

2302774 – Advance Organic Synthesis

Lecture 2

C–C Bond Formation – Enolate Chemistry 2

- Acylation
- Conjugate addition
- Asymmetric reactions

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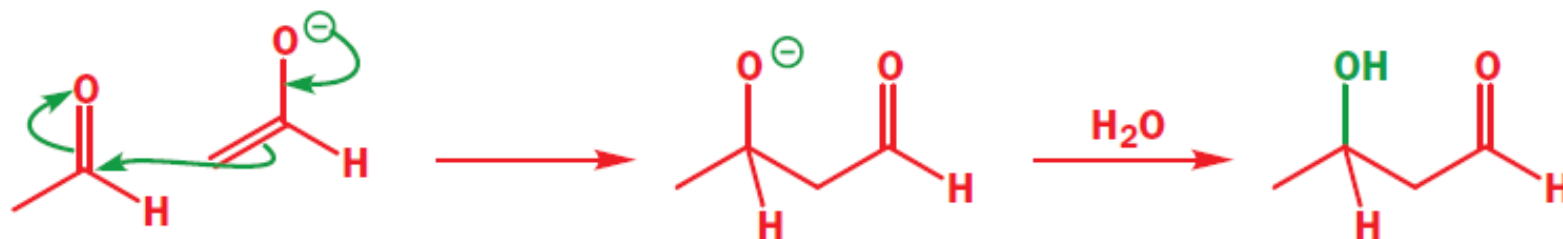
Recommended Textbook:

Chapter 28, 29, 33, 34 and 45 in *Organic Chemistry*, 1st Edition, J. Clayden, N. Greeves, S. Warren, **2001**, Oxford University Press

Claisen ester condensation

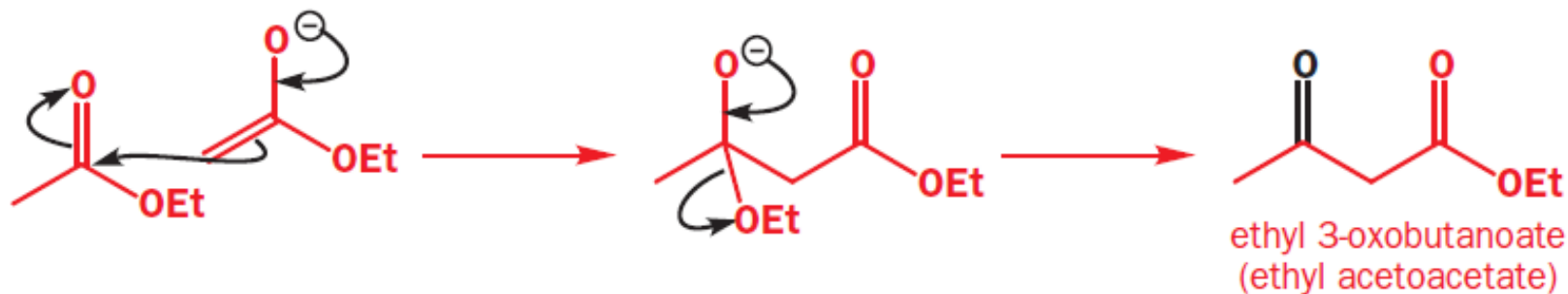
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completion of the aldol with acetaldehyde



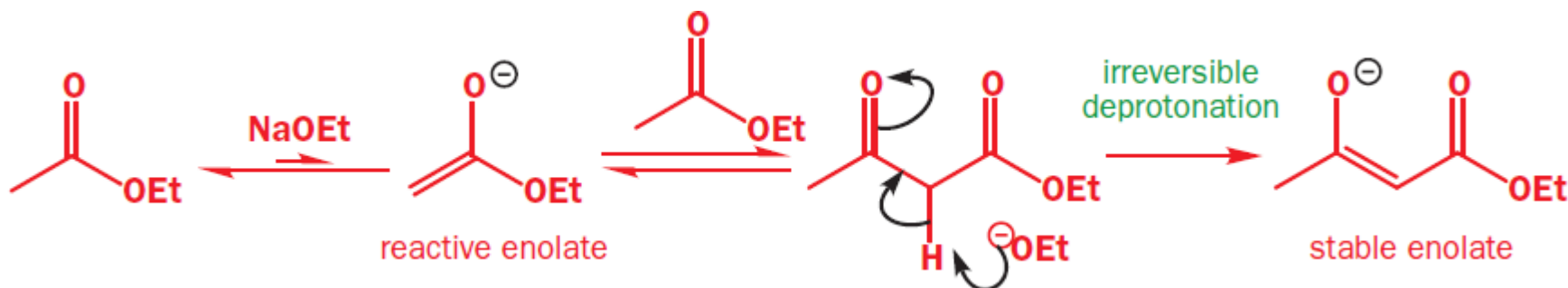
3-hydroxybutanal ('aldol')

the Claisen condensation with ethyl acetate



ethyl 3-oxobutanoate
(ethyl acetoacetate)

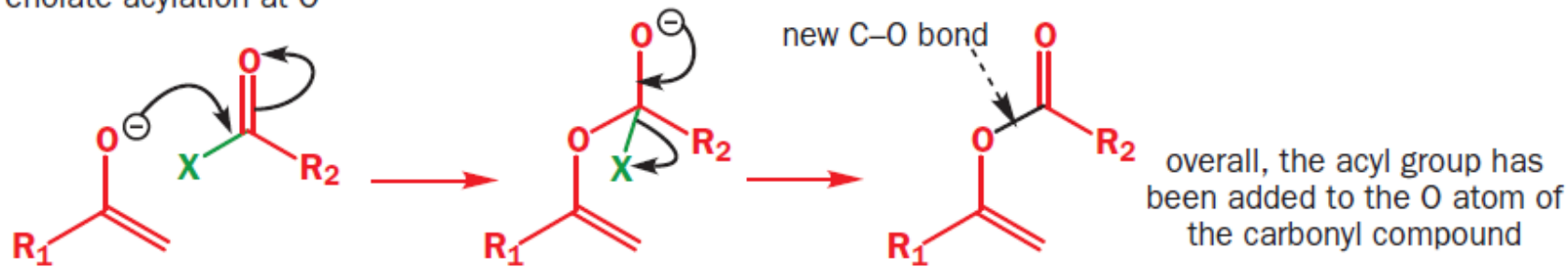
Ester dimerization works best when the product reacts with the ethoxide ion to give a **stable enolate ion**



Problems with Enolate Acylation

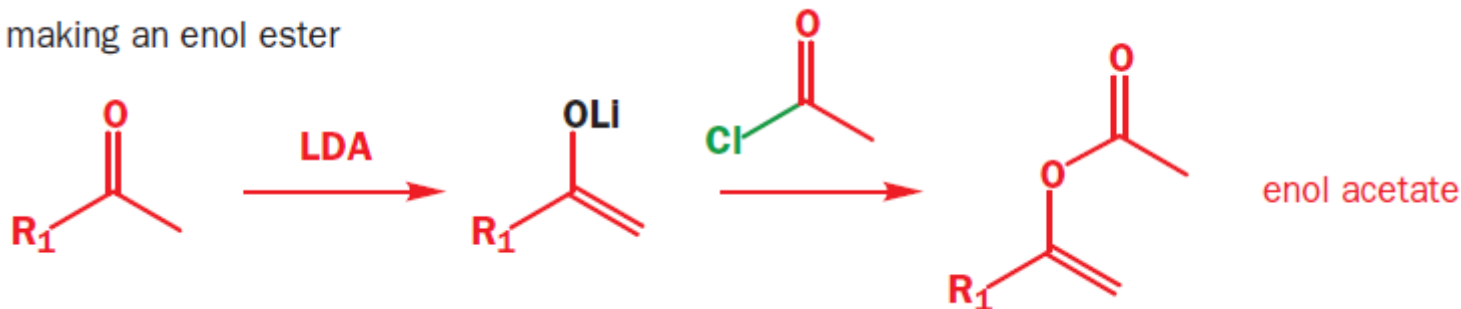
Reaction tends to occur at **oxygen** rather than at carbon

enolate acylation at O



The product of acylation on oxygen is an **enol ester**. The tendency to attack through oxygen is most marked with **reactive enolates** and **reactive acylating agents**

making an enol ester

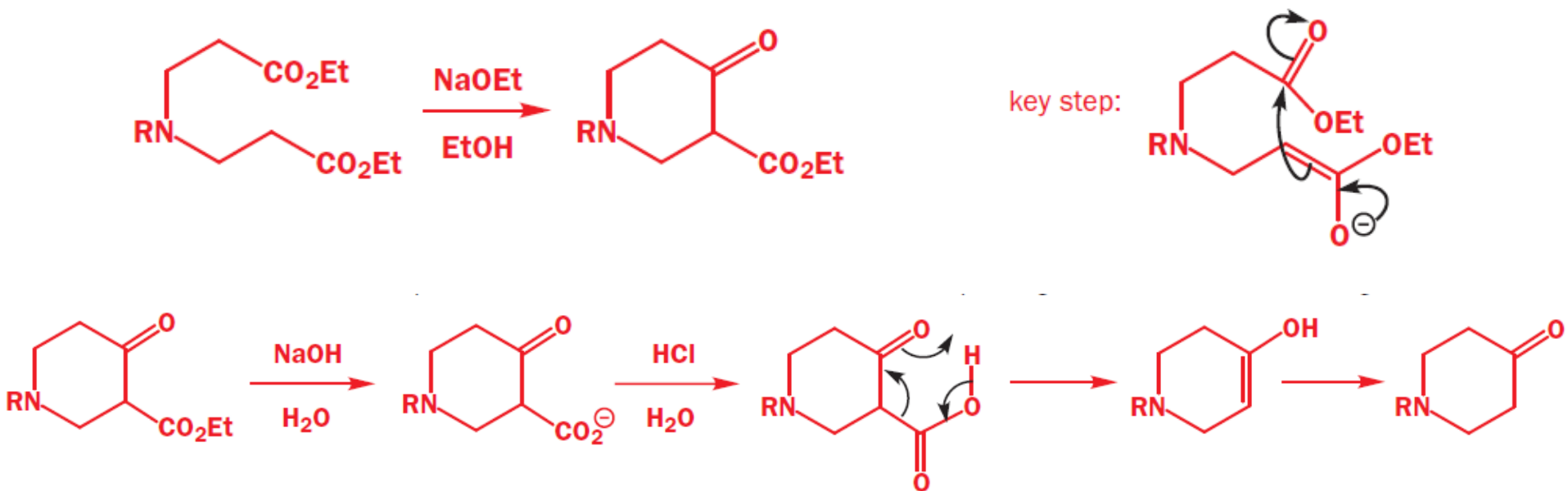
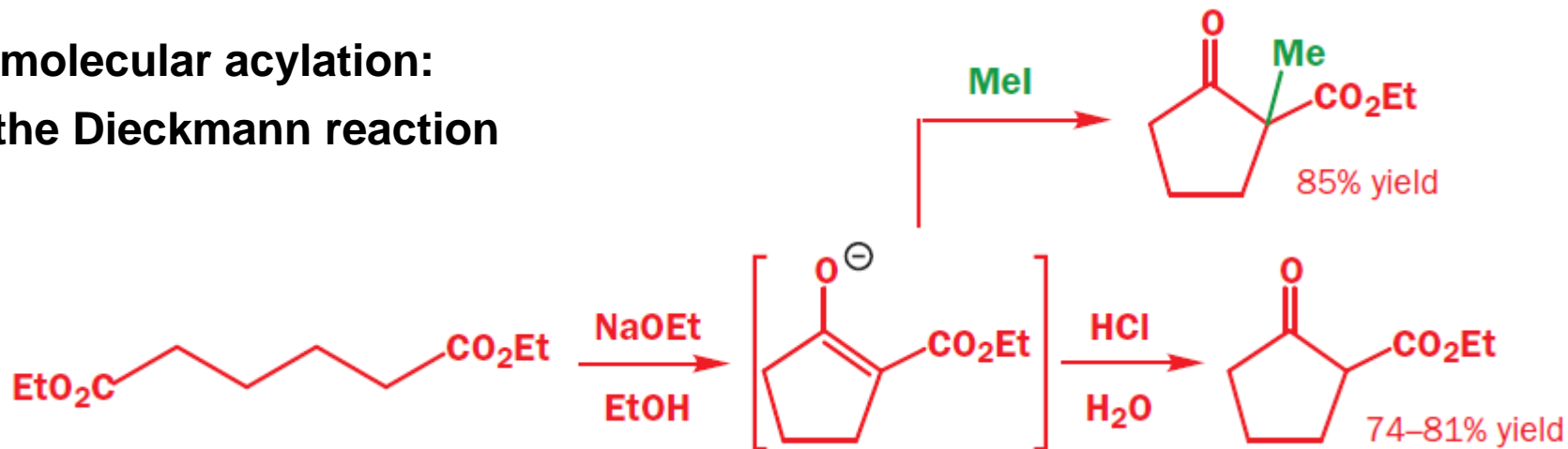


If we want acylation at carbon we must use either

- less reactive specific enol equivalents, such as **enamines** or **silyl enol ethers**, with reactive acylating agents such as **acid chlorides**
- reactive enols, such as the **enolate anions** themselves, with less reactive acylating agents such as **esters**

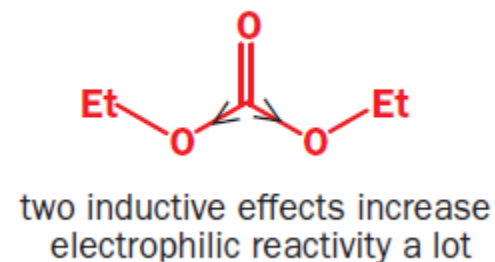
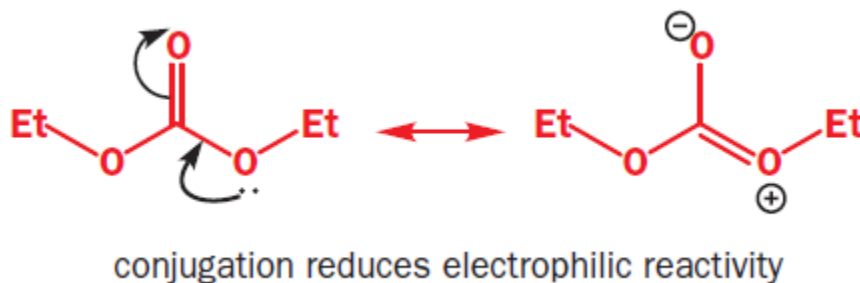
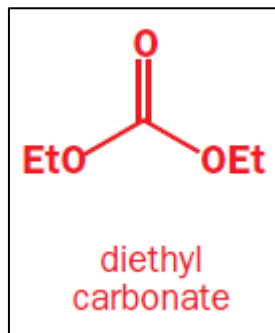
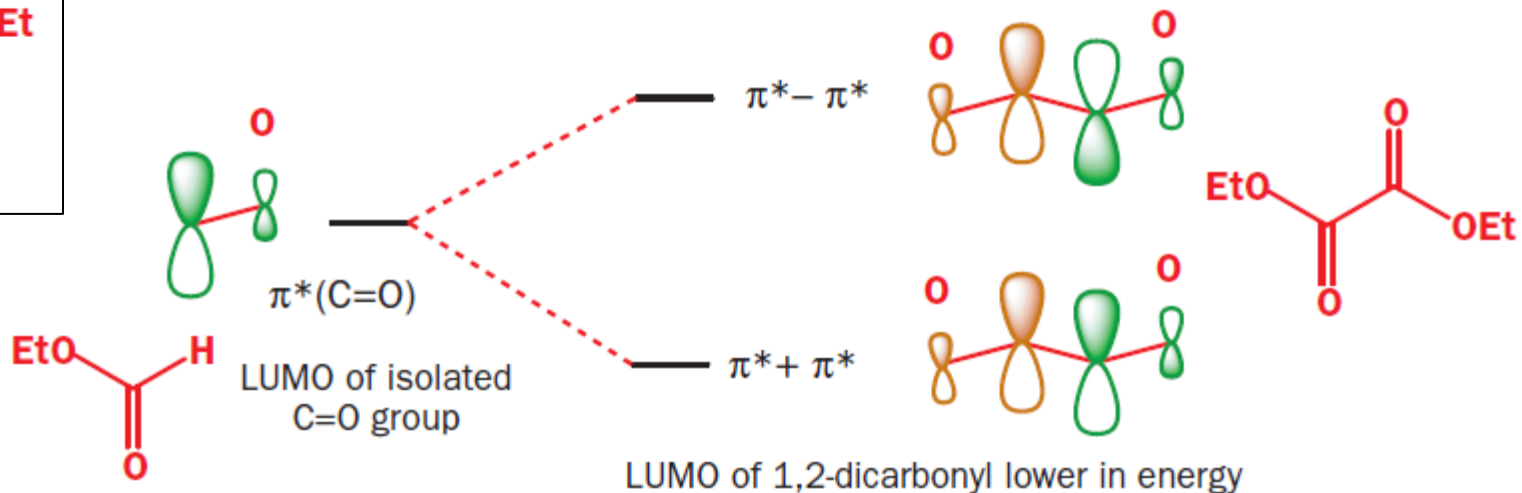
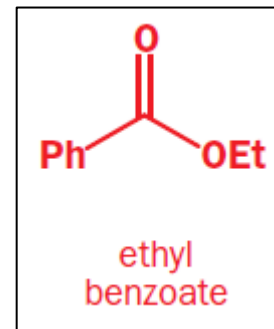
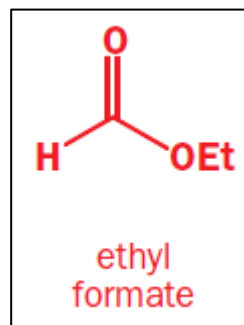
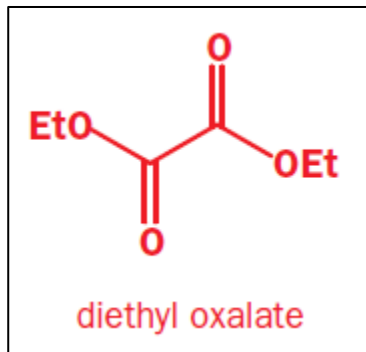
Acylation of enolates by esters

Intramolecular acylation:
the Dieckmann reaction

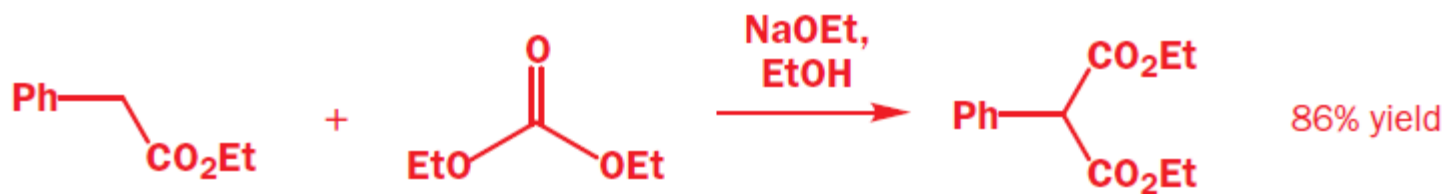
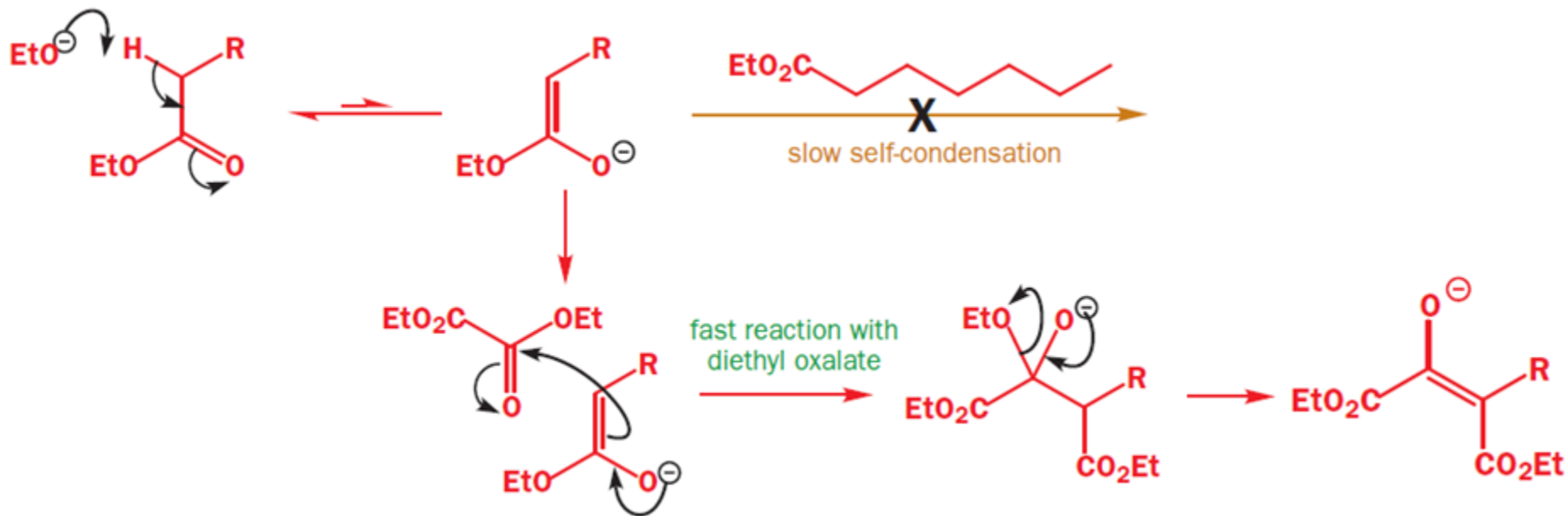
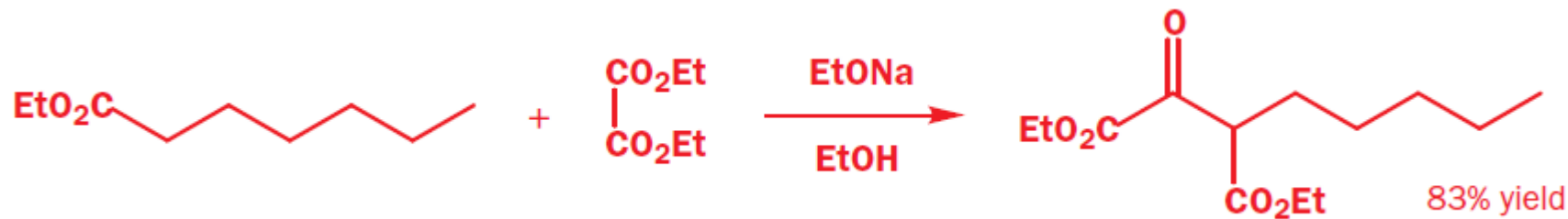


Crossed ester condensations

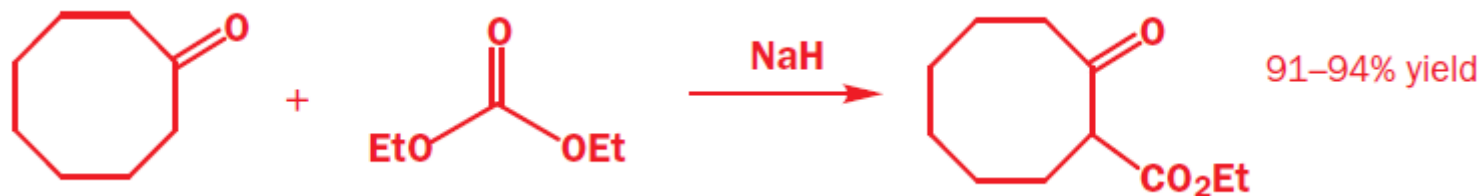
Reactive esters that cannot enolize



Crossed ester condensations



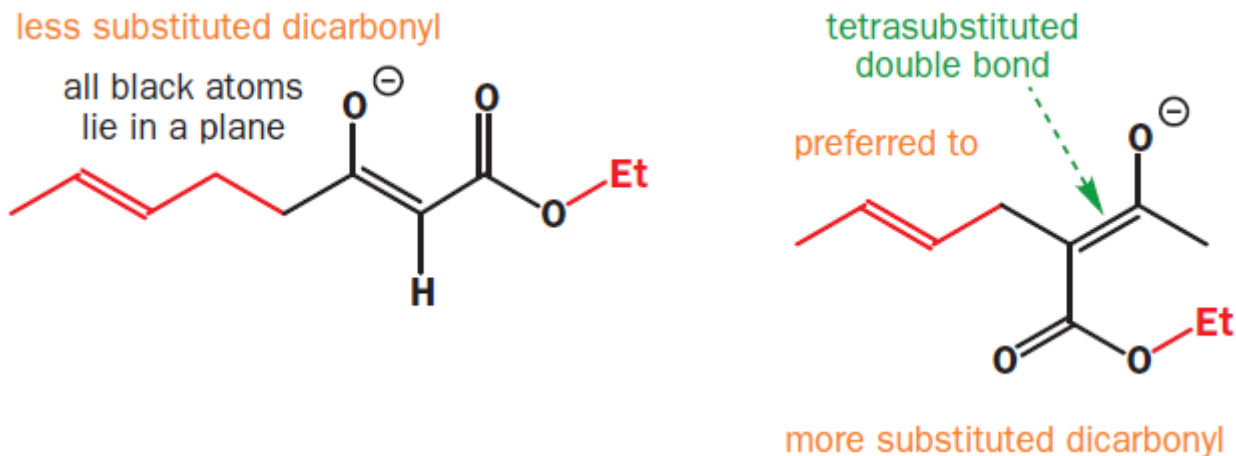
Crossed ester condensations



Unsymmetrical ketones often give a single product on the **less substituted side**

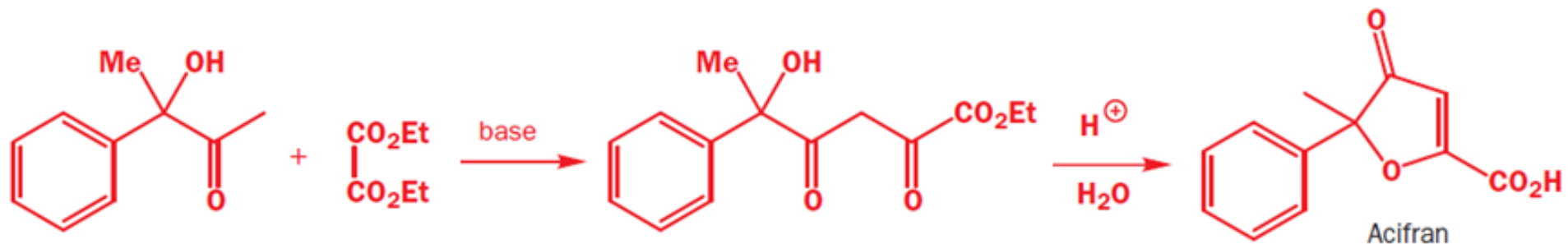


less substituted dicarbonyl enolate is preferred because it constrains fewer groups to lie in the **hindered plane** of the tetrasubstituted enolate double bond

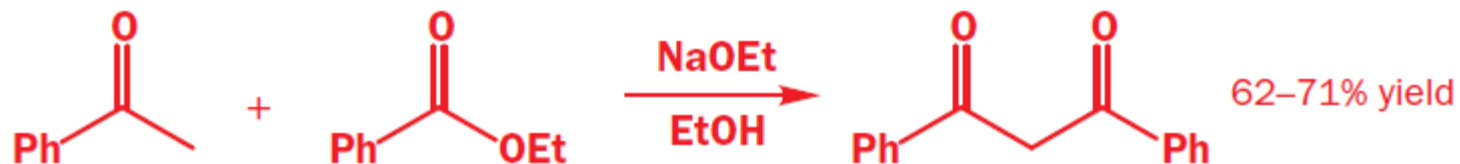


Crossed ester condensations

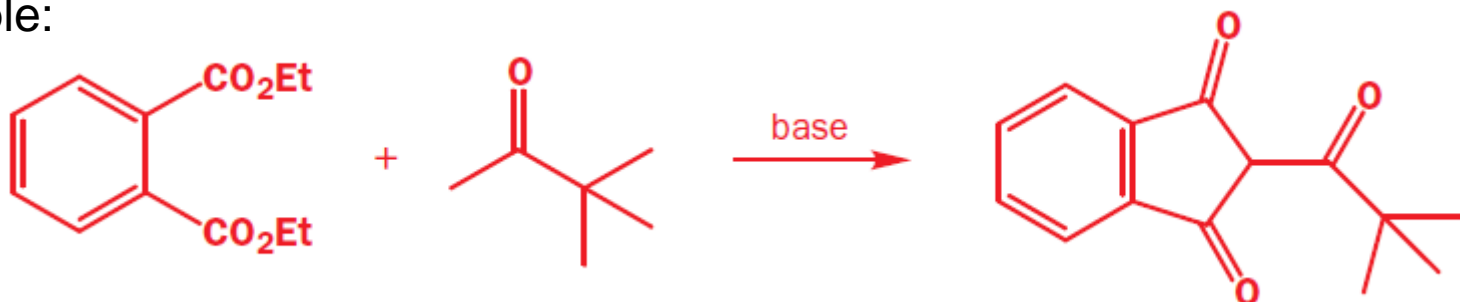
Example:



Example:



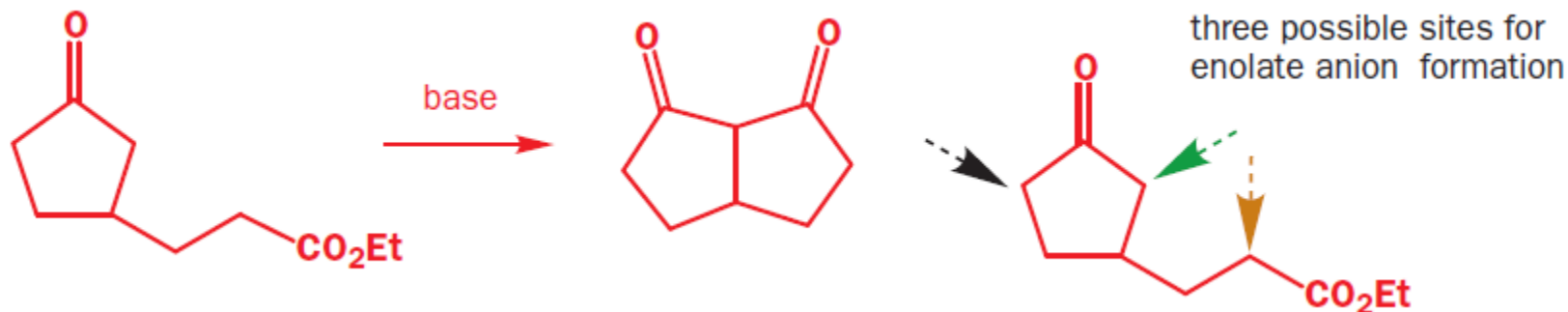
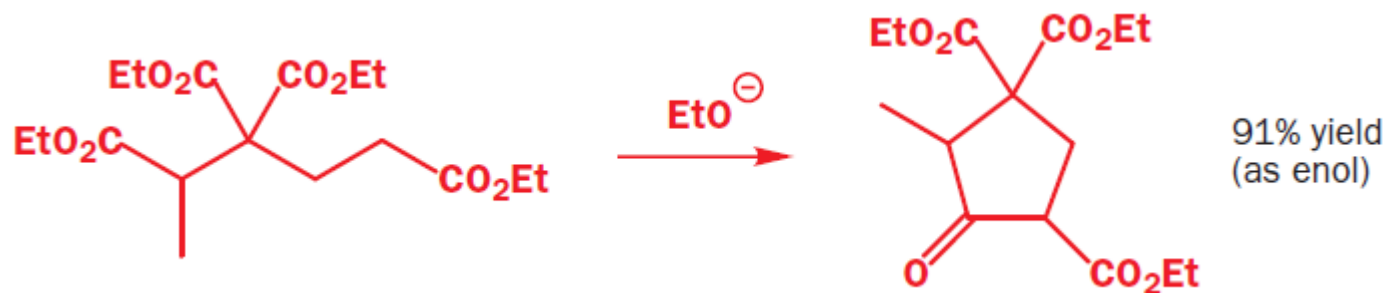
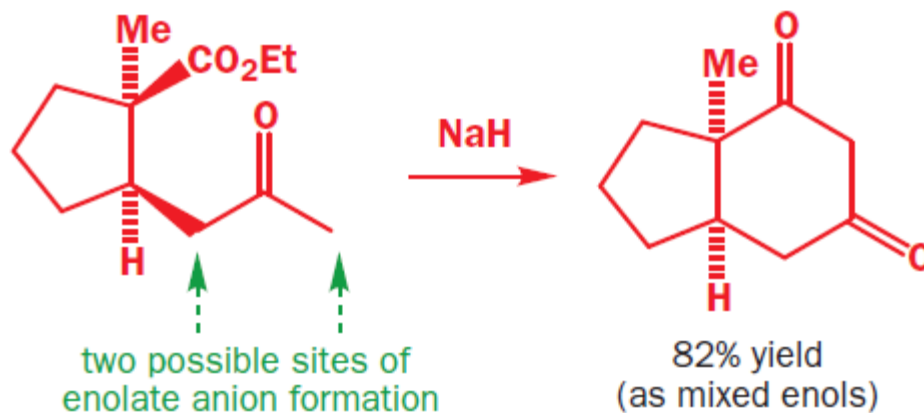
Example:



Intramolecular crossed Claisen ester condensations

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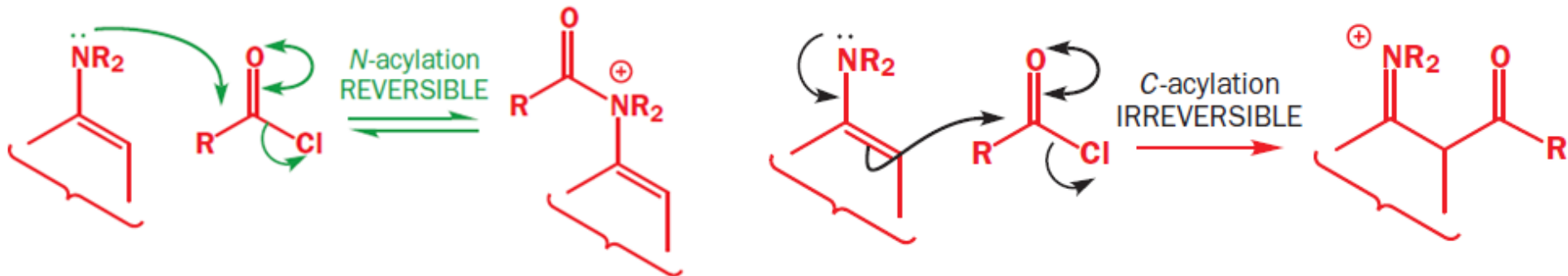
The reaction usually give the **most stable product** (thermodynamically controlled)



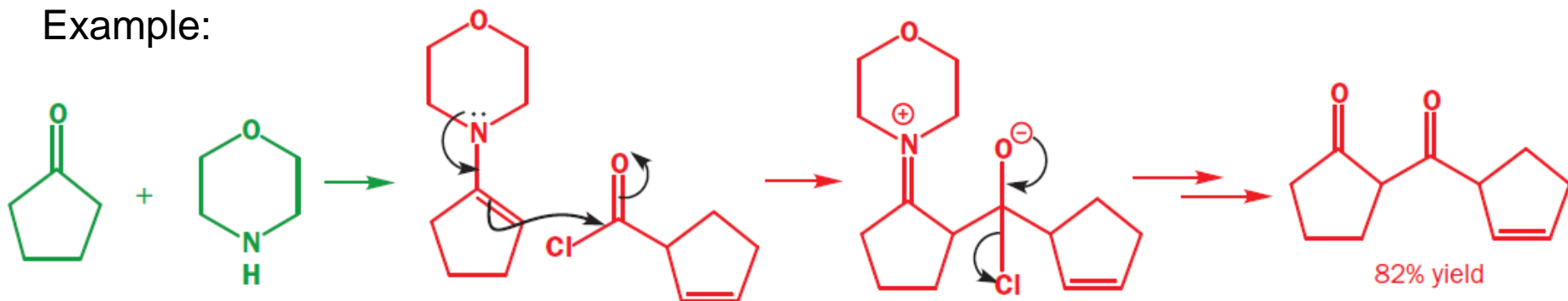
The acylation of enamines and aza-enolates

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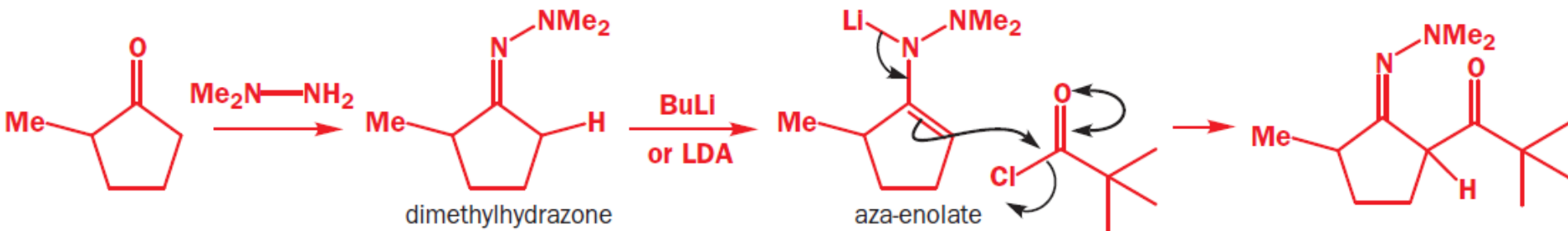
The product of **N-acylation** are unstable salts (**reversible**). Acylation on **carbon**, on the other hand, is **irreversible**



Example:

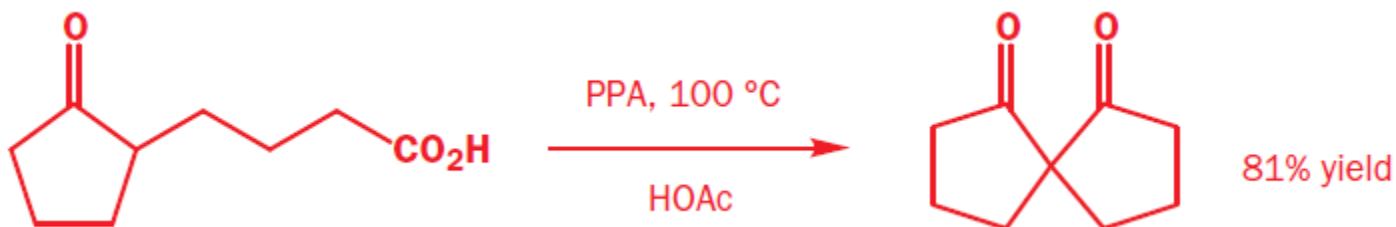
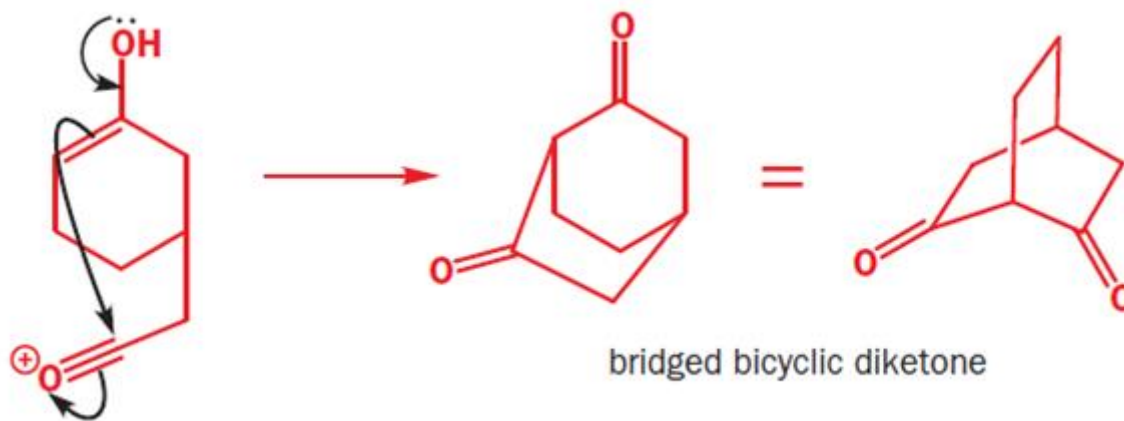
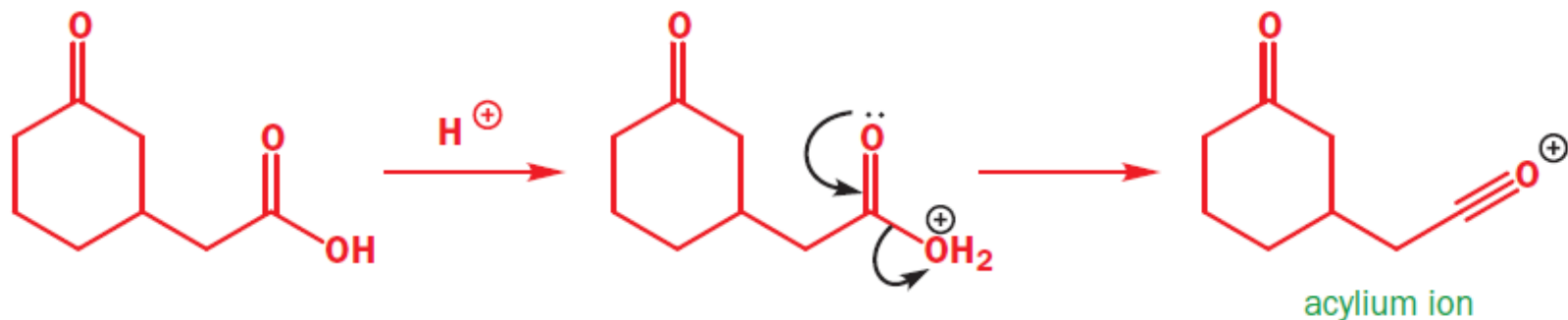


Aza-enolate forms on the **less substituted side**

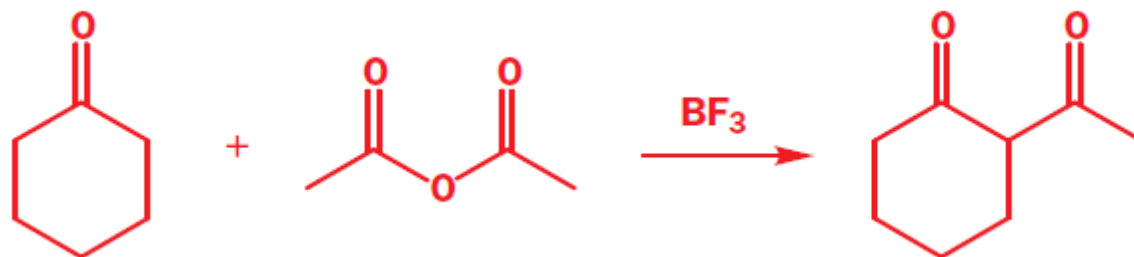


Acylation of enols under acidic conditions

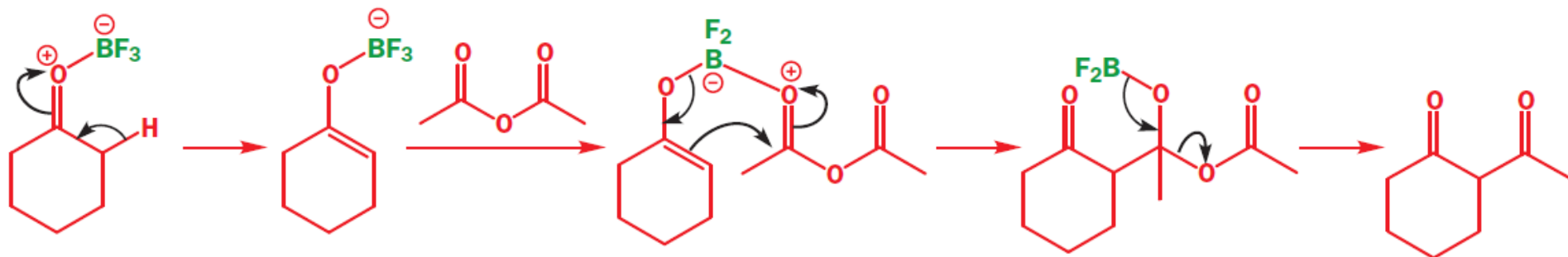
Under strongly acidic anhydrous conditions, carboxylic acids **dehydrate** to give the **acylium ions**



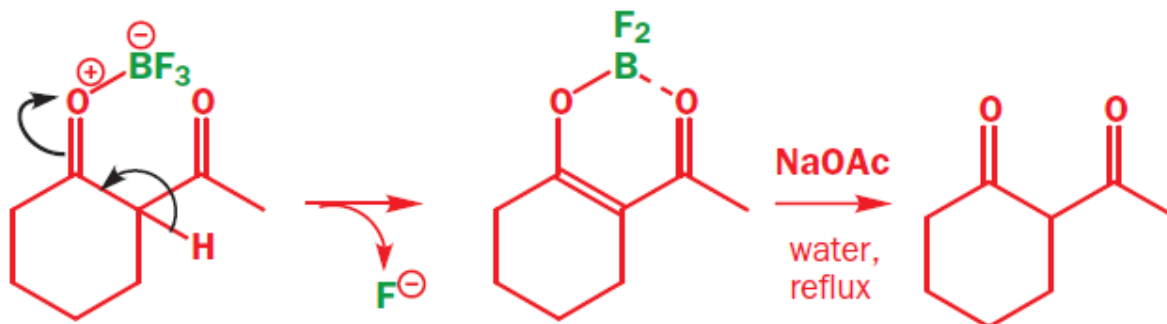
Lewis acid-catalysed acylation of enols



The mechanism obviously involves attack by the enol (or '**boron enolate**') of the ketone on the anhydride, catalysed by the Lewis acid

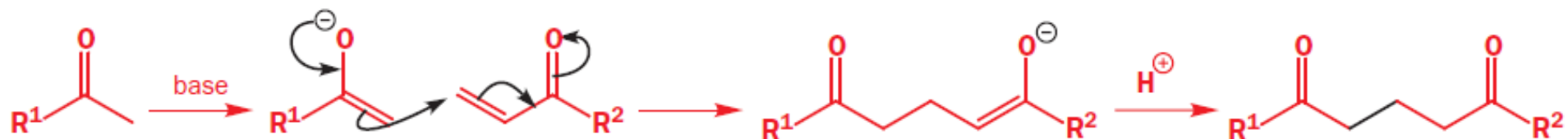


Under the conditions of the reaction, the product forms a **stable boron enolate**, which needs to be decomposed to the diketone

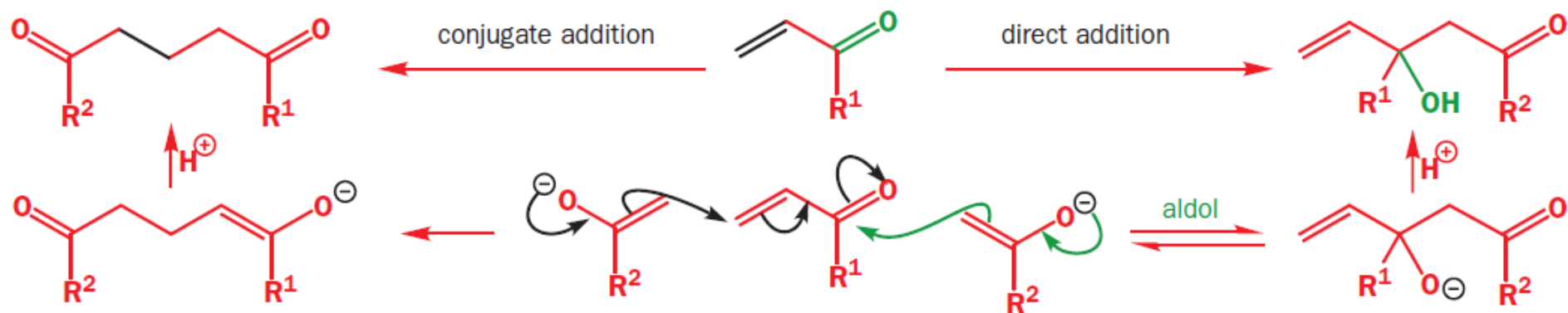


Conjugate Addition of Enolates

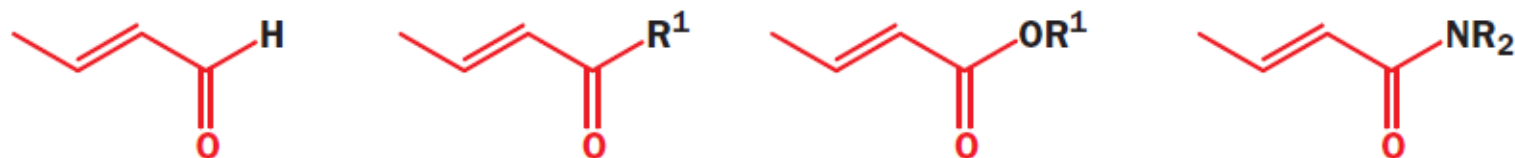
The product with **two carbonyl groups** are widely used in various synthesis



Conjugate addition of enolates is the result of **thermodynamic control**; The aldol product is **more sterically hindered** than the conjugate addition product



The **more electrophilic** carbonyl groups give **more direct addition**



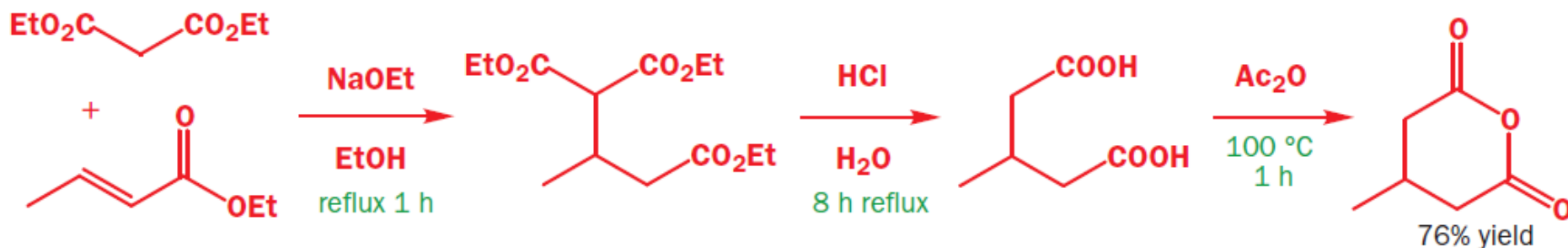
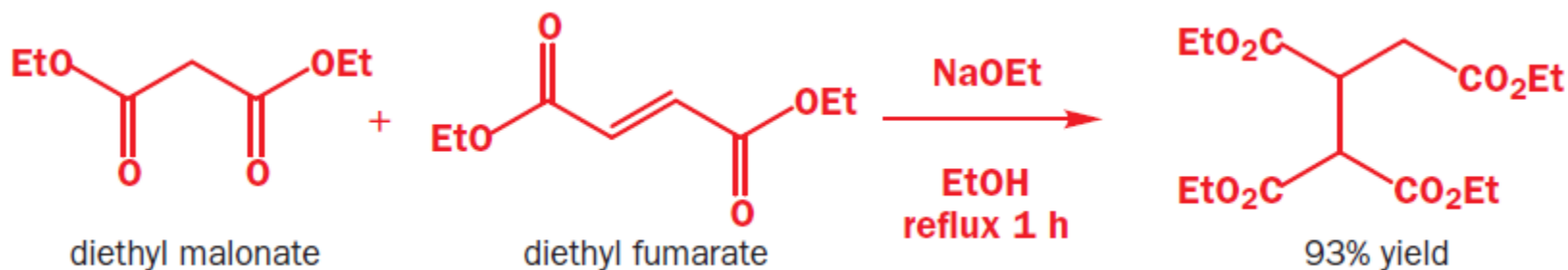
decreasing reactivity of carbonyl with nucleophiles

increasing tendency to conjugate addition

Conjugate Addition of Enolates

β -Diesters (malonates and substituted derivatives) combine three useful features

- They form **stable enolate anions** that undergo clean conjugate addition
- One of the ester groups can be removed by **decarboxylation**
- The remaining acid or ester is ideal for **conversion** into other functional groups

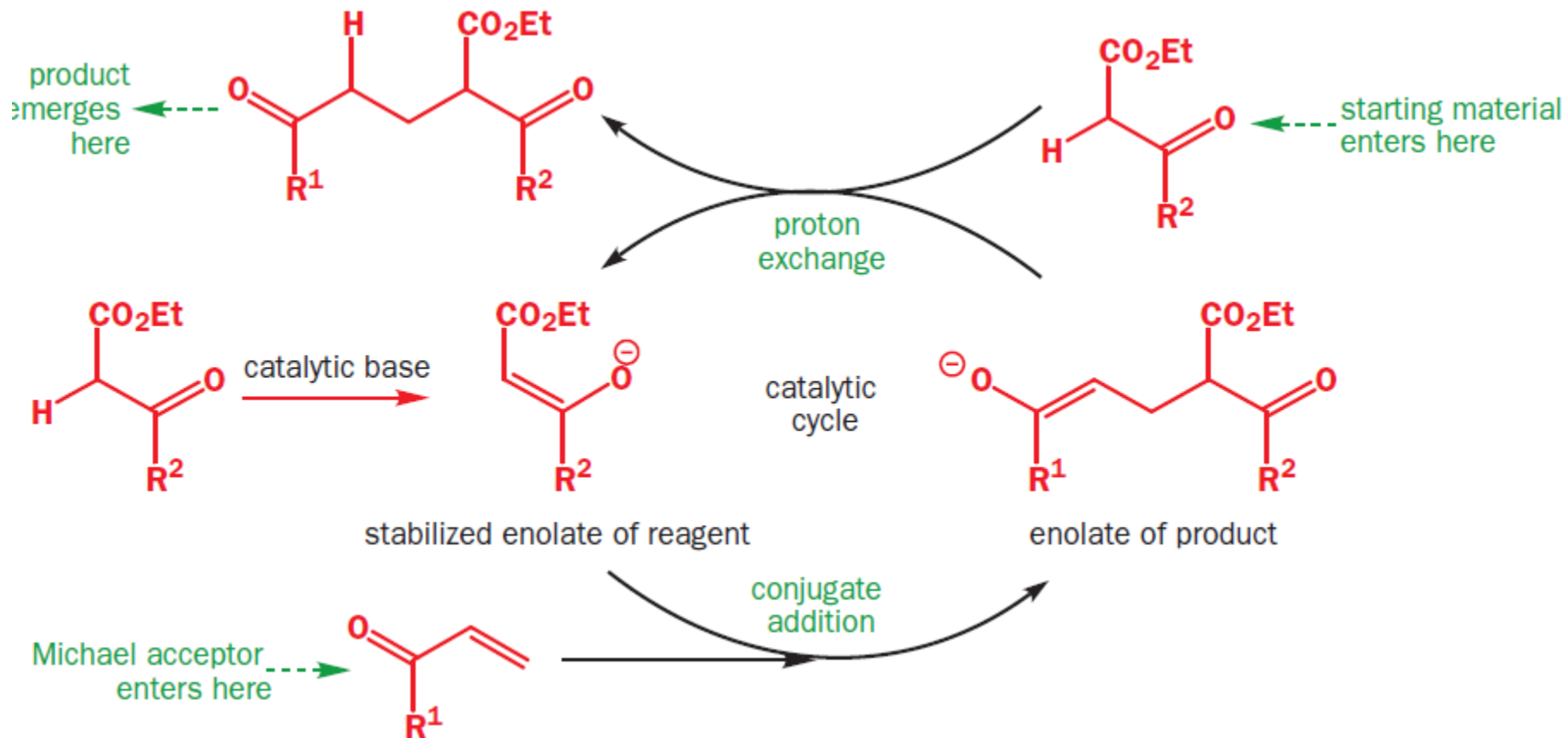


Conjugate addition can be catalytic in base

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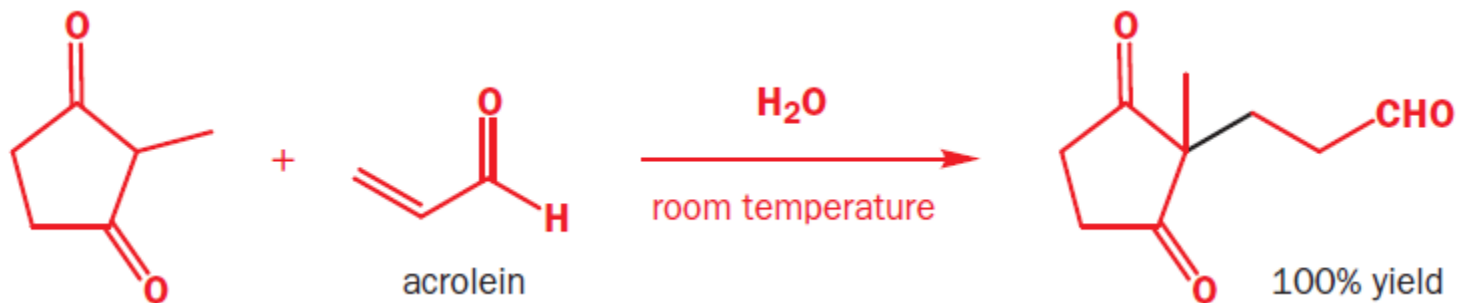
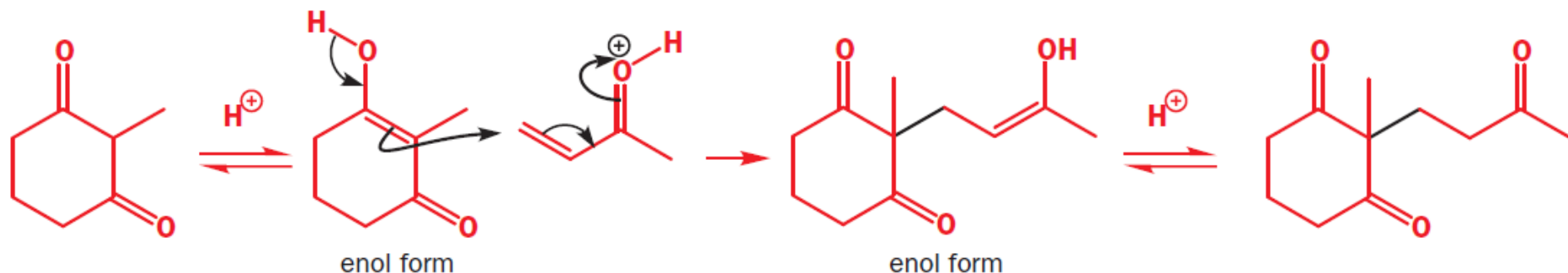
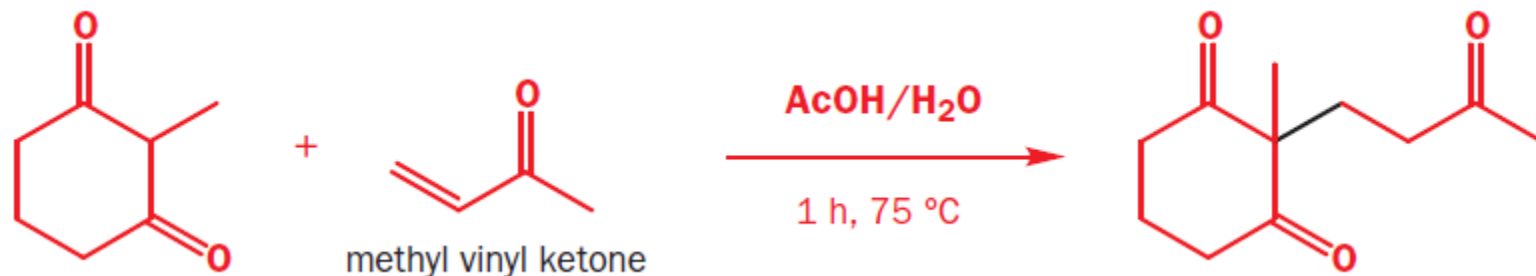


The **enolate anion of the product** is protonated by a molecule of **starting material** to give the neutral final product and another enolate anion of starting material



Conjugate addition of Enols

If the nucleophile is **sufficiently enolized** then the enol form is perfectly able to attack the unsaturated carbonyl compound. **Enols** are neutral and thus **soft** nucleophiles **favouring conjugate attack**

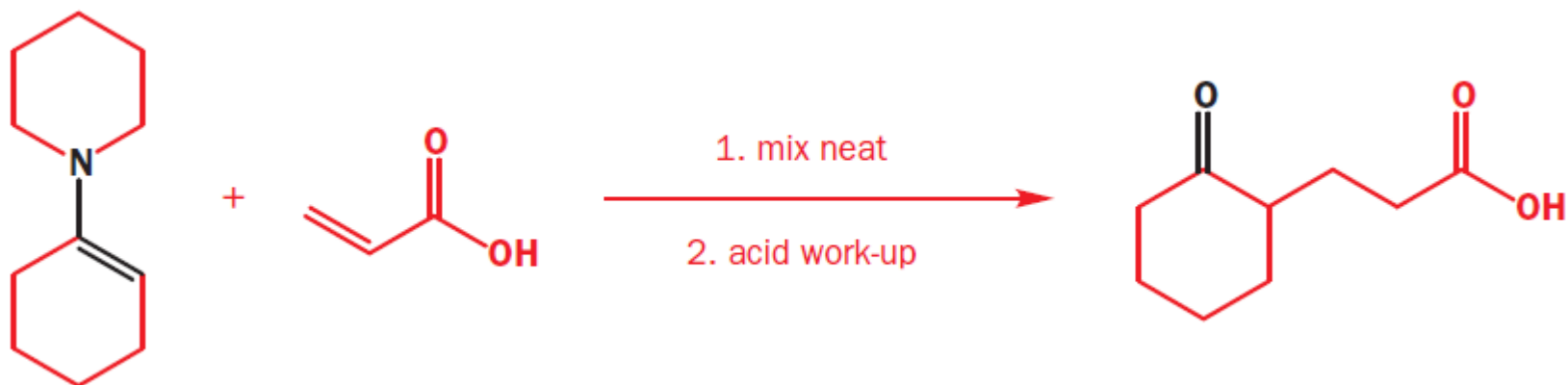


Conjugate addition of Enamines

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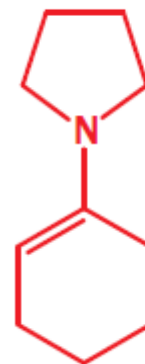
Enamines can be used to carry out conjugate addition of a carbonyl compound **without having a second anion stabilizing group**

They are **soft** nucleophiles (perfect for **conjugate addition**) but are **more reactive** than enols and can be prepared **quantitatively** in advance

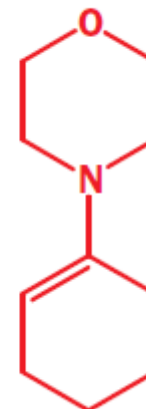


A range of secondary amines can be used to form the enamines but those formed from **piperidine**, **pyrrolidine**, and **morpholine** combine **reduced steric demands** at the reactive double bond with **good availability of the nitrogen lone pair**

pyrrolidine enamine



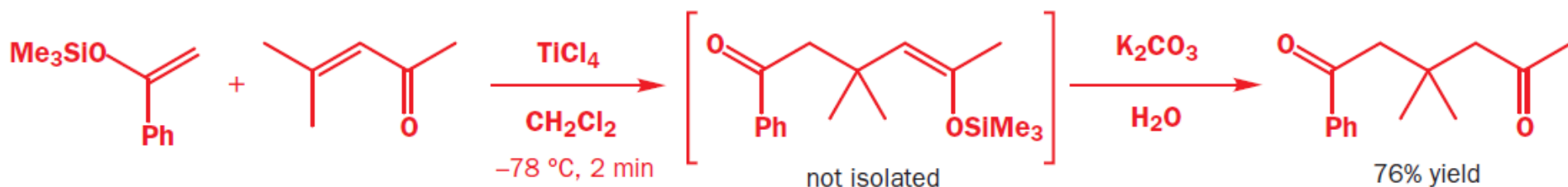
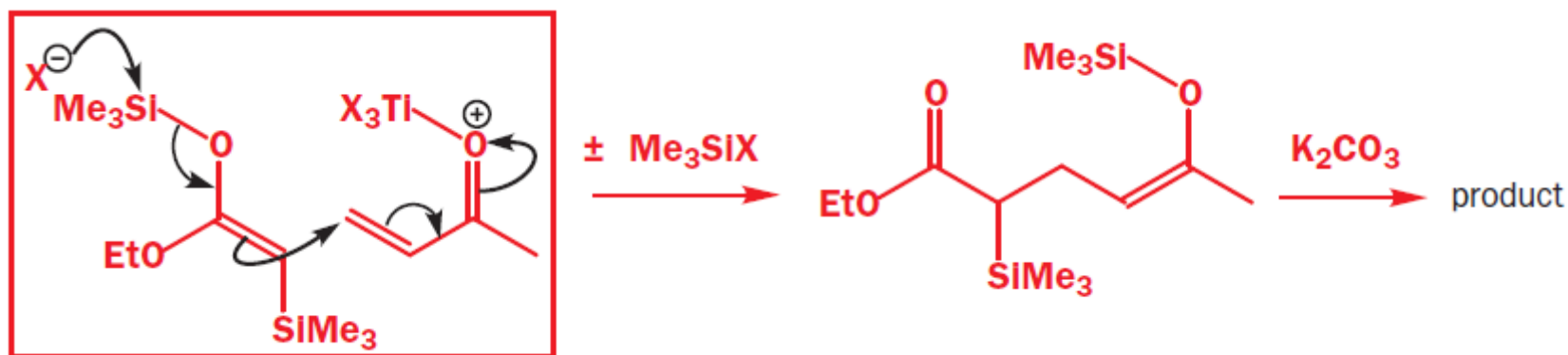
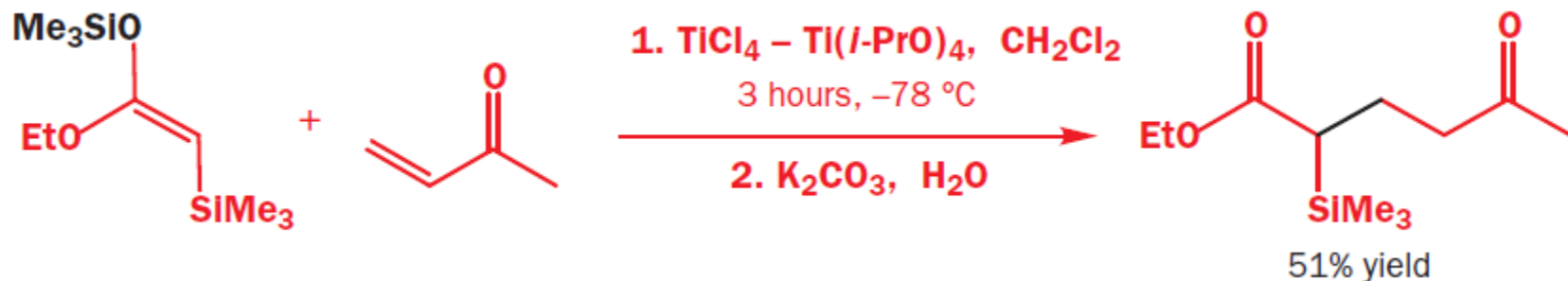
morpholine enamine



Conjugate Addition of Silyl Enol Ethers

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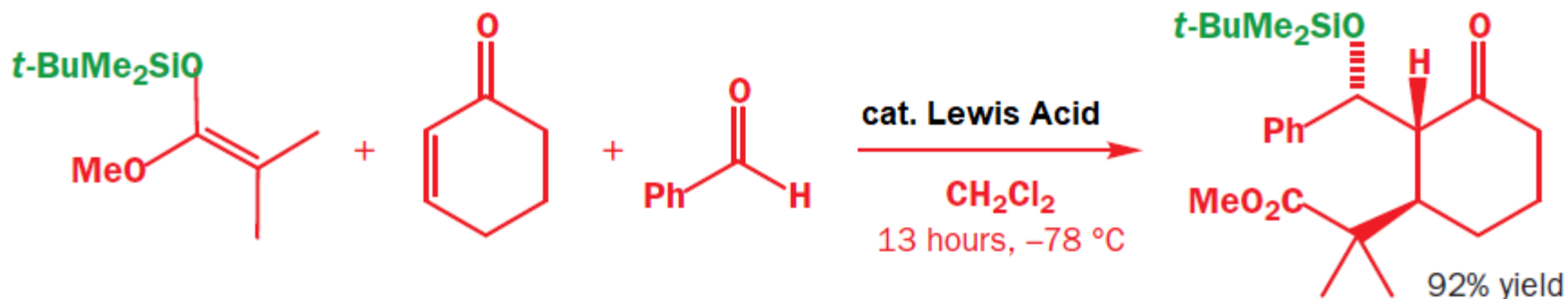
These stable neutral nucleophiles also react very well with Michael acceptors either **spontaneously** or with **Lewis acid catalysis at low temperature**, giving **silyl enol ether of the product**



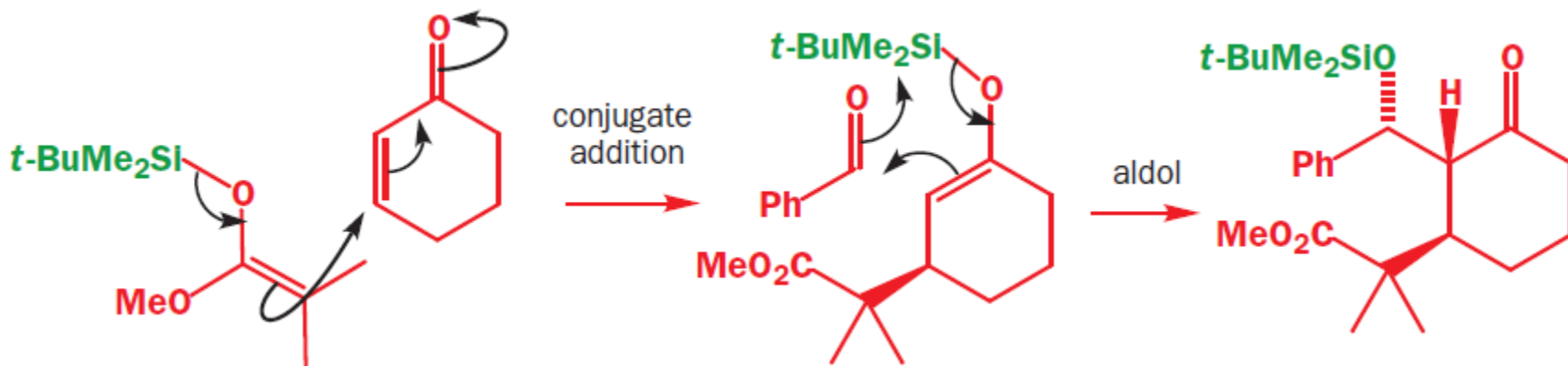
Conjugate Addition of Silyl Enol Ethers

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Sequential (**tandem**) **conjugate additions** and **aldol** reactions build complex molecules in a few steps

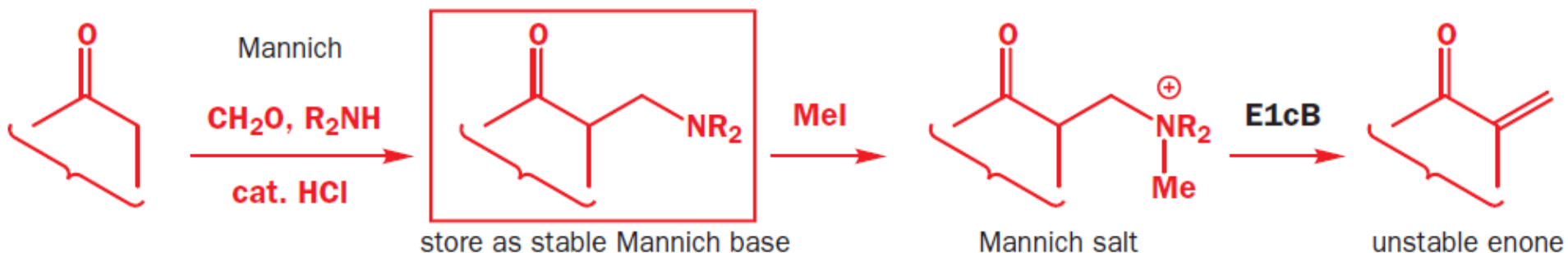


- **Chemoselective conjugate addition** of the silyl ketene acetal on the enone
- **Aldol reaction** of the intermediate silyl enol ether on the benzaldehyde: The **stereoselectivity** results, firstly, from attack of benzaldehyde on the **less hindered face**, and, secondly, from the **intrinsic diastereoselectivity of the aldol reaction**

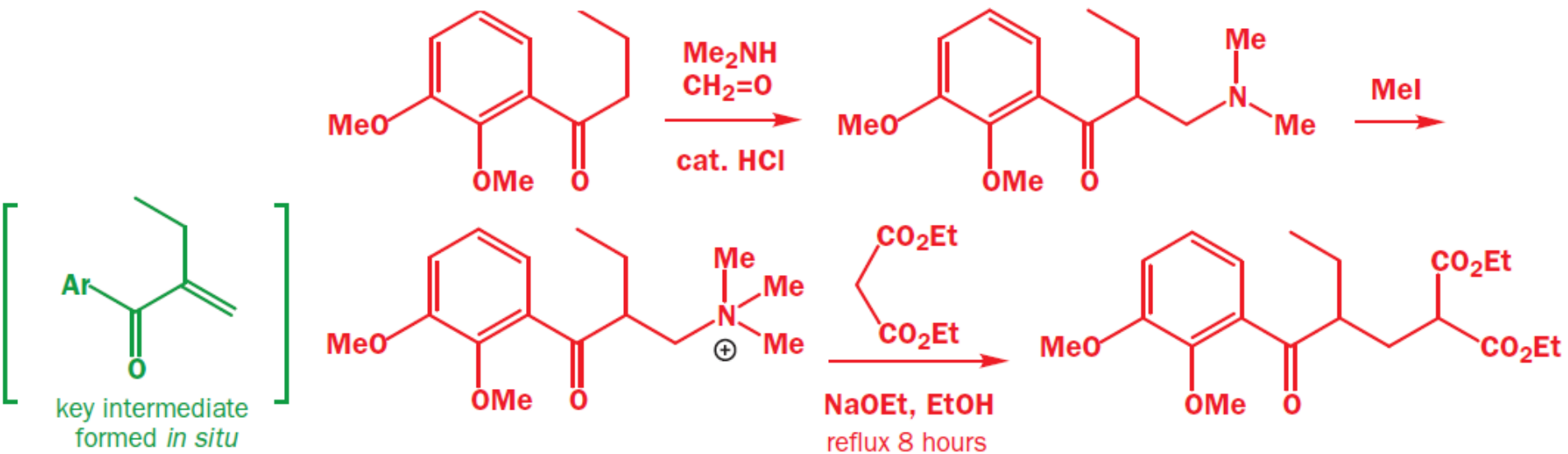


Mannich Reaction

The Mannich reaction provides **stable equivalents of exo-methylene ketones**

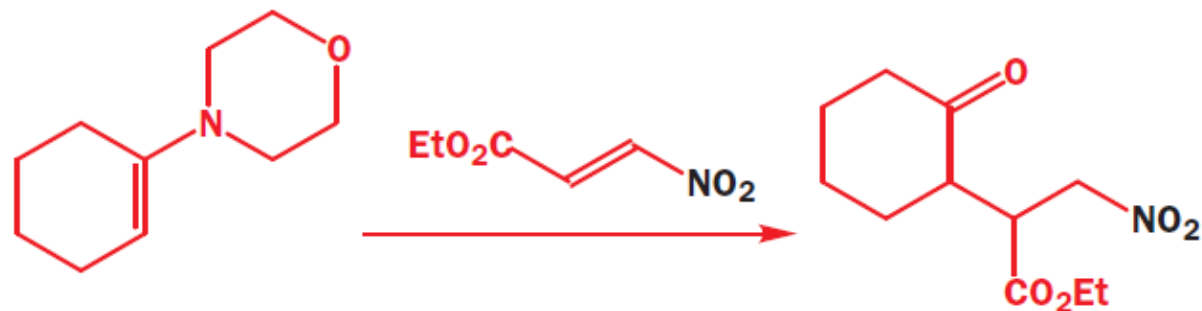
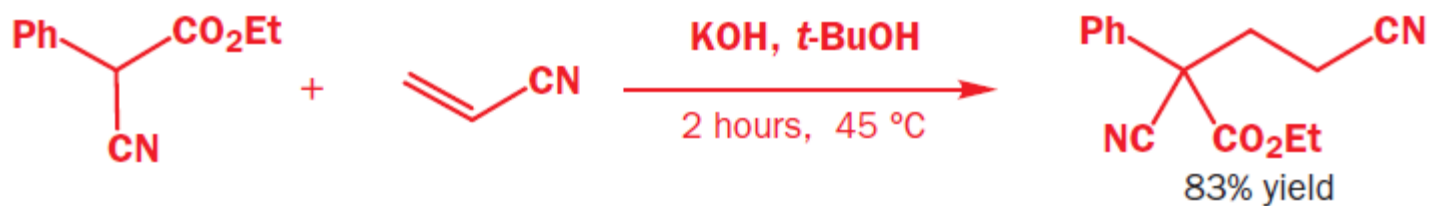
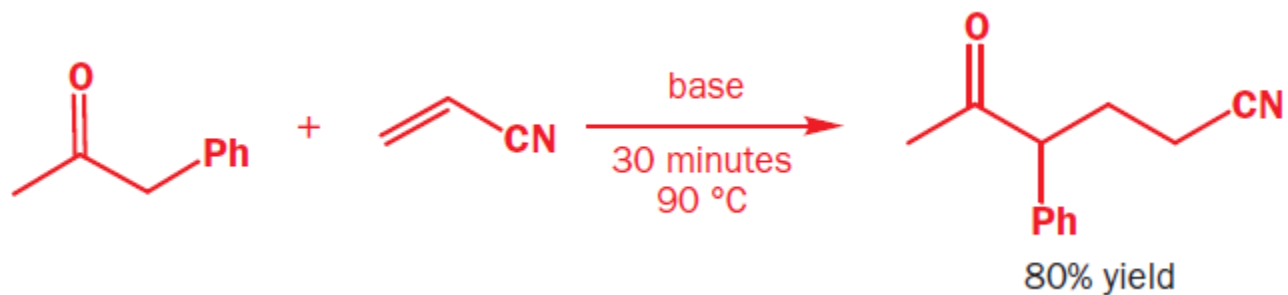
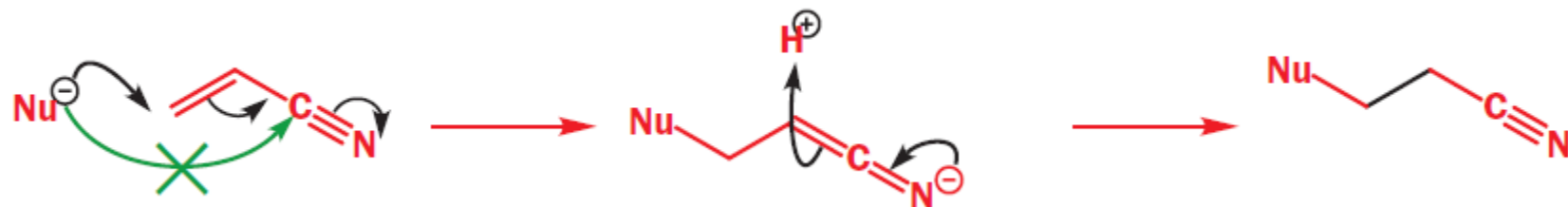


The compound is stored as the **stable Mannich base** and the unstable enone released by elimination of a tertiary amine with mild base at the same time as **conjugate addition**

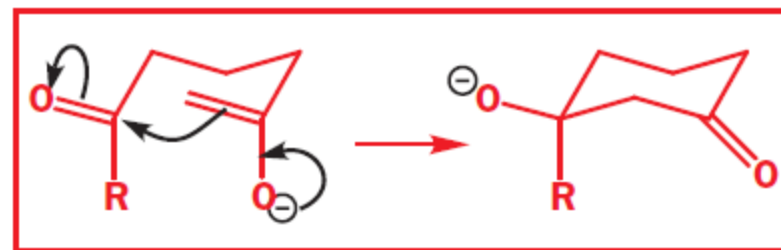
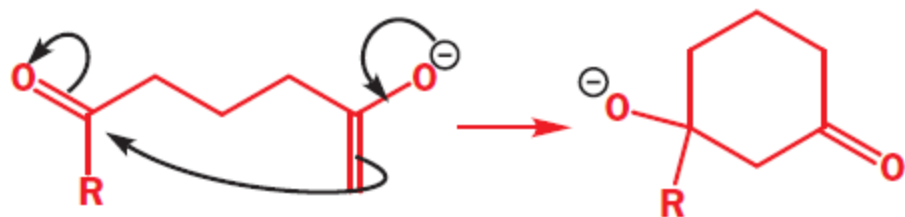
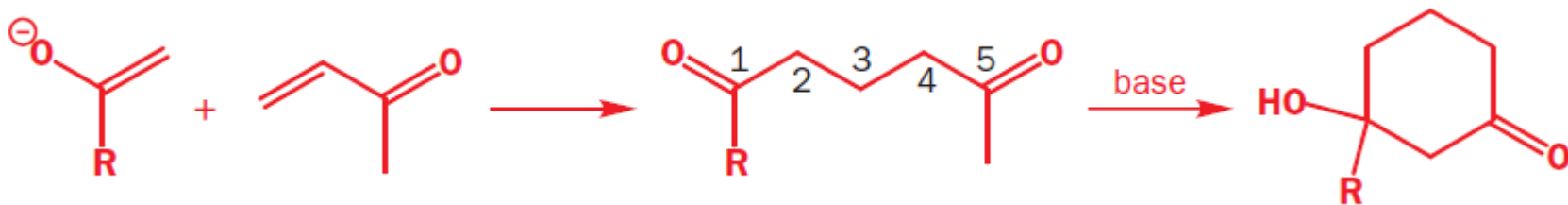


α,β -Unsaturated nitriles and nitro compounds

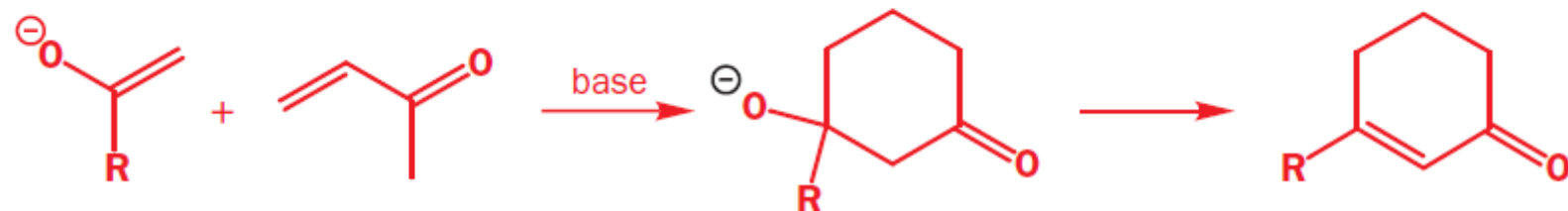
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Conjugate Addition followed by Cyclization



mechanism drawn on molecule in shape of product



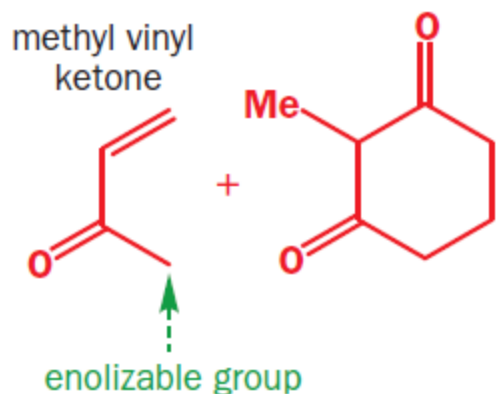
Robinson Annellation

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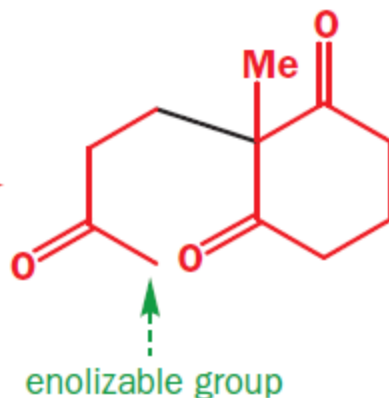
The Robinson annelation is the result of **conjugate addition followed by aldol cyclization**

The essential requirement is a Michael addition of an enolate to an **enone that has a second enolizable group on the other side of the ketone**

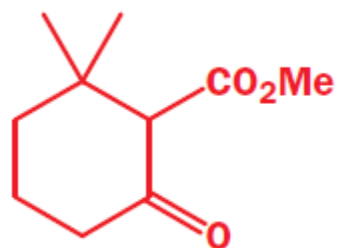
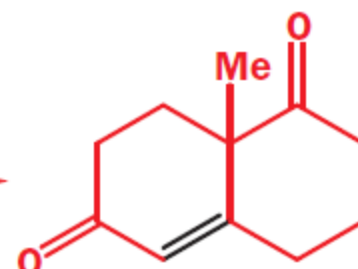
the Robinson annelation



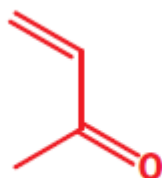
product of conjugate addition



product of intramolecular aldol



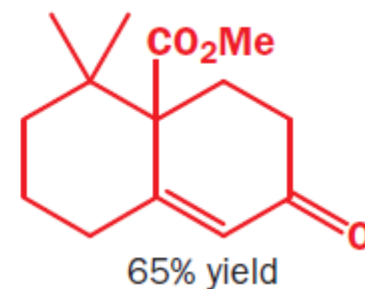
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1. MeOK, THF

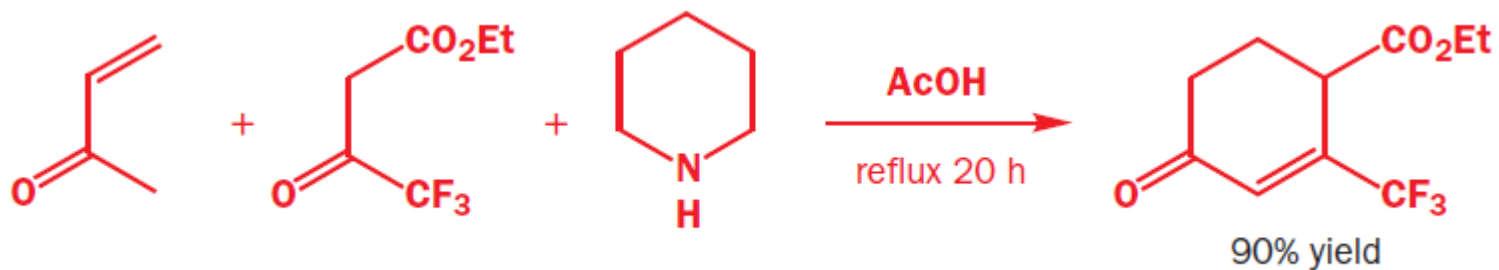
2. K₂CO₃ MeOH

reflux 1.5 hours

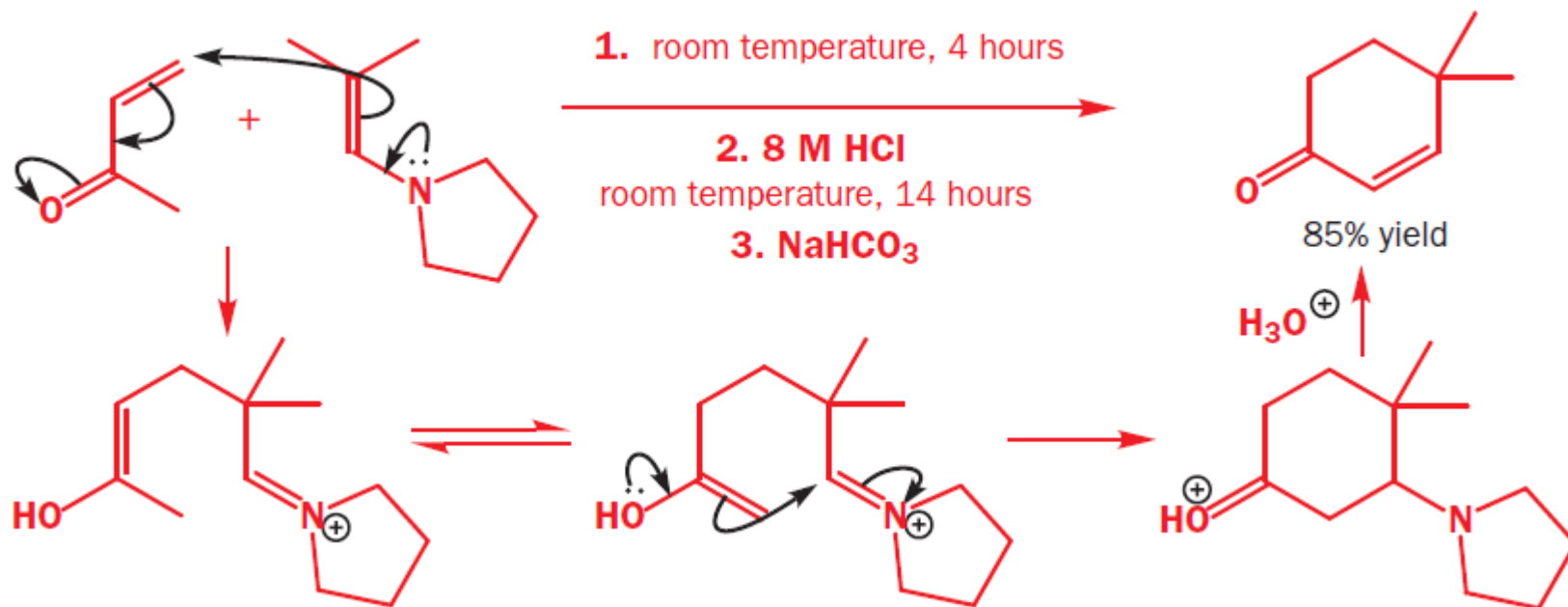


Robinson Annelation

Example:

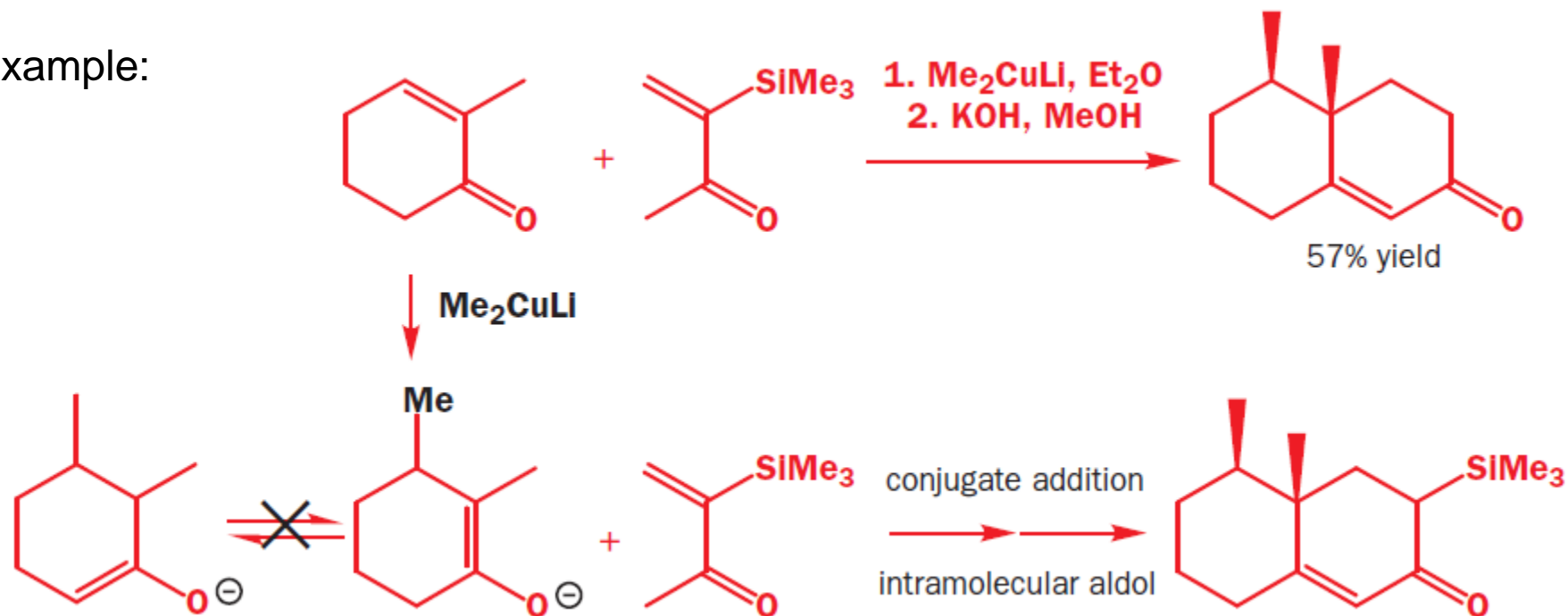


Example:

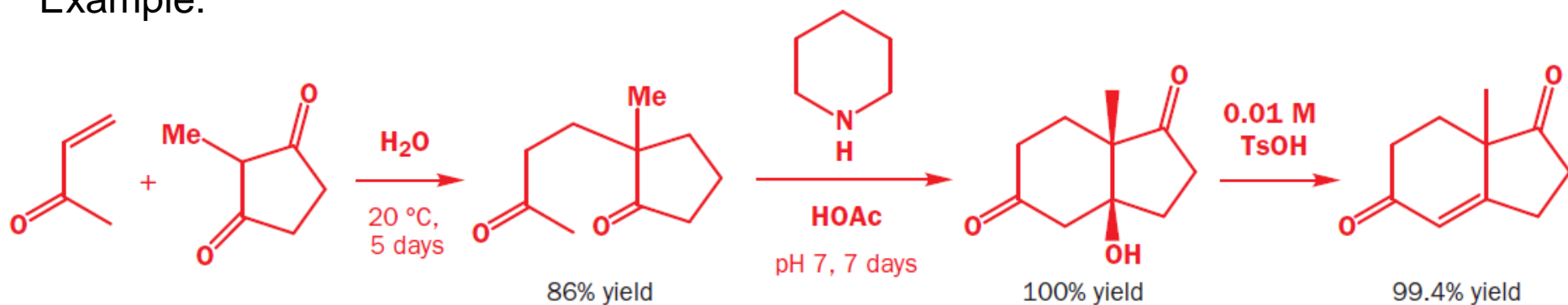


Robinson Annelation

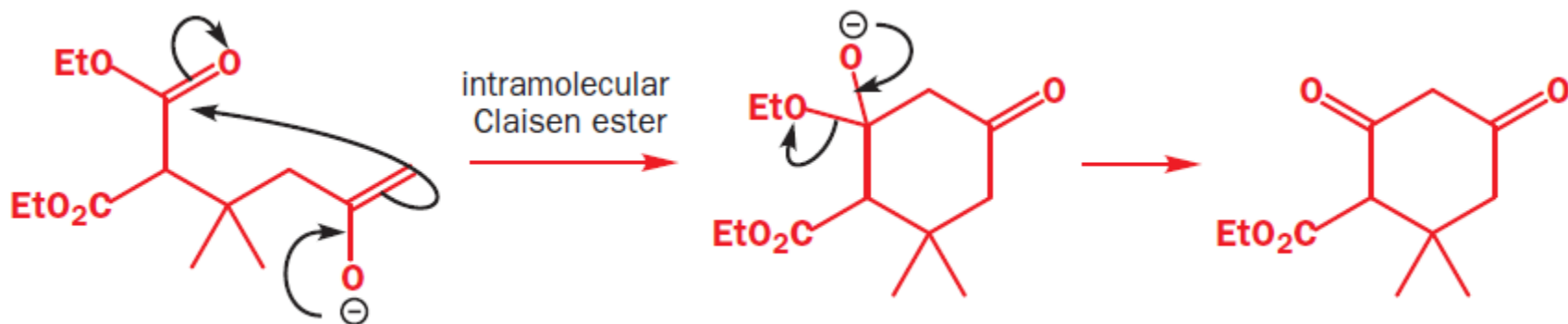
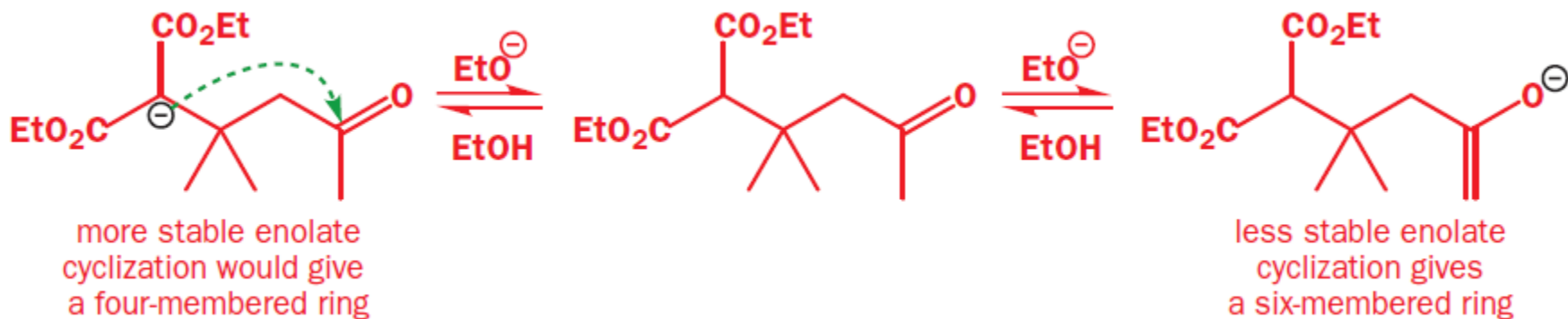
Example:



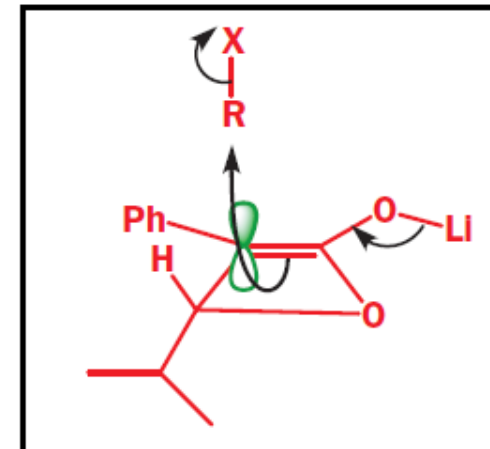
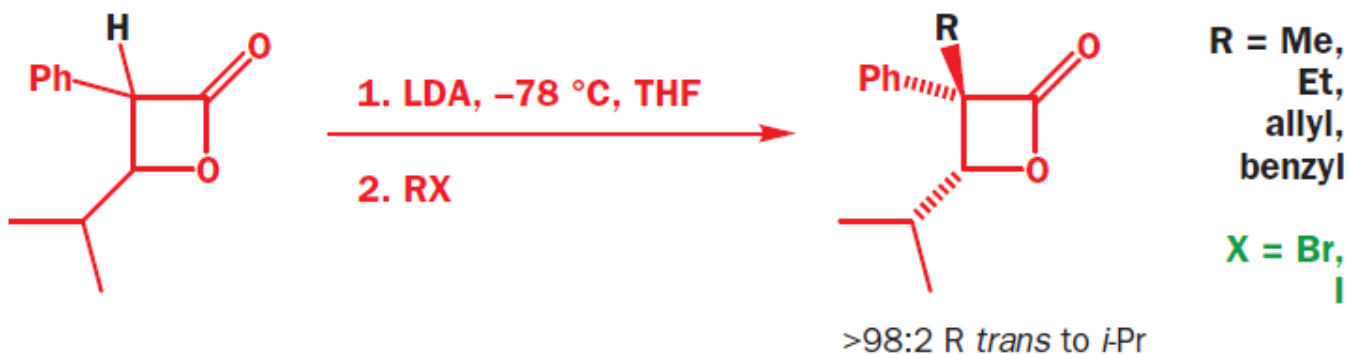
Example:



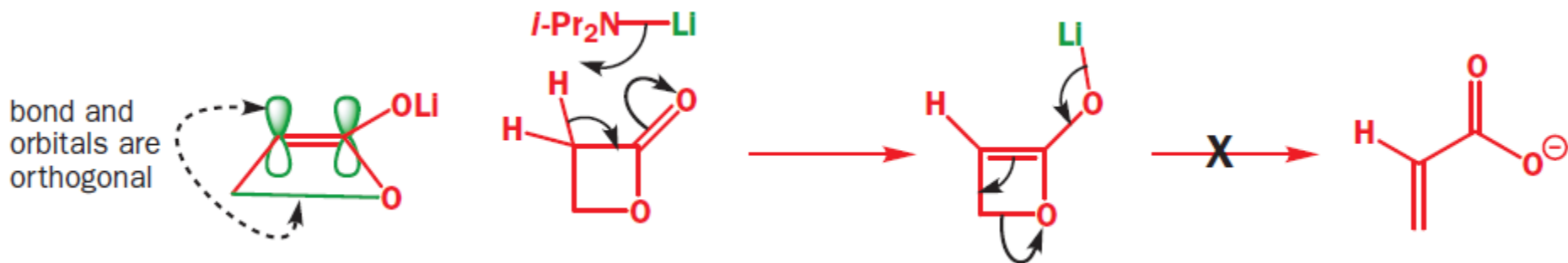
Conjugate Addition followed by Claisen cyclization



Four-Membered Ring



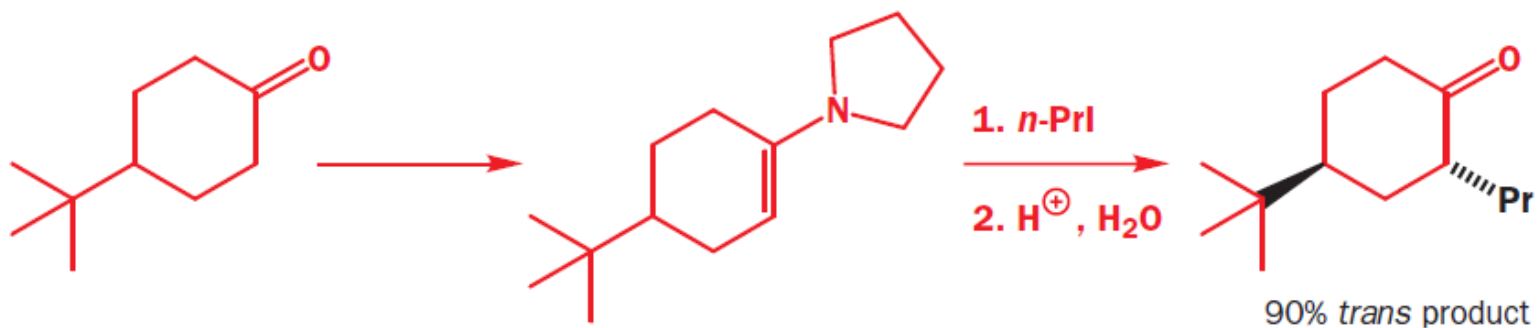
Note: the p orbitals of the enolate and the C–O single bond are **orthogonal** so that no interaction between them, and **no elimination** can occur



Stereoselective reactions of cyclic compounds

Six-Membered Ring

Alkylations of enolates, enamines, and silyl enol ethers of cyclohexanone usually show substantial preference for **axial attack**

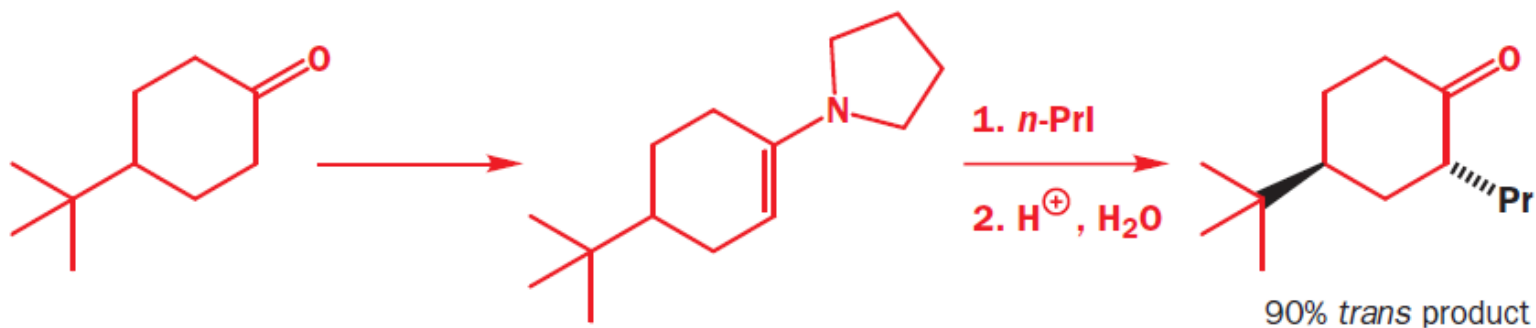


Stereoselective reactions of cyclic compounds

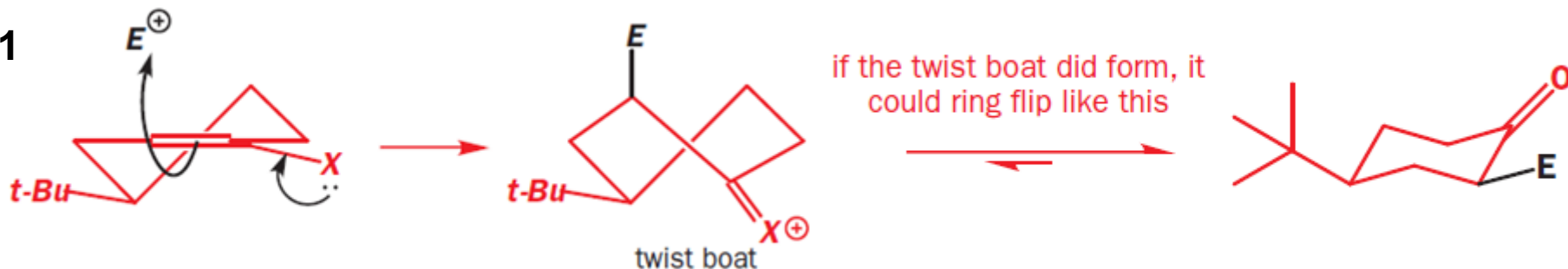
28

Six-Membered Ring

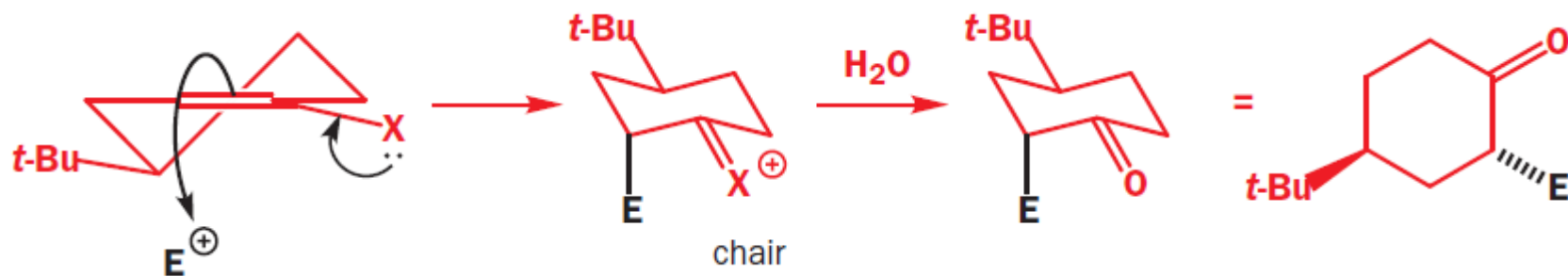
Alkylations of enolates, enamines, and silyl enol ethers of cyclohexanone usually show substantial preference for **axial attack**



#1



#2



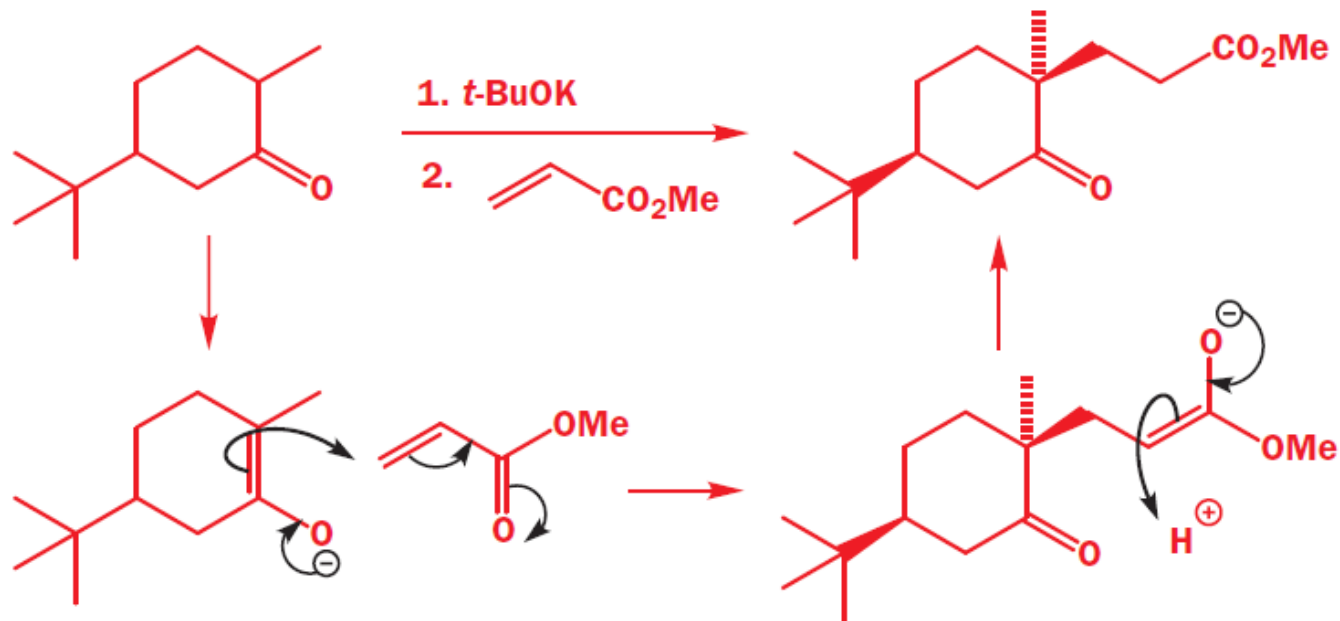
The ring goes directly to a **chair** form with the electrophile in the **axial** position

Stereoselective reactions of cyclic compounds

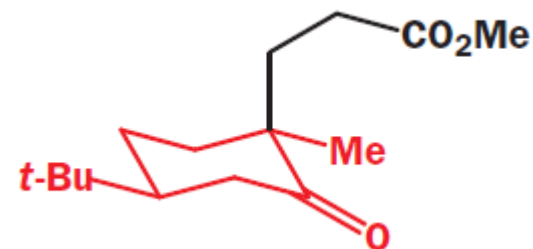
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Six-Membered Ring

Example:



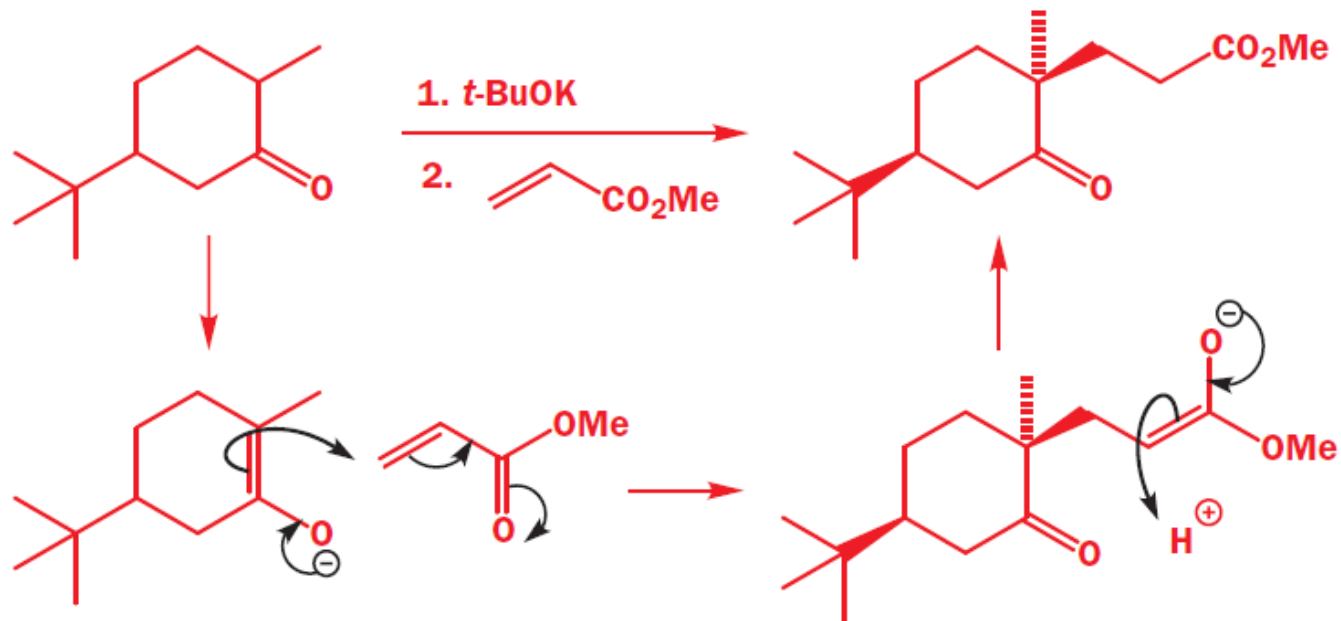
This result is more impressive because the **large electrophile ends up on the same side of the ring as the *t*-butyl group**, so the stereoselectivity cannot be based on any simple idea of reaction on the less hindered side of the ring. It is genuine **axial attack**, as the conformational diagram of the product confirms



Stereoselective reactions of cyclic compounds

Six-Membered Ring

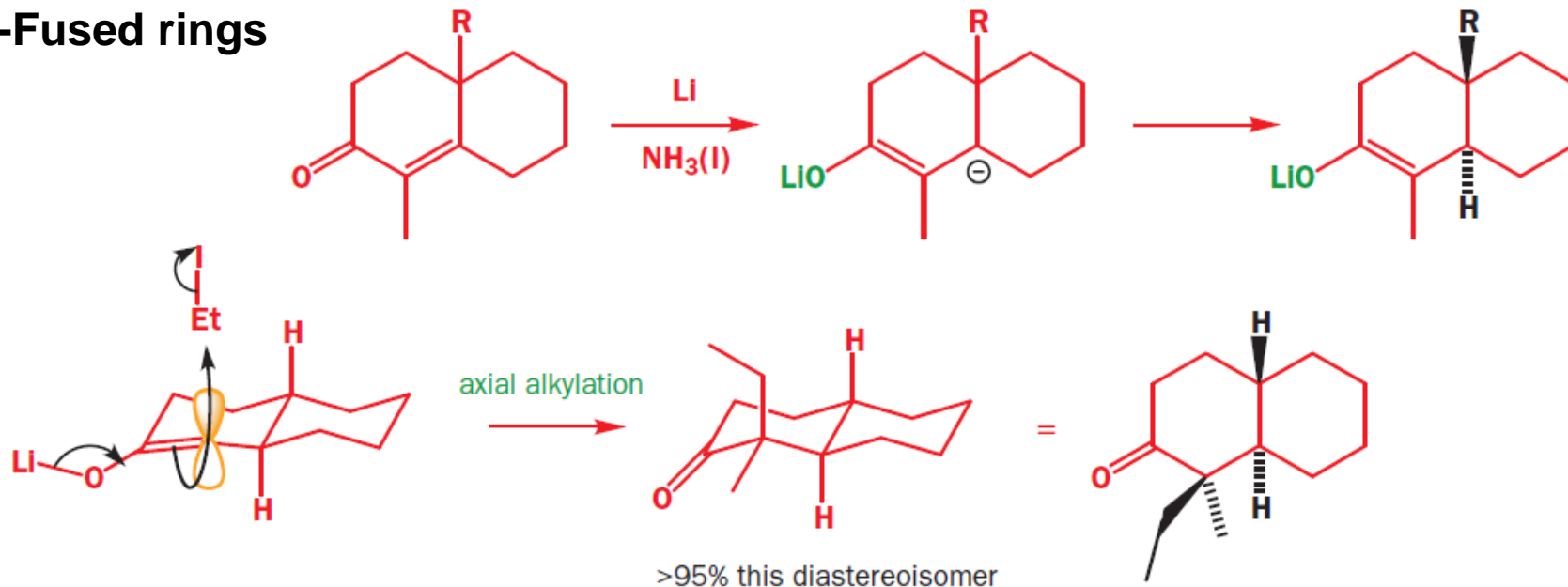
Example:



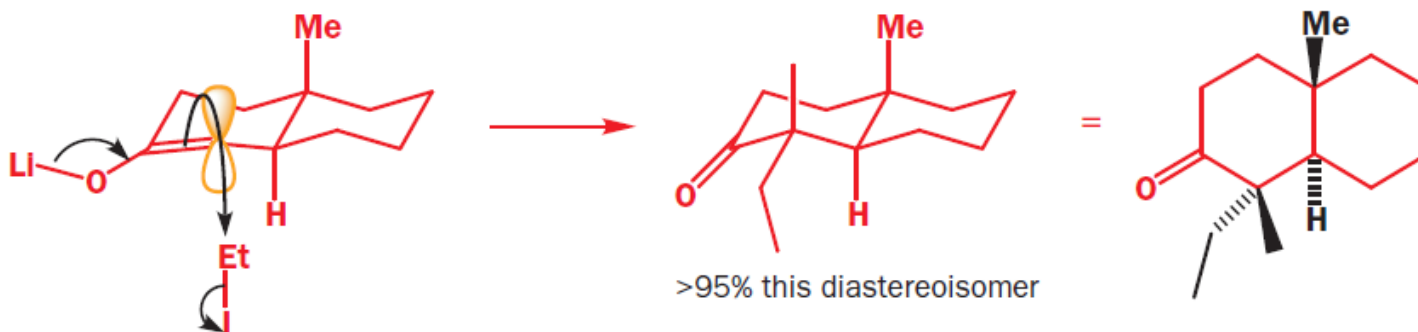
Stereoselective reactions of cyclic compounds

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trans-Fused rings



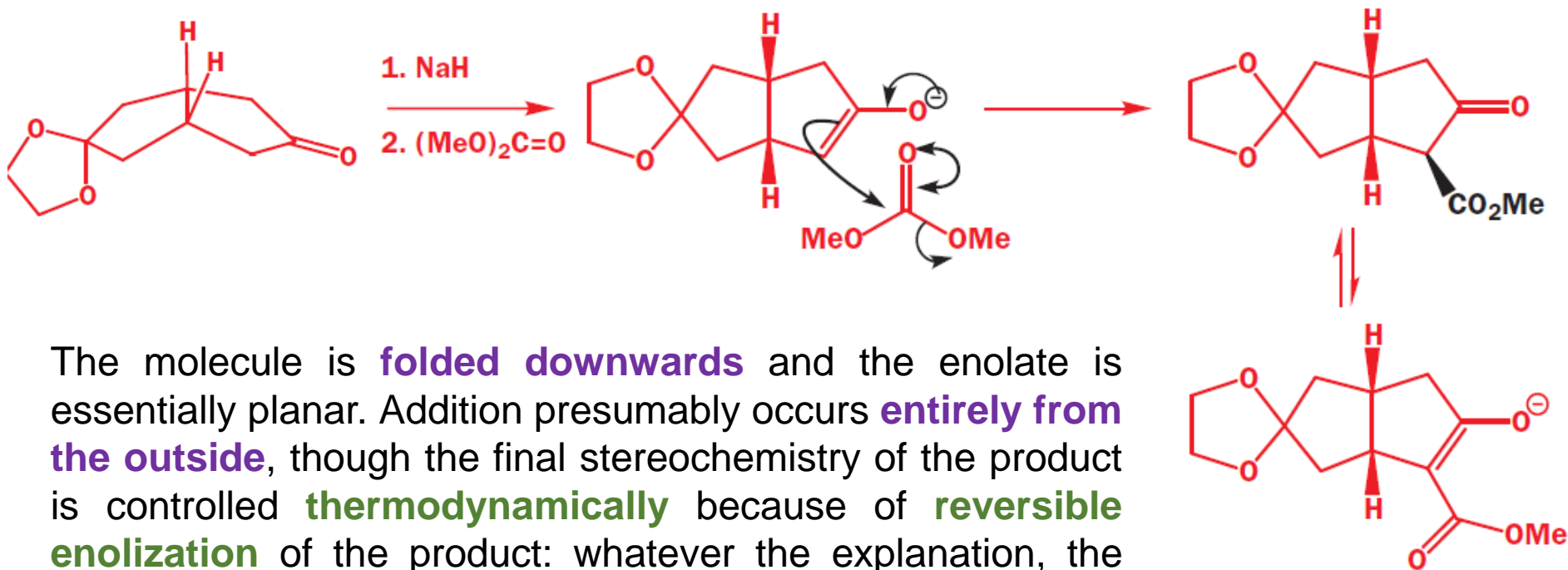
If there is anything else at the ring junction, so that axial approach would give a **bad 1,3-diaxial interaction** in the transition state, the stereoselectivity switches to **equatorial alkylation**. This unexpected reversal of normal stereoselectivity is a result of the **extra rigidity** of the *trans*-decalin system



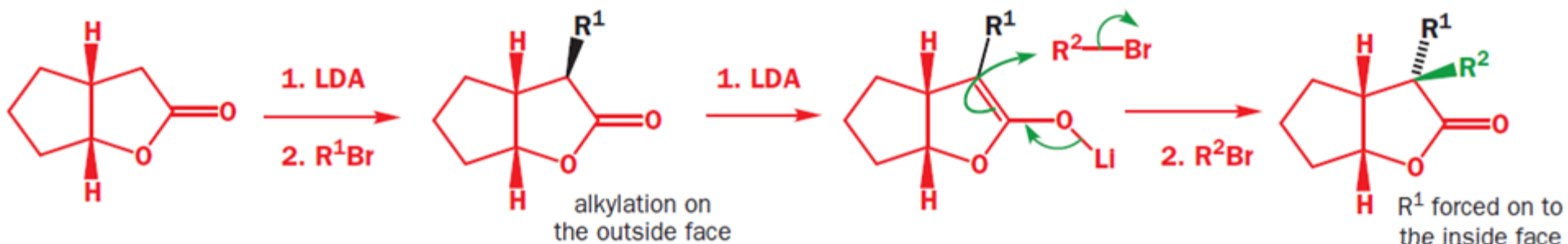
Stereoselective reactions of cyclic compounds

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cis-Fused rings



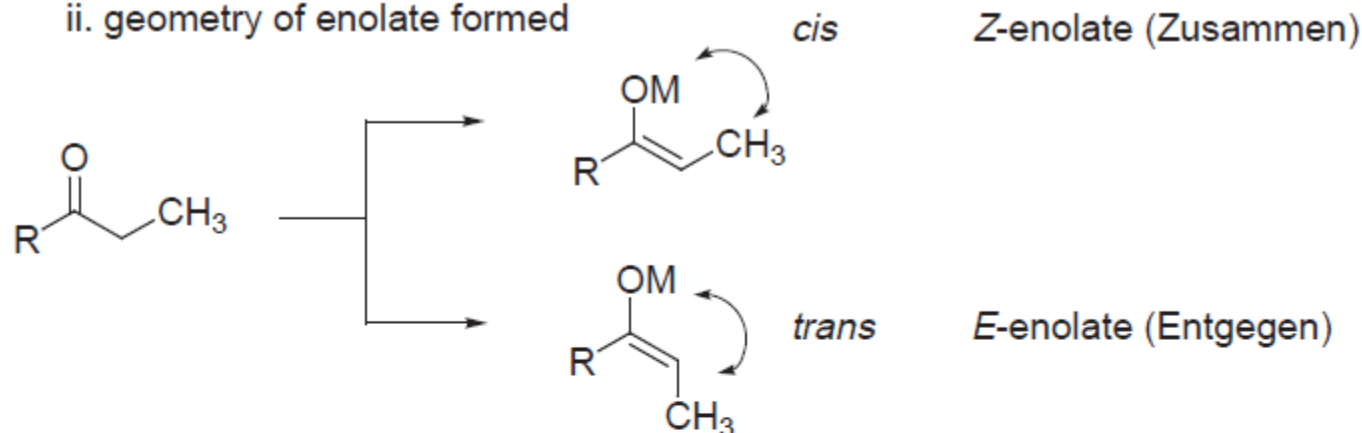
The molecule is **folded downwards** and the enolate is essentially planar. Addition presumably occurs **entirely from the outside**, though the final stereochemistry of the product is controlled **thermodynamically** because of **reversible enolization** of the product: whatever the explanation, the black ester group prefers the outside.



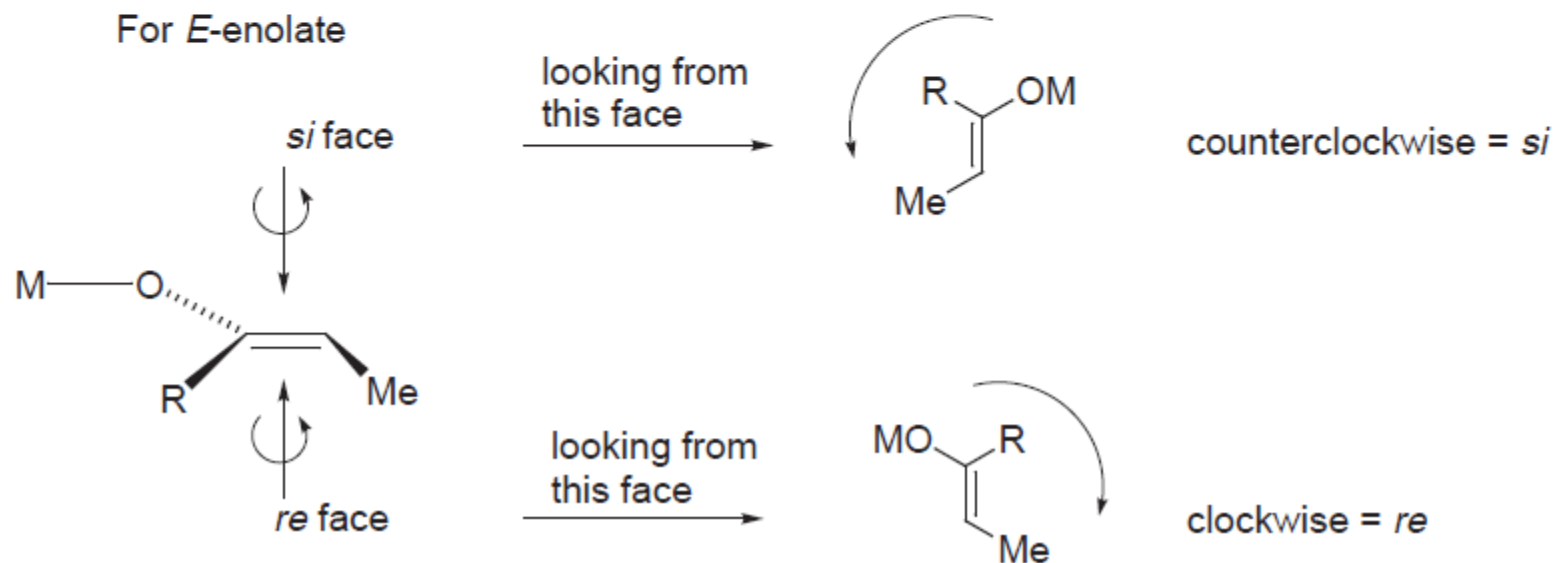
Acyclic Carbonyl Compounds

- Two issues: i. site of deprotonation

ii. geometry of enolate formed

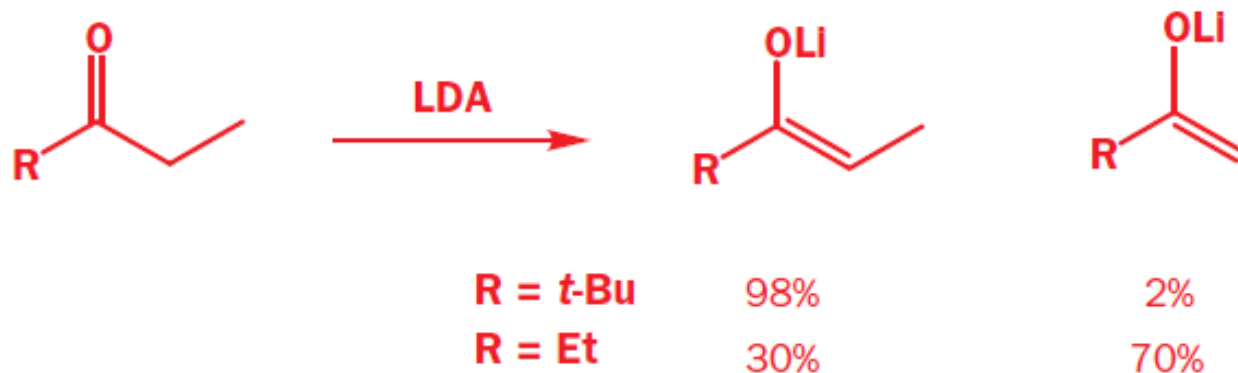


- Also: the enolate has two diastereotopic faces:



Diastereoselectivity: *Z*- or *E*-enolate

Stereoselective enolization is needed for stereoselective aldols

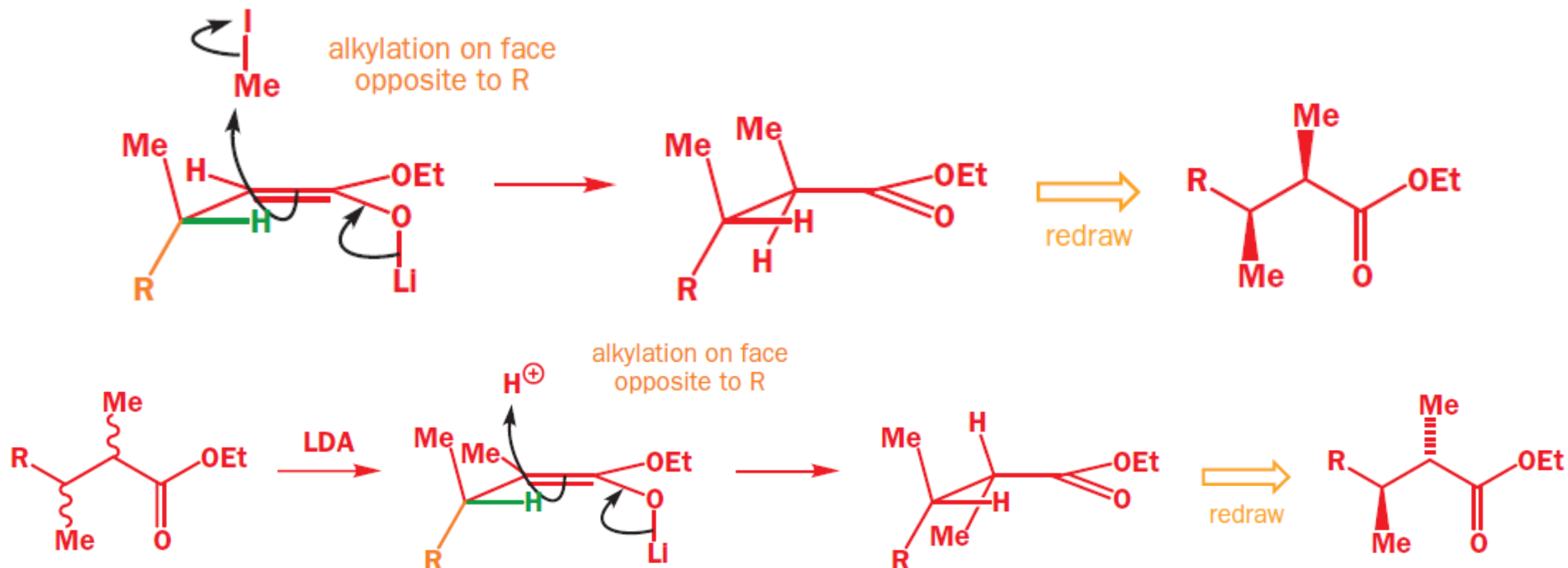
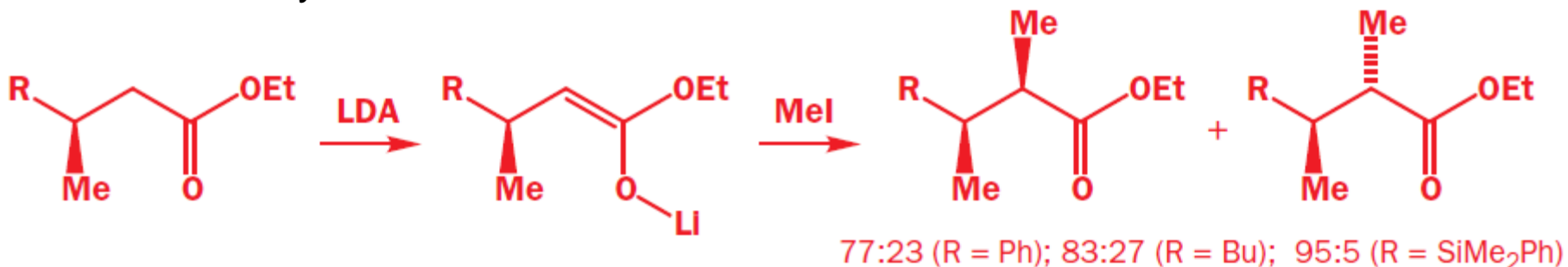


Large groups force the enolate to adopt the ***cis*** geometry; **small groups** allow the ***trans***-enolate to form

Because we **can't separate the lithium enolates**, we just have to accept that the reactions of ketones with small R will be less diastereoselective.

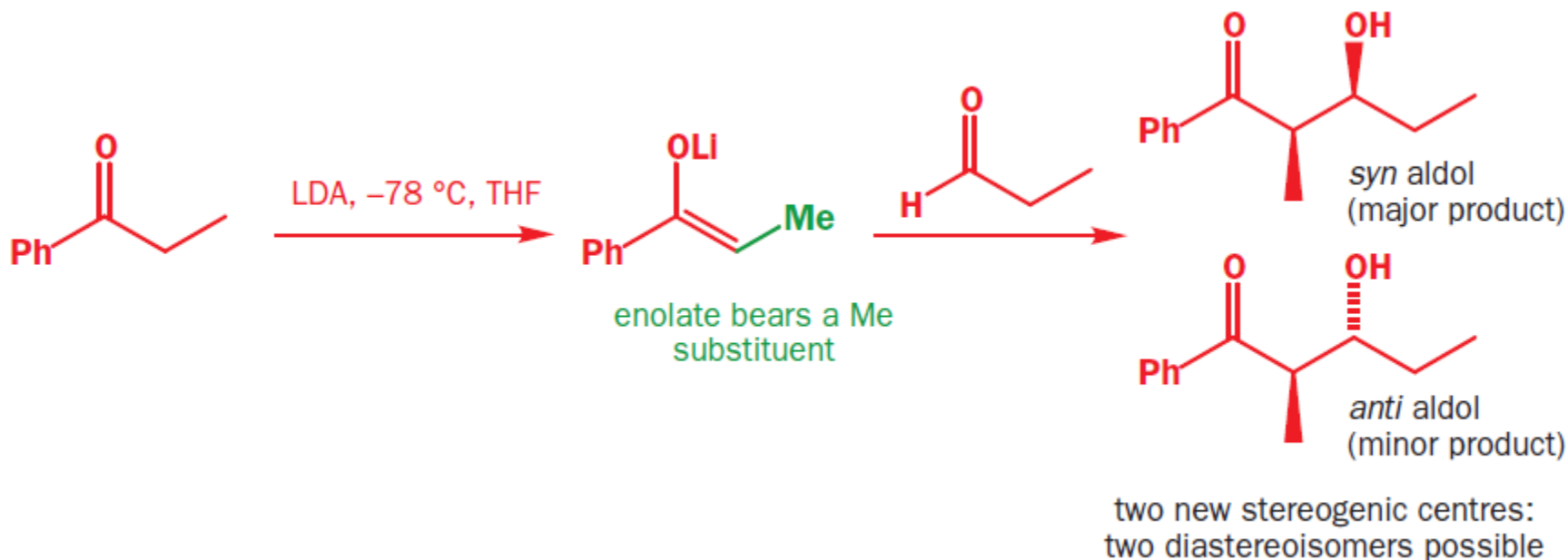
Diastereoselectivity in Enolate Alkylation

Chiral enolates can be made from compounds with a stereogenic centre β to a carbonyl group. Once the carbonyl is deprotonated to form the enolate, the **stereogenic centre is next to the double bond** and in a position to control the stereoselectivity of its reactions



Diastereoselectivity in Aldol Reaction

Aldol reaction with substituted enolates creates **two new stereogenic centres**



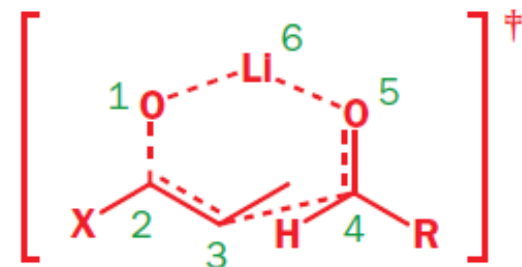
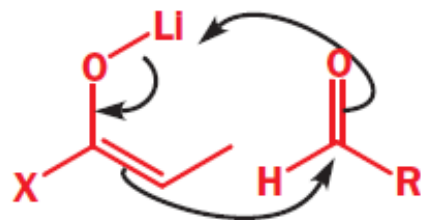
● Diastereoselectivity in aldol reactions

Generally (but certainly not always!) in aldol reactions:



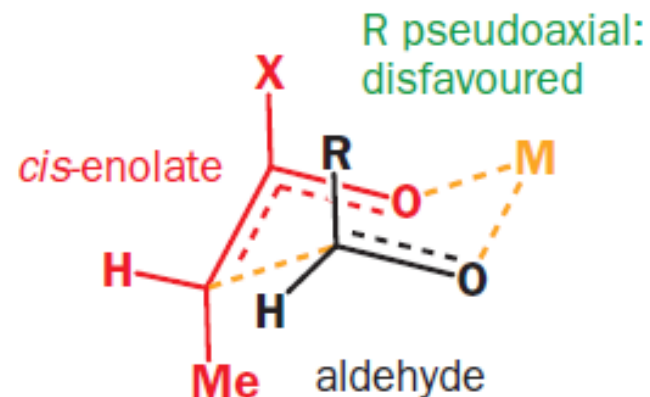
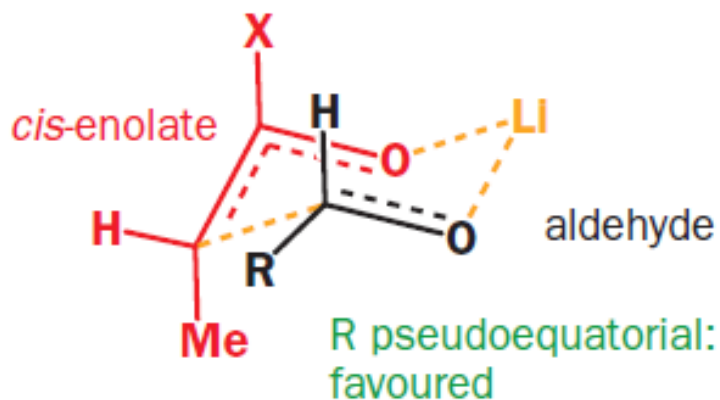
Diastereoselectivity in Aldol Reaction

The aldol reaction has a **chair-like transition state**

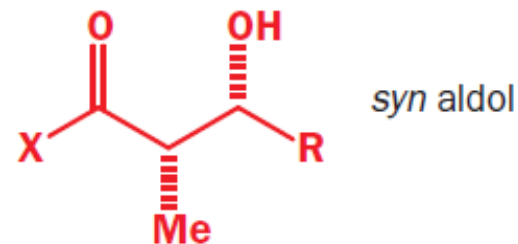
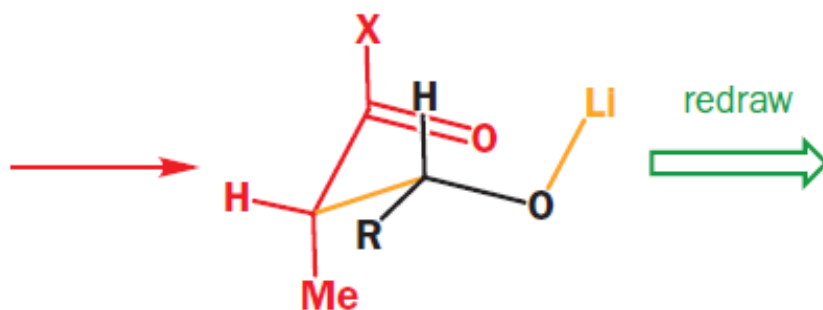
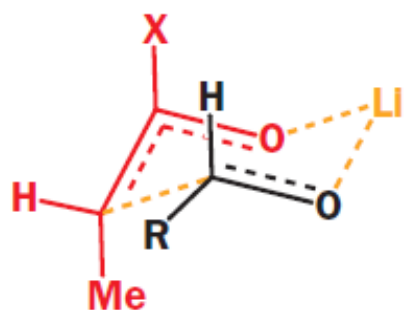


For *cis*-enolates

enolate has no choice over orientation: Me must be pseudoaxial

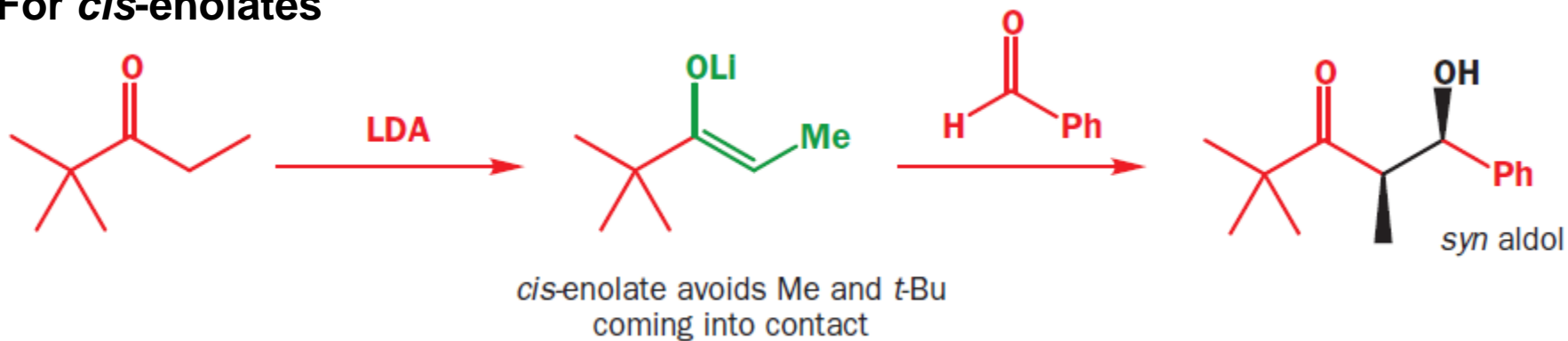


aldehyde chooses to react with R pseudoequatorial



Diastereoselectivity in Aldol Reaction

For *cis*-enolates

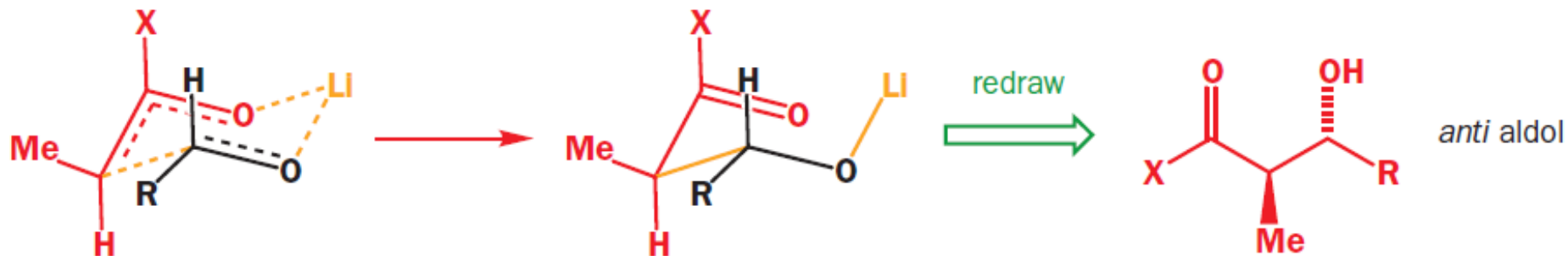
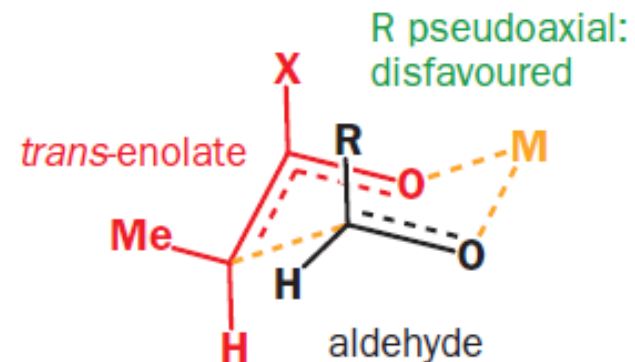
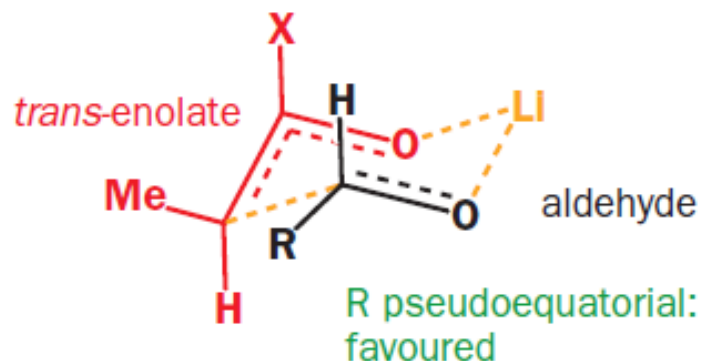


Diastereoselectivity in Aldol Reaction

For *trans*-enolates

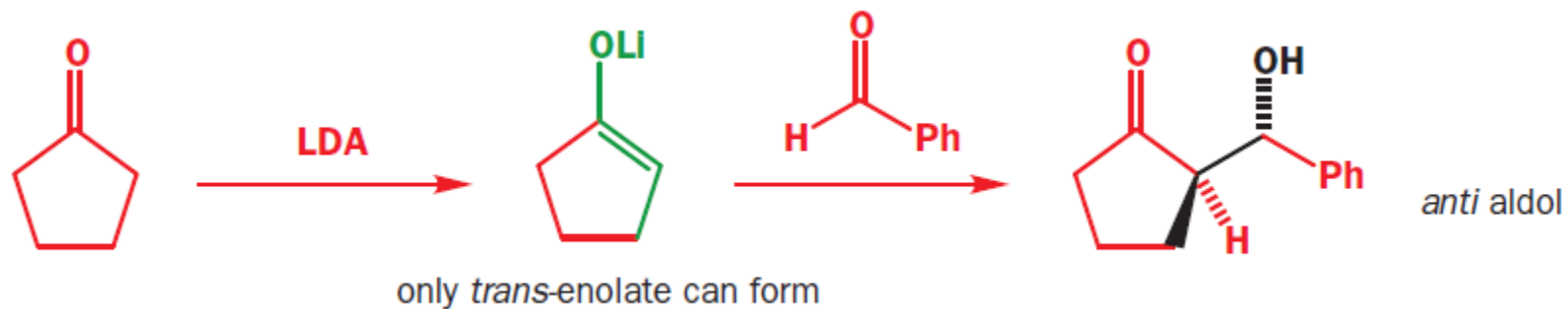
enolate has no choice over orientation: Me must be pseudoequatorial

aldehyde chooses to react with R pseudoequatorial



Diastereoselectivity in Aldol Reaction

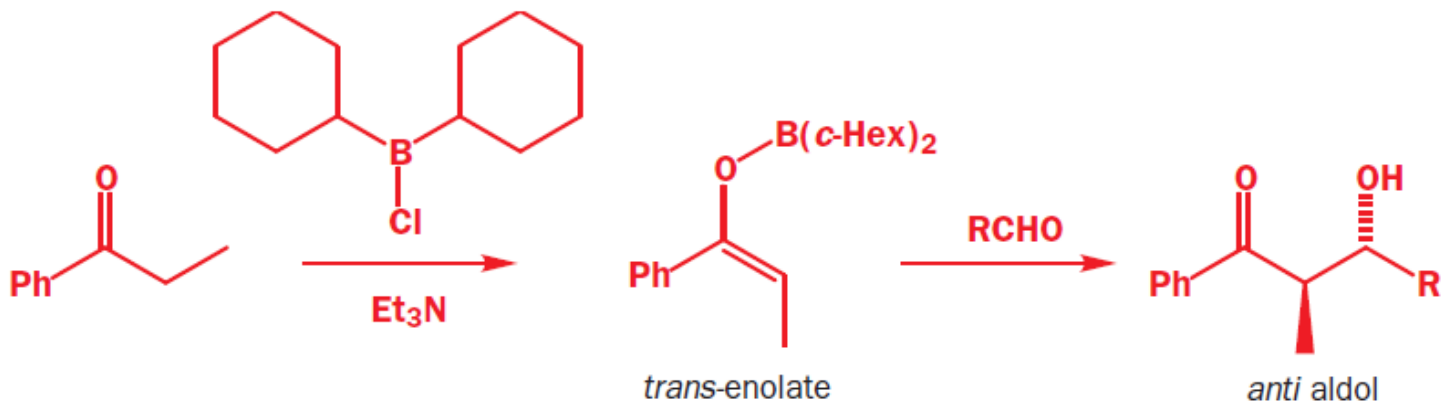
For *trans*-enolates



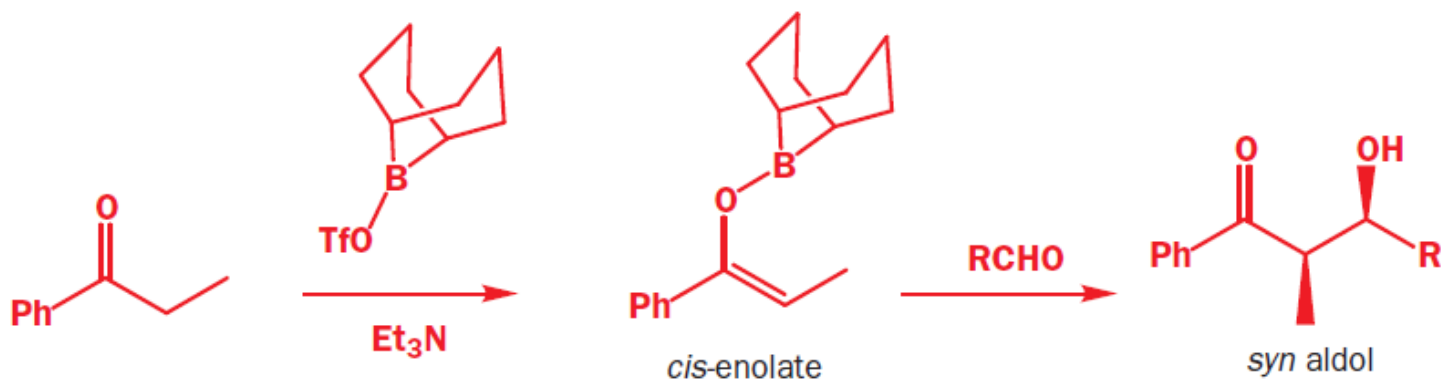
Diastereoselectivity in Aldol Reaction

With **boron enolates**, we can choose the **groups on boron**—and we can get either *cis* or *trans* depending on which groups these are

With **bulky groups** on boron, a ***trans***-enolate forms from most ketones



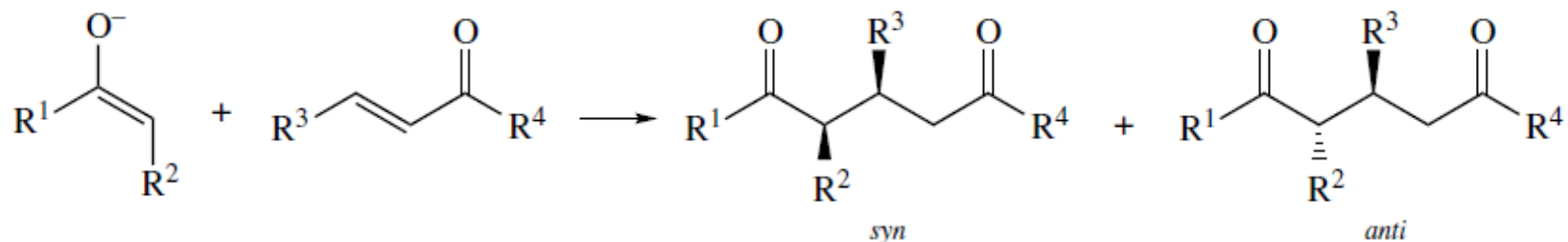
With **smaller B** substituents, the ***cis***-enolate forms selectively



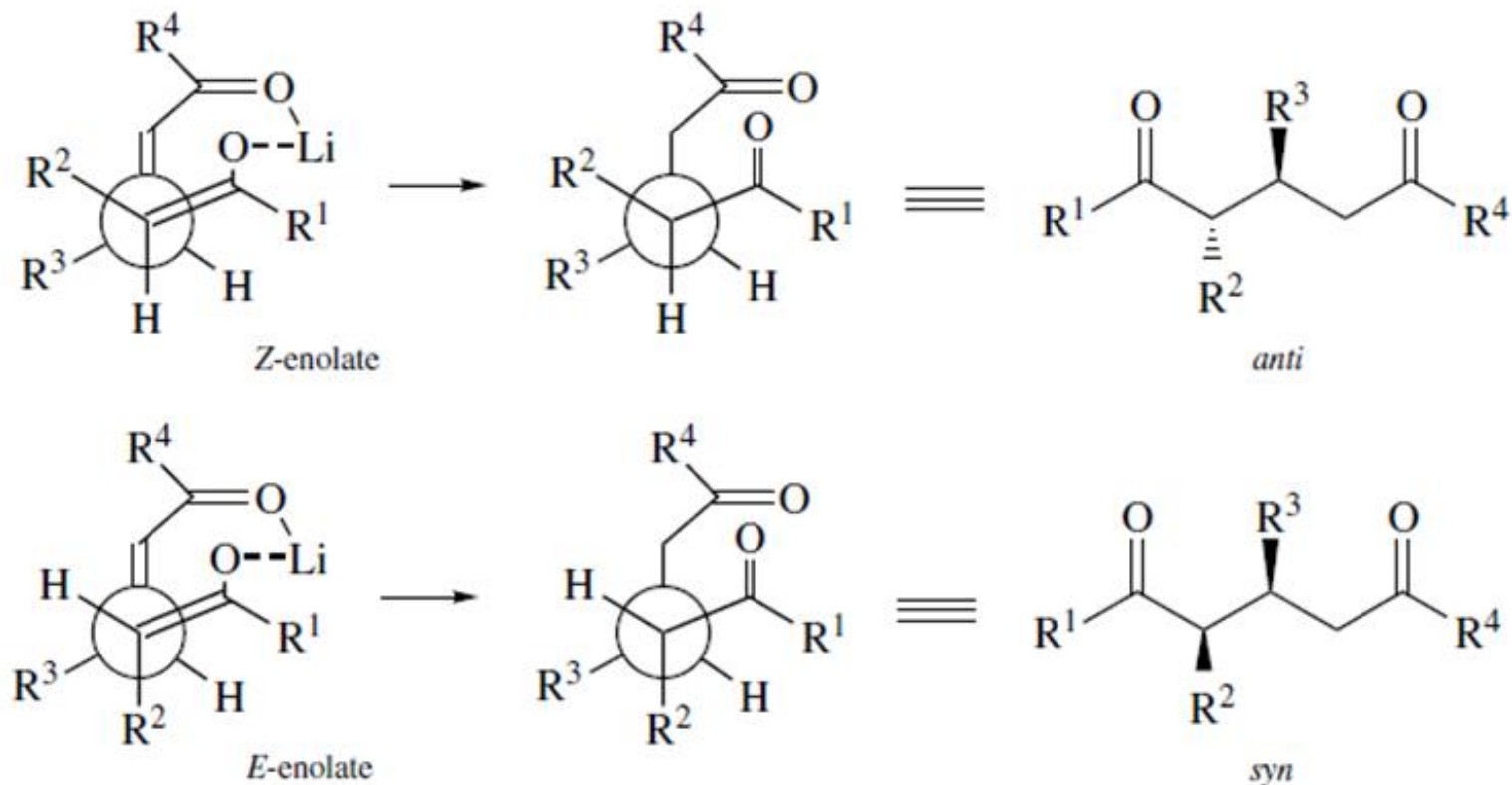
- Often much more diastereoselective in their aldol addition reactions
- This results from a shorter B-O bond length, tighter transition state

Diastereoselectivity in Conjugate Addition

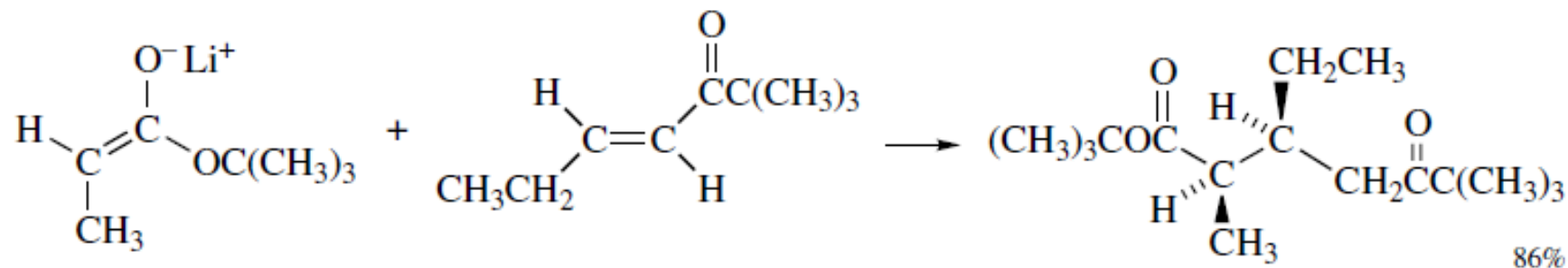
If there are substituents on both the nucleophilic enolate and the acceptor, either *syn* or *anti* adducts can be formed



Z-Enolates favour *anti* adducts and **E-enolates** favour *syn* adducts



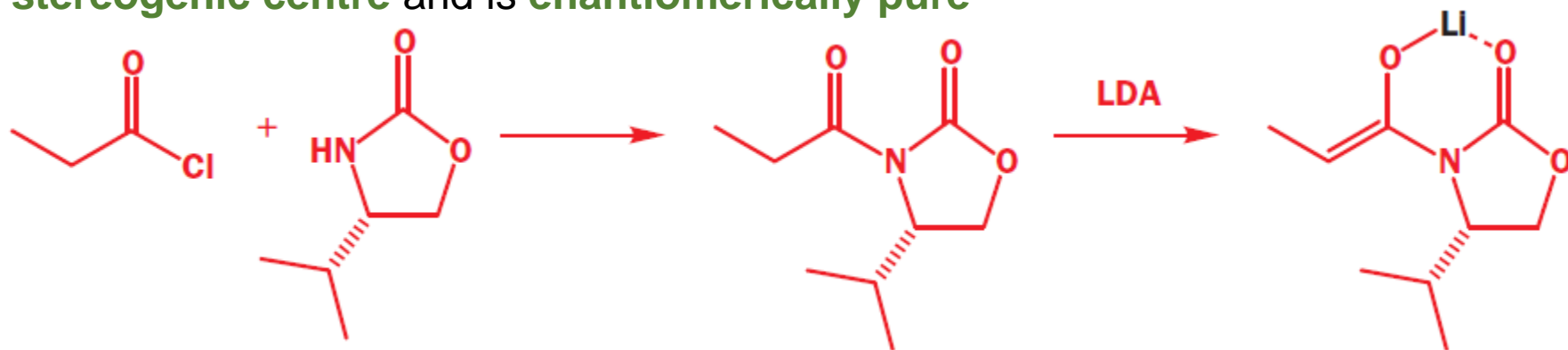
Diastereoselectivity in Conjugate Addition



Diastereoselectivity vs Enantioselectivity

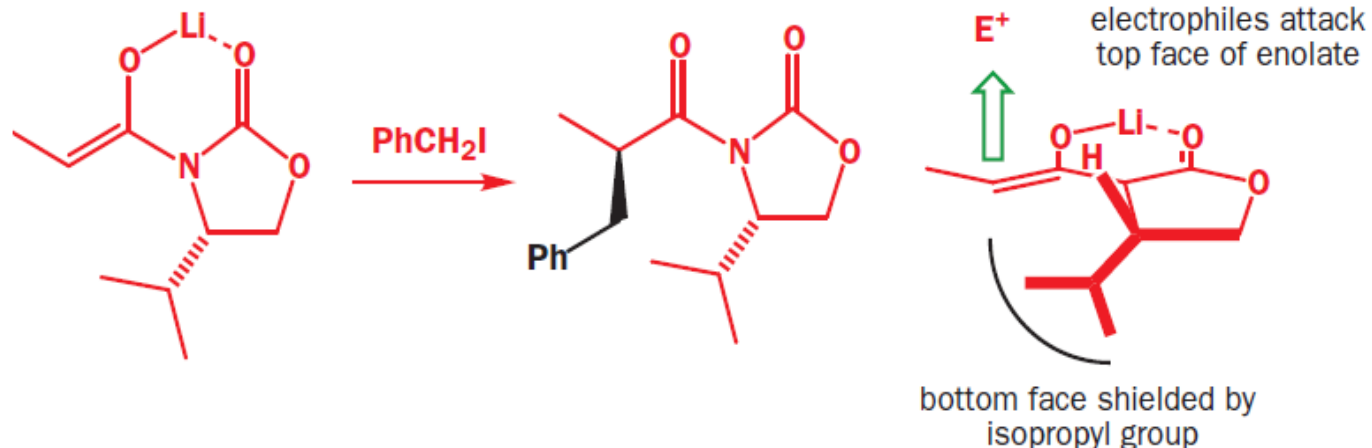
Alkylation using Chiral auxiliaries

Chiral auxiliary can be **pre-attached** to a non-chiral starting materials. It contains a **stereogenic centre** and is **enantiomerically pure**



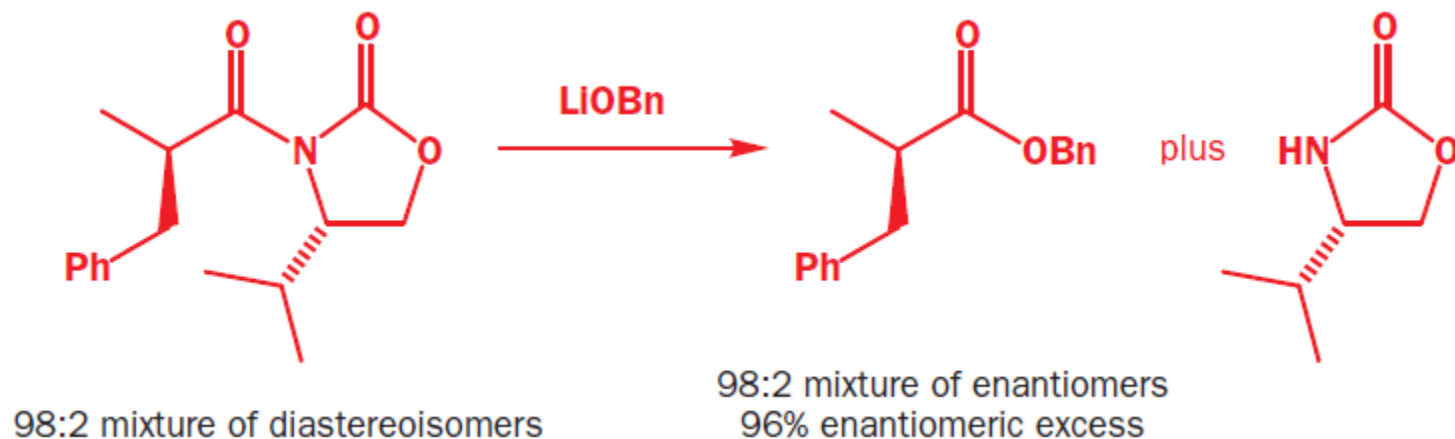
Treatment with base (usually LDA) at low temperature produces **Z-enolate** (due to steric), and you can clearly see that the auxiliary has been designed to favour **attack by electrophiles on only one face of that enolate**

Electrophile	Ratio of diastereoisomers
PhCH ₂ I	>99:1
allyl bromide	98:2
Etl	94:6



Asymmetric Synthesis using Enolates

When talking about compounds that are neither racemic nor enantiomerically pure (usually called **enantiomerically enriched**) chemists talk not about ratios of enantiomers but about **enantiomeric excess (ee)**; defined as **the excess of one enantiomer over the other, expressed as a percentage of the whole**

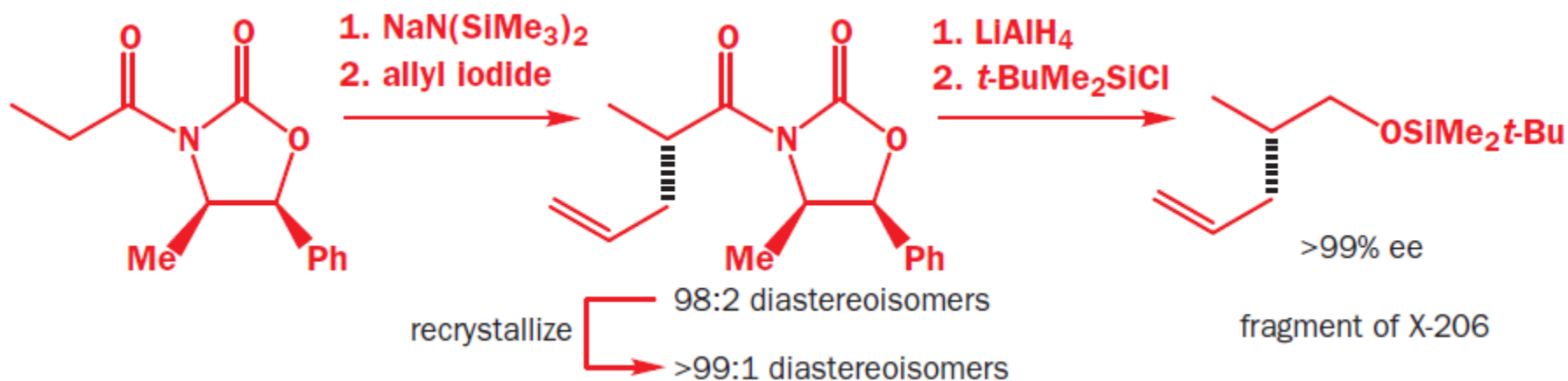


The 2% of the wrong enantiomer makes a racemate of 2% of the right isomer so the mixture contains **4% racemate** and **96% of one enantiomer. 96% ee**

Modern chemists usually use **chiral HPLC** to determine ee; the columns are packed with a **chiral stationary phase** such as this isoleucine derivative



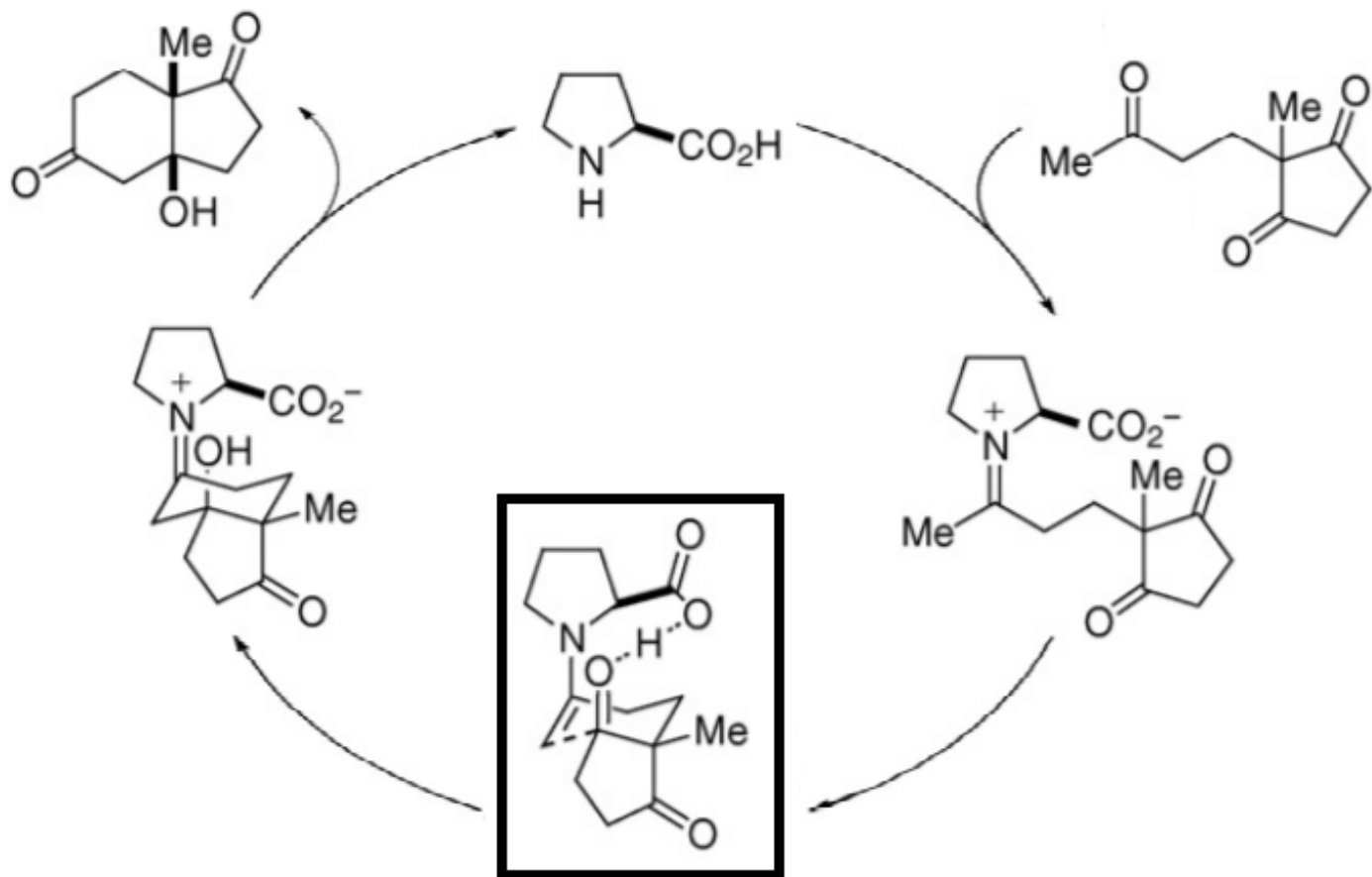
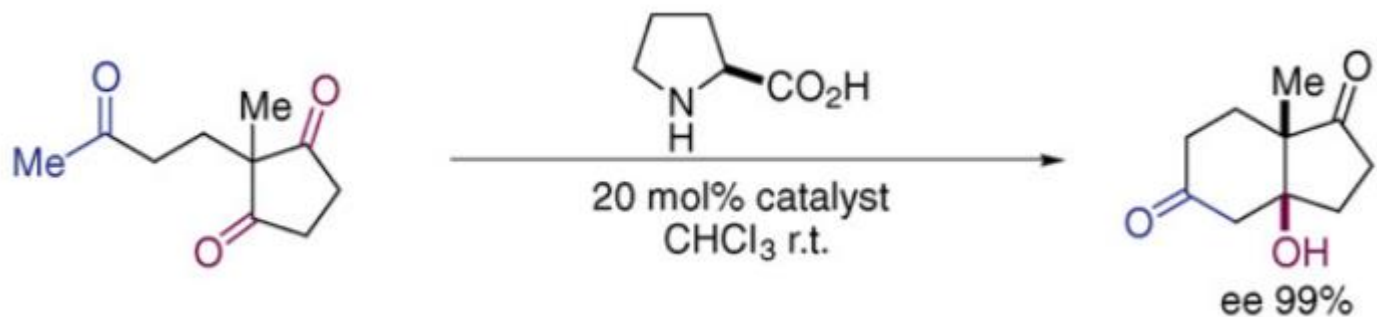
We can use a trick that essentially employs the **chiral auxiliary in a secondary role as a resolving agent**: Provided the products are crystalline, it will usually be possible to **recrystallize** our 98:2 mixture of diastereoisomers to give essentially a **single diastereoisomer**



Disadvantage of Chiral Auxiliary method

- It must be **attached** to the compound under construction, and after they have done their job they must be **removed (at least two 'unproductive' steps)**
- Discovering successful chiral auxiliaries requires painstaking research and most potential chiral auxiliaries give **low ees** in practice

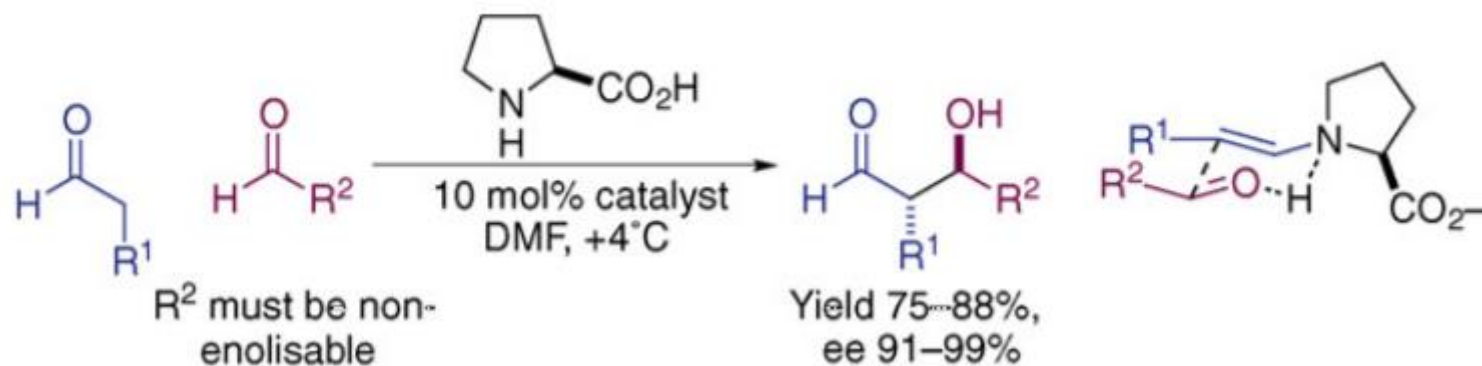
Asymmetric Enamine Catalysis – Aldol



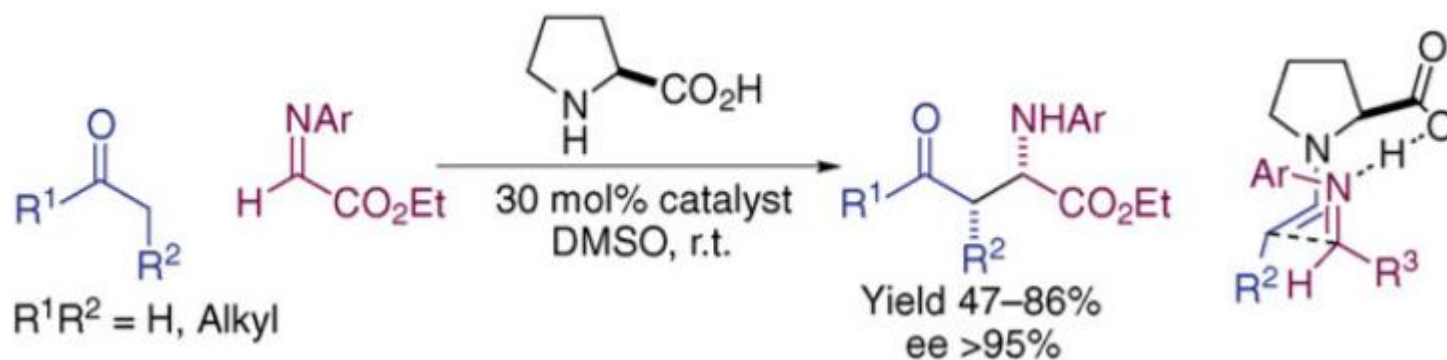
Asymmetric Enamine Catalysis – Aldol

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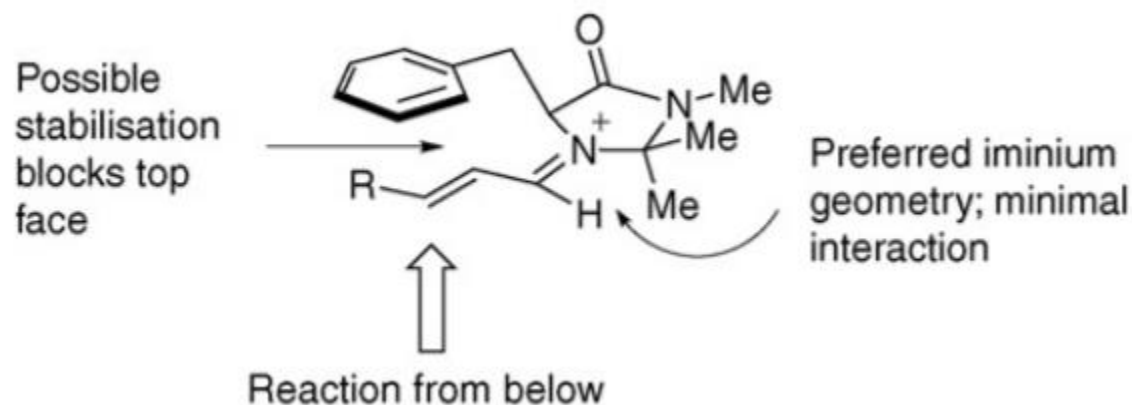
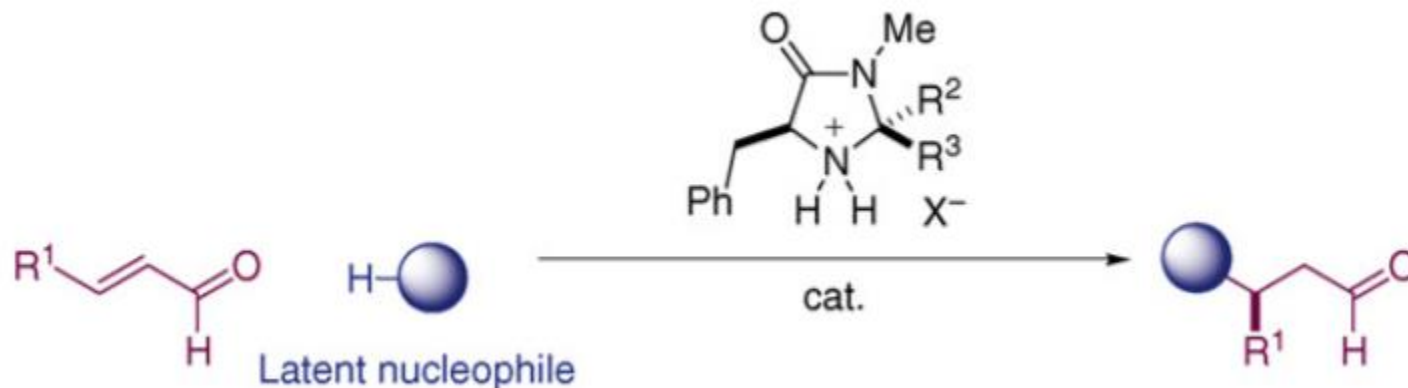
Proline-catalysed aldehyde cross aldol



Proline-catalysed mannich reaction



Asymmetric Catalysis via Iminium Ions



Asymmetric Catalysis via Iminium Ions

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Indoles

