Chemistry of Carbonyl Compounds
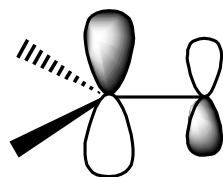
Carbonyl Group

The C-O bond is polarized towards the more electronegative oxygen
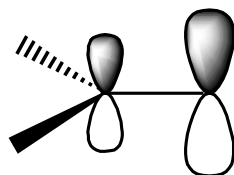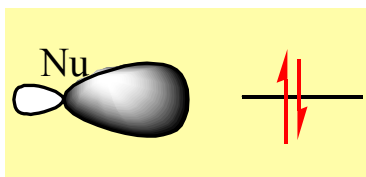
Bonding in carbonyl group

Unfilled orbital   LUMO

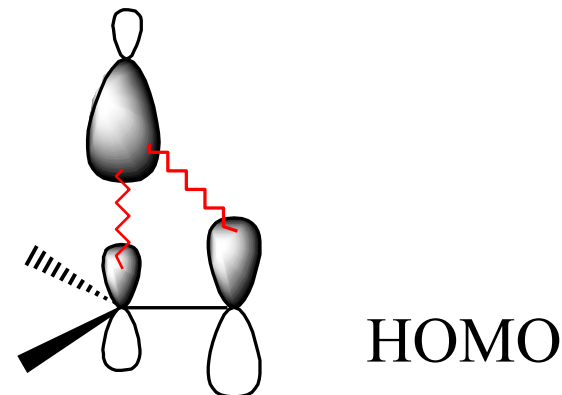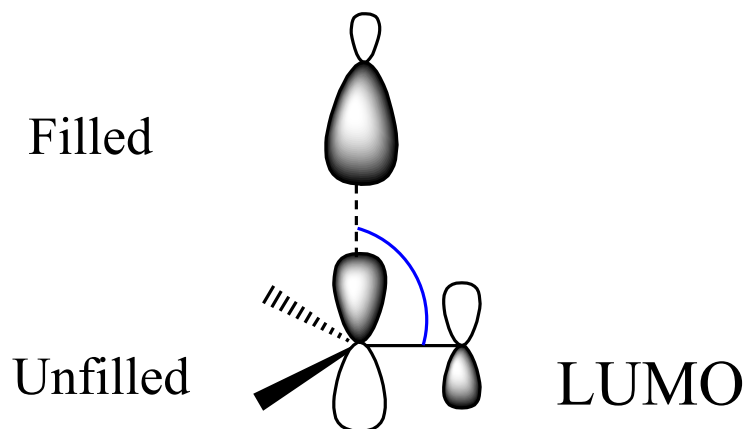Filled orbital   HOMO

Nucleophiles contain (i) **negative charge** or (ii) **lone pair** of electrons

Approach-1, 90°

Filled

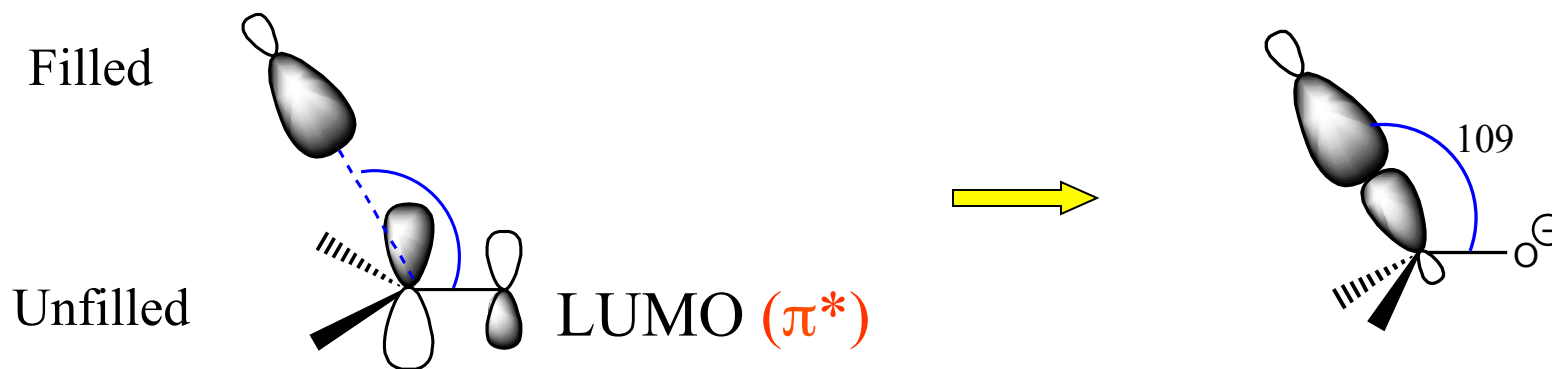Unfilled   LUMO

Maximum overlap!

HOMO

Maximum repulsion

Nucleophiles approach the carbonyl carbon at an angle of ~107°

Approach-2, 107°
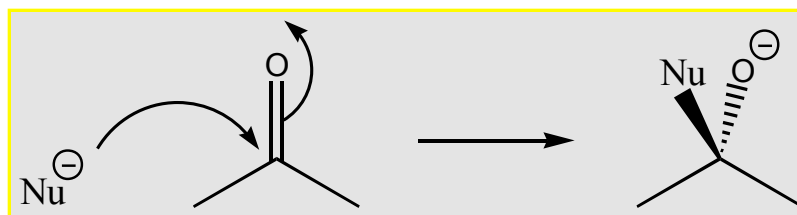

Filled

Unfilled   LUMO (π^*)

109

New C-Nu σ bond

Optimal overlap!

sp2 (trigonal planar carbon)   sp3 (tetrahedral carbon)

Net Reaction

Nucleophilic Addition Reactions of carbonyls

Carbonyl groups in aldehydes and ketones can undergo addition reactions with a range of nucleophiles

Nucleophile	Product
Water	hydration
Alcohols	acetal formation
HCN	cyanohydrin formation
Ammonia derivatives	Schiff bases
Grignard reagents	alcohols
Ylides	olefins
Hydrides	reduction
Oxygen	oxidation

Aldehydes are in general more reactive than ketones
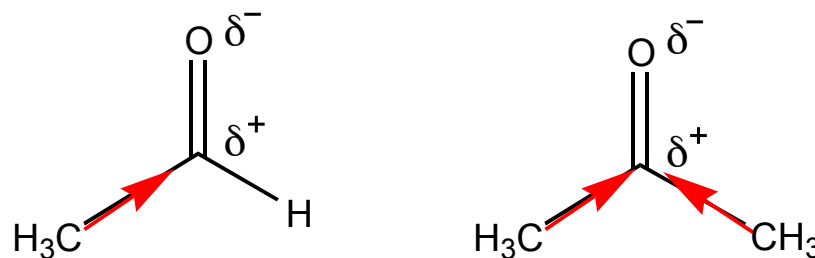
Aldehydic carbon is <u>more electrophilic</u> than ketonic carbon

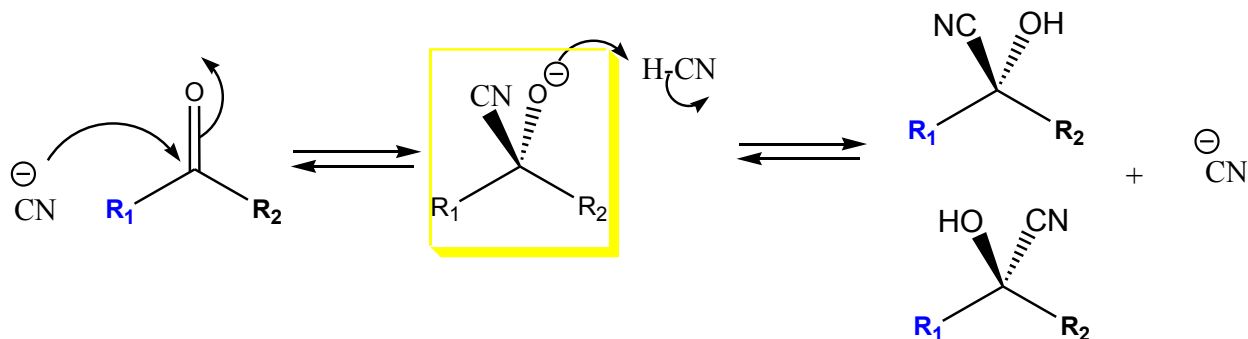Aldehydic carbon is <u>readily available</u> for attack by Nu

If the nucleophile is strong, it can <u>directly add</u> to the carbonyl carbon

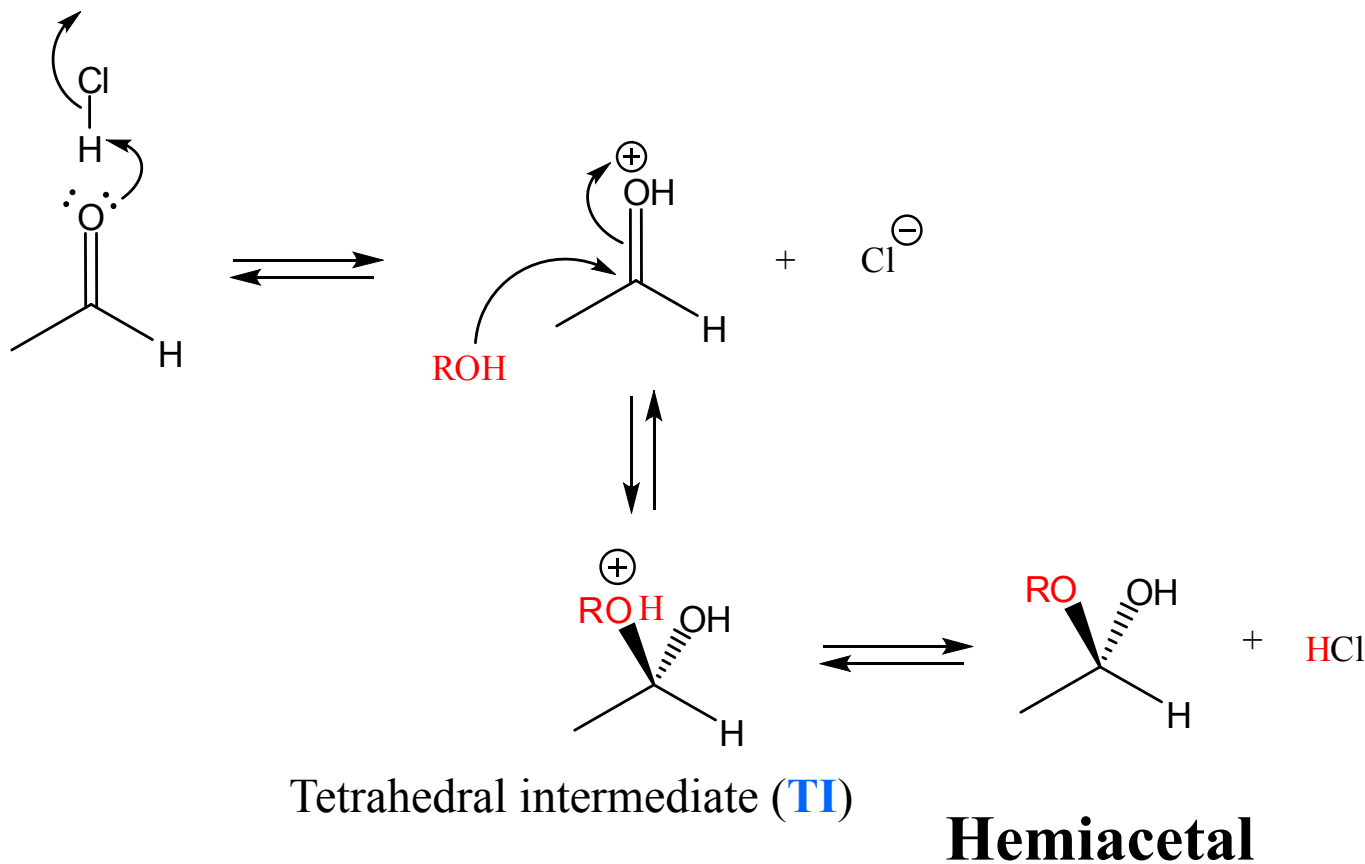If the nucleophile is weak, <u>acid catalysis</u> may be required

Strong nucleophiles add to carbonyl as,

Tetrahedral intermediate (**TI**)
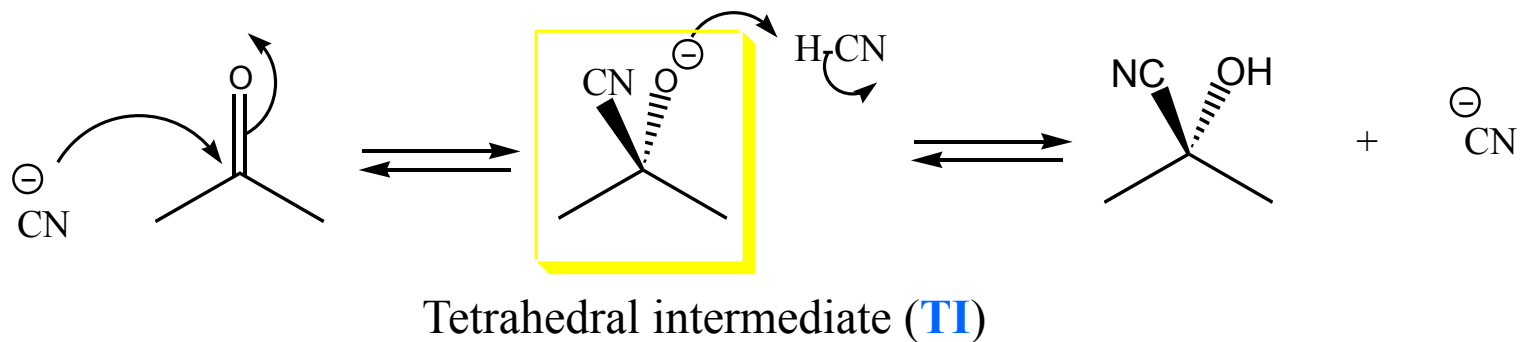
Achiral substrate to chiral products

Weak nucleophiles add to carbonyl group of aldehyde <u>under acid catalysis</u>,

Tetrahedral intermediate (**TI**)

Hemiacetal

(i) Identify the type of reaction (such as addition, elimination, substitution etc.,) by looking at the reactants and products

(ii) As far as possible, try to setup a 'balanced' equation

(iii) Push arrows only from electron rich to electron poor centers (Nucleophiles attack electrophiles, not the other way round!)

(iv) If the reaction is acid catalyzed, an initial protonation step would be followed by a deprotonation later in the reaction sequence

Alcohols add to ketones to yield <u>acetal</u>.

Acyclic <u>hemiacetals are not quite stable</u> enough to be isolated.
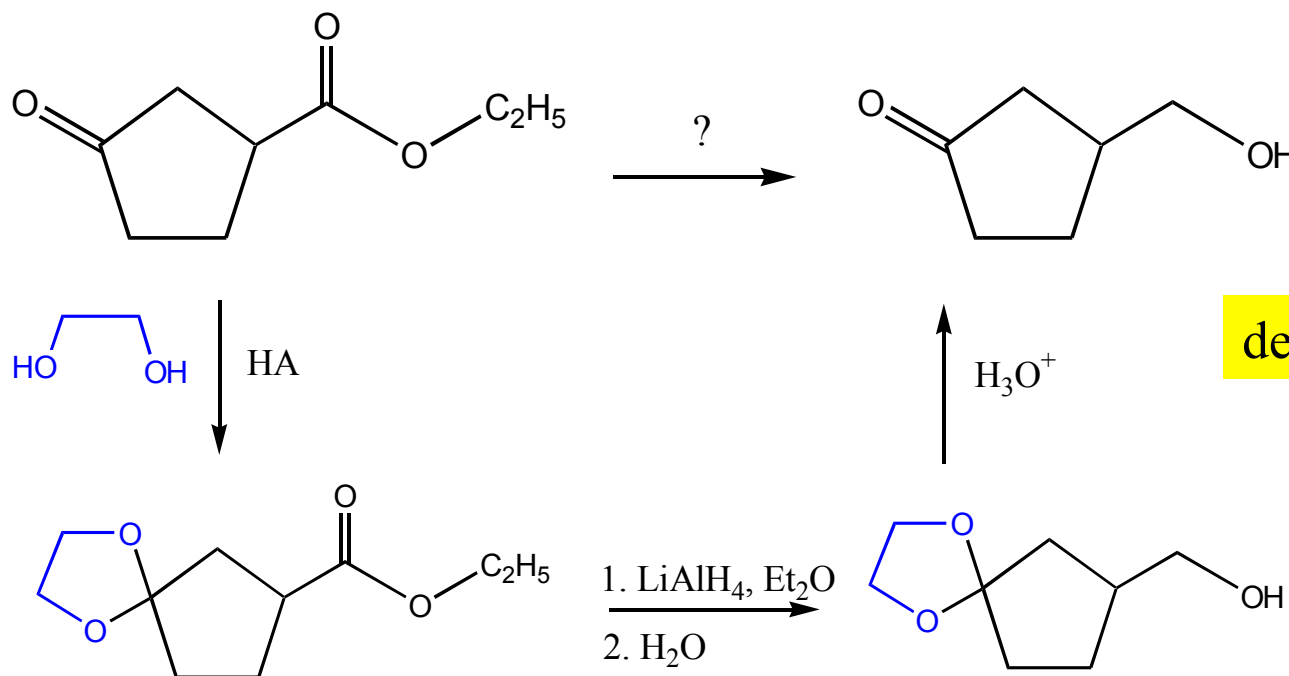
But **cyclic hemiacetals as well as acetals are stable**
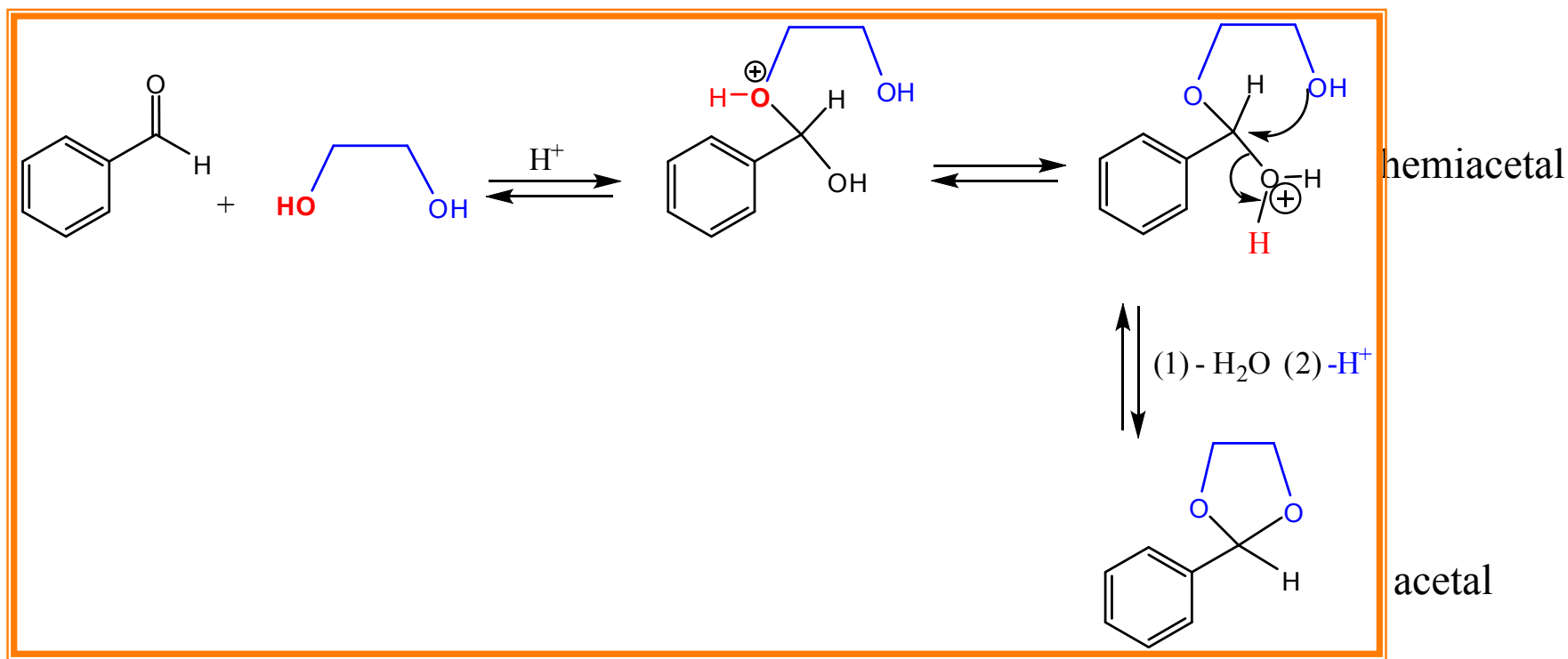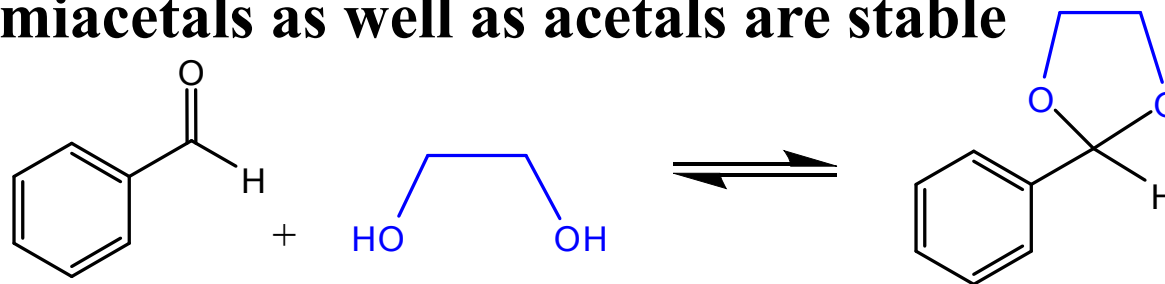
Cyclic acetals are stable to water, bases and nucleophiles but labile to acids

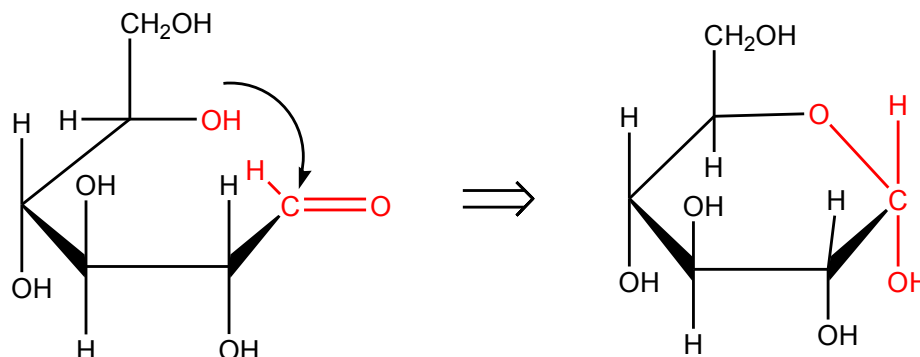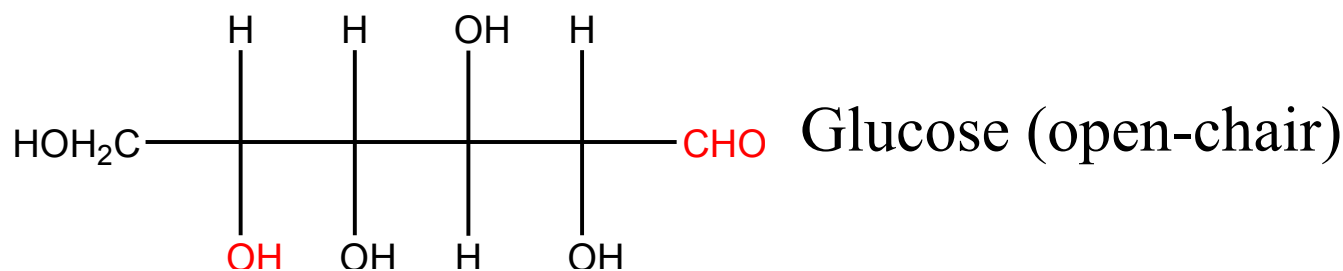**These features are useful as a means to 'protect' aldehydes and ketones**

Example for protection and deprotection,
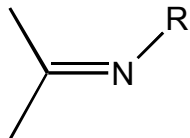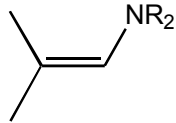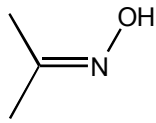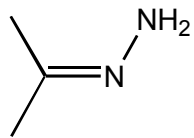

protection

deprotection

Nature uses the stability of cyclic hemiacetals

E.g., glucose prefers a cyclic hemiacetal structure than the corresponding open-chair structure

Glucose (open-chair)

Glucose (cyclic hemiacetal)

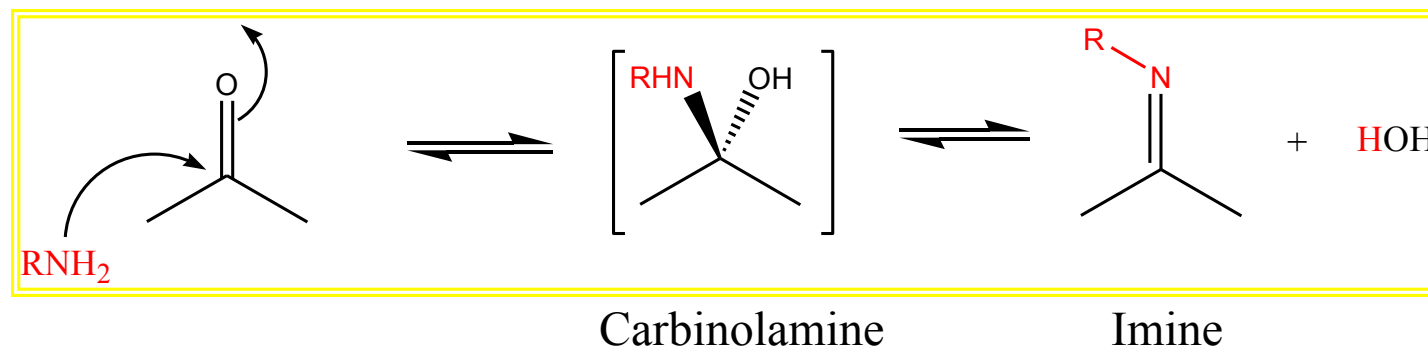Carbonyl compounds such as aldehydes and ketones can react with ammonia derivatives

Nature of amine	Name of the product	Structure
p-amine	Imine (Schiff bases)	
sec-amine	Enamine	
hydroxylamine	Oxime	
hydrazine	hydrazone	

Condensation reactions with ammonia derivatives

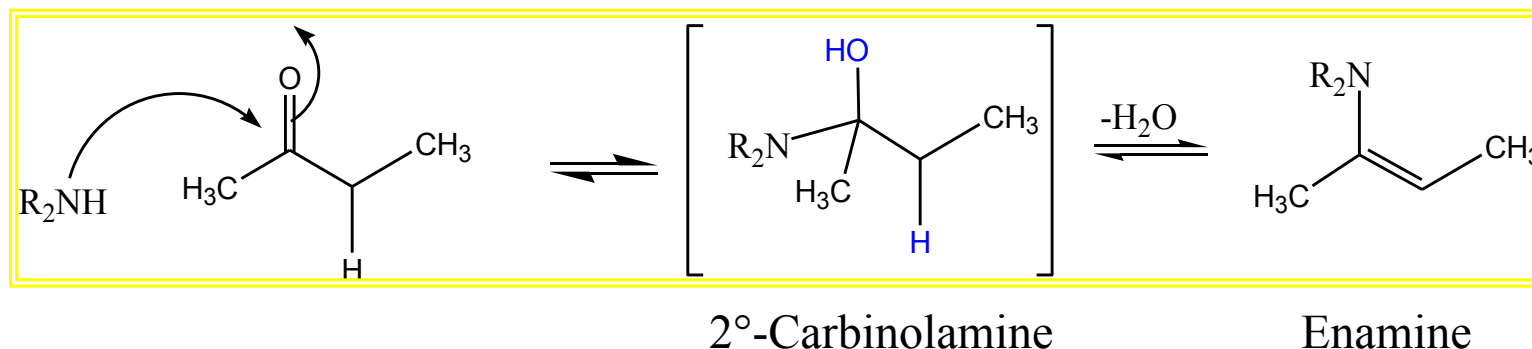Condensation reactions* with ammonia derivatives lead to <u>Schiff bases</u>

Addition $\longrightarrow$ Tetrahedral intermediate $\longrightarrow$ Elimination

Acid catalyzed

Carbinolamine   Imine

---

* One or more molecules are joined with the loss of water or another small molecules

Condensation reactions with ammonia derivatives

Generation of Enamines

2°-Carbinolamine   Enamine

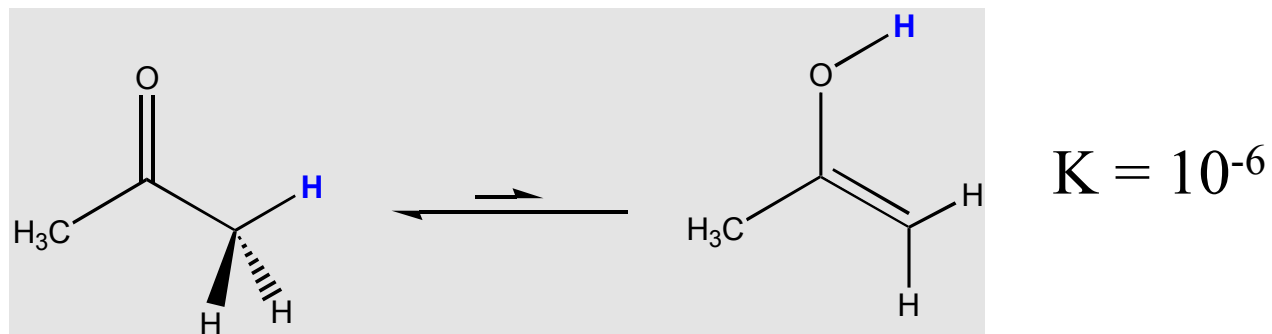Secondary amines can give **enamines** upon condensation with ketones
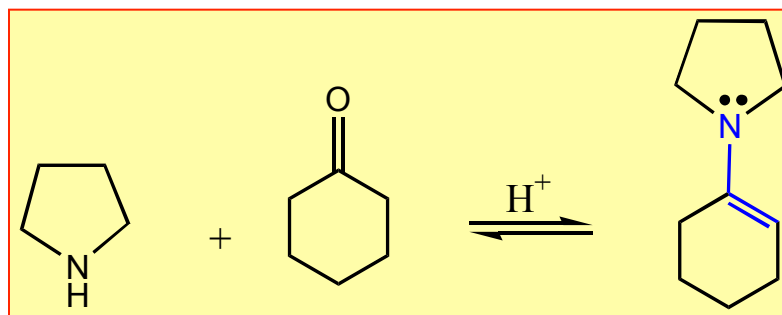
Enamines are **very good nucleophiles** for C-C bond formation
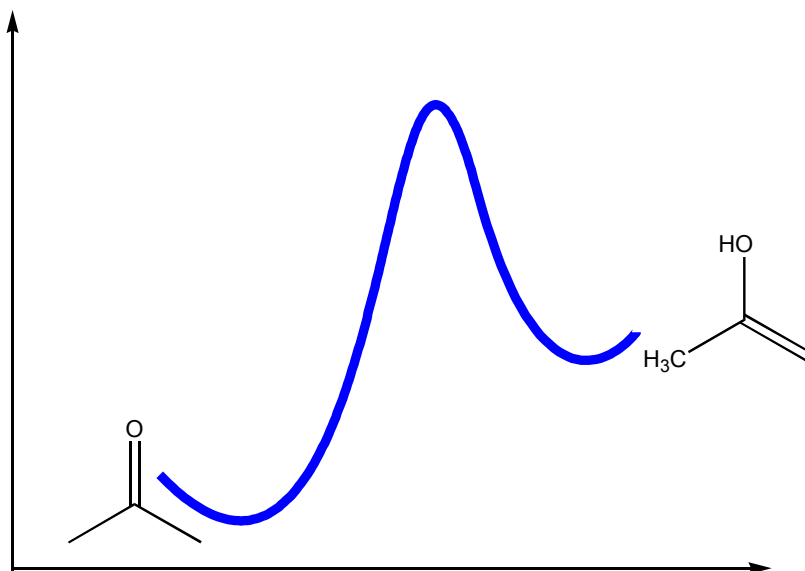
Chemistry of Carbonyl Compounds

Part-II: Enolates

1. Enols

Keto-Enol tautomeric equilibrium leads to enol formation

$$K = 10^{-6}$$

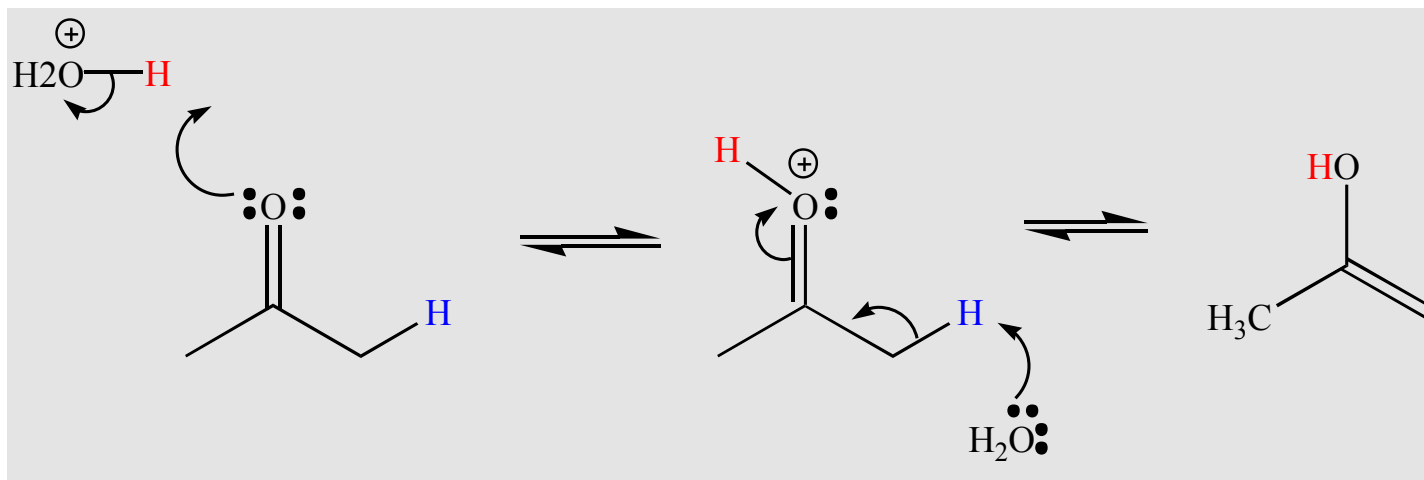For a normal ketone under ordinary conditions only **one in 10^6** exist as enol
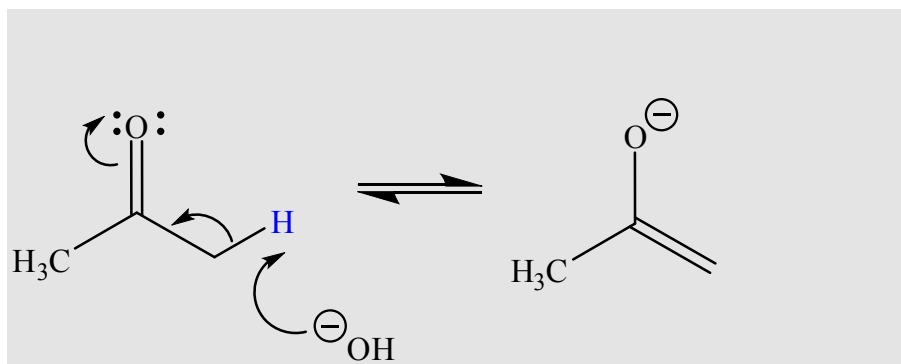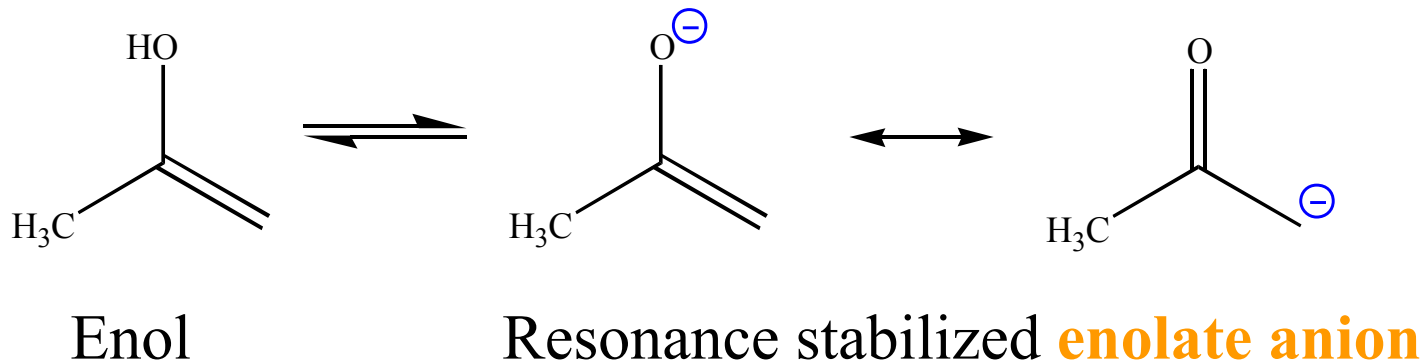
1a. Catalyzed enol formation

(i) Acid catalyzed enol formation

(ii) Base catalyzed enolate formation

2. Enloates are conjugate bases of enols

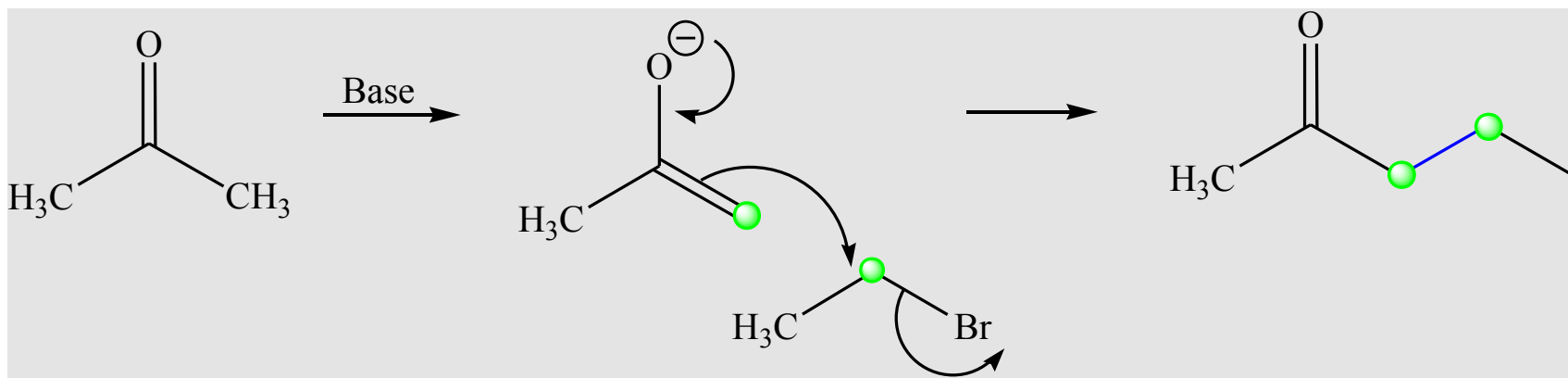Enol   Resonance stabilized **enolate anion**

Alternatively, the acidity of α-hydrogen (next to carbonyl carbon) helps to generate enolate anion
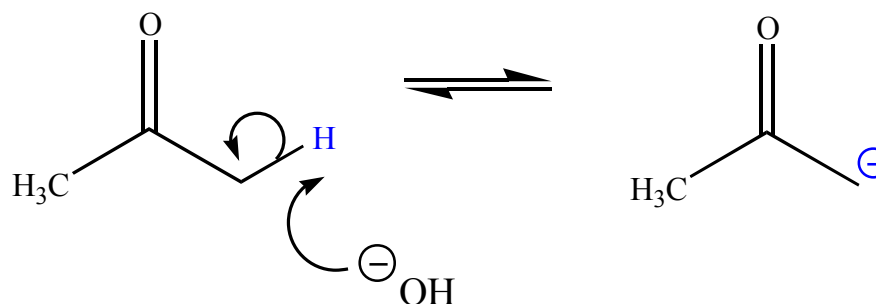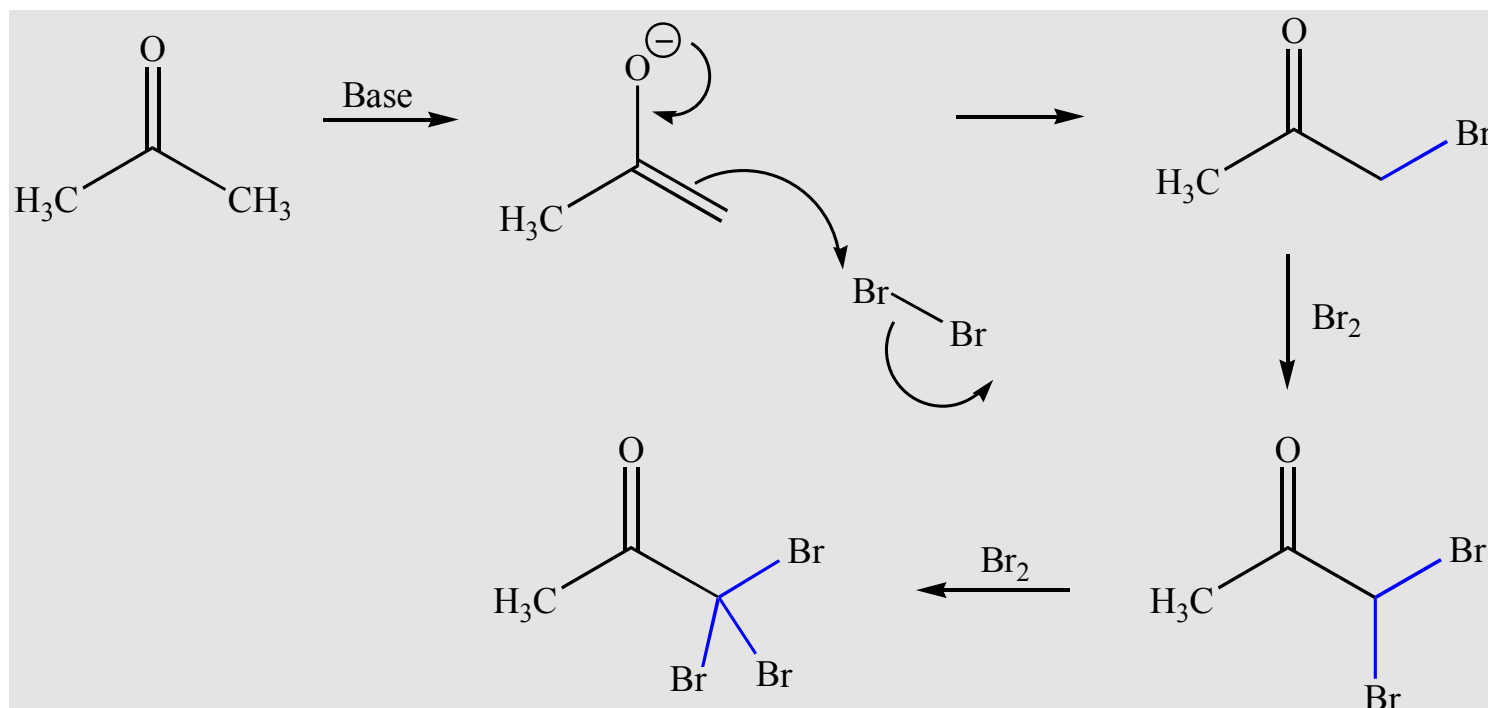

Enolates are powerful carbon nucleophiles!

Acetone → Pentanone

3-carbon ketone to 5-carbon ketone (upgrade)

○ Dots are to highlight the new connection (new C-C bond)

2b. Enolates in halogenation

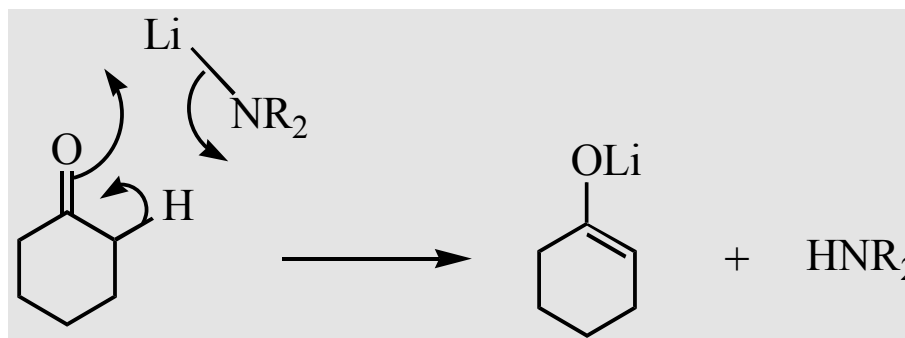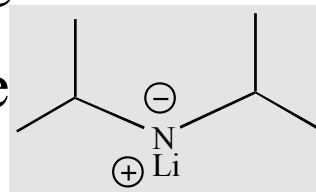Halogenation of the α-carbon can be achieved through base (or acid) catalyzed reaction

Even with strong bases (such as OH^-, OR^-), most carbonyl compounds are converted to enolates only to a small extent!

But, if enolates can be stabilized, more enolates can be generated. This is achieved with the help of strong bases such as,

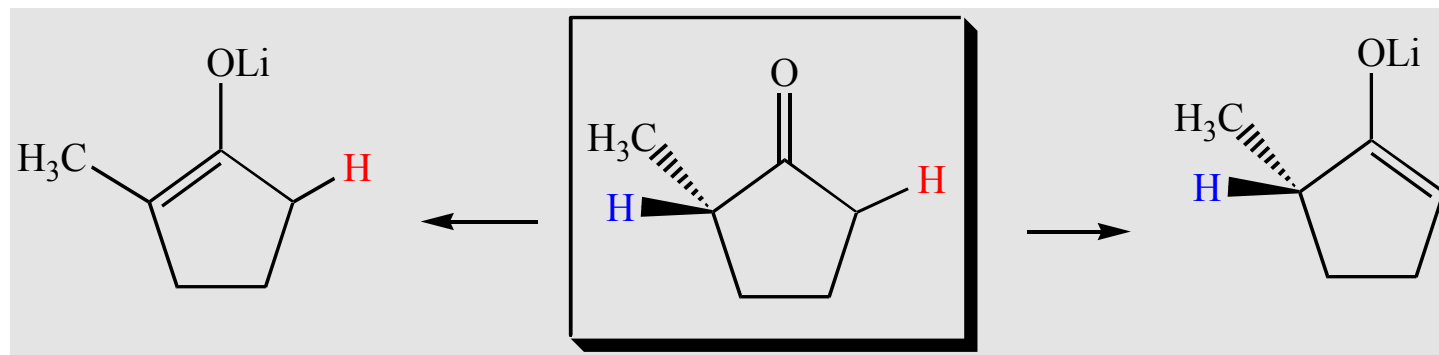**LDA** (**L**ithium **D**iisopropyl**A**mide)

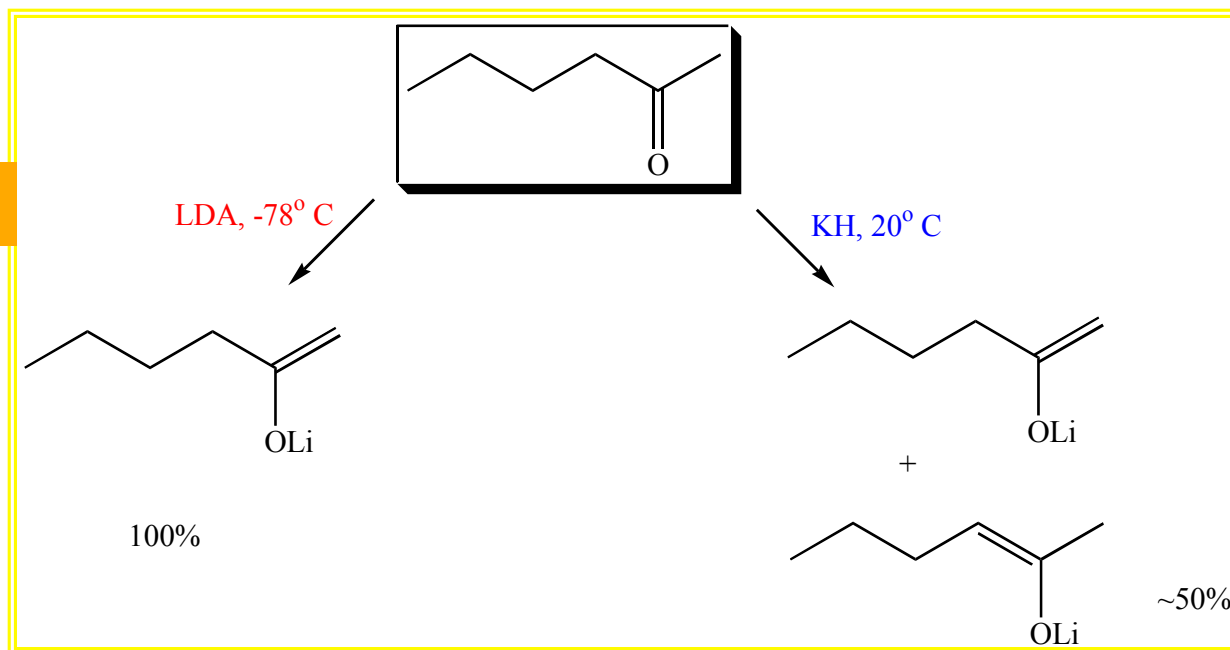

Lithium enolate is stable at **−78°C***

3a. Direction of enolization

With the help of suitable experimental conditions good **regio control** can be obtained in enolization

| Kinetic | | Thermodynamic |

LDA, -78° C
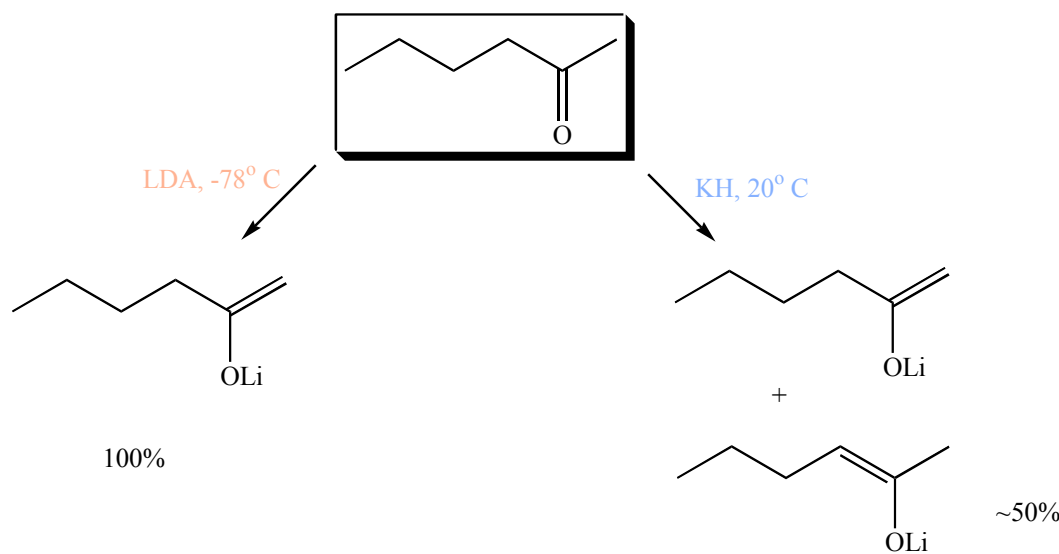
KH, 20° C

100%

+

~50%

General Features

Kinetic	Thermodynamic

•Kinetic refers to SPEED
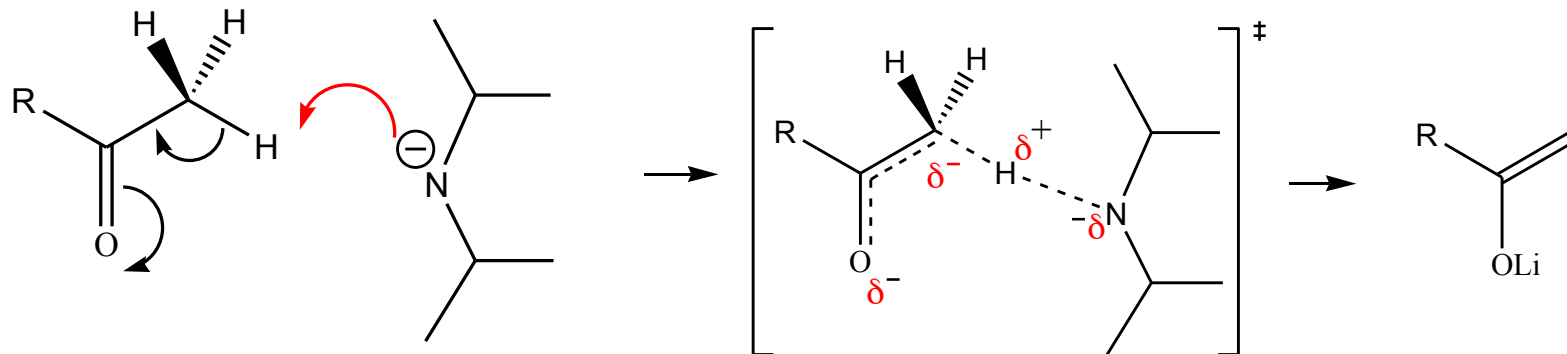
•Governed by activation energy

•Shows propensity to be reversible

•Thermodynamic refers to feasibility (stability)

•Governed by heat of reaction

•Products are usually not quite reversible

LDA, -78° C
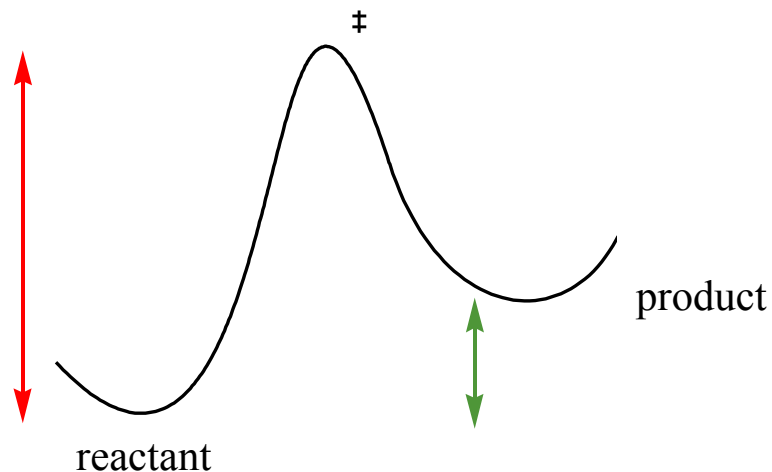
KH, 20° C

OLi

OLi

100%

+

OLi

~50%

Case-I   (i) LDA abstracts proton from the terminal CH_3 group

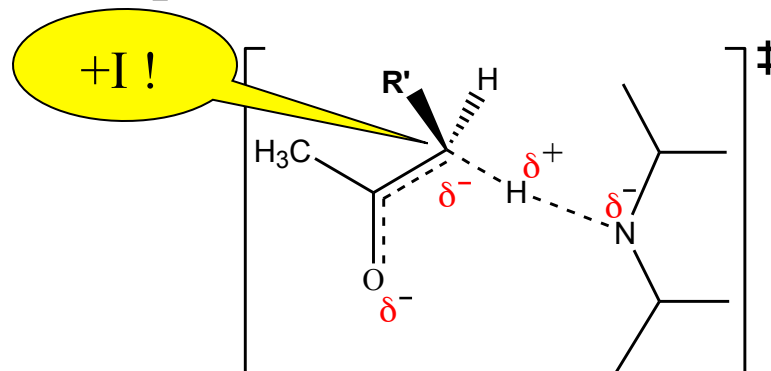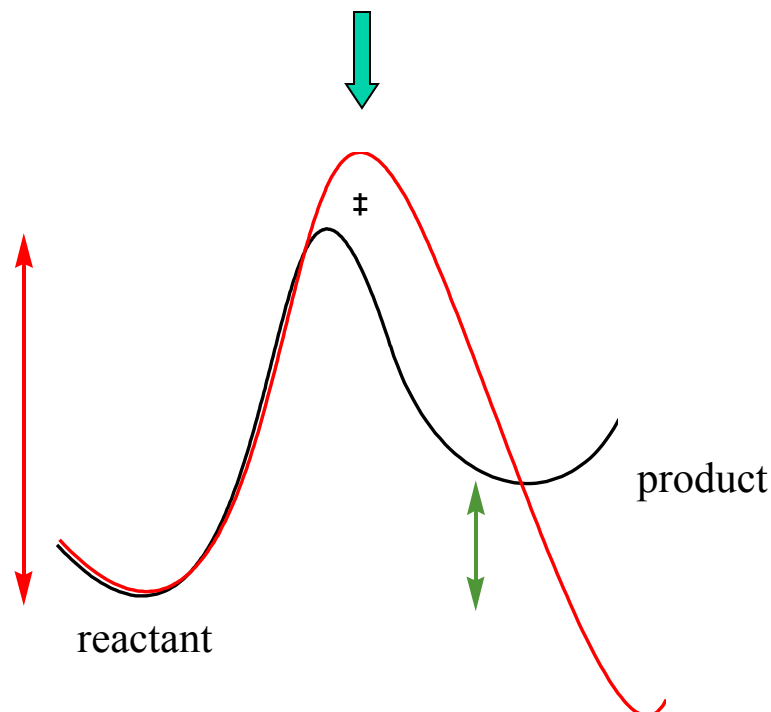Governed by activation energy

ΔG‡

Case-II (ii) If LDA abstracts proton from the internal CH$_2$ group

+I !

ΔG‡ much higher than the previous case!

(a) Difficult to abstract the proton from the more crowded internal methylene group

(b) The developing δ- charge on the internal carbon is destabilized due to +I effect of the 'R' group
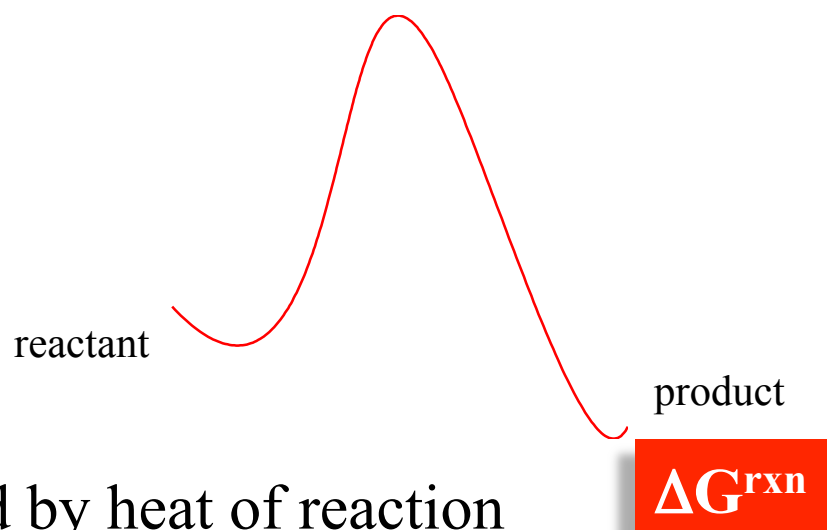
Product stability is the critical factor
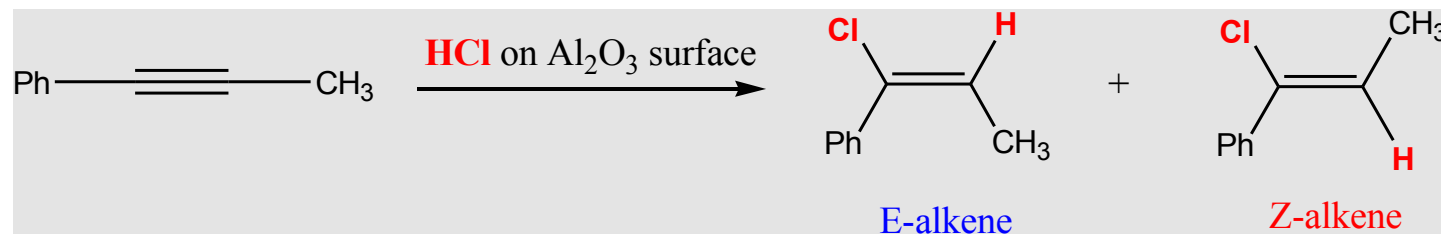
Less bulky base (e.g., KH) are preferred

Carried out at relatively higher temperature as compared to the kinetic control (can therefore go over larger barriers!)

Equilibrium is reached

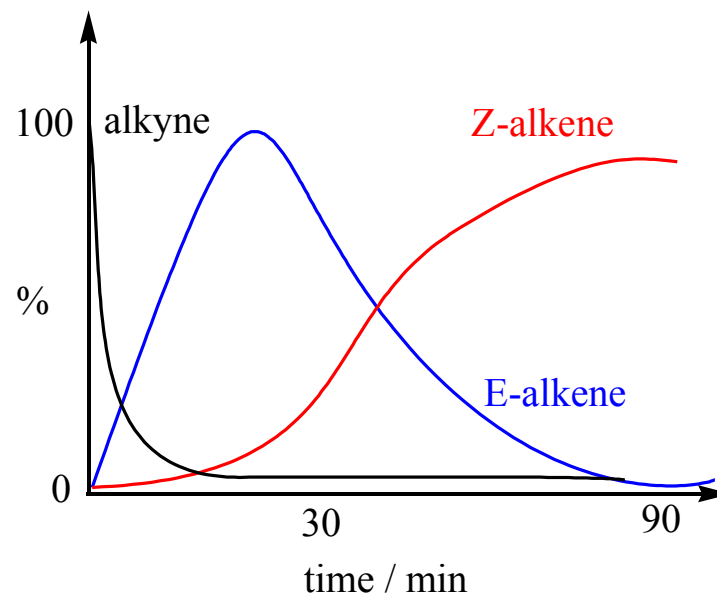reactant

product

ΔG^{rxn}

Governed by heat of reaction

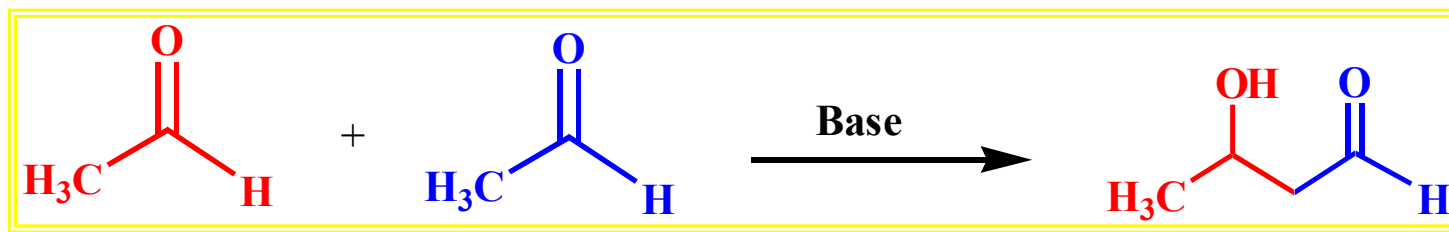Thermodynamic product is more stable than the kinetic product

Within 10 minutes alkyne % drops close to zero and only E-alkene is formed

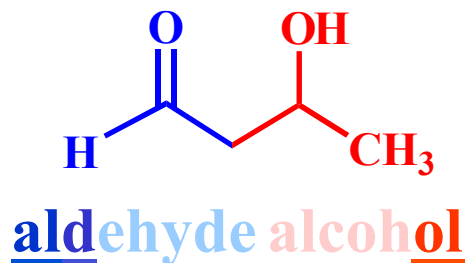Eventually, the proportions of E and Z alkenes do not change

4. The aldol reaction

Aldehyde (as well as ketones) can undergo self-condensation upon treatment with suitable bases

The product contains both <u>aldehyde</u> and <u>alcohol</u> functional groups, hence the reaction is known as aldol reaction
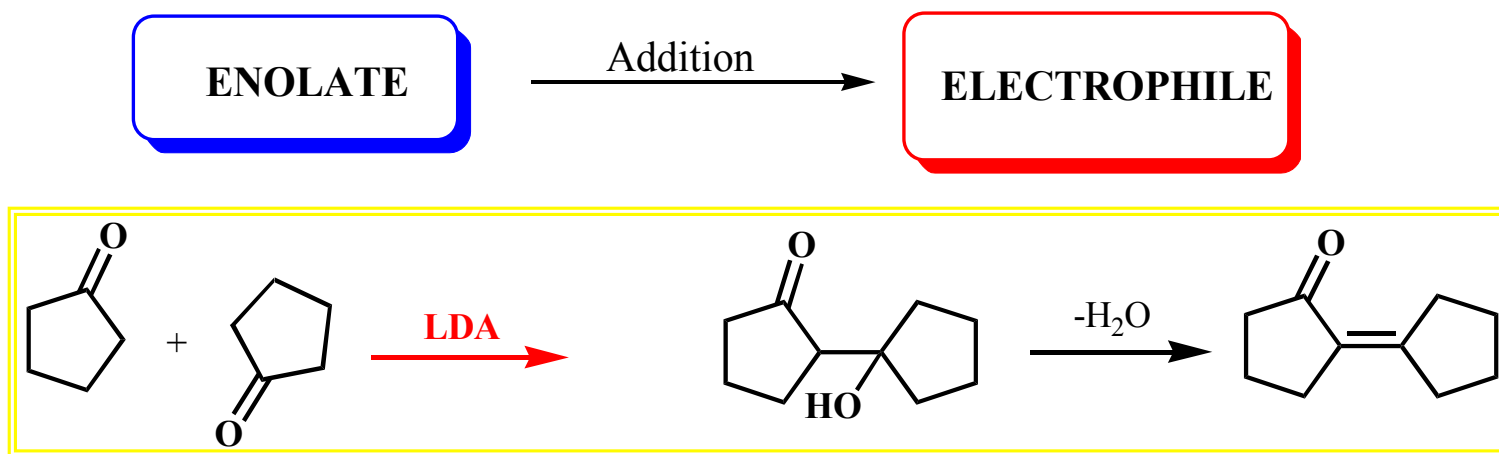

aldehyde alco**ol**

Remember: aldol is not 'named' after anyone!

The C-C bond formation requires a carbon nucleophile (enolate) and an electrophile (acceptor)

ENOLATE → *Addition* → ELECTROPHILE

Aldol reaction catalyzed by acids (or bases) is usually accompanied by dehydration leading to α,β-unsaturated carbonyl compounds
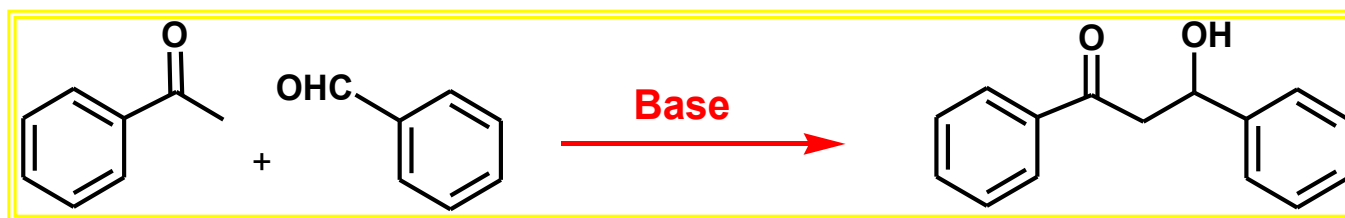
The above example is self aldol condensation

4a. Crossed aldol reaction

Two aldehydes among which only one can serve as carbon nucleophile (enolate) and the other simply serves as an electrophile (acceptor)

In other words, the acceptor molecule (or electrophile) is non-enolizable!

enolate   electrophile
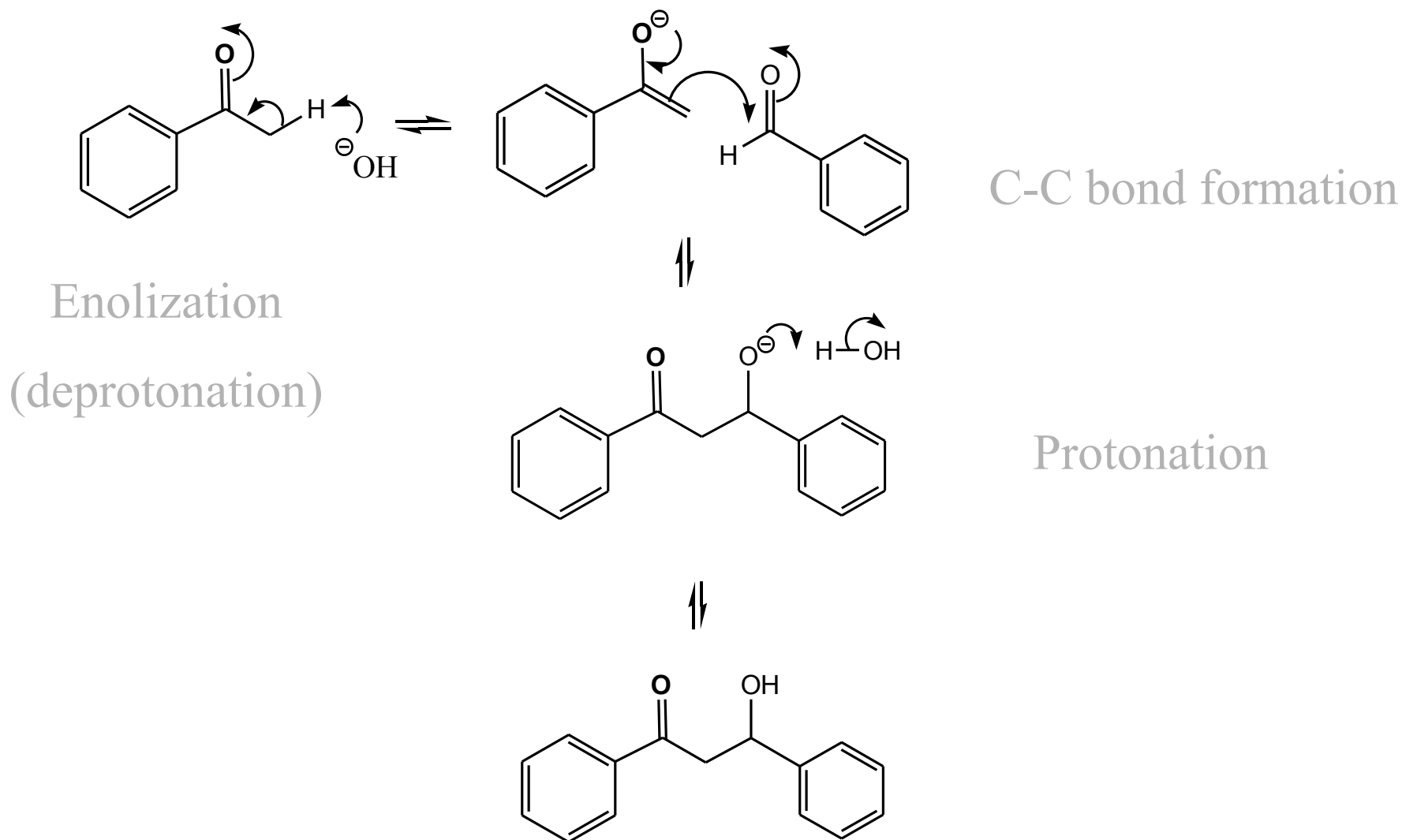
only

Mechanism

Enolization (deprotonation)

C-C bond formation

Protonation

Base

Enolization

(deprotonation)

C-C bond formation
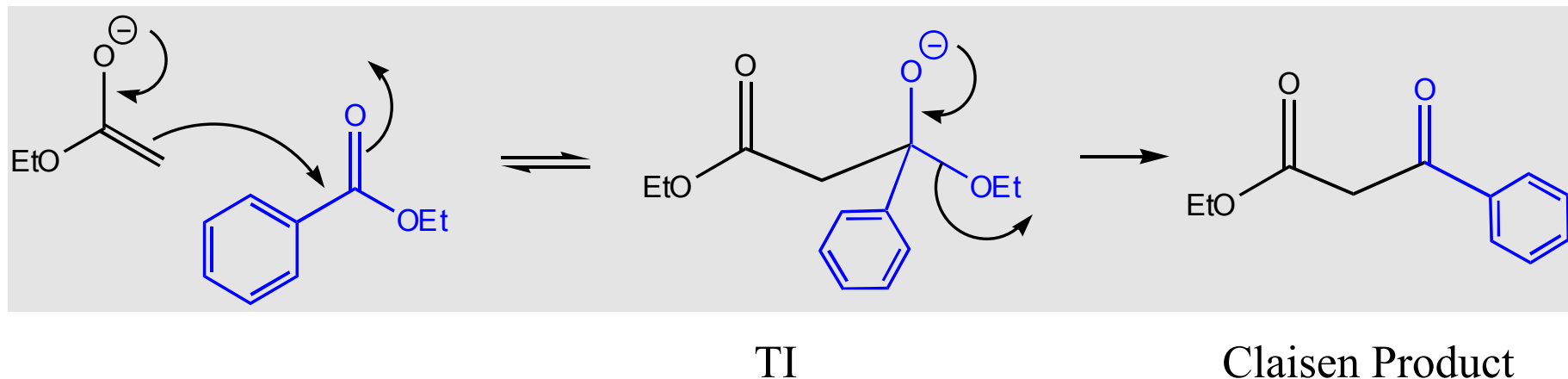
Protonation

Base catalyzed condensation between two esters.

Only one of the esters can undergo enolization while the other serves as an electrophile (acceptor)

In other words, one ester has acidic α-hydrogen and the electrophile(or acceptor molecule) do not have α-hydrogens

electrophile

TI   Claisen Product

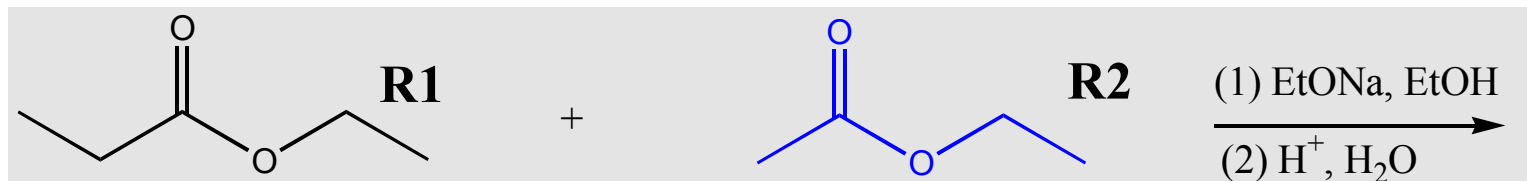What about the situation where both esters have acidic α-hydrogens?

OR

What if both esters can undergo enolization?
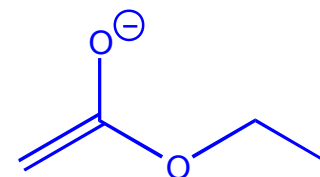
5b. Crossed-Claisen Condensation

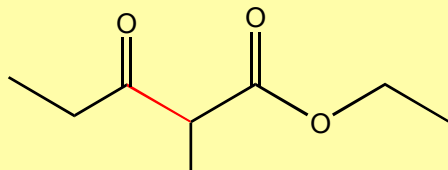If both esters can undergo enolization, a mixture of products are formed,

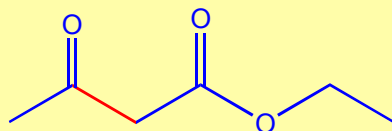**R1** + **R2**   (1) EtONa, EtOH / (2) H$^+$, H$_2$O
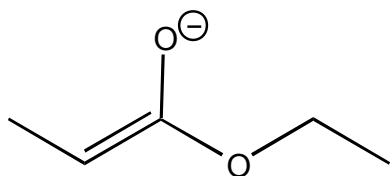
E1   **E2**

(i) Self condensation

E1R1

E2R2

(ii) Crossed condensation

E1R2
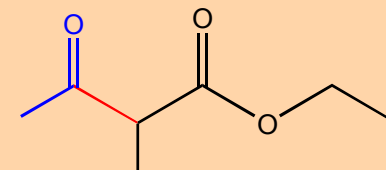
**E2R1**
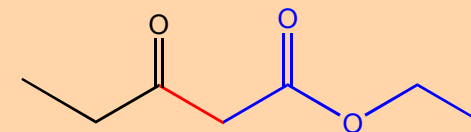
# **5c**. Intramolecular Claisen (Dieckmann) Condensation

In the case of acylic diesters, where the ester groups are at suitable positions, an <u>intramolecular Claisen condensation</u> would lead to a cylic ester as the product.

Intramolecular Claisen condensation where the ester enolate as well as the acceptor electrophile are part of the same molecule is known as **Dieckmann condensation**
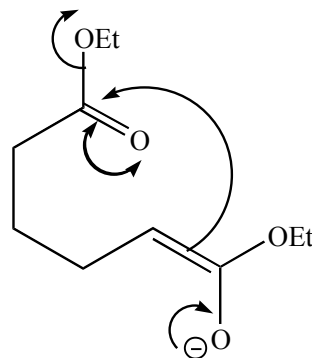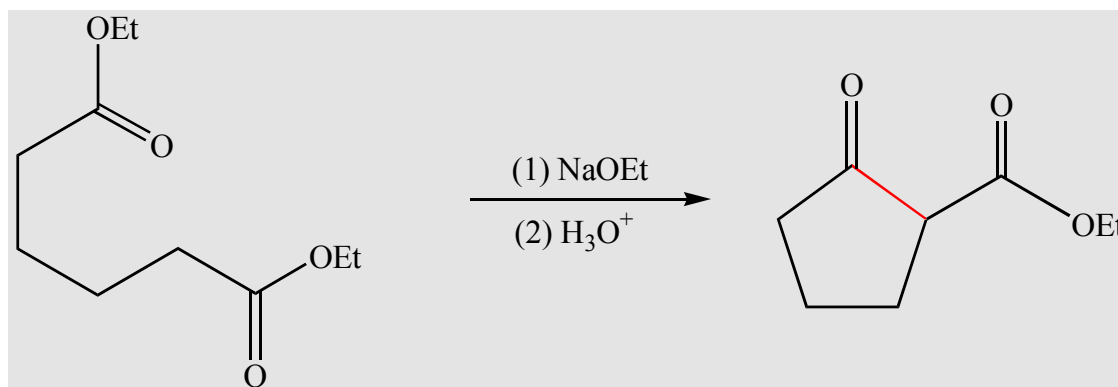
6. Conjugate addition

Activated double bonds are the ones which are connected to electron withdrawing groups such as CO, CHO, COOH, CN, NO_2 etc.,
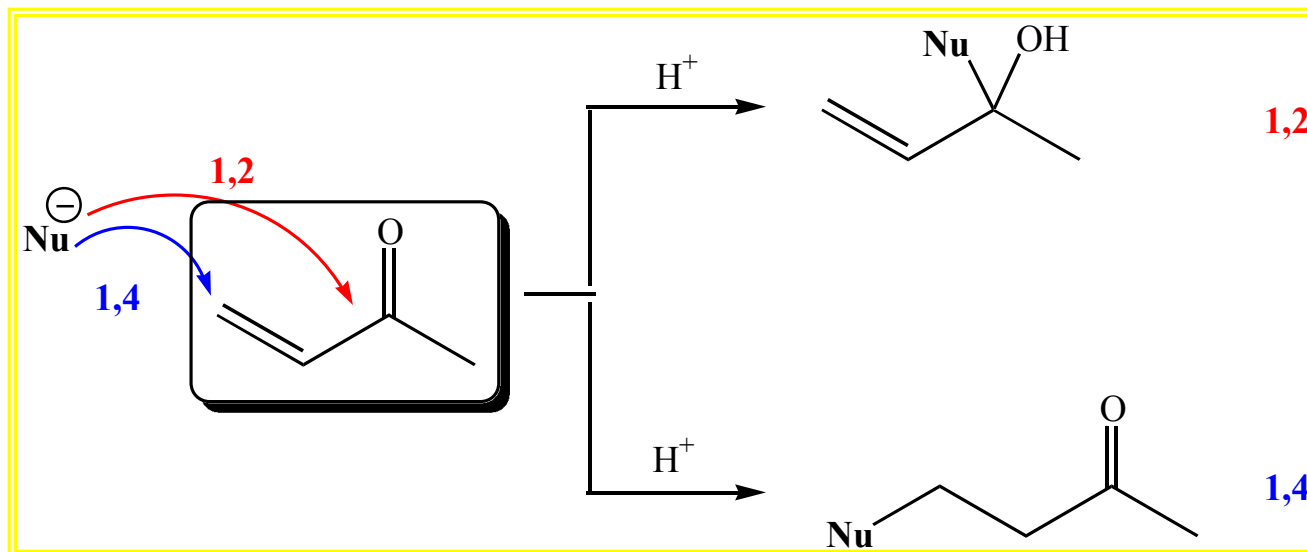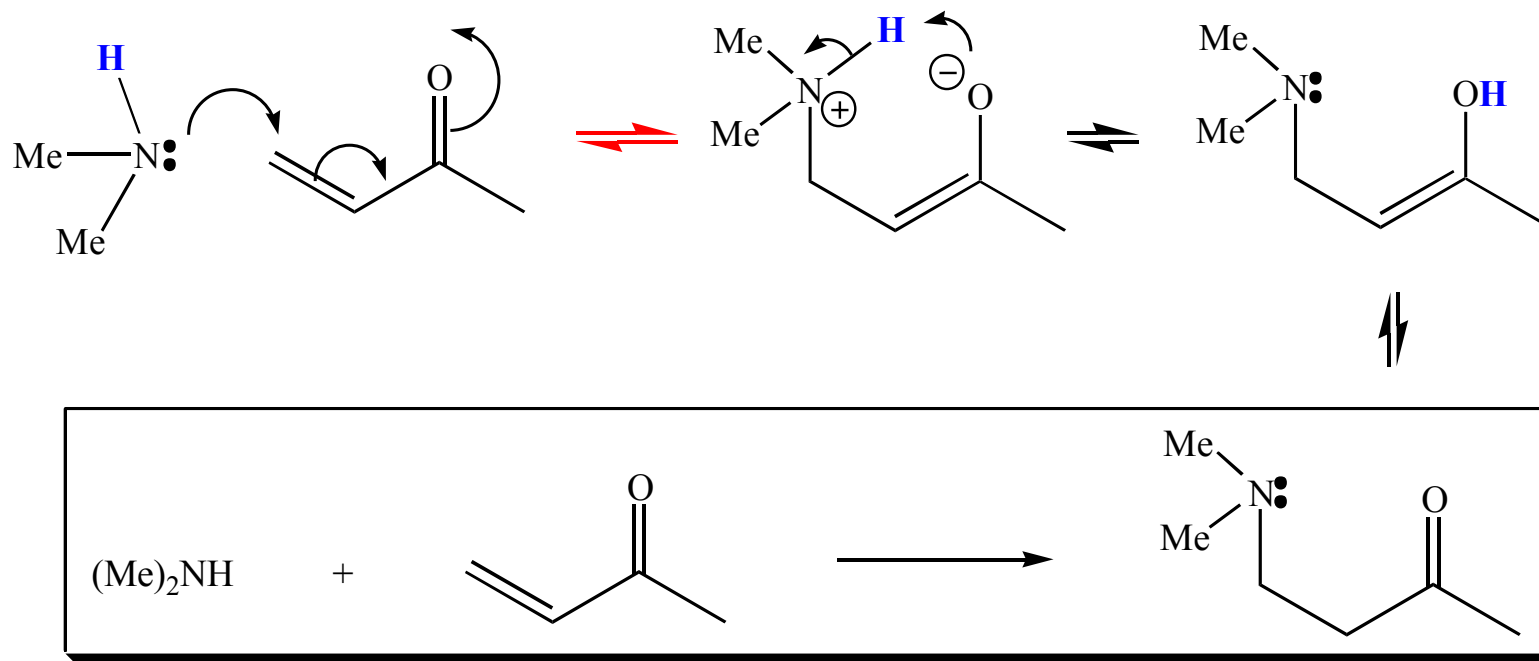

1,2-additions* are also known as **direct addition**

1,4-additions are known as **conjugate addition**

---

* Addition of Nu and H^+

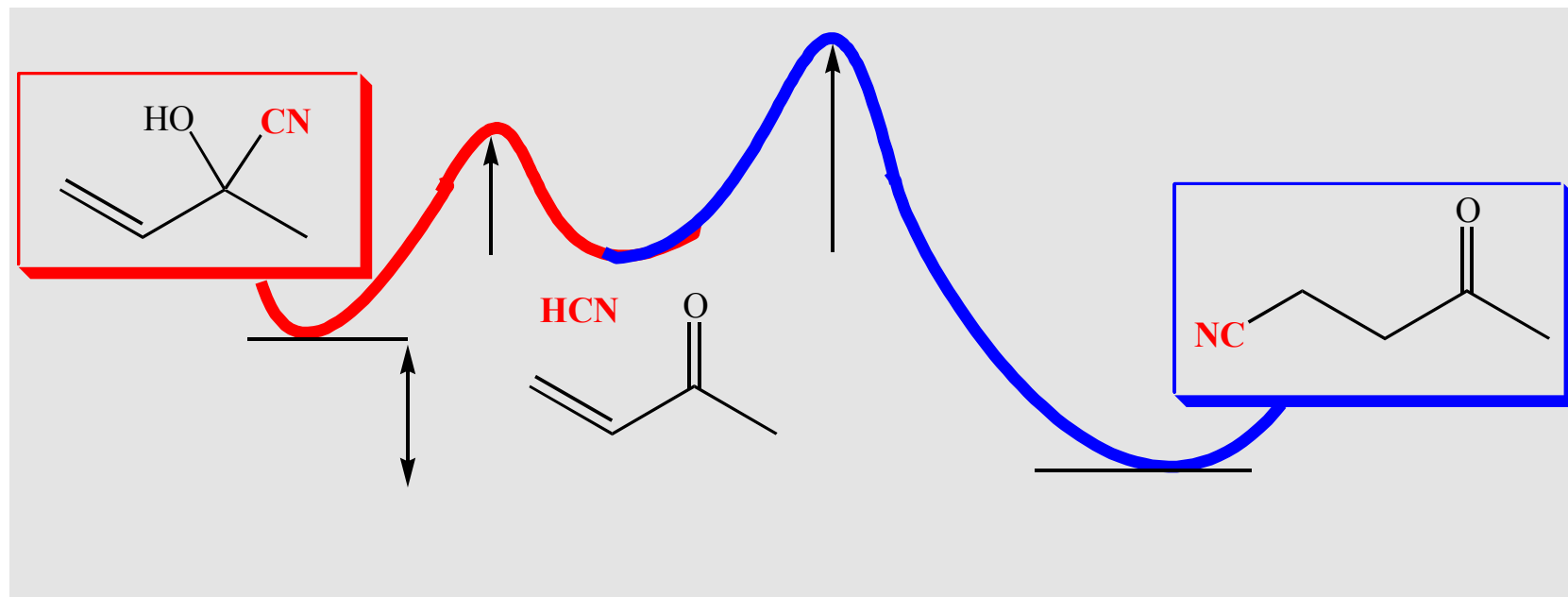# **6a**. Additions to α,β-unsaturated carbonyl compounds

Key factors that control conjugate addition are,

(i)   Reaction conditions

(ii) Nature of the α,β-unsaturated carbonyl compound

(iii) Type of nucleophile

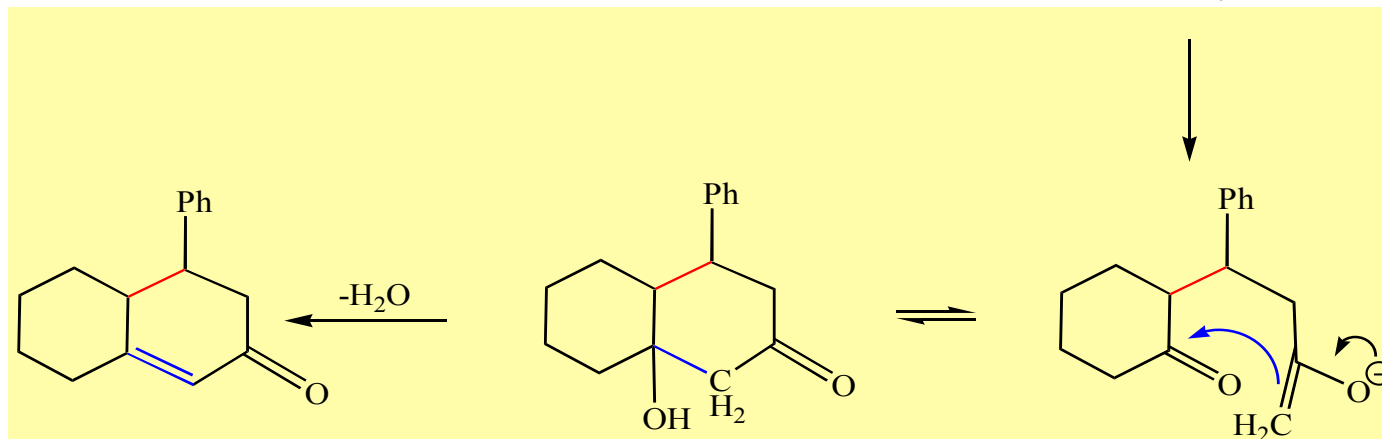| $\Delta G^{\ddagger}_{(reaction)}$	$\Delta G_{(reaction)}$
speed	product stability
reversible	irreversible
lower temp	higher temp

Nucleophilic addition of stabilized carbanion (carbon nucleophiles)
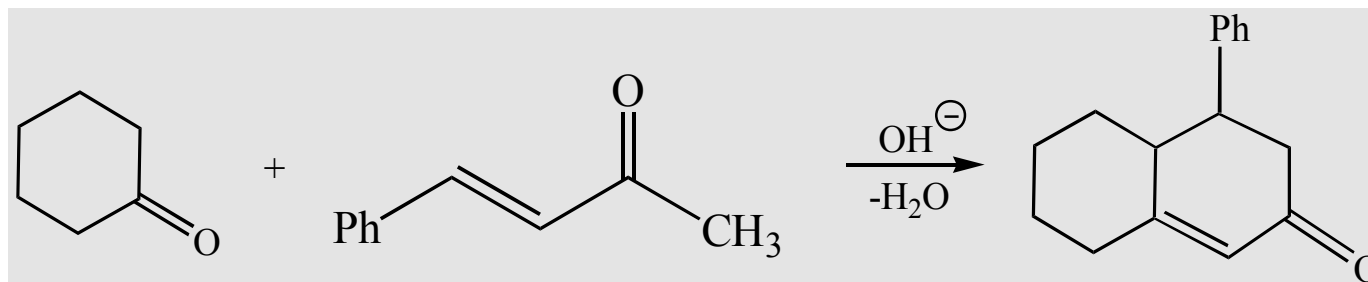α,β-unsaturated carbonyl compounds
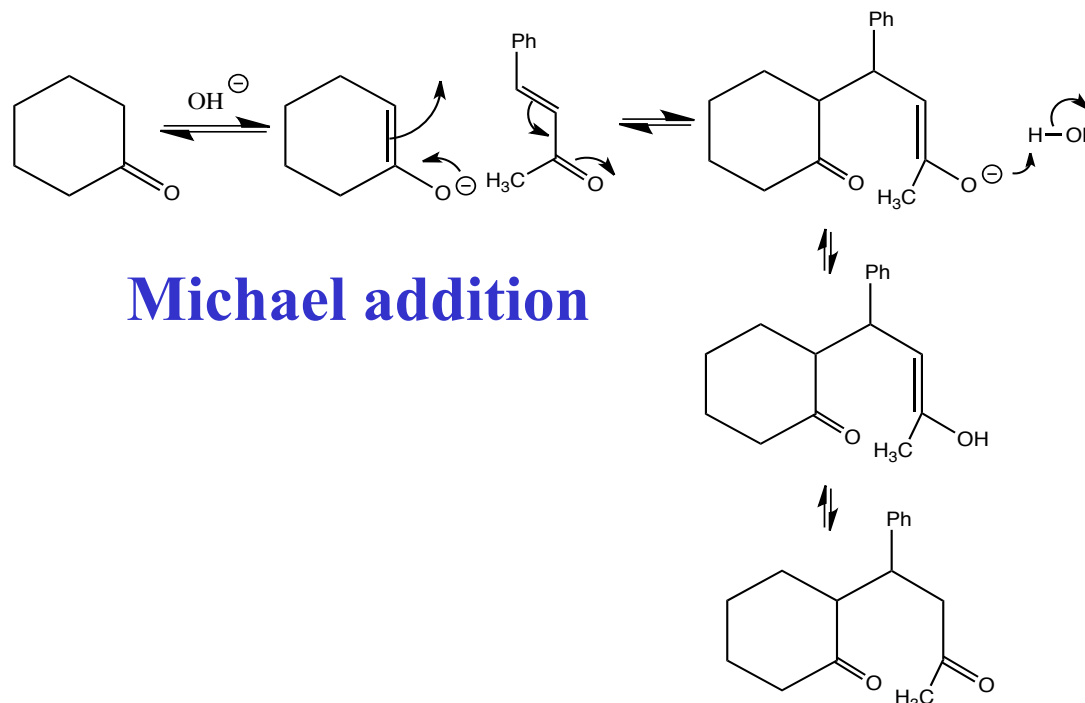
Michael addition

aldol

Michael addition   +   aldol   Followed by dehydration

Additional Slides, which were not discussed in the class. These are closely related content related to what was discussed and hence important too.
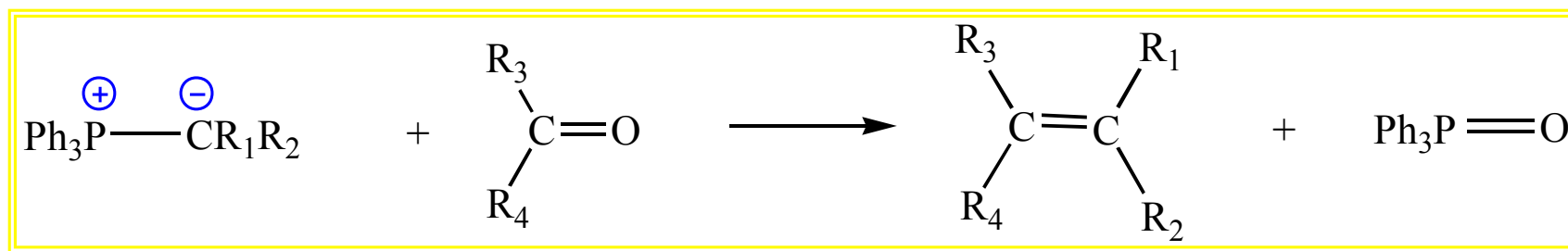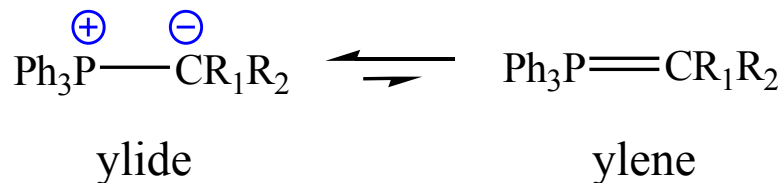
Self-study topics (up to slide number 56)

Georg Wittig (1954): Nobel prize winner 1979

Reactions of aldehydes or ketones with phosphorous ylides* to give alkene

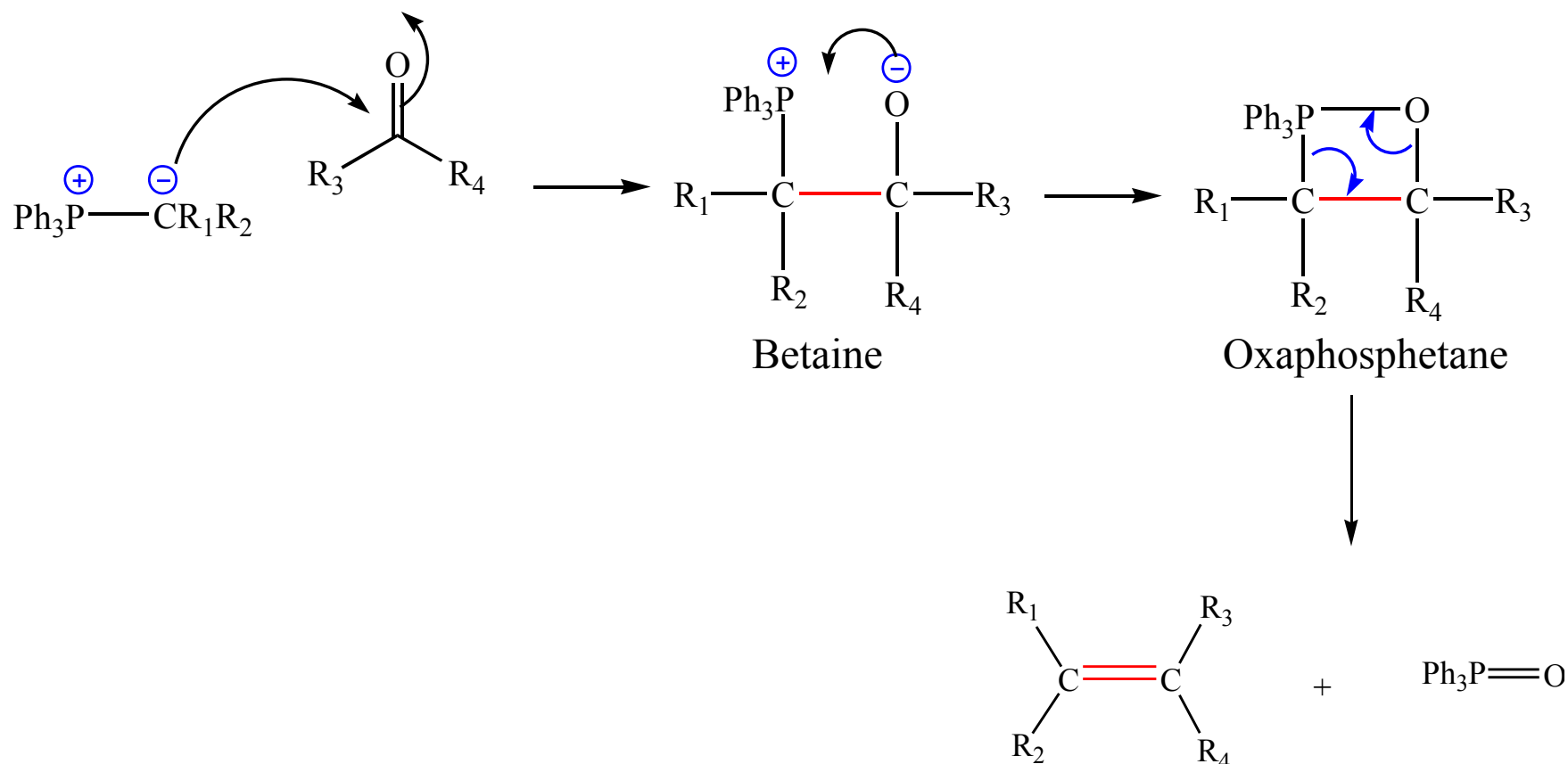$$Ph_3\overset{\oplus}{P}\!-\!\overset{\ominus}{C}R_1R_2 \quad + \quad \underset{R_4}{\overset{R_3}{>}}C\!=\!O \quad \longrightarrow \quad \underset{R_4}{\overset{R_3}{>}}C\!=\!C\underset{R_2}{\overset{R_1}{<}} \quad + \quad Ph_3P\!=\!O$$

Phosphorous <u>stabilized carbanions</u>

$$Ph_3\overset{\oplus}{P}\!-\!\overset{\ominus}{C}R_1R_2 \; \underset{\longrightarrow}{\longleftarrow} \; Ph_3P\!=\!CR_1R_2$$

ylide   ylene

**Due to carbanion character ylidic carbons are highly nucleophilic**

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* Ylides are neutral molecules with a negatively charged carbon atom and a positively charged heteroatom (P, S, N etc.,)

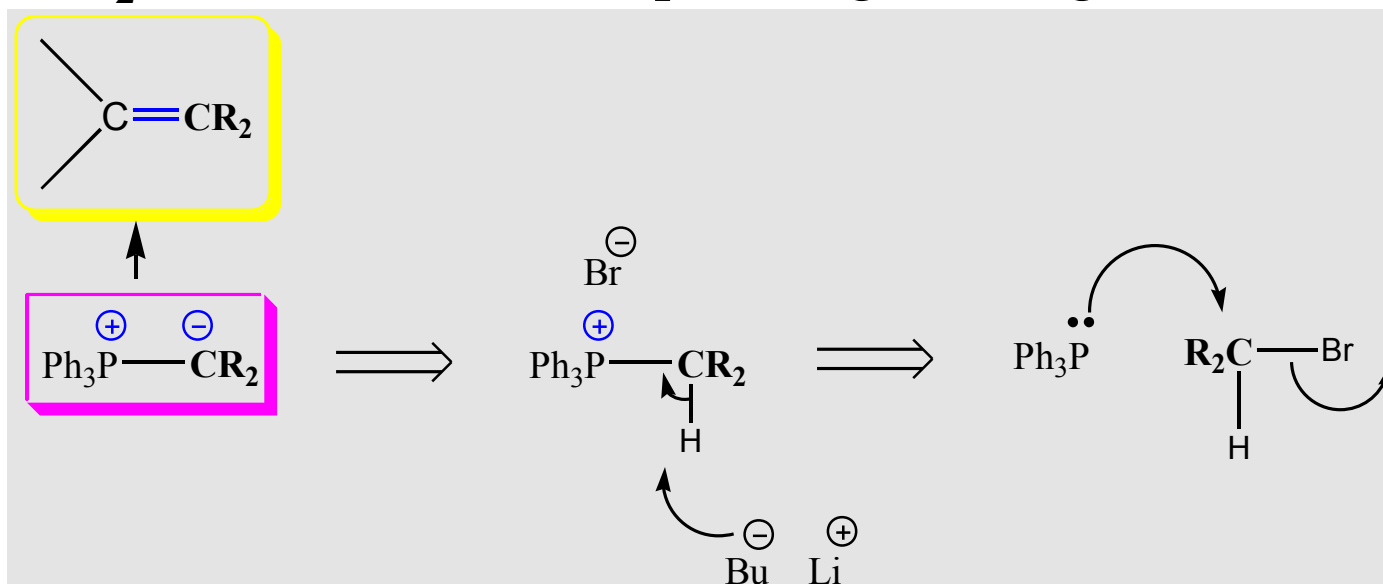# 7a. Mechanism of Wittig Reaction

Betaine

Oxaphosphetane

Phosphine oxide is a very stable species. Formation of alkene as well as phosphine oxide provides great thermodyanic drive for this reaction

7b. Wittig Reaction is an **olefination** reaction
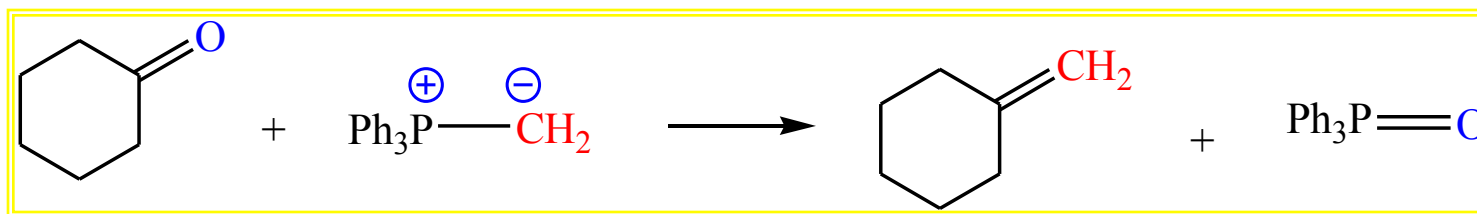
Choice of **R₂CX** is critical while planning a Wittig olefination reaction
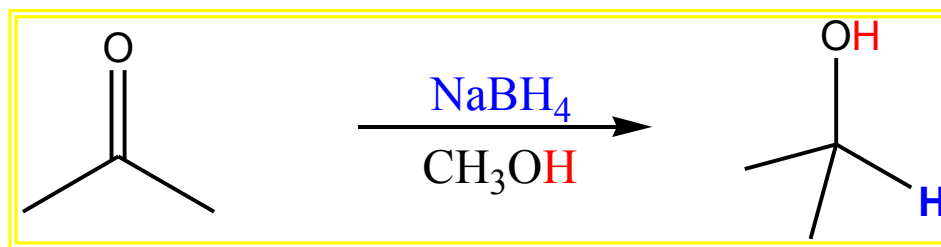

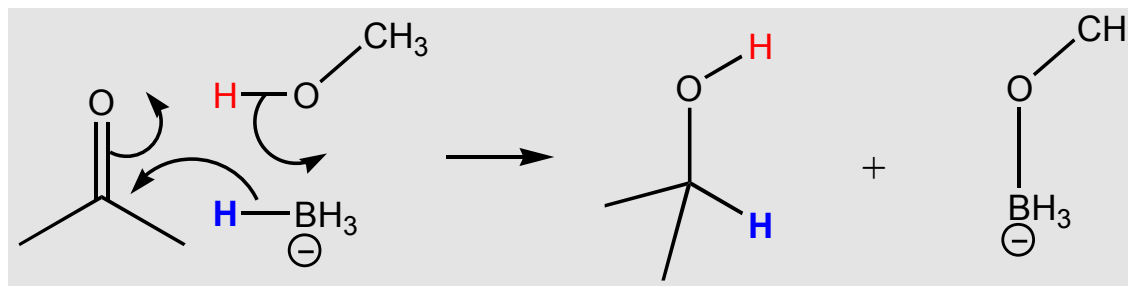Other bases used for the generation of ylides: t-BuOK, NaH

(i). Reduction of carbonyl groups using **NaBH$_4$**

Aldehydes and ketones can be reduced by NaBH$_4$ in MeOH (or EtOH) to produce alcohols

The actual reducing agent is **BH$_4^-$** OR **H$^-$** BH$_3$

8b. Addition of Hydride (LiAlH$_4$)

(ii). Reduction of carbonyl groups using **LiAlH$_4$**

The relative order of reactivity of carbonyl groups toward nucleophiles is
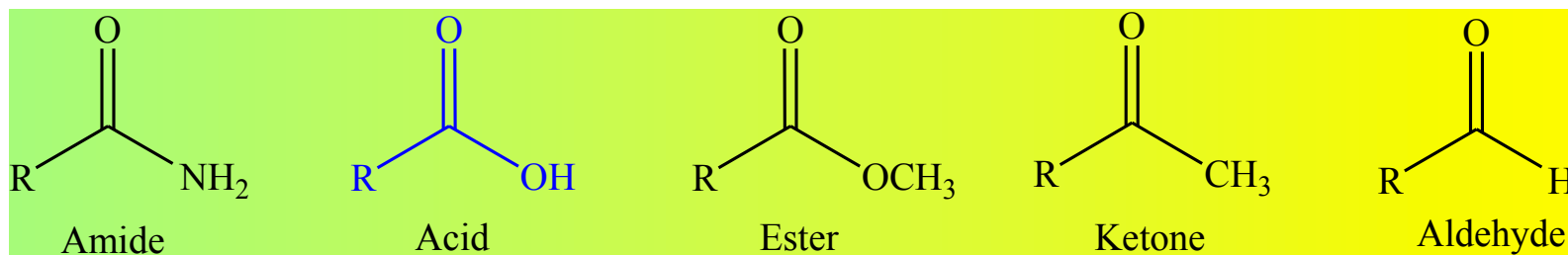
→ Increasing order of reactivity

Carbonyl groups as part of esters and carboxylic acids require more powerful reducing agents such as **LAH**

8c. Reduction of carboxylic acids

LAH reacts violently with protic reagents (solvents)

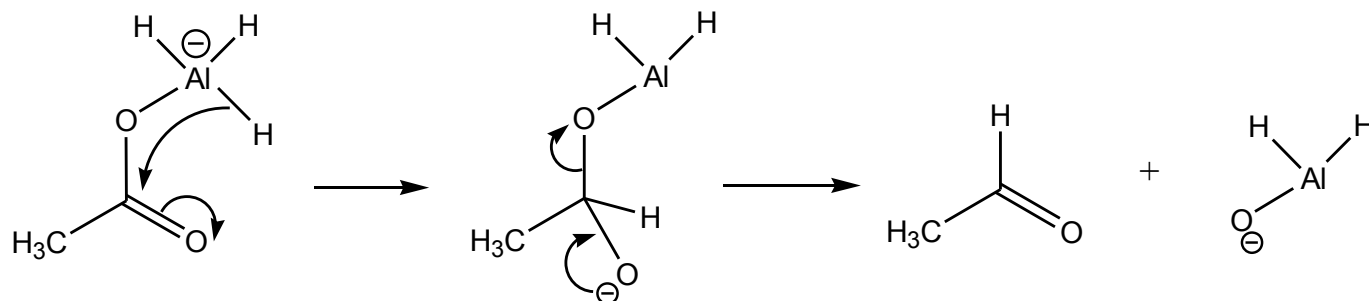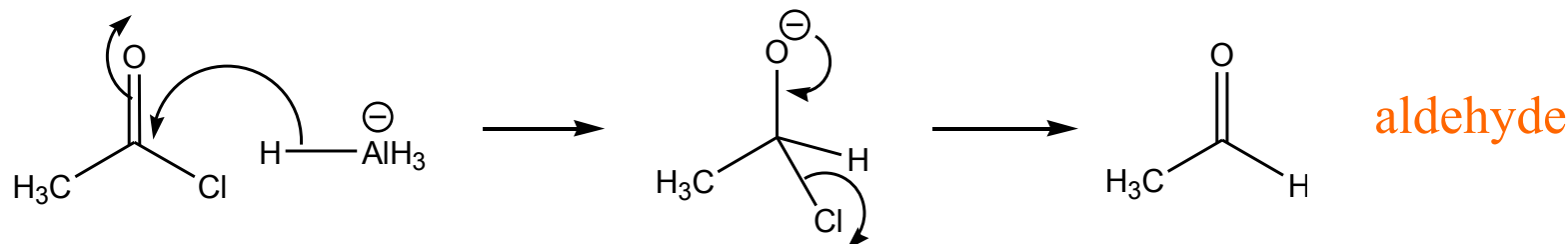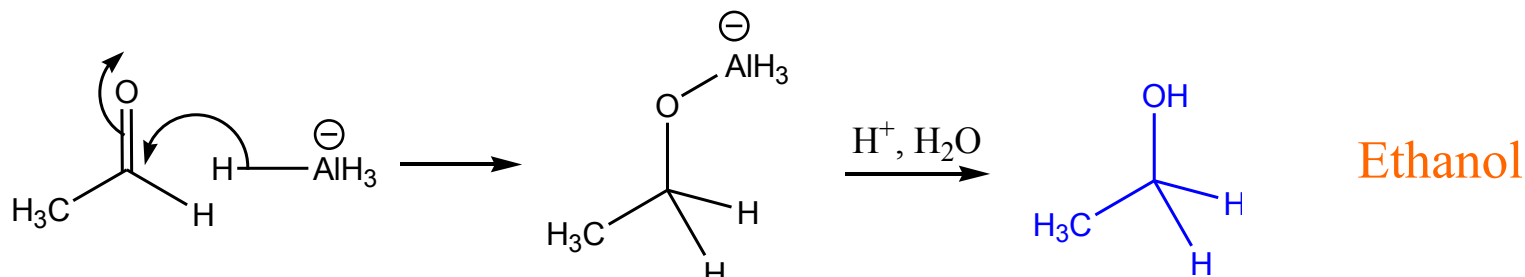Therefore, the reaction must be conducted in a <u>dry, aprotic solvent</u>
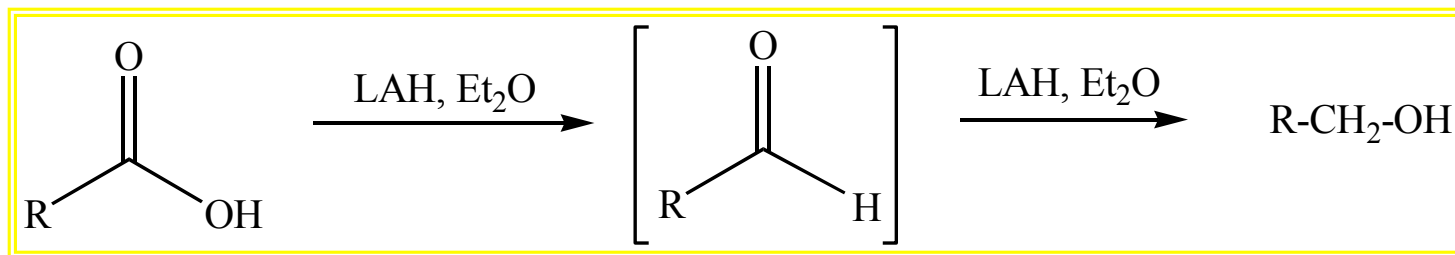
Mechanism

Step-I
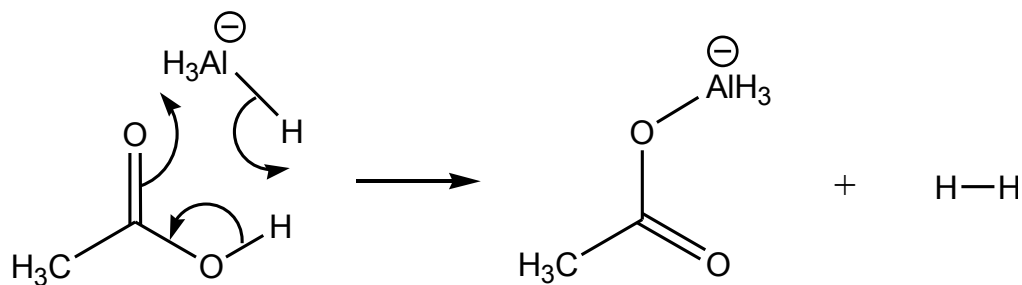
Step-II

8d. Reduction of other acid derivatives

Mechanism of reduction for acid derivatives
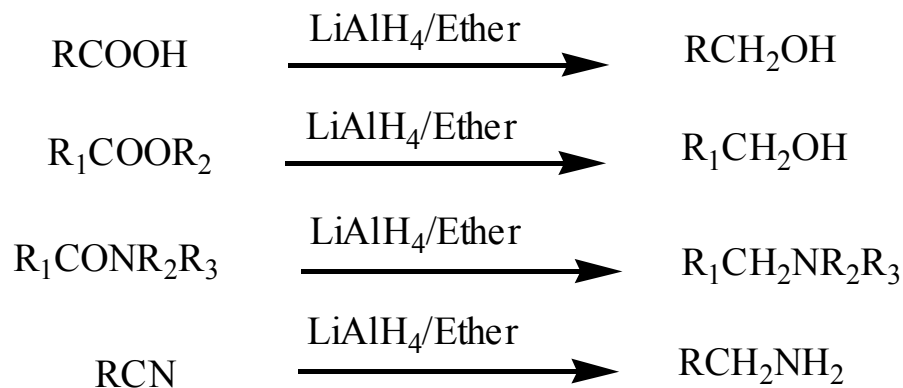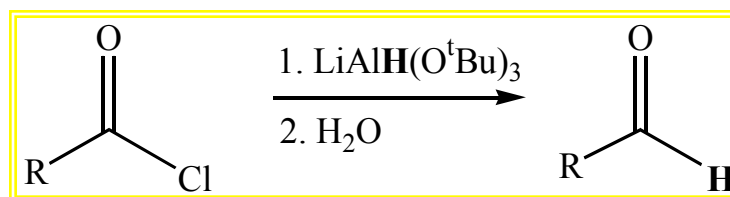
Step-I

aldehyde

Step-II

Ethanol

(iii). LiAlH$_4$ is too reactive!

The reaction cannot be stopped at the aldehyde stage

$$RCOOH \xrightarrow{\text{LiAlH}_4/\text{Ether}} RCH_2OH$$
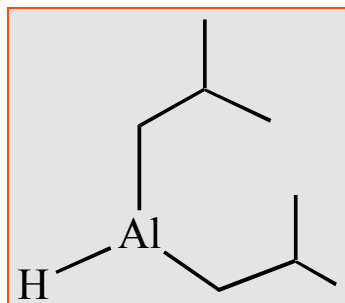
$$R_1COOR_2 \xrightarrow{\text{LiAlH}_4/\text{Ether}} R_1CH_2OH$$

$$R_1CONR_2R_3 \xrightarrow{\text{LiAlH}_4/\text{Ether}} R_1CH_2NR_2R_3$$

$$RCN \xrightarrow{\text{LiAlH}_4/\text{Ether}} RCH_2NH_2$$

Controlled reductions using less reactive LAH *derivatives*
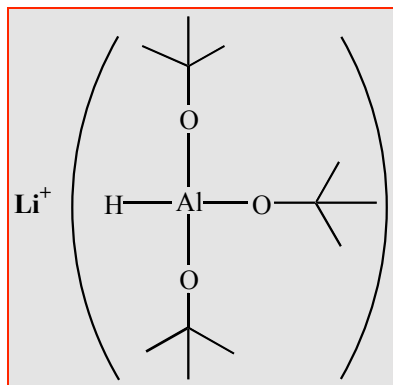
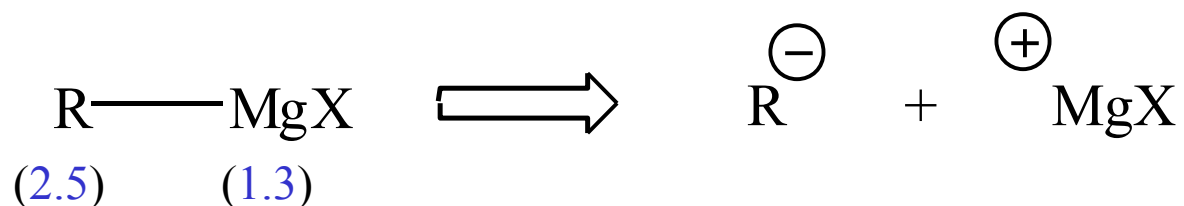Lithium tri-tert-butoxy aluminum hydride
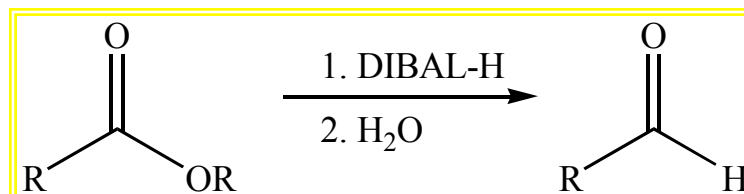
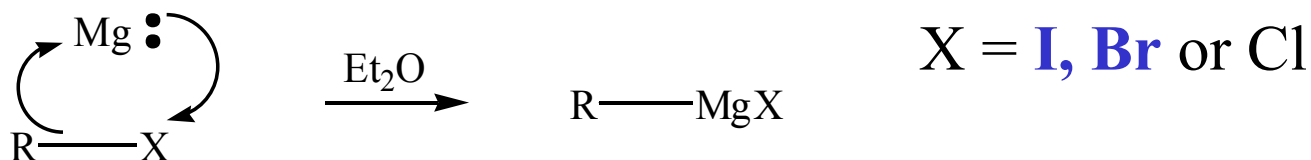Diisobutyl aluminum hydride (**DIBAL-H**)

9. Grignard Reagents

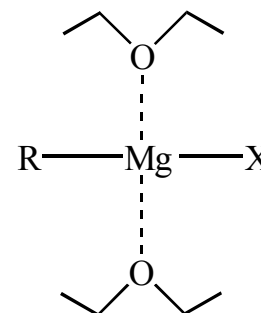**Victor Grignard** (1900): Nobel prize winner 1917

Organomagnesium reagents acts as nucleophiles towards electrophilic carbonyl group.

$$R\!\!-\!\!MgX \implies R^{\ominus} \quad + \quad {}^{\oplus}MgX$$

(2.5)　　(1.3)

Alkyl Grignard reagents can be made by reacting Mg with alkyl halides in ether solvents

Mg :

$$\xrightarrow{Et_2O}$$

R——X

R——MgX

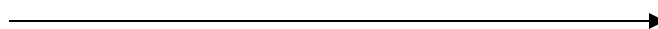X = **I, Br** or Cl

Ether offers additional stabilization through coordination

Grignard reagents are strong bases as well as nucleophiles

These compounds can be used for C-C bond formation reactions (construction of organic molecules)
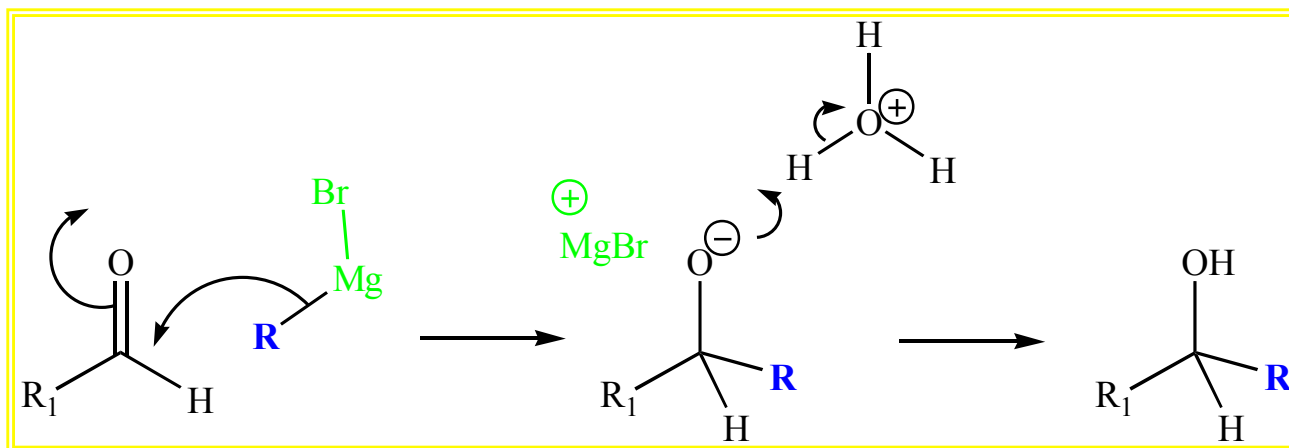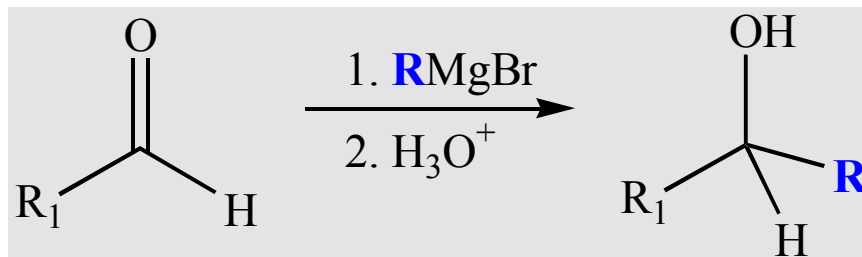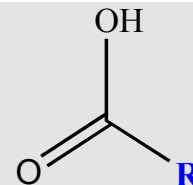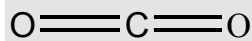

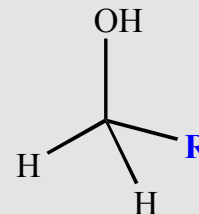Aldehyde ⟶ *sec*-alcohol
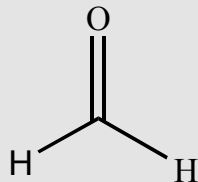
9b. Addition of Grignard Reagents

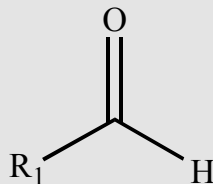Grignard reagents and add to a range of carbonyl compounds,
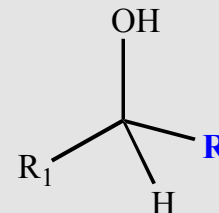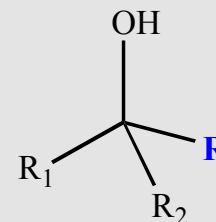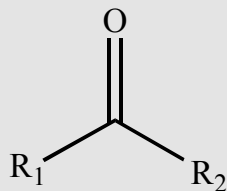
9c. Planning a Synthesis with Grignard reagents

There could be several possible combinations of Grignard reagents leading to the same product.

The choice is often decided by (i) easy availability or ease of preparation of Grignard reagents (ii) ease of reaction with other substrates