First Year Organic Chemistry

UNIVERSITY OF OXFORD

THE CHEMISTRY OF THE CARBONYL GROUP:

CORE CARBONYL CHEMISTRY

Professor Tim Donohoe

8 lectures, HT, weeks 1-4, 2015

Wednesday at 9am; Friday at 10am (Dyson Perrins)

Handout B

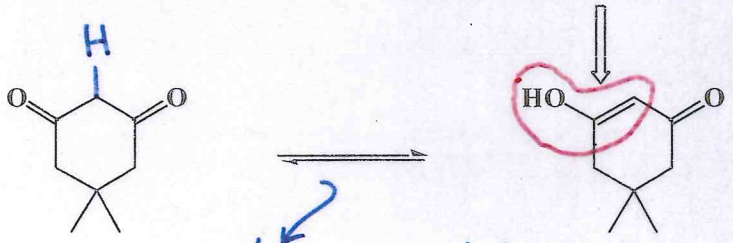
You will be able to download copies of the handouts from this course at http://donohoe.chem.ox.ac.uk/Teaching/Teaching.htm as well as through Weblearn

4) Enolisation of carbonyl compounds

A) keto-enol tautomerism

If one looks at the NMR spectrum of dimedone, it contains peaks for TWO different compounds.

KETONE ENOL



these are DIFFERENT distinguishable chemical species

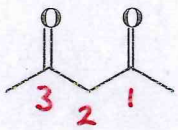
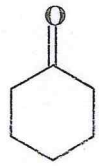
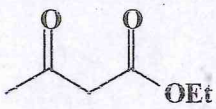
note : equilibrium

The two forms of dimedone are known as the keto and ENOL

They are known as TAUTOMERS (isomers that are interchangeable via the transfer of a proton):

and the process of exchange between them is called TAUTOMERISATION

However, if we look at the NMR spectra of simple aldehydes and ketones they have very little enol; mostly in the keto form

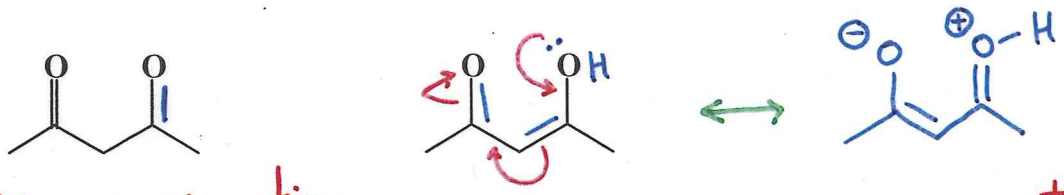
	% enol in neat liquid		% enol in neat liquid
	1.5×10^{-4}		76
	1.2		8

If we look at the bond strengths, we can see why

					Sum ($KJMol^{-1}$)
Keto	(C-H)	440	(C=O)*	720	1160
Enol	(O-H)	500	(C=C)	620	1120

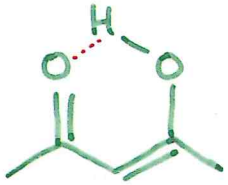
Thermodynamics favour the KETO form

Clearly, the presence of extra conjugation in the enol form is enough to tip the balance



No conjugation

+ enol has an intramolecular H-bond.



Another factor is the solvent

H_2O	15 % enol
hexane	92 % enol

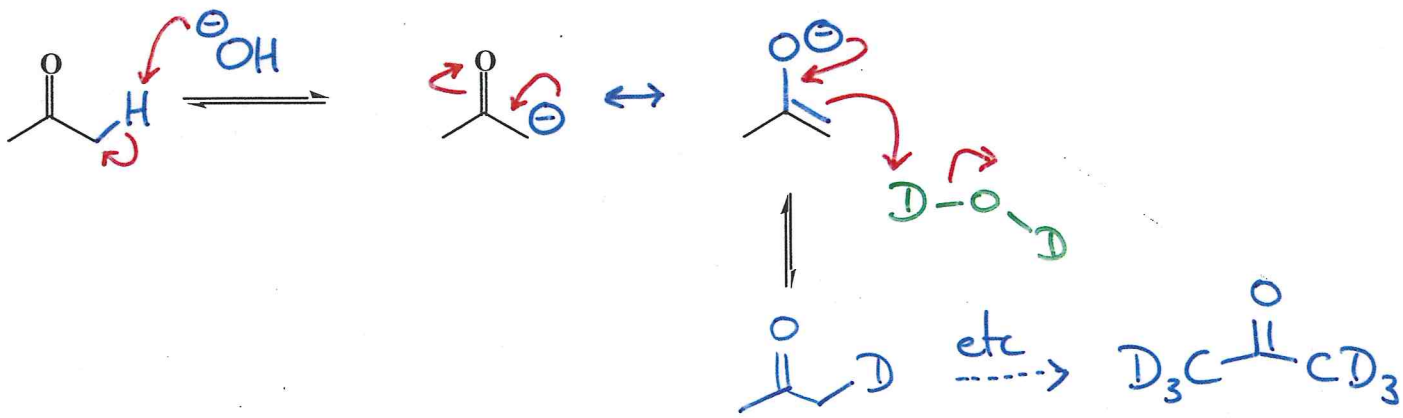
There is another way that we can detect the presence of enols in aldehydes and ketones.

When acetone is dissolved in D_2O it becomes CD_3COCD_3 over a long period of time: moreover, this reaction is catalysed by both Acids and bases

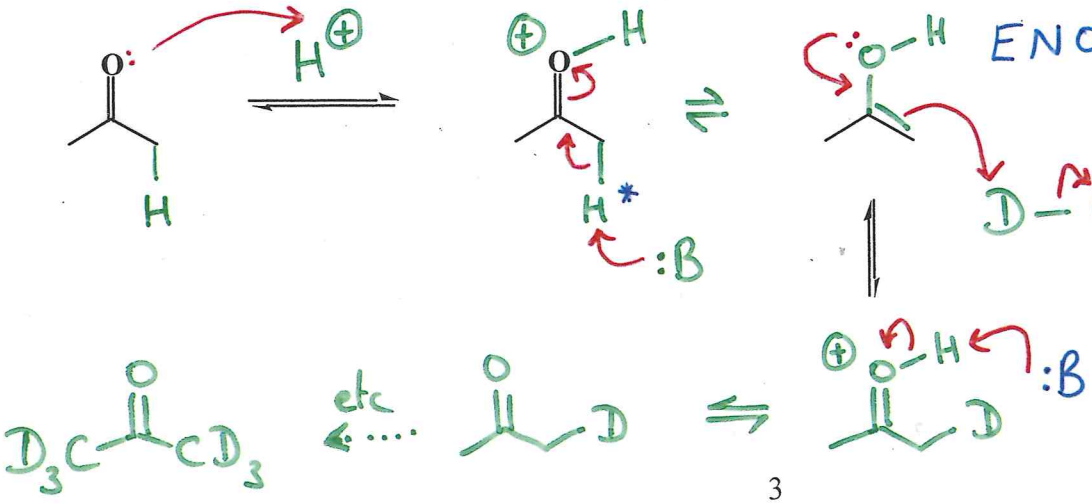
This process occurs through

IN BASE

ENOLATE



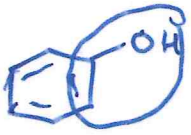
IN ACID



* = very acidic

Q. What would happen to $CH_3CH_2COCH_2CH_2Ph$ in D_2O with cat. H^+?

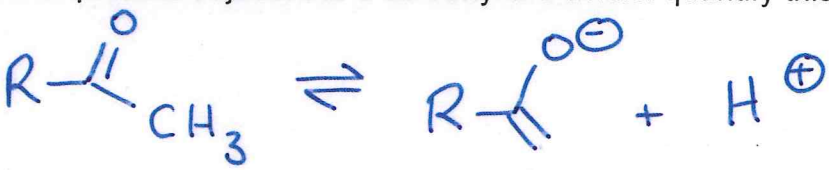
Think of a carbonyl compound that exists in 100% enol form?

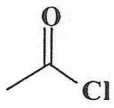


> Remember that the acid (or base) speeds up the rate at which the reaction proceeds ie equilibrium is reached, it does NOT AFFECT the Position of Equilibrium
>
> $A \rightleftharpoons B$ Only The Stability of A vs B Matters

ENOLATES

You have just seen that protons adjacent to a carbonyl are acidic: quantify this property by pKa





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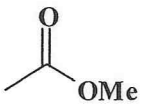

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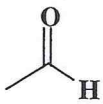

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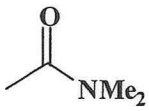

~30

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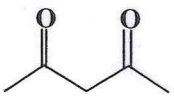
As the C=O becomes LESS electrophilic, then pKa INCREASE

Obviously, two carbonyl groups in a 1-3 array activate the protons in between even more. This manifests itself as a much lower pKa.



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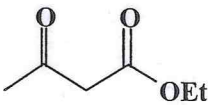

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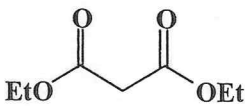

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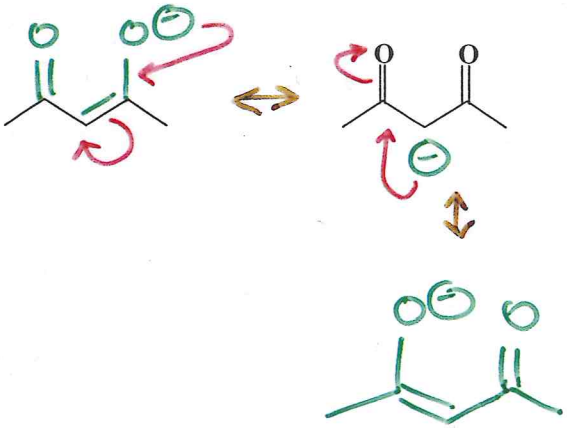
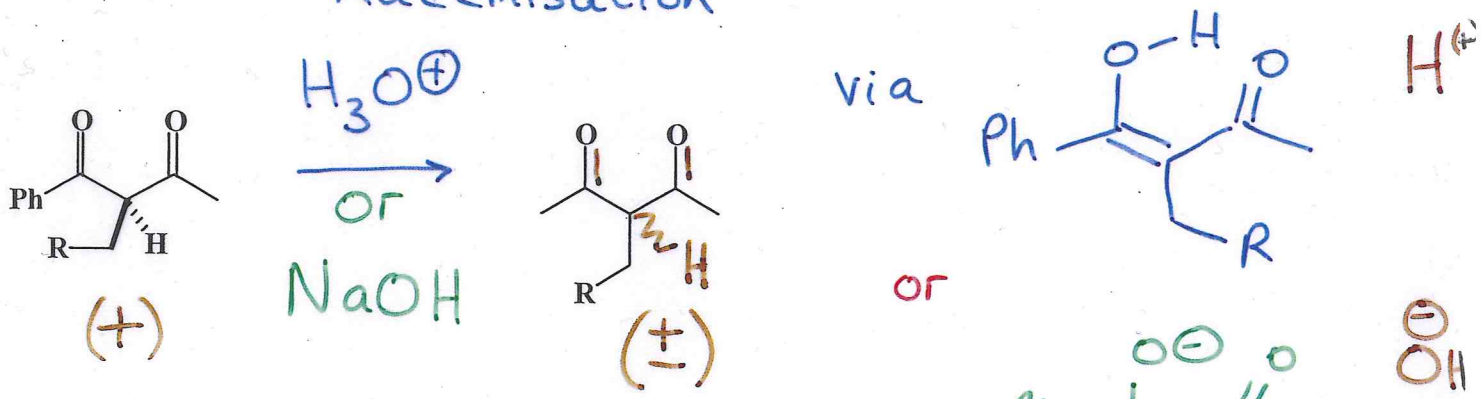


For a comprehensive collection of pKa values see:

http://www.chem.wisc.edu/areas/reich/pkatable/index.htm

As well as exchange at the alpha position, another (usually undesirable) consequence of enolisation is Racemisation

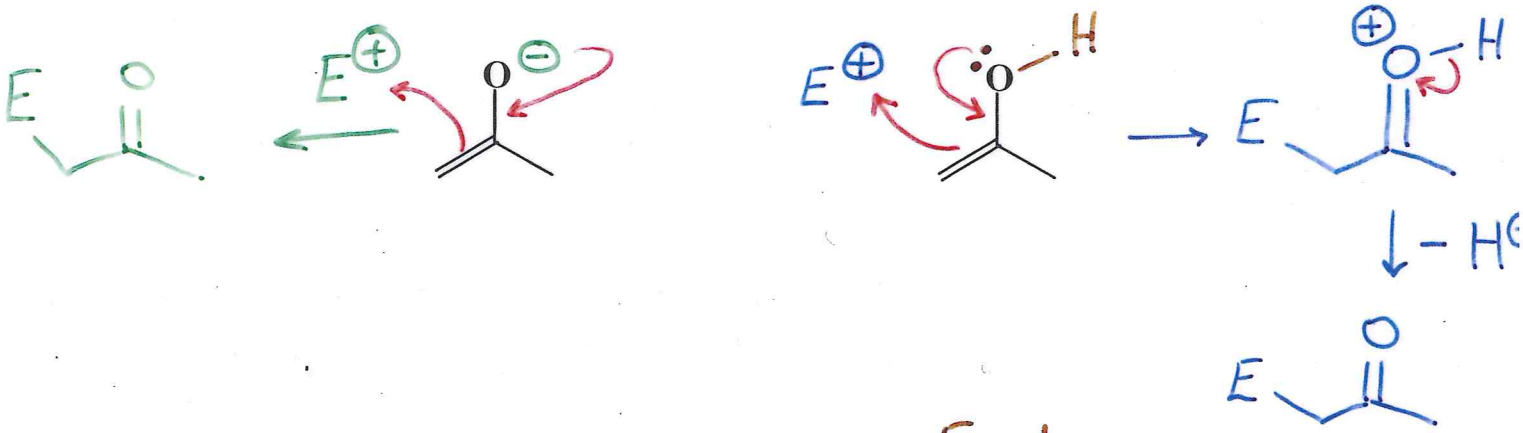


The more acidic the protons, the easier it is to racemise

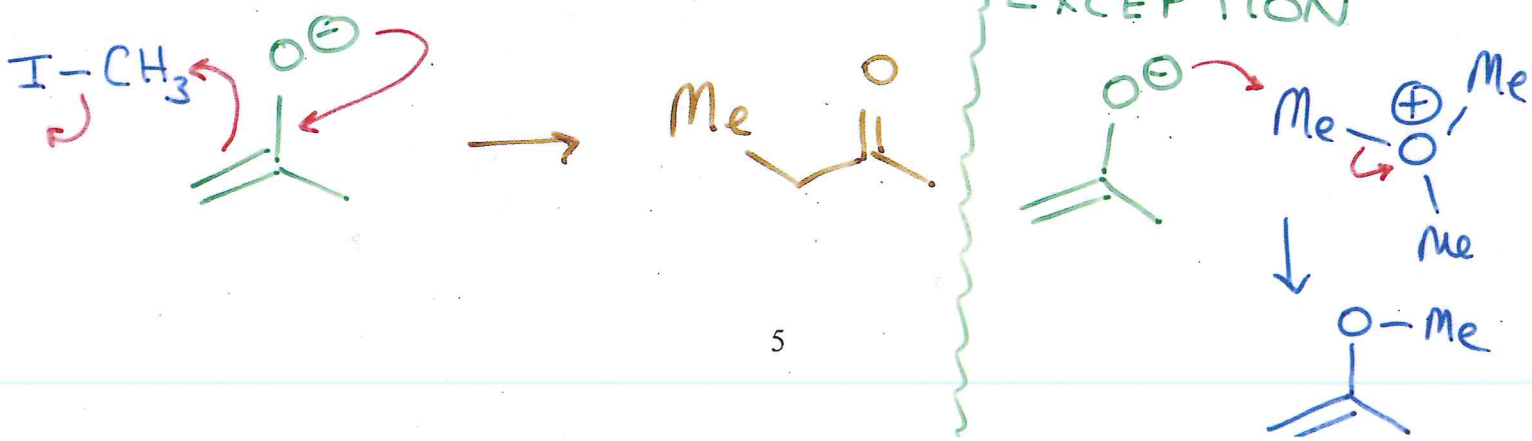
B) enols and enolates as nucleophiles

You should be familiar with the notion of alkenes acting as nucleophiles (using their relatively high energy, polarisable π-bonds-

Enols and enolates are simply electron-rich alkenes and so react rapidly

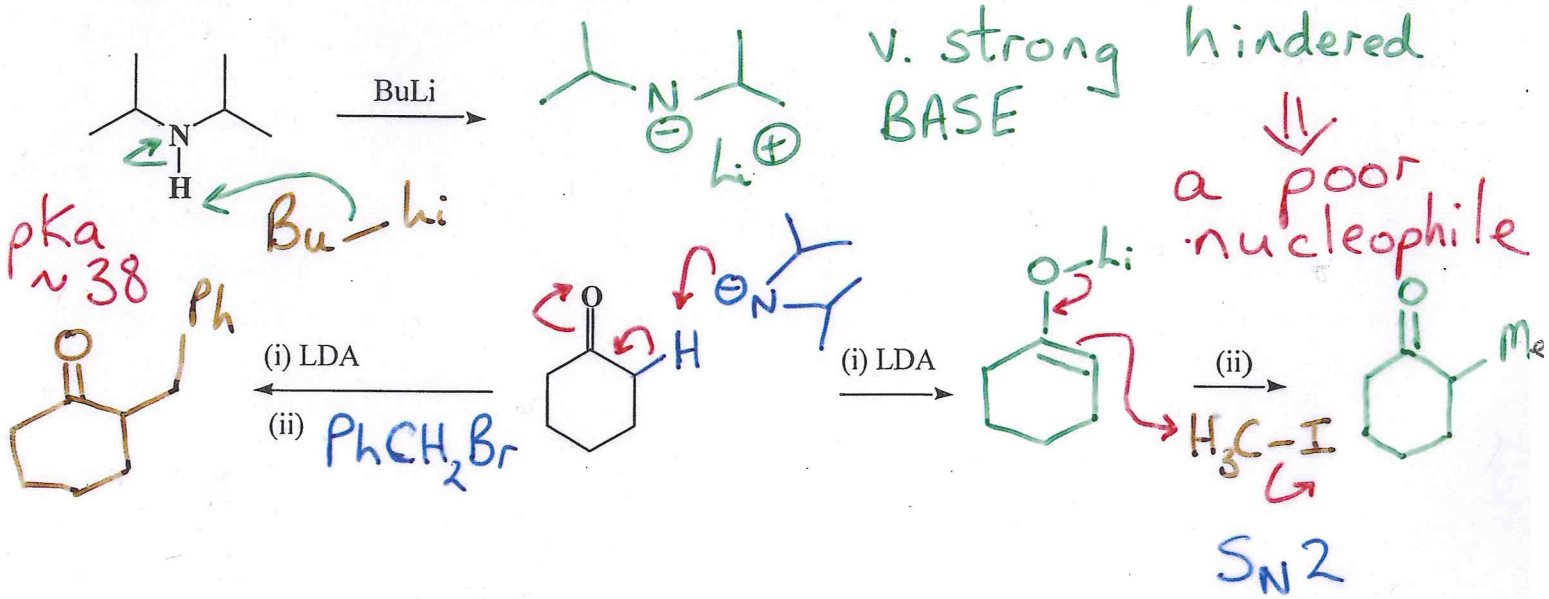


With the exception of highly reactive, charged, electrophiles, Enols and Enolates react on Carbon

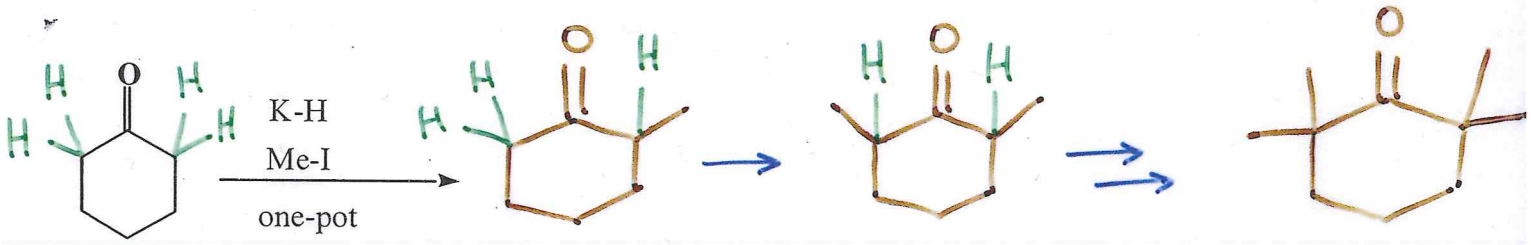


Simple reactions of enols and enolates

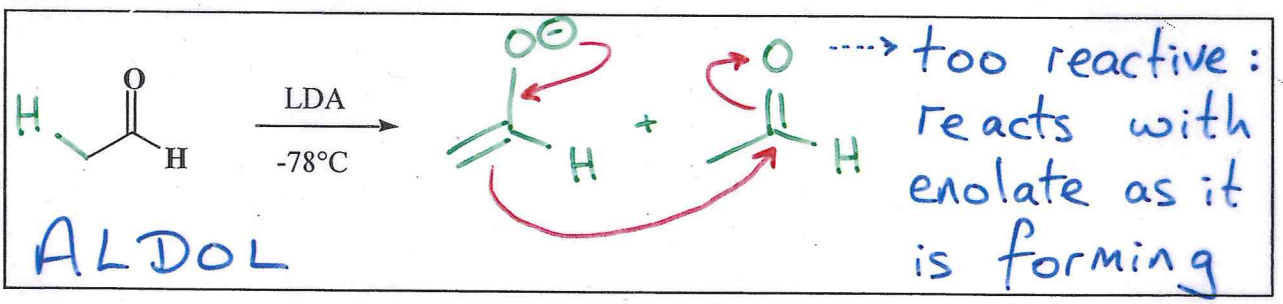
1) alkylation For simple ketones it is best to use a strong base such as LDA at low temp.



Using an excess of base and alkylating agent it is possible to over-alkylate



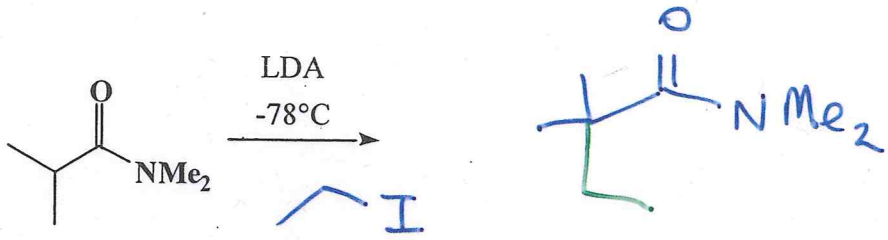
Note: there are problems with the alkylation of enolates derived from aldehydes.



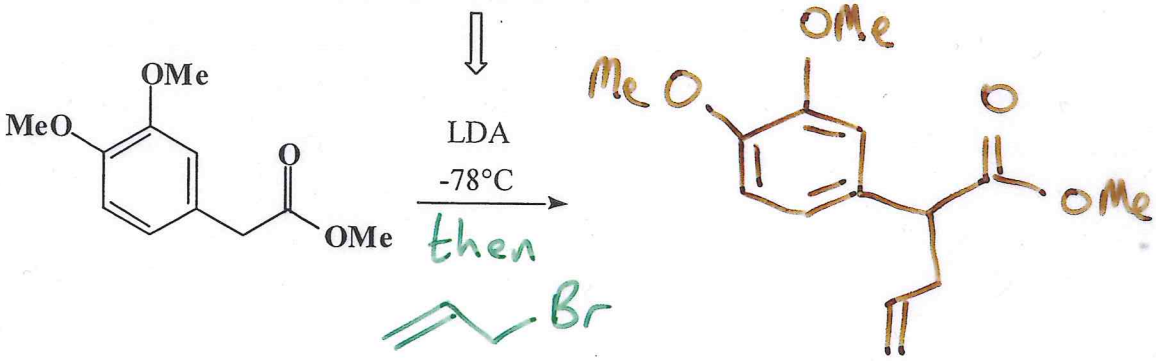
But, esters, acids and amides can all be alkylated successfully using these conditions.

i) LDA to form enolate

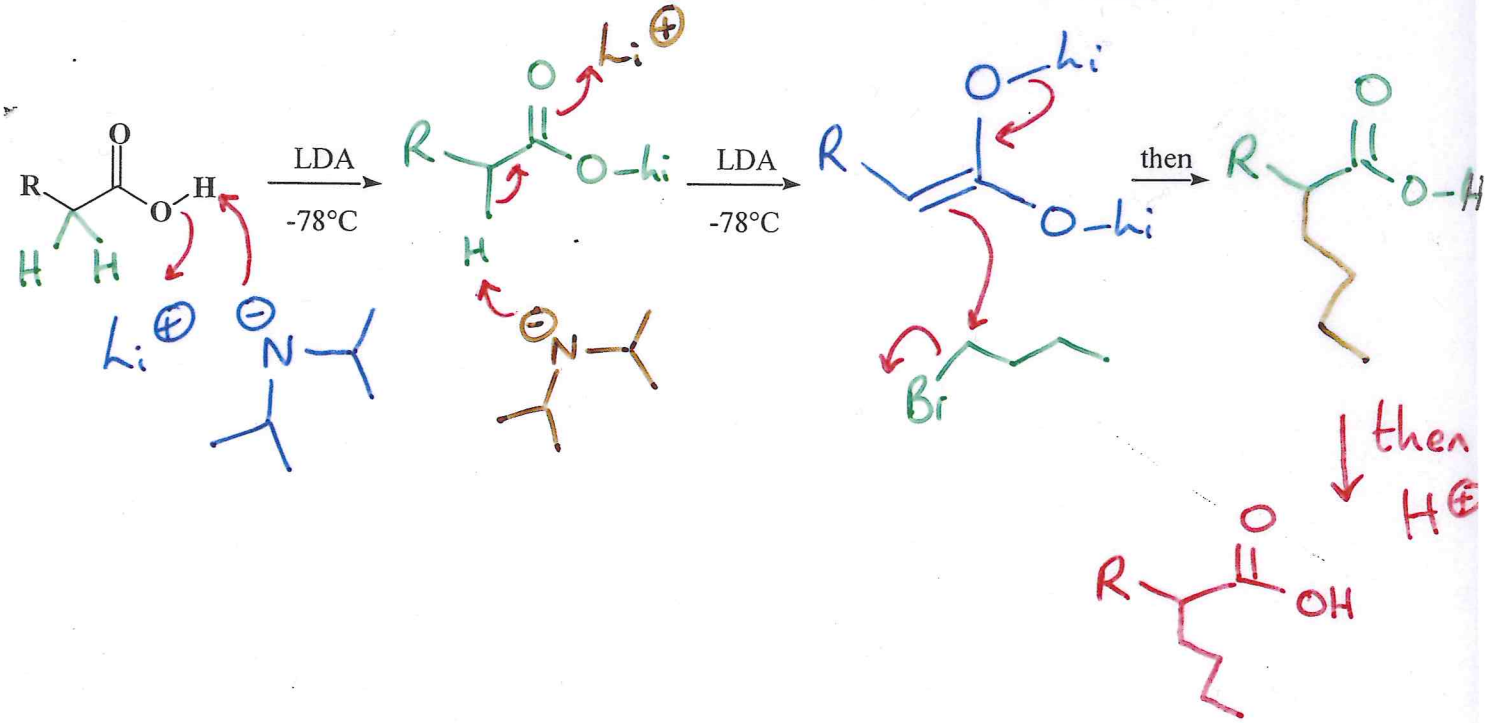
ii) S_N2 reaction with an electrophil



key step in the synthesis
of verapamil (angina)

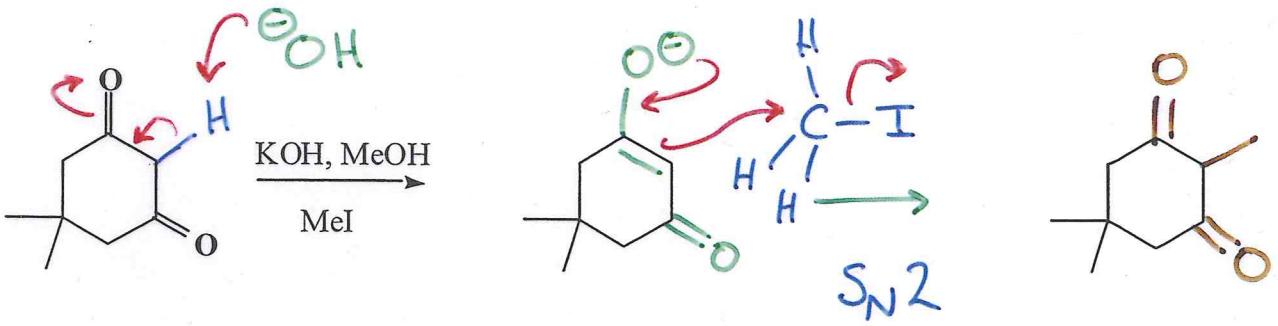


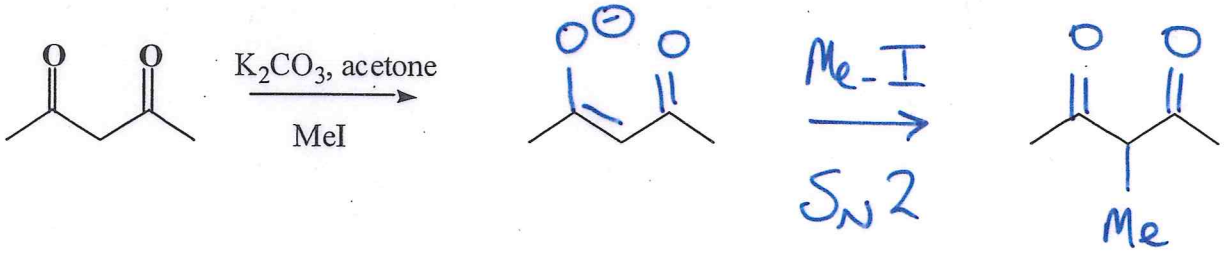
Remember that TWO equivalents of base are required to alkylate carboxylic acids:



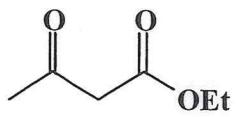
It is fair to say that the above conditions are not easy to replicate on a large scale. Remember that if a CH is flanked by TWO carbonyl groups then it is much more acidic: here alkylation doesn't need such a strong base.

lower pKa

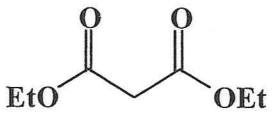




With respect to synthesis, the two most important β-dicarbonyl compounds are



ethyl acetoacetate pKa 11

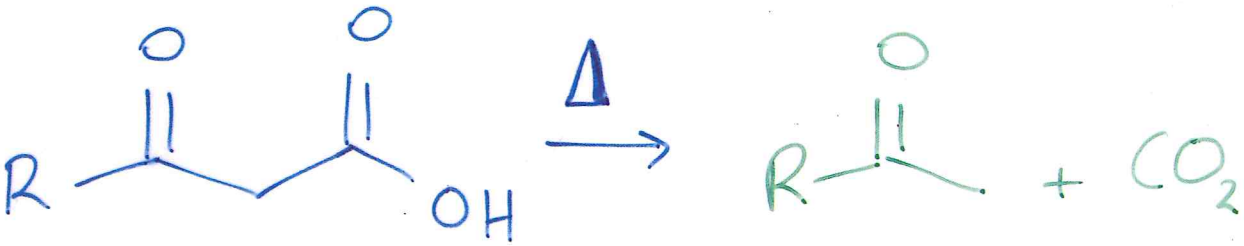


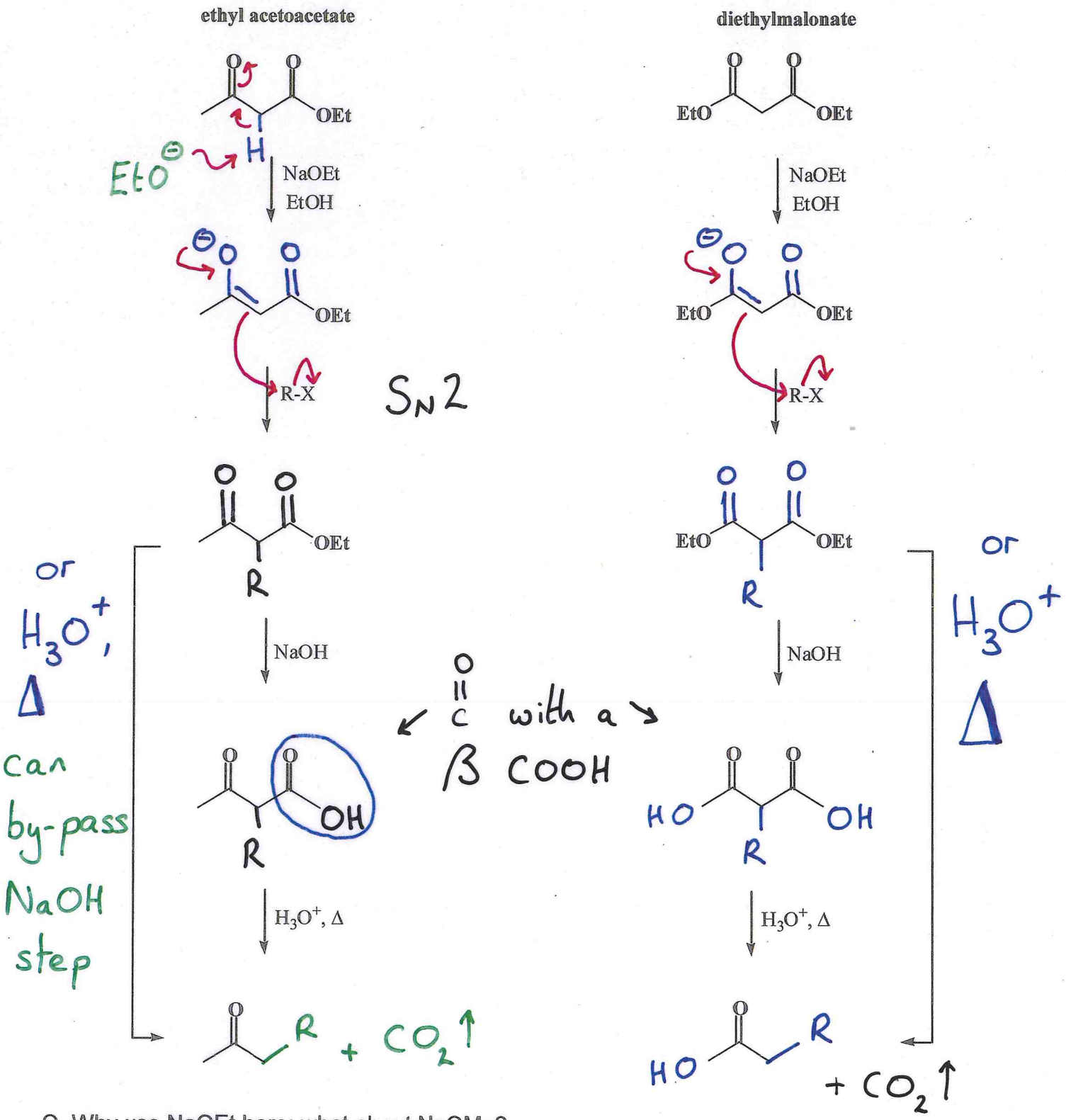
diethylmalonate pKa 13

Both of these are easily alkylated under mild conditions.

Ester hydrolysis and then heating with acid forms CO_2 (decarboxylation)

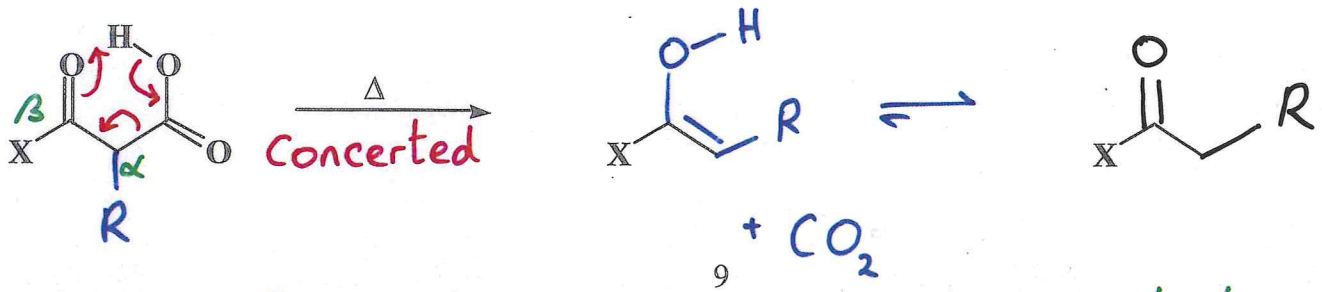
Acids with a β C=O group will LOSE CO_2 on heating





Q. Why use NaOEt here: what about NaOMe?

Look at the decarboxylation reaction in more detail. via β-keto acid

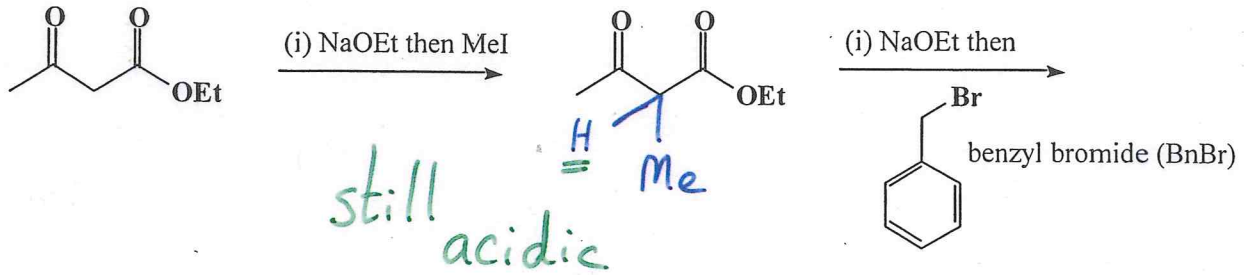


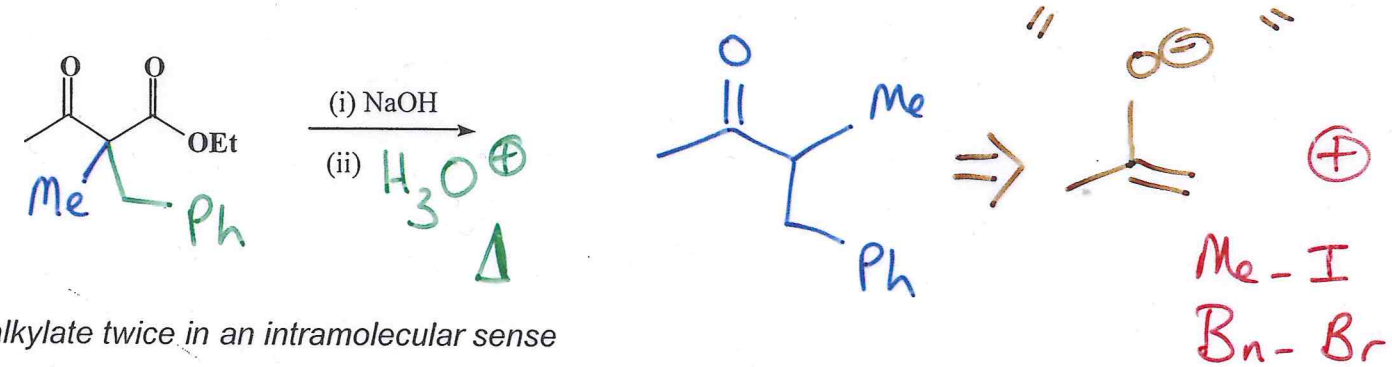
DRAW IN THIS CONFORMATION

enol

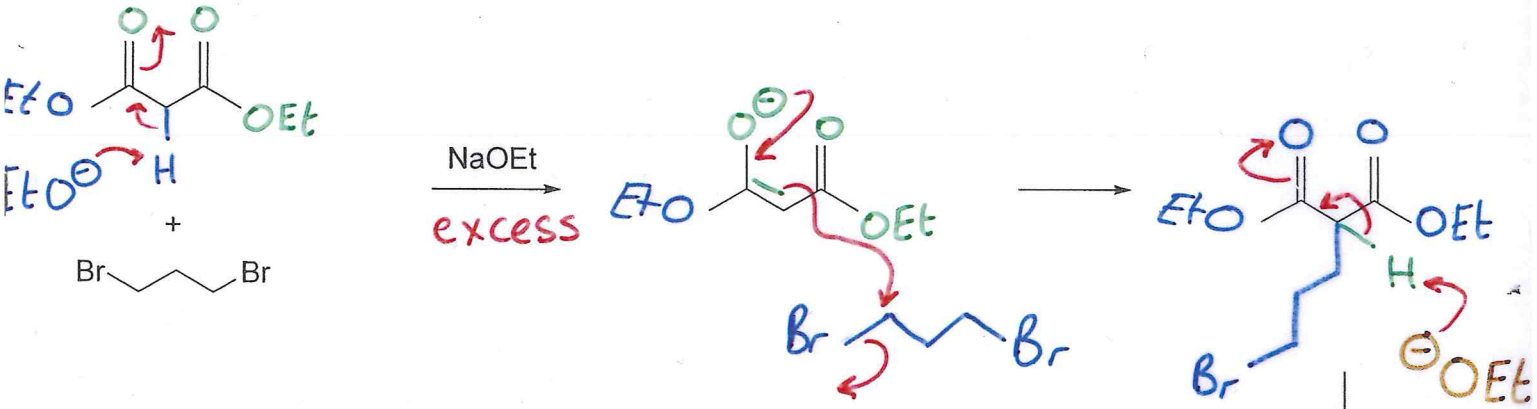
keto

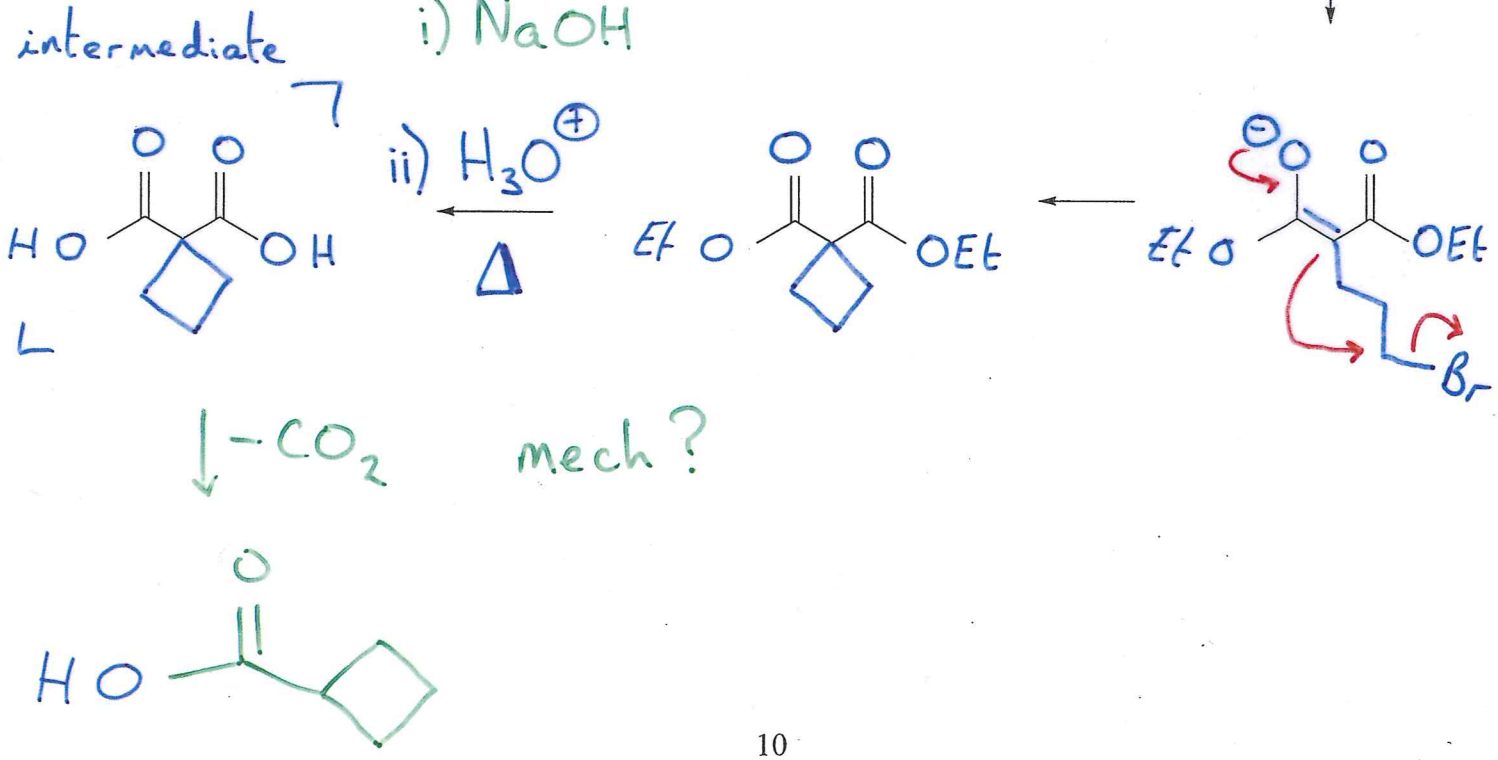
Also, there is no reason why we cannot alkylate twice:





Or alkylate twice in an intramolecular sense





2) Halogenation

a) Under basic conditions,

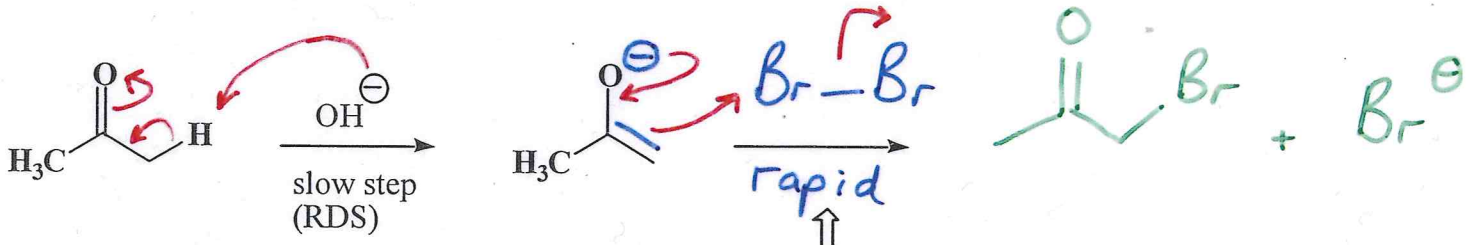
Consider the bromination of acetone with NaOH and Br_2

Experimentally, it has been shown that the rate of reaction $\propto$ [Ketone] AND [Base]

But is **not** related to $[Br_2]$

Also bromination and iodination proceed at exactly the same rate !

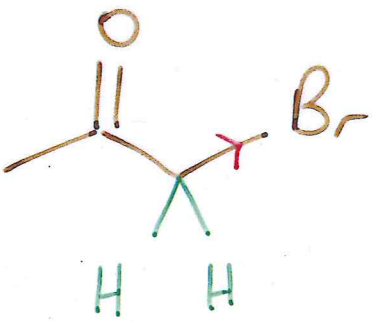
The only way to reconcile these observations is with the following mechanism:



no $[Br_2]$ here

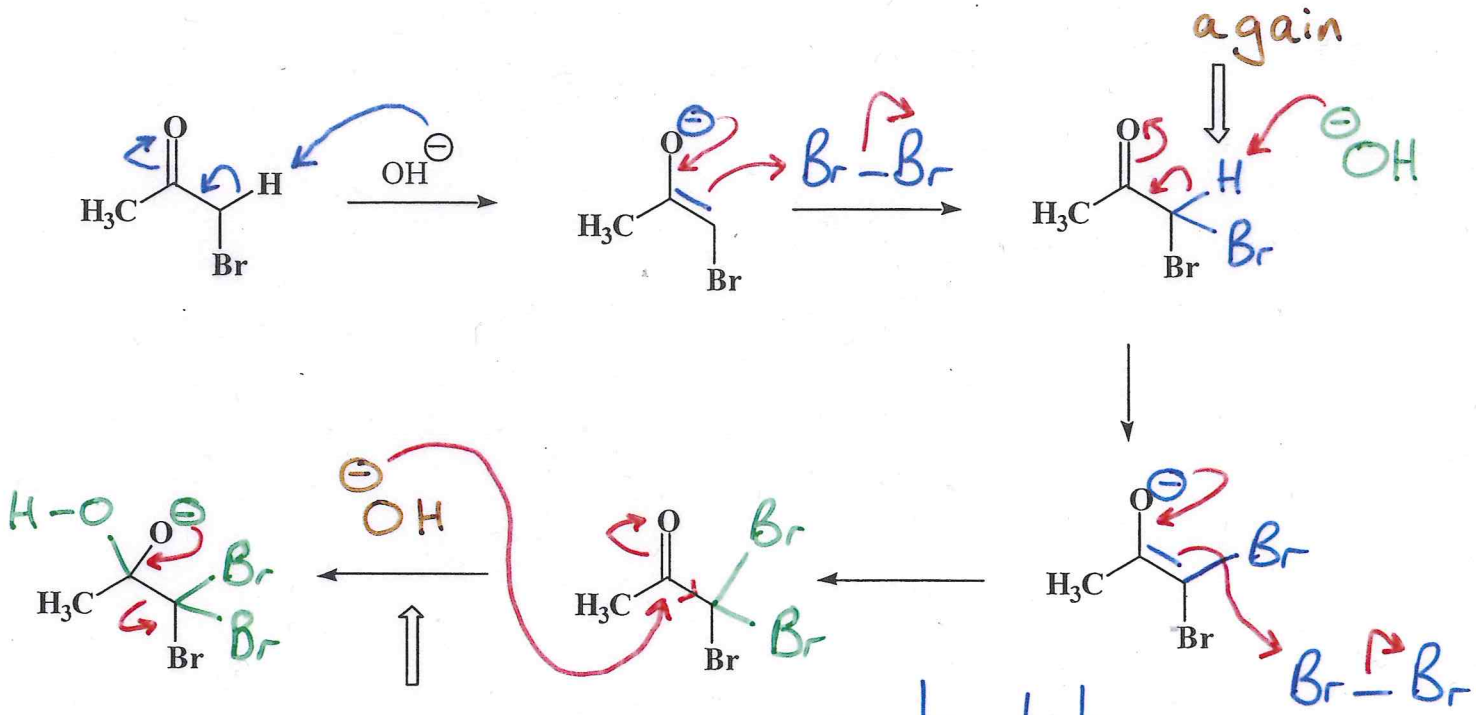
rapid reaction with an Electrophile (Br_2 or I_2 etc)

Unfortunately, the reaction does not stop here:



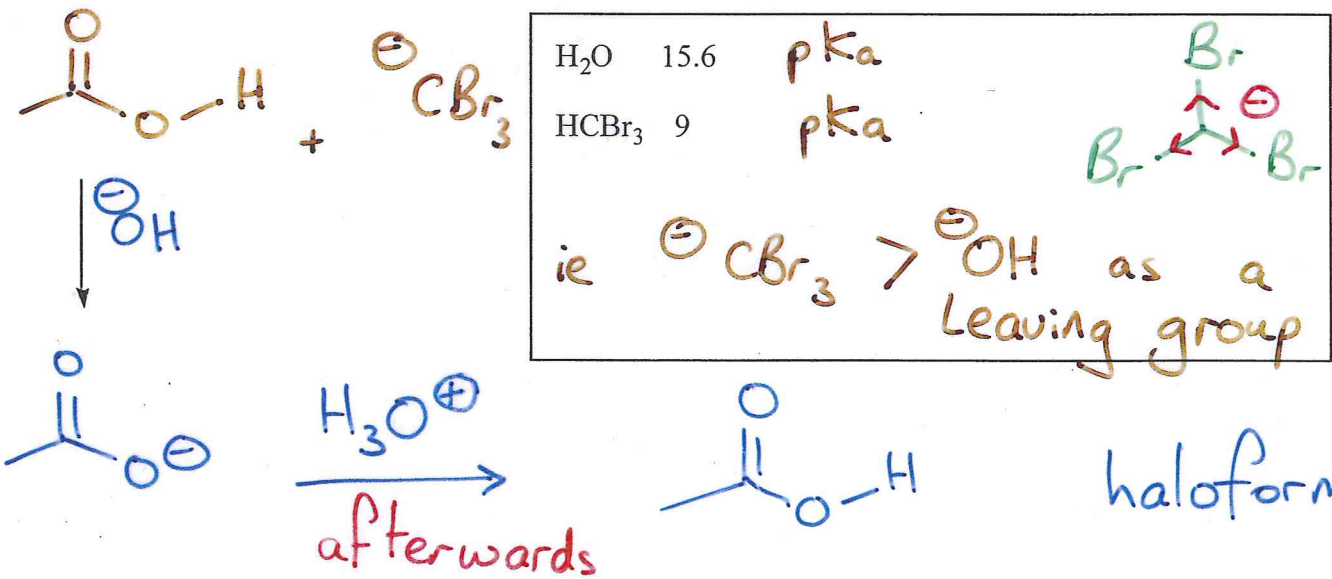
electron-withdrawing group (Br) acidifies the H atoms even more.

So, the reaction happens again ... but faster



No further deprotonation is possible; nucleophile attacks C=O

the best leaving group is lost ie $^{\ominus}CBr_3$

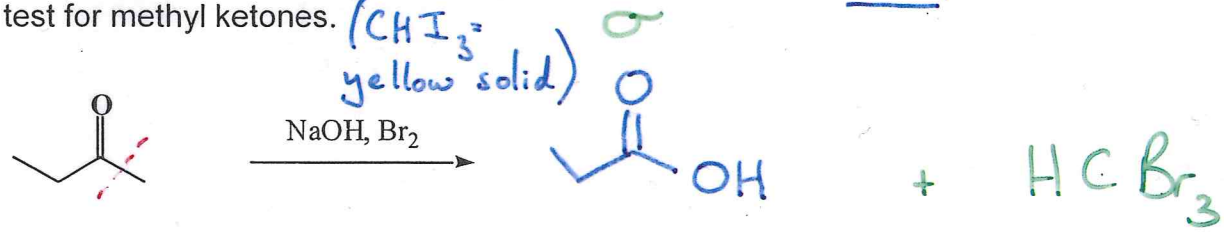


H_2O	15.6	pka
$HCBr_3$	9	pka

ie $^{\ominus}CBr_3$ > $^{\ominus}OH$ as a leaving group

Known as the bromoform (or iodoform with I_2) reaction.

This reaction is unusual because a carbon-carbon bond is broken; the reaction can be used as a test for methyl ketones. (CHI_3 = yellow solid)



$^{\ominus}CBr_3$ needs a $R-C(=O)-CH_3$ precursor

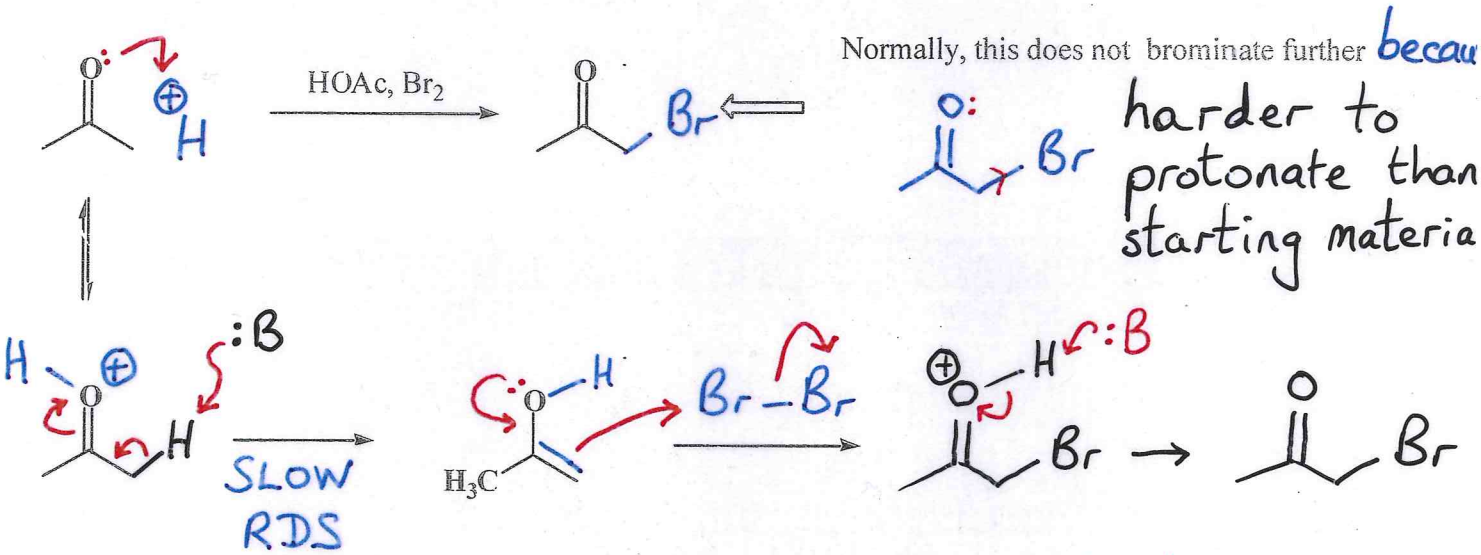
b) Under acidic conditions,

It is also possible to halogenate ketones under acidic conditions; again,

it has been shown that the rate of reaction is $\propto$ [ketone] and [H^+]

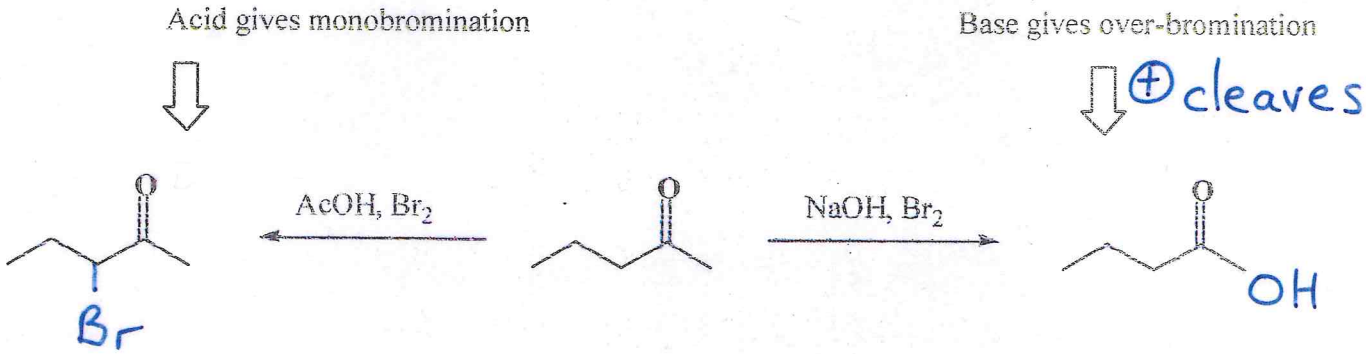
But is **not** related to [Br_2] again, rate of bromination = rate of iodination

So, we need to amend our previous mechanism to accommodate the rate limiting formation of an Enol



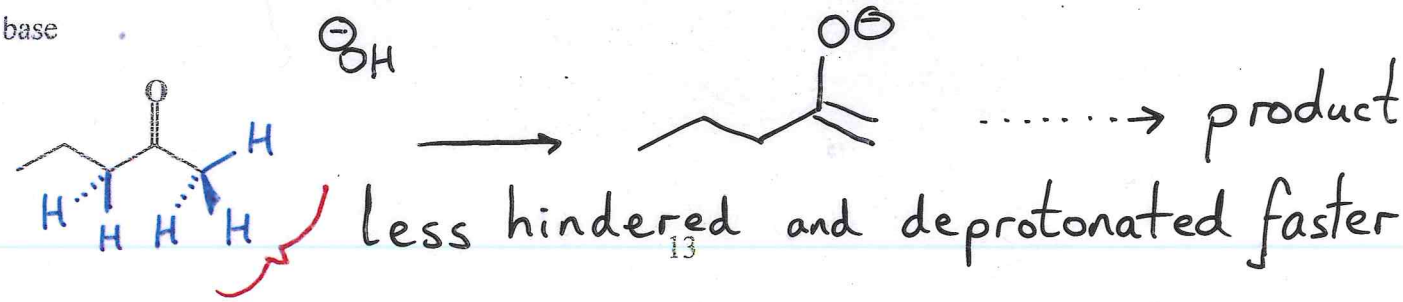
Clearly, for monobromination of aldehydes and ketones, ACID is superior to base

Compare the bromination of unsymmetrical ketones under the two sets of conditions,

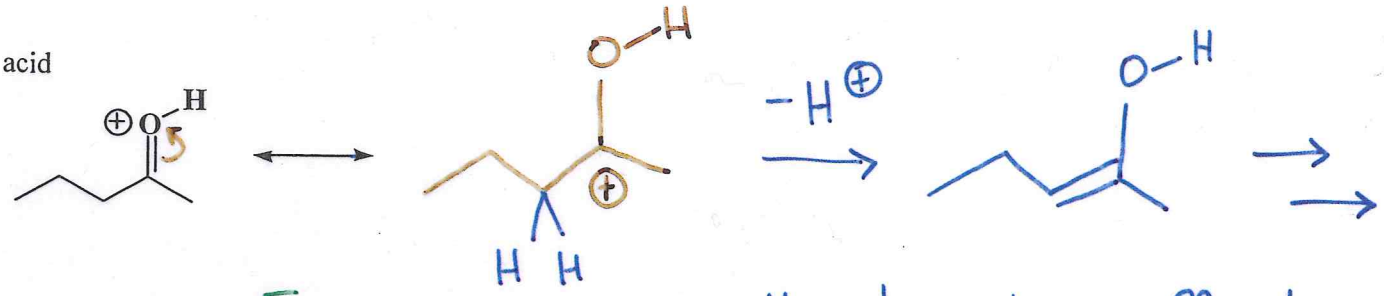


As for **regiochemistry**, consider the product determining step in each case:

In base



In acid



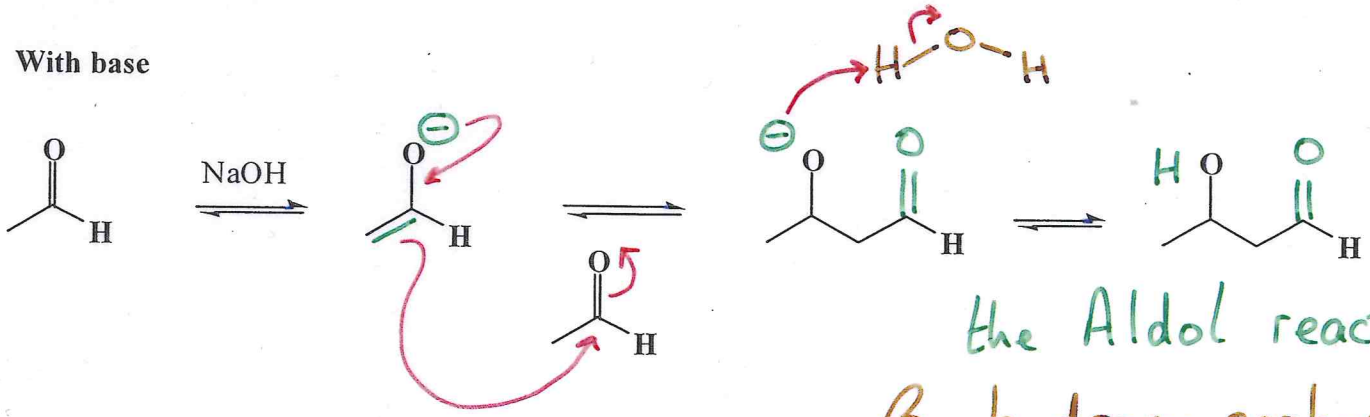
E_1 cations normally eliminate → Most substituted alkene

3) Reaction with carbonyl groups

A) reaction with aldehydes and ketones: the aldol reaction

Consider the reaction of an enol or enolate with a carbonyl compound:

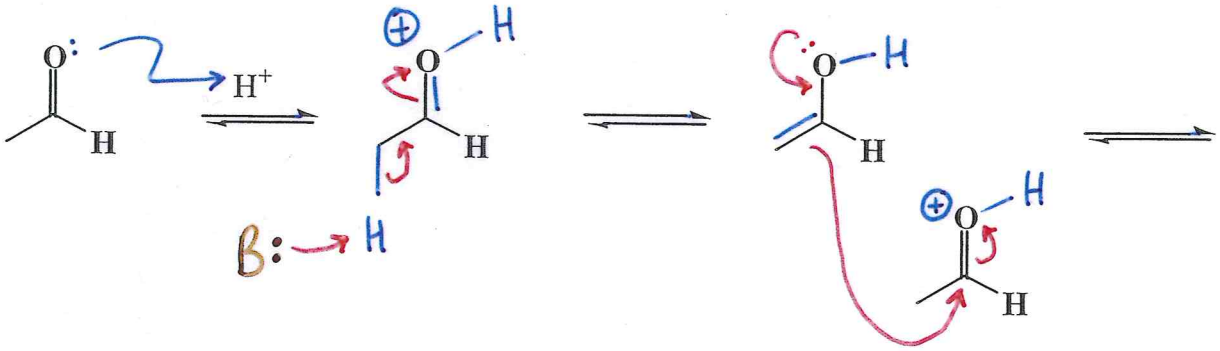
With base

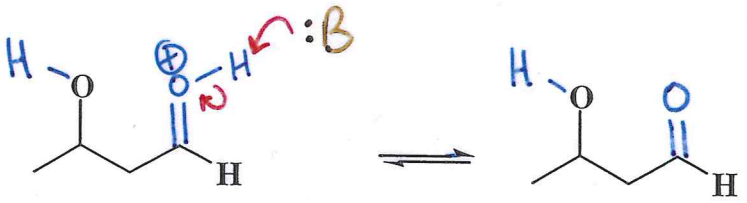


the Aldol reaction

β-hydroxy carbonyls

With acid





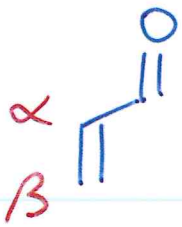
$H^{\oplus}$

- forms enol
- activates C=O

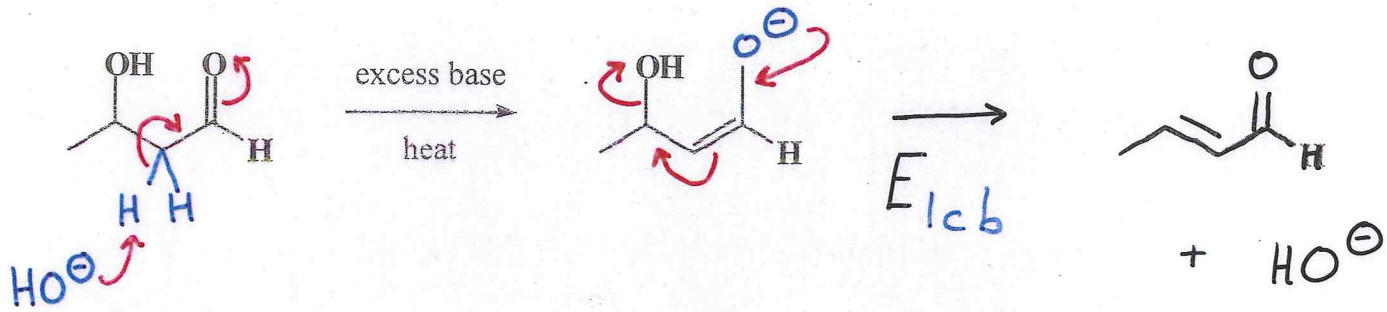
In this case the equilibrium favours the product- but this is not always the case and with acetone, for example, the equilibrium favours the starting materials. Difficult to Control

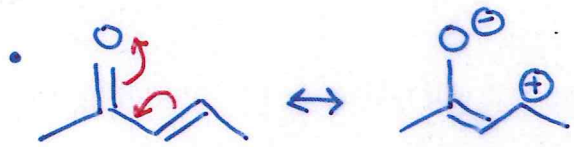
If these reactions are forced then **elimination** follows the aldol to form

α,β - unsaturated C=O



Elimination with base

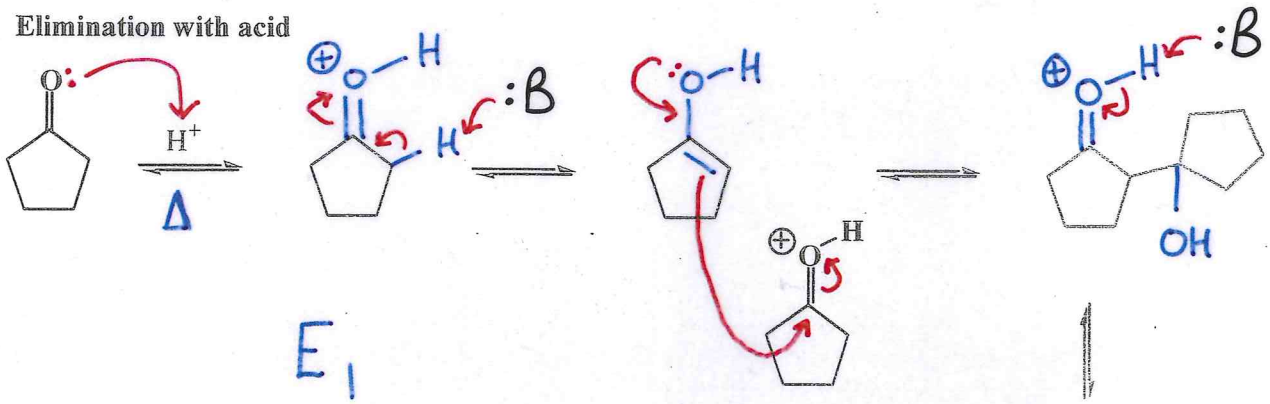


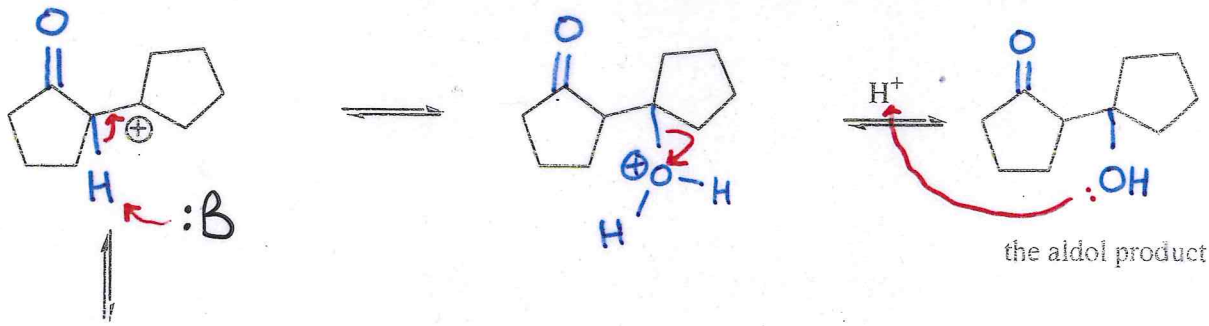


conjugation = extra stability

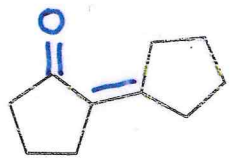
• rare example of ⊖OH as a leaving group

Elimination with acid





the aldol product



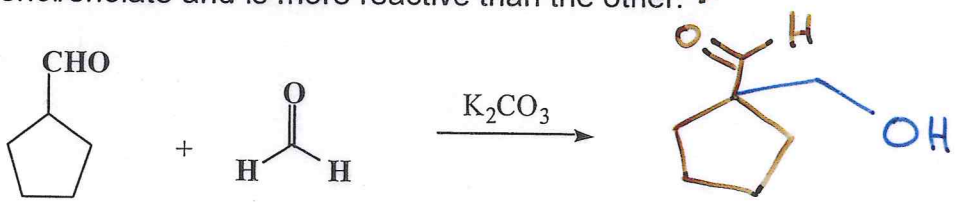
⟸ an α,β- unsaturated carbonyl compound

Base catalysed aldol reactions can give either the aldol product or the dehydrated product by an E_{1cb} mechanism

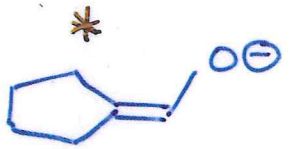
Acid catalysed aldol reactions can give the aldol product but usually give the dehydrated product by an E_1 mechanism

These are all examples of self condensation, crossed aldol reactions are clearly going to be complicated. For example, reaction of CH_3CHO with CH_3CH_2CHO will result in 4 different products (2 x self condensation + 2 x mixed condensation

In practice, the crossed aldol reaction only works well when one component cannot form an enol/enolate and is more reactive than the other.*

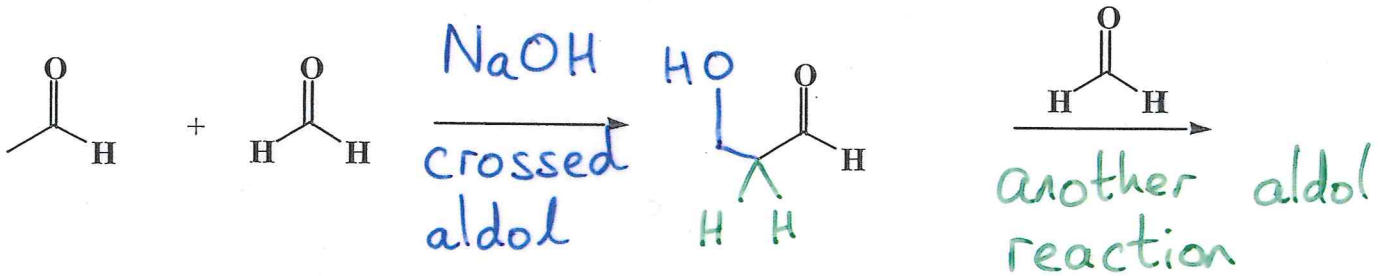


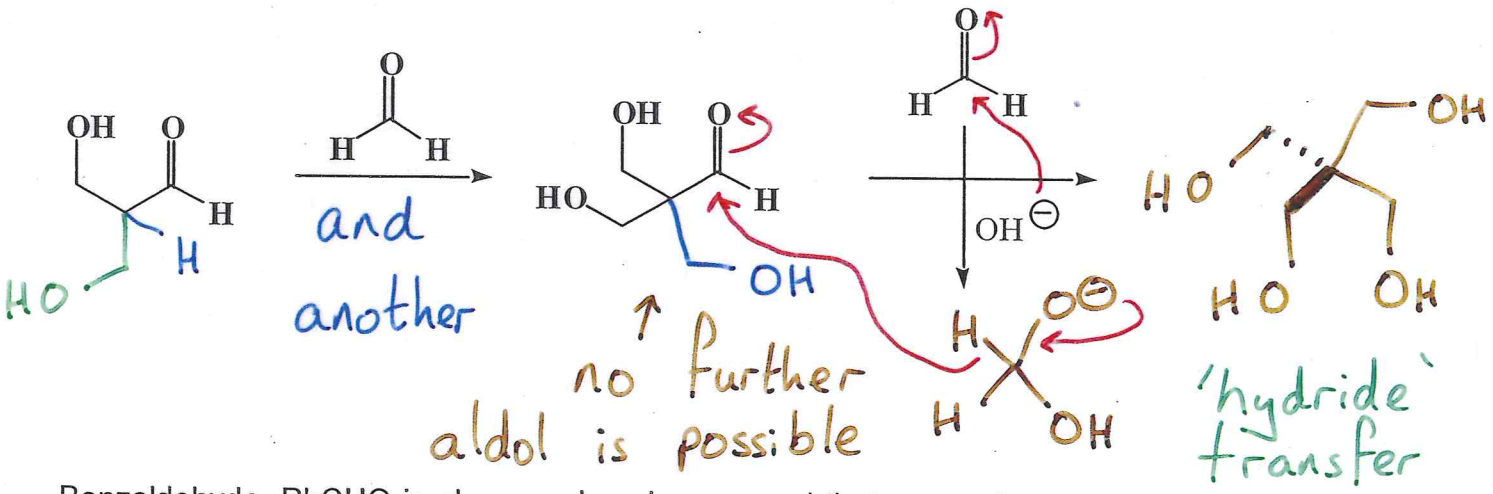
via



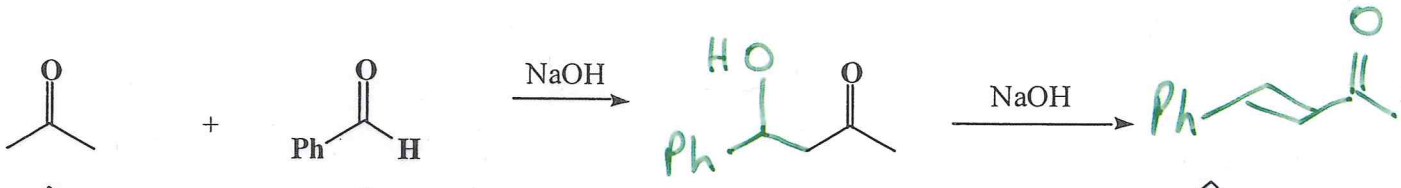
N.B. Enolate formation is NOT complete (weak base)

In fact it is difficult to stop this reaction:





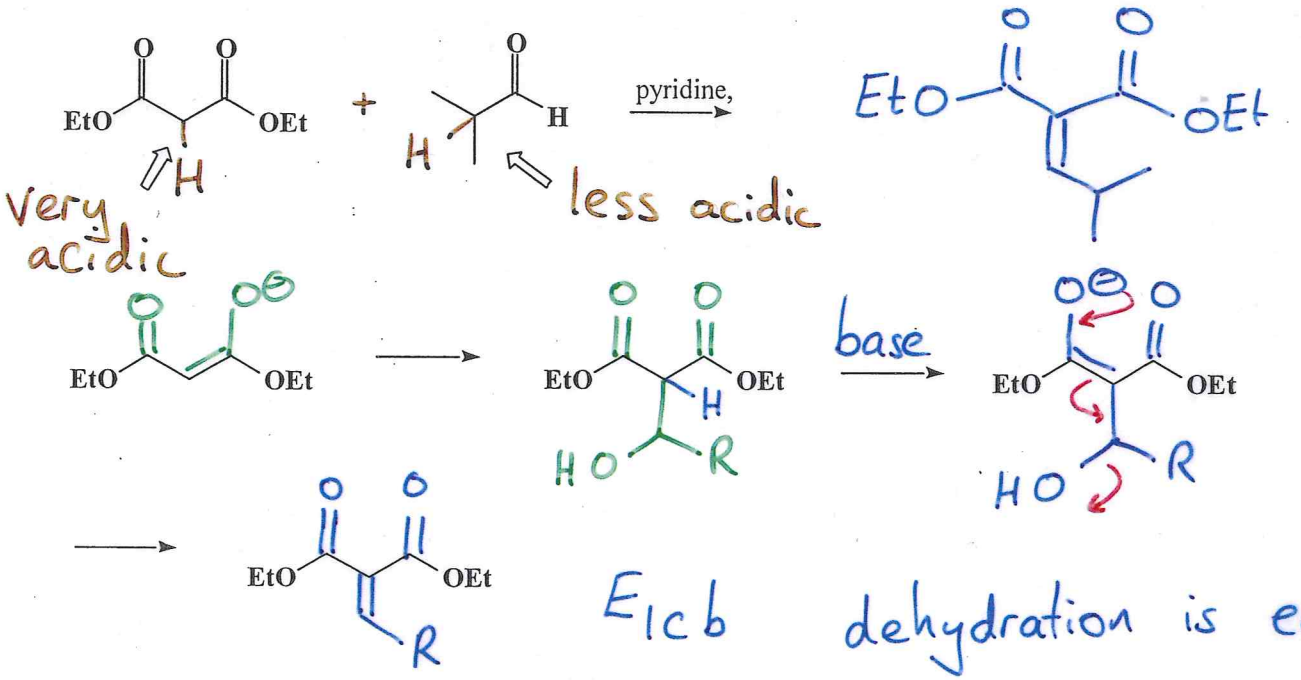
Benzaldehyde, PhCHO is also a carbonyl compound that cannot form an enolate; so it is a good partner in the aldol reactions with ketones.



forms enolate no enolate easy to dehydrate (extra delocalisation)

C=O unreactive C=O reactive

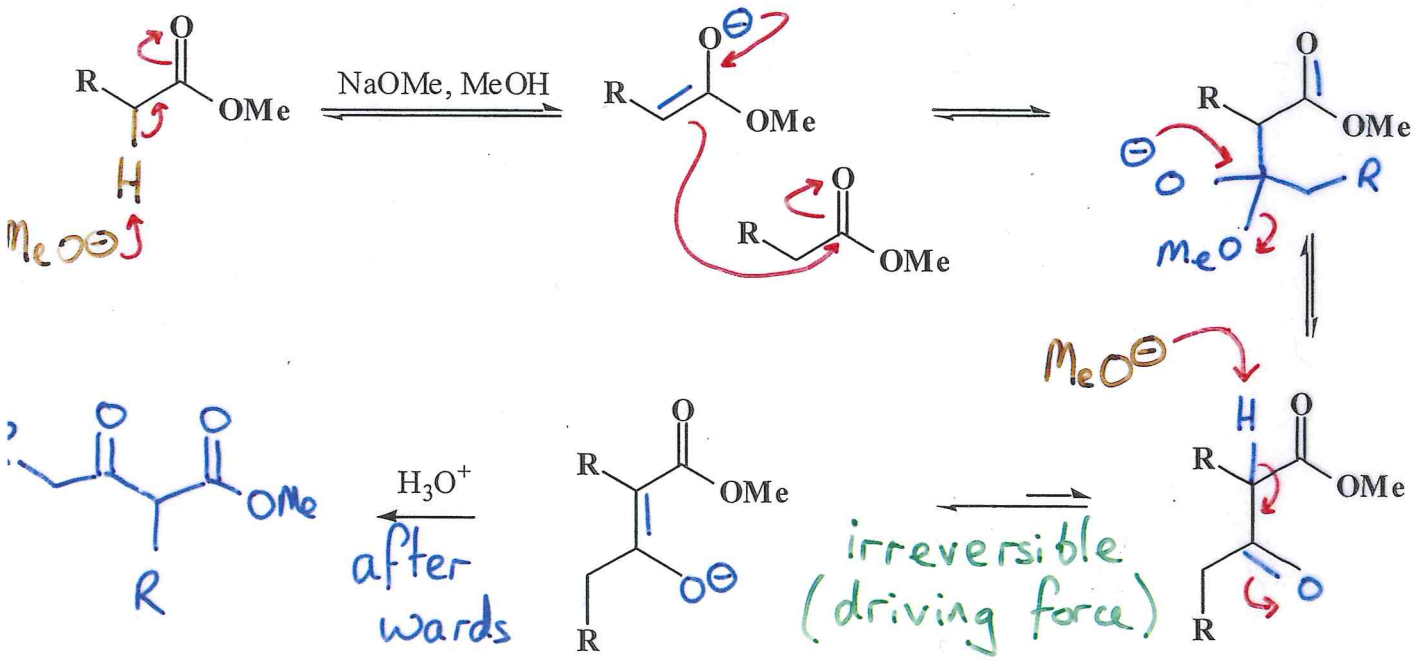
We can easily perform crossed aldol reactions with malonates and do not require a strong base to form an enolate.



dehydration is easy.

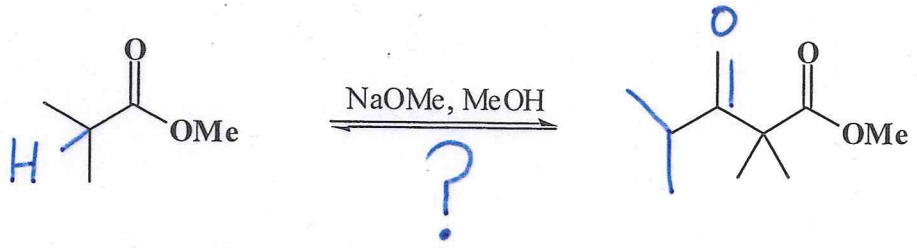
B) reactions of esters: the Claisen reaction

In essence, this is an equilibrium reaction of an ester enolate with the ester starting material.



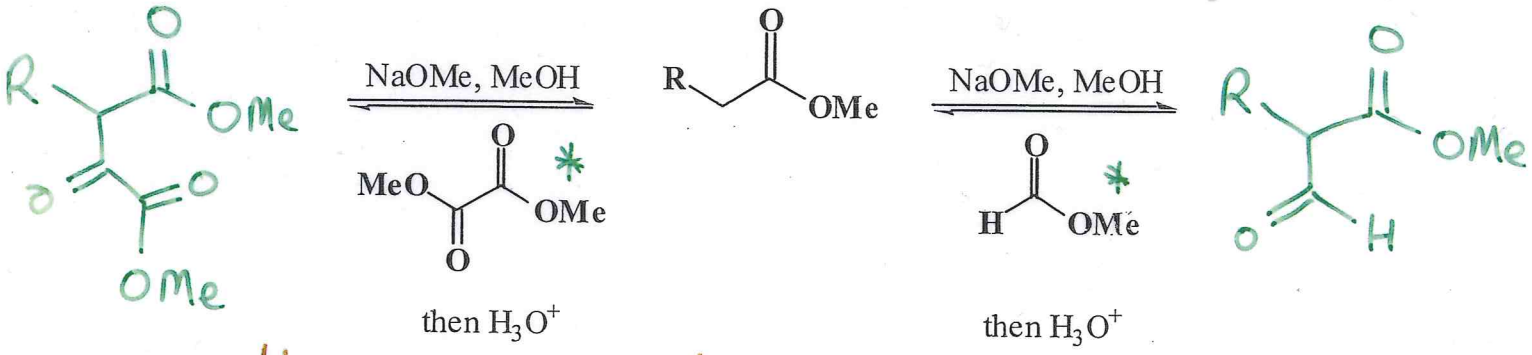
β-Keto ester – v. general reaction

How do we know that deprotonation drives the equilibrium? Try a Claisen with a disubstituted ester.



This reaction doesnt work - only observe starting material

Just like the aldol, crossed Claisen reactions are only viable if one component is more electrophilic than the other AND cannot enolise *

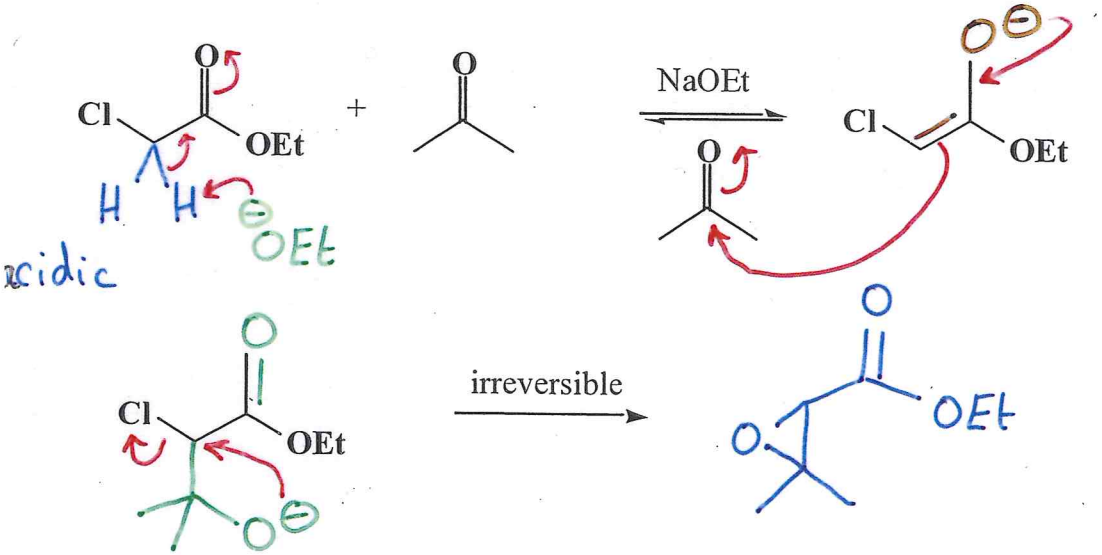


go through the two mechanisms

C) further reactions of esters: alpha-halo esters

(i) Darzens reaction

Aldehydes and ketones condense with alpha-halo esters in the presence of base. This works well for aromatic aldehydes and ketones and for aliphatic ketones.



is an epoxide

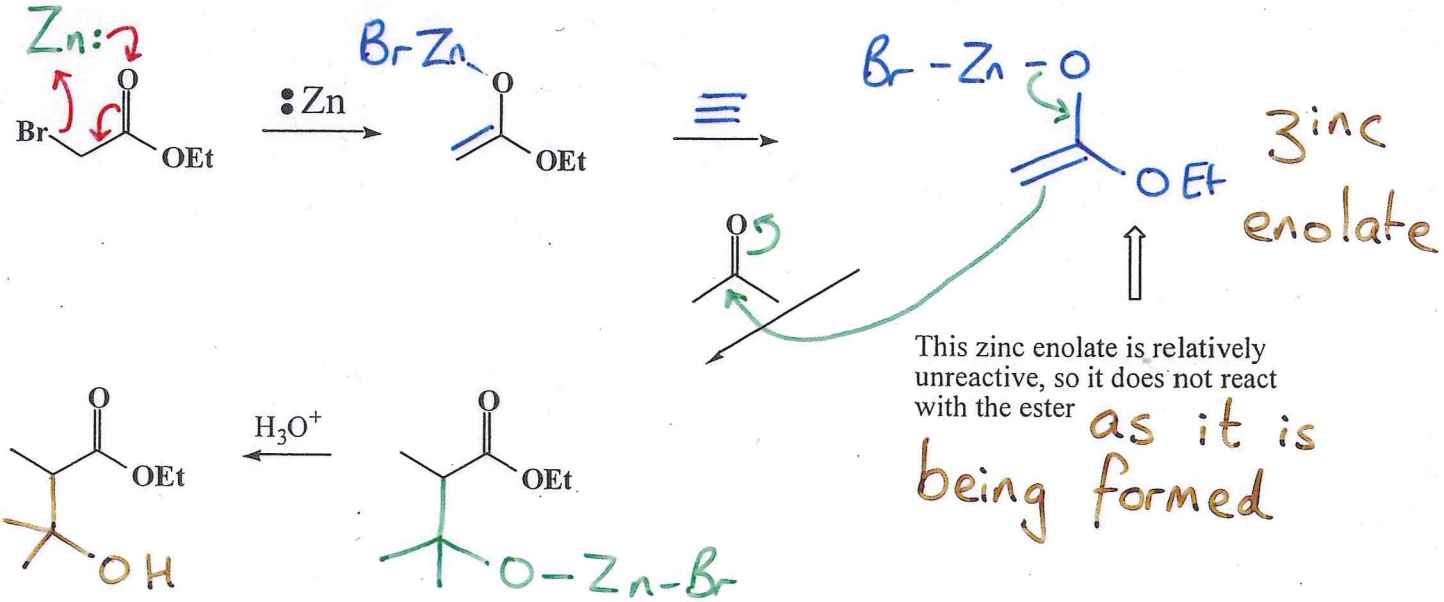
(ii) Reformatsky reaction of alpha bromo esters

Esters cannot be used in the crossed aldol condensation with aldehydes and ketones because aldehydes and ketones are

(I) More Acidic **(II) More** Reactive

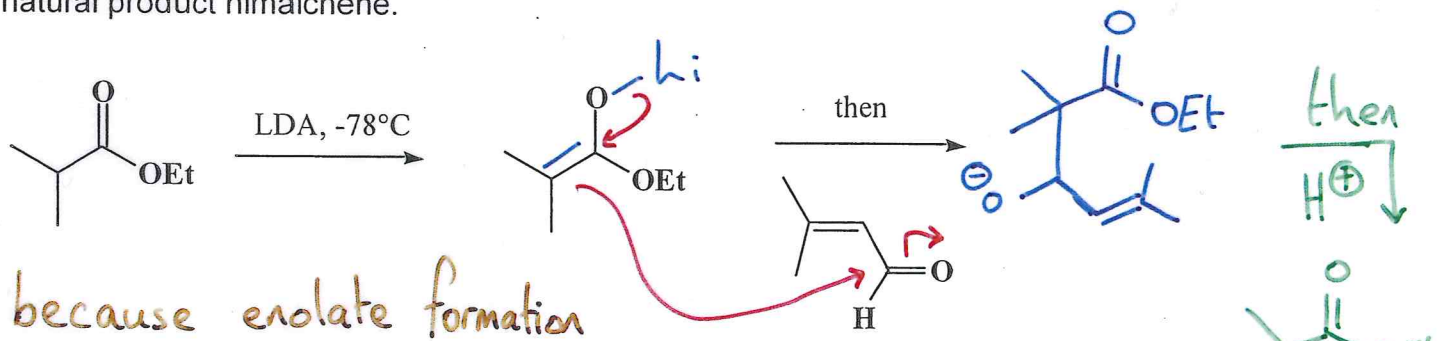
So, the aldehyde (or ketone) would simply self condense (hence the importance of Cl in the Darzens reaction).

One simple way of making ester enolates that can and do react with aldehydes and ketones is



Note: you cannot make zinc enolates from alpha bromo aldehydes and ketones via this chemistry- the carbonyl starting materials are too reactive; the zinc enolate self condenses as it is being formed.

A modern alternative to this involves making the ester enolate with a very strong base (LDA). This means that self condensation is not a problem.* Then, in a separate step, add the aldehyde (or ketone) electrophile. The reaction below was a key step in the laboratory synthesis of the natural product himalchene.



* because enolate formation is rapid and complete

Problems on a large scale Buhi / -78 °C

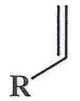
4) α,β-unsaturated carbonyl compounds as electrophiles (C=C bonds)

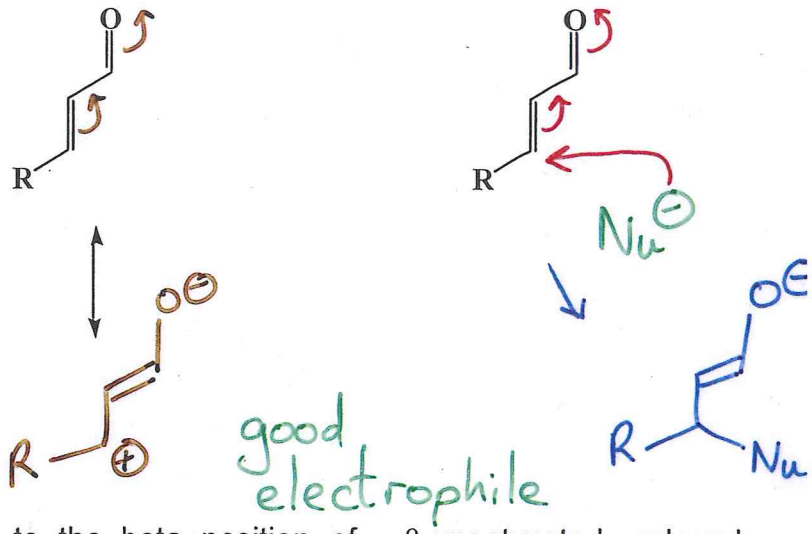
Earlier, we discussed the fact that delocalisation reduces the electrophilicity of carbonyl groups. By the same token, the alkene is a much worse nucleophile and indeed becomes an electrophile

Good nucleophile

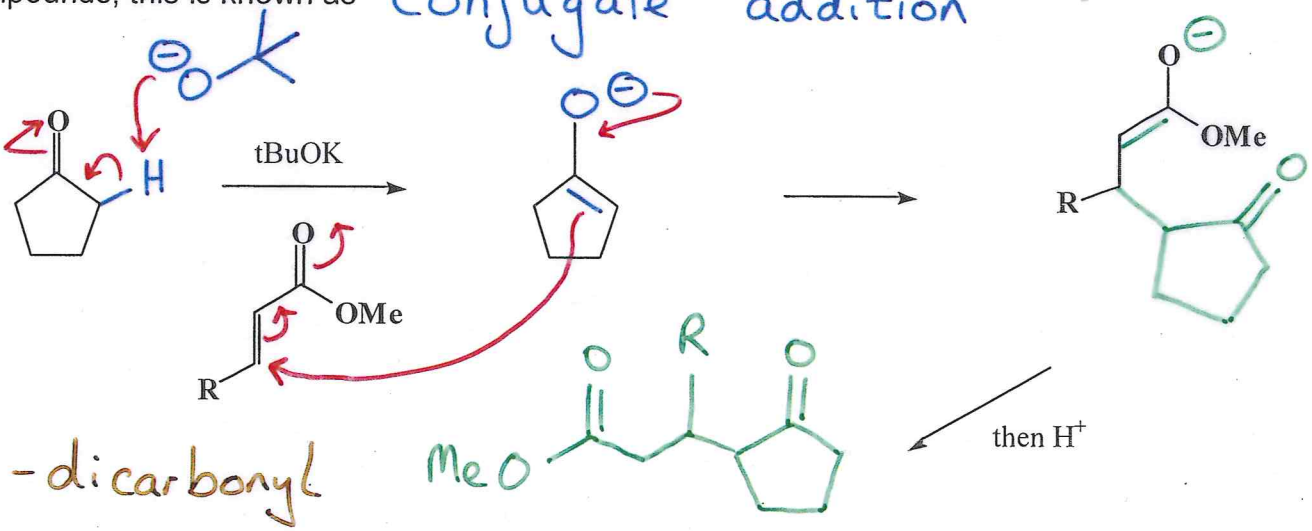
But

Poor electrophile

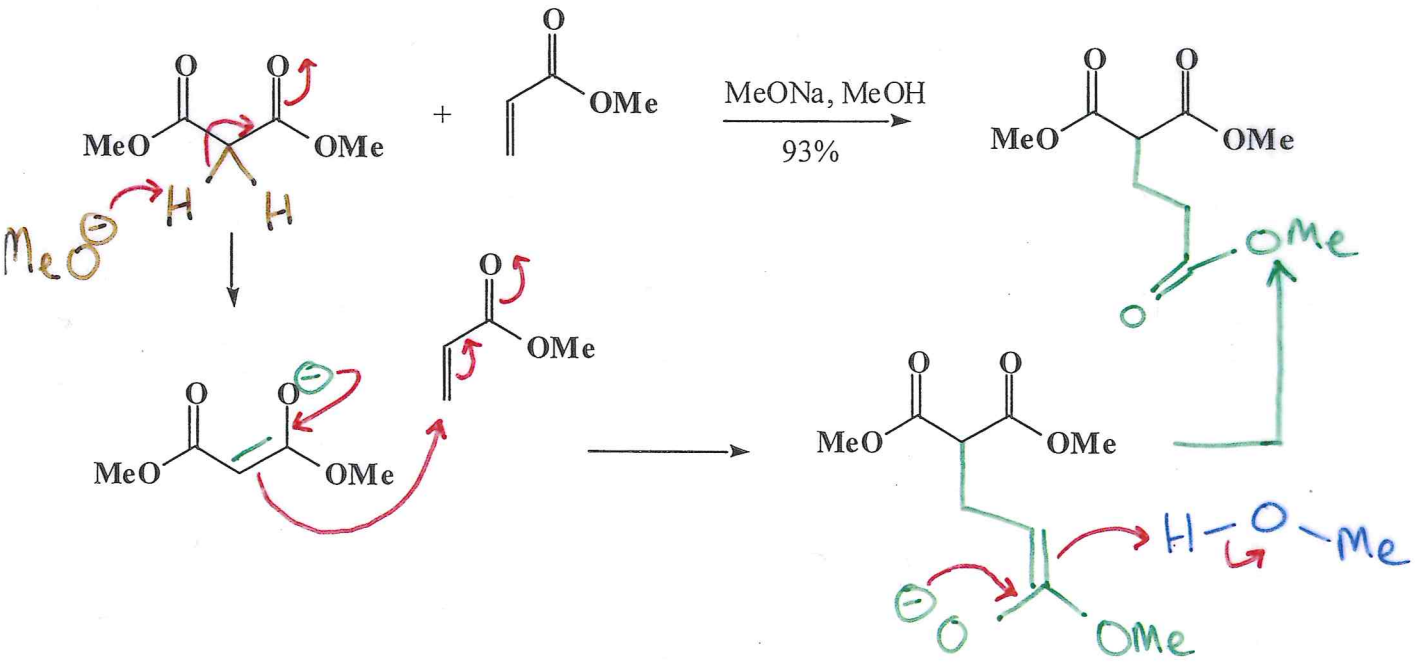




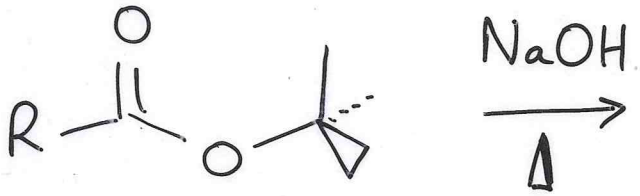
Enolates are particularly adept at addition to the beta position of α,β-unsaturated carbonyl compounds, this is known as Conjugate addition



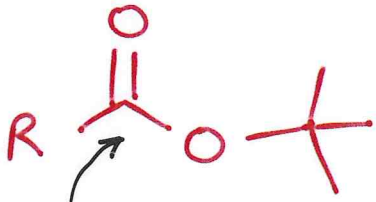
The reaction works particularly well when the enolate is easily formed with a weaker base, ie



Hydrolysis of tert-Butyl esters

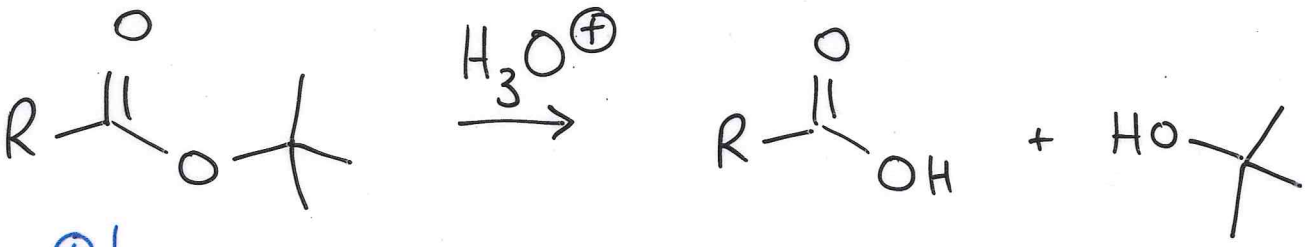


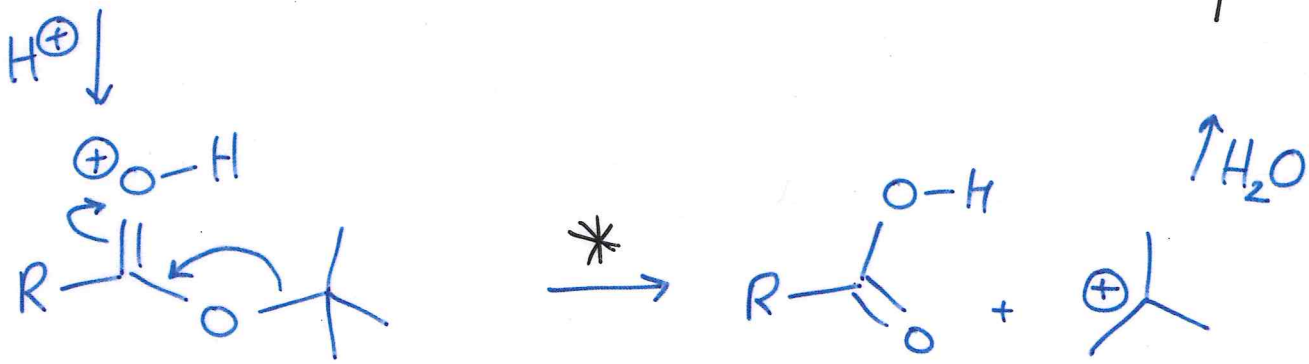
no reaction



$^{\ominus}OH$ too hindered

but

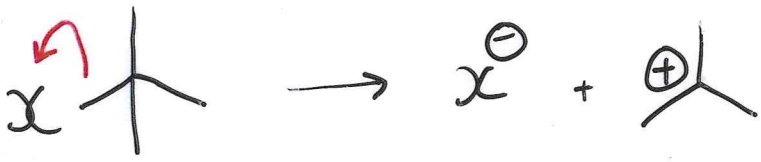


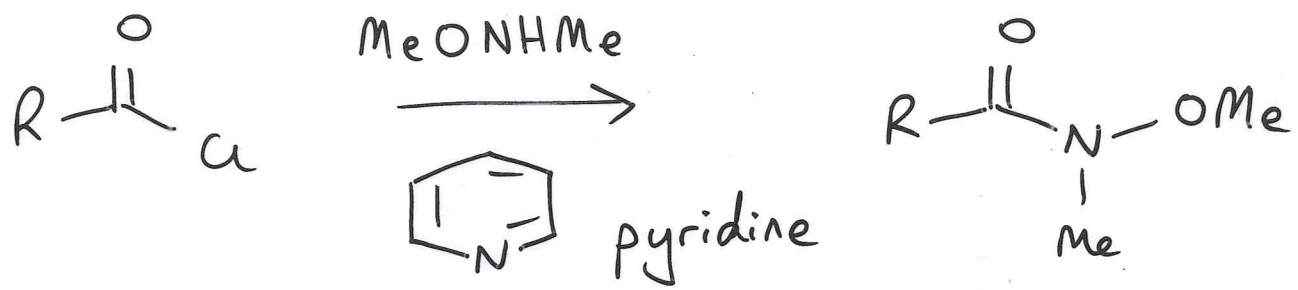


attack at C=O
still too hindered

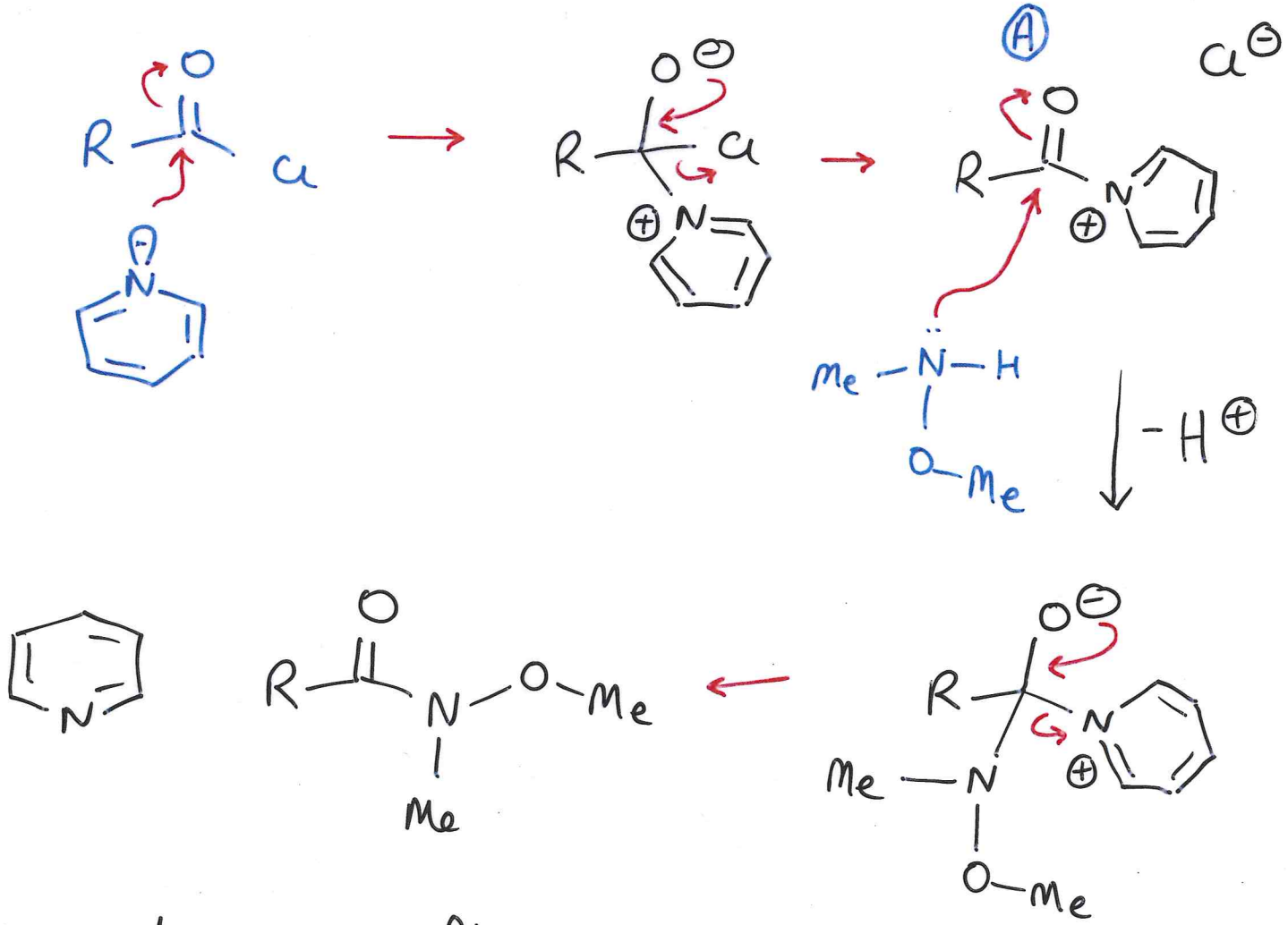
$A_{AL}1$ mechanism

* think of this as an S_N1 step





pyridine often helps the reactions of acid chlorides with weak nucleophiles.



pyridine is often used as the solvent, as it is also a base to mop-up HCl.

A is more reactive than RCOCl, because it is positively charged.