CHEM2201: Section 1

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Contents

1 Oxidation and Reduction Reactions

Alcohol to Carboxylic Acid 

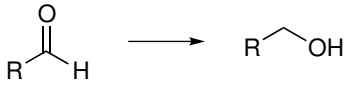
Use:

- $KMnO_4$
- CrO_3
- $Na_2Cr_2O_7$

Alcohol to Aldehyde 

Use:

- PCC

Aldehyde to Alcohol (+ Ketones and C=O of higher reactivity) 

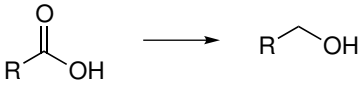
Use:

- $NaBH_4$
- $LiAlH_4$

Ester to Alcohol and RCONHR to RCH_2NHR 

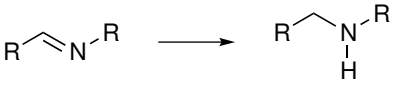
Use:

- $LiAlH_4$

Carboxylic Acid to Alcohol 

Use:

- $LiAlH_4$
- BH_3THF

$RCH{=}NR^1$ to RCH_2NHR^1 

Use:

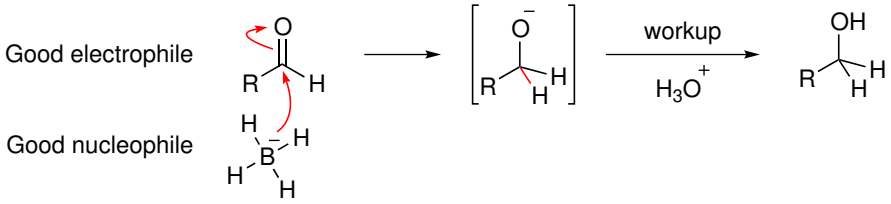
- $NaCNBH_3$

The basic principles of addition to C=O groupsa are:

- How reactive is the C=O group
- How reactive is the nucleophile
- Which is more reactive, the starting material or the product (Example 3)
- Will an unreactive C=O need activation (e.g. H^+)? If the nucleophile is unreactive?
- Can H_2O be eliminated.

1.1 Example Reactions

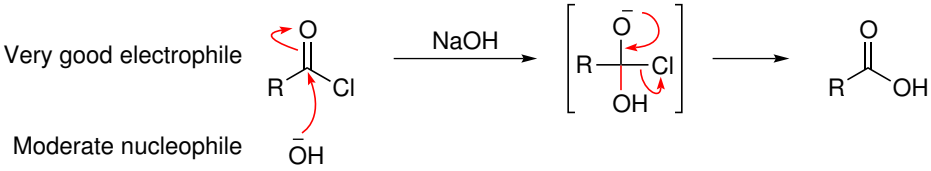
1. Reduction of aldehyde with $NaBH_4$



No further reactions can take place as there are no leaving groups

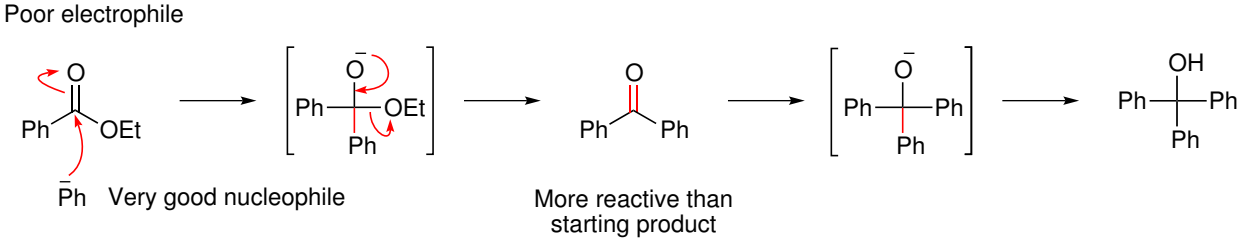
This reaction will not take place with esters as the electrophile is not sufficiently reactive. Instead use $LiAlH_4$

2. Carboxylic acid from acid chloride with NaOH

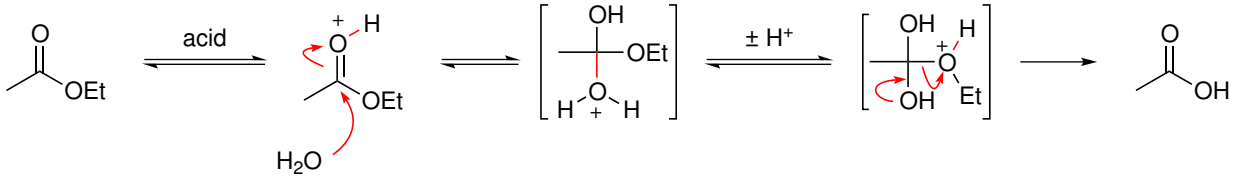


Cl is a good leaving group therefore there is a further reaction

3. Ester with a grignard reagent

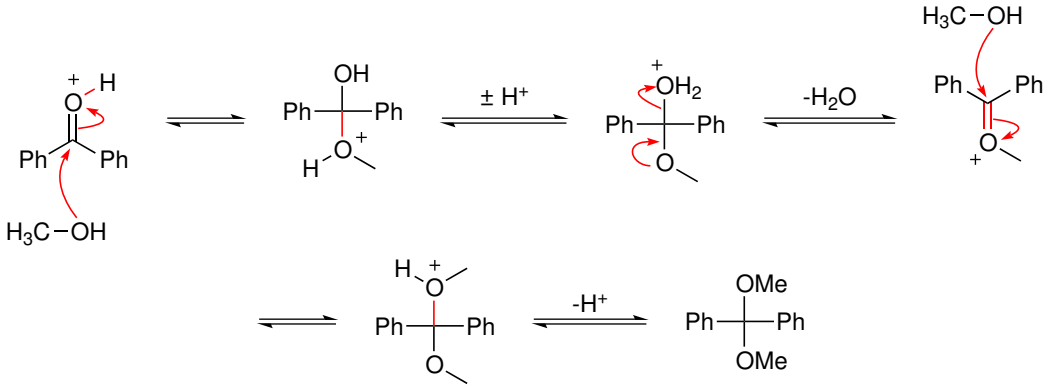


4. Addition of water



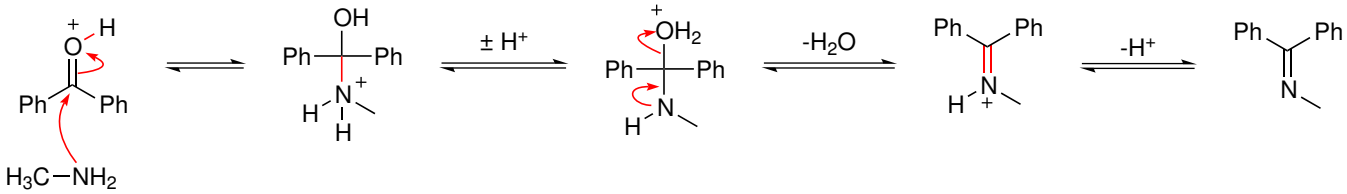
Poor electrophile and poor nucleophile therefore the C=O group is activated by adding water.

5. Elimination of H_2O



Reasonable electrophile and a poor nucleophile therefore activation of C=O required.

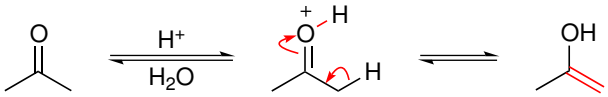
6. Elimination of H_2O using methylamine



Reasonable electrophile and poor nucleophile therefore activation of C=O required.

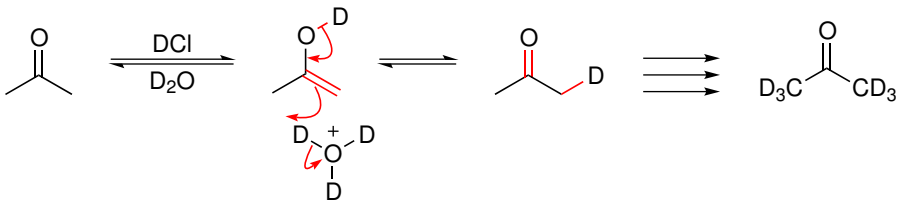
2 Enols and Enolates

Formation of an enol using acid + ketone



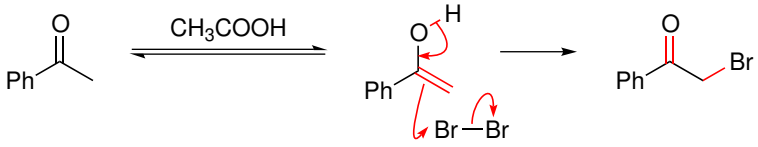
2.1 Example Reactions

Enol + DCl + D_2O



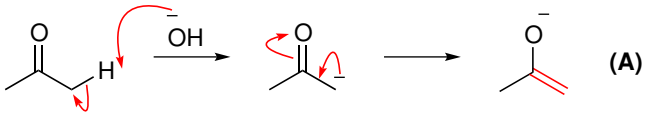
H $\longrightarrow$ D exchange takes place at the α-position

Enol + Acid and Br_2

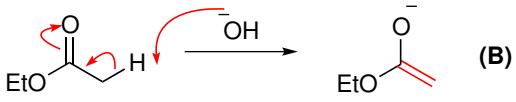


Forms a brominated ketone

Enolate formation using base + ketone

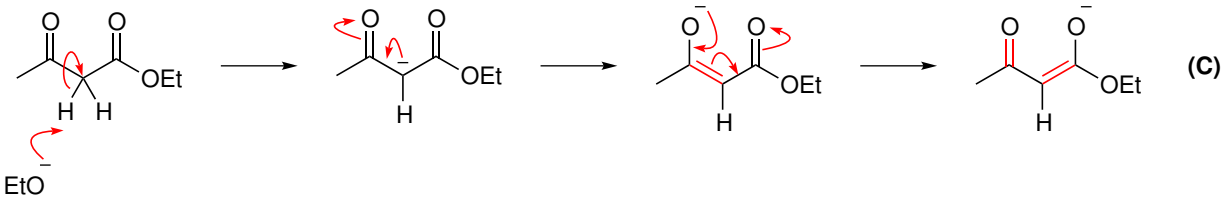


Enolate formation from esters



(B)

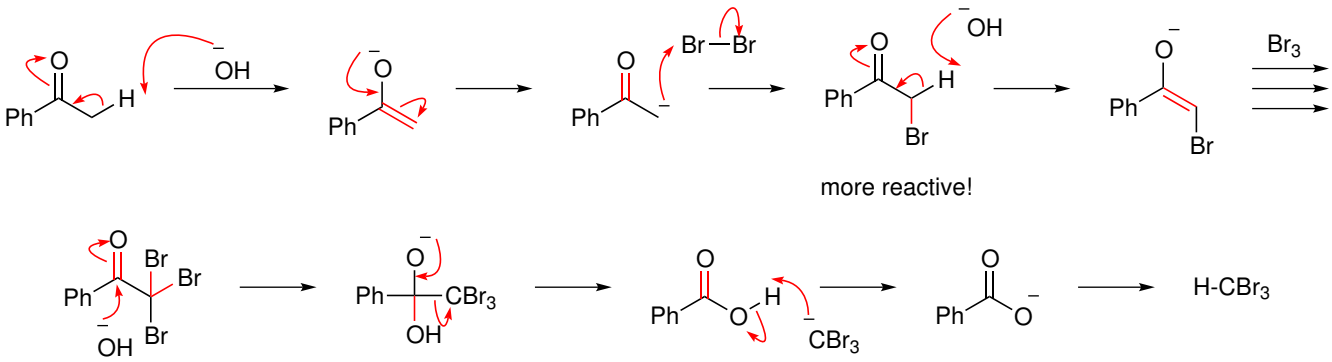
Enolate formation with diketone



(C)

Order of stability goes C > B > A

Enolate with Br_2 + base

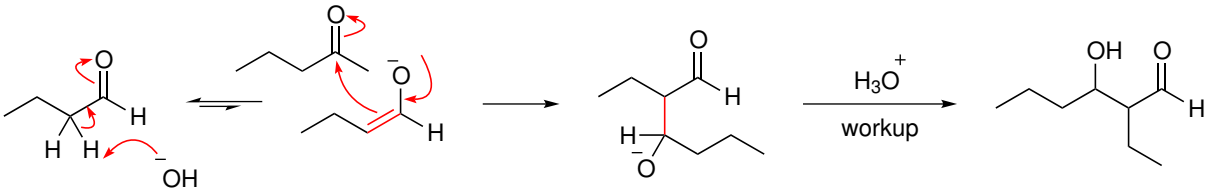


For compounds with α-H's:

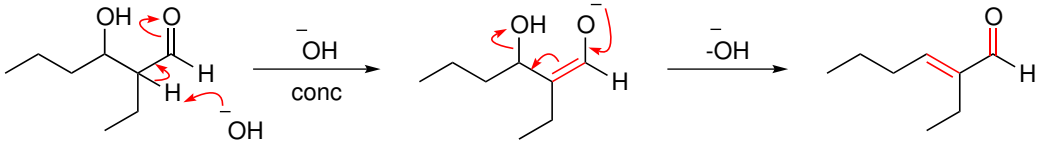
- Central protons are easier to remove as this further delocalises the negative charge.
- The pKa of the base must be no higher than the compound to deprotonate.

3 Aldol Reaciton

In mild or dilute base, results in the self condensation of an aldehyde or ketone.



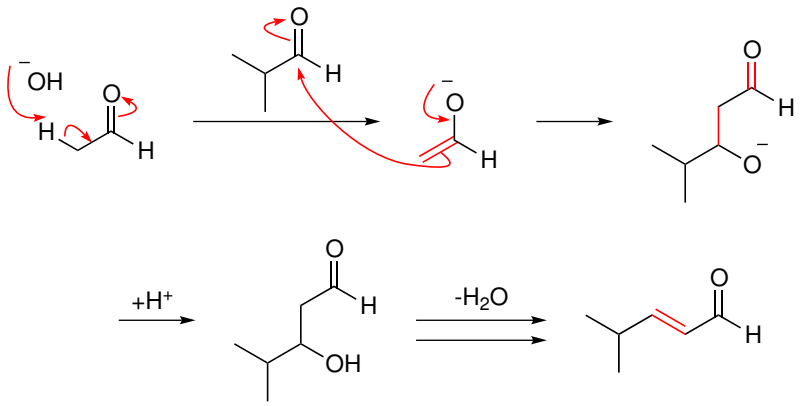
In presence of conc base a further reaction can take place



Forms a α,β-unsaturated aldehyde

If an unsymmetrical ketone with more than one α-H is used then 2 different products will be formed. However if the material only has 1 way to enolise, then the aldol reaction will only form one product.

Adol reactions can also occur between two different C=O compounds.

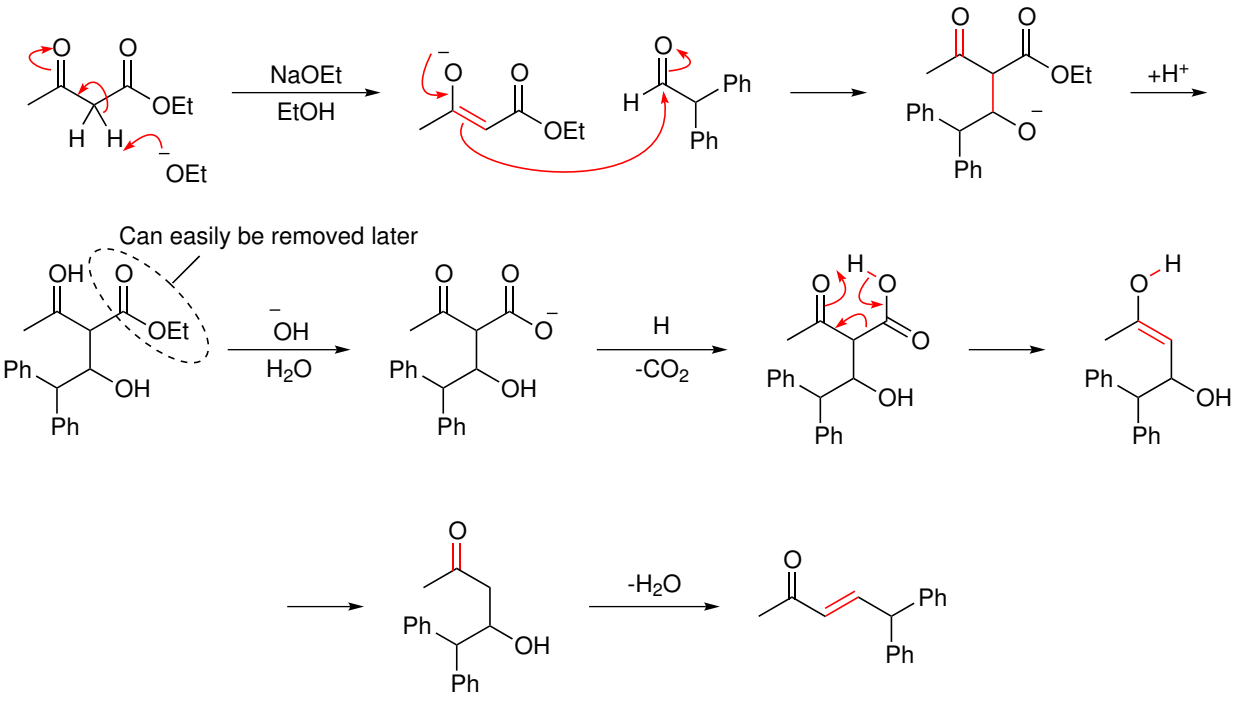


However other reactions can happen, e.g. it will react with itself and the other starting product may also enolise. NaOH is therefore not an efficient way to form a single product. However it is possible to form a single product by taking into account that:

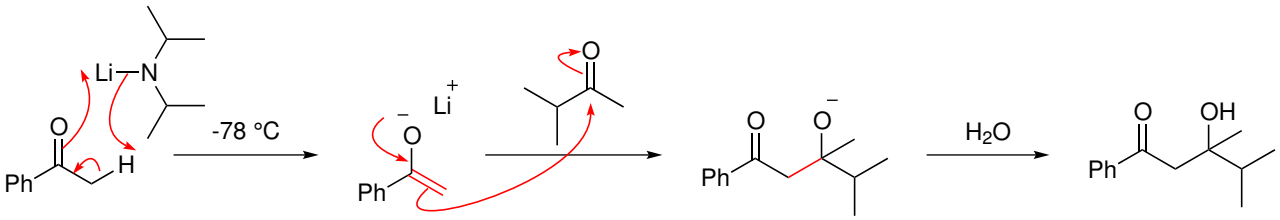
- A compound with no α-H cannot enolise
- Aldehydes are more reactive than ketones

Beware however that if you have a molecule with no α-H and it is a ketone reacting with an aldehyde the ketone will be ignored and a single product will be formed by the aldehyde reacting with itself.

Using acetoacetate as a reagent for 



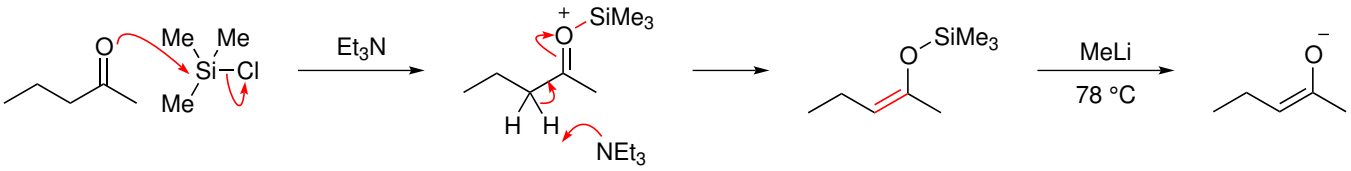
Crossed aldol product reaction with only one product using LDA to from lithium enolates.



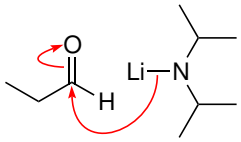
Addition of LDA results in complete conversion to lithium enolate

3.1 Unsymmetrical Ketones

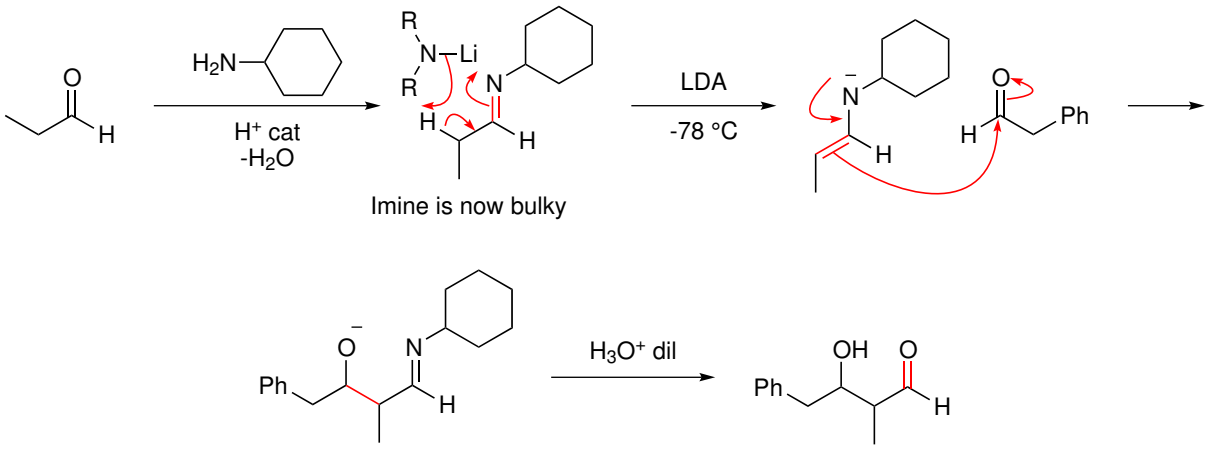
To remove the less sterically hindered protons, a bulky base is used. E.g. LDA -78 °C. If we need the more sterically hindered enolate, we can do this by acknowledging that this is the more stable enolate and use Me_3SiCl and Et_3N then MeLi. E.g.



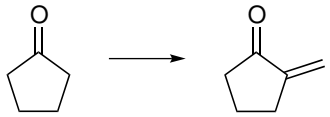
Et_3N is used as a mild unhindered base that an remove either protons

Aldehydes and LDA will not react to form enolates as 

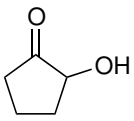
Instead to make an enolate from an aldehyde use cyclohexanamine, H^+ and then LDA.



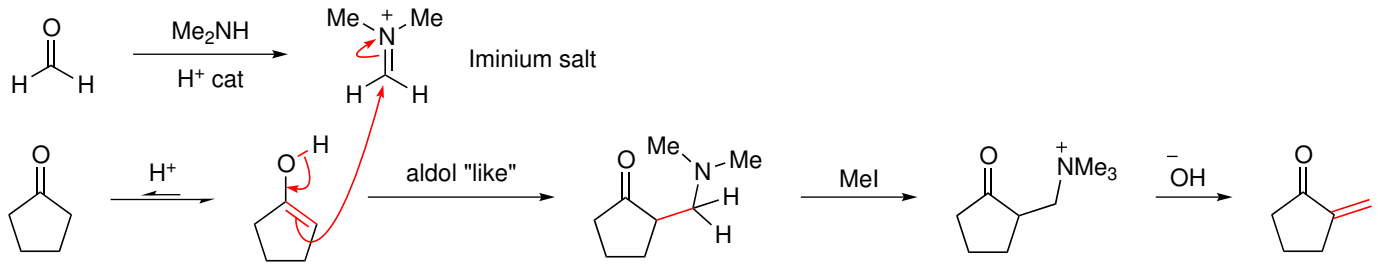
Formaldehyde is even more reactive than other aldehydes, this makes it impossible to control as an enol. Formaldehyde is therefore not useful for adding a CH_2-OH group to molecules. To convert



we can't therefore go through:



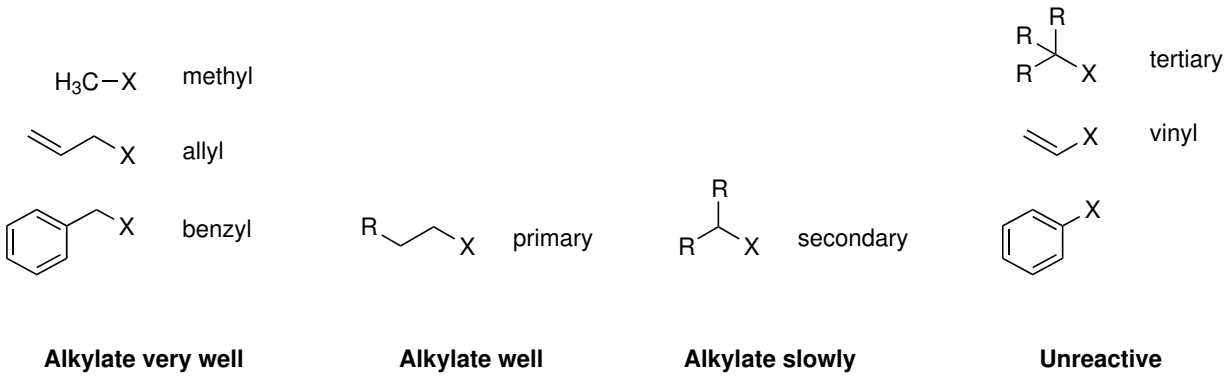
Instead the Mannich reaction is therefore used:



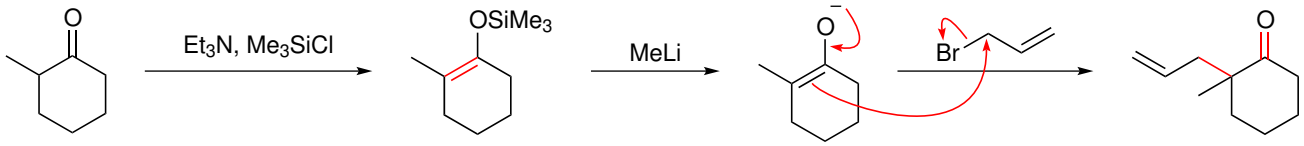
3.2 Electrophiles

The choice of electrophile for for enolate alkylation is important:

- Enolate alkylation are S_N2 reactions
- R−X: X must be a good leaving group
- Mesylate > Tosylate > I > Br > Cl

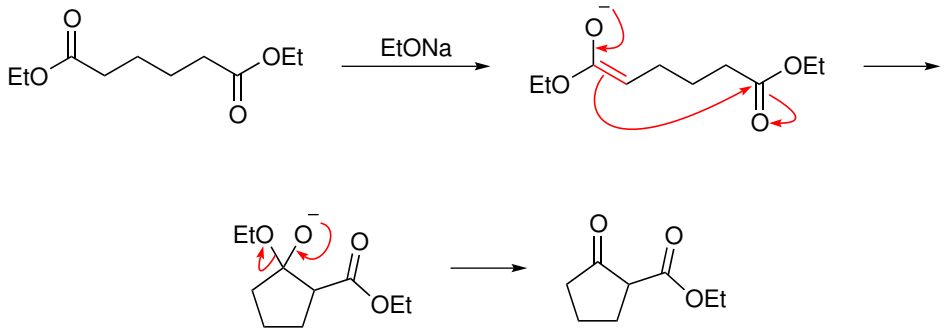


Example:



3.3 Other Reactions

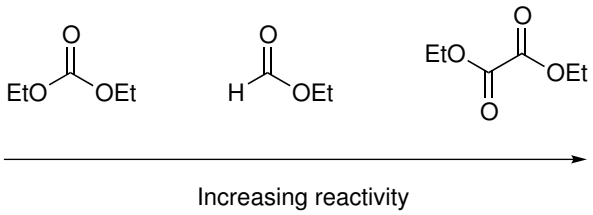
Diekman Condensation - Both esters in the same molecule:



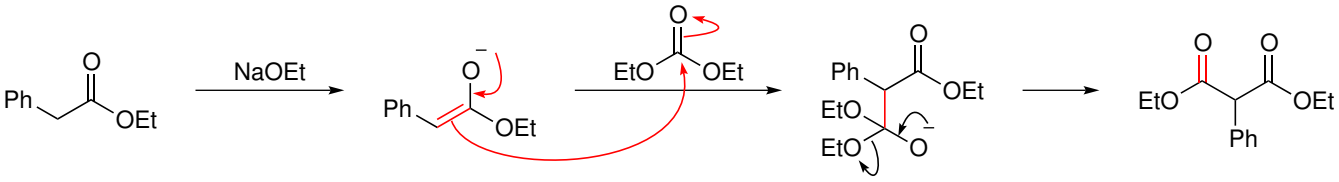
Crossed Claisen Reactions - Between 2 esters or one ester and a ketone. The conditions are:

- Need one ester that can't enolise
- This is ester must be a better electrophile

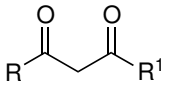
There are only 3 reagents. All are more reactive than simple esters.



Example:

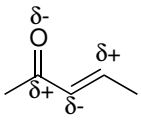


With Claisen you normally end up with a diketone, e.g.

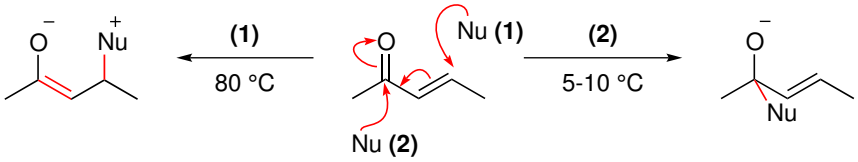


4 Conjugate Addition Reactions

Occurs due to the resonance effects of a α,β-unsaturated carbonyl compounds.

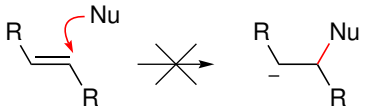


There are two types of conjugate addition:



(1) 1,4 Conjugate addition, produces the thermodynamic product which is more stable but ΔEa is greater.
(2) 1,2 Conjugate addition, produces the kinetic product, which is reversible at higher temperatures.

Conjugate addition only occurs with alkenes conjugated to a π electron withdrawing group. For example:



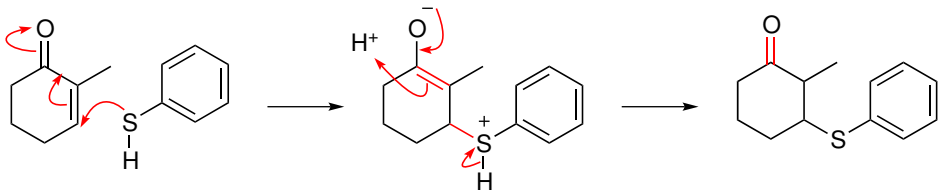
This does **not** occur as there is no way to stabilise the anion

1,4 vs 1,2 addition

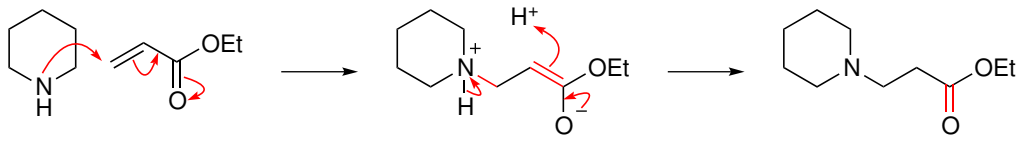
- 1,4 addition is favoured by less reactive C=O groups. 1,2 is favoured by more reactive C=O groups.
- Hard nucleophiles (RMgBr, RLi) react at the C=O group. Soft nucleophiles (RS^-, RCu) perform conjugated addition.
- Steric hindrance at the β carbon favours 1,2-addition, an unhindered β position favours 1,3 addition.

4.1 Nucleophiles for Conjugate Addition

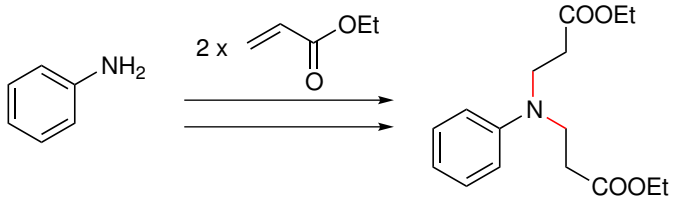
a) Thiols



b) Amines

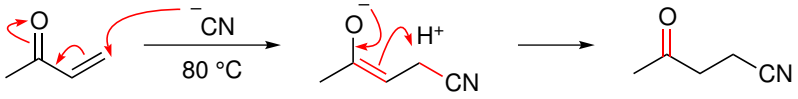


Amines such as aniline can perform 2 conjugate addition reactions by displacing the H's. E.g.

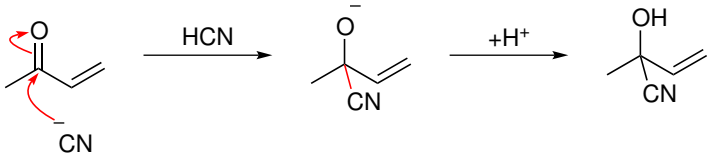


c) Nitrile

At high temp (80 °C) 1,4 addition will occur:

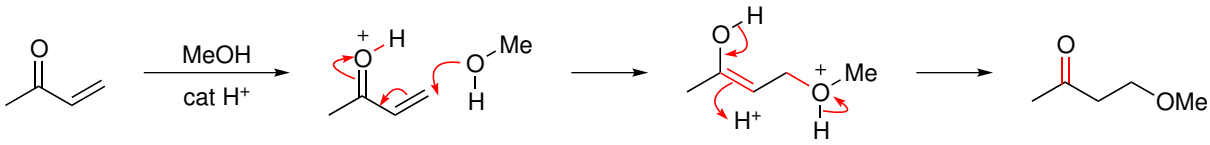


At low temp (5 – 10 °C) 1,2 addition will occur:

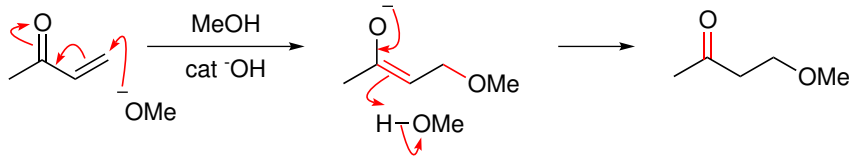


d) Alcohols

Acid catalysed:



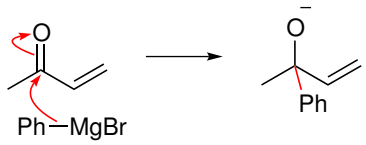
Base catalysed:



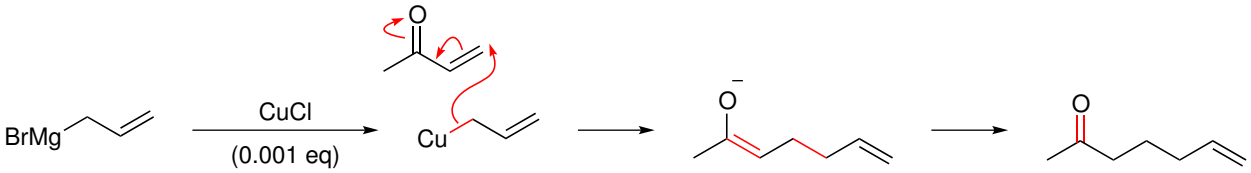
With acid catalysed there is competition with the conjugate addition and forming an acetal.

e) Organometallic Compounds

Grignard and organolithium reagents can perform 1,2 conjugate addition:



To make them perform 1,4 conjugate addition, react them with cuprates, e.g. CuCl.



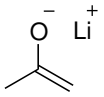
Hard reagents:

- Perform 1,2 conjugate addition
- Nucleophiles are small electronegative atoms (O, Cl) or small counter ions (R^-, Li^+)
- React with hard electrophile (more explicit charge) by electrostatic interaction.

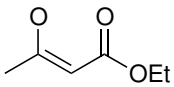
Soft reagents:

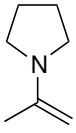
- Perform 1,4 conjugate addition
- Nucleophiles are larger atoms (S, I) or less polarised C metal bonds R−Cu
- React with soft electrophiles under orbital control.

f) Enolates, Enols and Equivalents

Hard enolates such as 

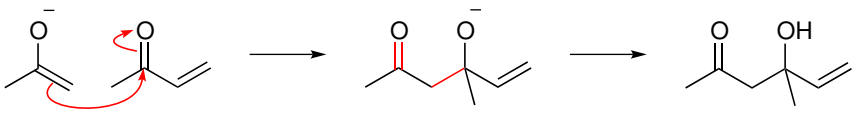
react via 1,2 conjugate addition.

Soft enolates such as 

which has a more delocalised charge, or 

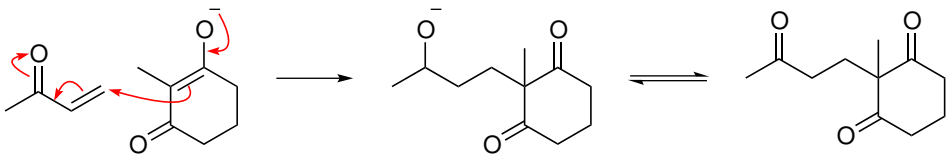
react via 1,4 conjugate addition.

E.g.

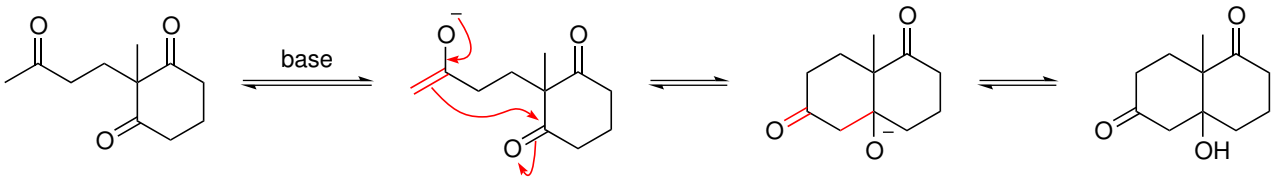


4.2 The Robinson Annelation

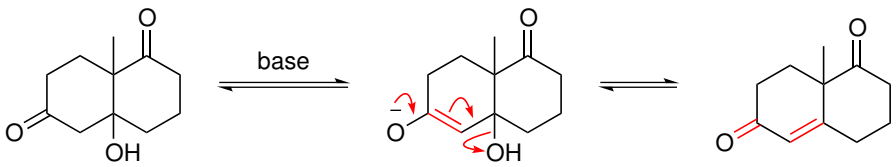
The Robinson annelation is the result of a conjugate addition followed by aldol cyclisation. The requirement for a Robinson annelation is a Michael addition of an enolate to an enone that has a second enolisable group on the other side of the ketone.
The first step is the formation of the stable enolate:



The second stage is the formation of a new enolate on the other side of the ketone from the first:

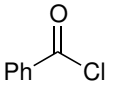
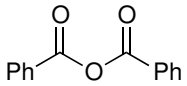


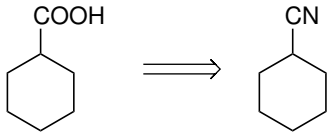
The final stage is the dehydration of the aldol and an E1cB reaction that involves the carbonyl group in a standard aldol reaction. Another enolate must form in the same position as the last.



5 Retrosynthetic Analysis

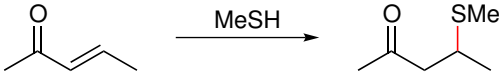
5.1 Terminology

Target molecule (TM) is the final product.
A synthon is an idealised reagent that shows the desired reactivity for the particular disconnection.
E.g.  is a synthon. Both  and  react like it.
A functional group interconversion is transforming one functional group into another without disconnecting anything. The aim is to make the next disconnection easier.

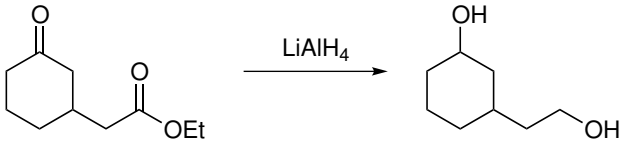


5.2 Useful Reactions

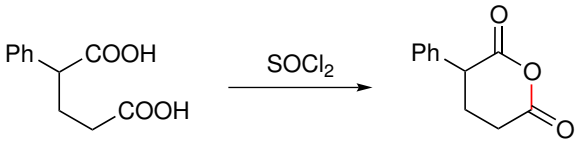
Adding SMe



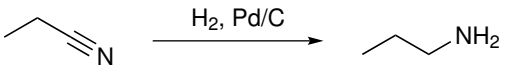
Reducing ketones + esters



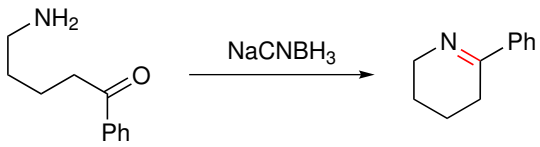
Joining a ring with two carboxylic acids



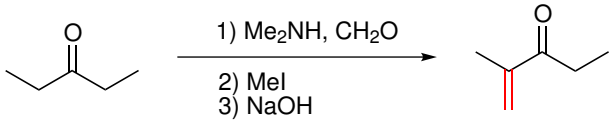
Hydrogenating C≡N



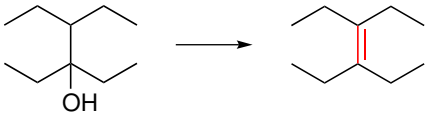
Creating ring with amide and ketone



Mannich Reaction



Another example of a functional group interconversion is



6 Spectroscopy

6.1 Summary of IR Frequencies

Single Bonds to Hydrogen

- sp^3	C−H	2850 – 2960s
- sp^2	C−H	3010 – 3095
- Aldehyde	O=C−H	2700 – 2900
- sp	C−H	3000 sharp
- Nitrile	N−H	3300 – 3500m
- Free	O−H	3590 – 3600s sharp
- Normally H-bonded	O−H	3200 – 3600s broad
- Strongly H-bonded	O−H	2500 – 3200s broad

Triple Bonds

- Nitriles	RCN	2200 – 2260v
- Alkynes	$RC{\equiv}CR^1$	2150 – 3095w
	RC≡CH	2100 – 2140w

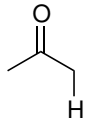
Double Bonds

- Alkenes	C=C	1620 – 1680v
- Enones	C=C−C=O	1590 – 1640s
- Aromatics, up to 3 of		1600, 1580, 1500v
- Nitro	NO_2	1560, 1350s

Carbonyl Group, C=O		1715 ± 10
- Dialkyl ketone	alkyl	0 (also carboxylic acid is ± 0)
- Anhydride	OCOR	+35, +110
- Acid chloride	COOCl	+85
- Ester	OCOR	+25
- Aldehyde	H	+15
- Aryl ketone	Ar	−25
- Enone	C=C	−35
- Amide	NH_2	−65

6.2 ^{1}H NMR

Most signals are from 0 – 12 ppm

- Carboxylic acids 10 – 12
- Aldehydes 9 – 10
- Aromatics 7 – 9
- Alkenes 5 – 7
-  3 – 5
-  2 – 3.5
-  2 – 3
-  2 – 3
- Alkynes 2 – 3
- Alkanes 0.5 – 1.5

R−OH, R−SH, R−NH_2 are hard to predict. Often 0 – 5 ppm with little H bonding. Higher if more H bonding. The more shielded the hydrogen the further upfield it appears (i.e. lower frequency).

6.2.1 Summary of Chemical Shifts

Methyl Groups

- CH_3−C 10 – 12
- CH_3−C=C 9 – 10
- CH_3−Ar 7 – 9
- CH_3−CO−R 5 – 7
- CH_3−O−R 3 – 5
- CH_3−N 2 – 3.5

Protons Attached to Unsaturated Linkages

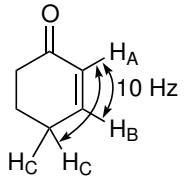
- Ar−CHO 9.7 – 10.5
- RCHO 9.4 – 10.0
- H−CO−O 8.0 – 8.2
- Aromatic 6.0 – 9.0 (usually $\approx$ 7)
- C=CH−CO 5.8 – 6.7
- C=CH 4.5 – 6.0
- C≡C−H 1.8 – 3.1

6.2.2 J Couplings

Methyl Groups

- Open chain single bond	7 Hz
- Trans alkene	12 – 18 Hz (typically 16 Hz)
- Cis alkene	7 – 11 Hz (typically 10 HZ)
- Ortho	6 – 9 Hz
- Meta	1 – 3 Hz
- Para	0 – 1 Hz
- Cyclohexane	10 – 12 Hz
- H_{ax} H_{eq}	3 – 5 Hz
- H_{eq} H_{eq}	3 – 4 Hz

If D_2O is added and a signal disappears, it means they acidic protons e.g. OH, NH_2, etc.
If the coupling is to inequivalent protons, coupling constants may not be the same and double doublets are observed. The major coupling always comes first.



Long range coupling occurs. H_A is split into a doublet with H_B and H_B is further split into a triplet by H_C forming a double triplet (or dt for short).

6.3 ^{13}C, ^{19}F, ^{31}P NMR Spectroscopy

If ^{19}F or ^{31}P are present in a sample, coupling can be seen in ^{1}H NMR spectra.

The number of resonances in ^{13}C spectra indicates the number of distinct ^{13} environments in the molecule. The usual solvent is $CDCl_3$ and a peak can be seen sometimes at 77 ppm.

Because the ^{13}C nucleus is is isotopically rare, it is unlikely that two adjacent carbon atoms will be ^{13}C therefore ^{13}C$-^{13}$C are not observed. However ^{13}C does strongly couple to any protons attached. These couplings are normally removed by irradiating the ^{1}H nuclei during ^{13} acquisition, resulting in a ^{1}H Decoupled ^{13} spectrum.

6.3.1 Summary of positions in ^{13}C NMR

Methyl Groups: CH_3-X where the table below shows X

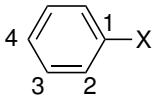
- CH_3	7.3 Hz
- CH_2CH_3	15.4 Hz (typically 16 Hz)
- Phenyl	21.4 Hz (typically 10 HZ)
- Cl	25.6 Hz
- NH_2	28.3 Hz
- $COCH_3$	30.7 Hz
- OH	50.2 Hz

Monosubstituted Alkanes: CH_3-CH_2-X

- Phenyl	34.3 Hz
- Cl	53.7 Hz (typically 16 Hz)
- OH	64.0 Hz (typically 16 Hz)

Alkenes $R-CH=CH_2$

- base value	123.3
- OH_3	+294
- $COCH_3$	+13.8

Aromatics 

- base value	128.5
- C1	+31.4
- C2	−14.4
- C3	+1.0
- C4	−7.7

6.4 Double Bond Equivalents

Double bond equivalents (DBE) is the number of double bonds and rings.

$$C_aH_bO_cN_d \qquad DBE = \frac{(2a+2)-(b-d))}{2}$$