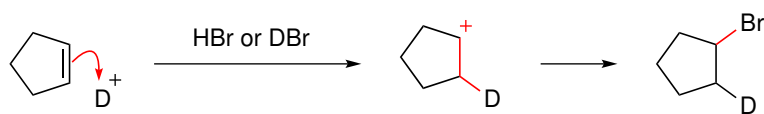

CHEM1201: Section 1

Alex Ganose

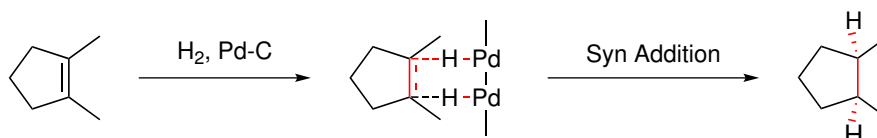
December 23, 2012

1 Alkenes

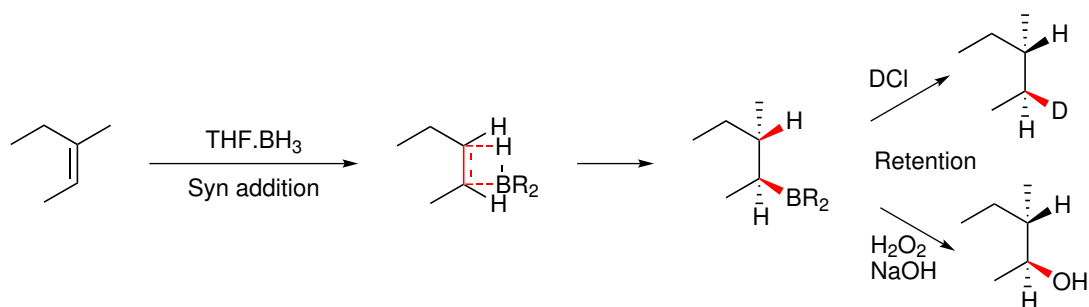
1.1 General



Carbocation mechanisms rarely permit stereocontrol.



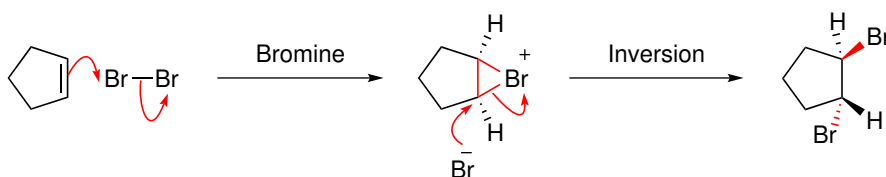
Carbocation mechanisms rarely permit stereocontrol.



1.2 Oxidations

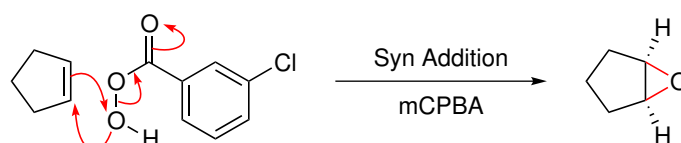
For each reaction, the first step involves synchronous bond formation.

1. Bromination

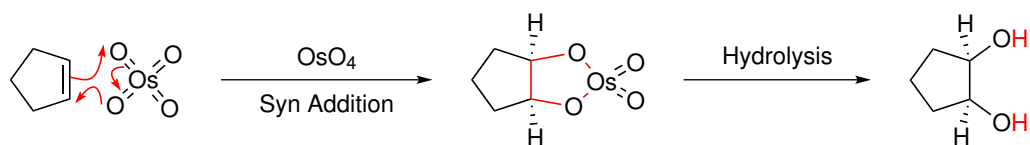


Overall an addition.

2. Epoxidation with mCPBA

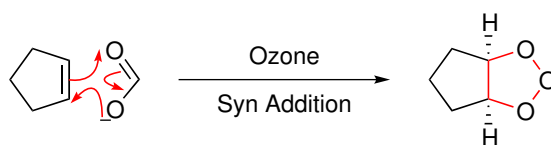


3. Formation of 1,2 Diols:



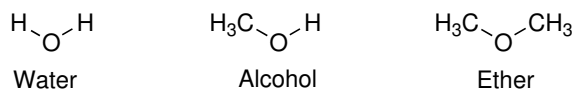
Proceeds with syn addition of osmium tetroxide.

4. Ozonolysis

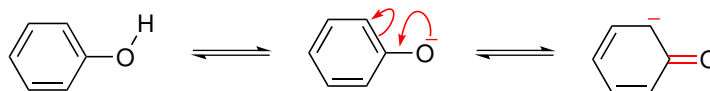


2 Alcohols

2.1 General



Owing to conjugation of O via the sp^2 carbon, phenols and enols behave differently and neither is referred to as an alcohol.



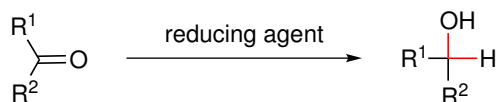
$\text{CH}_3\text{CH}_2\text{OH}$ cannot be oxidized as there is no $\alpha\text{-H}$

2.1.1 Physical Properties

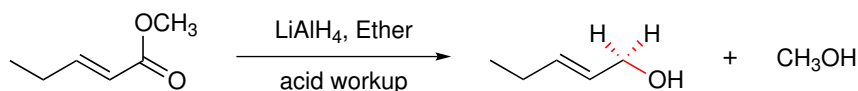
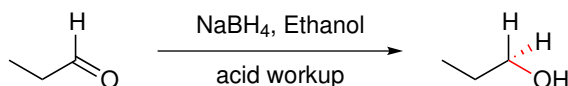
The electro-negativity of O means that alcohols are feebly acidic unlike amines that are only ever feebly basic. Alcohols are also feebly basic (O is less nucleophilic than N). They are also extensively hydrogen bonded which gives them much higher boiling points than alkyl halides.

2.2 Preparation of Alcohols

1. Reduction of $\text{C}=\text{C}$ compounds.

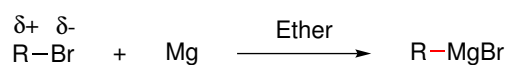


Examples:

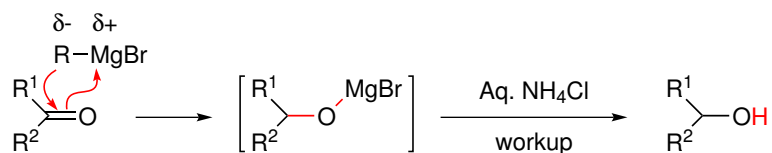


Note the double bond is unaltered.

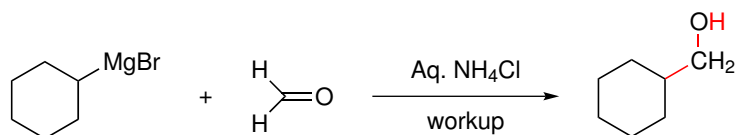
2. Addition of grignard (RMgX) to a carbonyl compound.



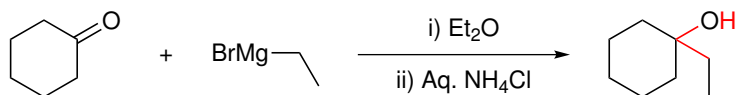
Mechanism



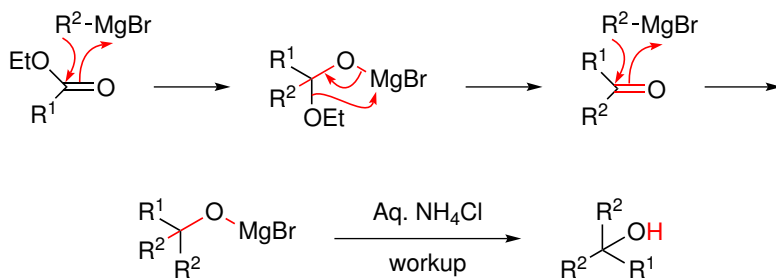
Example 1. Alcohols from aldehyde's.



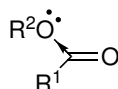
Example 2. Alcohols from ketone's.



Example 3. Alcohols from esters.

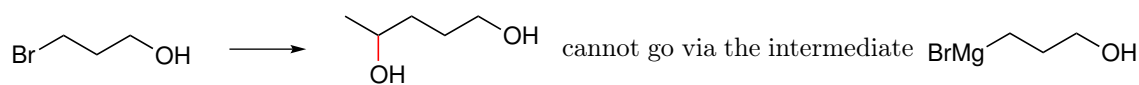


Esters only give alcohols with grignard reagents because the inductive effect increases reactivity but mesomeric effects are greater therefore the ketone's C=O is more reactive than an ester C=O.

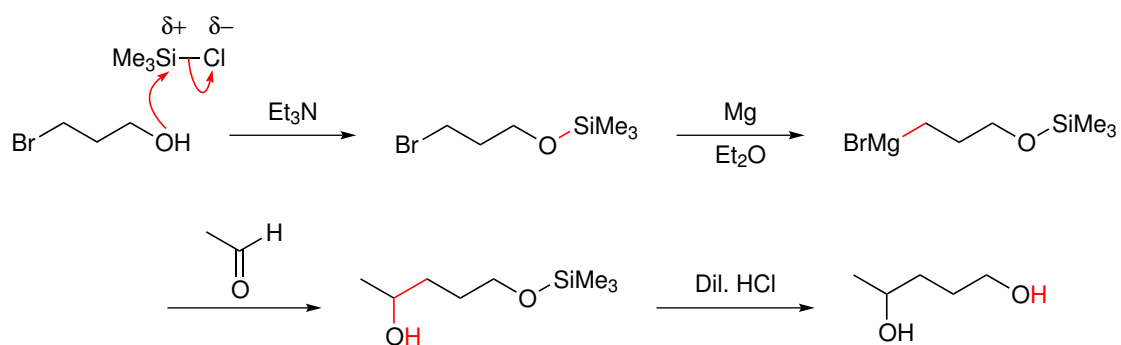


Grignard reagents are destroyed by groups with an exchangeable H e.g. OH, SH, NHR, COOH and thus require protective groups, e.g. silicon for an alcohol.

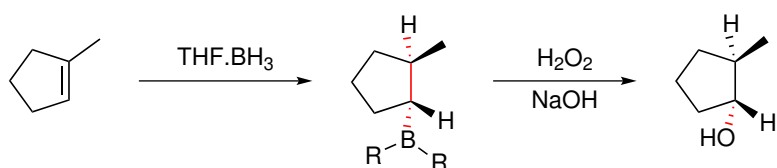
For example:



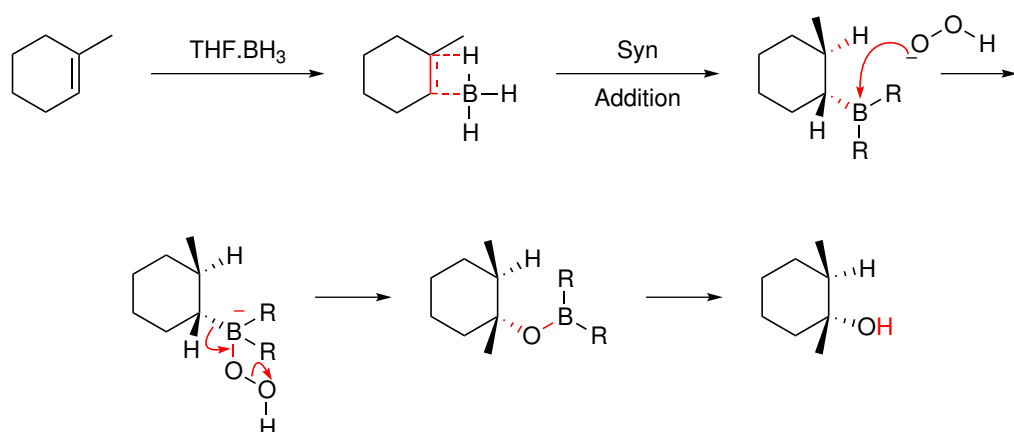
as the OH would destroy the grignard reagent formed. Therefore instead, silicon is used as a protective group.



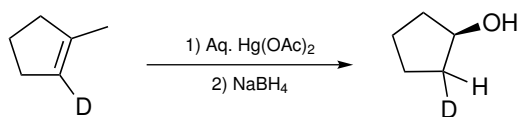
3. Hydroboration of alkenes (delivers OH to the less substituted C).



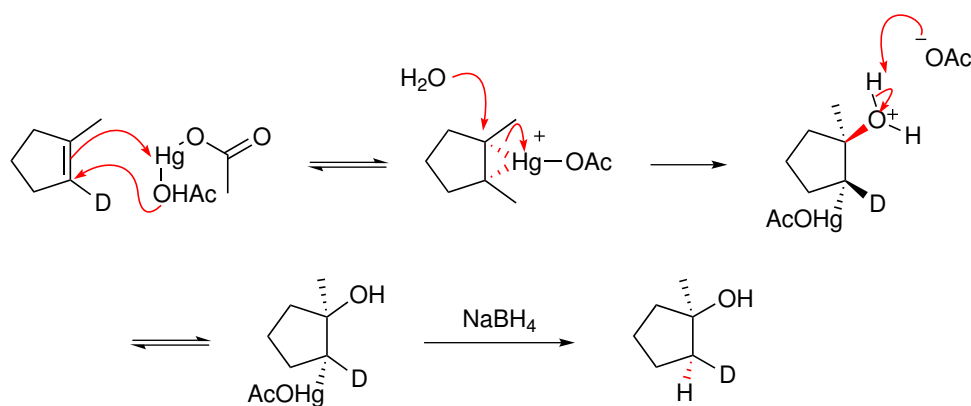
Mechanism



4. Oxymercuration of alkenes (delivering of OH to the more substituted C)



Mechanism

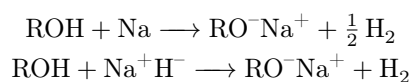


2.3 Reactions of Alcohols

2.3.1 Reaction at the alcohol oxygen atom.

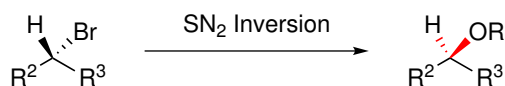
a) Formation of the alkoxide (Na, NaH)

With a strong base, the acidic H is lost and the alkoxide is formed. Grignard reagents must also be protected from this e.g.



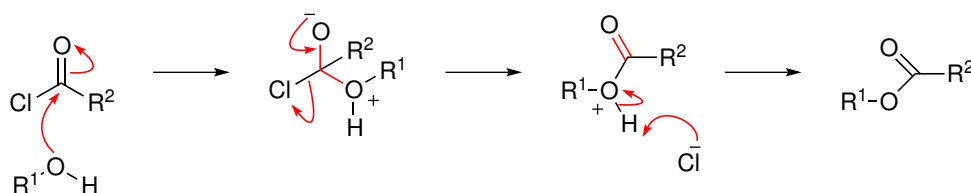
Alkoxides are good bases and good nucleophiles except tBuOH and 3° alcohols, which are good bases but non-nucleophilic due to their steric hindrance. NaH acts only as a base and is not a reducing agent.

b) O-Alkylation (alkoxide + alkyl halide)

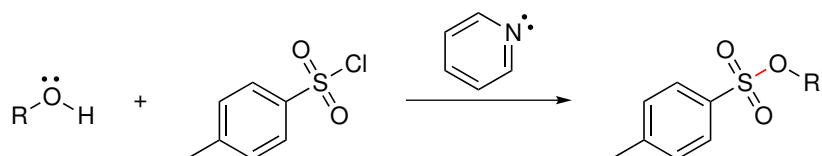


Williamson ether synthesis

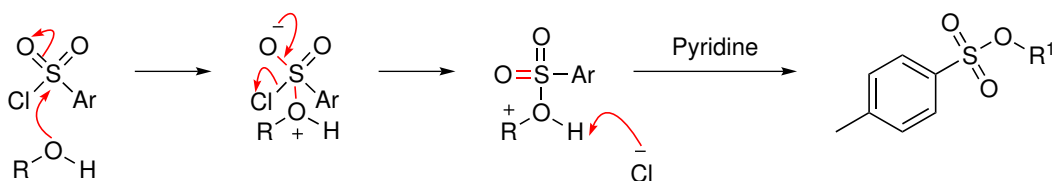
c) O-Acylation (alcohol + acid chloride)



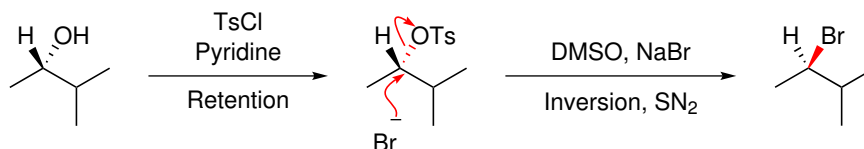
d) O-sulfonylation (p-TsCl + Pyridine)



Mechanism



Tosylate is a very good leaving group and can be displaced by many nucleophiles including all halides.

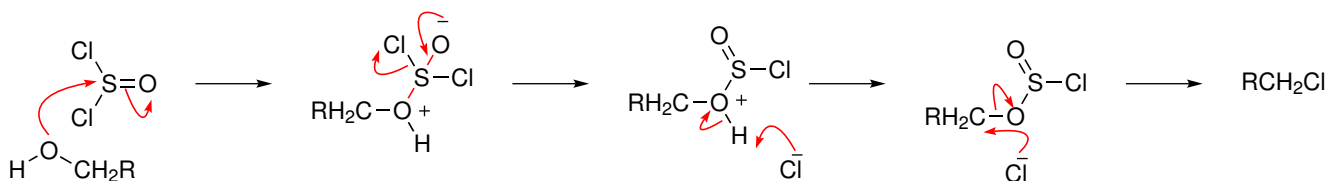


DMSO is $\text{Me}_2\text{S}=\text{O}$, a very popular solvent that gives fast rates of reaction.

2.3.2 Displacement at the alcohol carbon atom

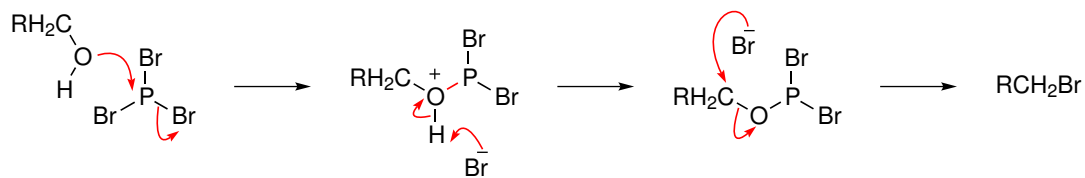
Activation of the OH group is the first step, in all cases a good leaving group (HOX) is generated.

a) Conversion of ROH into RCl (alkyl chloride)



The first transition state formed contains an O–S bond. This is followed by elimination of chlorine and loss of a proton. Then $\text{S}_{\text{N}}2$ displacement of the activated carbon atom occurs.

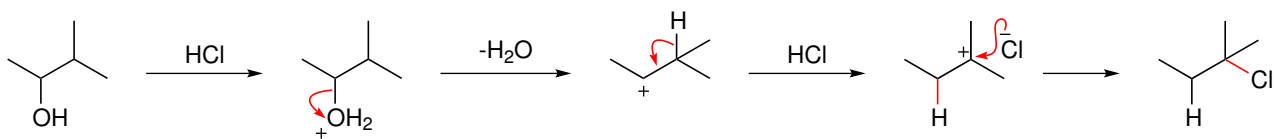
b) Conversion of ROH into RBr (alkyl bromide)



The limitations of using HCl/HBr to prepare alkyl halides are:

- 2° and 1° alcohols require forcing conditions ($100 - 120^\circ\text{C}$)
- incompatibility of any unsaturated sites, which will react.
- Likely to undergo rearrangement

c) Rearrangement using HCl/HBr 2° carbocation



Mechanism results in the formation of a 3° carbocation

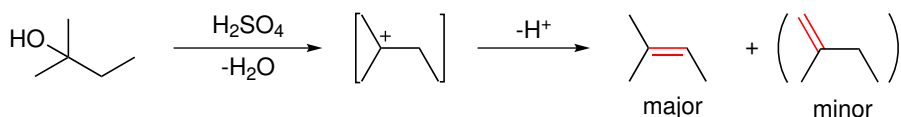
1,2 Hydride shifts are common where the resulting carbocation is more stable than the initial one.

2.3.3 Eliminations of Alcohols: Formal loss of water

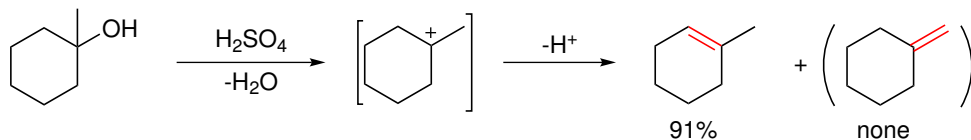
a) Where a carbocation is not trapped by a nucleophile (and does not rearrange) an elimination can occur. *t*BuOH reacts with H_2SO_4 to give a 3° carbocation, which then deprotonates to give 2-methylbutane. The conditions favour the most substituted alkene.

E.g.

i)



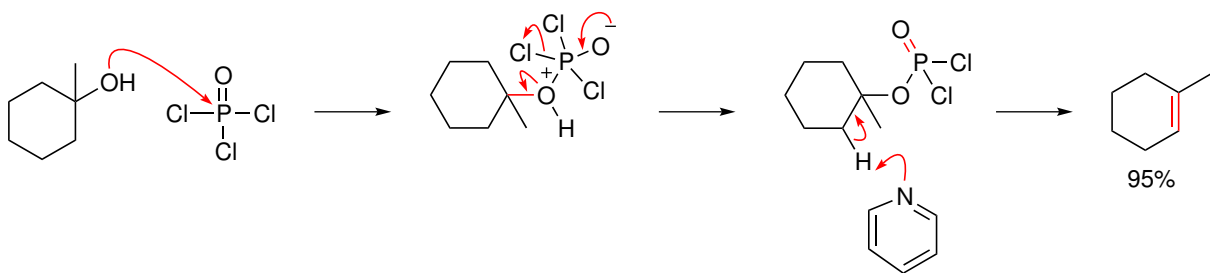
ii)



Limitations are that 2° and 1° alcohols require heating that may promote side reactions including rearrangements.

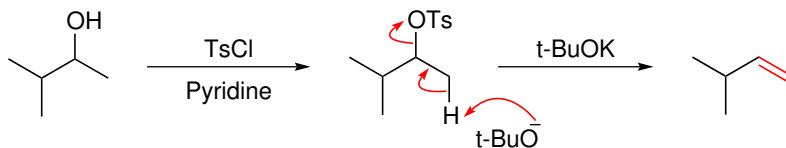
Alternatives are elimination using POCl_3 and pyridine and conversion of the alcohol into the tosylate followed by elimination with *t*BuOK.

b) E_2 elimination using POCl_3 and Pyridine (at 0 °C)



c) E₂ elimination of the tosylate using tBuOK

This is especially useful when the compound is sensitive to acidic reagents including (POCl₃)

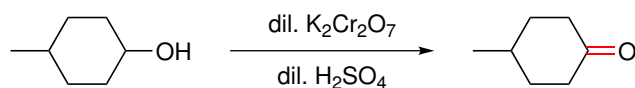


2.3.4 1,2 Elimination across the C–O: Oxidation of Alcohols

Oxidation can be loss of H, loss of e⁻ or gain of O.

a) Chromium (VI) reagents

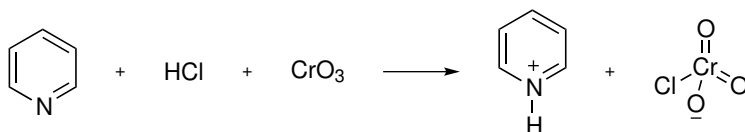
i) Dilute dichromate with dilute H₂SO₄



Over oxidation of 1° alcohols to RCOOH occurs. Any Cr(VI) reagent is good for 2° alcohols.

ii) Pyridinium Chlorochromate (PCC)

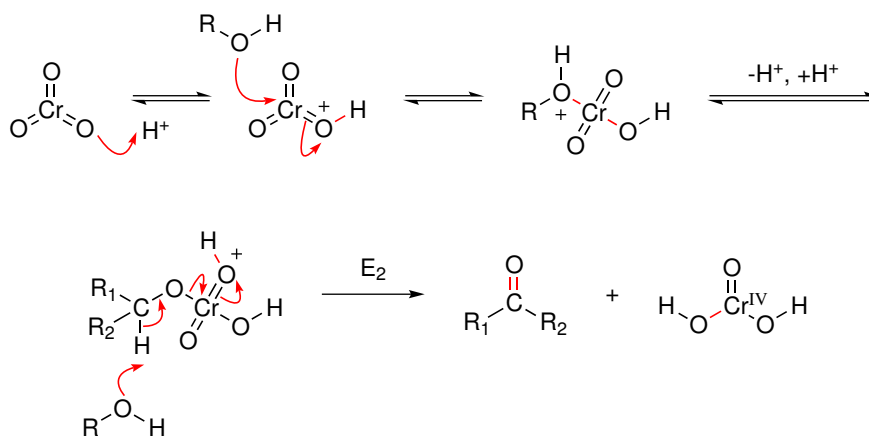
Good for converting 1° alcohols to aldehydes and 2° to ketones, with little over oxidation.



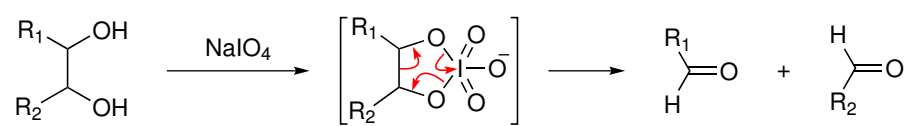
Formation of PCC

iii) CrO₃ in aqueous H₂SO₄: Jones reagent.

Oxidises 2° alcohols to the ketone and 1° to the acid. The mechanism of Cr(VI) oxidations all involve formation of a chromate ester that undergoes E₂ elimination.



b) Cleavage of 1,2-diols by sodium periodate, NaIO_4



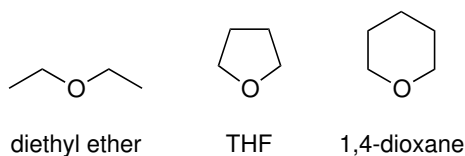
A central C–C bond is broken as part of the oxidation process

3 Ethers and Epoxides

3.1 Ethers

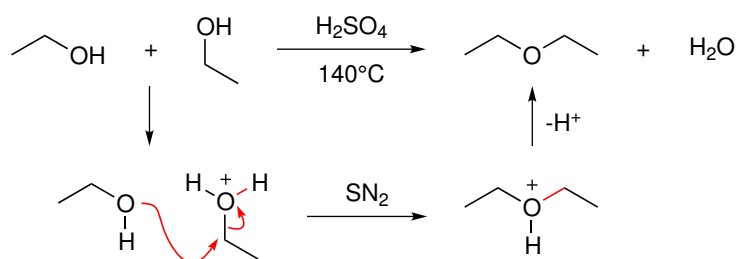
Ethers are good solvents as they are chemically inert but slightly polar. Old bottles become oxidised by the air to give explosive peroxides.

Examples of ethers are:

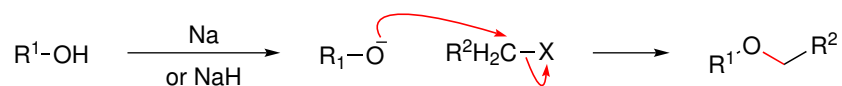


3.1.1 Preparation of ethers

a) For symmetrical ethers



b) Williamson ether synthesis; the most general route

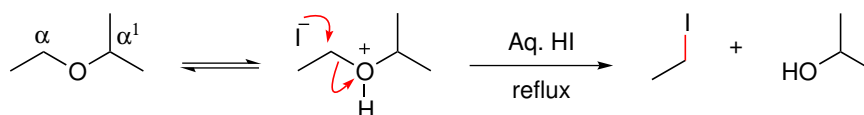


X = Br, I and OTs as long as there is not too much steric hindrance

$R-O^-$ is a very powerful nucleophile.

3.1.2 Reactions of Ethers: Cleavage by HI

I^- attacks the less substituted (less sterically hindered) α - C

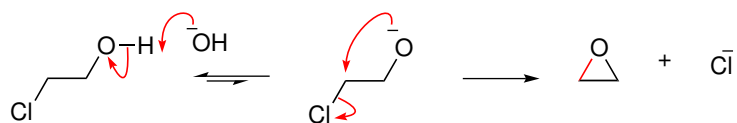


3.2 Epoxides

Epoxides are strained and highly reactive 3-membered ring ethers.

3.2.1 Synthesis of Epoxides

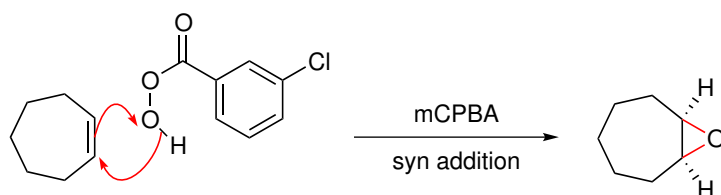
a) Cyclisation of halohydrins: Intramolecular Williamson ether synthesis



There is ring strain as the angles are normally 109° and in epoxides they are 60° .

b) Epoxidation of alkenes

The configuration of the alkene is retained in the epoxide.



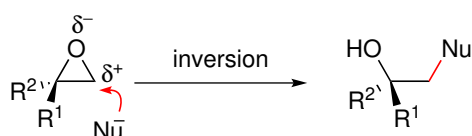
Does not work on many alkenes

3 membered rings are favoured as 4 membered rings have a lower entropy factor and therefore there is less chance of ring closure.

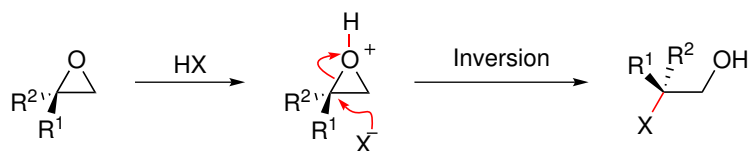
3.2.2 Reactions of Epoxides

3.2.3 Patterns of reactivity

i) All reagents except acid



ii) Acid attack by HX

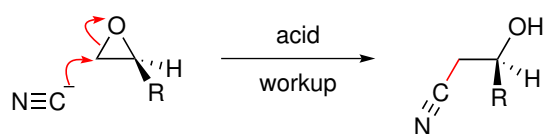


3.2.4 Nucleophilic attack of epoxides

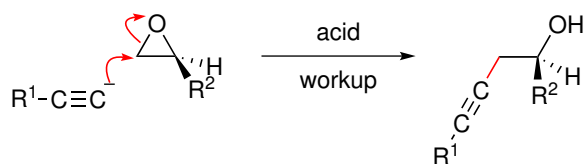
i) Attack by C-Nucleophiles

Powerful in synthesis as a new C–C bond is generated.

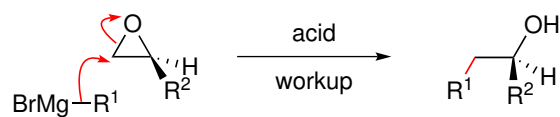
Example 1. Cyanide



Example 2. Alkynyl anions



Example 3. Grignard reagents

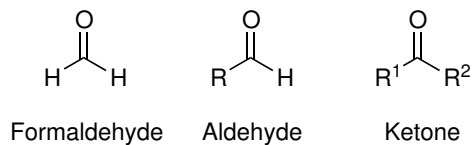


ii) Attack by Hydroxide, $\text{O}-\text{S}^-$ and N^- nucleophiles.

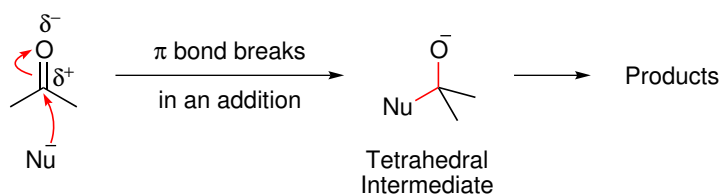
These all react according to the first pattern of reactions.

4 Aldehydes and Ketones

E.g.



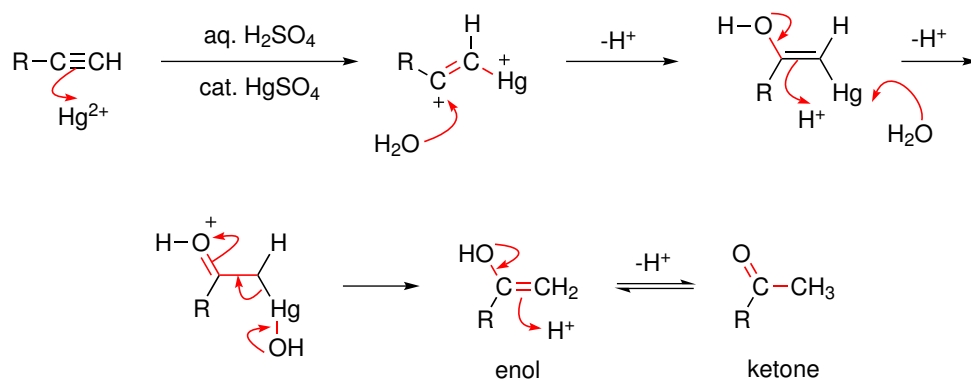
4.1 Reactivity



There is decreasing reactivity from formaldehyde to ketones as the inductive effect lowers the δ^+ value on the central carbon atom, and the steric bulk around the carbon atom increases.

4.2 Preparation of Aldehydes and Ketones

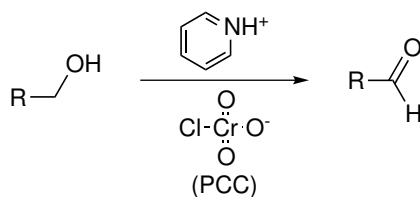
a) Alkynes with acid



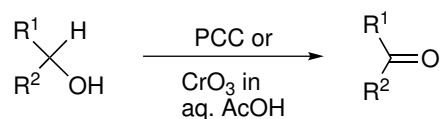
A terminal alkynes always produces a methyl ketone

b) Oxidation of alcohols (CrO_3/PCC)

i) 1° Alcohols



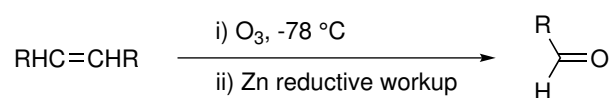
ii) 2° Alcohols



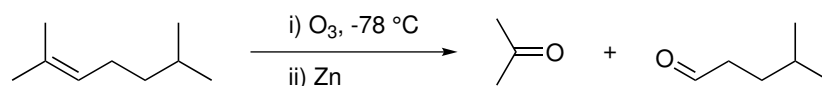
Oxidation of an alcohol followed by grignard reagent is a powerful synthetic method.

c) Ozonolysis of alkenes (see section 2 for mechanism)

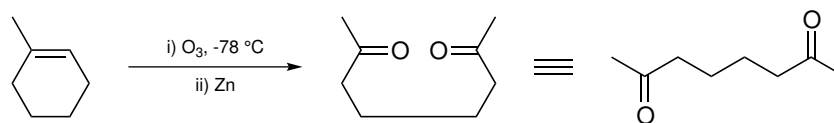
i)



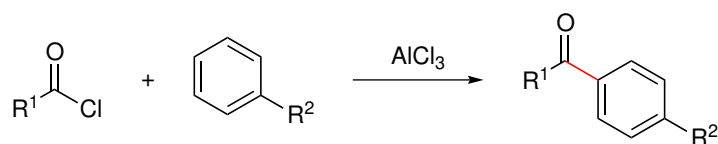
ii)



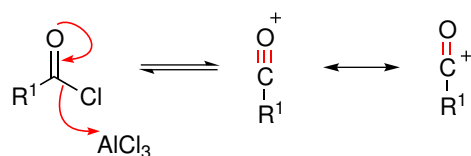
iii)



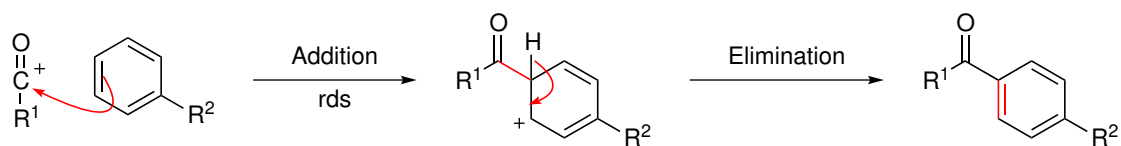
d) Friedal Crafts Acylation



This begins with the formation of the acylium ion



Followed by the mechanism



$R^2 = \text{H}$ or an e^- donating group such as Me, OMe or a halogen.

$R^1 = \text{anything except H}$.

4.3 Reactions of Carbonyl Compounds

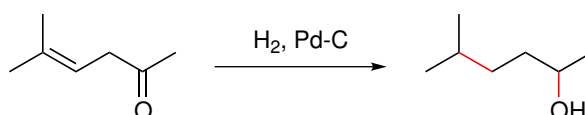
The general pattern of reactivity is:



a) Reduction of carbonyl compounds

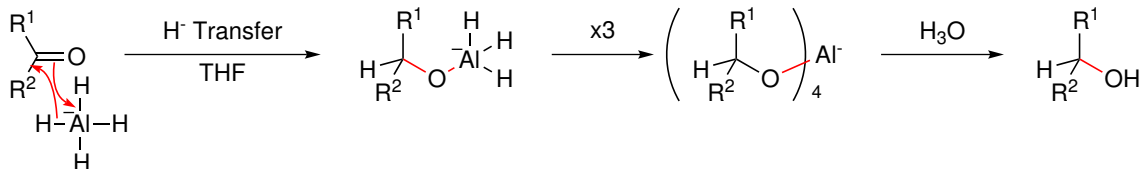
i) Using $\text{H}_2\text{Pd}-\text{C}$

Reduces aldehydes and ketones to alcohols, esters are only slowly reduced to alcohols. Inexpensive and no by products. Alkyne and alkene unsaturation is readily reduced to alkane.



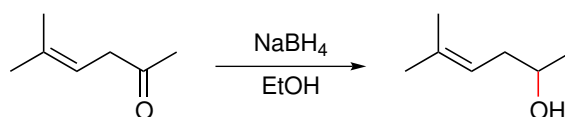
ii) Using metal hydrides

Requires coordination to O or N and therefore does not reduce alkyne or alkene unsaturation. I.e. Chemoselective

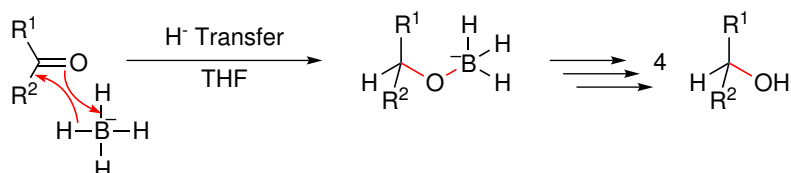


iii) Sodium borohydride

Reduces aldehydes and ketones by not esters or amides.

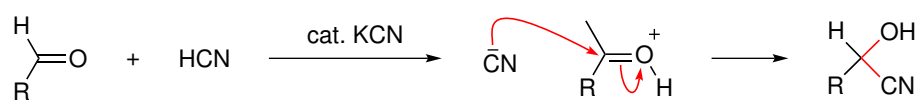


Mechanism

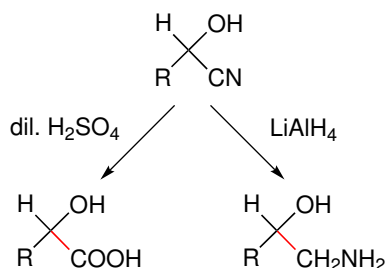


b) Addition of C-nucleophiles to give

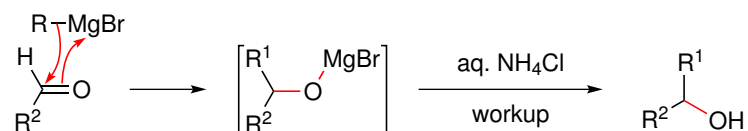
i) Cyanohydrins from HCN/KCN



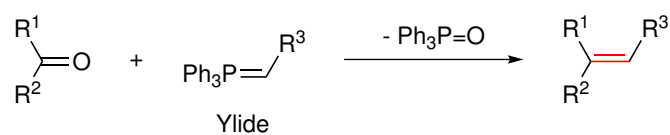
Use in synthesis is:



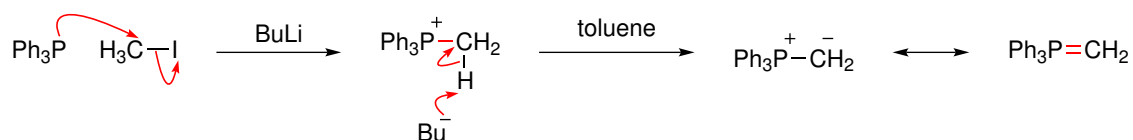
ii) Alcohols from a Grignard reagent.



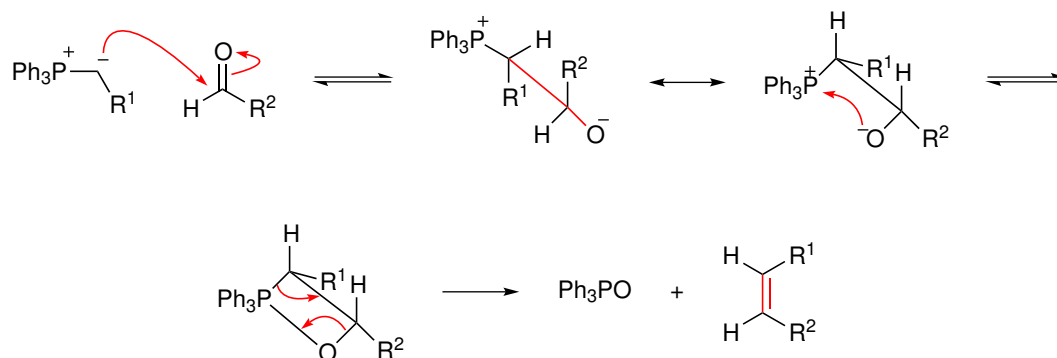
iii) Alkene from a Wittig reagent



The ylide is generated as so:

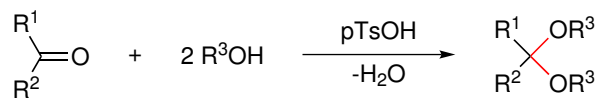


The overall mechanism is:

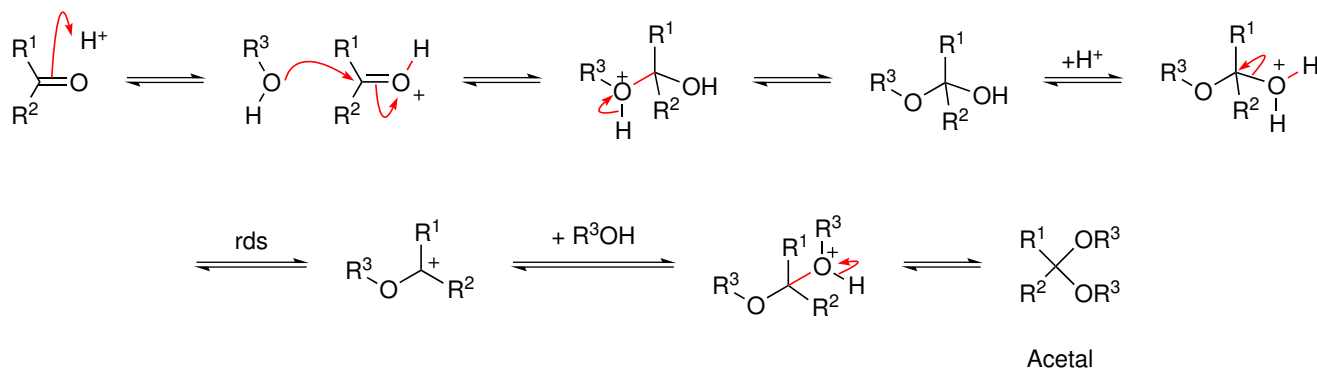


c) Addition of O-nucleophiles

i) Acetals from an alcohol with pTsOH

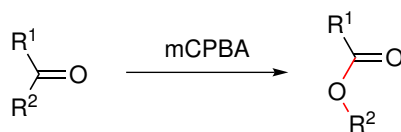


Mechanism:



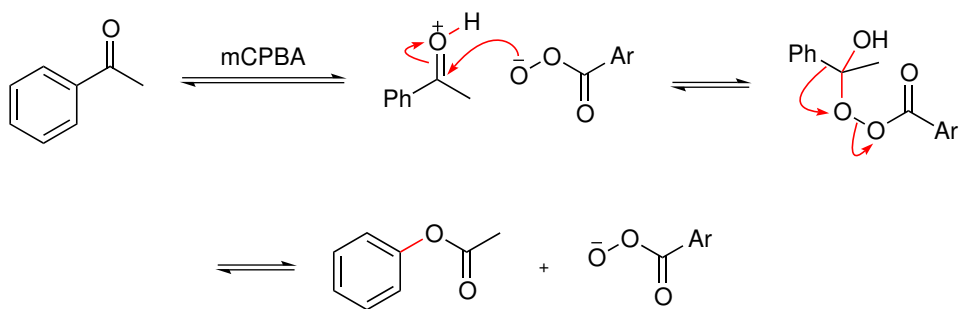
Acetals can be used to protect C=O of an aldehyde or ketone.

ii) Preparation of Esters with mCPBA; The Baeyer-Villiger Oxidation

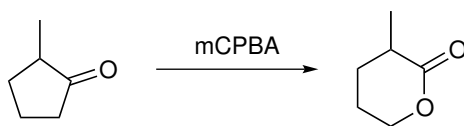


Ketones only

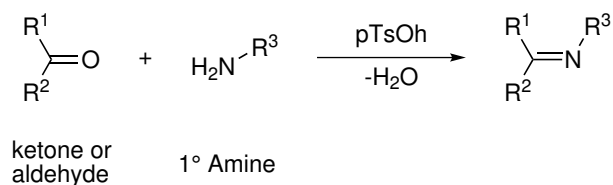
Mechanism



Another example is:



d) Addition of N-nucleophiles

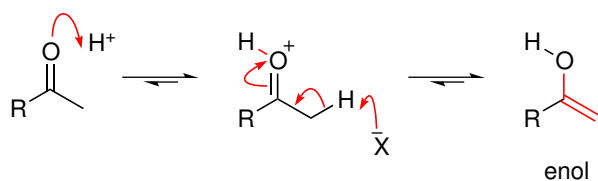


This is the same mechanism as the formation of acetals except with the elimination of water at the end.

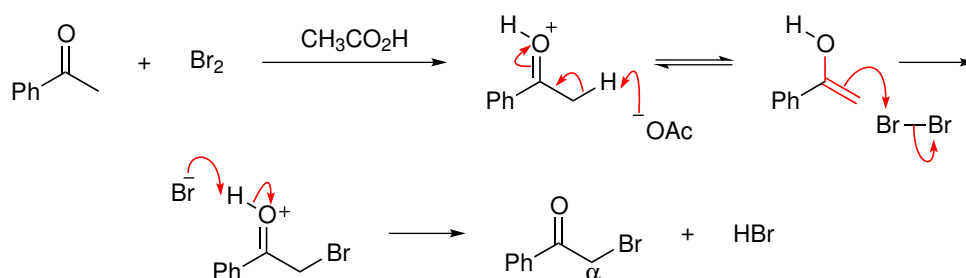
e) C-nucleophiles from aldehydes and ketones.

i) β -halocarbonyl compounds with Br_2

This proceeds via the acid catalysed formation of an enol.

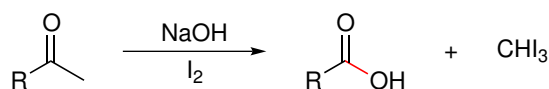


E.g. α -bromination of carbonyl compounds

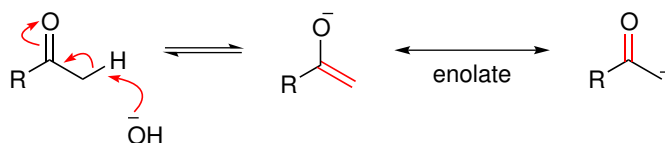


Here there is a low conversion of carbonyl compound into enol by acid catalysis. However, the reaction proceeds as the formation of the strong C-Br bond is irreversible.

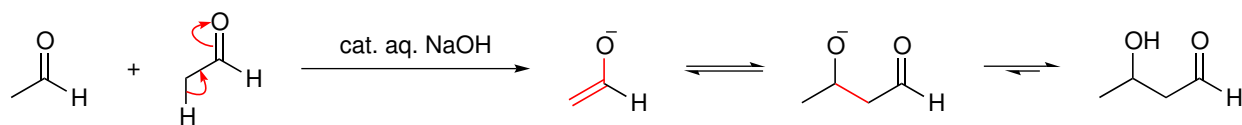
ii) Carboxylic acid with NaOH and I_2 (haloform reaction)



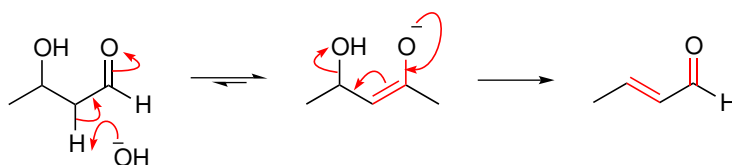
Mechanism:



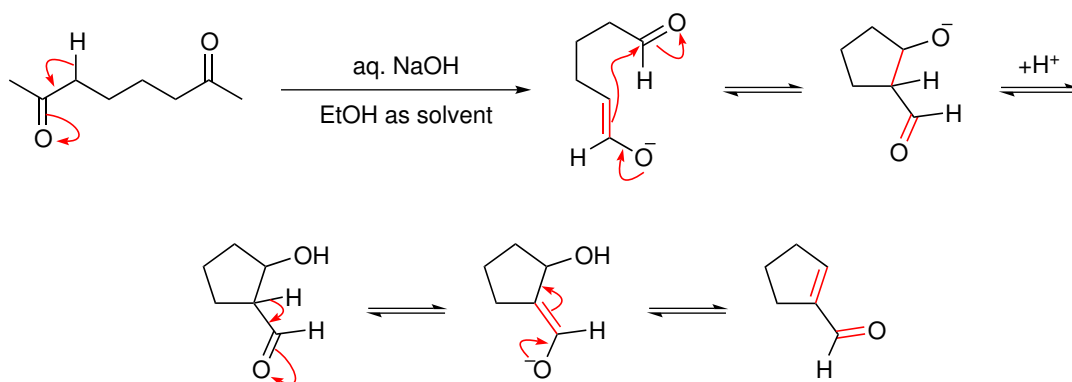
iii) Aldol addition



Aldol condensation is an aldol addition followed by elimination of water.



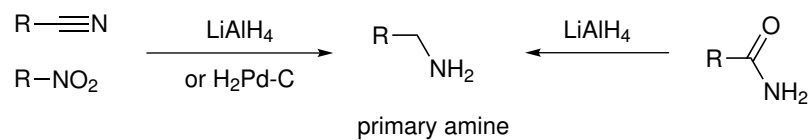
When a ring is formed the aldol addition product rapidly eliminates to give the enone:



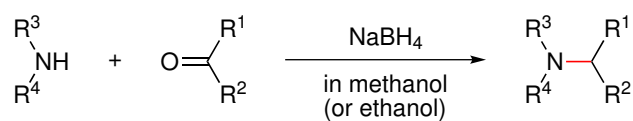
5 Amines

5.1 Preparation of Amines

a) By reductions of other nitrogen containing compounds

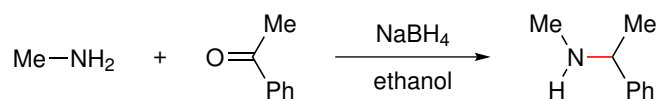


b) By reductive amination (amine + ketone)

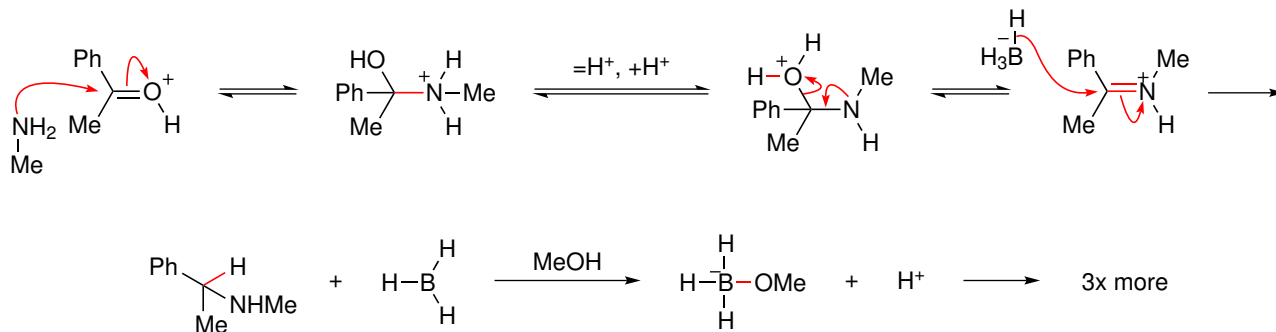


Industrially, H_2 over a nickel catalyst is used instead of NaBH_4

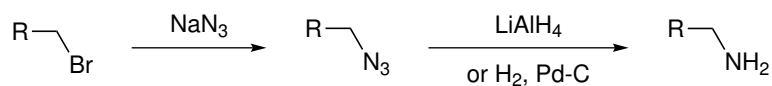
E.g.



Mechanism:



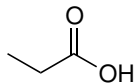
c) Reduction of azides



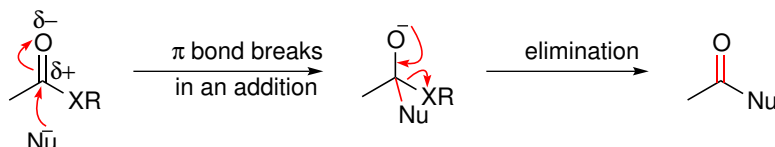
6 Carboxylic Acids

6.1 General

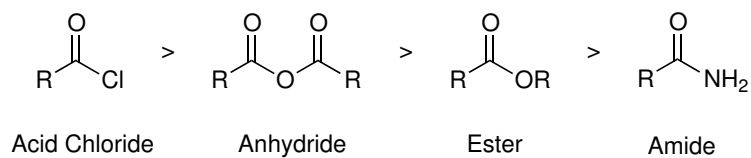
E.g.



Reactivity of carboxy derivatives towards nucleophiles:



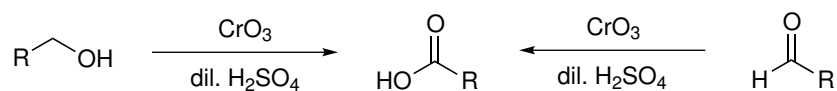
They decrease in reactivity as:



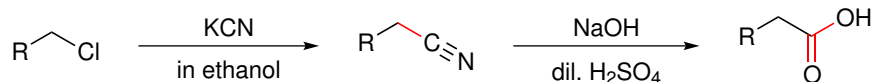
The inductive effect of Cl makes acid chlorides powerful electrophiles. The mesomeric effect of O and N lowers the electrophilicity of the carbonyl group.

6.2 Preparation of carboxylic acids

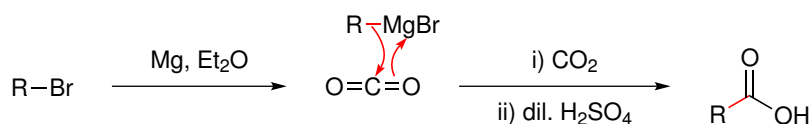
a) Oxidation of an alcohol or an aldehyde (Jones' Reaction)



b) Hydrolysis of nitrile group (NaOH then dil H₂SO₄)

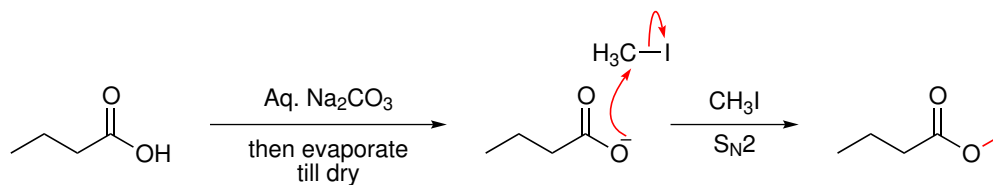


c) Addition of CO₂ to a Grignard reagent

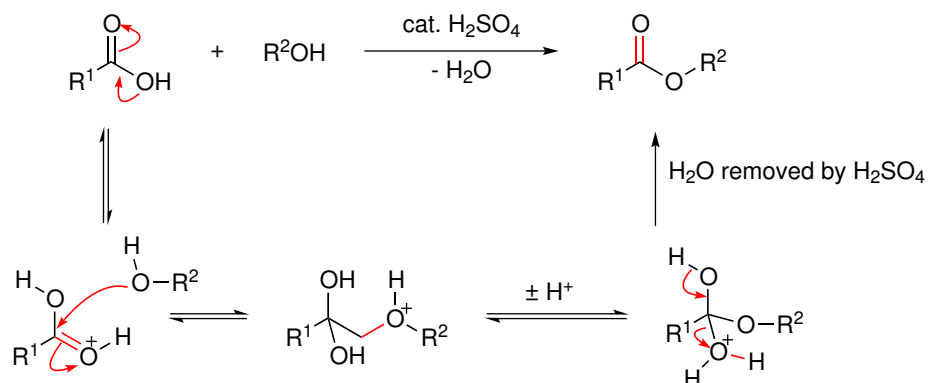


6.3 Reactions of carboxylic acids

a) Ester from an alkyl iodide

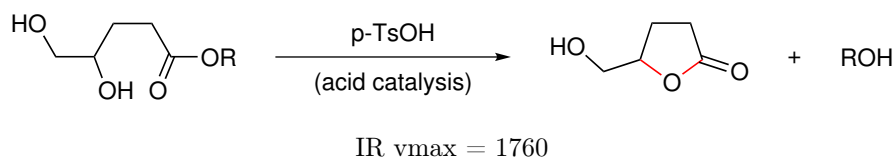


b) Ester from an alcohol with catalytic H_2SO_4 (Fischer Esterification)

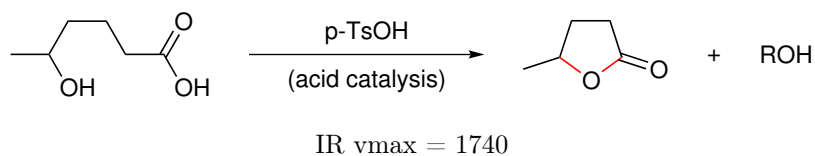


c) Lactone by cyclisation of a hydroxy acid or ester: 5 and 6 membered rings are easily formed under acid catalyst conditions and where both are possible, the 5 membered ring is favoured.

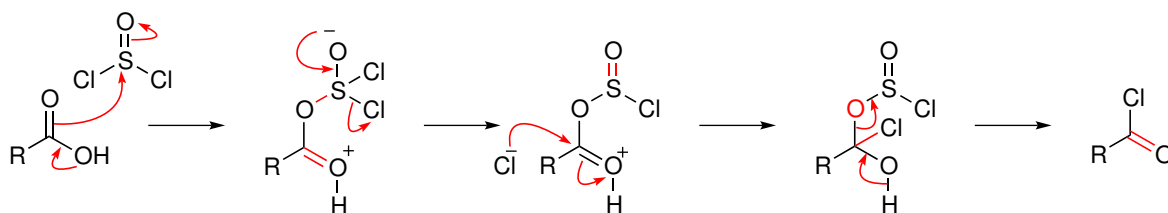
E.g. 1



E.g. 2



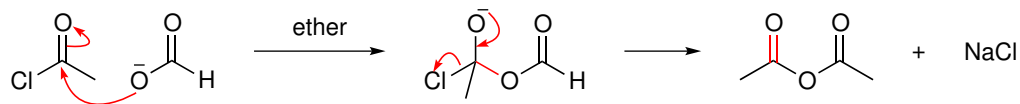
d) Acid chloride with SOCl_2



7 Acyl Chlorides

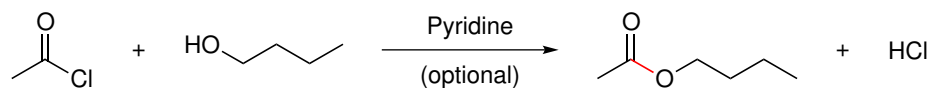
7.1 Reactions of Acyl Chlorides

a) Anhydride from a sodium carboxylate

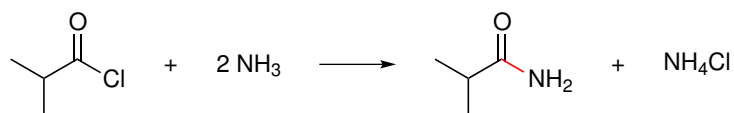


B

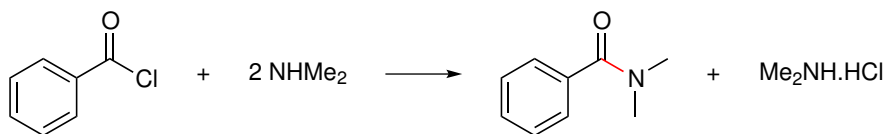
b) Ester from an alcohol



c) Amide from amines (NH_3 , 1° or 2° amine and a base) With NH_3 :

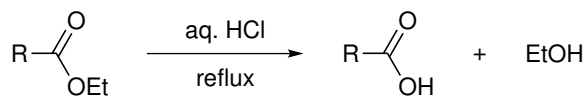


With a 2° amine:

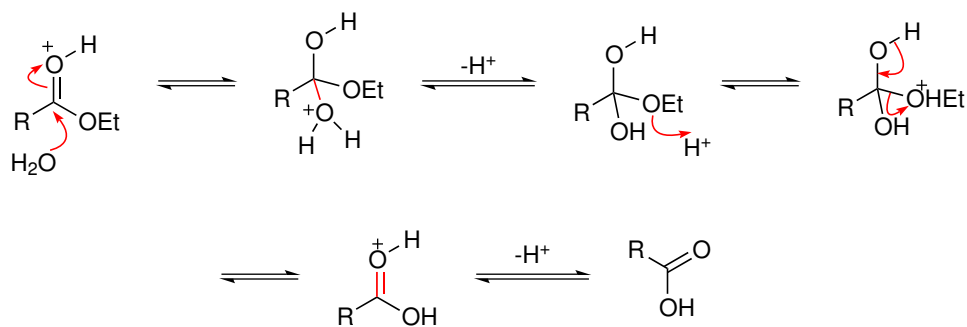


d) Hydrolysis to give carboxylic acids

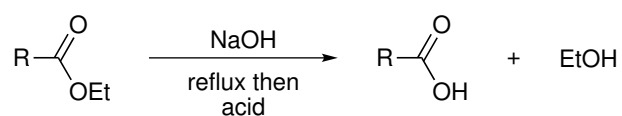
i) Esters



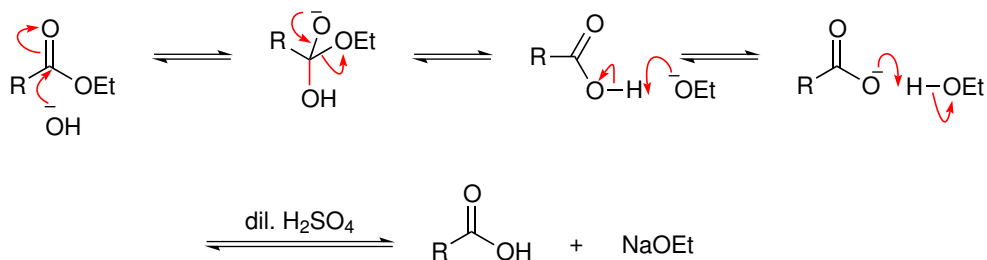
Mechanism



Esters are also hydrolysed by alkali to the carboxylic acid (after acidification)



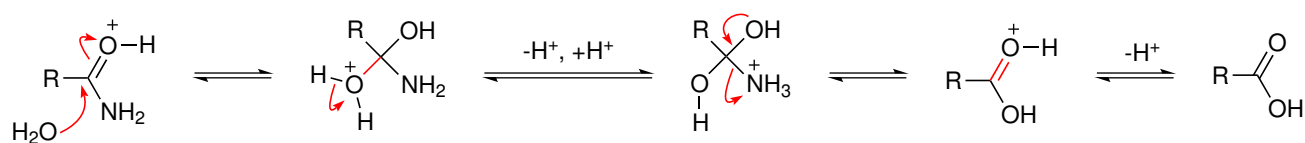
Mechanism



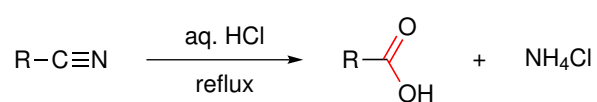
ii) Amides



Mechanism



iii) Nitriles



Mechanism

