Organic Chemistry CH-401 Course

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Molecular Rearrangements

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Molecular Rearrangements

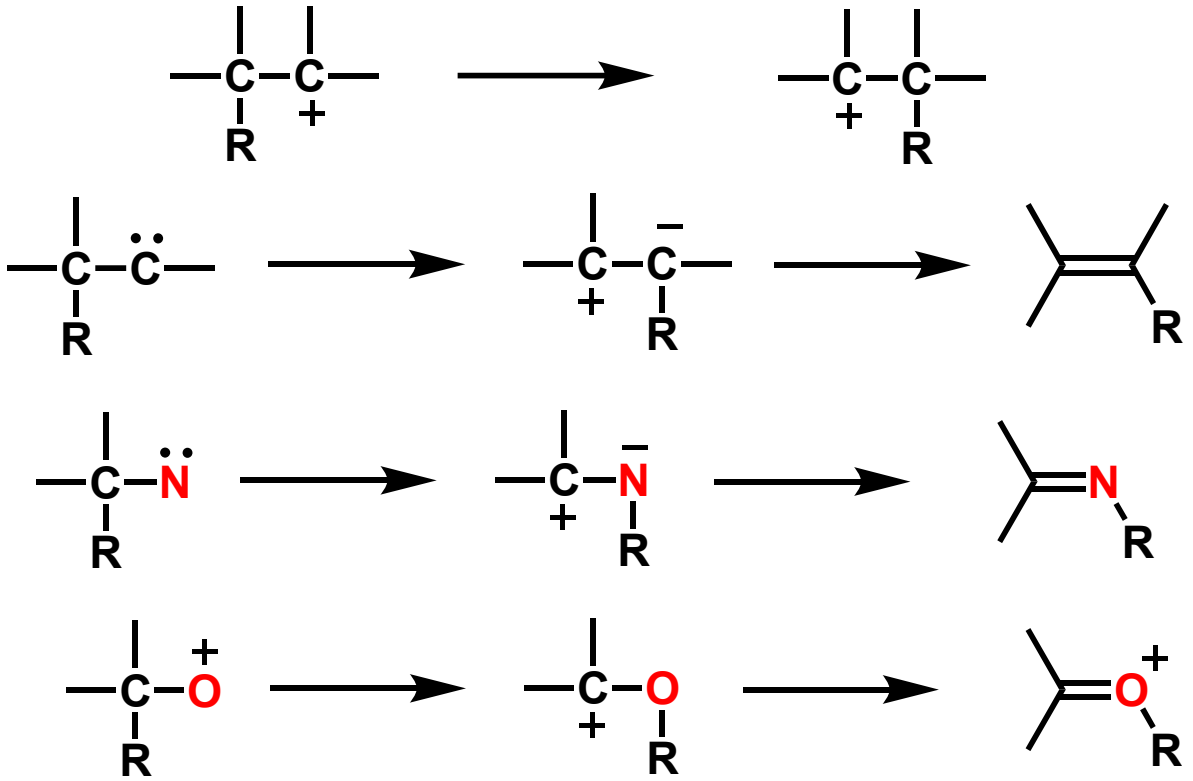
- Migration of one group from one atom to another within the molecule
- Generally the migrating group never leaves the molecule
- There are five types of skeletal rearrangements-

1. Electron deficient skeletal rearrangement
2. Electron rich skeletal rearrangement
3. Radical rearrangement
4. Rearrangements on an aromatic ring
5. Sigmatropic rearrangement

Electron Deficient Skeletal Rearrangements

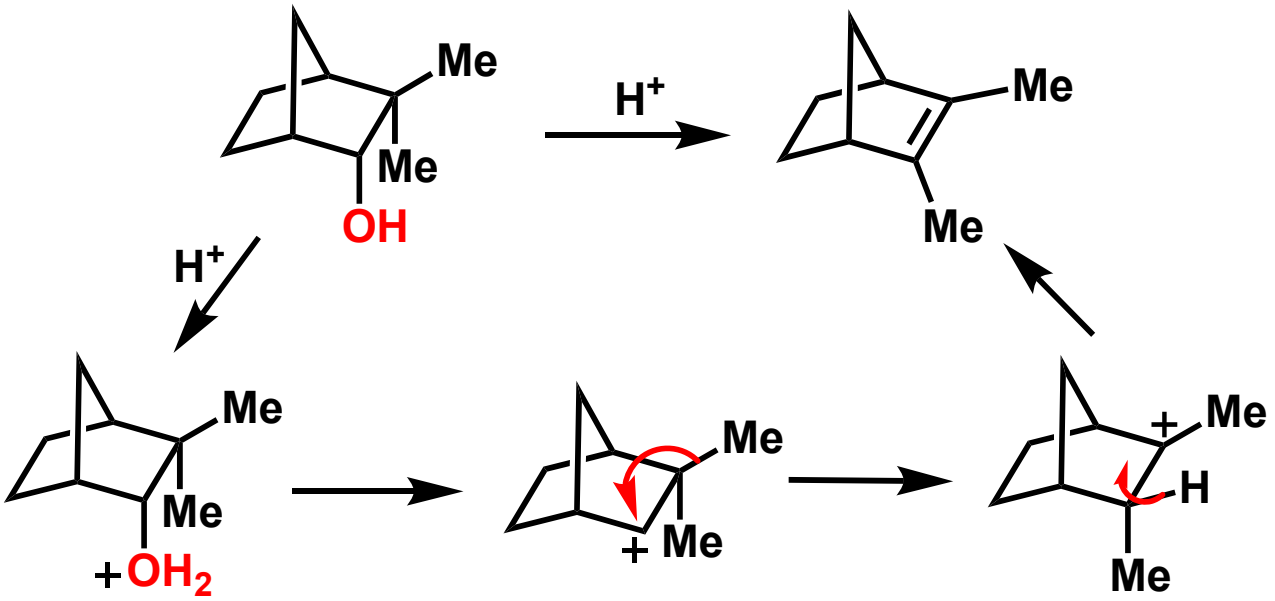
- Generally it involves **migration** of a group from one atom to an adjacent atom, having **six electrons in the valence shell**
- The molecular system may be either a **cation** or a **neutral** molecule

Examples:



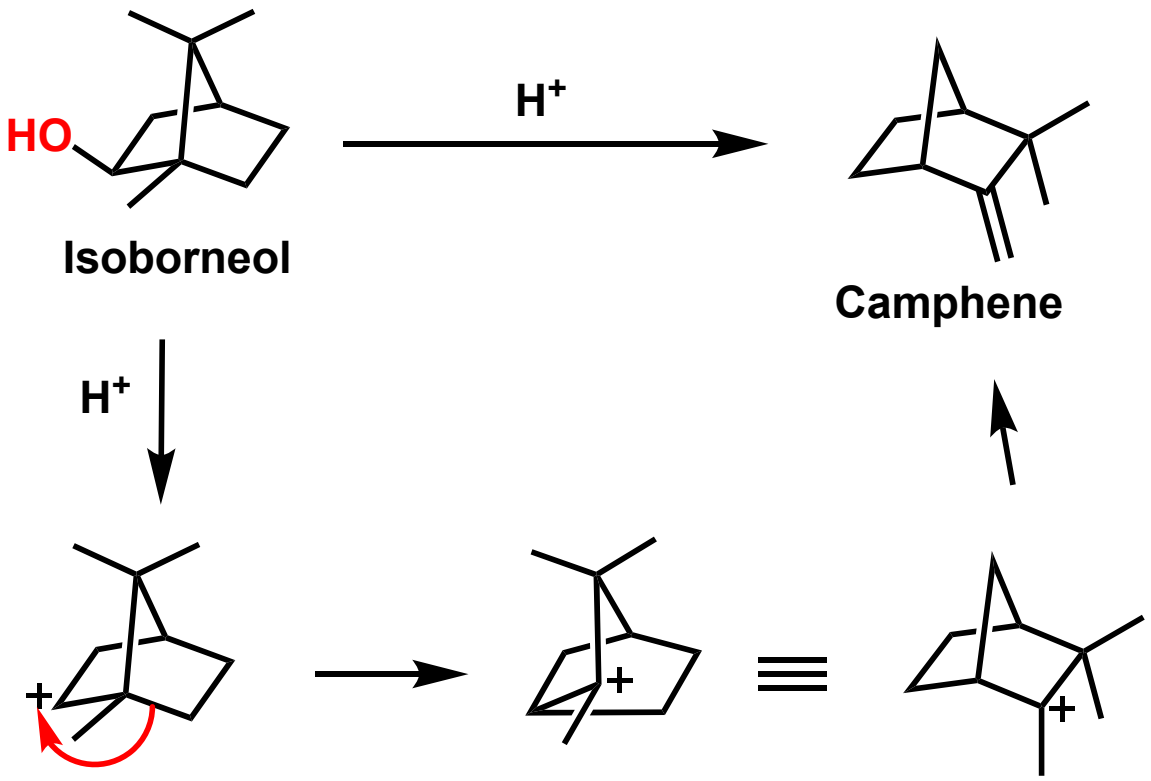
Wagner-Meerwin Rearrangement

- 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

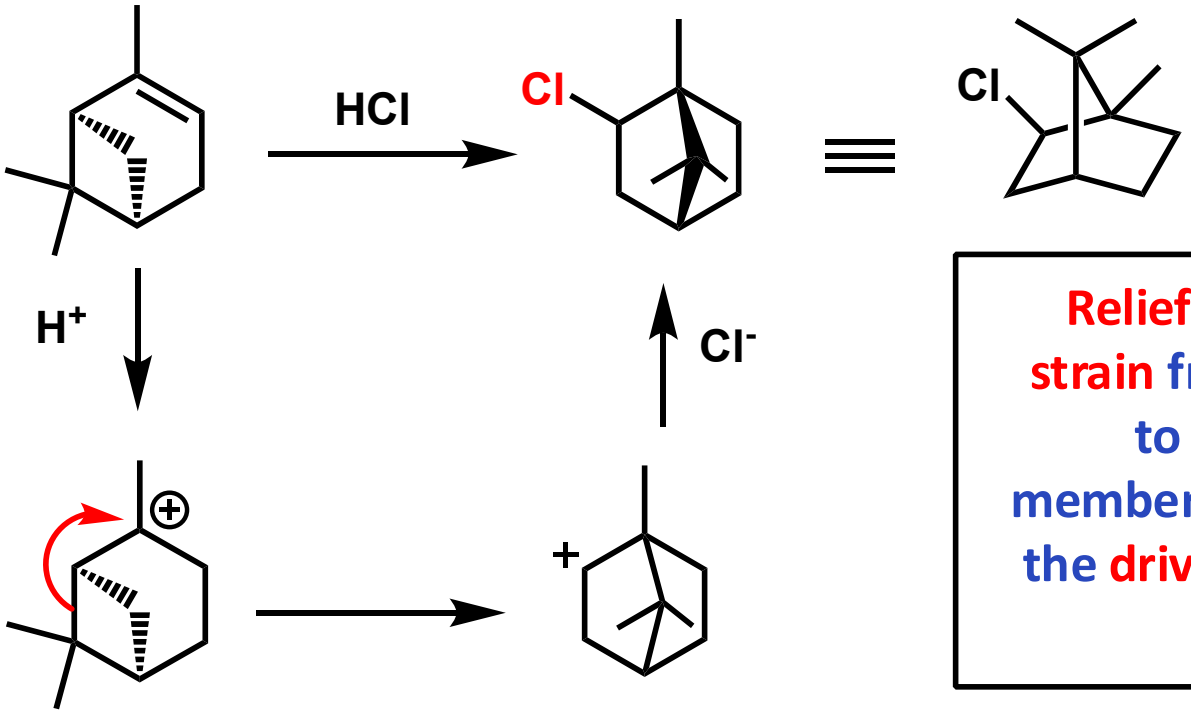


Ring Expansion

- More stable carbocation will be generated
- Stability of carbocations: 3° > 2° > 1°

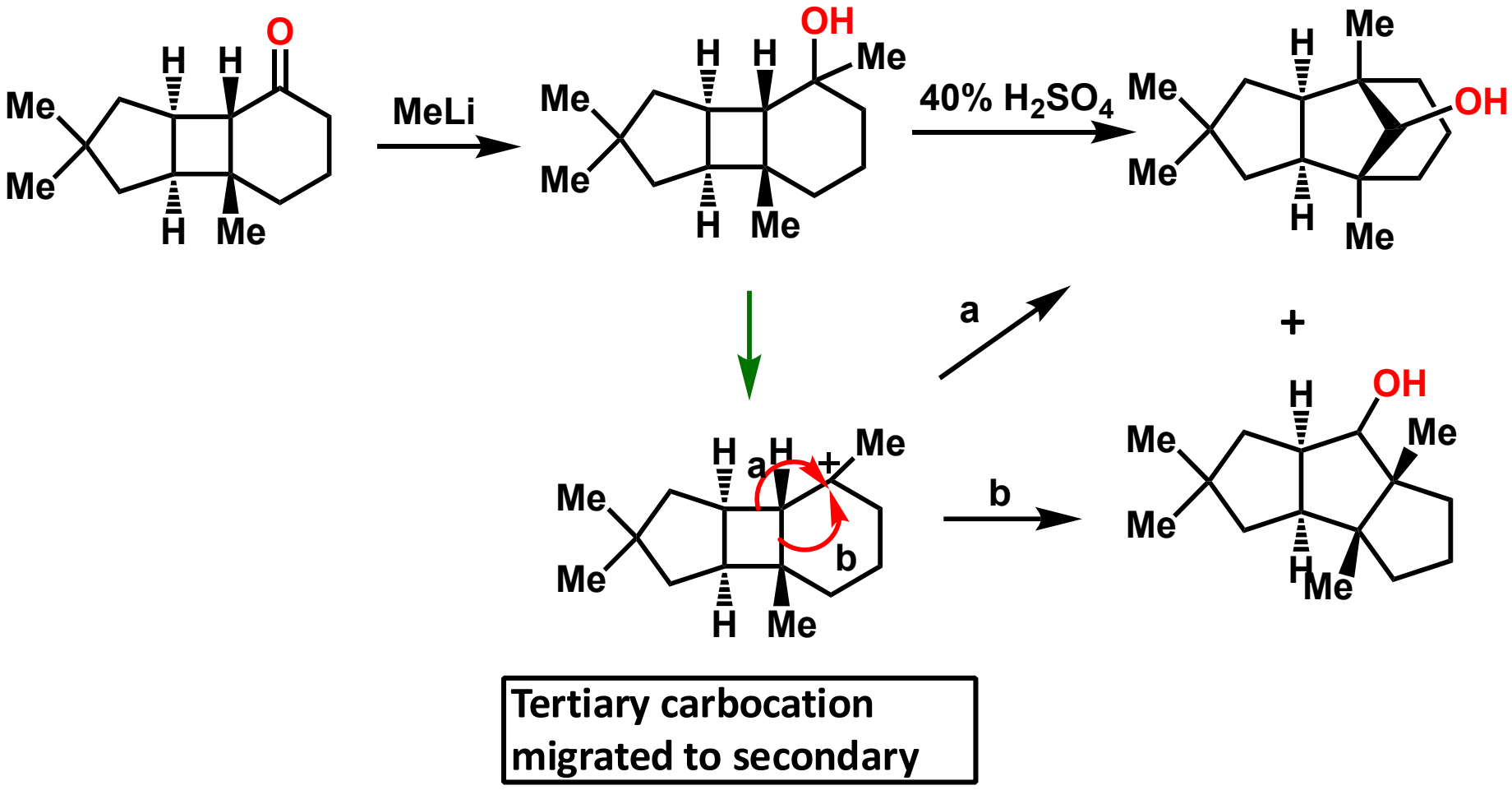
Can we go from 3° to 2° ??

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



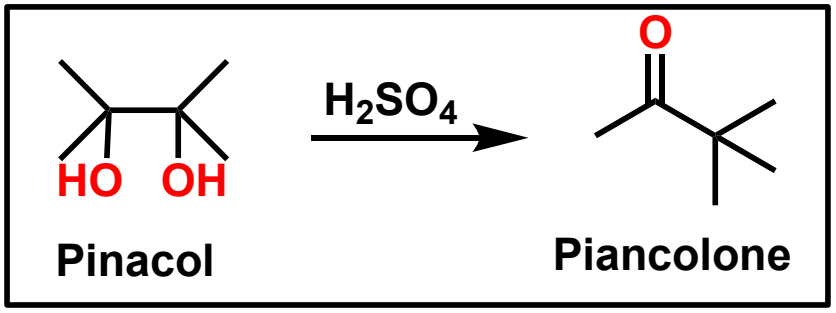
Relief in ring strain from four to five membered ring is the driving force

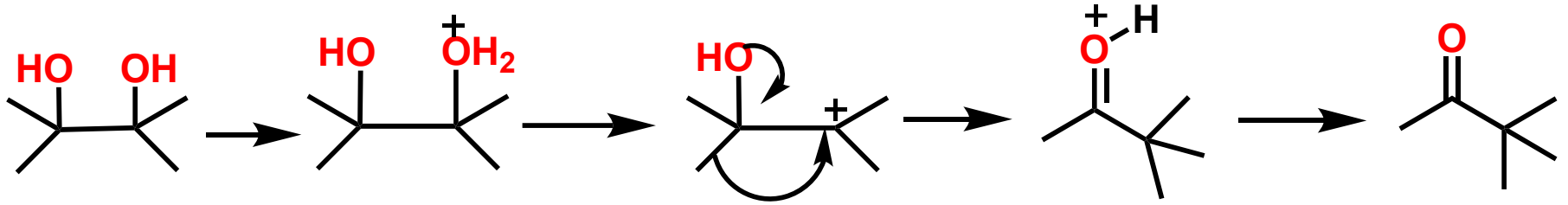
Ring Expansion



Tertiary carbocation migrated to secondary

Pinacol-Pinacolone Rearrangement





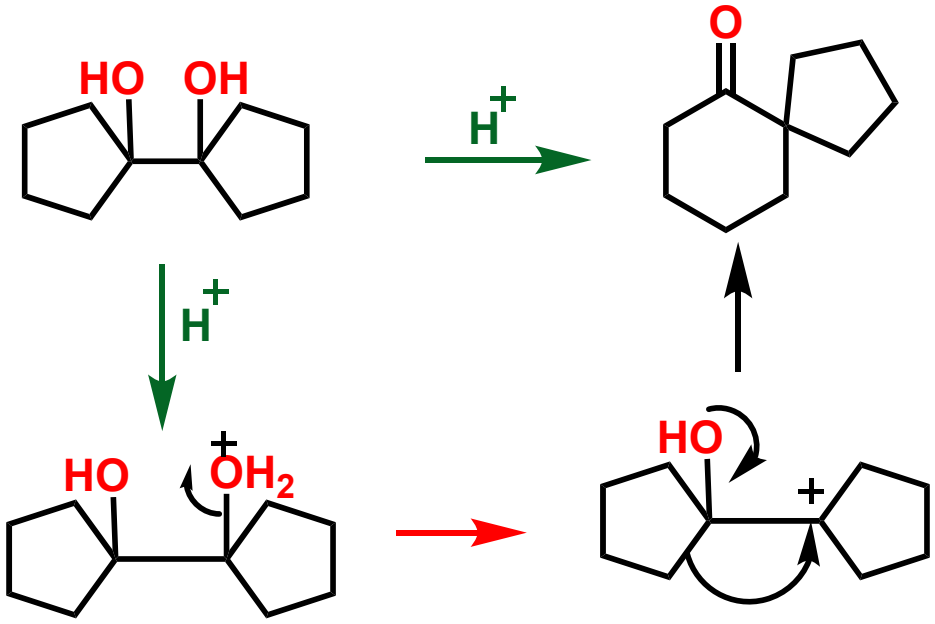
- Carbocation is already tertiary
- There is no ring strain
- Then why should it rearrange?

The lone pair of electrons on the oxygen is another source to stabilize the carbocation

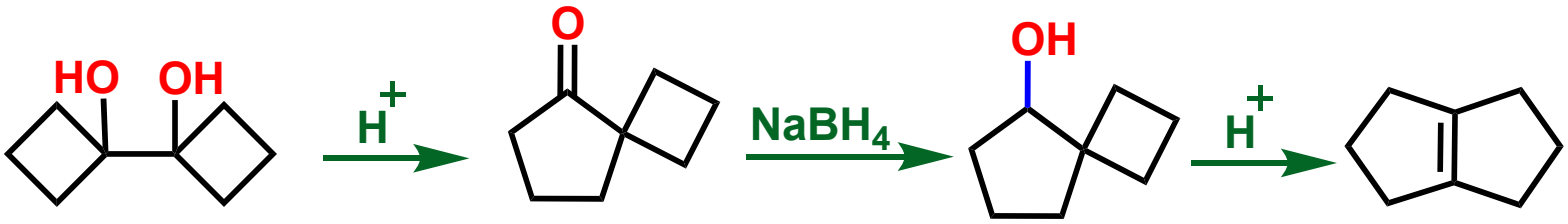
Pinacol-Pinacolone Rearrangement

- 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

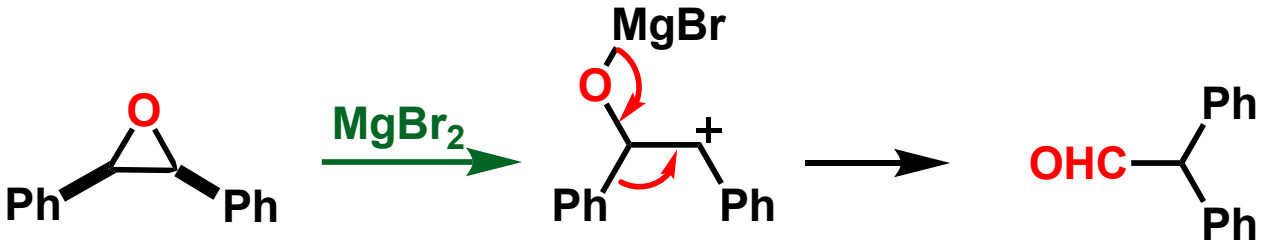
Preparation of Spiro System:



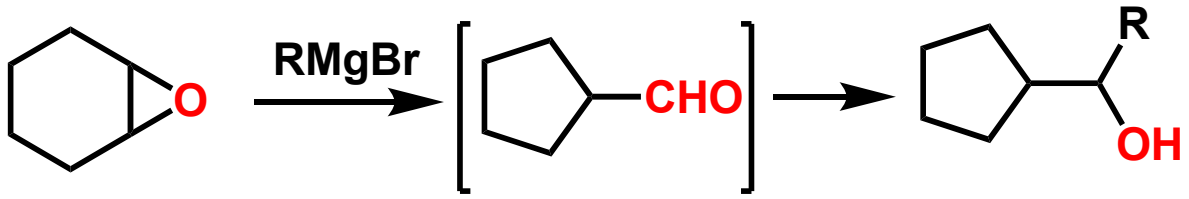
Pinacol-Pinacolone Rearrangement



Epoxides also undergo pinacol type rearrangement on treatment with acid



➢ **With a Grignard reagent, rearrangement occurs faster than addition to the epoxide**

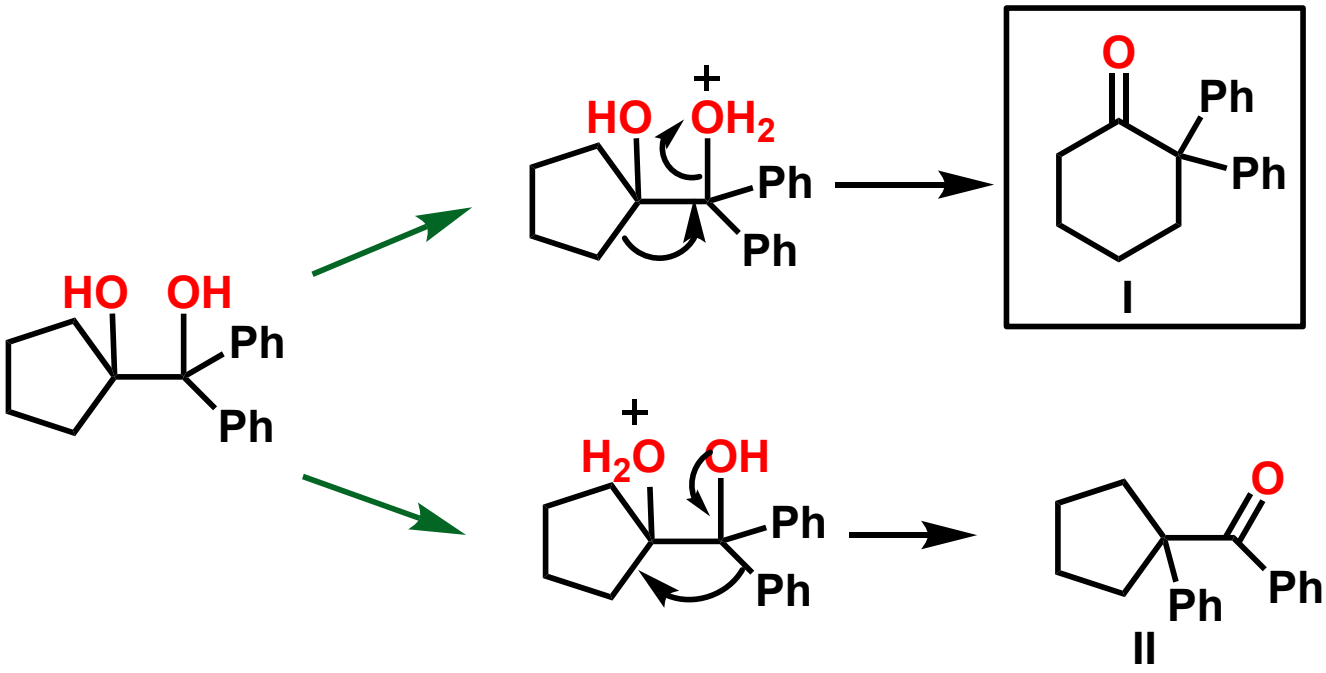


Pinacol-Pinacolone Rearrangement

Migrating group preference:

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

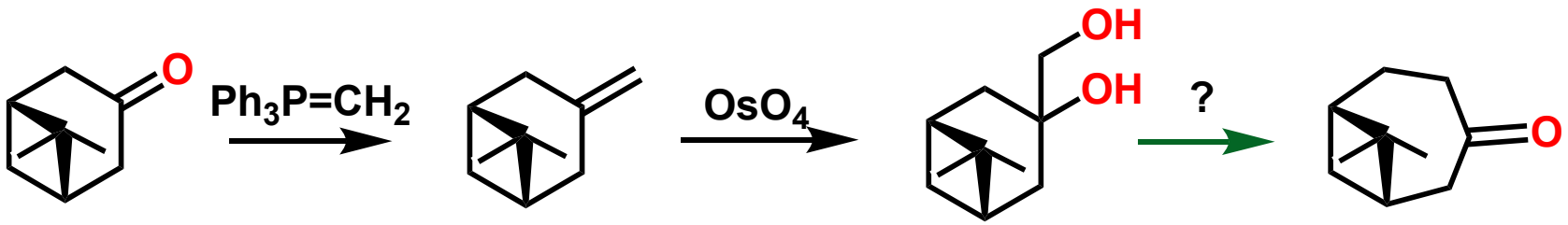
It matters when we have unsymmetrical epoxides & diols



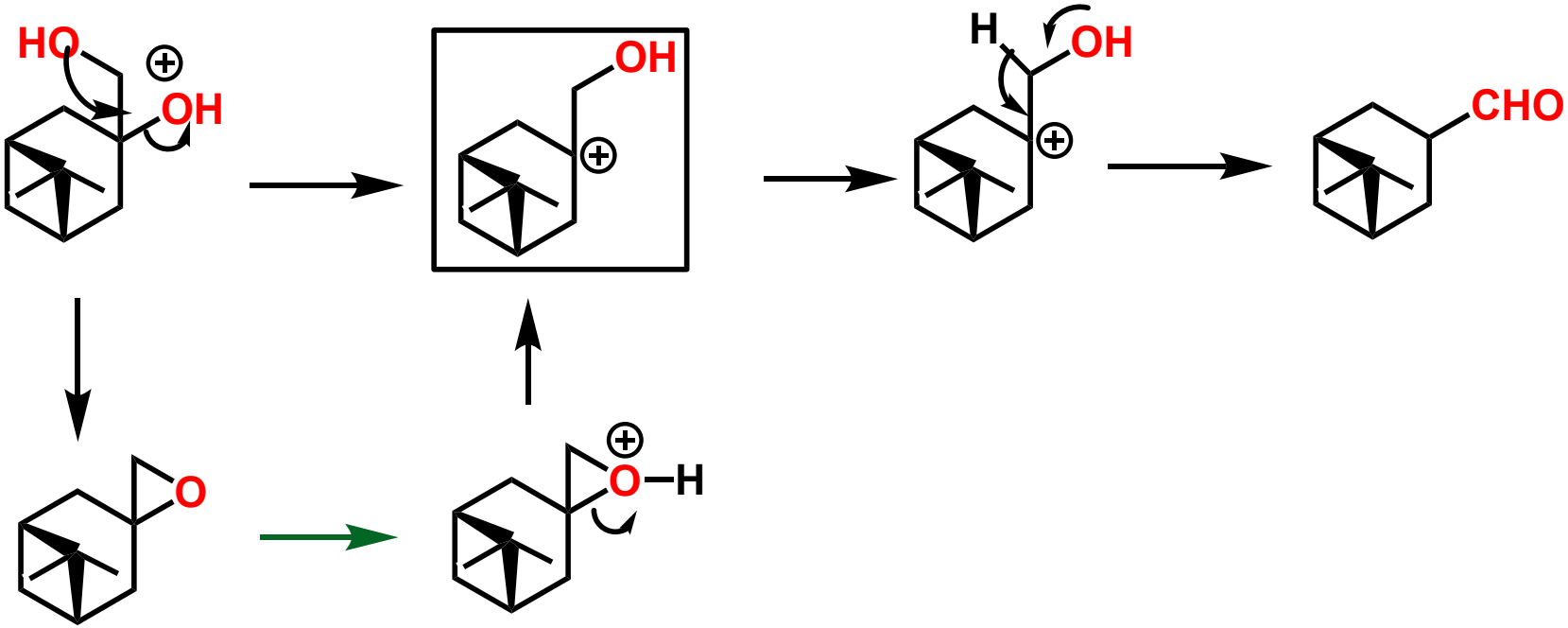
Only I is formed in quantitative amount because the carbocation is stabilized by two phenyl groups

Semi-Pinacolone Rearrangement

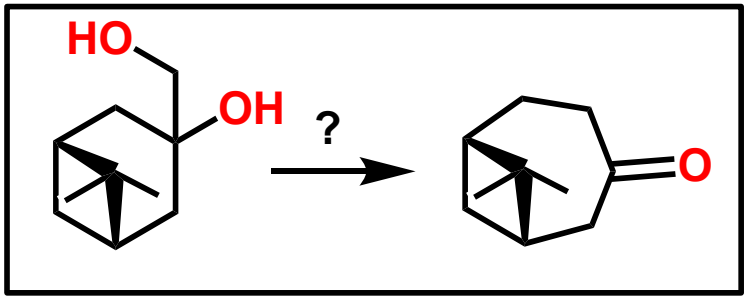
Pinacol rearrangement without choice



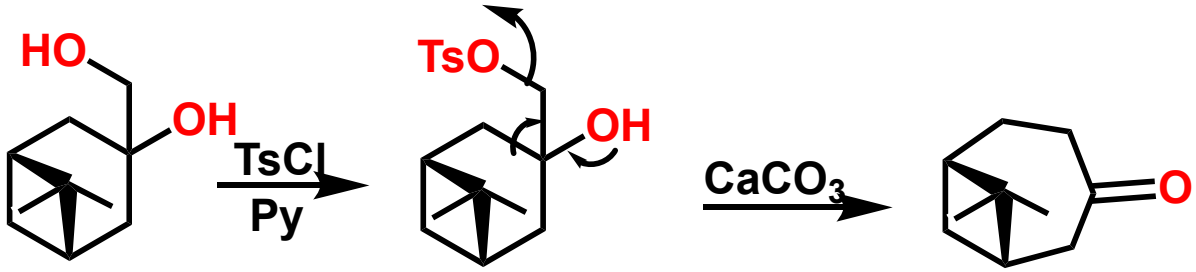
Under normal acidic conditions



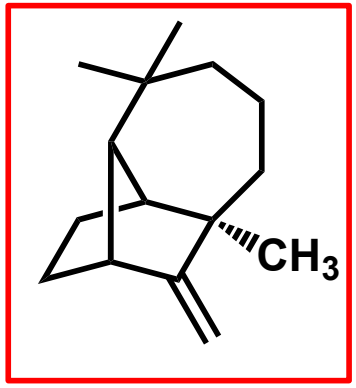
Semi-Pinacolone Rearrangement



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

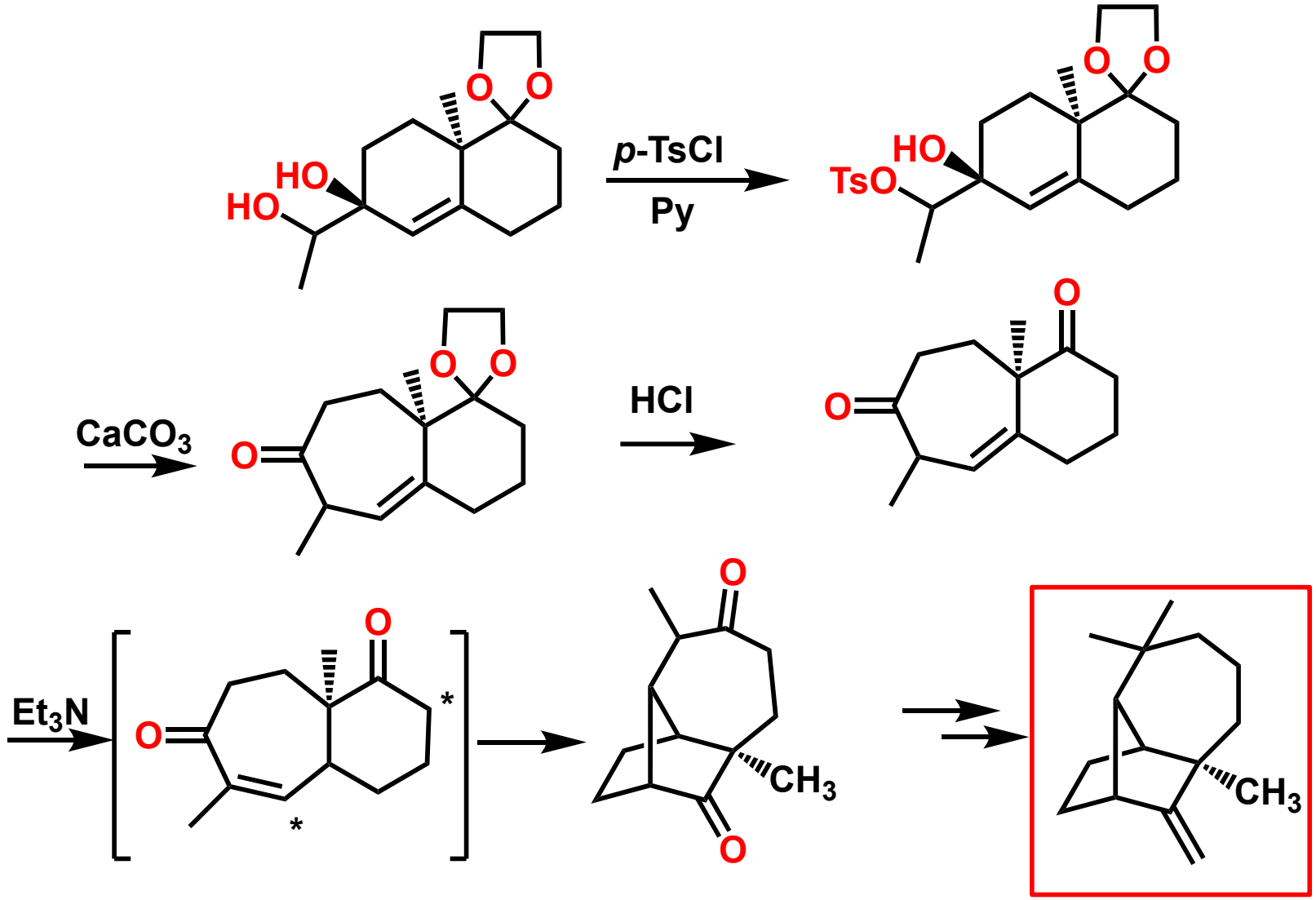


Corey exploited a similar sequence in the synthesis of longifolene



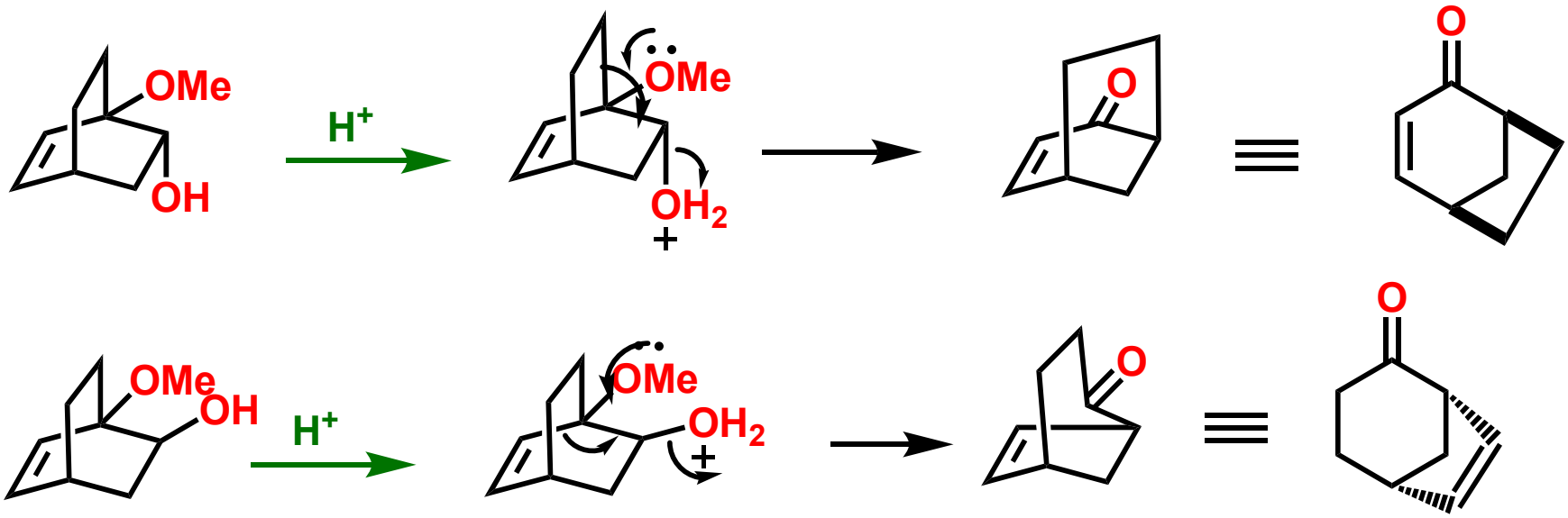
Semi-Pinacolone Rearrangement

Synthesis of Longifolene

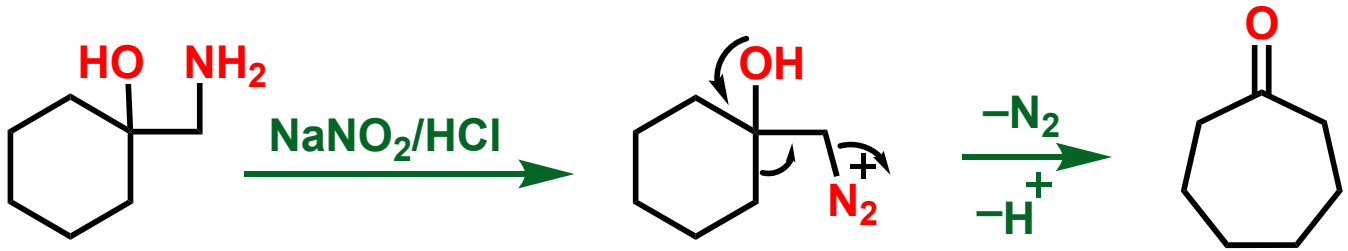


Semi-Pinacolone Rearrangement

Bicyclic Systems

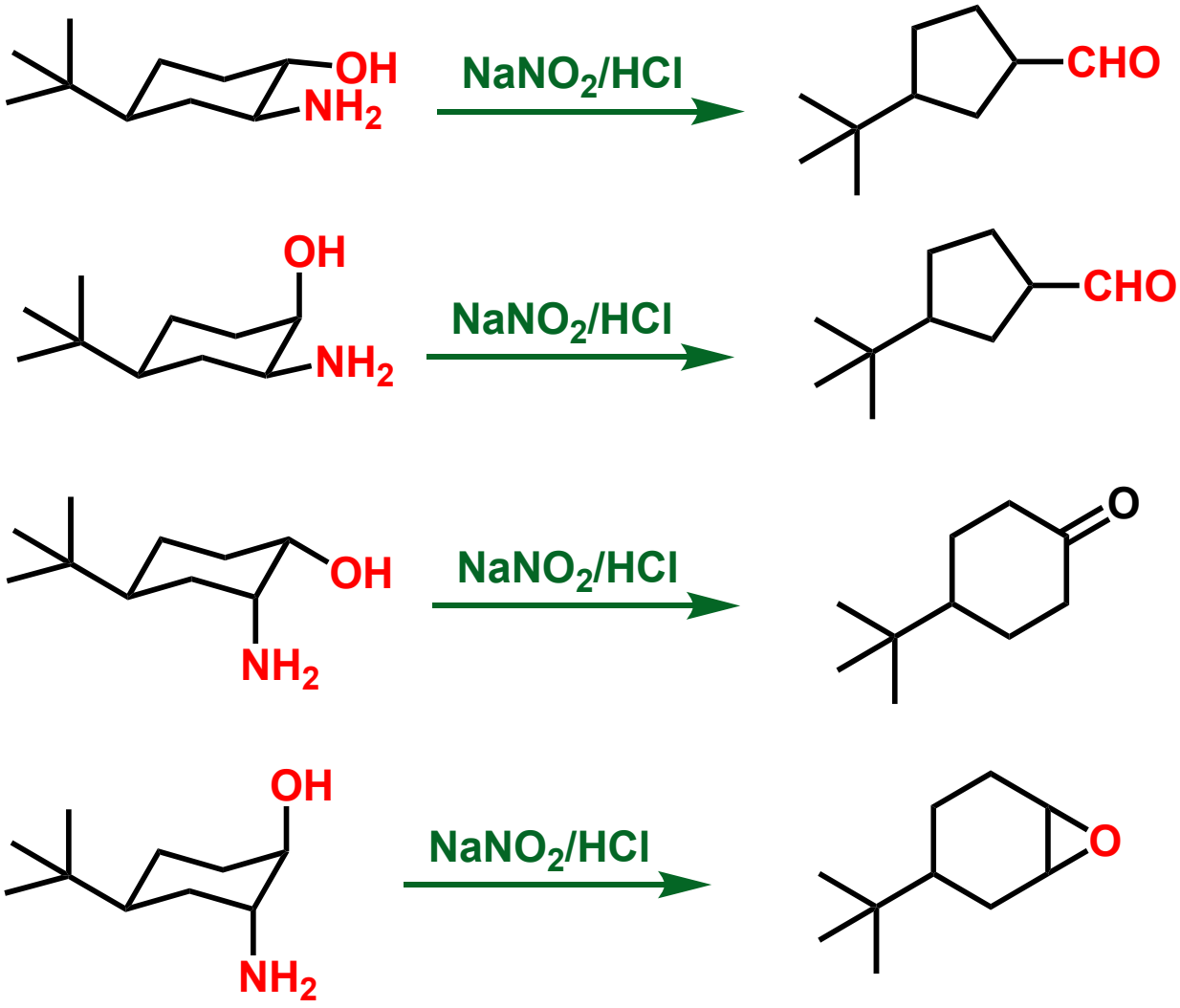


Tiffeneau-Demjanov Rearrangement:



Semi-Pinacolone Rearrangement

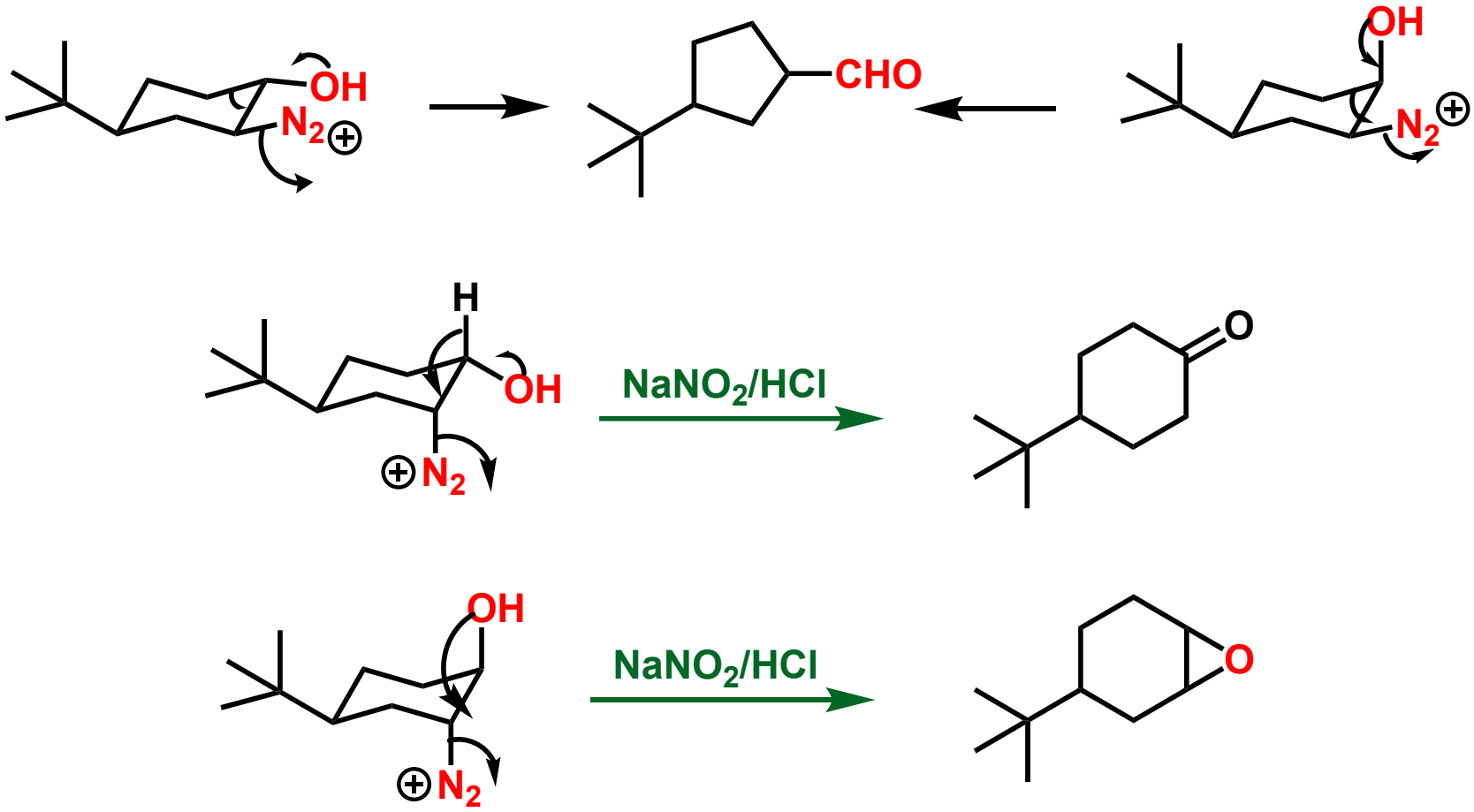
Diazonium Salts



Semi-Pinacolone Rearrangement

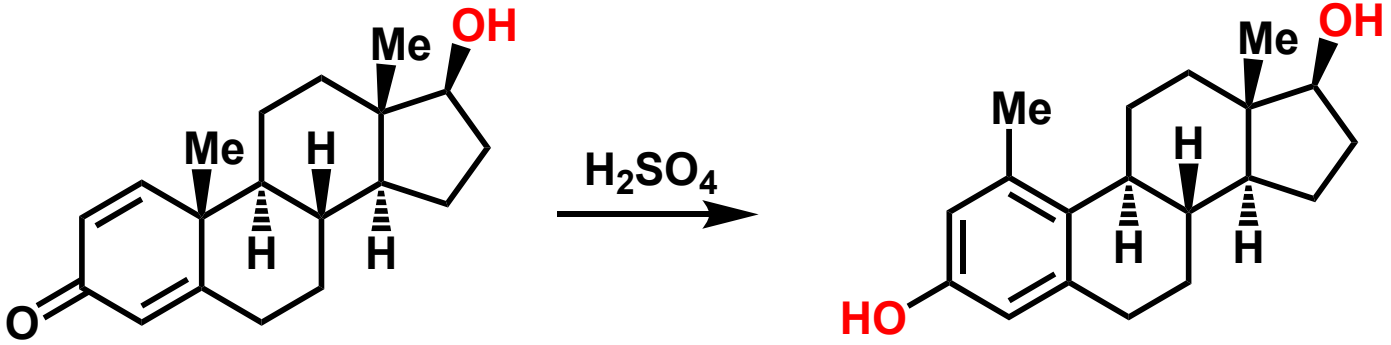
Diazonium Salts

Mechanism



Dienone-Phenol Rearrangement

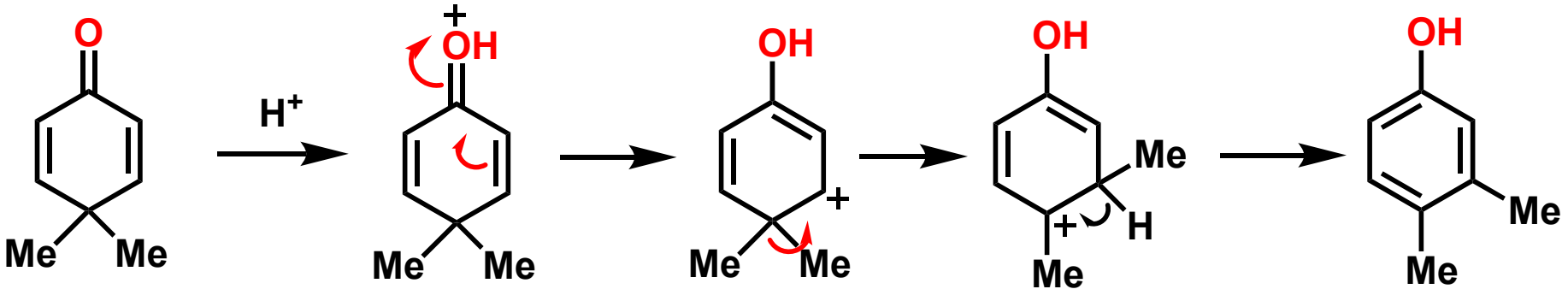
Carl Djerassi discovered that when he treated the dienone with an acid, it rearranged to a methyl phenol.

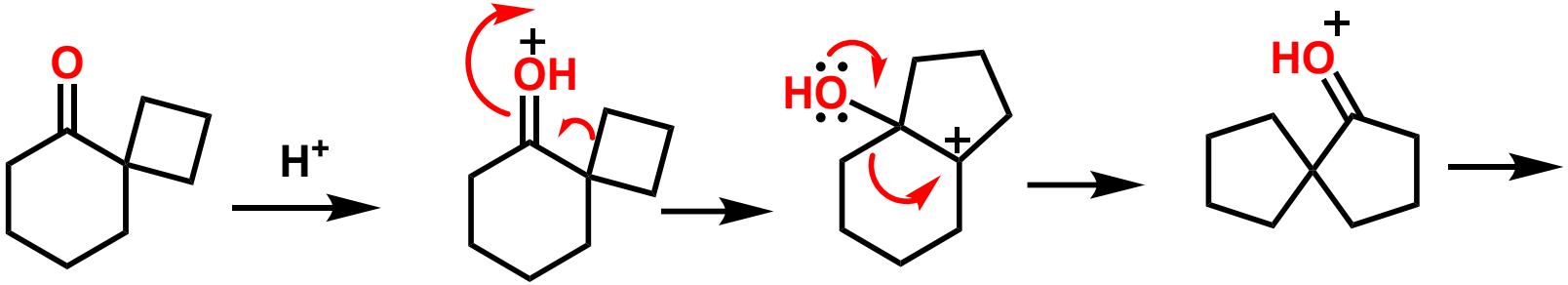


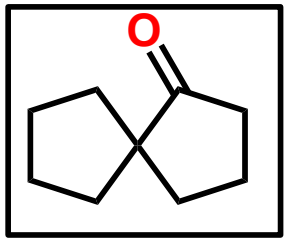
- Can be considered as a reversal of pinacol rearrangement
- Pinacol & semipinacol rearrangements are driven by the formation of a carbonyl group
- In dienone-phenol rearrangement protonation of carbonyl group rearranges to a tertiary carbocation
- The driving force for this reaction is the formation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

Dienone-Phenol Rearrangement

Mechanism



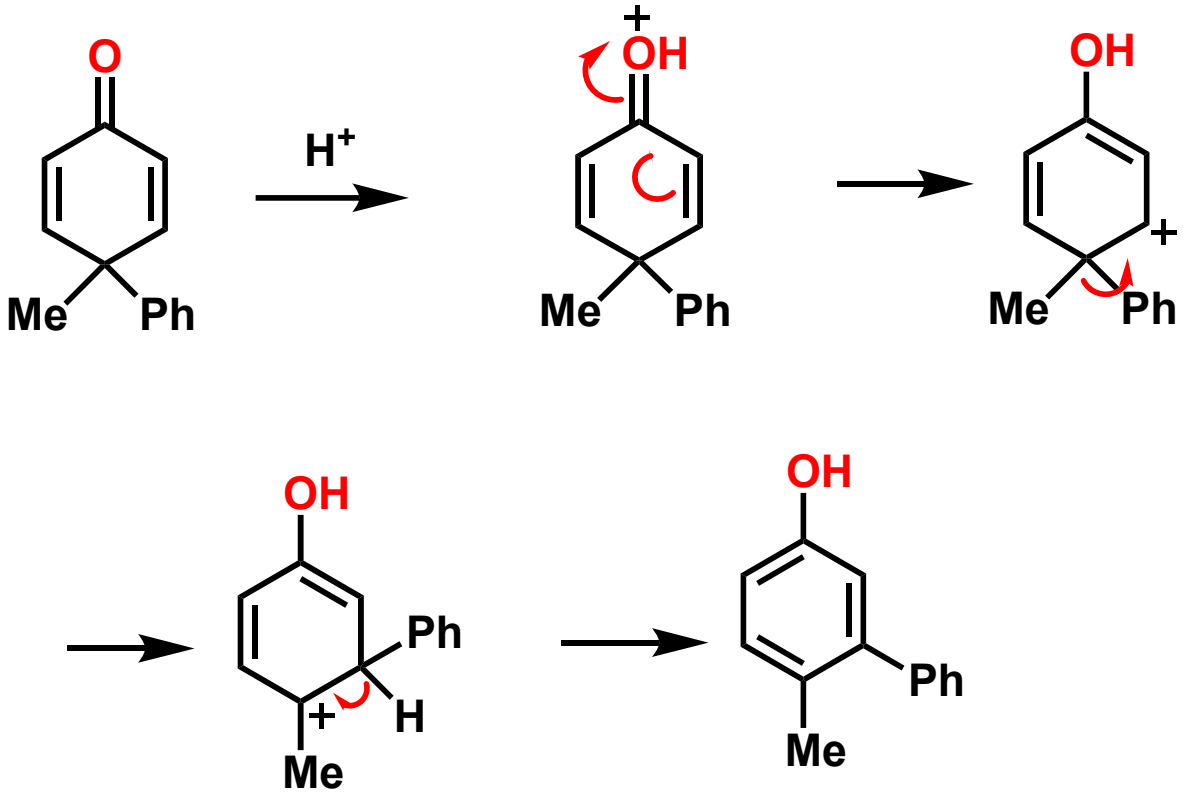




Reverse of Pinacol-Pinacolone rearrangement

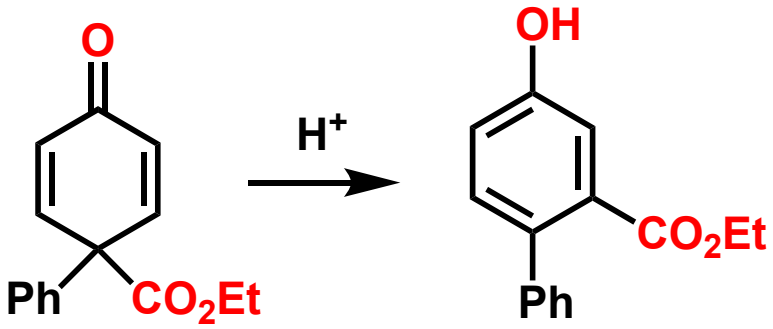
Dienone-Phenol Rearrangement

Migrating Group Aptitude



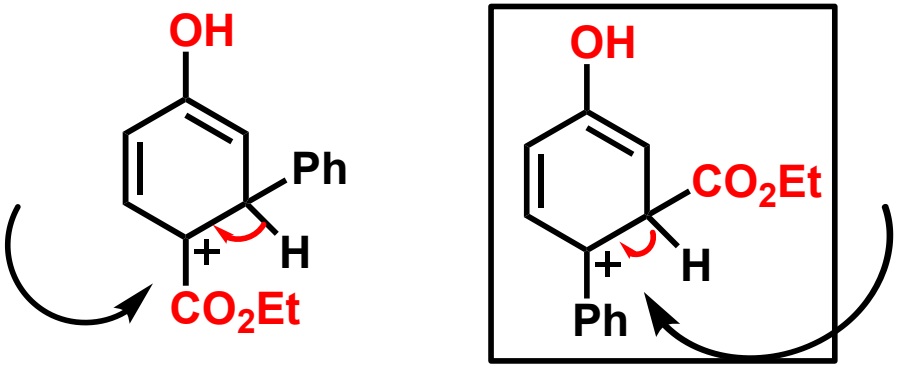
Dienone-Phenol Rearrangement

Migrating Group Aptitude



Why CO_2Et migrates?

CO_2Et destabilises the adjacent carbocation

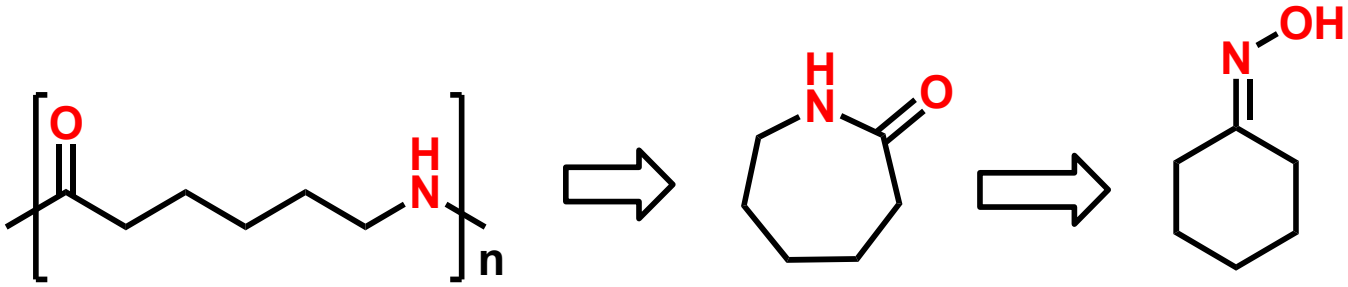


Ph stabilises the adjacent carbocation

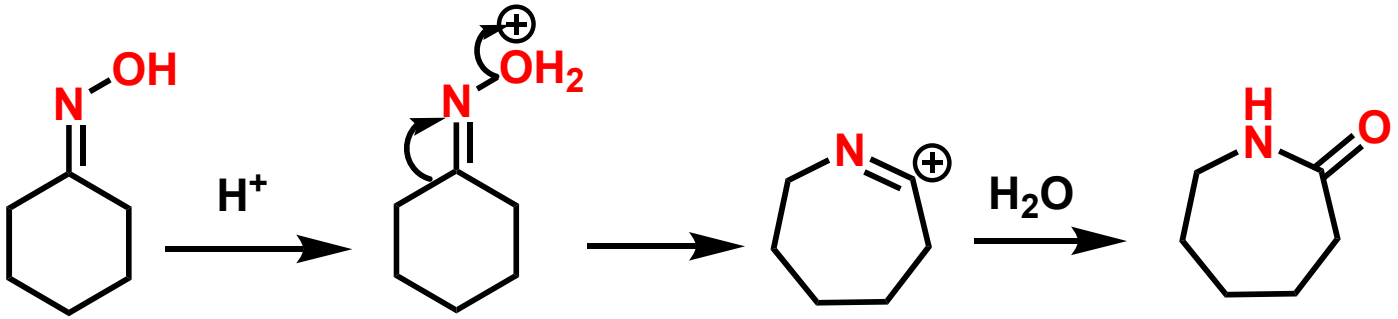
The CO_2Et is so cation destabilising that it is better to migrate than staying back next to the carbocation

Beckmann Rearrangement

The industrial formation of nylon relies upon the alkaline polymerization of a cyclic amide (lactam) known as caprolactam



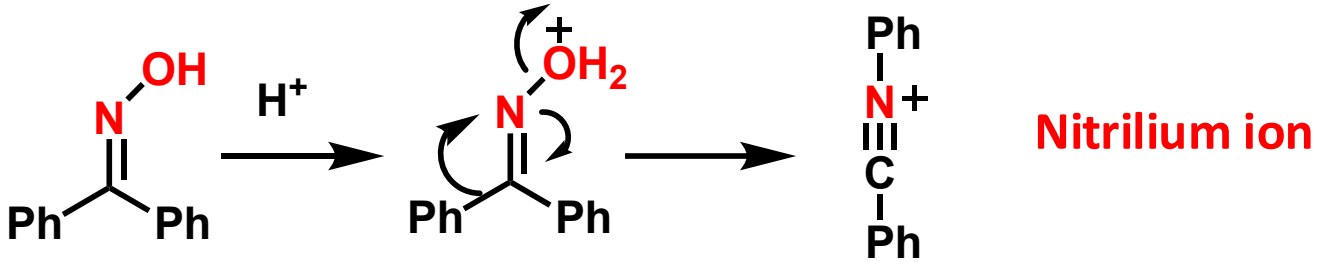
Caprolactam can be produced by the action of sulfuric acid on the oxime of cyclohexanone in a rearrangement known as the Beckmann rearrangement



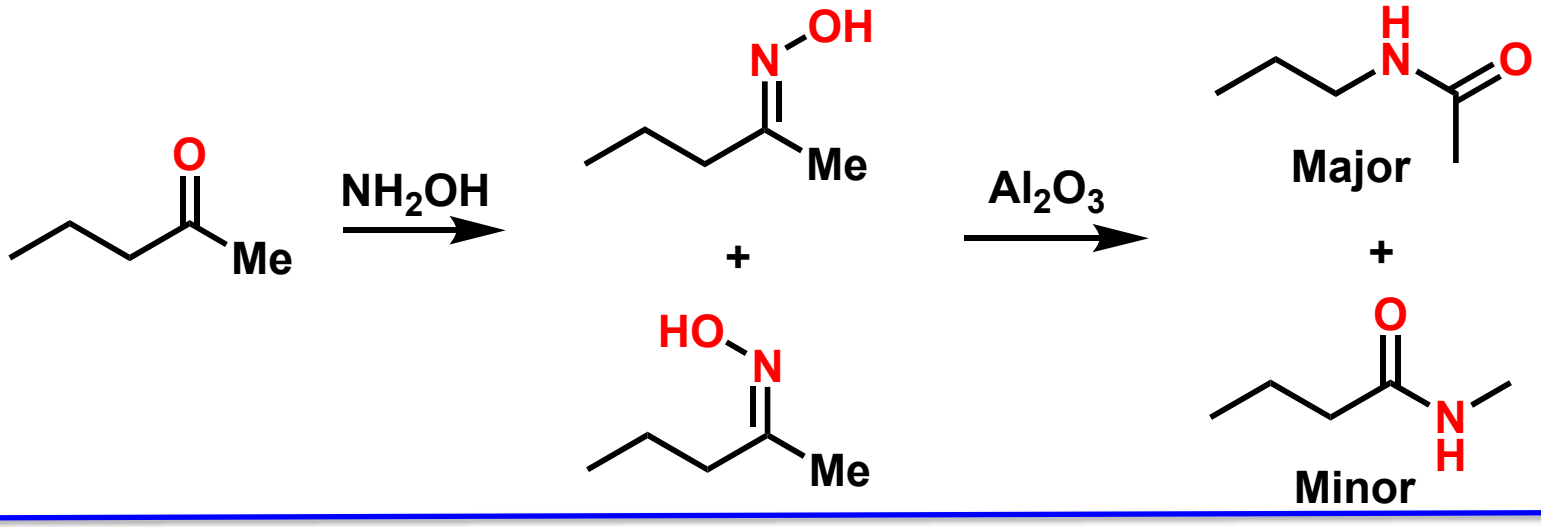
Converts oximes into good leaving group. After the migration of the *anti* bond, addition of water and tautomerization gives amide or lactam.

Beckmann Rearrangement

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



Migratory Aptitude



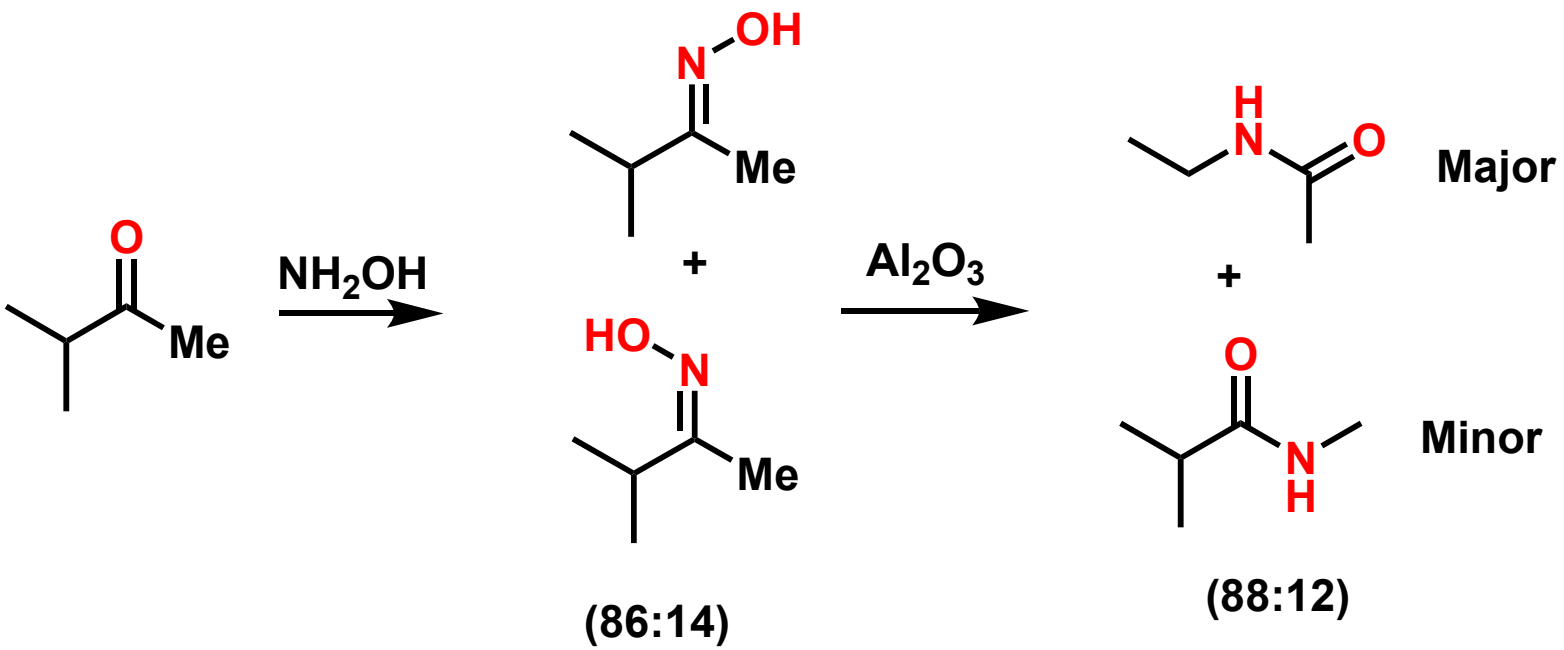
Beckmann Rearrangement

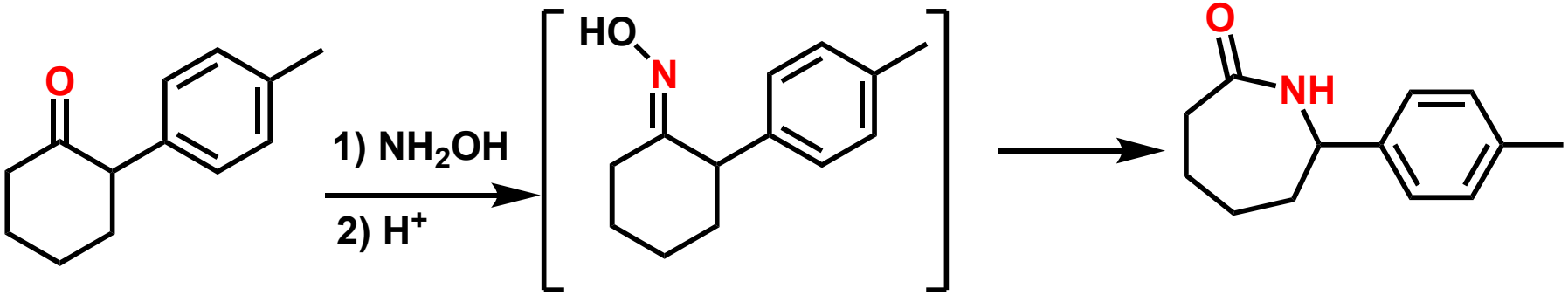
In case of unsymmetrical ketone

- 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

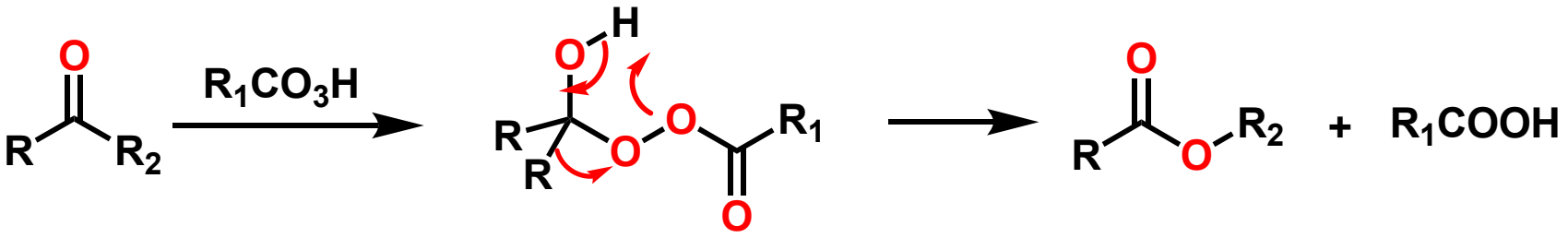
Beckmann Rearrangement

Unsymmetrical ketones

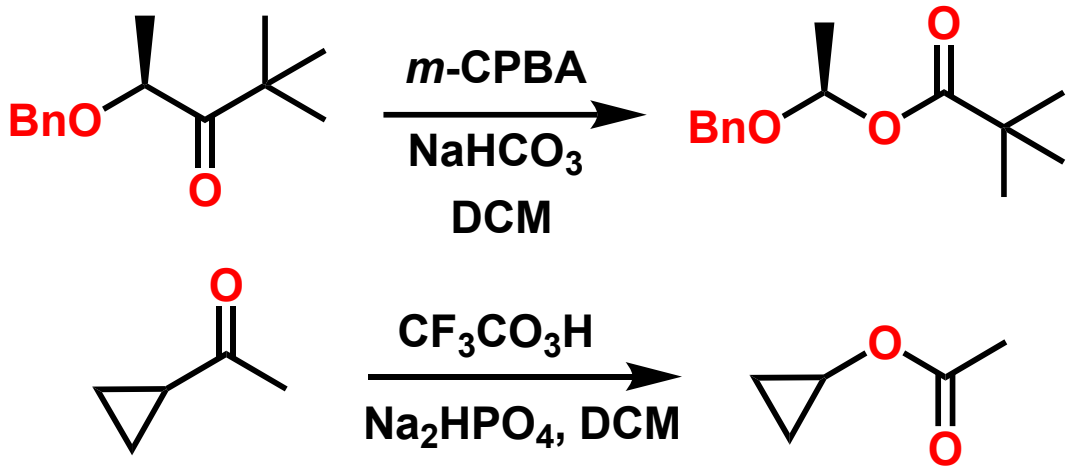




Baeyer Villiger Oxidation

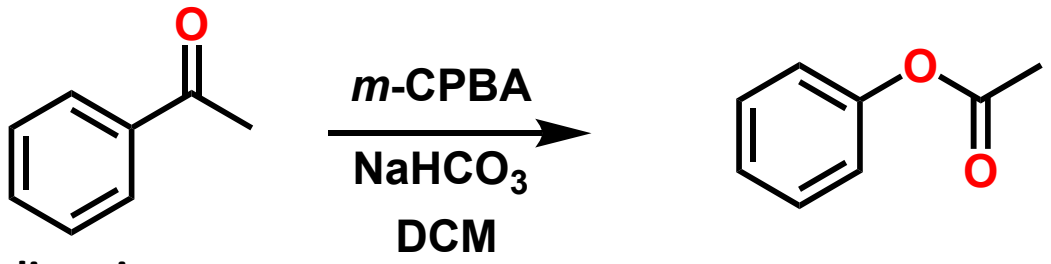


The migratory aptitudes are: Alkoxyalkyl >*t*-Alkyl>cyclohexyl=secondary alkyl=benzyl=Phenyl>vinylic>primary alkyl>cyclopropyl>methyl



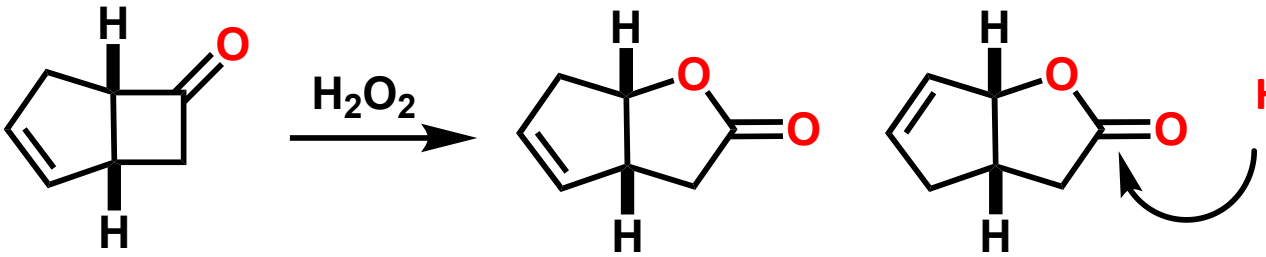
Acid catalyzed side reactions can be suppressed by phosphate buffer

Baeyer Villiger Oxidation



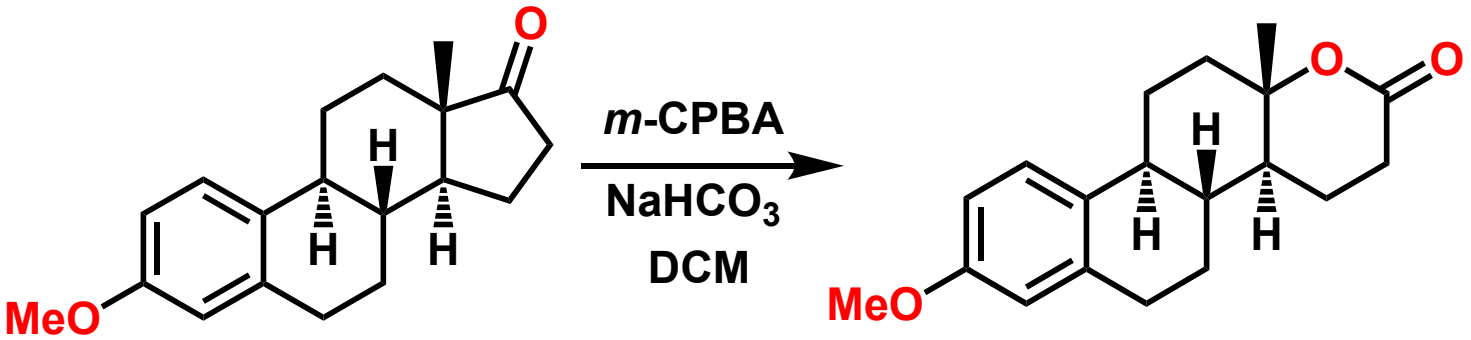
meta directing group

ortho & para directing group

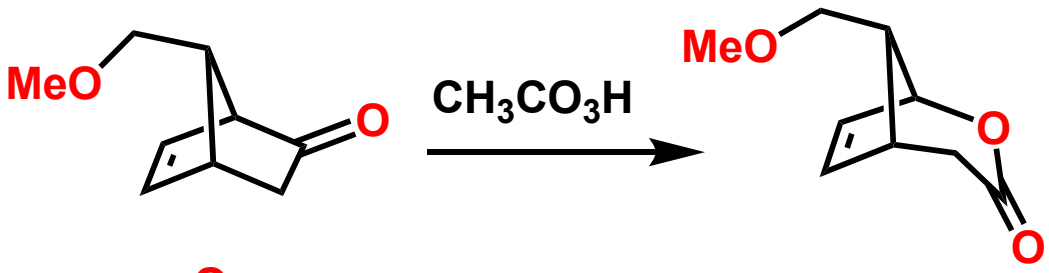


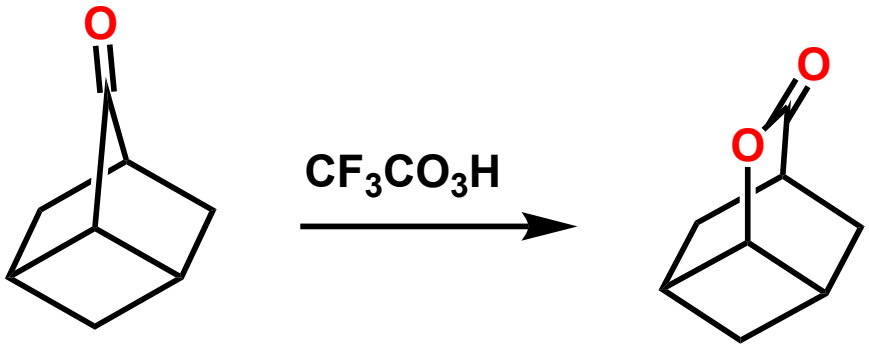
How do you make this?

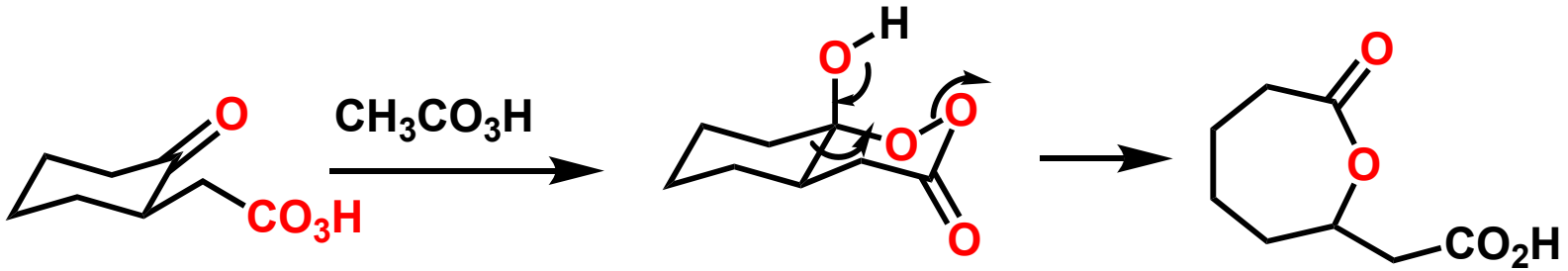
Normally, most ketones do not react with H_2O_2 but the above one does. Why?



Baeyer Villiger Oxidation

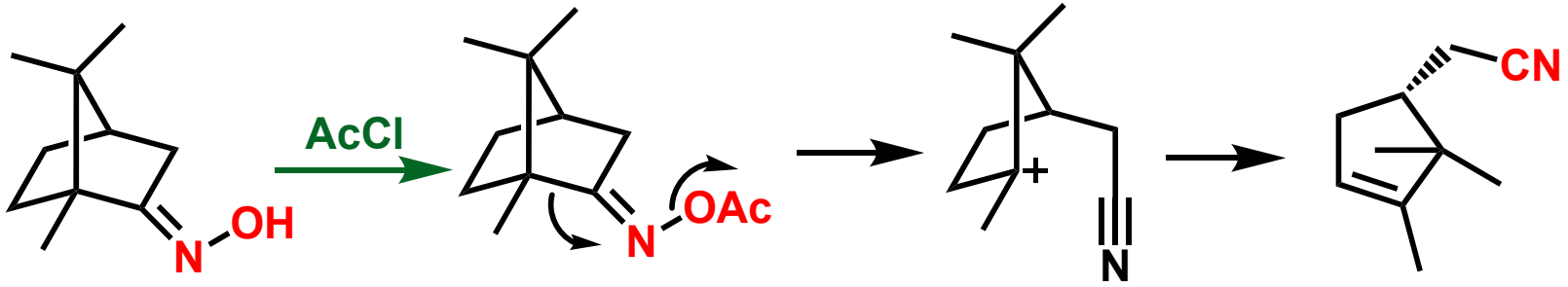






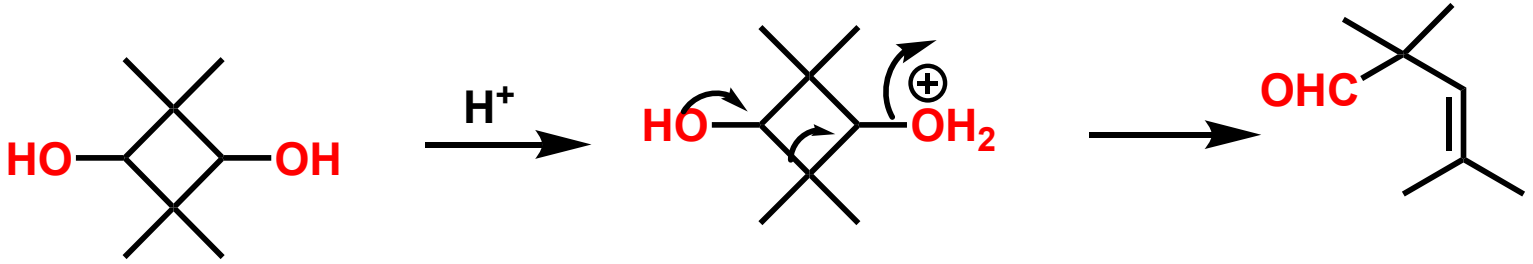
Fragmentation

Abnormal Beckmann Rearrangement

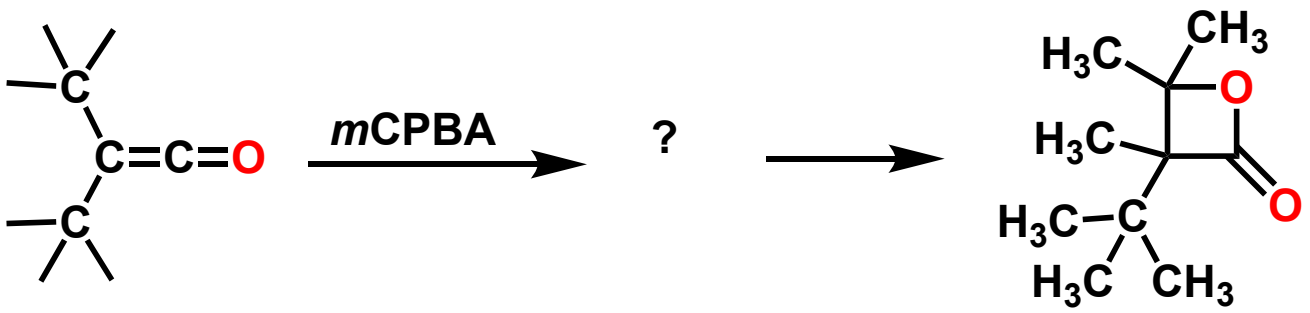


Stable carbocation

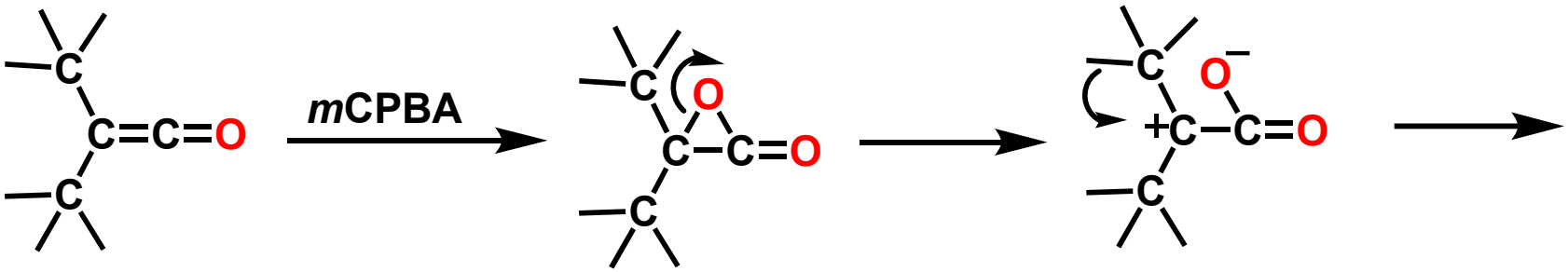
Fragmentations always require electron push and electron pull

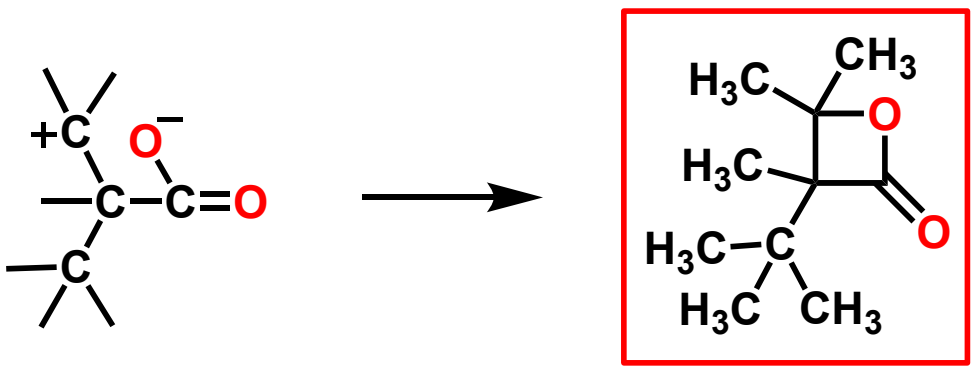


Ring Expansion



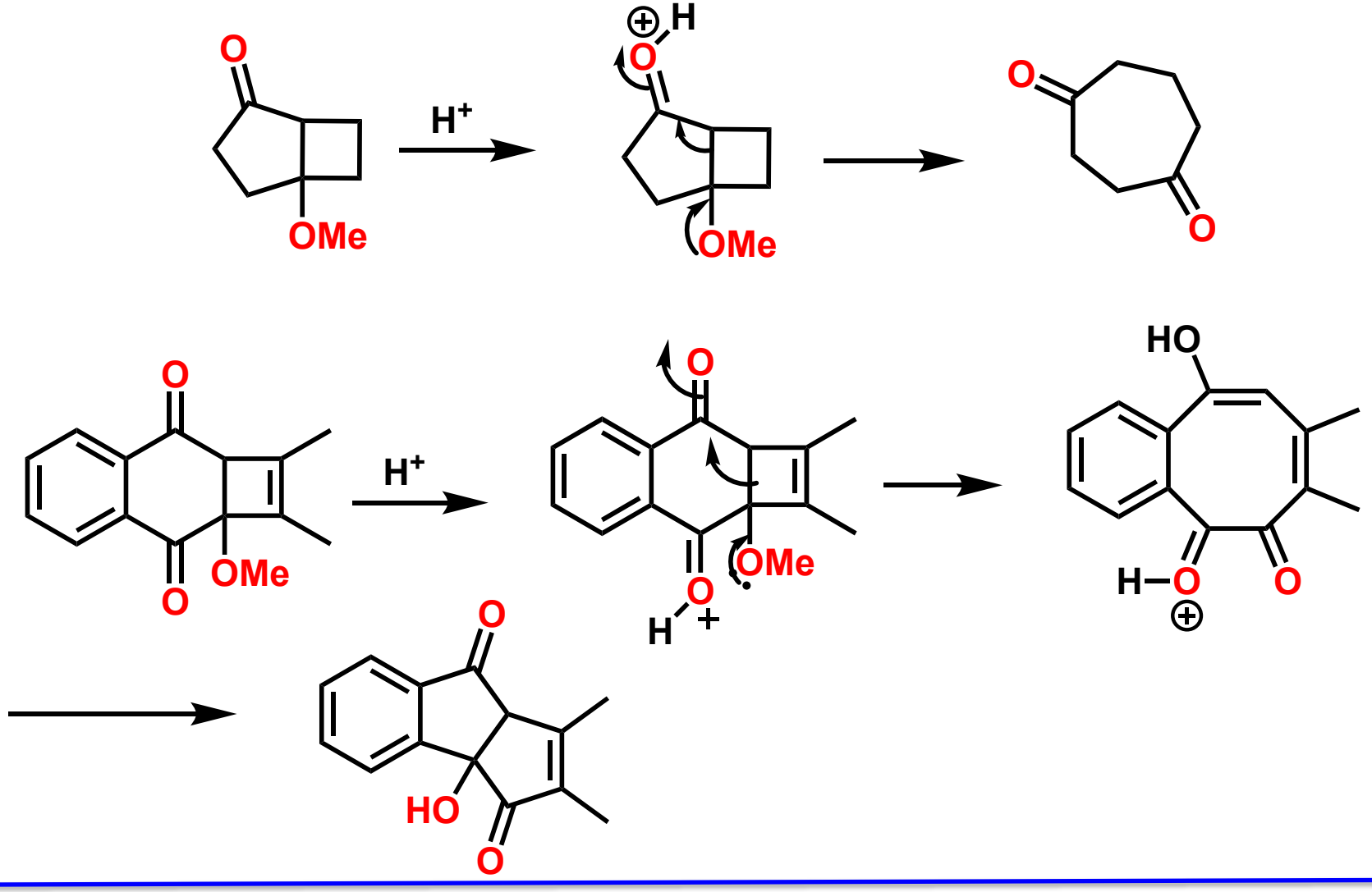
Mechanism





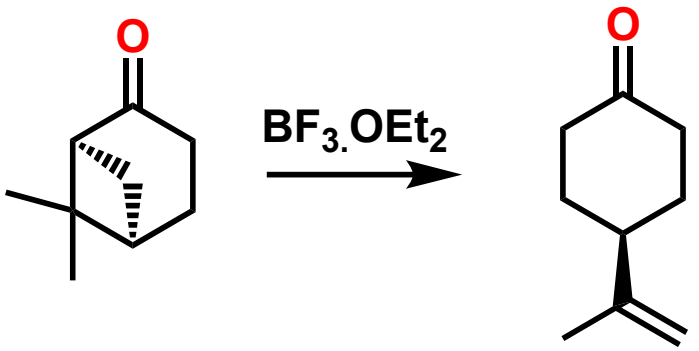
Fragmentation

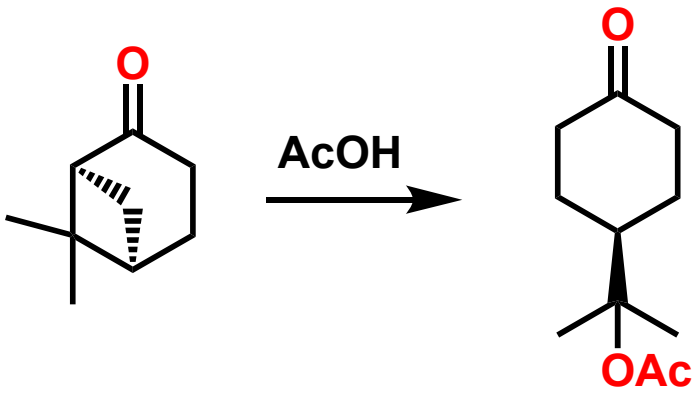
Ring Expansion to Higher Cycloalkanes



Ring Opening

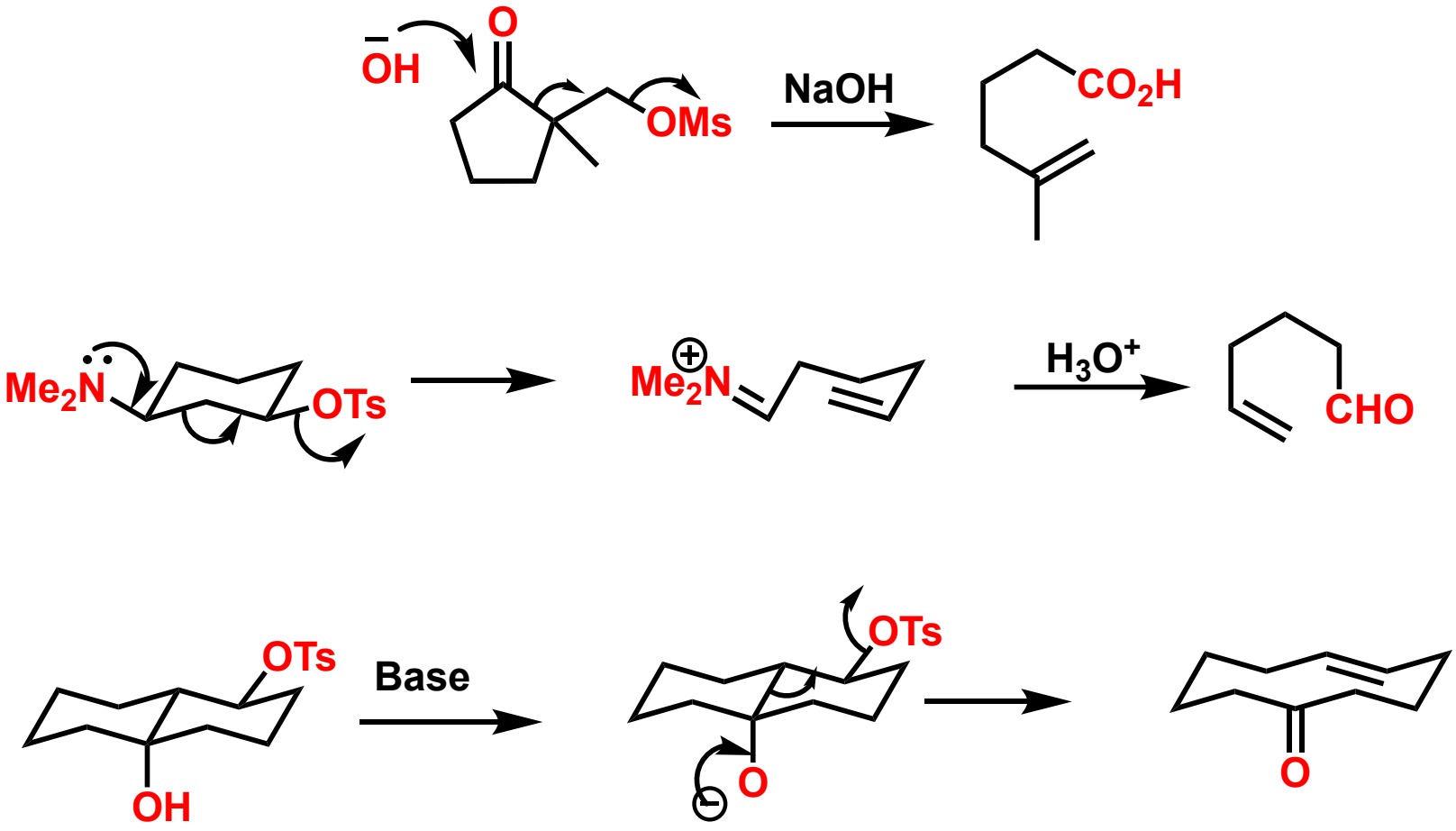
Under Acidic Conditions





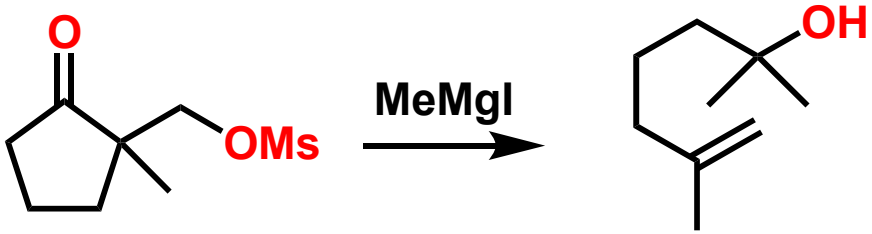
Ring Opening

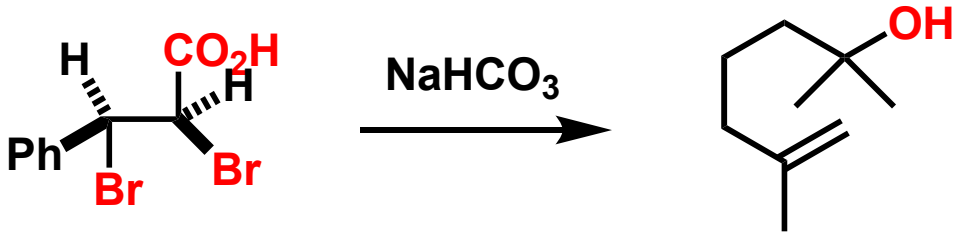
Grob Fragmentation



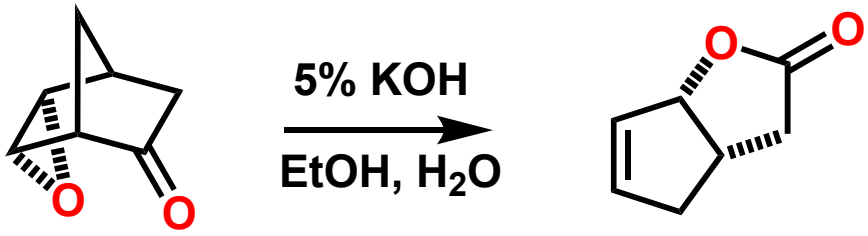
Ring Opening

Grob Fragmentation



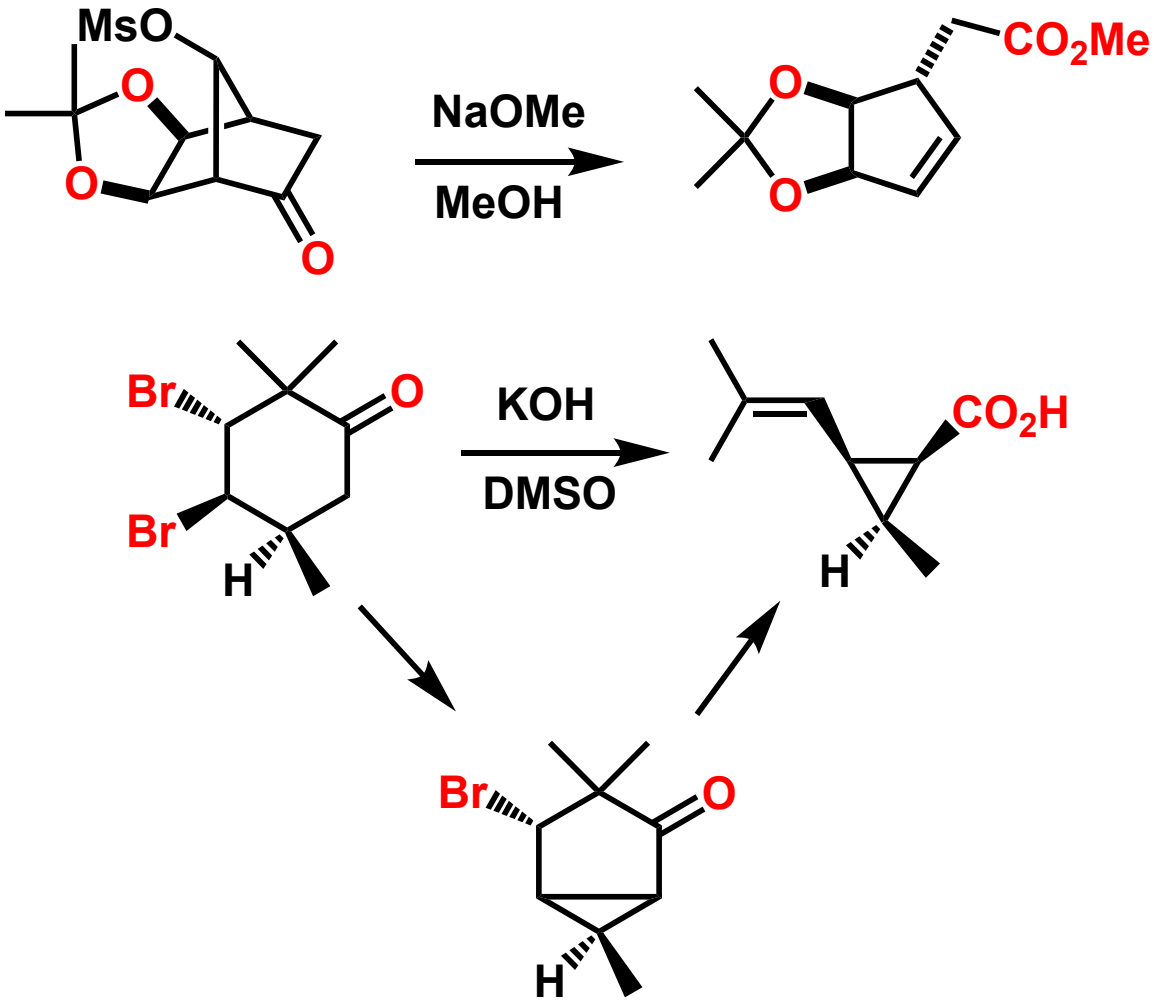


Mechanism?

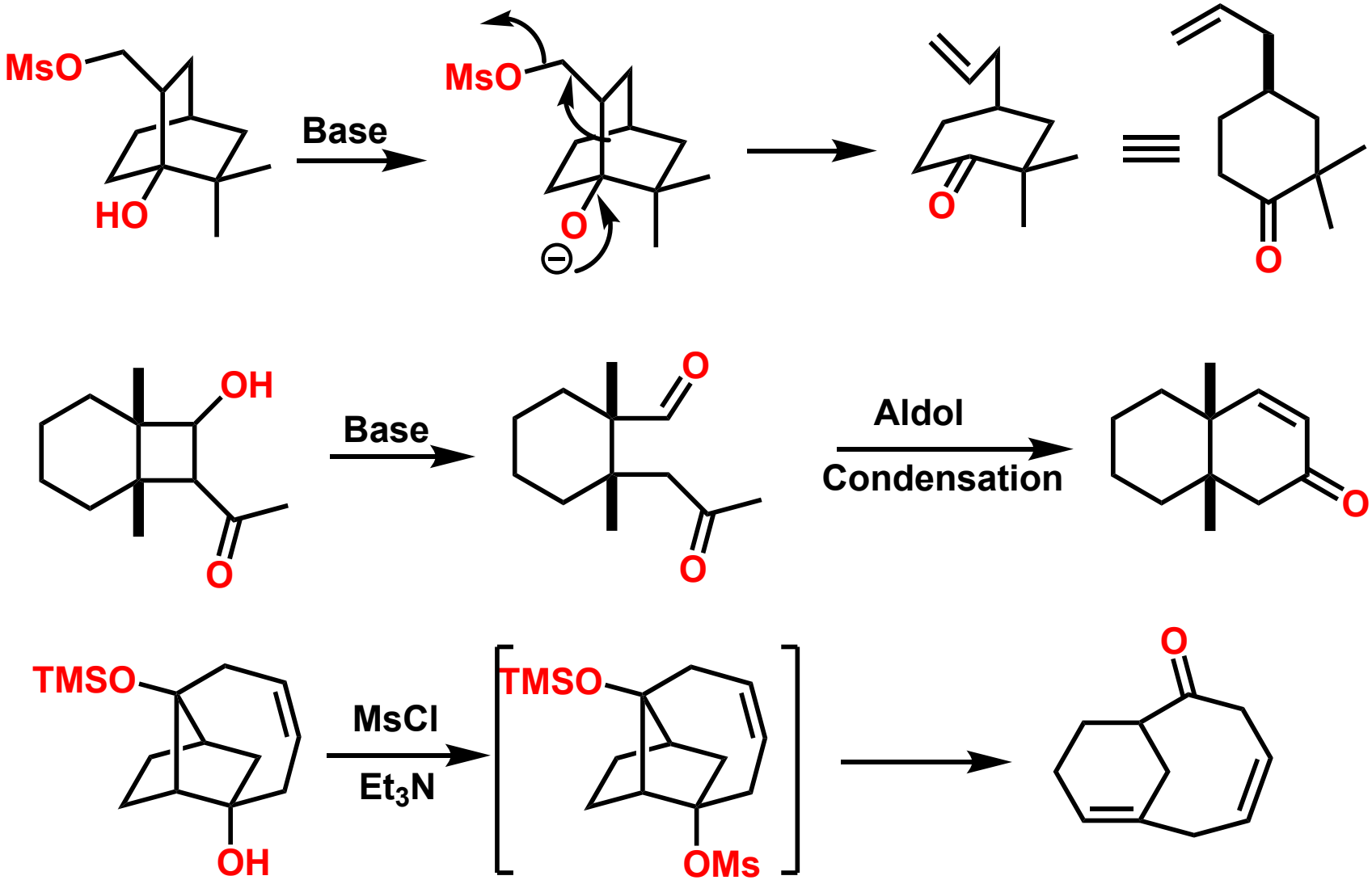


Ring Opening

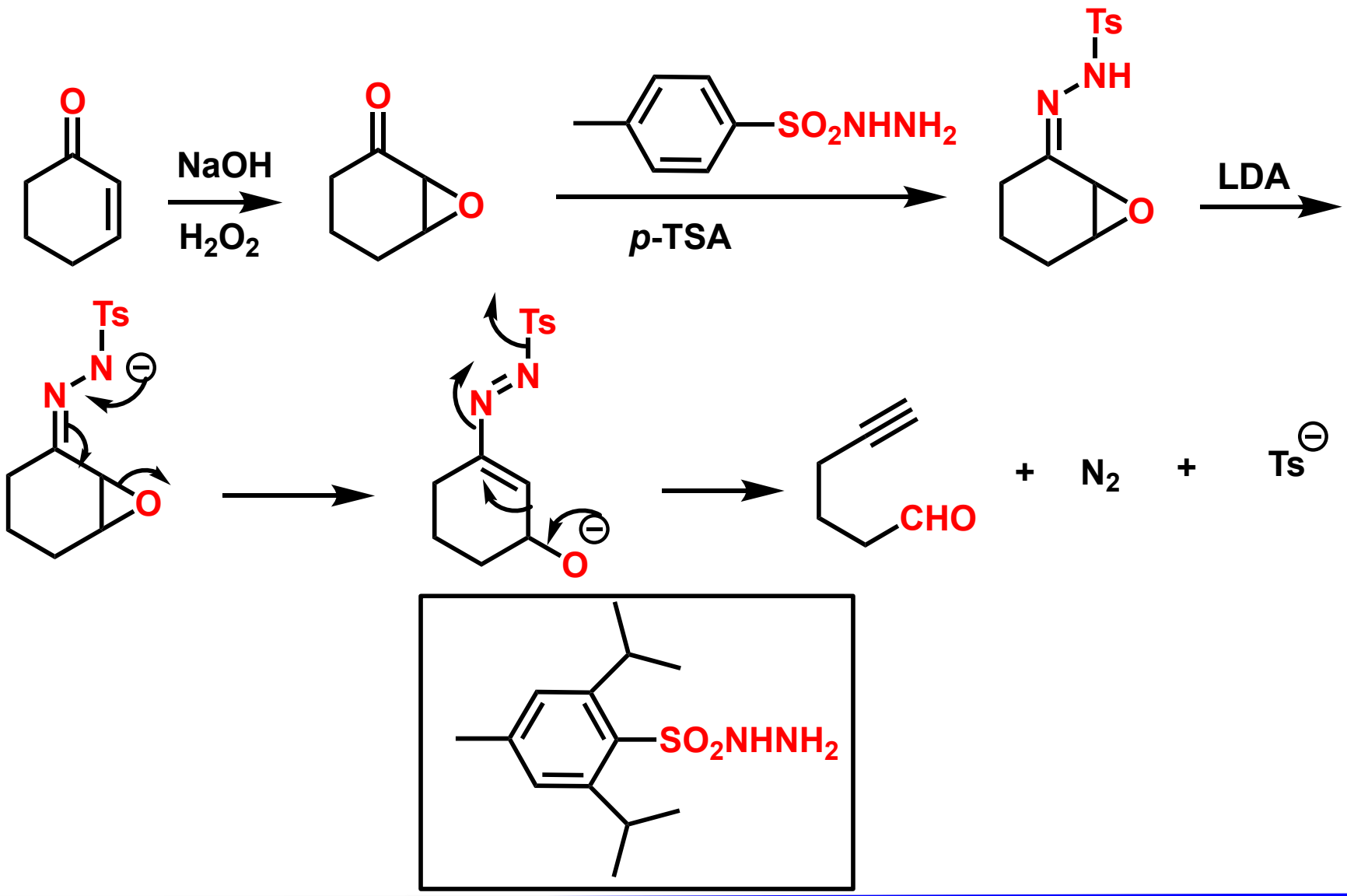
Grob Fragmentation



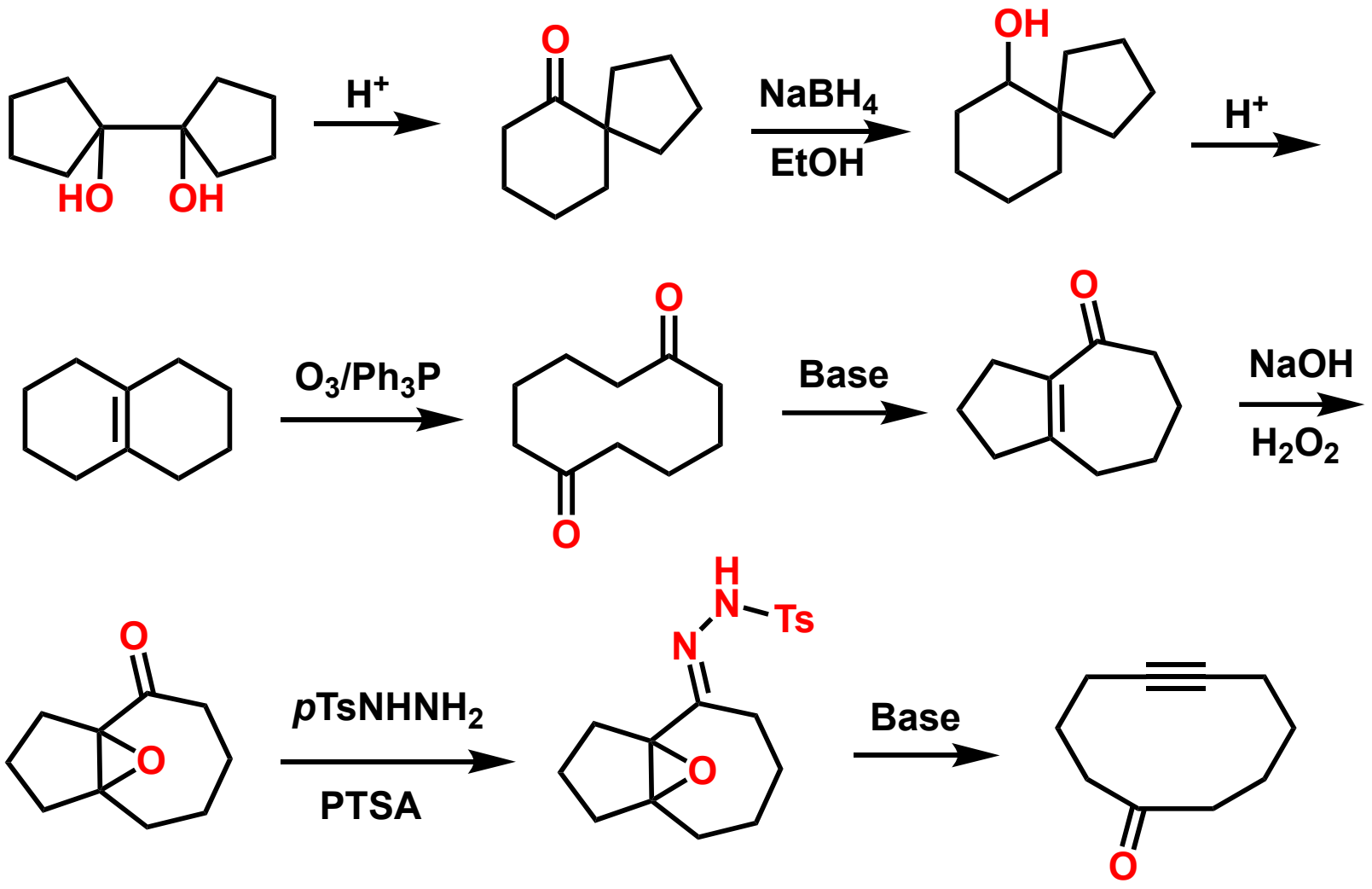
Ring Opening



Eschenmoser Fragmentation



Eschenmoser Fragmentation



Electron Rich Skeletal Rearrangements

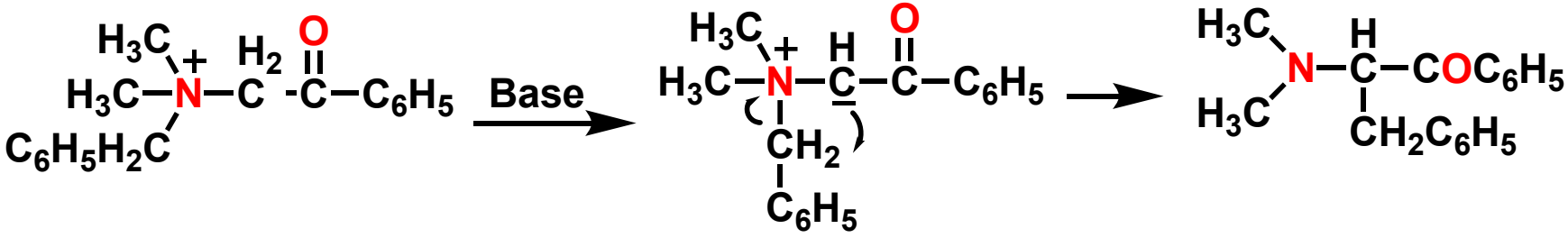
- The transition state has two more electrons
- Generally initiated by basic reagents which remove a group of an atom such as hydrogen
- The residual anion then stabilizes itself by rearrangement
- In the first step an acid strengthening substituent is necessary to stabilize the ionic center

  - Stevens Rearrangement
  - Wittig Rearrangement
  - Sommelet Hauser Rearrangement
  - Benzil-Benzilic acid Rearrangement
  - Favorski Rearrangement

Stevens Rearrangement

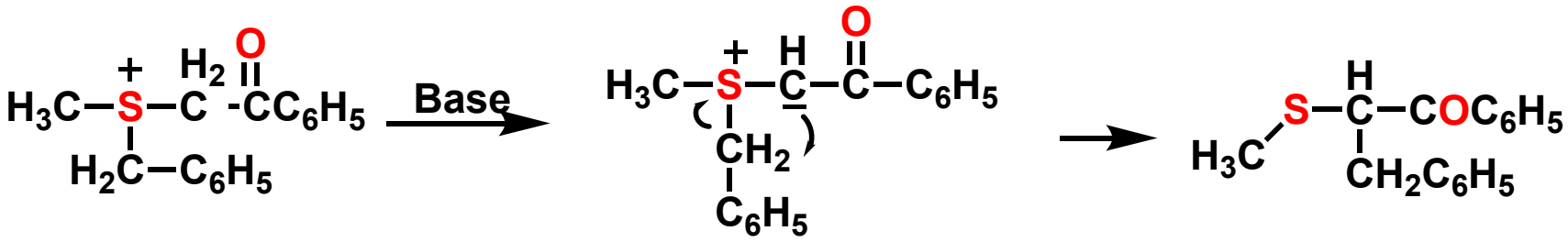
Under the influence of a strong base keto-quarternary ammonium or sulfonium salts rearrange to amino ketones. Reported in 1928

It was an accidental discovery while trying to find a suitable protecting group

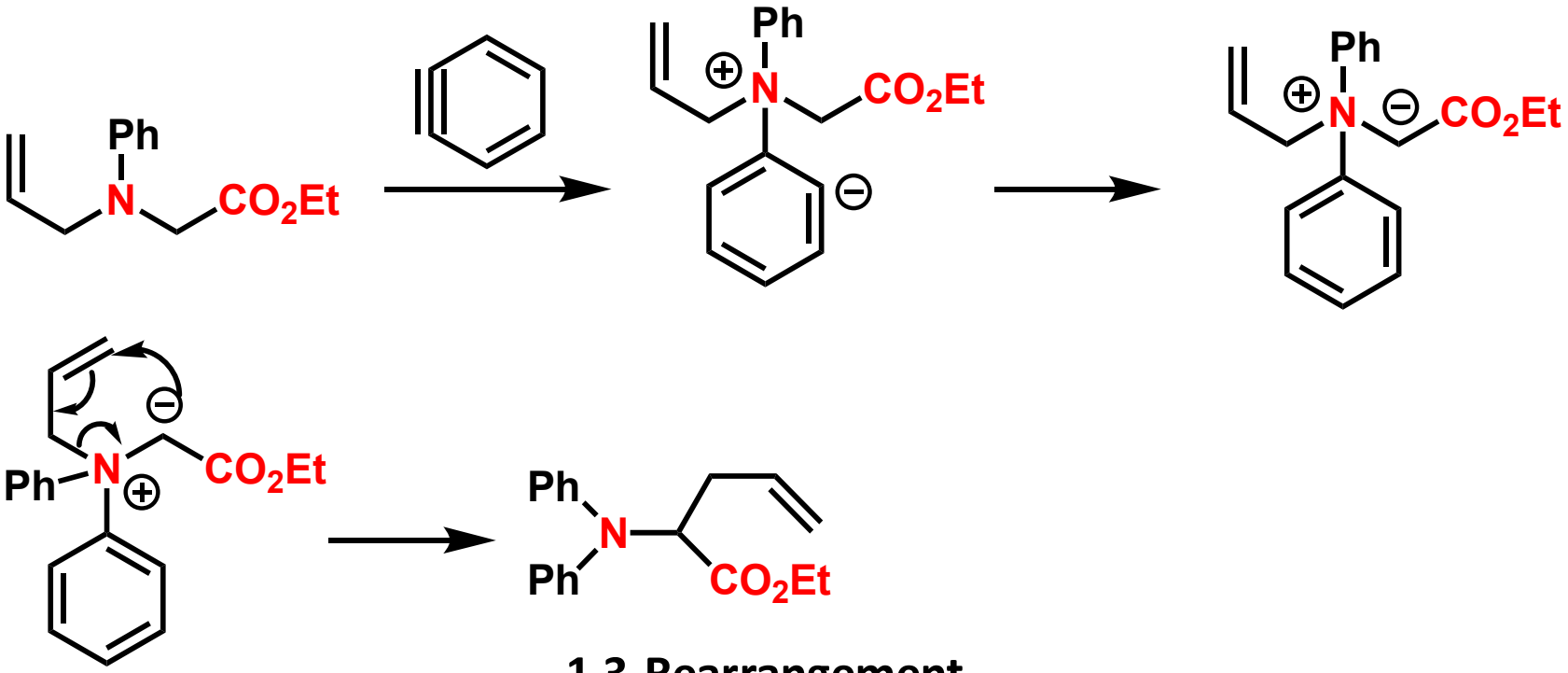


- Proton removal in the first step is facilitated by the positive charge in the cationic substrate and also by the enolate ion formation

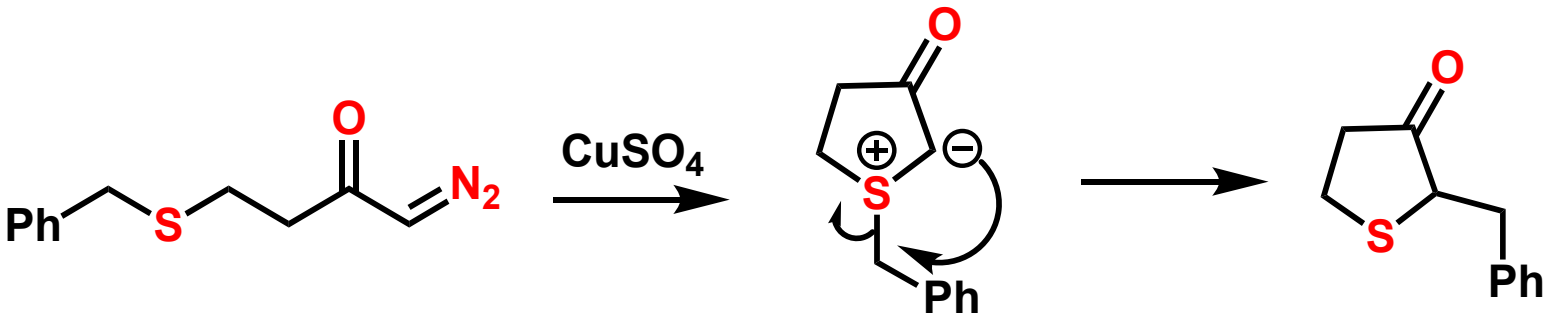
- Migrating groups are generally benzyl or allyl system



Stevens Rearrangement

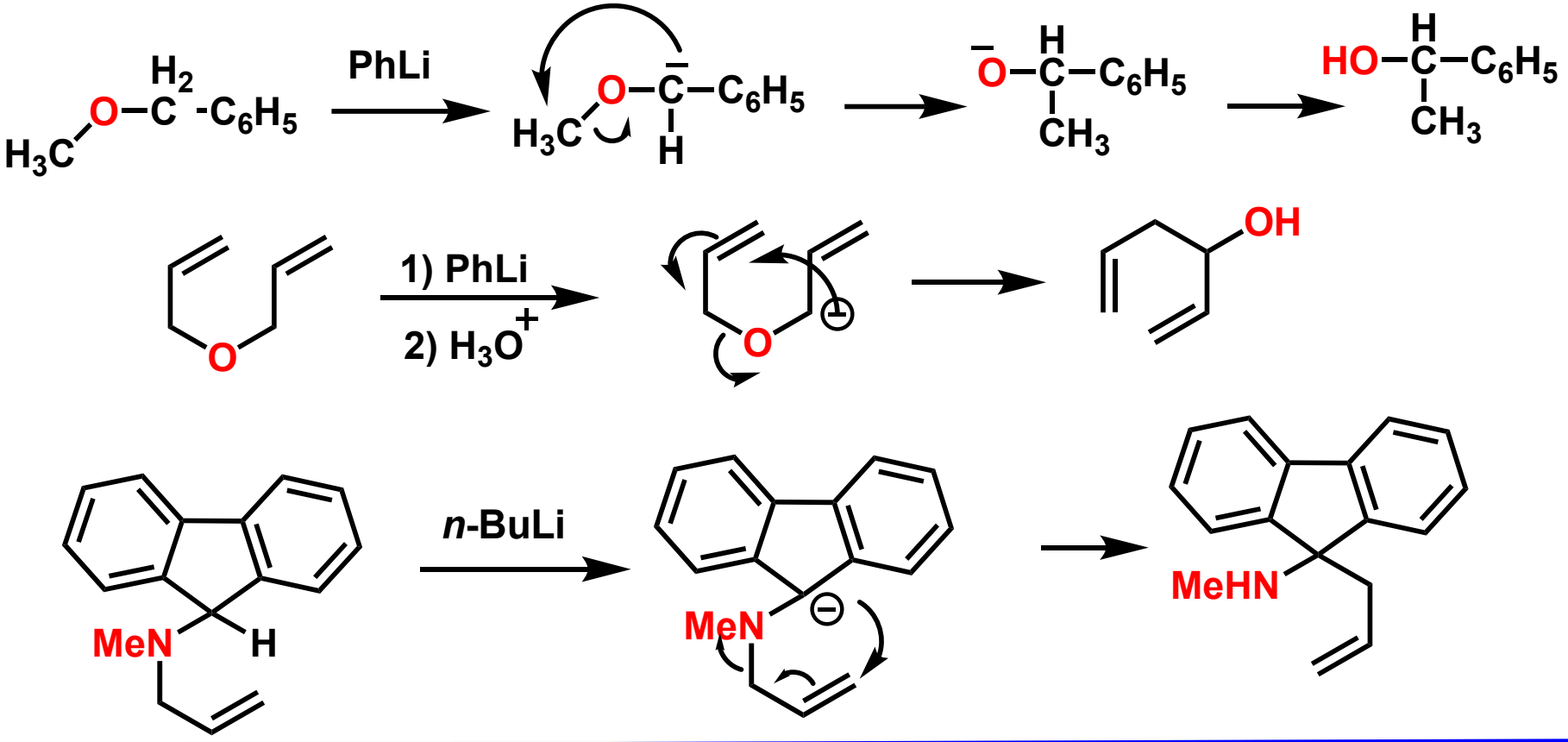


1,3-Rearrangement



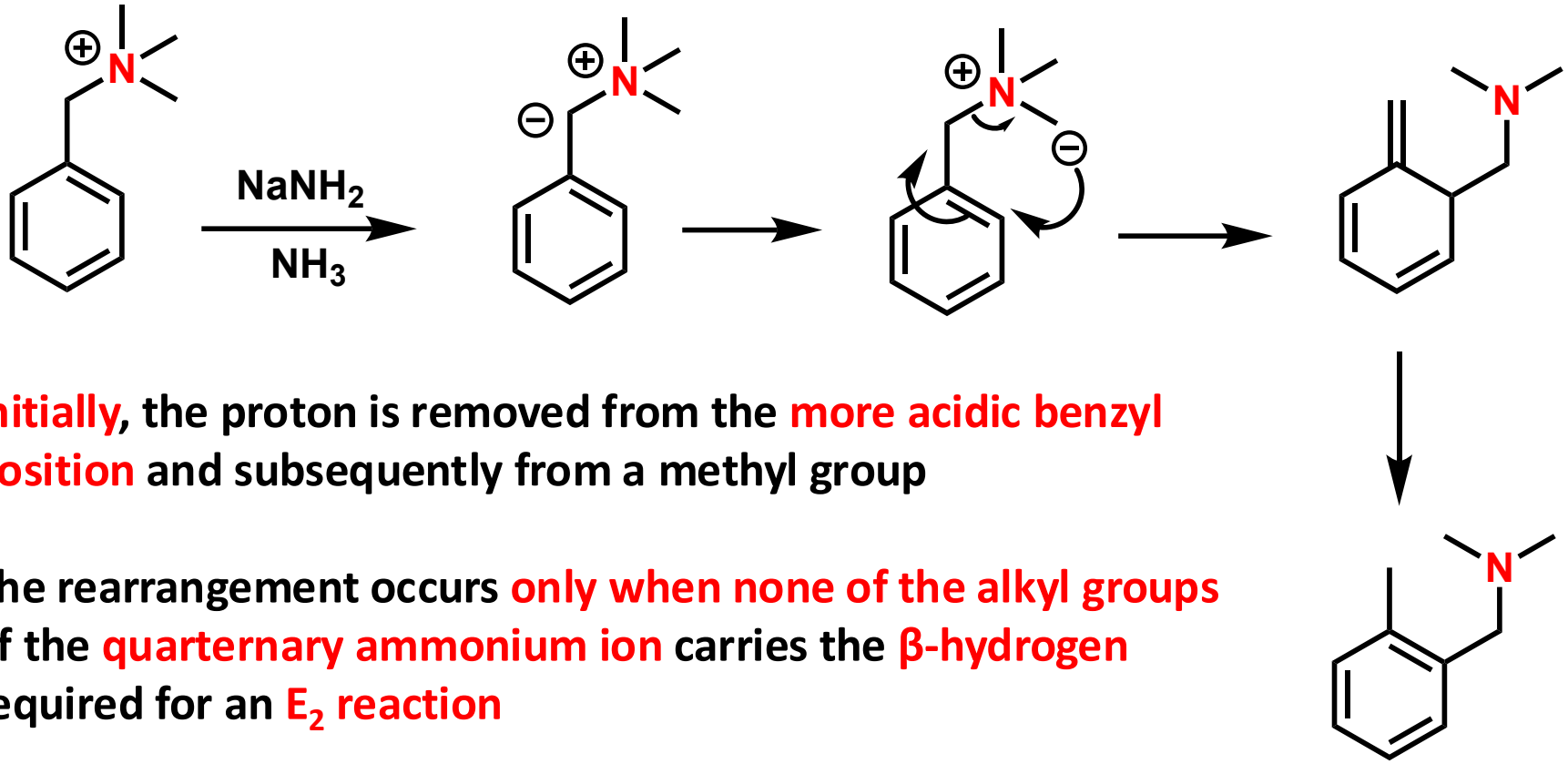
Wittig Rearrangement

- Only difference is substrates are much less acidic than those encountered in Stevens rearrangement
- Powerful basic reagents are required to cause the Wittig Rearrangement



Sommelet Hauser Rearrangement

Nucleophilic alkylation of the aromatic rings of a benzyltrimethyl-ammonium ion is called Sommelet Hauser Rearrangement



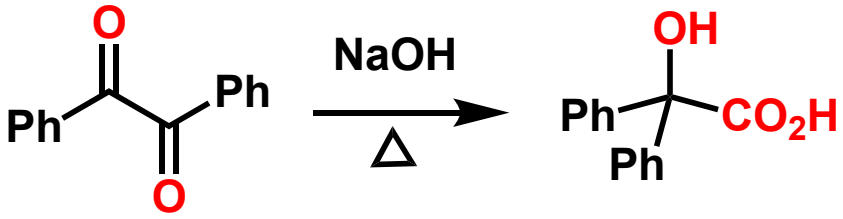
Initially, the proton is removed from the more acidic benzyl position and subsequently from a methyl group

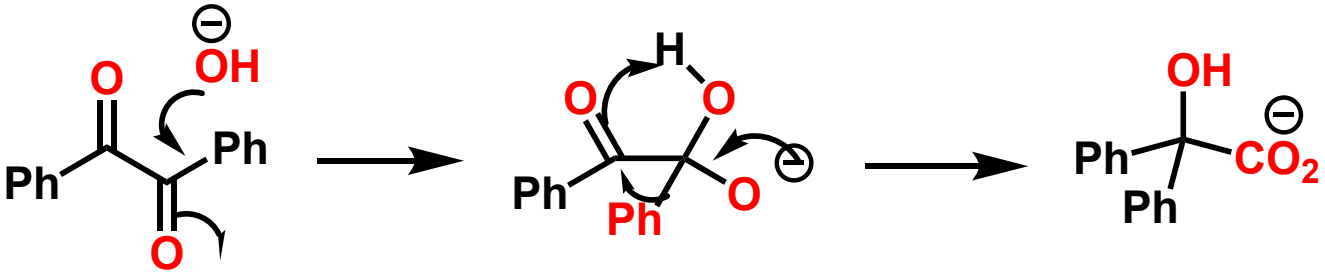
The rearrangement occurs only when none of the alkyl groups of the quarternary ammonium ion carries the β-hydrogen required for an E_2 reaction

Benzil-Benzilic Acid Rearrangement

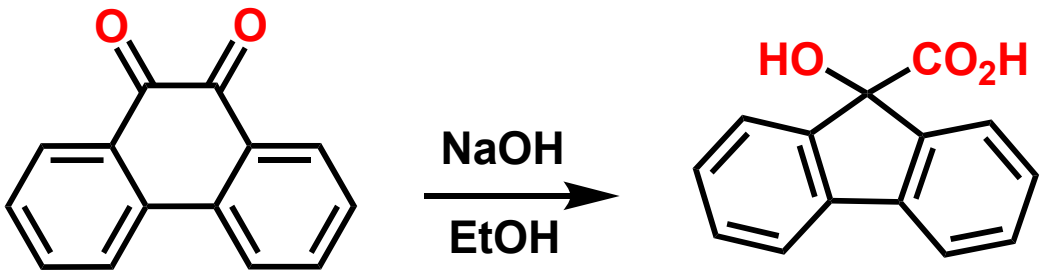
Rearrangement of α-diketones to α-hydroxyacids on treatment with alkali

Reported in 1838, by Leibig. First reported rearrangement





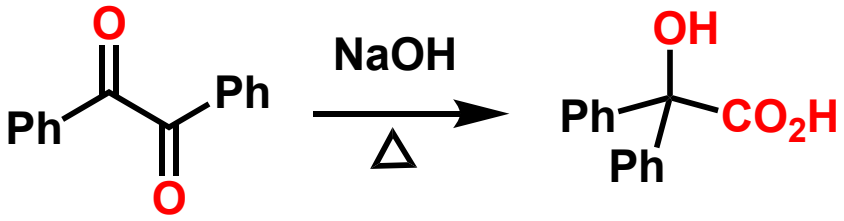
Driving force for the reaction is the formation of stable carboxylate salt



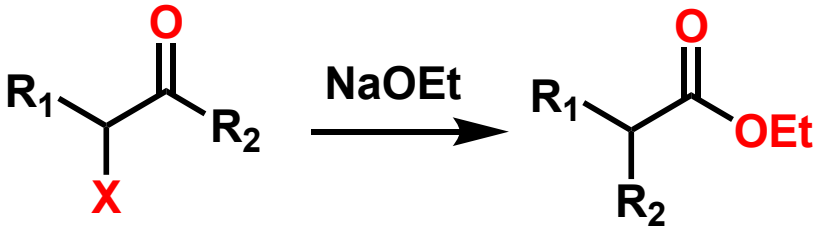
Favorski Rearrangement

Rearrangement of α-halo ketones to acids/esters on treatment with a base

Benzilic acid rearrangement

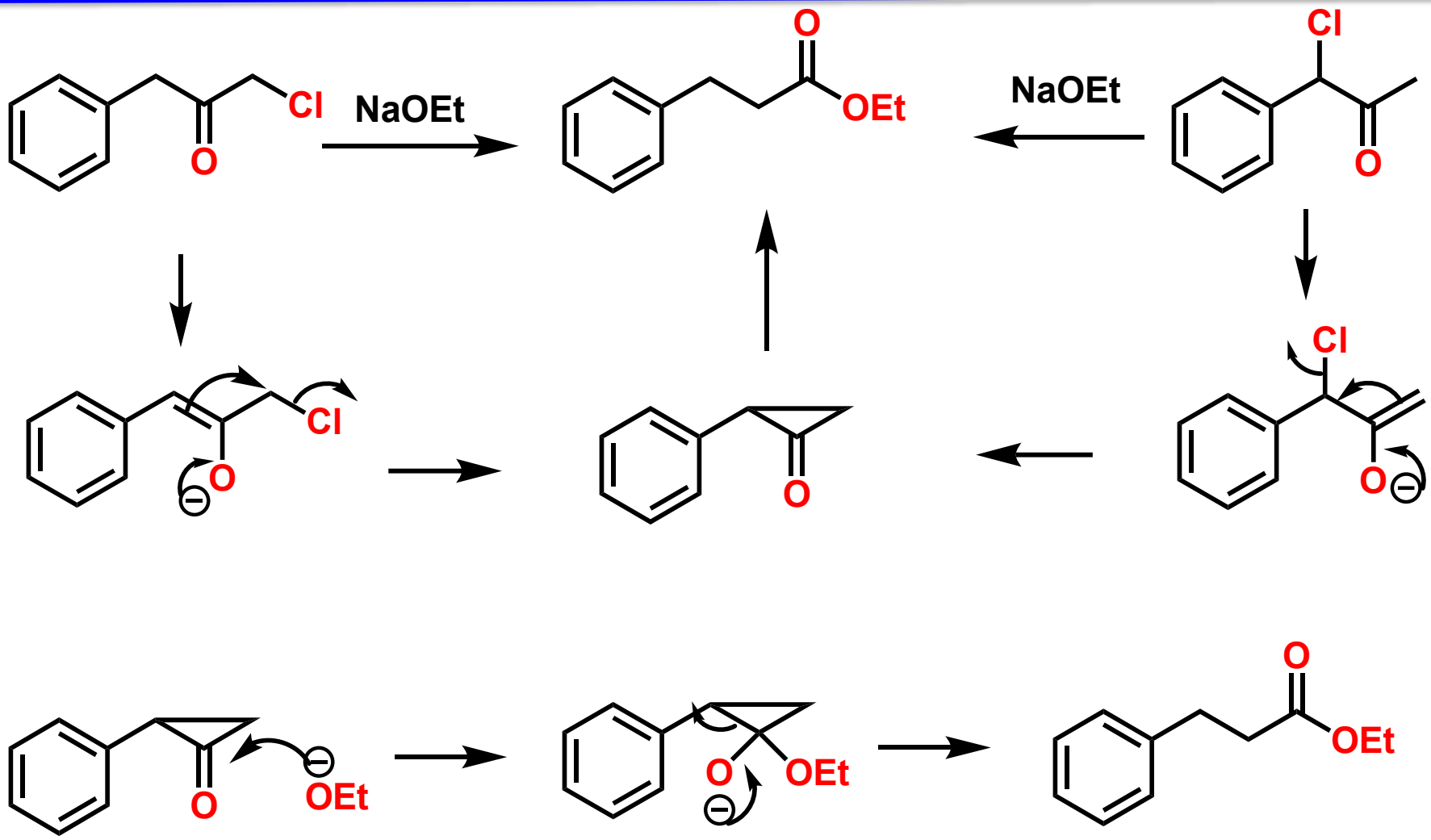


Favorski rearrangement

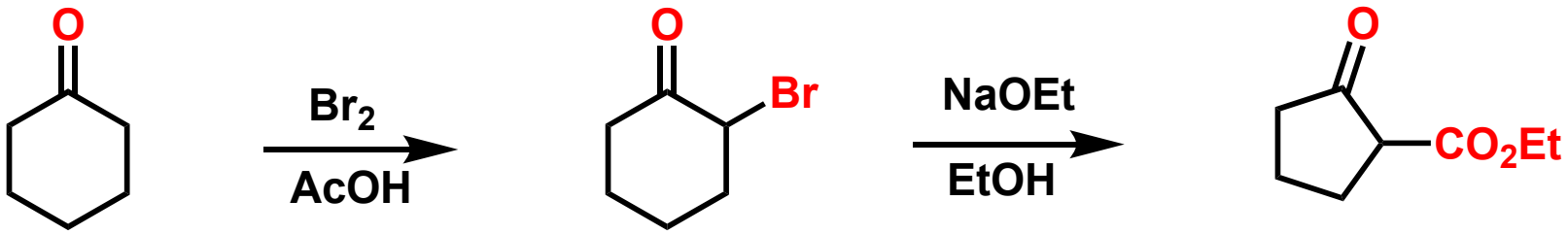


Mechanism is different

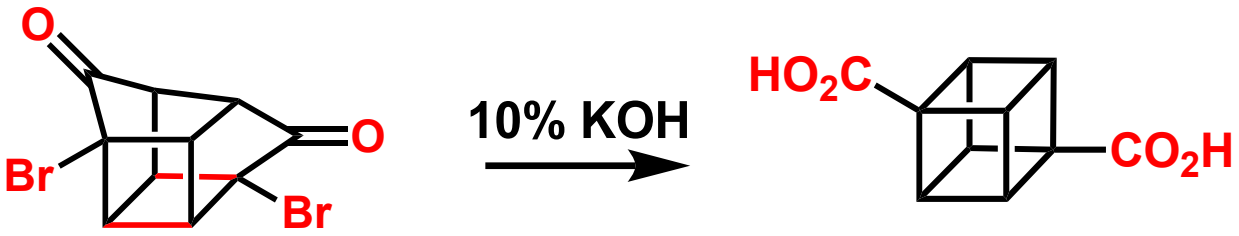
Favorski Rearrangement



Favorski Rearrangement

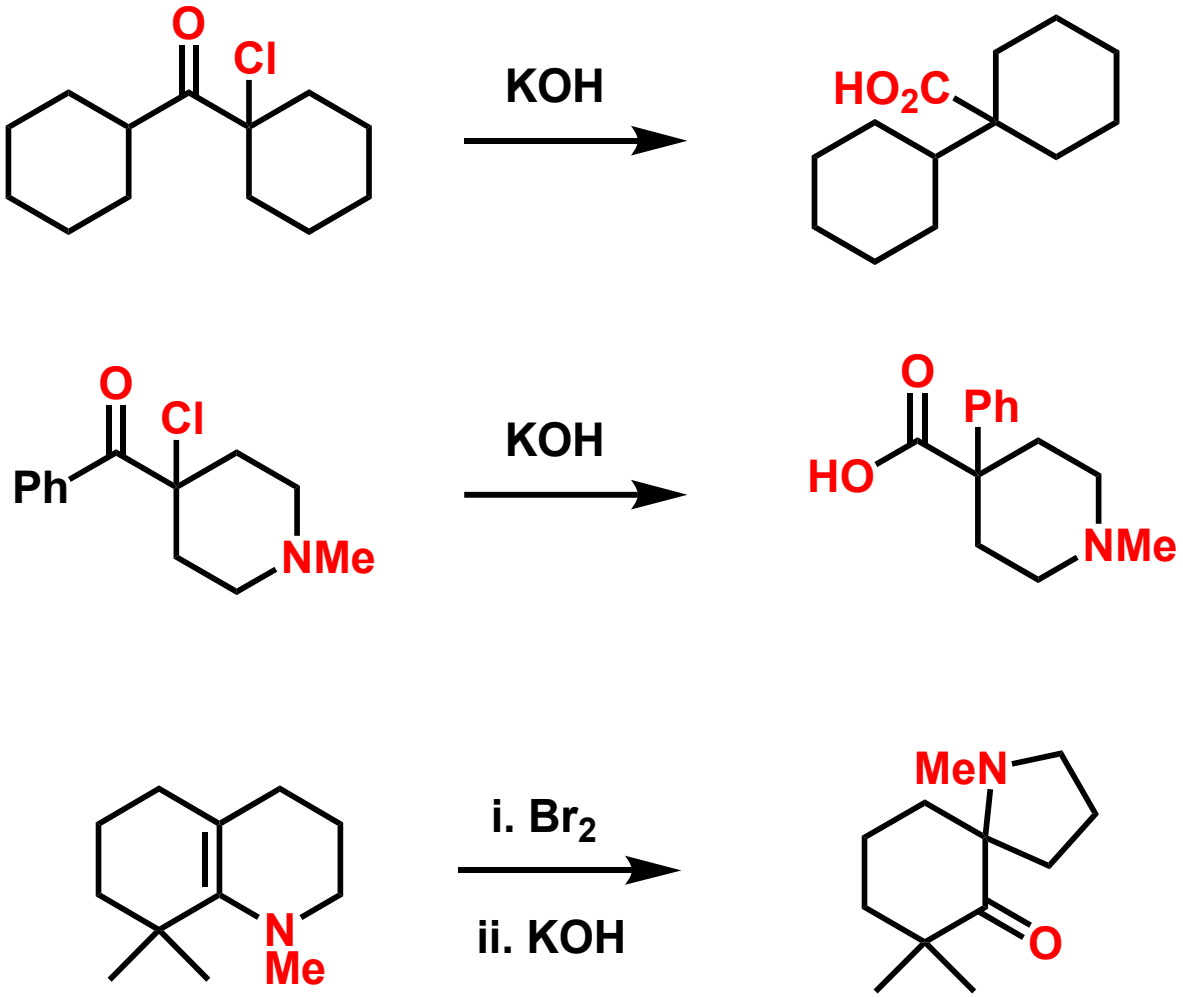


Write mechanism for the following transformations



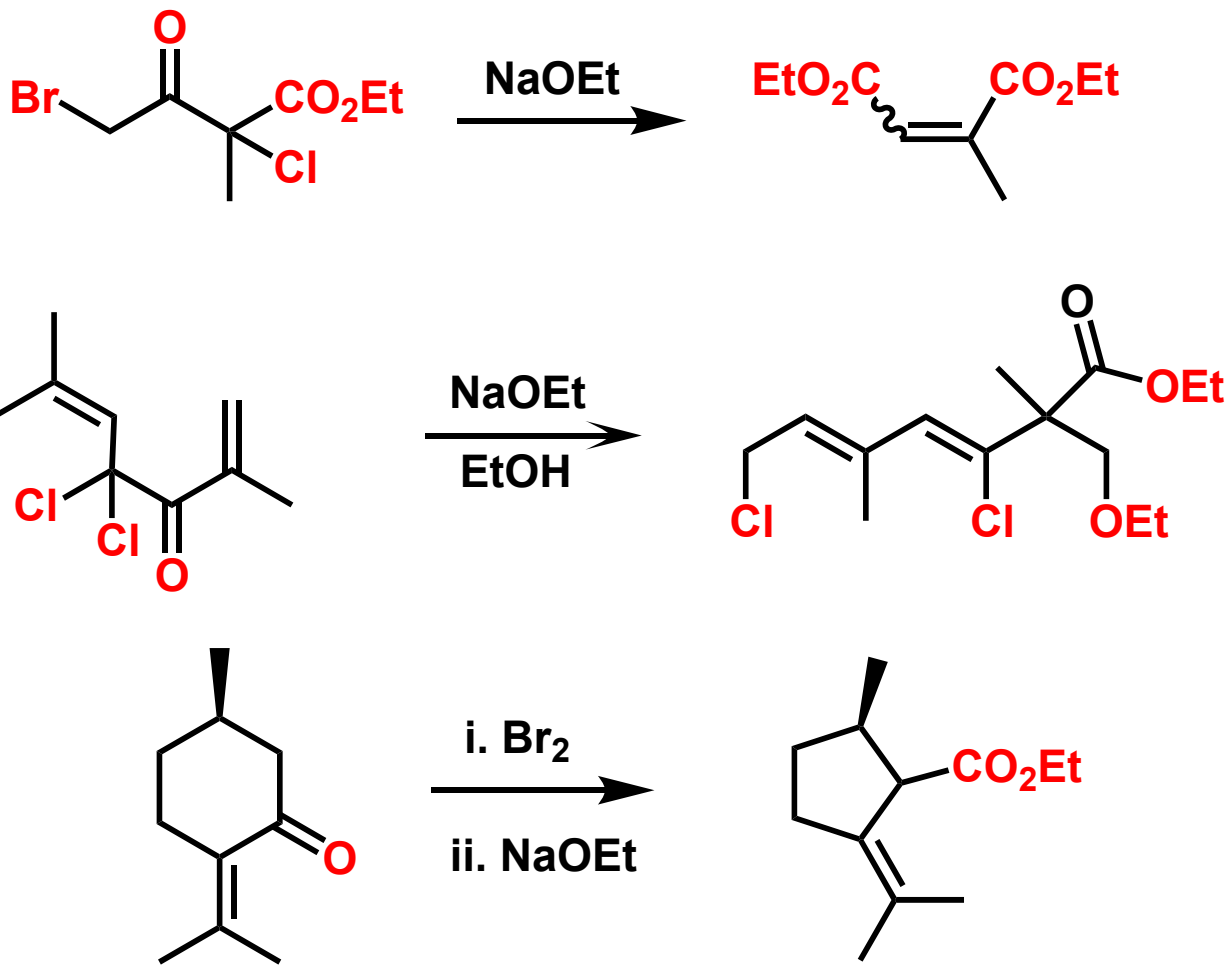
Favorski Rearrangement

Write mechanism for the following transformations



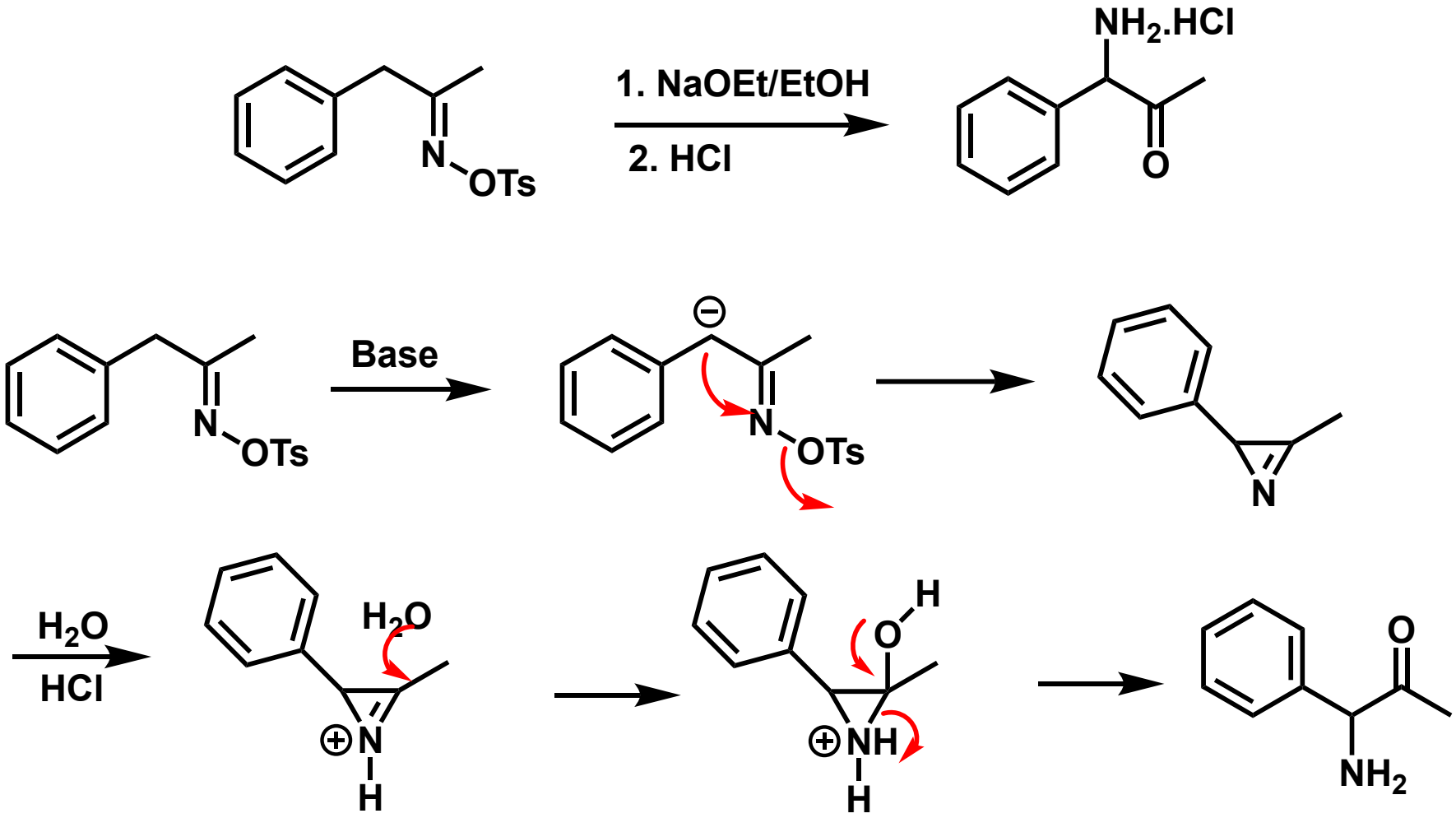
Favorski Rearrangement

Write mechanism for the following transformations



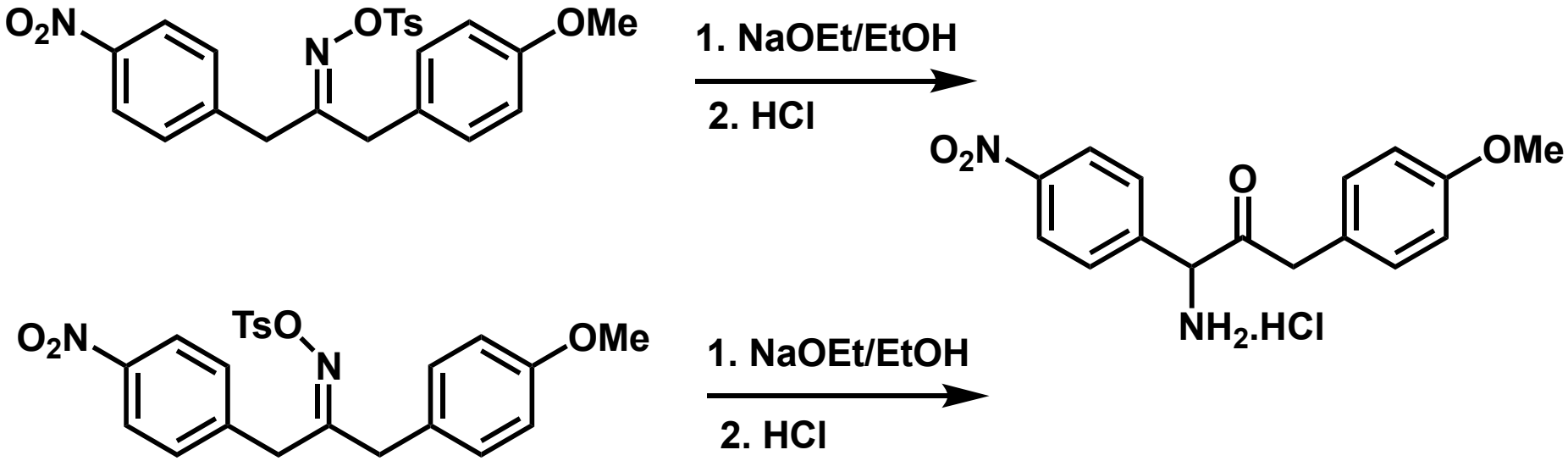
Neber Rearrangement

Ketoximes tosylates upon treatment with base can undergo rearrangement to give α-aminoketones



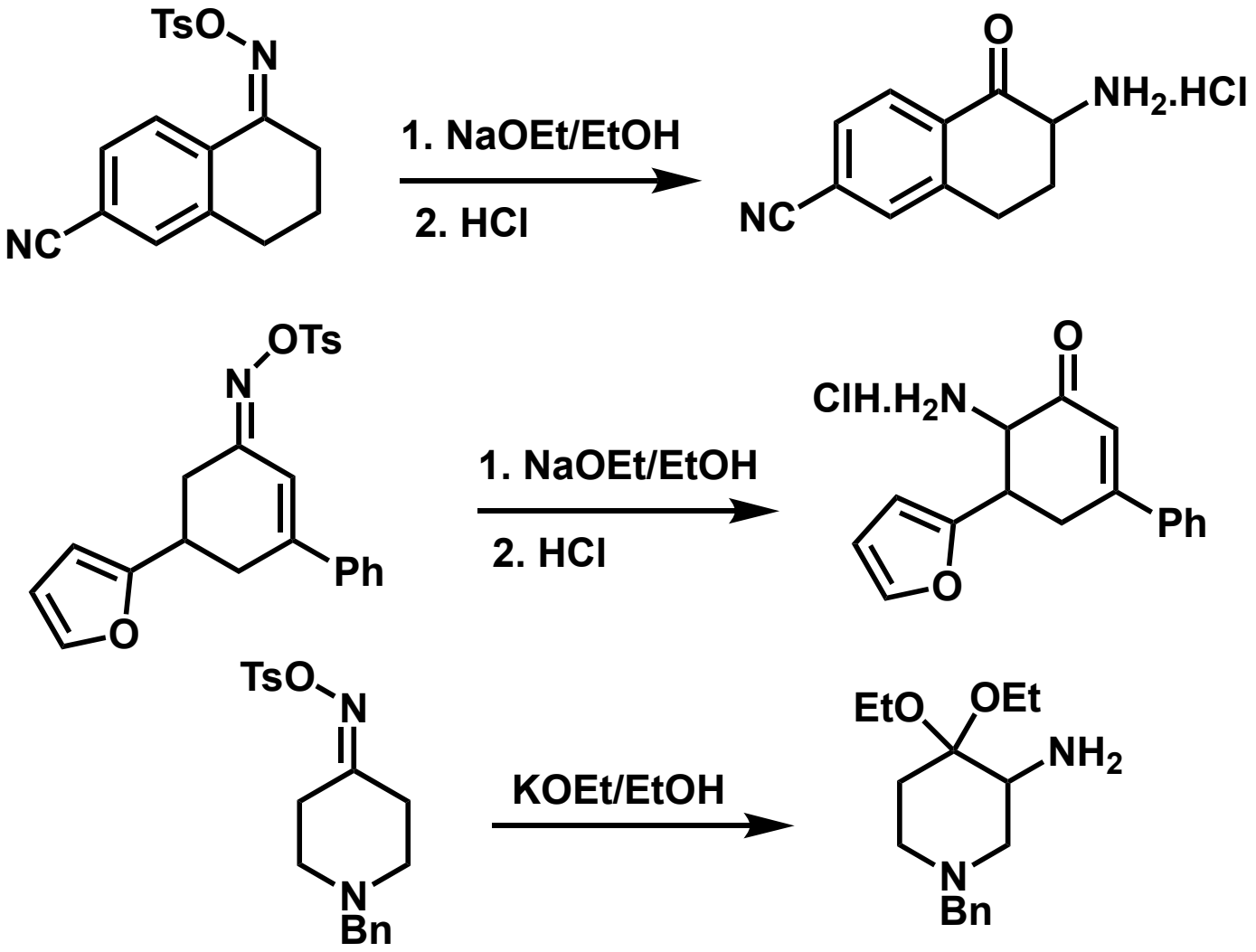
Neber Rearrangement

Regioselectivity depends on the acidic proton and not on the stereochemistry of the oximes



Neber Rearrangement

More Examples

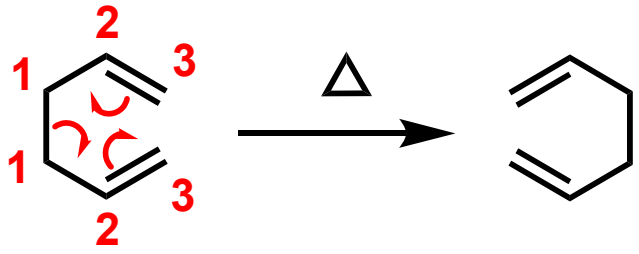


[3,3]-Sigmatropic Rearrangement

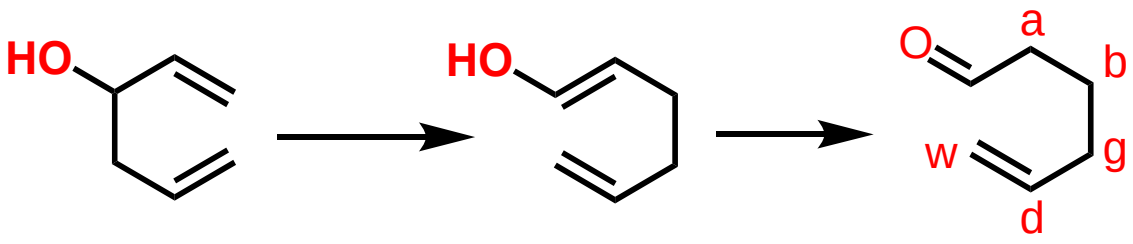
Cope Rearrangement

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

Why it is called [3,3] ?



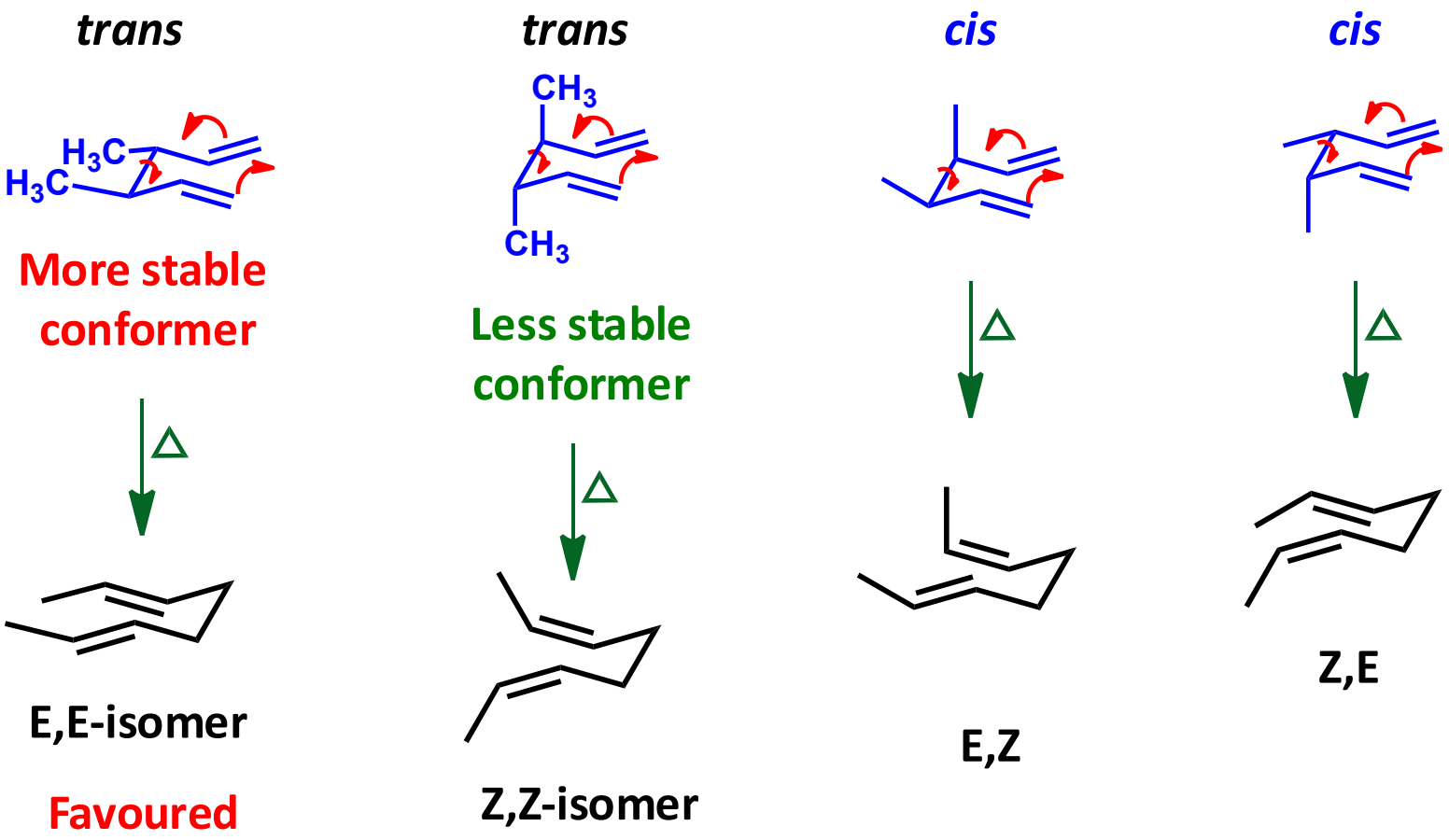
The new σ bond formed has 3,3- relationship with the old σ-bond



Sigmatropic Rearrangements

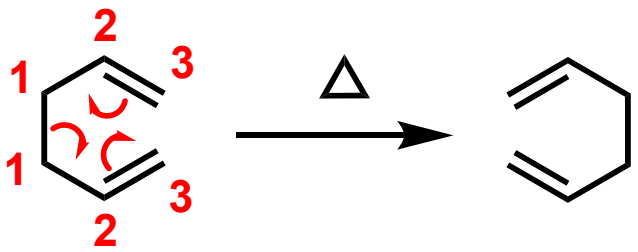
Mechanism

It goes via six-membered chair-like transition state

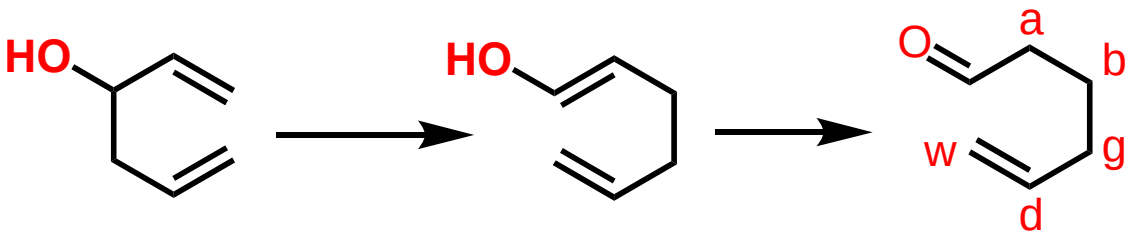


Sigmatropic Rearrangements

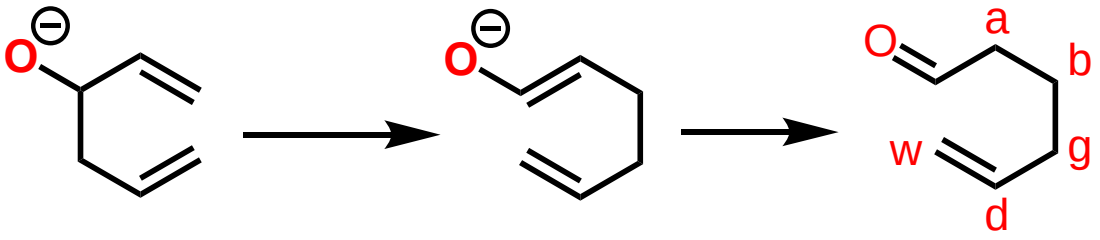
1) Cope:



2) Oxy-Cope:

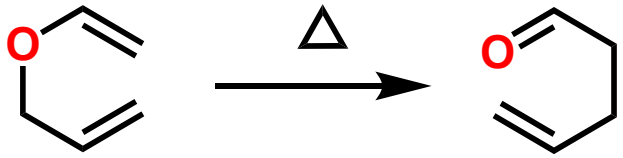


3) Anionic-Oxy-Cope:



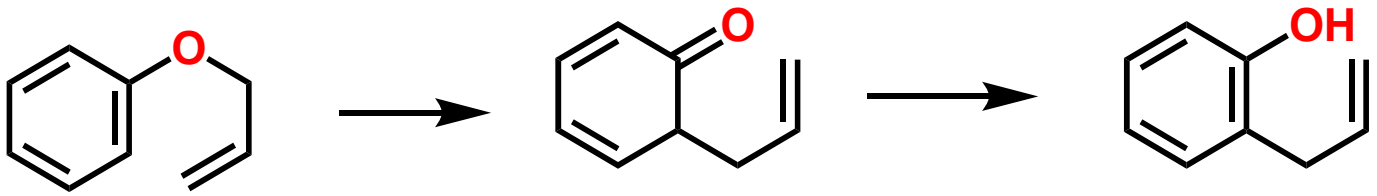
Sigmatropic Rearrangements

4) Claisen Rearrangement of Allylvinyl Ethers:

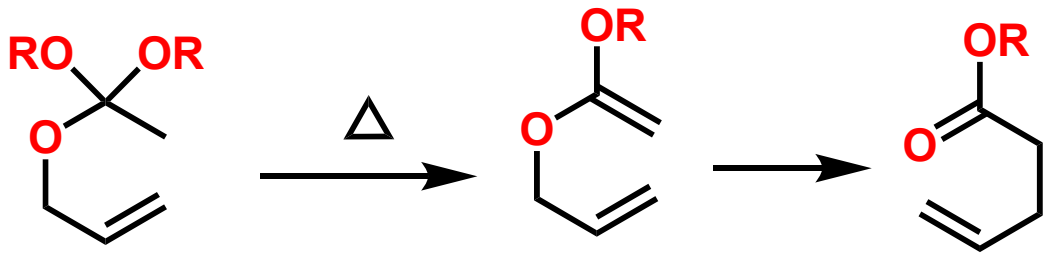


γ-δ-unsaturated aldehyde

5) Claisen Rearrangement of Allylphenyl Ethers:

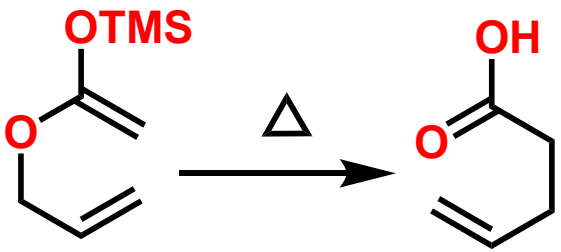


6) Ortho-Ester Claisen Rearrangement:

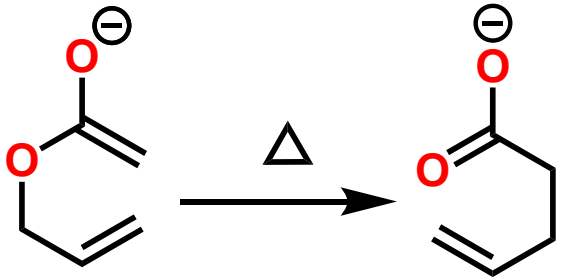


Sigmatropic Rearrangements

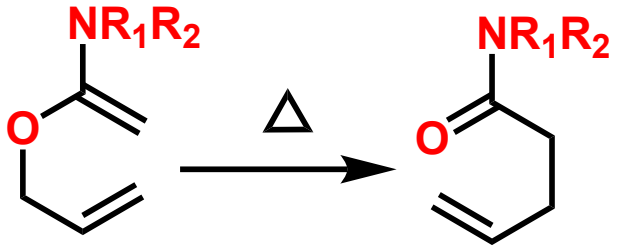
7) O-Allyl-O-TMS-Ketone Acetals:



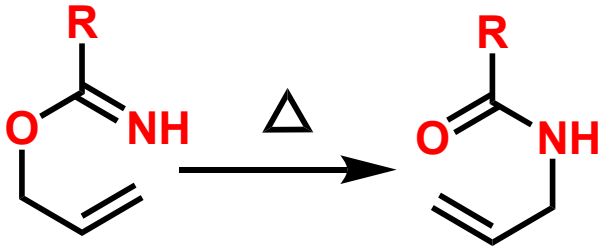
8) Ester-Enolate Claisen:



9) Ketene Aminals:

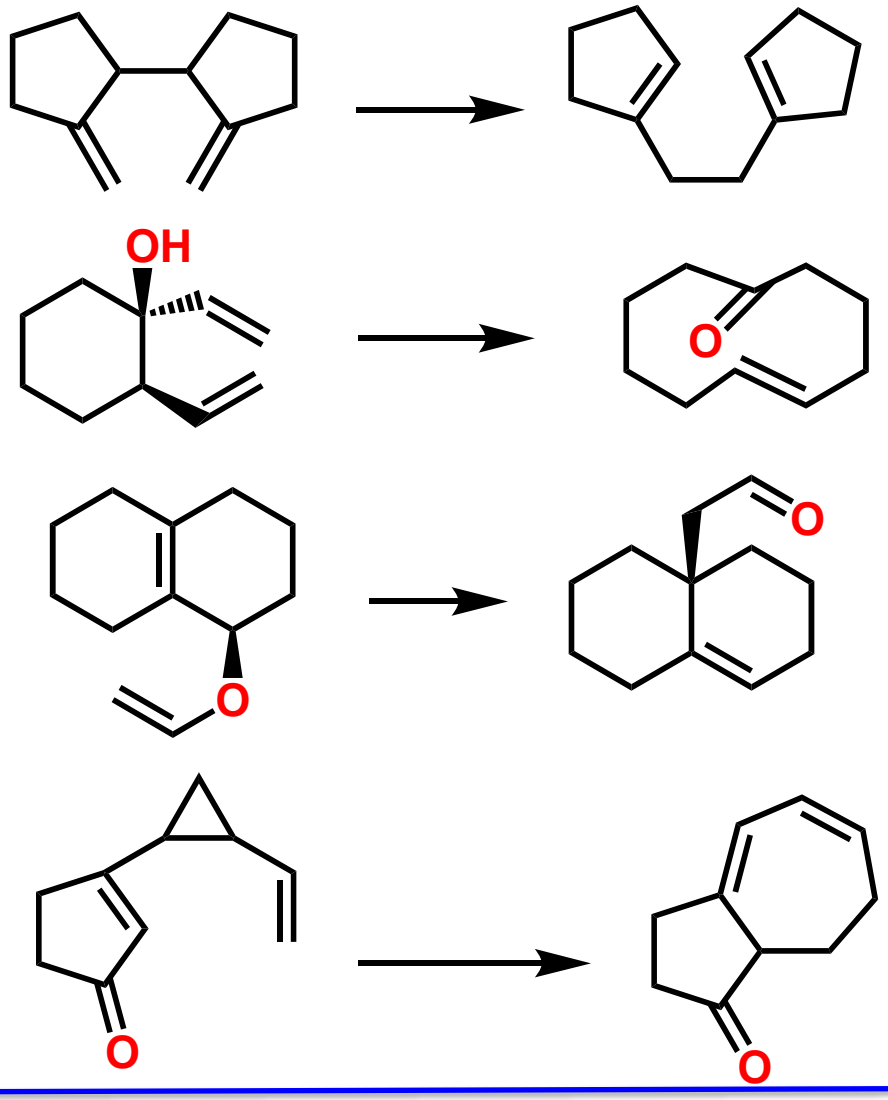


10) Aza-Claisen Rearrangement:



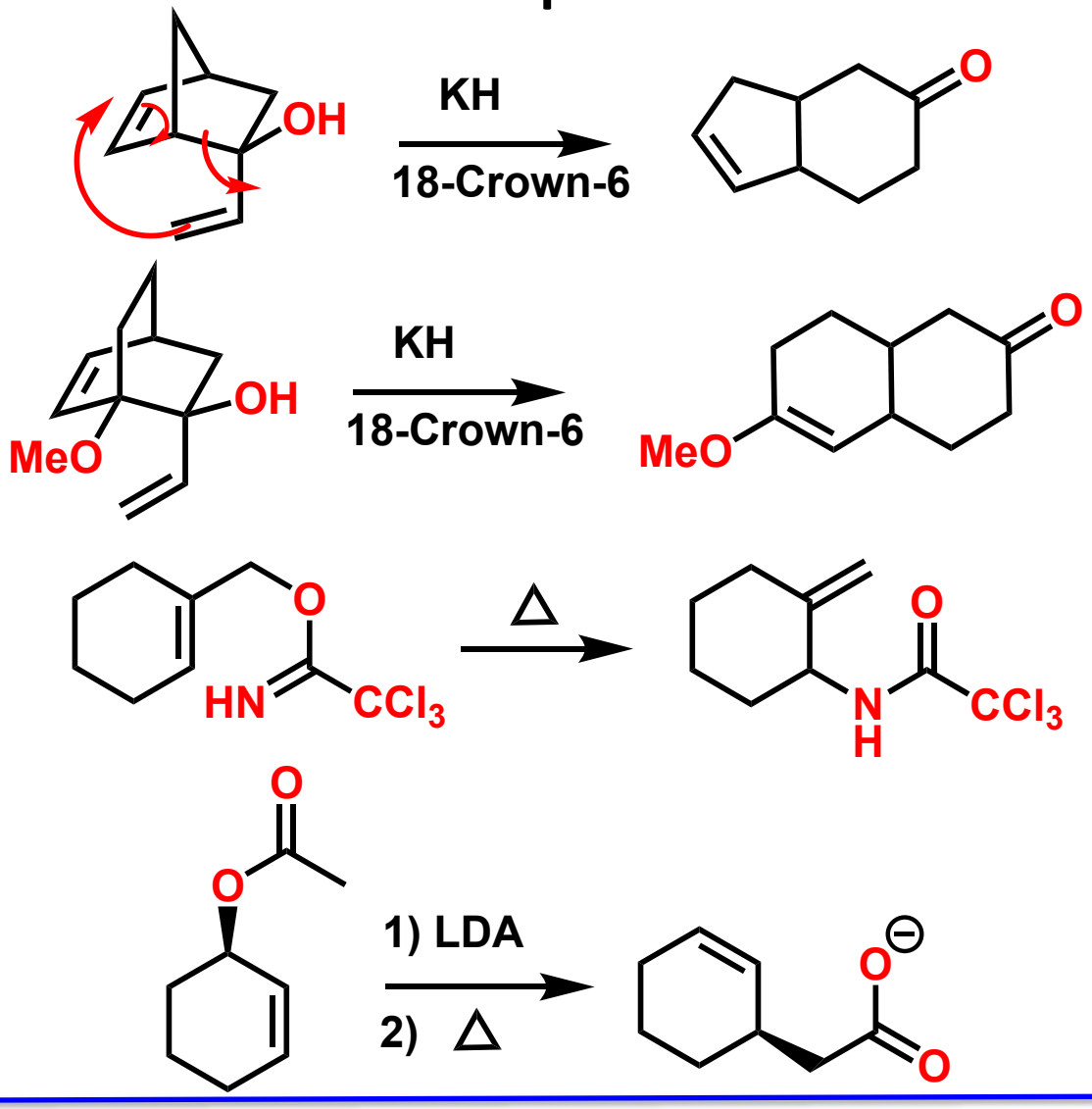
Sigmatropic Rearrangements

Examples



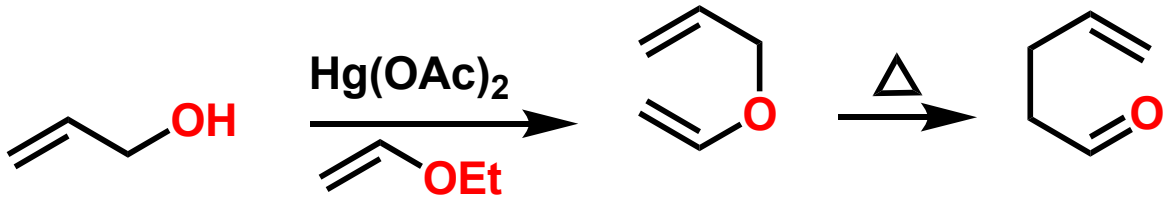
Sigmatropic Rearrangements

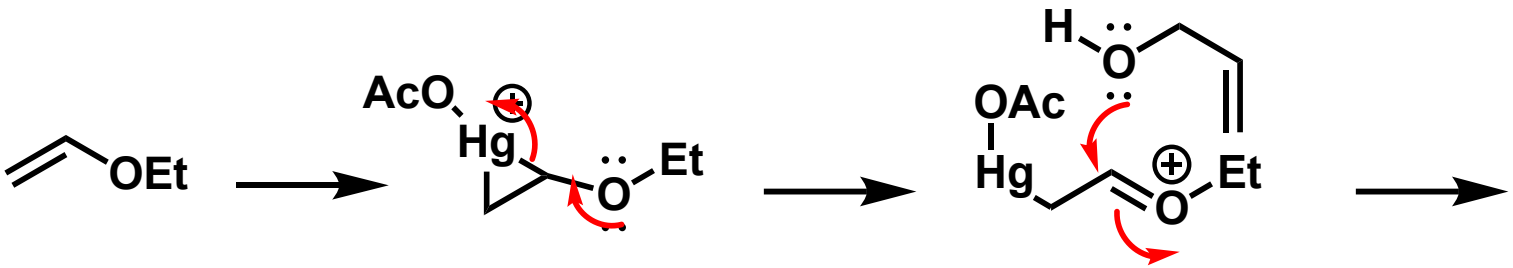
Examples

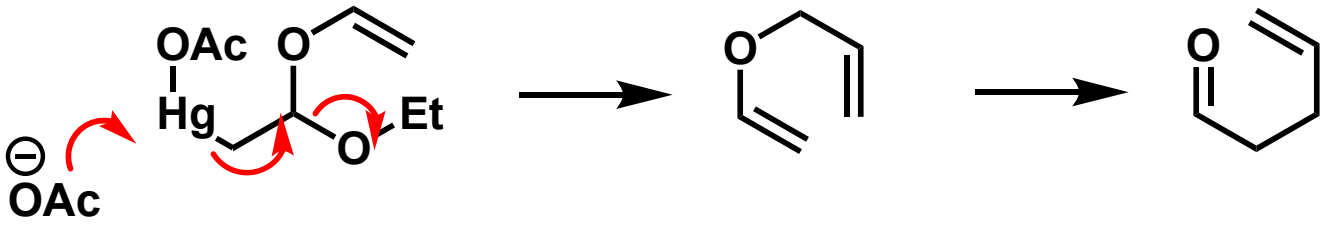


Claisen Rearrangement

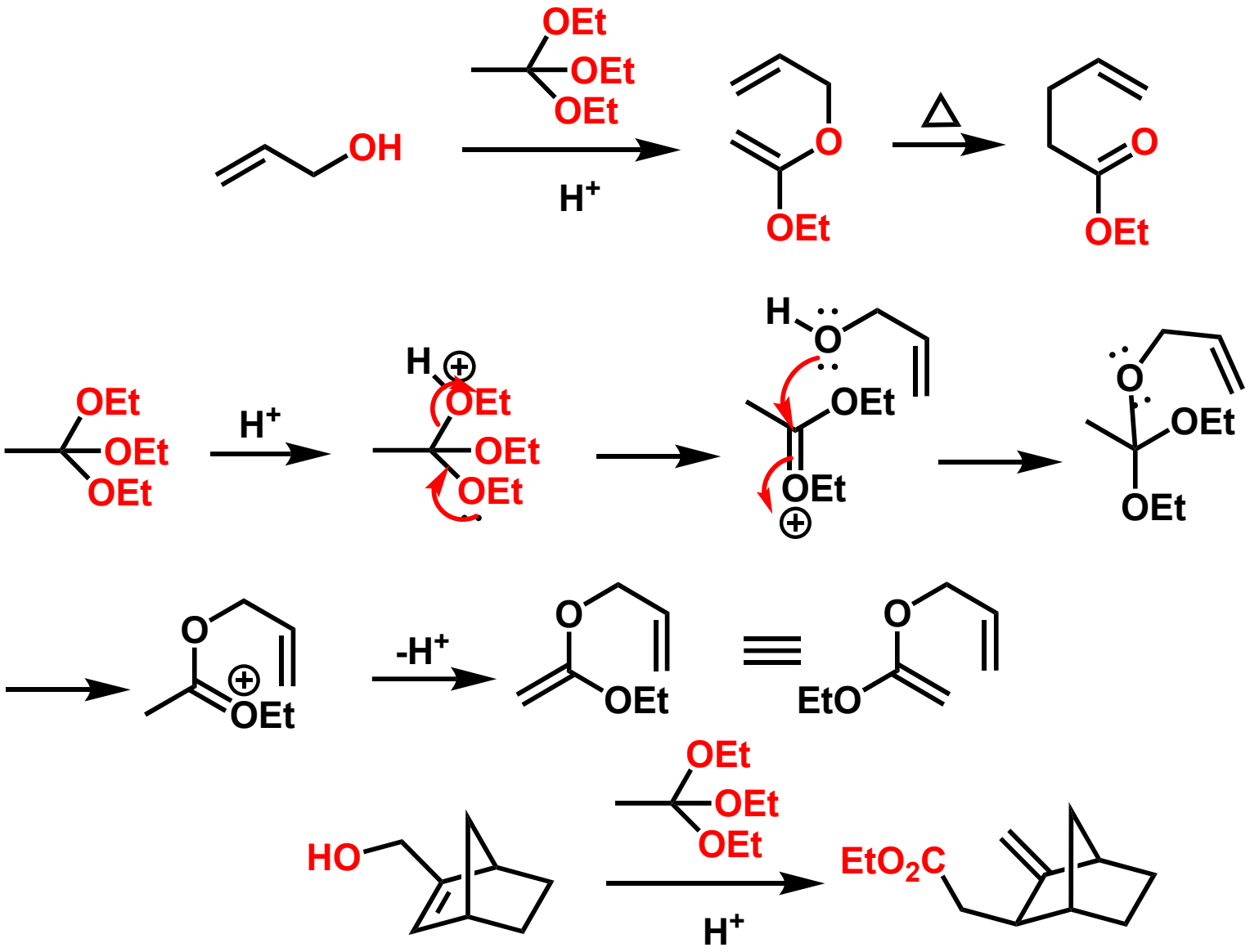
Examples



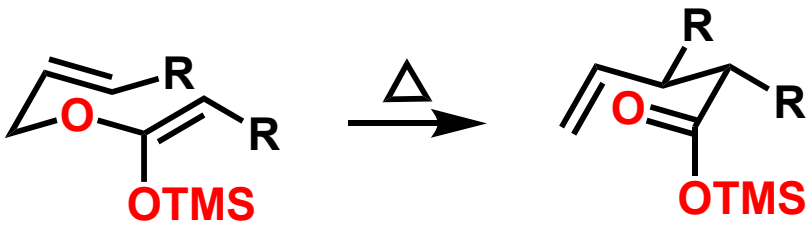




Claisen Rearrangement

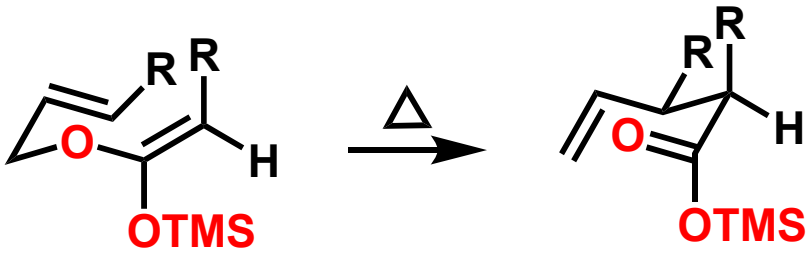


Z-silyl ether



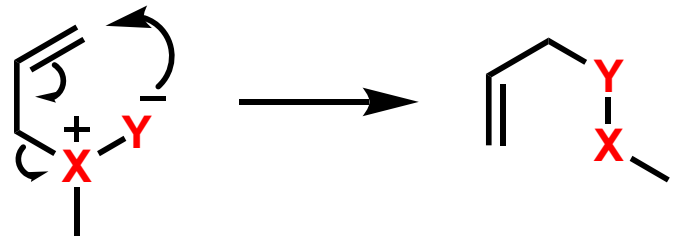
Trans

E-silyl ether



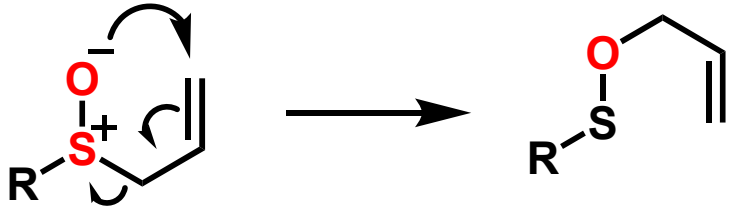
Cis

2,3-Sigmatropic Rearrangement

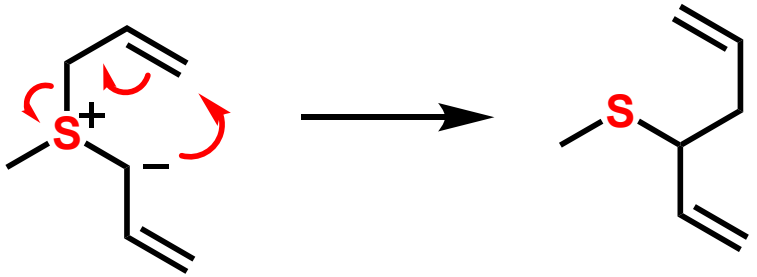


Charged Neutral

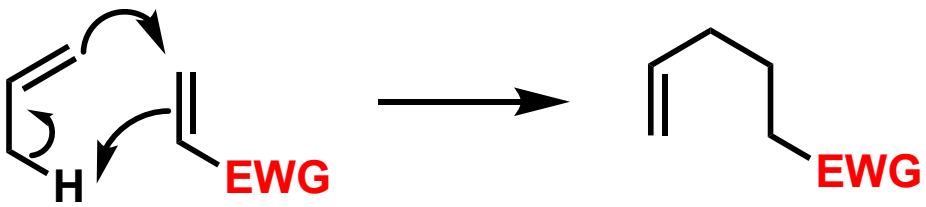
1) Allylic Sulfoxides:

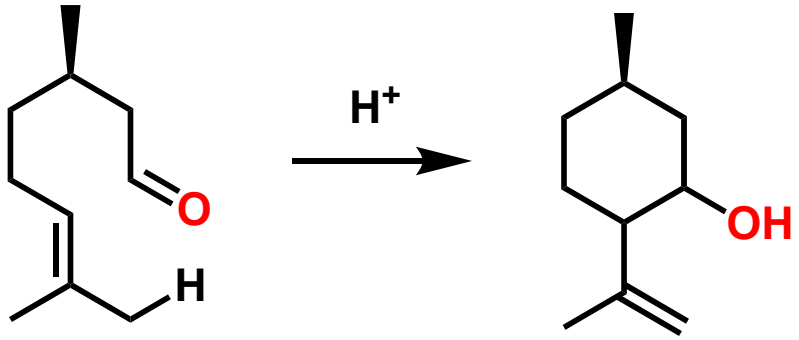


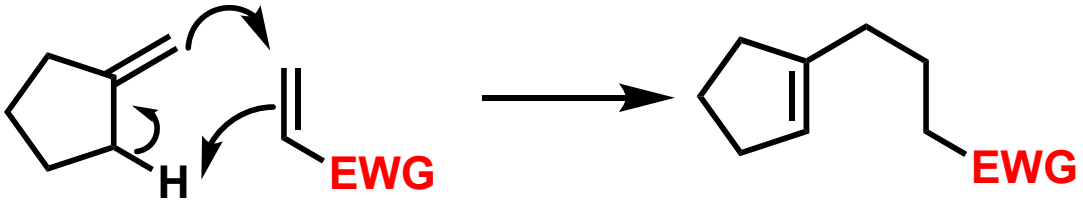
2) Allylic Sulfonium Ylides:



Ene Reaction

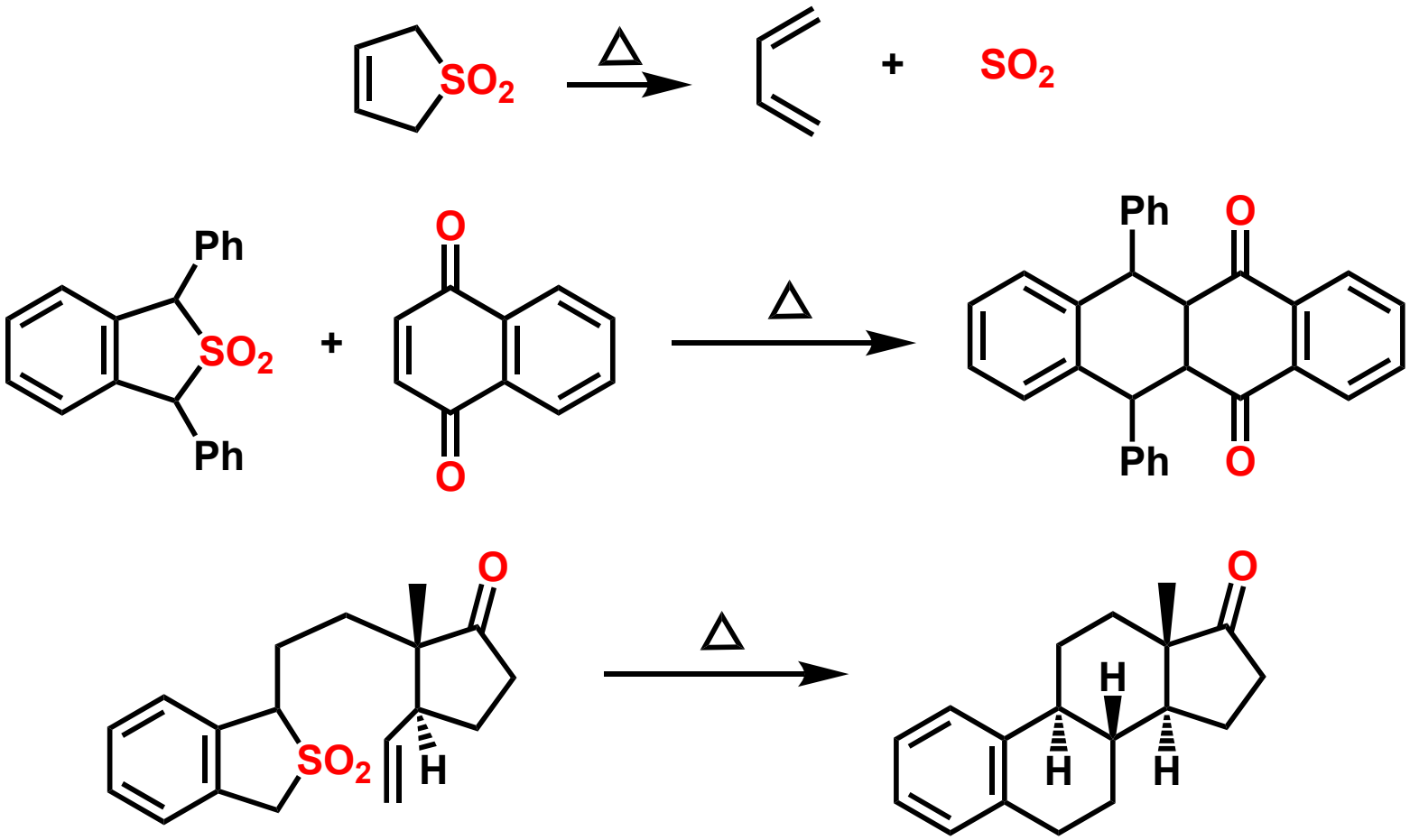






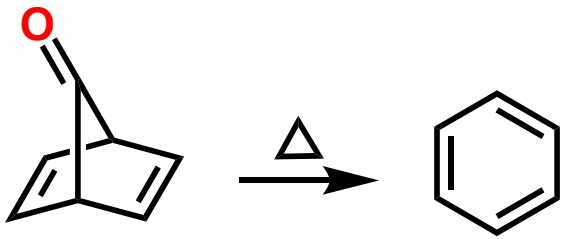
Cheletropic Elimination

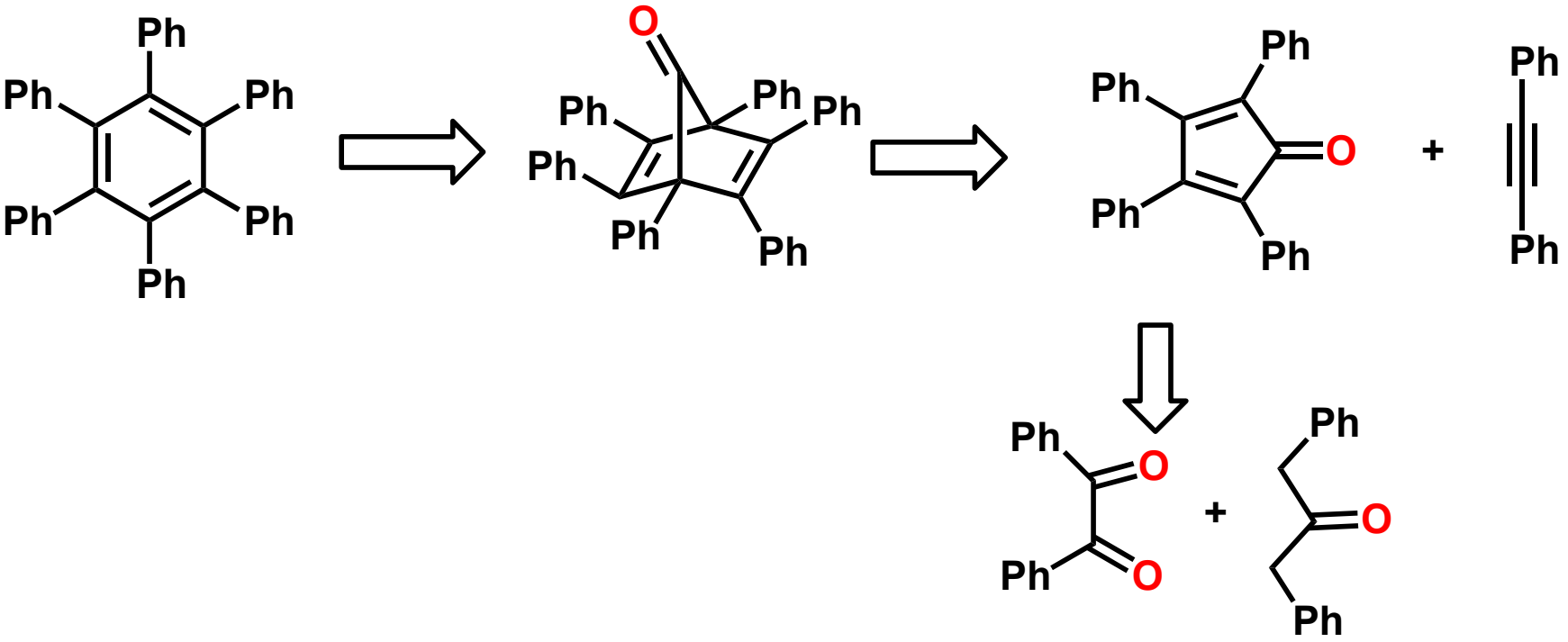
Two bonds are broken at a single atom



Cheletropic Elimination

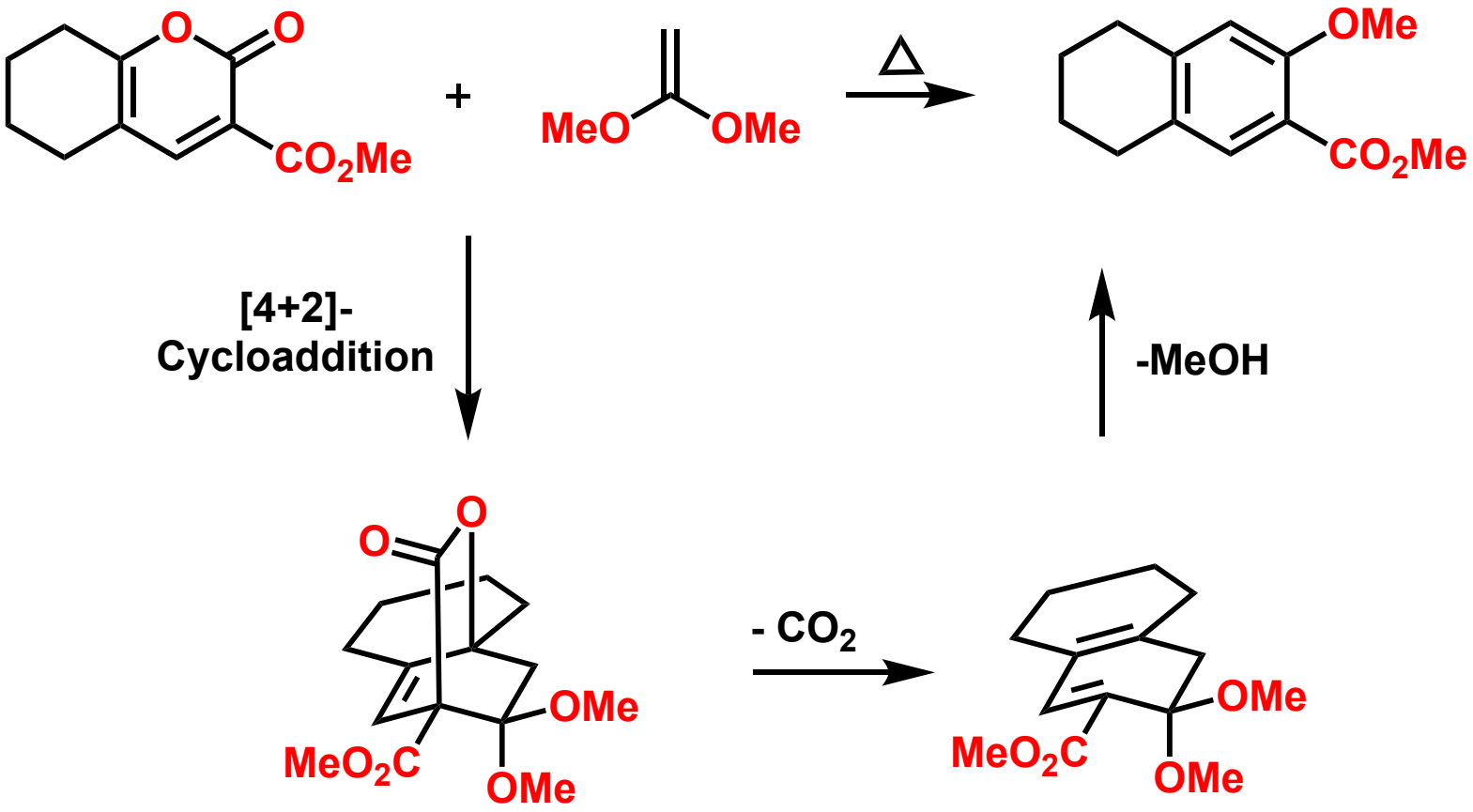
Elimination of CO





Cheletropic Elimination

Extrusion of CO_2



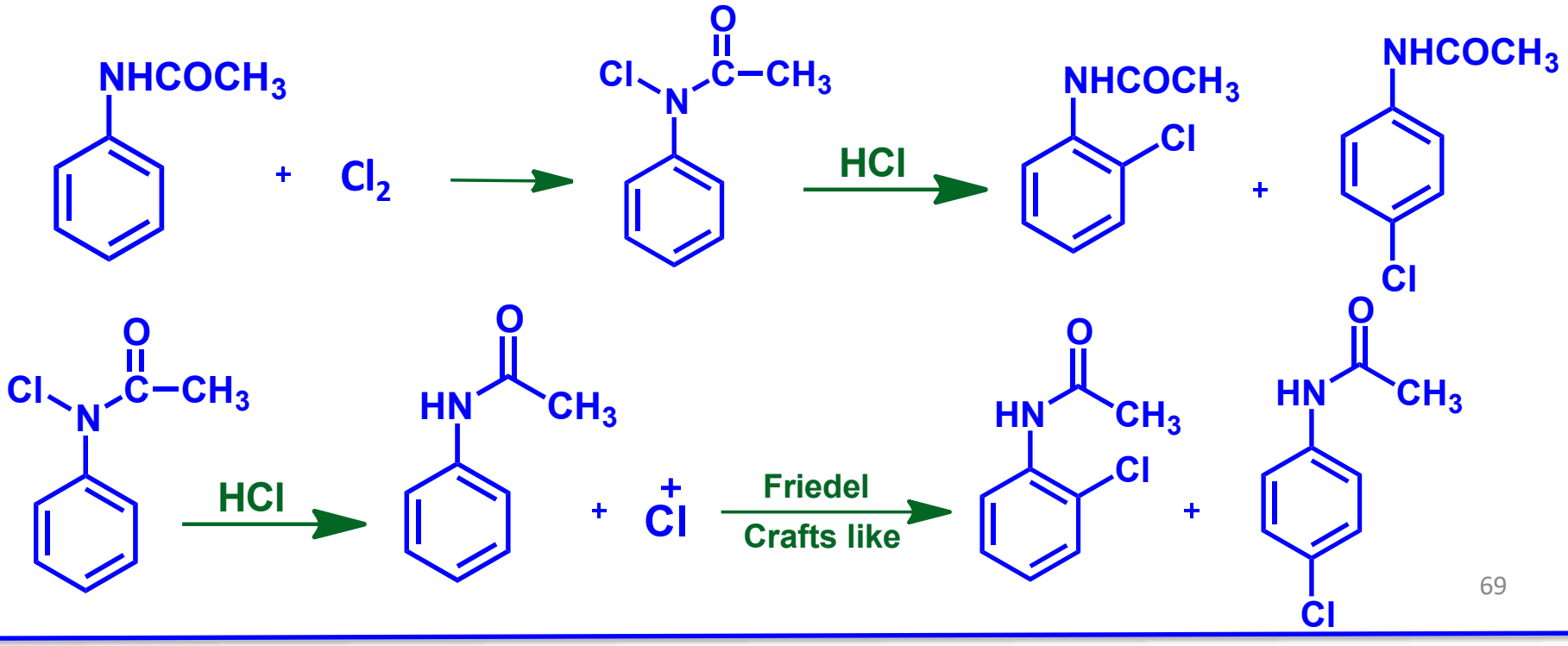
Rearrangements on Aromatic Rings

1) Fries Rearrangement

2) Claisen Rearrangement

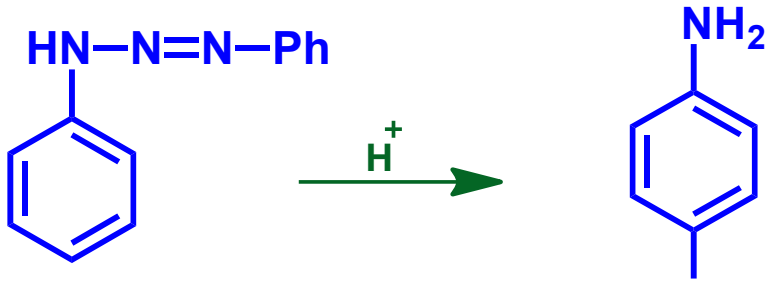
3) Rearrangements of derivatives of aniline

Rearrangements of Derivatives of Aniline



Rearrangements on Aromatic Rings

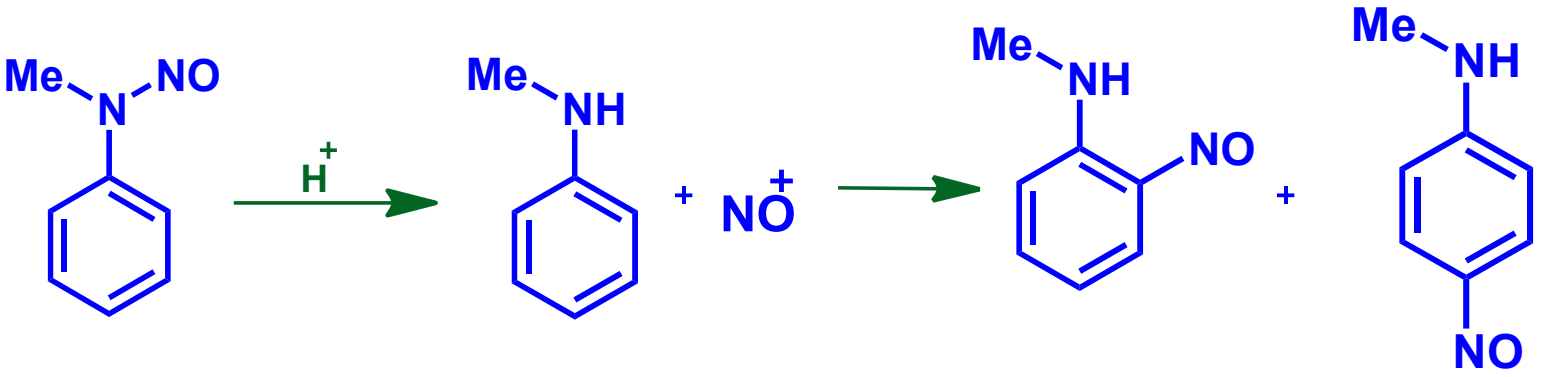
It is still not clear whether it involves inter or intramolecular mechanism



Diazoamino benzene

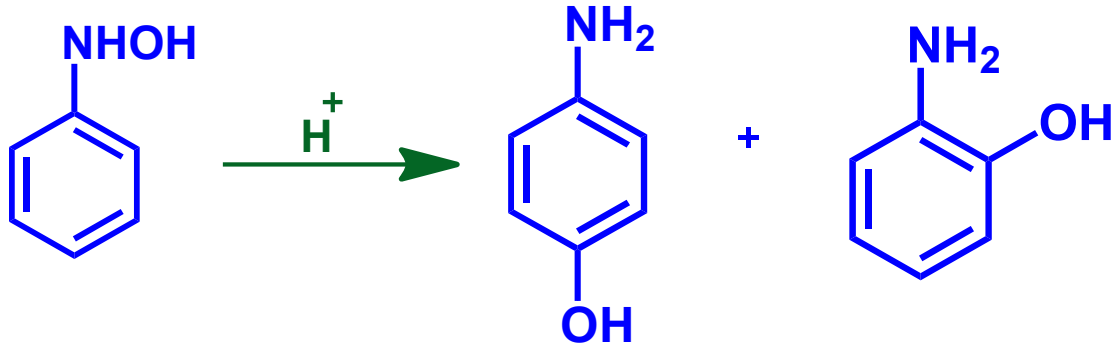
***p*-amino azo benzene**

N-Methyl-N-Nitrosoamine

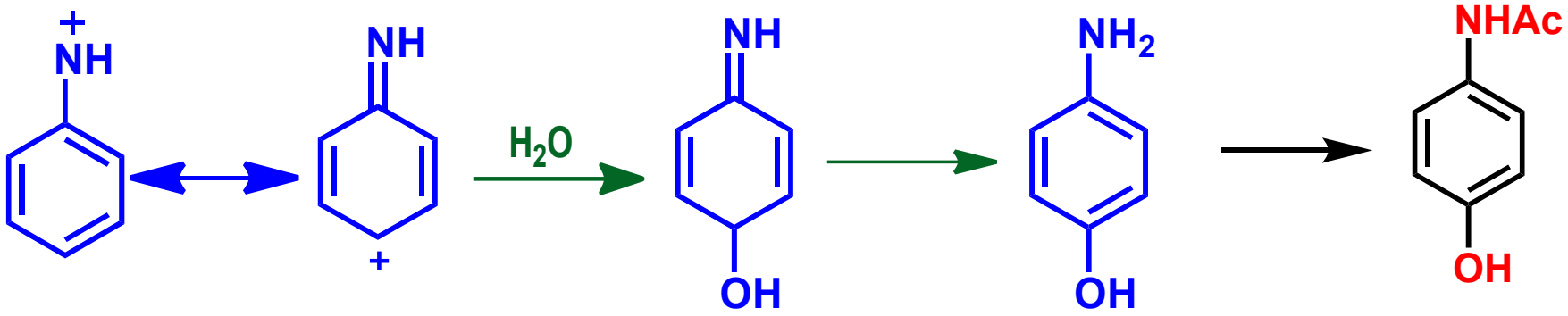


Rearrangements on Aromatic Rings

N-Phenylhydroxylamine

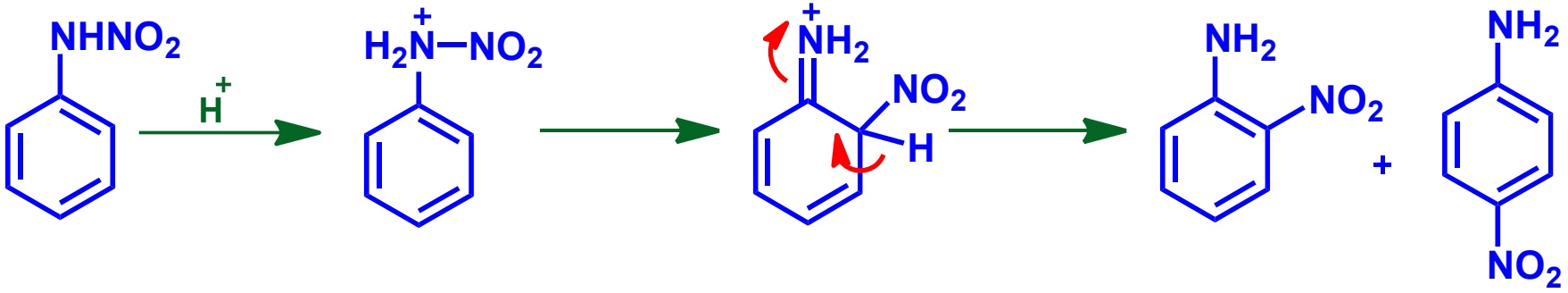


Mechanism

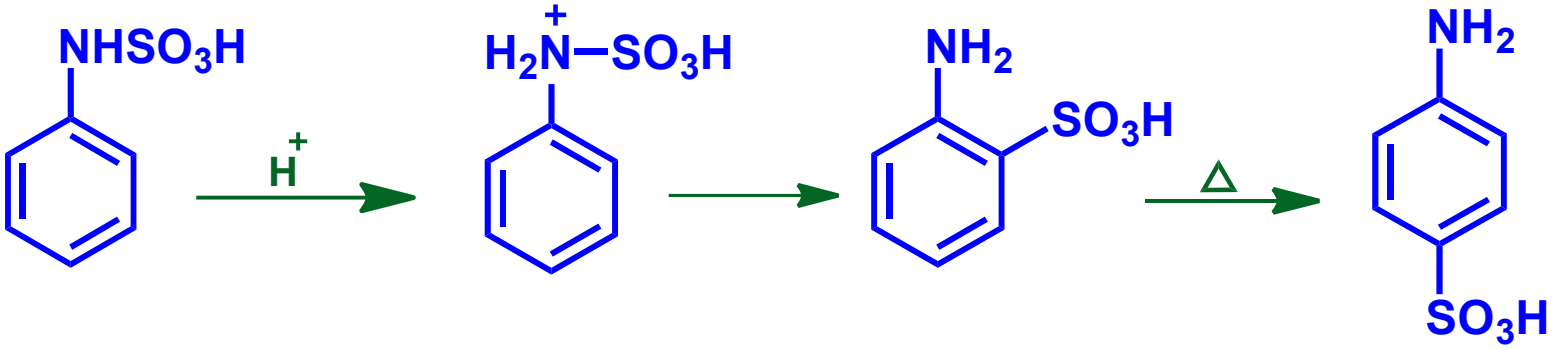


Rearrangements on Aromatic Rings

N-Phenylnitraamne

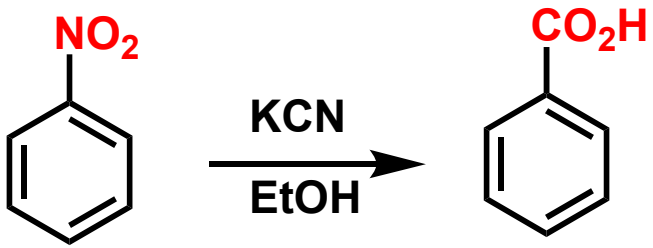


Phenyl sulfamic acid

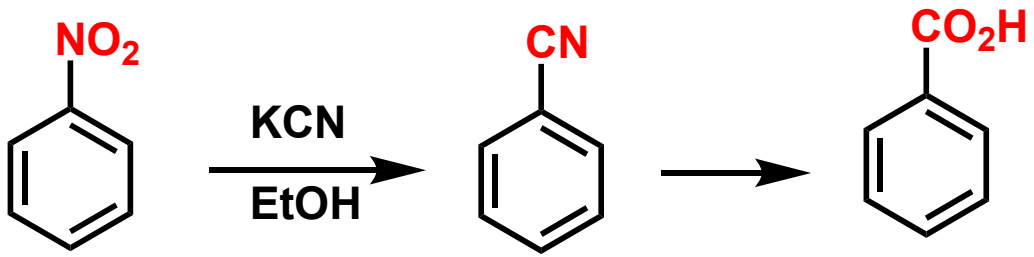


Von-Richter Rearrangement

Transformation of aromatic nitro group to carboxylic acid by alcoholic KCN was reported by von-Richter in 1871



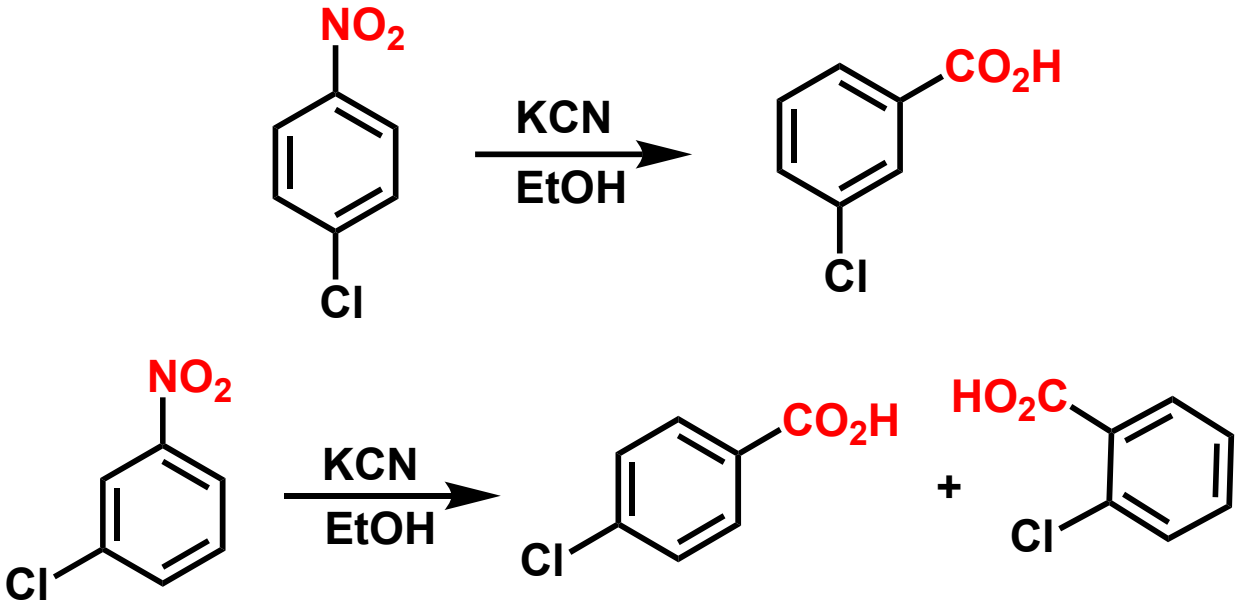
Since the reaction led to the loss of nitro group and was replaced by carboxylic acid, he proposed that it was a displacement reaction followed by hydrolysis of cyanide to carboxylic acid



Von-Richter Rearrangement

Subsequent experiments with substituted nitro arenes proved that the carboxylic acid occupies *ortho* to the nitro group in the product.

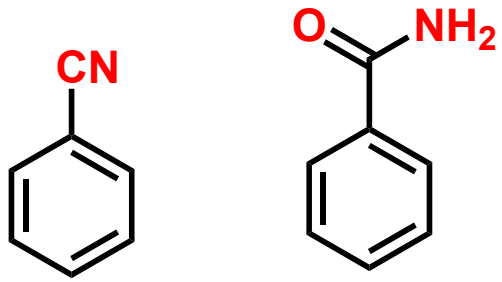
For example, if *p*-chloronitrobenzene was subjected to this condition, the product obtained was *m*-chlorobenzoic acid.



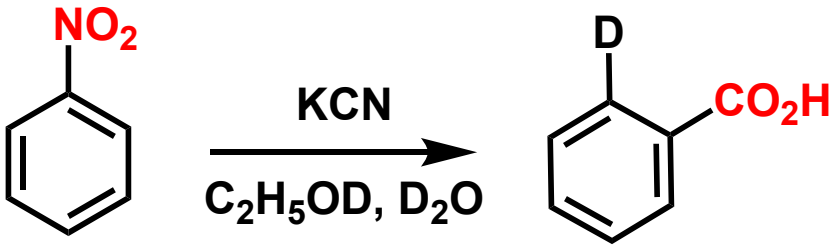
Recovered starting material was uncontaminated with other isomers

Mechanistic Studies

Neither the amide nor the nitrile was isolated as intermediates

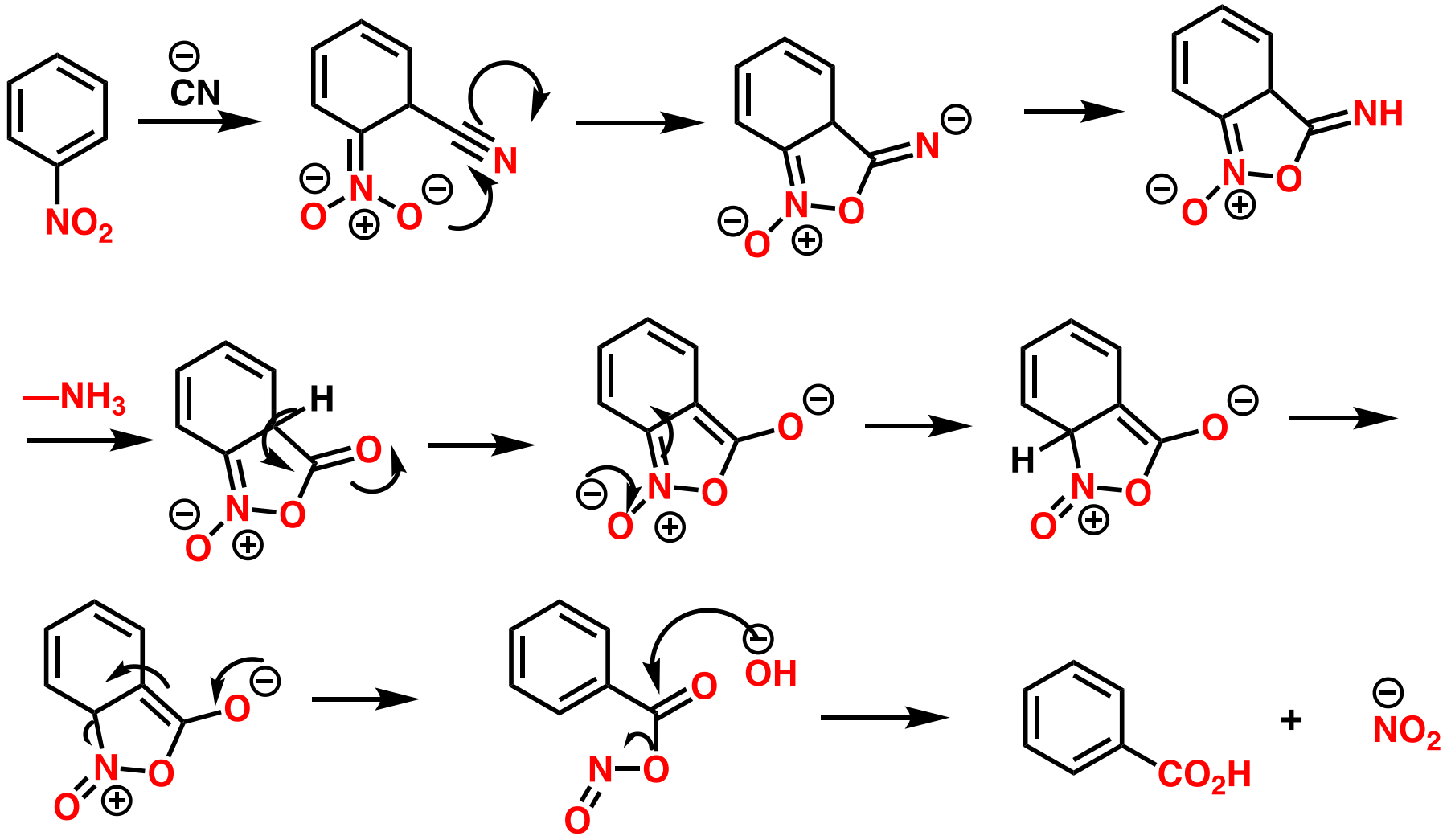


When the reaction was carried with D_2O-C_2H_5OD,



Proposed Mechanism-1

Based on the above, the following mechanism was proposed



Problems with Mechanism-1

This mechanism had two problems. (a) Ammonia was not detected
(b) Nitrite also was not isolated

However, it was observed that nitrogen gas was also evolved during this reaction

But, as per this mechanism, even if ammonia and nitrite have been formed as byproducts, they cannot react to form nitrogen also

Problems with Mechanism-1

To substantiate this $^{15}NH_3$ was added in the reaction mixture and found that the nitrogen formed in the reaction was normal and there was no incorporation of ^{15}N

When this reaction was carried out with aqueous EtOH containing H_2O enriched with H_2O^{18}, it was observed that the atom % of the oxygen atom of the carboxyl group was half that of the solvent

This tells clearly that one of the oxygen atoms of the carboxyl group comes from the nitro group

Accepted Mechanism

Thus, the below mechanism was proposed which explains all the above details