Enolate Formation and Reactivity

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MacMillan Group Meeting
March 12, 2008
Aspects of Enolates that will be Discussed

- (E) versus (Z) selectivity
- Enolate formation regioselectivity
- O vs. C alkylation
- Factors that influence $\pi$-facial selectivity

Aspects of Enolates that will NOT be Discussed

- Aldol reactions
- Chiral auxiliaries
- Chiral catalysts

Important references:

Carey & Sundberg, Advanced Organic Chemistry, Part B, Ch. 1
Ian Fleming, Frontier Orbitals and Organic Chemical Reactions
David A. Evans, Asymmetric Synthesis, Volume 3, Stereodifferentiating Additions Reactions, Part B
Primary literature cited within
(E) vs. (Z) Selectivity

• In the absence of a catalyst or auxiliary, enolate selectivity can be difficult to maintain.

• Rathke proposes an aldol addition-reversion process for ketone enolate equilibrium:

Sterics Affect Enolization by Lithium Amides

- Avoidance of a syn-pentane interaction in the transition state favors the (E)-enolate

Evans's 206 Notes, Lecture 24
Adaptation from Ireland, et al. JACS, 1976, 98, 2868.
Stereoelectronics Also Affect Enolization

Stereoelectronics Also Affect Enolization

Substantial stabilization of the electron density on the amide nitrogen leads to a significantly loose transition state, thus favoring the (Z)-enolate.

Enantioselective Alkylations of Tributyltin Enolates Catalyzed by a \{Cr(salen)\} Complex

\begin{align*}
\text{Me} & \quad \text{O} \quad \text{SnBu}_3 \\
\text{Et} & \quad \text{Me} & \rightleftharpoons & \quad \text{Me} & \quad \text{Et} + \quad \text{Me} & \quad \text{Me} \\
\text{Me} & \quad \text{Me} & \quad \text{Et} & \quad \text{Me} & \quad \text{Me} & \quad \text{Et} & \quad \text{Me} \\
1.8 & : & 1.0 & \quad \text{Me} & \quad \text{Et} & \quad \text{Me} & \quad \text{R}_3 \\
& & & 73-86\% \; \text{yield} & & & 76-81\% \; \text{ee} \\
\end{align*}

\begin{align*}
\text{Me} & \quad \text{O} \quad \text{SnBu}_3 \\
\text{nBu} & \quad \text{Me} & \rightleftharpoons & \quad \text{Me} & \quad \text{nBu} + \quad \text{Me} & \quad \text{Me} \\
\text{nBu} & \quad \text{Me} & \quad \text{nBu} & \quad \text{nBu} & \quad \text{Me} & \quad \text{Me} \\
1.5 & : & 1.0 & \quad \text{Me} & \quad \text{nBu} & \quad \text{Me} & \quad \text{R}_3 \\
& & & 77-97\% \; \text{yield} & & & 84-78\% \; \text{ee} \\
\end{align*}

• A variety of sp\(^3\) alkyl bromides and alkyl iodides used as electrophiles
• Enantioselectivity of disubstituted ketone product not limited by E/Z ratio of enolate isomers

Regioselectivity in Enolate Formation

• Kinetic vs. thermodynamic control

\[ \frac{[A]}{[B]} = \frac{k_a}{k_b} \]

Kinetic Control

• Product composition determined by relative rates of competing proton-abstraction reactions

• Deprotonation is rapid, quantitative, and irreversible.

• Favors less substituted enolate
Regioselectivity in Enolate Formation

• Kinetic vs. thermodynamic control

Thermodynamic Control

\[
\frac{[A]}{[B]} = K
\]

• Product composition determined by relative thermodynamic stability of the enolates.

• Favors more substituted enolate (Zaitzev’s Rule)
Kinetic vs. Thermodynamic Control

<table>
<thead>
<tr>
<th>base</th>
<th>temp</th>
<th>ratio (A/B)</th>
<th>control</th>
</tr>
</thead>
<tbody>
<tr>
<td>LiN(i-C₃H₇)₂</td>
<td>0 °C</td>
<td>99:1</td>
<td>kinetic</td>
</tr>
<tr>
<td>KN(SiMe₃)₂</td>
<td>-78 °C</td>
<td>95:5</td>
<td>kinetic</td>
</tr>
<tr>
<td>Ph₃ClLi</td>
<td>-78 °C</td>
<td>90:10</td>
<td>kinetic</td>
</tr>
<tr>
<td>Ph₃CK</td>
<td>25 °C</td>
<td>67:33</td>
<td>kinetic</td>
</tr>
<tr>
<td>Ph₃CK</td>
<td>25 °C</td>
<td>38:62</td>
<td>thermodynamic</td>
</tr>
<tr>
<td>NaH</td>
<td>25 °C</td>
<td>26:74</td>
<td>thermodynamic</td>
</tr>
<tr>
<td>Ph₃ClLi</td>
<td>25 °C</td>
<td>10:90</td>
<td>thermodynamic</td>
</tr>
</tbody>
</table>

**A-1, 3 Strain Controls Enolate Regioselectivity**

$$\text{TfO} \quad \text{H} \quad \text{HCN} \quad \text{NH}_2$$

$$\text{TsOH} \quad -40 ^\circ C$$

$$\text{50\%}$$

$$\text{H} \quad \text{Et} \quad \text{Me}$$

$$\text{H} \quad \text{Me}$$

$$\text{H} \quad \text{H}$$

$$\text{H} \quad \text{Me}$$

$$\text{0.98 equiv L-selectride}$$

$$\text{-78} ^\circ C \text{ to } 0 ^\circ C$$

$$\text{Ar} \quad \text{N} \quad \text{Ar} \quad \text{N}$$

$$\text{OTf}$$

$$\text{73\% yield}$$

A-1, 3 Strain Controls Enolate Regioselectivity

0.98 equiv L-selectride
-78 °C to 0 °C

**Enolates: Ambident Nucleophiles**

- Alkylation of an enolate can occur at either carbon or oxygen

\[
\text{R-} + \text{R'}X \rightarrow \text{R-} + \text{R'}X \rightarrow \text{C-alkylation}
\]

\[
\text{R} + \text{R'}X \rightarrow \text{OR'} \rightarrow \text{O-alkylation}
\]

- What factors influence the C/O-alkylation ratio?
Elements that Dictate O-Alkylation vs. C-Alkylation Ratios

- Dissociation vs. clustering of ions
  - Metal
  - Solvent
- Charge vs. Orbital Control
- Hard-soft compatibility
  - Leaving group
- Stereoelectronics
  - Orbital Overlap
Dissociated versus Aggregated Enolates

• O-alkylation is prevalent when the enolate is dissociated
• C-alkylation is prevalent where ion clustering occurs

O-Alkylation

• Prevalent in polar, aprotic solvents
• Metal chelators are effective additives

C-alkylation

• Favors smaller, harder cations due to tighter coordination
• Prevalent in protic & apolar solvents
• Ideal in THF & DME
Lithium, Sodium, and Potassium Enolates of Pinacolone
Examples of Ion Clustering

- Lithium enolate

- Sodium enolate

- Potassium enolate

**Dissociation vs. clustering of ions**

- O-alkylation is prevalent when the enolate is dissociated
- C-alkylation is prevalent where ion clustering occurs

\[
\begin{array}{c}
\text{Me} & \text{O} & \text{K} & \text{O} & \text{Et} \\
\text{EtO} & \text{SO}_3 & \text{EtO} & \text{Et} \\
\end{array}
\rightarrow
\begin{array}{ccc}
\text{Me} & \text{O} & \text{Et} & \text{OEt} \\
\text{Me} & \text{Et} & \text{Et} & \text{OEt} \\
\text{Me} & \text{OEt} & \text{Et} & \text{OEt} \\
\end{array}
\]

<table>
<thead>
<tr>
<th>solvent</th>
<th>A (%)</th>
<th>B (%)</th>
<th>C (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HMPA</td>
<td>15%</td>
<td>2%</td>
<td>83%</td>
</tr>
<tr>
<td>t-BuOH</td>
<td>94%</td>
<td>6%</td>
<td>0%</td>
</tr>
<tr>
<td>THF</td>
<td>94%</td>
<td>6%</td>
<td>0%</td>
</tr>
</tbody>
</table>

- HMPA promotes ion dissociation, favoring O-alkylation
- THF promotes ion clustering, favoring C-alkylation
- t-BuOH hydrogen-bonds with enolate anion, favoring C-alkylation

Using MO Theory to Understand Charge vs. Orbital Control

\[ \psi_3 \quad \begin{array}{c}
\text{LUMO}
\end{array} \]

\[ \psi_2 \quad \begin{array}{c}
\text{HOMO}
\end{array} \]

\[ \psi_1 \quad \begin{array}{c}
\text{orbital}
\end{array} \]
Using MO Theory to Understand Charge vs. Orbital Control

Charge control
- Reaction occurs at the atom carrying the highest total electron density
- Predominant with charged electrophiles (e.g., $H^+$)

Using MO Theory to Understand Charge vs. Orbital Control

Charge control
- Reaction occurs at the atom carrying the highest total electron density
- Predominant with charged electrophiles (e.g., H⁺)

Orbital control
- Reaction occurs at the atom whose frontier electron density is the highest
- Predominant with neutral electrophiles with relatively low-lying LUMOs

**Hard-Soft Acid Base Interactions**  
*(Leaving-Group Effects)*

*O-alkylation (charge control)*

- Predominant with hard leaving groups
- Favored by an early transition state, where charge distribution is the most important factor
- Favored by conditions that afford a dissociated, more reactive enolate

*C-alkylation (orbital control)*

- Predominant with soft leaving groups
- Favored by a later transition state, where partial bond formation is the dominant factor
- More stable than the O-alkylation product

\[
E (C=O + C-C) > E (C=C + C-O) \\
(745 + 347) \text{ kJ/mol} > (614 + 358) \text{ kJ/mol} \\
1097 \text{ kJ/mol} > 972 \text{ kJ/mol}
\]

*Bond energy values taken from Zumdahl, Chemical Principles, 5th ed.*
Nature of the Leaving Group

- Of the two nucleophilic sites on the enolate, oxygen is harder than carbon

\[
\text{Me}\text{C}═\text{C}═\text{OEt} + \text{EtX} \xrightarrow{\text{HMPA}} \text{Me}\text{C}═\text{C}═\text{OEt} \quad \text{A}
\]

\[
\text{Me}\text{C}═\text{C}═\text{OEt} + \text{EtCl} \xrightarrow{\text{HMPA}} \text{Me}\text{C}═\text{C}═\text{OEt} \quad \text{B}
\]

\[
\text{Me}\text{C}═\text{C}═\text{OEt} + \text{EtI} \xrightarrow{\text{HMPA}} \text{Me}\text{C}═\text{C}═\text{OEt} \quad \text{C}
\]

<table>
<thead>
<tr>
<th>X</th>
<th>A</th>
<th>B</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>OTs</td>
<td>11%</td>
<td>1%</td>
<td>88%</td>
</tr>
<tr>
<td>Cl</td>
<td>32%</td>
<td>8%</td>
<td>60%</td>
</tr>
<tr>
<td>Br</td>
<td>38%</td>
<td>23%</td>
<td>39%</td>
</tr>
<tr>
<td>I</td>
<td>71%</td>
<td>16%</td>
<td>13%</td>
</tr>
</tbody>
</table>

- **Hard**---OTs > Cl > Br > I---**Soft**

- Greater O-alkylation is observed with harder electrophiles
- Greater C-alkylation is observed with softer nucleophiles

Orbital Overlap
(Baldwin's Suggestions)

• For enolate cyclizations, orbital overlap is imperative
• Oxygen and carbon sites on the enolate have different hybridizations
• Hybridization can have drastic effect on atom reactivity

Elements that dictate enolate $\pi$-facial selectivity

• Intraannular Chirality Transfer
  Asymmetric center is connected to the enolate framework through cyclic array of covalent bonds.

• Extraannular Chirality Transfer
  Chiral moiety is not conformationally locked at $\geq$2 more contact points via covalent bonds to enolate

• Chelate-Enforced Intraannular Chirality Transfer
  Chelate provides organizational role in fixing orientation between resident asymmetric center and enolate system.

Intraannular Chirality Transfer
(Endocyclic Enolates)

Intraannular Chirality Transfer

• Lactone affords only (E)-enolate
• Ring shields one face of the formed enolate

\[
\text{Me} \quad \xrightarrow{\text{LDA}} \quad \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{H} \\
\text{O} \\
\text{H} \\
\text{O} \\
\text{Me} \\
\end{array}
\]

back face of enolate shielded by ring

\[
\text{Me} \quad \xrightarrow{\text{MeI}} \quad \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{H} \\
\text{O} \\
\text{H} \\
\text{O} \\
\text{Me} \\
\end{array}
\]

\text{major product}

• Syn-pentane interactions discourage transition state necessary for forming trans product

\[
\text{Me} \quad \xrightarrow{\text{LDA}} \quad \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{H} \\
\text{O} \\
\text{H} \\
\text{O} \\
\text{Me} \\
\end{array}
\]

\text{syn-pentane interaction}

\[
\text{Me} \quad \xrightarrow{\text{MeI}} \quad \begin{array}{c}
\text{Me} \\
\text{O} \\
\text{H} \\
\text{O} \\
\text{H} \\
\text{O} \\
\text{Me} \\
\end{array}
\]

\text{minor product}

Extraannular Chirality Transfer
(Exocyclic Enolates)

• A-1, 3 strain dictates conformation of the imidazolate
• Bulky phenyl group directs alkylation toward Re face

Chelation Affects Pi Facial Selectivity

Summary

• Enolate formation

• (E) vs. (Z) selectivity (sterics, electronics)

• Regioselectivity (thermodynamics vs. kinetics, sterics)

• Enolate Reactivity

• O vs. C alkylation (dissociation vs. clustering of ions, charge vs. orbital control, hard-soft interactions, orbital overlap)

• Pi facial selectivity (intraannular chirality transfer, extraannular chirality transfer, chelation)