Enolates:
- well established nucleophiles
- some consider one of the “backbones of organic synthesis”

Epoxides:
- well established electrophiles (polar, strained ring)
- many ways to make enantioselectively (Sharpless, Shi, Jacobsen, etc.)

And yet...

“In spite of their intrinsic synthetic potential, addition reactions of metal enolates of non-stabilized esters, amides, and ketones to epoxides are not widely used in the synthesis of complex molecules.”

- Paolo Crotti and Mauro Pineschi
Aziridines and Epoxides in Organic Synthesis

Things to keep in mind:
- Ketone and ester enolate alkylations of epoxides often require various additives, whereas standard amide enolates (more stable, more nucleophilic) and malonic enolates tend to readily undergo alkylation.
- Ketone enolates can equilibrate, and ester enolates can fragment to ketenes/alkoxides.
- Stable enolate = good alkylation

General Scheme

Some good reviews:
Tetrahedron, 2000, 56, 9, 1149-1163.
Aziridines and Epoxides in Organic Synthesis
edited by Andrei K. Yudin

Malonate

Oldest reported enolate alkylation of epoxides:

J. Am. Chem. Soc. 1942, 64, 11, 2606–2610

Cyclobutane formation:


Lactam formation:

Tet. Lett. 1995, 36, 14, 2487–2490

See also: Chem. Lett. 1983, 169-172
Tetrahedron 1996, 52, 29, 9909–9924
**Industry Adventures with Malonates**

Peptide analog synthesis:
- can access all 8 stereoisomers
- facile R group variability

1. Me$_3$SiCH$_2$MgCl
2. BF$_3$·OEt$_2$
3. Boc$_2$O
4. mCPBA or MMPP

**Epoxide Synthesis**
- retention of stereo.
- separable diast.

**Merck**

L-685,434 Analogs
HIV protease inhibitors


**can equilibrate undesired diastereomer with base**
Enolate Alkylation of Epoxides

Abbott

A-792611
HIV Protease Inhibitor

BocHN
Bn

O

EtO

O

BocHN
Bn

O

O

CO

2

Et

78% yield
1:1 d.r.

NaOEt
EtOH, 0 °C

BocHN
Bn

O

O

CO

2

Et

5:1 d.r.

82% yield
over 2 steps

97:3 d.r.
recrystallization

Ketones

Early work: imine salt workaround

CH3
OTMS

M = Li, MgBr

“low to moderate yields”

CH3
O

N

Cy

M = Li, MgBr

then

HOAc

75% yield


Seminal report: Schreiber’s total synthesis of (±)-recifeiolide

CH3

LDA

EtOH, 0 °C

Me

80% yield
96% brsm

J. Am. Chem. Soc. 1980, 102, 6163-6165

(±)-recifeiolide
**Enolate Alkylation of Epoxides**

First published method: Paolo Crotti’s time to shine

\[
\text{O}_2\text{Li}\xrightarrow{\text{LHMDS, THF}} \text{O}_2\text{Li}^+\text{R_1}
\]

\[
\text{HO}_\text{R_2} \xrightarrow{\text{LiClO}_4, \text{THF}} \text{HO}_\text{R_1}\text{R_2} \quad 24-72 \text{ h, 25-50°C}
\]

<table>
<thead>
<tr>
<th>Epoxide</th>
<th>R_1</th>
<th>Additive</th>
<th>α attack %</th>
<th>β attack %</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>tBu</td>
<td>LiClO_4</td>
<td>&lt;1</td>
<td>&gt;99</td>
<td>98</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>LiClO_4</td>
<td>&lt;1</td>
<td>&gt;99</td>
<td>86</td>
<td></td>
</tr>
<tr>
<td>tBu</td>
<td></td>
<td></td>
<td></td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>LiClO_4</td>
<td>&lt;1</td>
<td>&gt;99</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>tBu</td>
<td>LiClO_4</td>
<td>&lt;1</td>
<td>&gt;99</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>tBu</td>
<td></td>
<td>&lt;1</td>
<td>&gt;99</td>
<td>30</td>
<td></td>
</tr>
<tr>
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<td>&lt;1</td>
<td>&gt;99</td>
<td>76</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td></td>
<td>&lt;1</td>
<td>&gt;99</td>
<td>15</td>
<td></td>
</tr>
<tr>
<td>tBu</td>
<td>LiClO_4</td>
<td>9</td>
<td>91</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>tBu</td>
<td></td>
<td>9</td>
<td>91</td>
<td>30</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td>LiClO_4</td>
<td>12</td>
<td>88</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>Ph</td>
<td></td>
<td></td>
<td></td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

Crotti later discovers that Y(OTf)_3 promotes reaction in almost quantitative yields with milder, shorter reaction conditions (0°C - r.t., 18 hr).

- Same substrate scope has yields (80-99%).
- Worse α:β selectivity observed w/ styrene oxide

\( R_1 = \text{tBu} - 40:60, R_1 = \text{Ph} - 85:15 \)

“But wait - there’s more!” -Crotti, probably

\[
\text{R_1} \text{O}_\text{Li} \xrightarrow{\text{LHMDS, THF}} \text{LiO}\text{R_2} \xrightarrow{[M]\text{ cat.}} \text{HO}_\text{R_1}\text{R_2}
\]

Superior catalyst was determined to be 10 mol % Sc(OTf)_3 (78-95% yield).

Unfortunately, method has poor diastereoselectivity.

Slight syn preference - best syn:anti w/ Y(OTf)_3 60:40.

Other catalysts screened:

\[ Y(OTf)_3, Ti(Cp_2)(OTf)_2, Zr(Cp)_2(OTf)_2, Ph_4SbOTf, Yb(camph)_3 \]

Moral of the story:

- Lewis acids allow for milder epoxide enolate alkylation conditions.
Intramolecular Ketone Enolate Alkylation

4,5-epoxy ketone

\[
\text{Ph} \quad \text{O} \quad \text{R} \\
\text{O} \quad \text{C} \quad \text{Ph} \quad \text{R} \\
\text{O} \quad \text{C} \quad \text{Ph} \quad \text{R} \\
\text{LHMDS} \quad \text{Sc(OTf)}_3 \quad 20 \text{ mol}\% \\
\text{Ph} \quad \text{O} \quad \text{Li} \quad \text{Ph} \quad \text{R} \\
\text{O} \quad \text{C} \quad \text{Ph} \quad \text{R} \\
\text{O} \quad \text{C} \quad \text{Ph} \quad \text{R} \\
\text{Sc(OTf)}_3 \\
\text{Ph} \quad \text{R} \quad \text{OH} \\
\text{R} \quad \text{Yield} \\
\text{H} \quad 94\% \\
\text{Me} \quad 86\% \\
\]

6,7-epoxy ketone

\[
\text{Ph} \quad \text{O} \quad \text{R} \\
\text{O} \quad \text{C} \quad \text{Ph} \quad \text{R} \\
\text{O} \quad \text{C} \quad \text{Ph} \quad \text{R} \\
\text{LHMDS} \quad \text{Sc(OTf)}_3 \\
\text{Ph} \quad \text{O} \quad \text{Li} \quad \text{Ph} \quad \text{R} \\
\text{O} \quad \text{C} \quad \text{Ph} \quad \text{R} \\
\text{O} \quad \text{C} \quad \text{Ph} \quad \text{R} \\
\text{Sc(OTf)}_3 \\
\text{Ph} \quad \text{R} \quad \text{OH} \\
\text{R} \quad \text{Yield} \\
\text{H} \quad 98\% \quad 84:12 \\
\text{Me} \quad 92\% \quad 80:0 \\
\]

*with 5,6 epoxy ketones, reaction described as “unexpectedly inefficient” yielding only a complex mixture of products

Stereochemical studies:

Syn diastereomer = kinetic product. Equilibrating pure syn or anti product with KOH at r.t. for 2 days gives 2:3 ratio of syn:anti diastereomers. Use of NaHMDS instead of LHMDS increases yield but severely diminishes diastereoselectivity.

Use of enones over ketones improves stereoselectivity.

A modern building block

\[
\text{O} \\
\text{1. LiHMDS, THF, DME}  \\
\text{2. BF}_3 \cdot \text{OEt}_2, \quad \text{-78 °C, 0.5 hr} \\
\text{80% yield 89:11 dr} \\
\]

Tetrahedron. 1999, 55, 18, 5853-5866

"A modern building block"
**Enolate Alkylation of Epoxides**

**Enones**

1. LiSnMe$_3$
2. O

-78 °C, 5 min

50% overall yield

**Esters**

Aluminum enolates enable this transformation.

```
\[ \text{OLi} \quad \text{O} \quad \text{Et}_2\text{AlCl} \quad \text{PhMe, r.t.} \quad 12 \text{ hr} \]
```

8% yield

```
\[ \text{OLi} \quad \text{O} \quad \text{Et}_2\text{AlCl} \quad \text{PhMe, –40 °C to r.t.} \quad 6 \text{ hr} \]
```

68% yield

**Monocyclic epoxides - Stephen Taylor**

Three Step Total Synthesis of (±)-Phoracantholide

```
\[ \text{O} \quad \text{LiSnMe}_3 \quad \text{BF}_3\cdot\text{OEt}_2 \quad \text{–78 °C, 1 hr} \]
```

```
\[ \text{O} \quad \text{H}_2 \cdot \text{(Ph}_3\text{P)}_3\text{RhCl} \quad \text{Me} \]
```

(±)-phoracantholide

45% yield

**Table**

<table>
<thead>
<tr>
<th>R</th>
<th>Base</th>
<th>R'</th>
<th>Yield$^a$</th>
<th>syn:anti</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>LDA</td>
<td>Me</td>
<td>46</td>
<td>–</td>
</tr>
<tr>
<td>H</td>
<td>LDA</td>
<td>Et</td>
<td>52</td>
<td>–</td>
</tr>
<tr>
<td>H</td>
<td>LDA</td>
<td>t-Bu</td>
<td>49</td>
<td>–</td>
</tr>
<tr>
<td>Me</td>
<td>LDA</td>
<td>Me</td>
<td>56 (70$^b$)</td>
<td>84:16</td>
</tr>
<tr>
<td>Me</td>
<td>LDA</td>
<td>Et</td>
<td>43</td>
<td>84:16</td>
</tr>
<tr>
<td>Me</td>
<td>LDA</td>
<td>i-Pr</td>
<td>56</td>
<td>88:12</td>
</tr>
<tr>
<td>Me</td>
<td>LDA</td>
<td>t-Bu</td>
<td>38</td>
<td>95:5</td>
</tr>
<tr>
<td>H</td>
<td>LHMDS</td>
<td>Me</td>
<td>58 (66$^b$)</td>
<td>–</td>
</tr>
<tr>
<td>H</td>
<td>LHMDS</td>
<td>Et</td>
<td>71</td>
<td>–</td>
</tr>
<tr>
<td>H</td>
<td>LHMDS</td>
<td>t-Bu</td>
<td>54</td>
<td>–</td>
</tr>
<tr>
<td>Me</td>
<td>LHMDS</td>
<td>Me</td>
<td>12</td>
<td>56:44</td>
</tr>
<tr>
<td>Me</td>
<td>LHMDS</td>
<td>Et</td>
<td>28</td>
<td>62:38</td>
</tr>
</tbody>
</table>

$^a$ Distilled yields.
$^b$ GC yields.

*<1% product w/o Et$_2$AlCl
Monocyclic epoxides cont.

**Other lessons learned:**
- Low temp. minimizes Claisen condensation products
- Al NOT activating epoxide (no Markovnikov product)
- N of LHMDS coordinates less strongly to Al as LDA
- HMPA cosolvent presumed to coordinate with Al; does not improve selectivity with LHMDS
- α-substitution of ester has higher yields w/ LDA, but no α-substitution has higher yields w/ LHMDS

**E enolate predominates**

**syn preference**

J. Org. Chem. 1993, 58, 7304-7307

**Oxazolidinones**

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

1. KHMDS
2. Lewis acid
3. 

<table>
<thead>
<tr>
<th>Lewis Acid</th>
<th>Equiv</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>TiCl₄</td>
<td>3.3</td>
<td>0%</td>
</tr>
<tr>
<td>Bu₂BOTf</td>
<td>2.2</td>
<td>0%</td>
</tr>
<tr>
<td>BF₃·OEt₂</td>
<td>2.2</td>
<td>29%</td>
</tr>
<tr>
<td>Me₃Al</td>
<td>2.1</td>
<td>46%</td>
</tr>
<tr>
<td>Et₂AlCl</td>
<td>1.1</td>
<td>36%</td>
</tr>
<tr>
<td>Et₂AlCl</td>
<td>2.1</td>
<td>69%</td>
</tr>
<tr>
<td>Et₂AlCl</td>
<td>3.1</td>
<td>49%</td>
</tr>
</tbody>
</table>

Tet. Lett. 1994, 35, 48, 8977-8980

**Spirocyclic Lactone Synthesis**

\[
\begin{align*}
\text{OAIEt₂} & \quad \text{Me} \\
\text{OtBu} & \quad \text{CO₂Me} \\
\text{TsoH} & \quad \text{OTBDPS}
\end{align*}
\]

Only product (trace) was intermolecular Claisen condensation product.
Halohydrin formation observed with AlCl₃ and TiCl₄.
Enolate Alkylation of Epoxides

Amides

Early reports

1. NaNH$_2$/NH$_3$
2. LDA

MeO
Me

Et
N
Me

MeO

1. NaNH$_2$/NH$_3$
2. LDA

MeO

Me

1. NaNH$_2$/NH$_3$
2. LDA

MeO

1. NaNH$_2$/NH$_3$
2. LDA

MeO

‘Activated’ amides with HMPA

in situ lactonization

4 M HCl

80-90% yield

Secondary amides and a Lewis acid assist

Lewis Acid

<table>
<thead>
<tr>
<th>Lewis Acid</th>
<th>BF$_3$·OEt$_2$</th>
<th>SnCl$_4$</th>
<th>TiCl$_4$</th>
<th>Et$_2$AlCl</th>
<th>none</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yield</td>
<td>80%</td>
<td>64%</td>
<td>61%</td>
<td>53%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Synth. Commun. 1988, 18, 1159-1165

Diastereoselectivity improves with bulky epoxides and amides.
...and a very quick solvent “screen.”

Best yields observed with 1- and 1,1-substituted epoxides.

J. Org. Chem. 1977, 42, 10, 1688–1690


Myers: diastereoselectivity with pseudoephedrine amide enolates

A Remarkable Epoxide Opening. An Expeditious Synthesis of Vernolepin and Vernomenin

First time the ‘Danishefsky diene’ was used by the group.
Danishefsky cont. - oxygen directing groups

Syn oxy-functionality

\[
\begin{array}{ccc}
\text{OR} & \text{O} & \text{OR} \\
\xrightarrow{55 \, ^\circ \text{C}, 15 \, \text{hr}} & & \xrightarrow{55 \, ^\circ \text{C}, 15 \, \text{hr}} \\
\text{A} & \text{B} \\
\end{array}
\]

Ants oxy-functionality

\[
\begin{array}{ccc}
\text{OR} & \text{O} & \text{OR} \\
\xrightarrow{55 \, ^\circ \text{C}, 15 \, \text{hr}} & & \xrightarrow{55 \, ^\circ \text{C}, 15 \, \text{hr}} \\
\text{A} & \text{B} \\
\end{array}
\]

Dianion openings are affected by alpha-oxy-functionality, not by relative stereochemistry.

Spirecyclic lactone synthesis

Model System

\[
\begin{array}{ccc}
\text{Me} & \text{Me} & \text{Me} \\
\xrightarrow{\text{THF}} & \xrightarrow{40 \, ^\circ \text{C}, 18 \, \text{hr}} & \xrightarrow{91\% \, \text{yield}} \\
\text{A} & \text{B} & \\
\end{array}
\]

- HMPA did not improve yields or reaction homogeneity
- Acidic workup yields lactone
- Dianions can have solubility problems (large excess often used)

\[
\begin{array}{ccc}
\text{R} & \text{A : B} \\
\text{H} & 3 : 1 \\
\text{TMS} & 1 : 3.2 \\
\end{array}
\]