Rearrangement

I. Sigmatropic Rearrangements

- I.1. Cope rearrangement including Oxy-Cope, Anionic Oxy-Cope
- I.2. Claisen rearrangement

II. Cationic Rearrangements

- II.1. Wagner-Meerwein rearrangements
    - II.1.1. 1,2-Hydride shifts
    - II.1.2. 1,2-Alkyl shifts
- II.2. Pinacol rearrangement

III. Rearrangements of formal Electron-Sextet

- III.1. Baeyer-Villiger oxidation
- III.2. Beckmann rearrangement
- III.3. Rearrangement of nitrenoids
    - 4.4.3.1. Hofmann rearrangement
    - 4.4.3.2. Curtius reaction
    - 4.4.3.3. Lossen reaction
    - 4.4.3.4. Reactions of the formed isocyanates
- III.4. The Wolff rearrangement – Arndt Eistert homologation

Rearrangement

Bond re-organization to give a structural isomer of the original compound.

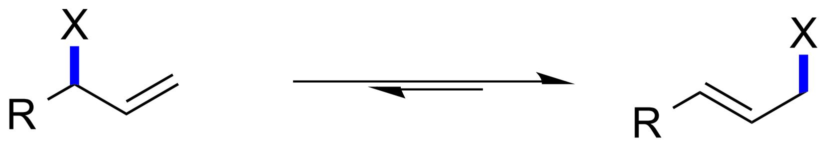
It often involves migration of a group (an atom) from one atom to another within the molecule.

Very often, rearrangment led to a significant structural modification.

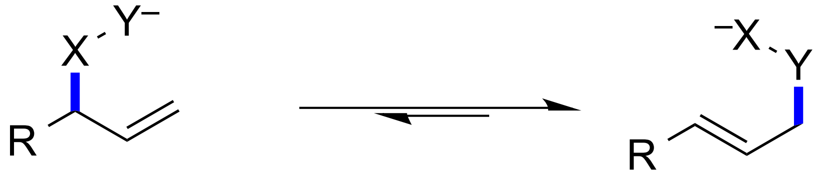
Reminder: reaction types we've already learnt:
Acid-base; Addition; Substitution; Elimination; Condensation…

Sigmatropic Rearrangement

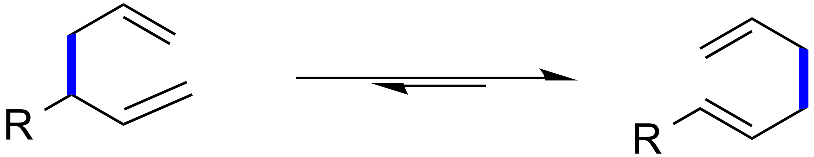
Those reactions in which a sigma bond and associated substituent interchanges termini on a conjugated π-system



[1,3]-sigmatropic rearrangement



[2,3]-sigmatropic rearrangement

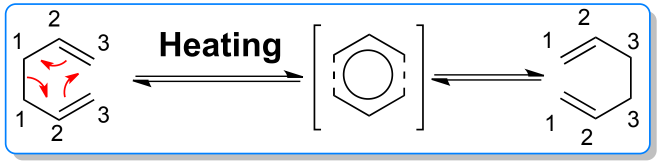


[3,3]-sigmatropic rearrangement

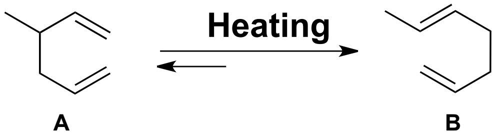
The suprafacial [1,3]-sigmatropic rearrangement is an orbital symmetry forbidden process and thus, typically has high activation barriers and potentially proceeds through radical or zwitterionic intermediates.

Cope Rearrangement

A thermal isomerization of 1,5-diene to a regioisomeric 1,5-diene. It is a pericyclic reaction with a concerted molecular rearrangement: 4πe + 2σ bonds. Consequently, the transition state has "aromatic character". It belongs to a family of [3,3]-sigmatropic rearrangements



Cope rearrangement is an equilibrium process leading to thermodynamically more stable isomer



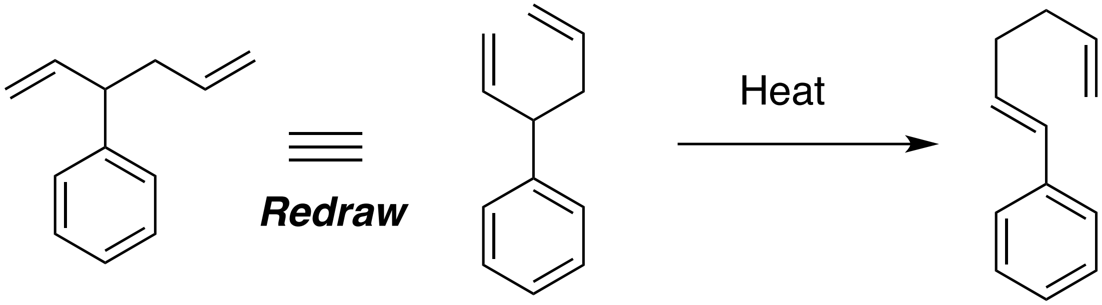
B is the major product, Why?

Definition of a pericyclic reactions:

Having a cyclic transition state and proceeding in a concerted manner.

Cope Rearrangement

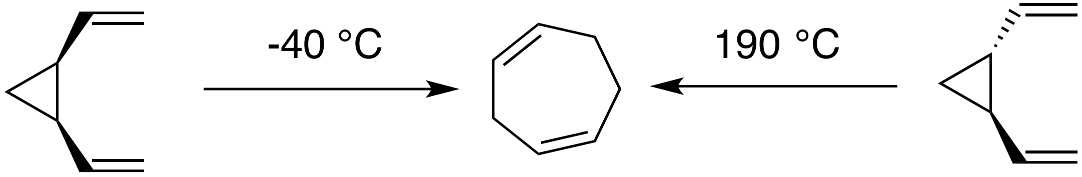
Key: ***To recognize the 1,5-diene unit***



A

B

B is thermodymanically more stable

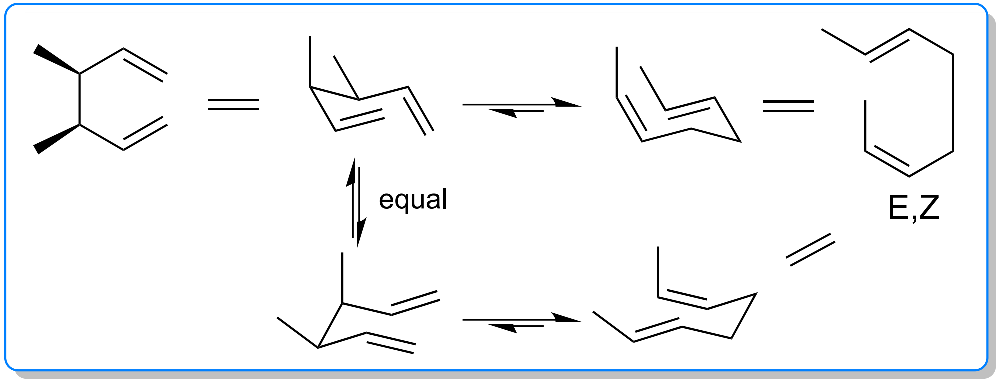


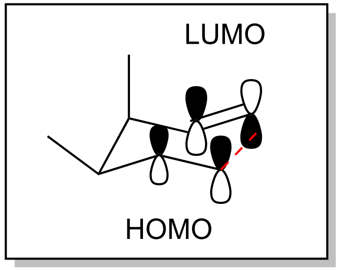
Driving force: Release of ring strain

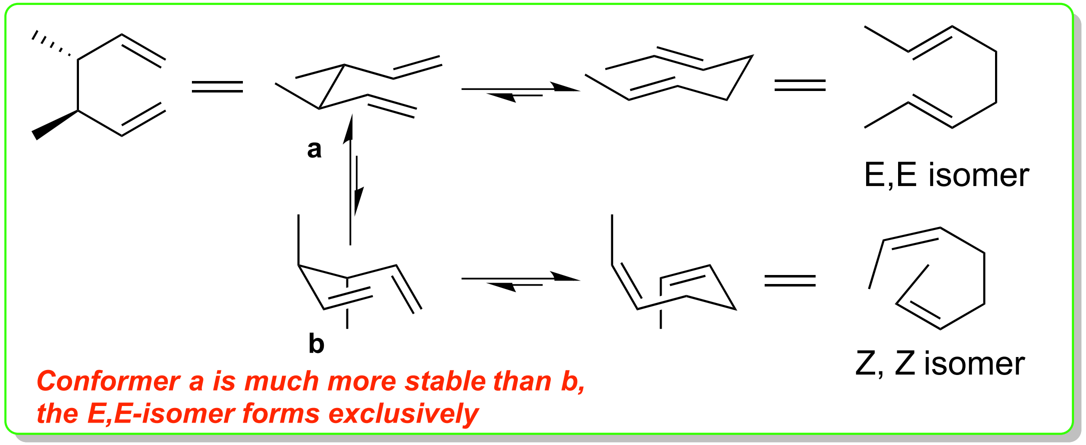
Cyclopropane ring strain: 27 kcal/mol

Cope Rearrangement

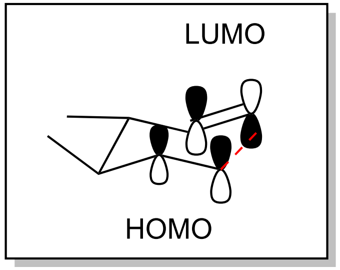
Key: For linear 1,5-diene, the rearrangement generally went through a chair-like transition state. The TS conformation determines the stereochemistry of the new double bonds





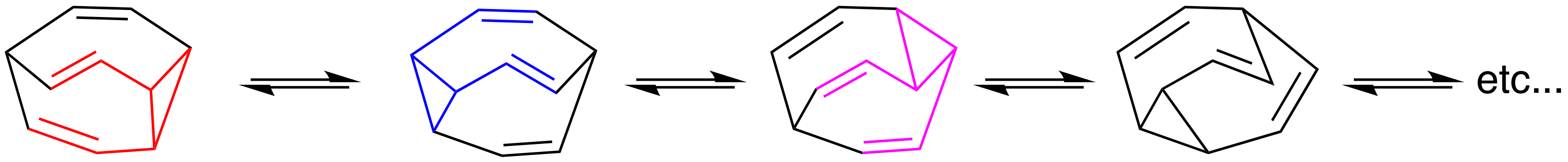


Conformer a is much more stable than b, the E,E-isomer forms exclusively



Very similar to Zimmerman-Traxler transition state for the aldol reaction
Avoid 1,3-diaxial interaction in drawing your transition state

Degenerative Cope Rearrangement: Case of Bullevalene



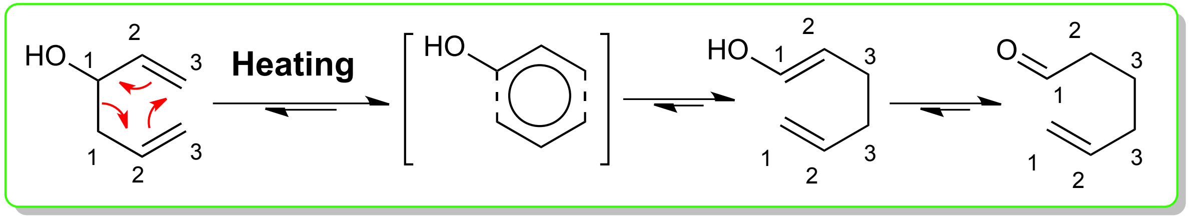
$C_{10}H_{10}$

***Doring's Prediction*:**

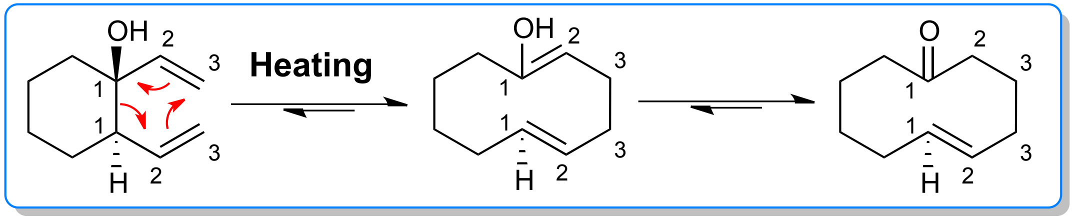
If each of the 10 CH groups of the molecule were individually labeled, there would be 1,209,600 arrangements of the molecule.

Oxy-Cope rearrangement

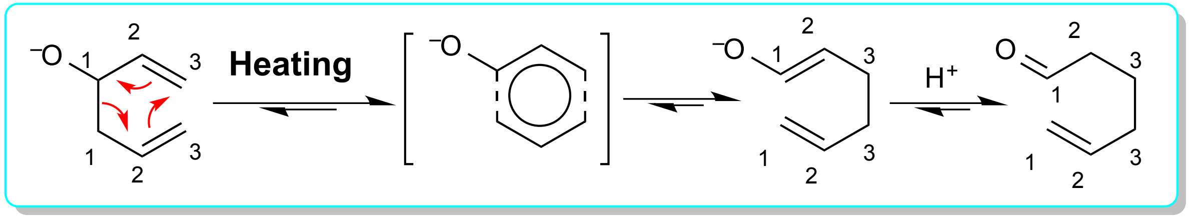
oxy-Cope rearrangement: aldehyde formation is the driving force



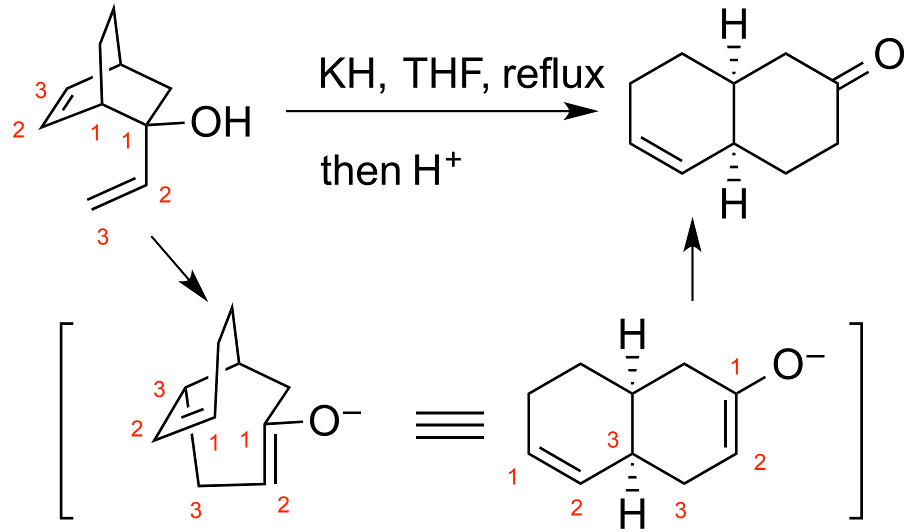
The carbonyl tautomer is more stable, removing the enol from the equilibrium.

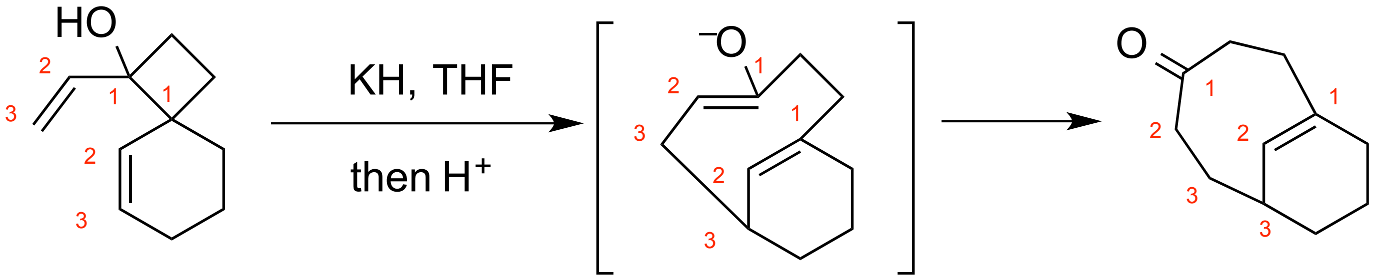


The oxy-Cope rearrangement is significantly accelerated when the hydroxy group is converted to alkoxide. The base-catalyzed reaction is called: **anionic oxy-Cope rearrangement**



Oxy-Cope rearrangement:
Example of complete structural re-organizaiton



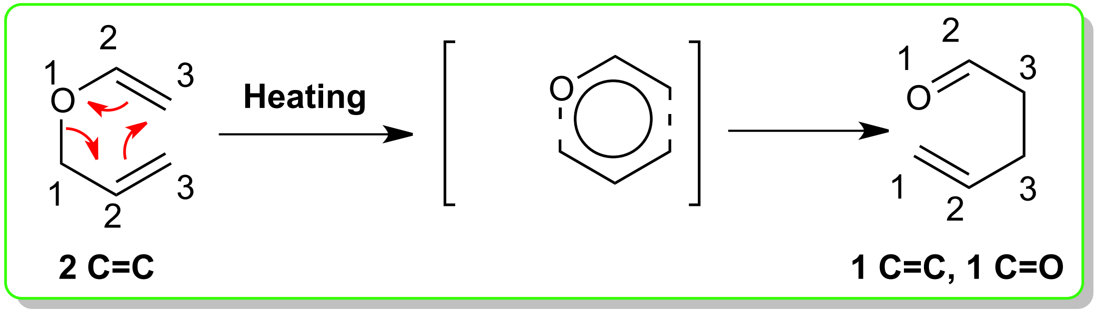


Claisen rearrangement

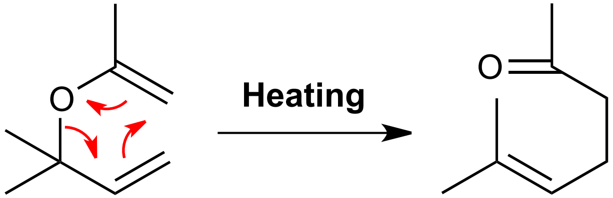
Claisen rearrangement involving a vinyl allyl ether is essentially the same as Cope rearrangement. However, the equilibrium is driven to the product (4-pentenal) which is thermadynamically more stable.

Driving force of the reaction = carbonyl group formation

Comparing the bond dissociation energies: C=C 146 kcal/mol, C=O 172 kcal/mol

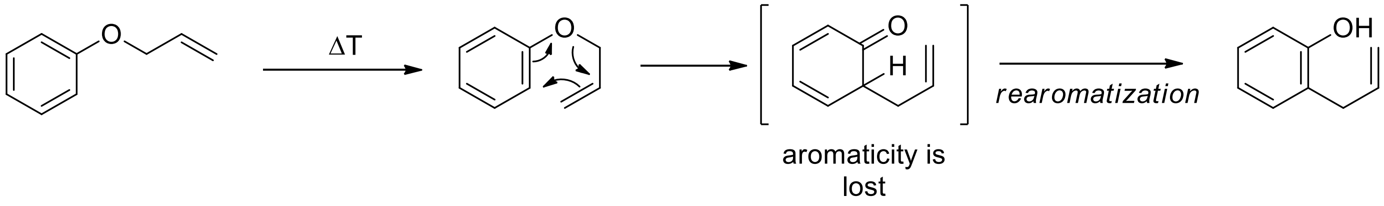


Example:

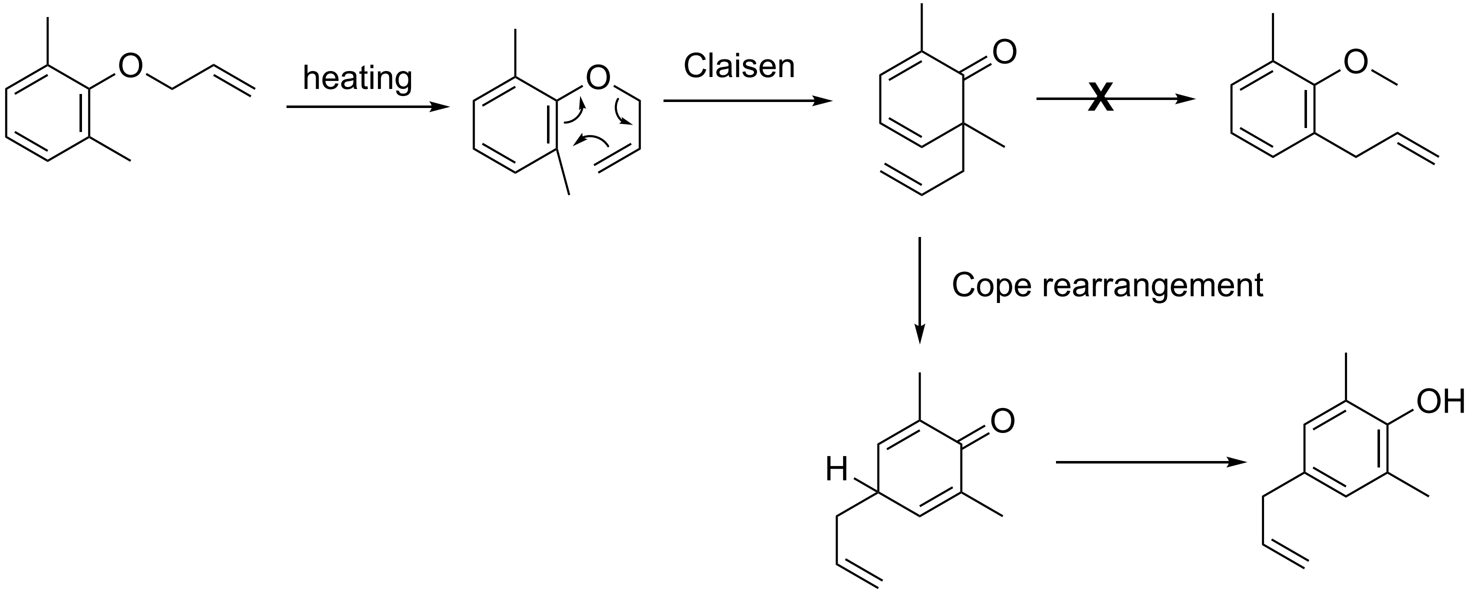


Claisen rearrangement

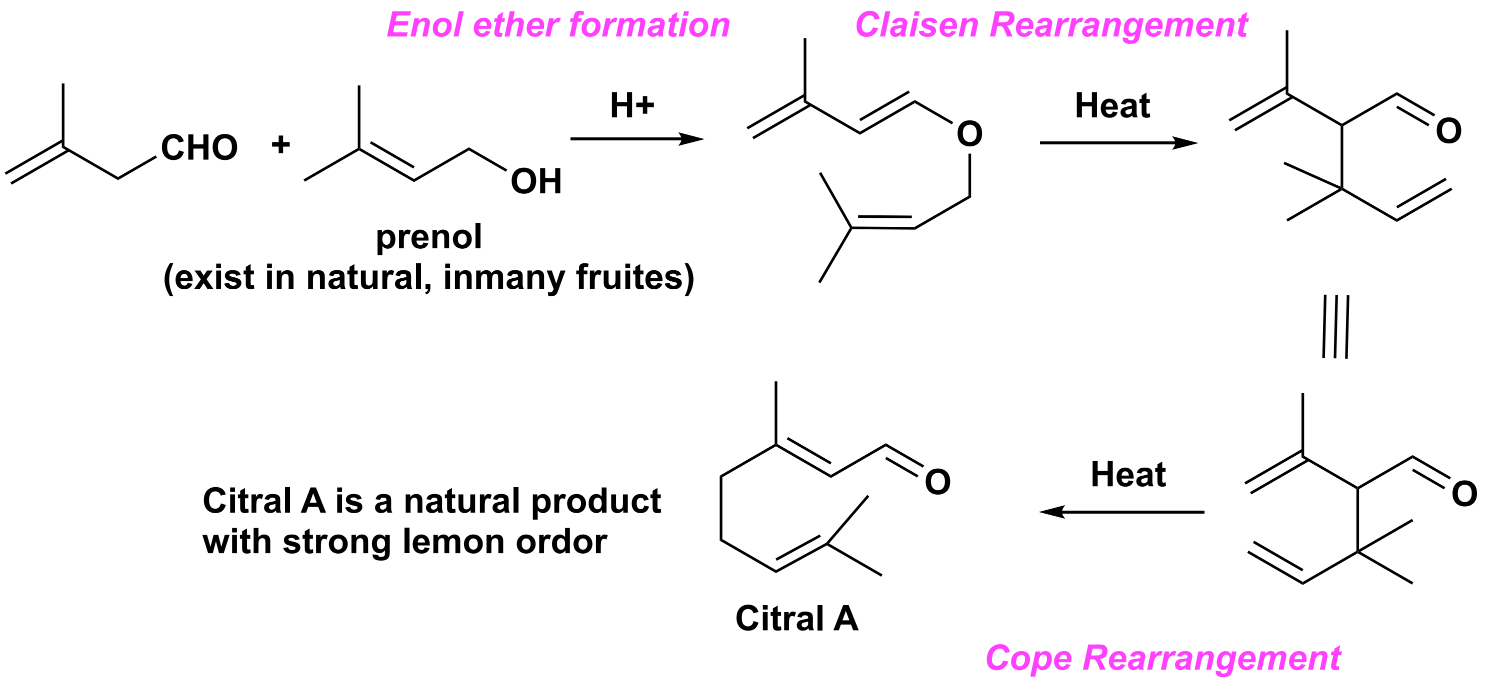
Aromatic Claisen rearrangement:



When the *ortho*-positions are occupied:



Industrial Application: Synthesis of Citral



Enol ether formation

Claisen Rearrangement

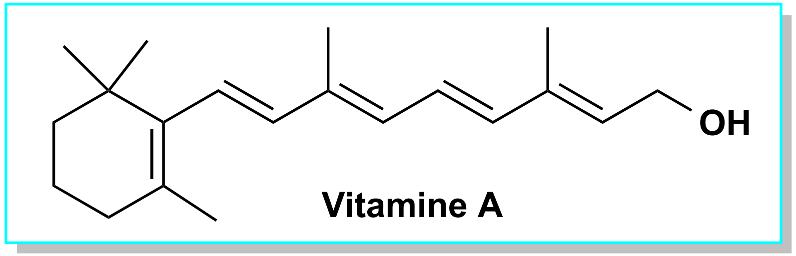
prenol
(exist in natural, inmany fruites)

Citral A is a natural product
with strong lemon ordor

Citral A

Cope Rearrangement

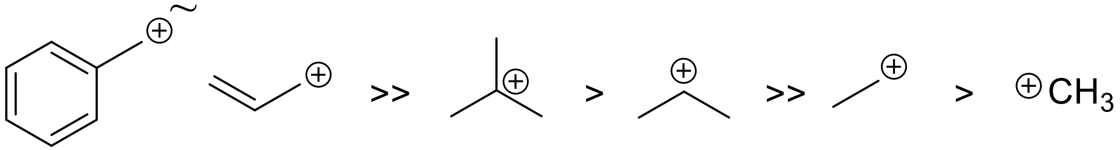
Citral A is a key intermediate in the synthesis of Vitamine A



Vitamine A

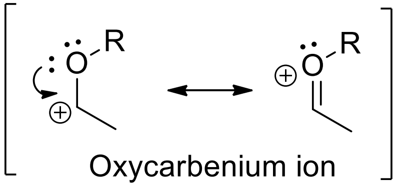
Cationic Rearrangements:

Recapitulation on the stability of carbenium ions:

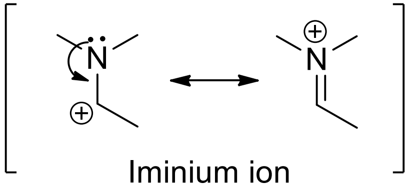


benzyl allyl tertiary alkyl secondary alkyl primary alkyl methyl

Even better:



Oxycarbenium ion
good stabilization



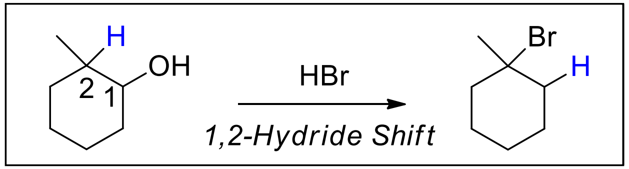
Iminium ion
good stabilization

Possible reactions with a cationic intermediate:
Add a nucleophile (S_N1 substitution), Loss a proton (Elimination) and **Rearrangement**

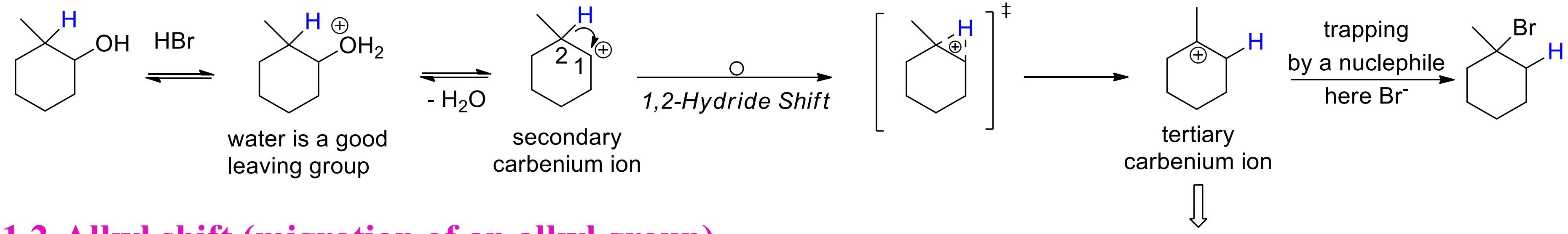
Driving forces and selectivity factors for cationic rearrangements:
*Reaction proceeds to form a better stabilized carbenium ion
*Release of ring strain
*Cleavage/release of small and uncharged molecules, for example: CO or CO_2

Wagner-Meerwein rearrangement: A cationic 1,2-rearrangement involving the migration of an alkyl or a hydride

1,2-Hydride Shift (migration of a hydride)



Mechanism:



water is a good leaving group

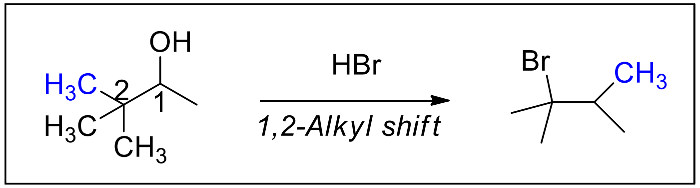
secondary carbenium ion

tertiary carbenium ion

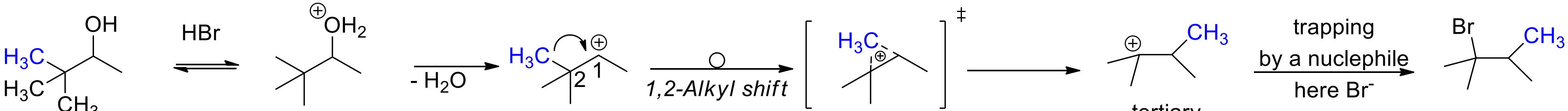
trapping by a nuclephile here Br$^-$

better stabilized

1,2-Alkyl shift (migration of an alkyl group)



Mechanism:



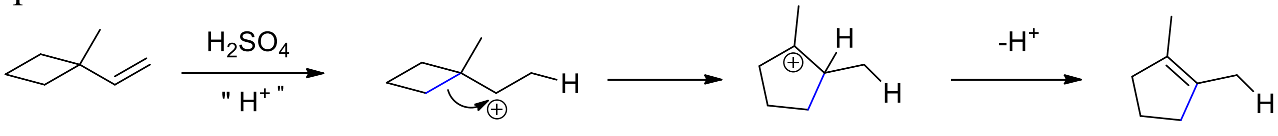
water is a good leaving group

secondary carbenium ion

tertiary carbenium ion

trapping by a nuclephile here Br$^-$

Example:



secondary carbenium ion

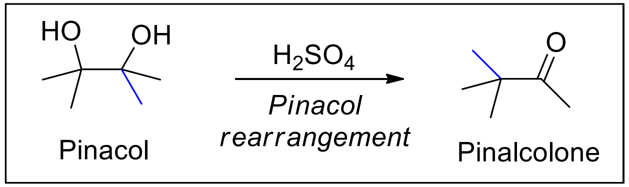
tertiary carbenium ion

higher substitued double bond is more stable

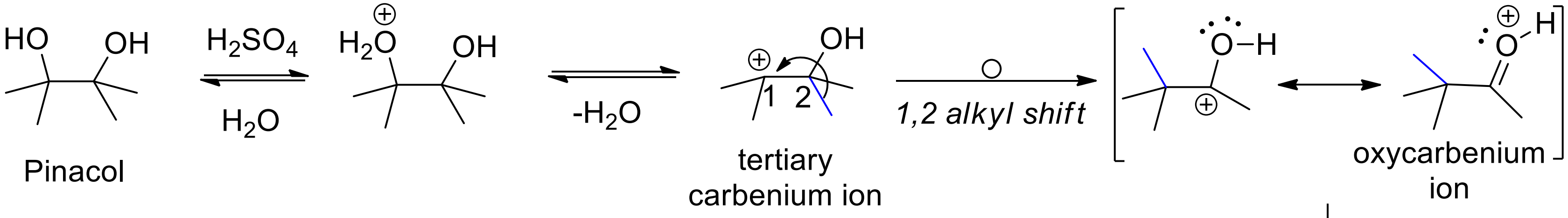
driving force = release of ring strain for the cyclobutane

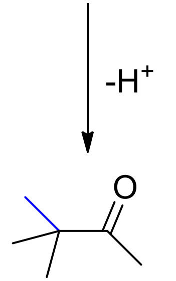
caution: HSO$_4^-$ is not nucleophilic, therefore E1 elimination

Pinacol Rearrangement



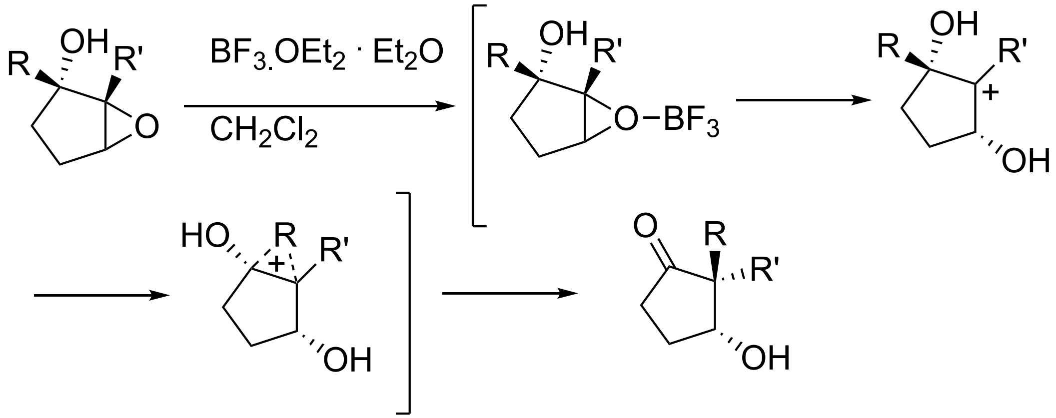
Mechanism:





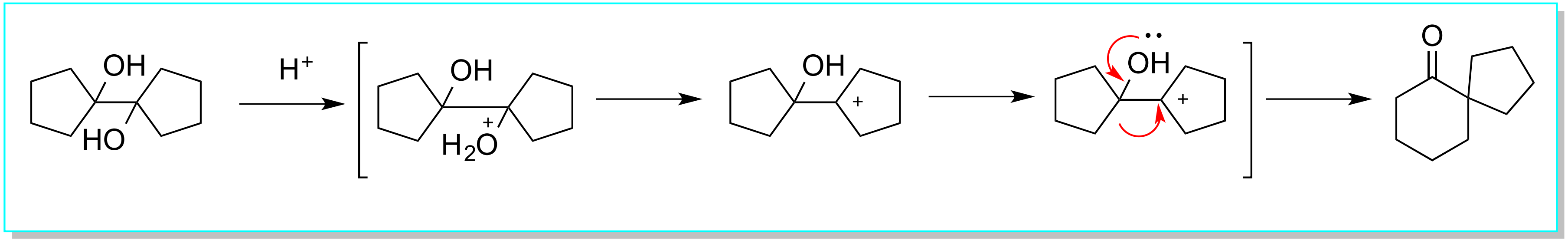
Pinalcolone

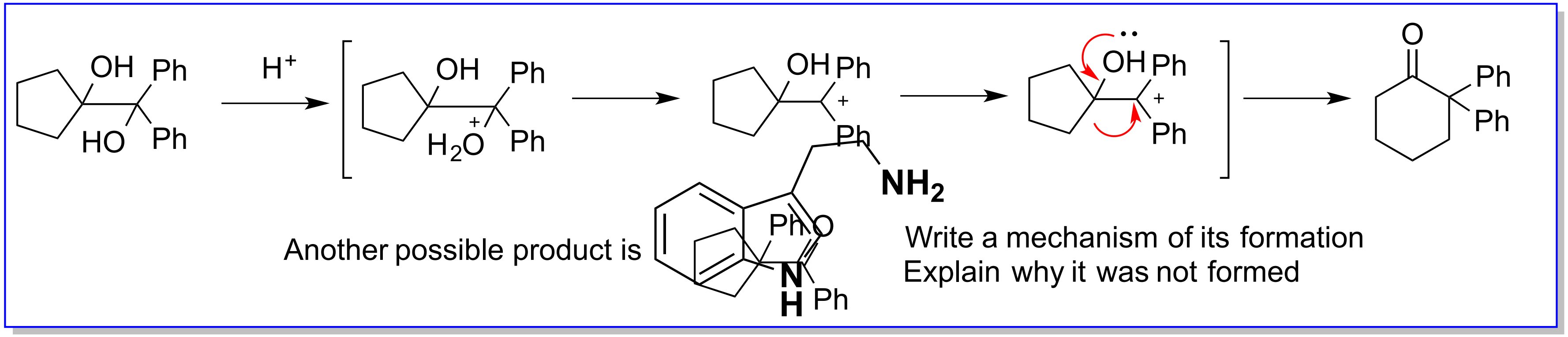
Semi-pinacol rearrangement



P. J. Walsh, et al. J. *Am. Chem. Soc.* **2003,** *125,* 9544-9545

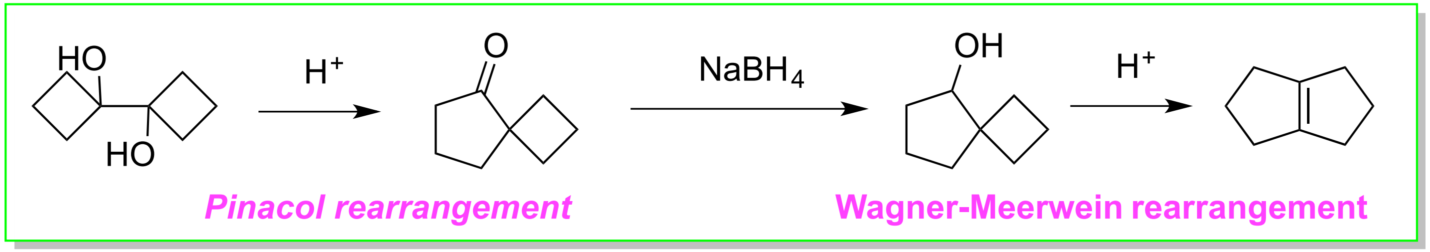
Pinacol Rearrangement: Examples





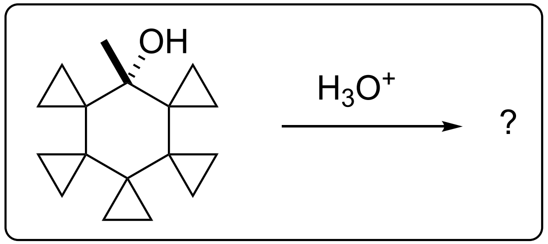
Another possible product is

Write a mechanism of its formation
Explain why it was not formed

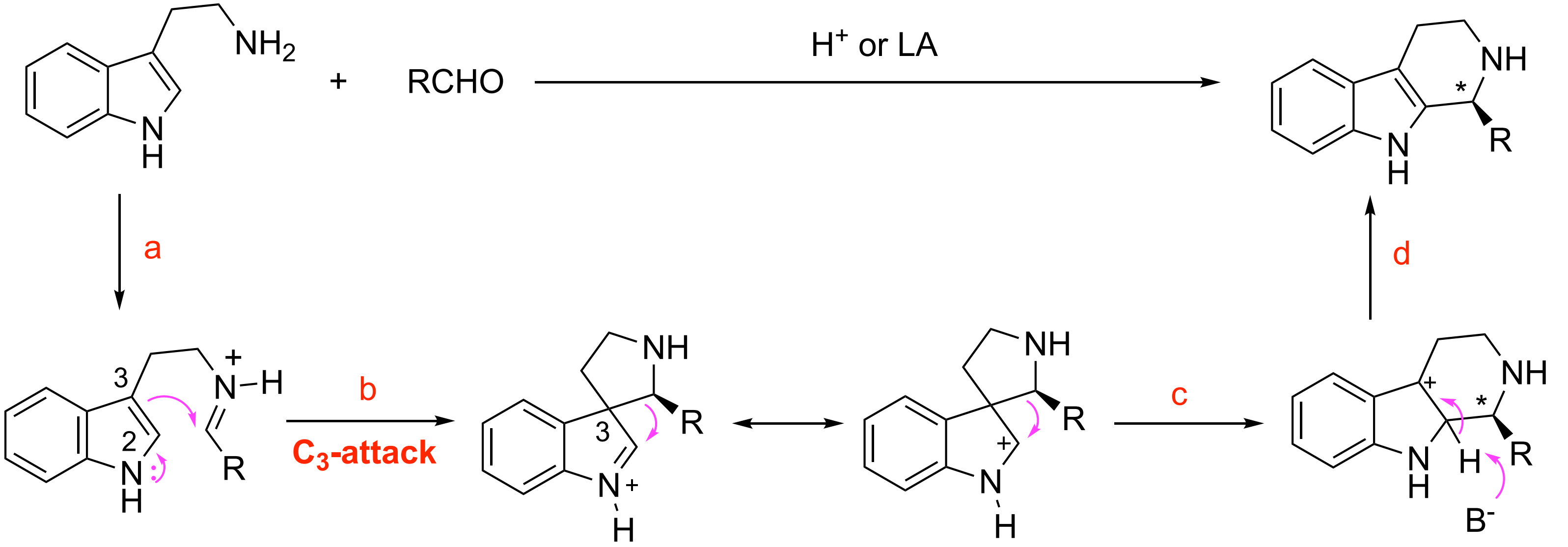


Pinacol rearrangement

Wagner-Meerwein rearrangement



Pictet-Spengler Reaction



Step a: Iminium formation

Step b: Type of Fridel-Crafts alkylation or aza-Mannich reaction.

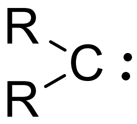
Why it occurred at the C_3 position?

Step c: Wagner-Meerwein rearrangement

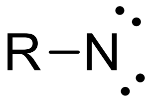
Step d: Re-aromatization

Rearrangements of Formal Electron-Sextet

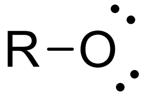
Electron sextets (6 valence electrons): violate the Octet-rules (8 valence electrons)



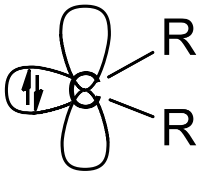
carbene



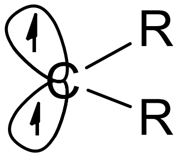
nitrene



oxene



Singlet carbene
Carbon atom is sp^2
hybridized with an
empty P_z orbital



Triplet carbene
Carbon atom is sp^3
hybridized

General:

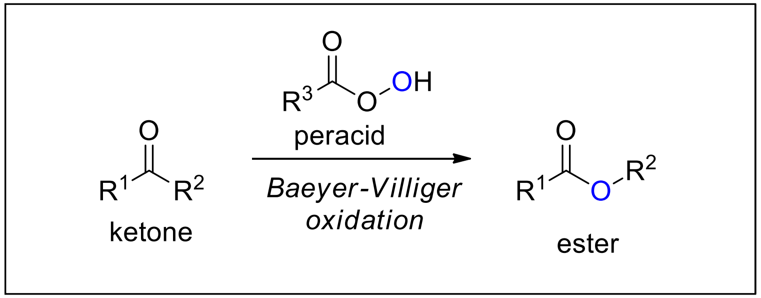
With carbon: stepwise mechanisms via carbene intermediate

With nitrogen: can either proceed with nitrene intermediates or concerted mechanisms (in between carbon and oxygen)

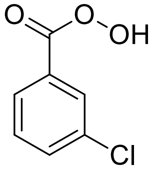
With oxygen: concerted mechanisms, no oxene intermediates are formed

Baeyer-Villiger oxidation

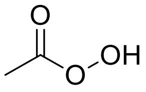
Reaction of ketone (aldehydes) with peroxyacids or hydrogen peroxide to give ester via a C to O Rearrangement. Both acid and base can catalyze the reaction.



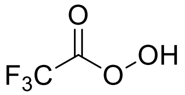
Commonly used peracids:



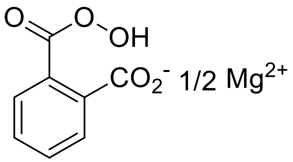
3-chlorobenzoperoxoic acid
(mCPBA)
often used in laboratory



Peracetic acid

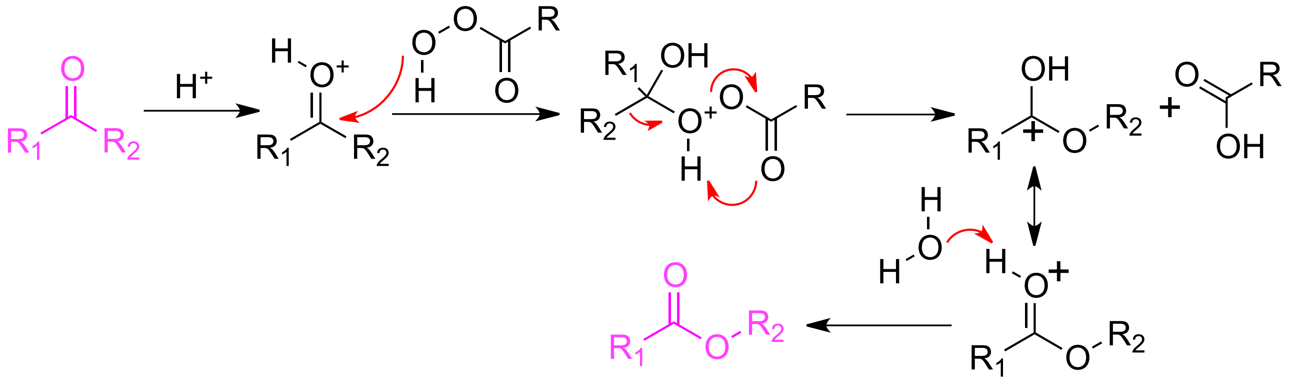


Trifluoroperacetic acid



applied in industry

Mechanism (acid-catalyzed):

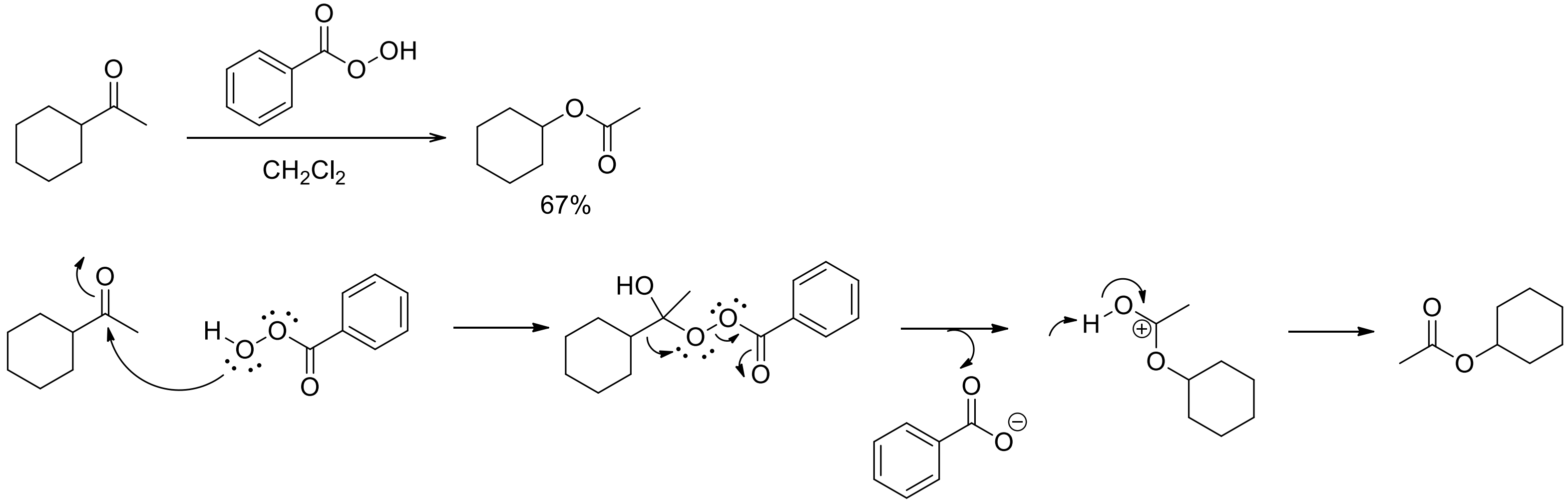


Baeyer-Villiger oxidation

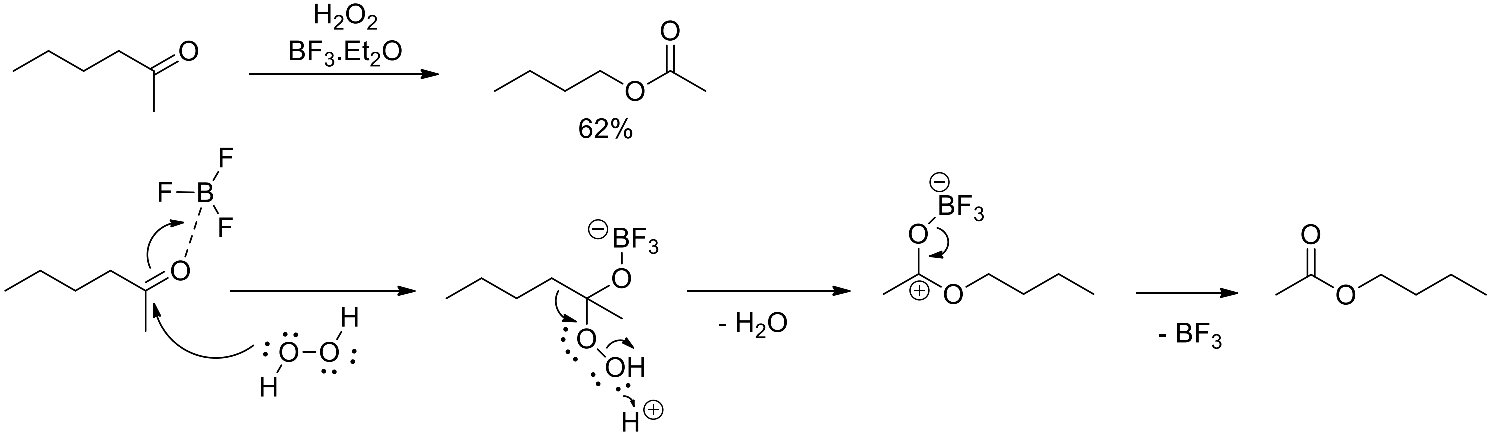
Migratory aptitude: **H >*** tertiary Alkyl > cyclohexyl > secondary Alkyl ≈ phenyl ≈ benzyl > vinyl > primary Alkyl > Cyclopropyl > methyl

* There are exceptions with H (eg in Dakin reaction, vide infra)

- Cyclohexyl *vs* Methyl:

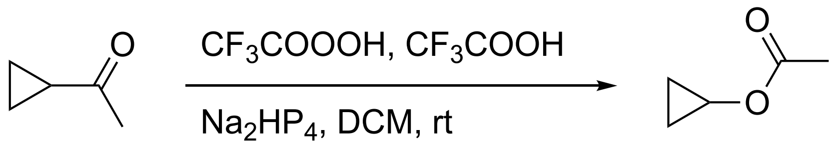


- *n*-Butyl *vs* Methyl



Baeyer-Villiger oxidation

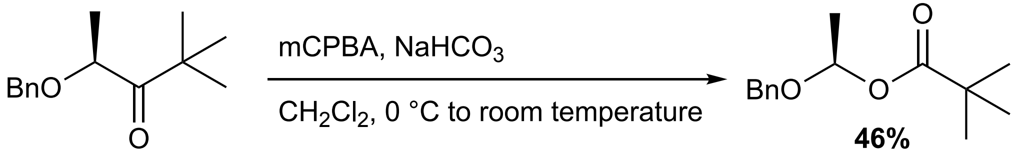
- Cyclopropyl vs Methyl



CF_3COOOH, CF_3COOH

Na_2HP_4, DCM, rt

- Alkoxyalkyl group has high migratory aptitude
- Migration occurs with retention of configuration

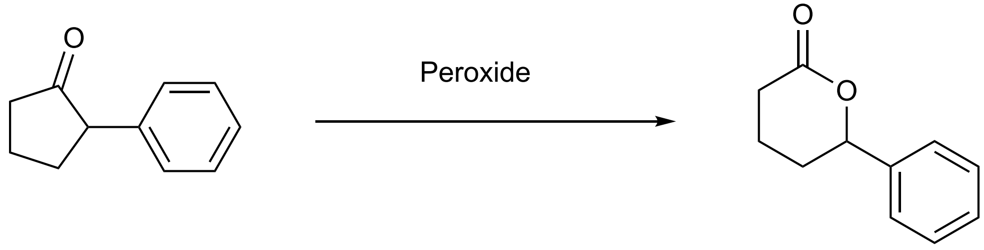


mCPBA, $NaHCO_3$

CH_2Cl_2, 0 °C to room temperature

46%

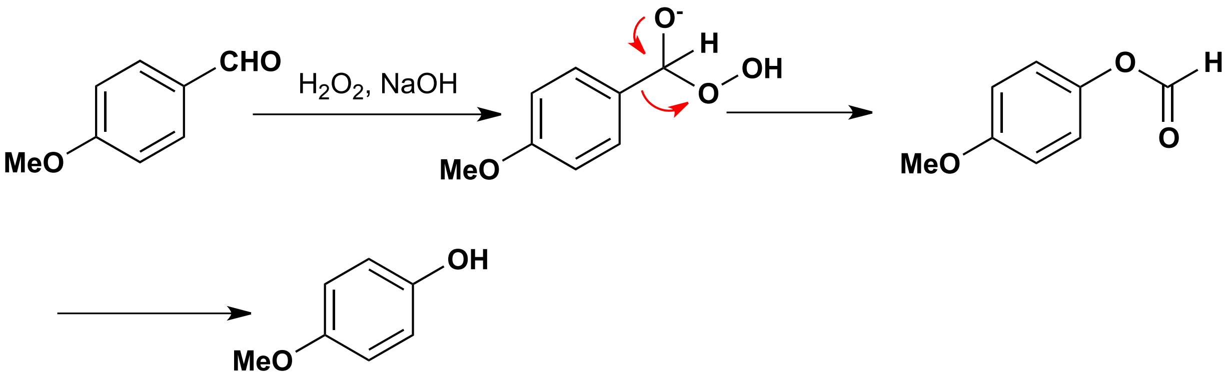
* Ketone to Lactone



Peroxide

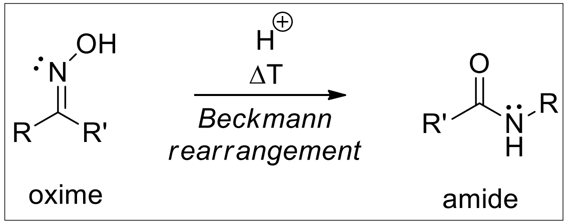
Dakin oxidation

H has high migratory aptitude and Baeyer-Villiger reaction of aldehyde generally give Acid. However, reaction of electron-rich aromatic aldehyde with hydrogen peroxide under basic conditions gave formate as the major product (aromatic ring migrate) which was then hydrolyzed to phenol. This reaction is called **Dakin reaction**.

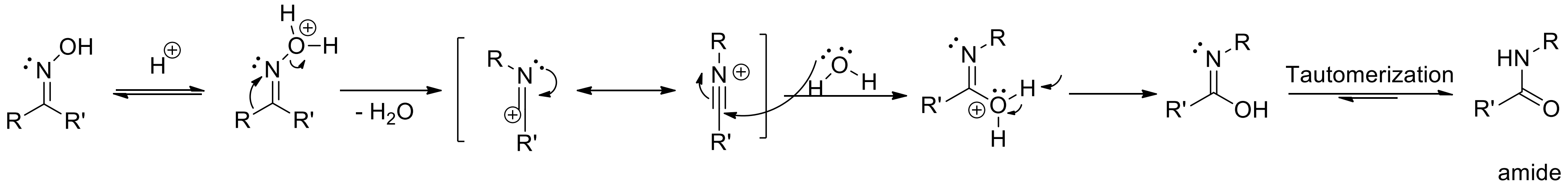


Beckmann rearrangement

Acid-catalyzed rearrangement of oximes to amides.
Cyclic oximes produce lactames



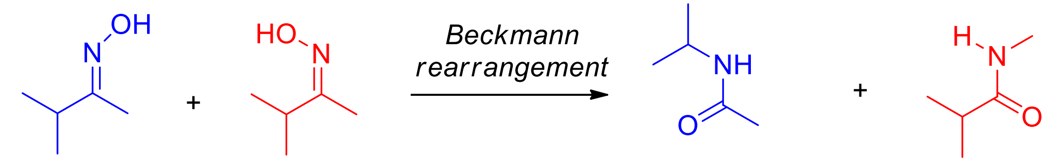
Mechanism:



Important:

The substituent that migrates is the one in *trans*-relation to the N-O bond. This one has the proper orbital overlap allowing migration.
This means that 1,2-shift is concerted with N-O bond cleavage

Example:



trans 86%

cis 14%

mixture of trans and cis isomers

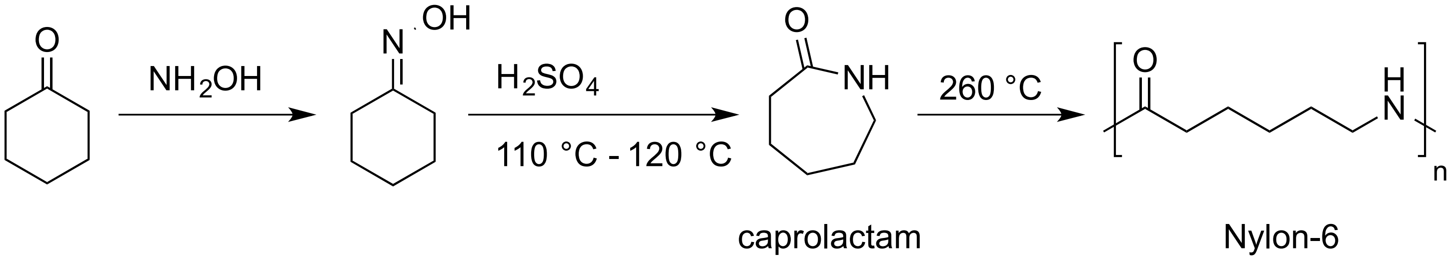
88%

12%

the *trans*-substituent migrates

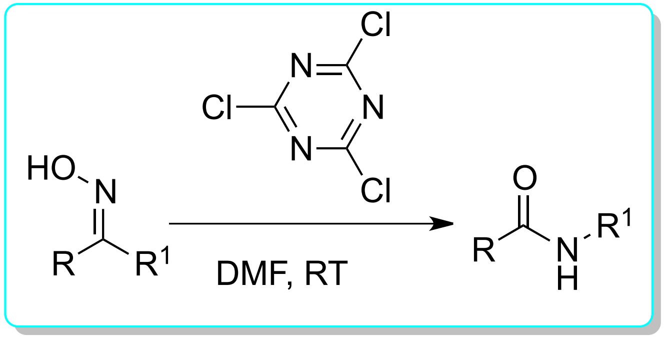
Beckmann rearrangement

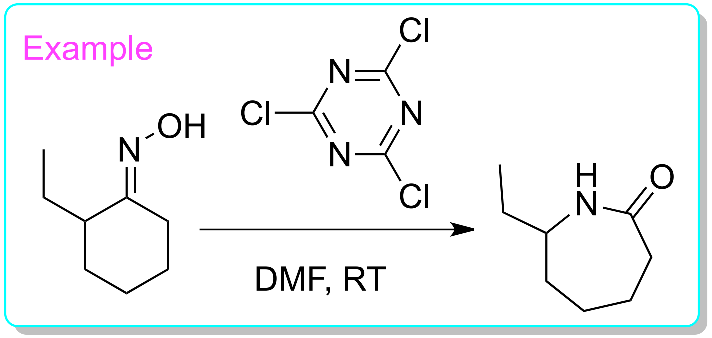
Important application of the Beckmann rearrangement:

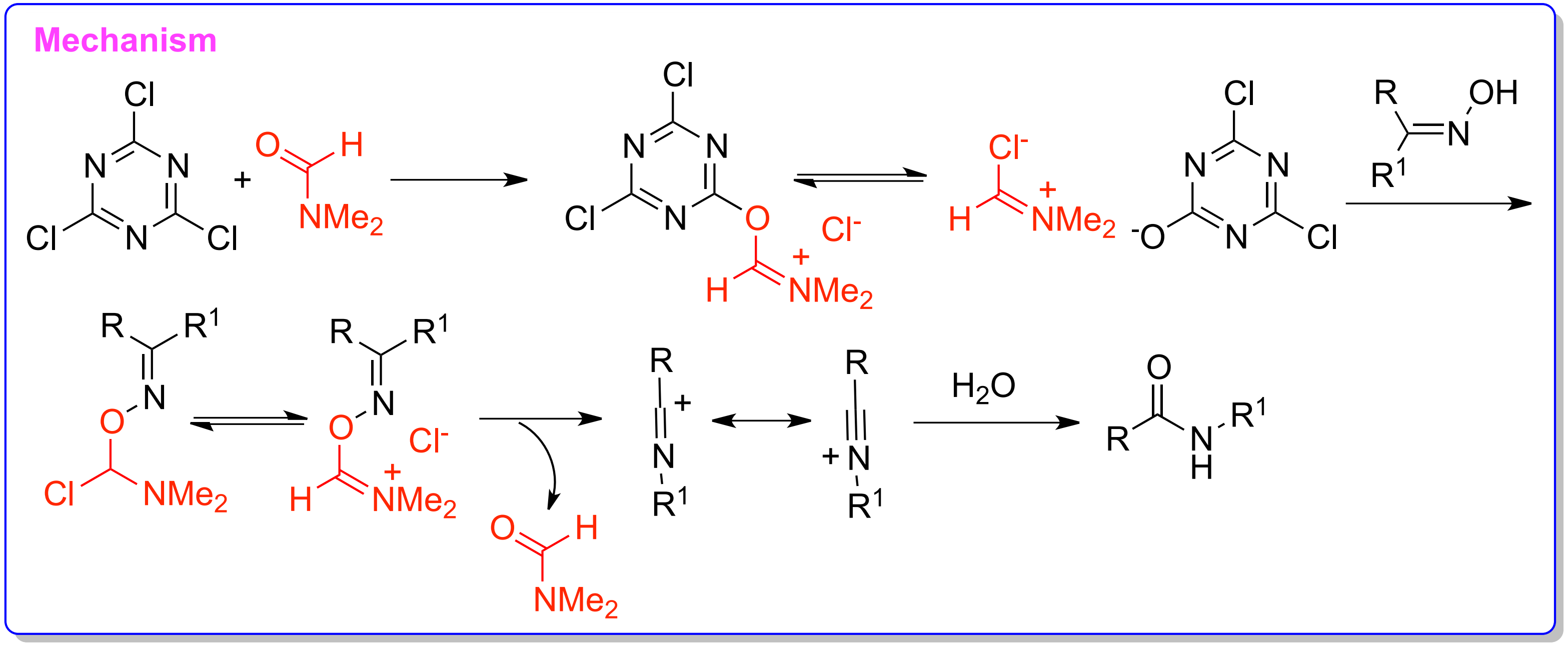


Beckmann rearrangement

Backmann rearrangement under mild conditions:
2,4,6-trichloro[1,3,5]triazine in N,N-dimethylformamide at room temperature

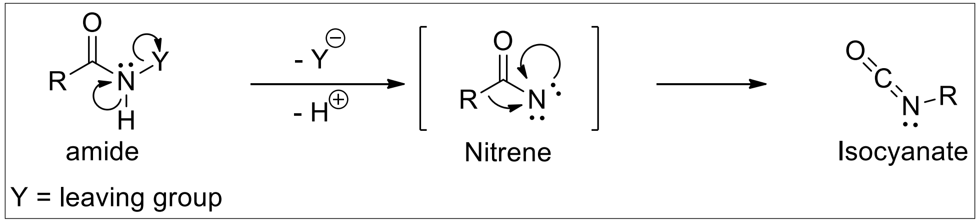






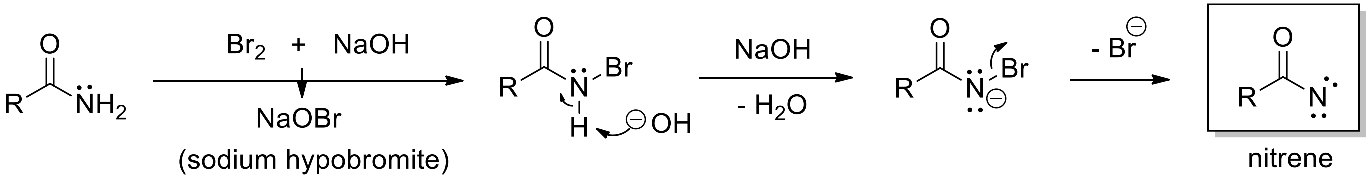
Rearrangement of nitrenoids

General principle:

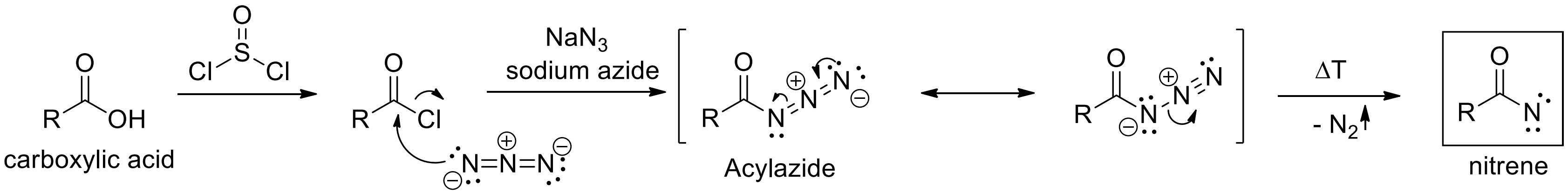


Methods to generate nitrenes:

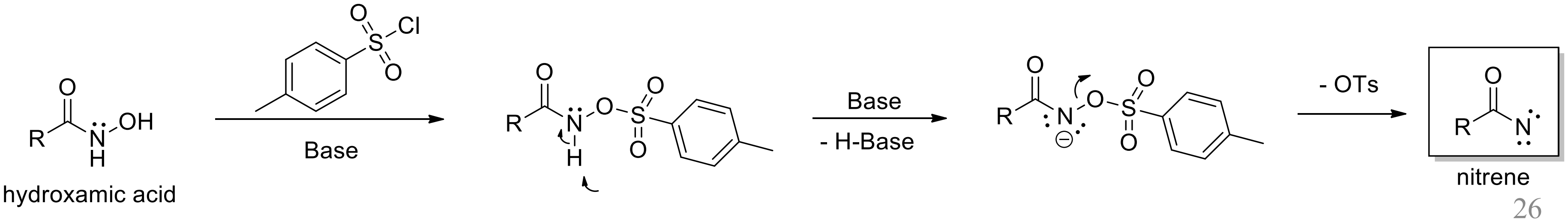
4.4.3.1. Hofmann-Rearrangement



4.4.3.2. Curtius reaction

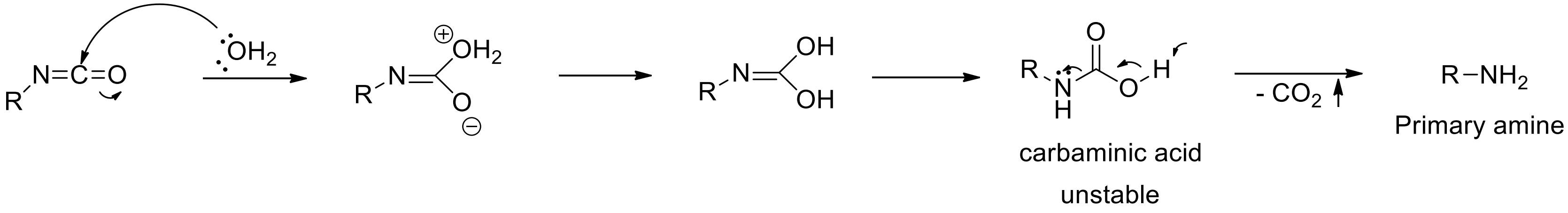


4.4.3.3. Lossen reaction

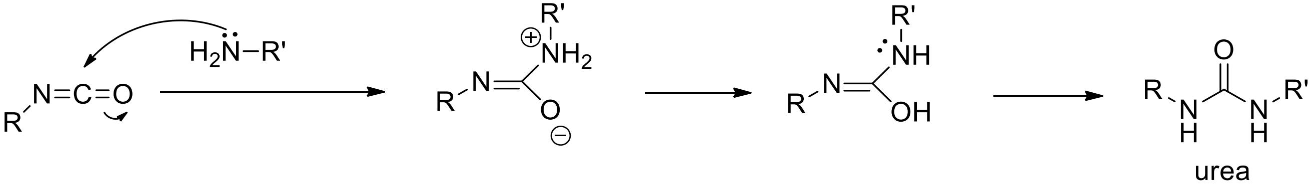


Reaction of Isocyanates (RN=C=O):
The central carbon of the isocyanate is electrophilic

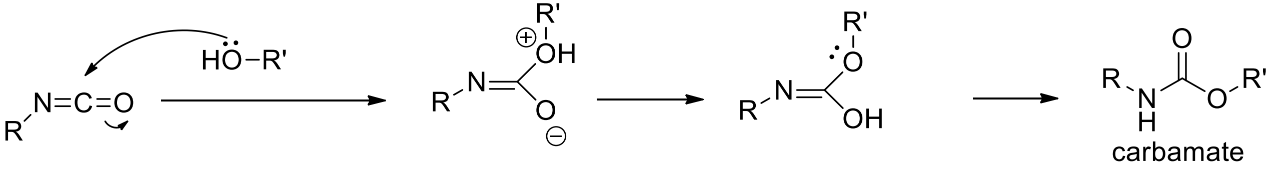
- Formation of primary amine (competitive side reaction: formation of urea) :



- Formation of an urea:



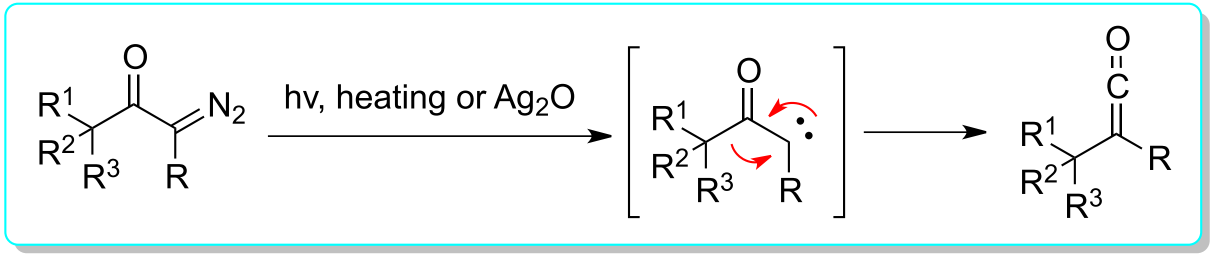
- Formation of a carbamate:



Carbamates are versatile protecting group for amines:
Cbz: R’=Bn; Boc: R’=^{t}Bu

The Wolff rearrangement

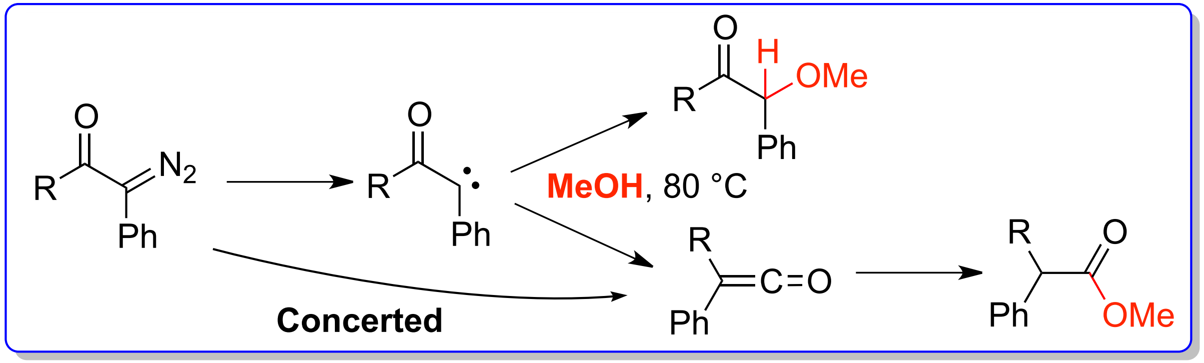
Generation of **ketenes** by 1,2-rearrangement of **α-diazo-ketones.**
The reaction is catalyzed by transition metals (eg silver and copper salt), heating and light. It is generally agreed that a carbene is generated in photochemical reactions while the reaction can be concerted under the thermal conditions



Migration occurs with retention of configuration

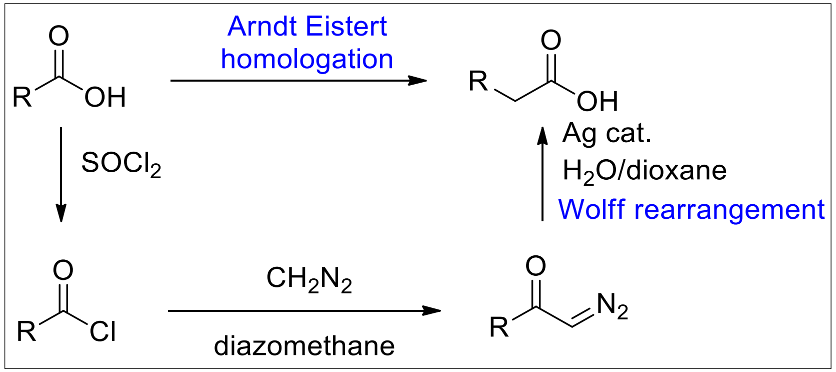
Ketenes like isocyanates are highly electrophilic and is generally in situ trapped by different nucleophiles such as H_2O, amine, etc…

When protic solvent (eg MeOH) was used and if the reaction went through carbene intermediate, O-H insertion could occur leading to different product.



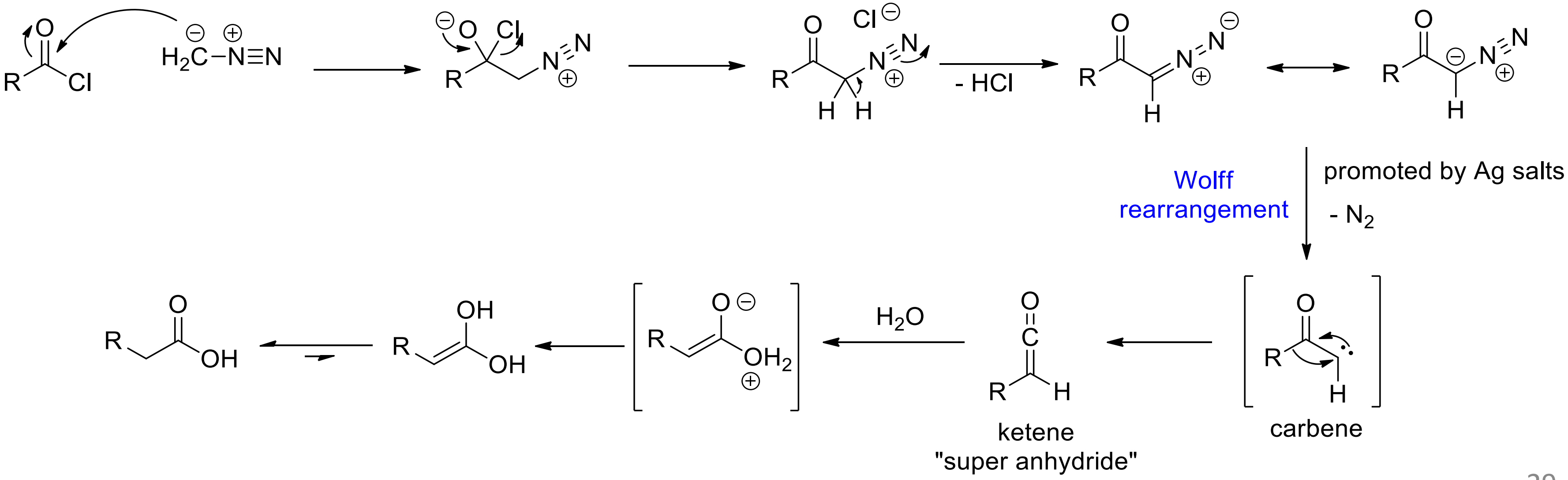
The Wolff rearrangement – Arndt Eistert Homologation

Homologation of a carboxylic acid by one CH_2 unit



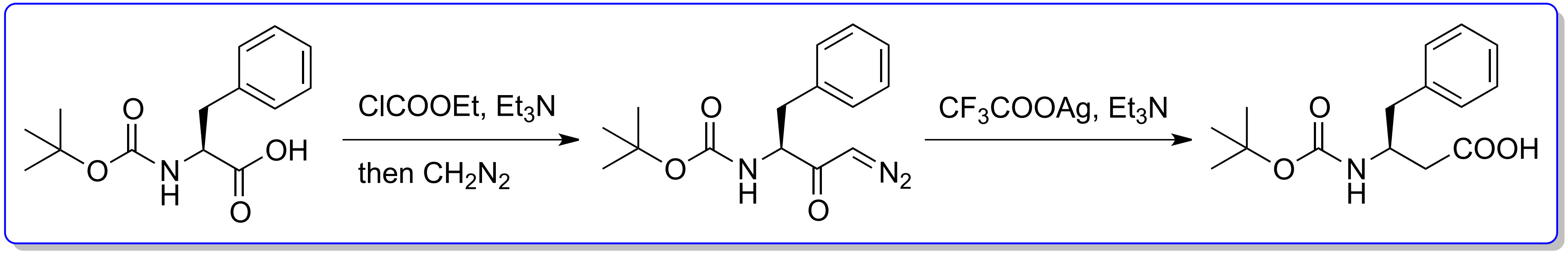
Diazomethane can be made as a solution in Et_2O.
Caution: highly explosive ! Needs polished glassware.

- Stepwise mechanism:



Arndt Eistert Homologation: Application

One important application of Arndt Eistert homologation is the **conversion of α-amino acids to ß-aminoacids**. The absolute configuration of the initial **α**-amino acids is retained after rearrangement.



If amine is used as a nucleophile, an amide bond is formed. This technique has been used for the production of ß-peptides.