GENERAL ORGANIC MECHANISMS NOTES

Acids & Bases

Strengths of H-A are expressed on the pK_a scale, where $pK_a = - \log_{10} K_a$. In order to have a unified scale for H-A and B strength, the acid strength of BH^+ rather than base strength of B is usually listed. If required, the latter value is easily calculated from the former.

As acid strength increases, K_a increases, pK_a decreases. As the base strength of B increases K_b increases and pK_a (of BH^+) increases.

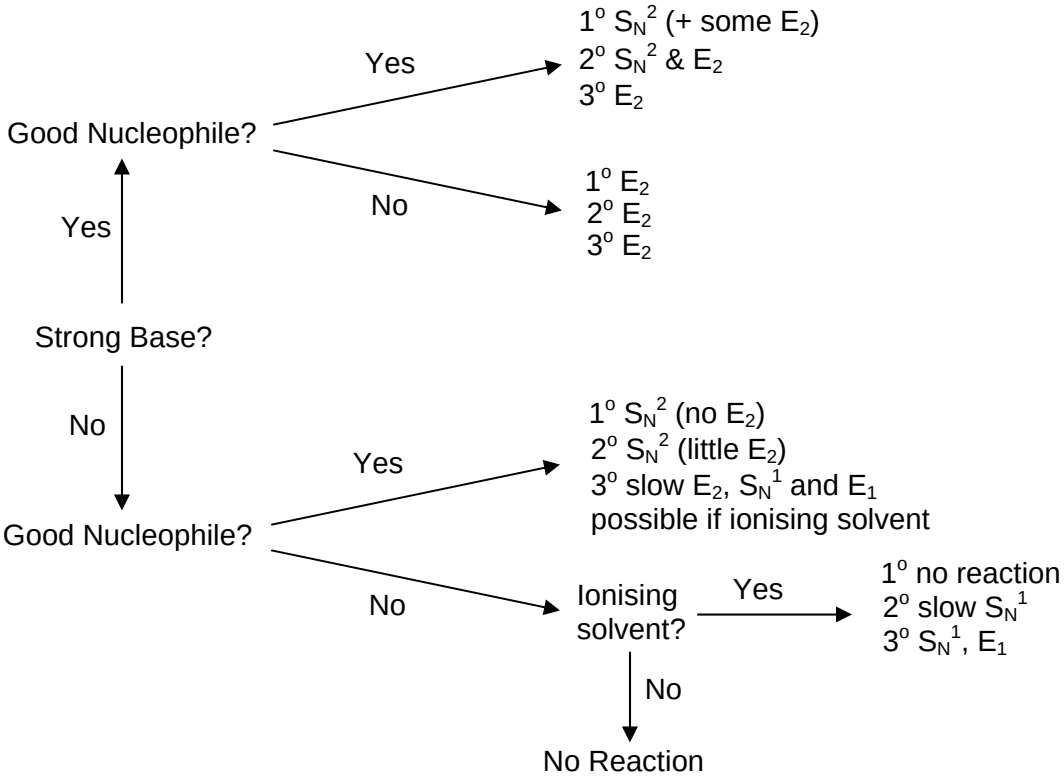
Some pK_a's:

Acid	***pK_a***	***pK_a of BH^+***
HCl	-7	
CCl_3CO_2H	0.9	
$ClCH_2CO_2H$	2.8	
$PhCO_2H$	4.2	
$MeCO_2H$	4.8	
O_2N-Ph-CO_2H	7.2	
$CH_3COCH_2COCH_3$	9	
HCN	9.2	
PhOH	10	
$CH_2(CO_2Et)_2$	13	
Neutral		
H_2O	15.7	
MeCHO	17	
EtOH	18	
Base		
O_2N-Ph-NH_2	19	1.0
Me_2CO	20	
$PhNH_2$	~27	4.6
Pyridine		5.3
NH_3	~36	9.2
$MeNH_2$	~37	10.4
Piperidine		11.2
^-OH		15.7
CH_4	~50	

Factors Determining Acidity:

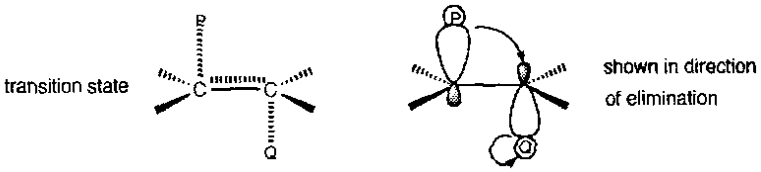
1) Weak A-H bond.
2) Electronegativity of A-H bond.
3) Stability of anion after H^+ lost (drives equilibrium to the right), e.g. inductive or mesomeric stabilisation of the negative charge, or lower hybridisation. Also stereoelectronic effects, e.g. bridgeheads can prevent the molecule becoming planar.
4) Solvation effects.

Nucleophilic Substitution

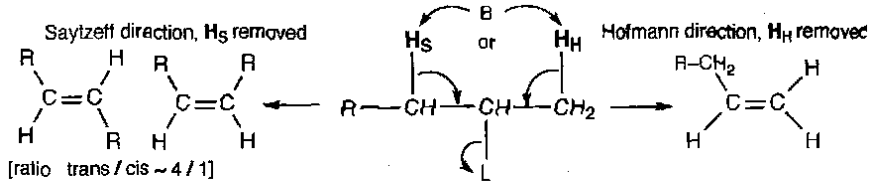


Eliminations

Stereoelectronics of transition state:



E2 Reactions



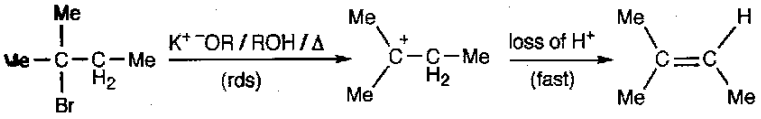
for R = Me, B = NaOEt / EtOH,

L =	Br	F	N^+Me_3
% Hofmann	19	80	95
% Saytzeff	81	20	5

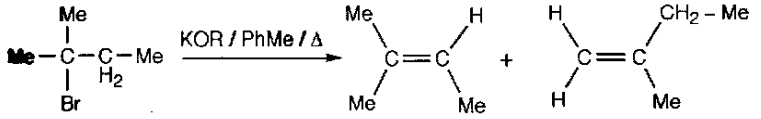
Hoffmann / Saytzeff Ratio increases as:

(i) Strength of B increases.
(ii) Electron withdrawal of L increases.
(iii) L^- becomes a poorer leaving group.
(iv) Size of B increases.
(v) Size of R or L increases.

E1 Reactions

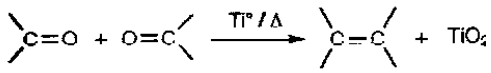


If conditions are changed so that E2 is more favoured:

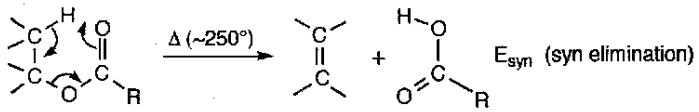


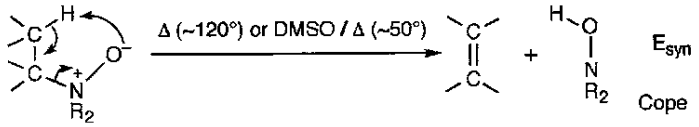
$RO^- = MeO^-$	81%	19%
$RO^- = Et_3O^-$	22%	78%

Other routes to alkenes include the Wittig Reaction (see Organoelements Notes) and the McMurray Coupling Reaction:

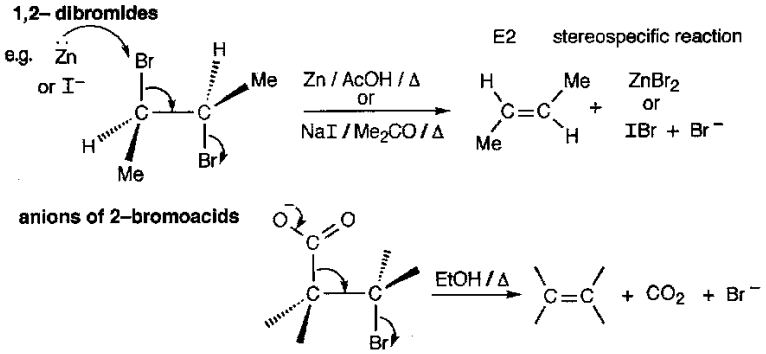


Also syn eliminations:





Note also that H-L does not have to be eliminated, can eliminate e.g. L-L:



Alkenes

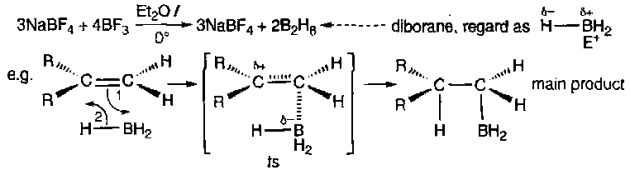
Addition to C=C bonds can take a variety of pathways.

Stepwise addition via a non-bridged intermediate usually gives rise a mixture of syn and anti products, although the anti tends to dominate. HX and H-OH react by this pathway.

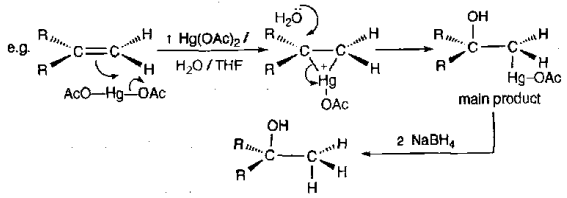
Bridged intermediates tend to be by X_2 and HO-X, the halonium being formed in both cases. Anti addition then results.

Concerted addition is also known for a variety of reagents:

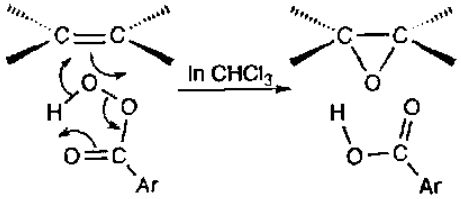
Hydroboration –



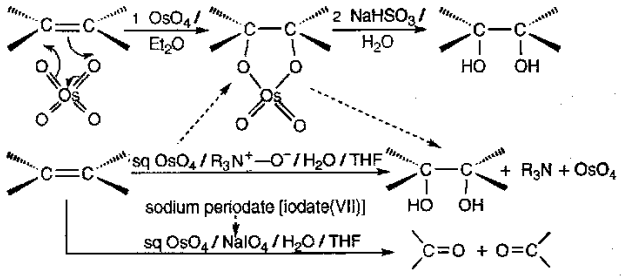
Mercuric Acetate –



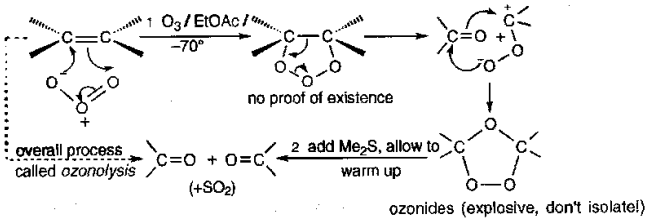
Peroxyacids –



Osmium Tetroxide –



Ozone –



Alkynes

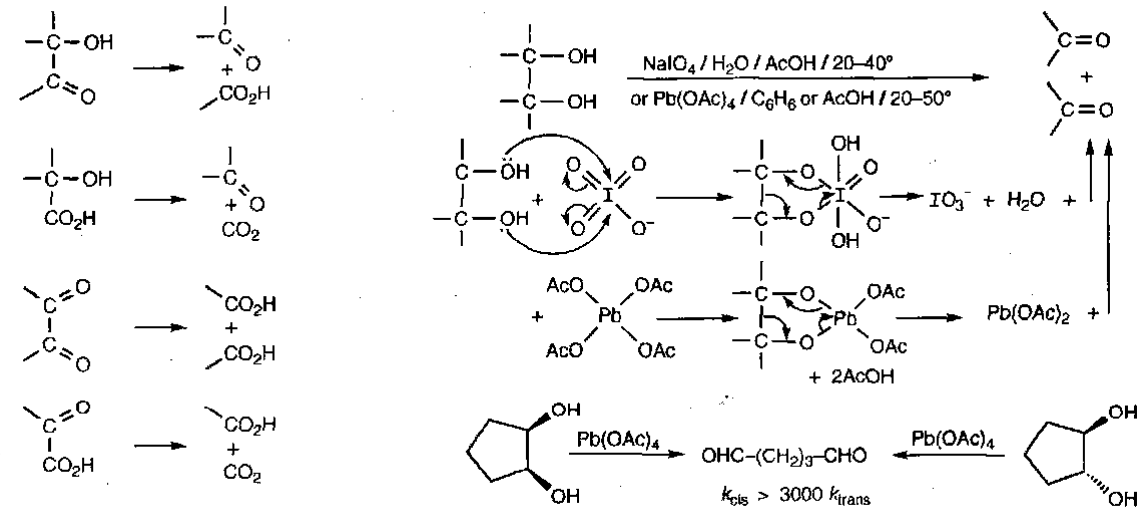
Alkynes can be synthesised from alkenes by first adding Br_2 across the double bond, and then eliminating twice using $NaNH_2$ in liquid NH_3. Similarly, diketones can be converted to alkynes by adding hydrazine. This forms a diazo intermediate at each C=O bond, which rapidly eliminates $2N_2$ to leave an alkyne.

Their principle use is in carbon-carbon bond forming reactions, as the H is acidic due to the sp hybridised carbon, so metallation is easy. They can be subsequently reduced by Lindlar's catalyst + H_2, or Na in NH_3 (methods give cis and trans respectively).

Alcohols

Chemistry of these is somewhat obvious. Particular reactions worth knowing are the methods of oxidation of 1,2-diols:

$NaIO_4$ and $Pb(OAc)_4$ oxidations:

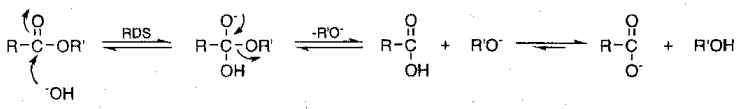


Carbonyls & Esters

Mechanisms for Ester Hydrolysis

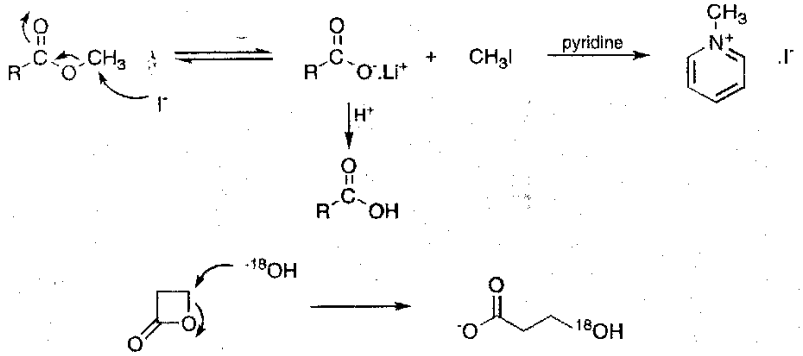
There are actually 8 possible mechanisms for this. The terminology used is A/B for acid/base catalysed, then a subscript **Ac/Al** for **acyl/alkyl** bond cleavage respectively, and finally 1 or 2 for uni-/bi-molecular rate determining step. There are two unknown mechanisms of the 8, these are the A_{Al}^2 and B_{Ac}^1. Some of the others are very uncommon as well.

B_{AC}^2 –



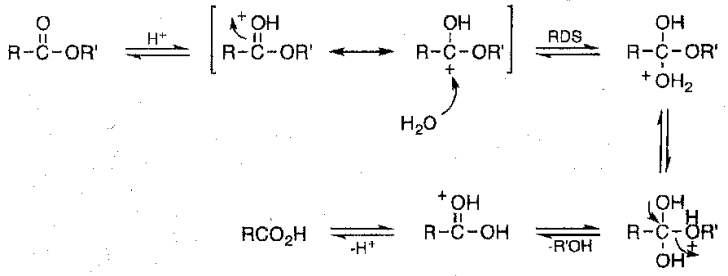
- Most common method for hydrolysis of simple alkyl esters (Me, Et, Ph, etc).
- ^{18}O incorporation experiments show acyl-oxygen cleavage.
- OH^- attack to form tetrahedral intermediate is rate determining.
- Carboxylic acid deprotonation renders reaction essentially irreversible.

B_{AL}^2 –



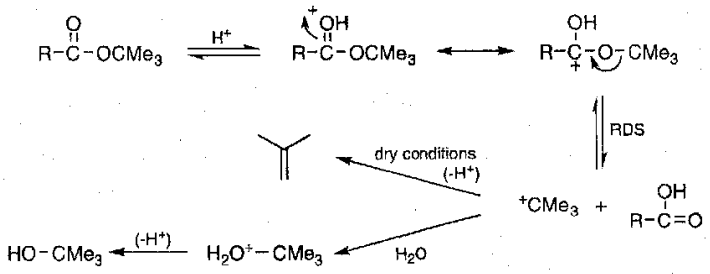
- Less common. Mechanism observed for Me esters and β-lactones.
- It requires a good nucleophile such as I^- or $PhSe^-$.
- Pyridine traps the CH_3I as a salt to displace the equilibrium to the right.

A_{Ac}^2 –



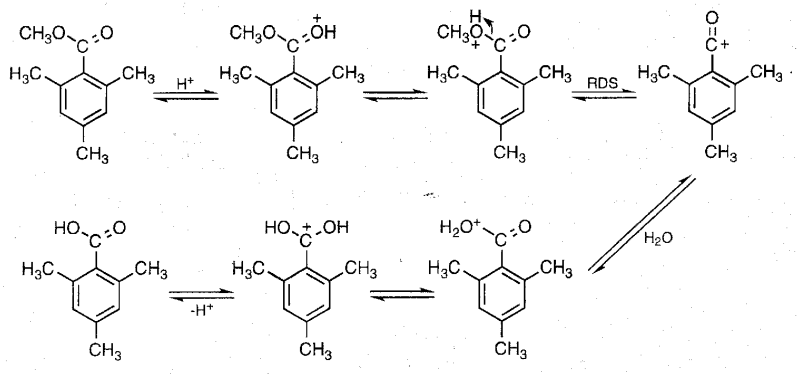
- Acid catalysed equivalent of B_{AC}^2 mechanism.
- Has been proven by ^{18}O substitution and NMR studies.
- More commonly used in reverse in ester formation.

A_{AL}^1 –



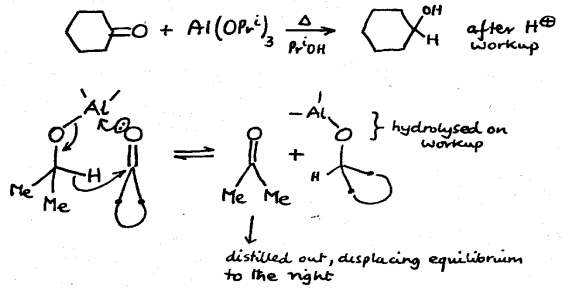
- Mechanism observed for RCO_2R' where R' can form a stable carbocation on alkyl-oxygen cleavage, e.g. R' = ^{t}butyl, $CHPh_2$.
- Can be used in reverse for formation of these esters (e.g. RCO_2H + 2-methylpropene + H^+).

A_{AC}^1 –



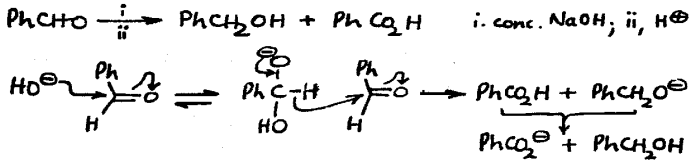
- Occurs for RCO_2R' where R is bulky (i.e. a tetrahedral intermediate would be too hindered).
- Occurs via an acyl cation, and only in powerfully ionising solvents.

Meerwein-Ponndorf-Varley Reaction

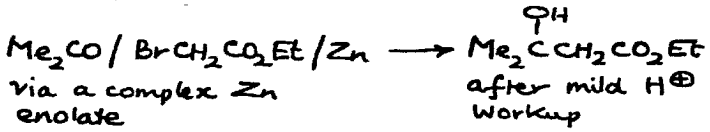


Equilibrium reaction, so can be reversed – oxidising secondary alcohols to ketones by treatment with excess acetone (normally called Oppenhauer Oxidation).

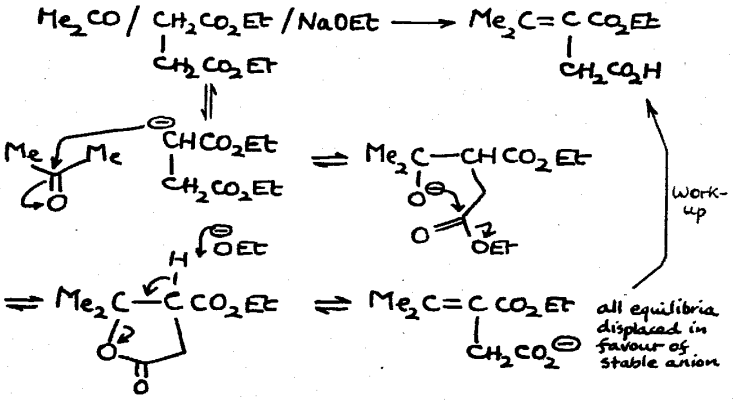
Cannizzaro Reaction



Reformatsky Reaction



Stobbe Reaction



Darzen's Reaction