Carbon- Carbon Bond Formation

1. Alkylation of enolates, enamines and hydrazones
   C&S: Chapt. 1, 2.1, 2.2  problems Ch 1: 1; 2; 3, 7; 8a-d; 9; 14  Ch. 2: 1; 2; 4)
   Smith: Chapt. 9
2. Alkylation of heteroatom stabilized anions  C&S: Chapt. 2.4 - 2.6)
3. Umpolung  Smith: Chapt. 8.6
4. Organometallic Reagents
   C&S: Chapt. 7, 8, 9  problems ch 7: 1; 2; 3, 6; 13  Ch. 8: 1; 2
   Smith: Chapt. 8
5. Sigmatropic Rearrangements . C&S Chapt. 6.5, 6.6, 6.7 # 1e,f,h,op
   Smith Chapt. 11.12, 11.13


- $\alpha$-deprotonation of a ketone, aldehyde or ester by treatment with a strong non-
  nucleophilic base.
- carbonyl group stabilizes the resulting negative charge.

- Base is chosen so as to favor enolate formation. Acidity of C-H bond must be greater
  (lower $\text{pK}_a$ value) than that of the conjugate acid of the base (C&S table 1.1, pg 3)

\[
\begin{align*}
\text{MeO}^- & : \text{pK}_a = 15 \\
\text{tBuO}^- & : \text{pK}_a = 19 \\
\text{unfavorable enolate concentration} \\
\text{H}_3\text{C} & \text{OEt} \ : \text{pK}_a = 10 \\
\text{more favorable enolate concentration}
\end{align*}
\]

- Common bases: NaH, EtONa, tBuOK, NaNH$_2$, LiNiPr$_2$, M N(SiMe$_3$)$_2$, Na CH$_2$S(O)CH$_3$

Enolate Formation:
- H$^+$ Catalyzed (thermodynamic)

\[
\begin{align*}
\text{H}_3\text{C} & \text{OCH}_3 \quad \text{MeO}^- \quad \text{pK}_a = 20 \\
\text{H}_3\text{C} & \text{CH}_3 \quad \text{tBuO}^- \quad \text{pK}_a = 19 \\
\text{more favorable enolate concentration}
\end{align*}
\]


- Kinetic enolate- deprotonation of the most accessible proton (relative rates of
  deprotonation). Reaction done under essentially irreversible conditions.
typical conditions: strong hindered (non-nucleophilic) base such as LDA

\[ R_2NH \text{ pKa} \approx 30 \]

Ester Enolates - Esters are susceptible to substitution by the base, even LDA can be problematic. Use very hindered non-nucleophillic base (Li isopropylcyclohexyl amide)

- Thermodynamic Enolate - Reversible deprotonation to give the most stable enolate: more highly substituted C=C of the enol form

typical conditions: RO⁻ M⁺ in ROH, protic solvent allows reversible enolate formation. Enolate in small concentration (pKa of ROH = 15-18 range)

- note: the kinetic and thermodynamic enolate in some cases may be the same
- for α,β-unsaturated ketones

Trapping of Kinetic Enolates
- enol acetates

\[ \text{Ph} \stackrel{1) \text{NaH, DME}}{\longrightarrow} \text{Ph} \stackrel{2) \text{Ac}_2\text{O}}{\longrightarrow} \text{Ph} \]

Regiochemically pure enolates
- silyl enolethers

\[
\text{Ph} \quad \text{O} \\
\text{1) LDA} \\
\text{2) Me}_3\text{SiCl}
\]

\[
\begin{align*}
\text{Ph} & \quad \text{OTMS} \\
\text{isotatable separate & purify}
\end{align*}
\]

\[
\text{CH}_3\text{Li, THF} \\
\text{or-} \\
\text{Bu}_2\text{NF} \quad \text{or-} \quad \text{TiCl}_4
\]

Geometrically pure enolates

- tetraalkylammonium enolates- "naked" enolates
- TMS silyl enol ethers are labile: can also use Et\text{3Si}-, iPr\text{3Si}- etc.
- Silyl enol ether formation with R\text{3SiCl}+ Et\text{3N} gives thermodyanic silyl enol ether

- From Enones

- From conjugate (1,4-) additions

- From reduction of α-halo carbonyls

\[
\text{Alkylation of Enolates} \quad \text{(condensation of enolates with alkyl halides and epoxides)}
\]


1° alkyl halides, allylic and benzylic halides work well
2° alkyl halides can be troublesome
3° alkyl halides don’t work
- Rate of alkylation is increased in more polar solvents (or addition of additive)

Mechanism of Enolate Alkylation: SN2 reaction, inversion of electrophile stereochemistry

Alkylation of 4-t-butylcyclohexanone:

on cyclohexanone enolates, the electrophile approaches from an "axial" trajectory. This approach leads directly into a chair-like product. "Equitorial approach leads to a higher energy twist-boat conformation.

Alkylation of α,β-unsaturated carbonyls
Stork-Danheiser Enone Transposition:
- overall $\gamma$-alkylation of an $\alpha,\beta$-unsaturated ketone

\[
\begin{align*}
\text{LDA, PhSHCl} & \quad \text{PhOCH₂Cl} \quad \text{CH₃Li} \quad \text{H₂O⁺} \\
\text{major product} \quad (96:4) & \quad \text{(96:4)}
\end{align*}
\]

Chiral enolates- Chiral auxilaries.
*Asymmetric Synthesis* 1984, 3, 1.
- N-Acyl oxazolidinones

\[
\begin{align*}
\text{LDA, THF, Et-I} & \quad \text{LiOH, H₂O, THF} \\
\text{major product} \quad (96:4) & \quad \text{(96:4)}
\end{align*}
\]

Complimentary Methods for enantiospecific alkylations
Diastereoselectivity: 92 - 98 % for most alkyl halides


\[
\begin{align*}
\text{NaN(SiMe₃)₂, THF, -78°C} & \quad \text{LDA, THF} \\
\text{(88 - 98 % de)} & \quad \text{(94 - 98 % de)}
\end{align*}
\]
diastereoselectivities on the order of 50 : 1

Asymmetric Acetate Aldol

Chiral lithium amide basess
Lewis Acid Mediated Alkylation of Silyl Enolethers- SN1 like alkylations

**OTMS**

\[
\begin{align*}
\text{OTMS} & \xrightarrow{\text{tBu-Cl, TiCl}_4, \text{CH}_2\text{Cl}_2, -40^\circ\text{C}} \text{CH}_3 \xrightarrow{\text{Note: alkylation with a 3° alkyl halide}} \text{C(CH}_3)_3 \\
\text{OTMS} & \xrightarrow{\text{SPh, TiCl}_4, \text{CH}_2\text{Cl}_2, -40^\circ\text{C}} \text{R} \xrightarrow{\text{Raney Ni}} \text{O} \\
\end{align*}
\]

(79%) (95%)


- Advantages: mono-alkylation, usually gives product from kinetic enolization

\[
\begin{align*}
\text{enamine} & \xrightarrow{\text{H}^+, (-\text{H}_2\text{O})} \text{enamine} \\
\text{enamine} & \xrightarrow{\text{R-I}} \text{ene} \xrightarrow{\text{H}_2\text{O}} \text{ene} \\
\end{align*}
\]

-Chiral enamines

**Imines** Isoelectronic with ketones

\[
\begin{align*}
\text{Imine} & \xrightarrow{\text{LDA, THF, -20°C}} \text{Imine} \\
\text{Imine} & \xrightarrow{1) \text{E} \quad 2) \text{H}_2\text{O}^+} \text{ene} \\
\end{align*}
\]

E = -CH(CH}_3, -Et, Pr, PhCH_2, allyl-

ee 87 - 99 %
- Hydrazone anions are more reactive than the corresponding ketone or aldehyde enolate.
- Drawback: can be difficult to hydrolyze.

Aldol Condensation

- The effects of the counterion on the reactivity of the enolates can be important
  Reactivity Li⁺ < Na⁺ < K⁺ < R₄N⁺ addition of crown ethers
- The aldol reaction is an equilibrium which can be "driven" to completion.

\[
\text{RC} \cdots O' \cdot M^+ + \text{RCHO} \leftrightarrow \text{H} \cdots \text{R} \cdots \text{R}' \cdots \text{O} \cdot M^+ \quad \text{work-up} \quad \xrightarrow{} \quad \text{HO} \cdots \text{R} \cdots \text{R}'
\]

In the case of hindered enolates, the equilibrium favors reactants. Mg\(^{2+}\) and Zn\(^{2+}\) counterions will stabilize the intermediate \(\beta\)-alkoxycarbonyl and push the equilibrium towards products. \(\text{(JACS 1973, 95, 3310)}\)

\[
\begin{align*}
\text{PhCHO, THF} & \quad \xrightarrow{\text{PhCHO, THF}} \\
\text{M} & = \text{Li} \quad 16\% \text{ yield} \\
\text{M} & = \text{MgBr} \quad 93\% \text{ yield}
\end{align*}
\]

- Dehydration of the intermediate \(\beta\)-alkoxy- or \(\beta\)-hydroxy ketone can also serve to drive the reaction to the right.

\[
\begin{align*}
\text{tBuO}^- \cdot \text{Na}^+, \text{tBuOH} & \quad \xrightarrow{} \\
\text{JACS 1979, 101, 1330}
\end{align*}
\]

Enolate Geometry
- two possible enolate geometries

\[
\begin{align*}
\text{O} & \quad \xrightarrow{\text{LDA, THF, -78°C}} \\
\text{E - enolate} & \quad + \\
\text{Z - enolate}
\end{align*}
\]

- enolate geometry plays a major role in stereoselection.

\[
\begin{align*}
\text{Z-enolate} & \quad \xrightarrow{\text{R}^3\text{CHO}} \\
\text{R}^1 \cdots \text{OM} \cdots \text{R}^2 & \quad \text{OH} \cdots \text{R}^1 \cdots \text{R}^2 \cdots \text{OH} \\
\text{erythrose (syn)} & \\
\text{E-enolate} & \quad \xrightarrow{\text{R}^3\text{CHO}} \\
\text{R}^1 \cdots \text{OM} \cdots \text{R}^2 & \quad \text{OH} \cdots \text{R}^1 \cdots \text{R}^2 \cdots \text{OH} \\
\text{threo (anti)}
\end{align*}
\]

- Zimmerman-Traxler Transition State: Ivanov condensation

\(\text{JACS 1957, 79, 1920.}\)

\[
\begin{align*}
\text{Ph} \cdots \text{H} & \quad + \quad \text{PHCHCO}_2 \cdot \text{MgBr} \\
\xrightarrow{} & \\
\text{"pericyclic" T.S.}
\end{align*}
\]
Analysis of Z-enolate stereoselectivity

\[
\begin{align*}
\text{Favored Chair} & \quad \text{Disfavored Chair}
\end{align*}
\]

Analysis of E-enolate stereoselectivity

\[
\begin{align*}
\text{Favored Chair} & \quad \text{Disfavored Chair}
\end{align*}
\]

Analysis of Boat Transition State for Z-Enolates

\[
\begin{align*}
\text{Favored Chair} & \quad \text{Disfavored Chair}
\end{align*}
\]
Analysis of Boat Transition State for E-Enolates

Summary of Aldol Transition State Analysis:
1. Enolate geometry (E- or Z-) is an important stereochemical aspect. Z-Enolates usually give a higher degree of stereoselection than E-enolates.
2. Li⁺, Mg²⁺, Al³⁺= enolates give comparable levels of diastereoselection for kinetic aldol reactions.
3. Steric influences of enolate substituents (R₁ & R₂) play a dominant role in kinetic diastereoselection.
4. The Zimmerman-Traxler like transition state model can involve either a chair or boat geometry.

Noyori "Open" Transition State for non-Chelation Control Aldols
Absence of a binding counterion. Typical counter ions: R₄N⁺, K⁺/18-C-6, Cp₂Zr²⁺
- Non-chelation aldol reactions proceed via an "open" transition state to give syn aldols regardless of enolate geometry.

Z- Enolates:
E- Enolate:

NMR Stereochemical Assignment.
Coupling constants (J) are a weighted average of various conformations.

- Alkali & alkaline earth metal enolates tend to be aggregates- complicates stereoselection models.
- Boron enolates are monomeric and homogeneous
- B-O and B-C bonds are shorter and stronger than the corresponding Li-O abd Li-C bonds (more covalent character)- therefore tighter more organized transition state.

Generation of Boron Enolates:
\[ \text{iPrEtN} \rightarrow \text{OBR}_2 \]
C-C BOND FORMATION

Diastereoselective Aldol Condensation with Boron Enolates

Asymmetric Aldol Condensations with Chiral Auxilaries -
- Li⁺ enolates give poor selectivity (1:1)
- Boron and tin enolates give much improved selectivity
C-C BOND FORMATION

Preferred conformation

Oppolzer Sultam

1) LDA
2) Bu$_3$SnCl
Chiral Boron

- In general, syn aldol products are achievable with high selectivity, anti aldols are more difficult

*Mukaiyama-Aldol* - Silyl Enol Ethers as an enolate precursors.

Lewis acid promoted condensation of silyl ketene acetics (ester enolate equiv.) with aldehydes: proceeds via "open" transition state to give anti aldols starting from either E- or Z- enolates.

Asymmetric Mukaiyama Aldol:
Mukaiyama-Johnson Aldol- Lewis acid promoted condensation of silyl enol ethers with acetals:

Fluoride promoted alkylation of silyl enol ethers

Meyer's Oxazolines:

\[
\begin{align*}
\text{Ester equiv.} & \xrightarrow{(ipc)_2\text{BOtf}} (ipc)_2B \\
1) \text{RCHO} & \xrightarrow{\text{3N} \text{H}_2\text{SO}_4} \xrightarrow{\text{3CH}_2\text{N}_2} \text{H}_2\text{C} \xrightarrow{\text{R} = \text{nPr}} \text{CH}_2\text{CO}_2\text{Me} + \text{R} \xrightarrow{\text{C}_2\text{H}_11 \text{tBu}} \text{H}_3\text{C} \xrightarrow{\text{anti} \text{ee} = 77} \text{R} \xrightarrow{\text{anti} = 91 : 9} \text{syn} = 95 : 5 \\
\end{align*}
\]

Anti-Aldols by Indirect Methods:

\[
\begin{align*}
\text{PhSe} & \xrightarrow{1) (C_5\text{H}_7)_2\text{BOTf} \text{R}_3\text{N}} \xrightarrow{2) \text{RCHO}} \text{SePh} \xrightarrow{1) \text{HF}} \xrightarrow{2) [\text{O}]} \xrightarrow{3) \text{NaIO}_4} \xrightarrow{4) \text{CH}_2\text{N}_2} \text{R} \xrightarrow{\text{syn : anti} = 97 : 3} \text{R} \xrightarrow{\text{syn} = 94 : 6} \text{CO}_2\text{Me} \xrightarrow{\text{anti Aldol Product}} \text{CO}_2\text{Me} \\
\end{align*}
\]

Syn Aldols by Indirect Methods:

\[
\begin{align*}
\text{MeO} & \xrightarrow{1) \text{LDA, THF,} -78 \, ^\circ \text{C}} \xrightarrow{2) \text{RCOCl}} \text{MeO} \xrightarrow{1) \text{KBEt}_3\text{H, Et}_2\text{O,} -78 \, ^\circ \text{C}} \xrightarrow{2) \text{Zn(BH}_4\text{)}_2} \text{syn} : \text{anti} = 100 : 1 \xrightarrow{1) \text{HIO}_6} \xrightarrow{2) \text{CH}_2\text{N}_2} \text{anti Aldol} \\
\end{align*}
\]
Aldol Strategy to Erythromycin:

Erythromycin aglycone

\[
\text{CHO} + \text{CHO} \rightarrow \text{CHO} + \text{CHO}
\]

syn aldol

Erythromycin seco acid

\[
\text{CHO} + \text{CHO} \rightarrow \text{CHO} + \text{CHO}
\]

syn aldol
Michael Addition
- 1,4-addition of an enolate to an \( \alpha,\beta \)-unsaturated carbonyl to give 1,5-dicarbonyl compounds

Organometallic Reagents
Grignard reagents:

\[
\text{R-MgBr} \quad \xrightarrow{\text{THF}} \quad \text{R-MgBr} \quad \xrightarrow{\text{THF}} \quad \text{R-MgBr} \quad \xrightarrow{\text{THF}} \quad \text{R-MgBr} \quad \xrightarrow{\text{THF}} \quad \text{R-MgBr}
\]

often a mixture of 1,2- and 1,4-addition
Organolithium reagents
- usually gives 1,2-addition products
- alkyl lithium are prepared from lithium metal and the corresponding alkyl halide
- vinyl or aryl- lithium are prepared by metal-halogen exchange from the corresponding vinyl or aryl- halide or trialkyl tin with n-butyl, sec-butyl or t-butyllithium.

Organocuprates
- selective 1,4-addition to \(\alpha,\beta\)-unsaturated carbonyls
**C-C Bond Formation**

**Stereoselective Addition to Aldehydes**

- Aldehydes are "prochiral", thus addition of an organometallic reagent to an aldehydes may be stereoselective.
- Cram's Rule *JACS* 1952, 74, 2748; *JACS* 1959, 84, 5828.
  - empirical rule

  - based on *ab initio* calculations of preferred geometry of aldehyde which considers the trajectory of the incoming nucleophile (Dunitz-Burgi trajectory).

- Chelation Control Model - "Anti-Cram" selectivity
  - When L is a group capable of chelating a counterion such as alkoxide groups

**Umpolung** - reversal of polarity *Aldrichimica Acta* 1981, 14, 73; *ACIE* 1979, 18, 239.
  - i.e: acyl anion equivalents are carbonyl nucleophiles (carbonyls are usually electrophilic)

**Benzoin Condensation** *Comprehensive Organic Synthesis* 1991, 1, 541.
Thiamin pyrophosphate—nature’s acyl anion equivalent for trans ketolization reactions

![Thiamin pyrophosphate structure](image)

Trimethylsilylcyanohydrins

![Trimethylsilylcyanohydrins structure](image)

Dithianes

![Dithianes structure](image)

Aldehyde Hydrazones

![Aldehyde Hydrazones structure](image)

Heteroatom Stabilized Anions

Sulfones

![Sulfones structure](image)

Sulfoxides

![Sulfoxides structure](image)
Epoxide Opening Asymmetric Synthesis 1984, 5, 216.

Basic (SN2) Condition

\[ \text{Nu}: \quad \text{R} \quad \text{Nu} \quad \text{R} \quad \text{Nu} \]

Steric Approach Control

Acid (SN1-like) Condition

\[ \text{Nu}: \text{attaches site that best stabilizes a carbocation} \]

\[ \begin{align*}
\text{BnO} & \quad \text{OH} \\
\text{Me}_3\text{CuLi} & \quad \text{AlMe}_3 \\
\text{Me}_3\text{Al} & \quad \rightarrow \\
\text{OH} & \quad \text{6:1} \\
\text{1:5} & \quad \text{JACS 1981, 103, 7520}
\end{align*} \]

\[ \begin{align*}
\text{JOC 1974, 3645}
\end{align*} \]

\[ \begin{align*}
\text{Ph} & \quad \text{OH} \\
\text{O} & \quad \text{O} \\
\text{Nu}: & \quad \text{O} \\
\text{H} & \quad \text{H} \\
\text{O} & \quad \text{H} \\
\text{H} & \quad \text{H} \\
\text{Nu} & \quad \text{Nu}
\end{align*} \]

\[ \text{Tetrahedron Lett. 1992, 33, 931} \]

Cyclic Sulfites and Sulfates (epoxide equivalents) Synthesis 1992, 1035.

\[ \begin{align*}
\text{Nu:} & \quad \text{Nu} \\
\text{SOCl}_2, \text{Et}_3\text{N} & \quad \text{SOCl}_2, \text{NaIO}_4
\end{align*} \]
Irreversible Payne Rearrangement

Payne Rearrangement of 2,3-epoxyalcohols *Aldrichimica Acta* 1983, 16, 60

**Sigmatropic Rearrangements***

**Asymmetric Synthesis** 1984, 3, 503.

Nomenclature:

- [3,3]-rearrangement
- [1,5]-Hydrogen migration

3,3-sigmatropic Rearrangements

Cope Rearrangements- requires high temperatures  *Organic Reaction* 1975, 22, 1
Chair transition state:

- E,Z (99.7%)
- E,E (0.3%)
- Z,Z (0%)

"Chirality Transfer"

- Diastereomers

- Diastereomers

Ring expansion to medium sized rings

Claisen Rearrangements - allyl vinyl ether to an $\gamma,\delta$-unsaturated carbonyl


Chair Transition State for Claisen
- Chorismate Mutase catalyzed Claisen Rearrangement - $10^5$ rate enhancement over non-enzymatic reaction

- Claisen rearrangement usually proceed by a chair-like T.S.

hydrophobically accelerated Claisen - *JOC* 1989, 54, 5849
Johnson ortho-ester Claisen:

\[
\text{OH} \quad \xrightarrow{\text{H}_3\text{C-}\text{C(OEt)}_3} \quad \Delta \quad \xrightarrow{\Delta - \text{EtOH}} \quad \text{OEt}
\]


<table>
<thead>
<tr>
<th>Reaction</th>
<th>Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>LDA, THF</td>
<td>OTMS</td>
</tr>
<tr>
<td>LDA, THF</td>
<td>OTMS-Cl</td>
</tr>
</tbody>
</table>

Eschenmoser

"Chirality Transfer"


**C-C BOND FORMATION**

![Chemical Structures and Reactions](image)

**Sulfoxide Rearrangement**


- Ene reaction with aldehydes is catalyzed by Lewis Acids (Et$_2$AlCl)

![Chemical Structures and Reactions](image)
C-C Bond Formation

- Metallo-ene Reaction


- intramolecular
Synthesis of Phyllanthiocin


\[ \begin{align*}
\text{Ph} & \quad \text{Me}_3\text{Si} \quad \text{NLi} \quad \text{Br} \\
\text{O} & \quad \text{O} \\
\text{O} & \\
\text{Ph} & \quad \text{CH}_3 \\
\end{align*} \]

1) LAH
2) BnBr

\[ \begin{align*}
\text{O} & \quad \text{Br} \\
\text{O} & \quad \text{N} \\
\text{O} & \\
\text{Ph} & \quad \text{CH}_3 \\
\end{align*} \]

1) $\text{O}_3$
2) H$_2$, Lindlar’s
3) MeAlCl

\[ \begin{align*}
\text{BnO} & \quad \text{CHO} \\
\text{BnO} & \\
\text{MeO} & \\
\text{CHO} & \\
\text{MeO} & \\
\end{align*} \]

1) MEM-Cl
2) $\text{O}_3$

\[ \begin{align*}
\text{BnO} & \quad \text{MEMO} \\
\text{BnO} & \\
\text{CH}_3 & \\
\text{OMEM} & \\
\text{CHO} & \\
\end{align*} \]

1) ZnCl$_2$
2) $\text{H}^+$
3) Swern

\[ \begin{align*}
\text{BnO} & \quad \text{MEMO} \\
\text{BnO} & \\
\text{MeO} & \\
\text{CHO} & \\
\text{OMEM} & \\
\text{CHO} & \\
\end{align*} \]

1) LDA, TMSCl
2) BnMe$_3$NF, MeI
3) RuO$_4$

\[ \begin{align*}
\text{BnO} & \quad \text{MEMO} \\
\text{BnO} & \\
\text{MeO} & \\
\text{CHO} & \\
\text{OMEM} & \\
\text{CHO} & \\
\end{align*} \]

1) DBU
2) $\text{H}_2$, Pd/C

\[ \begin{align*}
\text{HO}_2\text{C} & \quad \text{MeO}_2\text{C} \\
\text{Ph} & \quad \text{CH}_3 \\
\end{align*} \]

Phyllanthiocin