Chapter 11. Reactions of carbonyl compounds

The most important mechanistic feature of all reaction involving C=O (aldehydes, ketones, derivatives of carboxylic acids) is the addition of a nucleophile = formation of the tetracoordinate C intermediate: *tetrahedral intermediate*.

Addition of heteroatom nucleophiles to carbonyl compounds:
Numerous nucleophiles can add to the C=O compound. The mechanism for these reaction is essentially the same. Nucleophiles that are known to add readily: water (hydration), alcohols (acetalization, O-acetalization), thiols (S-acetalization), amines (N-acetals).

Acetalization—one example fits all:

Acetalization (O,O-acetalization)
The transition states, energy profiles (surfaces) depend largely on the structure of the carbonyl component. The Hammet treatment offers a very good description (more accurate for the first step—hemiacetal formation). HW: read this section in the Carey-Sundberg textbook.

Hydration and acetalization reactions compared

- hydration is slow / unfavored (HCH=O is an exception); acetalization does not proceed too well either (the equilibrium needs to be pushed by removing water; azeotropic removal; Dean-Stark appts). The actual equilibrium constants differ very much from derivative to derivative.

- hydration may be both acid/base catalyzed; acetalization is different: both acid/base catalyzed to the stage of hemiacetal (ketal). **The second step hemiacetal → acetal is specifically acid-catalyzed.**
  - this makes possible to synthesize hemiacetals and acetals selectively
  - this makes possible to use the acetals in organic synthesis in the presence of bases and organometallic reagents.
**Acetalization and S-acetalization reactions compared**
The most important feature is that O,O-acetals are pretty inert to bases, while S,S-acetals react with bases readily (Corey-Seebach synthesis).

\[
\begin{align*}
\text{aldehyde} + \text{SH} &\xrightarrow{\text{acid or Lewis A.}} \text{acetal} \\
\text{aldehyde} + \text{SH} &\xrightarrow{\text{acid or Lewis A.}} \text{acetal}
\end{align*}
\]

\[
\begin{align*}
\text{acetal} &\xrightarrow{\text{BuLi}} \text{hemiacetal} \\
\text{acetal} &\xrightarrow{\text{BuLi}} \text{hemiacetal} \\
\text{hemiacetal} &\xrightarrow{\text{RX}} \text{iminium ion} \\
\text{hemiacetal} &\xrightarrow{\text{RX}} \text{hemiacetal} \\
\text{hemiacetal} &\xrightarrow{\text{HgCl}_2, \text{CaCO}_3, \text{water-acetone}} \text{ketone}
\end{align*}
\]

**N,N-Acetalization and the chemistry of the iminium ion**
Ammonia, primary and secondary amines add to the C=O. The mechanism is the same like in the addition of the O- or S-nucleophiles: the hemiacetal structure is formed and the next step (protonation and elimination of water) proceeds fast to give the *iminium ion*.

**Addition of N-nucleophiles to carbonyl compound with subsequent E1 elimination**
Condensation of C=O compounds with primary amines ➔ Schiff bases
Note: 1) acid catalyzed, 2) deprotonation during the basic workup.
Condensation of C=O compounds with secondary amines \(\rightarrow\) enamines

Note: 1) acid catalyzed, 2) azeotropic distillation

\[
\begin{align*}
\text{Same mechanism as in acetalization} \\
\text{Condensation of C=O compounds with secondary amines} & \rightarrow \text{enamines} \\
\text{Note: 1) acid catalyzed, 2) azeotropic distillation} \\
\end{align*}
\]

Similar condensations
C=O compound with hydroxylamine (or hydroxylamine.HCl) \(\rightarrow\) oxime
C=O compound with hydrazine \(\rightarrow\) hydrazone

Addition of ylides to C=O

**Betaine, Ylide and Ylene**

**P- and S-ylides**

Are generated by strong bases (e.g. BuLi) from the respective phosphonium, sulfonium or sulfoxonium salts.

**Phosphonium ylide**

**Sulfonium ylide**

**Sulfoxonium ylide**
Addition of P-ylides to C=O: Wittig reaction

Phosphonium salts that are usually used in the W.r. are Ph₃P⁺-CH₂-R salts.

**Mechanism:**
1. Starts with a [2+2] cycloaddition of the ylide to the C=O (aldehydes react much faster) to form two oxaphosphetane isomers (cis- and trans-).
2. Oxaphosphetanes are in an equilibrium with an open metal-stabilized oxoylides.

**E/Z-Stereoselectivity** depends on the sterical demands of the R¹ and R² and the presence of the Li⁺ cation (lithium favors E-olefin).

Note: the cis-oxaphosphetane can revert back (reversible reaction) and irreversibly form the trans-oxaphosphetane. This isomerization is called **stereochemical drift**.

![Diagram of the mechanism](image)
**Addition of S-ylides to C=O: formation of three-membered rings**

**Two-step mechanism:**
1. Starts with nucleophilic attack of the carbanionic ylide carbon on the electrophilic carbon of the C(δ+)=O to produce zwitterion. This is rate-limiting step.
2. The negatively charged moiety of the zwitterions then attacks in the SN fashion the carbon to which the positively charged sulfonium salt is attached.

\[ \text{S-ylides can react also with C=C bonds: regioselectivity in } \alpha,\beta\text{-unsaturated ketones.} \]
Sulfoxonium ylide gives cyclopropane, while the sulfonium ylide gives epoxide.

The reason is different nucleophilicity of the ylide carbon(-). The sulfoxonium ylide has more of an ylene character $\Rightarrow$ preference for the softer center.
Horner-Wadsworth-Emmons reaction with achiral substrates

HWE reaction is an addition of $\alpha$-(alkoxycarbonyl)phosphonic acids or $\beta$-ketophosphonic acids to the C=O.

HWE reagents (the respective phosphonates) are obtained via the Arbuzov reaction (Lecture 22, p.4): the Arbuzov reaction:

$$\begin{align*}
\text{Arbuzov reaction:} \\
\text{OR'} \text{OR}' + \text{H}_2\text{C}_X \rightarrow \text{OR}' \text{OR}' + \text{X}^\ominus
\end{align*}$$

The HWE reaction mechanism:

Advantages over Wittig reaction:
- easy preparation of phosphonates by Arbuzov reaction, phosphates are inexpensive, stable
- phosphonate carbanions are more nucleophilic than the corresponding phosphorous ylides
- react with aldehydes and ketones at mild conditions
- react even with hindered ketones
- the $\alpha$-carbon of phosphonates may be derivatized prior to HWE (not possible with ylides)
- dialkylphosphate by-products are water-soluble

1. It starts with a formation of the delocalized phosphonate anion

2. In the next step the phosphonate anion adds to the C=O. It is not known, whether the first intermediate is the alkoxide ion A, or whether the oxaphosphetane B is formed directly in one-step cycloaddition (analogy to Wittig r.).

3. The decomposition of the oxaphosphetane B proceeds via one-step [2+2]-cycloreversion and yields $E$-olefin.
HWE: E/Z-Regioselectivity = E strongly prevalent

**E-selectivity is maximized by:** large R of the phosphite (isopropyl is the best)

**Z-selectivity** may be increased by using small R and strongly dissociated base (BuOK)

Example-synthesis of a cephalosporine analogue:

\[
\begin{align*}
\text{P(O)(OEt)}_2 & \quad \text{NaH, THF} \quad 85\% \\
t-\text{Bu-O}_2C & \quad \text{BocHN} \\
\end{align*}
\]
Horner-Wadsworth-Emmons reaction, Still-Gennari modification (SGm) was developed in 1983 by W.C. Still and C. Gennari to generate selectively Z-alkenes.

Features:
- $\text{--O-CH}_2\text{CF}_3$ esters of the phosphonate.
- the phosphonate residue must have electronegative/anion stabilizing functionality on $\alpha$-C otherwise the carbanion decomposes
- base must be dissociated and the metal cation must be non-coordinating, or trapped effectively by a crown ether (e.g. 18-crown-6 for K$^+$). Examples: KH, KHMDS
- CH$_2$CN as a phosphonate residue gives excellent Z-selectivity (as opposed to normal HWE)

Mechanism: key point = the rearrangement from the chelated adduct to form the oxaphosphetane is favored and the elimination step is faster than the initial addition

Example:

$\text{K}_2\text{CO}_3$, 18-crown-6
toluene, $-25^\circ\text{C}$, then

$\text{65\%}$
**Addition of organometallic C-nucleophiles to carbonyl compounds**

Numerous organometallic C-nucleophiles add to C=O compounds, for example R-Li, R-MgX, enolates, etc. The addition goes through the tetrahedral adduct (stable with aldehydes and ketones, less stable with carboxylate-derived C=Os).

**Kinetics: depends on the degree of aggregation of the C-nucleophile!!!!**

Example: addition of MeLi to ketone \[ \text{rate} = k[\text{MeLi}]^1[\text{ketone}]^4 \]

Similar reactivity is observed with **Grignard reagents**

**Stereoselectivity of nucleophiles addition ➔ Cram’s rule (see ⚫)**

**Addition of hydride donors to carbonyl compounds**

Numerous H-donors add to C=O compounds. Typical example: NaBH₄. The same for LiAlH₄. Aldehydes react much faster than ketones (steric reasons more than electronic).

Similar, yet **different** is the mechanism of addition of Dibal-H: Lewis base (C=O) coordinates to the aluminum (Lewis acid)
Diastereoselective addition of hydride donors to carbonyl compounds

Hydride-donor addition to α-chiral carbonyl compounds

aldehydes: hydrogen donor has to be deuteride to create the second stereocenter

Two products are possible: product according to Cram’s rule and product with opposite configuration of the second (just created) stereocenter (=anti-Cram product)

In the cases when the α-chiral center is a σ-EWG, different diastereoselectivity was observed, depending on the nature of EWG

**Nitrogen**

**Oxygen**

How do we explain the different stereoselectivity? → Analysis of the respective transition states

**Note:** nucleophile attacks in $103^\circ$ to the C=O. This is so-called Bürgi-Dunitz angle.
1. Additions of hydride donor to α-chiral carbonyl compounds do not have to reflect the preferred conformations of the substrate.

2. Additions to α-chiral carbonyl compounds do not have a heteroatom on α-stereocenter proceed according to Cram’s rule (see chapter about conformations). Nu approached from opposite side to the large alkyl residue.

3. Additions α-chiral carbonyl compounds that have a heteroatom on α-stereocenter and the hereoatom does not form five-membered chelate with metal ion present in the medium proceeds via Felkin-Anh transition state (Nu approaches from opposite side to the EWG).

4. Additions α-chiral carbonyl compounds that with a hereoatom that does form five-membered chelate with metal ion proceeds via Cram-chelate transition state (Nu approaches from opposite side to the R1).
Examples:

\[
\begin{align*}
\text{Zn}(\text{BH}_4)_2 & \quad 95 : 5 \\
K\text{BH}(\text{sec-Bu})_3 & \quad 10 : 90
\end{align*}
\]

\[
\begin{align*}
\text{R} & = \text{OBn} & \quad 98 : 2 \\
\text{R} & = \text{OTBDMS} & \quad 5 : 95
\end{align*}
\]
**Enantioselective addition of hydride donors to carbonyl compounds**

Hydride-donor addition to ketones with 2 different subst. and deuterioaldehydes results in the formation of a chiral center.

**Borane reductions: H.C. Brown, 1979 Nobel Prize in Chemistry**

Syn-addition

**Alpine-Borane** (Midland, Chem. Rev. 1989, 89, 1553)

Reduces aryl-ketones and aldehydes with S-selectivity

The mechanism of Alpine-Borane reduction of aromatic ketones and aldehydes:
Noyori reduction (2001 Nobel Prize in Chemistry)

This reaction utilizes an axially chiral ligand 2,2'-binaphthol (1), which upon treatment with LiAlH₄ gives an intermediate dihydride structure (2). Dihydride (2) has two homotopic hydrogens, Hₐ and Hₐ, and therefore it makes no difference which one is replaced by the reaction with aliphatic alcohol. Treatment of dihydride (2) with one equivalent of aliphatic alcohol (EtOH, MeOH) yields Noyori’s Hydride (BINAL-H) (3).

Binal-H reduces unsaturated ketones with at least one unsaturated chain connected to the carbonyl group with high R-enantioselectivity.

Chair-like six-membered transition states (12a and 12b) were proposed by Noyori to explain the stereochemical course of the reduction. These transition states involve co-ordination of lithium cation (from LiAlH₄) to the highest basicity oxygen of EtO group. Unsaturated and saturated chains are then differentiated on electronic grounds. Relative magnitude of electronic repulsion with a phenolic oxygen lone pair is following the order: aryl > alkenyl, alkynyl > alkyl > methyl > long chain alkyl.
Otherwise the mechanism of reduction is the same as above for DIBAL-H.