ADVANCED ORGANIC SYNTHESIS

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SYNTHETIC DESIGN

1. Retrosynthetic Analysis
2. Reversal of the Carbonyl Group Polarity (*Umpolung*)
3. Steps in Planning a Synthesis
4. Choice of Synthetic Method
5. Domino Reactions
6. Computer-Assisted Retrosynthetic Analysis
1. Retrosynthetic Analysis

Basic Concepts

- The construction of a synthetic tree by working backward from the *target molecule* (TM) is called *retrosynthetic analysis* or *antithesis*.
- The symbol $\Rightarrow$ signifies a reverse synthetic step and is called a *transform*.
  - The main transforms are *disconnections*,
  - or cleavage of C-C bonds, and *functional group interconversions* (FGI).
Synthons are fragments resulting from disconnection of carbon-carbon bonds of the TM.

The actual substrates used for the forward synthesis are the *synthetic equivalents* (SE).

Also, reagents derived from *inverting the polarity* (IP) of synthons may serve as SEs.

**Synthetic design** involves two distinct steps:

1) retrosynthetic analysis and
2) subsequent translation of the analysis into a "forward direction" synthesis.
Chemical bonds can be cleaved:

**heterolytic cleavage**

\[
\text{C} = \text{C} \quad \Rightarrow \quad \text{C}^+ \cdot \text{C}^- \quad \text{or} \quad \text{C} = \text{C}^\cdot \cdot \text{C}^\cdot
\]

**homolytic cleavage**

\[
\text{C} = \text{C} \quad \Rightarrow \quad \text{C}^\cdot \cdot \text{C}^\cdot
\]

**concerted transform**

\[
= C_6 H_6 \quad \Rightarrow \quad = C_3 H_6 + = H_2
\]
Donor and Acceptor Synthons

Heterolytic retrosynthetic disconnection of a carbon-carbon bond in a molecule breaks the TM into

- an acceptor synthon, a carbocation,
- and a donor synthon, a carbanion.

In a formal sense, the reverse reaction - the formation of a C-C bond - then involves the union of

- an *electrophilic* acceptor synthon
- and a *nucleophilic* donor synthon
<table>
<thead>
<tr>
<th>Synthon</th>
<th>Synthetic equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R^+$ (alkyl cation = carbenium ion)</td>
<td>RCl, RBr, RI, ROTs</td>
</tr>
<tr>
<td>$Ar^+$ (aryl cation)</td>
<td>$ArN_2X^-$</td>
</tr>
<tr>
<td>$HC=O$ (acylium ion)</td>
<td>$HC\cdot X (X = NR_2, OR)$</td>
</tr>
<tr>
<td>$RC=O$ (acylium ion)</td>
<td>$RC\cdot X (X = Cl, NR_2^{'}, OR^{'})$</td>
</tr>
<tr>
<td>$HO-C=O$ (acylium ion)</td>
<td>$CO_2$</td>
</tr>
<tr>
<td>$\overset{+}{\text{CH}_2\text{CH}_2\text{C-R}}$</td>
<td>$\overset{+}{\text{CH}_2=\text{CHC-R}} (R = \text{alkyl, OR'})$</td>
</tr>
<tr>
<td>$\overset{+}{\text{CH}_2-\text{CH}_2\text{C=NN}}$</td>
<td>$\overset{+}{\text{CH}_2=\text{CHC=NN}}$</td>
</tr>
<tr>
<td>$\overset{+}{\text{CH}_2\text{OH}}$ (oxocarbenium ion)</td>
<td>HCHO</td>
</tr>
<tr>
<td>$\overset{+}{\text{RCH-OH}}$ (oxocarbenium ion)</td>
<td>RCHO</td>
</tr>
<tr>
<td>$\overset{+}{\text{R}_2\text{C-OH}}$ (oxocarbenium ion)</td>
<td>$\overset{+}{\text{R}_2\text{C}=\text{O}}$</td>
</tr>
<tr>
<td>$\overset{+}{\text{HO}}$</td>
<td>$\overset{+}{\text{O}}$</td>
</tr>
<tr>
<td>$\overset{+}{\text{O}}$</td>
<td>$\overset{+}{\text{Br}_-\text{OC(=O)R}^a}$</td>
</tr>
</tbody>
</table>

*Note that α-halo ketones also may serve as synthetic equivalents of enolate ions (e.g., the Reformatsky reaction, Section 7.7).*
### Table 1.2  Common Donor Synthons

<table>
<thead>
<tr>
<th>Synthon</th>
<th>Derived reagent</th>
<th>Synthetic equivalent</th>
</tr>
</thead>
<tbody>
<tr>
<td>$R^-$ (alkyl, aryl anion)</td>
<td>RMgX, RLi, $R_2$CuLi</td>
<td>R$\rightarrow$X</td>
</tr>
<tr>
<td>$^-\text{CN}$ (cyanide)</td>
<td>NaC≡N</td>
<td>HCN</td>
</tr>
<tr>
<td>$RC\equiv C^-$ (acetylide)</td>
<td>RC≡CMgX, RC≡CLi</td>
<td>RC≡CH</td>
</tr>
<tr>
<td>$\text{O}$ (enolate)</td>
<td>$\text{O}^-$ (M = Li, BR$_2$)</td>
<td></td>
</tr>
<tr>
<td>$\text{Ph}_3\text{P}\equiv\text{C}$ (ylide)</td>
<td>$\left[\text{Ph}_3\text{P}\equiv\text{C}^-\right]X^-$</td>
<td>$\text{H} \equiv \text{C} \equiv \text{X}$</td>
</tr>
<tr>
<td>$R^-$NO$_2$ ($\alpha$-nitro anion)</td>
<td>R$\equiv$NO$_2$</td>
<td></td>
</tr>
</tbody>
</table>
Often, more than one disconnection is feasible: A & B

Retrosynthetic analysis A

\[
\begin{align*}
\text{Ph} & \quad \text{TM} \\
\text{TM} & \quad \text{inverting the polarity} \\
X = \text{Br, I} & \quad \delta^+ X \\
\text{SE of donor synthon} & \\
\end{align*}
\]

Synthesis A

PCC (Pyridinium Chlorochromate)
Retrosynthetic analysis B

\[
\text{Ph} \quad \overset{\text{TM}}{\longrightarrow} \quad \text{inverting the polarity} \quad \overset{\text{IP}}{\longrightarrow} \quad \text{Ph} \quad \overset{\text{Br}}{\longrightarrow} \quad \text{SE of donor synthon}
\]

Synthesis B

\[
\text{Ph-Br} \quad \overset{\text{TM}}{\longrightarrow} \quad \text{THF} \quad \overset{\text{TM}}{\longrightarrow}
\]
Alternating Polarity disconnection

- The question of how one chooses appropriate carbon-carbon bond disconnections is related to functional group manipulations since the distribution of formal charges in the carbon skeleton is determined by the functional group(s) present.
- The presence of a heteroatom in a molecule imparts a pattern of electrophilicity and nucleophilicity to the atoms of the molecule.
- The concept of *alternating polarities* or latent polarities (imaginary charges) often enables one to identify the best positions to make a disconnection within a complex molecule.
Functional groups may be classified as follows:

**E class:** Groups conferring electrophilic character to the attached carbon (+:)

-\( \text{-NH}_2 \), -\( \text{OH} \), -\( \text{OR} \), =\( \text{O} \), =\( \text{NR} \), -\( \text{X} \) (halogens)

**G class:** Groups conferring nucleophilic character to the attached carbon (-:)

-\( \text{-Li} \), -\( \text{MgX} \), -\( \text{AlR}_2 \), -\( \text{SiR}_3 \)

**A class:** Functional groups that exhibit ambivalent character (+ or -:)

-\( \text{-BR}_2 \), C=CR\(_2\), C≡CR\(_2\), -\( \text{NO}_2 \), ≡\( \text{N} \), -S(\( \text{OR} \), -SO\(_2\)R
The positive charge (+) is placed at the carbon attached to an **E class** functional group (e.g., =O, -OH, -Br) and the TM is then analyzed for **consonant** and **dissonant** patterns by assigning alternating polarities to the remaining carbons.

In a **consonant pattern**, carbon atoms with the same class of functional groups have matching polarities,

**Consonant patterns:**
Positive charges are placed at carbon atoms bonded to the **E class** groups.

![Consonant patterns diagram](image-url)
whereas in a **dissonant pattern**, their polarities are unlike.

If a **consonant pattern** is present in a molecule, a simple synthesis may often be achieved.

**Dissonant patterns:**

One E class group is bonded to a carbon with a positive charge, whereas the other E class group resides on a carbon with a negative charge.

Examples of choosing reasonable disconnections of functionally substituted molecules based on the concept of alternating polarity are shown below.
One Functional Group

Analysis

2-pentanol

FGI ↓

acceptor synthon

acceptor synthon

donor synthon

donor synthon

acceptor synthon

acceptor synthon

donor synthon

donor synthon
In the example shown above, there are two possible ways to disconnect the TM, 2-pentanol.

- Disconnection close to the functional group (path a) leads to substrates (SE) that are readily available.
- Moreover, reconnecting these reagents leads directly to the desired TM in high yield using well-known methodologies.
- Disconnection via path b also leads to readily accessible substrates.
- However, their reconnection to furnish the TM requires more steps and involves two critical reaction attributes:
  - quantitative formation of the enolate ion
  - and control of its monoalkylation by ethyl bromide.
Synthesis (path a)
Two Functional Groups in a 1,3-Relationship

Analysis

\[
\begin{align*}
\text{TM (consonant pattern)} & \quad \implies & \\
\text{donor synthon} & \quad + & \quad \text{acceptor synthon}
\end{align*}
\]

\[
\begin{align*}
\text{TM} & \quad \implies & \\
\text{donor synthon} & \quad + & \quad \text{acceptor synthon}
\end{align*}
\]
Synthesis (path a)

The consonant charge pattern and the presence of a β-hydroxyketone moiety in the TM suggest a retroaldol transform. Either the hydroxy-bearing carbon or the carbonyl carbon of the TM may serve as an electrophilic site and the corresponding α-carbons as the nucleophilic sites.

Synthesis (path b)

However, path b is preferable since it does not require a selective functional group interconversion (reduction).
Two Functional Groups in a 1,4-Relationship

Analysis

The dissonant charge pattern for 2,5-hexanediolone exhibits a positive (+) polarity at one of the α-carbons, as indicated in the acceptor synthon above.

Thus, the α-carbon in this synthon requires an inversion of polarity (Umpolung in German) from the negative (-) polarity normally associated with a ketone α-carbon.

An appropriate substrate (SE) for the acceptor synthon is the electrophilic α-bromo ketone.
It should be noted that an enolate ion might act as a base, resulting in deprotonation of an $\alpha$-halo ketone, a reaction that could lead to the formation of an epoxy ketone \textit{(Darzens condensation)}.

To circumvent this problem, a weakly basic enamine is used instead of the enolate.

Synthesis
In the case of 5-hydroxy-2-hexanone shown below, **Umpolung** of the polarity in the acceptor synthon is accomplished by using the electrophilic epoxide as the corresponding SE.

Analysis

5-hydroxy-2-hexanone

\[
\begin{align*}
\text{O} & \quad \text{or} & \quad \text{O} \\
\text{CH}_3 & \quad \text{OH} & \quad \text{CH}_3 & \quad \text{OH} \\
\text{TM} & \quad \text{(dissonant patterns)} & & \\
\end{align*}
\]

\[
\begin{align*}
\text{donor synthon} & \quad + & \quad \text{acceptor synthon} \\
\end{align*}
\]
The presence of a C-C-OH moiety adjacent to a potential nucleophilic site in a TM, as exemplified below, points to a reaction of an epoxide with a nucleophilic reagent in the forward synthesis. The facile, regioselective opening of epoxides by nucleophilic reagents provides for efficient two-carbon homologation reactions.
2. Reversal of the Carbonyl Group Polarity (Umpolung)

- In organic synthesis, the carbonyl group is intimately involved in many reactions that create new carbon-carbon bonds.
- The carbonyl group is electrophilic at the carbon atom and hence is susceptible to attack by nucleophilic reagents.
- Thus, the carbonyl group reacts as a formyl cation or as an acyl cation.
- A reversal of the positive polarity of the carbonyl group so it acts as a fomyl or acyl anion would be synthetically very attractive.
2. (Umpolung)- Continue ...

- To achieve this, the carbonyl group is converted to a derivative whose carbon atom has the negative polarity.
- After its reaction with an electrophilic reagent, the carbonyl is regenerated.
- Reversal of polarity of a carbonyl group has been explored and systematized by Seebach.
- **Umpolung** in a synthesis usually requires extra steps.
- Thus, one should strive to take maximum advantage of the functionality already present in a molecule.
"traditional" approach

\[
\begin{align*}
&\text{O}^\delta^- \quad \text{C} \quad \text{R}^\delta^+ \\
&\text{Nu}^- \\
&\text{O}^- \\
&\text{R} \quad \text{Nu}
\end{align*}
\]

Umpolung approach \((E^+ = \text{electrophile})\)

\[
\begin{align*}
&\text{O}^\delta^- \quad \text{C} \quad \text{R}^\delta^+ \\
&\text{\large \[} \quad \text{C} \quad \text{R}^\delta^- \text{\large \]}
\end{align*}
\]

\[
\text{\large \[} \quad \text{R} \quad \text{C}^\delta^- \text{\large \]}
\]

\[
\text{E}^+ \quad \rightarrow \quad \text{O} \quad \text{R} \quad \text{E}
\]

formyl anion when \(R = H\)

acyl anion when \(R = \text{alkyl}\)
The following example illustrates the normal disconnection pattern of a carboxylic acid with a Grignard reagent and carbon dioxide as SEs (path a) and a disconnection leading to a carboxyl synthon with an "unnatural" negative charge (path b). Cyanide ion can act as an SE of a negatively charged carboxyl synthon. Its reaction with R-Br furnishes the corresponding nitrile, which on hydrolysis produces the desired TM.
Formyl and Acyl Anions Derived from 1,3-Dithianes

• The most utilized *Umpolung* strategy is based on formyl and acyl anion equivalents derived from 2-lithio-1,3-dithiane species.

• These are readily generated from 1,3-dithianes (thioacetals) because the hydrogens at C(2) are relatively acidic (pK$_a$$\sim$3).

• In this connection it should be noted that thiols (EtSH, pK$_a$ 11) are stronger acids compared to alcohols (EtOH, pK$_a$ 16).
• Also, the lower ionization potential and the greater polarizability of the valence electrons of sulfur compared to oxygen make the divalent sulfur compounds more nucleophilic in $S_N2$ reactions.
• The polarizability factor may also be responsible for the stabilization of carbanions $\alpha$ to sulfur.

\[
\text{OH} + \text{H}^+ - \text{H}_2\text{O} \xrightarrow{\text{e.g., TsOH}} \text{O} + \text{H} \quad (\text{1,3-dioxane (an acetal) } pK_a \approx 40)
\]

\[
\text{SH} + \text{O} \xrightarrow{\text{Lewis acid}} \text{S} \quad (\text{1,3-dithiane (a thioacetal) } pK_a = 31)
\]
The anions derived from dithianes react with alkyl halides to give the corresponding alkylated dithianes.

Their treatment with HgCl₂-HgO regenerates aldehydes or ketones, respectively, as depicted below.
Dithiane-derived carbanions can be hydroxyalkylated or acylated to produce, after removal of the propylenedithiol appendage, a variety of difunctional compounds, as shown below.

In the presence of HMPA (hexamethylphosphoramide, [(Me₂N)₃P=O]), dithiane-derived carbanions may serve as Michael donor.

However, in the absence of HMPA, 1,2-addition to the carbonyl group prevails.
An instructive example of using a dithiane *Umpolung* approach to synthesize a complex natural product is the one-pot preparation of the multifunctional intermediate shown below, which ultimately was elaborated to the antibiotic *vermiculin*.

\[ \text{TMEDA} = N,N,N',N'-\text{tetramethylethylenediamine (Me}_3\text{NCH}_2\text{CH}_2\text{NMe}_2); \text{used to sequester Li}^+ \text{ and disrupt } n\text{-BuLi aggregates.} \]
Acyl Anions Derived from Nitroalkanes

✓ The $\alpha$-hydrogens of nitroalkanes are appreciably acidic due to resonance stabilization of the anion $[CH_3NO_2, pK_a 10.2; CH_3CH_2NO_2, pK_a 8.5]$.

✓ The anions derived from nitroalkanes give typical nucleophilic addition reactions with aldehydes (the Henry-Nef tandem reaction).

✓ Note that the nitro group can be changed directly to a carbonyl group via the Nef reaction (acidic conditions).

✓ Under basic conditions, salts of secondary nitro compounds are converted into ketones by the pyridine-HMPA(Hexamethyl phosphoramide) complex of molybdenum (VI) peroxide.
Nitronates from primary nitro compounds yield carboxylic acids since the initially formed aldehyde is rapidly oxidized under the reaction conditions.

\[
\begin{align*}
\text{Nitronate} & \quad \text{base} \quad \left[ \begin{array}{c}
\text{acyl anion SE} \\
\end{array} \right] \\
& \quad \text{Na}^+ \quad \text{R' CHO} \quad \text{Henry reaction} \\
\text{R' NO}_2 OH \\
\text{mixture of diastereomers}
\end{align*}
\]

\[
\begin{align*}
\text{R' NO}_2 & \quad \text{TiCl}_3, \text{H}_2\text{O} \\
& \quad \text{or} \quad \text{H}_2\text{SO}_4, \text{H}_2\text{O} \\
& \quad \text{Nef-type reactions}
\end{align*}
\]

\[
\begin{align*}
\text{R' NO}_2 & \quad \text{base (pyridine)} \quad \left[ \begin{array}{c}
\text{nitronate anion} \\
\end{array} \right] \\
& \quad \text{MoO}_5 \cdot \text{py} \cdot \text{HMPA} \\
\text{R' CO} & \quad \text{R' HNO}_2
\end{align*}
\]
An example of an \( \alpha \)-nitro anion **Umpolung** in the synthesis of jasmone (TM)

\[
\text{jasmone}
\]
Acyl Anions Derived from Cyanohydrins

O-Protected cyanohydrins contain a masked carbonyl group with inverted polarity.

\[ \text{RCHO} + \text{HC≡N} \rightarrow \text{R} - \text{C} - \text{CN} \]

cyanohydrin

\[ \text{H}_2\text{C=}\text{CHOEt} \rightarrow \text{OCHMe(OEt)} \]

\[ \text{R} - \text{C} - \text{CN} \rightarrow \text{OCHMe(OEt)} \]

O-protected cyanohydrin

The α-carbon of an O-protected cyanohydrin is sufficiently activated by the nitrile moiety \([\text{CH}_3\text{CH}_2\text{CN}, \text{pK}_a 30.9]\) so that addition of a strong base such as LDA generates the corresponding anion.

Its alkylation, followed by hydrolysis of the resultant alkylated cyanohydrin, furnishes the ketone.
The overall reaction represents alkylation of an acyl anion equivalent as exemplified for the synthesis of methyl cyclopentyl ketone.

\[ \text{Me} \overset{\text{O}}{\bigg|} \overset{\text{OEt}}{\bigg|} \overset{\text{H}_3\text{C} - \text{CN}}{\bigg|} \]

\[ \xrightarrow{\text{a. LDA, THF}} \]

\[ \text{Me} \overset{\text{O}}{\bigg|} \overset{\text{OEt}}{\bigg|} \overset{\text{H}_3\text{C} - \text{NC}}{\bigg|} \overset{\text{Br}}{\bigg|} \overset{\text{piperidine}}{\bigg|} \]

\[ \xrightarrow{\text{b.}} \]

\[ \text{H}_3\text{C} \overset{\text{O}}{\bigg|} \overset{\text{Et}}{\bigg|} \overset{\text{H}_3\text{C} - \text{CN}}{\bigg|} \overset{\text{Br}}{\bigg|} \overset{\text{piperidine}}{\bigg|} \]

\[ \xrightarrow{\text{c. H}^+, \text{MeOH}} \]

\[ \text{H}_3\text{C} \overset{\text{O}}{\bigg|} \overset{\text{Et}}{\bigg|} \overset{\text{H}_3\text{C} - \text{CN}}{\bigg|} \overset{\text{Br}}{\bigg|} \overset{\text{piperidine}}{\bigg|} \]

\[ \xrightarrow{\text{d. aq. NaOH}} \]

\[ \text{H}_3\text{C} \overset{\text{O}}{\bigg|} \overset{\text{Et}}{\bigg|} \overset{\text{H}_3\text{C} - \text{CN}}{\bigg|} \overset{\text{Br}}{\bigg|} \overset{\text{piperidine}}{\bigg|} \]

\[ \sim 100\% \]
An attractive alternative to the above protocol involves the nucleophilic acylation of alkylating agents with aromatic and heteroaromatic aldehydes via trimethylsilyl protected cyanohydrins.

\[
\text{PhCHO} \xrightarrow{\text{Me}_3\text{SiC≡N}, \text{cat. ZnI}_2} \text{Ph}-\overset{\text{OTMS}}{\text{C}}-\overset{\text{TMS}}{\text{CN}} \underset{-78\degree \text{C to } -25\degree \text{C}}{\xrightarrow{\text{i-PrI}}} \text{Ph}-\overset{\text{H}}{\text{C}}-\overset{\text{OTMS}}{\text{CN}}
\]

\[
\text{TMS} = \text{Me}_3\text{Si}
\]

\[
\text{Ph}-\overset{\text{OTMS}}{\text{C}}-\overset{\text{i-Pr}}{\text{CN}} \xrightarrow{\text{a. H}^+, \text{H}_2\text{O}} \xrightarrow{\text{b. aq. NaOH}} \text{Ph}-\overset{\text{O}}{\text{C}}-\overset{\text{C}}{\text{Ph}} \quad \text{95% overall}
\]
Acyl anion synthons derived from cyanohydrins may be generated catalytically by cyanide ion via the **Stetter reaction**. However, further reaction with electrophiles is confined to carbonyl compounds and Michael acceptors.

\[
\begin{align*}
\text{OH} & \quad \text{CN} \\
R-C^- & \quad CN \\
\end{align*}
\]

\[
\begin{align*}
R-C^- & \quad CN \\
+ & \quad R'CHO \\
\rightarrow & \quad R-C^- \quad CN \quad H \\
\end{align*}
\]

\[
\begin{align*}
\text{OH} & \quad \text{O}^- \\
R-C-C-R' & \quad \text{CN} H \\
\leftrightarrow & \quad R-C-C-R' \\
\end{align*}
\]

\[
\begin{align*}
R-C-C-R' & \quad \text{CN} H \\
\rightarrow & \quad R-C-C-R' \\
\text{(catalyst)} & \quad \text{OH} \\
\end{align*}
\]

\[
\begin{align*}
\text{CHO} & \quad \text{Ph} \\
\text{Ph} & \quad \text{Ph} \\
\rightarrow & \quad \text{Na}^+ \\
\end{align*}
\]

\[
\begin{align*}
\text{cat. NaCN} & \quad \text{DMF} \\
1,4\text{-addition} & \quad 93\%
\end{align*}
\]
Acyl Anions Derived from Enol Ethers

- The $\alpha$-hydrogens of enol ethers may be deprotonated with tert-BuLi.
- Alkylation of the resultant vinyl anions followed by acidic hydrolysis provides an efficient route for the preparation of methyl ketones.

\[
\begin{align*}
\text{H}_2\text{C} & \quad \text{H} \\
\text{enol ether} & \quad \rightleftharpoons \\
\text{a. t-BuLi, THF, } -65 \, ^\circ\text{C} & \quad \left[ \begin{array}{c}
\text{H}_2\text{C} \\
\text{Li}
\end{array} \right] \\
\text{b. R} & \quad \text{OEt} \\
\text{acyl anion equivalent} & \quad \text{H}_3\text{C} \\
\text{c. H}^+, \text{H}_2\text{O} & \quad \text{R}
\end{align*}
\]
Acyl Anions Derived from Lithium Acetylide

Treatment of lithium acetylide with a primary alkyl halide (bromide or iodide) or with aldehydes or ketones produces the corresponding monosubstituted acetylenes or propargylic alcohols. Mercuric ion-catalyzed hydration of these furnishes methyl ketones and methyl $\alpha$-hydroxy ketones, respectively.

\[ \text{R--Br + } [\text{Li--C} \equiv \text{C--H}] \rightarrow \text{R--C} \equiv \text{C--H} \quad \text{cat. HgSO}_4 \quad \text{H}_2\text{SO}_4, \text{H}_2\text{O} \rightarrow \text{R--C} \equiv \text{C--CH}_3 \]

(1° only)

\[ \text{RCHO + } [\text{Li--C} \equiv \text{C--H}] \quad \text{THF} \rightarrow \quad \text{R--C--C} \equiv \text{C--H} \quad \text{cat. HgSO}_4 \quad \text{H}_2\text{SO}_4, \text{H}_2\text{O} \rightarrow \text{HO--C--C--CH}_3 \]

(or ketone)
Darzens Condensation

\[
\begin{align*}
R^1\text{C}R^2 & \quad \text{H}_2\text{C}\text{OR} \quad \text{X} = \text{Cl, Br, I, OTs} \\
\text{Base} & \\
\rightarrow & \quad \text{R}^1\text{C}R^2\text{OR}R
\end{align*}
\]

Mechanism of the Darzens Condensation
Henry-Nef tandem reaction

Nitroalkane with α-hydrogen + Aldehyde or ketone → β-nitro alcohol

Henry reaction
Also known as: Henry nitroaldol reaction
The Nef reaction is an organic reaction describing the acid hydrolysis of a salt of a primary or secondary nitroalkane (1) to an aldehyde or a ketone (3) and nitrous oxide (4).
The **Stetter reaction** is a reaction used in organic chemistry to form carbon-carbon bonds through a 1,4-addition reaction utilizing a nucleophilic catalyst.