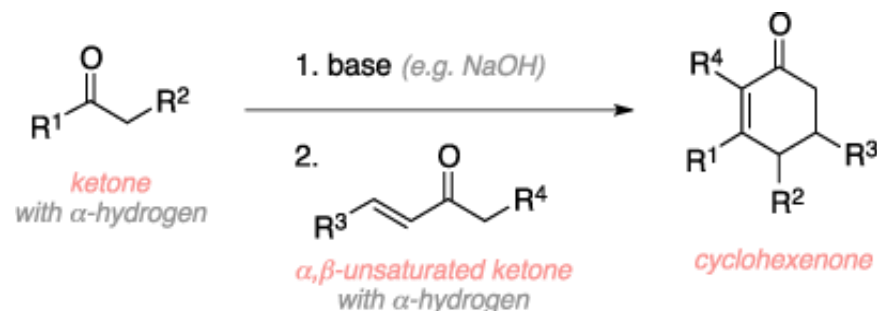
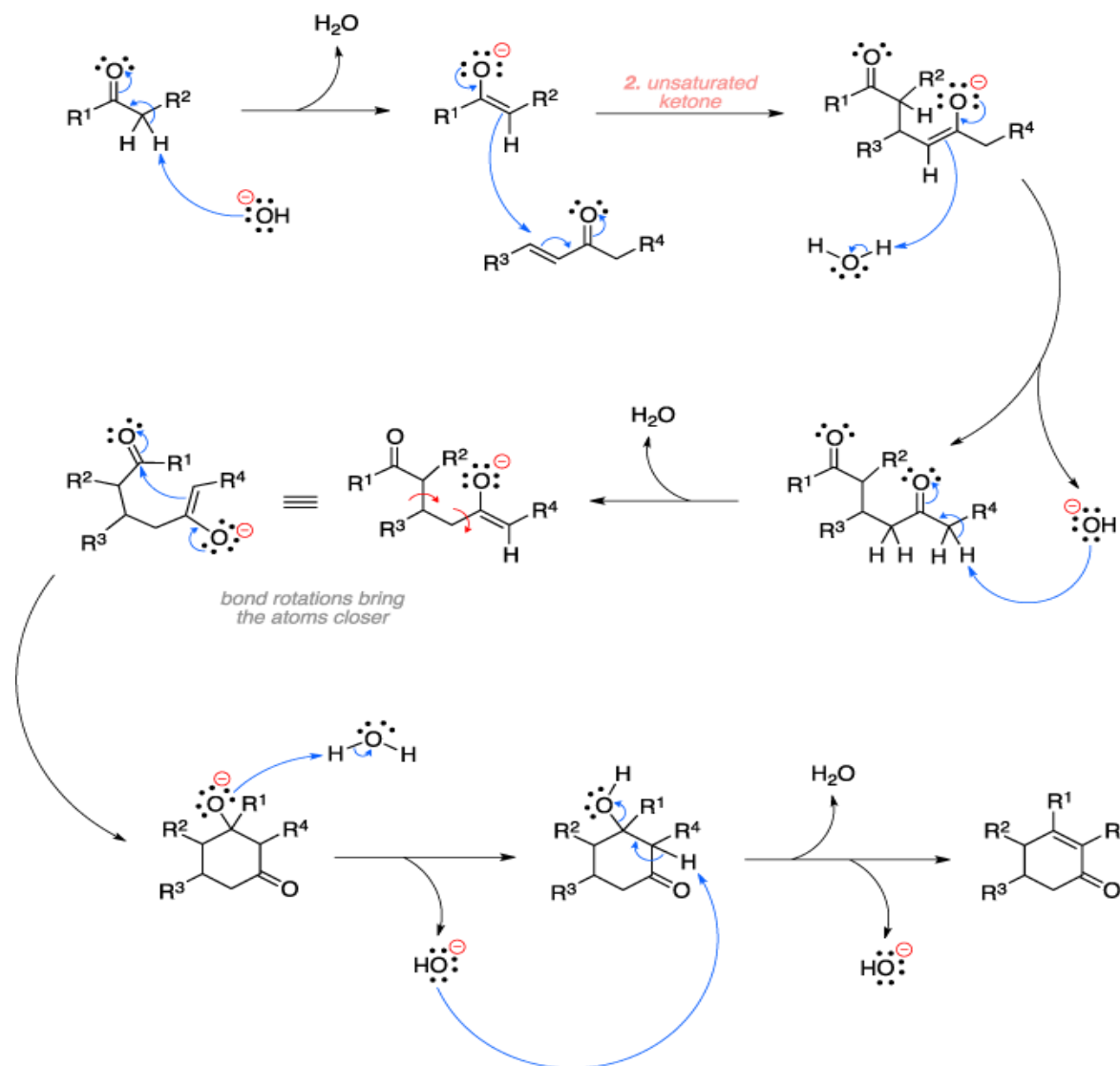


Robinson annulation

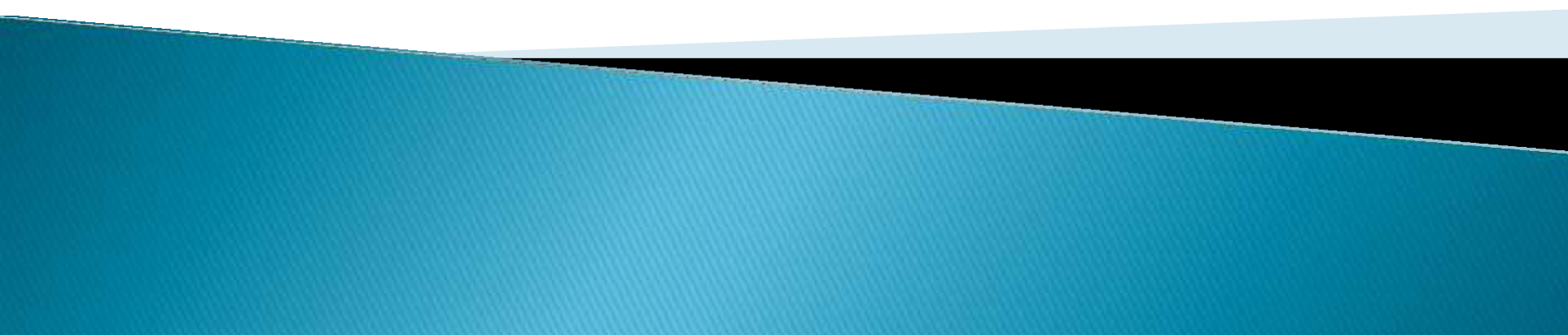


The Robinson annulation is an organic reaction used to convert a ketone and an α,β -unsaturated ketone to a cyclohexenone using base. The mechanism begins with deprotonation with the base of the α -hydrogen of the ketone to form an enolate. The enolate then does a 1,4 addition to the conjugated olefin ([Michael addition](#)), which then abstracts a proton from water to form a diketone. Deprotonation of the other α -hydrogen with base forms another enolate which then does intramolecular attack on the ketone group to give a cyclic alkoxy intermediate. Protonation of the alkoxy and a final elimination step result in the cyclo-hexenone product.

Mechanism

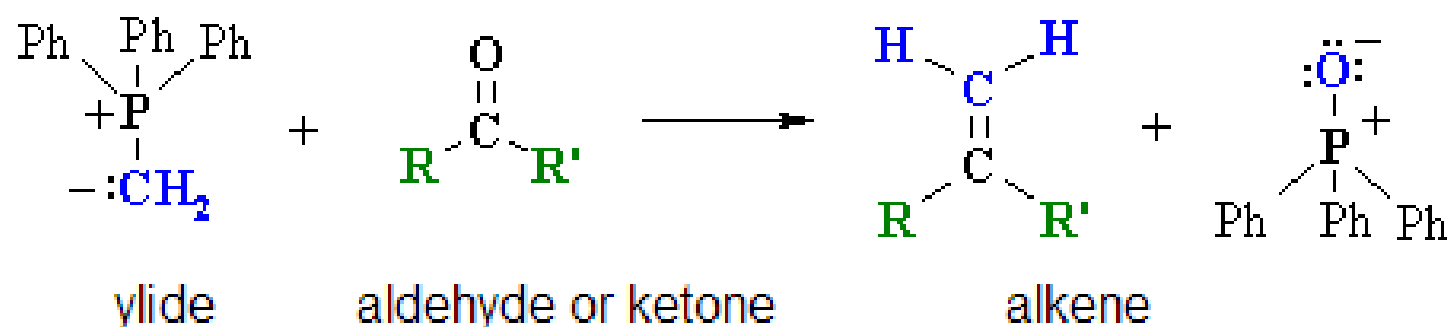


Wittig Reaction




Introduction

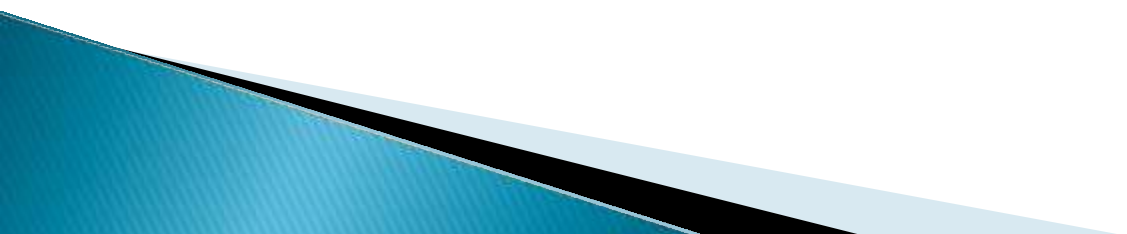
- The Wittig reaction or Wittig olefination is a chemical reaction of an aldehyde or ketone with a triphenyl phosphonium ylide (often called a Wittig reagent) to give an alkene and triphenylphosphine oxide.
- **Reaction type:** Nucleophilic Addition then Elimination



Wittig reaction

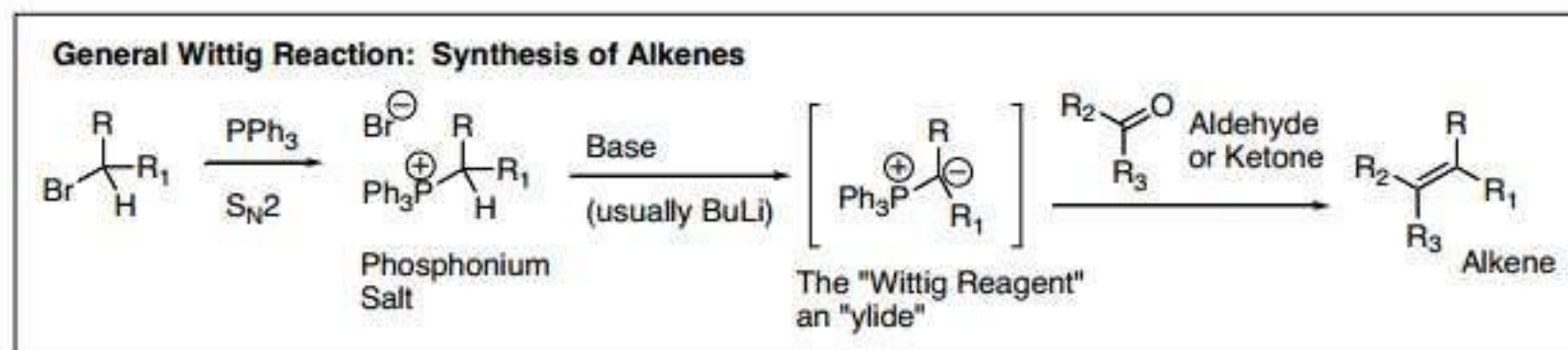
- Alkene formation from carbonyl compounds and phosphonium ylides, proceeding primarily through the proposed betaine and/or oxaphosphetane intermediates. The stereoselectivity can be controlled by the choice of ylide, carbonyl compound, and reaction conditions.
 - When the ylide is replaced with a phosphine oxide carbanion, the reaction is referred to as the **Horner reaction**.
 - When the ylide is replaced with a phosphonate carbanion, the reaction is referred to as the **Horner-Emmons-Wadsworth reaction**.
- 

General wittig reaction: Synthesis of alkenes

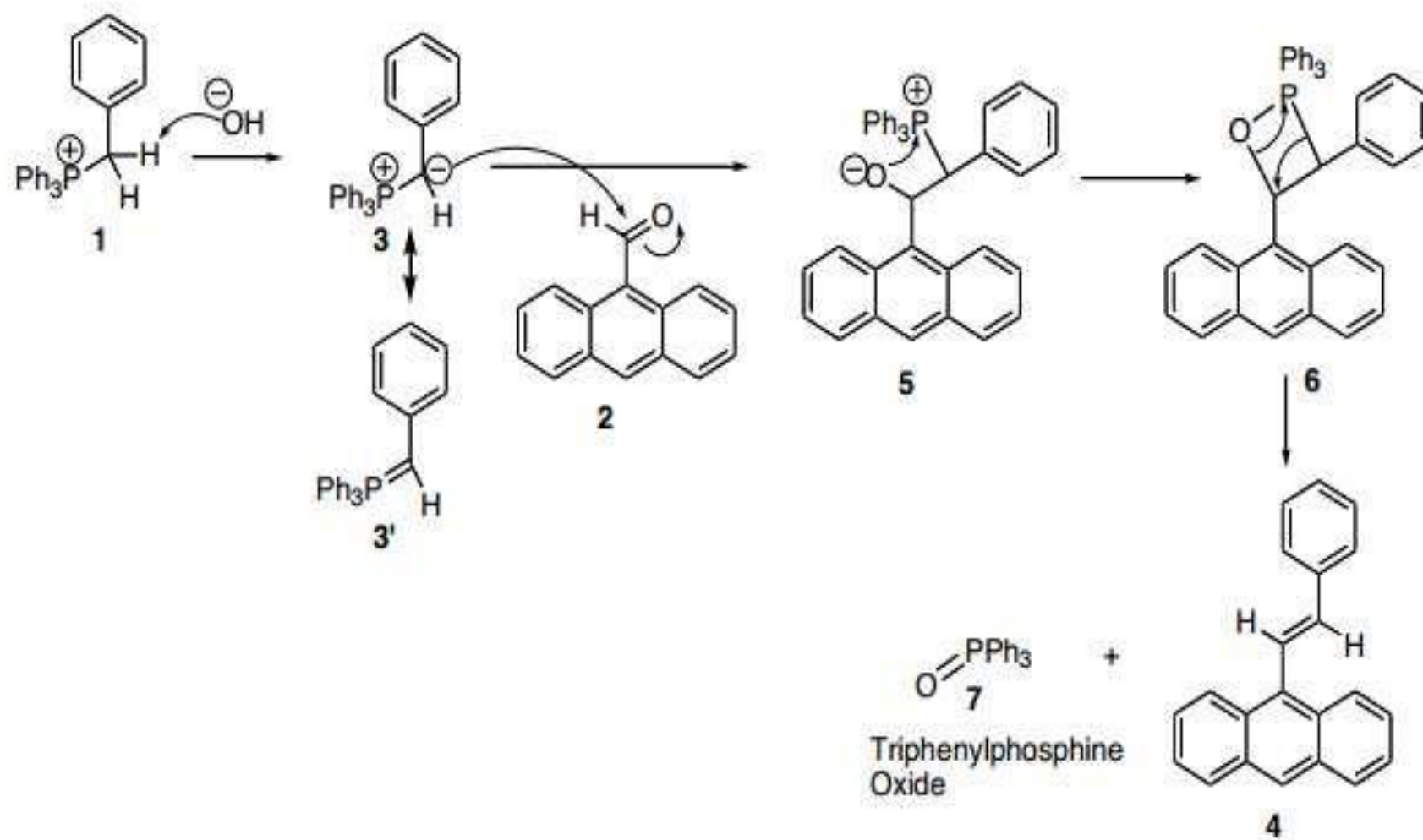
- The “Wittig Reaction” is one of the premier methods for the synthesis of alkenes.
 - It uses a carbonyl compound as an electrophile, which is attacked by a “phosphorus ylide”.
 - The Wittig reaction is nicely complementary to the aldol condensation, in which carbonyl compounds are attacked not by a phosphorus ylide but by an enolate. Aldol condensations always result in “enones”, alkenes with a carbonyl attached.
 - Wittig reactions are more general in that the product carbonyl does not need to have an attached carbonyl.
- 

Mechanism of wittig reaction

- Step:1 The phosphonium ion is deprotonated by base. The positively charged phosphorus atom is a strong electron-withdrawing group, which activates the neighboring carbon atom as a weak acid. For many phosphonium ions, a very strong base (commonly butyl lithium) is required in order to do the deprotonation.

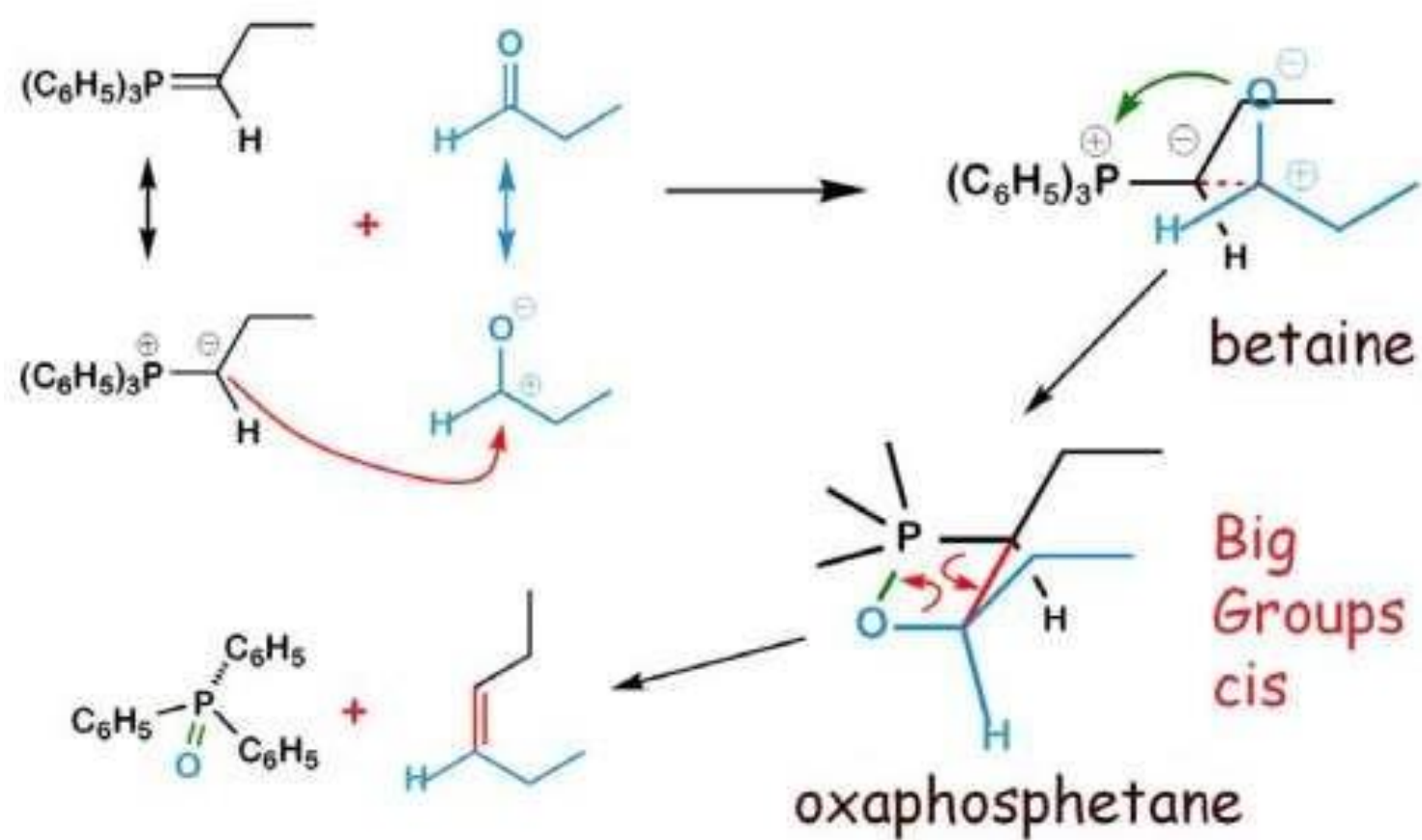


Wittig Mechanism

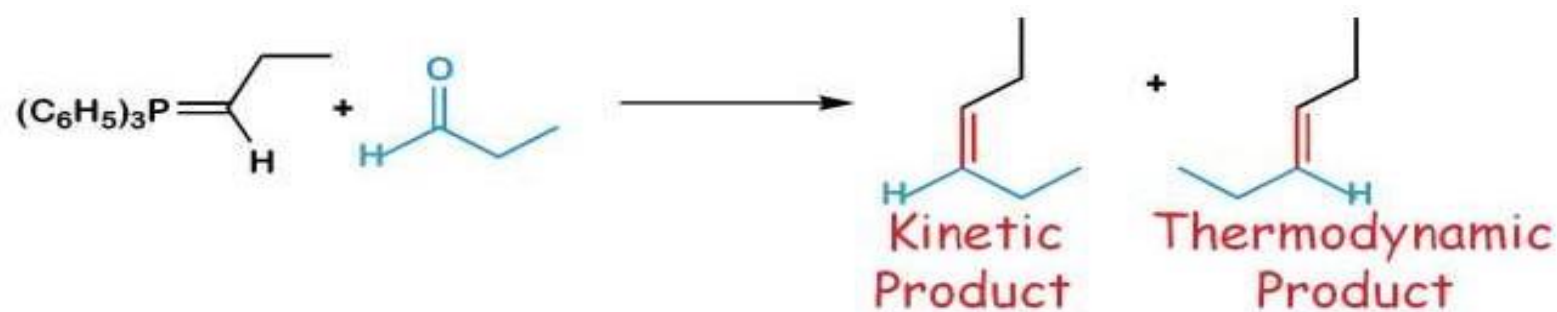


- The first step of the reaction between the ylide and the carbonyl involves the formation of an intermediate called a betaine.
- The carbonyl approaches the ylide carbon turned at a 90° angle with respect to the C-P bond.
-
- This path is the best path in terms of sterics and is also consistent with a detailed molecular orbital analysis of the problem.
- Once the betaine is formed the oxygen atom can swing over and form a new covalent bond to the phosphorous atom.
Phosphorous likes to form five bonds and forms very strong bonds to oxygen in particular.
-
- The result of this new bond is a four membered ring compound called a oxaphosphetane.

Carbonyl comes in turned 90°

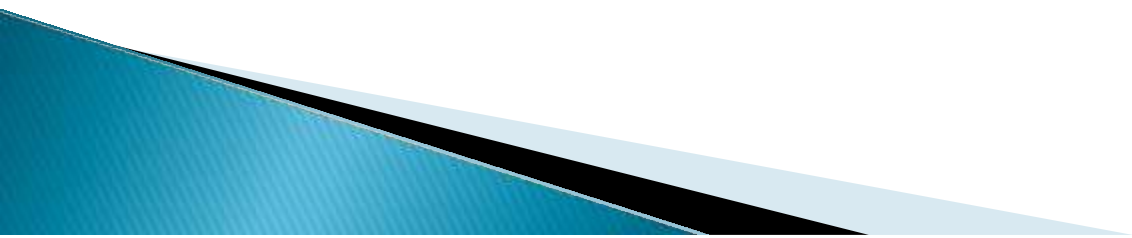


- When the oxaphosphatane forms the stereochemistry of the substituents turns out to be cis. This is due to the chosen path of the carbonyl when the betaine was formed. This means that the favored final alkene product is will be the Z isomer.



Summary

- The Wittig reaction is an important method for the formation of alkenes.
- The double bond forms specifically at the location of the original aldehyde or ketone.
- Ylides are neutral molecules but have +ve and -ve centers on adjacent atoms that are connected by a σ bond.
- The ylide is prepared via a two step process:
 - preparation of a phosphorous ylide.
- An S_N2 reaction between triphenyl phosphine and an alkyl halide followed by treatment with a strong base such as an organolithium reagent.



SHAPIRO REACTION

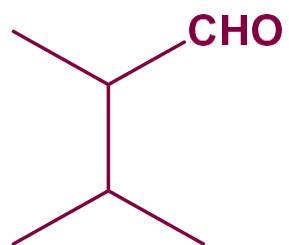
[TOSYL HYDRAZONE DECOMPOSITION]

- Discovered by Robert H. Shapiro in 1967
- Shapiro reaction (1967) involves the conversion of aryl sulfonyl hydrazones of aldehydes and ketones into olefins by reacting with alkyl lithium reagent, grignard reagent, or alkali metal amide.^[1]
- This reaction is carried out at a temperature of -78°C

The reaction similar to Bamford Stevens reaction where bases such as Na, NaOMe, LiH, NaH, NaNH₂, etc. are used.

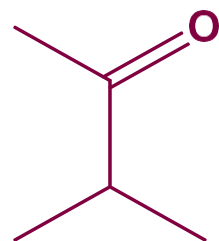
Another major difference between the two reactions is that Shapiro reaction yields less substituted olefins as kinetic products (the product that predominates when the reaction is done at low temperature.) While Bamford Stevens reaction yields more substituted olefins as the thermodynamic product (the product that predominates when the reaction is done at high temperature.)

GENERAL SCHEME



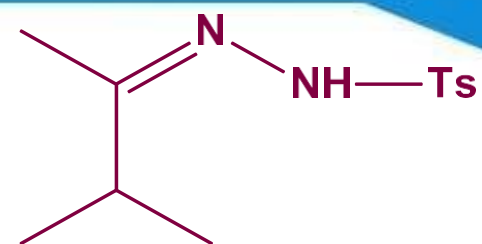
Aldehyde

OR



Ketone

Ts NHNH₂



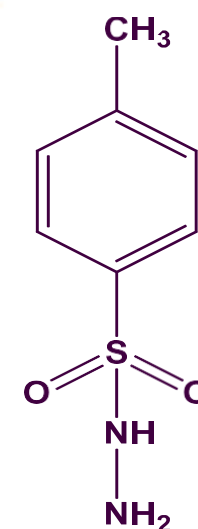
Tosyl hydrazone

(i) BuLi (2 Equivalent)
(ii) E⁺



Alkene

- Tosylhydrazone is a functional group with the general structure $RR'C=NNH-Ts$, where Ts is a tosyl group.
- Tosyl or Toluene sulfonyl group with the molecular formula $CH_3C_6H_4SO_2$
- This is used as “Protecting Group” for alcohols and amines.
- Protecting groups are introduced into a molecule by chemical modification of a functional group to obtain chemoselectivity in a multistep reaction.

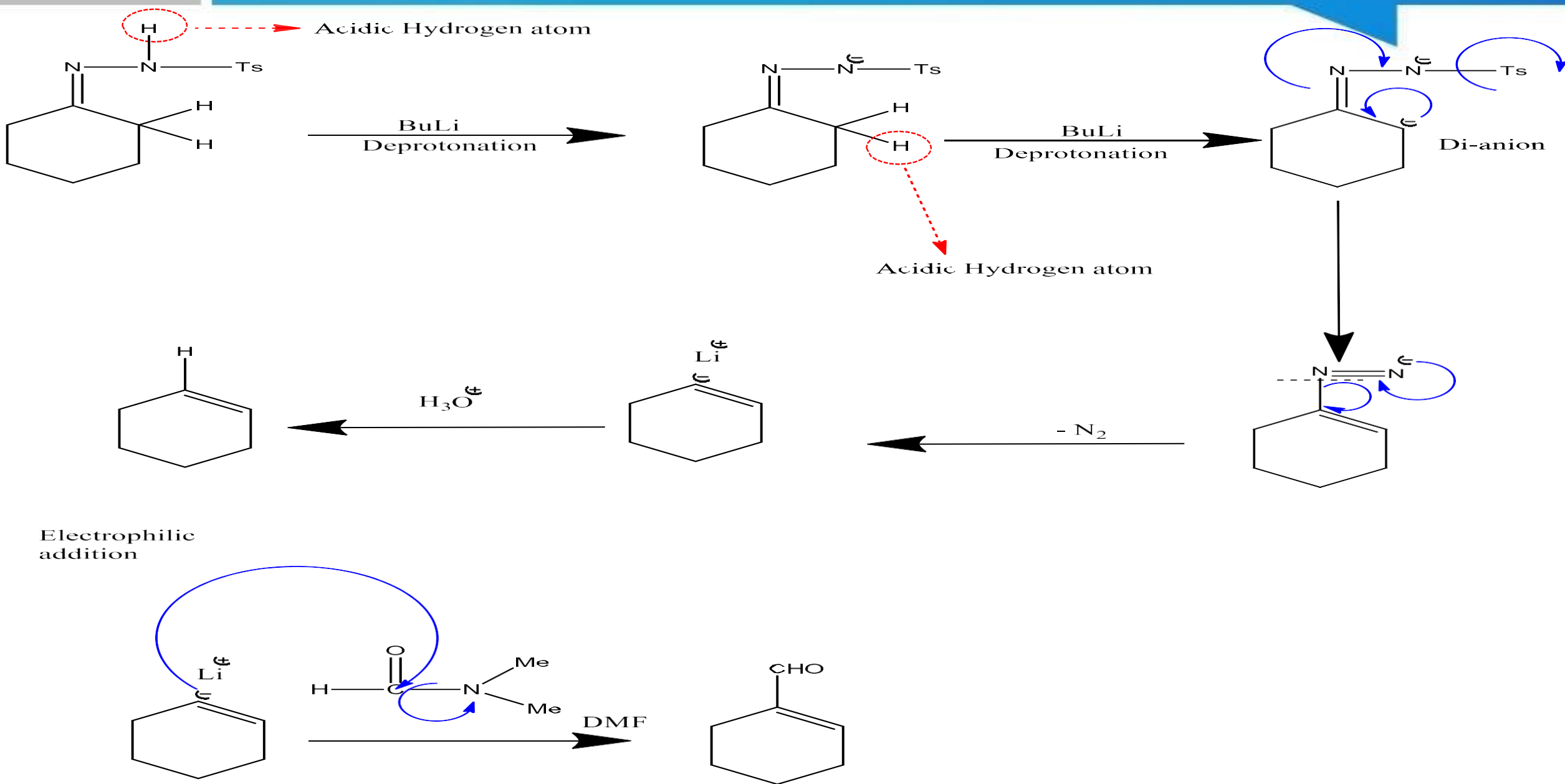


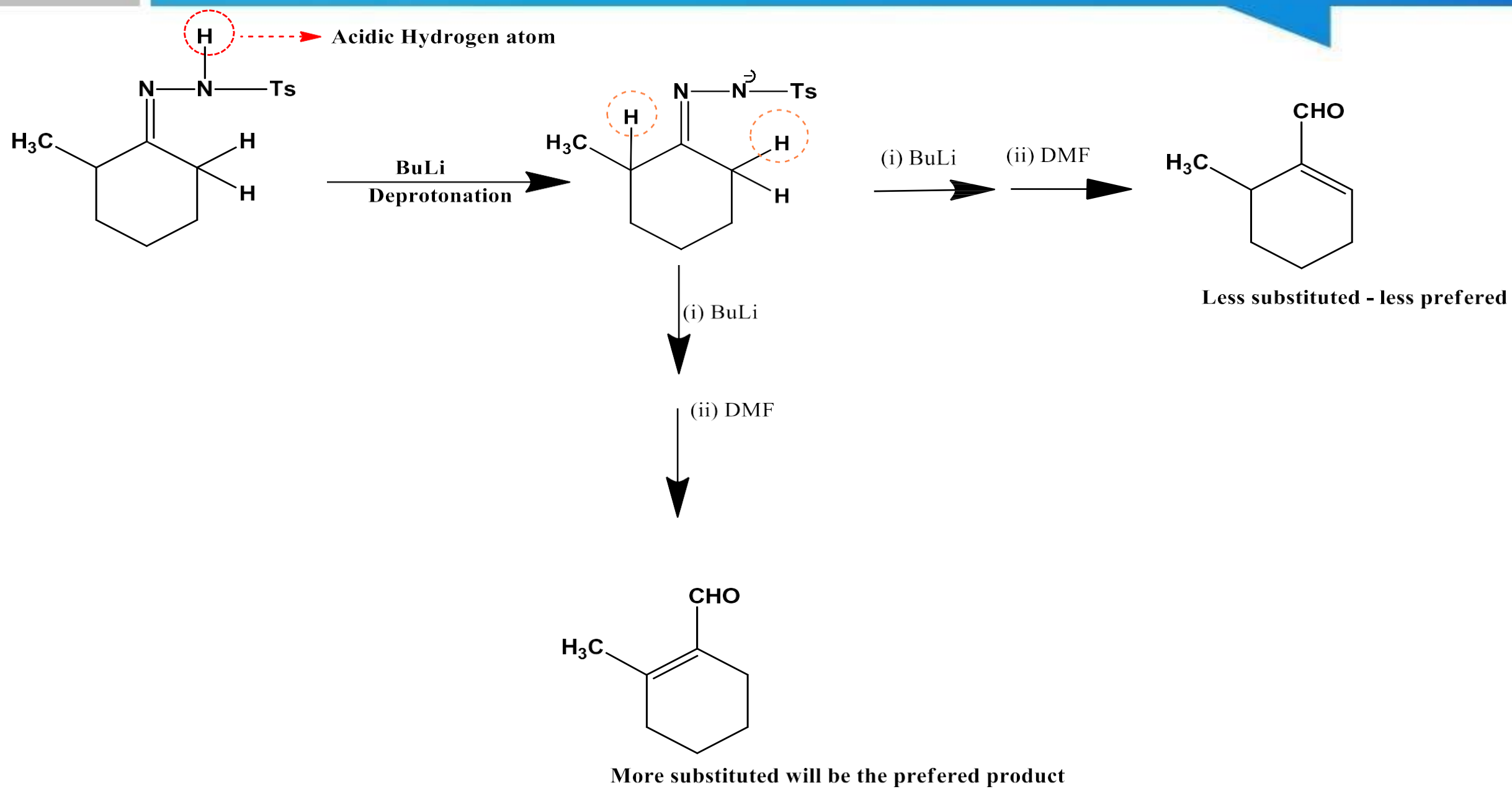
Tosyl Hydrazide

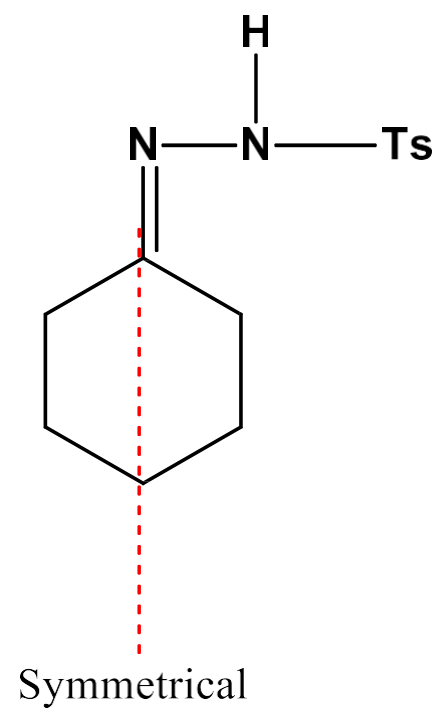
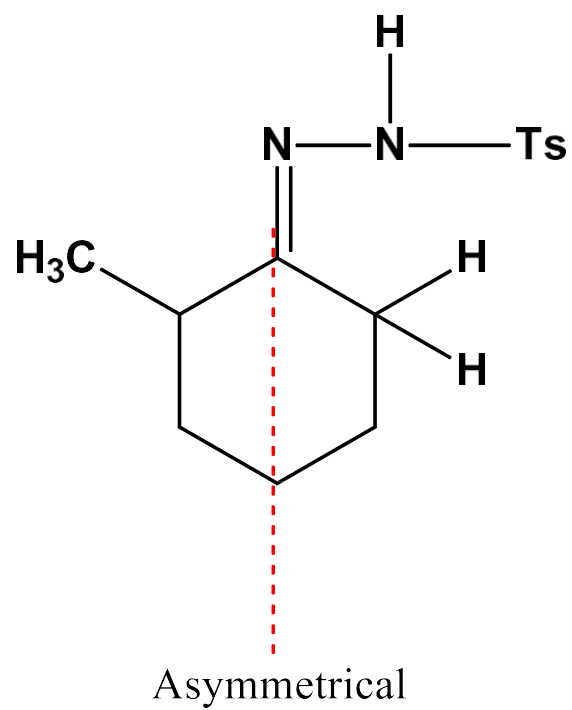
MECHANISM

1. Deprotonation of -NH proton from aryl sulfonyl hydrazone.
2. Second deprotonation adjacent to the hydrazone group to give a dianion.
3. Elimination of toluene sulfinate to form an intermediate (carbanion mechanism).
4. Loss of N_2 to form alkenyl lithium species which is then protonated (treated with an electrophile) to give olefins.^[1]

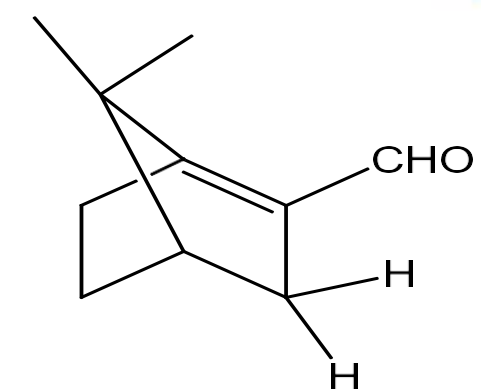
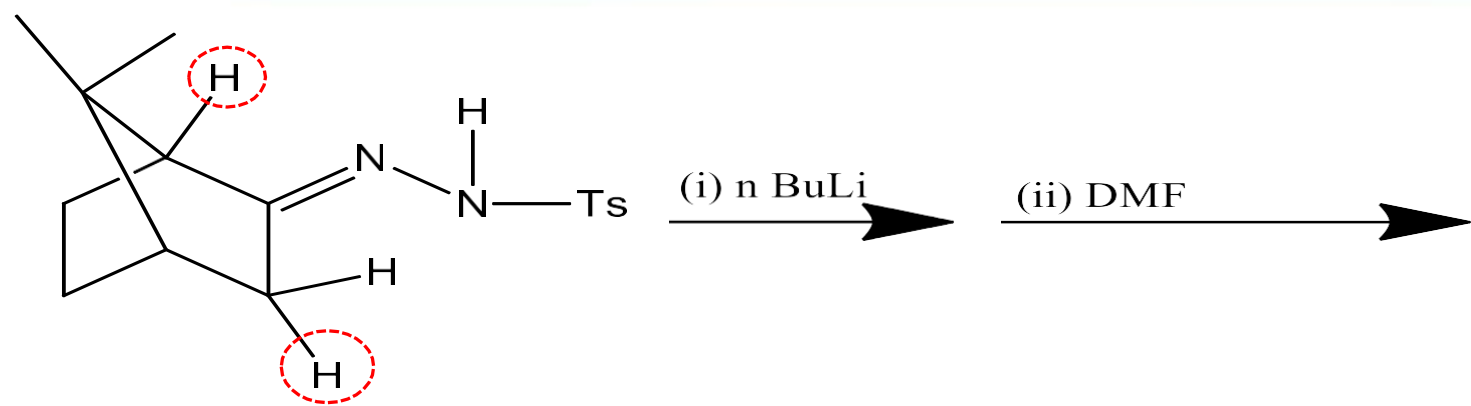
MECHANISM



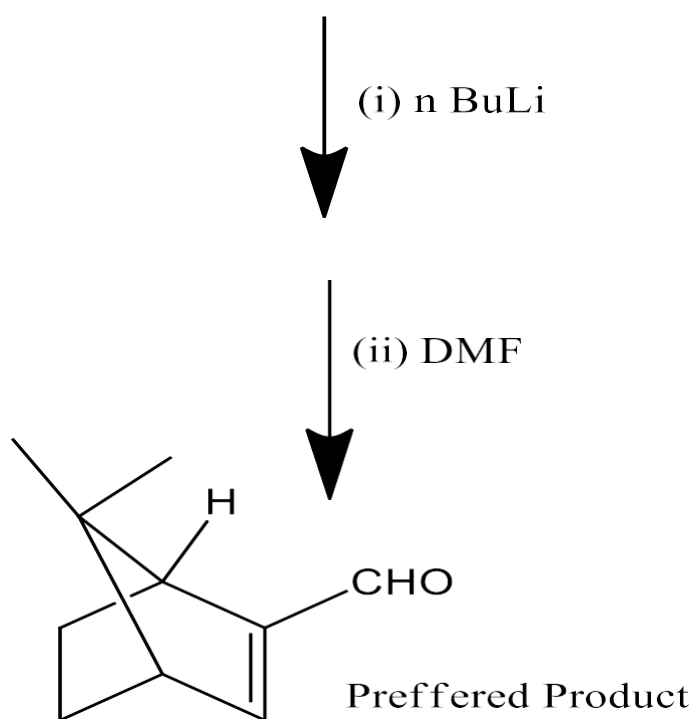


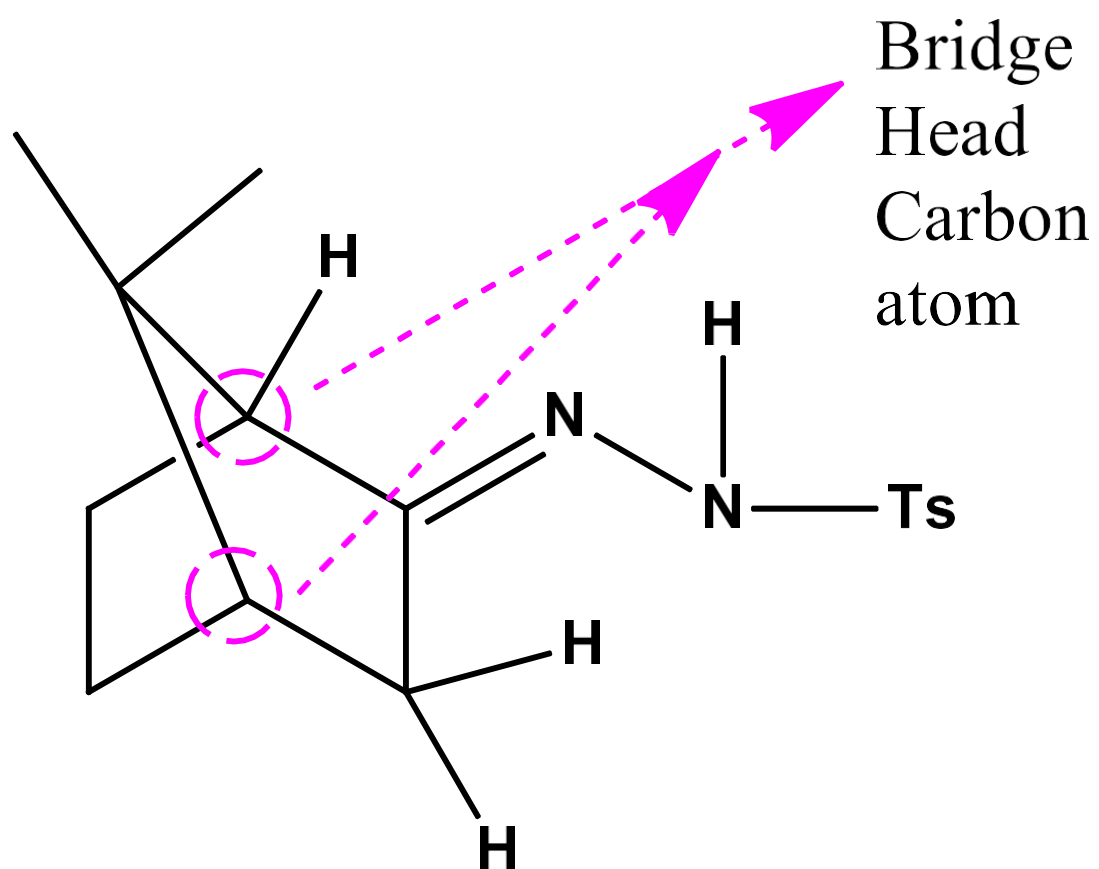


Asymmetrical highly substituted enolates are thermodynamically more stable.



Highly substituted Olefins
 - more stable
 - not formed



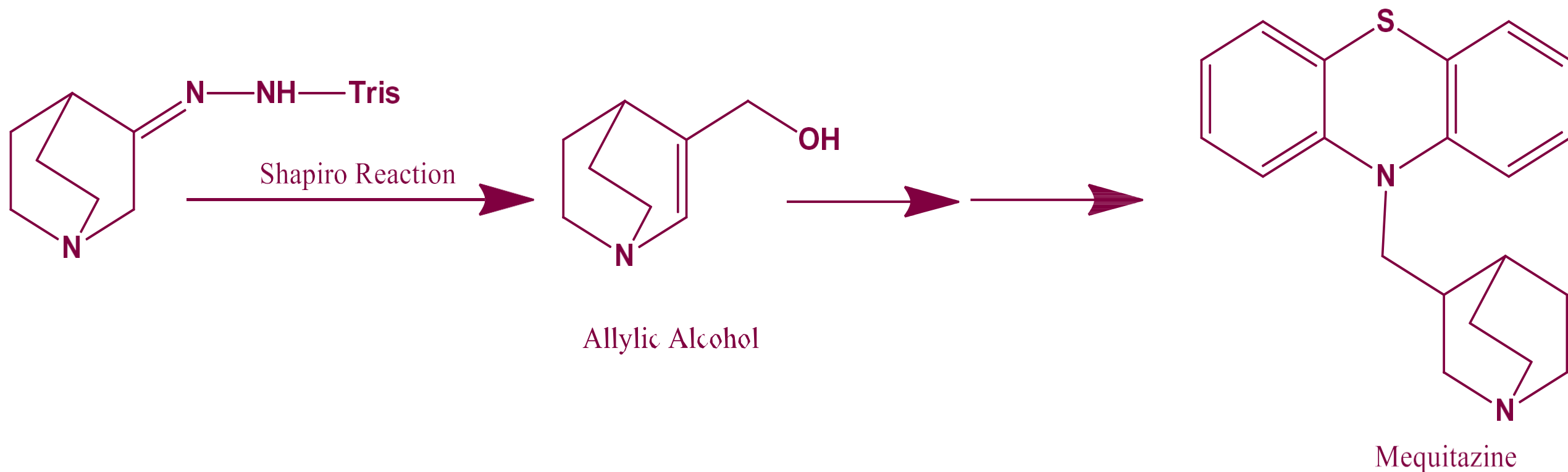


BREDT'S RULE

States that “ a double bond cannot be placed at the bridgehead of a bridgehead ring system, unless the rings are large enough.”

SYNTHETIC APPLICATIONS

- Synthesis of an allylic alcohol, which is an intermediate in the synthesis of Mequitazine, Which is an H1 anti histaminic used to treat allergies and rhinitis.



The background of the slide features a close-up, grayscale image of water droplets on a textured surface. The droplets vary in size and are scattered across the frame. A white rectangular box with rounded corners and a thin brown border is positioned in the upper-left quadrant, containing the title text.

Sonogashira reaction

History Of Sonogashira Coupling Reaction

The Sonogashira cross-coupling reaction was first reported by Kenkichi Sonogashira, Yasuo Tohda, and Nobue Hagiwara in their 1975 publication. It is an extension to the Cassar and Dieck and Heck reactions, which afford the same reaction products, but use harsh reaction conditions, such as high temperature, to do so. Both of these reactions make use of a palladium catalyst to carry out the coupling, while Sonogashira uses both palladium and copper catalysts simultaneously.

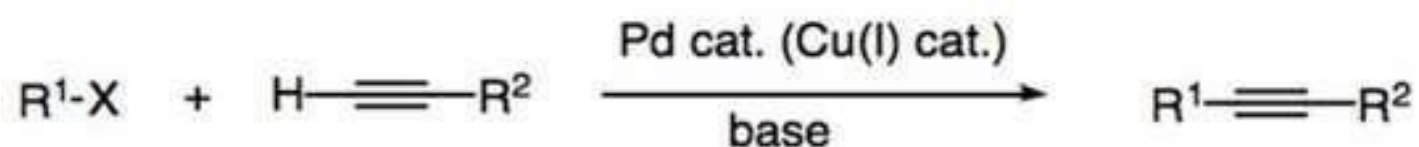


This results in the increased reactivity of the reagents and the ability of the reaction to be carried out at **room temperature**, making the Sonogashira cross-coupling reaction a highly useful reaction, particularly in the alkynylation of aryl and alkenyl halides.

The reaction's remarkable utility can be evidenced by the amount of research still being done on understanding and optimizing its synthetic capabilities.

Reaction

The **Sonogashira reaction** is a **cross-coupling reaction** used in **organic synthesis** to form **carbon-carbon bonds**. It employs a palladium catalyst to form a carbon-carbon bond between a **terminal alkyne** and an **aryl** or **vinyl halide**.



R^1 = aryl, hetaryl, vinyl

R^2 = aryl, hetaryl, alkenyl, alkyl, SiR_3

X = I, Br, Cl, OTf

The Sonogashira cross-coupling reaction has been employed in a wide variety of areas, due to its usefulness in the formation of carbon-carbon bonds.

The reaction can be carried out under mild conditions.

Like at room temperature, in aqueous media, and with a mild base, which has allowed for the use of the Sonogashira cross-coupling reaction in the synthesis of complex molecules.

Catalysts Of Reaction

Typically, **two** catalysts are needed for this reaction:

1. Zerovalent palladium complex

Examples of such palladium catalysts are $\text{Pd(PPh}_3)_4$, $\text{Pd(PPh}_3)_2\text{Cl}_2$.

Bidentate ligand catalysts, such as Pd(dppe)Cl , Pd(dppp)Cl_2 , and Pd(dppf)Cl_2 have also been used.

The drawback to such catalysts is the need for high loadings of palladium (up to 5 mol %), along with a larger amount of a copper co-catalyst.

Pd^{II} is often employed as a pre-catalyst since it exhibits greater stability than Pd^0 over an extended period of time.

The Pd^{II} catalyst is reduced to Pd^0 in the reaction mixture by either an amine, a phosphine ligand, or a reactant, allowing the reaction to proceed.

2. Halide salt of copper(I)

Such as **copper iodide**, react with the terminal alkyne and produce a copper(I) acetylide, which acts as an activated species for the coupling reactions.

Cu(I) is a co-catalyst in the reaction, and is used to increase the rate of the reaction.

Reaction Conditions And Solvents

It have already known that the reaction is carried out under **mild conditions** like at **room temperature**, **in aqueous media**, and with a **mild base**.

The cross-coupling is carried out at room temperature with a base, typically an amine, such as **diethylamine**.

Diethyl amine that also acts as the solvent. The reaction medium must be basic to **neutralize the hydrogen halide** produced as the byproduct of this coupling reaction, so **alkylamine** compounds such as **triethylamine** and **diethylamine** are sometimes used as **solvents**.

DMF(Dimethylformamide) or ether can also be used as solvent. Other bases such as potassium carbonate or cesium carbonate are occasionally used.

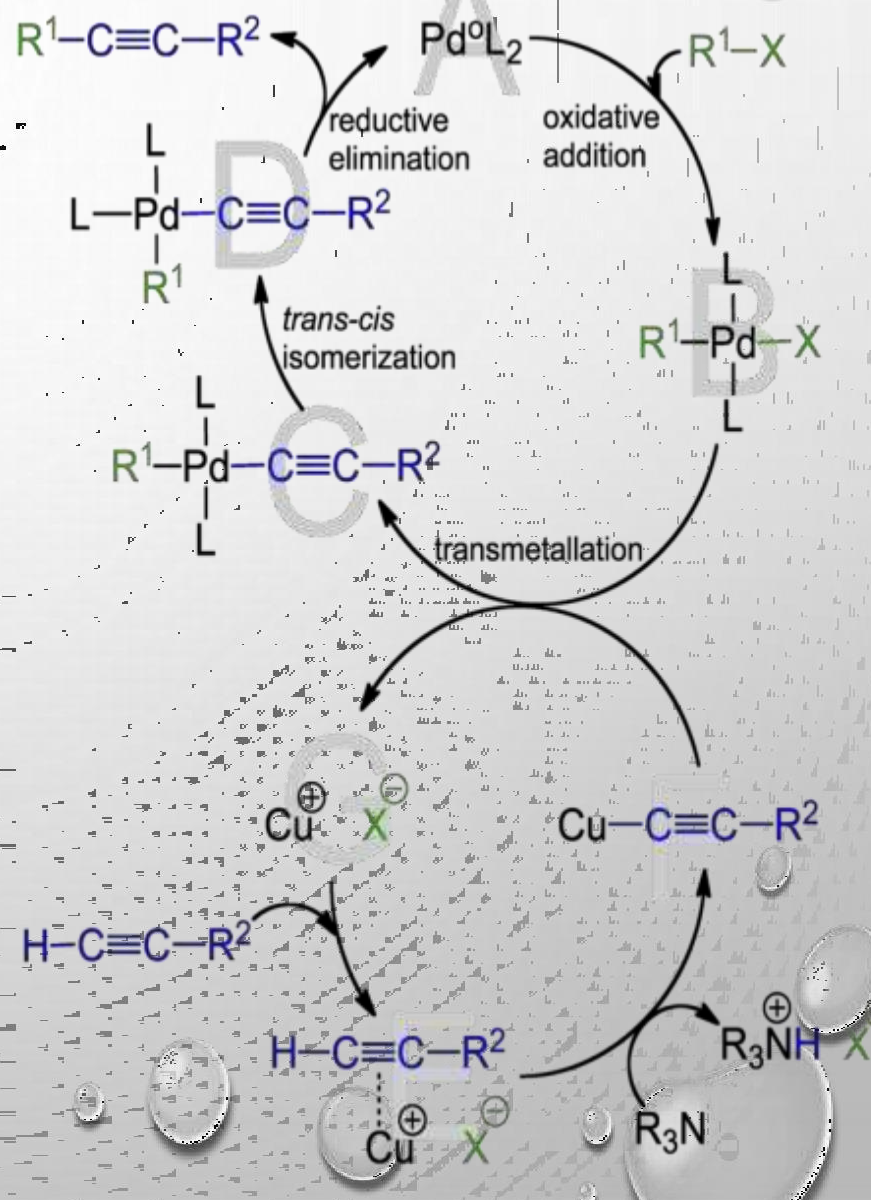
Conditions are formally needed for Sonogashira coupling reactions because the palladium(0) complexes are unstable in the air, and oxygen promotes the formation of homocoupled acetylenes.

Recently, development of air-stable organopalladium catalysts enable this reaction to be conducted in the ambient atmosphere.

Mechanism

The palladium cycle

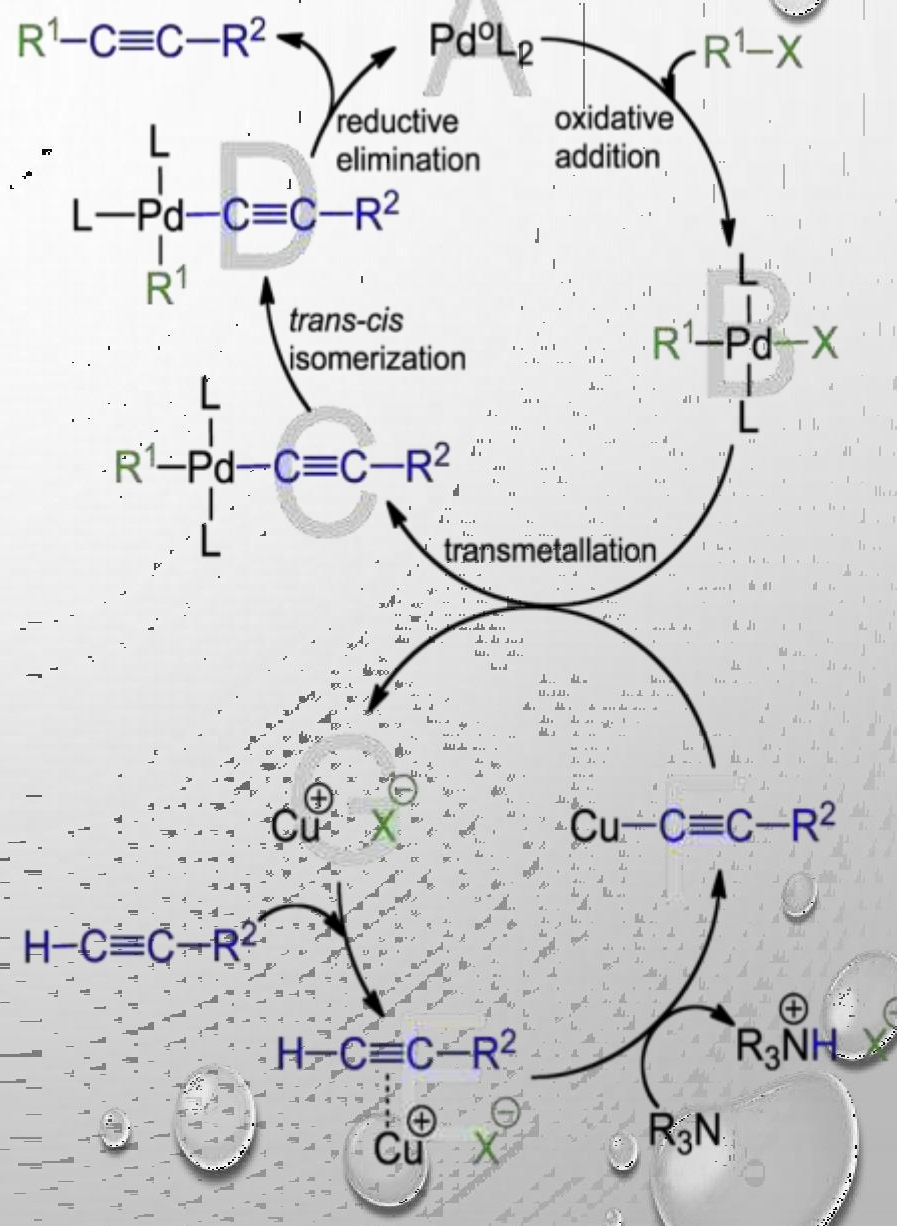
- 1) An inactive palladium Pd^{II} catalyst is activated by a reduction to the Pd^0 compound.
- 2) The active palladium catalyst is the 14 electron compound Pd^0L_2 , complex **A**, which reacts with the aryl or vinyl halide in an oxidative addition to produce a Pd^{II} intermediate, complex **B**. This step is believed to be the rate-limiting step of the reaction.



3) Complex **B** reacts in a transmetallation with the copper acetylide, complex **F**, which is produced in the copper cycle, to give complex **C**, expelling the copper halide, complex **G**.

4) Both organic ligands are trans oriented and convert to cis in a trans-cis isomerization to produce complex **D**.

5) In the final step, complex **D** undergoes reductive elimination to produce the alkyne, with the

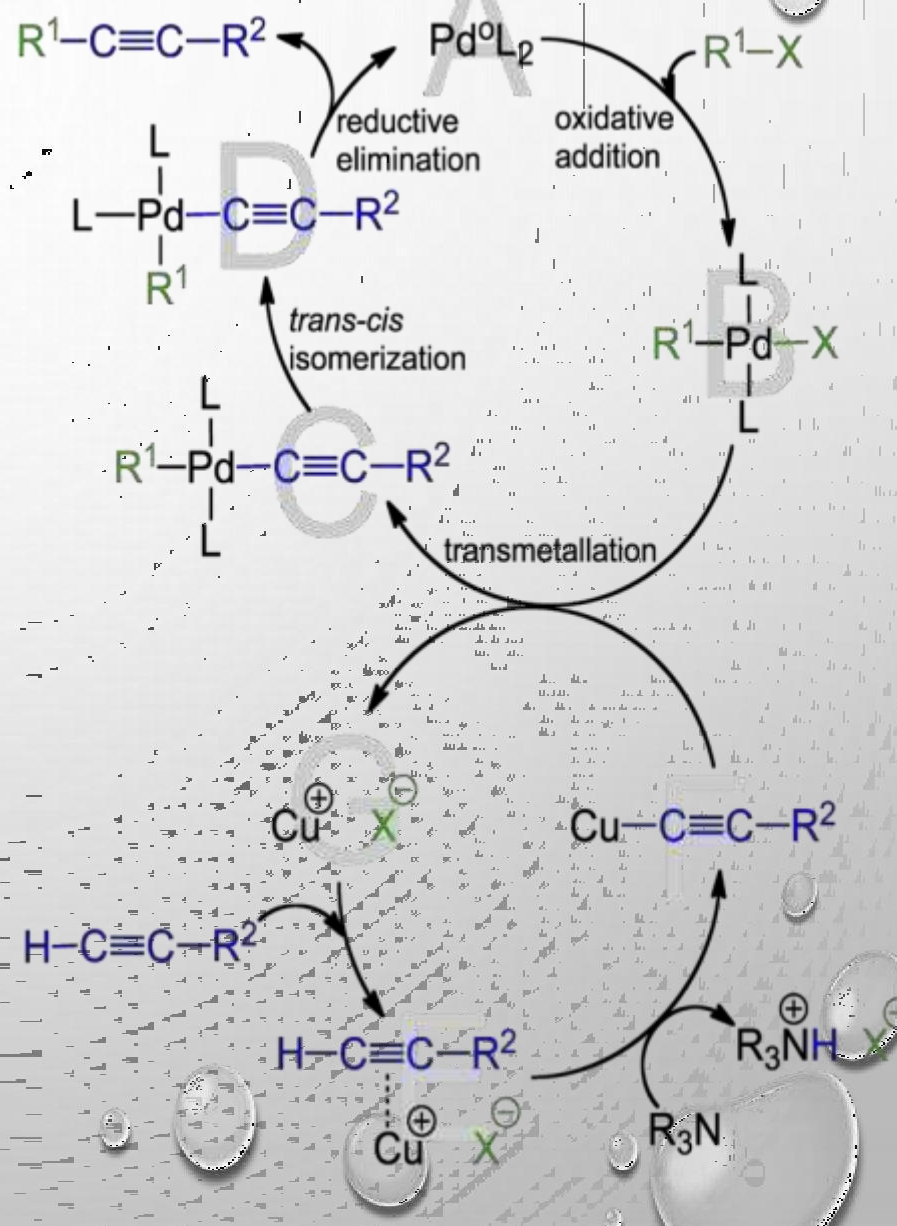


regeneration of the palladium catalyst.

The copper cycle

1) It is suggested that the presence of base results in the formation of a pi-alkyne complex, complex **E**, which makes the terminal proton on the alkyne more acidic, leading to the formation of the copper acetylide, compound **F**.

2) Compound **F** continues to react with the palladium intermediate **B**, with regeneration of the copper halide, **G**.



Complications

Due to the crucial role of base, specific amines must be added in excess or as solvent for the reaction to proceed. It has been discovered that secondary amines such as **piperidine**, **morpholine**, or **diisopropylamine** in particular can react efficiently and reversibly with $\text{trans-RPdX(PPh}_3)_2$ complexes by substituting one PPh_3 ligand.

The equilibrium constant of this reaction is dependent on R, X, a factor for basicity, and the amine's steric hindrance.

Applications

Its applications include **pharmaceuticals**, **natural products**, **organic materials**, and **nanomaterials**.

Specific examples include its use in the synthesis of **tazarotene**, which is a treatment for psoriasis and acne, and in the preparation of **SIB-1508Y**, also known as **Altinicline**, a nicotinic receptor agonist.

It has also some synthetic application like **Alkynylation reactions**, **enynes** and **enediynes** etc.

Limitations

While a copper co-catalyst is added to the reaction to increase reactivity, the presence of copper can result in the formation of alkyne dimers. This leads to what is known as the Glaser coupling reaction, which is an undesired formation of **homocoupling** products of acetylene derivatives upon oxidation. As a result, when running a Sonogashira reaction with a copper co-catalyst, it is necessary to run the reaction in an **inert atmosphere** to avoid the unwanted dimerization.

Now a days **Copper-free variations** to the Sonogashira reaction have been developed to avoid the formation of the homocoupling products.

HYDROBORATION

Definition:

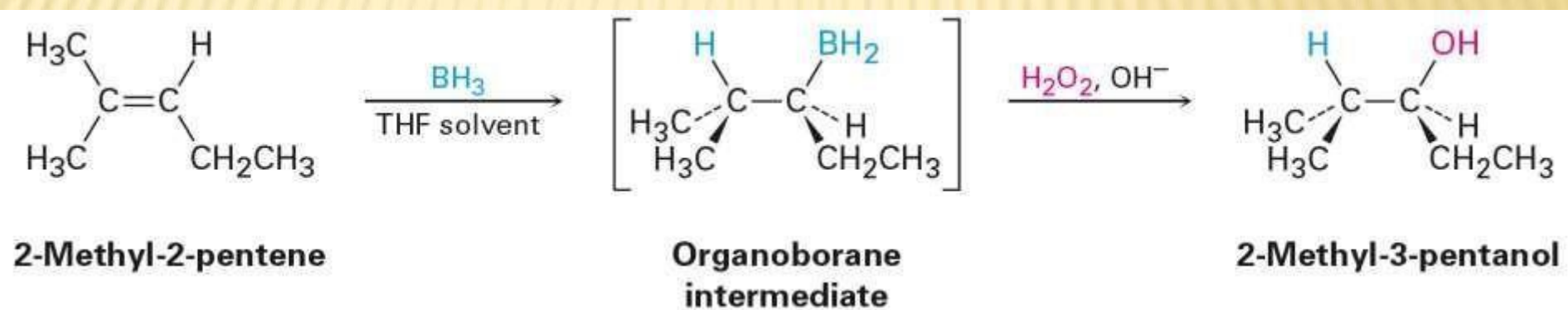
hydroboration refers to the addition of a hydrogen-boron bond to C-C, C-N, and C-O double bonds, as well as C-C triple bonds. This chemical reaction is useful in the organic synthesis of organic compounds

ADDITION OF WATER TO ALKENES: HYDROBORATION

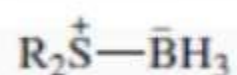
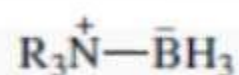
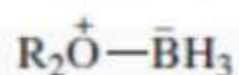
Herbert Brown (HB) invented hydroboration (HB) □

Borane (BH_3) is electron deficient and is a Lewis acid □

Borane adds to an alkene to give an organoborane □

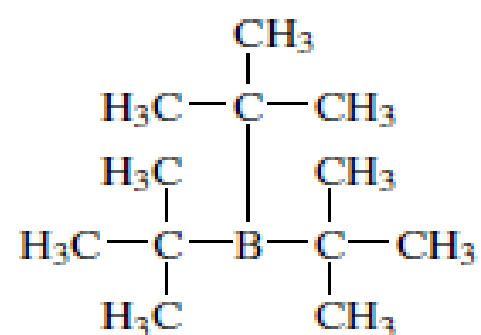


Borane, BH_3 \cdot is an avid electron-pair acceptor, having only six valence electrons on boron. Pure borane exists as a dimer in which two hydrogen's bridge the borons. In aprotic solvents that can act as electron donors such as ethers, tertiary amines, and sulfides, borane forms Lewis acid-base adducts.

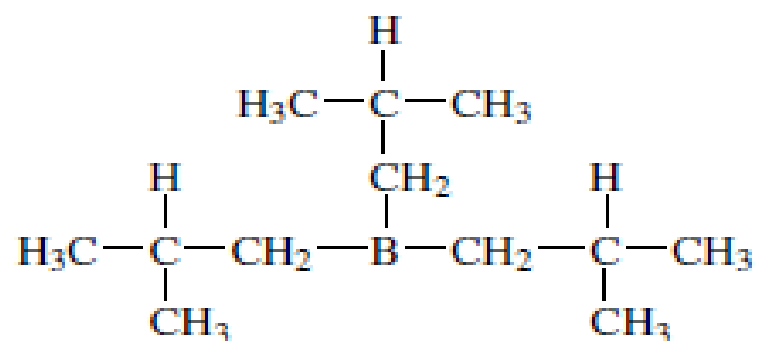


Borane dissolved in THF or dimethyl sulfide undergoes addition reactions rapidly with most alkenes. This reaction, which is known as hydroboration

Hydroboration is usually done under conditions in which the borane eventually reacts with three alkenes molecules to give a trialkyl borane. The second and third alkyl groups would result in severe steric repulsion if the boron were added at the internal carbon.

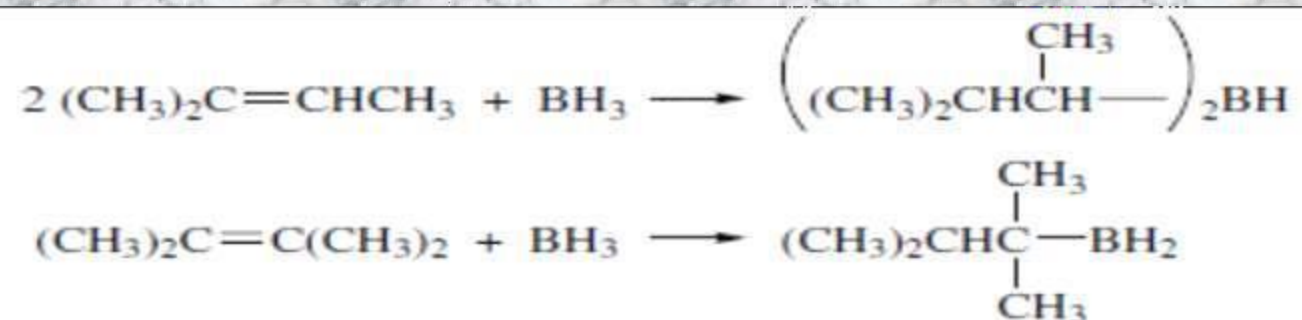


severe nonbonded
repulsions



nonbonded repulsions
reduced

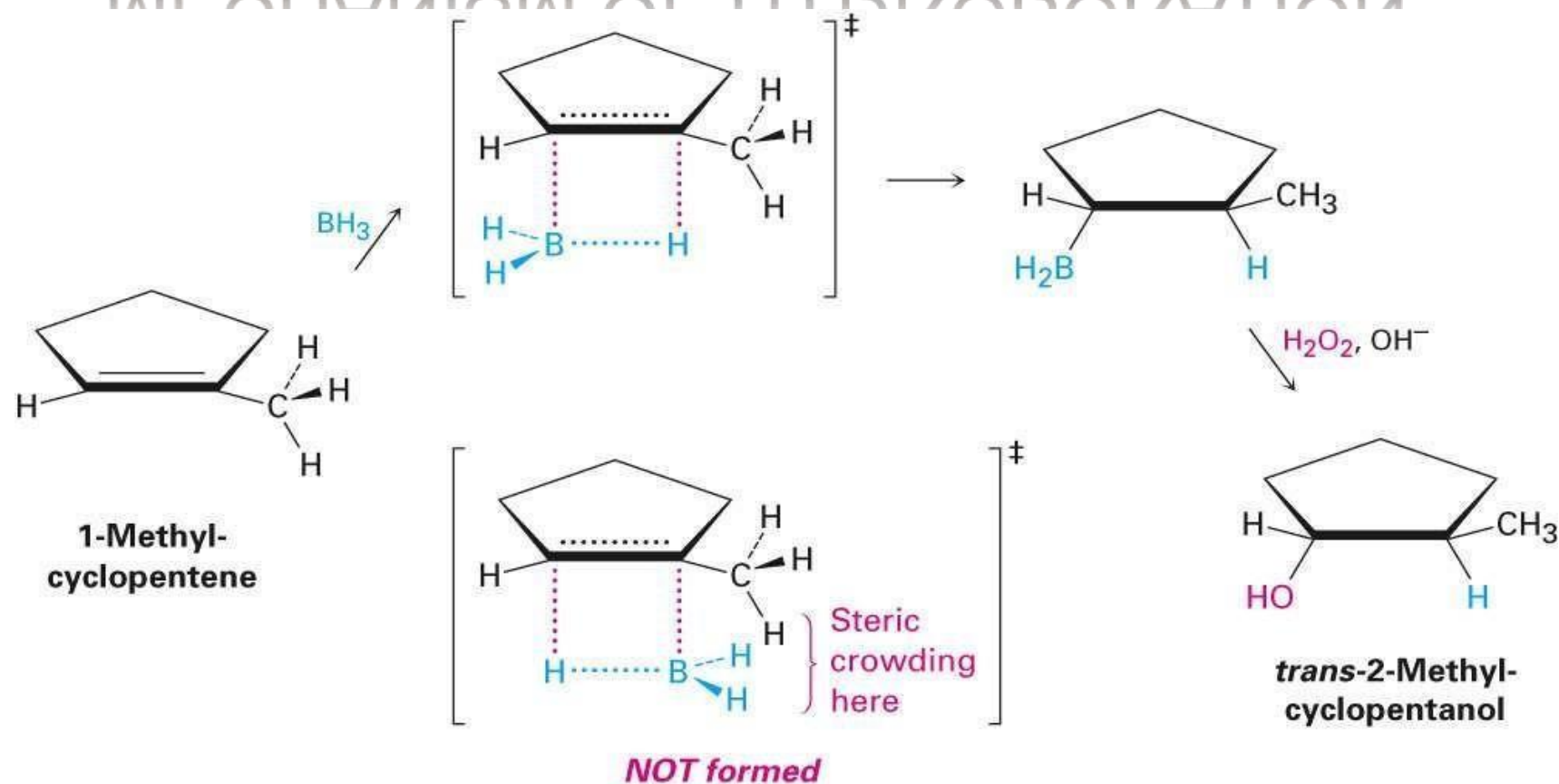
These reagents are prepared by hydroboration of the appropriate alkene, using control of stoichiometry to terminate the hydroboration at the desired degree of alkylation:



**Regioselective
stereoselectivity**

Hydroboration is a stereospecific syn addition. The addition occurs through a four-center transition state with essentially simultaneous bonding to boron and hydrogen. Both the new C-B and C-H bonds are, therefore, formed from the same side of the double bond. In molecular orbital terms, the addition is viewed as taking place by interaction of the filled alkene π orbital with the empty p orbital on boron, accompanied by concerted C-B bond formation

MECHANISM OF HYDROBORATION



© 2007 Thomson Higher Education

Borane is a Lewis acid ☐

Alkene is Lewis base ☐

Transition state involves anionic development on B ☐

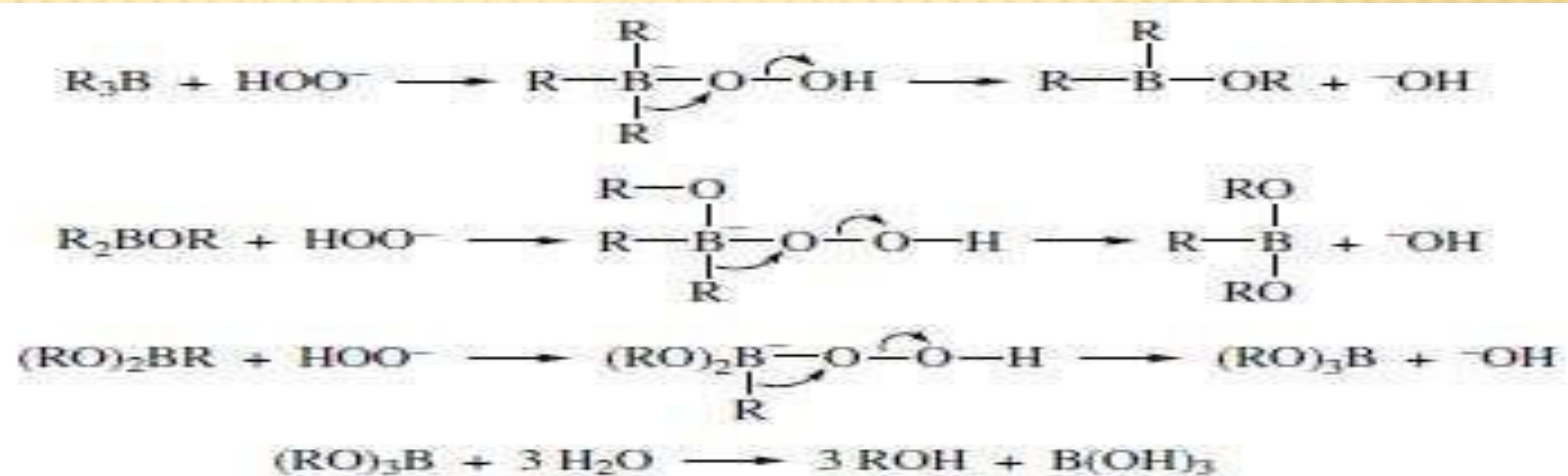
The components of BH_3 are added across $\text{C}=\text{C}$ ☐

More stable carbocation is also consistent with steric preferences ☐

Reaction of organoboranes

The organoboranes have proven to be very useful intermediates in organic synthesis.

In this section, we will discuss methods by which the boron atom can efficiently be replaced by hydroxyl, halogen, or amino groups.

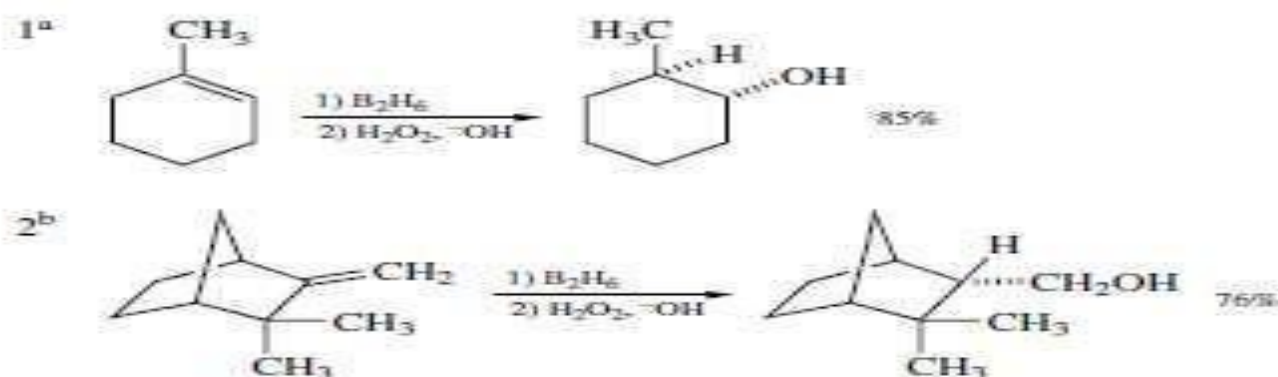




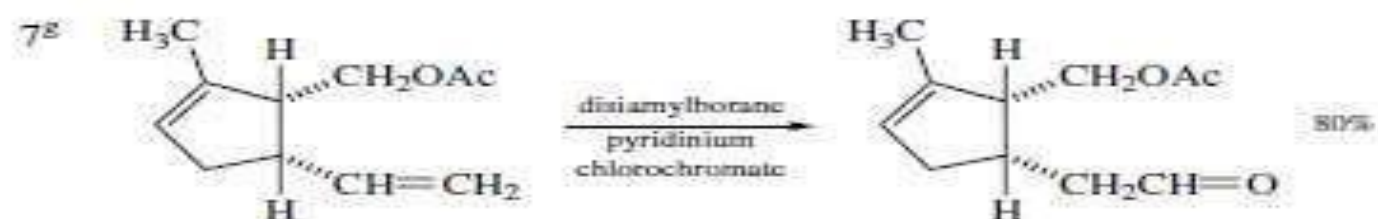
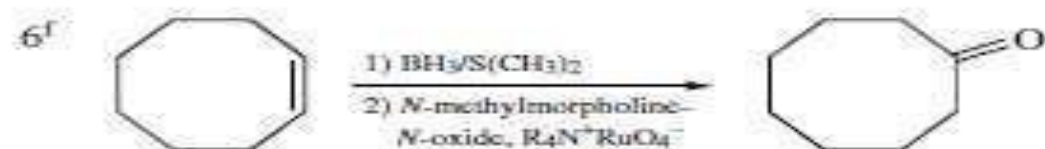
An alternative procedure for oxidation to ketones involves treatment of the alkylborane with a quaternary ammonium perruthenate salt and an amine oxide

Alcohols, Ketones, Aldehydes, and Amines from Organoboranes

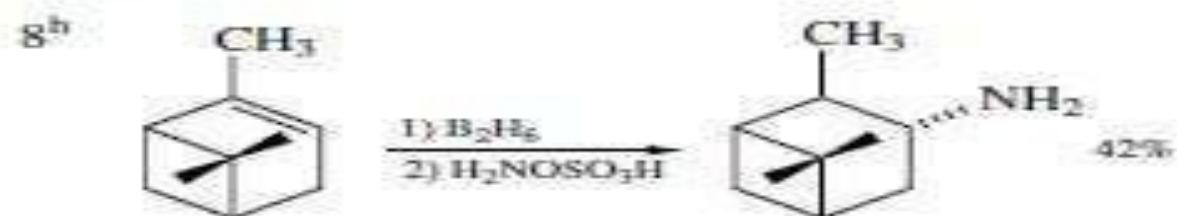
A. Alcohols



B. Ketones and aldehydes



C. Amines



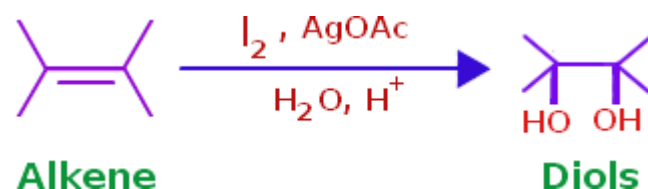
Summary

1. Hydroboration is a highly regioselective and *syn-stereospecific process*.
2. A wide variety of boranes are available. The number of hydrogen substituents on the borane determines the number of olefins with which it can react.
3. The rate of hydroboration is strongly affected by the substituents on the B atom - sterically bulky substituents can appreciably reduce the rate of successive hydroboration reactions.
4. sp^3 - C-B bonds can be manipulated in a number of ways including oxidation and amination

What is Woodward Reaction?

Woodward Hydroxylation is the synthesis of syn-diols or cis-diols from alkenes. This reaction is named after an American organic chemist, Robert Burns Woodward. When alkene is treated with iodine and silver acetate, it will undergo nucleophilic displacement with acetate in the presence of water. The intermediate product gives the desired diols on hydrolysis.

Woodward reaction of an anion with a double bond may be regarded as close to an S_N2 displacement – one of the two bonds of that double bond being displaced, by backside attack with the [stereochemistry](#) that is hard in certain cases.



Woodward Hydroxylation

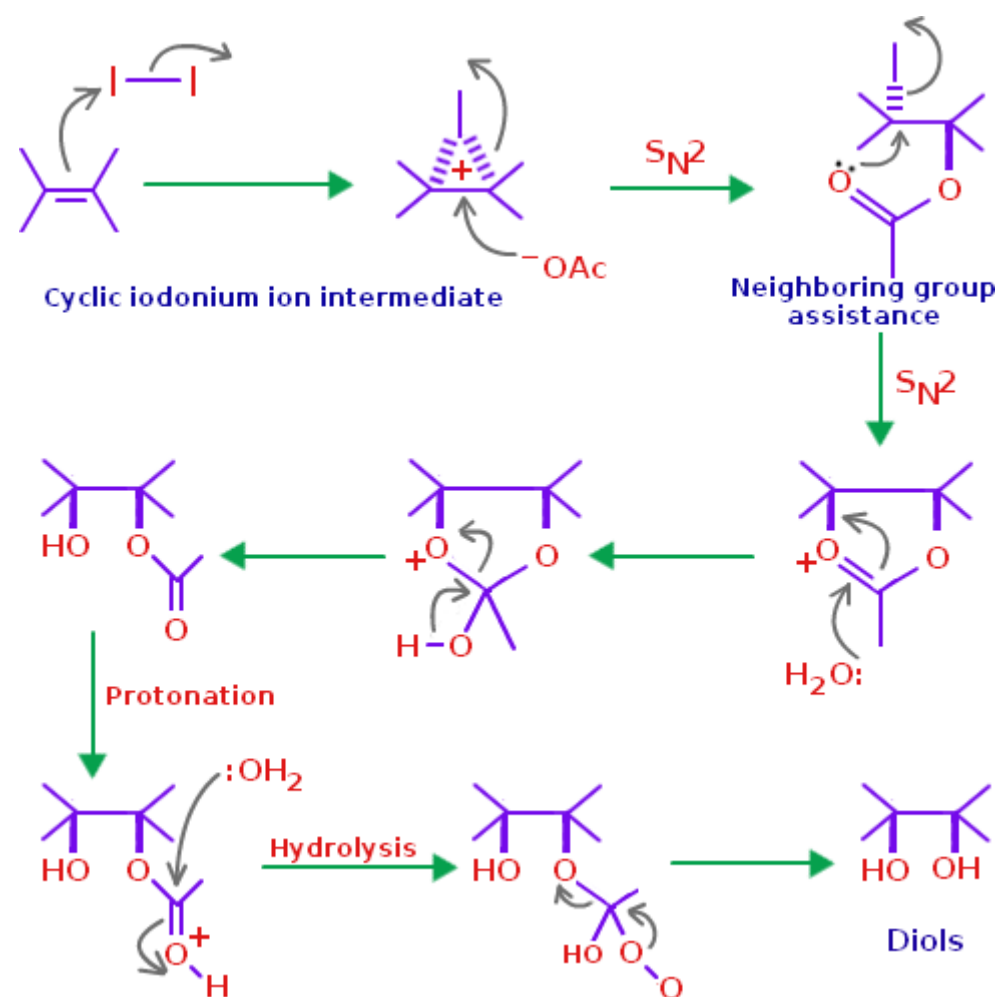
The reaction is cis-hydroxylation of an alkene and is known as Woodward cis-hydroxylation, after the name of its discoverer R.B. Woodward.

Woodward Reaction Mechanism

The woodward reaction allows the synthesis of syn-diols from alkenes by the addition of iodine followed by nucleophilic displacement with acetate in the presence of water. Hydrolysis of the intermediate ester gives the desired diol.

The steps involved in the mechanism of woodward reaction are listed below.

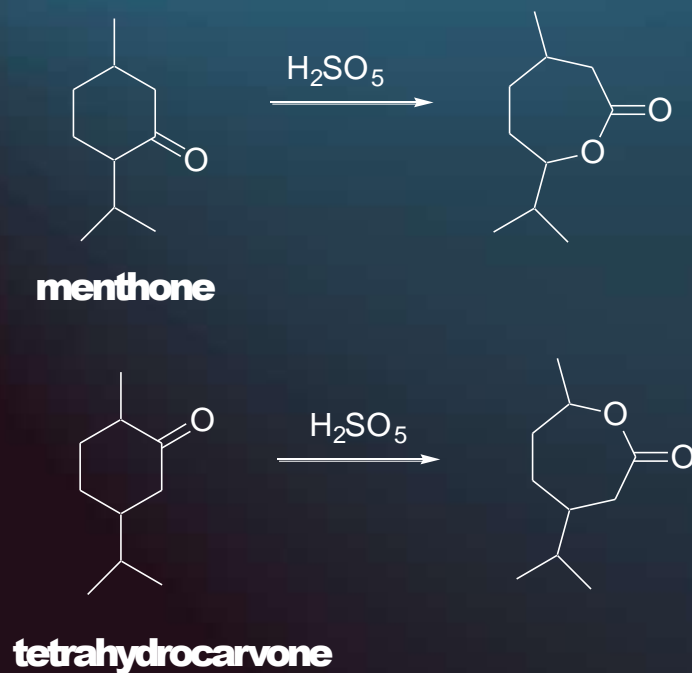
1. Iodine reacts with alkene forming a cyclic iodonium intermediate.
2. Further, the cyclic intermediate reacts with acetate ion in S_N2 fashion to form a five-membered ring compound.
3. The five-membered rings are opened by [Hydrolysis reaction](#).
4. Further protonation followed by hydrolysis gives the corresponding diols.



Woodward Reaction Mechanism

Baeyer-Villiger Oxidation

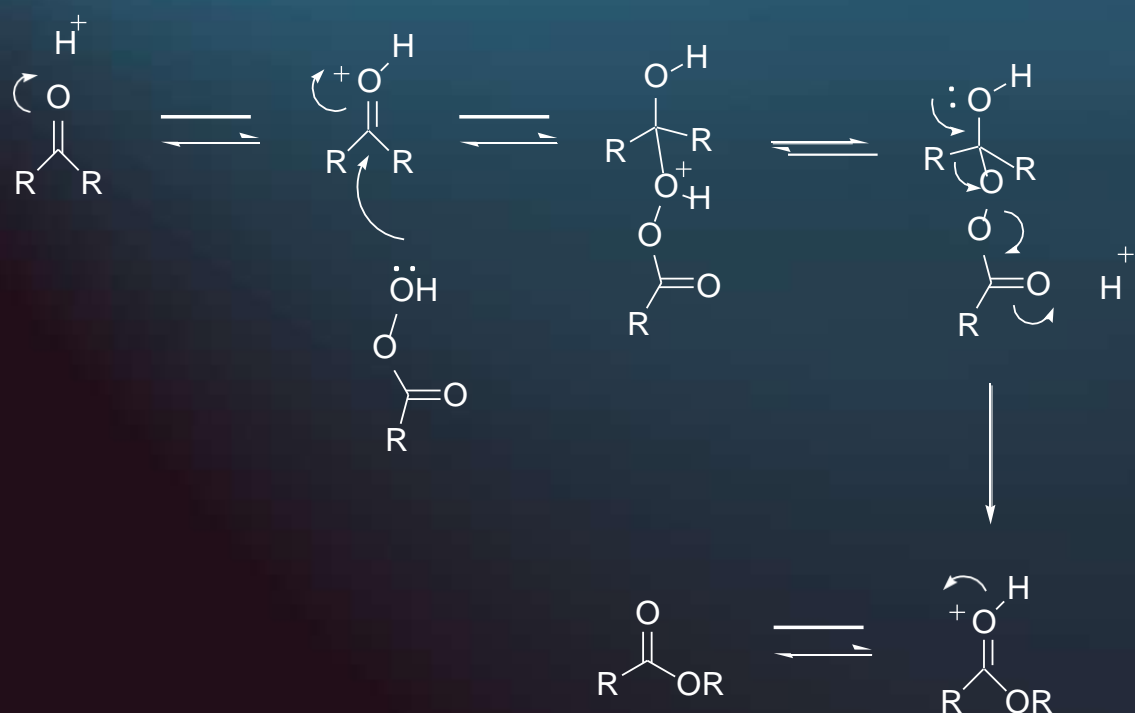
Introduction



The Baeyer-Villiger oxidation, also known as the Baeyer-Villiger rearrangement, was first reported on December 17, 1899 by Adolf Baeyer and Victor Villiger in *Chemische Berichte*. They referred to the oxidation of menthone and tetrahydrocarvone by monoperoxysulfuric acid. It is a popular synthetic tool for the conversion of cyclic ketones to lactones and acyclic ketones to esters; lactones are precursors to hydroxy acids and acyclic diols.

Peracids, hydrogen peroxide, magnesium salt of monoperoxyphthalic acid and oxone are established reagents for this reaction. Phenols and formates can be obtained from the corresponding aromatic aldehydes.

Mechanism



Initial protonation of the carbonyl oxygen is followed by addition of peracid to yield an adduct which undergoes rearrangement where the R group migrates to the electron deficient oxygen. This is followed by deprotonation.

Salient points are retention of stereochemistry by the migrating group, migration concerted with departure of leaving group and increased migratory aptitude of groups possessing greater electron donating power.

Overall, an example of a [1,2] rearrangement.

Mechanism

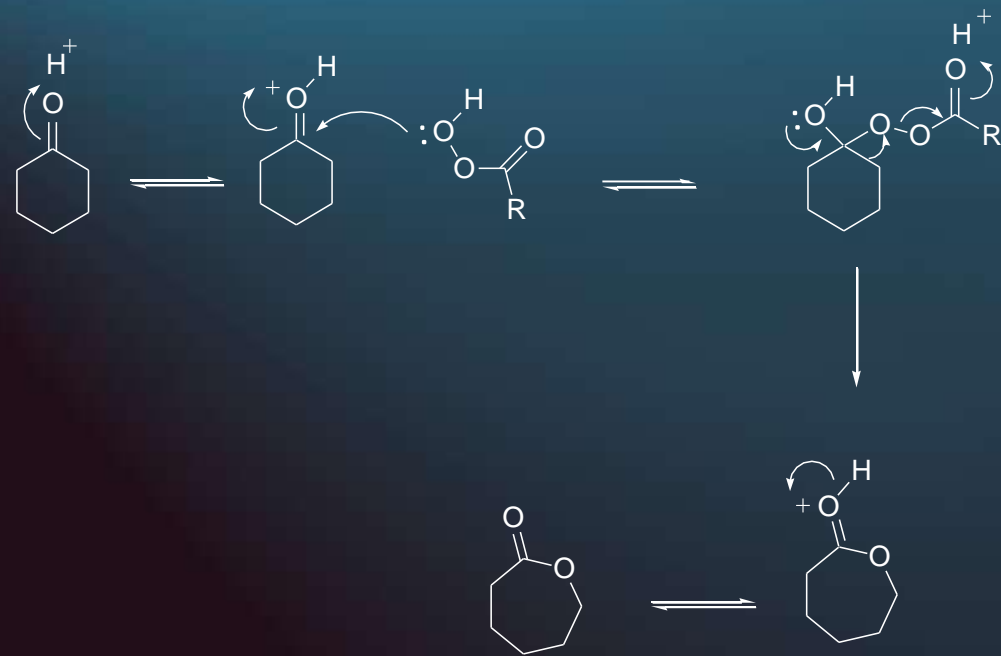
- 1) Retention of stereochemistry by the migrating group.
- 2) Migration is concerted with the departure of the leaving group. The concerted step is rate determining.
- 3) Migrating groups with greater electron donating power have correspondingly greater migratory aptitude because of the increased ability to stabilize a positive charge in the transition state. This renders stereoselectivity to the oxidation of *unsymmetrical ketones*.

General order of migration:

tertiary alkyl > cyclohexyl > secondary alkyl > benzyl > phenyl > primary alkyl > H

- 4) Migration is favored when the migrating group is antiperiplanar to the O-O bond of the leaving group; this is known as the primary stereoelectronic effect.

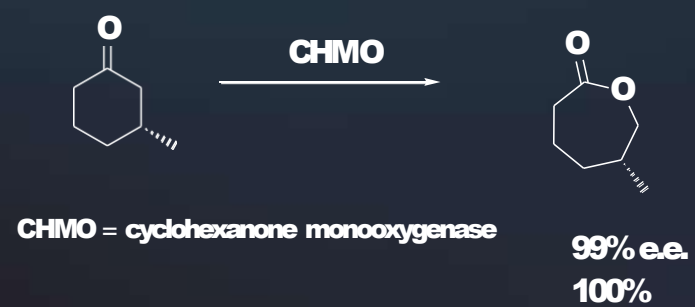
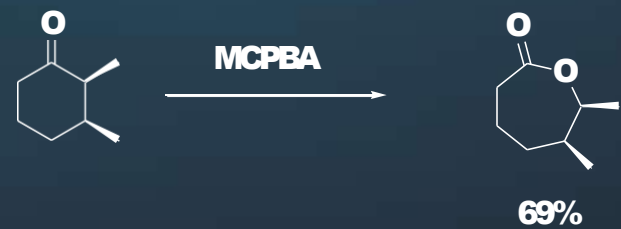
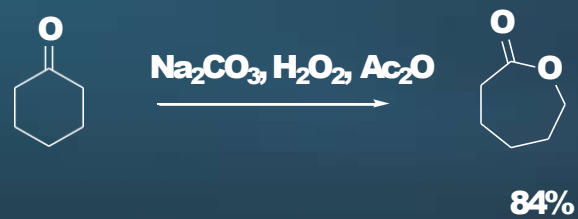
Lactone Synthesis



Cyclic ketones are converted to lactones as mentioned in the original publication of Baeyer and Villiger on the conversion of the cyclic ketones menthone and tetrahydrocarvone to the respective lactones by monoperoxy sulfuric acid.

The scope of lactonization has dramatically increased through the application of microbial Baeyer-Villiger monooxygenases, ionic liquids and modern reagent systems involving mesoporous magnesium-aluminum mixed oxides.

Examples



Reference Books:

- Designing Organic Synthesis, S. Warren. Wiley.
- Organic Synthesis: The Disconnection Approach, S. Warren, Wiley.
- Organic Synthesis-Concept, Method and Starting Materials, J. Fuhrhop.
- Some Modern Methods of Organic Synthesis. W. Carruthers, Cambridge Univ. Press.
- Modern Synthetic Reactions H.O. House, W.A. Benjamin.
- Advanced Organic Chemistry: Reactions, Mechanisms and Structure, J. March. Wiley.
- Principles of Organic Chemistry Part B.F. Carey and R.J. Sundberg, Plenum Press.