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-

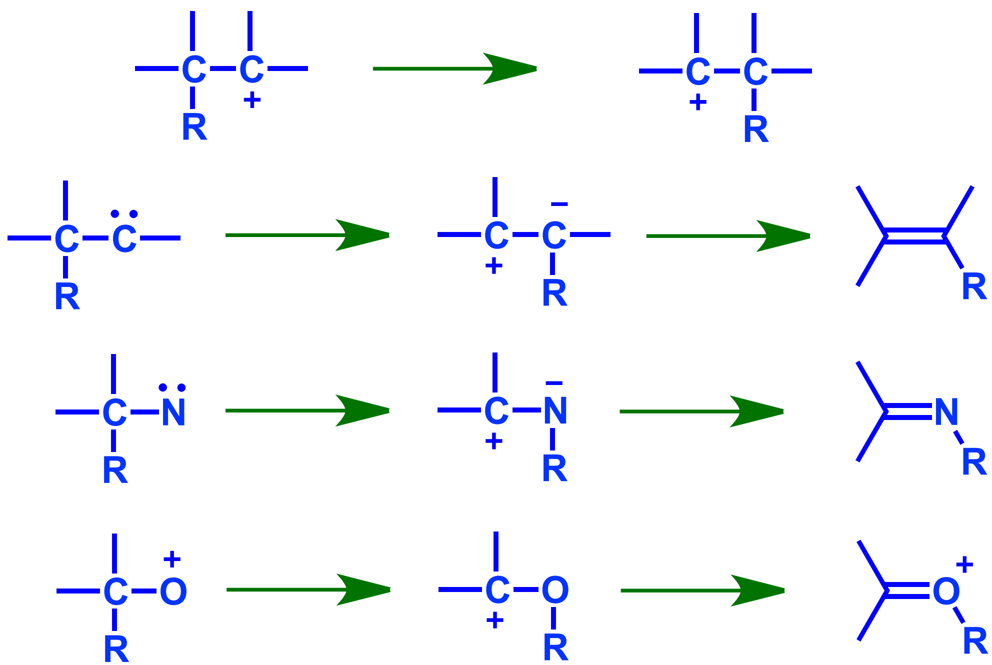
  1. Electron deficient skeletal rearrangement
  2. Electron rich skeletal rearrangement
  3. Radical rearrangement
  4. Rearrangements on an aromatic ring
  5. Sigmatropic rearrangement

Molecular Rearrangements

Electron Deficient Skeletal Rearrangement

- 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

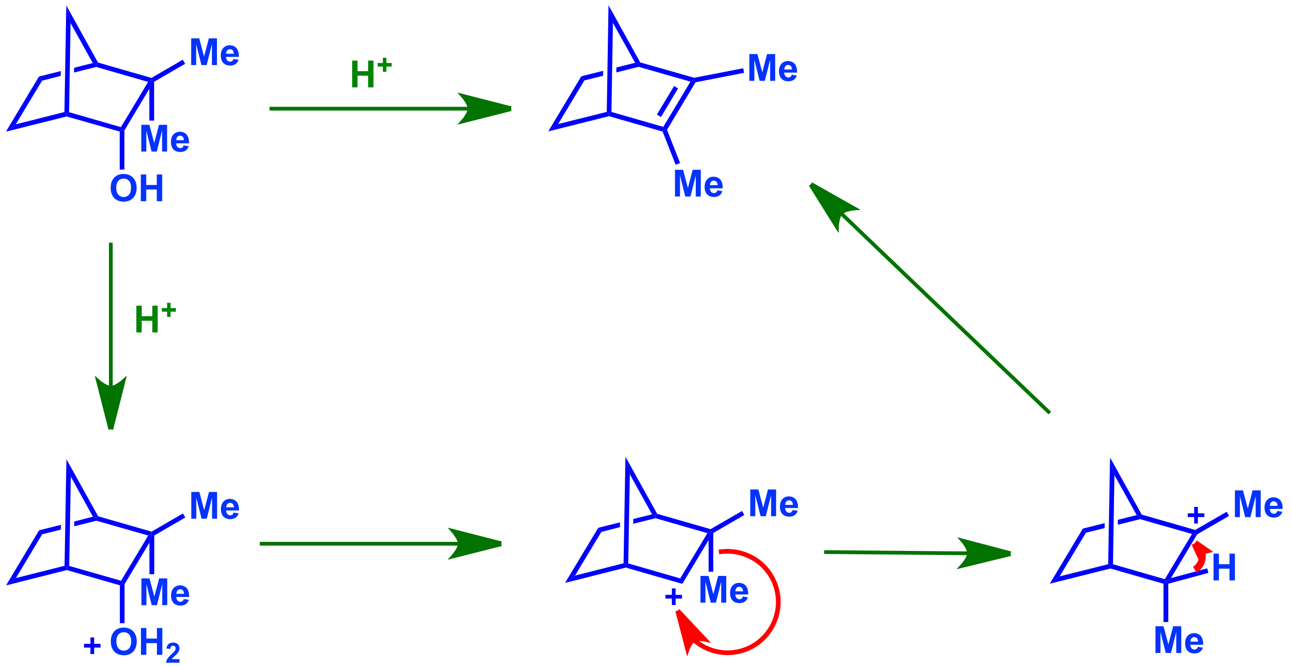
Examples:



Molecular Rearrangements

Wagner- Meerwin Rearrangement

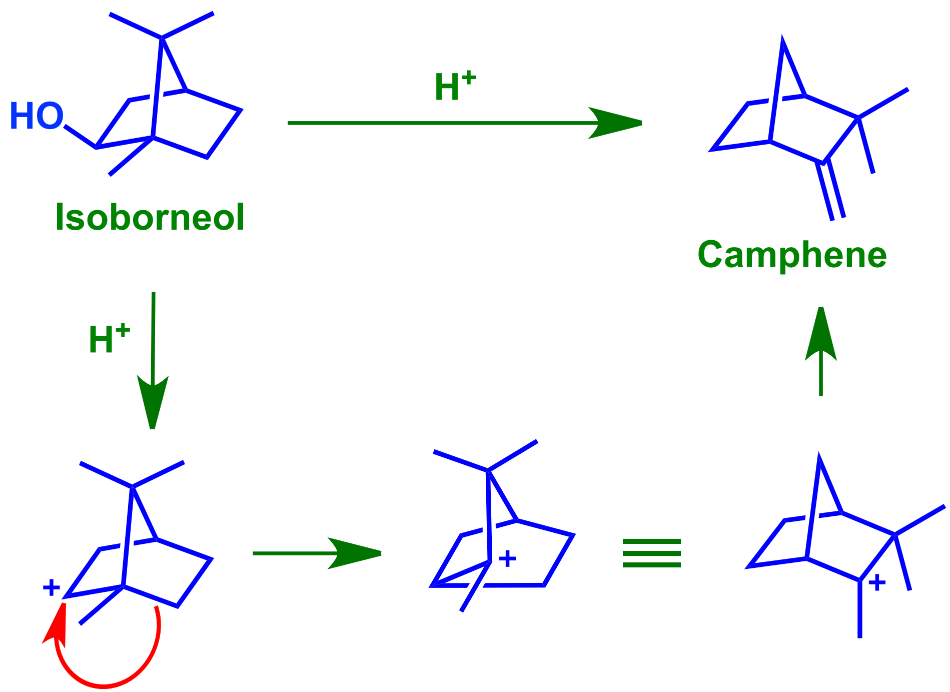
- Rearrangement of alcohols under acidic condition



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

Molecular Rearrangements

Wagner- Meerwin Rearrangement



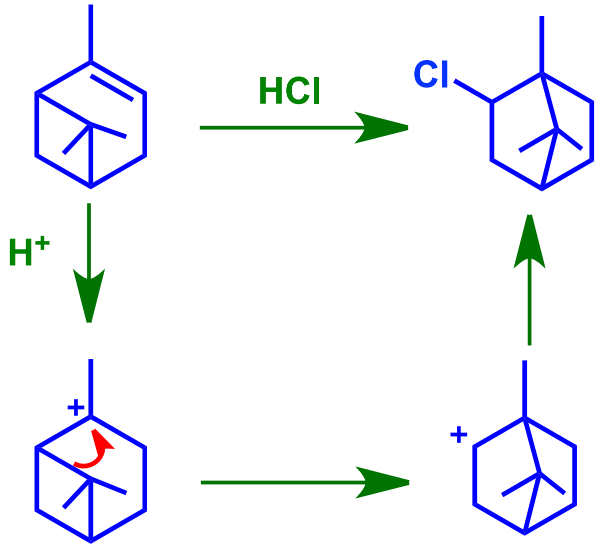
Molecular Rearrangements

Ring Expansion

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

Can we go from 3° to 2° ??

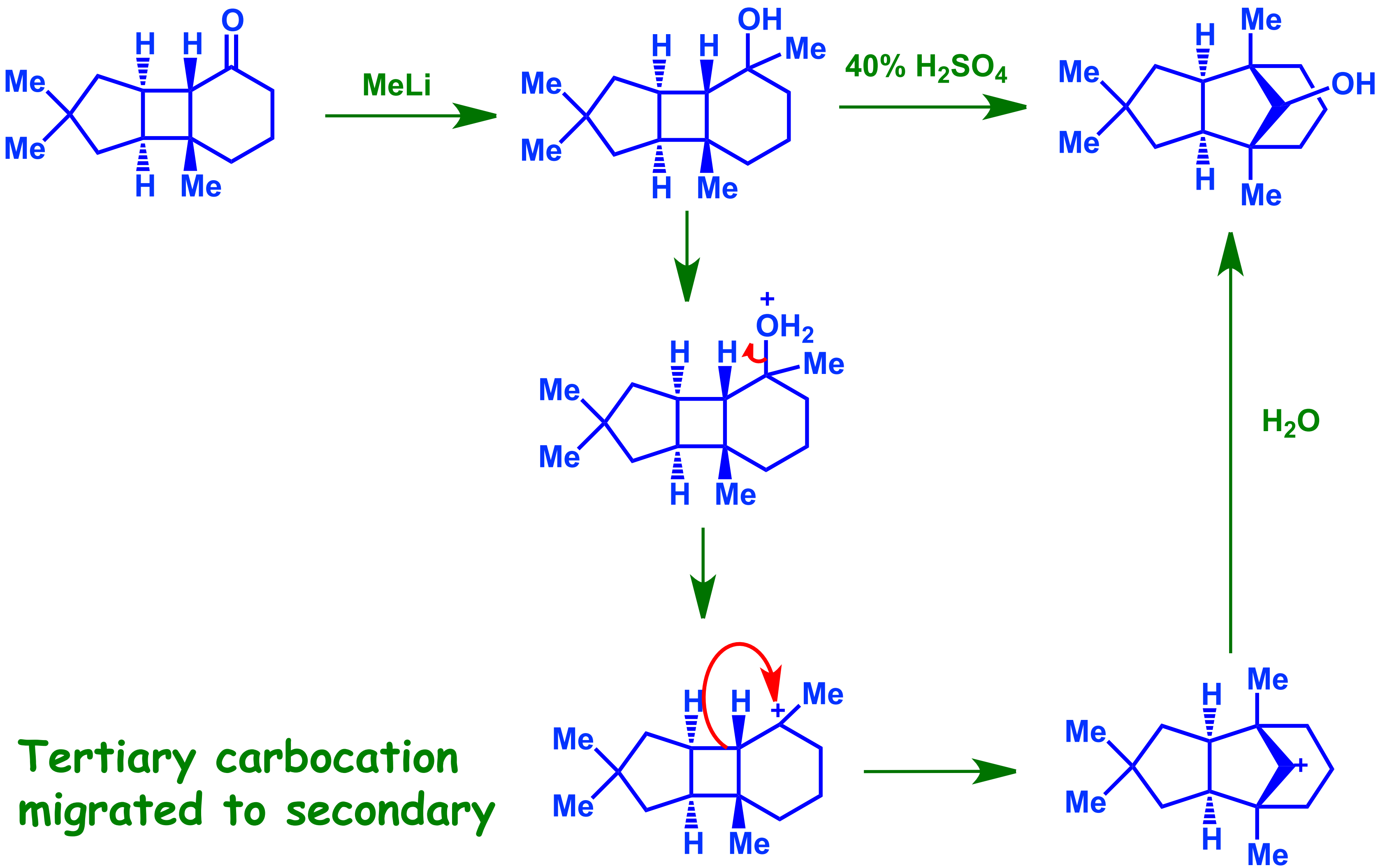
- Cations can be made more stable if they become less strained



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

Molecular Rearrangements

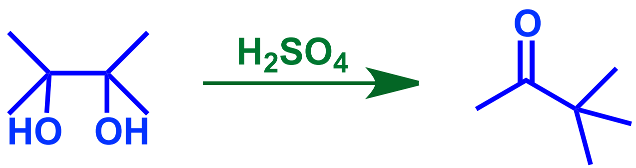
Ring Expansion

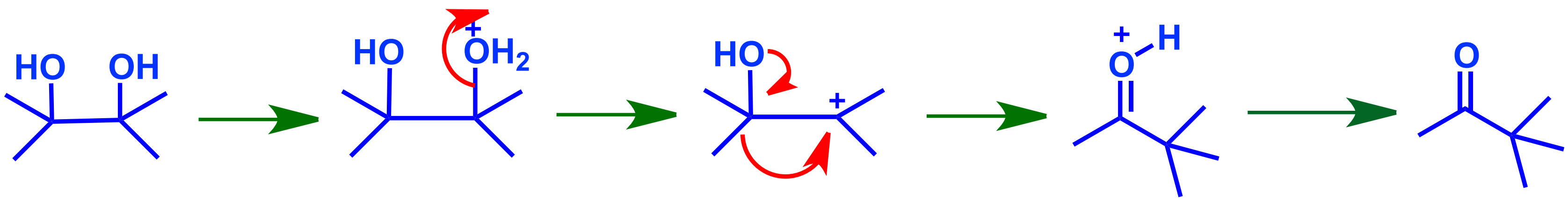


Tertiary carbocation migrated to secondary

Molecular Rearrangements

Pinacol-Pinacolone Rearrangement

Pinacol  Pinacolone



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

- **Reason:**

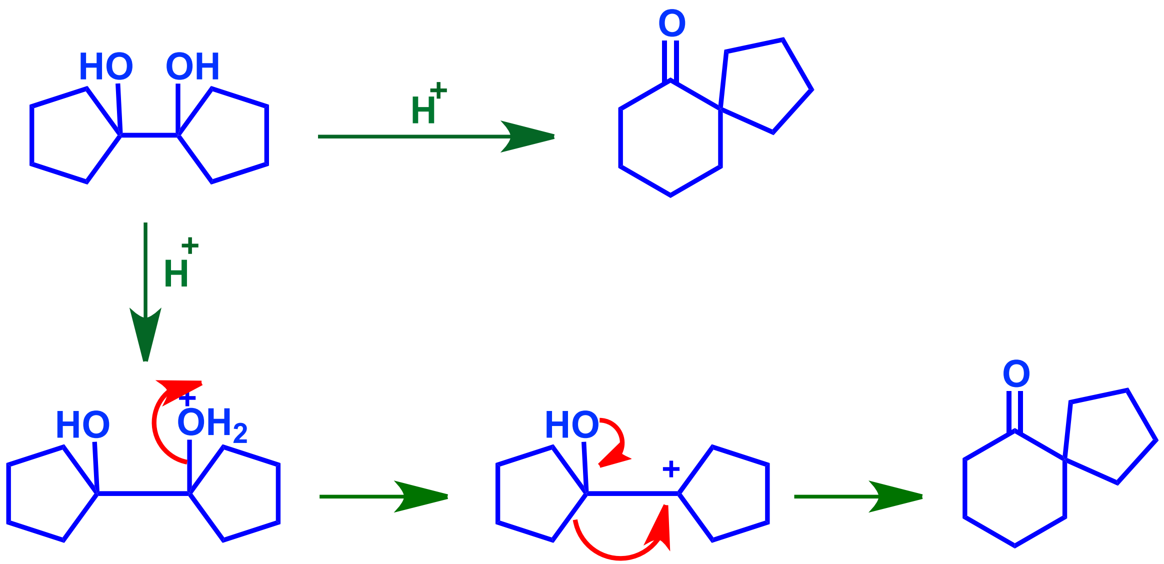
  The lone pair of electrons on the oxygen is another source to stabilize the carbocation

Molecular Rearrangements

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:

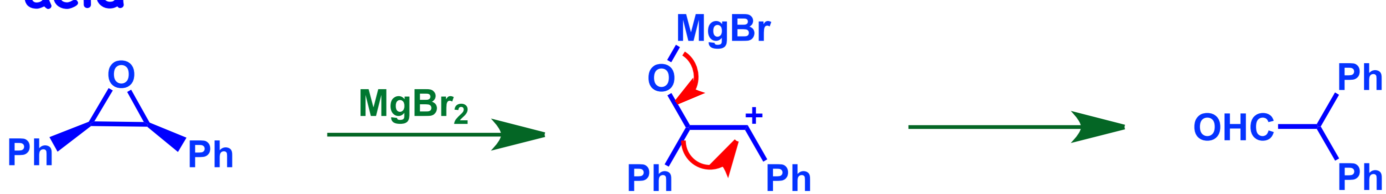


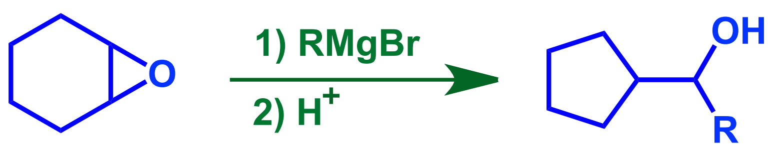
Molecular Rearrangements

Pinacol-Pinacolone Rearrangement

Epoxides :

Epoxides also undergo pinacol type rearrangement on treatment with acid





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

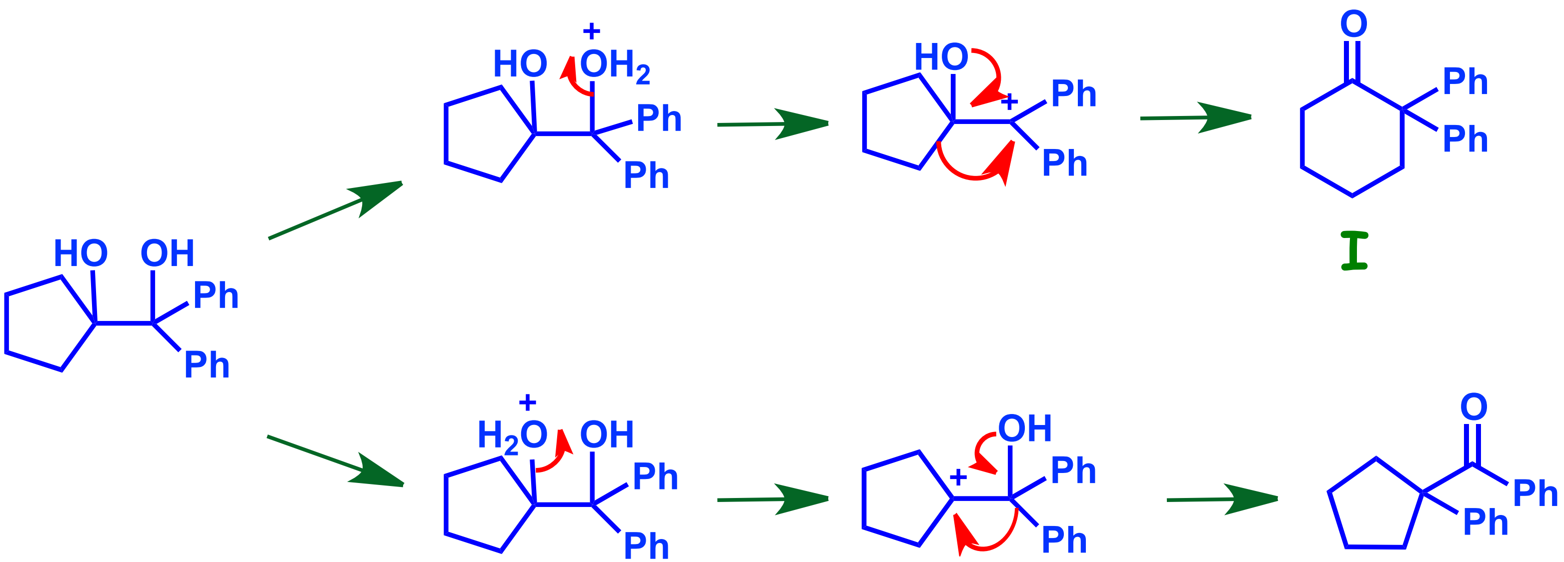
Molecular Rearrangements

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

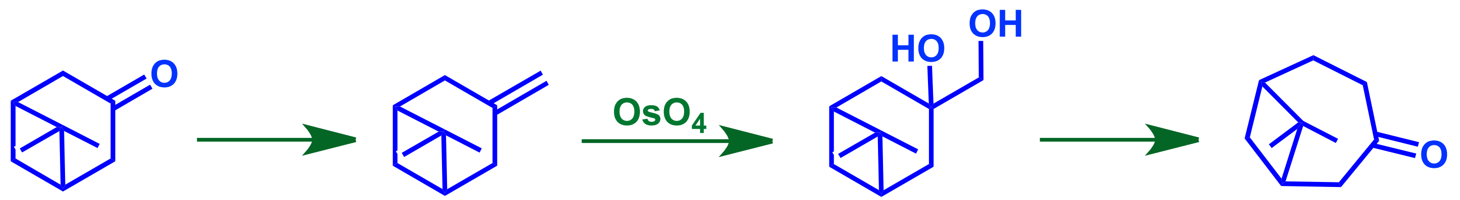
II

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

Molecular Rearrangements

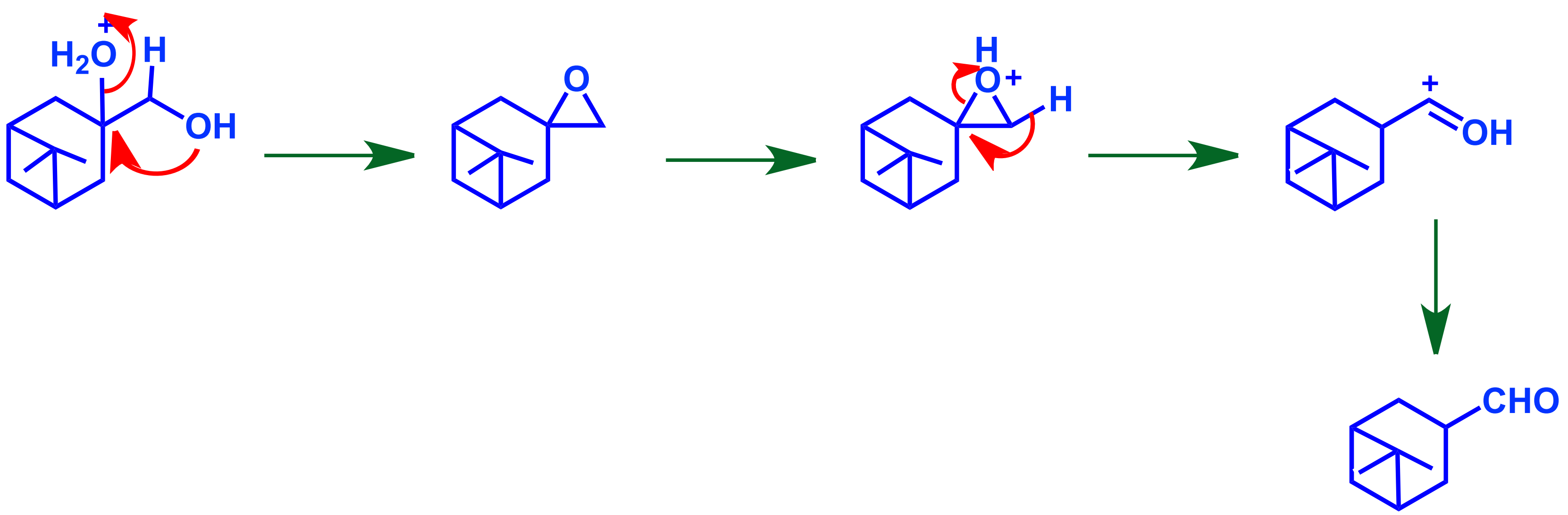
Semipinacol Rearrangement

They are nothing but pinacol rearrangement without choice



Isonopinone

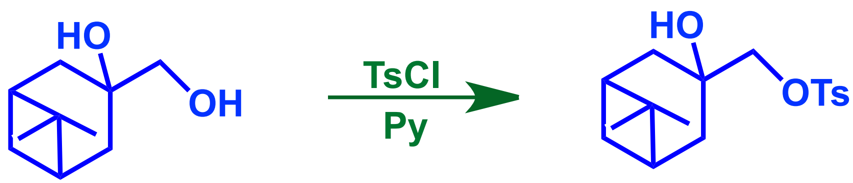
Under normal acidic conditions

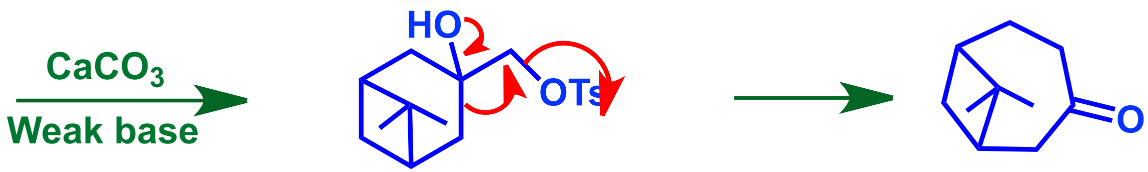


Molecular Rearrangements

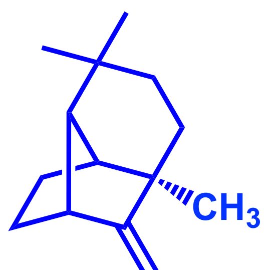
Semipinacol Rearrangement

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



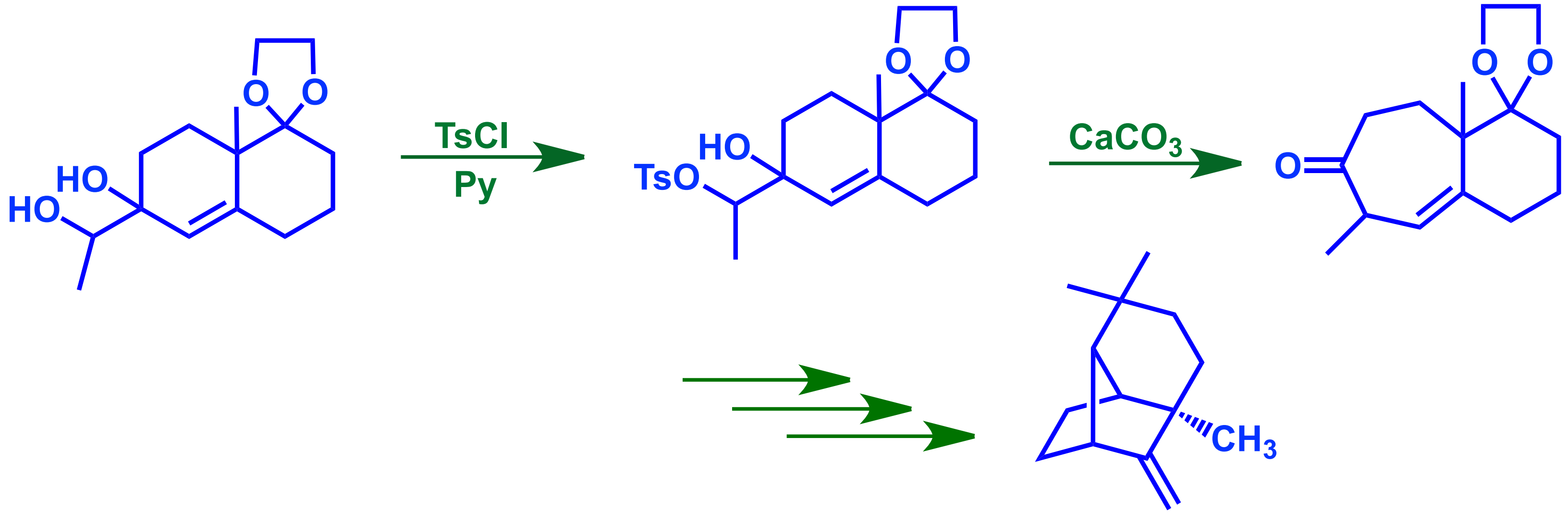


Corey exploited a similar sequence in the synthesis of longifolene



Molecular Rearrangements

Semipinacol Rearrangement

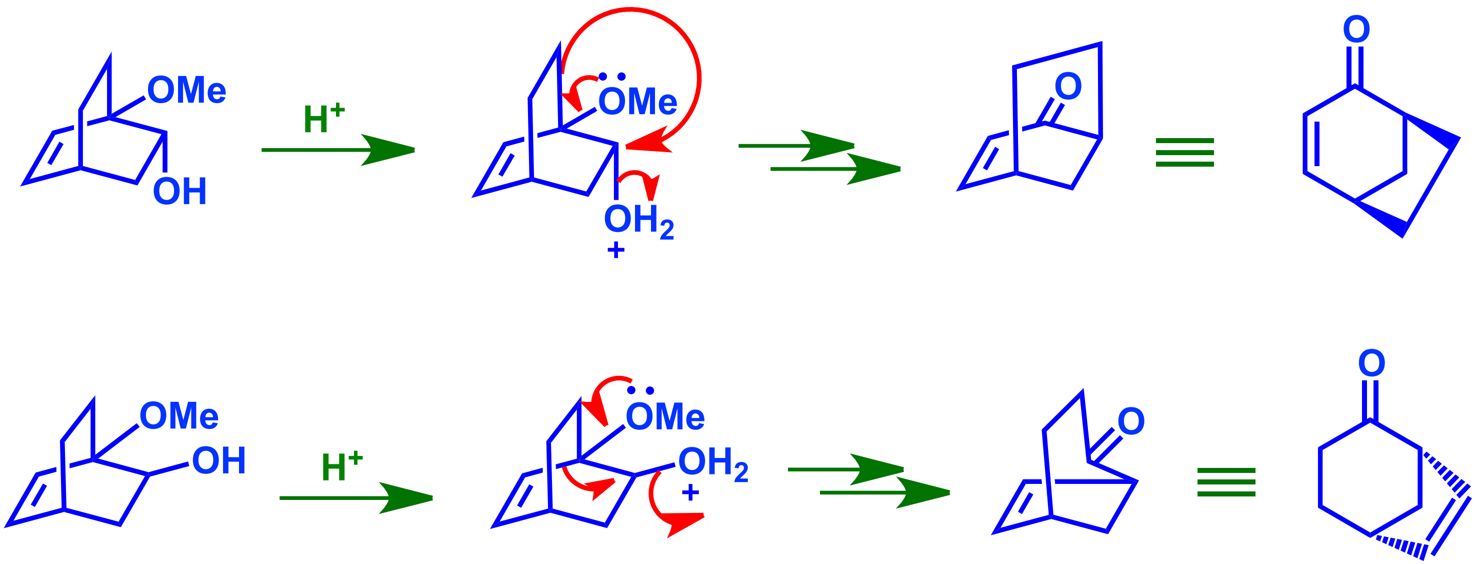


Longifolene

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

Molecular Rearrangements

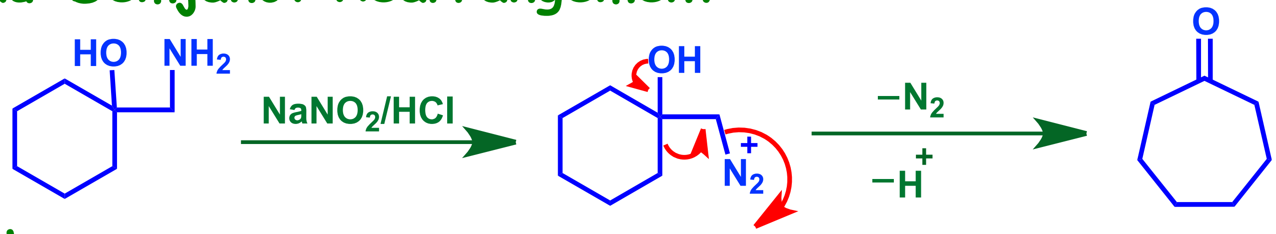
Semipinacol Rearrangement



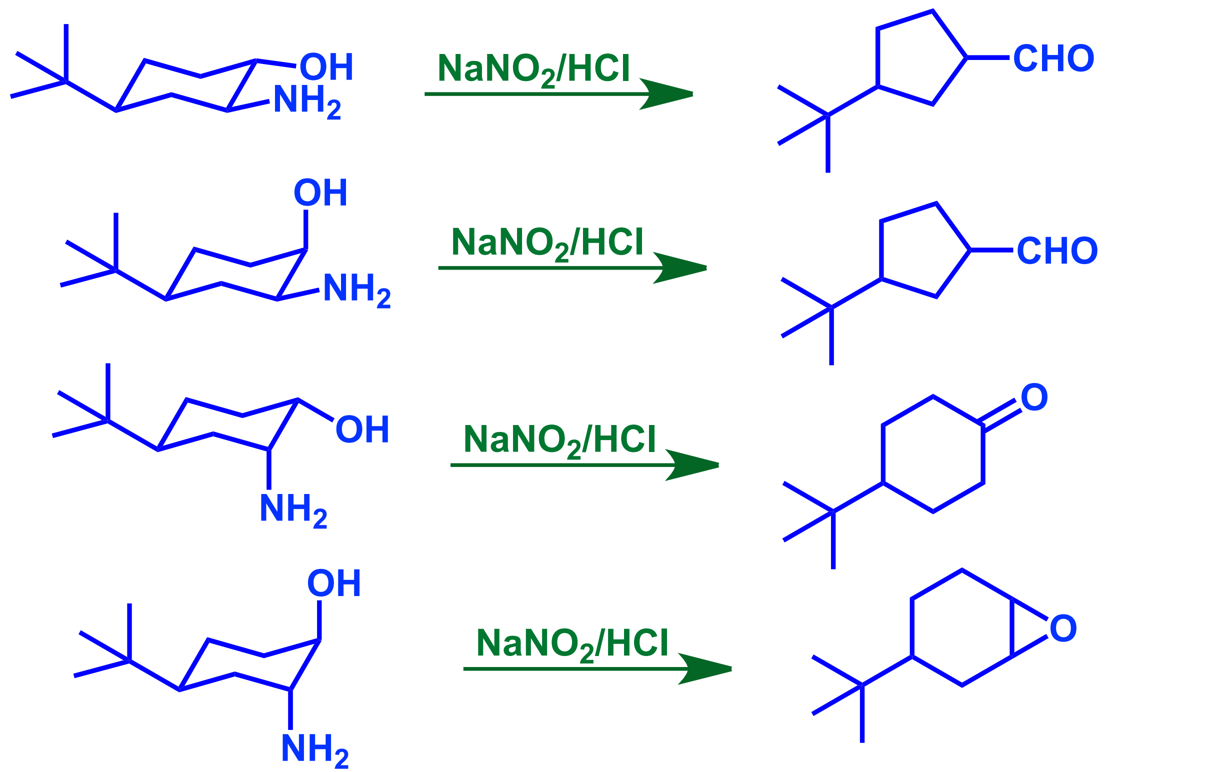
Molecular Rearrangements

Diazonium salts

Tiffeneau-Demjanov Rearrangement:



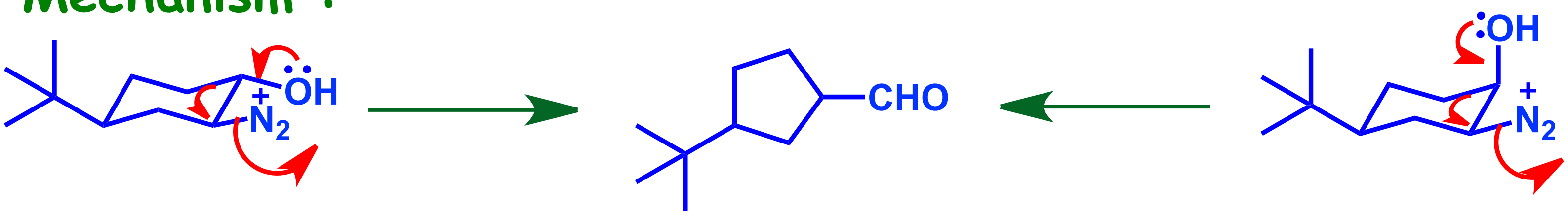
Selectivity :



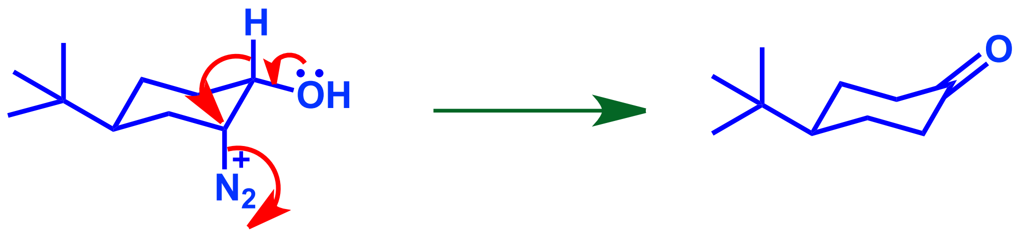
Molecular Rearrangements

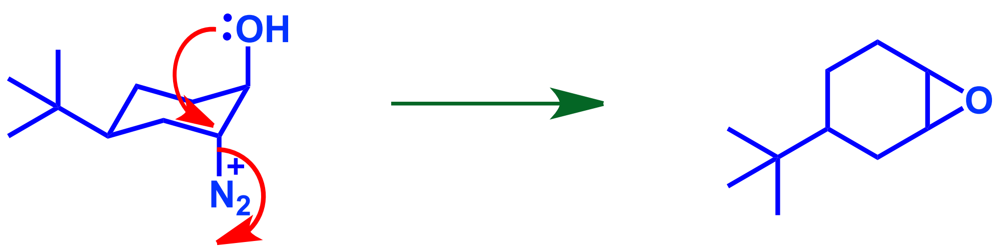
Diazonium salts

Mechanism :



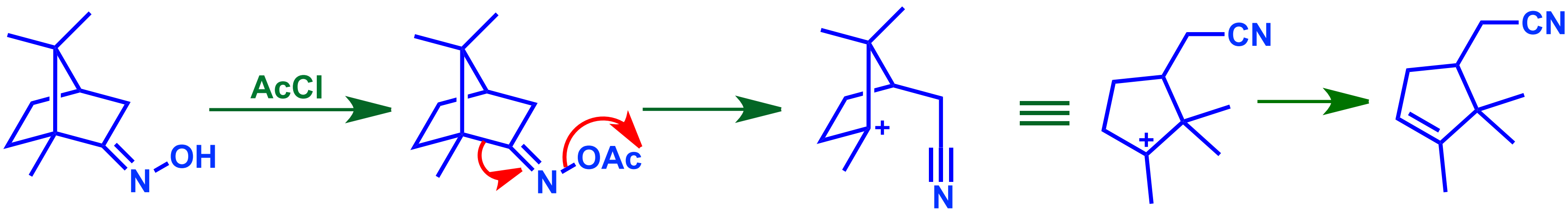
Alkyl group which is anti to the leaving group, will migrate



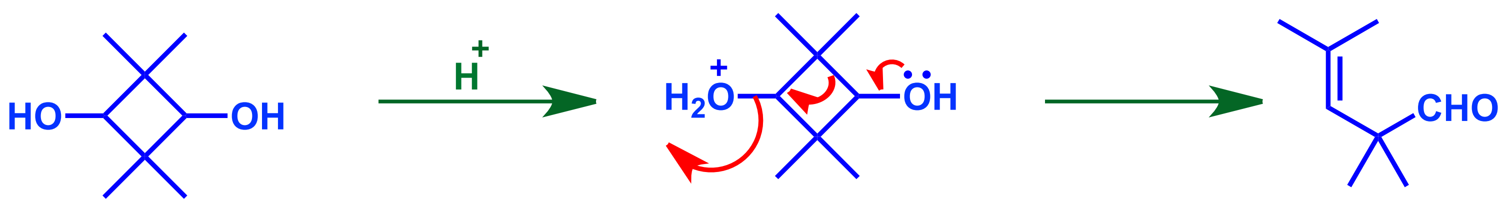


Molecular Rearrangements

Fragmentation:

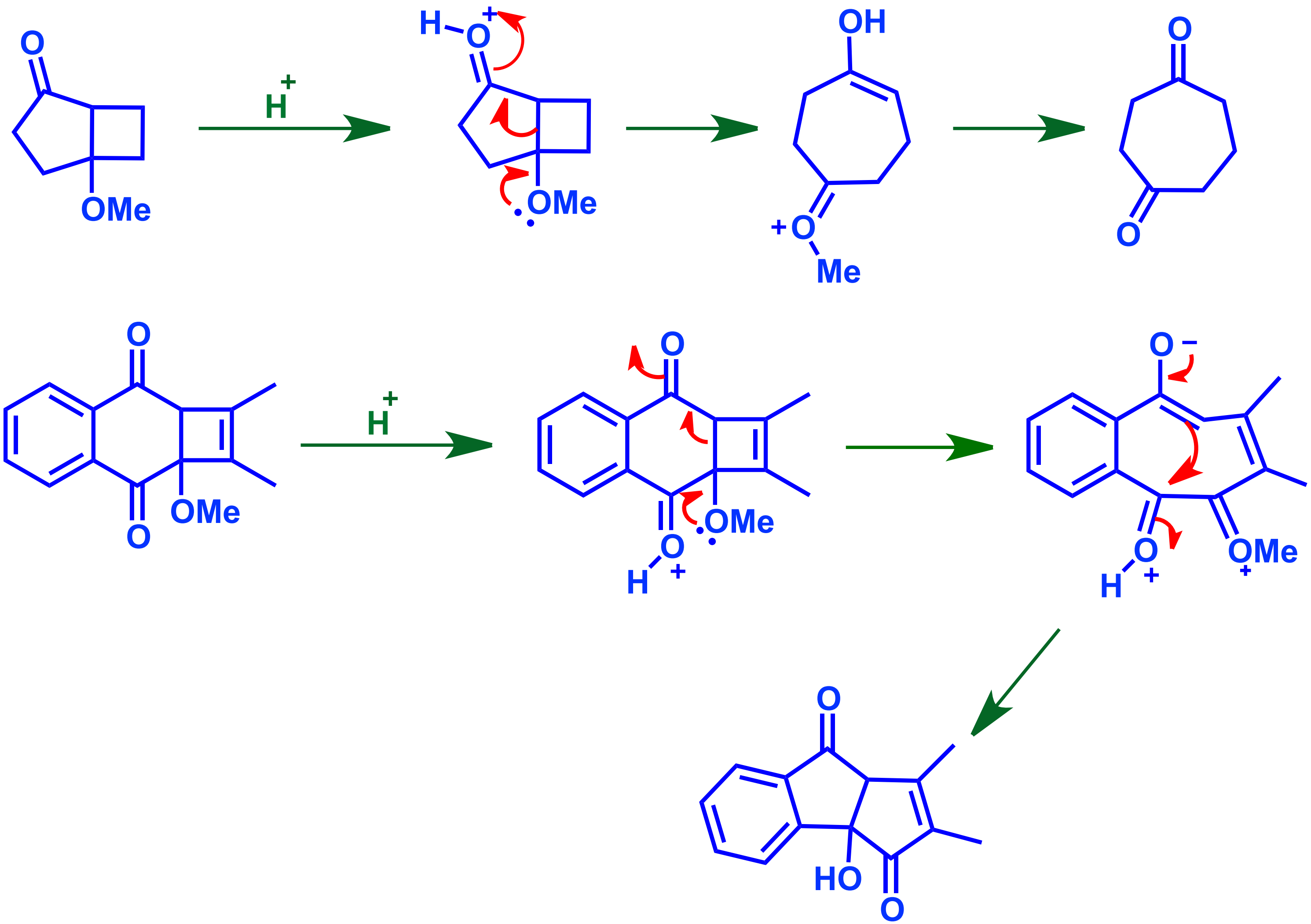


- **Fragmentations always require electron push and electron pull**



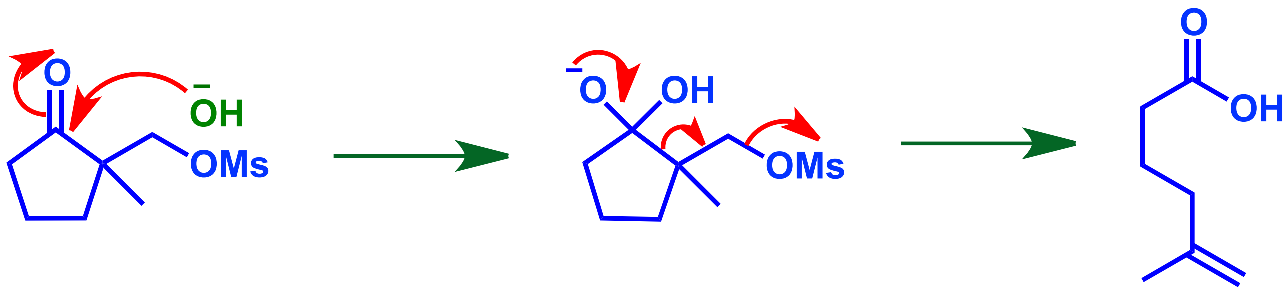
Molecular Rearrangements

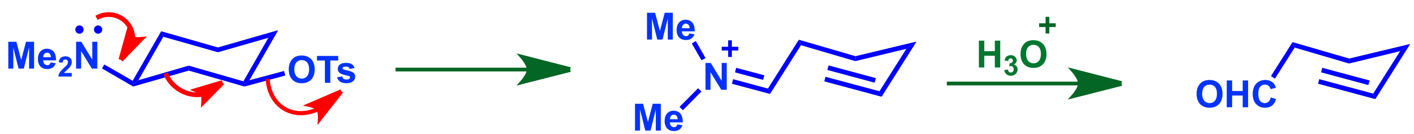
An Important Method to Make Higher Cycloalkanes:



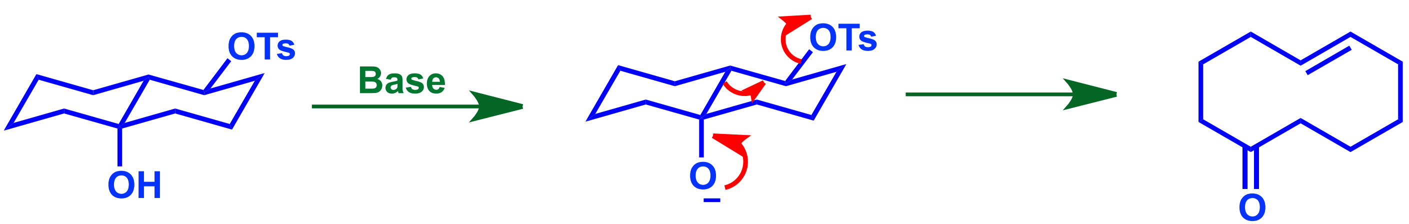
Molecular Rearrangements

Base Conditions or Nucleophilic Conditions:





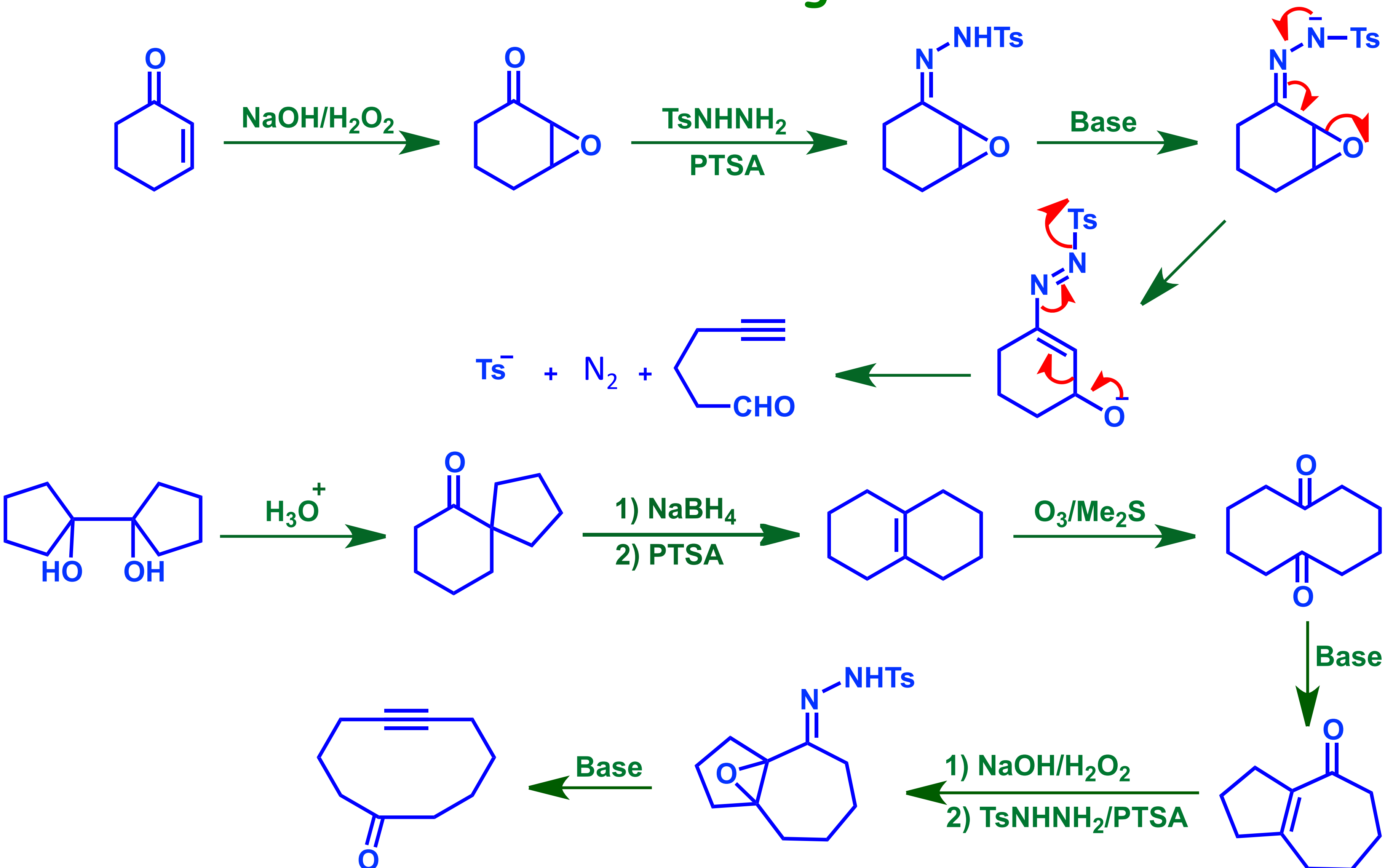
Antiperiplanar bond migrates



10-membered ring

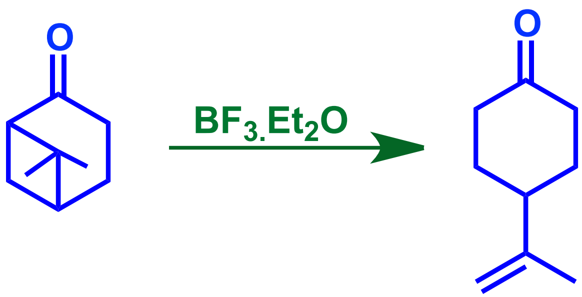
Molecular Rearrangements

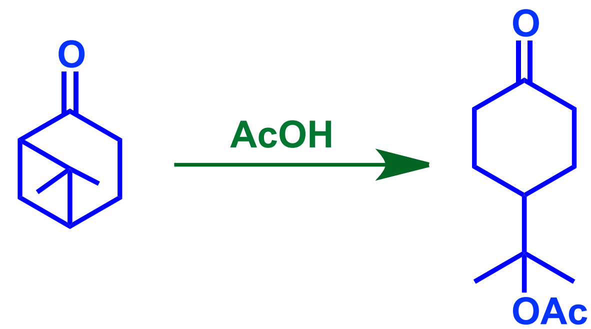
Eschenmoser Fragmentation



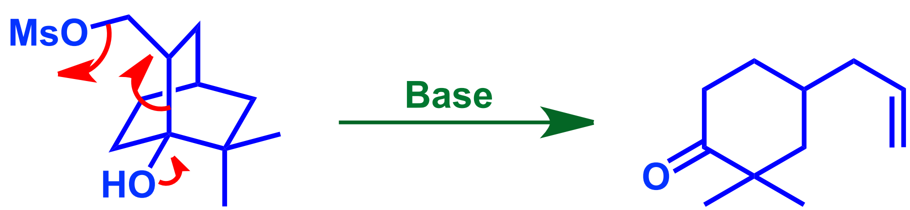
Molecular Rearrangements

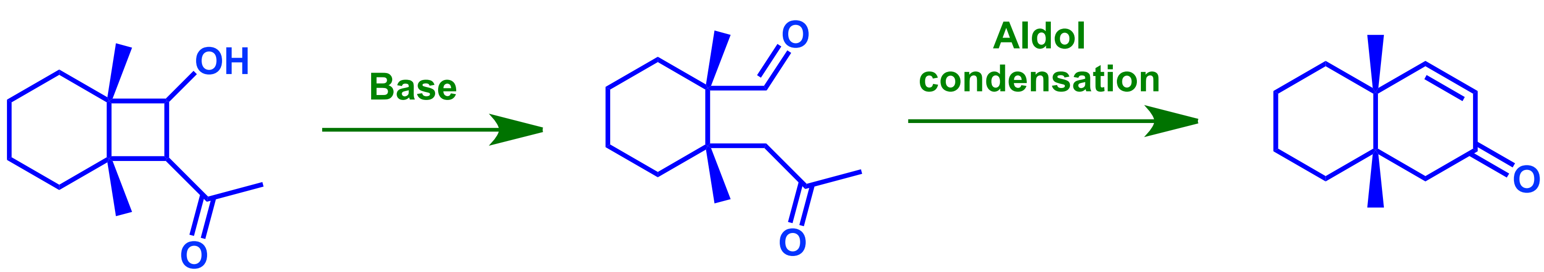
Fragmentation of Four-Membered Ring





Other Examples:





Molecular Rearrangements

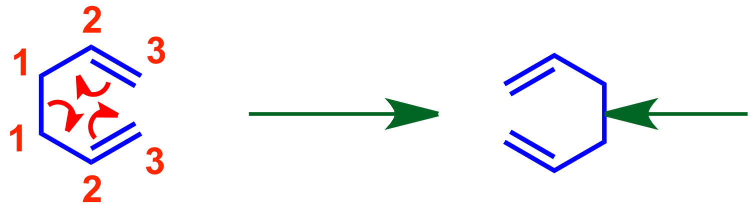
Sigmatropic Rearrangements

[3,3]-Sigmatropic Rearrangement

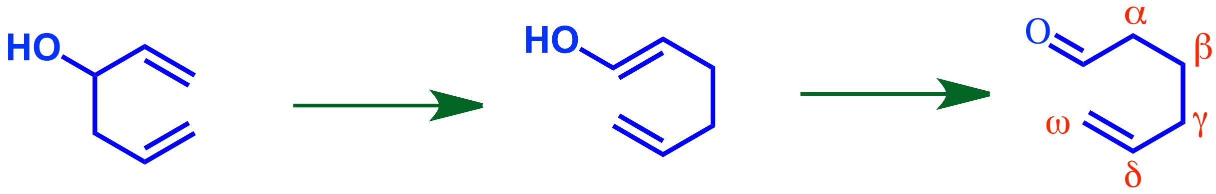
Cope Rearrangement :

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



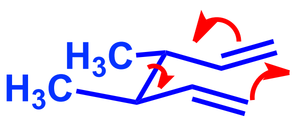
Molecular Rearrangements

Sigmatropic Rearrangements

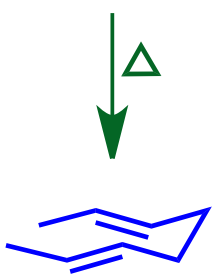
Mechanism :

It goes via six-membered chair-like transition state

trans



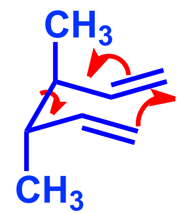
More stable conformer



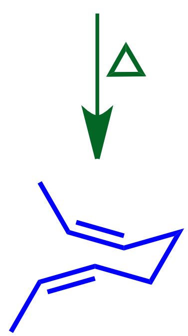
E,E-isomer

Favoured

trans

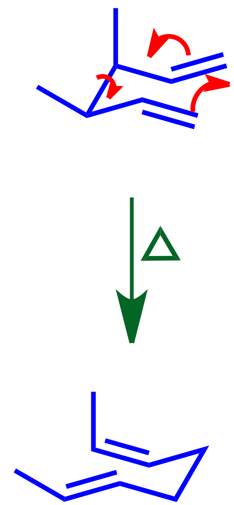


Less stable conformer



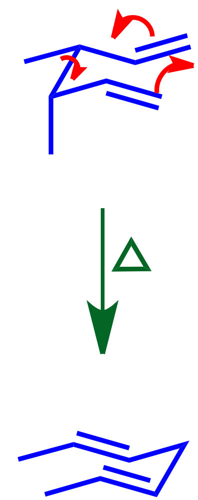
Z,Z-isomer

cis



E,Z

cis

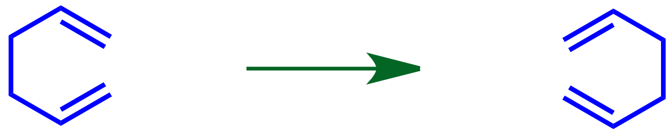


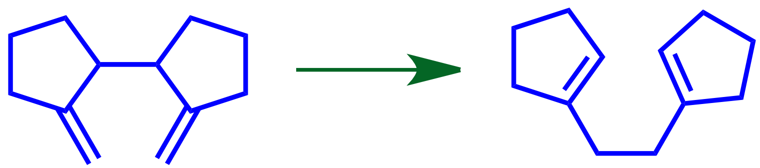
Z,E

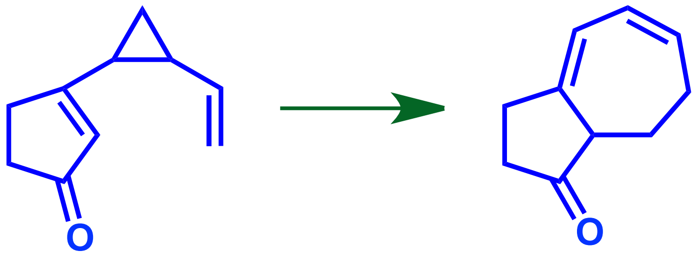
Molecular Rearrangements

Sigmatropic Rearrangements

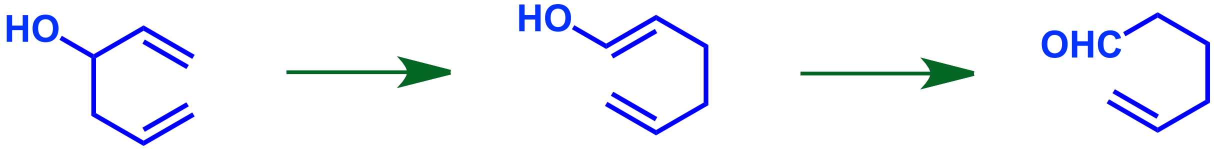
1) Cope:

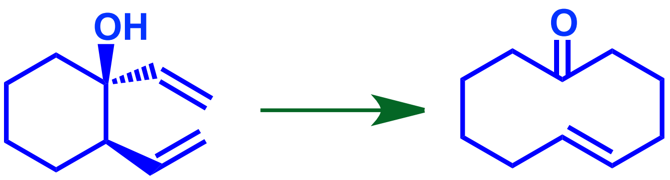


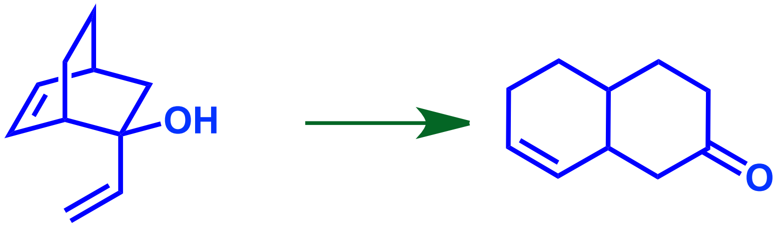




2) Oxy-Cope:



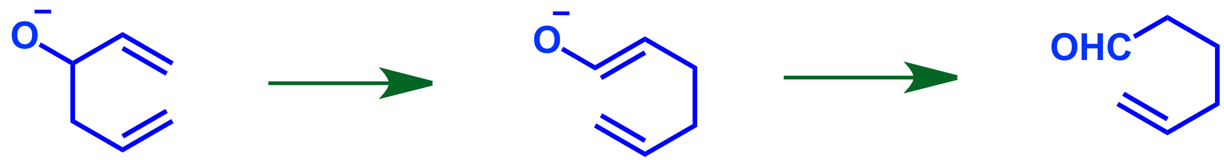


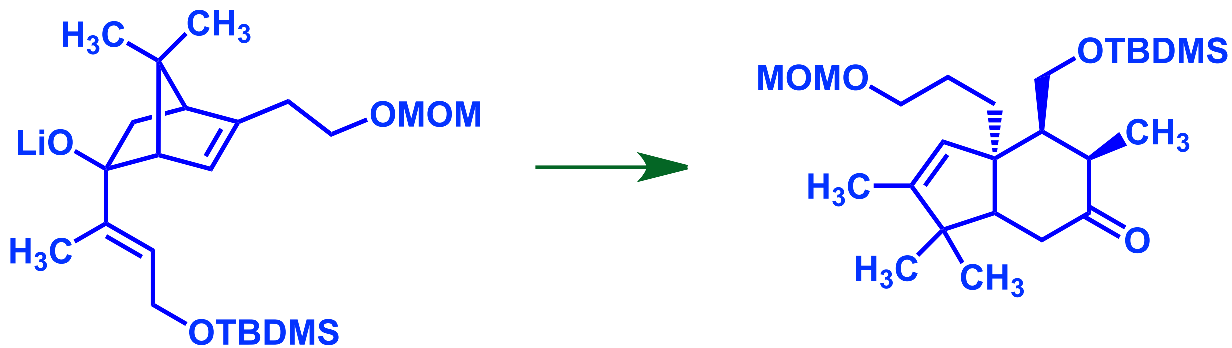


Molecular Rearrangements

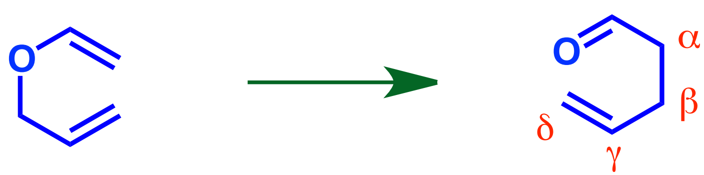
Sigmatropic Rearrangements

3) Anionic-Oxy-Cope:

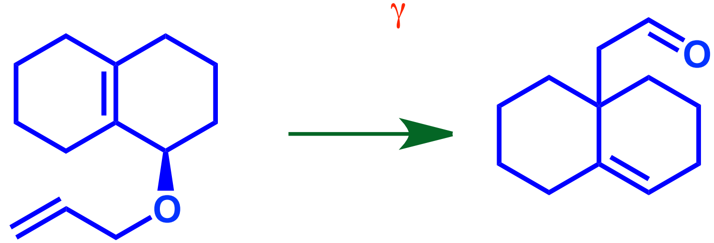




4) Claisen Rearrangement of Allylvinyl Ethers:



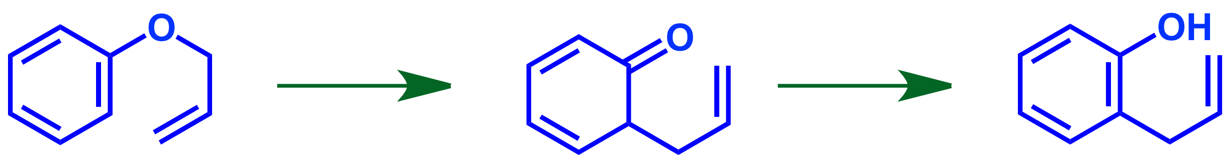
γ-δ-unsaturated aldehyde



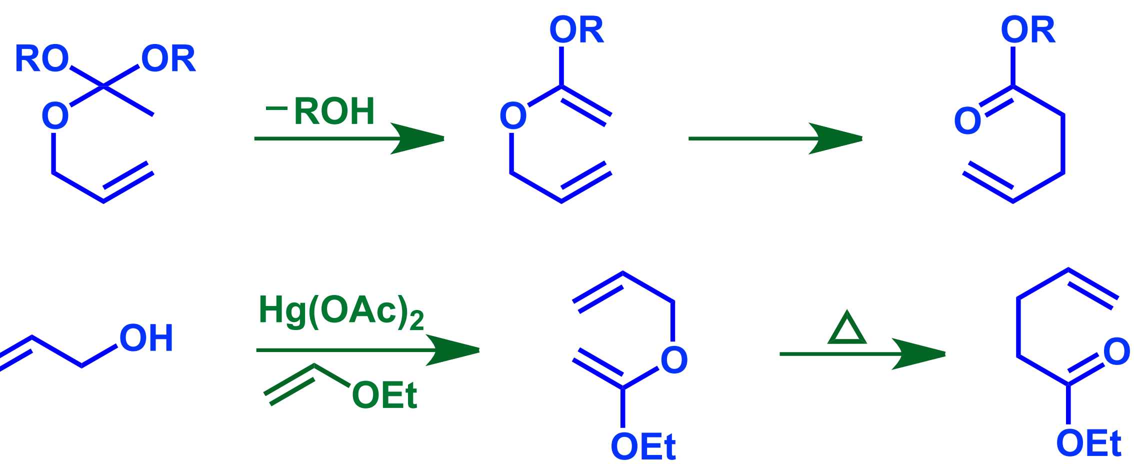
Molecular Rearrangements

Sigmatropic Rearrangements

5) Claisen Rearrangement of Allylphenyl Ethers:



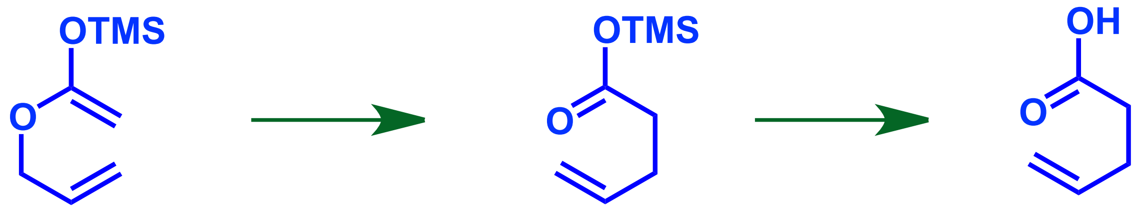
6) Ortho-Ester Claisen Rearrangement:



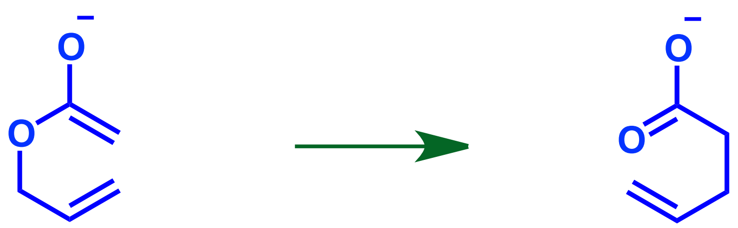
Molecular Rearrangements

Sigmatropic Rearrangements

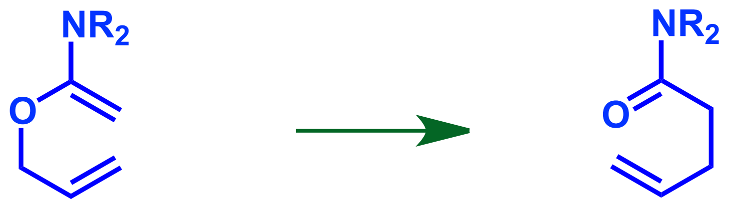
7) O-Allyl-O-TMS-Ketone Acetals:



8) Ester-Enolate Claisen:



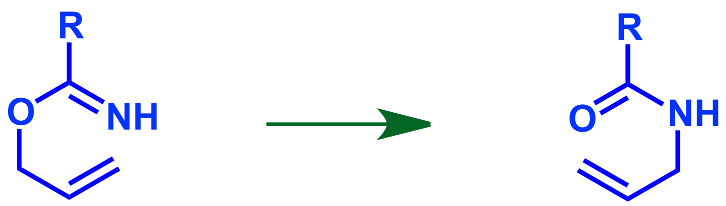
9) Ketene Aminals:



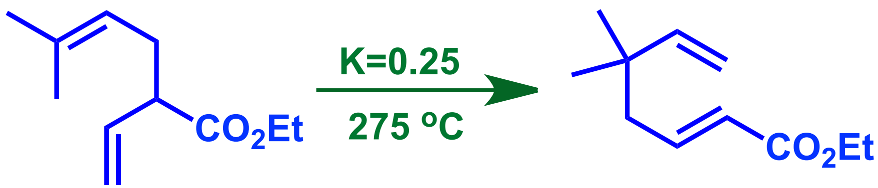
Molecular Rearrangements

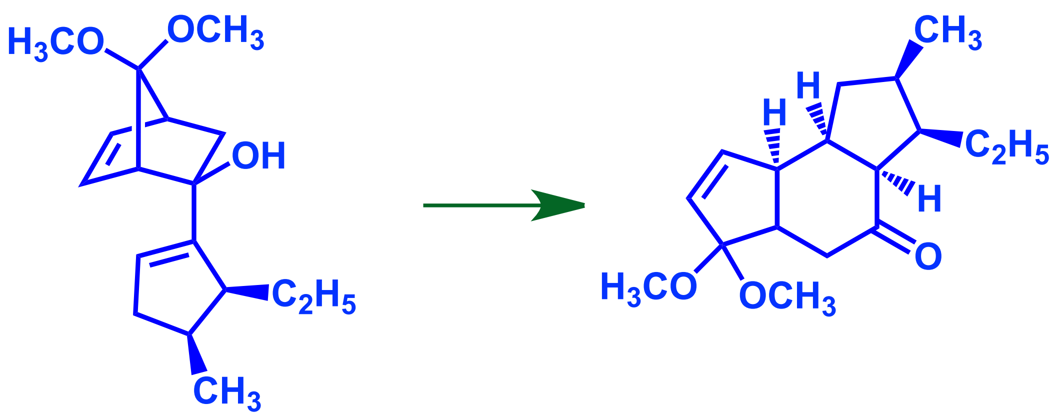
Sigmatropic Rearrangements

10) Aza-Claisen Rearrangement:



Other Examples:

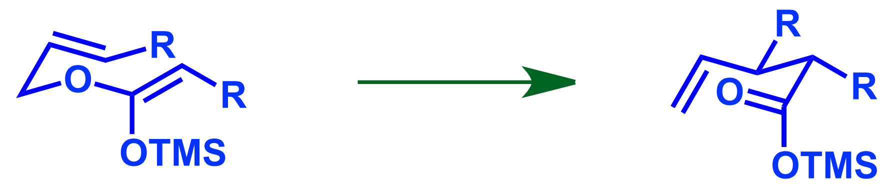




Molecular Rearrangements

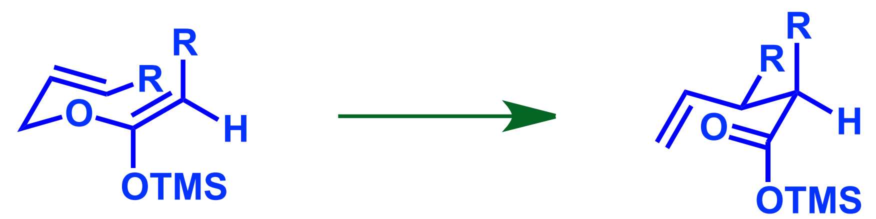
Sigmatropic Rearrangements

Stereochemistry:



Z-silyl ether

trans



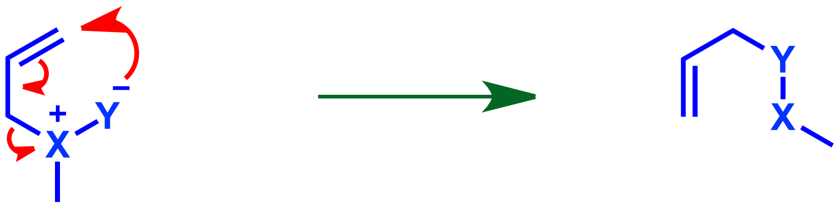
E-silyl ether

cis

Molecular Rearrangements

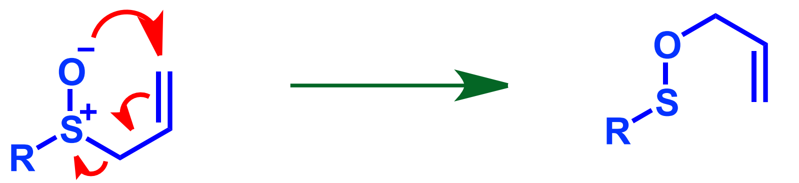
Sigmatropic Rearrangements

[2,3]-Sigmatropic Rearrangement

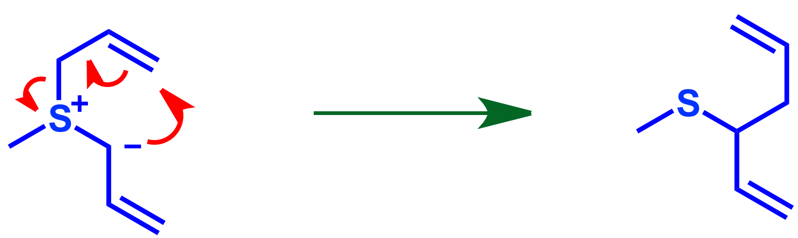


Charged   Neutral

1) Allylic Sulfoxides:



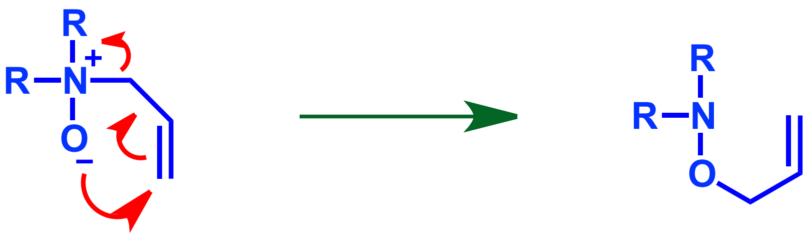
2) Allylic Sulfonium Ylides:



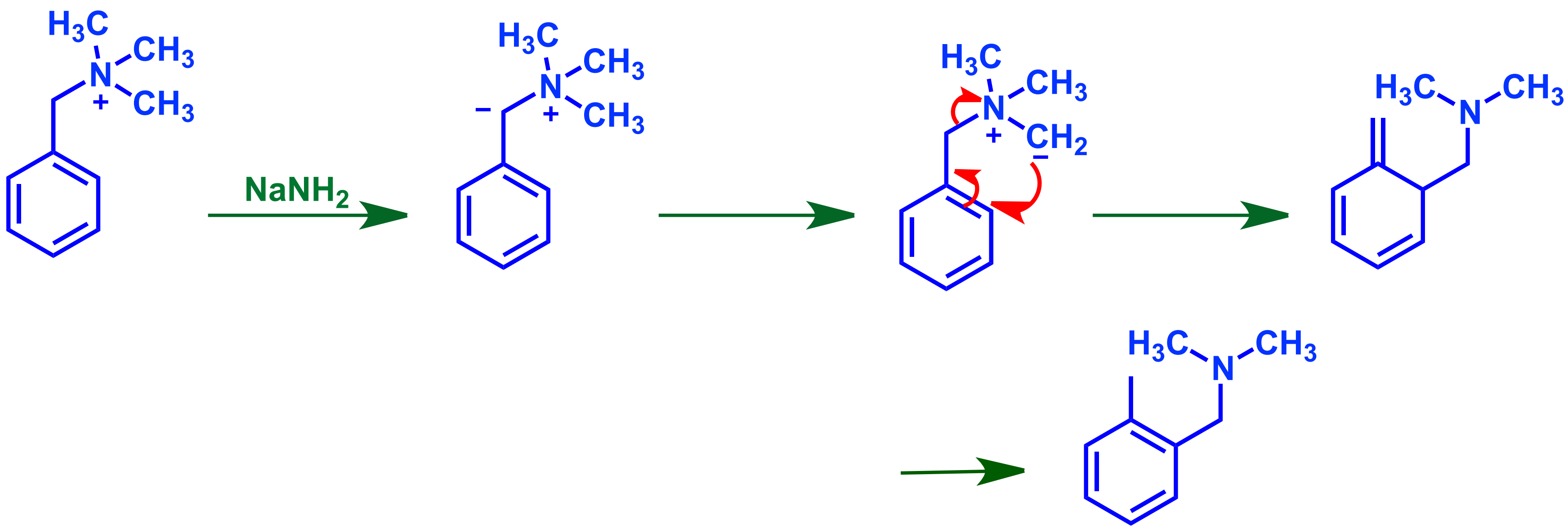
Molecular Rearrangements

Sigmatropic Rearrangements

3) N-Oxides:



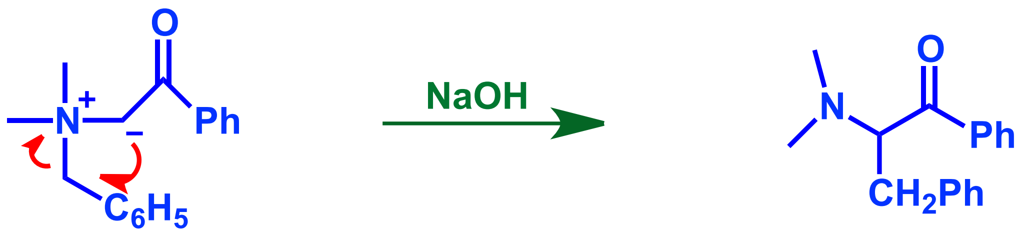
Sommelet-Hauser Rearrangement



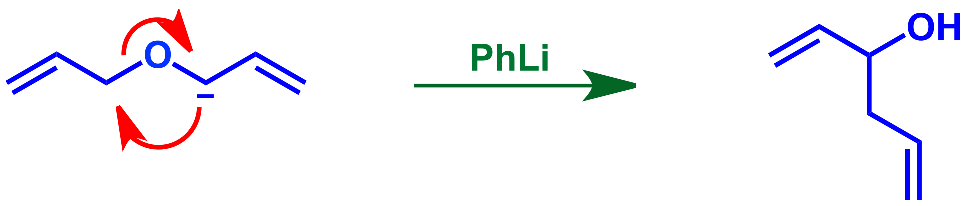
Molecular Rearrangements

Sigmatropic Rearrangements

Stevens Rearrangement



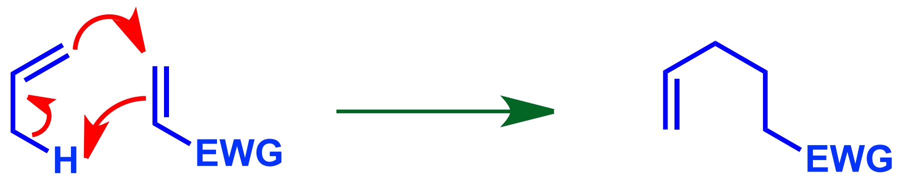
Wittig Rearrangement

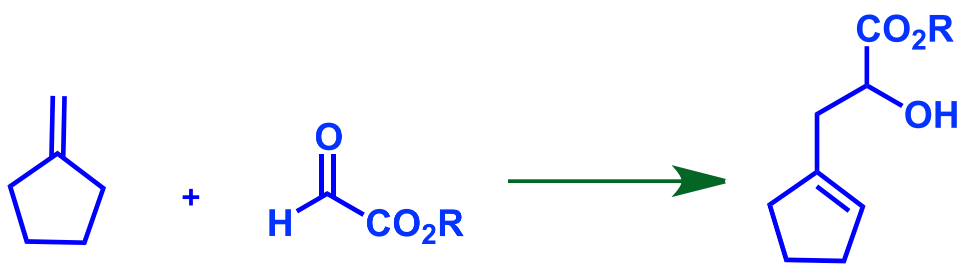


Molecular Rearrangements

Sigmatropic Rearrangements

Ene Reaction

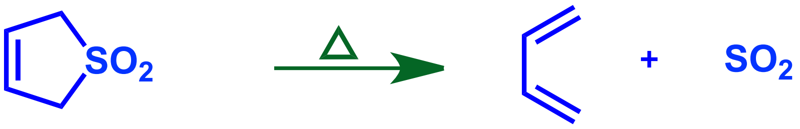


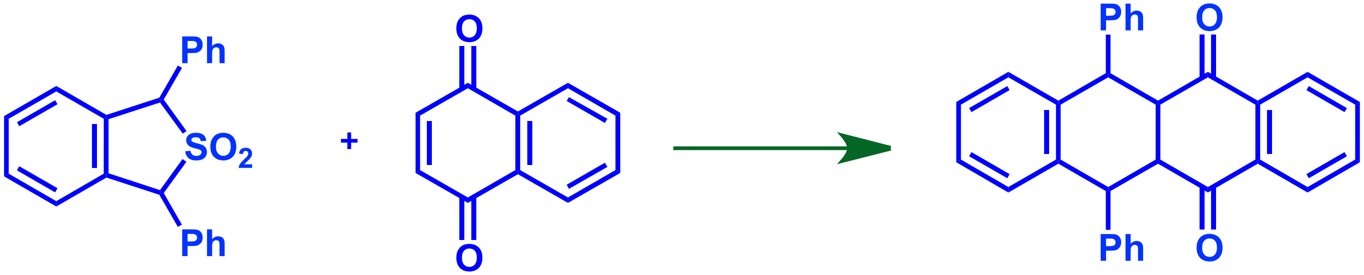


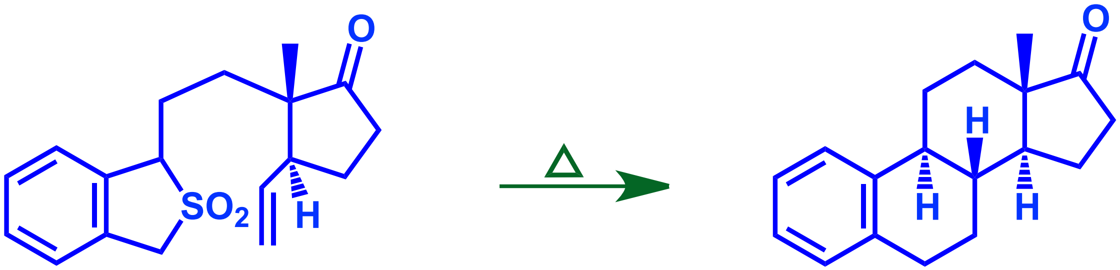
Molecular Rearrangements

Cheletropic Elimination

Two bonds are broken at a single atom

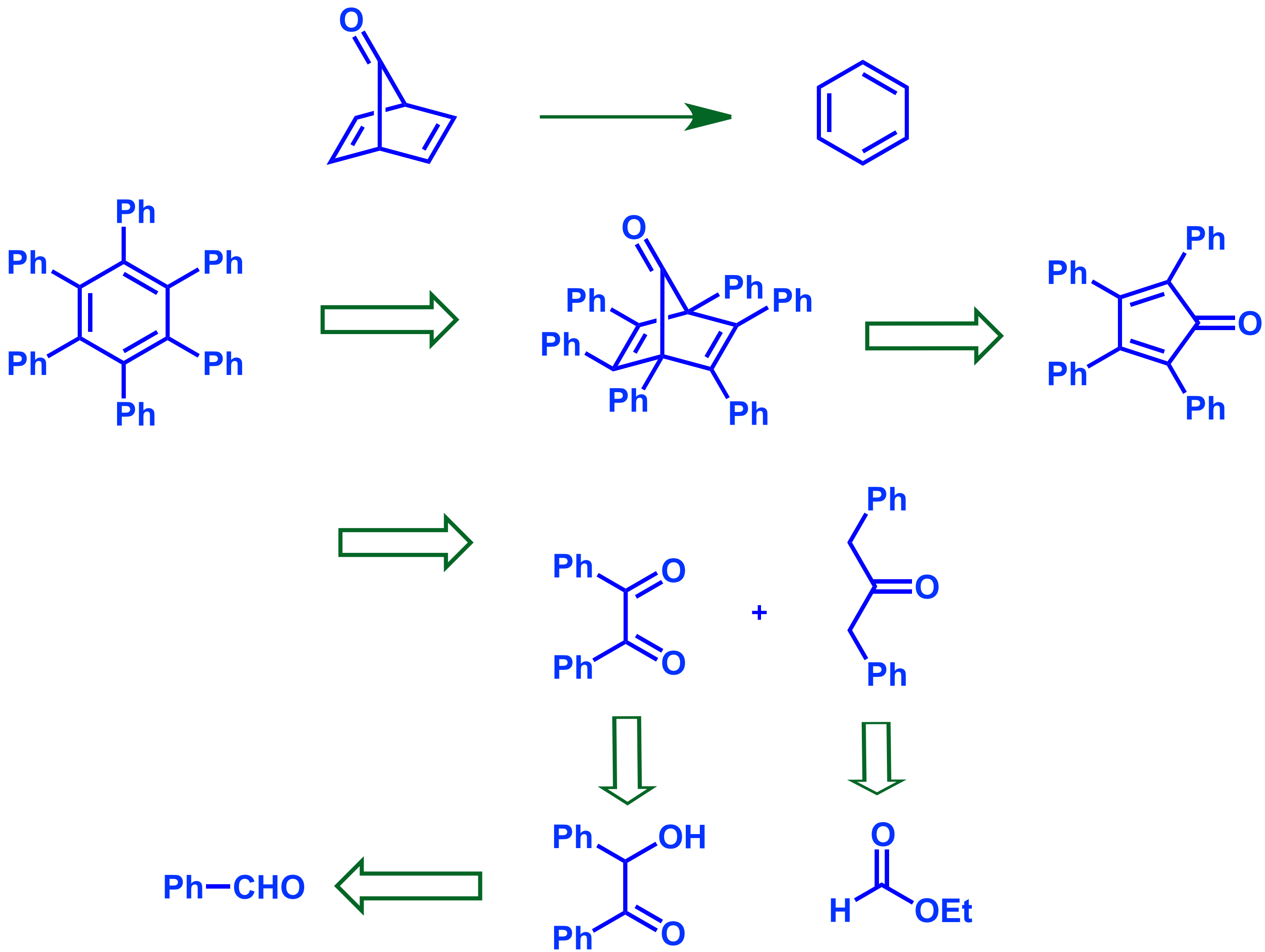






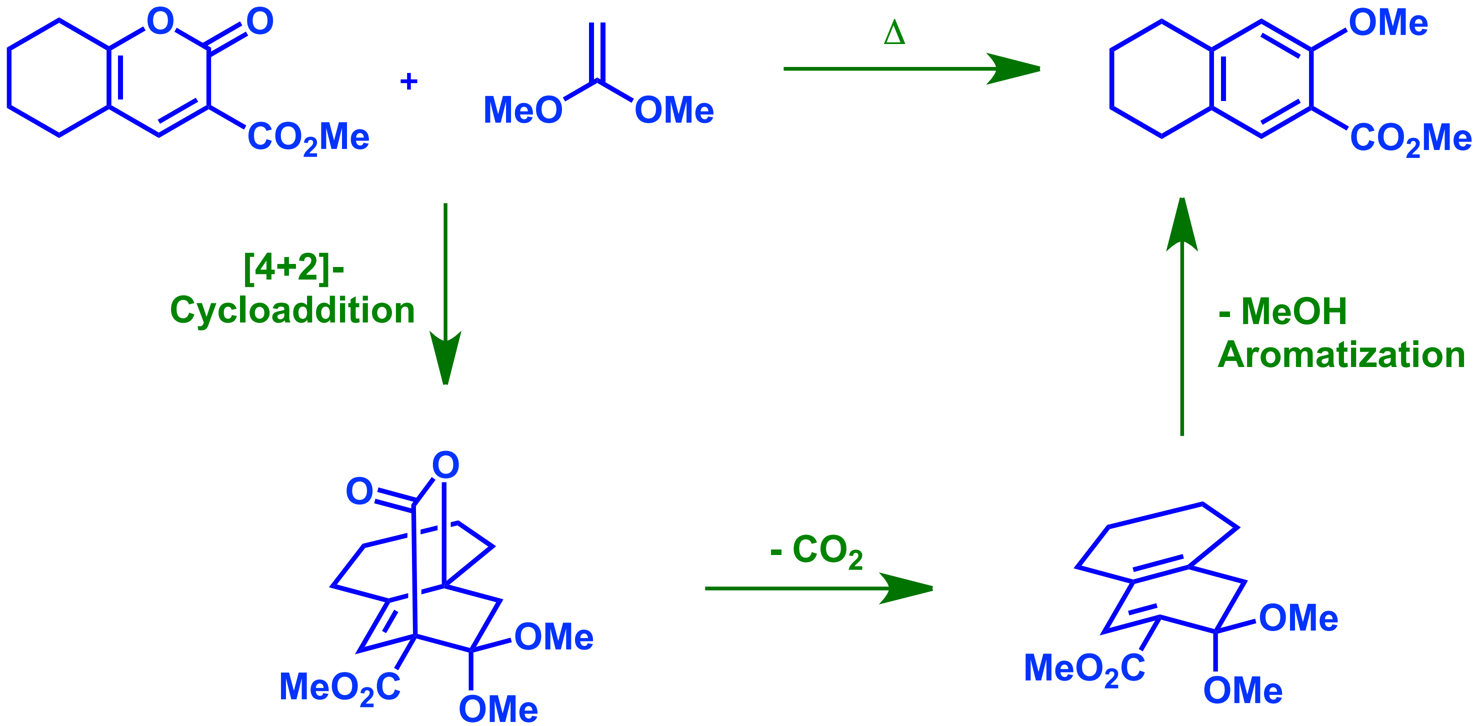
Molecular Rearrangements

Elimination of Carbon monoxide (CO)



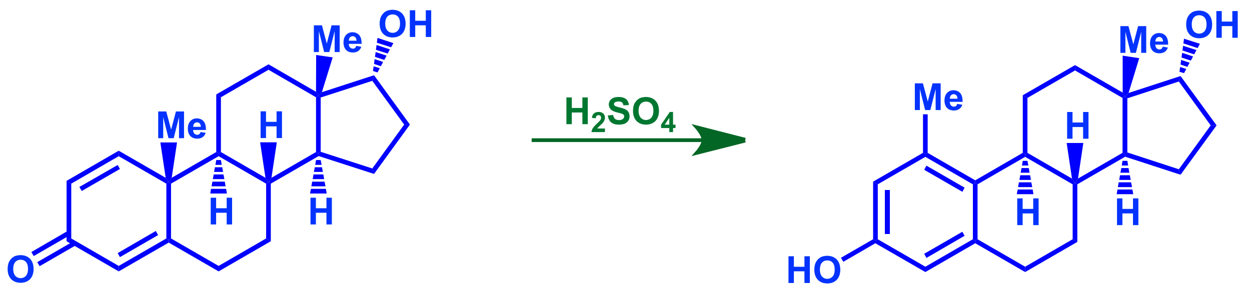
Molecular Rearrangements

Elimination of Carbon monoxide (CO)



Molecular Rearrangements

Dienone-Phenol Rearrangement

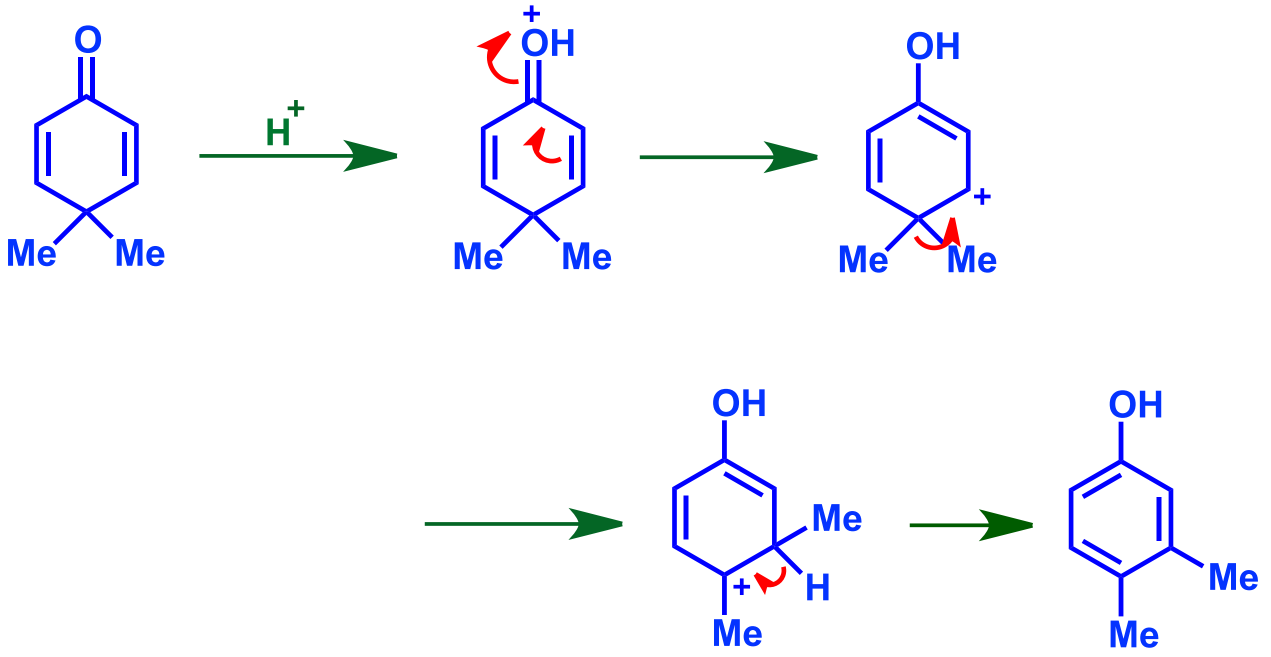


- Can be considered as a reversal of pinacol rearrangement
- Pinacol & semipinacol rearrangements are driven by the formation of a carbonyl group
- In dienone-phenol rearrangement protonation of carbonyl group Rearranges to a tertiary carbocation
- The driving force for this reaction is the formation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

Molecular Rearrangements

Dienone-Phenol Rearrangement

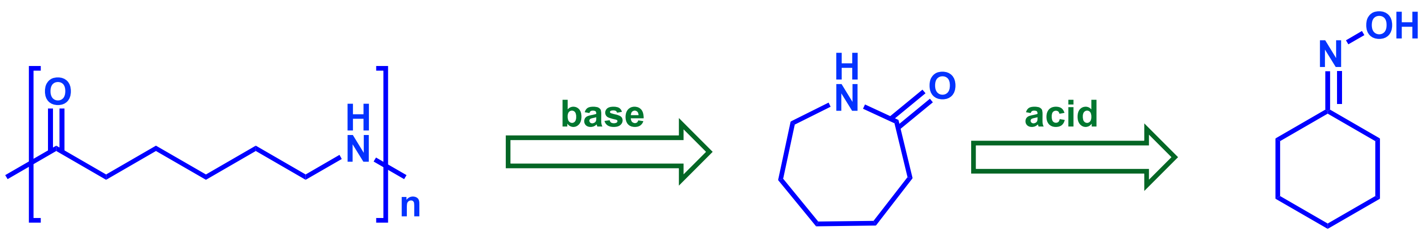
Mechanism:



Molecular Rearrangements

Beckmann Rearrangement

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



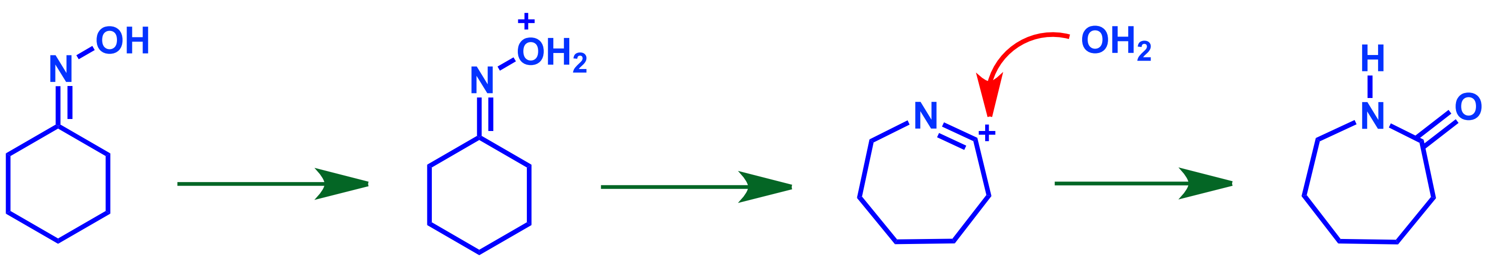
oxime

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

Molecular Rearrangements

Beckmann Rearrangement

Mechanism:

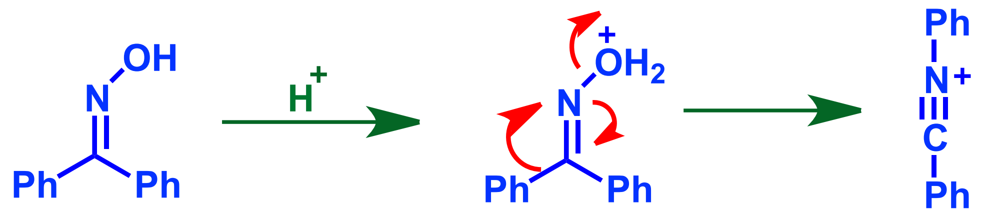


- Follows the same pattern as pinacol
- Converts the oxime into a good leaving group
- Alkyl/ Aryl group migrates on to nitrogen as water departs
- The product cation is then trapped by water to give an amide

Molecular Rearrangements

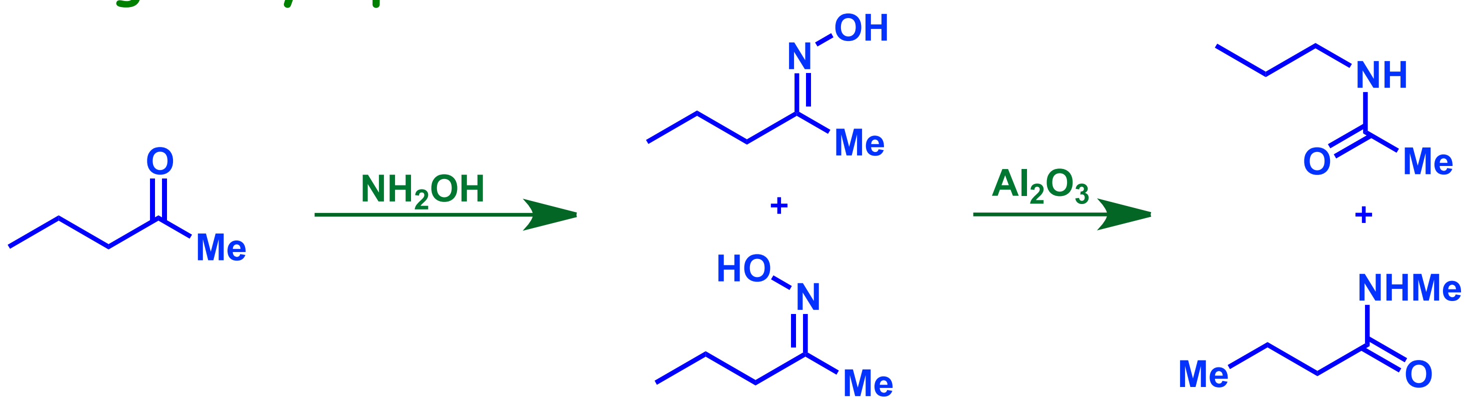
Beckmann Rearrangement

- 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

Molecular Rearrangements

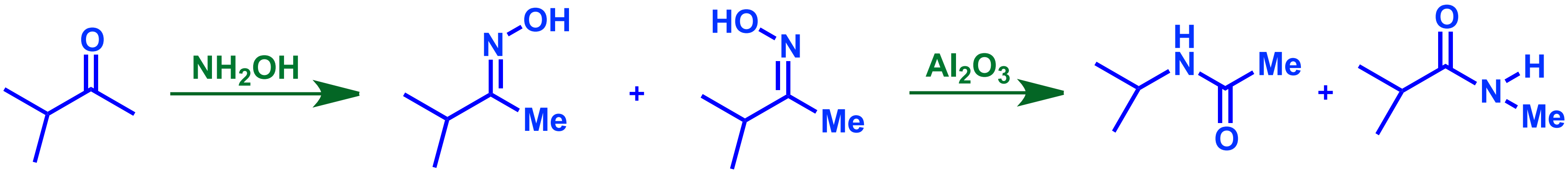
Beckmann Rearrangement

In case of unsymmetrical ketone:

- There are two groups that could migrate
- There are two possible geometrical isomers of unsymmetr-ical 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

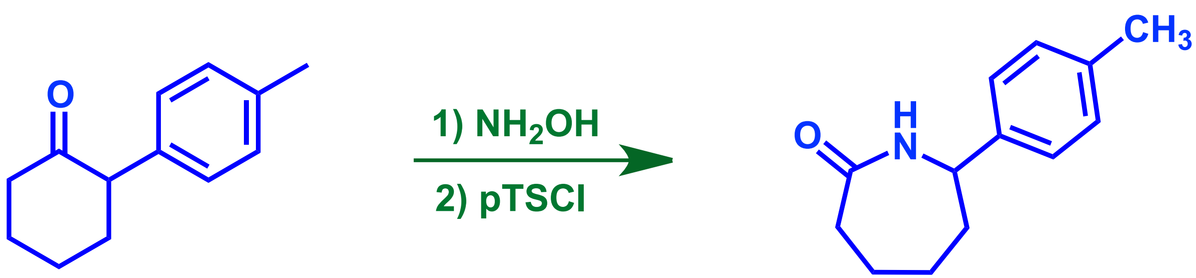
Molecular Rearrangements

Beckmann Rearrangement



86 : 14
Steric effect

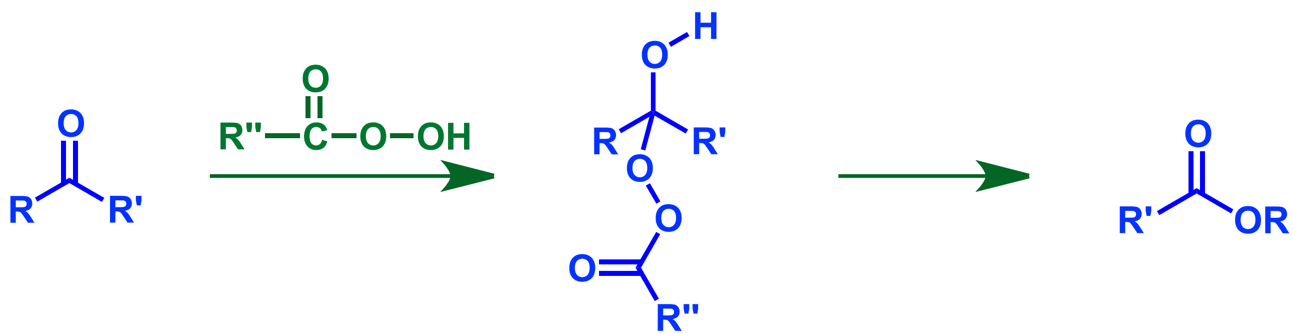
88 : 12



Molecular Rearrangements

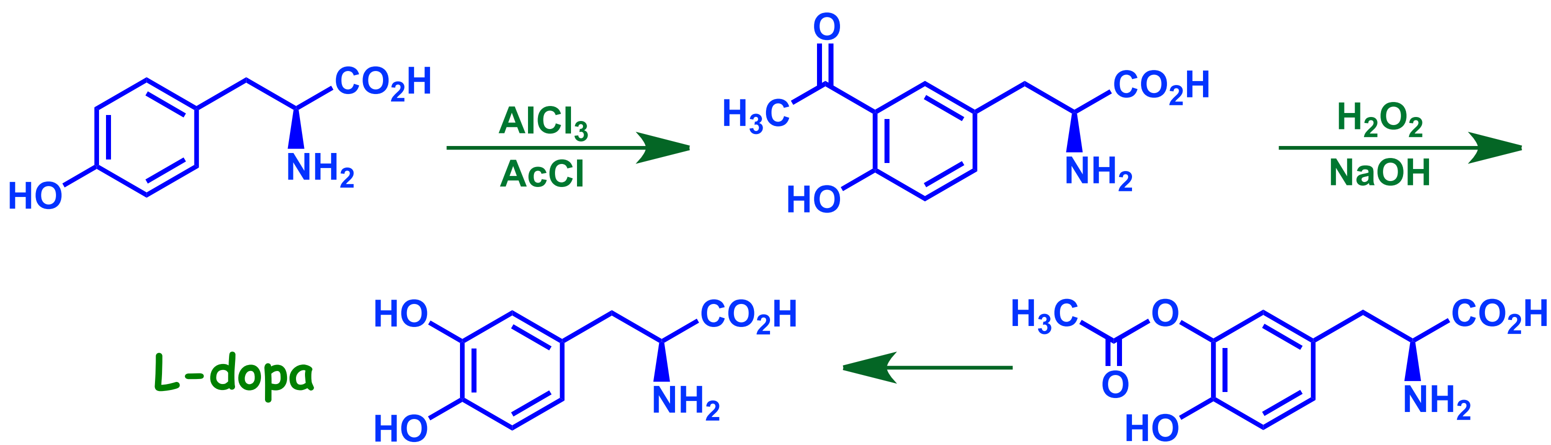
Baeyer Villiger Oxidation

Mechanism:



Migratory Aptitude:

t-Bu > i-Pr = Ph > Et > Me



Molecular Rearrangements

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

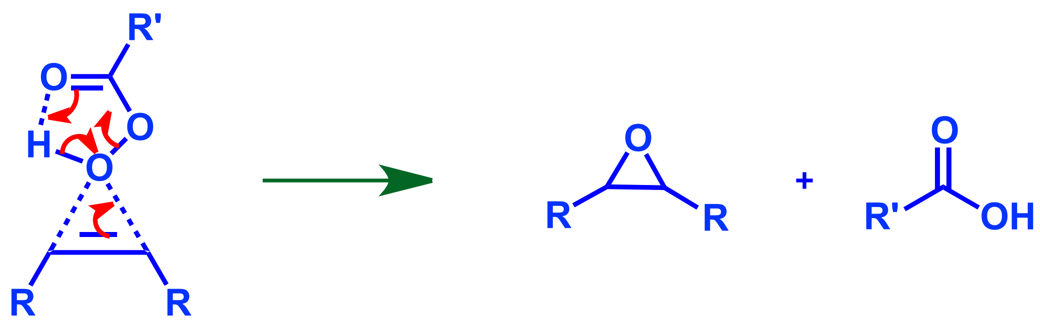
It is difficult to predict the outcome & it depends on-

1) Electrophilic nature of the ketone

2) Nucleophilic nature of the alkene

Molecular Rearrangements

Baeyer Villiger Oxidation

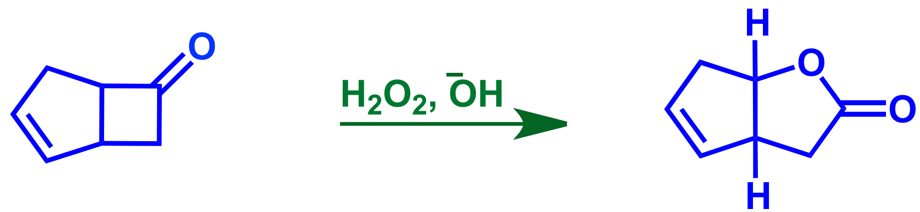


- Tertiary group migrates in preference of the secondary group
- The alkene is not as reactive as expected because of steric crowding

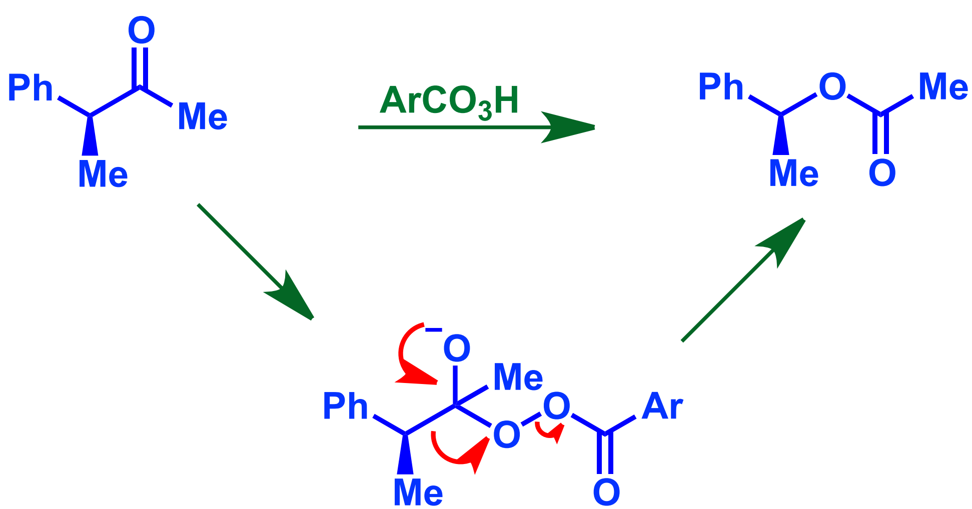
Molecular Rearrangements

Baeyer Villiger Oxidation

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



Starting material configuration is retained in the product



Molecular Rearrangements

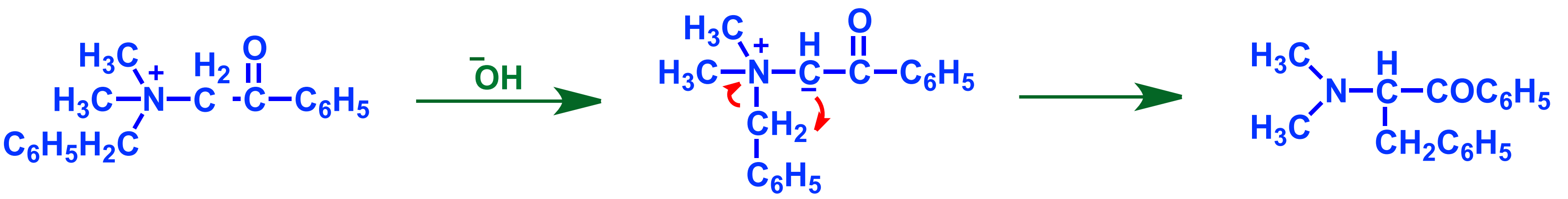
Electron-Rich (Anionic) Skeletal Rearrangements

- The transition state has two more electrons
- Generally initiated by basic reagents which remove a group or 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

Molecular Rearrangements

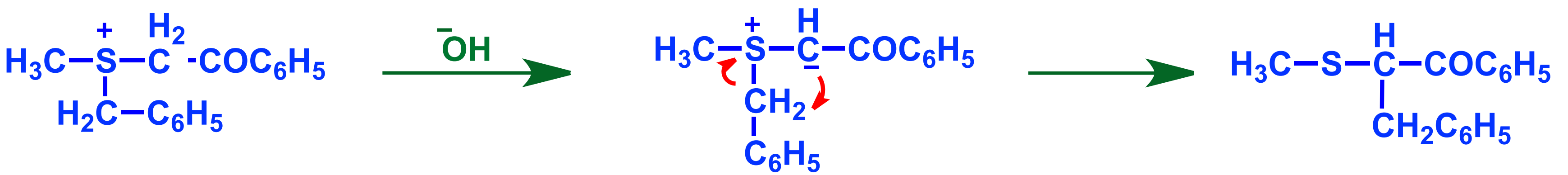
Electron-Rich (Anionic) Skeletal Rearrangements

Stevens Rearrangement



Proton removal 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

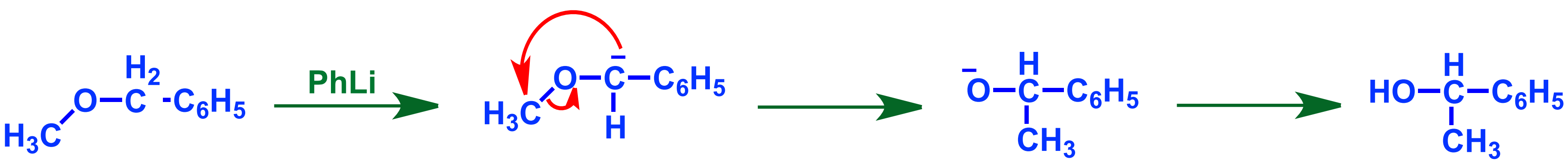


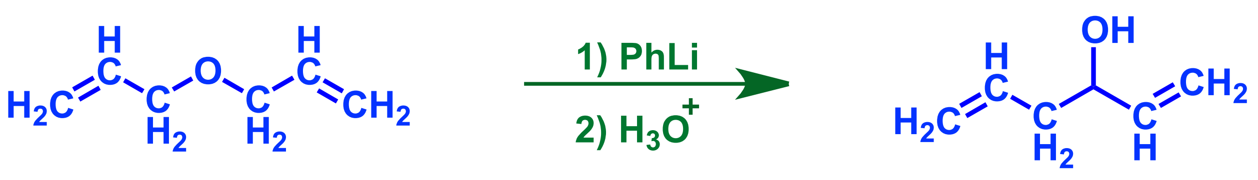
Molecular Rearrangements

Electron-Rich (Anionic) Skeletal Rearrangements

Wittig Rearrangement

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



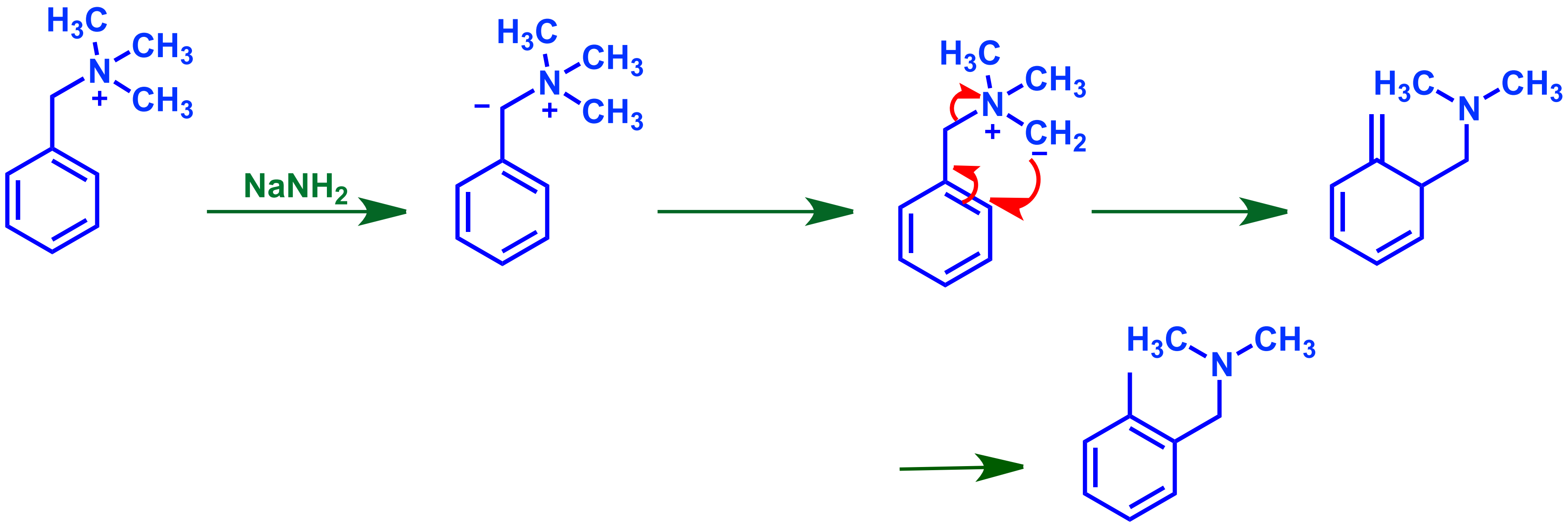


Molecular Rearrangements

Electron-Rich (Anionic) Skeletal Rearrangements

Sommelet-Hauser Rearrangement

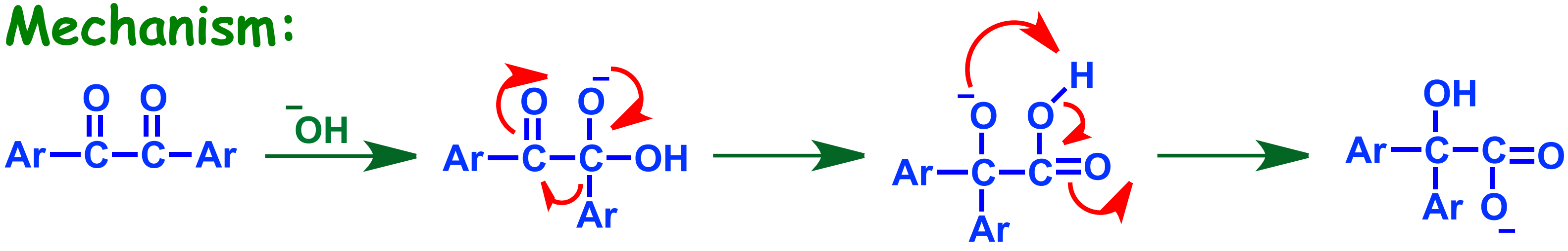
Nucleophilic alkylation of the aromatic rings of a benzyl-trimethylammonium ion



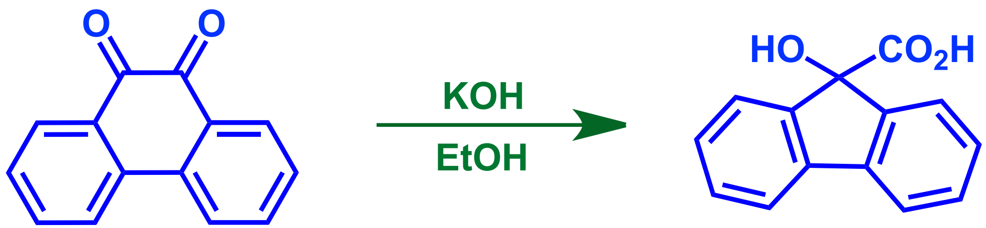
Rearrangements

Benzilic acid Rearrangement

Mechanism:



Formation of stable carboxylate salt is driving force for the reaction



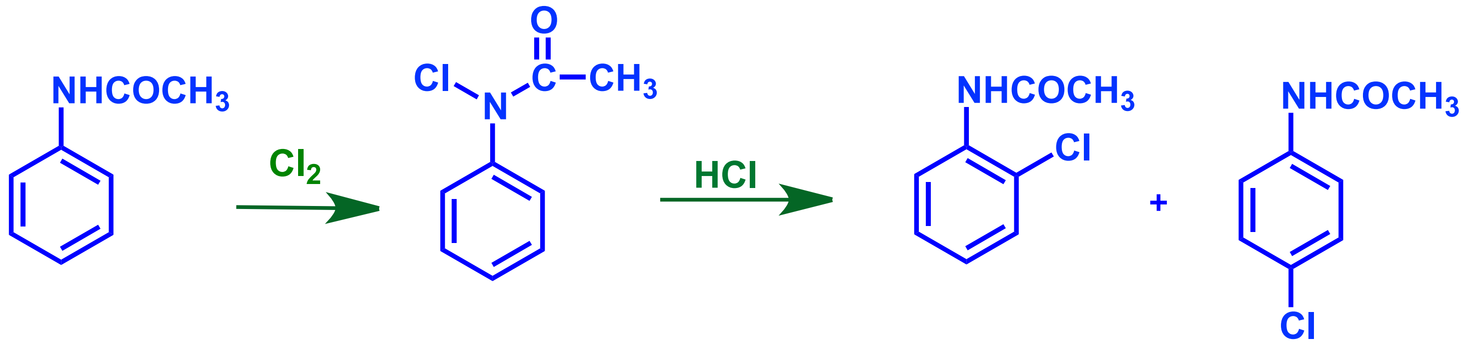
Application has been limited only to aromatic α-diketones

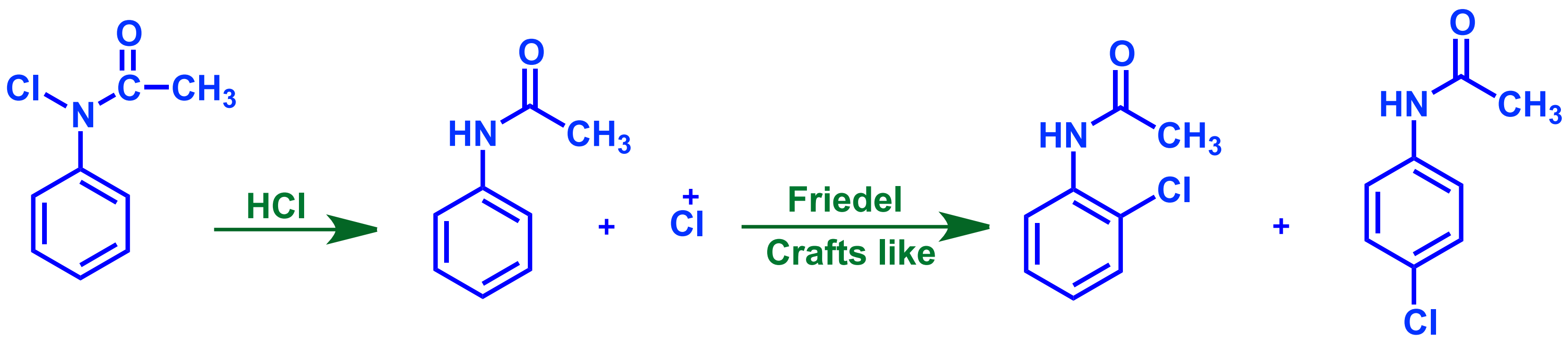
Rearrangements

Rearrangements on an Aromatic Ring

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

Rearrangements of Derivatives of Aniline:

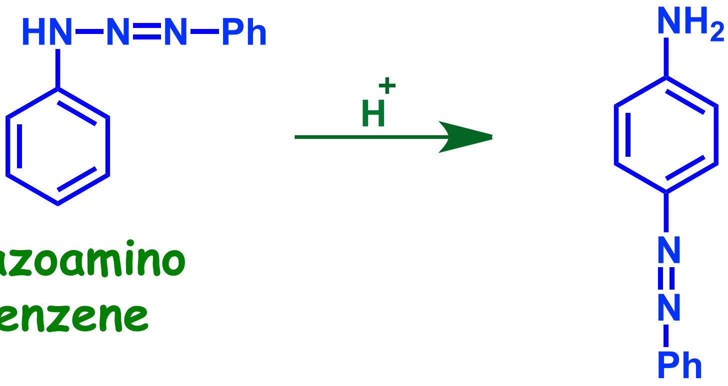




Rearrangements

Rearrangements on an Aromatic Ring

Rearrangements of Derivatives of Aniline:

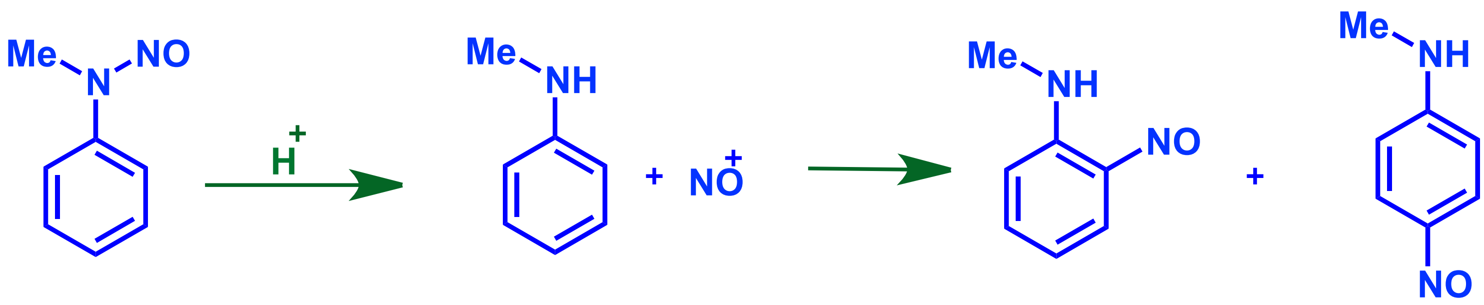


Diazoamino benzene

p-amino diazobenzene

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

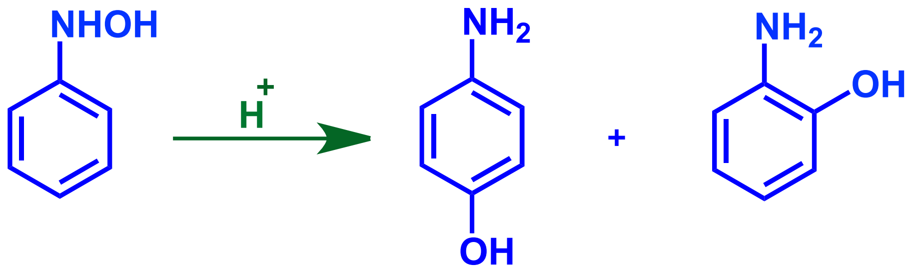
Rearrangement of N-Methyl-N-Nitrosoamine:



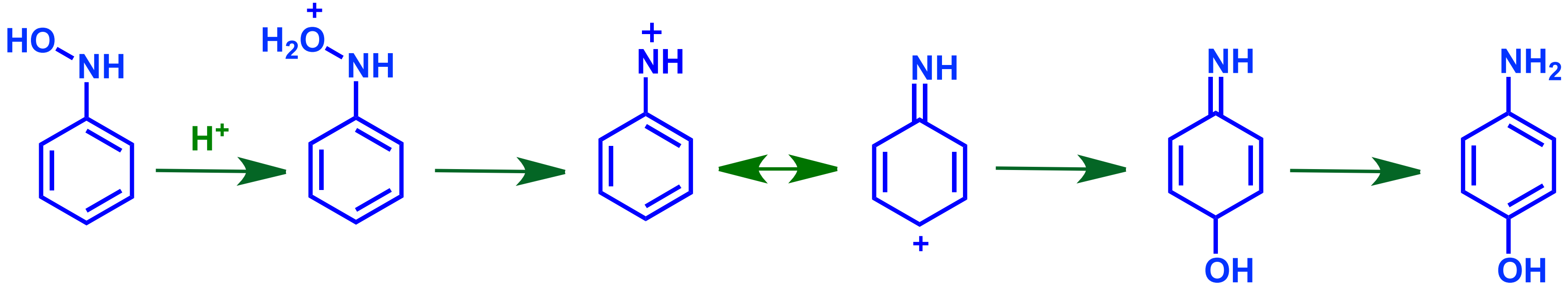
Rearrangements

Rearrangements on an Aromatic Ring

Rearrangement of N-Phenylhydroxylamine:



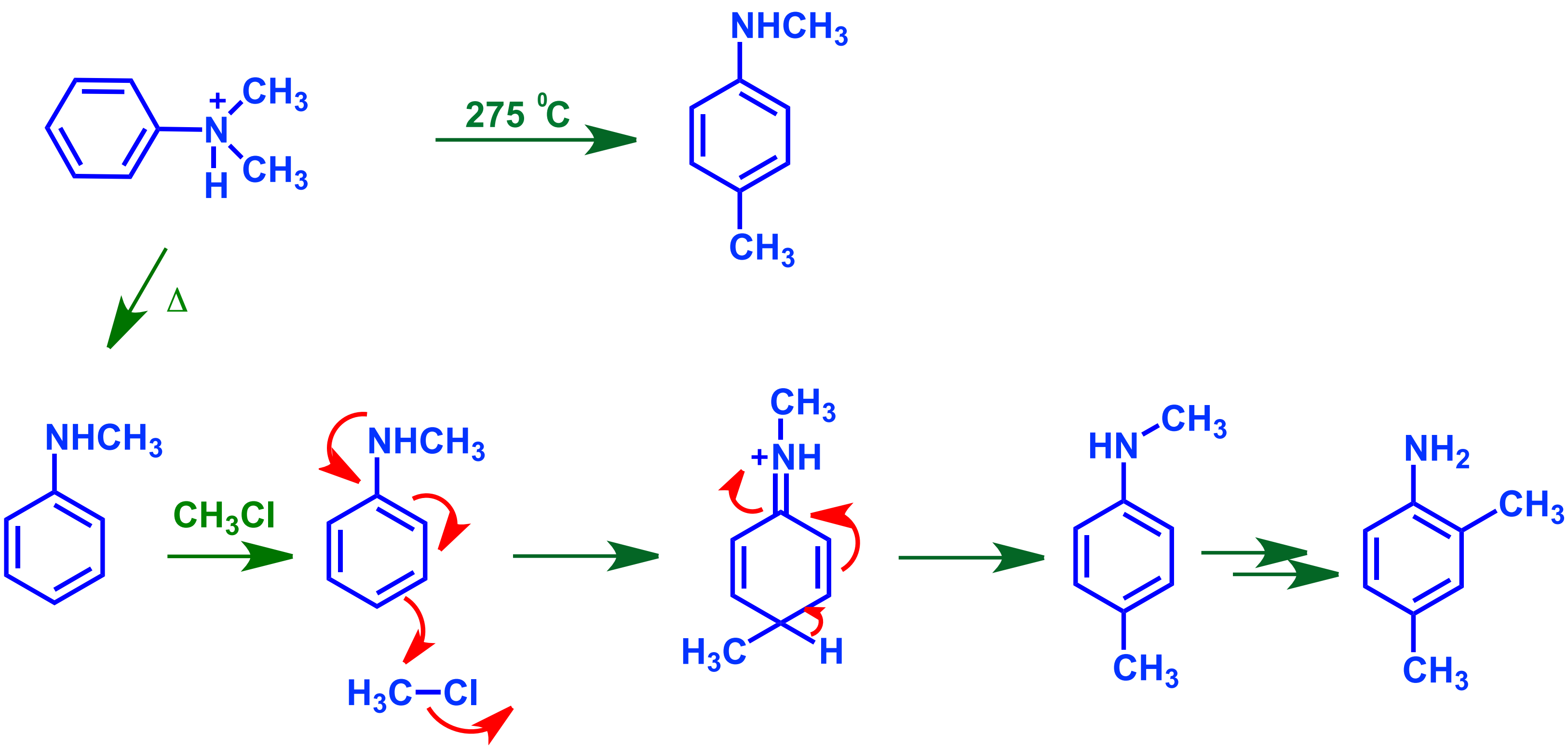
Mechanism



Rearrangements

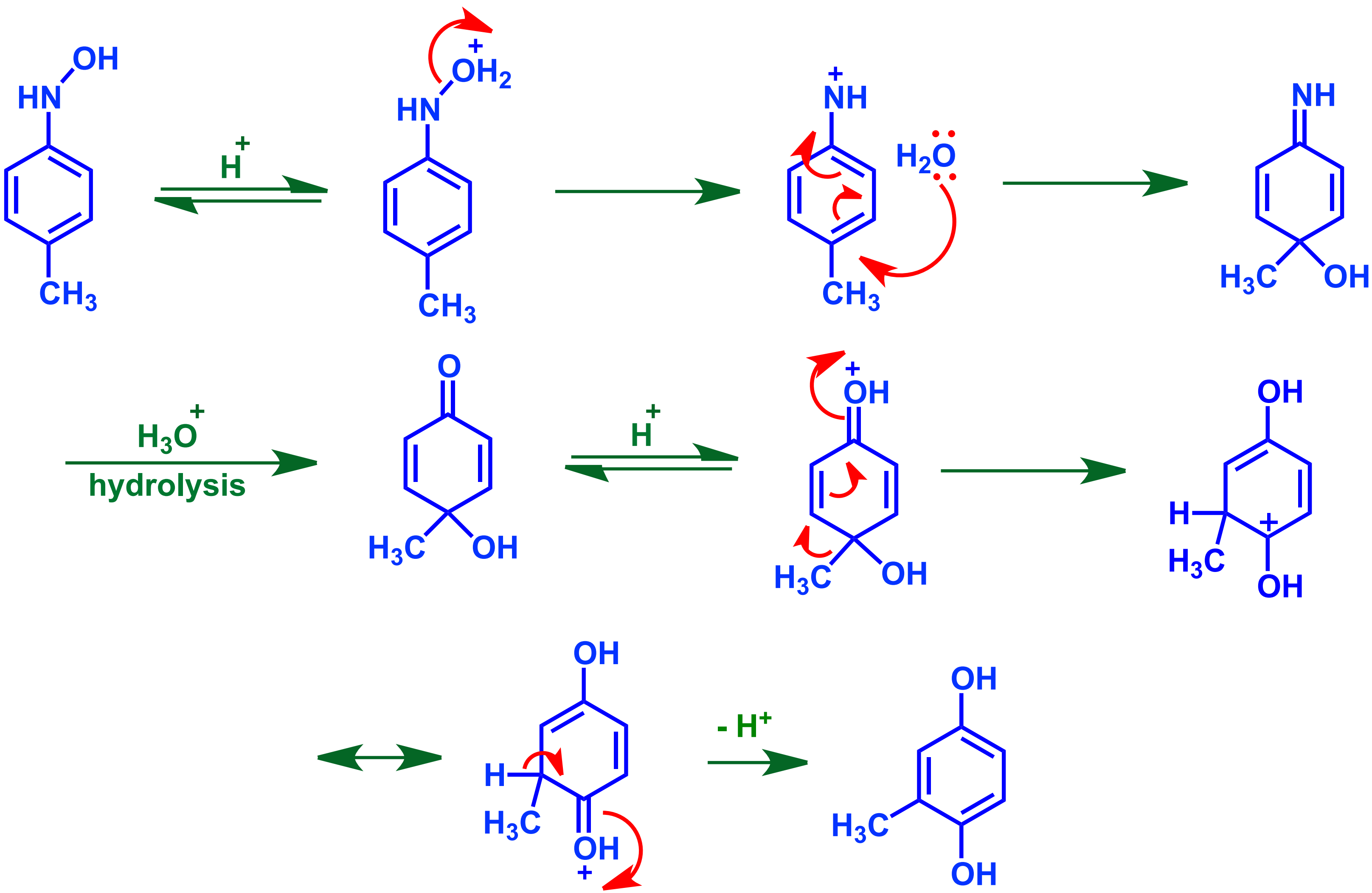
Rearrangements on Aromatic Ring

Rearrangement of N,N-Dimethylanilinium chloride:



Rearrangements

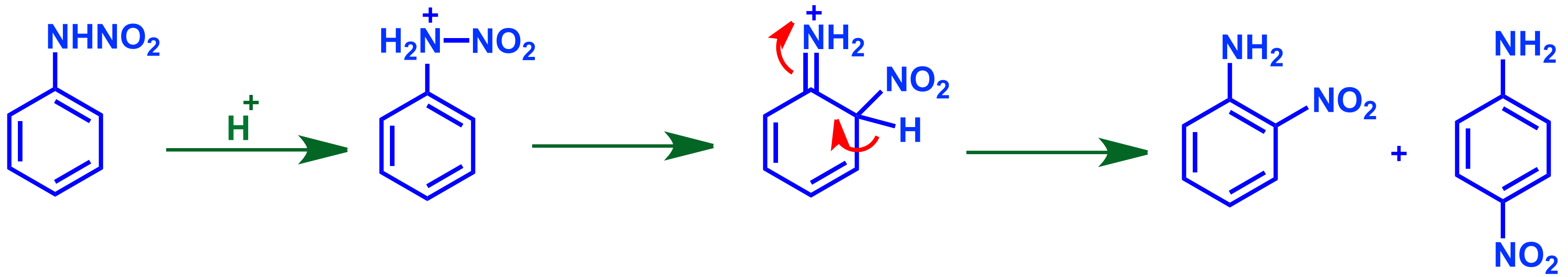
Rearrangements on Aromatic Ring



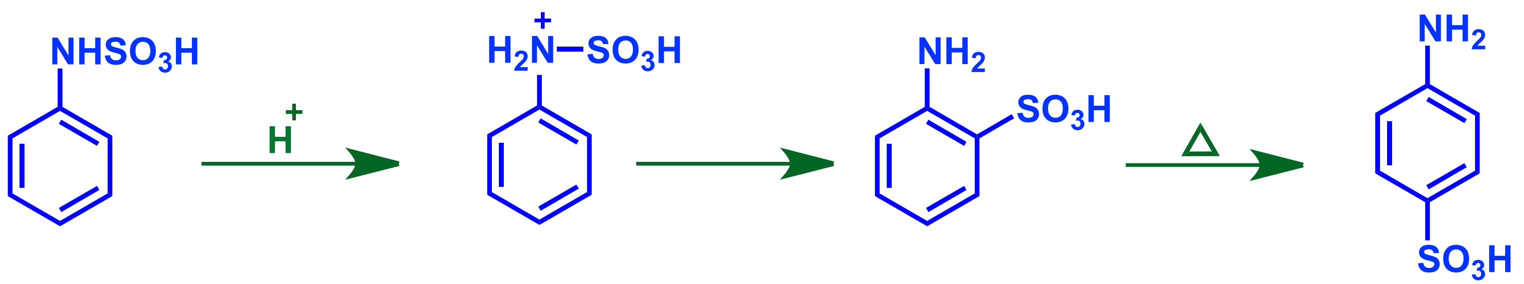
Rearrangements

Rearrangements on an Aromatic Ring

Rearrangement of Phenylnitramine:



Rearrangement of Phenylsulfamic acid:

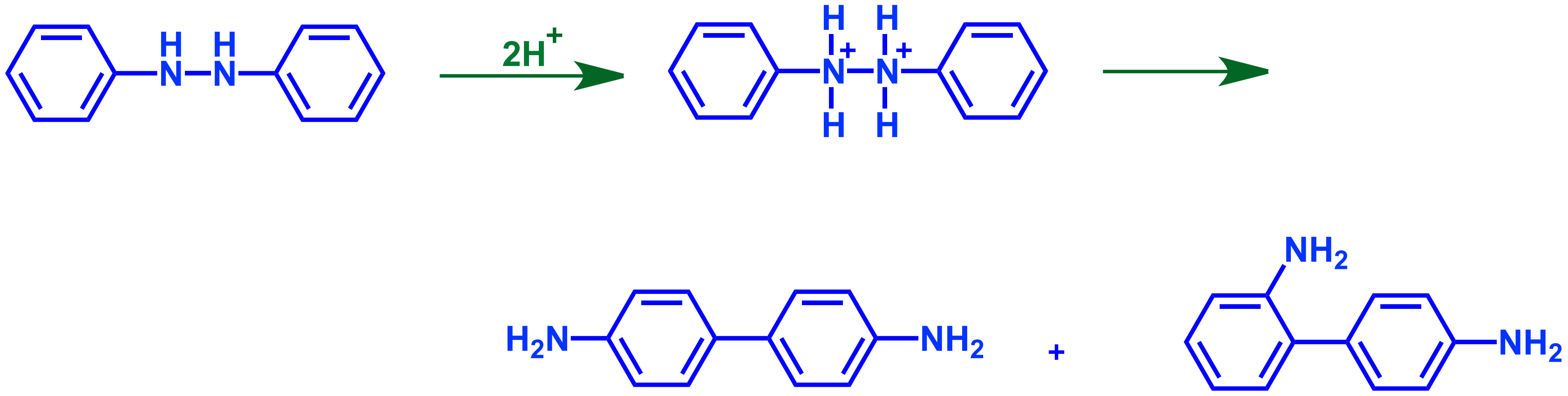


These reactions involve intramolecular pathway

Rearrangements

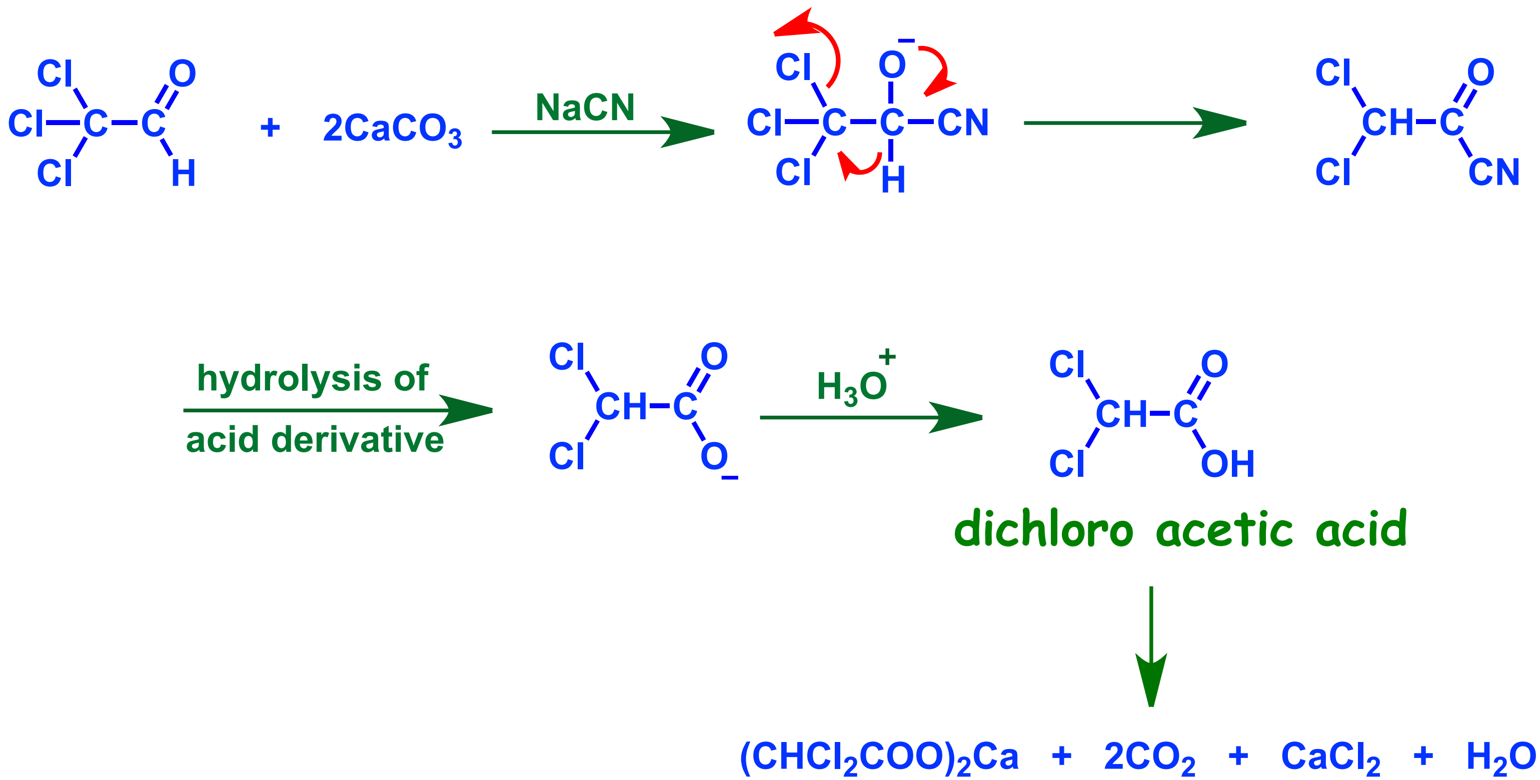
Rearrangements on an Aromatic Ring

Benzidine Rearrangement:



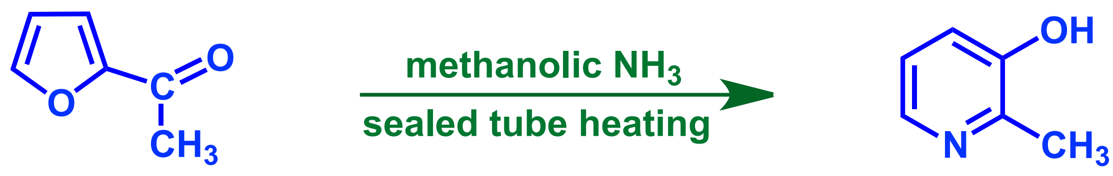
Rearrangements

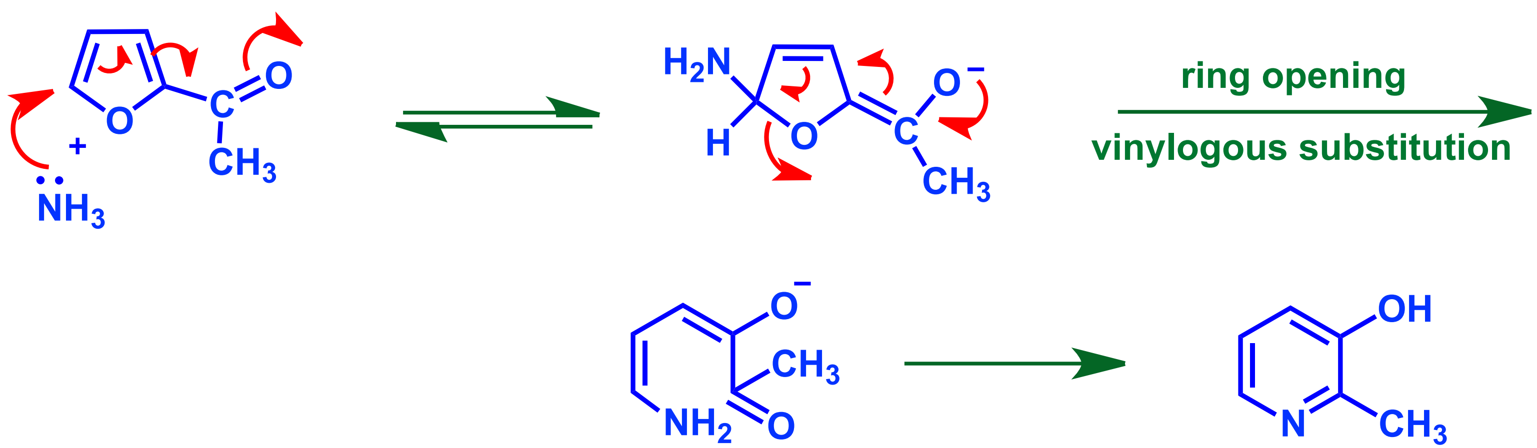
Some Additional Problems



Rearrangements

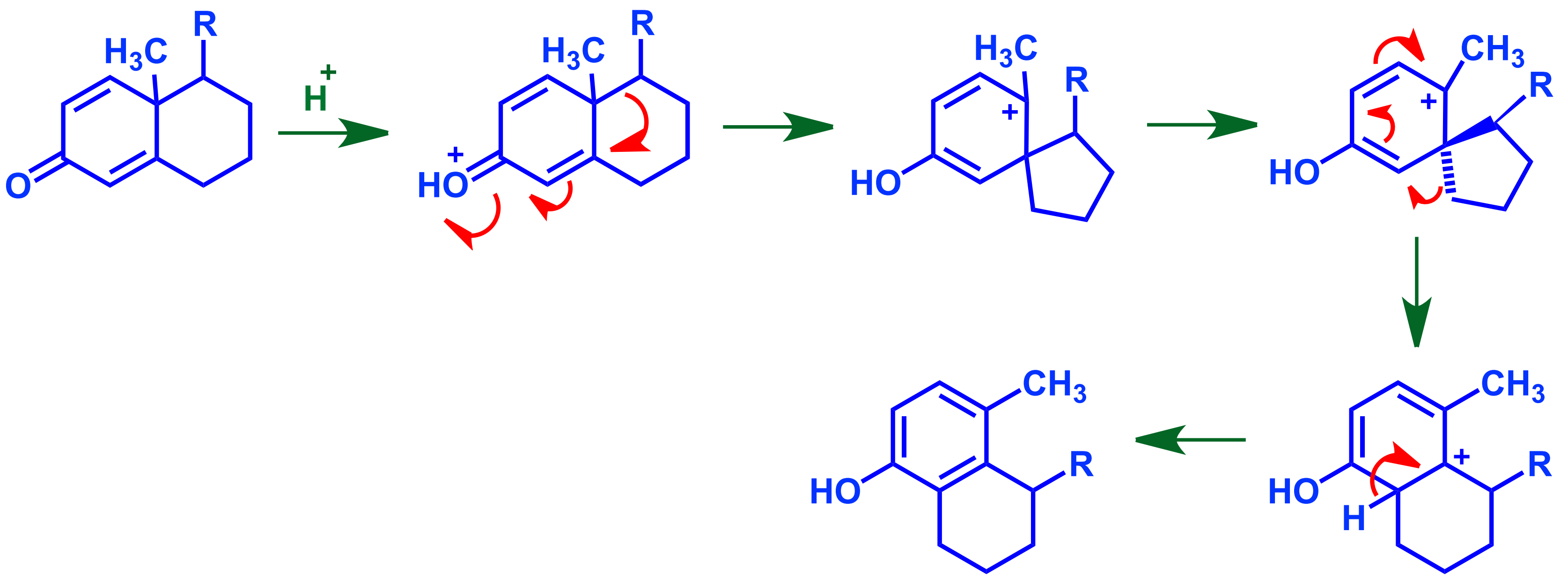
Some Additional Problems

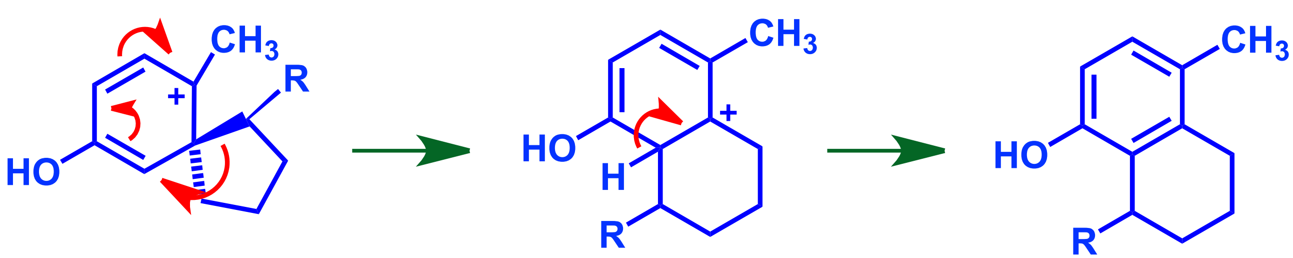




Rearrangements

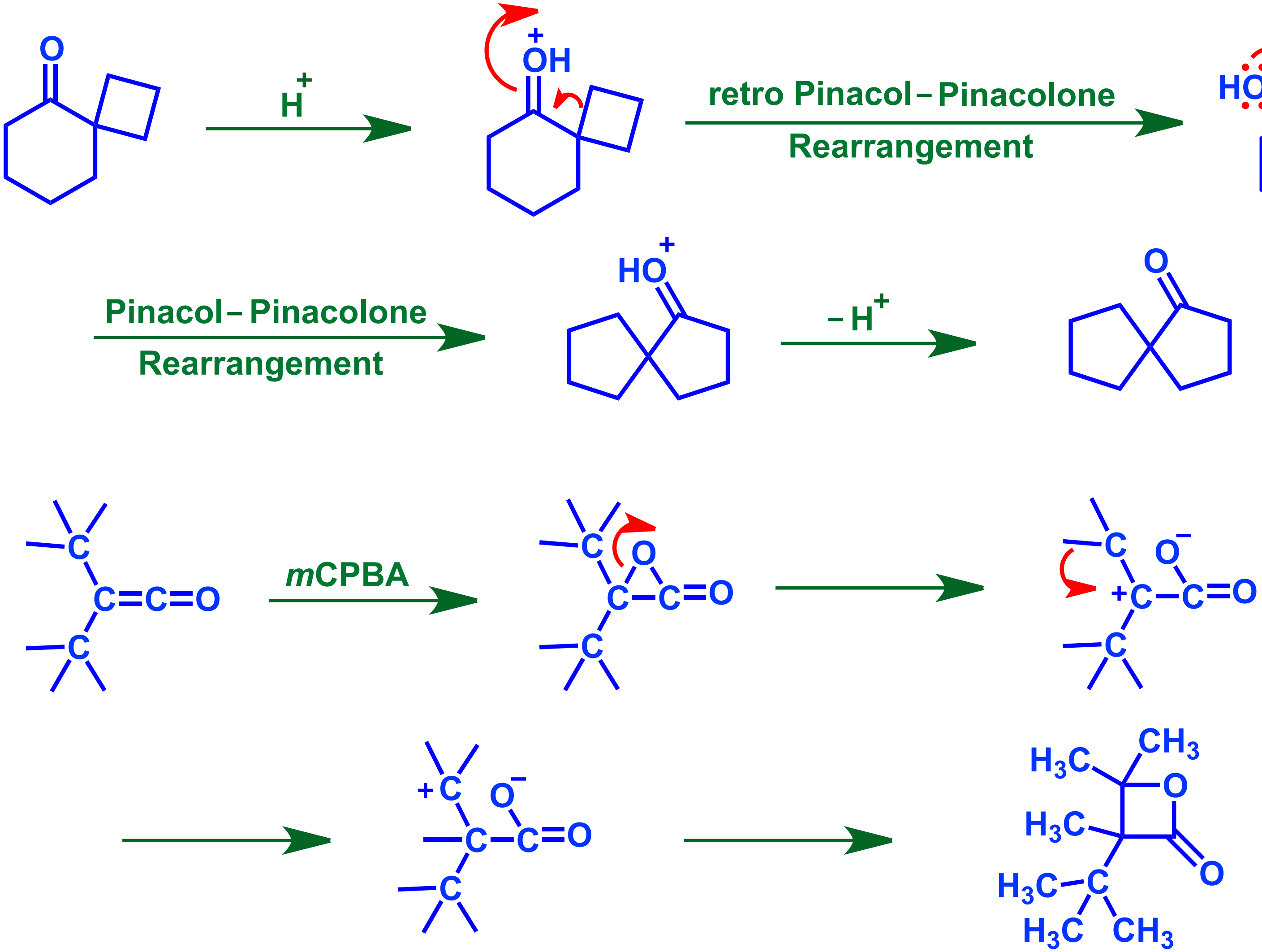
Some Additional Problems





Rearrangements

Some Additional Problems



Rearrangements

Some Additional Problems