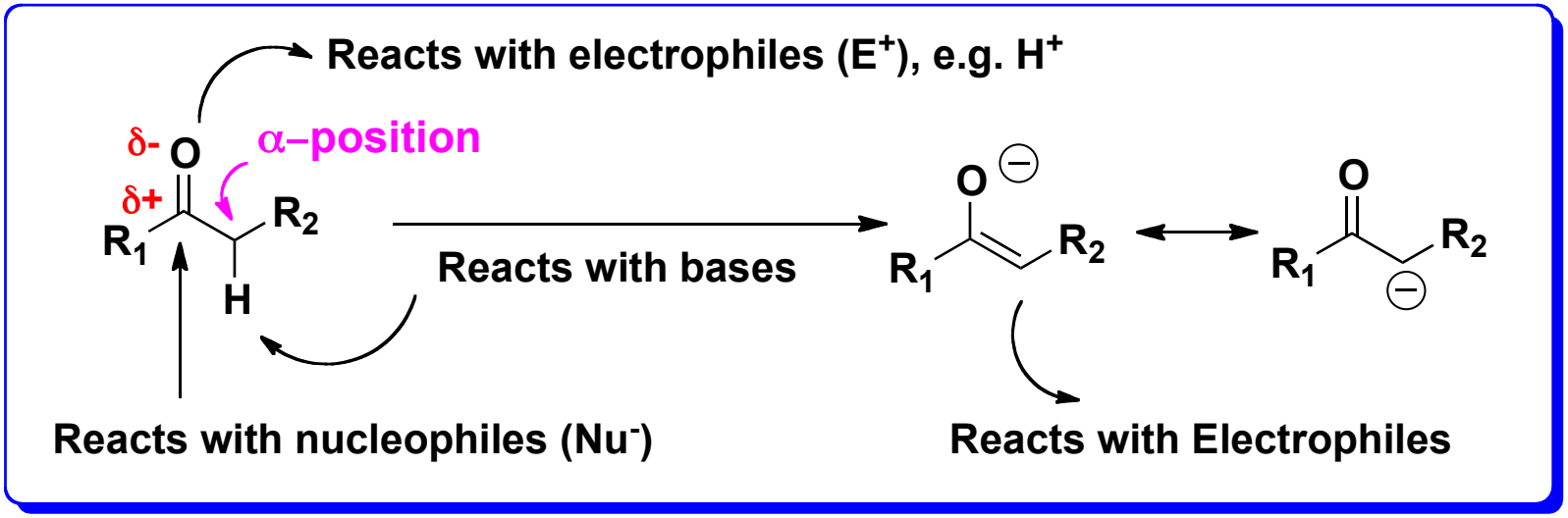
Carbonyl Compounds VII:
Enol and Enolate Chemistry

Enol and Enolate Chemistry



The α CH is acidic, deprotonation leading to enolate making the α-CH nucleophilic.
Possible reaction of a nucleophile:

a) Alkylation
b) Addition to polarized multiple bond (carbonyl, imine etc…)

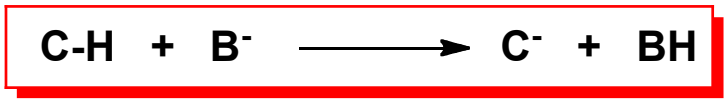
pKa values that Help You to Understand Enolate Chemistry

Carbonyl compounds	pKa (H_2O)	pKa (DMSO)
CH_3CHO	~17	
CH_3COCH_3	~20	26.5
CH_3COPh	~16	
CH_3COOEt	24.5	29.5
CH_3CONEt_2	30	35
CH_3CN	25	
$CH_3COCH_2COCH_3$	9	13.3
CH_3COCH_2COOEt	11.0	
$EtOOCCH_2COOEt$	12.7	
$NCCH_2CN$	11.2	
CH_3NO_2	10	17.2

Commonly used bases	pKa of conjugate acids
BuLi	50
iPr_2NLi	36
*t*BuOK	20
EtOK	16
Et_3N	10

Enolate Formation: Equilibrium constant

For a generic aicd-base reaction:

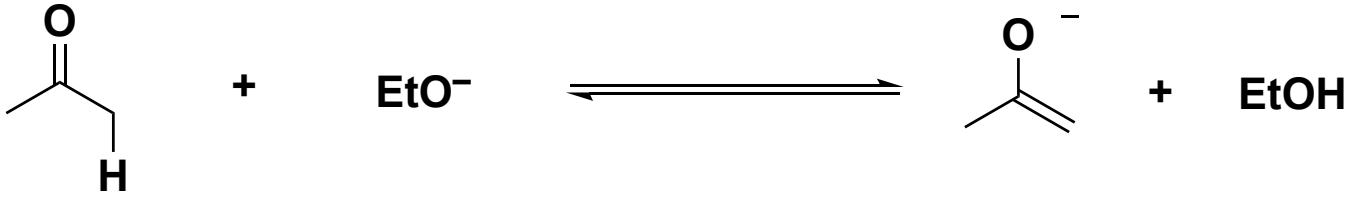


$$K = \frac{[BH]\,[C^-]}{[C\text{-}H]\,[B^-]} = \frac{[BH]\,[C^-]}{[C\text{-}H]\,[B^-]} \times \frac{[H^+]}{[H^+]} = \frac{[C^-]\,[H^+]}{[C\text{-}H]} \times \frac{[BH]}{[B^-]\,[H^+]}$$

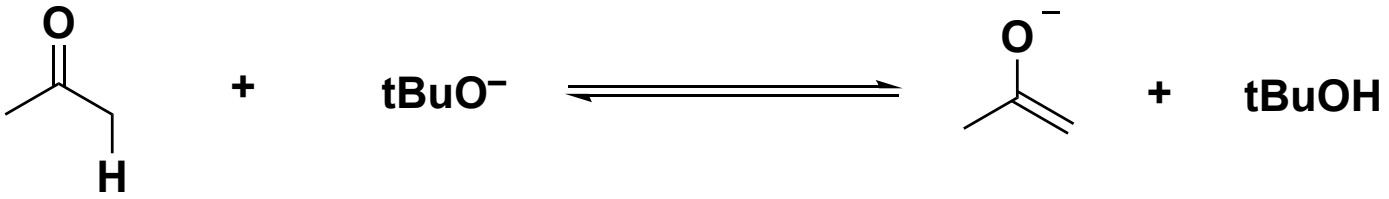
$$= \frac{K_{a(C\text{-}H)}}{K_{a(B\text{-}H)}} = \frac{10^{-pka(C\text{-}H)}}{10^{-pka(B\text{-}H)}} = 10^{pKa(B\text{-}H)-pKa(C\text{-}H)}$$

Therefore, by knowing the pKa of the organic C-H compound and that of conjugate acid of the base, it is easy to know if the deprotonation is complete or is under equilibrium (see next slide for examples)

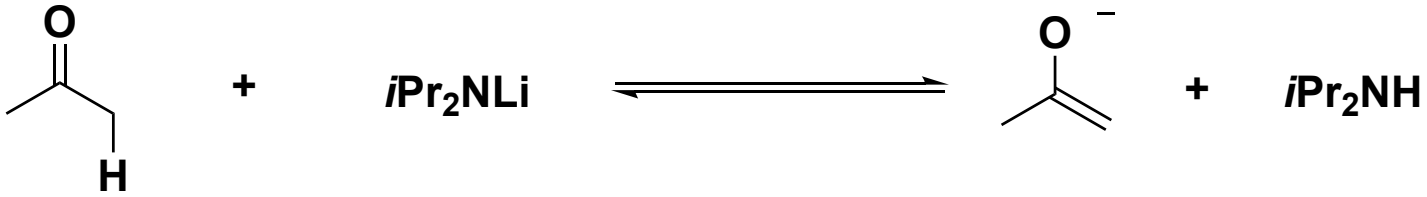
Enolate Formation



pKa(acetone) = 20, pKa(EtOH) = 16, δpKa = Pka(base)-Pka(C-H) = -4, [enolate]/[aetone] = 10^{-4}. Only a tiny amount of enolate in solution at equilibrium



pKa(acetone) = 20, pKa(*t*BuOH) = 18, δpKa = Pka(base)-Pka(C-H) = -2, [enolate]/[aetone] = 10^{-2} . There will be 1% of enolate in solution at equilibrium

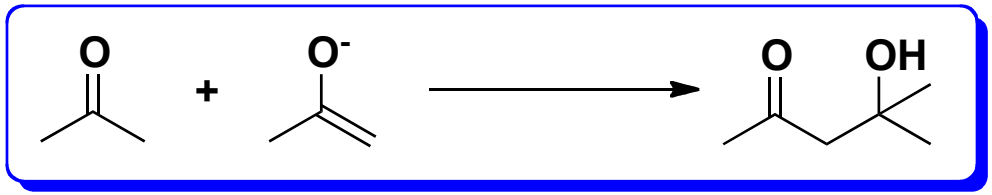


pKa(acetone) = 20, pKa(*i*Pr_2NH) = 36, δpKa = Pka(base)-Pka(C-H) = 16, [enolate]/[aetone] = 10^{16} . Acetone will be completely deprotonated to enolate

Enolate Formation

The greater is the difference in pKa's, the more heavily shifted is the equilibrium (to either left or right).

When enolate and ketone is in equilibrium, self condensation could take place that could be probmematic unless it is the desired transformation



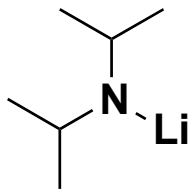
QUIZ: How to avoid the self-condensation?
Answer: Use a very strong base to shift the ketone-enolate equilibrium completely to the right; *i.e.* completely consume the ketone electrophile before it can react with the enolate nucleophile.

Enolate Formation

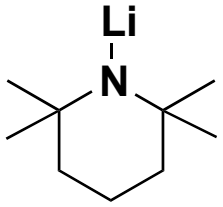
All bases are potential nucleophiles. Alkoxide addition to the carbonyl group is reversible in the case of ketones and is therefore usually not a problem. Other side-reactions, *e.g.* dehydration of the aldol product, can be competing side-reactions and cautions need to be taken to prevent such processes.

Using non-nucleophilic bases avoids many potential chemoselectivity problems. Most non-nucleophilic bases have the nucleophilic centre surrounded by sterically very demanding substituents.

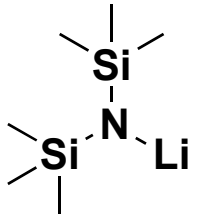
Examples of non-nucleophilic stronger bases:



LDA



LTMP

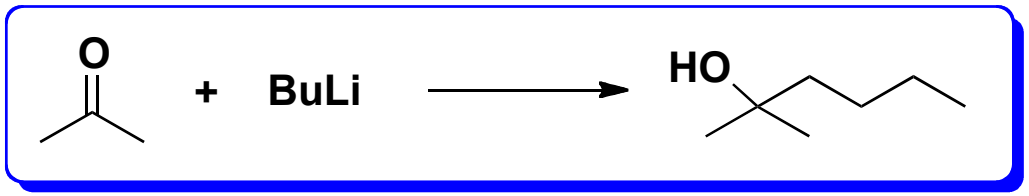


LHMDS

Enolate Formation *vs* Nucleophilic Addition

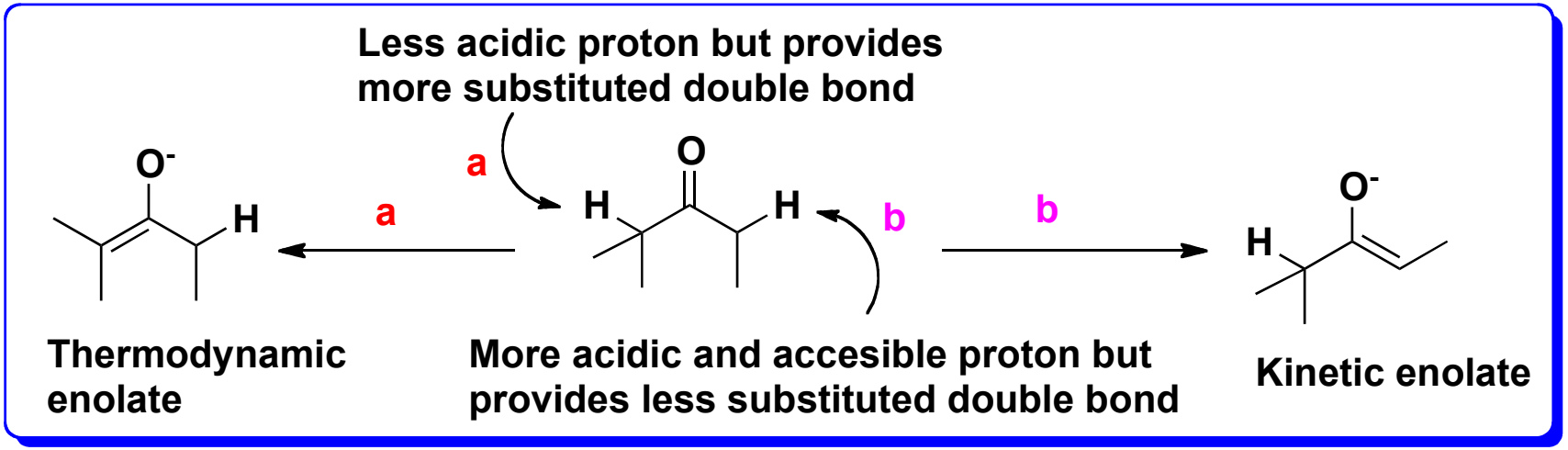
Quiz: BuLi is a very strong base (pKa of conjugate acid = 50), but it is rarely used to form enolate from ketone, why?

Anwser: BuLi is a base, but is also a nucleophile that can undergo nucleophilic addition to electrophilic carbonyl carbon to afford alcohol.



Regioselective Enolate Formation

For unsymmetric ketone, formation of two enolates is possible. It's important to be able to control the regioselectivity of enolate formation



For above example, although the pKa difference between the two sites is only 1-2 units, this difference, when combined with the relative steric accessibility of the α-protons, is usually enough to be able to form selectively the *kinetic* enolate.

***Caution*: The more substituted enolate is not always the thermodynamically more stable enolate (see next slides).**

Regioselective Enolate Formation

Enolate formation is just an acid-base reaction. The position of the equilibrium is controlled by a variety of factors such as solvent, base, cation and temperature.

Factors favoring the formation of kinetic enolate:

a) aprotic solvent, *e.g.* THF, Et_2O (no acidic proton to encourage the reverse reaction);
b) strong base;
c) oxophilic cation *e.g.* Li;
d) low temperature;
e) short reaction time

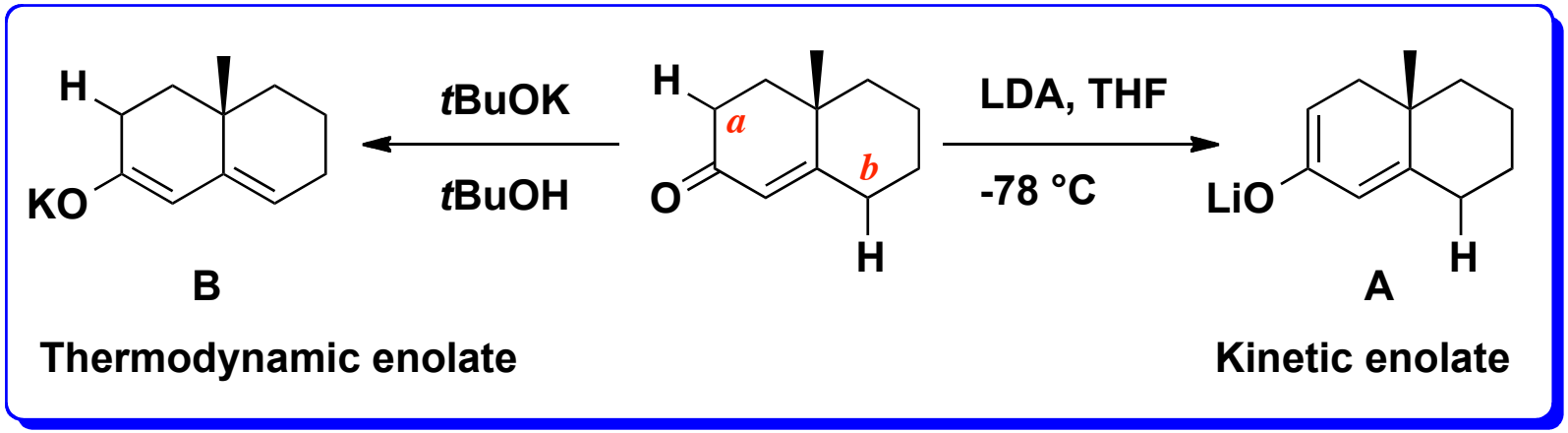
Factors favoring the formation of thermodynamic enolate:

a) protic solvents *e.g.* ROH which have slightly more acidic protons than the enolate allowing reprotonation, hence tautomerisation to thermodynamically more stable ketone (*i.e.* the reverse reaction);
b) weak base (which provide a relatively strong conjugate acid);
c) high temperature;
d) long reaction time.

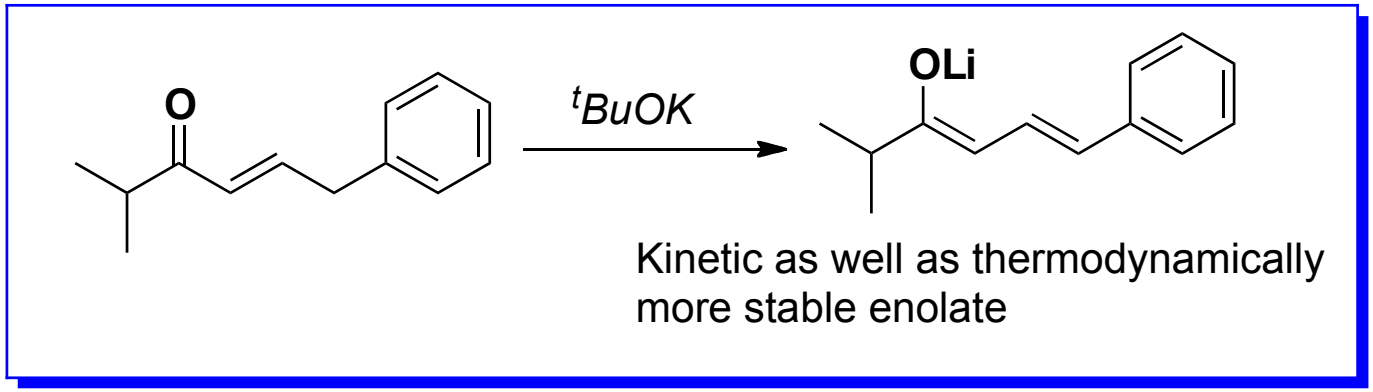
In general:

Kinetic enolate: All these conditions that suppress equilibrium and ensure the reaction to be essentially irreversible;
Thermodynamic enolate: All these conditions encourage the reverse reaction.

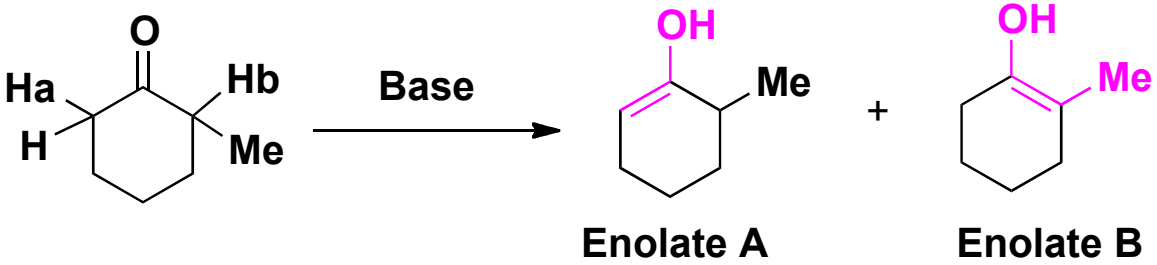
Kinetic vs Thermodynamic Enolate Formation



Enolate A has a cross-conjugated system. Oxygen can conjugate with only one double double. It is less stable stable than enolate B. C_a-H proton is slightly more acidic than C_b-H, A is formed under kinetic conditions, while B is formed under thermodynamic conditions.



Kinetic vs Thermodynamic Enolate Formation



	Enolate A	Enolate B
Base = LDA	99%	1%
Base = Et_3N	22%	78%

A is a kinetic product since Ha is more acidic than Hb, and is less hindered. B is thermodynamically more stable than A as the double bond in B is more substituted than in A.

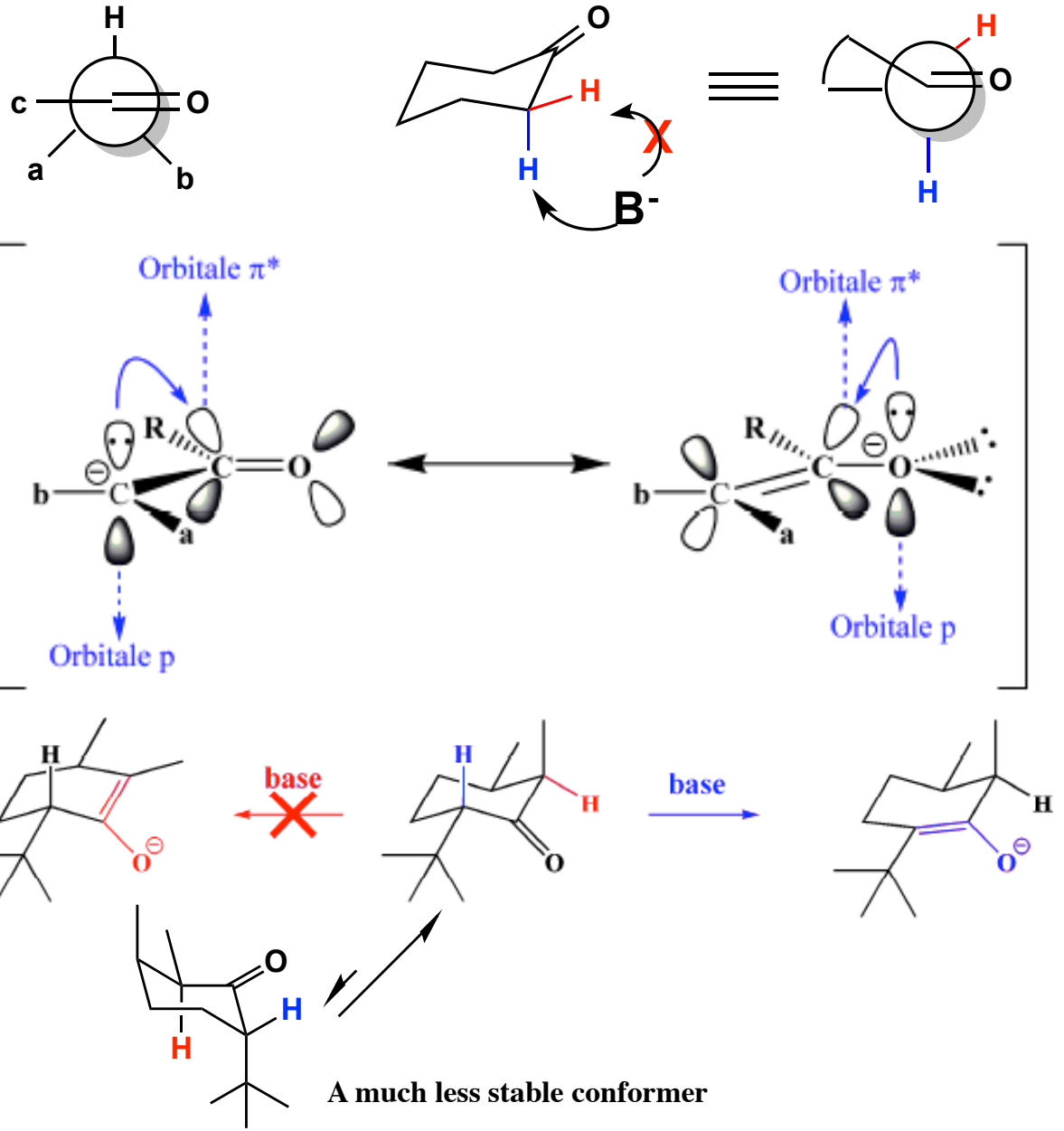
LDA being a strong base, it abstracts the least hindered hydrogen with greater ease, hence forming enolate A which is the Kinetic Product of the reaction.

Triethylamine being a weak base, it abstracts the alpha-hydrogen on the less hindered side, the reaction is reversible. Thus there will be an equilibrium between the reactants and products and thermodynamically more stable enolate B will be produced predominantly.
Et_3N^+H is also more acidic than *i*Pr_2NH, facilitating therefore the equilibrium.

Formation of enolate is essentially non-reversible with LDA, but reversible with Et_3N, why? (Using your knowledge of acid-base reaction)

Enolate Formation: Stereoelectronic effect

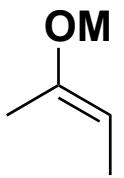
The proton that is perpendicular to carbonyl was removed by base.

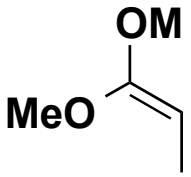


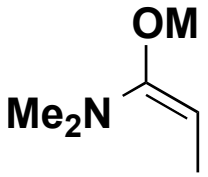
Z and *E* enolate Geometry of Enolate

Nomenclature: The *O*-metal bond of the enolate always takes priority on other residue attached to the same carbon.

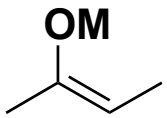
***E*-enolate**

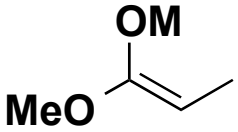


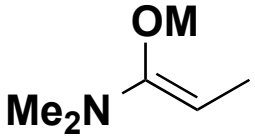




***Z*-enolate**



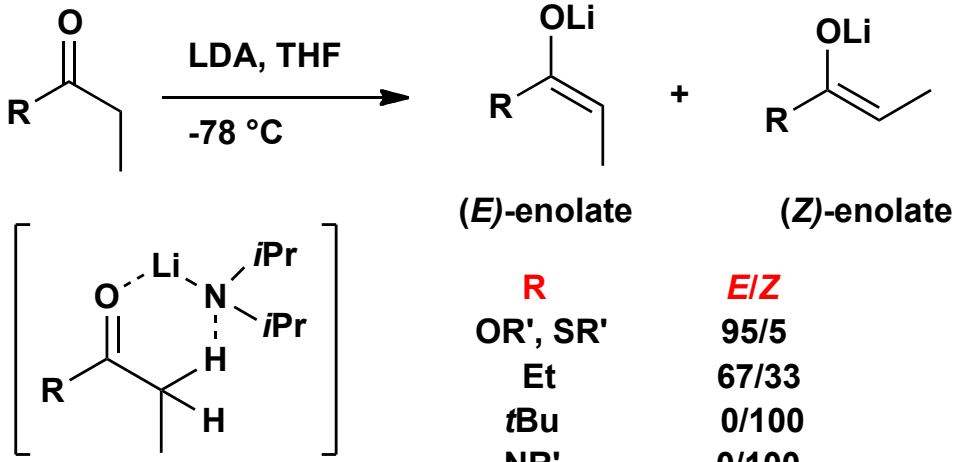




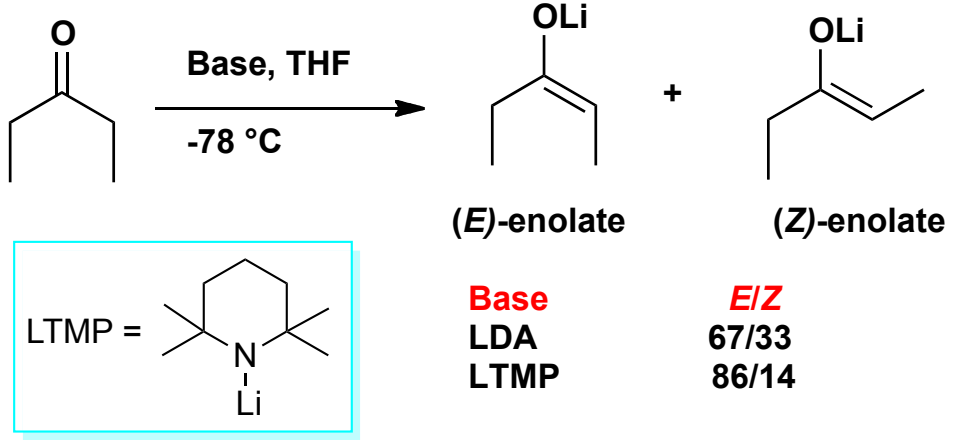
The geometry of a substituted enolate (*Z* or *E*) is very important in determining the stereochemical outcome of the subsequent reaction (e.g. aldol).

Many factors can influence the stereoselectivity of enolate formation and we can effectively control E/Z selectivity nowadays.

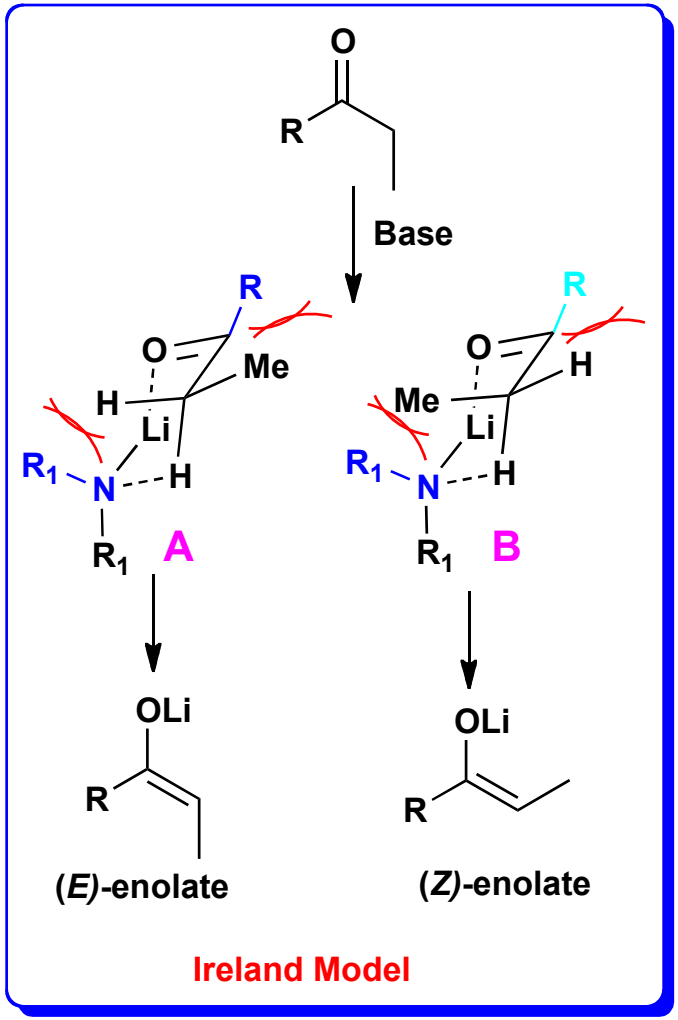
Z and *E* Enolate: Effect of Substrate Structure and Base



R	*E*/*Z*
OR', SR'	95/5
Et	67/33
*t*Bu	0/100
NR'_2	0/100



Base	*E*/*Z*
LDA	67/33
LTMP	86/14

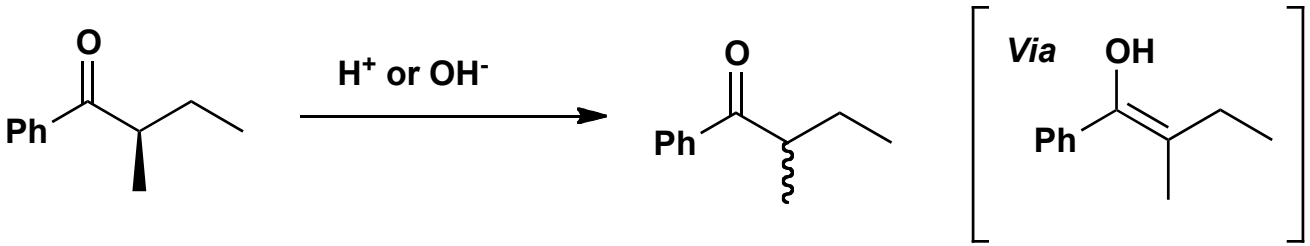


LTMP = Lithium 2,2,6,6-tetramethylpiperidine
***E*-enolate is favored with sterically bulky base.**

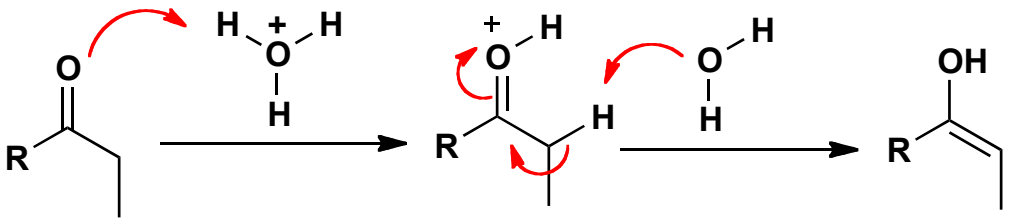
An oversimplified, nevertheless useful model has been proposed by Ireland to explain the stereoselective formation of enolate. The E/Z ratio depends on the relative importance of steric interaction R/Me, R_1/H vs R/H, R_1/Me in transition states A and B.

Enolate formation: Racemization

Optically active aldehydes or ketones with a chiral center at the α-carbon racemize in the presence of a catalytic amount of acid or base via enol or enolate intermediate which is prochiral with a Csp^2 hybridization.



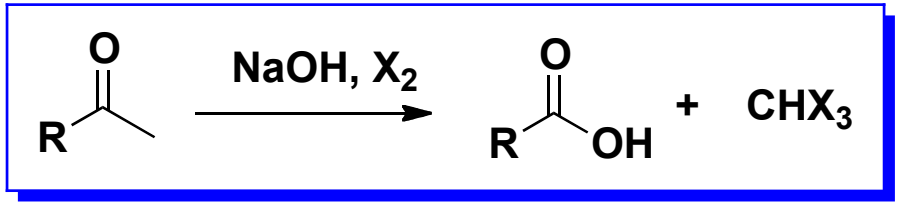
Mechanism of acid-catalyzed enolization:



Enolate Reactions

Enolate Reaction: Haloform Reaction

Exhaustive base-catalyzed halogenation of methyl ketones followed by C–C bond cleavage, yielding a carboxylate salt and haloform (X_3CH).

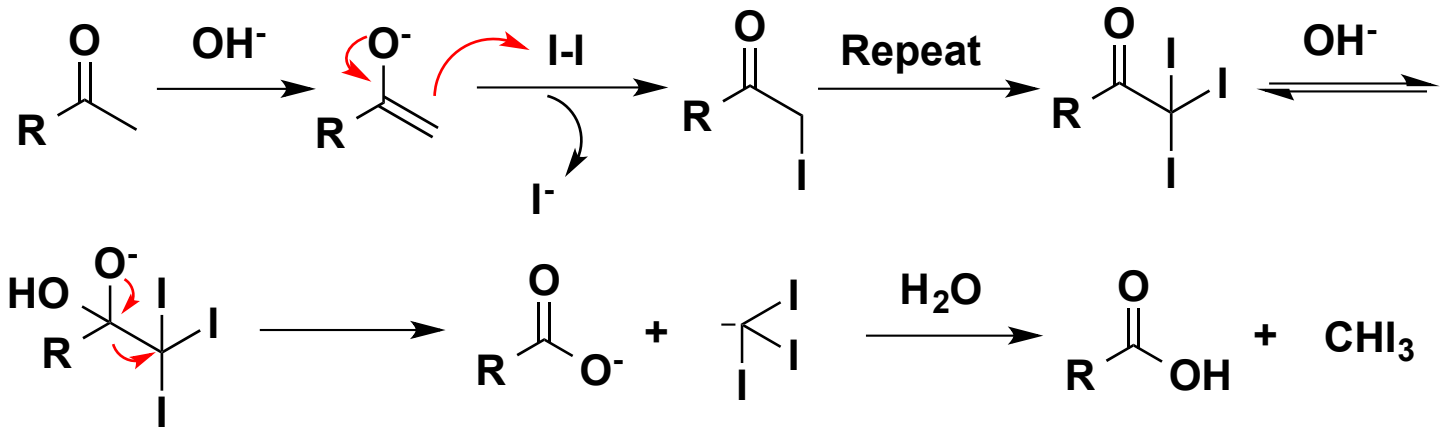


The reaction works with Cl_2, Br_2 and I_2, but not with F_2.
When iodine is used, Iodoform (CHI_3) is produced which is a yellow solide that precipitates from the reacion mixture. In the earlier days, this reaction is used as a qualitative method to identify the methyl ketone

One of the oldest organic reactions.

Traditionally used to determine the structure of methyl ketone

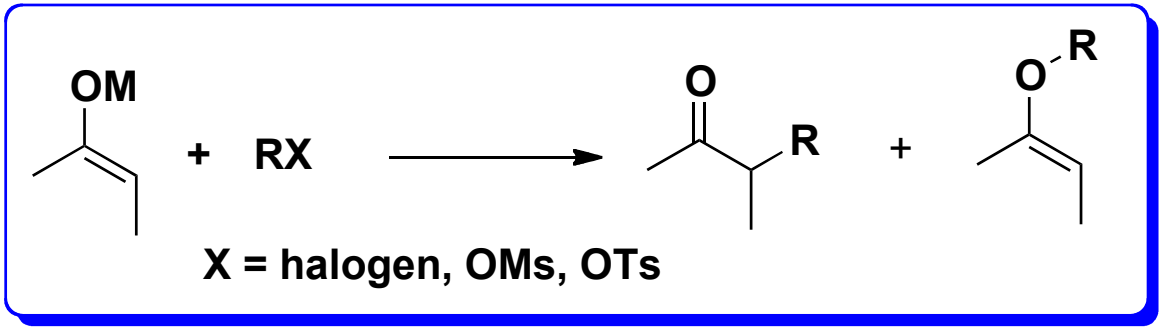
Haloform Reaction: Mechanism



* The reaction proceeds via three consecutive halogenations at the α-position (until the 3 H have been replaced).
* The second halogenation goes faster than the 1st one since the halogen stablizes the enolate negative charge and makes it easier to form. The 3rd one goes faster than the 2nd one for the same reason.
* Addition of hydroxyl to carbonyl group followed by elimination of X_3C^- affords, after protonation, the observed products.

Reaction of Enolate: Alkylation

*** Enolates are ambident nucleophiles and can react at either oxygen or carbon terminus.**



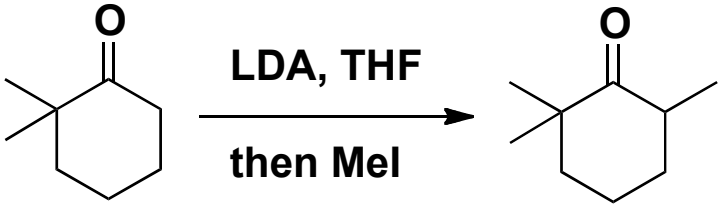
•HSAB Principle: SOFT electrophiles (*e.g.* most carbon electrophiles) tend to react at carbon (soft centre); HARD electrophiles tend to react at oxygen (hard centre)

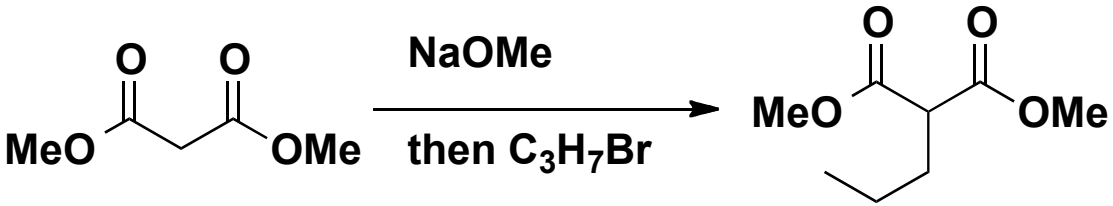
•Reaction parameters including the nature of the solvent, the conterion (M), the leaving group etc can influence the chemoselectivity (O vs C alkylation).

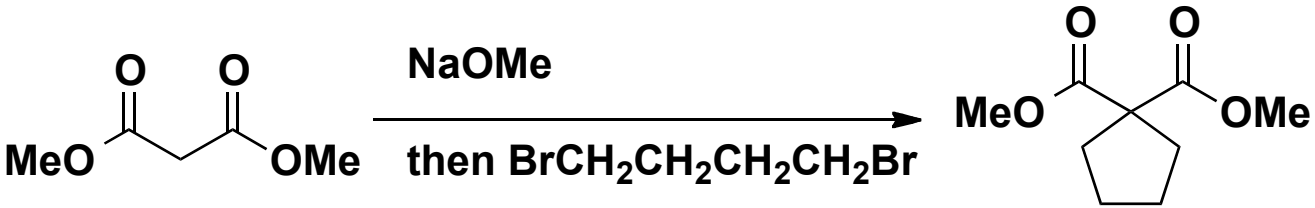
Hard acids and bases: small, high electronegativity, non-polarizable
Soft acids and bases: large, low electronegativity, polarizable.

Polarizability **is a measure of how easily an electron cloud is distorted from its normal shap by an electric field. The electric field could be caused, for example, by an electrode or a nearby cation or anion**

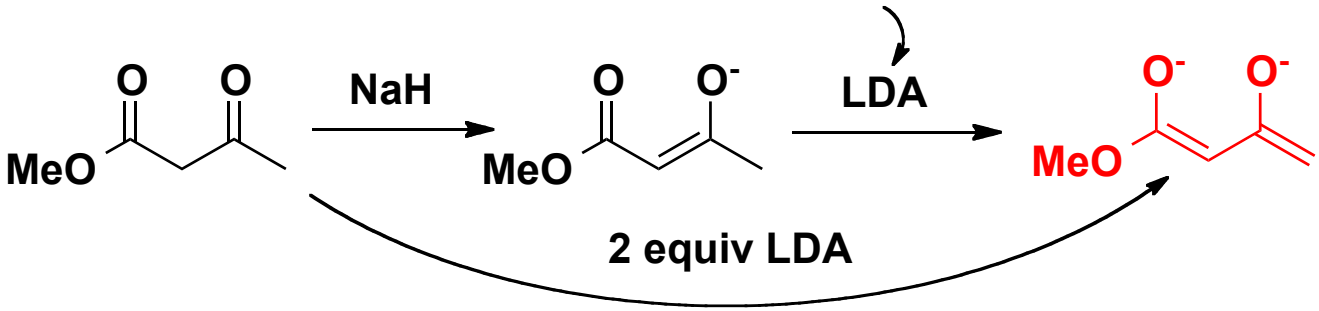
Alkylation of Enolate: Examples



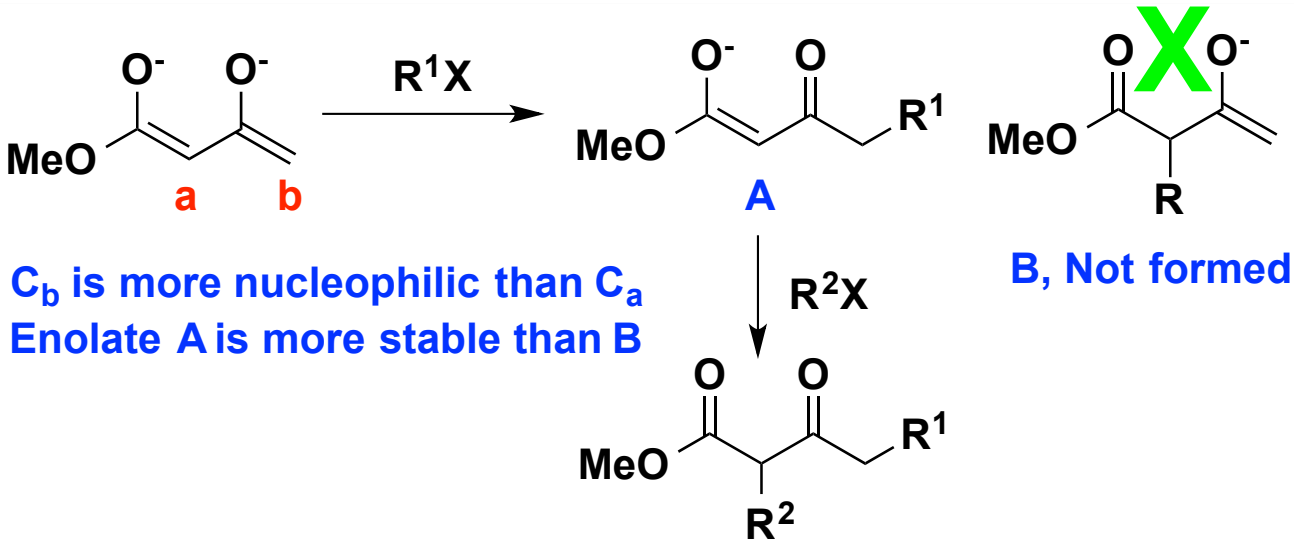




Alkylation of Dienolate of β-dicarbonyls

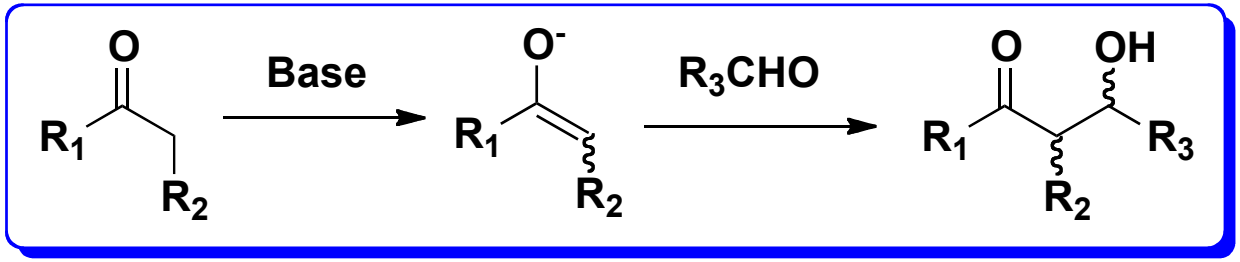


BuLi can be used instead of LDA in the 2nd step in this case



C_b is more nucleophilic than C_a
Enolate A is more stable than B

Reaction of Enolate: Aldolisation



Discovered in 1872 by Charles Adolphe Wurtz. The name "aldol" is an abbreviation of "aldehyde-alcohol". It is a generic name of "β-hydroxy carbonyl compounds".

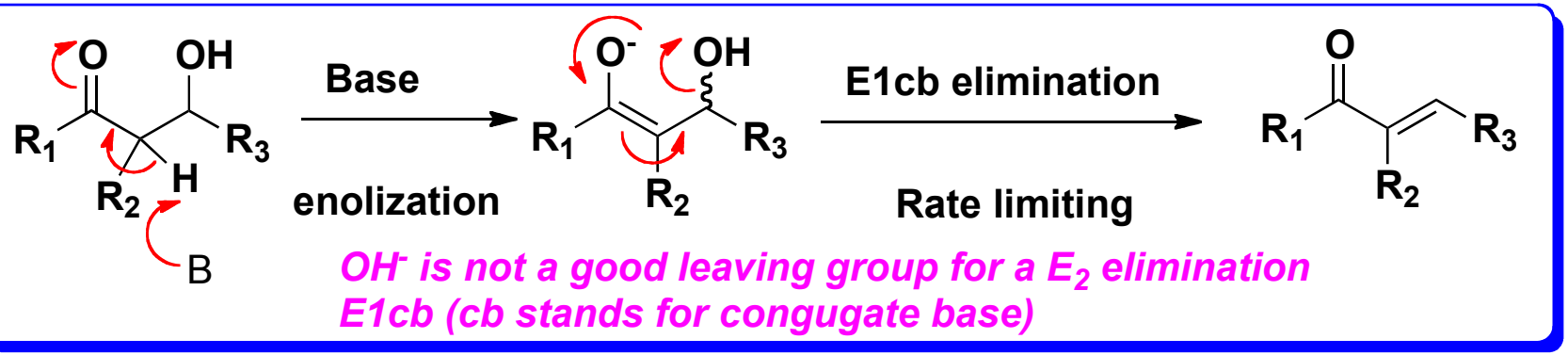
Aldolisation is one of the most important C−C bond forming reactions, widely used in organic synthesis

In the cross-aldol reaction, the enolate of one carbonyl group reacts with the carbonyl group (usually an aldehyde) of another.

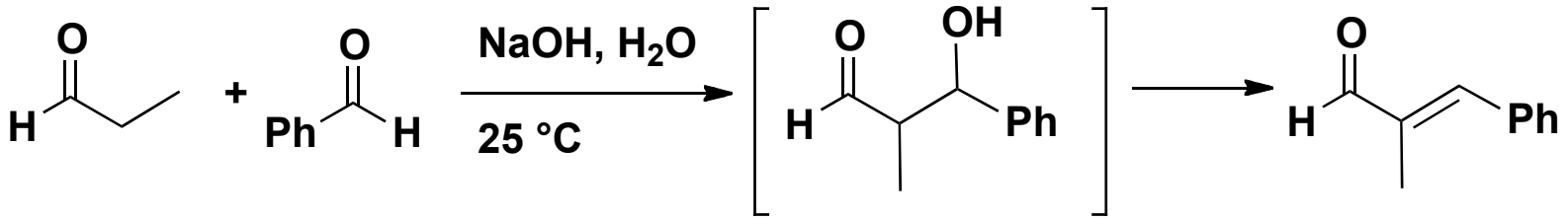
To avoide self condensation, the enolate component should be formed beforehand.

Reaction of Enolate: Aldol condensation

The aldol can undergo, under more forcing conditions, the β-elimination to give α,β-unsaturated carbonyl compound.
The addition of enolate to carbonyl leading to α,β-unsaturated carbonyl compound is called *aldol condensation*

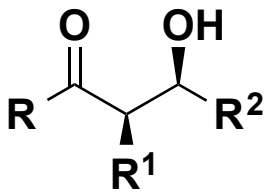


OH^- is not a good leaving group for a E_2 elimination
E1cb (cb stands for congugate base)

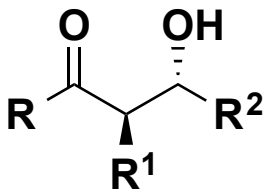


Acid can also promote the aldol condensation.

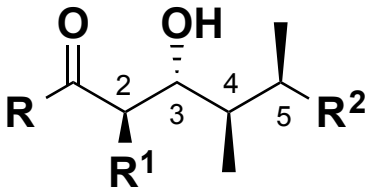
Stereoselective Aldolisation



Syn-aldol

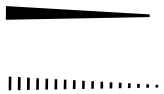


Anti-aldol



2,3-*Anti*, 3,4-*Anti*, 4,5-*Syn*

Wedged line:



indicating not only the relative stereochemistry, but also the absolute configuration.
Product is enantiomerically enriched

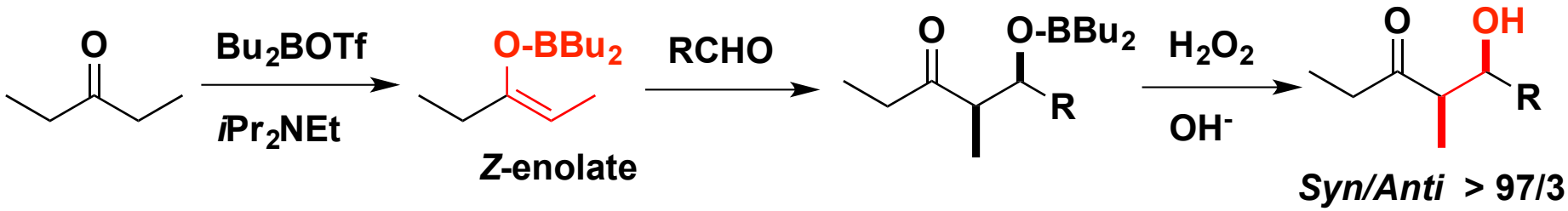
Straight line:

indicating only the relative stereochemistry.
Product is racemic.

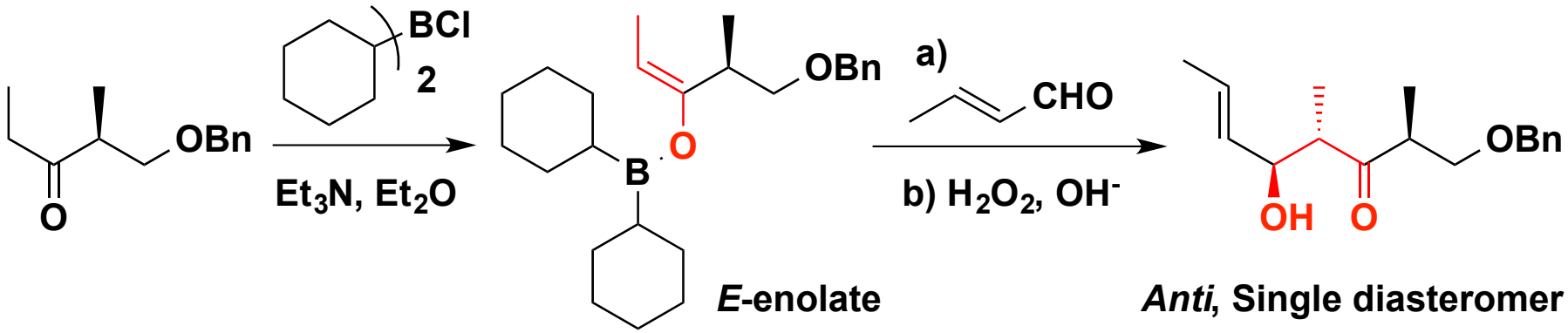
Boron Enolate in Aldol Reaction

Preparation of Boron Enolates

Z-Boron enolate: Usually formed from a dialkylboron halide or triflate and a sterically hindered tertiary amine base such as triethylamine or Hünig's base (*i*Pr_2NEt).



***E*-Boron enolate: using carefully controlled conditions, e.g. (c-hex)$_2$BCl, Et_3N, Et_2O**

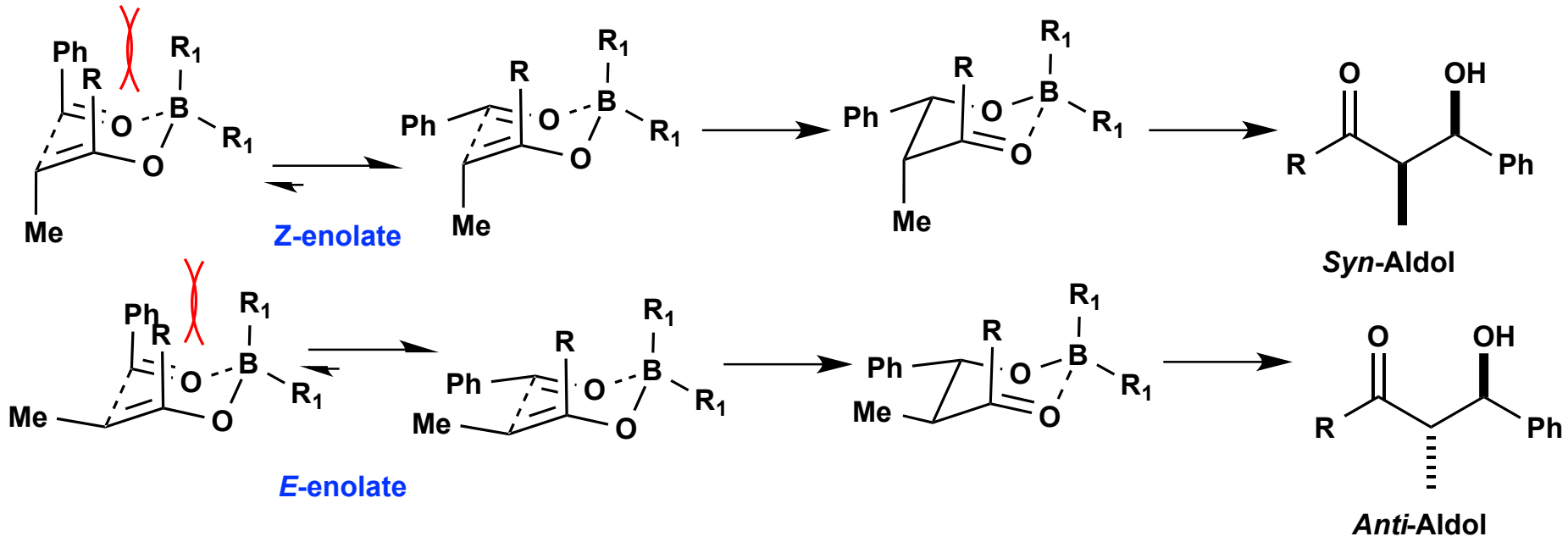


Water is not sufficient to cleave the O−B bond efficiently in the aldol product. Oxidative cleavage with alkaline peroxide is the standard method of work-up.

Boron Enolate in Aldol Reaction

* usually much more stereoselective than lithium enolates
* reaction is highly stereospecific: the *Z*-boron enolate gives the *syn* aldol product; the *E*-boron enolate provides the *anti* aldol product.
* the stereospecificity can be readily rationalized by invoking chair-like Zimmerman-Traxler T.S.
• the shorter B−O bond - compared with Li−O leading to a tighter T.S. and accounts for the improved stereoselectivity.

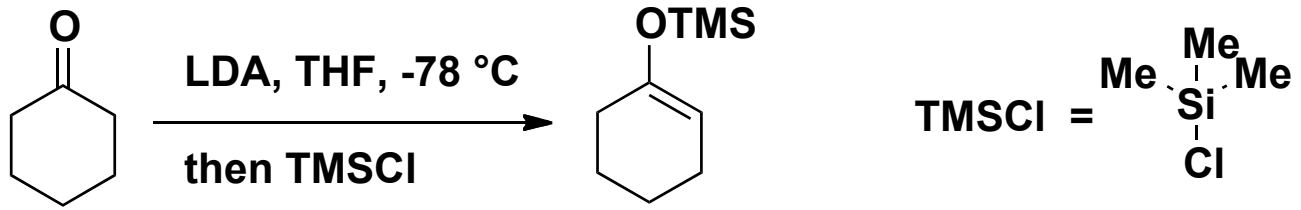
Destabilizing 1,3-diaxial interaction



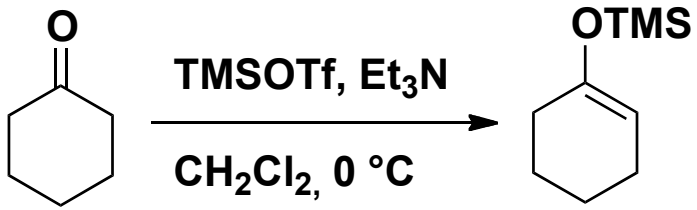
Silyl Enol Ether in Aldol Reaction: Mukayama aldol Reaction

Preparation of Silyl Enol ether

Basic conditions: trapping of lithium enolate by TMSCl



Lewis acidic conditions: TMSOTf or TMSCl in the presence of a tertiary amine (requires temperatures > 0 ° C).

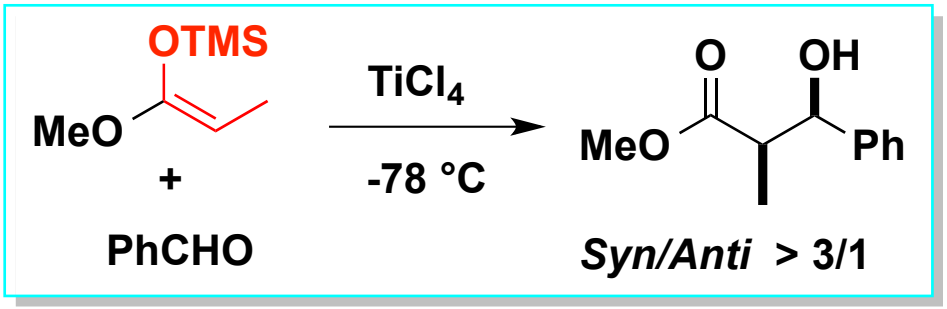


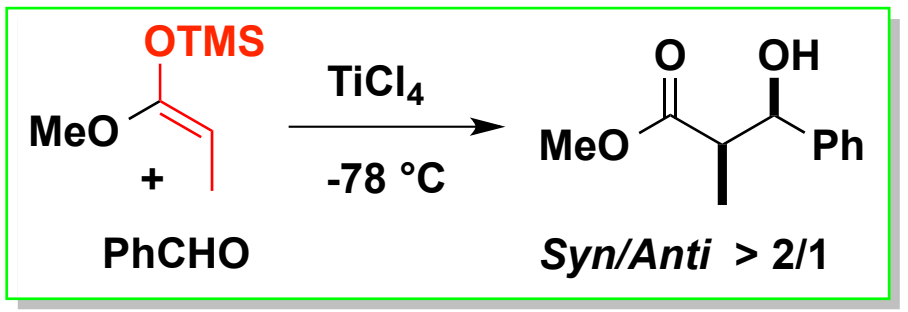
*** The strong Si−O bond is responsible for *O*-silylation being the major product.**
*** Silyl enol ether is less nucleophilic than metal enolates (lithium, zinc, boron etc)**
*** Lewis acid complexation increases the electrophilicity of aldehydes and this is sufficient to allow aldol reaction to take place.**

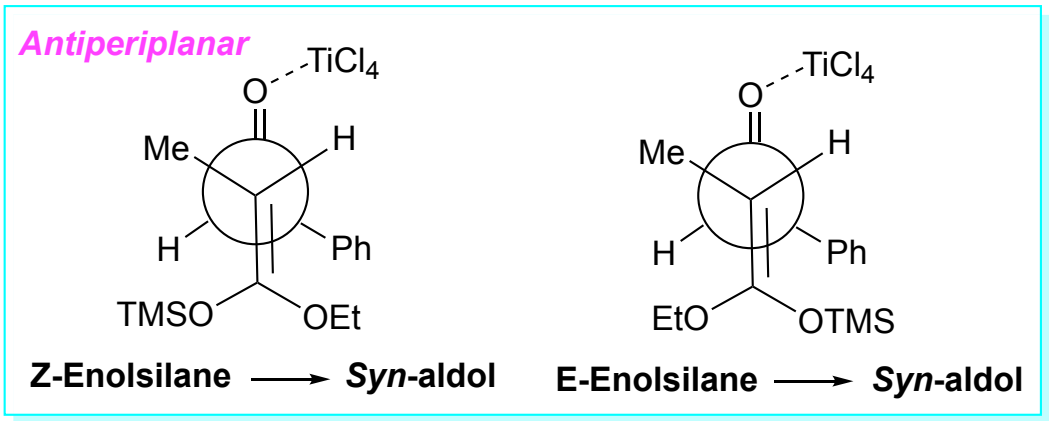
Silyl Enol Ether in Aldol Reaction: Mukayama aldol Reaction

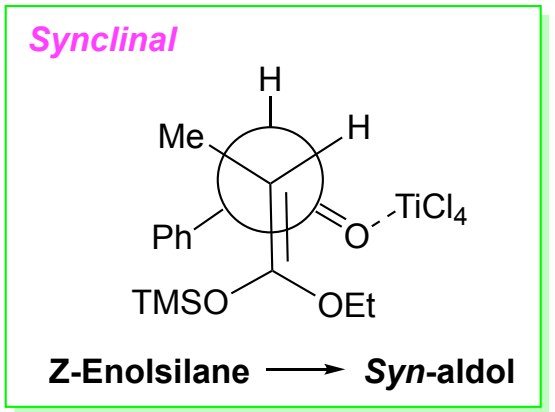
The mechanism of Lewis acid-catalyzed aldol reaction is quite different from that of lithium or boron enolates. Internal coordination and reaction through a 6-membered T.S. is impossible with silicon since the silicon atom is not Lewis acidic enough to compete with an added stronger Lewis acid.

Reaction proceeds through an *open T.S*. leading preferentially to *syn*-aldol *regardless the enolsilane geometry*. The stereoselectivity is however low.



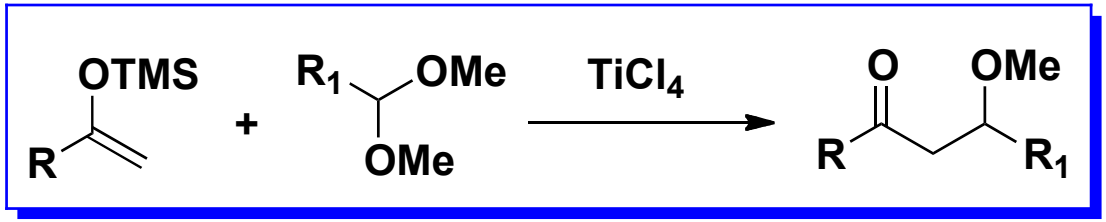




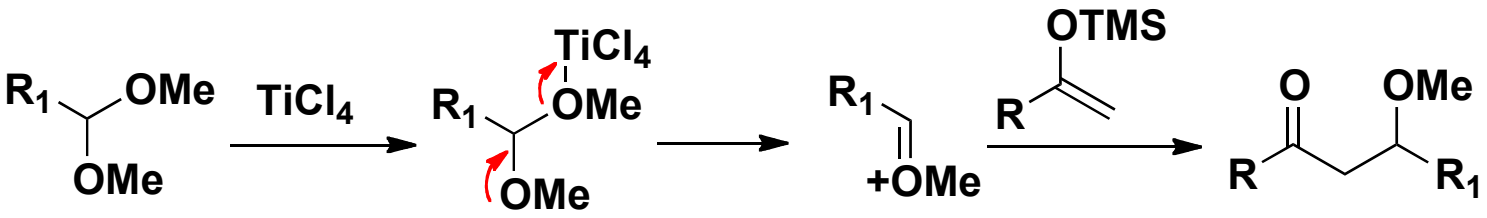


Silyl Enol Ether in Aldol Reaction: Mukayama aldol Reaction

Since Mukayame aldol is performed in the presence of a Lewis acid. These conditions allows the use of acetals as masked aldehydes.

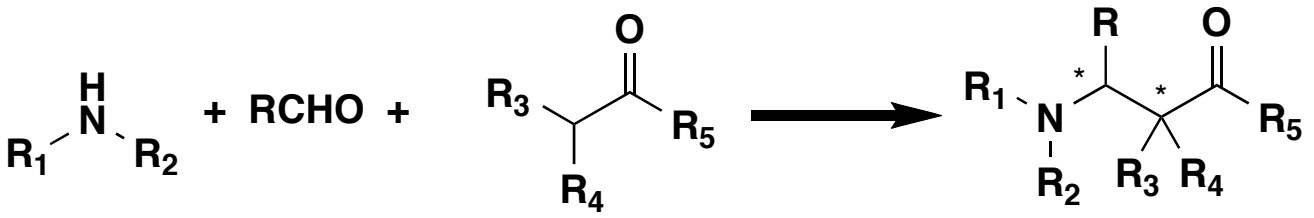


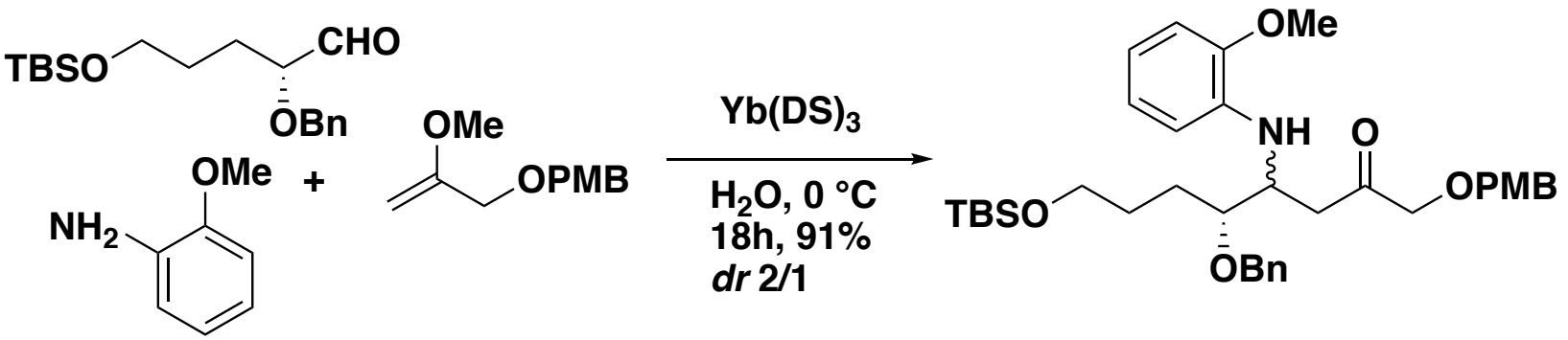
Mechanism

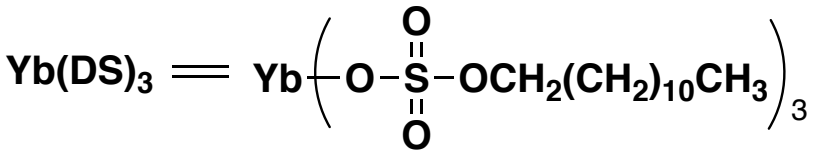


Mannich Reaction

Mannich reaction: condensation of a non-enolizable aldehyde, a primary or secondary amine and an enolizable carbonyl compound affords aminoalkylated products. It is one of the most powerful C-C bond forming reaction in organic chemistry. It is a three-component reaction.
The reaction between enolizable carbonyl (or an enol) and preformed imine is also called Mannich reaction.



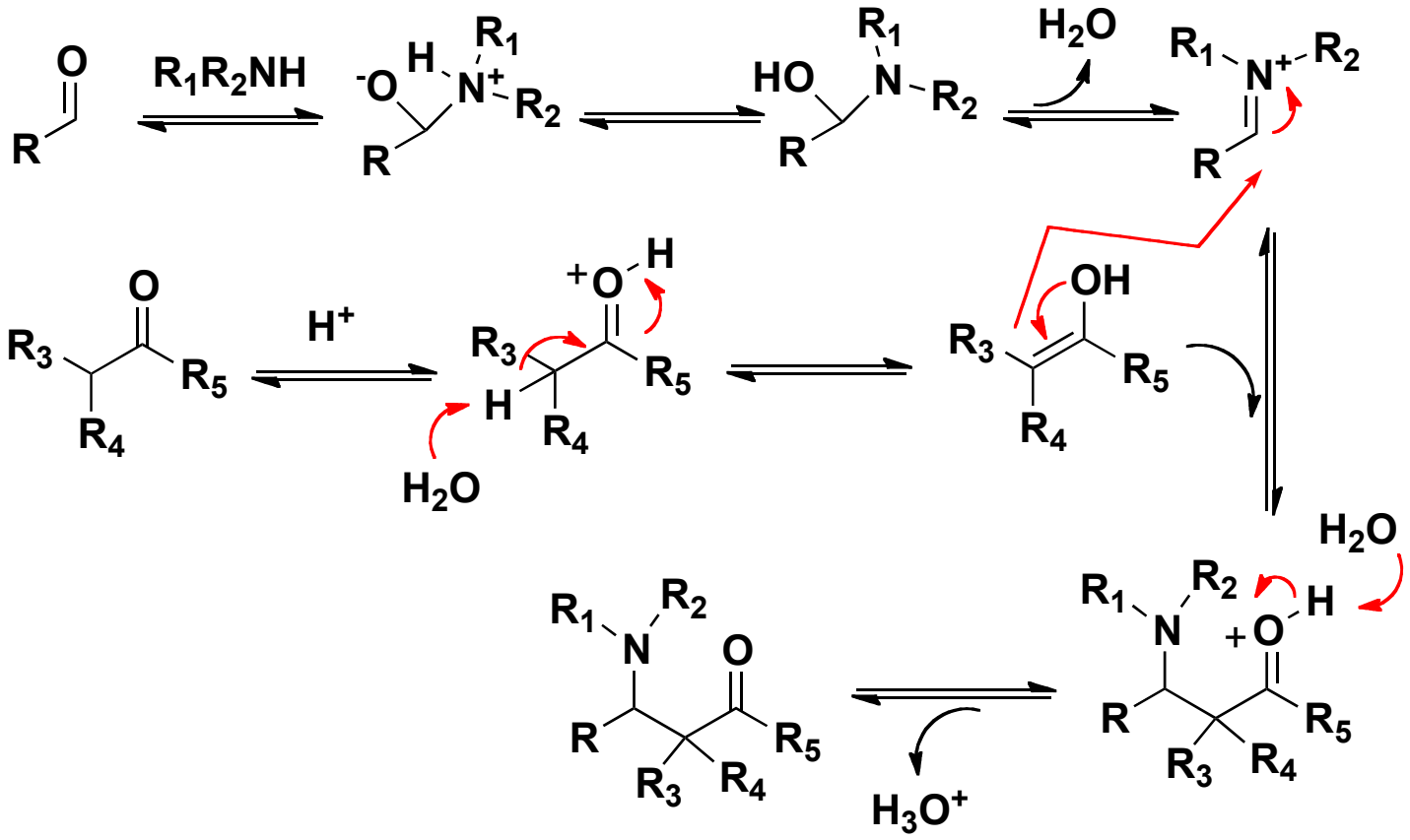




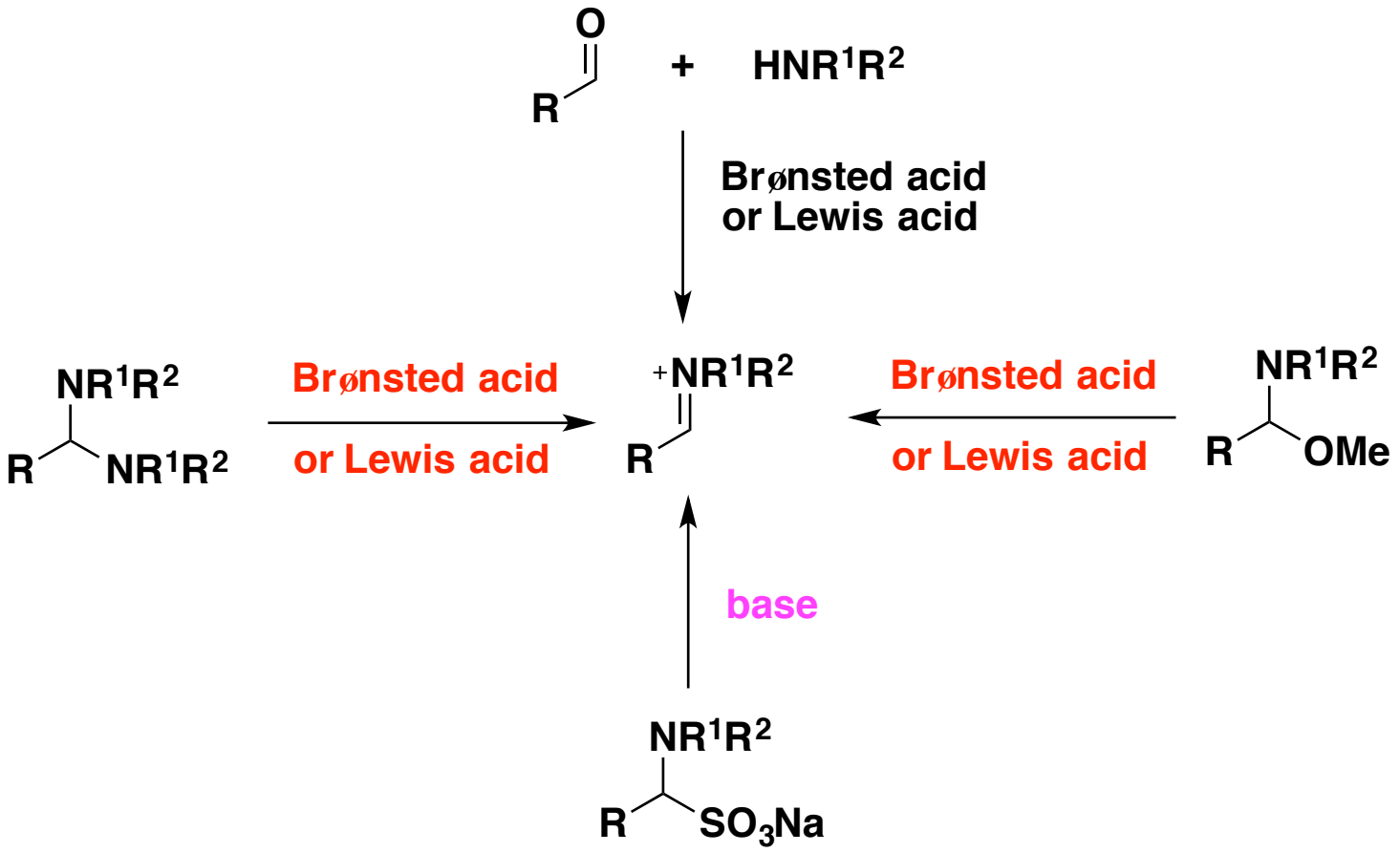
DS = Dodecyl sulfate

"dr" stands for diastereomeric ratio

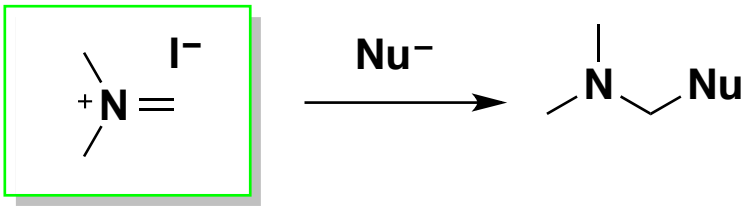
Mannich Reaction: Mechanism

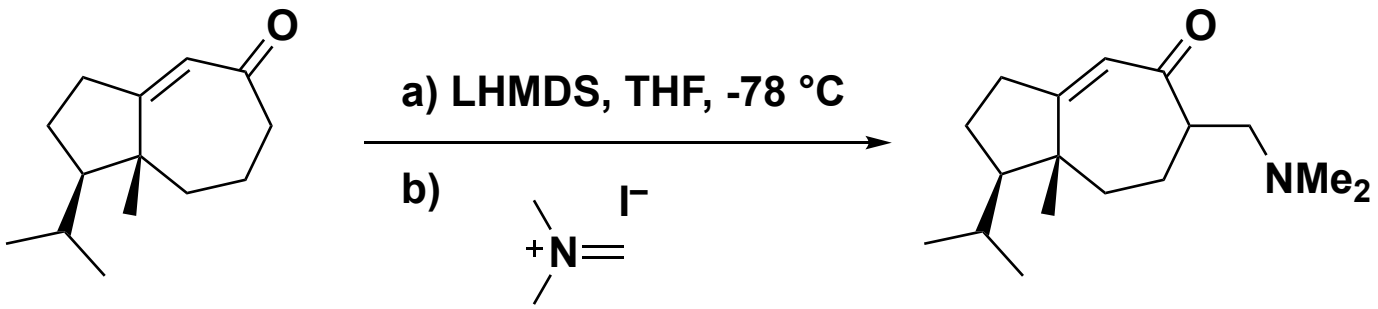


Mannich Reaction: Generation of Imine (Iminium)

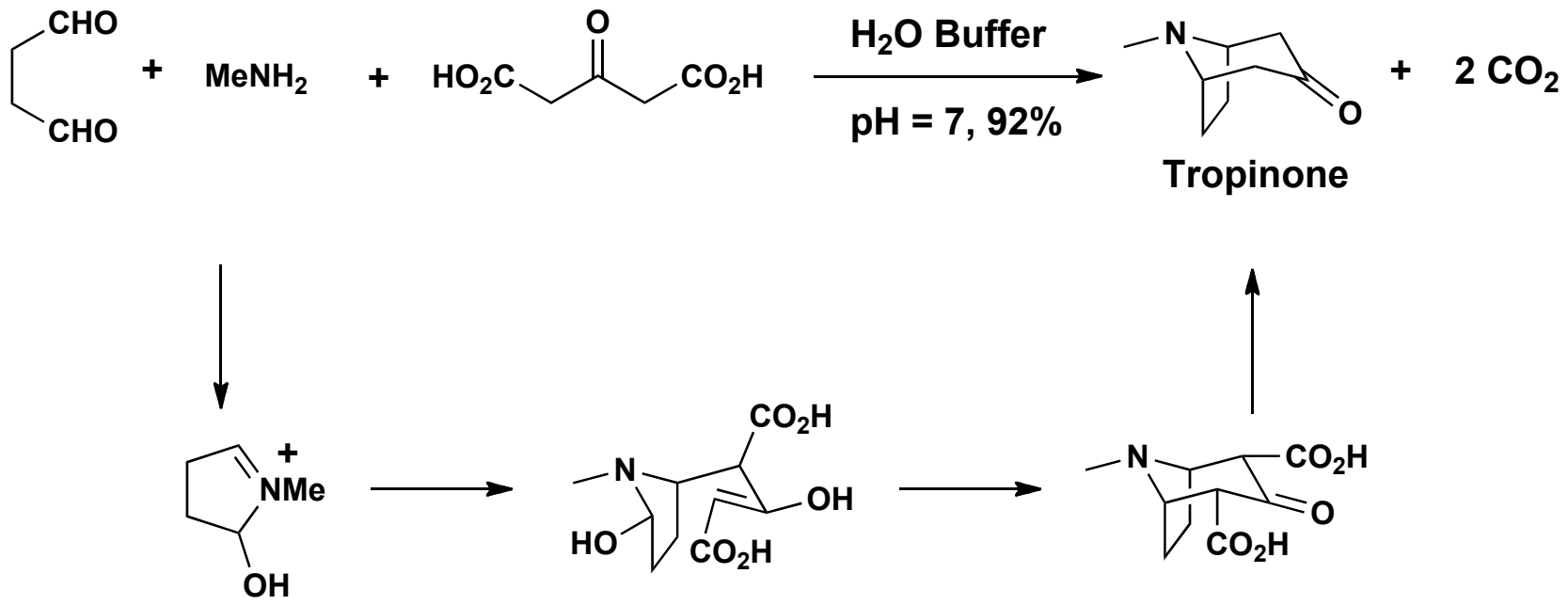


Mannich Reaction: Eschenmoser's salt





Robinson's Three-Component Synthesis of Tropinone

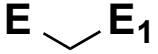


This is one of the most famous application of the Mannich reaction in natural product synthesis.
It is a biomimetic synthesis

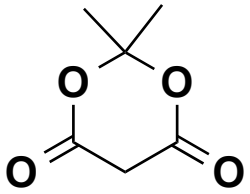
Reaction of Enolate: Knoevenagel condensation

Discovered by Emil Knoevenagel in 1898, it is the reaction of *stabilized carbanions* with carbonyl compounds leading to α,β-unsaturated carbonyls. It is a modification of *aldol condensation*

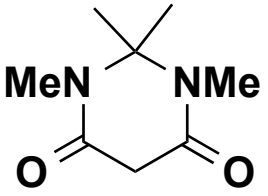
Most frequently used carbanion precursors:



E = E_1 = COOMe, methyl malonate
E = E_1 = CN, malonitrile
E = COOMe, E_1 = CN, Malonitrile

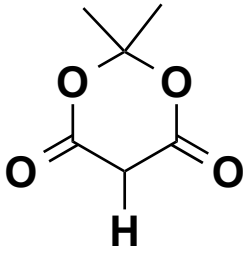


Meldrum's acid

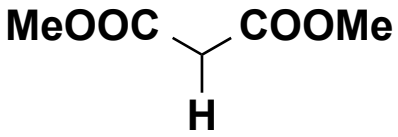


1,3-dimethyl barbituric acid

Acidity:

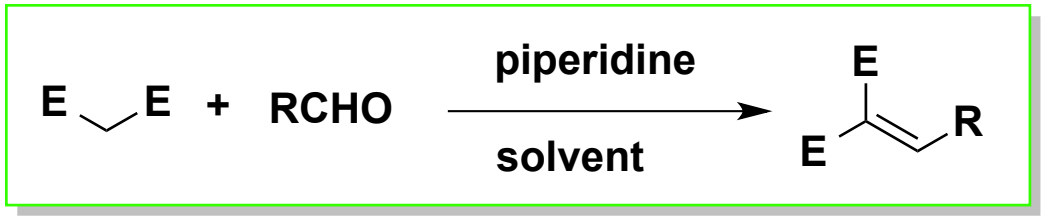


Pka ~ 5 **>>**

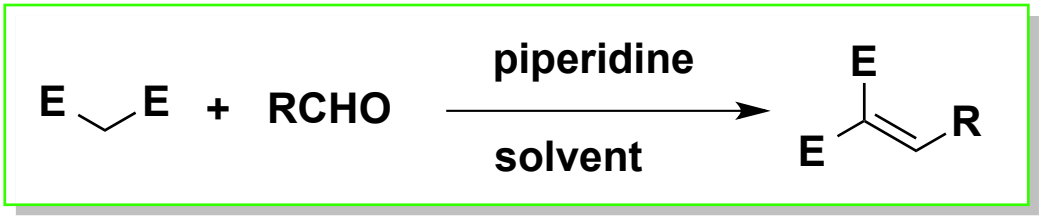


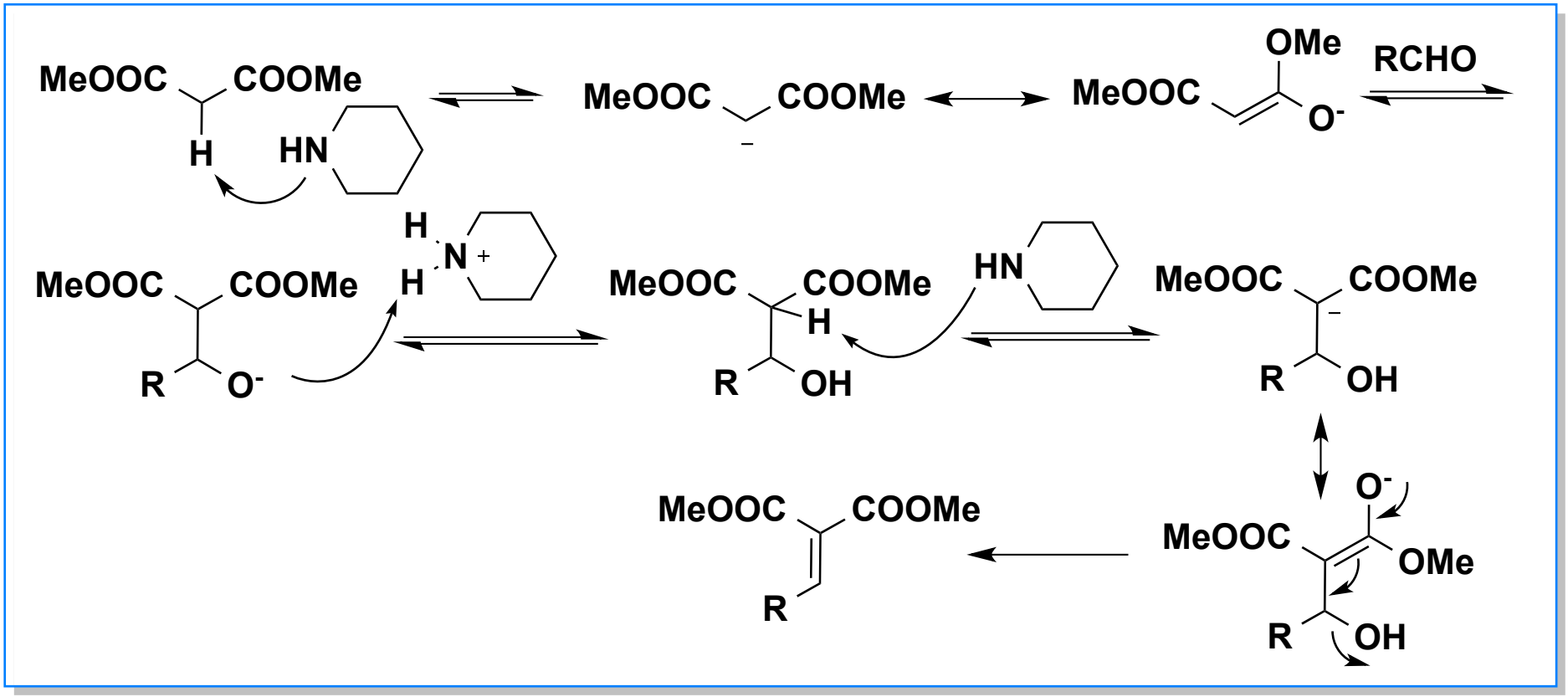
Pka ~ 13

Most frequently used base: secondary amines such as piperidine, morpholine



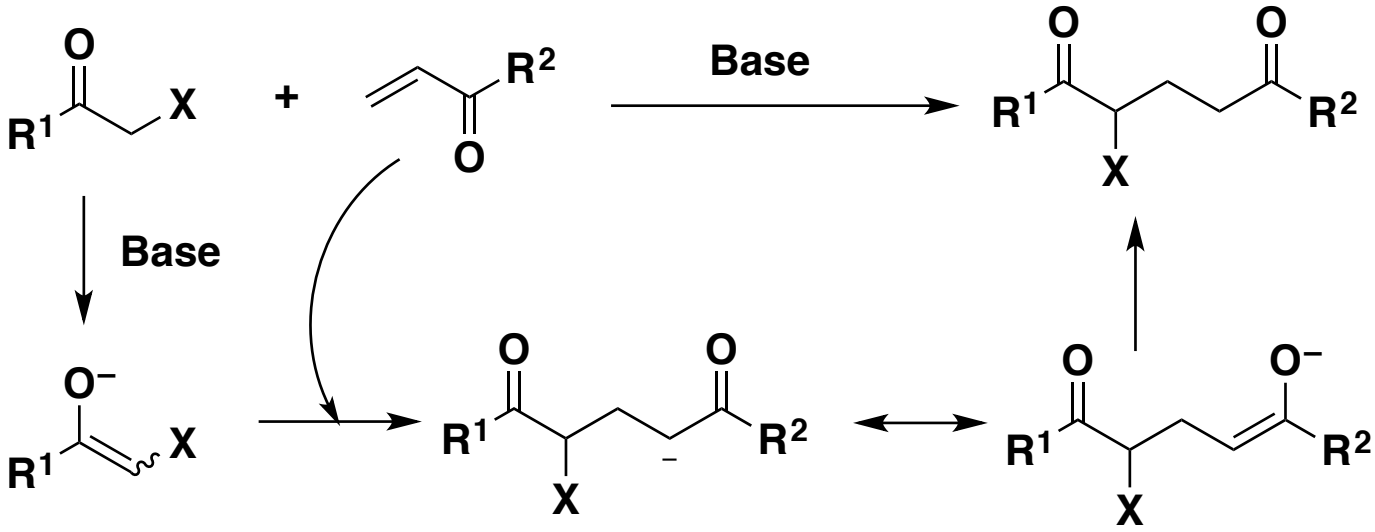
Knoevenagel condensation: Mechanism





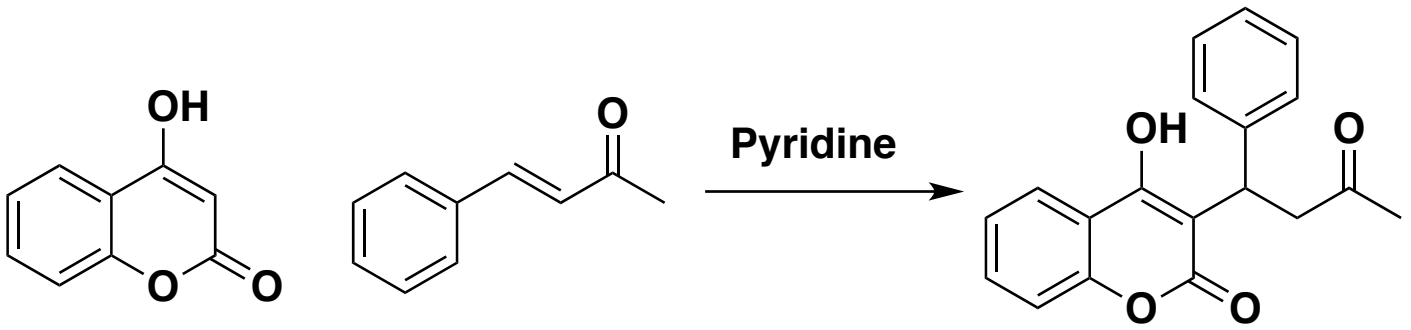
An alternative mechanism involving addition of enolate to the in situ generated iminium (Mannich reaction) has also been proposed for piperidine/AcOH promoted reaction

Michael Addition



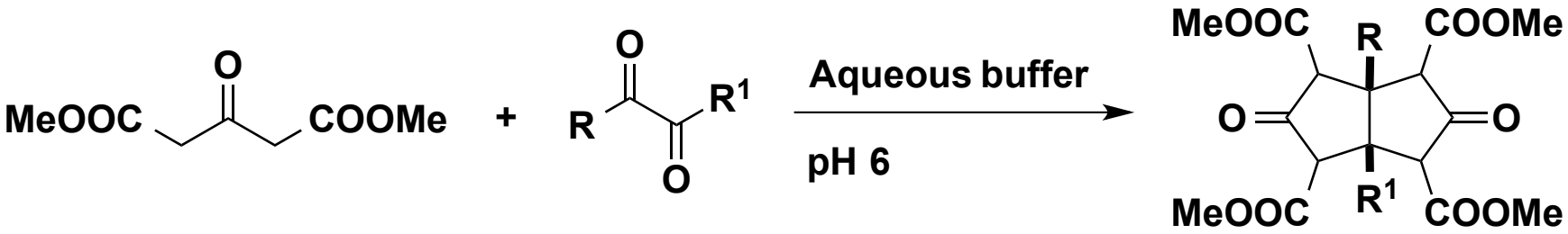
X = alkyl, aryl, COOR, COR, $CONR_2$, CN, NO_2 etc...

In a more general sense, all 1,4-addition of nucleophiles to α, β-unsaturated carbonyl compounds are called Michael addition.

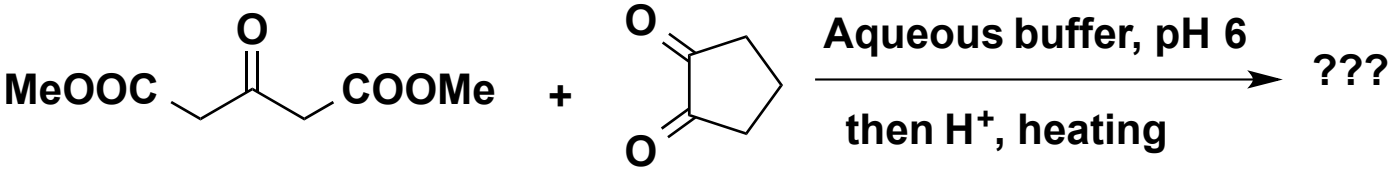


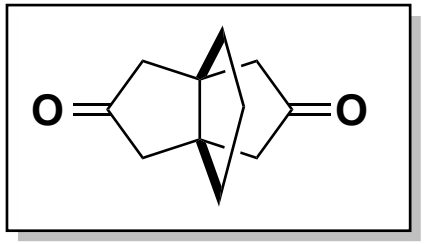
Warfarin
(Marketed Anti-coagulant drug)

Weiss-Cook Condensation

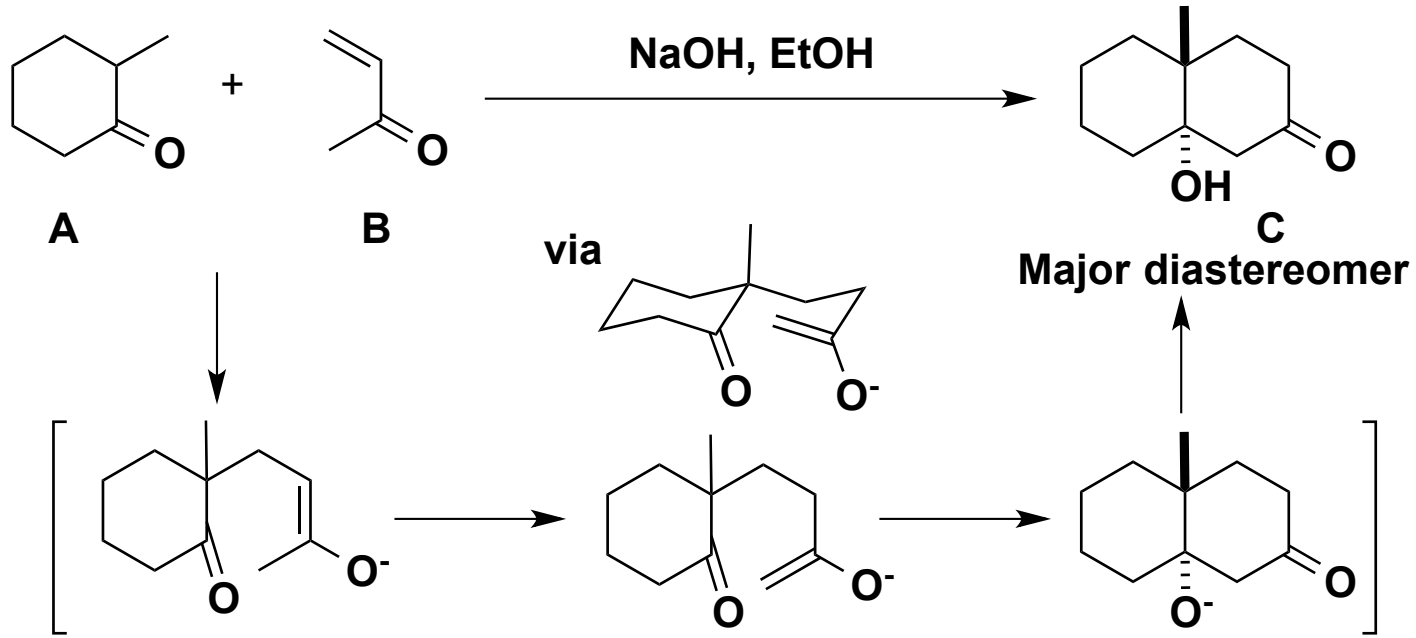


Write a Mechanism (Double Knoevenagel condensation followed double Michael addition)

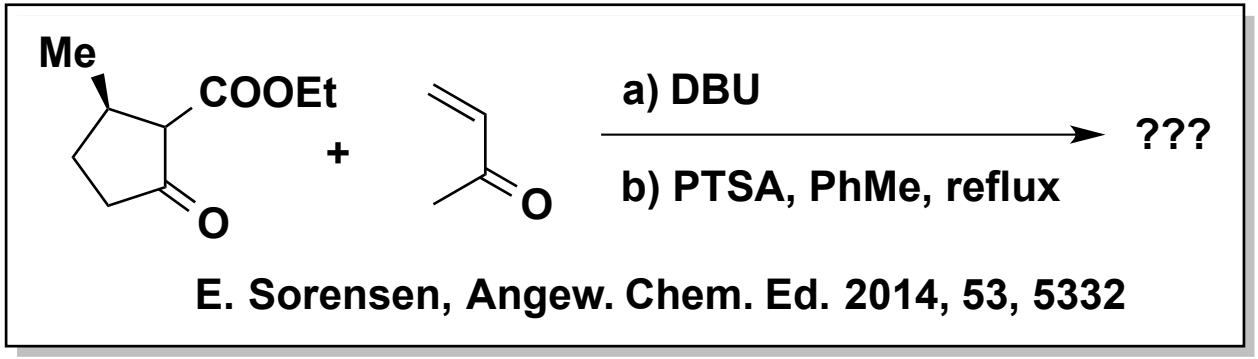




Robinson Annulation: Michael Addition followed by intramolecular Aldolization



The overall reaction from A and B leading to D is called Robinson Annulation. It is a combination of Michael addition and aldol condensation.

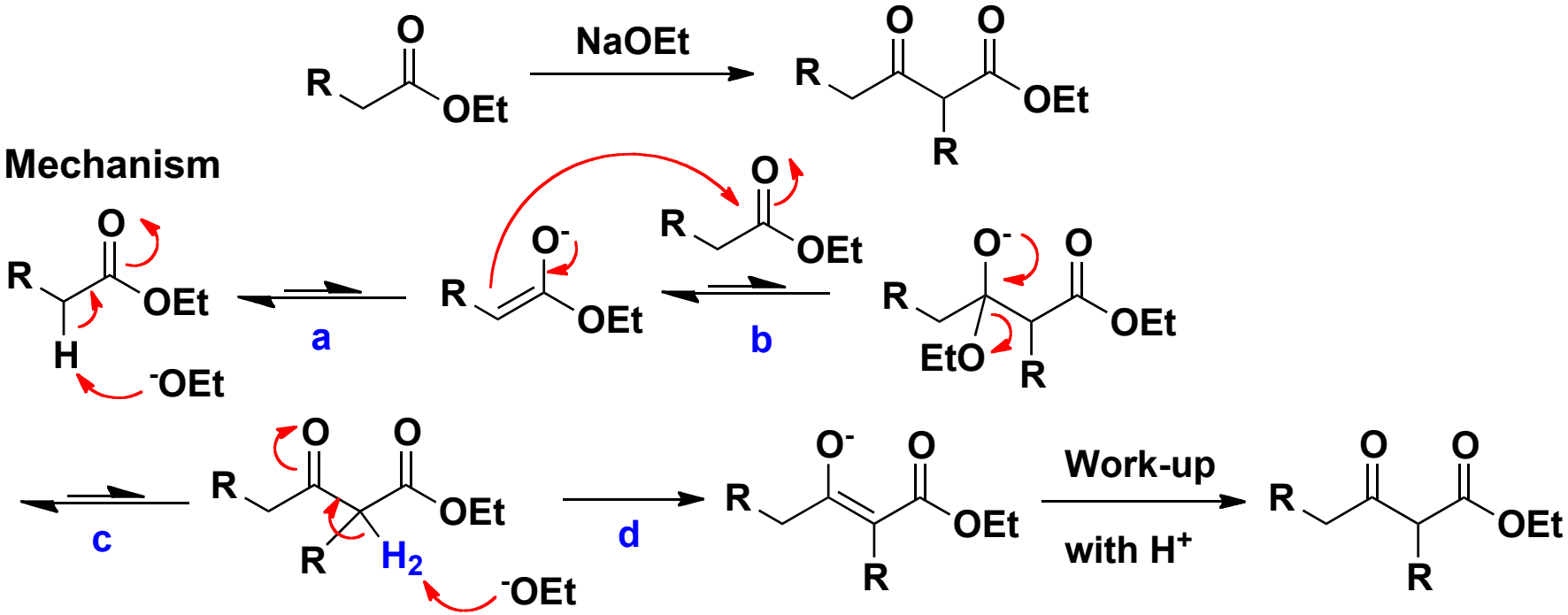


E. Sorensen, Angew. Chem. Ed. 2014, 53, 5332

α-Acylation of Ester: Claisen Condensation

Base-promoted condensation between two esters (or equivalents) leading to 1,3-dicarbonyl compounds. First discovered by Rainer Ludwig Claisen in 1881.

Self-Condensation:



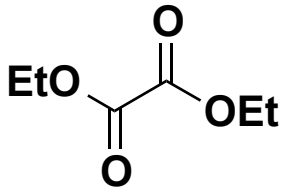
Note 1) NaOEt is not basic enough to convert the ester to ester enolate completely
2) Steps a, b and c are reversible and equilibrium went to the left side
3) *Step d is irreversible* because of the high acidity of H_2 [pKa ≈ 11; pka (EtOH) = 16]. This provided driving force for the oveall reaction. Work-up provided then the ketoester.

α-Acylation of Ester: Claisen Condensation

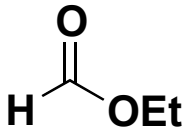
Cross-Claisen Condensation:

To be successful, one ester might exist in enol form to act as a nucleophile, while the other act as electrophile.

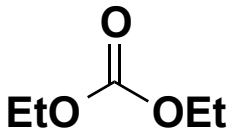
Case 1: Using reactive esters that cannot enolize.



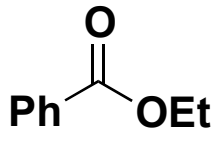
Diethyl oxalate



Ethyl formate

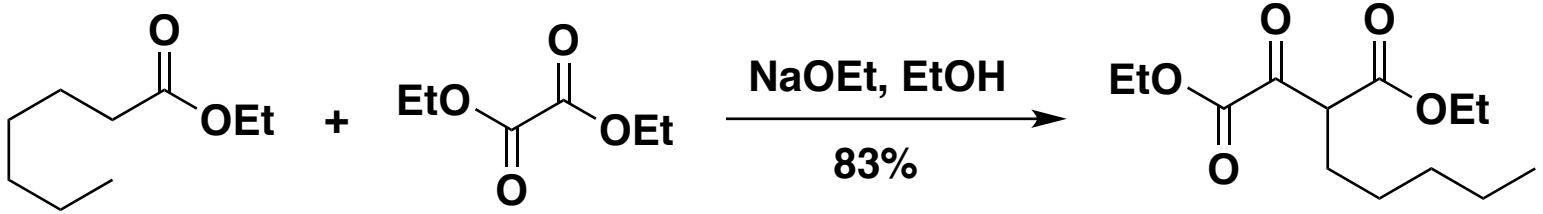


diethyl carbonate



ethyl benzoate

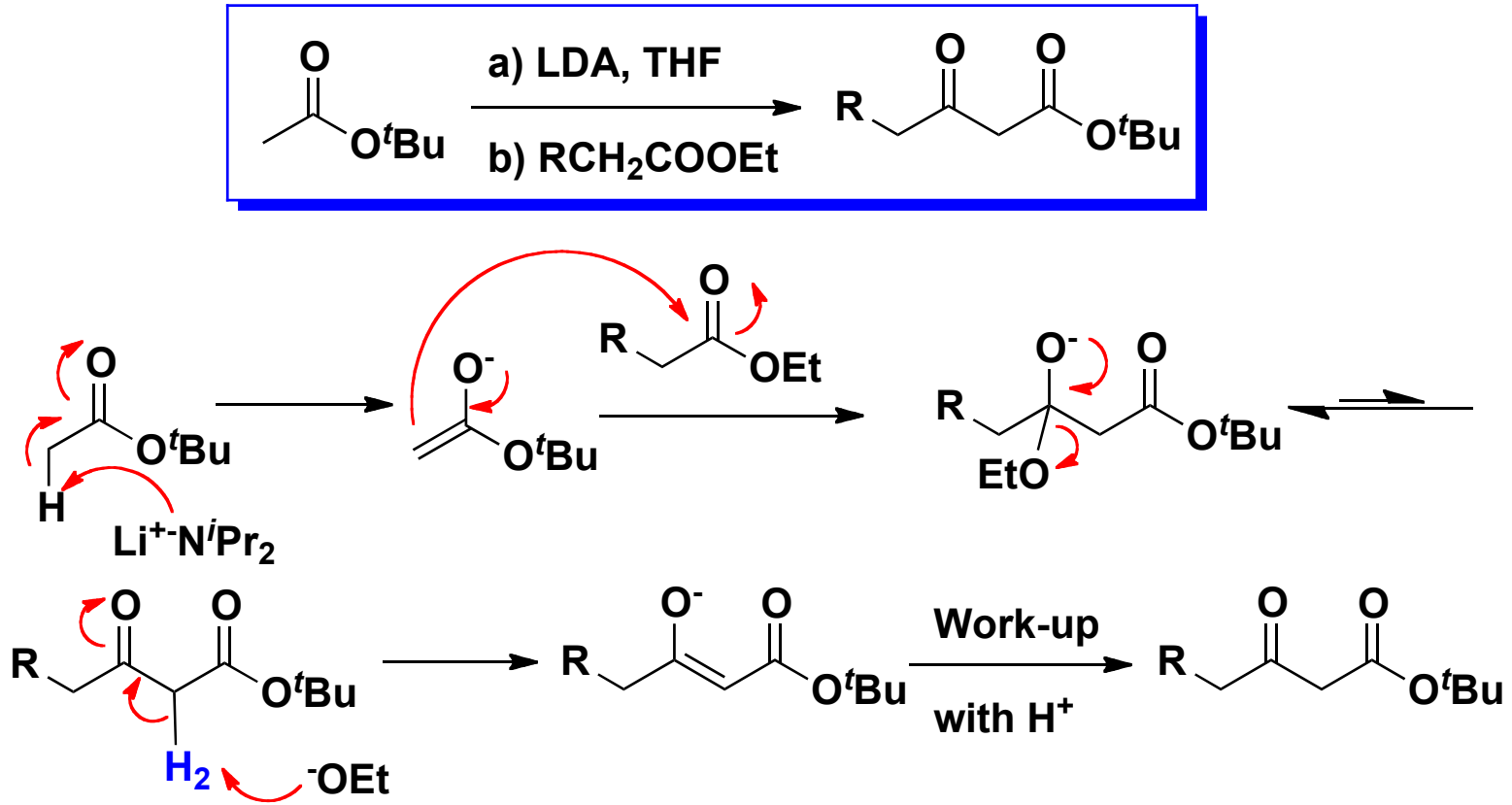
Increased electrophilicity



Note: With NaOEt as a base, only small amount of ethyl heptanoate is converted to the enolate. However, the carbonyl carbon of the ethyl heptanoate is far less reactive than that of the diethyl oxalate, so cross condendation occurred at the expense of the self-condensation of ethyl heptanoate.

α-Acylation of Ester: Claisen Condensation

Case 2: Cross-Claisen condensation between two esters having α-proton.



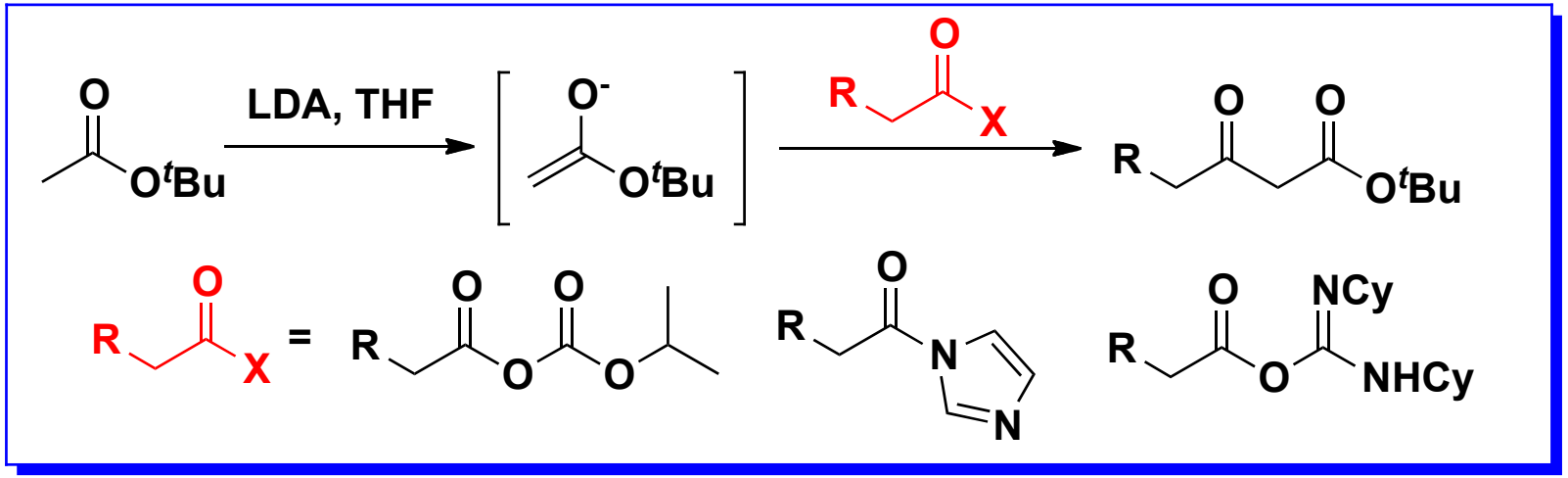
Note: 1) Using strong base (LDA) to convert fully one ester to its enolate that will acts as a nucleophile.

2) Order of addition for the formaiton of lithium enolate: Adding ester to LDA avoids the self-condensation (Pre-formation of enolate of one ester is a pre-requisite for performing the cross-Claisen condensation.

3) Using hindered t-butyl ester decreases the self-condensation process.

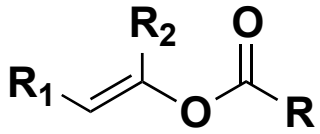
α-Acylation of Ester: Claisen Condensation

Using activated ester as electrophilic partner in Cross-Claisen Condensation can accelerate the nucleophilic addition step, increasing therefore the yield of the β-ketoester.



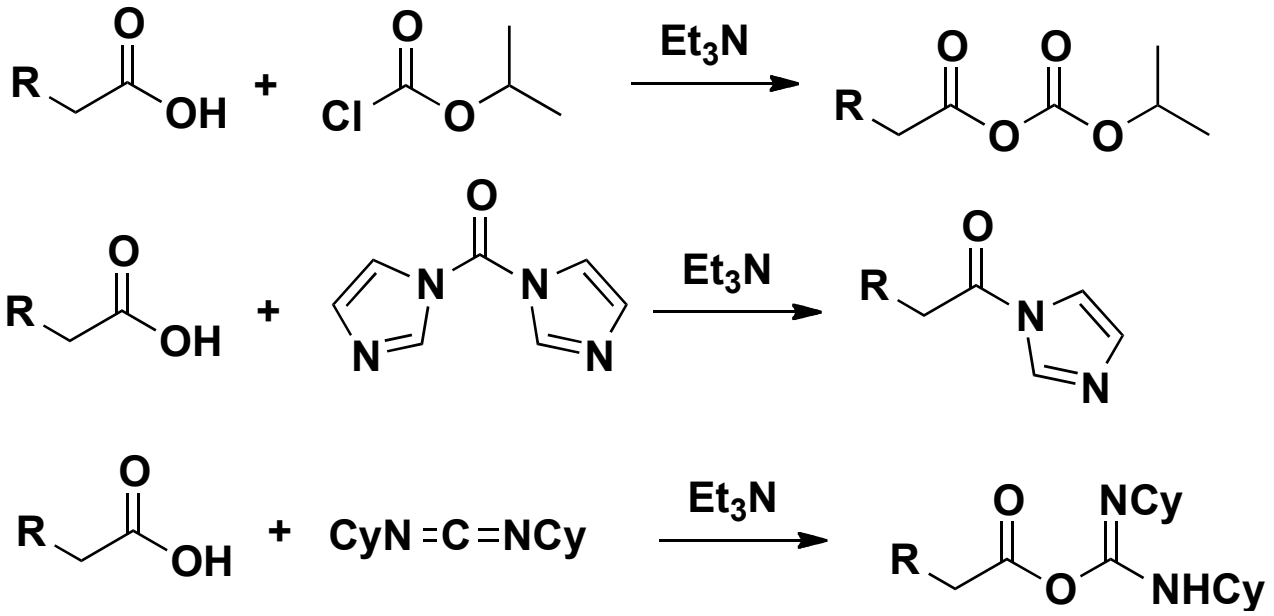
Most of these activated ester are formed in situ from the corresponding carboxylic acid and reacted directly with the enolate (*see next slide*)

Note: The acyl chloride is not a good acylating agent for lithium enolate due to the competitive *O*-acylation leading to Enol ester:



α-Acylation of Ester: Claisen Condensation

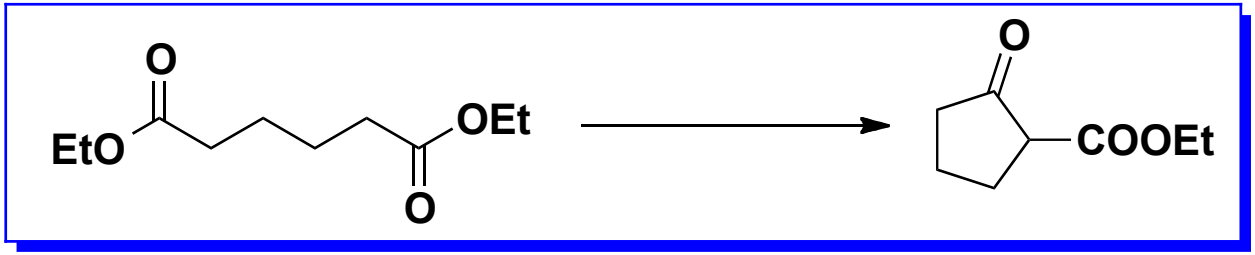
Preparation of activated ester



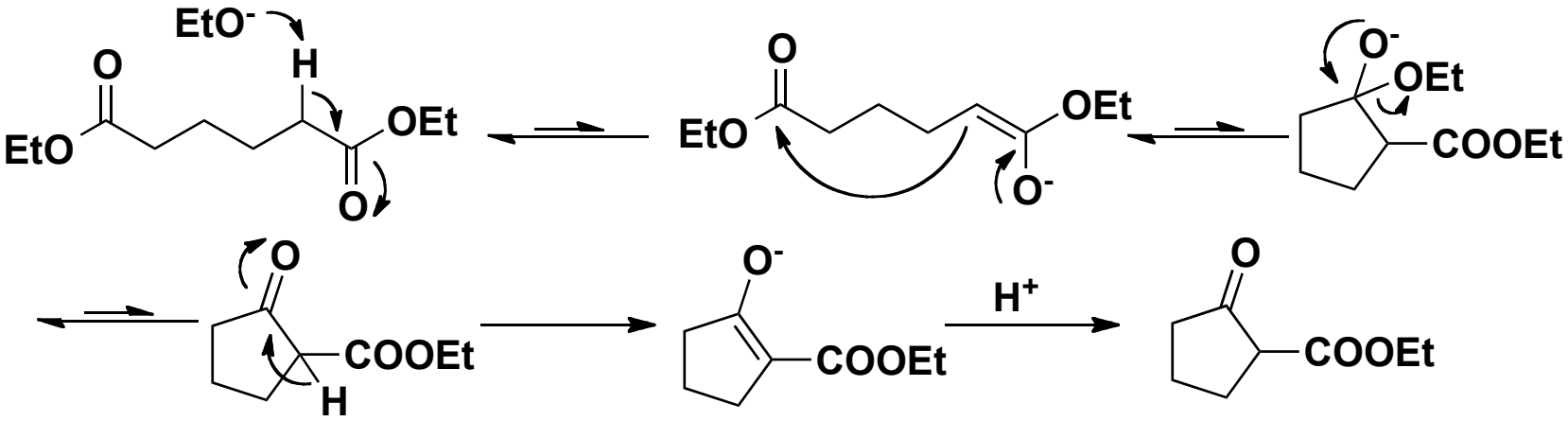
These activated esters are generally formed in a seperate flask and are added to the flask containing the enolate.

Dieckmann Condensation

Intramoleculaire condensation of diesters leading to cyclic β-keto ester. It is named after the German chemist Walter Dieckmann. It is the intramolecular variant of Claisen condensation.

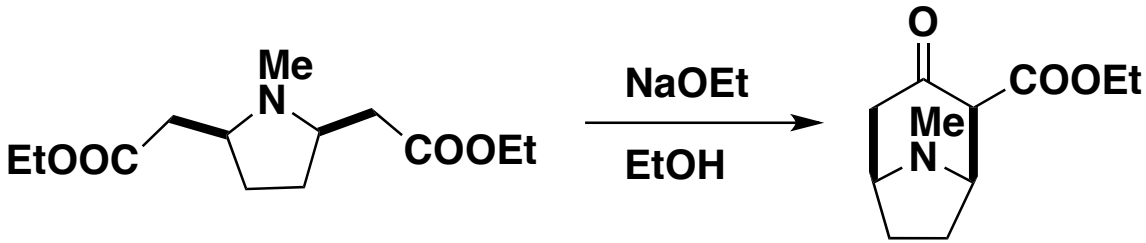


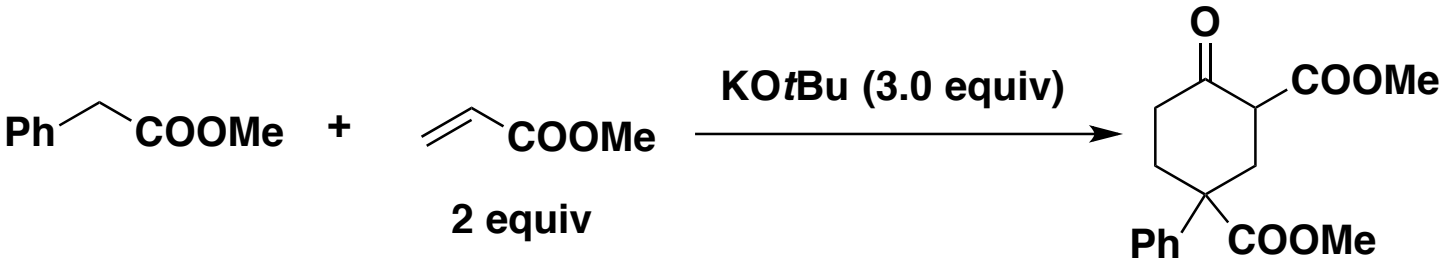
Mechanism:



Dieckmann condensation works efficiently for the formation of 5-member and 6-membered ring, reasonably well for 7-membered ring, but works badly for 8-membered ring.

Dieckmann Condensation: Example

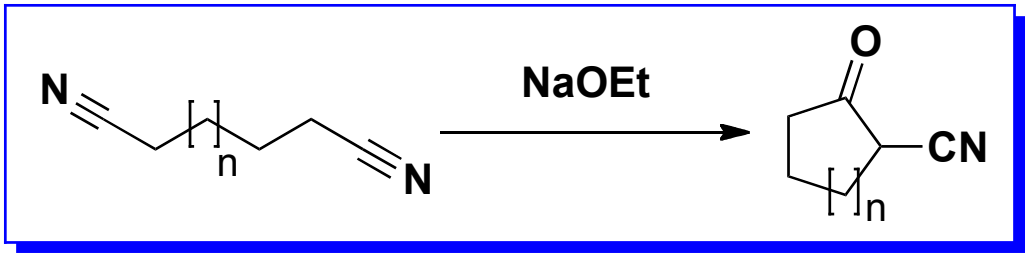




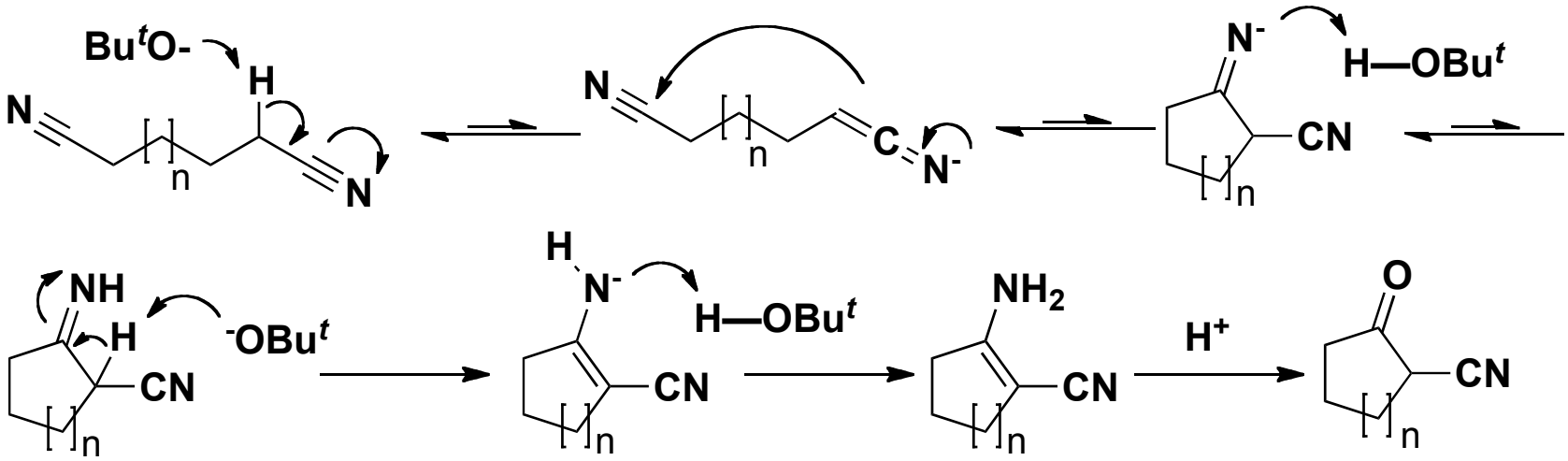
Mechanism?

Thorpe-Ziegler Condensation

Intramoleculaire condensation of dinitrile leading to cyclic α-cyano ketone. It is conceptually related to Dieckmann condensation.

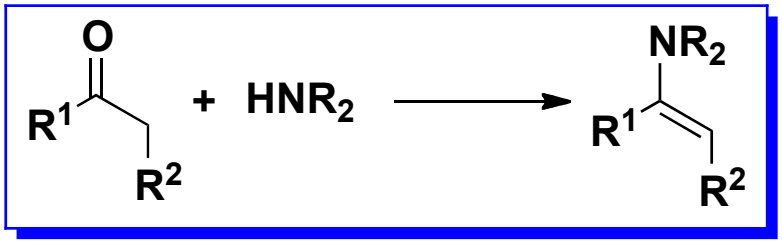


Mechanism:



Enamine

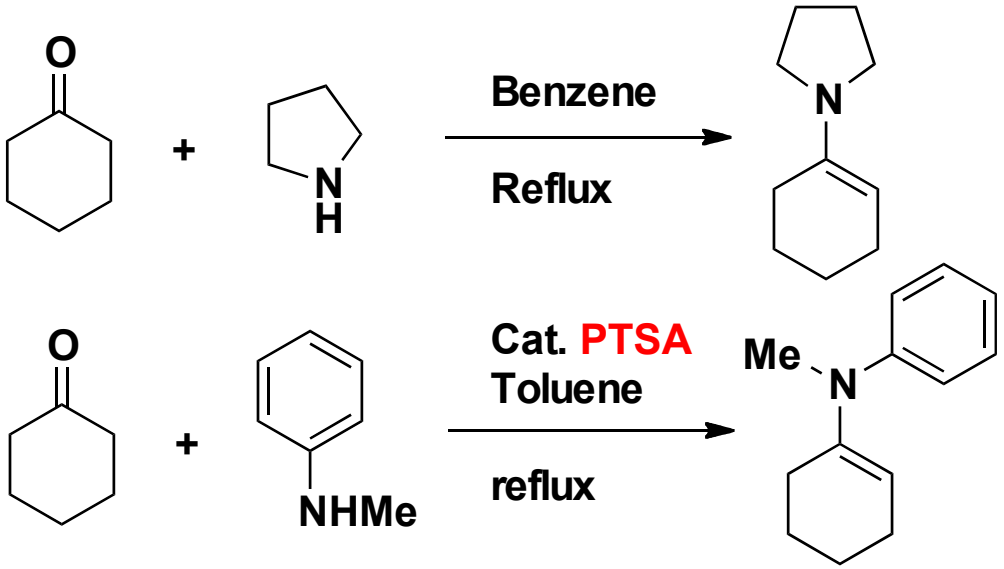
Condensation of secondary amine with aldehydes (ketones) affords enamine. G. Stork pioneered enamine chemistry in 1950's.



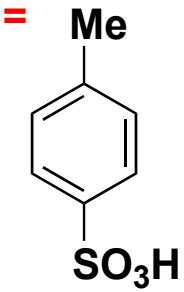
Enamine preparation: By condensation of carbonyl with amine, often in the presence of dehydrating agent such as $MgSO_4$, Na_2SO_4, molecular sieves or by Dean-Stark azeotropic removal of H_2O.

With nucleophilic amine (aliphtaic amines), the condensation proceed in the absence of acid catalyst

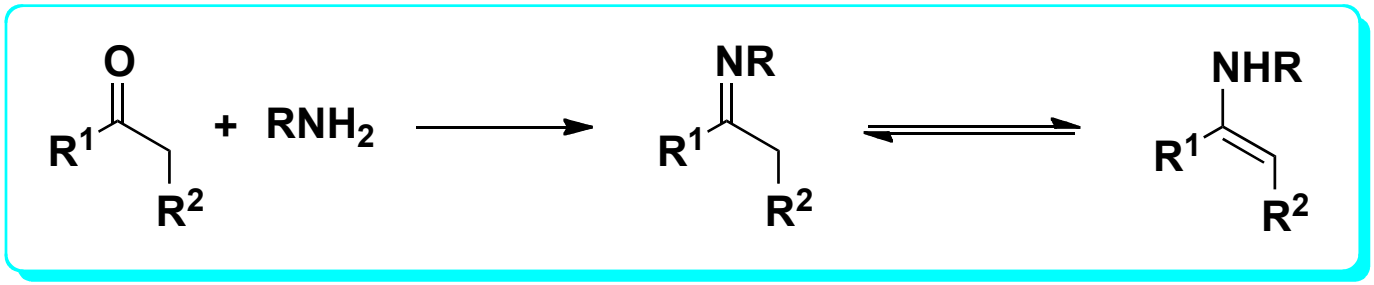
With aniline, an acid catalyst is required.



PTSA =

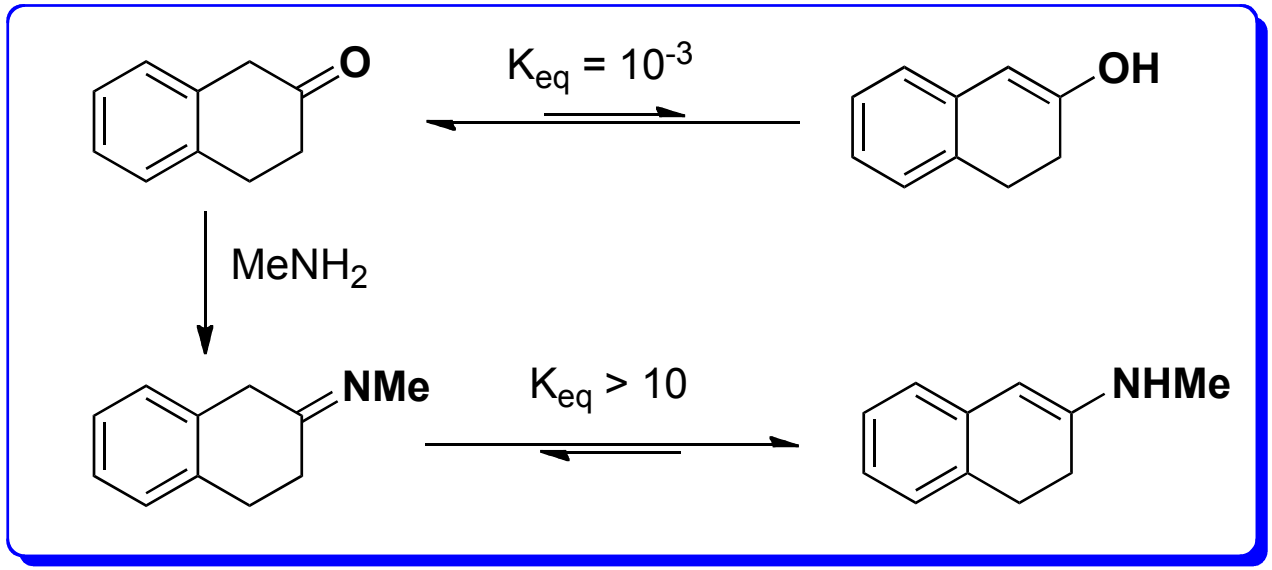


Equilibrium between Enamine and Imine



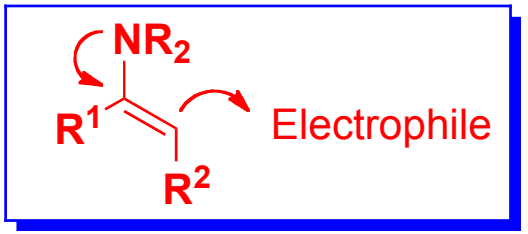
Imine tends to undergo rapid equilibrium with enamine, while ketone (aldehyde) is mch more stable than its enol form. It's understandable by looking at the bond energy:

C=C 146 kcal/mol
C=N 147 kcal/mol
C=O 172 kcal/mol

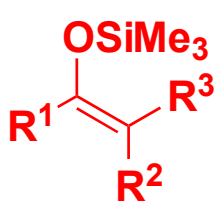


Enamine Reactivity

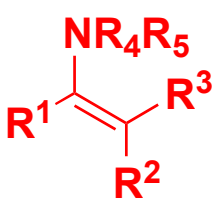
Enamine is structurally related to enol and is nucleophilic.
It readily undergoes the *C*-alkylation, aldolisation, *C*-acylation and Michael addition etc.



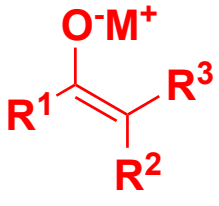
General ranking of nucleophilicity



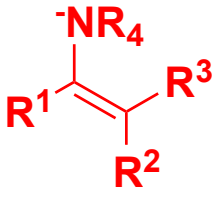
Silyl enol ether



Enamine



Enolate



Metalloenamine

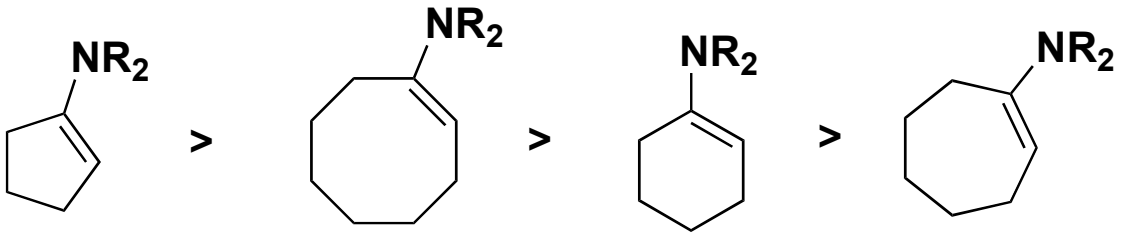
Nucleophilicity of the alpha-carbon

Enamine Reactivity

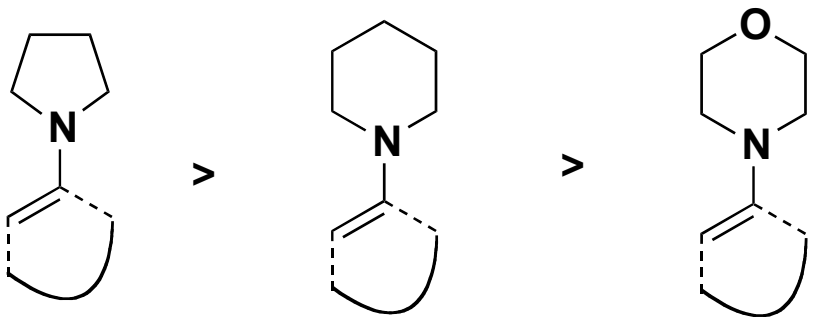
Enamine reactivity, depend on

a) The structure of carbonyl compounds
b) The structure of amines
c) Type of electrophiles
…….and reaction conditions

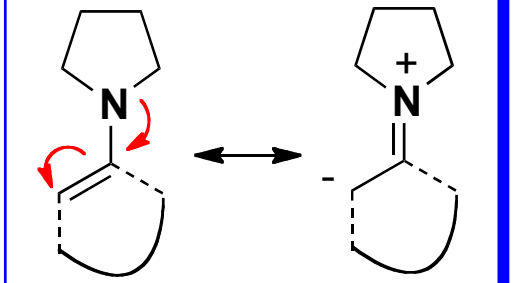
Cyclic ketone enamines



Reactivity of enamine derived from cyclic amine

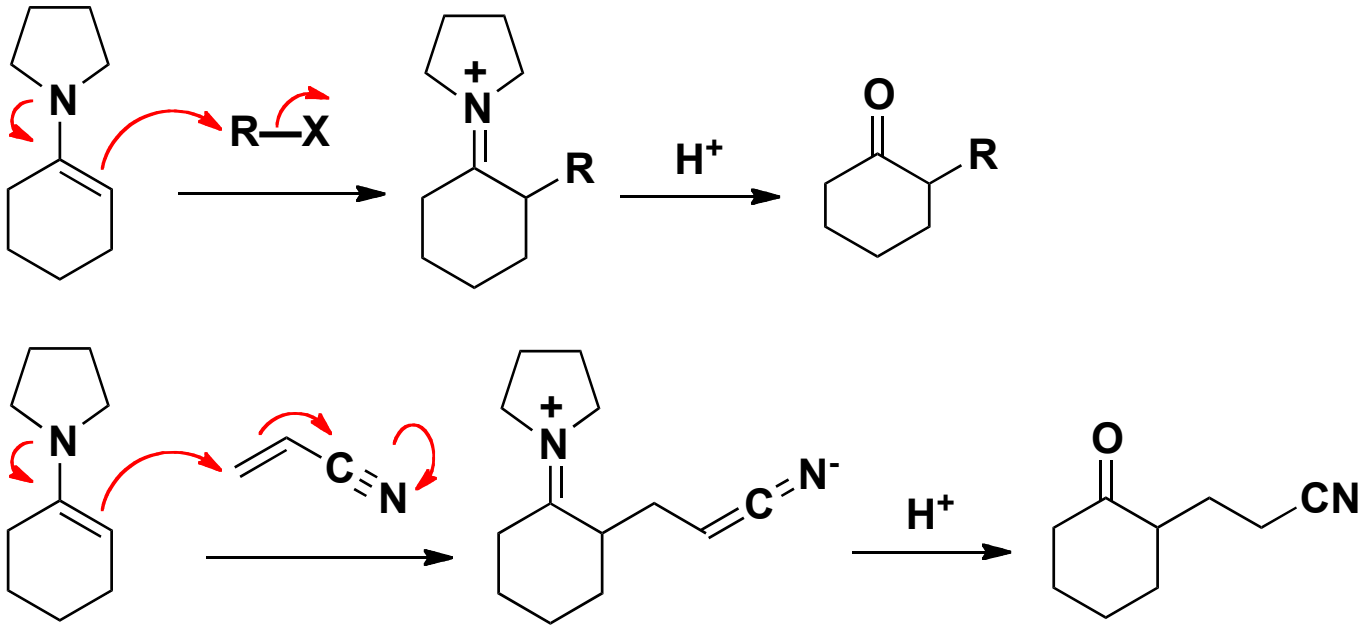


Increasing p characater of the N lon pair
Increasing p-π conjugation
Increasing nucleophilicity of β-carbon



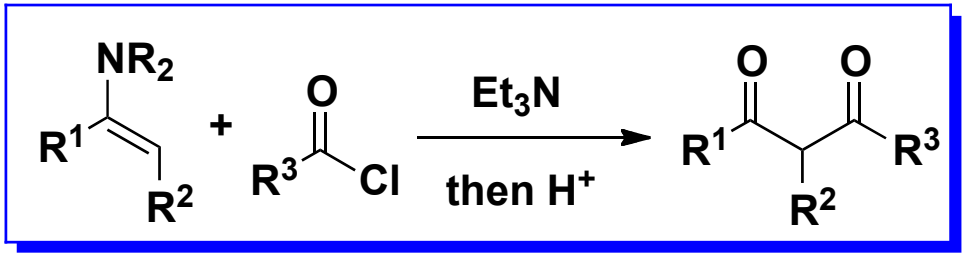
Enamine Reactivity

Enamine readily undergo the *C*-alkylation, aldolisation, *C*-acylation and Michael addition etc.

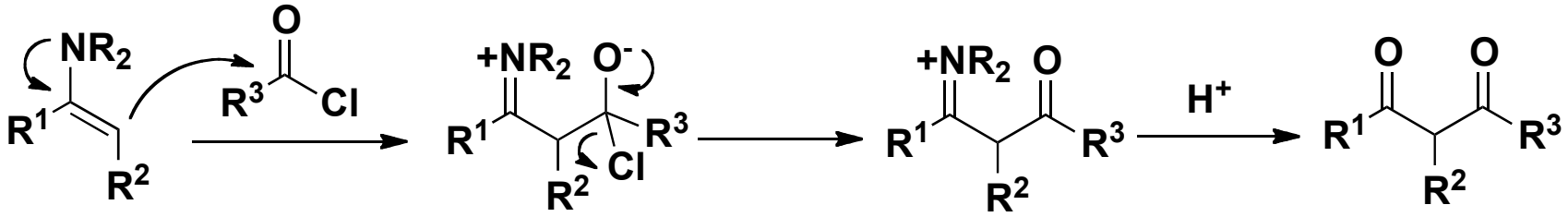


***Recent important advance in enamine chemistry*: In situ formation of enamine with a catalytic amount of chiral amine. Reaction became catalytic and enantioselective: This led to the now popular (and hot) field of organocatalysis.**

α-Acylation of Enamine



Mechanism:



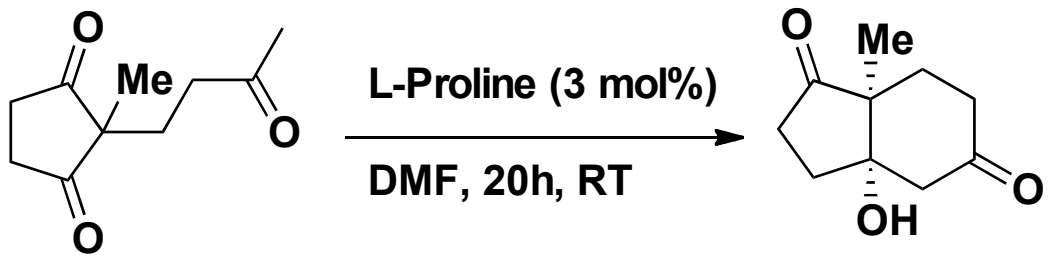
Note that:

a) Acylation of ***enolate*** with acyl chloride produce the stable enol ester as a major product.

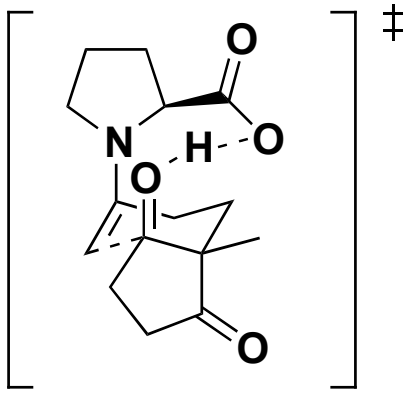
b) N-Acylation of ***enamine*** could take place as well. However, the resulting N-acylation product is unstable and the process is reversible. Acylation on the α-carbon, on the other hand, is irreversible.

Enamine-based catalytic enantioselective Transformations

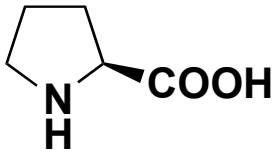
Synthesis of Hajos-Parrish ketone



Yield: quant; *ee*: 93%

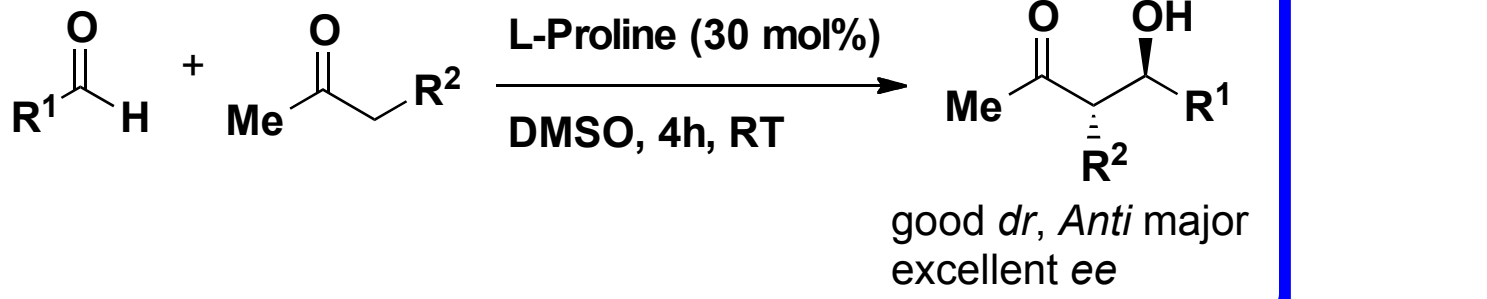


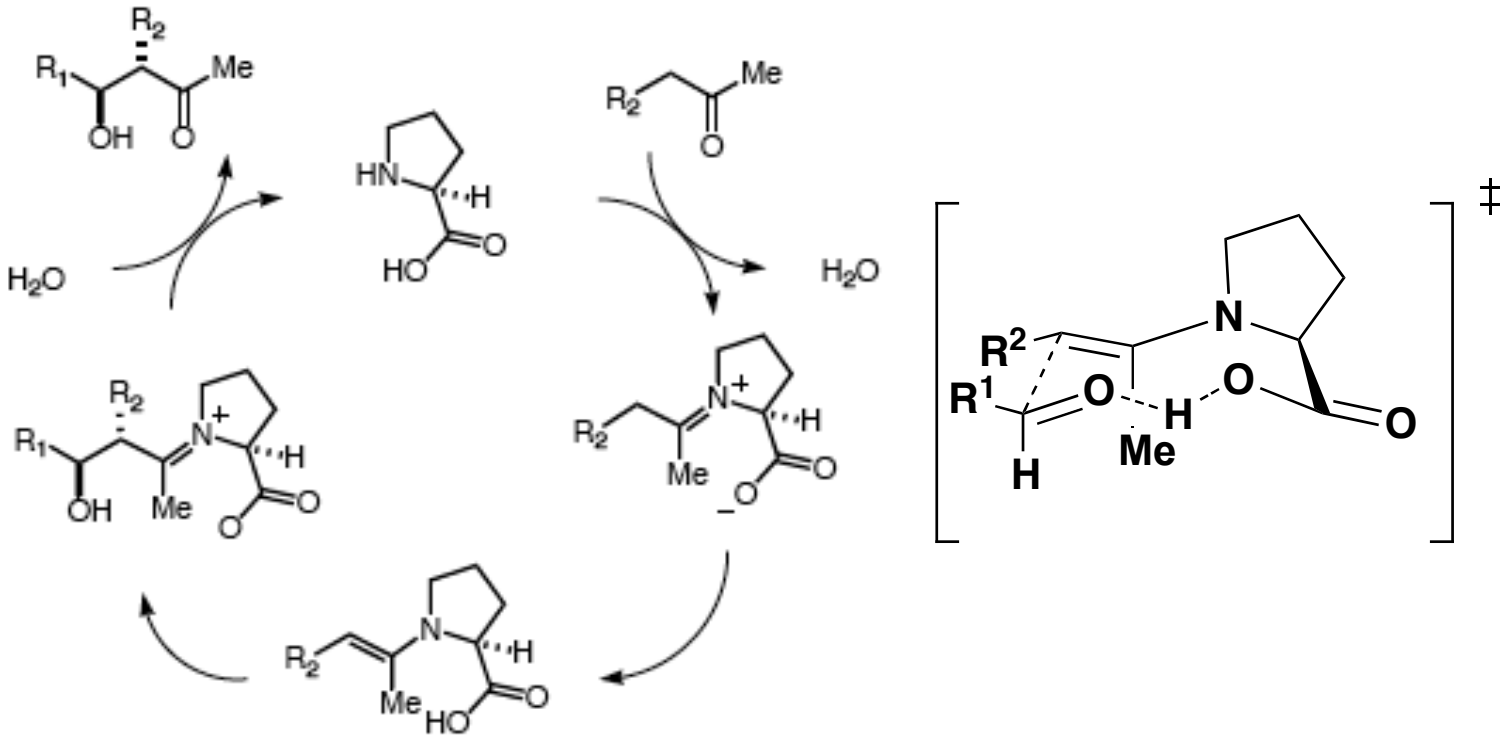
Structure of L-proline



L-Proline is a proteinogenic amino acid and is readily availble at lower cost.

Enantioselective Aldol





Enantioselective Mannich Reaction