

2302774 – Advance Organic Synthesis

Lecture 1

C–C Bond Formation – Enolate Chemistry 1

- Enol, enolates and their equivalents
- Alkylation
- Aldol reaction

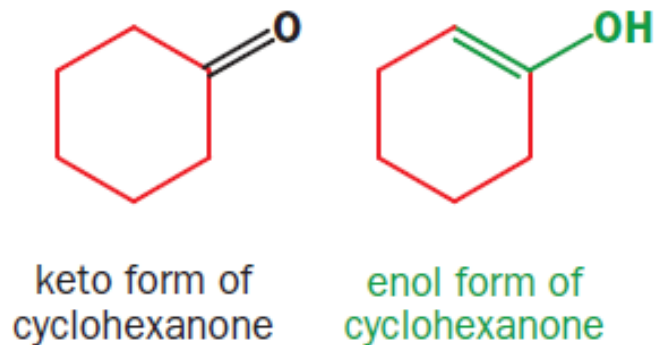
Instructor: Asst. Prof. Dr. Tanatorn Khotavivattana
E-mail: tanatorn.k@chula.ac.th

Recommended Textbook:

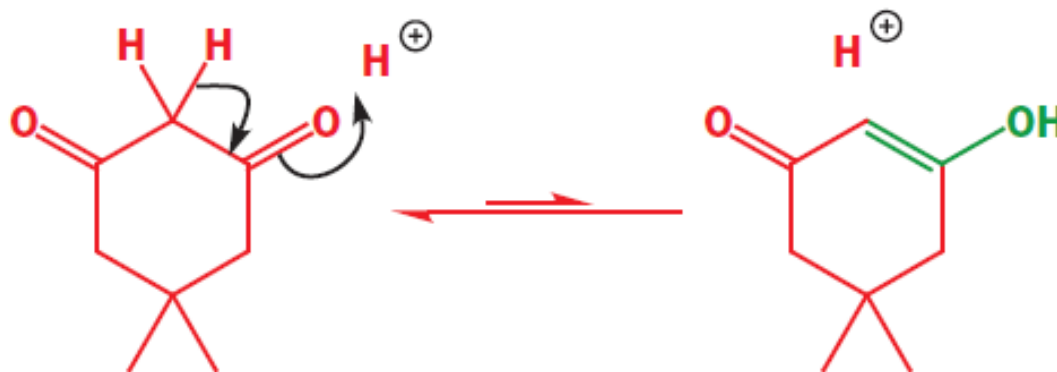
Chapter 21, 26 and 27 in *Organic Chemistry*, 1st Edition, J. Clayden, N. Greeves, S. Warren, **2001**, Oxford University Press

Keto-Enol Tautomerism

1



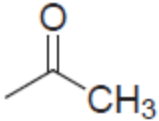
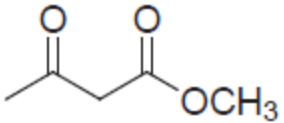
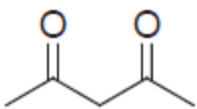
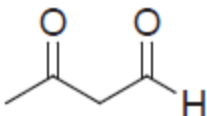
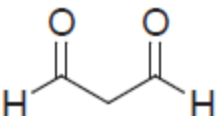
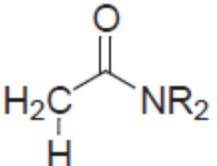
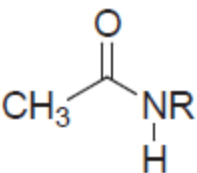
An enol has a **C=C double bond** and an **OH group** joined directly to it



In the case of dimedone, the enol must be formed by a **transfer of a proton** from the central CH₂ group of the keto form to one of the OH groups (**enolization**)

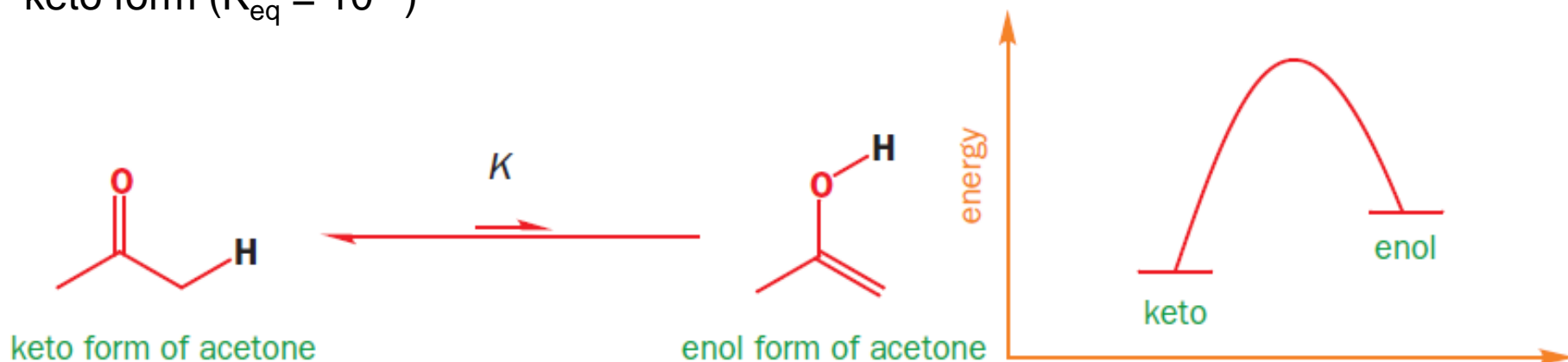
The only change is the transfer of one proton and the shift of the double bond. Reactions like this are given the name **tautomerism**

Keto-Enol Tautomerism

Compound	pK _a	Note
	20	
	13	} ketone better enolate stabilizer than ester
	11	
	9	
	5	~same as acetic acid
H ₂ O	14	
	25	
	15	

Why don't simple aldehydes and ketones exist as enols? ³

Simple carbonyl compounds like cyclohexanone or acetone have only a **trace of enol** present under ordinary conditions. The equilibrium lies well over towards the keto form ($K_{\text{eq}} = 10^{-6}$)



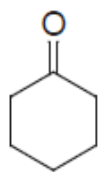
This is because the combination of a **C=C double bond and an O-H single bond** is (slightly) less stable than the combination of a **C=O double bond and a C-H single bond**

Typical bond strengths (kJ mol^{-1}) in keto and enol forms

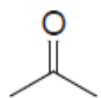
	Bond to H	π bond	Sum
keto form	(C-H) 440	(C=O) 720	1160
enol form	(O-H) 500	(C=C) 620	1120

Compound

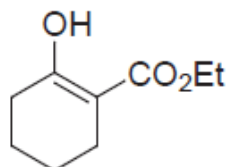
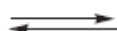
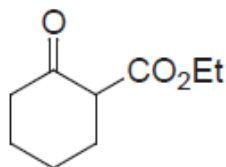
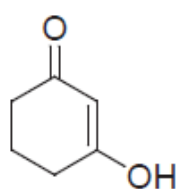
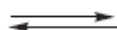
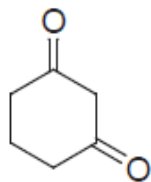
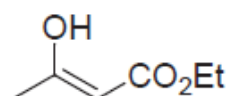
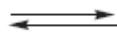
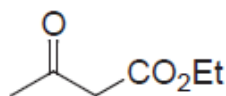
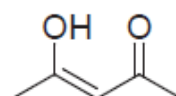
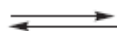
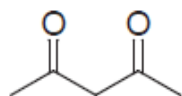
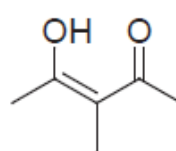
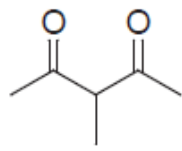
Enol content



0.0004%

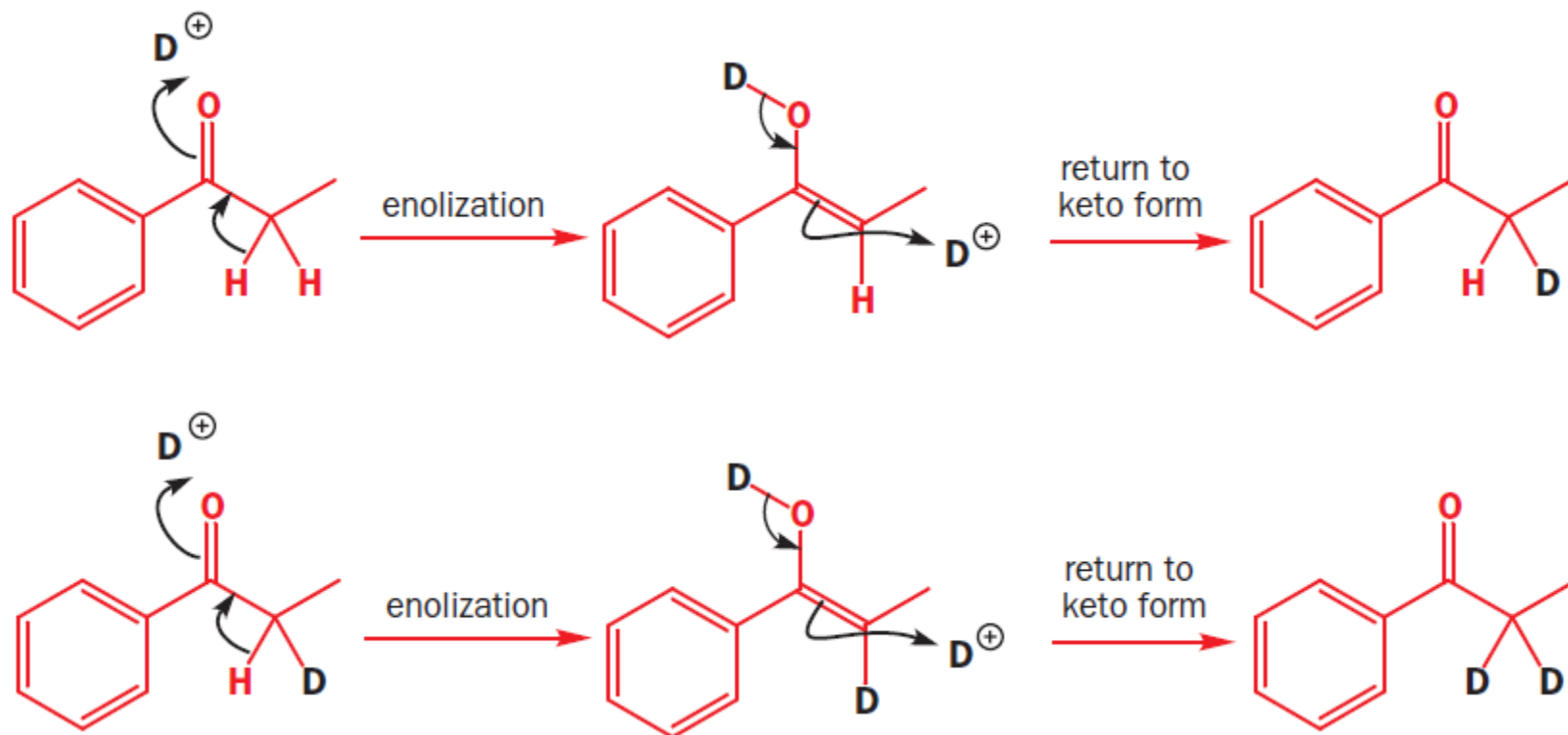


< 0.002%

40% (neat)
60% (EtOH)100% (neat)
95% (H₂O)
2-14% (cyclohexane)10-13% (EtOH)
50% (cyclohexane) ← intramolecular
H-bond16% (H₂O)
63% (EtOH)
92% (cyclohexane) ← intramolecular
H-bond3% (H₂O)
31% (EtOH)
55% (cyclohexane) ← intramolecular
H-bond

Evidence for Equilibration

If you run the NMR spectrum of a simple carbonyl compound in D_2O , the signal for protons next to the carbonyl group very **slowly disappears**

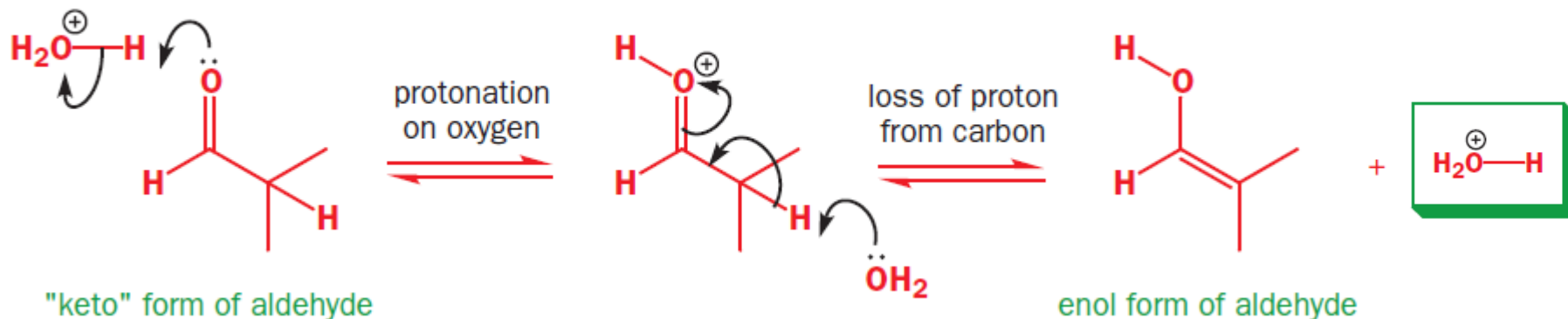


Notice that the double bond in this enol could be either *E* or *Z*. It is drawn as *Z* here, but in reality is probably a **mixture of both**

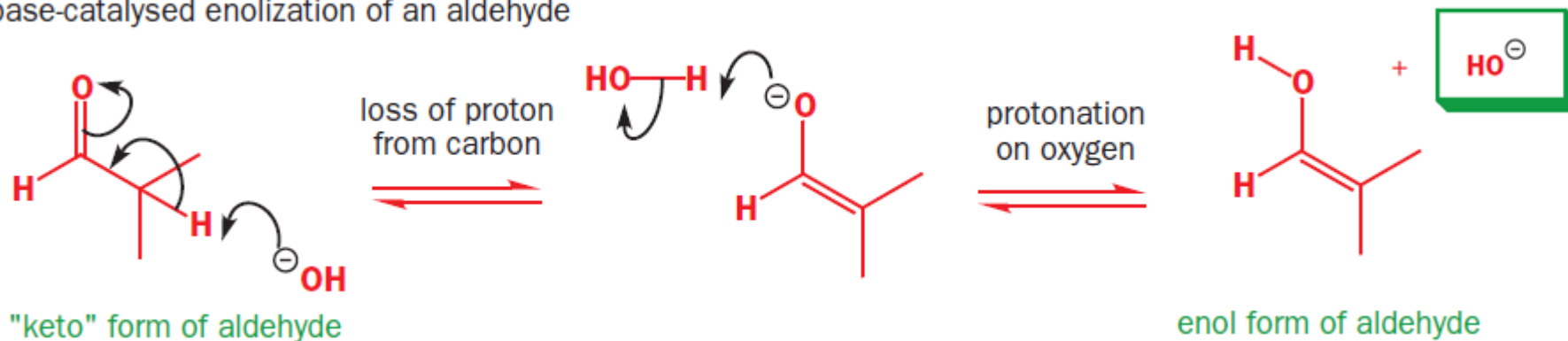
Enolization is catalysed by acids and bases

Enolization is, in fact, quite a **slow process** in **neutral** solution. However, it can be catalysed with **acid** or **base** if we really wanted it to happen.

acid-catalysed enolization of an aldehyde

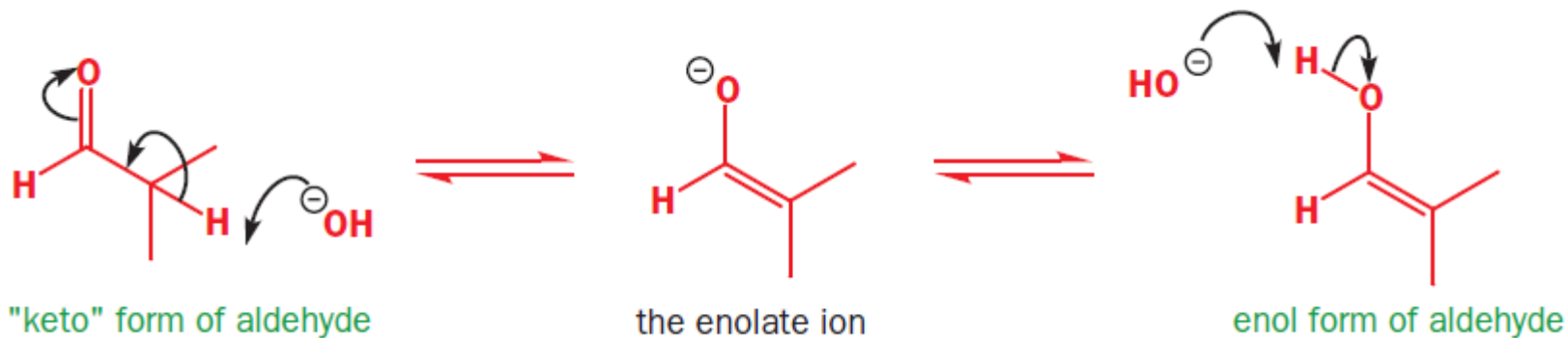


base-catalysed enolization of an aldehyde

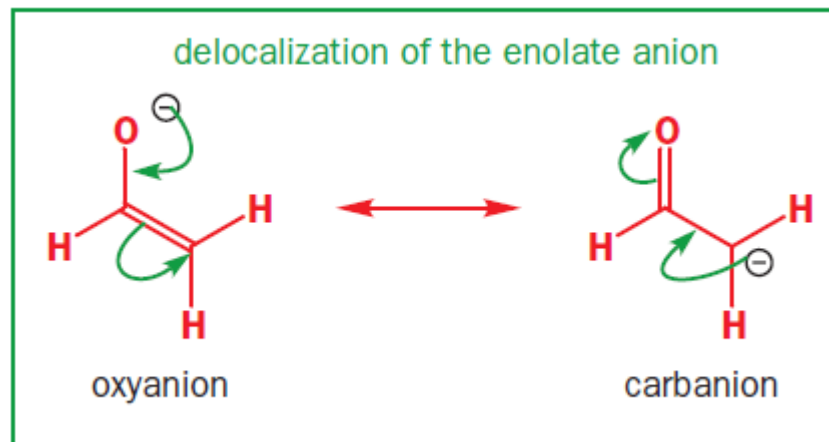
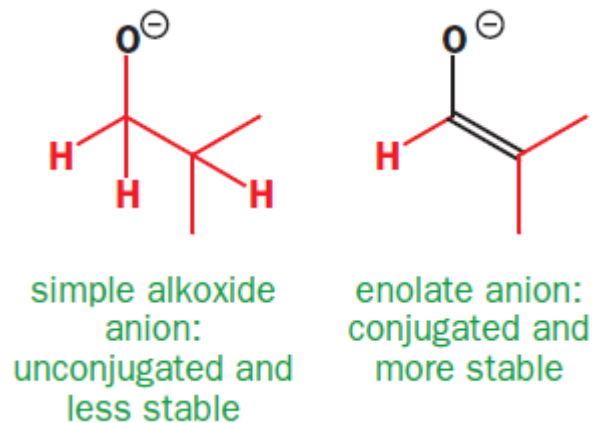


Enolate Ion

The intermediate in the base-catalysed reaction is the **enolate ion**. It is the **conjugate base of the enol** and can be formed either directly from the carbonyl compound by the loss of a C–H proton or from the enol by loss of the O–H proton



The enolate ion is an **alkoxide ion** as we have drawn it, but it is **more stable** than the corresponding saturated structure because it is **conjugated**



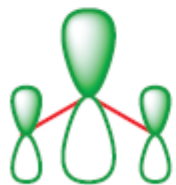
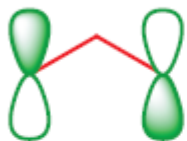
Enolate Ion

Because oxygen is more electronegative, both orbitals go **down in energy** compared to that of allyl anion. The orbitals are also **distorted**. The lower-energy atomic orbital of the more electronegative oxygen contributes more to the lower-energy orbital (Ψ_1)

populated π orbitals of the allyl anion



reactive
HOMO



populated π orbitals of the enolate anion



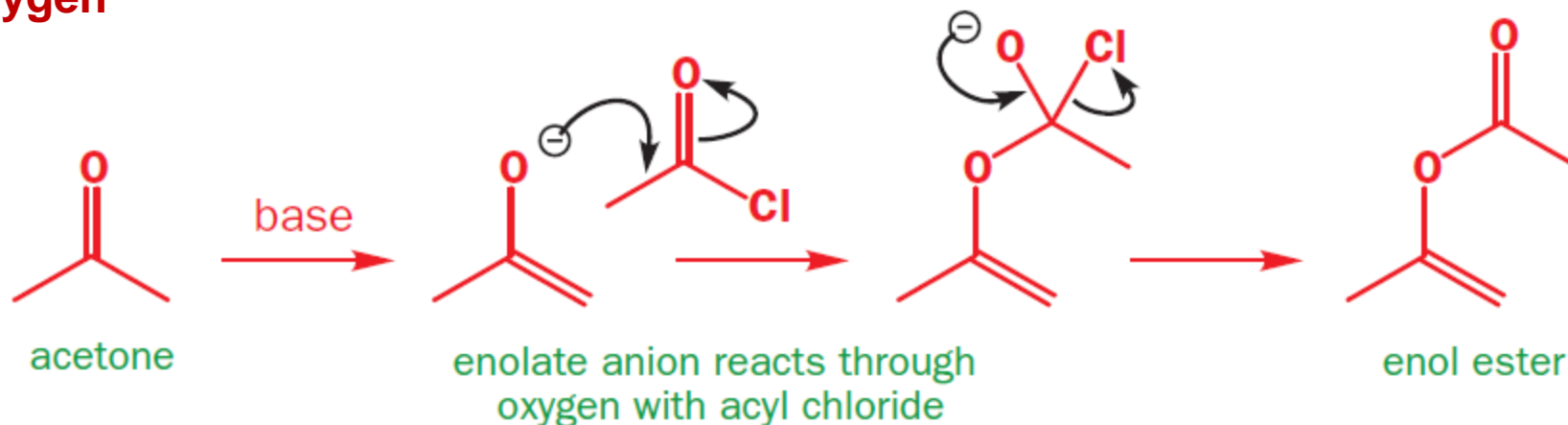
reactive
HOMO



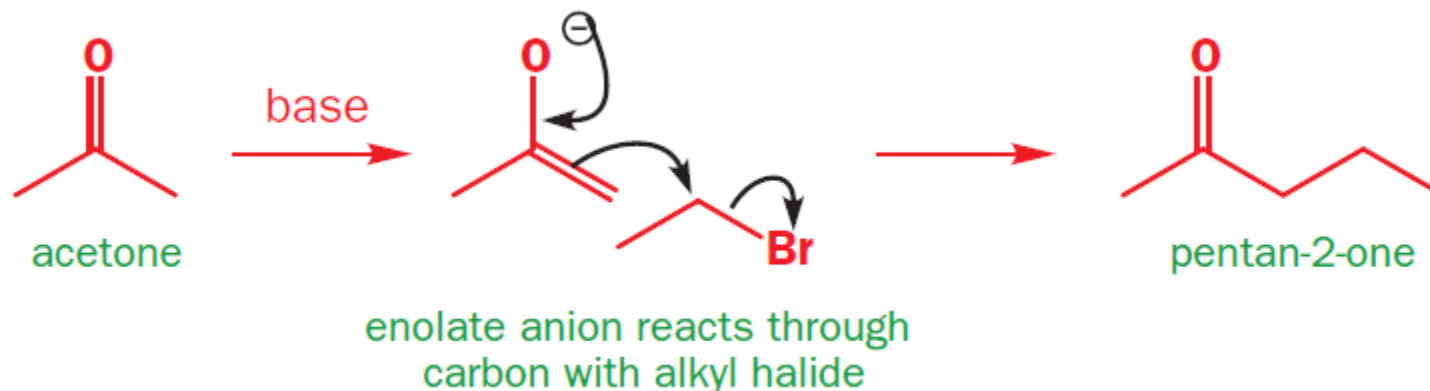
The important reactive orbital is the **HOMO** (Ψ_2) which has the **larger orbital** on the **terminal carbon atom**

Enolate Ion

In the enolate, the oxygen atom has more of the negative charge, but the carbon atom has more of the HOMO. One important consequence is that we can expect reactions dominated by **charges** and **electrostatic** interactions to occur on **oxygen**



and reactions dominated by **orbital interactions** to occur on **carbon**

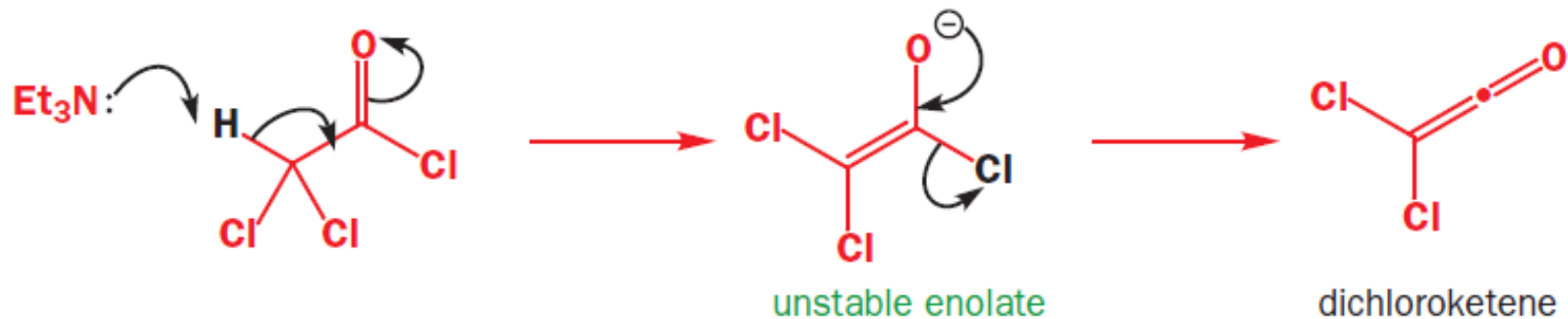


Types of Enol and Enolate

All the acid derivatives can form enols of some kind. Those of **esters** are particularly important and either enols or enolates are easily made. It is obviously necessary to **avoid water in the presence of acid or base (hydrolysis)** One solution is to use the **alkoxide belonging to the ester**



Acyl chlorides can be **enolised very easily** (as it is very electrophilic); To avoid nucleophilic attack, we use **nonnucleophilic base** such as a tertiary amine



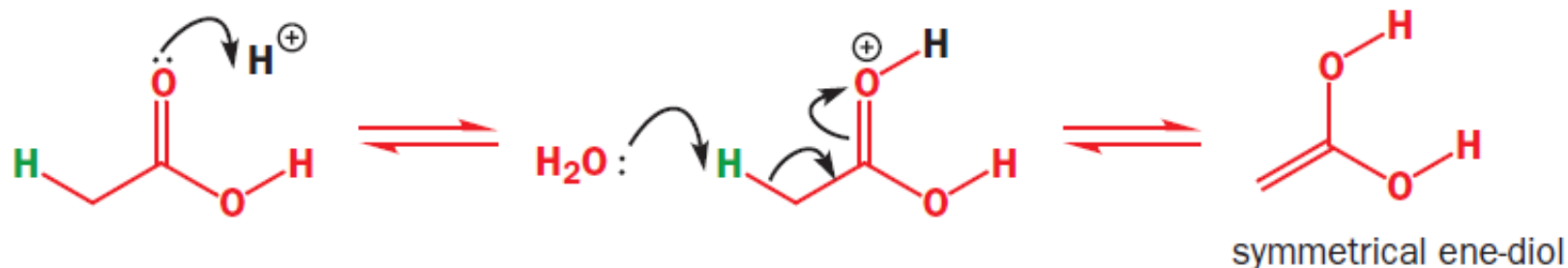
The resulting enolate is **not stable** as it can eliminate chloride ion, a good leaving group, to form a **ketene**

Types of Enol and Enolate

Carboxylic acids do not form enolate anions easily as the **base** first removes the acidic OH proton



In **acid** solution, there are no such problems and 'ene-diols' are formed



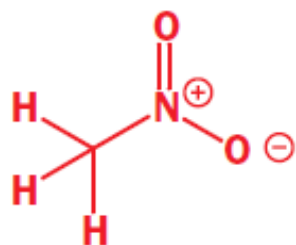
Amides also have rather acidic protons. Attempted enolate ion formation in base removes an N-H proton rather than a C-H proton. Amides are also the **least enolisable**, and their enols and enolates are rarely used in reactions



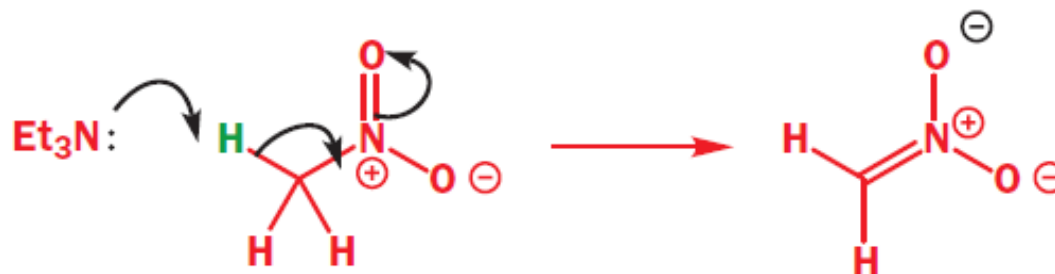
Types of Enol and Enolate

Nitroalkanes form enolate-like anions in quite weak base

nitromethane

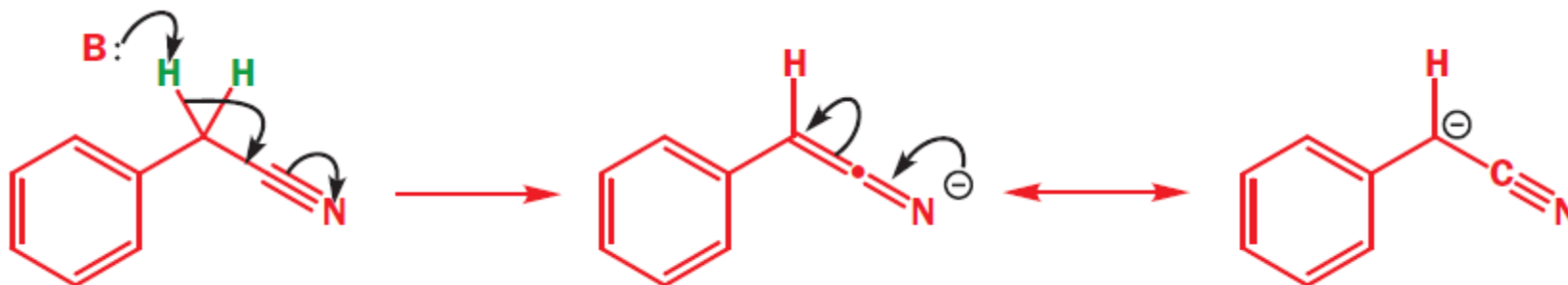
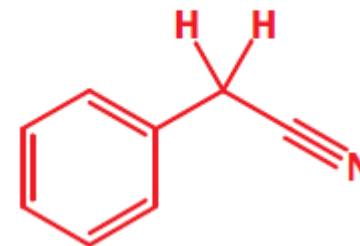


formation of nitromethane anion in base



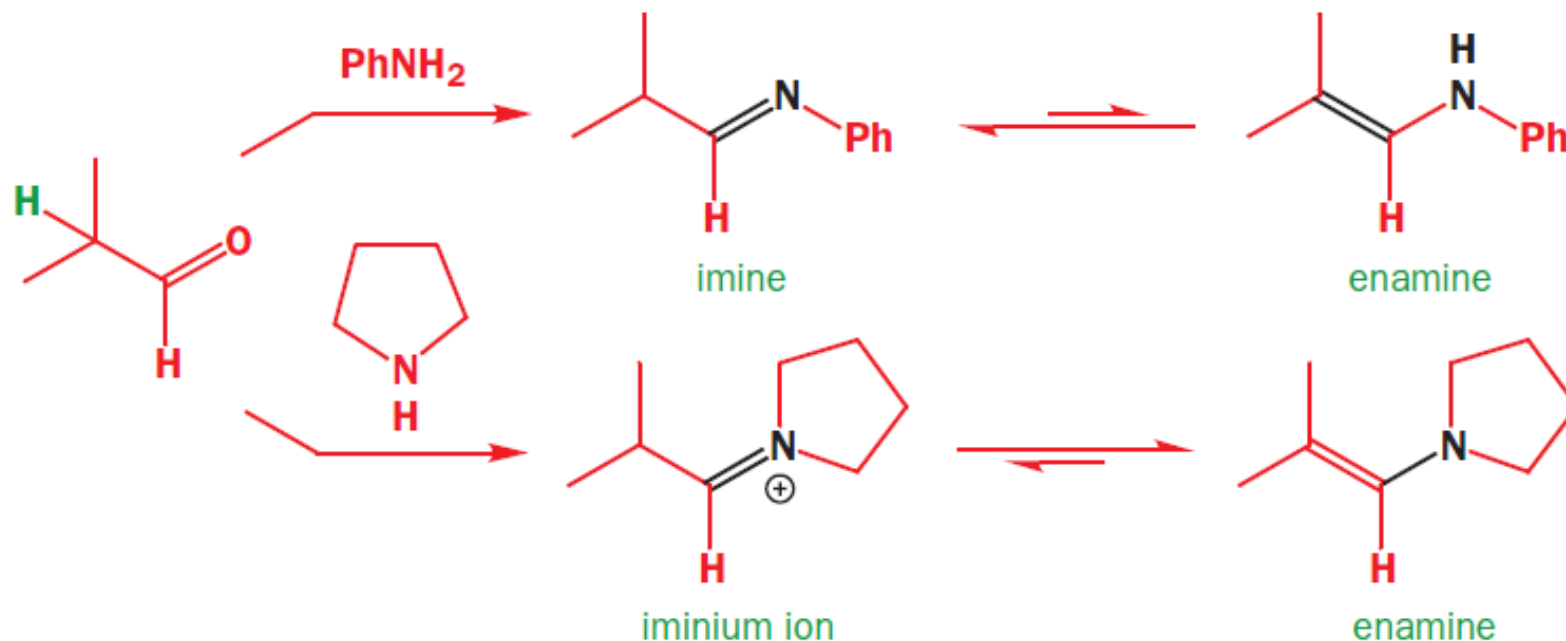
Nitriles (cyanides) also form anions but require **stronger base** as the negative charge is delocalized on to a single nitrogen atom rather than on to two oxygen atoms. The negative charge is mostly on a nitrogen atom

benzyl cyanide
(phenylacetonitrile)



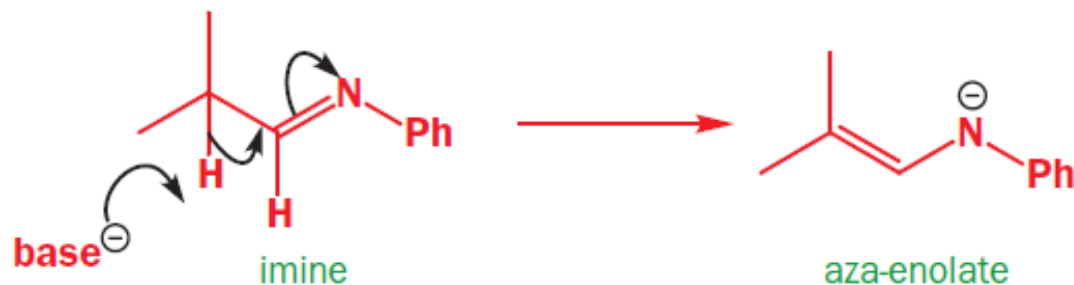
Types of Enol and Enolate

Imines and **enamines** are related by the same kind of **tautomeric equilibria**



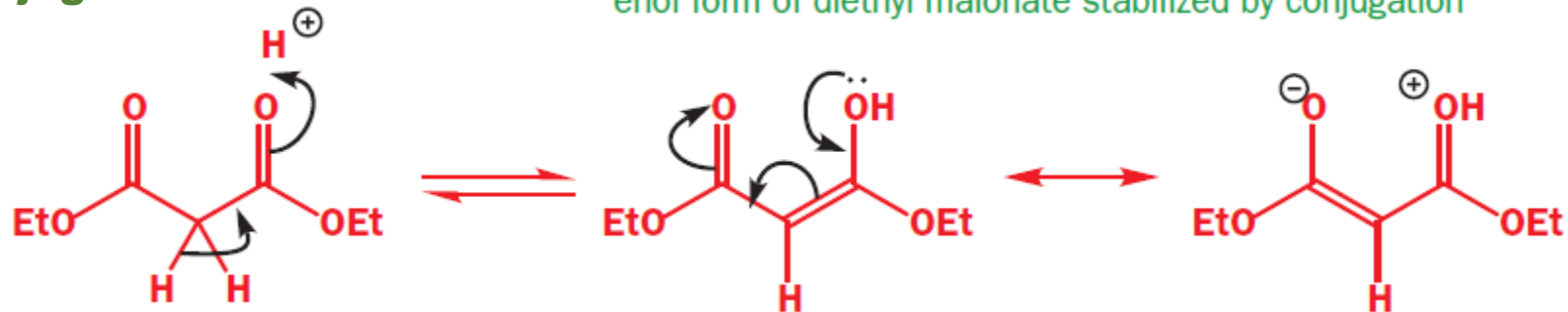
With a **primary amine** a reasonably stable **imine** is formed, but with a **secondary amine** the imine itself cannot be formed and the **iminium** salt is less stable than the **enamine**

Aza-enolates are the nitrogen analogues of enolates. They are made by **deprotonating enamines with strong base**

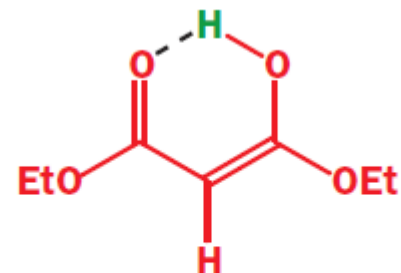


Thermodynamically Stable Enols

The enols of 1,3-dicarbonyl compounds are relatively more stable due to **conjugation**



In some examples there is an additional stabilizing factor, **intramolecular hydrogen bonding**



enol form of diethyl malonate stabilized by an intramolecular hydrogen bond

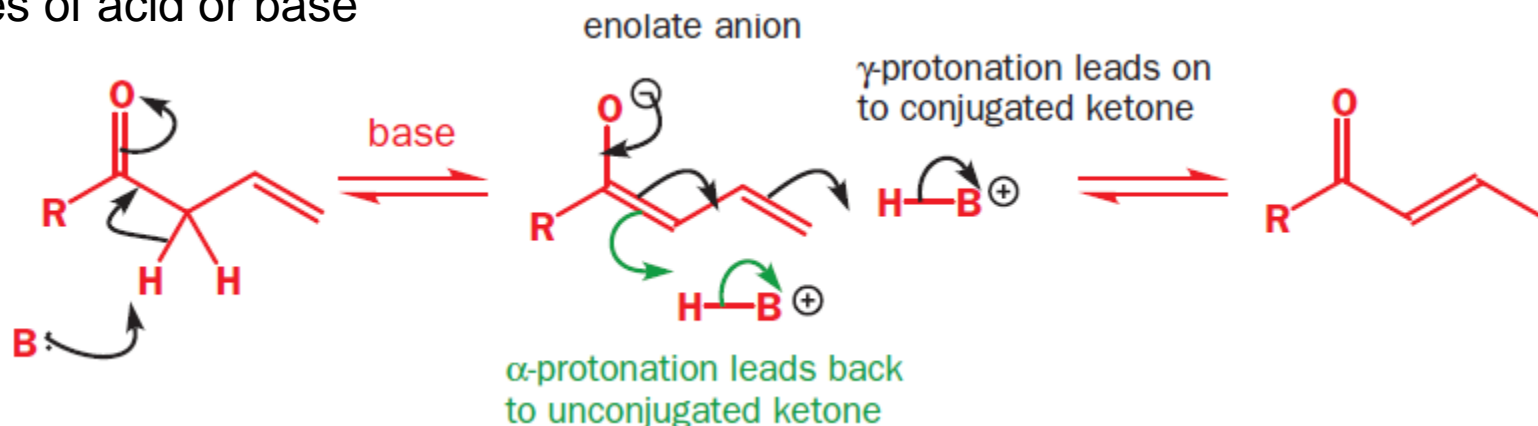
The ultimate in stable enols has to be the phenol which prefer the substantial advantage of **aromaticity**. They exist entirely in the phenol form

"ketonization" of phenol (not observed)



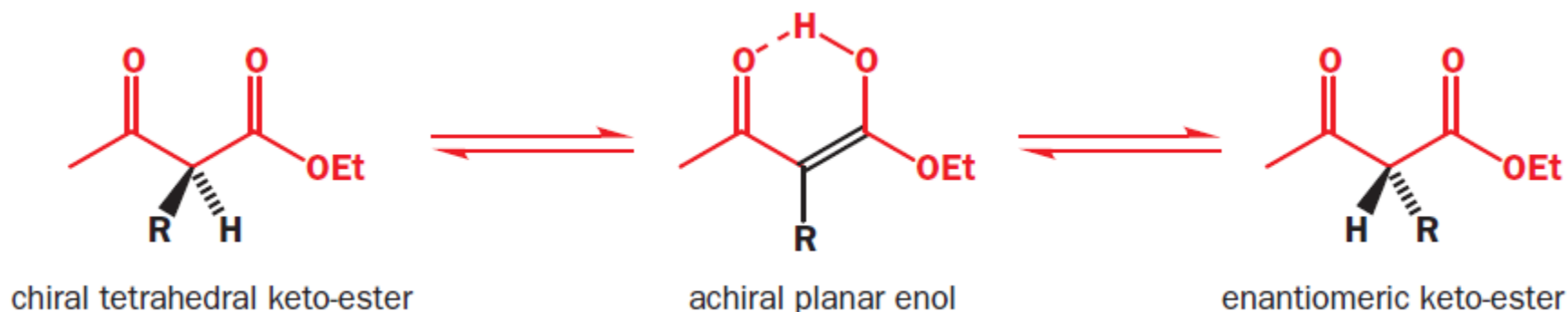
Unsaturated carbonyl compounds prefer to be conjugated

It is difficult to keep a **β,γ -unsaturated carbonyl compound** because the double bond tends to **move into conjugation** with the carbonyl group in the presence of traces of acid or base



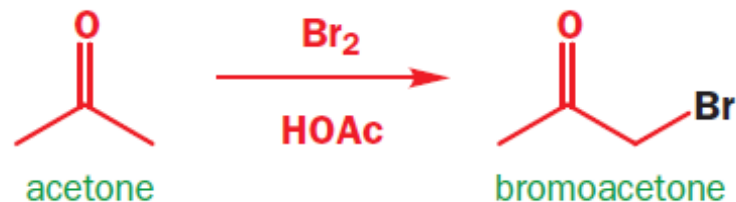
Racemization

Any **stereogenic centre** next to a carbonyl group is precarious because enolization will destroy it

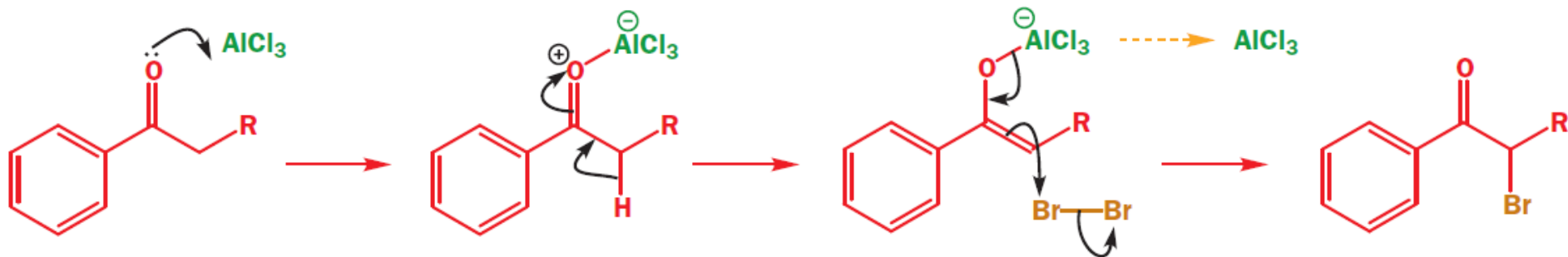
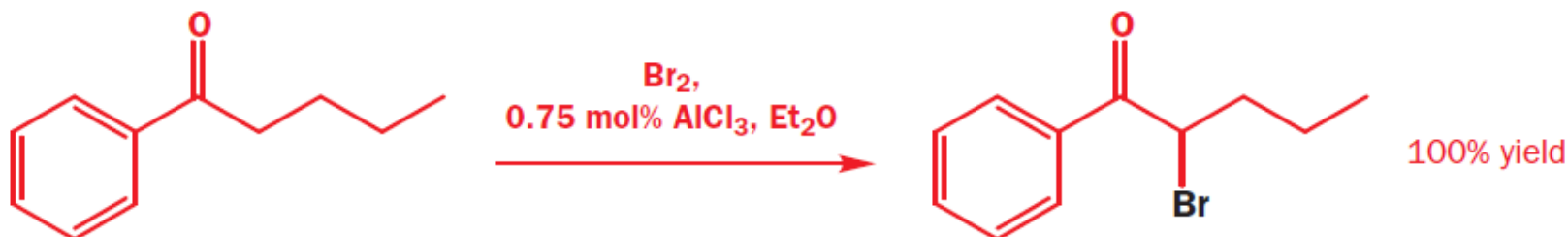


Acid-catalysed Halogenation

Carbonyl compounds can be **halogenated** in the **α position** by halogens (such as bromine, Br_2) in **acidic** or **basic** solutions

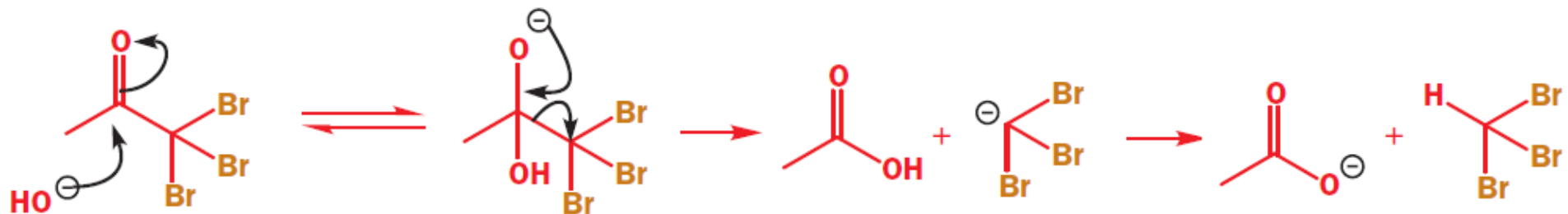
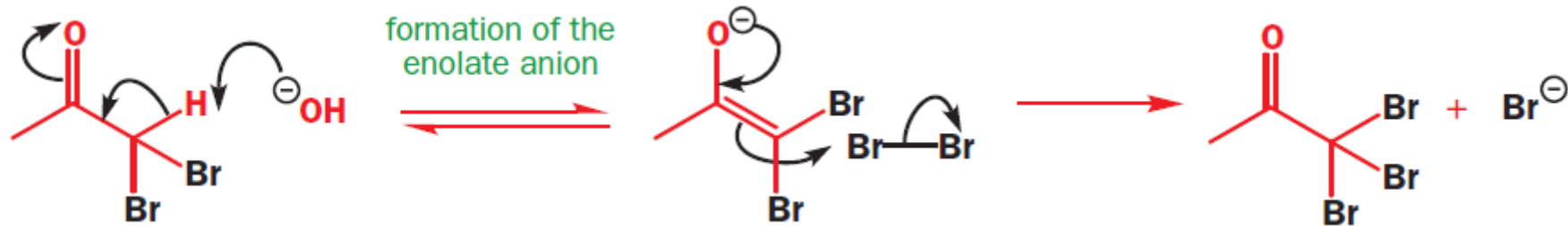
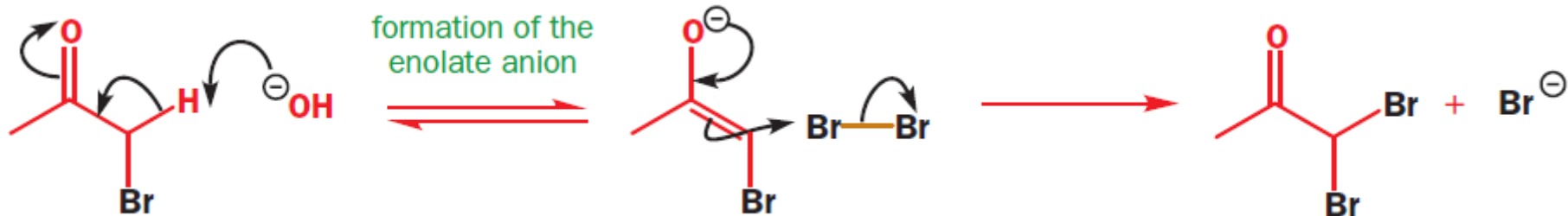


Lewis acids make excellent catalysts for the bromination of ketones



Reactions of Enols or Enolates

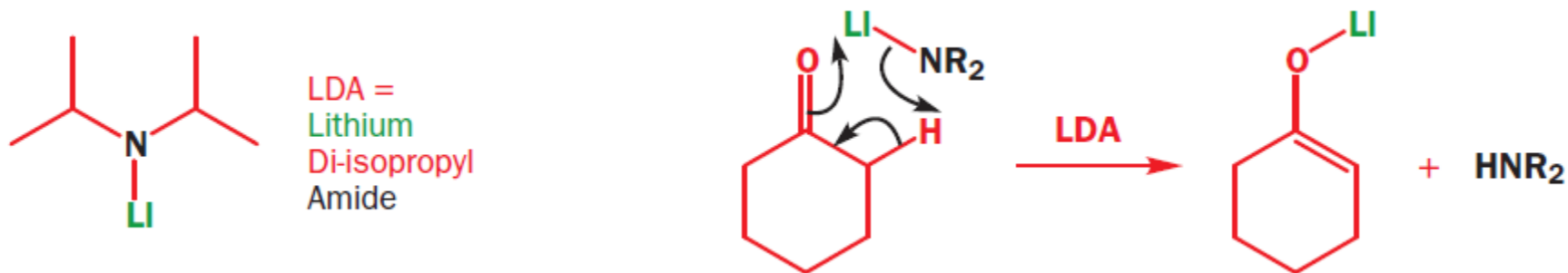
Base-catalysed Halogenation



Stable Enolate Equivalents

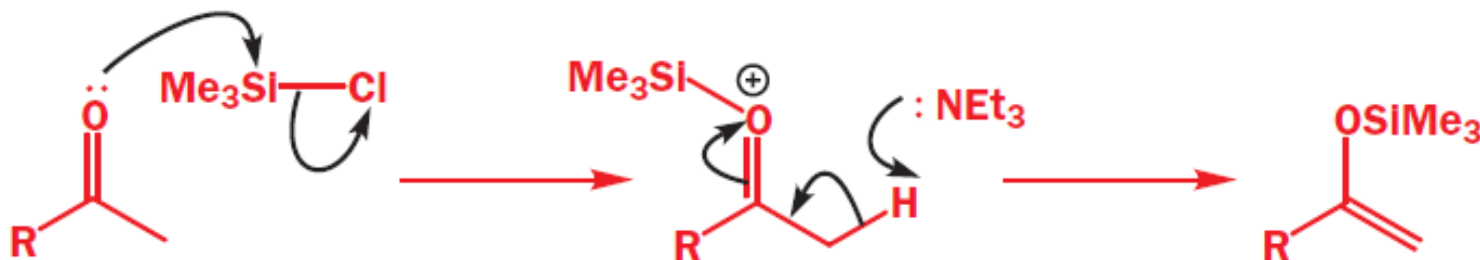
Even with fairly strong bases such as hydroxides or alkoxides, most carbonyl compounds are converted to their enolates only to a **very small extent**

With a much stronger base like **LDA**, the **lithium enolate** is formed **quantitatively** from the carbonyl compound; it is stable at low temperature (**-78 °C**)

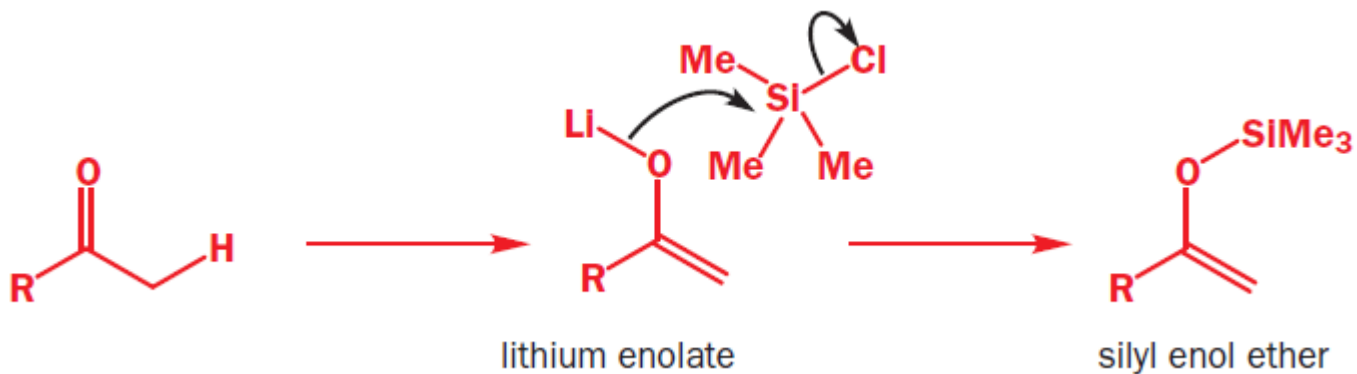


Lithium enolates are the most commonly used enolate equivalents in chemistry

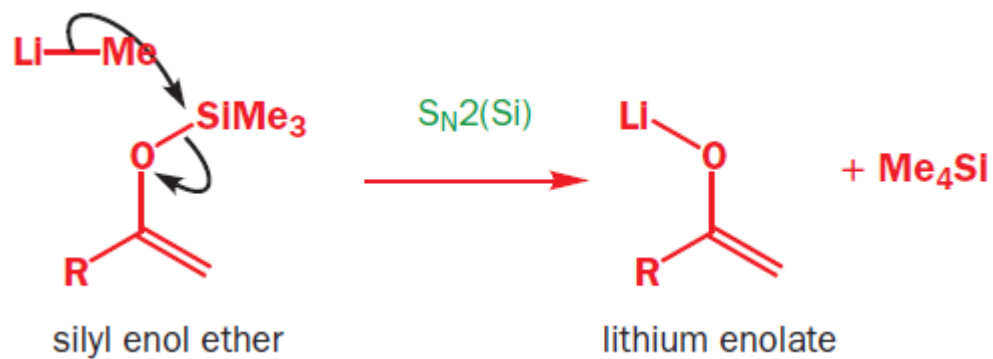
Second in usefulness are **silyl enol ethers**. Silicon is less electropositive than lithium, and silyl enol ethers are **more stable**, but **less reactive**. They are made by treating an enolate with a **silicon electrophile** and a **weak base**



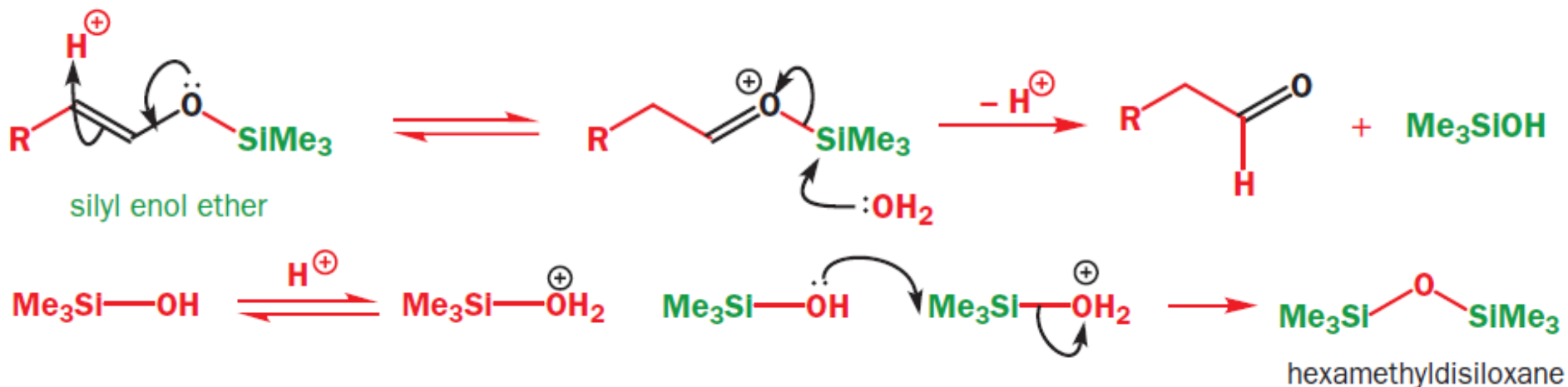
1) Conversion of lithium enolates to silyl enol ether



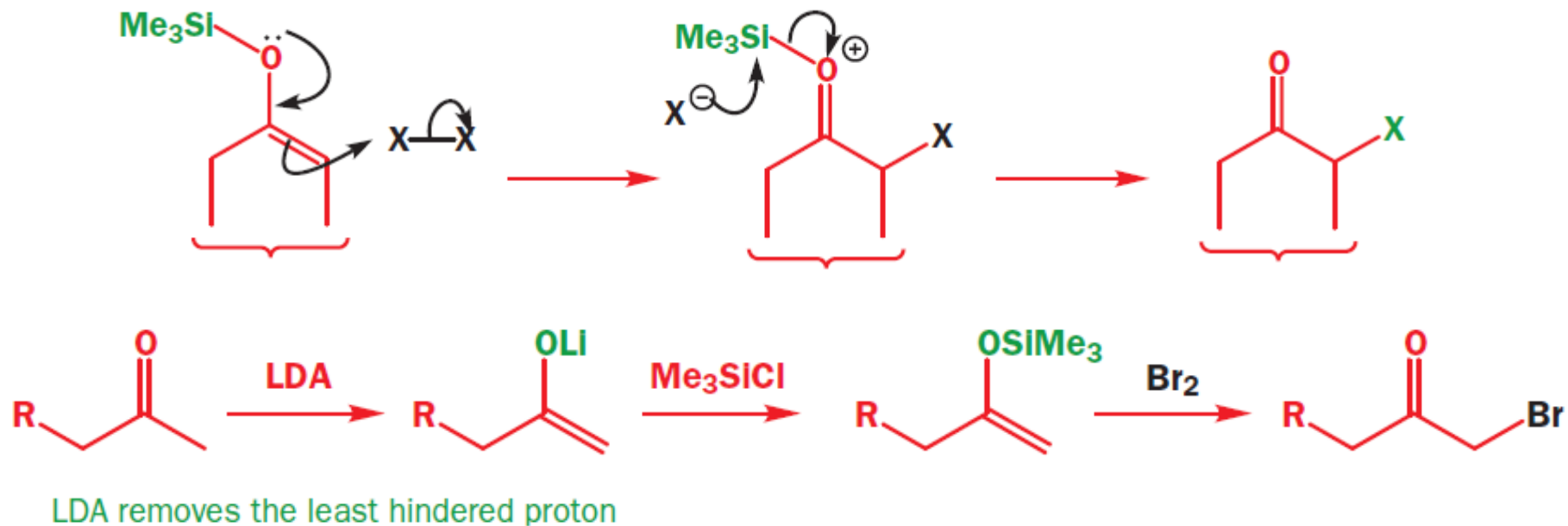
2) Conversion of silyl enol ether to lithium enolates



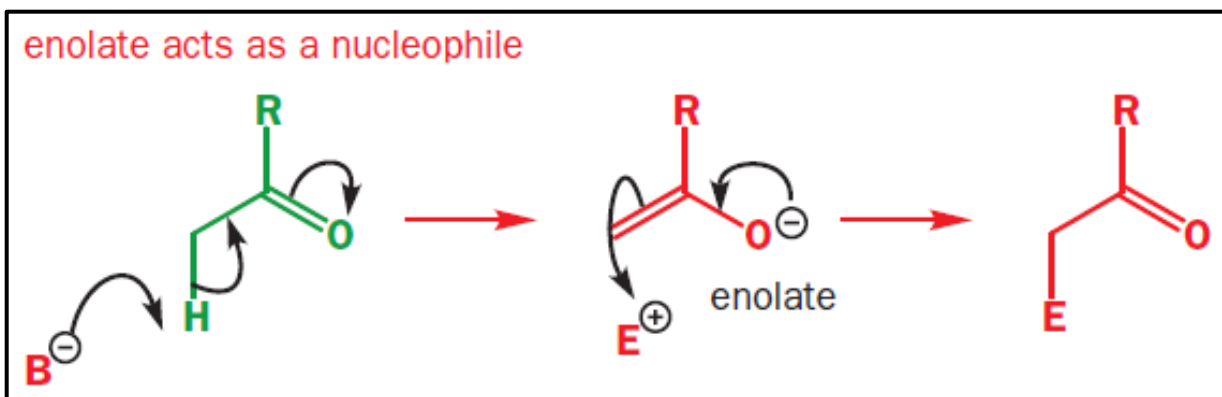
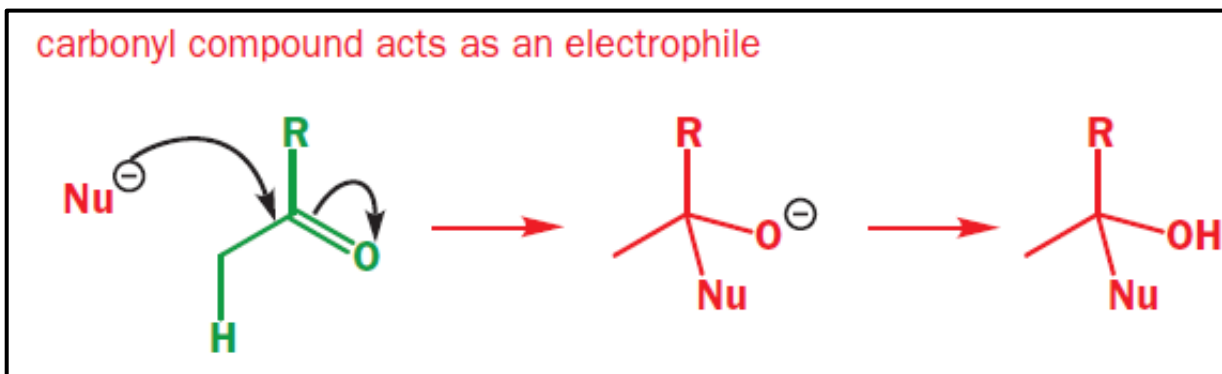
3) Hydrolysis of silyl enol ethers



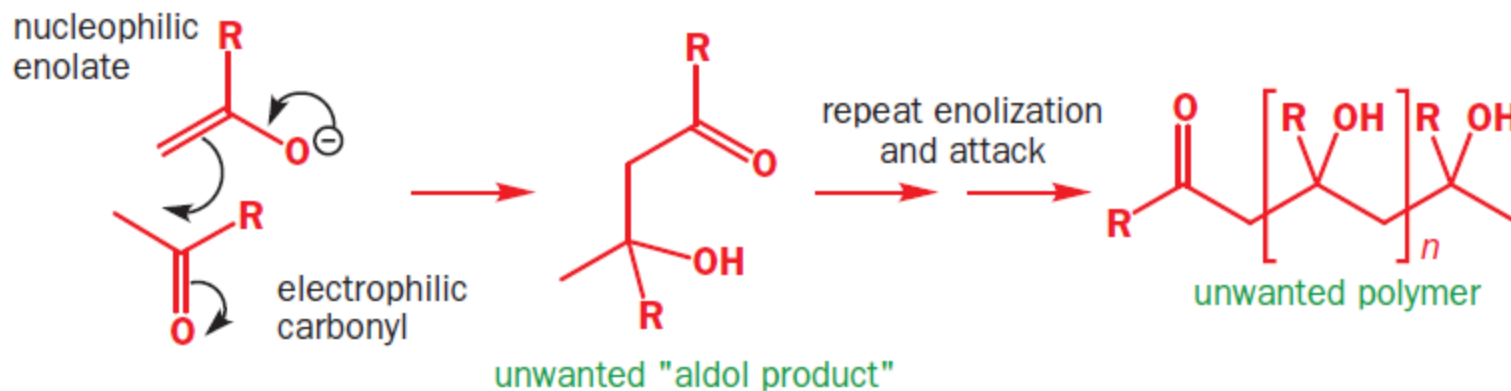
4) Reaction with electrophiles



C–C Bond Formation: Alkylation



aim to avoid an unwanted dimerization: the aldol reaction

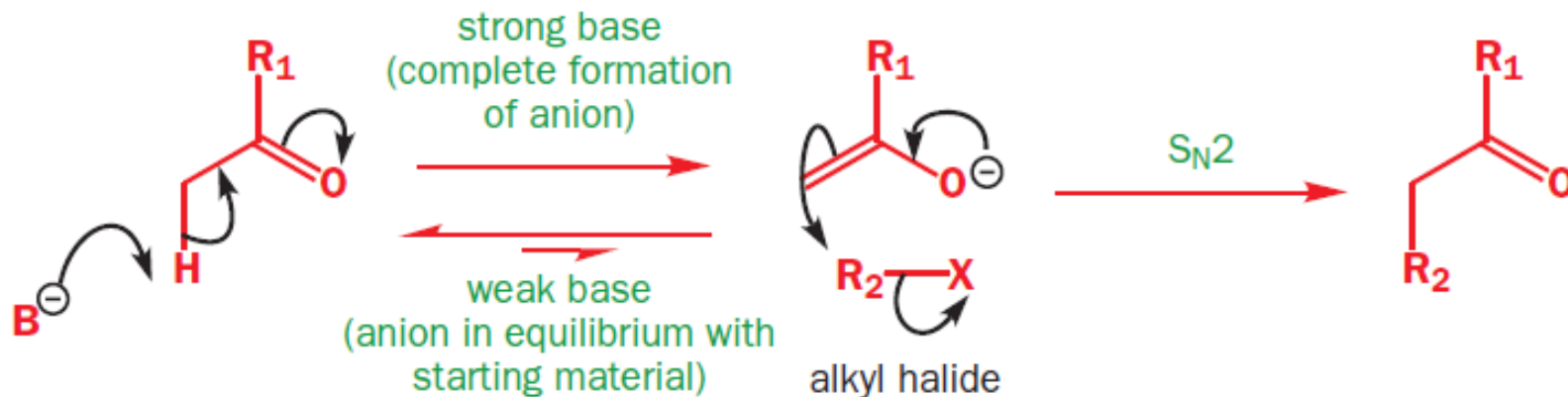


C–C bond formation: Alkylation

These reactions consist of two steps

step 1: formation of enolate anion

step 2: alkylation (S_N2 reaction with alkyl halide)

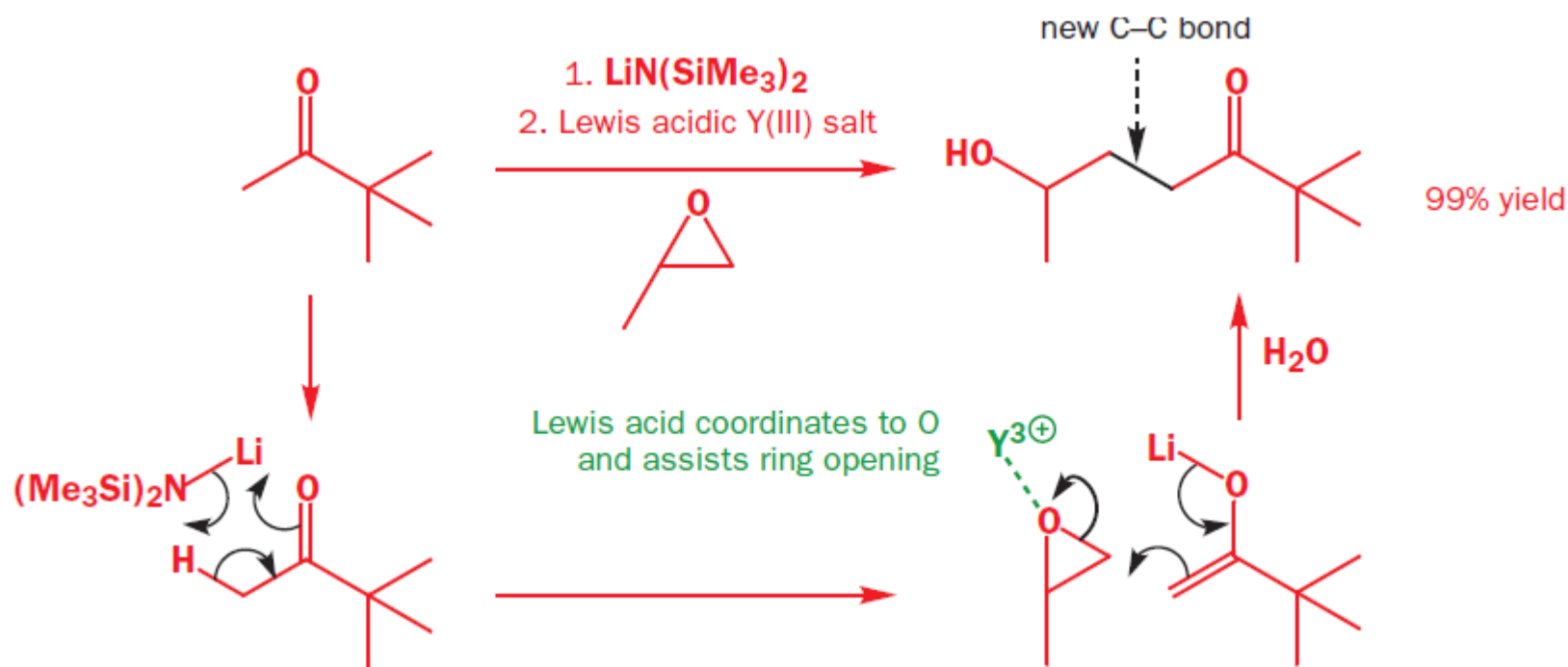
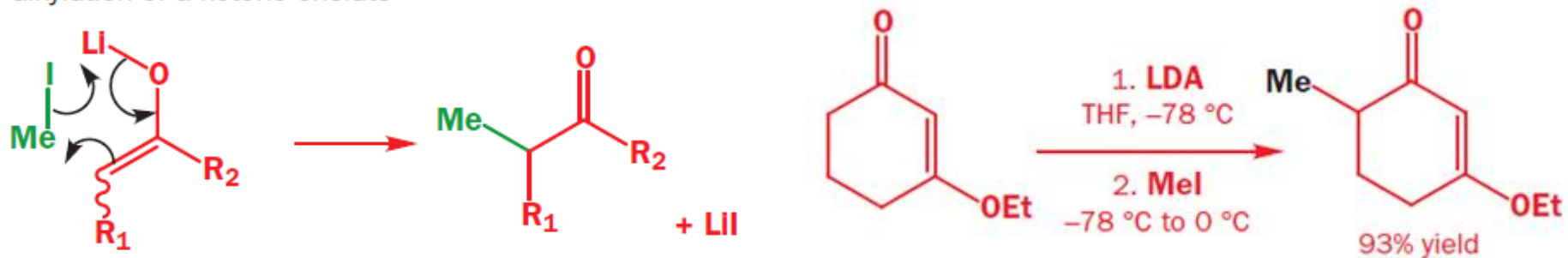


We shall take one of two approaches to the choice of base

- **Complete conversion** of the starting material to the anion (using **strong base**) before addition of the electrophile, which is added in a **subsequent step**
- **Weaker base** may be used **in the presence of the electrophile**;
[Advantage: easier practically]
[Disadvantage: works only if the base and the electrophile are compatible + risk of aldol by-products]

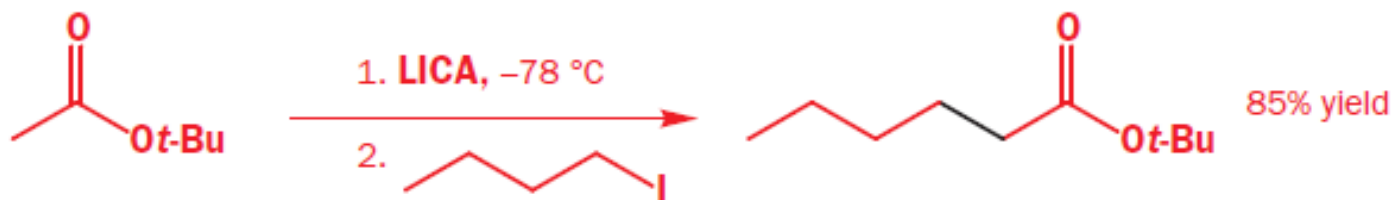
Ketones

alkylation of a ketone enolate

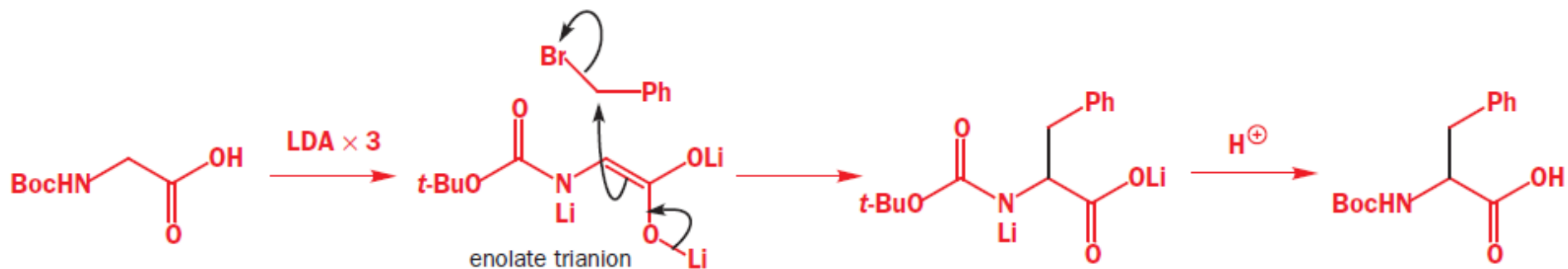
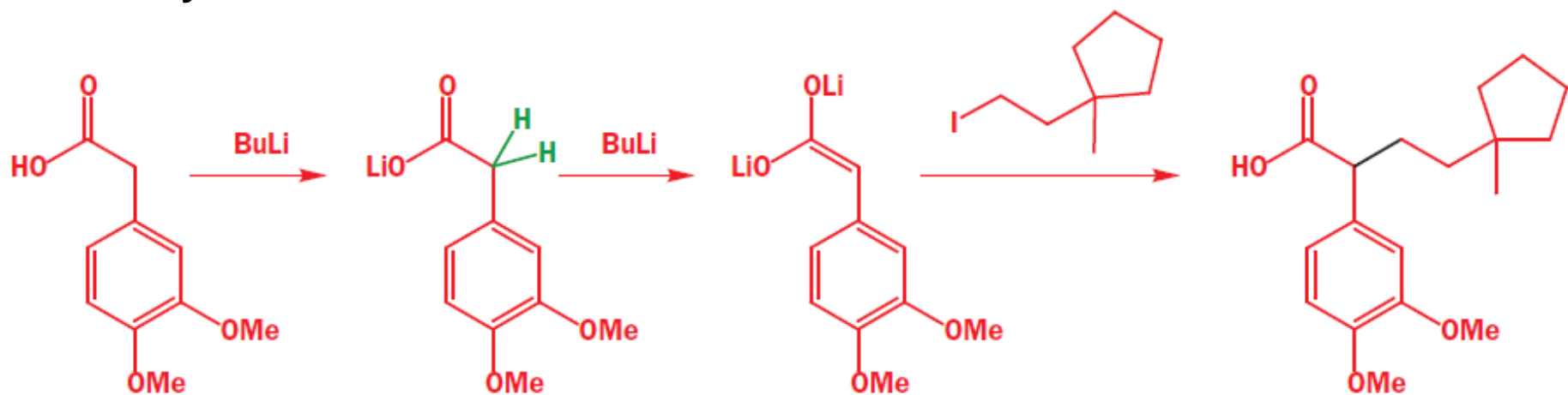


Complete Conversion: Lithium Enolates

Esters



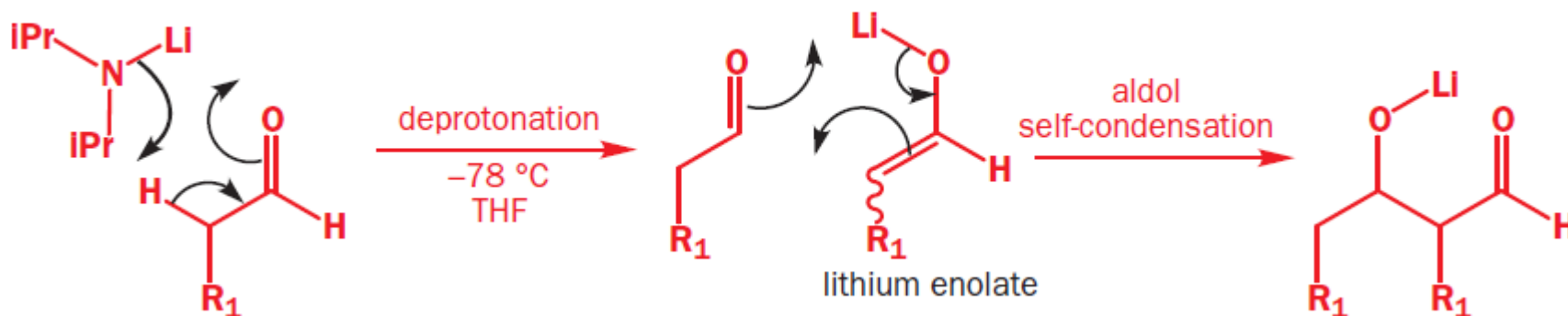
Carboxylic acids



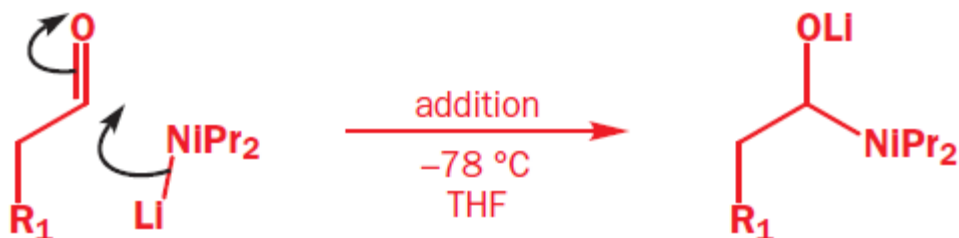
Aldehydes

Aldehydes are so **electrophilic** that, even with LDA at $-78\text{ }^{\circ}\text{C}$, the rate at which the deprotonation takes place is **not fast enough** to outpace reactions between the forming lithium enolate and still-to-be-deprotonated aldehyde remaining in the mixture

reactions which compete with aldehyde enolate formation

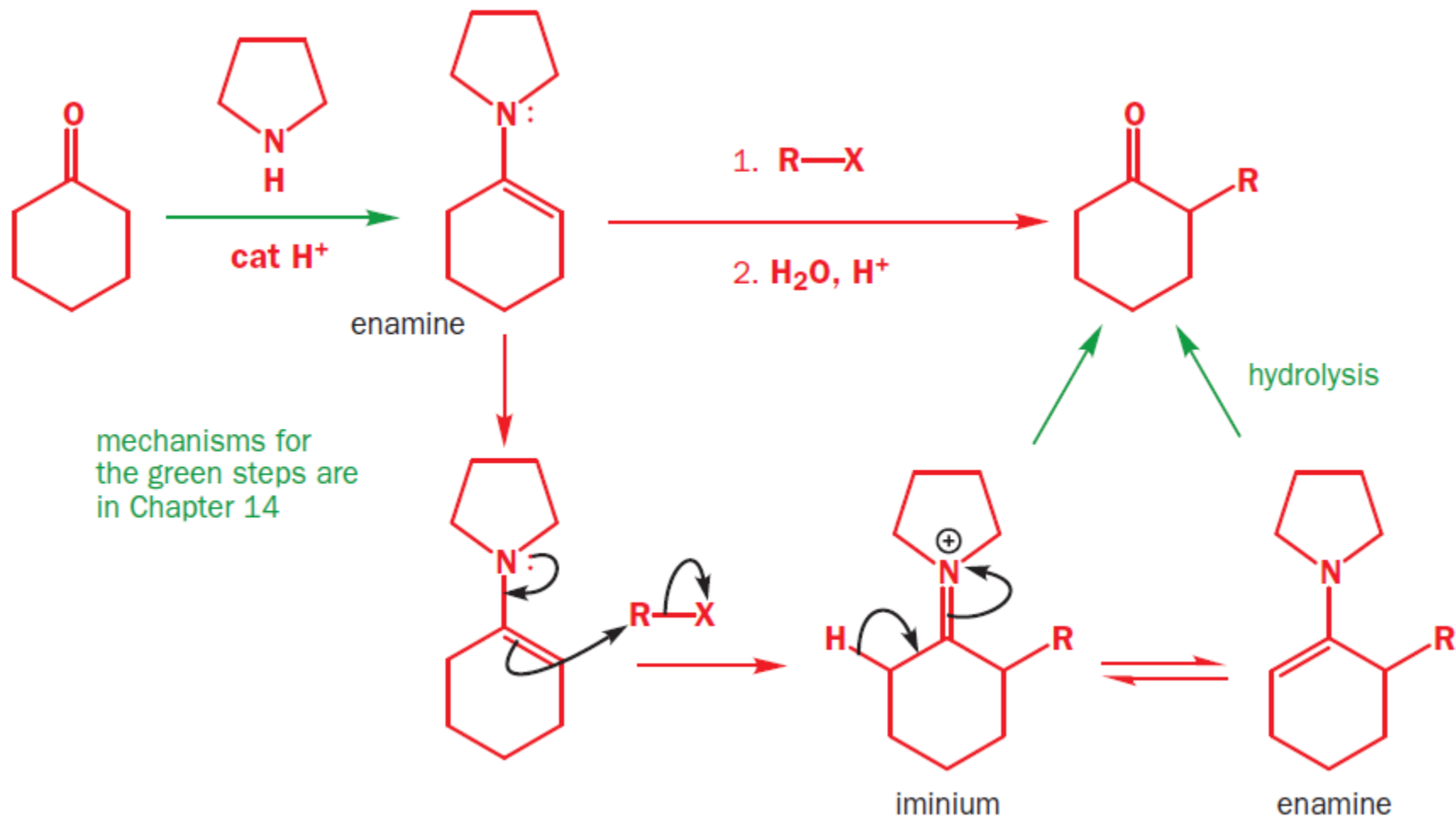


Direct addition of the base to the carbonyl group of electrophilic aldehydes can also pose a problem



Complete Conversion: Enamines

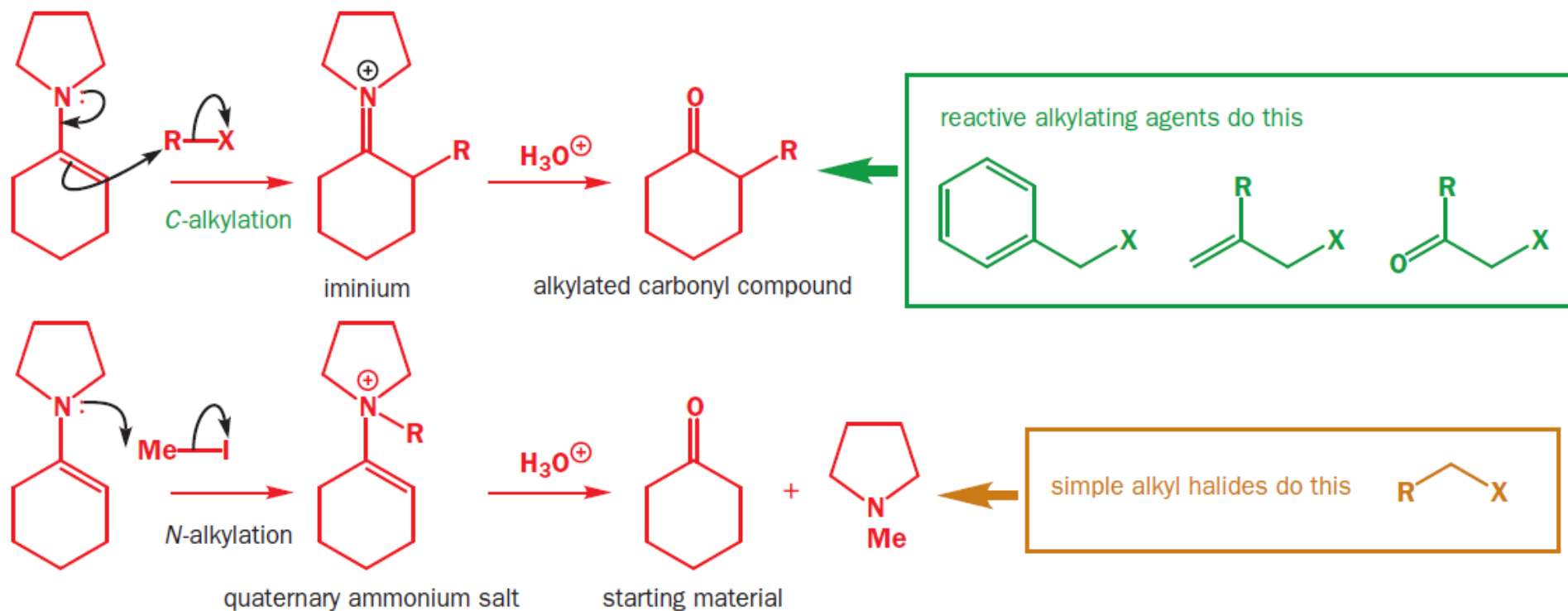
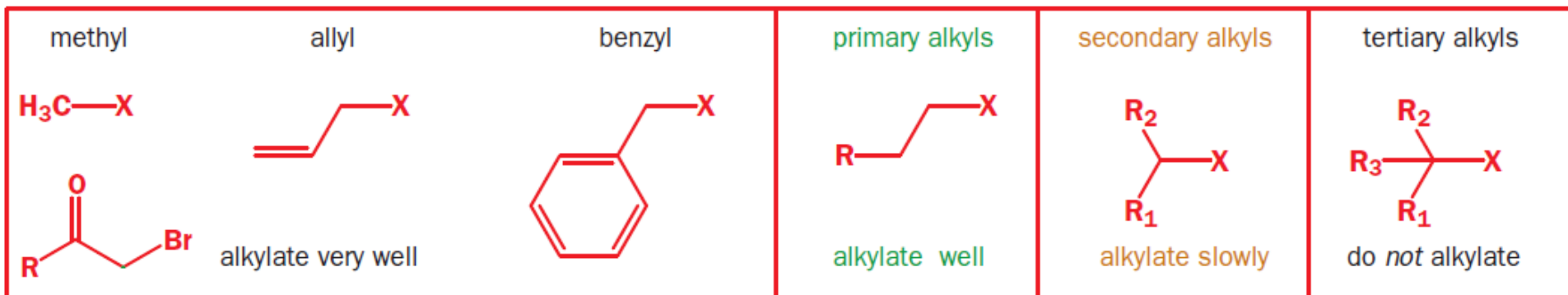
Enamines are formed when aldehydes or ketones react with **secondary amines**



Enamines are alkylated by **reactive electrophiles**

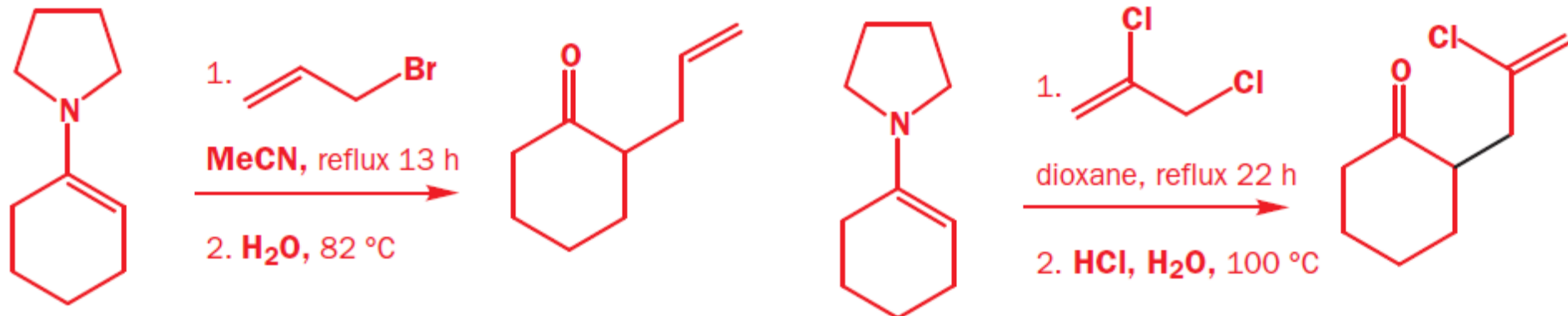
Complete Conversion: Enamines

Enamines are alkylated by **reactive electrophiles** (S_N2 reactive)

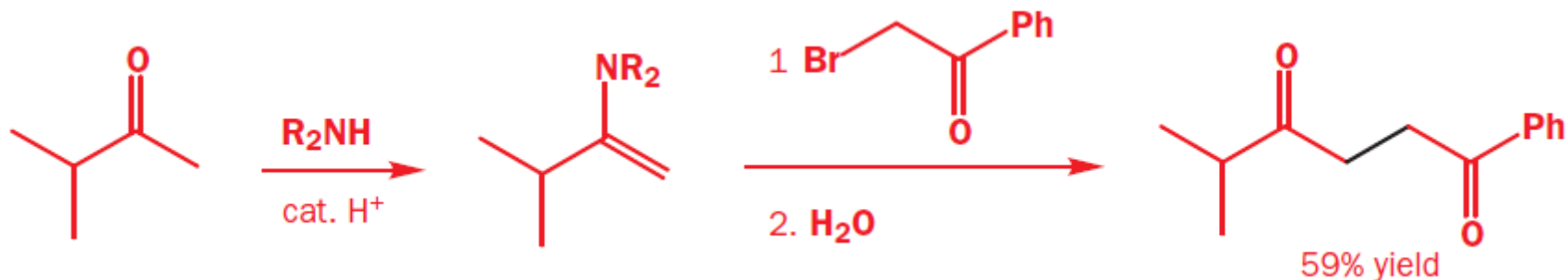
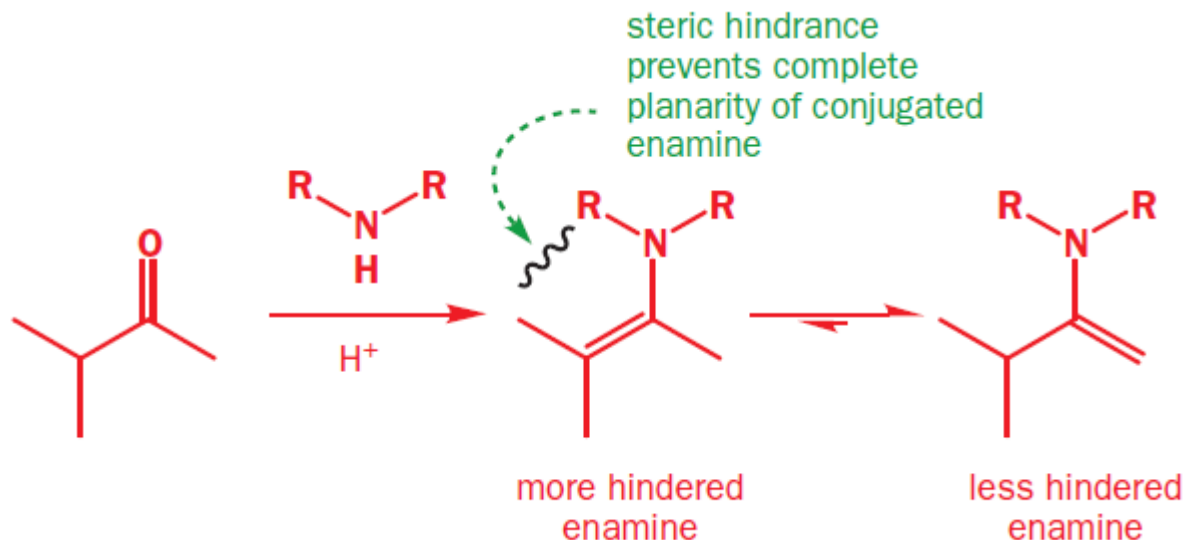


Complete Conversion: Enamines

28



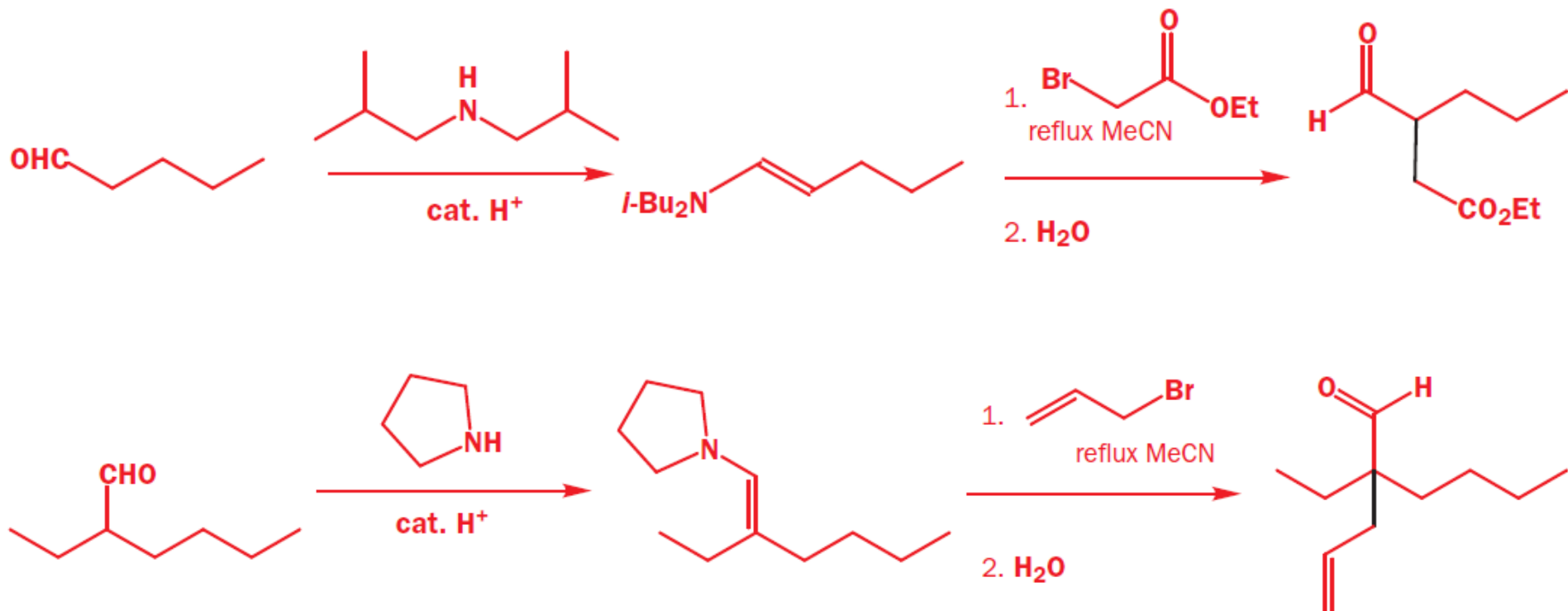
For the **more substituted enamine**, **steric hindrance** forces the enamine to lose planarity, and destabilizes it; the **less substituted enamine is more stable**. Note how the preference is **opposite to the preference for a more substituted enol**



Complete Conversion: Enamines

29

Enamines are a good solution to the **aldehyde enolate problem**. **Aldehydes form enamines very easily** (one of the advantages of the **electrophilic aldehyde**) and these are immune to attack by nucleophiles

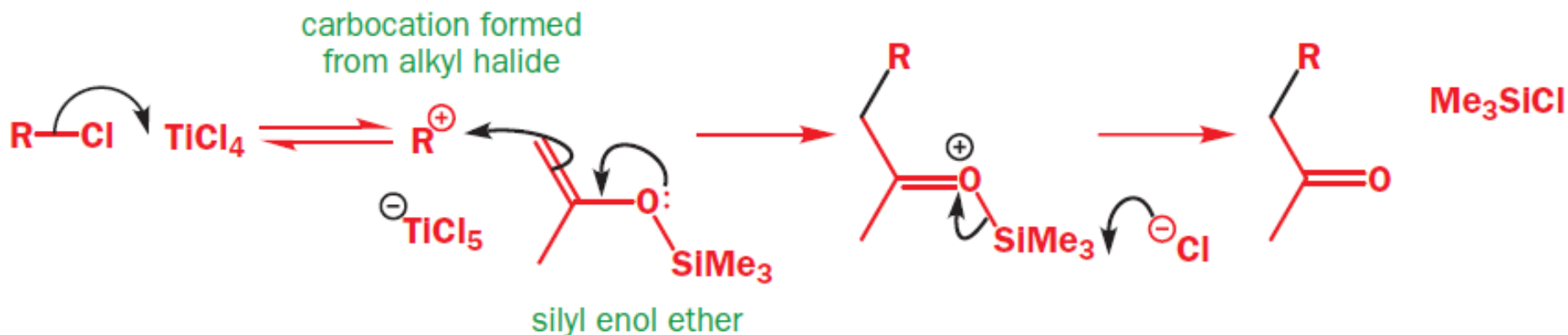


Drawback: require highly S_N2-reactive electrophiles

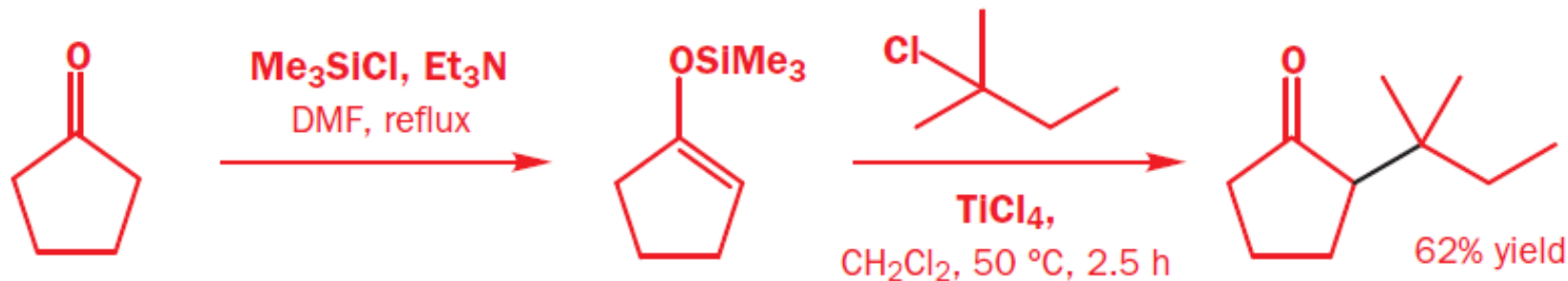
Complete Conversion: Silyl Enol Ethers

30

Silyl enol ethers are alkylated by **S_N1-reactive electrophiles** (such as **carbocations** generated from *in situ* abstraction of a leaving group from a saturated carbon centre by a **Lewis acid**)



The best alkylating agents for silyl enol ethers are **tertiary alkyl halides**: they form stable carbocations in the presence of Lewis acids such as $TiCl_4$ or $SnCl_4$: **complementary selectivity with lithium enolate or enamines (elimination side products)**



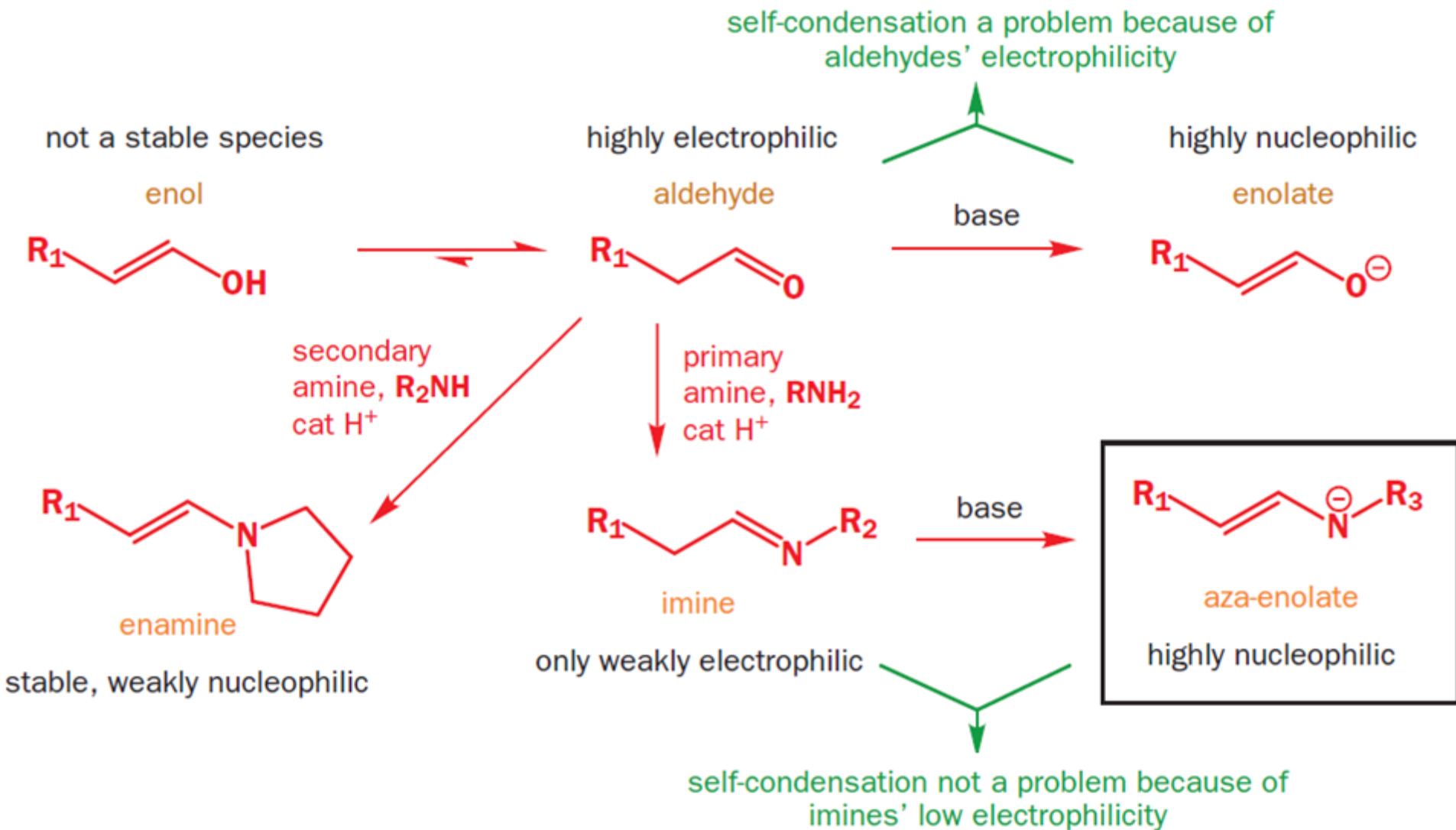
Complete Conversion: Aza-Enolates

31

Enamines are the nitrogen analogues of **enols**

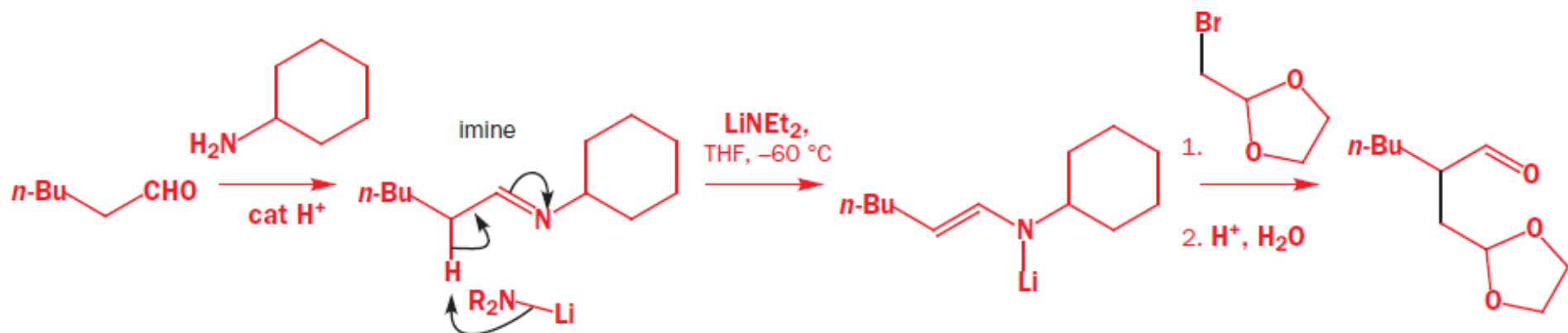
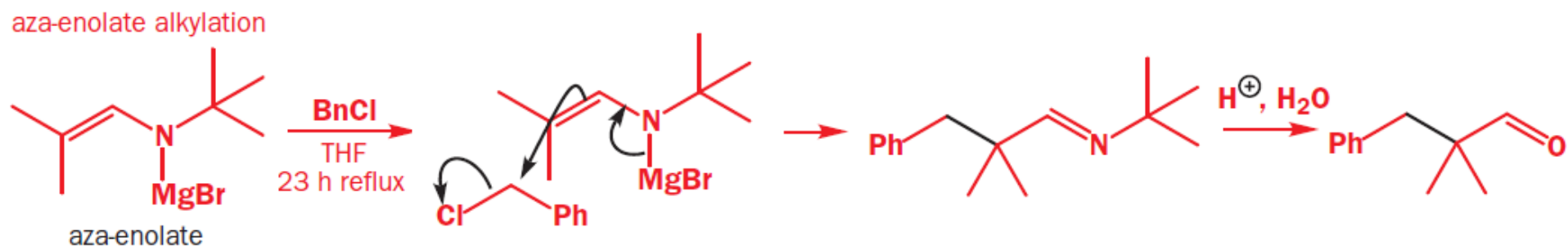
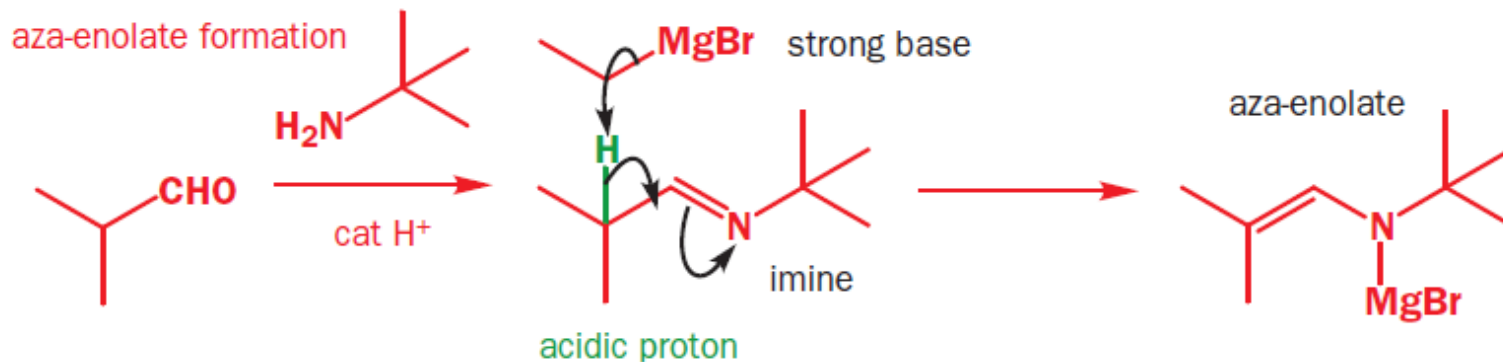
Imines are the nitrogen analogues of **aldehydes** and **ketones**

Aza-enolates are the nitrogen analogues of **enolates**



Complete Conversion: Aza-Enolates

32

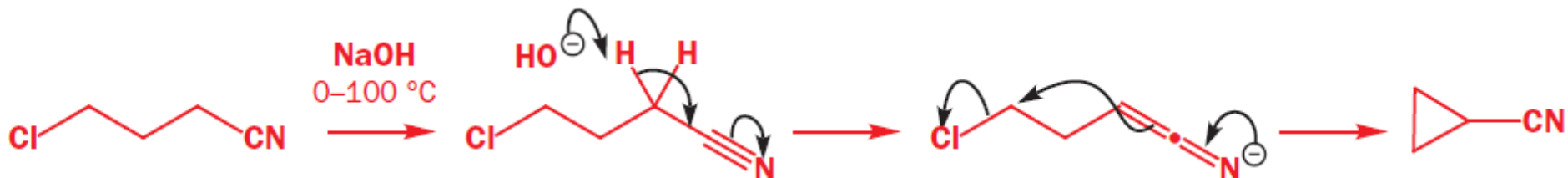
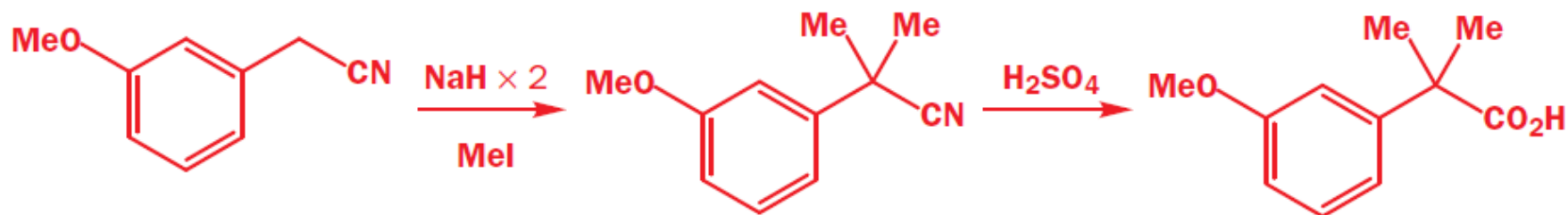
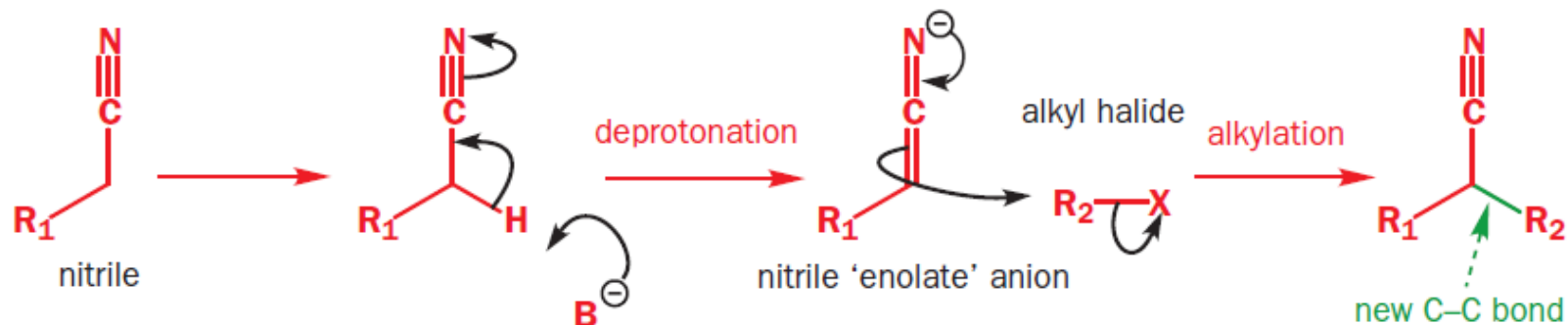


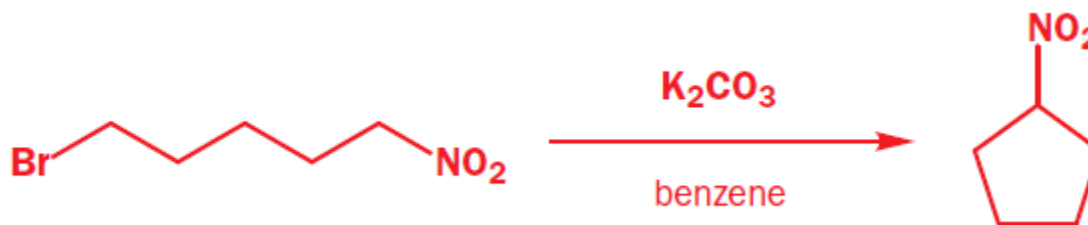
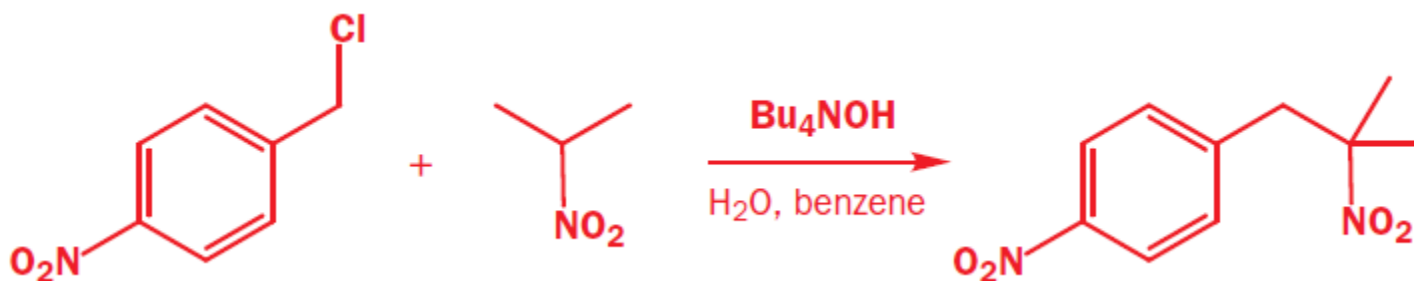
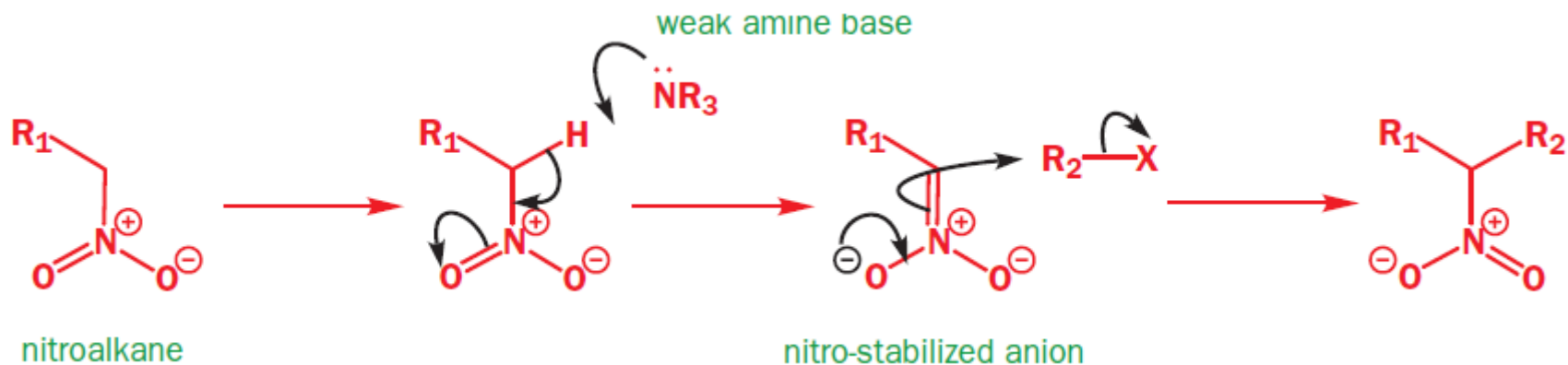
Aza-enolates are the best general solution for alkylating aldehydes with most electrophiles

● Specific enol equivalents for aldehydes and ketones

To summarize:

- Lithium enolates can be used with S_N2 -reactive electrophiles, but cannot be made from aldehydes
 - Aza-enolates of aldehydes or ketones can be used with the same S_N2 -reactive electrophiles, but *can* be made from aldehydes
 - Enamines of aldehydes or ketones can be used with allylic, benzylic, or α -halocarbonyl compounds
 - Silyl enol ethers of aldehydes or ketones can be used with S_N1 -reactive (tertiary, allylic or benzylic) alkyl halides
-
- **Complete conversion** of the starting material to the anion (using **strong base**) before addition of the electrophile, which is added in a **subsequent step**
 - **Weaker base** may be used **in the presence of the electrophile**;
[Advantage: easier practically]
[Disadvantage: works only if the base and the electrophile are compatible + risk of aldol by-products]

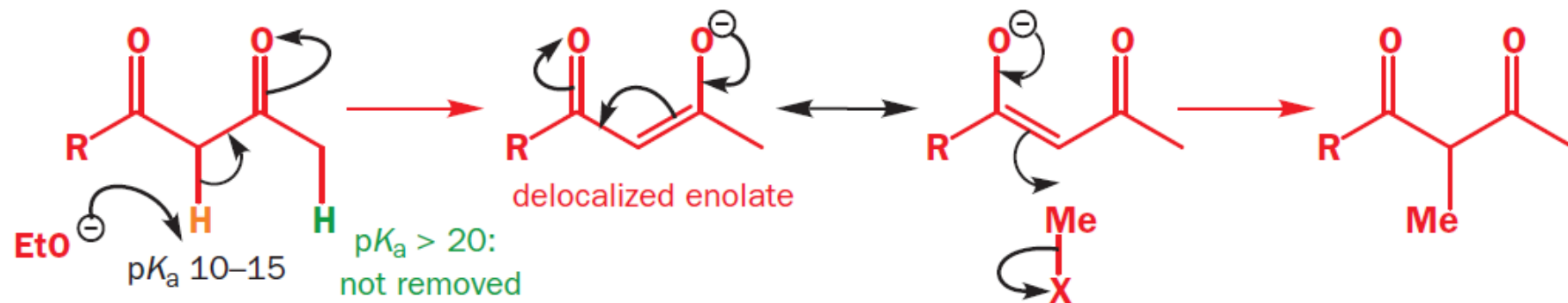




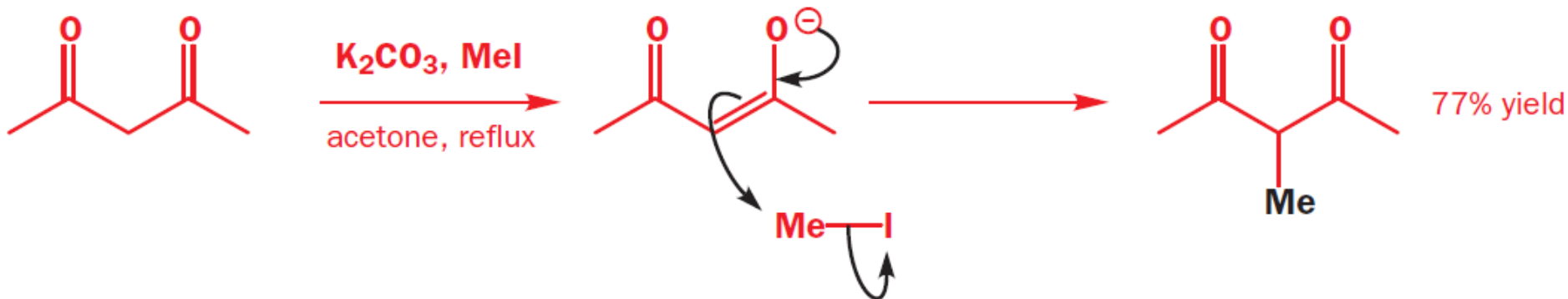
Weak Base: β -Dicarbonyl Compounds

The presence of **two electron-withdrawing groups** on a single carbon atom makes the remaining proton(s) appreciably **acidic** (pK_a 10–15), which means that even **mild bases** can lead to **complete enolate formation**

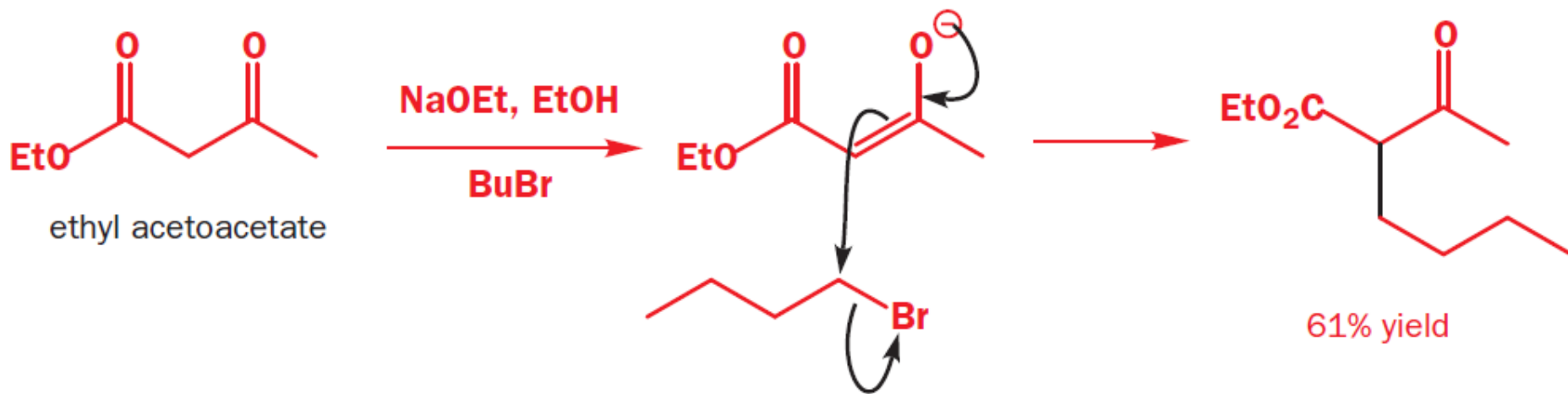
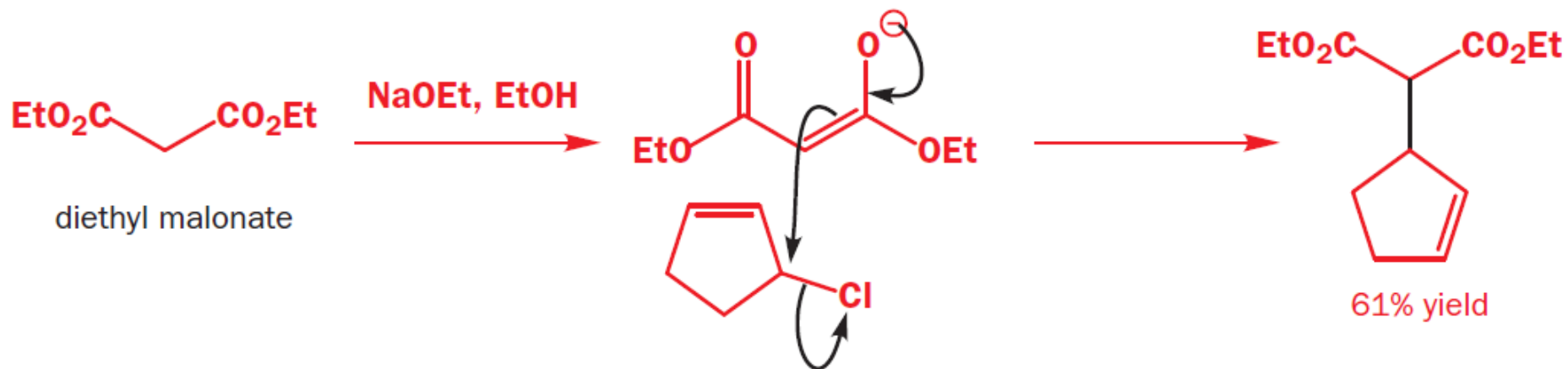
alkylation of a 1,3-dicarbonyl compound (or β -dicarbonyl compound)



The resulting anions are **alkylated very efficiently**. This diketone is enolized even by potassium carbonate, and reacts with methyl iodide in good yield

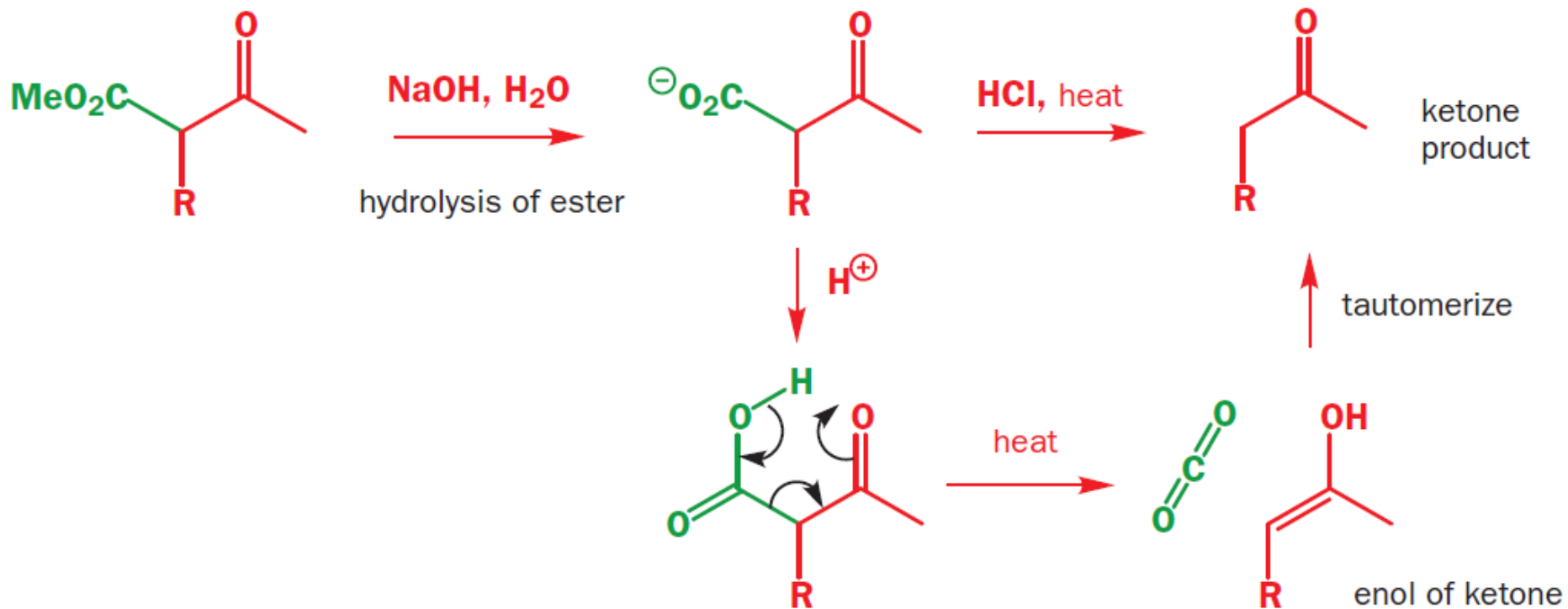


Weak Base: β -Dicarbonyl Compounds

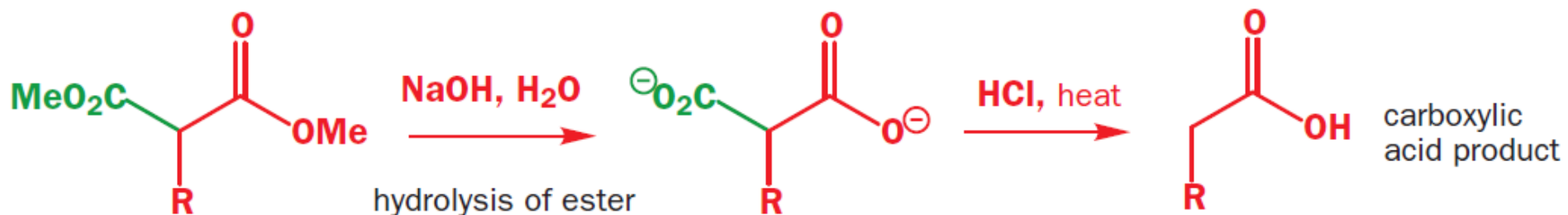


Weak Base: β -Dicarbonyl Compounds – Decarboxylation 38

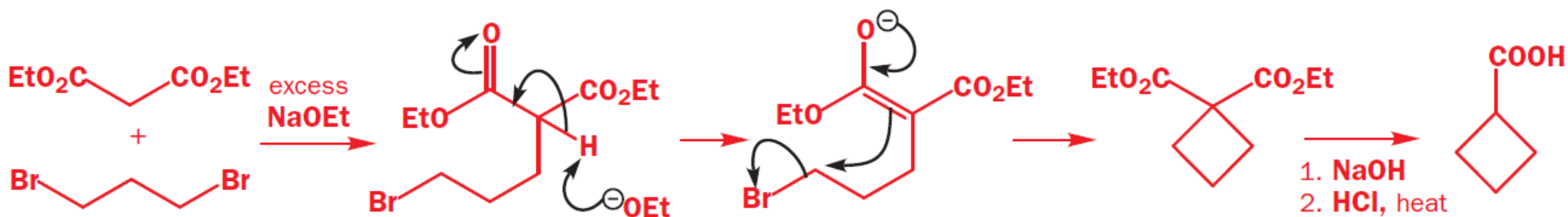
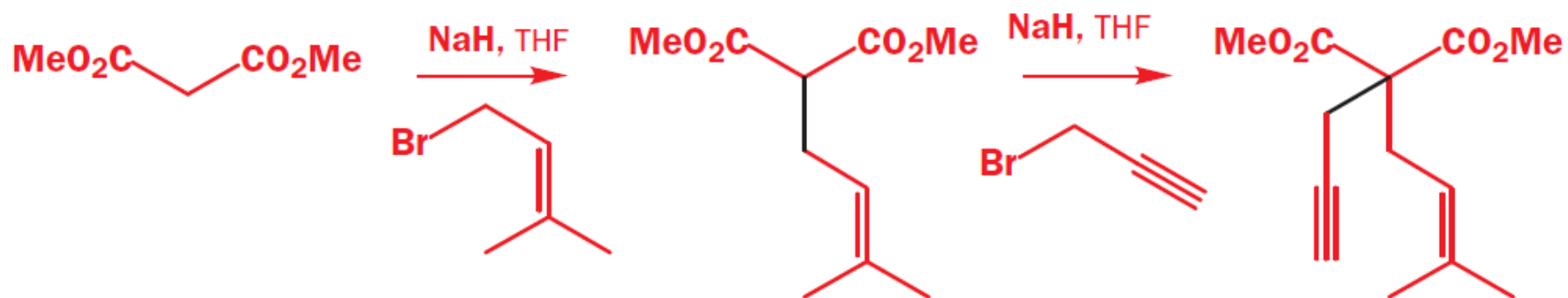
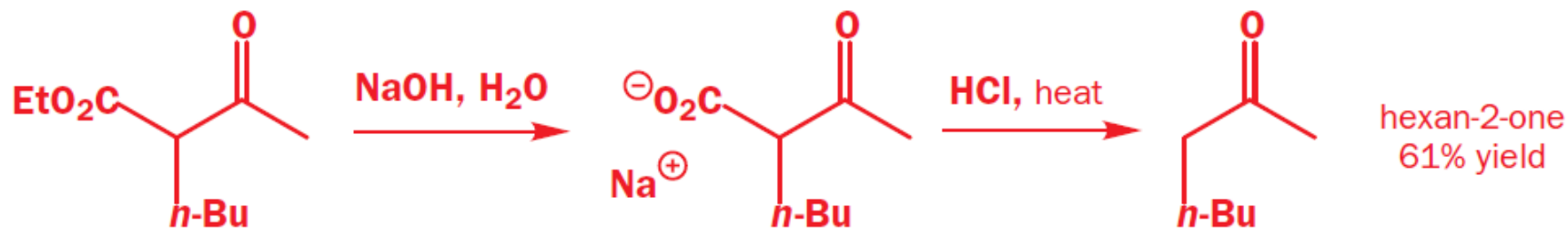
decarboxylation of acetoacetate derivatives to give ketones



decarboxylation of malonate derivatives to give carboxylic acids

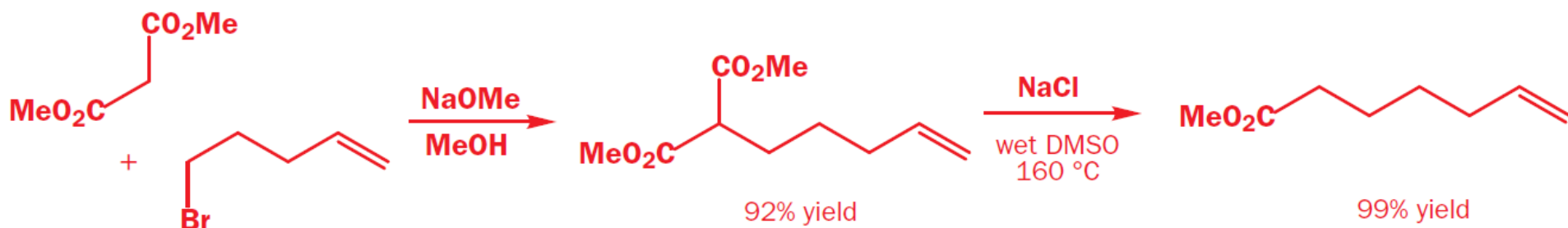
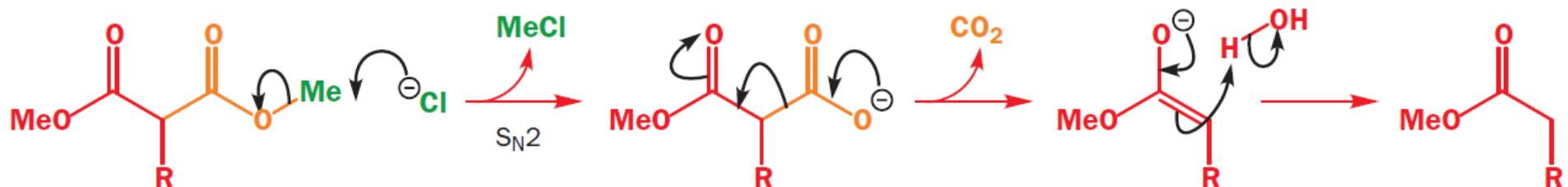


Weak Base: β -Dicarbonyl Compounds – Decarboxylation 39

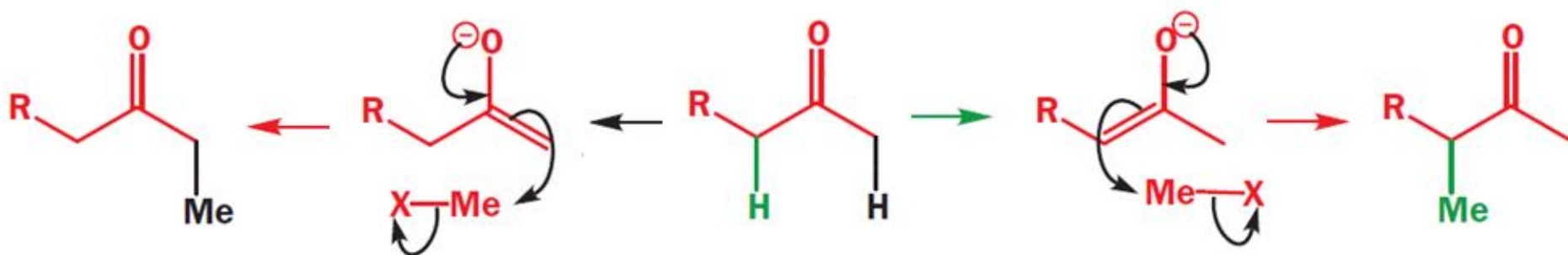


Weak Base: β -Dicarbonyl Compounds – Decarboxylation 40

Krapcho decarboxylation

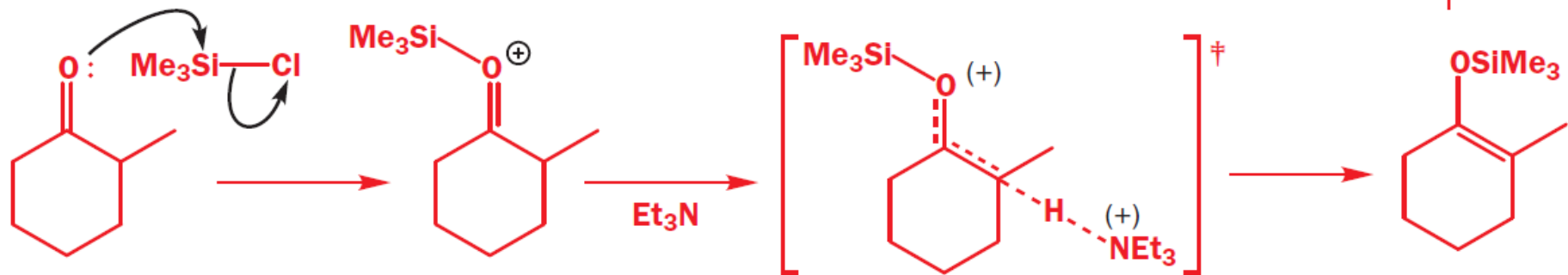
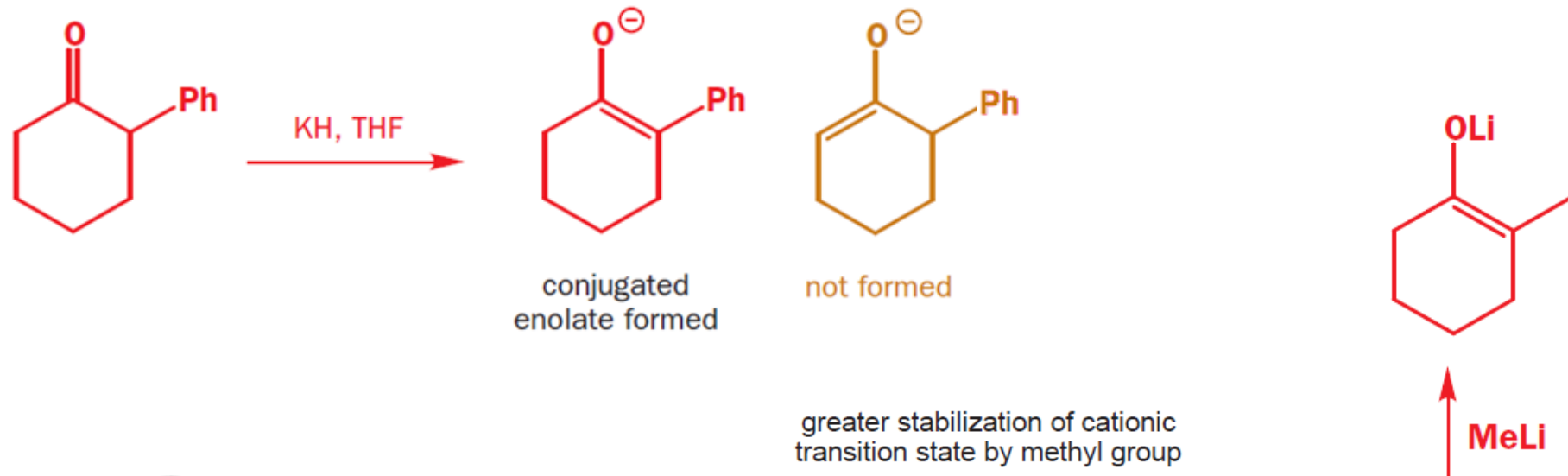
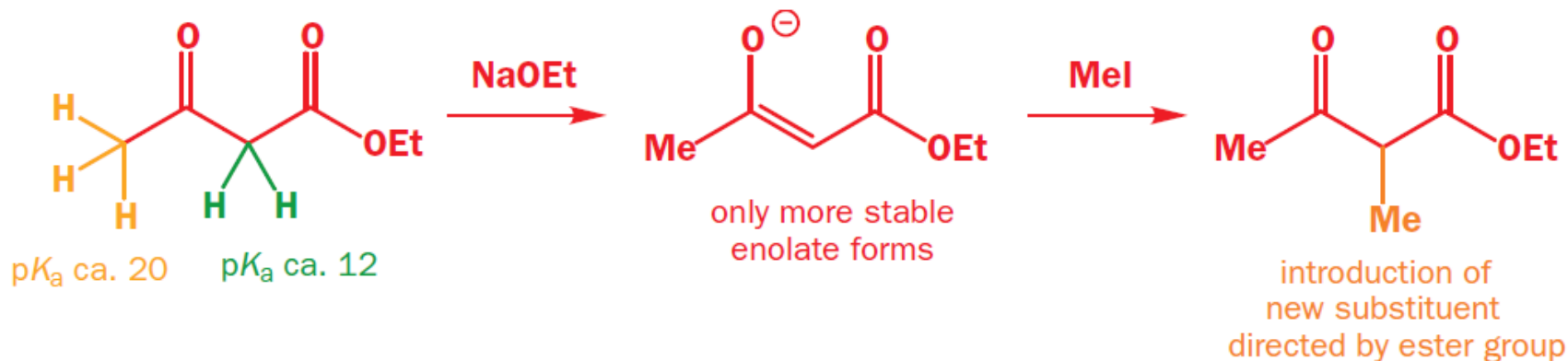


Regioselectivity in Alkylation



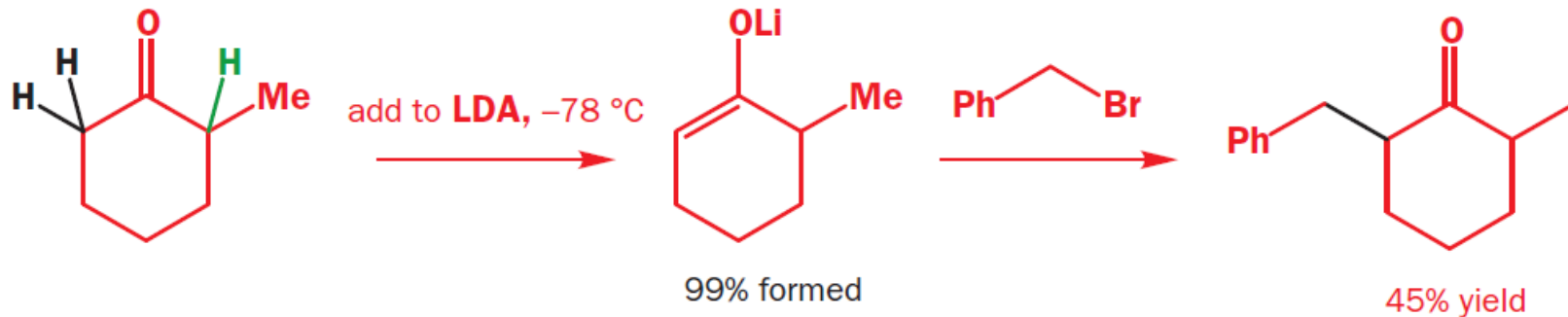
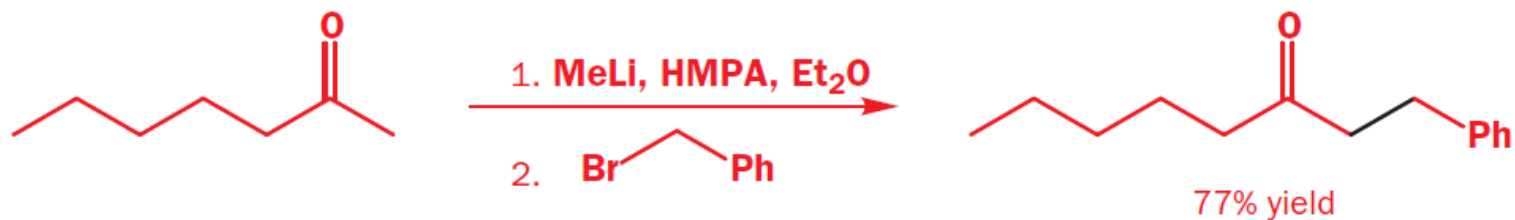
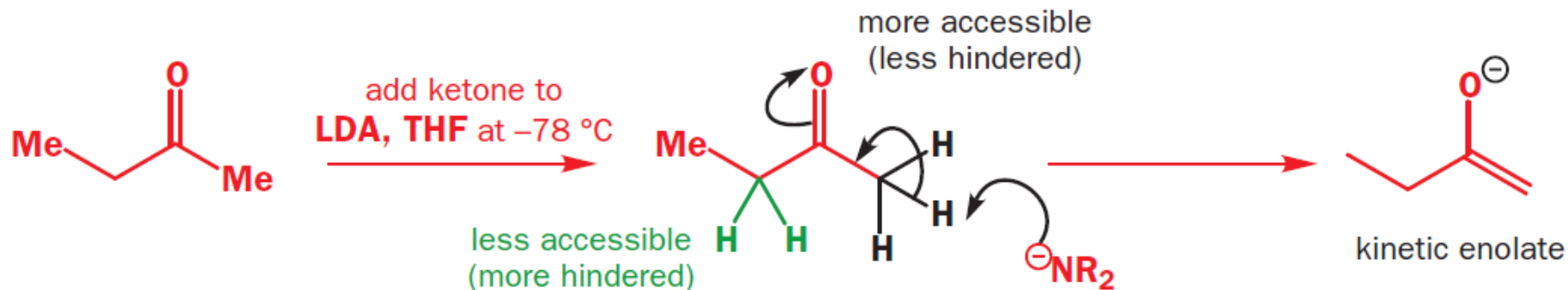
Thermodynamically controlled enolate formation

41



Kinetically controlled enolate formation

42

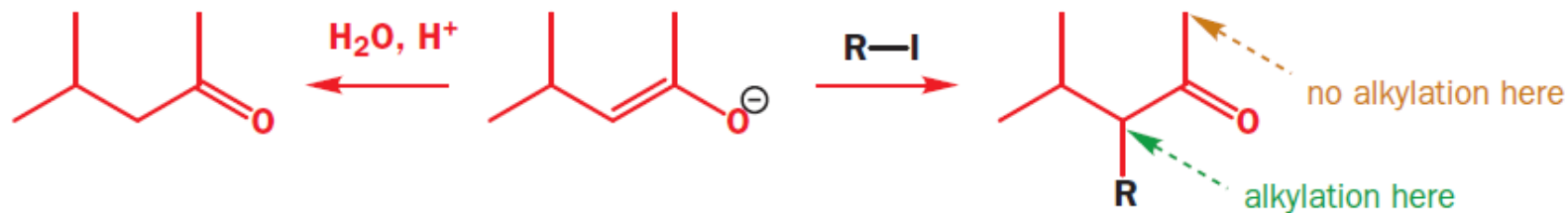
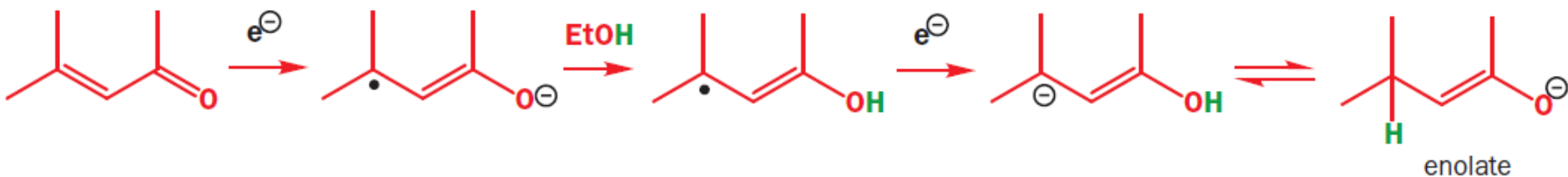
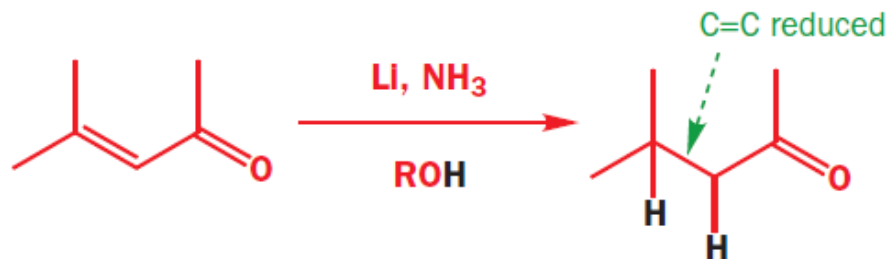


Enolate from Enones

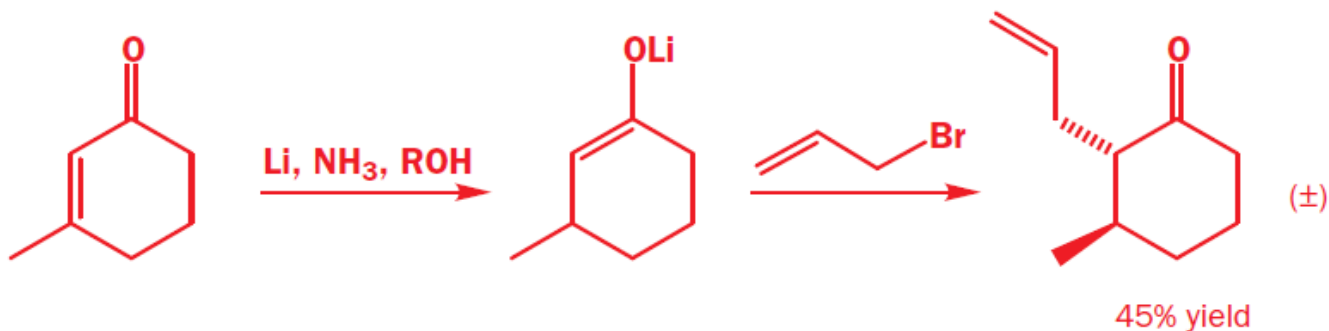
43

Enones provide a solution to regioselectivity problems

1) Dissolving metal reduction (similar to **Birch reduction**)

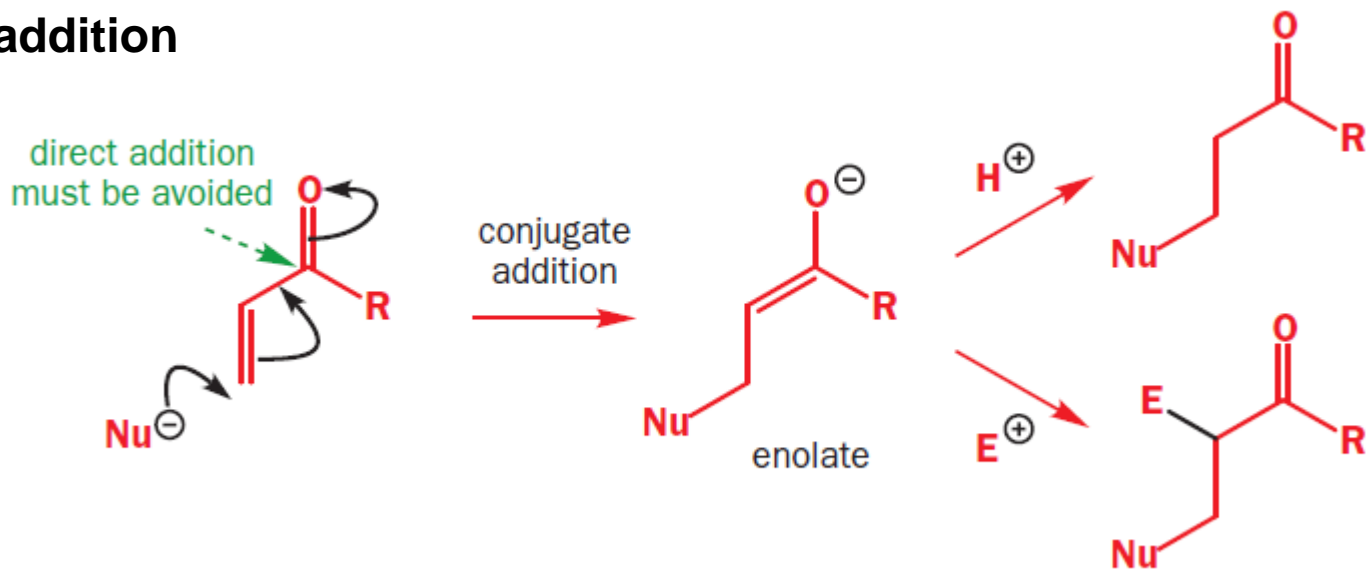


Example:

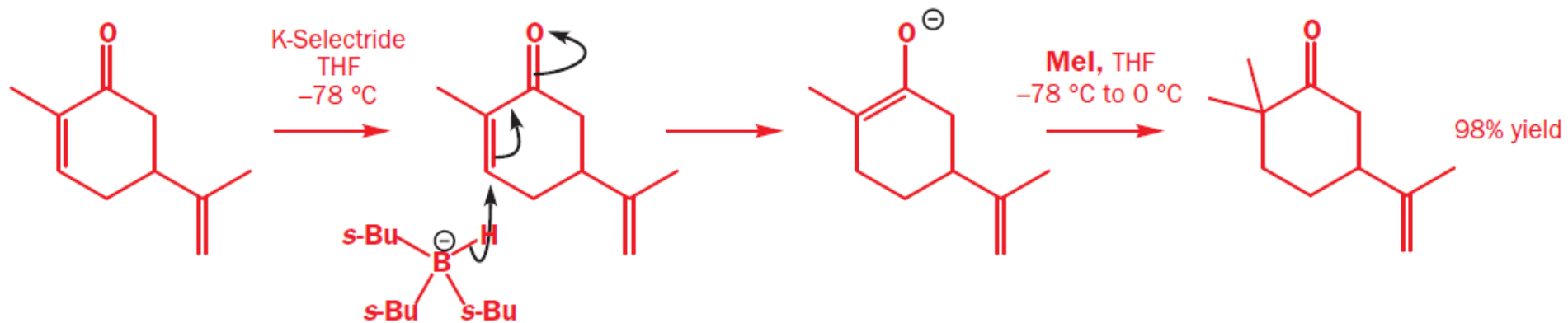


Enolate from Enones

2) Conjugate addition



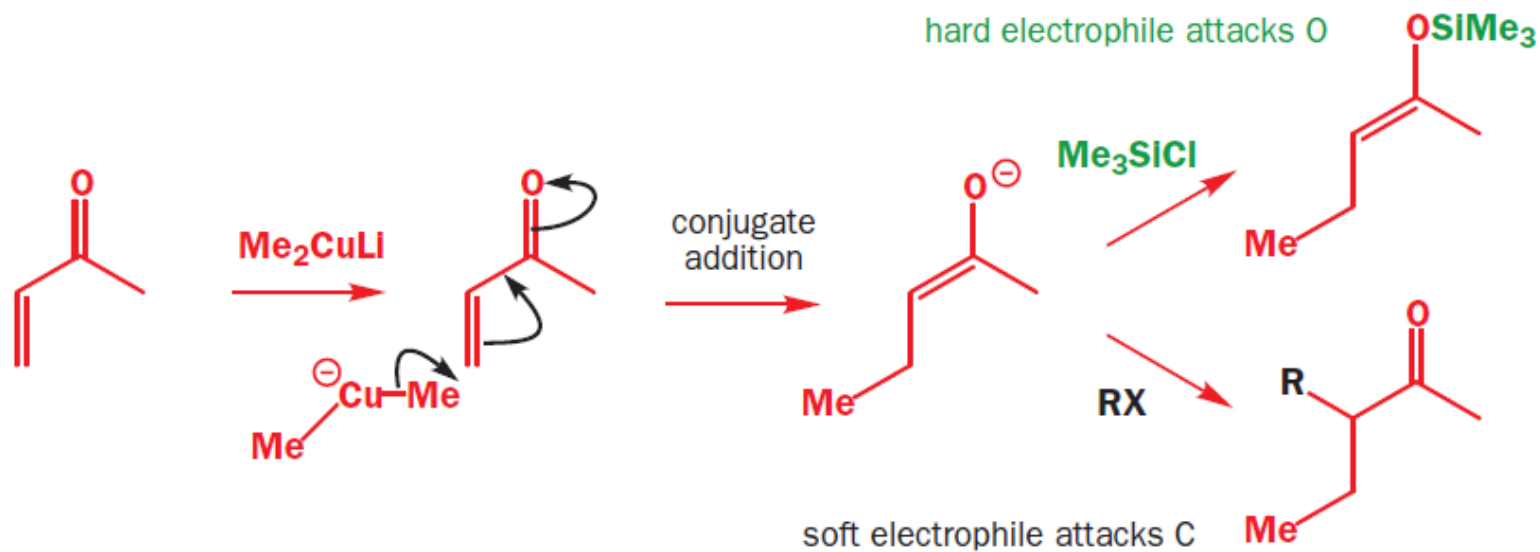
Nu = H



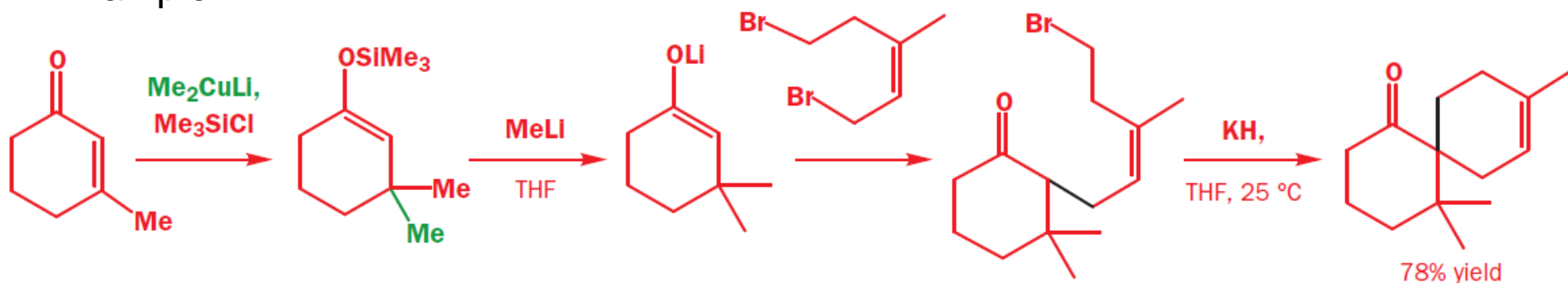
Enolate from Enones

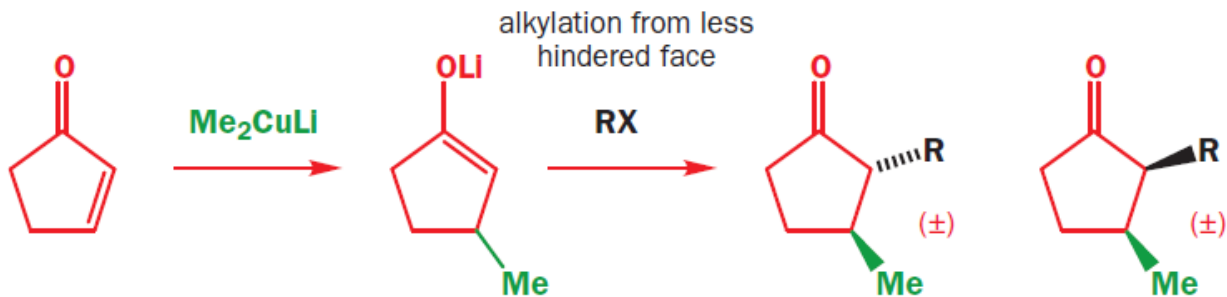
2) Conjugate addition

Nu = R

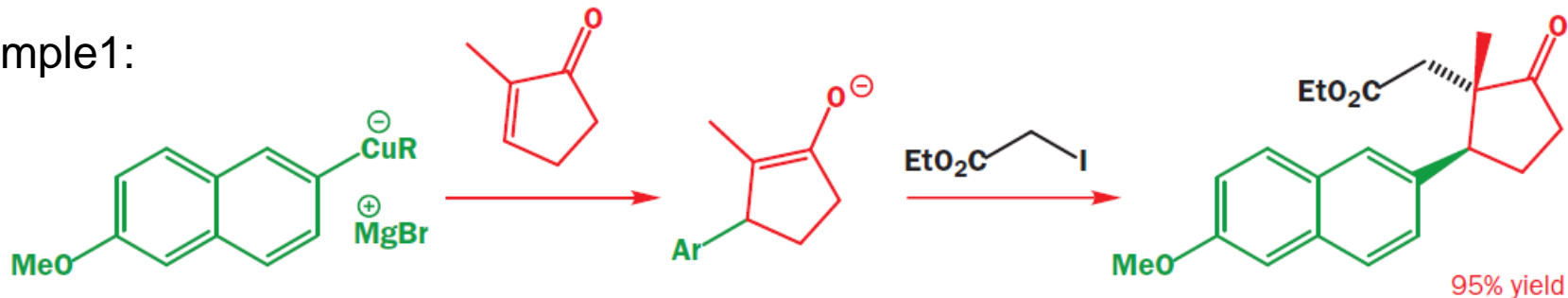


Example:

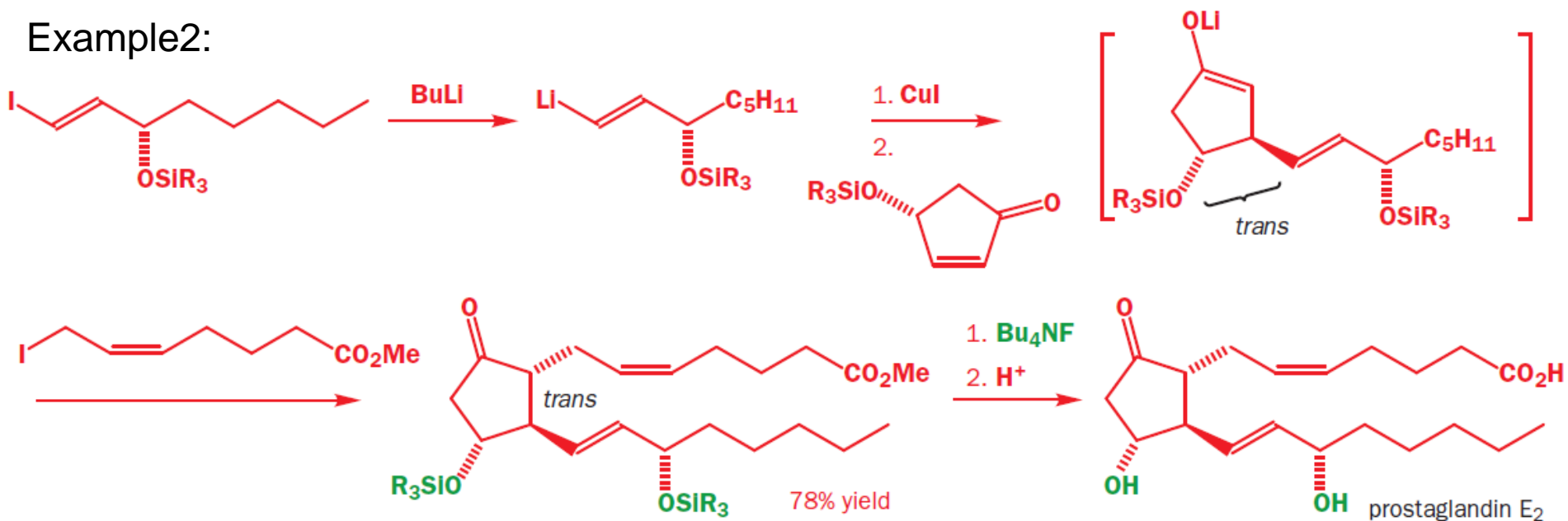




Example 1:



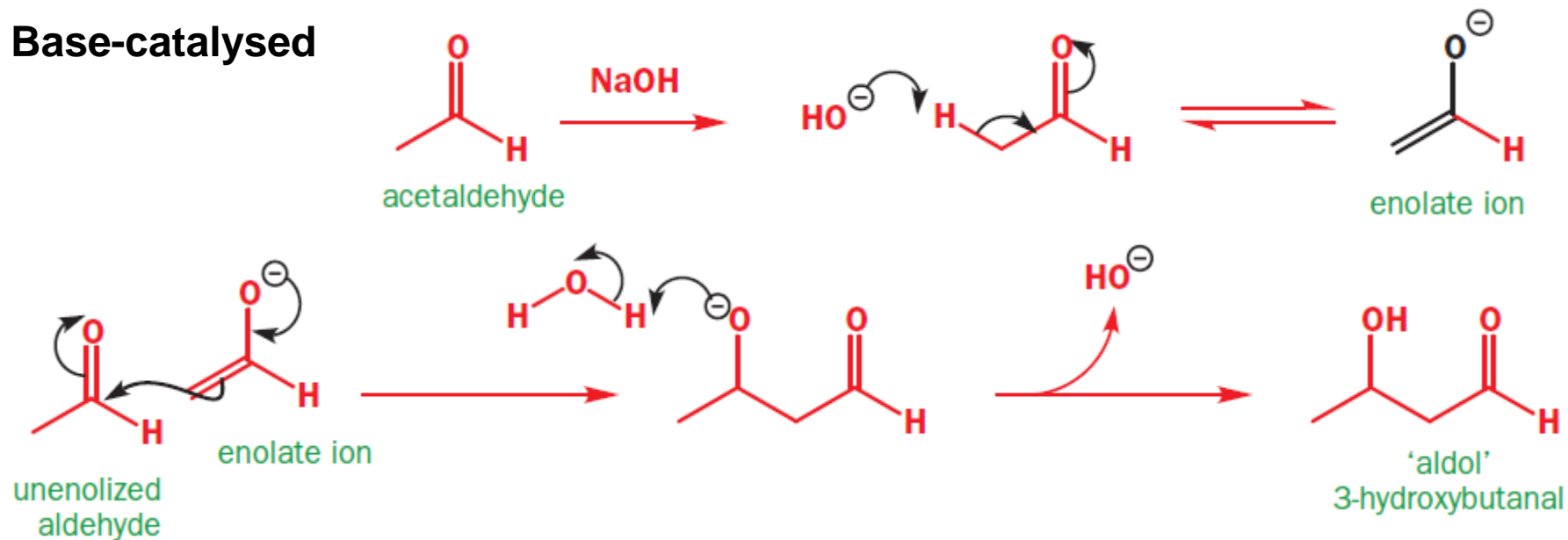
Example 2:



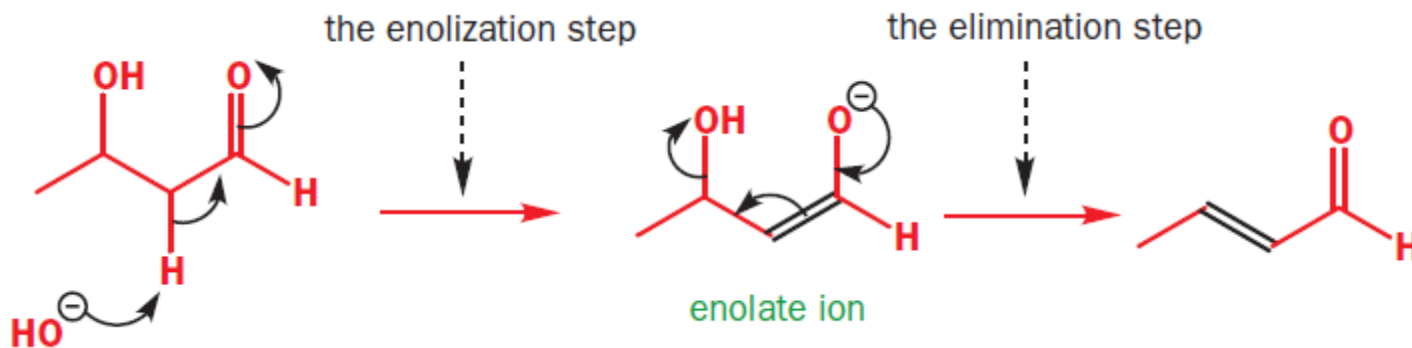
Aldol Reaction

Reaction of **enolates** with **aldehydes** or **ketones** as electrophiles

Base-catalysed



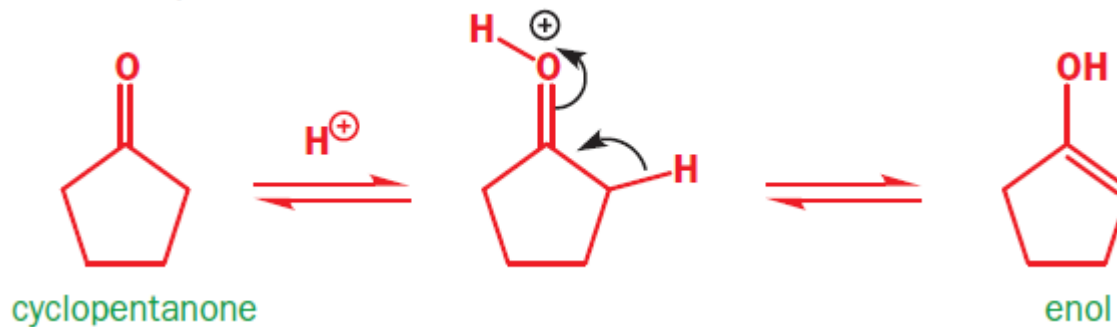
With **more base** or at **higher temperature**, further reactions occur, because the aldol products **dehydrate** rather easily through **E1cB** mechanism



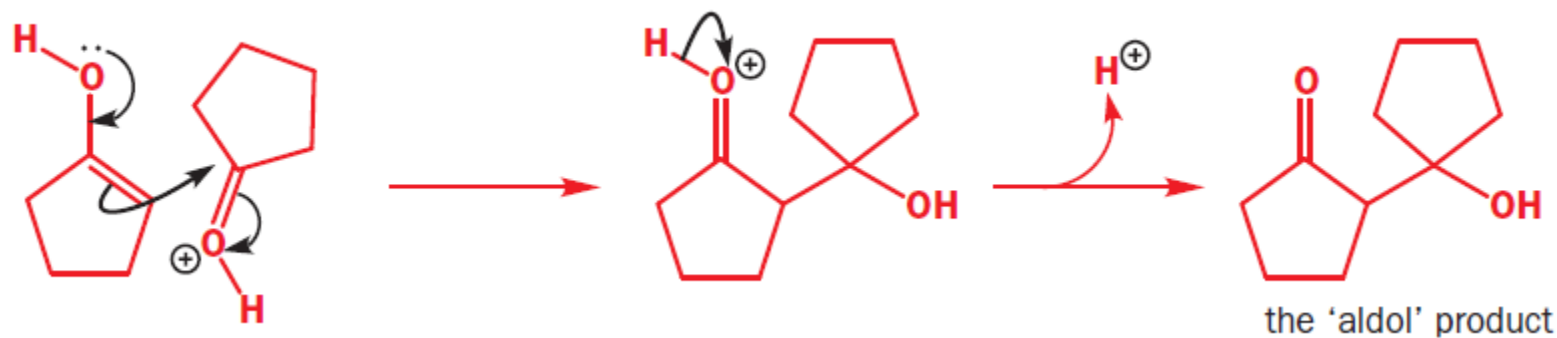
Aldol Reaction

Acid-catalysed

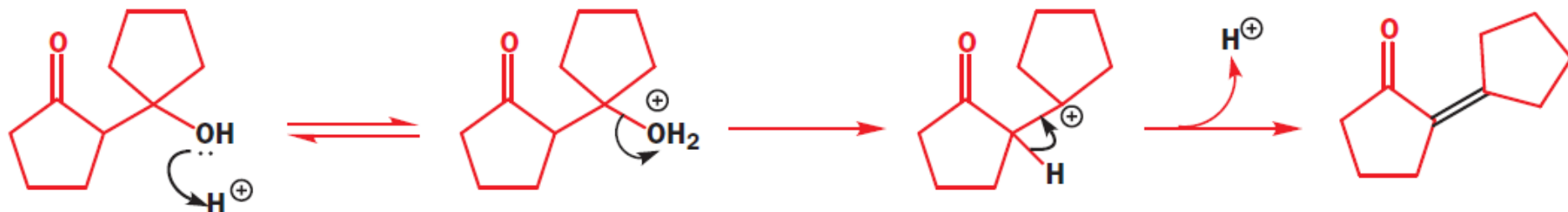
acid-catalysed enolization step



acid-catalysed aldol addition step



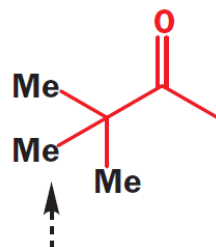
the acid-catalysed dehydration step (E1 elimination)



Aldol reactions of unsymmetrical compounds

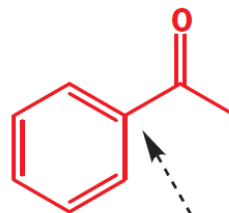
ketones which can enolize only one way:

a *t*-alkyl group cannot enolize as it has no α protons

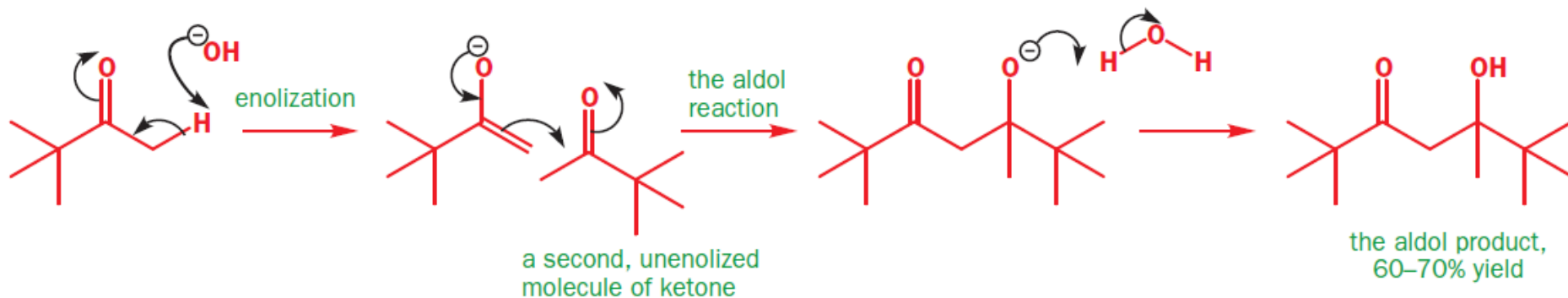


nine β protons
but no α protons

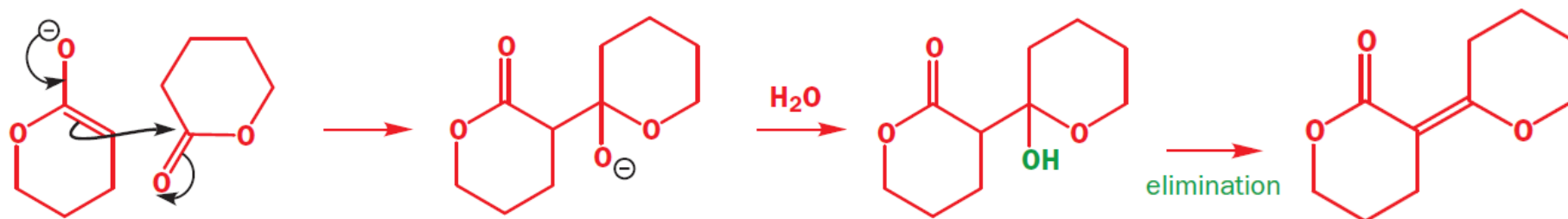
an aryl ketone has no substituents at the α position

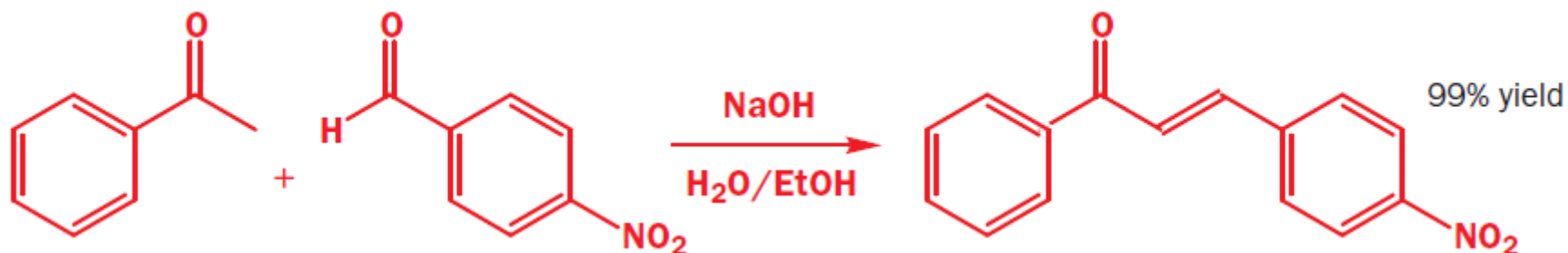


trigonal carbon atom in aryl
ring with no substituents



aldol reaction of a lactone (cyclic ester)



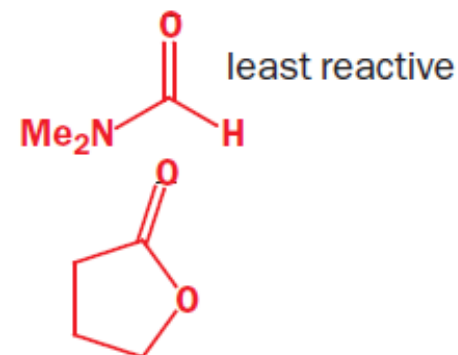
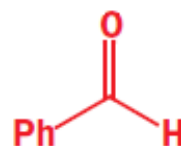
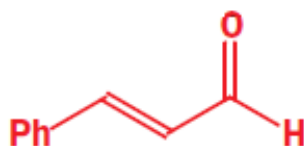
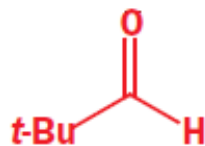
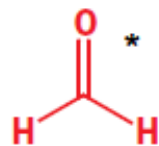


● Successful crossed aldol reactions

For this kind of crossed aldol reaction to work well we must have two conditions.

- One partner only must be capable of enolization
- The other partner must be incapable of enolization and be *more electrophilic than the enolizable partner*.

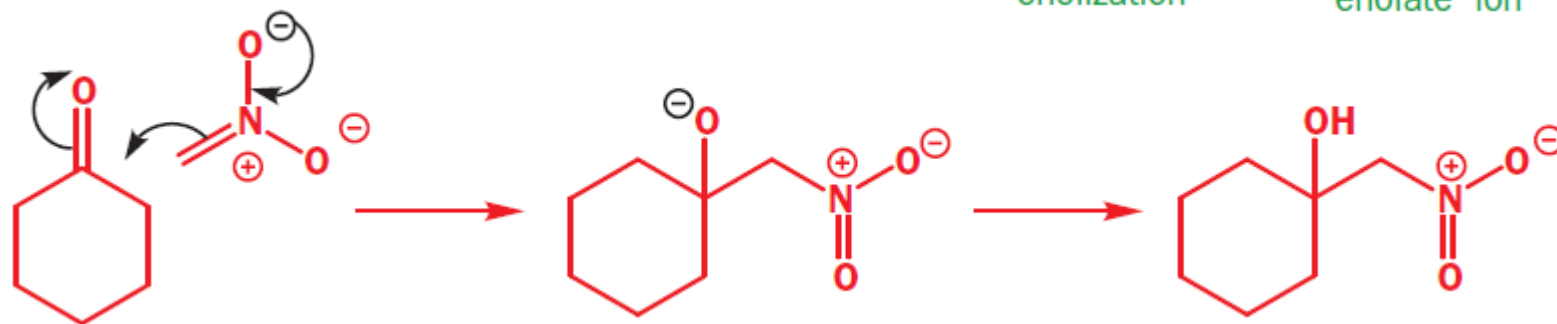
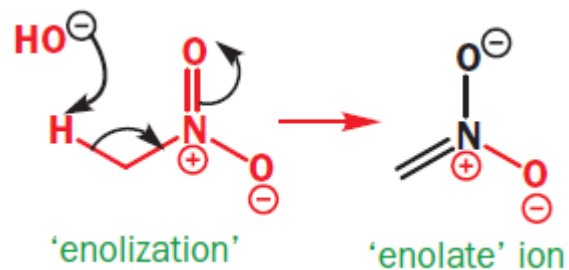
most reactive



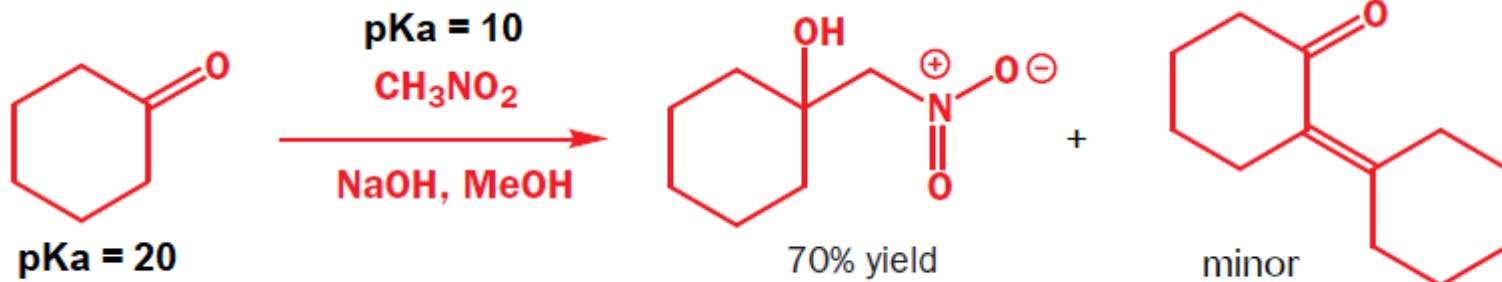
Cross-Condensations – nitroalkanes

Nitroalkanes can **enolize** but that they are **not electrophilic**

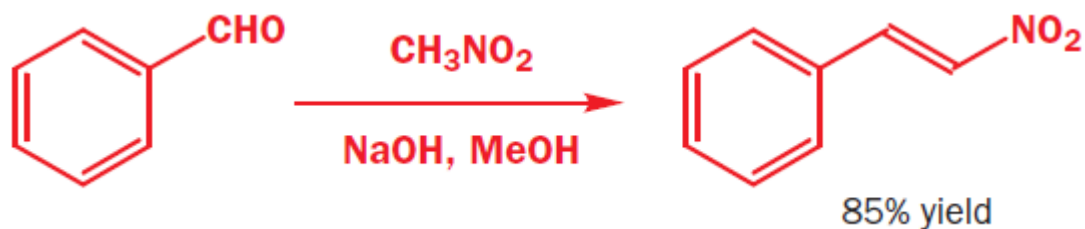
anion of nitromethane



Example:

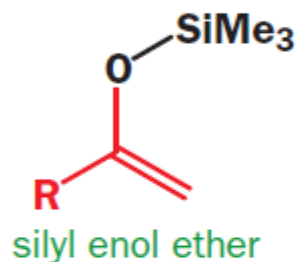
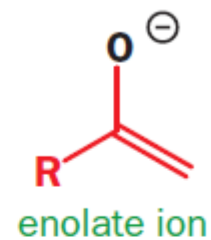
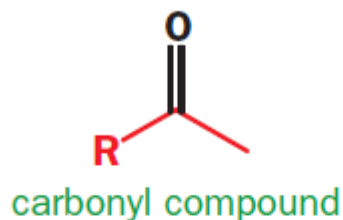
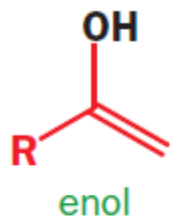


Example:

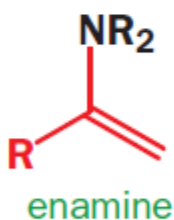
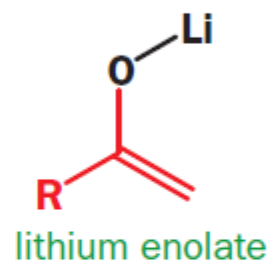


Controlling aldol reactions with specific enol equivalents 52

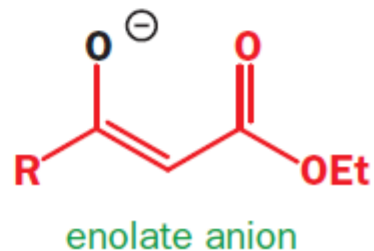
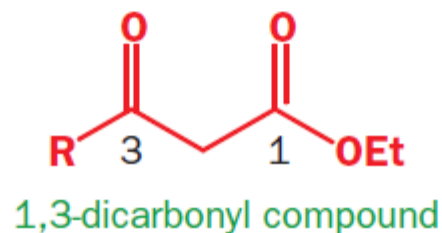
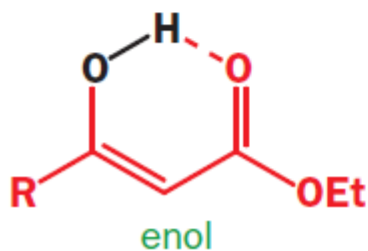
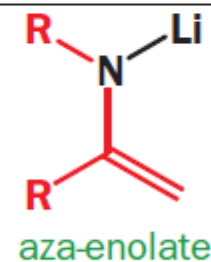
Important specific enol equivalents



oxygen derivatives



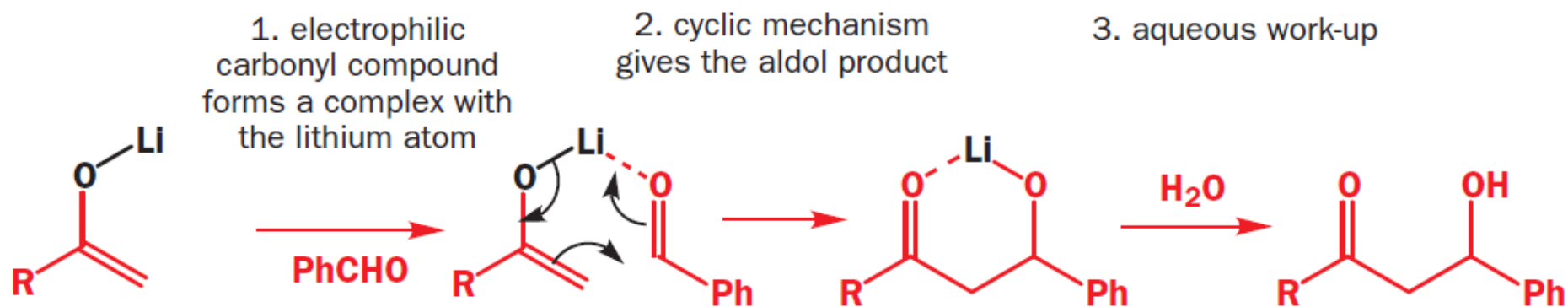
nitrogen derivatives



Lithium enolates in aldol reactions

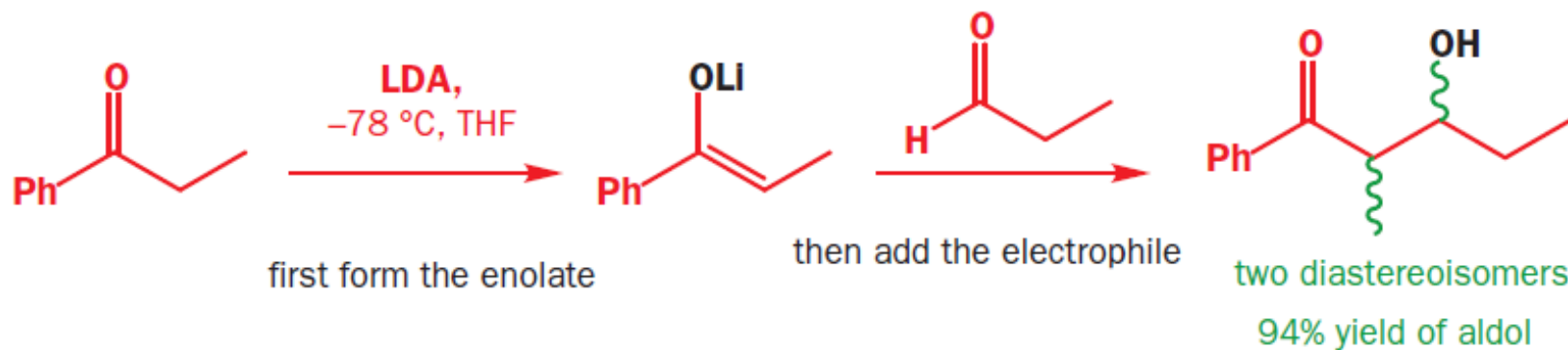
If a carbonyl compound is added to a lithium enolate, it too complexes with the same lithium atom. The aldol step itself is now a very favourable **intramolecular** reaction with a **six-membered cyclic transition state**

aldol reaction with a lithium enolate



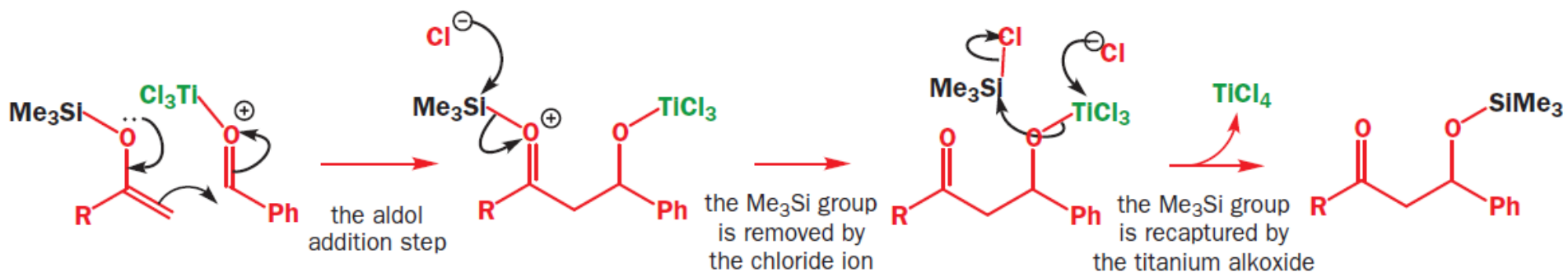
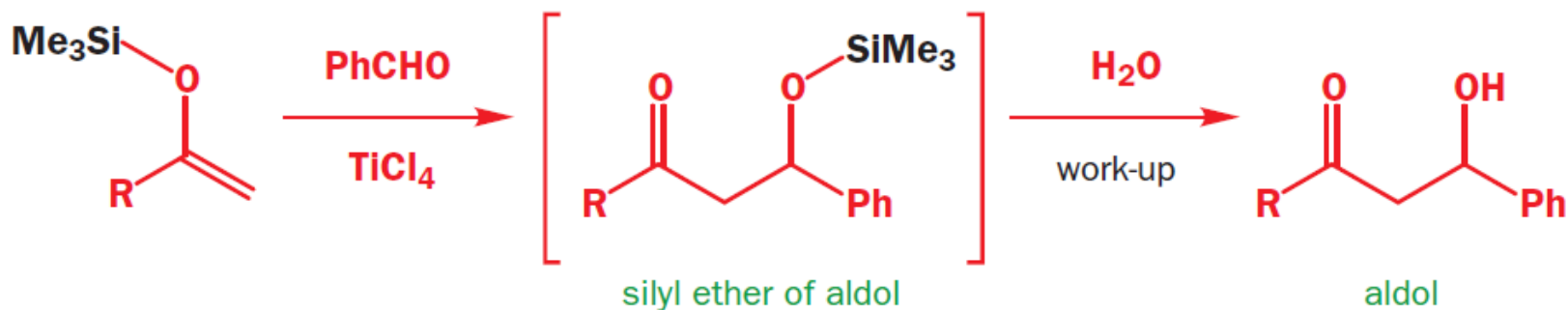
lithium enolate

Example:

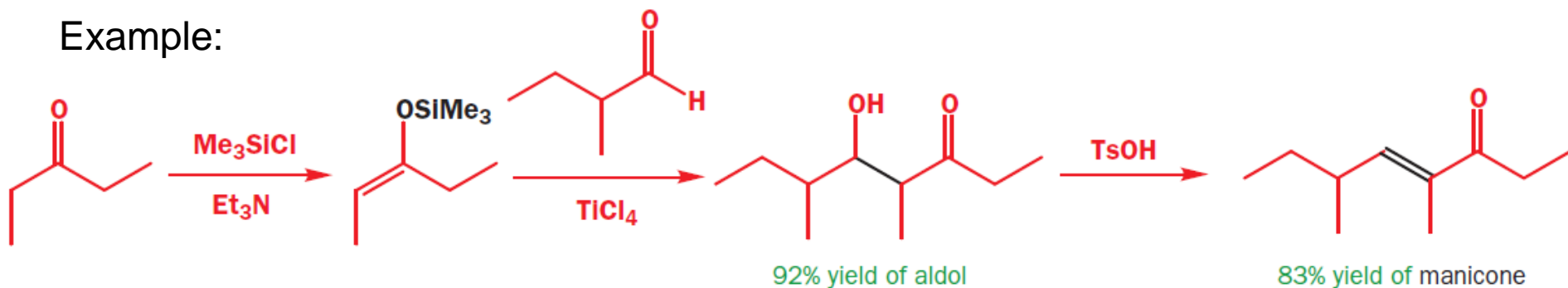


Silyl enol ethers in aldol reactions

Silyl enol ethers are much **less reactive** than lithium enolate. **Lewis acid catalyst** is needed to get the aldol reaction to work

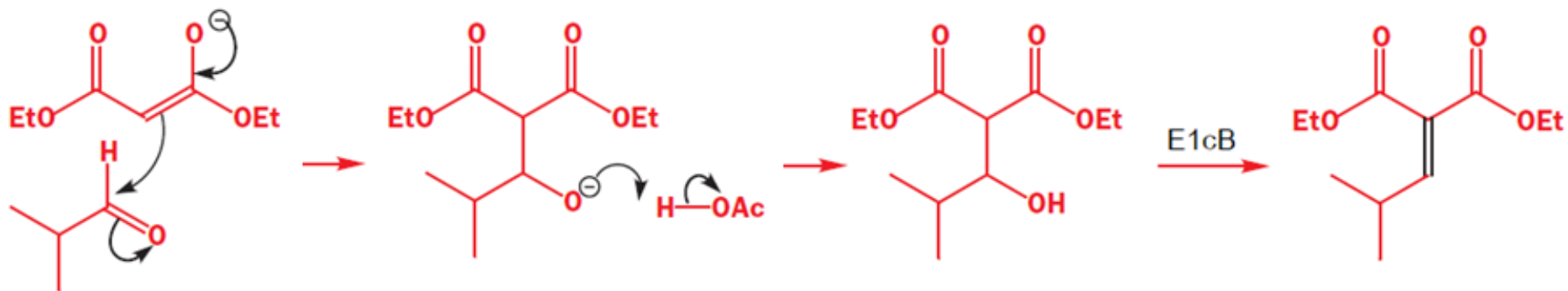
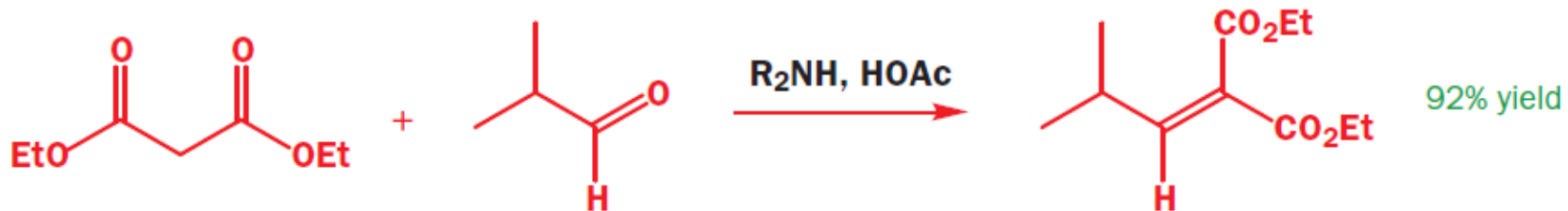


Example:

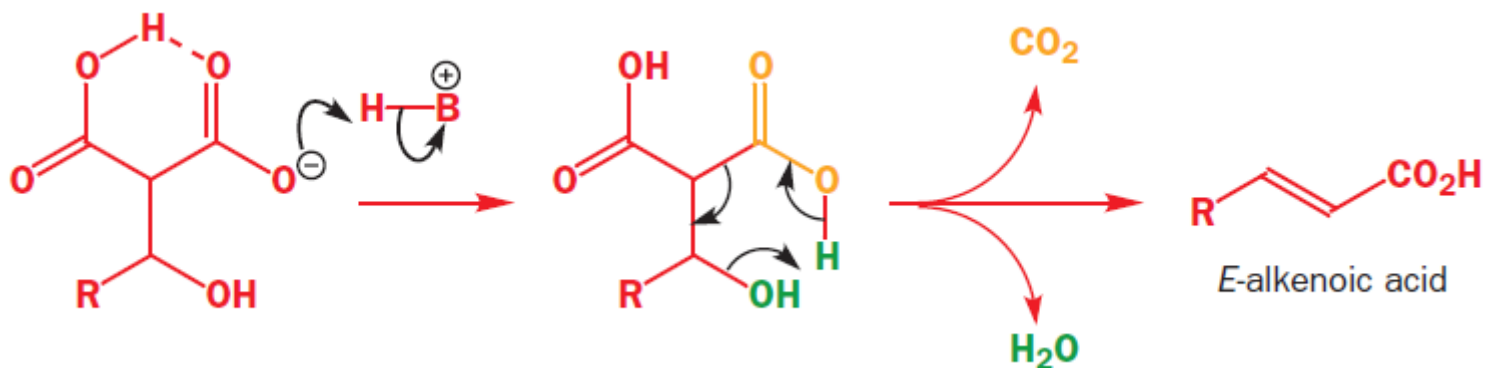
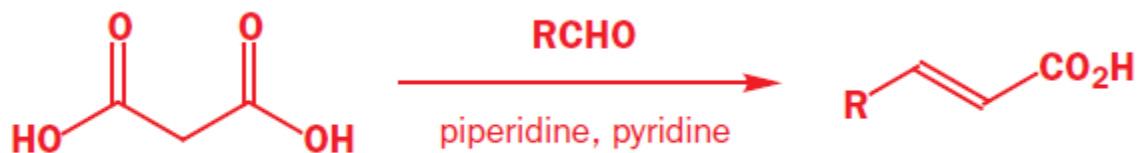


1,3-dicarbonyl compounds in aldol reactions

If we want a crossed aldol reaction, we simply add a **second, electrophilic carbonyl compound** such as an aldehyde, along with a **weak acid or base**



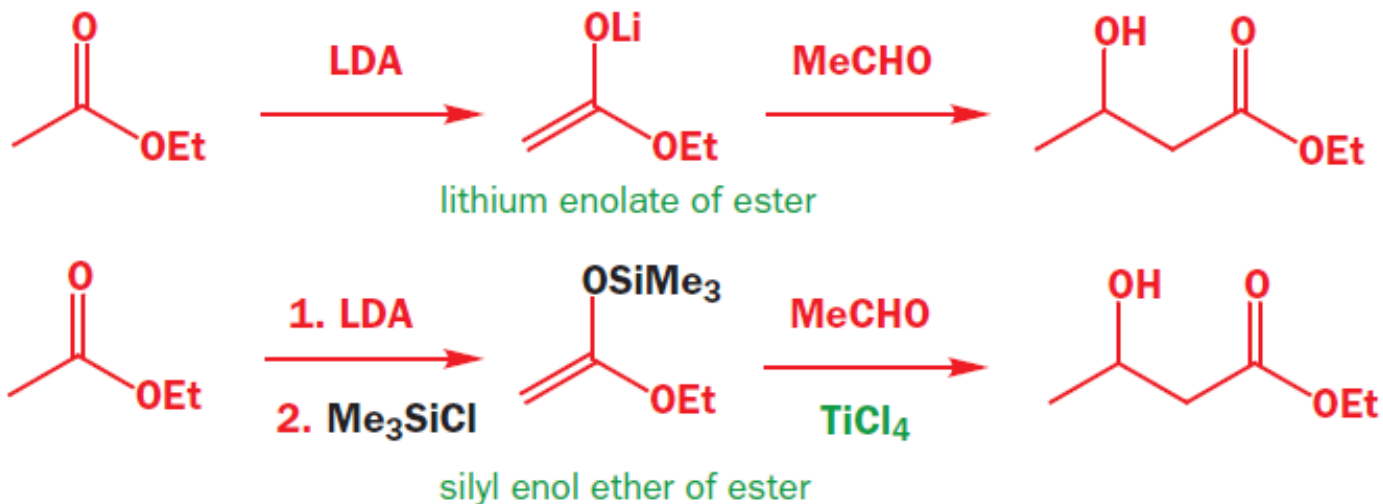
Decarboxylation



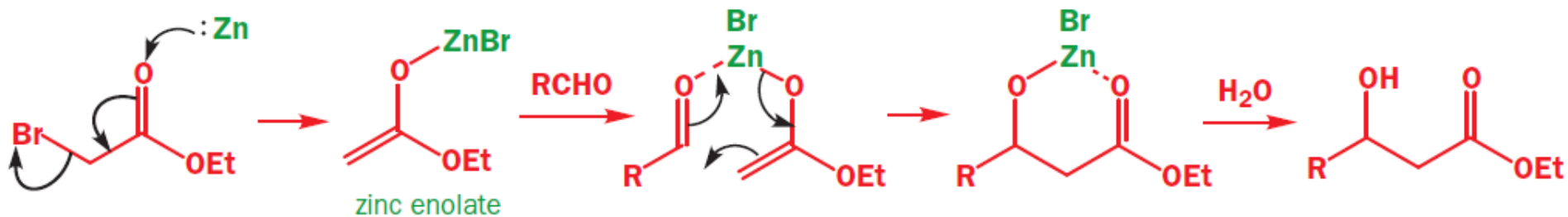
Enols and enolates from esters

56

Ester enolates **cannot be used in crossed aldols with aldehydes** because the aldehyde is both more enolizable and more electrophilic



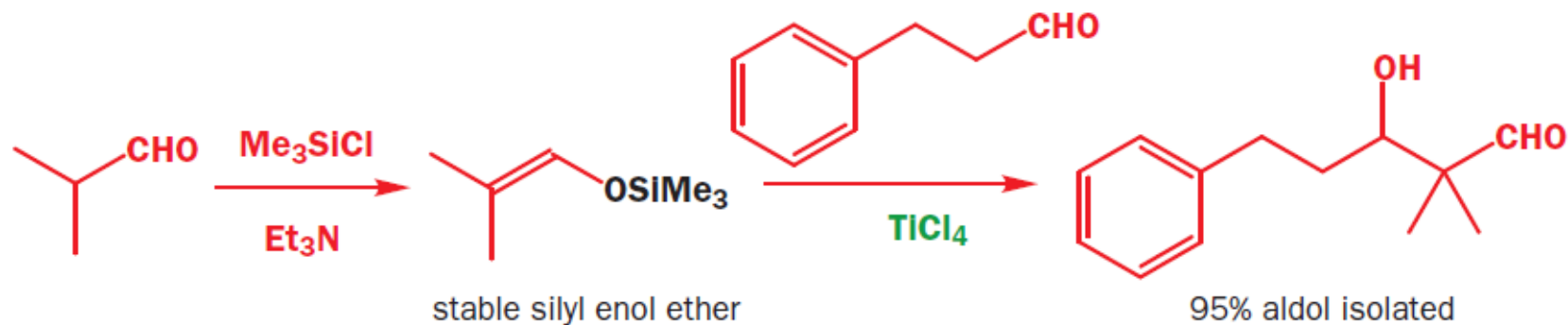
Zinc enolates, made from the **bromoesters**, are a good alternative to lithium enolates of esters (cf. Grignard reagent)



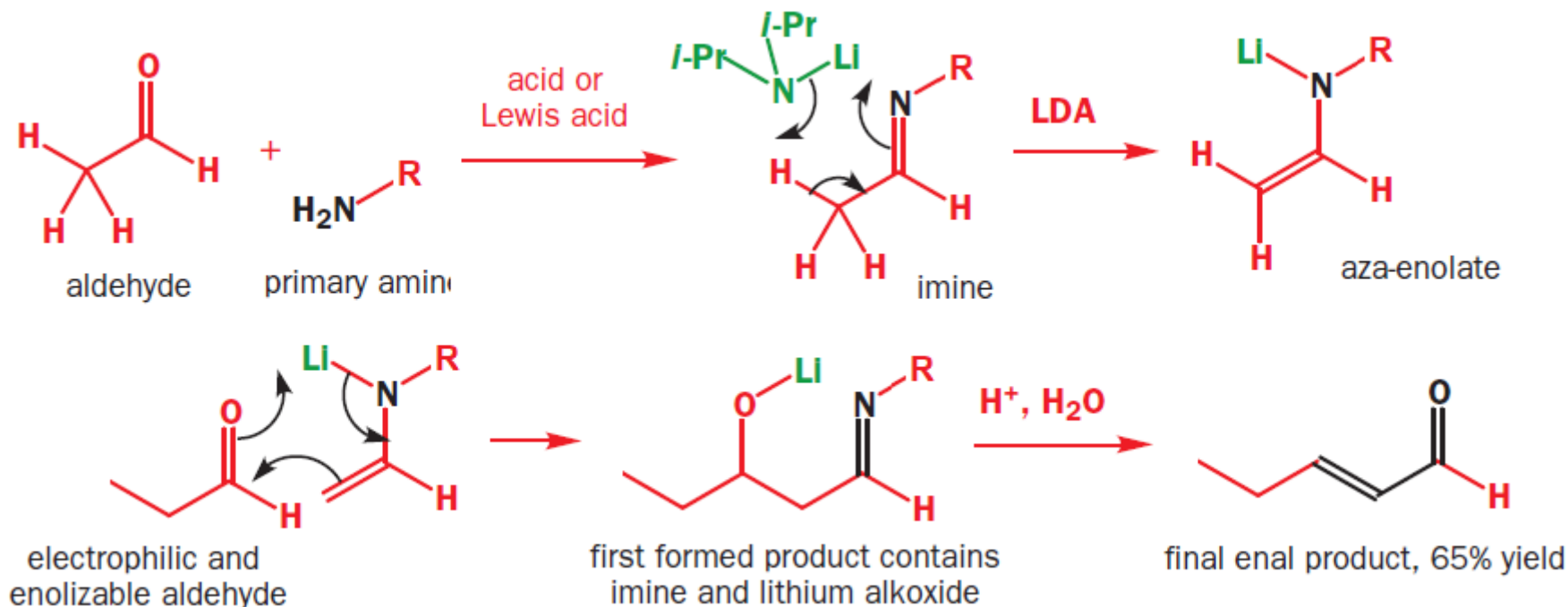
Specific enol equivalents for aldehydes

57

Lithium enolates can't be made cleanly, because the self-condensation reaction happens even at $-78\text{ }^{\circ}\text{C}$. **Silyl enol ethers** are a much better choice

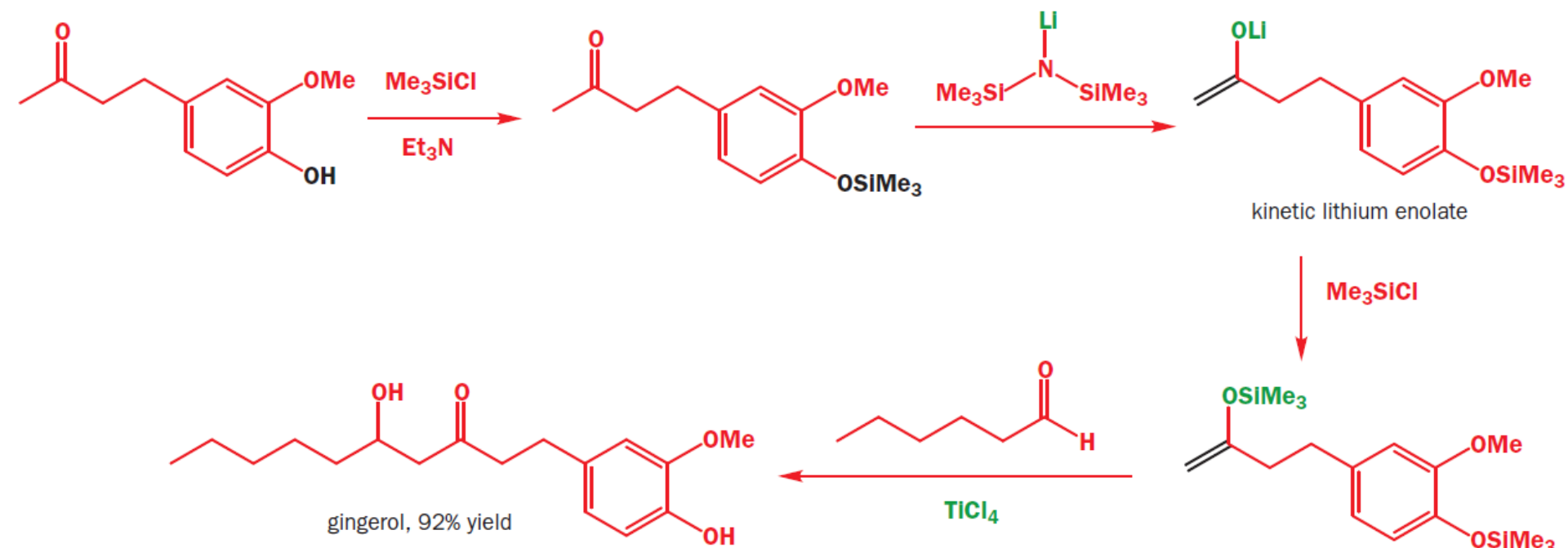
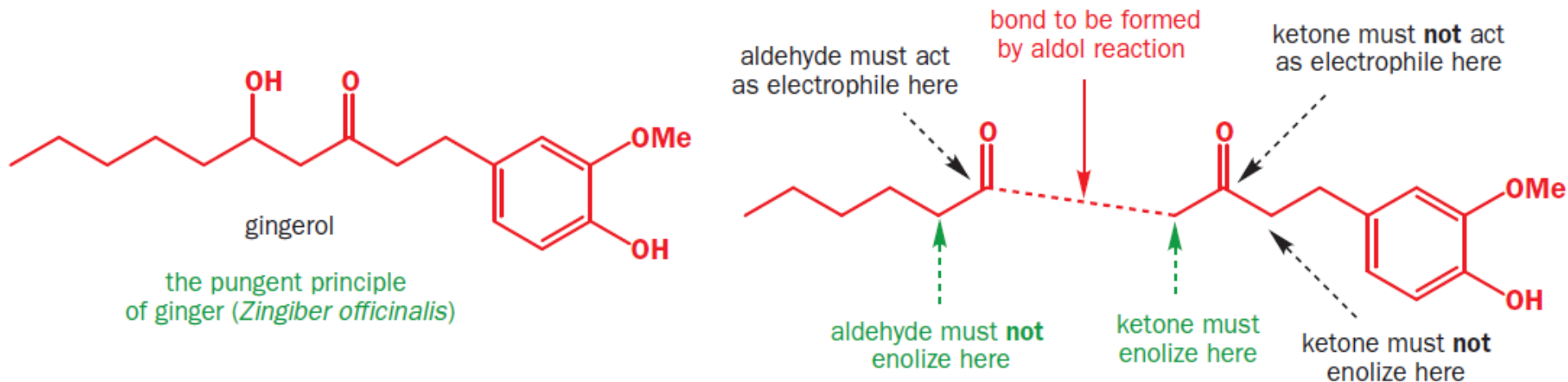


Other useful specific enol equivalents are **enamines** and **aza-enolates**



Example

58



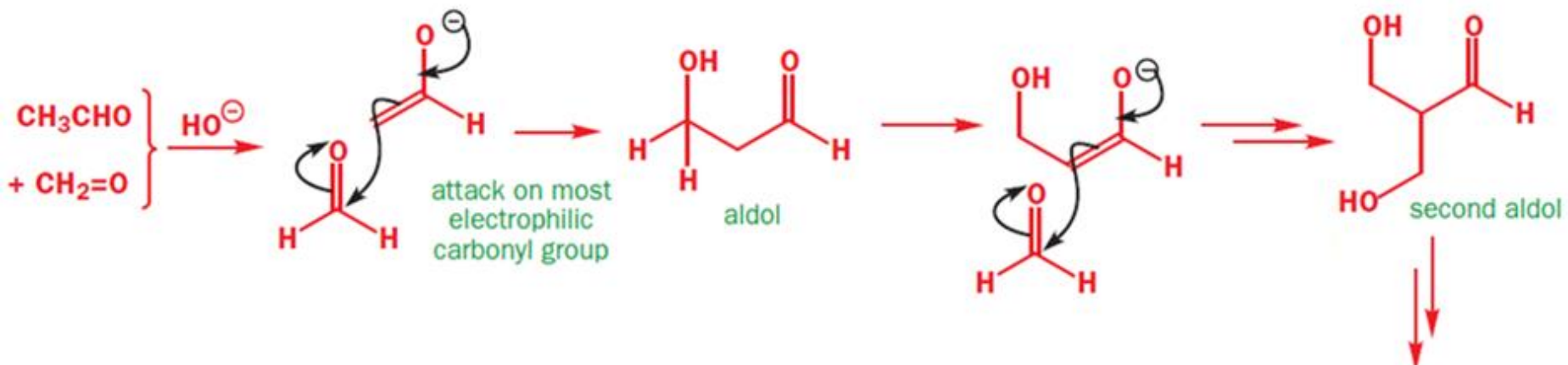
Useful enolates for the aldol reaction

Enolate type	Aldehyde	Ketone	Ester	Acid
lithium enolate	×	✓	✓	✓
silyl enol ether	✓	✓	✓	✓
enamine	✓	✓	×	×
aza-enolate	✓	✓	×	×
zinc enolate	×	×	✓	×

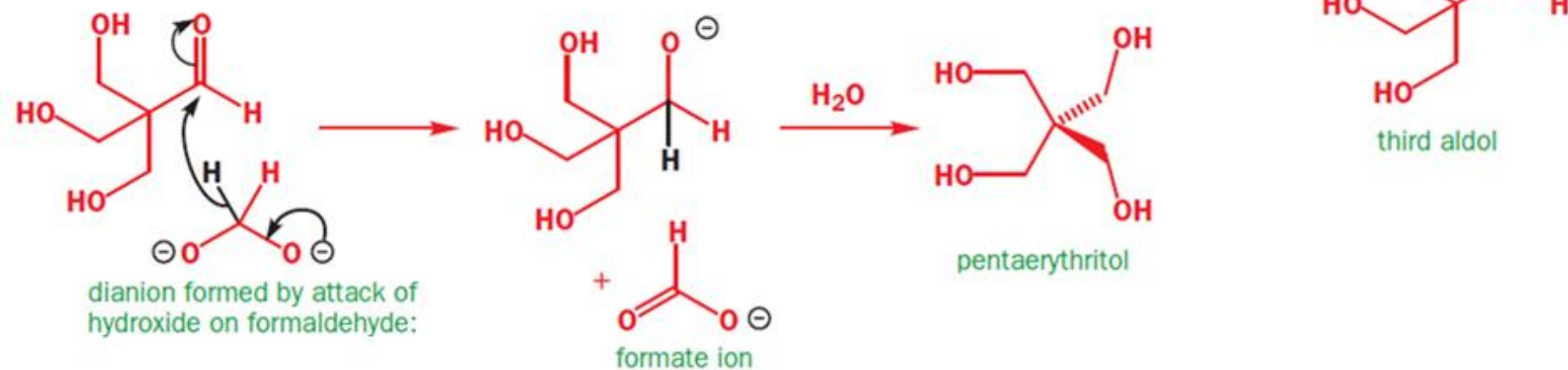
The Mannich reaction

Formaldehyde is **too reactive**. It tends to react more than once and to give extra unwanted reactions

crossed aldol reaction between acetaldehyde and formaldehyde



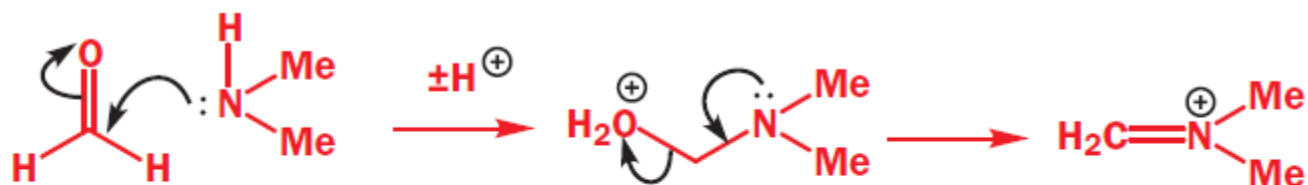
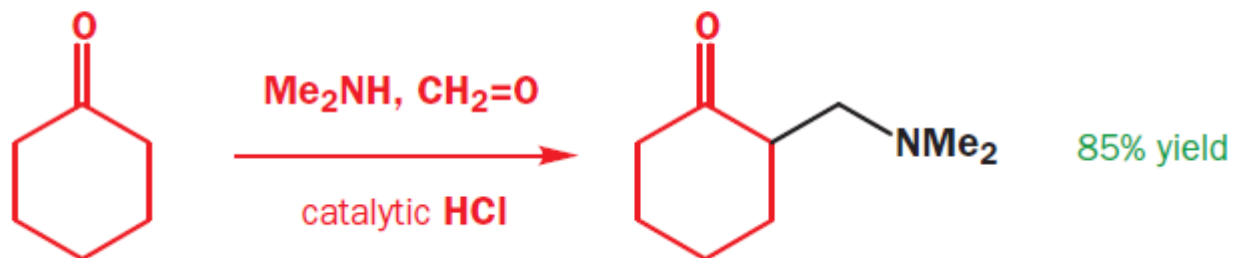
reduction by the Cannizzaro reaction



The Mannich reaction

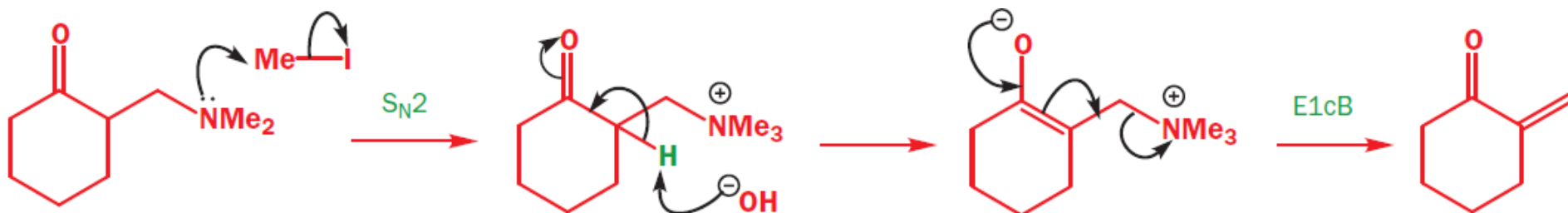
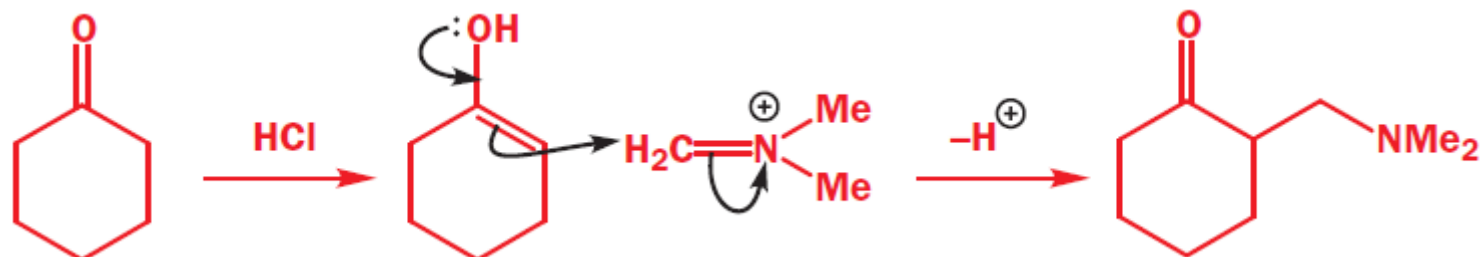
61

the Mannich reaction



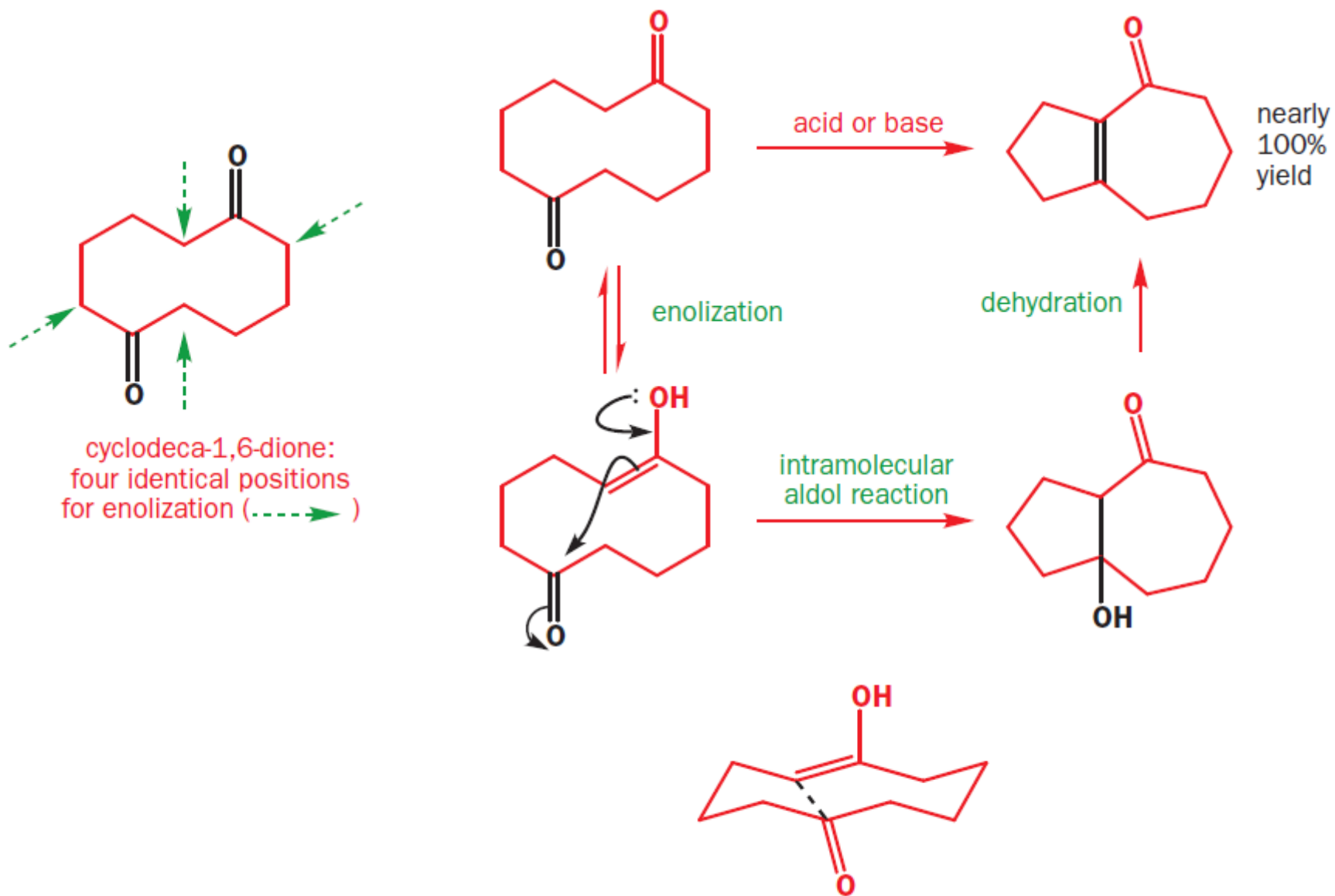
nucleophilic attack on more electrophilic C=O group

imine salt



1. alkylate amine to give ammonium salt 2. treat with base: E1cB elimination gives enone

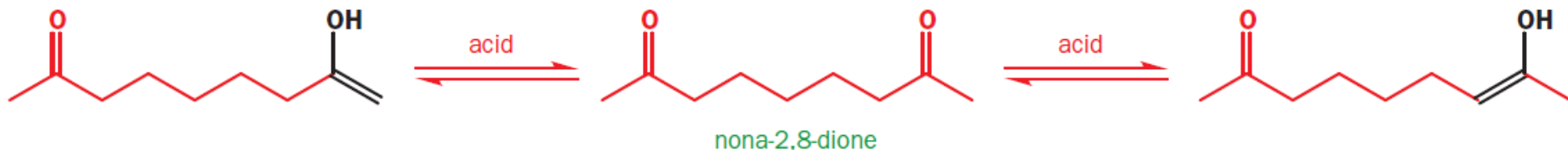
Intramolecular aldol reactions



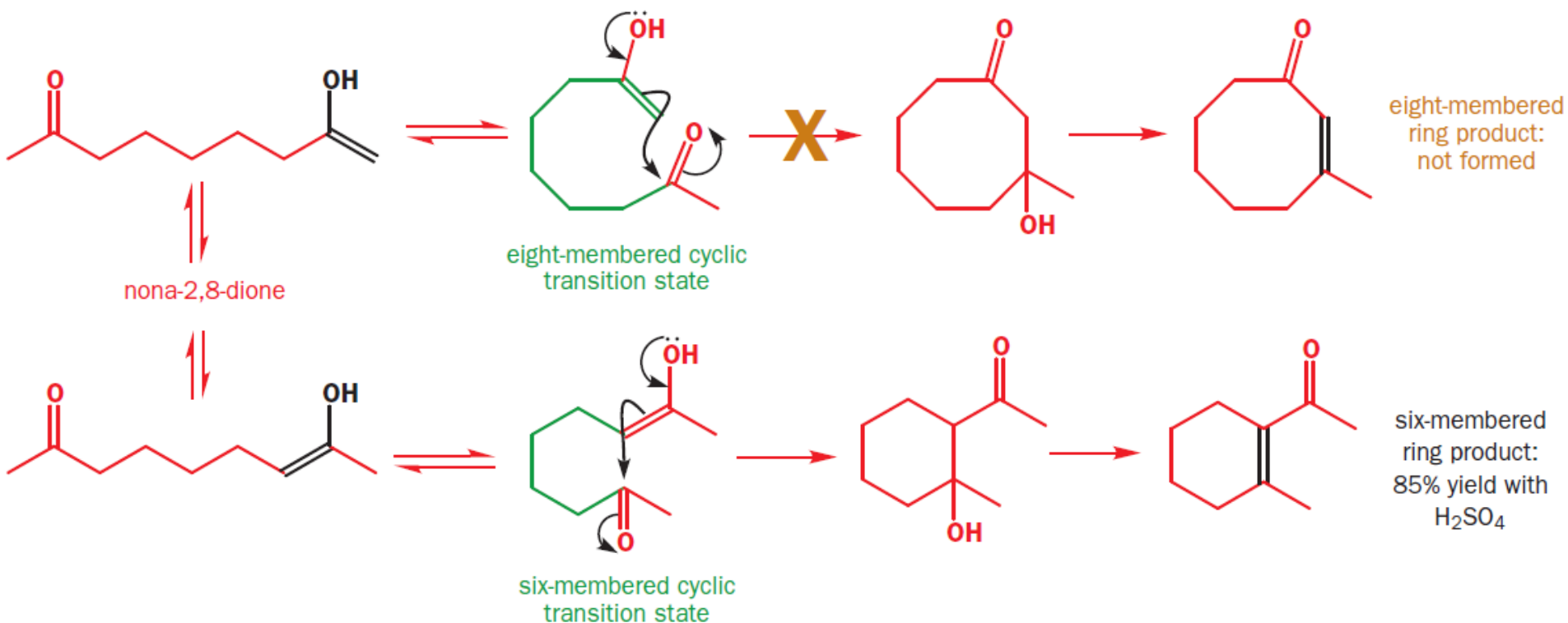
Intramolecular aldol reactions

63

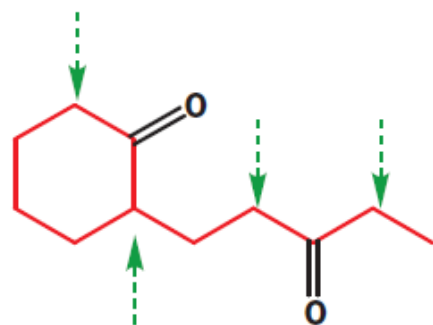
Acid-catalysed cyclization of the symmetrical diketone could give **two enols**



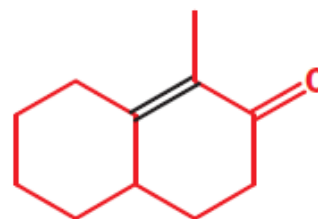
One enol can cyclize through an **eight-membered** cyclic transition state and the other through a **six-membered** ring



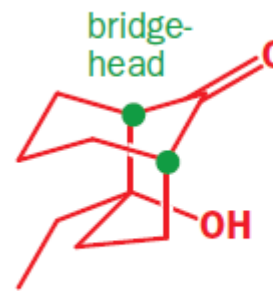
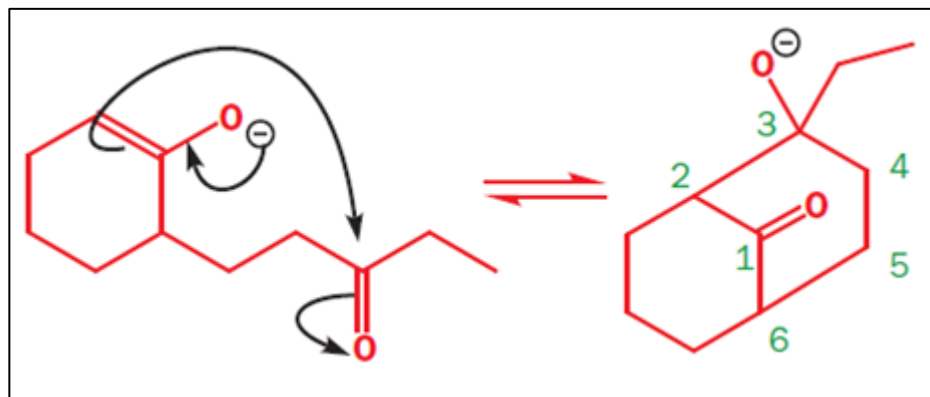
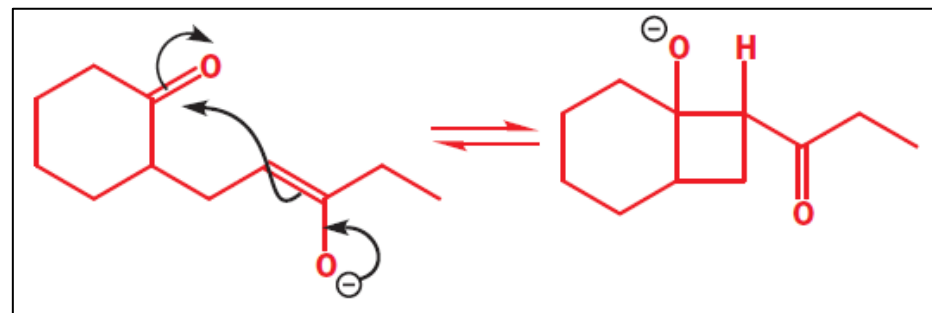
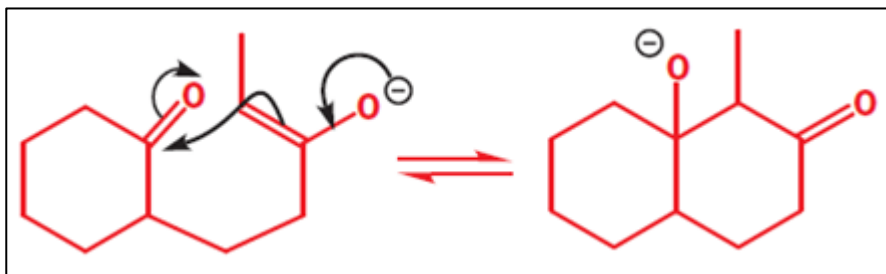
Intramolecular aldol reactions



four different positions where enolization is possible



one product formed in 90% yield



aldol product



impossible alkene

Intramolecular aldol reactions

