Rearrangement to electron-deficient carbon

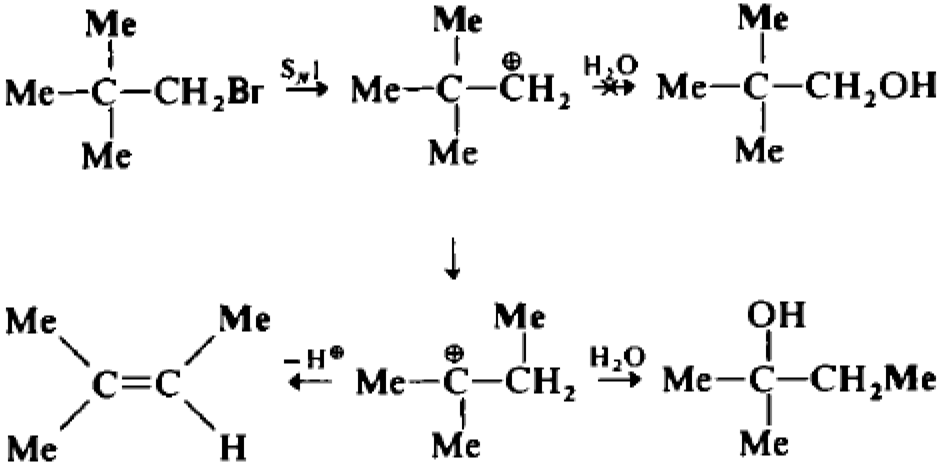
Wagner–Meerwein rearrangement

- We know that, the S_N2 reaction of neopentyl bromide is very slow, as backside attack is blocked by large neopentyl group. Under S_N1 conditions however, the rate is increased. But, even then, the desired product is not obtained. In stead, a neopentyl rearrangement takes place, to produce a rearranged product.

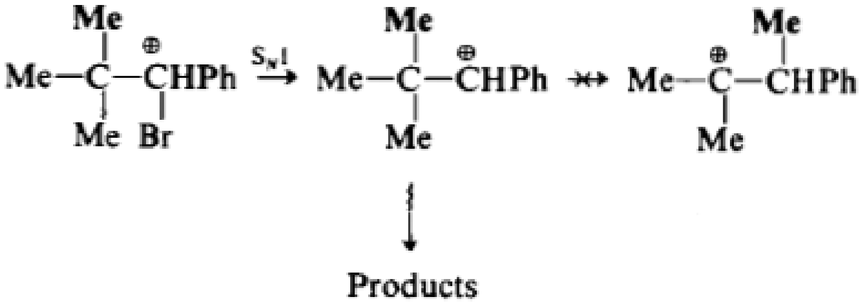
- The greater stability of tertiary carbocation than the initially formed primary carbocation is the driving force of this rearrangement.

- Involvement of the tertiary carbocation is further confirmed by the simultaneous formation of a rearranged alkene side product.

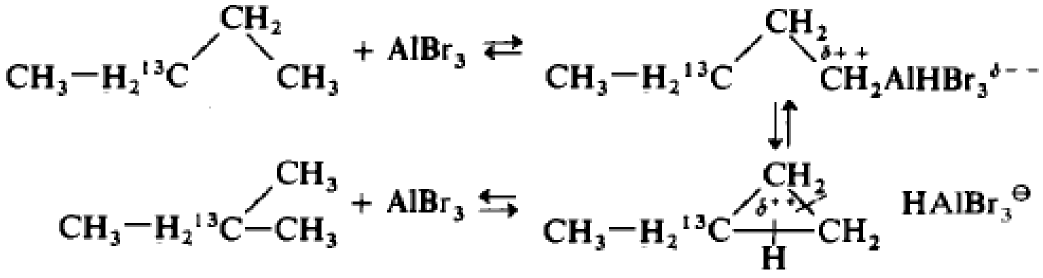
- Such changes in carbon skeleton, involving carbocation are collectively known as Wagner–Meerwein rearrangements.



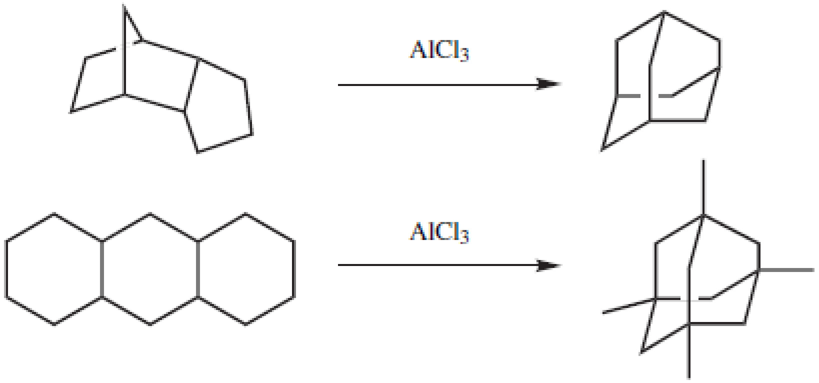
- Interestingly, no such reangement takes place in the following phenyl-analogue.
- Greater stability of benzylic carbocation is probably the driving force here.



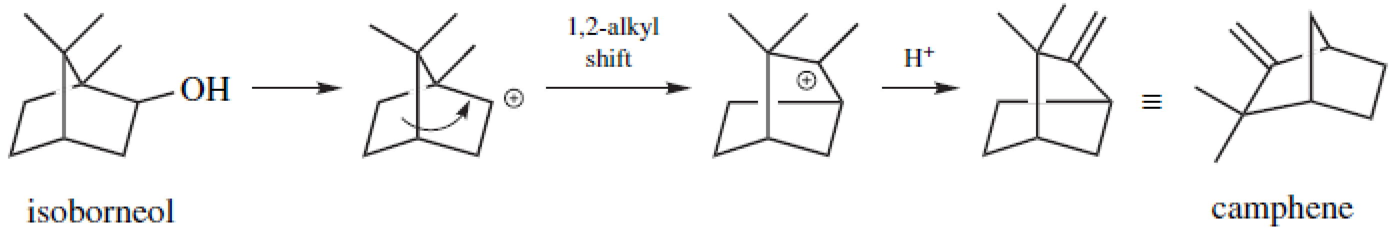
- Wagner–Meerwein rearrangement is also observed in petroleum cracking, especially when a Lewis acid catalyst is used. It leads to the formation of branched alkanes, which cause less knocking in the cylinders of internal combustion engines, than the straight chain alkanes.



- An interesting application of this reaction is the conversion of tricyclic molecules to adamantane and its derivatives. It has been found that all tricyclic alkanes containing 10 carbons are converted to adamantane by treatment with a Lewis acid, such as AlCl3. If the substrate contains >10 carbons, alkyl-substituted adamantanes are produced. The IUPAC name for these reactions is ***Schleyer adamantization***.

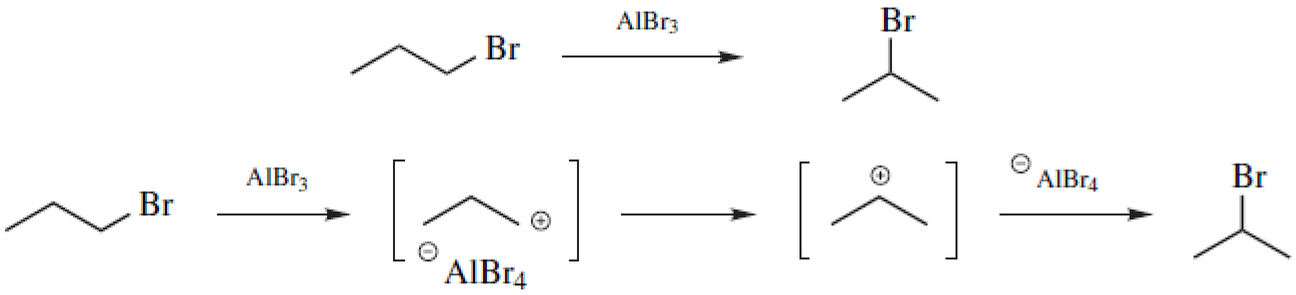


- Wagner–Meerwein rearrangements were first discovered in the bicyclic terpenes. An example is the conversion of isoborneol to camphene. It fundamentally involves a 1,2 alkyl shift of an intermediate carbocation.

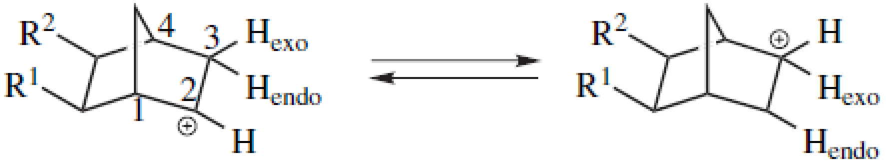


- Sometimes a different positive group is lost instead of a proton. Less often, the new carbocation stabilizes itself by combining with a nucleophile instead of losing a proton. The nucleophile may be the water that is the original leaving group, so that the product is a rearranged alcohol, or it may be some other species present (solvent, added nucleophile, etc.).

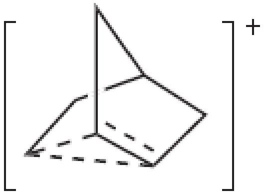
- Examples of Wagner–Meerwein-type rearrangements are also found in simpler systems, such as even 1-bromopropane, which shows that hydride ion can also migrate.



- 2-Norbornyl cations are also prone to rapid 3,2-hydride shifts, usually from the exo side. This stereoselectivity is analogous to the behavior of nucleophilic attack at norbornyl cations from the exo side and the addition to norbornenes from the exo direction, probably due to steric reasons.



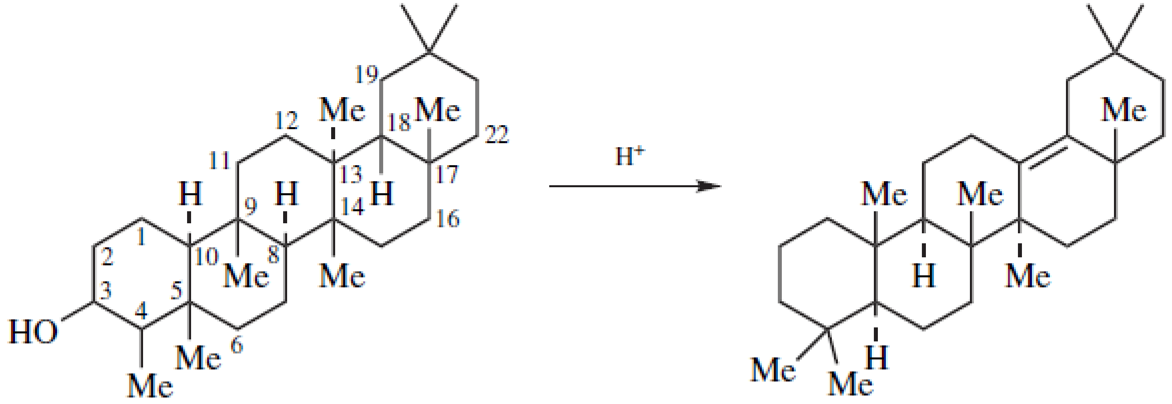
- However, without invoking these Wagner–Meerwein shifts, Winstein described these norbornyl cations in terms of the resonance structures represented by the following nonclassical carbocation and there is strong NMR evidence for such species in super acids at low temperatures.



- It is important to note that, the term "Wagner–Meerwein rearrangement" is not precise. Some use it to refer to all the rearrangements in this section and others use it only when an alcohol is converted to a rearranged alkene. Terpene chemists call the migration of a methyl group the ***Nametkin rearrangement***. Also, the term ***retropinacol rearrangement*** is often applied to some or all of these.

- A spectacular observation is found in 3β-friedelanol, when this compound is treated with acid, 13(18)-oleanene is formed. In this case, seven 1,2-shifts take place.

- On removal of H_2O from position 3 to leave a positive charge, the following shifts occur: hydride from 4 to 3; methyl from 5 to 4; hydride from 10 to 5; methyl from 9 to 10; hydride from 8 to 9; methyl from 14 to 8; and methyl from 13 to 14. This leaves a positive charge at position 13, which is stabilized by loss of the proton at the 18 position to give the product.

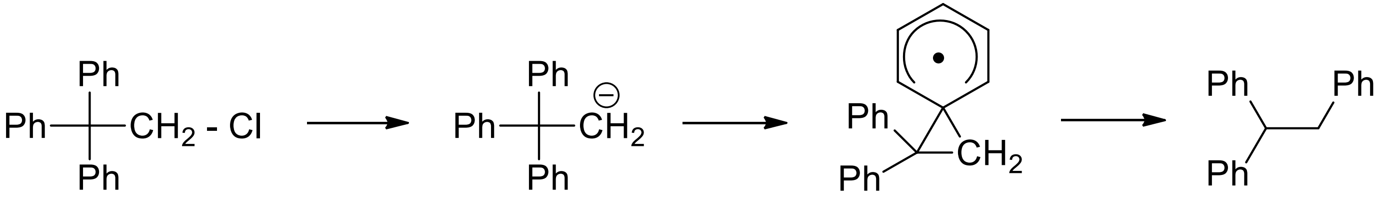


- All these shifts are stereospecific, the group always migrating on the side of the ring system on which it is located; that is, a group above the "plane" of the ring system moves above the plane (solid line), and a group below the plane (dashed line) moves below it.

- The mechanism of the Wagner–Meerwein rearrangement is usually nucleophilic, however, carbanion mechanisms (electrophilic) have also been found.

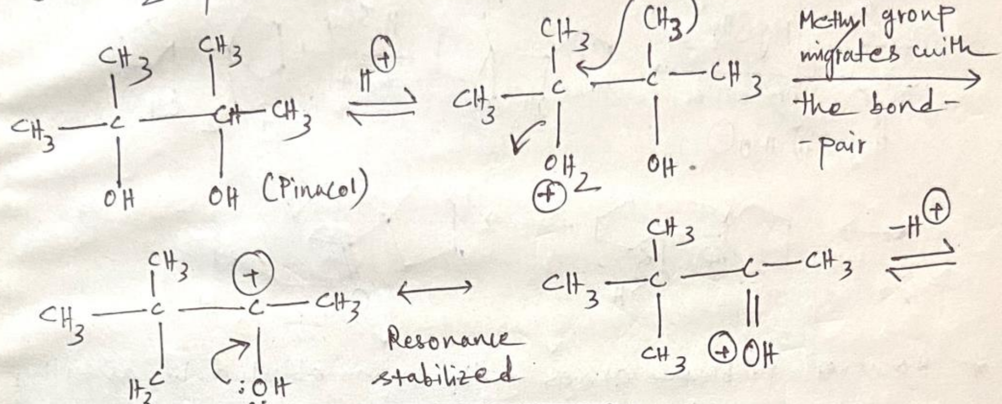
- Thus, when Ph_3CCH_2Cl is treated with sodium, it gave Ph_2CHCH_2Ph along with unrearranged products. Here, $Ph_3CCH_2^-$ is the intermediate. This is called the ***Grovenstein–Zimmerman rearrangement***. Here, the phenyl moves without its electron pair.

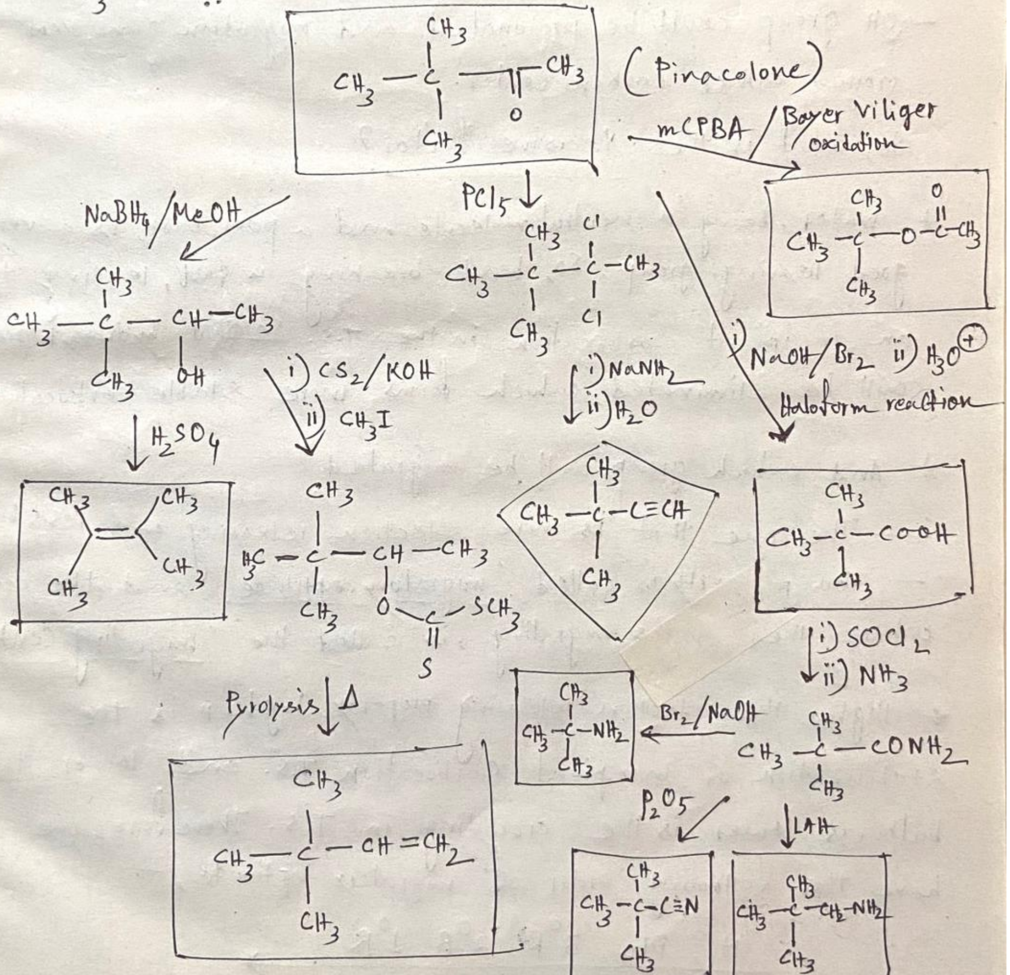
- Only aryl and vinylic, and not alkyl, groups migrate by the electrophilic and following transition state is likely.



Pinacol - Pinacolone Rearrangement:-

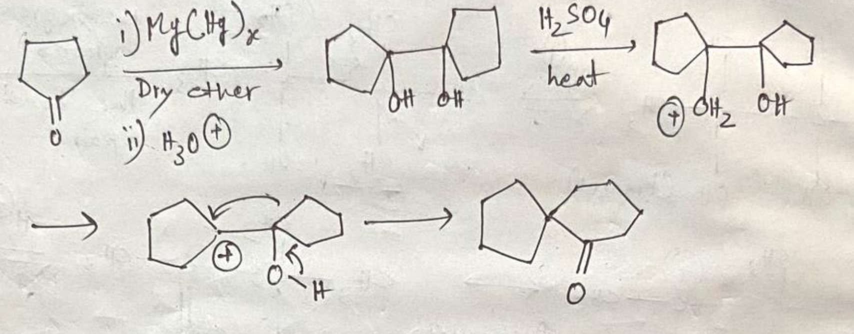
* Pinacolone, an important synthetic intermediate, can easily be obtained from pinacol, on treatment with 3M H_2SO_4.





* This rearrangement is a generalized property of 1,2-glycols and Known as, Pinacol-Pinacolone Rearrangement.

* Following example is an excellant application of this reaction, to prepare a spirocyclic Ketone.



* However, problem arises with unsymmetrical diols, as either —OH group could be protonated and migration can occur from either carbon center.

So, what is the decisive factor?

* Water, being a neutral molecule and a poor base, is a very good leaving group. So, bond-breaking is fast, leading to an incipient carbocation in the T.S. So, that hydroxyl group will be eliminated, which forms more stable carbocation.

* And which group will be migrated?

— The one that is more electron releasing and less bulky.

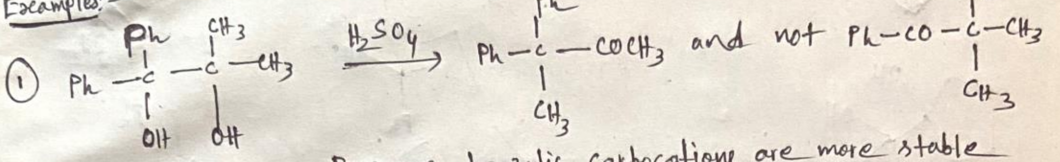
— This property is called 'migratory aptitude' and the center, where the group is migrating, is called the 'migrating center'

* Higher the election releasing property, higher is the stabilization of incepient carbocation T.S. and lower the bulkness, lower is the crowding in T.S. Therefore, we have the following order of migratory aptitude, —

$$\xrightarrow[\text{Migratory aptitude decreases}]{H,\ Ph,\ 3^{\circ}R,\ 2^{\circ}R,\ 1^{\circ}R}$$

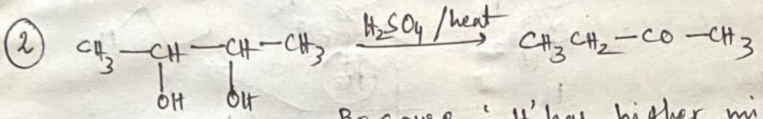
* There is also a stereochemical restriction: That group will migrate, which is conformationally anti with respect to the leaving group.

Examples:-

①


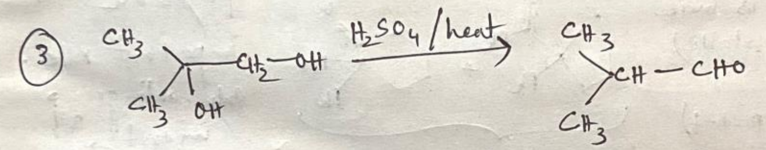
$Ph_2C(OH)-C(OH)(CH_3)_2 \xrightarrow{H_2SO_4} Ph_2C(CH_3)-COCH_3$ and not $Ph-CO-CPh(CH_3)_2$

— Because, benzylic carbocations are more stable

②


$CH_3-\underset{OH}{CH}-\underset{OH}{CH}-CH_3 \xrightarrow{H_2SO_4/heat} CH_3CH_2-CO-CH_3$

— Because, '–H' has higher migratory aptitude.

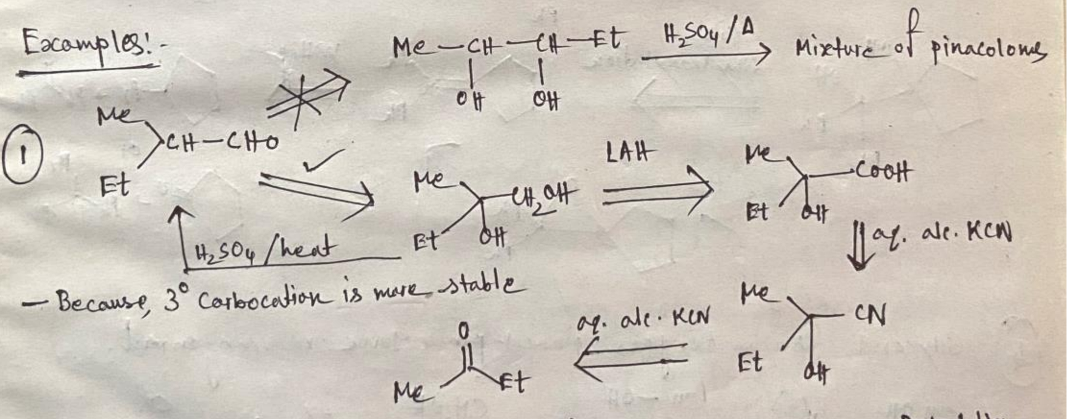
③


$(CH_3)_2C(OH)-CH_2-OH \xrightarrow{H_2SO_4/heat} (CH_3)_2CH-CHO$

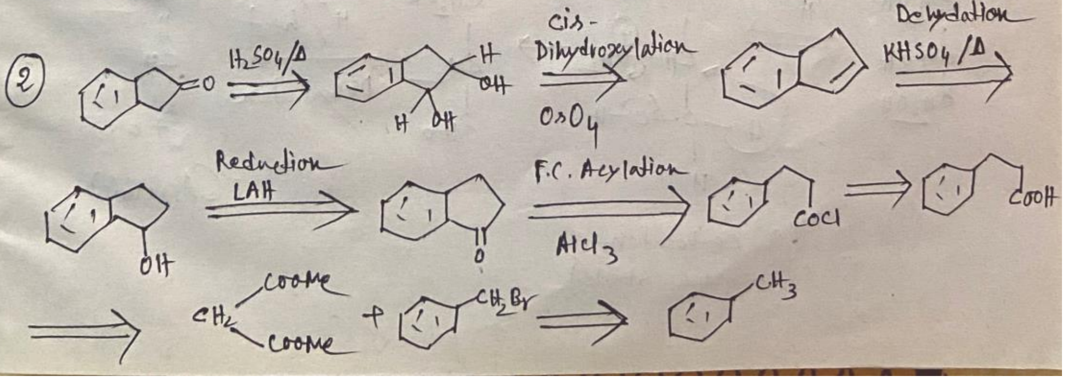
— Because, 3° carbocation is more stable.

* These logics can therefore be used in retrosynthetic analysis also.

Examples:-

①


— Because, 3° Carbocation is more stable

②


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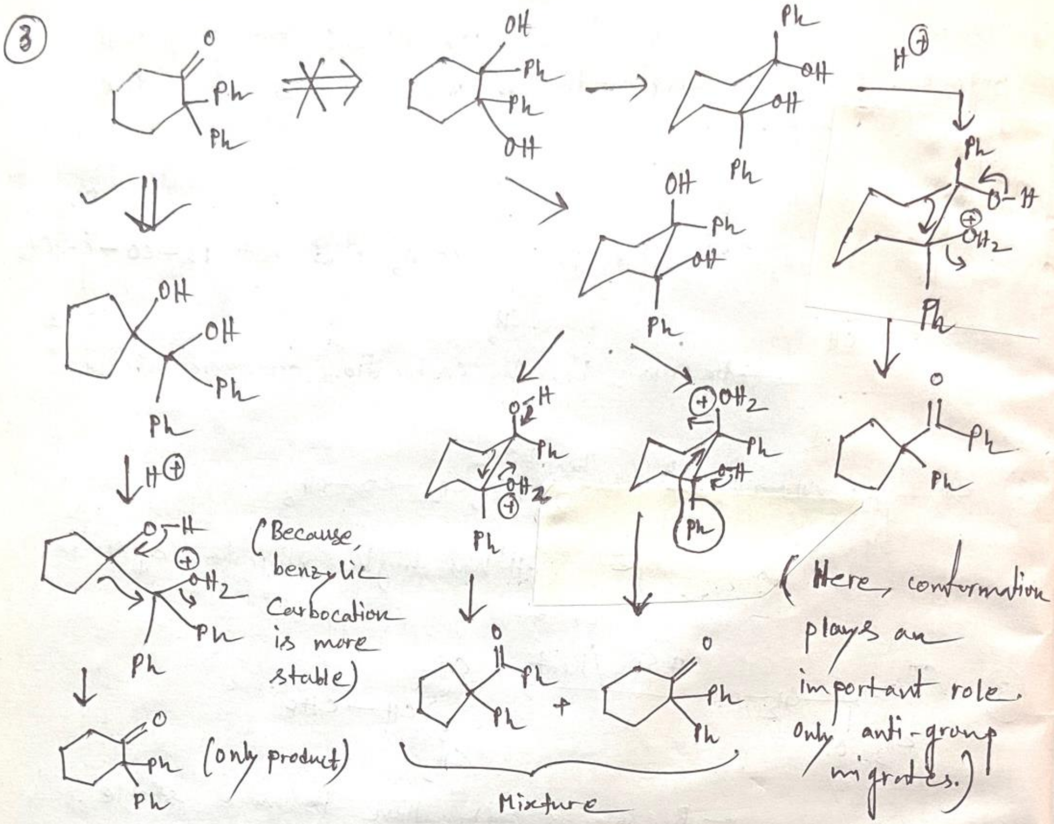


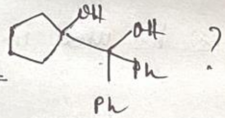
(Because, benzylic Carbocation is more stable)

(only product)

Mixture

(Here, conformation plays an important role. Only anti-group migrates.)

And how to obtain



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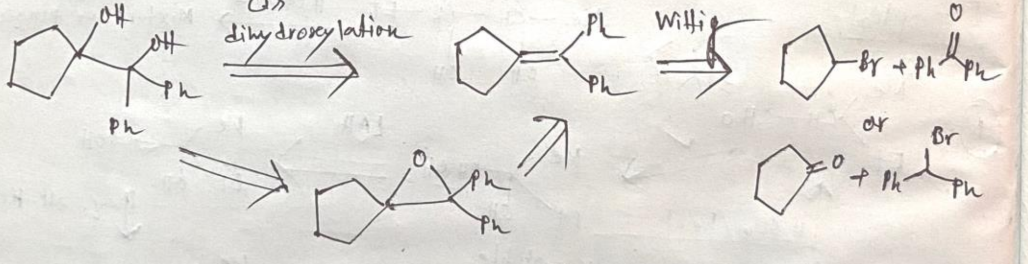
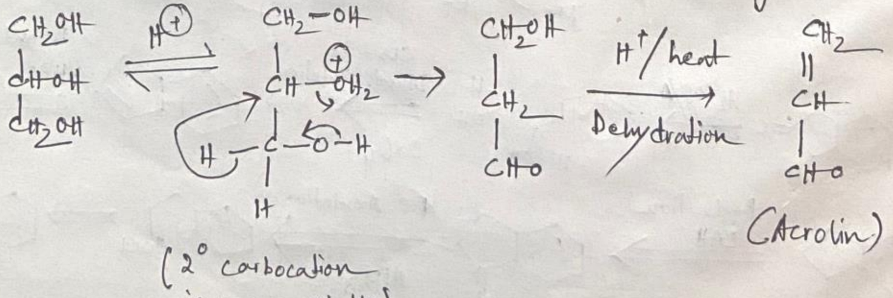


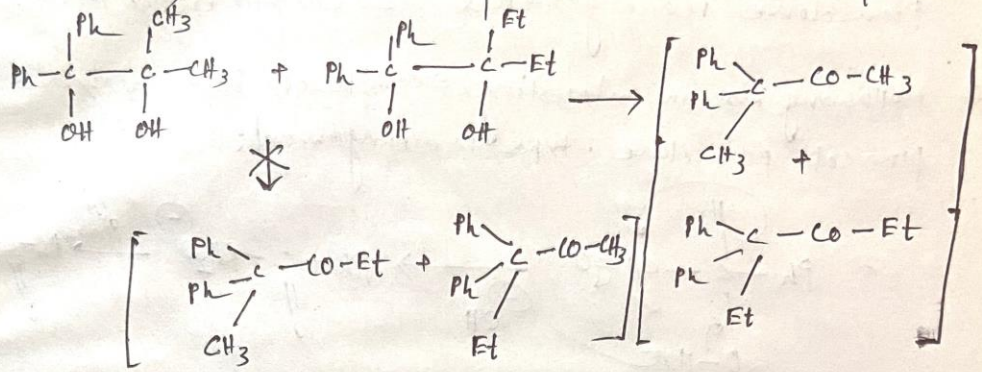
④ Glycerol, also undergoes pinacol-pinacolone rearrangement.



(Acrolin)

(2° carbocation is more stable)

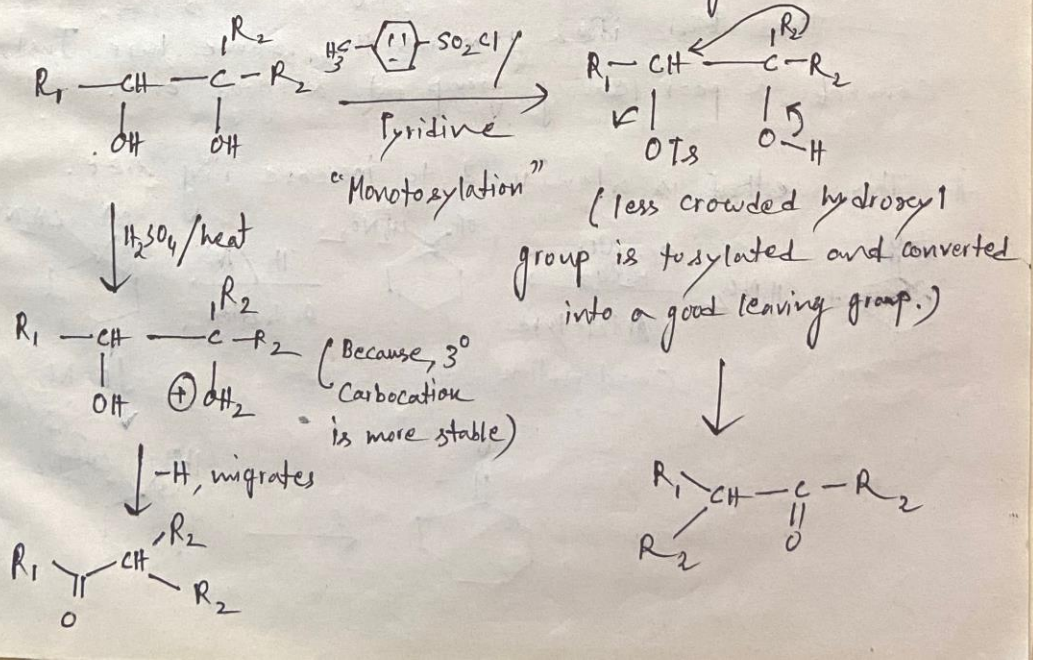
* The intramolecular nature of pinacol-pinacolone rearrangement is established by the cross-over experiment. → NO crossover product.



* Pinacol-pinacolone rearrangement can also be carried out under basic condition, via monotosylation. Interestingly, as tosylation leads to increase in bulkness, we have the following order of reactivity of —OH group.

$$\xrightarrow[\text{Tosylation increases}]{3^\circ\ \text{ROH} \quad 2^\circ\ \text{ROH} \quad 1^\circ\ \text{ROH}}$$

— of course, this trend is opposite to the trend in acid promoted pinacol-pinacolone rearrangement.

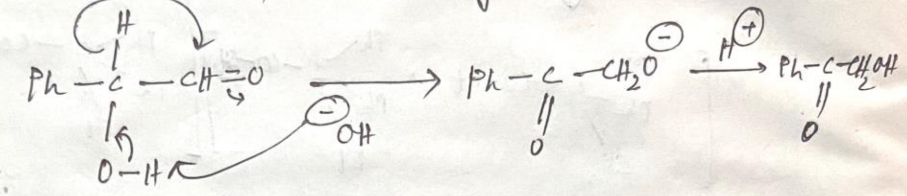


(less crowded hydroxyl group is tosylated and converted into a good leaving group.)

(Because, 3° Carbocation is more stable)

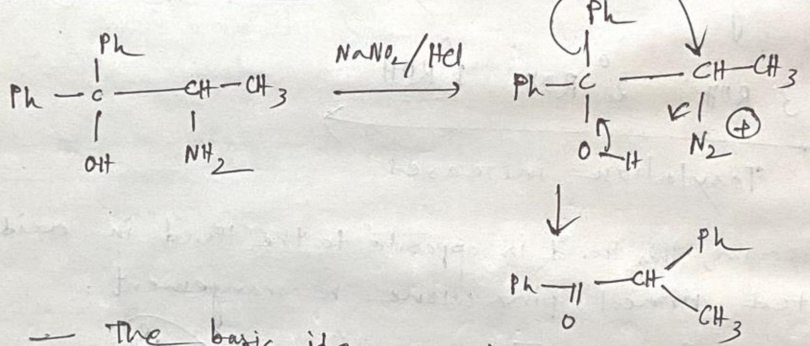
— Therefore, acid and base-catalysed Pinacol-Pinacolone rearrangements are complimentary to each other.

* Following is an interesting example of base-catalyzed pinacol-pinacolone-type rearrangement:



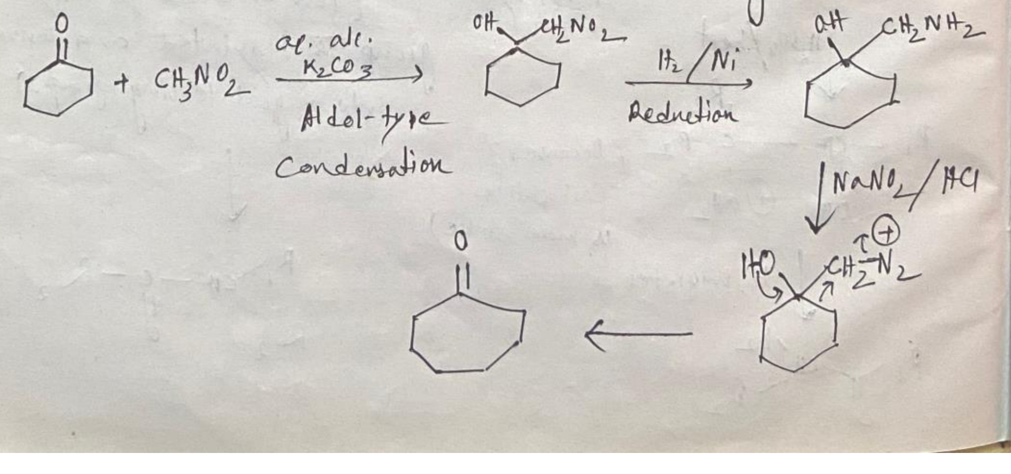
— Attainment of extended conjugation is probably the driving force here.

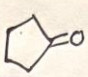
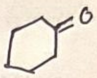
Pinacolic Deamination:-

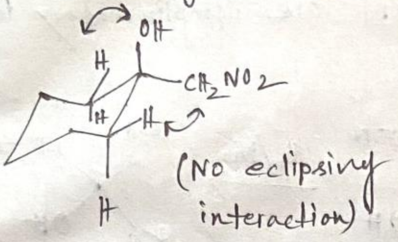


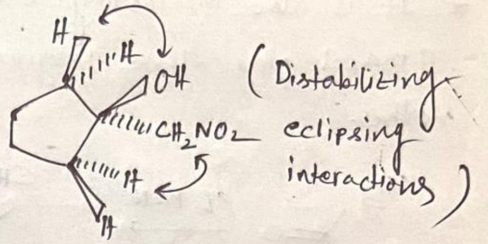
— The basic idea remains the same here. Just convert a poor leaving group into a good one.

* This method is often used to increase ring size.



But, the application of same logic to convert  into  is not so straight forward.

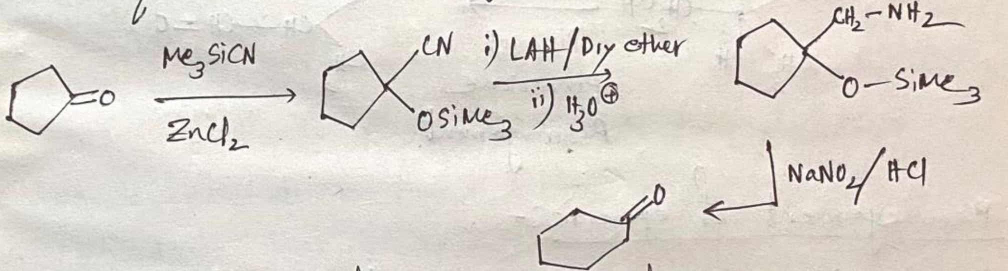




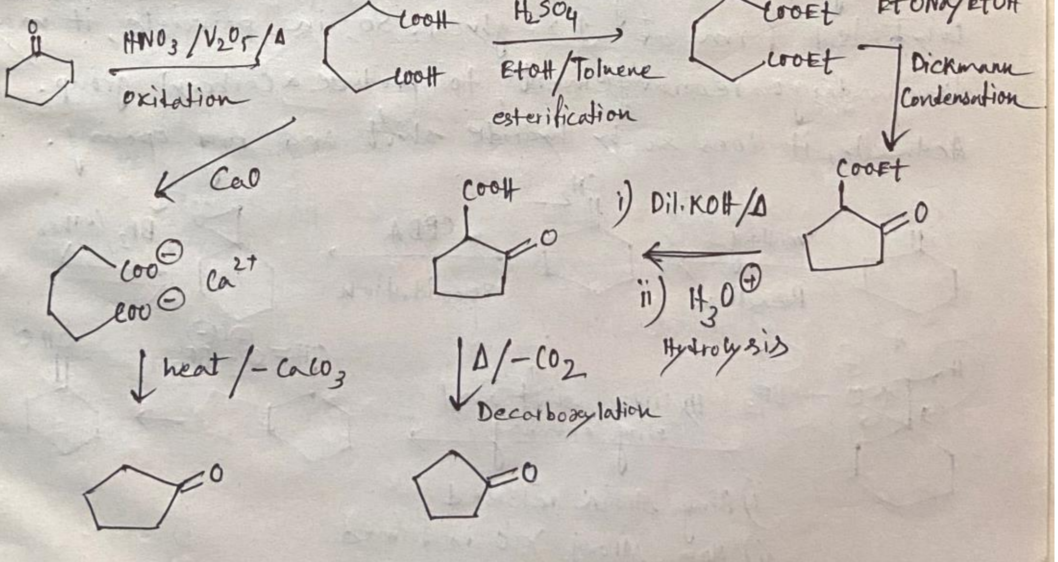
— In order to overcome this factor, following modification was done, -

i) A Lewis acid $ZnCl_2$ was used, to activate the $>$=O group

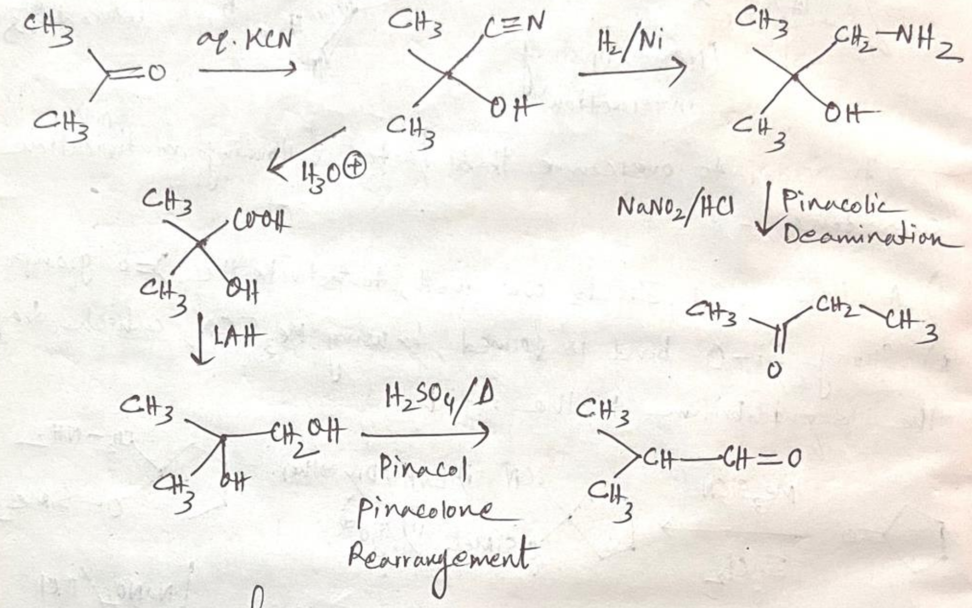
ii) Strong Si–O bond is formed, by using Me_3SiCN, which drags the equilibrium to the right.



In this context, the following techique for ring contraction may be noted:

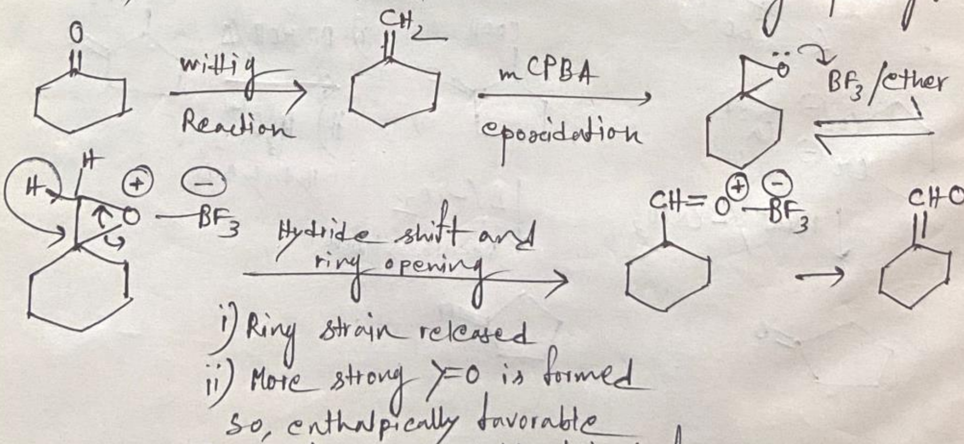


* It is also interesting to note that, pinacolic deamination and pinacol-pinacolone rearrangement are complimentary to each other.



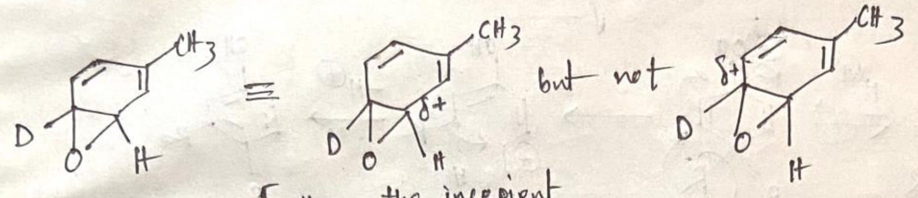
Rearrangement of epoxide :-

During pinacol-pinacolone rearrangement, dehydration occurs first, followedy by rearrangement. Now, epoxides are also a dehydrated form of 1,2-glycol. So, in principle, it may also undergo rearrangement, to produce a carbonyl group. Actually, it does so by hydride shift and ring opening.

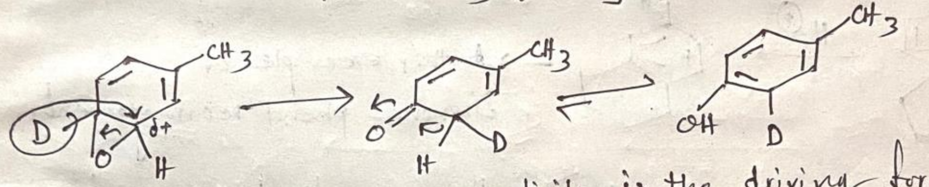


i) Ring strain released
ii) More strong $>C=O$ is formed
So, enthalpically favorable
iii) More flexible straight chain is formed
So, entropically favorable

* An important application of the above reaction can be found during 'NIH Shift'



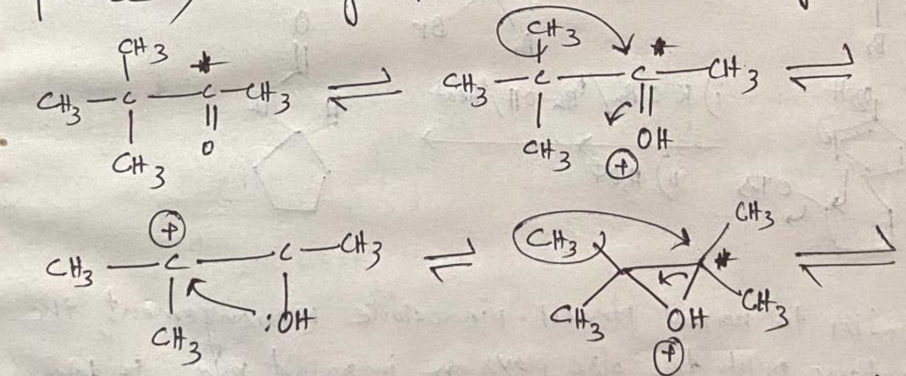
[Here, the incepient carbocation is more stabilized by +I effect from –CH3 group.]

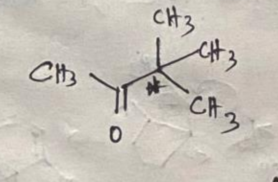


— Aromaticity is the driving force.

— weaker C–H bond is broken.

* Examples can also be found where an observation is explained by invoking epoxides and it's rearrangement.

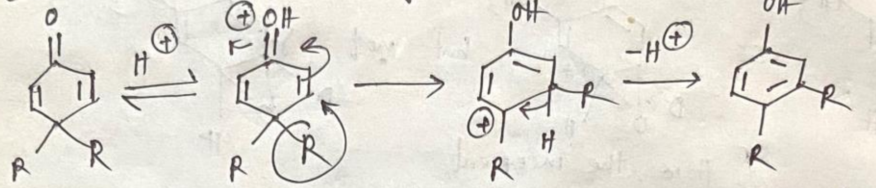




— Therefore, scrambling of C^{14} is found in this observation, which could be explained by invoking epoxide rearrangement.

Retro-pinacol rearrangements:-

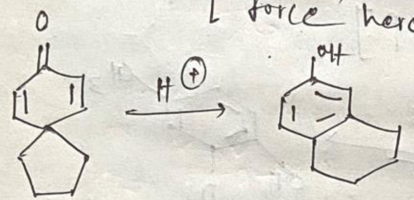
Dienone - Phenol rearrangement:-



Dienone

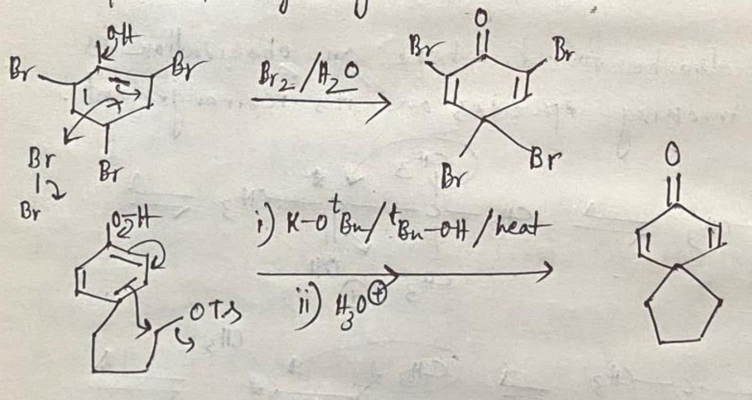
[Aromaticity is the driving force here.]

phenol

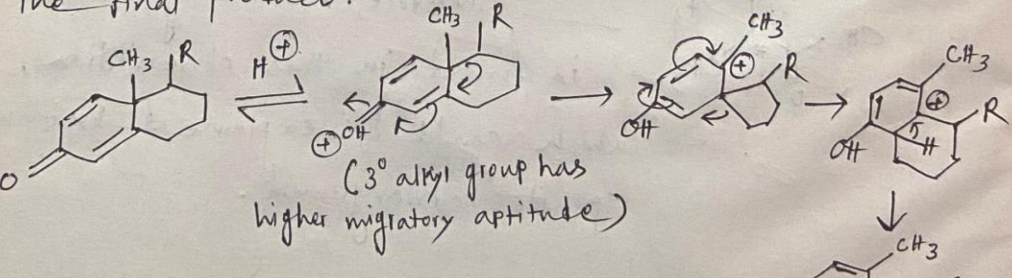


→ Another example of Dienone - phenol rearrangement.

* Sometimes, the opposite reaction can also be seen., i.e. a phenol might get converted into a dienone.



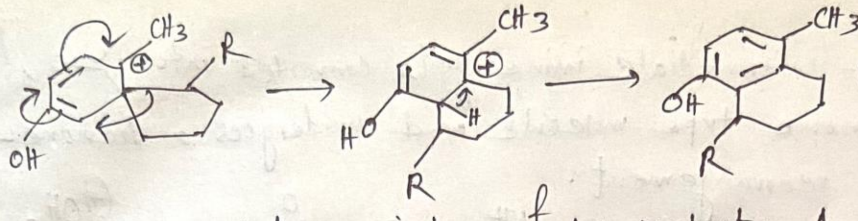
* Similar to normal pinacol-pinacolone rearrangement, the migratory aptitude also plays an important role, to determine the final product.



(3° alkyl group has higher migratory aptitude)

(A)

or,



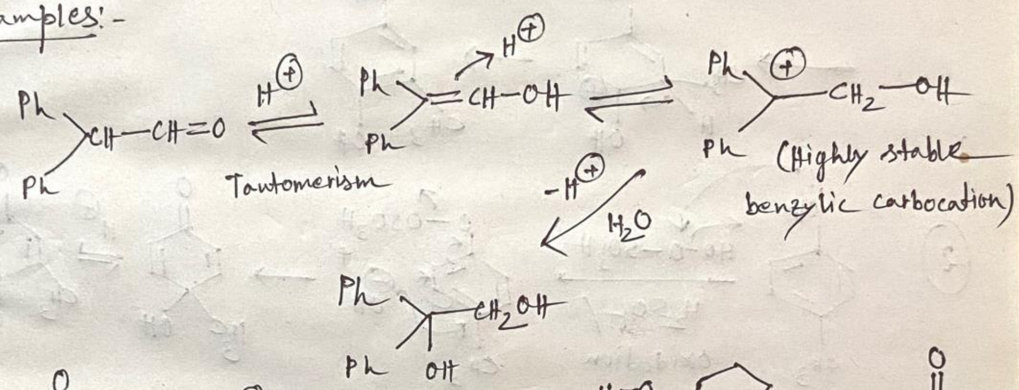
(B)

— So, we get a mixture of two products A and B.

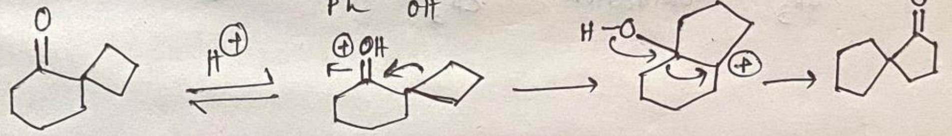
* There are many other reactions, which fall under retro-pinacol rearrangement:

<u>Examples:-</u>

①



②



Demyanov rearrangement

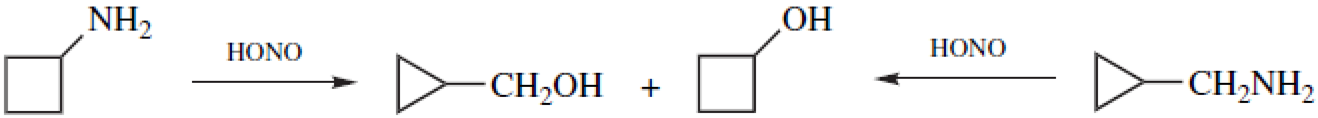
- When a positive charge is formed on an alicyclic carbon, migration of an alkyl group can take place to give ring contraction, producing a ring that is one carbon smaller.

- In a similar manner, when a positive charge is placed on a carbon of an alicyclic ring, ring expansion can take place.

- The new carbocation, and the old one, can then give products by combination with a nucleophile or by elimination.

- Often, both rearranged and unrearranged products are formed. For example, cyclobutylamine and cyclopropylmethylamine give similar mixtures of the two alcohols on treatment with nitrous acid.

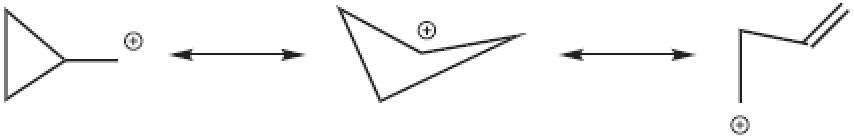
- When the carbocation is formed by diazotization of an amine, the reaction is called the ***Demyanov rearrangement***.



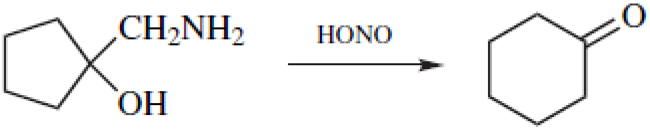
- The expansion reaction has been performed on rings of C3–C8, but yields are best with the smaller rings, where relief of small-angle strain provides a driving force for the reaction.

- The contraction reaction has been applied to four-membered rings and to rings of C6–C8, but contraction of a cyclopentyl cation to a cyclobutylmethyl system is generally not feasible because of the additional strain involved.

- Strain is apparently much less of a factor in the cyclobutyl–cyclopropylmethyl interconversion, as the positive charge is delocalized by a double or triple bond that is not in the allylic position or by a single bond.

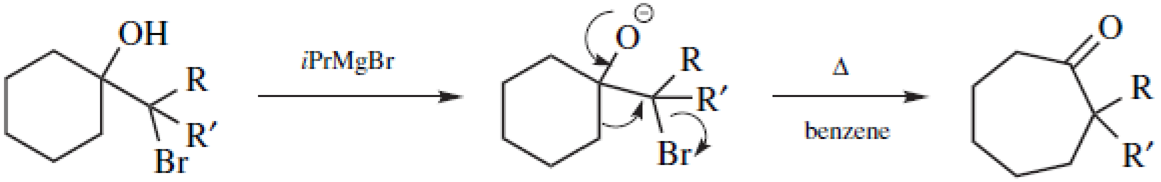


- Ring expansions of certain hydroxyamines are analogous to the semipinacol rearrangement. This reaction is called the ***Tiffeneau–Demyanov ring expansion***.



- A similar reaction, where a cyclic bromohydrin is treated with a Grignard reagent, brings about the ring enlargement.

- Here, at least one R group has to be phenyl or methyl. But it fails when both R groups are hydrogen, probably due to an unstable incipient carbocation.

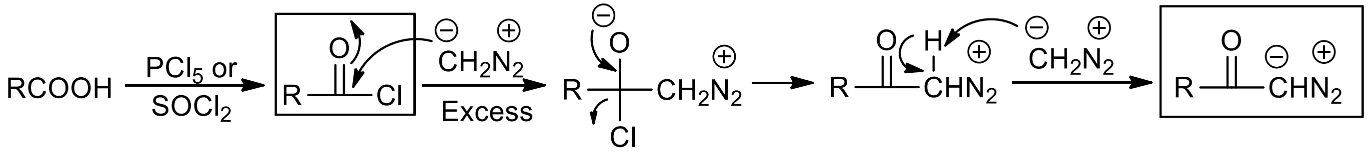


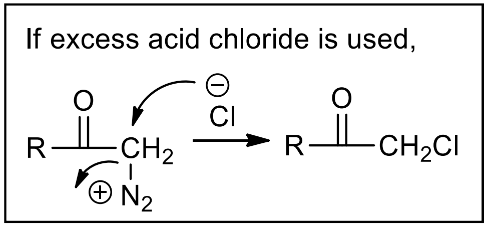
ARNDT-EISTERT REACTION

- It’s a technique, involving a series of a few simple reactions, to convert acids (aliphatic/aromatic/alicyclic/heterocyclic) into next higher homologous acid/amide/ester.

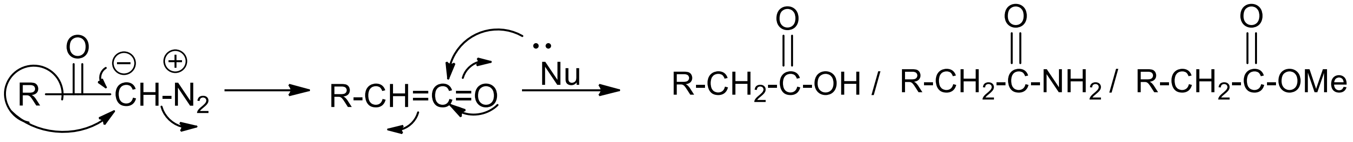
$$\mathbf{RCOOH} \longrightarrow \mathbf{RCH_2COOH\ /\ RCH_2CONH_2\ /\ RCH_2COOMe}$$

- Step-1 is the conversion of the acid into acid chloride, which on reaction with excess diazomethane (acid chloride is added to the etheral solution of diazomethane) in step-2, gets converted into a diazoketone. But, if the acid chloride is taken in excess, corresponding chloromethyl ketone is formed.




If excess acid chloride is used,

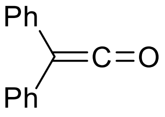
- Finally, a rearrangement, with the loss of nitrogen produces the acid (with H_2O/Colloidal Ag-Ag_2O catalyst), amide (with NH_3/$AgNO_3$ catalyst) or the ester (with MeOH/Ag_2O catalyst). This rearrangement step is called the “**Wolff rearrangement**”. An initial 1,2-shift leads to a ketene, which then reacts with H_2O/NH_3/MeOH to give the acid/amide/ester.



Wolff Rearrangement **(Nu = H_2O / NH_3 / MeOH)**

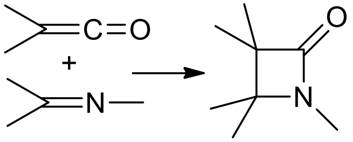
- The intramolecularity is evident from i) isolation of stable diphenyl ketene; ii) trapping of ketene with imine by forming β-lactum; iii) retention of configuration of chiral migrating groups; iv) retention of ^{14}C-isotope label on carbonyl carbon.

i)



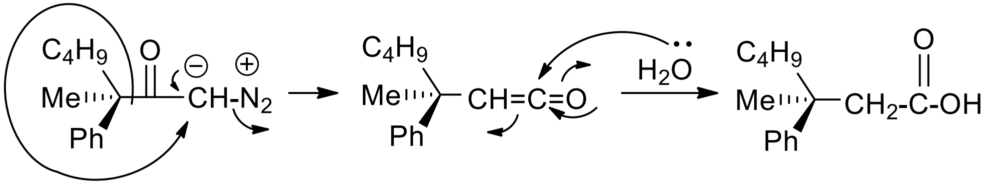
A stable ketene,
which was isolaed

ii)



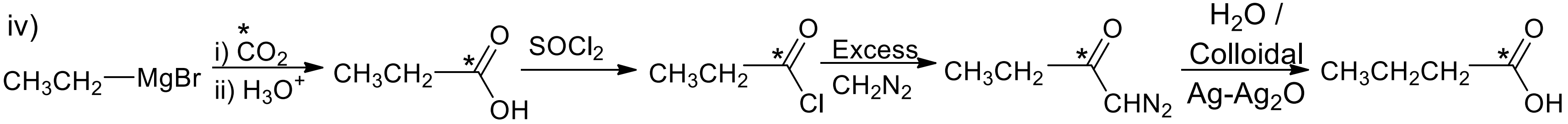
A trapped β-lactum

iii)



Retention of configuration of migrating group

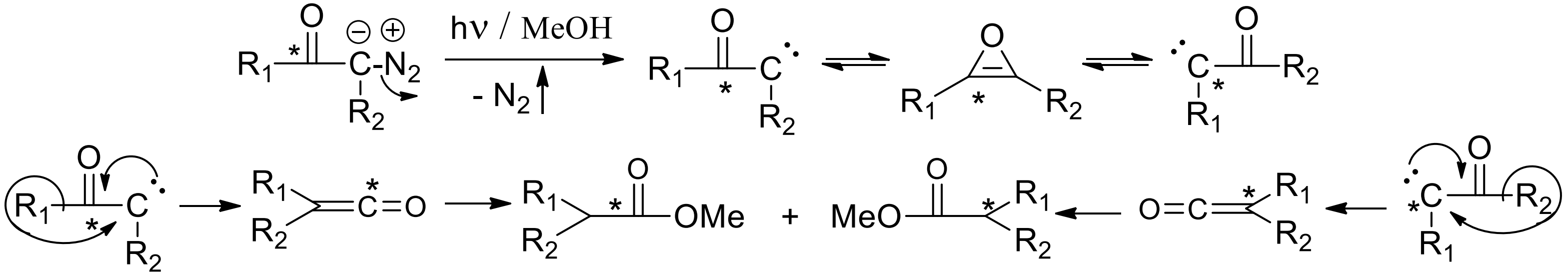
iv)



Retention of isotope labelling at carbonyl carbon

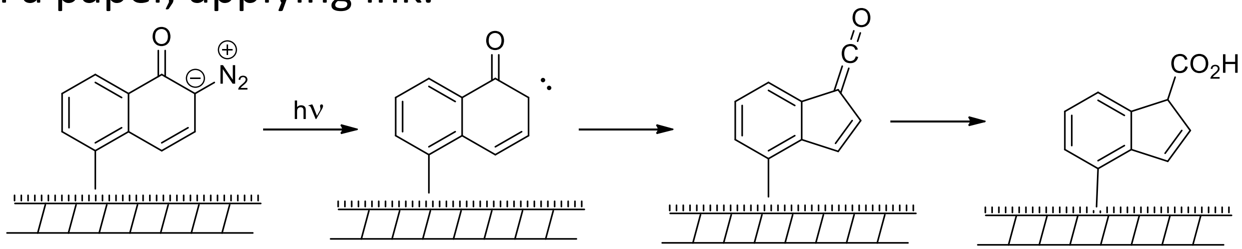
- Ag-catalyst promotes concerted rearrangement. But, in its absence, under photochemical condition, intermolecular rearrangement occurs, involving a carbene intermediate. Sometimes, Cu-catalyst also promotes the formation of a carbene intermediate.

- This carbene intermediate exists in an equilibrium with an oxirene species, which is proved by the equal ^{14}C distribution in the product, when a carbonyl-labelled diazoketone was employed under Wolff rearrangement, photochemically.



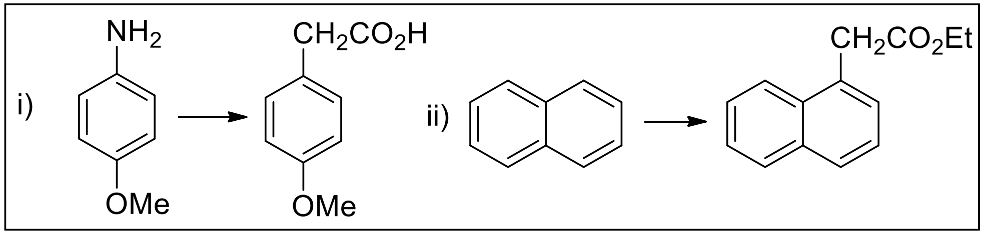
- This concept is utilized in developing diazoplates. These are lithographic plates, where a polymer bound photosensitive material (generally, diazo-substituted ortho-naphaquinones) is coated on the metal surface.

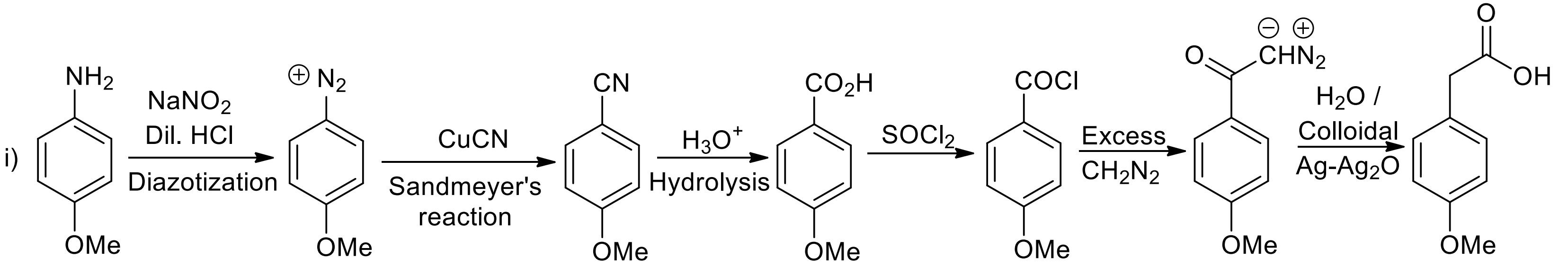
- In order to capture the image of the species of interest, these plates, along with the species were exposed to photochemical condition. The species of interest, shields a certain area of the plate, according to its shape. The remaining area stays exposed and gets converted to an acid, by reacting with trace amount of water present in the film. On treatment with alkali, the acid bound material dissolves out, leaving behind an unexposed polymer coating, according to the structure of the species of interest. This shape is then projected on a paper, applying ink.

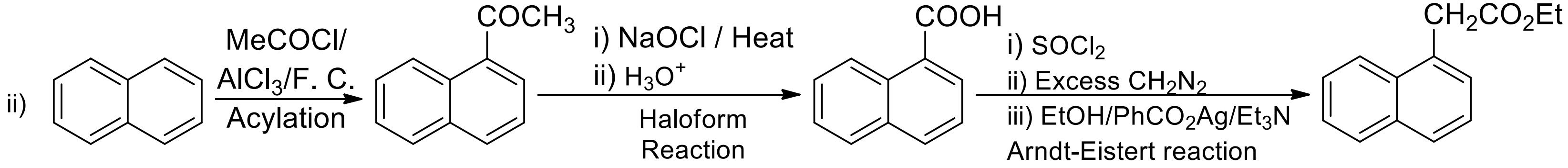


Problems:

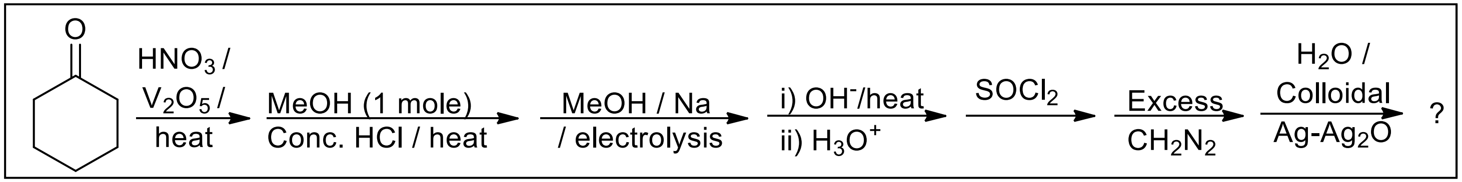
1. Complete the following conversions:

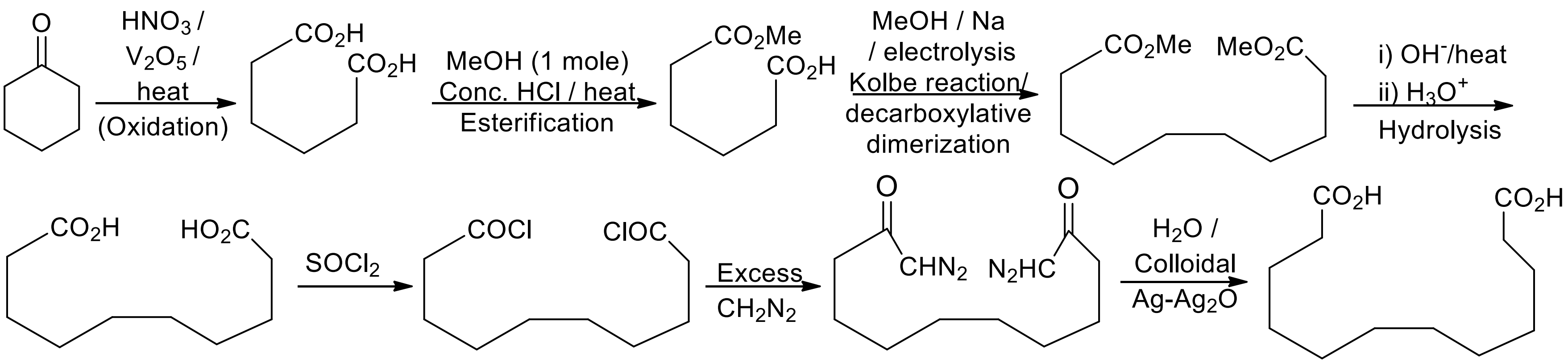




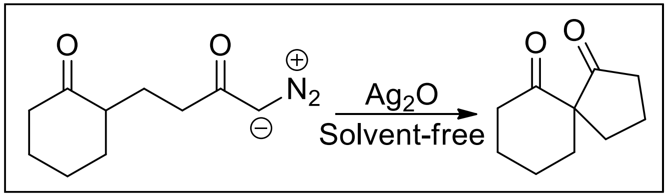


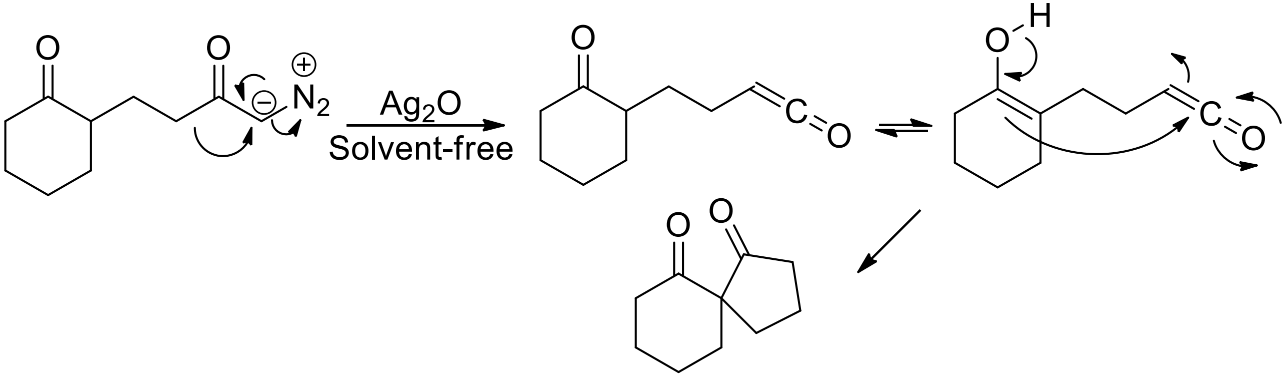
2. *Complete the following:*

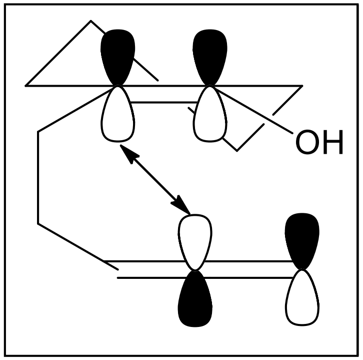




3. *Explain mechanistically:*

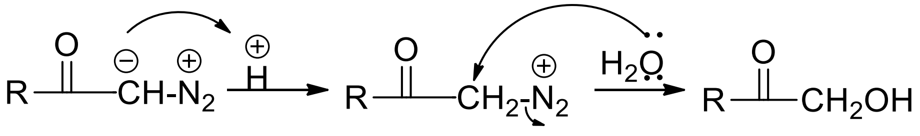




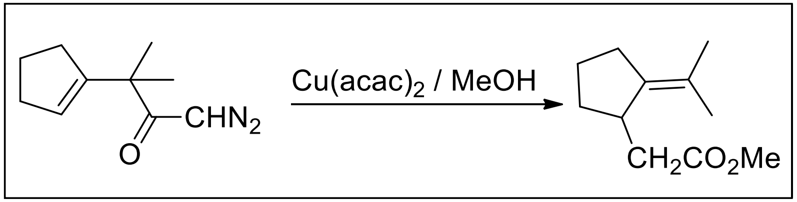


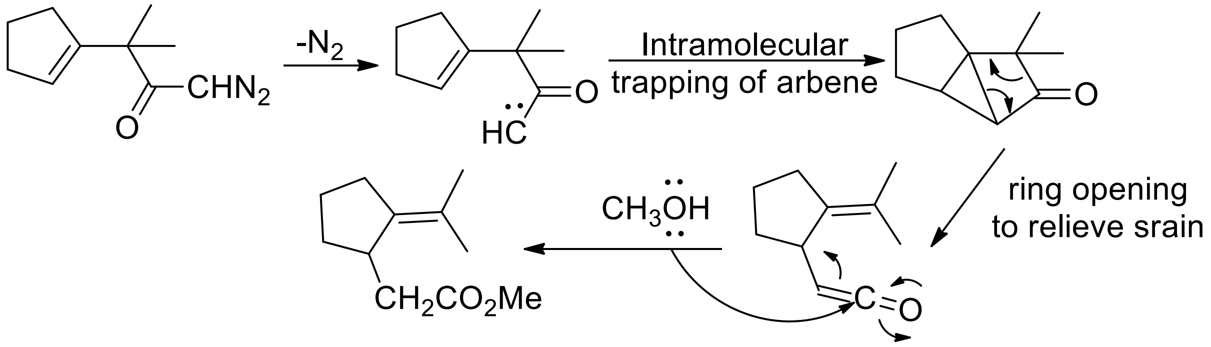
4. Explain mechanistically:

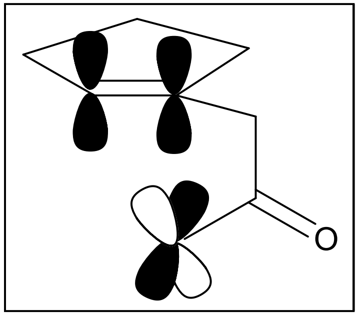
$RCOCHN_2 + H_2O + HCO_2H = RCOCH_2OH$



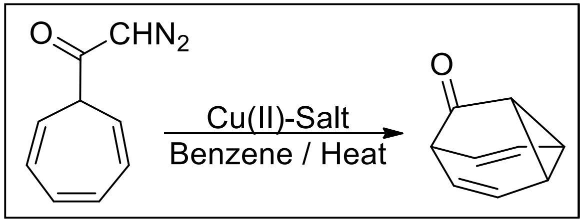
5. Explain mechanistically:

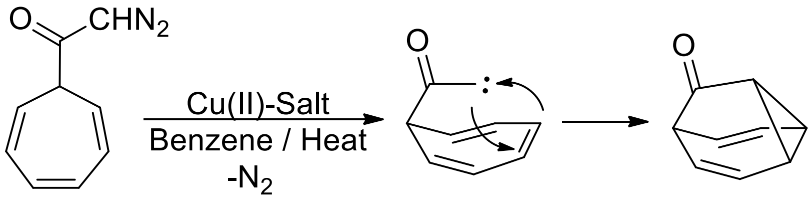






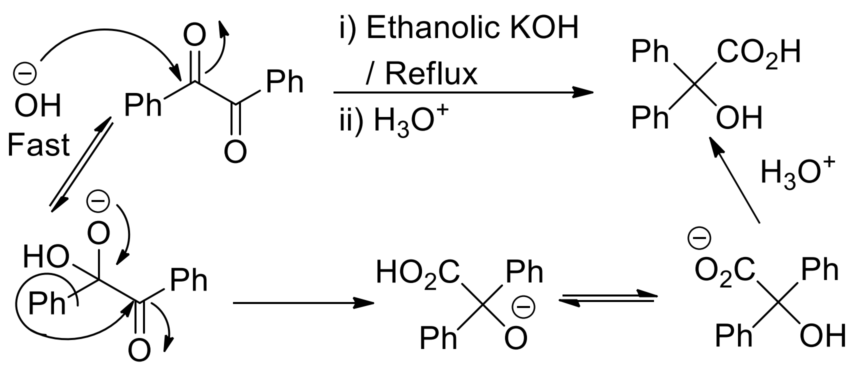
5. Explain mechanistically:

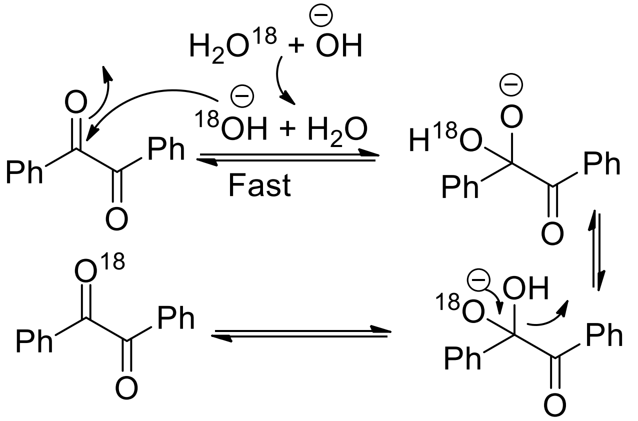




BENZIL-BENZILIC ACID REARRANGEMENT

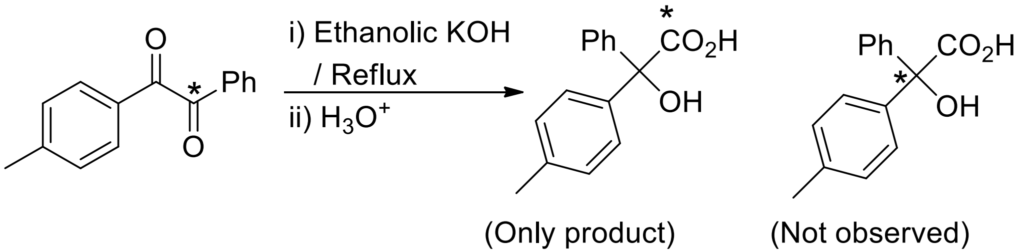
- The reaction begins with a fast nucleophilic attack on any of the carbonyl centers. Of course, in unsymmetrical diketones, the aryl group which contains electron releasing group will deactivate the α-keto group. So, the hydroxide will preferentially attack the other keto.





- The reversibility of step-1 was confirmed by heating benzil for a very short time, with ethanolic KOH in H_2O^{18} and isotopically labelled benzil was isolated, which is possible, only if step-1 is reversible.

- Step-2 observes a migration of the phenyl group from the tetrahedral center to the β-keto center.



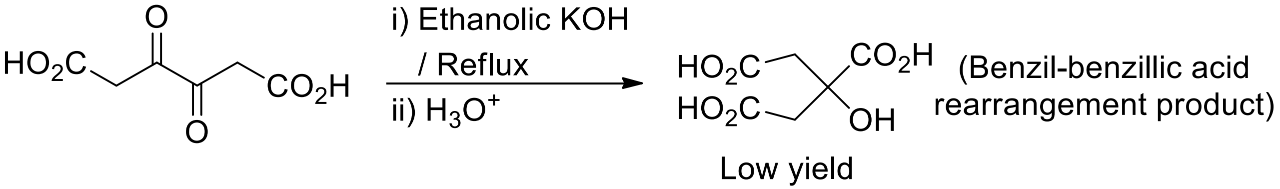
- Step-2 involves a C-C bond breaking and expected to be the r.d.s, as supported by the rate law, ***Rate = K[PhCOCOPh][OH^{-}].*** As expected, in unsymmetrical diketones, migration of less electron-releasing aryl group will occur. So, the above isotope-lebelled p-methylbenzil gave the acid-carbon-lebelled product and not the tertiary-carbon-lebelled product

- Finally, a proton exchange, followed by acidification leads to the final product.

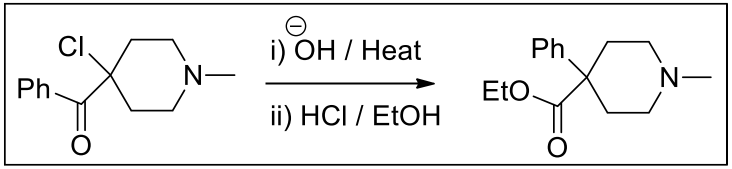
Problems:

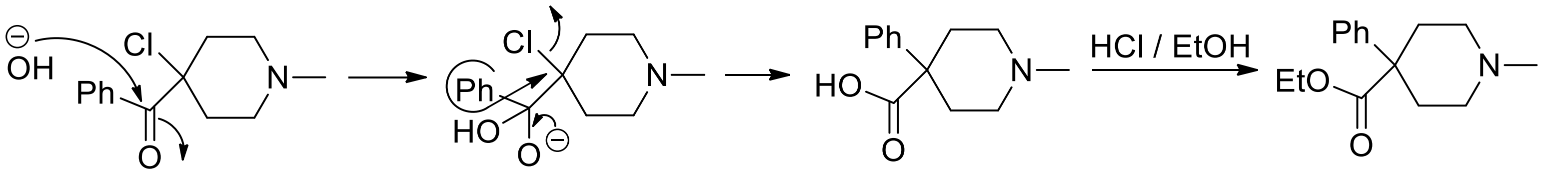
1. ***Citric acid is obtained in low yield, on heating $HO_2CCH_2COCOCH_2CO_2H$ with OH^-. Why?***

Only aromatic diketones undergo Benzil-Benzillic acid rearrangement when heated with OH^-. The same is not possible with aliphatic diketones, as they mainly undergo condensation reactions due to the presence of α-hydrogens. So, the benzil-benzillic acid rearrangement product is obtained with a low yield.



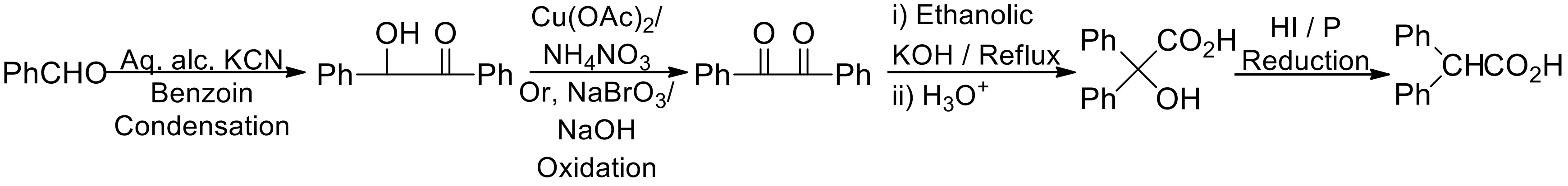
2. Explain the following conversion:





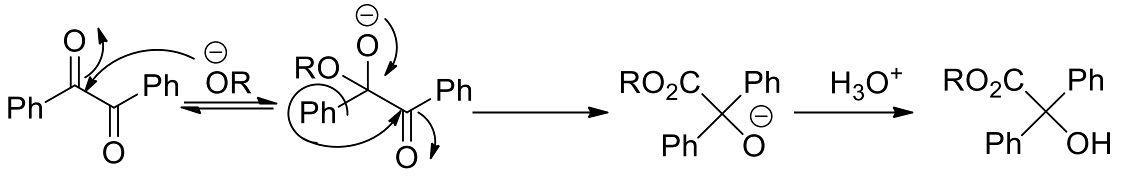
The reaction is analogous to Benzil-Benzillic acid rearrangement and is known as "***Quasi Favorskii Rearrangement***". The mechanism is called "***Semi benzillic mechanism***".

3. Complete the following conversion: PhCHO to $(Ph)_2CH\text{-}CO_2H$

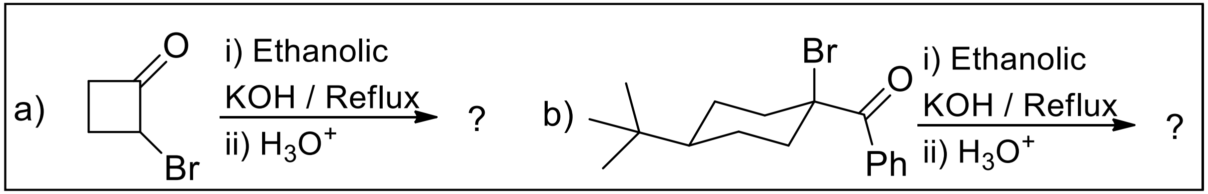


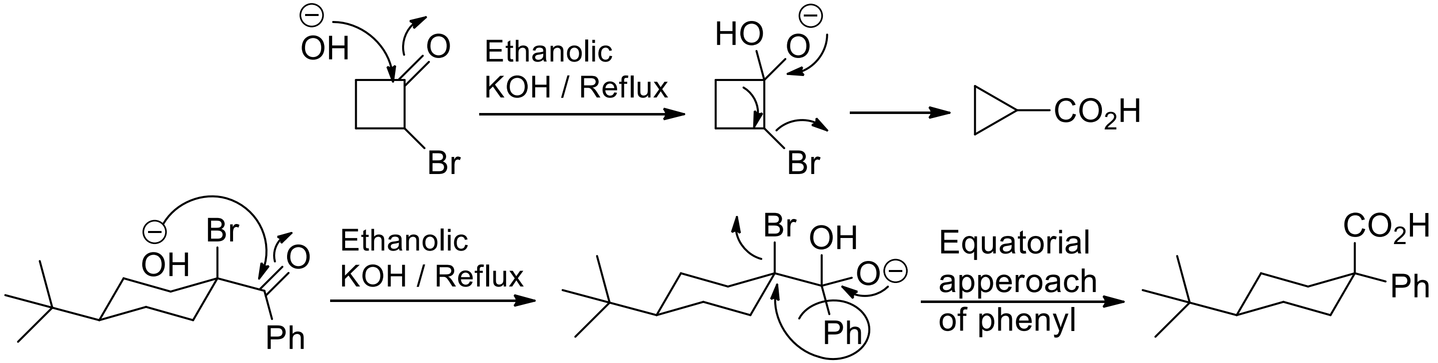
4. “Alkoxides can also promote Benzil-Benzillic acid type rearrangement”. Explain.

Methoxides and tert-butoxides can promote a Benzil-Benzillic acid type rearrangement as shown below, which leads to a hydroxy-ester. However, alkoxides of type $^{-}OCH(Me)_2$, is not useful, as they act as reducing agent and reduces benzil.



5. Complete the following:





6. What happens when phenanthrene is heated with alkaline $KMnO_4$?