This big chapter will cover:

1) Stability of Carbocations

2) Formation of Carbocations   (a) ionization

         (b) addition to a π bond

         (c) Alkyl Halide and a Lewis Acid

3) The Fate of Carbocations

4) Rearrangements of Carbocations

5) Electrophilic Addition   (a) Regiospecificity

         (b) Stereochemistry

6) Acid catalyzed Reactions of Carbonyl Compounds

         (a) Hydrolysis of Carboxylic Acids derivatives

         (b) Acetals and Orthoesters

         (c) 1,4-addition

7) Electrophilic Aromatic Substitution

8) Carbenes   (a) Singlet and Triplet Carbenes

         (b) Formation

         (c) Reactions

9) Electrophilic Heteroatoms   (a) Electron Deficient Nitrogen

         (b) Rearrangements Involving Electrophilic Nitrogen

         (c) Rearrangement involving Electron Deficient Oxygen [1]

Reactions involving Electrophiles and Acids

Acids and **electrophiles** are electron deficient species.

According to the Lewis theory, <u>all</u> electrophiles (e.g. carbocations, carbenes, metal ions, etc) are acids.

Frequently people prefer to use
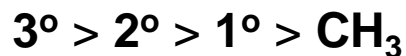
Acid = **proton donor**

Protic **Acid** = **proton donor**

<u>**Lewis**</u> **acid** = **electron pair acceptor**

1) Stability of carbocations

Reactions with acids often result in cations (esp. **carbo**cations).

A **carbo**cation is a trivalent, positively charged **carbon** atom.

The stability order of carbocations bearing only **alkyl** groups is

$$3° > 2° > 1° > CH_3$$

Cation stability is influenced by **FOUR** factors:

a) Hyperconjugation

Increasing the number of alkyl substituents **increases** the stability of the carbocation. This is due to orbital overlap between the σ bond and the empty p orbital on the sp^2 carbon.

b) Inductive Effects

Neighbouring alkyl groups contain electrons that are **polarizable**, and these can shift towards the positive charge. (Small Hydrogen substituents cannot do this as well).

c) Resonance Effects

Conjugation with a multiple bond or lone pairs of electrons **increase** the stability of a carbocation.

Therefore allylic and benzylic systems are more stable than their saturated counterparts.

Be aware of the potential for **heteroatoms** to stabilize carbocations (since they can have **lone pairs**).

E.g.

$$R - \overset{\overset{\displaystyle R}{|}}{\underset{\oplus}{C}} \overset{\frown}{-} \ddot{O} - CH_3 \quad \longleftrightarrow \quad R - \overset{\overset{\displaystyle R}{|}}{C} = \overset{\oplus}{\ddot{O}} - CH_3$$

$$R - \overset{\frown}{\underset{\oplus}{C}} = \ddot{O} \quad \longleftrightarrow \quad R - C \equiv \overset{\oplus}{\ddot{O}}$$

$$R - \overset{\overset{\displaystyle :\ddot{Cl}:}{|}}{\underset{\oplus}{C}} - R \quad \longleftrightarrow \quad R - \overset{\overset{\displaystyle :\ddot{Cl}^{\oplus}}{||}}{C} - R$$

d) Hybridization also influences cation stability.

The *more* **s** character in an orbital, the *less stable* the cation.
Therefore sp hybrid cations are very unstable.

Approx order of stability:

CH_3CO^+ ~ $(CH_3)_3C^+$ *(Resonance versus Alkyls)*

>> $PhCH_2^+$ **>** $(CH_3)_2CH^+$ **>** $CH_2=CHCH_2^+$
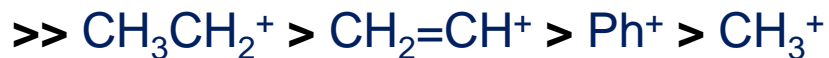
>> $CH_3CH_2^+$ **>** $CH_2=CH^+$ **>** Ph^+ **>** CH_3^+ *(Hybridization and Alkyls)*

2) Formation of carbocations

a) ionization

Unimolecular ionization results in a **carbocation** and a **leaving group**.

If the carbocation leads to a substitution product = S_N1 reaction.
If the carbocation leads to an elimination product = **E1** reaction.

In both cases the *ionization* is the **rate determining step**.

E.g. Acid catalysed dehydration (loss of water)

The protonation (and deprotonation) occur **faster** than the loss of water from the protonated alcohol.

E.g. Spontaneous ionization of a triflate.
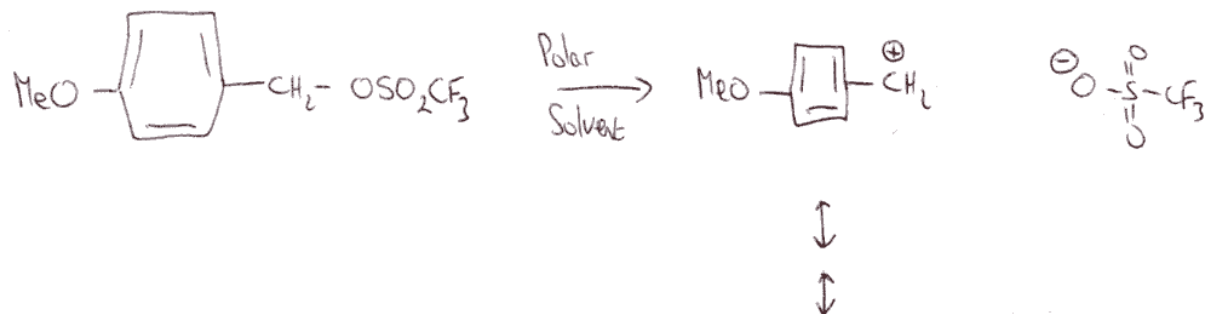
Ionization is *encouraged* here by several factors:

i) benzylic cation is resonance stabilized
ii) *para* MeO- group further stabilizes the cation
iii) excellent leaving group
iv) Polar solvent stabilizes the ionic species.

b) Addition of an Electrophile to a π bond

A common way to generate cations is an **addition** of a Lewis acid (often a H+) to a π bond.

E.g. protonation of an alkene:

E.g. protonation of a carbonyl group:
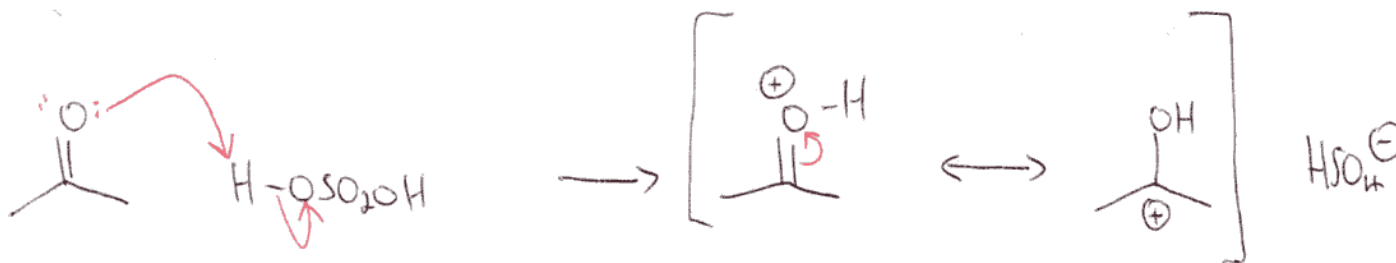
In acid, carbonyl compounds become protonated on the O, although there is significant +ve charge on the carbon (activated carbonyl complex towards nuc attack).

Protonation of **Esters** occurs at the **carbonyl oxygen** as this leads to an extensively delocalised cation.
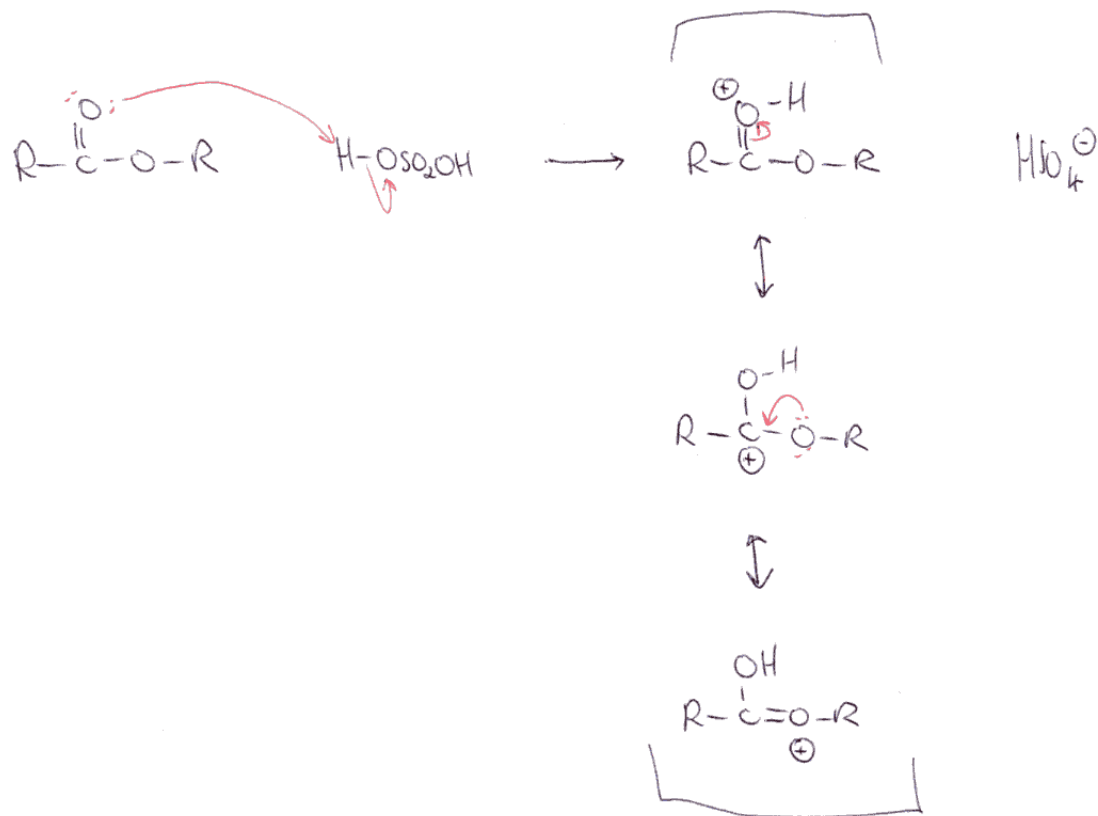
Reaction of a carbonyl compound with a Lewis acid.

The **basicity** of the carbonyl **oxygen** allows reaction with Lewis acids such as $AlCl_3$, BF_3 and $SnCl_4$, leading to complexes which are usually reactive intermediates.

E.g.

Friedel Crafts Acylation.
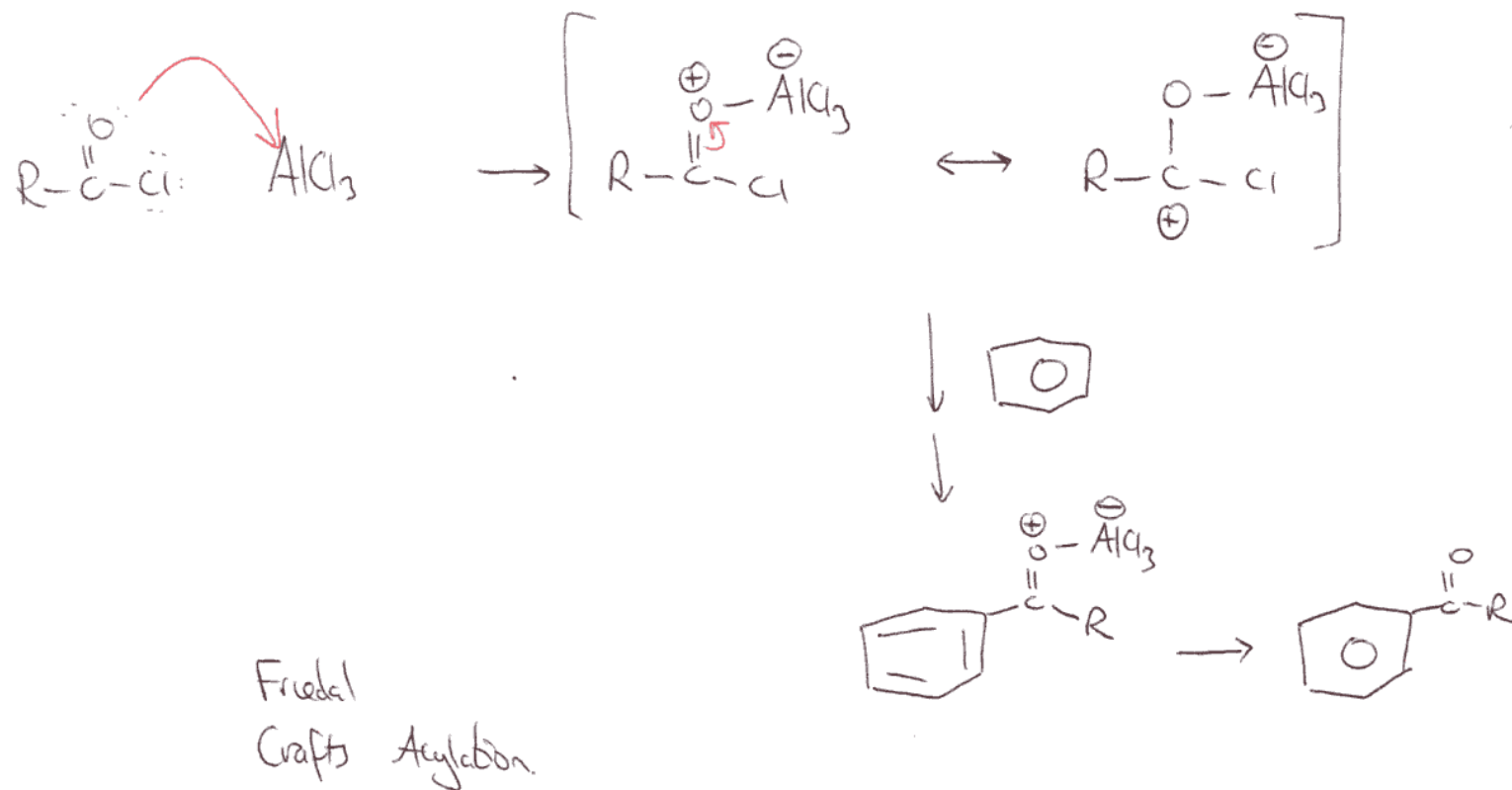
EAS will be covered in more detail later in this chapter (section 7).

c) Reaction of an alkyl halide with a Lewis Acid

E.g. AlCl$_3$ with 2-chloropentane.

The LA removes the chloride to generate the **carbocation**.

3) The fate of carbocations

Once a carbocation is formed, **4** things can occur:

1. Reaction with the leaving group to return to the starting material.
2. Reaction with a nucleophile to give S_N1 product.
3. Loss of a H^+ to give an E1 product.
4. Rearrangement to another carbocation.

4) Rearrangements of Carbocations

Rearrangements of cations **only** occur to give cations of *similar* or *increased* stability.

Generally there are only low energy barriers to cation rearrangements, so they can occur easily, often and quickly.

Rearrangement of a carbocation frequently involves a 1,2 shift of a(n) alkyl / hydride / phenyl to the **cationic** centre.

The **1,2** shift means the migration is from the carbon **adjacent** to the carbocation.

The question of migratory aptitude is complex, but in general:

aryl and branched alkyl groups **>** unbranched chains

Hydrogen is comparable to **alkyl** groups.

Often the overriding factor has to do with other considerations, such as:
-relief of ring strain
-stereochemistry
-reaction conditions, etc.

In general it is **difficult** to predict the product of a reaction involving a carbocation. It is **easier** to identify a reasonable mechanistic pathway by which an experimentally obtained product was formed from a given starting material.

E.g. a hydride shift rearrangement:

Protonation of the alcohol creates a good leaving group, which leaves, generating a primary carbocation.
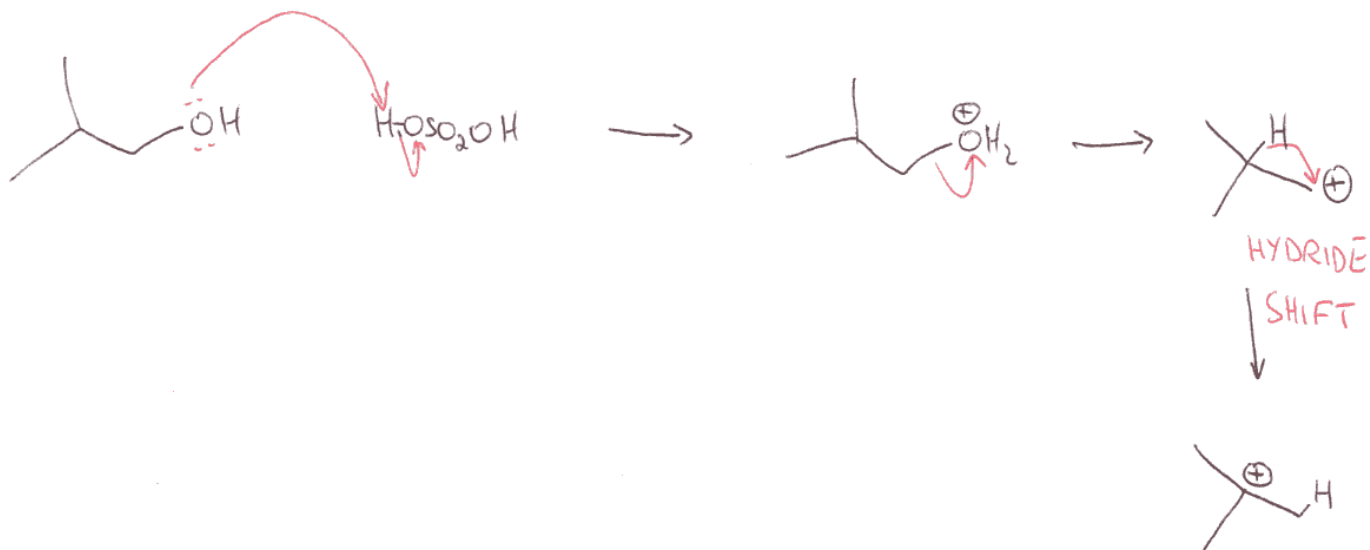
The hydrogen (*with its C-H bond electrons*) move to the **adjacent** carbon which is the carbocation.

Because the hydride took the bond electrons, the carbon where the H migrated from becomes the new carbocation.

Overall **1°** has been rearranged to **3°**.

The product is then formed by nucleophilic attack at the new, more stable carbocation.

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When dealing with rearrangements (or deciding if one has occurred), the numbering of atoms in the starting material and product is very helpful.

For example:
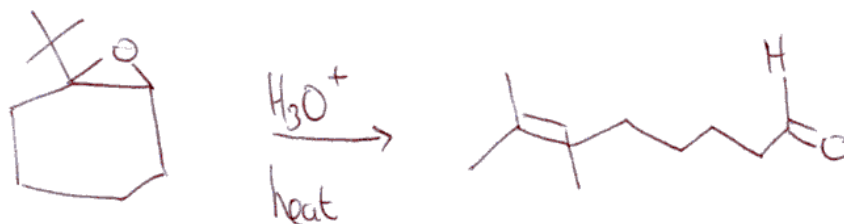
Obviously some type of rearrangement has occurred since there is no ^t**Butyl** group in the product.

Numbering gives us:
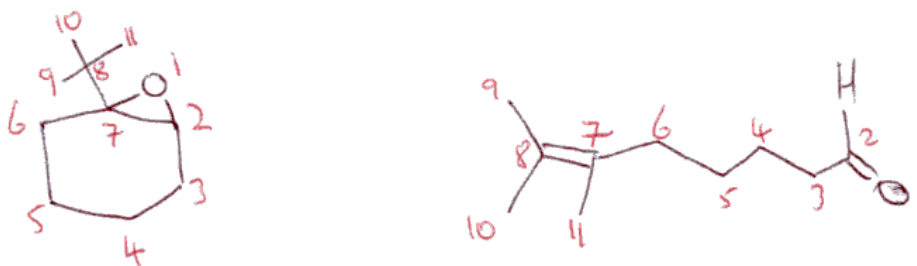
So one of the **methyls** has moved from C-8 to C-7, and C-2 is no longer bound to C-7.

Forearmed with this type of knowledge (and along with our good organic chemistry rules) we can propose a good mechanism.

The reaction takes place in acid – *so what gets protonated?*

The only basic site in the molecule is the Oxygen, so there is a good chance that this is the first step!
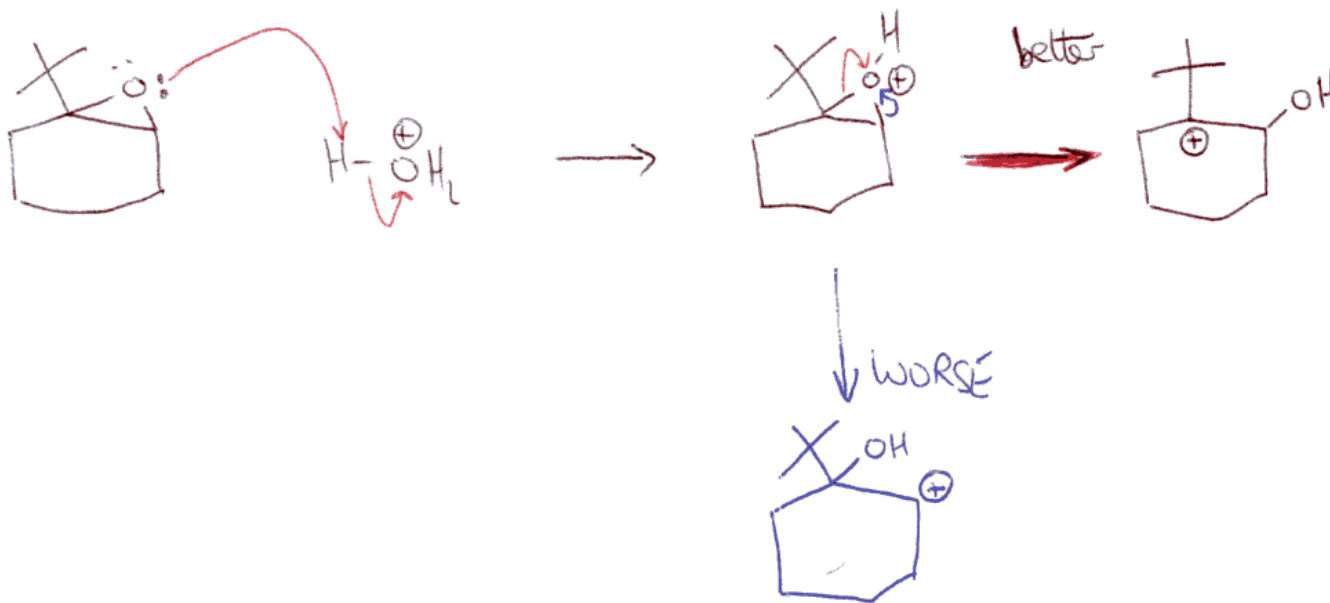
The protonated epoxide is unstable due to the large **ring strain**, and so it will ring open easily – but which way?

Applying our cation stability knowledge, the tertiary cation is preferred.

The tertiary carbocation can **rearrange** to another tertiary carbocation, where the cation is **not** in the ring (reduces ring strain).
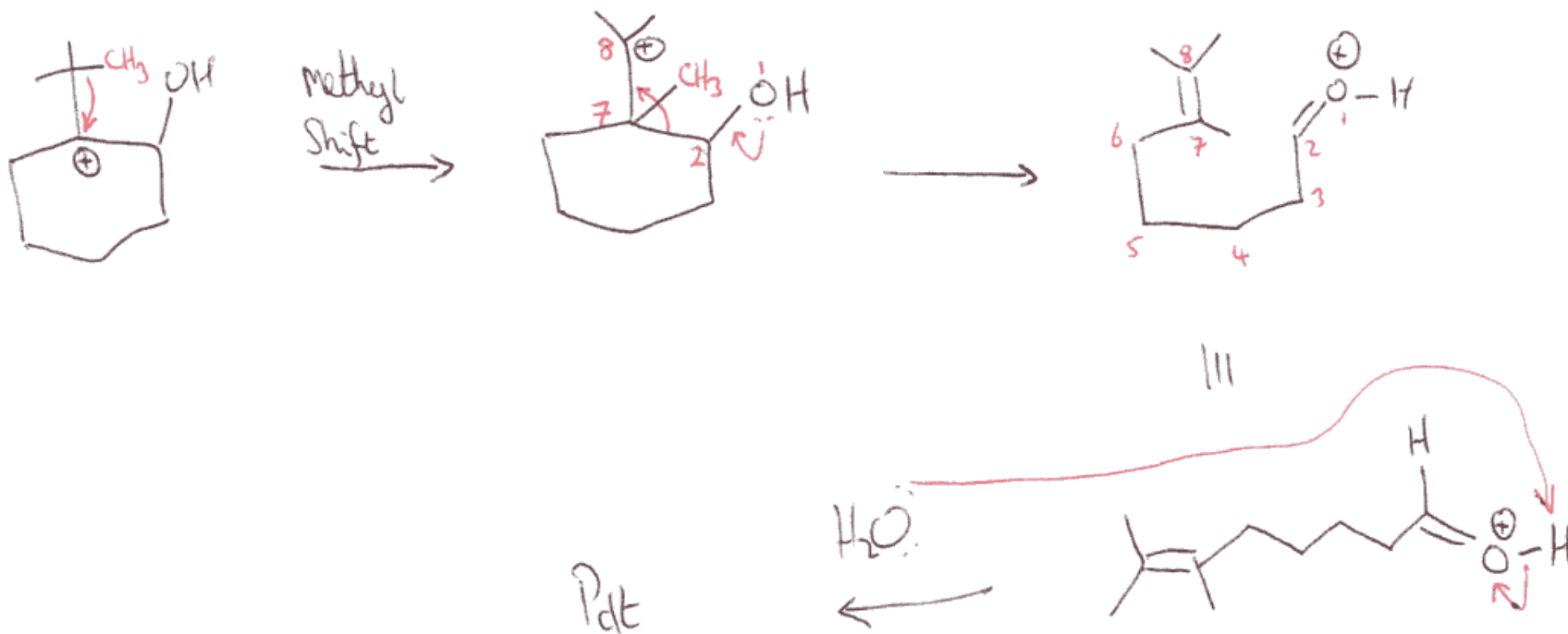
If we compare our **intermediate** and the **product**, we see that the methyl has moved onto the *correct* carbon (7), but we still need to:

       -form our aldehyde, and

       -break the C2-7 bond, and

       -make a double bond between C7-8.

       -deprotonation yields our final product.

Here are two famous "named" rearrangements.

(i) The Dienone – Phenol rearrangement

It is so named, because the SM = **dienone**, and the product = **phenol** !
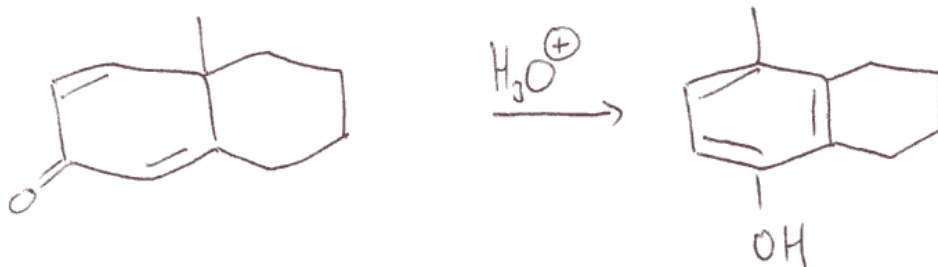
Clearly some type of **rearrangement** occurs in this transformation.
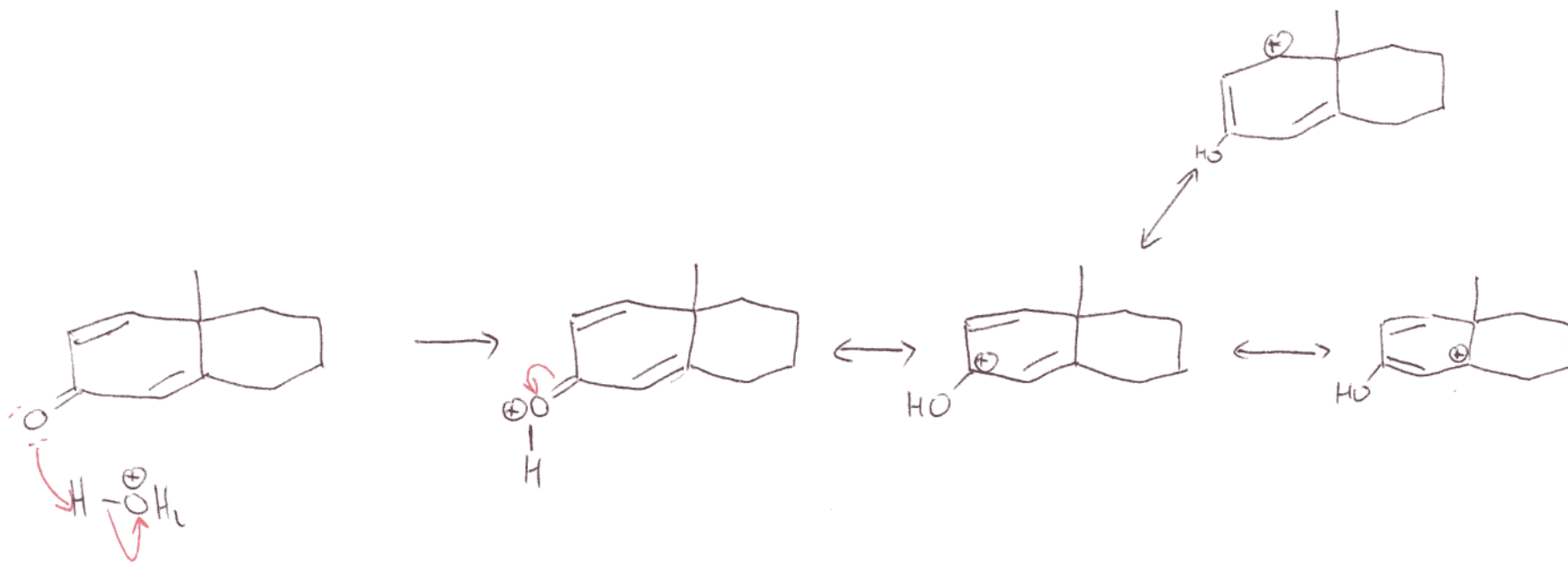
The first step is **protonation** of the **most basic site** in the molecule, resulting in a resonance delocalised cation.

The cation undergoes an **alkyl shift**, resulting in another resonance stabilized cation. This cation then undergoes another **alkyl shift**, and deprotonation yields the phenolic product.
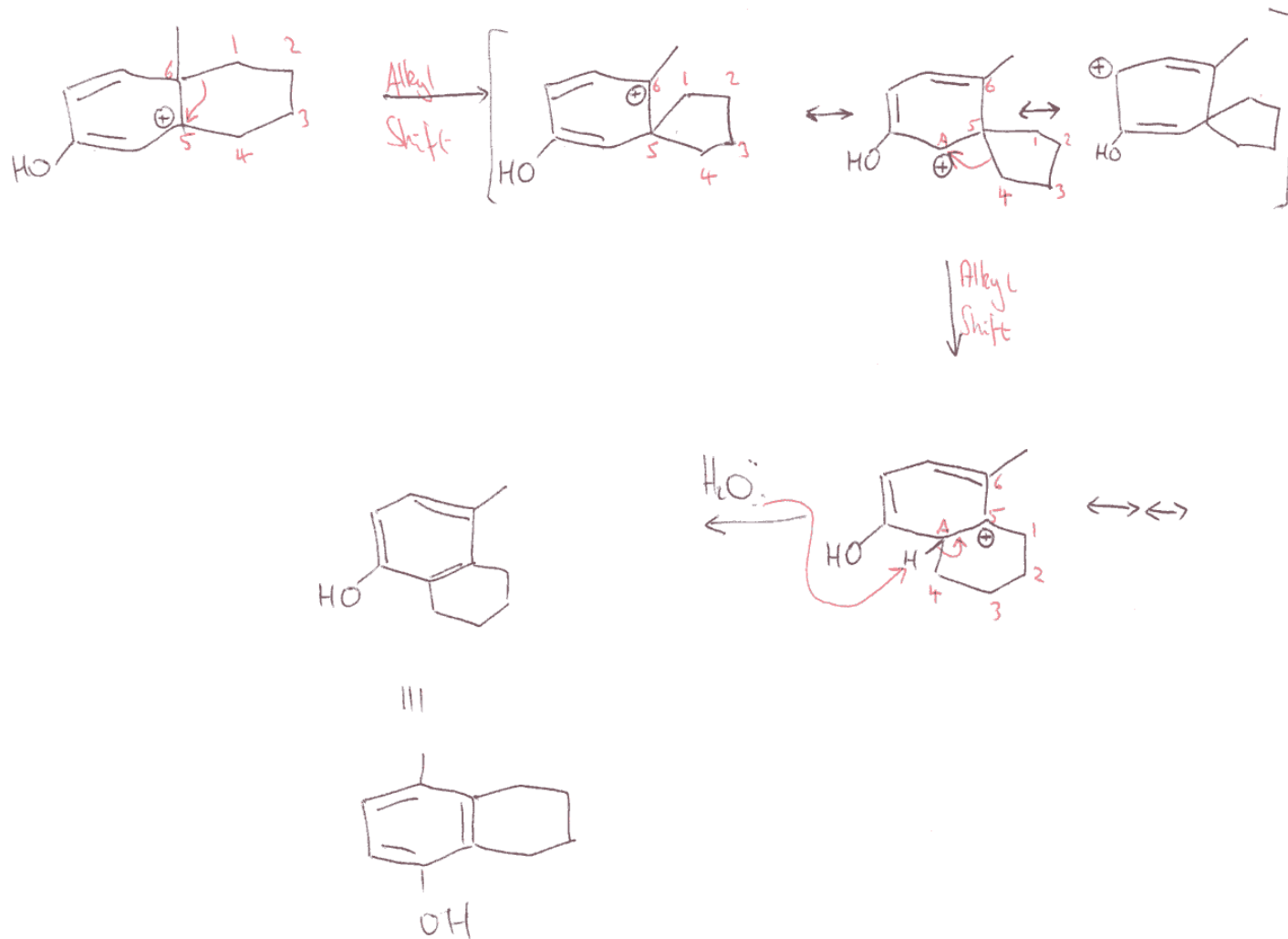
All the cations involved are resonance stabilized, and are of comparable energy to one another (which means all are interconverting = equilibrium).

The driving force for the transformation is the formation of an AROMATIC product.

Note that a complicated transformation is simply a **series** of **simple** steps.

Write mechanisms for:

(a)

H_2O →

(b)

H_3O^+ →

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(ii) The Pinacol Rearrangement

PINACOL → PINACOLONE (via H_2SO_4)
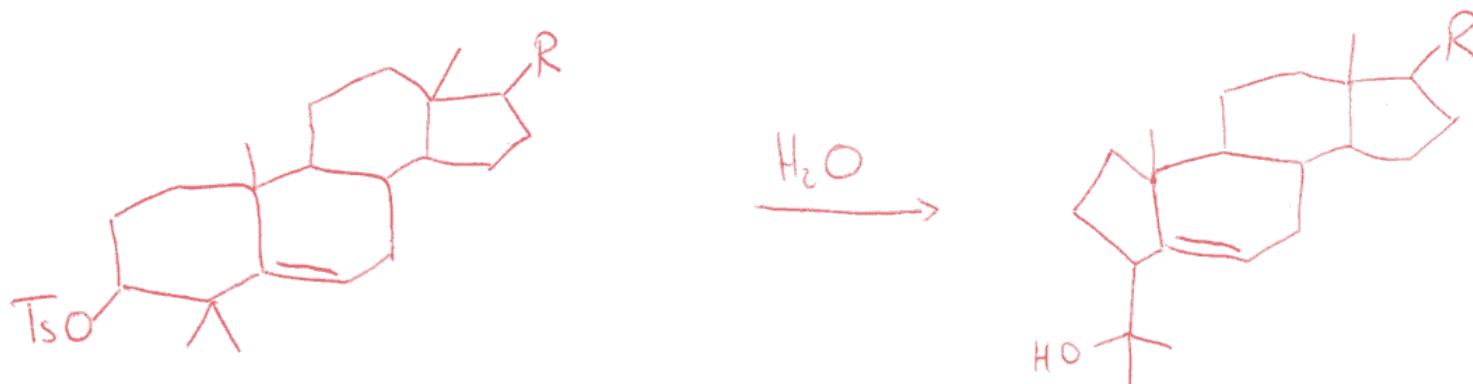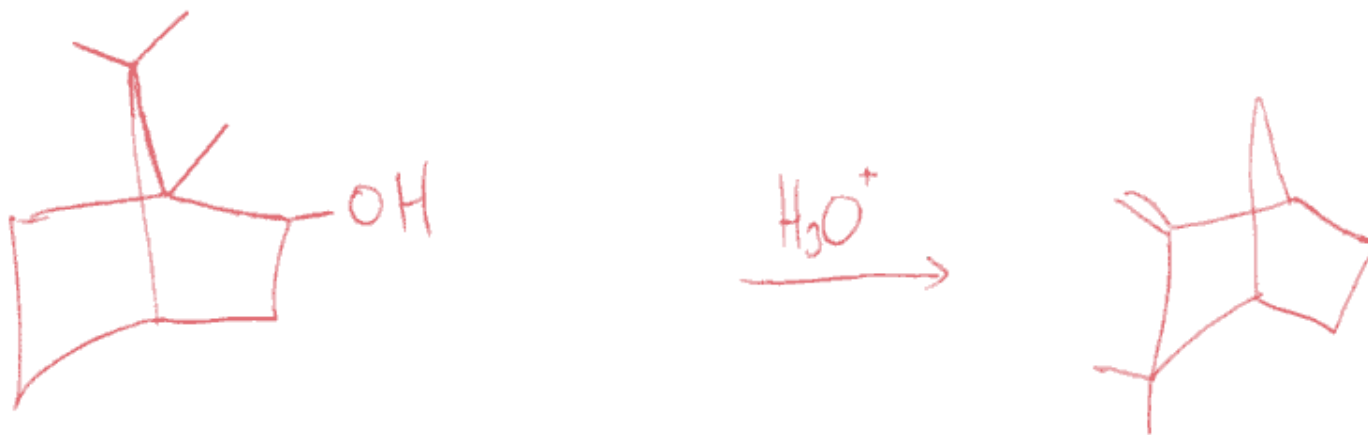
1,2-Dihydroxy compounds will often rearrange to carbonyl compounds. This is a common and widely occurring type of rearrangement.

It is called the **Pinacol** rearrangement because the most studied example is the pinacol → pinacolone transformation.

E.g. 1,2-diphenyl-1,2-ethanediol.
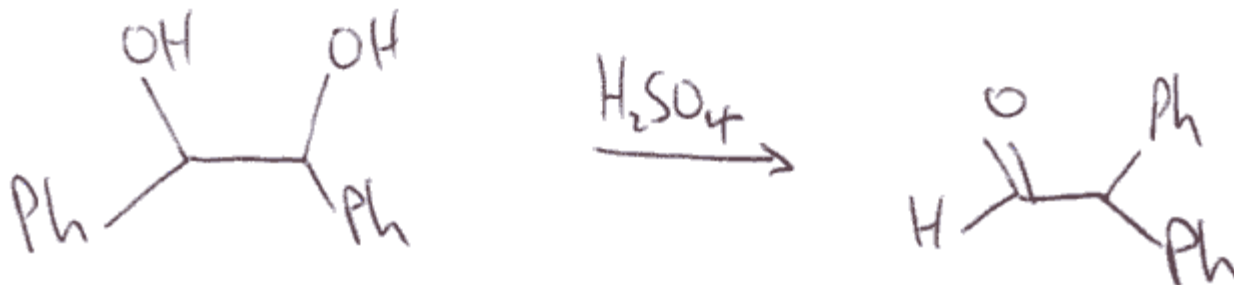
The mechanism of this rearrangement involves cation formation via acid catalysed dehydration, which then **rearranges**, followed by proton loss to yield the product.

Write the mechanism for :

OH OH

H_2SO_4 →

24
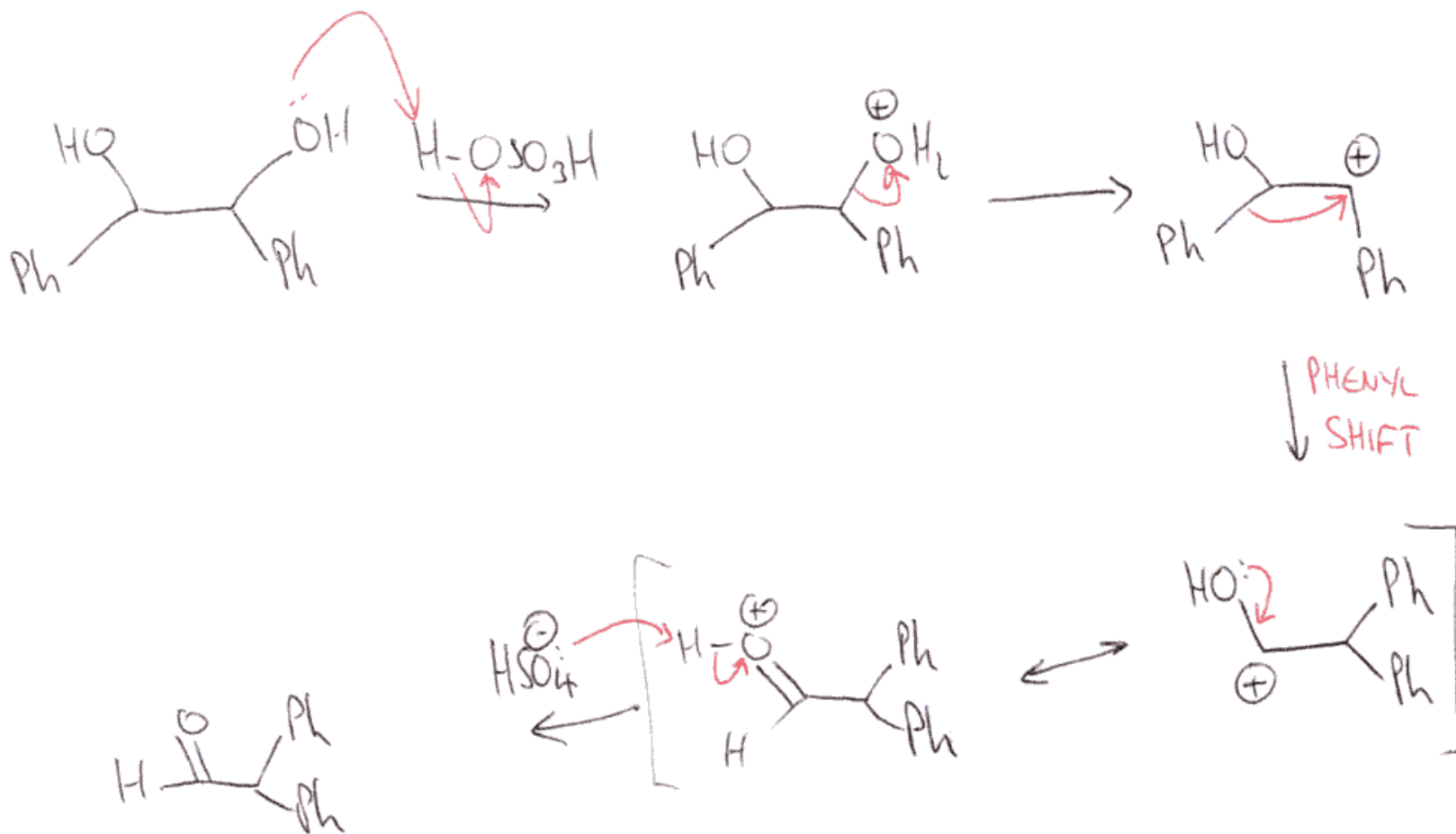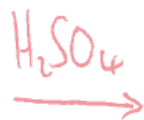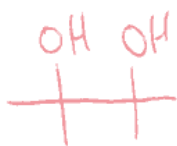
Write a Mechanism that explains the stereochemistry

BF$_3$·$(C_2H_5)_2O$

C$_6$H$_6$

Write a Mechanism for:

HCl / MeOH
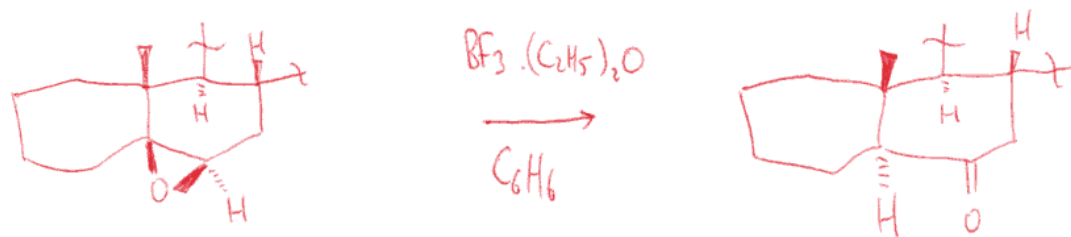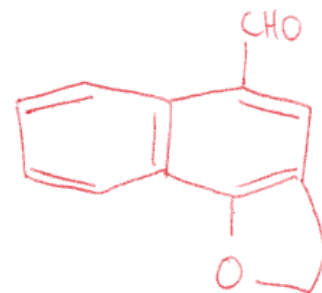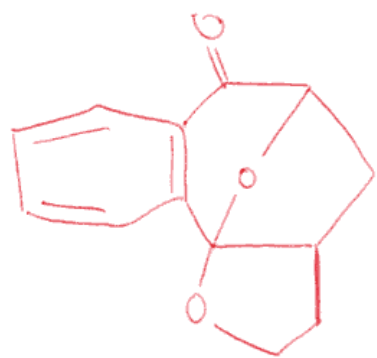
5) Electrophilic addition

Addition of an electrophile to an (aliphatic) π bond involves two major steps:

i) addition to the π bond which generates an intermediate cation,

ii) reaction of the cation with a nucleophile.

Common electrophiles include Cl_2, Br_2, Lewis acids, cations, H^+ from HCl, HBr, HI, H_2SO_4, H_3PO_4, etc.

The nucleophile in step (ii) is usually the anion / conjugate base from the electrophile (e.g. Cl^- if it was Cl_2), or a nucleophilic solvent.

a) Regiospecificity

Additions to π bonds can *theoretically* occur at either end, and therefore lead to two possible cations – although often one is preferred – thus electrophilic additions are **regiospecific**.

E.g. when HI adds to the double bond below, only one **regio-isomer** is formed. (We see no traces of 1-iodo-2-methylcyclohexane).
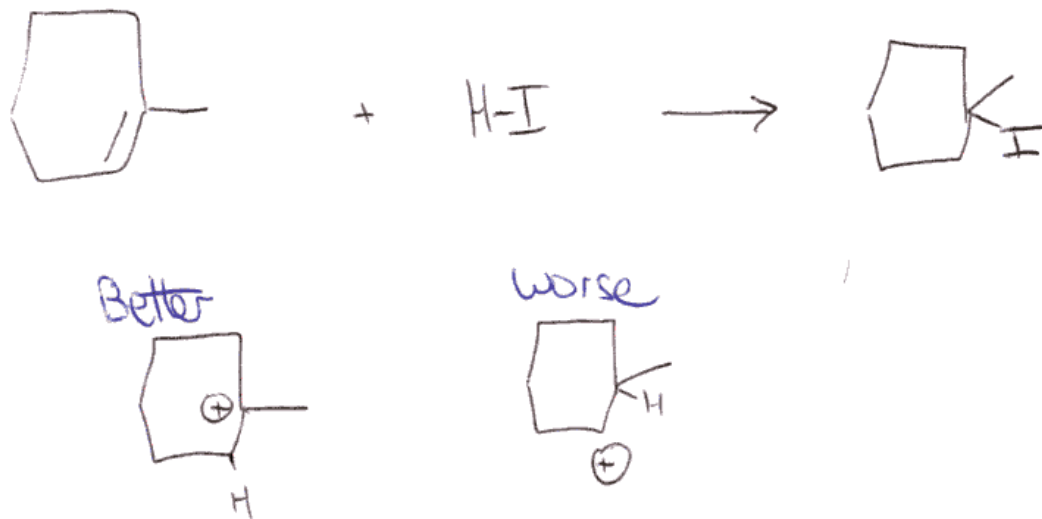
We explain this by comparing the different stabilities of the potential cation intermediates.

b) Stereochemistry

i) *Anti* addition

In some electrophilic additions, 3 membered cyclic intermediates are formed, which leads exclusively to ANTI arrangements of electrophile and nucleophile.

E.g. stereospecific *anti* addition of Br_2.

(Here, the bromonium ring formation on the top and bottom faces leads to the **same** intermediate).

Bromination of *cis*-2-butene, via the bromonium ring, leads to enantiomeric products (actually the *d and l* diastereomer pair; top is R,R the bottom is S,S).
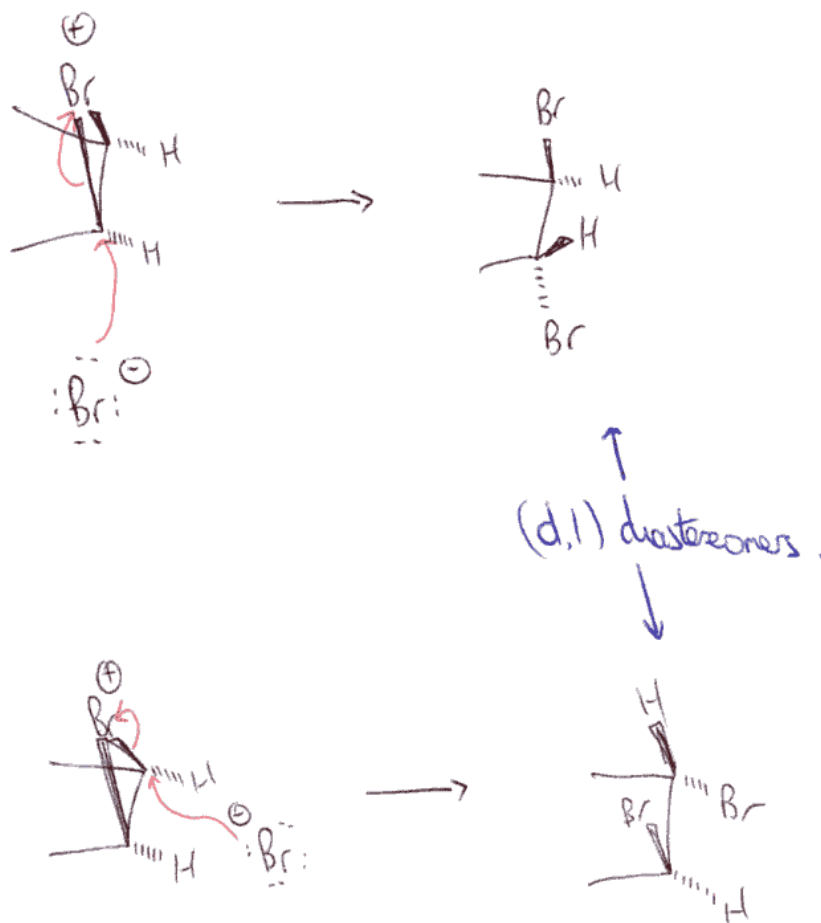
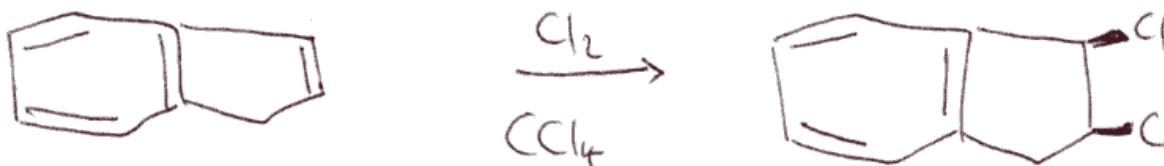The ring must be opened via **S$_N$2** reaction, leading to an *anti* arrangement of bromines in the final product.

The same bromination reaction with *trans*-2-butene leads to an *anti* dibromide which is the (achiral) *meso* diastereomer (R,S – same as S,R).
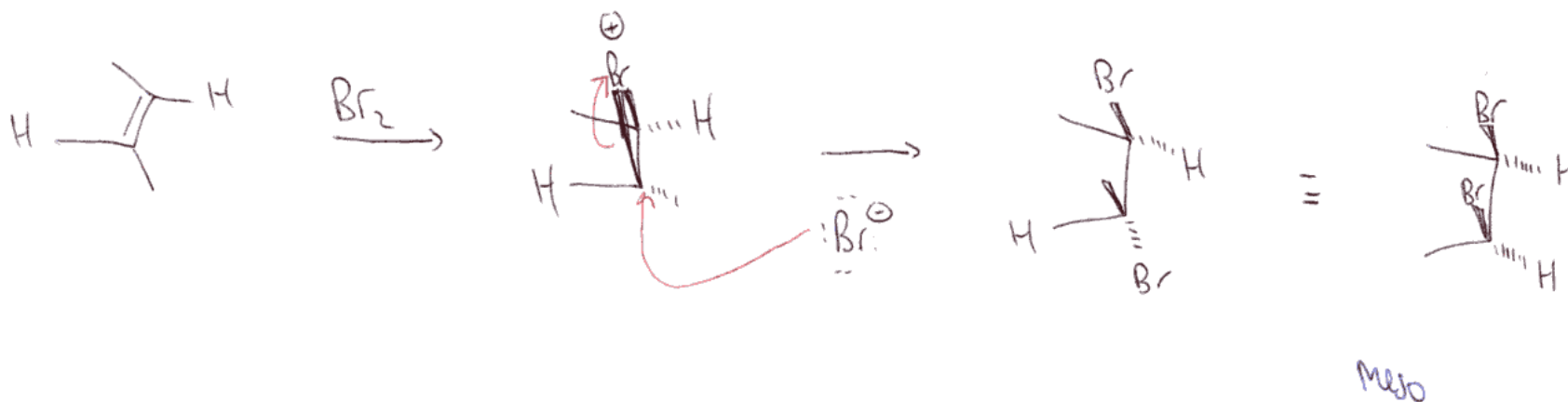
ii) *Syn* addition

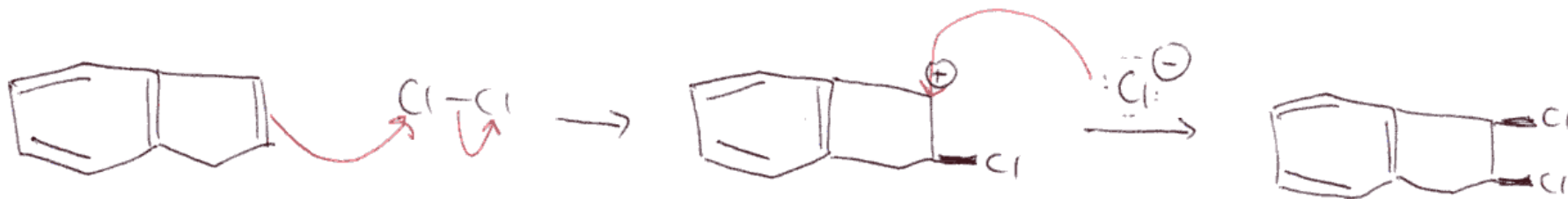Sometimes halogenations can be *encouraged* to result in *syn* addition.

E.g. Chlorination of indene.

There are several factors that promote *syn* addition here:

i. Cl_2 rather than Br_2 is used
ii. the π bond is conjugated with an aromatic ring
iii. the reaction is in a non-polar solvent

Chlorine is smaller and less polarizable than Bromine, and so has less of a tendency to form bridged intermediates.

The cation formed is resonance stabilized (benzylic) and so wishes to be planar.

The non-polar solvent does not solvate the ionic species, and so they will remain close together in an ion pair. If the Cl⁻ stays where it was formed, it will attack the cation from the same location, leading to overall *syn* addition.

iii) Non-stereospecific addition

In the absence of the previously described features, some electrophilic additions can lead to mixtures of *syn* and *anti* products.
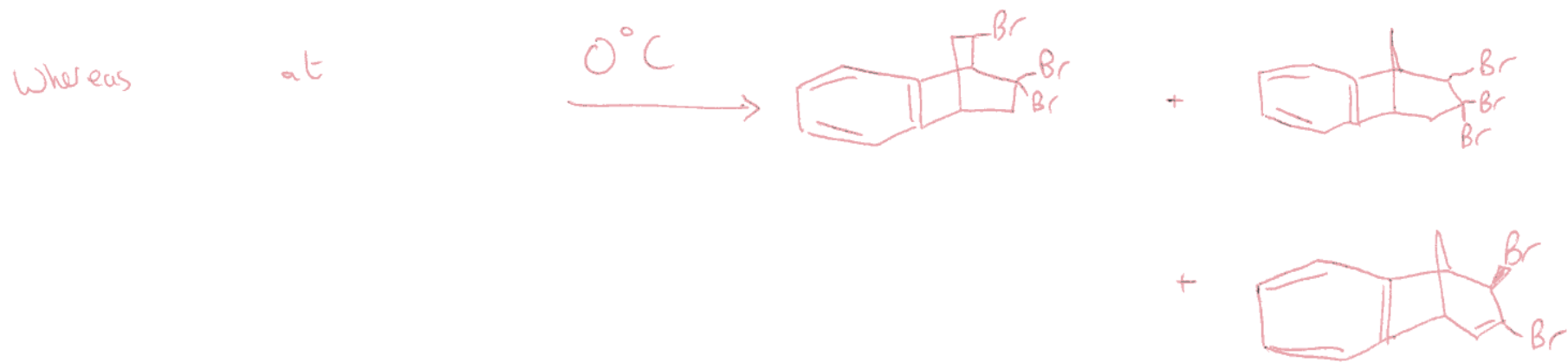
E.g. bromination in CCl_4 versus acetic acid.
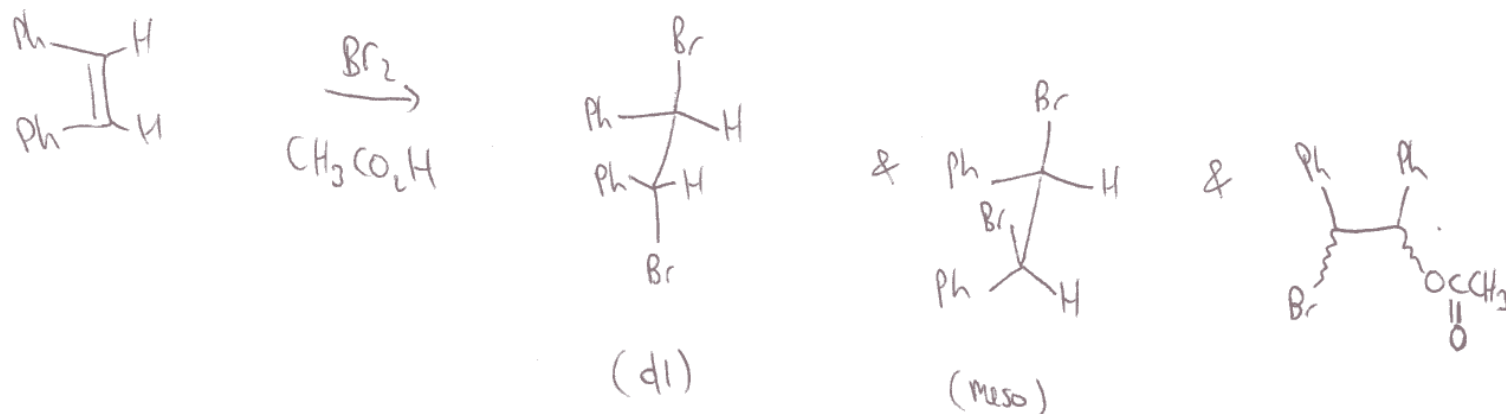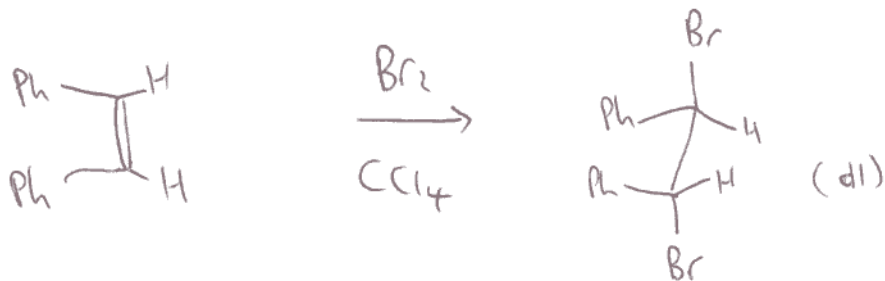
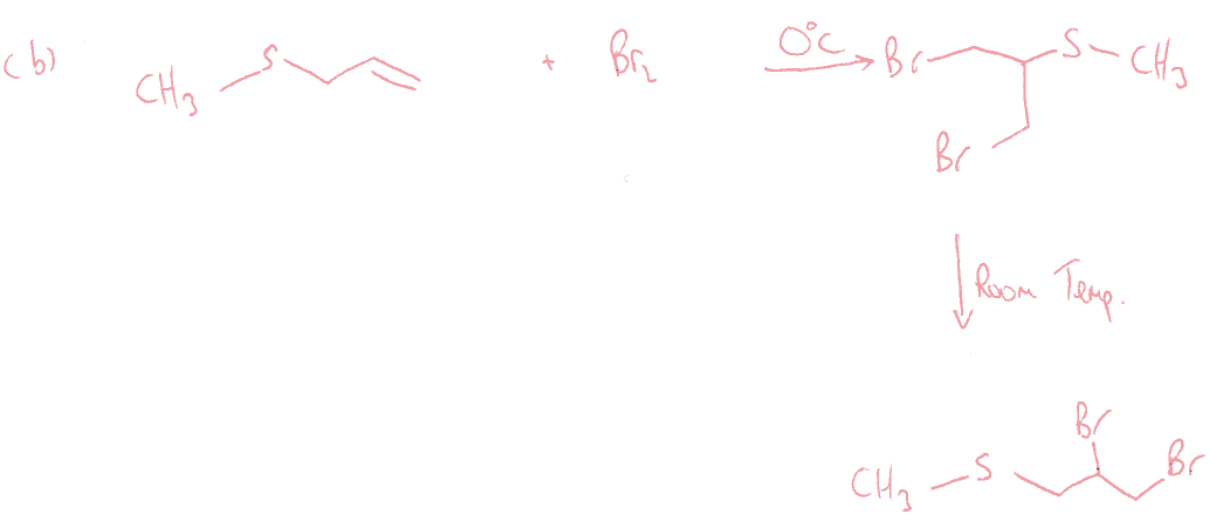The highly polar solvent encourages cation formation, and Br⁻ attacks from both faces of the planar cation.

The side product arises from the nucleophilic solvent trapping the intermediate cation.

Write mechanisms for the following:

(a)

$\xrightarrow[-50°C]{Br_2}$

Whereas   at

$\xrightarrow{0°C}$

  +

+

(b)

CH_3—S—CH$_2$—CH=CH$_2$ + Br_2 $\xrightarrow{0°C}$ Br—CH$_2$—CH(S—CH$_3$)—CH$_2$—Br

$\downarrow$ Room Temp.

CH_3—S—CH$_2$—CH(Br)—CH$_2$—Br

6) Acid catalysed Reactions of Carbonyl Compounds

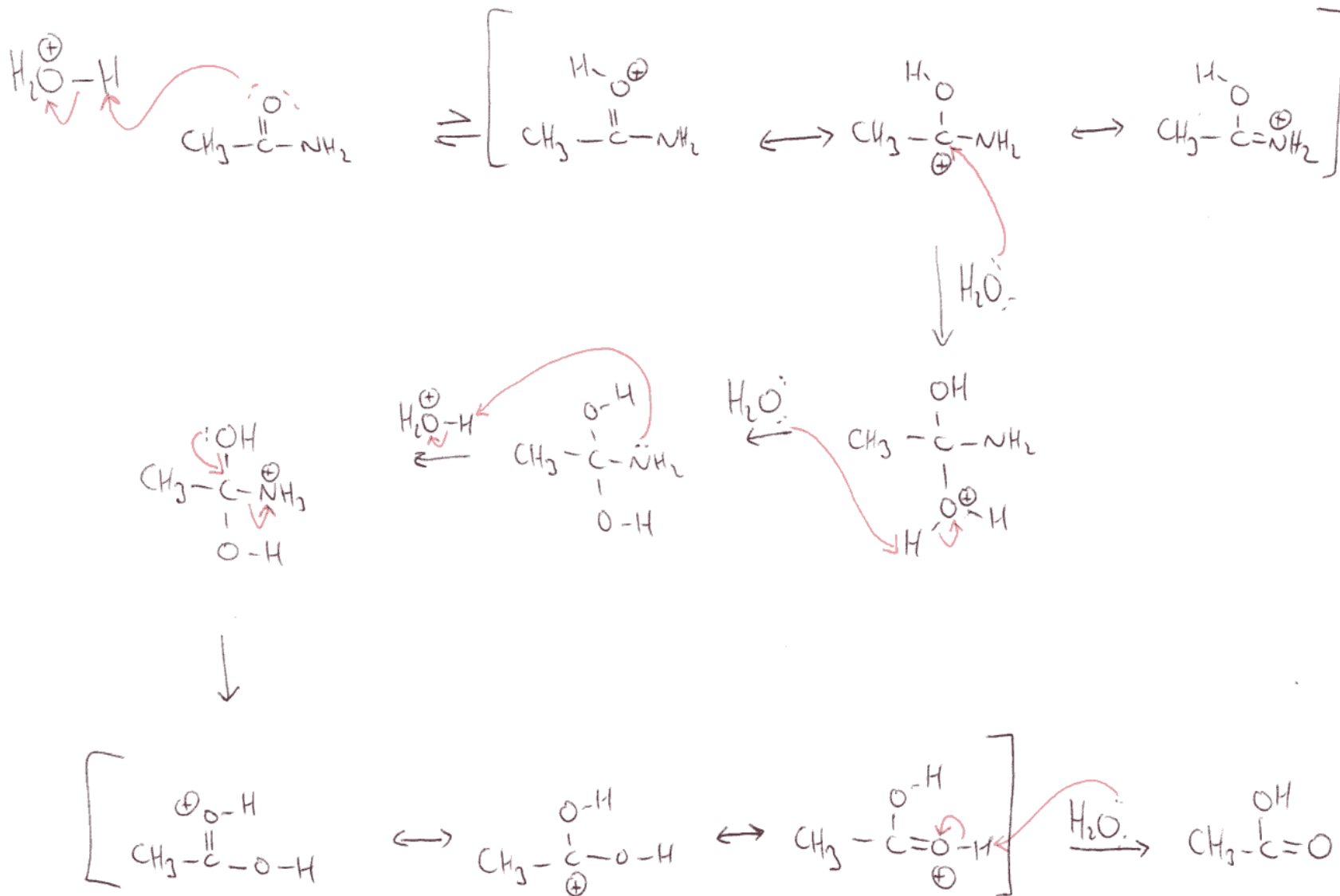a) Hydrolysis of Carboxylic acid derivatives

Acidic hydrolysis of all carboxylic derivatives (esters, amides, acid chlorides) yields the corresponding carboxylic acid.

The same 5 steps occur in all these processes:

i.   protonation of the carbonyl oxygen (increases electrophilicity of the carbonyl carbon)

ii.   the oxygen of water acts as a nucleophile and adds to the carbonyl carbon

iii.   loss of a H^+ from the oxygen of the now attached water

iv.   the leaving group leaves (either without initial protonation Cl^-, or with initial protonation for esters / amides)

v.   A H^+ is lost from the protonated carboxylic acid.

E.g. Hydrolysis of an amide

The overall reaction is

$$CH_3CONH_2 \quad + \ H_3O^+ \ \rightarrow \quad CH_3CO_2H \quad + \quad NH_4^+$$

E.g. hydrolysis of an ester

$$CH_3\overset{O}{\underset{||}{C}}-O-CH_3 \quad \underset{\rightleftharpoons}{\overset{H^+, H_2O}{\rightleftharpoons}} \quad CH_3\overset{O}{\underset{||}{C}}-O-H \quad + \quad CH_3OH$$

All the steps for ester hydrolysis are *reversible*, and the course of the reaction is governed by the reaction conditions.
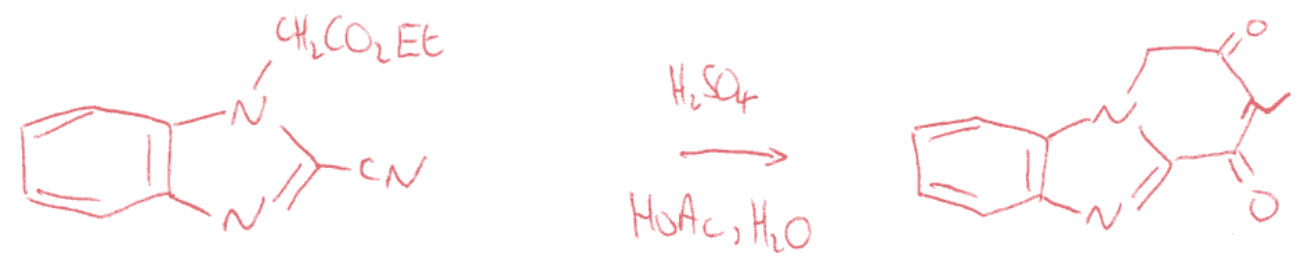
Specifically the amount of water (or alcohol) drives the equilibrium towards carboxylic acid (or ester).

Common experimental setups involve use of excess reagents, dehydration agents, distillation, etc. to influence the equilibrium.
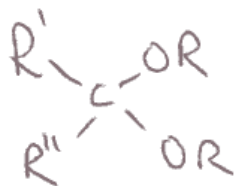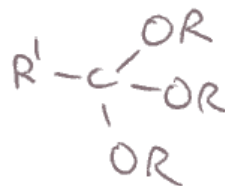
Write mechanism for the following:

(a)
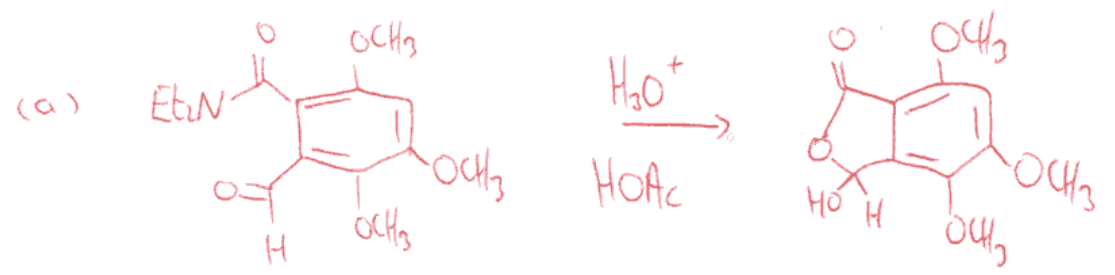
(b)

b) Hydrolysis and Formation of Acetals and Orthoesters

These compounds are types of *polyethers*.

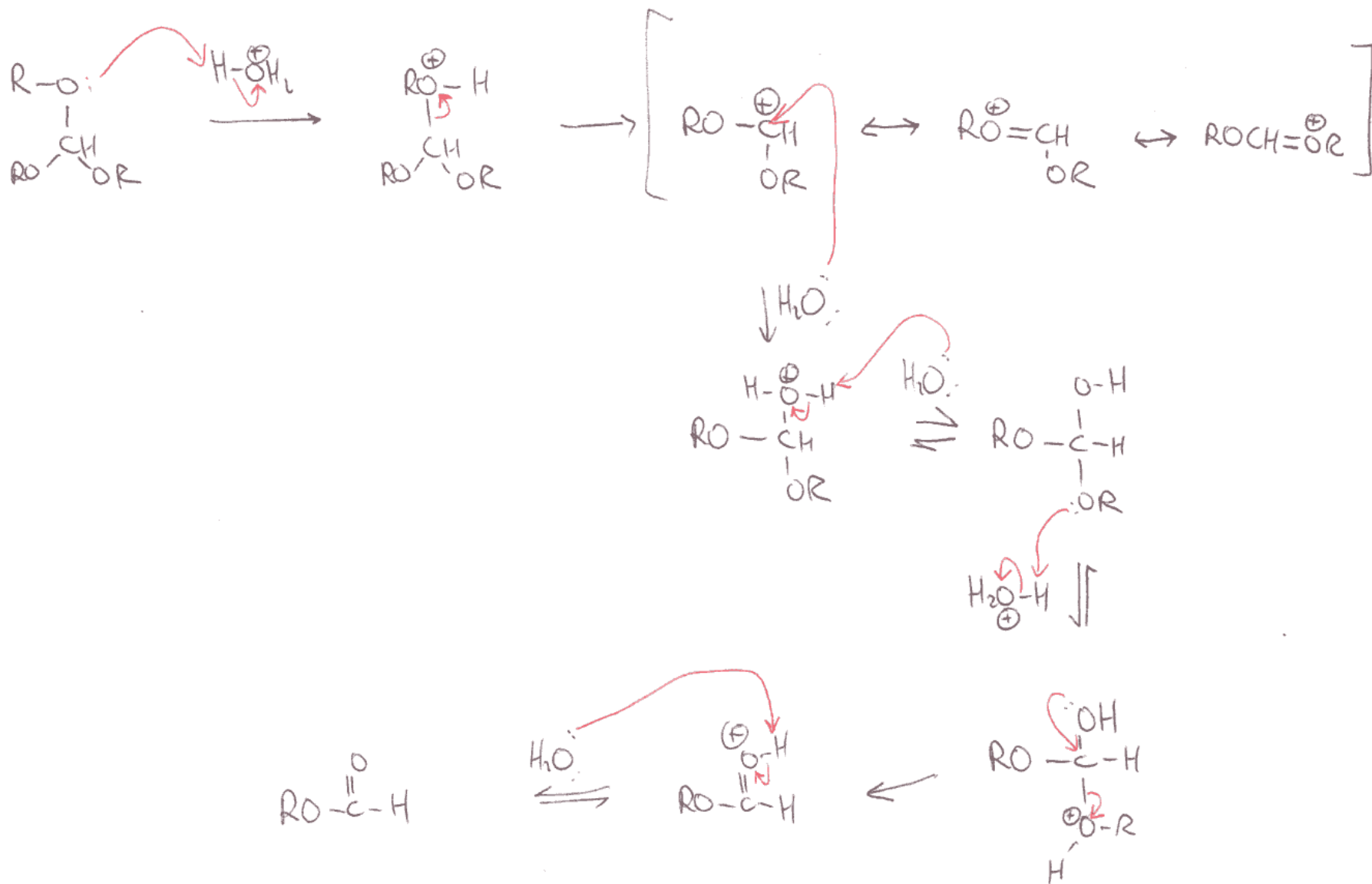Acetal   Orthoester

E.g. Hydrolysis of ethyl orthoformate to ethyl formate.

The first step involves protonation of the most basic atom, which creates a better leaving group, which leaves.

$$R-O: \quad \xrightarrow{H-\overset{\oplus}{O}H_2} \quad \overset{\oplus}{RO}-H$$

$$\underset{RO}{\overset{R-O:}{\diagdown}} \underset{OR}{\overset{CH}{\diagup}} \longrightarrow \underset{RO}{\overset{\overset{\oplus}{RO}-H}{\diagdown}}\underset{OR}{\overset{CH}{\diagup}} \longrightarrow \left[RO-\overset{\oplus}{\underset{OR}{C}H} \leftrightarrow \overset{\oplus}{RO}=\underset{OR}{CH} \leftrightarrow ROCH=\overset{\oplus}{O}R \right]$$

$$\downarrow H_2O:$$

$$\underset{RO-CH}{\overset{H-\overset{\oplus}{O}-H}{|}}\underset{OR}{} \quad \rightleftharpoons \quad \underset{RO-\overset{|}{C}-H}{\overset{O-H}{|}}\underset{:OR}{}$$

$$H_2\overset{\oplus}{O}-H$$

$$RO-\underset{\underset{H}{\overset{\oplus}{O}-R}}{\overset{OH}{\underset{|}{C}}}-H$$

$$RO-\overset{O}{\overset{\|}{C}}-H \quad \rightleftharpoons \quad RO-\overset{\overset{\oplus}{O}-H}{\overset{\|}{C}}-H \quad \leftarrow$$

$$H_2O$$

The cation formed is resonance stabilized by the adjacent heteroatoms.

The presence of a large excess of water means the cation is trapped by H_2O.

The same type of process occurs to remove the second alkoxy group, leading to the ester product.

The equilibrium of all these processes means addition of an excess of alcohol would send it back to SM.

c) 1,4-Addition

Electrophilic addition to α,β-unsaturated carbonyl compounds is analogous to electrophilic addition to C=C bonds except that electrophile adds to the carbonyl **oxygen**.

Then the nucleophile adds to the β carbon, and the resulting enol intermediate tautomerizes to the carbonyl product.

They can be viewed as the electrophilic version of Michael / 1,4-additions as discussed in the "Nucs and Bases" course.

E.g. Addition of HCl to Acrolein

The first step is reaction of the most basic atom in the molecule reacting with the protic end of HCl.
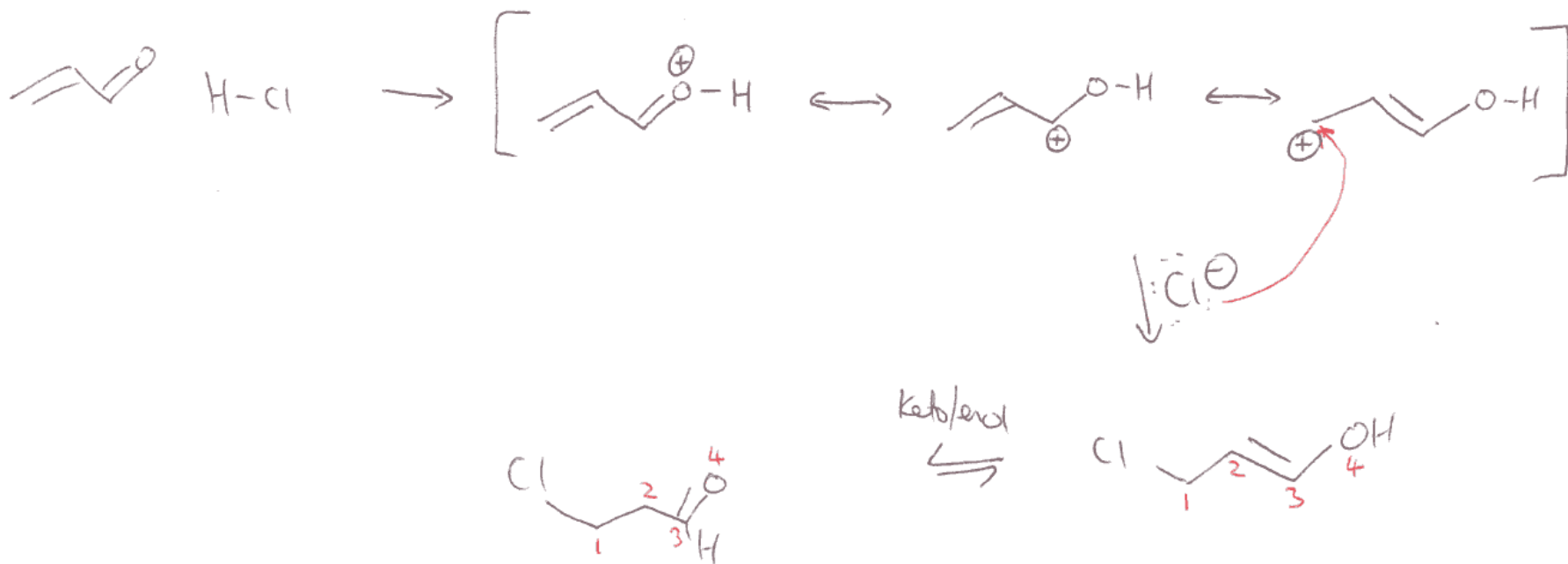
The resonance stabilized cation delocalises +ve charge over the molecule, and the nucleophile attacks the β carbon.

The enol tautomerizes to the product.

Note that Cl⁻ is not strong enough to do a *nucleophilic* 1,4-addition by itself.

Write a mechanism for

(a)

$$Cl\diagdown\diagup\diagup=\diagdown O\diagdown H \rightleftharpoons Cl\diagdown\diagup\diagdown CHO$$

(b)

$$\text{(structure with Ph, CO}_2\text{H)} + D_2SO_4 \longrightarrow \text{(lactone with Ph, D, O, =O)}$$

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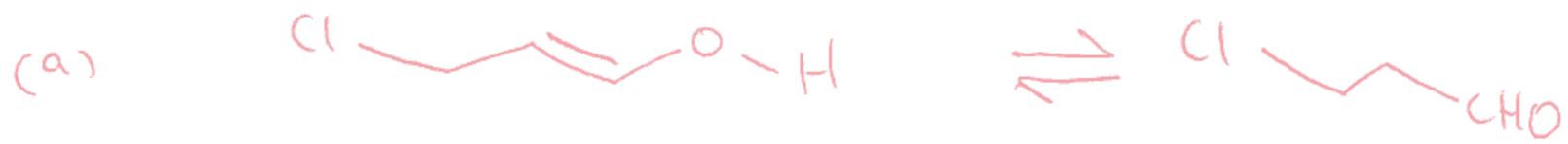
7) Electrophilic Aromatic Substitution

Certain electrophiles react with aromatic systems yielding product of substitution.

Typically these reactions involve the formation of an intermediate carbocation, followed by the loss of a positively charged species (usually H^+) to regenerate the aromatic system.

Common electrophiles for EAS include:

HAL_2 / Lewis Acid

Nitronium ion

SO_3

alkyl and acyl halides / Lewis Acid

cations

E.g. EAS of toluene with Sulfur Trioxide

The aromatic ring is the nucleophile, the S atom is the electrophilic centre.
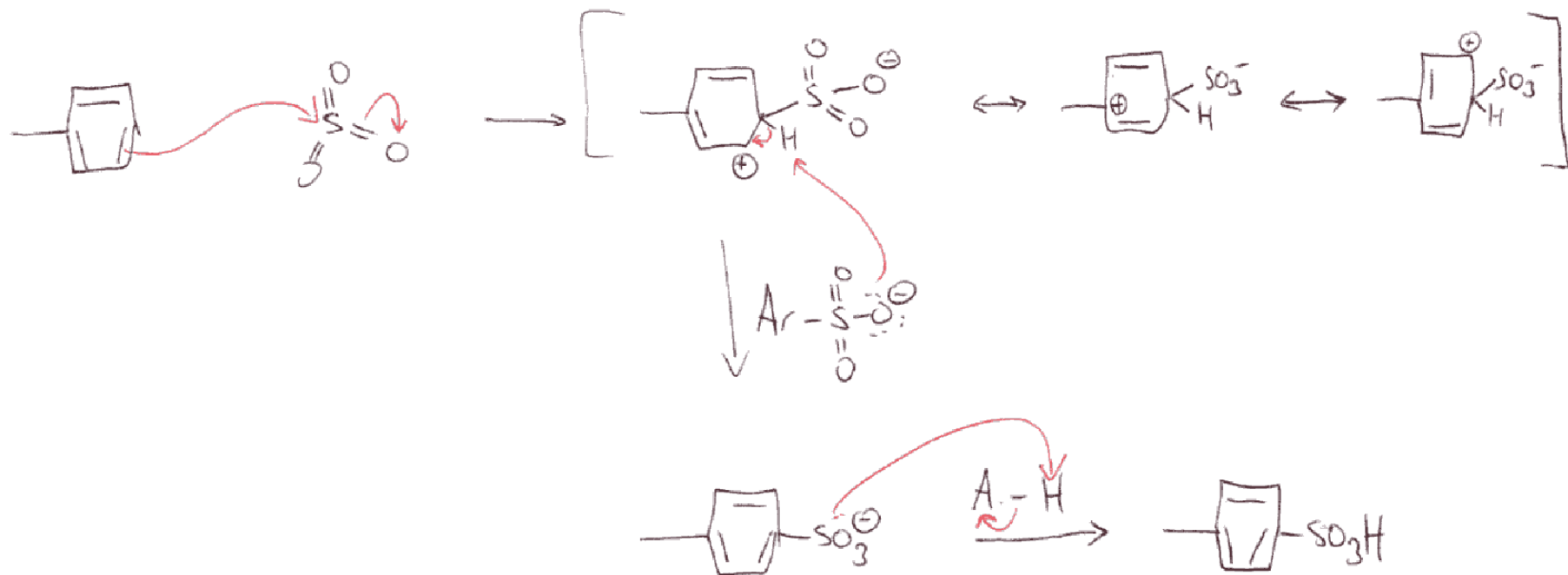
The intermediate cation (Sigma complex) is resonance stabilized (but non-aromatic!)
A basic species will deprotonate the ring, thus returning the aromaticity.

Rates of EAS are increased by electron donating substituents, and slowed by electron withdrawing substituents.

Remember that the stability of the intermediate cations dictates:

i.   electron donors are ortho / para directors and activators
ii.   electron withdrawers are meta directors and deactivators
iii.   halogens are ortho / para directors but deactivators (due to π donation and σ withdrawal).

TABLE 4.1   Influence of Substituents in Electrophilic Aromatic Substitution

Strongly activating and *ortho*- or *para*-directing
  $-NR_2$, $-NRH$, $-NH_2$, $-O^-$, $-OH$
Moderately activating and *ortho* or *para*-directing
  $-OR$, $-NHCOR$
Weakly activating and *ortho*- or *para*-directing
  $-R$, $-Ph$
Weakly deactivating and *ortho*- or *para*-directing
  $-F$, $-Cl$, $-Br$
Strongly deactivating and *meta*-directing
  $-\overset{+}{S}R_2$, $-\overset{+}{N}R_3$, $-NO_2$, $-SO_3H$, $-CO_2H$, $-CO_2R$,
  $-CHO$, $-COR$, $-CONH_2$, $-CONHR$, $-CONR_2$, $-CN$

Explain the orientation of the following reactions.

(a)

$\langle O \rangle - SO_3H$ $\xrightarrow[HNO_3]{H_2SO_4}$ $O_2N - \langle O \rangle - SO_3H$

(b)

$\langle O \rangle - NHCOCH_3$ + $\langle O \rangle - \overset{O}{\overset{\|}{C}} - Cl$ $\xrightarrow{AlCl_3}$ $PhCO - \langle O \rangle - NHCOCH_3$

50
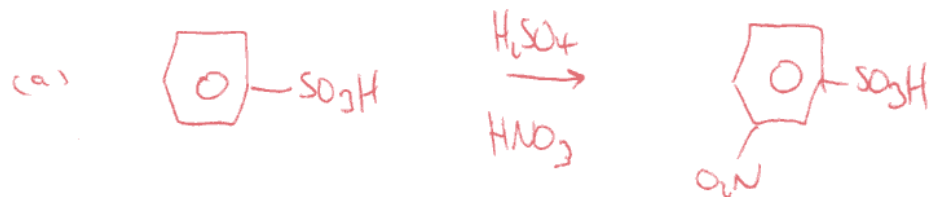
E.g. A metal catalyzed intramolecular EAS.
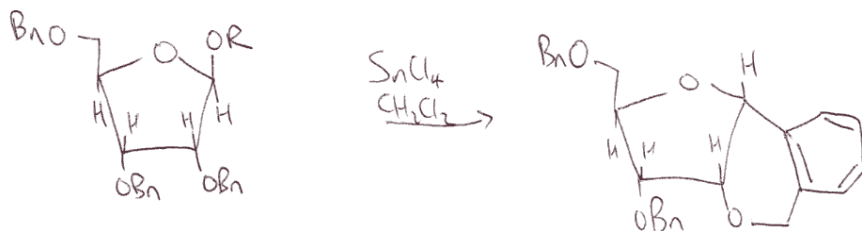
The first step is the Lewis Acid is attacked by the nucleophilic oxygen, which generates a superior leaving group, which leaves with assistance from the ring oxygen.
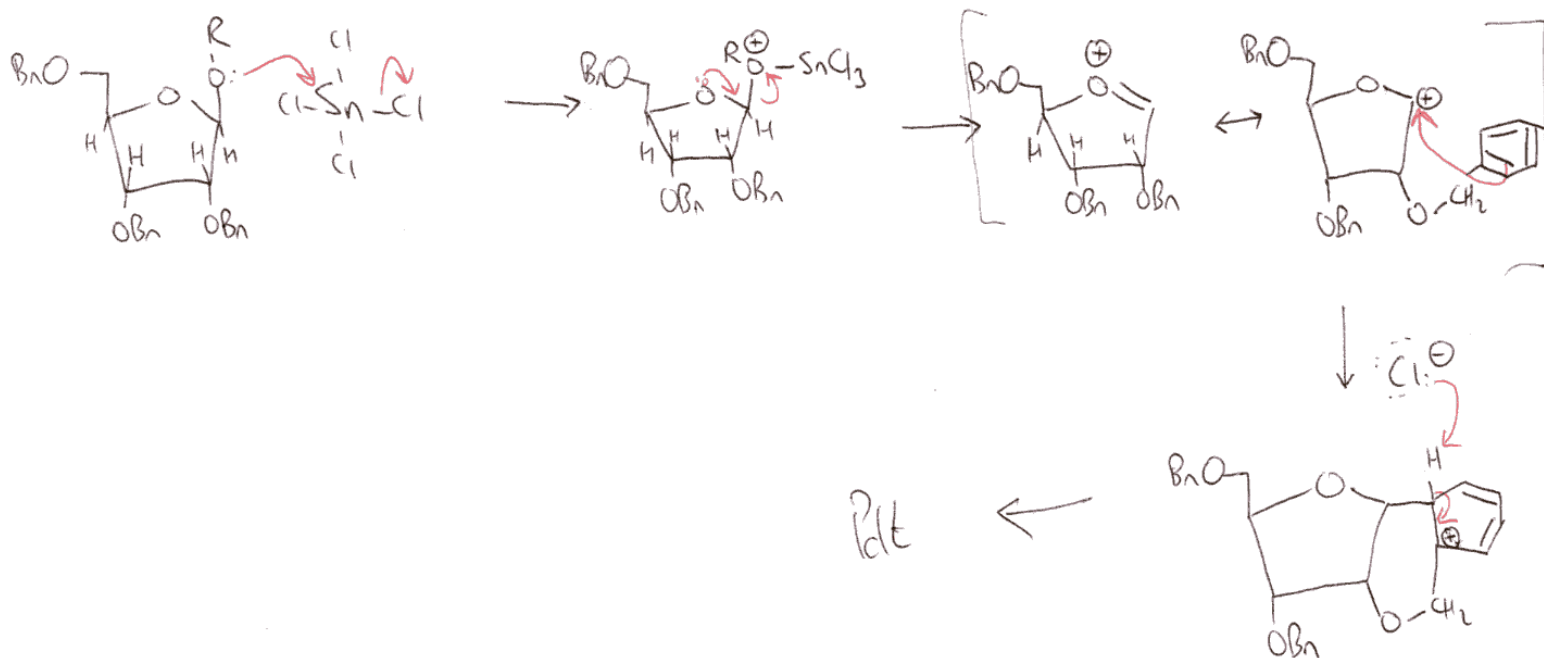
The Ph group is ideally located to perform EAS on the electrophilic carbon, with the liberated Cl⁻ acting as base to regenerate aromaticity.

Write mechanisms for the following

(a)

HCl →

1) conc. H_2SO_4
2) H_2O

(b)

RSO_3H →
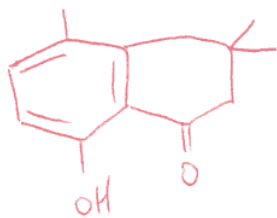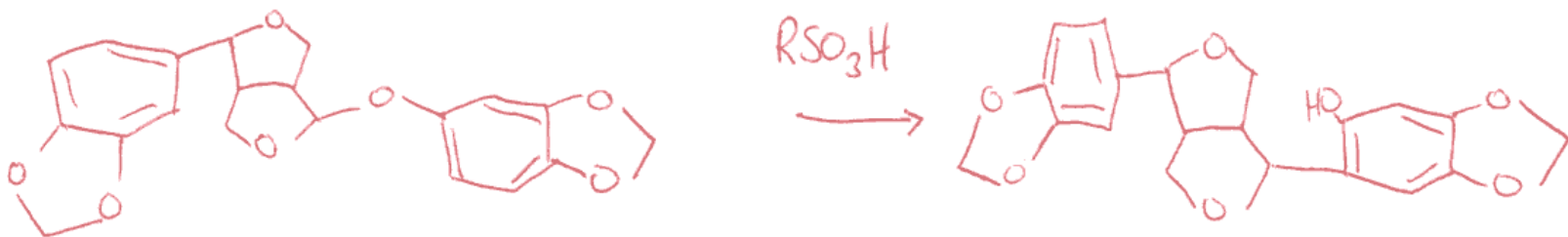
8) Carbenes

a) Singlet and Triplet Carbenes

Carbenes are very reactive intermediates, and are generally very short lived under normal conditions.

Even though carbenes are usually generated in basic media, they act as electrophiles.

A carbene is a **neutral** divalent carbon species with two electrons which are not shared with any other atoms.

These two electrons can be a lone pair (opposite spins, same orbital, SINGLET), or a diradical (parallel spins, different orbitals, TRIPLET).

singlet Carbene   triplet Carbene   carbocation   radical   Carbanion   Carbanion.
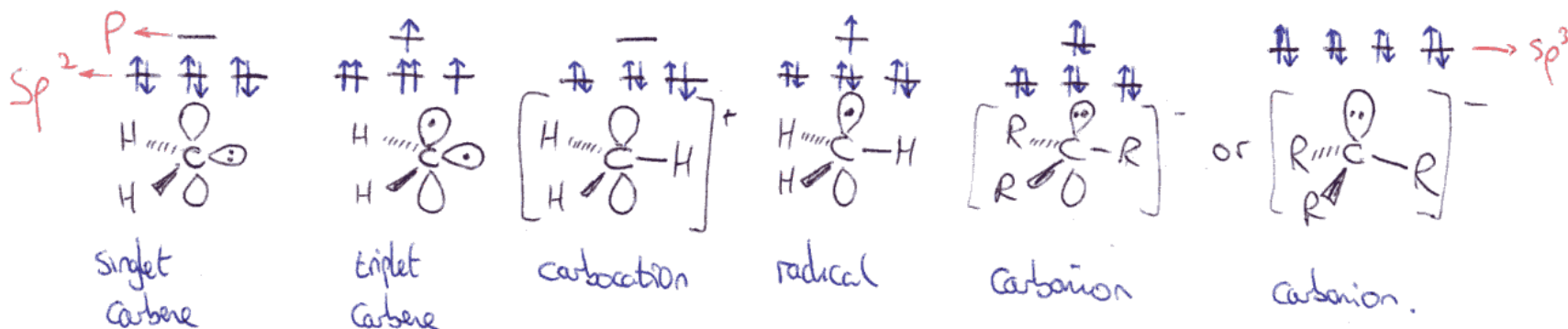
The term *Carbenoid* refers to a moiety which behaves like a carbene.

b) Formation of Carbenes

E.g. the reaction of alkyl halides and base.

(i) from chloroform

The base removes the acidic hydrogen from chloroform, and the anion loses chloride ion (an α elimination), leaving dicholorcarbene. (CCl_2 is always a singlet carbene).

(ii) from benzal bromide

When benzal bromide reacts with potassium ᵗbutoxide, a species is formed that acts like it is phenylbromocarbene.

(iii) Some alkyl halides react with alkyl lithium reagents to generate carbenoid species.
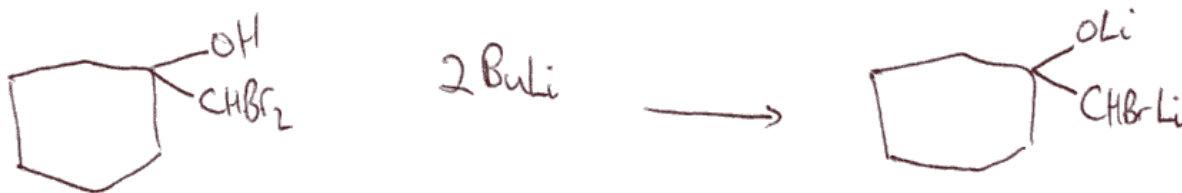
(iv) Simmons-Smith Reagent

Di-iodomethane reacts with zinc-copper couple to form a carbenoid species. ICH_2ZnI is the Simmons-Smith reagent, perhaps the single most common way to form cyclopropanes.

$$CH_2I_2 \; + \; ZnCu \; \longrightarrow \; ICH_2ZnI$$

(v) from diazo compounds.

The lose of N_2 is a common way to generate carbenes.

Copper (I) salts tend facilitate this process.
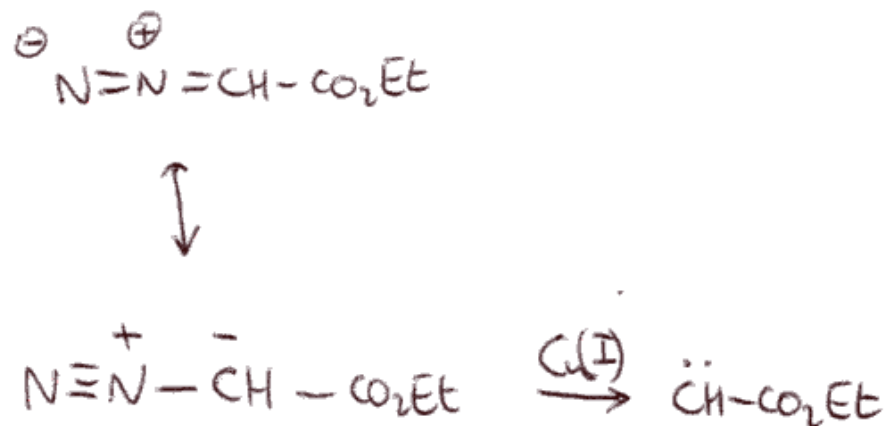
c) Reactions of Carbenes

Once carbenes are formed, these highly reactive species can react in a variety of different ways including:

> addition
>
> substitution
>
> insertion
>
> rearrangement
>
> hydrogen abstraction
>
> halogen abstraction.

The two most widely employed types of carbene reaction are

(i) addition to C=C bonds → cyclopropanes

(ii) EAS reactions → aromatic aldehydes

(i) Addition reactions

Electrophilic addition to C=C bonds is the most common carbene reaction, and it can proceed with up to 100% stereospecificity – that is with stereochemistry maintained.

Stereochemistry is maintained if the carbene is a singlet, and the reaction is a concerted process.

When the reaction is not 100% stereospecific, this points to a triplet carbene, and the reaction proceeds through a diradical intermediate.
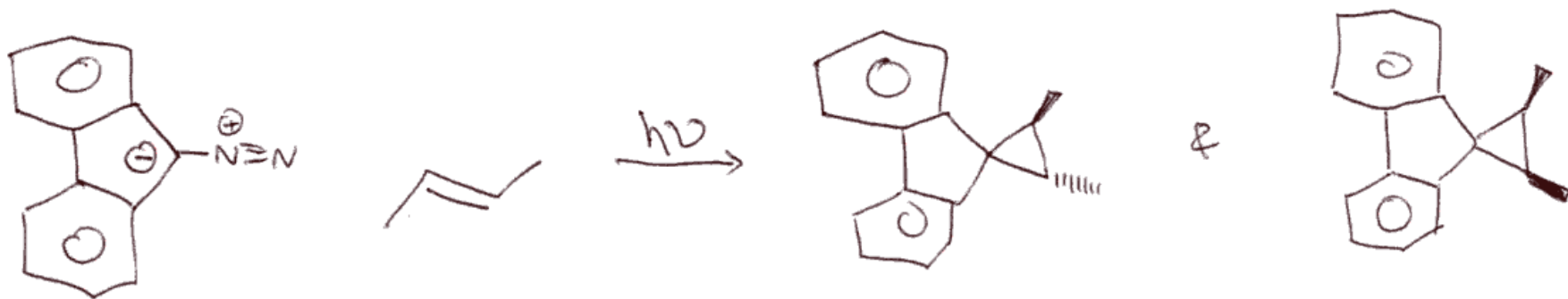
The intermediate diradical has time to rotate and lose stereochemistry.
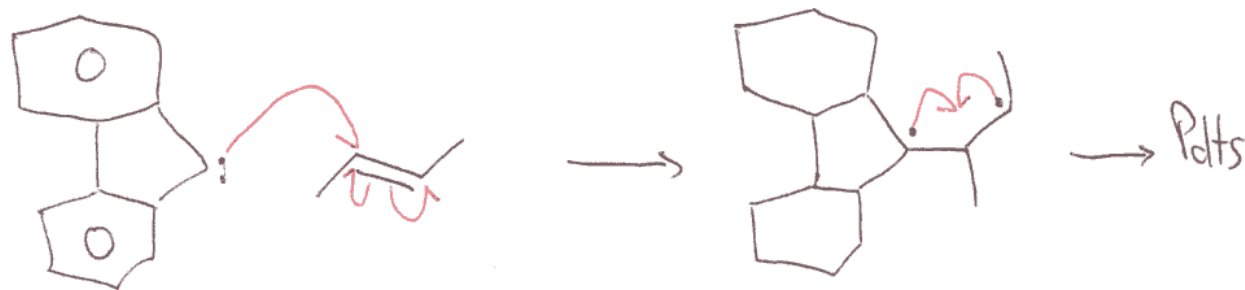
ii) Substitution

Besides C=C, carbenes will react with other nucleophiles.

Common nucleophiles include hydroxide, thiolate and phenoxide (= Reimer-Tiemann reaction).

In the presence of strong aqueous base, phenols react with chloroform to generate ortho (and para) hydroxybenzaldehydes.
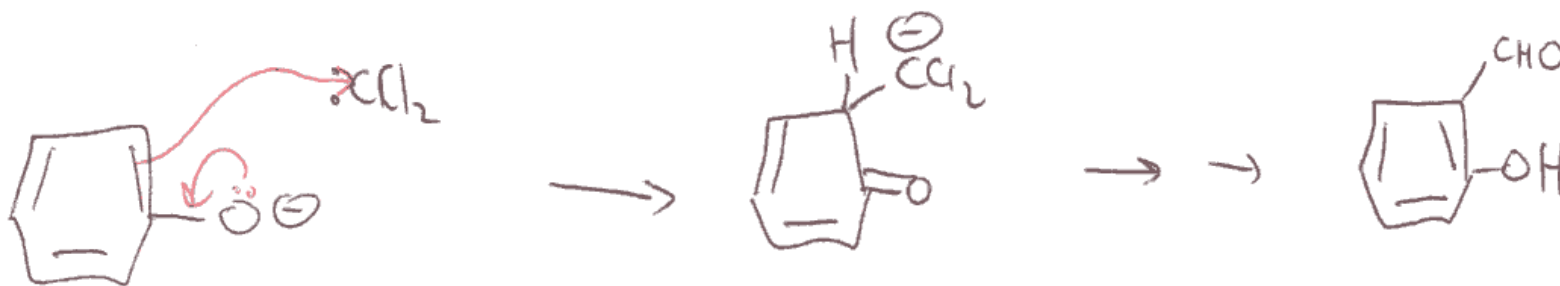
Such Reimer-Tiemann reactions involve   -formation of dichlorocarbene

- nucleophilic attack on the carbene

-hydrolysis

Write the mechanism for:

CHBr$_3$

NaOH
80°C
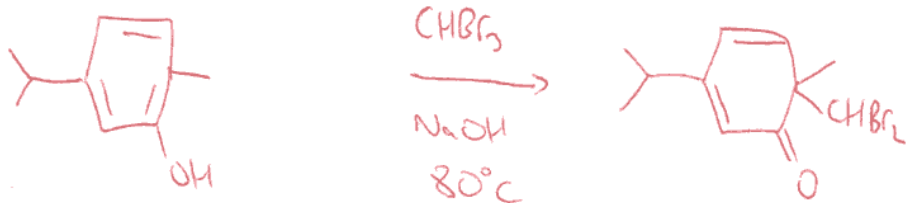
iii) Insertion

Here the carbene inserts itself between two bound atoms.

Commonly into   C-H
                          C-C
                          C-Hal
                          N-H
                          O-H
                          S-S
                          S-H
                          C-Metal

The mechanism for a carbene insertion is normally written as a concerted process involving a three centered transition state.

$$\overset{+}{CH_2} = \overset{+}{N} = \overset{-}{\underset{..}{N}} \colon + CH_3CH_2CH_2CH_2CH_3 \xrightarrow{h\nu} CH_3(CH_2)_4CH_3 + CH_3 - \overset{CH_3}{\underset{|}{CH}} - CH_2CH_2CH_3$$

$$\sim 49\% \qquad\qquad\qquad \sim 34\%$$

$$+ \; CH_3CH_2 - \overset{CH_3}{\underset{|}{CH}} - CH_2CH_3$$

$$\sim 17\%$$
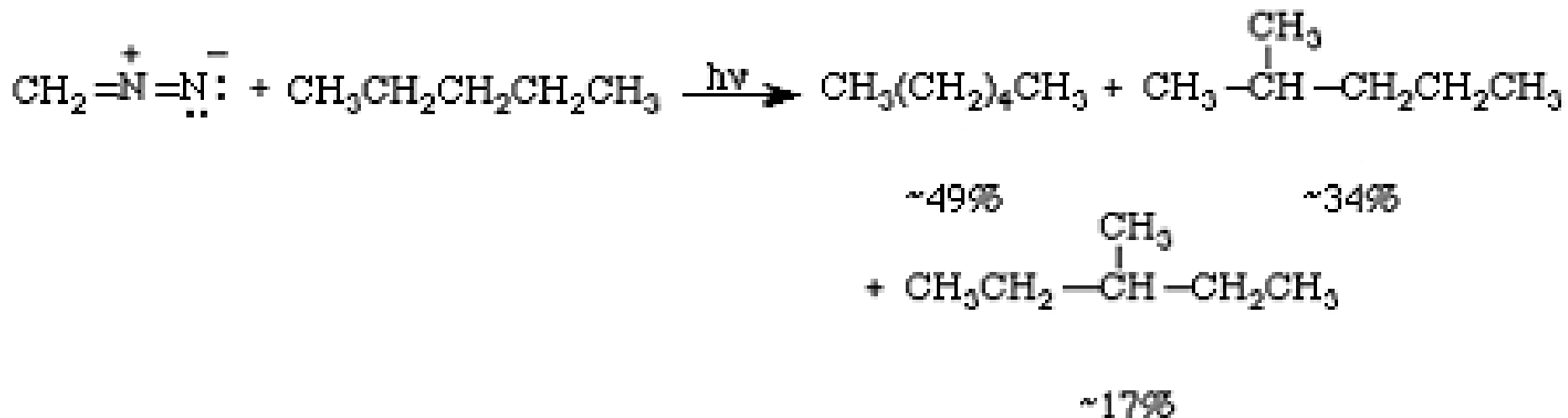
iv) Rearrangement

Carbenes are so reactive, they can be generated as reactive intermediates that undergo very fast subsequent reaction such as rearrangements.

Often these involve ring expansion / contraction.

e.g. Cycloheptanone synthesis.

The below carbenoid leads to ring expansion, and the enolate tautomerizes to the cyclic ketone.

The Wolff Rearrangement.

$$Ph\overset{O}{\overset{\|}{C}}CH=\overset{\oplus}{N}=\overset{\ominus}{N} \quad \xrightarrow[CH_3OH]{CuI} \quad PhCH_2\overset{O}{\overset{\|}{C}}OCH_3$$
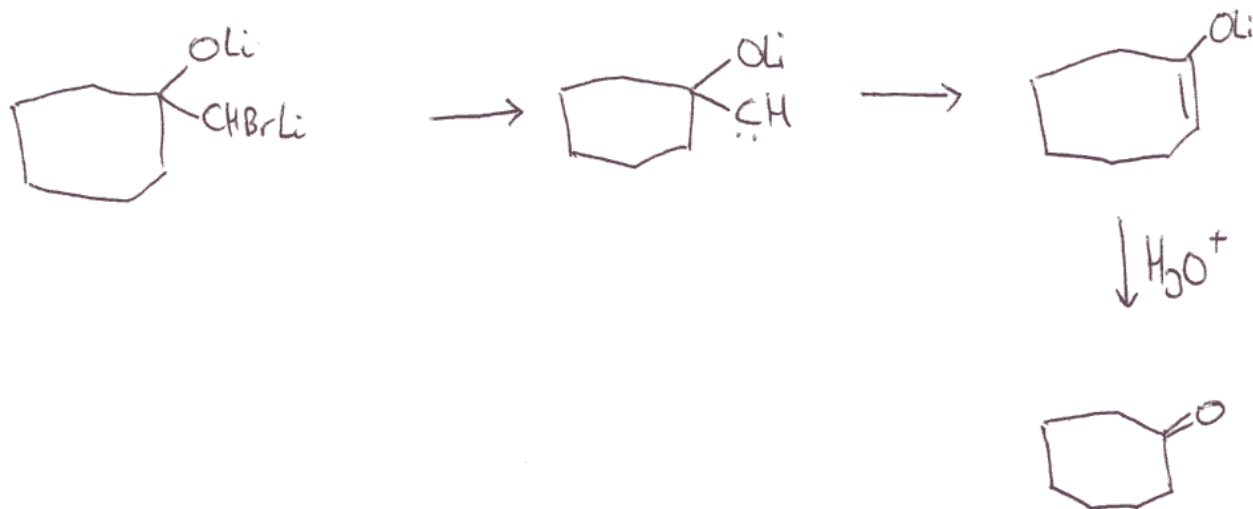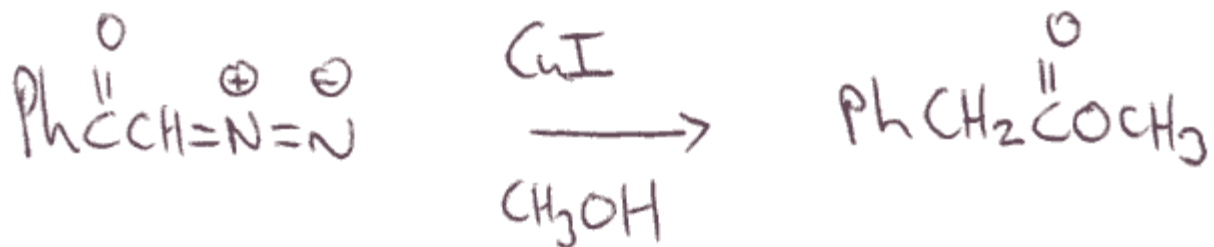
This reaction is believed to proceed through the formation of a ketene intermediate.

Wolff Rearrangement Mechanism

The diazoketone decomposes into a carbene with the help of copper salts (or heat / hν).

The carbene rearranges into a ketene, which undergoes further reaction with the alcohol solvent to yield the product ester.

KETENE
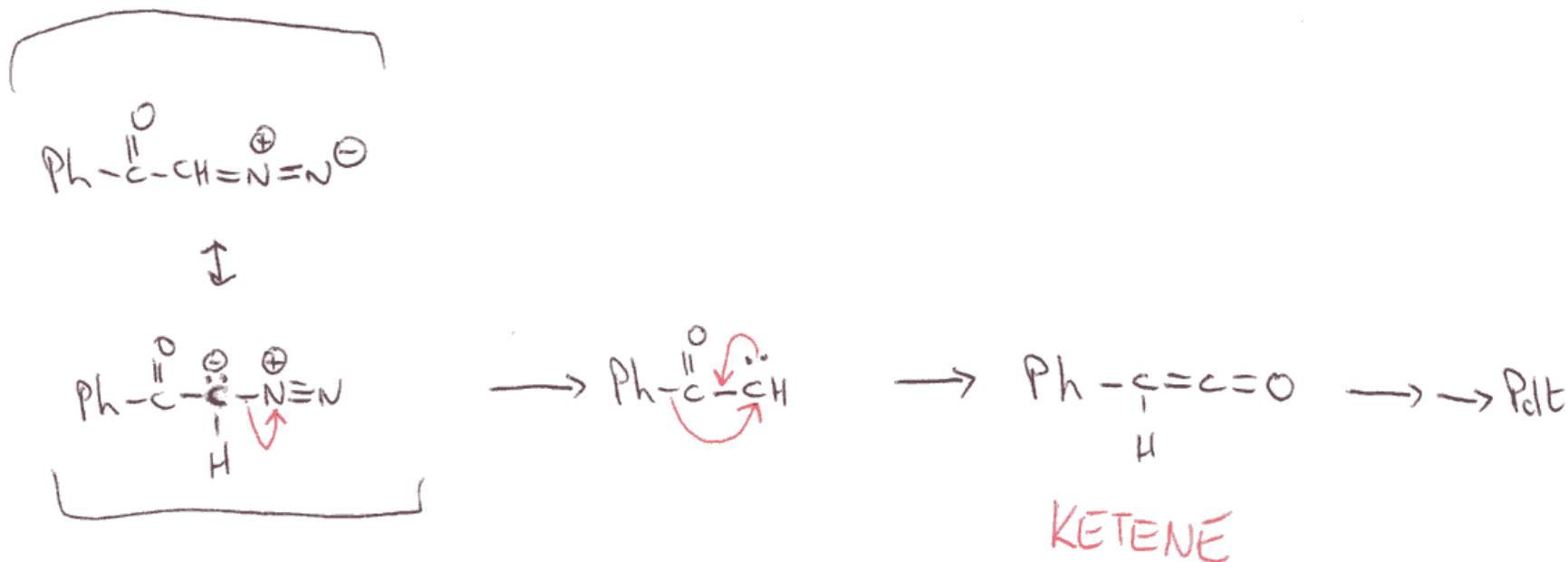
9) Electrophilic Heteroatoms

a) Electron deficient Nitrogen

i) Nitrenes are the Nitrogen version of a carbene.
It is a N which contains one bond and two lone pairs of electrons.

Phenyl Nitrene

Nitrenes are generated by the same approaches as for Carbenes, and do the same type of chemistry (addition, insertion), but they are more reactive than their C analogues.

The most common method of nitrene formation is from acyl azides either thermally or photochemically.

$$Ar-N_3 \quad \xrightarrow[\text{or } \Delta]{h\nu} \quad Ar-\ddot{N}: \quad \& \; N_2$$

$$R-\overset{O}{\underset{}{\overset{\|}{C}}}-N_3 \quad \xrightarrow{h\nu} \quad R-\overset{O}{\underset{}{\overset{\|}{C}}}-\ddot{N}: \quad \& \; N_2$$

The nitrene rearranges to an isocyanate just as in the Wolff rearrangement.

$$R-\overset{O}{\underset{}{\overset{\|}{C}}}-N_3 \quad \xrightarrow{\Delta} \quad R-N=C=O$$

ISOCYANATE

ii) Nitrenium Ions

These are positively charged divalent nitrogen species with one lone pair, they are very reactive. (isoelectronic with a carbene).

Nitrenium ions are commonly formed with metal assisted ionization of a N-Hal bond. E.g.
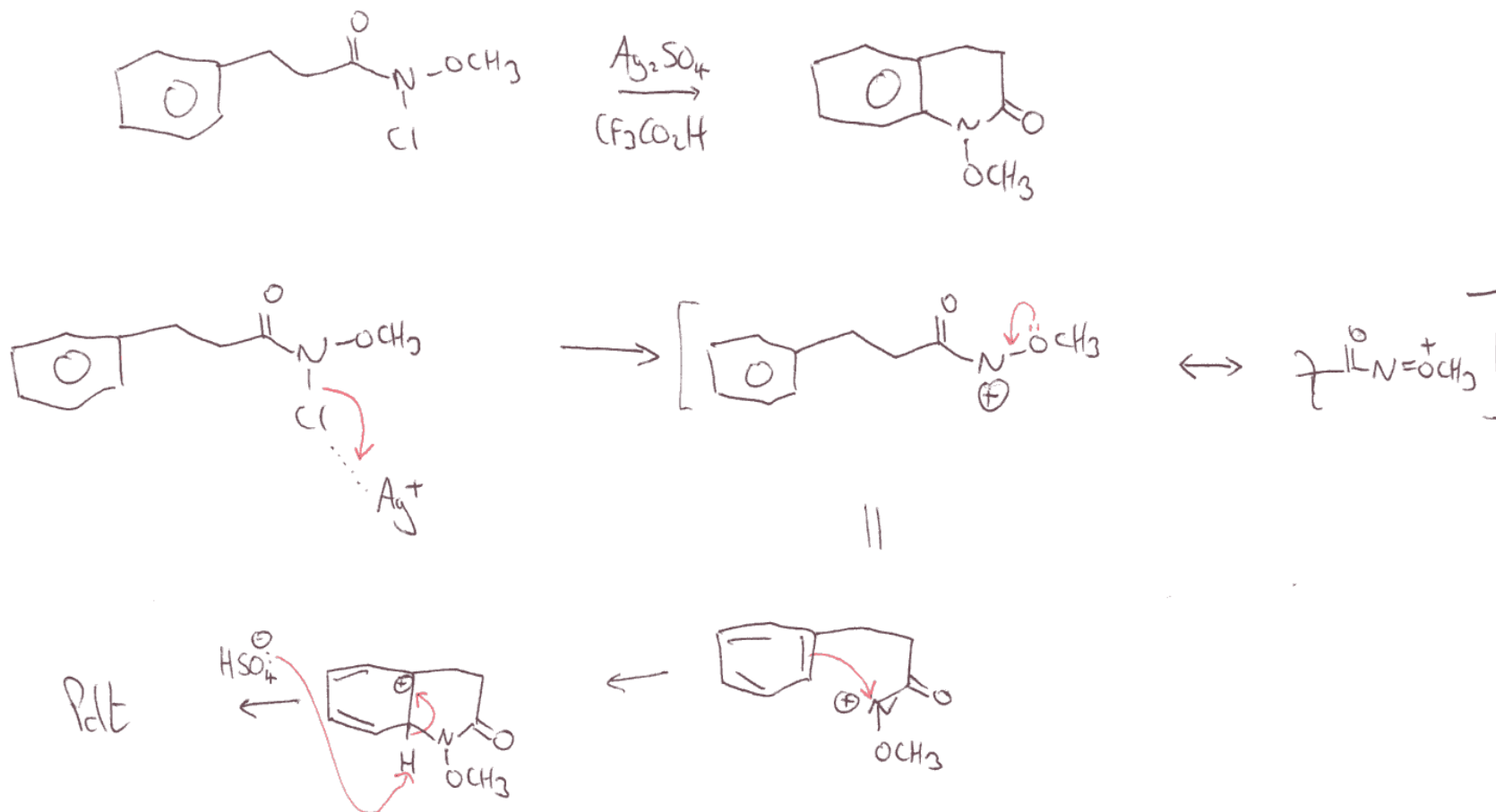
b) Rearrangements involving Electrophilic Nitrogen

The Beckmann Rearrangement

Under acidic conditions, an **oxime** in the presence thionyl chloride (or PCl_5) generates a *rearranged* **amide**.
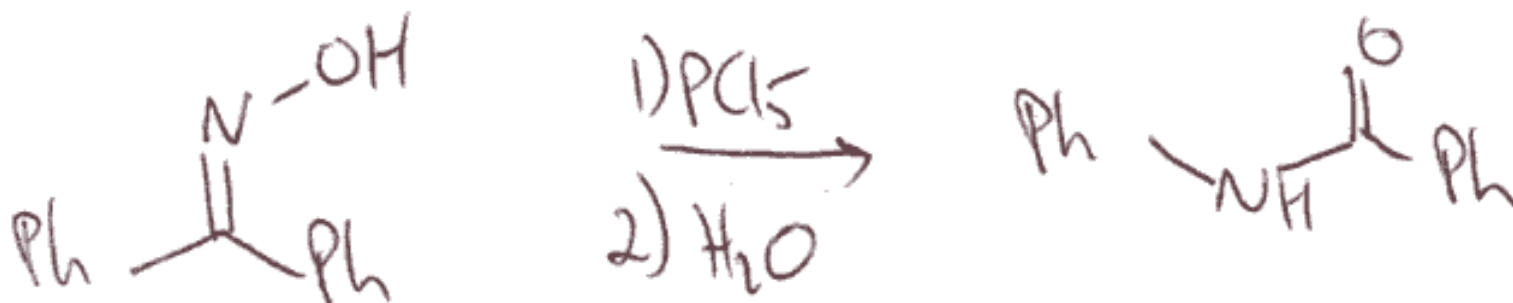
The OH is converted into a good leaving group by reaction with PCl_5. Phenyl migration expels the leaving group, and hydrolysis generates the amide product.

PHENYL MIGRATION

H_2O

H_2O

"KETO"

"ENOL"

Write a mechanism for:

$$\xrightarrow[\text{2) } H_2O]{\text{1) } PCl_5}$$

$NC(CH_2)_6CHO$
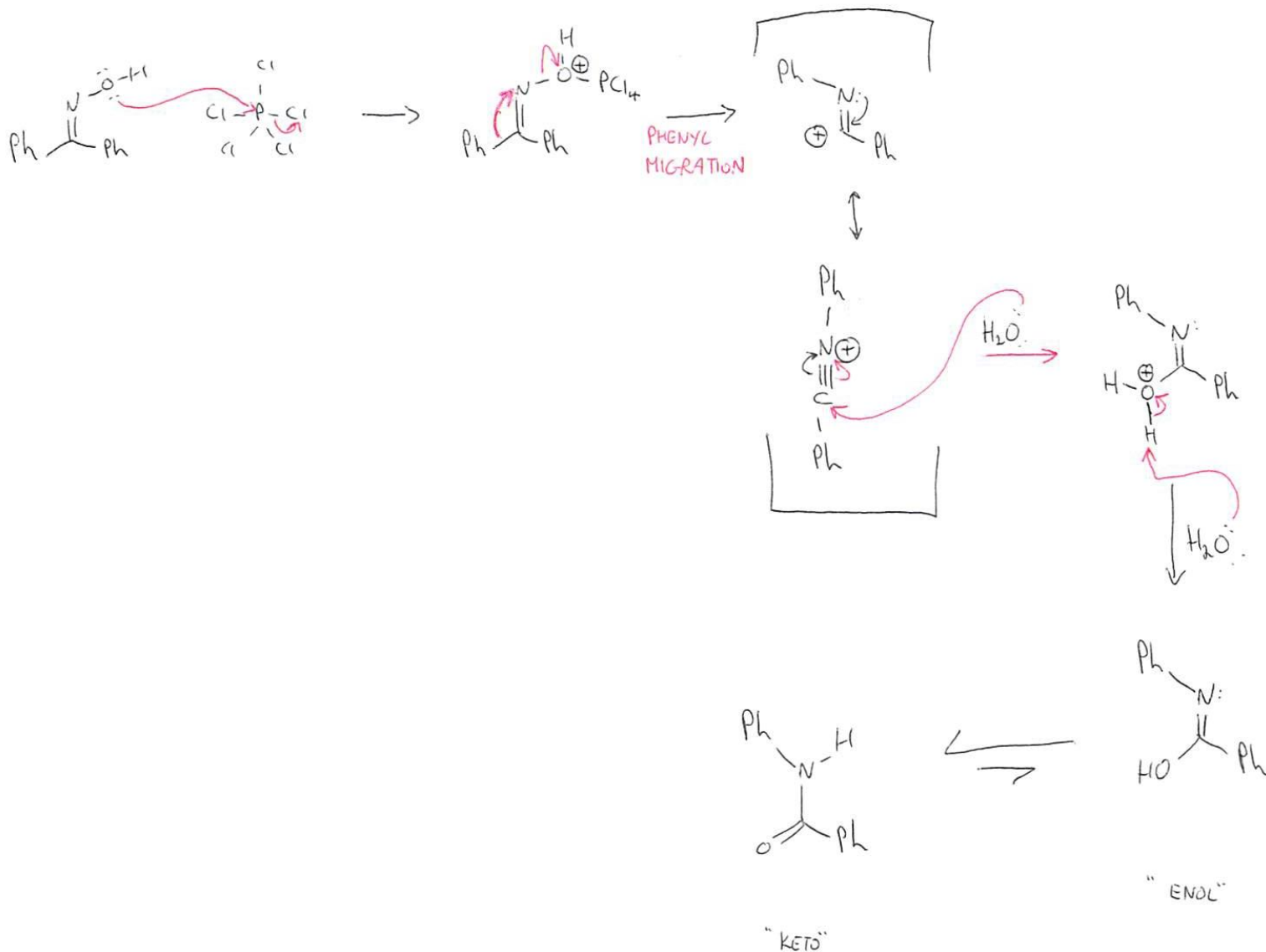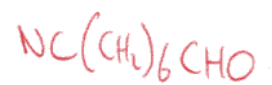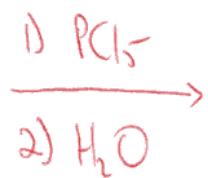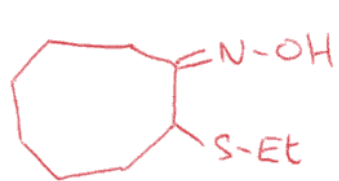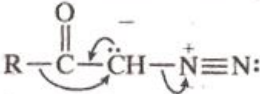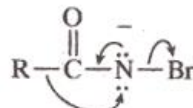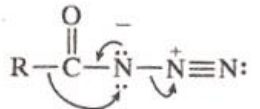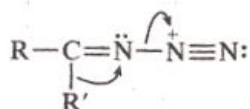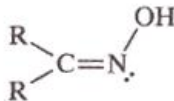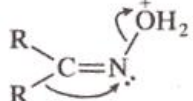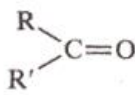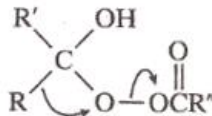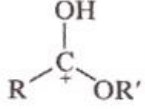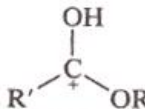
Nitrogen Analogues of the Wolff Rearrangement

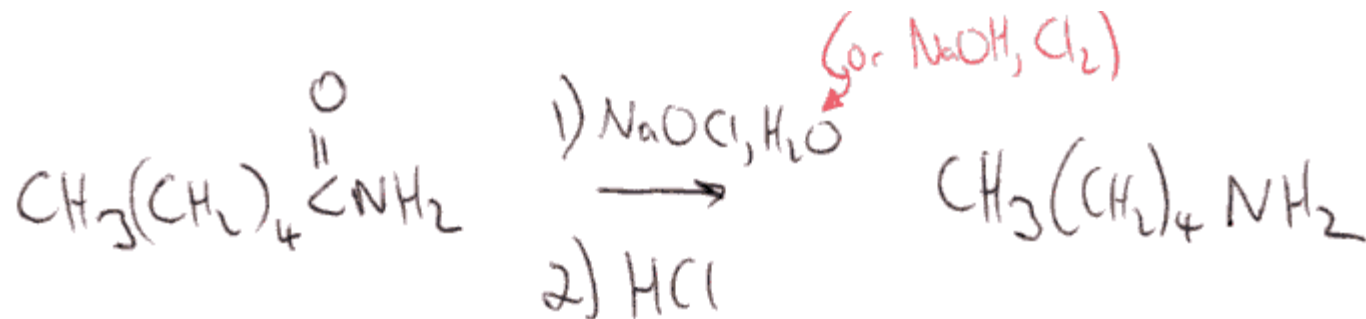Wolff type rearrangements involving nitrenoid species are very common and are summarized in the table below.

TABLE 4.2 Parallels in Electrophilic Rearrangements

Hofmann Rearrangement

A primary amide is converted into a *chain shortened* amine.

$$CH_3(CH_2)_4 \overset{\overset{\displaystyle O}{\|}}{C} NH_2 \quad \xrightarrow[\text{2) HCl}]{\text{1) NaOCl, H}_2\text{O} \ (\text{or NaOH, Cl}_2)} \quad CH_3(CH_2)_4 NH_2$$

The most acidic hydrogen is removed and a halogen ends up on the nitrogen. This further acidifies the N-H, which is deprotonated (= nitrenoid species).
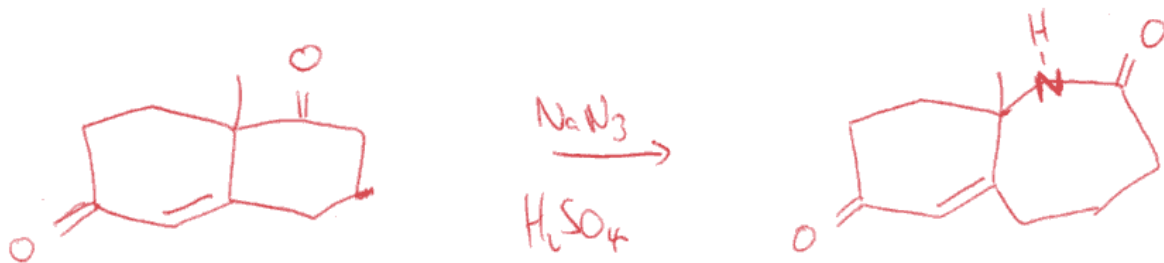
Rearrangement occurs with an alkyl group migration expelling the halide leaving group, leading to an isocyanate.

74
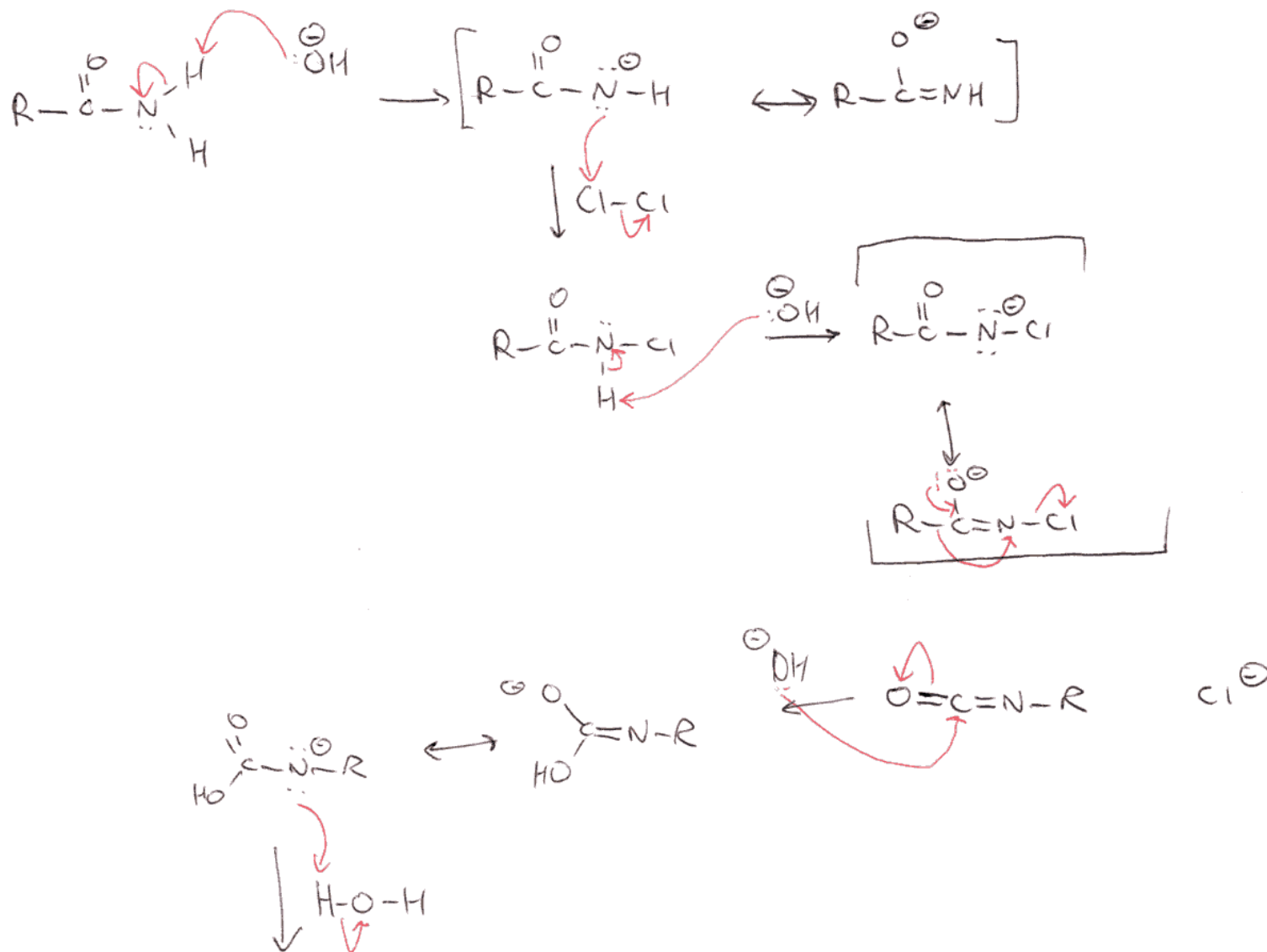
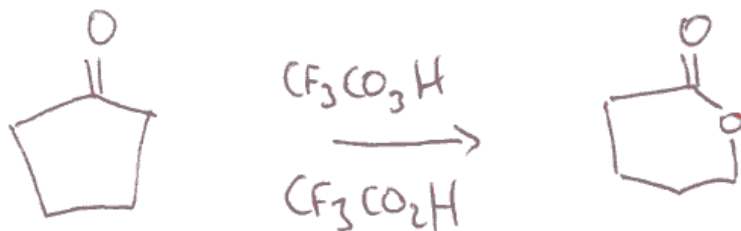The isocyanate is hydrolysed to a carbamic acid, which then decarboxylates, leading to the chain shortened amine.

Write a mechanism for :

NaN₃

H₂SO₄
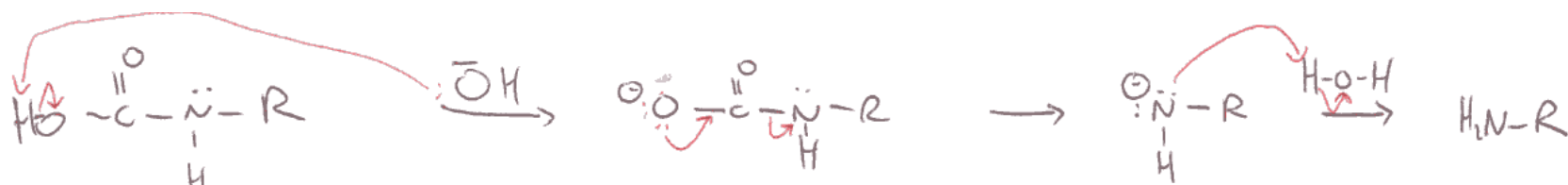
c) Rearrangements Involving Electron Deficient Oxygen
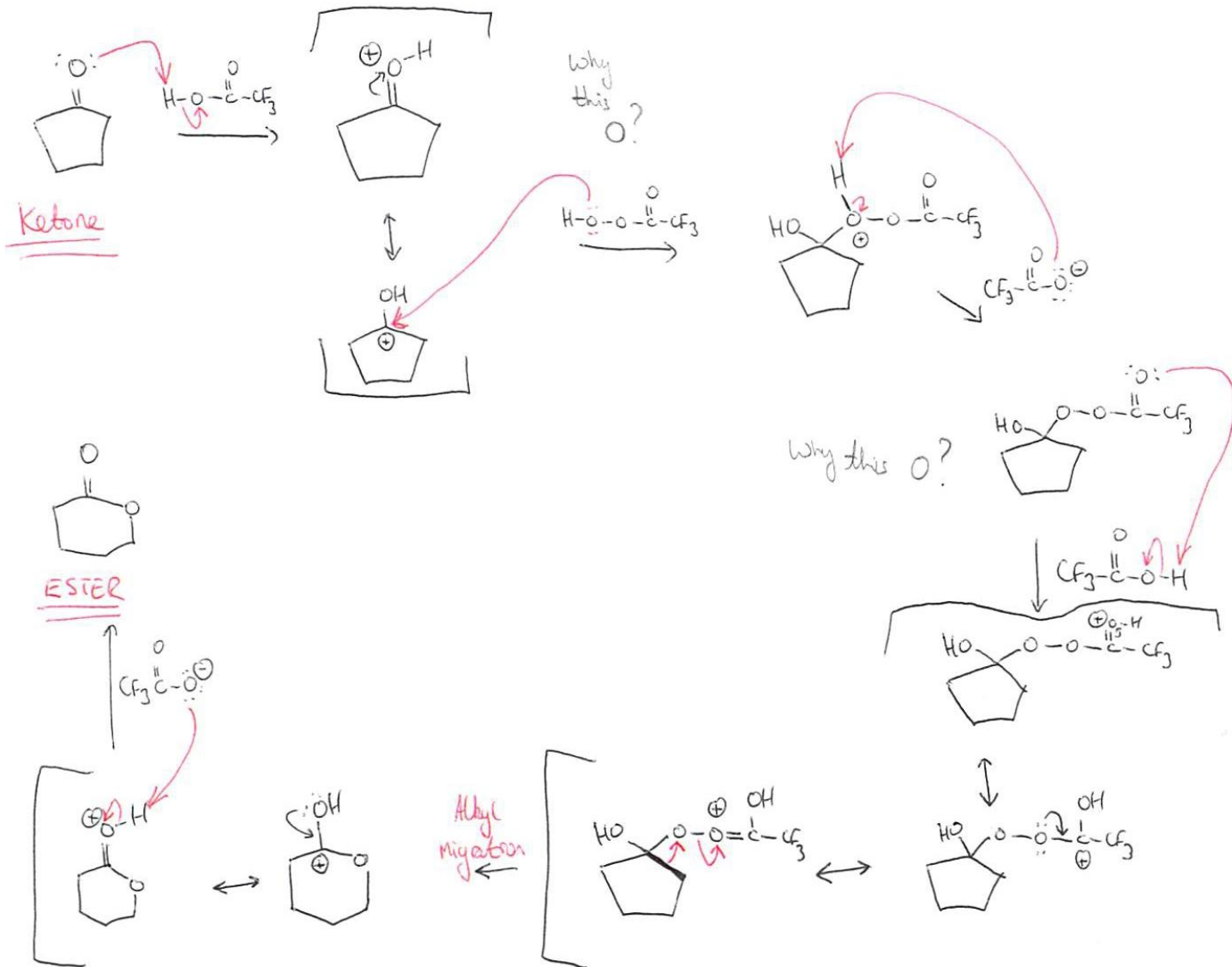
The most common example of this is the Baeyer Villager oxidation, which converts a **ketone** to an **ester** using a peroxyacid.
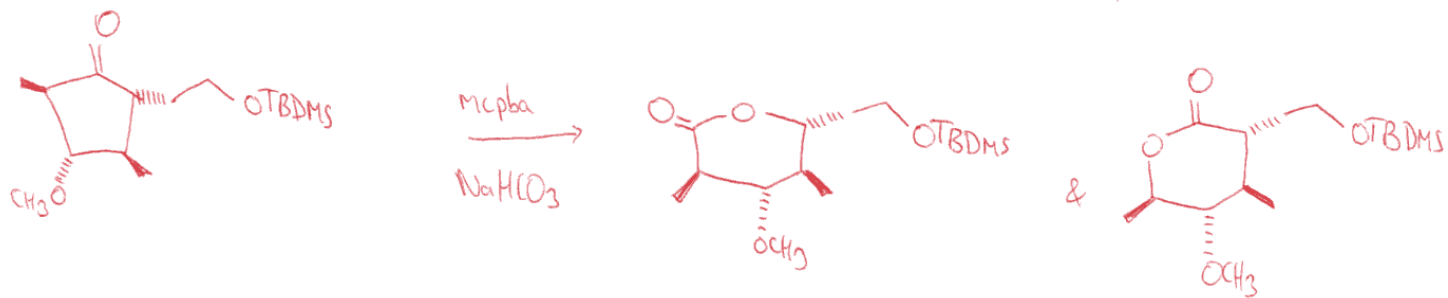

Protonation of the ketone by the acid promotes nucleophilic attack, which is followed by the rearrangement (**alkyl migration to electron poor Oxygen**).

Deprotonation yields the ester product.

Baeyer Villager oxidation mechanism.

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Write a mechanism & comment on the mixture of products.

mcpba = (cyclohexane ring with -CO₃H and Cl substituents)

TBDMS = +Si+

3:1 ratio

Write mechanisms for the following:

(a)

HO–N(Ph)–C(=O)–CH₂CH₂Ph + CF₃SO₃H → [bicyclic lactam with N–Ph and C=O]

(b)

[pyrrolidinone with HO and allyl/Ph substituents] →(HCO₂H)→ [H–C(=O)–O bicyclic lactam with Ph] & [H–C(=O)–O bicyclic lactam with Ph]

(c)

[methylphenol]–OH + (CH₃OCONH)₂CHCOCH₃ →(CH₃SO₃H / CH₂Cl₂)→ [benzofuran with methyl, methyl and NHCO₂CH₃ substituents]

80

(d)

1) $SnCl_4$, CH_3NO_2
2) H_2O

(e)

Ag_2CO_3

CF_3CO_2H

(f)

1) $SnCl_4$, CH_2Cl_2
2) H_2O