

COMMONWEALTH OF AUSTRALIA

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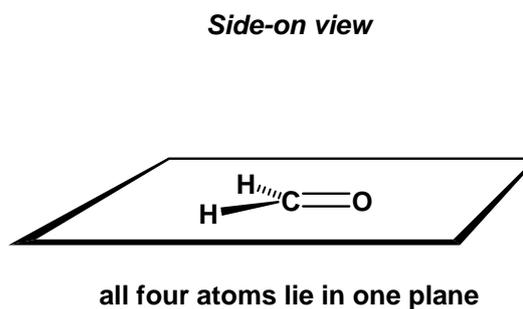
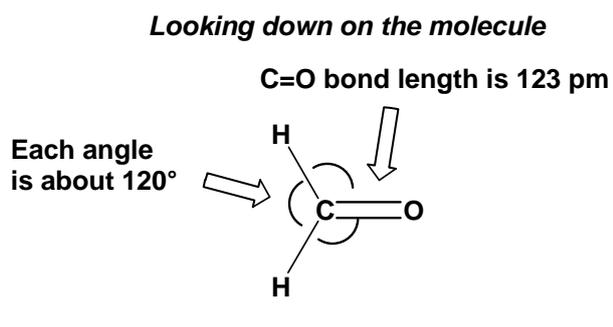
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Aldehydes and Ketones

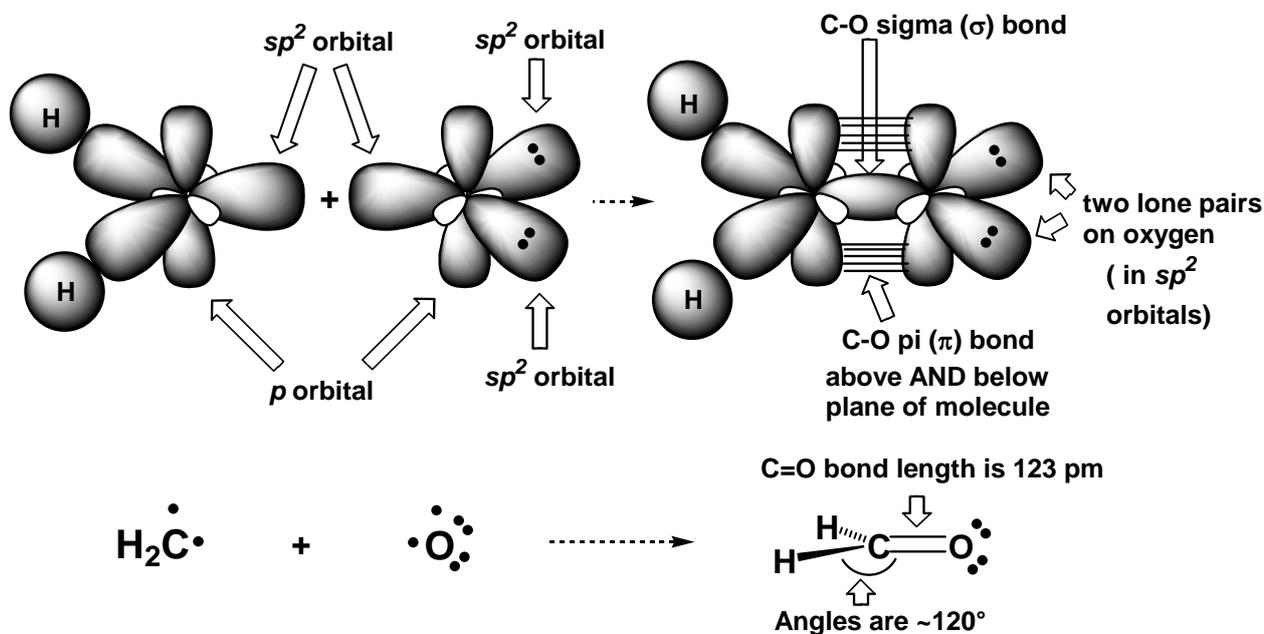
- Contain a C=O bond
- C of C=O is sp^2 -hybridised



formaldehyde



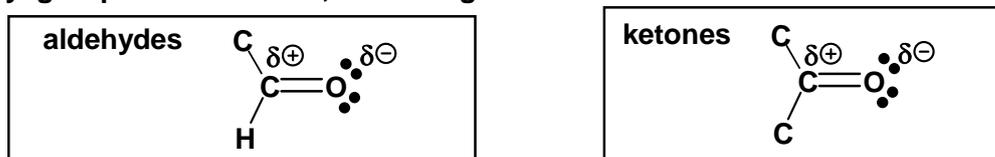
The bonding in formaldehyde



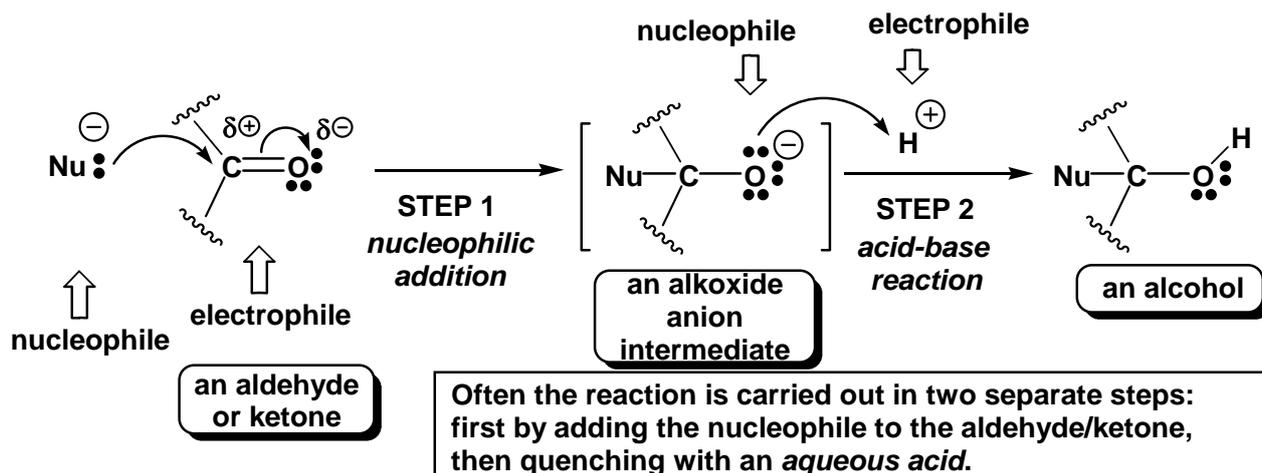
- No rotation about C=O bond of formaldehyde at RT.
- π bond weaker than σ bond due to less efficient orbital overlap.

"Simple" Nucleophilic Addition Reactions Of Aldehydes and Ketones.

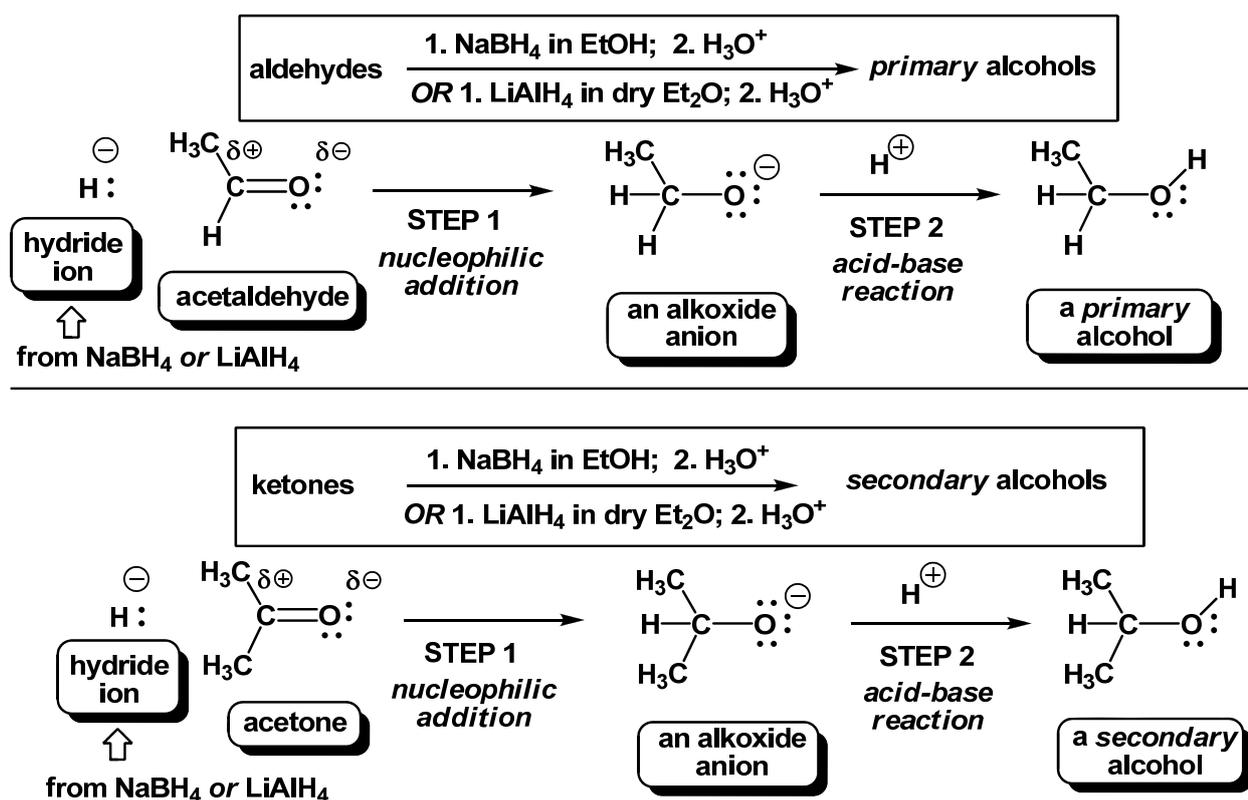
- Carbonyl group is strongly polarised.
- Carbonyl carbon has partial positive charge, ie. is electrophilic (so reacts with *nucleophiles*).
- Carbonyl group is unsaturated, so undergoes *addition* reactions.



Nucleophiles react with both aldehydes and ketones. General mechanism:



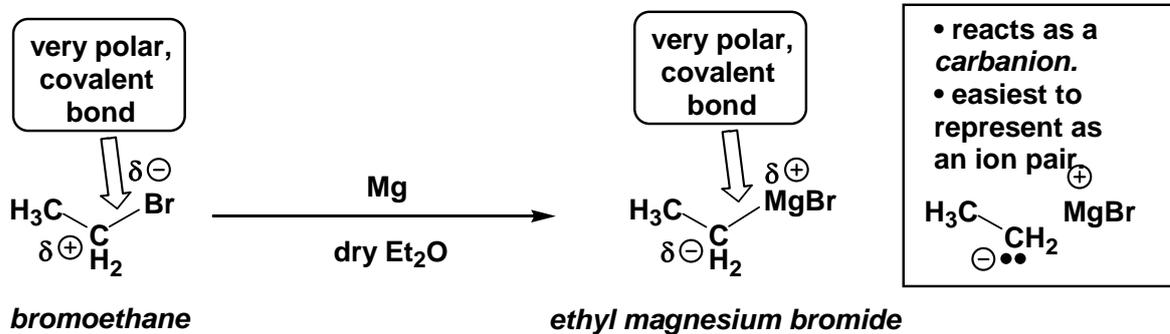
Reaction Of Aldehydes And Ketones With Hydride Reagents: *examples*



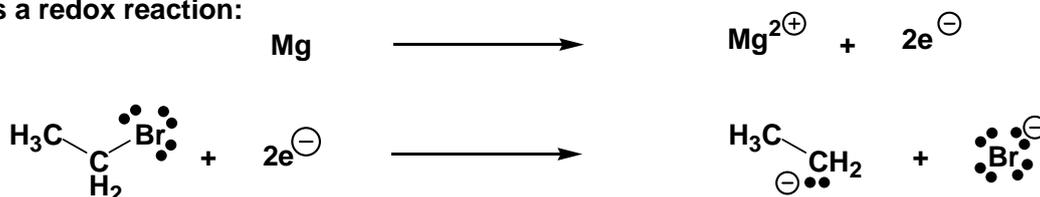
Grignard Reagents: *preparation*

• Alkyl halides and aryl halides react with magnesium metal in dry diethyl ether solvent to form *Grignard reagents*.

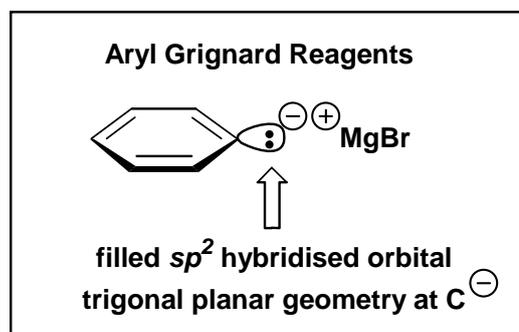
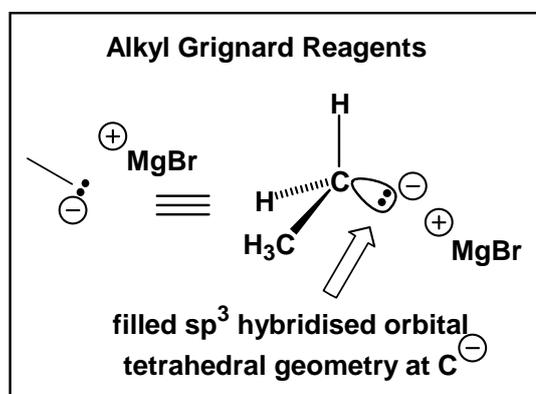
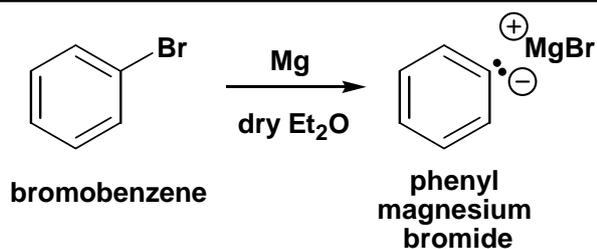
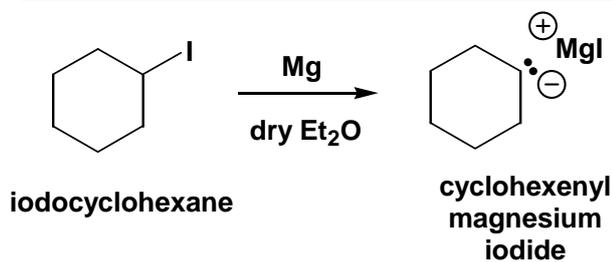
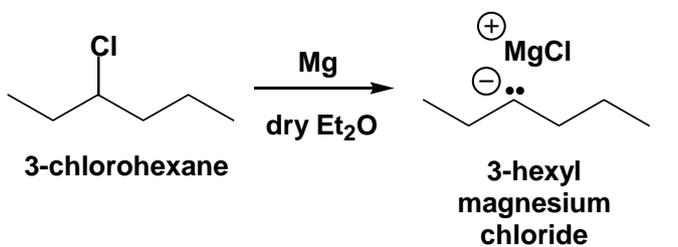
• Grignard reagents are organometallic compounds (contain carbon-metal bonds).



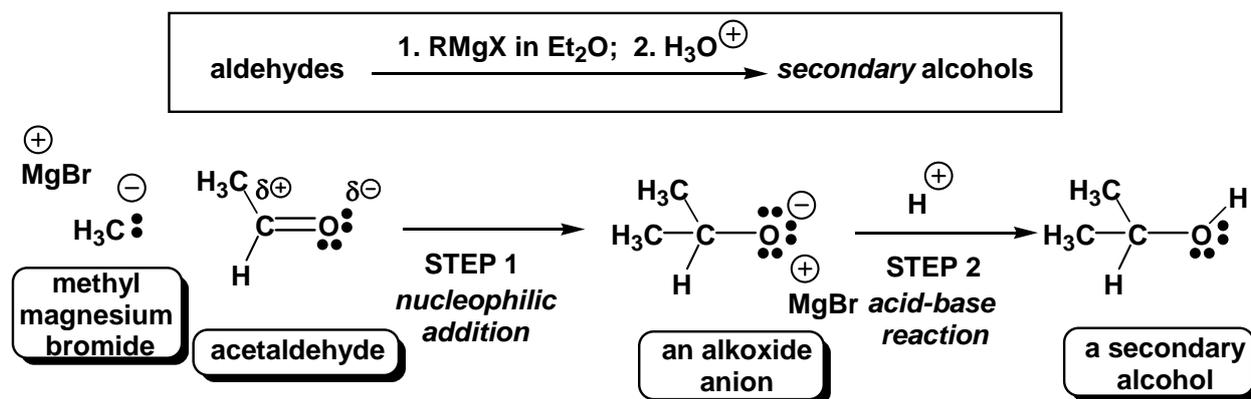
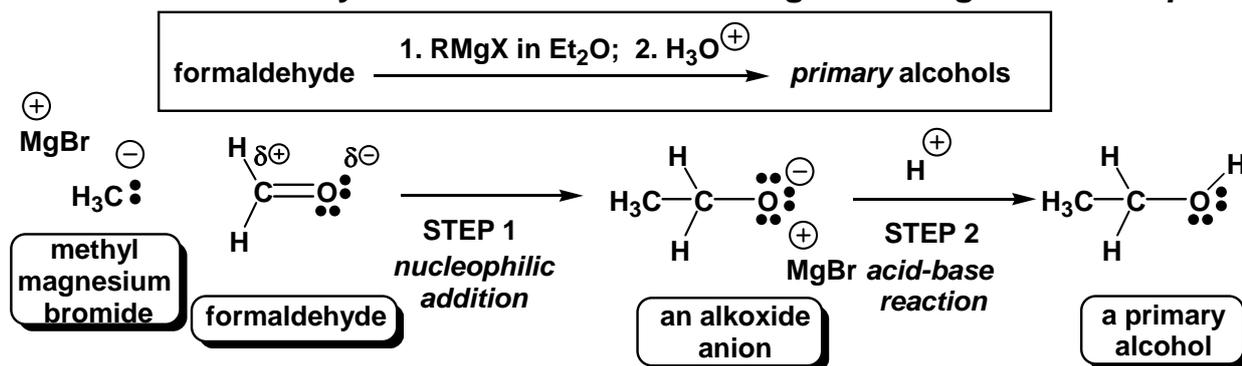
This is a redox reaction:



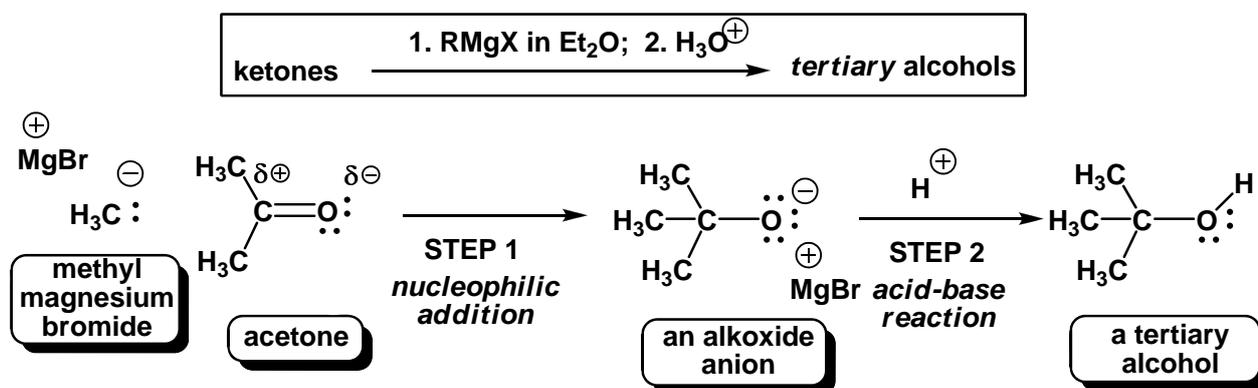
Grignard Reagents: *preparation*



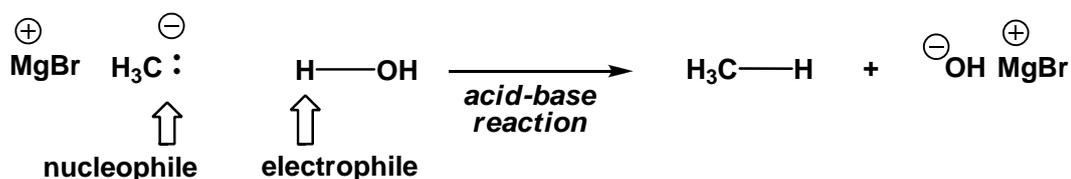
Reaction Of Aldehydes And Ketones With Grignard Reagents: *examples*



Reaction Of Aldehydes And Ketones With Grignard Reagents: *examples*

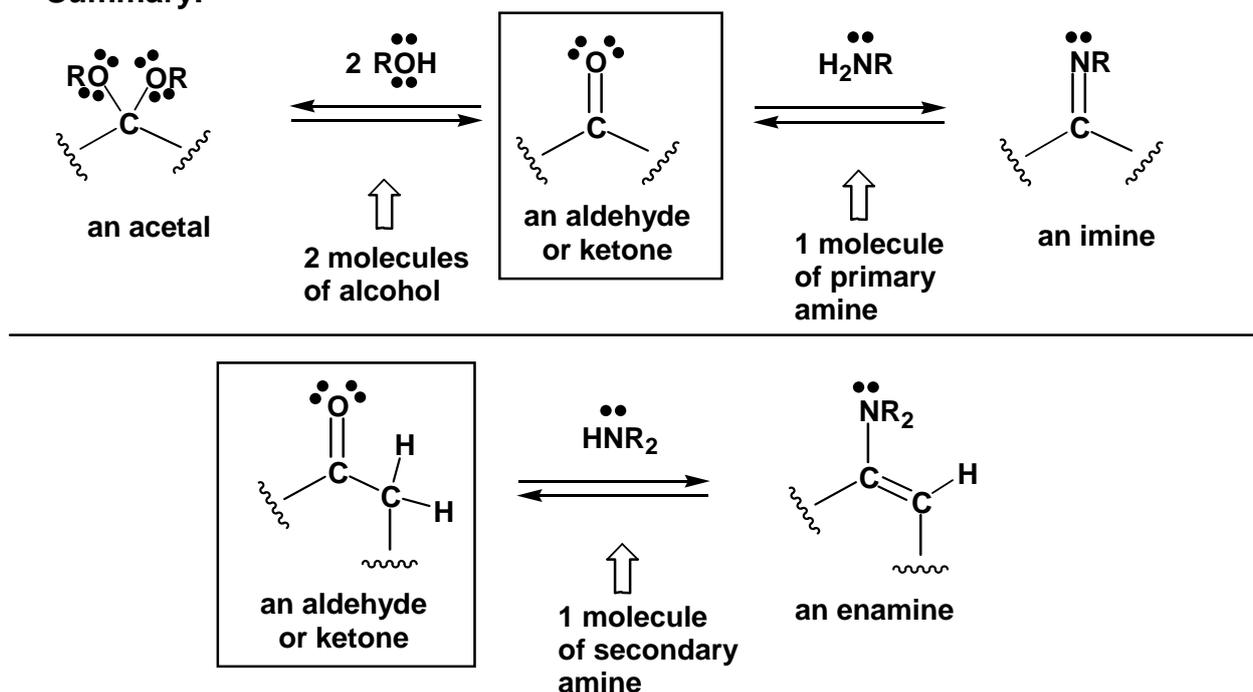


• Why dry Et_2O ?



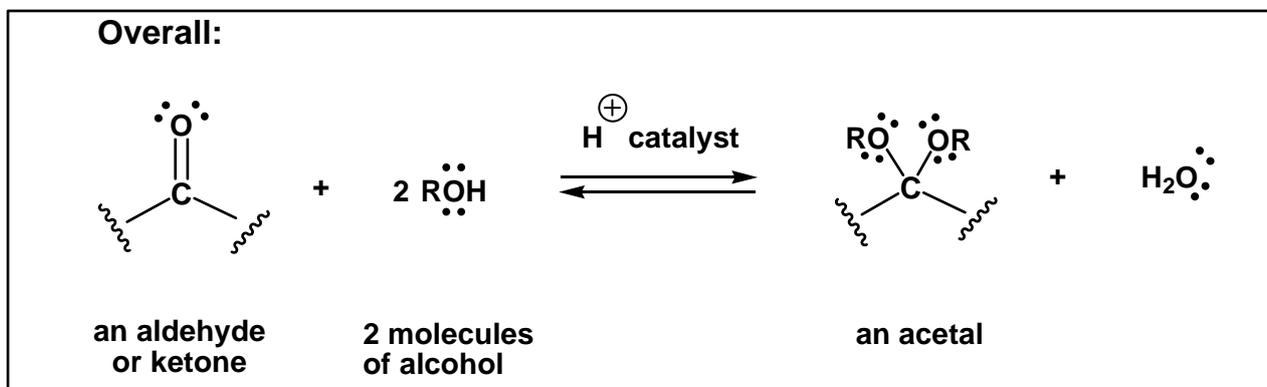
Nucleophilic Addition - Elimination Reactions Of Aldehydes and Ketones.

Summary:

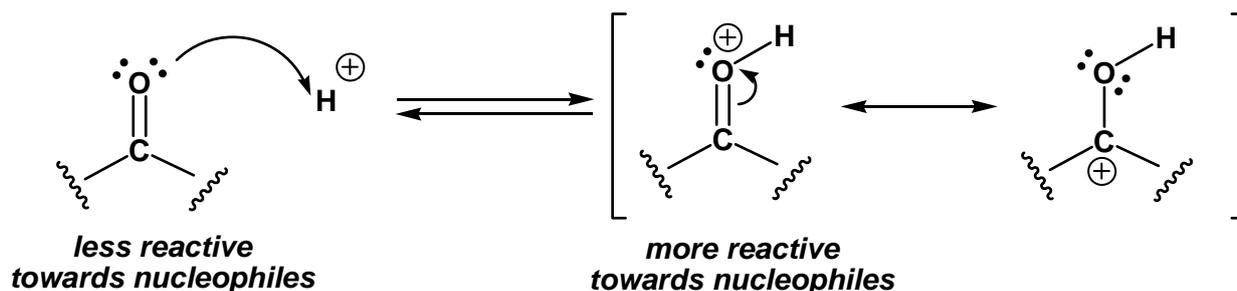


- All three reactions involve elimination of one molecule of water.
- All three reactions are catalysed by acids.

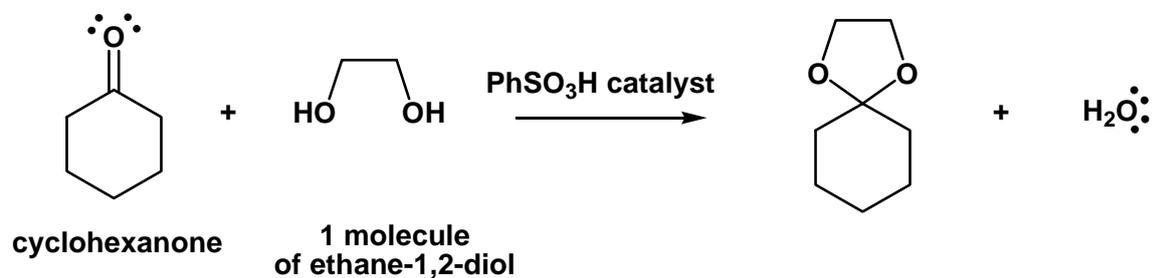
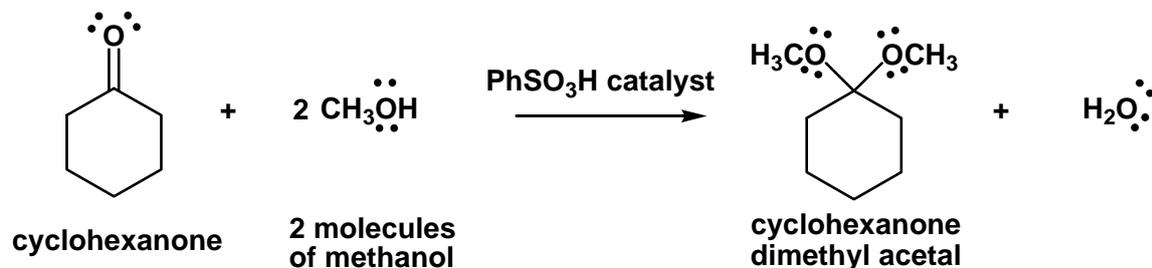
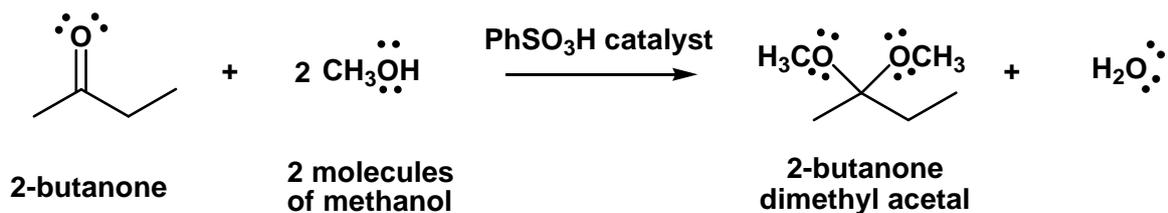
Acetal Formation



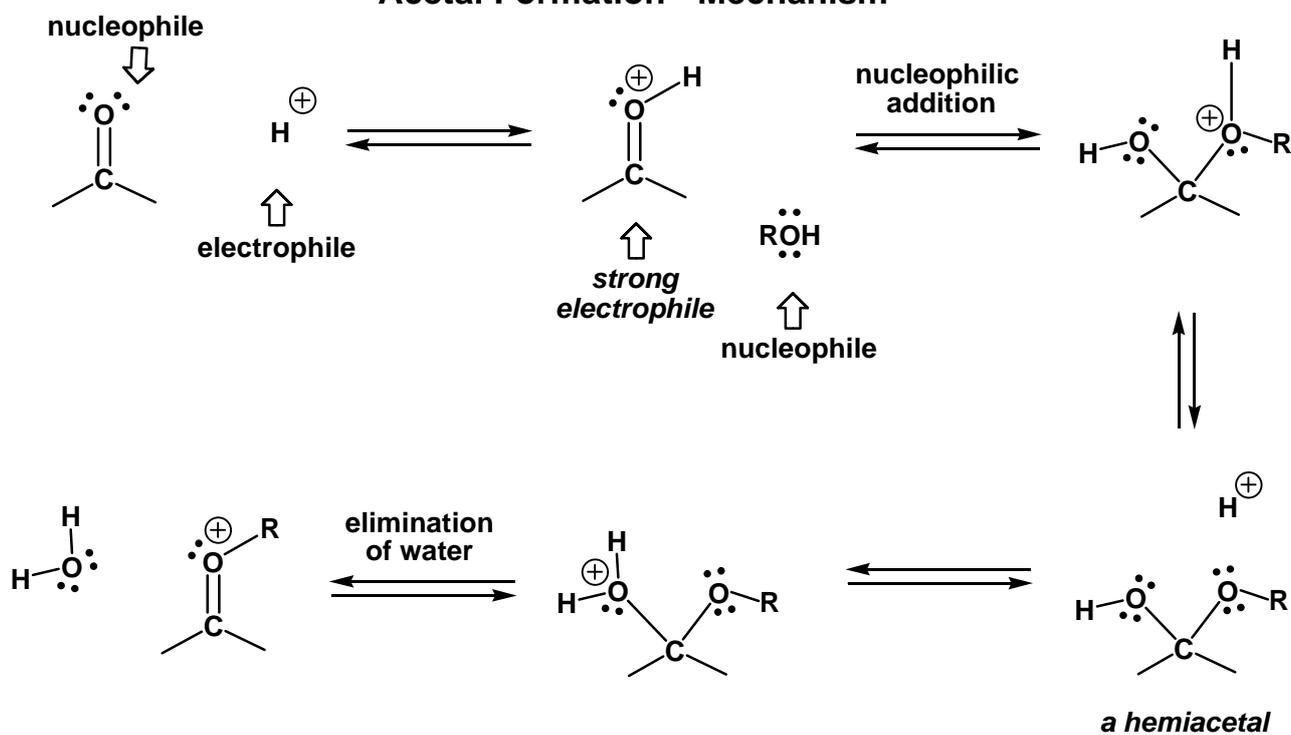
- Acetal functional group is very common in natural products (especially sugars).
- Acid catalyst activates the aldehyde/ketone - allows weak nucleophiles (such as alcohols) to react:



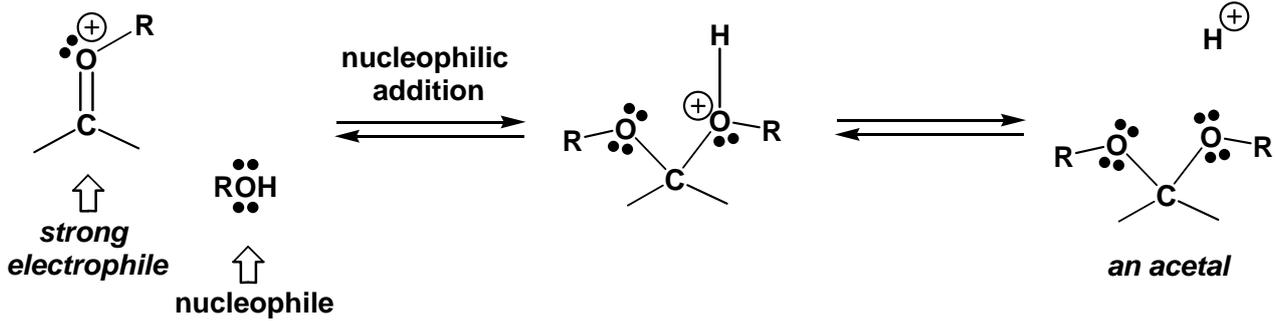
Acetal Formation - Examples:



Acetal Formation - Mechanism

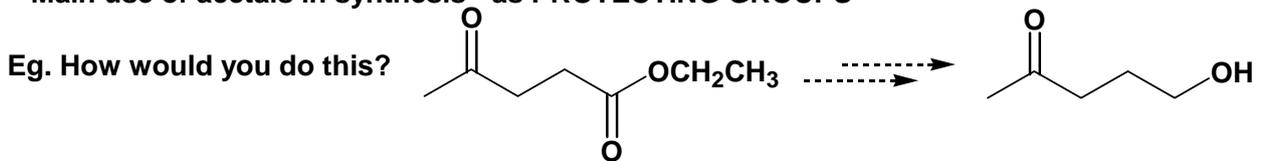


Acetal Formation - Mechanism

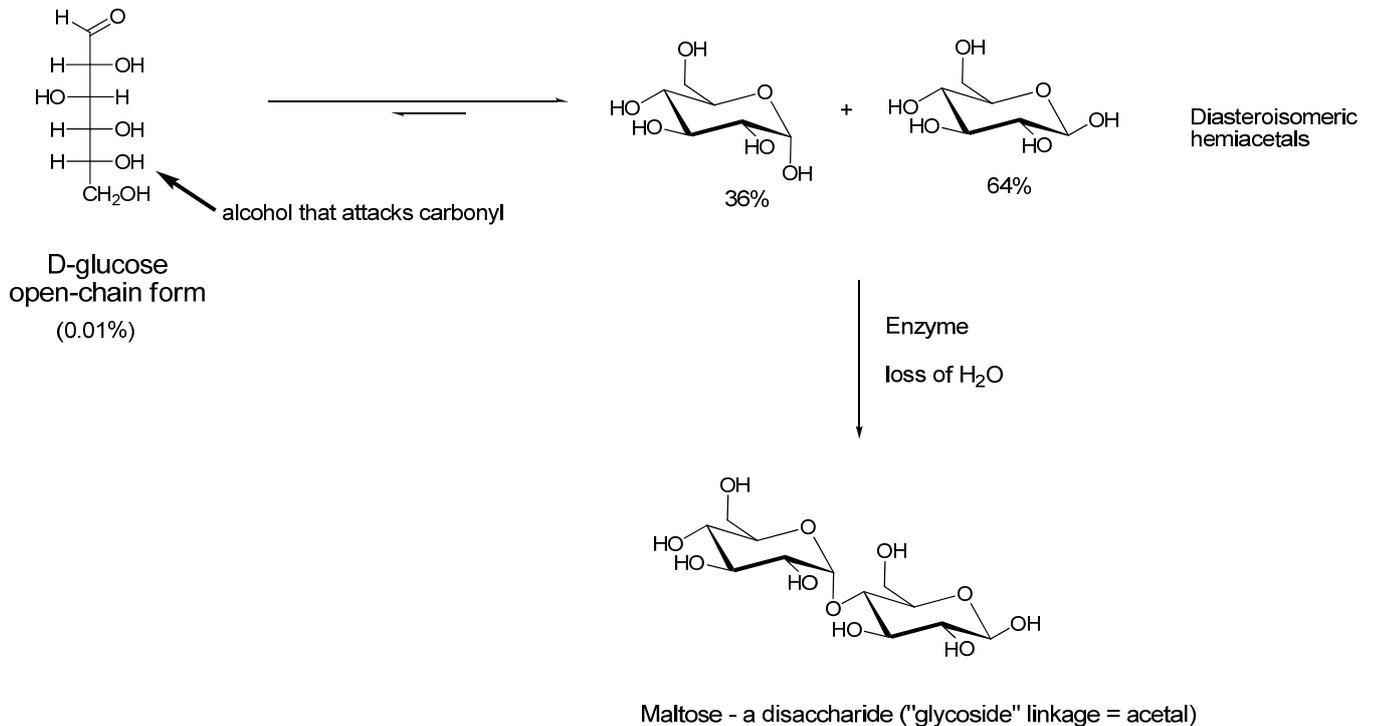


Notes:

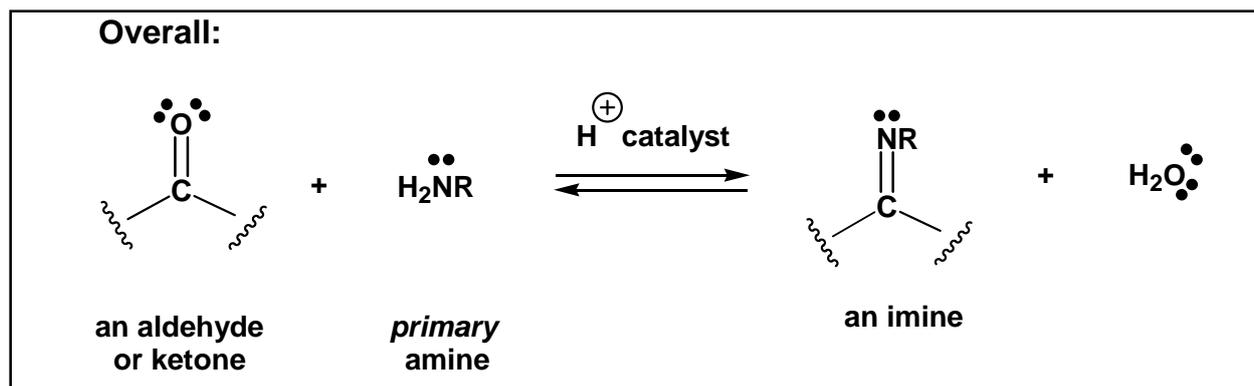
- Catalytic in acid (proton consumed in first step and produced in last step).
- Reversible reaction: drive forward reaction (from aldehyde/ketone to acetal) by removing water as it forms; drive backward reaction (from acetal to aldehyde/ketone) by mixing acetal with dilute aqueous mineral acid (eg. HCl, H₂SO₄)
- Main use of acetals in synthesis - as PROTECTING GROUPS



Hemiacetals and Acetals in Carbohydrates (Chem 2403)

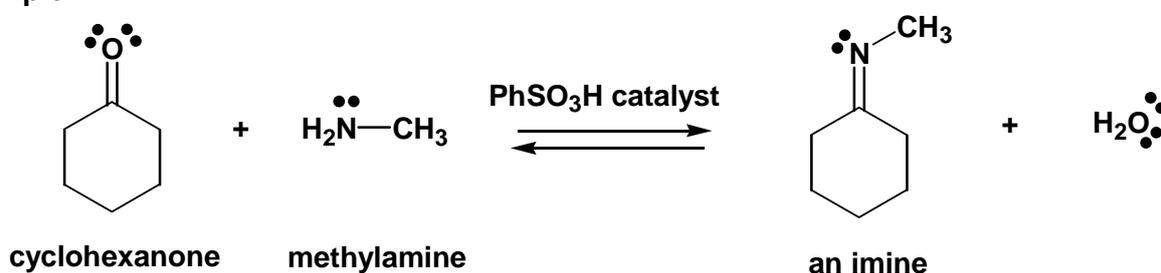


Imine Formation

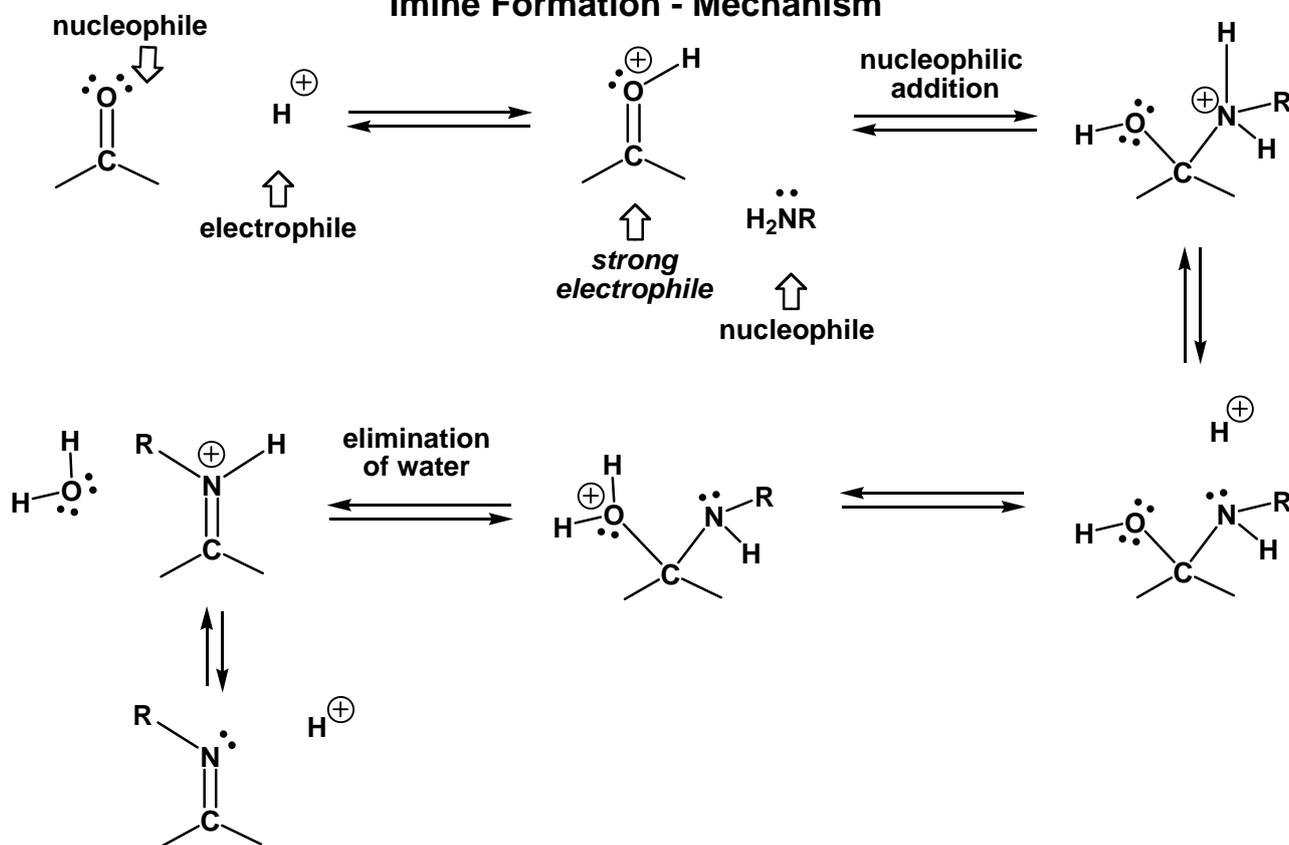


- Imine functional group is very important biologically, in organometallic/coordination chemistry, in synthetic organic chemistry and historically.
- Also known as "Schiff bases".

Example:

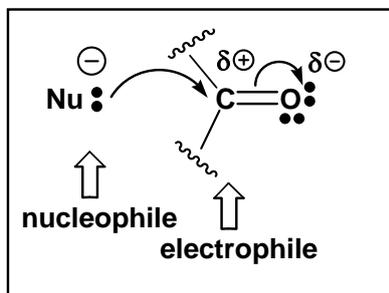
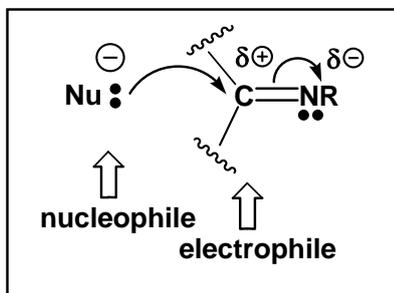


Imine Formation - Mechanism



Imines in Chemical Synthesis: amine formation

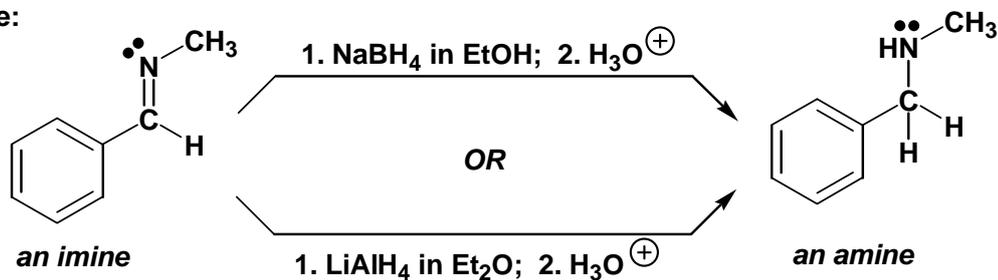
Imines react with strong nucleophiles in the same way as aldehydes/ketones!



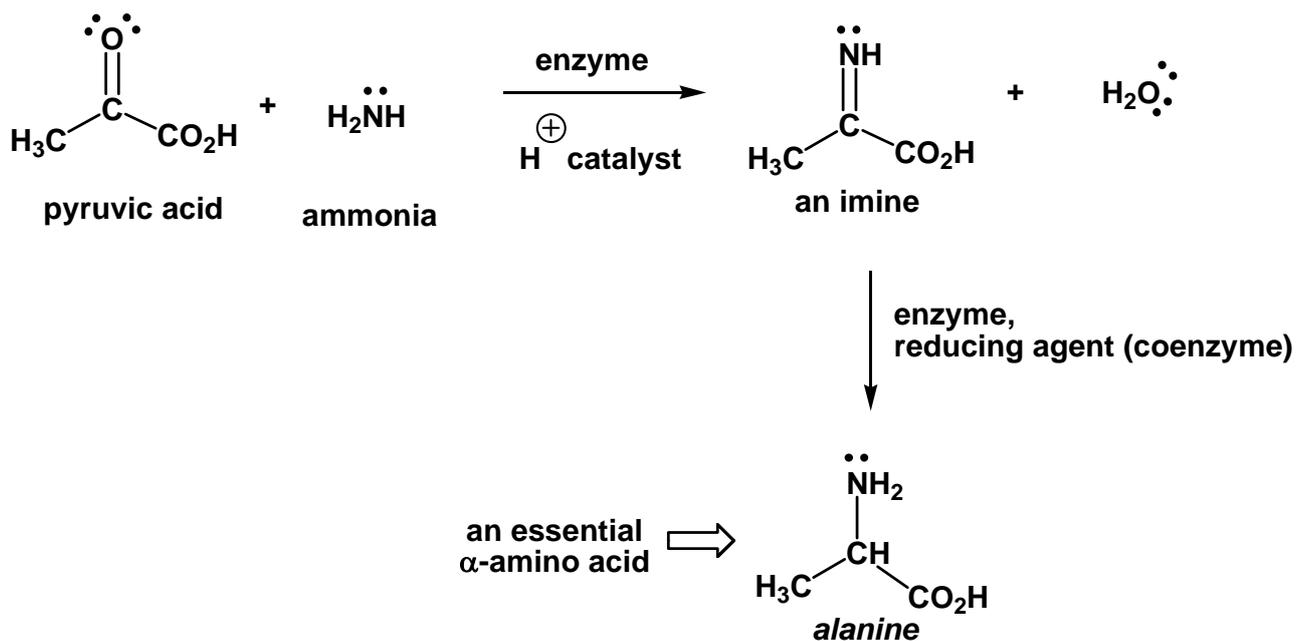
Where \ominus = \ominus / \ominus

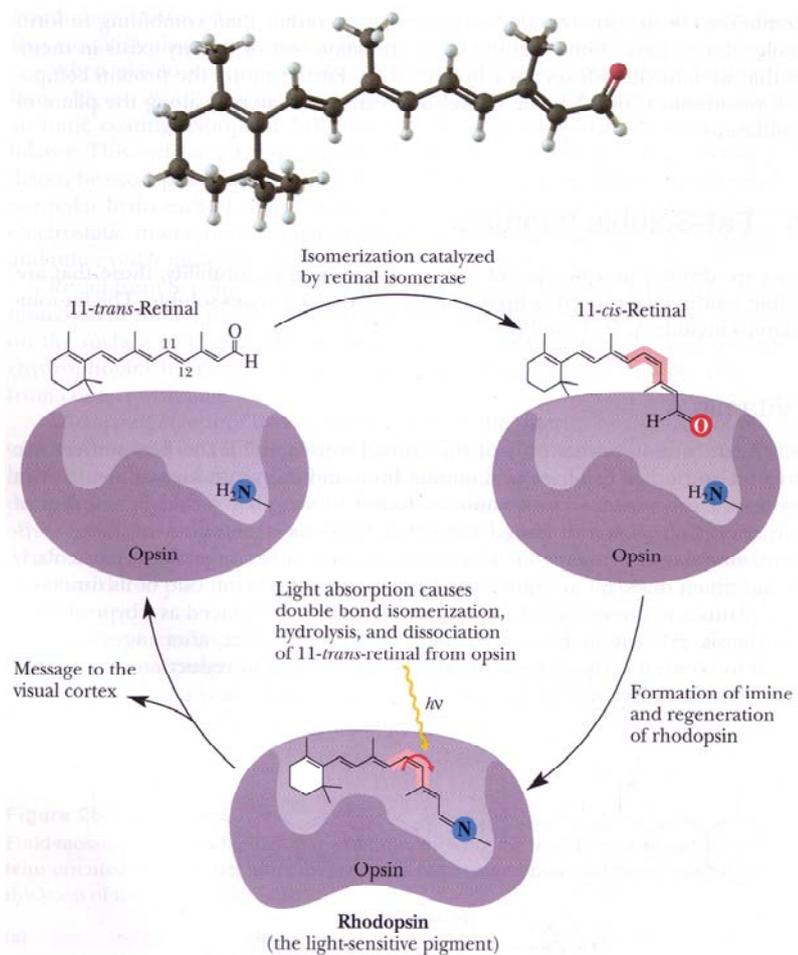
See "Simple Nucleophilic Addition Reactions Of Aldehydes and Ketones".

Example:



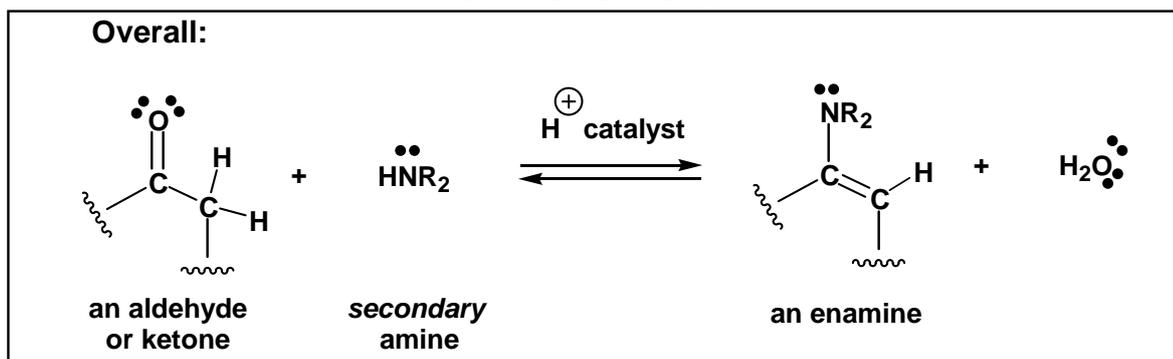
Imines in Biological Environments: amine formation





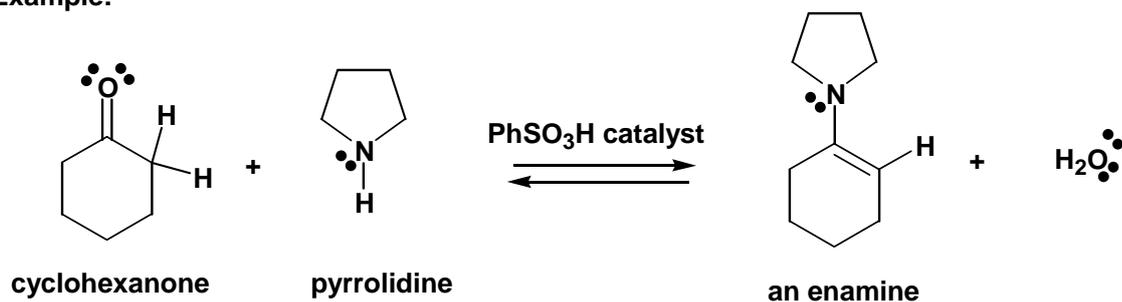
(Reproduced from *Introduction to Organic Chemistry*, W.H. Brown, Saunders College Publishing, 1997)

Enamine Formation

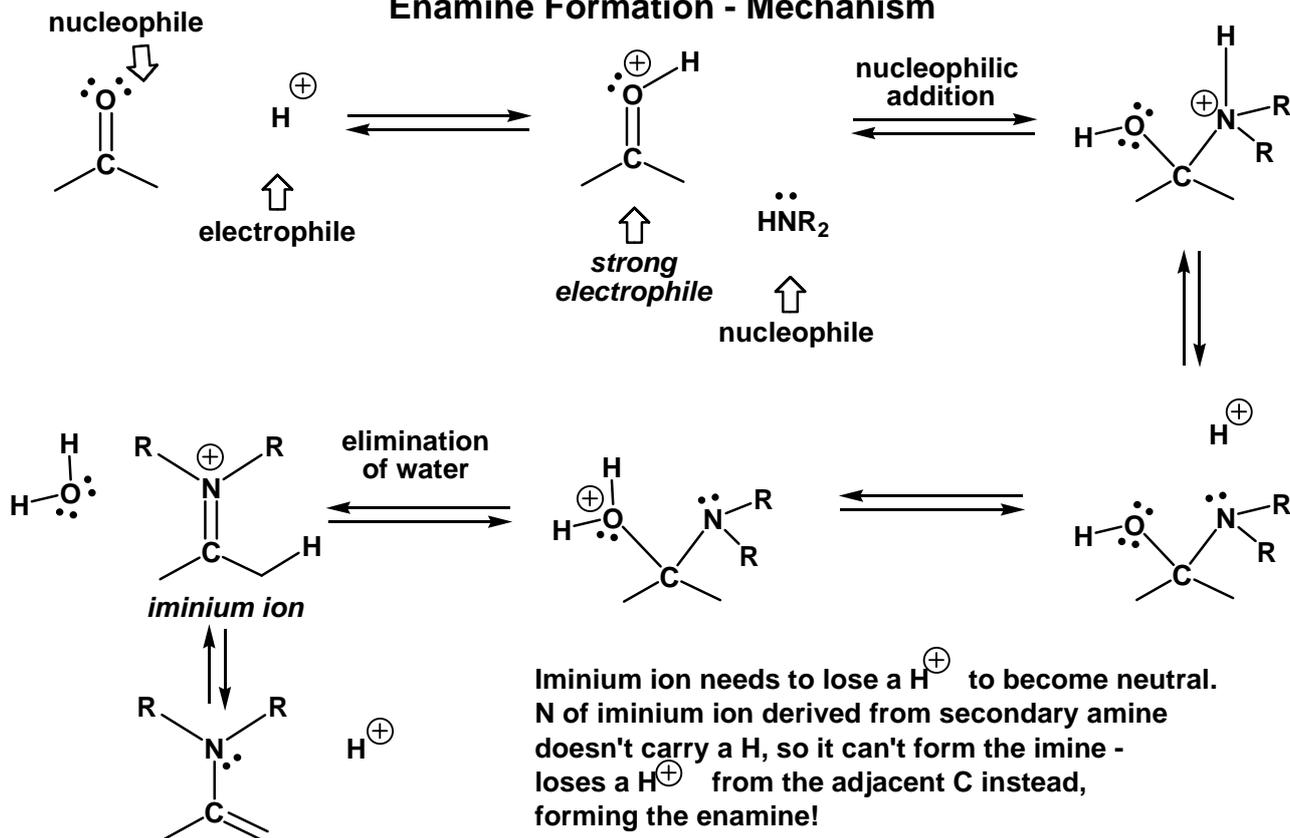


• Enamines are very important in C-C bond formation.

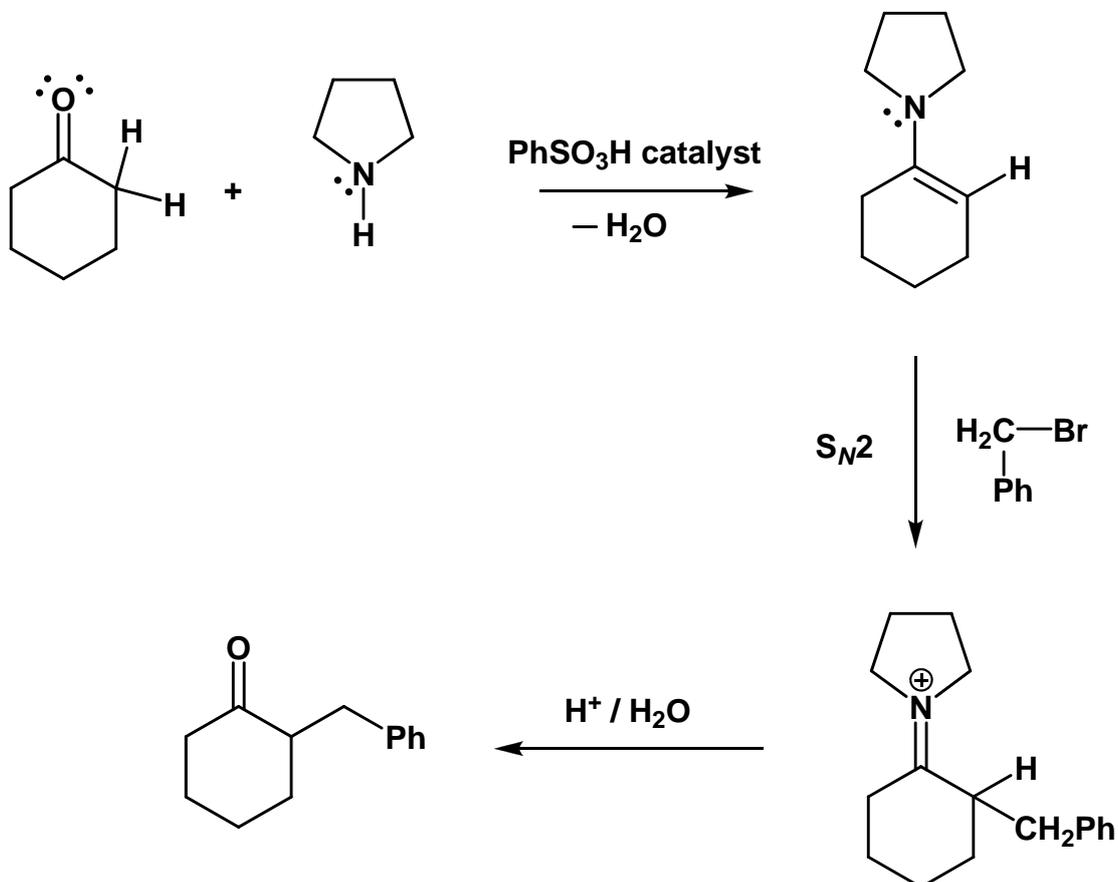
Example:



Enamine Formation - Mechanism

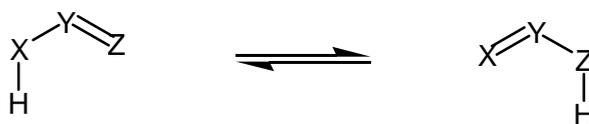


Enamines in Synthesis



TAUTOMERISM

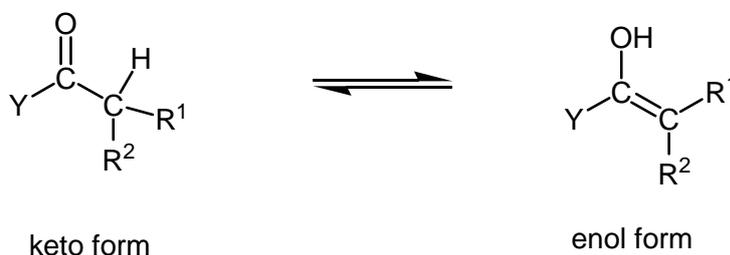
Tautomers are constitutional isomers that differ from one another through the rearrangement of a double bond and a hydrogen that is positioned α to the double bond:



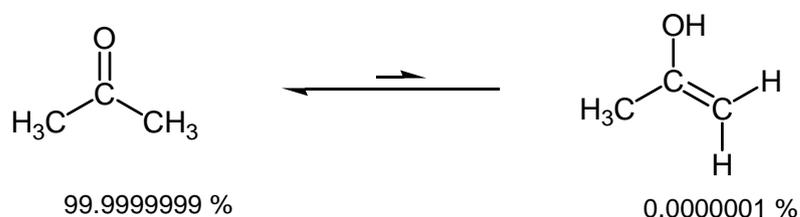
The interconversion of tautomers can be catalysed by acid or base and the position of equilibrium is determined by the relative stability of the isomers.

Keto–Enol Tautomerism

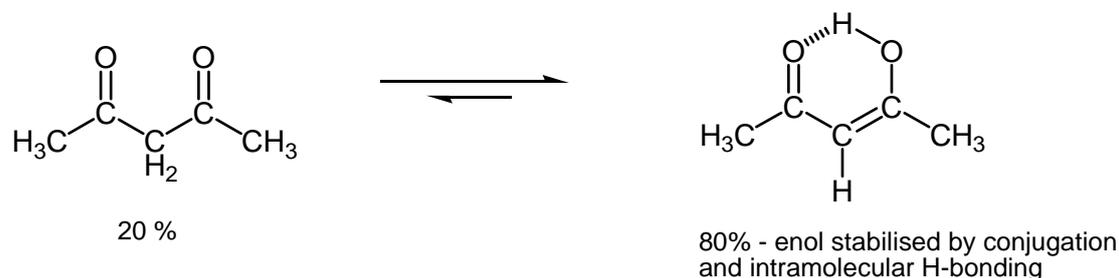
Carbonyl compounds [aldehydes, ketones, carboxylic acids and acid derivatives (esters, amides, etc.)] with at least one α -hydrogen can exist in either *keto* or *enol* tautomeric forms:



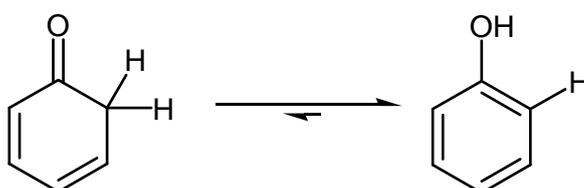
For the vast majority of carbonyl compounds the keto form is greatly preferred:



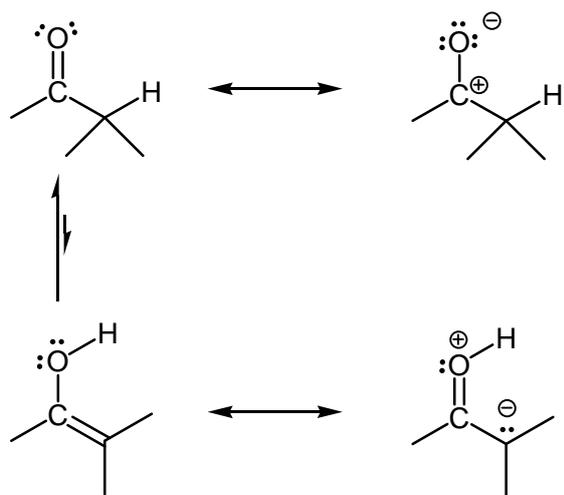
However, in some cases the enol form is favoured:



An extreme case:

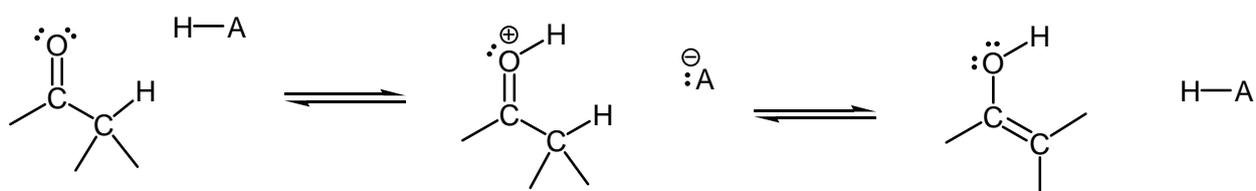


Reactivity of Keto and Enol Tautomers

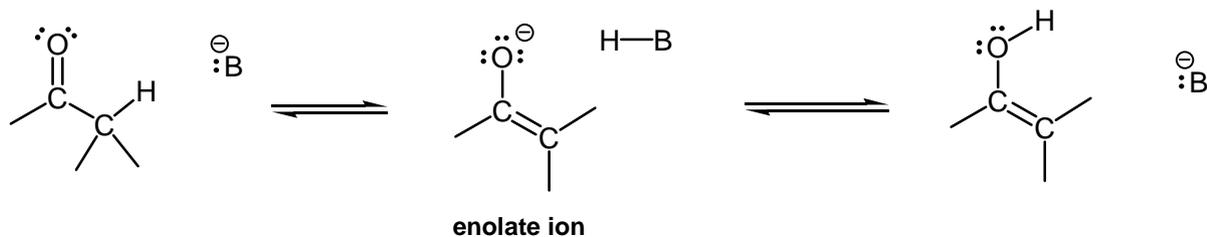


Provided the equilibration of keto and enol forms is rapid, an α -H in carbonyl compounds can be substituted with an electrophile *via* reaction of the enol form (or enolate ion under basic conditions).

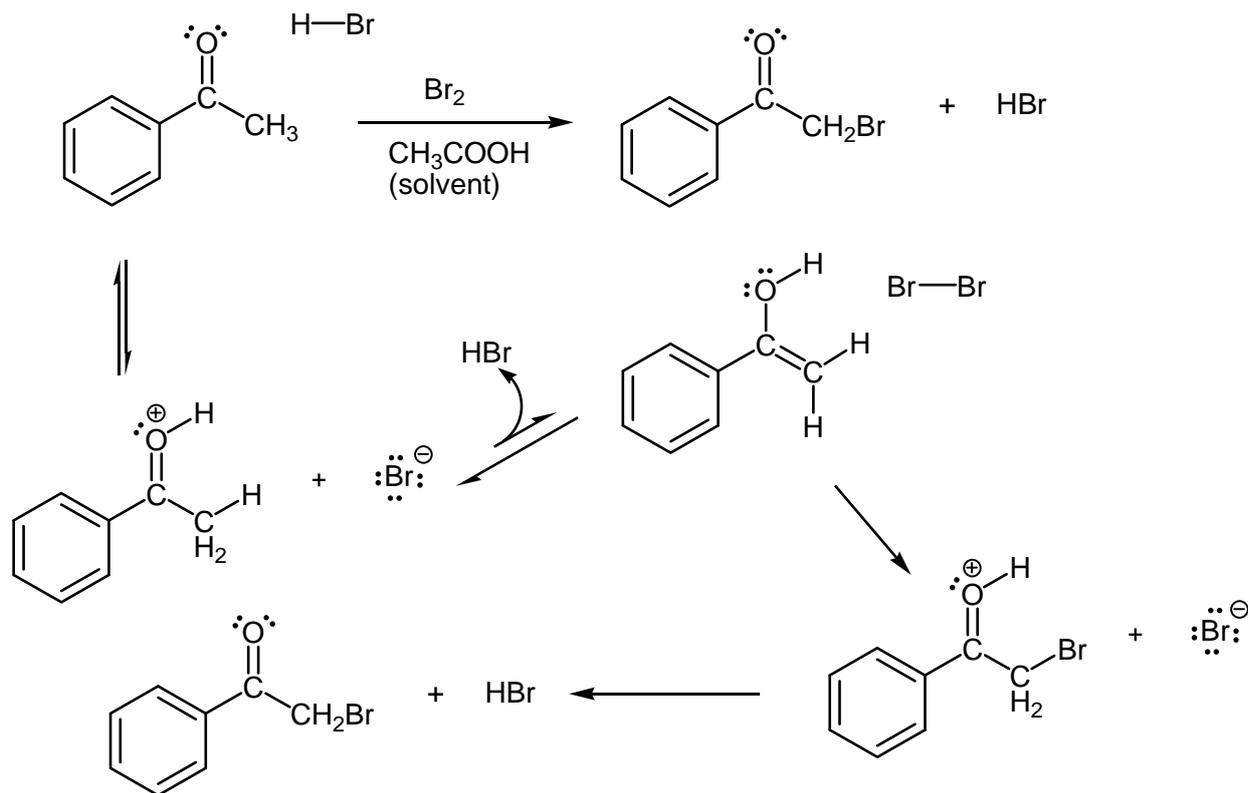
Acid-Catalysed Keto-Enol Interconversion



Base-Catalysed Keto-Enol Interconversion

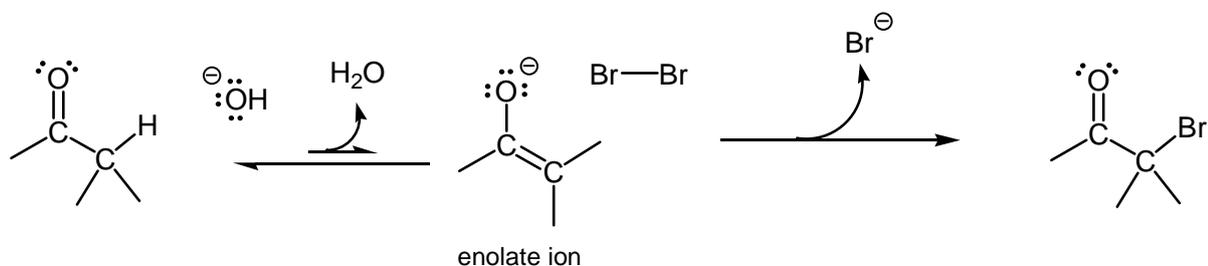


Acid-Catalysed α -Halogenation of Aldehydes and Ketones

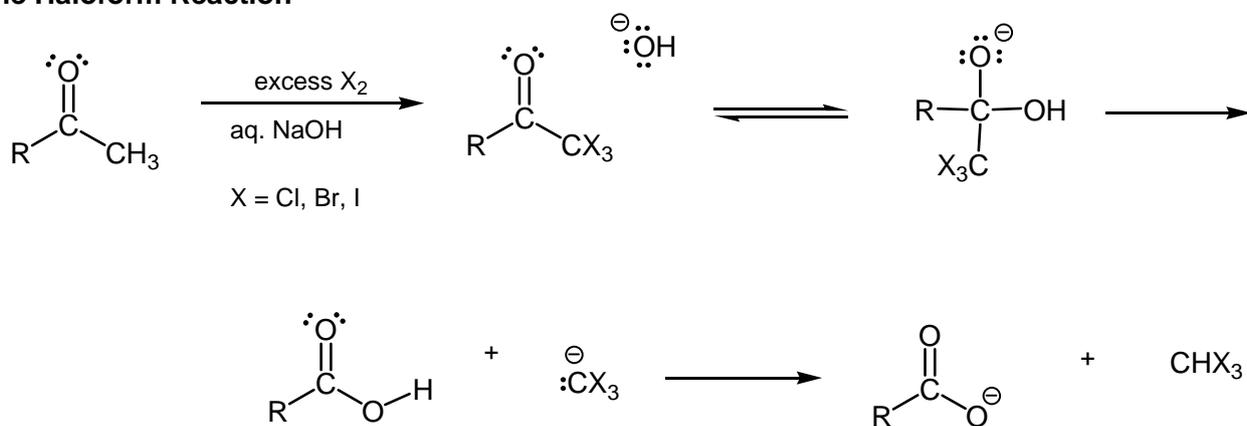


NB: reaction is "auto-catalytic" in HBr

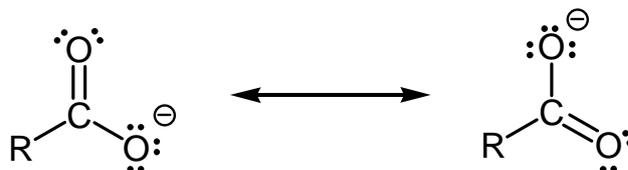
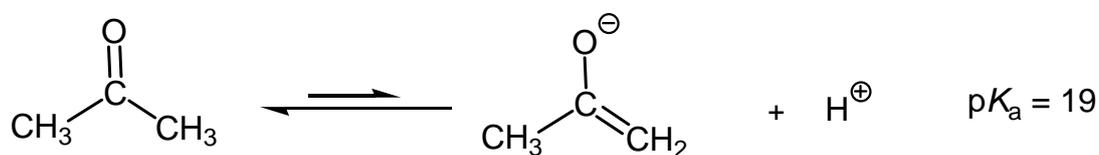
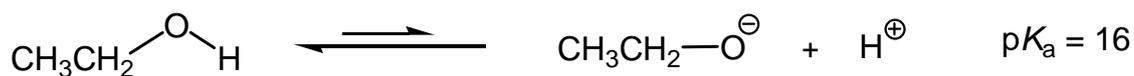
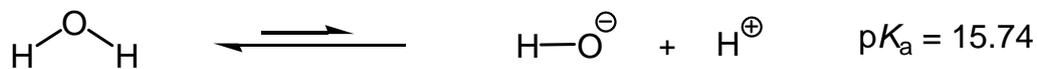
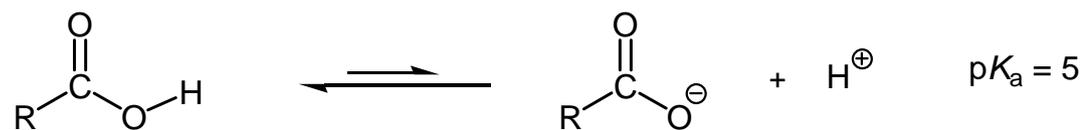
Base-Catalysed α -Halogenation of Aldehydes and Ketones



The Haloform Reaction



Acidity of α -Hydrogens in Carbonyl Compounds



Equivalent resonance contributors

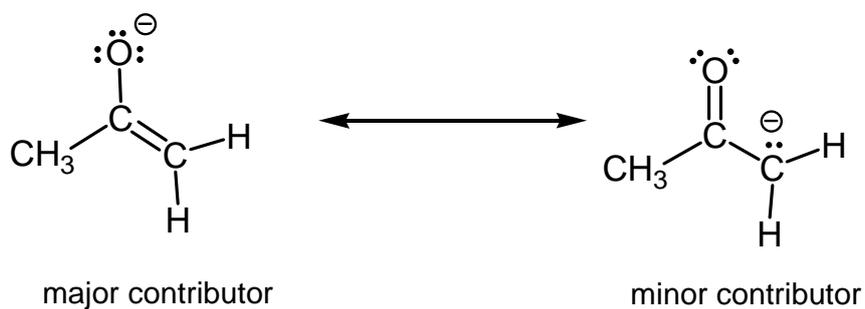
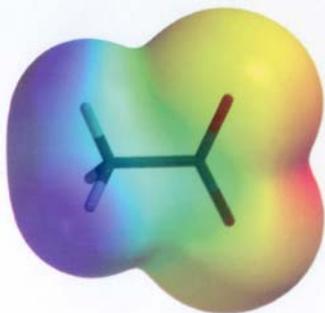
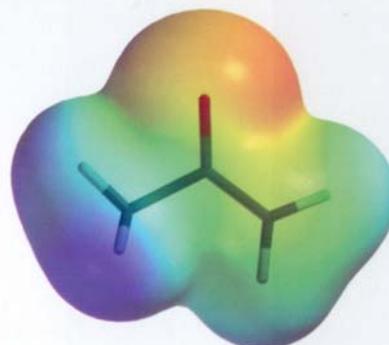
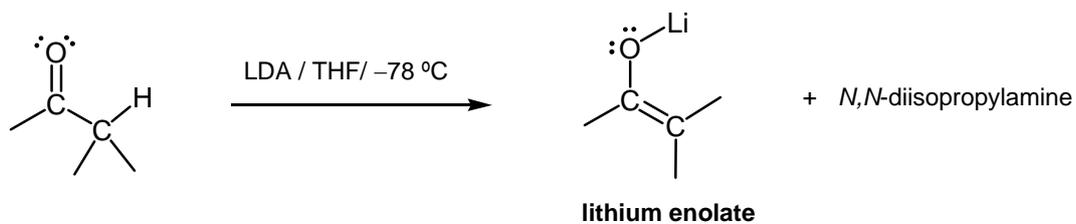
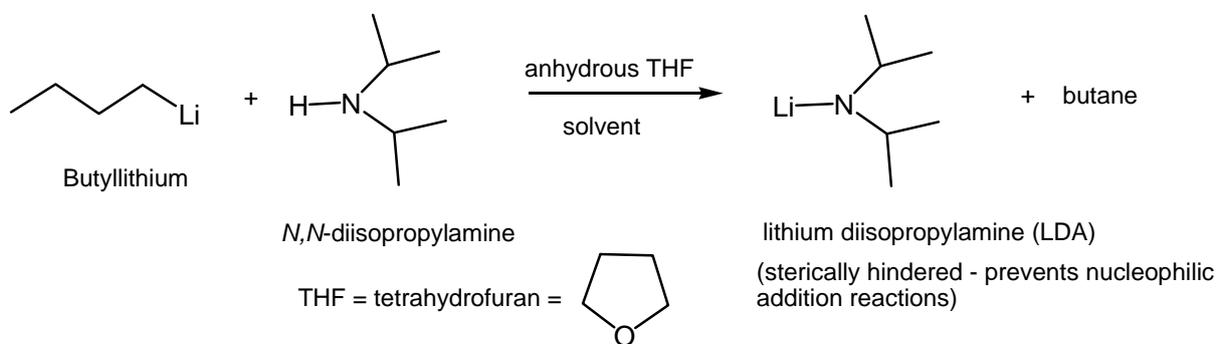


Figure 2.4

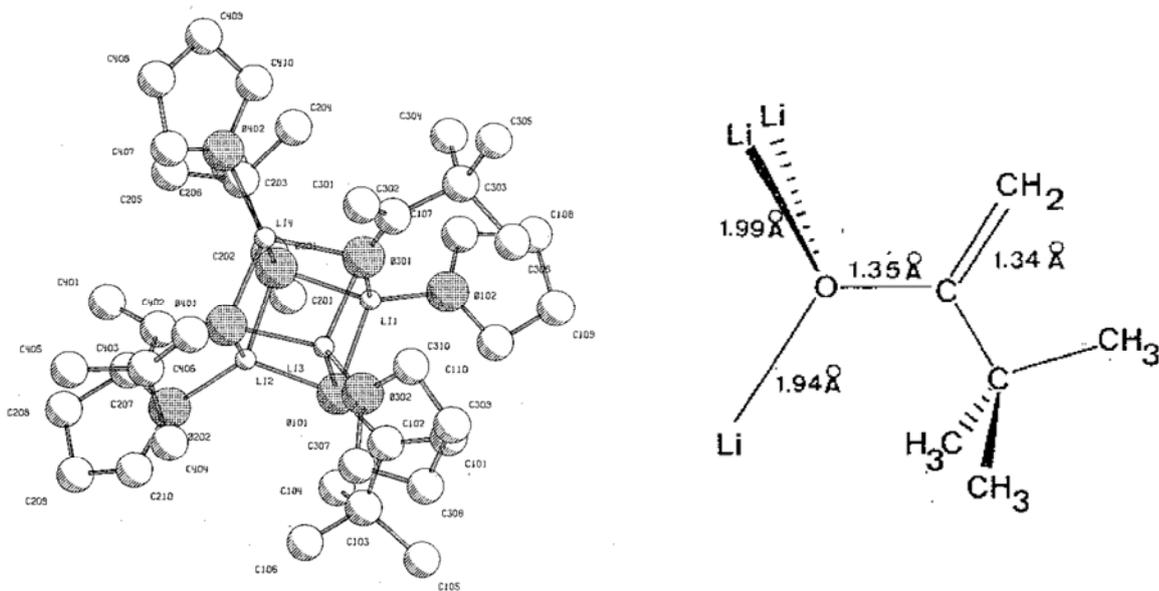
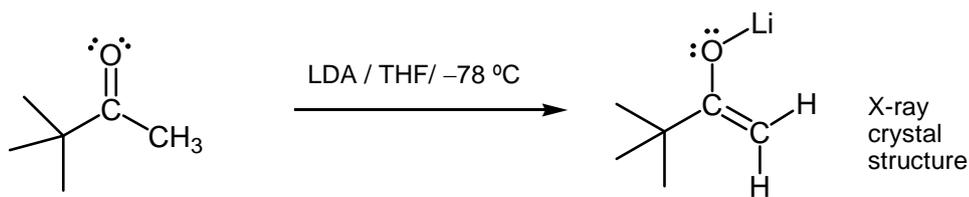
Electrostatic potential maps of some bases(a) CH_3O^- (b) CH_3CO_2^- (c) $\text{CH}_3\text{COCH}_2^-$

(Reproduced from *Organic Chemistry*; John McMurry, Brooks/Cole; 5th ed., 2000)

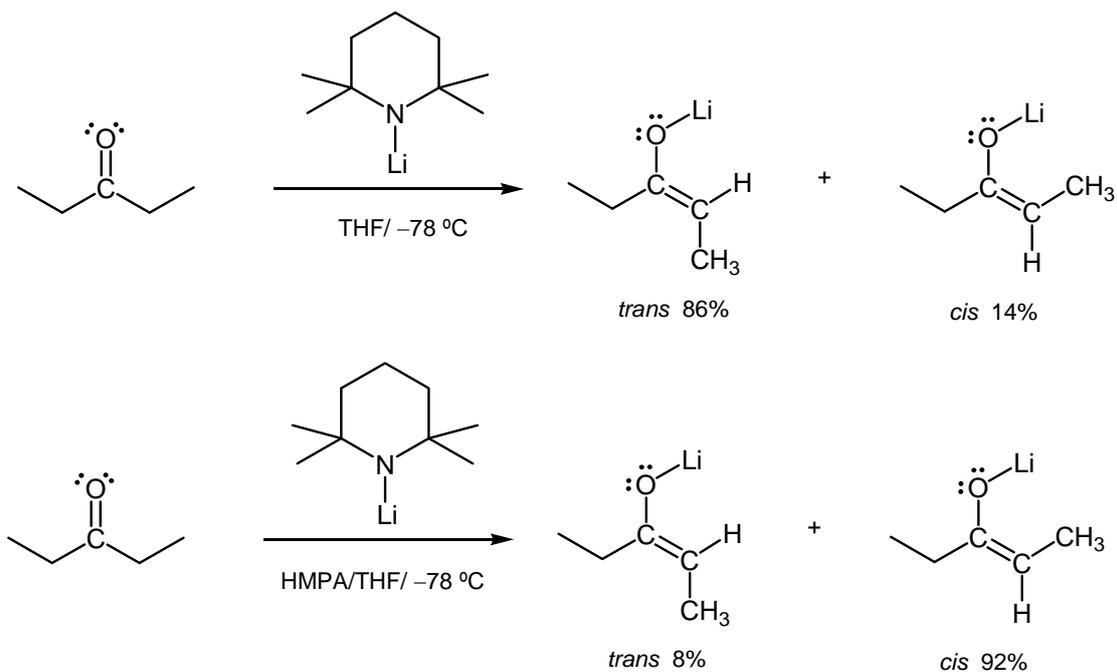
Formation of Enolates with Strong Bases

aldehydes, ketones,
esters, N,N -dialkylamides

Structure of Lithium Enolates

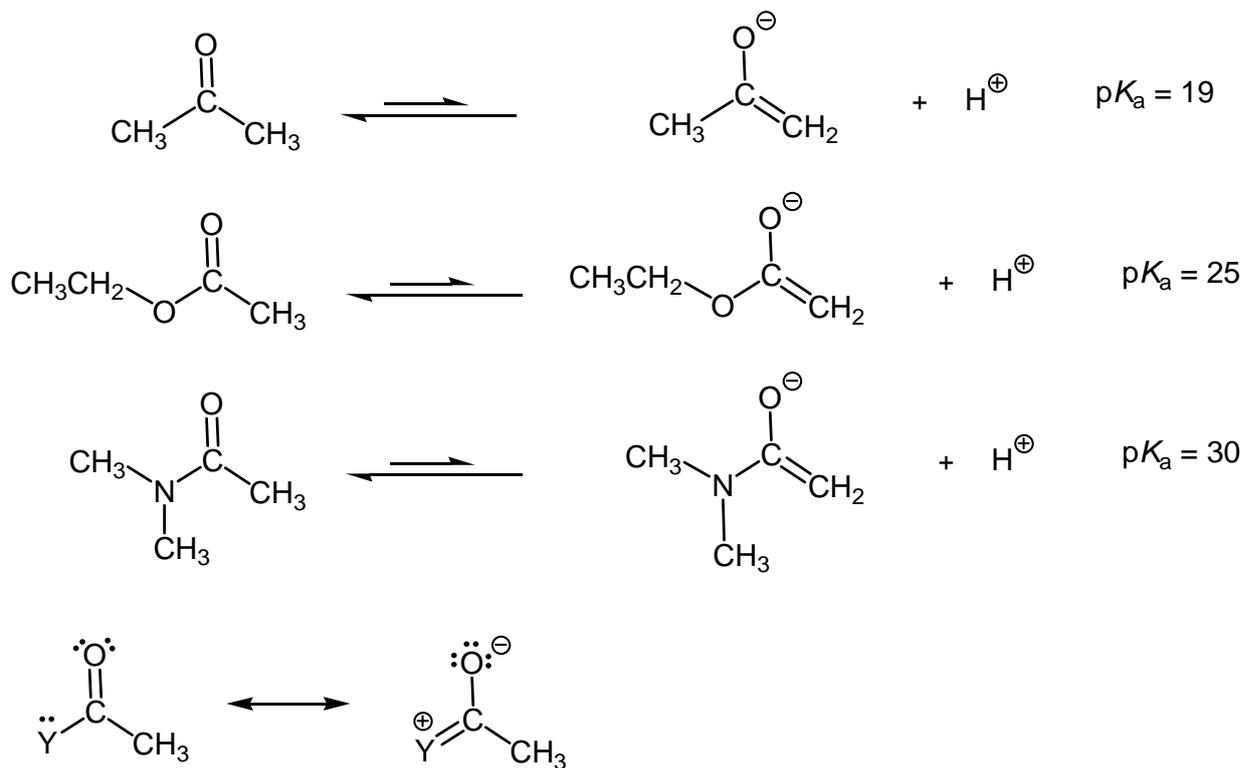


(Reproduced from Amstutz, R.; Schweizer, W. B.; Seebach, D.; Dunitz, J. D. *Helv. Chim. Acta* **1981**,*64*, 2617)



HMPA = HEXAMETHYLPHOSPHORAMIDE $[(CH_3)_2N]_3P=O$; promotes enolate equilibration

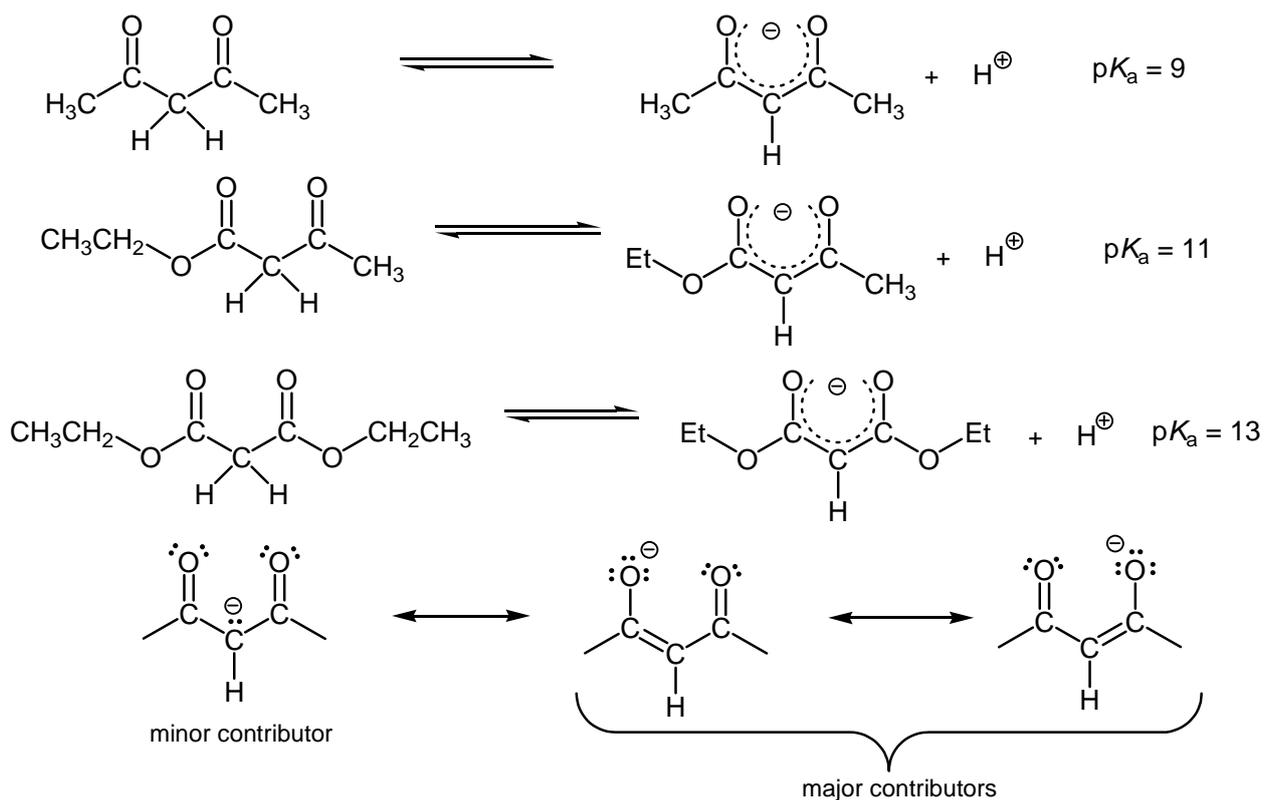
Acidity of Other Carbonyl Compounds



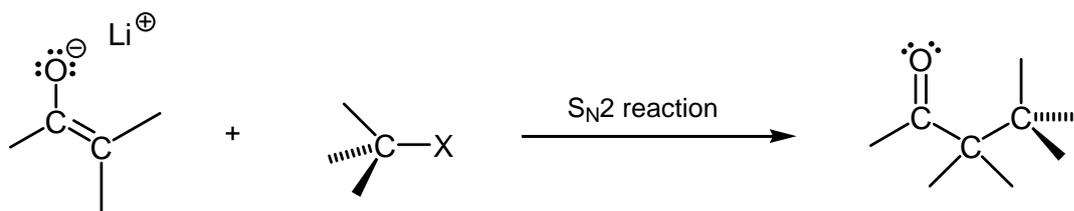
Y = O or N

Conjugate **acid** of esters and amides stabilised by resonance

Acidity of β -Dicarbonyl Compounds

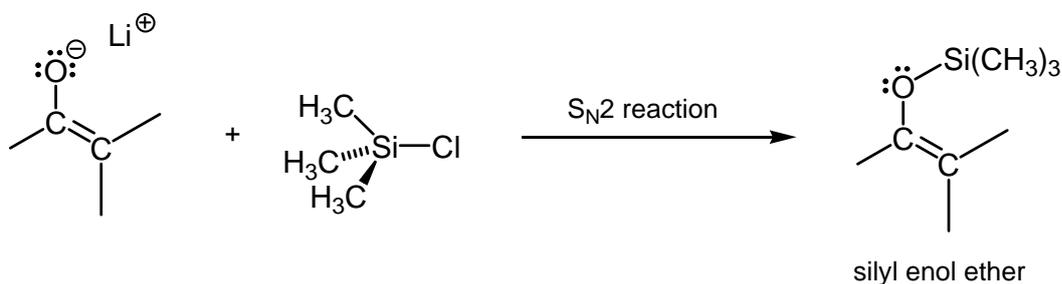


Alkylation and Silylation of Enolate Ions

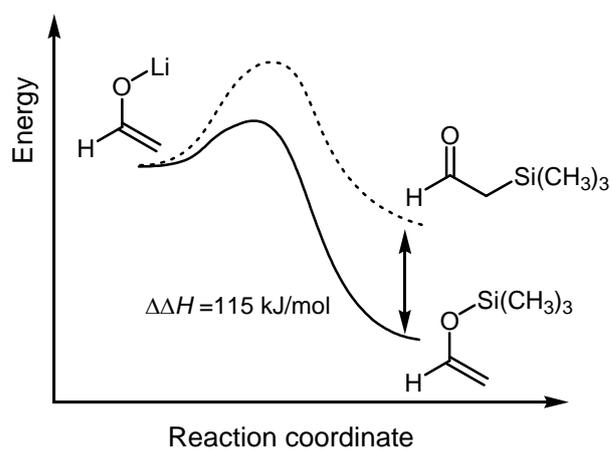
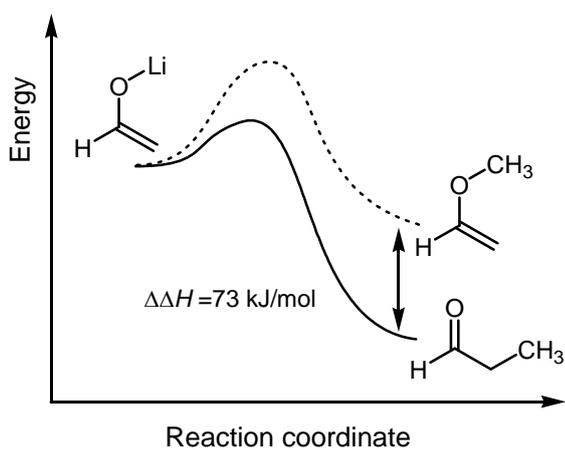


Reactivity: $X = I > Br > Cl$

$C = \text{benzylic/allylic} > CH_3 > RCH_2$ (secondary predominately undergo elimination and tertiary cannot undergo S_N2 and undergo exclusive elimination)

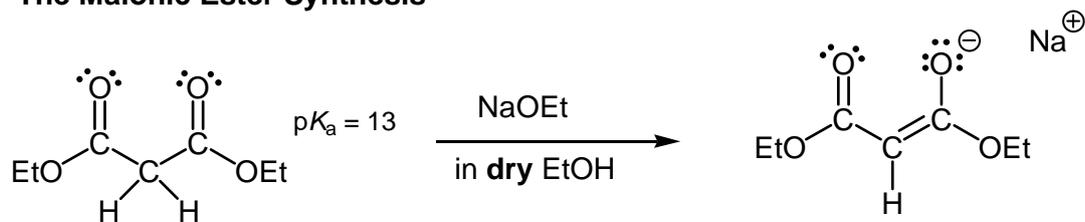


Note: S_N2 possible at tertiary Si as $C-Si = 1.85 \text{ \AA}$ vs $C-C = 1.54 \text{ \AA}$

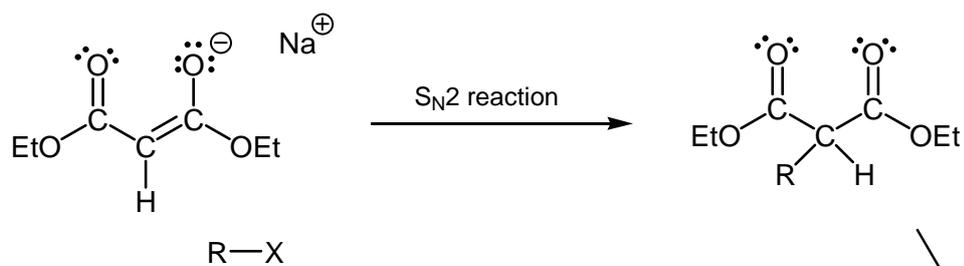
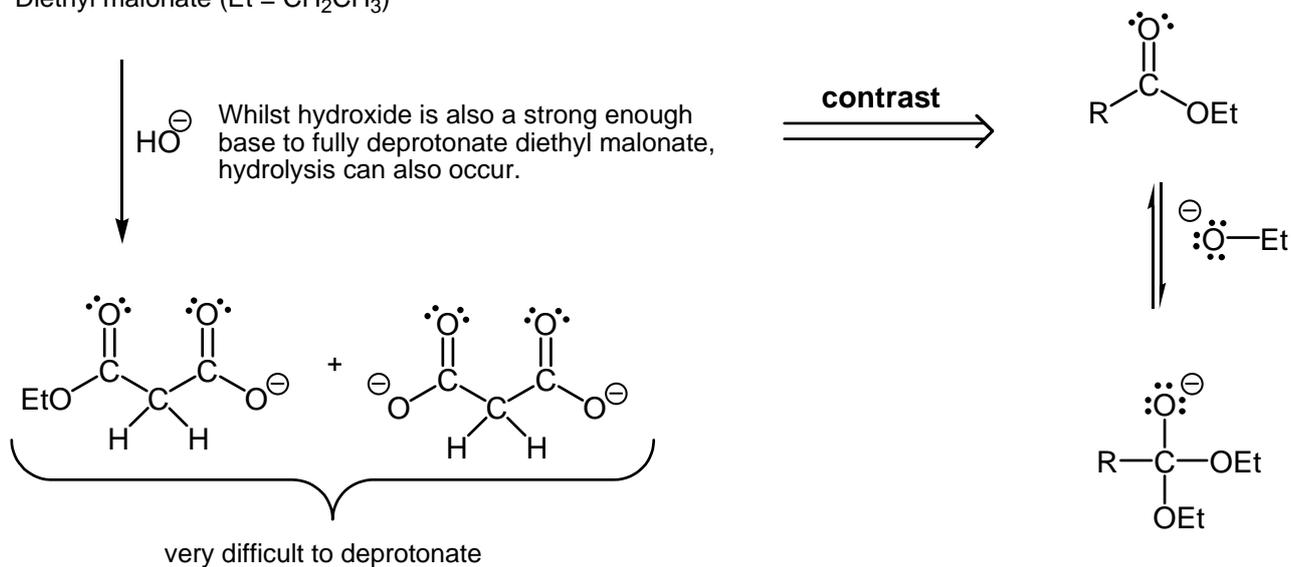


Average bond enthalpies: $C-C = 348 \text{ kJ/mol}$; $C-O = 358 \text{ kJ/mol}$; $C-Si = 285 \text{ kJ/mol}$; $Si-O = 451 \text{ kJ/mol}$;
 $C=C = 614 \text{ kJ/mol}$; $C=O = 745 \text{ kJ/mol}$.

The Malonic Ester Synthesis

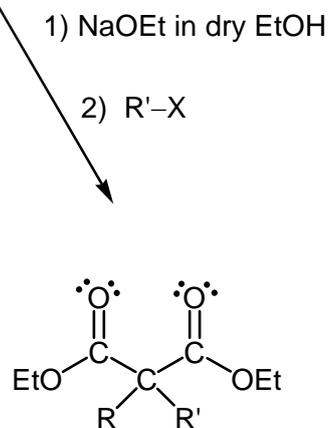


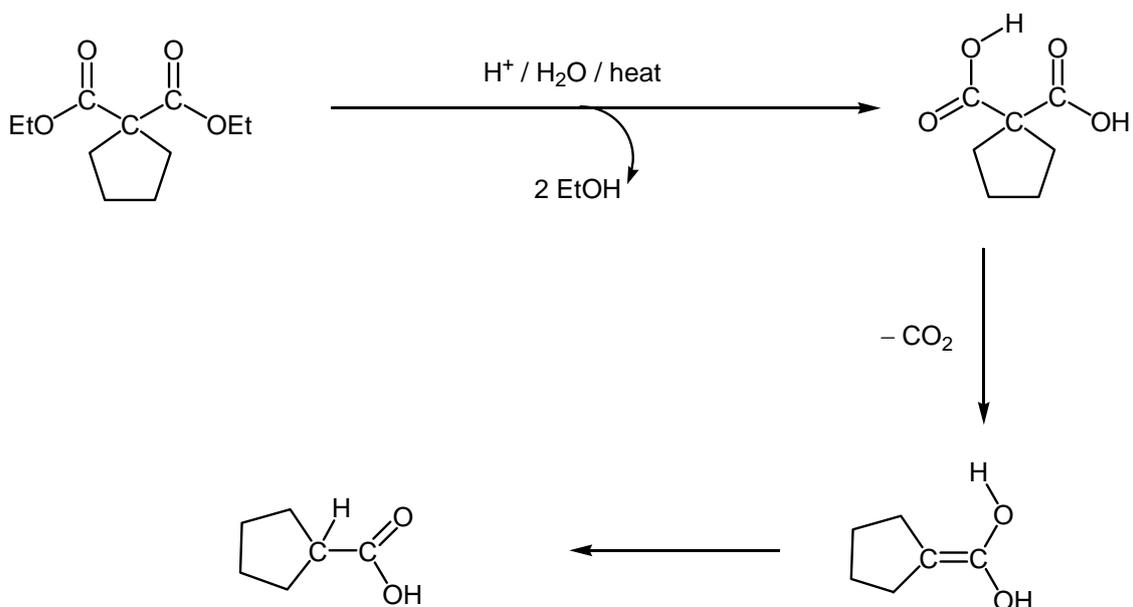
Diethyl malonate (Et = CH₂CH₃)



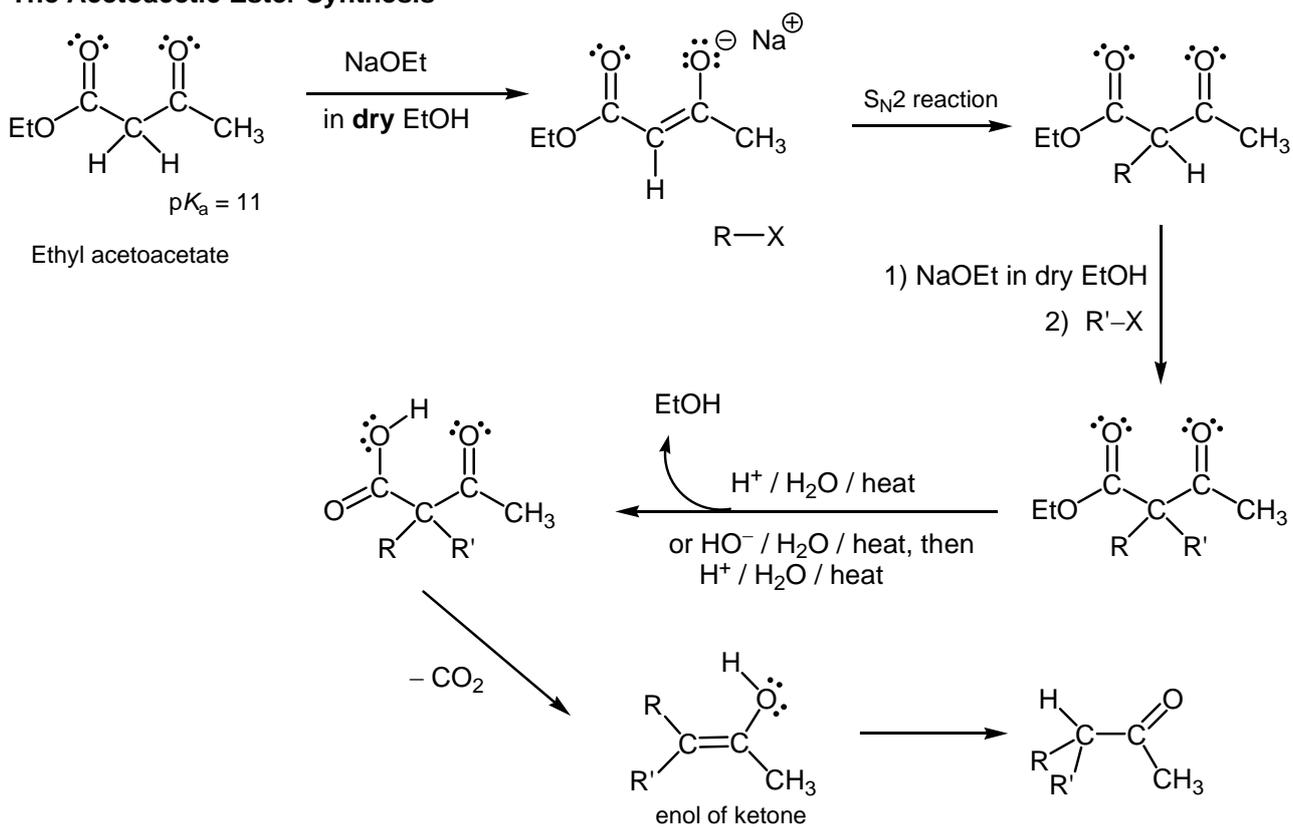
Reactivity: X = I > Br > Cl

R = benzylic/allylic > CH₃ > RCH₂ (secondary predominately undergo elimination and tertiary cannot undergo S_N2 and undergo exclusive elimination)

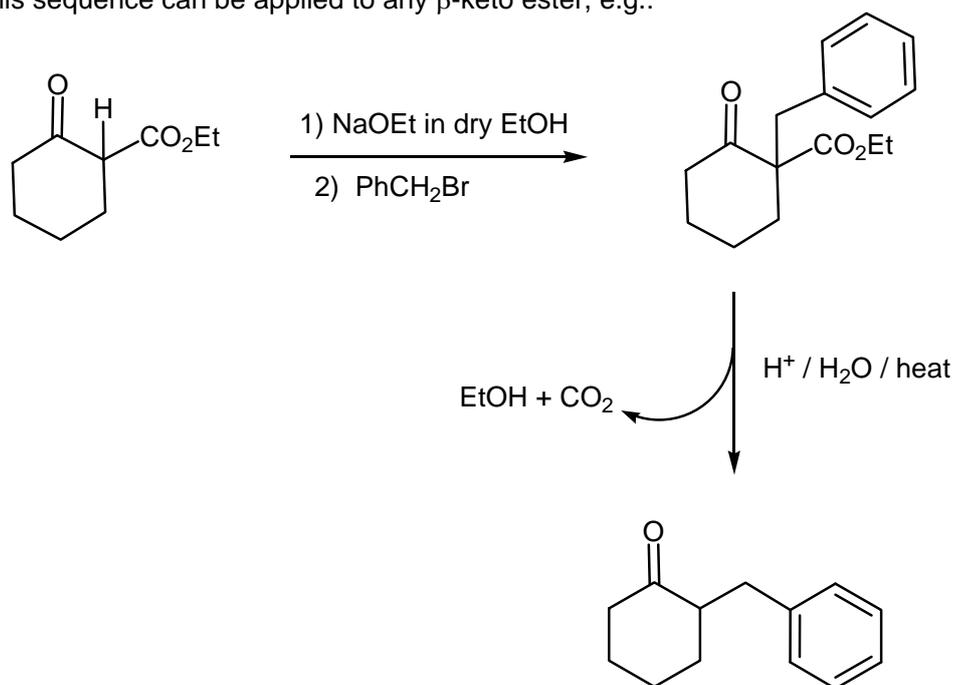




The Acetoacetic Ester Synthesis



This sequence can be applied to any β -keto ester, e.g.:



Direct Alkylation of Enolates

