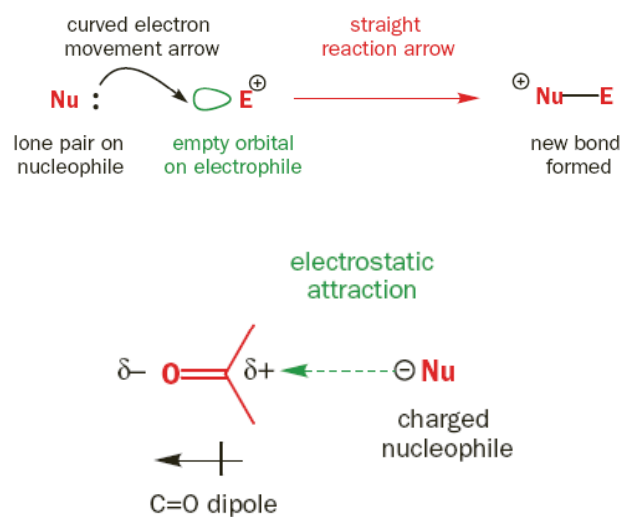


Topic: IV

Chemistry of Carbonyl Compounds

Lecture slides are courtesy of : **Prof. R.B Sunoj, IIT Bombay**
Prof. Peter Volhardt, UC Berkeley
Prof. J. M McBride, Yale University
Oxford University Press

Nucleophilic Addition to C=O

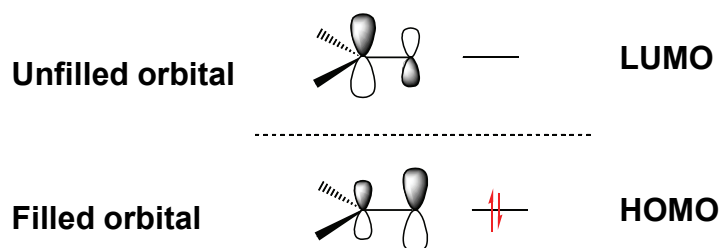


Carbonyl Group

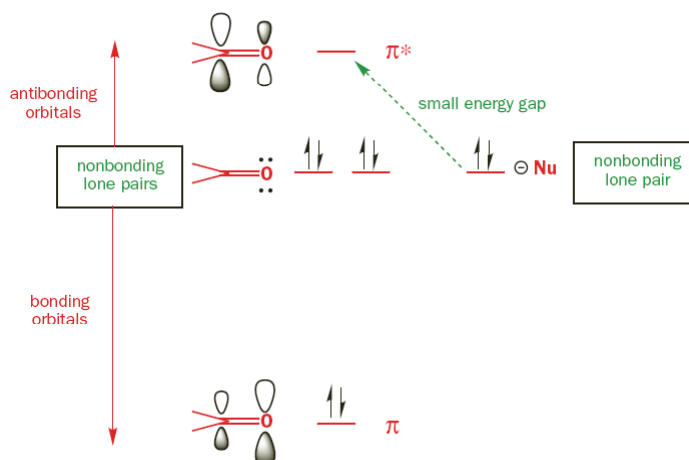


The C-O bond is polarized towards the more electronegative oxygen

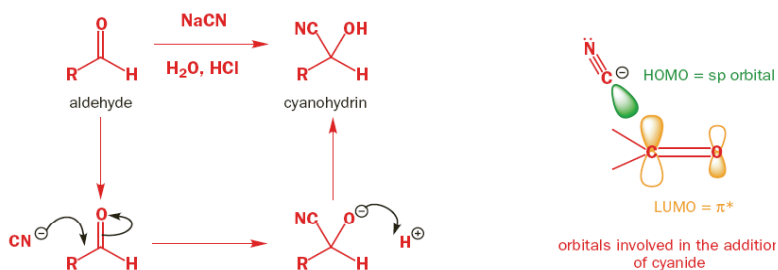
Bonding in carbonyl group



MOs Involved in the Nucleophilic Addition to C=O

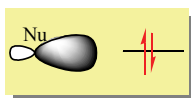


Example: Cyanohydrin Formation

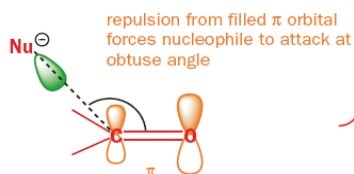
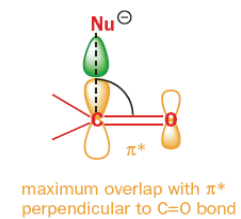


Reactions of carbonyl group with nucleophiles

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



Burgi-Dunitz Trajectory



nucleophile attacks $C=O$ at 107° angle

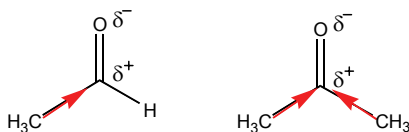
combined effect:

Net Reaction



Relative Reactivity of Aldehydes and Ketones

Aldehydes are in general more reactive than ketones



Aldehydic carbon is more electrophilic than ketonic carbon

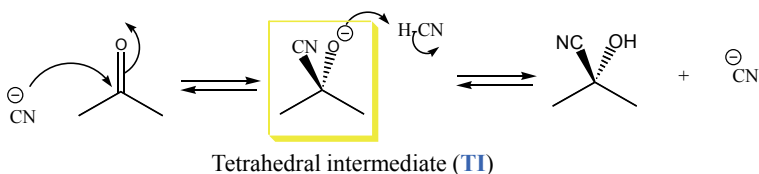
Aldehydic carbon is readily available for attack by Nu

If the nucleophile is strong, it can directly add to the carbonyl carbon

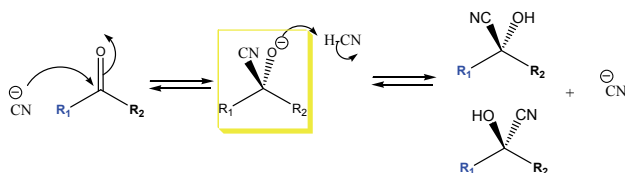
If the nucleophile is weak, acid catalysis may be required

1. Addition of HCN

Strong nucleophiles add to carbonyl as,



Achiral substrate to chiral products



prochiral faces

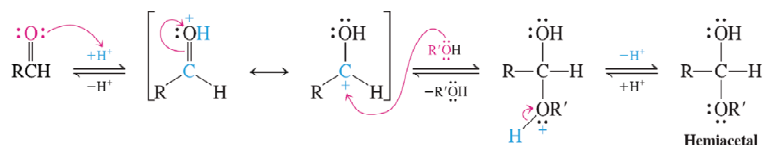
General Instructions on Reaction Mechanisms

- (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 attacks electrophiles**, not the otherway round!)
- (iv) If the reaction is acid catalyzed, an initial **protonation** step would be followed by a **deprotonation** later in the reaction sequence

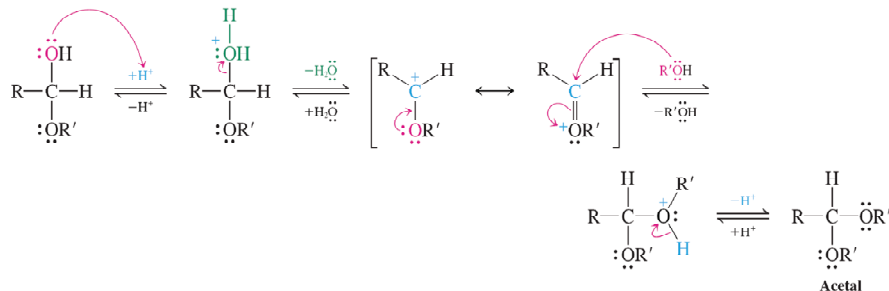
2a. Addition of alcohol

Weak nucleophiles add to carbonyl group of aldehyde under acid catalysis,

STEP 1. Hemiacetal generation



STEP 2. Acetal generation

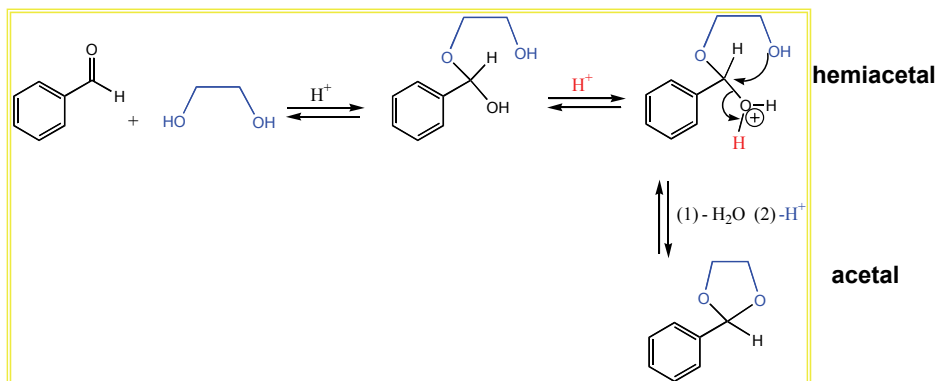


2b. Addition of alcohol-intramolecular

Alcohols add to ketones to yield acetal.

Acyclic hemiacetals are not quite stable enough to be isolated.

But cyclic hemiacetals as well as acetals are stable

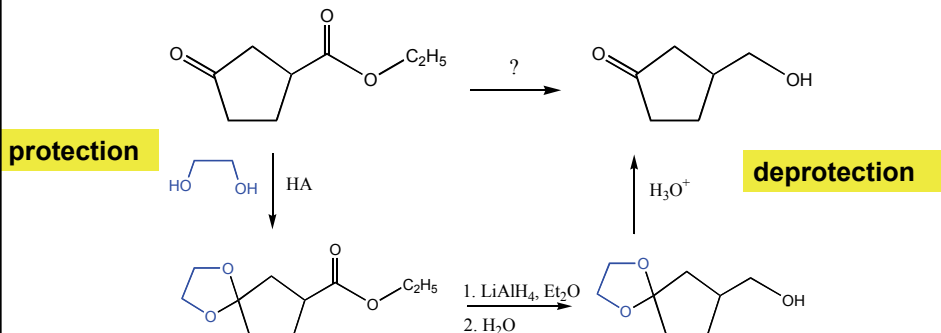


2c. Importance of cyclic acetals

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,



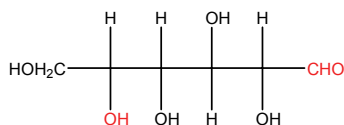


Picture courtesy: cricketnext.com

2d. Importance of cyclic acetals

Nature uses the stability of cyclic hemiacetals

E.g., glucose has a cyclic hemiacetal structure than the corresponding open-chain structure

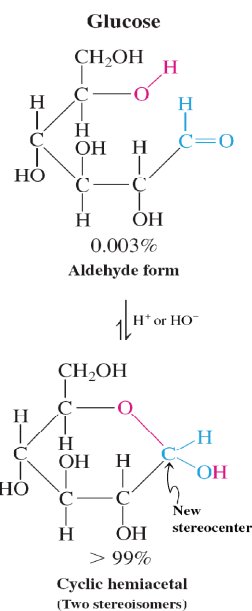


Glucose (open-chain)

Favored by entropy relative to intermolecular addition;

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

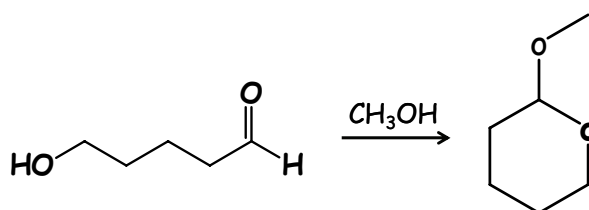
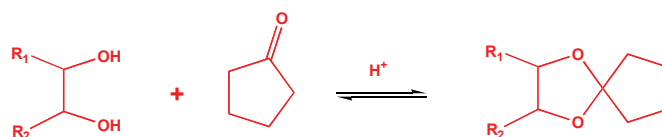
ΔS° is less negative for intramolecular reaction.



2e. Importance of cyclic acetals

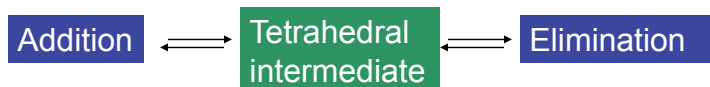
1,2-diols can be protected using acetals

Example for protection and deprotection,

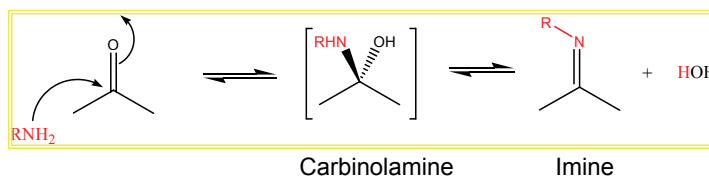


Condensation reactions with ammonia derivatives

Condensation reactions* with ammonia derivatives lead to **Schiff bases**



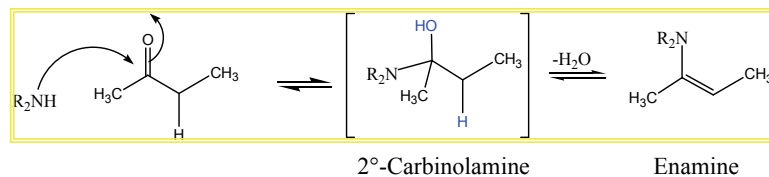
Acid catalyzed



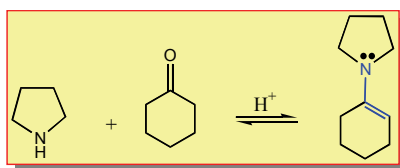
* One or more molecules are joined with the loss of water or another small molecules

Condensation reactions with ammonia derivatives

Generation of Enamines

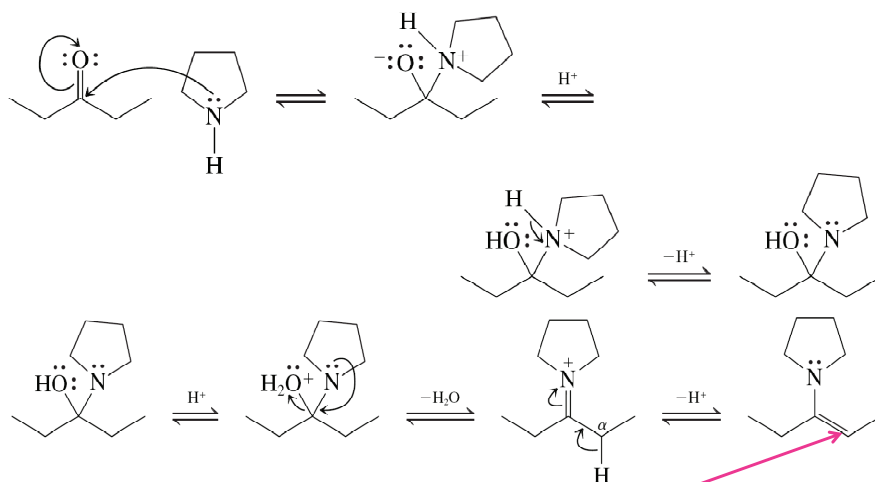


Secondary amines can give **enamines** upon condensation with ketones



Enamines are **very good nucleophiles** for C-C bond formation

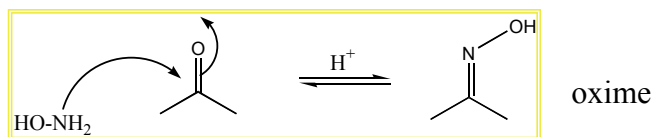
Mechanism of enamine formation



Enamines are useful, can be alkylated

3c. Condensation reactions with ammonia derivatives

(i) Reactions with hydroxylamine ($\text{H}_2\text{N-OH}$) give **oxime**



(ii) Condensation of ketones with hydrazine ($\text{H}_2\text{N-NH}_2$) gives **hydrazone**

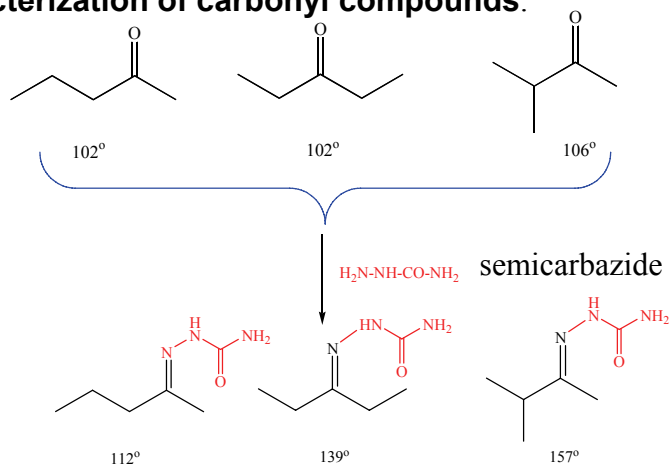
(iii) Condensation of ketones with phenylhydrazine (Ph-NH-NH_2) gives **phenylhydrazone**

3d. Importance of hydrazones

Hydrazones are crystalline solids with sharp melting points.

Hydrazone formation can be used for separation as well as characterization of carbonyl compounds.

E.g.,



semicarbazones

Nucleophilic Addition Reactions of carbonyls

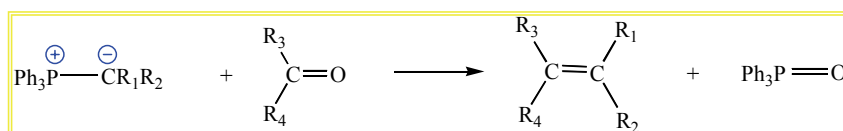
Nucleophile	Product
Water	hydration
Alcohols	acetal formation
HCN	cyanohydrin formation
Ammonia derivatives	Schiff bases
Ylides	olefins
Hydrides	reduction
Grignard reagents	alcohols
Oxygen	oxidation

4. The Wittig Reaction

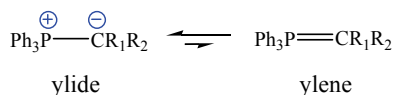
[carbanions as nucleophiles]

Georg Wittig (1954): Nobel prize winner 1979

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



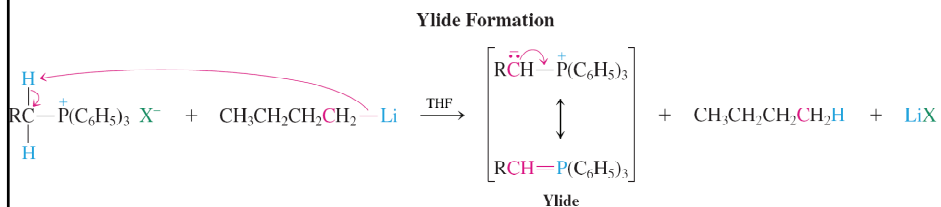
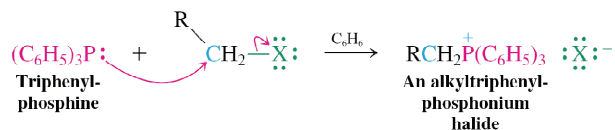
Phosphorous stabilized carbanions



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

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

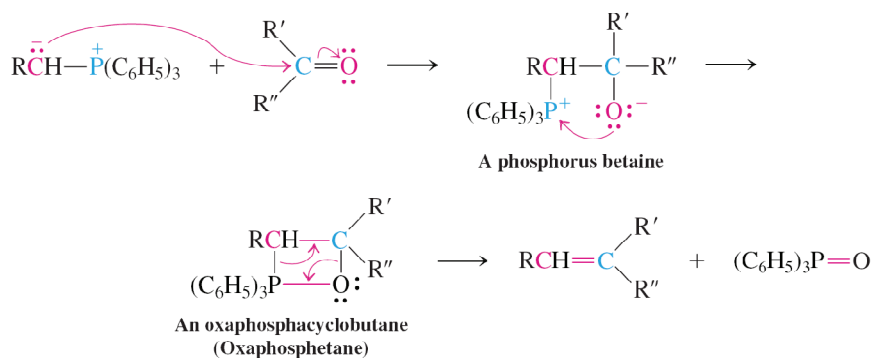
4a. Mechanism of Wittig Reaction



Other (weaker) bases OK, such as CH_3O^- , CH_3OH , generate the ylide in equilibrium concentrations sufficient for the next step: Attack on carbonyl carbon and formation of alkenes.

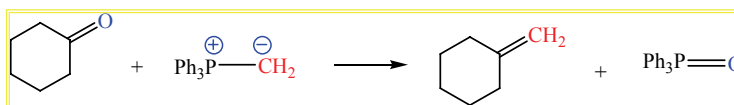
4a. Mechanism of Wittig Reaction

Mechanism of the Wittig Reaction

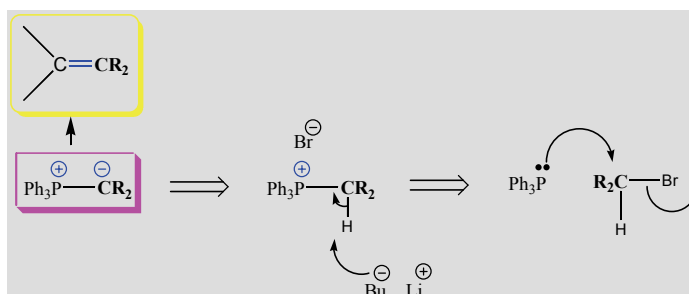


Phosphine oxide is a very stable species. Formation of alkene as well as phosphine oxide provides great thermodynamic drive for this reaction

4b. Wittig Reaction is an olefination reaction



Choice of R_2CX is critical while planning a Wittig olefination reaction



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

Nucleophilic Addition Reactions of carbonyls

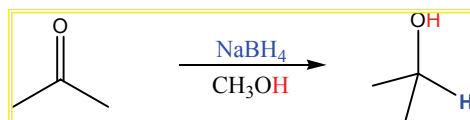
Nucleophile	Product
Water	hydration
Alcohols	acetal formation
HCN	cyanohydrin formation
Ammonia derivatives	Schiff bases
Ylides	olefins
Hydrides	reduction
Grignard reagents	alcohols
Oxygen	oxidation

5. Addition of Hydride

[hydride as nucleophiles]

(i). Reduction of carbonyl groups using NaBH_4

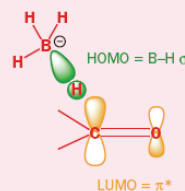
Aldehydes and ketones can be reduced by NaBH_4 in MeOH (or EtOH) to produce alcohols



The actual reducing agent is BH_4^- OR $\text{H}^- \text{BH}_3$



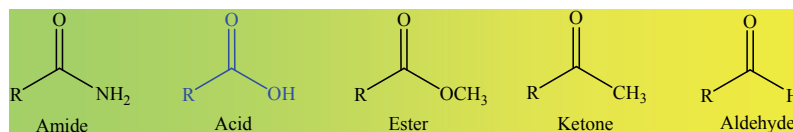
► The reason that H^- never acts as a nucleophile is that its 1s orbital is too small. The orbitals involved in borohydride reductions are the π^* of the $\text{C}=\text{O}$ group as the LUMO and a $\text{B}-\text{H}$ σ orbital as the HOMO, so there is a much better orbital match.



5b. Addition of Hydride (LiAlH_4)

(ii). Reduction of carbonyl groups using LiAlH_4

The relative order of reactivity of carbonyl groups toward nucleophiles is



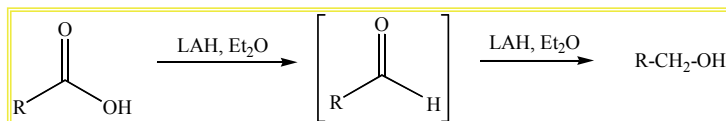
➡ Increasing order of reactivity

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

5c. Reduction of carboxylic acids

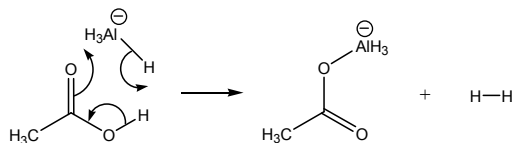
LAH reacts violently with protic reagents (solvents)

Therefore, the reaction must be conducted in a dry, aprotic solvent

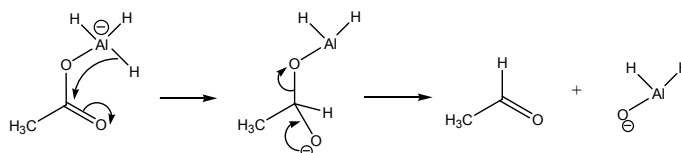


Mechanism

Step-I



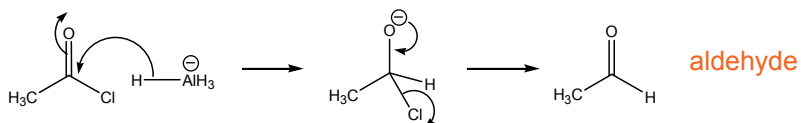
Step-II



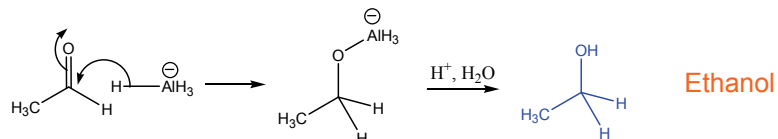
5d. Reduction of other acid derivatives

Mechanism of reduction for acid derivatives

Step-I

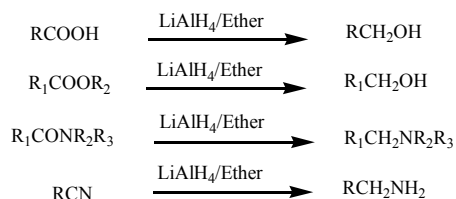


Step-II



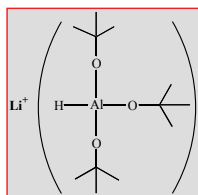
(iii). LiAlH₄ is too reactive!

The reaction cannot be stopped at the aldehyde stage

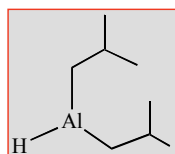
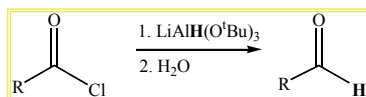


5e. Addition of Hydride

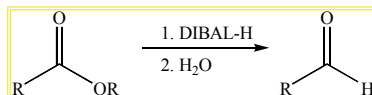
Controlled reductions using less reactive LAH derivatives



Lithium tri-tert-butoxy aluminum hydride



Diisobutyl aluminum hydride (**DIBAL-H**)



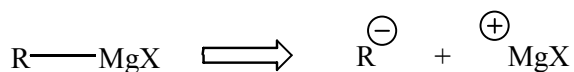
Nucleophilic Addition Reactions of carbonyls

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

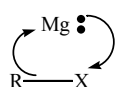
6. Grignard Reagents

Victor Grignard (1900): Nobel prize winner 1917

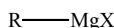
Organomagnesium reagents act as nucleophiles towards electrophilic carbonyl groups.



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

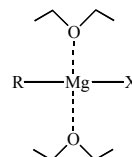


$\xrightarrow{\text{Et}_2\text{O}}$



X = I, Br or Cl

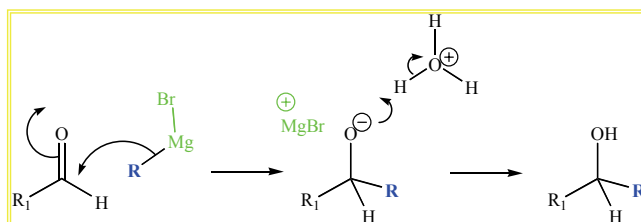
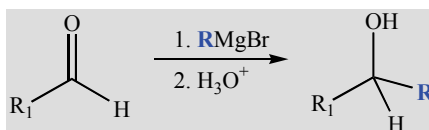
Ether offers additional stabilization through coordination



6a. Addition of Grignard Reagents [carbon nucleophiles]

Grignard reagents are strong bases as well as nucleophiles

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

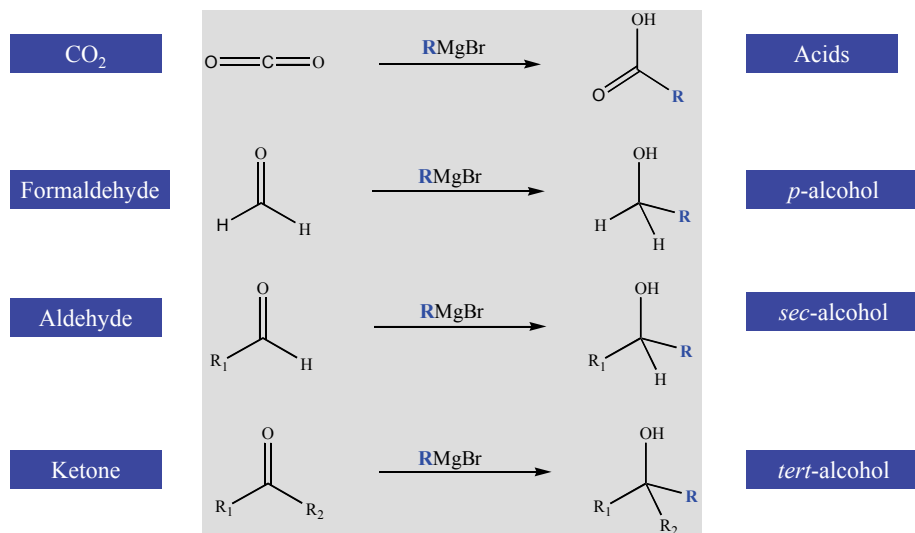


Aldehyde

sec-alcohol

6b. Addition of Grignard Reagents

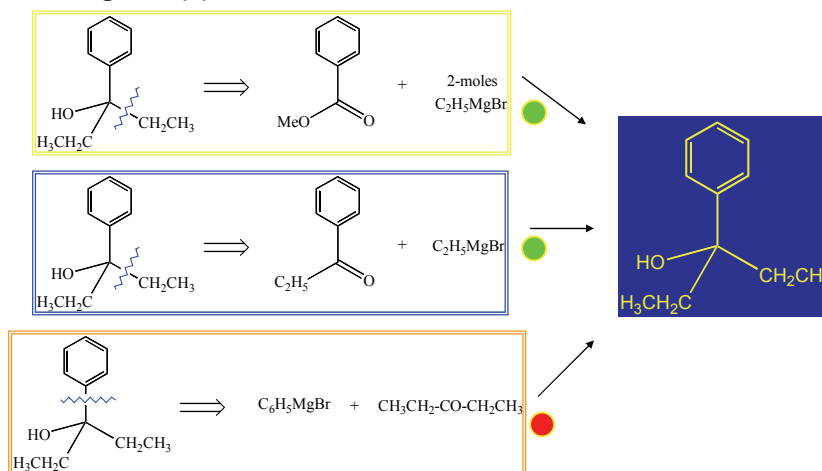
Grignard reagents add to a range of carbonyl compounds,



6c. Planning a Synthesis with Grignard reagents

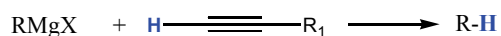
There could be several possible combinations of Grignard reagents leading to the same product.

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



6d. Issues with Grignard Reagents

Grignard reagents are very sensitive to any proton source (acids-including weak acids)



Grignard reagents with following functional groups can not be prepared, OH, NH₂, COOH, SH, CHO, COOR, CONH₂, NO₂, CN

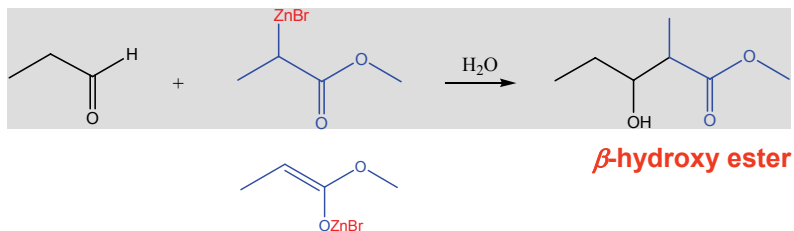
Grignard reagents are quite reactive! A way to generate carbon nucleophiles with *reduced reactivity* is to use “Zinc reagents”

7. The Reformatsky Reaction

The addition of organozinc reagent to the carbonyl group of an aldehyde or ketone is called the Reformatsky reaction

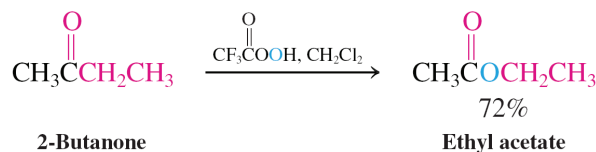
Advantages: (i) less reactive as compared to Grignard reagents

(ii) Nucleophilic addition to ester group does not occur



8. Bayer Villiger Oxidation (oxygen nucleophile)

Oxidation of ketones by peroxycarboxylic acids gives **esters**:

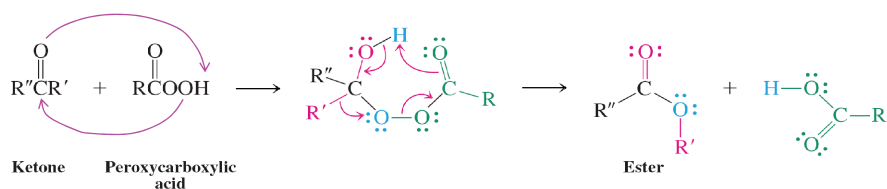


Adolf von Baeyer
(1835-1917)
NP 1905.

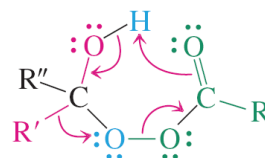


Victor Villiger

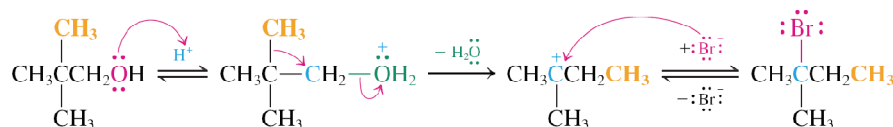
Mechanism:



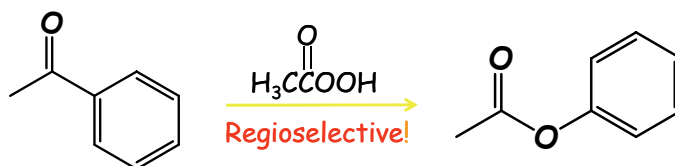
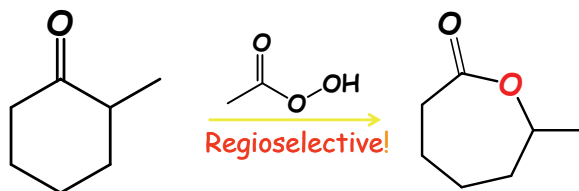
The transition state of the Baeyer-Villiger oxidation involves migration of **R'** through a push-pull electronic relay:



Mechanism of Concerted Alkyl Shift



Examples:



Migratory Aptitudes in the Baeyer-Villiger Reaction

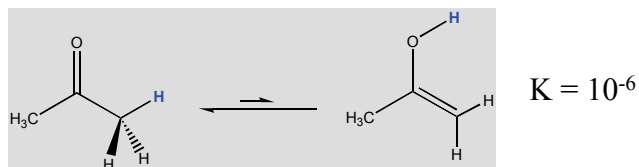
Methyl < primary < phenyl \sim secondary < tertiary

Chemistry of Carbonyl Compounds

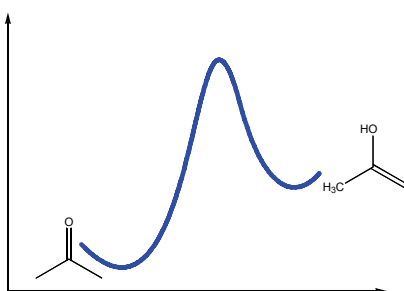
Part-II: Enols & Enolates

1. Enols

Keto-Enol tautomeric equilibrium leads to enol formation



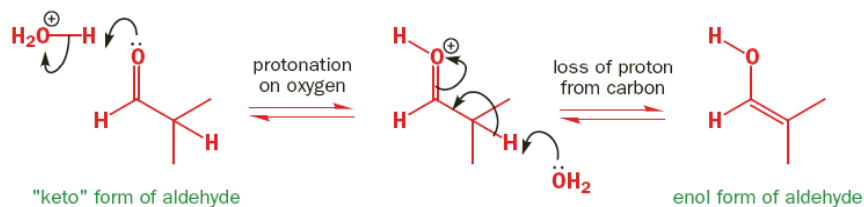
For a normal ketone under ordinary conditions only one in 10^6 exist as enol



1a. Catalyzed enol formation

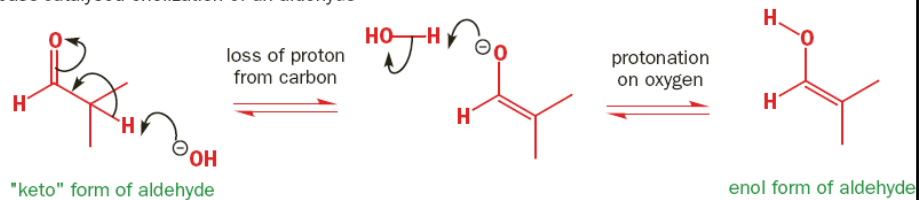
(i) Acid catalyzed enol formation

acid-catalysed enolization of an aldehyde

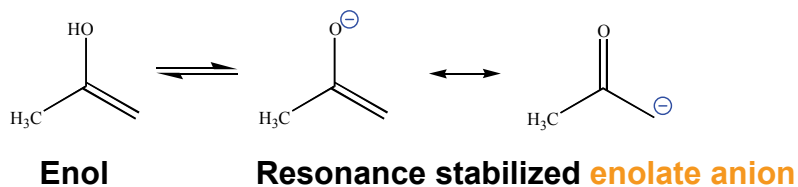


(ii) Base catalyzed enol formation

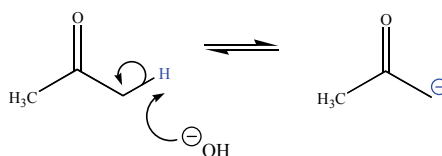
base-catalysed enolization of an aldehyde



2. Enloates are conjugate bases of enols



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

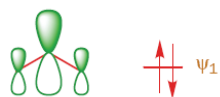


Enolates are powerful carbon nucleophiles!

2a. Special Features of Enolates

symmetrical **allyl anion**

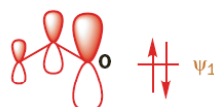
populated π orbitals of the allyl anion



enolate anion

unsymmetrical

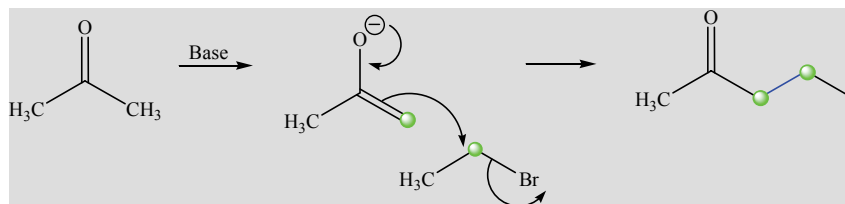
populated π orbitals of the enolate anion



More negative charge on electronegative oxygen atom and **larger orbital coefficient on carbon atom**, making it more nucleophilic

These features are due to orbital polarization caused by oxygen

2b. Enolates as carbon nucleophiles for C-C bond formation



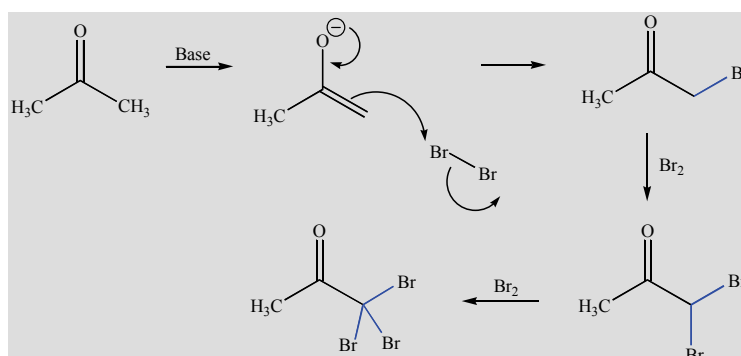
Acetone \rightarrow Pentanone

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

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

2c. Enolates in halogenation

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

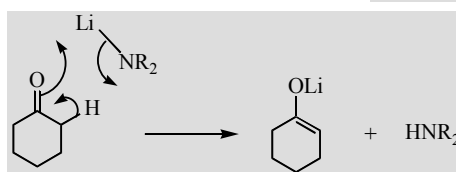
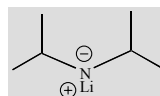


3. Stabilized enolates and Stable enol equivalents

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 (Lithium DiisopropylAmide)

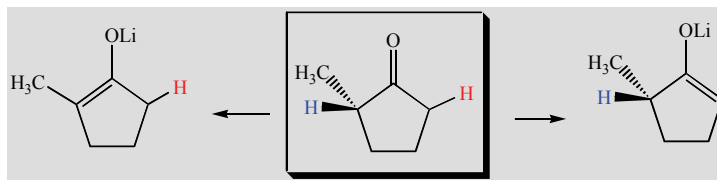


Lithium enolate is stable at -78°C^*

* $\text{Liq-N}_2/\text{EtOAc}$ OR Acetone-dry ice

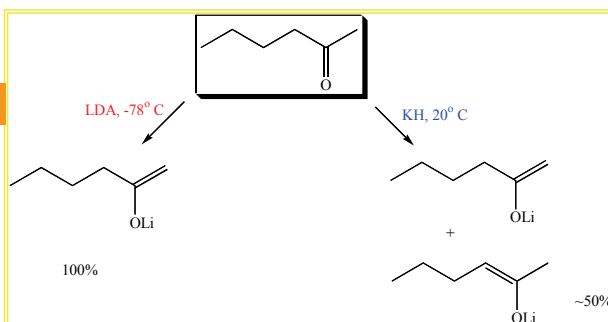
3a. Direction of enolization

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



Excess ketone, Ph_3CLi (base)

Kinetic



Thermodynamic

Kinetic and Thermodynamic Control

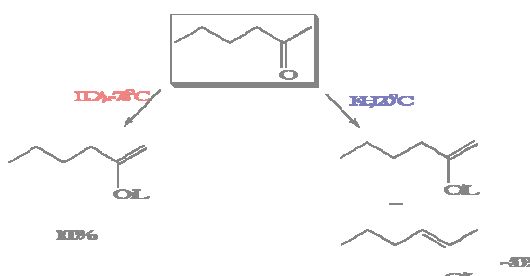
General Features

Kinetic

- Kinetic refers to **SPEED**
- Governed by activation energy
- Shows propensity to be reversible

Thermodynamic

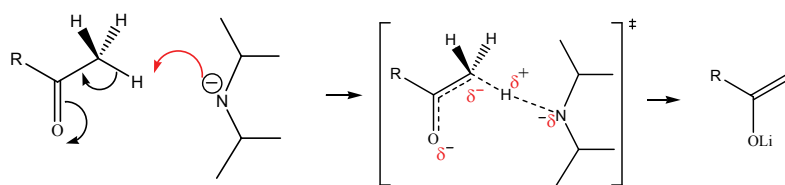
- Thermodynamic refers to **feasibility (stability)**
- Governed by heat of reaction
- Products are usually not quite reversible



Kinetic Control

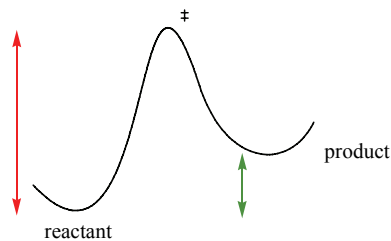
Case-I

(i) LDA abstracts proton from the terminal CH_3 group



Governed by activation energy

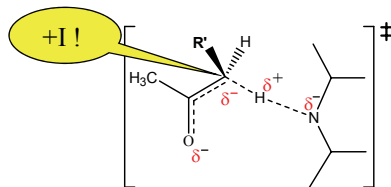
ΔG^{\ddagger}



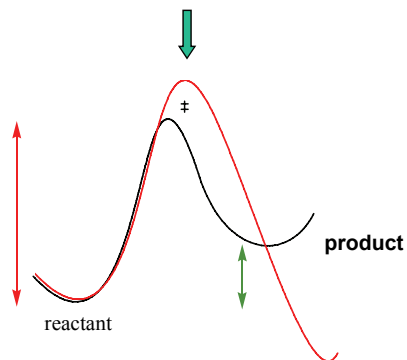
Kinetic Control

Case-II (ii) If LDA abstracts proton from the internal CH₂ group

ΔG^\ddagger 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



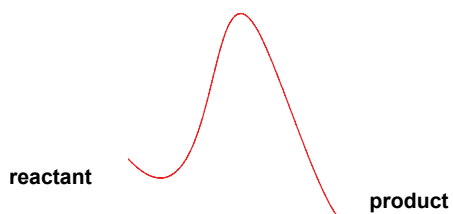
Thermodynamic Control

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



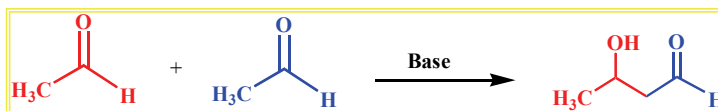
Governed by heat of reaction

ΔG_{rxn}

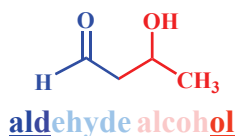
Thermodynamic product is more stable than the kinetic product

4. The aldol reaction

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



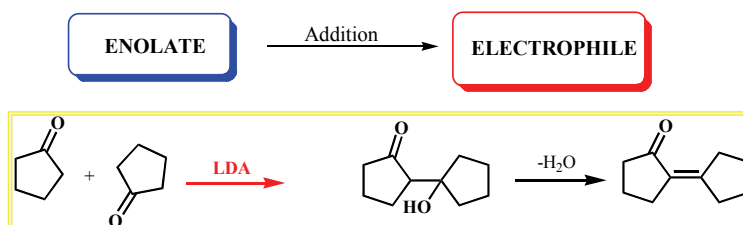
The product contains both aldehyde and alcohol functional groups, hence the reaction is known as aldol reaction



Remember: aldol is not 'named' after anyone!

4a. C-C bond formation using aldol reaction

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

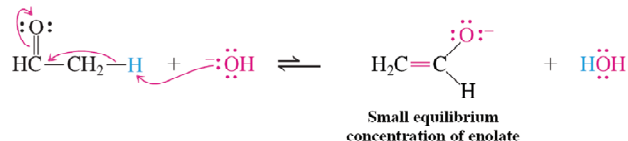


Aldol reaction catalyzed by acids (or bases) is usually accompanied by dehydration leading to α,β-unsaturated carbonyl compounds

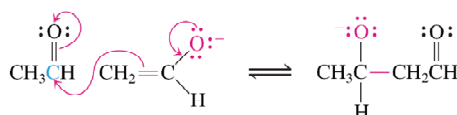
The above example is **self aldol** condensation

4a. Mechanism of Aldol formation

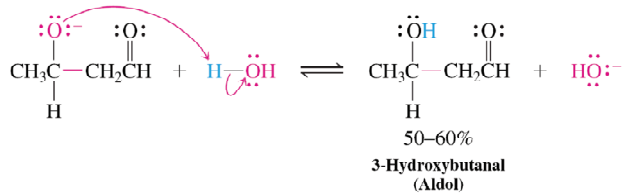
STEP 1. Enolate generation



STEP 2. Nucleophilic attack

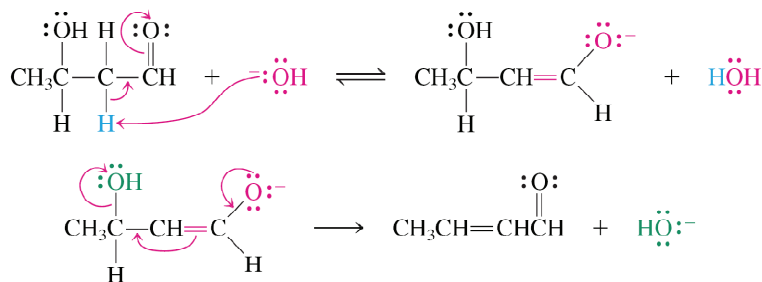


STEP 3. Protonation



4a. Mechanism of Aldol Dehydration

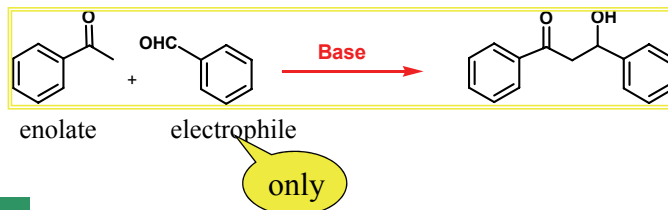
Mechanism of Aldol Dehydration



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!



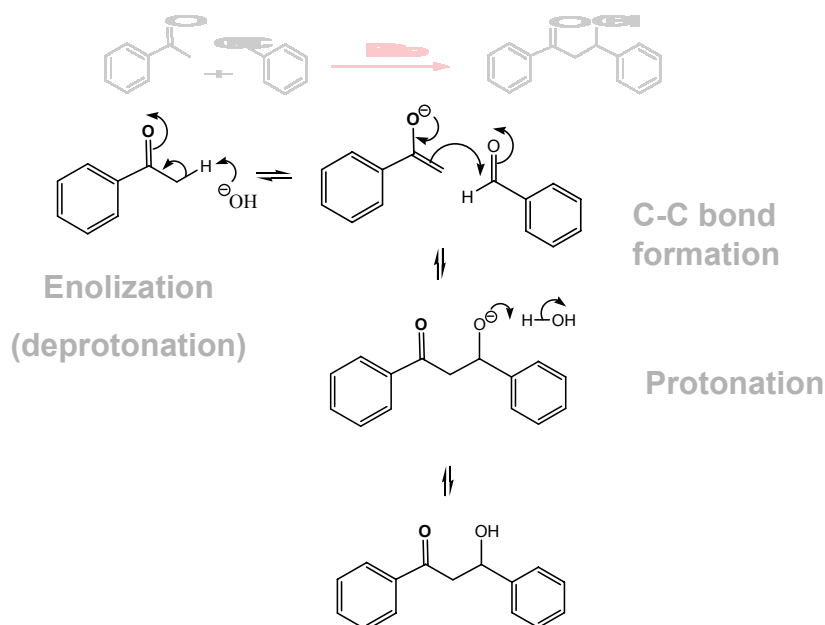
Mechanism

Enolization
(deprotonation)

C-C bond formation

Protonation

4a. Crossed aldol reaction-Mechanism

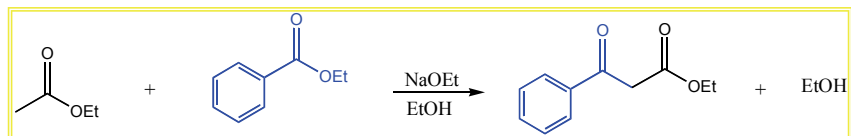


5. The Claisen Condensation

Base catalyzed condensation between two esters.

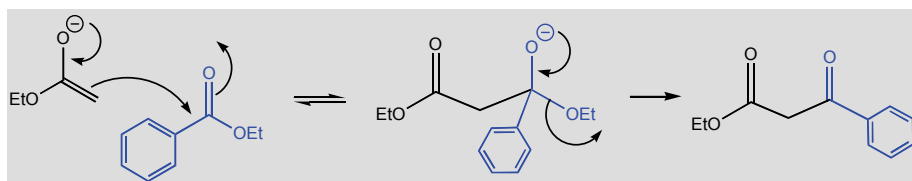
Only one of the esters can undergo enolization while the other serves as an electrophile (acceptor)

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



electrophile

5a. Mechanism of Claisen Condensation



TI

Claisen Product

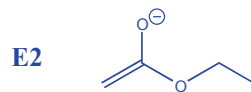
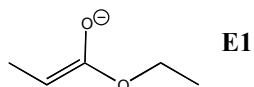
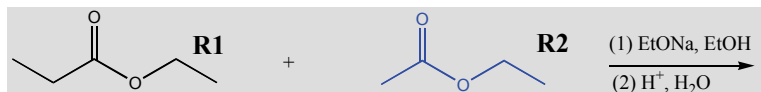
What about the situation where both esters have acidic α -hydrogens?

OR

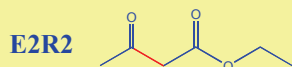
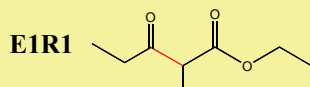
What if both esters can undergo enolization?

5b. Crossed-Claisen Condensation

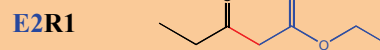
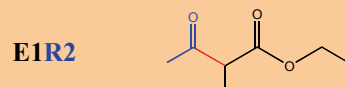
If both esters can undergo enolization, a mixture of products are formed,



(i) Self condensation



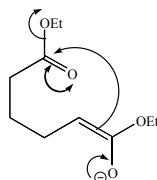
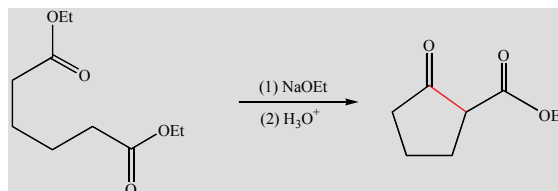
(ii) Crossed condensation



5c. Intramolecular Claisen (Dieckmann) Condensation

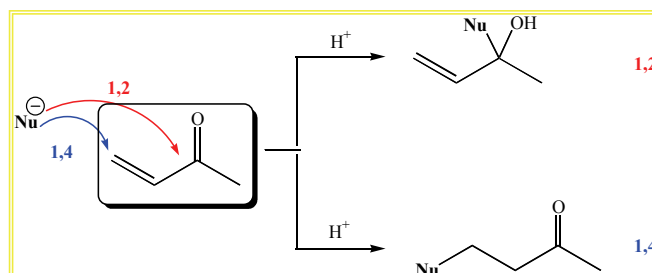
In the case of acyclic diesters, where the ester groups are at suitable positions, an intramolecular Claisen condensation would lead to a cyclic ester as the product.

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, NO₂ etc.,

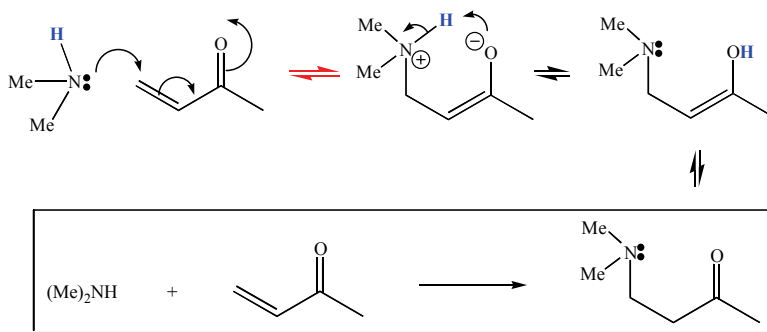


1,2-additions* are also known as **direct addition**

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

* Addition of Nu and H⁺

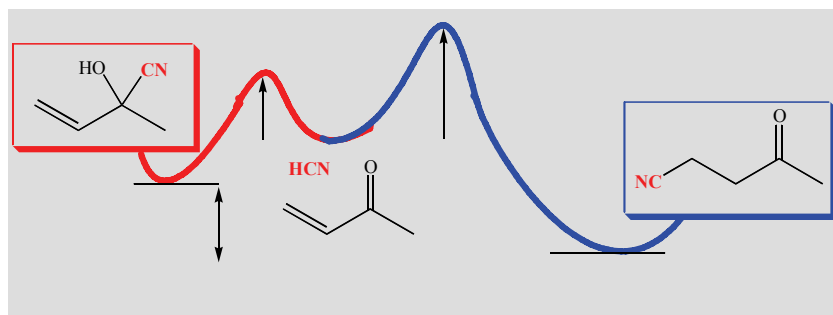
6a. Additions to α,β-unsaturated carbonyl compounds



Key factors that control conjugate addition are,

- (i) Reaction conditions
- (ii) Nature of the α,β-unsaturated carbonyl compound
- (iii) Type of nucleophile

6b. Kinetic versus thermodynamic products



$\Delta G^\ddagger_{\text{(reaction)}}$

speed

reversible

lower temp

$\Delta G_{\text{(reaction)}}$

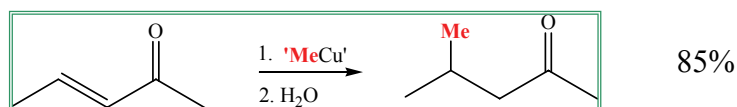
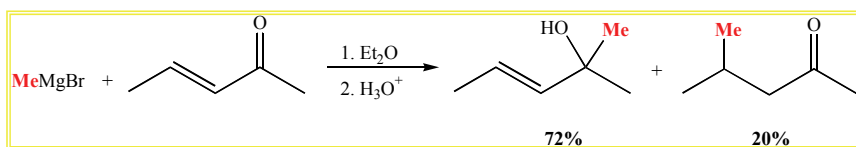
product stability

irreversible

higher temp

6c. Direct versus Conjugate additions

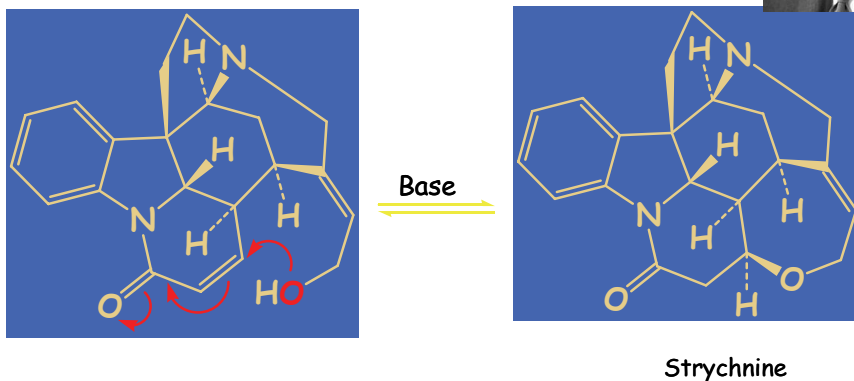
Strong nucleophiles generally exhibit direct addition



'Me₂Cu' generated by mixing MeMgBr and CuCl

Copper is less electropositive than Mg [Cu(1.9), Mg(1.3)]. Hence the C-Cu bond is less polarized and gives less partial negative charge as compared to that with Mg

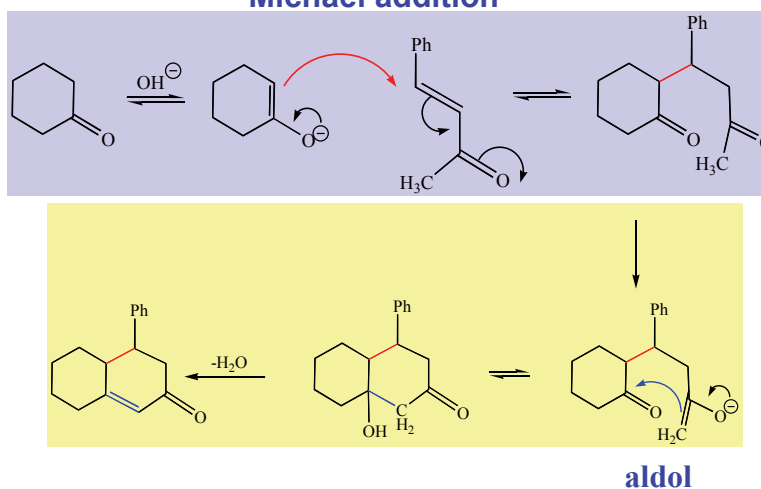
Ether Formation: Strychnine Synthesis by Woodward



6d. Michael Additions

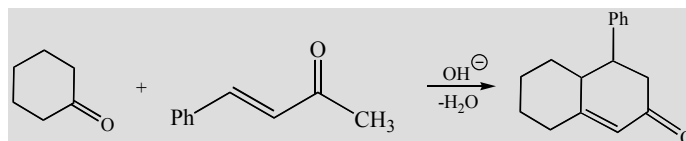
Nucleophilic addition of stabilized carbanion (carbon nucleophiles) α,β -unsaturated carbonyl compounds

Michael addition

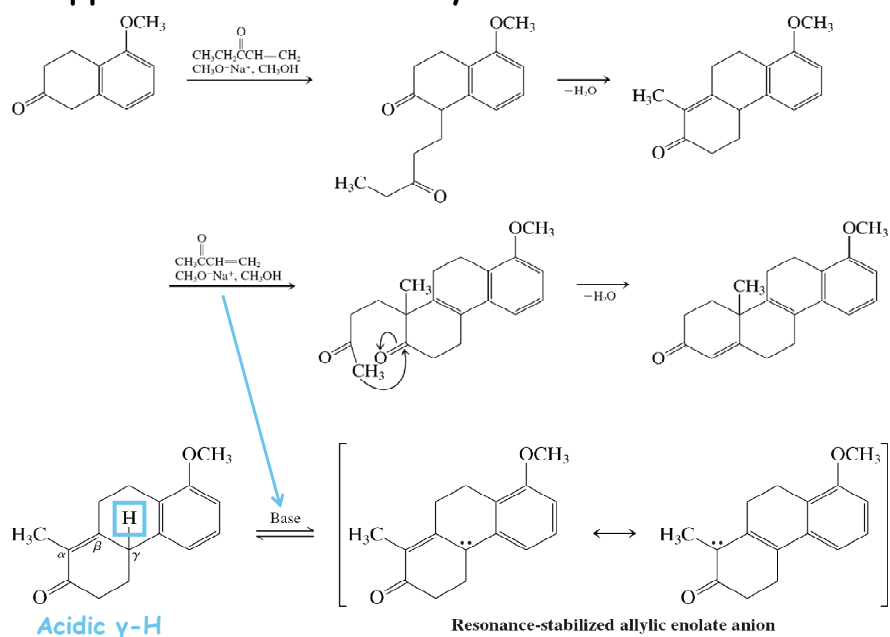


6e. Robinson Annulation

Michael addition + aldol Followed by dehydration



Application to steroid synthesis:



Think on These Things



Prof. Yashpal

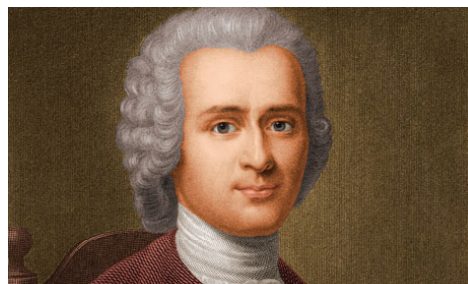
"Specialists are dangerous people"

"Science is the belief in the ignorance of experts"



R Feynman

"Man is born free but everywhere he is in chains. Those who think themselves the masters of others are indeed greater slaves than they."



**Jean-Jacques Rousseau
(1712-1778)**

"Social Contract"

“There is no end to education. It is not that you read a book, pass an examination, and finish with education.”



J Krishnamurthy

“Reading, writing, arithmetic are important only if they serve to make our children more human.”

Use office hours (take prior appointment by phone or by E-mail)

All the Best