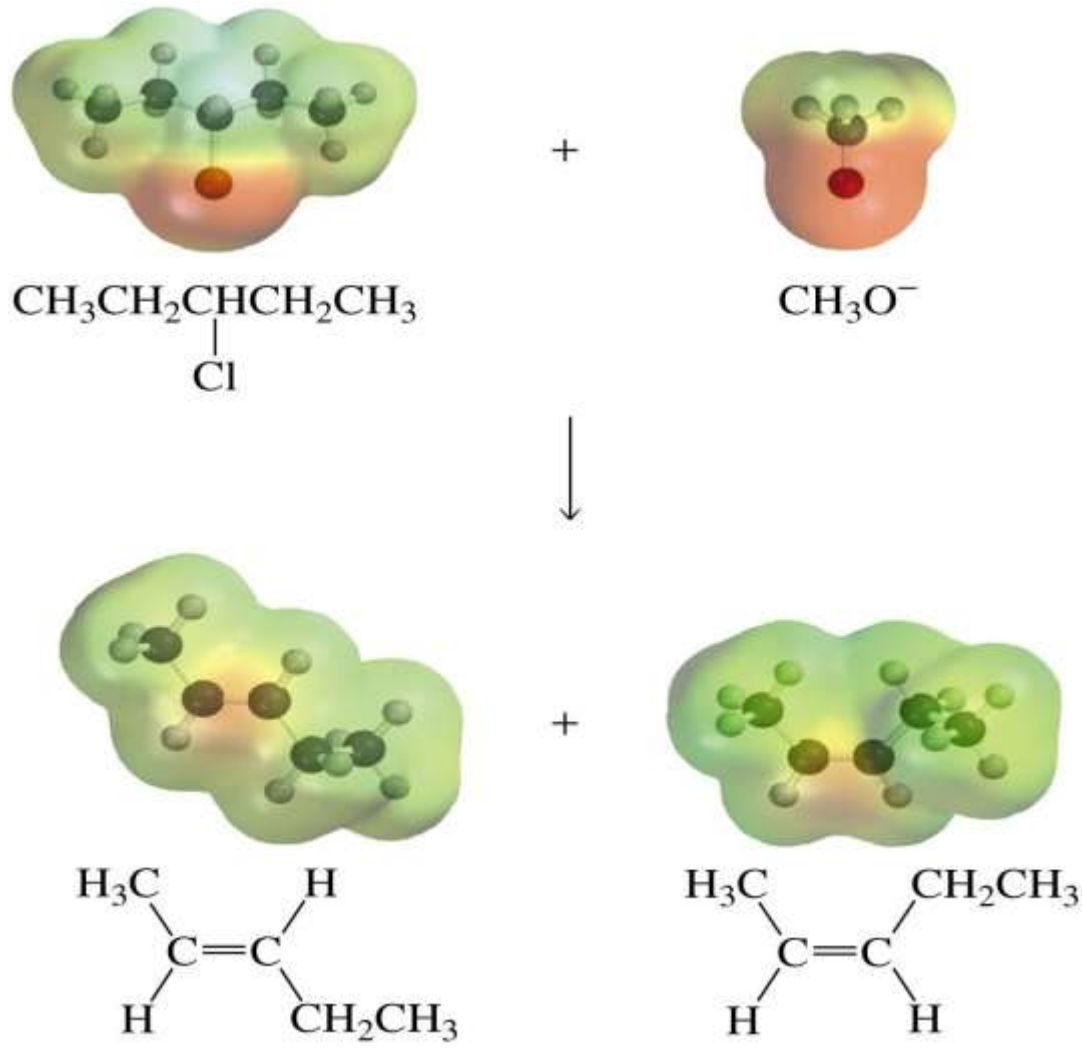
Elimination Reactions (Unit I)

Outline

1. Introduction
2. E2, E1, and E1 cb mechanisms
3. Regiochemistry of Elimination reactions
4. Stereochemistry of Elimination reactions
6. Dehydration of Alcohols
7. Competition Between E2 and E1 Reactions
8. Summary

Introduction



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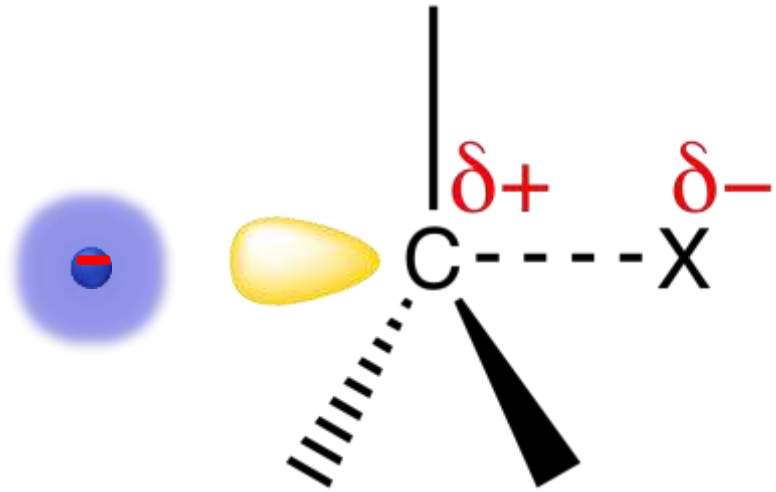
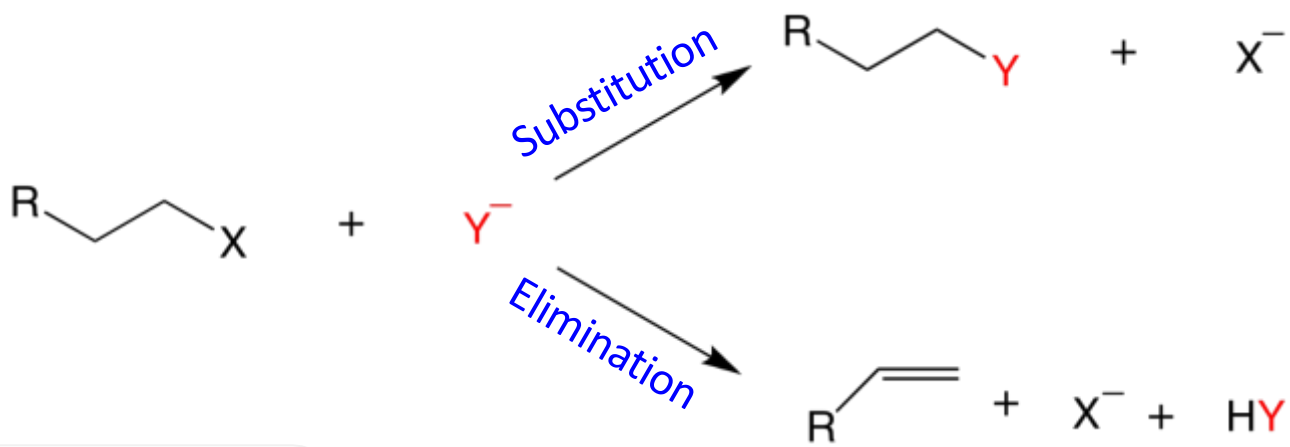
Organic compounds with an electronegative atom or an electron-withdrawing group bonded to a sp^3 carbon undergo substitution or elimination reactions





Halide ions are good leaving groups. Substitution reaction on these compounds are easy and are used to get a wide variety of compounds

R—F	R—Cl	R—Br	R—I
alkyl fluoride	alkyl chloride	alkyl bromide	alkyl iodide

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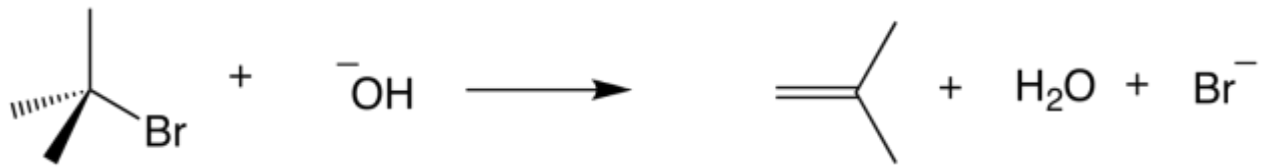
Elimination Reactions



1-bromo-1,1-dimethylethane

2-methylpropene

Rate law:

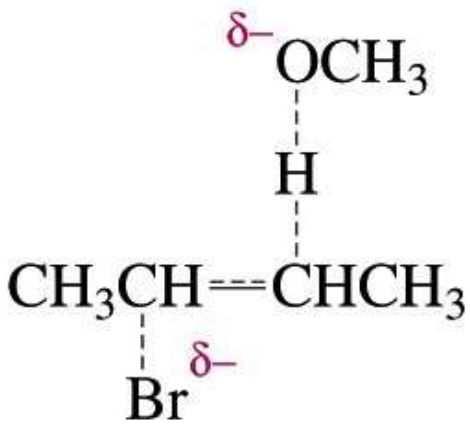
rate = k [1-bromo-1,1-dimethylethane][OH^-]

this reaction is an example of a E2 reaction.

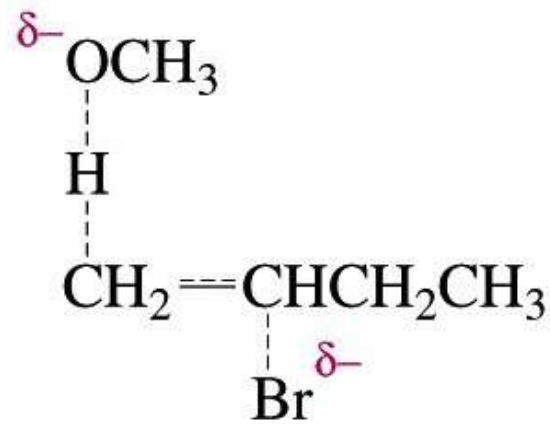
E stands for elimination
2 stands for bimolecular

Zaytzeff's rule

The more substituted alkene will be formed in elimination reactions

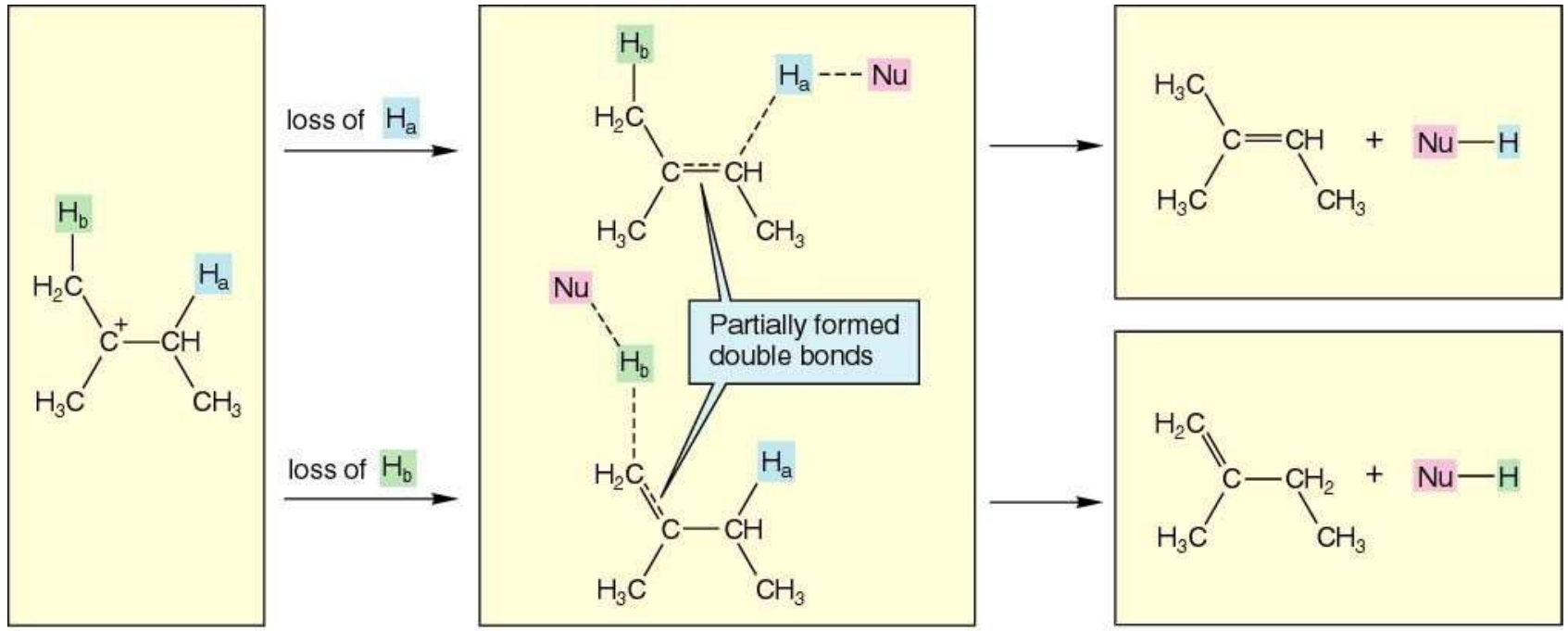


transition state leading to 2-butene
more stable



transition state leading to 1-butene
less stable

Zaytzeff's rule



Transition states for proton removal by a base, $\ddot{:}Nu^-$ to give the alkene and Nu–H

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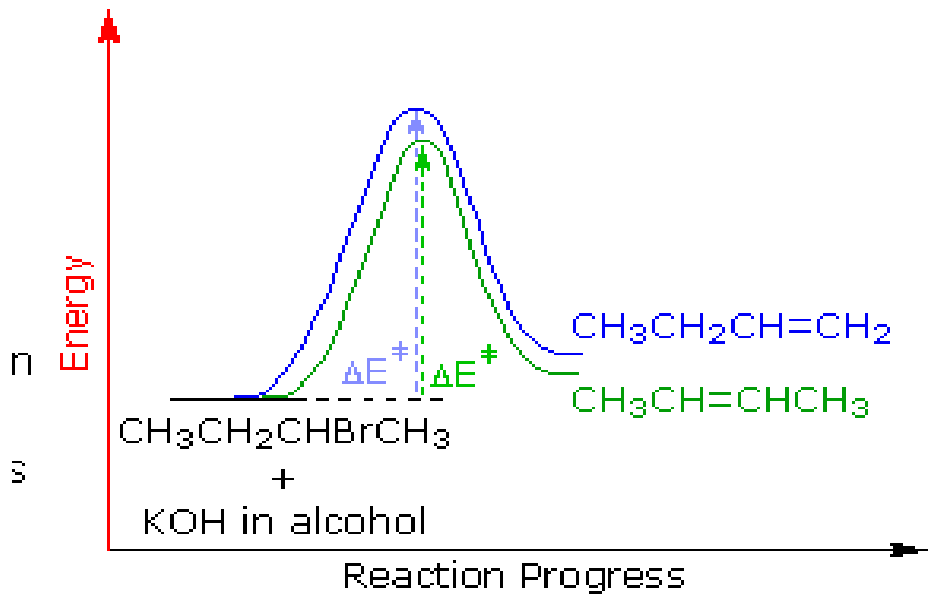
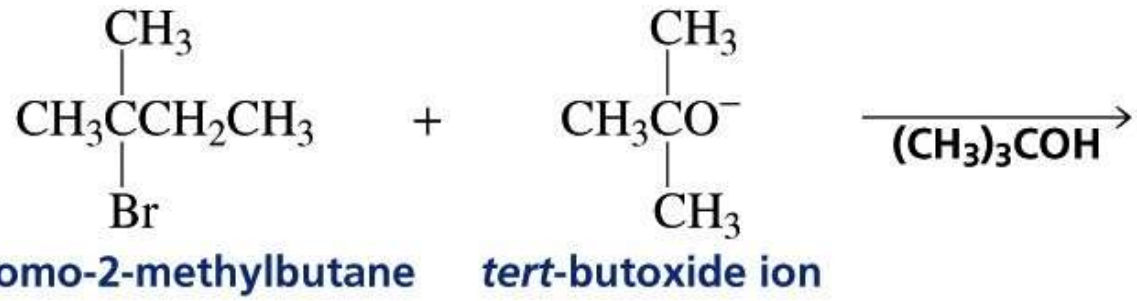
Zaytzeff's rule

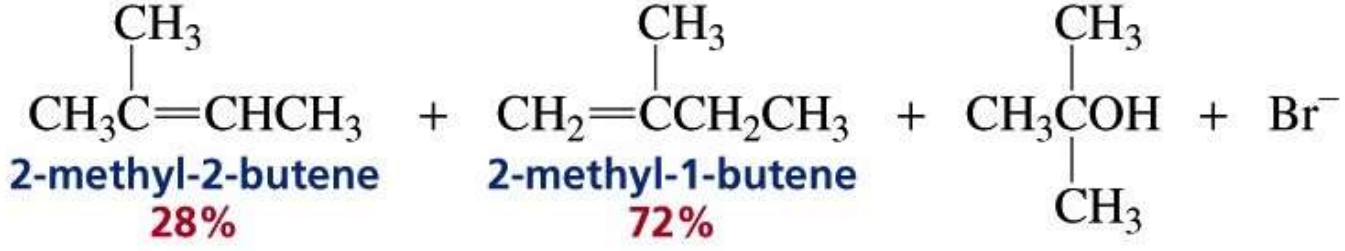
- In the transition state for elimination, the increased stability of the most substituted double bond is already felt so that there is a lower energy barrier for elimination of Ha



Zaytzeff's rule

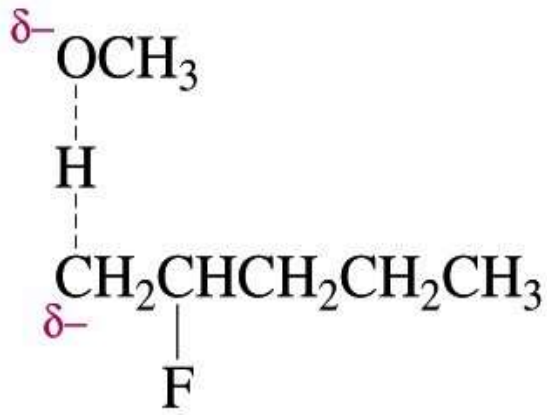
- Zaytzeff's rule dose not apply when the base is bulky



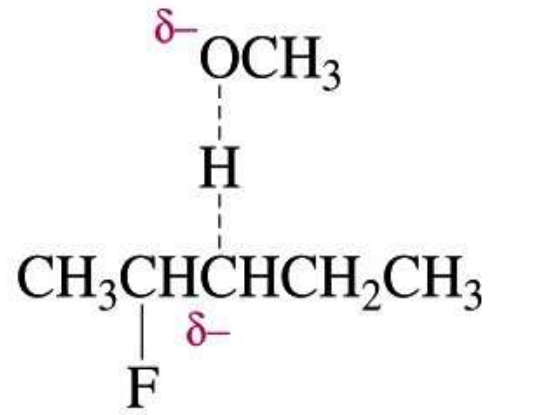


Zaytzeff's rule

- Zaytzeff's rule does not apply when the leaving group is poor
- E2-carbanion mechanism operative



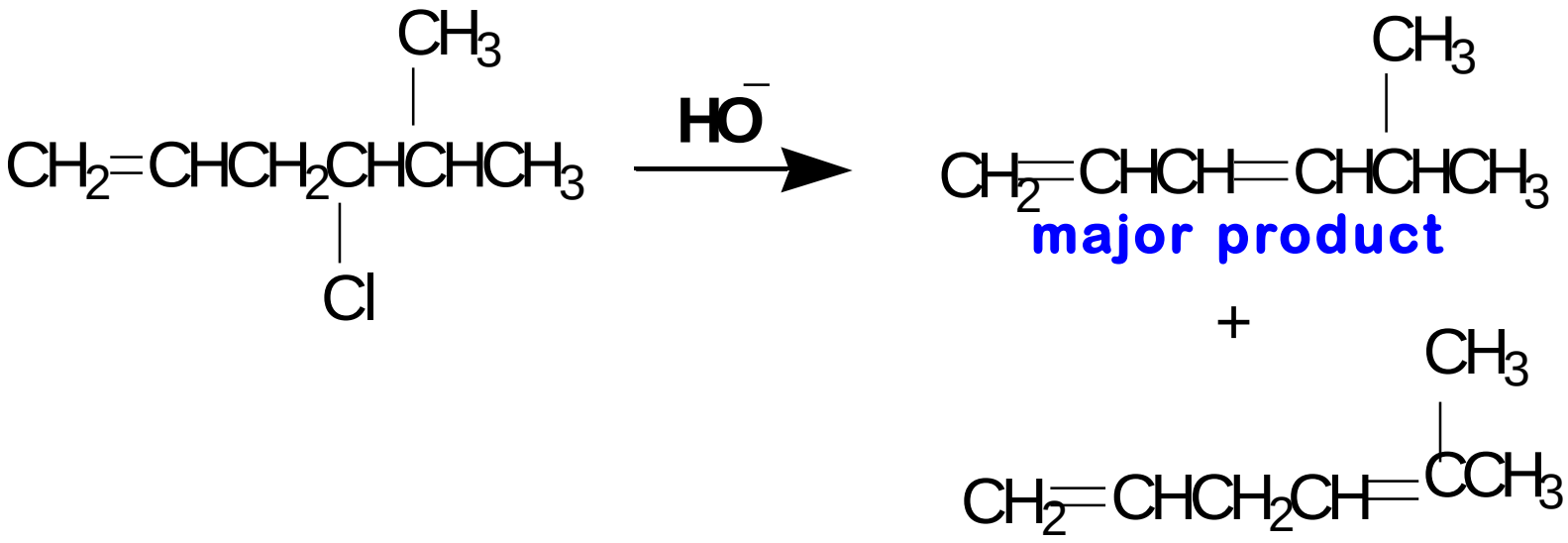
transition state leading to 1-pentene
more stable



transition state leading to 2-pentene
less stable

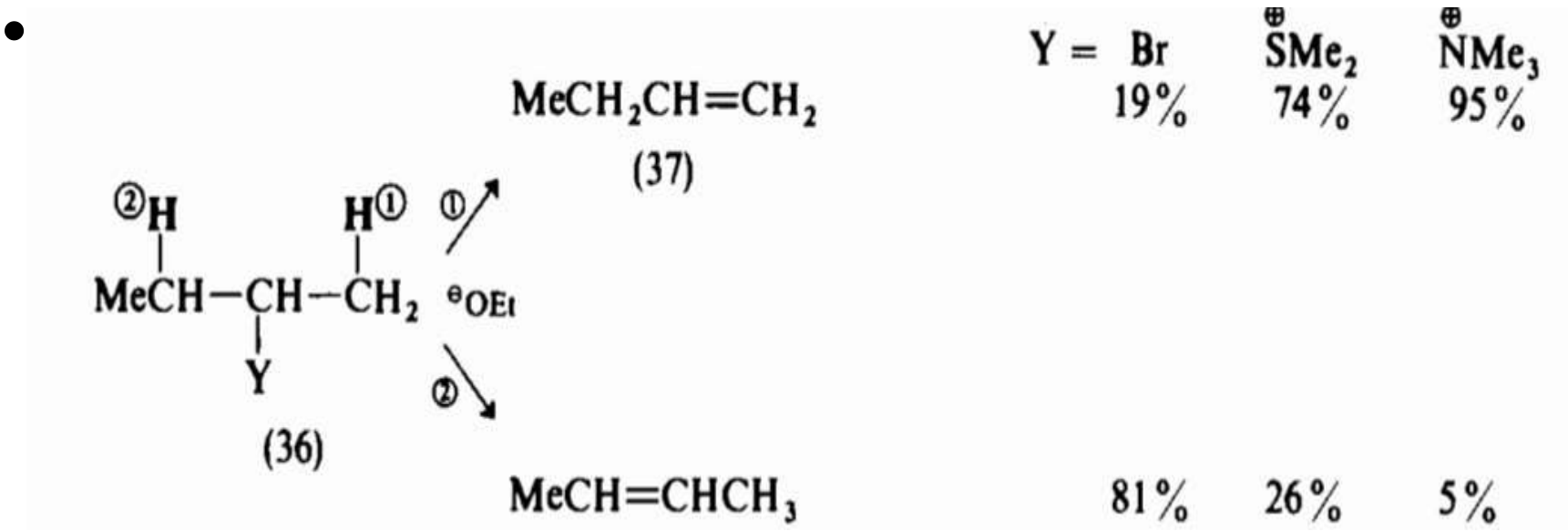
Zaytzeff's rule

Zaytzeff's rule may not apply when conjugated dienes might be formed



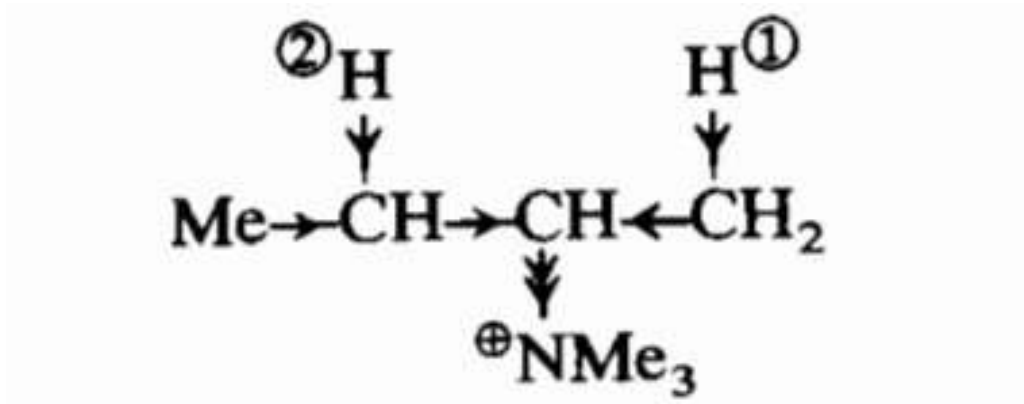
Hofman's rule

- Hofman: the alkene will predominate which has least alkyl substituents on the double bond carbon (1851; working on $RN^{+}Me$ compounds, i.e. $Y={}^{+}NMe$)
-



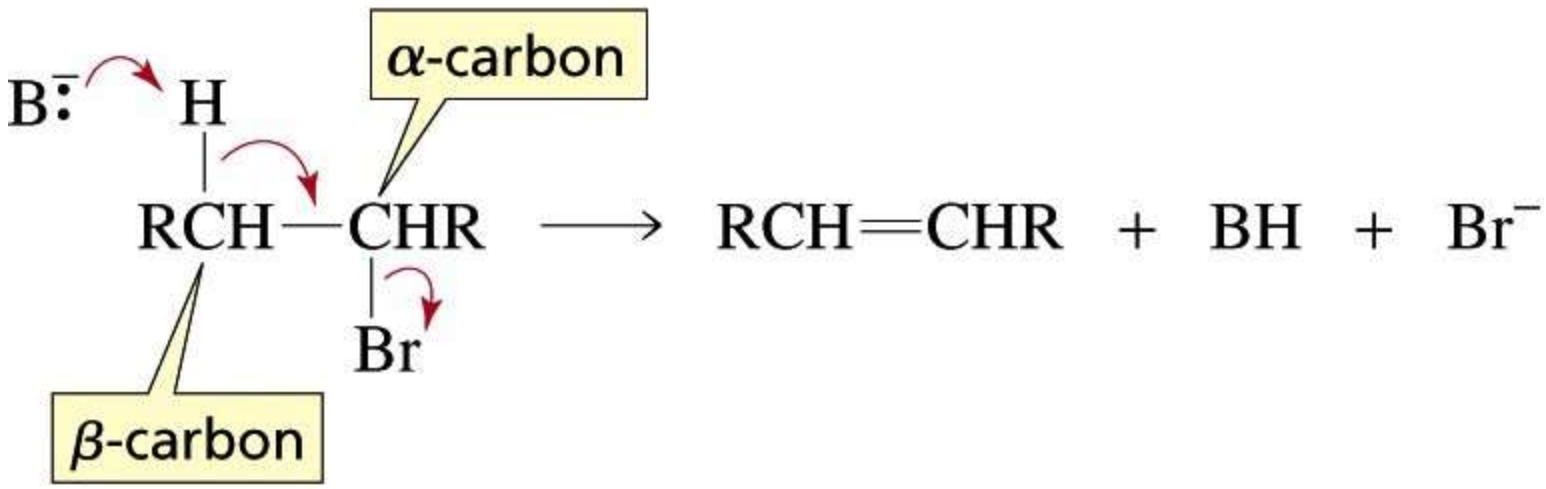
Hofman's rule

$^{+}$NMe will exert a powerful, electron-withdrawing, inductive/field affect on both β-carbon atoms

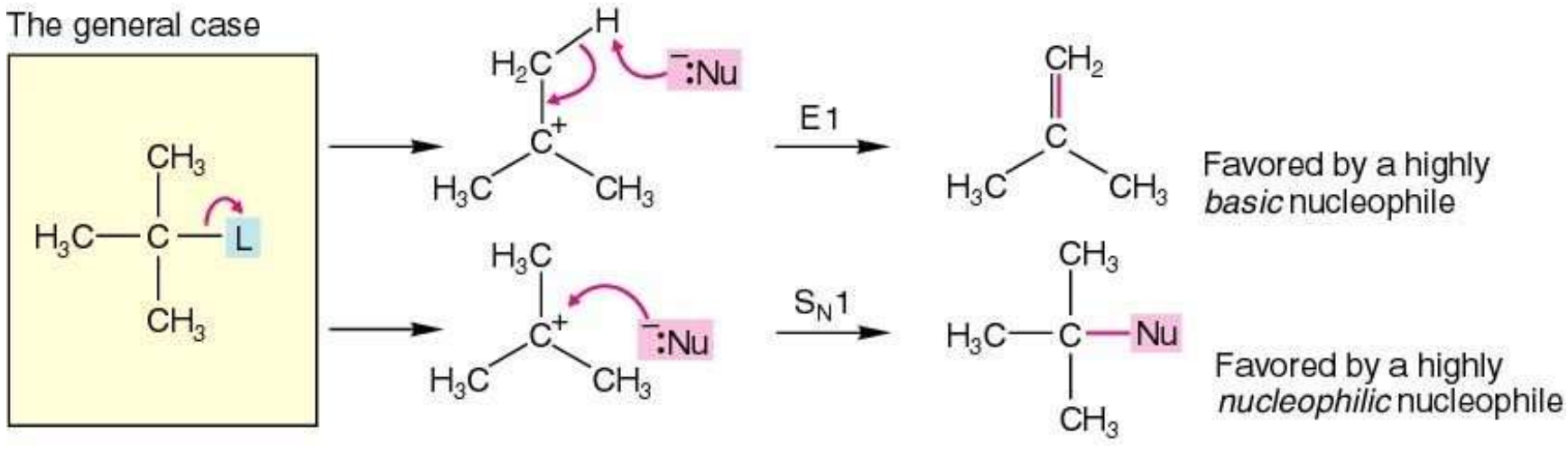


E2, E1, and E1 cb mechanisms

- Mechanism of E1 elimination reaction



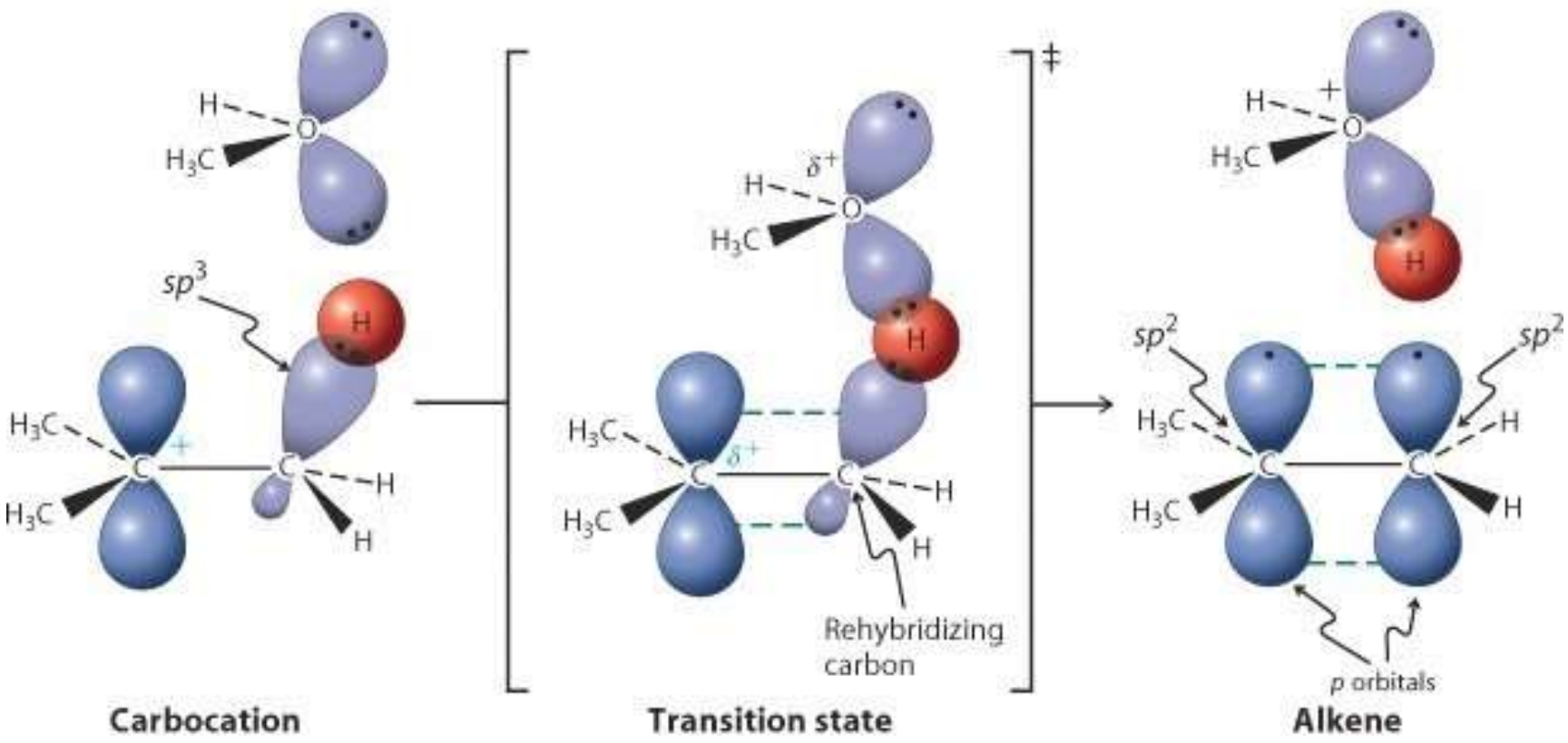
E1-elimination



$\nu = k$ [substrate]

- The mechanism is similar to that of the S_N1 reaction: the first step is formation of the carbocation via heterolytic cleavage

E1 Orbital Picture



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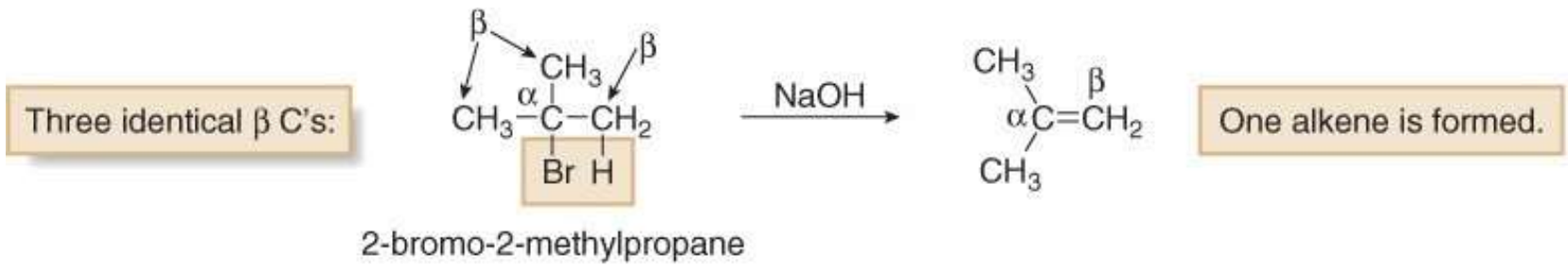
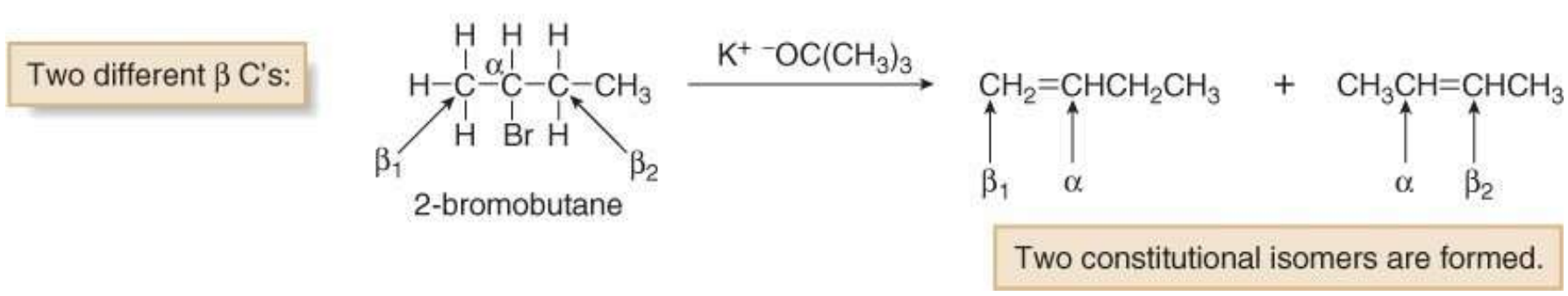
Products of Elimination

- To draw any product of dehydrohalogenation—Find the α carbon. Identify all β carbons with H atoms. Remove the elements of H and X form the α and β carbons and form a π bond.





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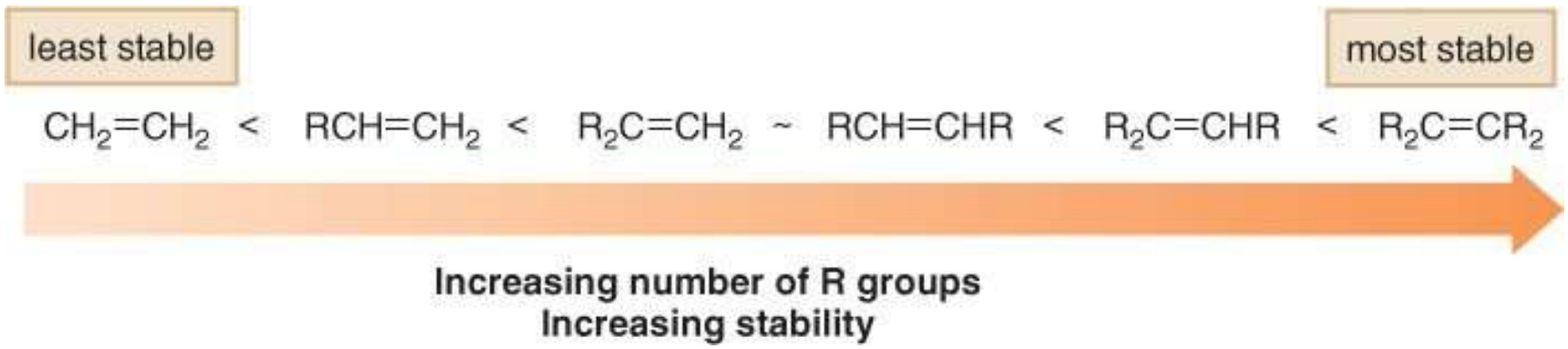
Order of Alkene Stability

- The stability of an alkene increases as the number of R groups bonded to the double bond carbons increases.



- The higher the percent *s*-character, the more readily an atom accepts electron density. Thus, sp^2 carbons are more able to accept electron density and sp^3 carbons are more able to donate electron density.
- Consequently, increasing the number of electron donating groups on a carbon atom able to accept electron density makes the alkene more stable.

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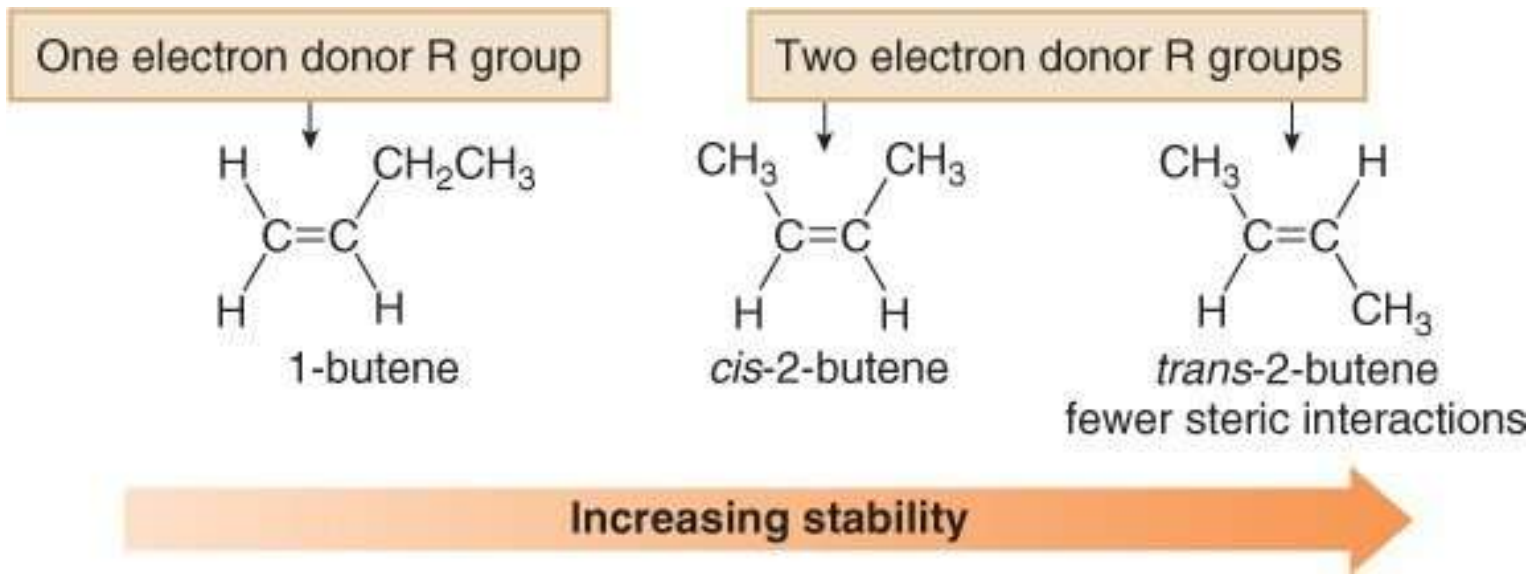
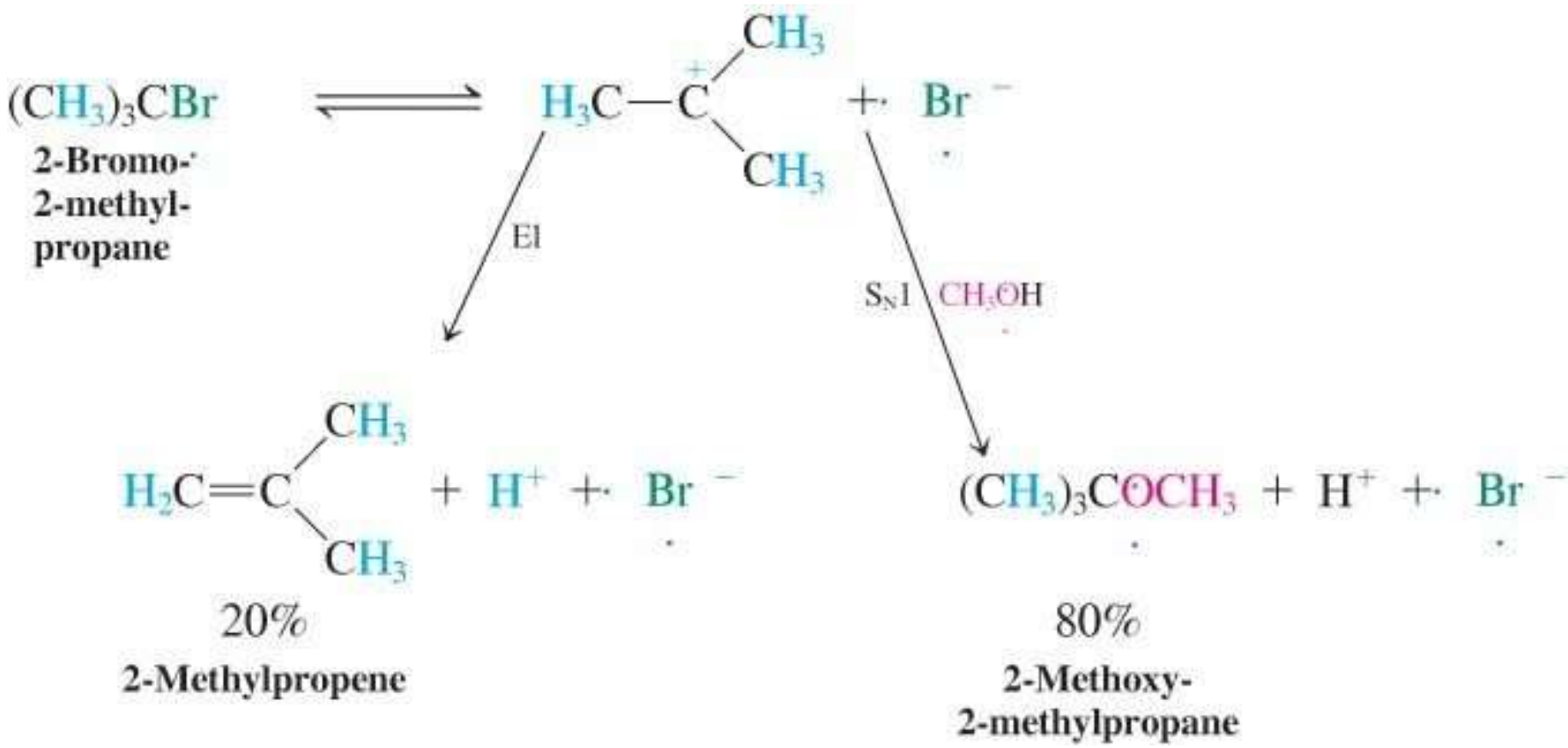
Stability of Trans Substituted Alkenes

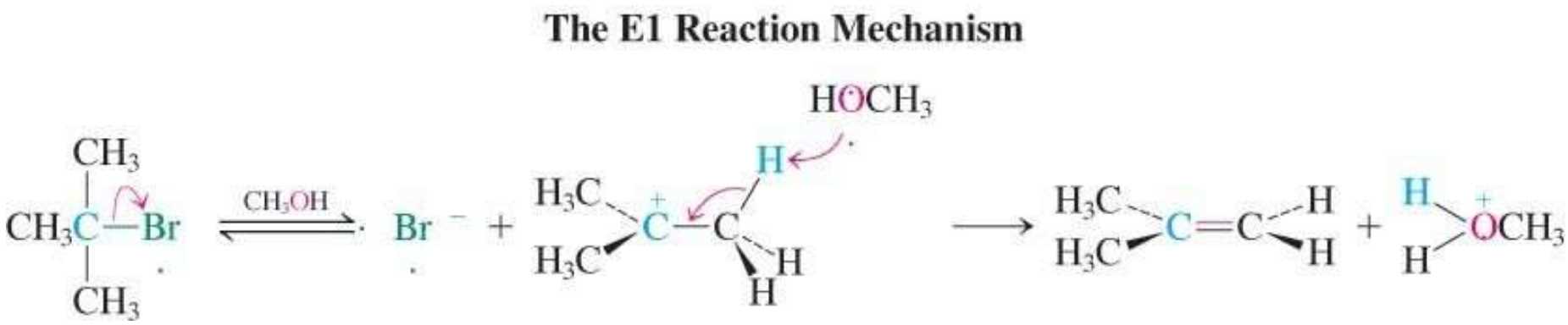
- *trans*-2-Butene (a disubstituted alkene) is more stable than *cis*-2-butene (another disubstituted alkene), but both are more stable than 1-butene (a monosubstituted alkene).



The E1 Pathway Competes with S_N1



First Step: Same as S_N1



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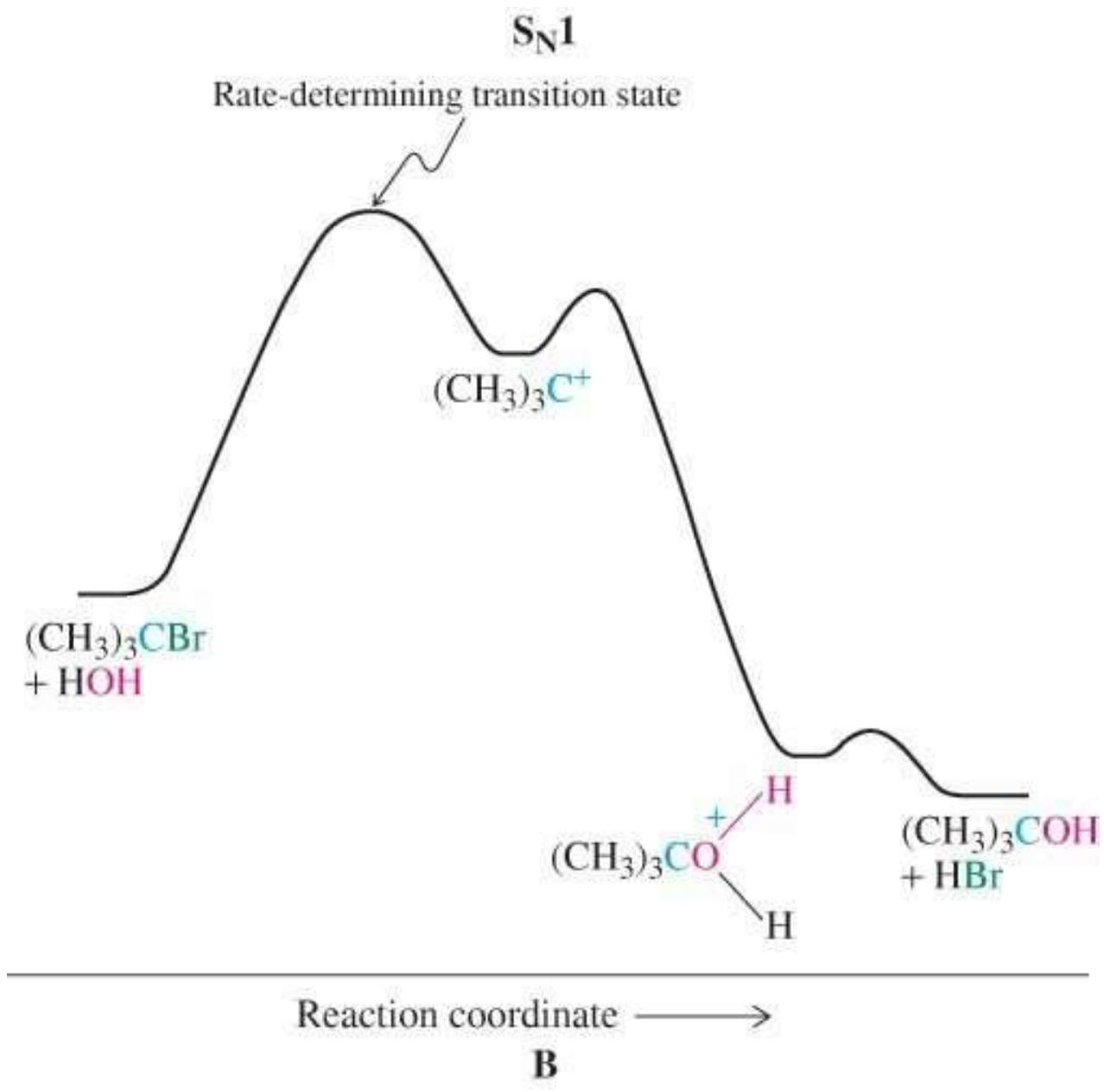

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Characteristics of the E1 Mechanism

Characteristic	Result
Mechanism	• Two steps
Identity of R	• More substituted halides react fastest • Rate: $R_3CX > R_2CHX > RCH_2X$
Base	• Favored by weaker bases such as H_2O and ROH
Leaving group	• A better leaving group makes the reaction faster because the bond to the leaving group is partially broken in the rate-determining step.
Solvent	• Polar protic solvents that solvate the ionic intermediates are needed.

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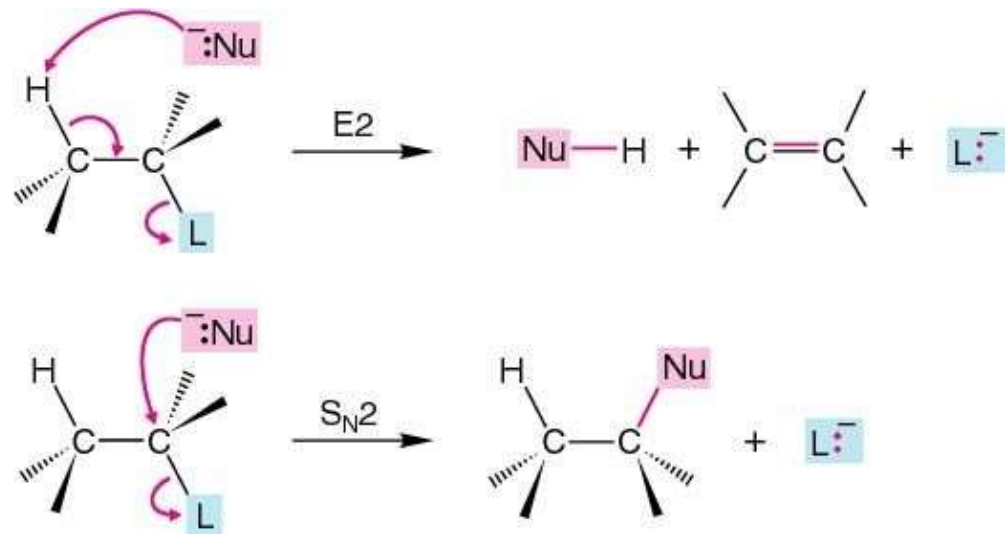
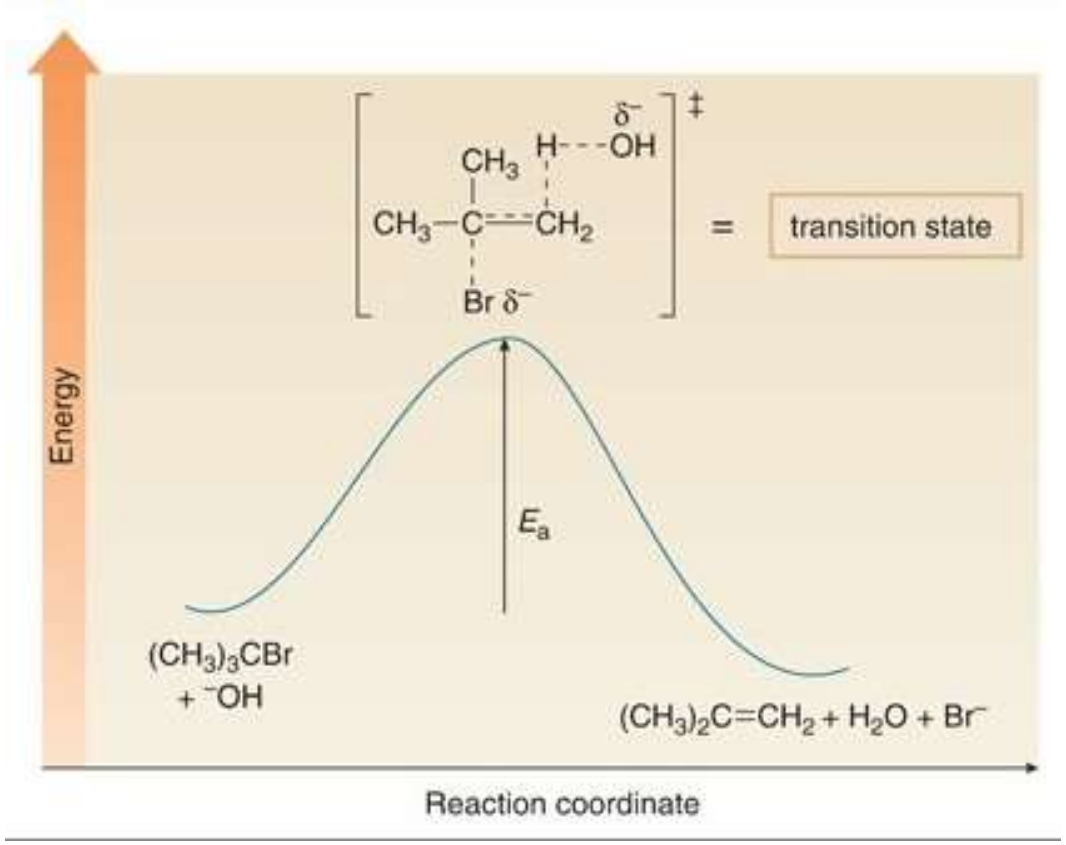
The E2 elimination



$\nu = k$ [substrate] [base]

- As in the S_N2 reaction, the rate is dependent on the concentration of both reaction partners

Energy Diagram for the E2 Mechanism



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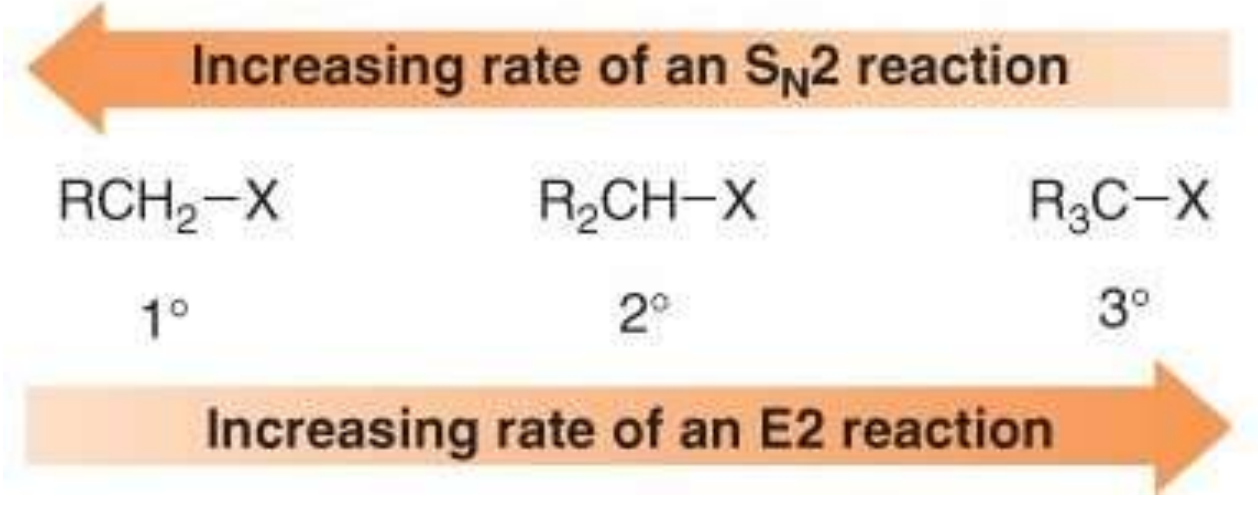
Effect of the Substrate on E2 Reactivity



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Characteristics of the E2 Mechanism	
Characteristic	**Result**
Mechanism	• One step
Identity of R	• More substituted halides react fastest • Rate: $R_3CX > R_2CHX > RCH_2X$
Base	• Favored by strong bases
Leaving group	• Better leaving group --→ faster reaction
Solvent	• Favored by polar aprotic solvents

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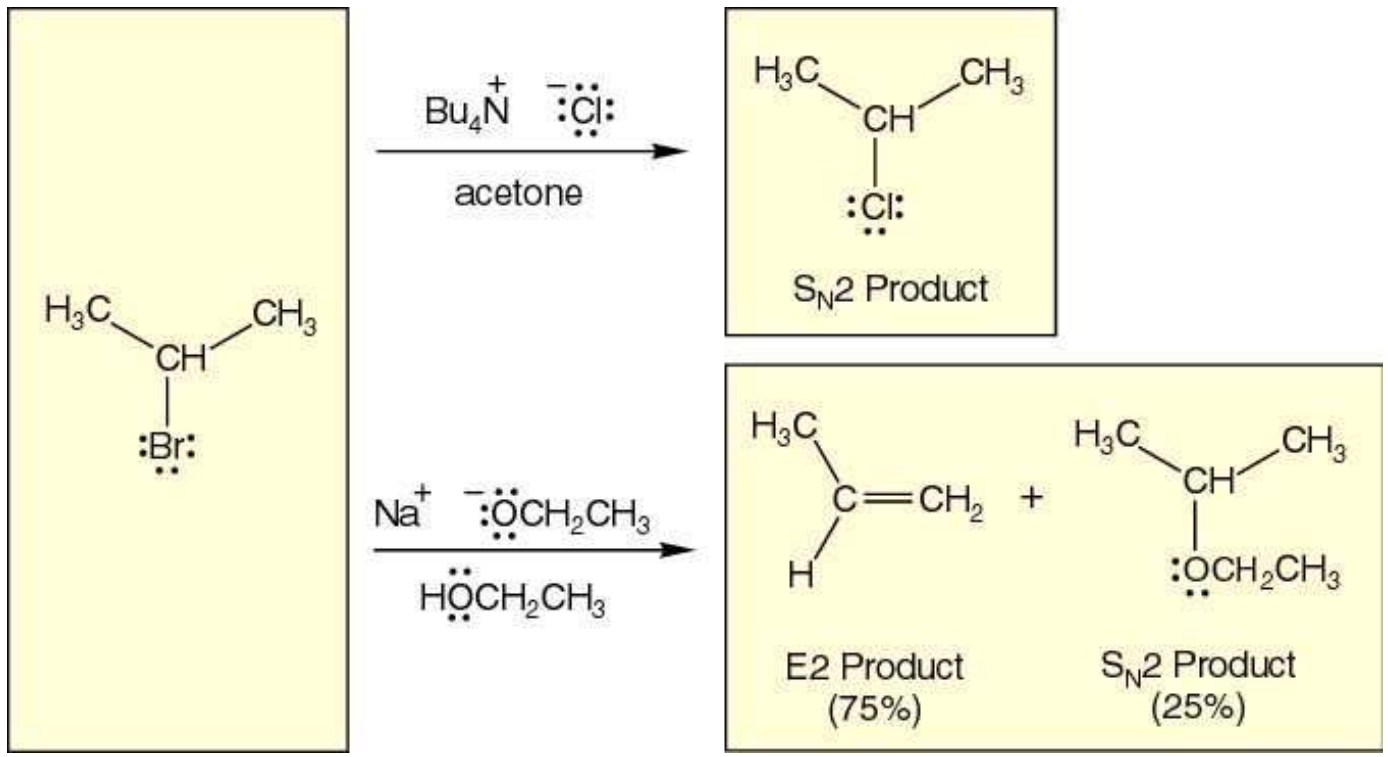
E2 *vs* S_N2



- There is a strong similarity between the E2 and S_N2 reactions: strong nucleophiles favor substitution, while strong bases favor elimination

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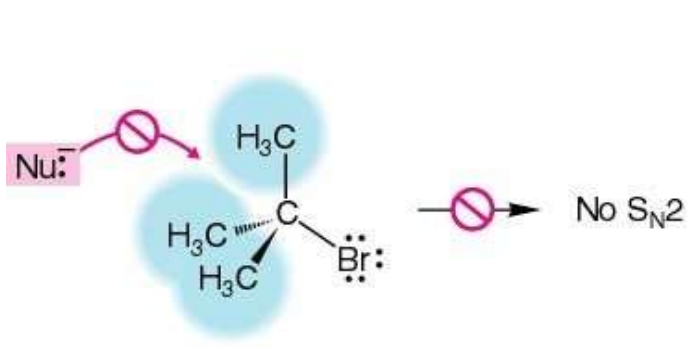
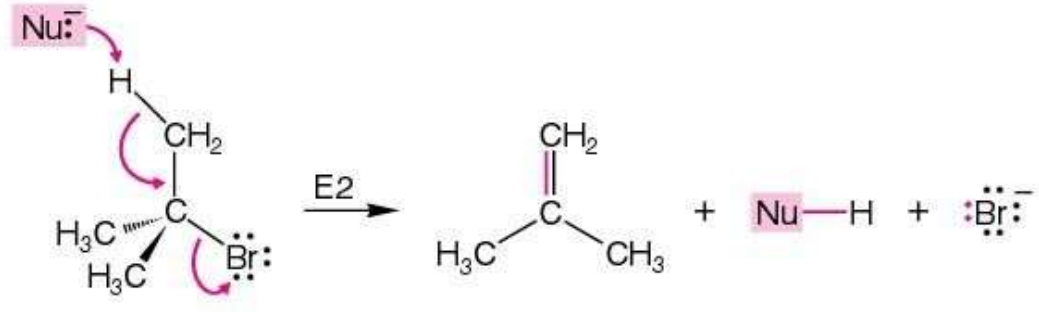
Steric bulk favors elimination

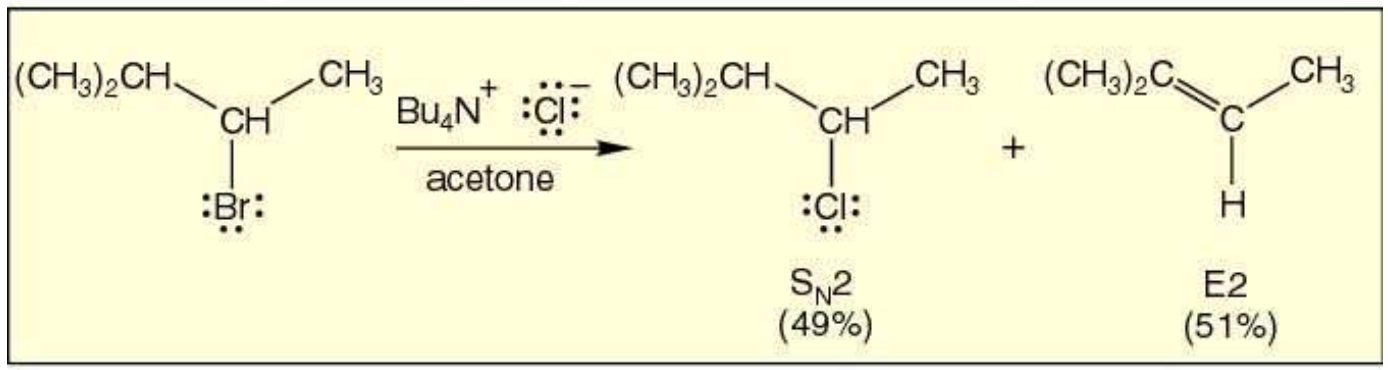




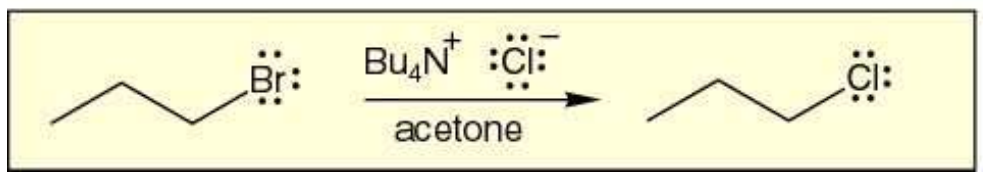
- We already saw that S_N2 substitution on a tertiary carbon is not possible, therefore E2 elimination will prevail (beside E1 elimination)

Other examples

For this secondary substrate, the S_N2 and E2 reactions are competitive

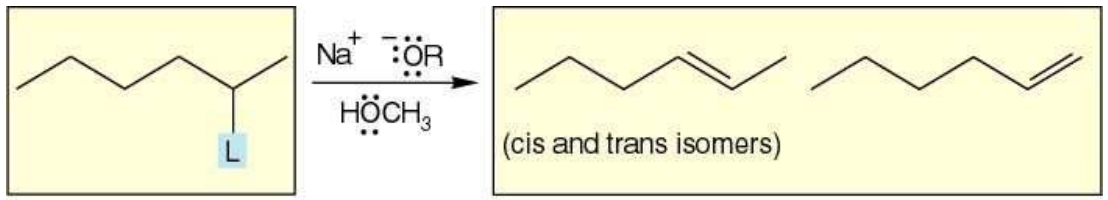


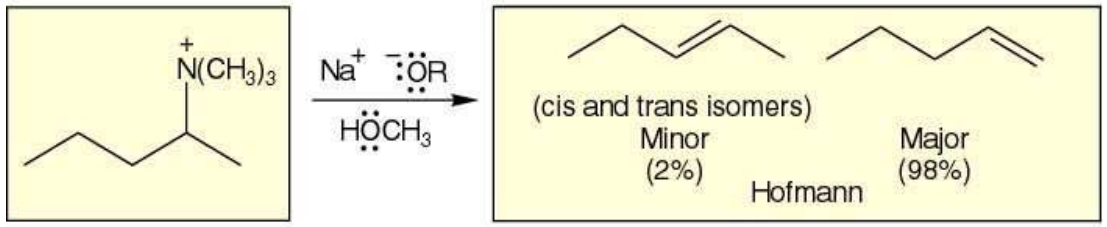
In this primary example, the S_N2 reaction is the only process



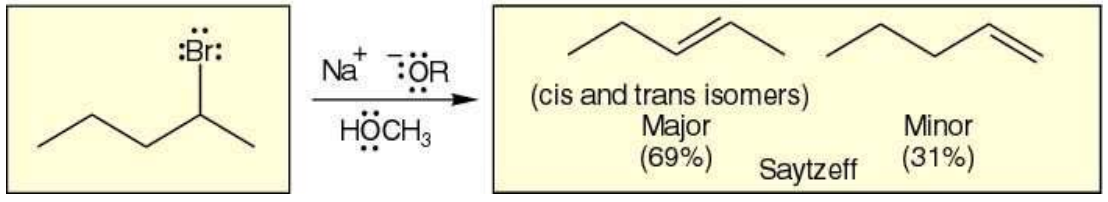
- Note that at a primary carbon atom, only S_N2 and no S_N1 substitution is possible

Effect of the leaving group





L	2-Alkene (%)	1-Alkene (%)
I	81	19 Saytzeff preferred
Br	72	28 Saytzeff preferred
Cl	67	33 Saytzeff preferred
F	30	70 Hofmann preferred



- Especially quarternary ammonium leaving groups favor the Hofmann product

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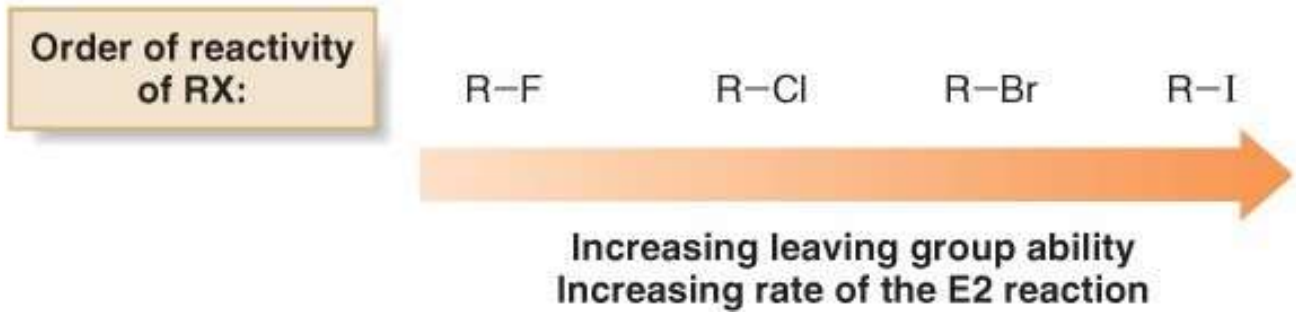
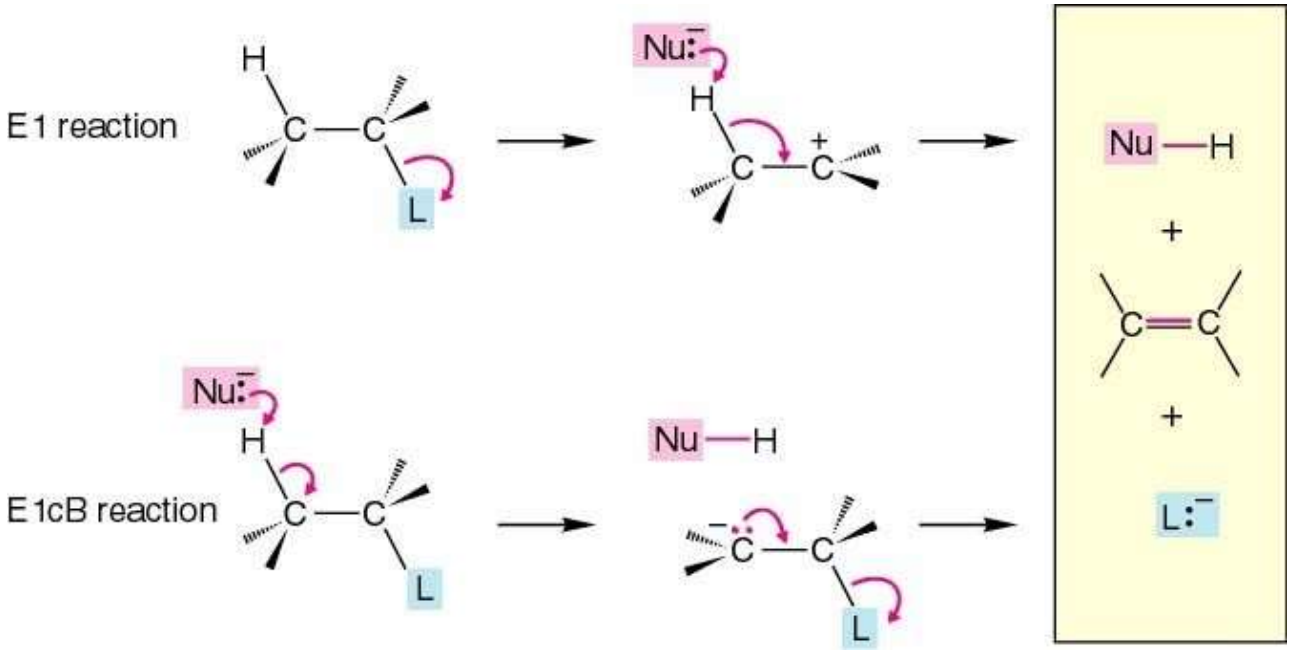
Effect of the LG on E2 Reactivity



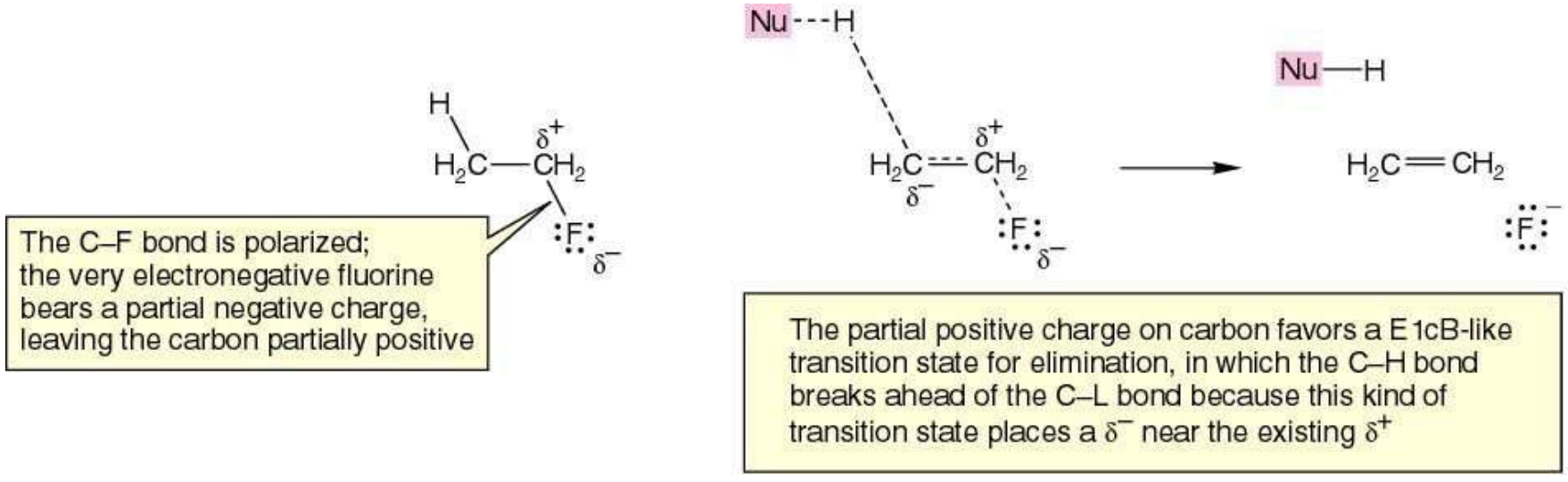
- Polar aprotic solvents increase the rate of E2 reactions.

The E1cB elimination



- The E1cB reaction resembles the S_N2 reaction, with the difference that there is an anion formed prior to the loss of the leaving group

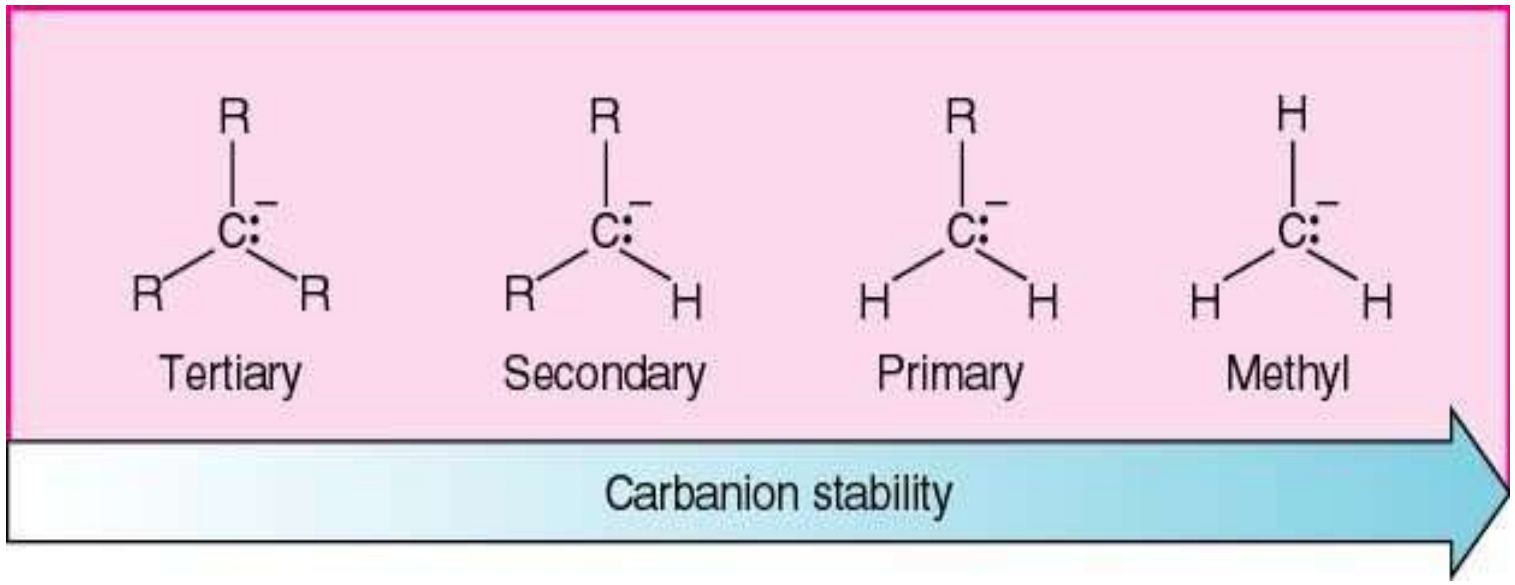
Example of an E1cB reaction



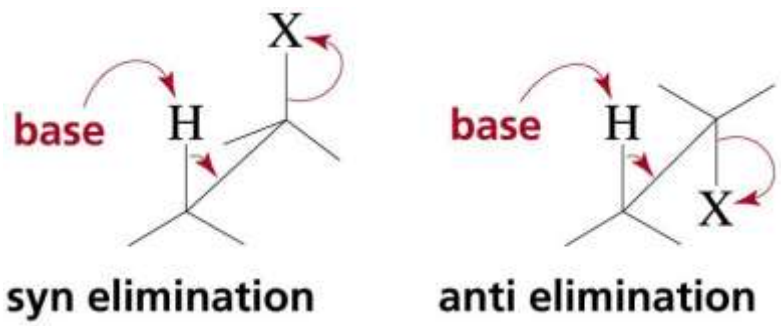
- This reaction is possible if there is a group present that can stabilize the negative charge

Stability of anions

- The more substituted the carbanion, the less stable it is; this is a result of the inductively electron donating alkyl groups



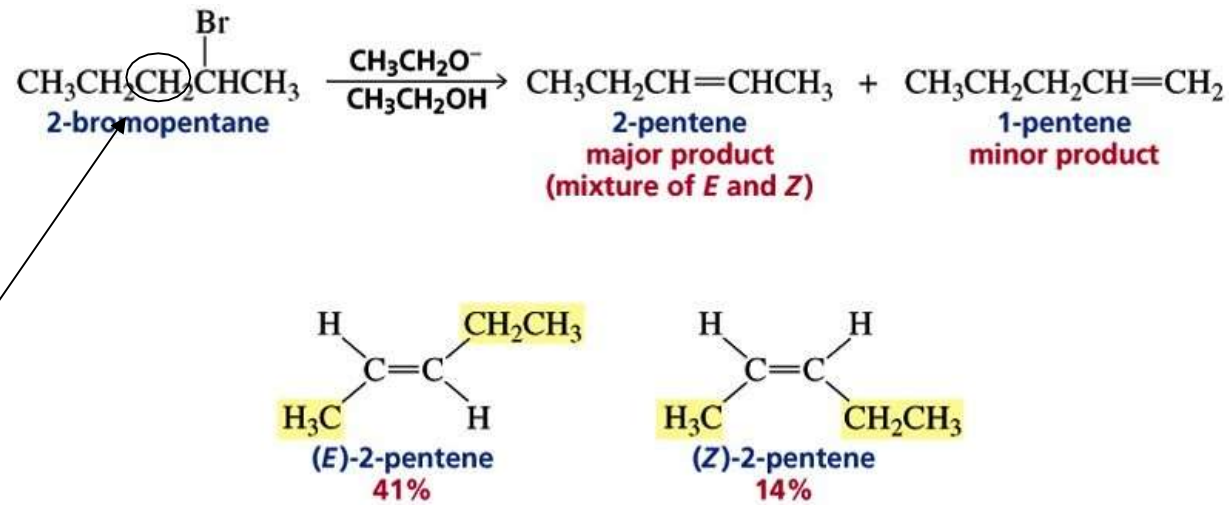
Stereochemistry of Elimination Reactions



syn elimination anti elimination

- If the elimination reaction removes two substituents from the same side of the molecule it is **syn elimination**
- If the elimination reaction removes two substituents from opposite sides of the molecule it is **anti elimination**

The E2 Reaction: Stereochemistry

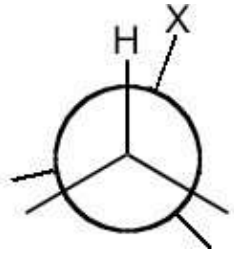


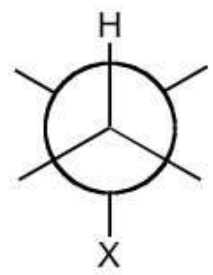
- The E2 Reaction is **<u>stereoselective</u>**, but **<u>not stereospecific</u>** if 2 β H's are available on carbon bearing eliminated H
- The H leading to more stable E isomer is selected to be extracted from β carbon regardless of streochem at α carbon

The E2 Reaction: Stereochemistry

- In an E2 reaction, the bonds to the eliminated substituents must be in the same plane
- In this course E2 eliminations will all go via **anti-periplanar** conformation
- Product analysis possible by drawing Newman projections if only 1 β H is available

syn-periplanar

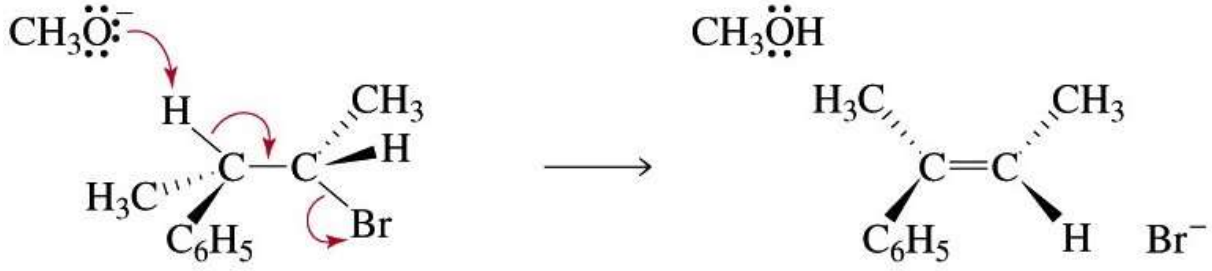




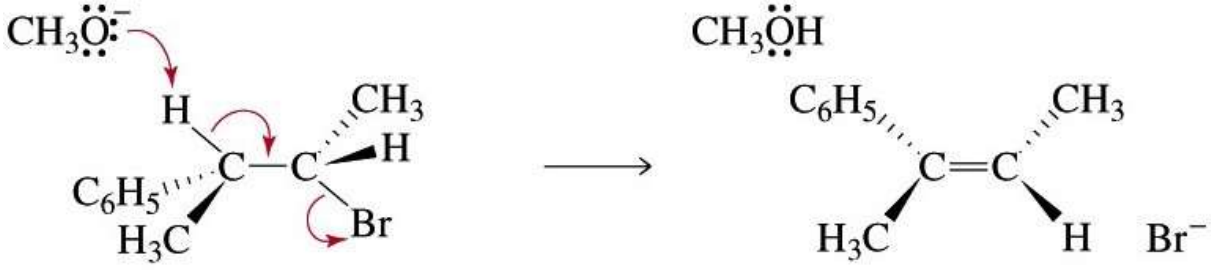
anti-periplanar

The E2 Reaction: Stereochemistry

When only one hydrogen is on the β carbon predominantly anti elimination leads to high stereospecificity



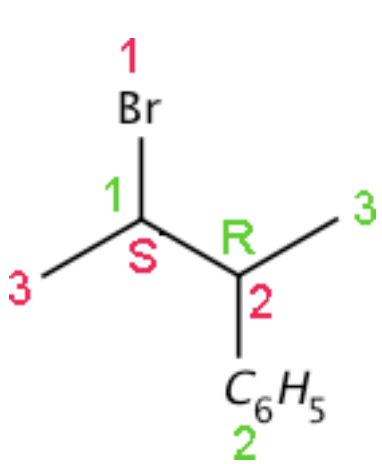
(2*S*,3*S*)-2-bromo-3-phenylbutane **(*E*)-2-phenyl-2-butene**

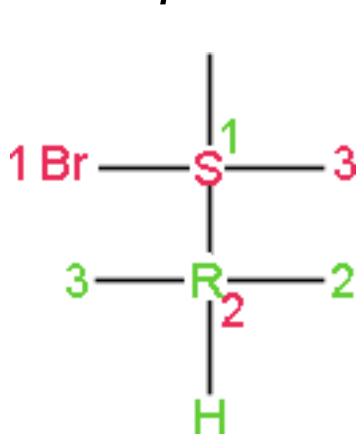


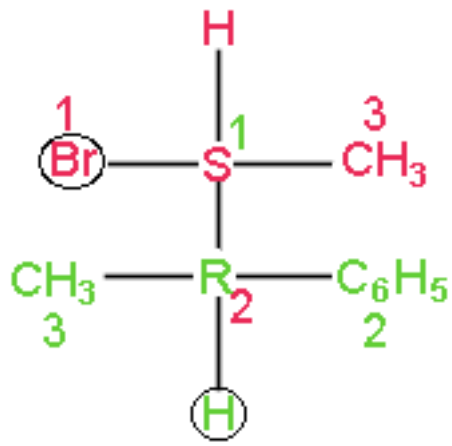
(2*S*,3*R*)-2-bromo-3-phenylbutane **(*Z*)-2-phenyl-2-butene**

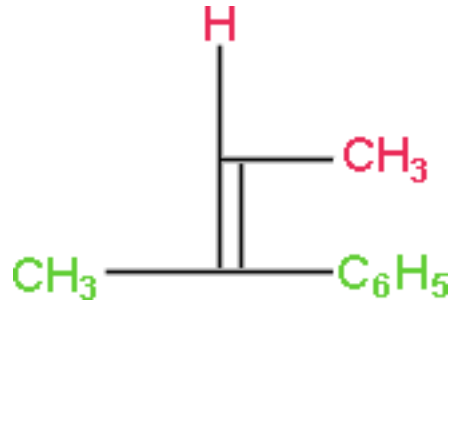
The E2 Reaction: Stereochemistry

- Retro-pro-Fischer analysis can be done to track stereochemistry of reaction
- For anti elimination put β H on vertical and leaving group on horizontal pos'n
- Erase LG and β H, draw double bond







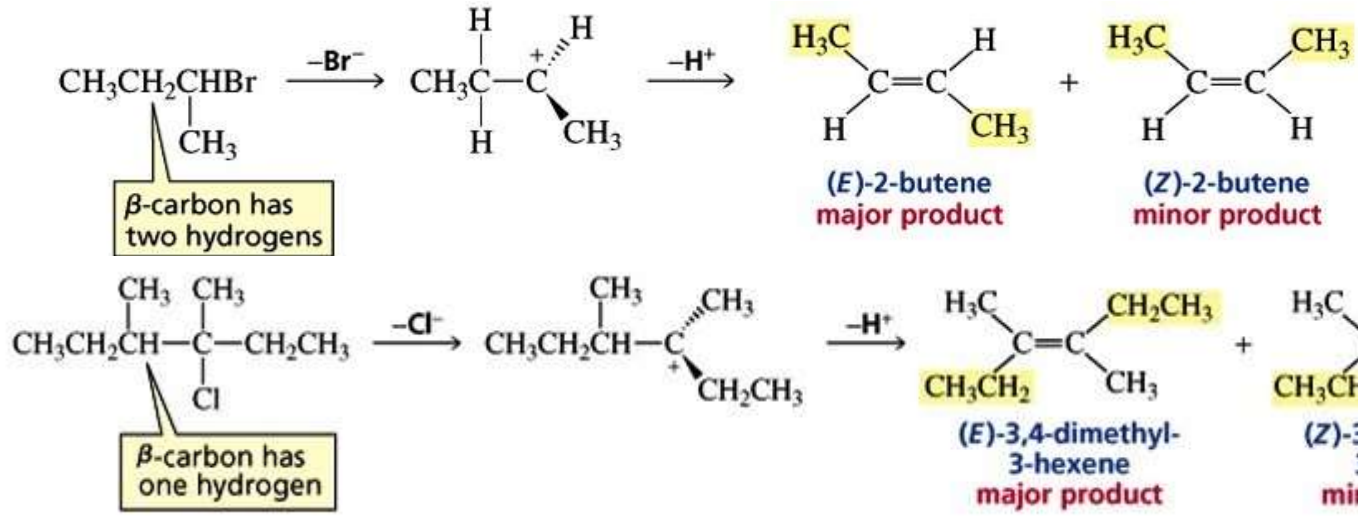


(2S,3R)-2-bromo-3-phenylbutane

Z isomer

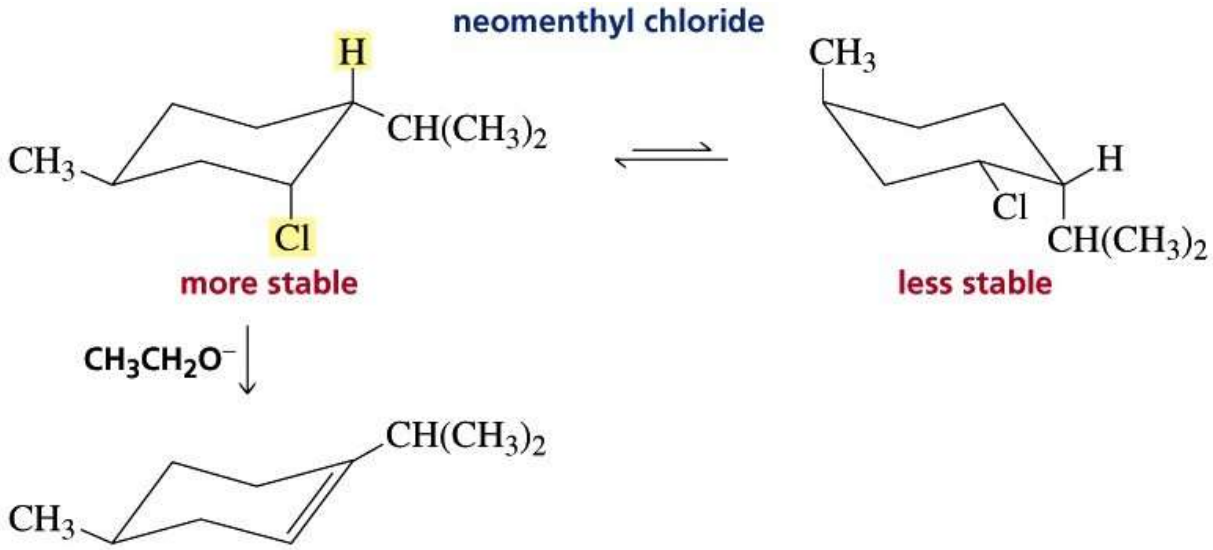
The E1 Reaction: Stereochemistry

- With C+ both syn and anti elimination can occur, so E1 reaction forms both *E* and *Z* products regardless of whether β-carbon is bonded to one or two H's
- Product stability leads to stereoselectivity but not stereospecificity



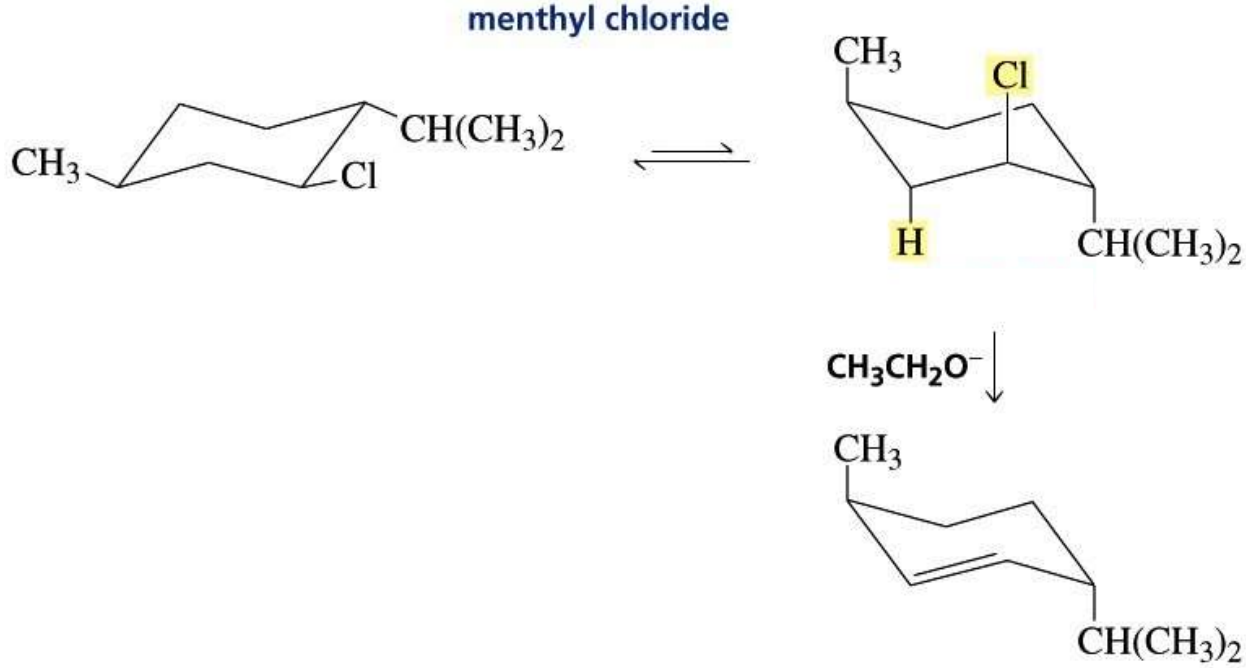
E2 Reactions of Cyclic Compounds

E2 reaction of cyclic compounds follows the same stereochemical rules as from open-chain compounds



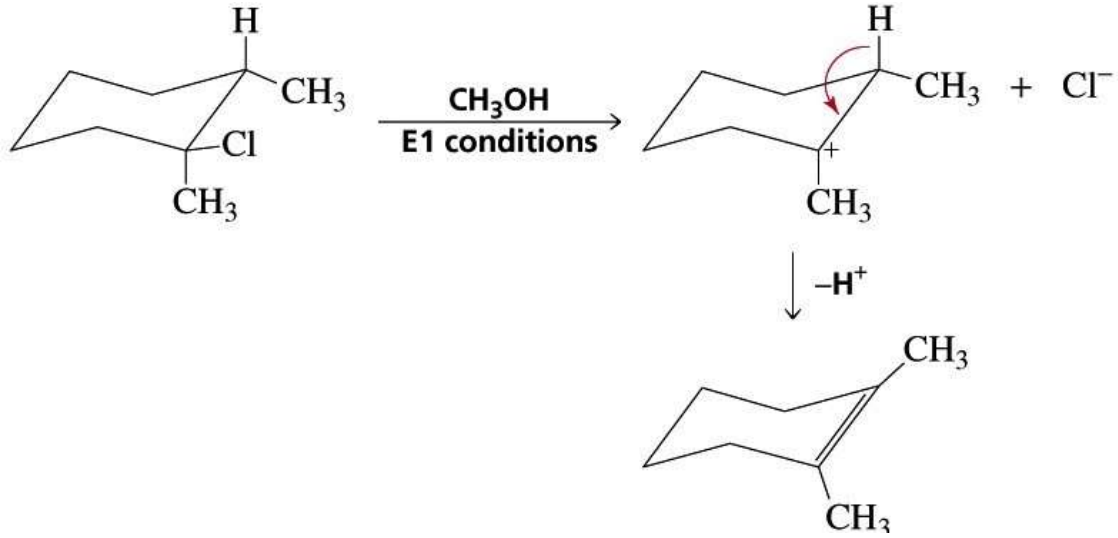
E2 Reactions of Cyclic Compounds

The E2 reaction of menthyl chloride violates Zaitsev's rule



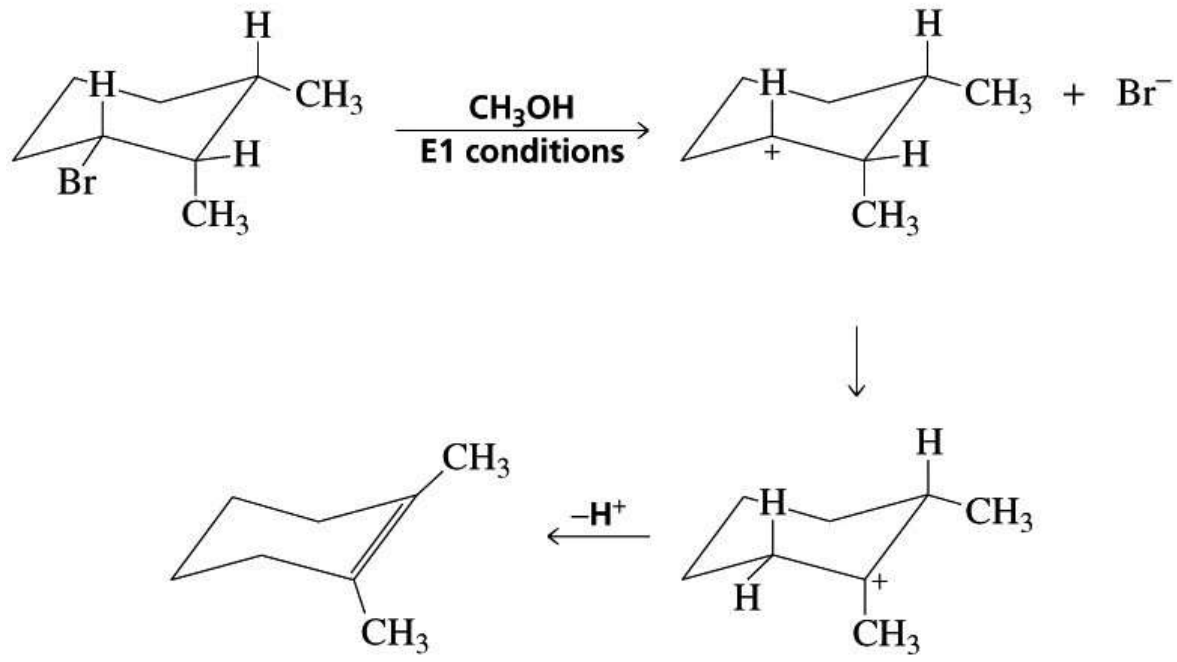
E1 Reactions of Cyclic Compounds

When a cyclohexyl chloride undergoes an E1 reaction, there is no requirement that the two groups to be eliminated be diaxial



E1 Reactions of Cyclic Compounds

Carbocation rearrangements must be considered for E1 reactions



Competition Between Substitution and Elimination

- Conditions that favor E2 also favor S_N2
- Conditions that favor E1 also favor S_N1
- No need to worry about S_N2/E1 or S_N1/E2 combinations
- First decide whether the reaction would favor S_N2/E2 or S_N1/E1 reactions
  - —If the halide is primary, only S_N2/E2 need be considered
  - —If the halide is secondary or tertiary, S_N2/E2 or S_N1/E1 depends on reaction condition

Competition Between Substitution and Elimination

- S_N2/E2 reactions are favored by high conc of a good nuc/strong base and polar aprotic solvent.
- S_N1/E1 reactions are favored by poor nuc/ weak base and polar protic solvents

Competition Between S_N2 and E2

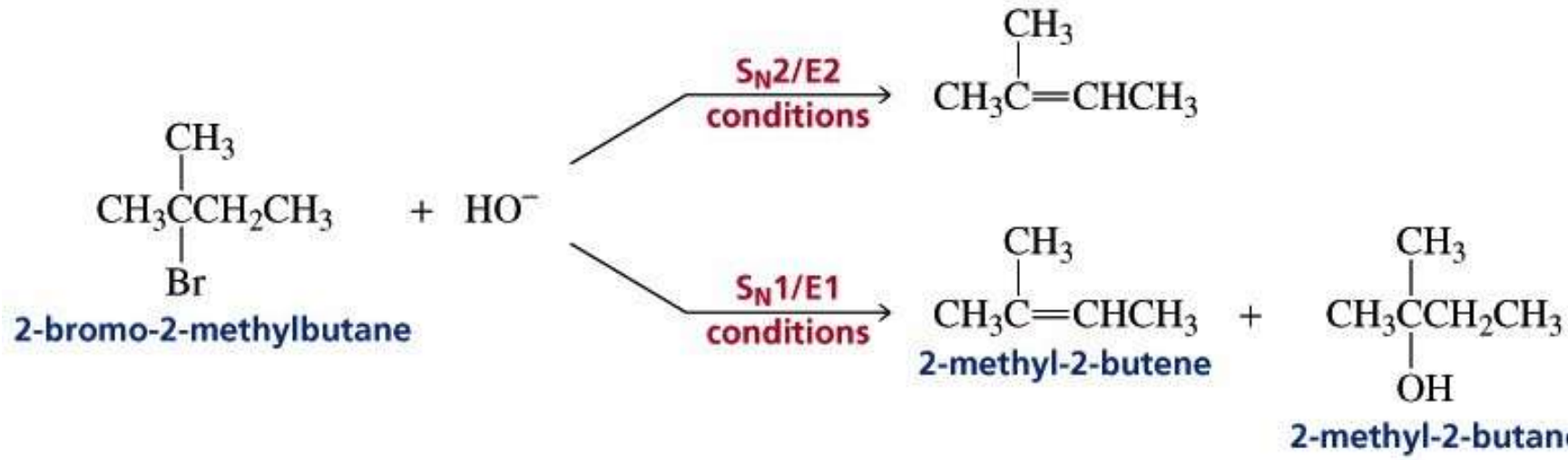
- Primary halides generally undergo substitution, although if the halide or the base is hindered, elimination is possible, favorable if heated
- Secondary halides are more difficult to predict
  - The stronger and more hindered the base, the more elimination product is produced
  - The higher the temperature, the more elimination product is produced
- Tertiary halides never undergo S_N2 reaction - elimination is the only possibility

Competition Between S_N1 and E1

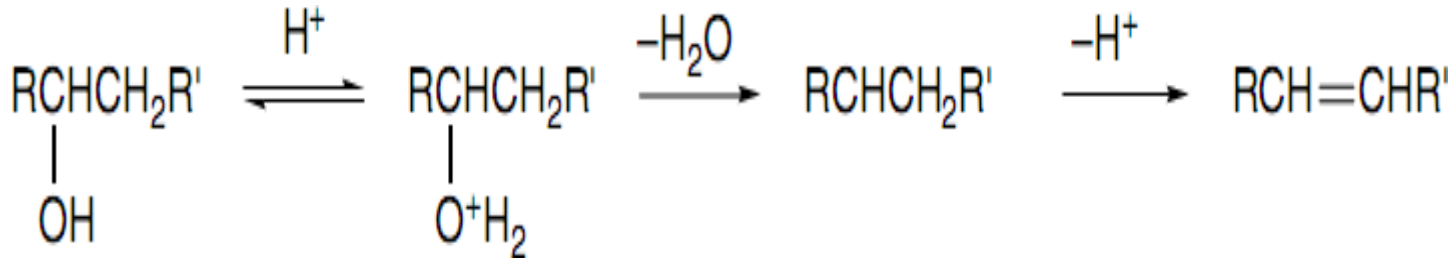
- Because S_N1 and E1 reactions both proceed through a carbocation, they have the same rate-determining step
- Primary halides do not undergo either S_N1 or E1 reactions
- For secondary and tertiary halides, raising the temperature increases the elimination product

Substitution and Elimination Reactions in Synthesis

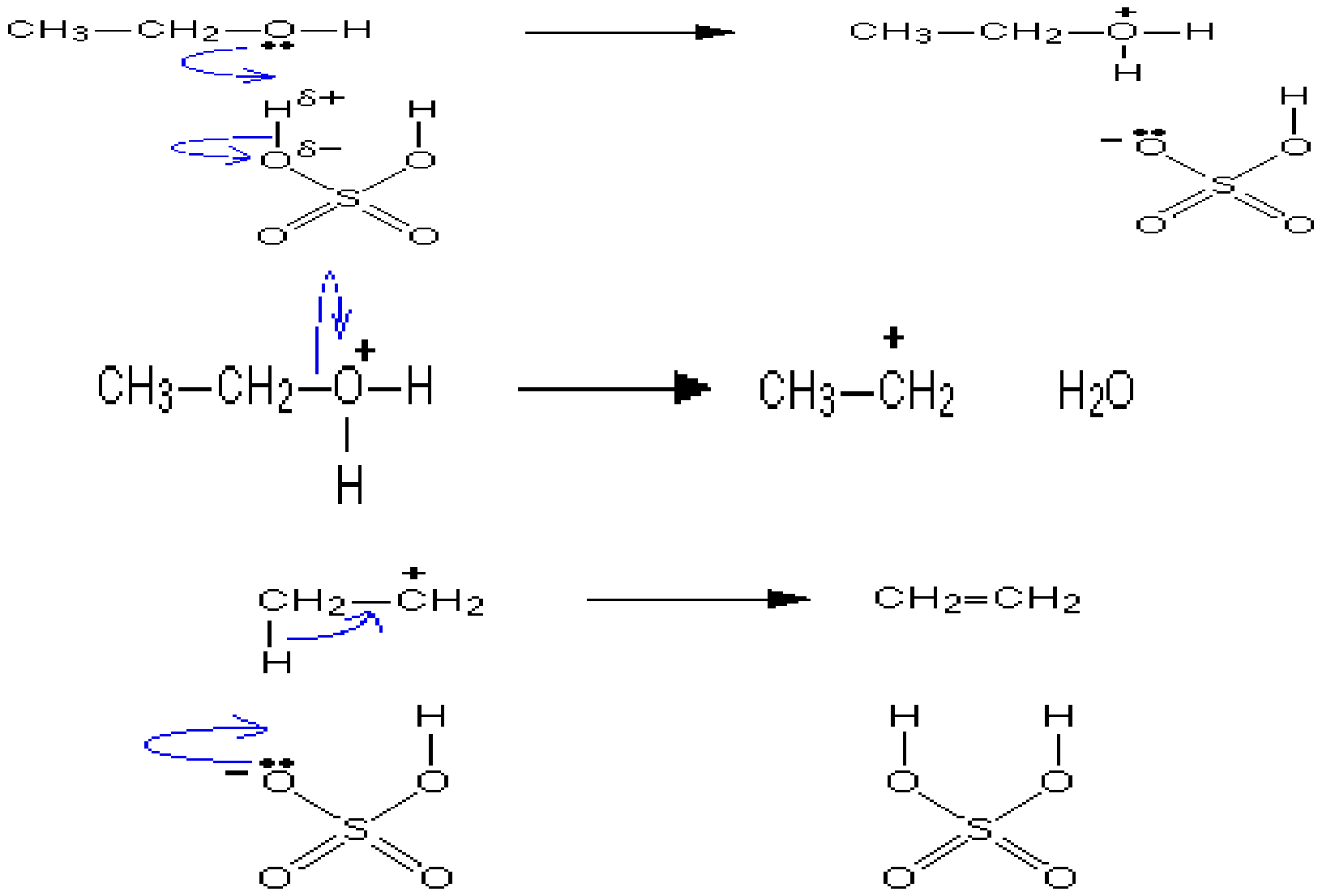
S_N1/E1 conditions are rarely useful synthetically



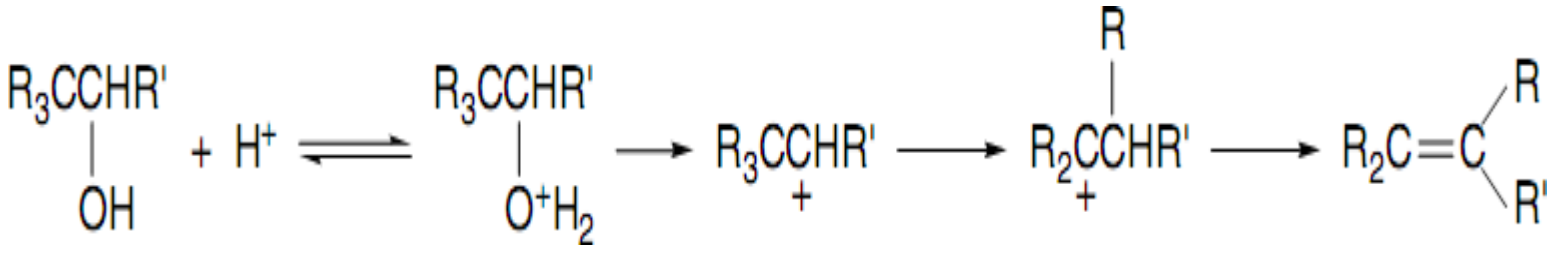
Dehydration of alcohol



Under the acidic reagent and involves an E1 mechanism

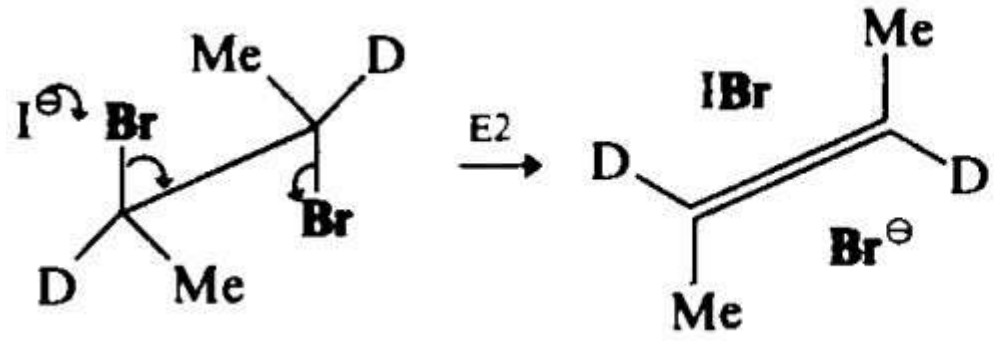


Dehydration of alcohol

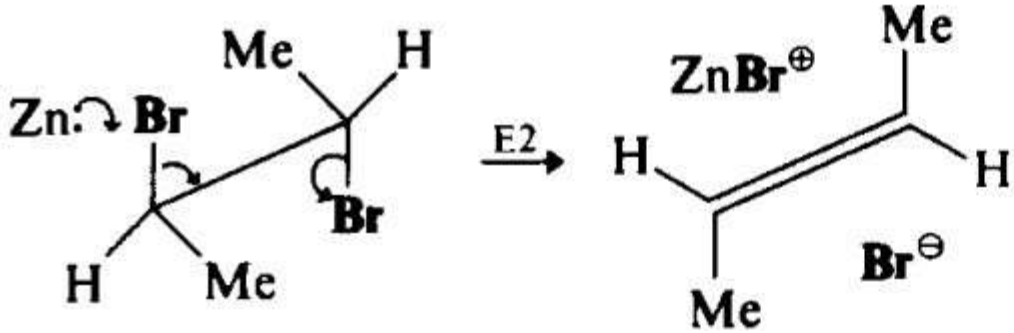


Rearrangement of products

Other 1,2-Elimination



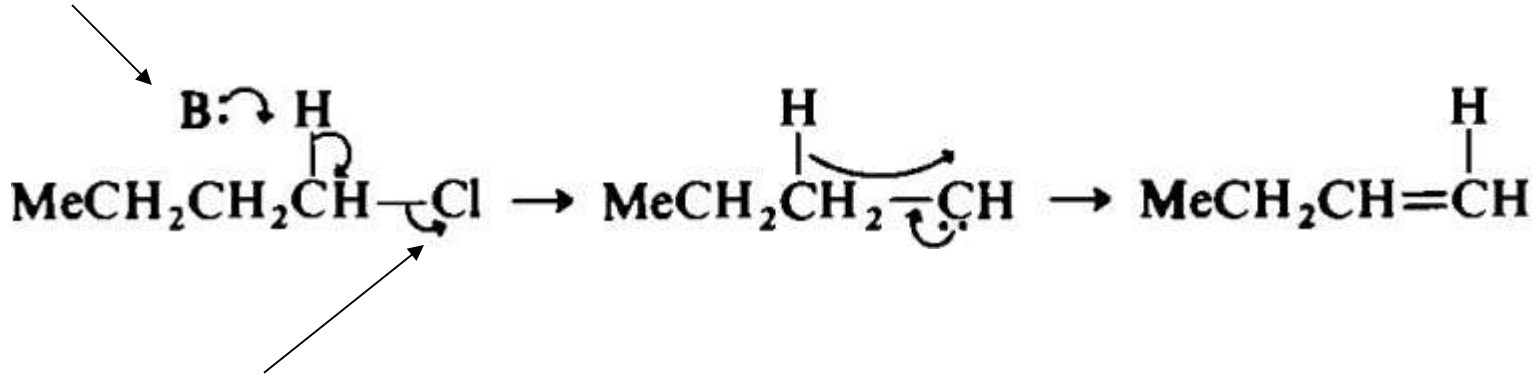
$$IBr + I^{\ominus} \rightarrow I_2 + Br^{\ominus}$$



$$ZnBr^{\oplus} + Br^{\ominus} \rightarrow ZnBr_2$$

1,1-(α)-Elimination

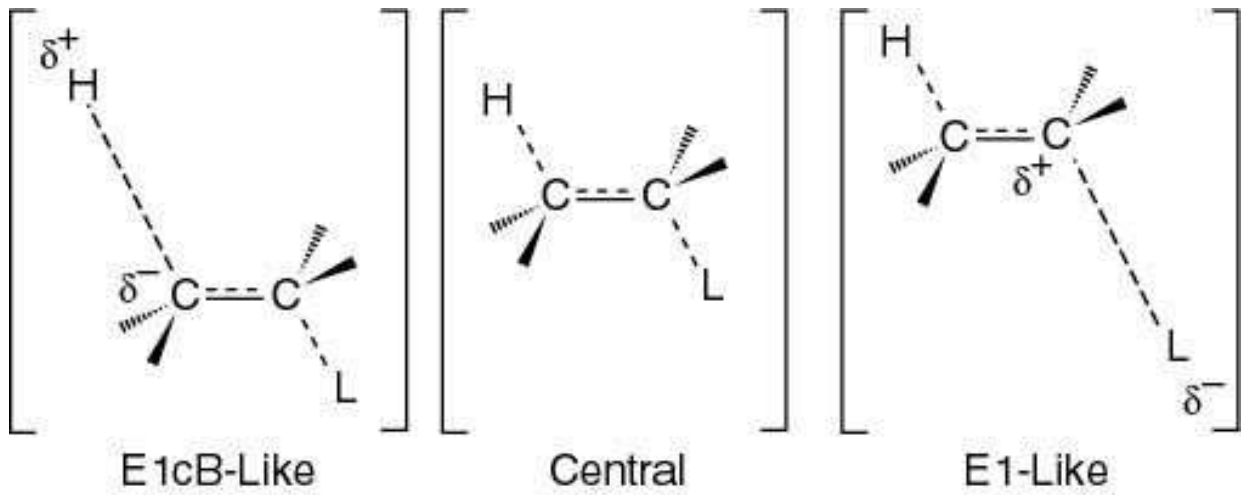
A very strong base



Powerfully electron-withdrawing group

Absence of β-H atom

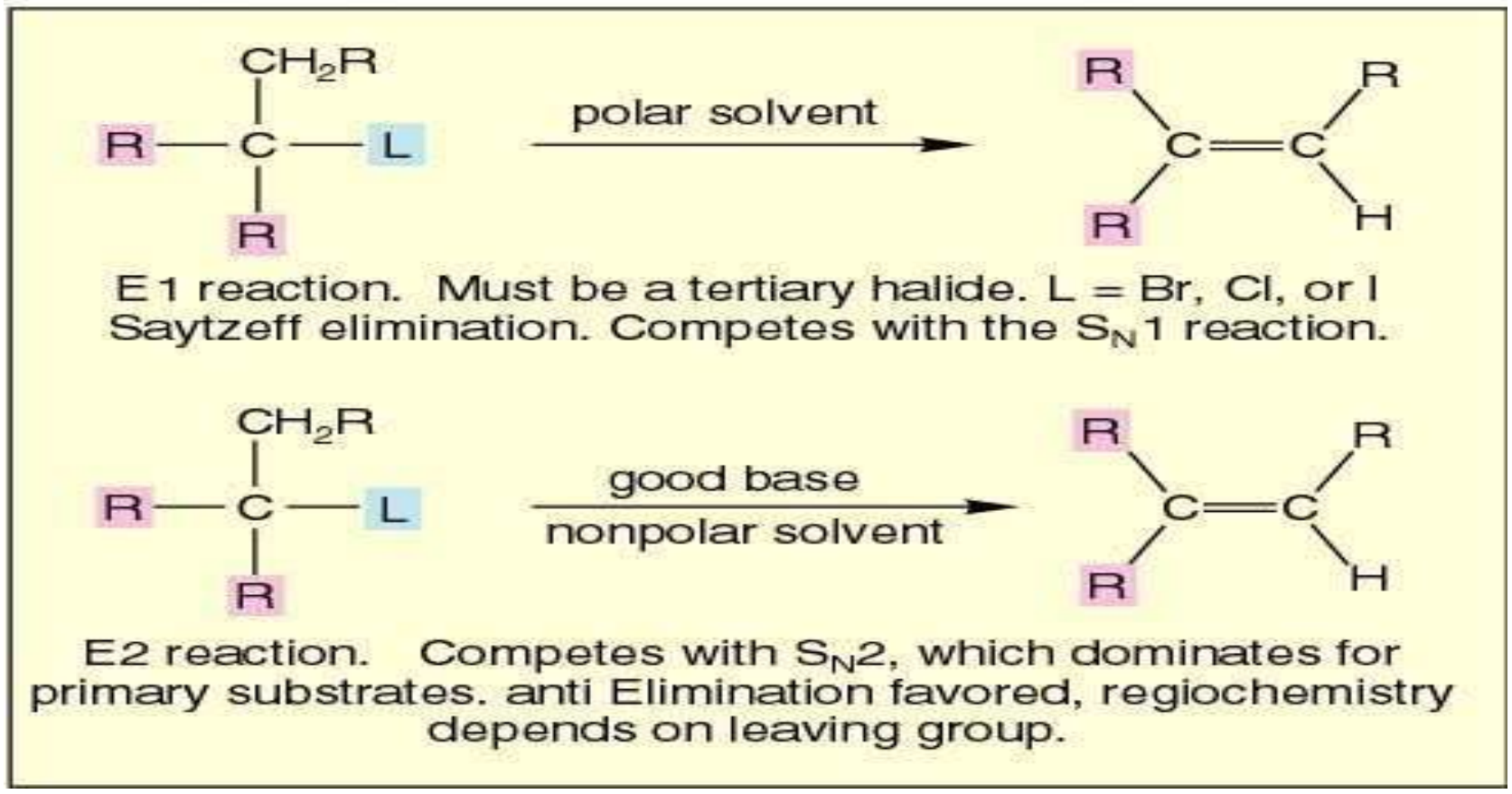
Summary



- E1cB: the proton is removed first, an anion is formed
- E_1: the leaving group departs first, a cation is formed
- E_2: all processes occur at the same time

Summary

1. Alkenes



Highlights of Elimination Reaction

- Elimination Reactions.
- E1 & E2 Reactions & Mechanisms.
- Energy Diagrams of E1 & E2.
- Transition States of E1 & E2.
- Characteristics of E1 & E2.
- The Saytzeff Rule (Z-rule).
- Elimination with Bulky Leaving Groups and Bulky Bases -- Hofmann Rule -- E2

Elimination Reactions

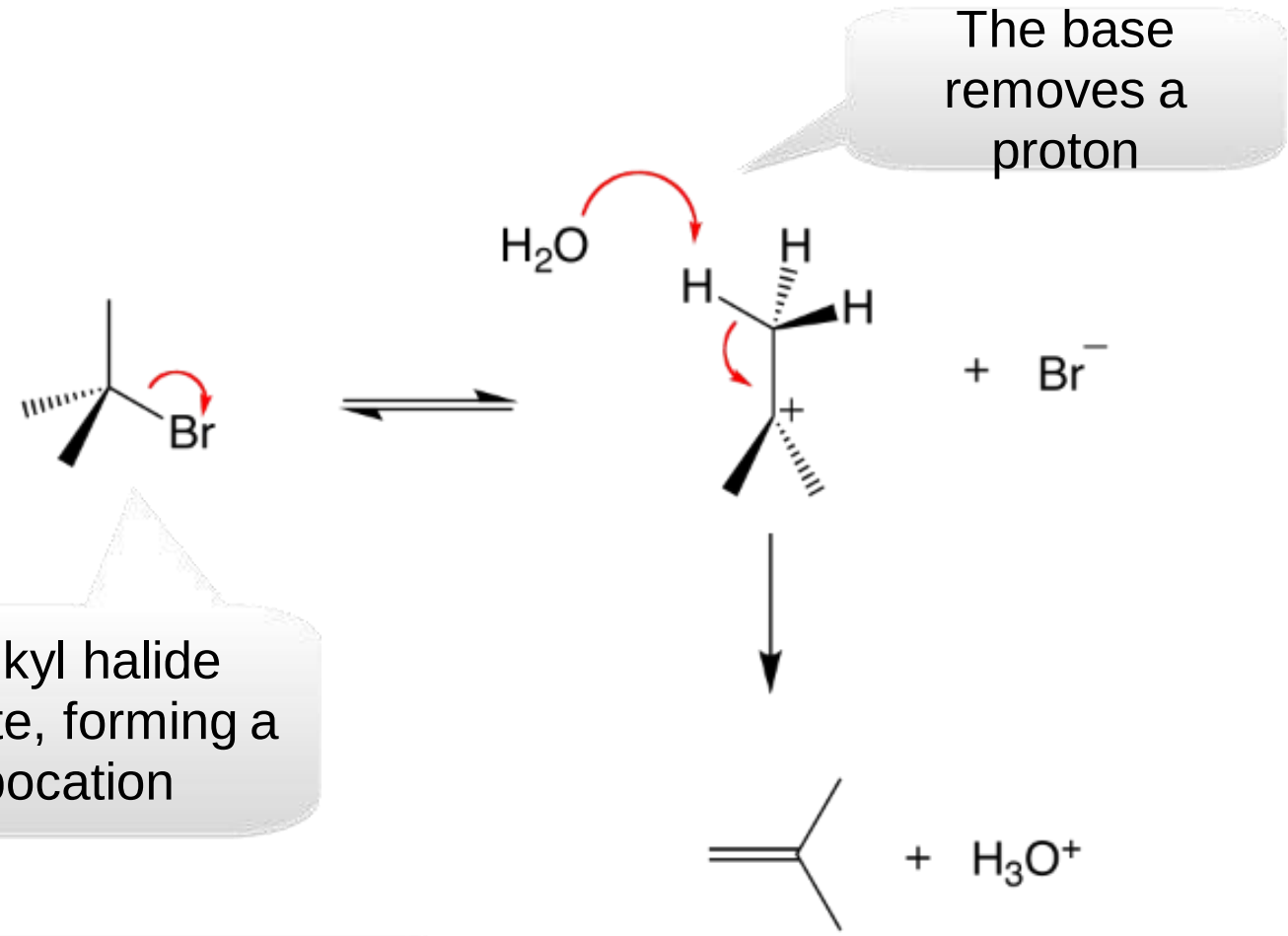
- An **elimination reaction** is a type of organic reaction in which two substituents are removed from a molecule in either a one or two-step mechanism.
- Either the unsaturation of the molecule increases (as in most organic elimination reactions) or the valence of an atom in the molecule decreases by two, a process known as reductive elimination.
- An important class of elimination reactions are those involving alkyl halides, or alkanes in general, with good leaving groups, reacting with a Lewis base to form an alkene in the reverse of an addition reaction. When the substrate is asymmetric, regioselectivity is determined by Saytzeff rule.

The one and two-step mechanisms are named and known as **E2 reaction** and **E1 reaction**, respectively.

E1 Reactions

- These reactions proceed under neutral conditions where a ***polar*** solvent helps to stabilize the carbocation intermediate.
- This solvent also acts as a weak base and removes a proton in the fast step.
- These types of reactions are referred to as ***solvolysis*** reactions.

The E1 Reaction



The mechanism shows that an E1 reaction is a two-step reaction

Alkyl Halides and Elimination Reactions

Mechanisms of Elimination—E1

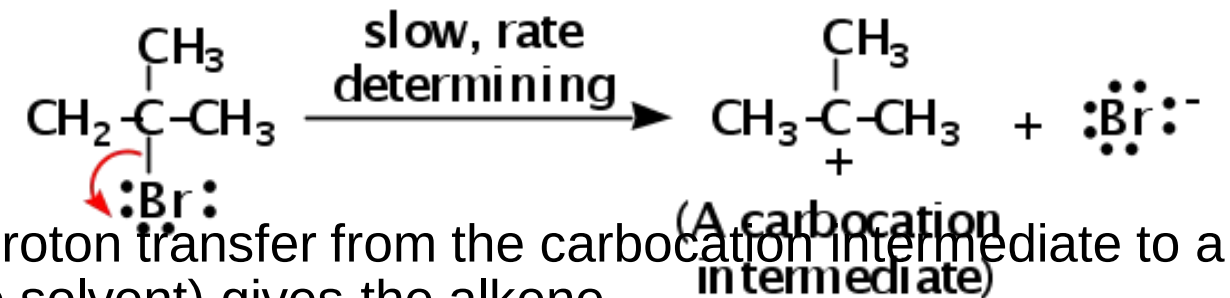
- **An E1 reaction exhibits first-order kinetics:**

rate = k[(CH3)3CI]

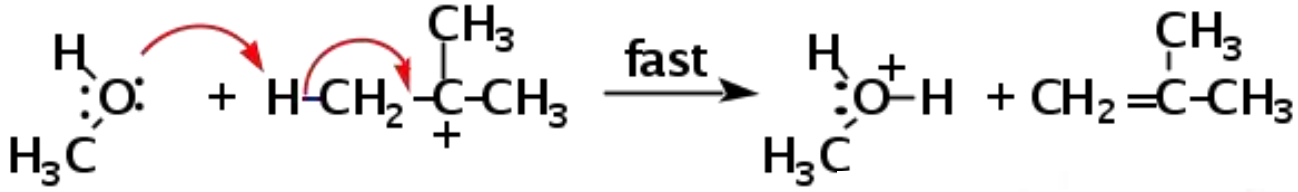
- **The E1 reaction proceed via a two-step mechanism: the bond to the leaving group breaks first before the flbondis formed. The slow step is unimolecular, involving only the alkyl halide.**
-
- **The E1 and E2 mechanisms both involve the same number of bonds broken and formed. The only difference is timing. In an E1, the leaving group comes off before the e proton is removed, and the reaction occurs in two steps. In an E2 reaction, the leaving group comes off as the . proton is removed, and the reaction occurs in one step.**

E1 Mechanism

- Step 1: ionization of C-X gives a carbocation intermediate

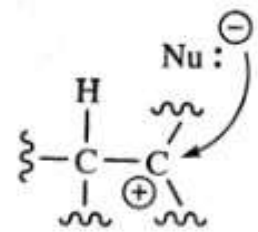


- Step 2: proton transfer from the carbocation intermediate to a base (in this case, the solvent) gives the alkene



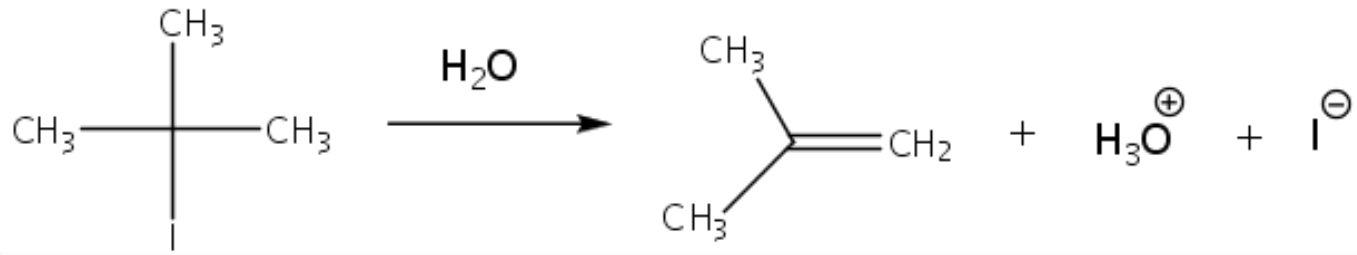
Nucleophile
-> acting as a strong base

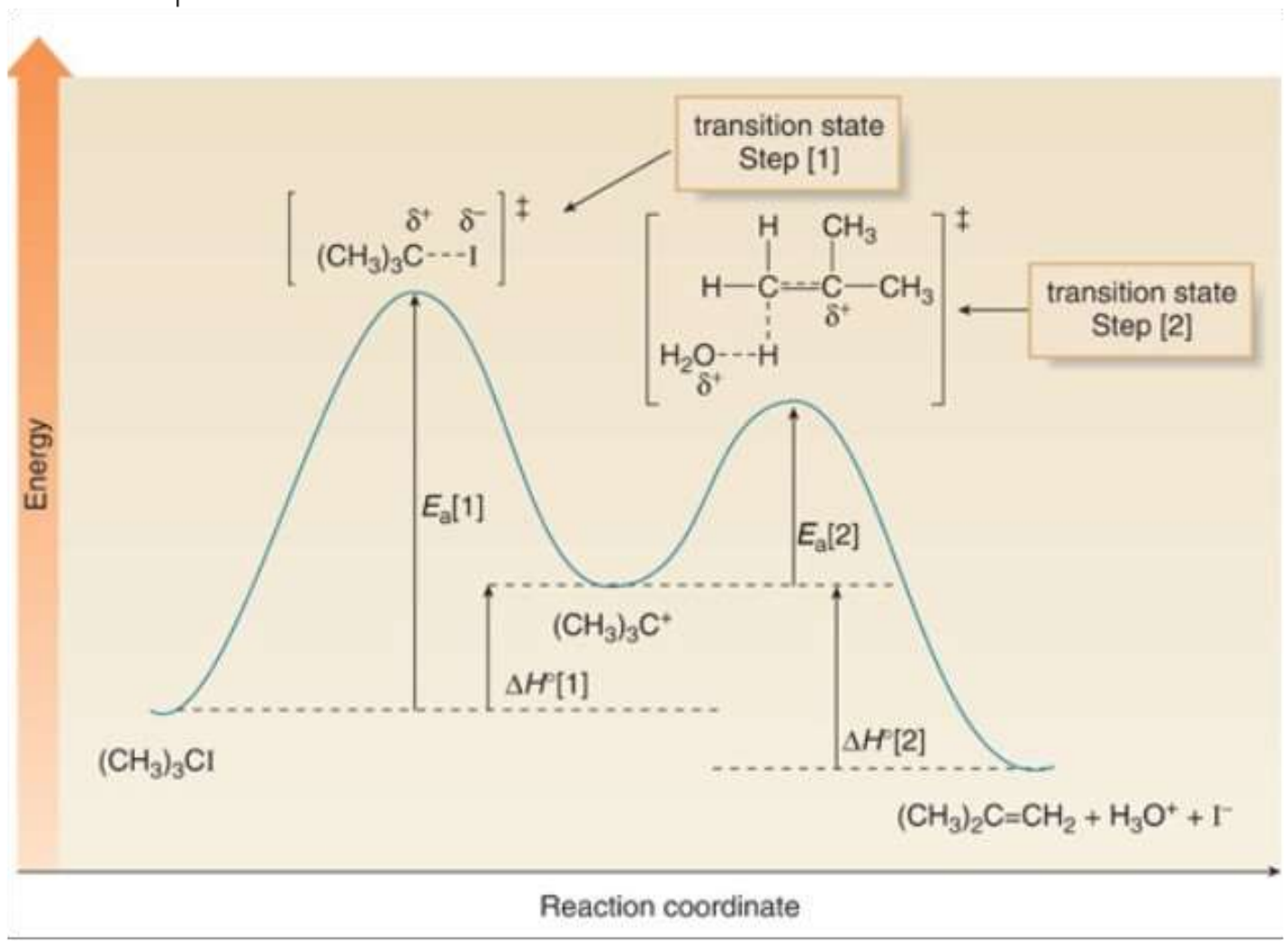
compare an S_N1 mechanism



nucleophile *(acting as a nucleophile)*

Energy Diagram for E1



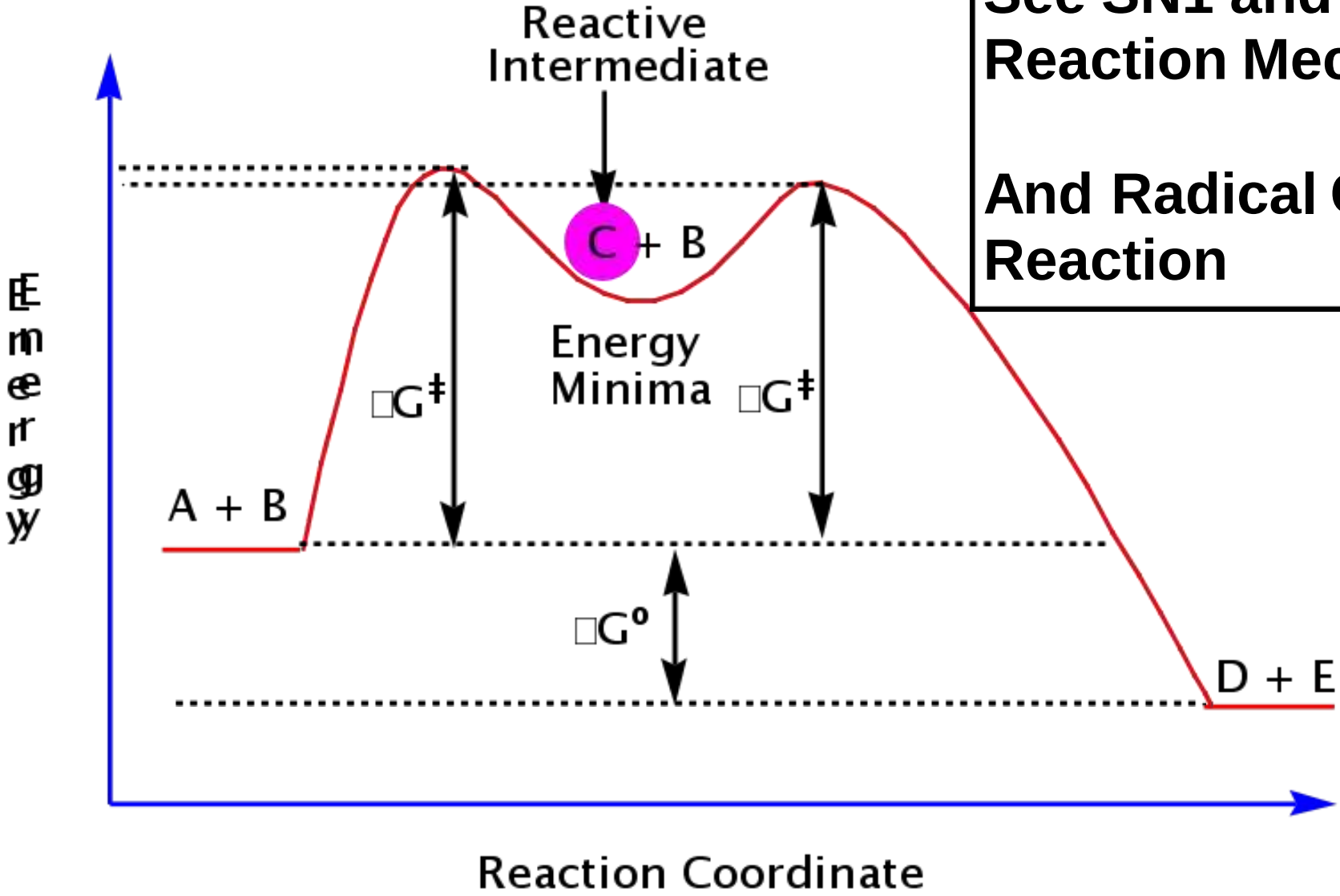


Transition States

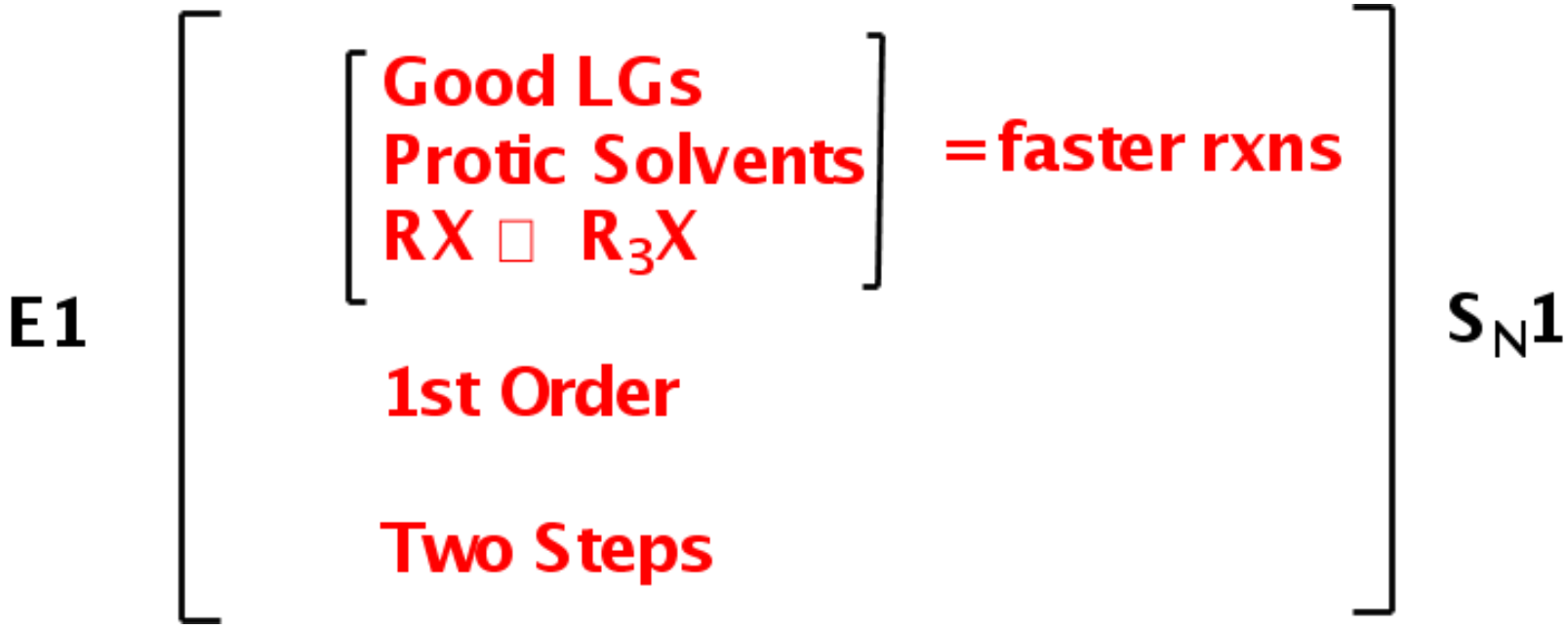
Rate = *k*[A]

See SN1 and E1 Reaction Mechanisms

And Radical Chain Reaction

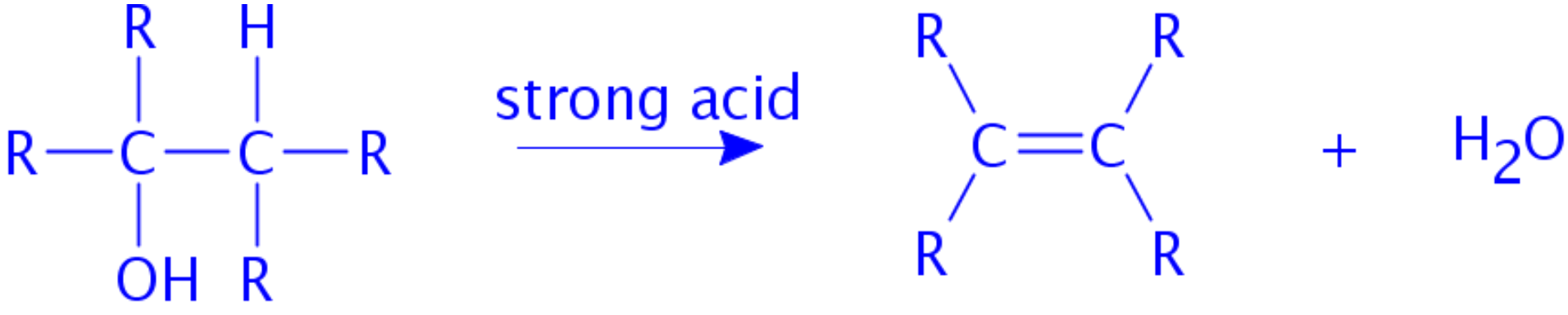


Here are four characteristics that the E1 / SN mechanisms have in common.

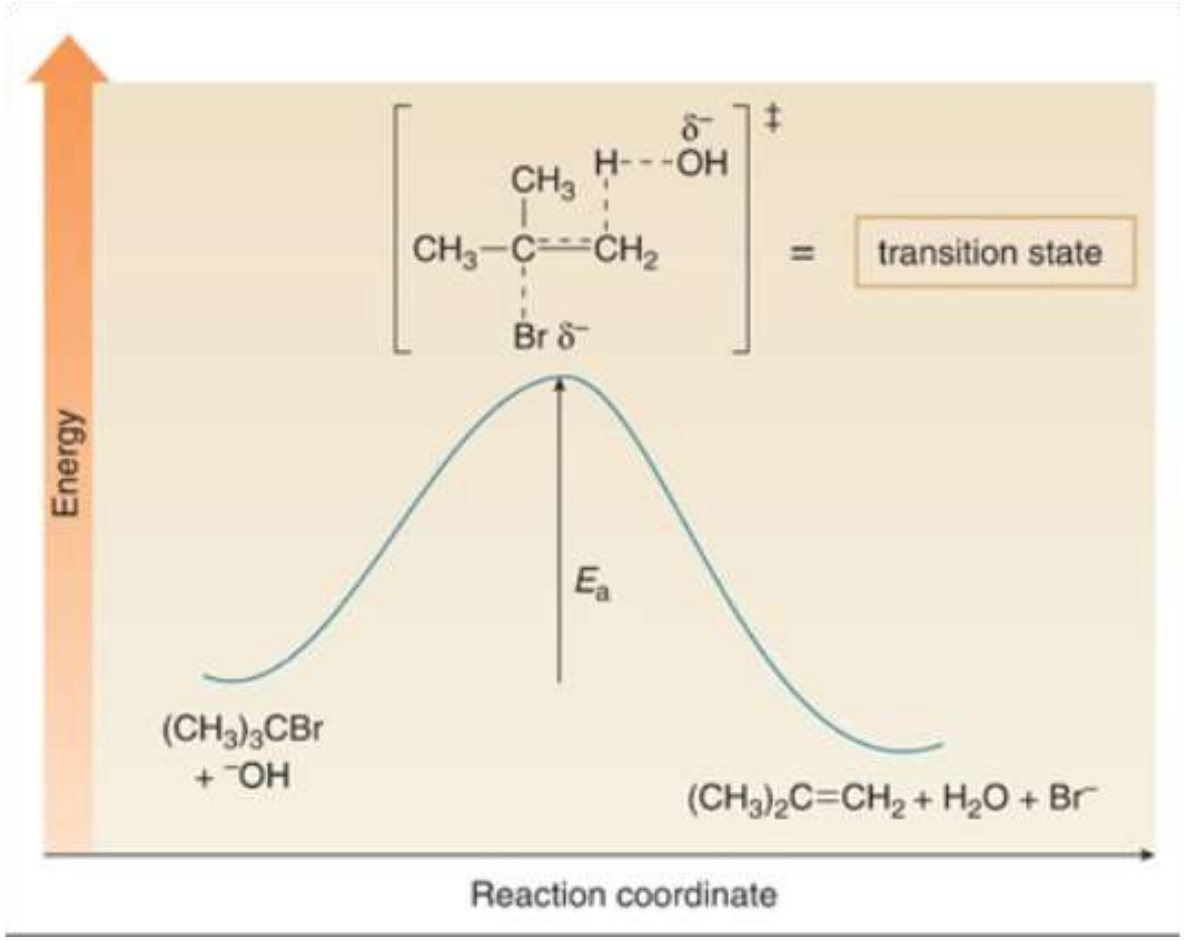


Dehydration of Alcohols

Acid assisted reactions are always E1



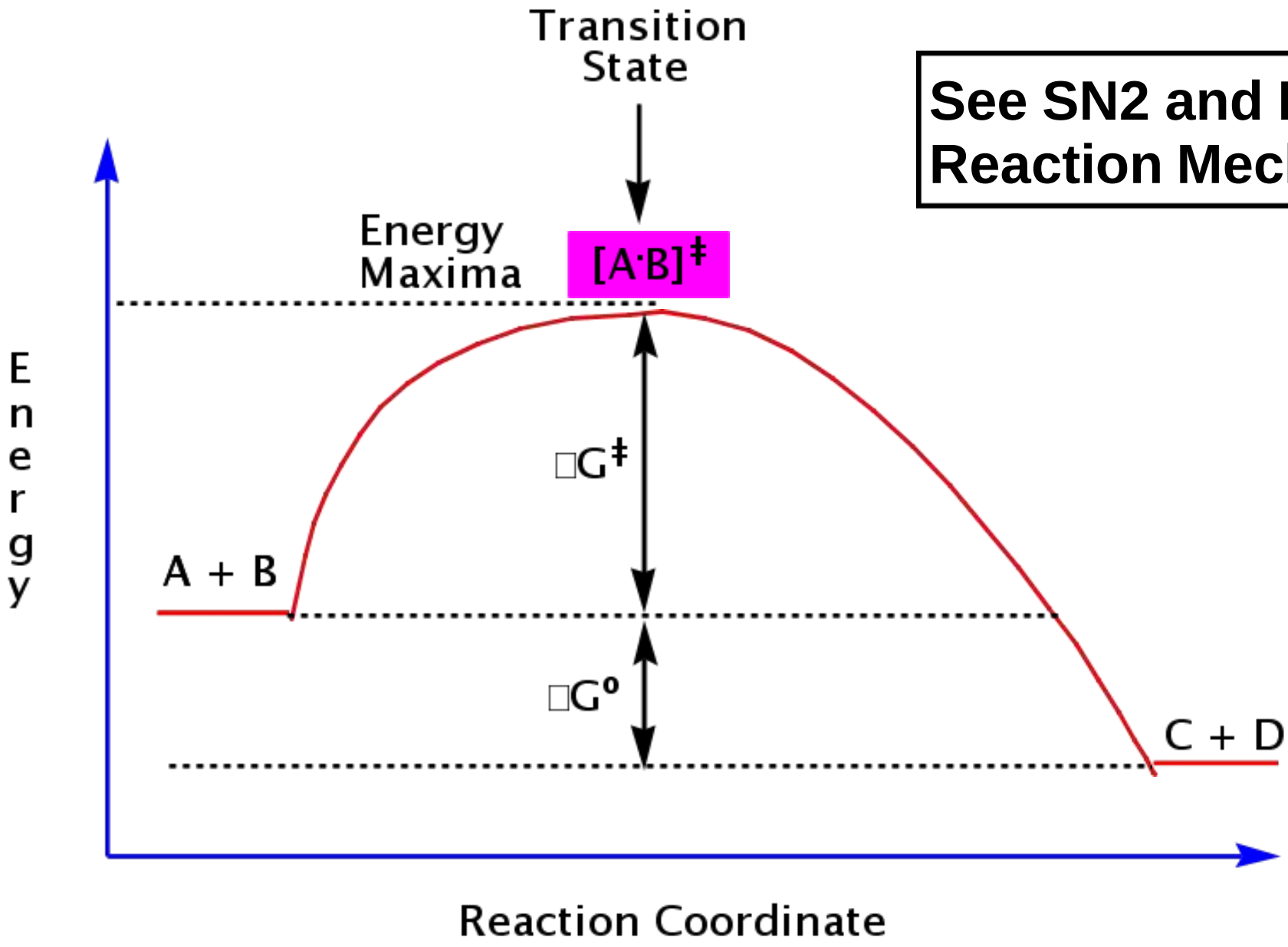
Energy Diagram for the E2 Mechanism



Transition States

Rate = *k*[A][B]

See SN2 and E2 Reaction Mechanisms



Alkyl Halides and Elimination Reactions

Mechanisms of Elimination—E2

- **The most common mechanism for dehydrohalogenation is the E2 mechanism.**
- **It exhibits second-order kinetics, and both the alkyl halide and the base appear in the rate equation i.e.**

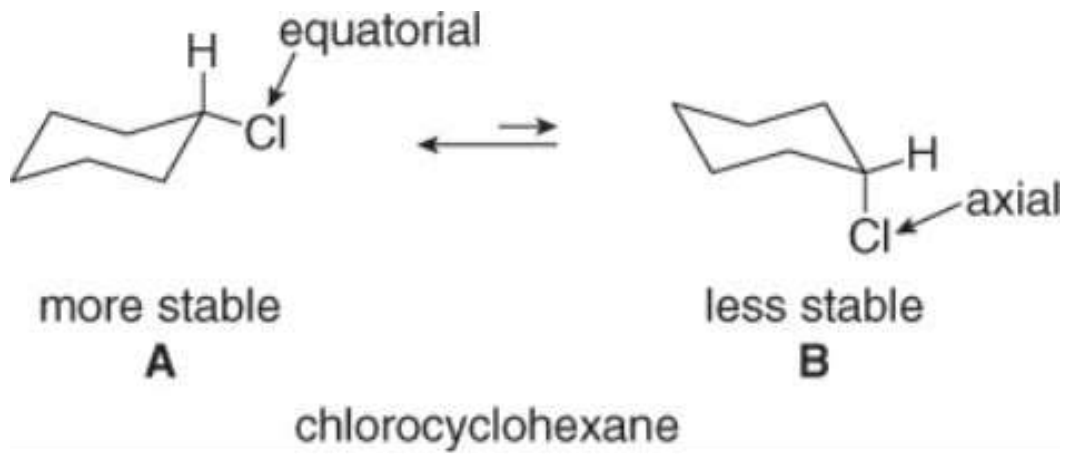
$$\text{rate} = k[(CH3)3CBr][^{-}OH]$$

- **The reaction is concerted—all bonds are broken and formed in a single step.**

Alkyl Halides and Elimination Reactions

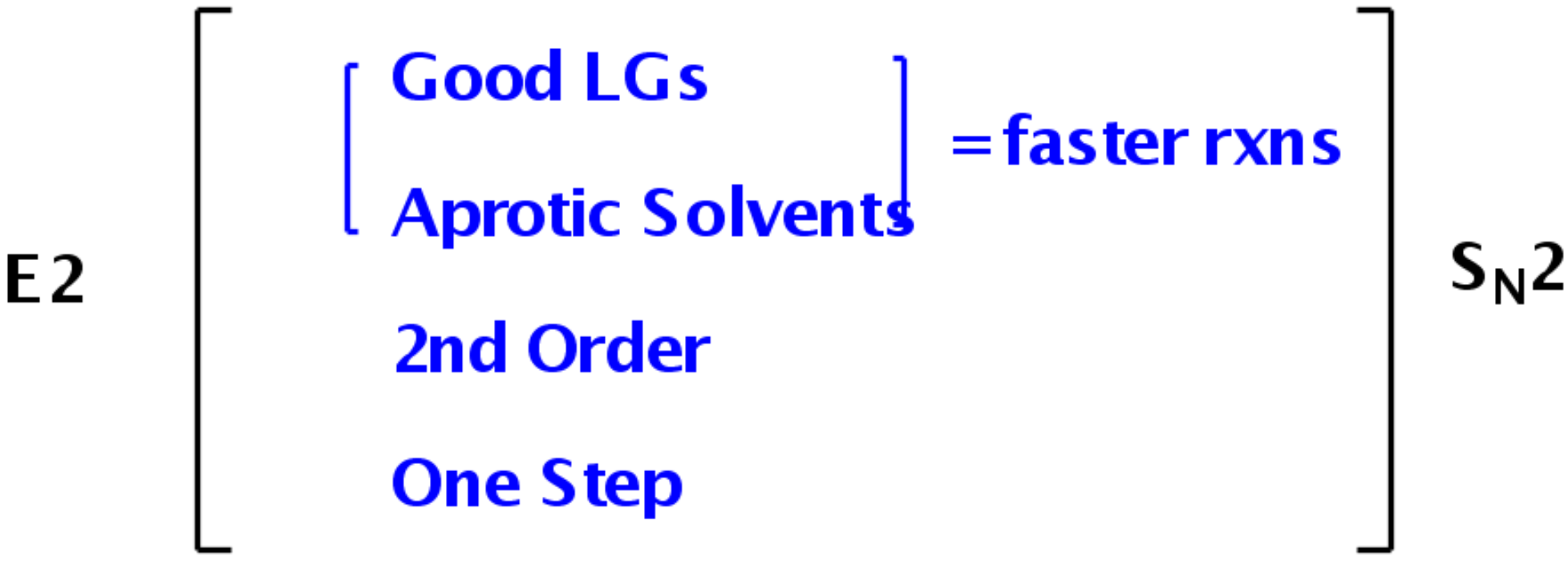
Stereochemistry of the E2 Reaction:

- **The stereochemical requirement of an anti periplanar geometry in an E2 reaction has important consequences for compounds containing six-membered rings.**
- **Consider chlorocyclohexane which exists as two chair conformations. Conformation A is preferred since the bulkier Cl group is in the equatorial position.**

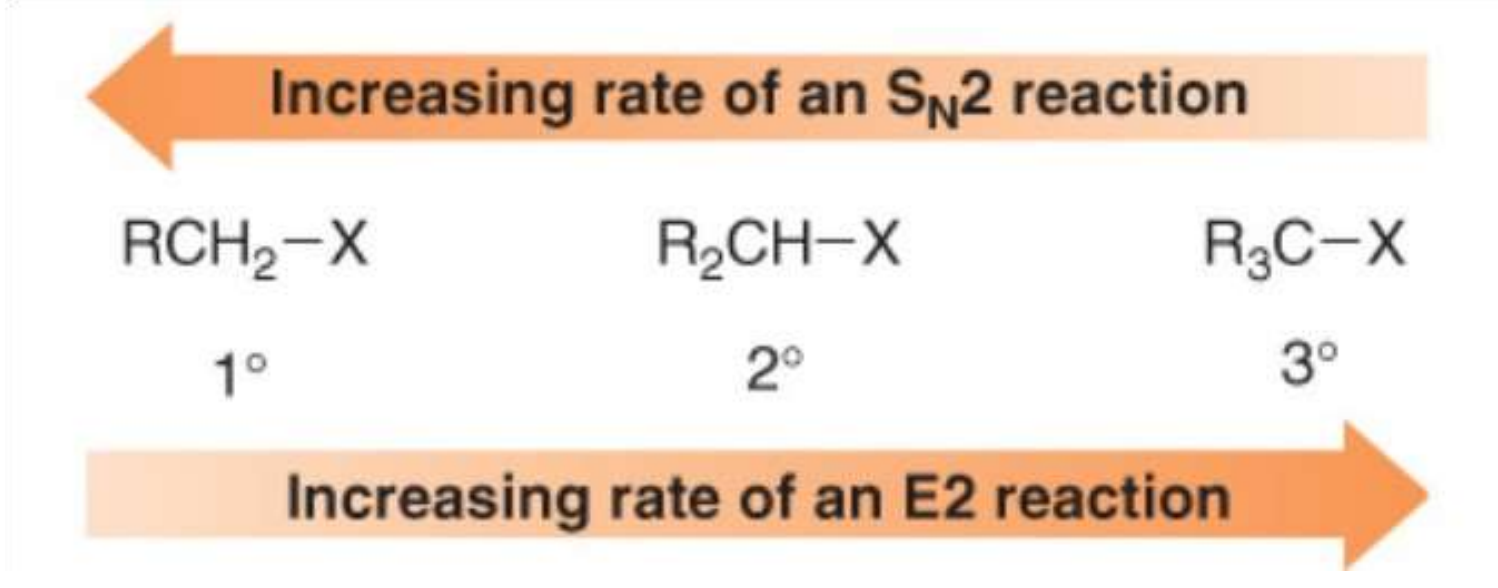


- **For E2 elimination, the C-Cl bond must be anti periplanar to the C—H bond on a £**
  Cl atoms are both in the axial position. The requirement for *trans* diaxial geometry means that elimination must occur from the less stable conformer, B.

Here are four characteristics that the E2 / SN2 mechanisms have in common.

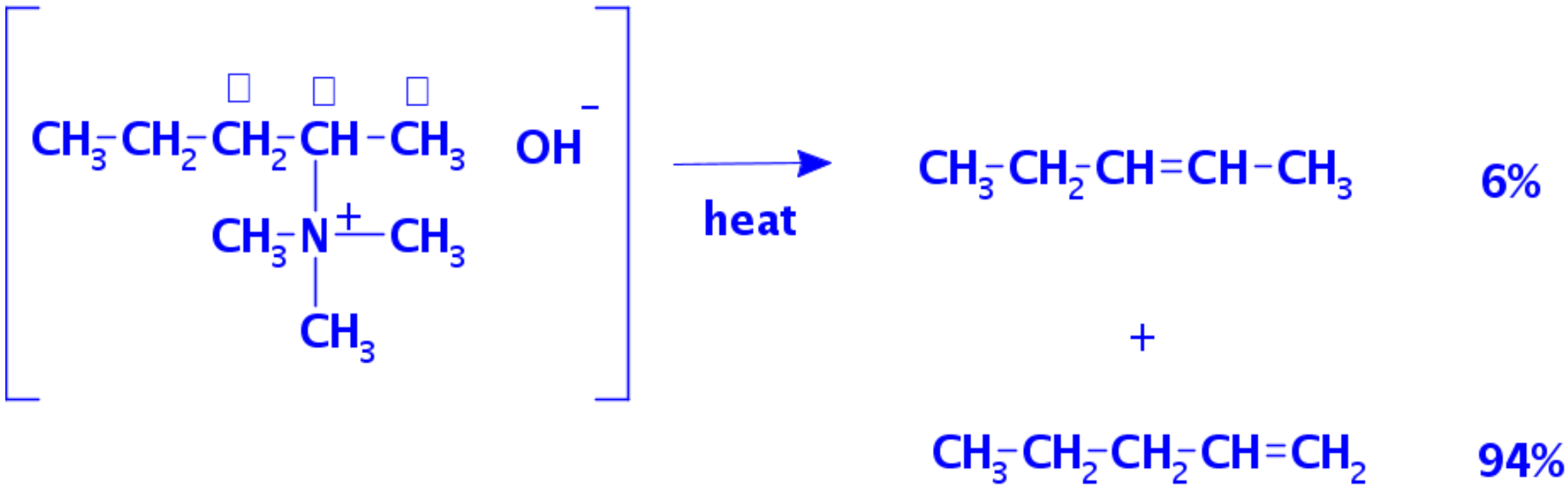


Effect of the Substrate on E2 Reactivity



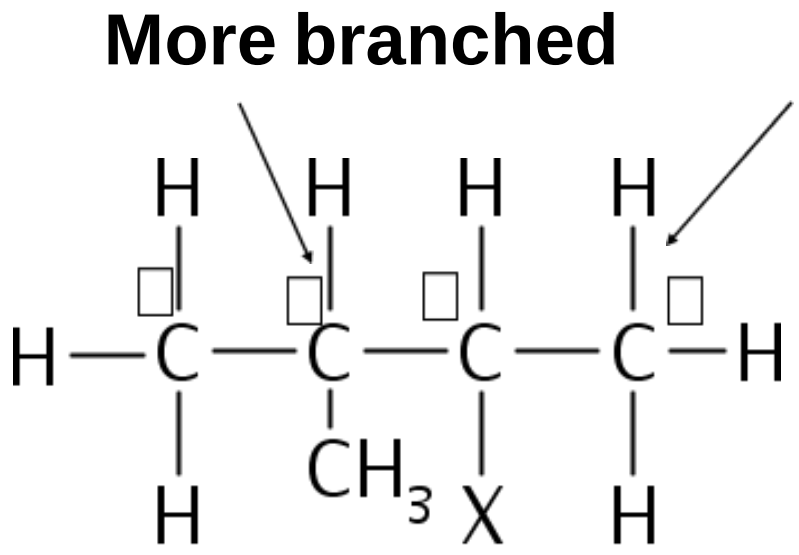
Bulky leaving groups: Hofmann Elimination

This give the *anti-Saytzeff* product (least substituted product is formed)!



Orientation of elimination: regiochemistry/ Hofmann's Rule

- In bimolecular elimination reactions in the presence of either a bulky leaving group or a bulky base, the *hydrogen* that is lost will come from the ***LEAST*** *highly-branched i* -carbon.

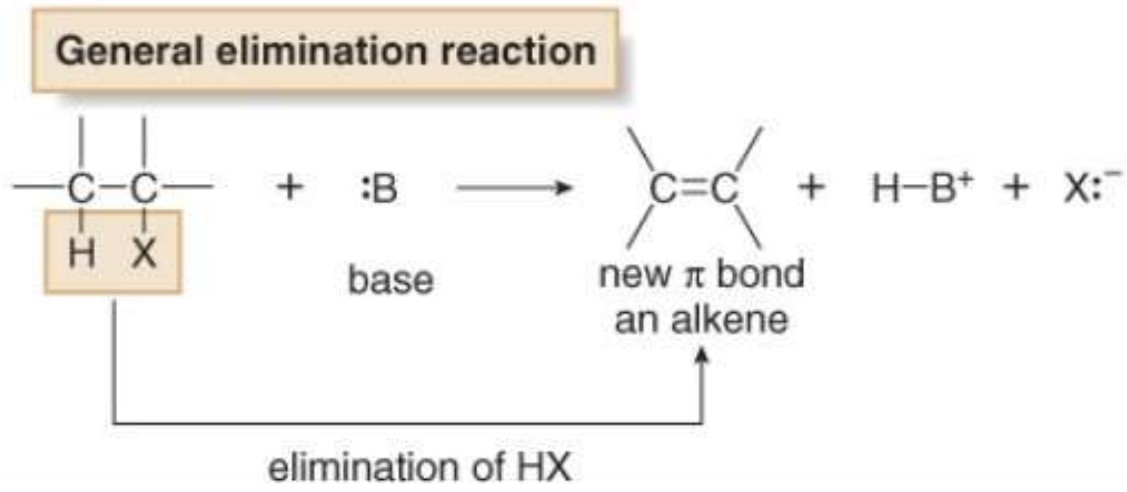


Alkyl Halides and Elimination Reactions

General Features of Elimination

- **Elimination reactions involve the loss of elements from the starting material to form a new s product.**

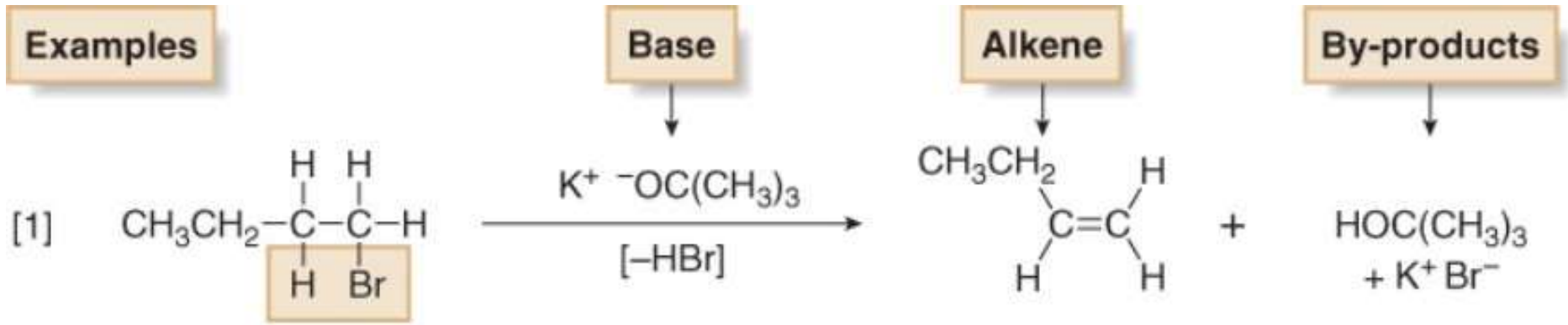
◆ Alkyl halides undergo elimination reactions with Brønsted–Lowry bases. The elements of HX are lost and an alkene is formed.

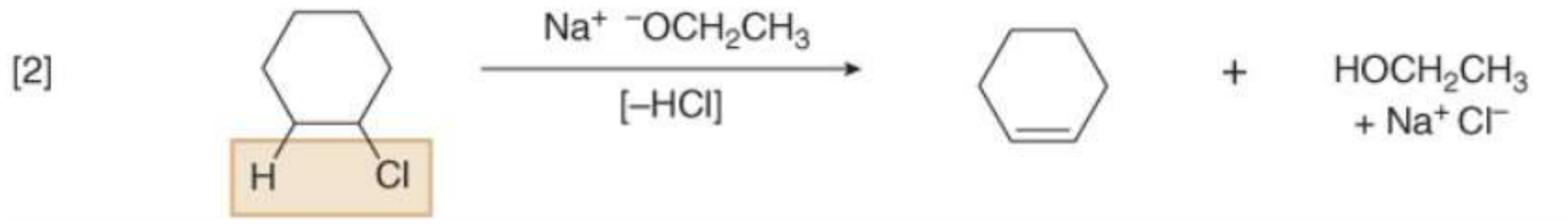


Alkyl Halides and Elimination Reactions

General Features of Elimination

- **Equations [1] and [2] illustrate examples of elimination reactions. In both reactions a base removes the elements of an acid, HX, from the organic starting material.**

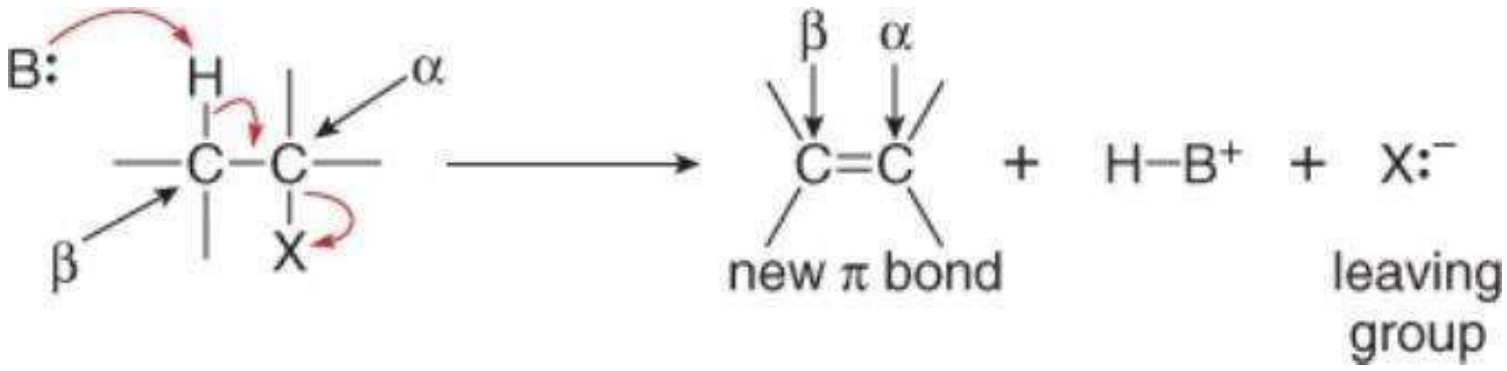




Alkyl Halides and Elimination Reactions

General Features of Elimination

- **Removal of the elements HX is called dehydrohalogenation.**
- **Dehydrohalogenation is an example of n elimination.**
- **The curved arrow formalism shown below illustrates how four bonds are broken or formed in the process.**



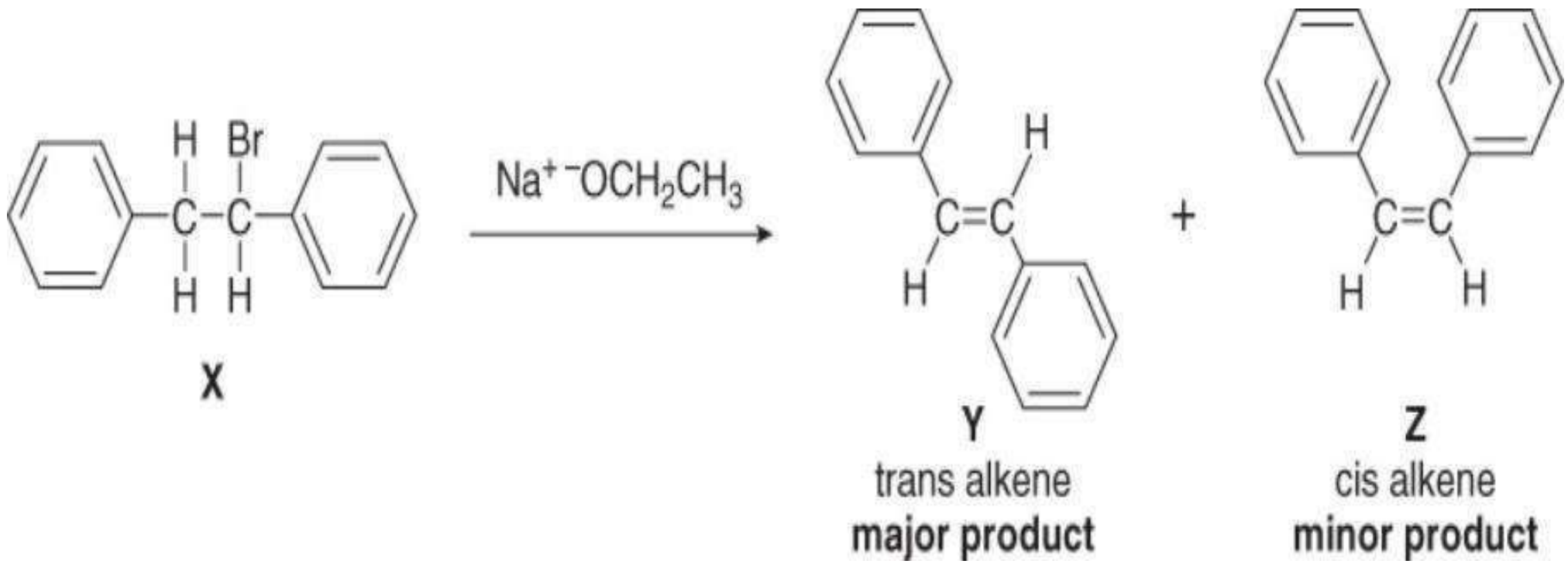
Alkyl Halides and Elimination Reactions

General Features of Elimination

- **The most common bases used in elimination reactions are negatively charged oxygen compounds, such as HO^- and its alkyl derivatives, RO^-, called alkoxides.**

The Saytzeff) Rule (Z-rule)

According to the Z-rule, the major product in a dehydrohalgenation is the *most stable product*.

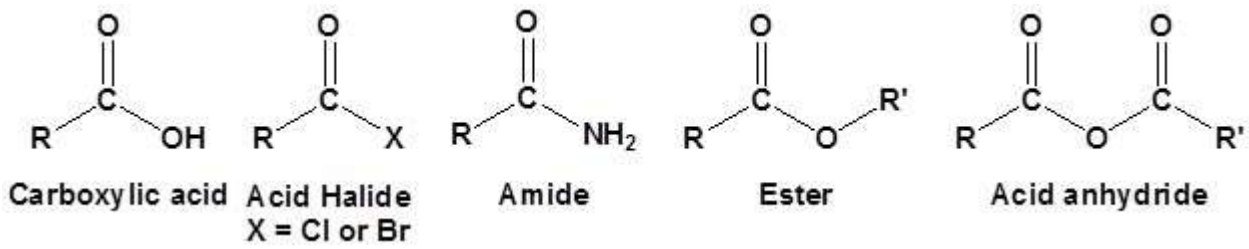


Summary

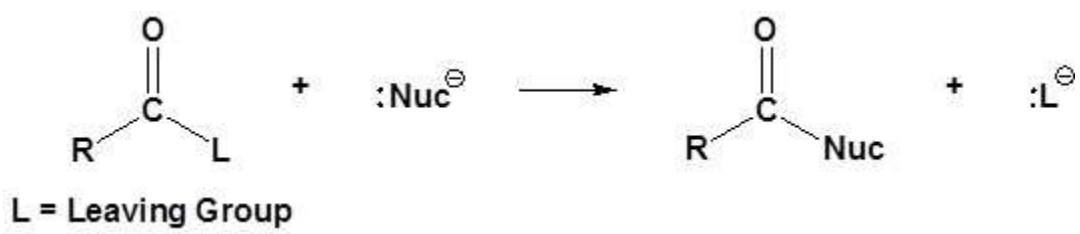
- Alkyl halides undergo two kinds of nucleophilic subtitutions: SN1 and SN2, and two kinds of elimination: E1 and E2.
- SN2 and E2 are bimolecular one-step reactions
- SN1 and E1 are unimolecular two step reactions
- SN1 lead to a mixture of stereoisomers
- The major product of a elimination is the most stable alkene
- SN2 are E2 are favoured by strong nucleophile/strong base
- SN2 reactions are favoured by primary alkyl halides
- E2 reactions are favoured by tertiary alkyl halides

Nucleophilic Substitution at the carbonyl (C=O)

Carbonyl compounds with leaving groups have reactions similar to aldehydes and ketones.

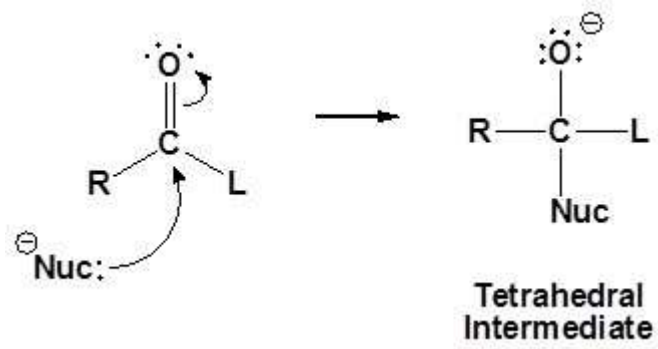


General reaction

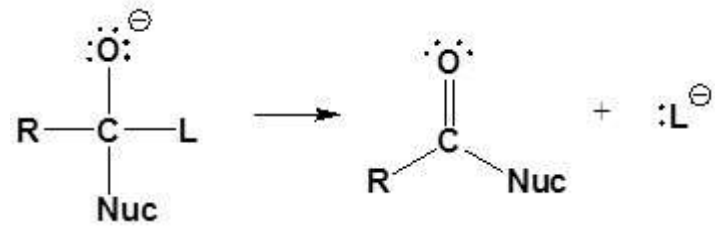


General mechanism

1) Nucleophilic attack on the carbonyl

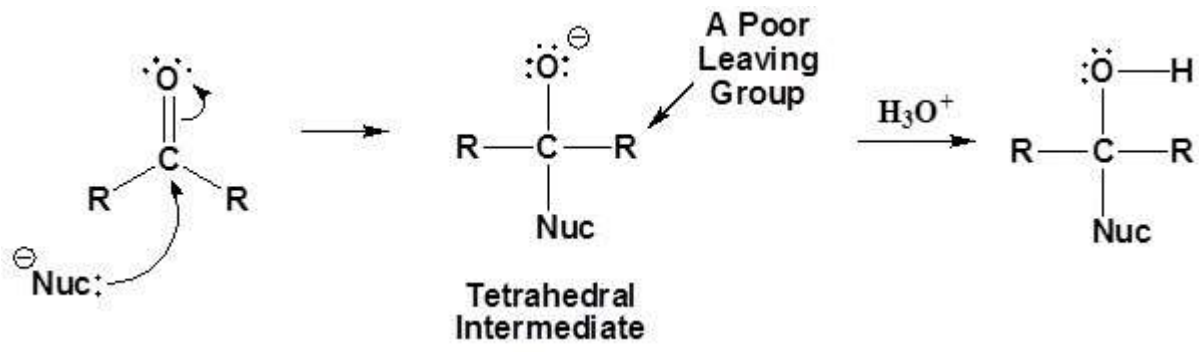


2) Leaving group is removed



Once a tetrahedral intermediate is formed, aldehydes and ketones cannot reform their carbonyls.

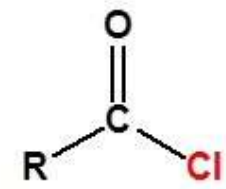
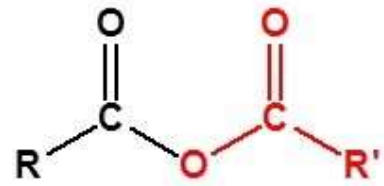
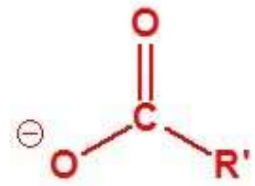
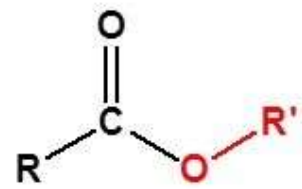
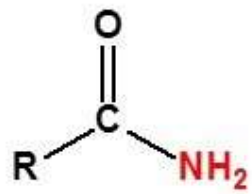
Because of this, aldehydes and ketones typically undergo nucleophilic additions and not substitutions.



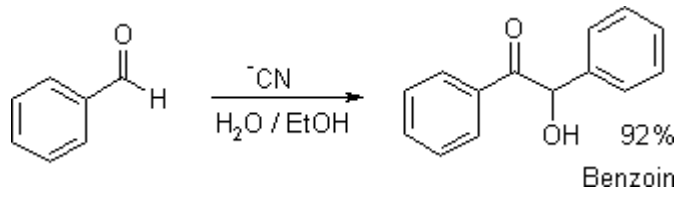
The relative reactivity of carboxylic acid derivatives toward nucleophilic substitutions is related to the electronegative leaving group's ability to activate the carbonyl.

The more electronegative leaving groups withdraw electron density from the carbonyl, thereby increasing its electrophilicity.

Reactivity

Functional Group	Leaving Group
 Acid Chloride	$Cl^{\ominus}$
 Acid anhydride	
 Ester	
 Amide	$^{\ominus}NH_2$

Benzoin Condensation

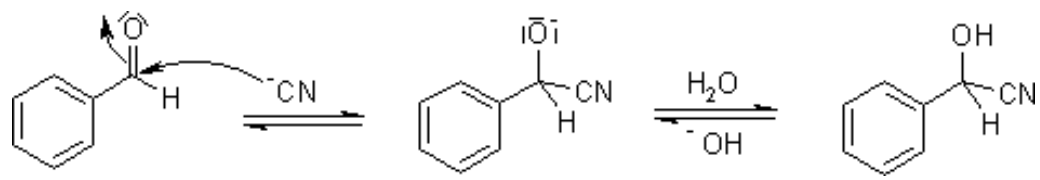


The Benzoin Condensation is a coupling reaction between two aldehydes that allows the preparation of α-hydroxyketones.

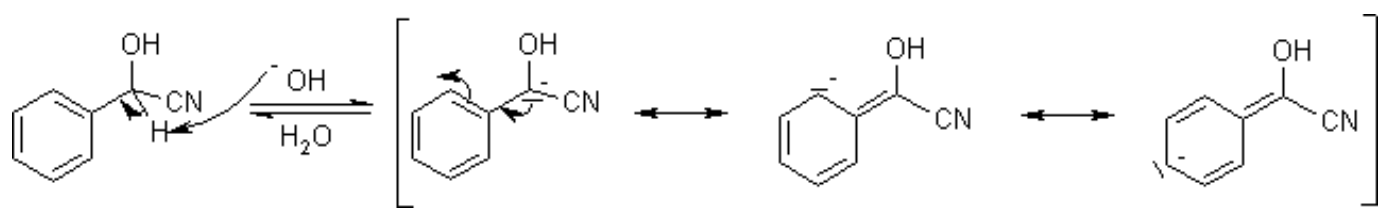
The first methods were only suitable for the conversion of aromatic aldehydes.

Mechanism of Benzoin Condensation

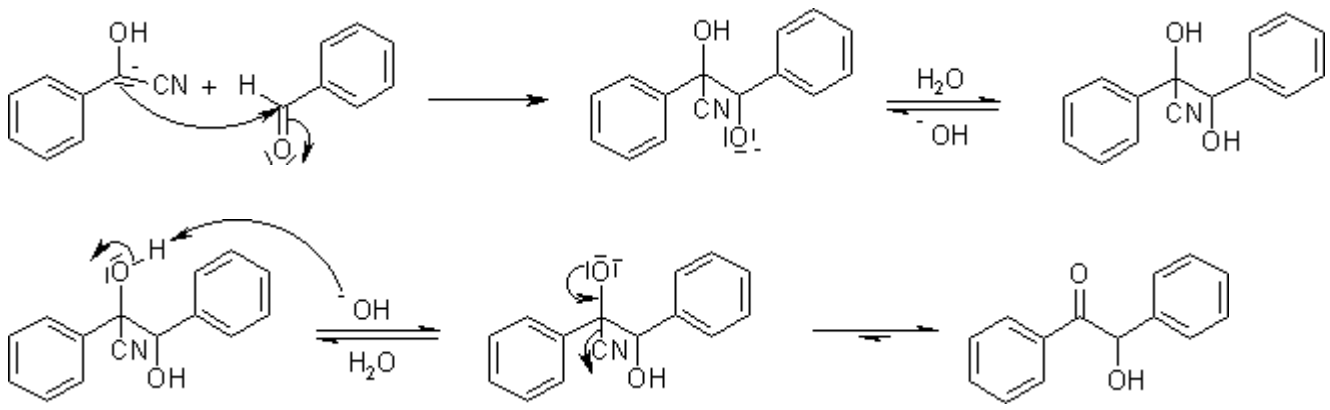
Addition of the cyanide ion to create a cyanohydrin effects an umpolung of the normal carbonyl charge affinity, and the electrophilic aldehyde carbon becomes nucleophilic after deprotonation: A thiazolium salt may also be used as the catalyst in this reaction.



A strong base is now able to deprotonate at the former carbonyl C-atom:

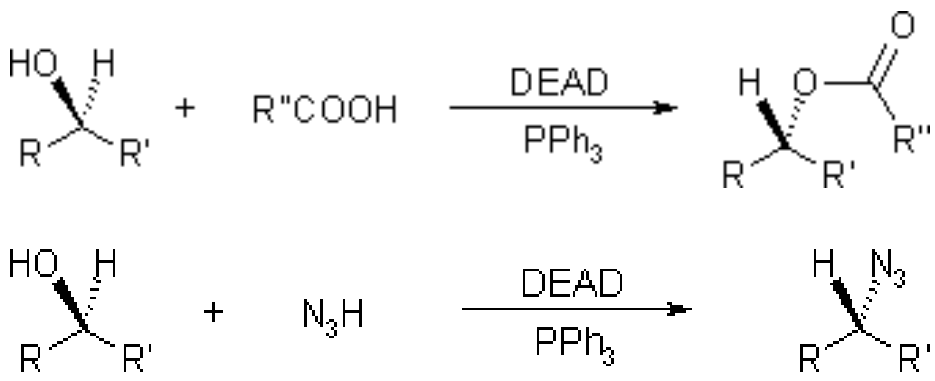


A second equivalent of aldehyde reacts with this carbanion; elimination of the catalyst regenerates the carbonyl compound at the end of the reaction:



Nucleophilic Substitution at the Alcohol

Mitsunobu Reaction



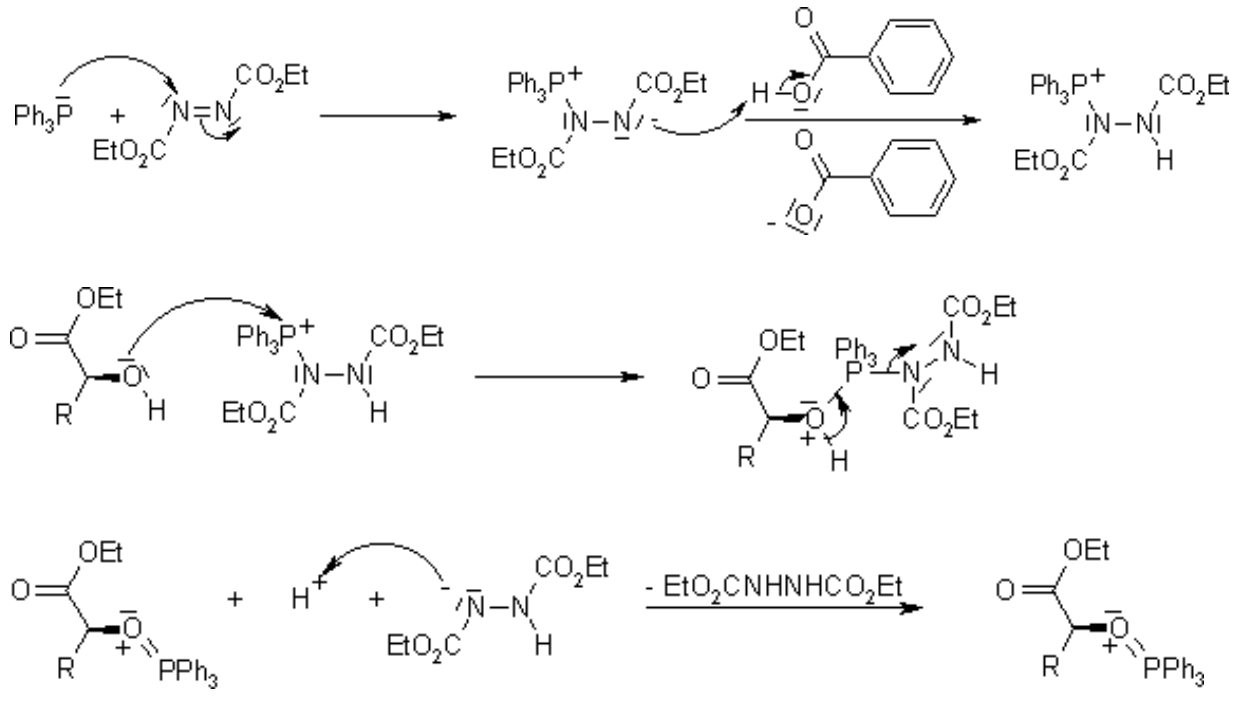
The Mitsunobu Reaction allows the conversion of primary and secondary alcohols to esters, phenyl ethers, thioethers and various other compounds.

The nucleophile employed should be acidic, since one of the reagents (DEAD, diethylazodicarboxylate) must be protonated during the course of the reaction to prevent from side reactions.

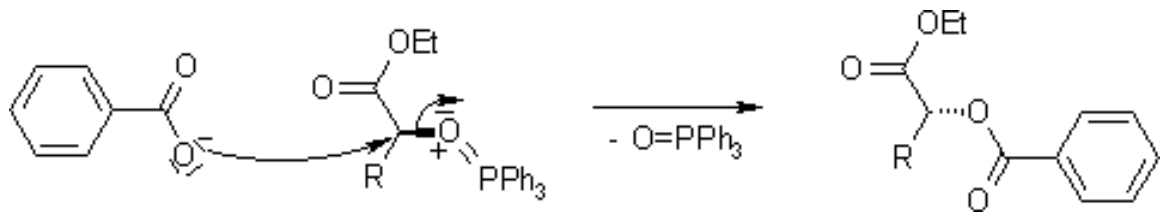
Mechanism of the Mitsunobu Reaction

The triphenylphosphine combines with DEAD to generate a phosphonium intermediate that binds to the alcohol oxygen, activating it as a leaving group.

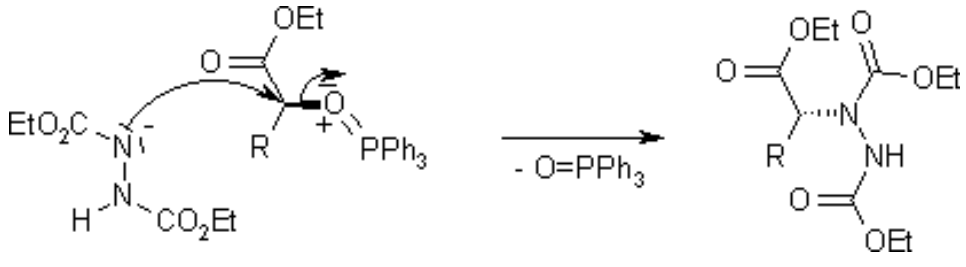
Substitution by the carboxylate, mercaptyl, or other nucleophile completes the process.



The reaction proceeds with clean inversion, which makes the Mitsunobu Reaction with secondary alcohols a powerful method for the inversion of stereogenic centers in natural product synthesis.



Side Reaction:



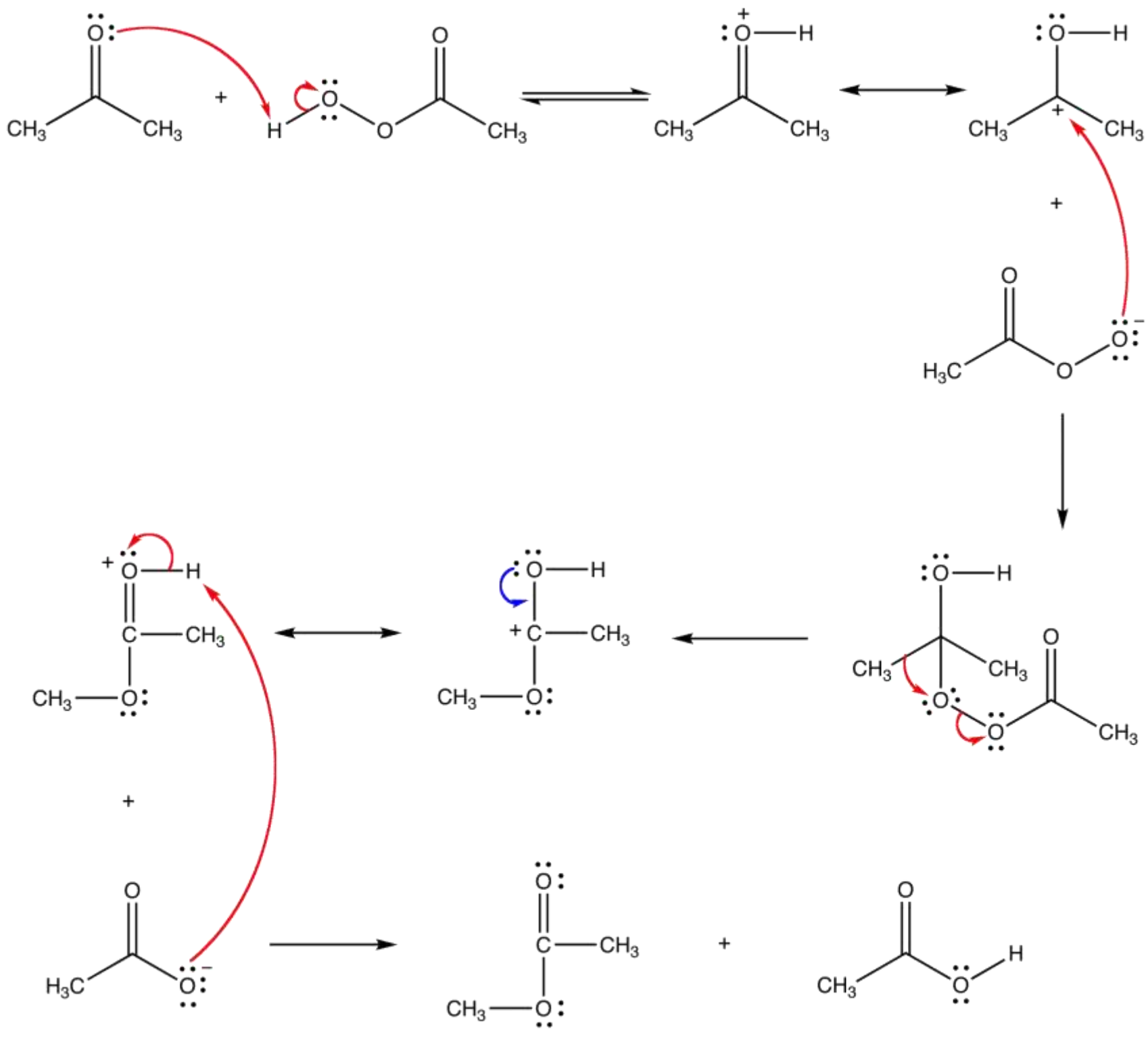
New protocols have been developed which allow better removal of side products and/or the conversion of more basic nucleophiles.

Baeyer-Villiger Oxidation

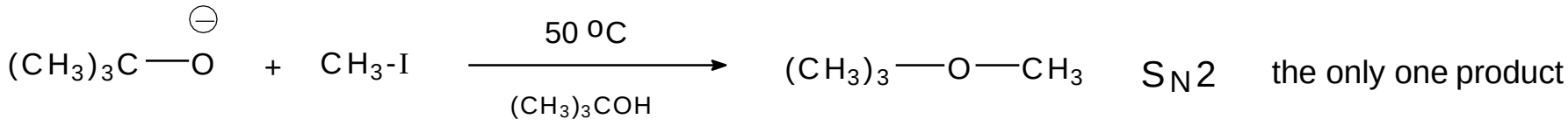
The Baeyer-Villiger oxidation, also known as the Baeyer-Villiger rearrangement, was first reported on December 17, 1899 by Adolf Baeyer and Victor Villiger in Chemische Berichte. They referred to the oxidation of menthone and tetrahydrocarvone by monoperoxysulfuric acid.

It is a popular synthetic tool for the conversion of cyclic ketones to lactones and acyclic ketones to esters; lactones are precursors to hydroxy acids and acyclic diols.

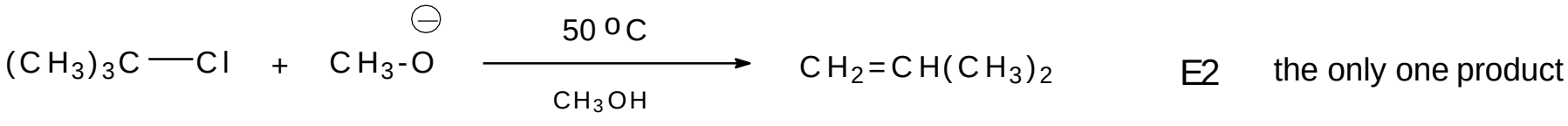
Peracids, hydrogen peroxide, magnesium salt of monoperoxyphthalic acid and oxone are established reagents for this reaction. Phenols and formates can be obtained from the corresponding aromatic aldehydes.



Examples for solution

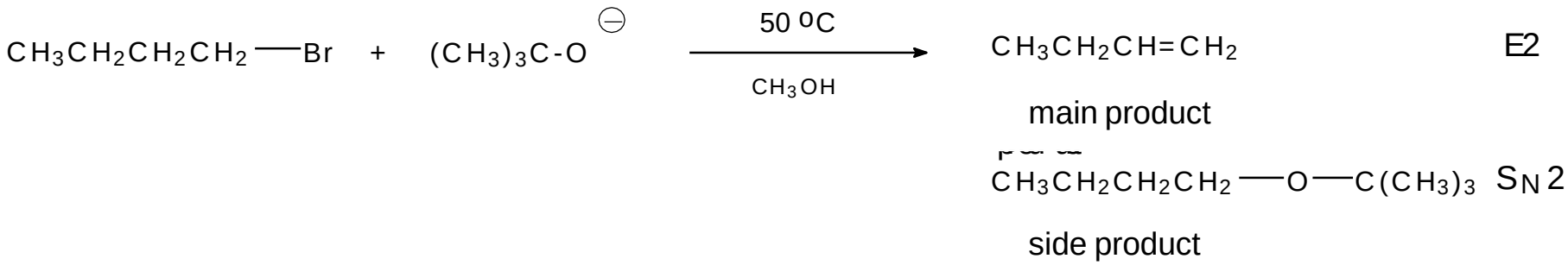


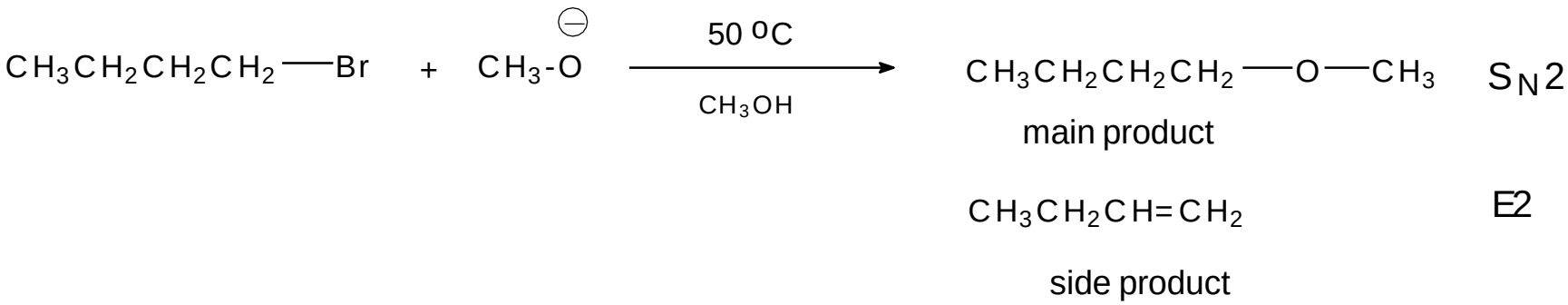
S_N2 the only one product



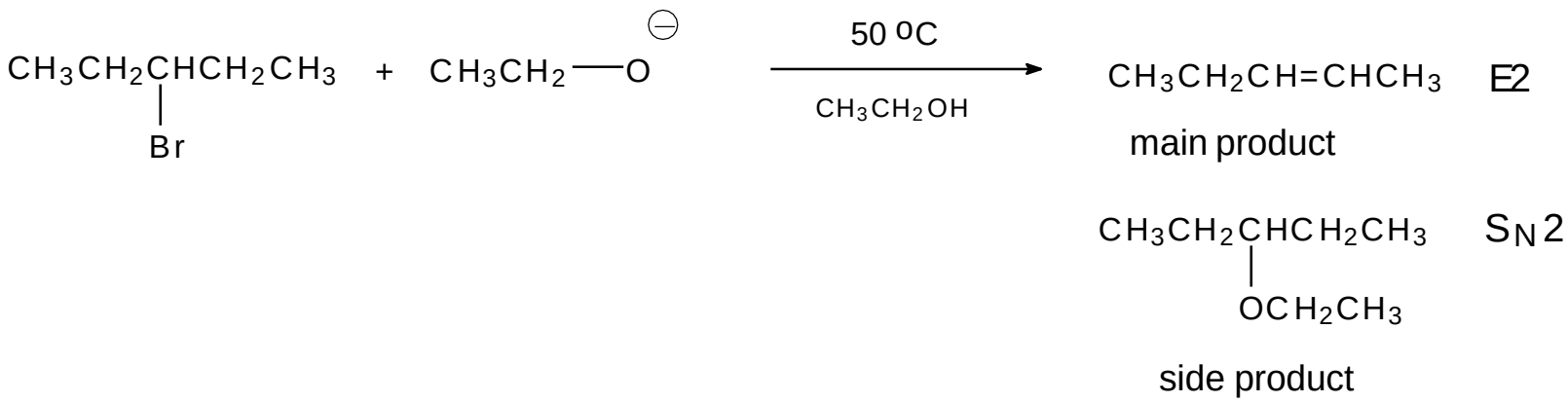
E2 the only one product

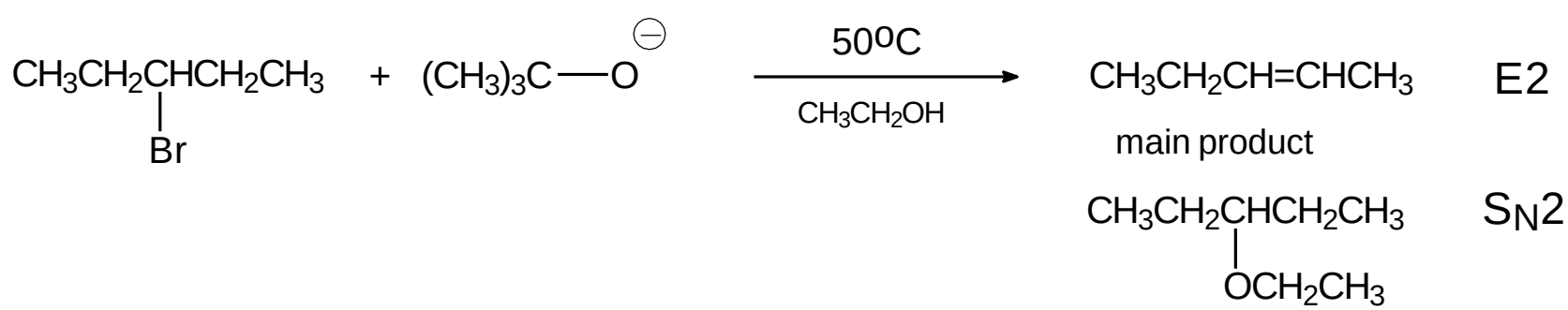
Examples for solution



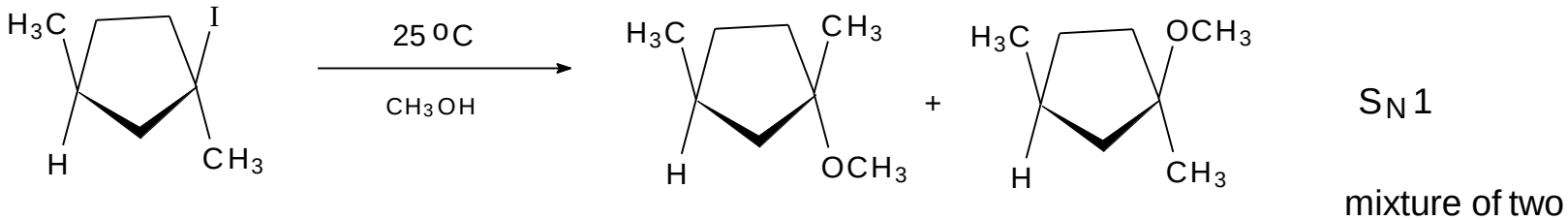


Examples for solution



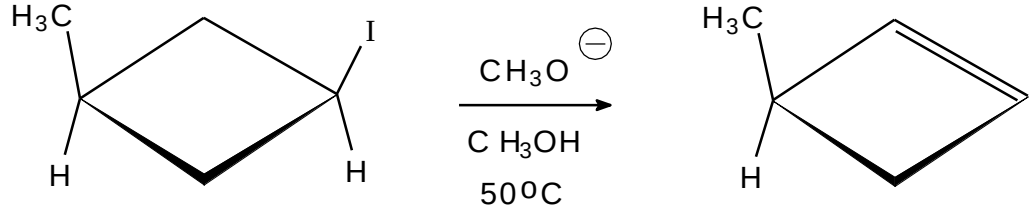


Examples for solution



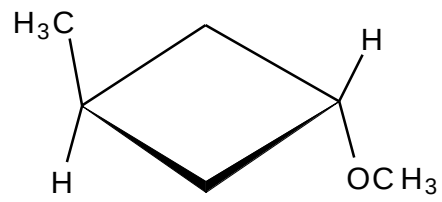
S_N1

mixture of two components



E2

main product

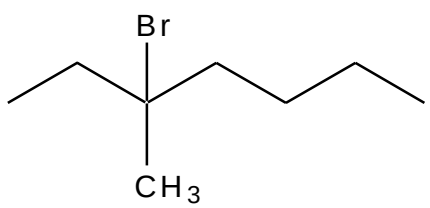


S_N2

side product

Examples for solution

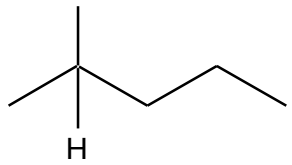
(*S*)-3-bromo-3-methylhexane $\xrightarrow[\text{MeOH}]{25^{\circ}\text{C}}$ (*S*)-3-methoxy-3-methylhexane + (*R*)-3-methoxy-3-methylhexane — mixture — S_N1



(*R*)-2-bromobutane + $\ominus$OH $\xrightarrow{25^{\circ}\text{ C}}$ $CH_3-\underset{H}{C}=CH-CH_3$ — main product — E2

$H_2C=CH-CH_2CH_3$ — side product — S_N2

(*S*)-2-butanol

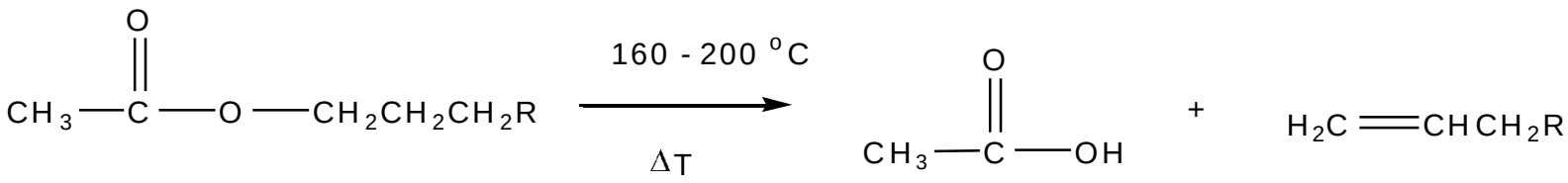


Pyrolytic elimination

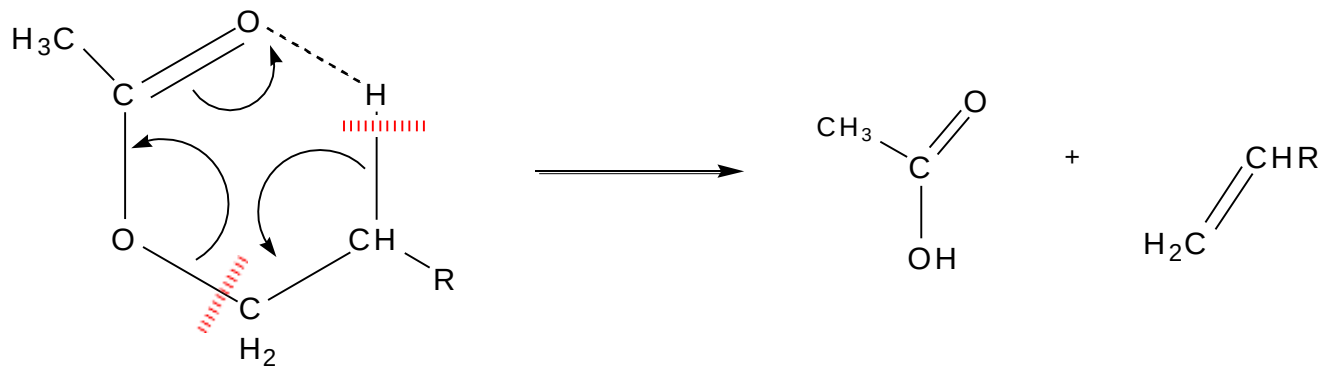
Reactions are characteristic for acetates or xanthates –Chugaev reaction and *t*-aminoxides – Cope elimination

Acetates pyrolysis

Reactions are *cis*- stereospecific and regiospecific

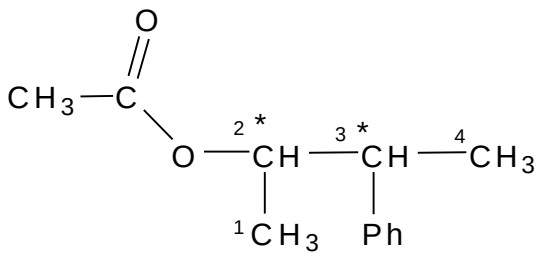


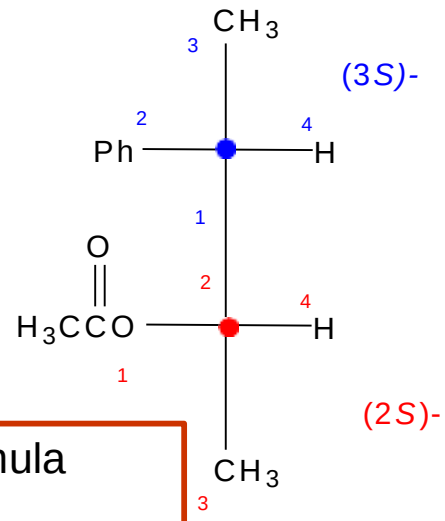
Reaction proceeds via cyclic intermediate

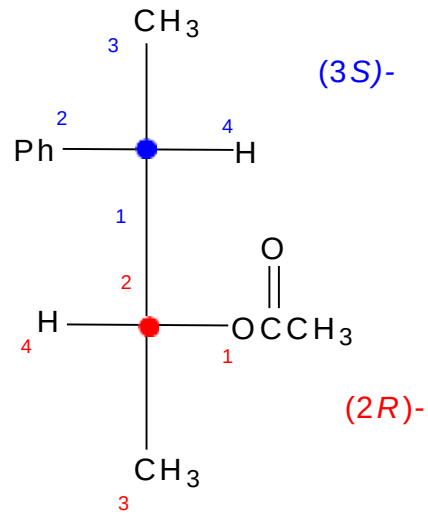


Pyrolytic elimination

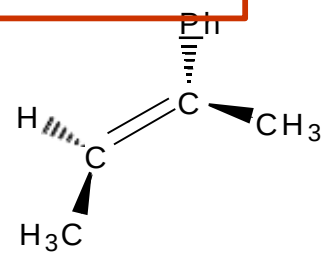
What is the product of (2*R*,3*S*)-2-(3-phenylbutyl)acetate?

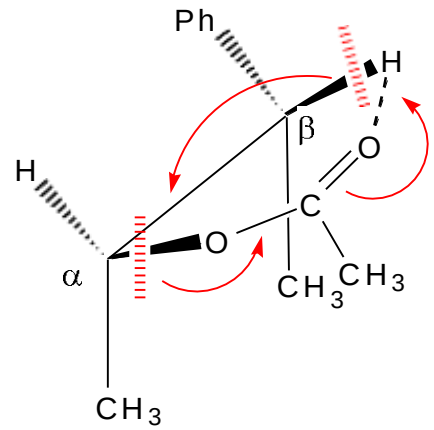






1. Composition of corresponding formula
2. Configuration determination
3. Transformation into perspective formula
4. *Cis*- (*syn*-) elimination
5. Determination of olefine configuration
6. Composition of proper name

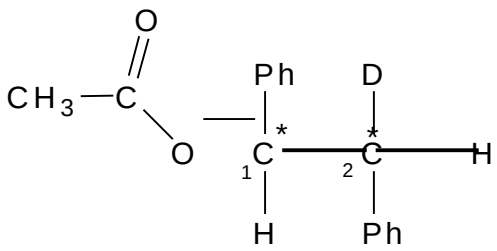


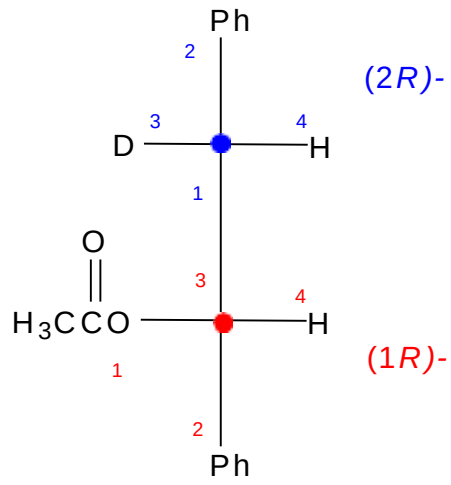


(*E*)-2-phenylbut-2-ene

Pyrolytic elimination

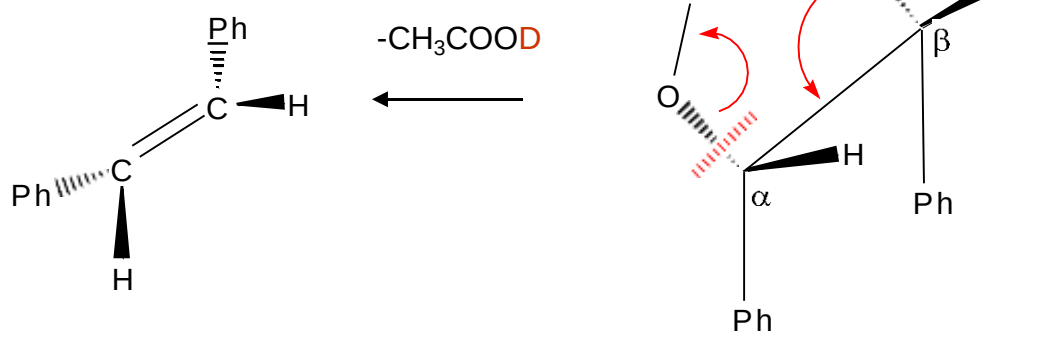
What is the product of pyrolysis of (1*R*,2*R*)-1,2-diphenyl-2-deuterioethylacetate?





1. Composition of corresponding formula
2. Configuration determination
3. Transformation into perspective formula
4. *Cis*- (*syn*-) elimination
5. Determination of olefine configuration
6. Composition of proper name

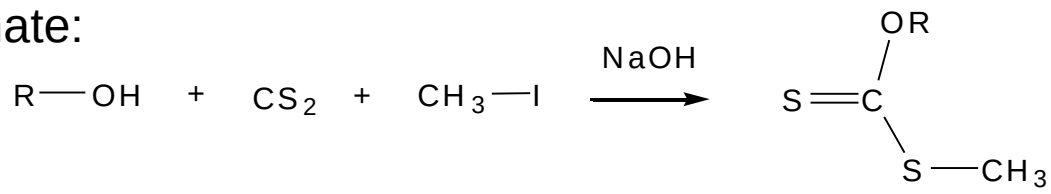
(*Z*)-diphenylethene

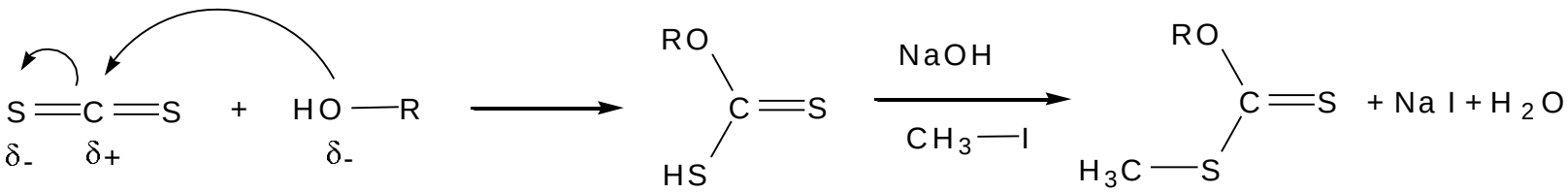


Pyrolytic elimination – Chugayev reaction

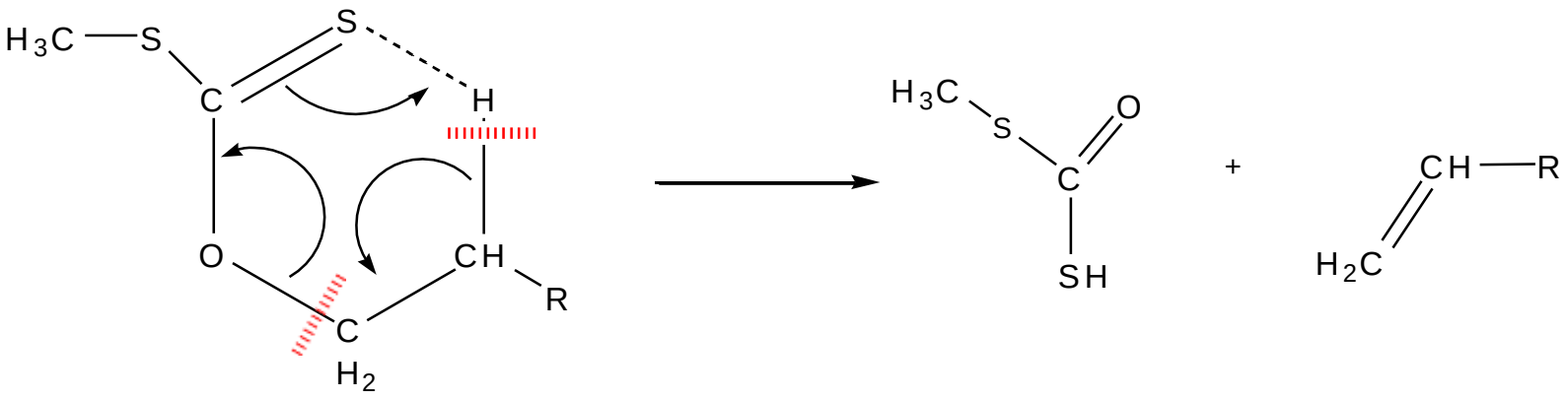
Reactions are *cis*- stereospecific and regiospecific

Preparation of xanthate:



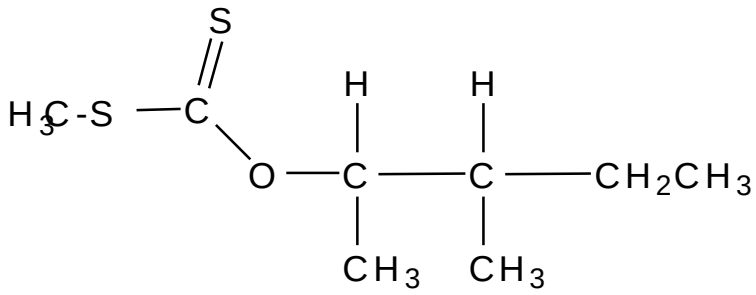


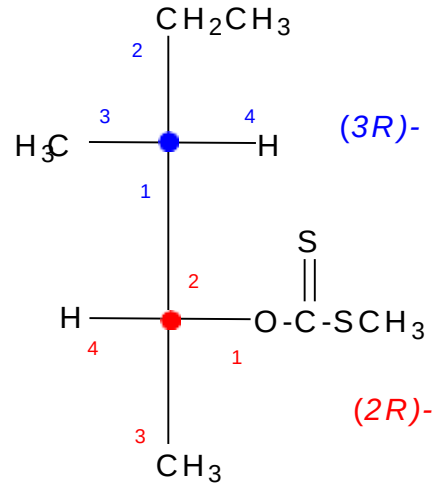
Reactions proceed via cyclic state



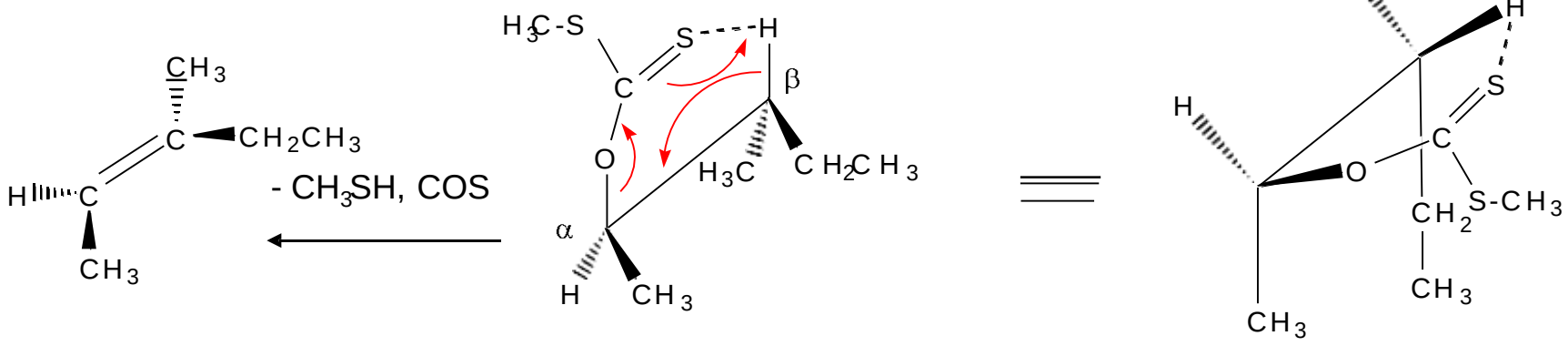
Pyrolytické eliminace

What is the product of (*S*)-methyl-(2*R*,3*R*)-O-(3-methylpent-2-yl) xanthate pyrolysis?





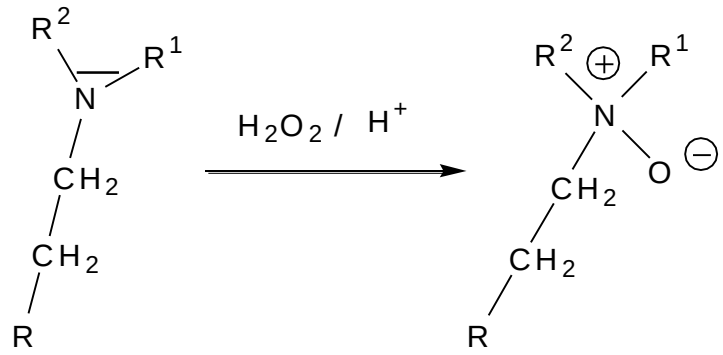
(*Z*)-3-methylpent-2-ene



Pyrolytic elimination – Cope reaction

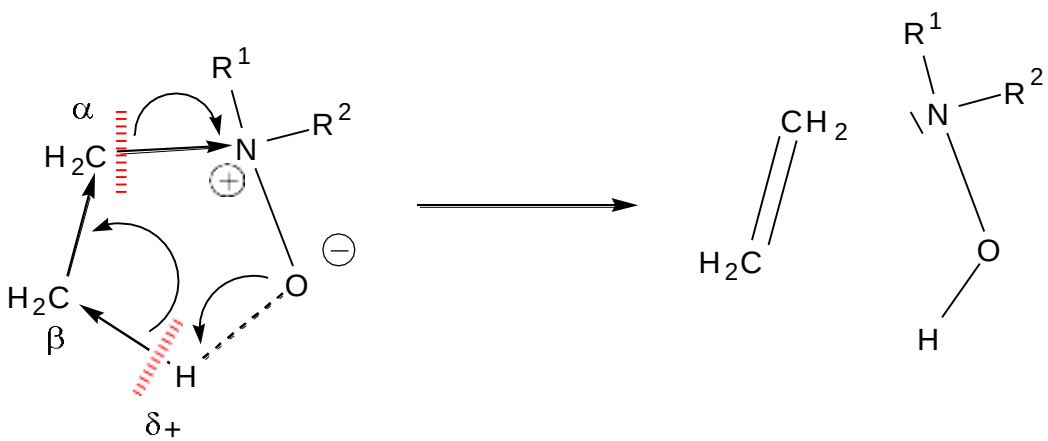
Reactions are *cis*- stereospecific and regiospecific

Preparation of *t*-aminoxide



oxidation of *t*-amines

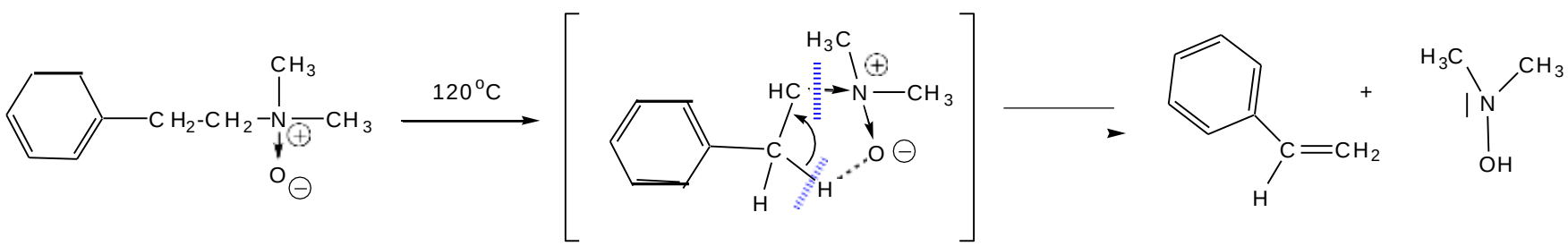
Reactions proceed via cyclic intermediate

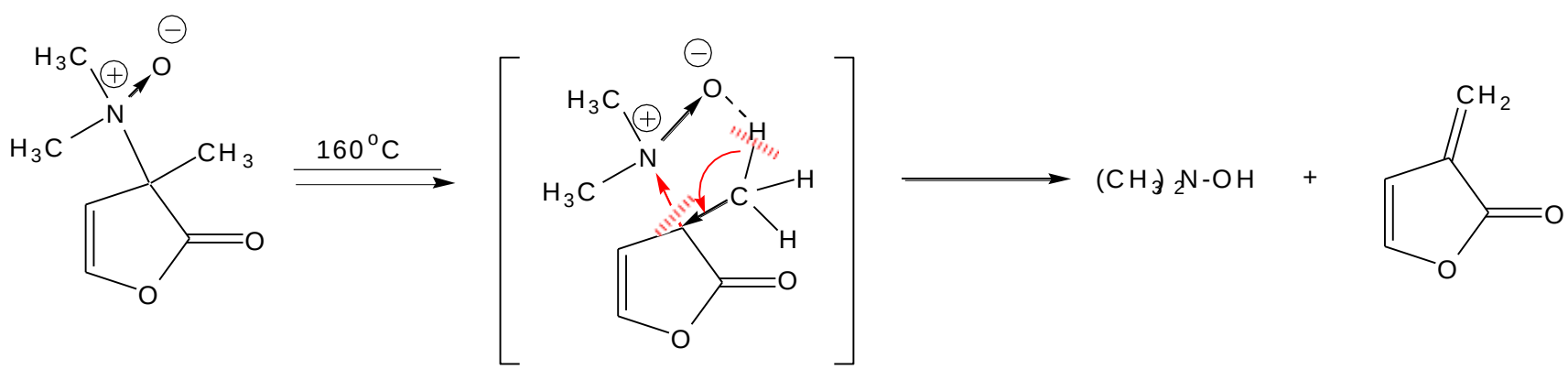


after reaction olefin and substituted hydroxylamin are obtained

Pyrolytic elimination

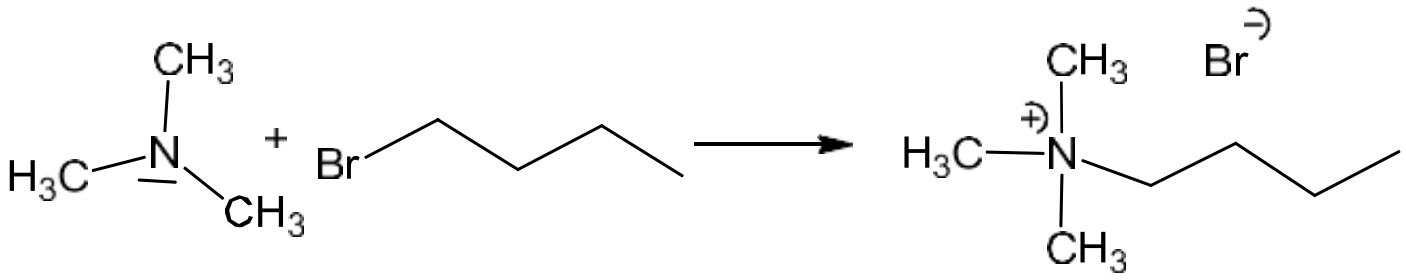
Cope elimination of N-oxides



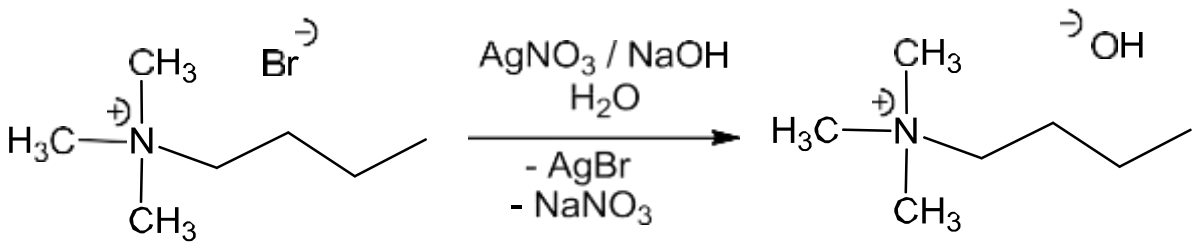


Hofmann elimination of quarternary ammonium hydroxides

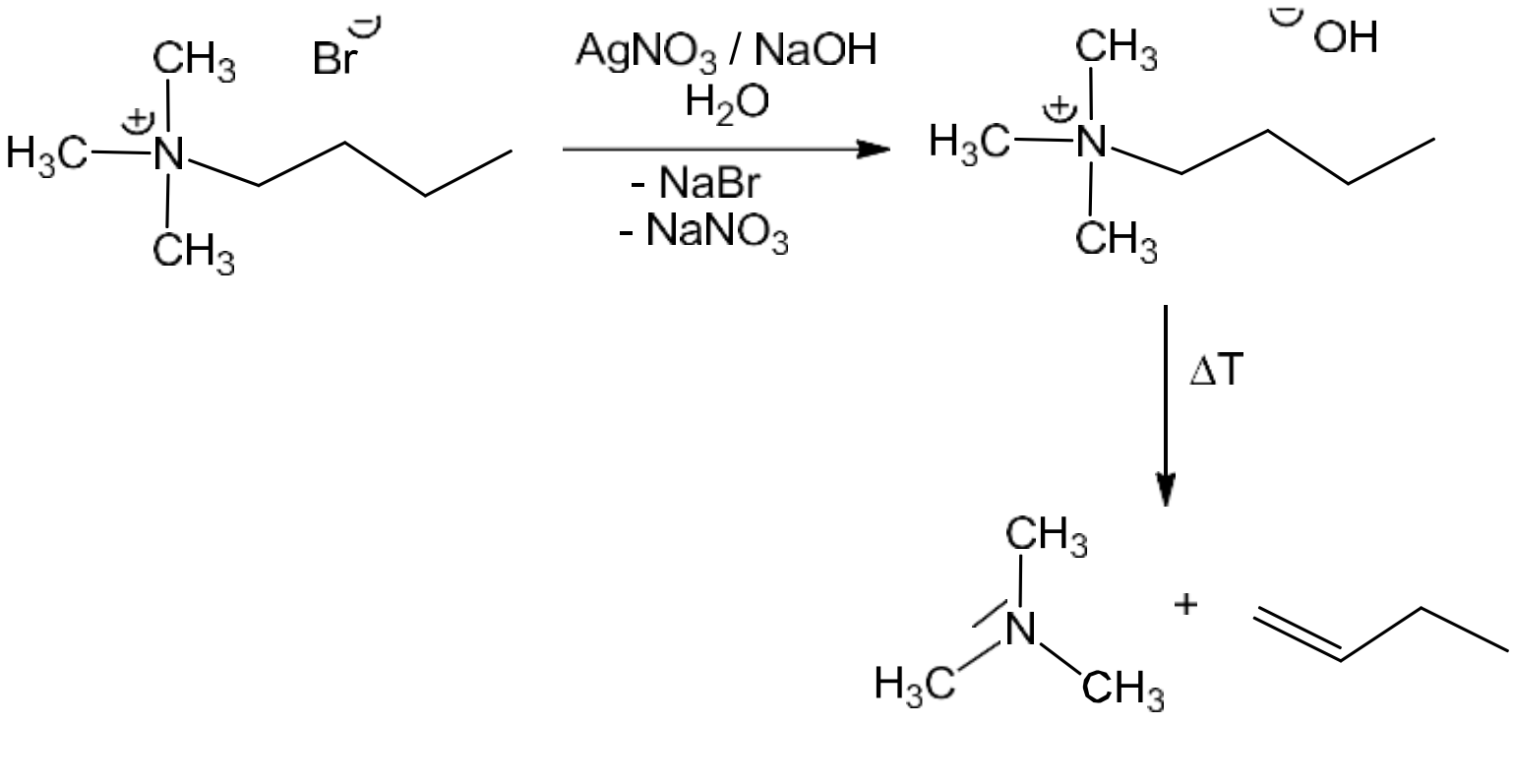
Reaction starts with t-alkylamines, which in the following reaction are alkylated to quaternary ammonium salts



In the further step they are transferred into quaternary ammonium hydroxides



Hofmann elimination of quarternary ammonium hydroxides

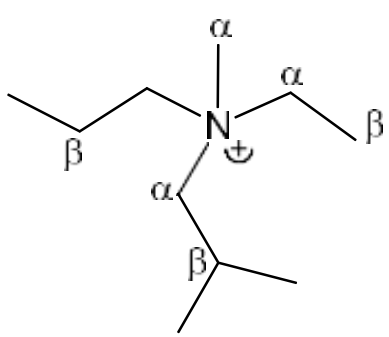


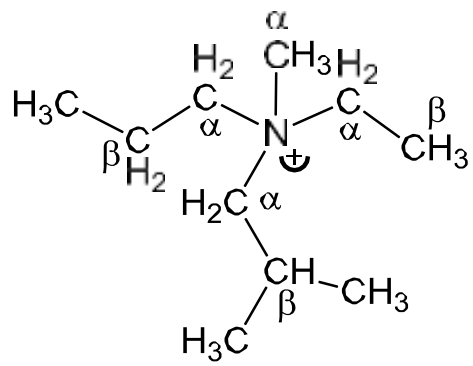
Hofmann elimination of quarternary ammonium hydroxides

Reactions are regiospecific, but not stereospecific

During the reaction the most acidic β-hydrogen atom is split off.

(„antisaytzeff rule“ – that β-hydrogen atom splits off to produce the least branched olefin



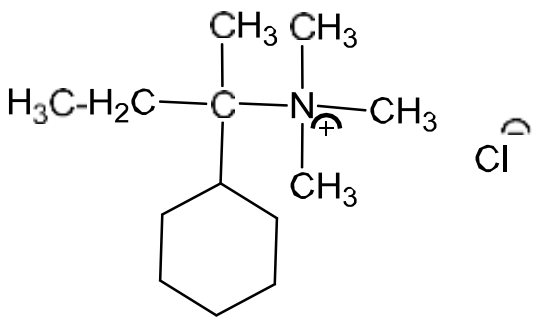


In the molecule there are 3 β-hydrogen atoms, which might be eliminated ----

in the reaction the most acidic proton splits off and the least branched olefin is formed

Hofmann elimination of quarternary ammonium hydroxides

During reaction the most acidic β-hydrogen atom splits off



Name this compound and carry out the Hofmann elimination

in the molecule they are 2 different β- hydrogen atoms, which might be eliminated ----

during the reaction the most acidic hydrogen is eliminated and the least branched olefin is formed

Neighboring group Participation in Nucleophilic substitution

Neighbouring group Participation in Nucleophilic substitution

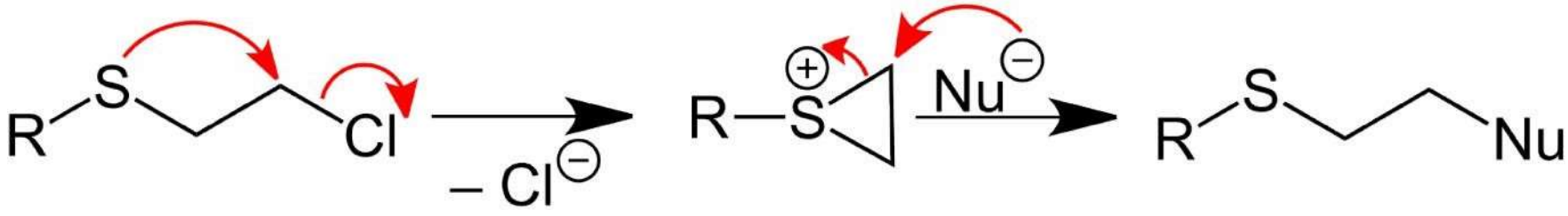
- **Neighbouring group participation** (**NGP**) in organic chemistry is defined by IUPAC as the interaction of a reaction centre with a lone pair of electrons in an atom or the electrons present in a sigma bond or pi bond contained within the parent molecule but not conjugated with the reaction centre.

- When NGP is in operation it is normal for the reaction rate to be increased.

- It is also possible for the stereochemistry of the reaction to be abnormal (or unexpected) when compared with a *normal* reaction.

NGP by heteroatom lone pairs

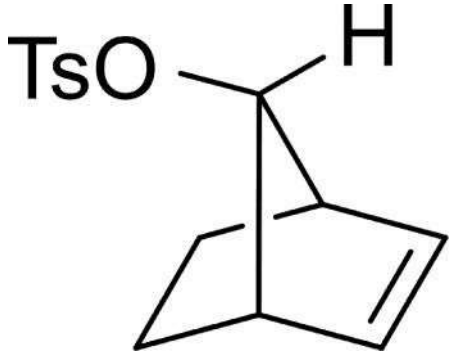
- A classic example of NGP is the reaction of a sulfur or nitrogen mustard with a nucleophile, the rate of reaction is much higher for the sulfur mustard and a nucleophile than it would be for a primary alkyl chloride without a heteroatom.

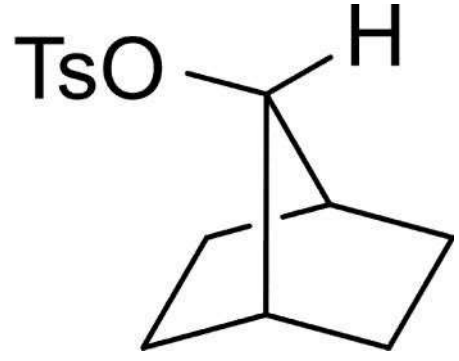


Ph-S-CH_2-CH_2-Cl reacts with water 600 times faster than CH_3-CH_2-CH_2-Cl

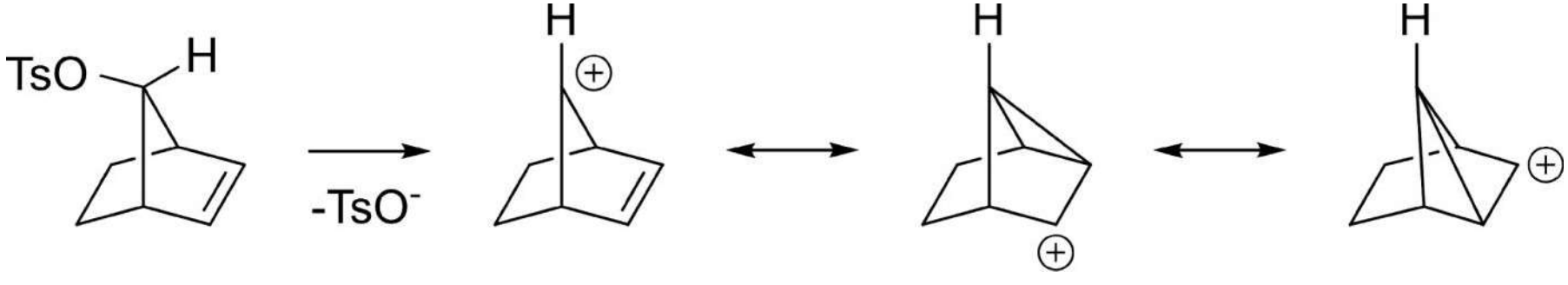
NGP by an alkene

• The π orbitals of an alkene can stabilize a transition state by helping to delocalize the positive charge of the carbocation. For instance the unsaturated tosylate will react more quickly (10^{11} times faster for aqueous solvolysis) with a nucleophile than the saturated tosylate.



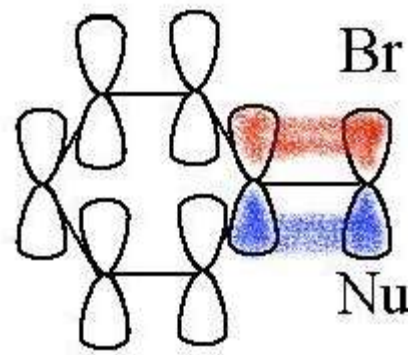


- The carbocationic intermediate will be stabilized by resonance where the positive charge is spread over several atoms, in the diagram below this is shown.

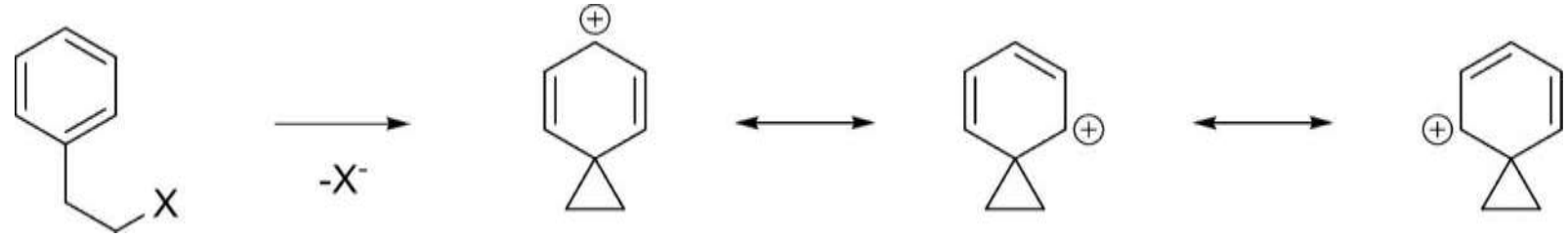


NGP by an aromatic ring

- In the case of a benzyl halide the reactivity is higher because the S_N2 transition state enjoys a similar overlap effect to that in the allyl system.



- An aromatic ring can assist in the formation of a carbocationic intermediate called a **phenonium ion** by delocalising the positive charge.



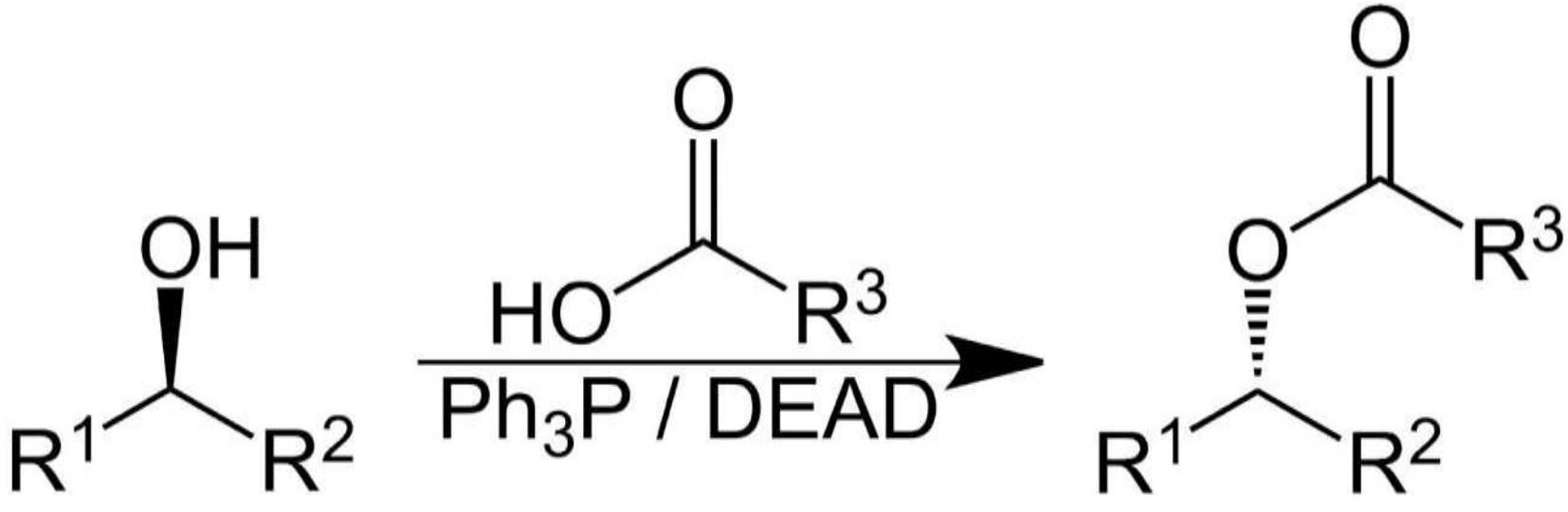
NGP by aliphatic C-C or C-H bonds

- Aliphatic C-C or C-H bonds can lead to charge delocalization if these bonds are close and antiperiplanar to the leaving group. Corresponding intermediates are referred to a nonclassical ions, with the 2-norbornyl system as the most well known case.

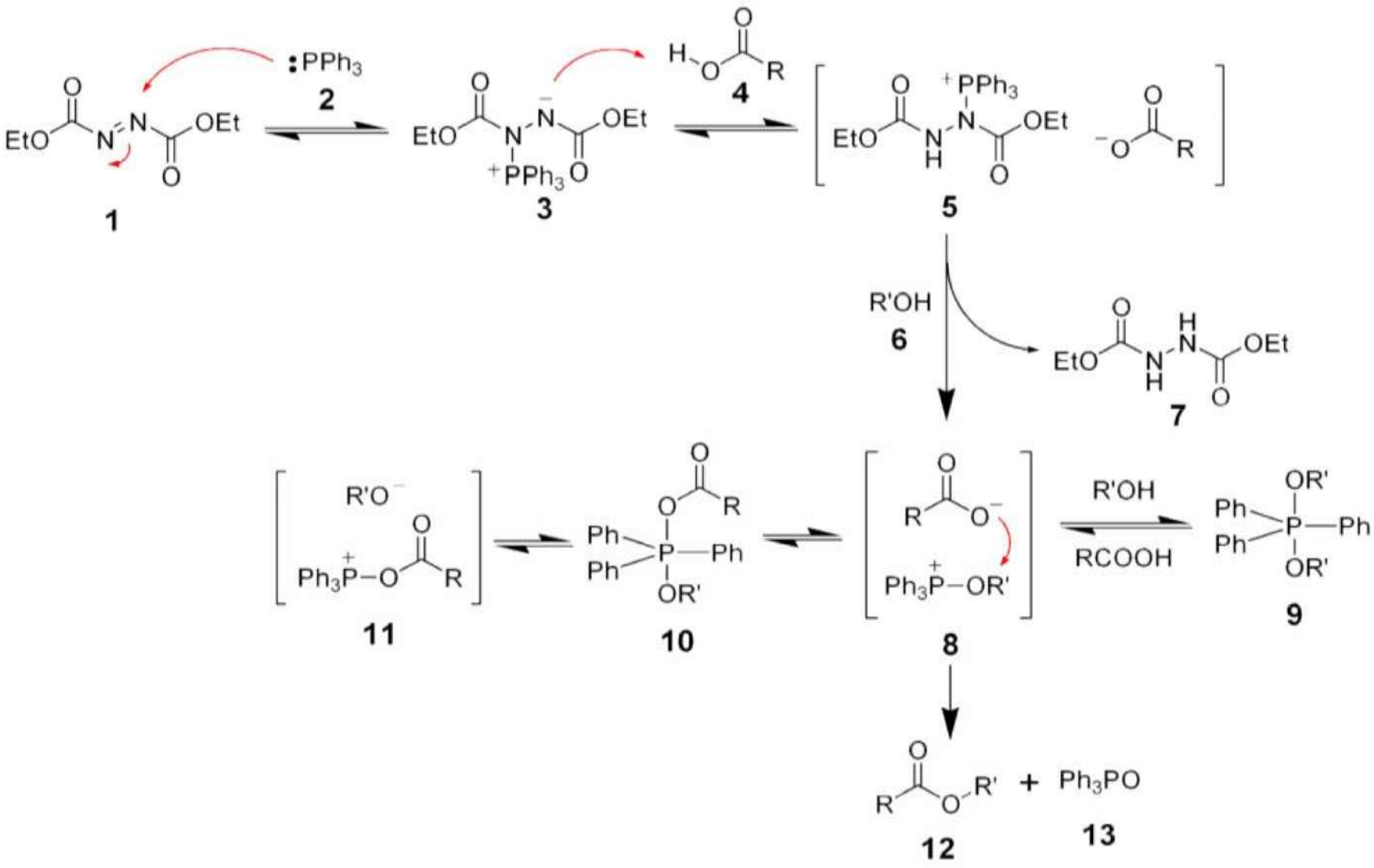
Mitsunobu reaction

- The **Mitsunobu reaction** is an organic reaction that converts an alcohol into a variety of functional groups, such as an ester, using triphenylphosphine and an azodicarboxylate such as diethyl azodicarboxylate (DEAD) or diisopropyl azodicarboxylate (DIAD).
- The alcohol undergoes an inversion of stereochemistry.
- It was discovered by Oyo Mitsunobu (1934–2003)

Mitsunobu reaction



Mitsunobu reaction Mechanism



Mitsunobu reaction mechanism

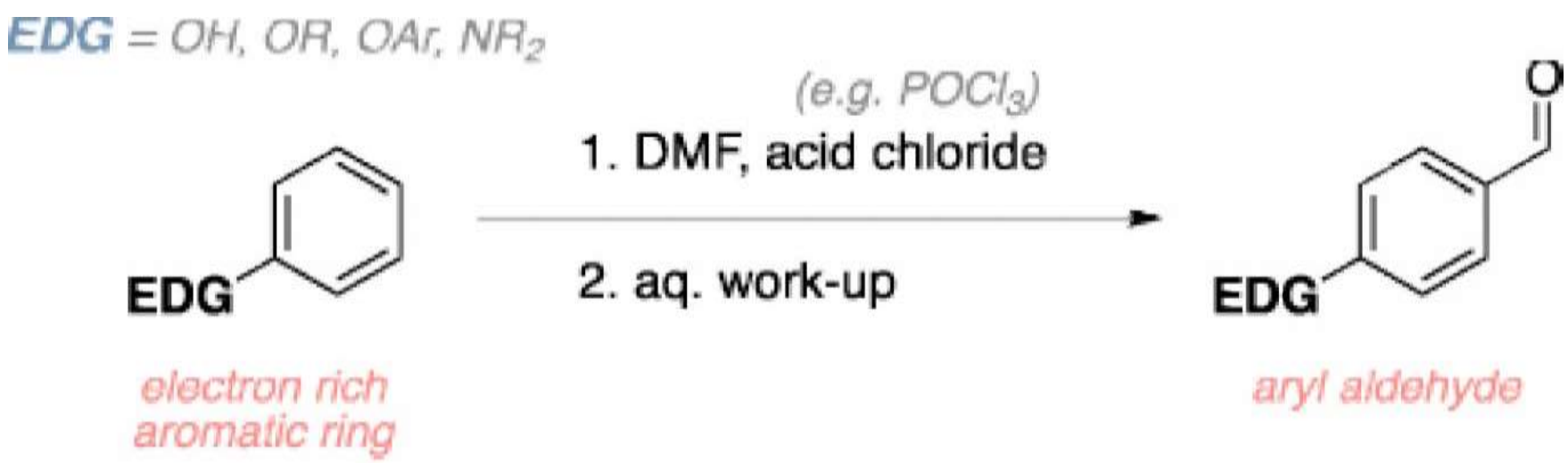
- Initially, the triphenyl phosphine (**2**) makes a nucleophilic attack upon diethyl azodicarboxylate (1)producing a betaine intermediate **3**, which deprotonates the carboxylic acid (**4**) to form the ion pair **5**.
- DEAD itself deprotonates the alcohol (**6**) forming an alkoxide that can form the key oxyphosphonium ion **8**. The ratio and interconversion of intermediates **8–11** depend on the carboxylic acid pKa and the solvent polarity.

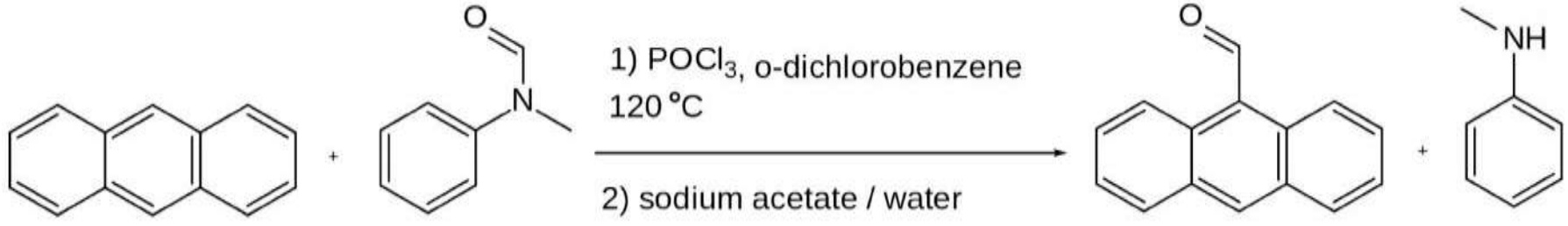
Mitsunobu reaction mechanism

- Although several phosphorus intermediates are present, the attack of the carboxylate anion upon intermediate **8** is the only productive pathway forming the desired product **12** and triphenylphosphine oxide (**13**).

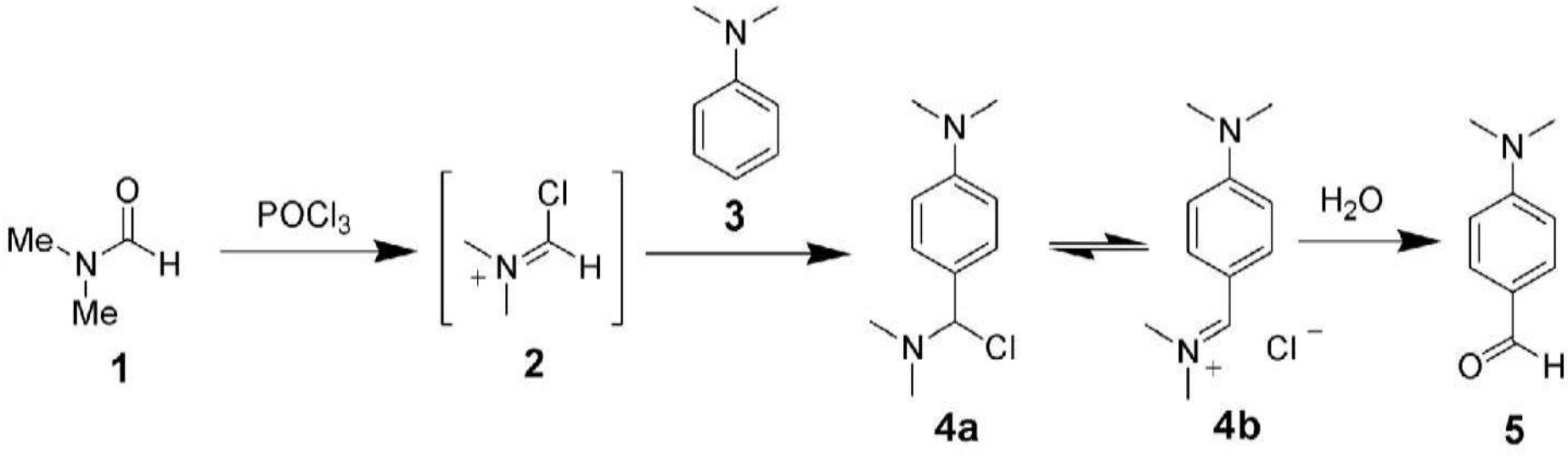
- The formation of the oxyphosphonium intermediate **8** is slow and facilitated by the alkoxide. Therefore, the overall rate of reaction is controlled by carboxylate basicity and solvation.

Vilsmeier-Haack reaction





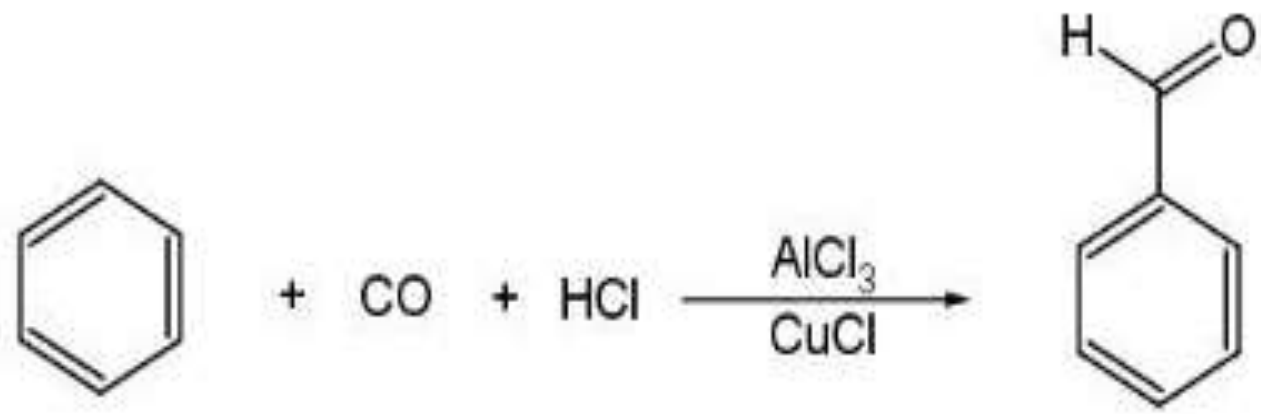
Vilsmeier-Haack reaction mechanism



The reaction of a substituted amide with phosphorus oxychloride gives a substituted chloroiminium ion (**2**), also called the Vilsmeier reagent. The initial product is an iminium ion (**4b**), which is hydrolyzed to the corresponding ketone or aldehyde during workup.

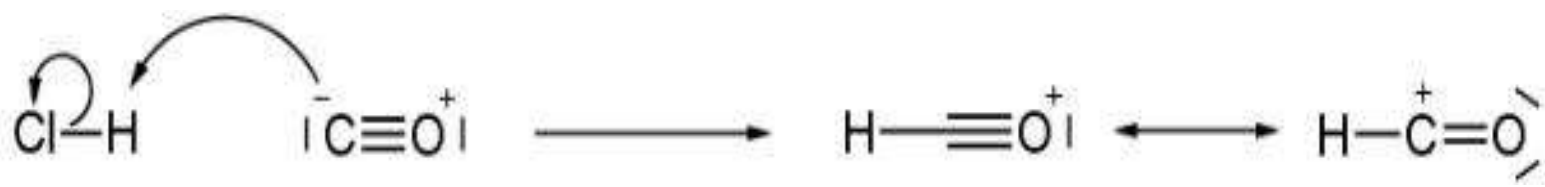
Gattermann – Koch Reaction

- Gattermann Koch Reaction Mechanism begins with the formation of the reactive species with the help of the acid. The overall aim of the reaction is to attach a formyl group (-CHO group) to an aromatic system. An example of the Gattermann – Koch reaction is given below.



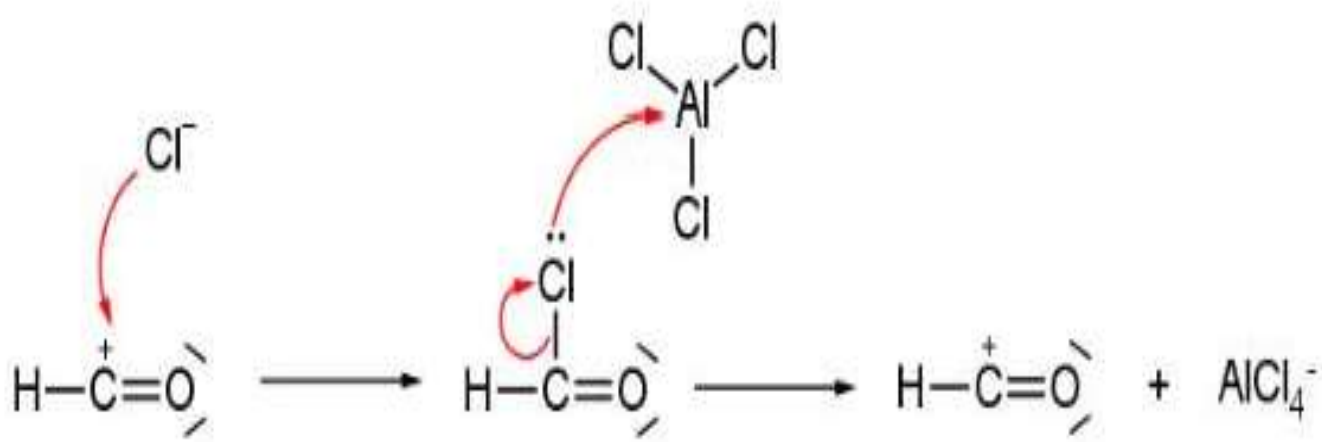
Gattermann – Koch Reaction Mechanism

- **Step 1**
- The first step of the Gattermann Koch reaction mechanism is the generation of the reactive species which can later be used to react on the aromatic ring. Since carbon monoxide acts as a lewis base, it can accept a proton from the hydrochloric acid.
- This results in a positively charged molecule which has different resonance structures. One such resonance structure displays a positive charge on the carbon, explaining the reactivity of the hybrid. This species can act as an electrophile while reacting with the aromatic ring. However, it is more likely to be the target of a nucleophilic attack from the chloride ion in the hydrochloric acid.



Gattermann – Koch Reaction Mechanism

Step 2- When a Lewis acid (aluminium chloride) is added, it easily removes a chloride ion from the species. The species now reverts back to the reactive formyl cation.



Gattermann – Koch Reaction Mechanism

Step 3

An electrophilic aromatic substitution occurs at the aromatic ring. The aromatic ring acts as a nucleophile and donates an electron pair to the formyl cation. The temporary loss of aromaticity is quickly solved by the expulsion of a proton.