

Organic Chemistry III
Core-VI

Molecular Rearrangements and Named Reactions



Dr. Samim Akhtar

Department of Chemistry
Bidhan Chandra College Asansol

Molecular Rearrangements

Molecular Rearrangements

- Rearrangement reactions are an interesting class of reactions wherein a group or an atom migrates during the course of the reaction. While most of the rearrangements are designed in that fashion, it can also be undesirable in some cases. Depending on the reaction conditions, the nature of rearrangement (and the product) could also change.
- Rearrangements are divided into intramolecular and intermolecular processes. In intramolecular process, the group that migrates is not completely detached from the system in which rearrangement is taking place. In contrast, in intermolecular process, the migrating group is first detached and later re-attached at another site.
- Emphasis has been placed on examples involving skeletal rearrangements that are practically used in day-to-day organic synthesis.

Molecular Rearrangements

- Rearrangement reactions involve the migration of a group or an atom from one center (**migration origin**) to another (**migration terminus**) within the same molecule.
- In this module, various rearrangement reactions are presented. These rearrangements can be roughly classified on the basis of the migration origin and migration terminus.

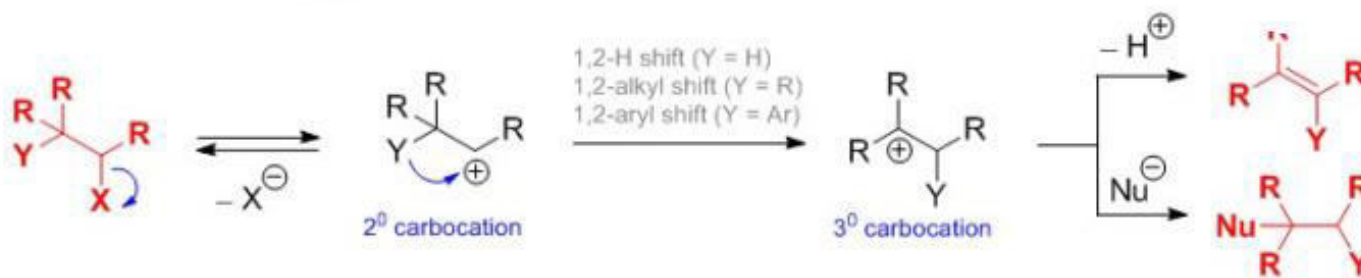
1. Rearrangements to Electron Deficient Carbon
2. Rearrangements to Electron Deficient Nitrogen
3. Rearrangements to Electron Deficient Oxygen
4. Sigmatropic Rearrangements
5. Other Rearrangements

Rearrangements to Electron Deficient Carbon

- ✚ Wagner-Meerwin Rearrangement
- ✚ Pinacol-Pinacolone Rearrangement
- ✚ Demjanov Rearrangement
- ✚ Benzil-Benzilic acid Rearrangement
- ✚ Wolff Rearrangement
- ✚ Dienone-Phenol Rearrangement

Wagner-Meerwin Rearrangement

➤ It is one of the simplest systems where an alkyl group migrates, with its bonding pair, to an electron-deficient carbon atom.

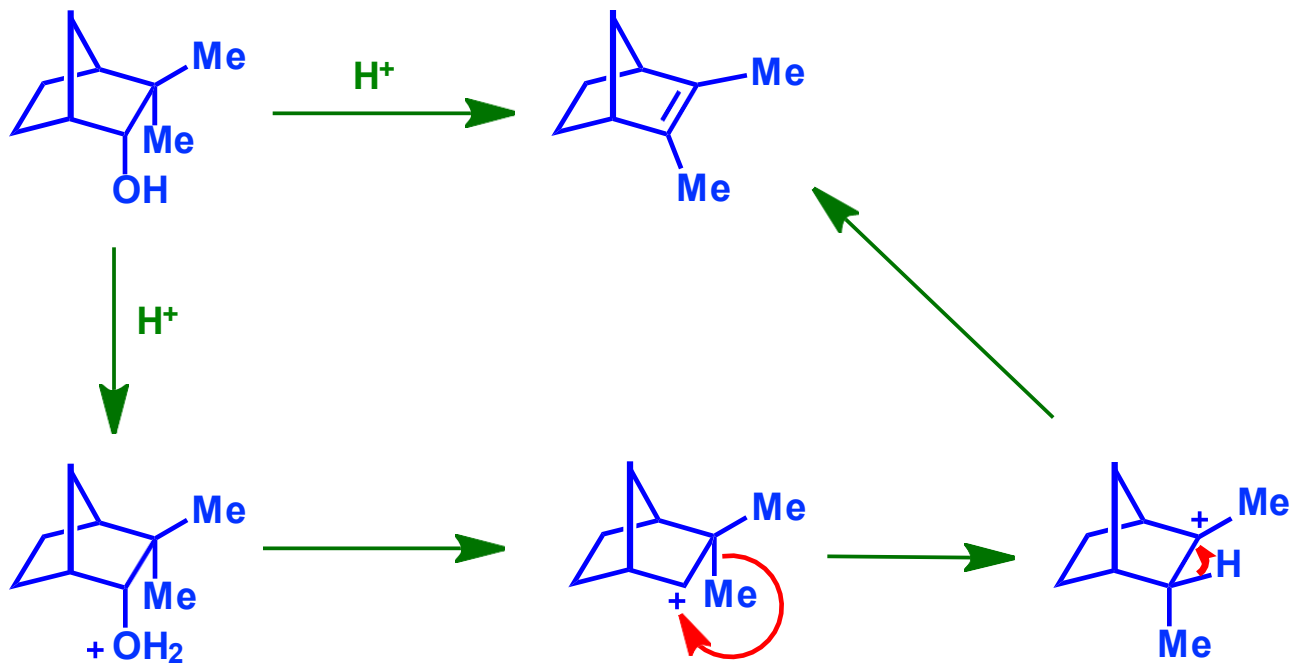


Example:



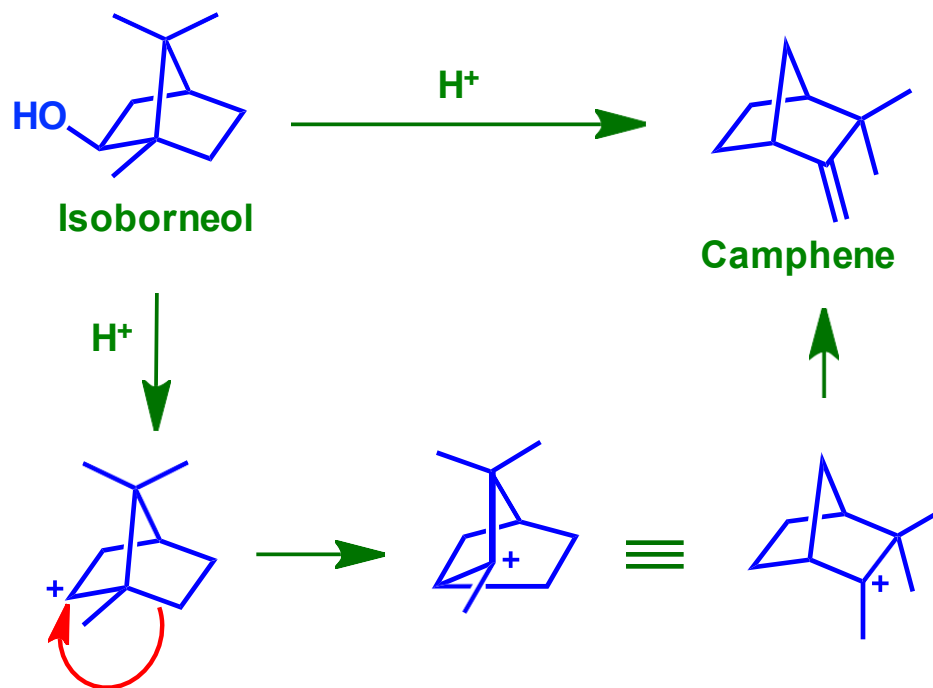
Wagner-Meerwin Rearrangement

- Rearrangement of alcohols under acidic condition



- Alkyl migration occurs to give stable carbocation
- This is the driving force for the migration of alkyl, aryl or even hydrogen atom

Wagner-Meerwin Rearrangement



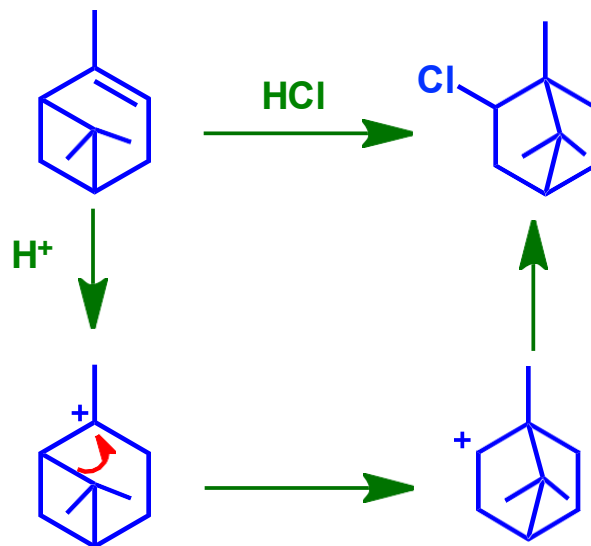
Ring Expansion

- More stable carbocation will be generated
- Stability of carbocations-



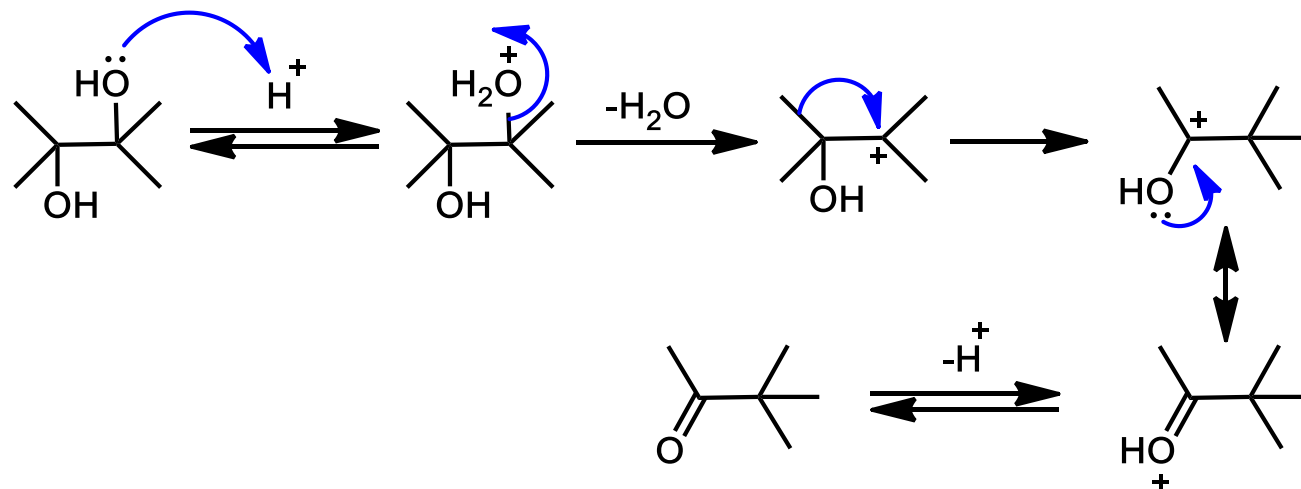
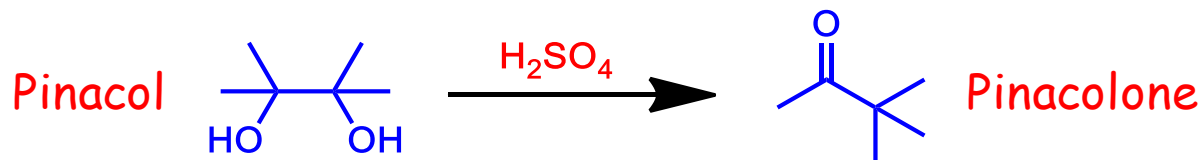
Can we go from 3° to 2° ??

- Cations can be made more stable if they become less strained



Relief in strain from four to five membered ring is driving force

Pinacol-Pinacolone Rearrangement



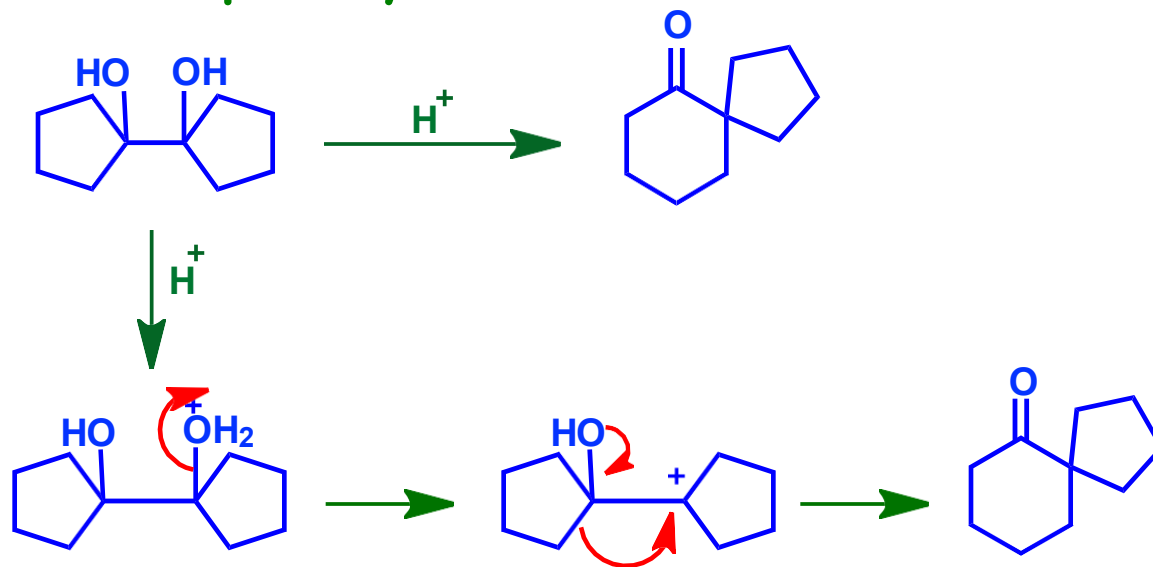
- Carbocation is already tertiary
- There is no ring strain
- Then why should it rearrange?

Reason: The lone pair of electrons on the oxygen is another source to stabilize the carbocation generated after methyl migration

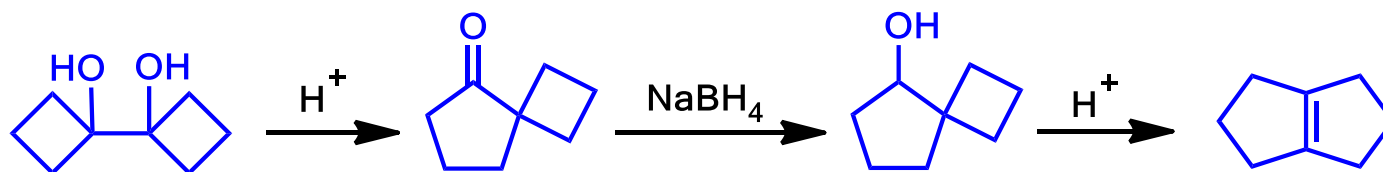
Pinacol-Pinacolone Rearrangement

- Pinacol-Pinacolone rearrangement can be viewed as a push and a pull rearrangement
- The carbocation formed as a result of loss of H_2O , pulls the migrating group
- Lone pair on oxygen pushes the migrating group

Preparation of Spiro System:

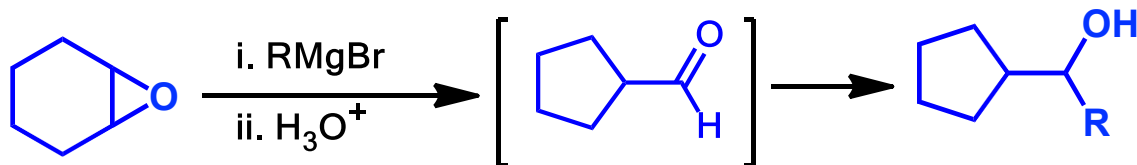
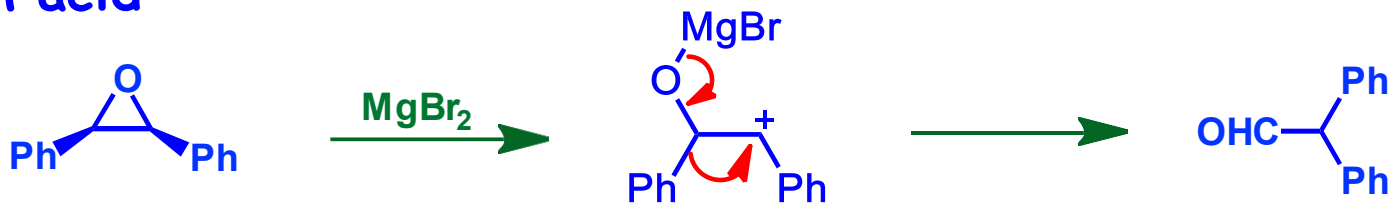


Pinacol-Pinacolone Rearrangement



Epoxides :

Epoxides also undergo pinacol type rearrangement on treatment with acid

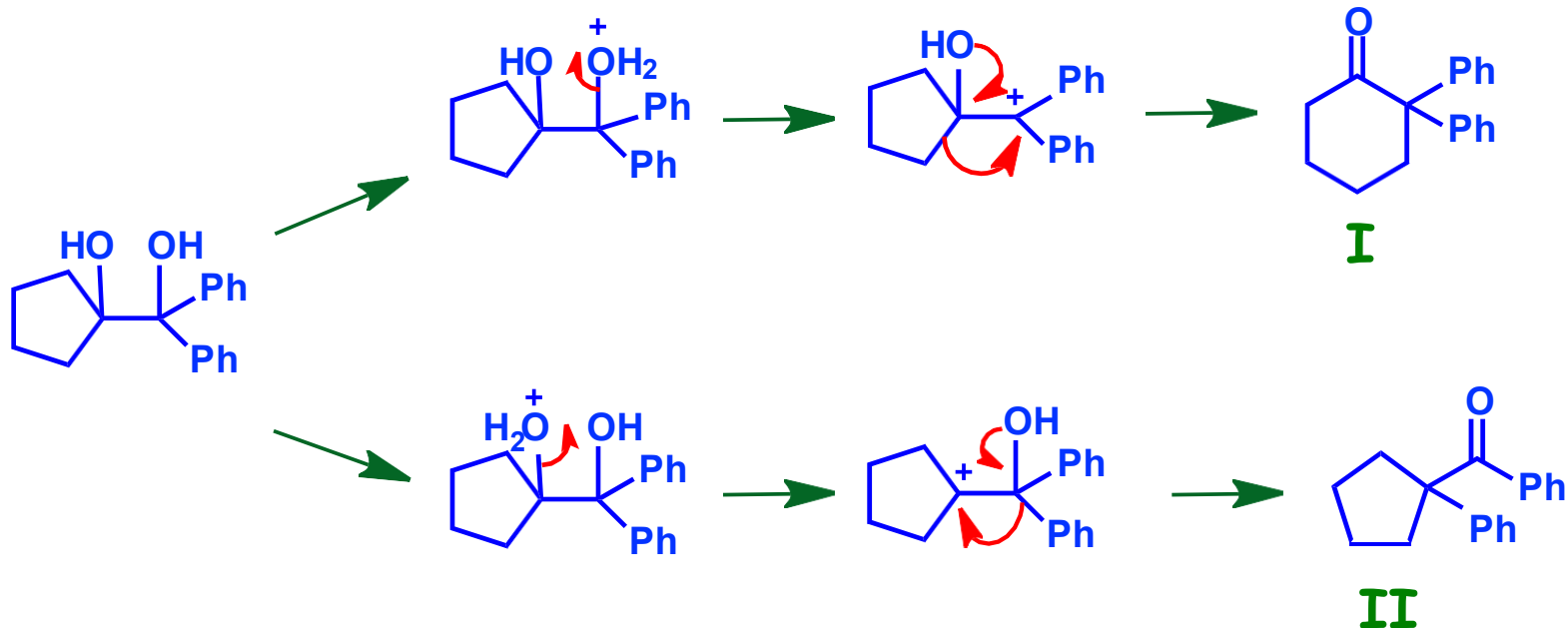


➤ With a Grignard reagent, rearrangement occurs faster than nucleophilic attack to the epoxide

Pinacol-Pinacolone Rearrangement

➤ Migrating group preference:

It doesn't matter when we have symmetrical diols & epoxides It doesn't matter when we have unsymmetrical epoxides & diols



Only I is formed in quantitative amount because the carbocation is stabilized by two phenyl groups

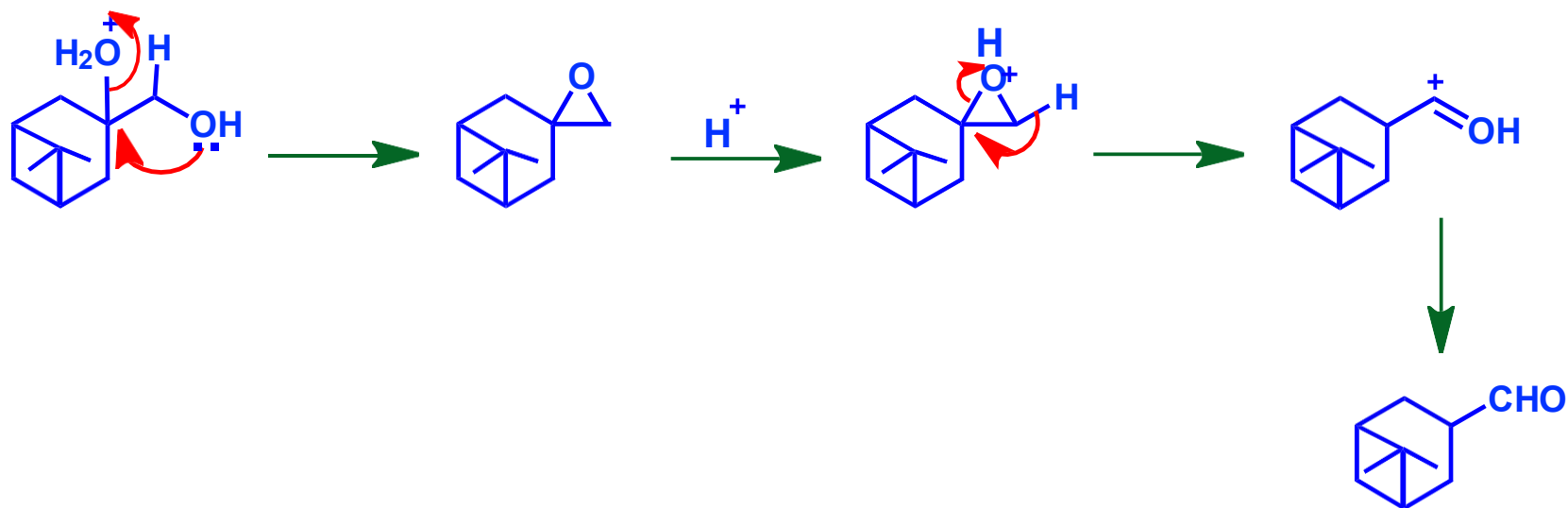
Pinacol-Pinacolone Rearrangement

Semipinacol Rearrangement

They are nothing but pinacol rearrangement without choice



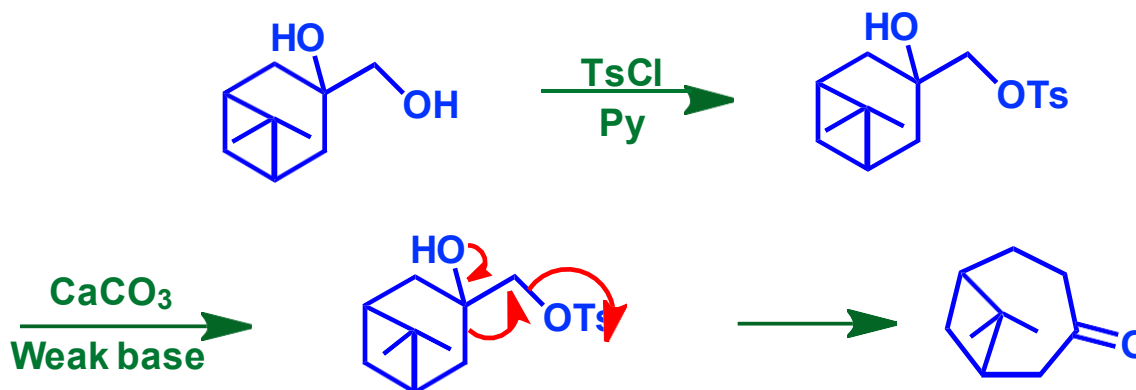
Under normal acidic conditions



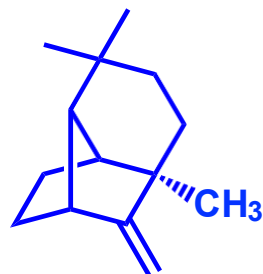
Pinacol-Pinacolone Rearrangement

Semipinacol Rearrangement

For the required product, the primary hydroxyl group needs to be made as better leaving group

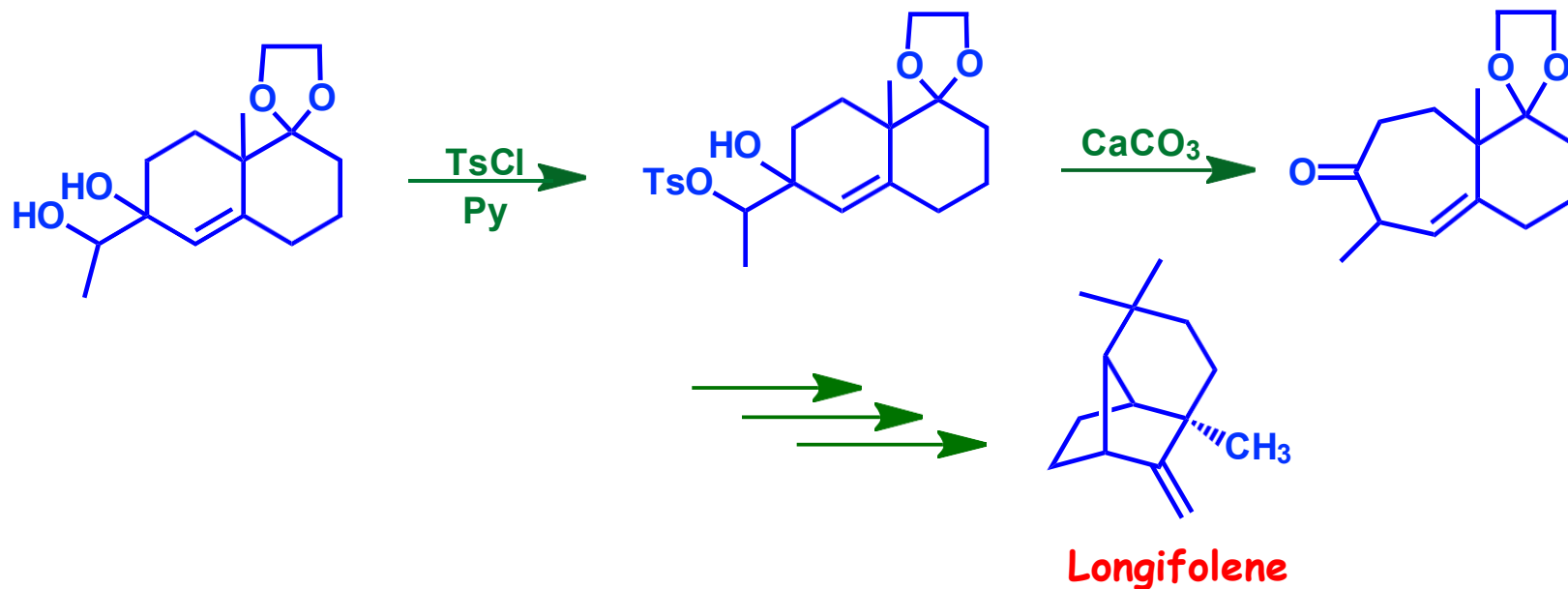


Corey exploited a similar sequence in the synthesis of longifolene



Pinacol-Pinacolone Rearrangement

Semipinacol Rearrangement

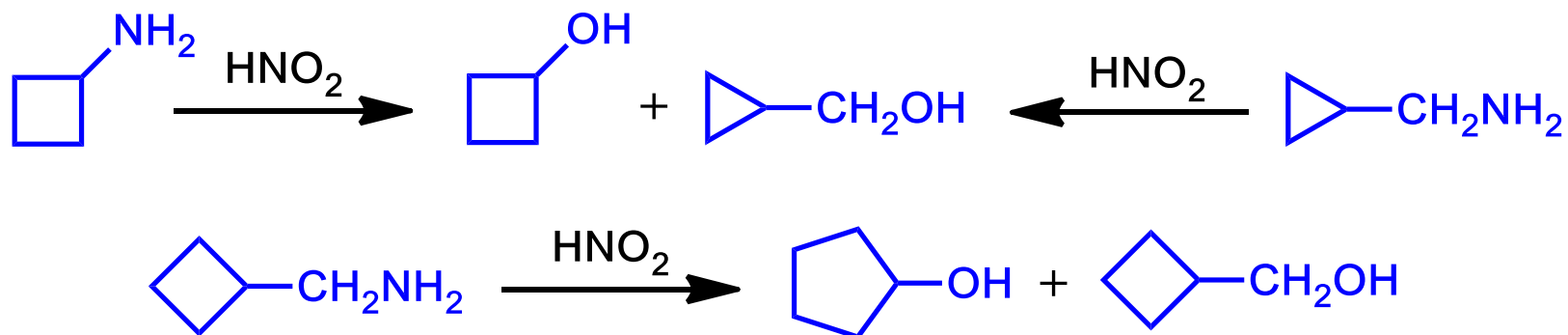


Leaving group need not be tosylated and it can be anything which can readily leave



Demjanov Rearrangement

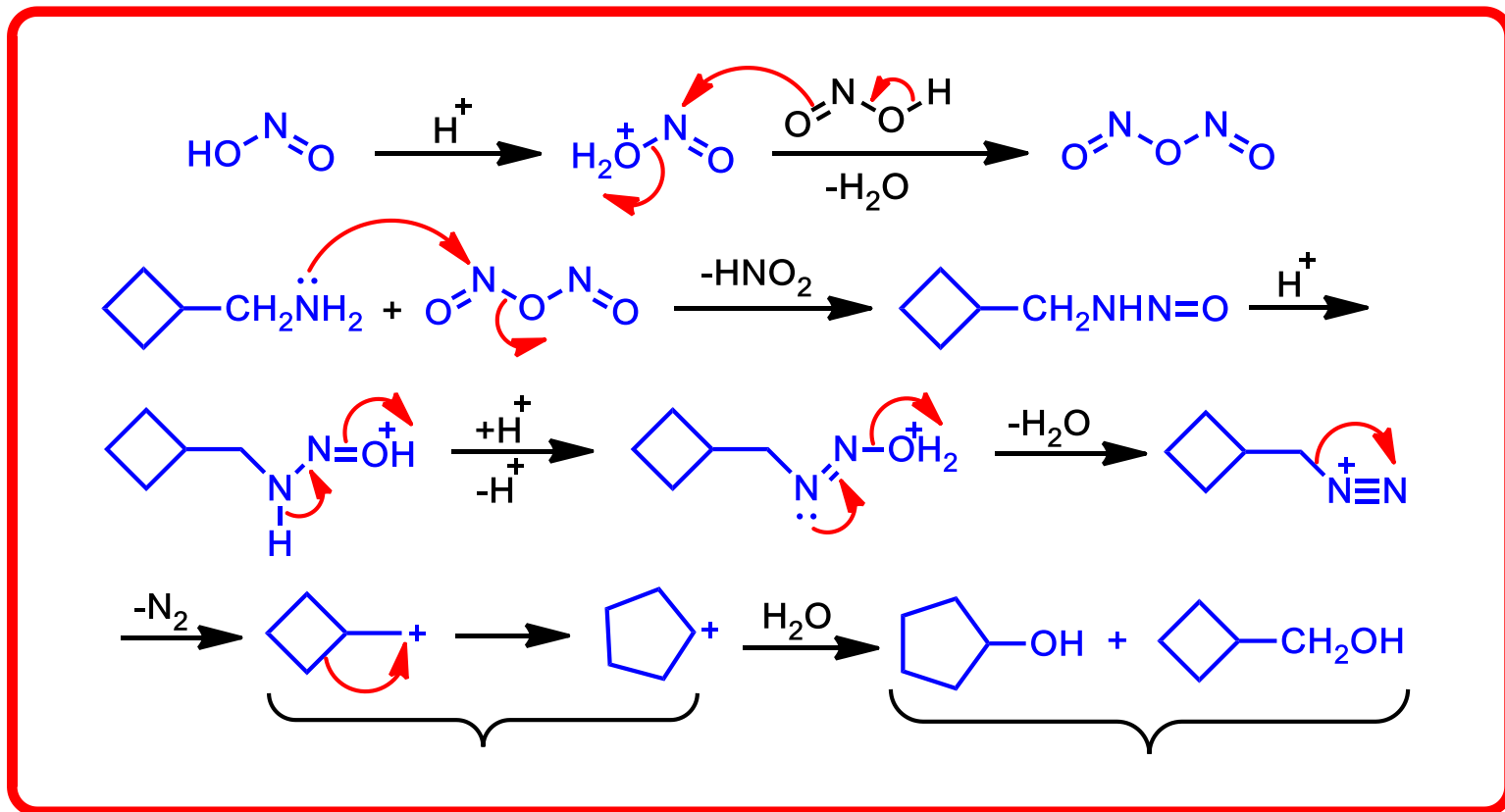
The following reaction represents a special case of Wagner-Meerwein rearrangement. Generally, a mixture of rearranged and non-rearranged products is formed.



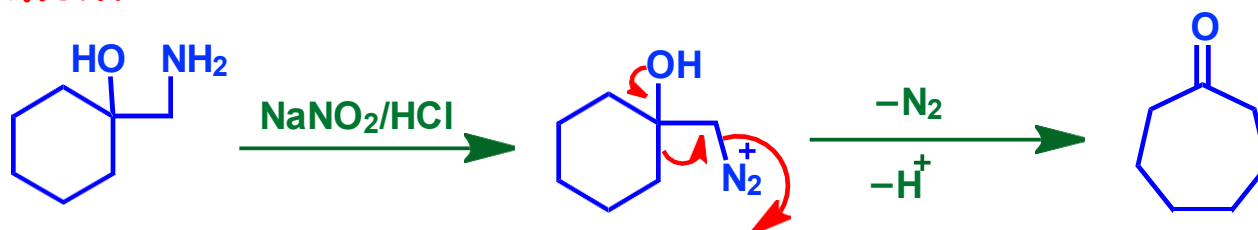
These reactions in which a carbocation is generated by diazotization is called **Demjanov rearrangement**.

Demjanov Rearrangement

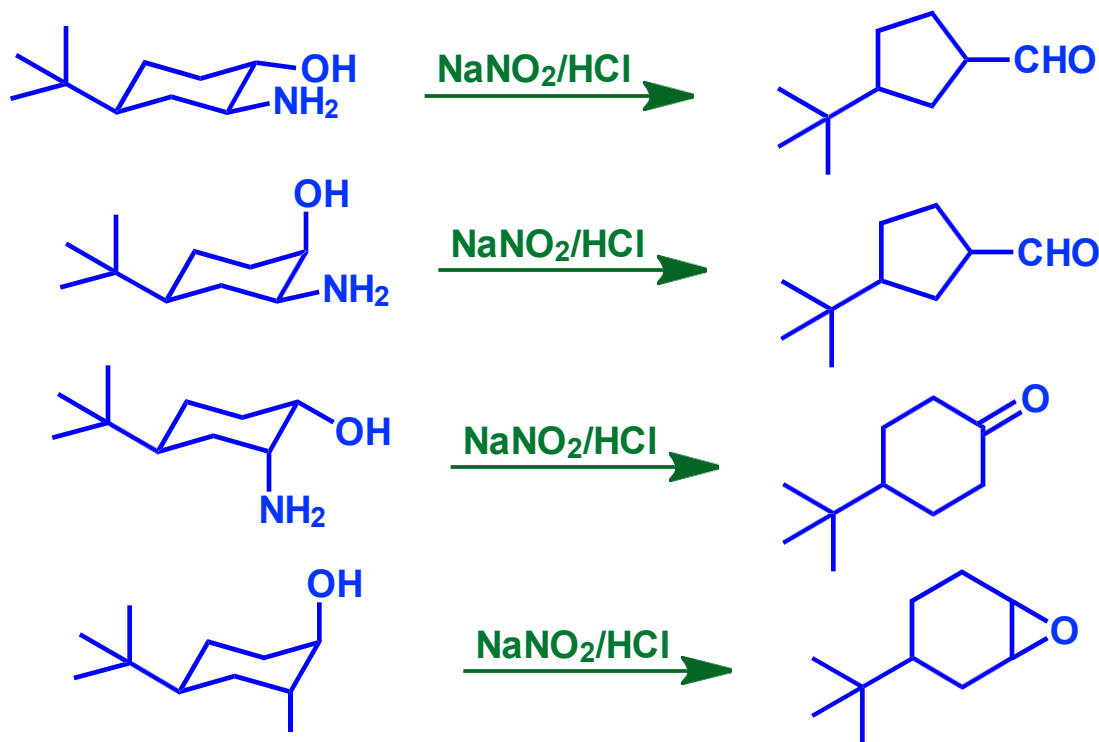
Mechanism:



Tiffeneau-Demjanov Rearrangement: Reaction of certain **amino alcohols** give analogous reaction to semipinacol rearrangement. The following is one such example known as **Tiffeneau-Demjanov rearrangement**



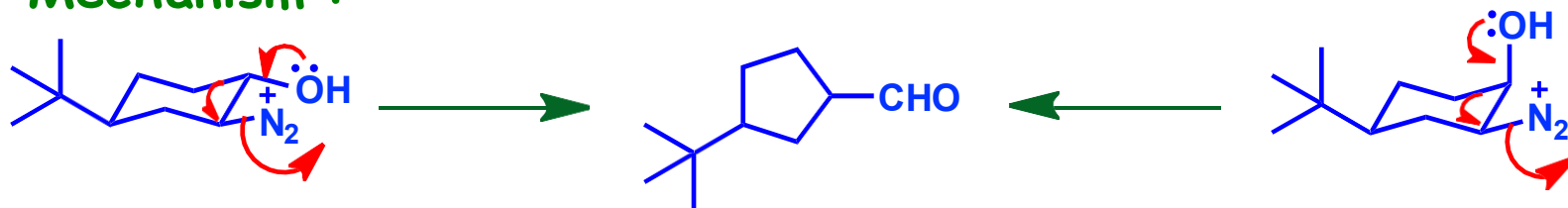
Selectivity :



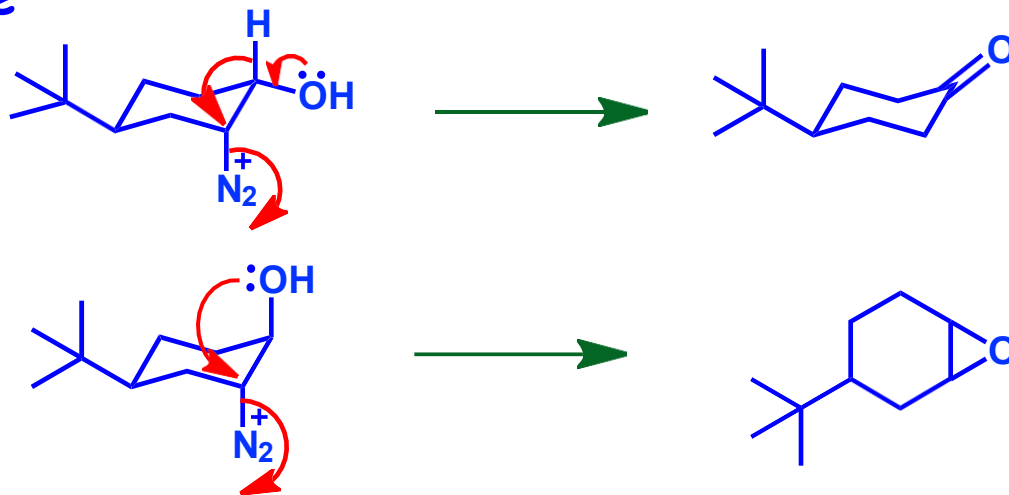
Tiffeneau-Demjanov Rearrangement

Diazonium salts

Mechanism :

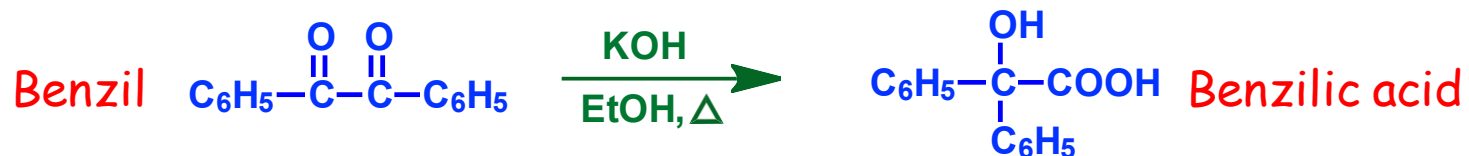


➤ Alkyl group which is anti to the leaving group, will migrate

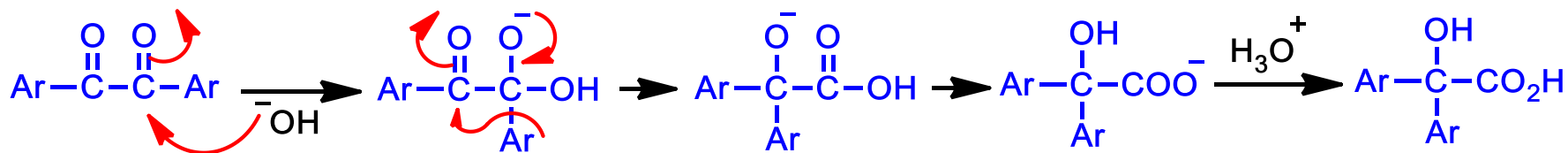


➤ These reactions are known to work better with four to eight membered ring systems as compared to the analogous Demjanov rearrangement.

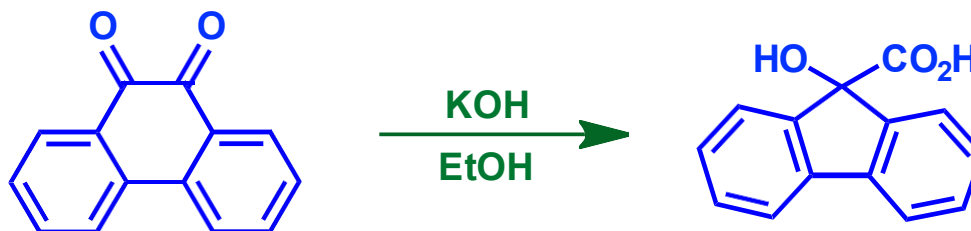
Benzil-Benzilic acid Rearrangement



Mechanism:



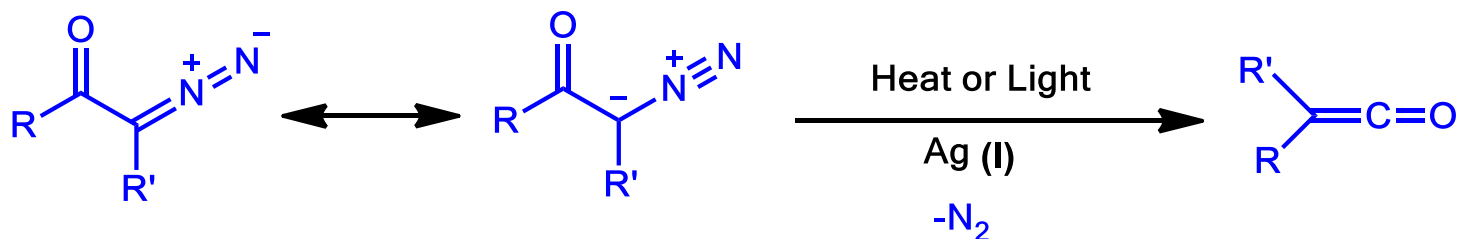
Formation of stable carboxylate salt is driving force for the reaction



Application has been limited only to aromatic α -diketones

Wolff Rearrangement

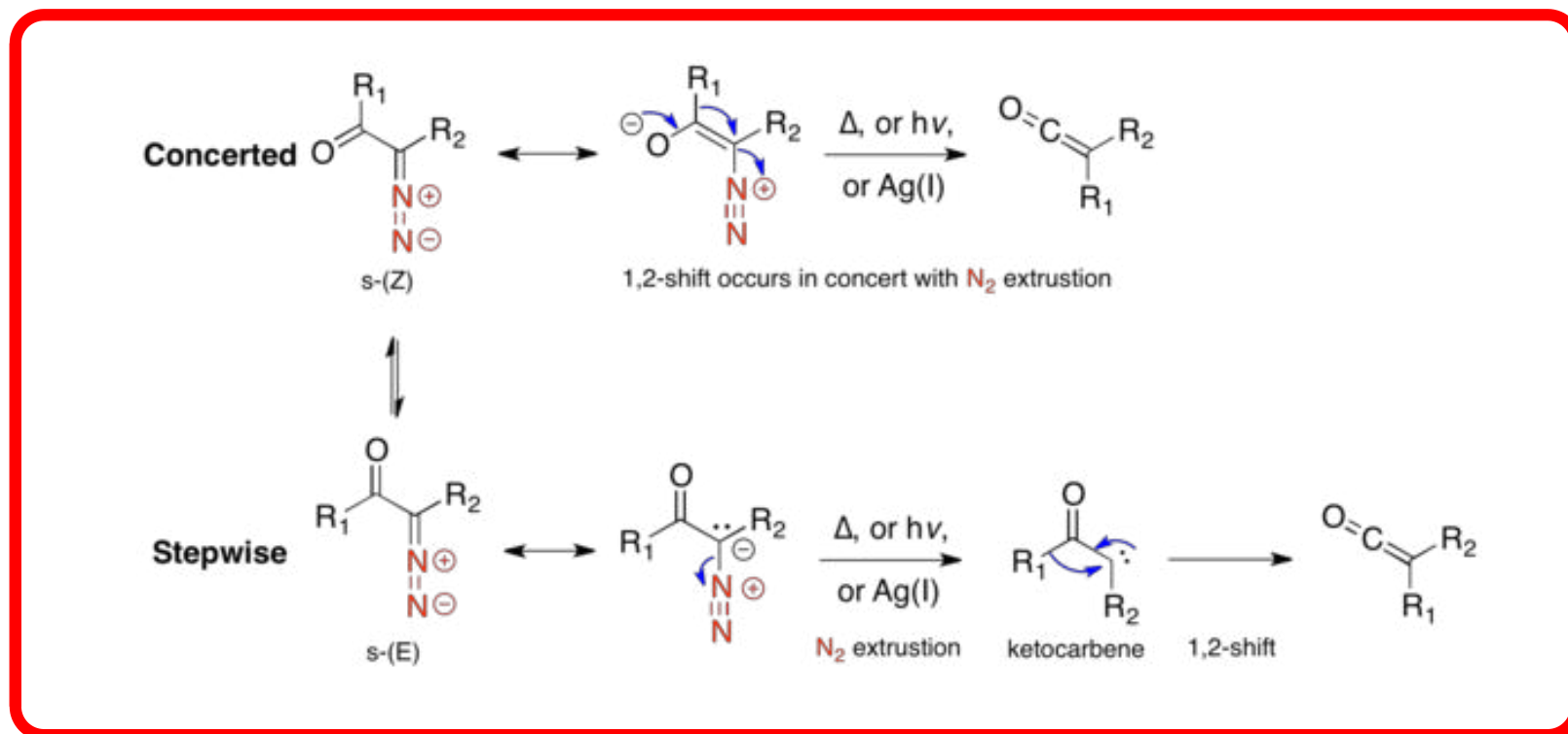
Wolff rearrangement is rearrangement reaction, in which a **diazo ketone** is converted into ketene.



- This reaction takes place in the presence of light, heat or transition metal catalyst such as Ag_2O .
- The mechanism is suggested to proceed through the involvement of a carbene in presence of heat or light. It may also proceed through a concerted pathway in the presence of Ag_2O with out carbene.

Wolff Rearrangement

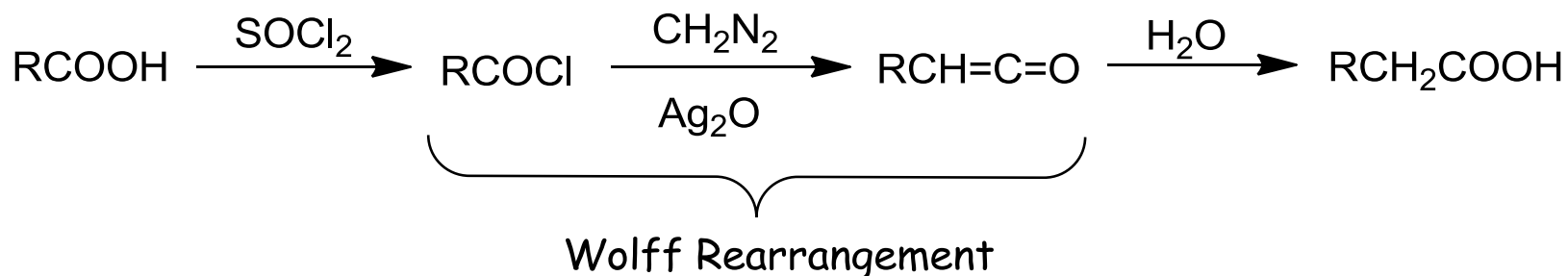
Mechanism :



➤ The reaction follows the course depending on whether the reaction is carried out under thermal or photochemical condition. In the photochemical pathway the reaction is supposed to proceed through carbene intermediate in stepwise mechanism, while in thermal pathway the reaction preferentially follows a concerted mechanism.

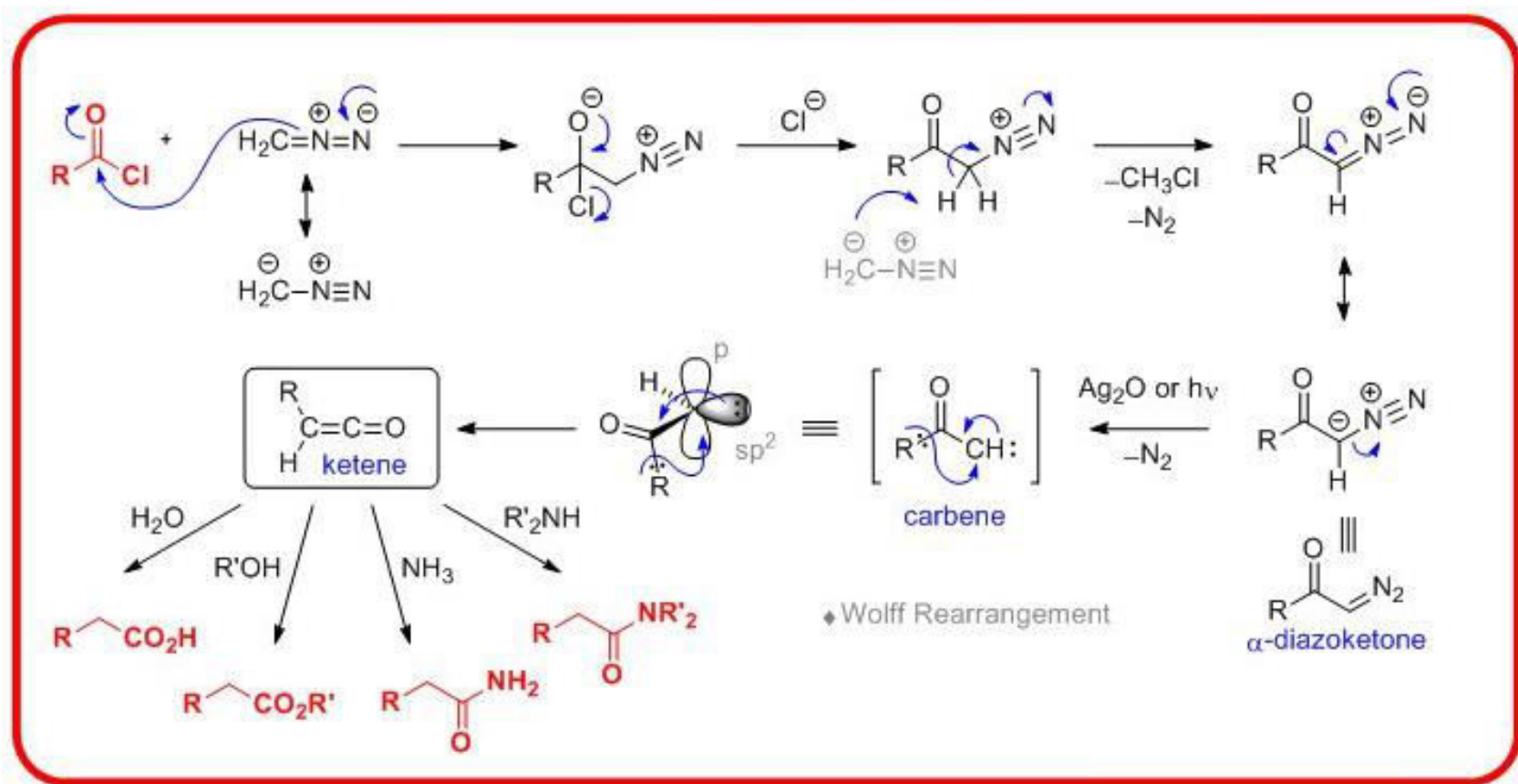
Wolff Rearrangement

➤ The reaction of acid chloride with diazomethane gives a diazoketone which is in the presence of silver oxide under heating proceeds through Wolff rearrangement to yield a ketene that is directly converted into an acid in the presence of water. This is known as **Arndt-Eistert Homologation Reaction**.

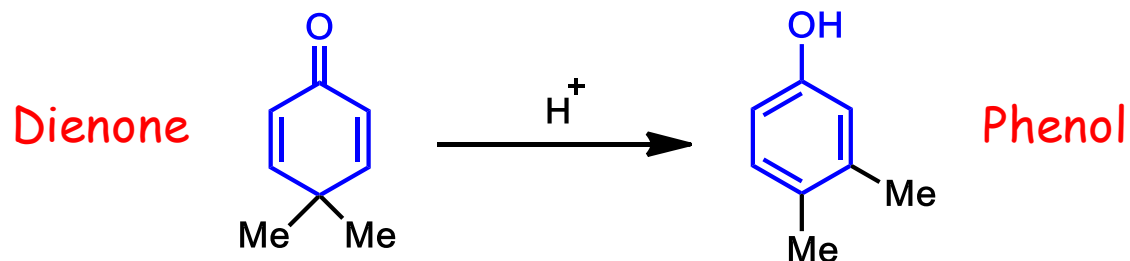


Arndt-Eistert Homologation Reaction

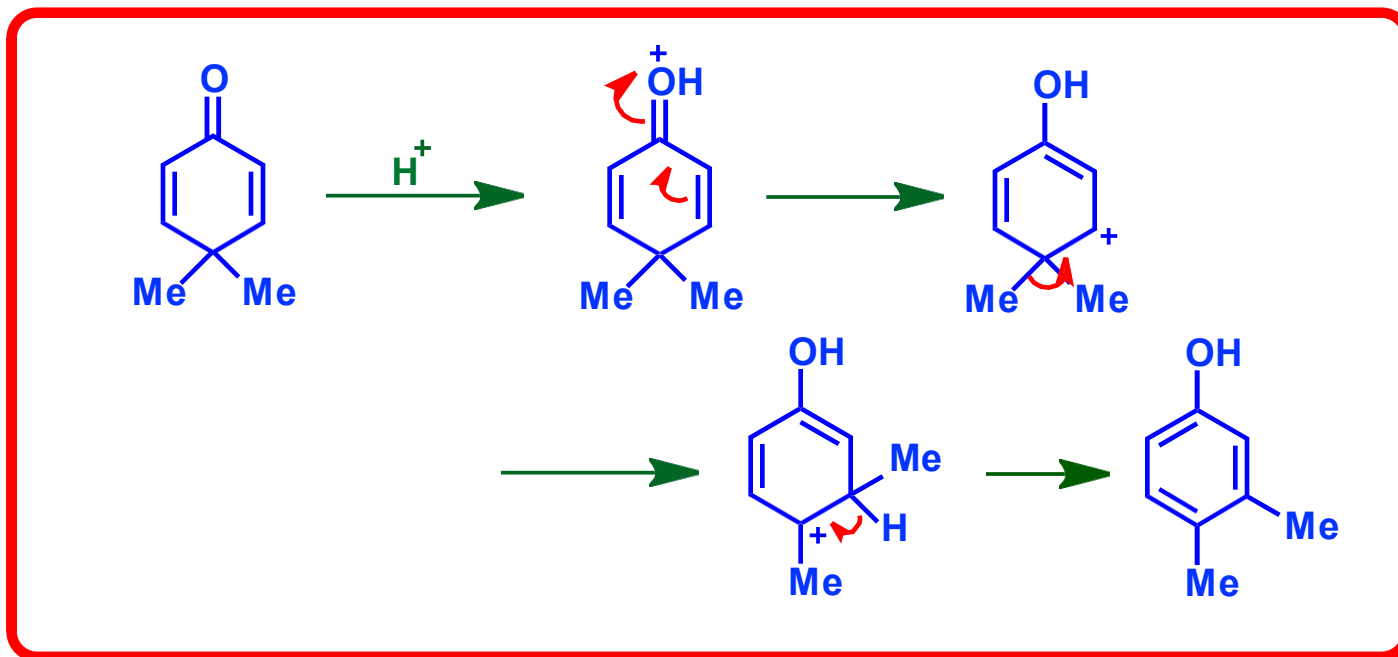
Mechanism :



Dienone-Phenol Rearrangement



Mechanism:



Dienone-Phenol Rearrangement

Example:



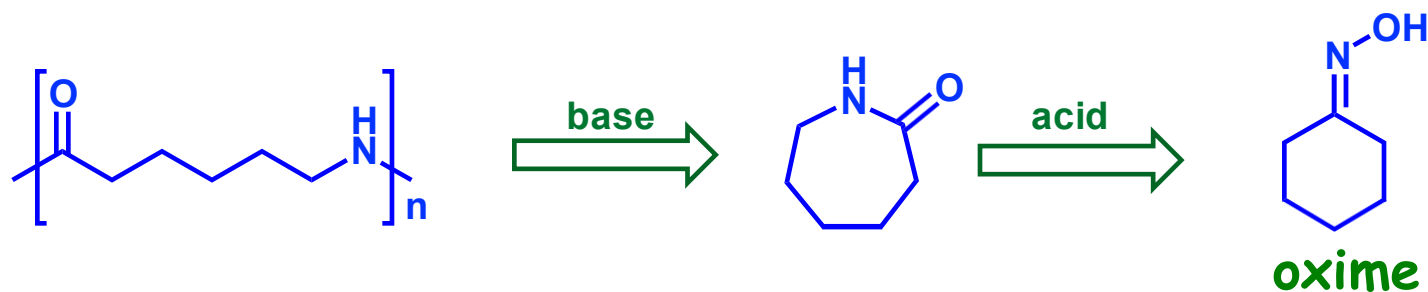
- Can be considered as a reversal of pinacol rearrangement
- Pinacol & semipinacol rearrangements are driven by the formation of a carbonyl group
- In dienone-phenol rearrangement protonation of carbonyl group Rearranges to a tertiary carbocation
- The driving force for this reaction is the formation of aromatic rings

Rearrangements to Electron Deficient Nitrogen

- ✚ Beckmann Rearrangement
- ✚ Hofmann Rearrangement
- ✚ Curtius rearrangement
- ✚ Lossen Rearrangement
- ✚ Schmidt Rearrangement

Beckmann Rearrangement

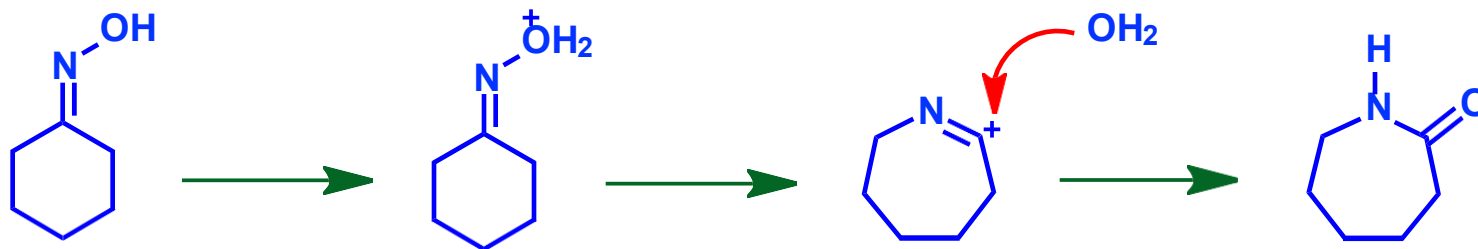
The industrial formation of nylon relies upon the alkaline polymerization of a acyclic amide known as caprolactam



Caprolactam can be produced by the action of sulfuric acid on the oxime of cyclohexanone in a rearrangement known as the Beckmann rearrangement

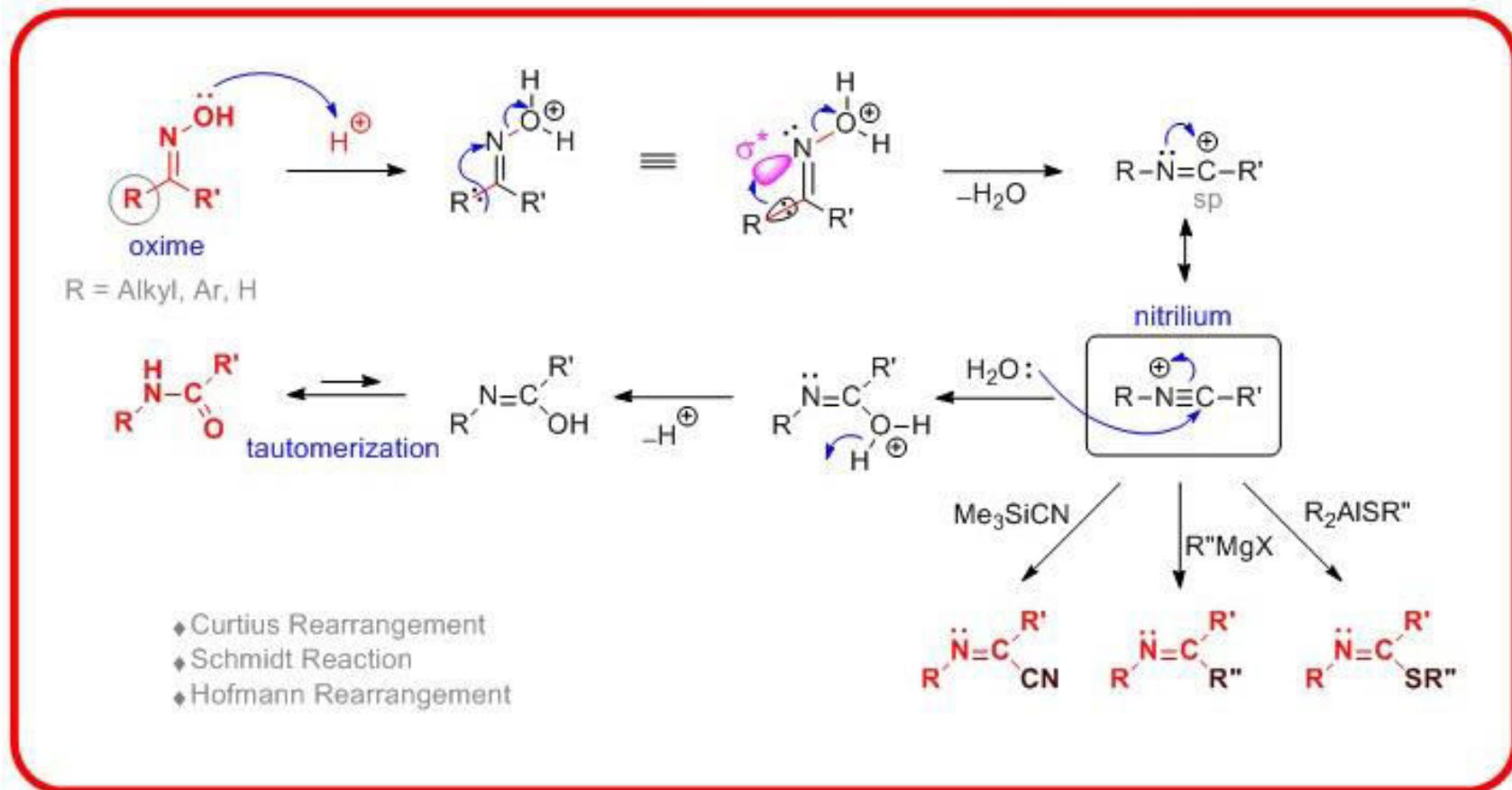
Beckmann Rearrangement

Mechanism:



- Follows the same pattern as pinacol
- Converts the oxime into a good leaving group
- Alkyl/ Aryl group migrates on to nitrogen as water departs
- The product cation is then trapped by water to give an amide

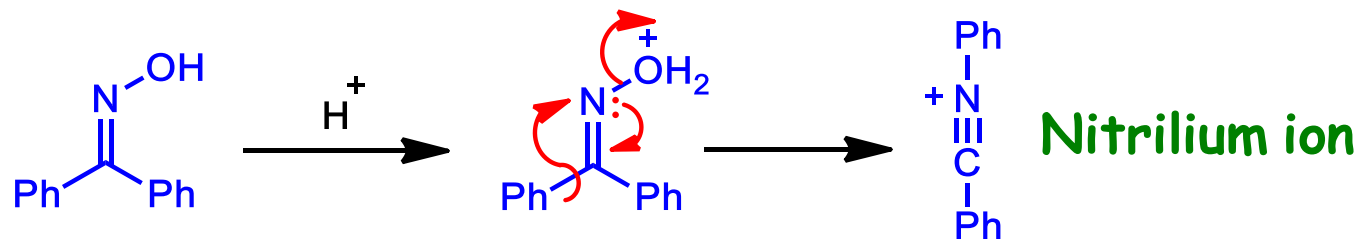
Beckmann Rearrangement



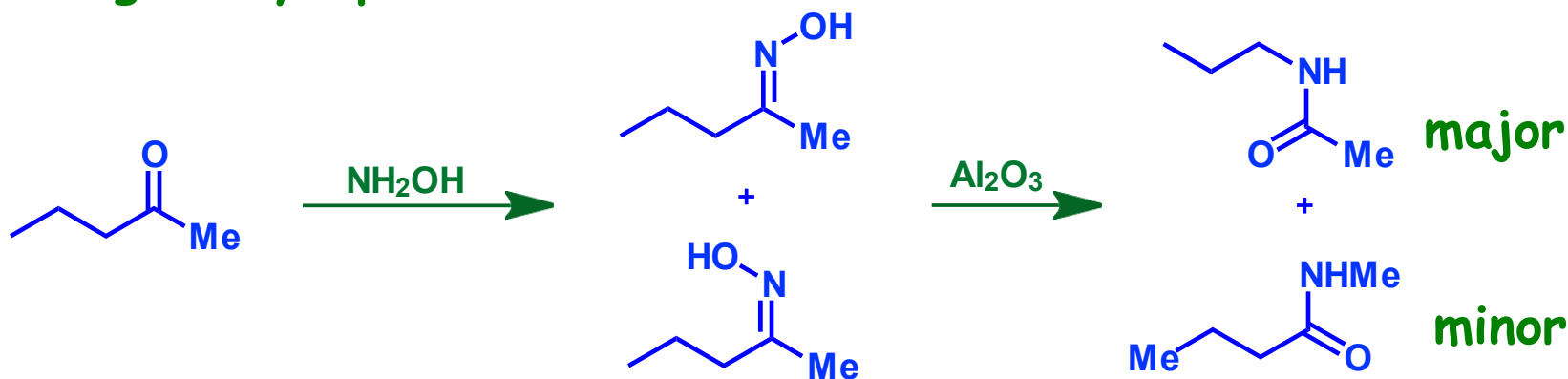
➤ The proposed mechanism is supported by detection of nitrillium ion by NMR and UV spectroscopy.

Beckmann Rearrangement

- It can also work with acyclic oximes
- PCl_5 , SOCl_2 & other acyl or sulfonyl chlorides can be used instead of acid



Migratory Aptitude:

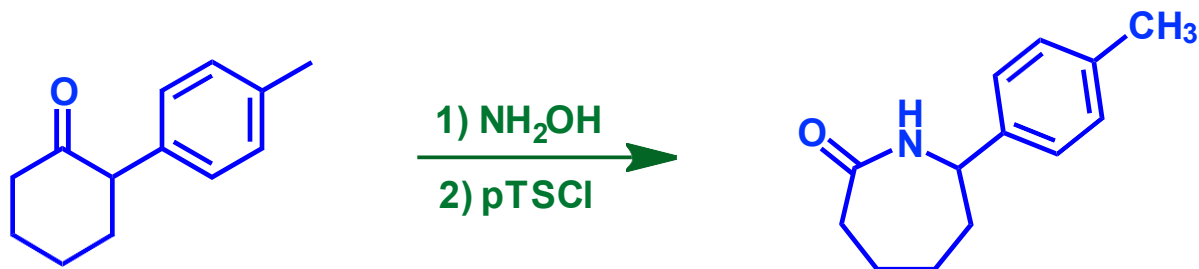
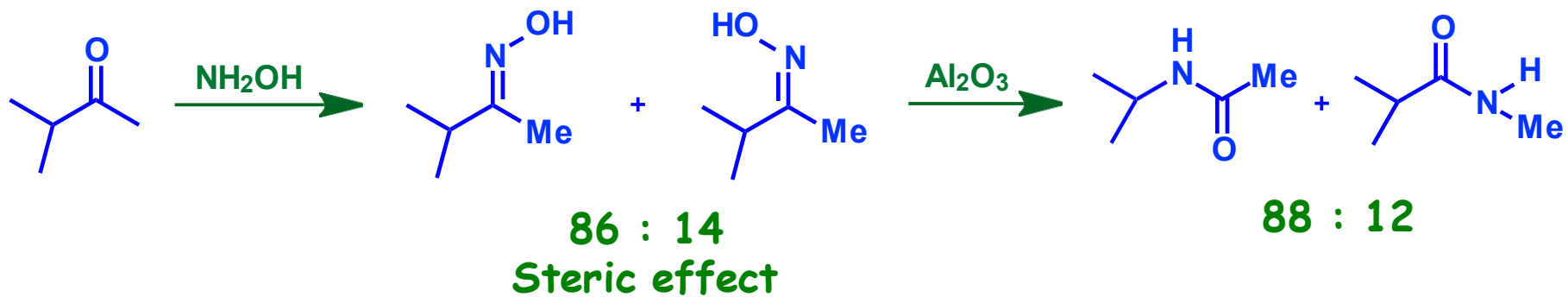


Beckmann Rearrangement

In case of unsymmetrical ketone:

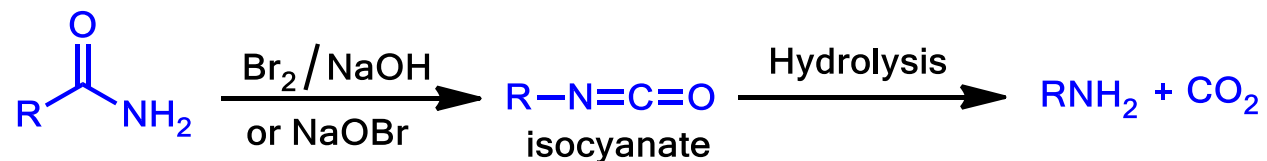
- There are two groups that could migrate
- There are two possible geometrical isomers of unsymmetrical oxime
- When the mixtures of geometrical isomer of oximes are rearranged, mixtures of products result
- Interestingly, the ratio of products mirrors exactly the ratio of geometrical isomers in the starting materials
- The group that has migrated, is trans to the -OH group

Beckmann Rearrangement



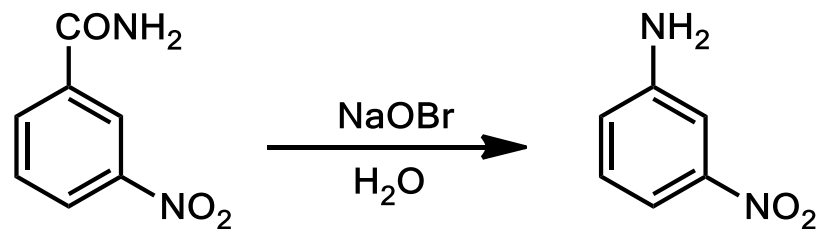
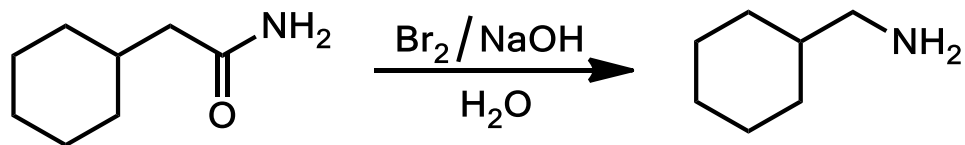
Hofmann Rearrangement

When an unsubstituted amide is treated with sodium hypobromite, corresponding primary amine with one carbon less is produced. This reaction involves **Hofmann rearrangement**.



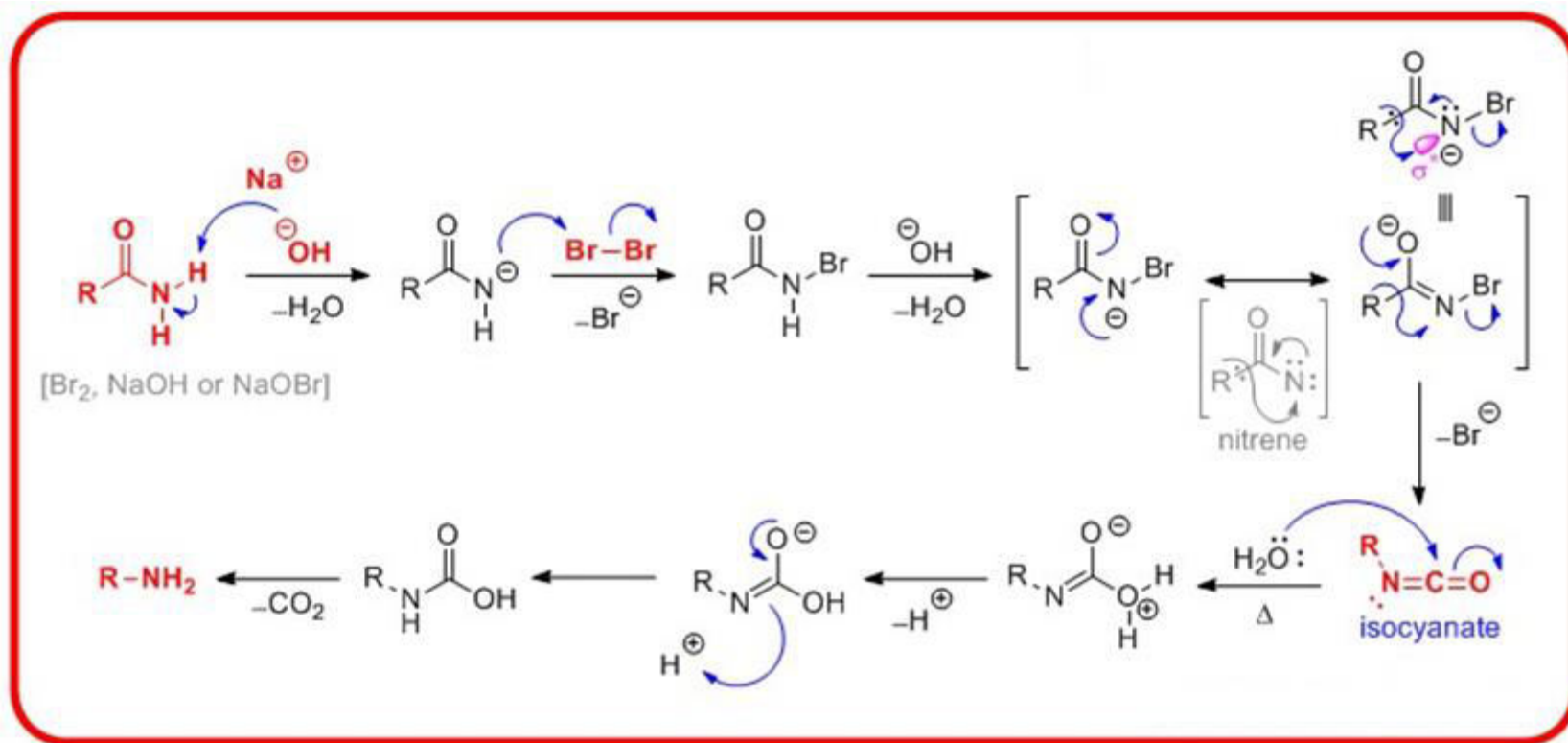
➤ R in this reaction can be alkyl or aryl.

Examples



Hofmann Rearrangement

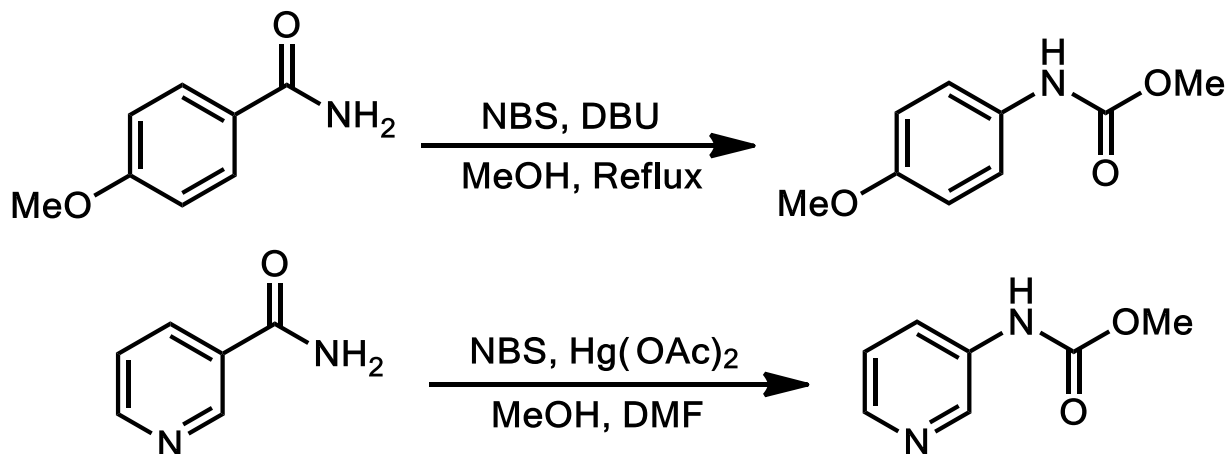
Mechanism:



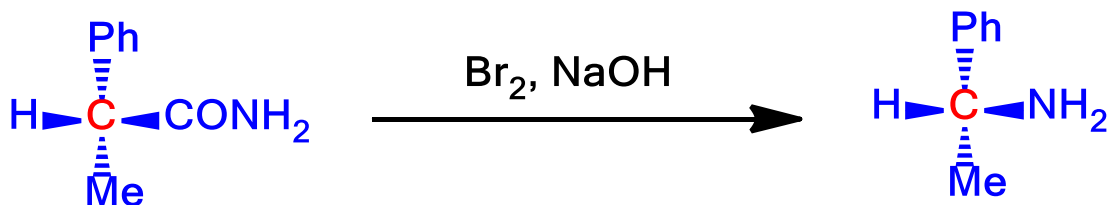
➤ In the first step, base removes a proton from amide. The conjugate base of amide, thus formed, reacts with bromine to give N-bromoamide. Acidity of proton on nitrogen is increased by this bromine atom and its removal followed by 1,2-shift of alkyl group gives corresponding isocyanate. This isocyanate on hydrolysis gives primary amine with one carbon less than starting material.

Hofmann Rearrangement

➤ When methanol is used as a solvent instead of water, then the corresponding carbamate ester can be obtained.



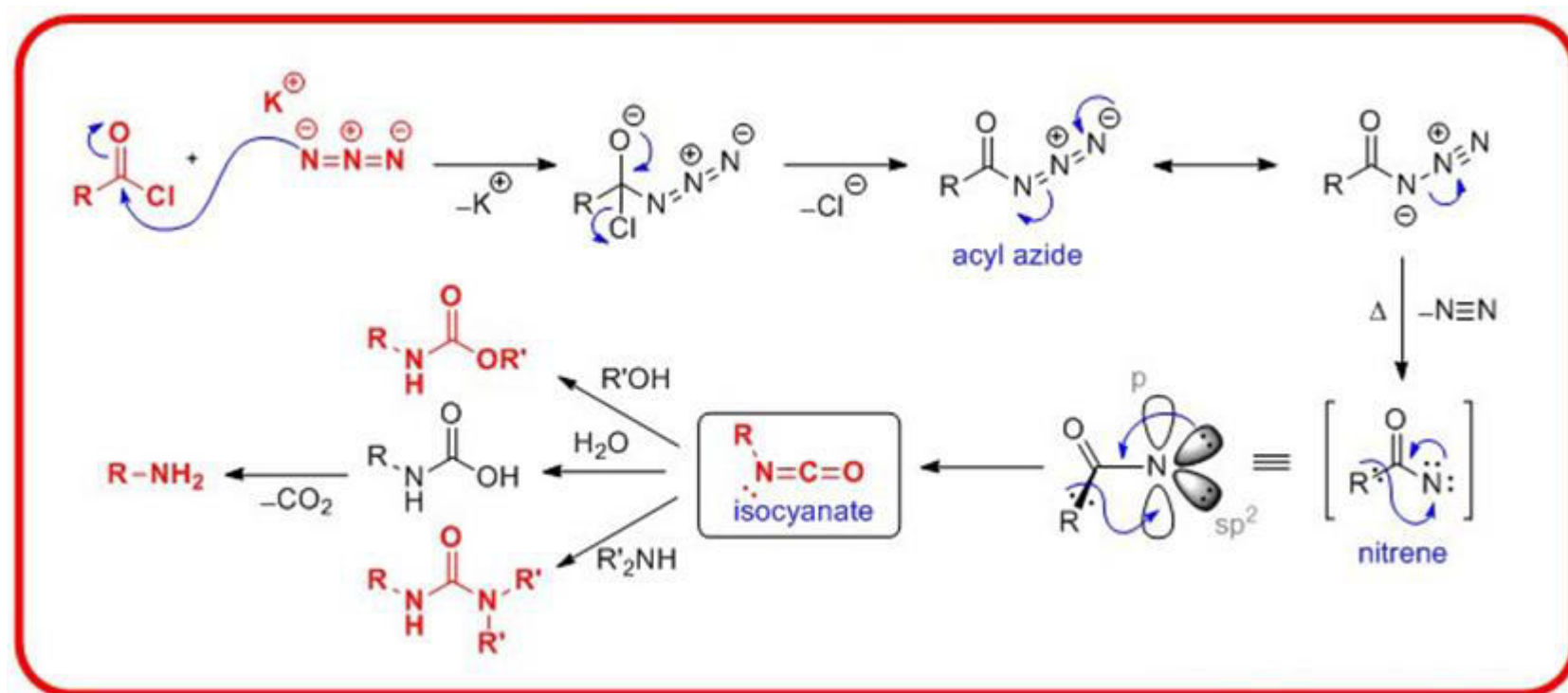
➤ When optically active α -phenylpropionamide undergoes Hofmann degradation, α -phenylethylamine of same configuration and optical purity: **retention of configuration.**



Curtius rearrangement

➤ This rearrangement describes the transformation of **acyl azide** into **isocyanate** by decomposition on heating and its application for the synthesis of primary amines, urethanes and ureas as presented in Hofmann rearrangement.

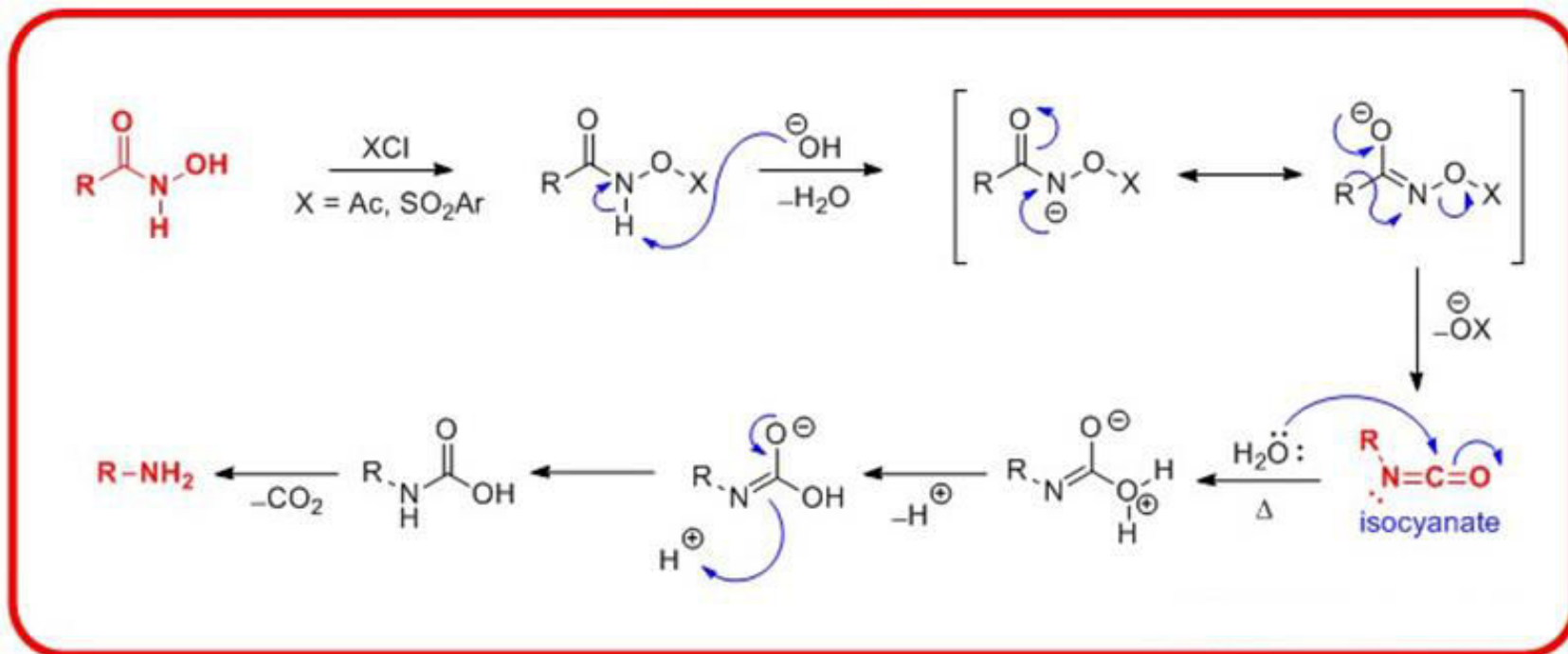
Mechanism:



Lossen Rearrangement

➤ **O-acyl derivatives of hydroxamic acids** on heating with a base converts to the corresponding isocyanate. This reaction is known as Lossen rearrangement. The isocyanate thus produced can be further converted to corresponding primary amines, urethanes and ureas as presented in Hofmann rearrangement.

Mechanism:

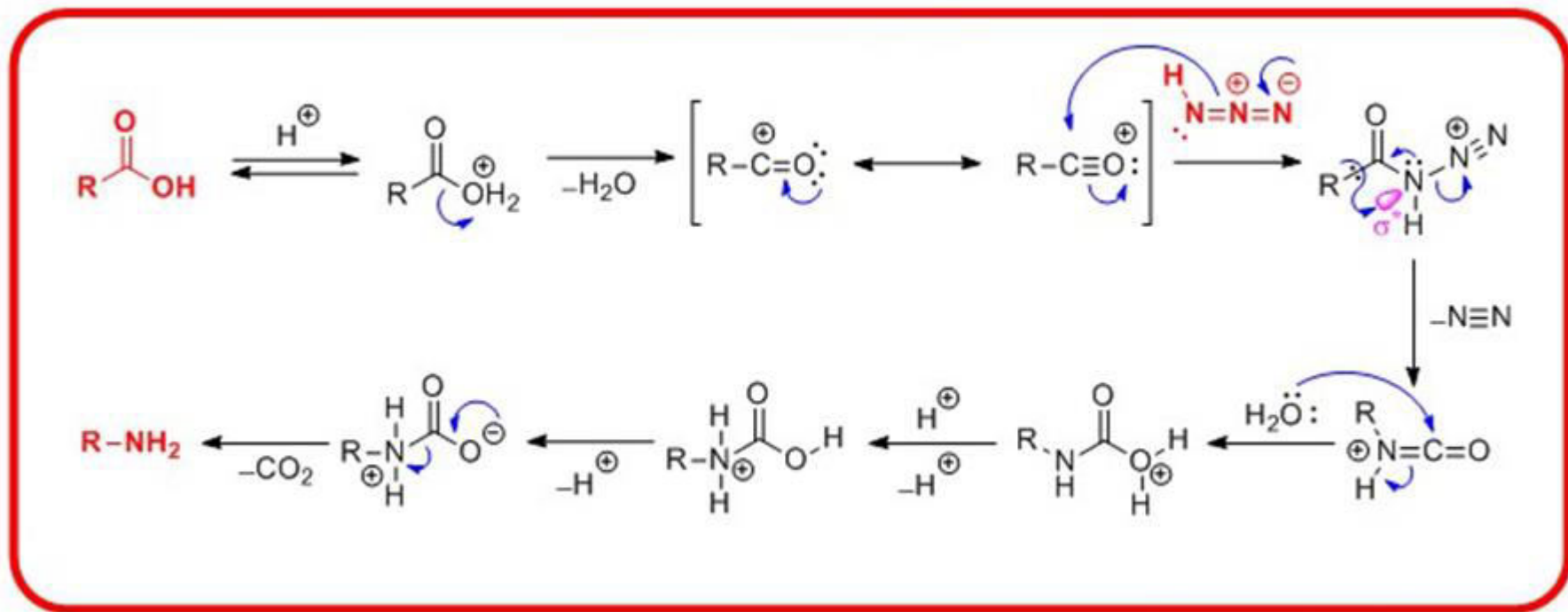


Schmidt Rearrangement

➤ Reaction of carboxylic acid or aldehyde or ketone with **hydrazoic acid** in the presence of strong mineral acid or Lewis acid to provide **isocyanate** (for carboxylic acid) or **nitrilium ion** (for aldehyde or ketone) that further hydrolysed to give corresponding primary amine or amide is known as Schmidt rearrangement.

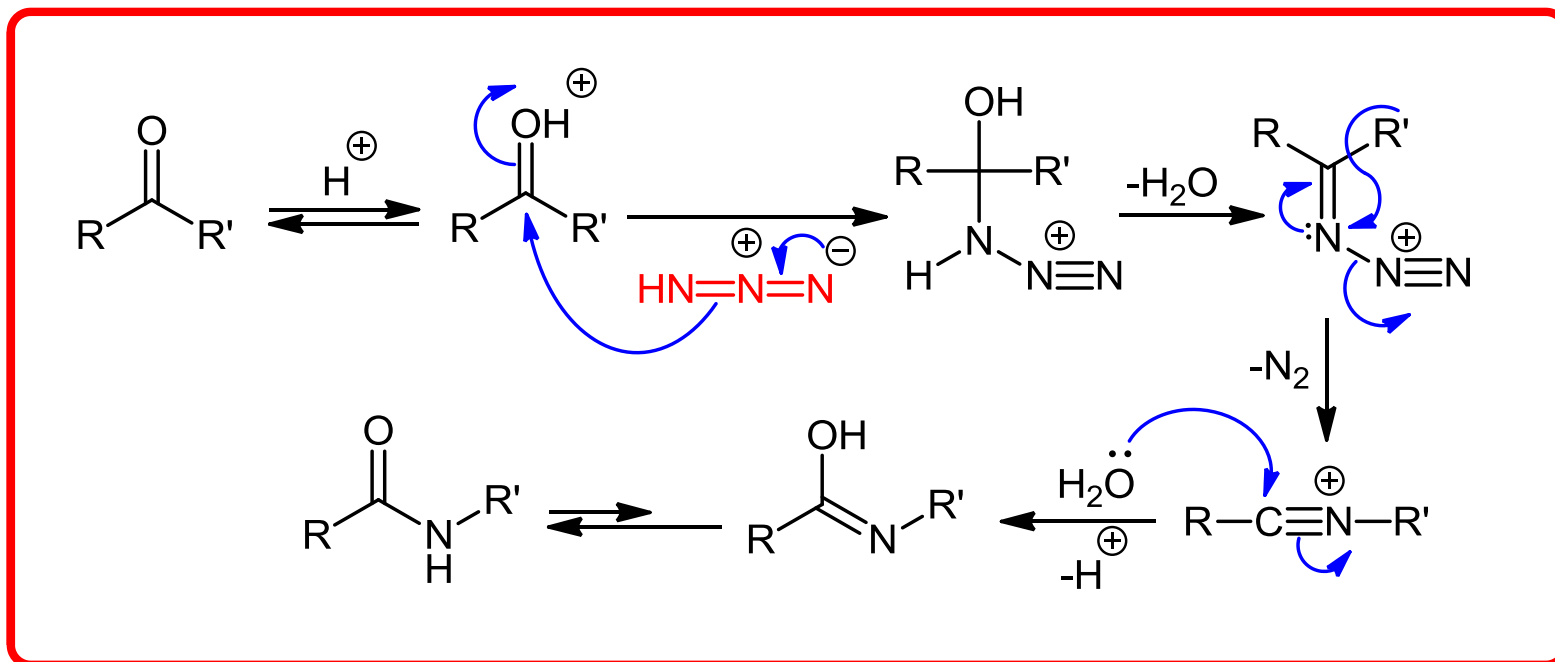
Mechanism:

Rearrangement for acid:



Schmidt Rearrangement

Rearrangement for aldehyde and ketone:

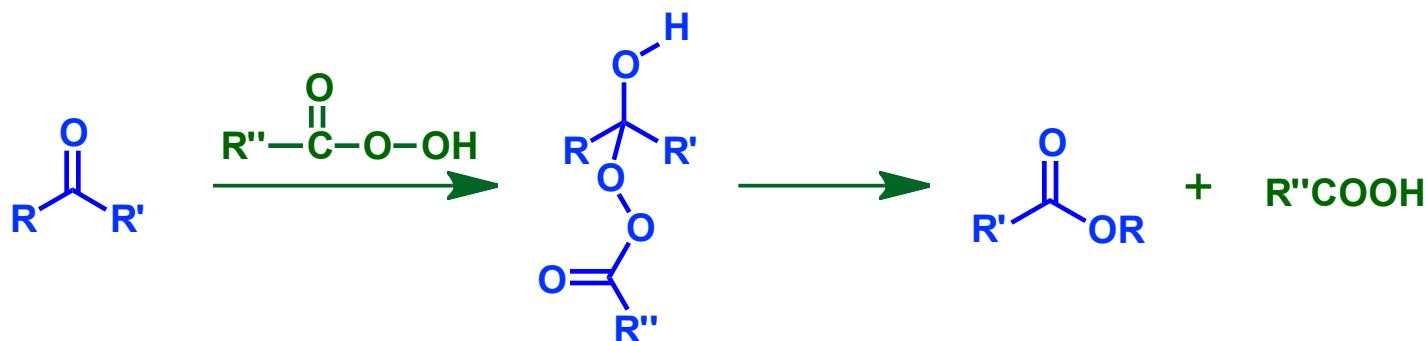


Rearrangements to Electron Deficient Oxygen

- ✚ Baeyer Villiger Oxidation
- ✚ Dakin Reaction

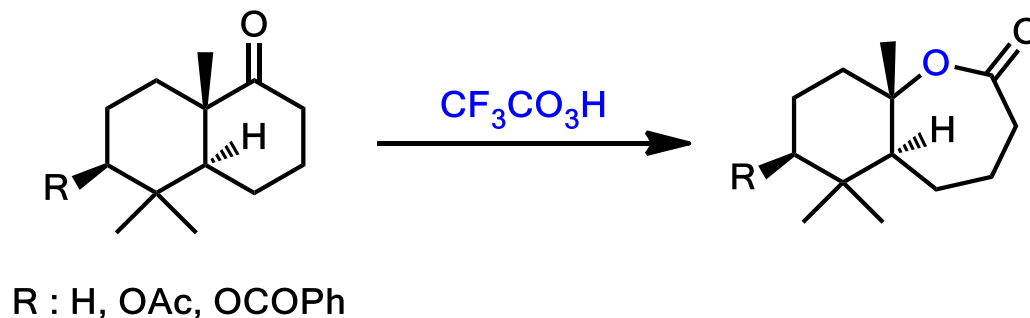
Baeyer Villiger Oxidation

Treatment of ketones with **peroxyacid** gives **ester** by oxy-insertion. Nucleophilic attack by the peroxyacid on the carbonyl group gives an intermediate that rearranges to corresponding ester with the expulsion of the **anion of the acid**. This is known as **Baeyer Villiger Oxidation**.



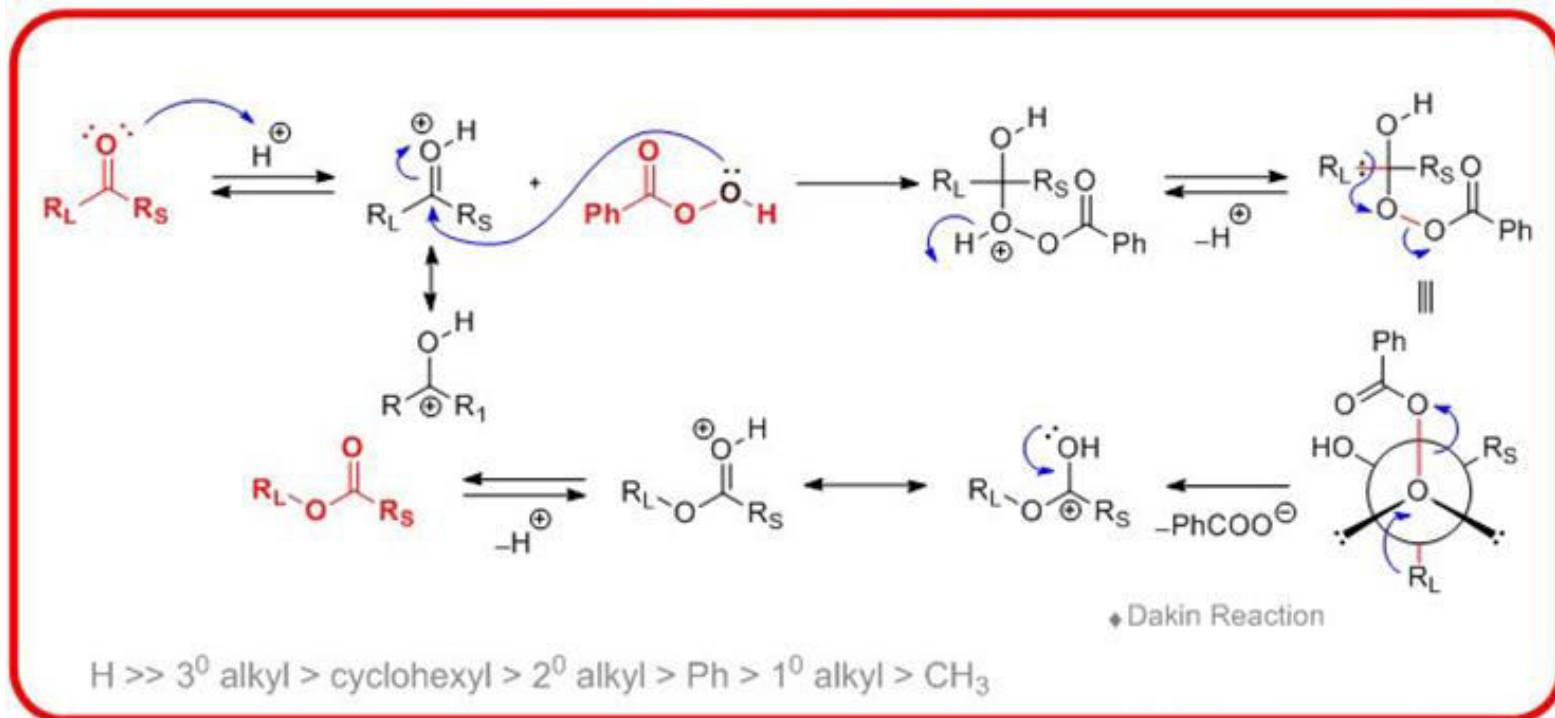
➤ Migratory Aptitude: $t\text{-Bu} > i\text{-Pr} = \text{Ph} > \text{Et} > \text{Me}$

➤ Reaction is particularly useful for synthesis of lactones.



Baeyer Villiger Oxidation

Mechanism:



- The mechanism is supported by fact that oxidation of Ph₂C¹⁸O yields only PhC¹⁸OOPh (i.e. there is no scrambling of ¹⁸O label in the product Ester.)
- The **loss of carboxylates and migration of R is concerted**, as the reaction is known to be faster when electron withdrawing substituents are present in the leaving group and electron donating substituents in migrating group.

Baeyer Villiger Oxidation

B.V.O. of Unsaturated Ketones:

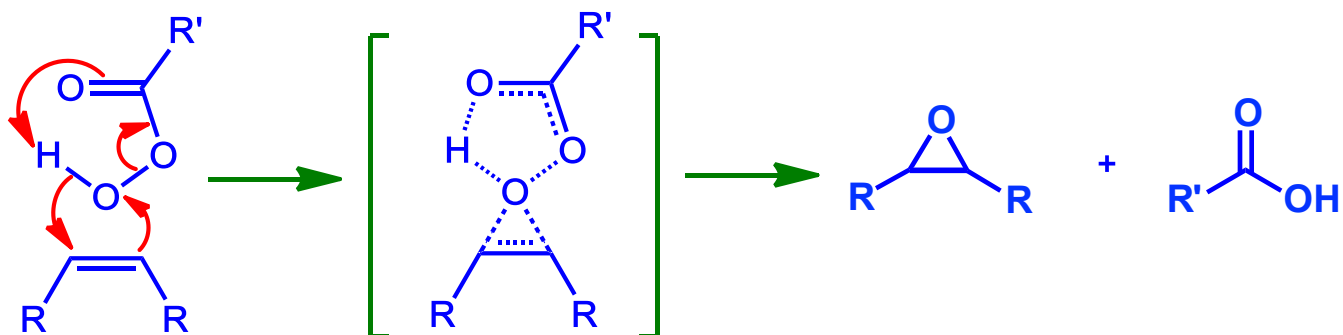
There are three possibilities

- 1) Peracids can selectively epoxidize
- 2) Peracids can selectively carry out B.V.O
- 3) Can carry out both reactions

It is difficult to predict the outcome & it depends on-

- 1) Electrophilic nature of the ketone
- 2) Nucleophilic nature of the alkene

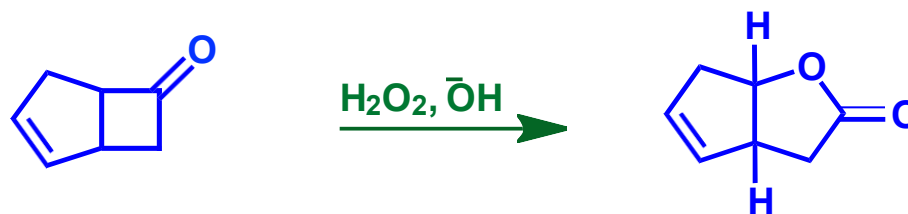
Baeyer Villiger Oxidation



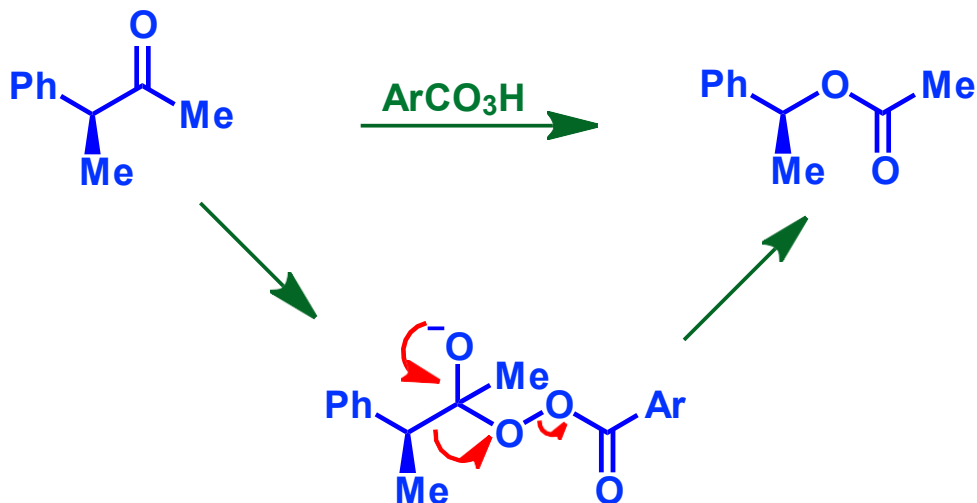
- Tertiary group migrates in preference of the secondary group
- The alkene is not as reactive as expected because of steric crowding

Baeyer Villiger Oxidation

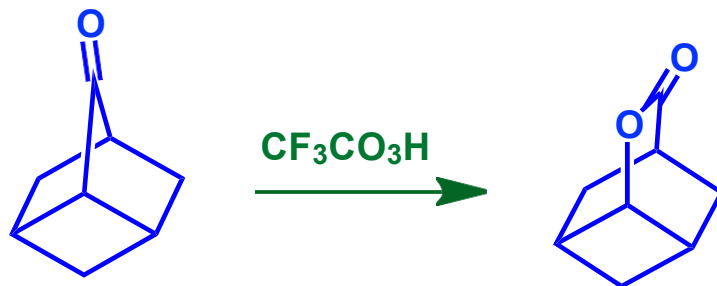
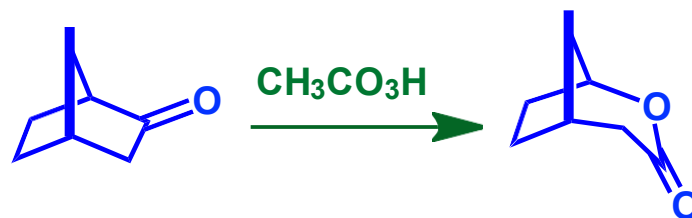
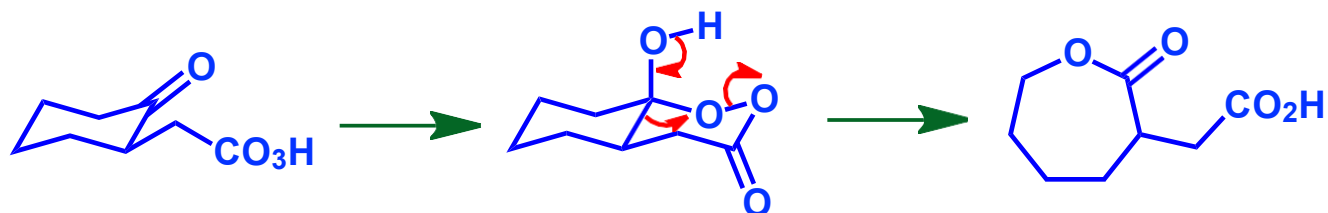
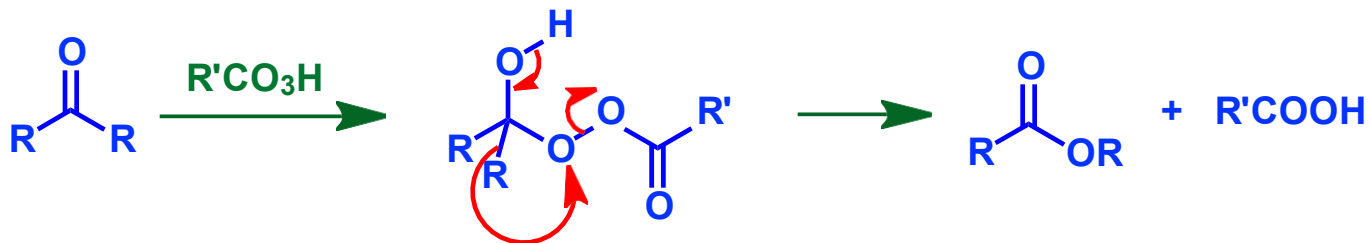
➤ Small ring ketones will readily undergo B.V.O.



➤ Starting material configuration is retained in the product

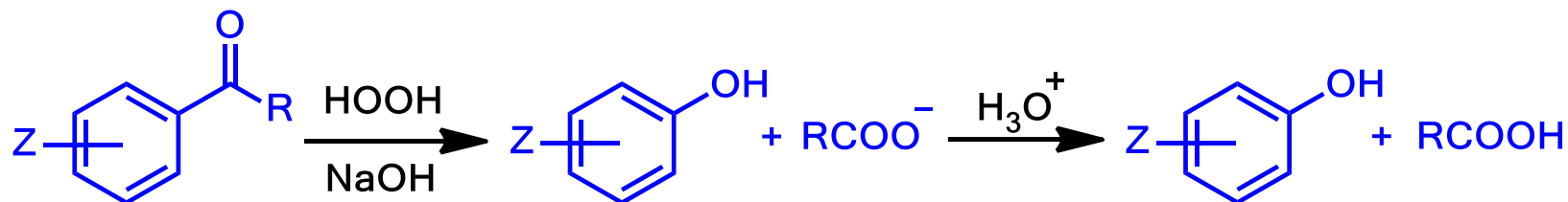


Baeyer-Villiger oxidation



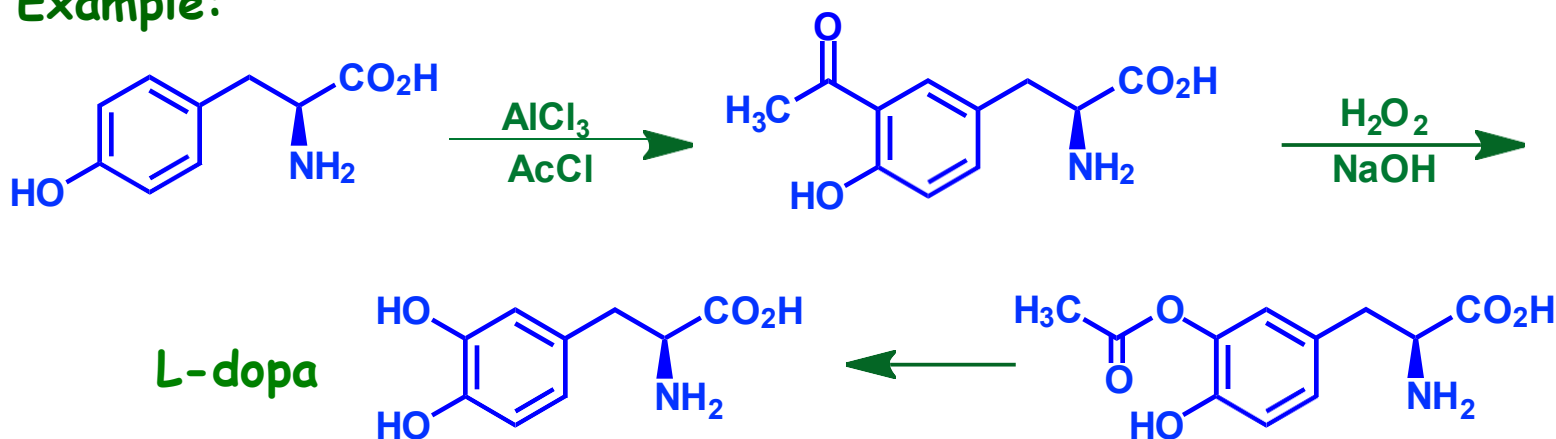
Dakin Reaction

Benzaldehyde or acetophenone bearing **hydroxyl substituent in the *ortho* or *para* position** proceed rearrangement to give **catechol** or **quinol**, respectively known as Dakin Reaction. The reaction is performed in the presence of alkaline hydrogen peroxide and the mechanism is similar to that of Baeyer-Villiger reaction.



Z : **ortho/para-hydroxyl**

Example:



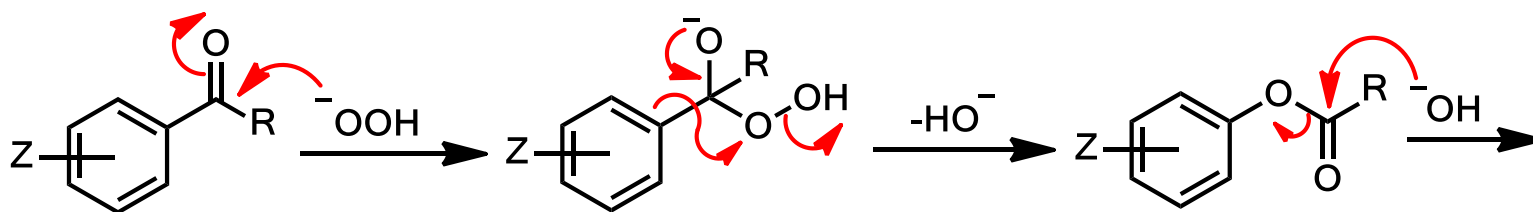
Dakin Reaction

Mechanism:

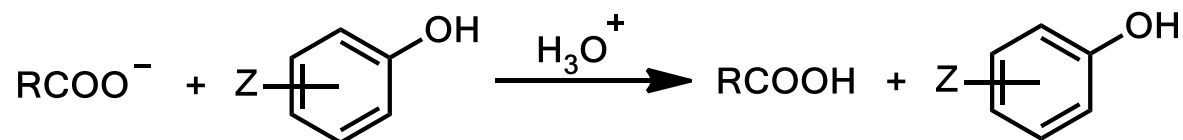


Base source : NaOH

Base : HO^-



Z : ortho/para-hydroxyl



Sigmatropic Rearrangements

- ✚ Cope Rearrangement
- ✚ Claisen Rearrangement
- ✚ Benzidine-Semidine Rearrangement

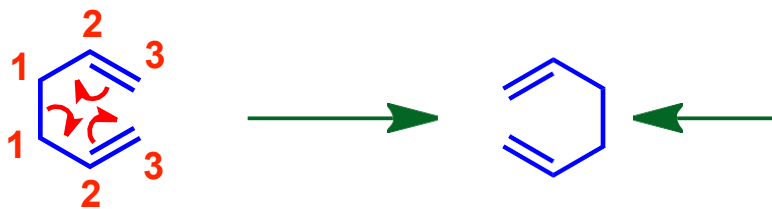
Sigmatropic Rearrangements

[3,3]-Sigmatropic Shift

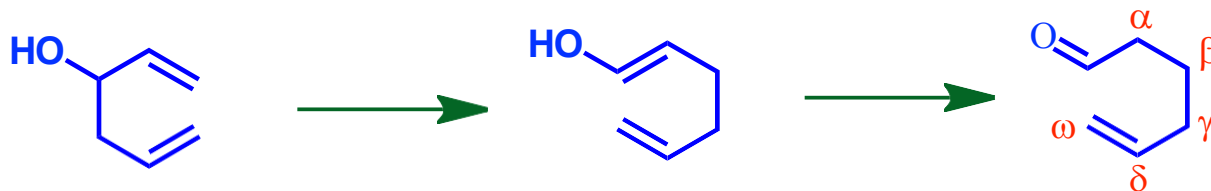
Cope Rearrangement

It is a [3,3]- sigmatropic rearrangement with only carbon atoms involved in a six membered transition state

Why is it called [3,3] ?



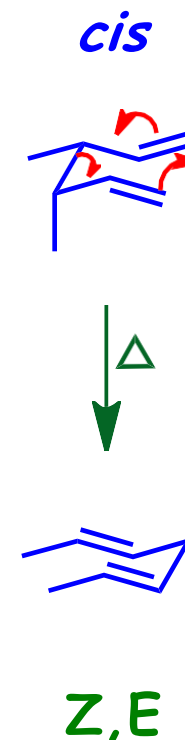
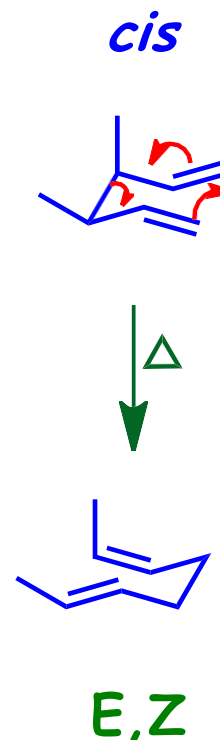
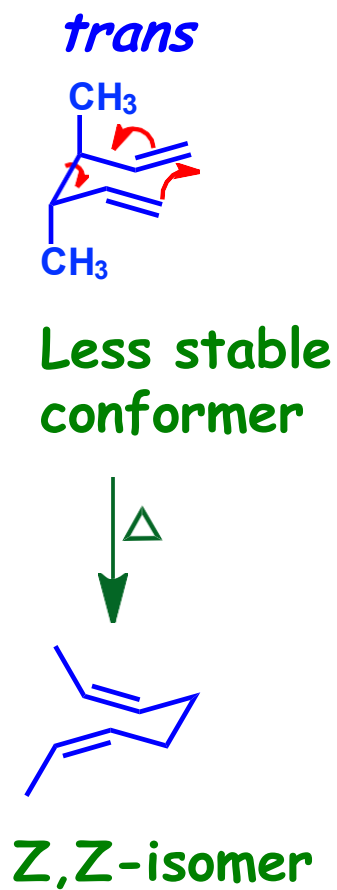
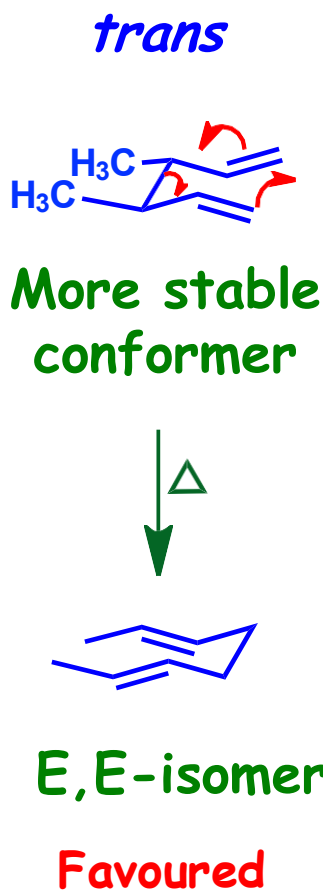
The new σ bond formed has 3,3- relationship with the old σ -bond



Cope Rearrangement

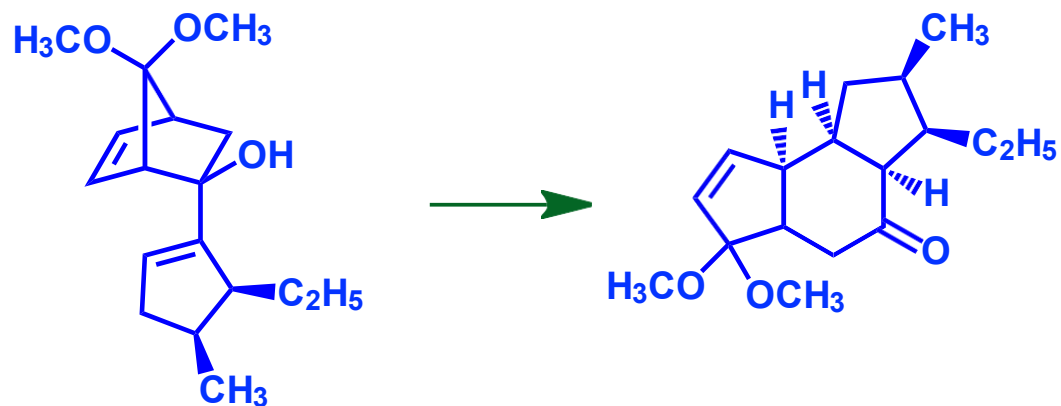
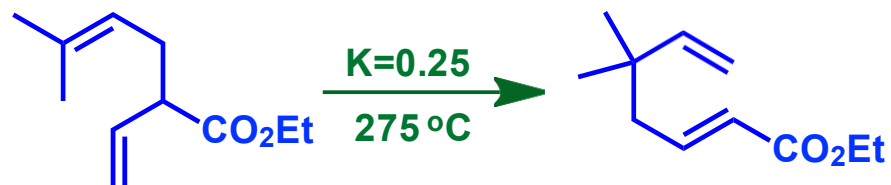
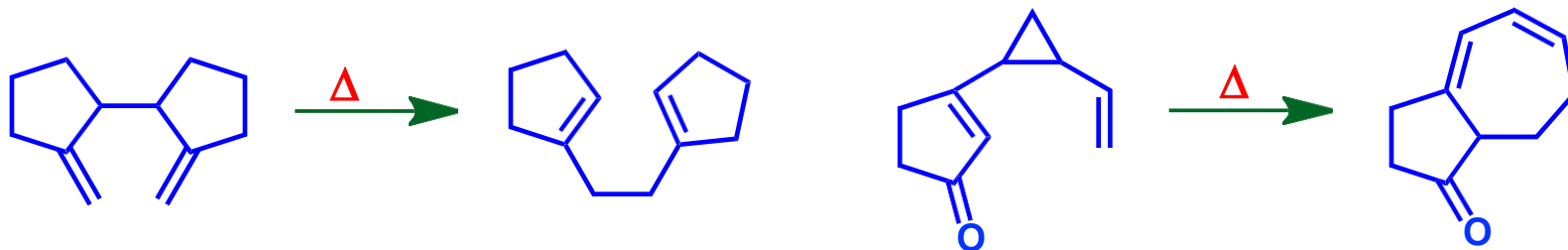
Mechanism :

It goes via six-membered chair-like transition state



Cope Rearrangement

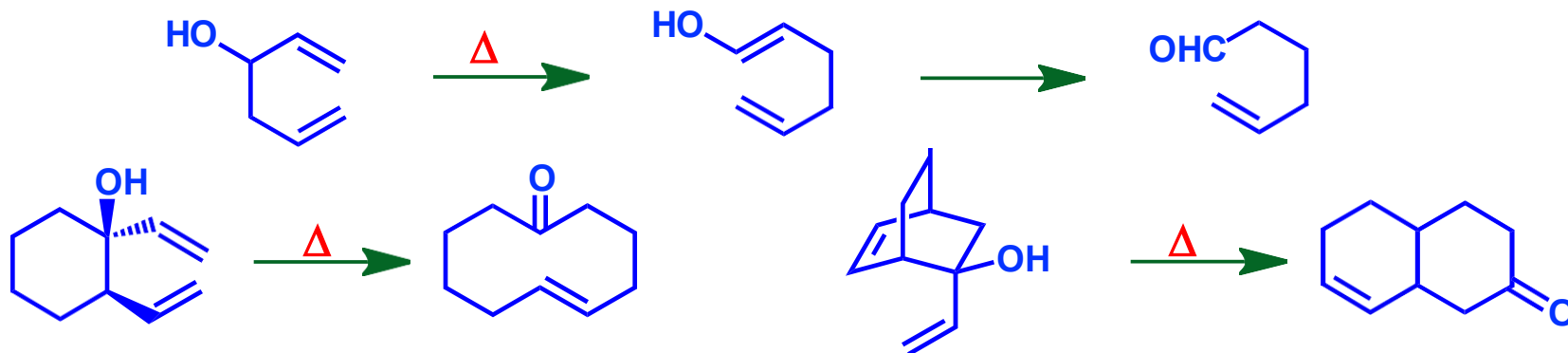
Other Examples:



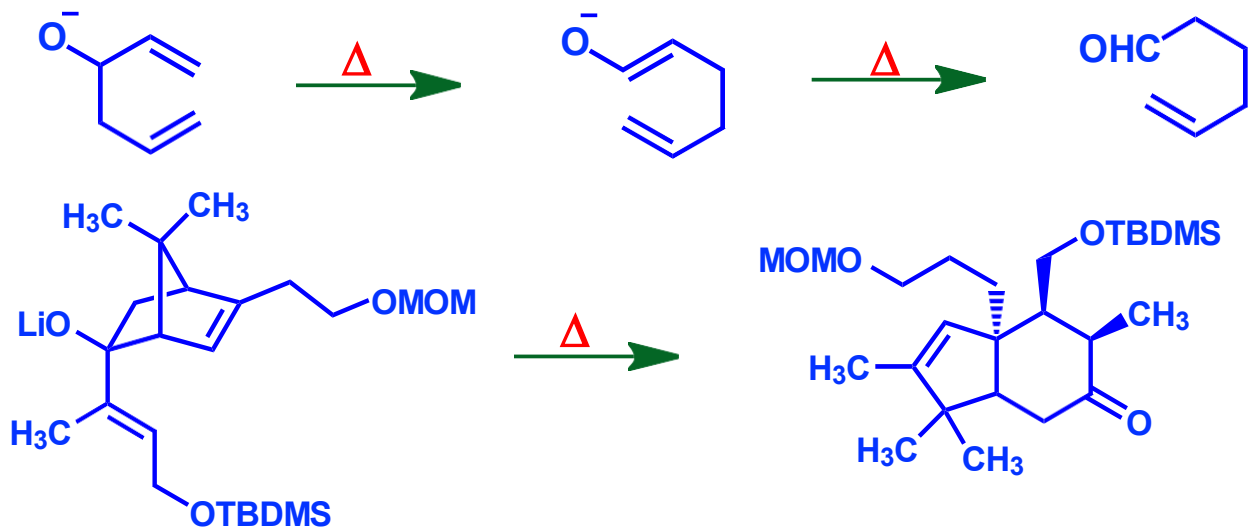
Cope Rearrangement

➤ Two important variations of Cope Rearrangement given here

1) Oxy-Cope:



2) Anionic-Oxy-Cope:



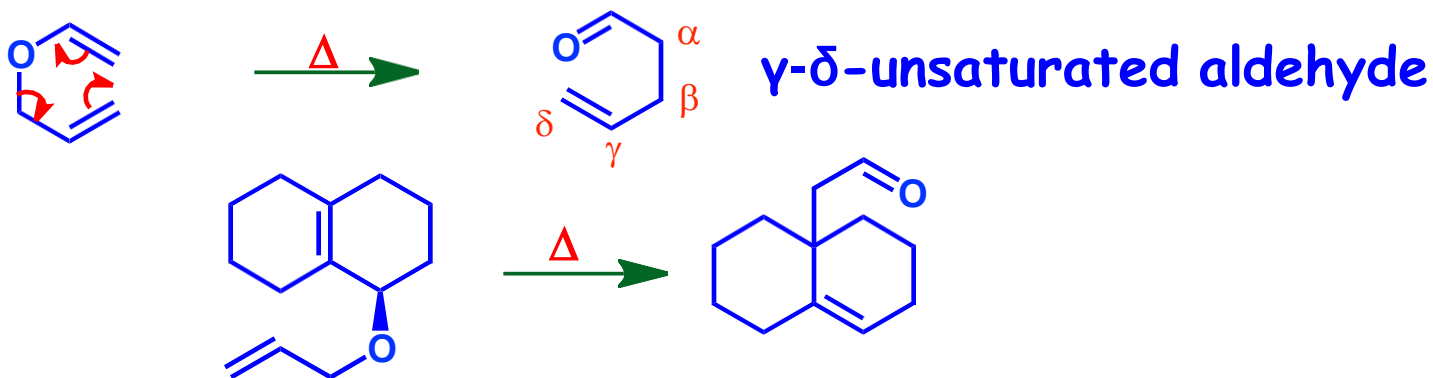
Sigmatropic Rearrangements

[3,3]-Sigmatropic Shift

Claisen Rearrangement

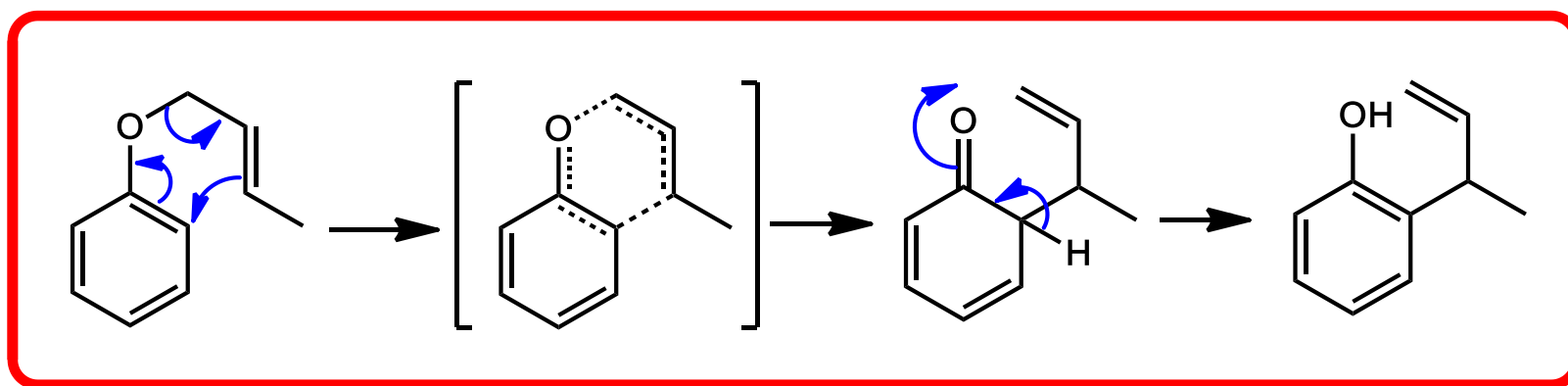
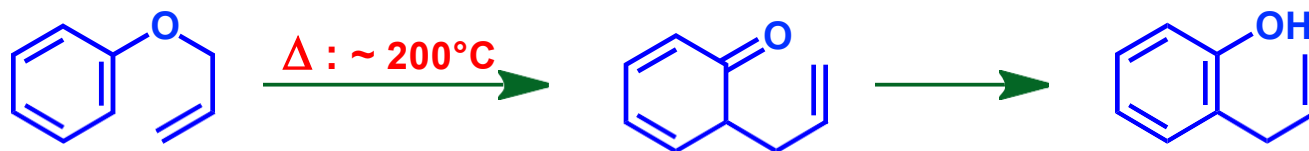
It is a [3,3]-sigmatropic rearrangement with only carbon atoms except one oxygen involved in a six membered transition state. Claisen Rearrangement are of two types:

1) Claisen Rearrangement of Allylvinyl Ethers:

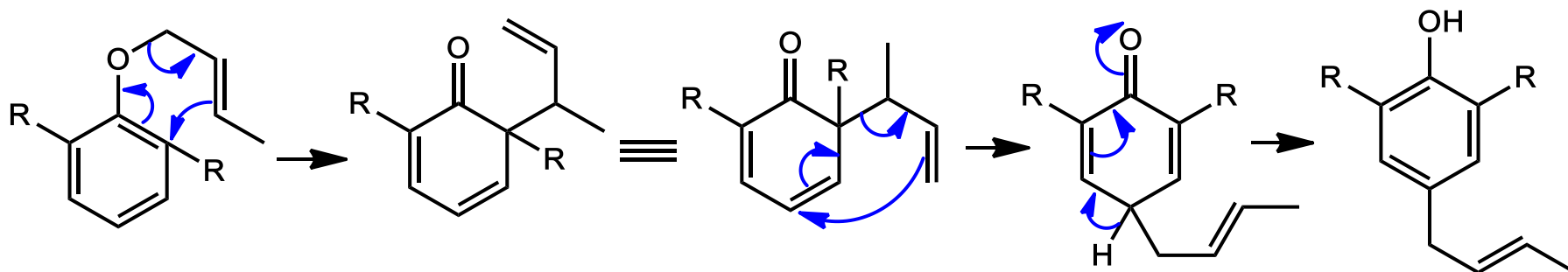


2) Claisen Rearrangement of Allylphenyl Ethers:

Aryl allyl ethers undergo [3,3]-sigmatropic rearrangement on being heated to allylphenols.

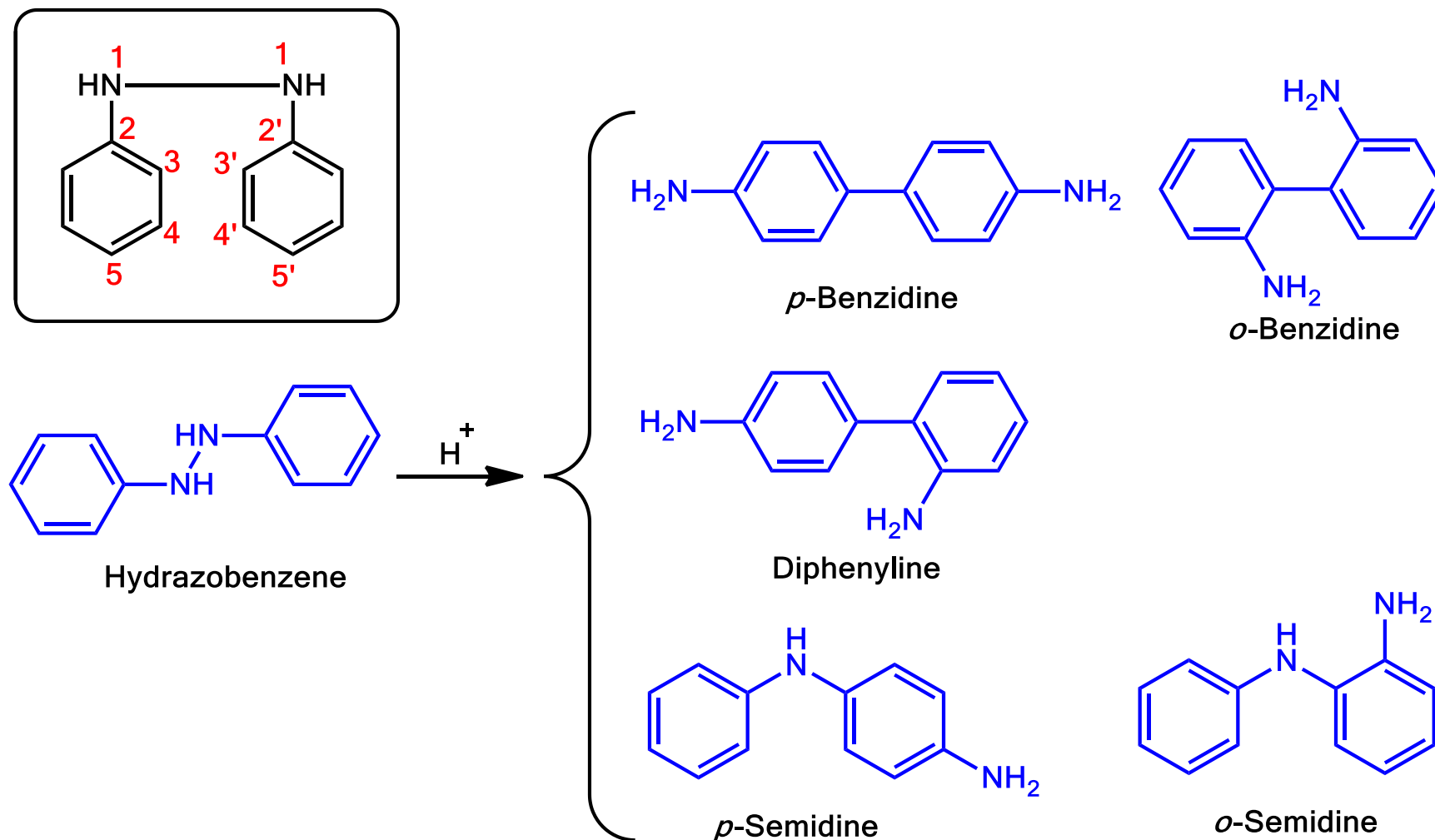


➤ If *ortho* position is blocked, rearrangement continues to give *para*-product.



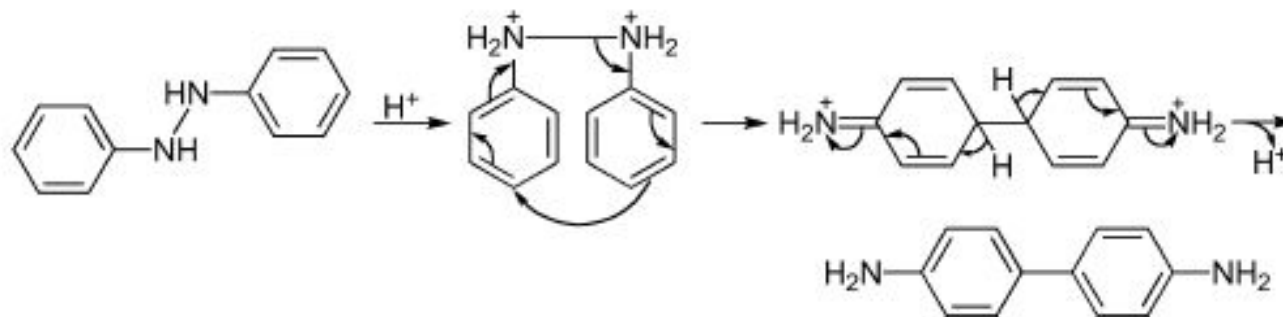
Benzidine-Semidine Rearrangement

Hydrazobenzene undergoes sigmatropic rearrangement in the presence of acid to give **Benzidines**, **Diphenylene** and **Semidines**.

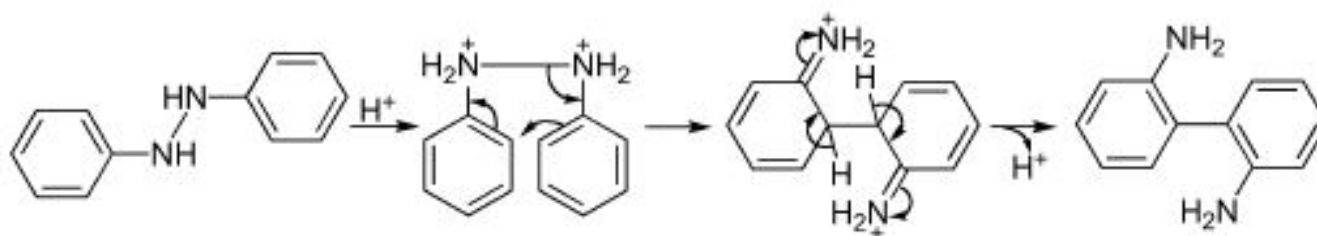


Mechanism:

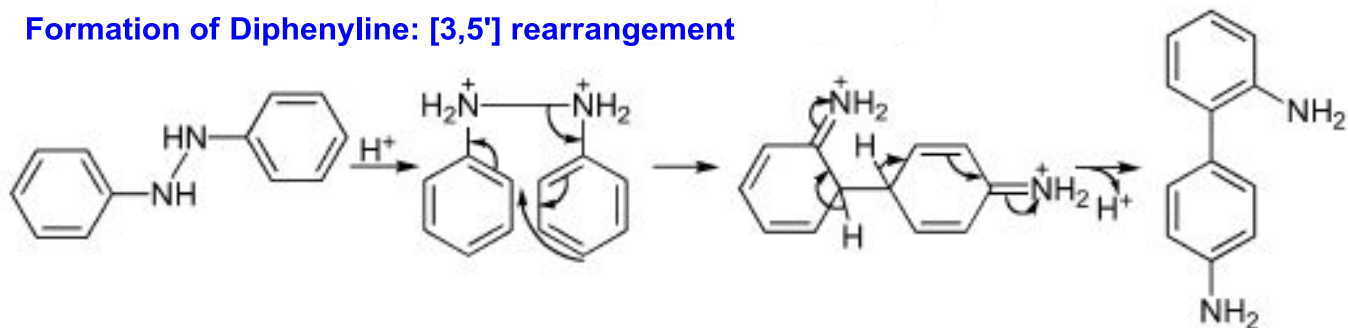
Formation of *p*-Benzidine: [5,5'] rearrangement



Formation of *o*-Benzidine: [3,3'] rearrangement

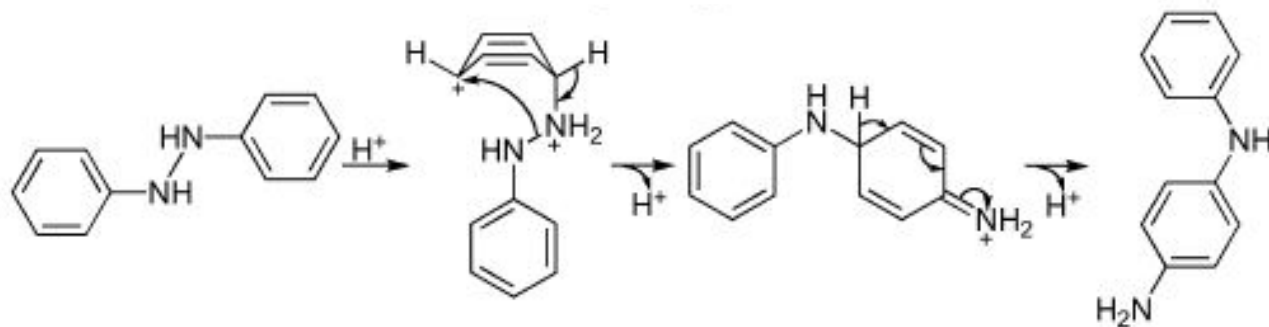


Formation of Diphenylene: [3,5'] rearrangement

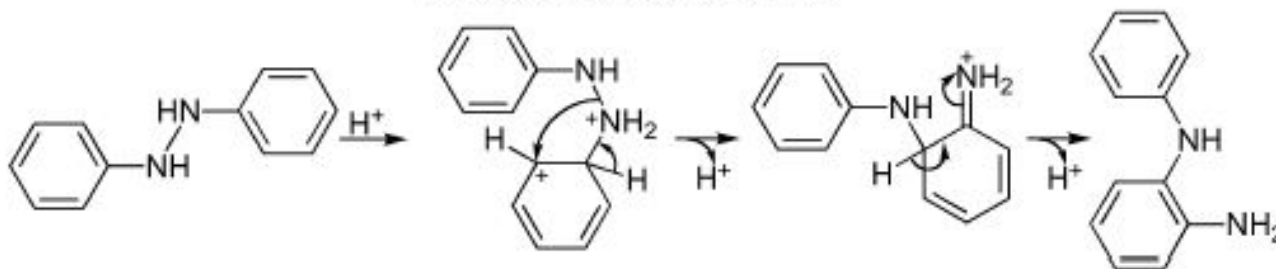


Mechanism Contd...

Formation of *p*-Semidine: [1,5'] Rearrangement



Formation of *o*-Semidine: [1,3'] Rearrangement

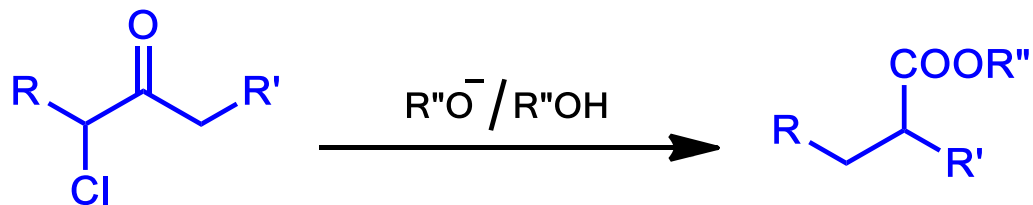


Other Rearrangements

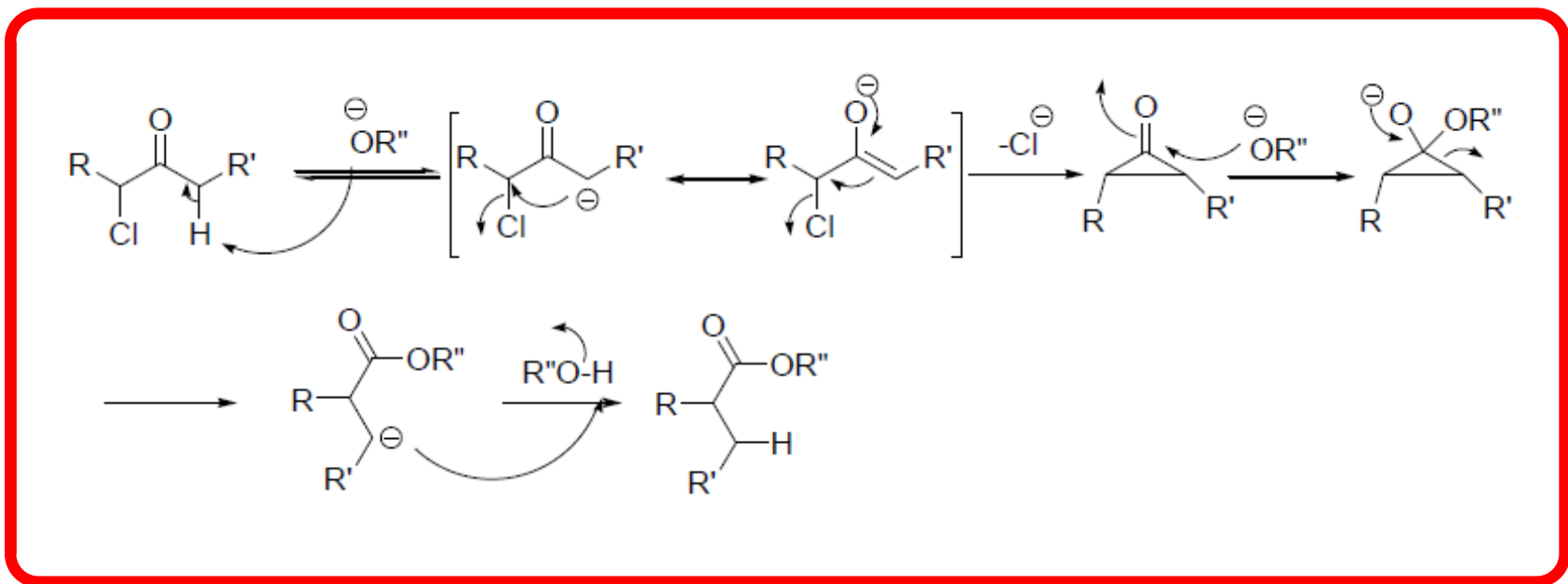
- ✚ Favorskii Rearrangement
- ✚ Fries Rearrangement
- ✚ Rearrangements of Derivative of aniline

Favorskii Rearrangement

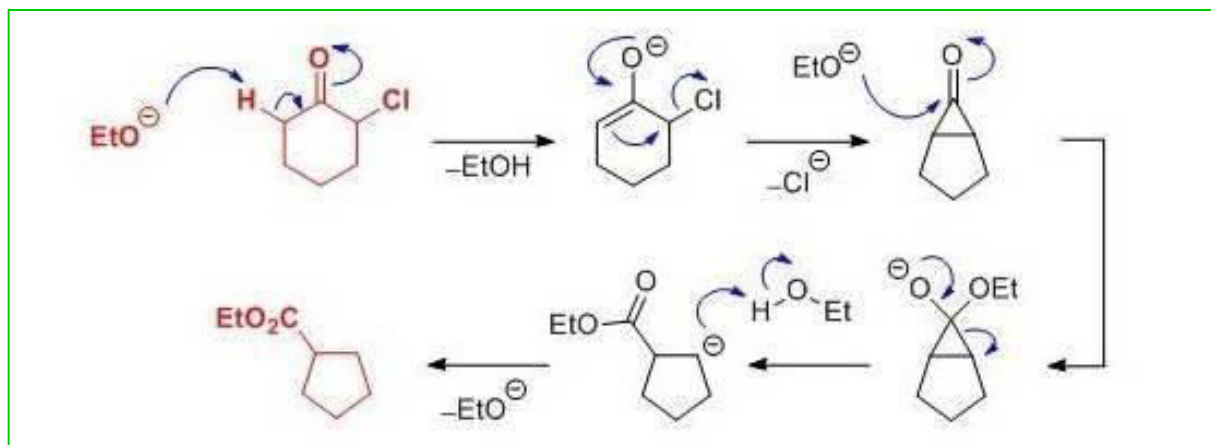
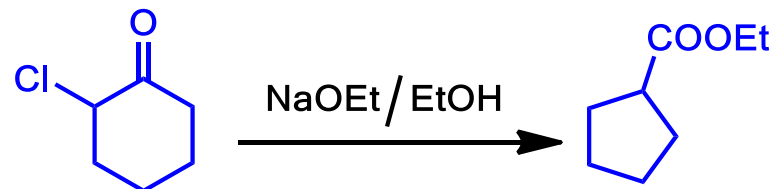
α -Haloketones with base afford enolates which rearrange to give esters *via* cyclopropanones popularly known as Favorskii Rearrangement.



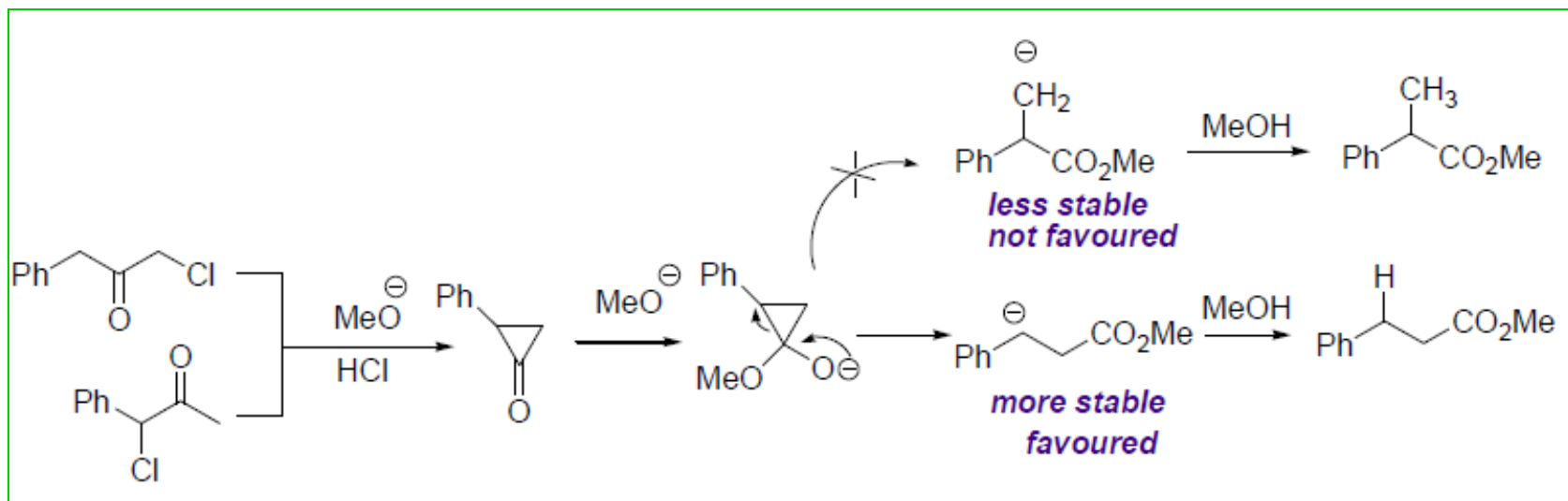
Mechanism:



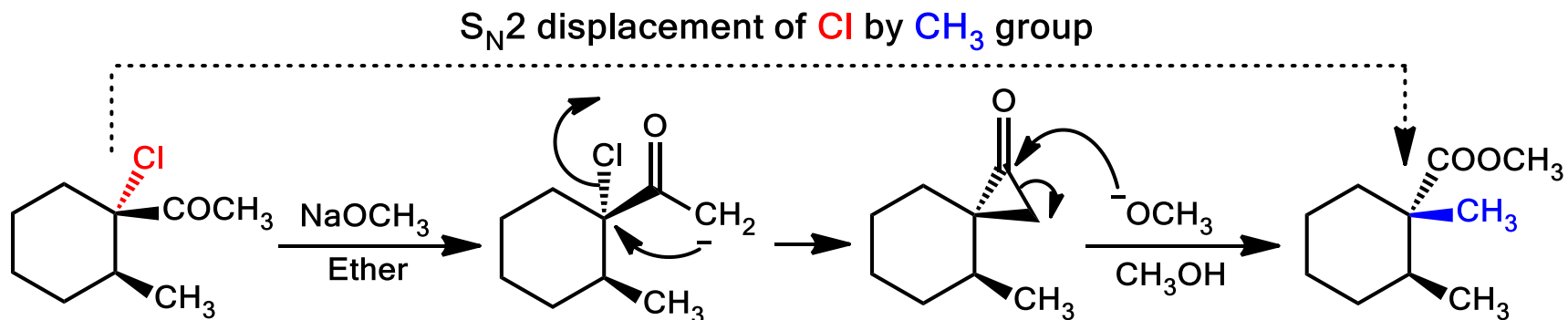
➤ This reaction can be used for ring contraction



➤ The direction of ring opening of cyclopropanone is determined by the more stable carbanion, formed in the reaction.

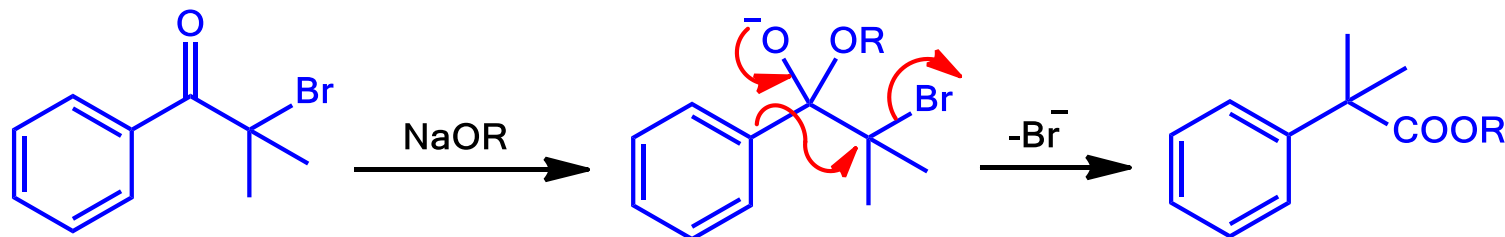


➤ In some interesting cases, Favorskii rearrangement results in intramolecular substitution. For example shown below, internal S_N2 displacement of halide ion results in inversion of configuration of the halogenated carbon.

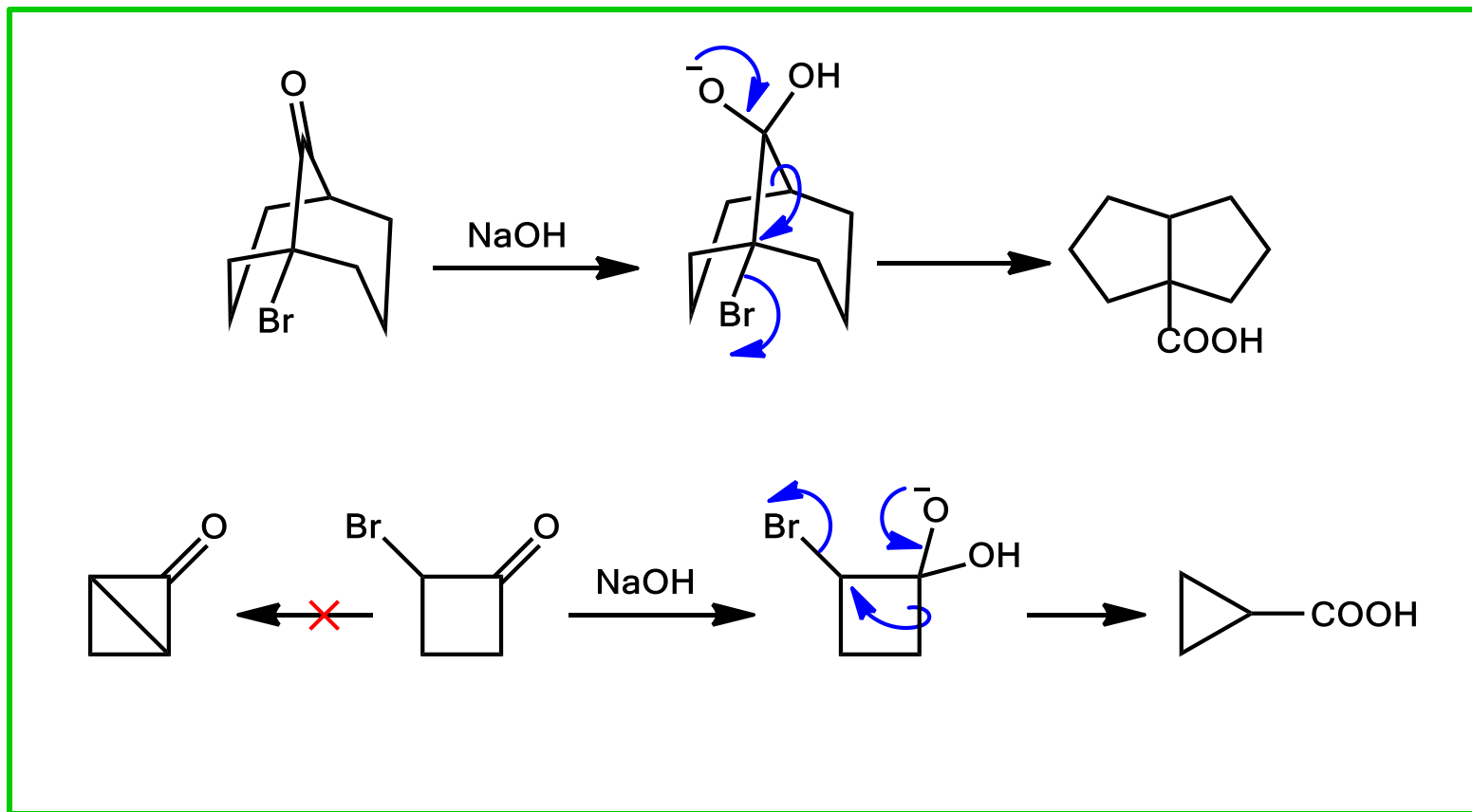


Actually, in absence of resonance stabilization of one of the two possible anions, the less-substituted alkyl anion is formed.

➤ **Quasi-Favorskii rearrangement:** Many ketones lacking hydrogens on their unhalogenated α -carbon undergo a Benzil-Benzilic acid type of rearrangement that yield products of Favorskii rearrangement.

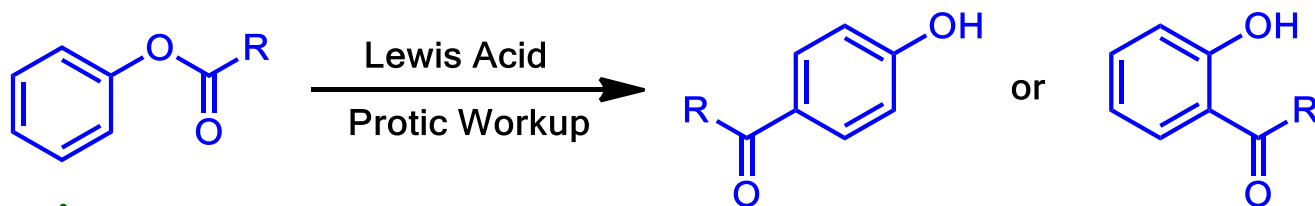


Examples of Quasi-Favorskii Rearrangement



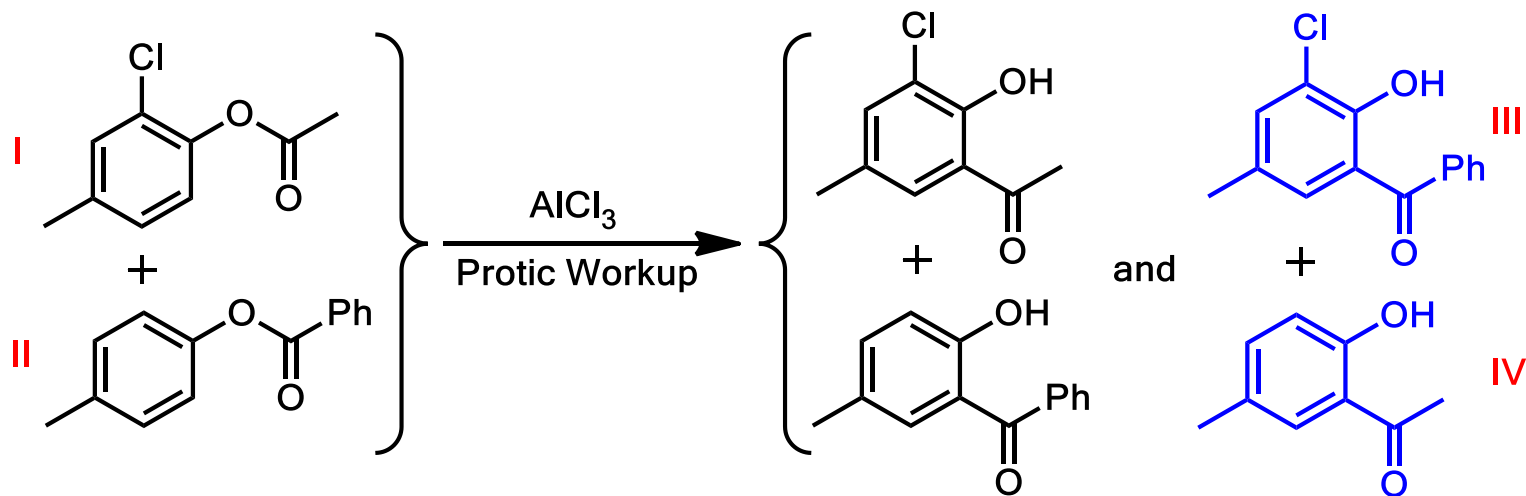
Fries Rearrangement

Aryl esters with Lewis acid undergo rearrangement to give *ortho* and *para*-keto substituted phenols. The complex between the ester and Lewis acid gives an **acylium ion** which reacts at the *ortho* and *para* positions as in Friedel-Crafts acylation.

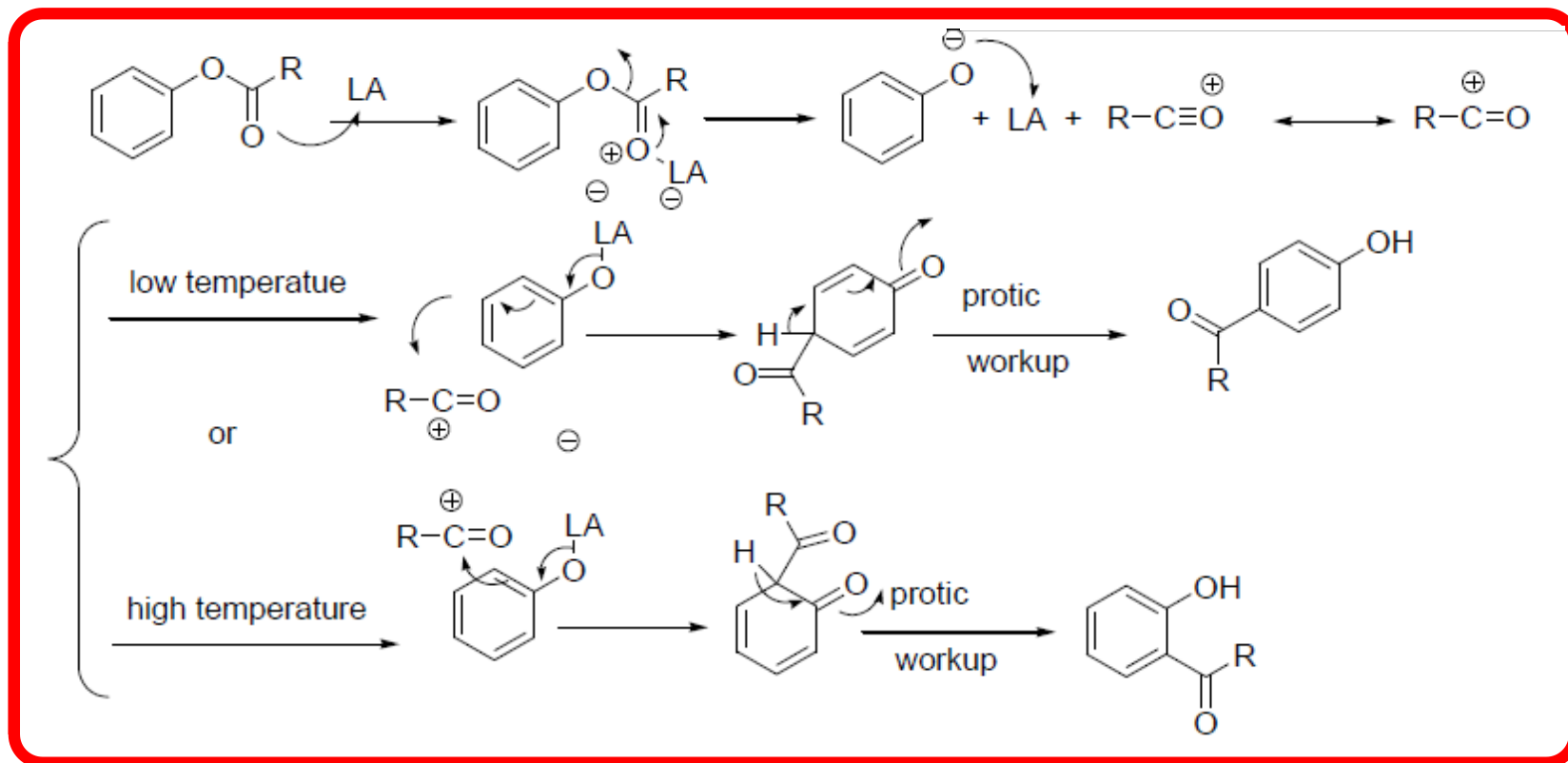


Mechanism

➤ A mixture of aryl esters **I** and **II** reacted to form their corresponding keto substituted phenols along with crossover products **III** and **IV**.



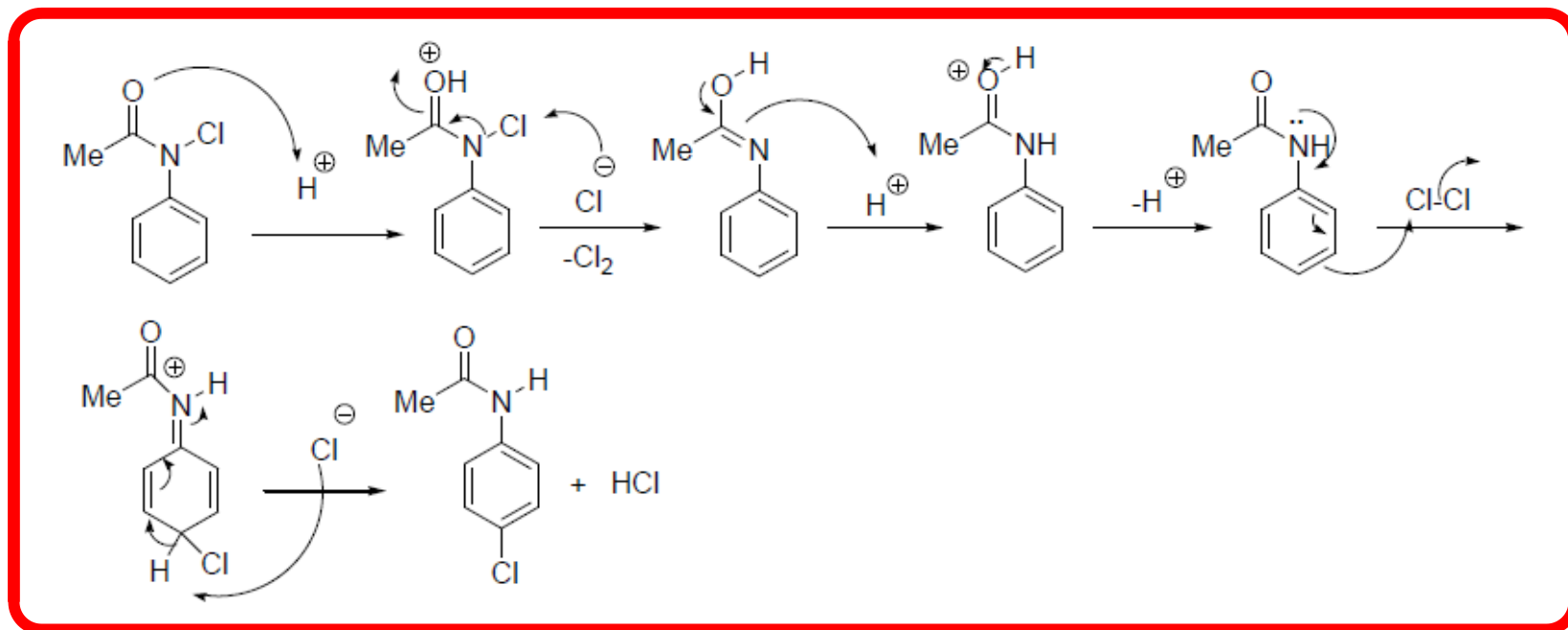
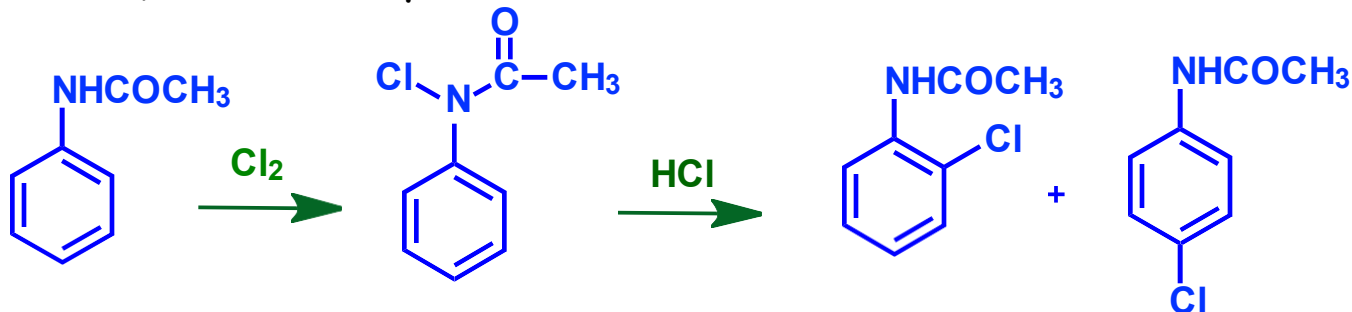
➤ Low temperature favors the formation of *para*-product (kinetic control) and high temperature favors *ortho*-product (thermodynamic control).



Rearrangements of Derivative of aniline

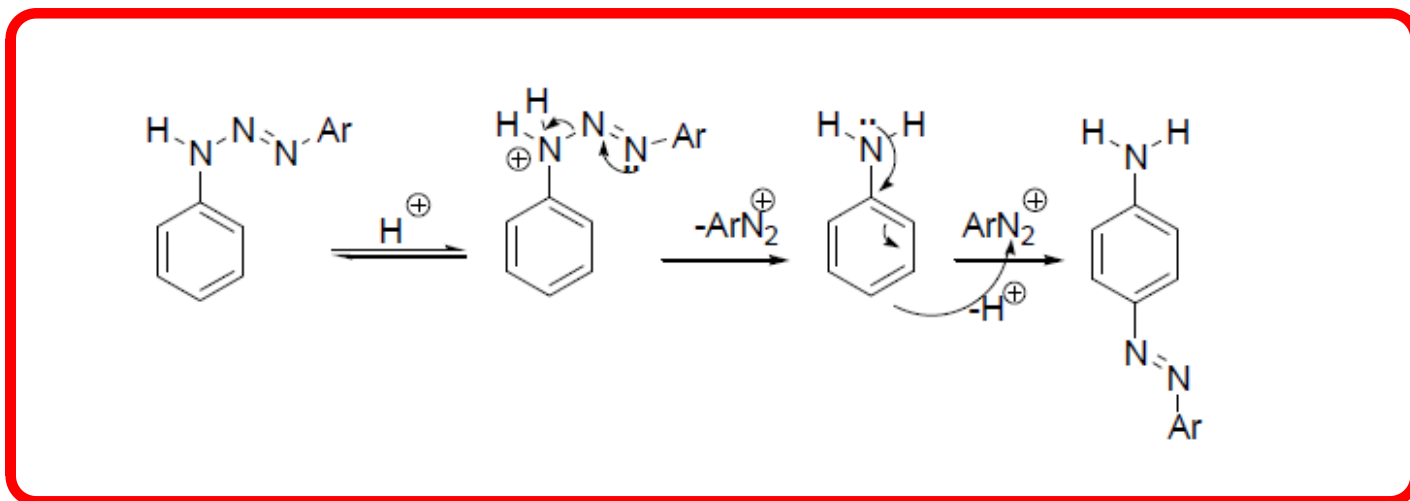
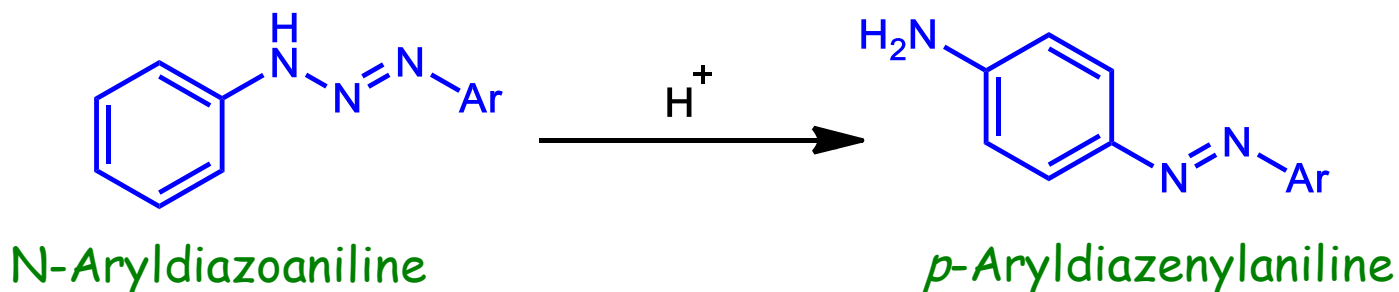
Rearrangements of N-Haloanilides (Orton Rearrangement)

Treatment of *N*-chloroacetanilide with hydrochloric acid affords a mixture of *ortho* and *para*-chloracetanilides in the same proportions as in the direct chlorination of acetanilide.



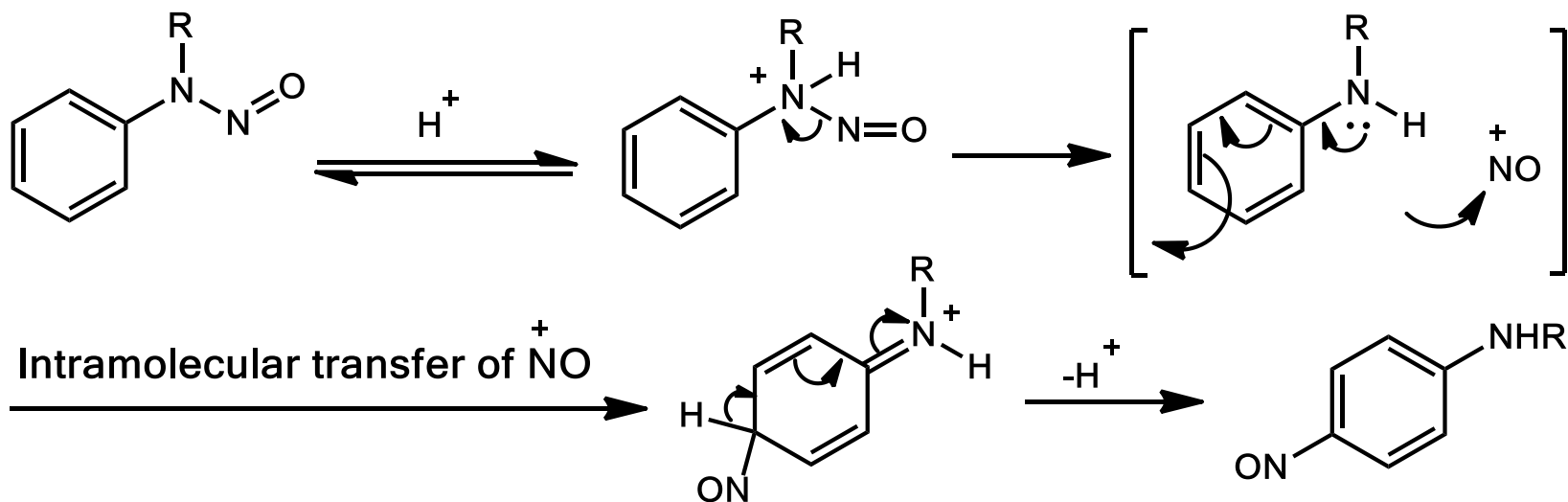
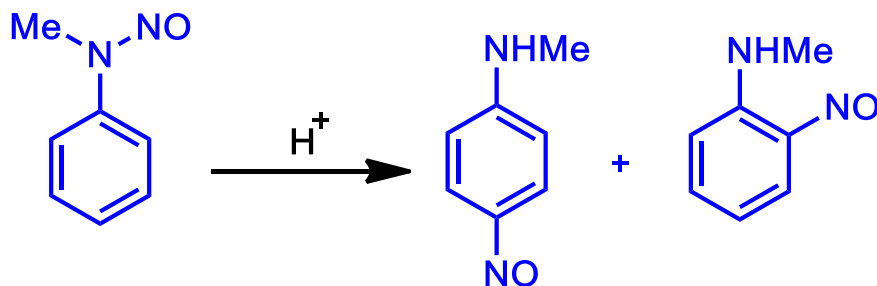
Rearrangements of N-Aryldiazoanilines :

N-Aryldiazoanilines undergo rearrangement in presence of an acid to produce *p*-Aryldiazenylanilines. On treatment with acid, aryldiazonium ion is formed from the conjugate acid of amine, which migrates to the *para* position almost selectively.



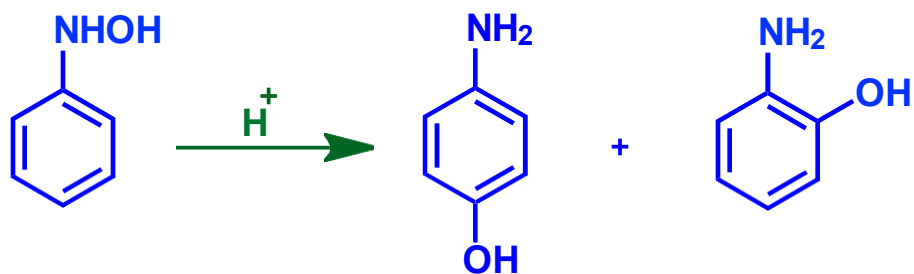
Rearrangement of N-Alkyl-N-nitrosoanilines (Fisher-Hepp Rearrangement) :

The conjugate acid of the N-Alkyl-N-nitrosoanilines supply the nitrosonium ion which reacts mainly at the *para*-position in intramolecular fashion to give the *p*-nitroso product.

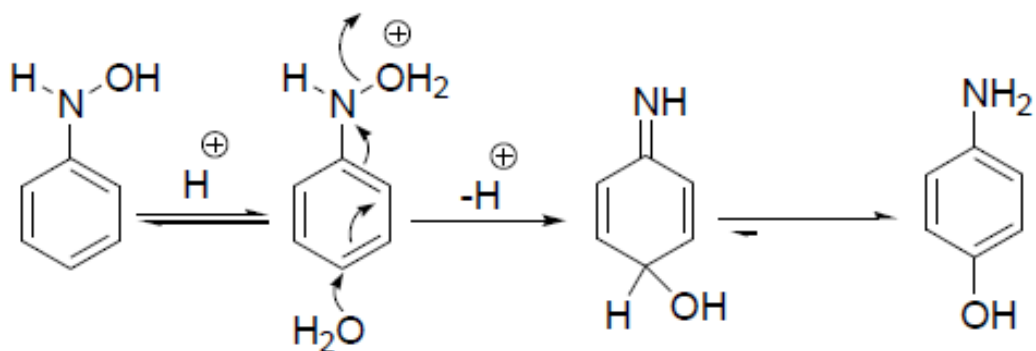


Rearrangement of N-Arylhydroxylamines (Bamberger Rearrangement):

N-Arylhydroxylamines with **acid** undergoes rearrangement to give **aminophenols**. In this rearrangement, the conjugate acid of the hydroxylamine undergoes nucleophilic attack by the **solvent**.

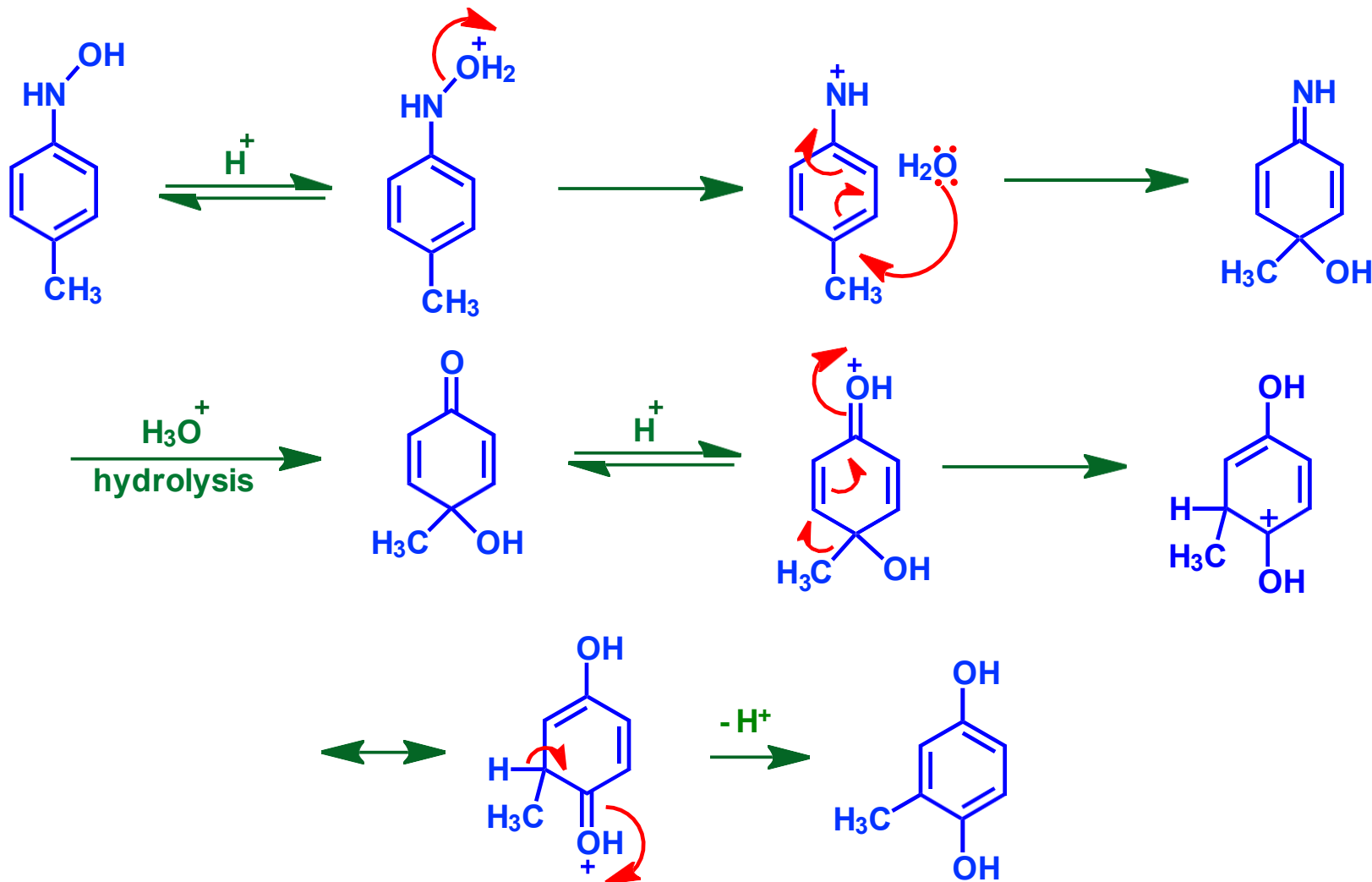


Mechanism



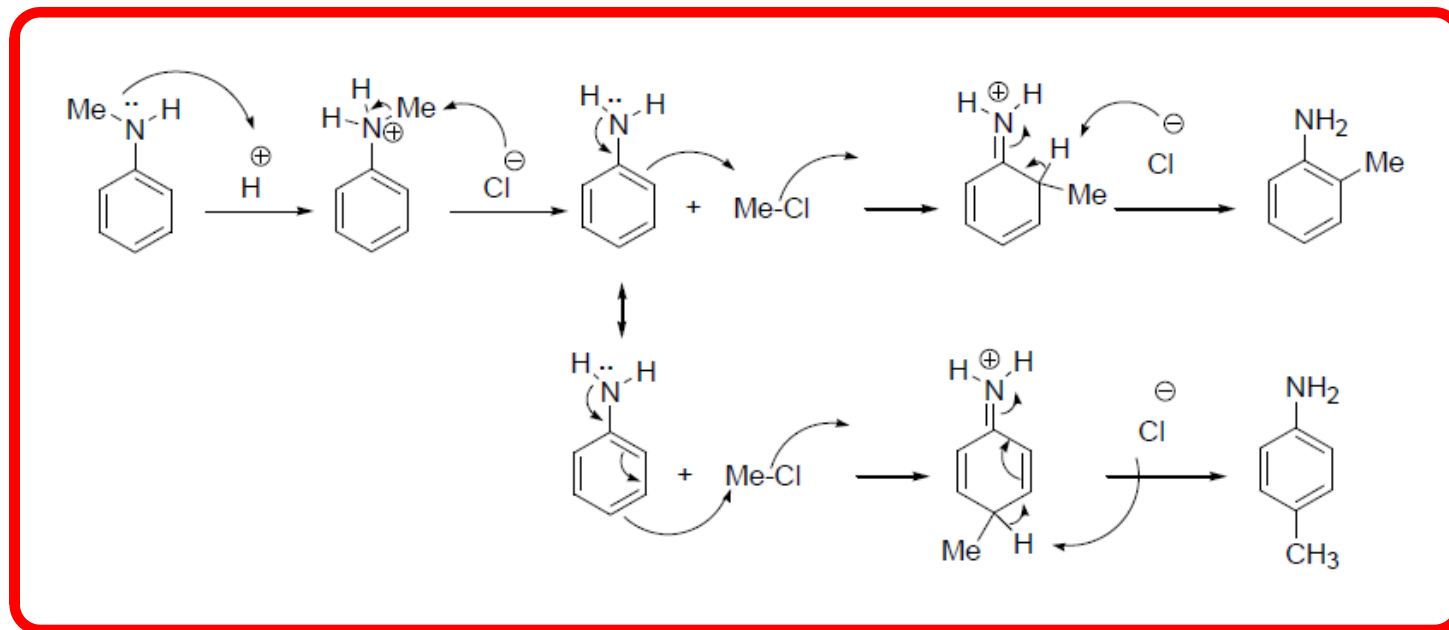
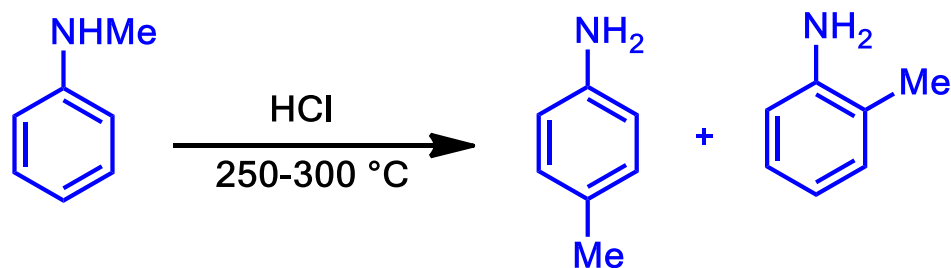
When para-position is already occupied ???

➤ Hydrolysis followed by Dienone-phenol type of rearrangement occurs.



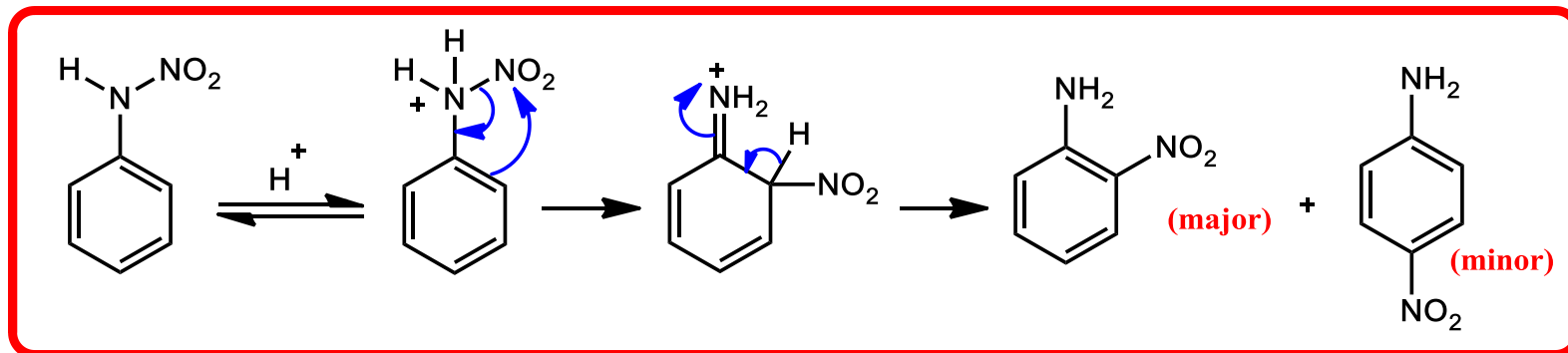
Rearrangement of N-Alkylanilines (Hofmann-Martius Rearrangement):

N-alkylanilines in presence of acid at very high temperature rearranged to ortho and para alkylated products.



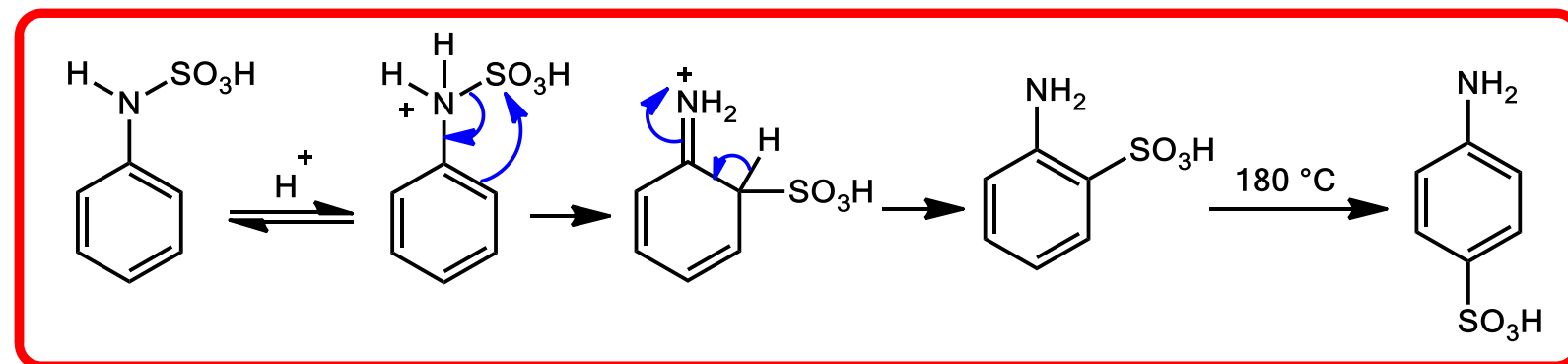
Rearrangement of Phenylnitramines:

Phenylnitramines on heating with acid rearrange to give mainly the *o*-nitro-derivative.



Rearrangement of Phenylsulfamic acids:

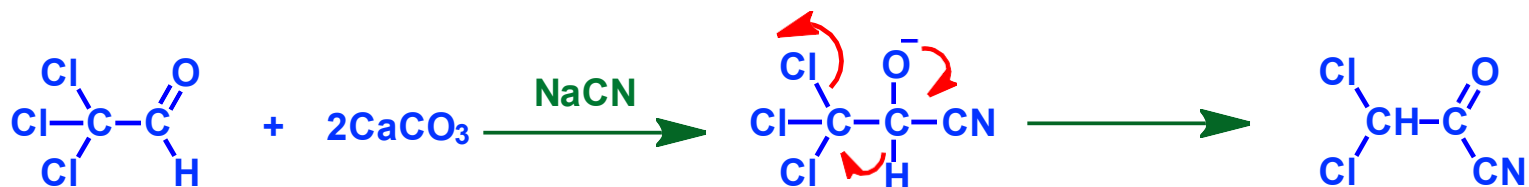
Phenylsulfamic acids rearrange on heating to give *o*-sulfonic acid derivative that further rearranges at high temperature to afford *p*-sulfonic acid derivatives.



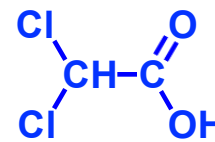
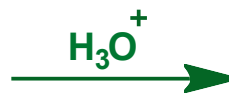
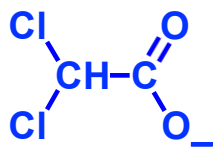
➤ The mechanisms of these reactions are not fully understood and are supposed to follow an intramolecular pathway.

Rearrangements

Some Additional Problems



hydrolysis of
acid derivative

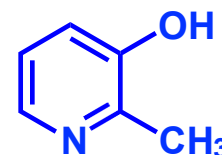
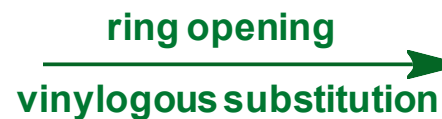
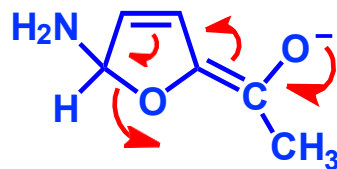
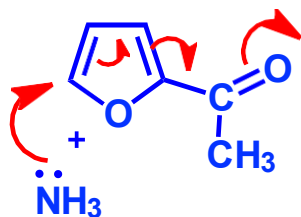
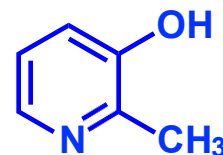
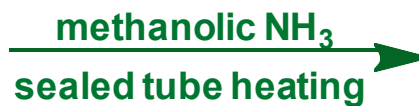
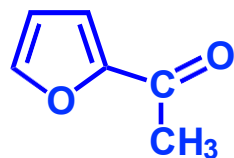


dichloro acetic acid



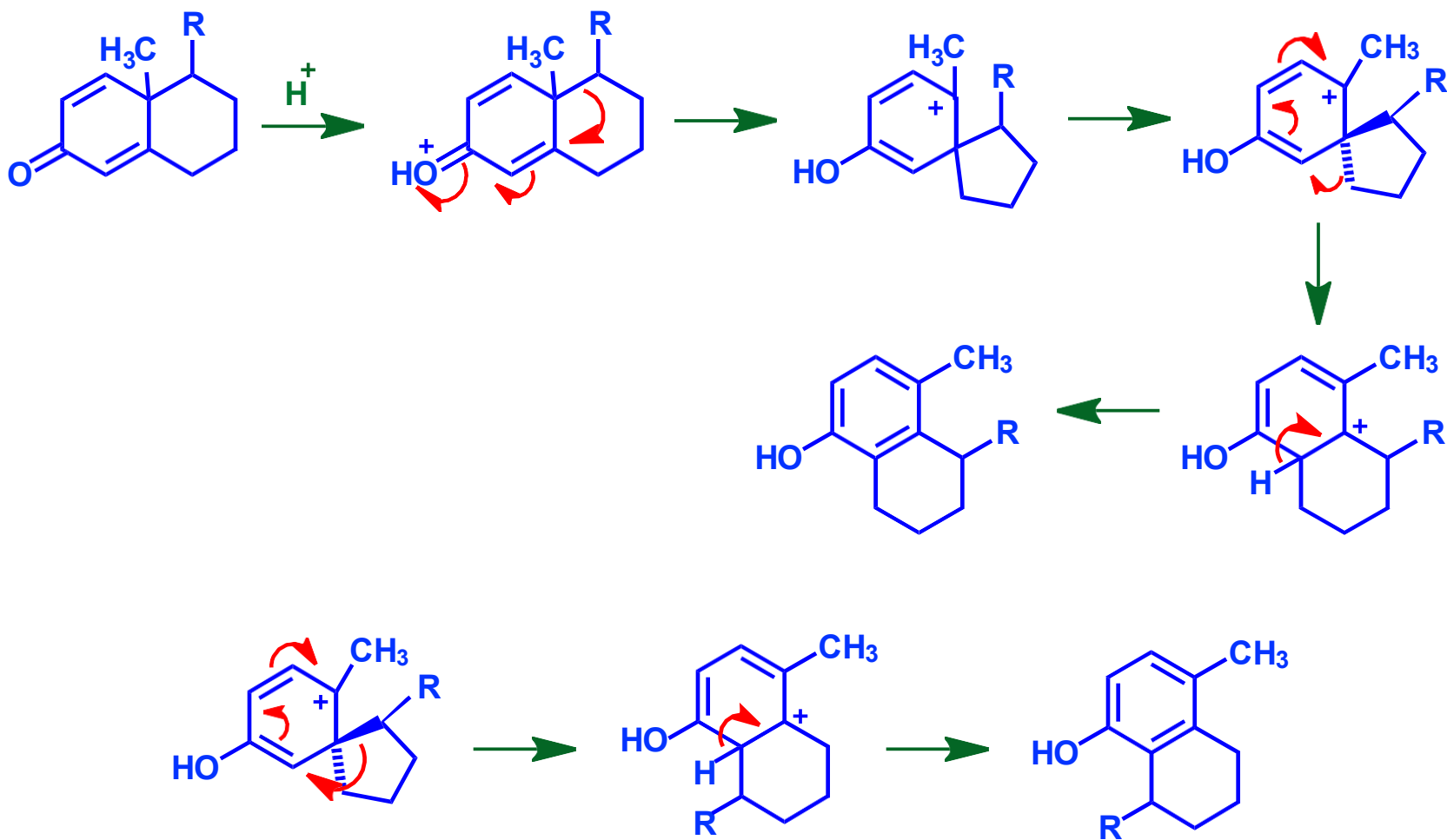
Rearrangements

Some Additional Problems



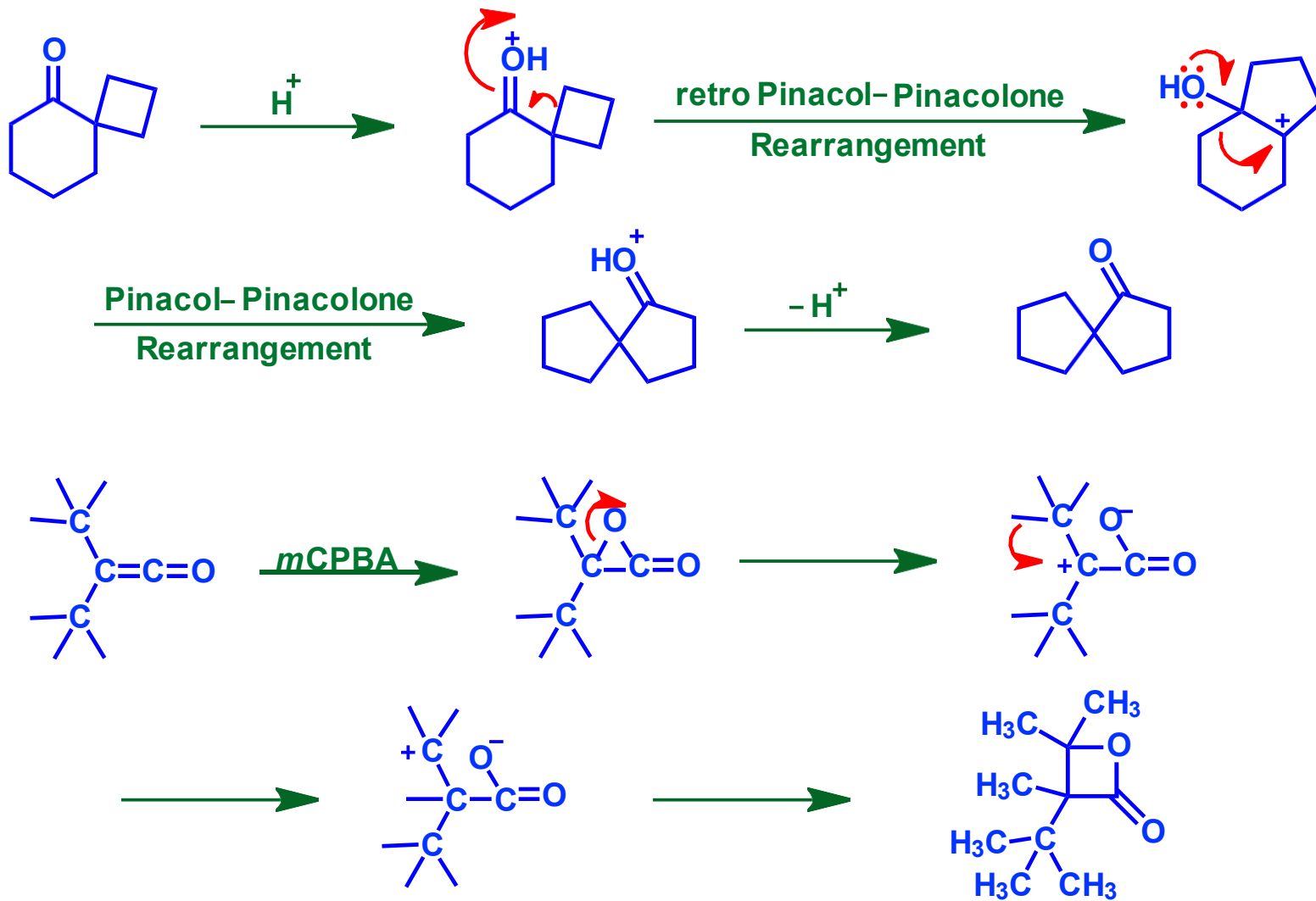
Rearrangements

Some Additional Problems



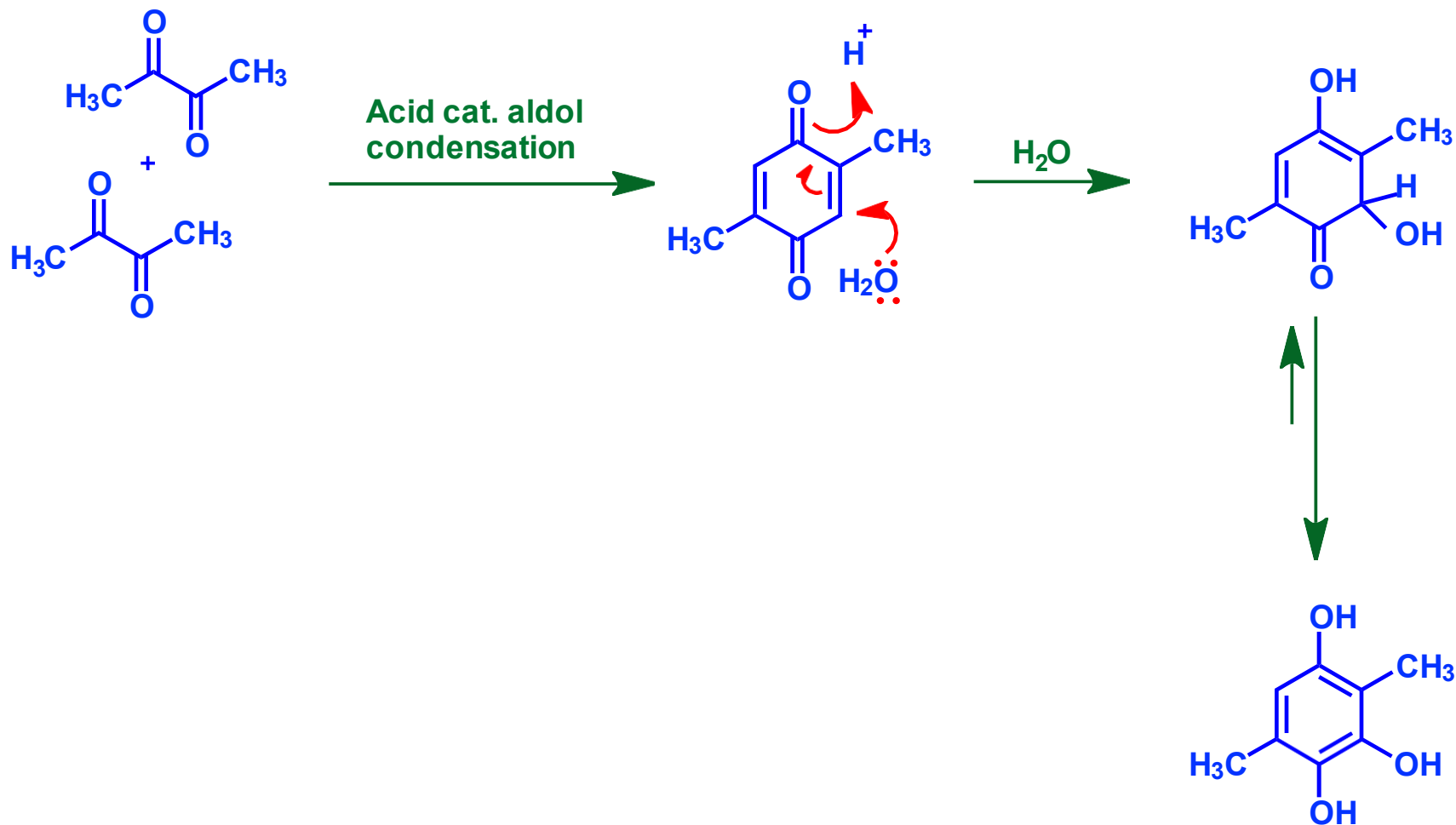
Rearrangements

Some Additional Problems



Rearrangements

Some Additional Problems



Named Reactions

Birch Reduction

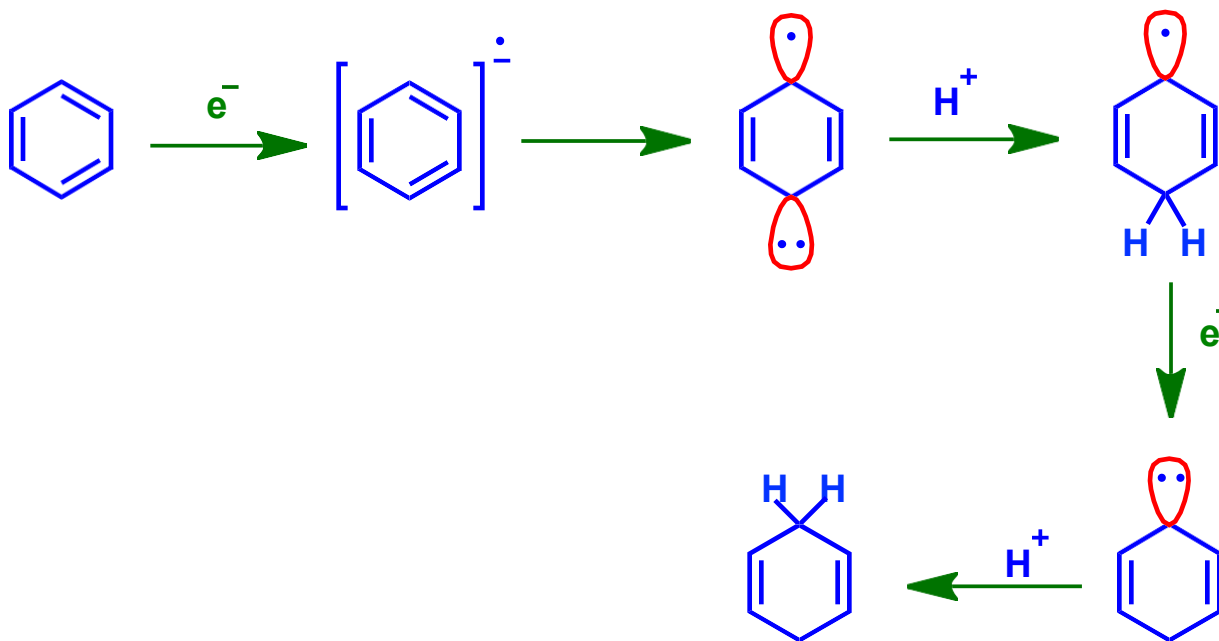
Dissolving Metal Reduction

Reducing Agent:



M = Li, Na, K, Ca **A** = Liquid ammonia, Et₂NH, EtNH₂, ROH, H₂O

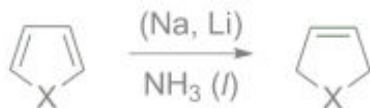
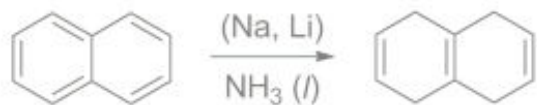
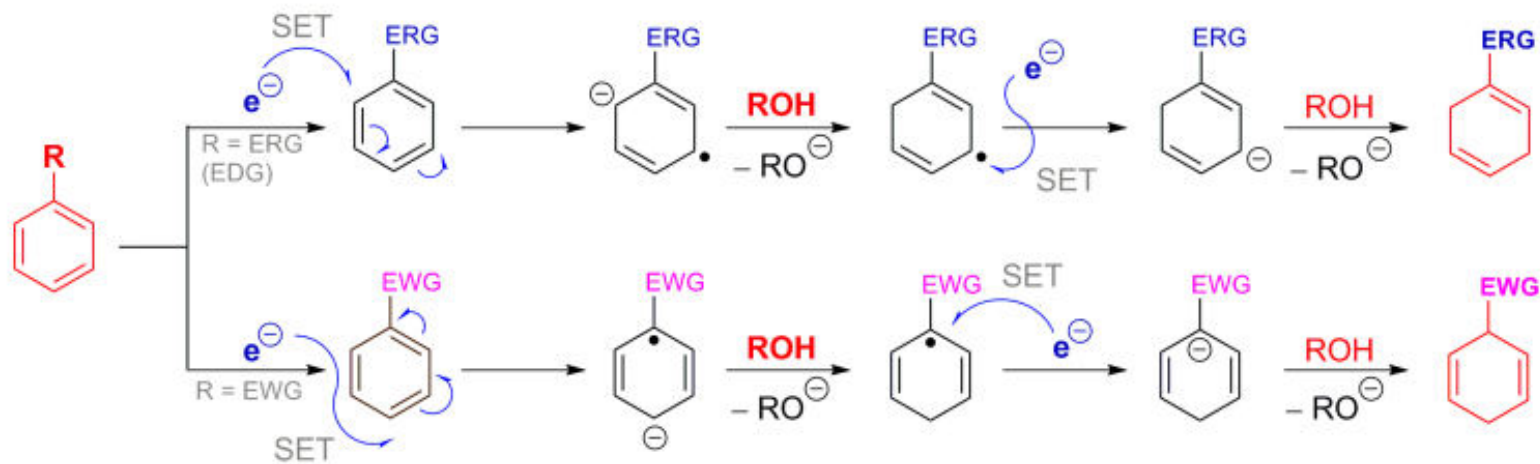
Partial Reduction Of Aromatic Rings:



Birch Reduction

Dissolving Metal Reduction

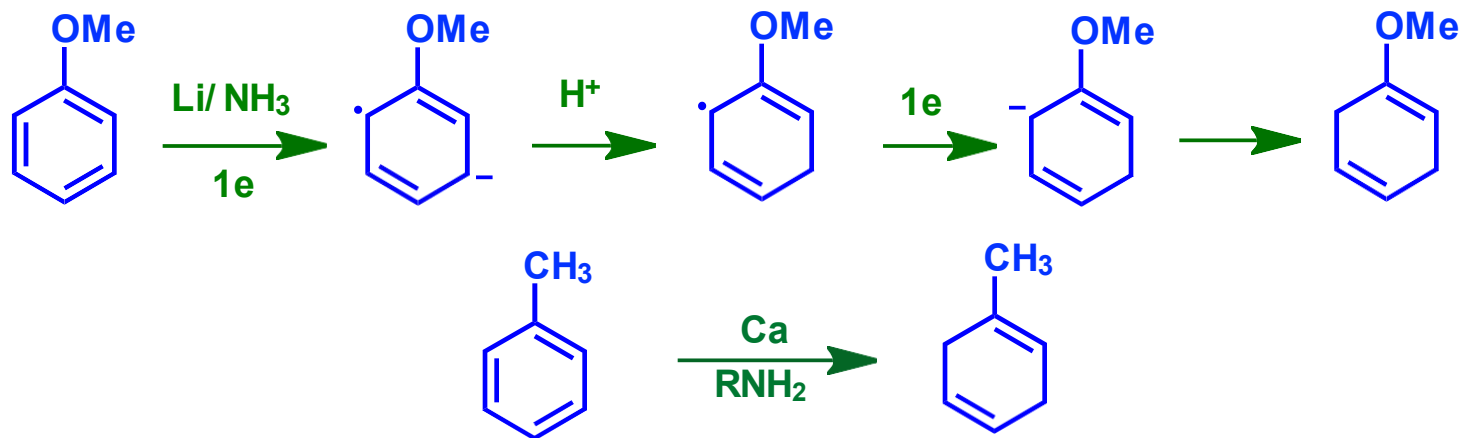
Mechanism



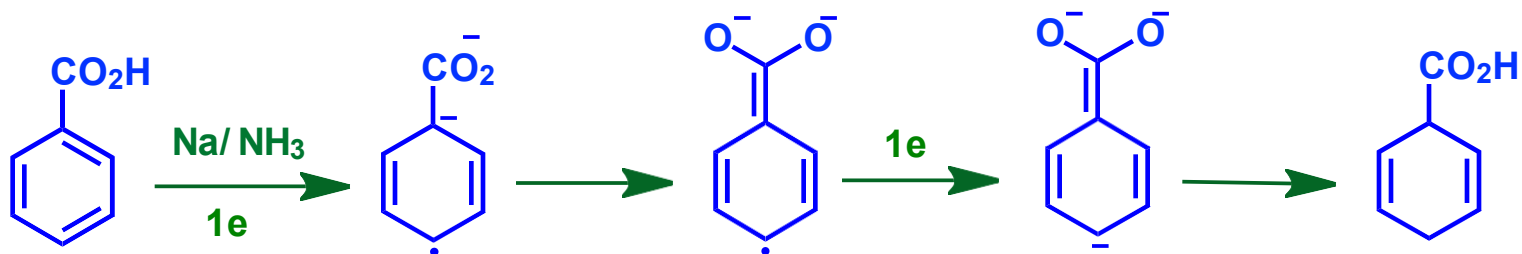
Birch Reduction

Dissolving Metal Reduction

Electron Donating Substituents:



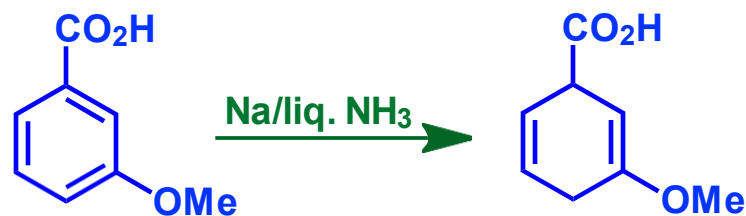
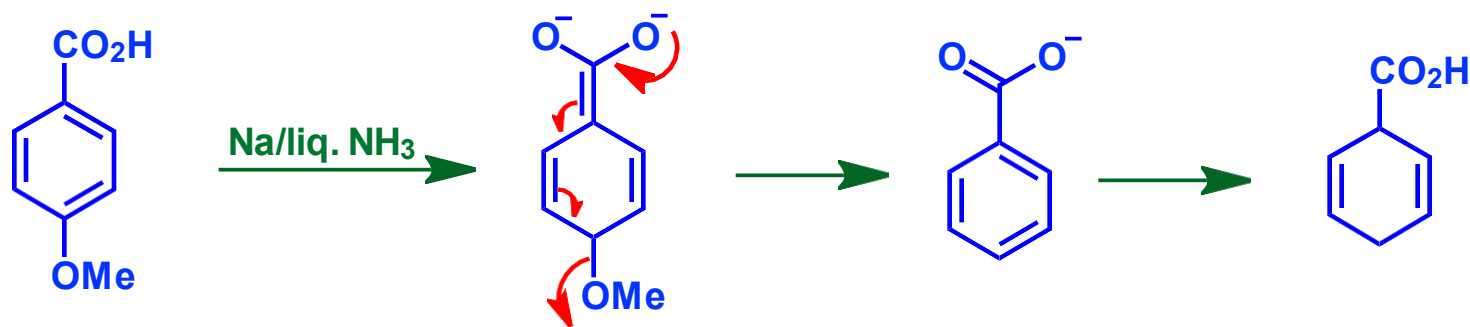
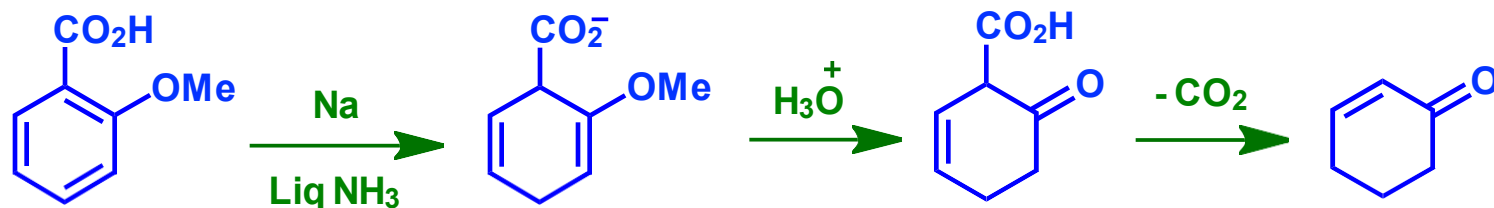
Electron Withdrawing Substituents:



Birch Reduction

Dissolving Metal Reduction

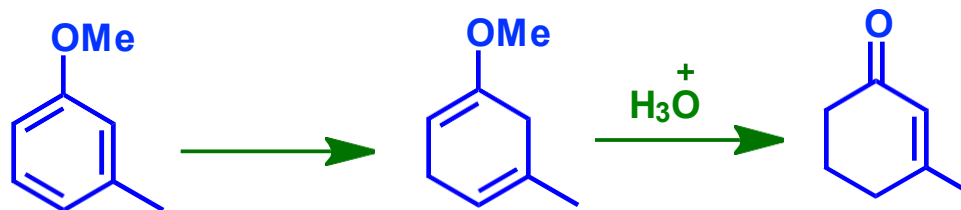
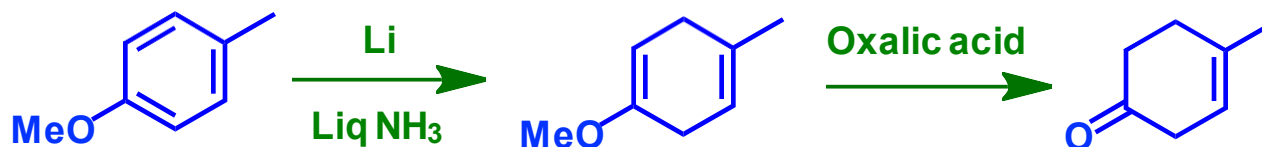
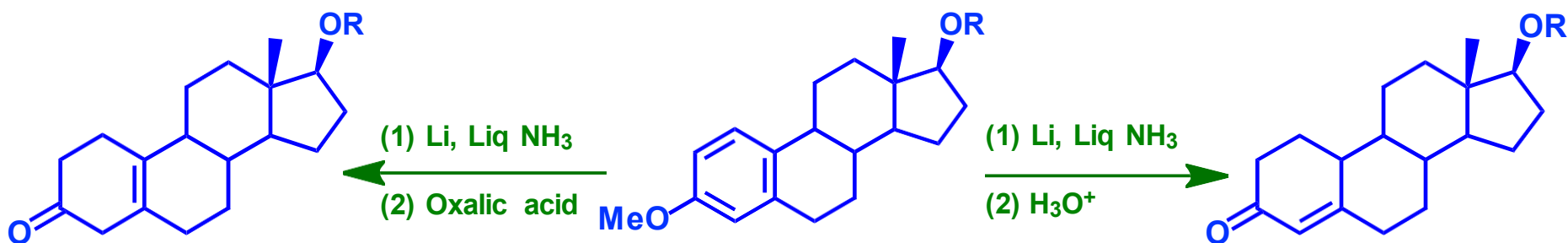
Both Electron Donating And Electron Withdrawing Substituents:



Birch Reduction

Dissolving Metal Reduction

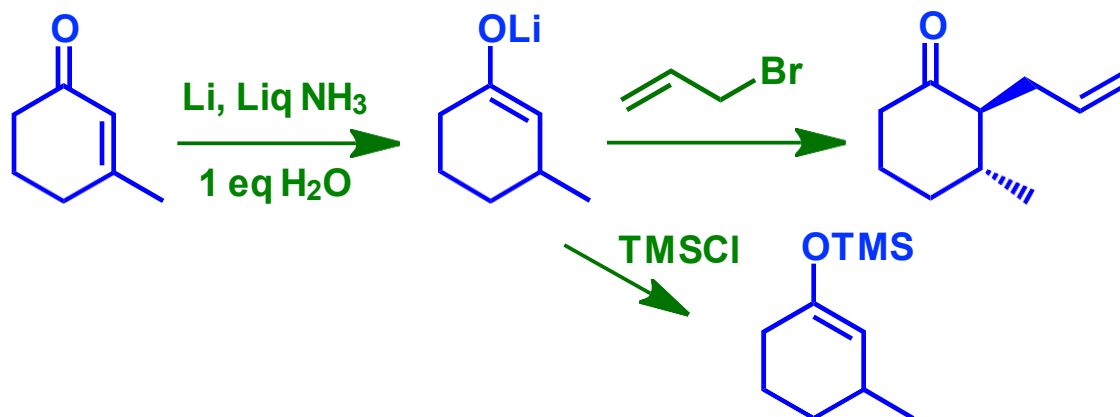
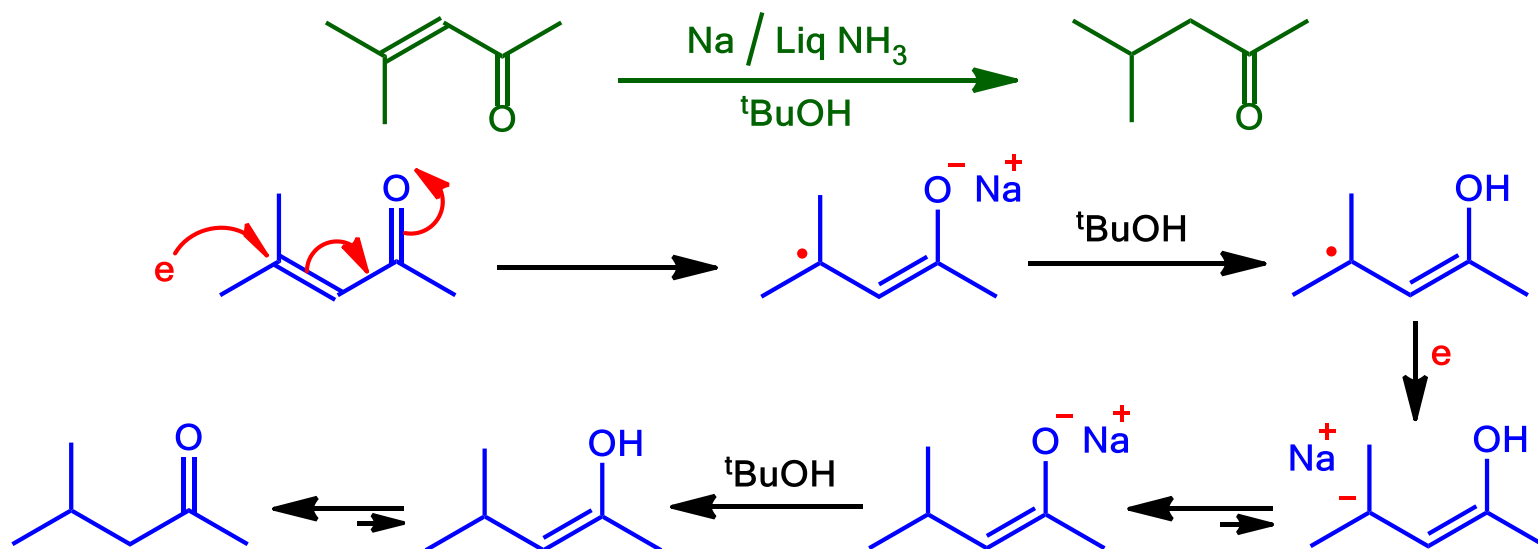
- **Ketones** and **nitro** groups get reduced keeping **esters** and **nitriles** untouched



Birch Reduction

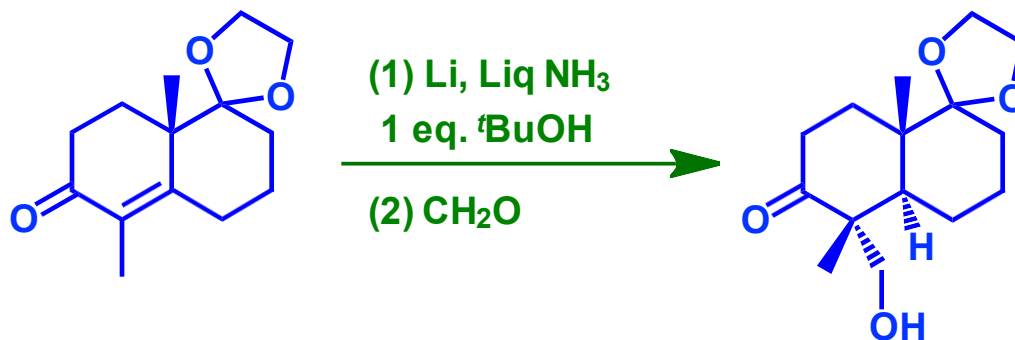
Dissolving Metal Reduction

- α,β -unsaturated compounds are reduced in 1,4-fashion

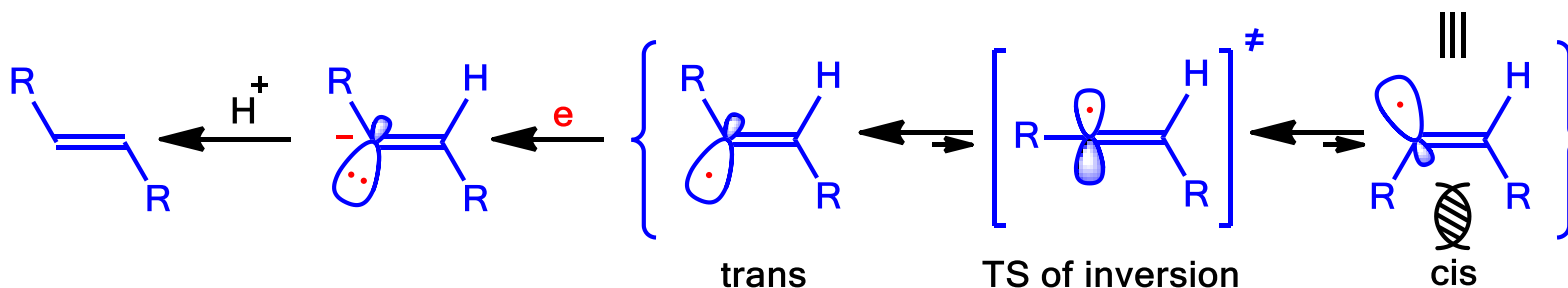
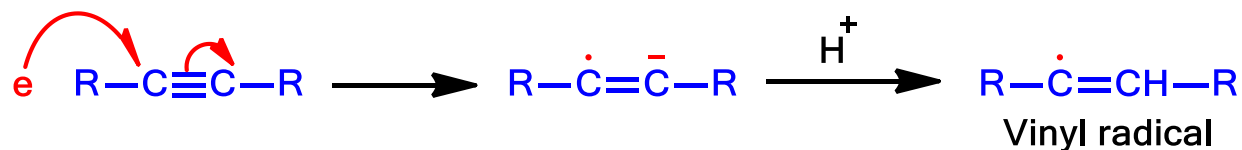


Birch Reduction

Dissolving Metal Reduction

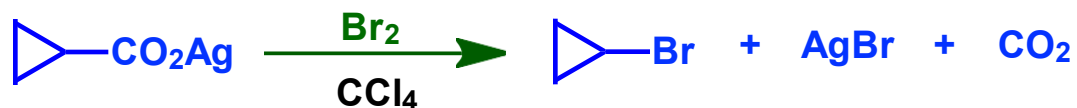


- **Alkynes** reduced to provide **trans-alkene** exclusively



Hunsdiecker Reaction

The **Hunsdiecker reaction** (also called the **Borodin reaction** or the **Hunsdiecker-Borodin reaction**) is a decarboxylative reaction whereby **silver salts of carboxylic acids** react with a halogen to produce one **carbon less organic halides**.

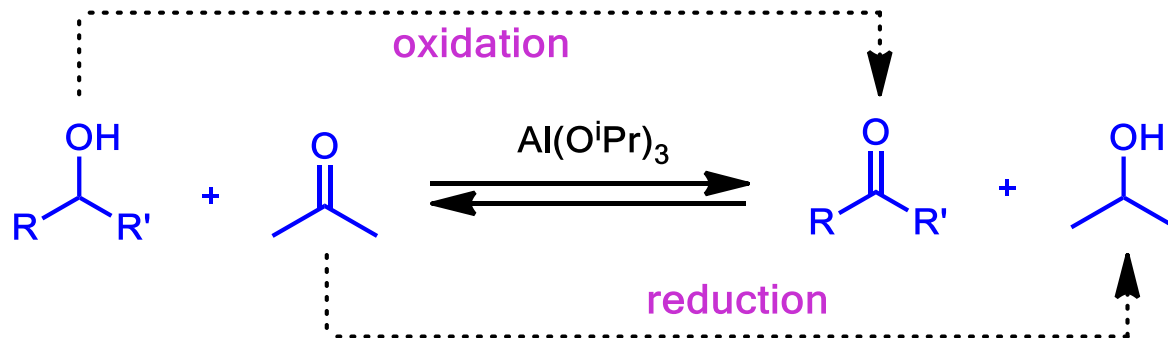


Mechanism

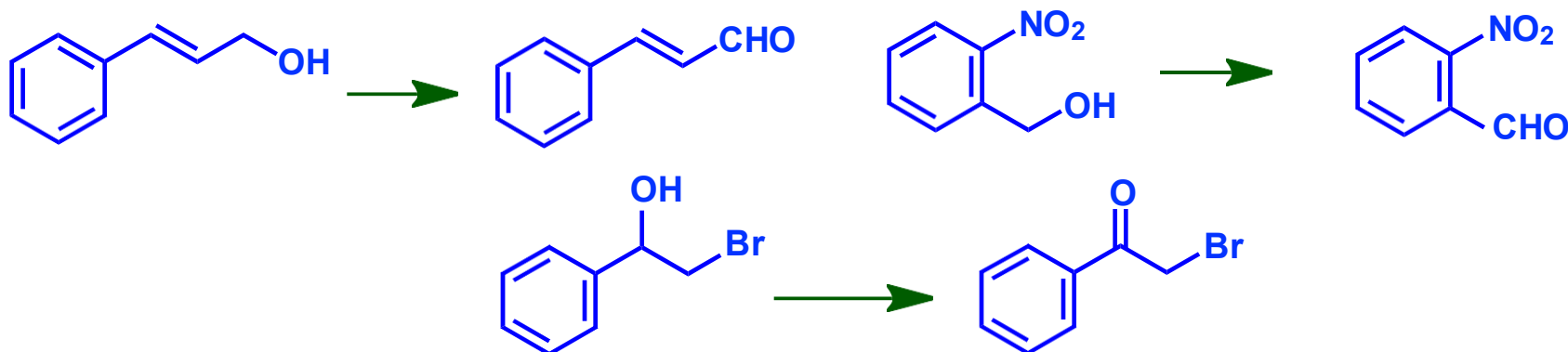


Oppenauer oxidation

Aluminum-based reagent Reduction



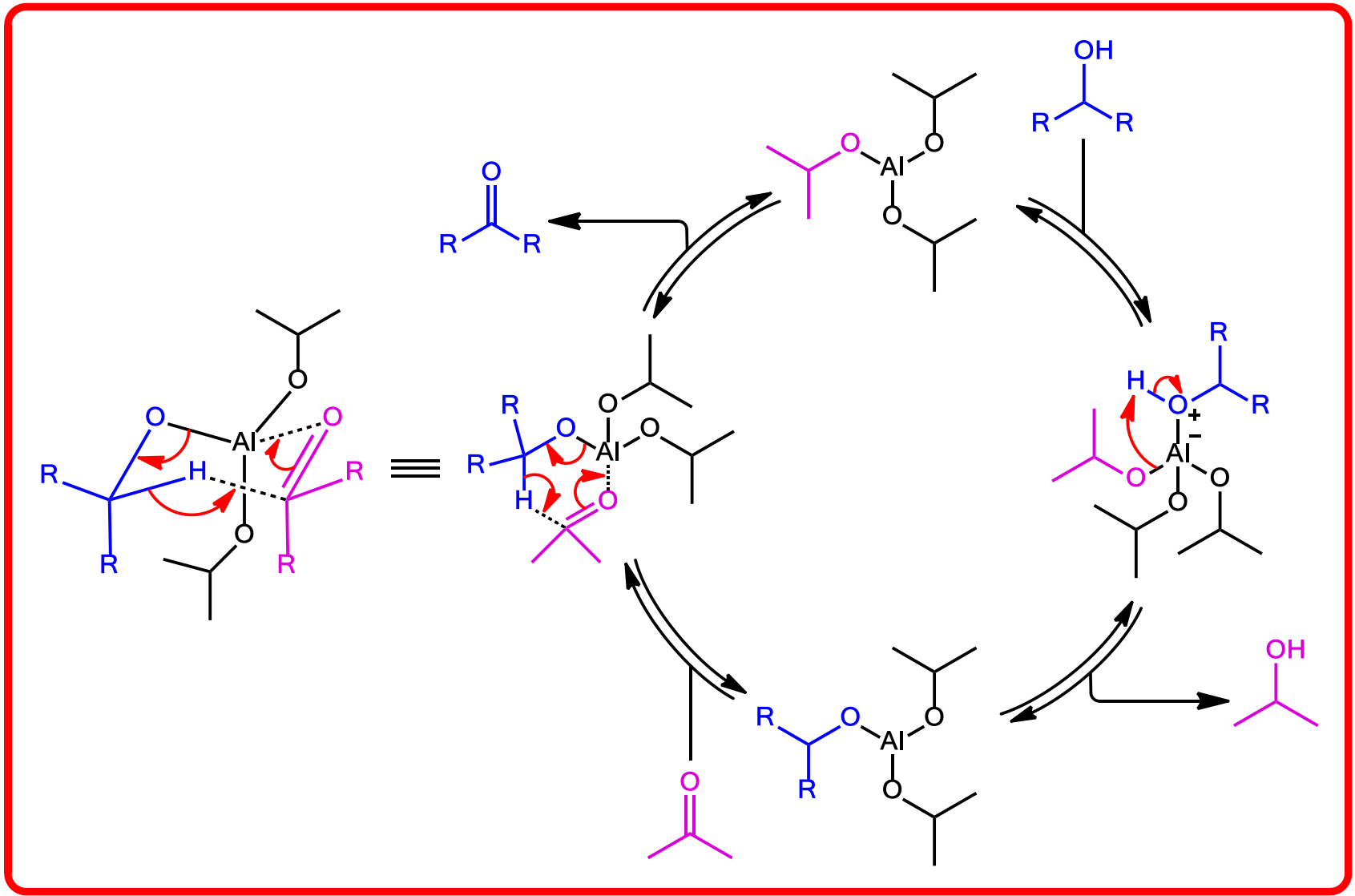
- Excess amount of acetone is used to shift the equilibrium towards right-hand side
- This is a very selective oxidation method as shown below.



Oppenauer oxidation

Aluminum-based reagent Reduction

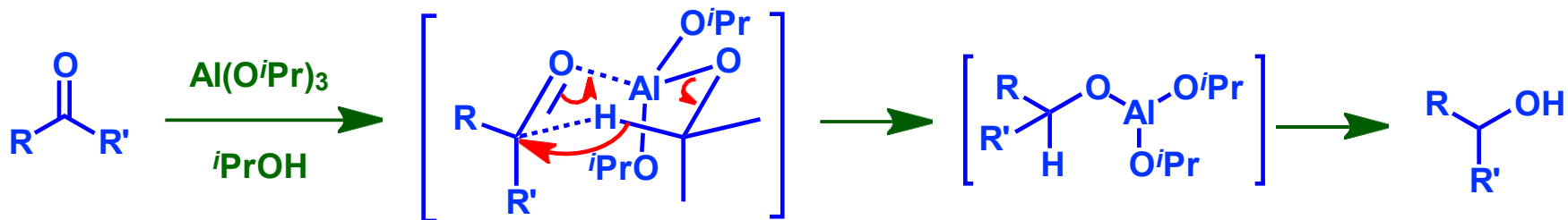
Mechanism



Oppenauer oxidation

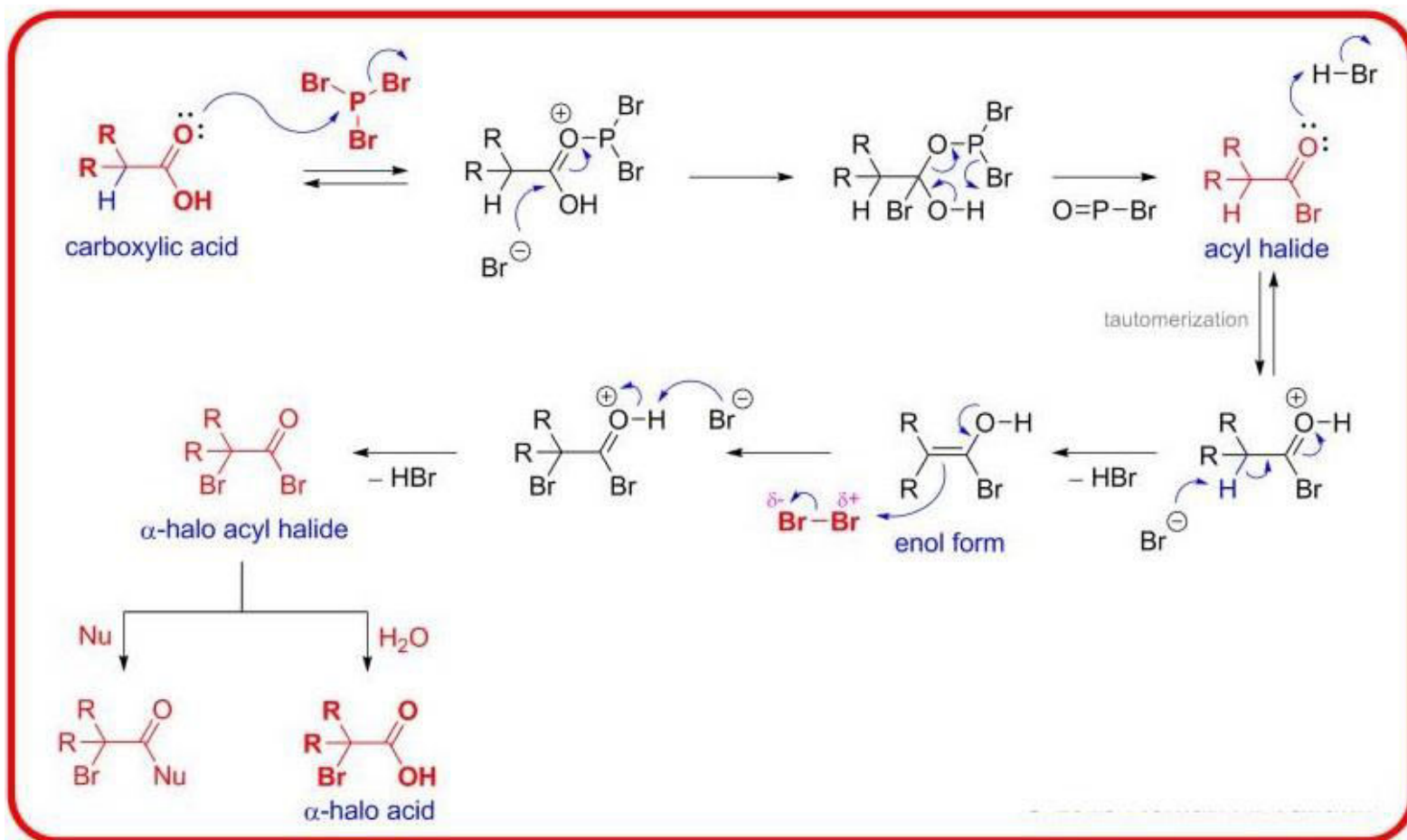
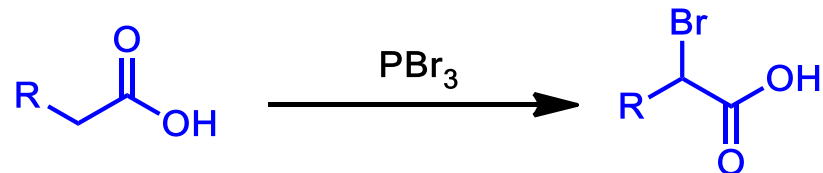
Aluminum-based reagent Reduction

- $\text{Al}(\text{O}^i\text{Pr})_3$ is the reagent
- Acetone accepts the hydride from alcohol and reduced
- By-product is isopropanol
- Reverse process is known as Meerwein-Pondorff-Verley (MPV) Reduction



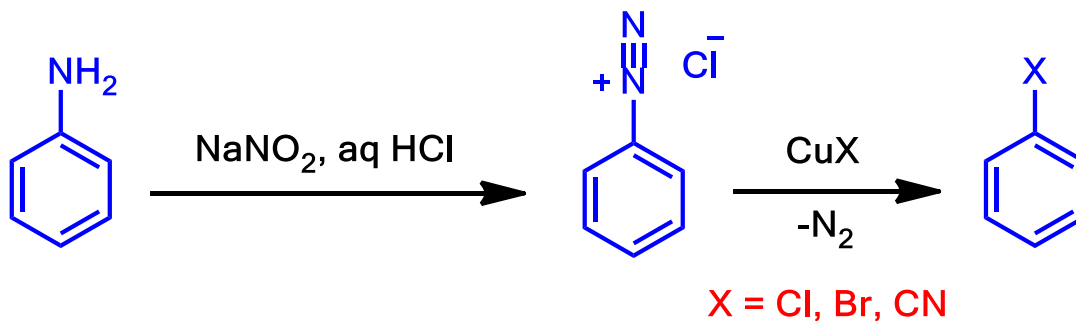
HVZ Reaction

The Hell-Volhard-Zelinsky **halogenation** reaction (HVZ Reaction) halogenates **carboxylic acids** at the **α carbon**.



Sandmeyer Reaction

The Sandmeyer reaction is a radical-nucleophilic aromatic substitution reaction in which an aryl diazonium salt is reacted with a chloride, bromide, or cyanide, using their copper salts as reagents or catalysts affording the corresponding aryl halide or aryl nitrile product. Including all the variations of the Sandmeyer reaction allow the unique transformations on benzene, such as halogenation, cyanation, trifluoromethylation, and hydroxylation.



➤ The most commonly employed Sandmeyer reactions are the chlorination, bromination, cyanation, and hydroxylation reactions using CuCl, CuBr, CuCN, and Cu₂O, respectively.

Chlorination: ArN₂⁺Cl⁻, CuCl, HCl (36% aq.), 50 - 100 °C

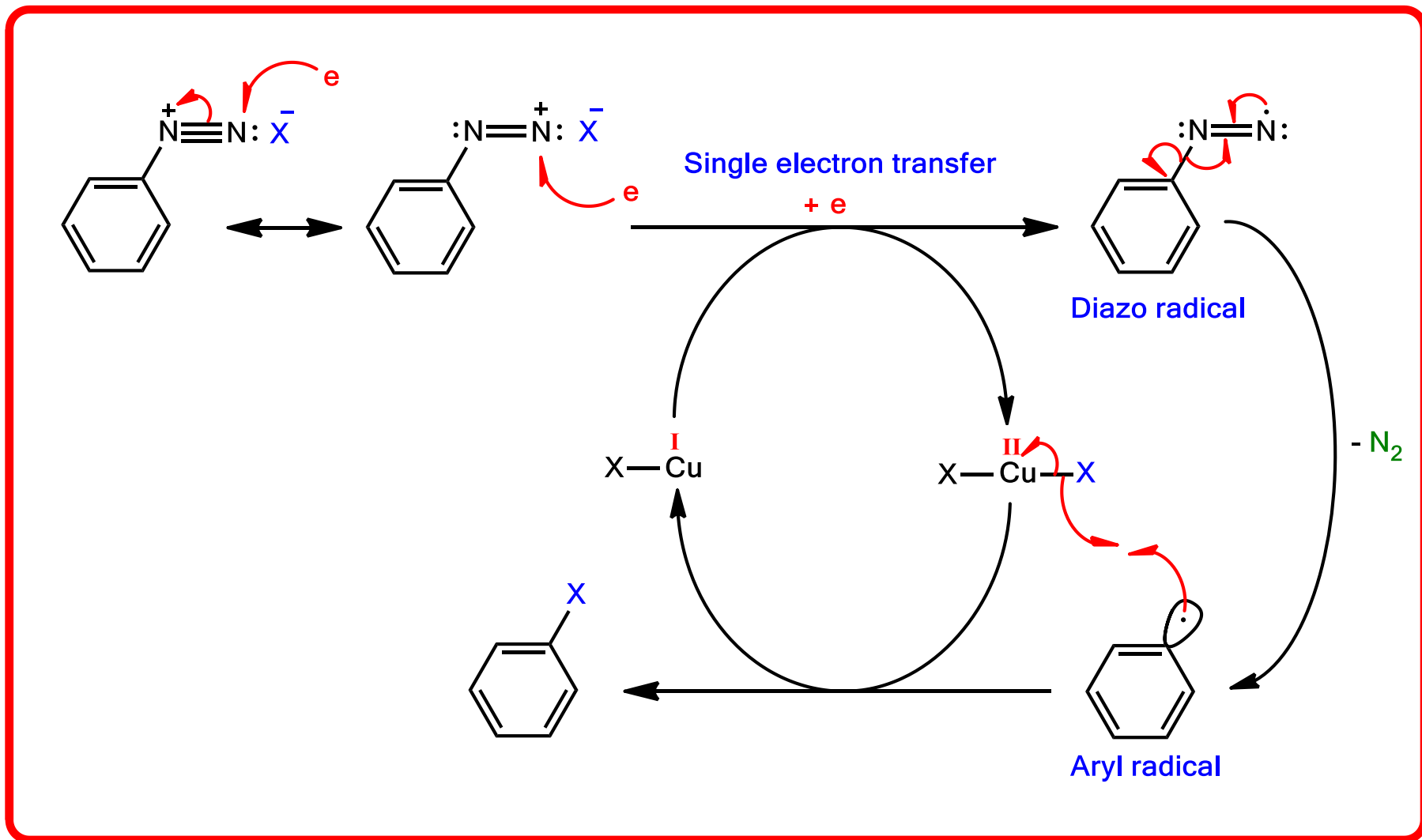
Bromination: ArN₂⁺HSO₄⁻, CuBr, HBr (48% aq.), 50 - 100 °C

Cyanation: ArN₂⁺Cl⁻, CuCN, KCN, H₂O, benzene, 0 °C

Hydroxylation: ArN₂⁺HSO₄⁻, Cu₂O, Cu(NO₃)₂, H₂O, 25 °C.

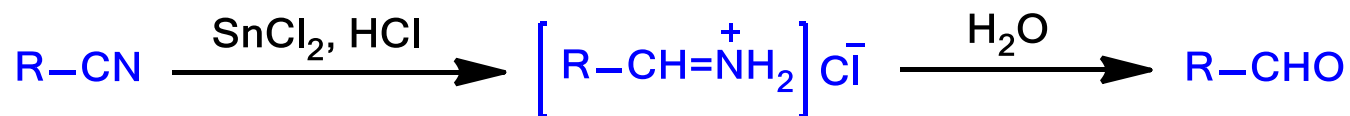
Sandmeyer Reaction

Mechanism

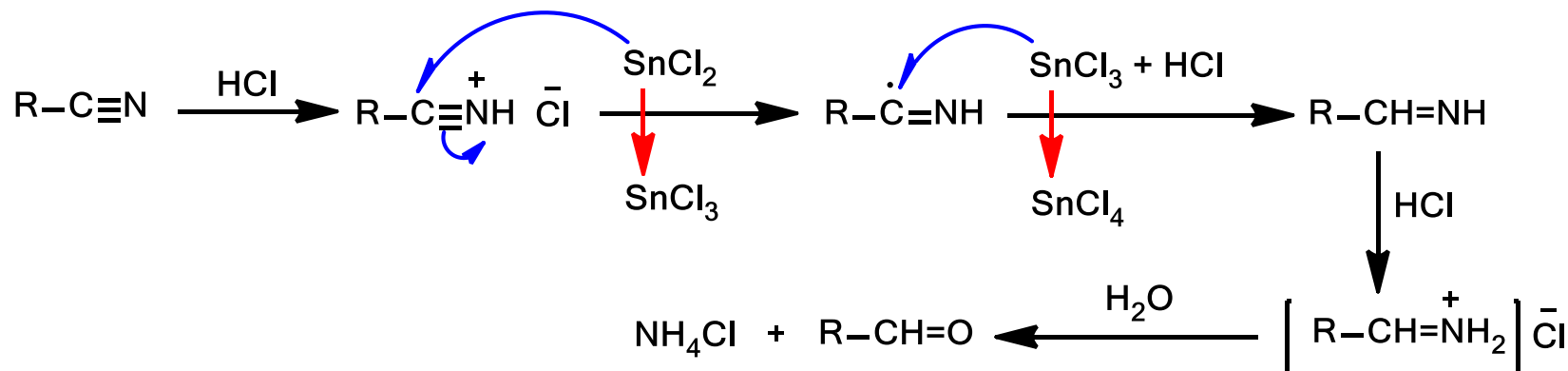


Stephen Reaction

Stephen aldehyde synthesis or Stephen Reaction involves the preparation of aldehydes from nitriles using tin(II) chloride (SnCl_2), hydrochloric acid (HCl) and quenching the resulting iminium salt with water (H_2O).

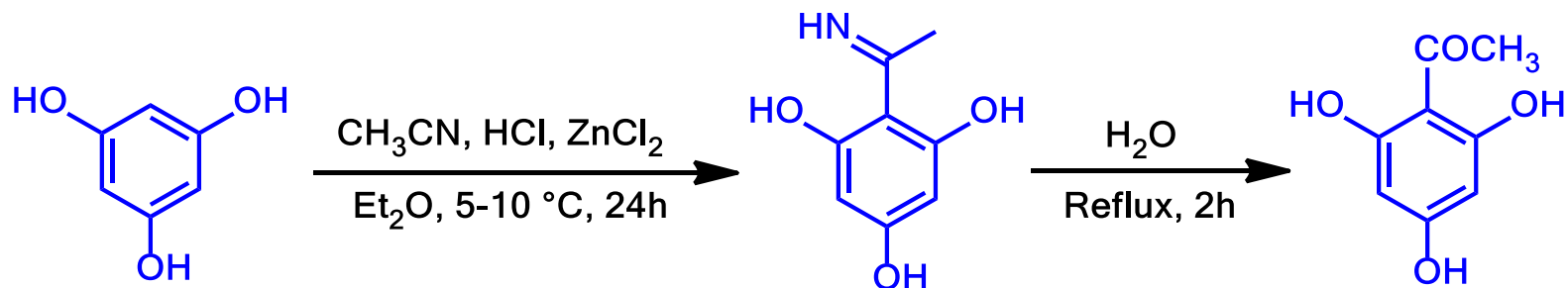


Mechanism

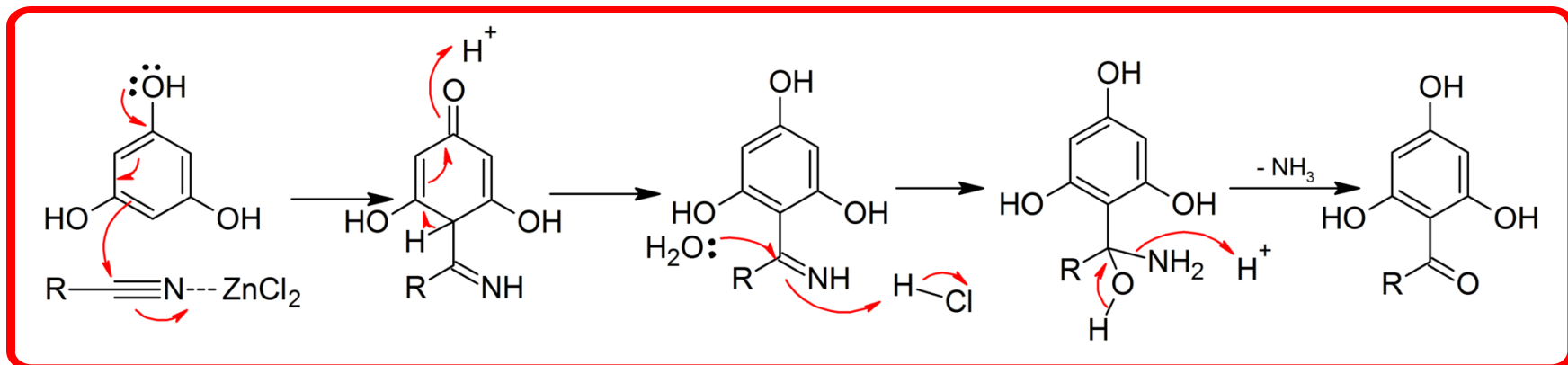


Houben-Hoesch reaction

The Hoesch reaction or Houben-Hoesch reaction is an organic reaction in which an alkylnitrile reacts with an arene compound to form an arylketone. The reaction is a type of Friedel-Crafts acylation in presence of hydrogen chloride and a Lewis acid catalyst. The synthesis of 2,4,6-Trihydroxyacetophenone (THAP) from phloroglucinol is representative.

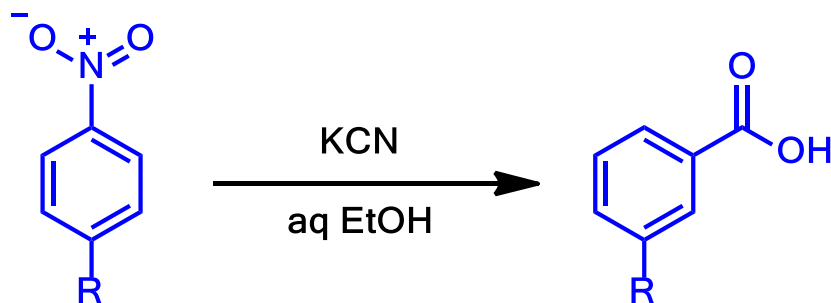


Mechanism



Von Richter reaction

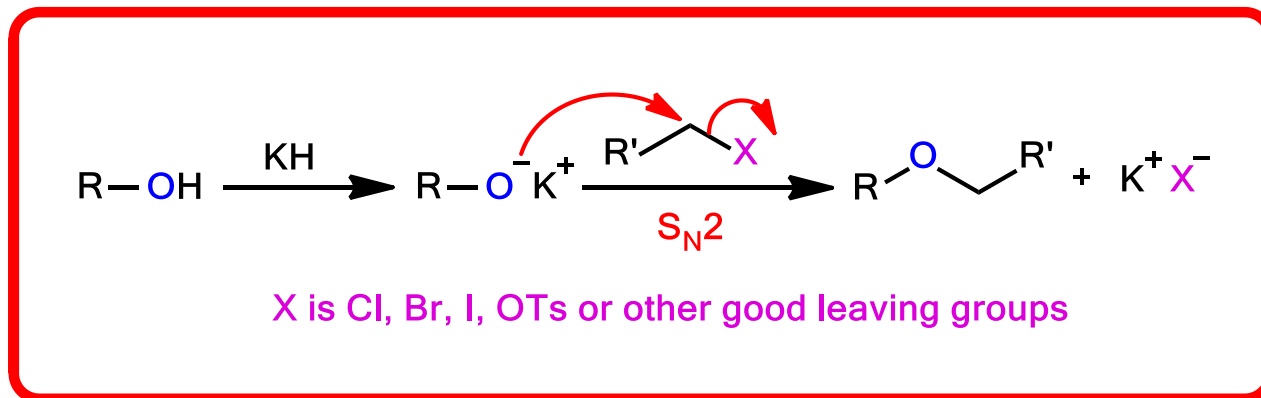
It is the reaction of aromatic nitro compounds with potassium cyanide in aqueous ethanol to give the product of *cine* substitution (ring substitution resulting in the entering group positioned adjacent to the previous location of the leaving group) by a carboxyl group.



➤ Although it is not generally synthetically useful due to the low chemical yield and formation of numerous side products, its mechanism was of considerable interest, eluding chemists for almost 100 years before the currently accepted one was proposed.

Williamson ether synthesis

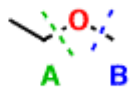
The **Williamson ether synthesis** is an organic reaction used to convert an **alcohol** and an **alkyl halide** to an **ether** using a **base** such as NaOH. The mechanism begins with the base abstracting the proton from the alcohol to form an **alkoxide** intermediate. The alkoxide then attacks the alkyl halide in a **nucleophilic substitution reaction** (S_N2), which results in the formation of the final ether product and a metal halide by-product.



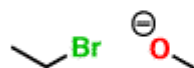
➤ **Primary halides and tosylates work best**, since competitive E2 elimination of HX can occur with more hindered substrates. Hence, unsymmetrical ethers are synthesized by reaction between **the more hindered alkoxide partner and the less hindered halide partner**, rather than vice-versa.

Ethyl Methyl Ether (Methoxyethane)

Two possibilities: "retrosynthetically" break bonds A or B



Possibility A:



S_N2 on primary alkyl halide
- works well!

Possibility B:

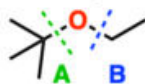


S_N2 on methyl halide -
works well!

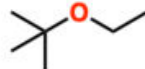
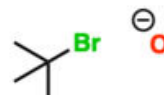
Both of these are perfectly good S_N2 reactions

t-Butyl Ethyl Ether

Two possibilities: "retrosynthetically" break bonds A or B

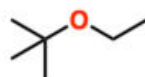


Possibility A:



NOT a good S_N2 - tertiary
alkyl halide.
This will not work!!
(E2 will happen instead)

Possibility B:

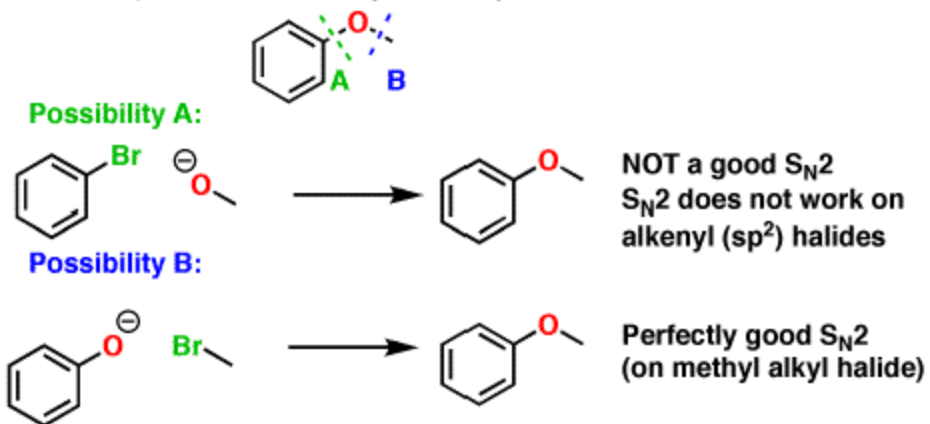


This will work
(primary alkyl halide)

Only one of our two possible Williamsons works here

Phenyl Methyl Ether

Two possibilities: "retrosynthetically" break bonds A or B



Only one of our two possible Williamsons works here

Acknowledgement:

The material has been developed with the help of different text books, journal material and web help.