Organic Chemistry III
Core-VI

# Molecular Rearrangements and Named Reactions

Dr. Samim Akhtar

Dept. of Chemistry
Bidhan Chandra College Asansol

# Molecular Rearrangements

# Molecular Rearrangements

- Rearrangment reactions are an interesting class of reactions wherein a group or an atom migration 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

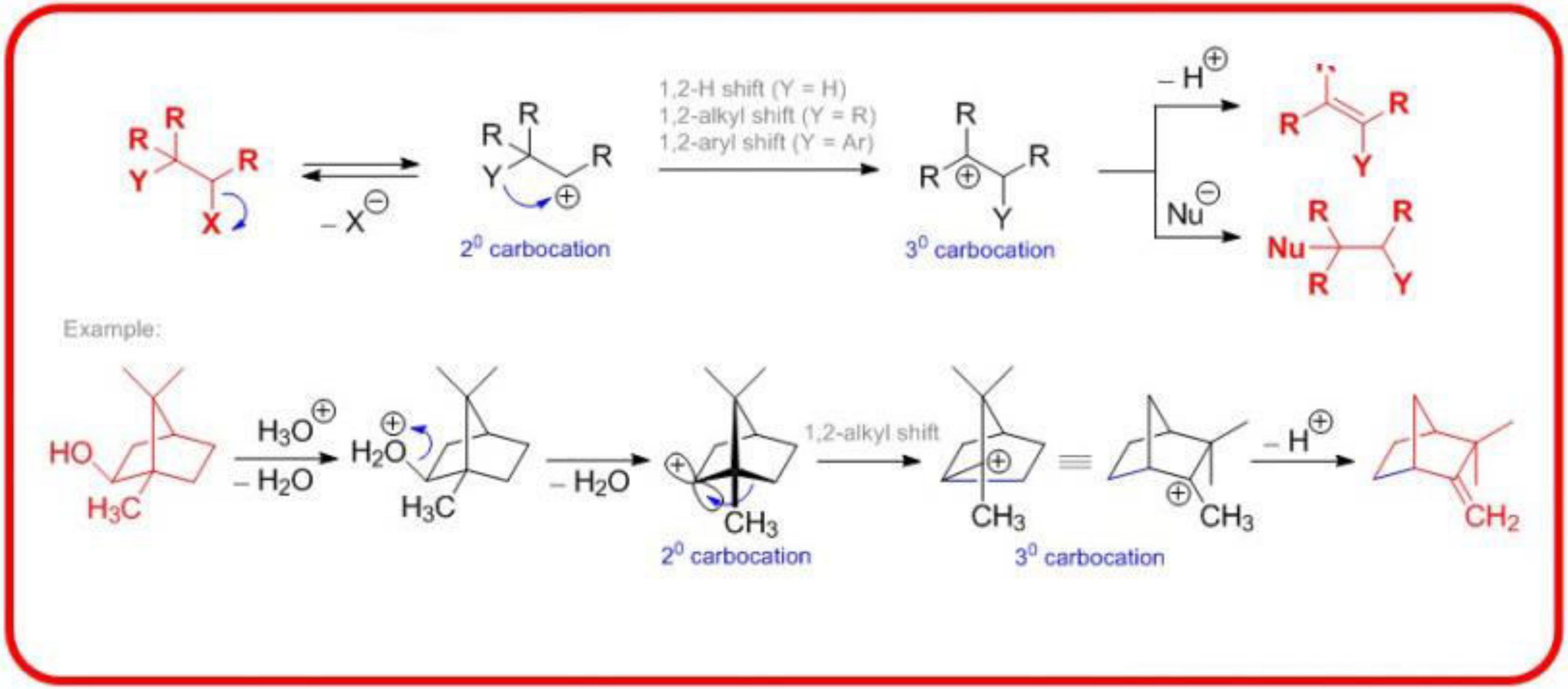
- Rearrangement reactions involve the migration of a group or an atom from one center (**migration origin**) to another (**migration terminus**) within the same molecule.
- In this module, various rearrangement reactions are presented. These rearrangements can be roughly classified on the basis of the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

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

# Rearrangements to Electron Deficient Carbon

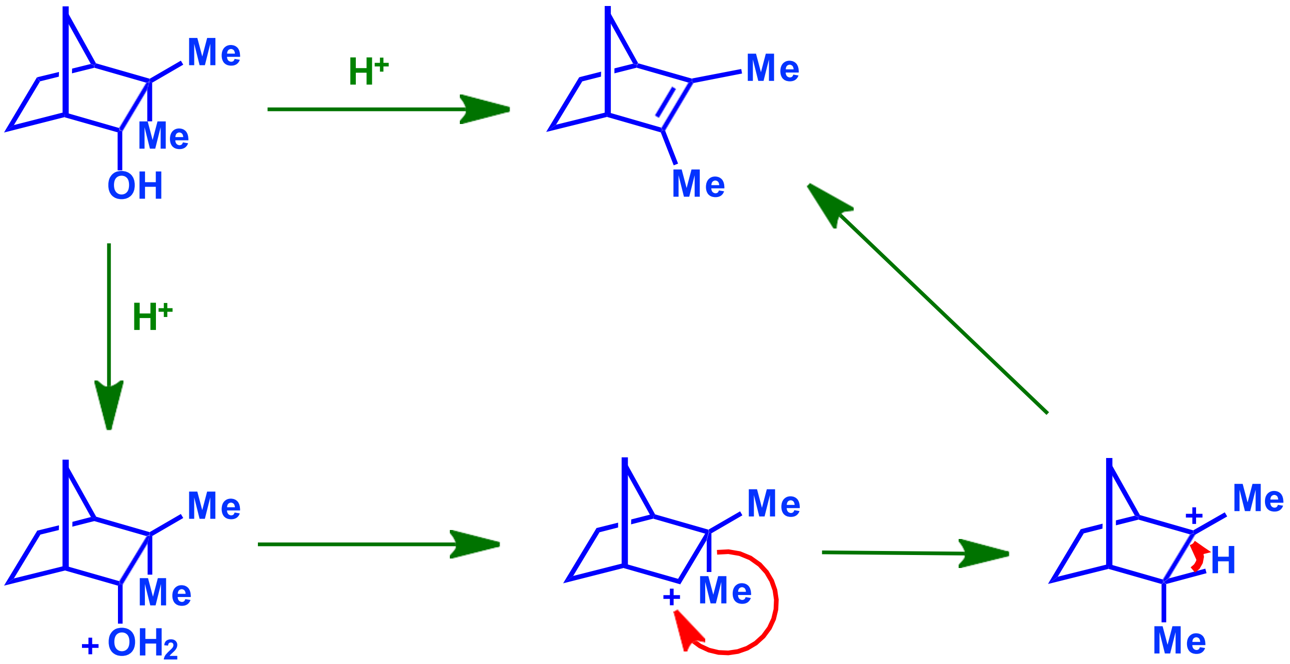
# Wagner-Meerwin Rearrangement

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



# Wagner-Meerwin Rearrangement

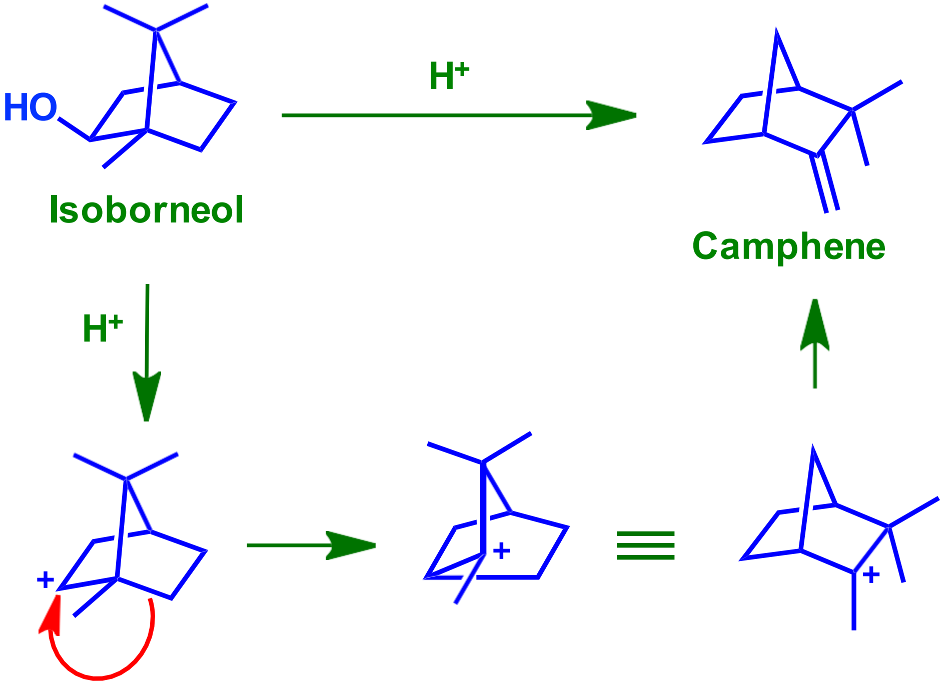
- Rearrangement of alcohols under acidic condition



- 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



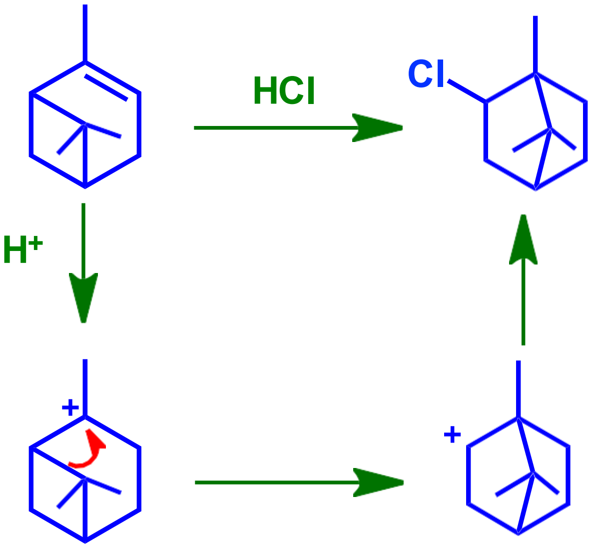
# Ring Expansion

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

3°> 2°> 1°

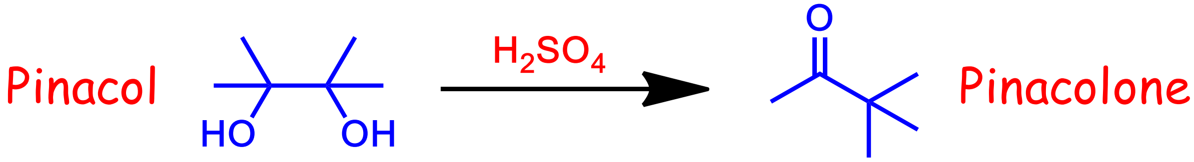
Can we go from 3° to 2° ??

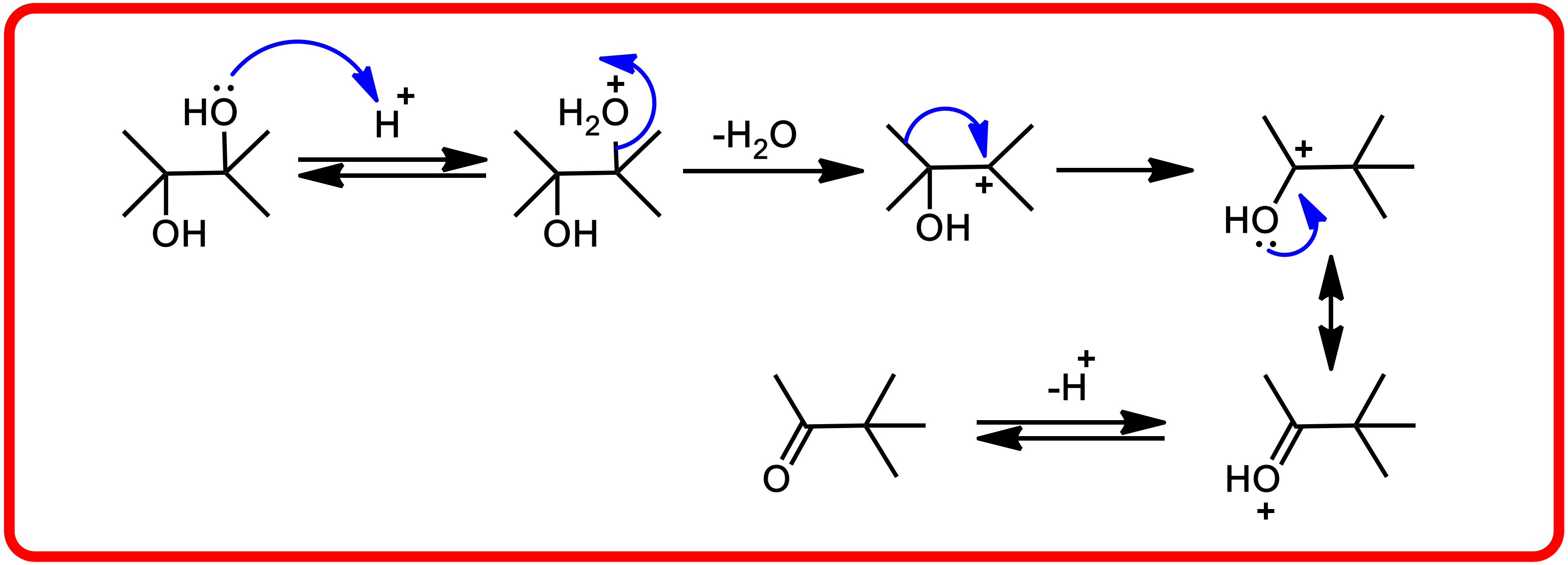
- Cations can be made more stable if they become less strained



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

# Pinacol-Pinacolone Rearrangement





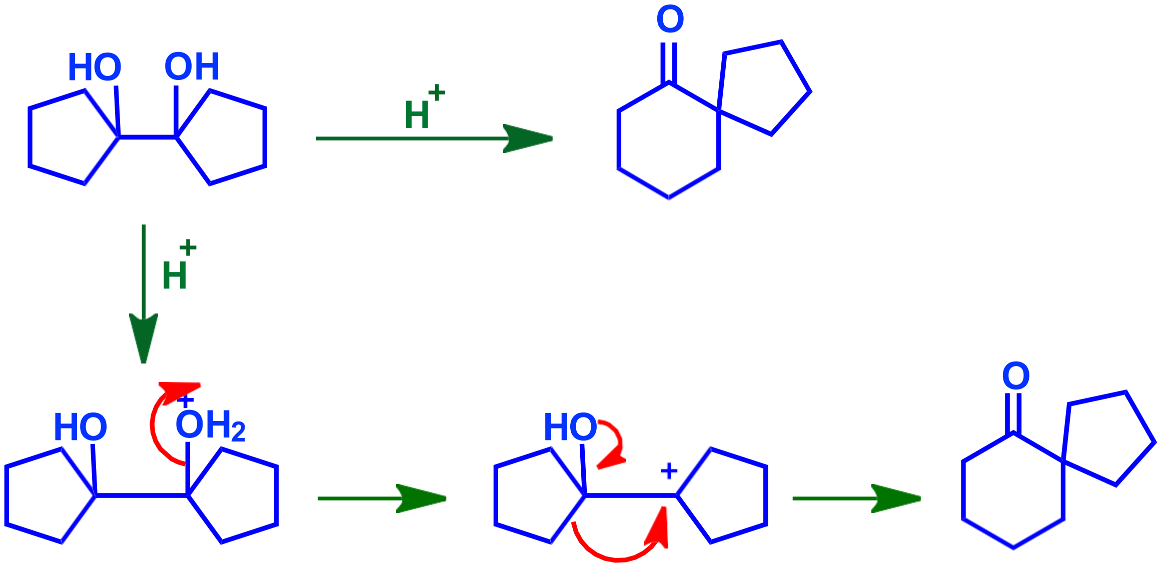
- Carbocation is already tertiary
- There is no ring strain
- Then why should it rearrange?

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

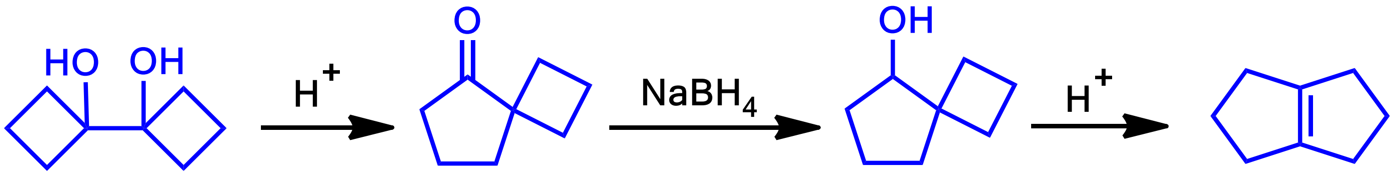
# Pinacol-Pinacolone Rearrangement

- 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:

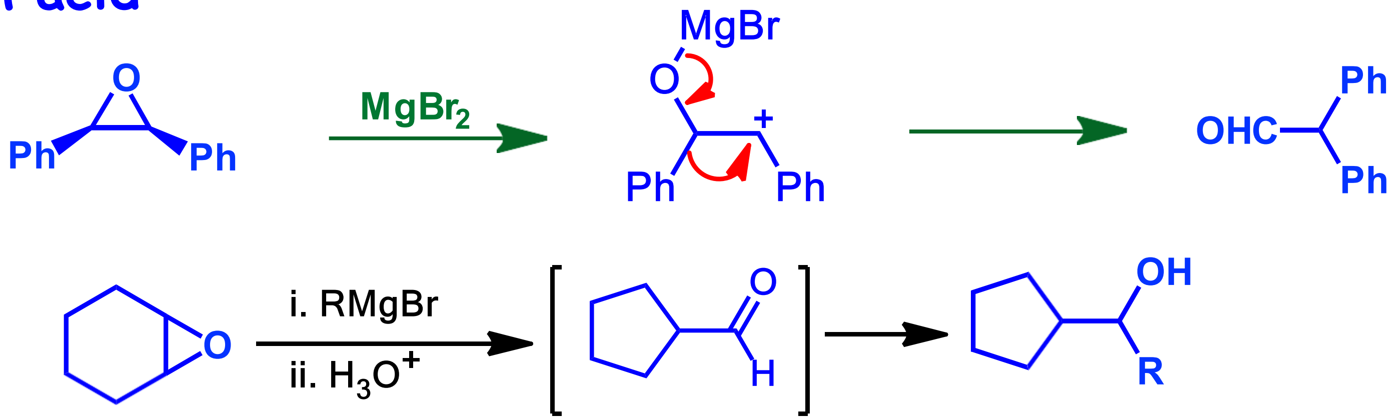


# Pinacol-Pinacolone Rearrangement



## Epoxides :

Epoxides also undergo pinacol type rearrangement on treatment with acid

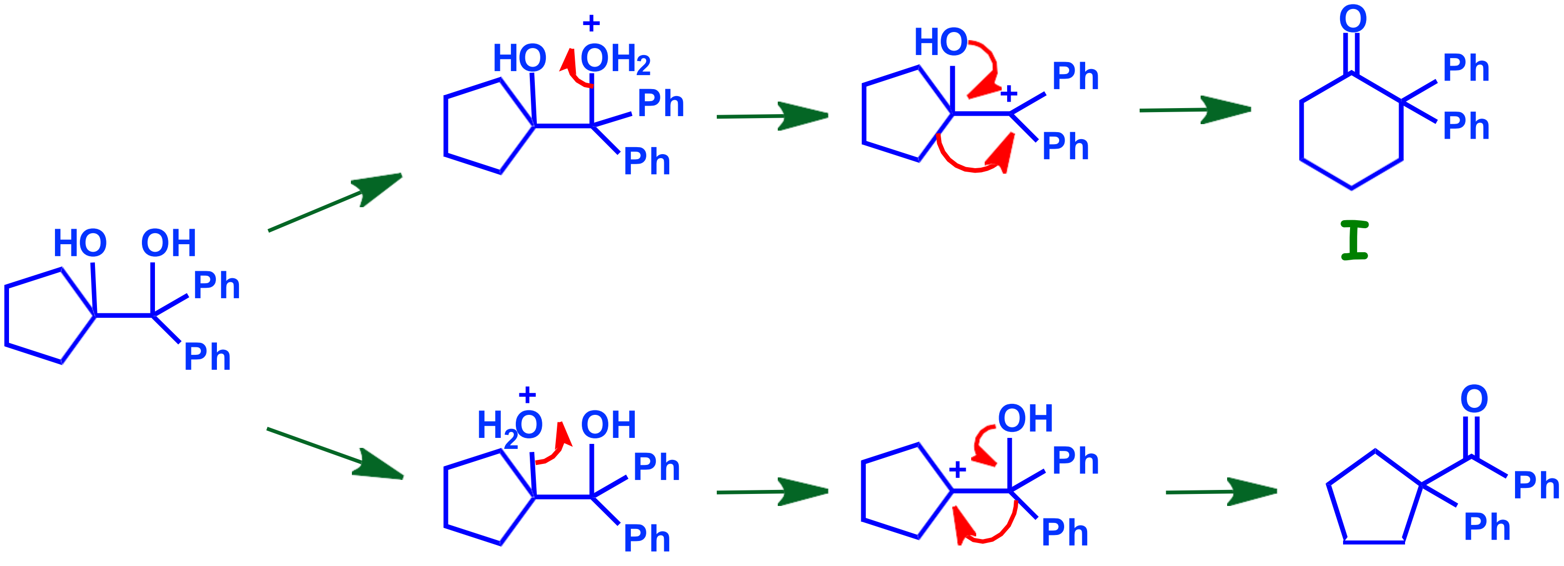


- With a Grignard reagent, rearrangement occurs faster than neucleophilic attack to the epoxide

# 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



**I**

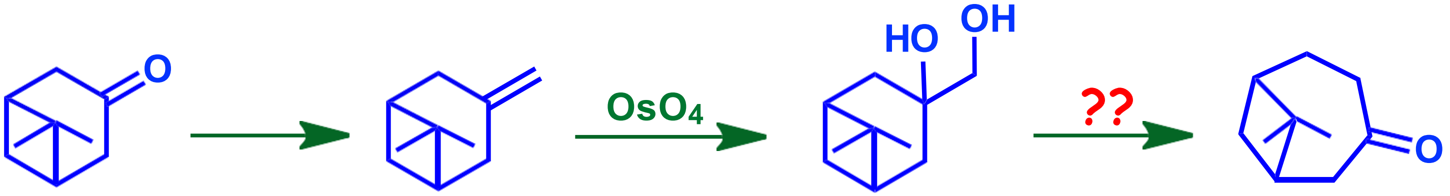
**II**

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

# Pinacol-Pinacolone Rearrangement

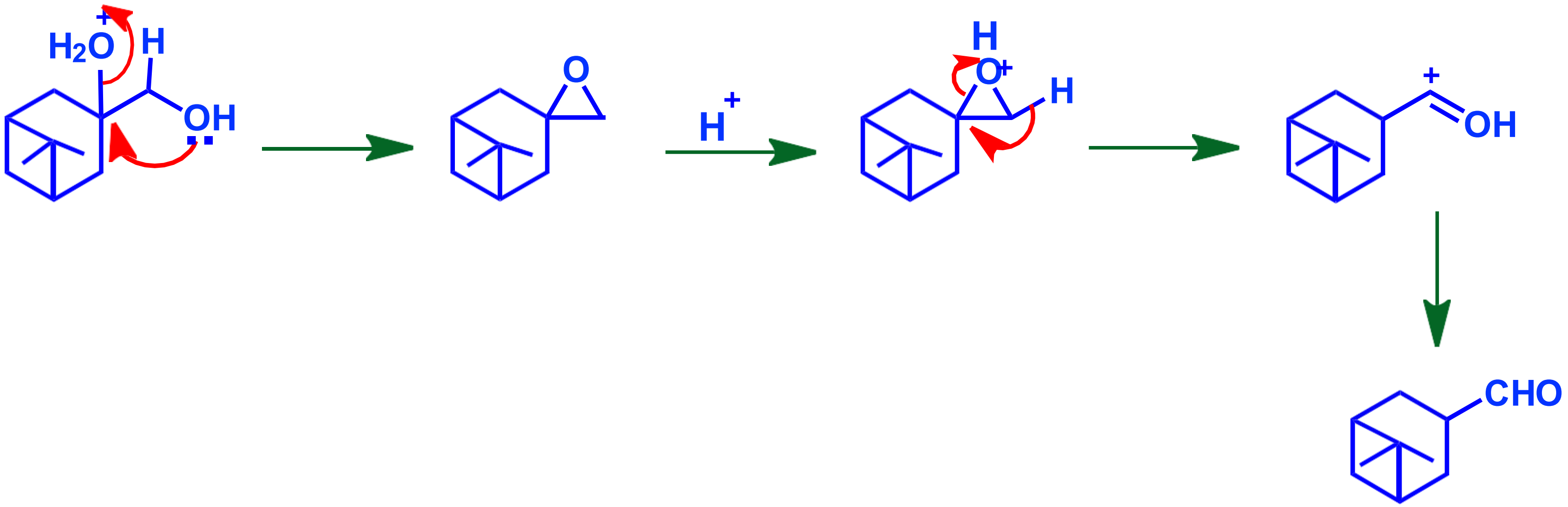
## Semipinacol Rearrangement

### They are nothing but pinacol rearrangement without choice



Isonopinone

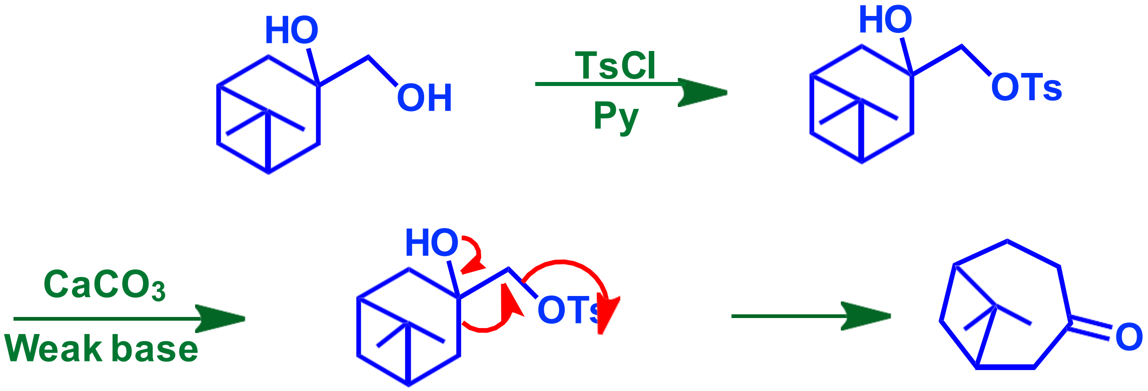
### Under normal acidic conditions



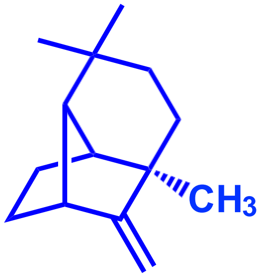
# Pinacol-Pinacolone Rearrangement

## Semipinacol Rearrangement

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

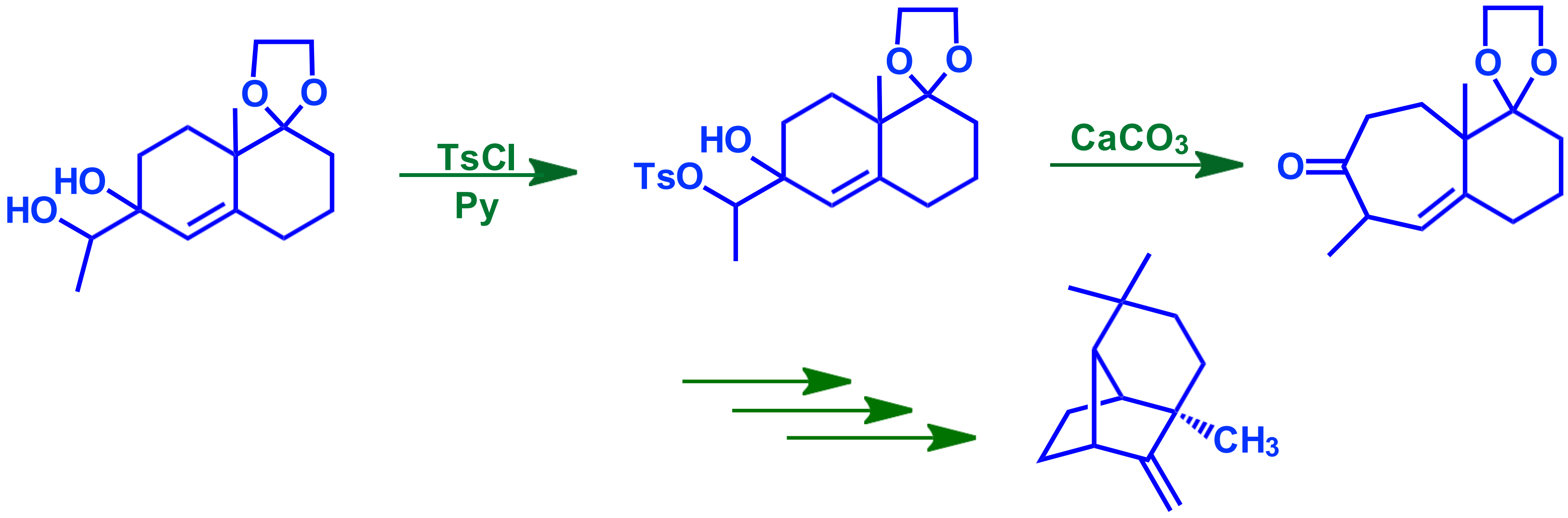


Corey exploited a similar sequence in the synthesis of longifolene



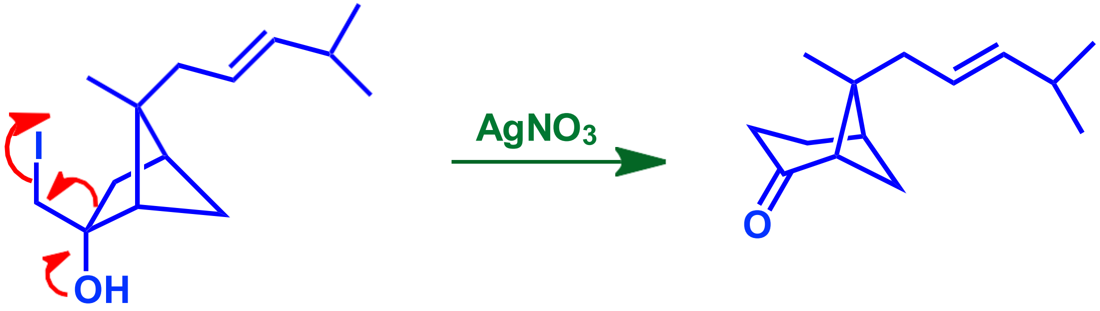
# Pinacol-Pinacolone Rearrangement

## Semipinacol Rearrangement



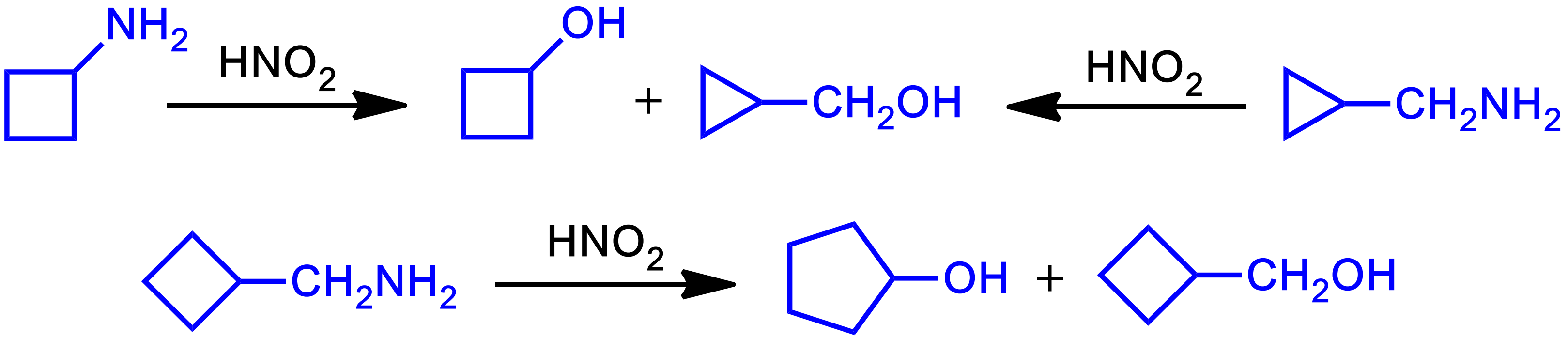
Longifolene

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



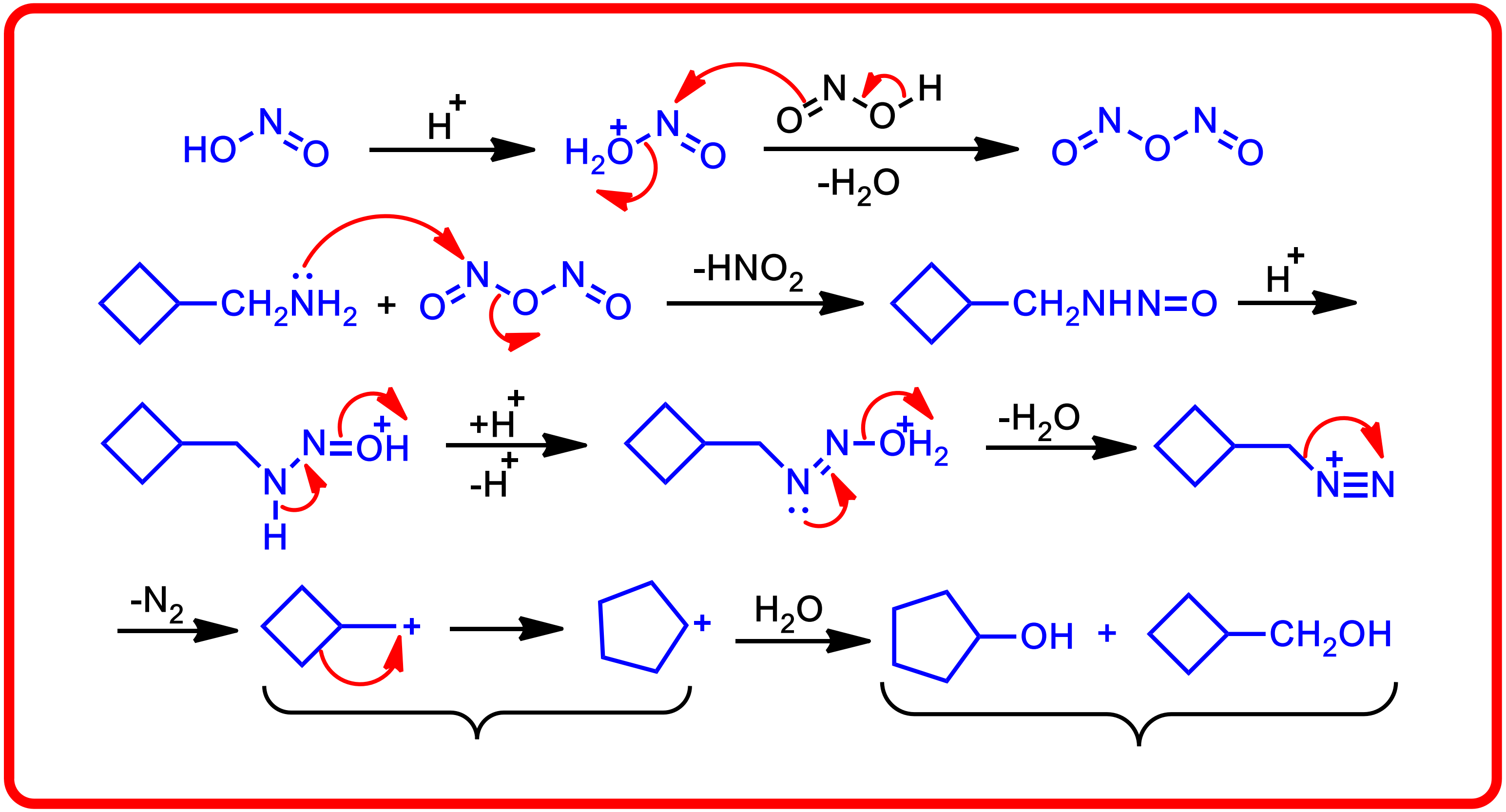
# Demjanov Rearrangement

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

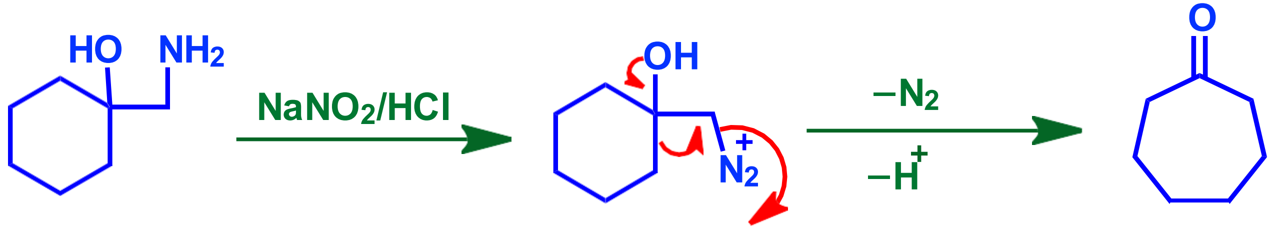


These reactions in which a carbocation is generated by diazotization is called Demjanov rearrangement.

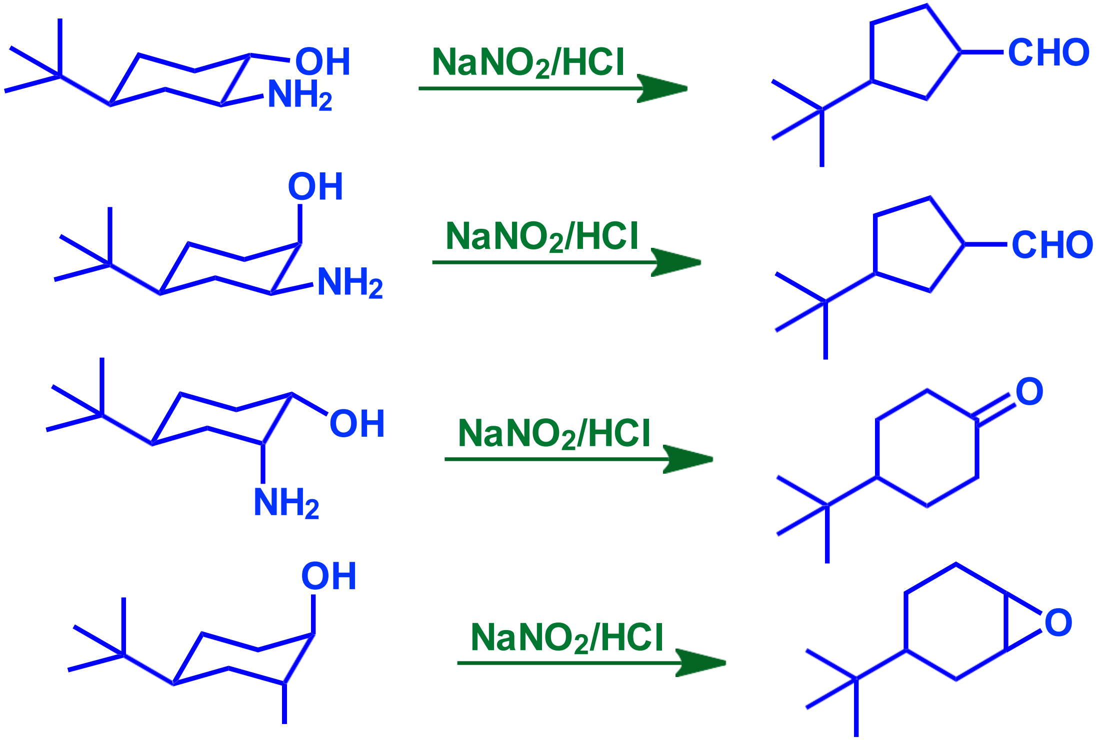
## Mechanism:


HO–N=O
H⁺
$H_2\overset{+}{O}$–N=O
O=N–O–H
-$H_2O$
O=N–O–N=O
$CH_2NH_2$
+
-$HNO_2$
$CH_2NHN=O$
H⁺
$N=\overset{+}{O}H$
N–H
+H⁺
-H⁺
$N-\overset{+}{O}H_2$
N
-$H_2O$
$\overset{+}{N}\equiv N$
-$N_2$
+
+
$H_2O$
OH
+
$CH_2OH$

**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**



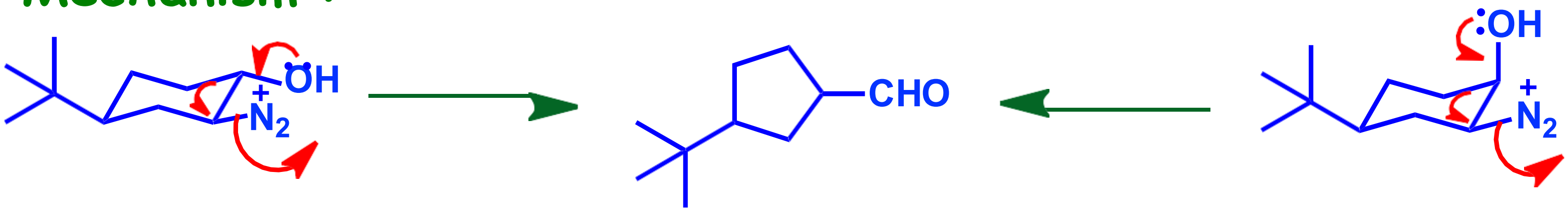
**Selectivity :**



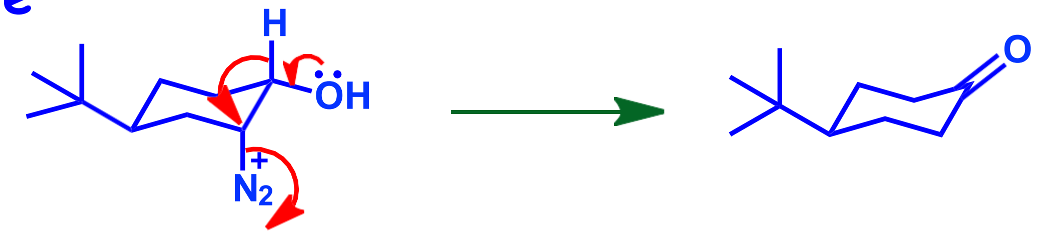
# Tiffeneau-Demjanov Rearrangement

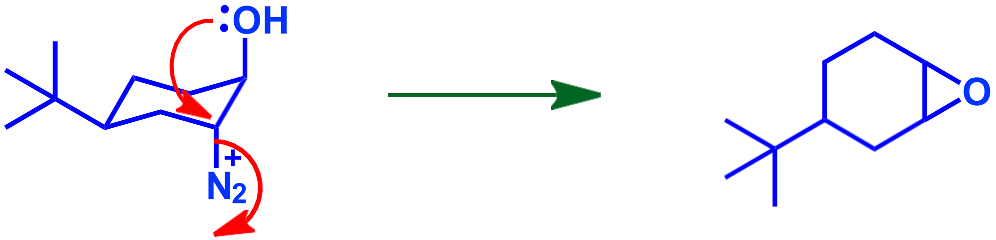
## Diazonium salts

**Mechanism :**



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





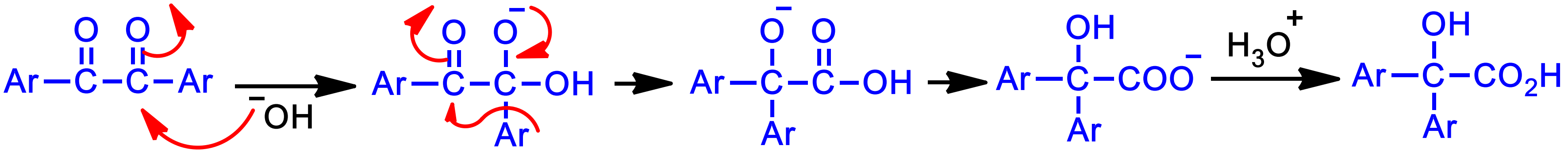
- These reactions are known to work better with four to eight membered ring systems as compared to the analogous Demjanov rearrangement.

# Benzilic acid Rearrangement

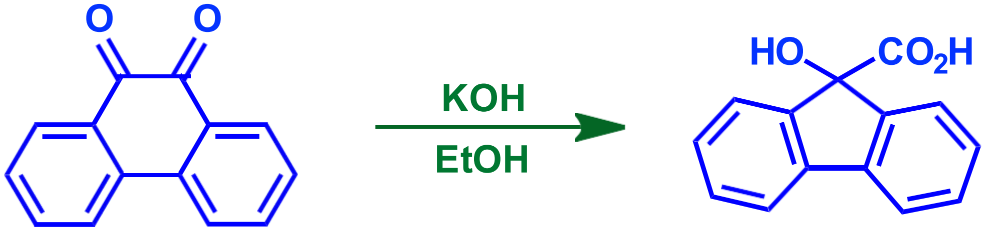
Benzil  Benzilic acid

$$C_6H_5-\overset{O}{\overset{\|}{C}}-\overset{O}{\overset{\|}{C}}-C_6H_5 \xrightarrow[\text{EtOH},\,\Delta]{\text{KOH}} C_6H_5-\underset{C_6H_5}{\underset{|}{\overset{OH}{\overset{|}{C}}}}-COOH$$

**Mechanism:**



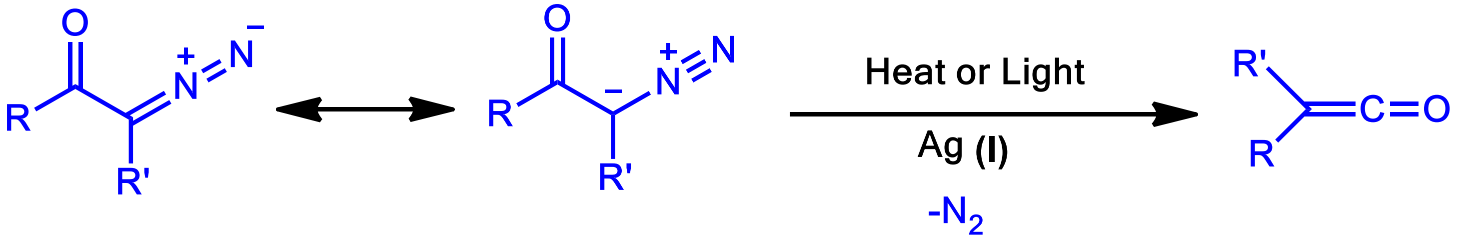
**Formation of stable carboxylate salt is driving force for the reaction**



**Application has been limited only to aromatic α-diketones**

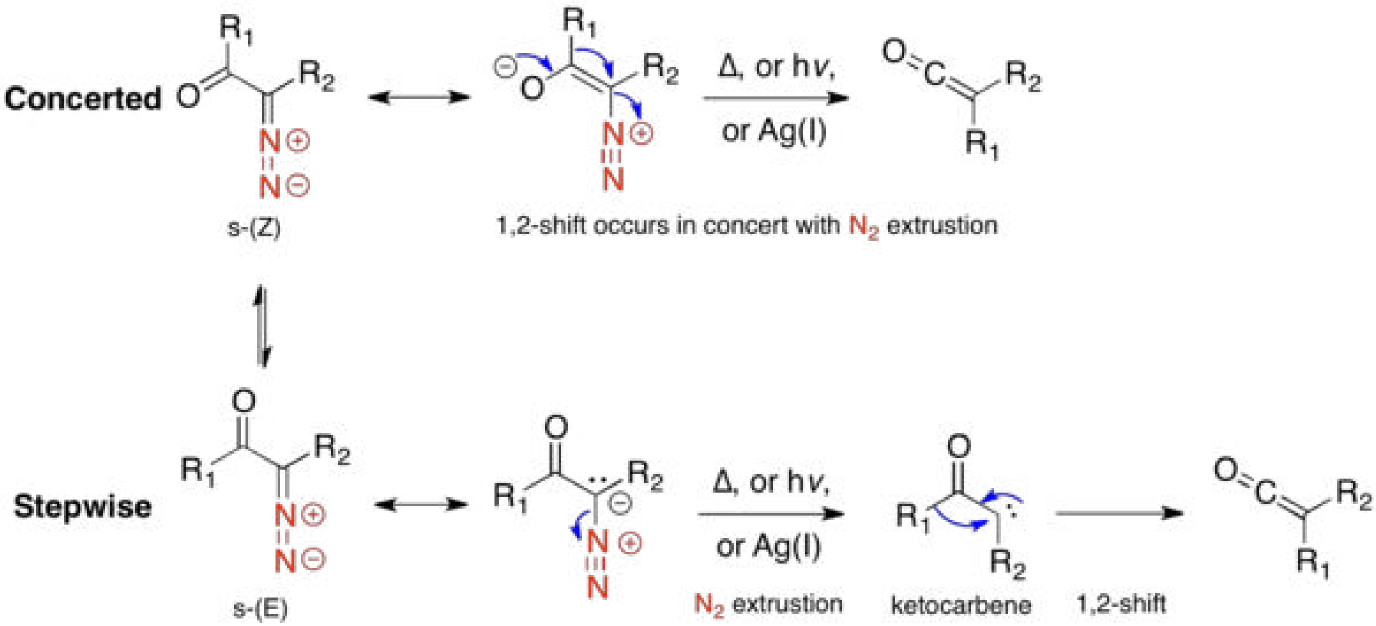
# Wolff Rearrangement

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.

## Mechanism :

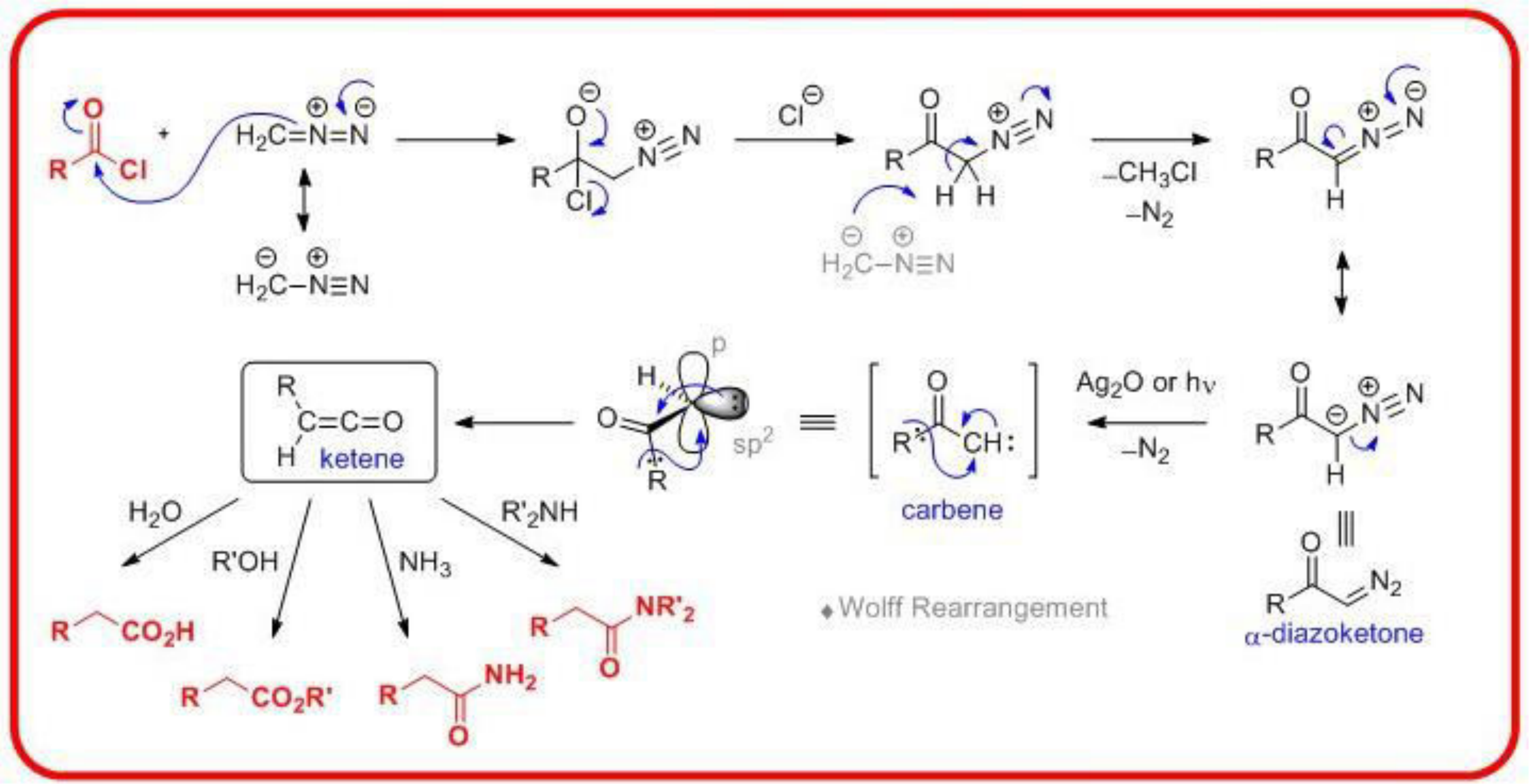


- The reaction follows the course depending on whether the reaction is carried out under thermal or photochemical condition. In the photochemical pathway the reaction is supposed to proceed through carbene intermediate in stepwise mechanism, while in thermal pathway the reaction preferentially follows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

- 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.

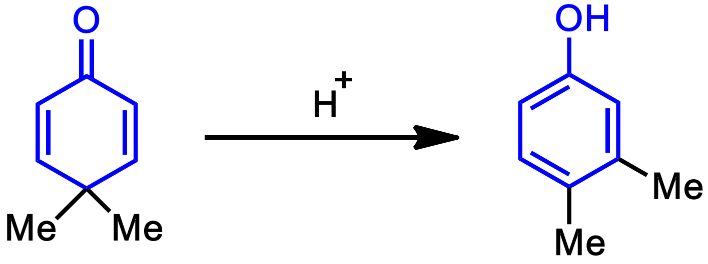
$$\mathrm{RCOOH} \xrightarrow{\mathrm{SOCl_2}} \underbrace{\mathrm{RCOCl} \xrightarrow[\mathrm{Ag_2O}]{\mathrm{CH_2N_2}} \mathrm{RCH{=}C{=}O}}_{\text{Wolff Rearrangement}} \xrightarrow{\mathrm{H_2O}} \mathrm{RCH_2COOH}$$

# Mechanism :


H2C=N=N
H2C−N≡N
Cl⊖
−CH3Cl
−N2
Ag2O or hν
−N2
carbene
sp2
p
ketene
R C=C=O H
H2O
R'OH
NH3
R'2NH
R CO2H
R CO2R'
R NH2
R NR'2
Wolff Rearrangement
α-diazoketone

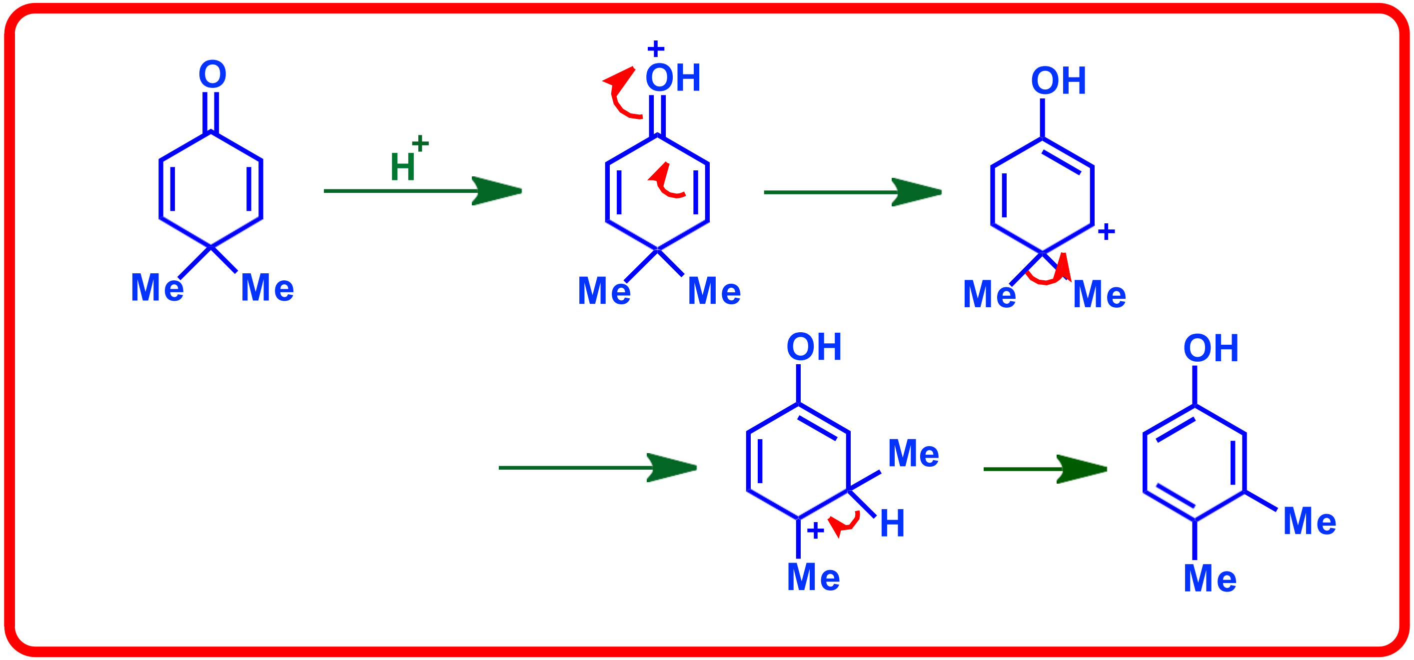
# Dienone-Phenol Rearrangement

Dienone



Phenol

**Mechanism:**



# Dienone-Phenol Rearrangement

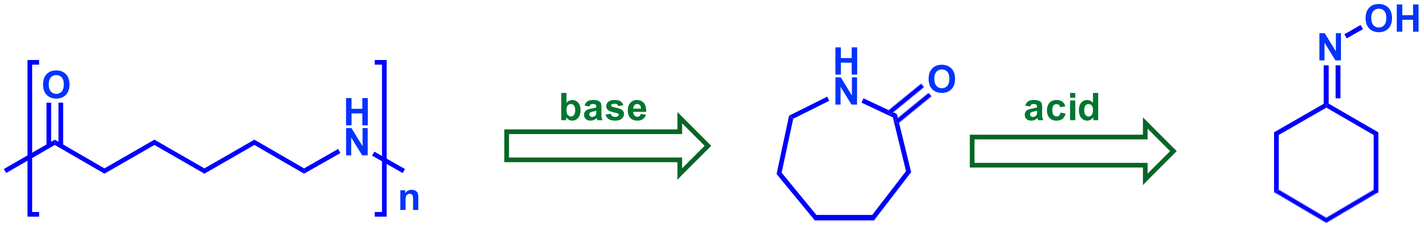
Example:

- 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 Oxygen

# Beckmann Rearrangement

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

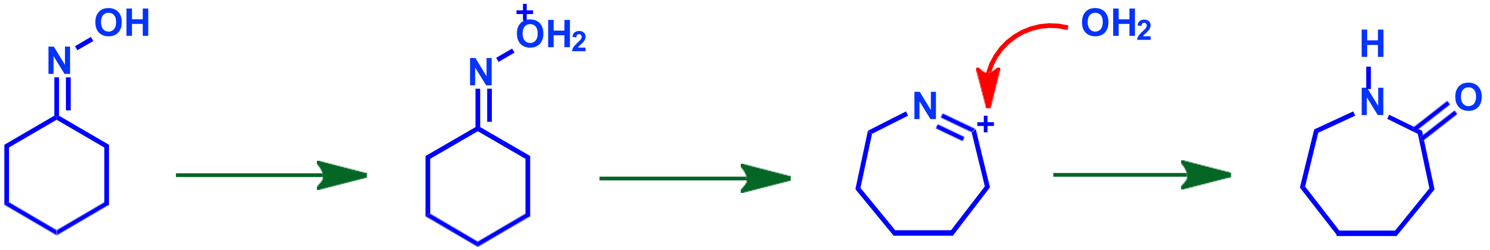


oxime

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

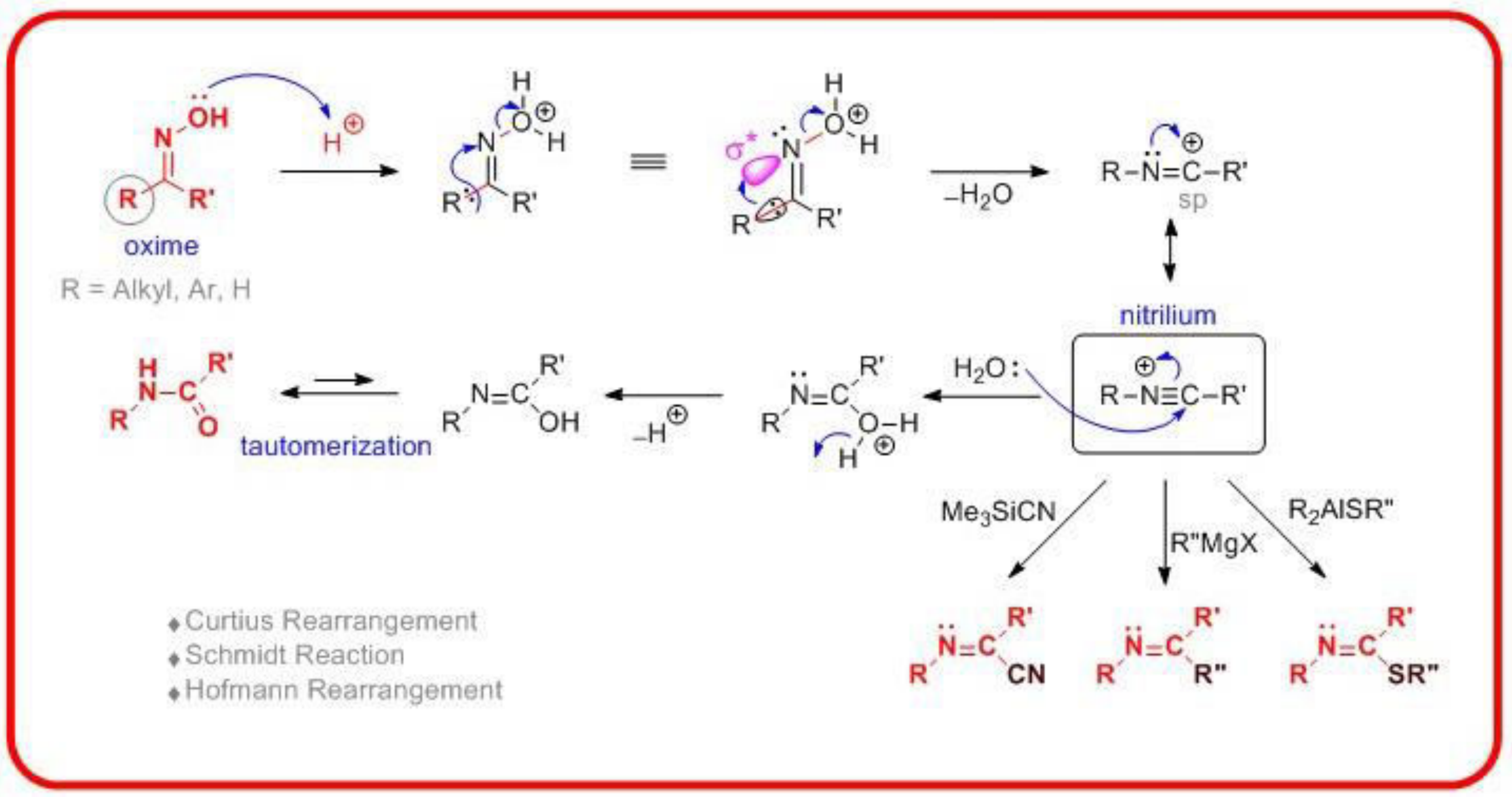
# Beckmann Rearrangement

## 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

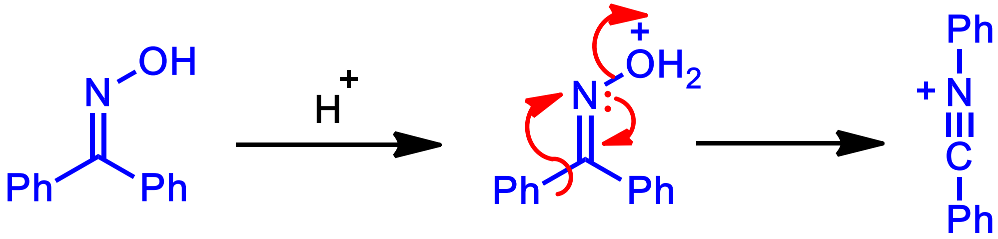
# Beckmann Rearrangement



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

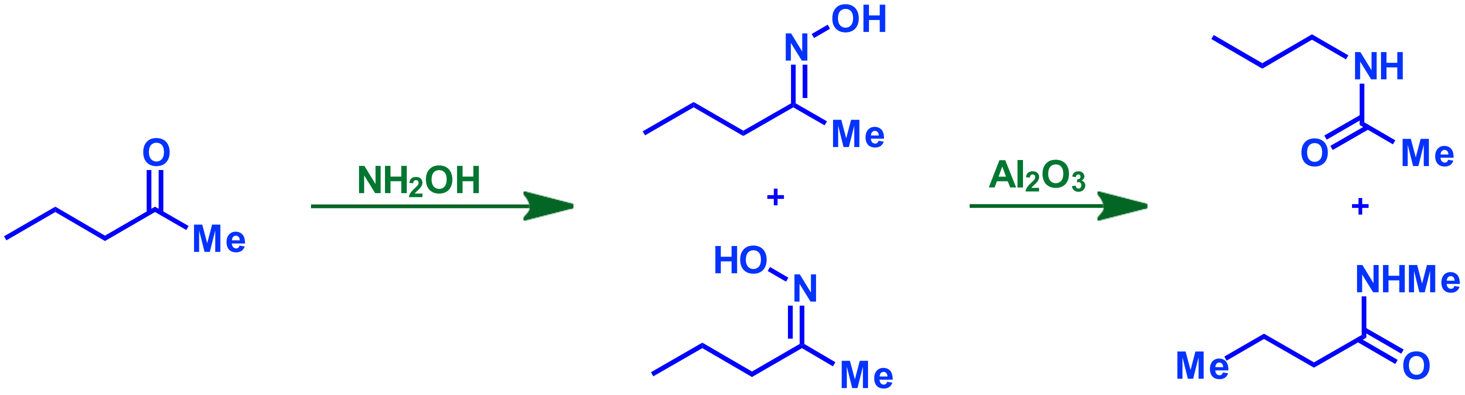
# Beckmann Rearrangement

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



Nitrilium ion

## Migratory Aptitude:



major

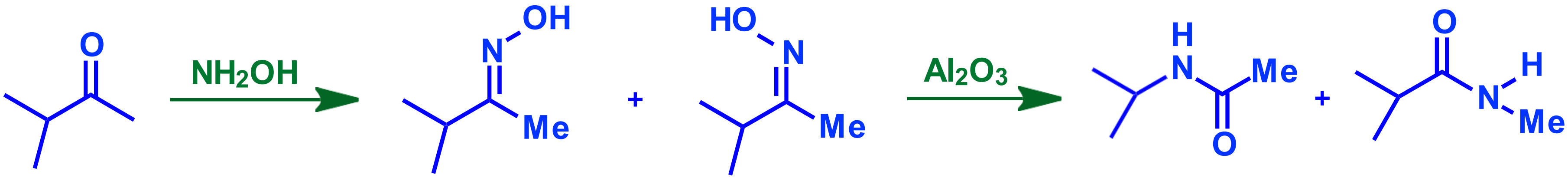
minor

# 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

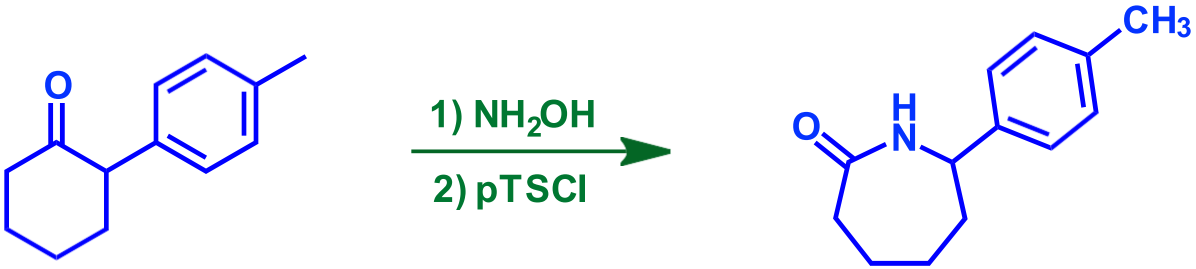
# Beckmann Rearrangement



86 : 14

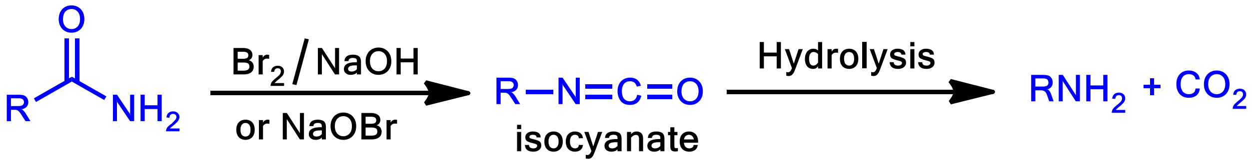
Steric effect

88 : 12



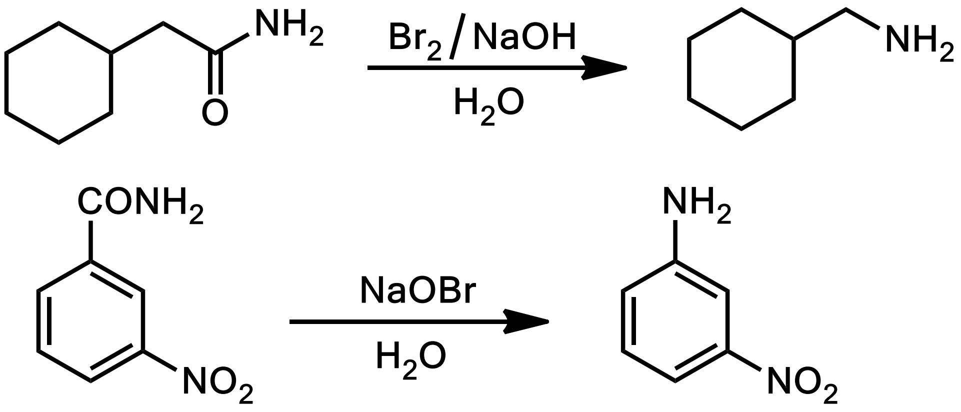
# Hofmann Rearrangement

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



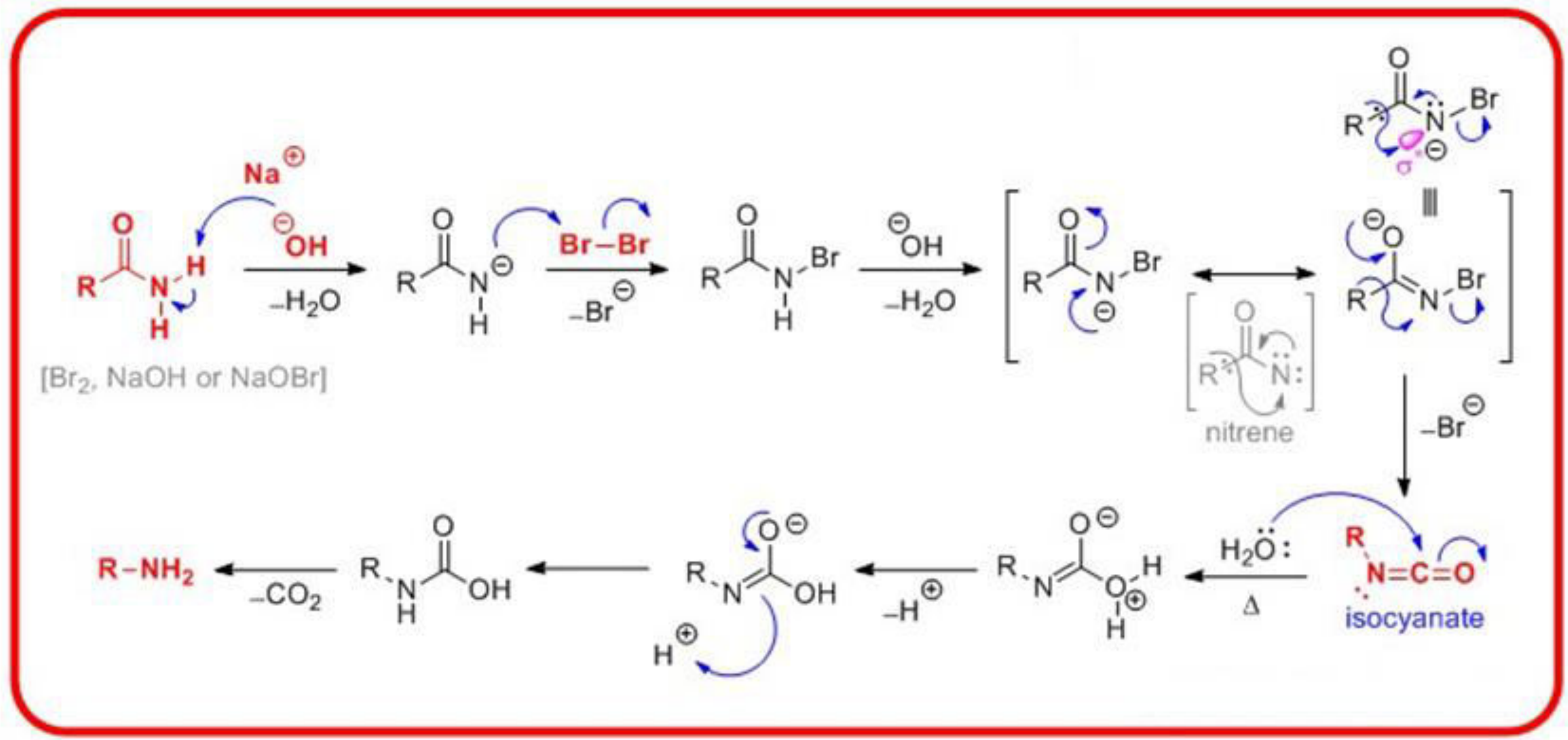
- R in this reaction can be alkyl or aryl.

Examples



# Hofmann Rearrangement

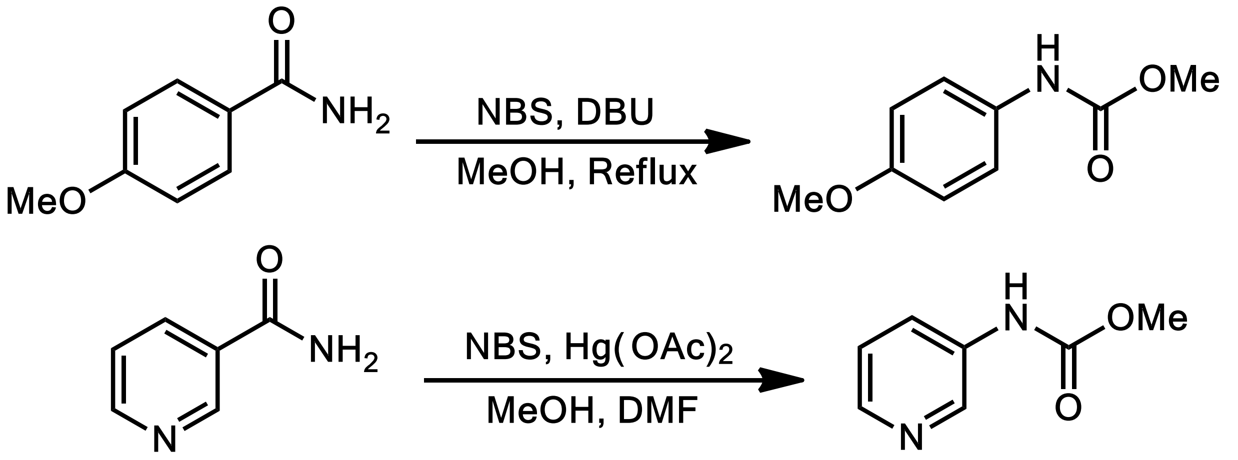
## Mechanism:



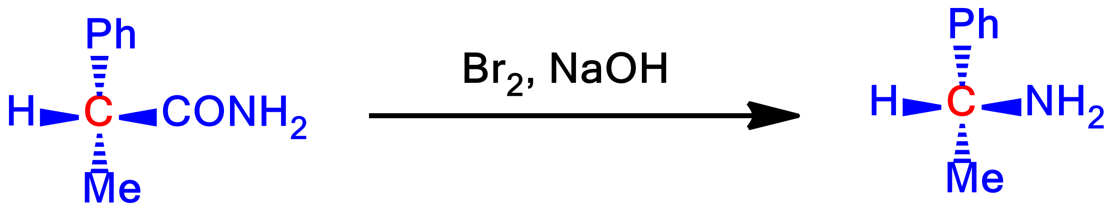
- ➢In the first step, base removes a proton from amide. The conjugate base of amide, thus formed, reacts with bromine to give N-bromoamide. Acidity of proton on nitrogen is increased by this bromine atom and its removal followed by 1,2-shift of alkyl group gives corresponding isocyanate. This isocyanate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



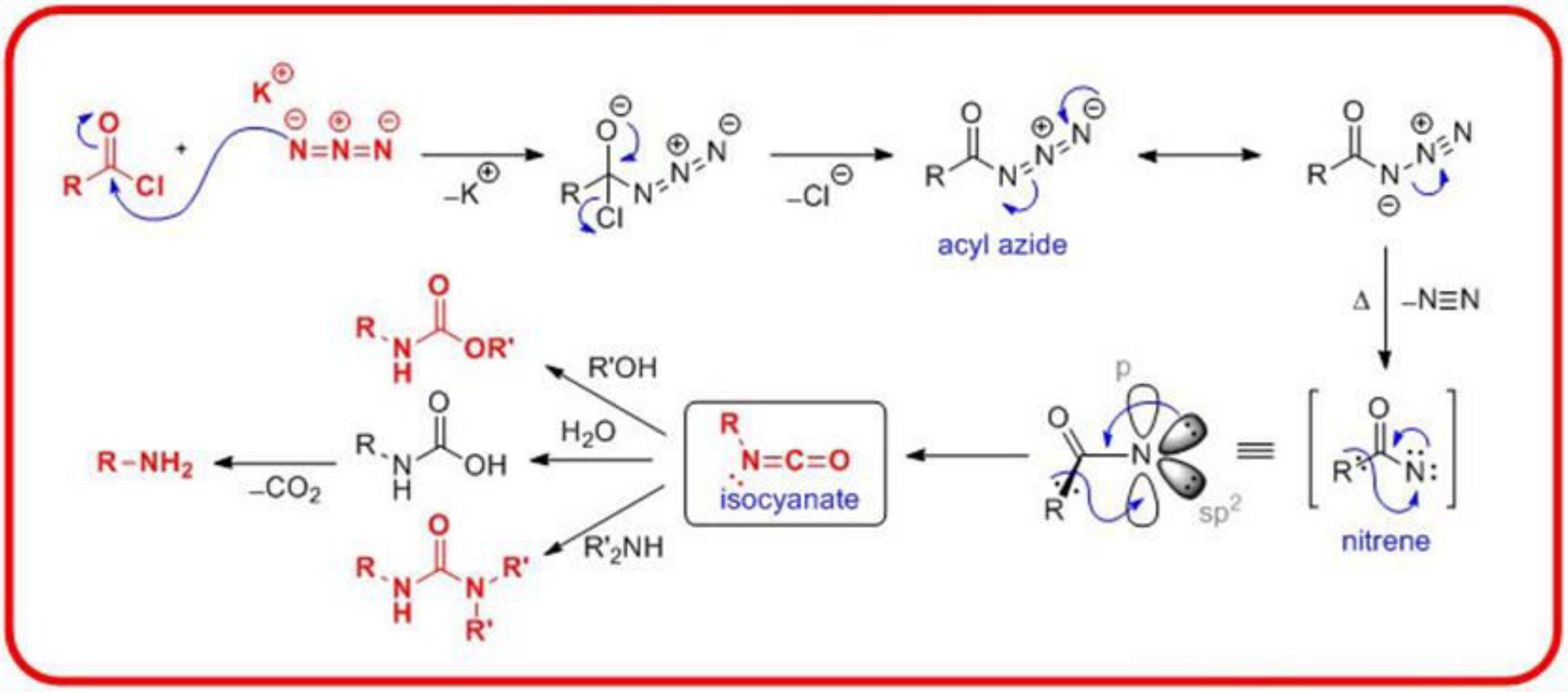
- When optically active α-phenylpropionamide undergoes Hofmann degradation, α- phenylethylamine of same configuration and optical purity: retention of configuration.



# 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.

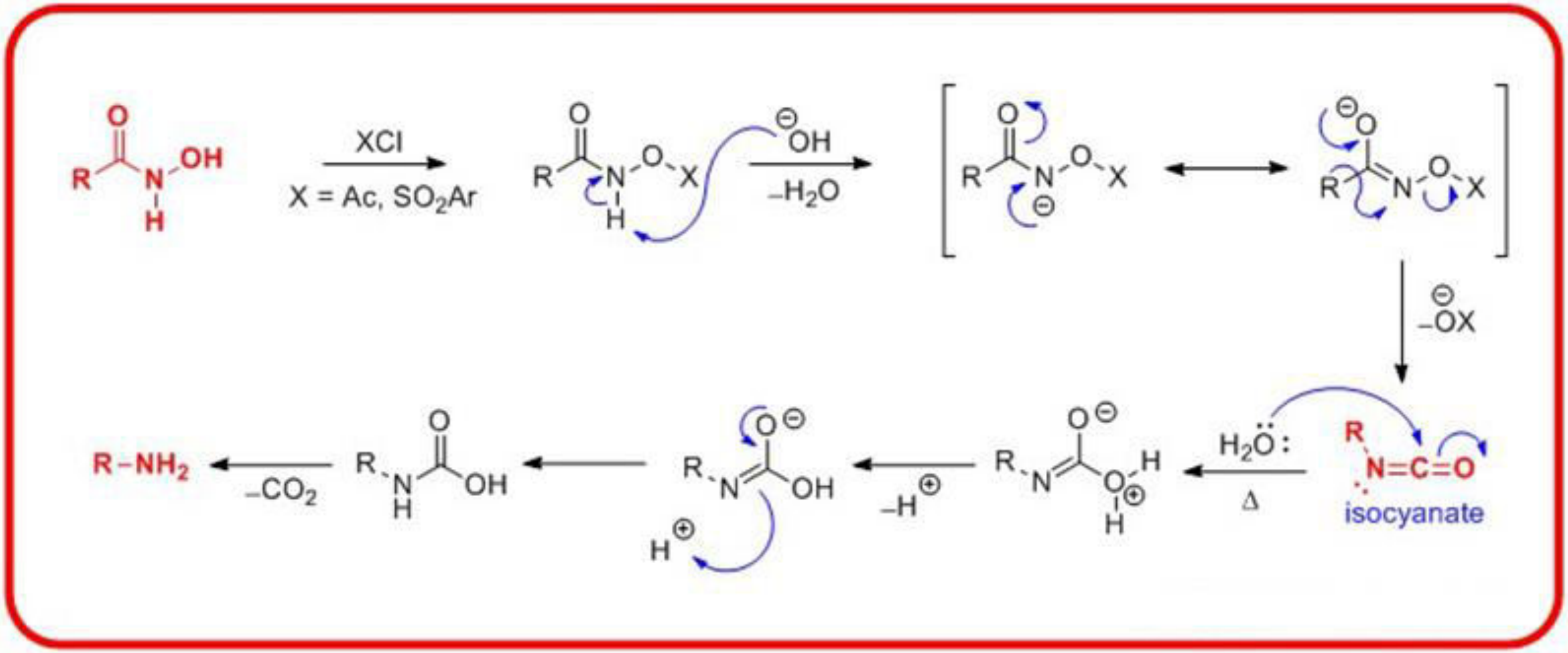
**Mechanism:**



# Lossen Rearrangement

- O-acyl derivatives of hydroxamic acids on heating with a base concerts 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:**

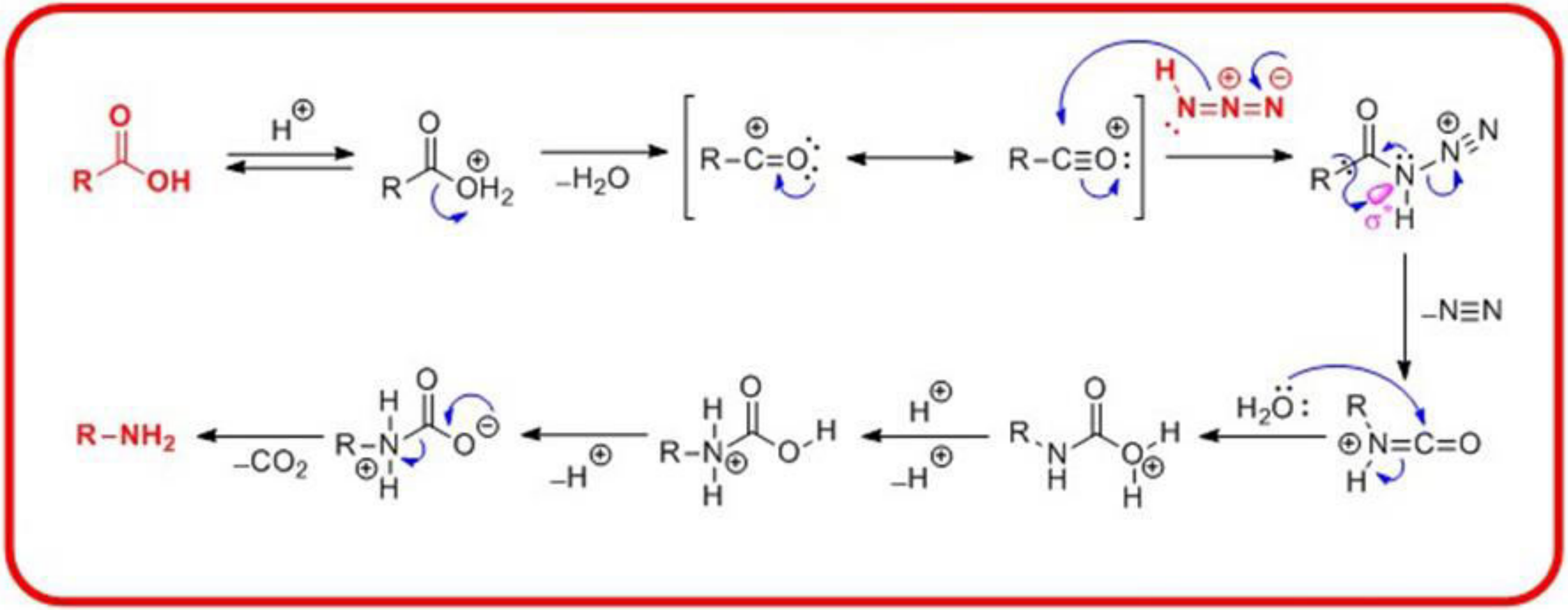


# Schmidt Rearrangement

- 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.

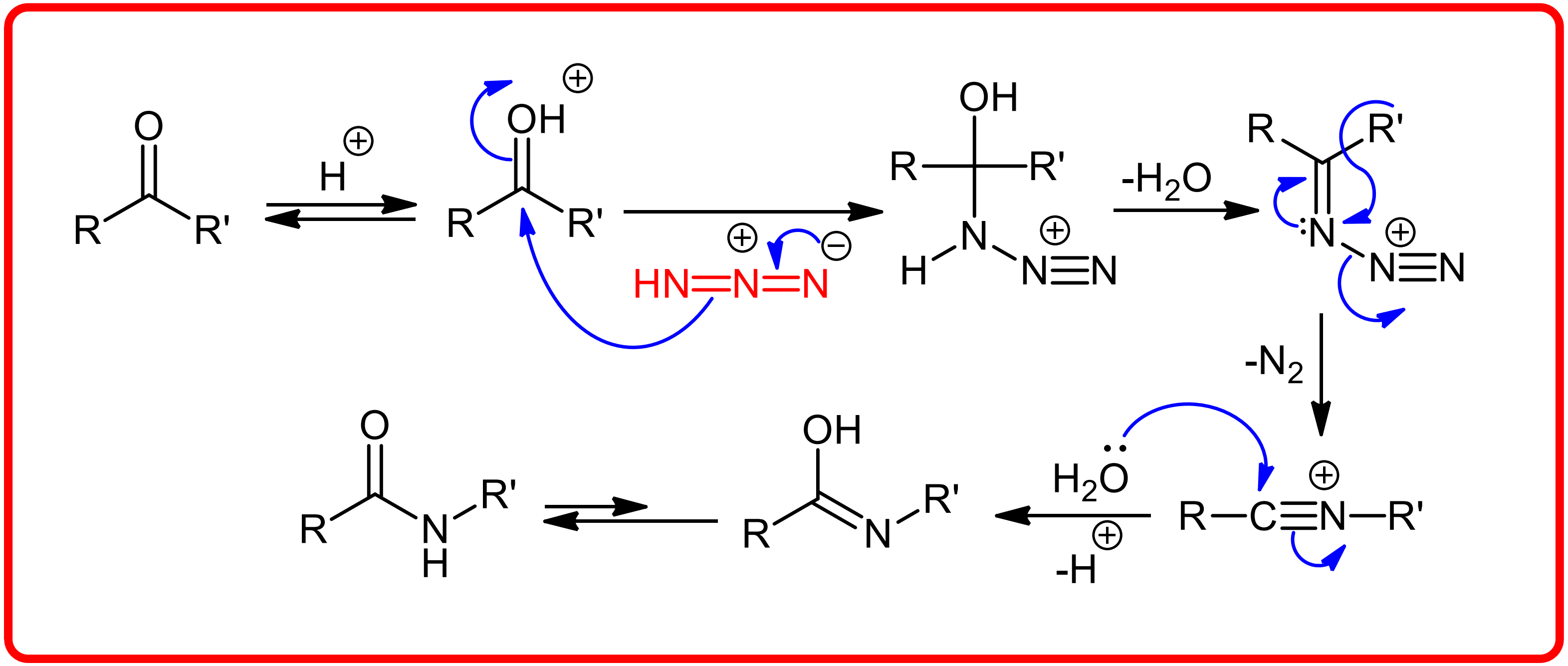
**Mechanism:**

Rearrangement for acid:



# Schmidt Rearrangement

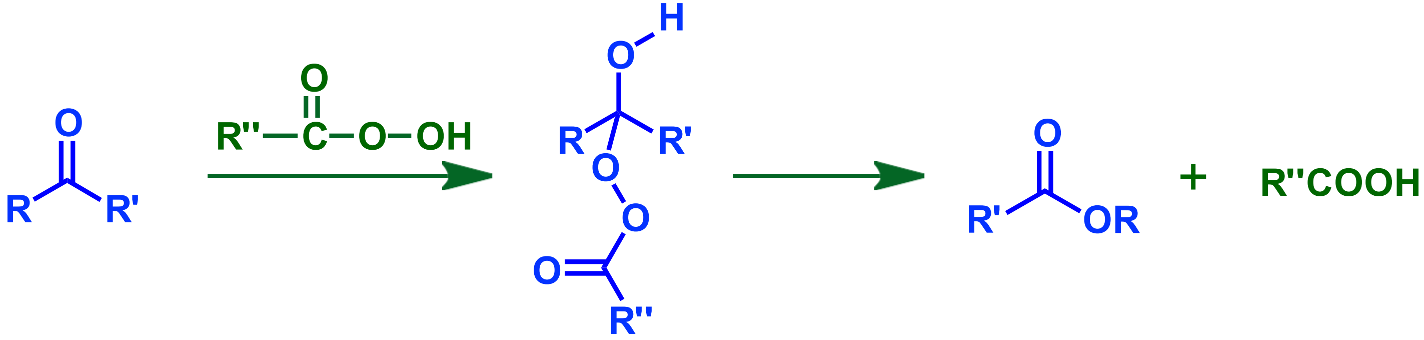
Rearrangement for aldehyde and ketone:



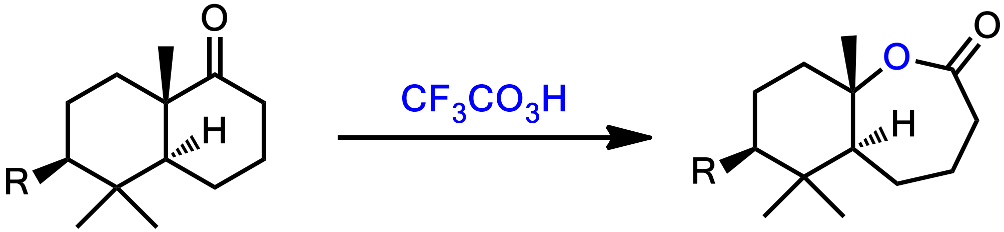
# Rearrangements to Electron Deficient Nitrogen

# 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.

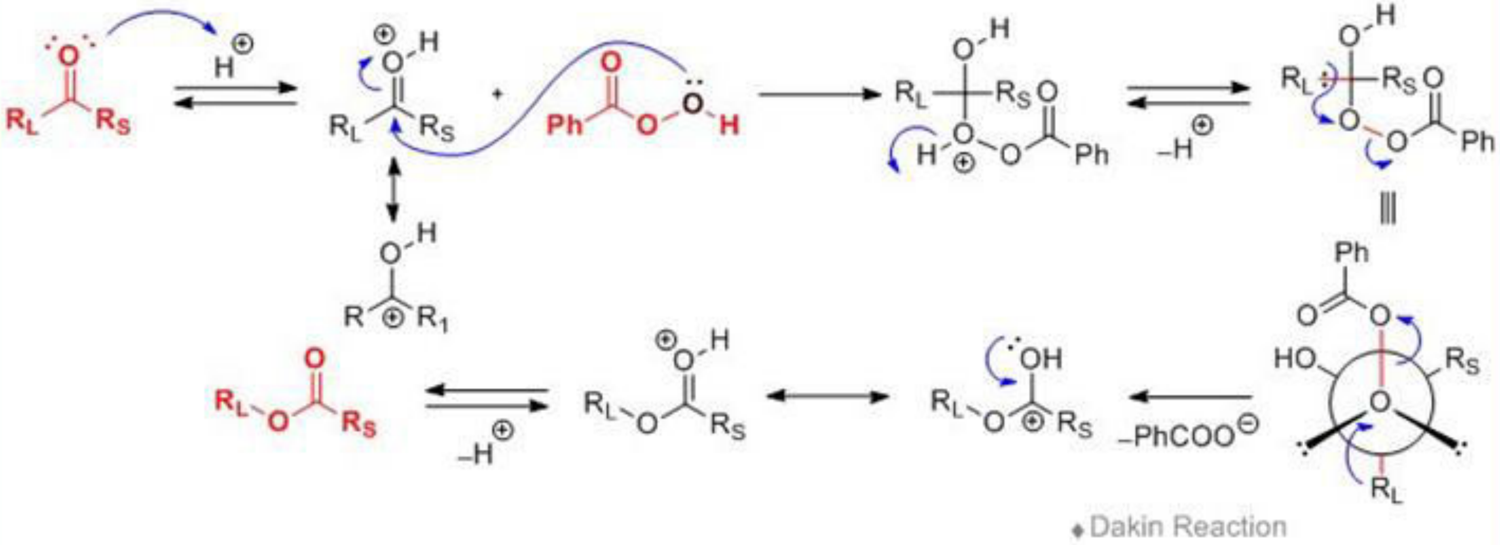


- Migratory Aptitude: t-Bu > i-Pr = Ph > Et > Me
- Reaction is particularly useful for synthesis of lactones.



R : H, OAc, OCOPh

## Mechanism:



H >> $3^0$ alkyl > cyclohexyl > $2^0$ alkyl > Ph > $1^0$ alkyl > $CH_3$

- ➢The mechanism is supported by fact that oxidation of $Ph_2C^{18}O$ yields only $PhC^{18}OOPh$ (i.e. there is no scrambling of $^{18}O$ 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

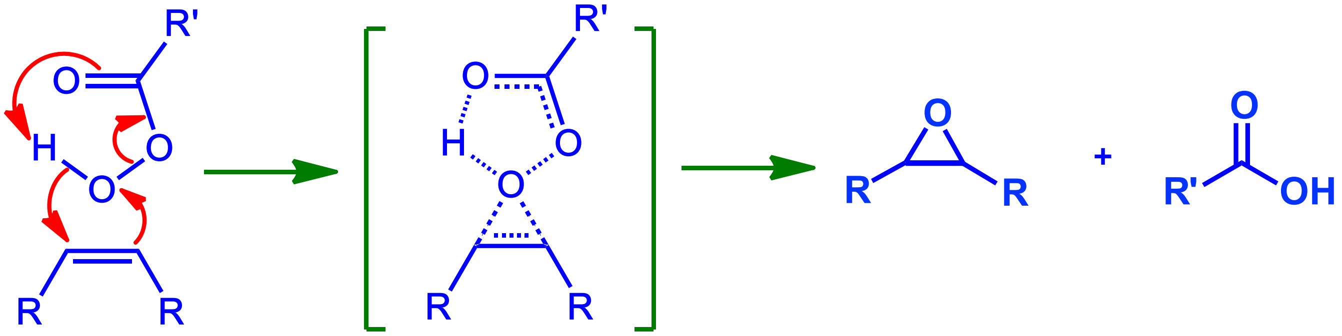
3)Can carry out both reactions

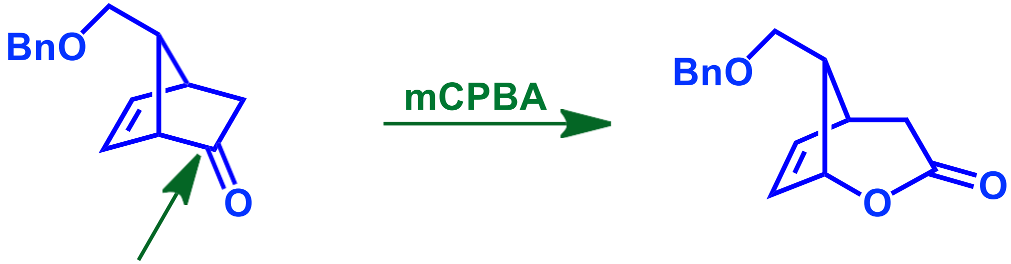
It is difficult to predict the outcome & it depends on-

1) Electrophilic nature of the ketone

2) Nucleophilic nature of the alkene

# Baeyer Villiger Oxidation

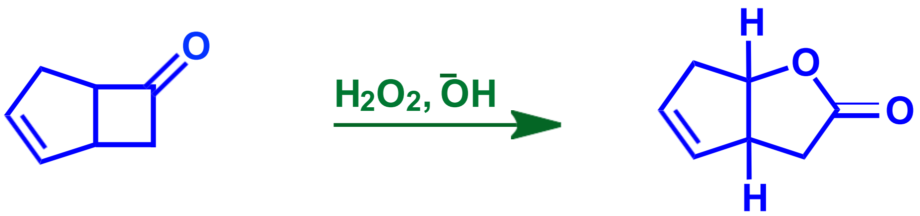




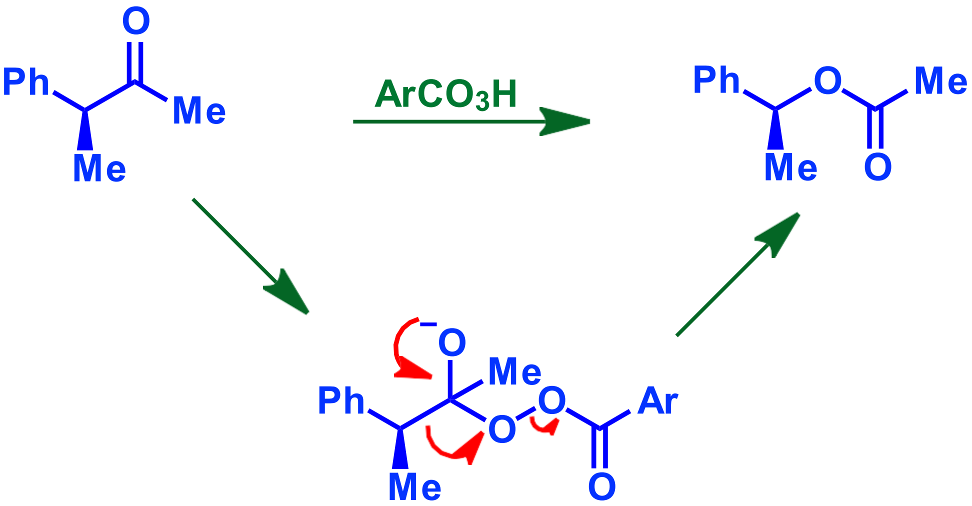
- ➢ Tertiary group migrates in preference of the secondary group
- ➢ The alkene is not as reactive as expected because of steric crowding

# Baeyer Villiger Oxidation

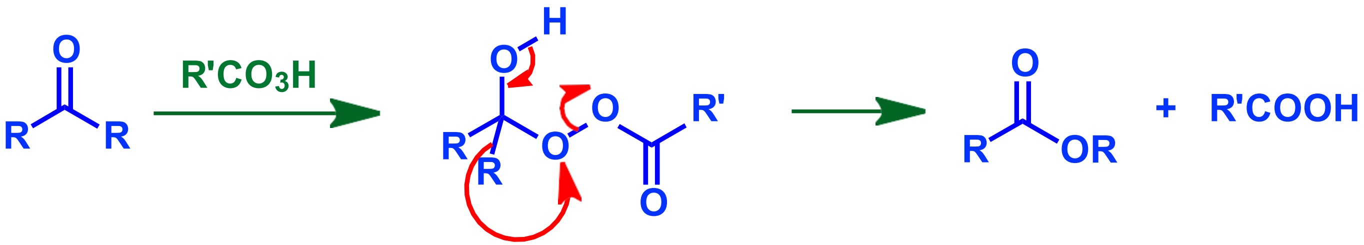
- Small ring ketones will readily undergo B.V.O.

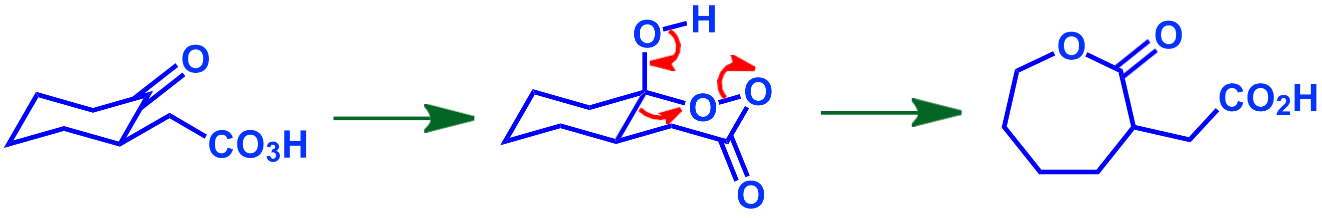


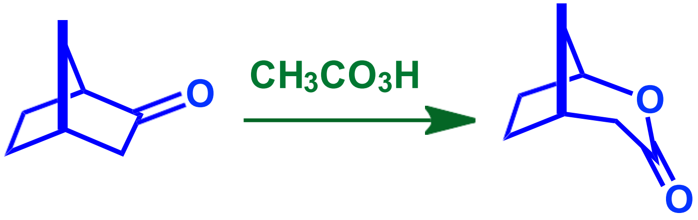
- Starting material configuration is retained in the product

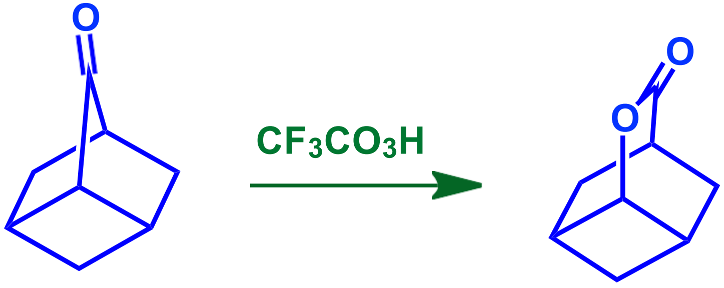


# Baeyer- Villiger oxidation



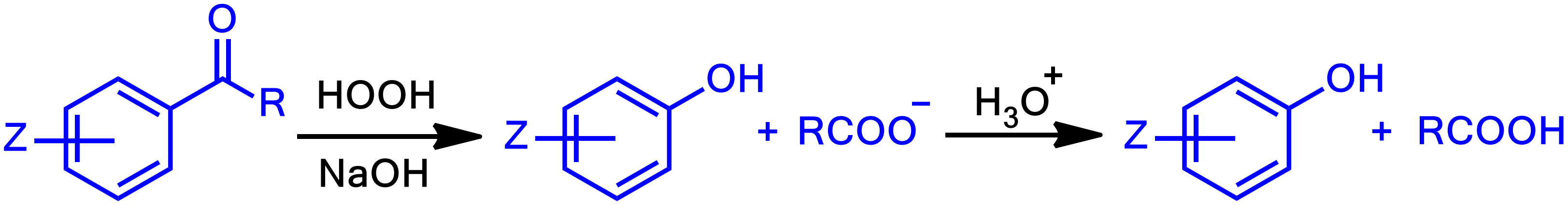






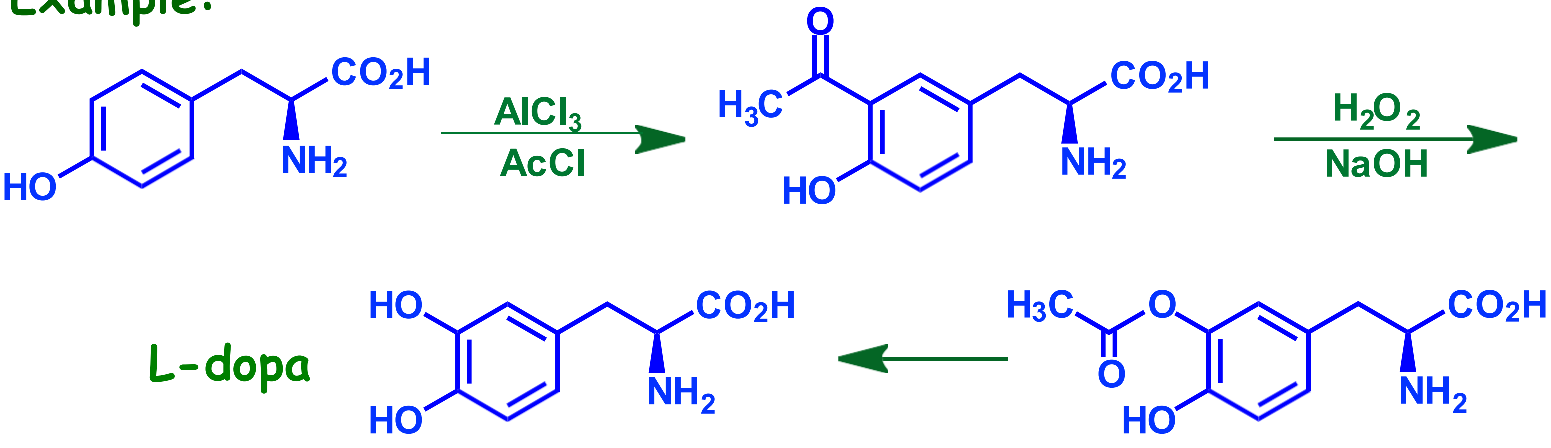
# Dakin Reaction

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.



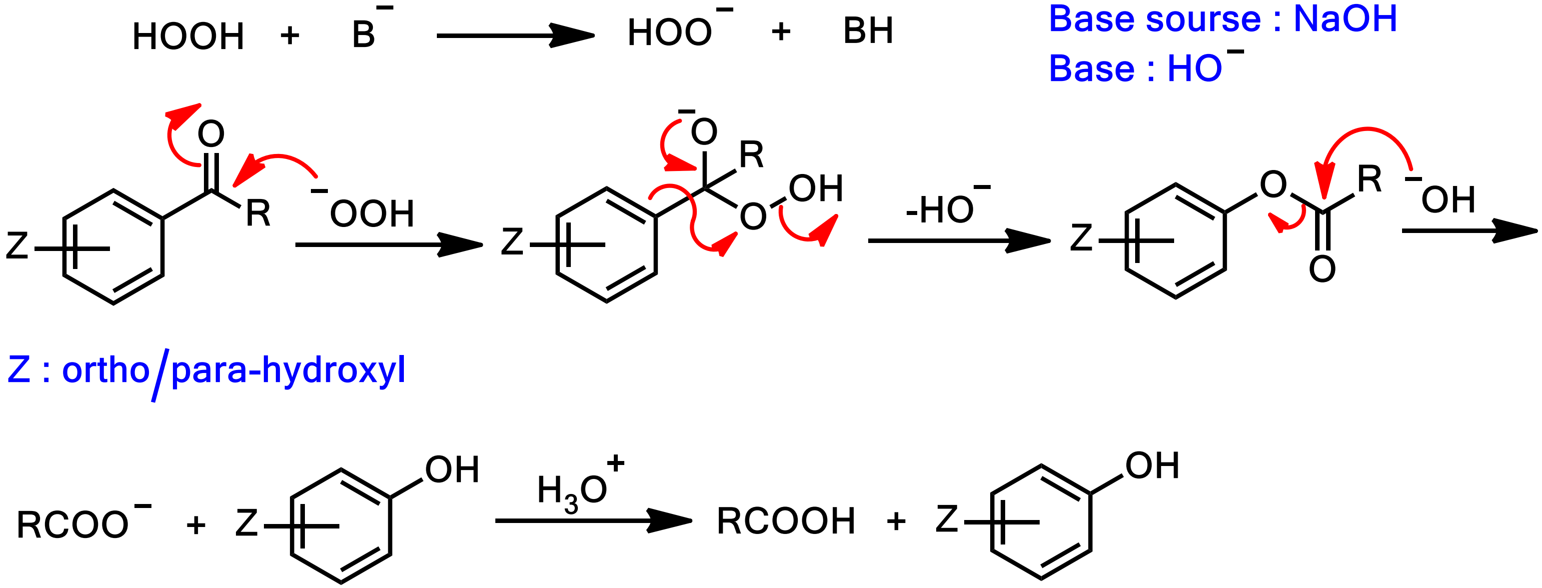
Z : ortho/para-hydroxyl

**Example:**



L-dopa

# Mechanism:



Base sourse : NaOH

Base : HO⁻

Z : ortho/para-hydroxyl

# Sigmatropic Rearrangements

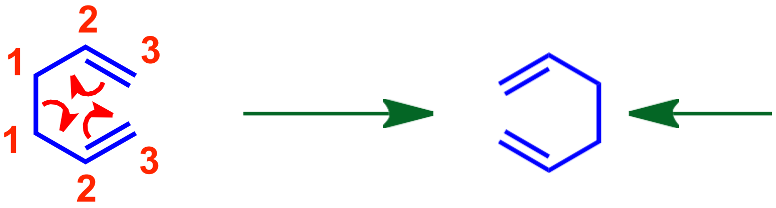
# Sigmatropic Rearrangements

## [3,3]-Sigmatropic Rearrangement

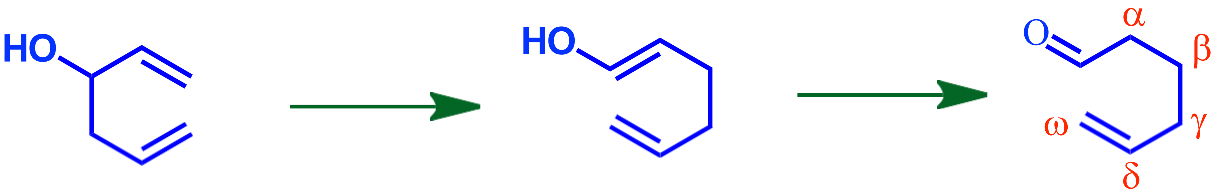
### Cope Rearrangement :

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

### Why is it called [3,3] ?



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

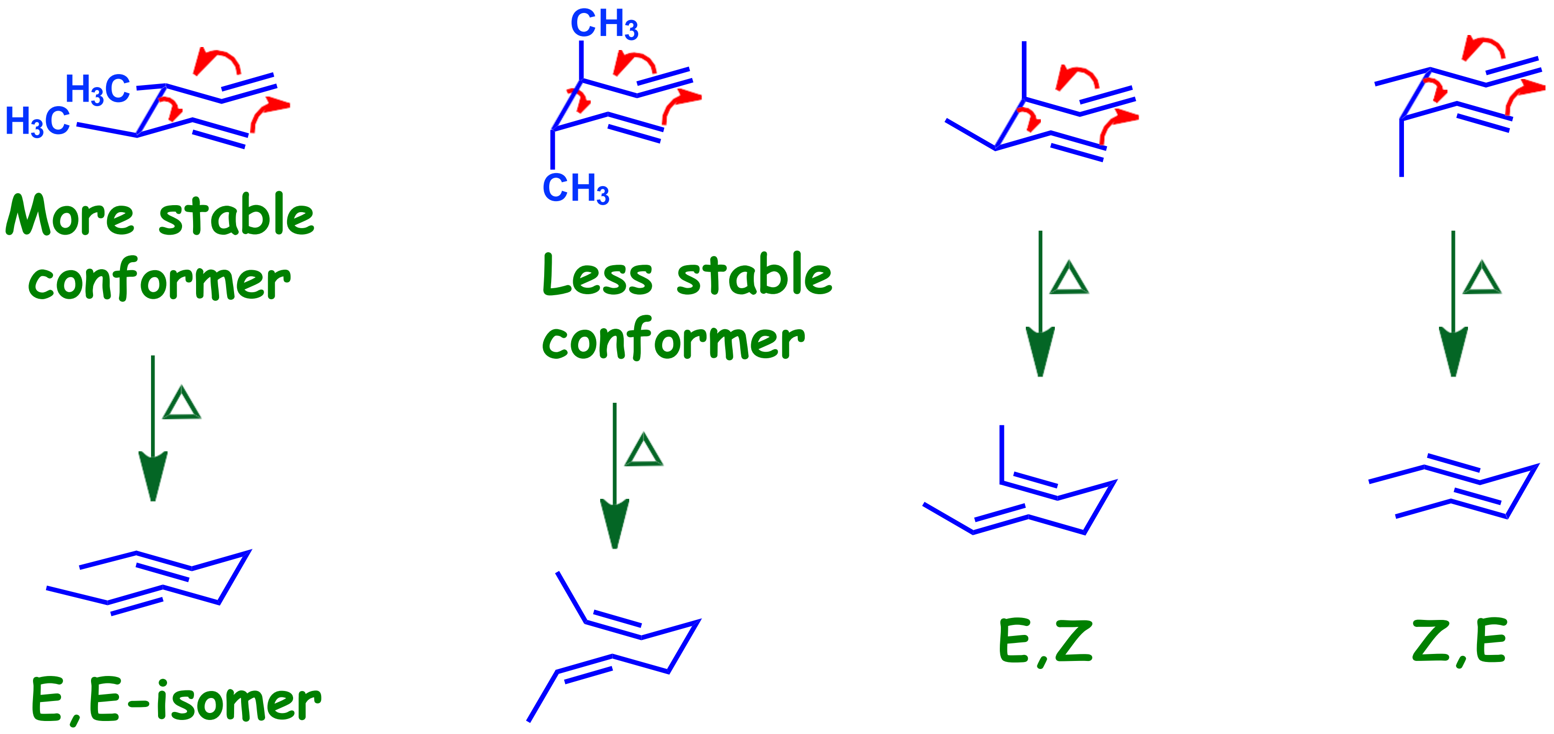


# Sigmatropic Rearrangements

**Mechanism :**

**It goes via six-membered chair-like transition state**

*trans* *trans* *cis* *cis*



More stable conformer

E,E-isomer

Favoured

Less stable conformer

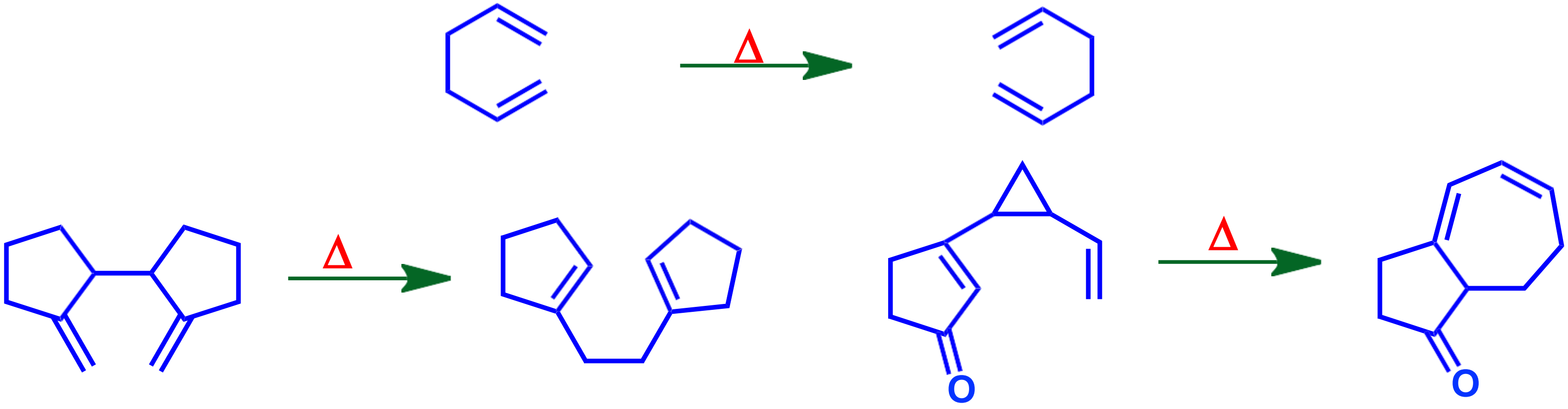
Z,Z-isomer

E,Z

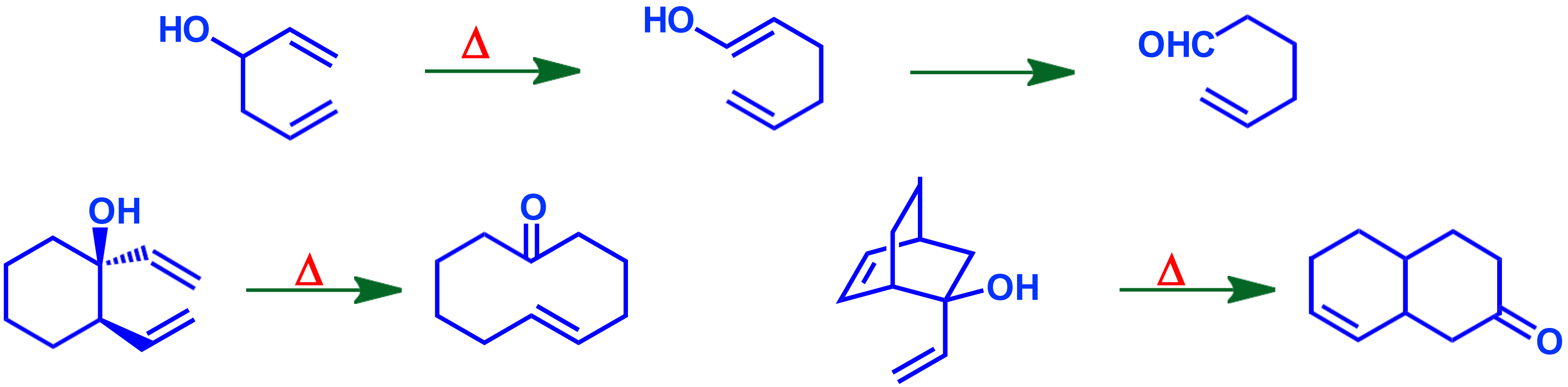
Z,E

# Sigmatropic Rearrangements

## 1) Cope:

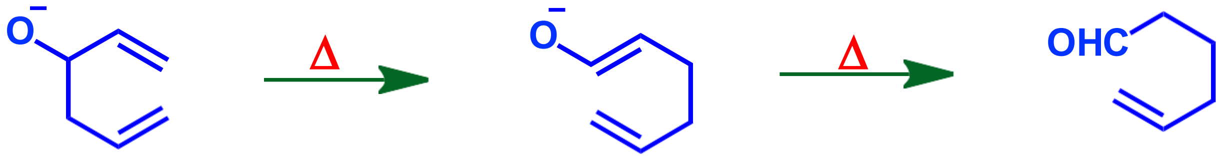


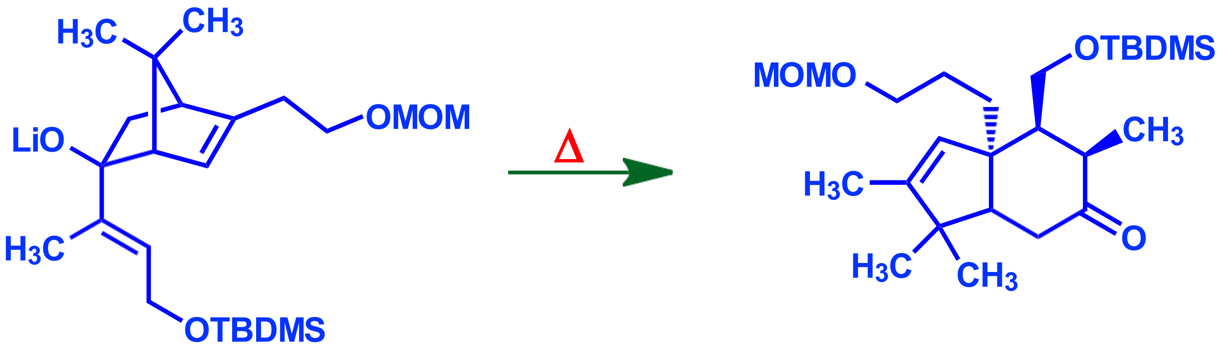
## 2) Oxy-Cope:



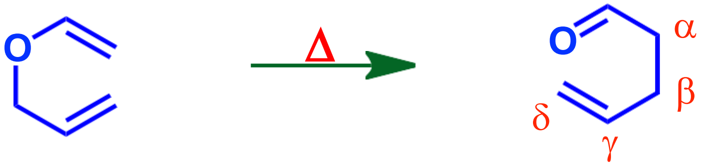
# Sigmatropic Rearrangements

## 3) Anionic-Oxy-Cope:

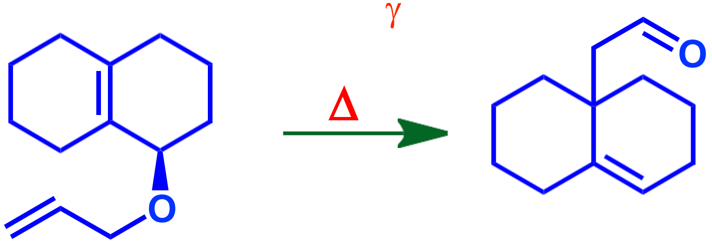




## 4) Claisen Rearrangement of Allylvinyl Ethers:

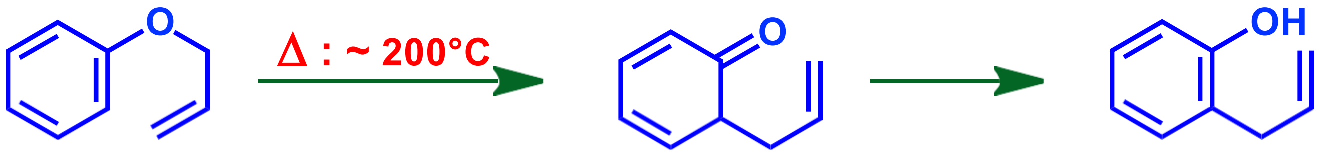


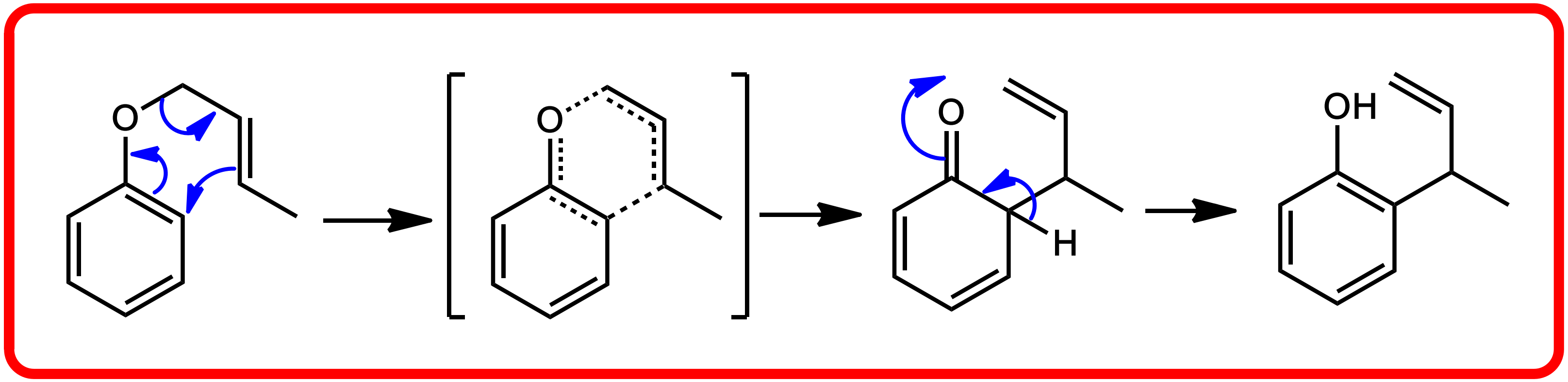
**γ-δ-unsaturated aldehyde**



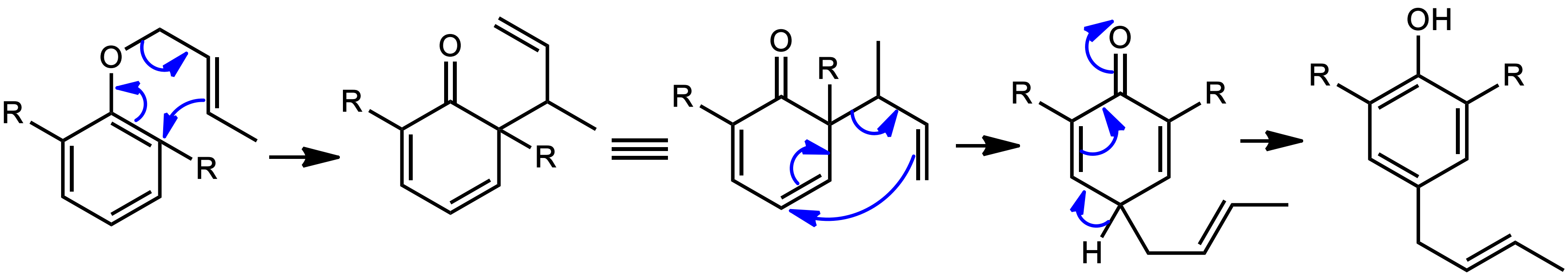
# 5) Claisen Rearrangement of Allylphenyl Ethers:

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



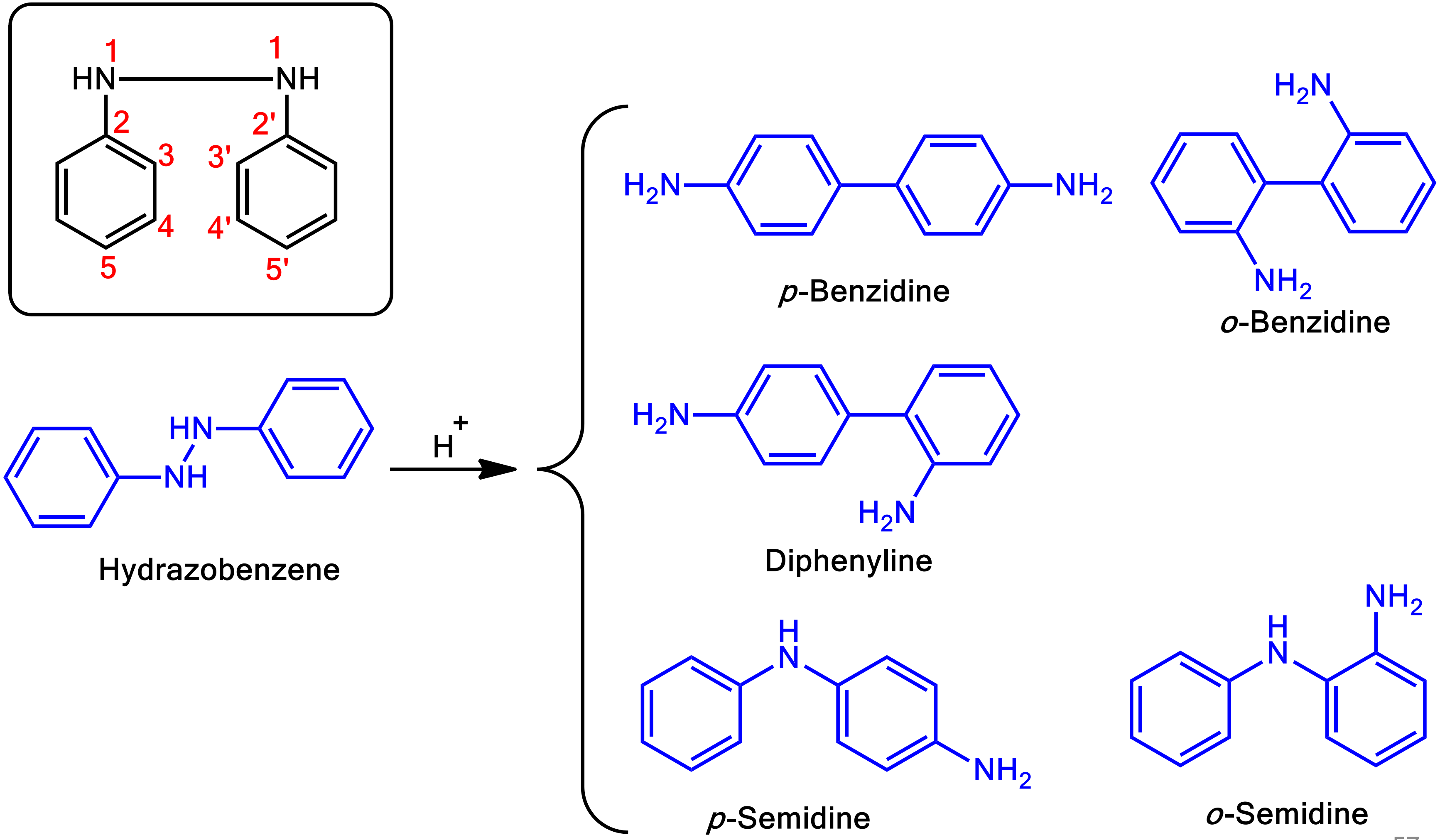


- ➢If *ortho* position is blocked, rearrangement continues to give *para*-product.



## 6) Benzidine-Semidine Rearrangement:

Hydrazobenzene undergos sigmatropic rearrangement in the presence of acid to give Benzidines, Diphenyline and Semidines.



Hydrazobenzene

*p*-Benzidine

*o*-Benzidine

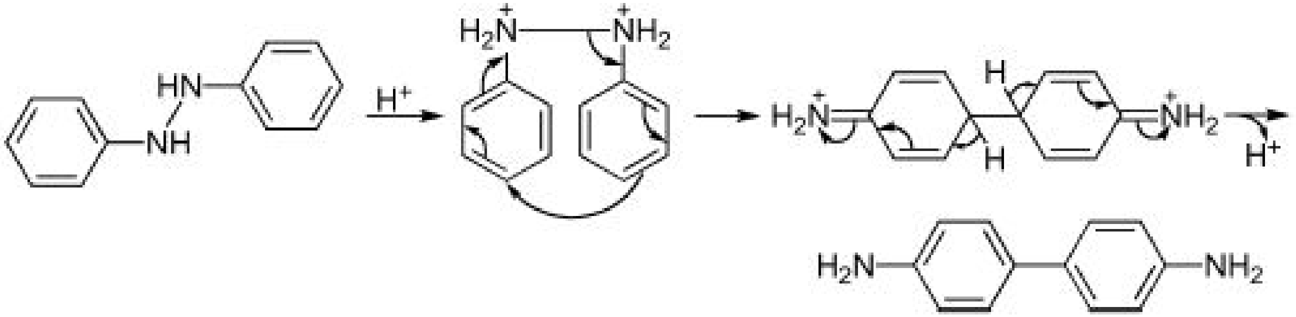
Diphenyline

*p*-Semidine

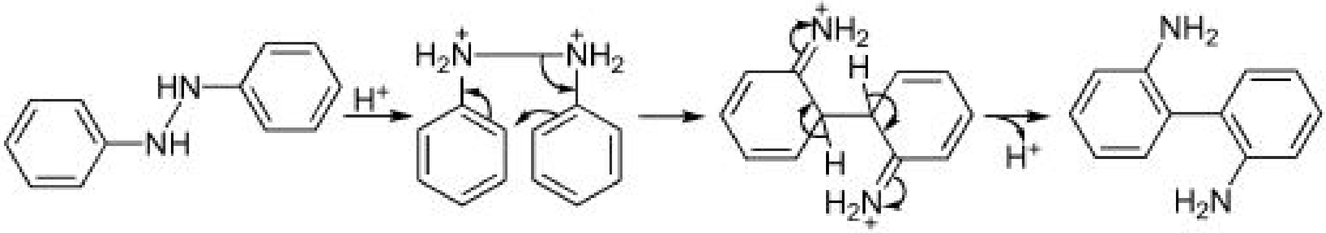
*o*-Semidine

# Mechanism:

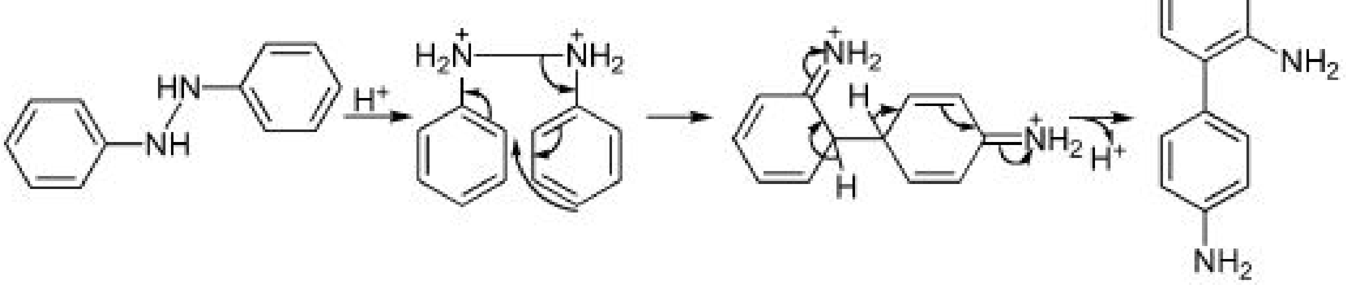
## Formation of *p*-Benzidine: [5,5'] rearrangement



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

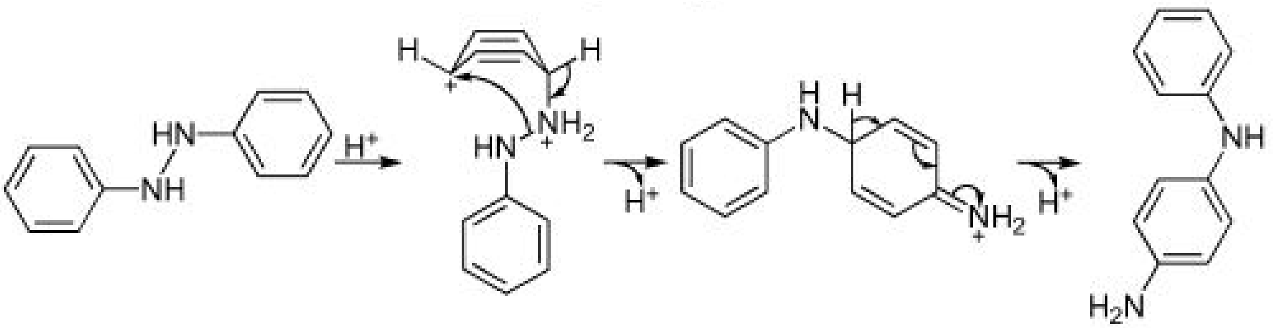


## Formation of Diphenyline: [3,5'] rearrangement

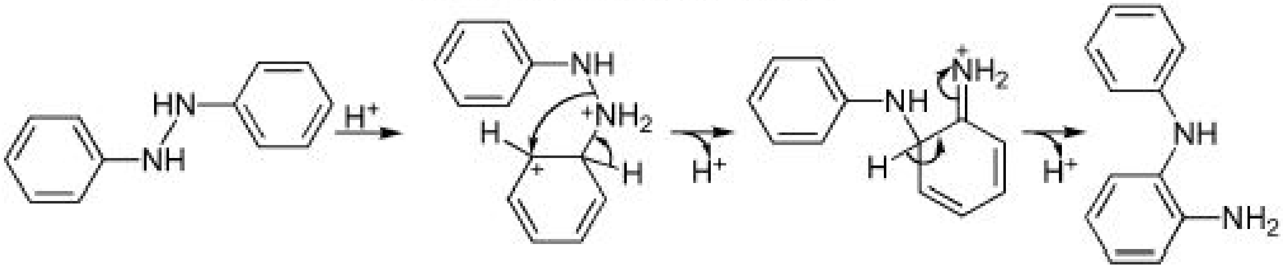


# Mechanism Contd…

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



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

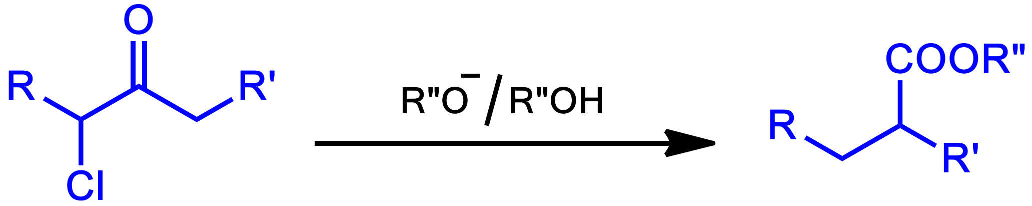


# Other Rearrangements

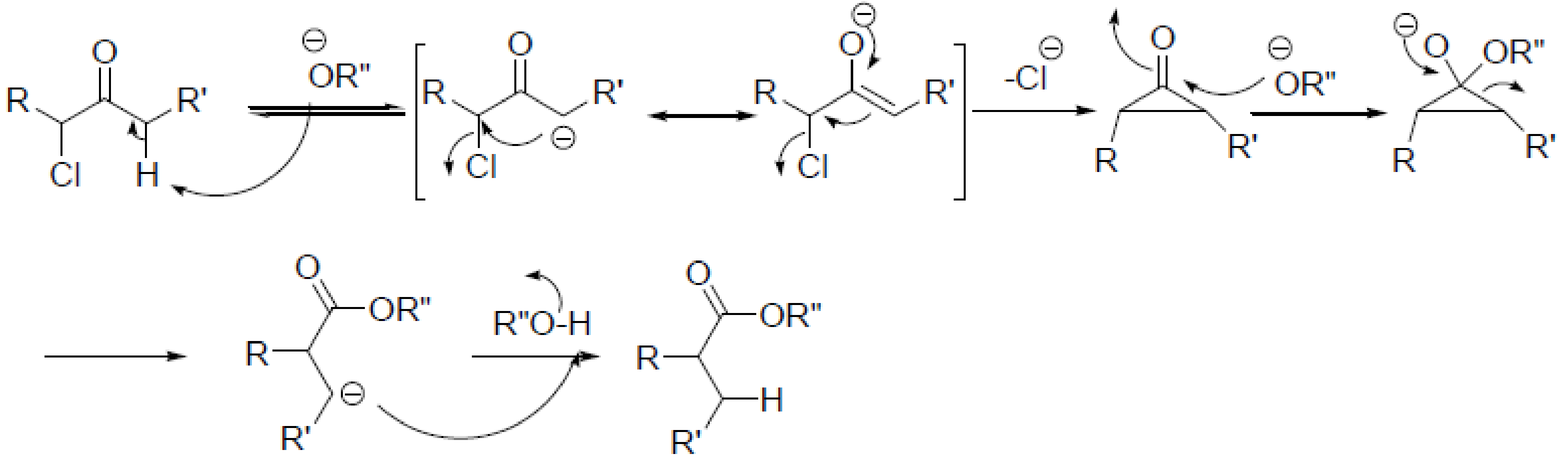
1. Favorskii Rearrangement
2. Fries Rearrangement
3. Rearrangements of Derivative of aniline

# Favorskii Rearrangement

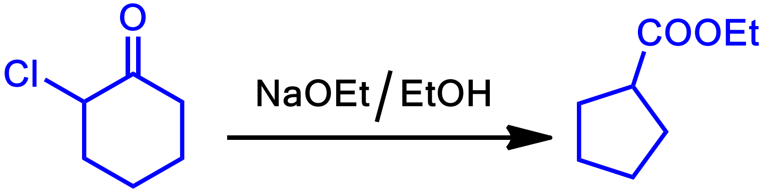
α-Haloketones with base afford enolates which rearrange to give esters *via* cyclopropanones popularly known as Favorskii Rearrangement.

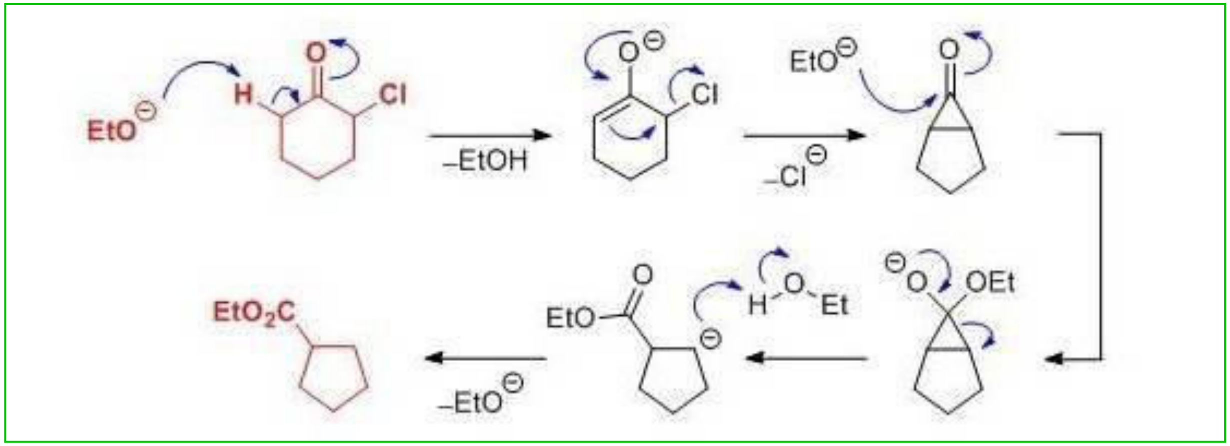


## Mechanism:

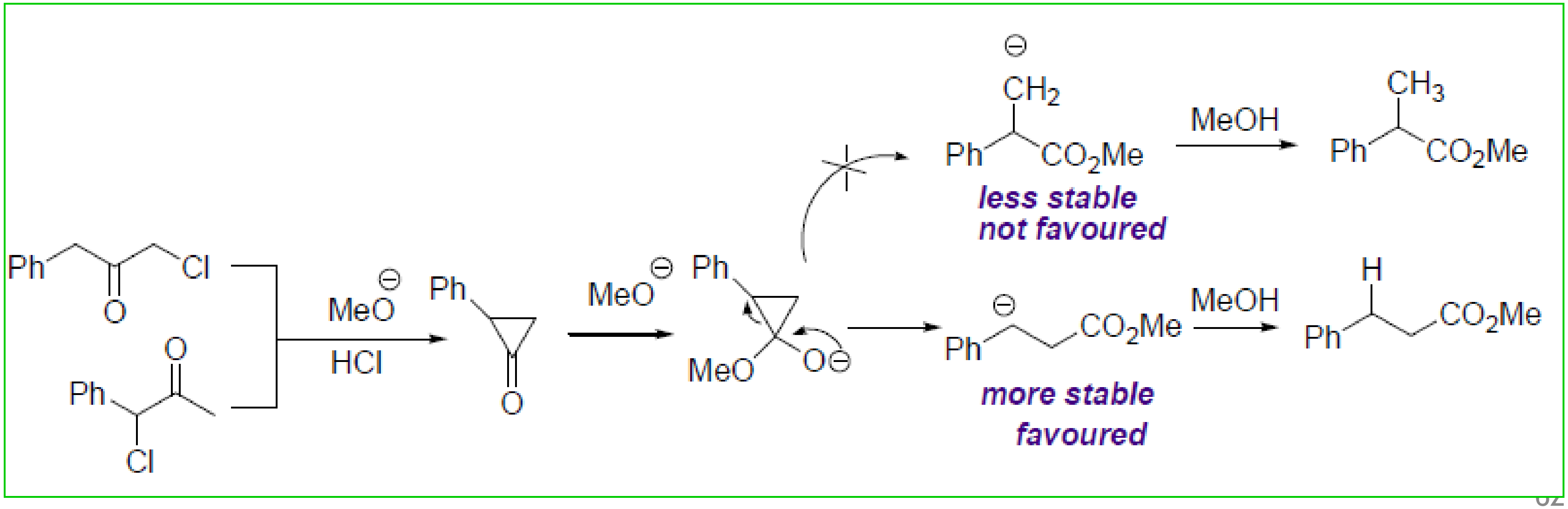


- This reaction can be used for ring contraction

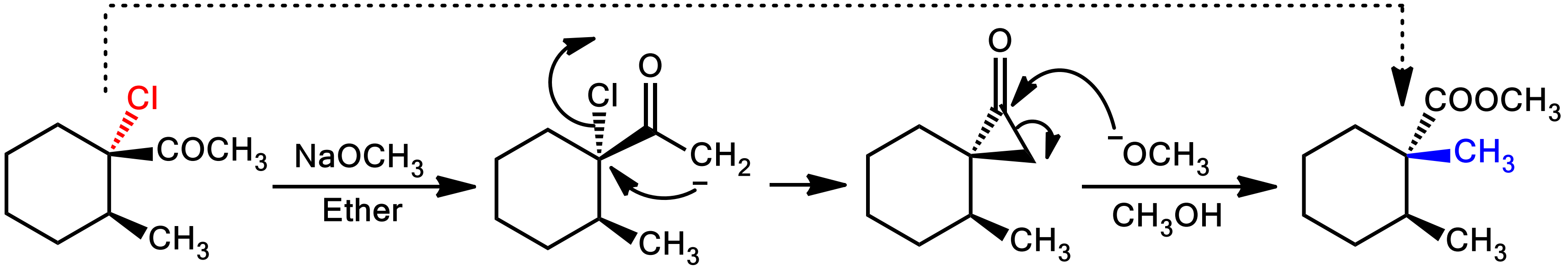




- The direction of ring opening of cyclopropanone is determined by the more stable carbanion, formed in the reaction.



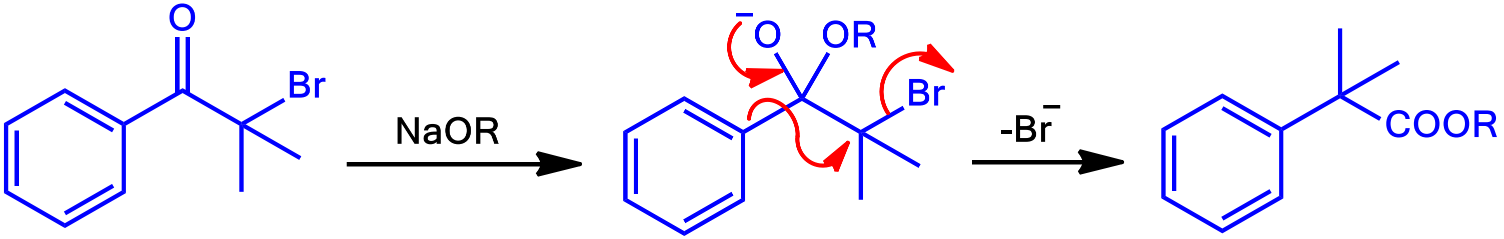
- In some interesting cases, Favorskii rearrangement results intramolecular substitution. For example shown below, internal $S_N2$ displacement of halide ion results in inversion of configuration of the halogenated carbon.



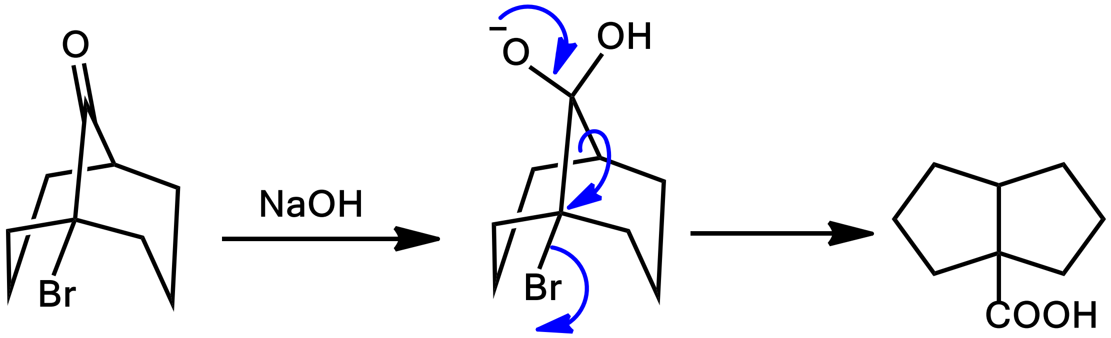
$S_N2$ displacement of Cl by $CH_3$ group

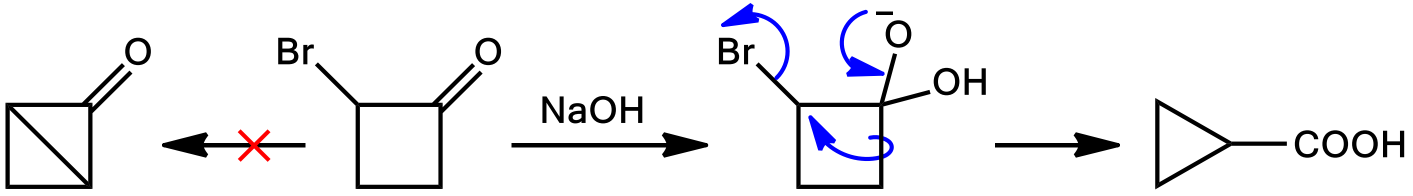
Actually, in absence of resonance stabilization of one of the two possible anions, the less-substituted alkyl anion is formed.

- **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.



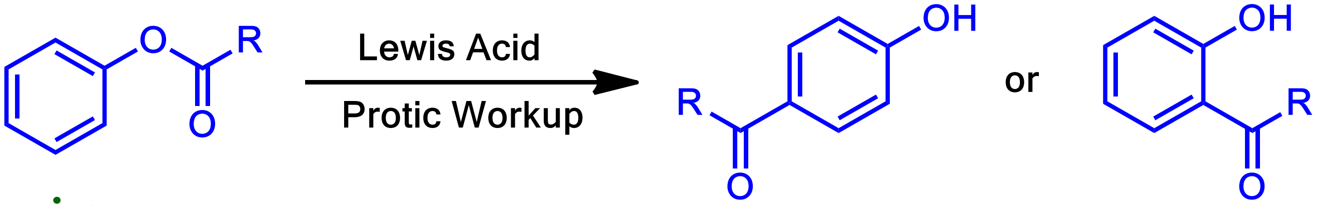
# Examples of Quasi-Favorskii Rearrangement





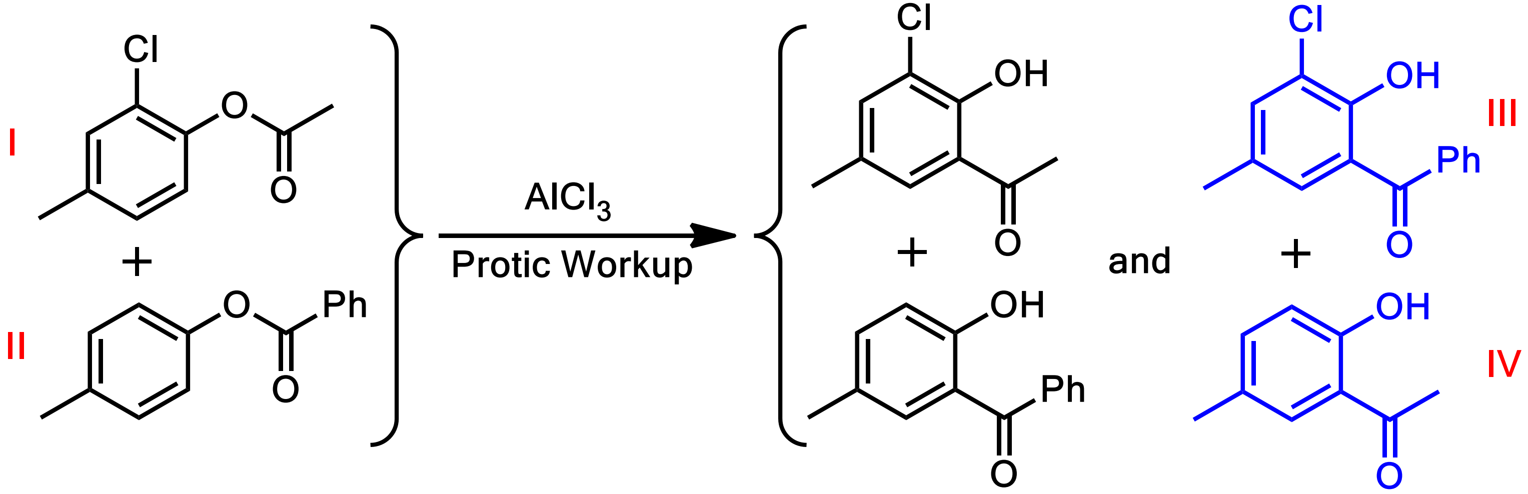
# Fries Rearrangement

*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.

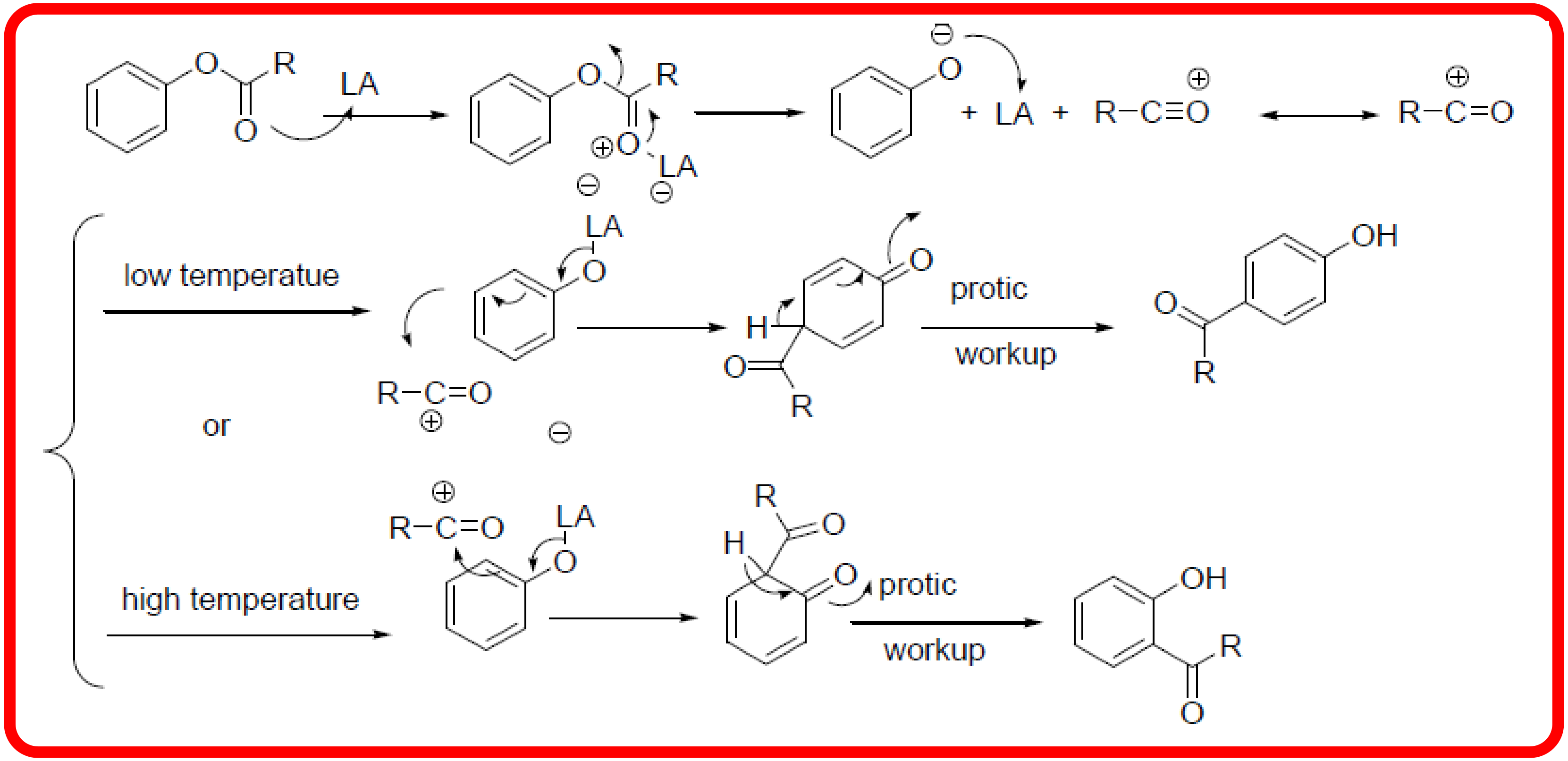


## Mechanism

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



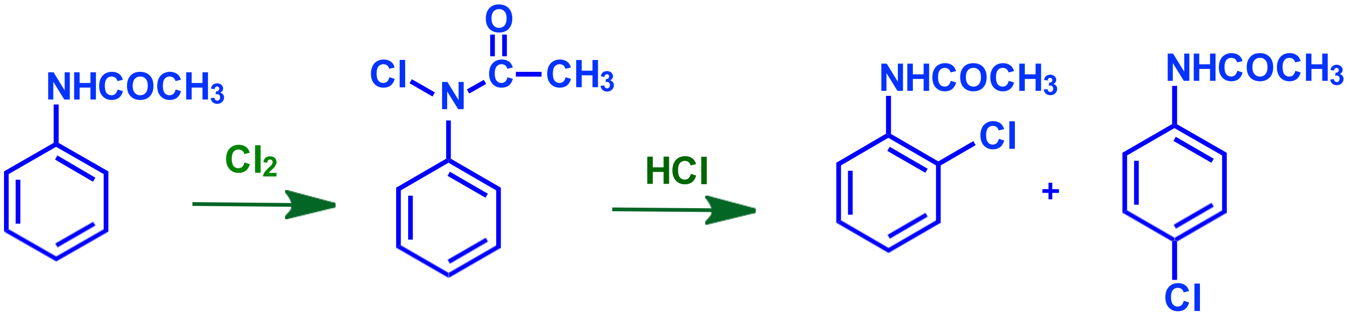
➢Low temperature favors the formation of *para*-product (kinetic control) and high temperature favors *ortho*-product (thermodynamic control).

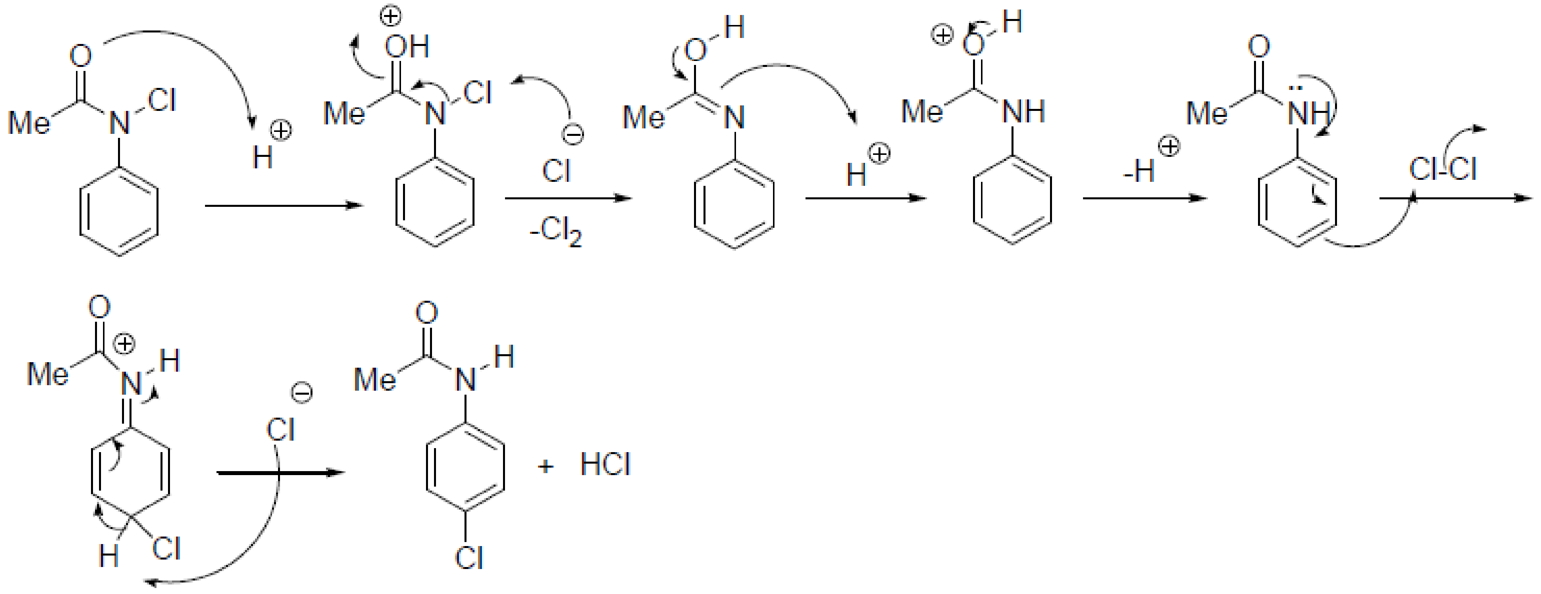


# Rearrangements of Derivative of aniline

## Rearrangements of N-Haloanilides (Orton Rearrangement)

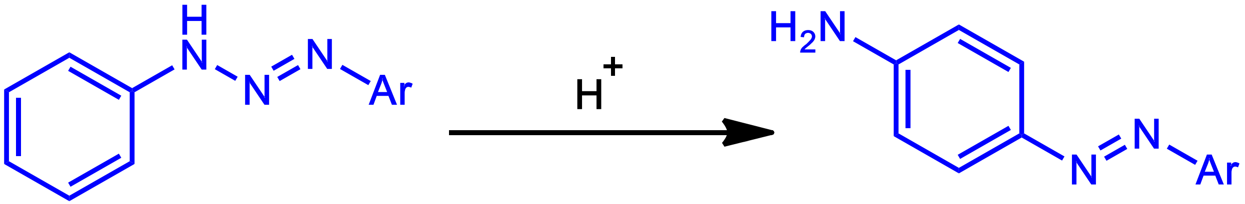
Treatment of N-chloroacetanilide with hydrochloric acid affords a mixture of *ortho* and *para*-chloracetanilides in the same proportions as in the direct chlorination of acetanilide.





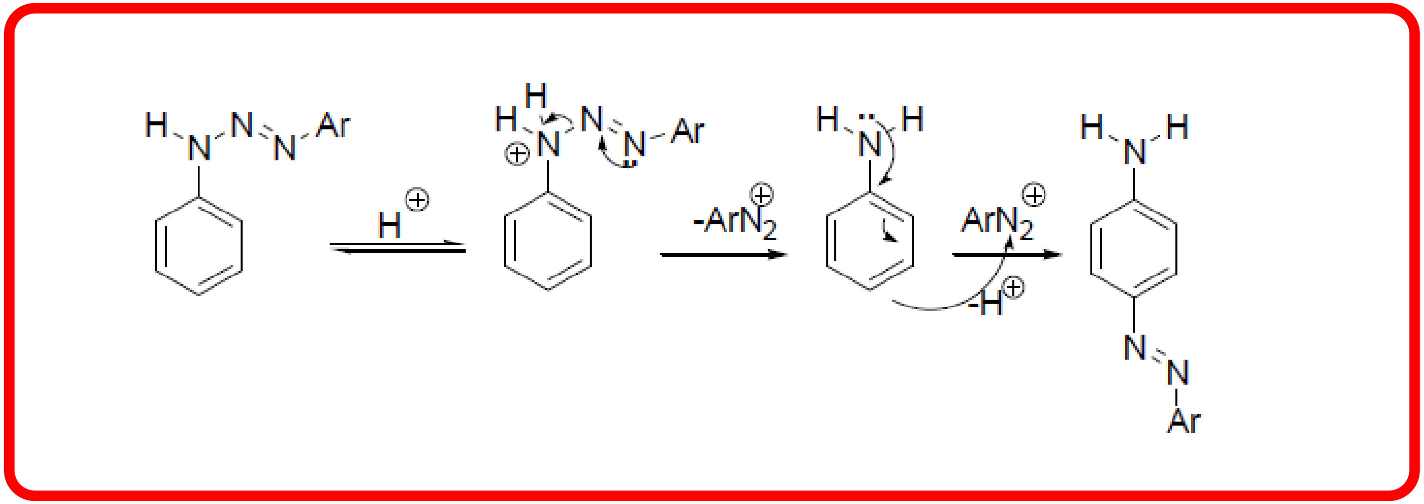
# Rearrangements of N-Aryldiazoanilines :

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.



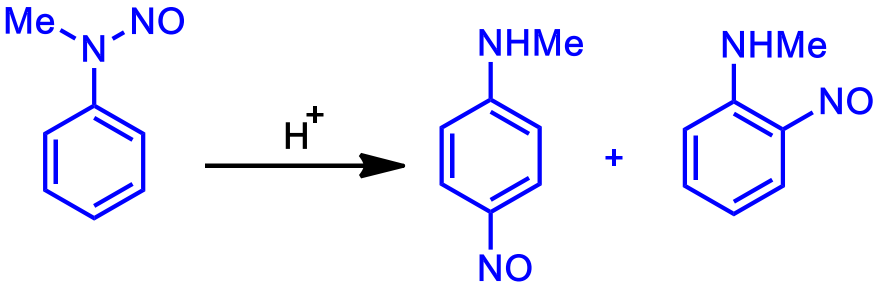
N-Aryldiazoaniline

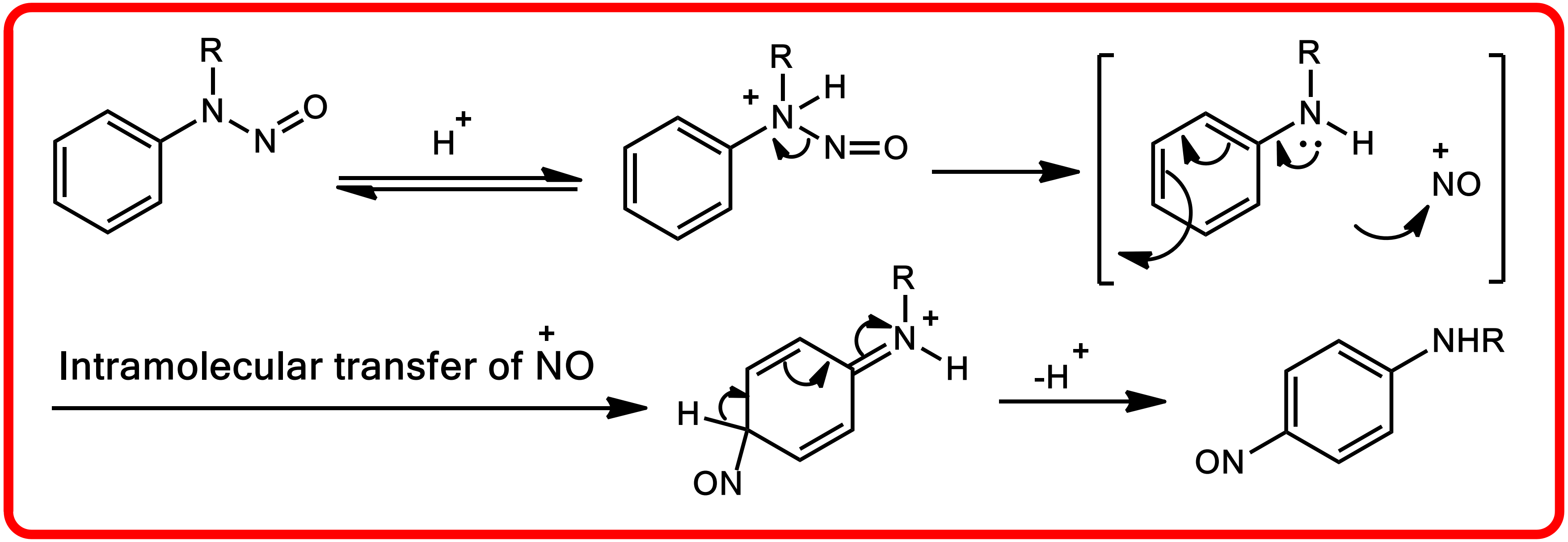
*p*-Aryldiazenylaniline



# **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.

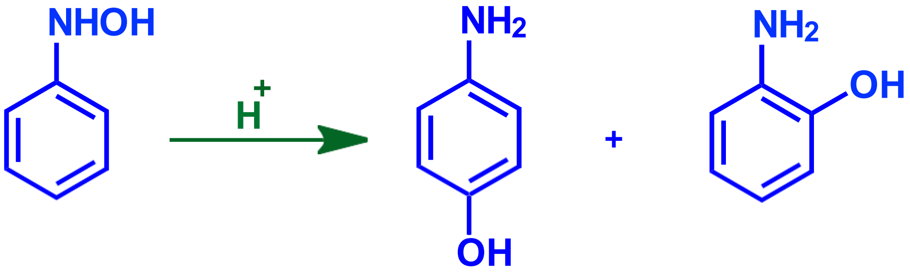




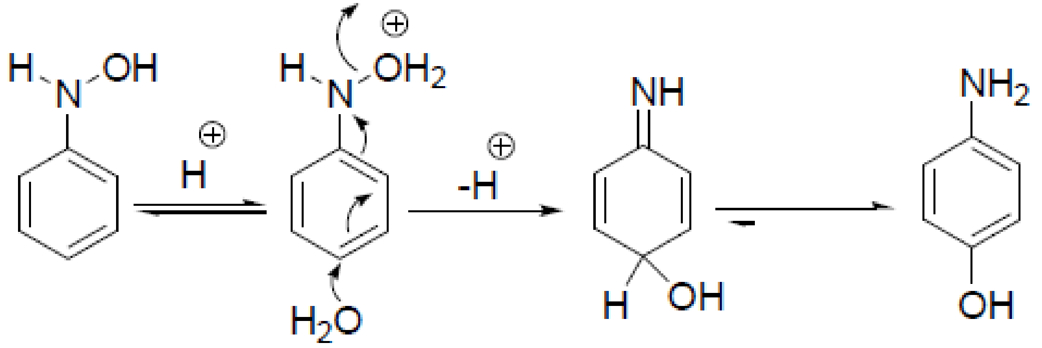
Intramolecular transfer of $\overset{+}{NO}$

# Rearrangement of N-Arylhydroxylamines
## (Bamberger Rearrangement):

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

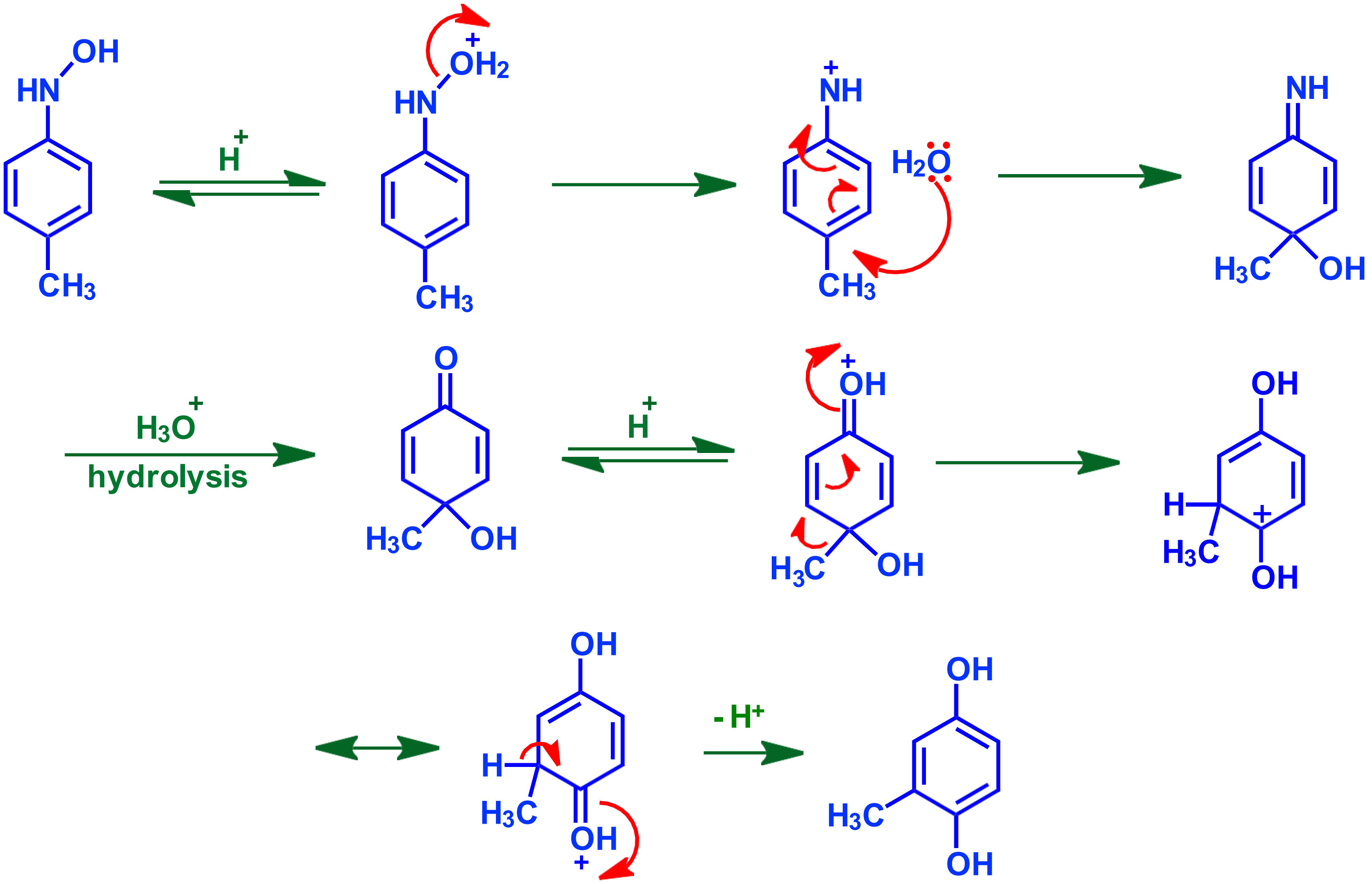


## Mechanism



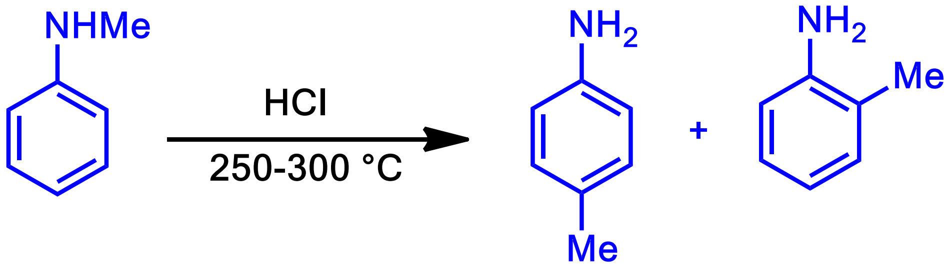
# When para-position is already occupied ???

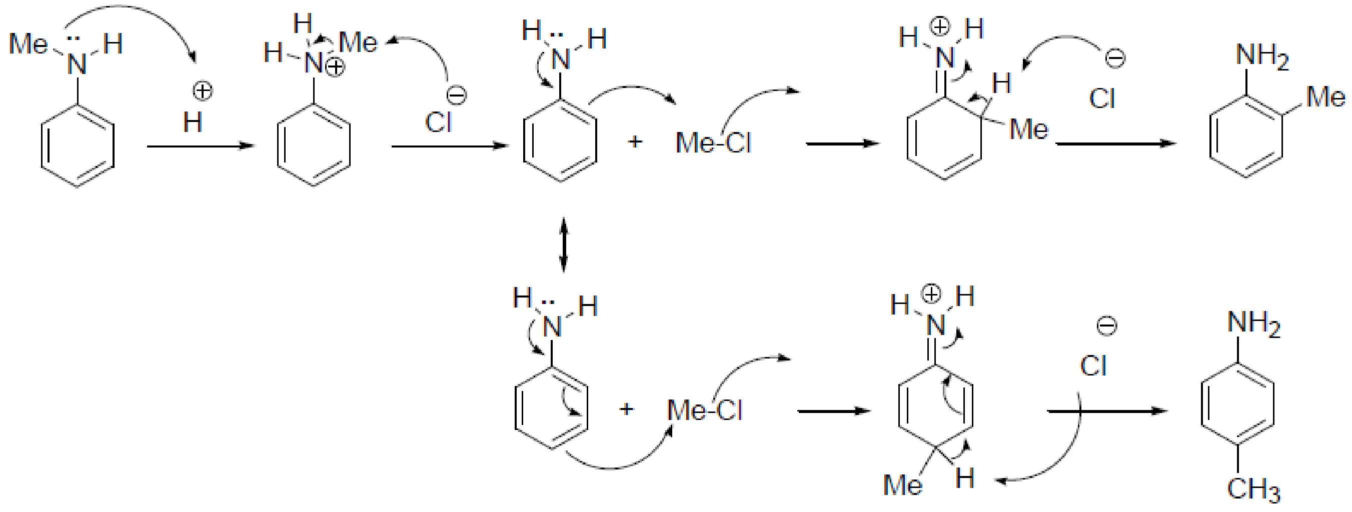
- Hydrolysis followed by Dienone-phenol type of rearrangement occurs.



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

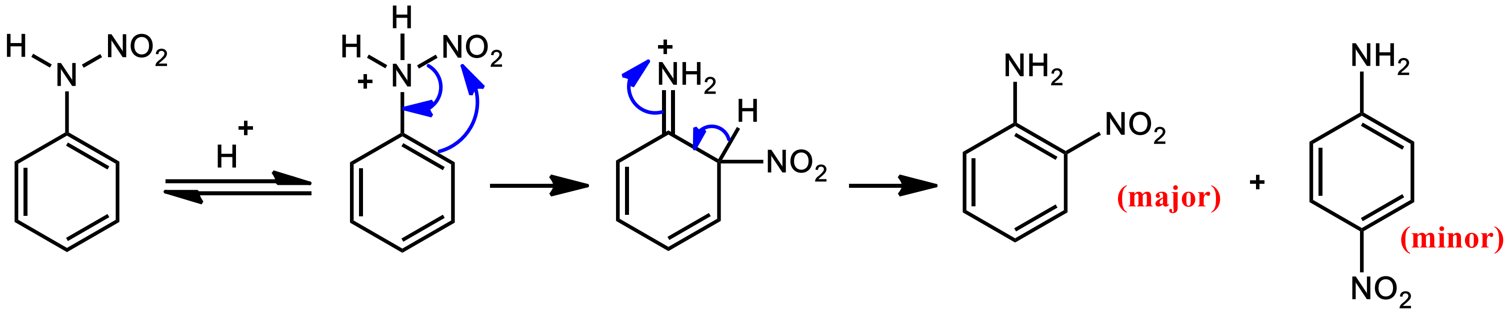
N-alkylanilines in presence of acid at very high temperature rearranged to ortho and para alkylated products.





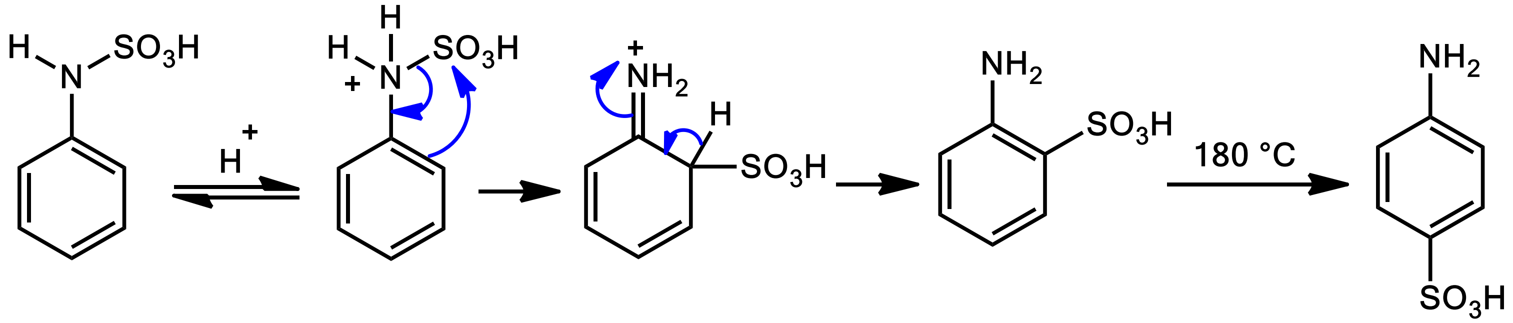
## Rearrangement of Phenylnitramines:

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



## Rearrangement of Phenylsulfamic acids:

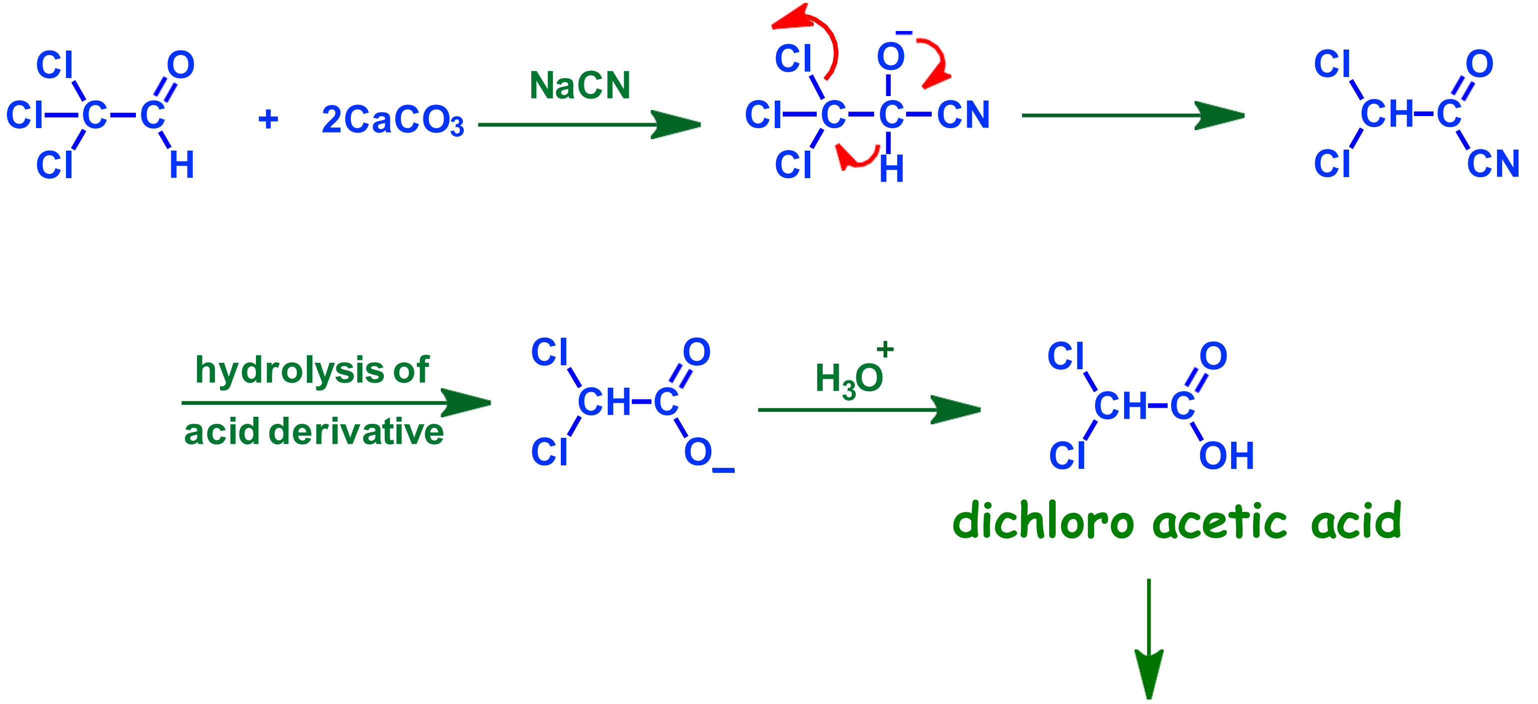
Phenylsulfamic acids rearrange on heating to give *o*-sulfonic acid derivative that further rearranges at high temperature to afford *p*-sulfonic acid derivatives.



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

# Rearrangements

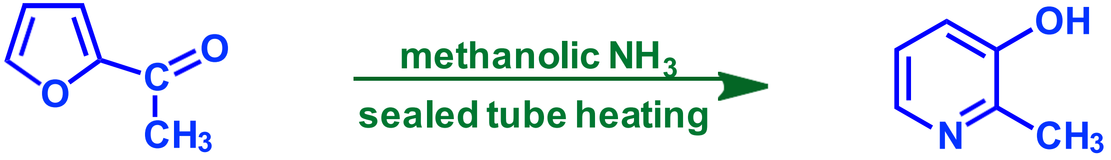
## Some Additional Problems



$(CHCl_2COO)_2Ca + 2CO_2 + CaCl_2 + H_2O$

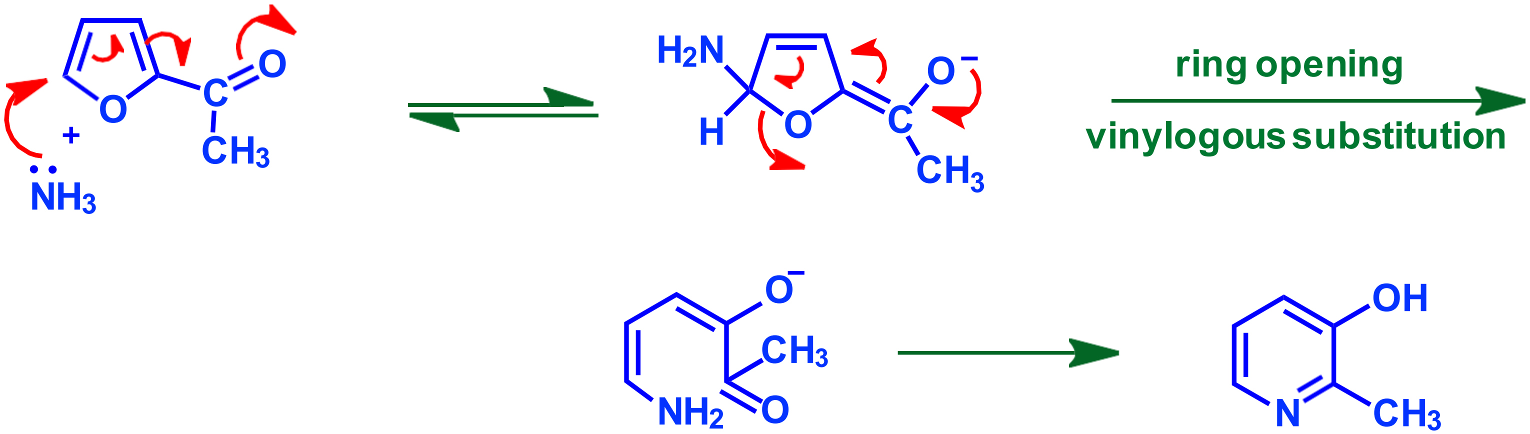
# Rearrangements

## Some Additional Problems



methanolic $NH_3$

sealed tube heating

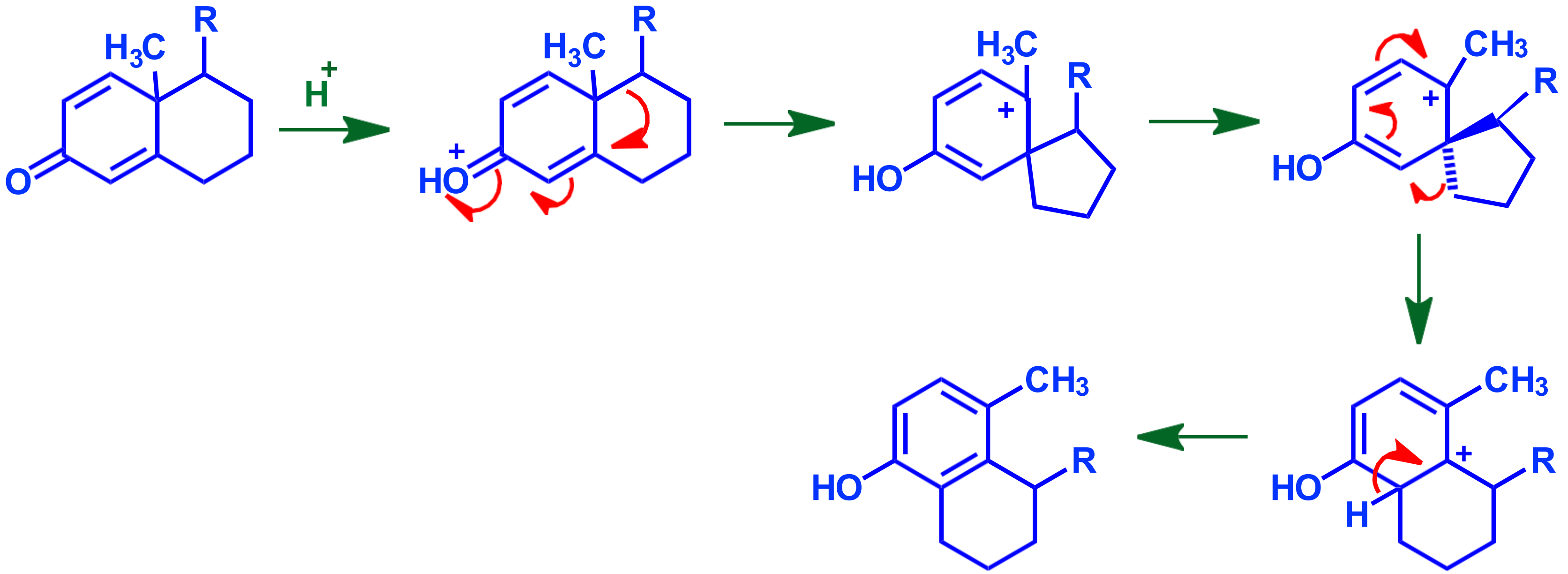


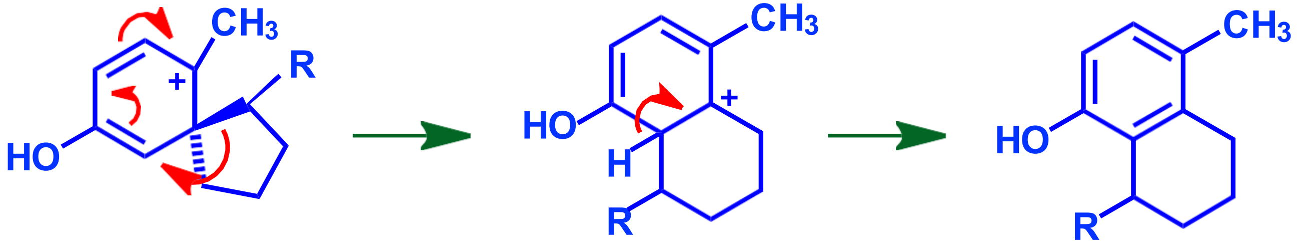
ring opening

vinylogous substitution

# Rearrangements

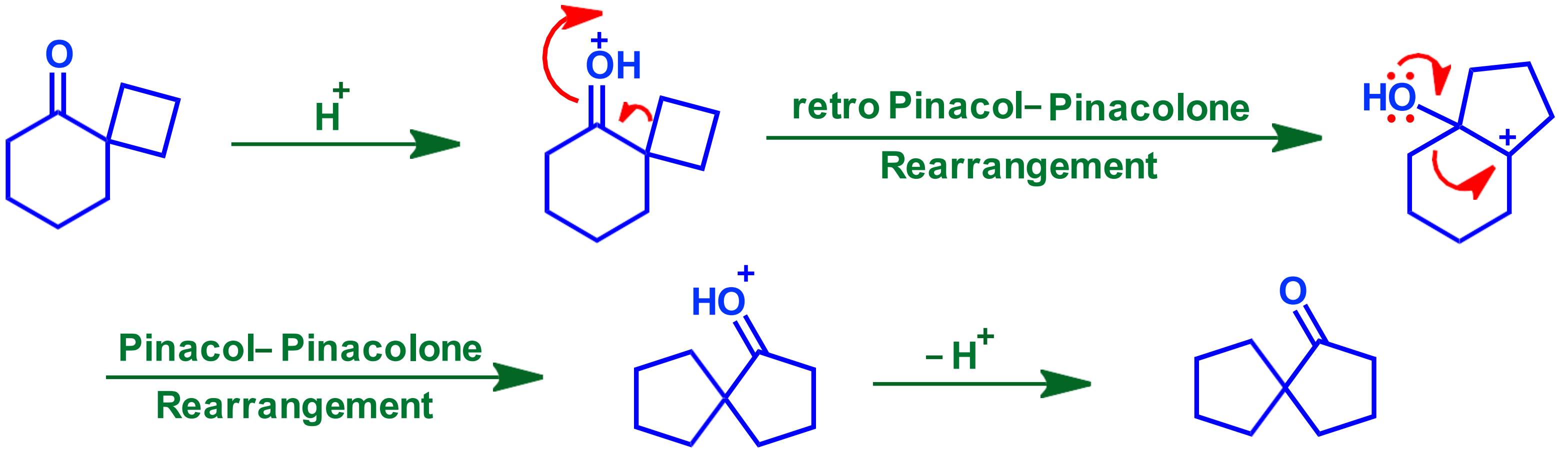
## Some Additional Problems

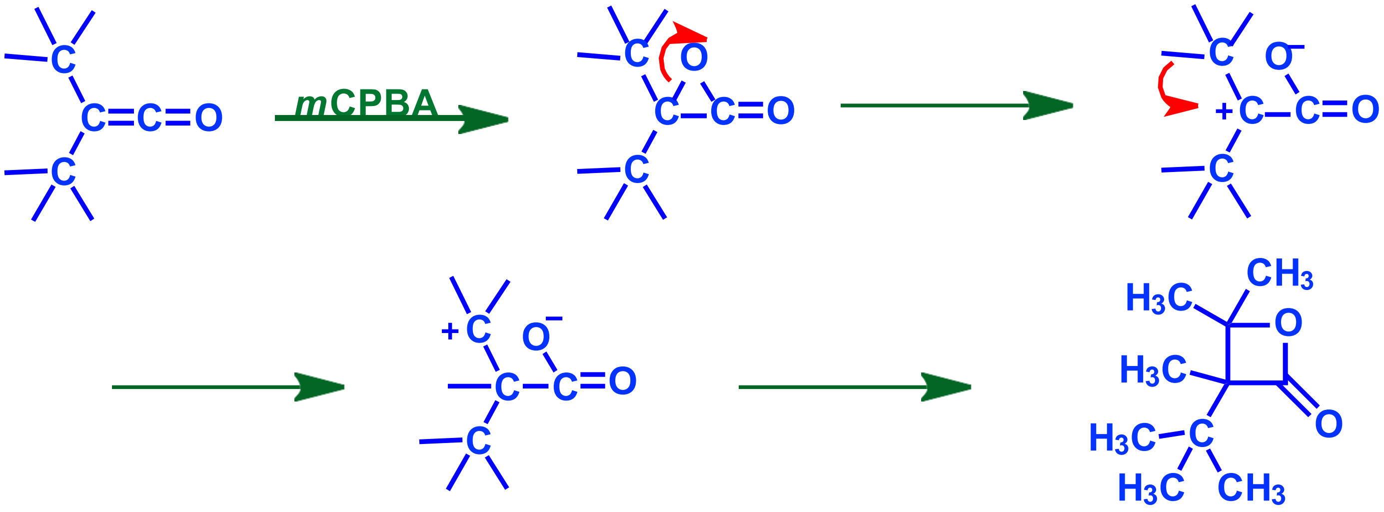




# Rearrangements

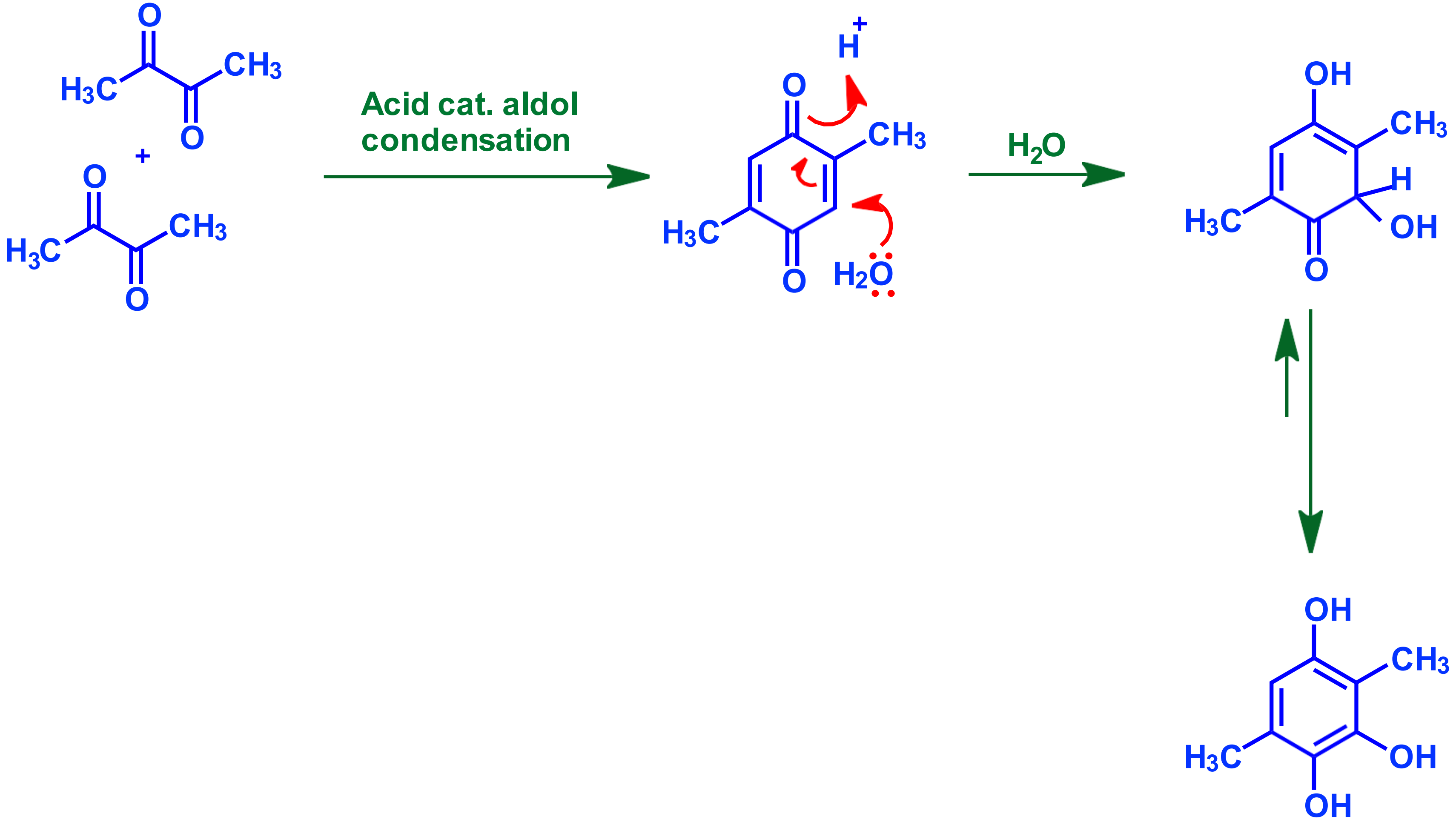
## Some Additional Problems





# Rearrangements

## Some Additional Problems



# Named Reactions

# Birch Reduction

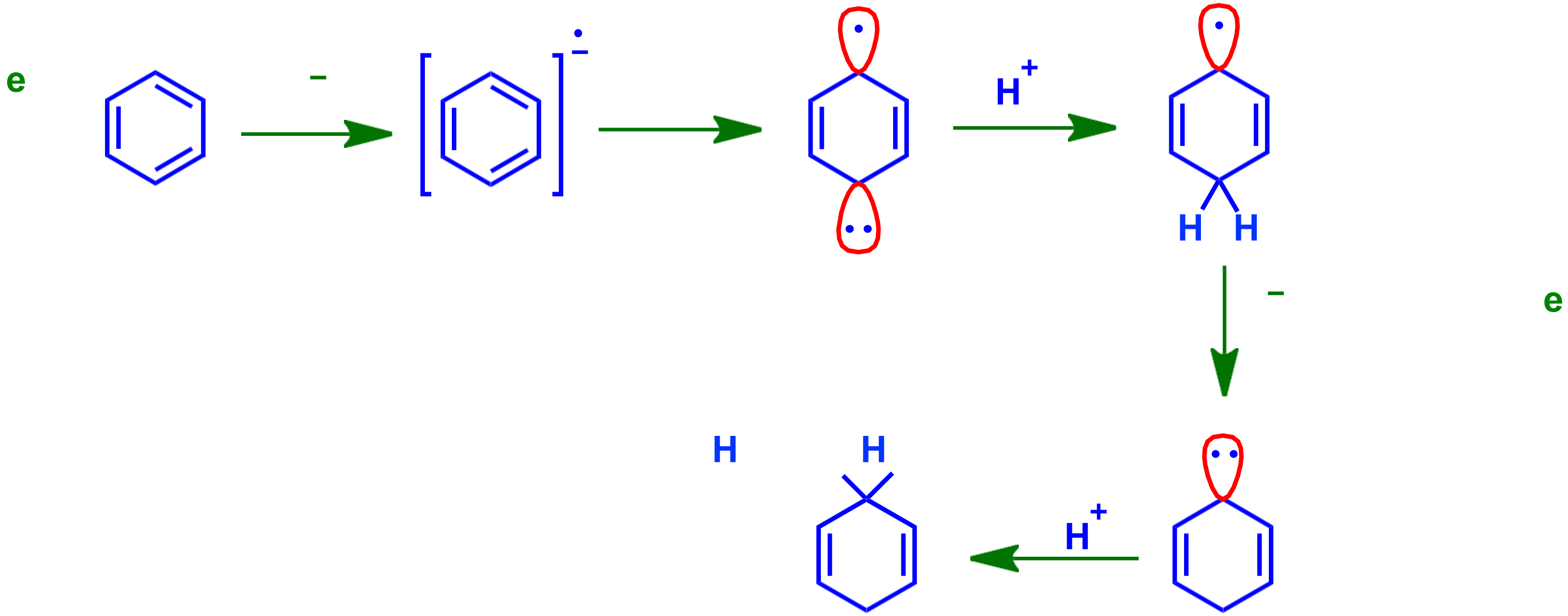
## Dissolving Metal Reduction

### Dissolving Metal Reducing Agent

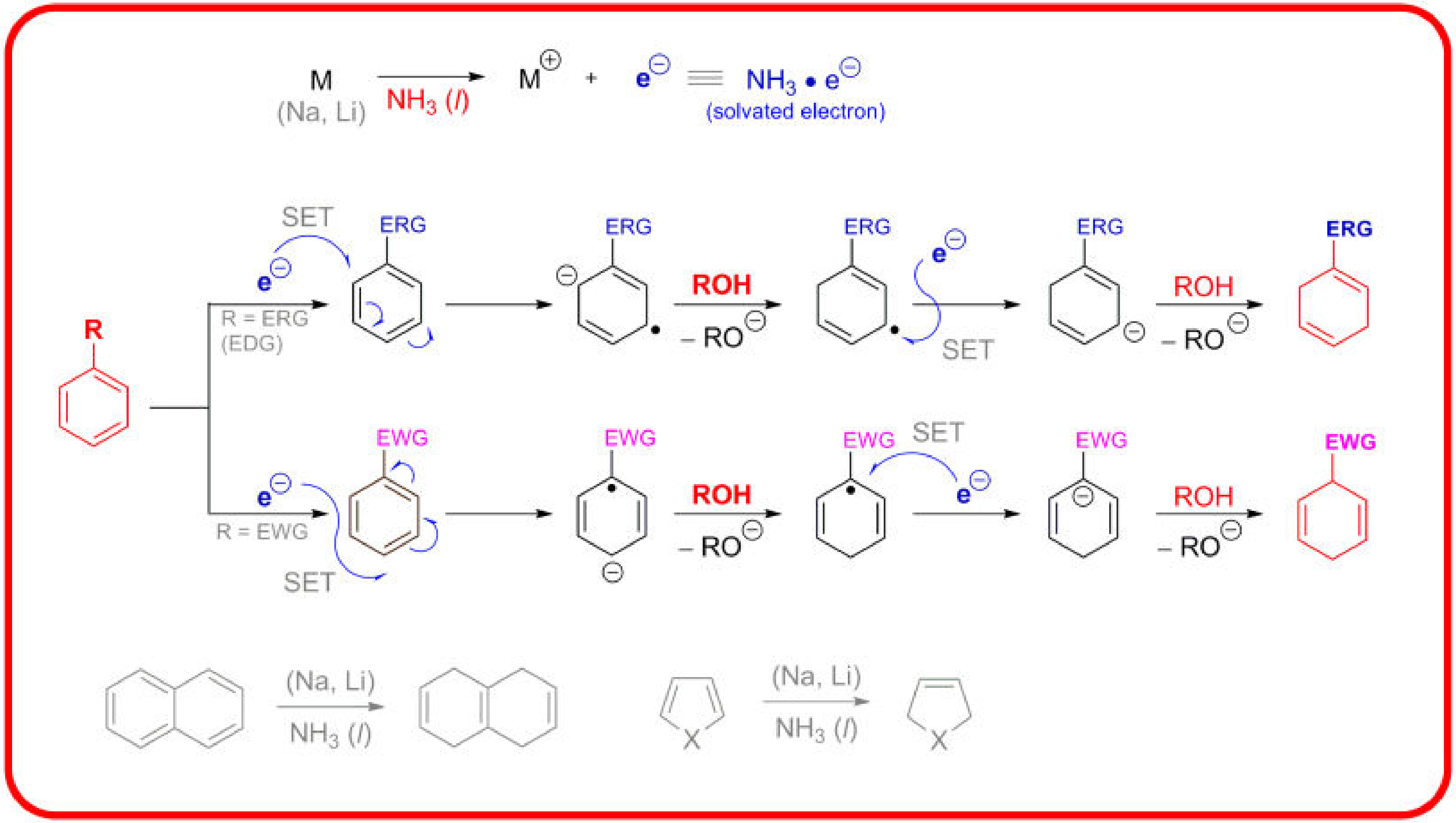
$$M + A \longrightarrow \overset{+}{M} + \overset{-}{e}(A)n$$

**M** = Li, Na, K, Ca **A** = Liquid ammonia, $Et_2NH$, $EtNH_2$, ROH, $H_2O$

### Partial Reduction Of Aromatic Rings:



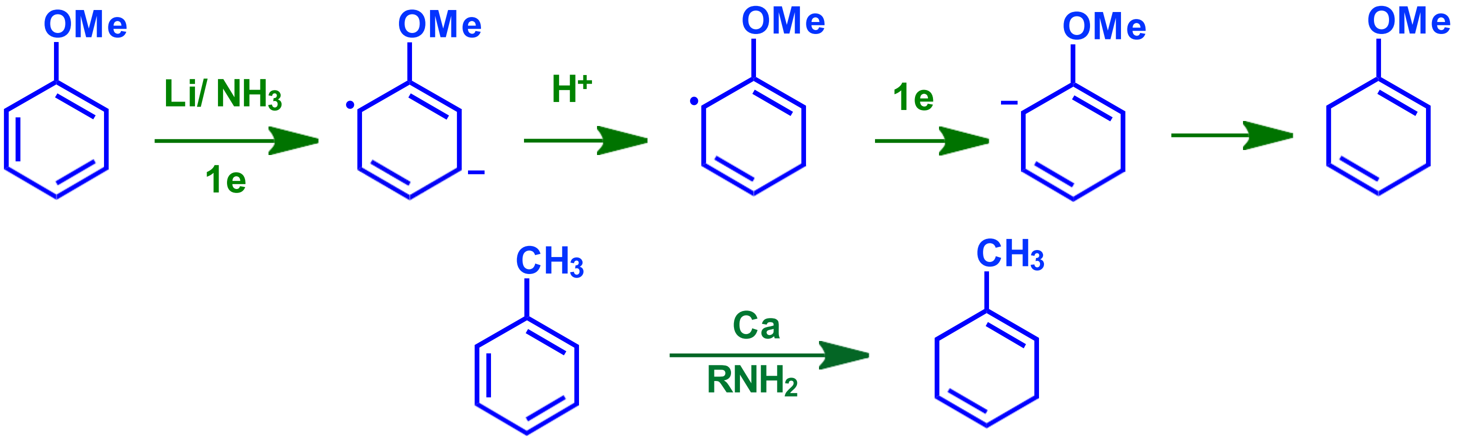
# Mechanism


M
(Na, Li)
NH3 (l)
M⊕ + e⊖ ≡ NH3 • e⊖
(solvated electron)
R
SET
e⊖
R = ERG
(EDG)
ERG
ROH
– RO⊖
SET
e⊖
R = EWG
EWG
(Na, Li)
NH3 (l)
X

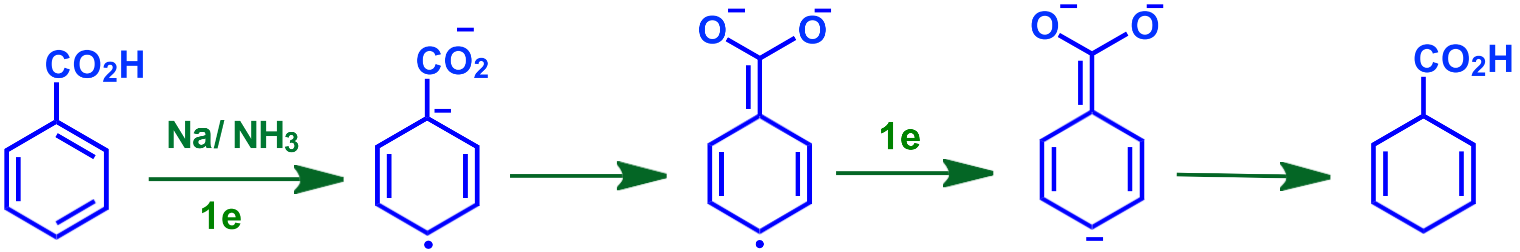
# Birch Reduction

## Dissolving Metal Reduction

### Electron Donating Substituents:



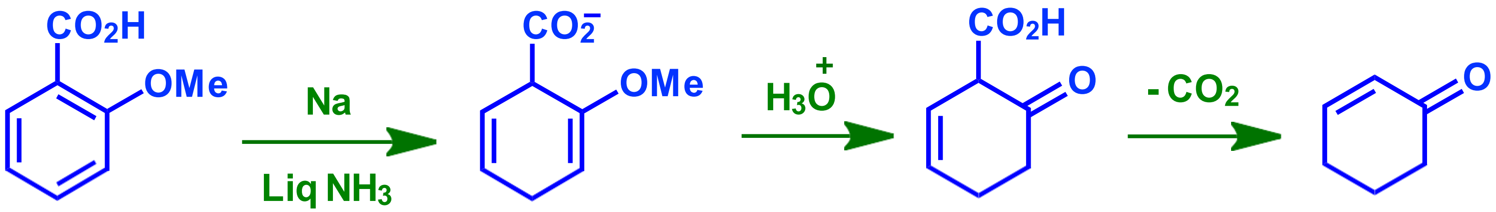
### Electron Withdrawing Substituents:

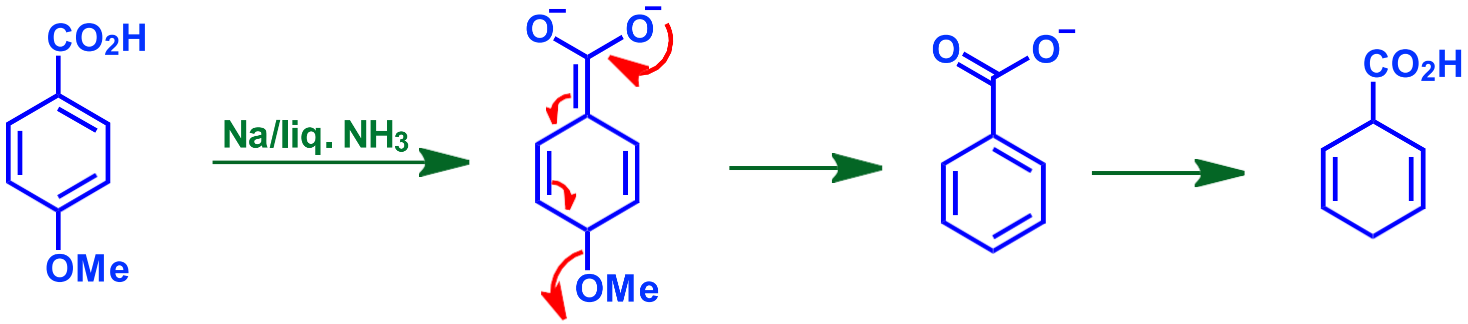


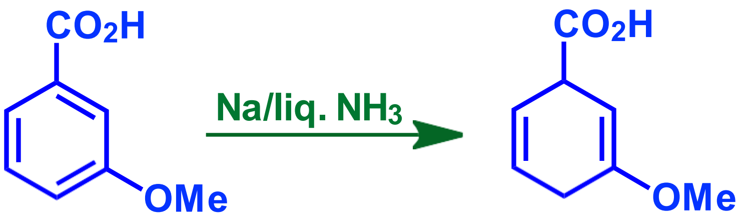
# Birch Reduction

## Dissolving Metal Reduction

### Both Electron Donating And Electron Withdrawing Substituents:



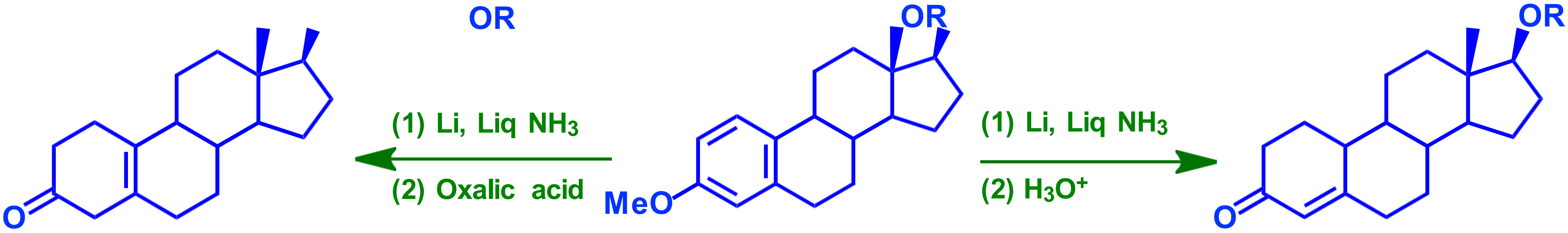


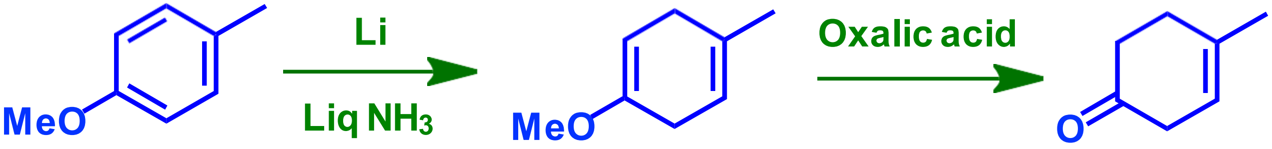


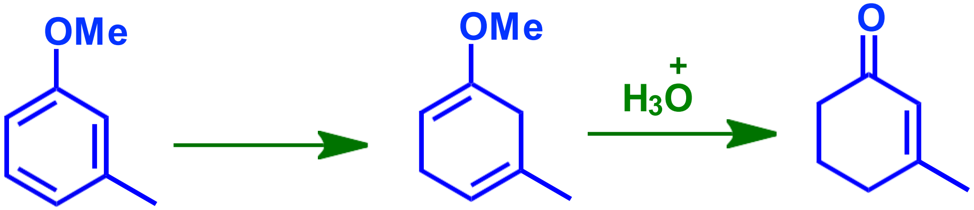
# Birch Reduction

## Dissolving Metal Reduction

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



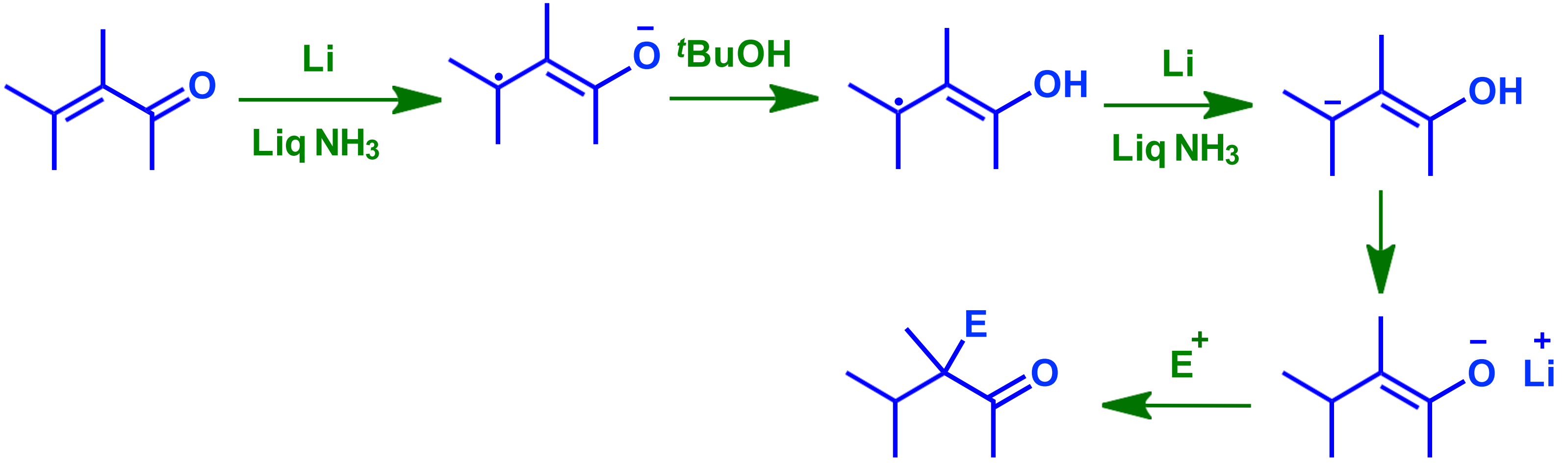


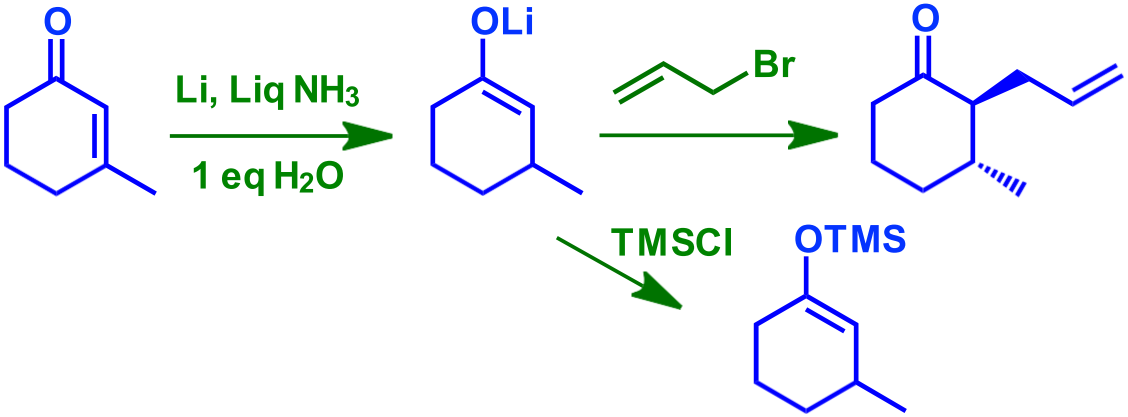


# Birch Reduction

## Dissolving Metal Reduction

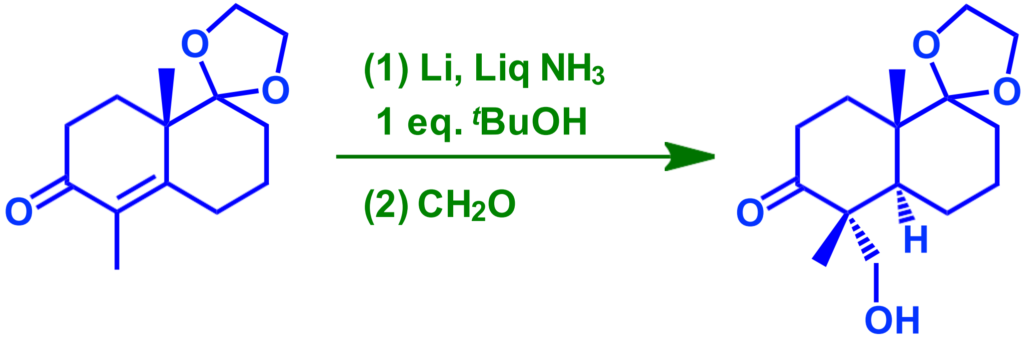
### α,β-unsaturated compounds are reduced in 1,4-fashion



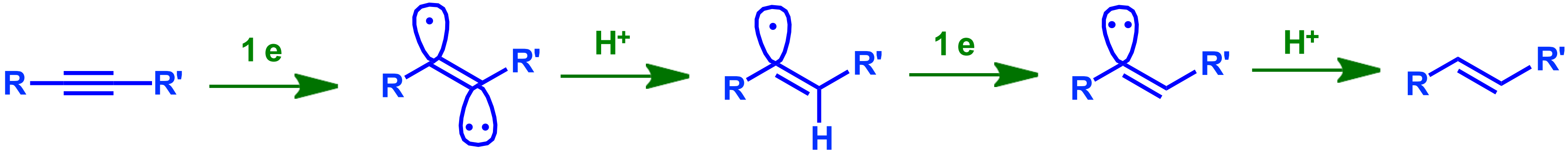


# Birch Reduction

## Dissolving Metal Reduction

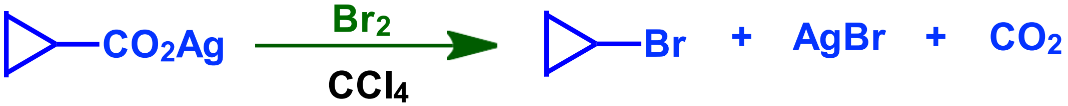


### Reduction of Alkynes:



# 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

$$RCOOAg + X_2 \longrightarrow RCOOX + AgX$$

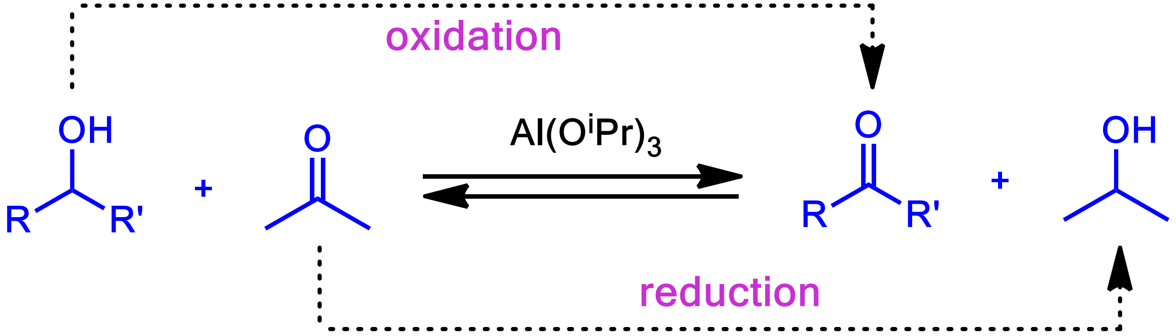
$$RCOOX \xrightarrow{\Delta} RCO\dot{O} + \dot{X} \quad \text{(Initiation)}$$

$$RCO\dot{O} \longrightarrow \dot{R} + CO_2 \quad \text{(Decarboxylation)}$$

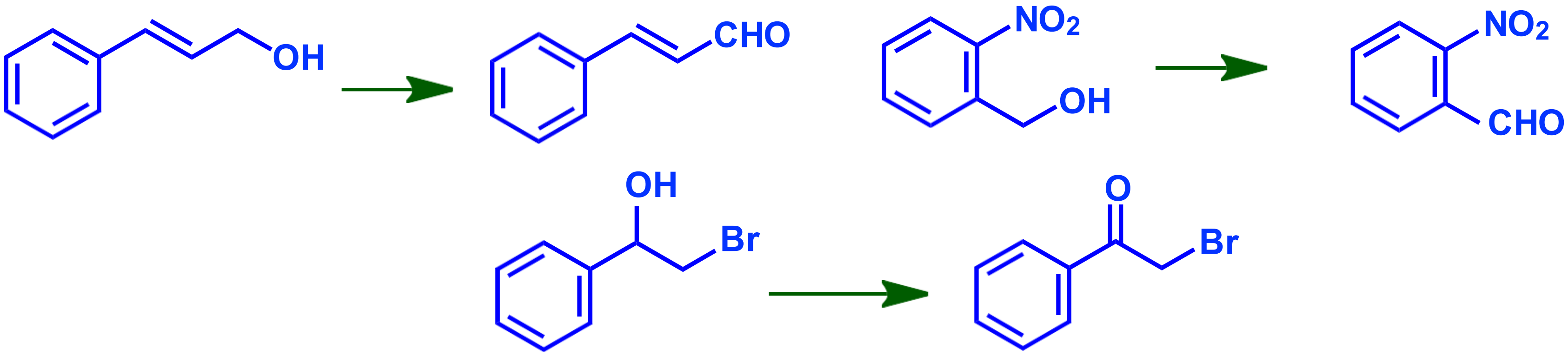
$$\dot{R} + RCOOX \longrightarrow RX + RCO\dot{O} \quad \text{(Propagation)}$$

# Oppenauer oxidation

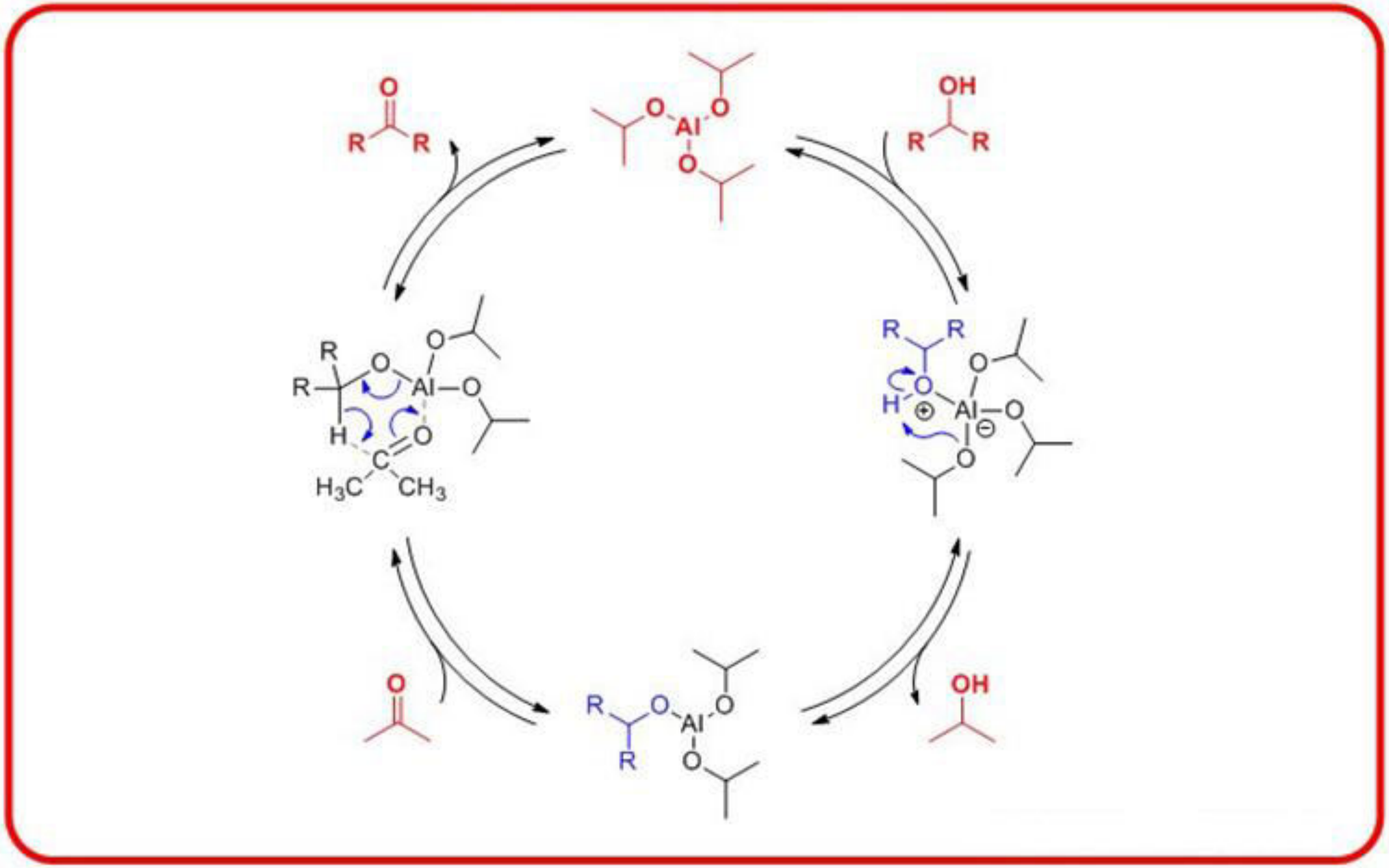
## Aluminum-based reagent Reduction



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



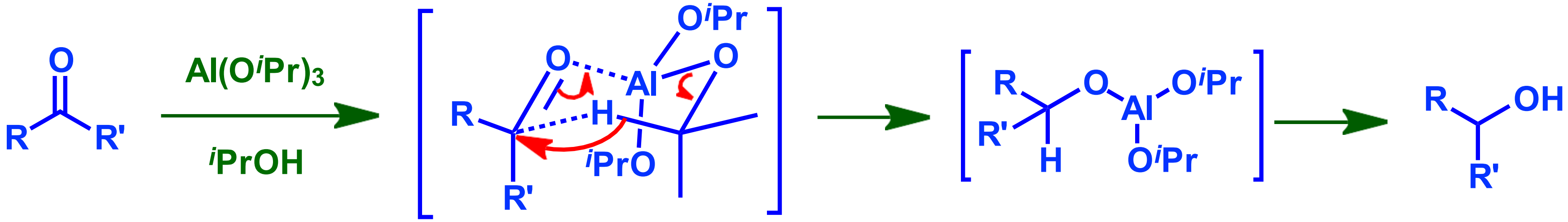
# Mechanism



# Oppenauer oxidation

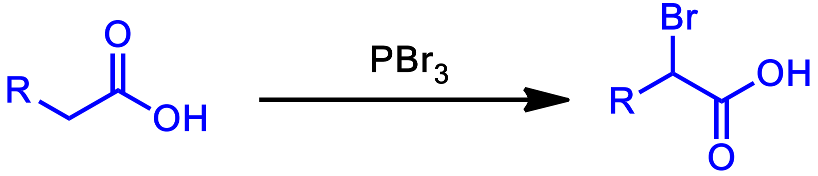
## Aluminum-based reagent Reduction

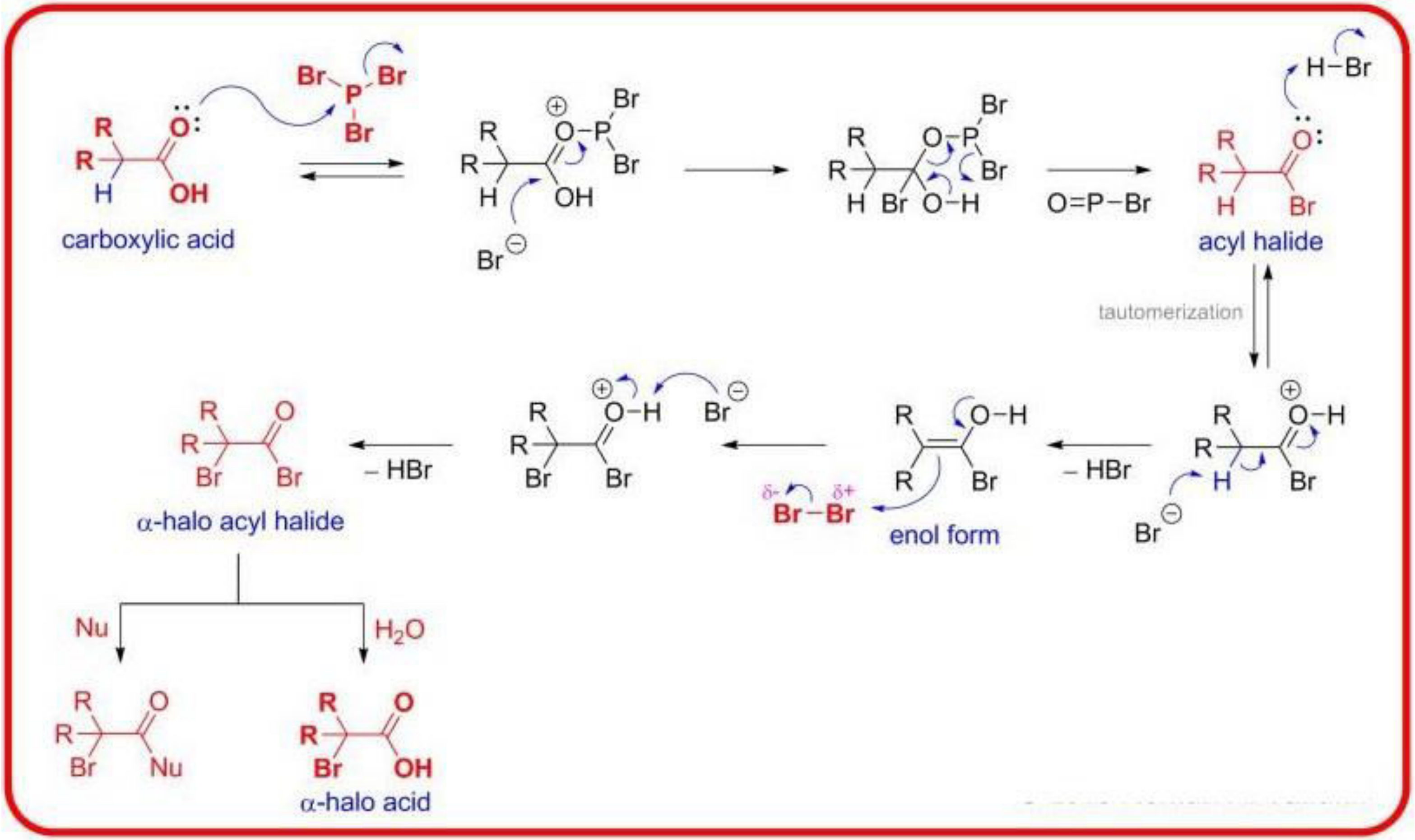
- Al(O$^i$Pr)$_3$ is the reagent
- Acetone accepts the hydride from alcohol and reduced
- By-product is isopropanol
- Reverse process is known as Meerwein–Pondorff-Verley (MPV) Reduction



# HVZ Reaction

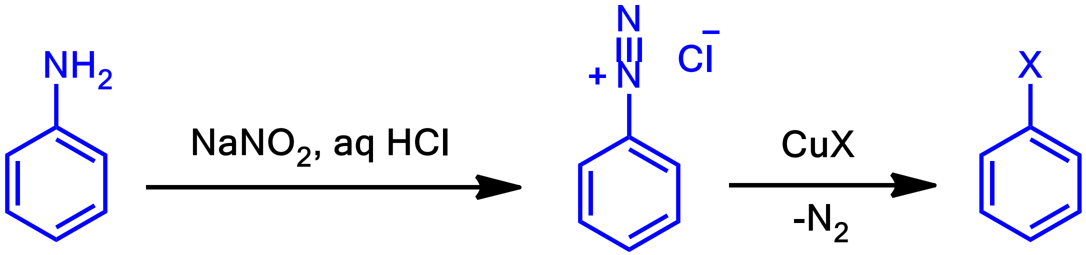
The Hell–Volhard–Zelinsky halogenation reaction (HVZ Reaction) halogenates carboxylic acids at the α carbon.





# Sandmeyer Reaction

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



X = Cl, Br, CN

- The most commonly employed Sandmeyer reactions are the chlorination, bromination, cyanation, and hydroxylation reactions using CuCl, CuBr, CuCN, and $Cu_2O$, respectively.

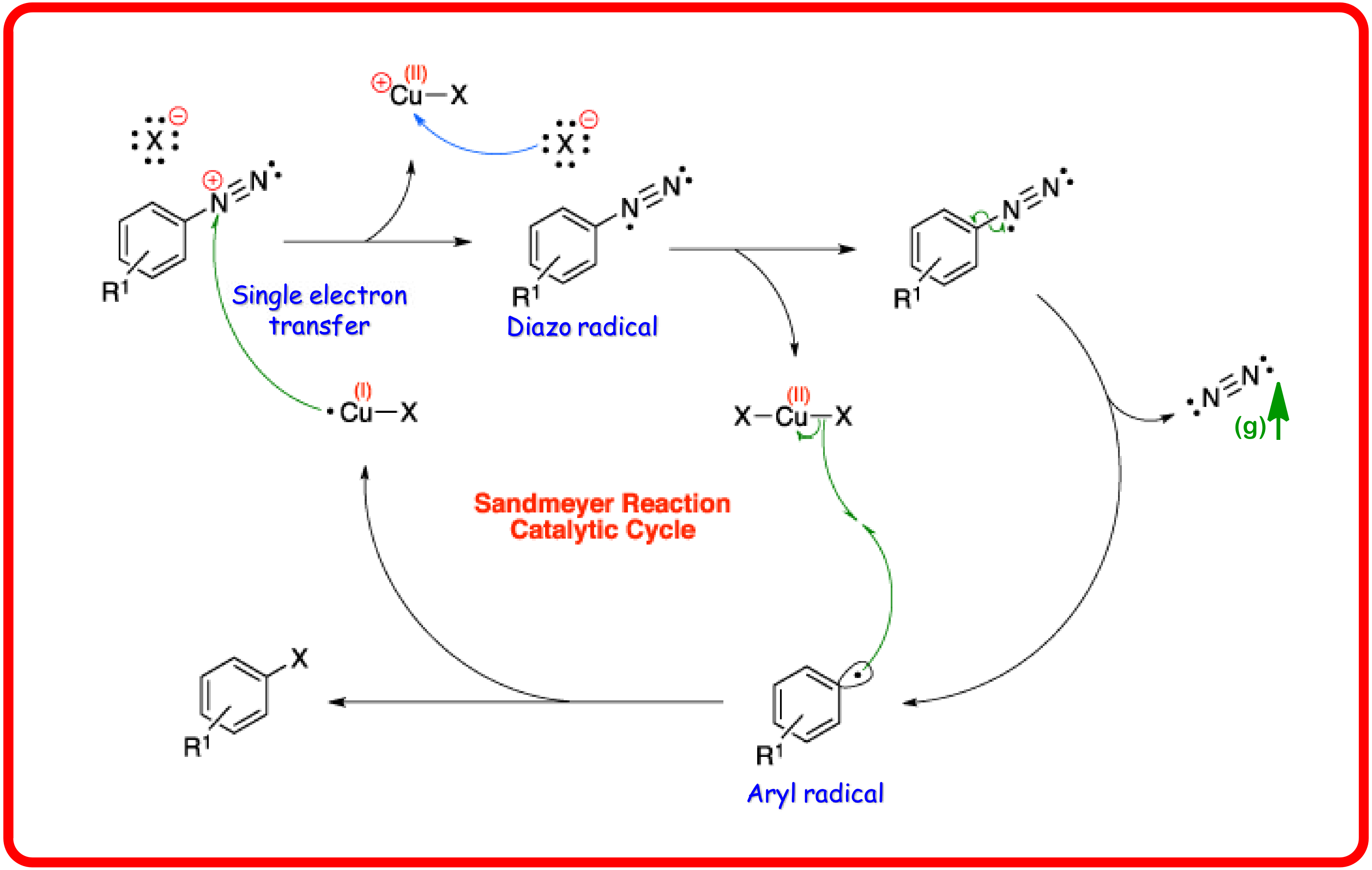
Chlorination: $ArN_2^+Cl^-$, CuCl, HCl (36% aq.), 50 – 100 °C

Bromination: $ArN_2^+HSO_4^-$, CuBr, HBr (48% aq.), 50 – 100 °C

Cyanation: $ArN_2^+Cl^-$, CuCN, KCN, $H_2O$, benzene, 0 °C

Hydroxylation: $ArN_2^+HSO_4^-$, $Cu_2O$, $Cu(NO_3)_2$, $H_2O$, 25 °C.

# Mechanism



Single electron transfer

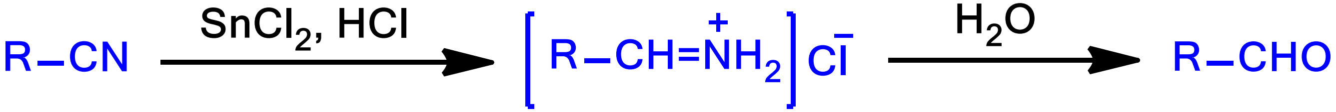
Diazo radical

Sandmeyer Reaction Catalytic Cycle

Aryl radical

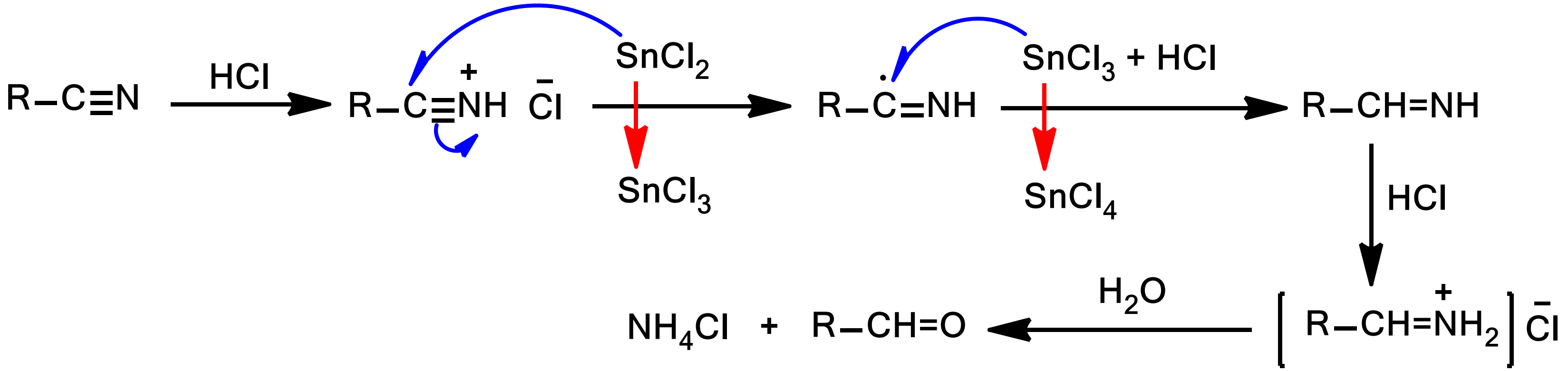
# Stephen Reaction

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 ($H_2O$).



$$R-CN \xrightarrow{SnCl_2,\ HCl} \left[R-CH=\overset{+}{N}H_2\right]\overset{-}{Cl} \xrightarrow{H_2O} R-CHO$$

## Mechanism

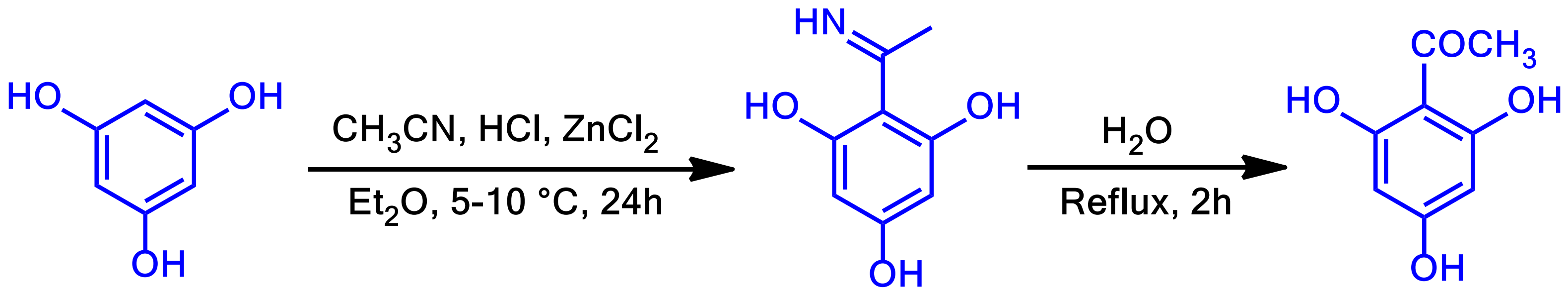


$$R-C\equiv N \xrightarrow{HCl} R-C\equiv\overset{+}{N}H\ \overset{-}{Cl} \xrightarrow[SnCl_3]{SnCl_2} R-\dot{C}=NH \xrightarrow[SnCl_4]{SnCl_3 + HCl} R-CH=NH$$

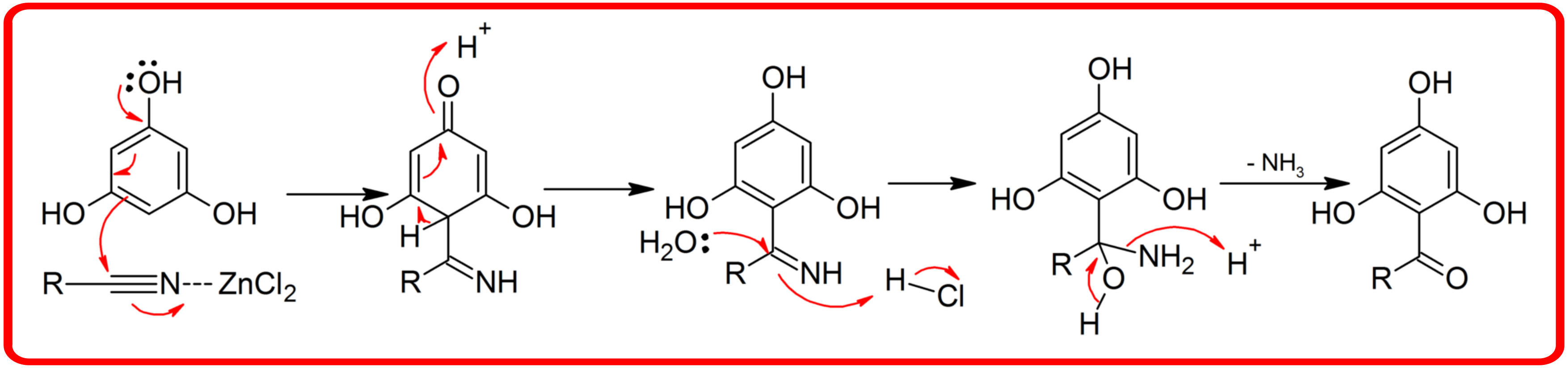
$$R-CH=NH \xrightarrow{HCl} \left[R-CH=\overset{+}{N}H_2\right]\overset{-}{Cl} \xrightarrow{H_2O} R-CH=O + NH_4Cl$$

# 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.

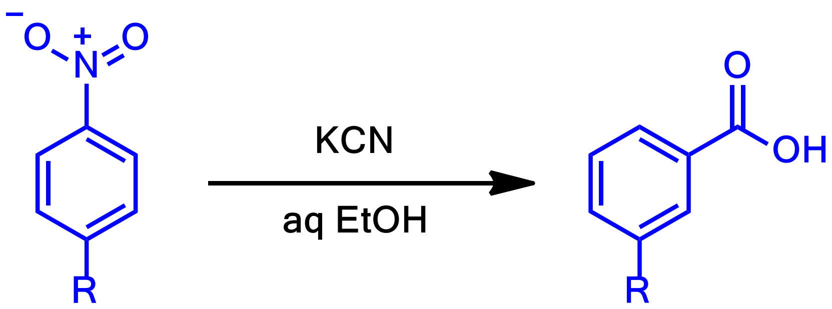


## Mechanism



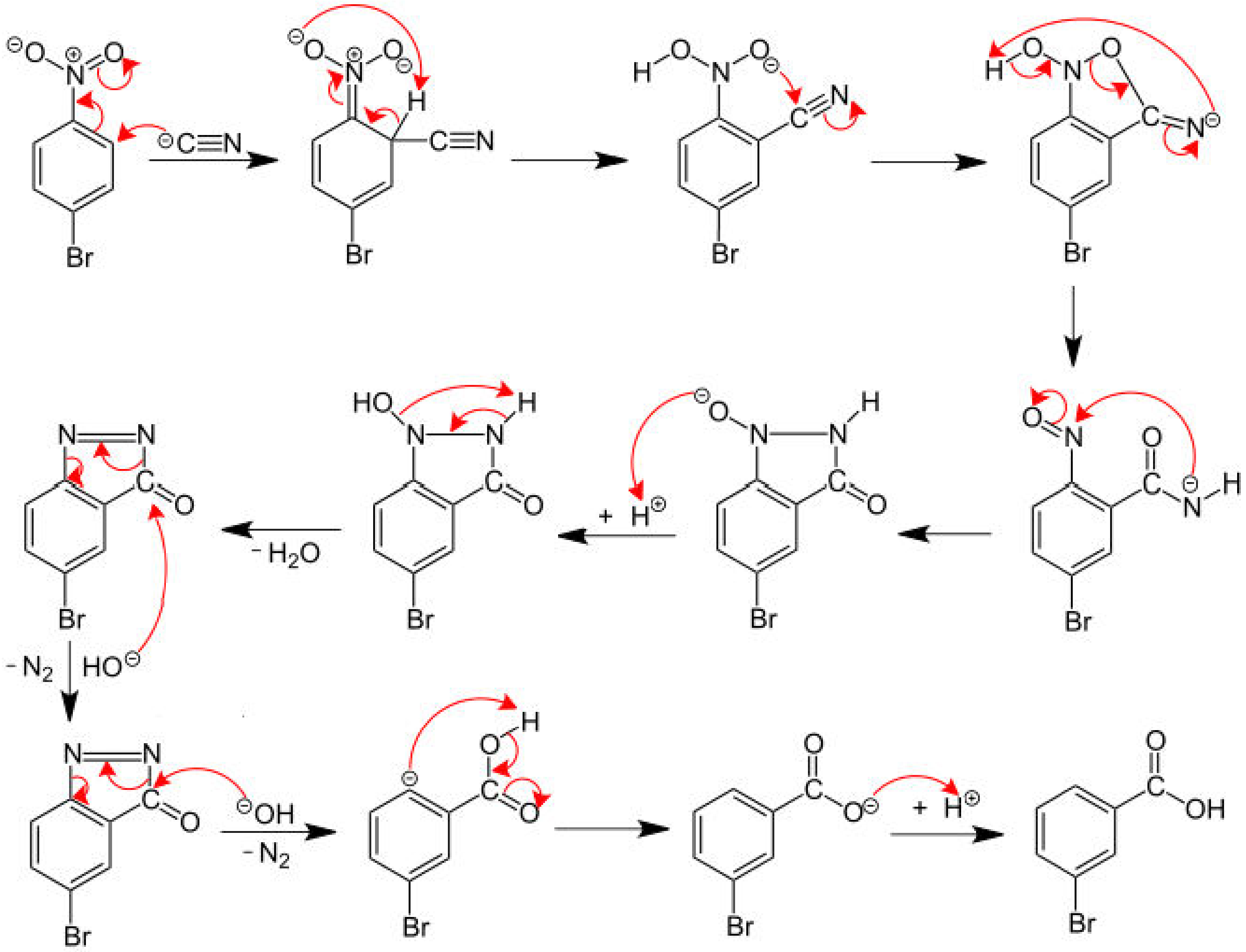
# Von Richter reaction

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.



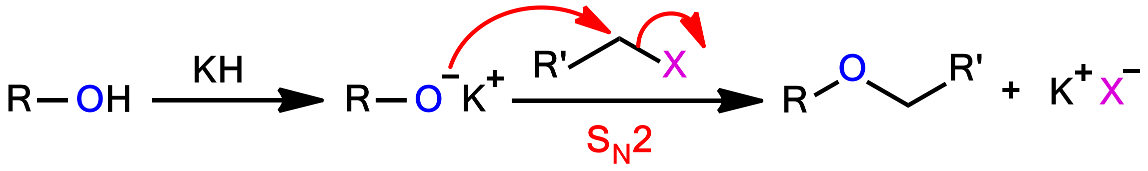
- Although it is not generally synthetically useful due to the low chemical yield and formation of numerous side products, its mechanism was of considerable interest, eluding chemists for almost 100 years before the currently accepted one was proposed.

# Mechanism



# 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.



X is Cl, Br, I, OTs or other good leaving groups

- Primary halides and tosylates work best, since competitive E2 elemination 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!

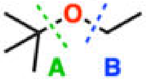
**Possibility B:**

$S_N2$ on methyl halide -
works well!

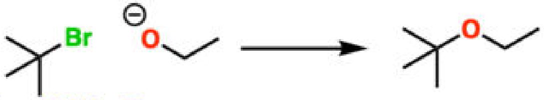
Both of these are perfectly good $S_N2$ reactions

## *t*-Butyl Ethyl Ether

*Two possibilities: "retrosynthetically" break bonds A or B*

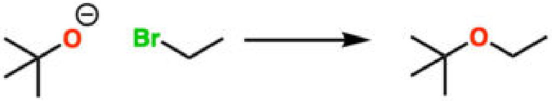


**Possibility A:**



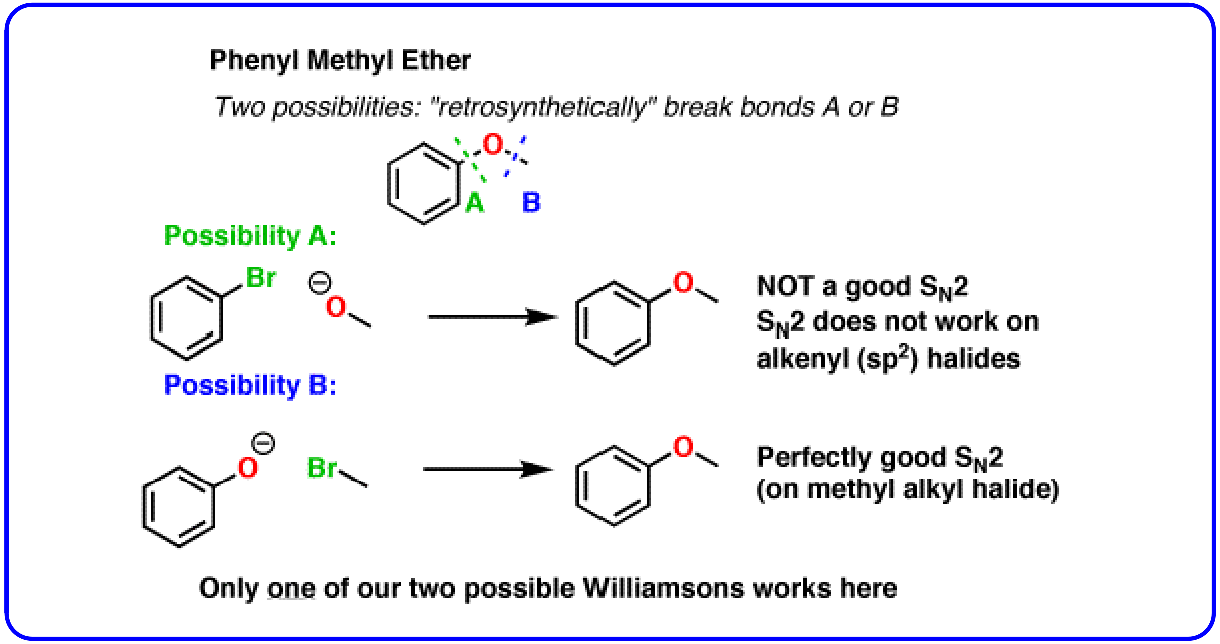
NOT a good $S_N2$ - tertiary
alkyl halide.
This will not work!!
(E2 will happen instead)

**Possibility B:**



This will work
(primary alkyl halide)

Only <u>one</u> of our two possible Williamsons works here



**Phenyl Methyl Ether**

*Two possibilities: "retrosynthetically" break bonds A or B*

**Possibility A:**

NOT a good $S_N2$
$S_N2$ does not work on
alkenyl ($sp^2$) halides

**Possibility B:**

Perfectly good $S_N2$
(on methyl alkyl halide)

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.**