BHARATHIDASAN UNIVERSITY

Tiruchirappalli- 620024, Tamil Nadu, India

Programme: M.Sc., Chemistry

Course Title: Organic Reaction Mechanism, Pericyclic and Photochemistry

Course Code: CHE623CO

UNIT III: Addition and Elimination Reactions

Dr. A. ILANGOVAN
Senior Professor and Chair, School of Chemistry
ilangovan@bdu.ac.in

SYLLABUS

ADDITION REACTION

Addition to carbon-carbon multiple bonds: Electrophilic, nucleophilic and free radical additions – Orientation of the addition – Stereochemical factors influencing the addition of bromine and hydrogen bromide, hydroxylation, 1,2-dihydroxylation – Hydroboration leading to formation of alcohols – Oxidation – Sharpless asymmetric epoxidation and ozonolysis. Addition to carbonyl and conjugated carbonyl systems – Mechanism – Grignard reagents – 1,2 and 1,4-additions (dimethyllithiumcuprate type).

Addition to carbon-oxygen double bond: A study of benzoin, Knovenagel, Stobbe and Darzen-glycidic ester condensation reactions.

Elimination Reactions

Mechanisms; E1, E2, E1cB – Stereochemistry of elimination, Hofmann and Zaitsev rules, Bredt's rule - Pyrolytic *cis* elimination, Chugaev reaction – Cope elimination.

ELIMINATION REACTIONS

Outline

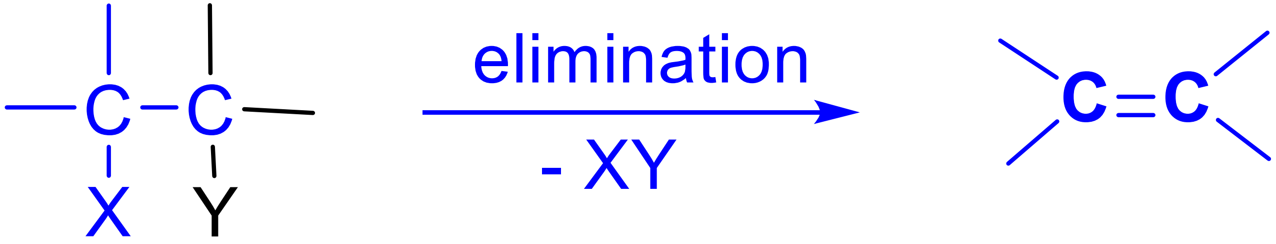
- beta-Eliminations
- E1, E2 and $E1_{c}B$ Mechanisms
- Stereochemical considerations of these reactions
- Examples of E1, E2 and $E1_{c}B$ reactions
- Alpha eliminations and generation of carbene

Introduction

- From a practical standpoint, elimination reactions are widely used for the generation of double and triple bonds in compounds from a saturated precursor molecule.
- The presence of a good leaving group is a prerequisite in most elimination reactions.
- Traditional classification of elimination reactions, in terms of the molecularity of the reaction is employed. How the changes in the nature of the substrate as well as reaction conditions affect the mechanism of elimination are subsequently discussed.
- The stereochemical requirements for elimination in a given substrate and its consequence in the product stereochemistry is emphasized.

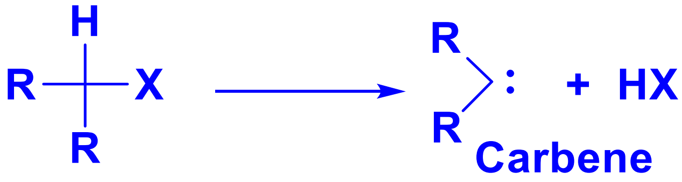
ELIMINATION REACTIONS

- Elimination reactions involve the loss of fragments or groups from a molecule to generate multiple bonds.
- A generalized equation is shown below for 1,2-elimination wherein the X and Y from two adjacent carbon atoms are removed



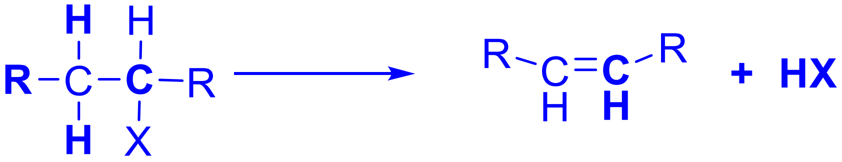
Types are three major types of eliminations known

α-elimination: Two atoms are groups are removed from the same atom. It is known as 1,1' elimination

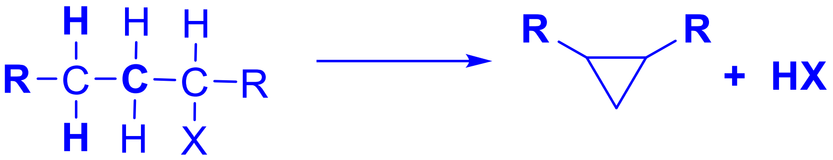


Both H and X are removed from same carbon atom.

β-elimination: loss of atoms or groups on adjacent atoms. It is also known as 1,2- elimination.



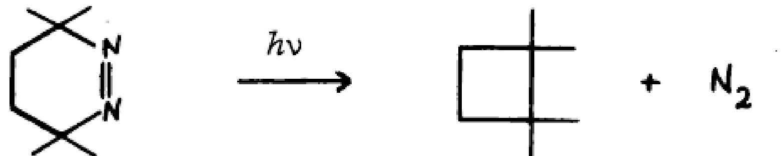
γ-elimination: loss of atoms or groups from the 1st and 3rd positions as shown below. Generally such elimination reactions result in cyclic compounds.



Apart from these three, there is one more way i.e., extrusion reaction: A cleaving reaction in which a skeletal atom or group of atoms is removed from the middle of a molecule.

$X \quad Y-Z \longrightarrow X-Z + Y$

or



Three Types of β-eliminations

- ✓ ***β*-Eliminations can be further subdivided into three categories depending upon the mechanistic pathway.**
- ✓ **The important aspect is to establish the number of molecules taking part in the elimination step (molecularity of the reaction)**

Three types of β-eliminations are

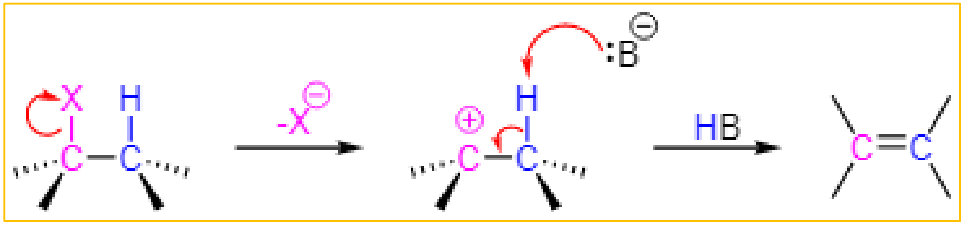
1. **E2,**
2. **E1,**
3. **E1cB**

https://chem.libretexts.org/Bookshelves/Organic_Chemistry/Organic_Chemistry_%28Morsch_et_al.%29/11%3A_Reactions_of_Alkyl_Halides-_Nucleophilic_Substitutions_and_Eliminations/11.07%3A_Elimination_Reactions-_Zaitsev%27s_Rule

Three types of β-eliminations are E1, E2, E1cB

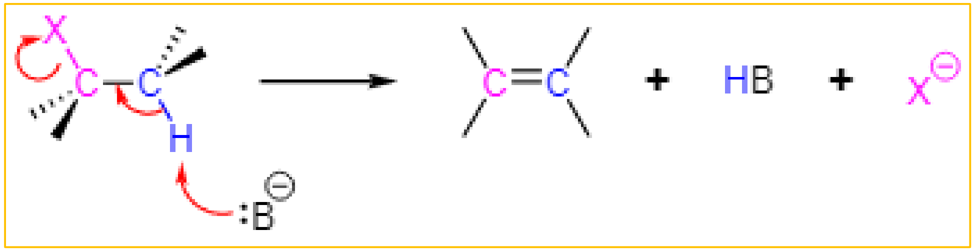
E1 - Elimination unimolecular: mechanism starts the breaking of the C-X to provide a carbocation intermediate. A base removes a hydrogen adjacent to the original electrophilic carbon. The electrons from the broken H-C bond move to form the pi bond of the alkene.

In much the same fashion as the S_N1 mechanism, the first step of the mechanism is slow making it the rate determining step. This means that the reaction kinetics are unimolecular and first-order with respect to the substrate.



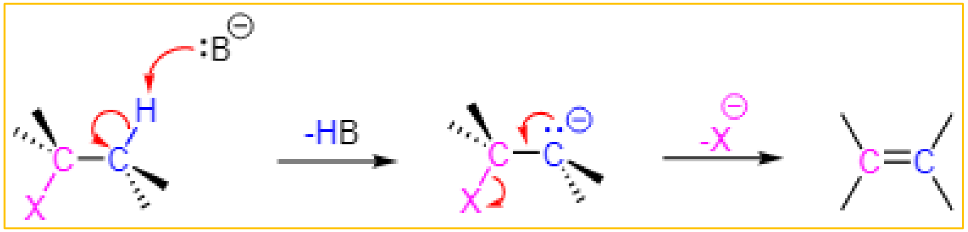
E2 - Elimination bimolecular: mechanism takes place in a single concerted step. The rate at which this mechanism occurs follows second order kinetics, and depends on the concentration of both the base and alkyl halide.

The base removes a hydrogen from a carbon adjacent to the leaving group. The electrons of the broken H-C move to form the pi bond of the alkene. In doing this the C-X bond is broken causing the removal of the leaving group.



E1cB - Elimination unimolecular conjugate base: mechanism starts with the base deprotonating a hydrogen adjacent to the leaving to form a carbanion.

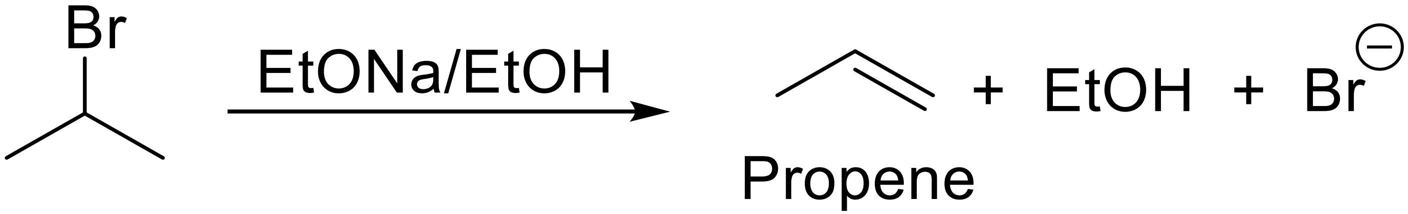
In the second step of the mechanism the lone pair electrons of the carbanion move to become the pi bond of the alkene. This causes the C-X bond to break and the leaving group to be removed.



E2 Elimination

Key mechanistic features of E2 Elimination are

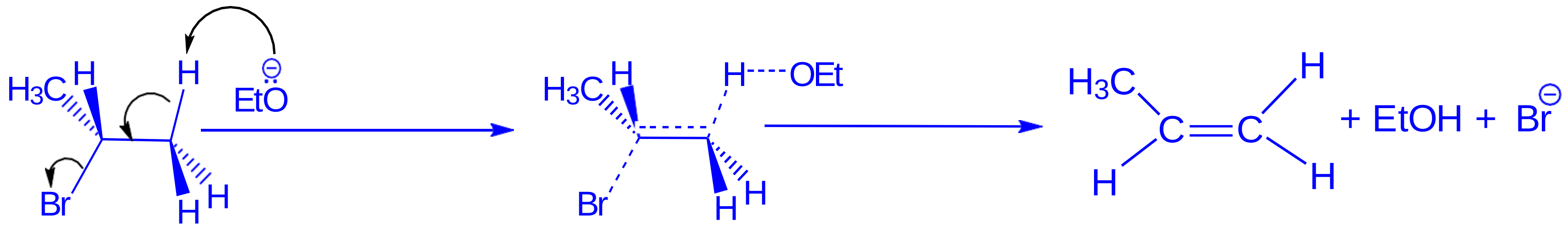
- Two groups depart simultaneously
- Involves one step (in other words, no intermediates are involved)
- Bimolecular reaction i.e., both substrate and nucleophile participate in a single step.
- The base abstracts the β hydrogen and leaving group simultaneously leaves such that it forms a multiple bond between α and β carbon atoms.



- In the example given above, sodium ethoxide acts as the base, abstracting beta hydrogen. Bromine is the leaving group.

E2 elimination

An illustration of a common elimination reaction is given below

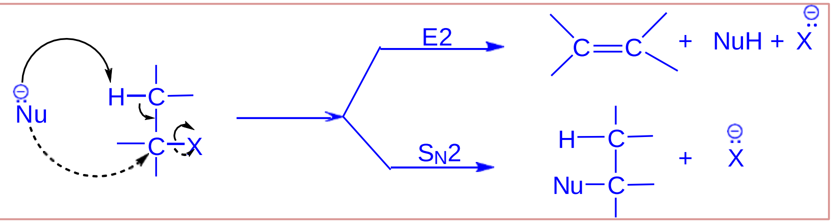


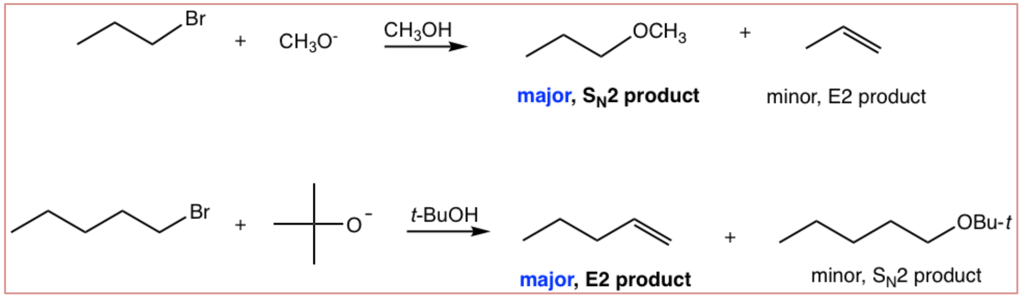
The sequence of events involved are,

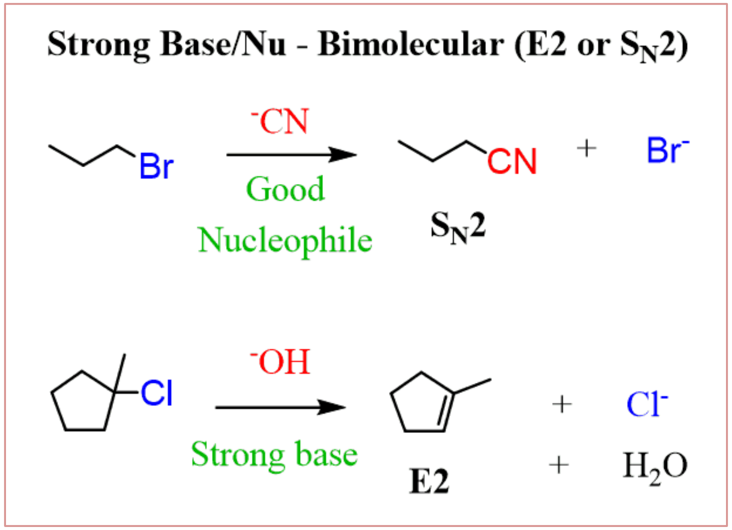
- **The attack of ethoxide on β hydrogen and its abstraction as a proton is the first event. This will leave two electrons of the C-H bond available for the formation of a new double bond between the carbon atoms.**
- **As the new double bond is created, the C-Br bond begins to break away (leaving group). This will result in the departure of the bromide ion.**
- **The events summarized above are the general steps, the extend of bond formation/breaking would depend on a number of factors described later.**

E2 elimination vs S_N2 reaction

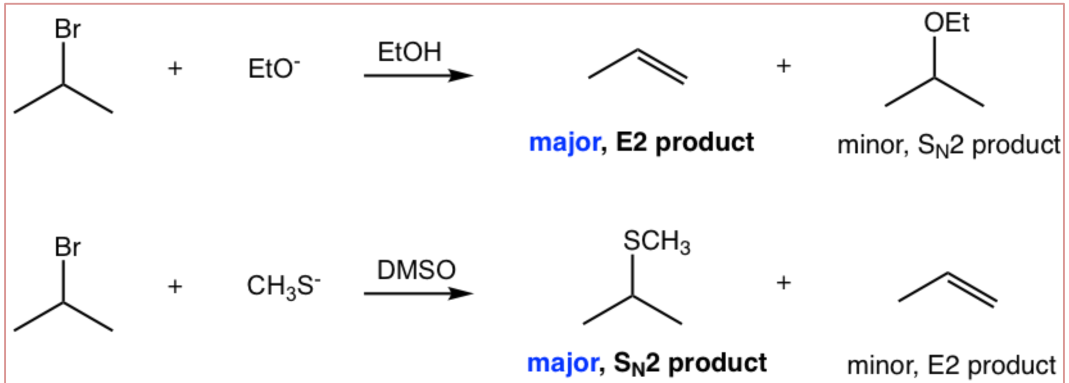
- ❖ **Often E2 elimination competes with S_N2 reactions.**
- ❖ **Inherent propensity of the incoming nucleophile also attacking the carbon atom bearing the leaving group will lead to substitution products.**
- ❖ **Primary (1°) substrates cannot go with any unimolecular reaction, that is no S_N1/E1, because primary carbocations are too unstable to be formed.**
- ❖ Since primary substrates are very good candidates for **S_N2 reactions, SN2 is the predominant pathway when good nucleophile is used**. The only exception is that when a big bulky base/nucleophile is used, E2 becomes the major reaction.





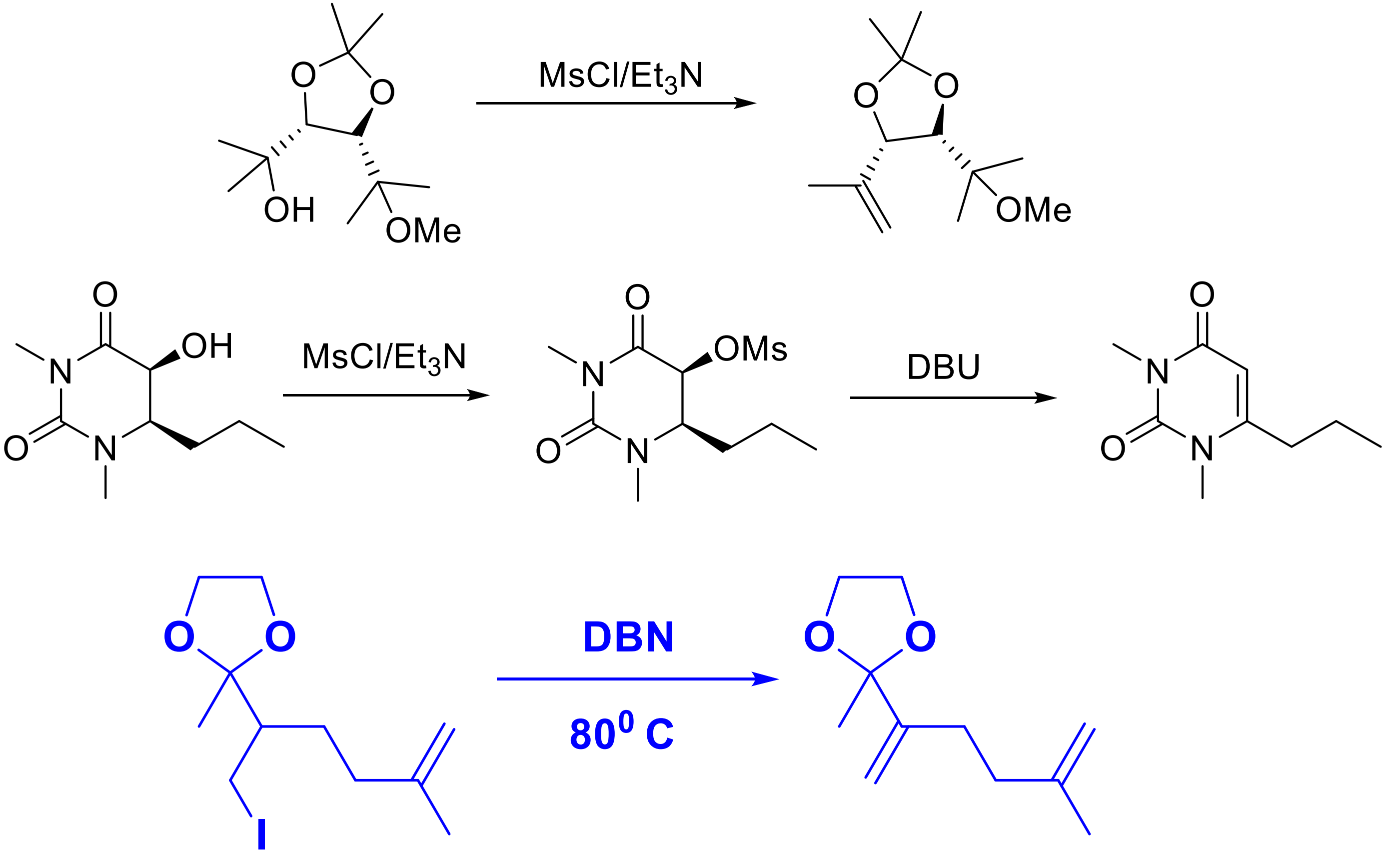


Strong Base/Nu - Bimolecular (E2 or S_N2)



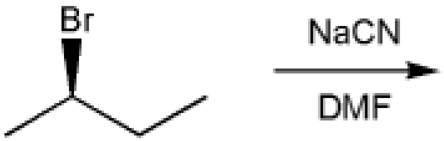
Examples for E2 elimiations

- Look at the given reactions and reagents first.
- Do not worry about the complexity of the given substrates.
- Focus on the ‘site-of-reaction’ In the above examples, Et_3N is obviously the base, and ‘OH-group’ should be removed.
- Now, note that OH is a poor leaving group and conversion to O-mesyl is required here (achieved through the use of mesyl chloride, MsCl).

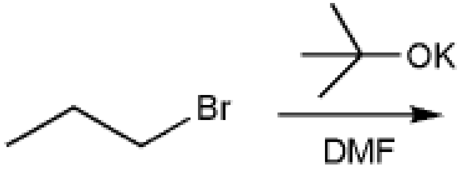


SN1/SN2/E1/E2 Trends and Competition Reactions

a)



b)



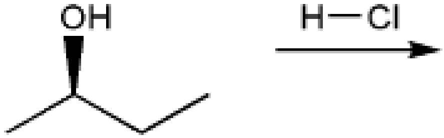
c)

d)

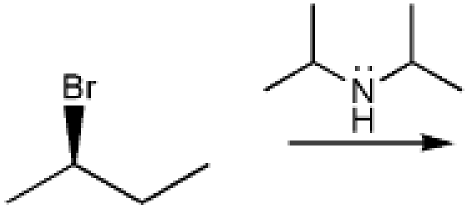
e)

f)

g)

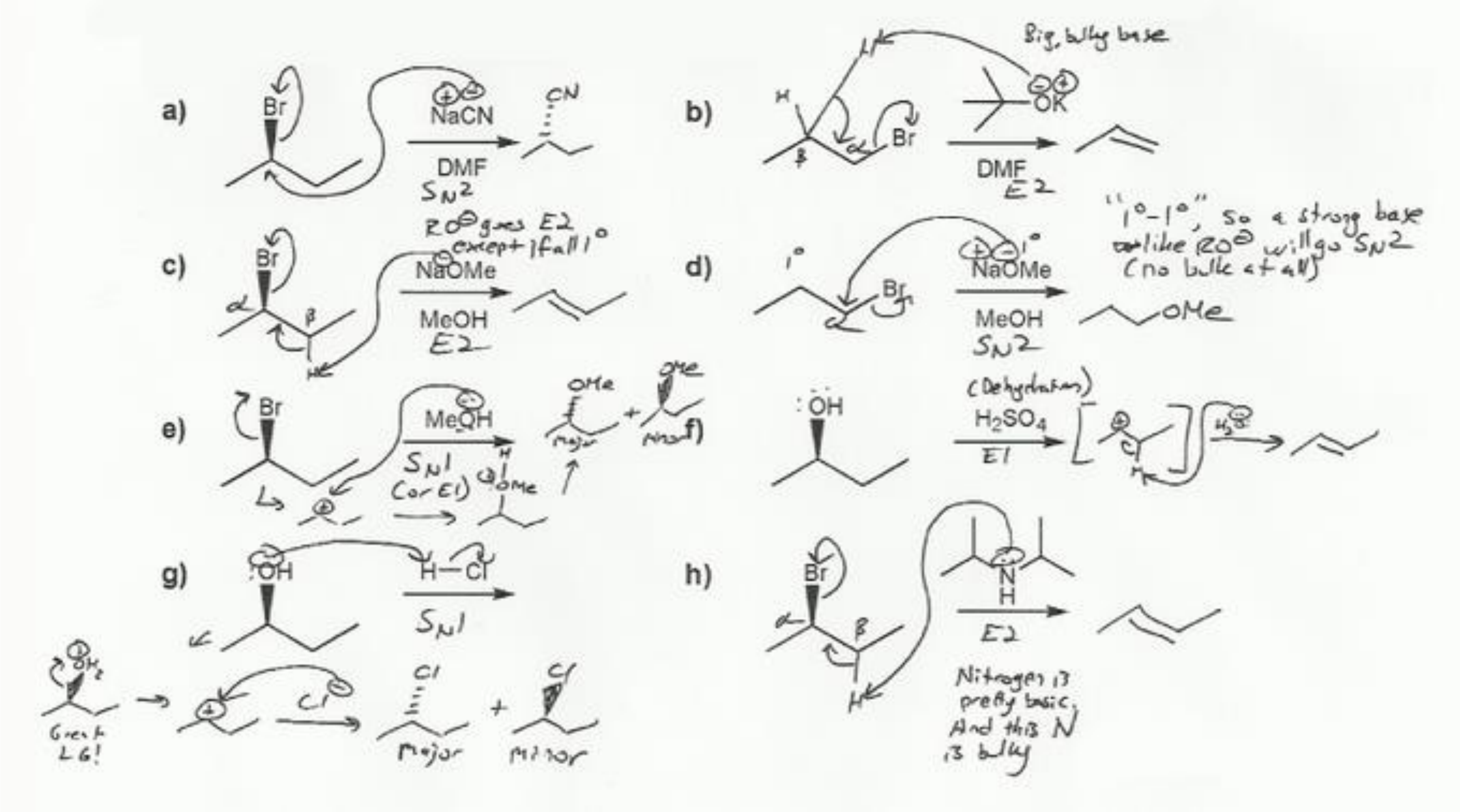


h)



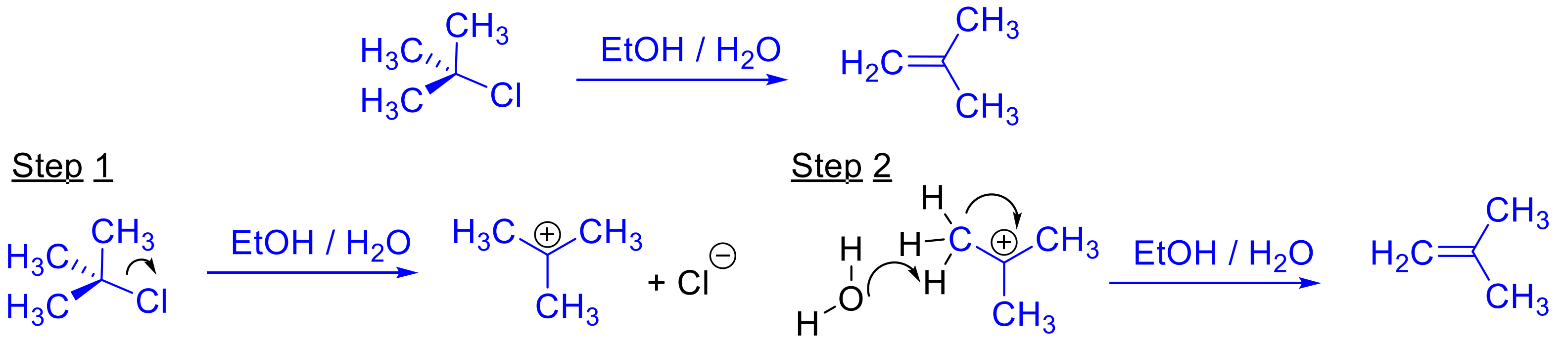
http://www.mendelset.com/category/subject-topics/organic-chemistry/sn1sn2e1e2-trends-and-competition-reactions

SN1/SN2/E1/E2 Trends and Competition Reactions



http://www.mendelset.com/category/subject-topics/organic-chemistry/sn1sn2e1e2-trends-and-competition-reactions

II. E1 Eliminations



✓ **It is two step reaction.**

✓ **First step is similar to that of S_N1 reaction i.e., the generation of carbocation intermediate. Subsequently, hydrogen is abstracted by the base rather than attack on the carbocation as in S_N1**

✓ **Only one of the substrates is involved in the rate determining step i.e., unimolecular reaction.**

✓ **Attack of water or solvent molecule on the β hydrogen and subsequent movement of electron pair to the developing carbon carbon double bond.**

✓ **Even though a sp3 C-H bond is not acidic in a general sense, the presence of a carbocationic center adjacent to it renders increased acidity such that even a weak base such as water can deprotate.**

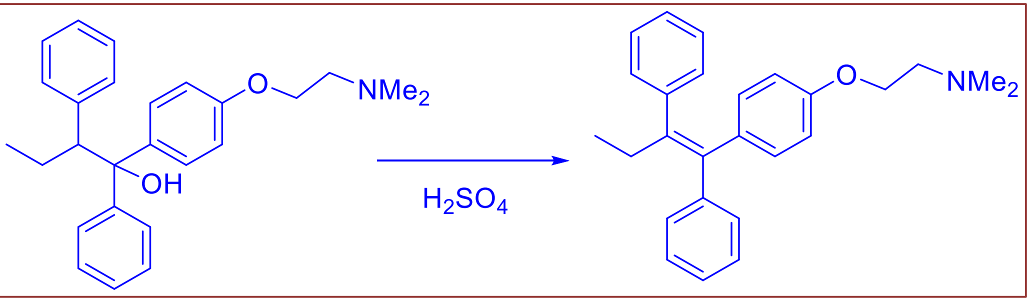
II. E1 Eliminations

- Similar to the competition between E2 and S_N2 pathways, E1 mechanism competes with S_N1.

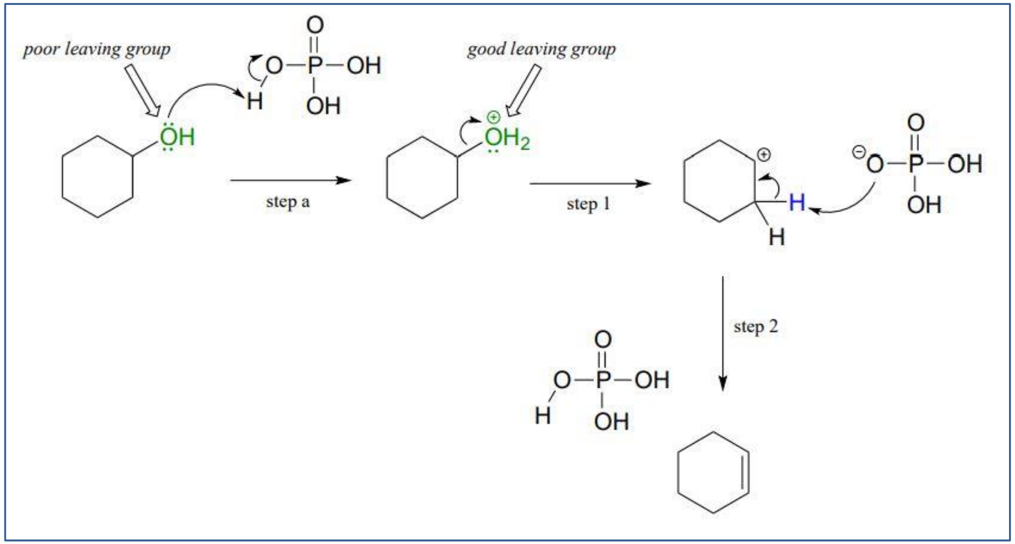
- Formation of carbocation is a slower process, as compared to the reaction between a ‘reactive-carbocation’ and a base/solvent. Hence, carbocation formation is the rate determining step.

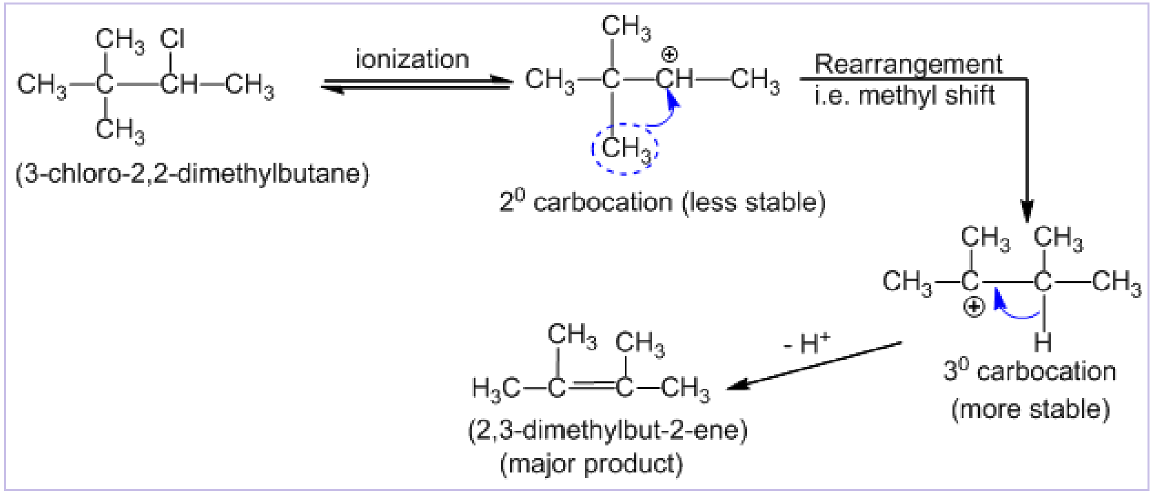
- Ideal conditions are for E1 mechanism are (a) highly substituted carbon atom for the carbocation center, such as a tert-carbon atom, (b) use of polar solvents (which can stabilize the resulting carbocation in addition to stabilizing a polar transition state involved in the heterolytic bond cleavage.

Examples for E1 elimination



The carbocation generated in the first step is being stabilized due to effective delocalization promoted by the presence of two phenyl groups on the tert-carbon.

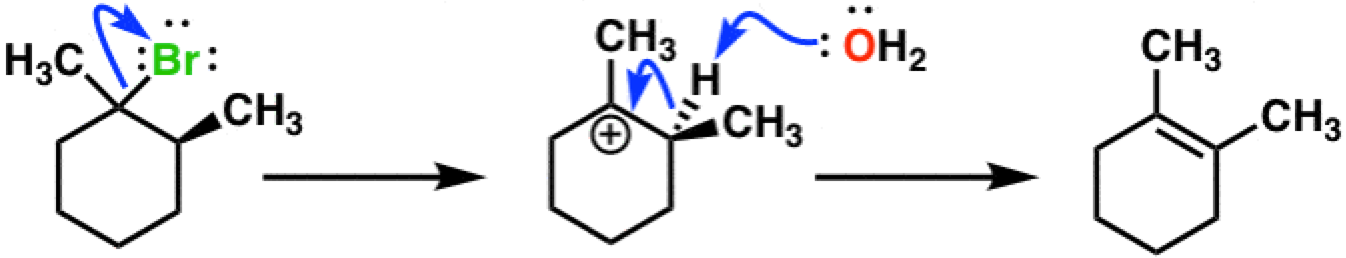




Comparison between for E1 and E2 elimination

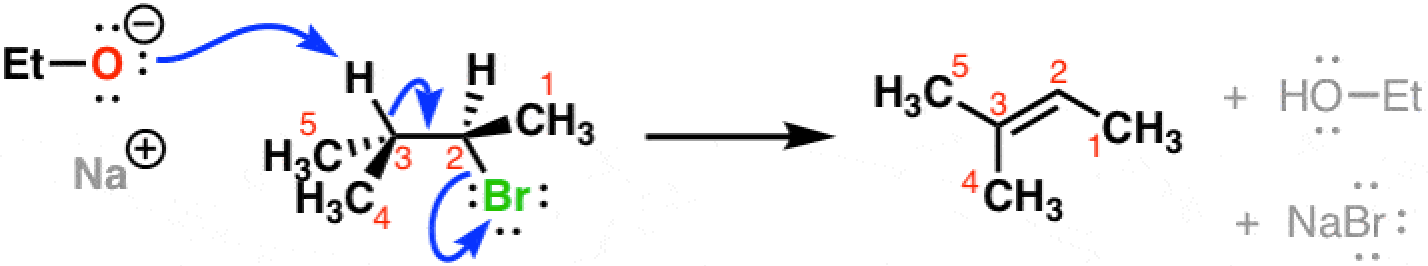
The E_1 Mechanism

Step 1: Loss of leaving group *Step 2: Deprotonation*



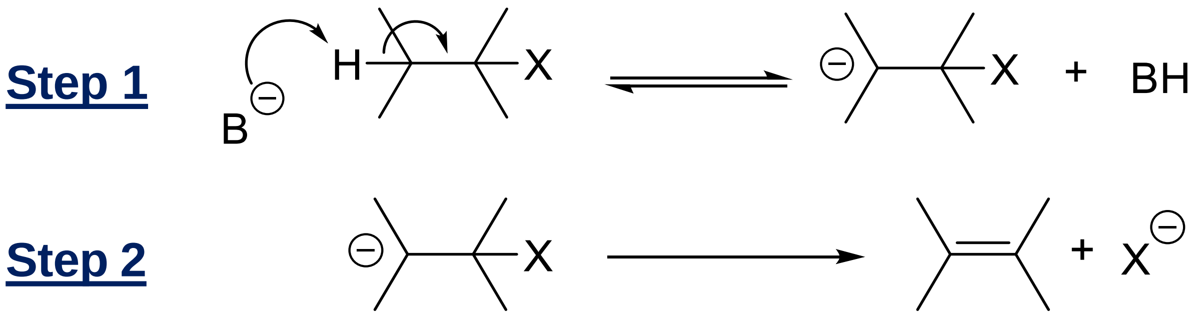
Carbocation

The E_2 Mechanism



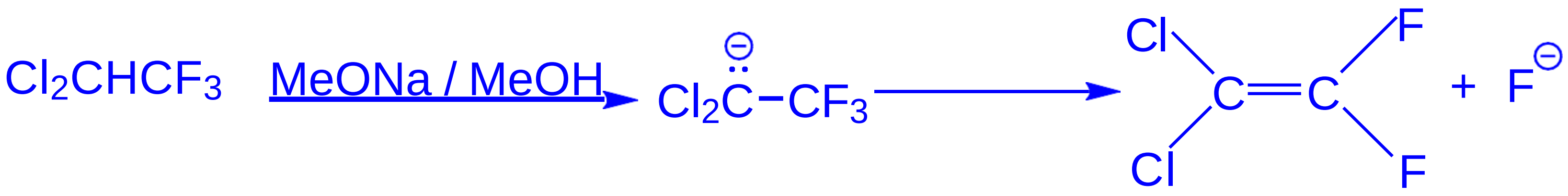
One step! Hydrogen removed must be "anti" to the leaving group (dihedral angle 180°)

III. E1cB Eliminations ….



- ✓ This is a two-step base-induced β elimination.
- ✓ In the first step base abstracts β hydrogen. β-hydrogen leaves without its carbon electron pair forming a carbanion or conjugate base of the substrate from which the leaving group departs subsequently to form the product.
- ✓ The electron pair then move towards the new C-C double bond to be generated.
- ✓ An interesting comparison can be done with the E1 pathway. The timing of departure of the groups is reversed as compared to that in E1 reaction. In E1cB, the deprotonation occurs ahead of leaving group departure.
- ✓ Reaction usually follows second order kinetics but is designated as E1cB to indicate that the departure of the leaving group is from the initially formed conjugate base (i.e., carbanion).

III. E1cB Eliminations ….



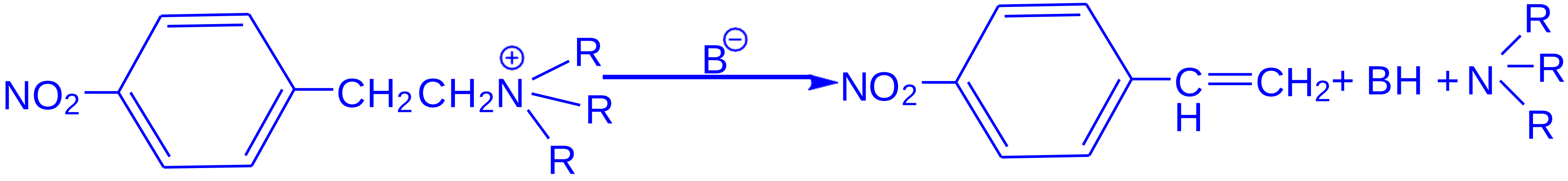
a. These reactions require substrate which contain groups that can stabilize carbanions i.e., presence of electron withdrawing group.

b. Additional Details on E1cB: Depending on the nature of the rate-determining step, there are different ways by which reaction can proceed.

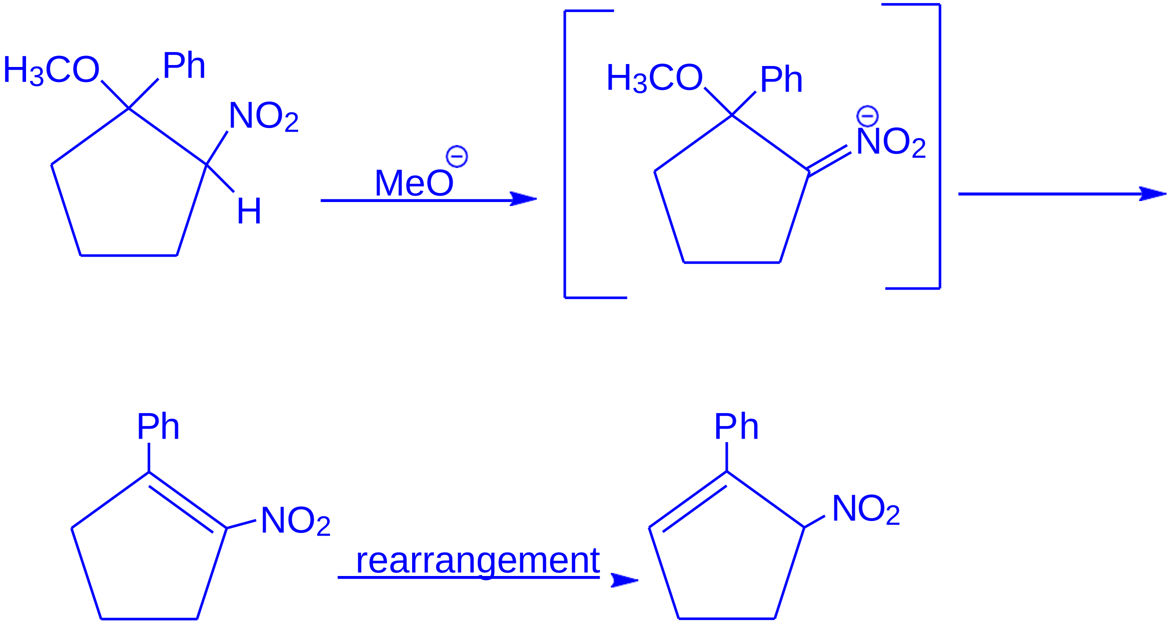
c. Carbanion returns to the starting material faster than the product formation. Step 1 is reversible and step 2 is slow. It is designated as $(E1cB)_R$.

d. Product formation is faster as compared to return of proton to carbanion. Step 2 is irreversible and step 1 is slow. It is designated as $(E1cB)_I$.

III. E1cB Eliminations…..



Carbanion goes slowly to product formation as it is very stable. Step 1 is rapid and irreversible. It is designated as $(\mathrm{E1})_{\mathrm{anion}}$.



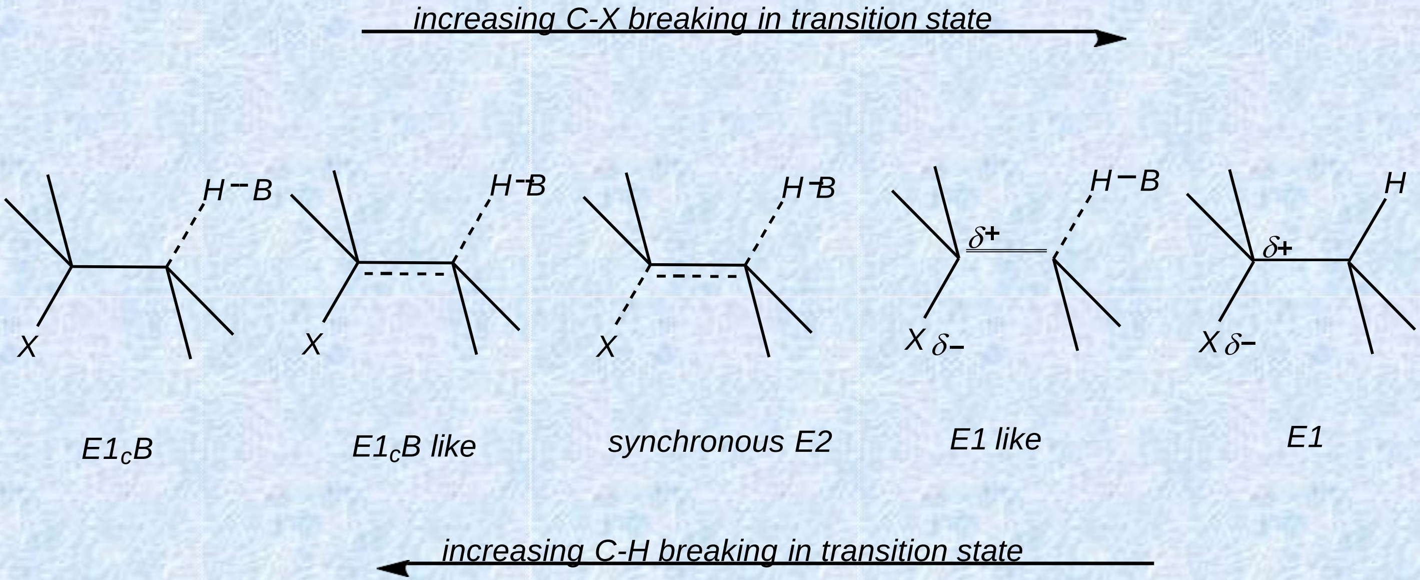
E2, E1, and E1cB Eliminations…..

- Thus far we have studied three major classes of elimination reactions.
- E2, E1, and E1cB can be regarded as ‘extremities’ or ‘ideal’ situations.
- In reality, the nature of substrates and reaction conditions have a huge influence on the course of the reaction.
- In fact, one can use what is known as ‘variable E2 transition state theory’ to explain the continuum of mechanistic possibilities. In other words, clear demarcation between these mechanistic types are difficult.

IV.Variable transition state theory for elimination reaction

Many β elimination reactions proceed via mechanisms, which are intermediate between the extremities such as E1cB and E1. This is called variable E2 transition state theory.

The timing of deprotonation and departure of the leaving group is the key to the following mechanistic continuum



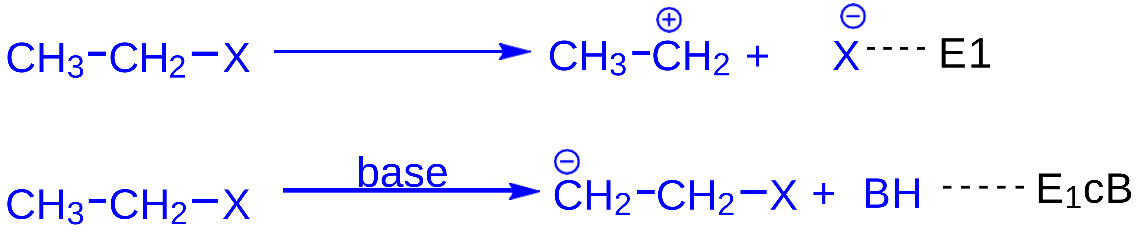
increasing C-X breaking in transition state

increasing C-H breaking in transition state

IV.Variable transition state theory for elimination reaction

The other way to depict the variable transition state theory is to construct three dimensional potential energy diagram.

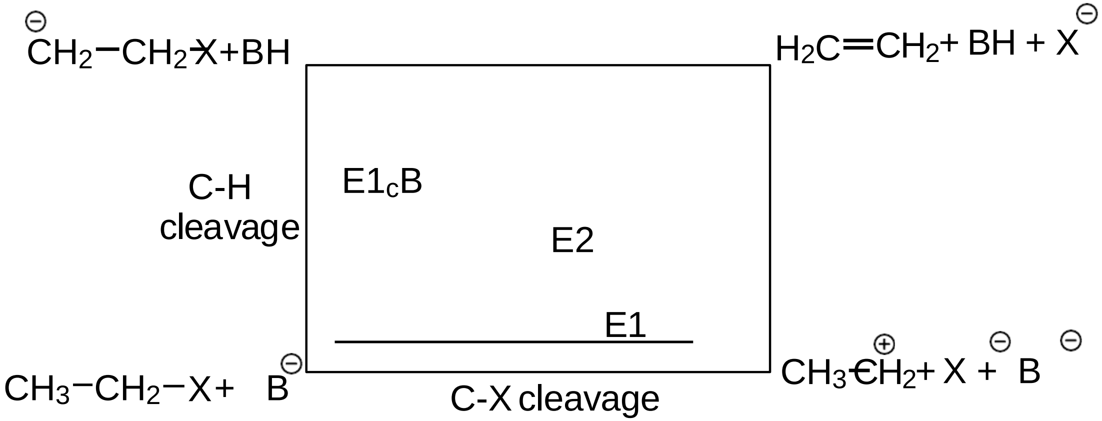
Consider example of ethyl halide. The two intermediates involved in two extreme processes are;



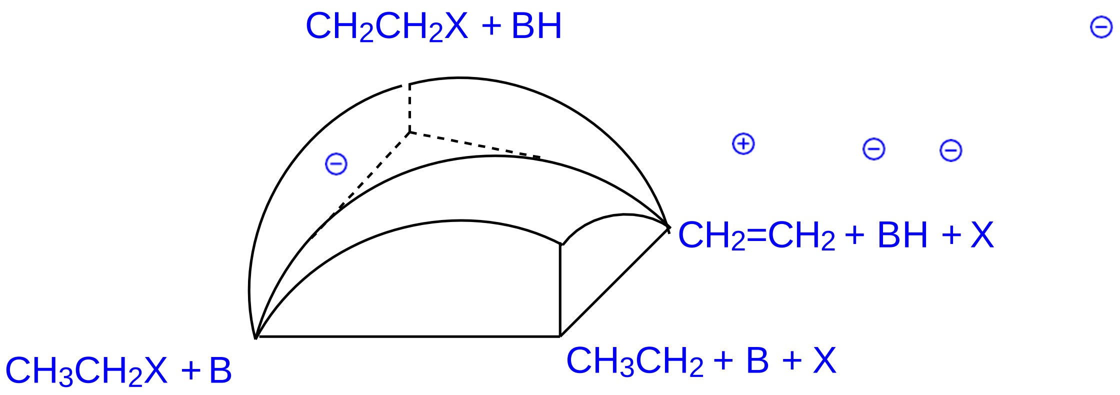
$$CH_3{-}CH_2{-}X \longrightarrow CH_3{-}\overset{\oplus}{C}H_2 + \overset{\ominus}{X} \text{ ---- E1}$$

$$CH_3{-}CH_2{-}X \xrightarrow{\text{base}} \overset{\ominus}{C}H_2{-}CH_2{-}X + BH \text{ ----- } E_1cB$$

When there are no suitable stabilizing groups, both primary carbocation and primary carbanion are highly unstable. If we construct a diagram in which progress of C-H bond breaking is one dimension, progress of C-X bond breaking is second dimension and energy of reactant system is third dimension, then following diagram is obtained.



This is two dimensional representation which shows that **E1** corresponds to complete C-X breakage before C-H bond breaking while **E1cB** corresponds to complete C-H breakage before C-X. When energy axis is also included in this diagram it looks like



three dimensional diagram depicting transition state locations for E1, E1cB and E2 mechanisms

In this diagram, E1 and E1cB intermediates are respectively placed at front right and back left corners. These two are high energy intermediates.

The lowest energy path is a concerted E2 path which is almost diagonally across energy surface. Reason for this is that double bond character developing between α and β carbon compensates for the energy required for breaking the C-H and C-X bonds.

Following paragraph is only for additional reading

If the substituent can stabilizes the developing carbocation, then that would cause lowering of right front corner of diagram. The E2 transition state will then move closer to point where it resembles E1 transition state.

Similarly, for substituents which can stabilize the developing carbanion, will lower the back left corner of diagram and subsequently E2 transition state will begin to resemble closely to that of E1cB transition state.

In E1 like transition state C-X bond cleavage is more advanced than C-H bond cleavage and vice versa for E1cB transition state.

Important factors that influence the reaction mechanism

E1

i. electron donating ability of

ii. substituents good leaving group

iii. solvents of high polarity

These factors will favor E1 pathway. Base is not important in the rate determining step but its presence is important.

E2

Base participates in the rate-determining step

i. strength of base ii.

nature of leaving group

iii. nature of the solvent

❖ If strong base is used reaction will move towards E1cB like pathway whereas good leaving group with strongly ionizing solvent will cause it to move towards E1 pathway.

Orientation of double bond

In a substrate where the double bond can be generated in different regions of the molecule, the obvious question is whether one can predict which one is likely to be the major product. Here comes the issue of ‘regio’ ‘selectivity’

In many substrate, more than one kind of β hydrogens can be removed in an elimination reaction. Which of the β hydrogens is lost depends on various factors.

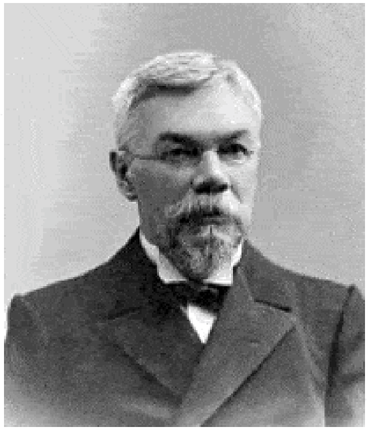
Three **rules** generally **govern regiochemistry**.

(1) Zaitsev’s Rule

(2) Hofmann Rule

(3) Bredt’s Rule

Zaitsev's Rule

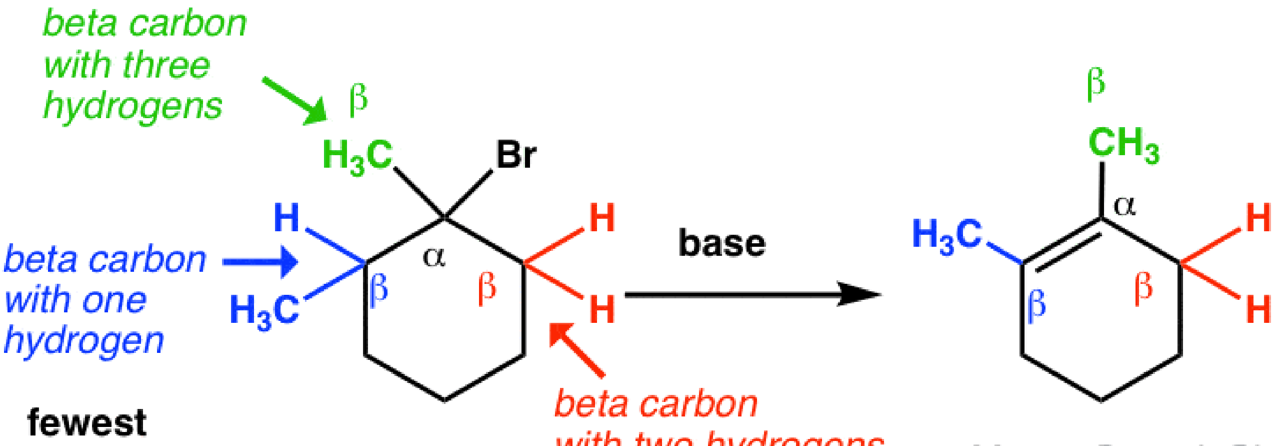


> "The alkene formed in greatest amount is the one that corresponds to removal of the hydrogen from the β-carbon having the fewest hydrogen substituents"
>
> Alexander M. Zaitsev, 1875

alpha (α) **carbon**: the carbon attached to the leaving group

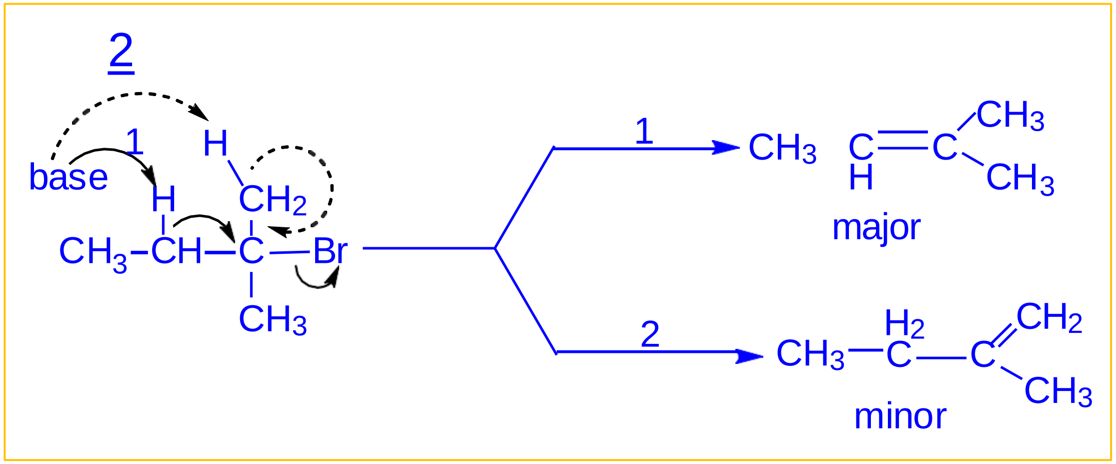
beta (β) **carbon**: the carbon **adjacent** to the carbon attached to the leaving group

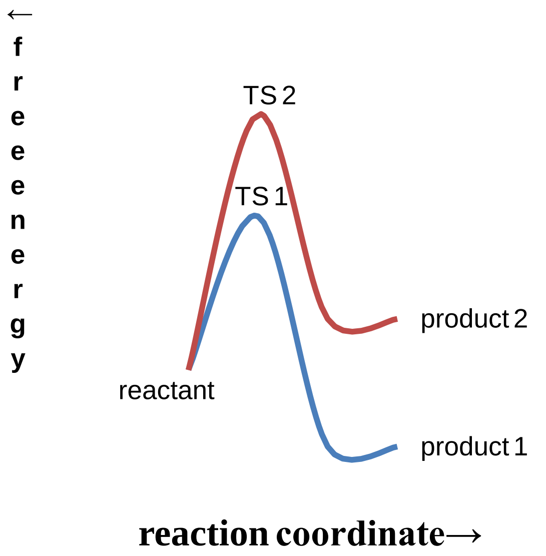
In this case the **blue** β carbon has the fewest hydrogens, and therefore the alkene formed from this alkyl halide in an elimination reaction would be **this:**



Zaitsev`s rule

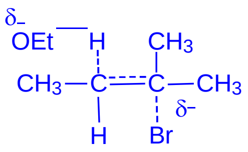
In an elimination reaction, the major product formed will be a more substituted alkene. This means that removal of the hydrogen form the more substituted β-carbon atom should occur.





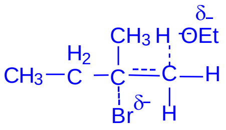
Transition state for path 1 leading to more substituted olefin is lower in energy than in path 2.

The relative positions (energies) of TS-I and TS-II is shown in the figure



T S (I)

more stable - resembles tri-substituted alkene



T S (II)

Less stable - resembles di-substituted alkene

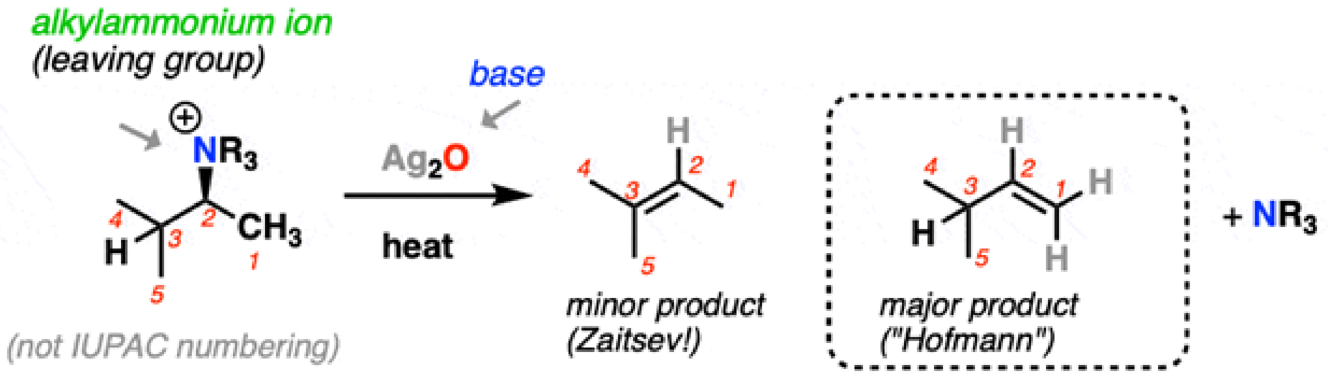
Additionally The product stability (more substituted olefin generated as a result of the elimination reaction) can be explained using the concept of orbital interaction between the CH_3 orbitals and that of the pi-bond.

Hofmann Elimination

- ✓ The is an elimination reaction of quaternary ammonium or sulfonium salts that forms C-C double bonds [pi bonds]. It proceeds through a concerted E2 mechanism.
- ✓ In contrast with most elimination reactions that make alkenes, which follow the Zaitsev (Saytzeff) rule, the Hofmann elimination tends to provide the *less* substituted alkene.
- ✓ Hofmann elimination is observed for compounds containing bulky leaving groups such as.

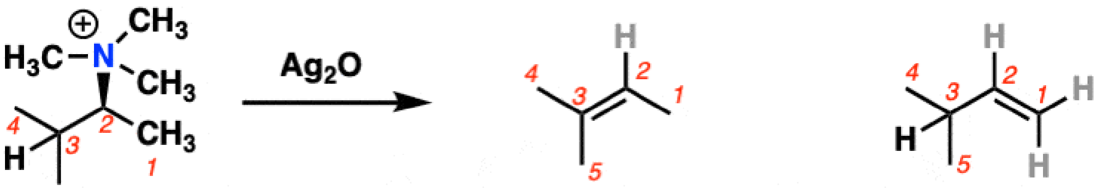
When the leaving group in an E2 elimination is a charged alkylammonium ion, the elimination product tends to be the **less**-substituted (*non-Zaitsev*) alkene rather than the more substituted ***(*****Zaitsev*****)*** alkene.

This type of elimination is sometimes called the “Hofmann” elimination and the less-substituted alkene is called the “Hofmann” product



• The less-substituted alkene is favored is due to unfavorable steric interactions (*gauche interactions)* between the bulky NR_3 leaving group and neighboring alkyl groups in the E2 transition state leading to the Zaitsev product.

Why isn't the Zaitsev the major product? **Because of the bulky leaving group!!!**



(not IUPAC numbering)

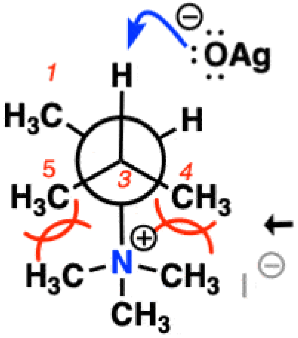
minor product
(Zaitsev!)

major product
("Hofmann")

Draw out the conformations (Newman projections) that lead to the two different products
(Because goes through E2, C–H bond and C–N bonds must be anti-periplanar)

Newman projection of conformation giving "Zaitsev" product:

looking along C_2-C_3 bond
(C_3 in front, C_2 behind)



gauche interaction

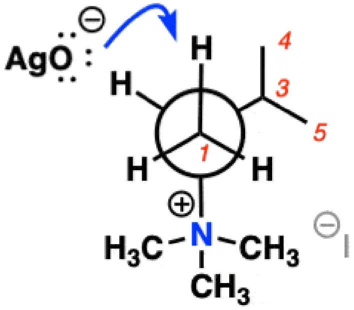
gauche interaction

"Zaitsev" *(disfavored)*

higher energy transition state
due to steric clash with leaving group

Newman projection of conformation giving "Hofmann" product:

looking along C_1-C_2 bond
(C_1 in front, C_2 behind)

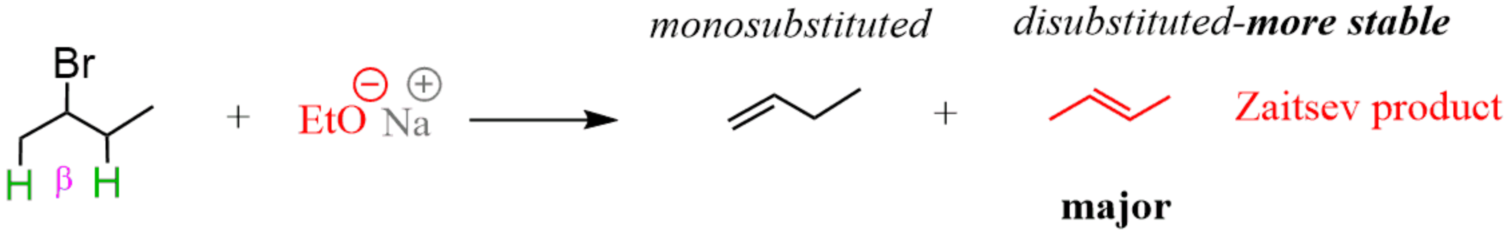


"Hofmann" *(favored)*

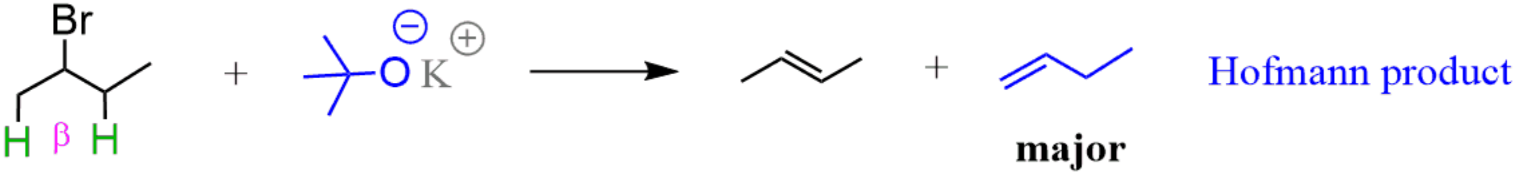
lower energy transition state
fewer steric interactions

Zaitsev vs Hofmann Product

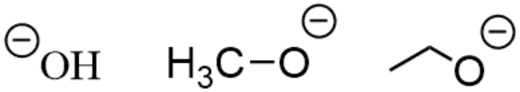
Sterically unhindered bases produce the more substituted/stable alkene as the major product.



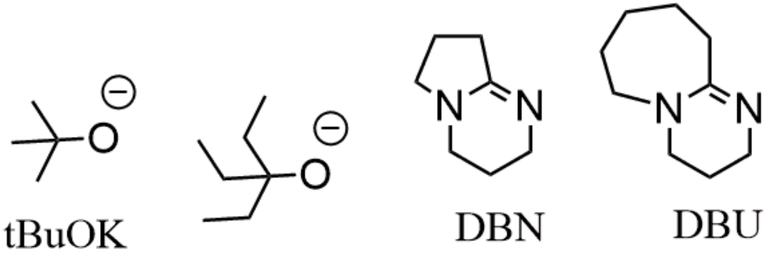
Sterically hindered/bulky bases produce the less substituted alkene as the major product.



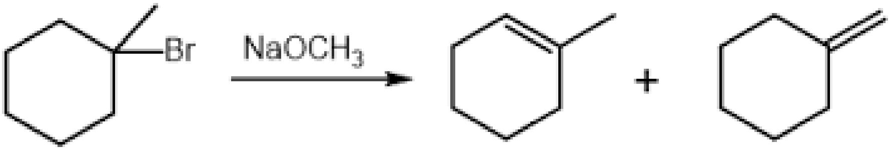
Unhindered base - Zaitsev



Hindered base - Hofmann



Zaitsev vs Hofmann Product

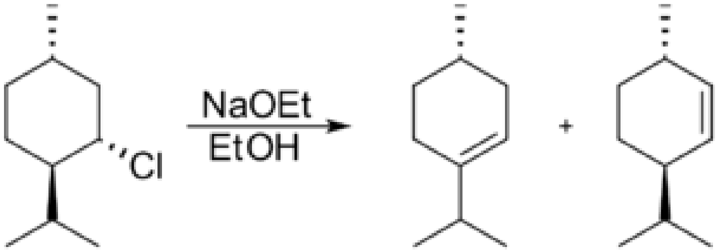


MAJOR

Zaitsev
Product

MINOR

anti-Zaitsev
Product
(Hofmann)



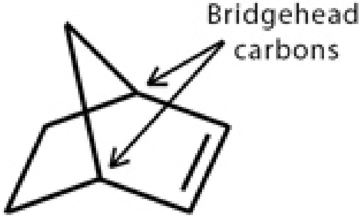
Zaitsev
0%

Hofmann
100%

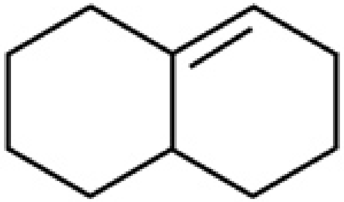
Bredt's Rule

Double Bond Formation in Bicyclic Compounds

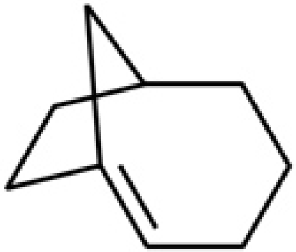
Possible



Bicyclo[2.2.1]hept-2-ene

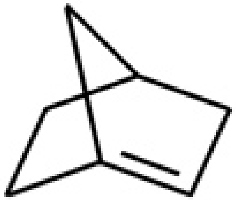


Bicyclo[4.4.0]
dec-1-ene

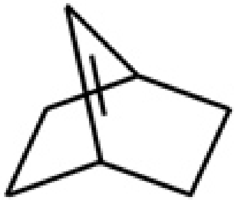


Bicyclo[4.2.1]
non-1-ene

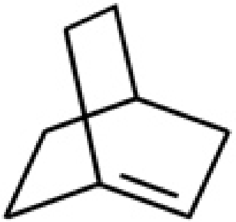
Not possible



Bicyclo[2.2.1]
hept-1-ene



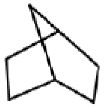
Bicyclo[2.2.1]
hept-1(7)-ene



Bicyclo[2.2.2]
oct-1-ene

Bredt`s rule:

- In a bicyclic molecule having bridge, the bridge C cannot be sp2 hybridised. Therefore, a double bond cannot be formed at the bridgehead.
- No double bond can be generated on a bridge head carbon of bicyclic compounds unless size of ring is sufficiently large.
- The origin of why Bredt’s rule can be rationalized by considering the need for lateral overlap between two adjacent p-orbitals.
- Two p-orbitals can’t remain parallel due to the bridged bicyclic structure.

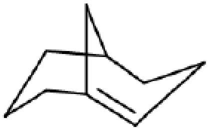


Camphane

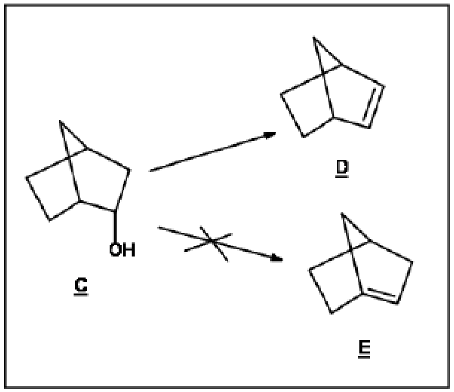
A

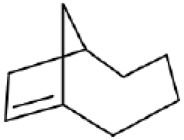
Pinane

B

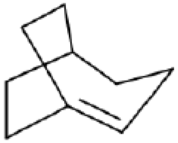


F

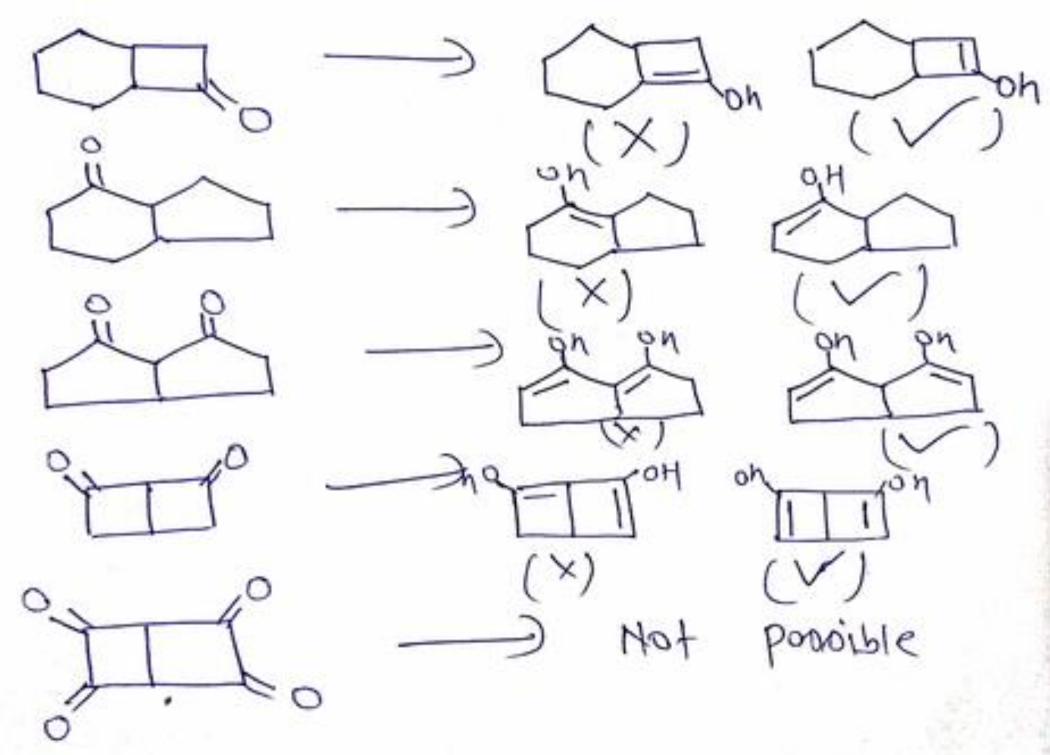




G



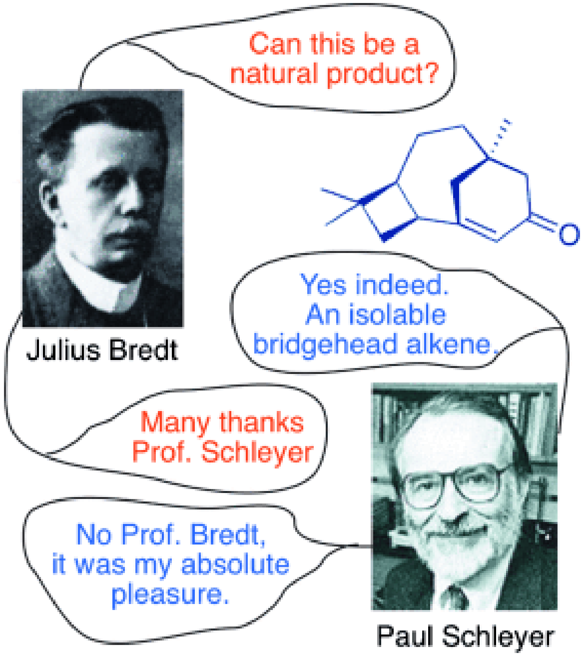
H

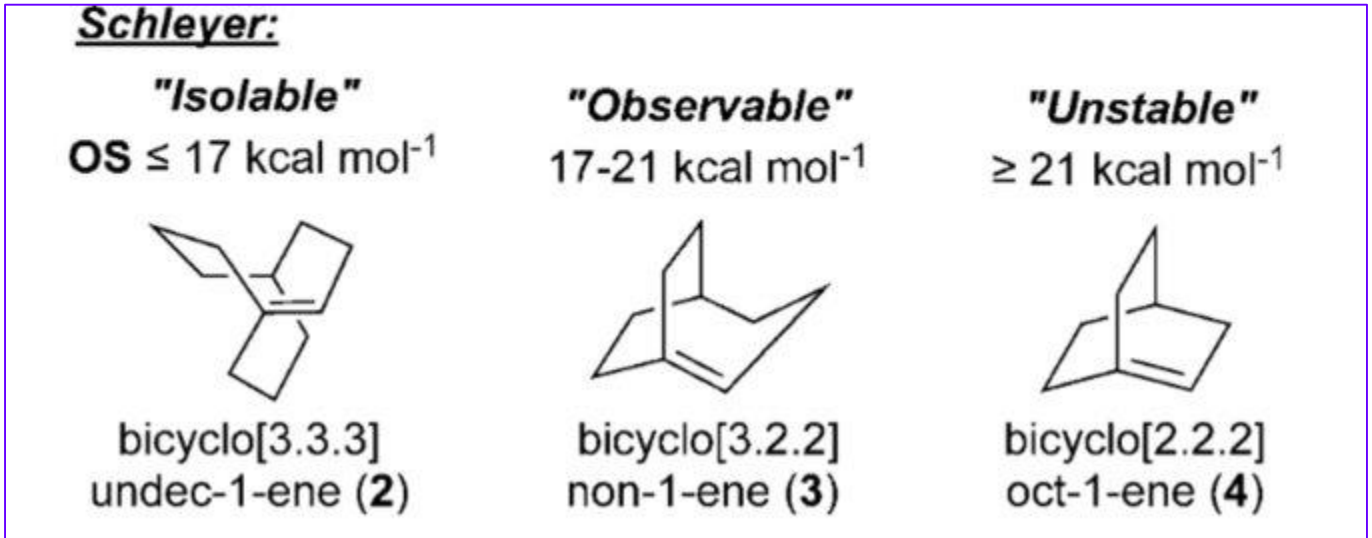


Do Anti-Bredt Natural Products Exist?
Olefin Strain Energy as a Predictor of Isolability

Dr. Elizabeth H. Krenske, Assoc. Prof. Craig M. Williams,
Angewandte Chemie, 2015, 54 (36), 10608-10612.

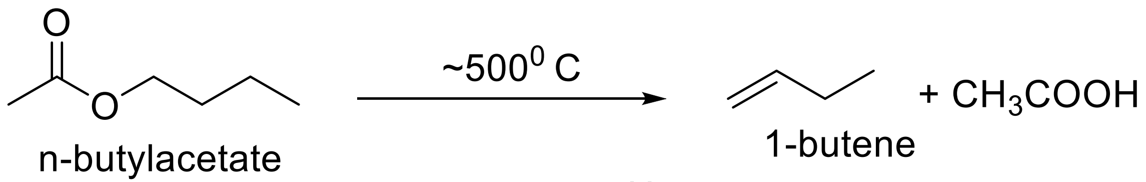
- **Bredt founded his namesake rule while studying the structures of monoterpenes.**
- **Schleyer's anti-Bredt predictive rules were the pinnacle of much physical organic chemistry interest, but the natural product element continued unabated.**
- **Olefin strain energy calculations lead to the definitive conclusion that Bredt's rule should not be applied to natural products containing a bridgehead alkene.**

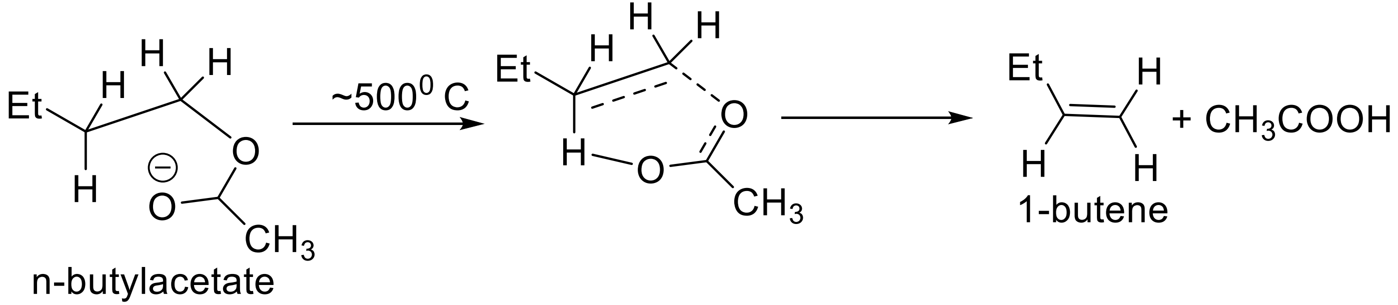




Pyrolytic cis Elimination

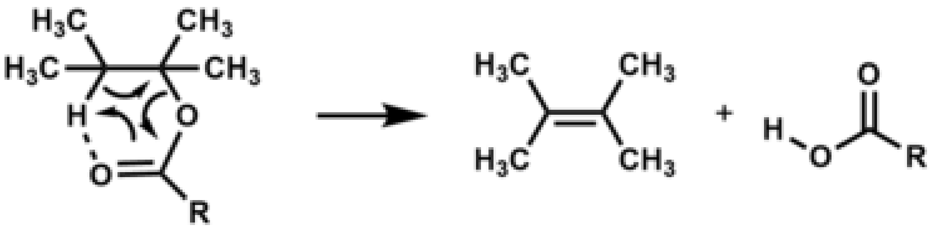
- Some substrates such as esters and amine oxides do not require any external agent for elimination. Simply heating such substrates provides elimination product. These reactions are known as pyrolytic elimination.
- Pyrolytic elimination are suggested to proceed through a concerted, cyclic, six membered transition state. They are often designated as Ei (i.e., Elimination internal).
- The pyrolytic elimination has a common mechanistic feature: a concerted reaction via a cyclic transition state within which an intramolecular proton transfer is accompanied by syn-elimination to form a new carbon-carbon double bond.
- Pyrolytic Elimination follow stereospecific syn elimination pathway i.e. leaving group must assume syn-periplanar conformation with respect to each other.



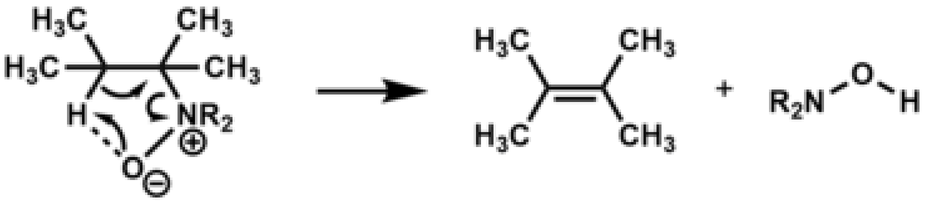


Pyrolytic cis Elimination

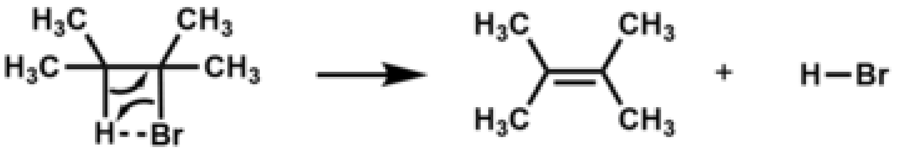
- **Pyrolytic Elimination follow stereospecific syn elimination pathway i.e. leaving group must assume syn-periplanar conformation with respect to each other.**
- **Depending on the compound, elimination takes place through a four, five, or six-membered transition state.**



6 membered transition state



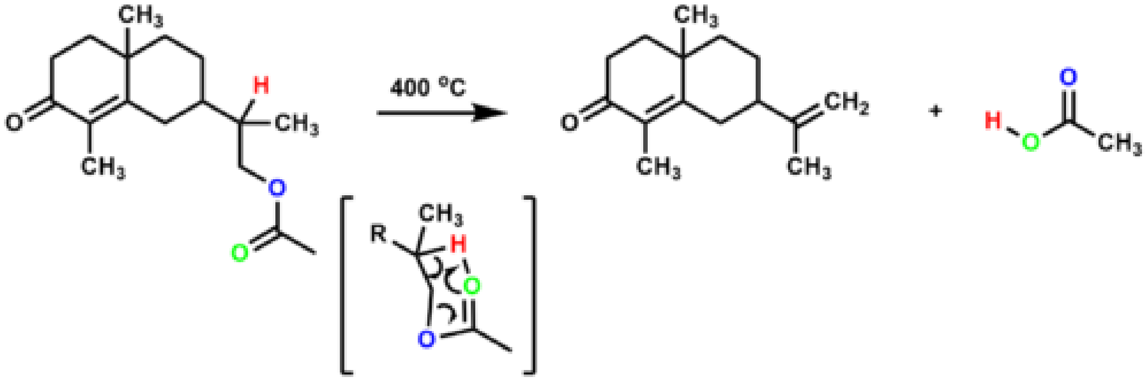
5 membered transition state



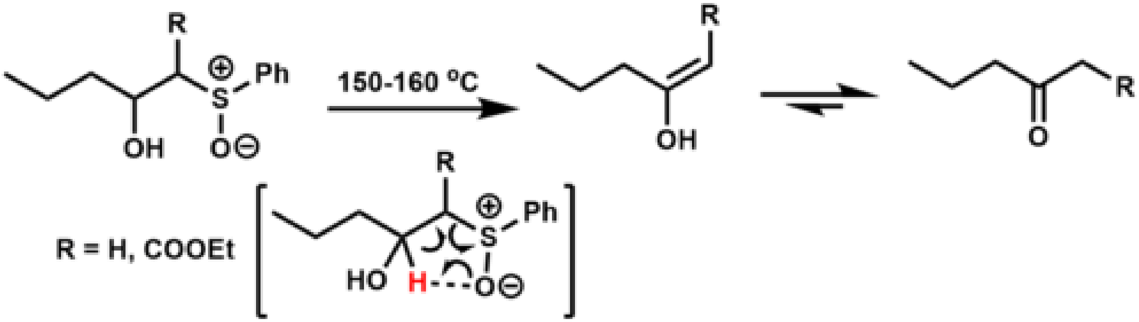
4 membered transition state

Pyrolytic cis Elimination

- **Ester (acetate) pyrolysis: The pyrolytic decomposition of esters is an example of a thermal *syn* elimination. When subjected to temperatures above containing β-hydrogens can eliminate a carboxylic acid through a 6-membered transition state, resulting in an alkene.**

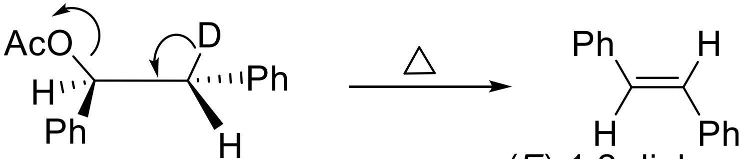


- **Sulfoxide elimination: β-hydroxy phenyl sulfoxides were found to undergo thermal elimination through a 5-membered cyclic transition state, yielding β-keto esters and methyl ketones after tautomerization and a sulfenic acid.**



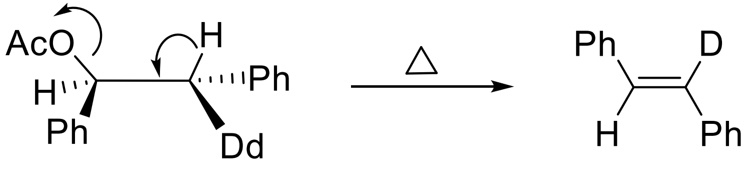
Examples for pyrolytic cis eliminations

Example-1



threo-2-deutro
-1,2-diphenylethyl-2-acetate

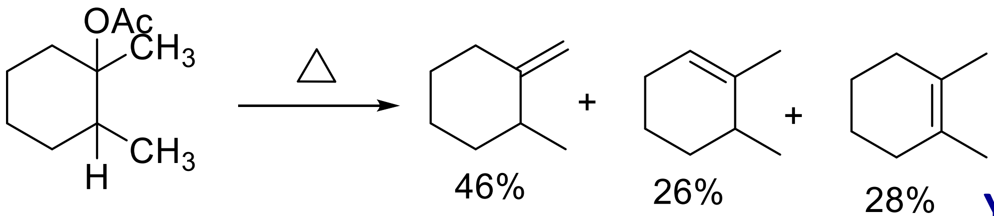
(*E*)-1,2-diphenylethene



erythro-2-deutro
-1,2-diphenylethyl-2-acetate

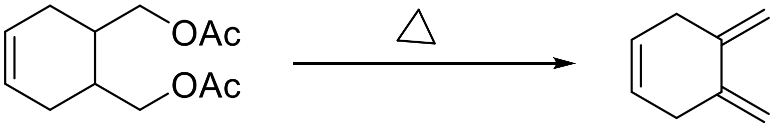
(*E*)-1-deuteriostilbene

Example-2



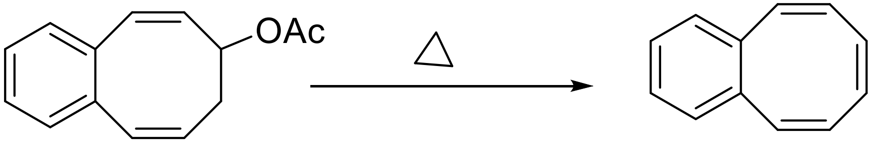
You are expected to write the mechanism for these additional examples.

Example-3



4,5-dimethylenecyclohexane

Example-4

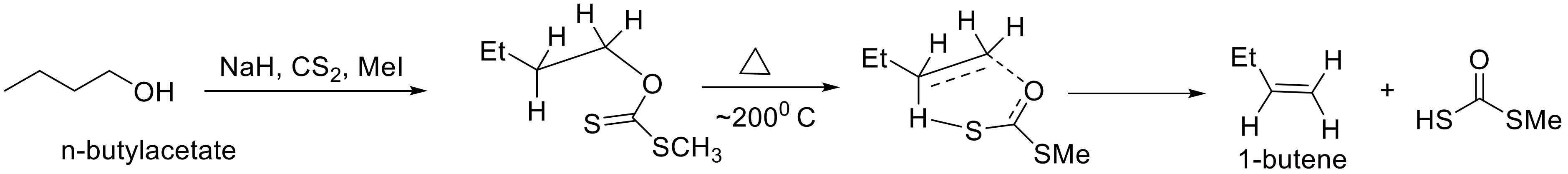


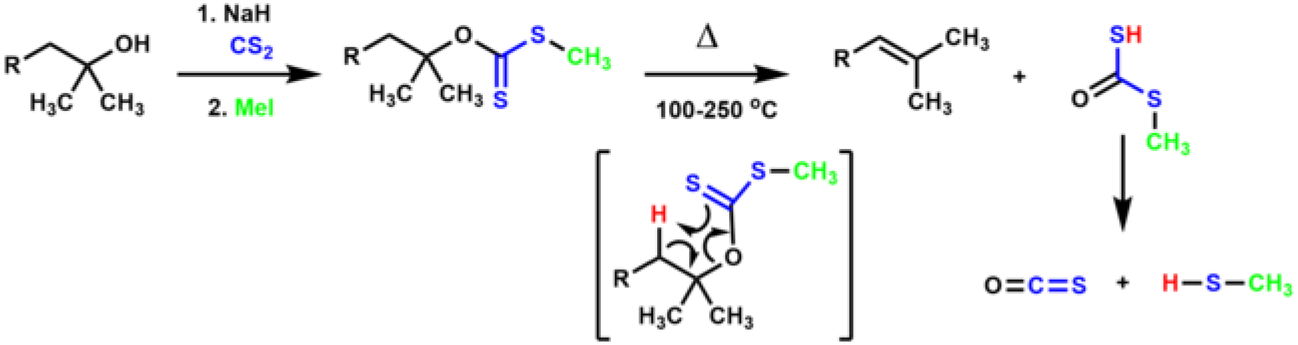
Benzocyclooctatetraene

DePuy, C. H.; King, R. W. Chem. Rev. **1960**, 60, 431-457.

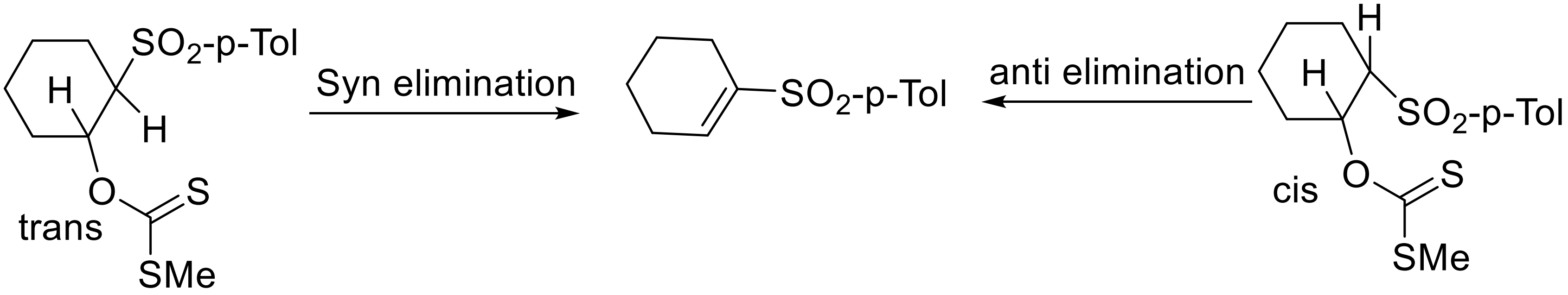
Chugaev Elimination

- In these reactions, O-alkyl-S-methyl xanthates are pyrolysed to olefin, (oxysulfide and methanethiol) at about 200^0C.
- These reactions are of particular use due to its relatively milder reaction conditions as compared to other pyrolitic eliminations.
- The Chugaev elimination is very similar to the ester pyrolysis, but requires significantly lower temperatures to achieve the elimination, thus making it valuable for rearrangement-prone substrates.
- Using this method, alkenes which are labile or tend to undergo rearrangement can be prepared.
- These reactions take place via six membered cyclic transition state and generally proceed through syn elimination, although anti elimination is also reported.

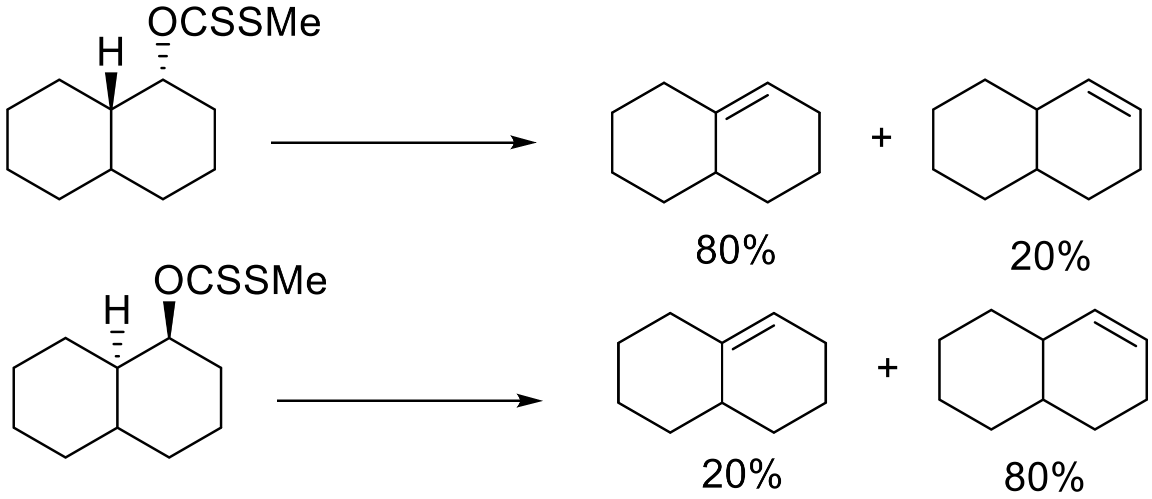




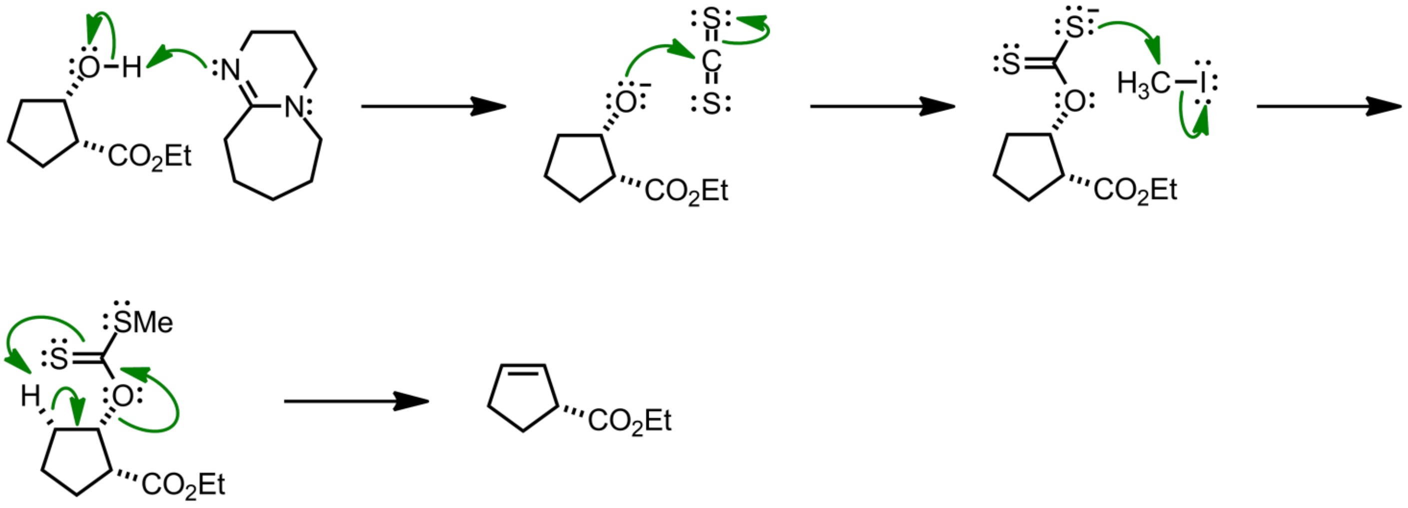
Chugaev Elimination

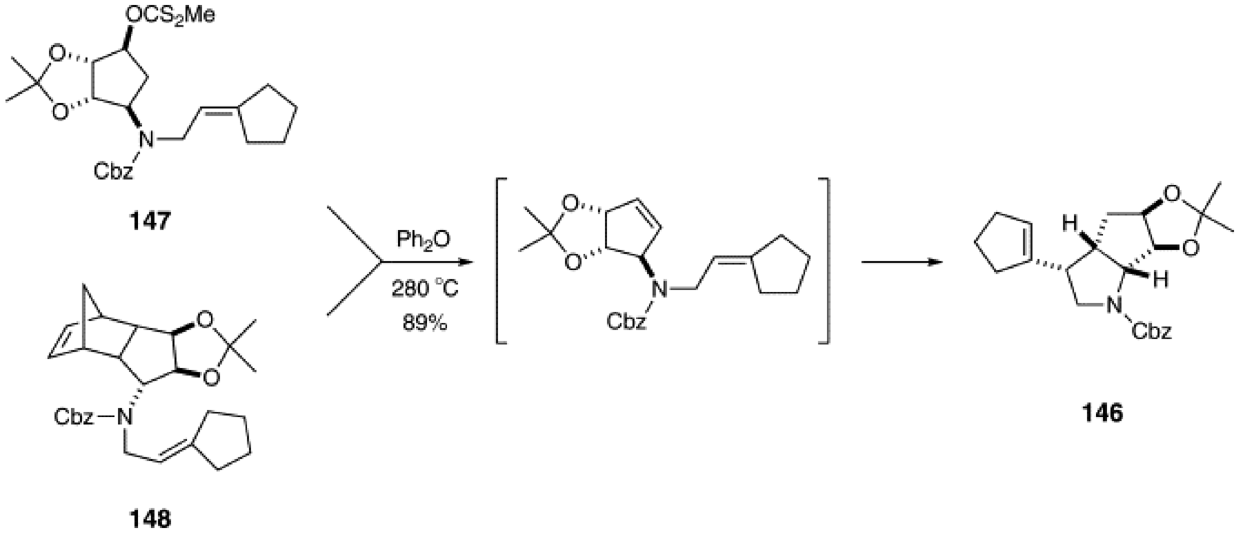


F. G. Brodwell; P. S. Zandis, J.A.C.S., 1958, 80, 2450-2453.
C. H. DePuy; R. W. King, Chem.Rev., 1960, 60, 431-457.

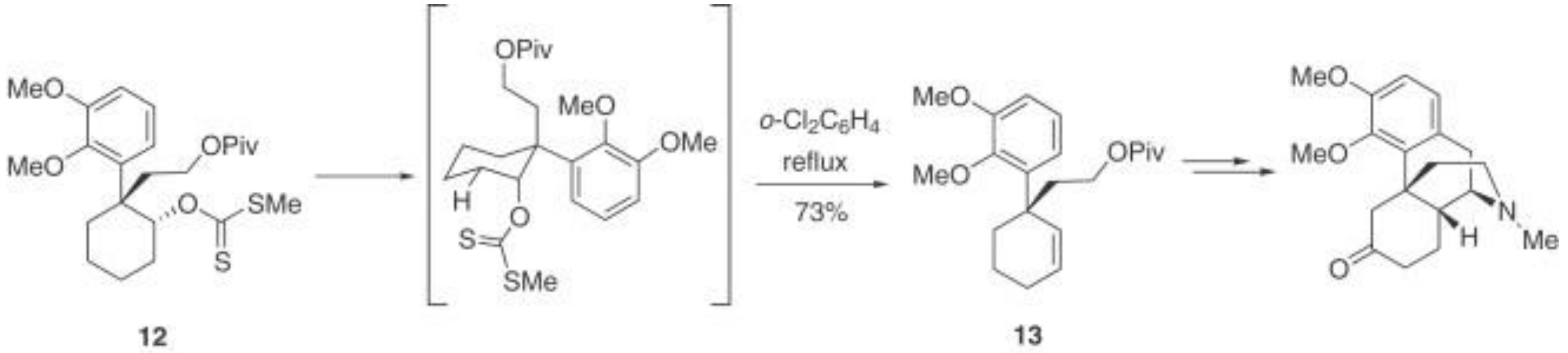


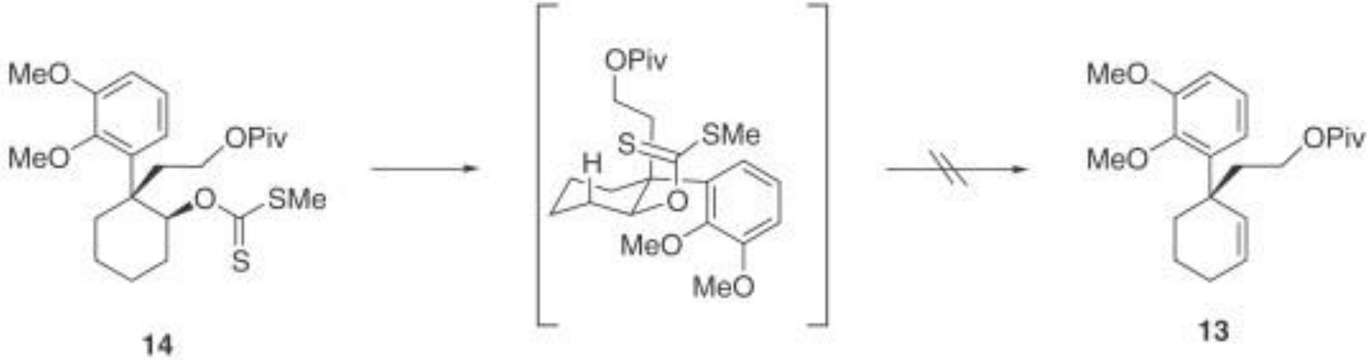
Examples on Chugaev Elimination





Examples on Chugaev Elimination

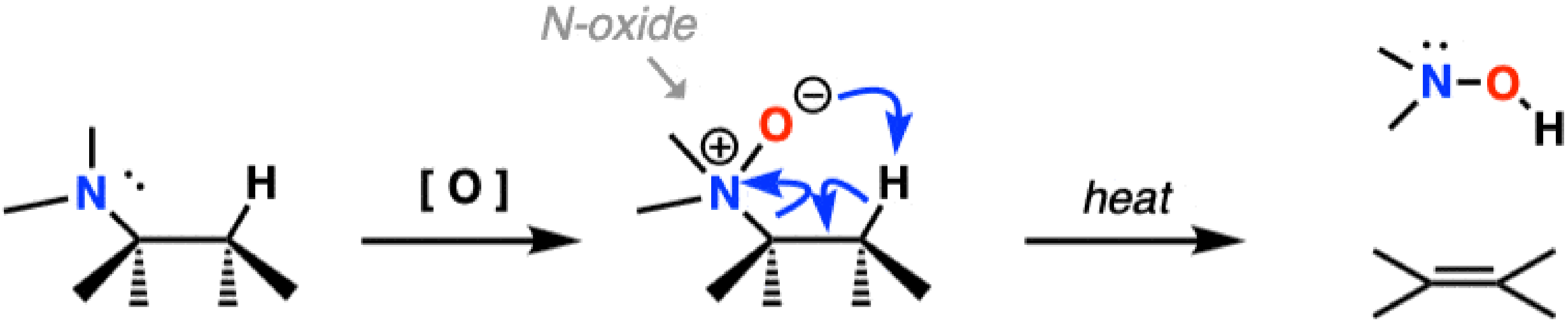




Cope Elimination Reaction

The Cope Elimination

The Cope elimination is an intramolecular **syn** elimination of *N*-oxides to give alkenes.



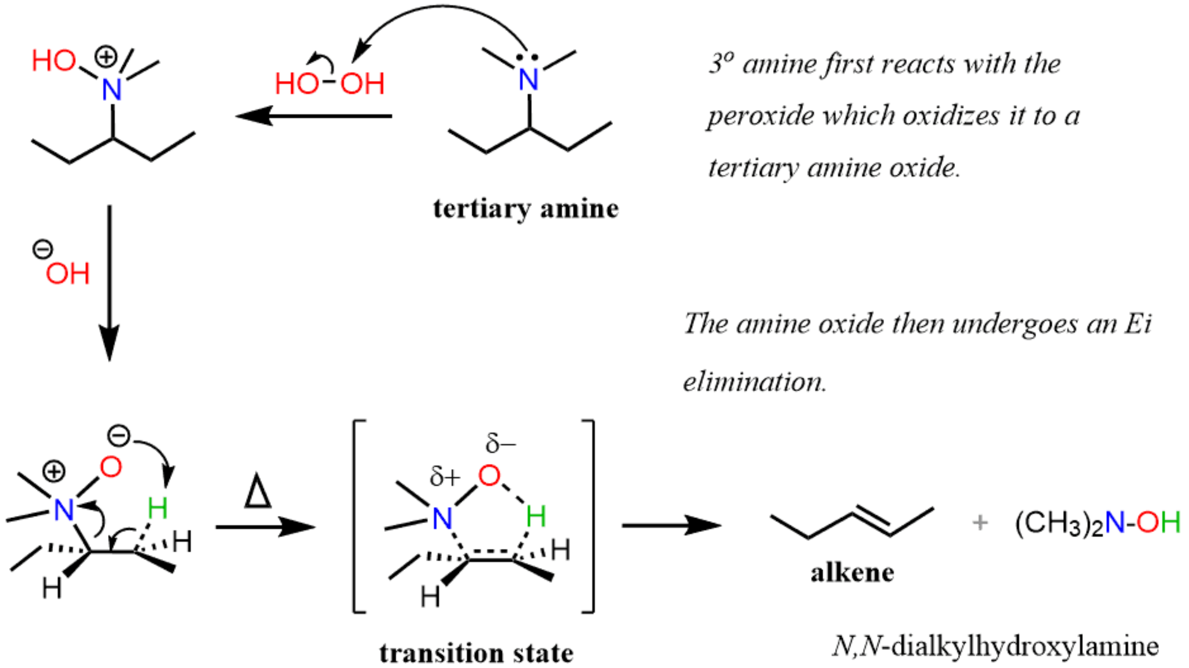
Tertiary amine **N-oxide** **Alkene**

- *N*-oxides can be made through oxidation of **tertiary** amines with H_2O_2.
- Heating the *N*-oxide results in a **concerted** elimination reaction where both the C–N and C–H bond depart from the **same face** of the C–C bond, resulting in a new C–C pi bond
- The Cope elimination is an example of a **stereospecific** reaction.

❖ **Pyrolytic elimination of amine oxide can be done under mild conditions, to give olefin. This reaction is called as Cope reaction.**

❖ **Internal base attacks β proton, so highly basic nucleophile is not required**.

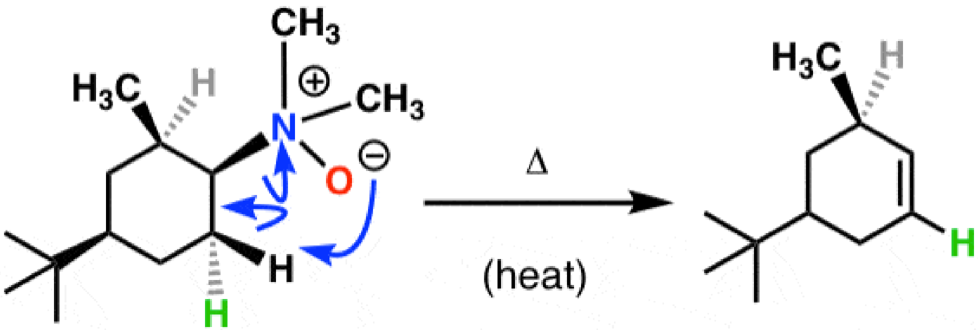
Cope Elimination Reaction Mechanism



3º amine first reacts with the peroxide which oxidizes it to a tertiary amine oxide.

The amine oxide then undergoes an Ei elimination.

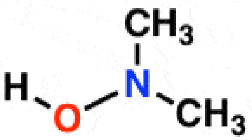
Cope Elimination: Mechanism



***N*-oxide**

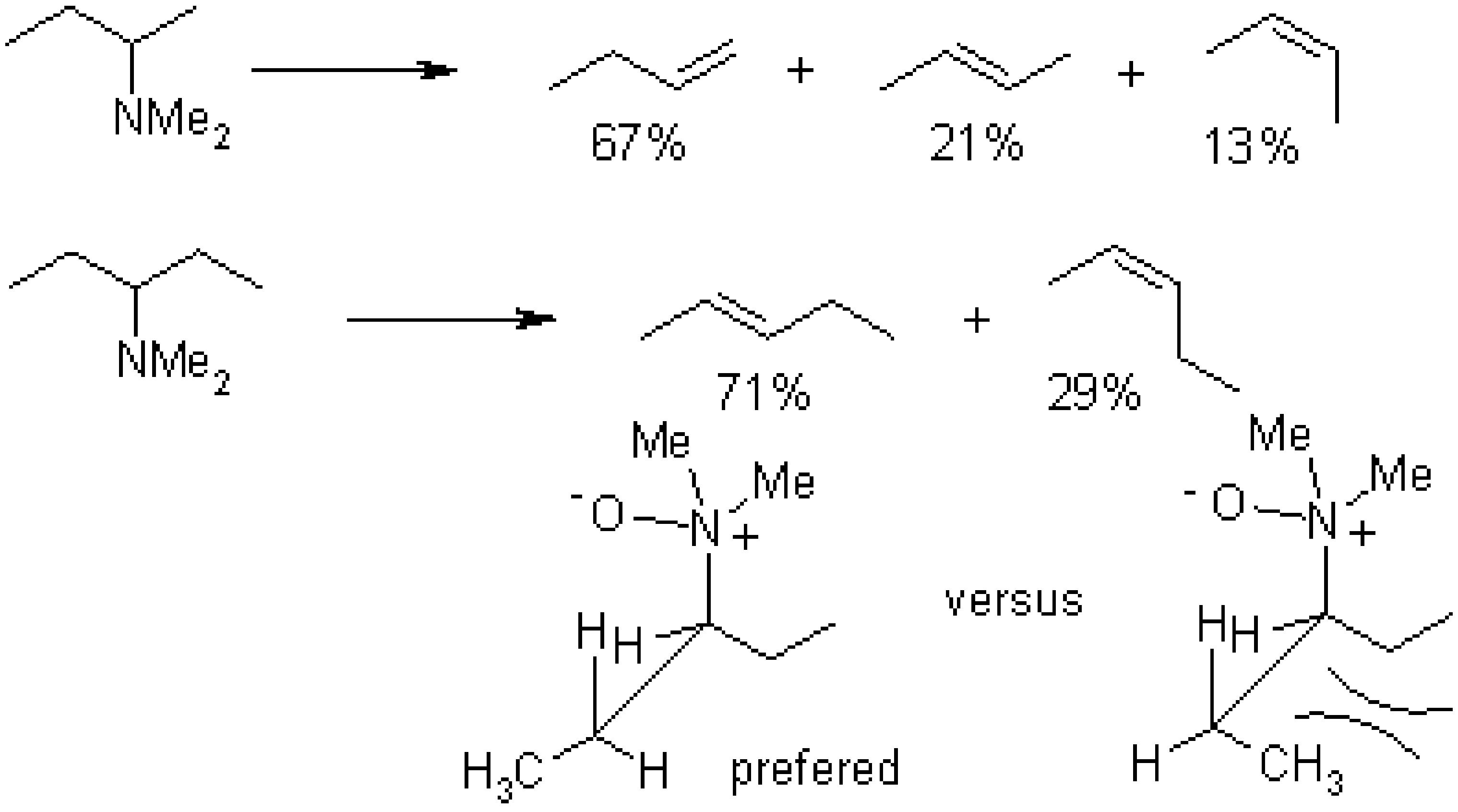
Alkene

Bonds Formed	**Bonds Broken**
C–C (pi)	C–H
O–H	C–N

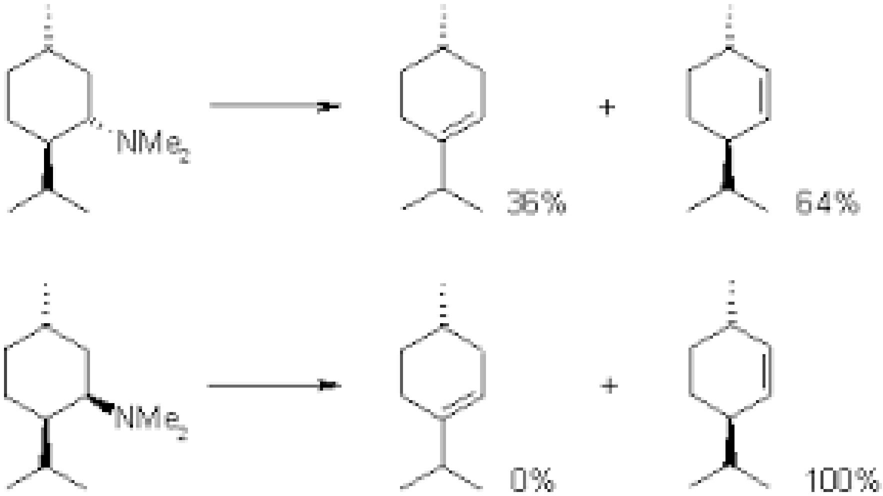


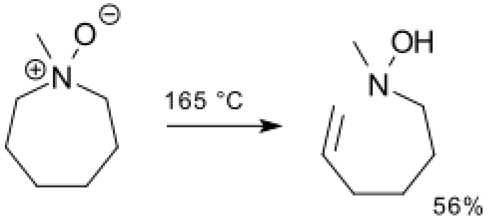
Cope Elimination Reaction Examples

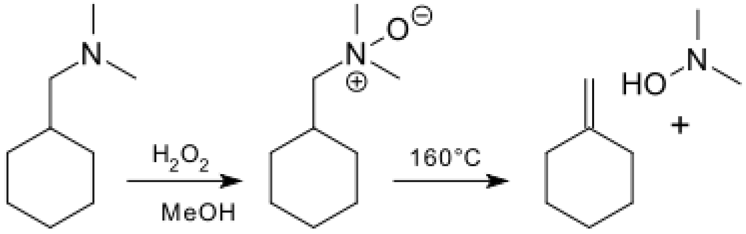
Cope Elimination should not be confused with Cope rearrangement. The Cope reaction or Cope elimination, developed by Arthur C. Cope, is an elimination reaction of the N-oxide to form an alkene and a hydroxylamine.



Cope Elimination Reaction Examples

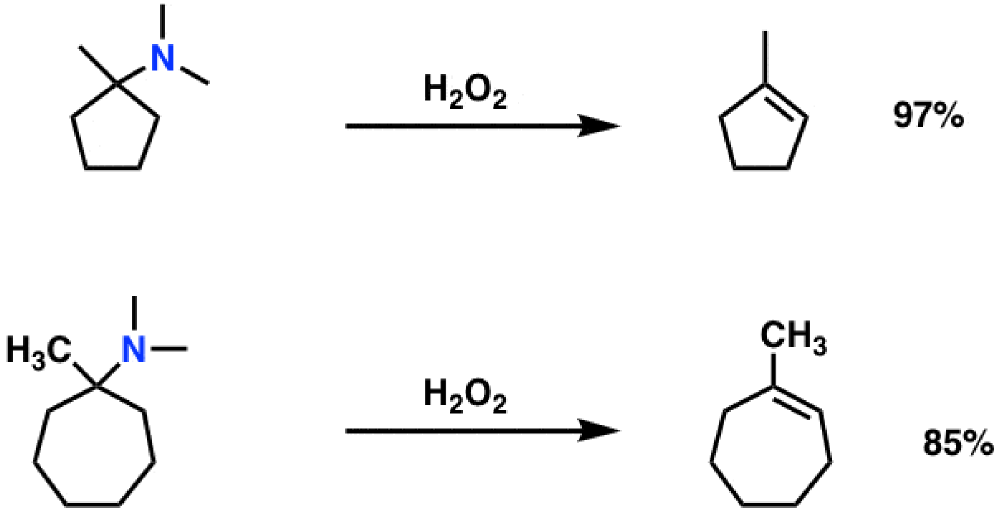






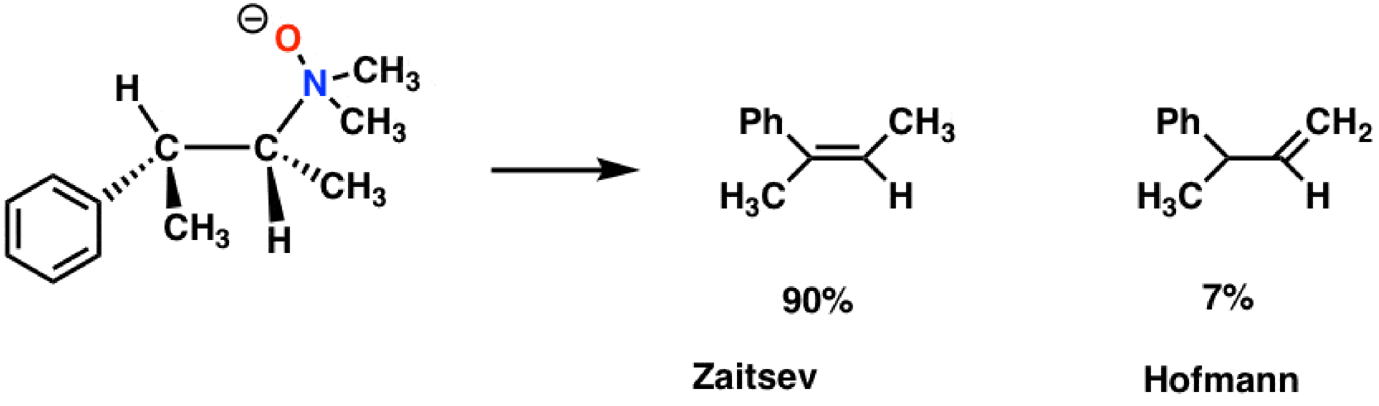
Cope Elimination Reaction Examples

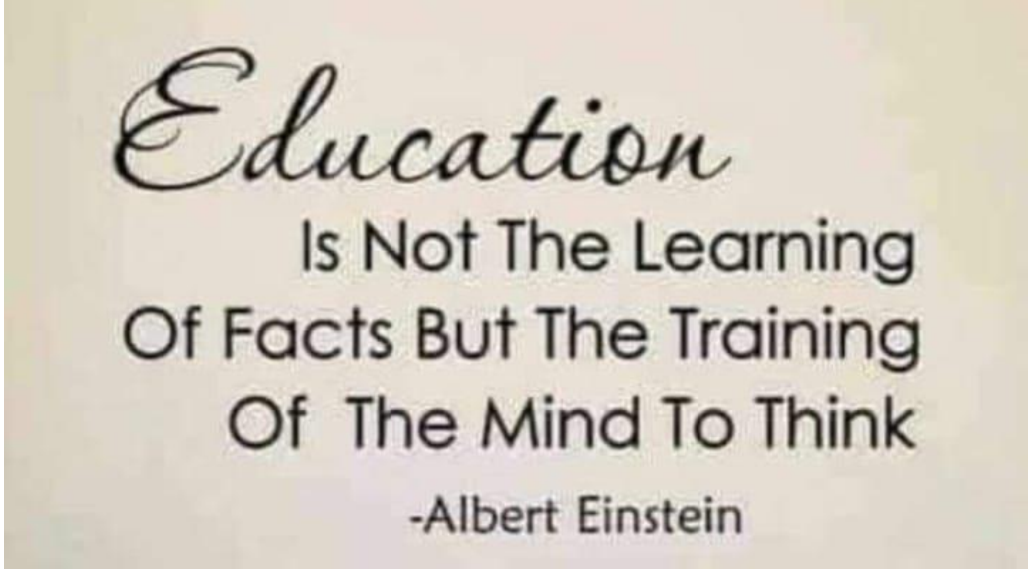
No, the Cope Elimination tends to give mostly Zaitsev products:



see: Journal of the American Chemical Society, **1960**, *82*, 4663.

The Zaitsev products are also favored in this example:





Education
Is Not The Learning
Of Facts But The Training
Of The Mind To Think

-Albert Einstein