Introduction to Organic Reaction

- ✓ A chemical reaction is the transformation of one chemical or collection of chemicals into another chemical or collection of chemicals.
- ✓ A chemical reaction involves making new chemical bonds and breaking old chemical bonds in both organic and inorganic chemistry.
- ✓ Therefore, Organic reactions are chemical reactions involving organic compounds.
- ✓ This reactions can be organized broadly in two ways by:
- ✓ (i) What types of reactions? and (ii) How these reactions occur?

Types of Organic Chemistry

- ✓ The basic organic chemistry reaction types are
  - a) addition reactions,
  - b) elimination reactions,
  - c)substitution reactions,
  - d) pericyclic reactions,
  - e) rearrangement reactions,
  - f) photochemical reactions and
  - g) redox reactions.
- ✓ But in organic synthesis, organic reactions are used in the construction of new organic molecules.

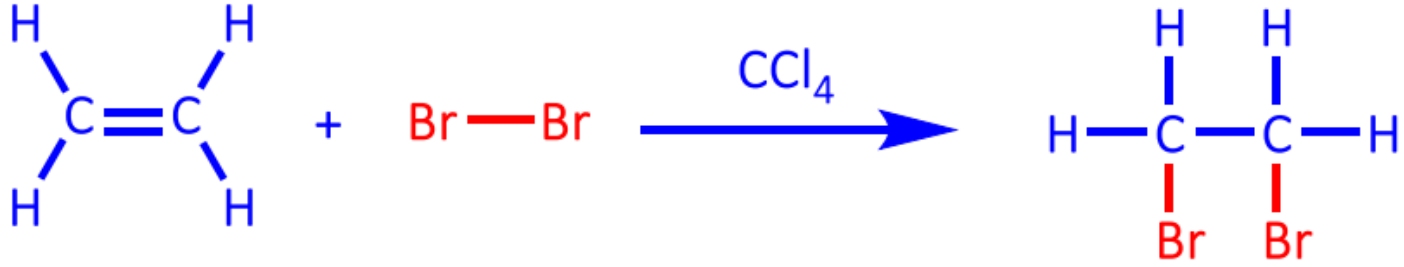
REACTION TYPE	SUBTYPE	COMMENT
Addition Reactions	• Electrophilic Addition • Nucleophilic Addition • Radical Addition	Include such reactions as halogenation, hydrohalogenation and hydration.
Elimination Reaction		Include processes such as dehydration and are found to follow an E1, E2 or E1cB reaction mechanism
Substitution Reactions	• Nucleophilic Aliphatic Substitution	With S_N1, S_N2 and S_Ni reaction mechanisms
	• Nucleophilic Aromatic Substitution • Nucleophilic Acyl Substitution • Electrophilic Substitution • Electrophilic Aromatic Substitution • Radical Substitution	
Rearrangement Reactions	• 1,2-Rearrangements • Pericyclic Reactions • Metathesis	

ADDITION REACTIONS

✓ Addition Reactions reaction are those in which atoms or groups of atoms are simply added to a double bond without the elimination of atoms or other molecules.



✓ In an addition all parts of the adding reagent appear in the product; two molecules become one.





X = I, Br, Cl

Addition reaction…,

- ✓ In this reaction at least one pie (π) bond is lost while two new sigma (σ) bonds are formed.
- ✓ Double bonds become saturated, triple bonds are converted into double bonds or many become saturated by further addition.
- ✓ Molecules containing carbon-hetero double bonds like carbonyl (C=O) groups, or imine (C=N) groups, can undergo addition, as they too have double bond character.
- ✓ An addition reaction is the reverse of an elimination reaction.

Cont'd...

- ✓ For instance, the hydration of an alkene to an alcohol is reversed by dehydration.
- ✓ There are two main types of polar addition reactions:

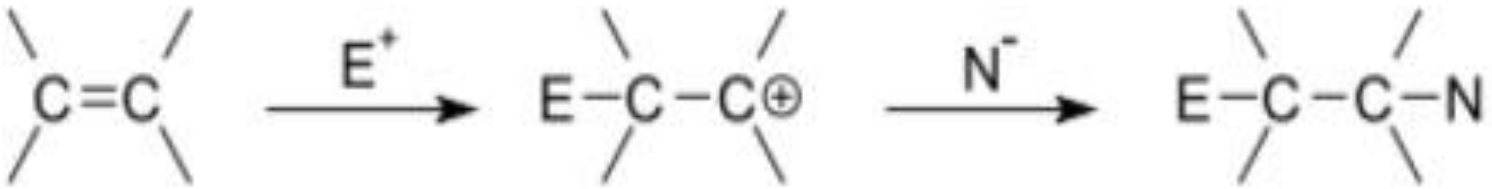
  (i) electrophilic addition and

  (ii) nucleophilic addition.
- ✓ Two nonpolar addition reactions exist as well,

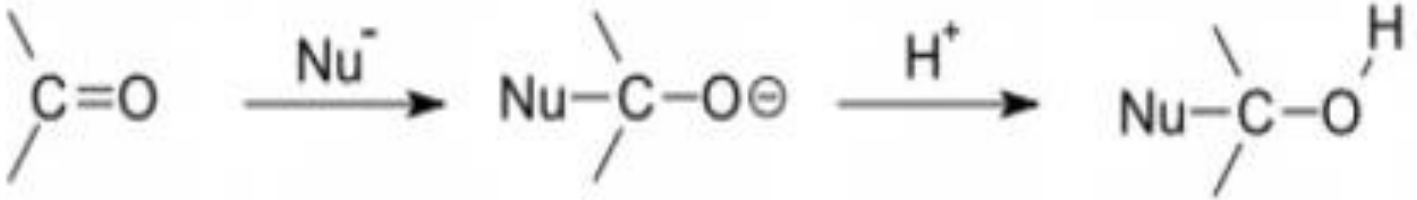
  (i) free radical addition and

  (ii) cycloadditions.
- ✓ Addition reactions are also encountered in polymerizations and called addition polymerization.

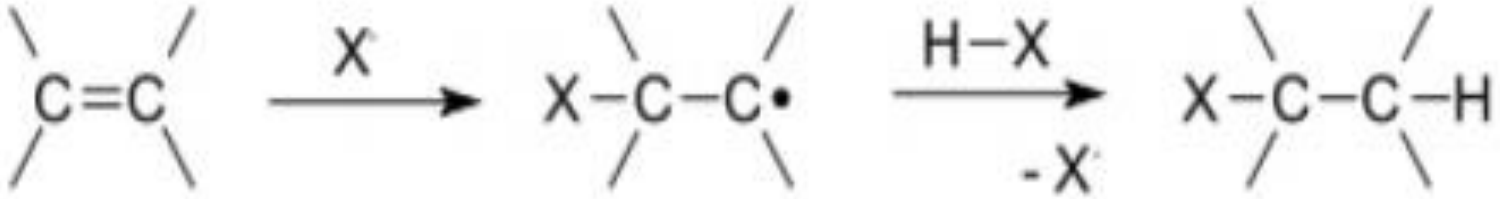
For instance;



Electrophilic addition to alkene



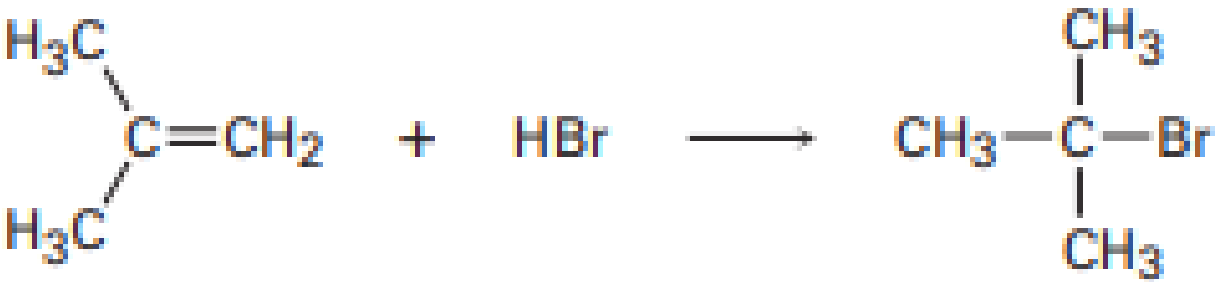
Nucleophilic addition of nucleophile to carbonyl



Free radical addition of halide to alkene

Electrophilic addition Reaction of Alkenes

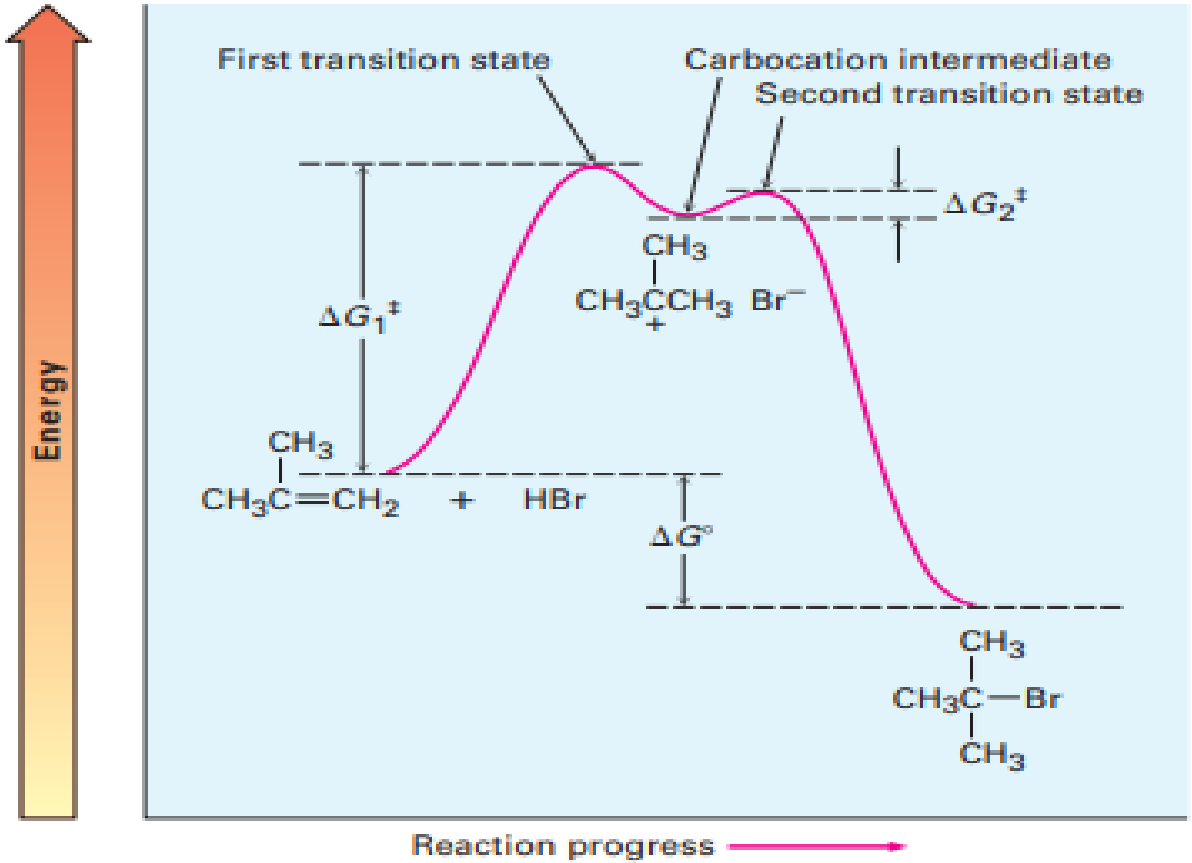
- ✓ alkenes behave as nucleophiles (Lewis bases) in polar reactions, donating a pair of electrons from their electron-rich C=C bond to an electrophile HX (Lewis acid).
- ✓ For example, reaction of 2-methylpropene with HBr yields 2-bromo-2-methylpropane.
- ✓ A hydrogen atom on the electrophile HBr is attacked by electrons from the nucleophilic double bond, forming a new C–H bond.



2-Methylpropene 2-Bromo-2-methylpropane

Cont'd...

- ✓ Bromide ion donates an electron pair to the positively charged carbon atom, forming a C–Br bond and yielding the neutral addition product.
- ✓ Energy diagram for the two-step electrophilic addition of HBr to 2-methylpropene.

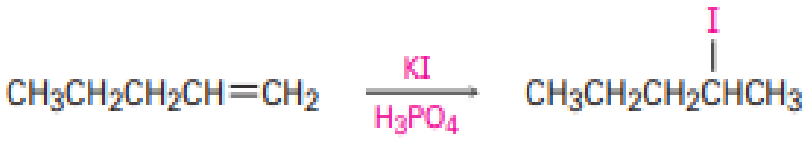


Additional Examples

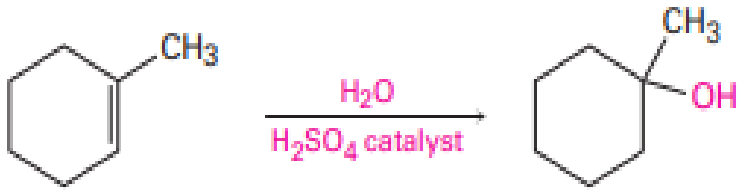
- ✓ Electrophilic addition to alkenes is successful not only with HBr but with HCl, HI, and H_2O as well.
- ✓ Note that HI is usually generated in the reaction mixture by treating potassium iodide with phosphoric acid and that a strong acid catalyst is needed for the addition of water.



2-Methylpropene — 2-Chloro-2-methylpropane (94%)



1-Pentene — (HI) — 2-Iodopentane

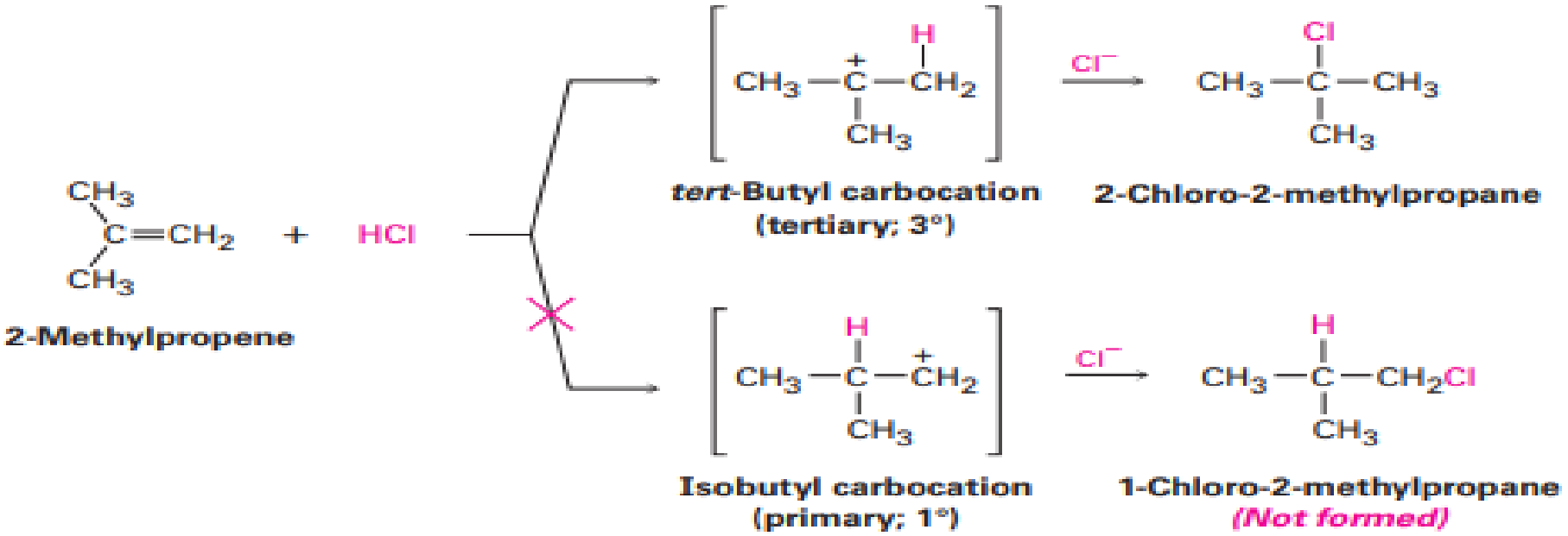


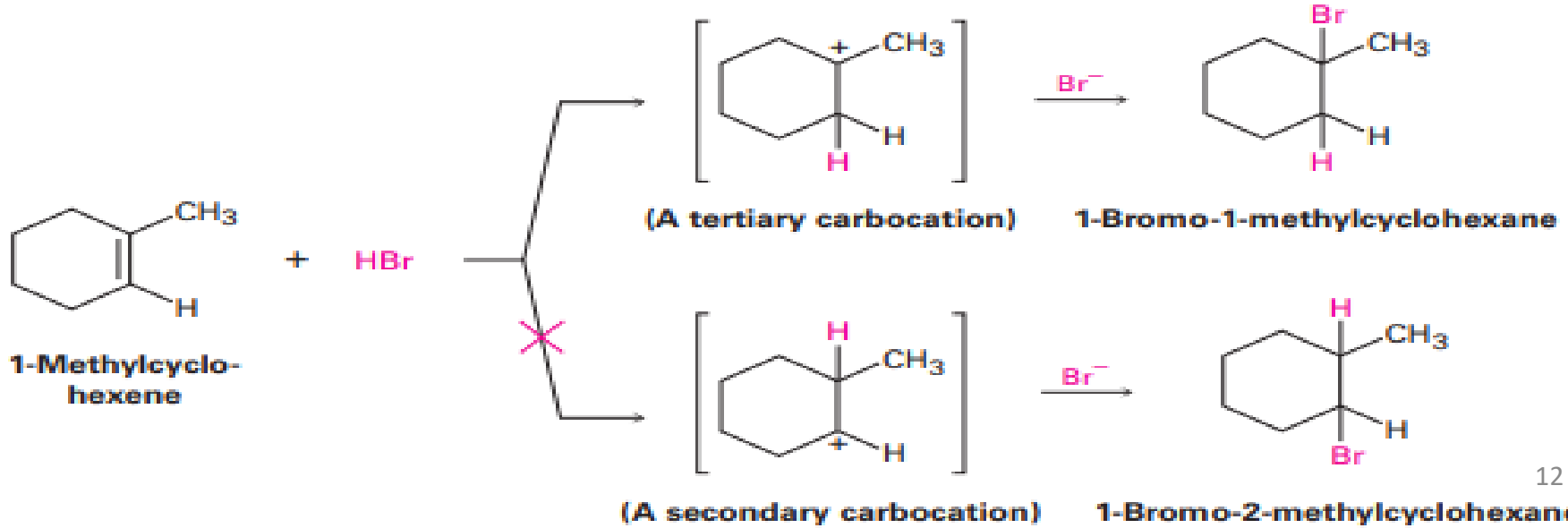
1-Methylcyclohexene — 1-Methylcyclohexanol

Orientations of electrophilic additions Rxn; Markonvikov's rule

- ✓ The reactions are regiospecific and it is only one of two possible orientations of addition occurs.
- ✓ In the addition of HX to an alkene, the more highly substituted carbocation is formed as the intermediate rather than the less highly substituted one
- ✓ For example, addition of H^+ to 2-methylpropene yields the intermediate tertiary carbocation rather than the alternative primary carbocation, and addition to 1-methylcyclohexene yields a tertiary cation rather than a secondary one.

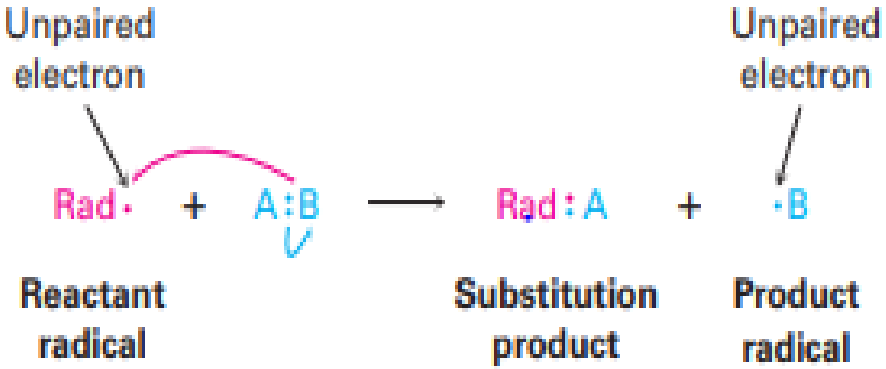
Possible reaction





Radical reactions

- ✓ Radical reactions are not as common as polar reactions but are nevertheless important in some industrial processes and biological pathways.
- ✓ It is highly reactive because it contains an atom with an odd number of electrons (usually seven) in its valence shell.



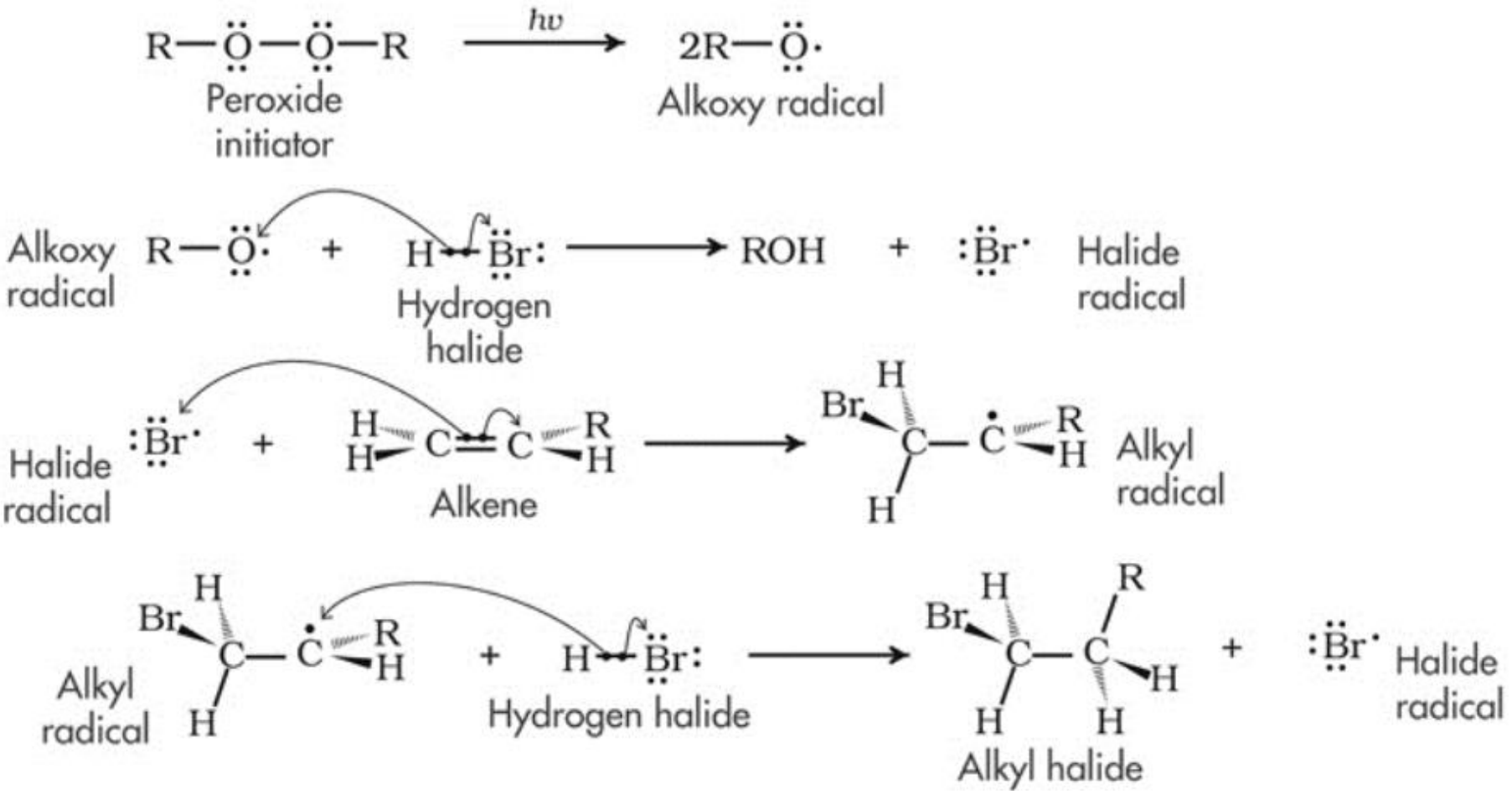
- ✓ The radical reactions in the laboratory, methane chlorination requires three kinds of steps: initiation, propagation, and termination.



Radical addition; Cont'd...

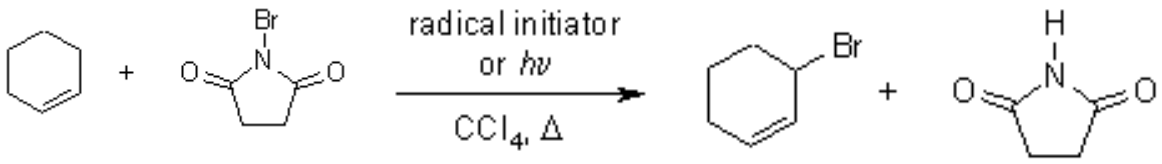
- ✓ Anti Markovnikov addition reaction is found to follow a free radical mechanism. The peroxide compound involved helps in the generation of free radicals.
- ✓ Generation of free radical through homolytic cleavage of peroxide compound.
- ✓ Attack of generated free radical on hydrogen halide to form halide radical through hemolysis
- ✓ Attack of generated halide radical on alkene molecule to form alkyl radical through hemolysis.
- ✓ Attack of a generated alkyl radical on hydrogen halide to form alkyl halide through homolytic cleavage of hydrogen halide

Cont'd...


hv
Peroxide initiator
Alkoxy radical
Alkoxy radical
Hydrogen halide
ROH
Halide radical
Halide radical
Alkene
Alkyl radical
Alkyl radical
Hydrogen halide
Alkyl halide
Halide radical

For instance

✓ **Consider the Wohl-Ziegler Reaction**



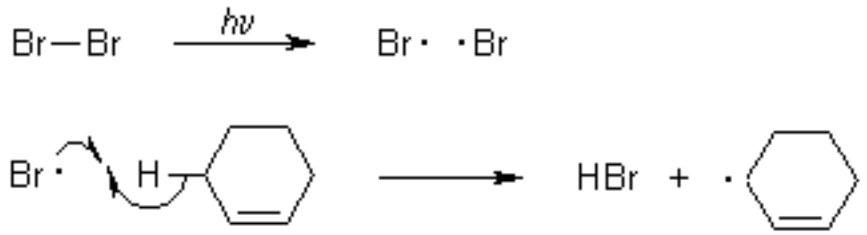
✓ Mechanism of the Wohl-Ziegler Reaction

✓ It is very important to keep the concentration of Br_2 and HBr low to prevent side reactions derived from simple ionic addition with the alkene.

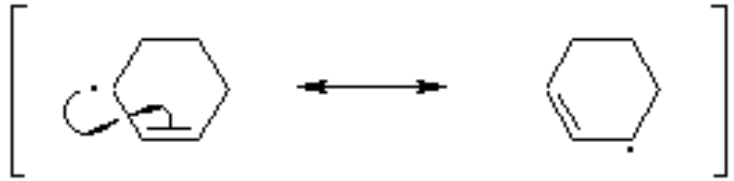
✓ These reagents are therefore generated in situ from NBS. The catalytically active species is Br_2, which is almost always present in NBS samples (red colour).

✓ A radical initiator (UV, AIBN) is needed for the homolytic bond cleavage of Br_2.

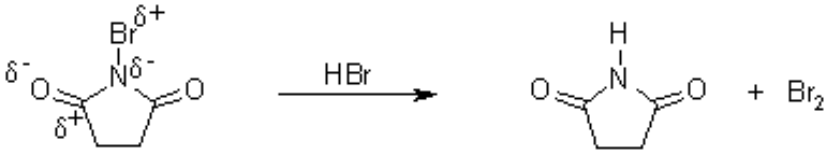
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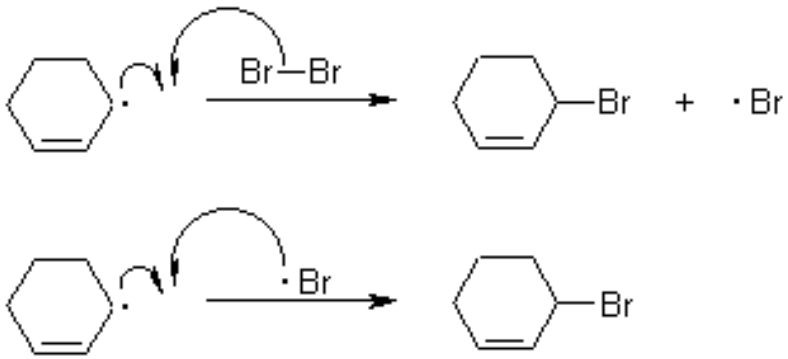
✓ The allylic position is favoured for hydrogen abstraction, because the resulting radical intermediate is resonance stabilized:



Regeneration of Br_2:



Bromination:



✓ Bromination is favored to occur at the more highly substituted position, because the corresponding intermediate radicals are better stabilized.

Application of free radicals

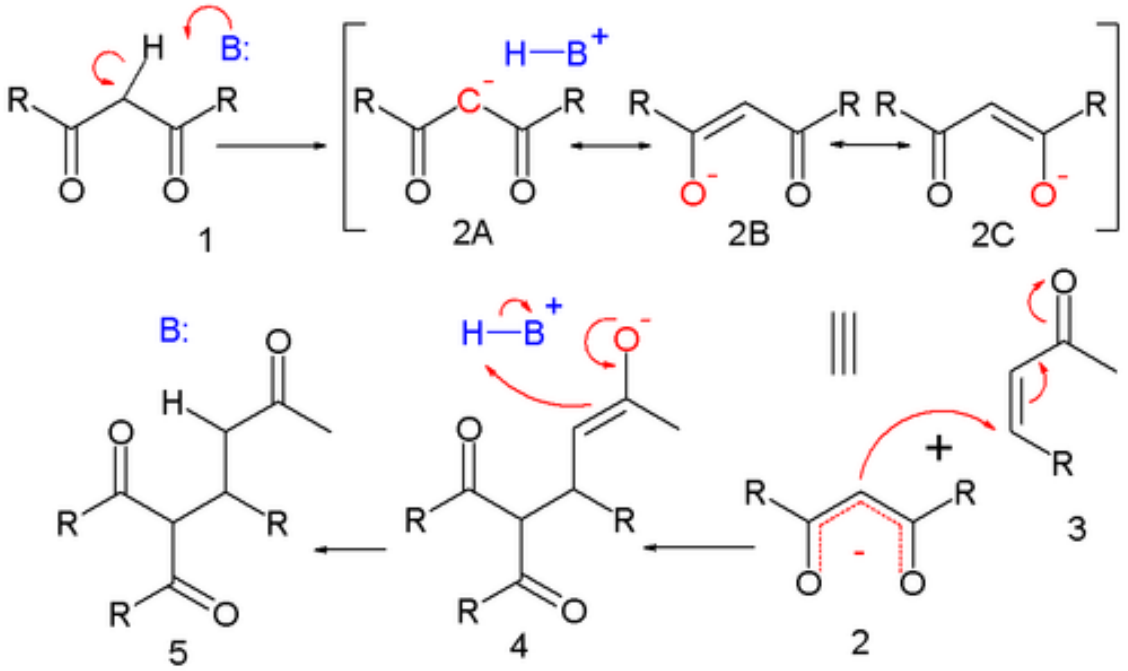
- ✓ Free radicals play an important role in a number of biological processes.
- ✓ Many of these are necessary for life, such as the intracellular killing of bacteria by phagocytic cells such as granulocytes and macrophages.
- ✓ Researchers have also implicated free radicals in certain cell signalling processes, known as redox signaling.
- ✓ The two most important oxygen-centered free radicals are superoxide and hydroxyl radical.
- ✓ They derive from molecular oxygen under reducing conditions.

Cont'd...

- ✓ However, because of their reactivity, these same free radicals can participate in unwanted side reactions resulting in cell damage.
- ✓ Excessive amounts of these free radicals can lead to cell injury and death, which may contribute to many diseases such as cancer, stroke, myocardial infarction, diabetes and major disorders.
- ✓ Many forms of cancer are thought to be the result of reactions between free radicals and DNA, potentially resulting in mutations that can adversely affect the cell cycle and potentially lead to malignancy

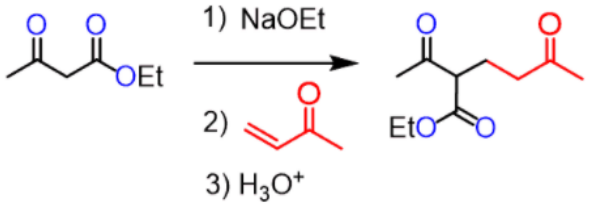
Rules of addition reaction; Michael reaction

- ✓ During a Michael reaction the enolate acts as a nucleophilic donor and the α, β-unsaturated carbonyl acts as the electrophilic acceptor.
- ✓ The mechanism is a mixture of an alpha-substitution for the enolate and a conjugate addition for the α, β-unsaturated carbonyl.

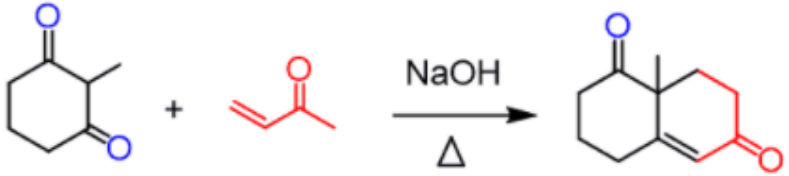


For instance

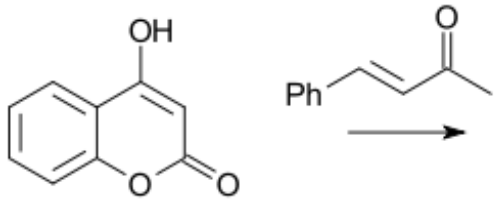
i) Describes the detail reaction mechanism of the following reaction?



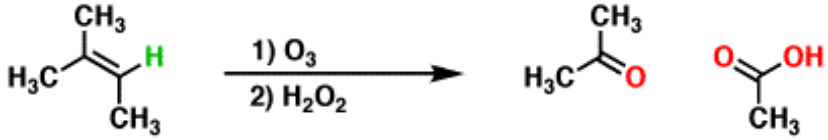
ii) Show the detail reaction mechanism of the following product?



iii) Show the detail reaction mechanism and predict the product?

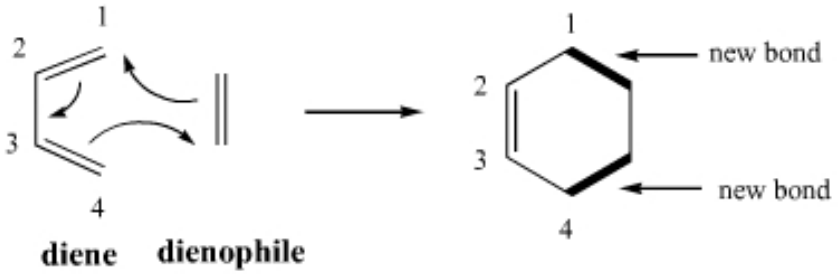


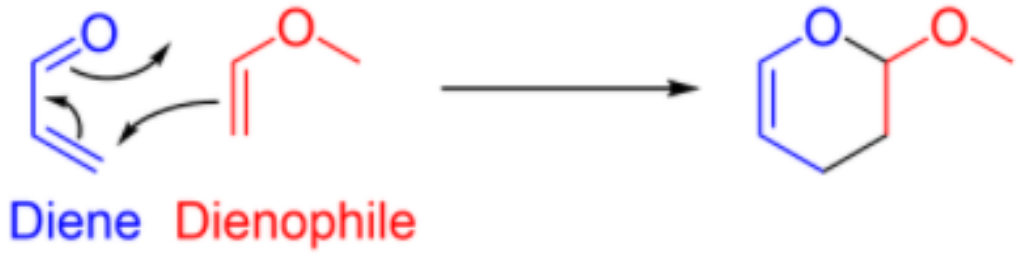
iv) Show briefly the reaction mechanism of oxidative ozonolysis



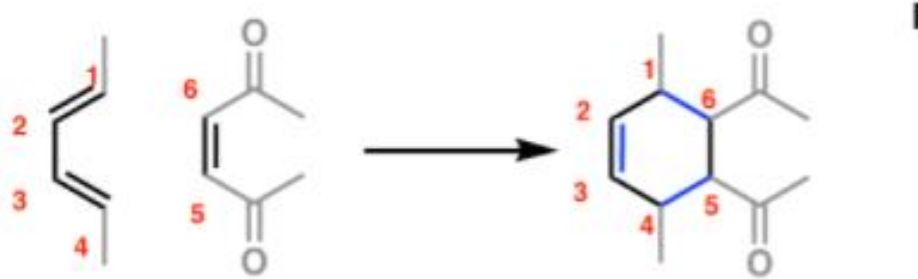
Diels-Alder reaction Cycloadditions

- ✓ cycloaddition reaction- a concerted combination of two π-electron systems to form a ring of atoms having two new σ bonds and two fewer π bonds.





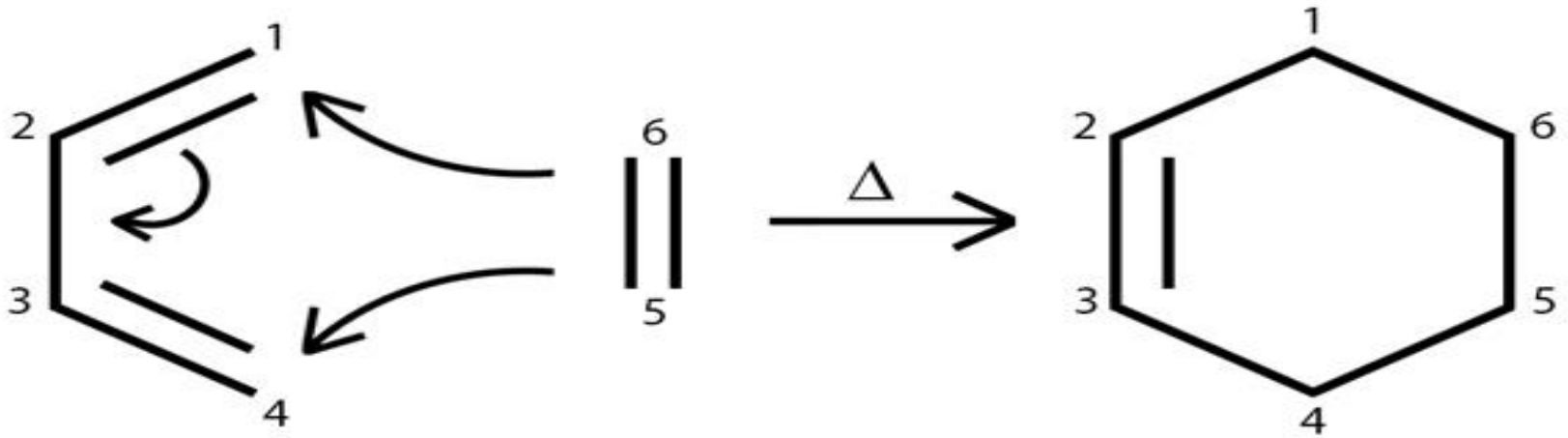
The Diels-Alder Reaction:
(an example)



Bonds Formed	Bonds Broken
C_1–C_6	C_1–C_2 (π)
C_2–C_3 (π)	C_3–C_4 (π)
C_4–C_5	C_5–C_6 (π)

Mechanism of Diels-Alder Reaction

1. Electrons from the dienophile attack carbon (C) 1 on the diene resulting in a single bond between C1 and C6.
2. Electrons from the double bond between C1 and C2 relocates to between C2 and C3.
3. Double bond between C3 and C4 are broken and the electrons form a single bond between C4 and C5 to form the product.
4. All processes take place in a single step.

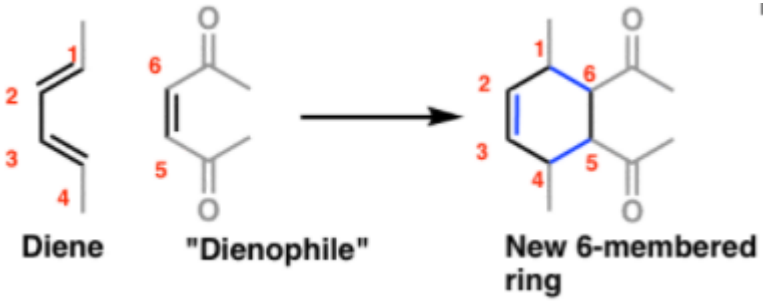


Diene (Butadiene) Dienophile (Ethylene) Cyclic adduct (Cyclohexene)

ChemistryLearner.com

Stereochemistry of the Diels-Alder Reaction

✓ For Example:

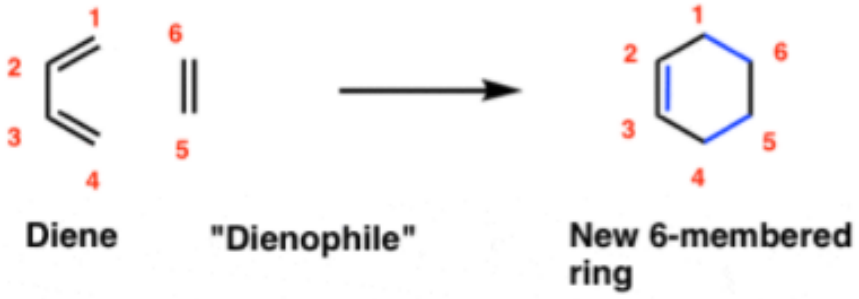


Bonds Formed	Bonds Broken
C_1–C_6	C_1–C_2 (π)
C_2–C_3 (π)	C_3–C_4 (π)
C_4–C_5	C_5–C_6 (π)

(A)

- ✓ 3 pi bonds are always broken;
- ✓ 2 sigma bonds and a pi bond are always formed, resulting in a new six-membered ring
- ✓ electron withdrawing groups on the dienophile increase the reaction rate

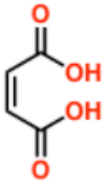
The Diels-Alder Reaction:



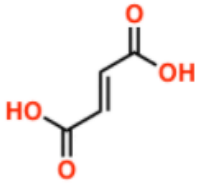
Bonds Formed	Bonds Broken
C_1–C_6	C_1–C_2 (π)
C_2–C_3 (π)	C_3–C_4 (π)
C_4–C_5	C_5–C_6 (π)

(B)

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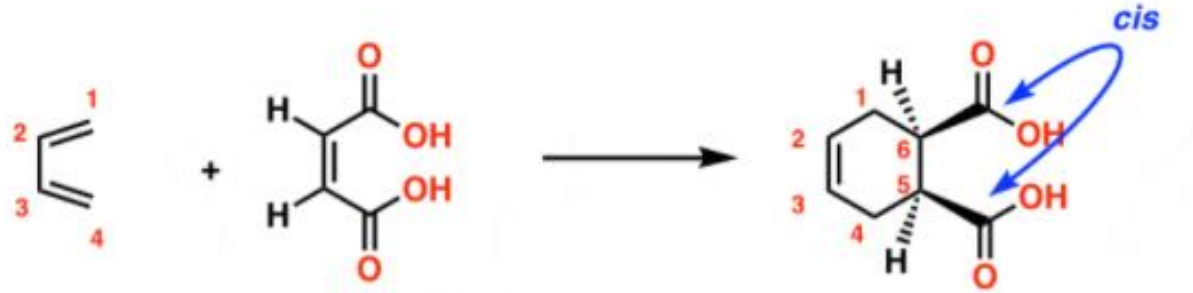
Maleic acid
(Z) or *cis*



Fumaric acid
(E) or *trans*

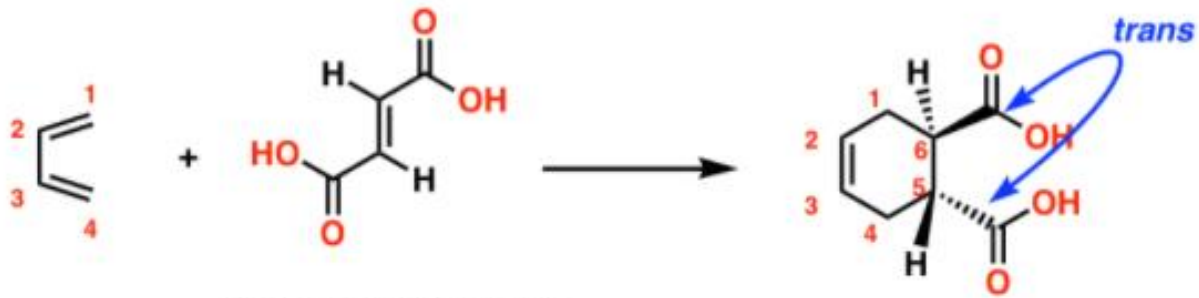
maleic acid and fumaric acid are diastereomers

The stereochemistry about the double bond in the dienophile is preserved



A *cis* arrangement along the double bond...

...results in a *cis* arrangement in the Diels-Alder product



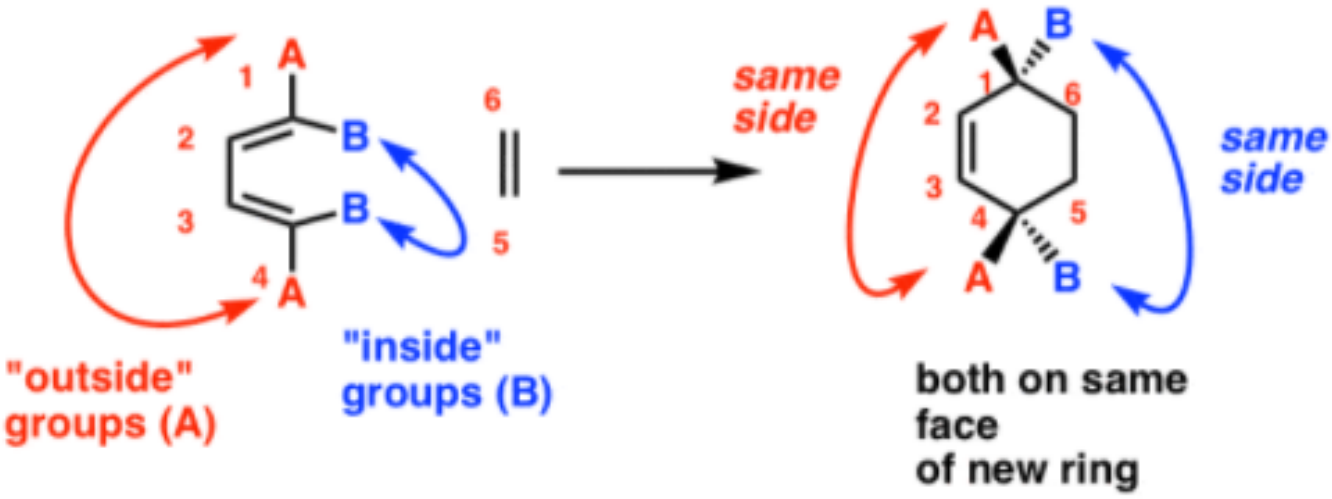
A *trans* arrangement along the double bond...

...results in a *trans* arrangement in the Diels-Alder product

Stereochemistry of the Diene Substituents in the Diels-Alder Product: "Outside" And "Inside" Substituents

- ✓ Substituents on C-2 and C-3 of the diene aren't an issue: they start the reaction on a (flat) sp^2 hybridized carbon and end the reaction on a (flat) sp^2 hybridized carbon.

The two "outside" groups (A) on the diene end up on one face of the new six-membered ring, and the two "inside" groups (B) both end up on the opposite face.



Applying the "Outside / Inside" Rule for Dienes

Applying the Rule

Example 1: *(E,E)*-2,4-hexadiene



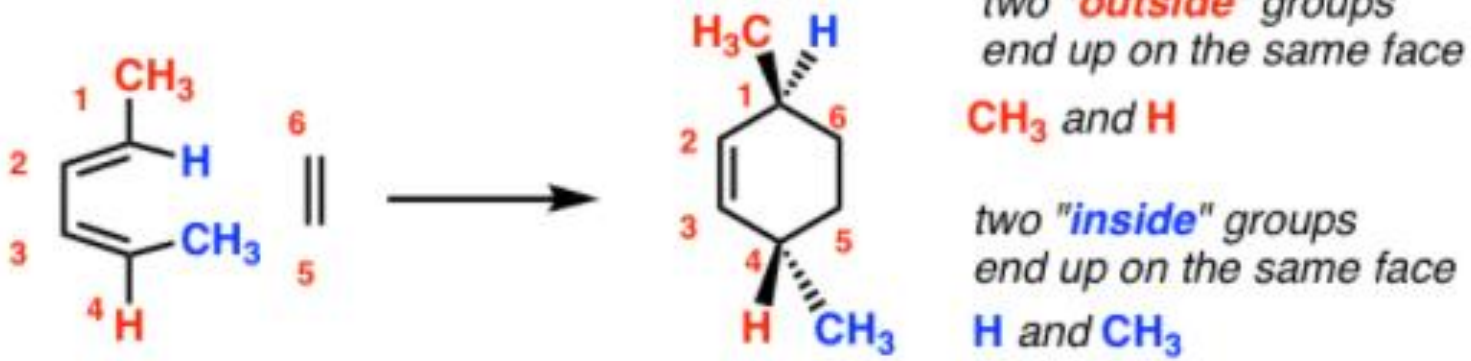
*two "**outside**" groups end up on the same face*

CH_3 *and* CH_3

*two "**inside**" groups end up on the same face*

H *and* H

Example 2: *(E,Z)*-2,4-hexadiene



*two "**outside**" groups end up on the same face*

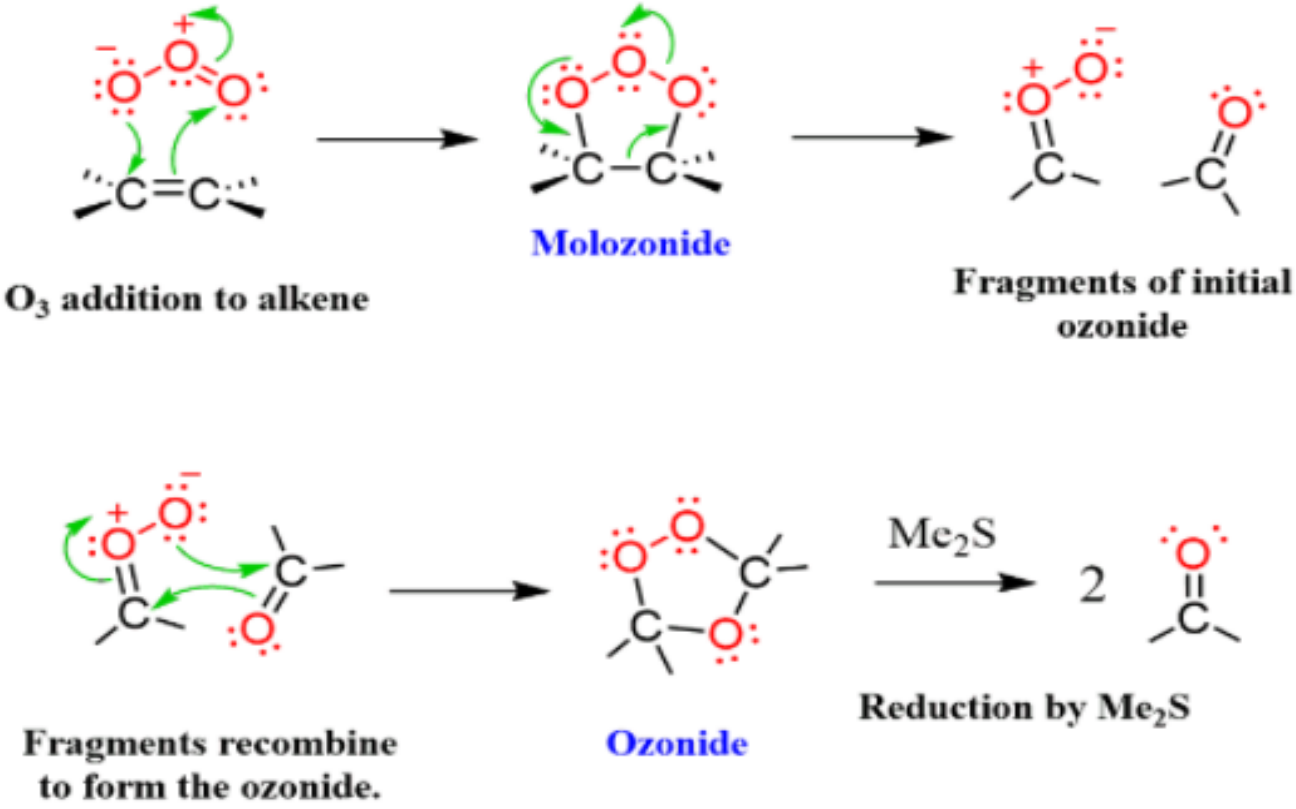
CH_3 *and* H

*two "**inside**" groups end up on the same face*

H *and* CH_3

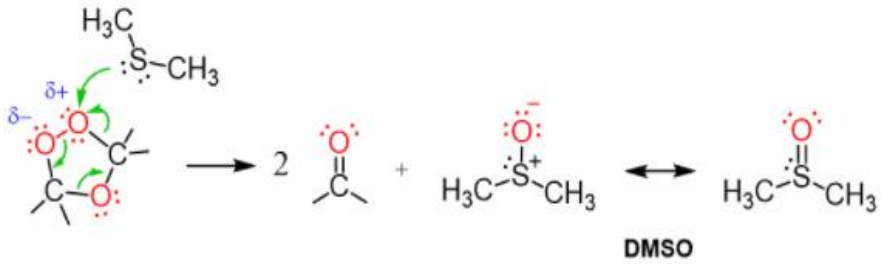
Ozonolysis Mechanism

- ✓ The oxidation is achieved by bubbling ozone into the reaction mixture at low temperatures (-78°C).
- ✓ The first step is the formation of a cyclic intermediate called molozonide (initial ozonide) which quickly rearranges into the more stable ozonide.



Cont'd...

- ✓ In the last step, a reducing agent dimethyl sulfoxide (Zn and Acetic acid are also used) is used.
- ✓ Sulfur, being a polarizable atom, induces a partial positive charge on one of the connected oxygens and attacks it cleaving the weak O-O bond:

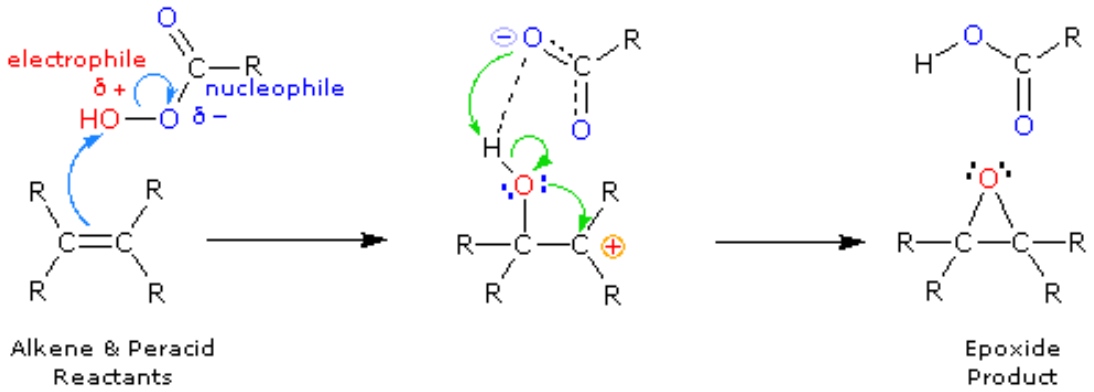


- ✓ Dimethyl sulfoxide dissolves a variety of organic substances like carbohydrates, polymers (polyacrylonitrile, polysulfone and polyethersulfone, polyetherimide, polyurethane), peptides, as well as many inorganic salts and gases.
- ✓ In manufacturing, DMSO is used as an industrial solvent for herbicides, fungicides, antibiotics, and plant hormones.
- ✓ It is also extensively used as an extractant in biochemistry and cell biology.

- ✓ It can extract aromatic compounds selectively from mixtures containing both

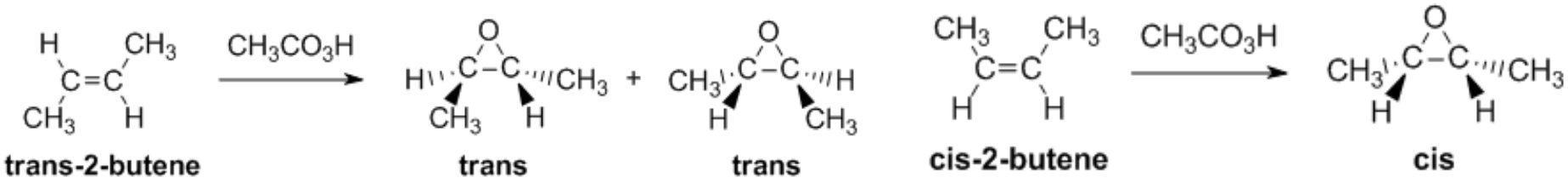
Peracid addition reaction

- ✓ An important method for preparing epoxides is by reaction with peracids, RCO_3H.
- ✓ The oxygen-oxygen bond of such peroxide derivatives is not only weak (ca. 35 kcal/mole),
- ✓ but in this case is polarized so that the acyloxy group is negative and the hydroxyl group is positive (recall that the acidity of water is about ten powers of ten weaker than that of a carboxylic acid).



For instance

1) Show the detail mechanism of the following reaction



➢ Glycol formation of addition reaction

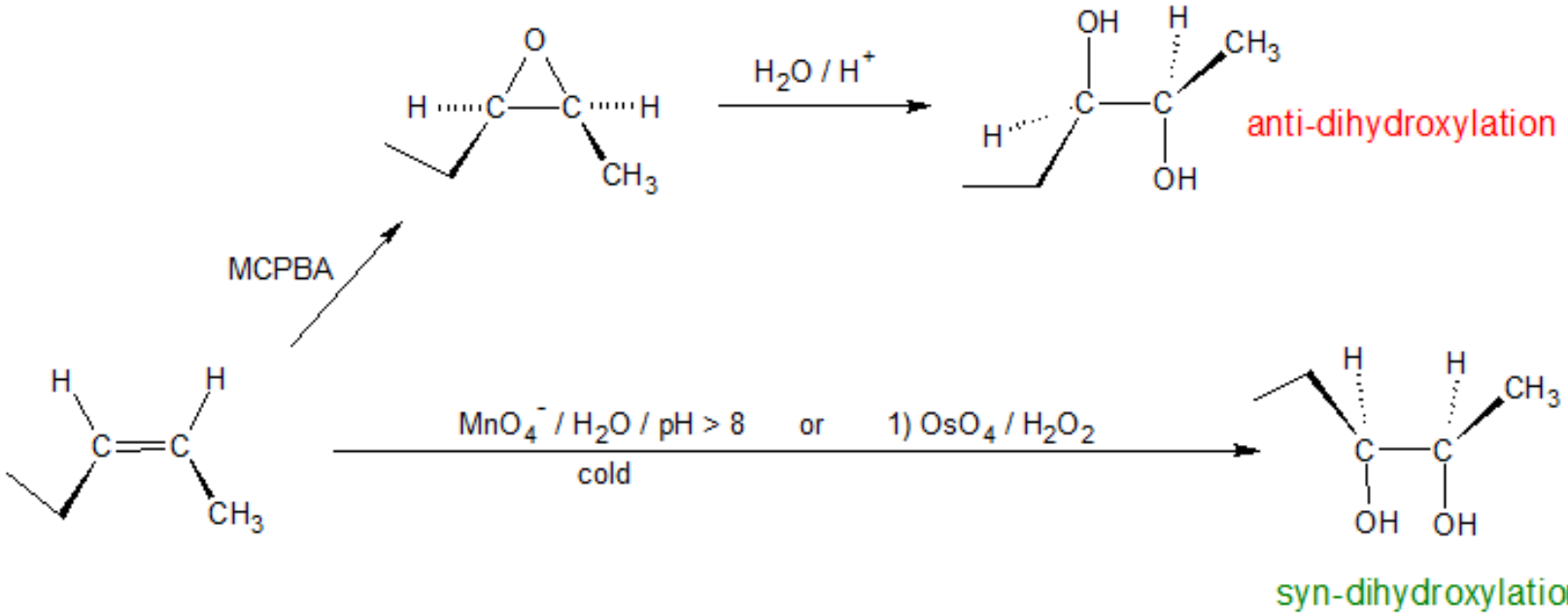
i) Dihydroxylation of alkenes

- ✓ Alkenes can be dihydroxylated by two different stereochemical pathways: anti-dihydroxylation or syn-dihydroxylation.
- ✓ The opening of epoxides follows the anti-dihydroxylation mechanism, while potassium permanganate or osmium tetroxide produce the syn-dihydroxylated products.

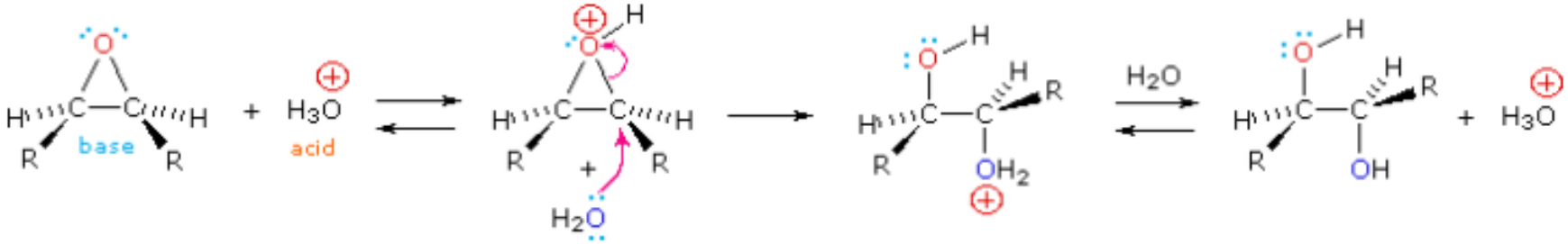
Cont'd...

✓ The osmium tertroxide reaction can also take place by a two-step process:

1) OsO_4 in pyridine followed by 2) H_2S or $NaHSO_3$.

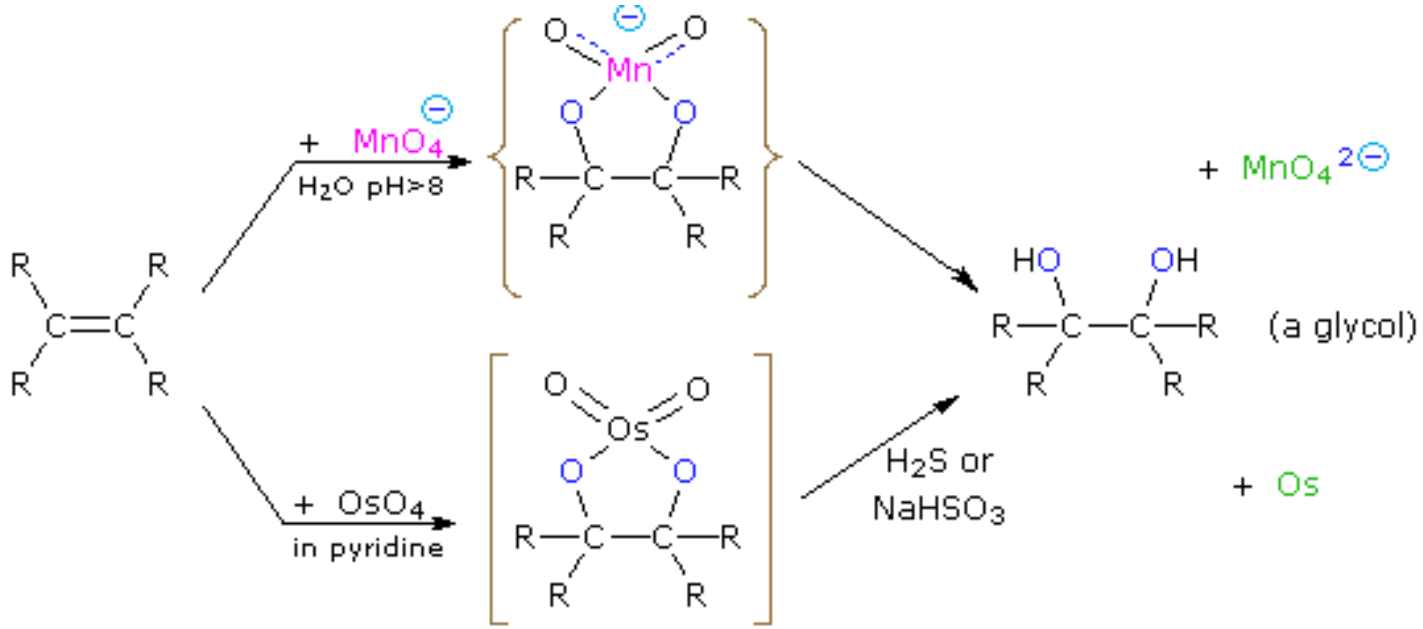


Anti Dihydroxylation



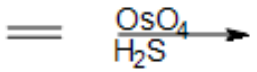
Syn Dihydroxylation

- ✓ Osmium tetroxide oxidizes alkenes to give glycols through syn addition.
- ✓ A glycol, also known as a vicinal diol, is a compound with two -OH groups on adjacent carbons.

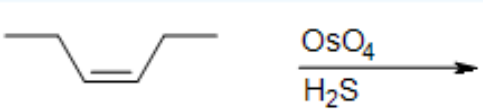


Exercise (1)

1. Give the major product.



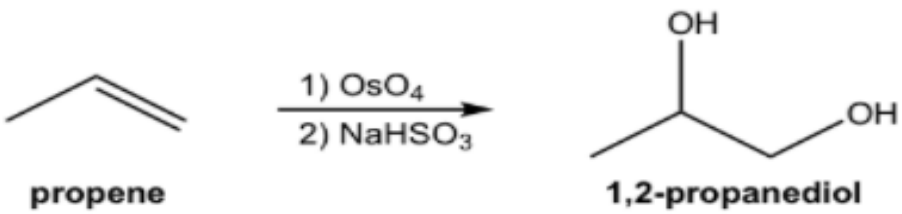
2. What is the product in the dihydroxylation of (Z)-3-hexene?

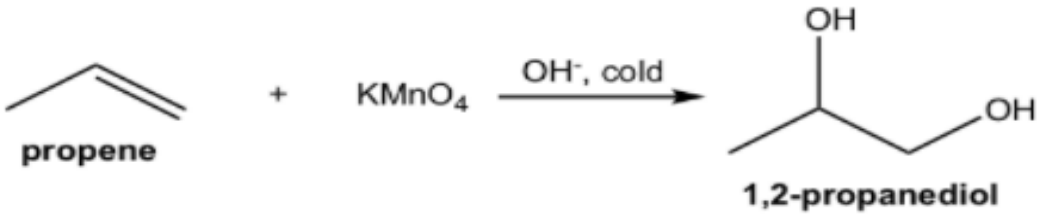


3. What is the product in the dihydroxylation of (E)-3-hexene?



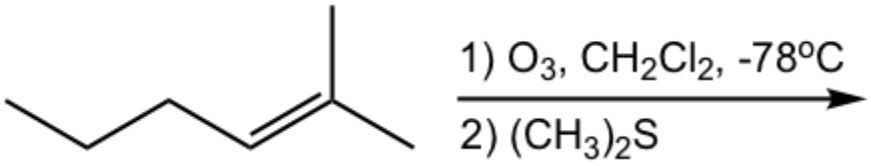
Exercise (2) show the detail mechanism

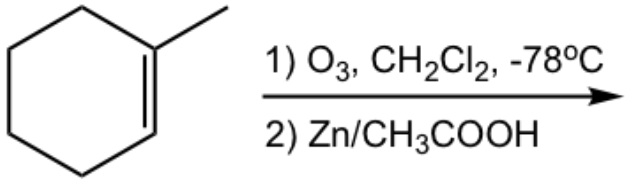


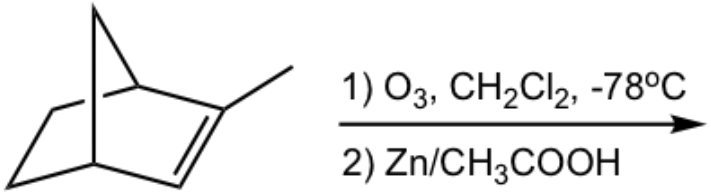


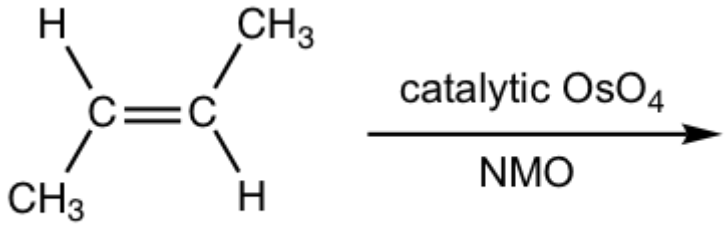
Exercise (3)

1) Show ozonolysis products of following reactions:





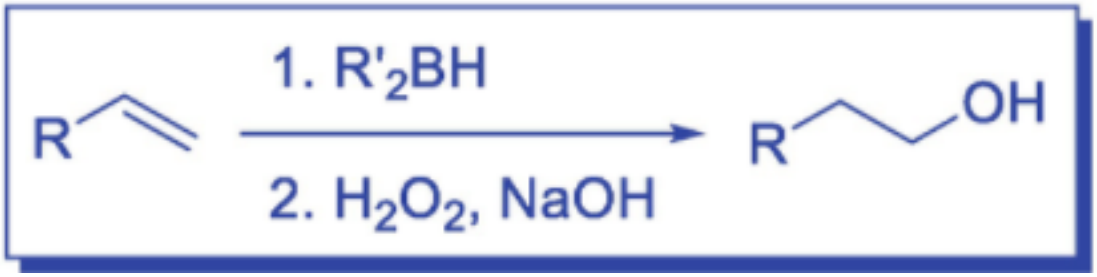




(*E*)-2-butene

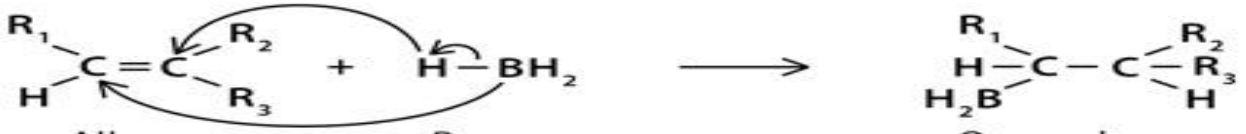
Hydroboration addition reaction

- ✓ 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.
- ✓ Hydroboration–oxidation reaction is a two-step hydration reaction that converts an alkene into an alcohol.
- ✓ The most widely known reaction of the organoboranes is oxidation to produce alcohols typically by hydrogen peroxide.
- ➢ Reaction Mechanism; eg.,



Mechanism of Hydroboration-Oxidation

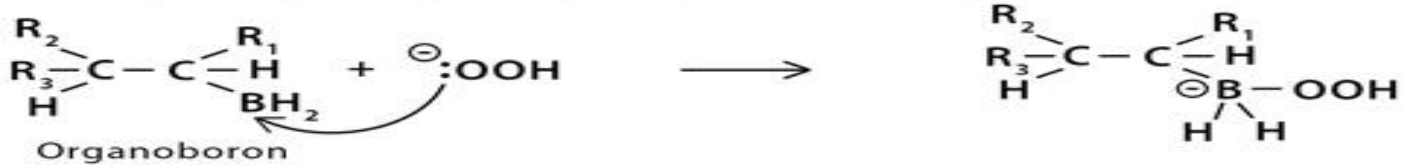
Step 1: The electrophilic boron attacks the pi electrons of alkene and forms a bond with carbon resulting in an organoboron compound.



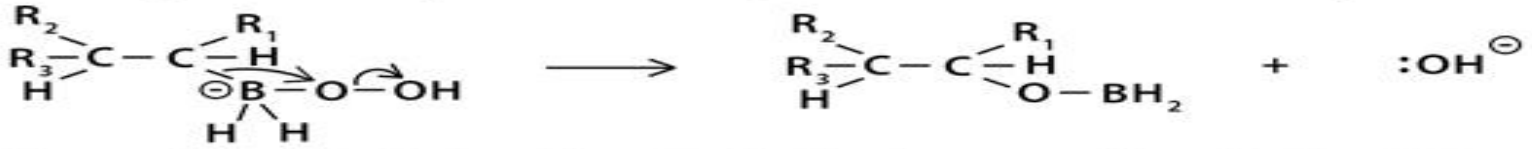
Step 2: The hydrogen peroxide is deprotonated by the sodium hydroxide to give a conjugate base.



Step 3: The deprotonated peroxide anion then adds to the organoboron forming a negatively charged organoboron species.



Step 4: The organoboron species rearranges itself to a neutral compound.



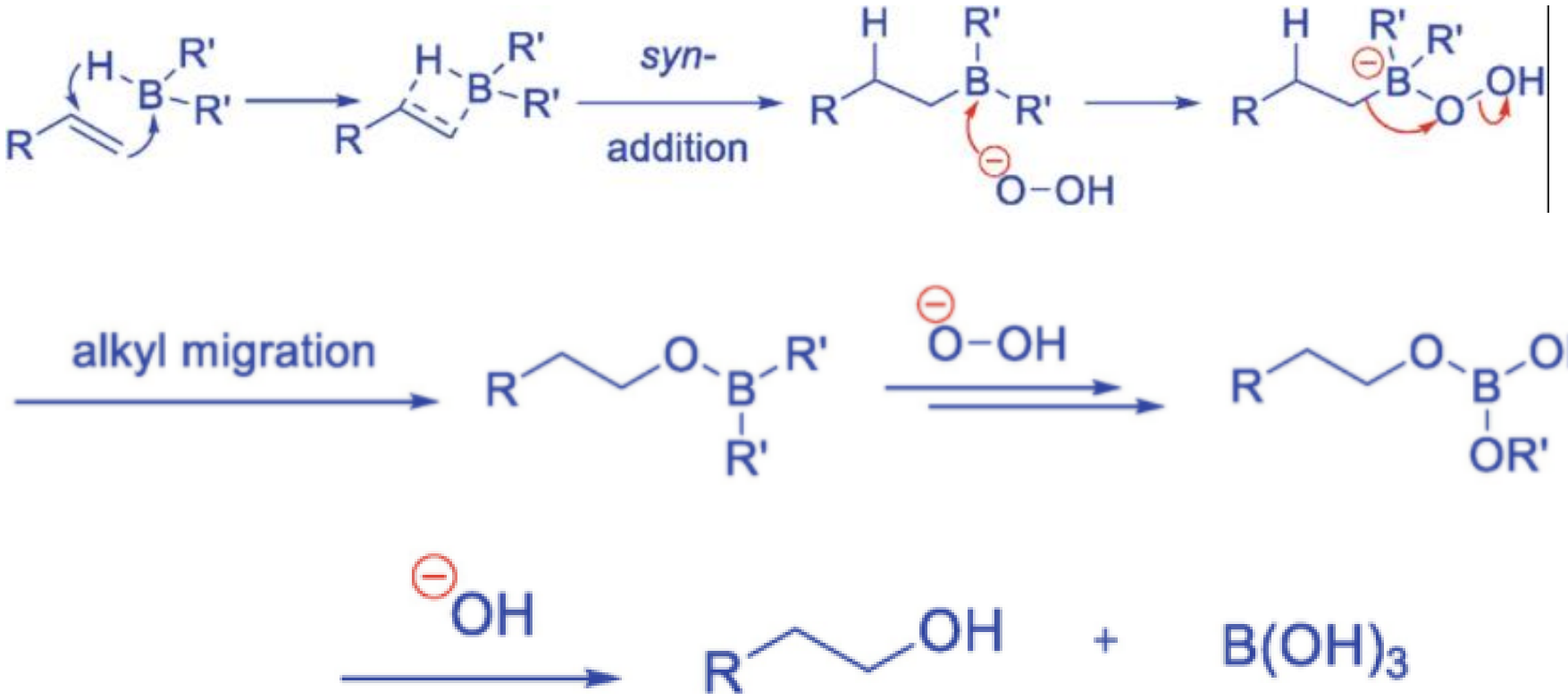
Step 5: The nucleophilic hydroxide attacks the boron and breaks the O-B bond resulting in an alkoxide.



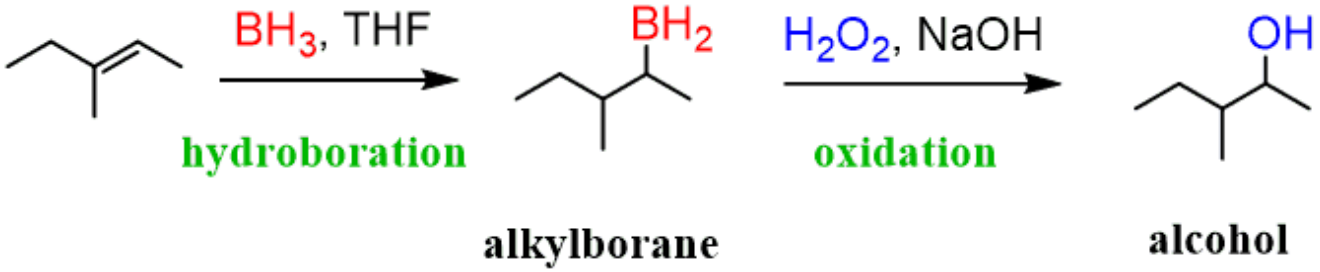
Step 6: The alkoxide is protonated by water to give an alcohol.



Cont'd...

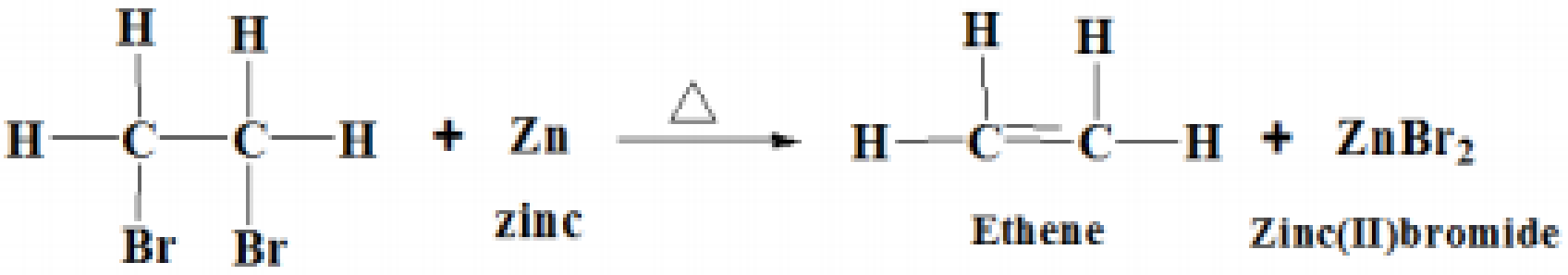


- Example: show the detail Reaction mechanism



ELIMINATION REACTION

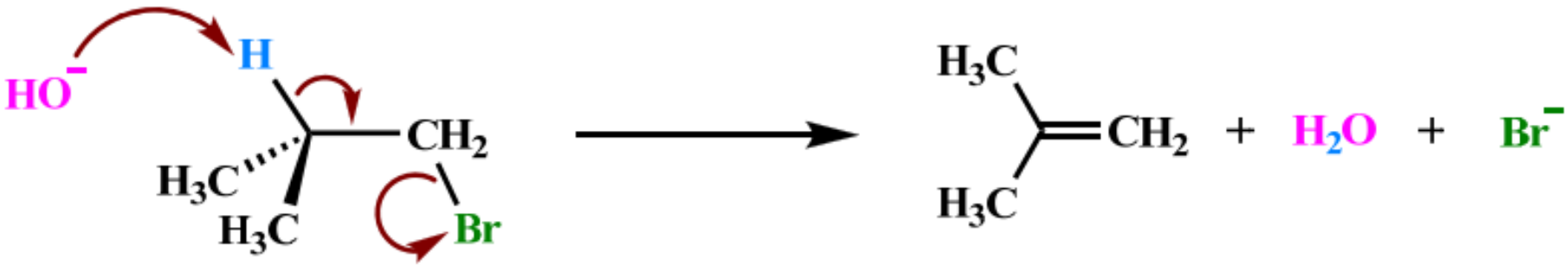
- ✓ Elimination Reaction are those which involve the removal of atom or group of atom from two adjacent in the substrate molecules to form a multiple bond.
- ✓ it may be regarded as reverse of addition reactions.
- ✓ In this reaction two sigma (σ) bonds are lost and a new pie (π) bond is formed.
- ✓ It results unsaturated compound from saturated.



Types of elimination rxn

- ✓ An elimination reaction is a type of organic reaction in which two substituents are removed from a molecule in either a one or two-step mechanism.
  - ➢ The one-step mechanism is known as the E2 reaction, and
  - ➢ the two-step mechanism is known as the E1 reaction.
- ✓ **E2 Eliminations**
- ✓ 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.

Possible examples...,



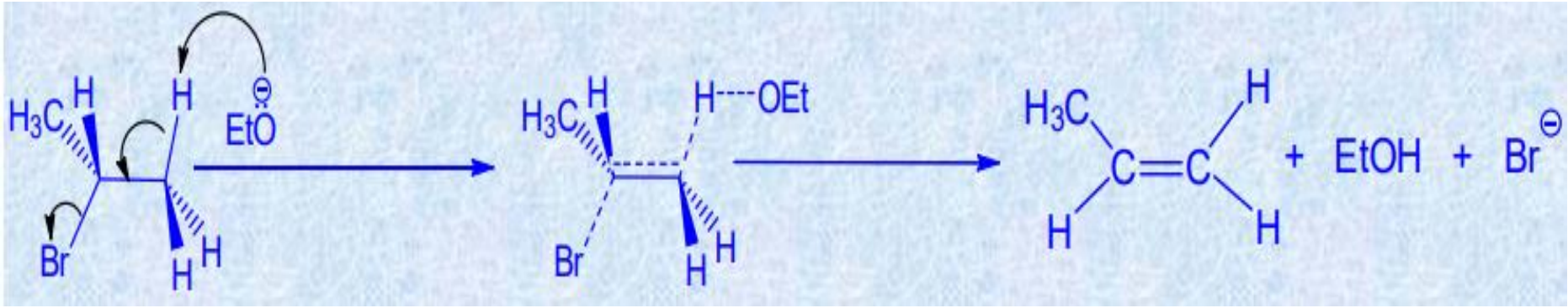
- ✓ It exhibits second-order kinetics, and both the alkyl halide and the base appear in the rate equation.

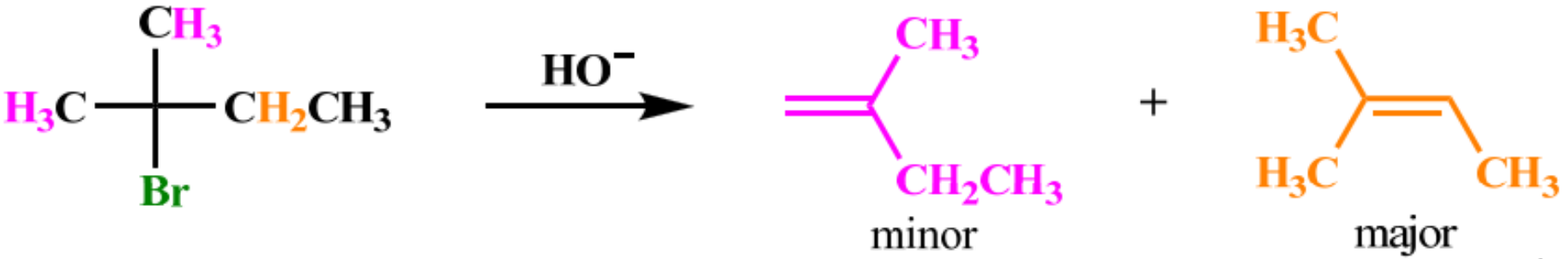
$$\text{rate} = k[(CH_3)_3CBr][HO^-]$$

- ✓ The reaction is concerted and all bonds are broken and formed in a single step.
- ✓ E2 reactions are regioselective and favor the formation of Zaitsev products.

E2-Eliminations…,

- ✓ The base abstracts the β hydrogen and leaving group simultaneously leaves such that it forms a multiple bond between α and β carbon atoms.Eg.





Factors Affecting the Rate of an E2 Reaction

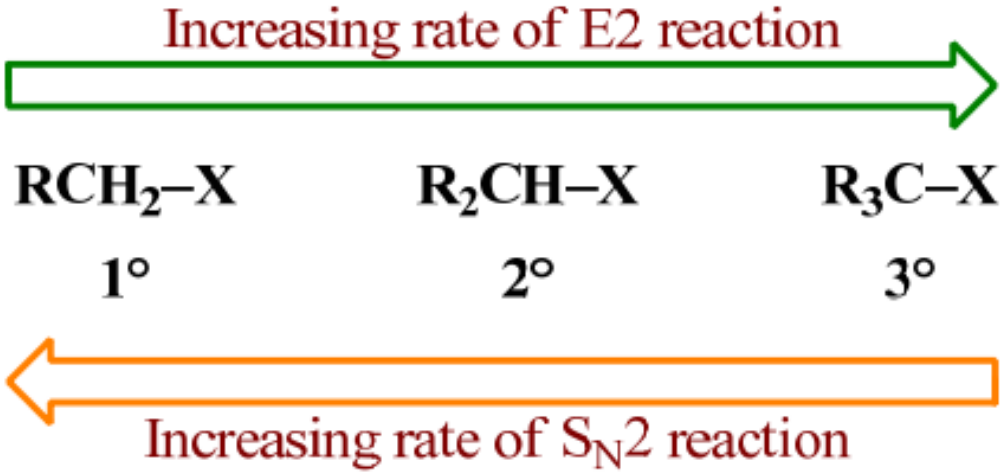
- There are close parallels between E2 and SN2 mechanisms in how the identity of the base,
- ✓ the leaving group and the solvent affect the rate.
- ✓ The base appears in the rate equation, so the rate of the E2 reaction increases as the strength of the base increases.
- ✓ reactions are generally run with strong, negatively charged bases like OH and OR−.
- ✓ Polar aprotic solvents increase the rate of E2 reactions.
- ✓ There is a partial breaking of the bond to the leaving group in the transition state. So, the better the leaving group the faster the E2 reaction.

Cont'd...,

- ✓ **Rate of reaction follows the order**

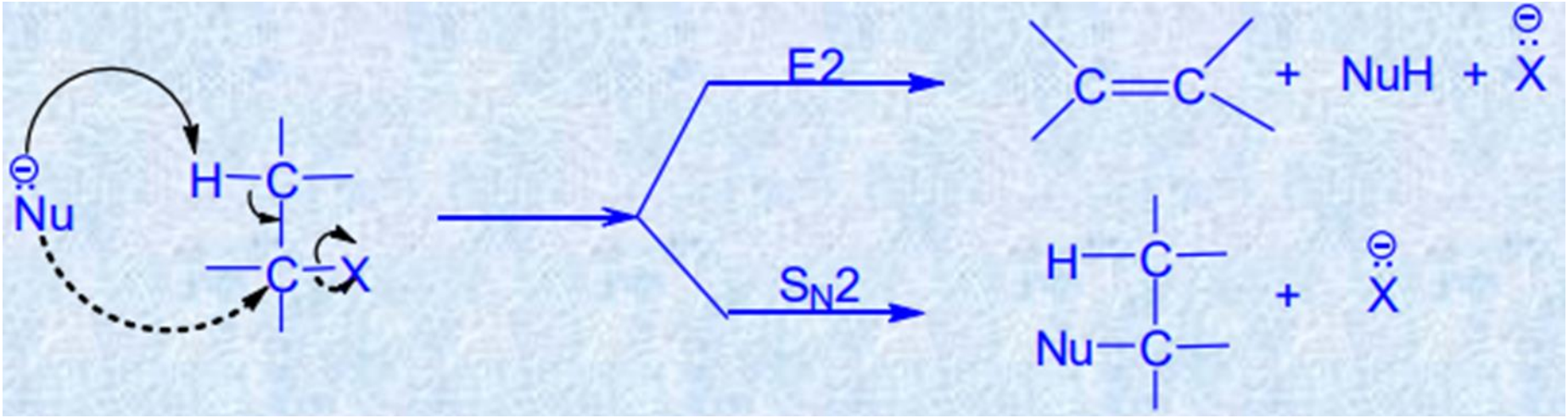
$$R{-}I > R{-}Br > R{-}Cl > R{-}F$$

- ✓ The S_N2 and E2 mechanisms differ in how the R group affects the reaction rate.
- ✓ As the number of R groups on the carbon with the leaving group increases, the rate of the E2 reaction increases.



Further illustration...,

- ✓ E2 elimination competes with S_N2 reactions.
- ✓ This is due to the inherent propensity of the incoming nucleophile also to attack the carbon atom bearing the leaving group. Such situations will lead to substitution products.



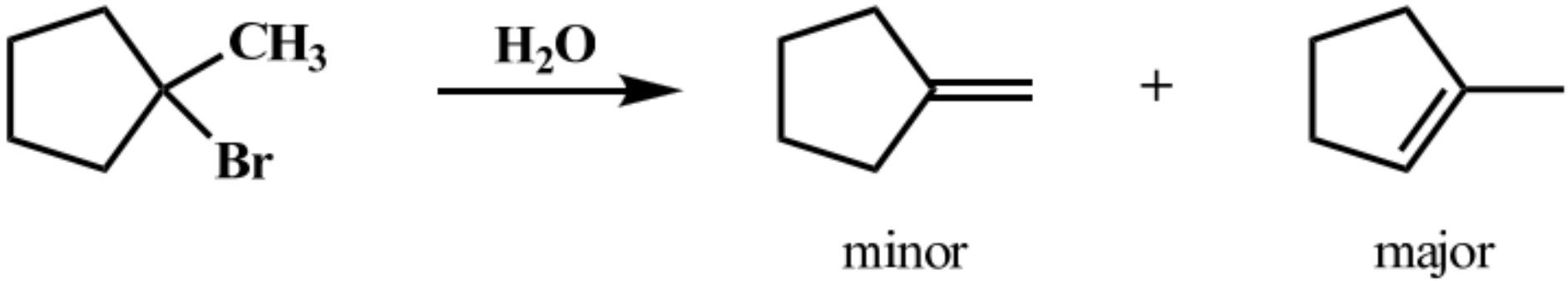
Characteristics of an E2 Reaction

Kinetics	–	Second order
Mechanism	–	Single step
Identity of R group	–	More substituted halides react faster Rate: $R_3CX > R_2CHX > RCH_2X$
Strength of the base	–	Stronger bases favor the reaction
Leaving group	–	Better leaving group leads to faster reaction rates
Type of solvent	–	Favored by polar aprotic solvents

✓ E2 reactions are stereoselective, resulting in the formation of trans-double bonds preferably.

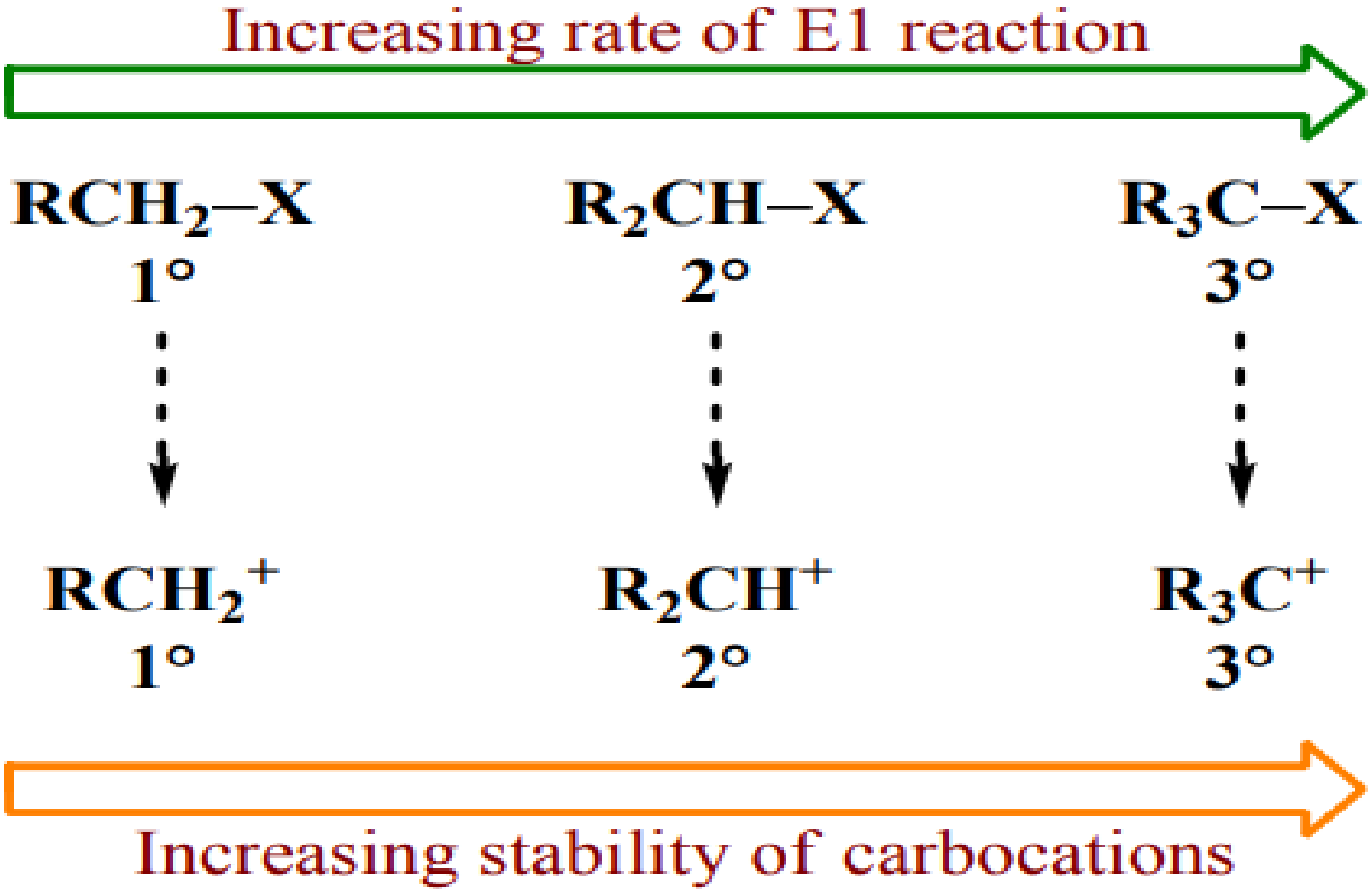
The E1 Mechanism

- ✓ The E1 reaction proceeds via a two-step mechanism: the bond to the leaving group breaks first before π bond is. The slow step is unimolecular, involving only the alkyl halide.
- ✓ It exhibits first-order kinetics; $\mathbf{rate = k[(CH_3)_3CCl]}$
- ✓ E1 reactions also are regioselective and follow Zaitsev rule.



Factors Affecting the Rate of an E1 Reaction

✓ The rate of an E1 reaction increases as the number of R groups on the carbon with the leaving group increases.



Further illustration

- ✓ The strength of the base usually determines whether a reaction follows the E1 or E2 mechanism.
- ✓ Strong bases like OH− and OR− favor E2 reactions,
- ✓ whereas weaker bases like H_2O and ROH favor E1 reactions.

➢ **SUBSTITUTION REACTIONS**

- ✓ are those reaction in which atoms or groups of atoms are directly attached to a carbon in the substrate molecule is replaced by another atom or group of atoms.



Nucleophilic Substitution Reaction an S_N2 Reaction

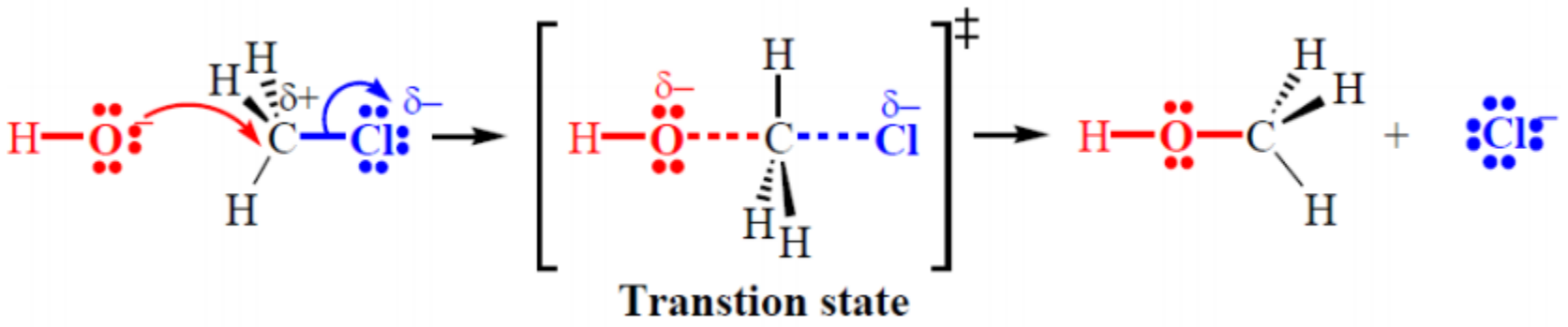
- ✓ The rate of the reaction depends on the concentration of methyl chloride and the concentration of hydroxide ion;
- ✓ The reaction is second order overall.

$$\text{Rate} \propto [CH_3Cl]\,[OH^-] \Rightarrow \text{Rate} = k\,[CH_3Cl]\,[OH^-]$$

- ✓ The nucleophile attacks the carbon bearing the leaving group from the back side.
- ✓ The bond between the nucleophile and the carbon atom is forming, and
- ✓ the bond between the carbon atom and the leaving group is breaking.

For instance;

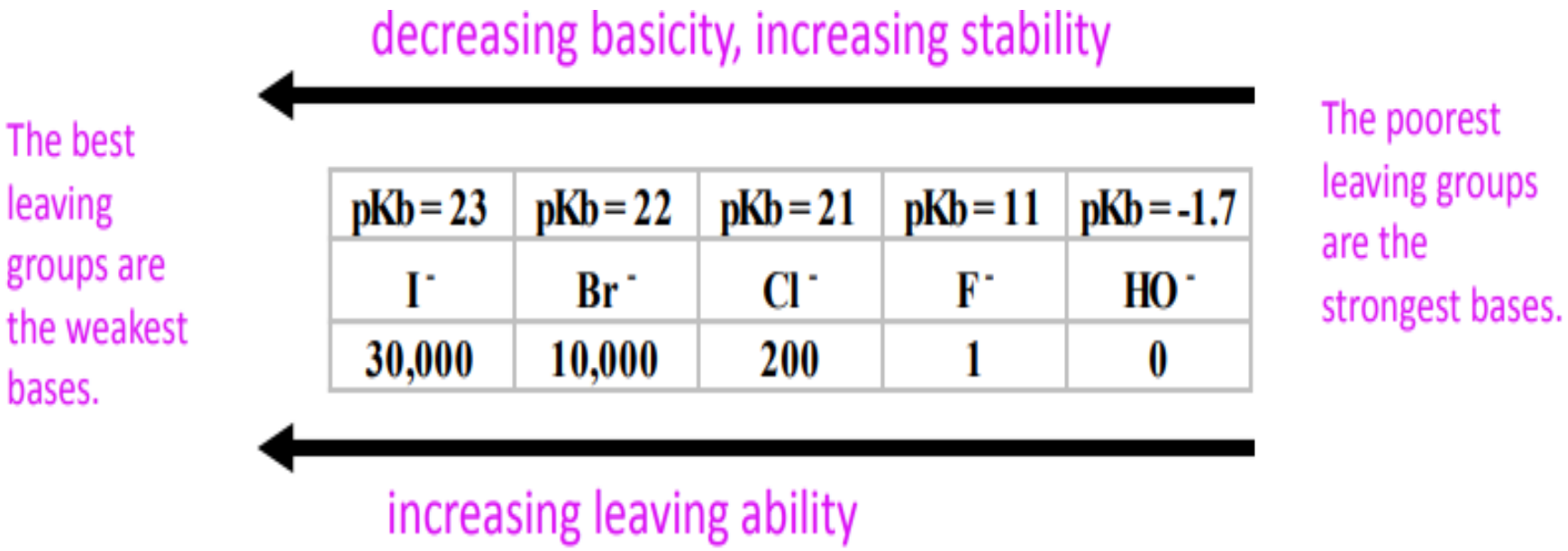
- ✓ Simple Mechanism



Because bond formation and bond breaking occur simultaneously in a single transition state, the SN2 reaction is a concerted reaction.

- ✓ The α-carbon in an alkyl halide is electrophilic (electron accepting) for either or both of two reasons;
- ✓ a) the C to X (F, Cl, Br) bond is polar making carbon $\delta+$
- ✓ b) X (Cl, Br, I) is a leaving group.

In summary,

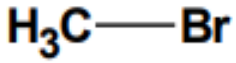


pKb = 23	pKb = 22	pKb = 21	pKb = 11	pKb = -1.7
I^-	Br^-	Cl^-	F^-	HO^-
30,000	10,000	200	1	0

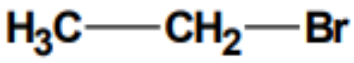
- ✓ The rate of an SN2 reaction depends upon the factors:
- ✓ The nature of the substrate (the alkyl halide)
- ✓ The power of the nucleophile,
- ✓ The ability of the leaving group to leave,
- ✓ The nature of the solvent.

Further illustration

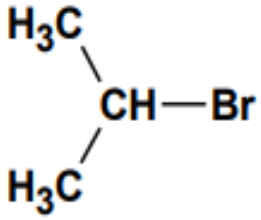
- ✓ **Effect of nature of substrate on rate of S_N2 reactions:**



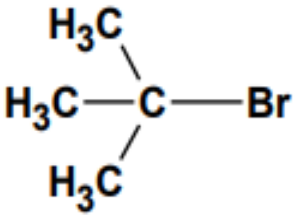
methyl bromide



ethyl bromide

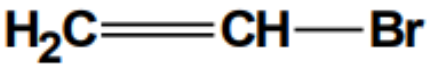


isopropyl bromide

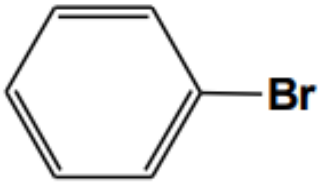


t-butyl bromide

- ✓ **Effect of the nucleophile on rate of SN2 reactions:**
- ✓ The α-carbon in vinyl and aryl halides, as in 3° carbocations, is completely hindered and these alkyl halides do not undergo S_N2 reactions



vinyl bromide



bromobenzene

Consider the power of the nucleophile

✓ The better the nucleophile, the faster the rate of S_N2 reactions

Reactivity	Nu:⁻	Relative Reactivity
very weak	HSO_4^-, $H_2PO_4^-$, RCOOH	< 0.01
weak	ROH	1
	HOH, NO_3^-	100
fair	F^-	500
	Cl^-, $RCOO^-$	20×10^3
	NH_3, CH_3SCH_3	300×10^3
good	N_3^-, Br^-	600×10^3
	OH^-, CH_3O^-	2×10^6
very good	CN^-, HS^-, RS^-, $(CH_3)_3P$:, NH_2^- ,RMgX, I^-, H^-	$> 100 \times 10^6$

increasing

✓ The best nucleophiles are the best electron donors.

nature of the leaving group

- ✓ The leaving group usually has a negative charge
- ✓ Groups which best stabilize a negative charge are the best leaving groups, i.e., the weakest bases are stable as anions and are the best leaving groups.

pKb = 23	pKb = 22	pKb = 21	pKb = 11	pKb = -1.7	pKb = -2	pKb = -21
I^-	Br^-	Cl^-	F^-	HO^-	RO^-	H_2N^-
30,000	10,000	200	1	0	0	0

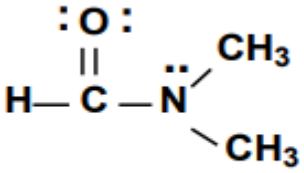


Increasing leaving ability

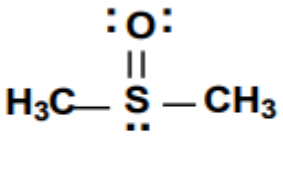
- ✓ Iodine is a good leaving group because it is non basic.
- ✓ The hydroxyl group is a poor leaving group because it is a strong base.

the nature of the solvent

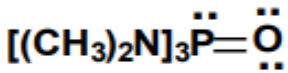
- Protic solvents, which contain –OH or –NH_2 groups. it slows down S_N2 reactions.
- Eg. H_2O, MeOH, EtOH, CH3COOH, etc.)
- Polar aprotic solvents like acetone, which contain strong dipoles but no –OH or –NH_2 groups.It speeds up SN2 reactions.
- Eg. acetonitrile (CH3 CN), acetone (CH3 COCH3), dimethylformamide (DMF) [$(CH_3)_2$ NC=OH], dimethyl sulfoxide, DMSO [(CH3)2 SO],



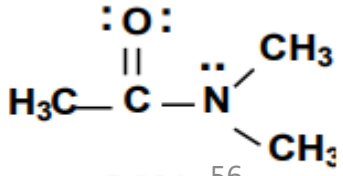
DMF



DMSO



HMPA



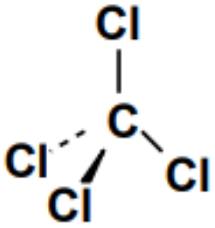
DMA

Nature of solvents...,

- Non polar solvents, e.g., hydrocarbons. SN2 reactions are relatively slow in non polar solvents.
- Eg. benzene, carbon tetrachloride, hexane, etc.) do not solvate or stabilize nucleophiles



benzene



carbon tetrachloride

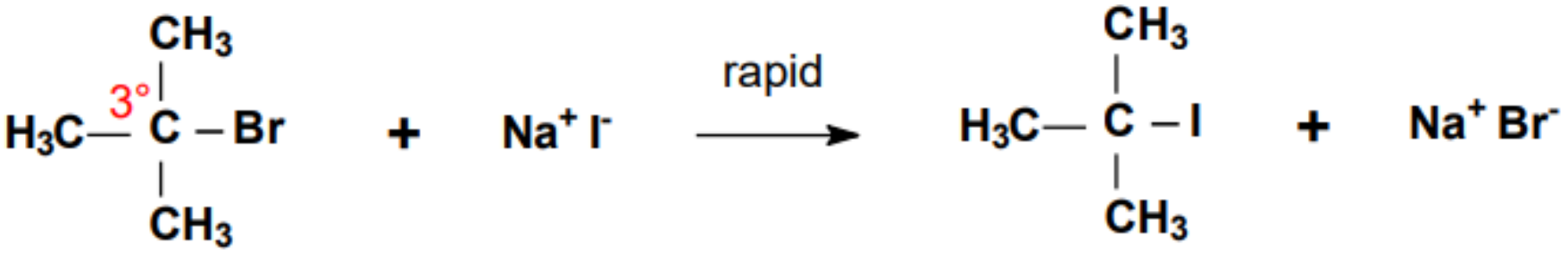
$CH_3CH_2CH_2CH_2CH_2CH_3$

n-hexane

- SN2 reactions are relatively slow in non polar solvents similar to that in protic solvents.

AN S_N1 REACTION

- ✓ It is reactions obey 1st order kinetics, i.e., Rate = k[RX].



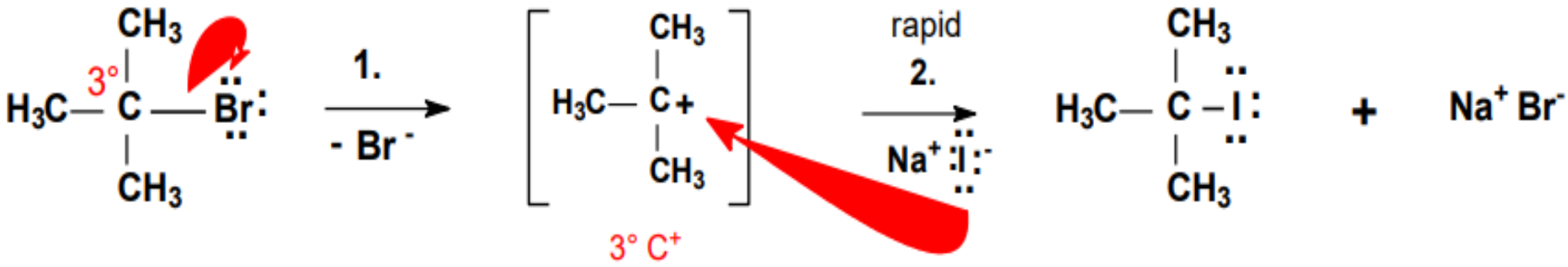
- ✓ 3º alkyl halides are essentially inert to substitution by the SN2 mechanism because of steric hindrance at the back side of the a-carbon.
- ✓ Despite this, 3º alkyl halides do undergo nucleophilic substitution reactions quite rapidly , but by a different mechanism, i.e., the S_N1 mechanism.
- ✓ The order of reactivity of substrates for SN1 reactions is the reverse of SN2.

For instance;

- 3° > 2° > 1° > vinyl > phenyl > Me°
- R_3C-Br R_2HC-Br RH_2C-Br CH_2=CH-Br ϕ-Br H_3C-Br

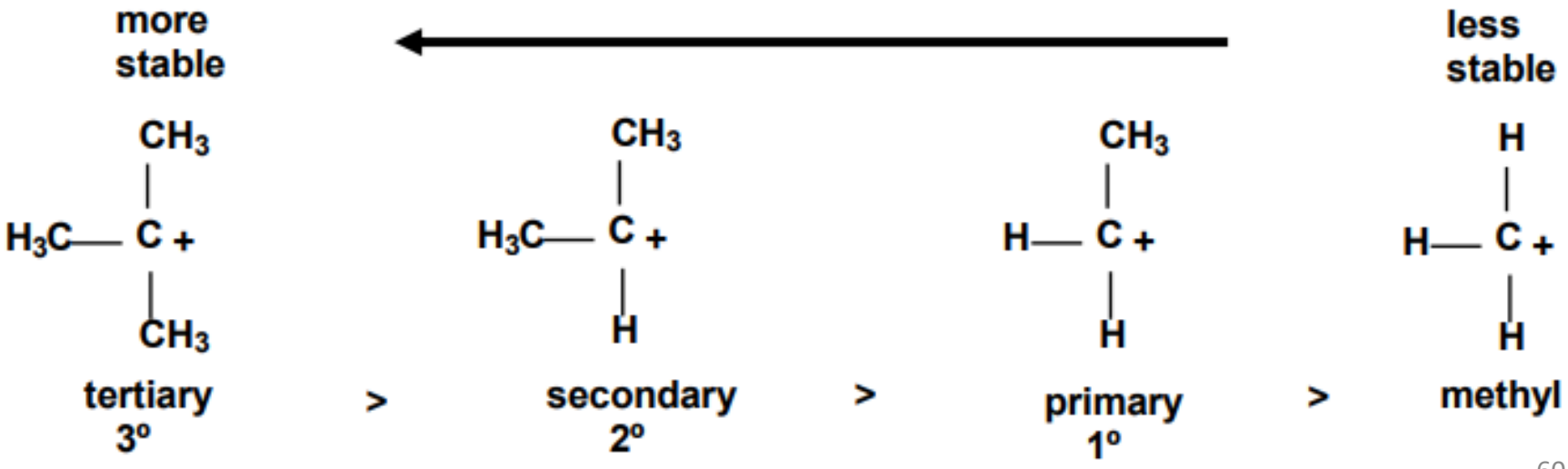
increasing rate of S_N1 reactions

✓ The mechanism of an SN1 reaction occurs in 2 steps:



The rate of an SN1 reaction depends upon 3 factors:

- ✓ The nature of the substrate (the alkyl halide)
- ✓ The ability of the leaving group to leave
- ✓ The nature of the solvent .
- ✓ But the rate is independent of the power of the nucleophile



Reactivity of alkyl halides towards to Sn and E

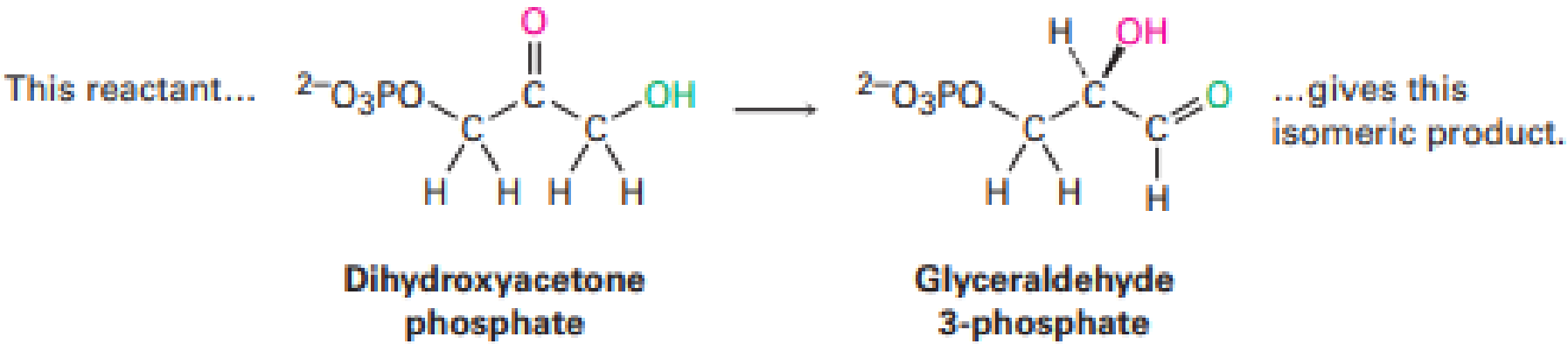
Halide type	*S_N1*	*S_N2*	*E1*	*E2*
Primary halide	Does not occur	**Highly favored**	Does not occur	Occurs when strong, hindered bases are used
Secondary halide	Can occur under solvolysis conditions in polar solvents	**Favored by good nucleophiles in polar aprotic solvents**	Can occur under solvolysis conditions in polar solvents	**Favored when strong bases are used**
Tertiary halide	**Favored by nonbasic nucleophiles in polar solvents**	Does not occur	Occurs under solvolysis conditions	**Highly favored when bases are used**

Effects of reaction variables on SN and E rxn

Reaction	*Solvent*	*Nucleophile/base*	Leaving group	Substrate structure
S_N1	**Very strong effect**; reaction favored by polar solvents	**Weak effect**; reaction favored by good nucleophile/weak base	**Strong effect**; reaction favored by good leaving group	**Strong effect**; reaction favored by 3°, allylic, and benzylic substrates
S_N2	**Strong effect**; reaction favored by polar aprotic solvents	**Strong effect**; reaction favored by good nucleophile/ weak base	**Strong effect**; reaction favored by good leaving group	**Strong effect**; reaction favored by 1°, allylic, and benzylic substrates
E1	**Very strong effect**; reaction favored by polar solvents	**Weak effect**; reaction favored by weak base	**Strong effect**; reaction favored by good leaving group	**Strong effect**; reaction favored by 3°, allylic, and benzylic substrates
E2	**Strong effect**; reaction favored by polar aprotic solvents	**Strong effect**; reaction favored by poor nucleophile/ strong base	**Strong effect**; reaction favored by good leaving group	**Strong effect**; reaction favored by 3° substrates

Rearrangement reactions, for what??

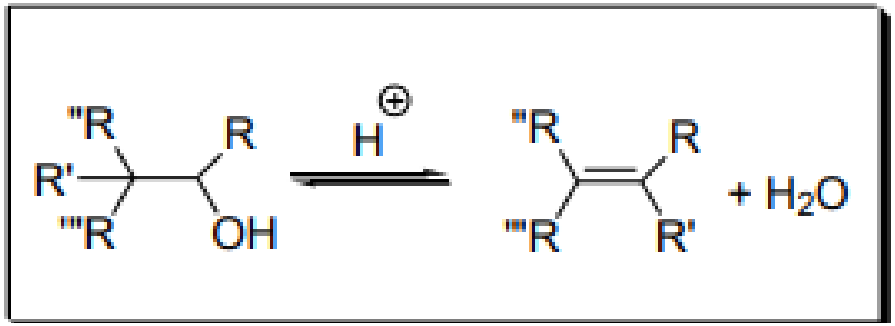
- ✓ Occur when a single reactant undergoes a reorganization of bonds and atoms to yield an isomeric product.
- ✓ For example: in the step in the glycolysis pathway by which carbohydrates are metabolized, the conversion of dihydroxyacetone phosphate into its constitutional isomer glyceraldehyde 3-phosphate.



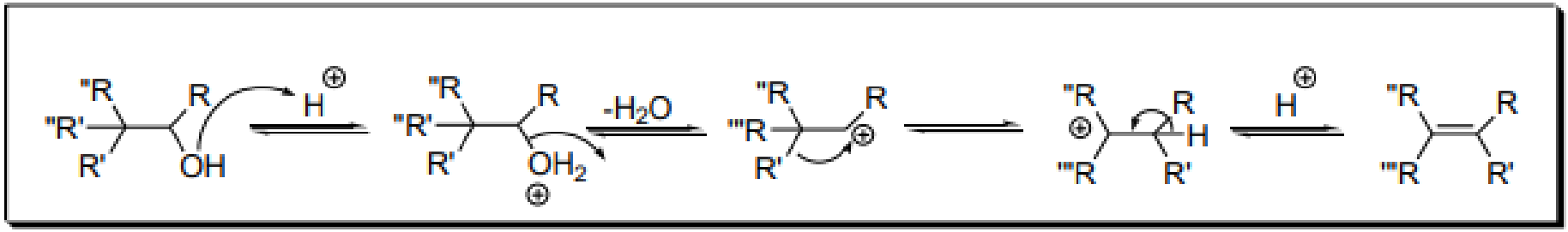
Rearrangement reaction

- ✓ Therefore; It is a broad class of organic **reactions** where the carbon skeleton of a molecule is **rearranged** to give a structural isomer of the original molecule.
- ✓ Often a substituent moves from one atom to another atom in the same molecule.

Eg. Carbon Migration



Mechanism



Carbocation Rearrangements

- ✓ C+ rearrangements are extremely common in organic.
- ✓ It is defined as the movement of a carbocation from an unstable state to a more stable state through the use of various structural reorganizational "shifts" within the molecule.
- ✓ Once the carbocation has shifted over to a different carbon, we there is a structural isomer of the initial molecule.
- ✓ These rearrangements usually occur in many types of carbocations.
- ✓ Once rearranged, the molecules can also undergo further S_N1 or E1.

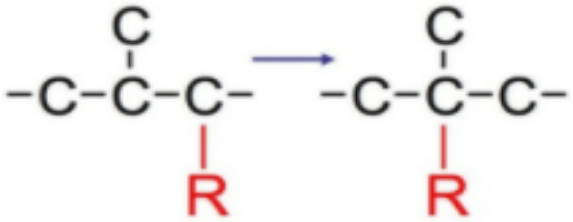


Illustration on S_N1

- ✓ Consider the reaction below shows the mechanism of an S_N1 reaction of an alkyl halide with water. Since water is also the solvent, this is an example of a solvolysis reaction.

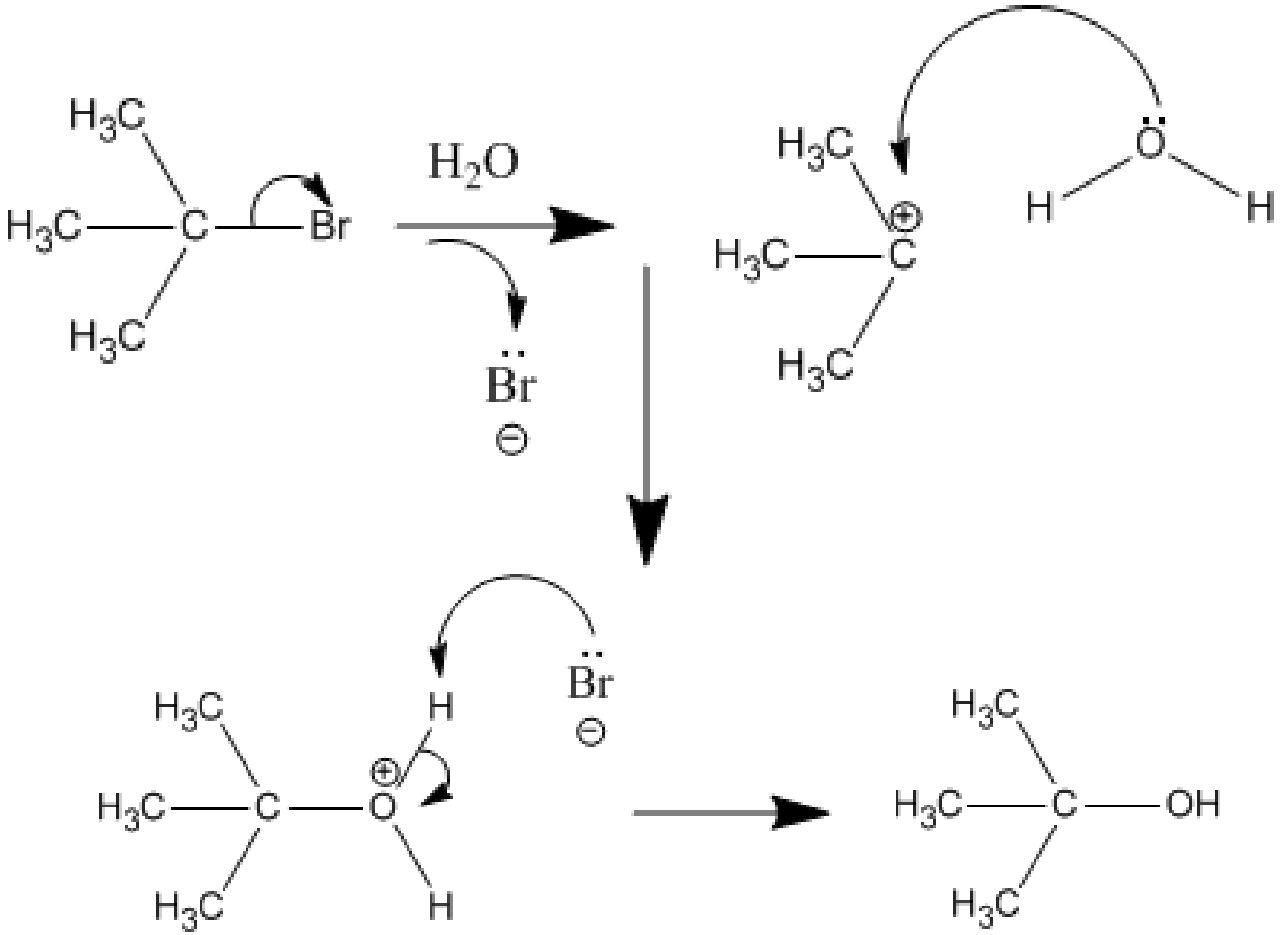
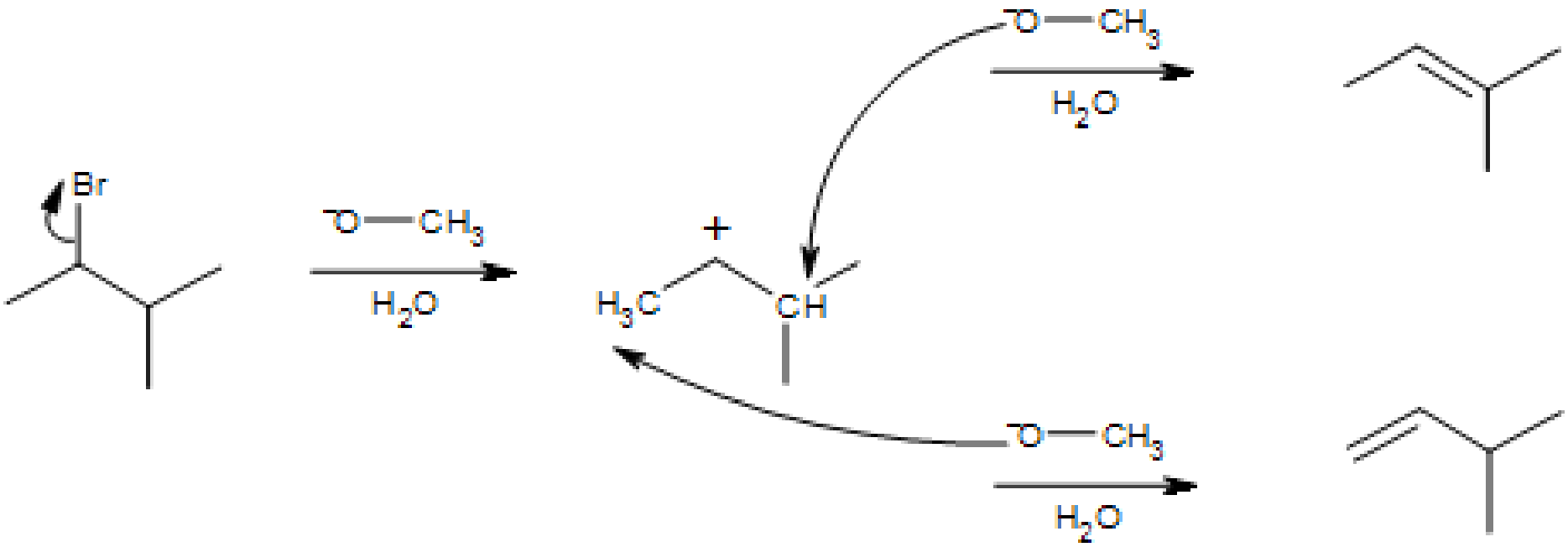


Illustration on E1

- ✓ This mechanism is a common application of E1 reactions in the synthesis of an alkene.

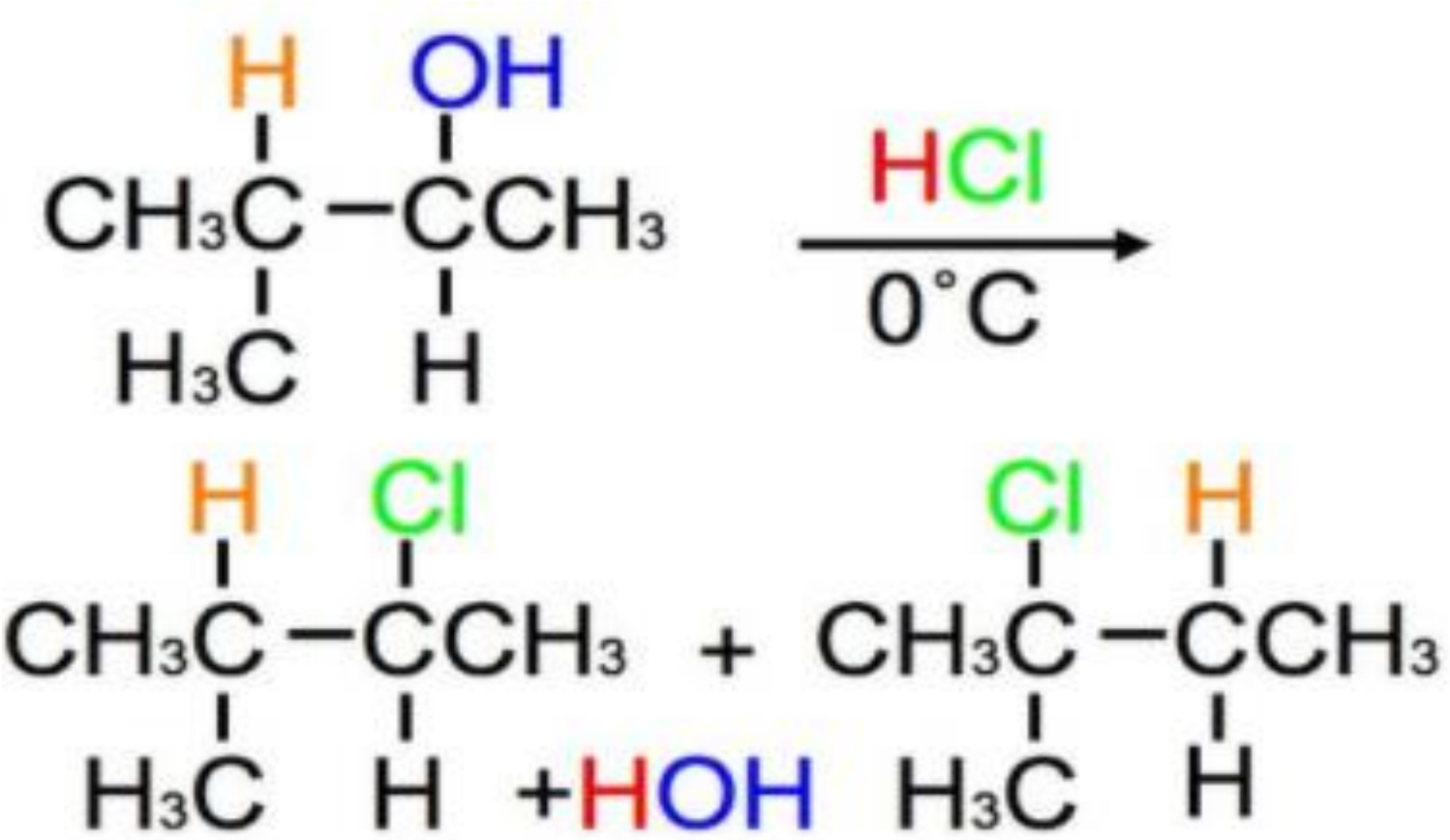


Hydride Shift

- ✓ Whenever a nucleophile attacks some molecules, we typically see *two* products.
- ✓ However, in most cases, we normally see both a major product and a minor product.
- ✓ The major product is typically the rearranged product that is *more substituted* (i.e. more stable).
- ✓ The minor product, in contract, is typically the normal product that is *less substituted* (i.e., less stable).
- ✓ This means that the two electron hydrogen from the unimolecular substitution moves over to the *neighboring* carbon.

Hydride shift…,

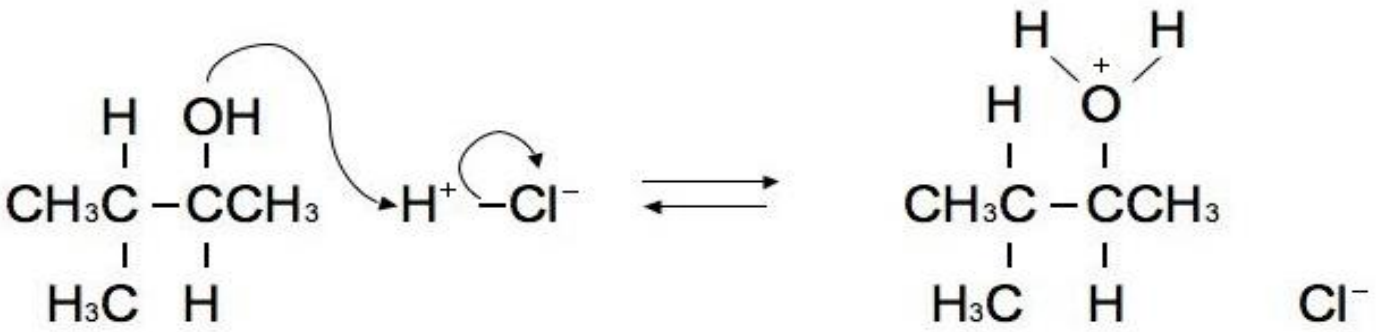
- ✓ the phenomenon of hydride shift is typically with the reaction of an R-OH and HX, which (X= Br, Cl, and I).



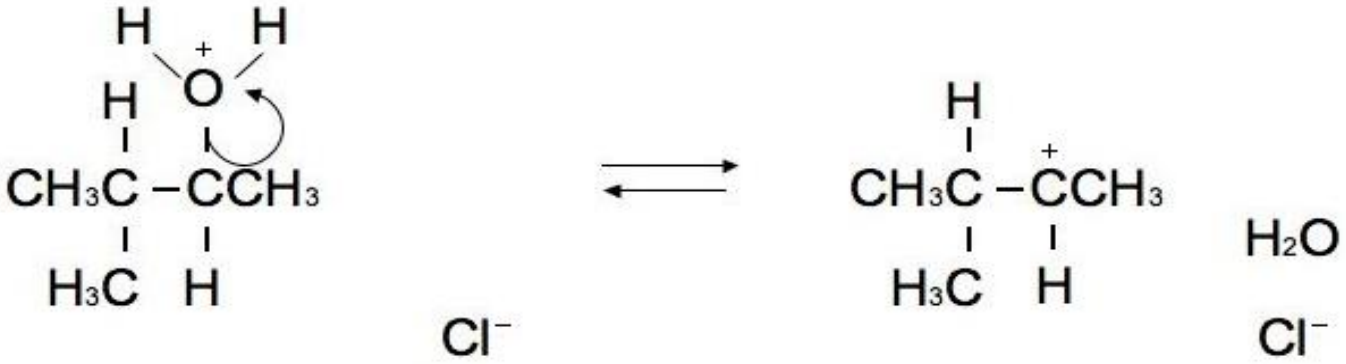
Possible mechanism...,

- ✓ The mechanism for hydride shift occurs in *multiple steps* that includes various intermediates and transition states.

Step 1: Protonation



Step 2: Loss of H_2O



Cont'd...

Step 3: Hydride Shift



Step 4: Chlorine Attacks

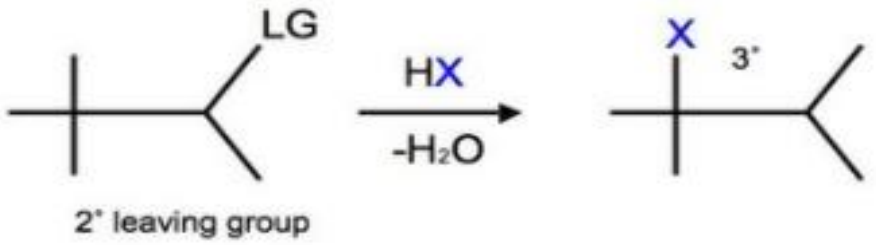


Alkyl Shift

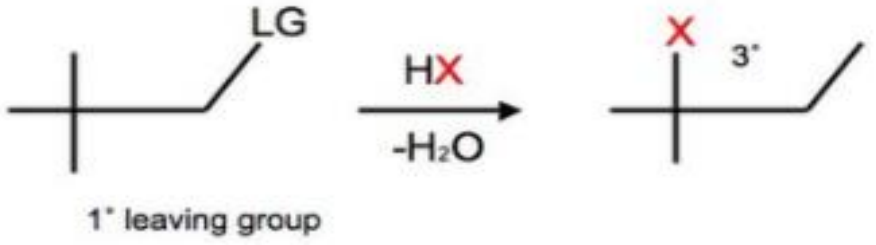
- ✓ Not all carbocations have suitable hydrogen atoms (either secondary or tertiary) that are on adjacent carbon atoms available for rearrangement.

- ✓ In this case, the reaction can undergo a different mode of rearrangement known as **alkyl shift** (or alkyl group migration).

Reaction #1: Secondary Substrate

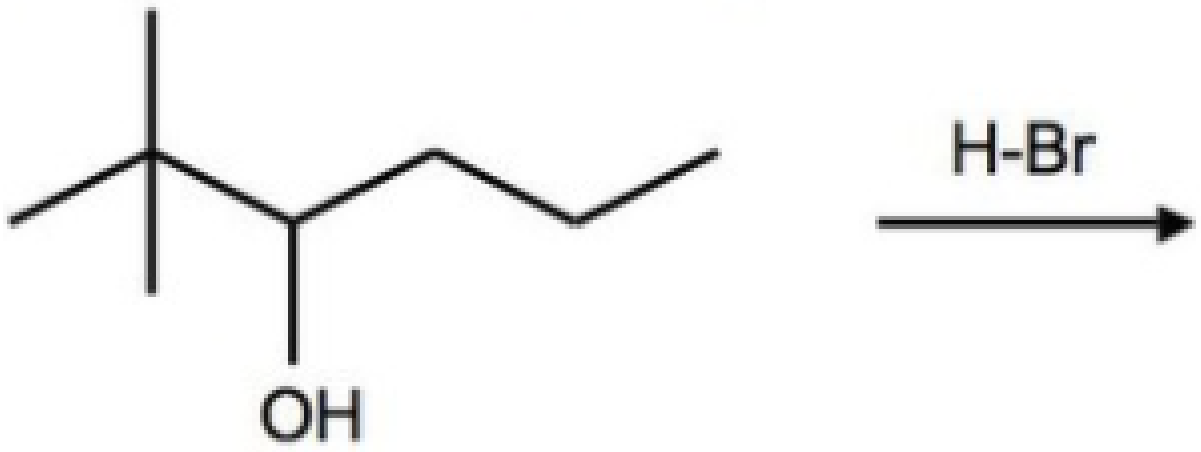


Reaction #2: Primary Substrate

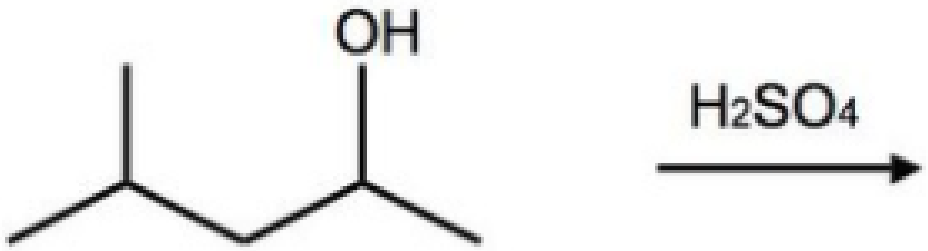


Problems

1) Please show the arrow pushing mechanism and major final product?



2) Please show the mechanism with hydride shift and show the final product?



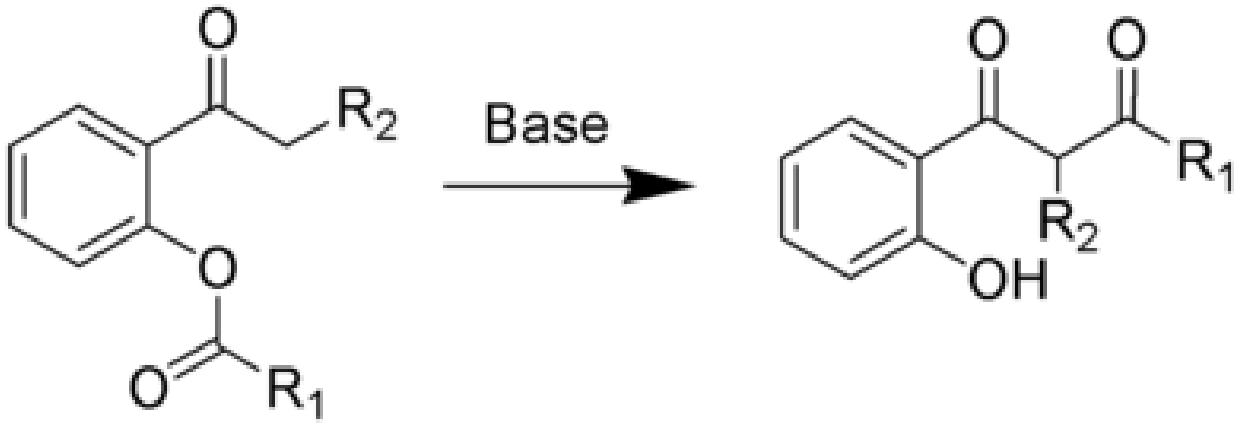
Types of Rearrangement Reaction;

✓ Baker-Venkataraman Rearrangement

✓ The base-induced transfer of the ester acyl group in an o-acylated phenol ester, which leads to a 1,3-diketone.

✓ The reaction is related to the Claisen Condensation.

✓ **For example;**

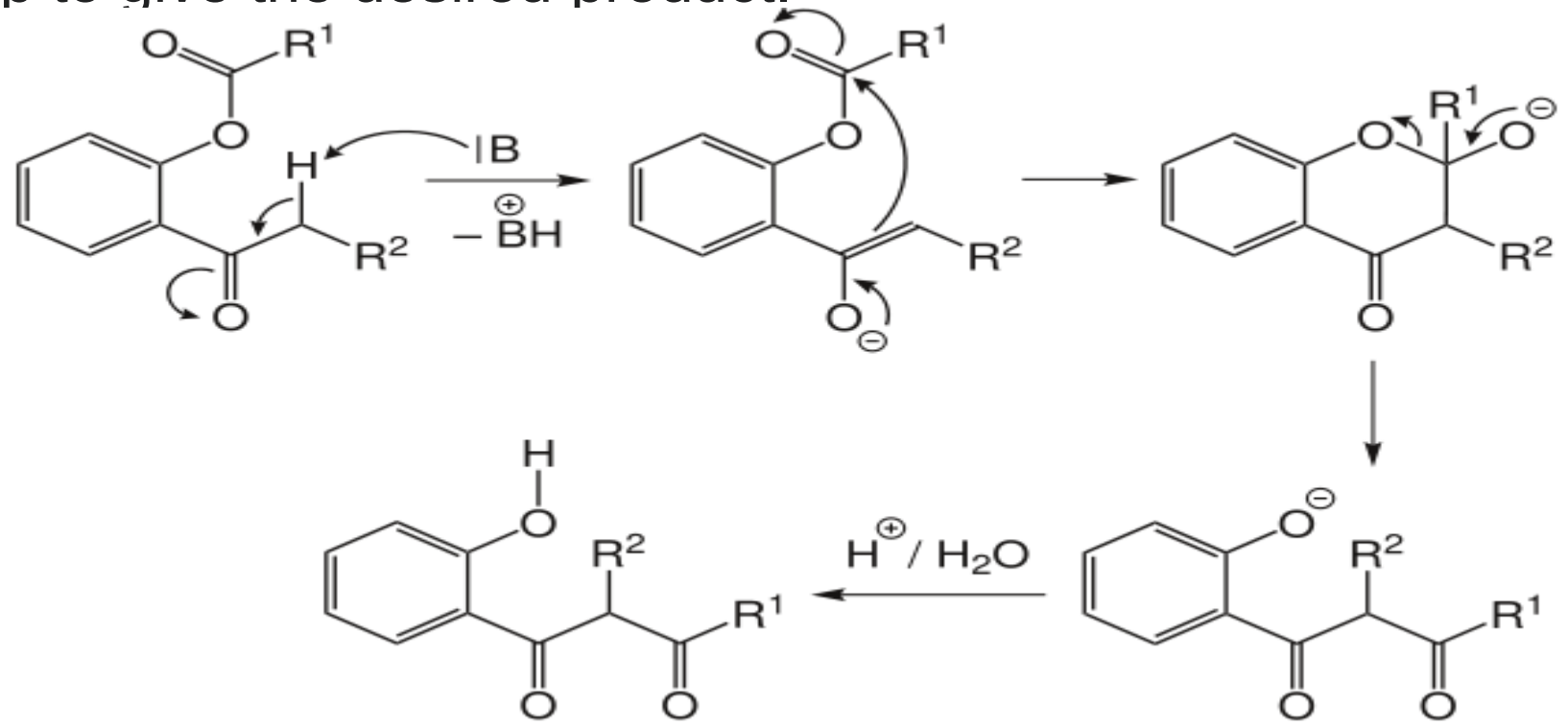


➢ Possible mechanism;

✓ A base abstracts the hydrogen atom alpha to the aromatic ketone, forming an enolate.

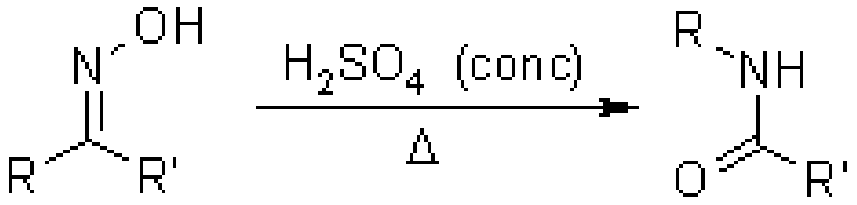
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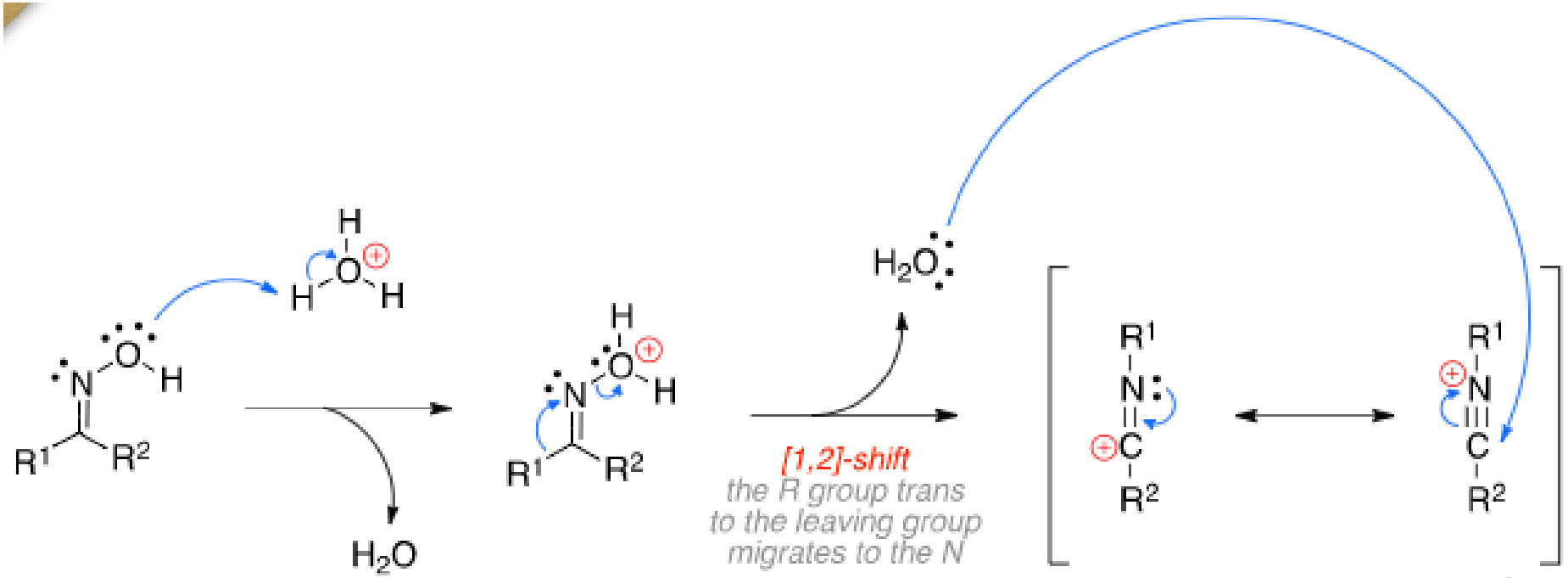
- ✓ Then, the enolate attacks the ester carbonyl to form a cyclic alkoxide.
- ✓ The cyclic intermediate is opened up to form a more stable phenolate and finally it is protonated during acidic work-up to give the desired product.

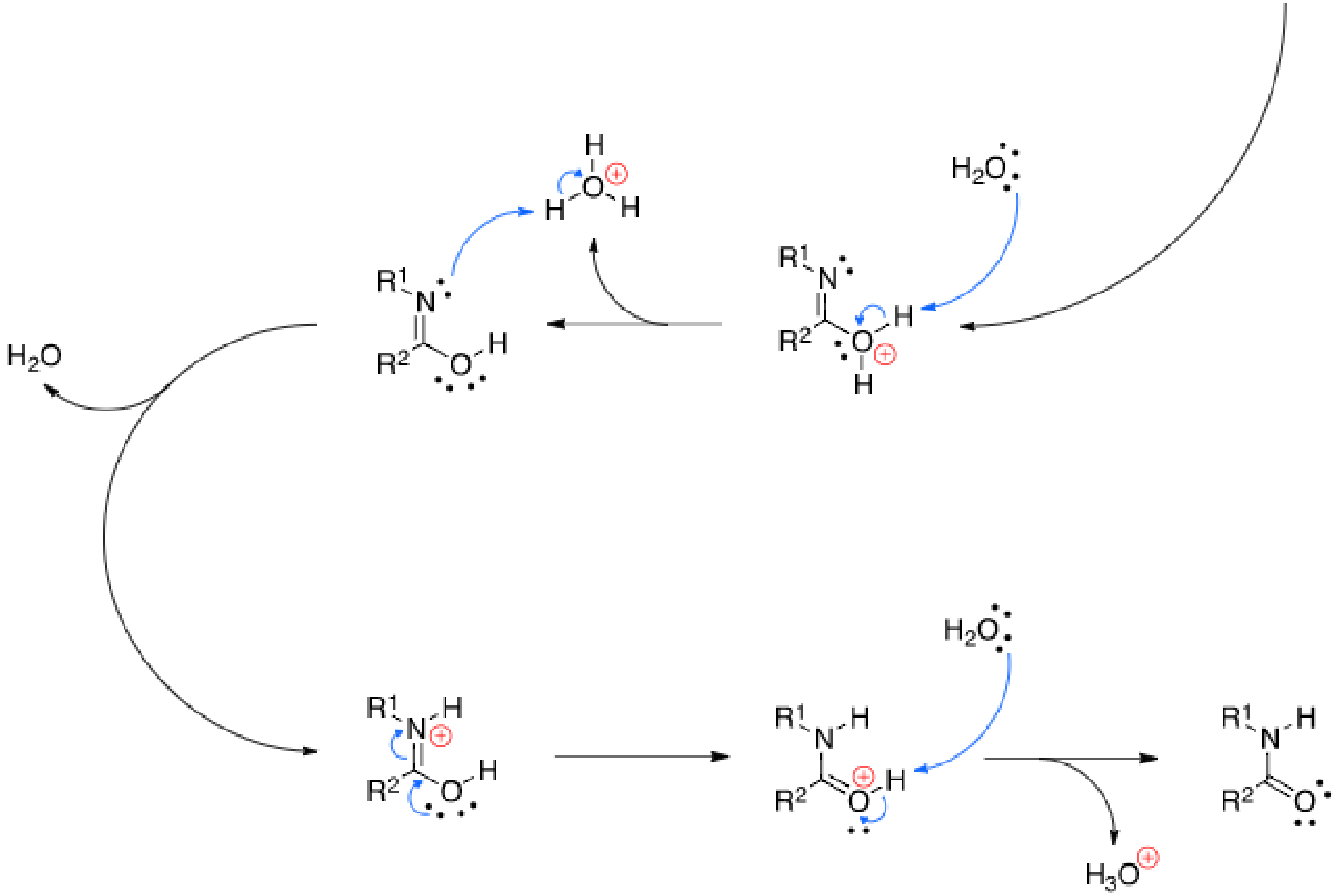


Beckmann Rearrangement

✓ The Beckmann rearrangement is an organic reaction used to convert an oxime to an amide under acidic conditions.

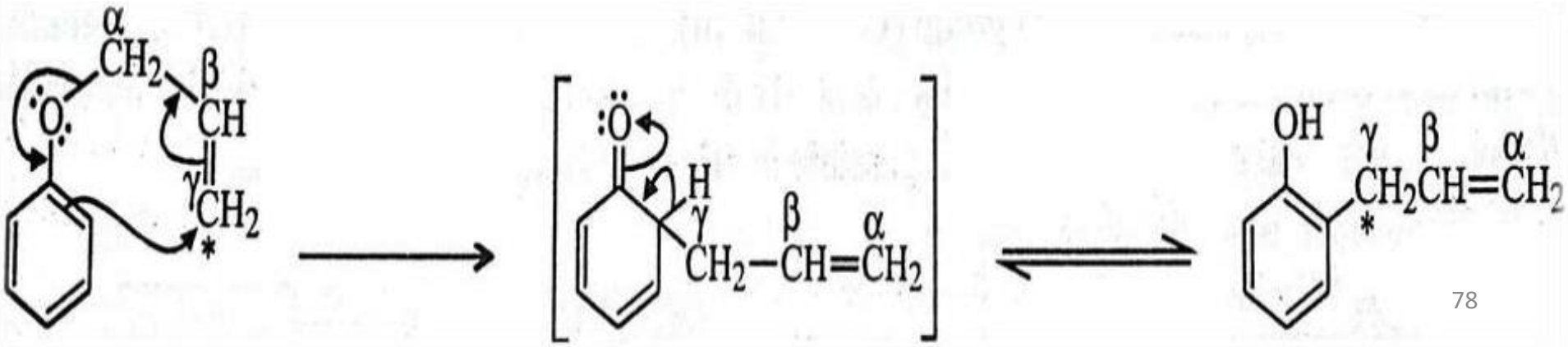





H2O
R1
N
R2
O
H
H2O
H3O

Claisen Rearrangement

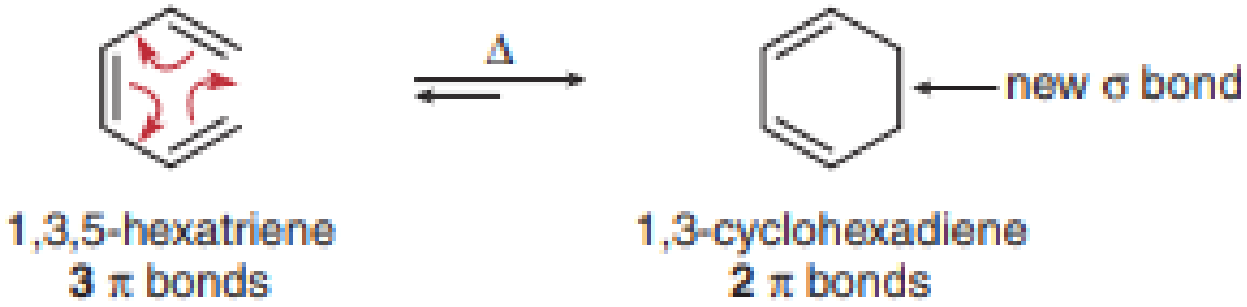
- ✓ The Claisen Rearrangement is a powerful C-C bond forming chemical reaction discovered by RAINER LUDWIG CLAISEN.
- ✓ It is the first Sigmatropic Rearrangement.
- ✓ Rearrangement of mixtures of allyl phenyl ethers do not give cross product,
- ✓ The cyclic mechanism, outlined below accounts for the intramolecular rearrangement of allyl ether to ortho allyl phenol.



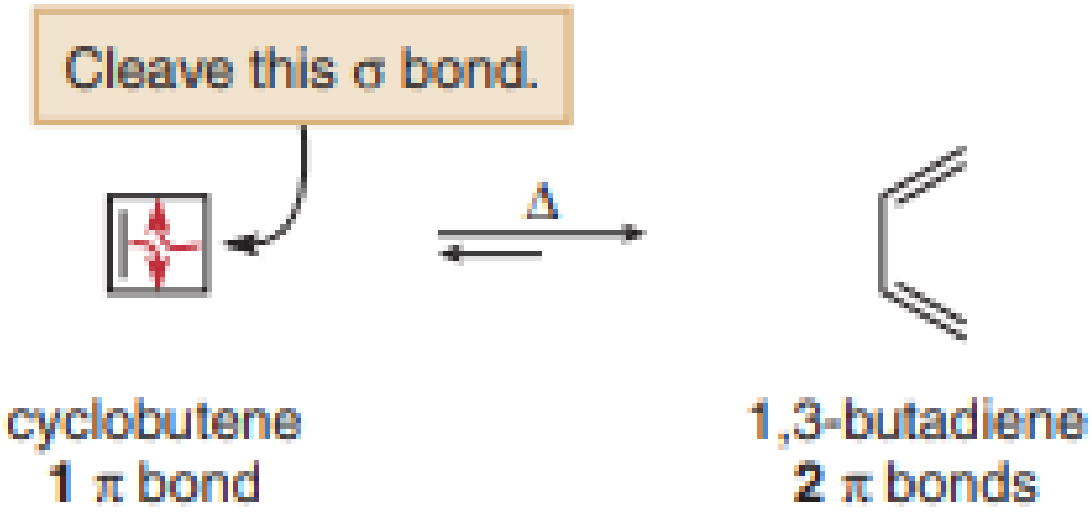
PERICYCLIC REACTIONS

- ✓ A pericyclic reaction is a concerted reaction that proceeds through a cyclic transition state.
- ✓ It requires light or heat and are completely stereospecific;
- ✓ that is, a single stereoisomer of the reactant forms a single and stereoisomer of the product..
- ✓ Let consider some types of pericyclic reactions: electrocyclic reactions and cycloadditions.
- ✓ An electrocyclic ring closure is an intramolecular reaction that forms a cyclic product containing one more σ bond and one fewer π bond than the reactant.

For instance;

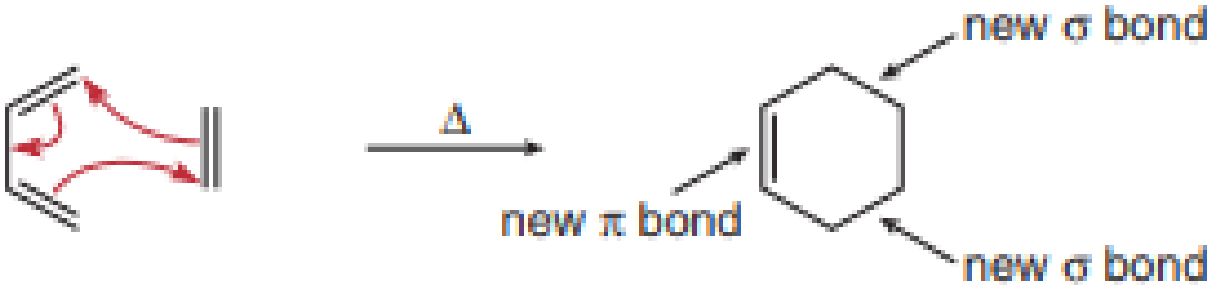


✓ An electrocyclic ring-opening reaction is a reaction in which a σ bond of a cyclic reactant is cleaved to form a conjugated product with one more π bond.



Cycloaddition Reaction

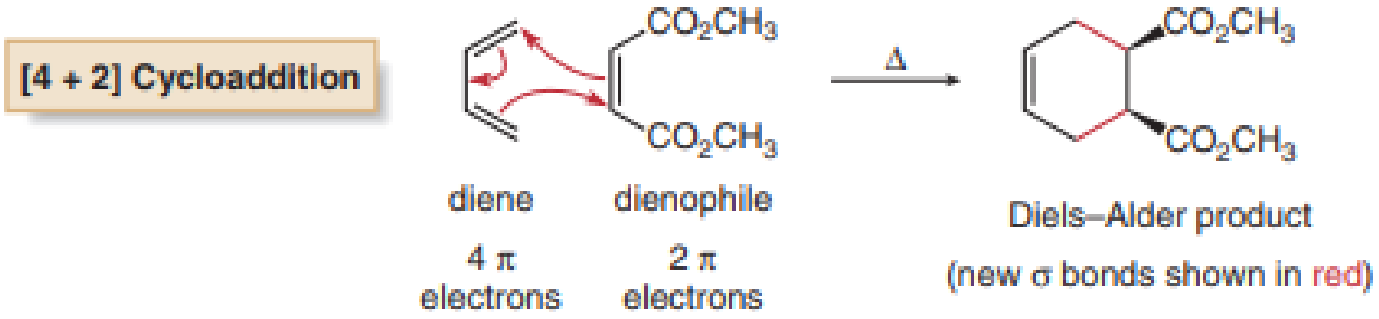
- ✓ A cycloaddition is a reaction between two compounds with π bonds to form a cyclic product with two new σ bonds.



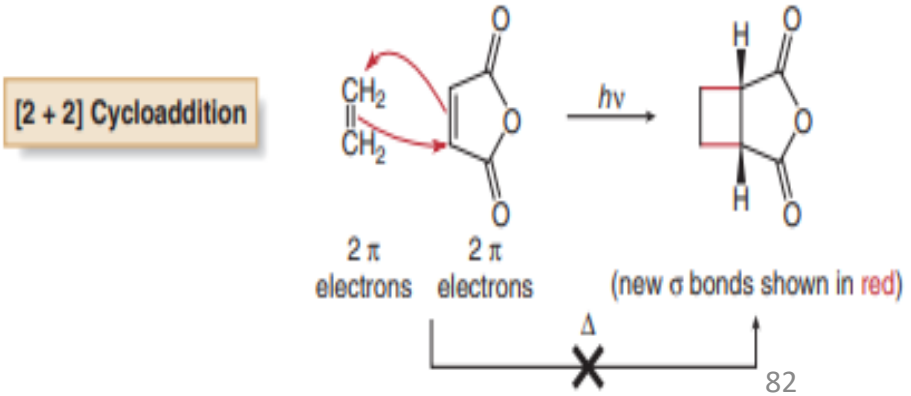
- ✓ Example: Diels–Alder reaction.
- ✓ Two features determine the course of the cycloaddition reactions:
- ✓ the number of π bonds involved and whether the reaction occurs in the presence of heat (thermal conditions) or light (photochemical conditions)

The Diels–Alder reaction is a thermal [4 + 2] cycloaddition

- ✓ It occurs between a diene with four π electrons and an alkene (dienophile) with two π electrons.

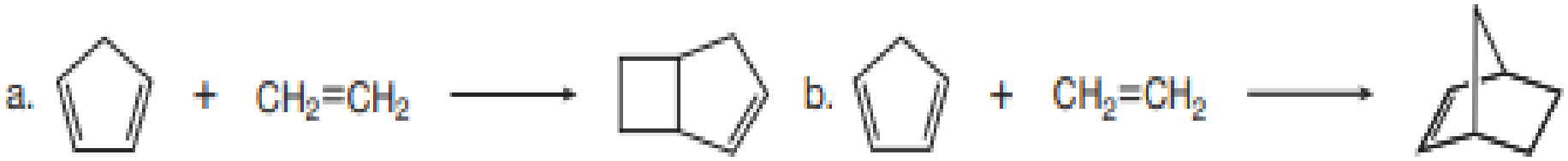


- ✓ **A photochemical [2 + 2] cycloaddition**
- ✓ It occurs between two alkenes, each with two π electrons, to form a cyclobutane.
- ✓ Thermal [2 + 2] cycloadditions do not take place by heat



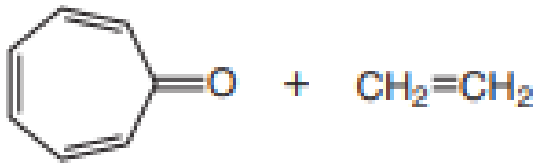
Problem(1)

i) What type of cycloaddition is shown in each equation?



Problem (2)

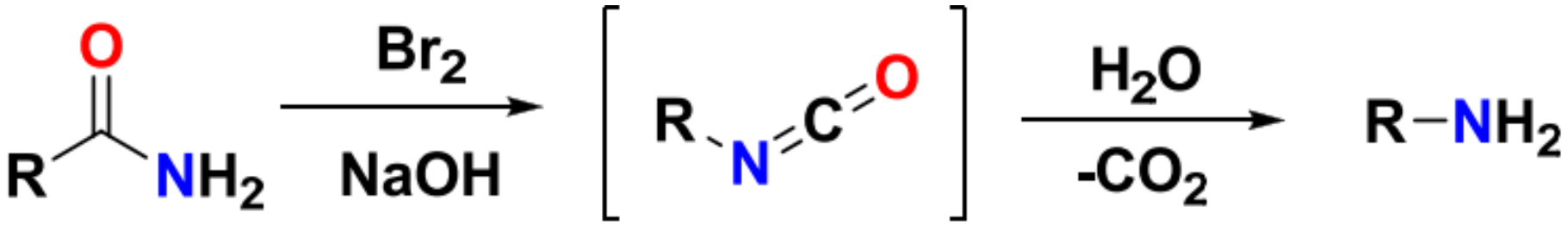
✓ Consider cycloheptatrienone and ethylene, and draw a possible product formed from each type of cycloaddition: (a) [2 + 2]; (b) [4 + 2]; (c) [6 + 2].show its mechanism!



cycloheptatrienone

The Hofmann Rearrangement

✓ Treatment of amides with bromine in basic solution gives an amine with loss of the carbonyl carbon.



➢ **Possible step mechanism reaction of the Hofmann Rearrangement**

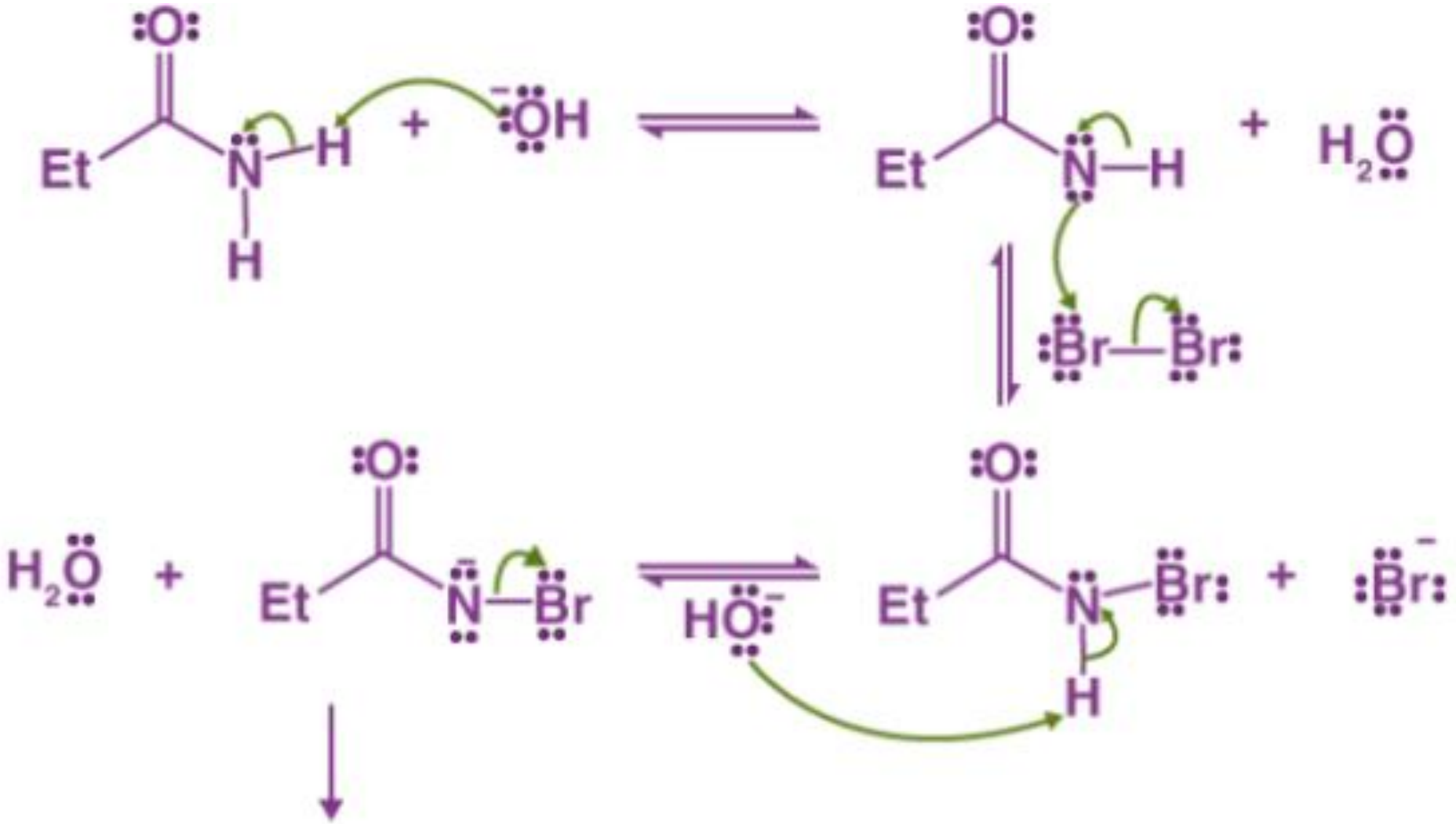
✓ The Hofmann rearrangement involves 6 steps in 3 stages:

(1) formation of an N-bromo amide (2 steps)

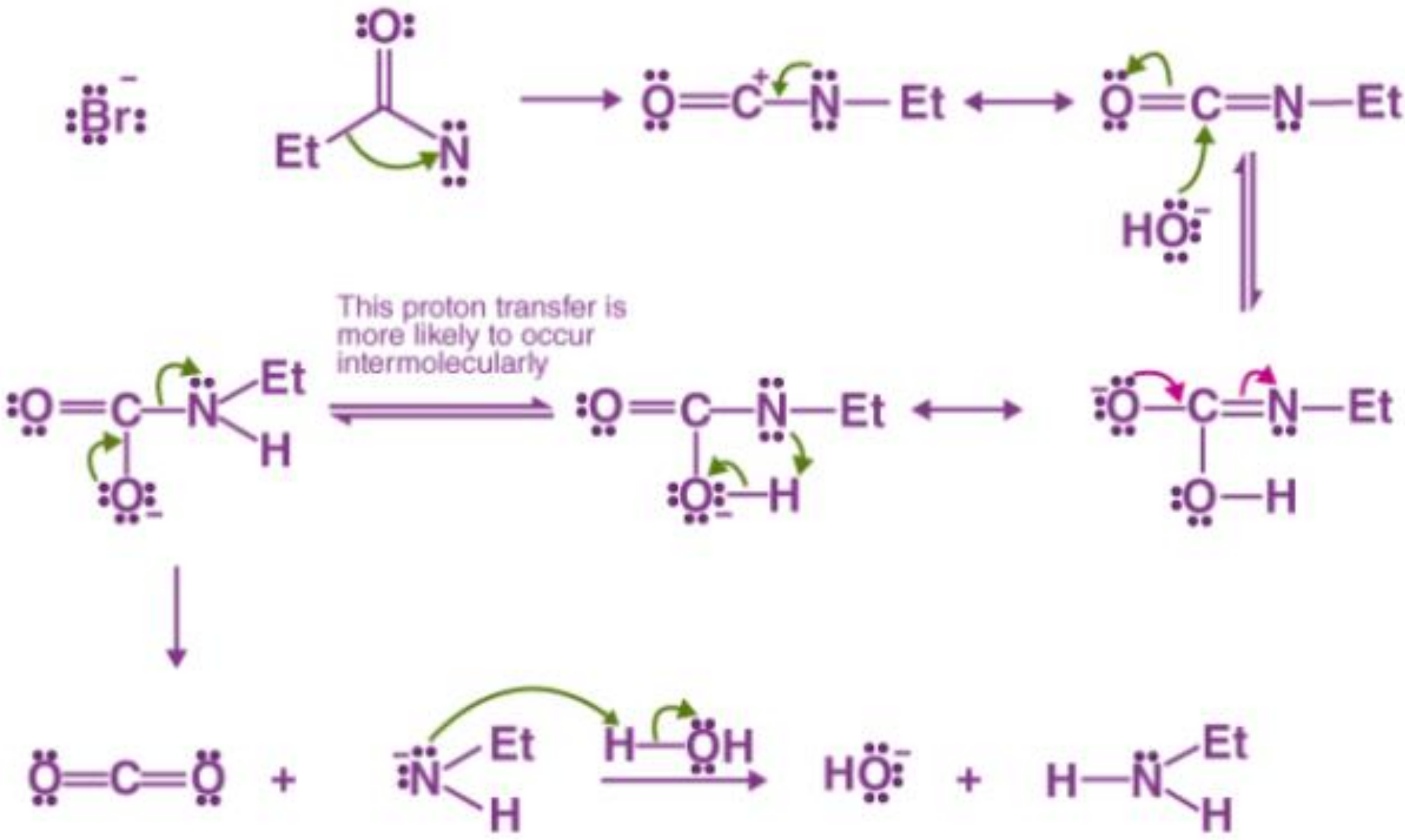
(2) conversion of the N-bromo amide to an isocyanate (2 steps)

(3) hydrolysis of the isocyanate (2 steps)

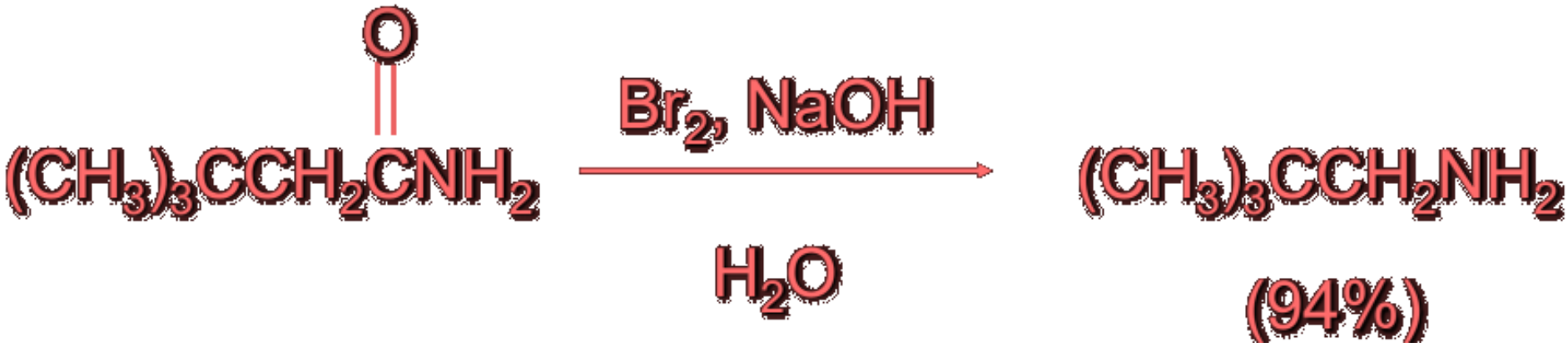
For examples

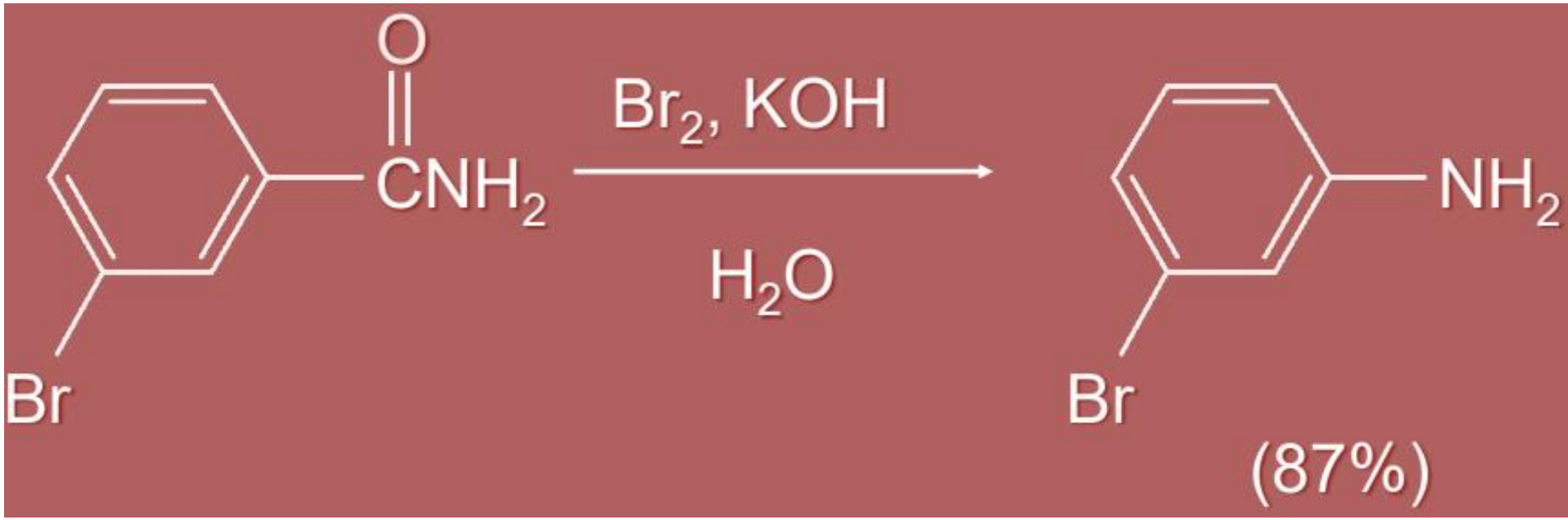


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This proton transfer is more likely to occur intermolecularly

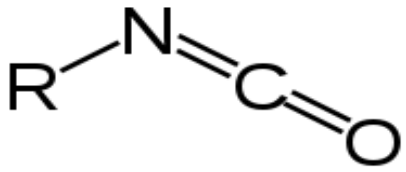
For instance;





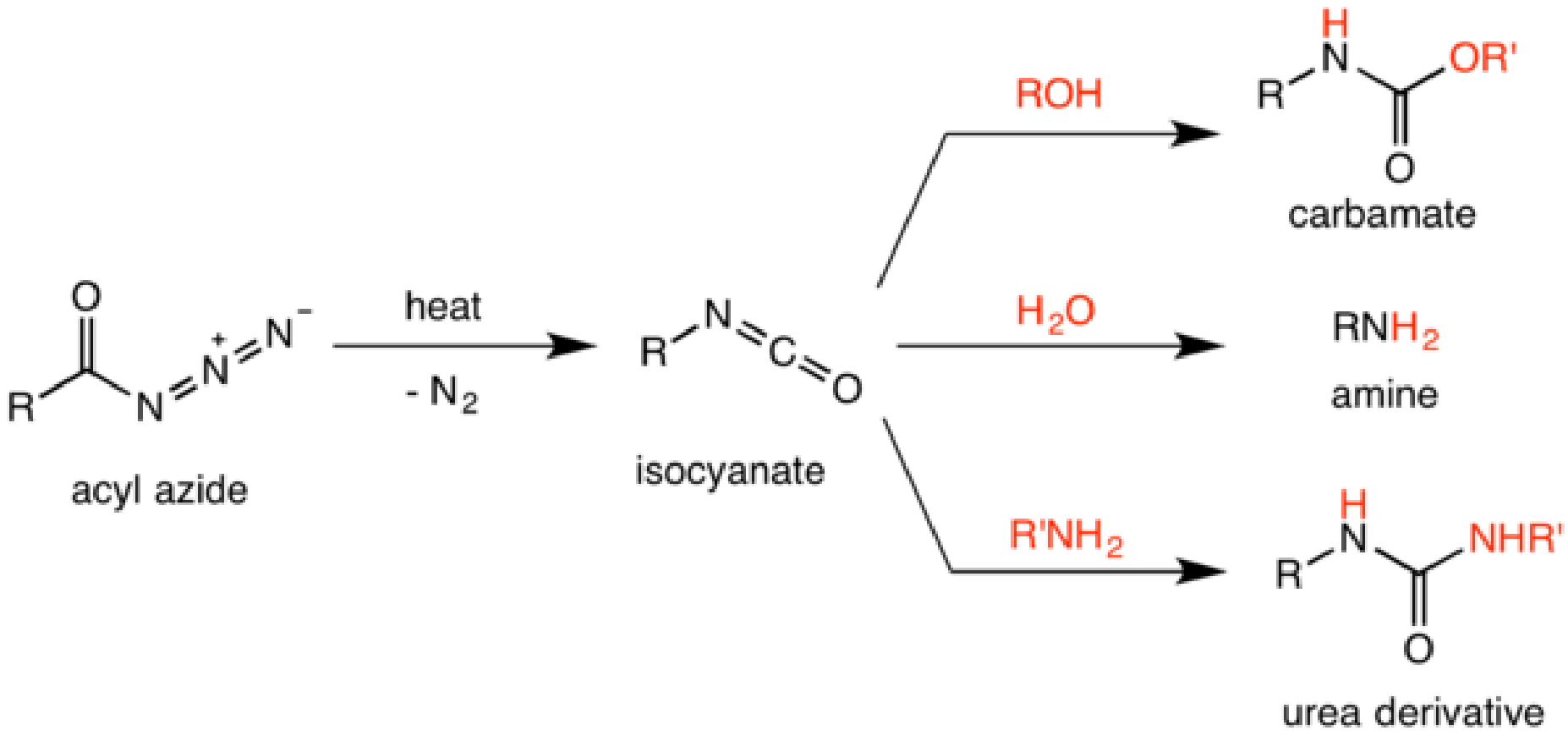
Curtius Rearrangement

- ✓ It is the thermal decomposition of carboxylic azides to produce an isocyanate.



- ✓ These intermediates may be isolated, or their corresponding reaction or hydrolysis products may be obtained.
- ✓ The isocyanate then undergoes attack by a variety of nucleophiles such as water, alcohols and amines, to yield a primary amine, carbamate or urea derivative respectively

For instance....



✓ The acyl azide is usually made from the reaction of acid chlorides or anydrides[6] with sodium azide or trimethylsilyl azide.

Further reaction

