Reactions involving carbonyl compounds

Chapter Introduction

The reactions of carbonyl compounds are one of the most important class of synthetically useful reaction in organic chemistry. The carbonyl functional group is also regarded as the most important functional group. This functional group can participate in multiple modes of reactions. The reactions of carbonyls can be broadly classified as the direct **nucleophilic addition reactions** wherein a nucleophile adds to the carbonyl carbon atom. The other equally important and versatile family of reactions of carbonyl arise due to the acidity of the alpha-C-H groups. Upon treatment with a base, such compounds are capable of yielding a very useful nucloeophile, known as enolate. The **chemistry of enolates** are widely exploited for the generation of C-C bonds in various reaction. This module is therefore very important for the practice of organic reaction and its mechanisms.

I. Nucleophilic addition reactions

Introduction

Addition of cyanide to acetone gives acetone cyanohydrin.

Carbonyl group of aldehyde, ketone, carboxylic acid, ester etc., a very common of all functional groups in organic chemistry, shows most important and simplest of all reactions i.e. nucleophilic addition.
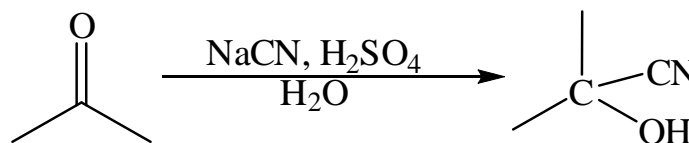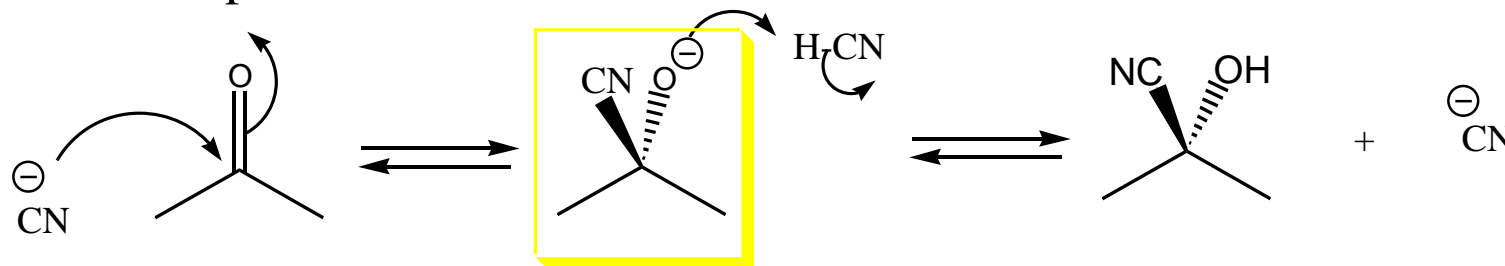

Reaction proceeds in two steps. In first step nucleophilic addition of cyanide occurs followed by a protonation of the resulting alkoxide anion.

In fact, this is general feature of all nucleophilic addition reaction of carbonyl compound.

Mechanism of nucleophilic addition

Reactivity of carbonyl group towards nucleophiles

Orbital considerations give a clear picture of these addition reactions.

C=O of carbonyl compounds is sp^2 hybridized and is planar. It has shorter bond length than typical C-O and is twice strong than C-O. What makes it reactive toward addition reaction is polarization of C=O bond.
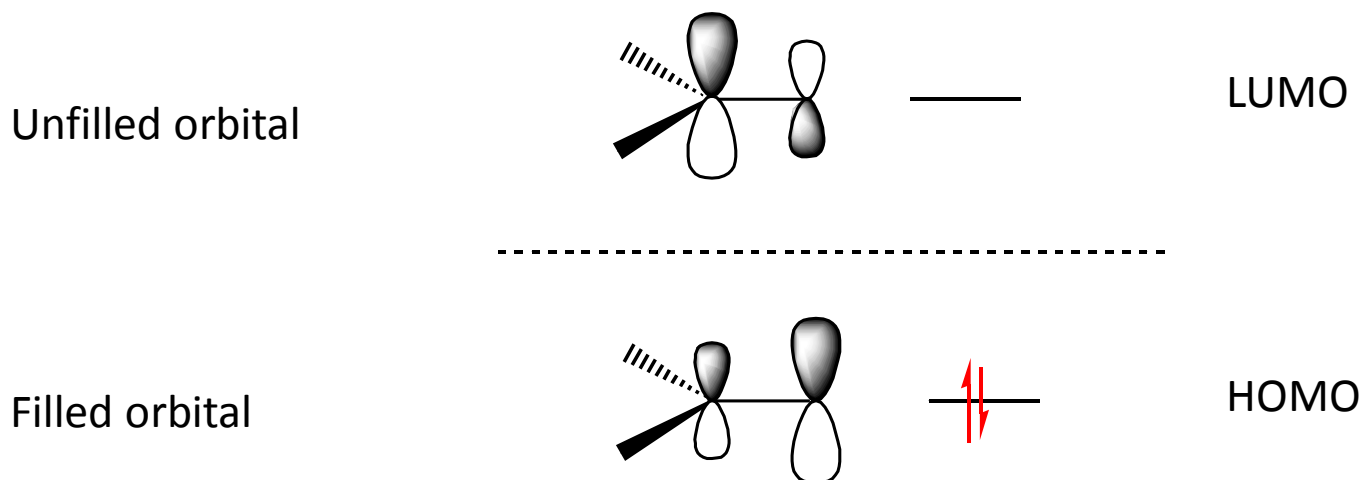
(Electronegativity of C is 2.5 while that of O is 3.5)

Polarization makes carbon partially positive which encourages addition of negatively charged cyanide ion.

Orbital considerations: Why carbonyl groups are electrophiles?

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

<u>Bonding in carbonyl group</u>

Unfilled orbital

LUMO

Filled orbital

HOMO

Complete diagram of filled orbitals of carbonyl compounds

When nucleophile adds to carbonyl group, its HOMO reacts with LUMO of carbonyl group. So when this LUMO is more polarized i.e., coefficient of LUMO at carbon is greater, then this interaction is better.

When the HOMO of a nucleophile interacts with the LUMO of a carbonyl group, a new σ bond is formed and π bond is broken due to filling of electrons to the antibonding π* orbital of carbonyl group. Electrons from HOMO of nucleophile now migrate towards oxygen giving it negative charge.

new σ bond is formed at expense of π bond.

LUMO of C=O   HOMO-LUMO interaction   electrons from pi bond end up as negative charge on oxygen
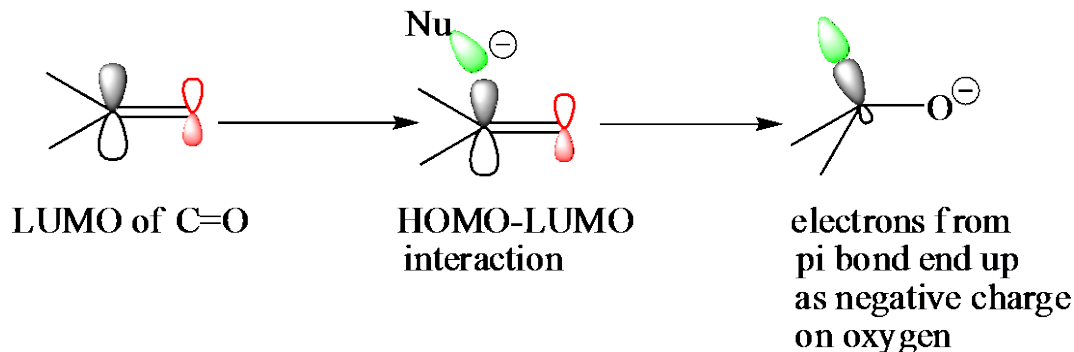
Cyanohydrin formed from this cyclic ketone is used in syntheses of 5HT$_3$ agonists.

NaCN, H$_2$O
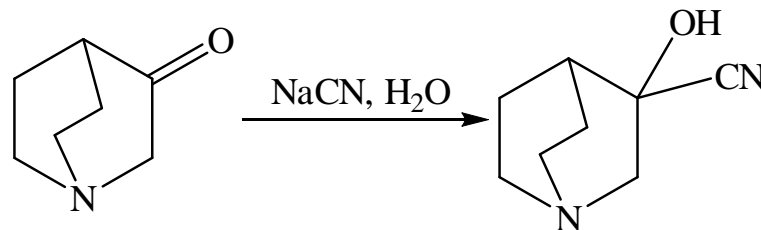
The reaction is facilited by acid catalyst and is in equilibrium with starting material. Hence only reaction favoring product will give good yield.

Cyanohydrins can also be obtained from addition of trimethylsilylcyanide.

100% (56% ee)
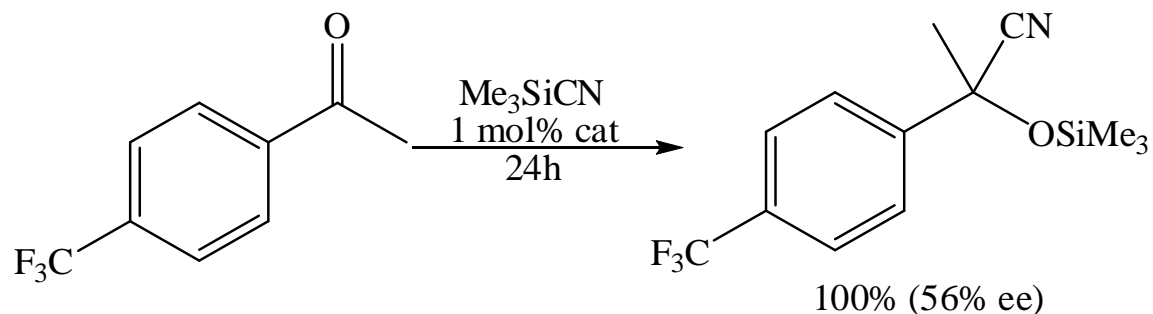
Bolokon,Y.N; Green,B; Ikonnikov, N.S; North,M; Parsons,T; Tararov,V.I; *Tet. Lett.*, 2001, 57, 771.

Catalyst :
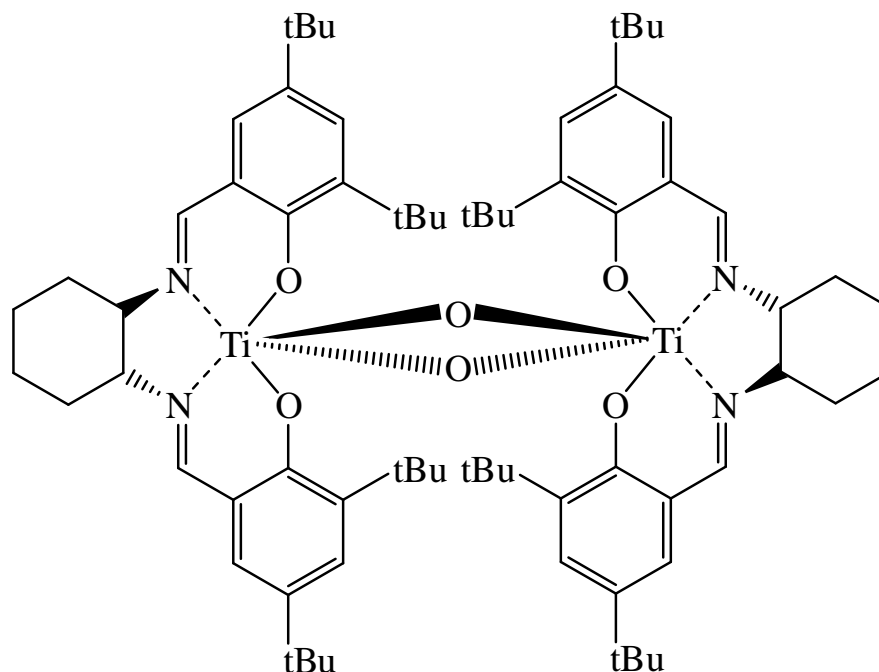
(A). Reactions with organometallic compounds

Reaction of organometallic compound with carbonyl compound is a very important reaction as it gives alcohols by C-C bond formation.

(**A.1**) Lithium and magnesium in nucleophilic addition reaction

Lithium and magnesium containing organometallic compounds are of importance in these reactions.

Lithium and magnesium are very electropositive metals and hence electron density is highly polarized towards carbon in these reagents. Hence, making them good nucleophiles which attack carbonyl compounds.

Reaction of methyllithium with aldehyde
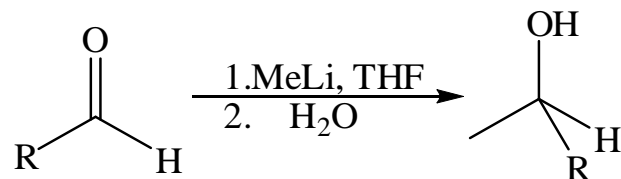
Mechanism is similar to typical nucleophilic addition reaction.
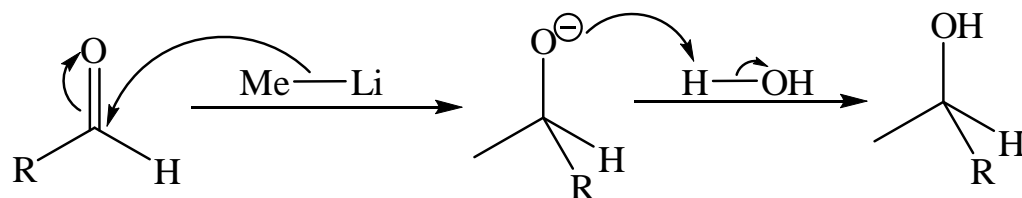
Orbital diagram gives clear picture of reaction.

Orbitals involved in addition of methyllithium

HOMO of MeLi

LUMO of C=O
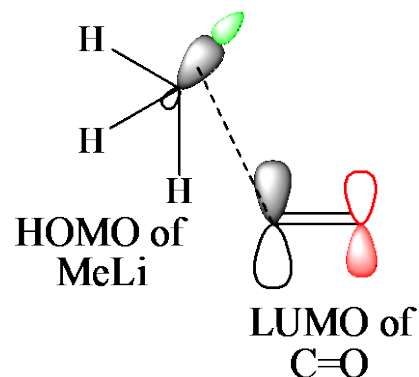
In these reactions, water is added in last step of reaction, after methyllithium is added to carbonyl compound. Organolithium or organomagnesium compounds are very reactive

towards water and react readily to give alkane. To avoid this kind of side reaction, reaction is carried out in presence of aprotic solvent like THF, Et_2O etc.,

Buhler,J.L, *JOC*, 1973, 38, 904.

nBuLi
hexane
-78^0C

nBu

OH

98%
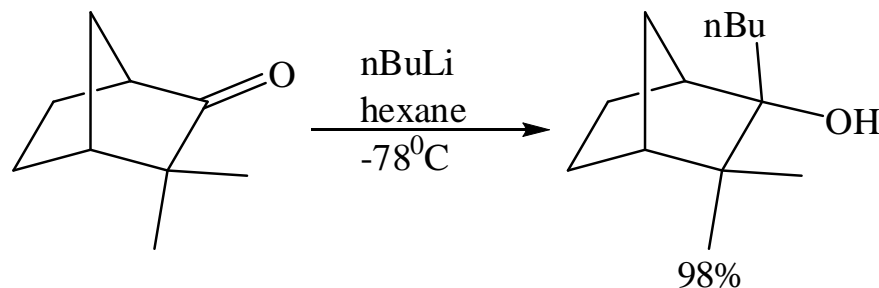
Maruoka,K; Nonoshita,K; Yamamoto,H; *Tet. Lett*., 1987, 28, 5723.

Catalyst for reaction

MAD-Methylaluminiumbis(2,6-ditert.butyl-4-methylphenoxide)

MeLi
MAD
toluene
-78^{0}C

77%
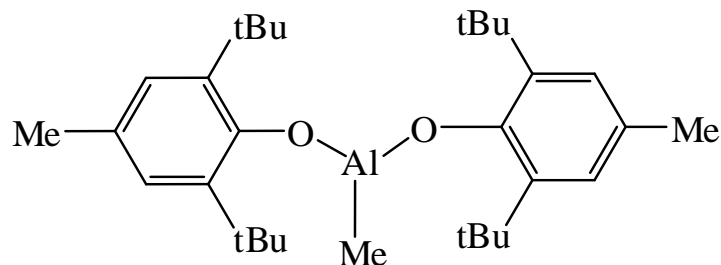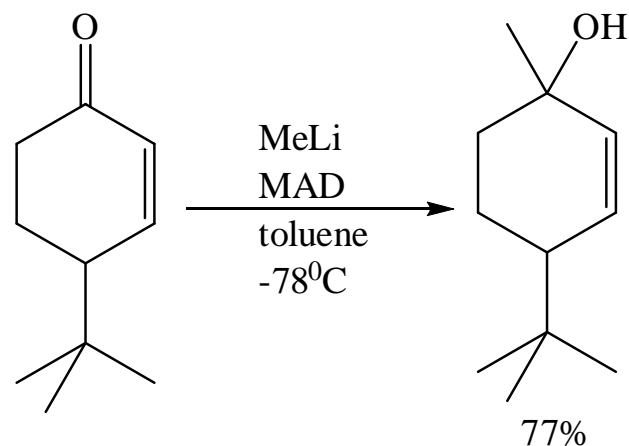
Organomagnesium reagents are known as [Grignard](#) reagent and these class of compounds also react in same way as that of organomagnesium and organolithium compounds.

Reaction of Grignard's reagent with carbonyl compound
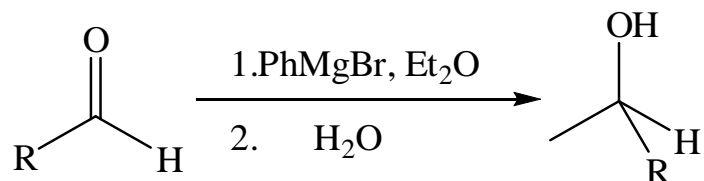
Product of reaction of Grignard's reagent with carbonyl compound and that of analogous organolithium compound is same.

Victor Grignard is the name of a German scientist. Pronounced as "Grini-yard"

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)
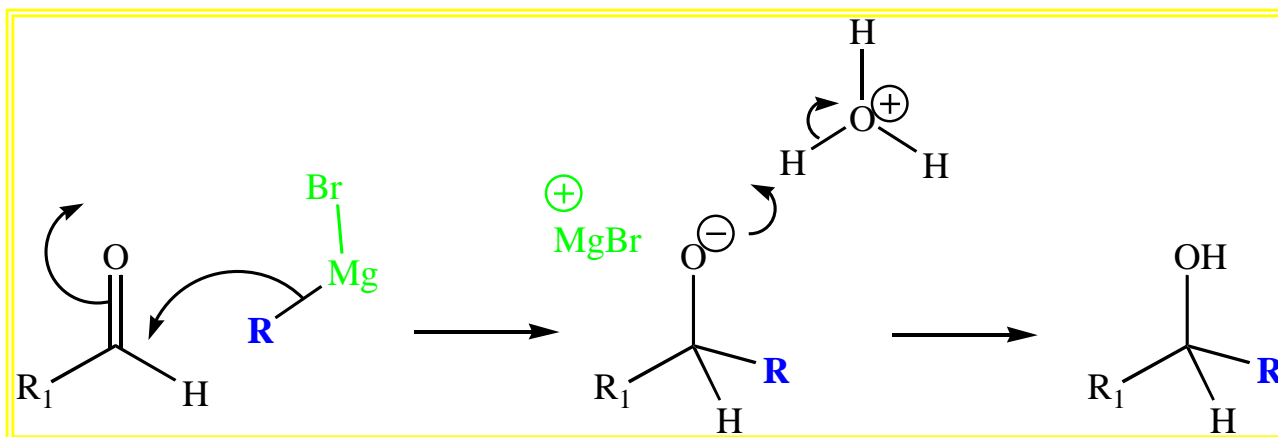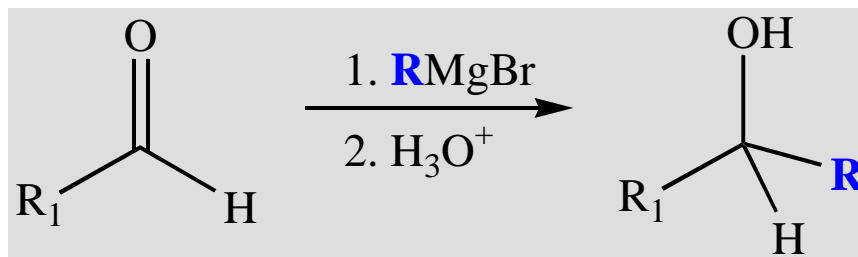
Aldehyde ⟶ *sec*-alcohol

Addition of Grignard Reagents

Grignard reagents and add to a range of carbonyl compounds,
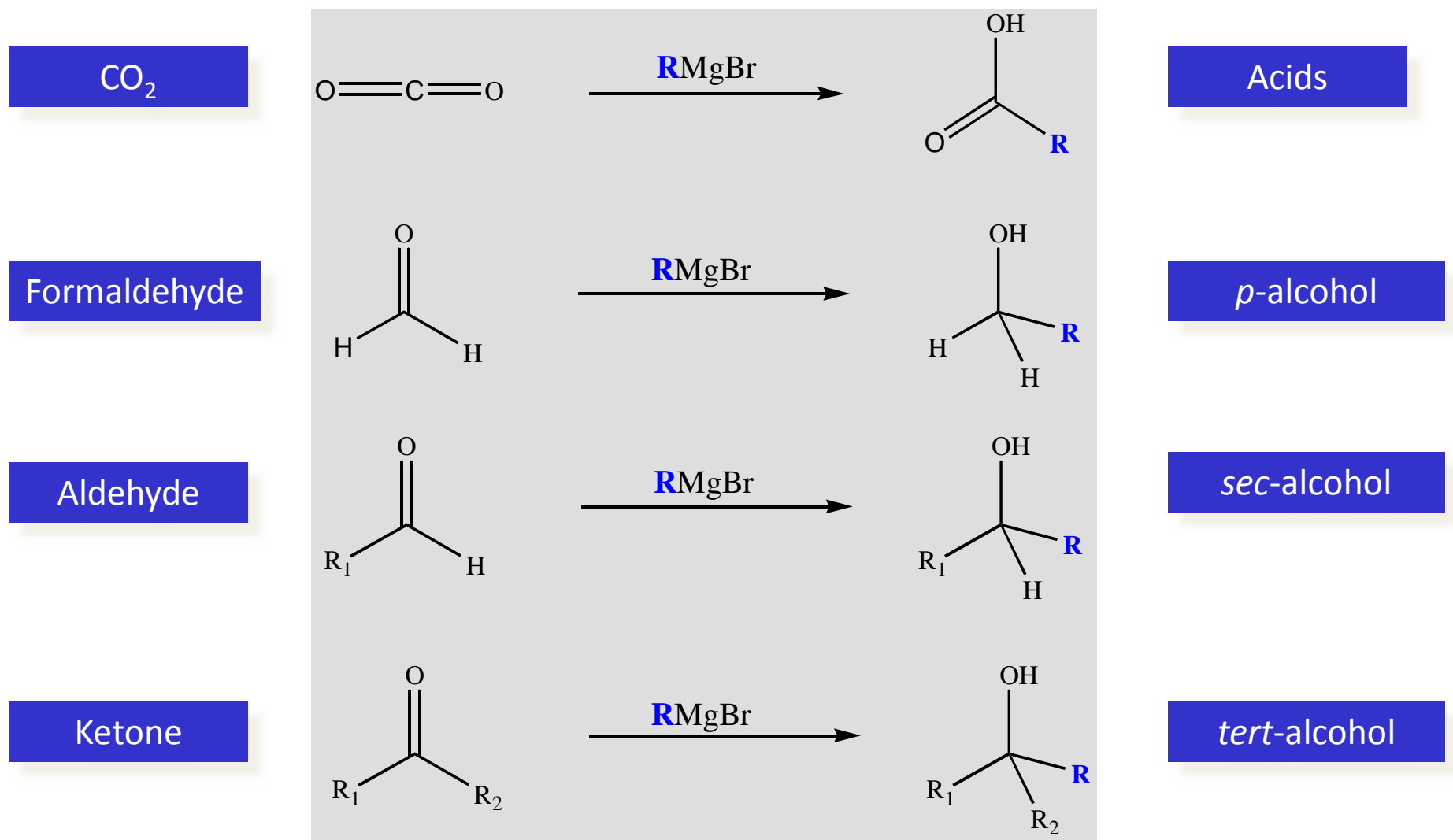
Formaldehyde on reaction with Grignard's reagent gives primary alcohol whereas other aldehydes give secondary alcohol and ketones give tertiary alcohols. [**More examples**]

Formation of primary alcohol
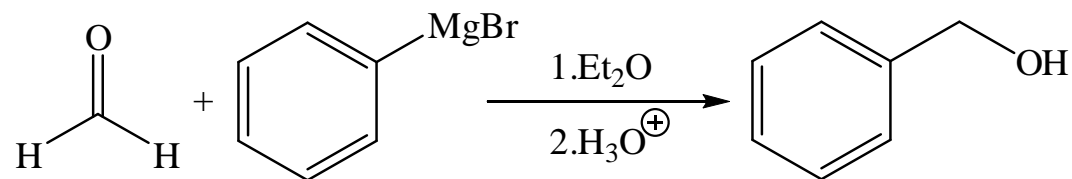
Formation of secondary alcohol
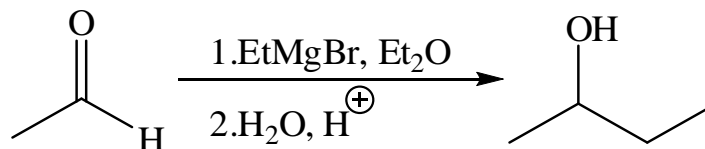
Formation of tertiary alcohol
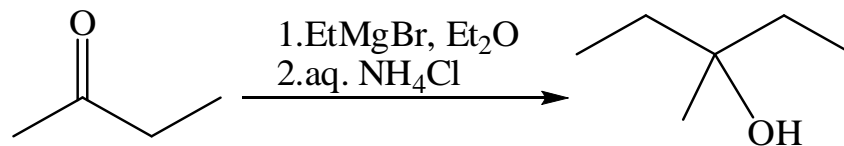
More examples

In presence of strong acid, elimination product is obtained.

Reaction of cyclohexanol with methylmagnesiumbromide
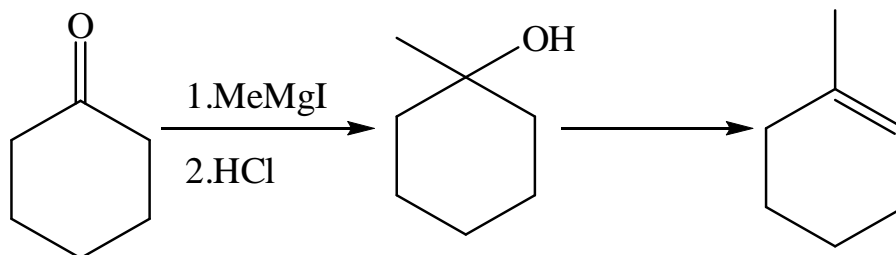
Use of alkylmagnesiumate in Grignard's type reaction

Manabu,H; Tokihiko, M; Kazuak,I; *Org.Lett.*, 2005, 7, 573.

(A.2) Reformatsky reaction

In Reformatsky reaction, aldehydes and ketones on treatment with α-haloesters in presence of metallic zinc give β-hydroxyester.
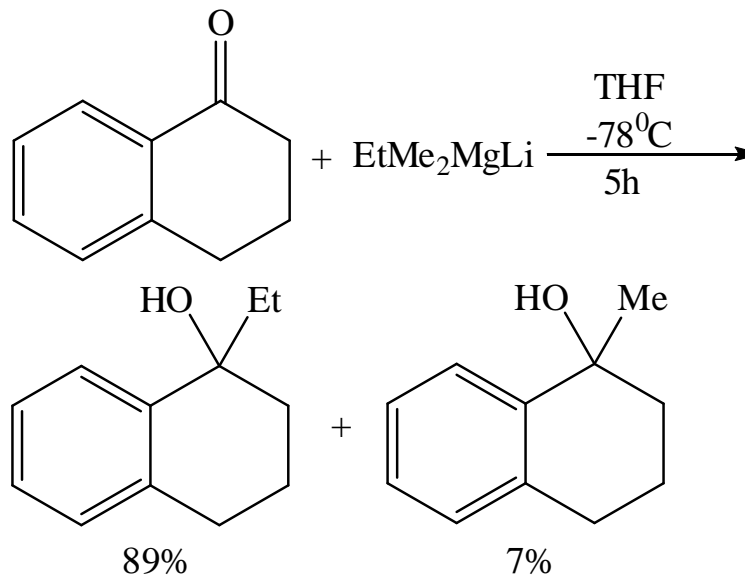
General reaction for Reformatsky reaction
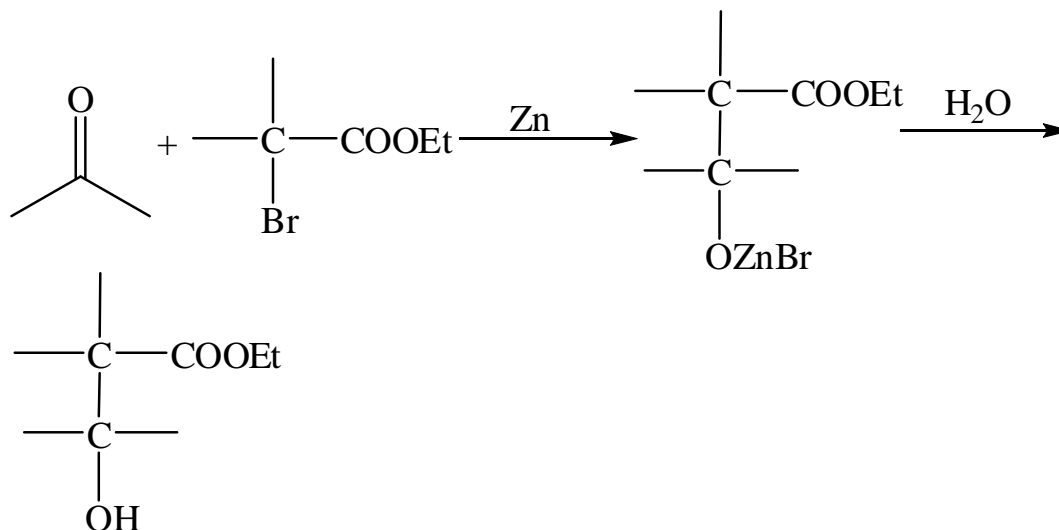
Reaction goes through intermediate analogous to Grignard's reagent.

Reaction may, particularly, in case of aldehydes produce olefin by elimination.

Reaction of benzaldehyde with
Ethyl 2-bromopropionate
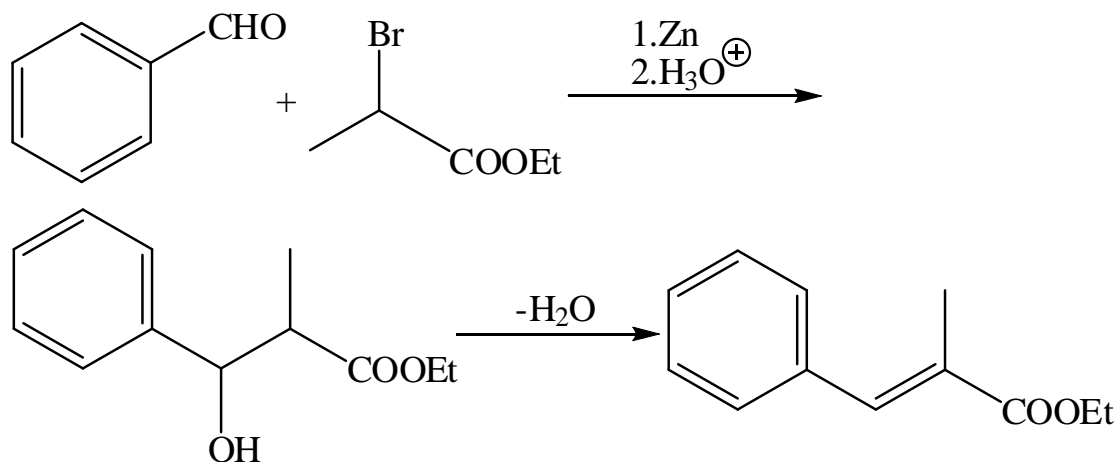
Organozinc reagents are less reactive than
Grignard reagent or organolithium reagents.
Thus, they do not react with esters and
substitution product may result instead.
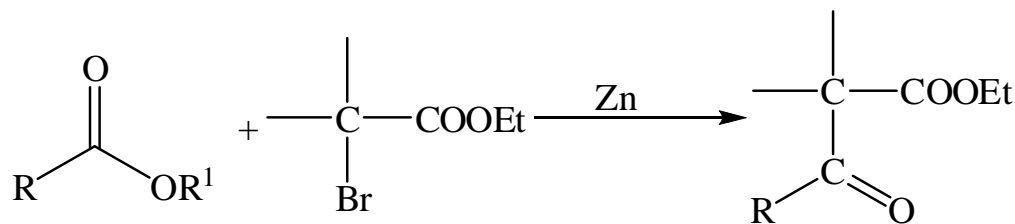
Reaction of benzaldehyde
with
t-butyl 2-bromoethanoate

$\text{BrCH}_2\text{COOtBu}$ / Zn
THF, 0^0C

90% (62% ee)

+

Zn, THF
60^0C

HCl, THF
rt, 10h

92%
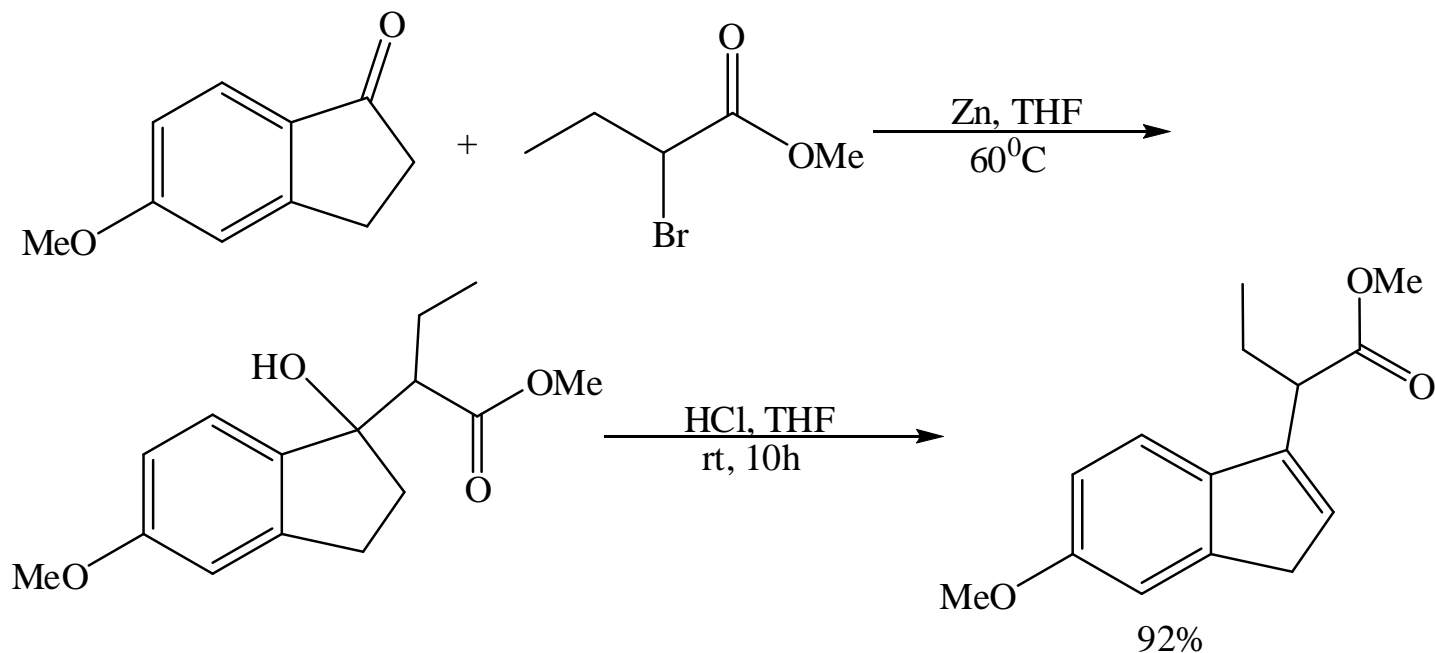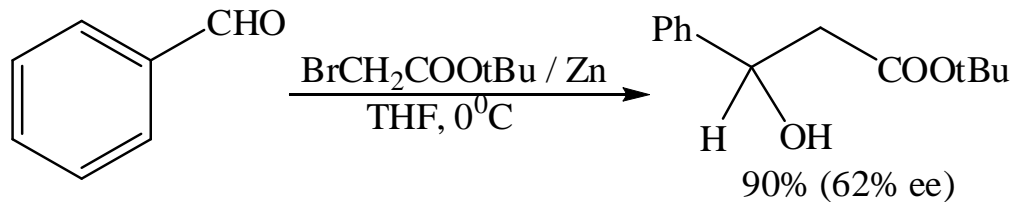
(B). Hydration and hemiacetal formation

Water and alcohol, when added to carbonyl compound, behave as nucleophiles and add to them giving corresponding hydrates and hemiacetals or hemiketal respectively.

Hydration
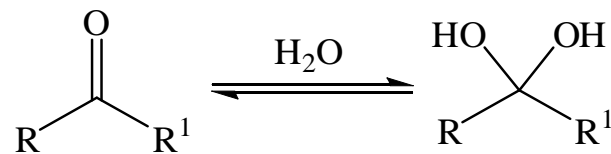
Hemiacetal formation
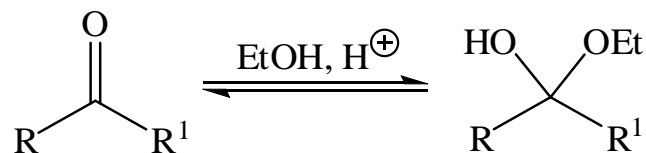
Reaction is in equilibrium and position of equilibrium depends upon nature of carbonyl compound.

Formaldehyde reacts readily than any other carbonyl compound and exists mostly in hydrate form in water.

Formaldehyde is present in hydrated form in aqueous solution
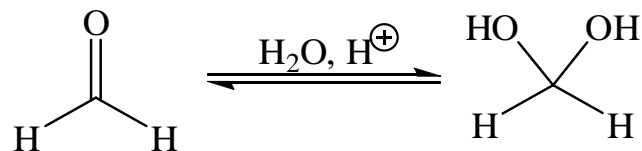
Mechanism for hydration/acetal formation (example given is for acetal formation)

Water is a weak nucleophile and hence activation of carbonyl by way of protonation is required for effective addition of water.
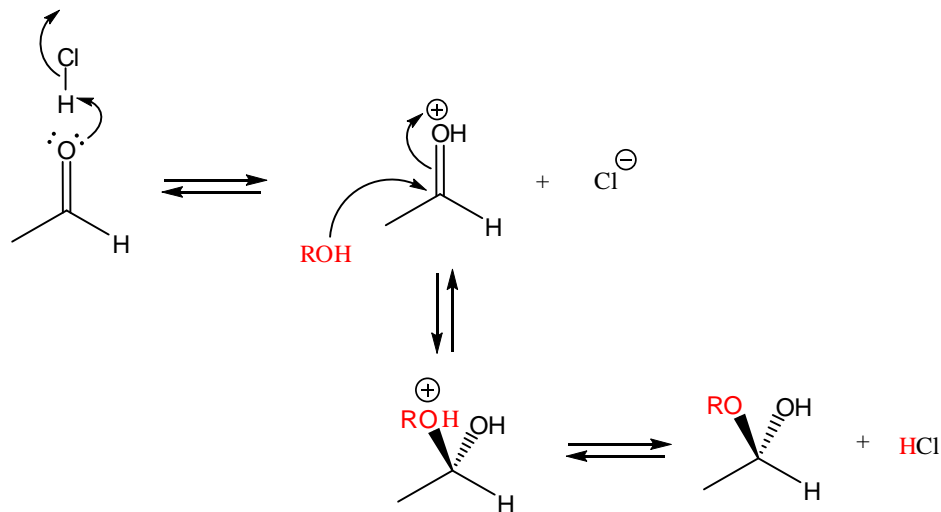
Hydration of chloral is favorable reaction and most of chloral is in hydrated form.
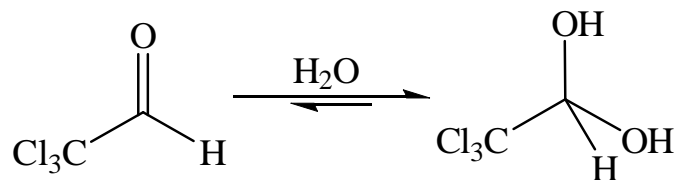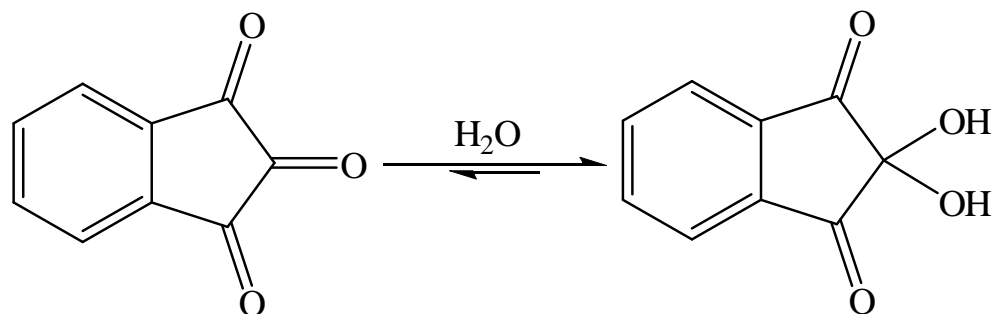
Mechanism for hemiacetal formation follows same route. It is called hemiacetal because it is halfway to acetal.

Intramolecular hemiacetal formation reaction

When carbonyl and hydroxy group are present within same molecule, intramolecular reaction occurs to give cyclic hemiacetal.

Reaction of 4-hydroxybutyraldehyde gives cyclic hemiacetal
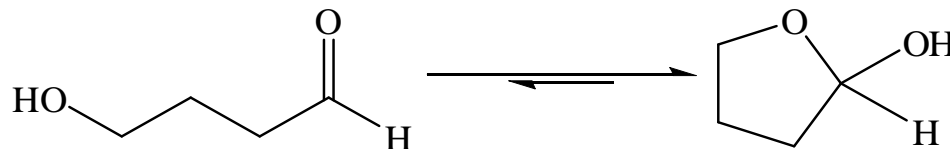
Hydroxyketones can also form cyclic hemiacetals
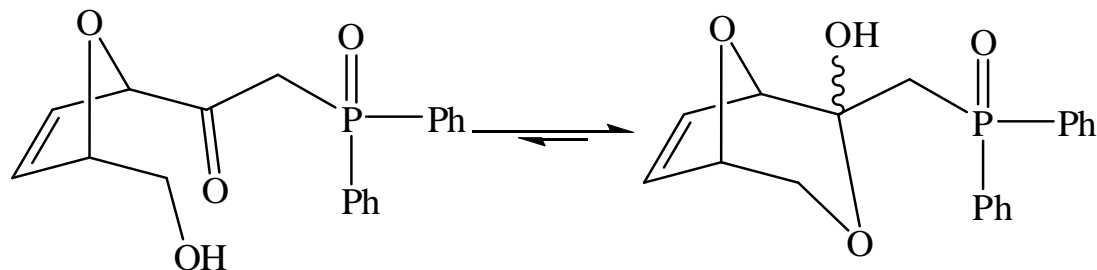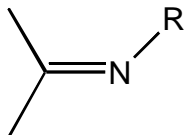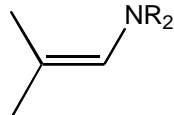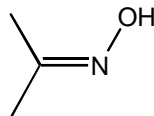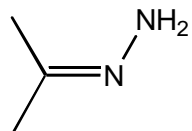
Glucose and ribose mainly
exists in cyclic hemiacetal
form

glucose (>99%)

ribose
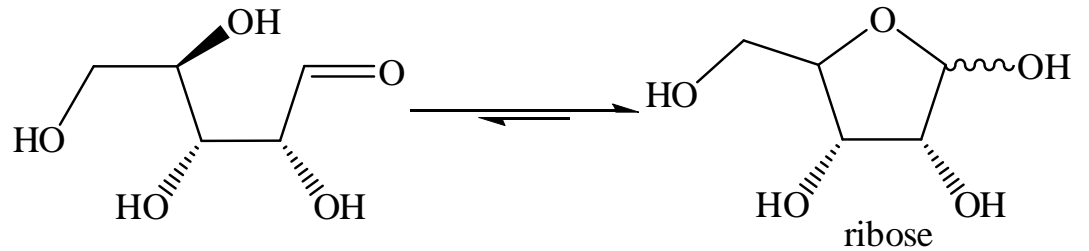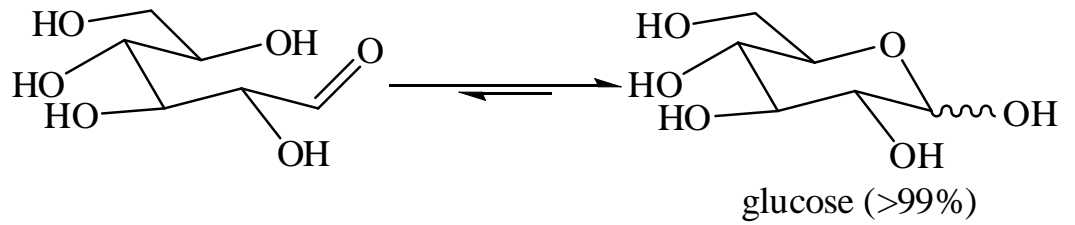
C. Addition of Amines

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)	$\diagup\!\!\diagdown C{=}N\diagdown R$
sec-amine	Enamine	$C{=}C\diagup NR_2$
hydroxylamine	Oxime	$\diagup\!\!\diagdown C{=}N\diagdown OH$
hydrazine	hydrazone	$\diagup\!\!\diagdown C{=}N\diagdown NH_2$

Condensation reactions with ammonia derivatives

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

Addition $\rightleftarrows$ Tetrahedral intermediate $\rightleftarrows$ Elimination

Acid catalyzed

Carbinolamine   Imine

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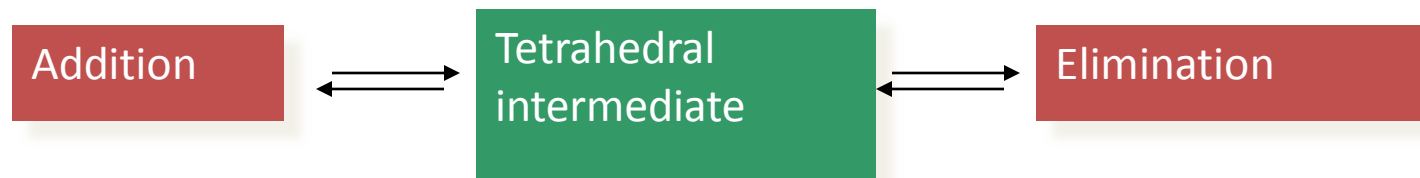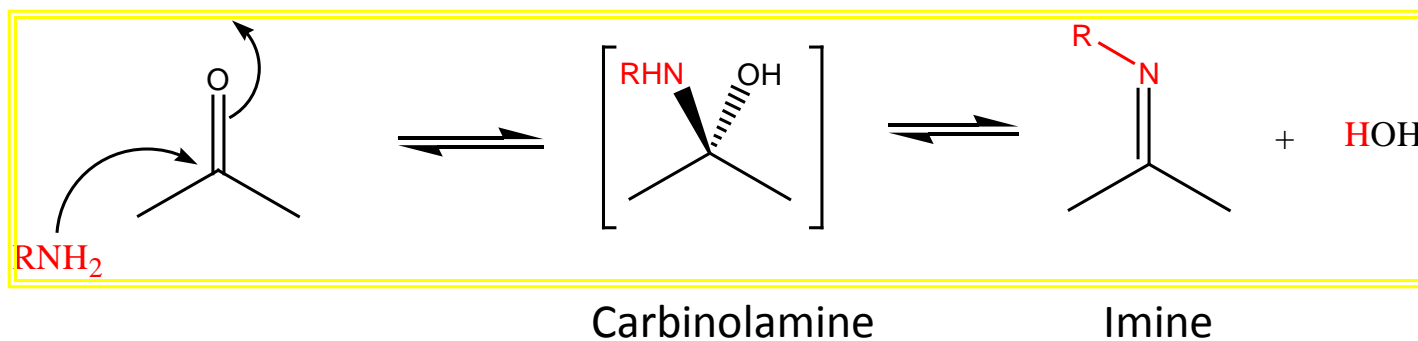
* One or more molecules are joined with the loss of water or another small molecules

C.1. Condensation reactions with ammonia derivatives

Generation of Enamines

2°-Carbinolamine   Enamine
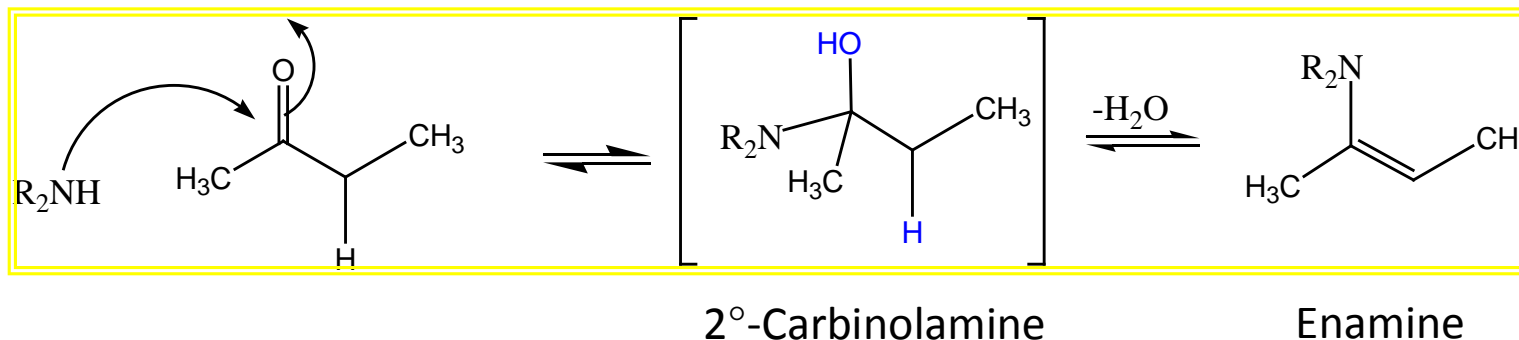
Secondary amines can give **enamines** upon condensation with ketones
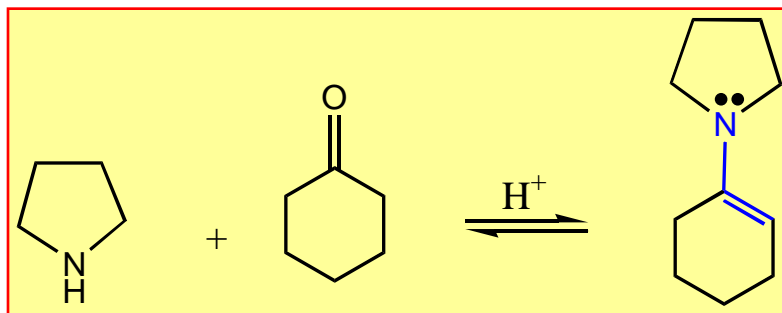
Enamines are **very good nucleophiles** for C-C bond formation

D. The Wittig Reaction   [carbanions as nucleophiles]

Georg Wittig (1954): Nobel prize winner 1979

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

$$\overset{\oplus}{Ph_3P}\!-\!\overset{\ominus}{CR_1R_2} \quad + \quad \overset{R_3}{\underset{R_4}{}}C=O \quad \longrightarrow \quad \overset{R_3}{\underset{R_4}{}}C=C\overset{R_1}{\underset{R_2}{}} \quad + \quad Ph_3P=O$$
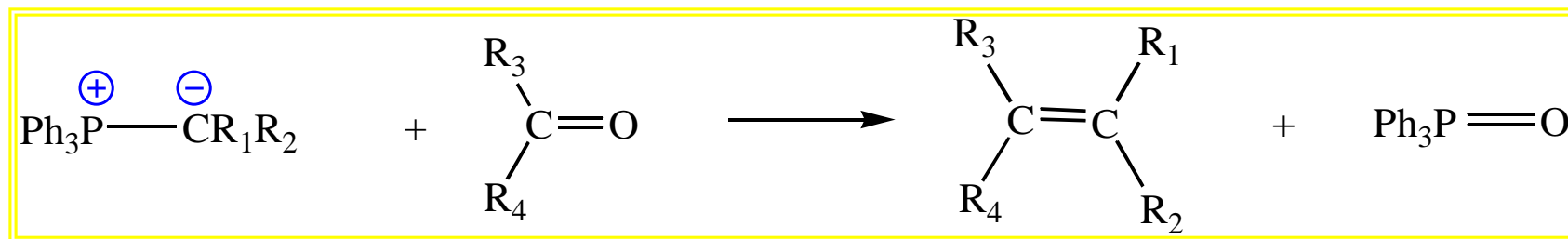
Phosphorous <u>stabilized carbanions</u>

$$\overset{\oplus}{Ph_3P}\!-\!\overset{\ominus}{CR_1R_2} \quad \rightleftharpoons \quad Ph_3P=CR_1R_2$$

ylide   ylene
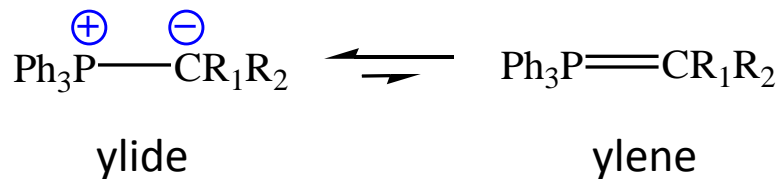
Due to carbanion character ylidic carbons are highly nucleophilic

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

Mechanism of Wittig Reaction

Betaine

Oxaphosphetane

$Ph_3P \mathbin{=\!=} O$
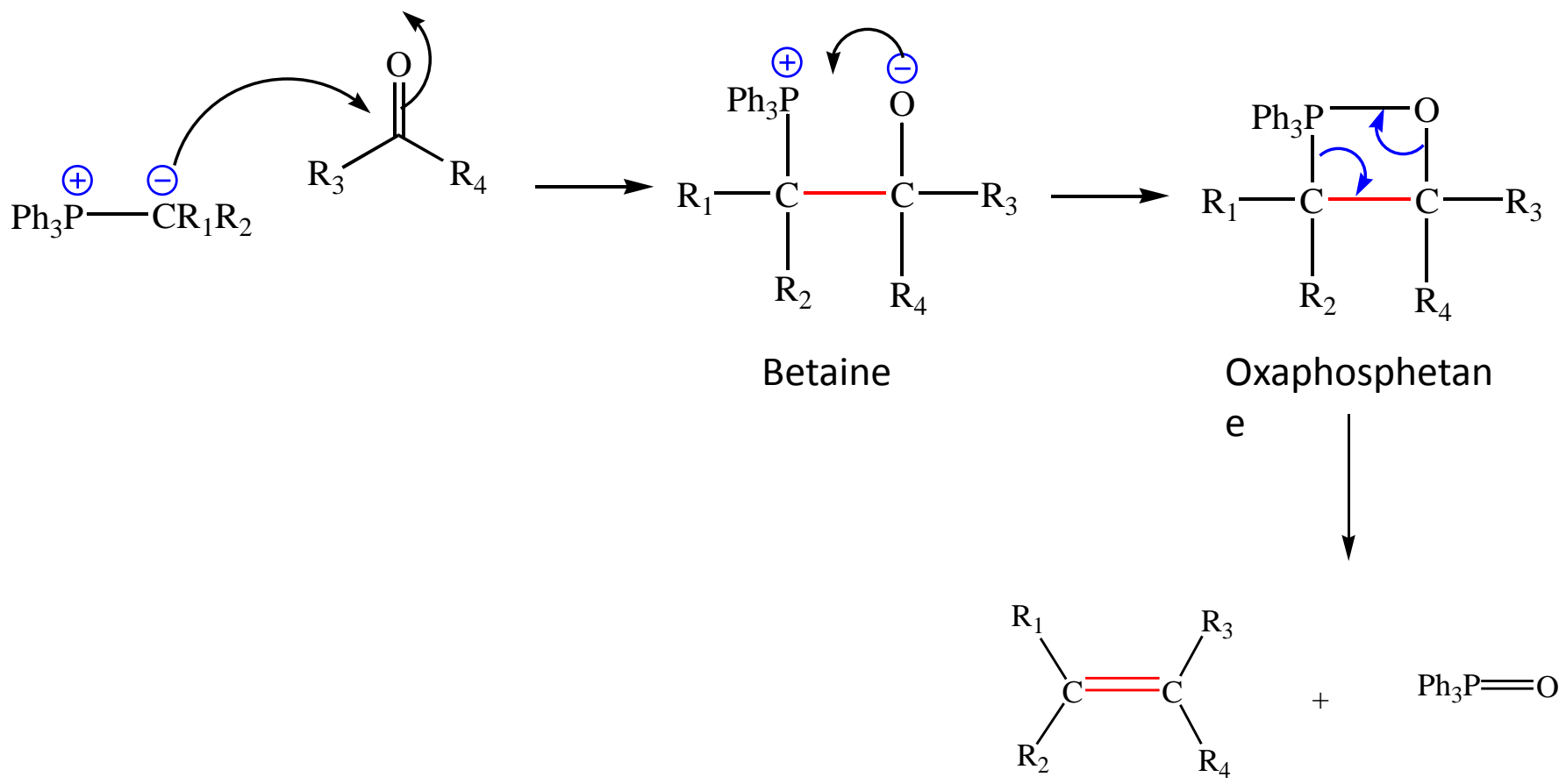
Phosphine oxide is a very stable species. Formation of alkene as well as phosphine oxide provides great thermodyanic drive for this reaction

Wittig Reaction is an **olefination** reaction
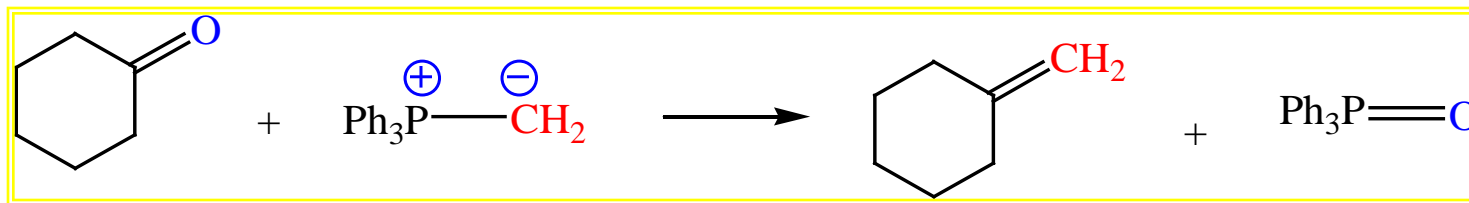
Choice of **R₂CX** is critical while planning a Wittig olefination reaction
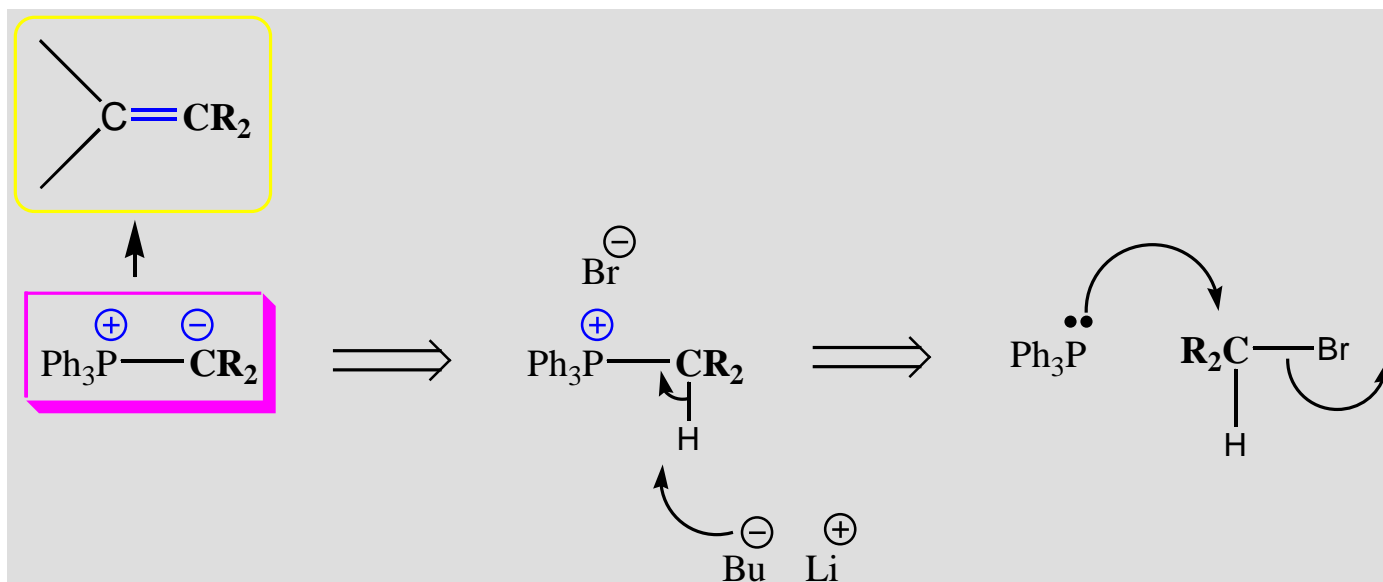
Other bases used for the generation of ylides: t-BuOK, NaH

II. Reaction of enolates

Carbonyl compound containing α-hydrogen atom, when reacted with base, loses its acidic proton and forms an enolate.

Formation of enolate ion
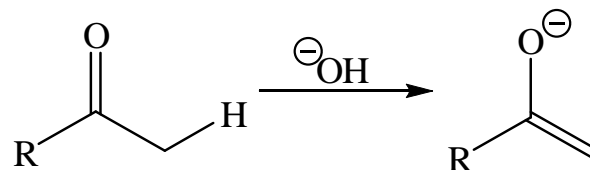
Enolate ion is an alkoxide ion but is more stable to that of corresponding enol form because it is a conjugated, three atom, four electron system.

Delocalization of enolate ion
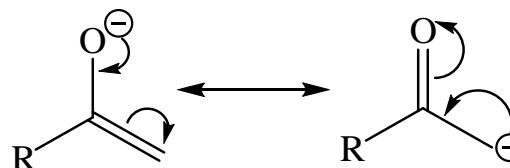
Charge is mainly on oxygen atom, more electronegative atom.

Same can be shown by use of orbitals involved.

Populated π orbital of
enolate ion
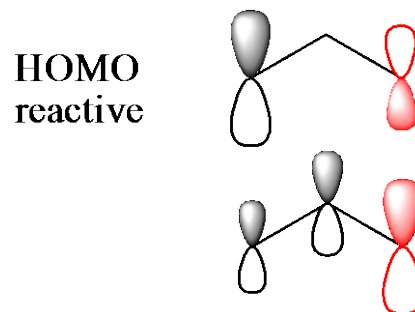
HOMO
reactive

In enolate, thus, more of negative charge is on

oxygen and the HOMO is centered more on the
carbon atom.

Various reactions are shown to proceed via

enolate ion formation.

II. (A). Aldol condensation

Aldol condensation is a self condensation reaction between molecules containing α-hydrogen atom in presence of base.

The product of reaction is a β-hydroxy carbonyl compound.

Base catalyzed Aldol condensation of acetaldehyde

Mechanism for Aldol condensation

Base first abstracts proton from carbonyl compound and gives enolate which then adds to other molecule of carbonyl compound to give β–hydroxycarbonyl compound
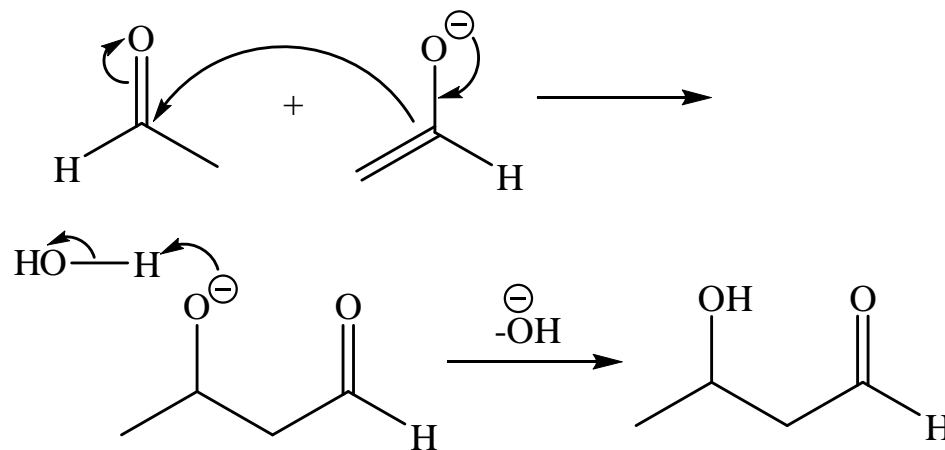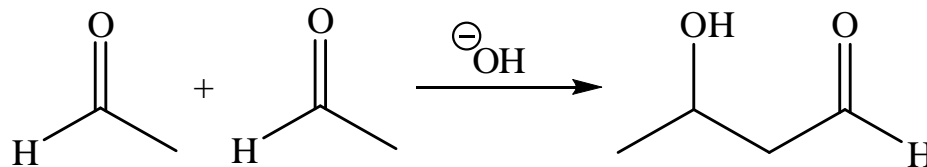
Reaction is also furnished by ketones.

Base catalyzed Aldol
condensation of acetone
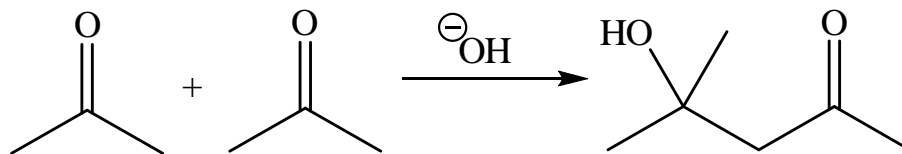
In high basic conditions, further reaction occur
i.e. elimination.
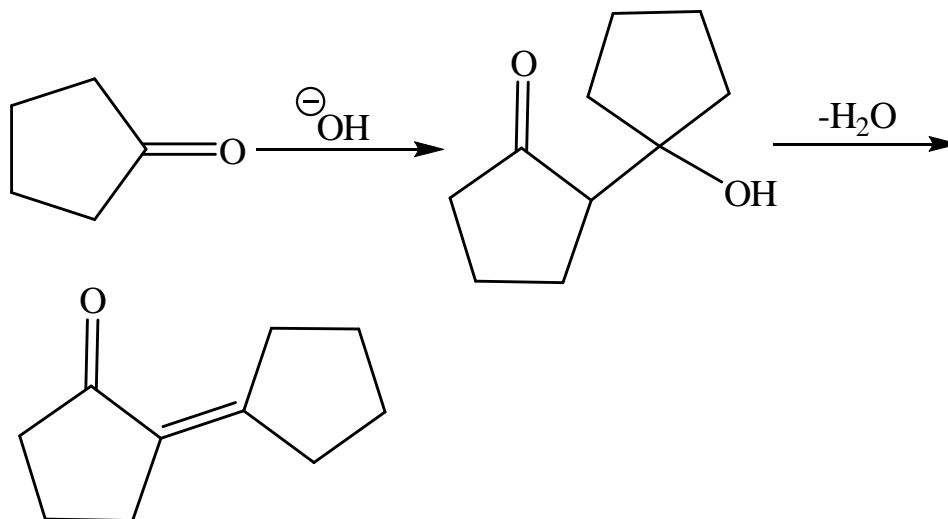
Elimination of water
molecule proceeds via
E1cB mechanism

In case of symmetrical carbonyl compound, which way enolisation occurs is unimportant. Similarly, in case of unsymmetrical carbonyl compounds, containing only one α-hydrogen atom, which way it is enolized is unquestionable.

Base catalyzed Aldol condensation of acetophenone
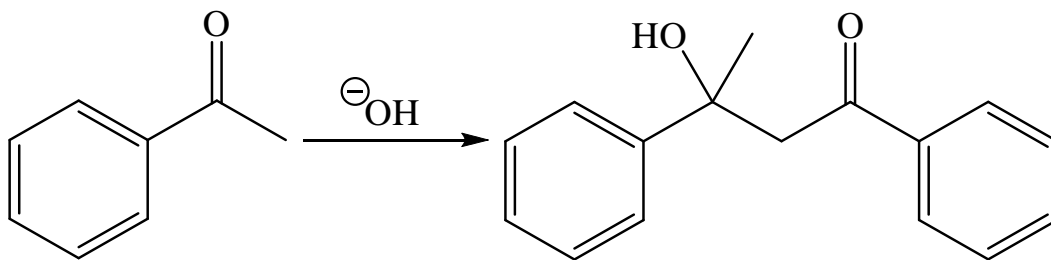
In acetophenone, only methyl protons can be enolized.

Similarly, in case of lactones, only methylene protons are available for enolisation.

Base catalyzed Aldol condensation of cyclic ester
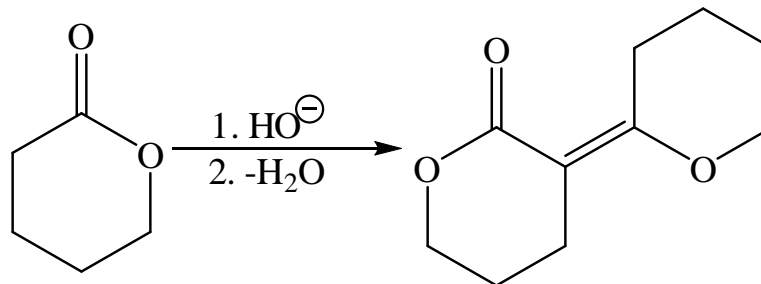
Aldol reactions can also be furnished using specific enol equivalent, such as, lithium or silyl enol ether etc.

Aldol reaction using lithium enolate

82%
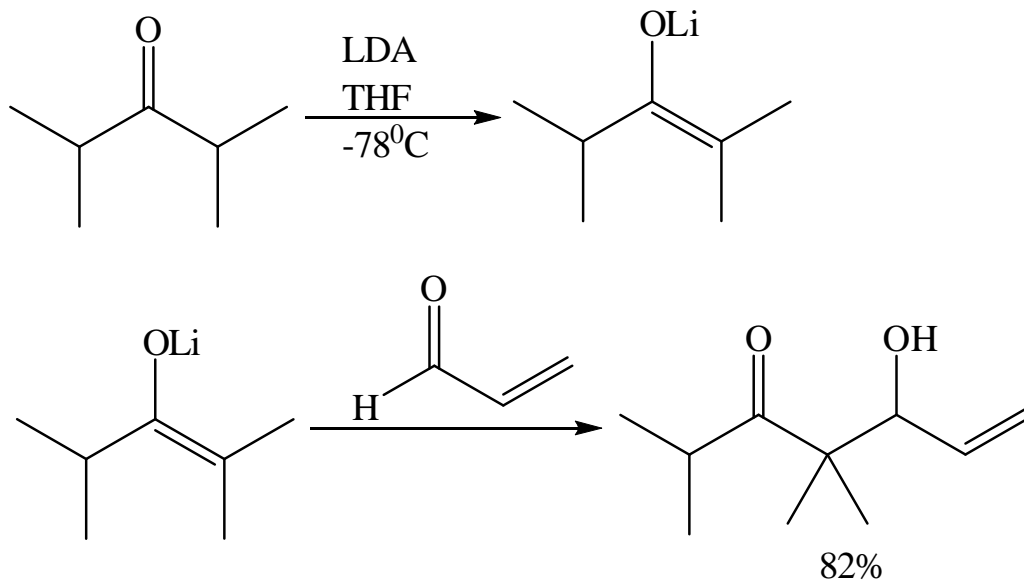
Aldol reaction using silyl enol ether
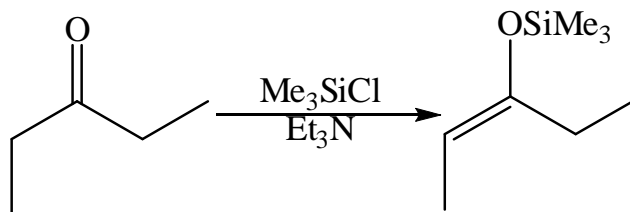
Reaction of 2-methylbutyraldehde with silyl enol ether of 3-pentanone
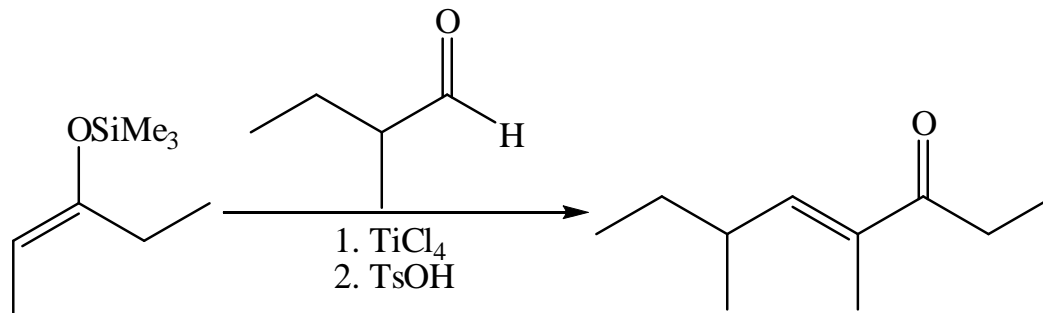
When two different carbonyl compound are treated with base, condensation is observed, similar to that of self condensation. This reaction is known as cross-aldol condensation.

Cross-Aldol reaction between acetophenone and 4-nitrobenzaldehyde
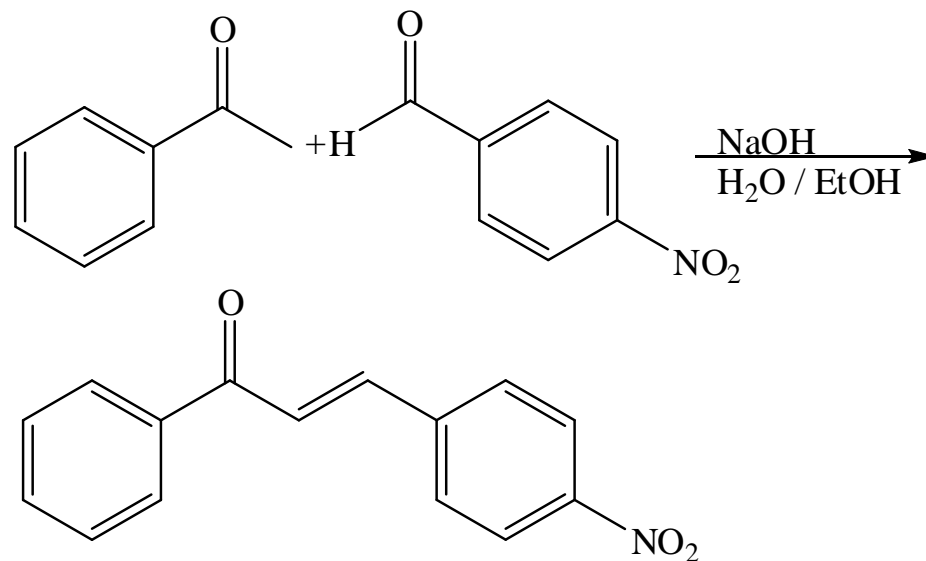
For these kind of reactions to work, there must be present at least one component which can not be enolized and is electrophilic enough for nucleophilic attack to occur and other component must be enolizable.

When, in a molecule present, two carbonyl functional groups such that one can be enolized and other is electrophilic, intramolecular Aldol reaction takes place.

Intramolecular Aldol reaction of 1,6-diketone
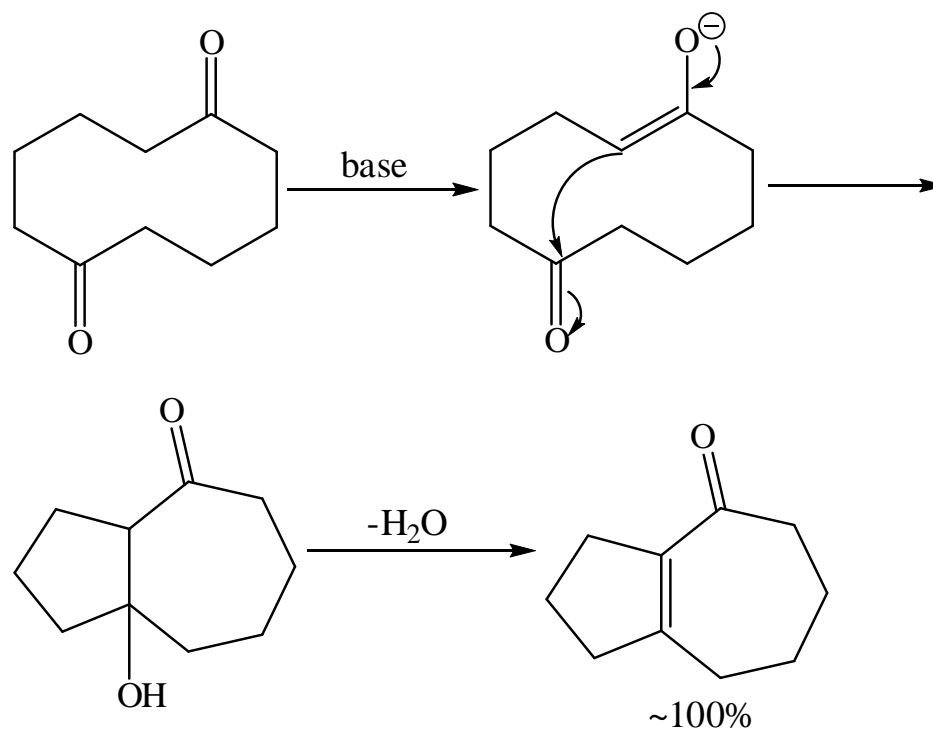
In case of unsymmetrical diketones, there are four different sites for enolisation and the final product depends on whether reaction is kinetically controlled or thermodynamically controlled.

Intramolecular Aldol reaction of 1,5-diketone

KOH

90%
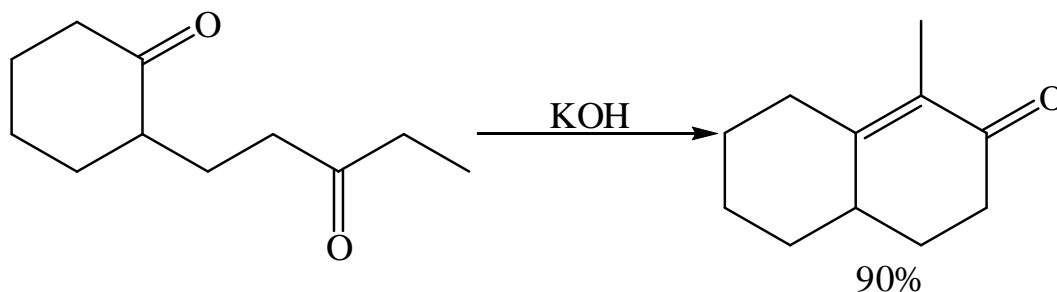
In this reaction, though there are several possibilities of inter and intra molecular condensation, only this product is formed in 90% yield. This is because it leads to stable conjugated enone in six membered ring.

Intramolecular Aldol
reaction of 1,4-diketone
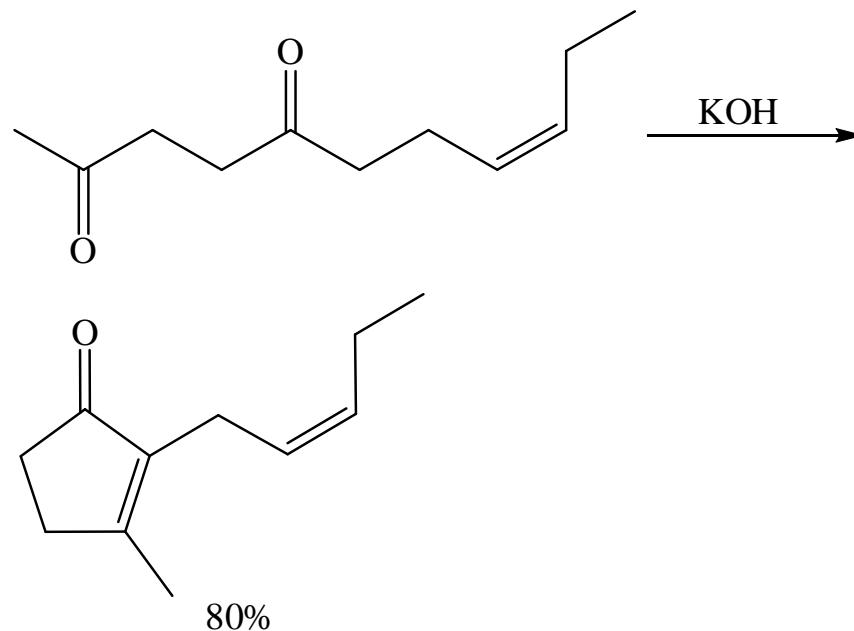
In this reaction, 80% of the product, cis-jasmone is formed, as reaction is under thermodynamic control.

II. (B). Knoevenagel reaction

Knoevenagel reaction is modified aldol reaction, in which reaction of carbonyl compound with active methylene compound, proceeds through enolate formation, in presence of weakly basic conditions.
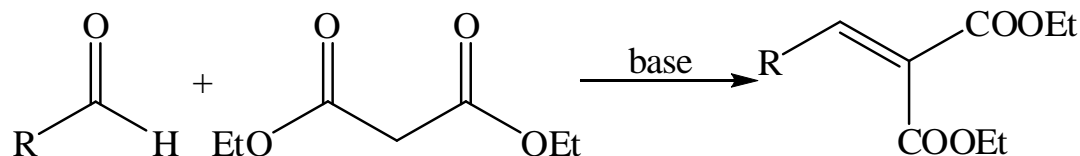
Active methylene compound in the reaction can be diethylmalonate, ethylacetoacetate, malonic acid, Meldrum's acid, cyanoacetic ester etc. Weakly basic conditions can be maintained by use of pyridine or piperidine in reaction. Mechanism is as follows.

Attack of base on active methylene compound to give enolate
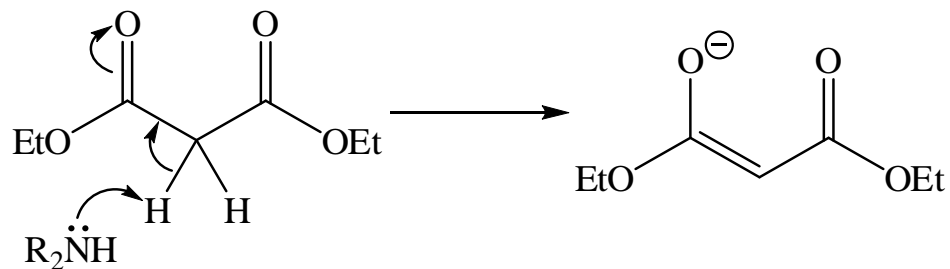
Electrophilic addition of enolate to carbonyl compound
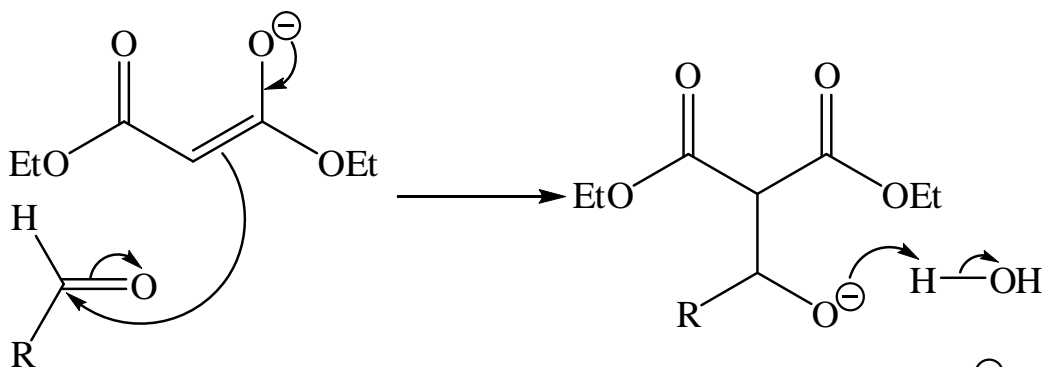
Removal of water molecule by E1cB mechanism to give final product
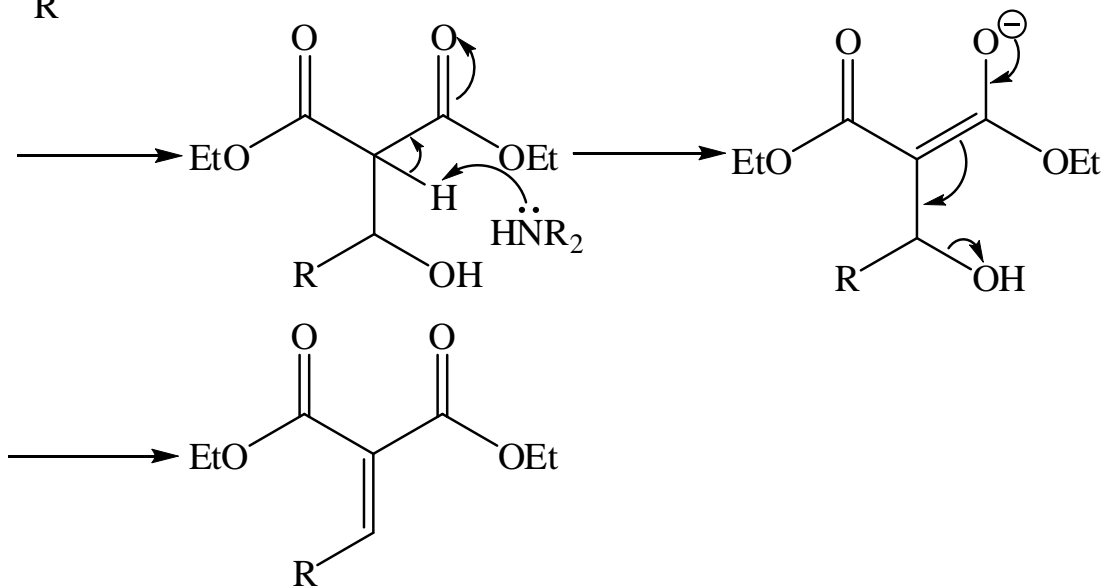
Few more examples of Knoevenagel reaction

ethylammonium nitrate, rt, 10h

87%

**pH 7.8
H$_2$O
40^{0}C
4h**

86%
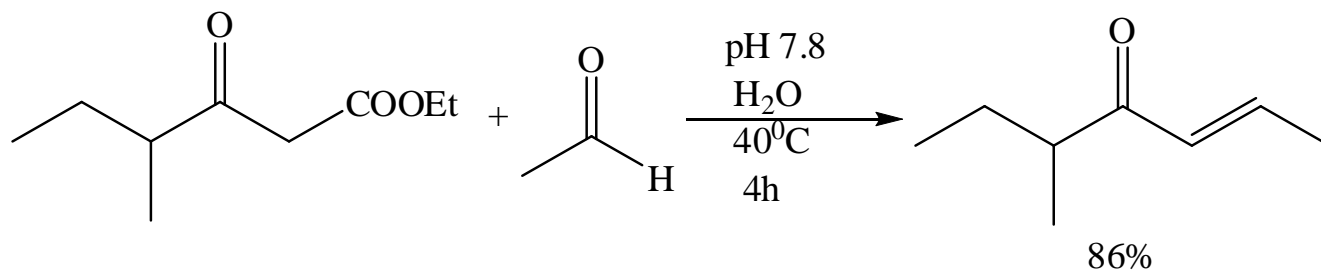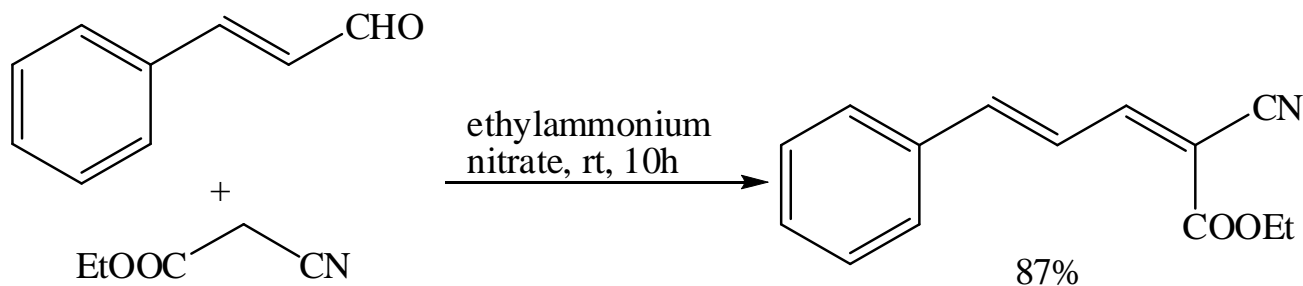
Kourouli, T; Kefalas, P; Ragoussis, N; Ragoussis, V, *JOC*, 2002, 67, 4615

II. (C). Perkin reaction

Reaction of acid anhydride and aromatic aldehyde in presence of strong base, is <u>Perkin</u> reaction.
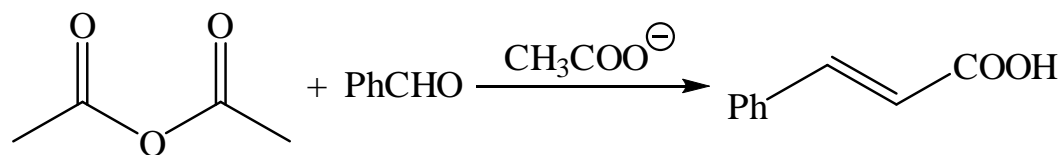
Mechanism of reaction

Formation of enolate of anhydride
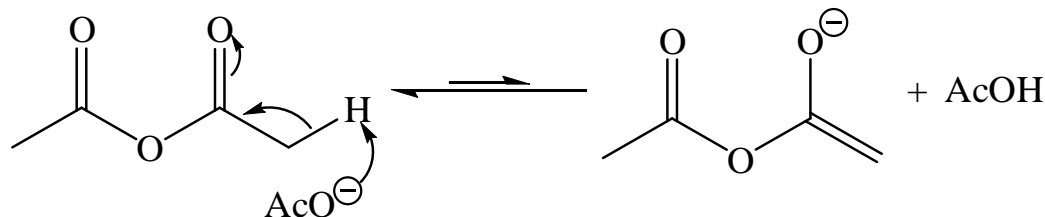
Aldol type addition of enolate to carbonyl compound
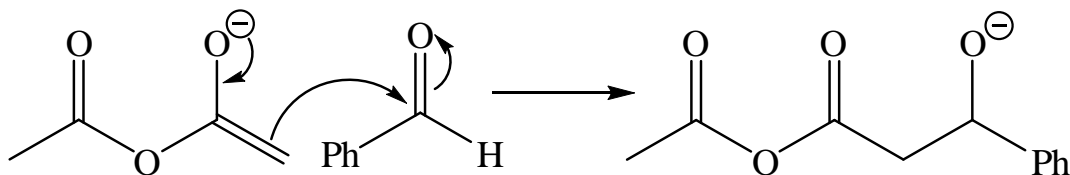
Intramolecular acylation followed by loss of carboxylate
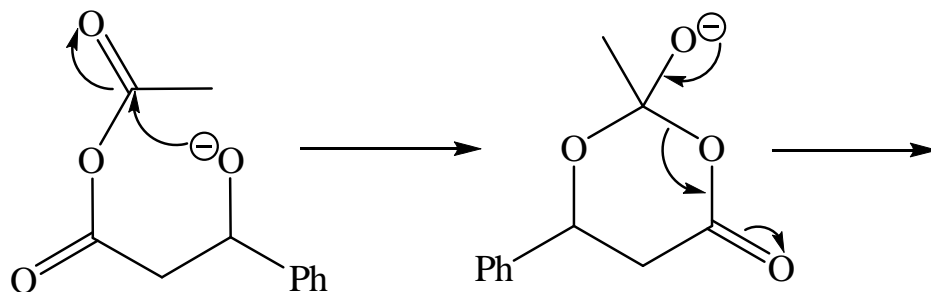
In next step mixed anhydride formed by addition of acetic anhydride loses acetic acid and is hydrolyzed in single step to give unsaturated acid
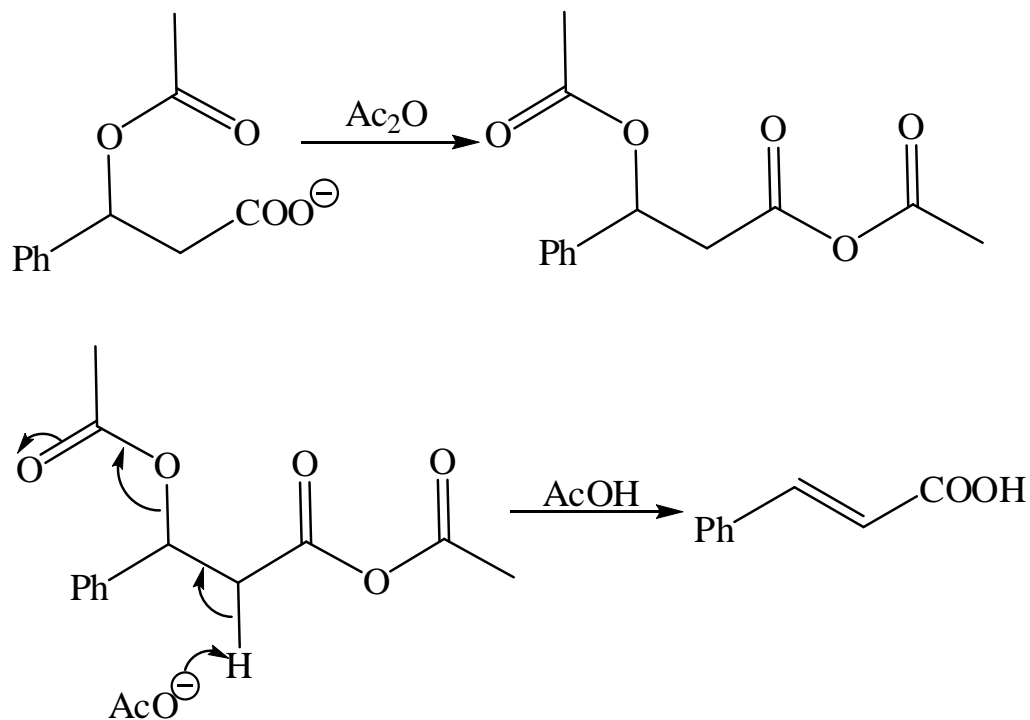
Mechanism is supported by fact that, when anhydride containing no enolizable protons is used, then final product of the reaction is one corresponding to the one obtained by loss of carboxylate.

Ketcham, R, *J. Chem. Educ*., 1964, 41, 565

O_2N—⟨ ⟩—CHO + MeO—⟨ ⟩—CH_2COOH

pyridine
$(CH_3CO)_2O$
30 min

HOOC

O_2N—⟨ ⟩— ⟨ ⟩—OMe

trans= 82% & cis= 10%
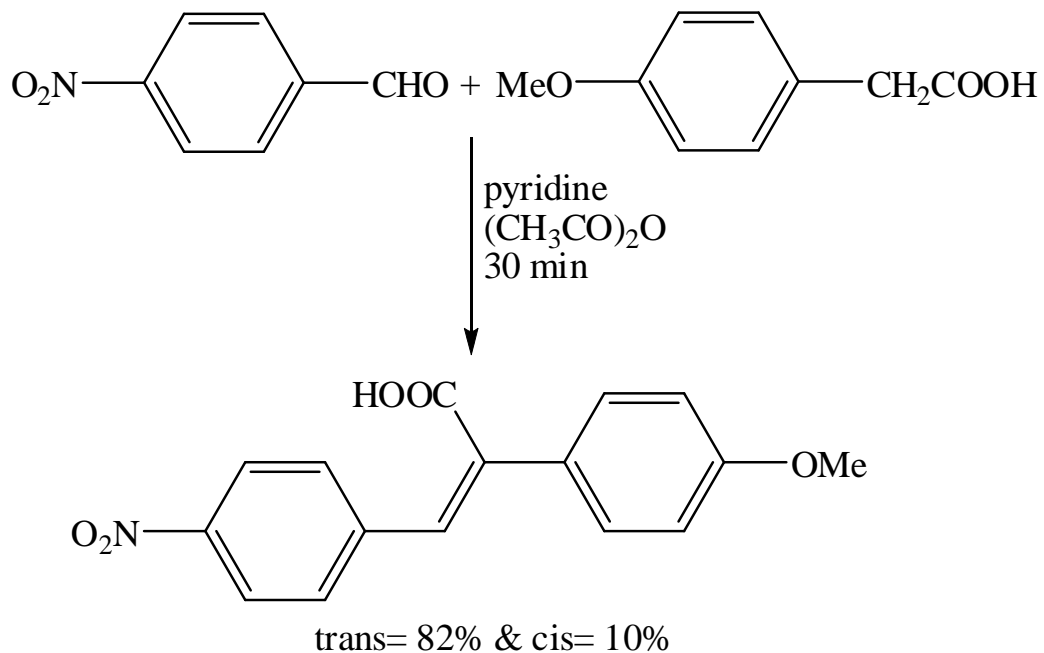
More examples

Gaukroger, K; Hadfield, J.A; Hepworth, L.A; Lawrence, N.J; McGown, A.T, *JOC*, 2001, 66, 8135

NEt$_3$, Ac$_2$O

60%
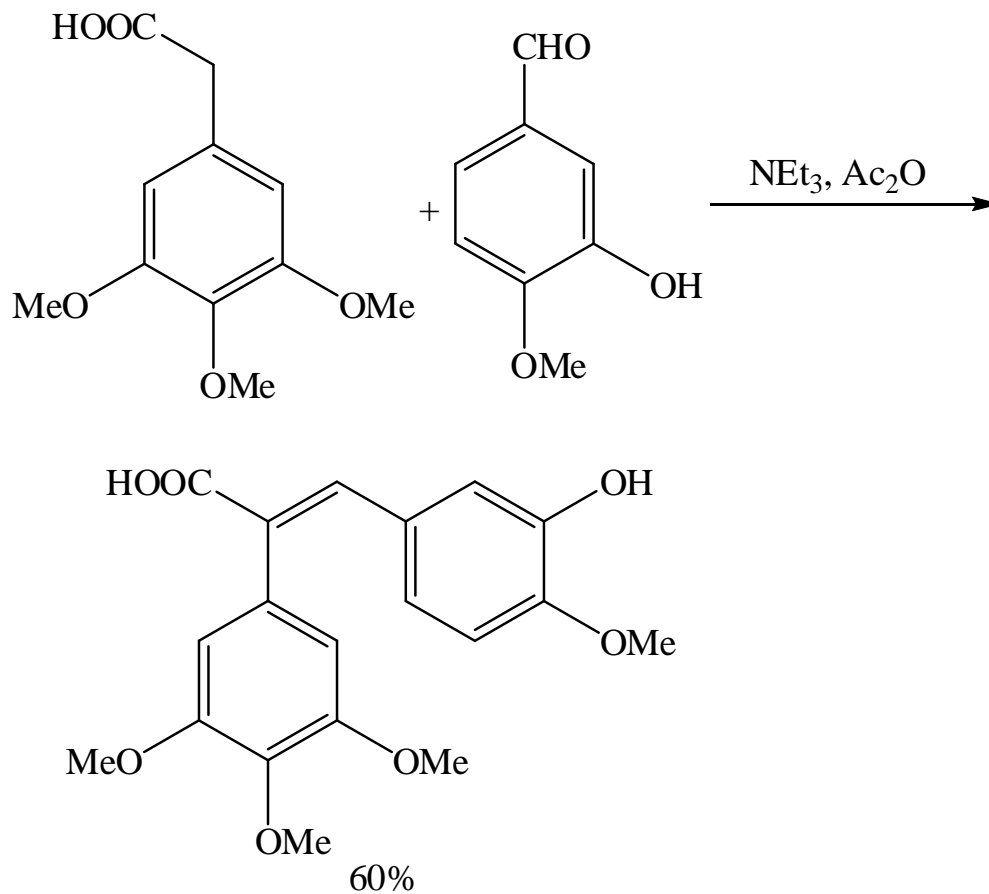
II. (D). Claisen condensation

Self condensation reaction of enolizable ester, in the presence of base, is <u>Claisen</u> condensation.

Ethylacetate on reaction with sodiumethoxide gives ethylacetoacetate.

Mechanism of reaction
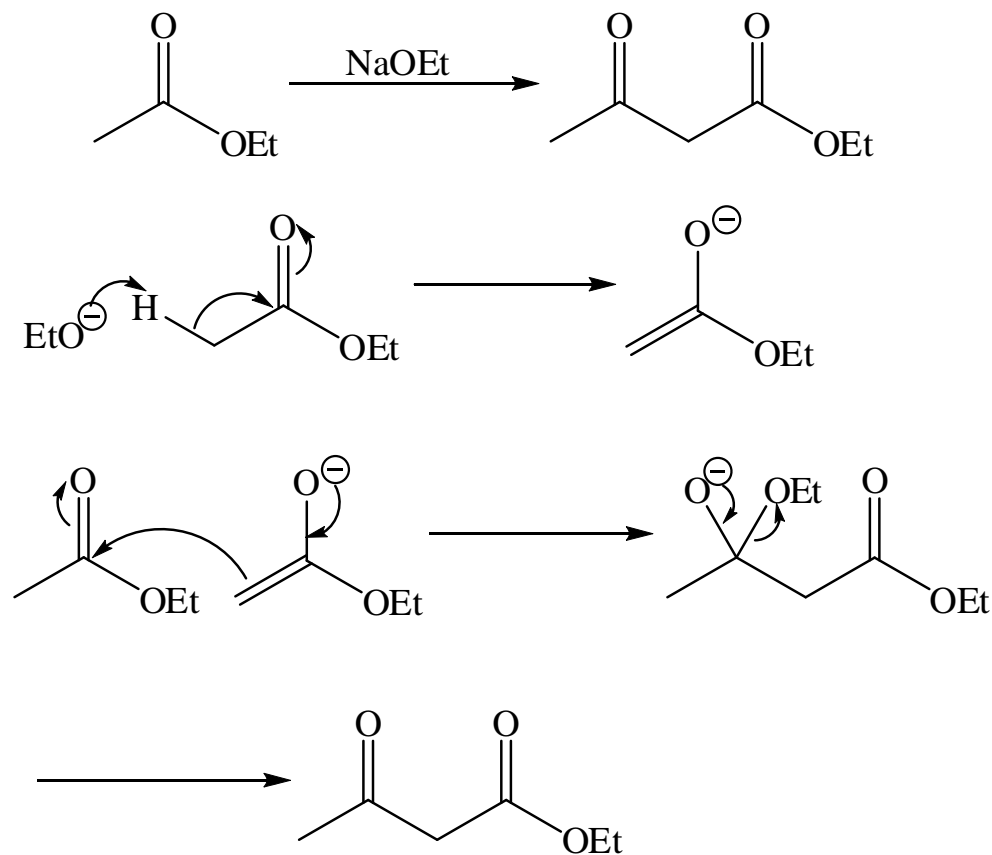
Mechanism is similar to that of Aldol condensation. In this reaction, first ester
is enolized. It then attacks another molecule of ester in the same way as that
in aldol condensation. Adduct of the reaction then loses ethoxide, as it is
good leaving group.

Product of the reaction is β-ketoester.
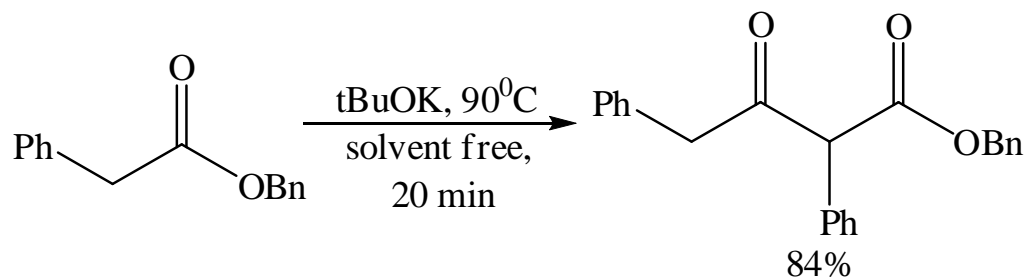
Cross-Claisen condensation are those in which two different molecules of ester
or ester and other carbonyl compound are treated in presence of base.
It often forms mixture of products. Synthetically useful products are obtained,
when one of the component of reaction is non-enolizable.

Cross-Claisen condensation of benzaldehyde and ethylacetate
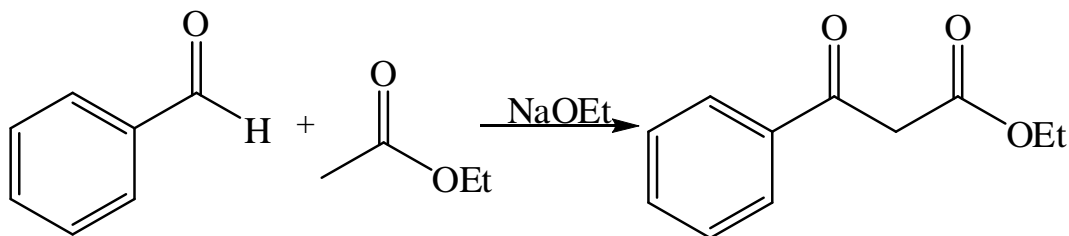
Cross-Claisen condensation of ethylbenzoate and ethylacetate
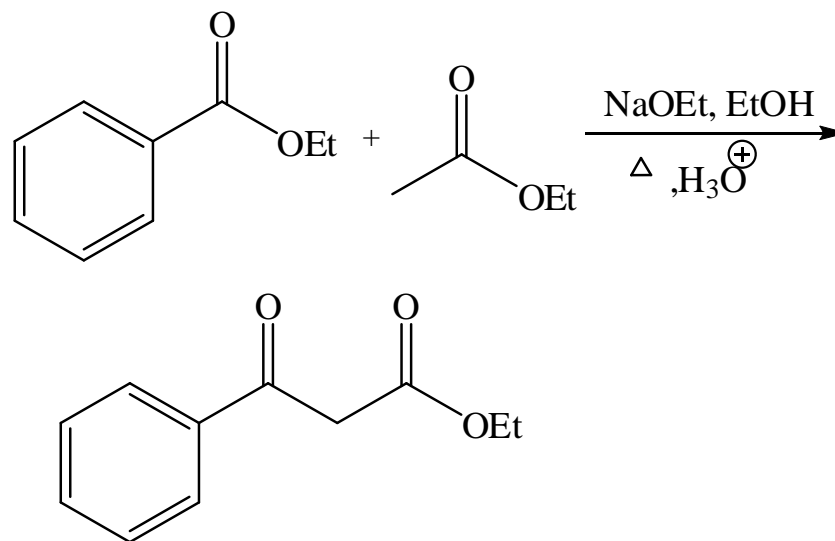
Cross-Claisen condensation of ethylbenzoate and acetophenone
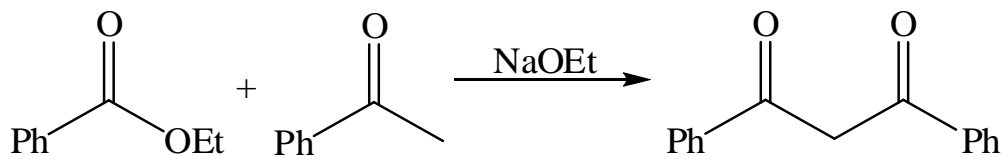
Cross-Claisen condensation of cyclohexanone and ethylformate
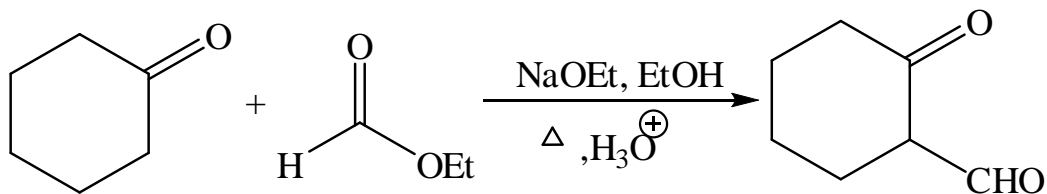
Honda, Y; Katayama, S; Kojima, M; Suzuki, T; Izawa, K, *Org. Lett*., 2002, 4, 447

97%
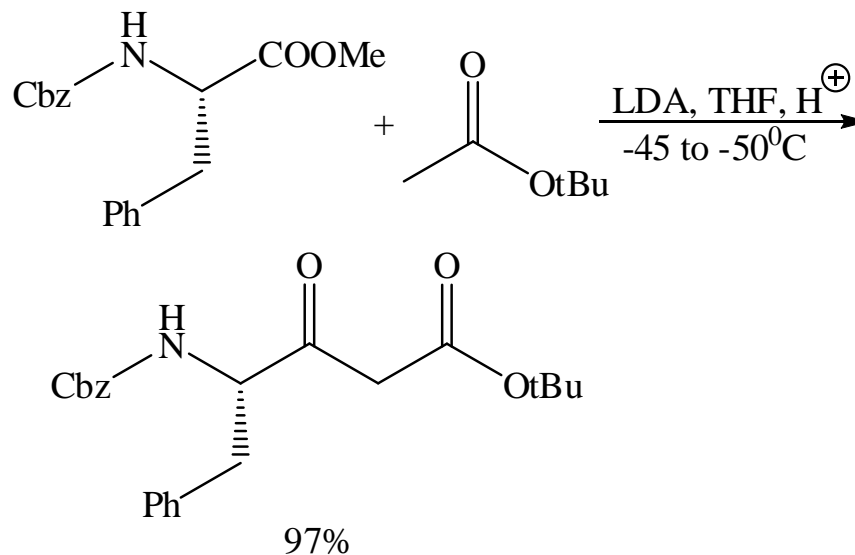
Thioesters also undergo Claisen condensation.

Claisen condensation of thioester gives β-ketothioester
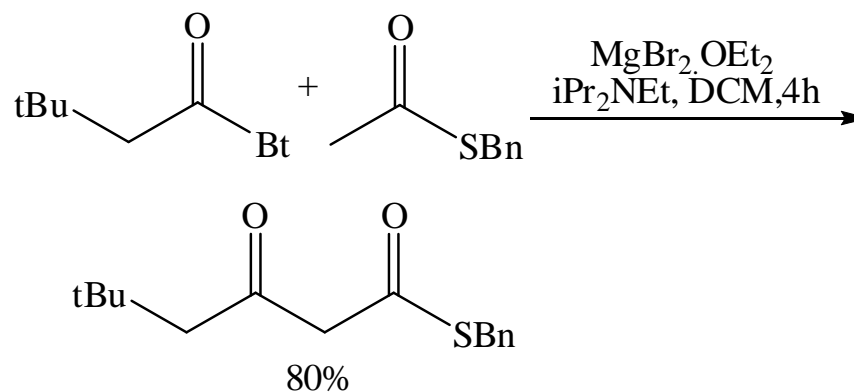
Zhou, G; Lim, D; Coltart, D.M, *Org.Lett*., 2008, 10, 3809

80%

II. (E). Dieckmann cyclisation

Intramolecular Claisen condensation of diesters in presence of a base is Dieckmann cyclisation.
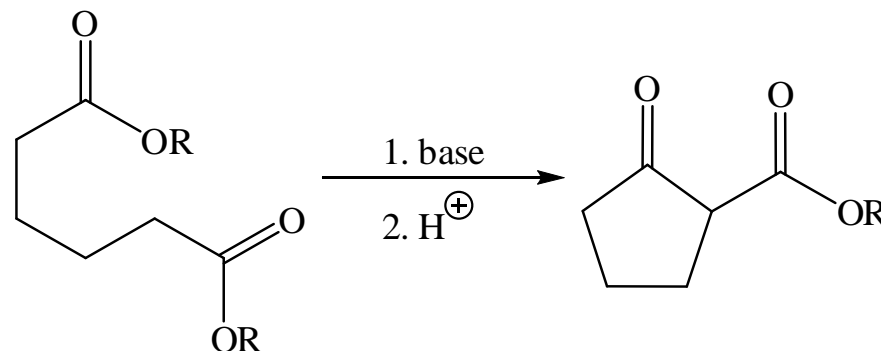
The mechanism for the Dieckmann cyclisation is analogous to that of the Claisen condensation.

Firstly one of the two esters is converted into an enolate ion. This enolate then attacks the second ester via nucleophilic acyl substitution resulting in a cyclic β-keto ester.
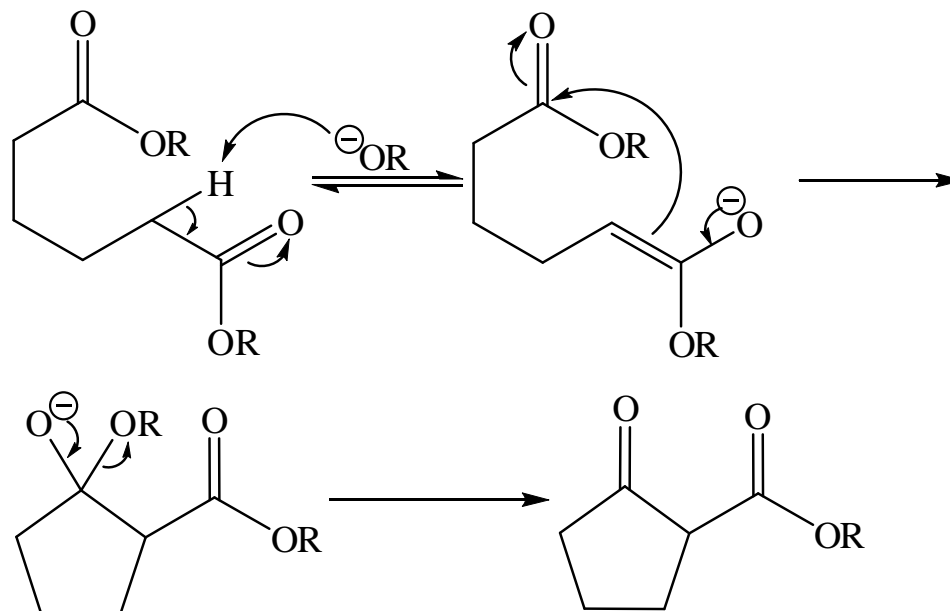
Reaction can best be carried out for 1,6 and 1,7-diesters, which give five and six membered rings respectively.

1. tBuOK, tol
   reflux
   5 min
2. 18N H$_2$SO$_4$
   THF, 4 h

61%
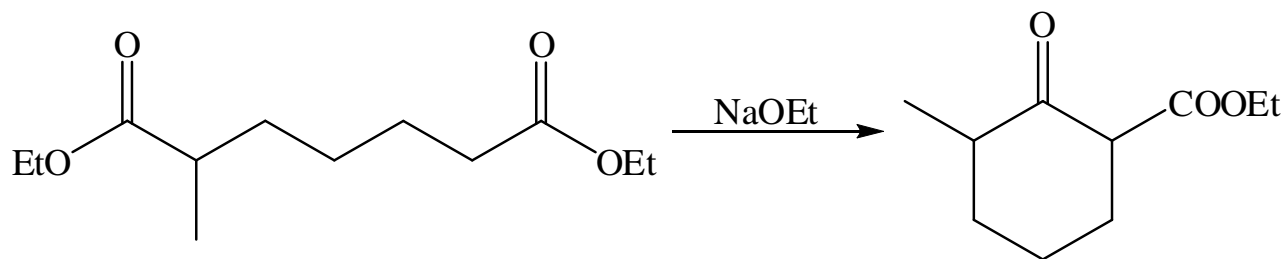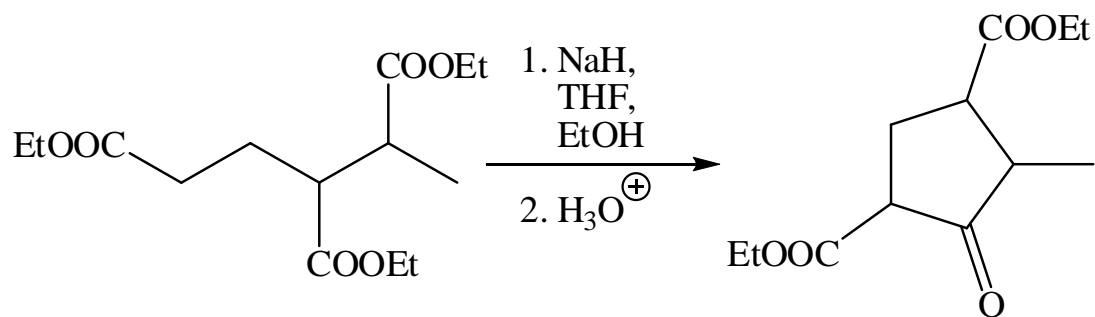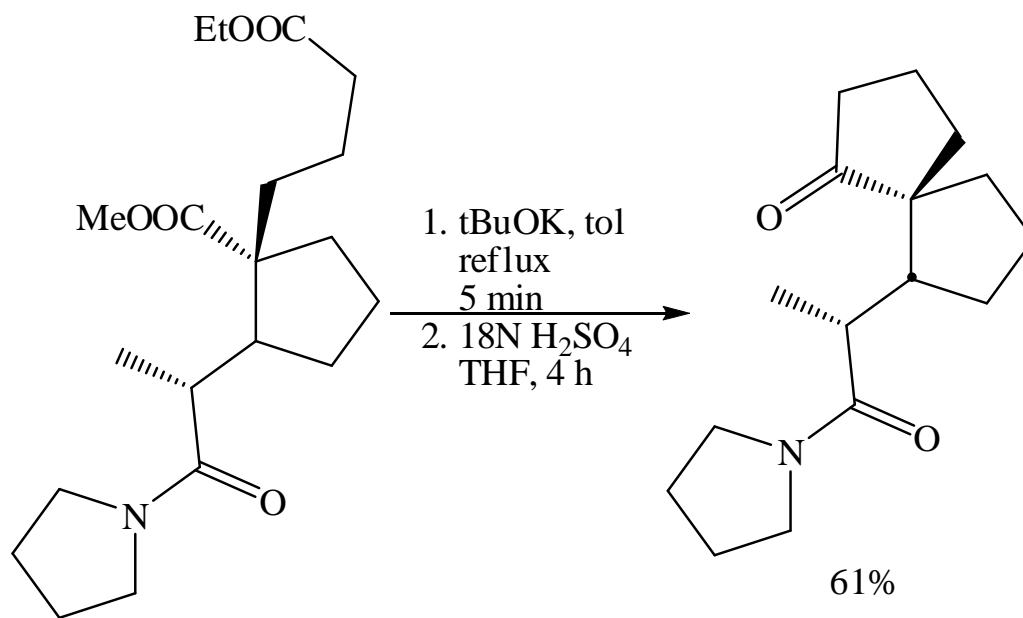
More examples

Toda, F; Suzuki, T; Higa, S, *J. Chem. Soc.*, 1998, 1, 3521
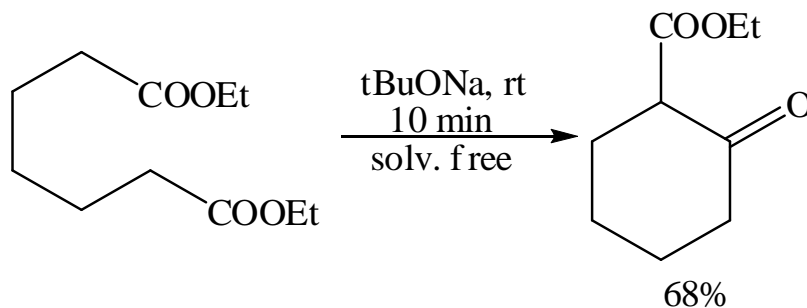
Jackson, B.G; Gardner, J.P; Heath, P.C, *Tet. Lett.*, 1990, 31, 6317
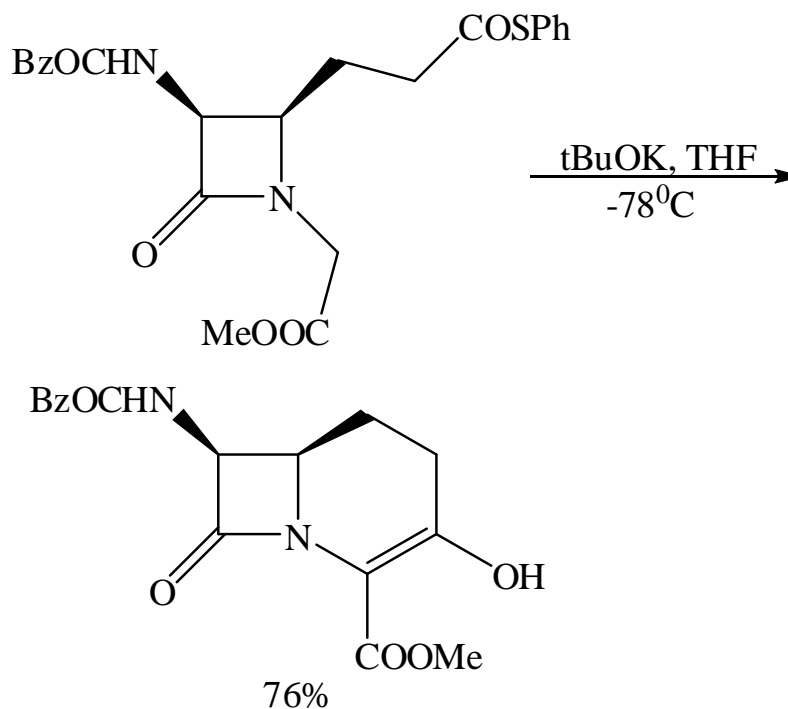
More examples

DeGraffenreid, M.R, et.al,
JOC, 2007, 72, 7455
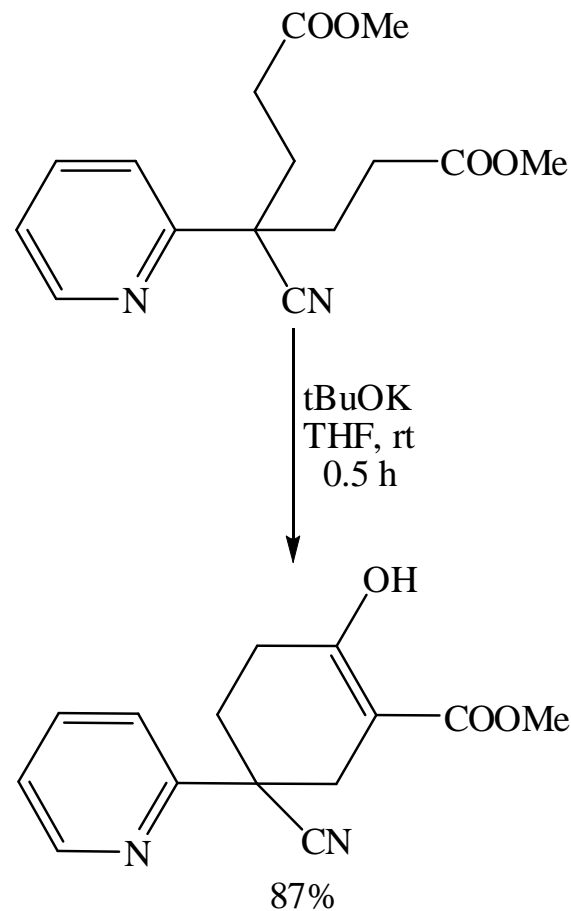
Ho, J.Z; Mohareb,
R.M; Ahn, J.H; Sim,
T.B; Rapoport, H,
JOC, 2003, 68, 109
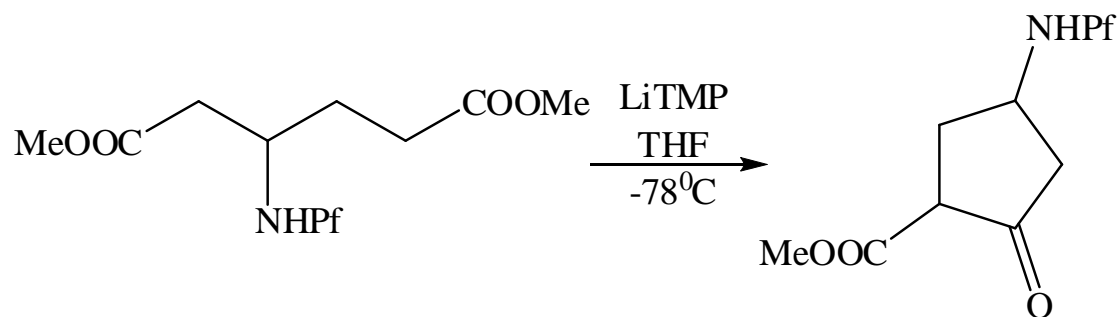
III. **Michael addition**

Michael addition is nucleophilic addition of enolate to α, β-unsaturated carbonyl compound in presence of base.
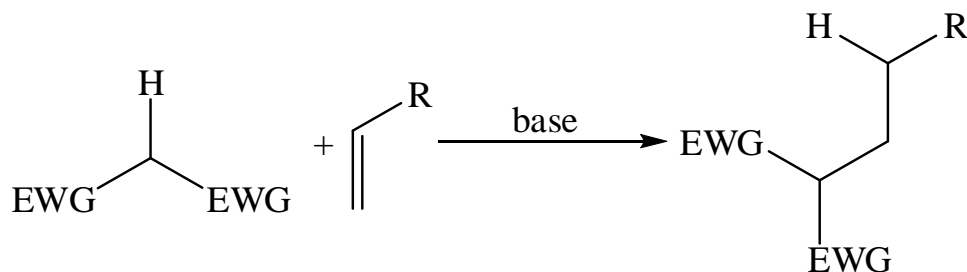
Michael reaction is conjugate addition of enolate to activated olefin and is thermodynamically controlled.

There are two components of reaction, one is Michael donor, which is usually, 1,3-dicarbonyl compound, acetoacetic ester, active methylene compound, etc. The other component is, Michael acceptor which is usually, α, β-unsaturated carbonyl compound, α, β-unsaturated ester, etc.
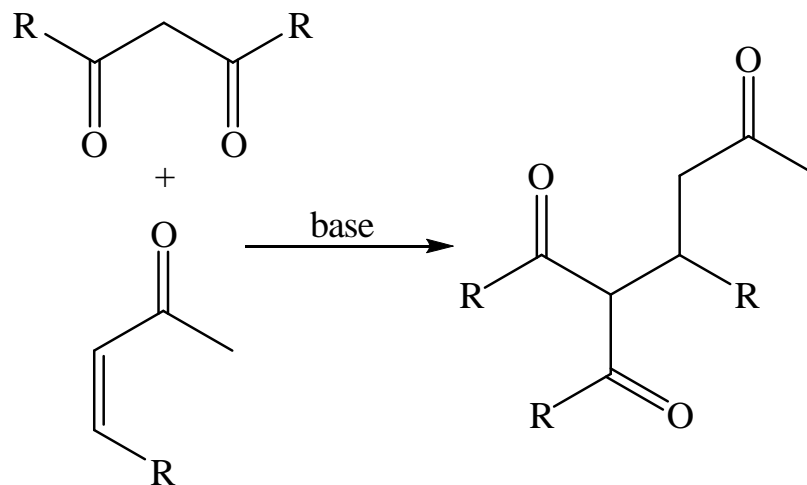
Mechanism :

Base first, abstracts proton from donor and forms enolate.
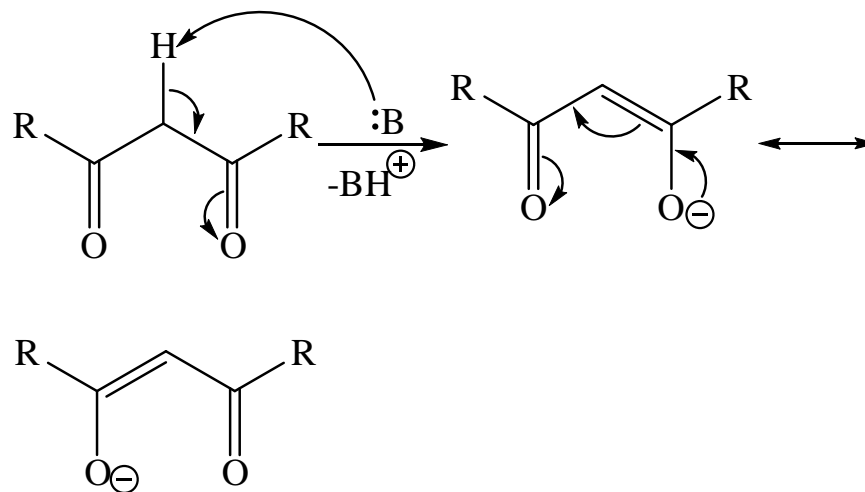
Enolate then attacks Michael acceptor and adds to it, giving Michael addition product.
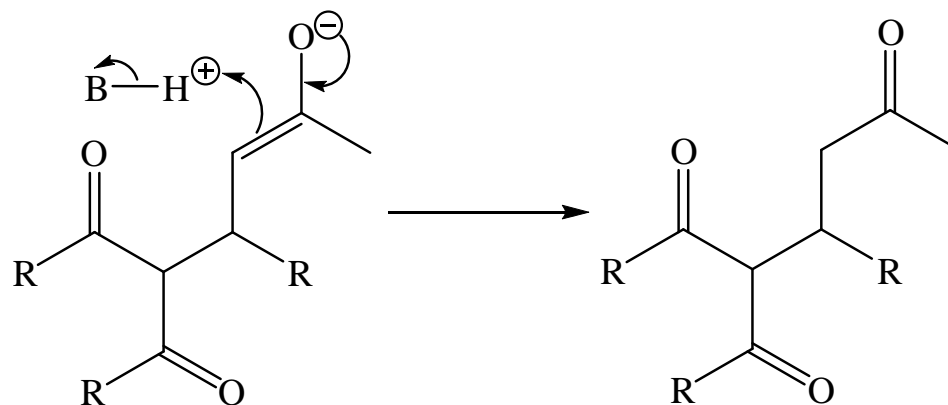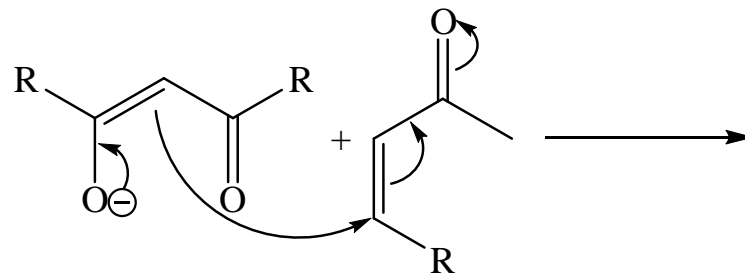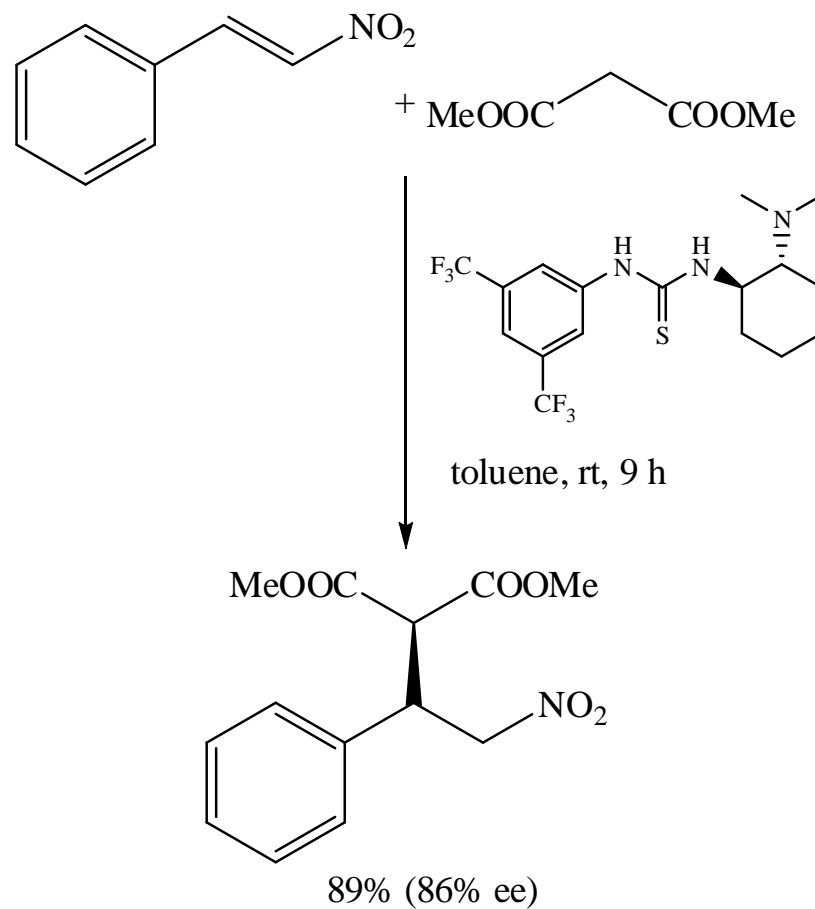

Pansare, S.V, Pandya, K, *JACS*, 2006, 128, 9624

DMF, rt
pTsOH

86% (>99%ee)
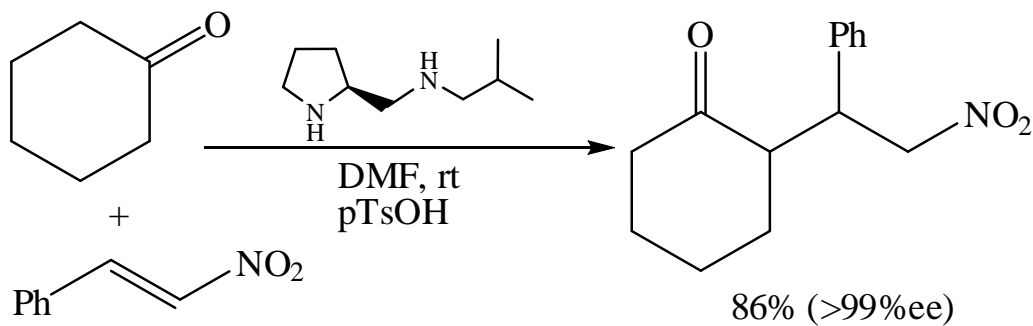
Ranu, B.C; Banerjee, S,
Org. Lett., 2005, 7, 3049

[bmim]OH
3.5 h, rt

90%
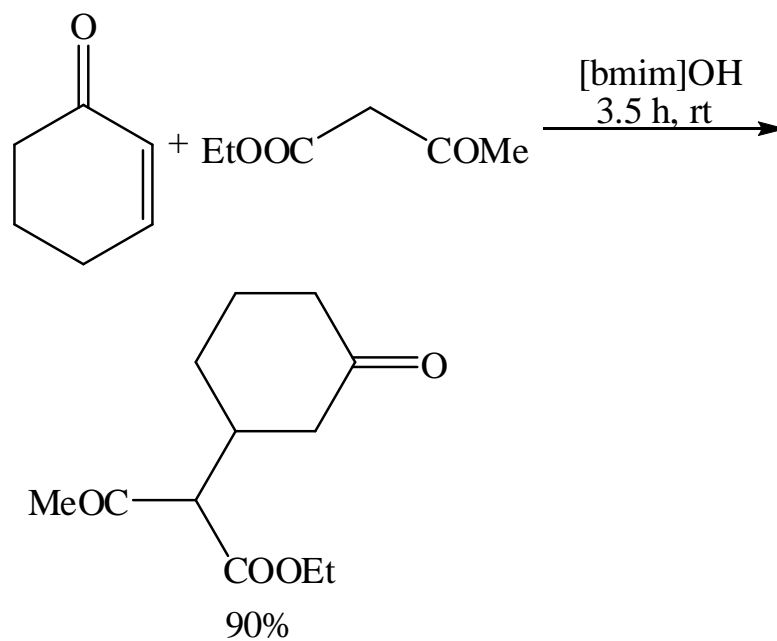
Okimo, T; Hoashi, Y; Furukawa, T; Xu, X; Takemoto, Y, *JACS*, 2005, 127, 119

toluene, rt, 9 h

89% (86% ee)

IV. Robinson annulation

Robinson annulation is Michael addition of methyl vinyl ketone to carbonyl compound followed by Aldol condensation to give annulene.
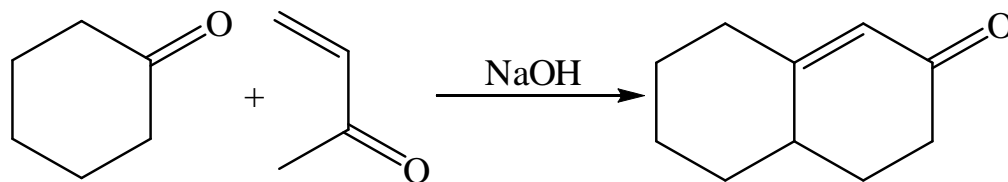
Mechanism :
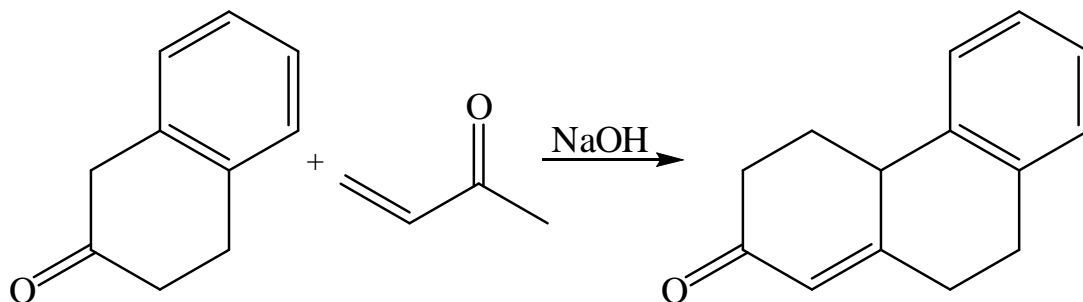
Base abstracts proton from ketone and forms enolate
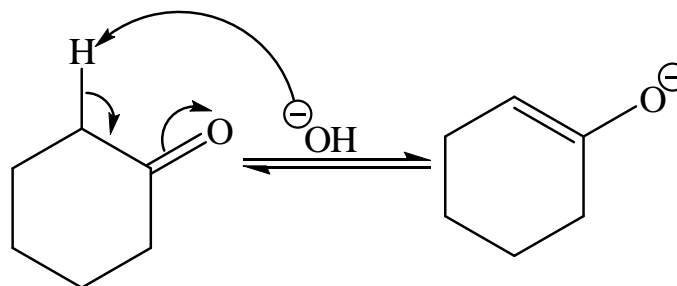
Enolate adds to Michael acceptor via conjugate addition
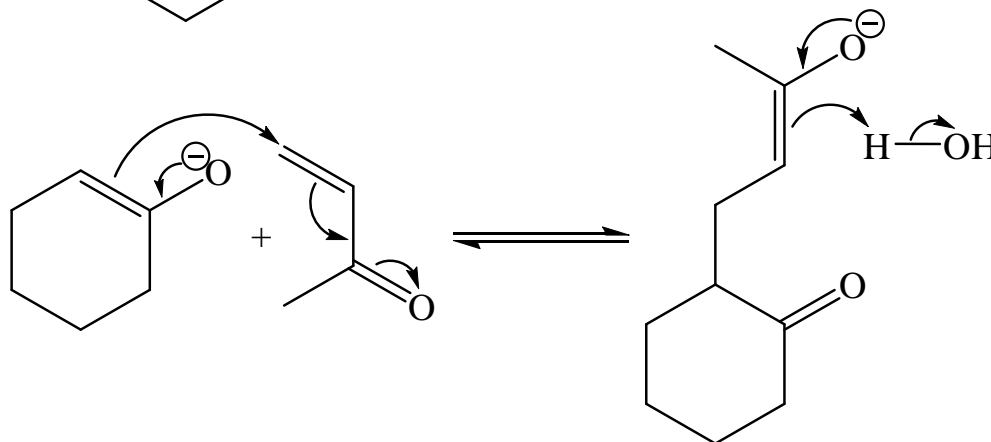
Michael addition product, through intramolecular Aldol condensation, gives final product i.e.
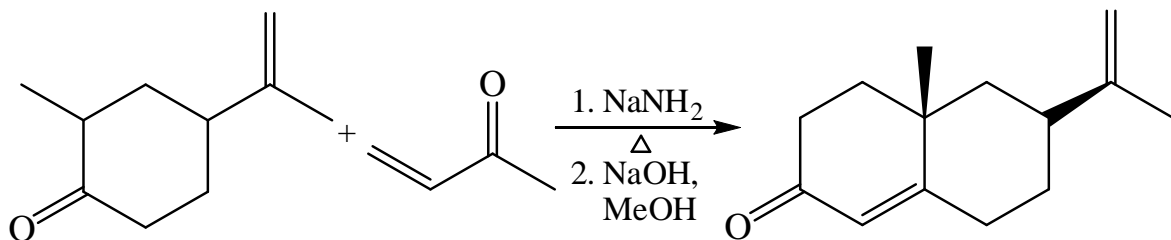α, β-unsaturated ketone
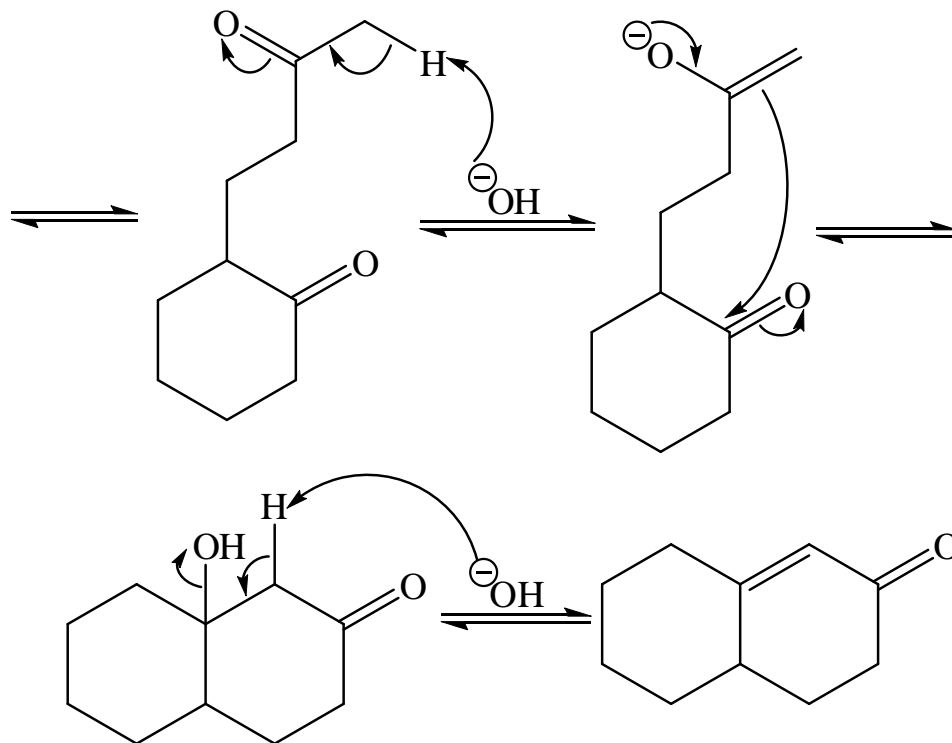
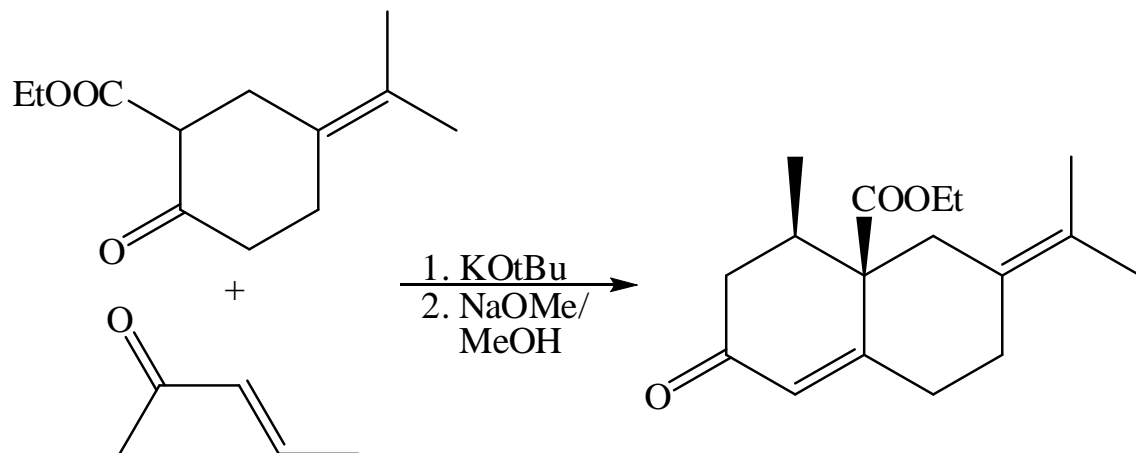Reaction is useful in syntheses of six membered ring in polycyclic compounds

NaOH

Michael addition of enolate having second
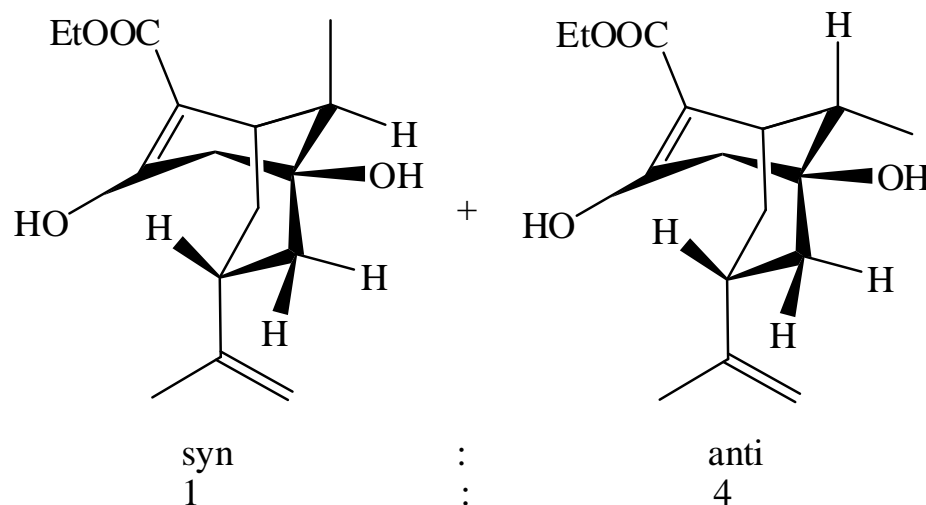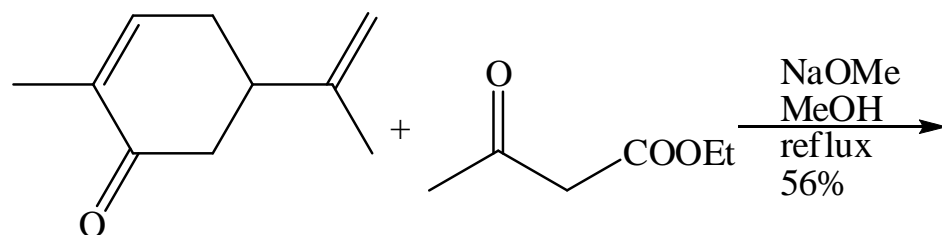enolizable group, to an enone, is necessity for
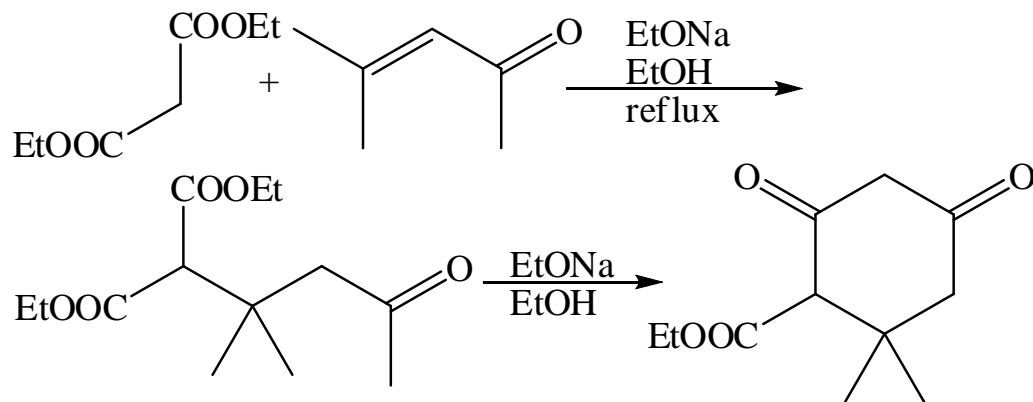reaction to occur.
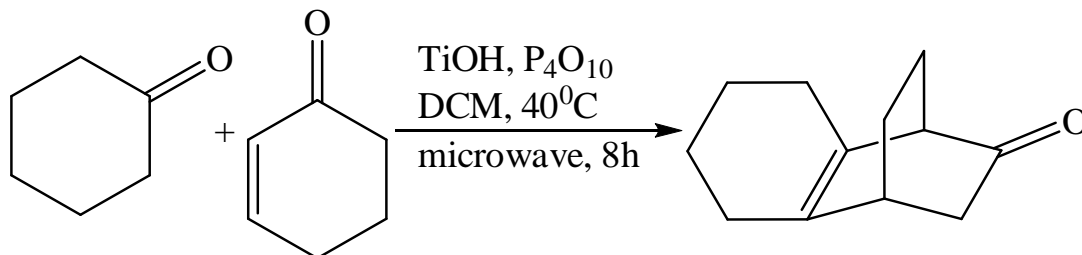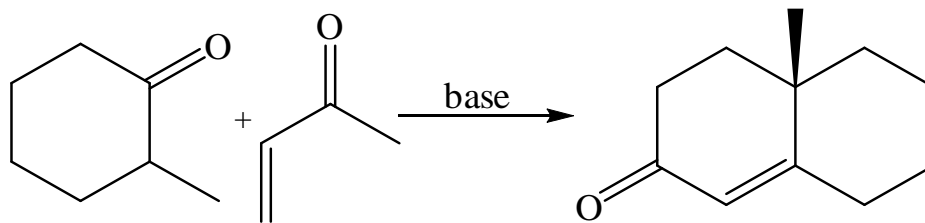
Mc Murry, **JOC**, 1975, 40,
1823

Marshall, *JOC*, 1971, 36, 178

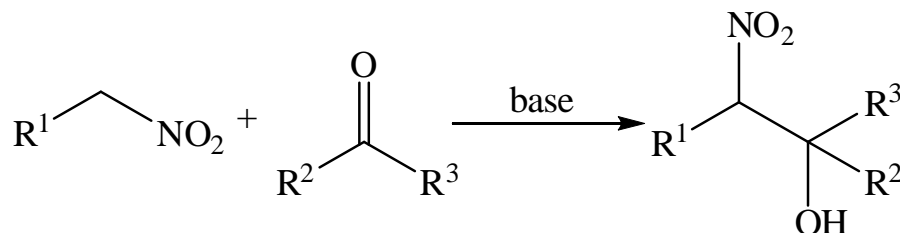Wang, D; Crowe, W.E, Org. Lett., 2010, 12, 1232

syn : anti
1 : 4

When diester is used as Michael donor, Claisen condensation, instead of Aldol condensation is seen. This reaction gives cyclic diketone.
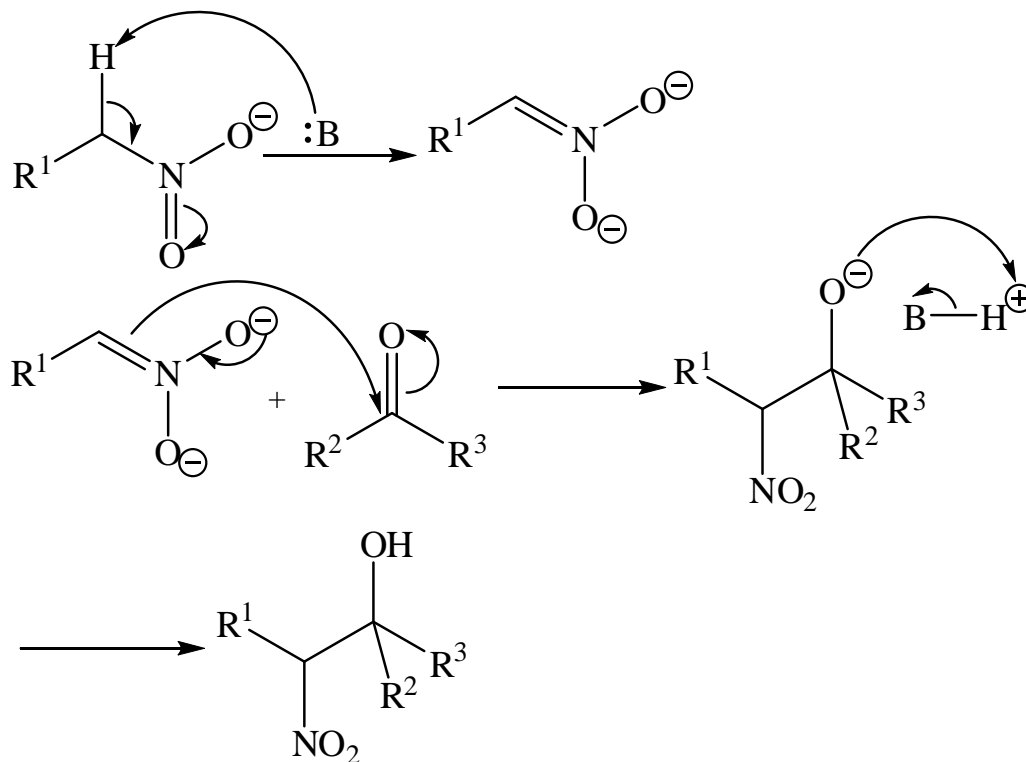
V. Henry reaction

Base catalyzed reaction between nitroalkane and carbonyl compound is Henry reaction.
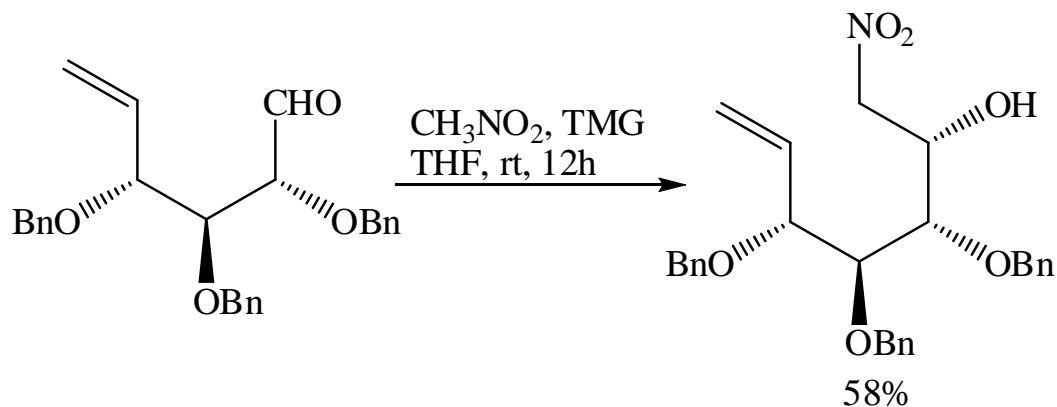

Mechanism :

Mechanism is similar to aldol condensation.

First base abstracts proton from nitro compound and gives enolate equivalent. It adds to carbonyl compound in similar way as that in Aldol reaction, to give β-nitro alcohol as product.

Reaction is analogous to aldol condensation and generally referred to as
Nitro-Aldol reaction.

Nitro group, like, carbonyl moiety is powerful electron withdrawing group. It
renders acidic properties to protons α to it and can form enolate equivalent.
Acidic nature of nitro compounds is so profound that very mild bases can
catalyze reaction.

Like Aldol condensation, α,β-unsaturated nitro compound can be obtained, by elimination of water molecule.
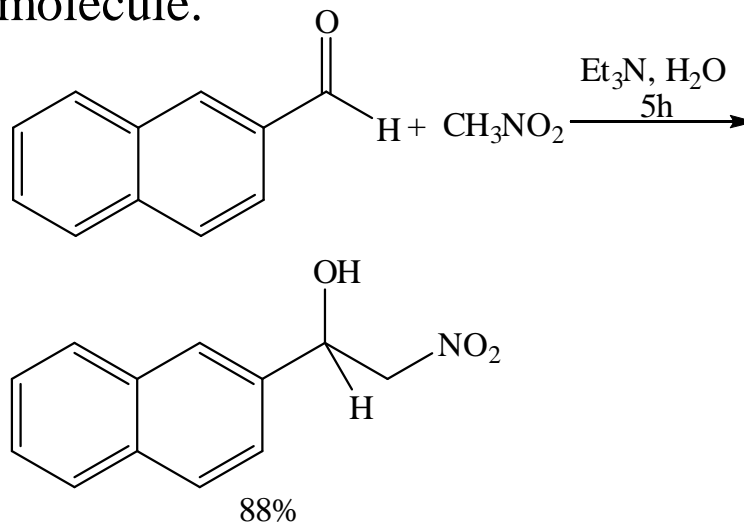
Zhou, C.L; Zhou, Y.Q; Wang, Z.Y, *Chinese Chem. Lett.*, 2003, 14, 355
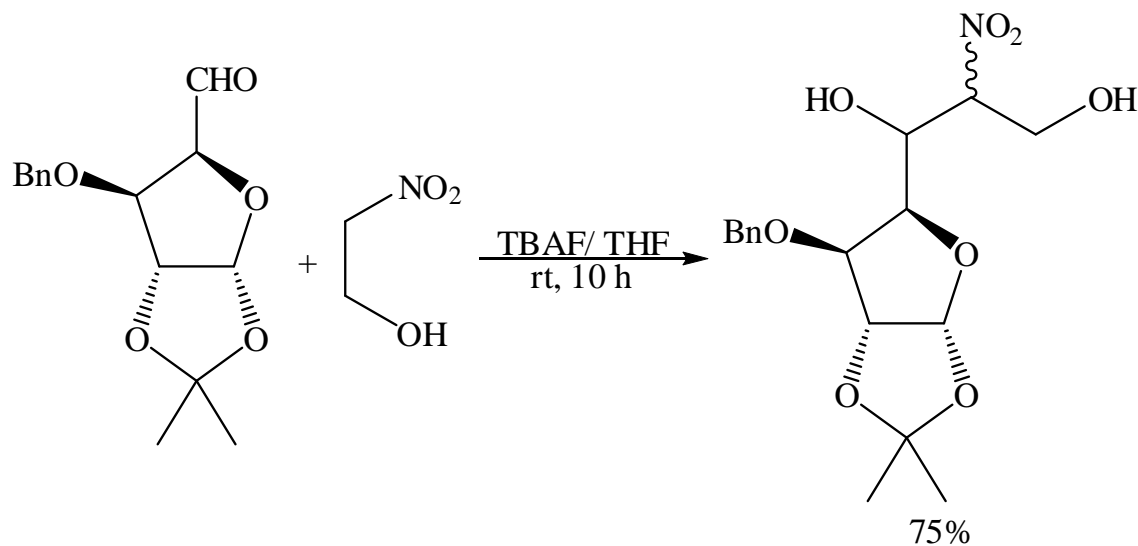
VI. Ester hydrolysis

Hydrolysis is a chemical process in which a certain molecule is split into two parts by the addition of a molecule of water. One fragment of the parent molecule gains a hydrogen ion, other group collects the remaining hydroxyl group.

Ester is hydrolyzed when treated with excess of water. This reaction is reverse of ester synthesis from corresponding carboxylic acid and alcohol.

General reaction for ester hydrolysis
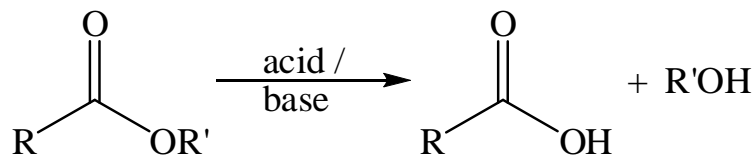
Reaction is catalyzed by acid or base. Both yield same product, except that, in base catalyzed reaction salt of carboxylic acid is obtained from which acid can be regenerated by acidic work up.

Acid catalyzed reaction is reversible. In order to get product in good yields, it is necessary to use dilute acid and ample amount of water, in contrast to that of ester synthesis, where concentrated acid is used.

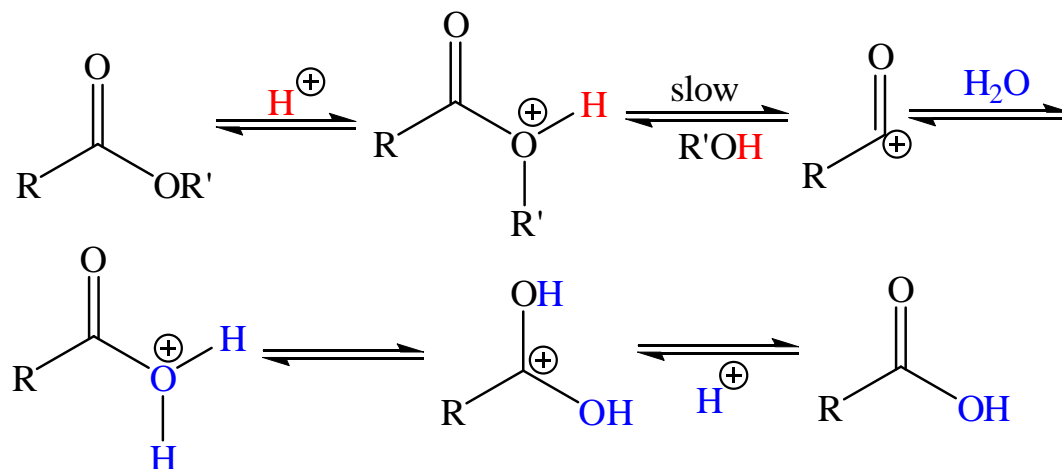Ingold in 1940 classified these mechanisms according to following factors;

➢ Nature of reagent
➢ Point of cleavage
➢ Reaction kinetics

Mechanism of ester hydrolysis

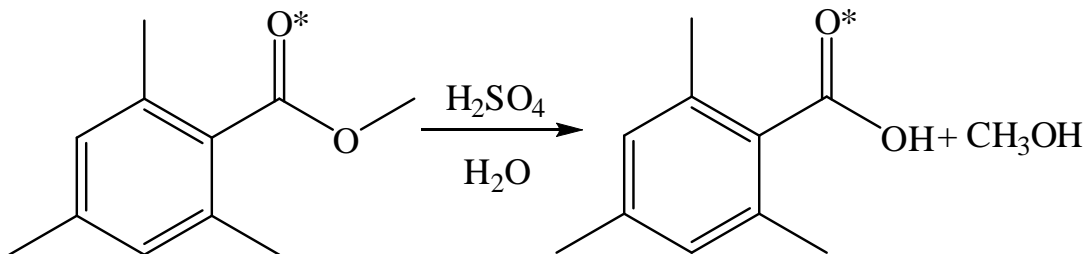**A$_{AC}$1** mechanism :

Ester hydrolysis can take place by eight possible mechanisms.

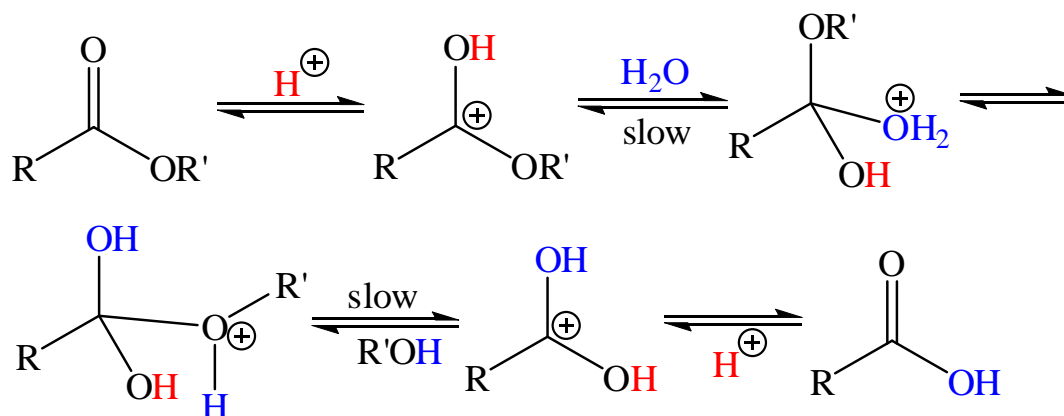Acid catalyzed, unimolecular, acyl oxygen fission
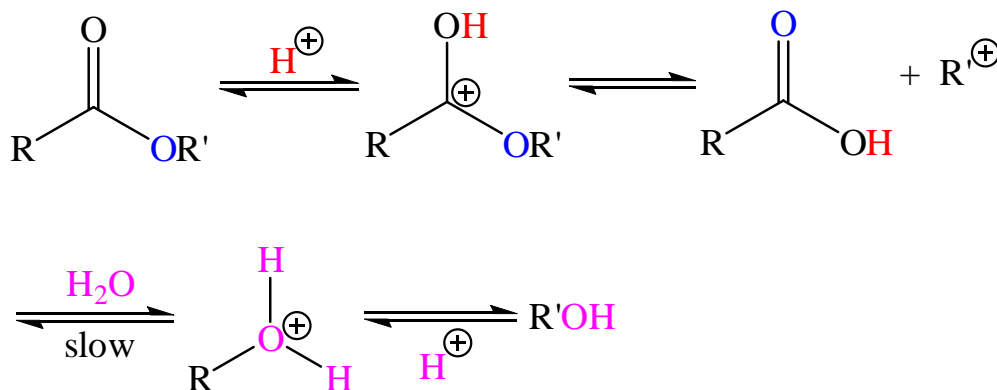

Hydrolysis of methyl mesitoate
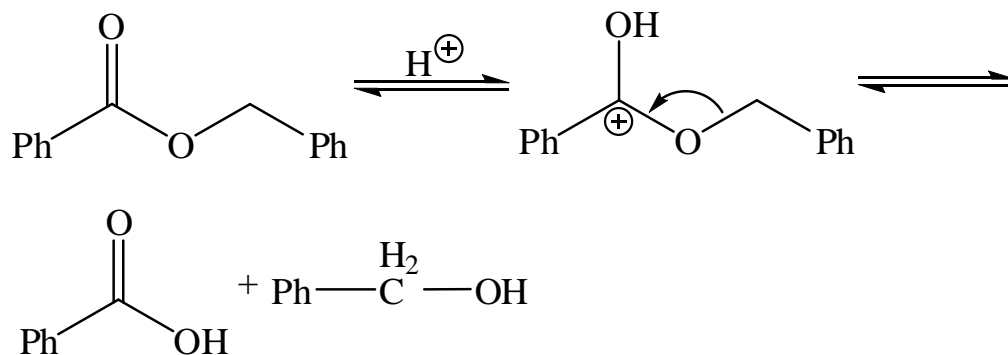
A$_{AC}$2 mechanism : Acid catalyzed, bimolecular, acyl oxygen fission
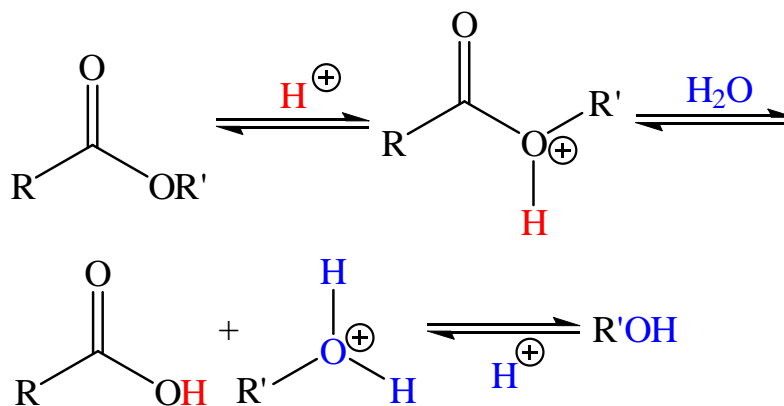

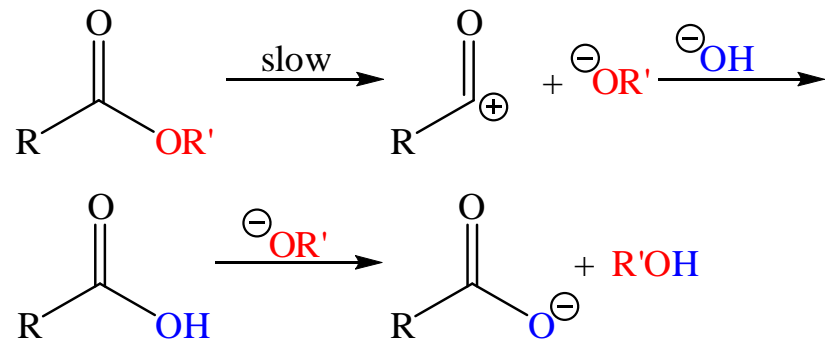**A$_{AL}$1 mechanism :** Acid catalyzed, unimolecular, alkyl oxygen fission

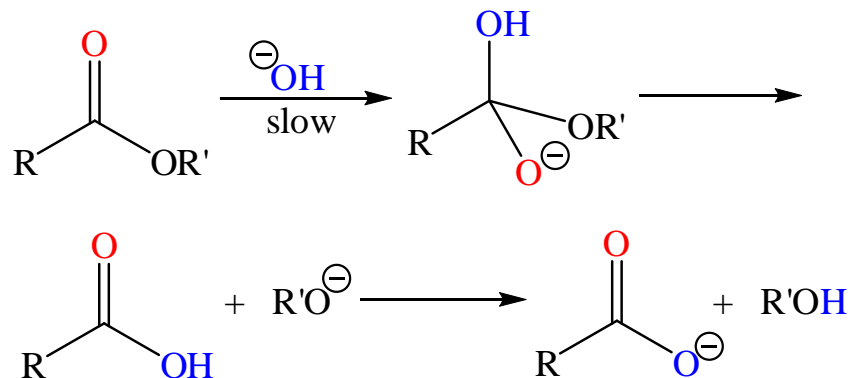**A_{AL}2** mechanism :   Acid catalyzed, bimolecular, alkyl oxygen fission
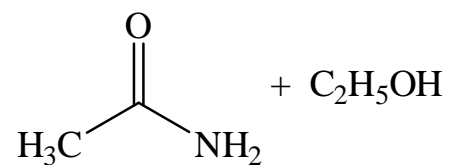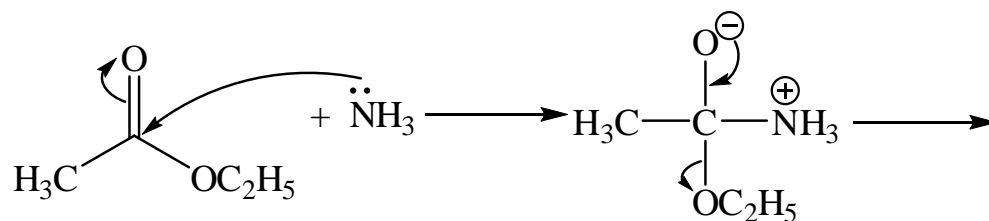
B$_{AC}$1 mechanism :

Base catalyzed, unimolecular, acyl oxygen fission
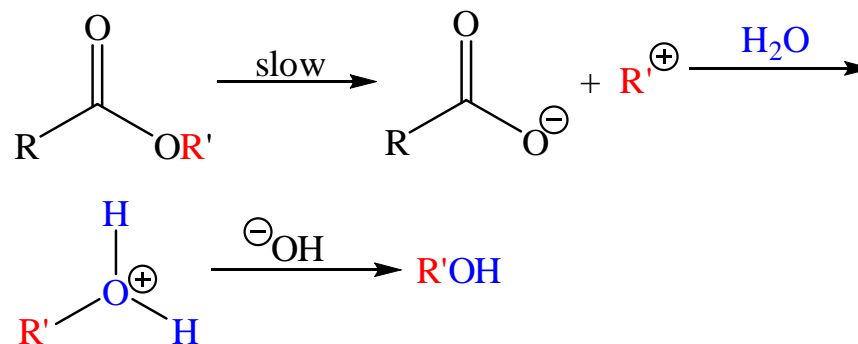

B$_{AC}$2 mechanism :

Base catalyzed, bimolecular, acyl oxygen fission
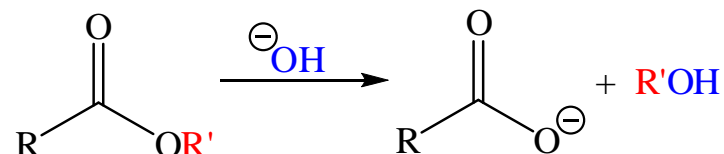
B$_{AL}$1 mechanism :   Base catalyzed, unimolecular, alkyl oxygen fission

B$_{AL}$2 mechanism :   Base catalyzed, bimolecular, alkyl oxygen fission

Though all these mechanisms are observed in many cases, A$_{AL}$2 and B$_{AC}$1 are not observed for any substrate.

Most common of all these mechanisms are A$_{AC}$2 and B$_{AC}$2

Evidence of acyl oxygen fission is obtained by following experiments.

➢ Hydrolysis with H$_2{}^{18}$O, results in ^{18}O appearing in acid and not alcohol

➢ Esters with chiral R^1 group, give alcohol with retention of configuration

➢ Allylic R^1 group, does not give allylic rearrangement

➢ Neopentyl R^1 group, does not give rearrangement

All these observations indicate that O-R^1 bond is not broken.

Different nomenclature and summary of features of ester hydrolysis

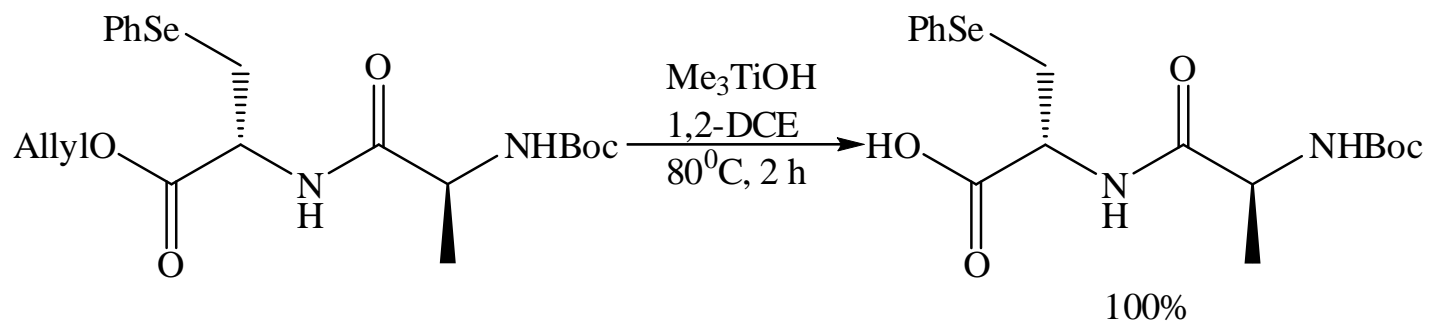| Ingold notation	Type	Hydrolysis
$A_{AC}1$	S_N1	Special case
$A_{AC}2$	Tetrahedral	Very common
$A_{AL}1$	S_N1	Very common for tertiary alcohols
$A_{AL}2$	S_N2	-----
$B_{AC}1$	S_N1	-----
$B_{AC}2$	Tetrahedral	Very common
$B_{AL}1$	S_N1	Special case
$B_{AL}2$	S_N2	Rare

Examples of ester hydrolysis

Reagents and conditions: 1. 4mol KOH, MeOH, 60 min, ~35⁰C; 2. 6N HCl; 90%
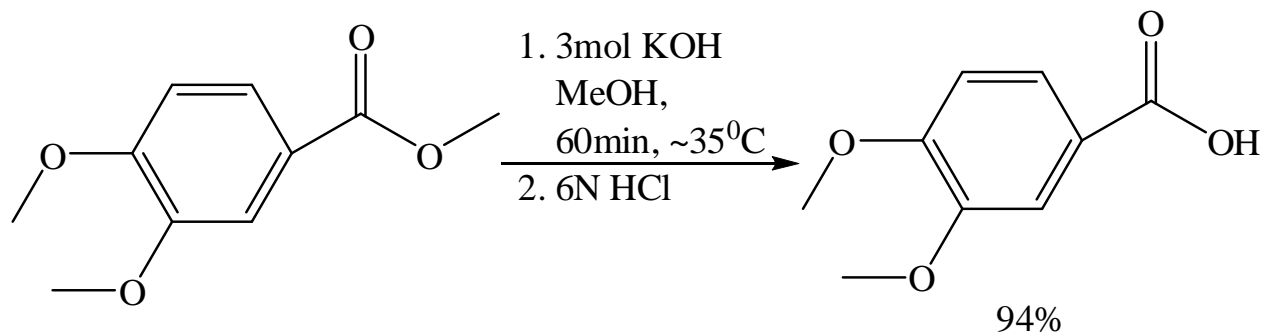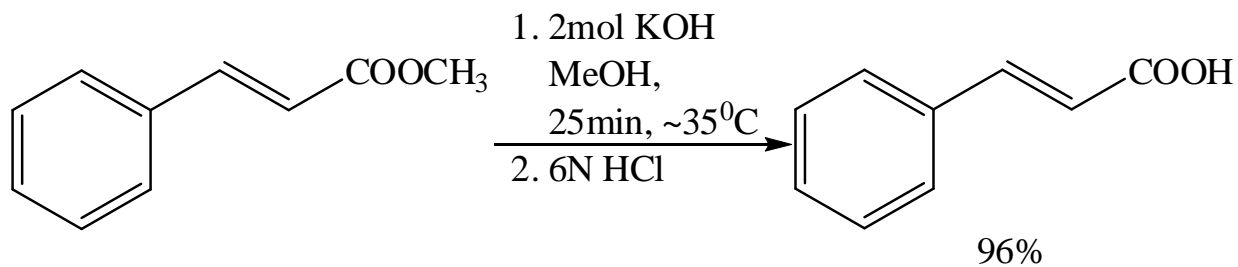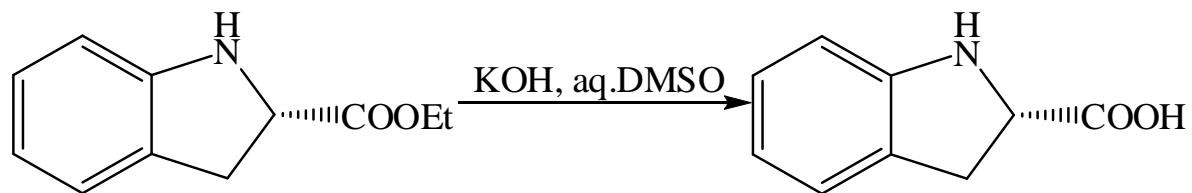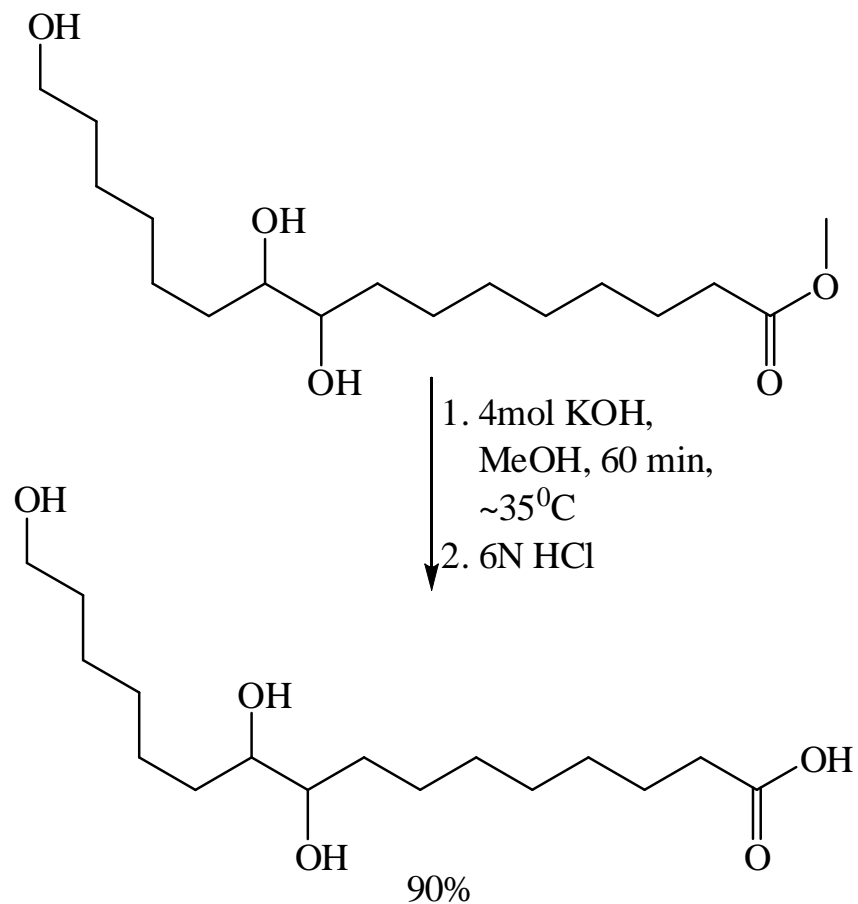
Khurana, J.M; Chauhan, S; Bansal, G, *Monatshefte fur Chiemie*, 2004, 135, 83

Reaction conditions: Me$_3$TiOH, 1,2-DCE, 80^{0}C, 2 h, 100%

Wallner, S.R; Nestl, B; Faber, K, *Tet*., 2005, 61, 1517

Reaction conditions: 30mol% I$_2$, 5h, MeCN, reflux, 89%

MeO—⟨benzene ring⟩—COOtBu

MeO, OMe (on ring)

30mol% I₂, 3h
MeCN, reflux
→
MeO—⟨benzene ring⟩—COOH

MeO, OMe (on ring)

82%

---

nC_4H_9 —CH=CH— CH_2 —COOEt

1. O.2N NaOH
30min, rt,
DCM/ MeOH
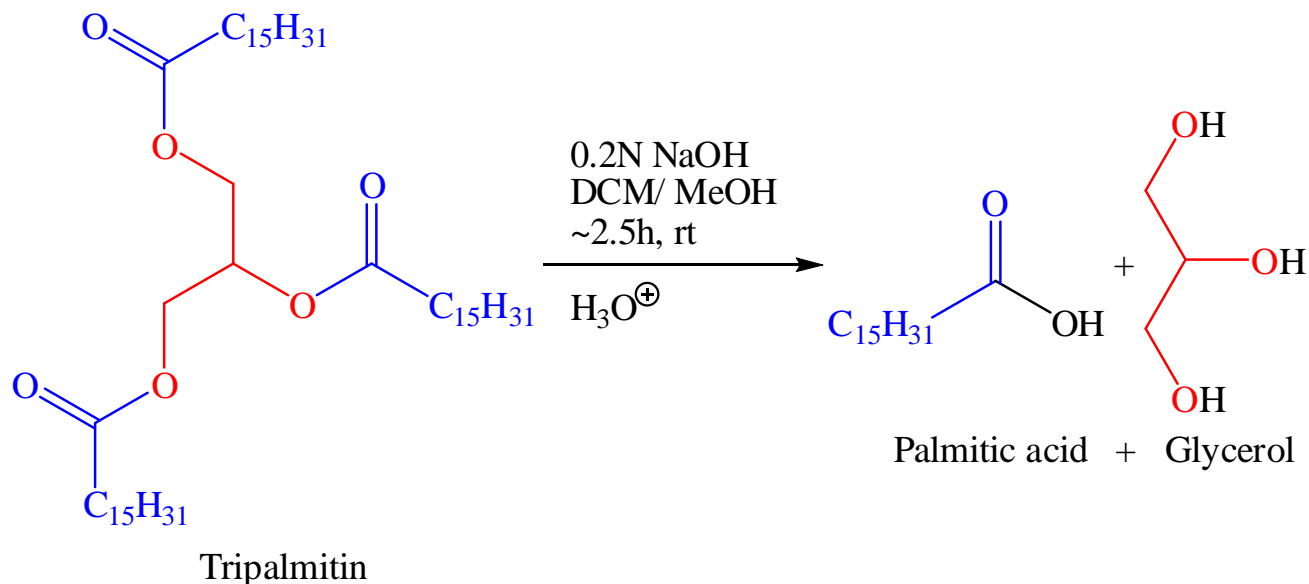**2. $H_3O^{\oplus}$**
→
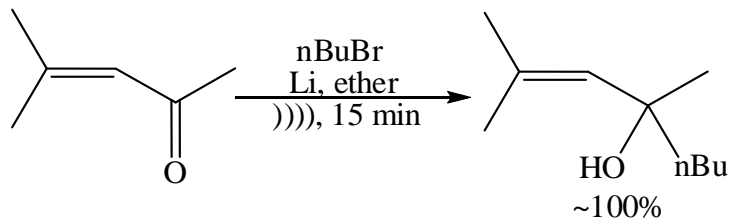nC_4H_9 —CH=CH— CH_2 —COOH
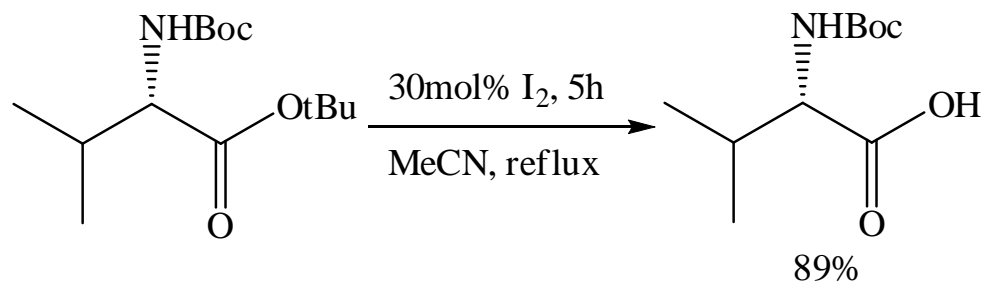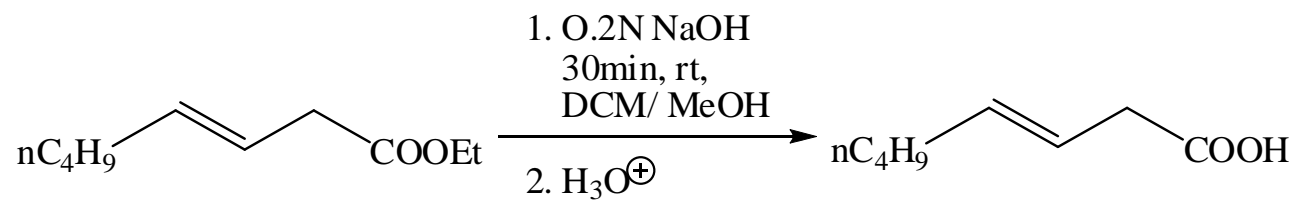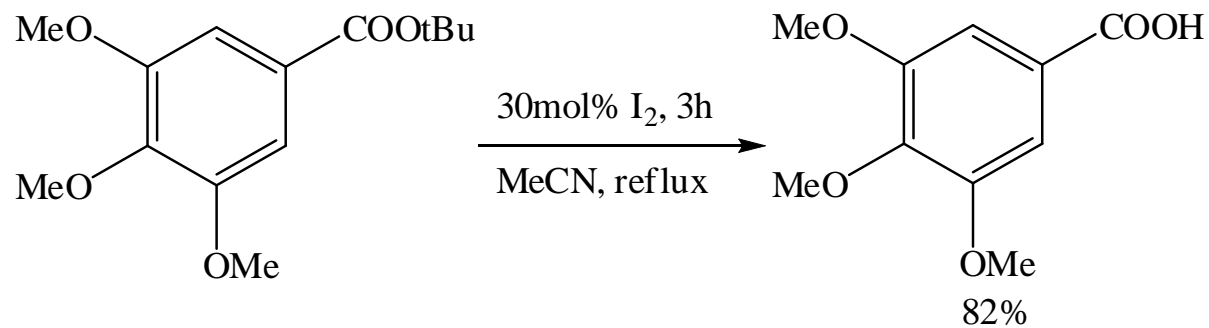
Saponification

The alkaline hydrolysis of esters to give carboxylate salts is known as saponification. Principal content of soap is sodium or potassium salt of higher carboxylic acid i.e. a fatty acid.

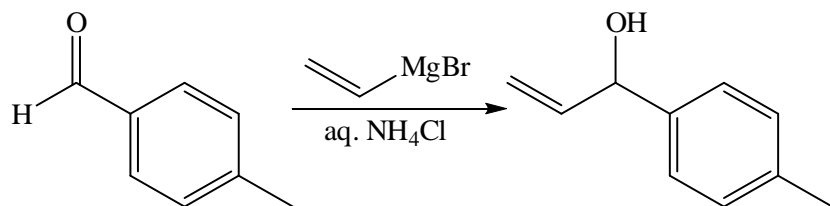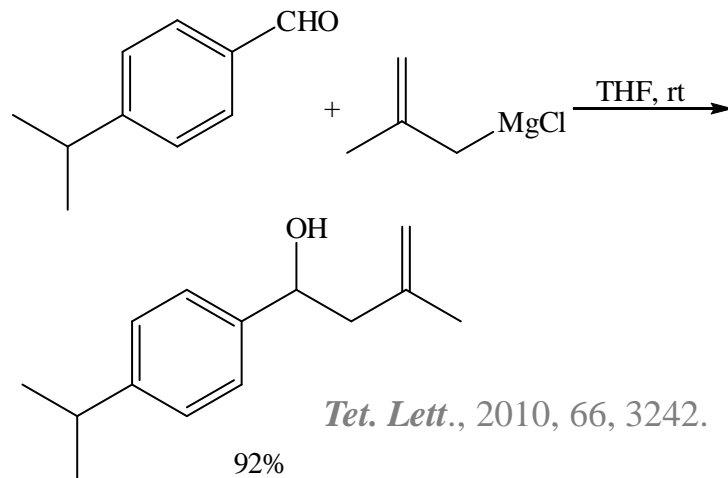Alkaline hydrolysis of tripalmitin gives palmitic acid and glycerol

0.2N NaOH
DCM/ MeOH
~2.5h, rt

$H_3O^\oplus$

Tripalmitin

Palmitic acid + Glycerol

Practice problems

(1)

nBuBr
Li, ether
)))), 15 min

HO   nBu
~100%

(3)

CHO

+   MgCl

THF, rt

(2)

MgBr

aq. NH₄Cl

OH

OH

92%

(4)

EtMgCl
CeCl₃
THF, 0⁰C

OH

Et

76%

(5)

HO

HO

O

PTSA
toluene

O

O

(6)

Wada, S; Suzuki, H, *Tet. Lett*., 2003, 44, 399

97%

S. Sebi, et.al, *Tet. Lett*., 2002, 43, 1813

(7)

Calcium phosphate
NaNO₃, MeOH, 15min

81%

(8)

Al₂O₃
3 min

88%

Francoise, T.B; Foucaud, A, *Tet. Lett*., 1982, 23, 4927

(9)

NaOEt, EtOH

(10)

MeOOC

H OBn

OTBS

NaHMDS
THF,-78⁰C

$$\xrightarrow{\text{NaHMDS}}$$

O

H OBn

OTBS

MeOOC

58%

(11)

MeOOC

COOMe

Bn

KHMDS
THF, 1h
-78⁰C

$$\xrightarrow{\text{KHMDS}}$$

Bn

N

OH

COOMe

90%
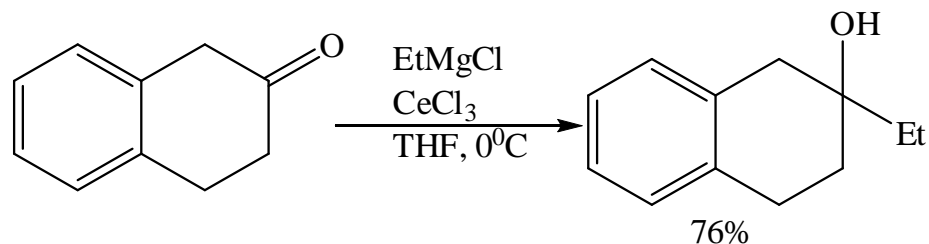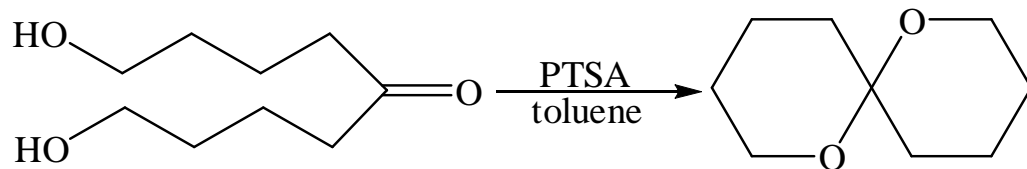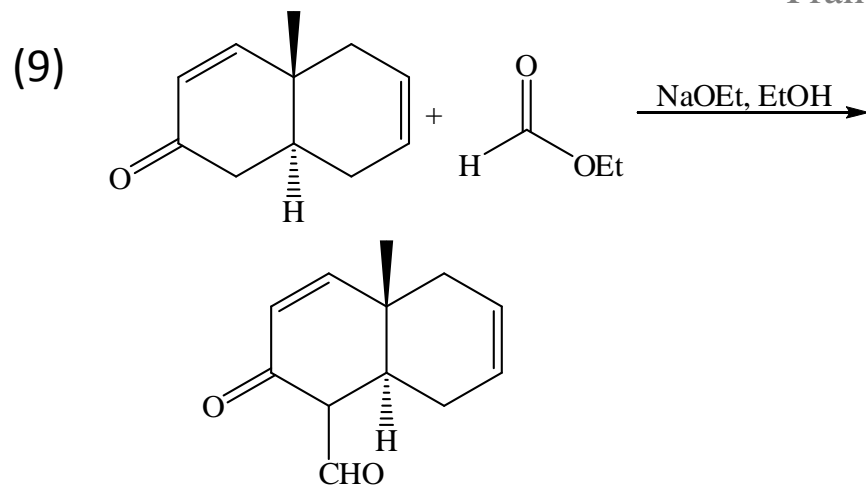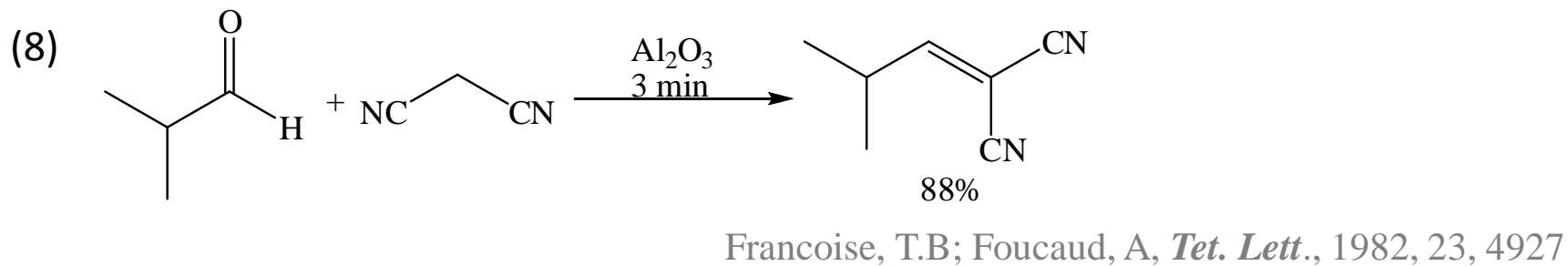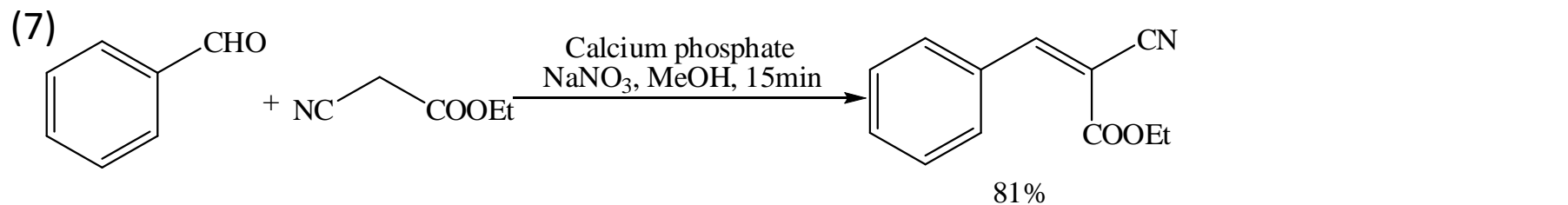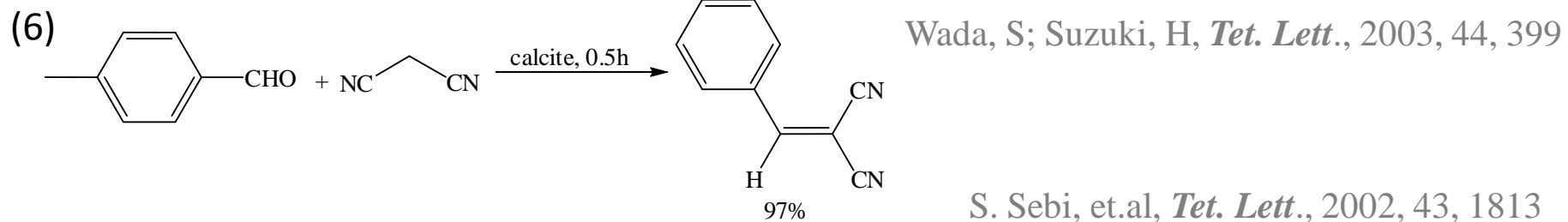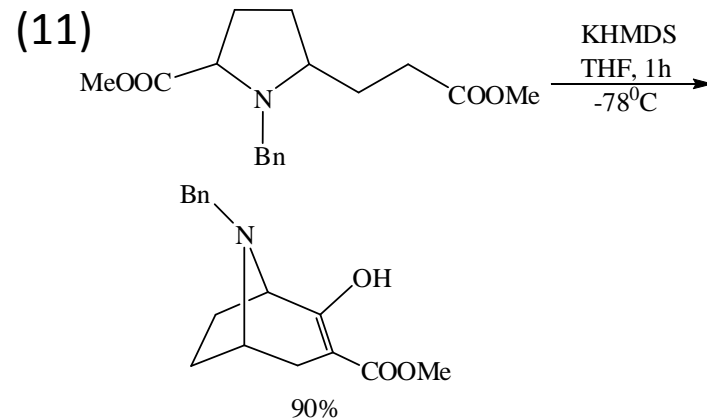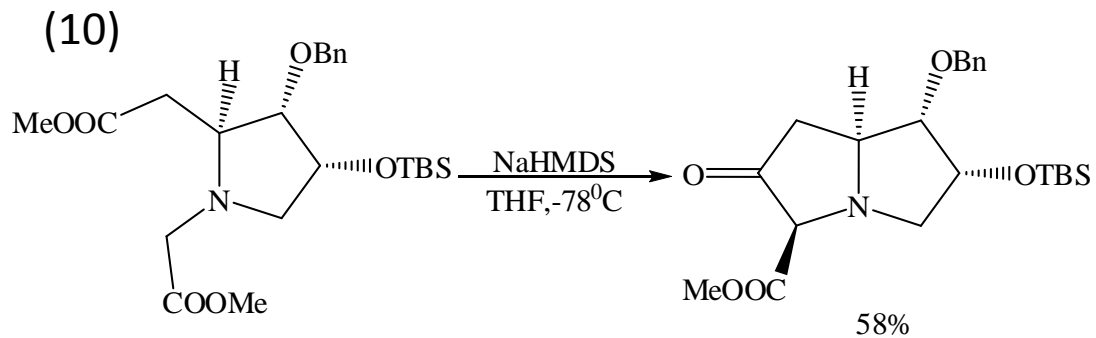
Lin, R; Castells, J; Rapoport, H, *JOC*, 1998, 63, 4069