First Year Organic Chemistry

THE CHEMISTRY OF THE CARBONYL GROUP:

CORE CARBONYL CHEMISTRY

Professor Tim Donohoe

8 lectures, HT, weeks 1-4, 2017

Weeks 1 +3 Monday at 10am; Wednesday at 9am (Dyson Perrins)

Weeks 2 +4 Wednesday at 9am; Thursday at 10am (Dyson Perrins)

Handout A

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

Course Structure

*1) Nucleophilic addition **to** C=O*

A) Nucleophiles and electrophiles: General principles

B) Reversible addition (hydrates and hemiacetals)

C) Irreversible addition (organometallic addition and reduction)

*2) Nucleophilic substitution **of** C=O*

A) Acetals

B) Imines, oximes and hydrazones

C) Formation of C=C bonds from carbonyls

D) Removal of C=O from carbonyls

*3) Nucleophilic substitution **at** C=O*

A) Tetrahedral intermediates in substitution;

B) Factors that affect reactivity of C=O towards nucleophiles; leaving group ability; IR spectroscopy

C) The reactivity of acid chlorides (RCOCl)

D) The reactivity of anhydrides $(RCO)_2O$

E) The reactivity of esters COOR

F) The reactivity of amides $CONR_2$

4) Enolisation of carbonyl compounds

A) keto-enol tautomerism

B) enols and enolates as nucleophiles

C) condensation reactions with carbonyl groups

D) conjugate additions

<u>Suggested Reading:</u>

Core Carbonyl Chemistry, J. Jones, Oxford Primer

Organic Chemistry, Clayden, Greeves, Warren and Wothers

Organic Chemistry, Volhard and Schore

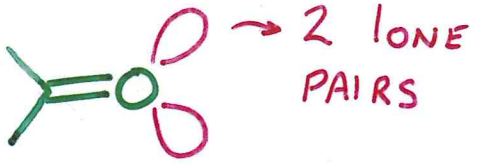
A guidebook to mechanism in organic chemistry, Sykes

The Chemistry of the Carbonyl Group, Warren

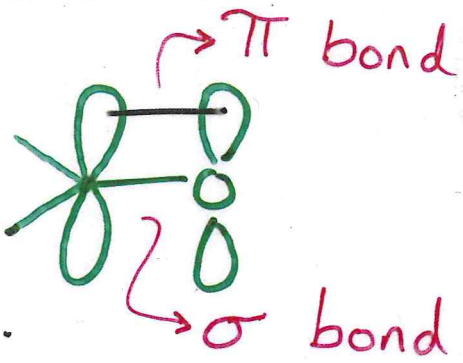
1. Nucleophilic addition **to** C=O

A) Nucleophiles and Electrophiles

Structure of carbonyl compounds



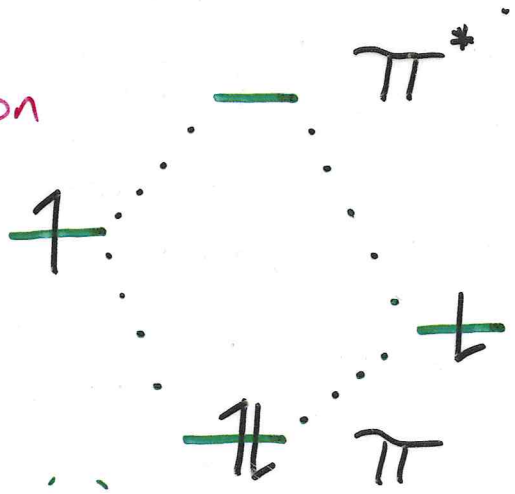
consider the σ and π framework



MO picture of a C=O

Antibonding orbital resembles the 'p' on carbon more

A p-orbital on carbon

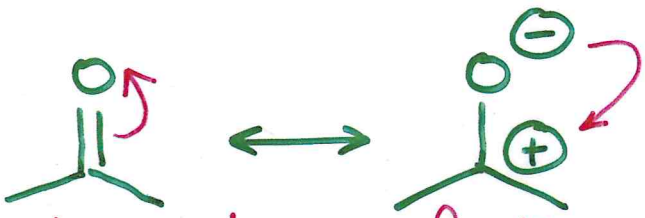


a p-orbital on O is lower in energy 'O' more electroneg- orbitals contracte

Bonding orbital resembles the 'p' orbital on oxygen more

So, C=O have a low energy (unfilled) π* orbital that has a large coefficient on carbon and this is crucial to its reactivity.

Canonicals show the C is electron deficient



This shows the polarisation of the π electrons towards oxygen (c.f. MO picture)

In order to break a bond we place two electrons in the antibonding orbital; the bond order then becomes

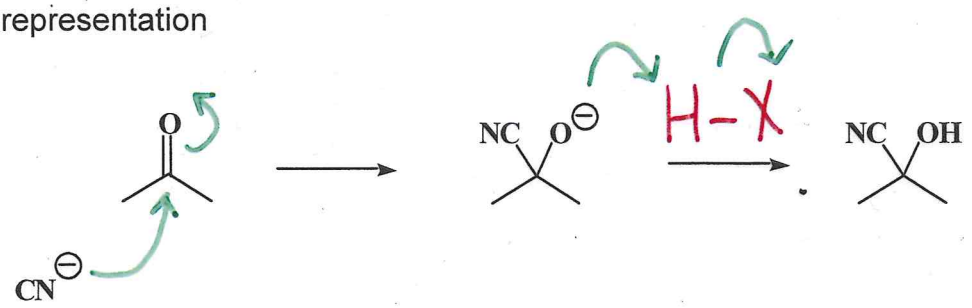
Bond order is:

$$\frac{\text{BONDING ELECTRONS} \ominus \text{ANTIBONDING ELECTRONS}}{2}$$

When nucleophiles attack the C=O group they do so by passing electrons from their highest occupied molecular orbital (HOMO) to the lowest unoccupied molecular orbital (LUMO) of the carbonyl ie. BREAK THE π BOND (ELECTRONS → π*)
Negatively charged species are also attracted to the electron deficient carbon atom.

So, in the addition of cyanide to acetone, the following electron movements are involved.

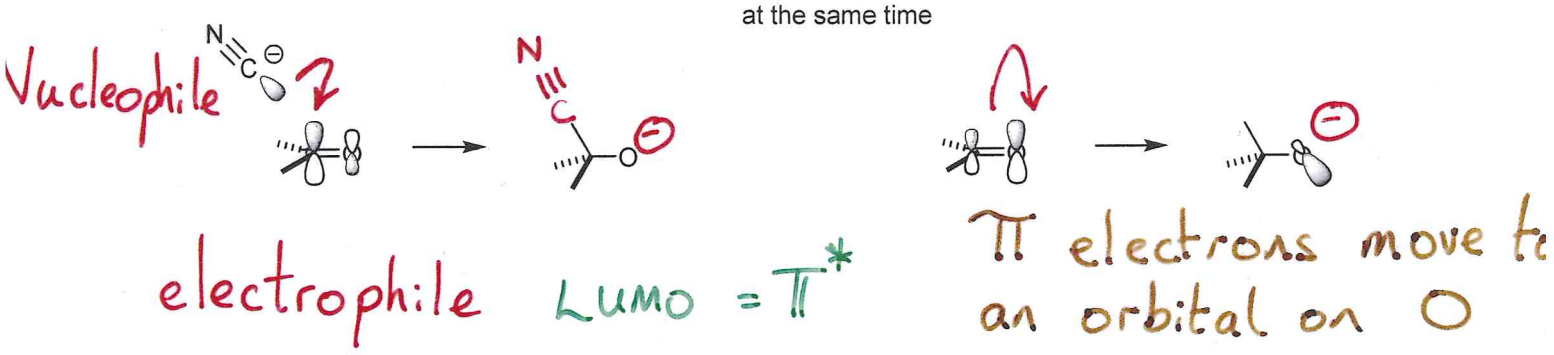
a) Curly arrow representation



b) orbitals involved

HOMO = filled orbital on C

at the same time

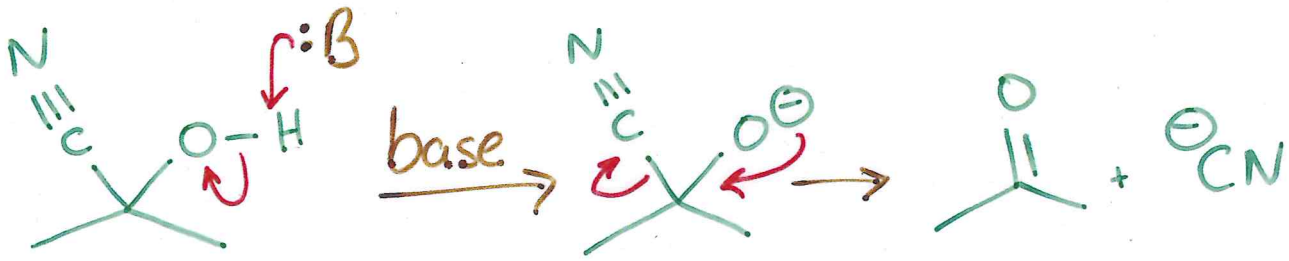


electrophile LUMO = π*

All additions to C=O follow the same pattern of events, but the nature of the HOMO depends on the particular nucleophile used. Once you understand the orbitals involved you do not need to draw the orbitals for every addition to a carbonyl.

We must make a distinction between reversible and irreversible additions:

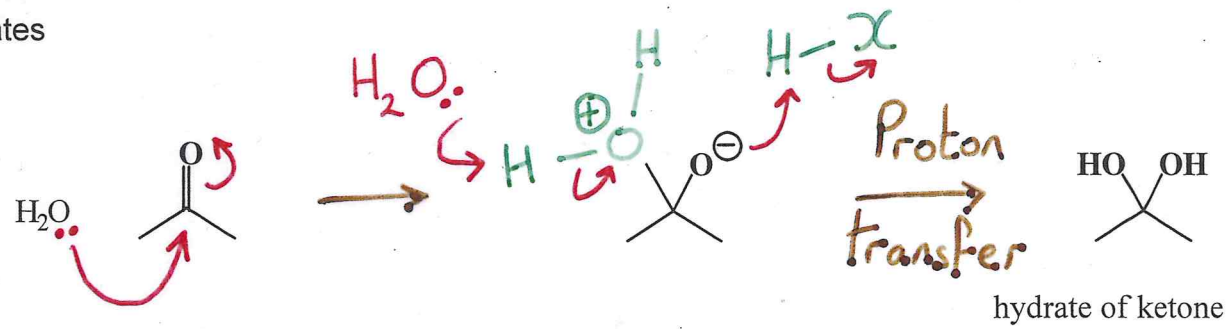
B Reversible addition: eg. The addition of cyanide can be reversed by adding a base



This happens because $^-$CN is a good LEAVING GROUP

H-CN pKa = 9

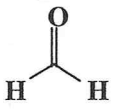
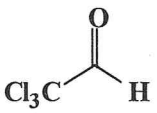
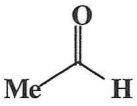
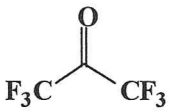
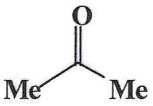
The addition of water is also reversible and observed through the formation and collapse of hydrates



hydrate of ketone

For this reversible reaction, the thermodynamic stability of the carbonyl versus the hydrate will determine the percentage of hydrate at equilibrium. ie Thermodynamic Control

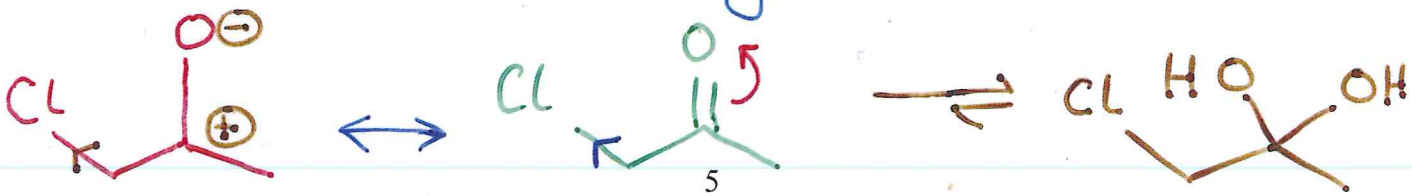
Standard ketones (acetone) contain very little hydrate:

	Keq (in water, 25°C)		Keq (in water, 25°C)
	18		36
	0.01		22000
	1.8×10^{-5}		v. large number

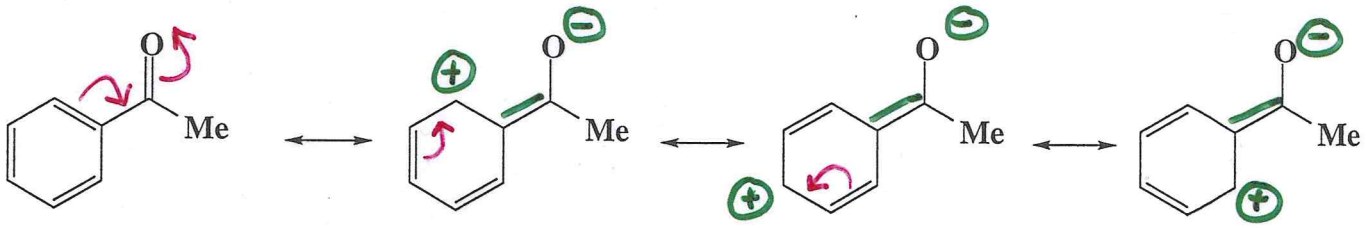
Factors influencing extent of hydration

i) Steric hindrance: repulsion between groups that are close in space: Ketones are less hydrated than aldehydes

ii) Electron withdrawing groups. Inductive effect increases the reactivity of the C=O to nucleophiles Gives more hydrate



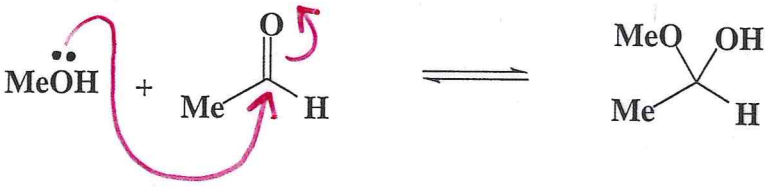
iii) Delocalisation (conjugation) REDUCES HYDRATION



THIS DELOCALISATION IS LOST IN A HYDRATE

These three factors influence other C=O reactions too.

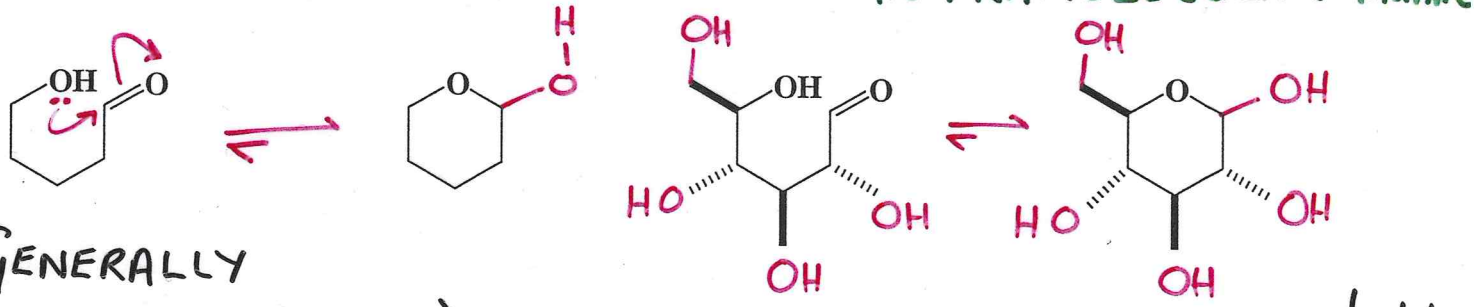
Of course, the addition of alcohols to C=O is also easy (and reversible).



HEMI ACETAL

Stability governed by the same factors as hydrate

Some hemiacetals are stable because the alcohol attacks in an INTRAMOLECULAR manne

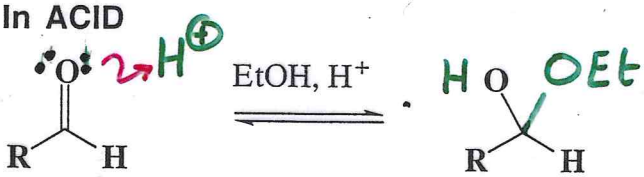


GENERALLY

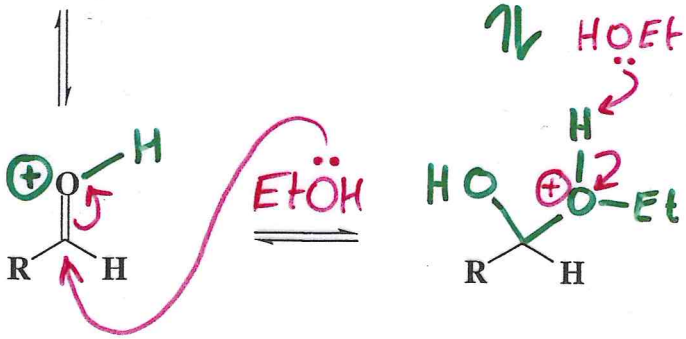
INTRAMOLECULAR > INTERMOLECULAR reactions more stable

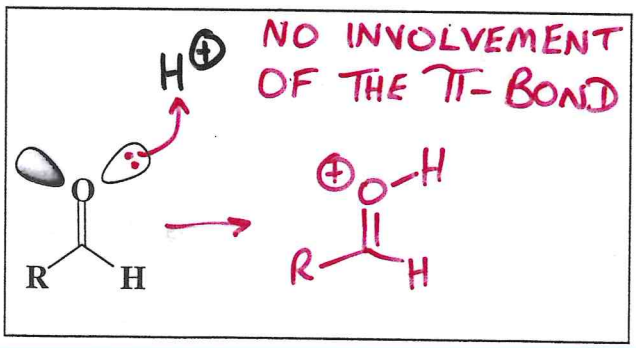
The formation of hemiacetals is catalysed by either ACID or BASE ie EQUILIBRIUM is reached faster

In ACID

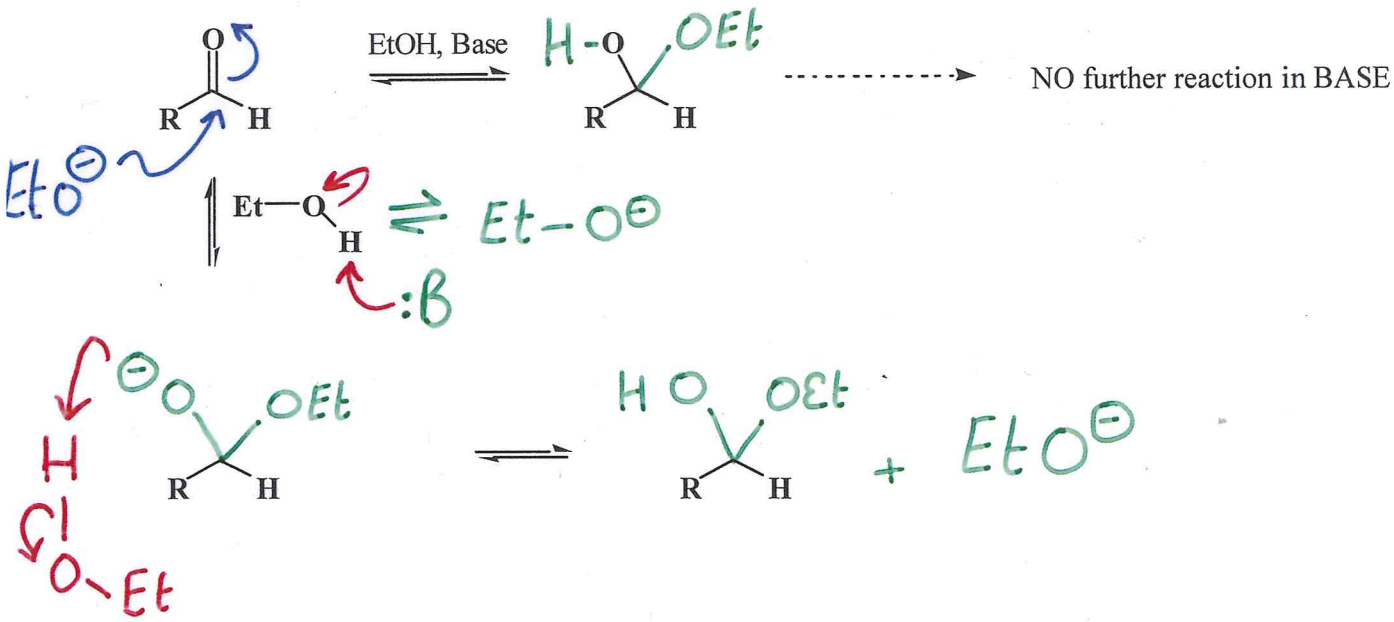


further reaction in ACID





In BASE

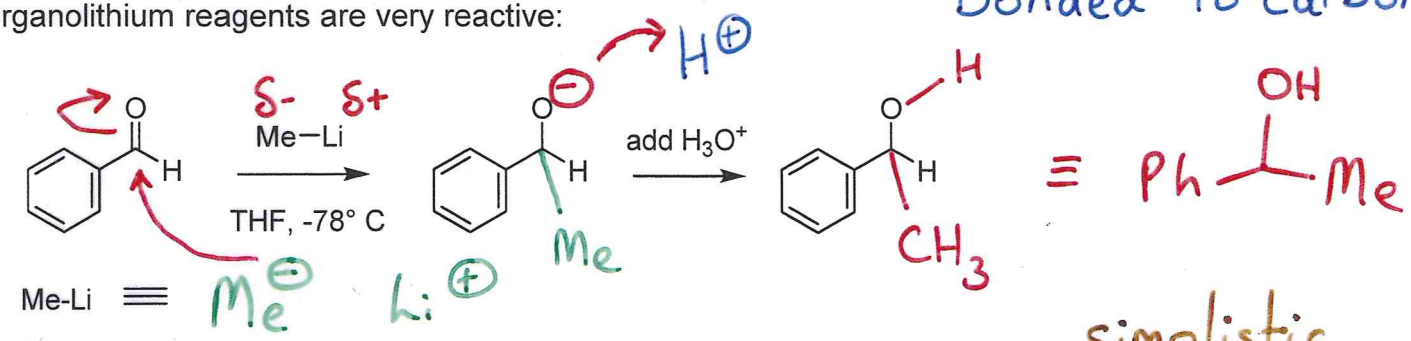


Further reading: look up the (reversible) addition of bisulfite to carbonyl compounds and also the Meerwein Pondorff Verley reduction. $HSO_3^{\ominus}$

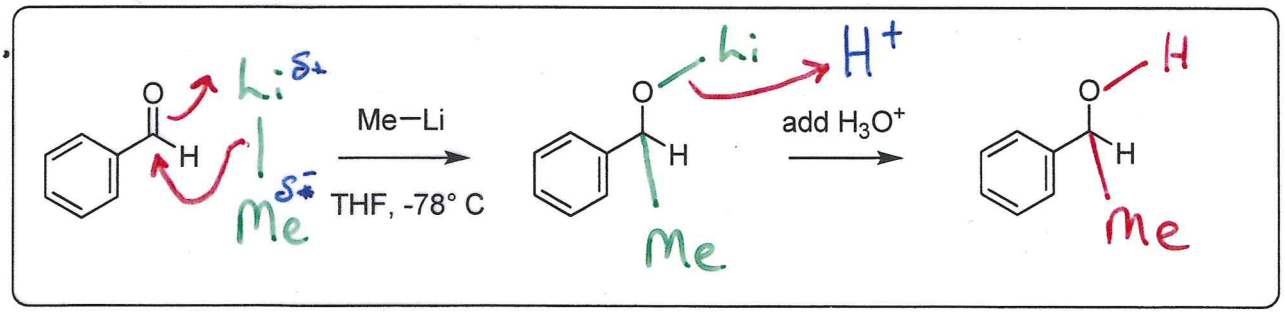
C. Irreversible addition at a carbonyl is perhaps more common:

Nucleophile remains bonded to carbon

i) Organolithium reagents are very reactive:



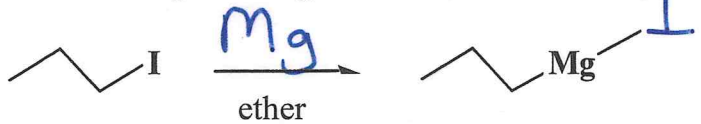
simplistic



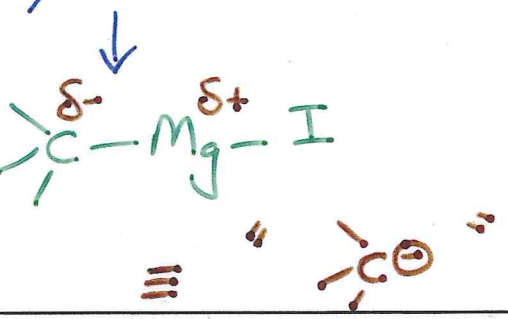
Me–Li has some covalent character more accurate

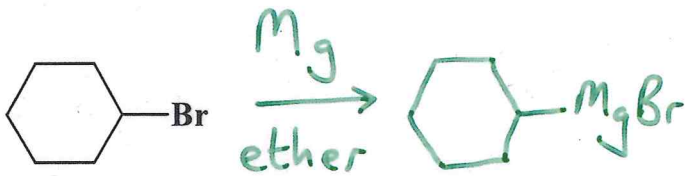
ii) Addition of organomagnesium reagents, such as Grignards, is v. important in synthesis

formation of Grignard reagents

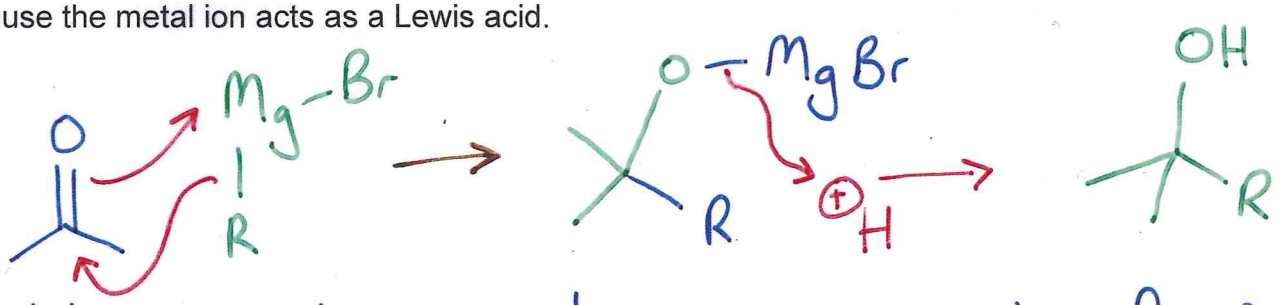


Insertion of Mg^0 into C–I bond

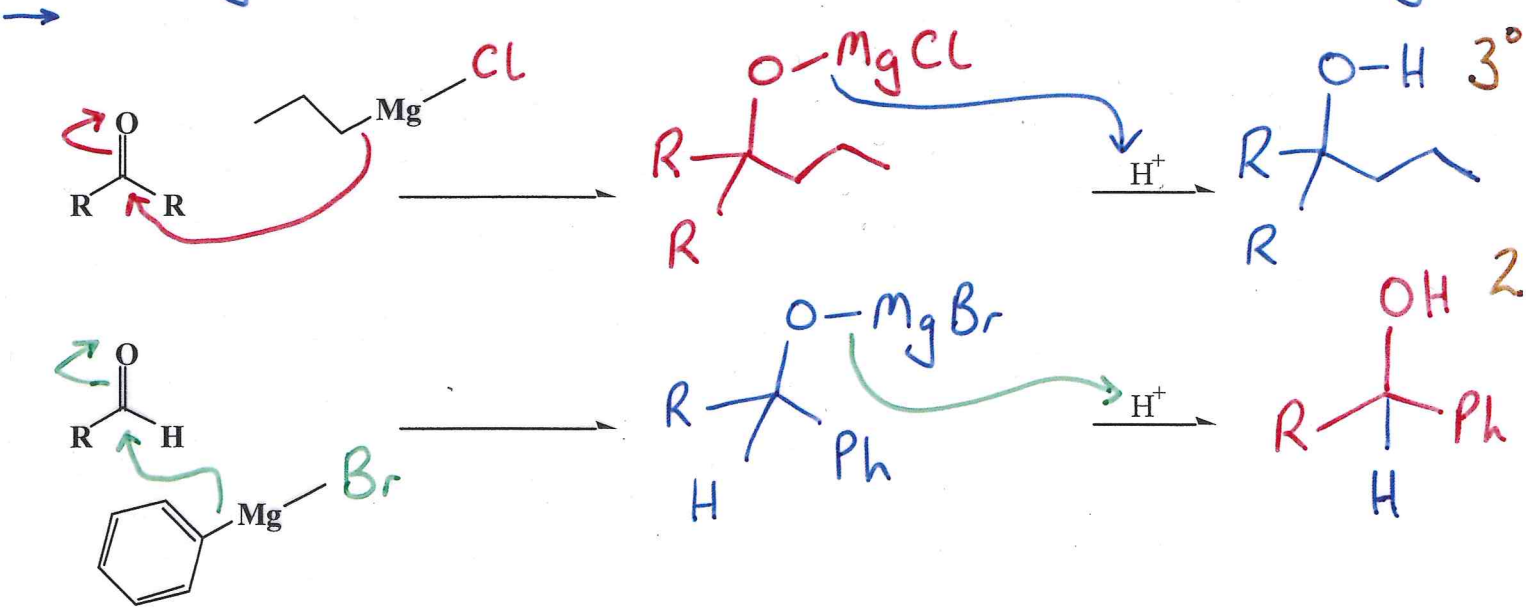




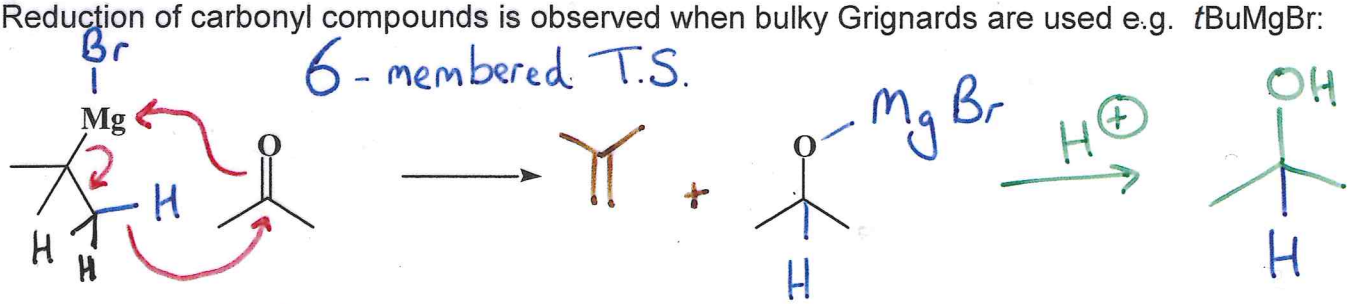
These organometallic reagents add to C=O, although the precise details of the attack are complex because the metal ion acts as a Lewis acid.



in reality: addition involves >1 molecule of RMgBr

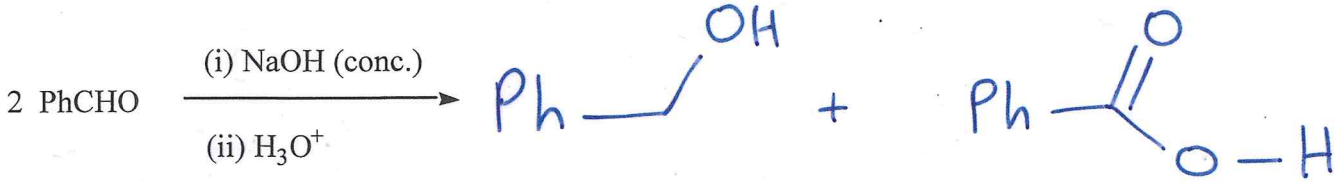


Reduction of carbonyl compounds is observed when bulky Grignards are used e.g. *t*BuMgBr:

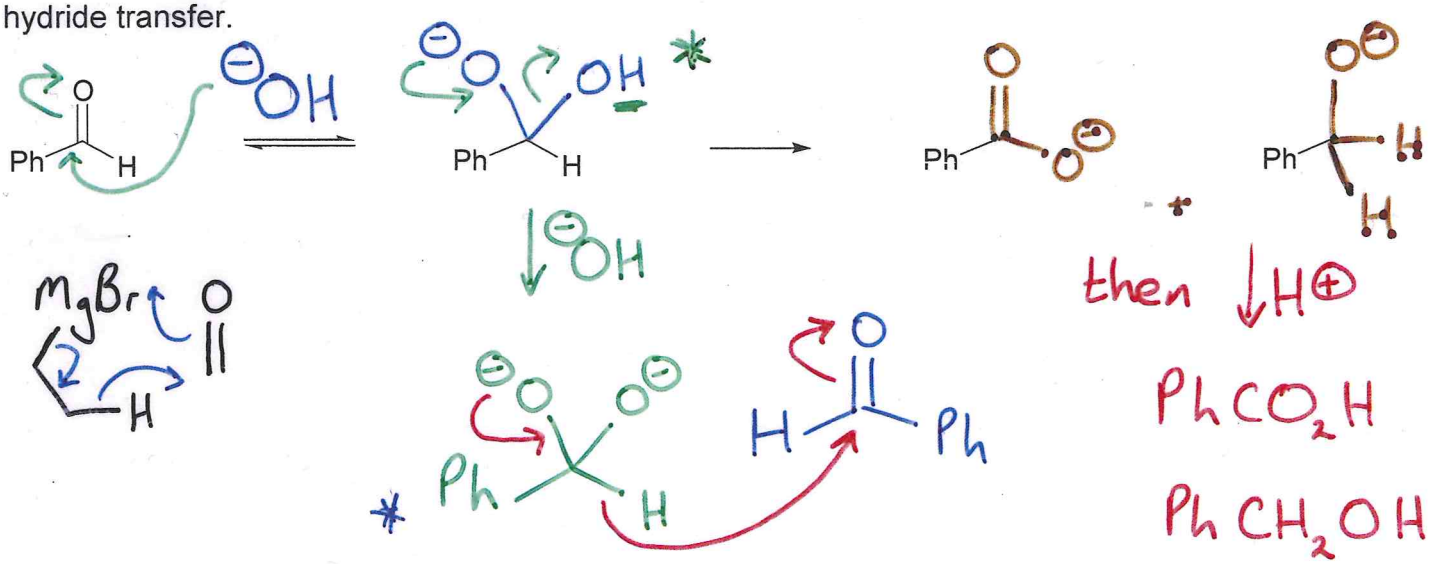


Slow 

We see a similar pattern of reactivity during the **Cannizzaro** reaction:



The mechanism involves base catalysed addition of hydroxide to the aldehyde; followed by hydride transfer.

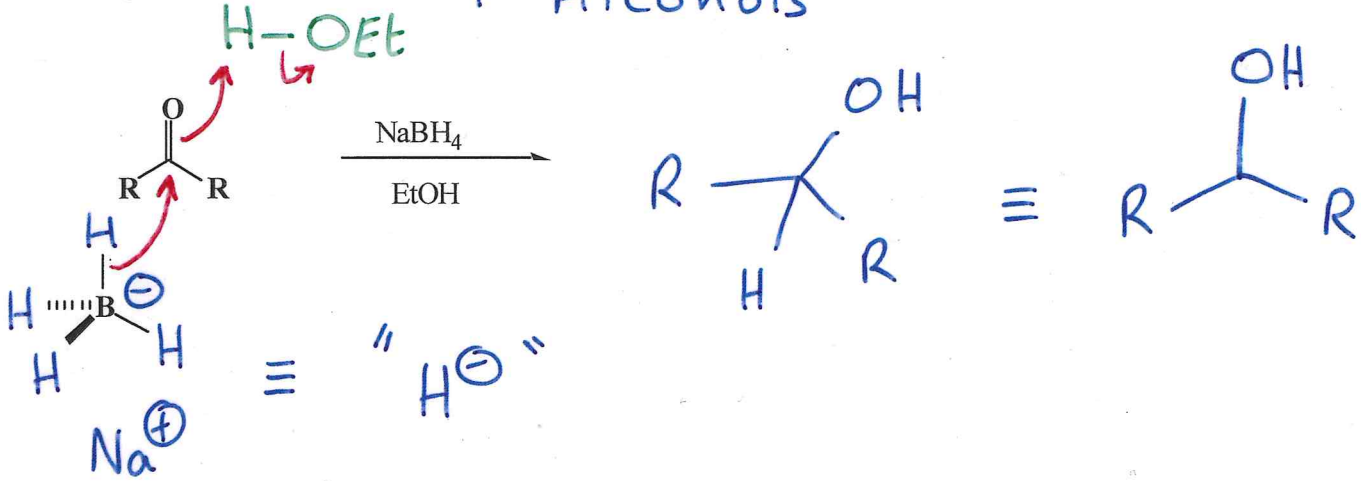


Q. Why does this reaction only work with aldehydes that have NO alpha protons?

However, reduction of a carbonyl is best accomplished with $NaBH_4$ or $LiAlH_4$

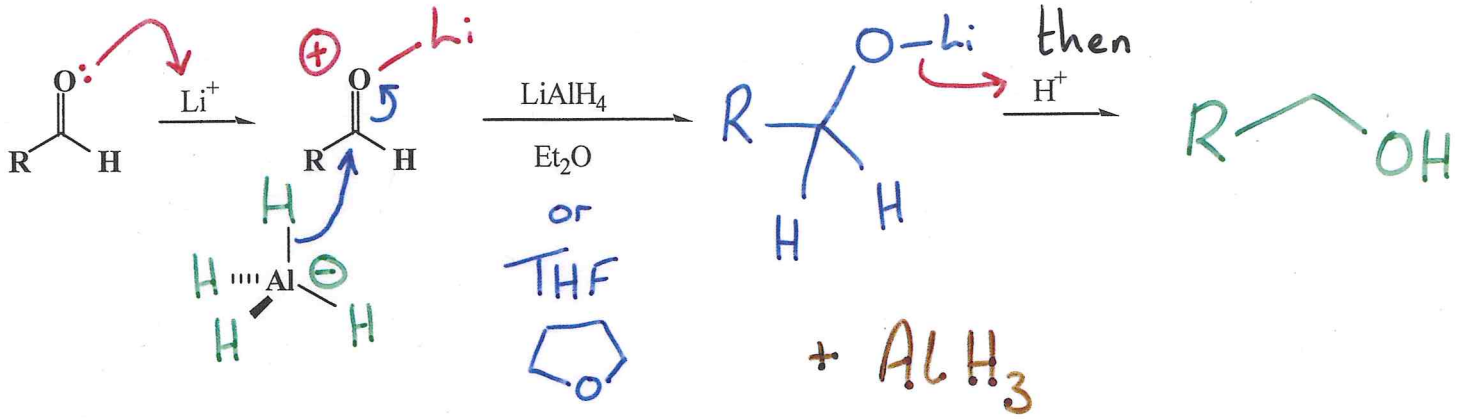
Ketones are reduced to 2° Alcohols

Aldehydes are reduced to 1° Alcohols



Reaction mechanism with $LiAlH_4$ is more complex and takes place in an inert solvent such as ether (this is because $LiAlH_4$ is MORE reactive

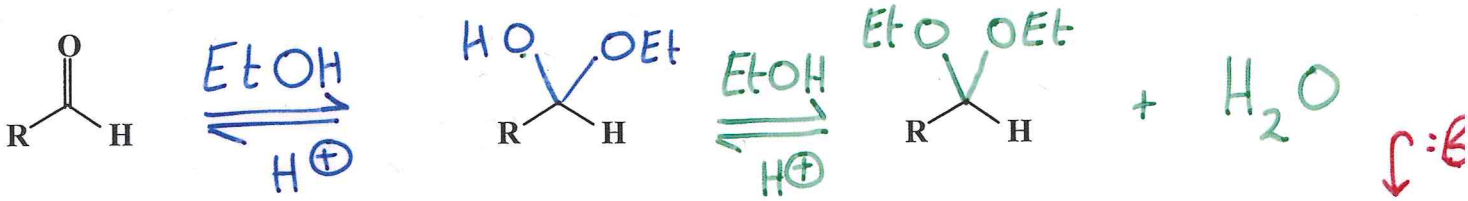
Violent reaction with ROH

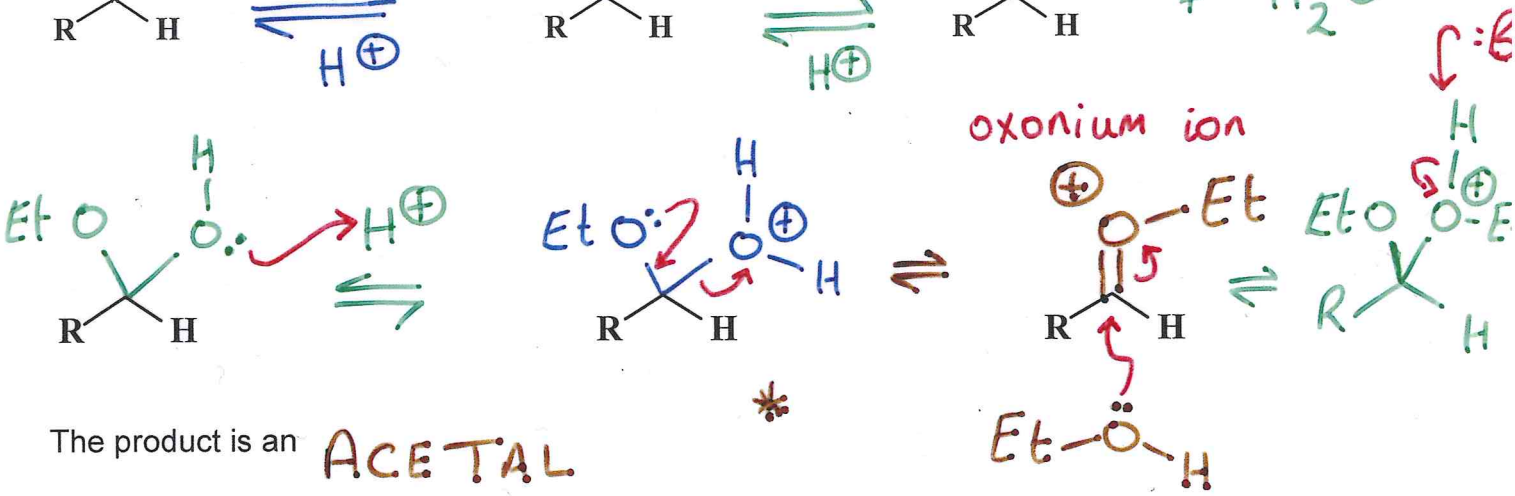


2. Nucleophilic substitution **of** C=O

A) Acetals: In <u>acid</u>, hemiacetal formation from an aldehyde or ketone does not STOP

The acid allows further reaction





The product is an ACETAL

Remember, acetals **only** form in ACID

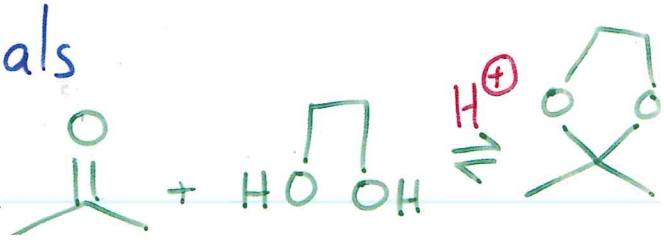
Also

This process is an equilibrium and can be shifted in either direction by removal of the products or addition of excess of one reagent.

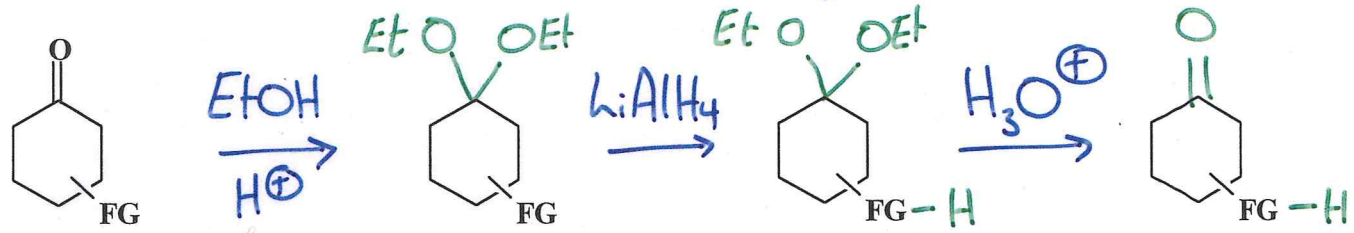
To **form** an acetal use: Anhydrous conditions { Excess EtO / Remove H_2O

To **hydrolyse** an acetal use: EXCESS WATER /H^+

Diols form cyclic acetals



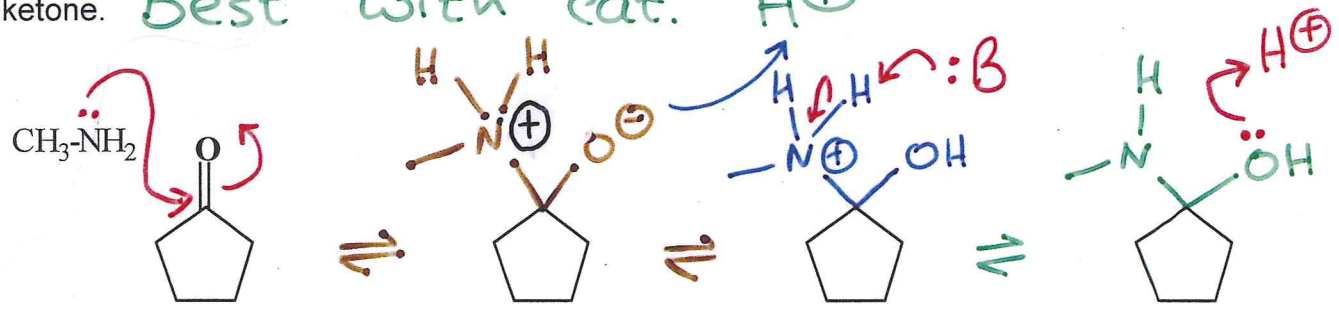
Acetals are stable to base, nucleophiles and oxidants; so they are commonly used as a protecting group for aldehydes and ketones

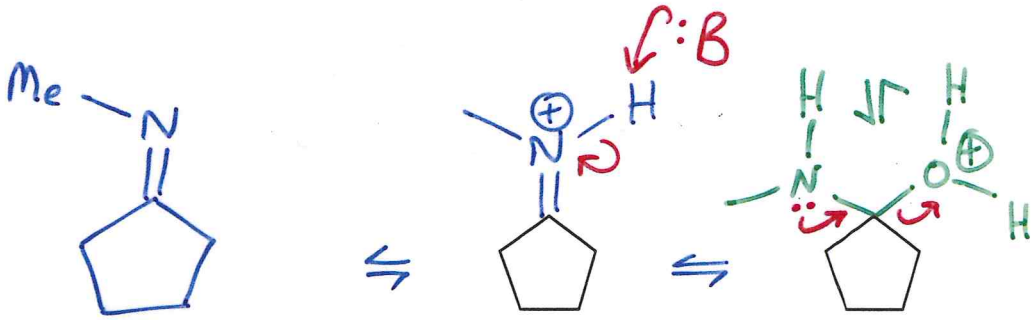


Imagine we want to transform FG using $LiAlH_4$

B) Formation of Imines and related derivatives from carbonyls

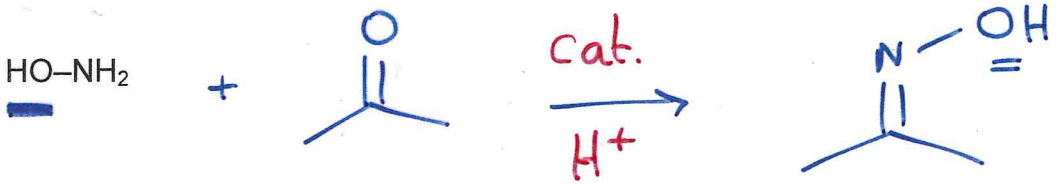
Nitrogen based nucleophiles also add to carbonyl compounds: consider attack of a primary amine at a ketone. Best with cat. H⊕



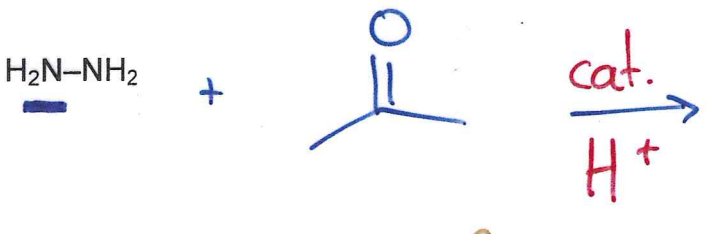


IMINE

Other amine derivatives add to carbonyl compounds in an analogous manner.



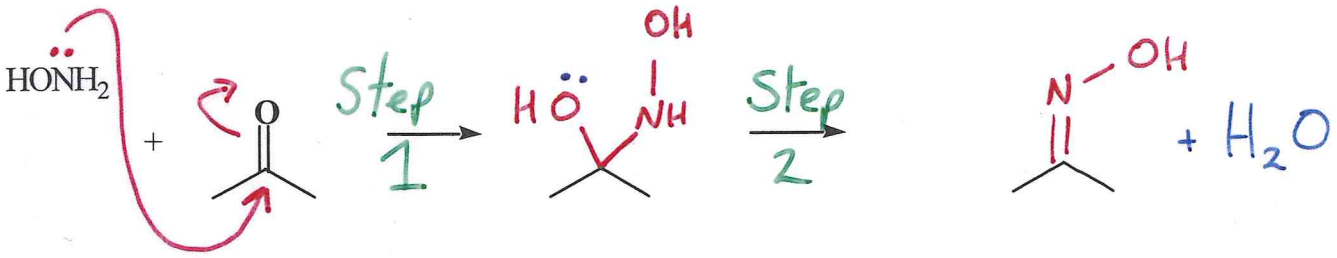
OXIME



HYDRAZONE

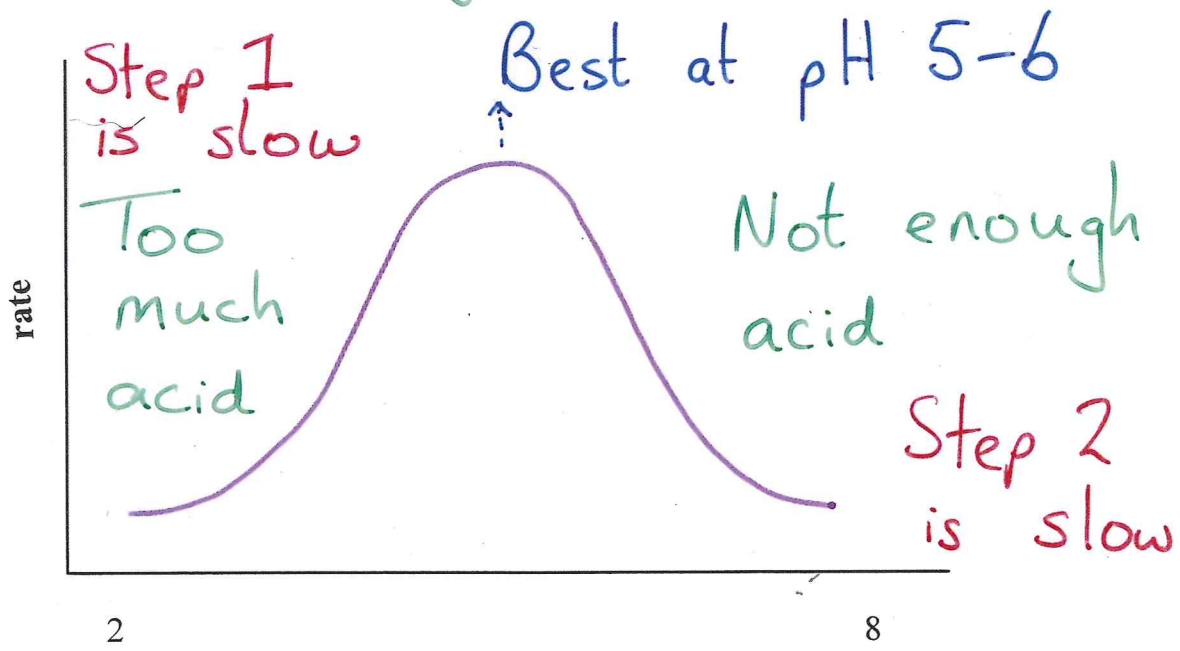
N–R

These condensations are very pH dependent

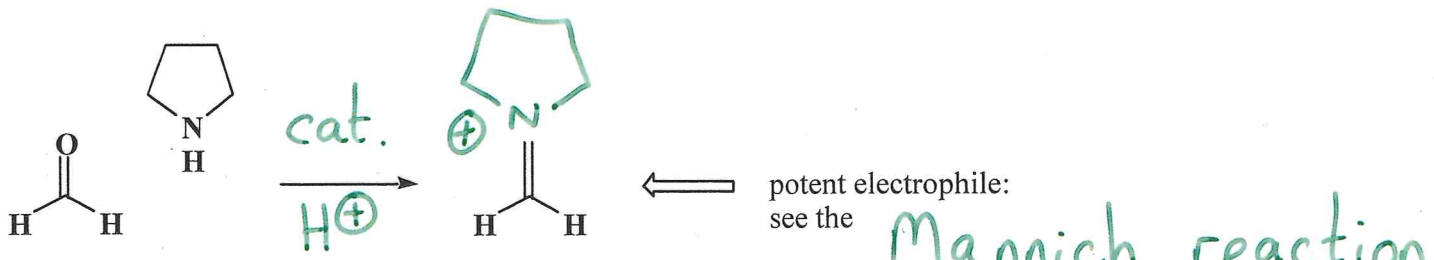


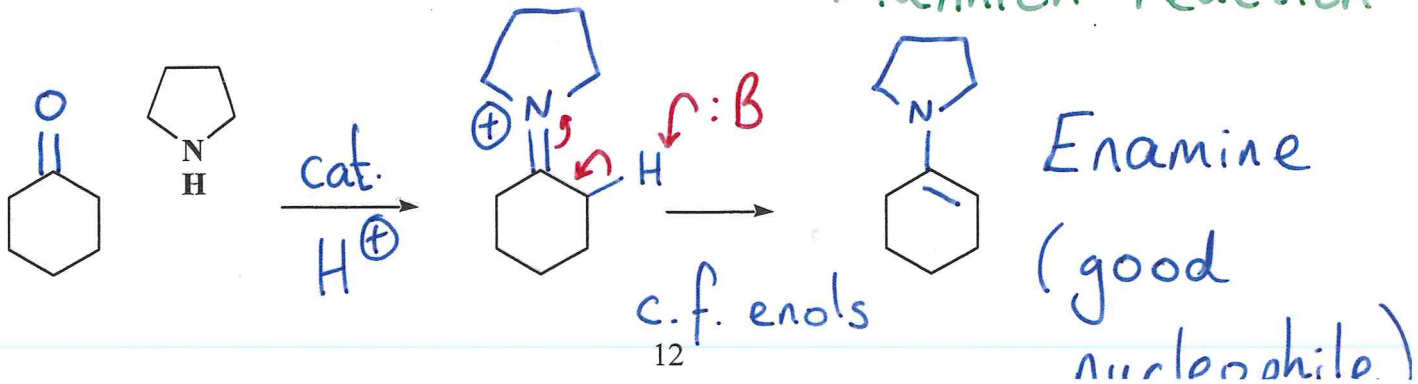
Step 1 Requires the Free Base : Too much acid

Step 2 Is acid catalysed $HO-\overset{\oplus}{N}H_3\ X^{\ominus}$

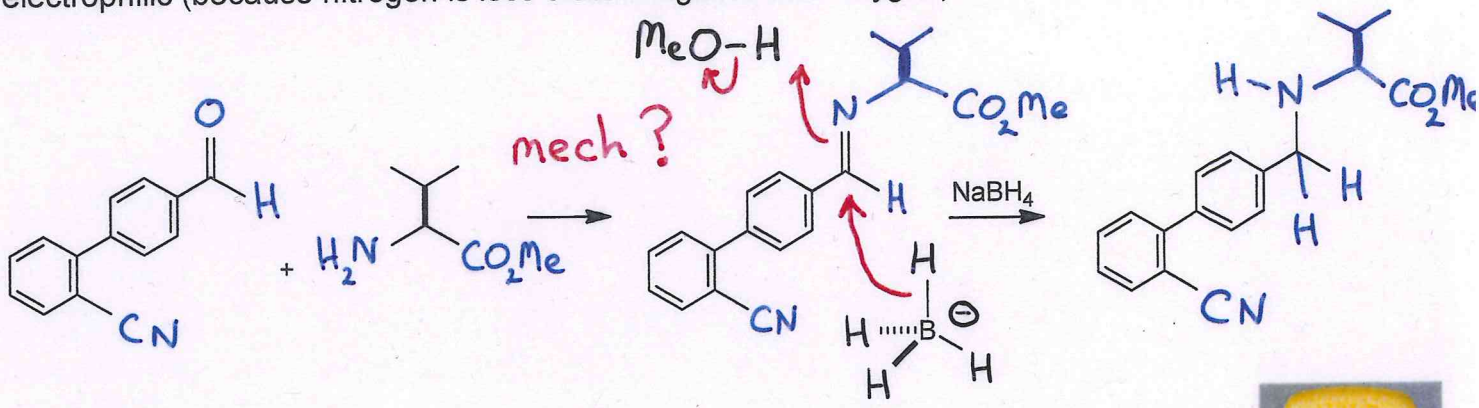


Aside on 2° amines: Note that secondary amines cannot condense with a carbonyl to produce a neutral compound

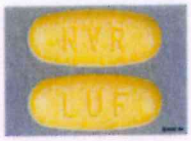




And, just like aldehydes and ketones, imines are useful electrophiles although they are less electrophilic (because nitrogen is less electronegative than oxygen)

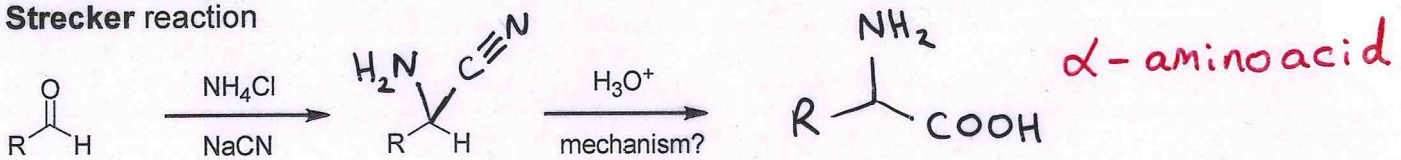


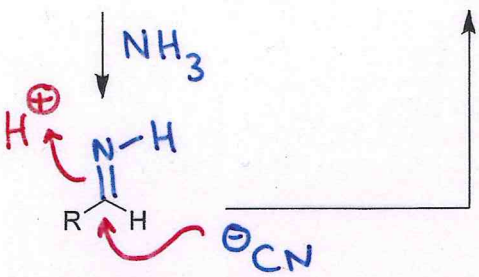
A key step in the synthesis of Valsartan (Diovan) 2010 sales $6 billion

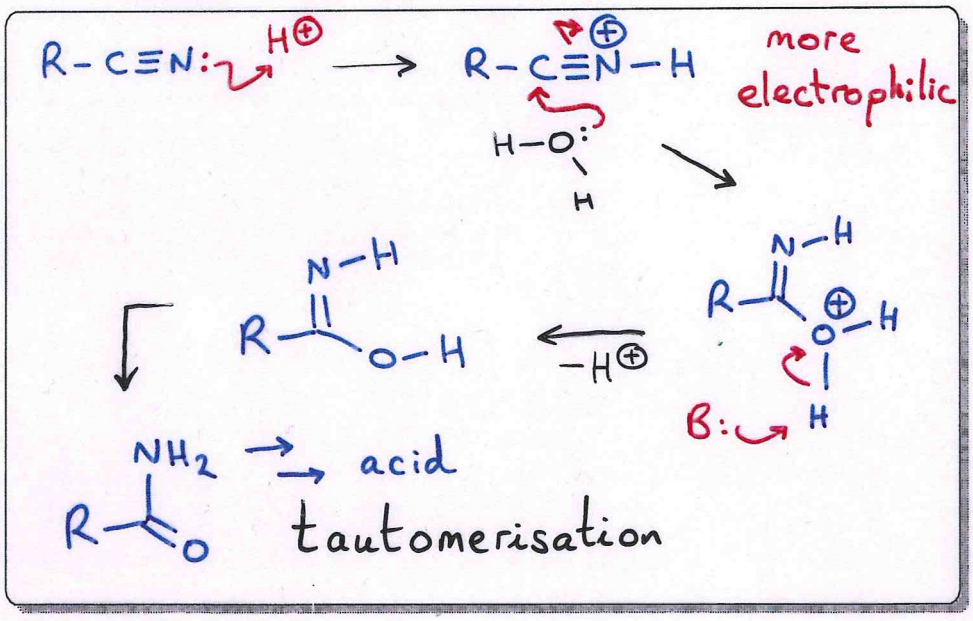


This is called <u>reductive amination</u>: a method for converting aldehydes and ketone to amines

Bearing in mind the reaction of aldehydes and ketones with cyanide, we can rationalise the **Strecker** reaction





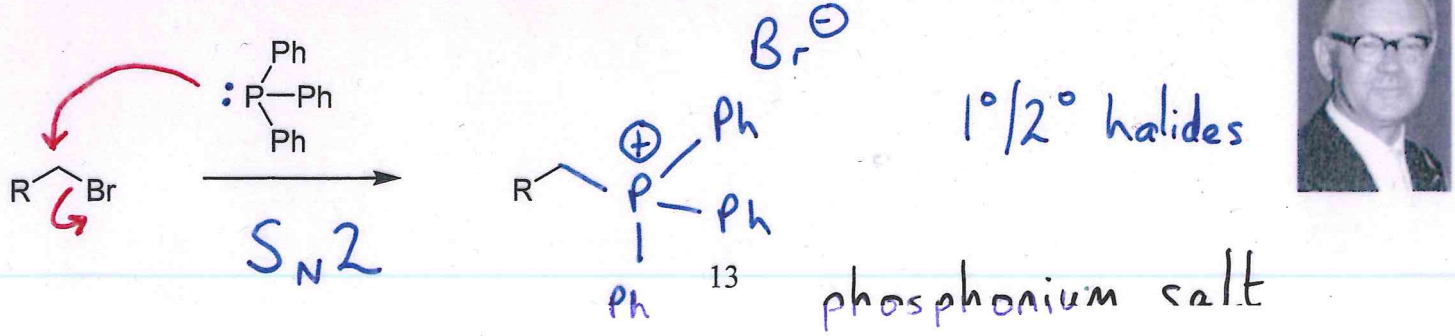


$NaCN + NH_4Cl \rightleftharpoons NaCl + HCN + NH_3$

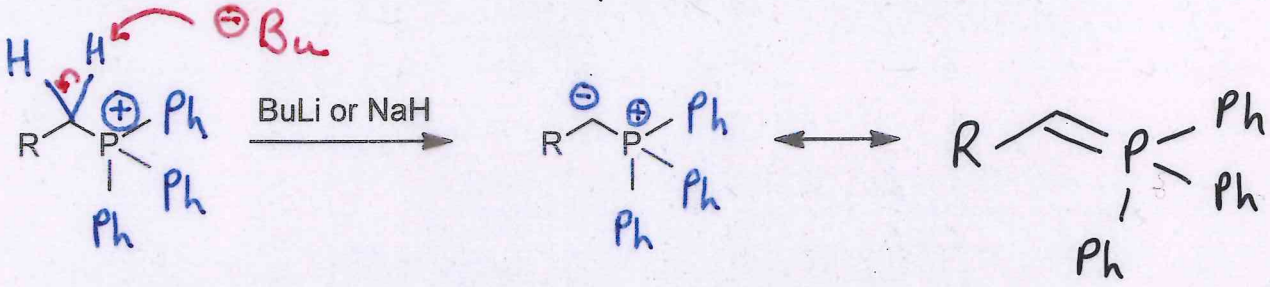
C) Formation of C=C bonds from carbonyls

i) Making alkenes from carbonyl compounds: the Wittig reaction (which consists of

1) Reaction of an alkyl halide with triphenylphosphine

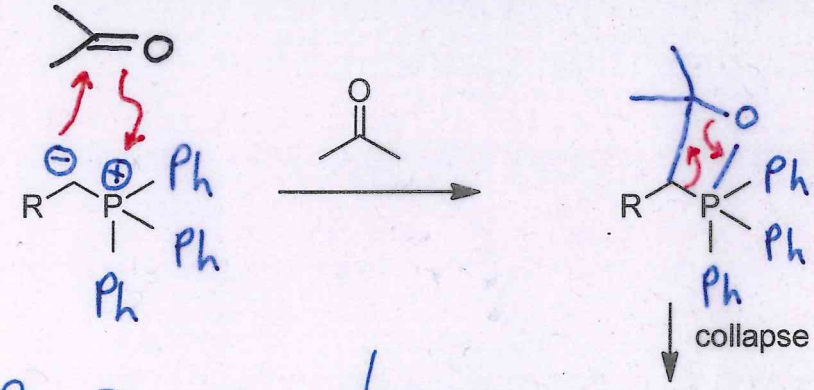


2) *Treatment of the phosphonium salt with strong base to make an YLID*



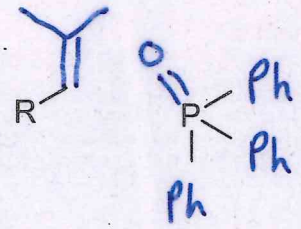
3) *Immediate reaction of the ylid with a carbonyl compound to form an alkene*

aldehyde or ketone

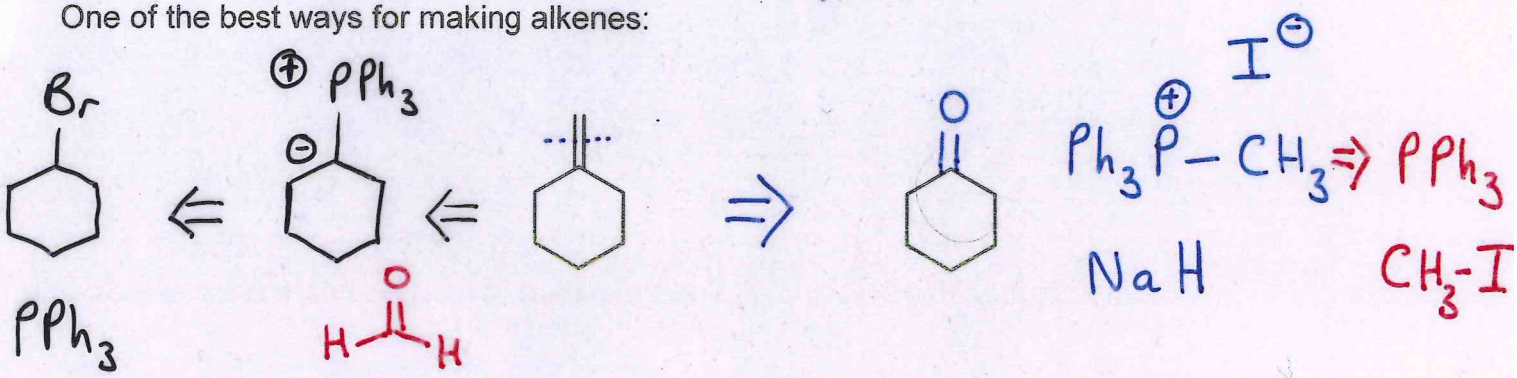


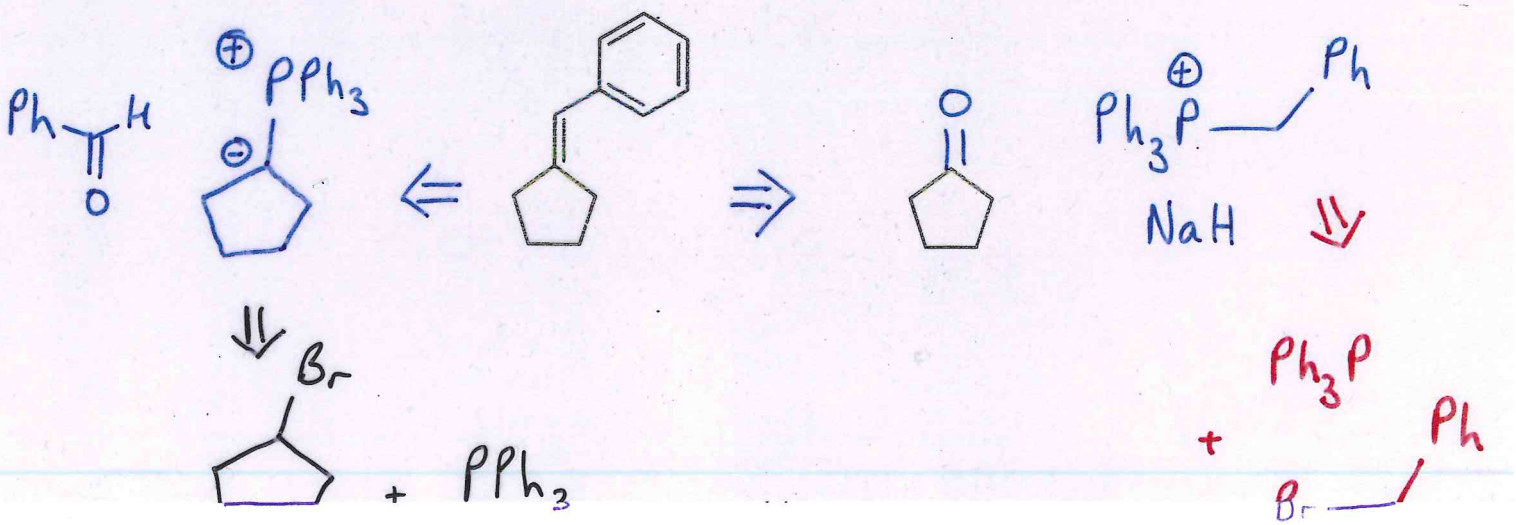
Oxa-phosphetane thought to be formed in one (concerted) step

P=O very strong, driving force for the Wittig reaction →

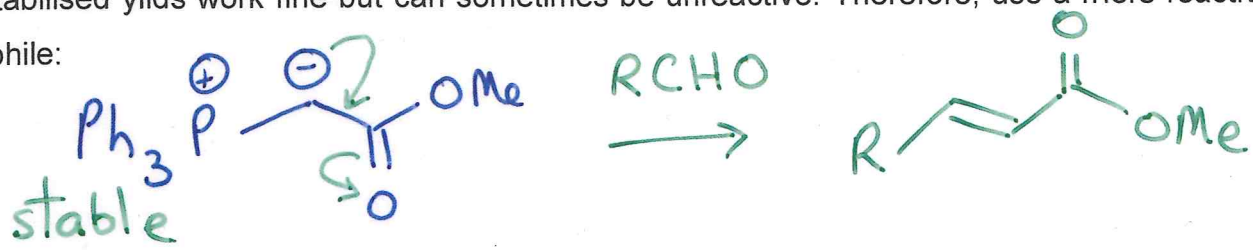


One of the best ways for making alkenes:

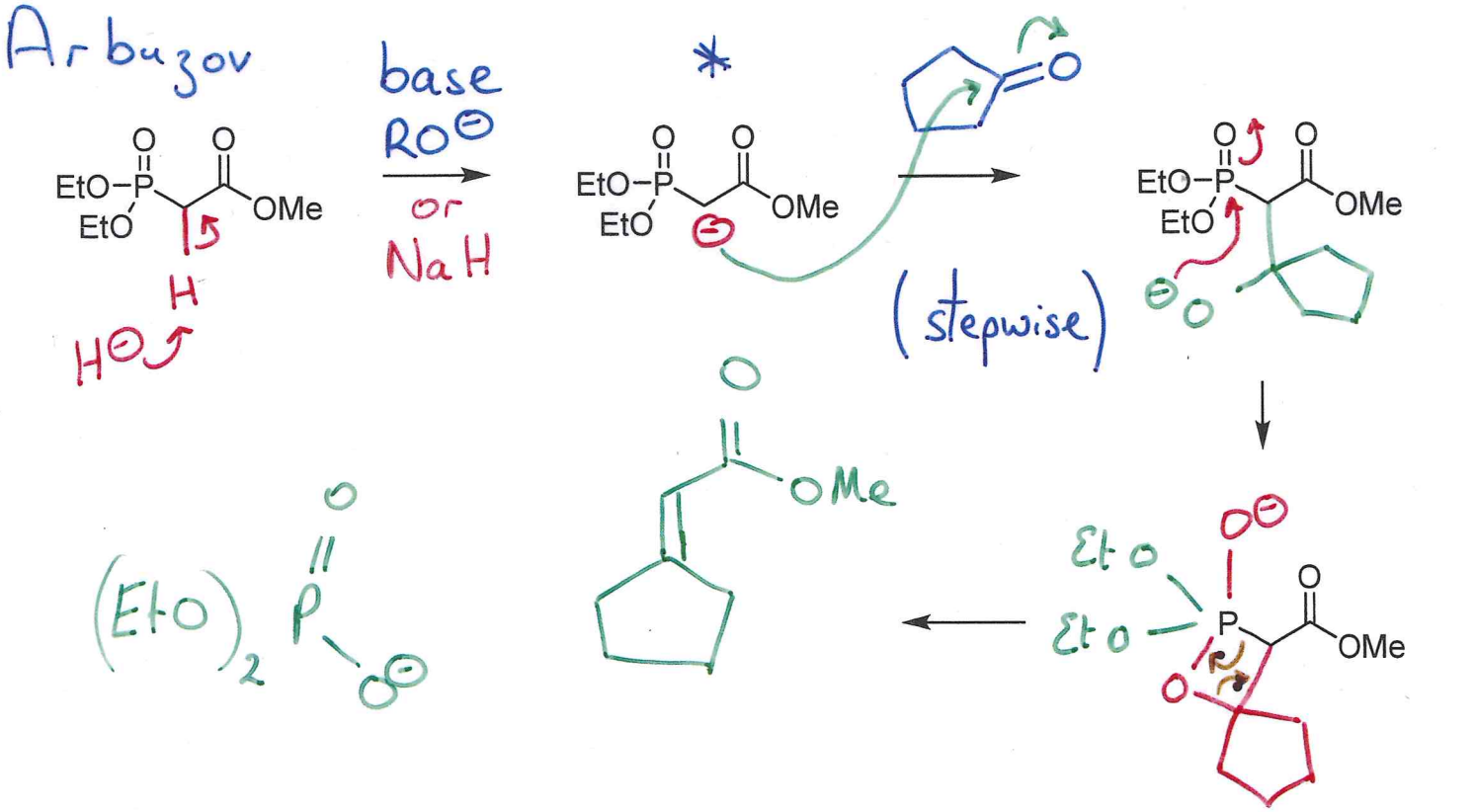




Ester stabilised ylids work fine but can sometimes be unreactive. Therefore, use a more reactive nucleophile:



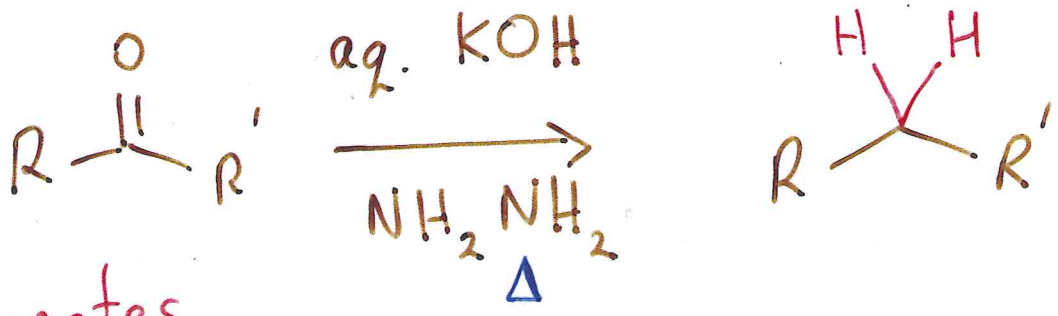
i) More reactive phosphorous derived compounds: the Horner Wadsworth Emmons reaction



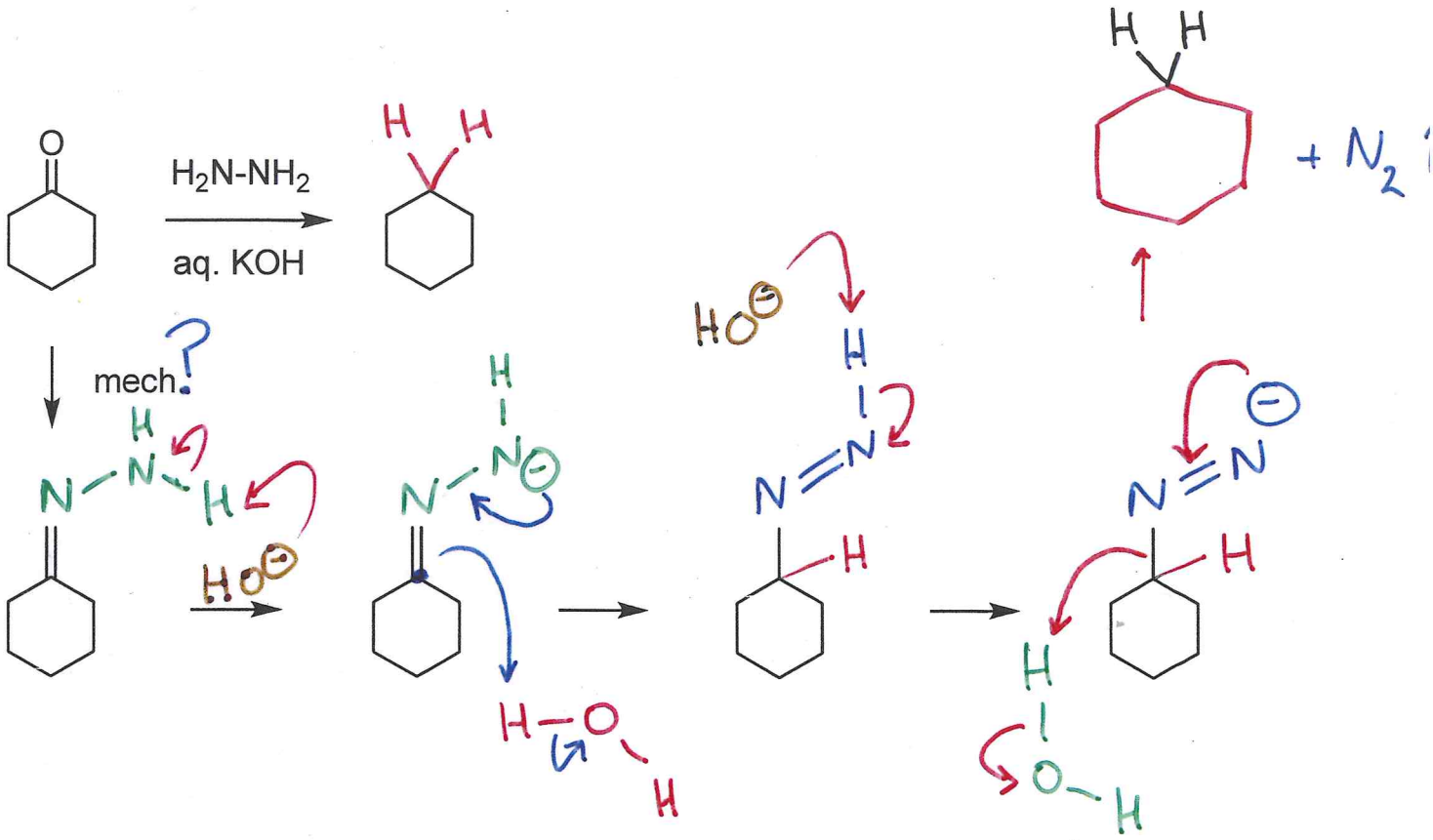
* anion is negatively charged > ylid which is neutral

D) Removal of C=O from carbonyls: the Wolff Kishner reaction

It is sometimes useful to be able to remove a C=O completely from a molecule. There are several ways of doing this, dependent upon whether the molecule can tolerate acid or base.



deoxygenates

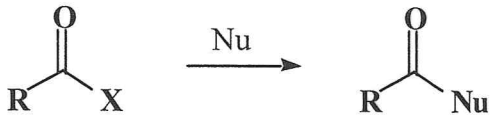


3. Nucleophilic substitution **at** C=O

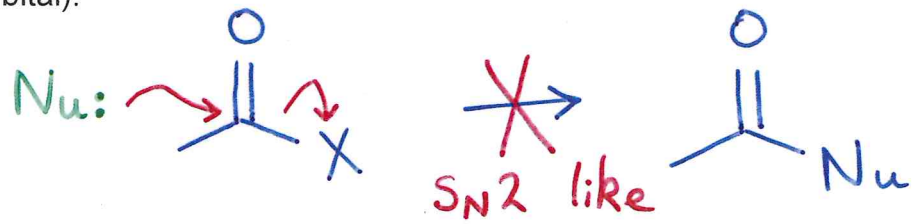
A) Tetrahedral intermediates in substitution

Overall, the substitution process can be represented as:

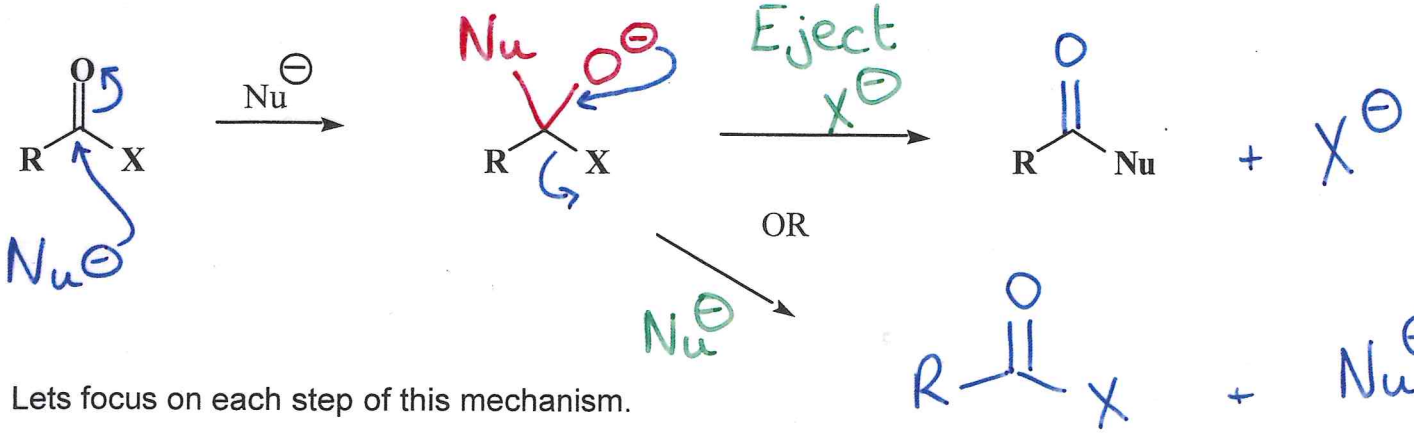
Substitution of X



This reaction does **NOT** go through a direct displacement: instead, the nucleophile finds it easier to add to the carbonyl group (the π^* is lower in energy and more accessible to the HOMO of the nucleophile than a σ^* orbital).



The intermediate (known as a TETRAHEDRAL INTERMEDIATE) can do two things,

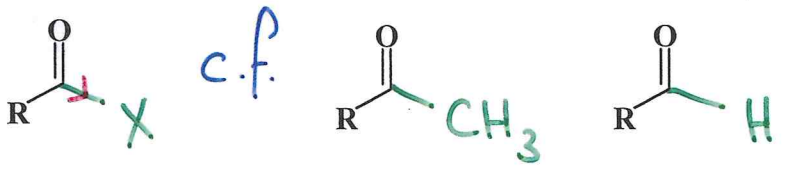


Lets focus on each step of this mechanism.

B) Step 1: *How does the nature of X affect the reactivity of the carbonyl group towards nucleophiles?*

There are two effects here:

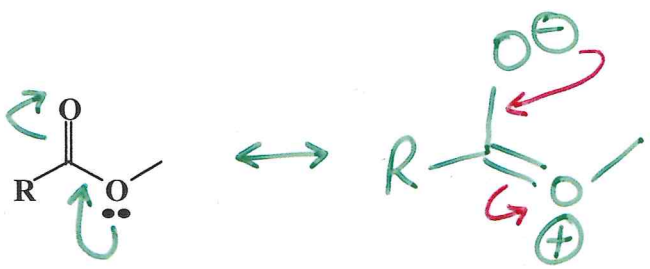
(i) Inductive electron withdrawal if X is electronegative (O, N, Cl etc)



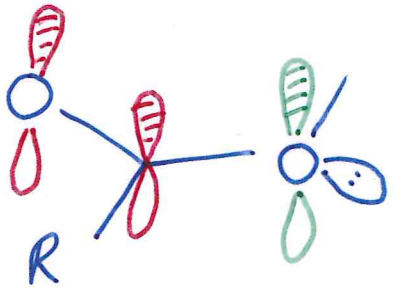
Increased electronegativity of X

Increases δ^+ on C=O ⇒ Increases reactivity

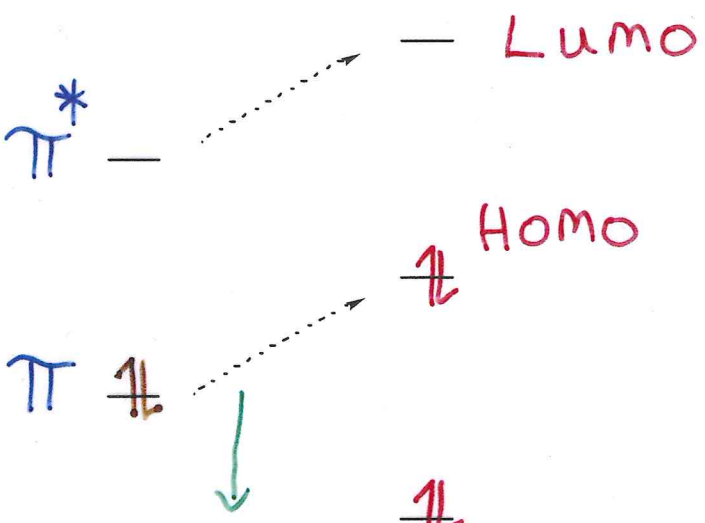
(ii) Conjugation of a lone pair on X with the C=O



Think about the shape of the ester oxygen



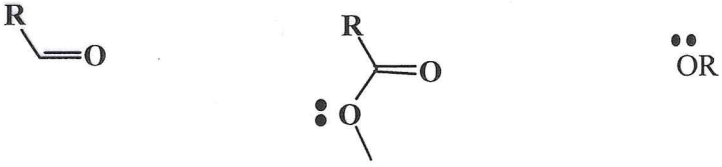
In molecular orbital terms:

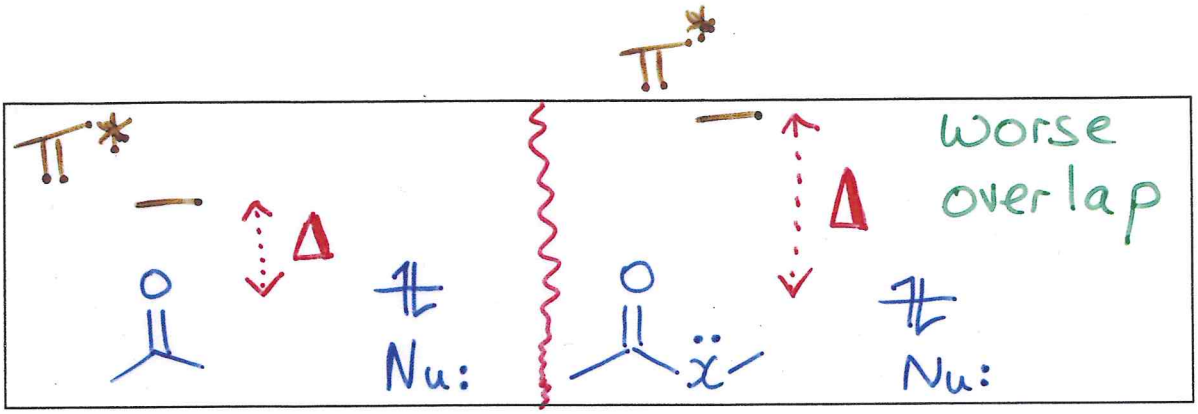


By conjugating the two species the LUMO is raised

p orbital on oxygen and the HOMO is raised

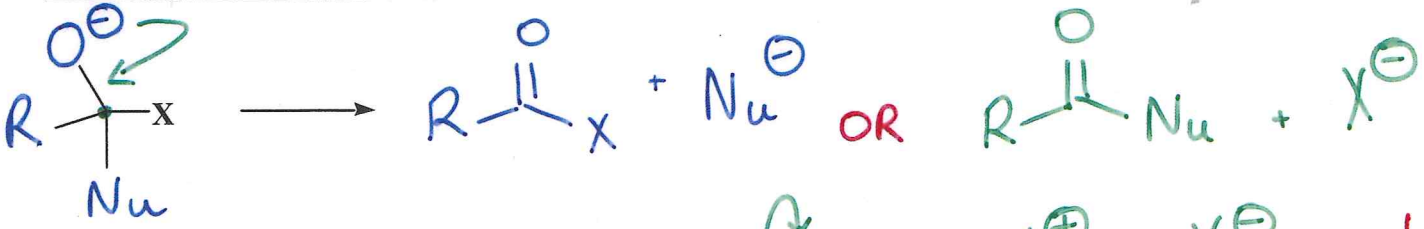
Conjugation LOWERS the electrophilicity of the C=O - LESS REACTIVE





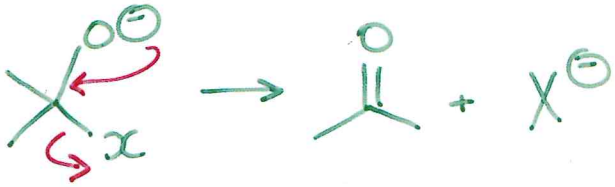
***B) Step 2**: Leaving group ability determines which product is formed*

Leaving group ability: correlation with pKa How do we know which is the best leaving group?



There is already a scale that can help us: pKa:  similar

$pKa = -\log Ka$

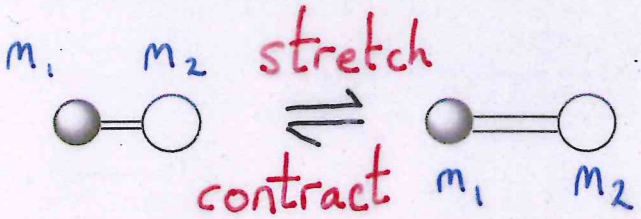


Large values of pKa mean small values of Ka ie H–X is a weak acid $H-X \rightleftharpoons H^{\oplus} + X^{\ominus}$ and $X^{\ominus}$ is a poor leaving group
Small values of pKa mean large values of Ka ie H–X is a strong acid $H-X \rightleftharpoons H^{\oplus} + X^{\ominus}$ and $X^{\ominus}$ is a good leaving group

Leaving group X^-	**pKa of H-X**	
$Me^{\ominus}$	50	
$H^{\ominus}$	40	↑ weak acids Poor L.G.
$NH_2^{\ominus}$	34	
→ $EtO^{\ominus}$	16	
$HO^{\ominus}$	15.5	↓ strong acids Good L.G.
$MeCO_2^{\ominus}$	4	
$Cl^{\ominus}$	-7	

Probing the nature of the carbonyl group by Infra-red (IR) spectroscopy

IR spectroscopy measures Stretching of bonds



small amounts of energy; λ lies in the infra-red (heat radiation)

Can be described using Hooke's Law: →

$$\nu = \frac{1}{2\pi c}\sqrt{\frac{k}{\mu}}$$ k = force constant ie strength of 'spring'

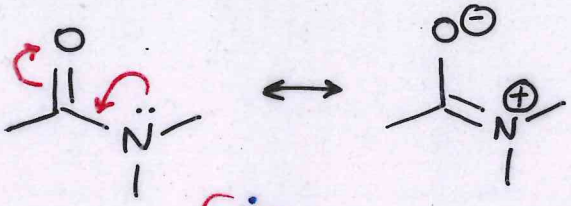
$$\mu = \frac{m_1 m_2}{m_1 + m_2}$$ = reduced mass

Remember that $E = h\nu = \frac{hc}{\lambda}$ so $\nu \propto \frac{1}{\lambda}$ = wavenumber $\bar{\nu}$ cm^{-1}

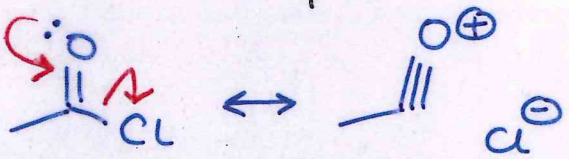
So, strong bonds absorb at high ν and high $\bar{\nu}$

The factors discussed earlier will influence the strength of the C=O bond in the following ways:

1) Delocalisation WEAKENS the C=O

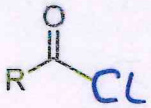
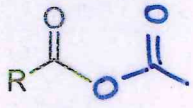
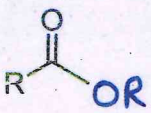
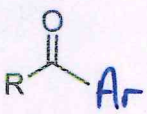
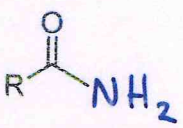


2) Inductive effects STRENGTHEN the C=O



The derivatives shown earlier have a combination of the 2 effects and this can be seen in the IR.

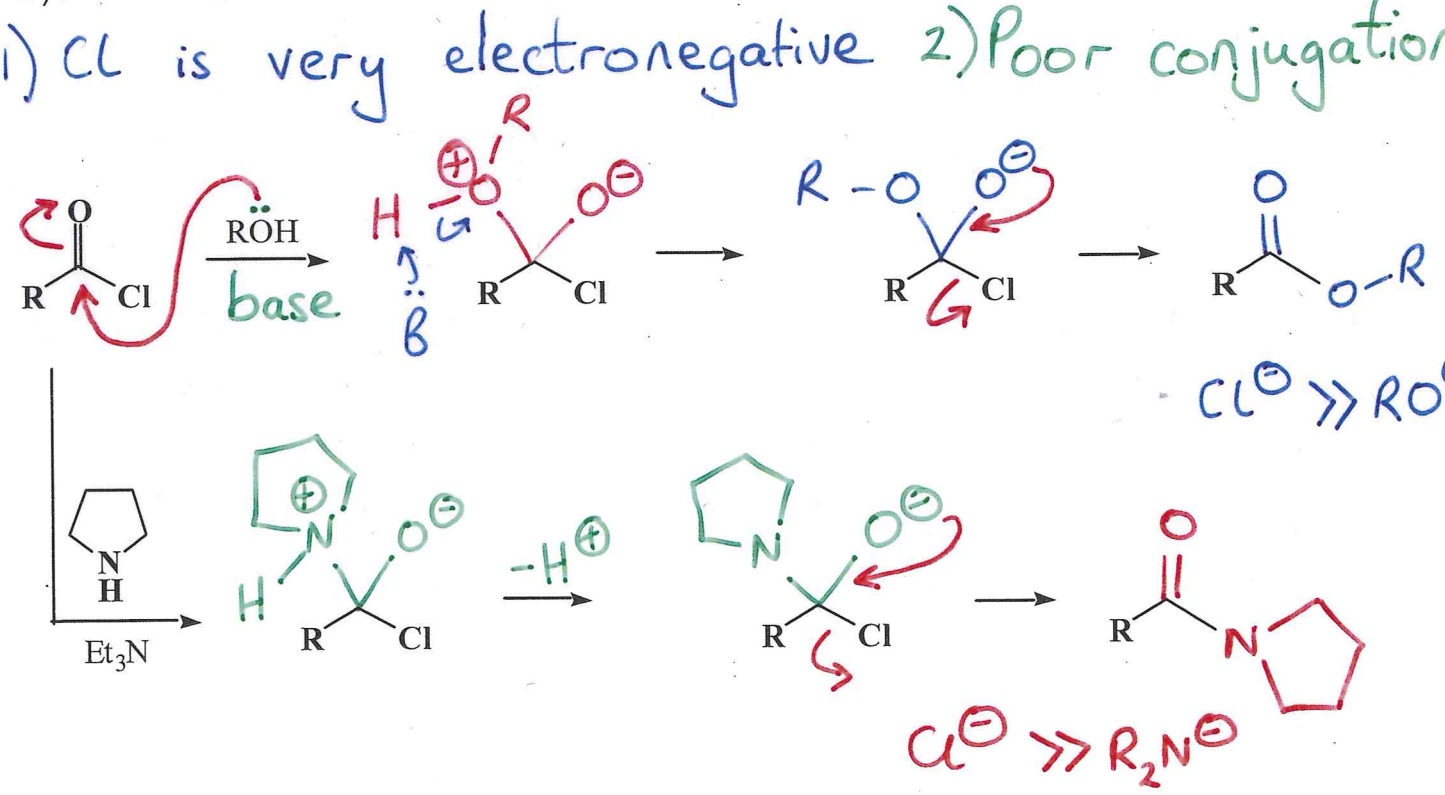
Compare the C=O stretch of  ~ 1715 cm^{-1}

					
~ C=O ,cm^{-1})	1815	1825 / 1748	1745	1690	1670
comment	strong inductive	good inductive	some inductive	deloc^n	strong deloc^n

Functional groups in action.

C) **X= chlorine** then we have an **acid chloride** which are very reactive species because

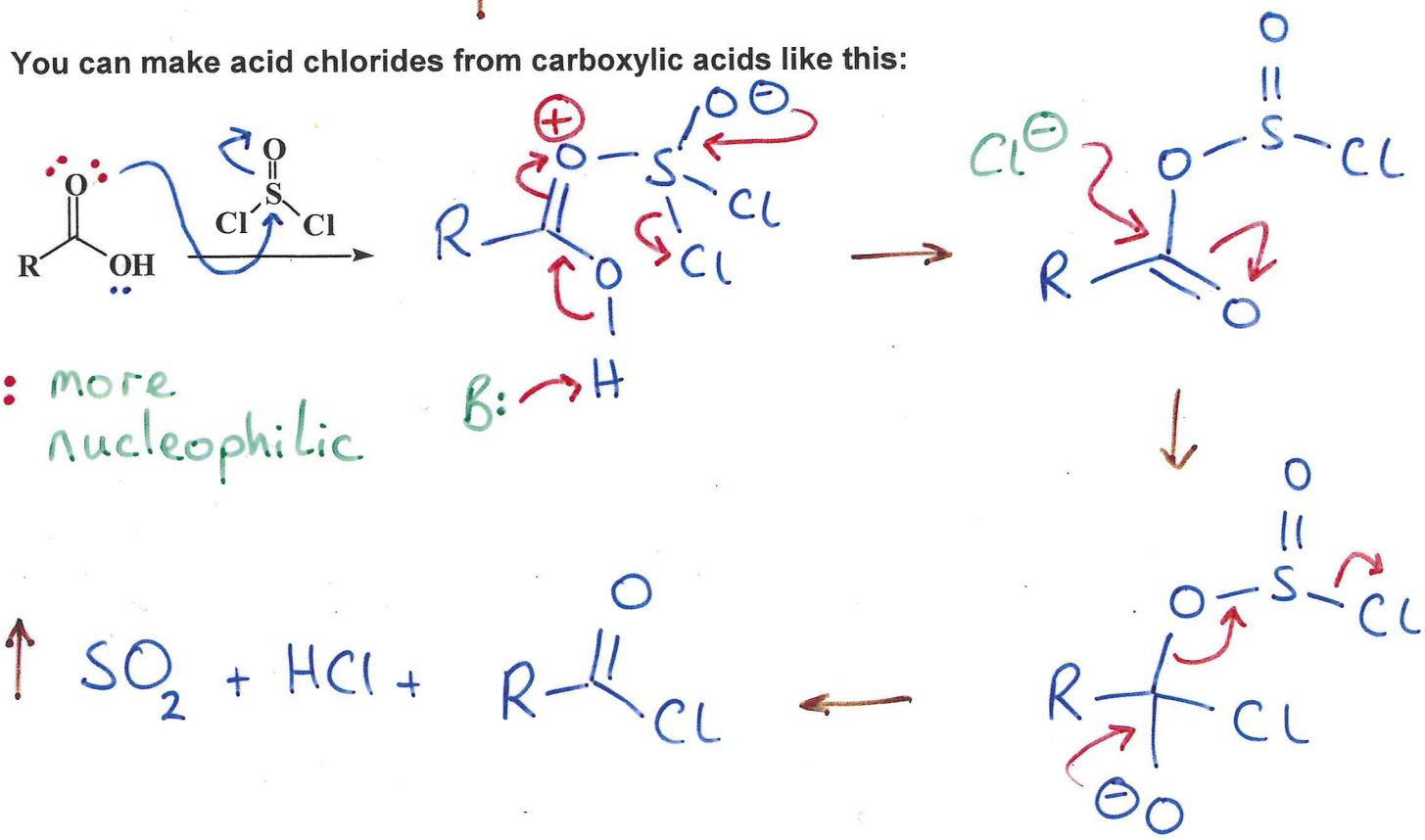
1) Cl is very electronegative 2) Poor conjugation



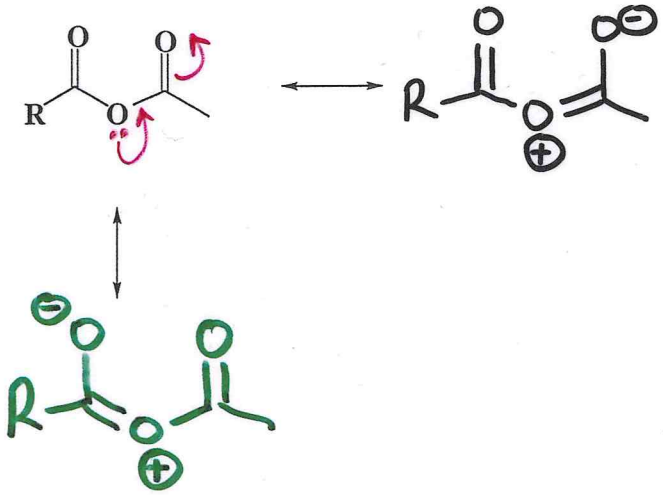
Note that a base must be present here because

the HCl protonates the amine and stops.

You can make acid chlorides from carboxylic acids like this:



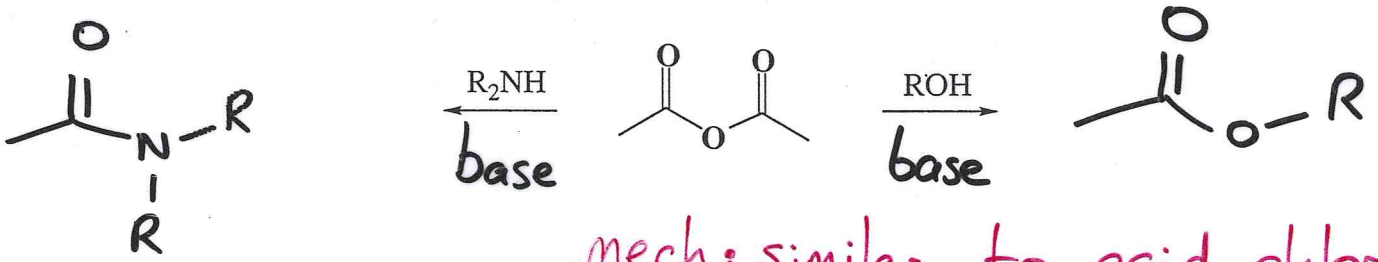
D) When X=OCOR these are called **anhydrides** and are slightly less reactive than acid chlorides, but still useful electrophiles



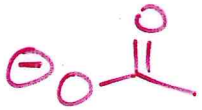
So, oxygen shares its lone pair with 2 C=O and delocalisation is weakened: inductive effect still operative.

Reasonably reactive

As one would expect, reaction of anhydrides mirrors that of acid chlorides



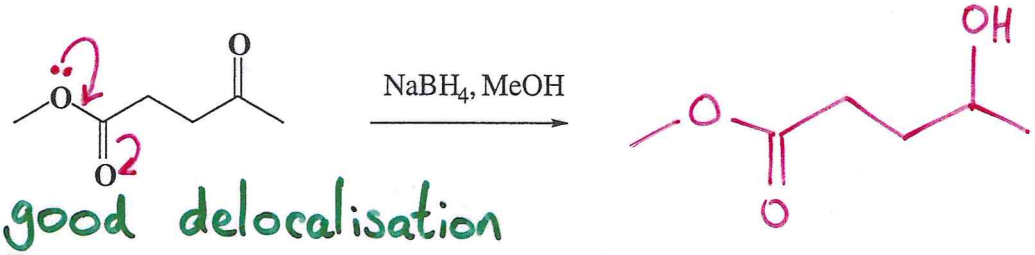
mech: similar to acid chloride



leaving group

E) X= OR, esters

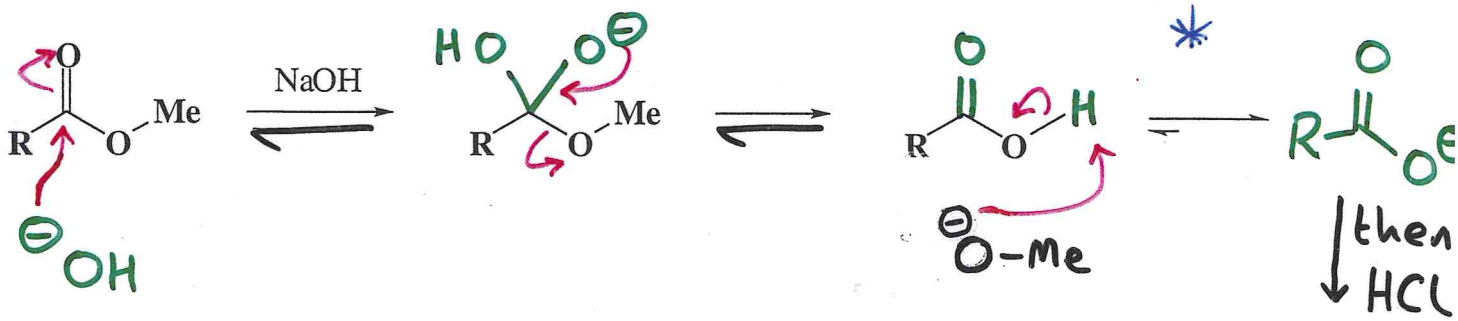
Esters are substantially less reactive towards nucleophiles than aldehydes and ketones; or RCOCl or $(RCO)_2O$



good delocalisation

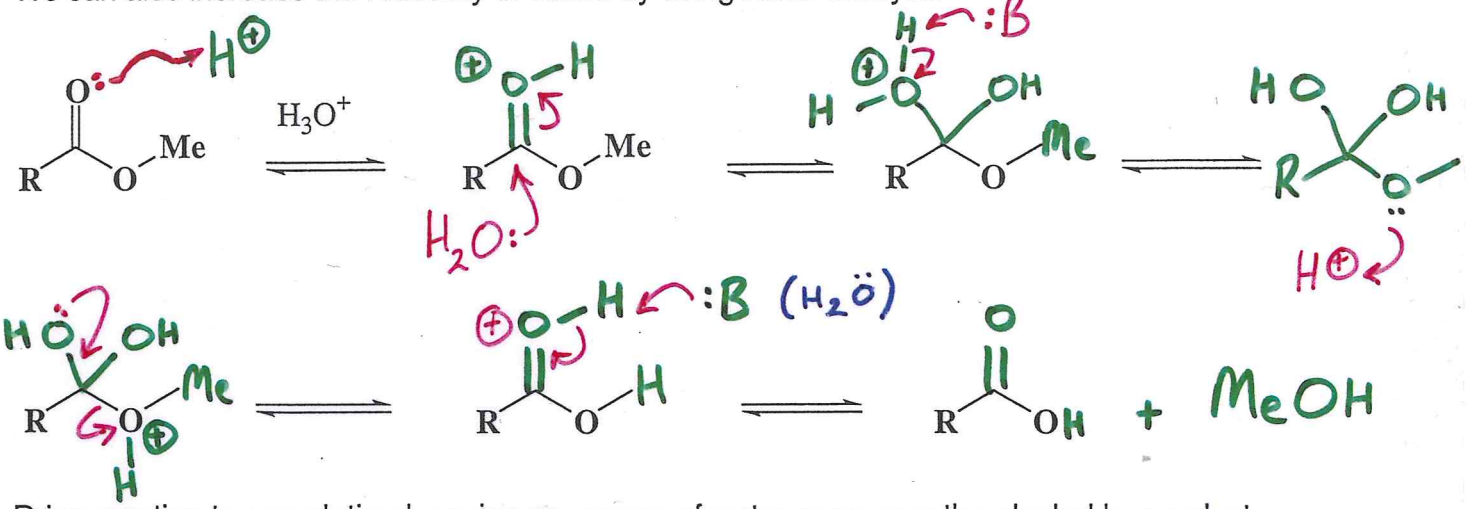
$NaBH_4$ no reaction with ester

Esters do react, but only with more powerful nucleophiles, eg NaOH



* irreversible; drives the reaction

We can also increase the reactivity of esters by using ACID catalysis



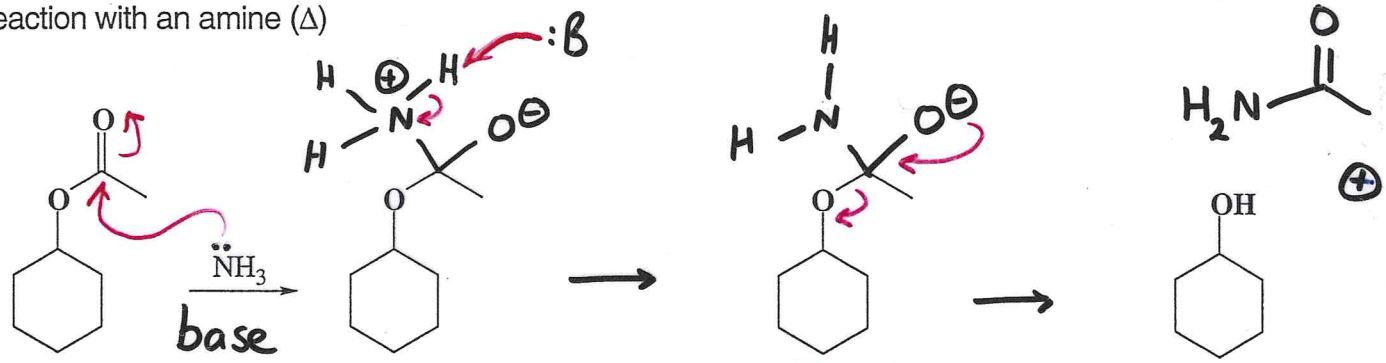
Drive reaction to completion by using an excess of water or remove the alcohol by-product

Further reading: the acid and base catalysed hydrolysis of esters can be classified into 8 different catagories ($A_{AC}1$, $A_{AC}2$, $A_{AL}1$, $A_{AL}2$, $B_{AC}1$, $B_{AC}2$, $B_{AL}1$, $B_{AL}2$) depending upon the mechanism-see J. March, Advanced Organic Chemistry, Fourth Ed, P378.

$RCO_2{}^+Bu$

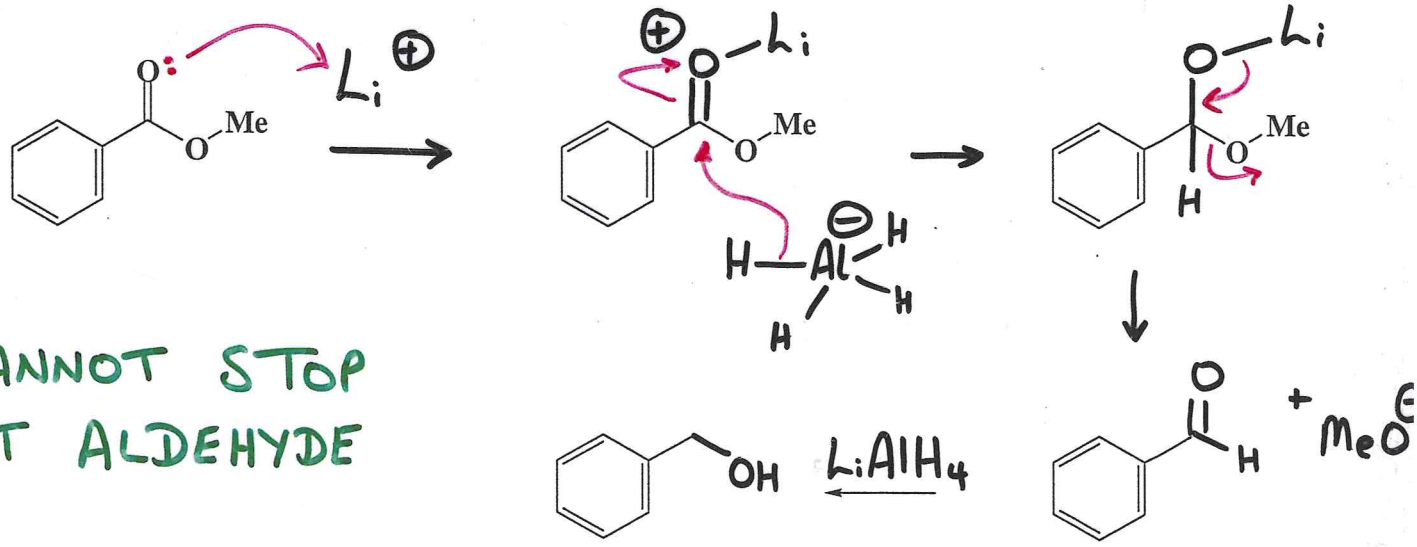
Given the above, the following should come as no surprise:

1) reaction with an amine (Δ)



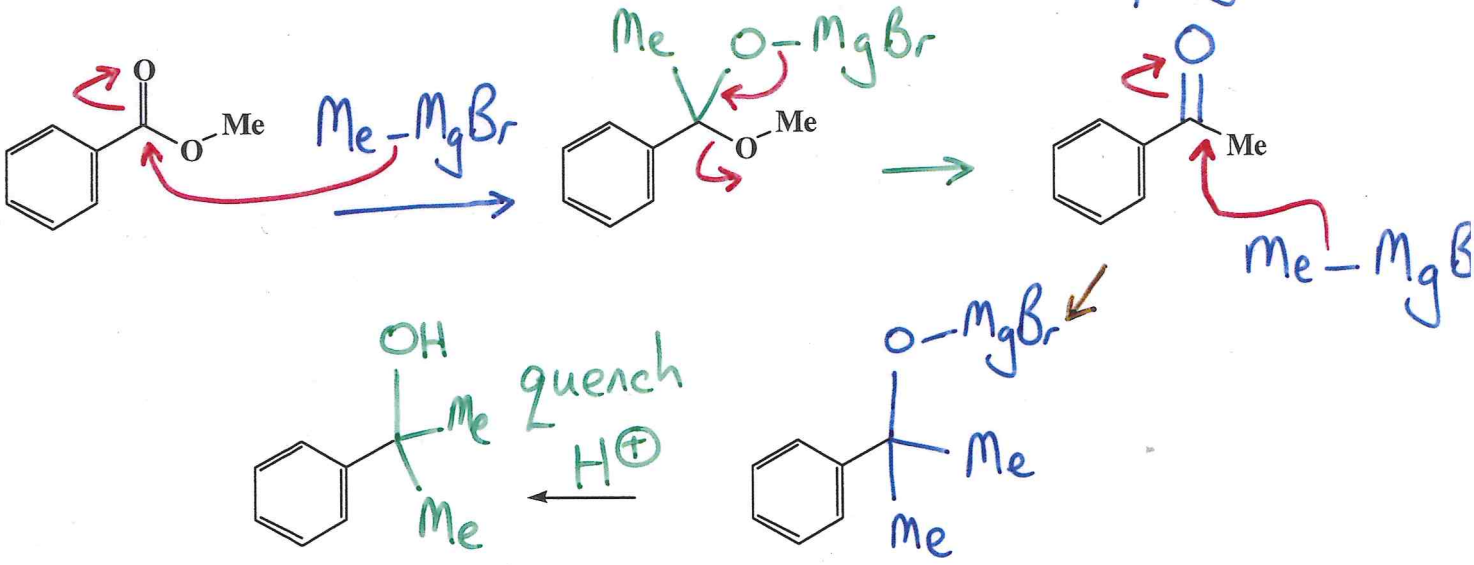
$RO^\ominus > H_2N^\ominus$

2) reduction with $LiAlH_4$

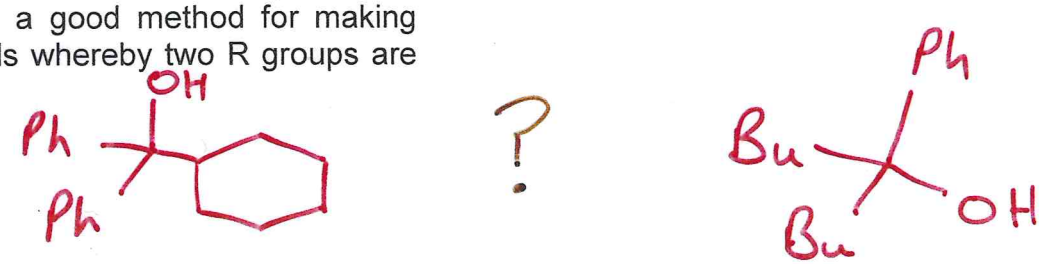


CANNOT STOP AT ALDEHYDE

So, what happens if we try to make a ketone via reaction of an ester with a Grignard?

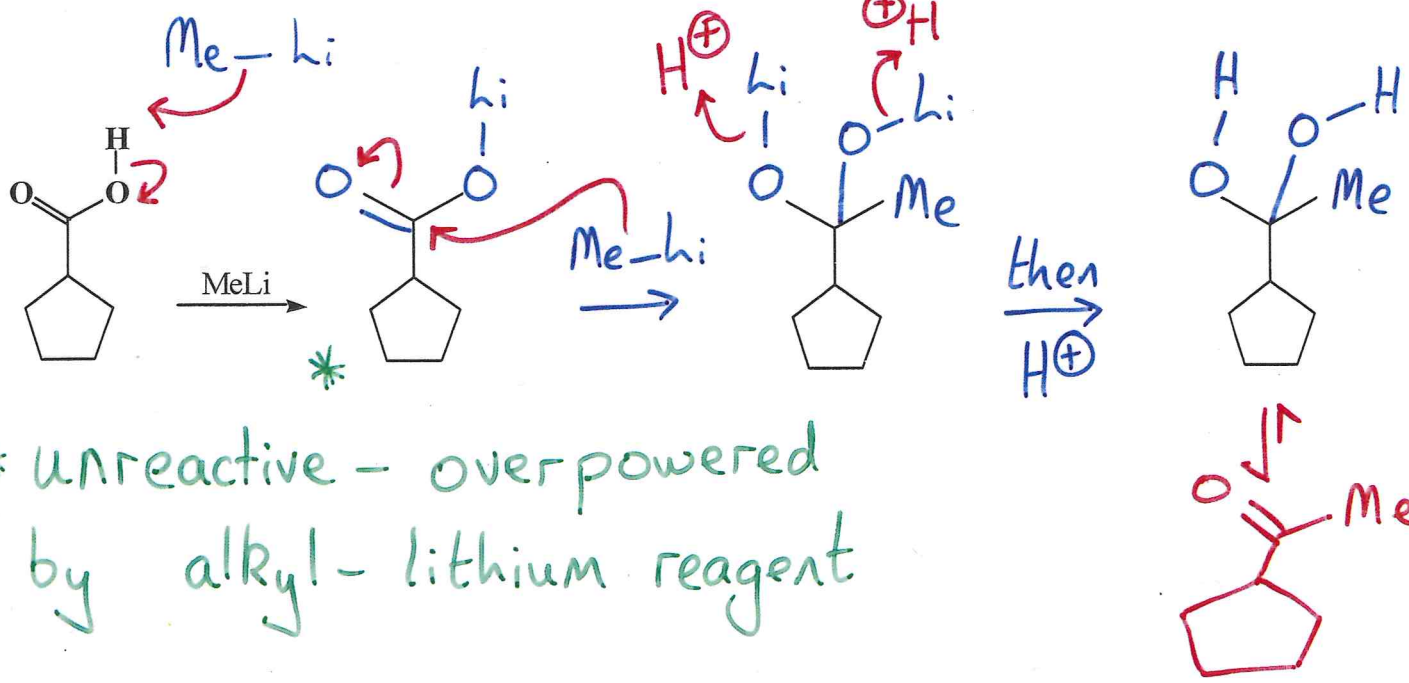


In fact, this is a good method for making tertiary alcohols whereby two R groups are the same



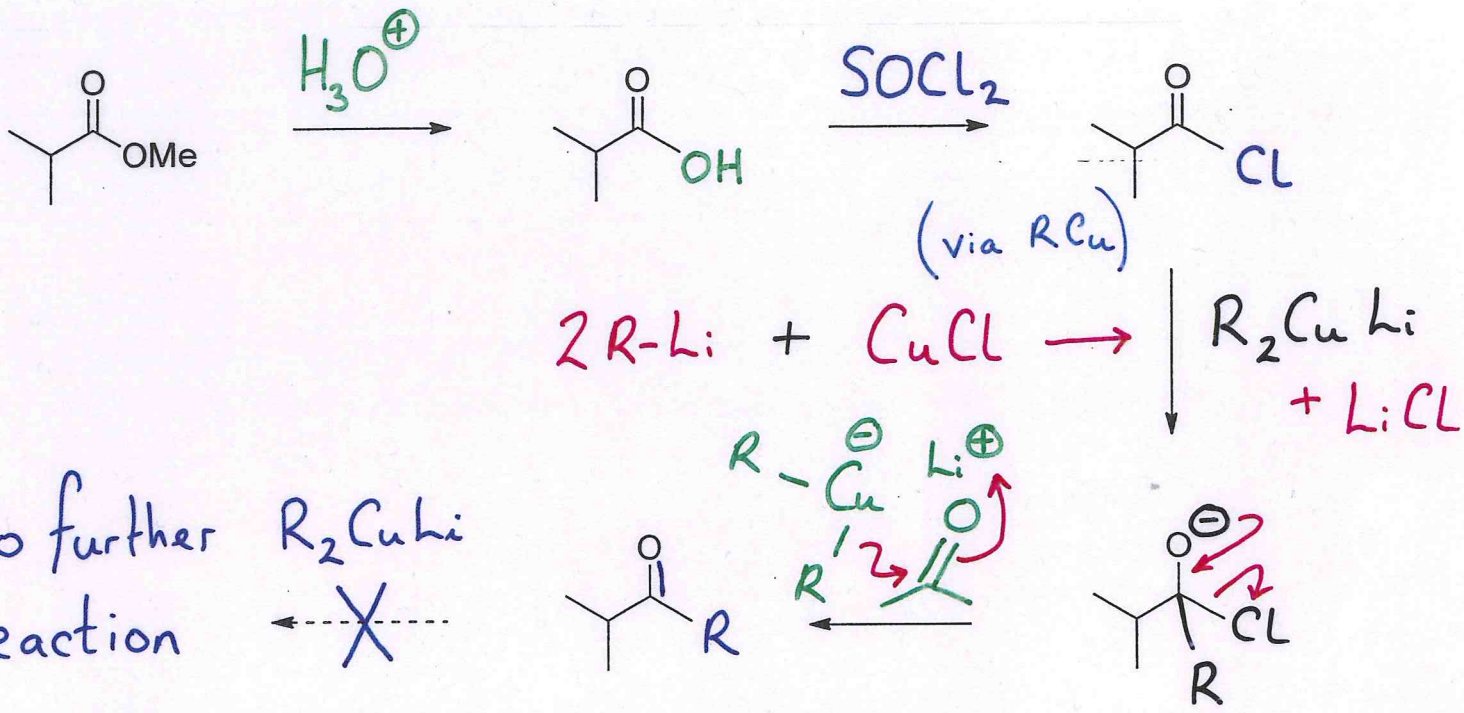
Clearly there is a problem in making ketones with this chemistry. Three solutions are available.

1) React a <u>carboxylic acid</u> with TWO equivalents of a reactive <u>organolithium</u> reagent

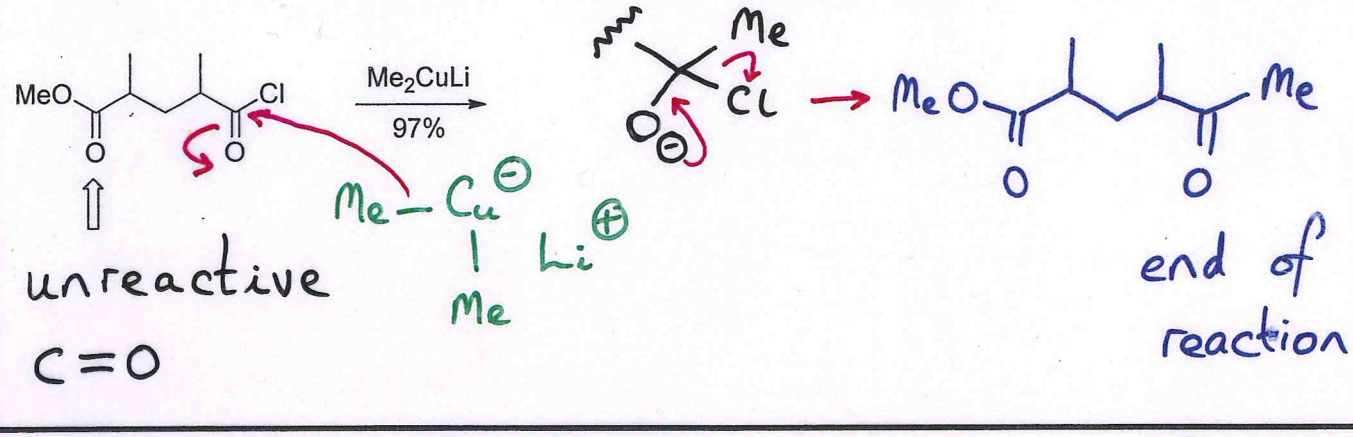


* unreactive – overpowered by alkyl-lithium reagent

2) Use an acid chloride rather than an ester; AND decrease the reactivity of the nucleophile by changing the metal counterion from lithium to COPPER



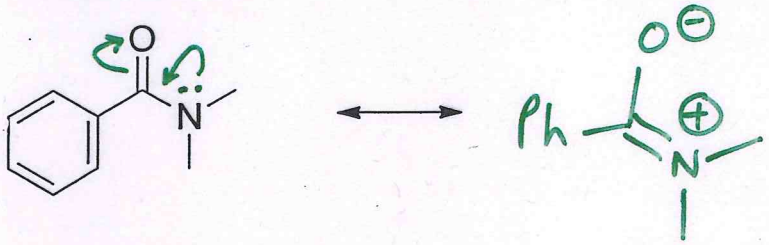
The selectivity displayed below was used as a key step in the synthesis of an antibiotic, septamycin



Solution 3 can wait until we have discussed amides:

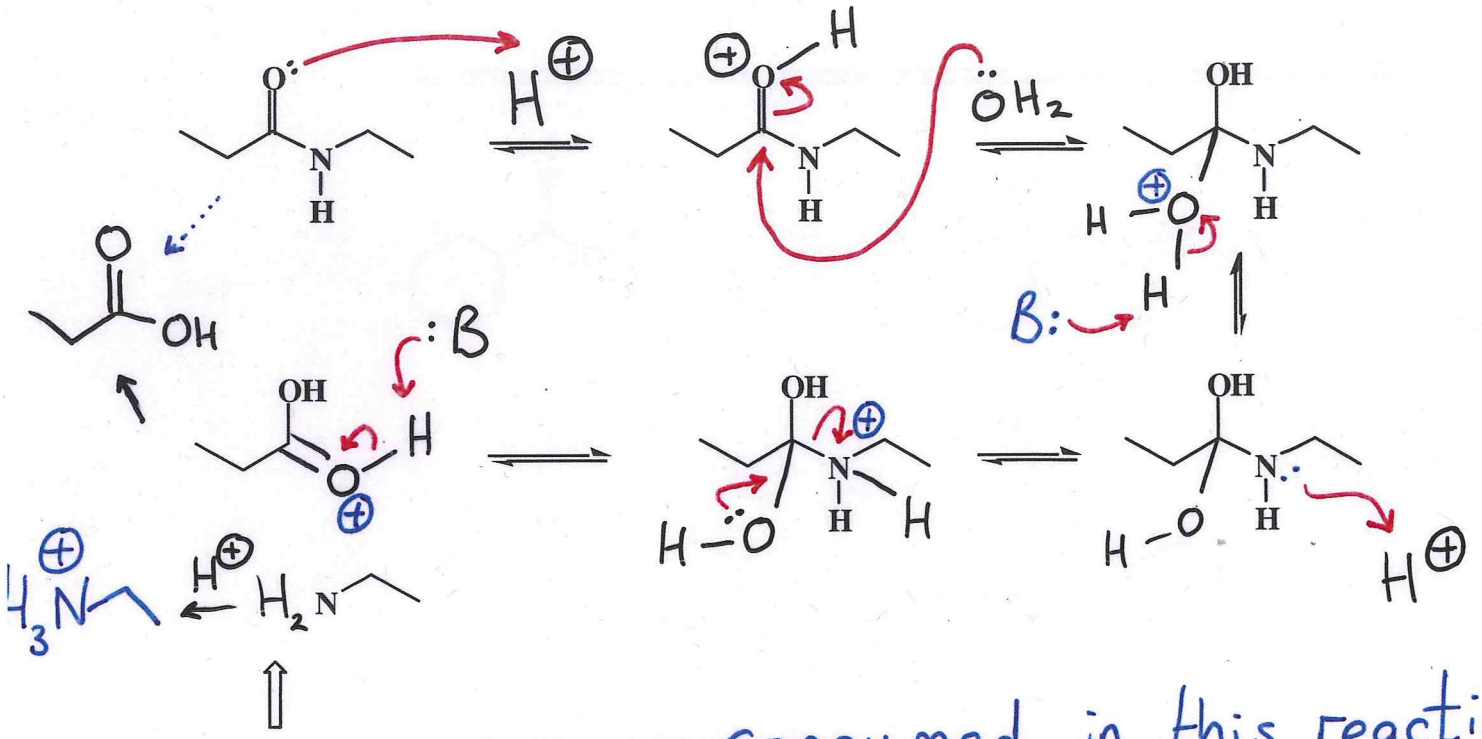
F) X= NR_2, amides

These are the least reactive of the derivatives (towards nucleophiles) discussed so far because of the excellent delocalisation (N is less electro negative than O)



As the constituents of poly amides (ie peptides) these functional groups are essential parts of biological systems.

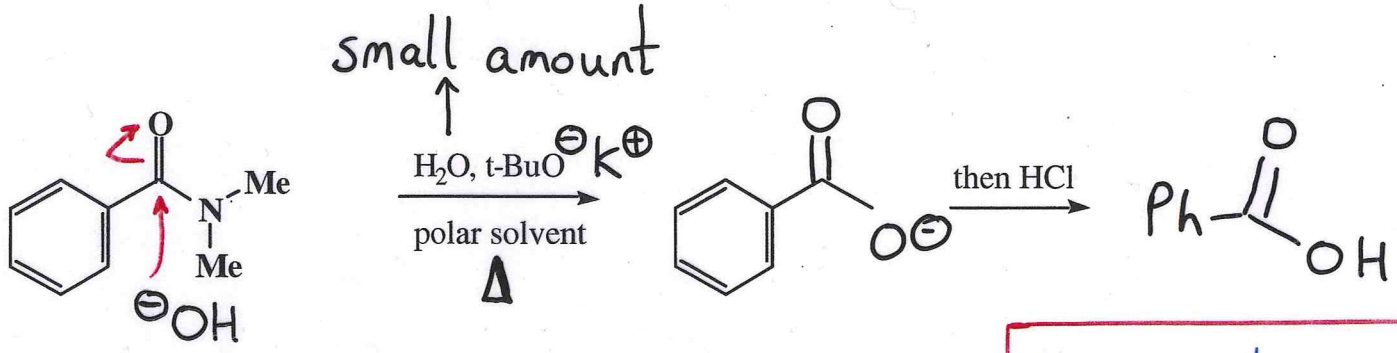
We can hydrolyse an amide bond in the laboratory, but require harsh acidic or basic conditions to do it

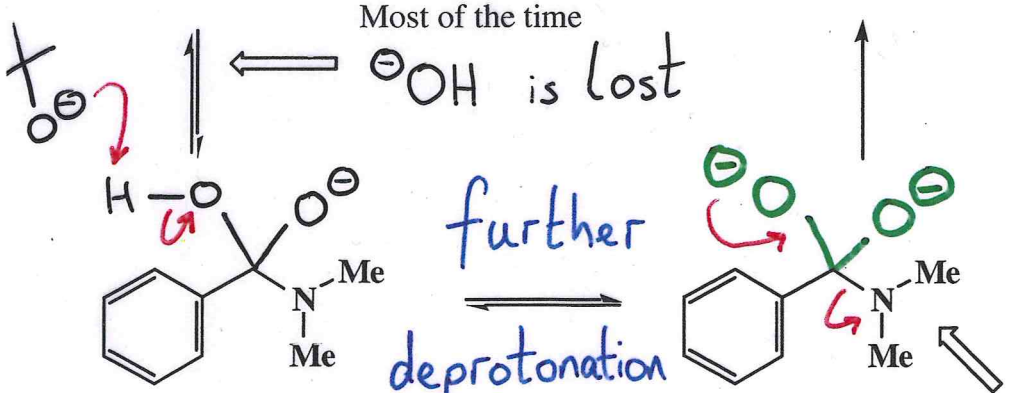


notice that one equivalent of acid is consumed in this reaction

c.f. acetal hydrolysis with catalytic $H^{\oplus}$

Generally, acid is better than base for hydrolysing amide, although strong bases such as $^tBuO^{\ominus}K^{\oplus}$ can do the hydrolysis.

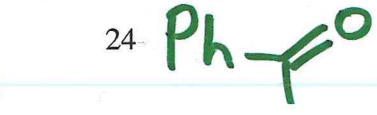




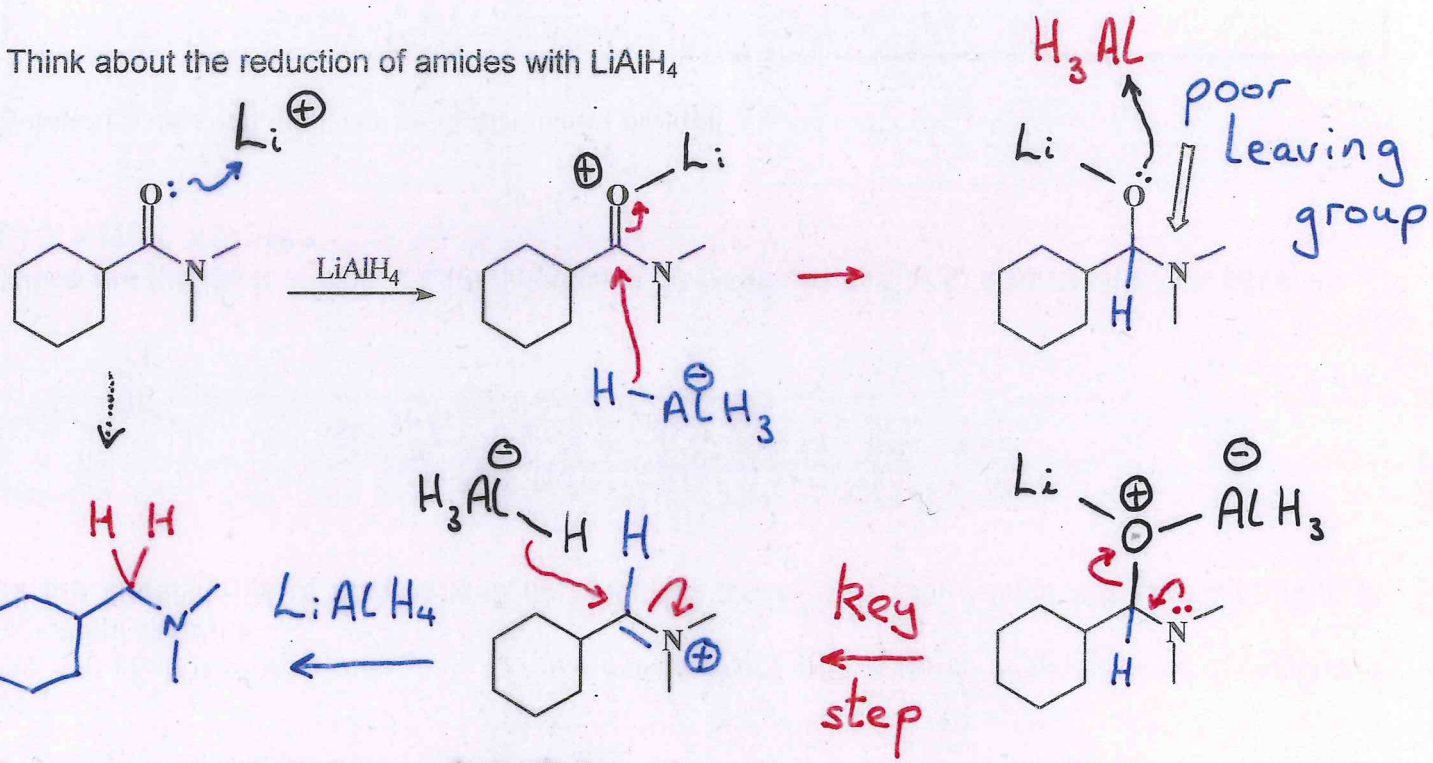
$H_2O + {}^tO^{\ominus} \rightleftharpoons HO^{\ominus} + {}^tOH$

This has no alternative but to leave as $Me_2N^{\ominus}$

compare with Cannizaro reaction

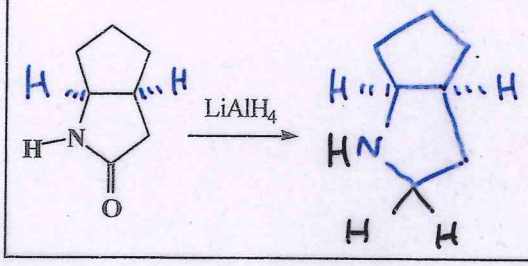


Think about the reduction of amides with $LiAlH_4$



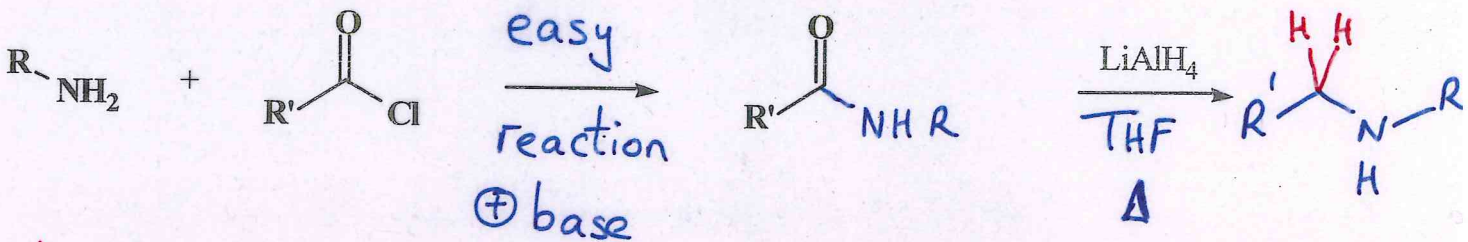
DEOXYGENATES AMIDES

Keystep in the synthesis of ramipril (hypertension)

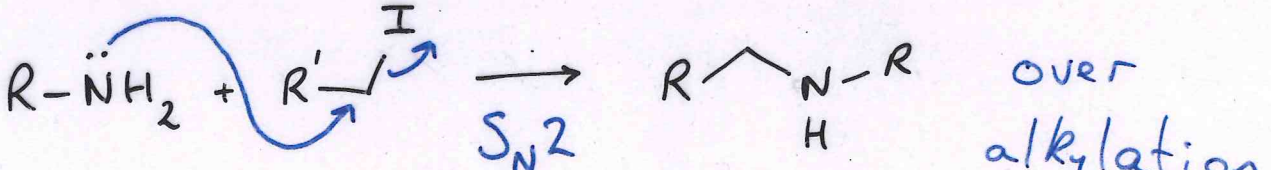


cyclic amide (lactam) is deoxygenated

A simple way of making substituted amines involves coupling of an acid chloride with an amine to give an amide, followed by



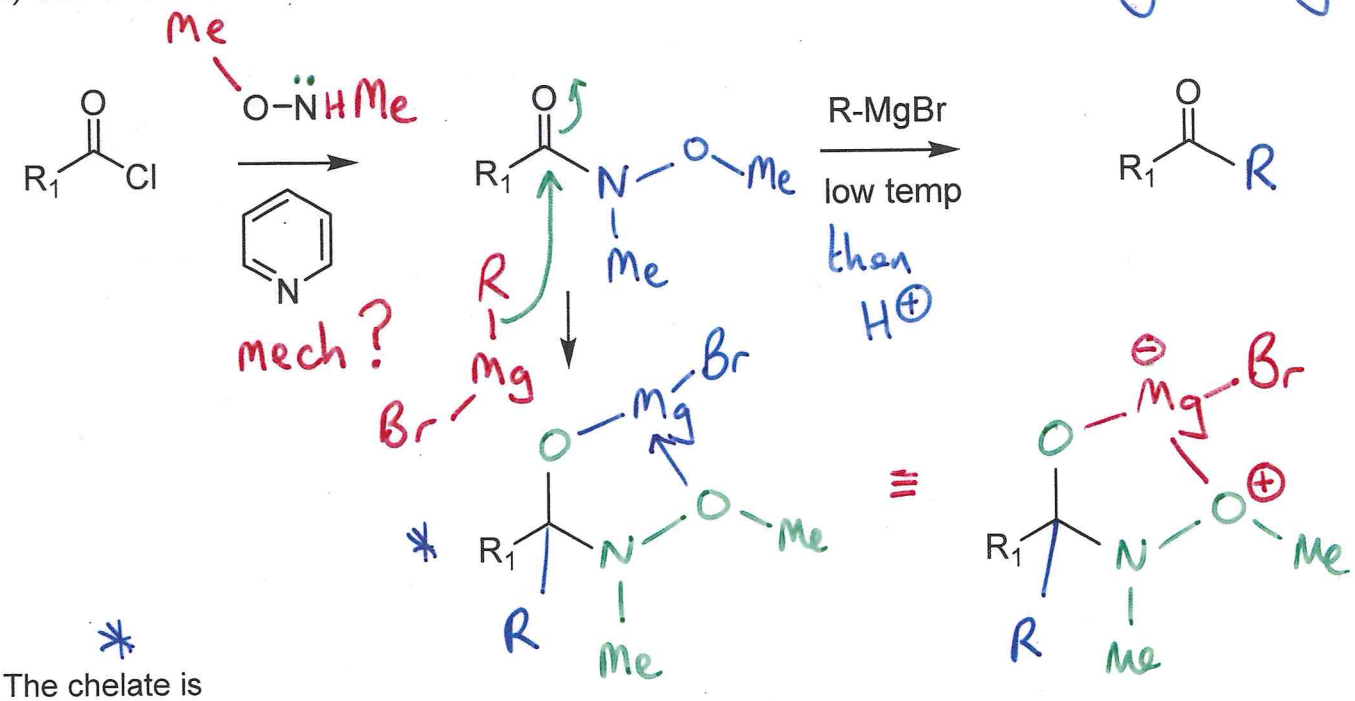
note: problems with



Now we can return to solution 3 for making ketones from addition to carbonyl compounds without over-reaction.

3) Use a Weinreb's amide

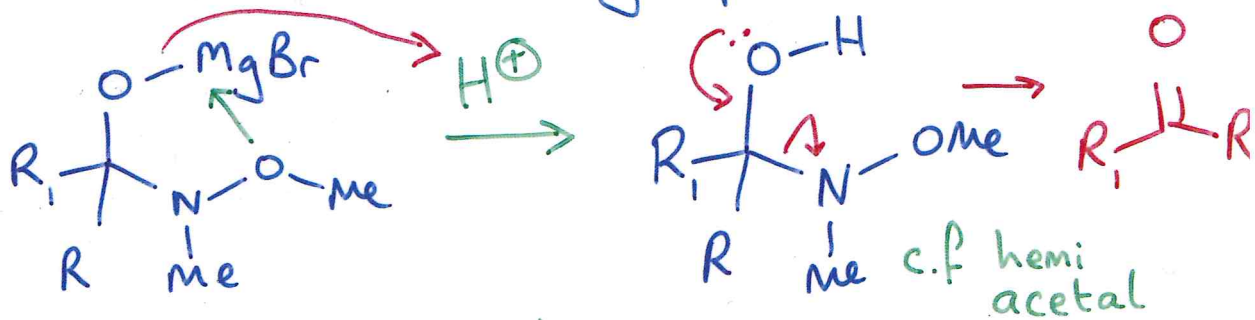
good yields



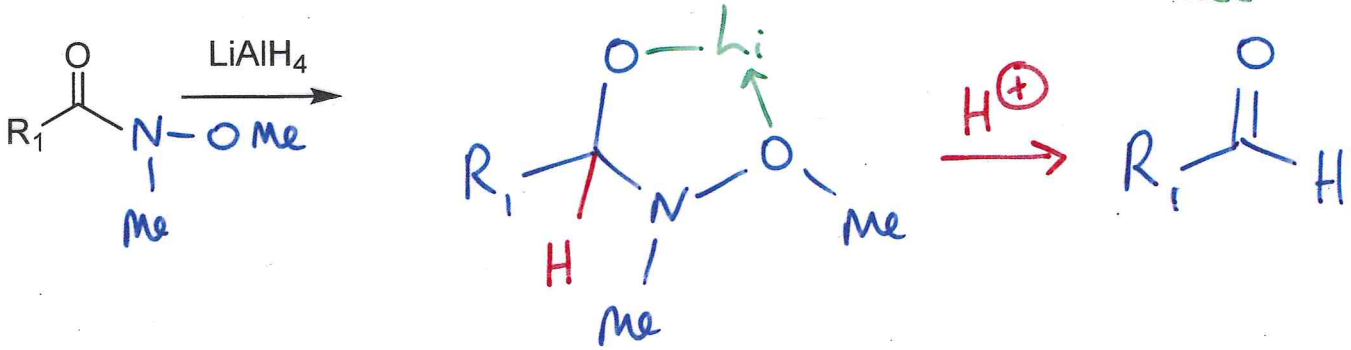
* The chelate is Stable

Doesn't collapse or react further

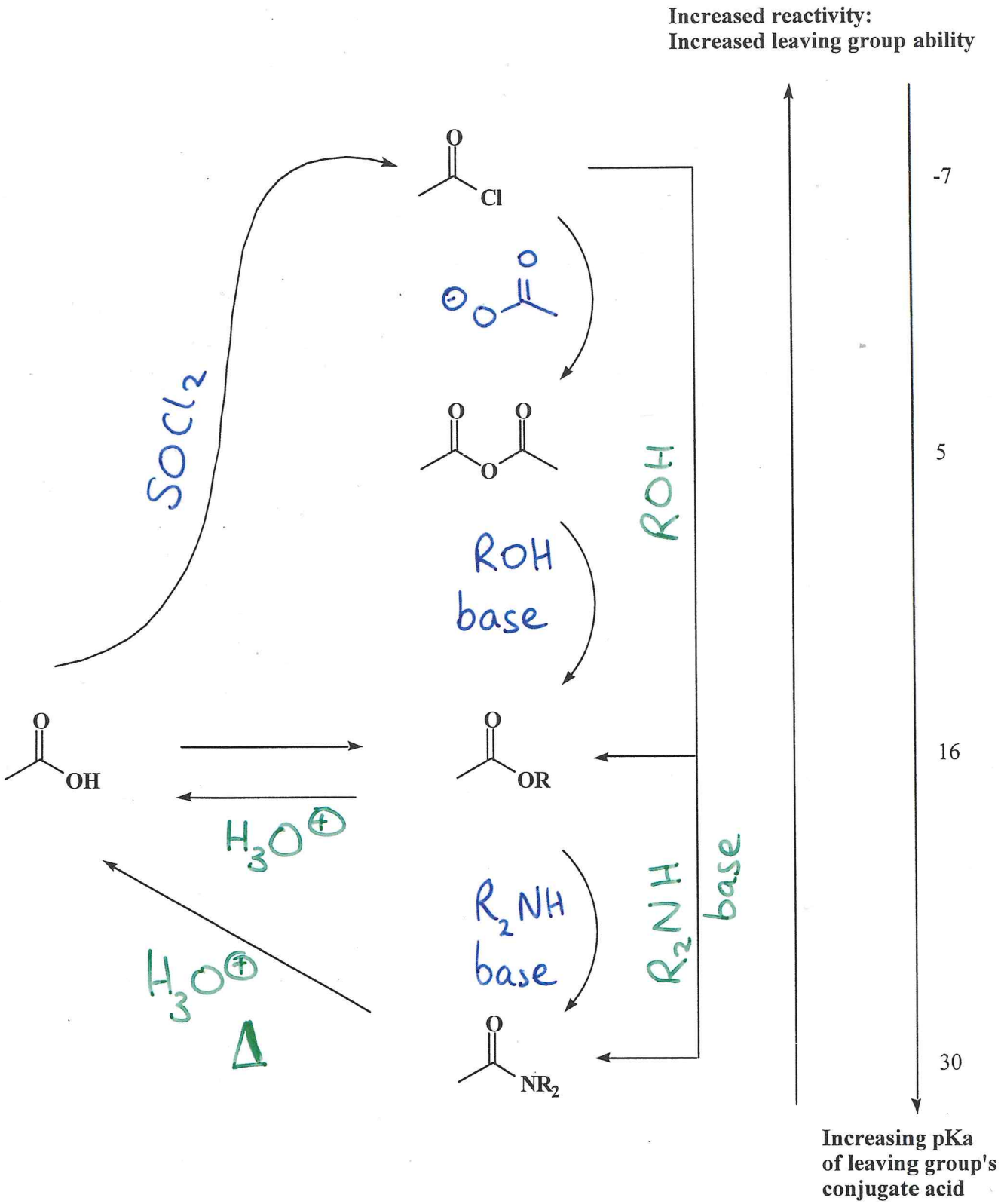
Quenching with acid destroys the chelate by protonation



Also c.f hemi acetal

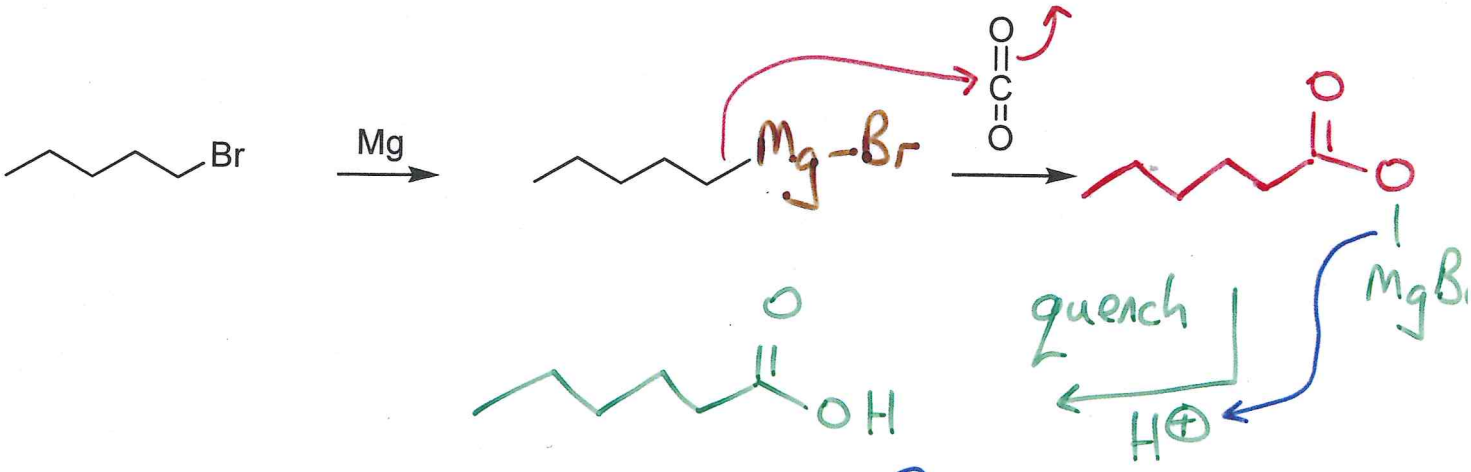


The following scheme says it all



Finally, note the central position that carboxylic acids have- they can be transformed into any other derivative

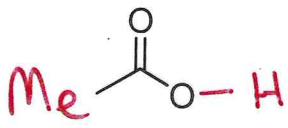
Recall methods for making carboxylic acids:



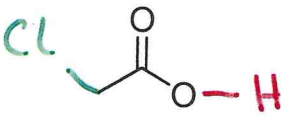
The pKa of a carboxylic acid can tell us a lot about the nature of the R group

Advanced reading: for a comprehensive list of pKa values for organic compounds (and more) see: *http://research.chem.psu.edu/brpgroup/pKa_compilation.pdf*

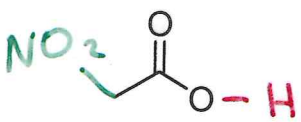
pKa



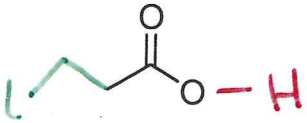
4.8



3



2



4.1

we can use pKa to probe the electron donating or withdrawing effects of the R group