad \text{O}$$

\[\begin{align*}
\text{BnO} & \quad \text{O} & \quad \text{CHO} & \quad \text{BnO} & \quad \text{O} \\
\text{then NaOH, H}_2\text{O}_2 & \quad \text{(85\%)}
\end{align*}\]

\text{dr} 8:1

\text{Org. Lett. 2011, 13, 4652–4655.}

\[\begin{align*}
\text{CHO} & \quad \text{OPMB} & \quad \text{OPMB} \\
\text{then NaOH, H}_2\text{O}_2 & \quad \text{(85\%)}
\end{align*}\]

\text{dr} 12:1

\text{Org. Lett. 2011, 13, 2722–2725.}

\[\begin{align*}
\text{TBSO} & \quad \text{CHO} & \quad \text{TBSO} \\
\text{then NaOH, H}_2\text{O}_2 & \quad \text{(70\%)}
\end{align*}\]

\text{dr} >10:1

\text{Synlett 2010, 107.}

Although the stereochemical outcome of the allylboration of aldehydes using $B$-allyldiisopinocampheylborane is typically reagent controlled, this selectivity may be challenged with certain substrates:

\[\begin{align*}
\text{H}_3\text{C} & \quad \text{O} & \quad \text{H}_3\text{C} \\
\text{Ph} & \quad \text{Ph} & \quad \text{Ph}
\end{align*}\]

\text{allylboration \quad \text{at} \quad -78 \degree \text{C}, \text{Et}_2\text{O}}

\text{(-)-ipc}_2\text{BAllyl} \quad \text{67 : 33}

\text{ (+)-ipc}_2\text{BAllyl} \quad \text{2 : 98}

\text{JOC 1987, 52, 319-320.}

How can you explain the different ratios above?

Note: Removal of the campheol byproduct can be problematic.
The Aldol Reaction: An Alternative to Crotylation for Propionate Synthesis.

Consider the following aldol reaction:

\[
\begin{align*}
R^1\text{CH}_3 & \rightarrow \text{LDA then} \\
& \rightarrow R^2\text{CHO}
\end{align*}
\]

How many possible stereoisomers can be formed? What needs to be controlled in order to select for a single stereoisomer?

1. Enolate Geometry:

\[
\begin{align*}
R^1\text{CH}_3 & \rightarrow \text{Base} \\
& \rightarrow R^1\text{Z-enolate} \quad \text{OR} \\
& \rightarrow E\text{-enolate}
\end{align*}
\]

2. Enolate Facial Selectivity:

Nature's Method:

[Chemical structures and reactions are shown, including enolate geometry and facial selectivity diagrams.]
3. Aldehyde Facial Selectivity

Consider a Z-enolate reacting via a closed transition state:

In general, Z-enolates give syn-propionate products while E-enolates give anti products.

- Z-enolates:

- E-enolates:

How do we control enolate geometry?

Recall the Ireland deprotonation model:

Depending on the nature of R, one can select for E or Z using LDA, although in practice a mixture is generally observed.

Example:
Boron Enolates

Formation of a boron enolate occurs in two steps, activation of the carbonyl followed by deprotonation with base:

\[
\begin{align*}
&\text{Formation of a boron enolate occurs in two steps, activation of the carbonyl followed by deprotonation with base:} \\
&\begin{align*}
&\text{R} - CH_3 &\xrightarrow{R_2BX} &\xrightarrow{\text{activation}} &\xrightarrow{\text{Base}} &\text{R} - CH_3 \\
&\text{Br} &\text{Cl} &\text{Et}_3N &\text{9-BBNOTf, i-Pr}_2\text{EtN} \\
&\text{Et} &79:21 &3:97 \\
&i-\text{Pr} &97:3 &12:88 \\
t-\text{Bu} &97:3 &90:10 \\
\end{align*}
\end{align*}
\]

What are the important orbital interactions during the activation step?

What is the purpose of the activation step?

Depending on the nature of the borane (BR₂X) and Base one can select for either the E or Z enolate:

Case Study: Enantioselective Aldol Reactions using chiral oxazolidinone auxiliaries:


Exclusive Z-enolate formation:

- Facial Selectivity:
Ch. 7 Alkene Synthesis.

1. Phosphorous-Based Methods

a) G. Wittig received the 1979 Nobel Prize in Chemistry for “many significant contributions to Organic Chemistry.” The Wittig reaction is arguably the most widely used alkene synthesis protocol, due in part to its predictable selectivity:

\[
\begin{align*}
\text{cis} & \quad \text{R}^* \quad \text{R}^*\text{CHO} & \quad \text{Ph}_3\text{P} & \quad \text{R}^*\text{CHO} & \quad \text{R}^*\text{CH}_2\text{R} \\
\text{trans} & \quad \text{For R = alkyl} & \quad \text{non-stabilized} & \quad \text{For R = CO}_2\text{R, CN, etc} & \quad \text{stabilized}
\end{align*}
\]


Some Examples:

- \(\text{TBSO}-\text{CHO}\) with \(\text{Ph}_3\text{P}=\text{CO}_2\text{Et}\)
- \(\text{OH}\) with \(\text{Ph}_3\text{P}=\text{CO}_2\text{Et}\)

Corey *JACS* 1969 91, 5675
The reaction involves addition of a phosphorous ylide to an aldehyde or ketone to generate a betaine intermediate that is in equilibrium with the corresponding oxaphosphetane:

\[
\begin{align*}
  \text{R}^\text{X} & \xrightarrow{\text{PPh}_3} \text{R}^\text{PPh}_3^- \text{Br}^- \\
  \text{H}_3\text{C}^- & \xrightarrow{\text{Base}} \text{R}^- \text{PPh}_3^- \\
  \text{O}^- & \xrightarrow{} \text{R'}^- + \text{PPh}_3^- 
\end{align*}
\]

(X = Br, I, Cl)

The Wittig reaction is thought to proceed via a “puckered” transition state.

The reaction of *non-stabilized ylids* to give *cis*-alkene products is under *kinetic control* while the reaction of *stabilized ylids* is under *thermodynamic control*. 
b) Horner-Wadsworth-Emmons Reaction.

Similar to the Wittig reaction, the HWE reaction involves phosphonate stabilized carbanions. The carbanion stabilizing group \( W \) is necessary for elimination to occur. Non-stabilized phosphonates give stable beta-hydroxyphosphonates.

\[
(RO)_2P\quad W \quad \text{Base then} \quad R'\text{CHO} \quad \rightarrow \quad R'\text{C} = \text{W}
\]

\( W = \text{CO}_2R, \text{C(O)R}, \text{CN}, \text{etc.} \)


Z-alkenes from the HWE: Stille-Gennari Modification


\[
(RO)_2P\quad \text{CO}_2\text{Me} \quad \text{Base then} \quad R'\text{CHO} \quad \rightarrow \quad R'\text{C} = \text{W} + \quad R'\text{C} = \text{W}
\]

<table>
<thead>
<tr>
<th>Base</th>
<th>( R' )</th>
<th>trans:cis</th>
</tr>
</thead>
<tbody>
<tr>
<td>( t)-BuOK</td>
<td>Me</td>
<td>5 : 2</td>
</tr>
<tr>
<td>KHMDS, 18-C-6</td>
<td>Me</td>
<td>8 : 1</td>
</tr>
<tr>
<td>( \text{K}_2\text{CO}_3 ), 18-C-6</td>
<td>( \text{CH}_2\text{CF}_3 )</td>
<td>1 : 6</td>
</tr>
<tr>
<td>KHMDS, 18-C-6</td>
<td>( \text{CH}_2\text{CF}_3 )</td>
<td>1 : 12</td>
</tr>
</tbody>
</table>

The electron withdrawing effects are presumed to decrease oxephosphetane lifetime and prevent equilibration.

The HWE reaction is particularly useful for macrocyclizations:

2. Sulfur-Based Methods: The Julia Olefination

Classically the reaction is carried out in two steps:
The mechanism for elimination is thought to proceed by first E2 elimination of the acyl group followed by single electron reduction of a vinyl sulfone:

\[
\begin{align*}
\text{H} & \text{SO}_2\text{Ph} \\
\text{R} & \text{OAc} \\
\text{R'} & \text{Na(Hg)} \\
\text{MeOH} & \\
\end{align*}
\]

Samarium diiodide (Sml₂) can be used for the elimination of benzoyloxy sulfones. This reaction involves first single-electron-transfer (SET) to the benzoyl group followed by elimination of the sulfone:

Consider the following chemoselective elimination:

\[
\begin{align*}
\text{BzO} & \text{SO}_2\text{Ph} \\
\text{O}:\text{SO}_2\text{Ph} & \text{O} \text{Bz} \\
\text{Sml₂, DMPU} & \xrightarrow{\text{THF, -78 °C}} \text{BzO} \\
& \text{SO}_2\text{Ph} \\
& \text{1h. (76\%)} \\
\end{align*}
\]


Manipulations at sulfur has led to the development of a one-step “modified Julia” reaction. These typically involve phenyltetrazole (PT) or benzothiazole (BT) sulfones.
Installation is typically via Mitsunobu displacement of the corresponding alcohol followed by oxidation:

\[
\text{MeO} \quad \text{OH} \quad \begin{array}{c}
\text{1. BTSH, DIAD} \\
\text{2. mCPBA}
\end{array} \quad \text{MeO} \quad \text{H} \quad \text{O} \quad \text{SO}_2 \text{BT}
\]


Mechanism:

While understanding and predicting the stereoselectivity of a modified Julia reaction can be challenging (see Blakemore ref. above), some generalizations can be made:

- PT-sulfones tend to be more stereoselective than BT.

\[
\text{SO}_2 \text{Ar} \quad \begin{array}{c}
\text{(Me}_3\text{Si)}_2\text{NK} \\
\text{Cy-C}_6\text{H}_1\text{CHO}
\end{array} \quad \text{THF} \quad \text{Ar = BT, 54 : 46} \quad \text{Ar = PT, 97 : 3}
\]

- BT-sulfones work best with \(\alpha,\beta\)-unsaturated aldehydes.

\[
\text{Tet. Lett. 2008, 49, 4145} \quad 75\%, E:Z = 95:5
\]

- Pyridine sulfones give predominantly the **cis**-alkene.

\[
\text{Tet. Lett. 2001, 42, 5149} \quad \text{E:Z} = 17:83
\]

Stereochemistry is determined upon sulfone addition to the carbonyl.

This is presumably the result of reversible carbonyl addition and an inability of the **anti** hydroxysulfone intermediate to undergo the Smiles rearrangement.
Ch. 8  Alkene Metathesis.

Olefin metathesis is one specific type of metathesis reaction:

- **Sigma bond metathesis**
  \[
  \text{R} - X + Y - R_1 \rightarrow \text{R} - R_1 + X - Y
  \]

- **Alkyne Metathesis**
  \[
  \text{R} - \equiv - R_1 + \equiv - R_1 \rightarrow \text{R} - \equiv - R_1 + \equiv - R_1
  \]

- **Enyne Metathesis**
  \[
  \text{R} - \equiv - R_1 + \equiv - R_2 \rightarrow \text{R} - \equiv - R_1 + \equiv - R_2
  \]

- **Alkene Metathesis**
  \[
  \text{R} - \equiv + \equiv - R_1 \rightarrow \text{R} - \equiv - R_1 + \equiv - \text{CH}_2 - \text{CH}_2
  \]

Historically, olefin metathesis was used in polymer chemistry Ti, W, Mo, and Ru catalysts with poor functional group tolerance.

**Ruthenium catalysts**: most widely used metathesis catalysts because of their relative air/moisture stability (can be handled without special precautions) and excellent functional group tolerance.

\[
\text{RuCl}_2(\text{PPh}_3)_3 + \text{Ph} - \equiv - \text{Ph} \rightarrow \text{Cl}_n - \text{Ru} = \equiv - \text{Ph} \]

\[
\text{L} = \text{PPh}_3 \quad = \text{P}(\text{i-Pr})_3 \quad = \text{PCy}_3
\]

**Schrock catalyst**

Schrock J. Am. Chem. Soc. 1988, 110, 1423

**Grubbs' 1st Generation Catalyst**


**Catalyst Initiation:**

- Electron-donating phoshines with large cone-angles increase catalyst activity \([\text{PCy}_3 > \text{P}(\text{i-Pr})_3 > \text{PPh}_3]\).
- Initiation is faster if \(R_1 = \text{Ar}\) compared to \(\text{CH} = \text{CPh}_2\).
- If \(R_1 = \text{electron-withdrawing (-COOR) or electron-donating (-OR, -SR, -NR}_2\)\), initiation is much slower.
**Types of Alkene Metathesis:**

*Olefin cross-metathesis*

\[ R\equiv CH_2 + H_2C\equiv R' \xrightarrow{\text{catalyst}} R\equiv R' + H_2C=CH_2 \]

*Ring-closing metathesis*

\[ \text{catalyst} \rightarrow \text{catalyst} + H_2C=CH_2 \]

*Ring-opening metathesis polymerization*

Note that each step in a metathesis reaction is reversible.

Recent investigations suggest that a pathway involving dissociation of one of the phosphine ligands is dominant:


"Caught in the act":

• Effect of Alkene Substitution:

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(E = CO₂Me)</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
</tr>
<tr>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
<td><img src="image5" alt="Image" /></td>
</tr>
<tr>
<td><img src="image6" alt="Image" /></td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
</tr>
<tr>
<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
<td><img src="image11" alt="Image" /></td>
</tr>
</tbody>
</table>


Reactions above performed using Grubbs’ second generation catalyst:

Tetrasubstituted alkenes:

![Image](image12)

Effect of Alkene Substitution:

- Tetrasubstituted alkenes:

\[
\text{RCM} \quad \text{H}_2\text{C} = \text{CH}_2 \quad \text{RCM} \quad \text{H}_2\text{C} = \text{CH}_2 (g)
\]

Recently there have been reports of performing metathesis reactions under slight vacuum to remove gaseous products.


• Effect of Ring Size: 5-, 6-, and 7-membered ring formations are generally straightforward, however larger rings can be challenging.

\[
\text{3 \text{ ROMP}} \quad \text{O}_{2007}, 9, 1339
\]

\[
\text{n} = 0, 1, 2, 3
\]

There is an entropic driving force for RCM with the generation of ethylene:
Conformational Requirements:

Grubbs' high dilution — oligomers


Polar functional groups are thought to provide an internal conformational bias for cyclization.

It is important however that this interaction not be too strong/stable:

diminished activity

Despite the challenges, there are many complex examples of large ring formation by ring-closing metathesis. Note the dense functionality in the following examples:

"Total Synthesis of Epothilone A" Nicolau et al.

"Total Synthesis of (-)-Dictyostatin" O'Neil and Phillips
2. **Cross-Metathesis.** Challenging due to the mixture of products that are possible:

Through the accumulation of data, alkenes can now be characterized in terms of their reactivity toward cross-metathesis:

<table>
<thead>
<tr>
<th>Type</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type I</strong></td>
<td>(fast homodimerization) terminal alkenes, allyl alcohols, styrenes, allyl-silanes, allyl-sulfides, protected allyl-amines</td>
</tr>
<tr>
<td><strong>Type II</strong></td>
<td>(slow homodimerization) Acrylates, vinyl ketones, acrolein, 3° / 2° allylic-alcohols, vinyl epoxides</td>
</tr>
<tr>
<td><strong>Type III</strong></td>
<td>(no homodimerization) 1,1-disubstituted alkenes, phenyl vinyl-sulfone, 4° allylic carbons, protected 3° allylic-alcohols</td>
</tr>
<tr>
<td><strong>Type IV</strong></td>
<td>(spectator to CM) vinyl nitro-olefins, trisubstituted allylic alcohols</td>
</tr>
</tbody>
</table>

**Statistically:**

\[
R\equiv + R_1\equiv \xrightarrow{Ru} R\equiv R_1\equiv
\]

<table>
<thead>
<tr>
<th>R:R₁</th>
<th>CM Selectivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>1:1</td>
<td>50%</td>
</tr>
<tr>
<td>2:1</td>
<td>66%</td>
</tr>
<tr>
<td>4:1</td>
<td>80%</td>
</tr>
<tr>
<td>10:1</td>
<td>91%</td>
</tr>
<tr>
<td>20:1</td>
<td>95%</td>
</tr>
</tbody>
</table>

This then allows for the design and execution of selective cross-metathesis reactions:

\[
\text{BzO} + \text{OAc} \xrightarrow{\text{GII}} \text{BzO} + \text{OAc} \quad \text{Type II} \quad 92\%
\]

\[
\text{Type I} \quad 1.0 \text{ eq} \quad 2.0 \text{ eq}
\]

\[
\text{Type III} \quad \text{OAc} \quad \text{OAc} \xrightarrow{\text{GII}} \text{OAc} \quad 91\%
\]

\[
\text{Type I} \quad \text{1.0 eq} \quad \text{1.0 eq}
\]

More recently, Z-selective cross-metathesis catalysts have been developed:

Hoveyda et al. Nature 2011, 471, 461

**Putting it all together:**

\[
\text{MO} + \text{OAc} \xrightarrow{\text{GII, C}_{2}H_{5} \text{SH}, 80^\circ C} \text{TIPS} \quad \text{then TscOH (87%)}
\]

\[
\text{(1 eq)}
\]

\[
\text{R} = \text{H} \quad \text{R} = \text{MOM}
\]

\[
\text{QL 2006 8, 2369}
\]