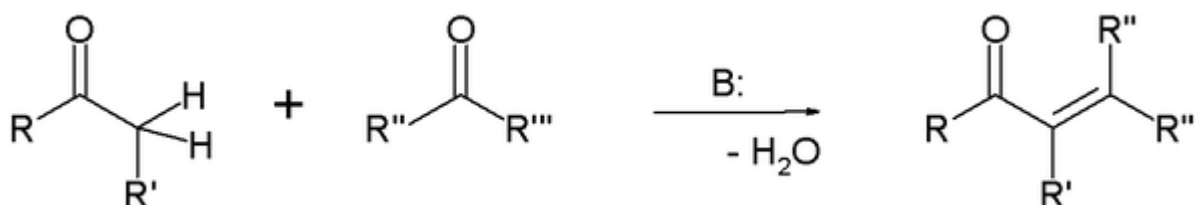


## CHAPTER-12

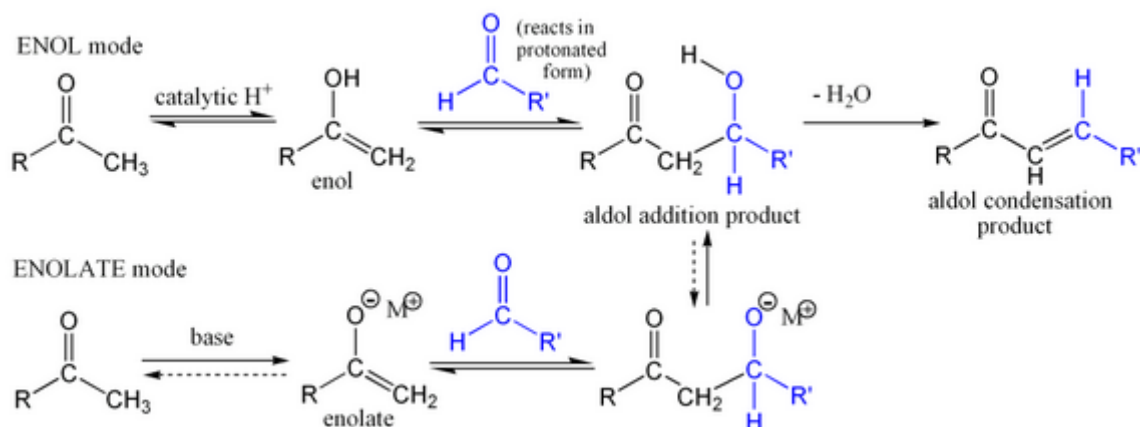
### MECHANISM OF REACTION

#### **ALDOL CONDENSATION:**

An **aldol condensation** is an organic reaction in which an enol or an enolate ion reacts with a carbonyl compound to form a  $\beta$ -hydroxyaldehyde or  $\beta$ -hydroxyketone, followed by a dehydration to give a conjugated enone.



Aldol condensations are important in organic synthesis, providing a good way to form carbon-carbon bonds. The Robinson annulation reaction sequence features an aldol condensation; the Wieland-Miescher ketone product is an important starting material for many organic syntheses. Aldol condensations are also commonly discussed in university level organic chemistry classes as a good bond-forming reaction that demonstrates important reaction mechanisms. In its usual form, it involves the nucleophilic addition of a ketone enolate to an aldehyde to form a  $\beta$ -hydroxy ketone, or "**aldol**" (**aldehyde** + **alcohol**), a structural unit found in many naturally occurring molecules and pharmaceuticals.



The name **aldol condensation** is also commonly used, especially in biochemistry, to refer to the aldol reaction itself, as catalyzed by aldolases. However, the aldol reaction is not formally a condensation reaction because it does not involve the loss of a small molecule.

The reactions between a ketone and a carbonyl compound lacking an  $\alpha$ -Hydrogen (Cross Aldol condensation) is called **Claisen-Schmidt condensation**.

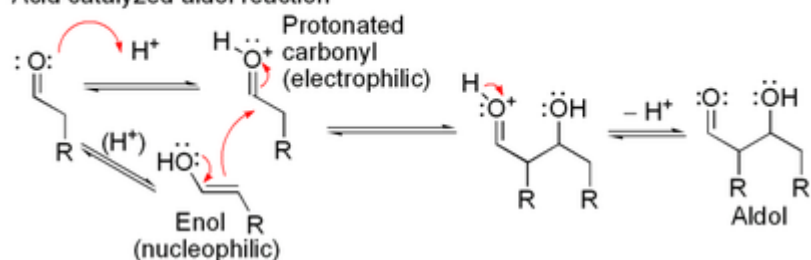
These reactions are named after two of its pioneering investigators Rainer Ludwig Claisen and J. G. Schmidt, who independently published on this topic in 1880 and 1881. An example is the synthesis of dibenzylideneacetone.

#### **MECHANISM:**

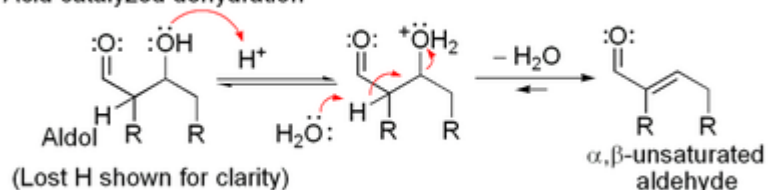
The first part of this reaction is an aldol reaction, the second part a dehydration—an elimination reaction. Dehydration may be accompanied by decarboxylation when an activated carboxyl group is present.

The aldol addition product can be dehydrated via two mechanisms; a strong base like potassium *t*-butoxide, potassium hydroxide or sodium hydride in an enolate mechanism, or in an acid-catalyzed enol mechanism.

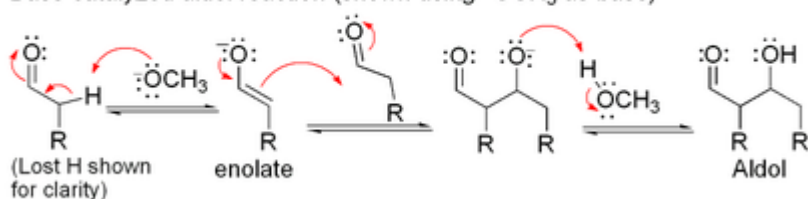
### Acid catalyzed aldol reaction



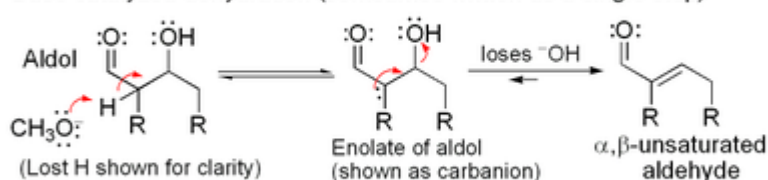
### Acid catalyzed dehydration



### Base catalyzed aldol reaction (shown using <sup>-</sup>OCH<sub>3</sub> as base)



### Base catalyzed dehydration (sometimes written as a single step)



## TYPES OF CONDENSATIONS

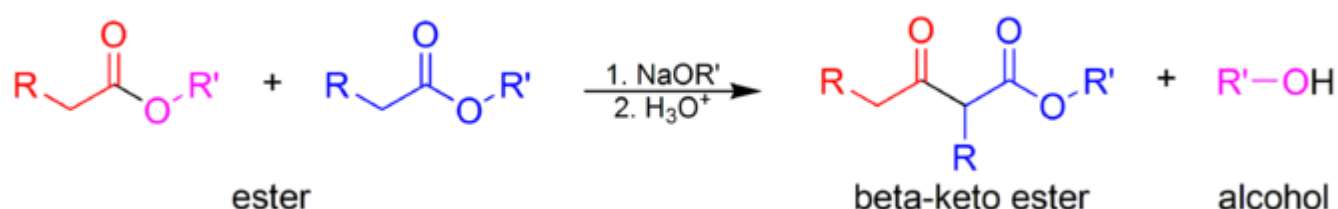
It is important to distinguish the aldol condensation from other addition reactions to carbonyl compounds.

- When the base is an amine and the active hydrogen compound is sufficiently activated the reaction is called a Knoevenagel condensation.
- In a Perkin reaction the aldehyde is aromatic and the enolate generated from an anhydride.
- A Claisen condensation involves two ester compounds.

- A Dieckmann condensation involves two ester groups in the *same molecule* and yields a cyclic molecule
- A Henry reaction involves an aldehyde and an aliphatic nitro compound.
- A Robinson annulation involves a  $\alpha,\beta$ -unsaturated ketone and a carbonyl group, which first engage in a Michael reaction prior to the aldol condensation.
- In the Guerbet reaction, an aldehyde, formed *in situ* from an alcohol, self-condenses to the dimerized alcohol.
- In the Japp-Maitland condensation water is removed not by an elimination reaction but by a nucleophilic displacement

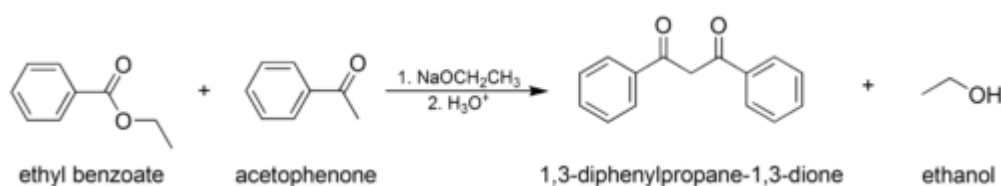
### CLAISEN CONDENSATION

The **Claisen condensation** (not to be confused with the Claisen rearrangement) is a carbon-carbon bond forming reaction that occurs between two esters or one ester and another carbonyl compound in the presence of a strong base, resulting in a  $\beta$ -keto ester or a  $\beta$ -diketone. It is named after Rainer Ludwig Claisen, who first published his work on the reaction in 1881.

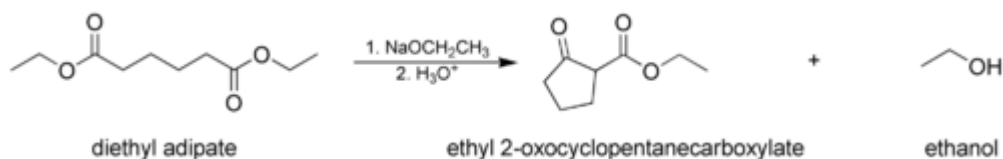


### TYPES:

The classic Claisen condensation, where only one enolizable ester is used.



The mixed (or "crossed") Claisen condensation, where an enolizable ester or ketone and a nonenolizable ester are used.



The Dieckmann condensation, where a molecule with two ester groups reacts intramolecularly, forming a cyclic  $\beta$ -keto ester. In this case, the ring formed must not be strained, usually a 5- or 6-membered c.

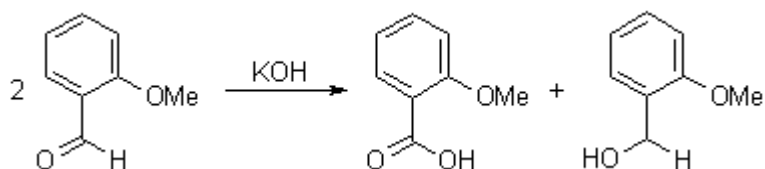
### MECHANISM

In the first step of the mechanism, an  $\alpha$ -proton is removed by a strong base, resulting in the formation of an enolate anion, which is made relatively stable by the delocalization of electrons.

- Next, the carbonyl carbon of the (other) ester is nucleophilically attacked by the enolate anion.
- The alkoxy group is then eliminated (resulting in (re)generation of the alkoxide), and the alkoxide removes the newly-formed doubly  $\alpha$ -proton to form a new, highly resonance-stabilized enolate anion.
- Aqueous acid (e.g. sulfuric acid or phosphoric acid) is added in the final step to neutralize the enolate and any base still present.
- The newly-formed  $\beta$ -keto ester or  $\beta$ -diketone is then isolated. Note that the reaction requires a stoichiometric amount of base as the removal of the doubly  $\alpha$ -proton thermodynamically drives the otherwise endergonic reaction.
- That is, Claisen condensation does not work with substrates having only one  $\alpha$ -hydrogen because of the driving force effect of deprotonation of the  $\beta$ -keto ester in the last step.

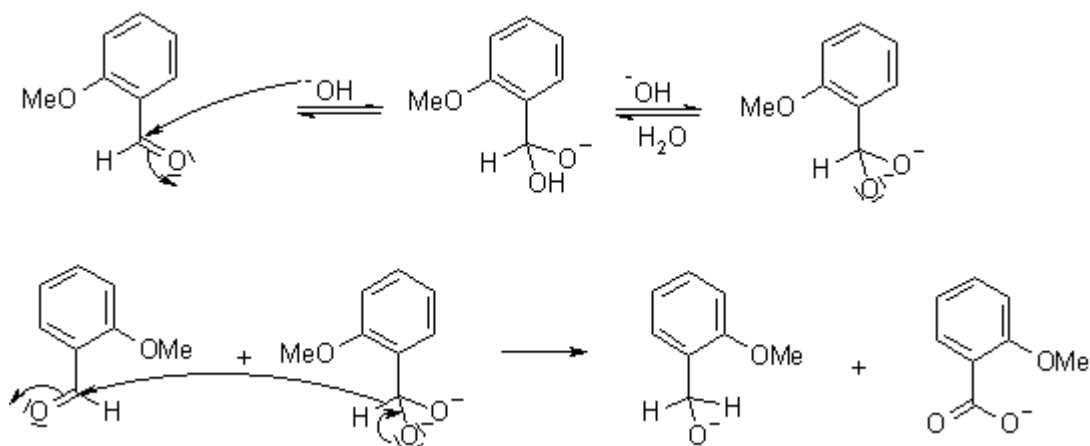
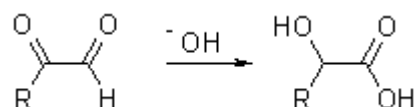
## CANNIZZARO REACTION

The Cannizzaro reaction, named after its discoverer Stanislao Cannizzaro, is a chemical reaction that involves the base-induced disproportionation of an aldehyde.



This redox disproportionation of non-enolizable aldehydes to carboxylic acids and alcohols is conducted in concentrated base.

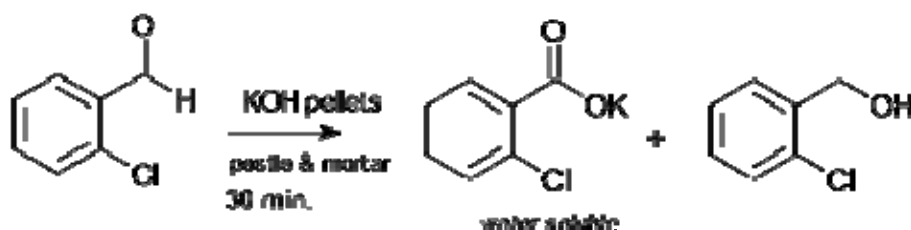
$\alpha$ -Keto aldehydes give the product of an intramolecular disproportionation in excellent yields.



An interesting variant, the Crossed Cannizzaro Reaction, uses formaldehyde as reducing agent.

**Application:**

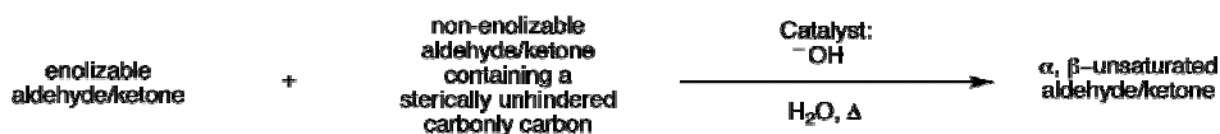
The reaction is limited to aldehydes lacking alpha hydrogen centers. Under ideal conditions the reaction produces only 50% of the alcohol and the carboxylic acid. The latter is obtained only after acidification of the highly basic reaction mixture, typically 30% base.<sup>[5]</sup> To avoid the low yields, it is more common to conduct the **crossed Cannizzaro reaction** with a sacrificial aldehyde. In this variation, the reductant is formaldehyde, which is oxidized to sodium formate and the corresponding alcohol is obtained in a high yield, although the atom economy is still low. A solvent-free reaction has been reported involving grinding liquid 2-chlorobenzaldehyde with potassium hydroxide in a mortar and



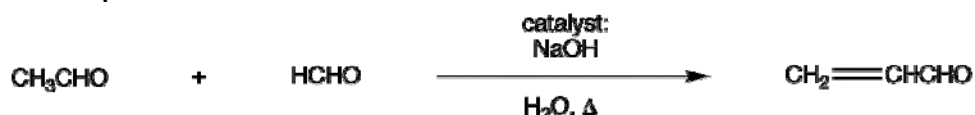
pestle.

## CROSSED ALDOL CONDENSATION

Crossed aldol condensation is a variation of aldol condensation.



example:

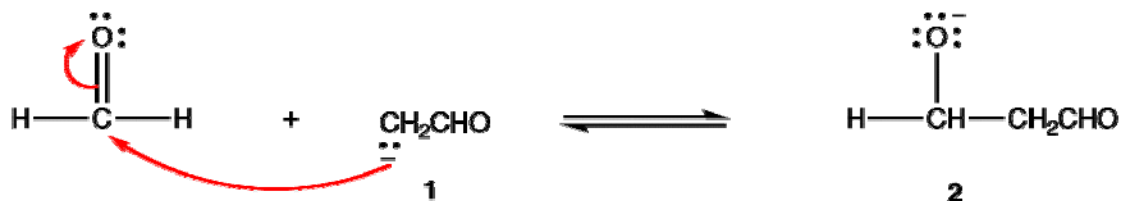


### Mechanism

**Step 1:** The hydroxide ion deprotonates the enolizable aldehyde reversibly.



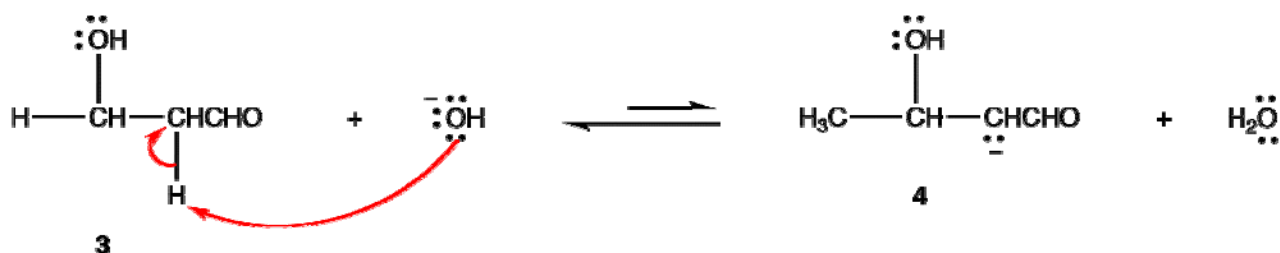
**Step 2:** Enolate ion 1 preferentially adds to the non-enolizable aldehyde, which has the sterically less hindered and, therefore, more accessible carbonyl carbon.



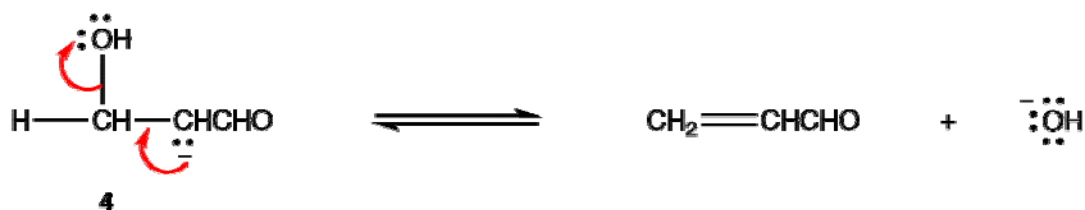
**Step 3:** Alkoxide ion 2 is protonated by water.



**Step 4:** Aldol 3 is an enolizable aldehyde. A small amount of it is converted to the corresponding enolate ion (**4**) by the hydroxide ion.



**Step 5:** Enolate ion **4** loses a hydroxide ion.



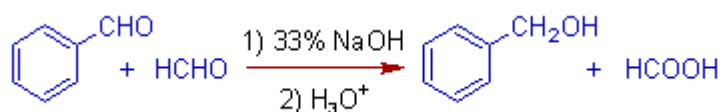


Step 1 through 3 are a crossed aldol reaction, steps 4 and 5 a 1,2-elimination via E1cB mechanism. Thus, crossed aldol condensation is crossed aldol reaction followed by 1,2-elimination.

### Crossed cannizzaro reaction:

When a mixture of formaldehyde and a non enolizable aldehyde is treated with a strong base, the later is preferentially reduced to alcohol while formaldehyde is oxidized to formic acid. This variant is known as ***crossed Cannizzaro reaction***.

**E.g.** Benzyl alcohol and formic acid are obtained when a mixture of benzaldehyde and formaldehyde is treated with alkali.

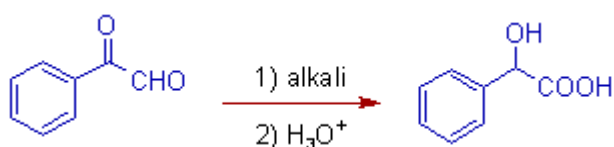


*The reason may be the initial nucleophilic addition of hydroxide anion is faster on formaldehyde as there are no electron donating groups on it.*

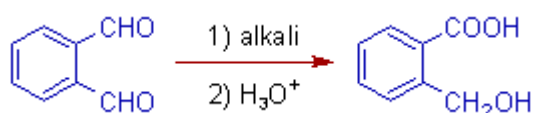
The preferential oxidation of formaldehyde in crossed Cannizzaro reactions may be utilized in the quantitative reduction of some aldehydes.

5)  $\alpha$ -keto aldehydes can be converted to  $\alpha$ -hydroxy carboxylic acids by an intermolecular Cannizzaro reaction.

**E.g.** Phenylglyoxal undergoes *intramolecular cannizzaro reaction* by giving Mandelic acid ( $\alpha$ -hydroxyphenylacetic acid or 2-Hydroxy-2-phenylethanoic acid)

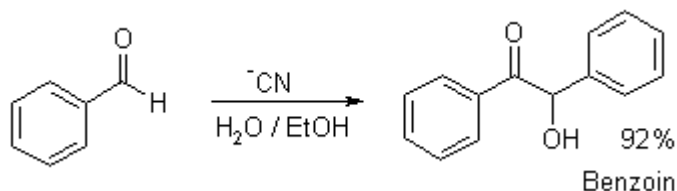


6) Phthalaldehyde can undergo **intramolecular Cannizzaro reaction** by giving (o-hydroxymethyl) benzoic acid.



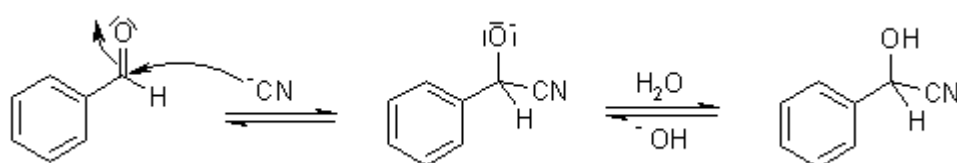
### BENZOIN CONDENSATION

The Benzoin Condensation is a coupling reaction between two aldehydes that allows the preparation of  $\alpha$ -hydroxyketones. The first methods were only suitable for the conversion of aromatic aldehydes.

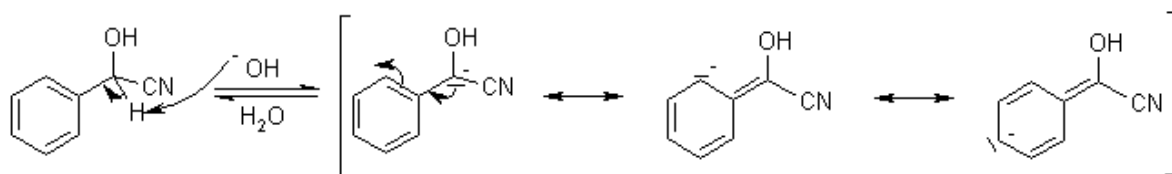


### Mechanism of Benzoin Condensation

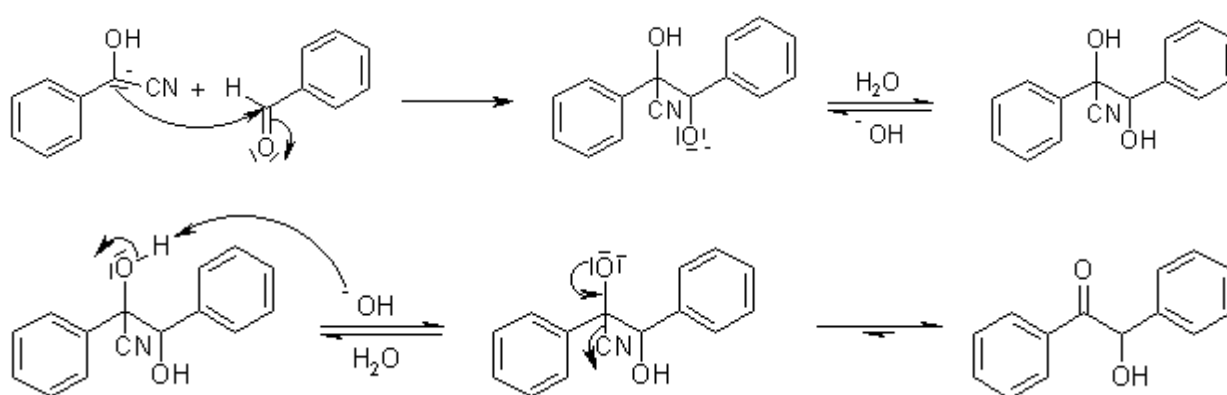
Addition of the cyanide ion to create a cyanohydrin effects an umpolung of the normal carbonyl charge affinity, and the electrophilic aldehyde carbon becomes nucleophilic after deprotonation: A thiazolium salt may also be used as the catalyst in this reaction .



A strong base is now able to deprotonate at the former carbonyl C-atom:

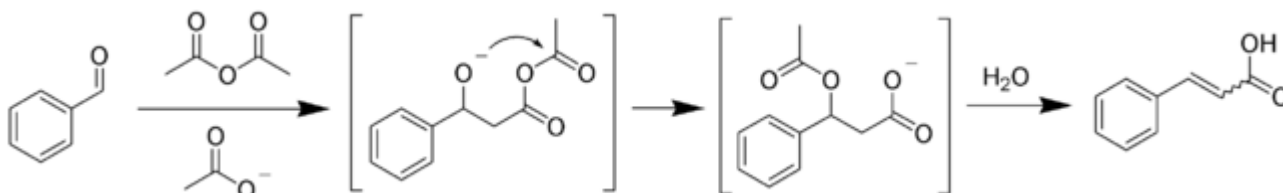


A second equivalent of aldehyde reacts with this carbanion; elimination of the catalyst regenerates the carbonyl compound at the end of the reaction:



## PERKIN CONDENSATION

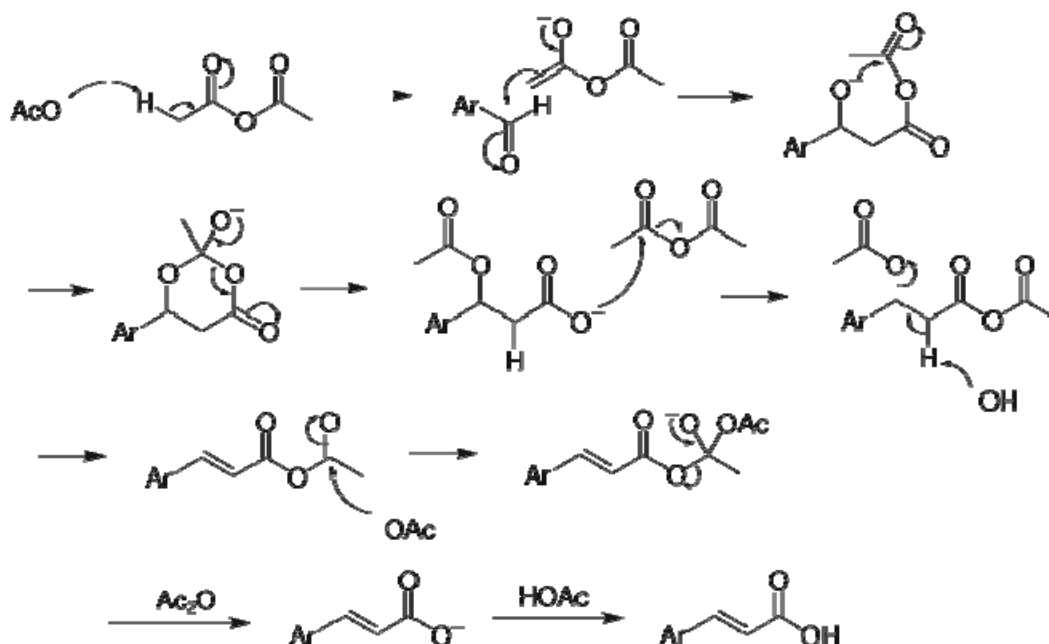
The **Perkin reaction** is an organic reaction developed by William Henry Perkin that can be used to make cinnamic acids i.e.  $\alpha$ - $\beta$ -unsaturated aromatic acid by the aldol condensation of aromatic aldehydes and acid anhydrides in the presence of an alkali salt of the acid.



Several reviews have been written. The reaction of phenylacetic acid and benzaldehyde with triethylamine and acetic

anhydride to alpha-phenylcinnamic acid is an example of this reaction type.

Reaction mechanism



The above mechanism is not universally accepted, as several other versions exist, including decarboxylation without acetic group transfer

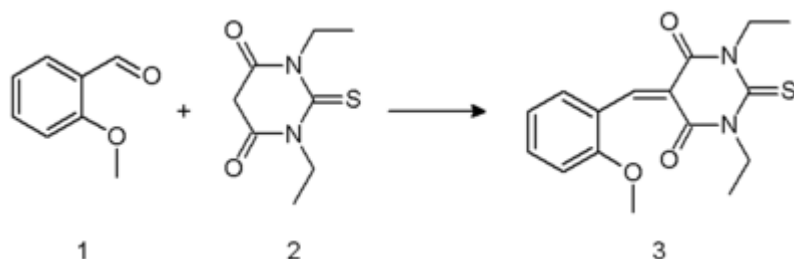
### Knoevenagel condensation

The **Knoevenagel condensation** reaction is an organic reaction named after Emil Knoevenagel. It is a modification of the aldol condensation.

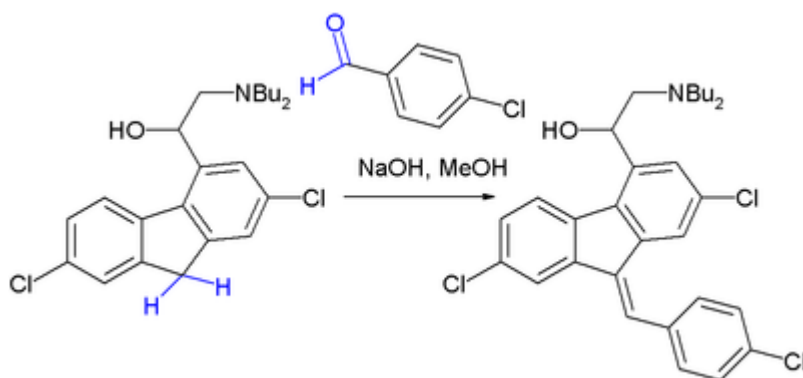
A Knoevenagel condensation is a nucleophilic addition of an active hydrogen compound to a carbonyl group followed by a dehydration reaction in which a molecule of water is eliminated (hence *condensation*). The product is often an alpha, beta conjugated enone.

## APPLICATION

A Knoevenagel condensation is demonstrated in the reaction of 2-methoxybenzaldehyde **1** with the barbituric acid **2** in ethanol using piperidine as a base. The resulting enone **3** is a charge transfer complex molecule.

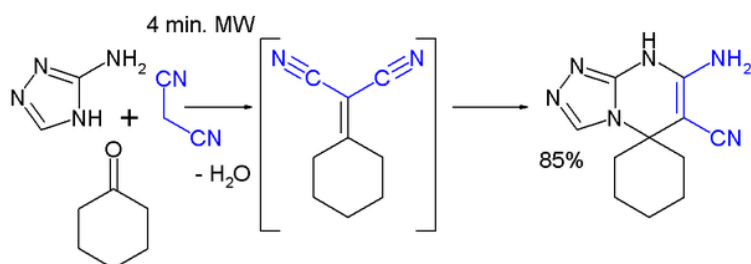


The Knoevenagel condensation is a key step in the commercial production of the antimalarial drug lumefantrine (a component of Coartem)



The initial reaction product is a 50:50 mixture of E and Z isomers but because both isomers equilibrate rapidly around their common hydroxyl precursor, the more stable Z-isomer can eventually be obtained.

A multicomponent reaction featuring a Knoevenagel condensation is demonstrated in this MORE synthesis with cyclohexanone, malononitrile and 3-amino-1,2,4-triazole



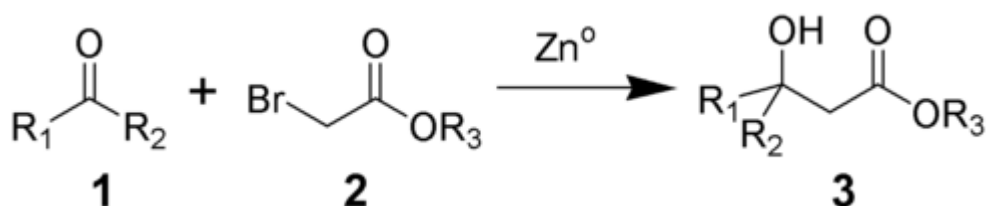
## REFORMATSKY REACTION

The **Reformatsky reaction** is an organic reaction which condenses aldehydes (or ketones),

1, with  $\alpha$ -halo esters,

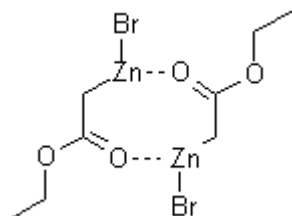
2, using a metallic zinc to form  $\beta$ -hydroxy-esters,

3. It was discovered by Sergey Nikolaevich Reformatsky.



### Mechanism of the Reformatsky Reaction

Organozinc compounds are prepared from  $\alpha$ -halogenesters in the same manner as Grignard Reagents. This reaction is possible due to the stability of esters against organozincs. Due to the very low basicity of zinc enolates, there is hardly any competition from proton transfer, and the scope of carbonyl addition partners is quite broad. In presence of ketones or aldehydes, the organozinc compounds react as the nucleophilic partner in an addition to give  $\beta$ -hydroxy esters.

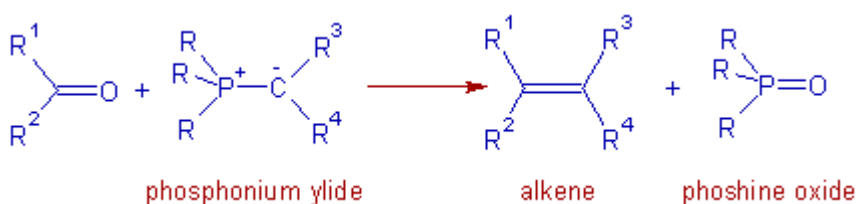


An ester-stabilized organozinc reagent Compared to organolithiums and organomagnesium halides (Grignard reagents), the organozinc halide reagents used in the

Wittig Reaction are relatively stable, and many are available commercially.

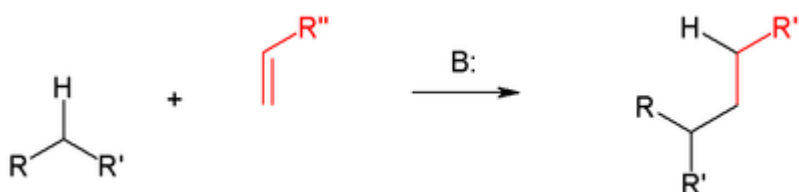
## WITTIG REACTION

The **Wittig reaction** or Wittig Olefination is a chemical reaction of an aldehyde or ketone with a triphenyl phosphonium ylide to give an alkene and triphenylphosphine oxide.



## MICHAEL ADDITION

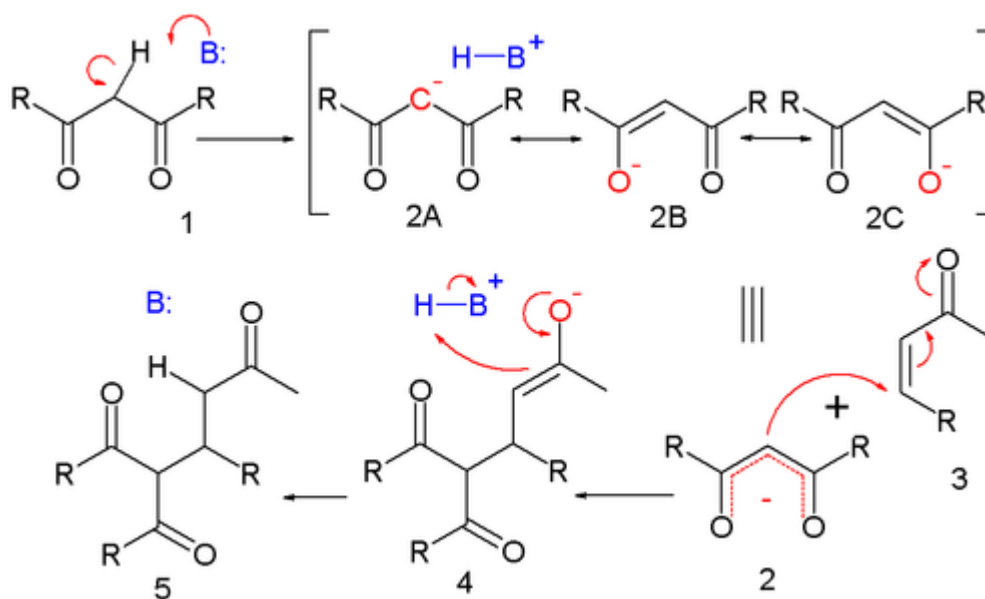
The **Michael reaction** or **Michael addition** is the nucleophilic addition of a carbanion or another nucleophile to an  $\alpha,\beta$ -unsaturated carbonyl compound. It belongs to the larger class of conjugate additions. This is one of the most useful methods for the mild formation of C-C bonds.<sup>[4]</sup> Many asymmetric variants exist.



- The reaction is the addition of an enolate of a ketone or aldehyde to an  $\alpha,\beta$ -unsaturated carbonyl compound at the  $\beta$  carbon. A newer definition, proposed by Kohler, is the 1,4-addition of a doubly stabilized carbon nucleophile to an  $\alpha,\beta$ -unsaturated carbonyl compound.

- Some examples of nucleophiles include beta-ketoesters, malonates, and beta-cyanoesters. The resulting product contains a highly useful 1,5-dioxygenated pattern.

The reaction mechanism is **1** (with R an alkoxy residue) as the nucleophile



Deprotonation of **1** by base leads to carbanion **2** stabilized by its electron-withdrawing groups. Structures 2a to 2c are three resonance structures that can be drawn for this species, two of which have enolate ions. This nucleophile reacts with the electrophilic alkene **3** to form **4** in a conjugate addition reaction. Proton abstraction from protonated base (or solvent) by the enolate **4** to **5** is the final step.

The course of the reaction is dominated by orbital, rather than electrostatic, considerations. The HOMO of stabilized enolates has a large coefficient on the central carbon atom while the LUMO of many alpha, beta unsaturated carbonyl compounds has a large coefficient on the beta carbon. Thus, both reactants can be considered soft. These polarized frontier orbitals are of similar energy, and react efficiently to form a new carbon-carbon bond.



Like the aldol addition, the Michael reaction may proceed via an enol, silyl enol ether in the Mukaiyama-Michael addition, or more usually, enolate nucleophile. In the latter case, the stabilized carbonyl compound is deprotonated with a strong base (hard enolization) or with a Lewis acid and a weak base (soft enolization). The resulting enolate attacks the activated olefin with 1,4-regioselectivity, forming a carbon-carbon bond. This also transfers the enolate to the electrophile. Since the electrophile is much less acidic than the nucleophile, rapid proton transfer usually transfers the enolate back to the nucleophile if the product is enolizable; however, one may take advantage of the new locus of nucleophilicity if a suitable electrophile is pendant. Depending on the relative acidities of the nucleophile and product, the reaction may be catalytic in base. In most cases, the reaction is irreversible at low temperature.