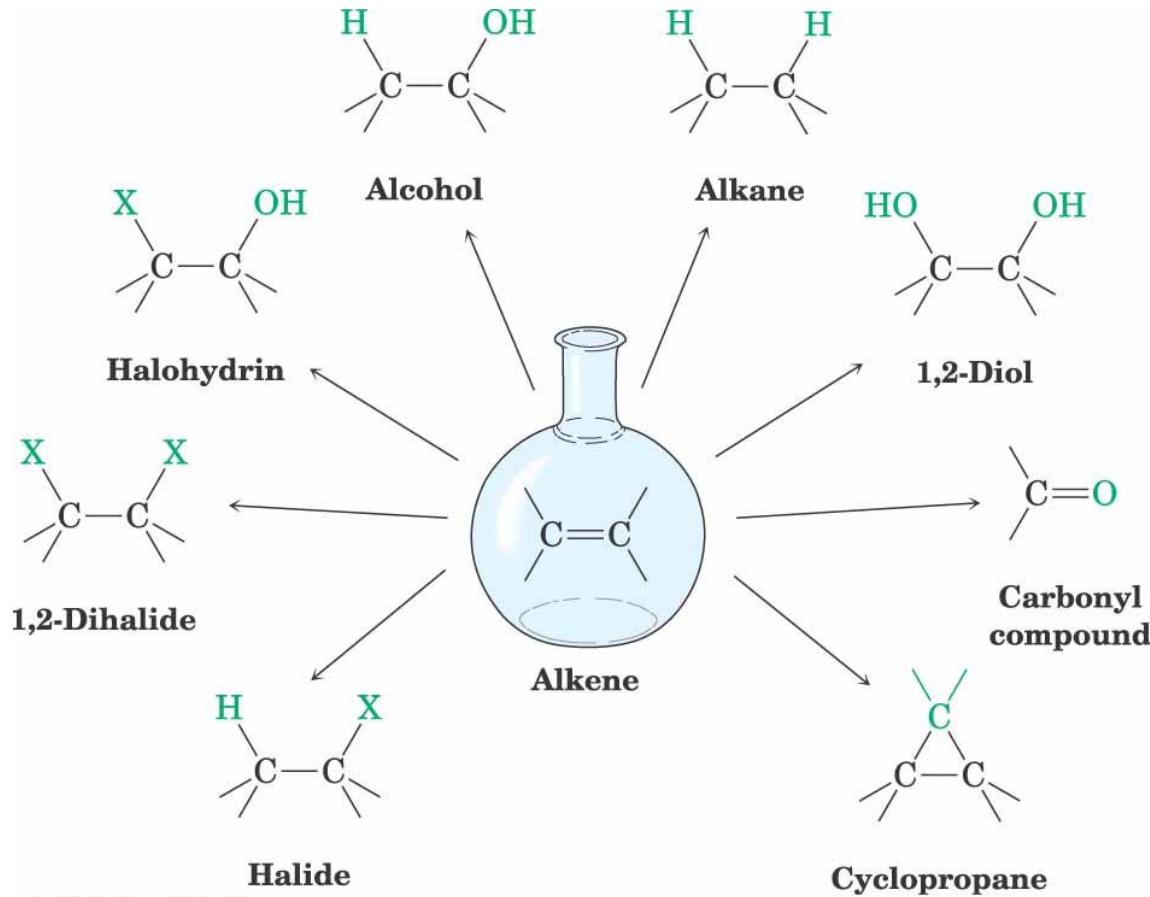


Chapter 6

Reactions of Alkenes

Stereochemistry of Addition Reactions



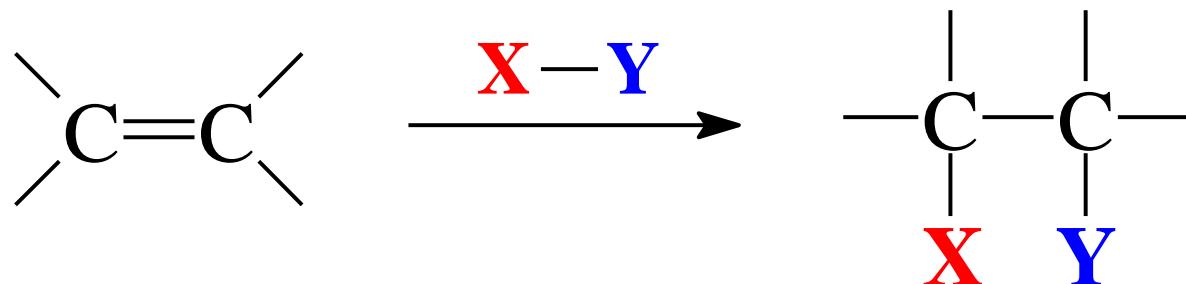
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Chapter Objectives

- Understand the concept of electrophilic addition reactions and mechanism
- Understand heterolytic & homolytic cleavage of bonds.
- Know the order of carbocation stability, and be able to explain the order, using different explanations for the stabilities, e.g. hyperconjugation, inductive electron donation.
- Understand why & when carbocation rearrangements will occur.
- Understand regioselectivity.
- Understand, and use, Markovnikov's Rule.
- Understand, and be able to explain, the order of stabilities of various alkenes.
- Know the reaction products and mechanisms when pi bonds react with: HX; $\text{X}_2/\text{CH}_2\text{Cl}_2$; $\text{H}_2\text{O}/\text{H}^+$, $\text{CH}_3\text{OH}/\text{H}^+$, $\text{Hg}(\text{OAc})_2$, H_2O , THF followed by NaBH_4 ; BH_3/THF followed by $\text{H}_2\text{O}_2/\text{HO}^-$; Pd/C or Pt/C or Ni with H_2 ; peroxyacids & epoxides .

Electrophilic Addition Reaction

- Alkenes typically react by an **ELECTROPHILIC ADDITION** mechanism



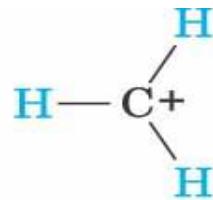
- Alkene π bond breaks, **X-Y** σ bond breaks, two new σ bonds are formed
- Sp^2 carbon in reactant become sp^3 carbons in product
- X - Y** can represent **H-Br**, **H-Cl**, **H-H**, **H-OH** (lots of others)

Reaction Of Propene With HBr

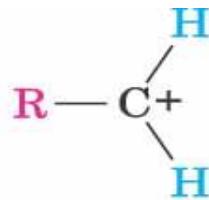
- In practice 2-bromopropane is formed **quantitatively** (100%) - **NO 1-bromopropane**
- This reaction is _____ - two isomeric products possible but **ONLY ONE OBSERVED (or formed in higher ratio compared to other)**
- Why is this the case - **why not a 50%:50% mixture of the two products?**
- Look again at mechanism of reaction

Reaction of Propylene with HBr

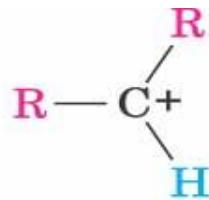
Stability:



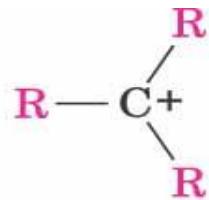
Methyl



Primary (1°)



Secondary (2°)



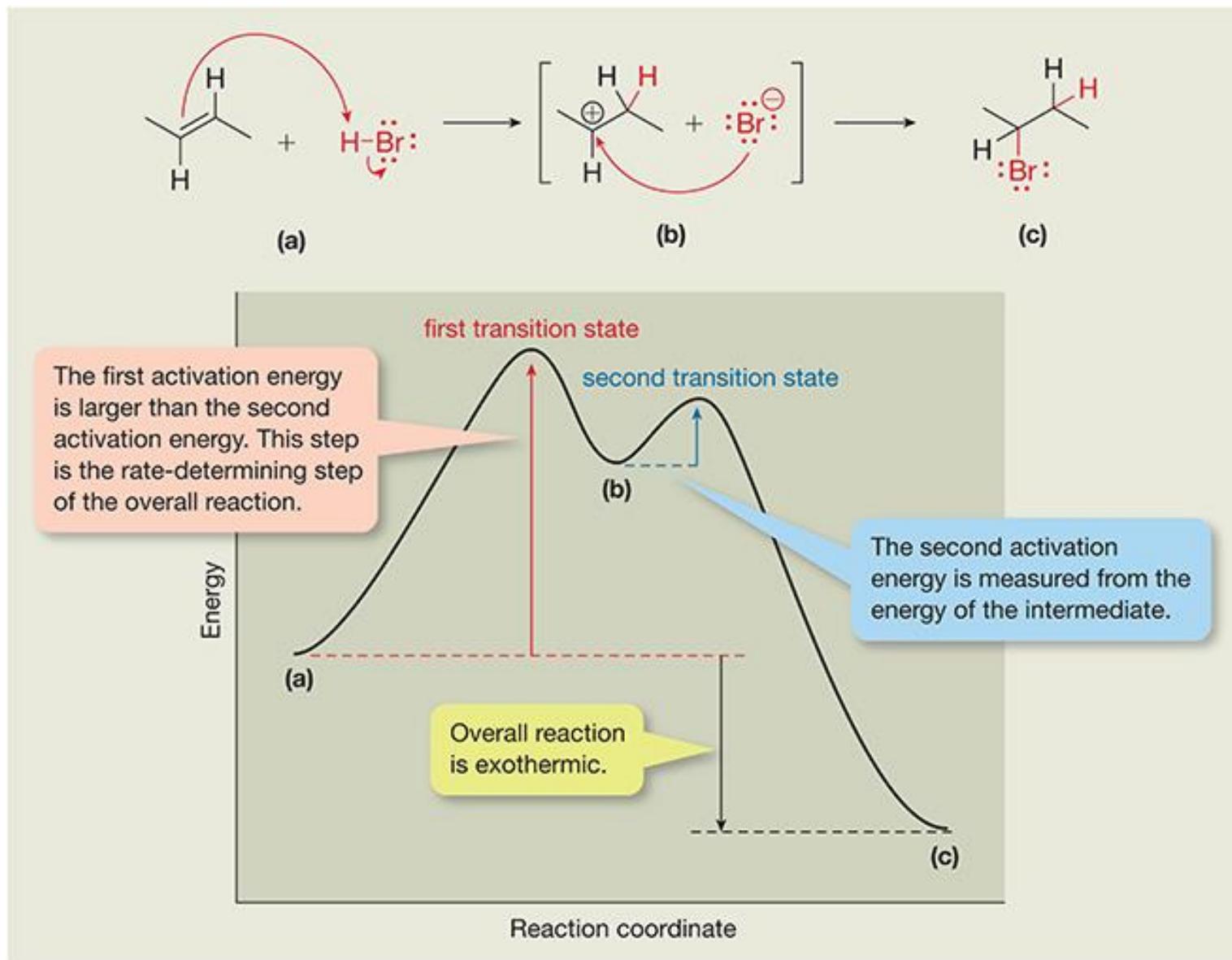
Tertiary (3°)

Less stable

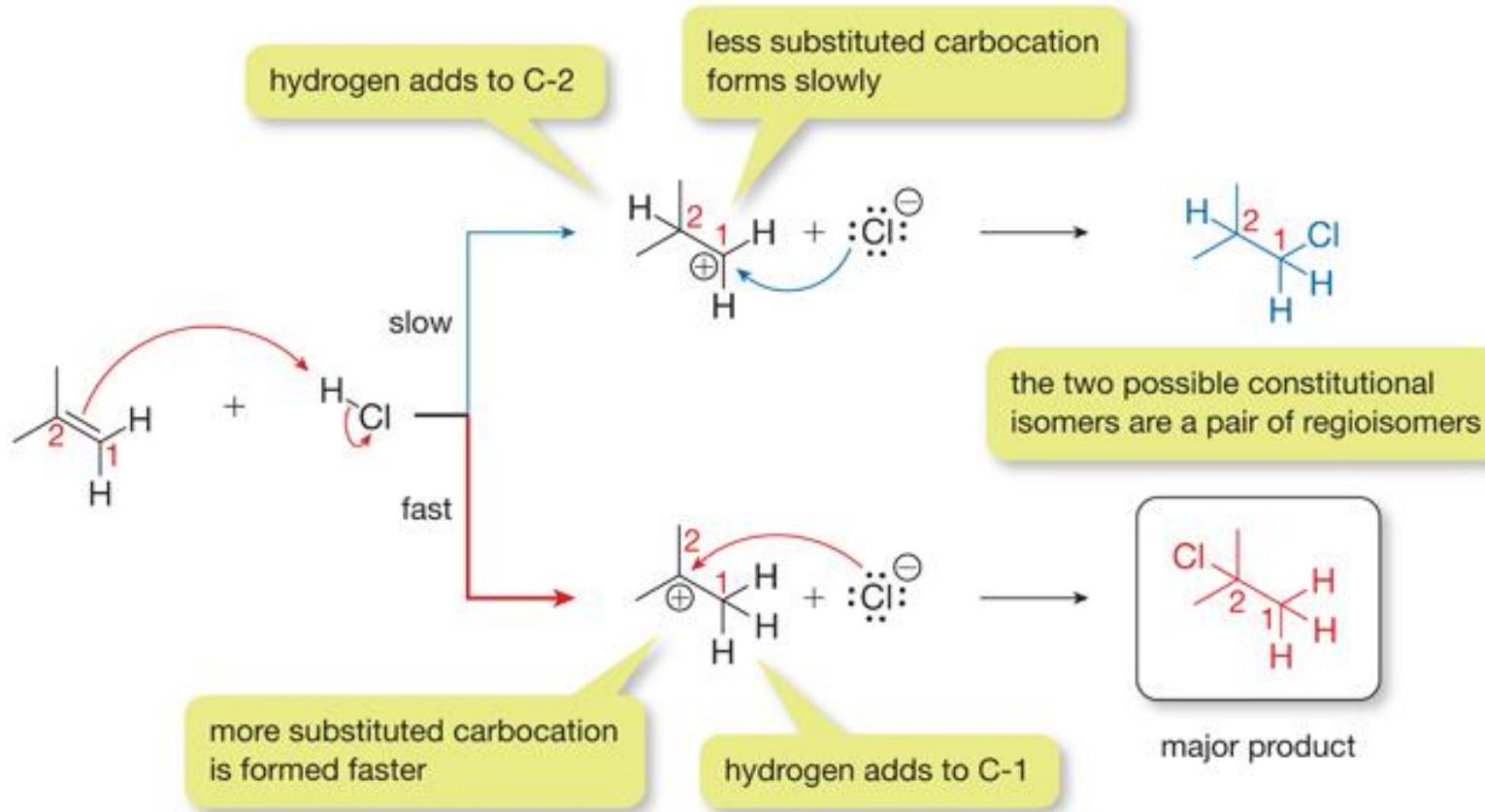
Stability

More stable

Carbocation formation is the rate-determining step.



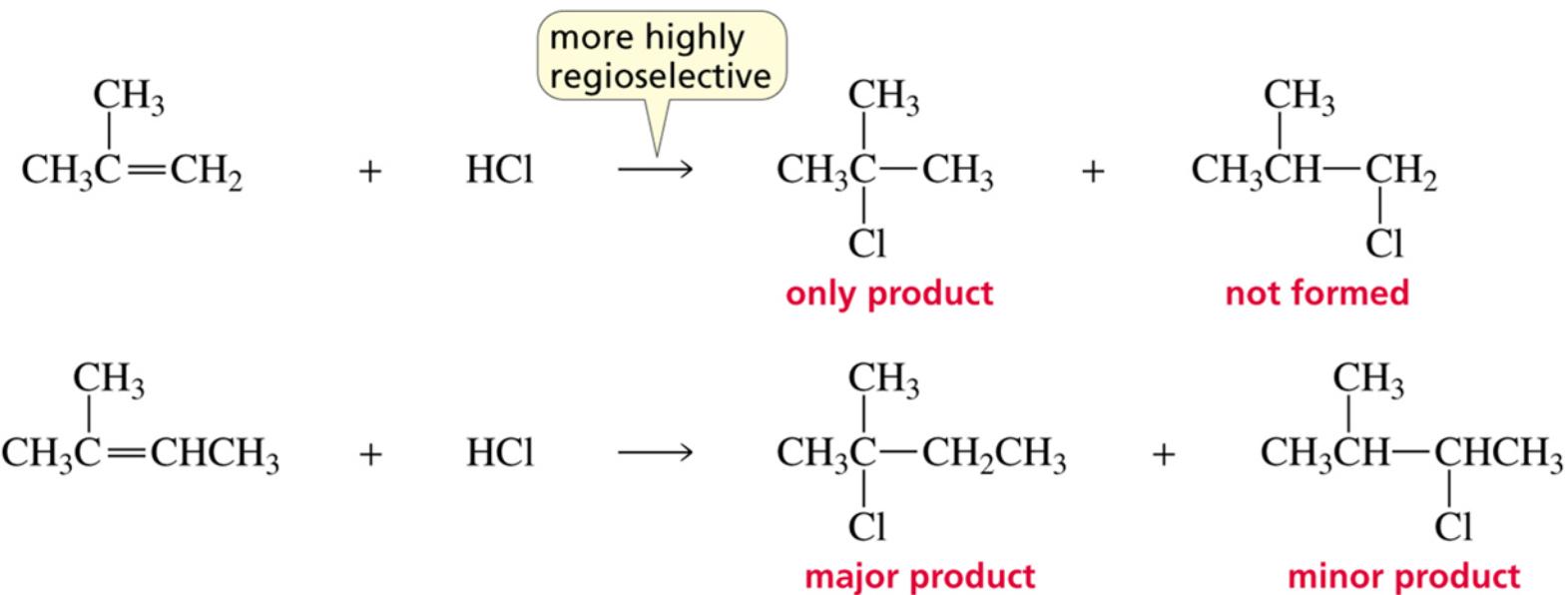
Regioselectivity of electrophilic addition is controlled by carbocation stability.



Regioselective Reaction

A regioselective reaction is a reaction that forms more of one constitutional isomer than of another.

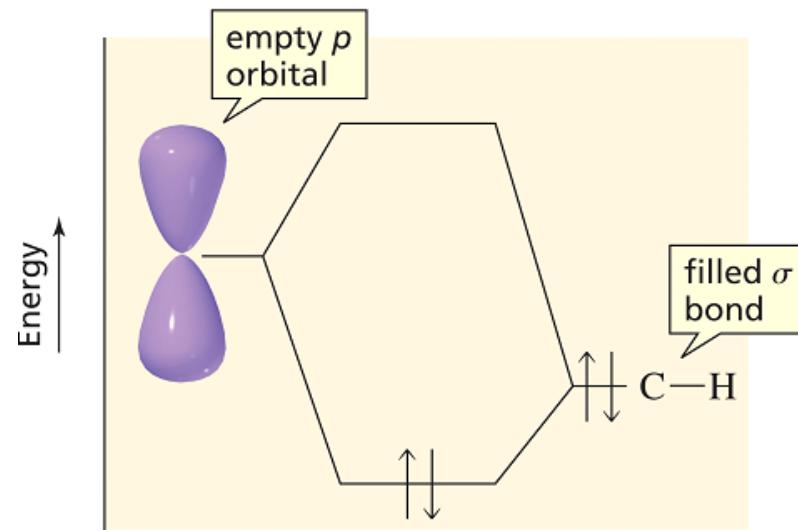
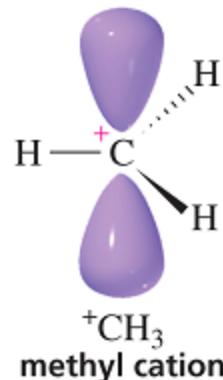
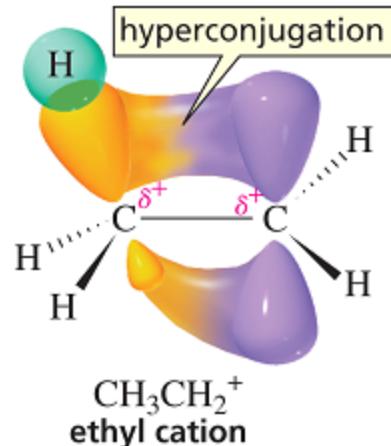
The reaction can be: moderately regioselective, highly regioselective, completely regioselective



Carbocation Stability (1)

More substituted carbocations are more stable (lower energy) due to:

Hyperconjugation – a stabilizing interaction between a vacant p orbital on C⁺ and a filled sp³ hybrid on the adjacent carbon.

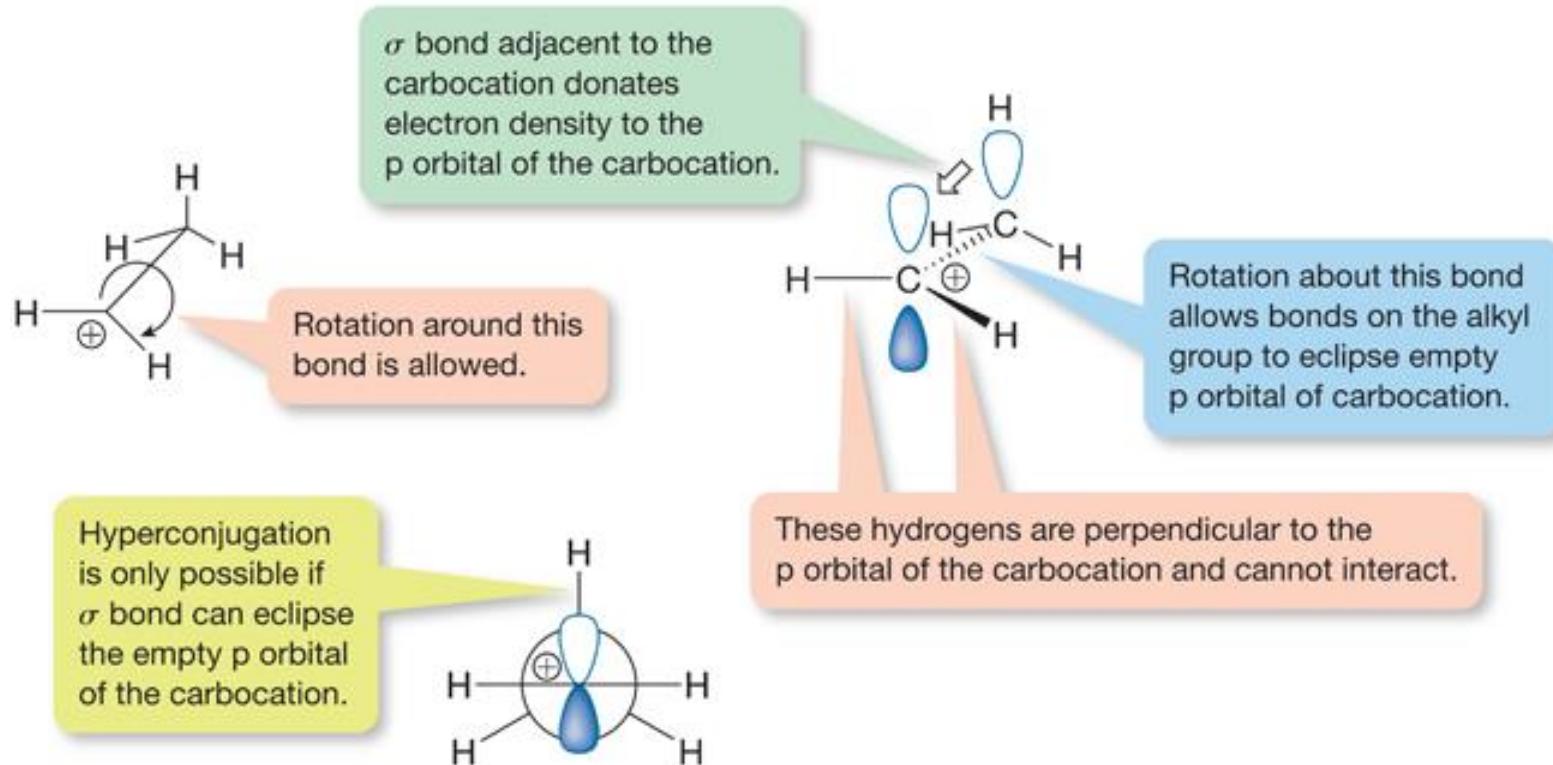


Alkyl groups decrease the concentration of positive charge in the carbocation

Stabilization of carbocations by hyperconjugation

Hyperconjugation:

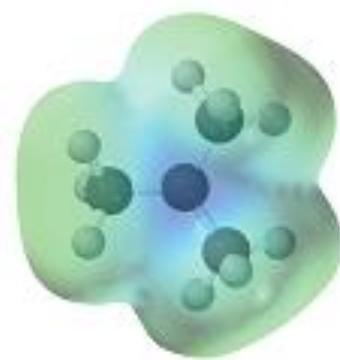
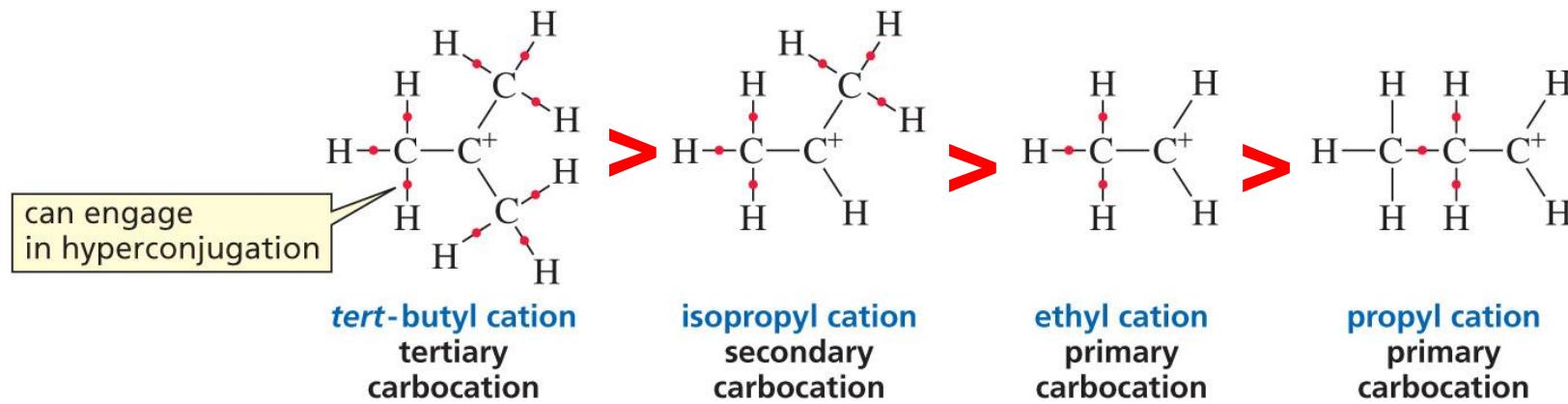
- electron donation from a σ bond



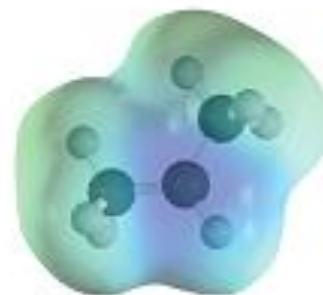
Carbocation Stability (2)

Inductive effects – alkyl groups can donate electron density towards C+, stabilizing the positive charge.

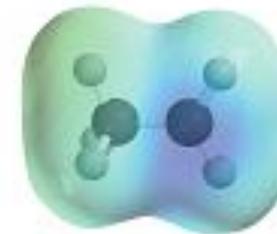
Stability:



electrostatic potential map for the tert-butyl cation



electrostatic potential map for the isopropyl cation



electrostatic potential map for the ethyl cation



electrostatic potential map for the methyl cation

Markovnikov's Rule

"in the electrophilic addition of H-X to an alkene, H attaches to the carbon which has the most hydrogens" ("them that has, gets")

OR

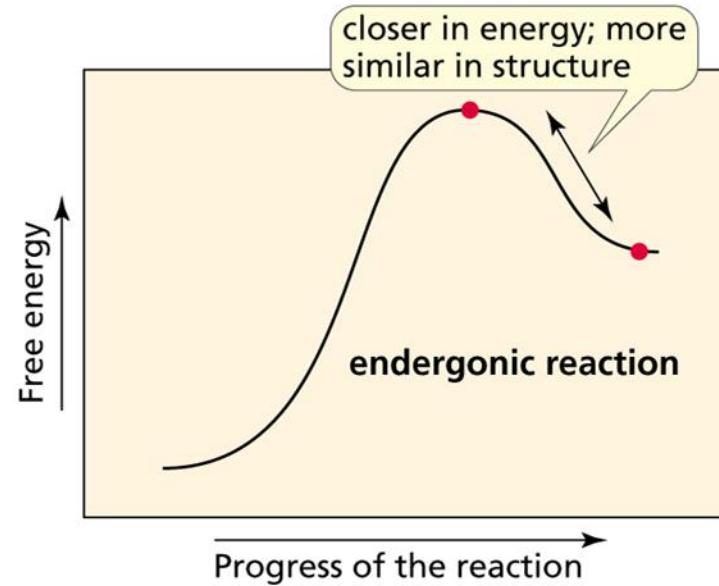
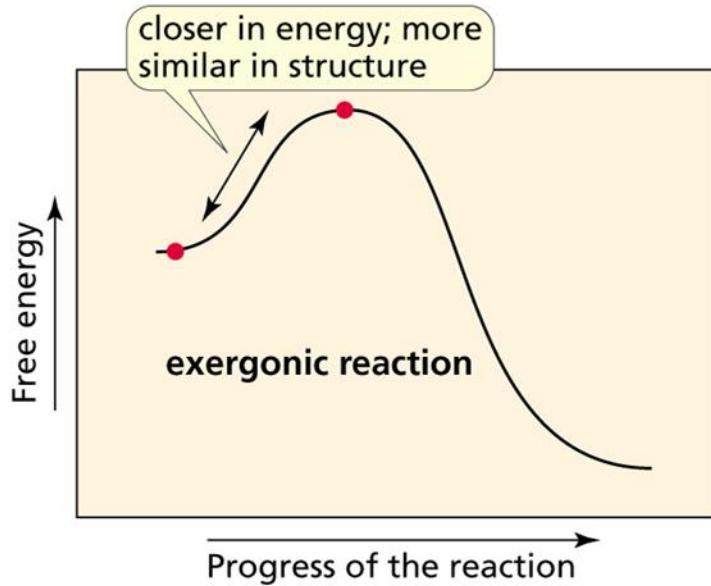
"the H attaches in a manner to form the **more stable carbocation intermediate**"

OR

"the electrophile adds to the sp^2 carbon that is bonded to the greater number of hydrogens"

The Hammond Postulate

The transition state resembles what it is closer to in energy.

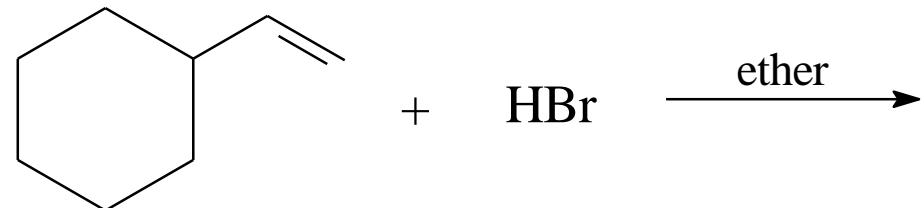


exergonic reaction: The transition state resembles the reactants.

endergonic reaction: The transition state resembles the products.

Evidence For Carbocations

- Why do we propose **carbocations** as intermediates?
- “Unusual” products sometimes occur



3,3-dimethyl-1-butene

- A “carbocation rearrangement” has occurred

Evidence For Carbocations (1)

1)

- 2° carbocation rearranges to 3° via **1,2-hydride shift** (H migrates with electron pair)

Evidence For Carbocations (2)

2)

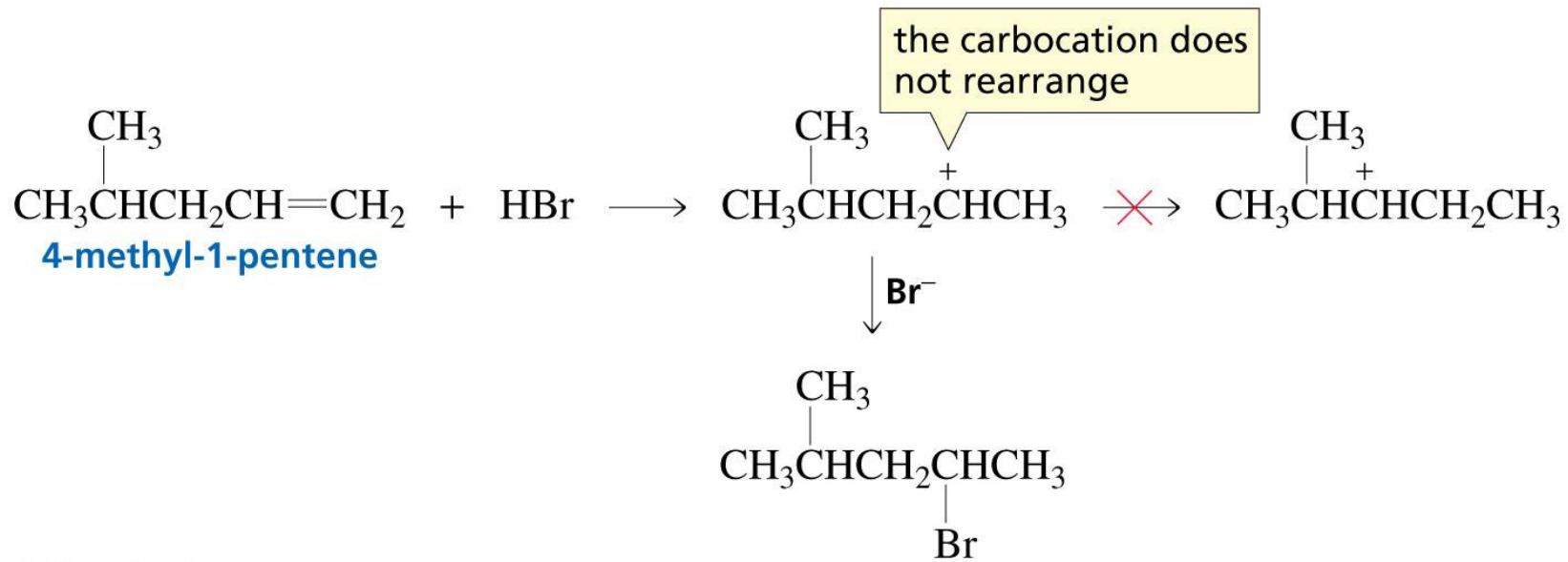
3,3-dimethyl-1-butene

- Another carbocation rearrangement has taken place (this time a **1,2-methyl shift** - CH_3 migrates with electron pair) ¹⁶

Evidence For Carbocations (3)

3) Ring expansion via carbocation rearrangement:

A carbocation does not always rearrange:

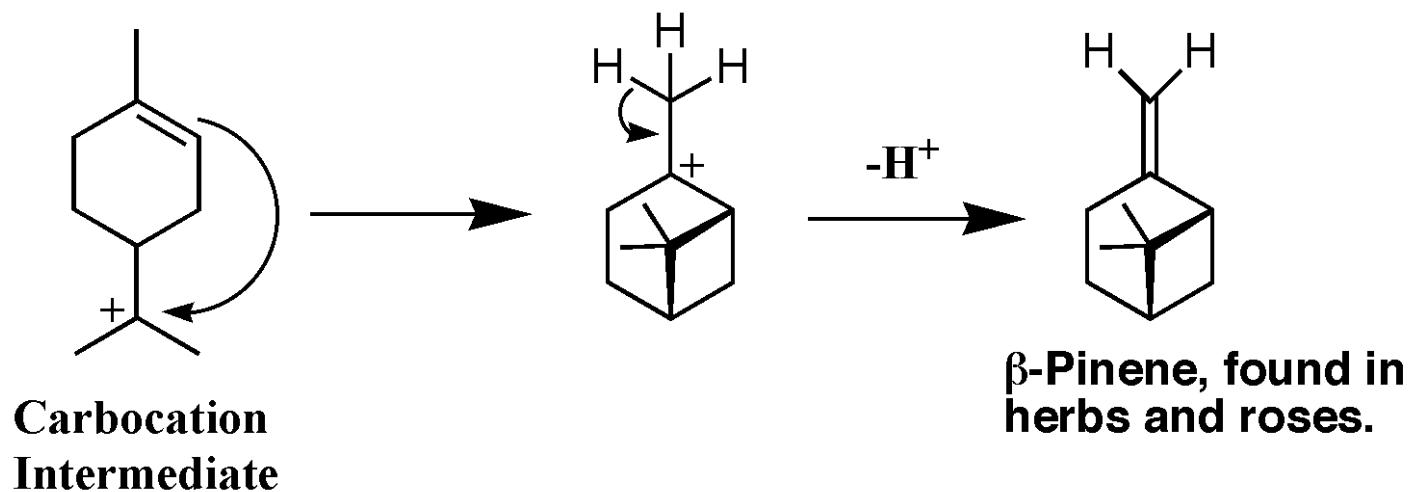


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Not Regioselective

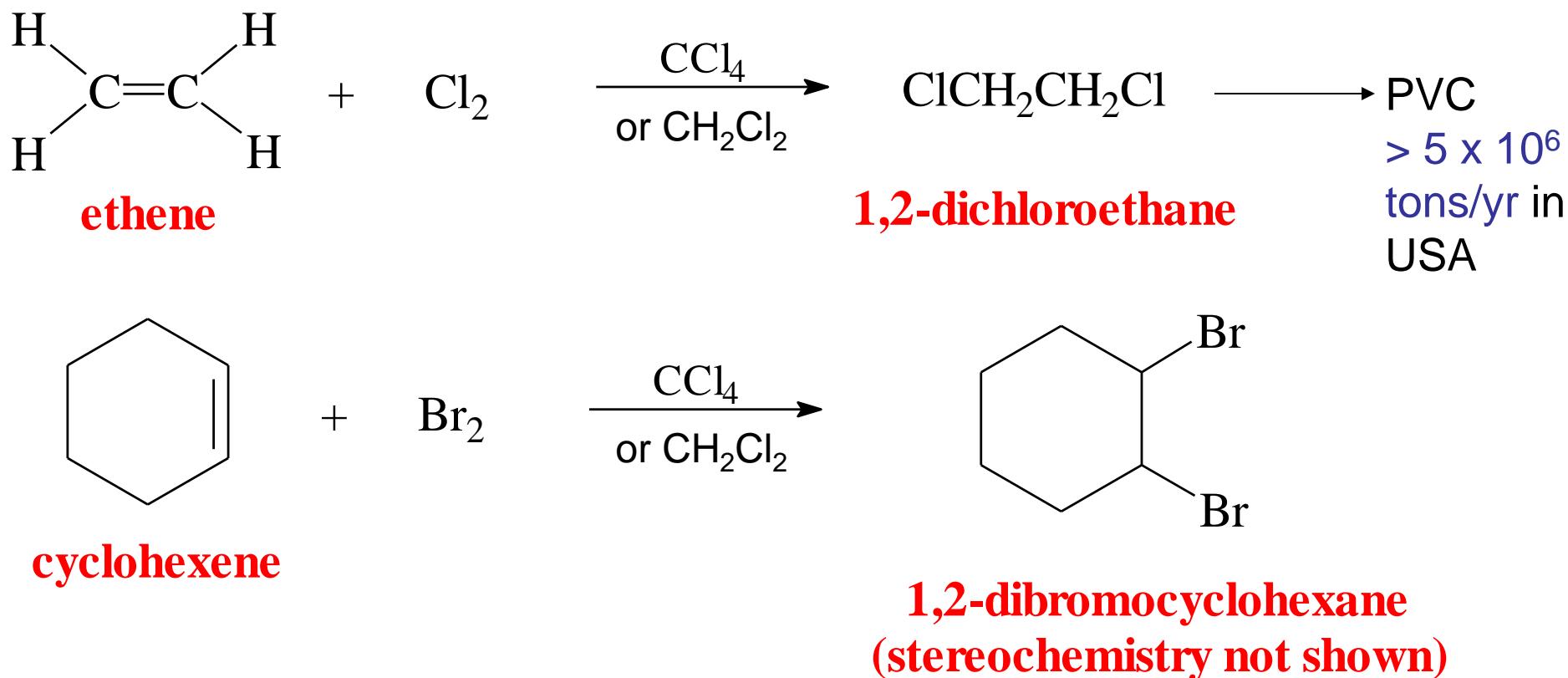
Why? Because rearrangement has not resulted in a more stable carbocation.

Carbocation Reactions in Nature



Halogenation (1)

- $X-Y = Br-Br$ or $Cl-Cl$



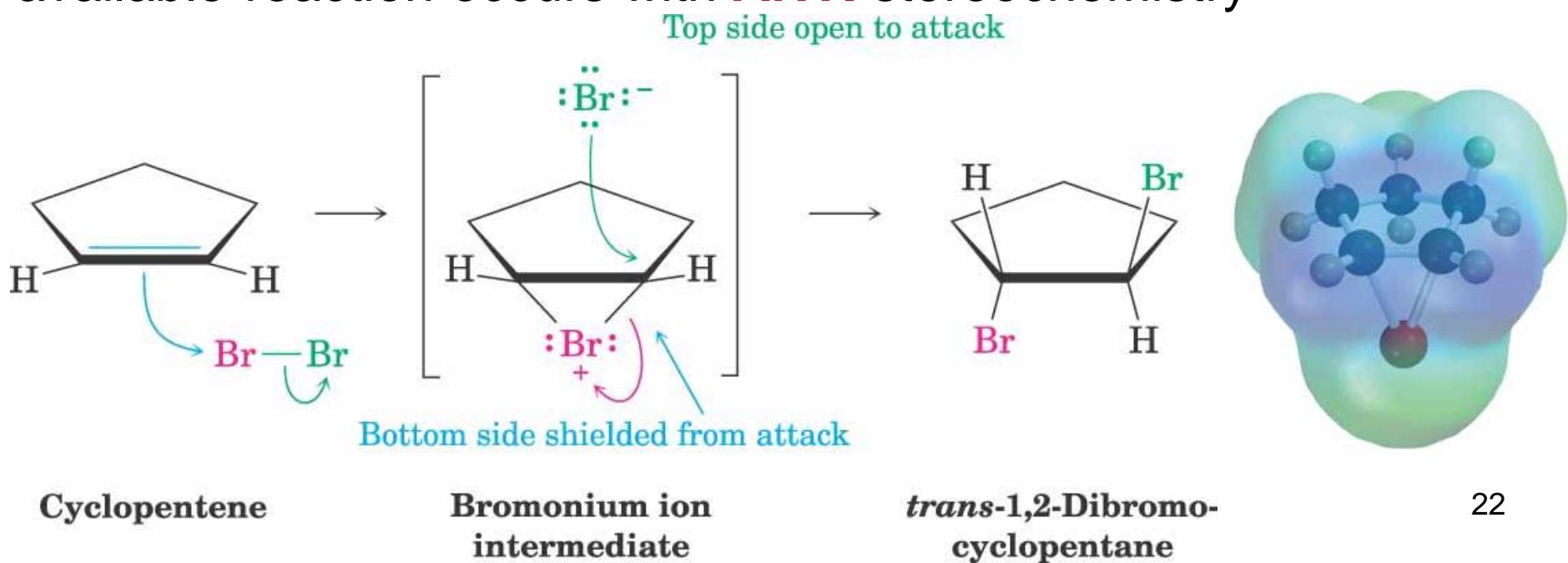
- What is a possible mechanism for the addition? ²⁰

Halogenation (2)

- Possible mechanism (based on H-X addition):
- By this mechanism should see a 50:50 mixture of *cis* and *trans* 1,2-dibromocyclohexane
- In reality - only the *trans* isomer is observed

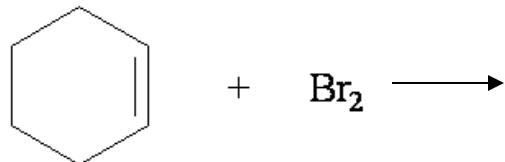
Halogenation: Addition of X_2

Bromonium ion “shields” bottom face of ring. Only the top face is available-reaction occurs with **ANTI** stereochemistry



Halohydrin Formation (1)

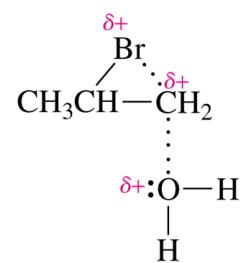
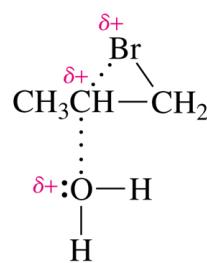
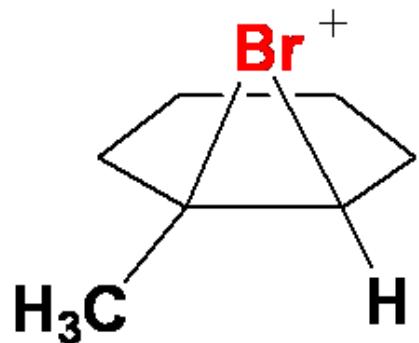
- “**Halohydrin**” - a molecule containing a hydroxy group and a halogen
- Mechanism of formation the same as halogenation, **except** attacking nucleophile is **H₂O**



cyclohexene

- **ANTI ADDITION** again apparent
- Note that water has replaced CCl₄ or CH₂Cl₂ as the reaction solvent and that it is participating as a reactant

Halohydrin Mechanism:



more stable transition state

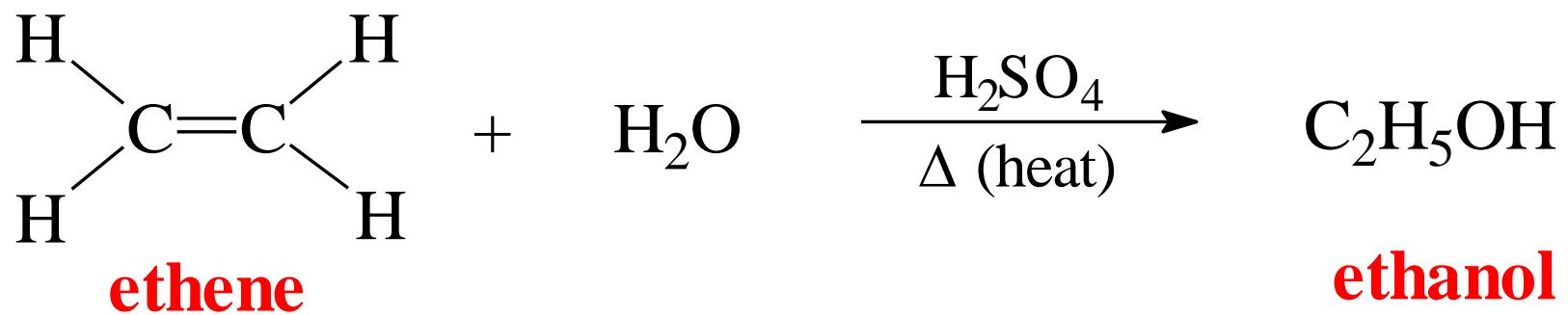
less stable transition state

The electrophile (X_2) adds to the sp^2 carbon bonded to the most hydrogens (Markovnikov rule)

Br ends up on sp^2 C atom with greater number of H atoms...WHY??

Industrial Hydration (1)

- “Hydration” - addition of **water**, forming an **alcohol** product
- Industrially



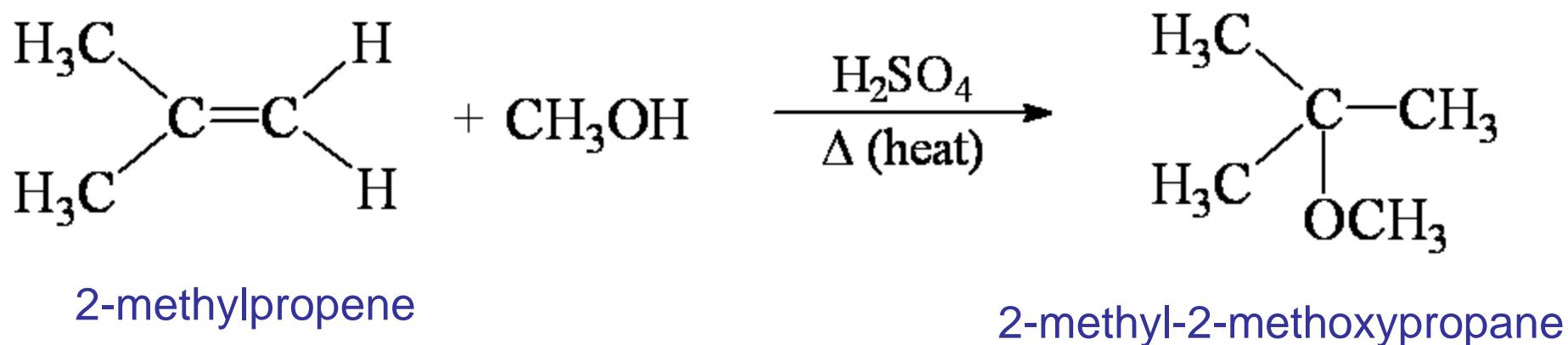
- Mechanism involves a carbocation intermediate, followed by nucleophilic attack of H₂O

Industrial Hydration (2)

- Note that acid is **catalytic** (regenerated at end of reaction)

Alcohol Addition to Alkene

- If use alcohol as nucleophile, product of reaction is ether-mechanism same as hydration

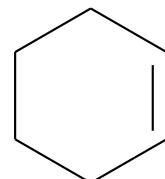


(write out mechanism for practice on your own)

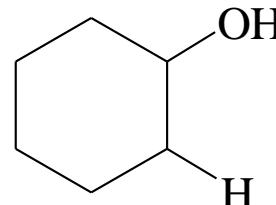
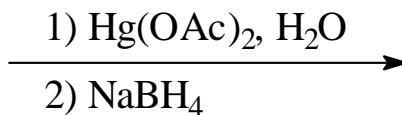
- Reaction proceeds via more stable tertiary carbocation, **Markovnikov's rule** is obeyed

Hydration By Oxymercuration (1)

- Industrial method not used in laboratory due to high temperatures needed
- Advantages:** a) no acidic conditions to damage other parts of molecule; b) no carbocation rearrangements seen

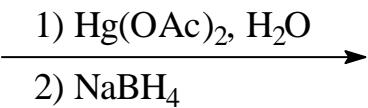
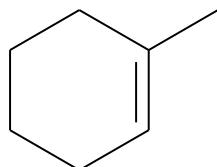


cyclohexene

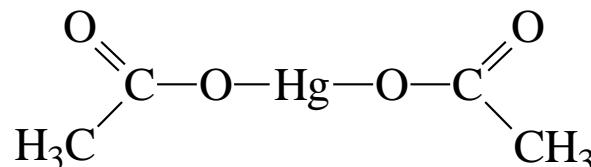


cyclohexanol

- Hg(OAc)_2 = mercury (II) diacetate

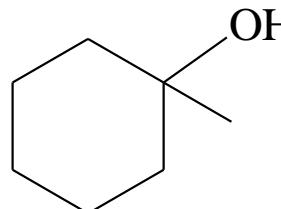


???

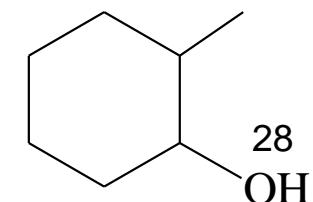


1-methylcyclohexene

- Might expect to form a mixture of:



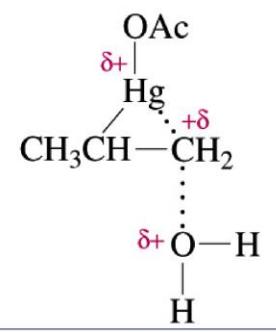
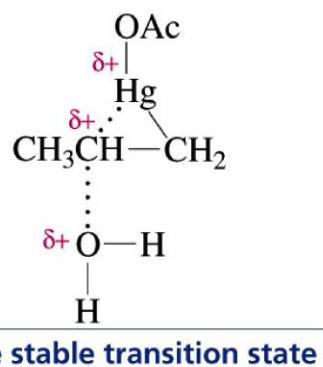
+



²⁸
OH

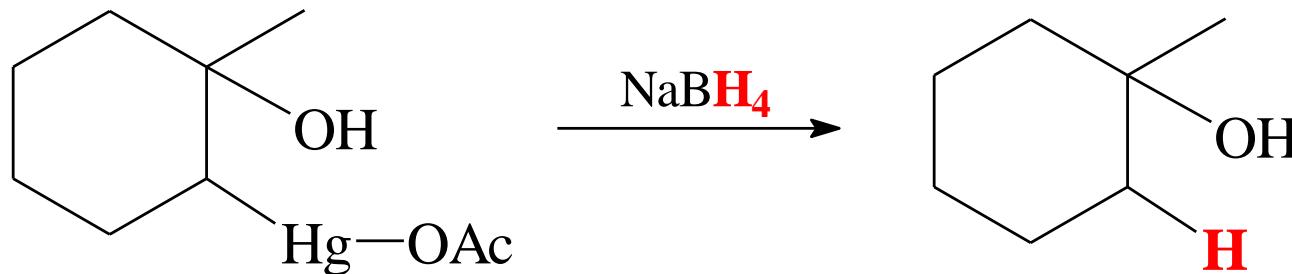
Hydration By Oxymercuration (2)

- Mechanism



Hydration By Oxymercuration (3)

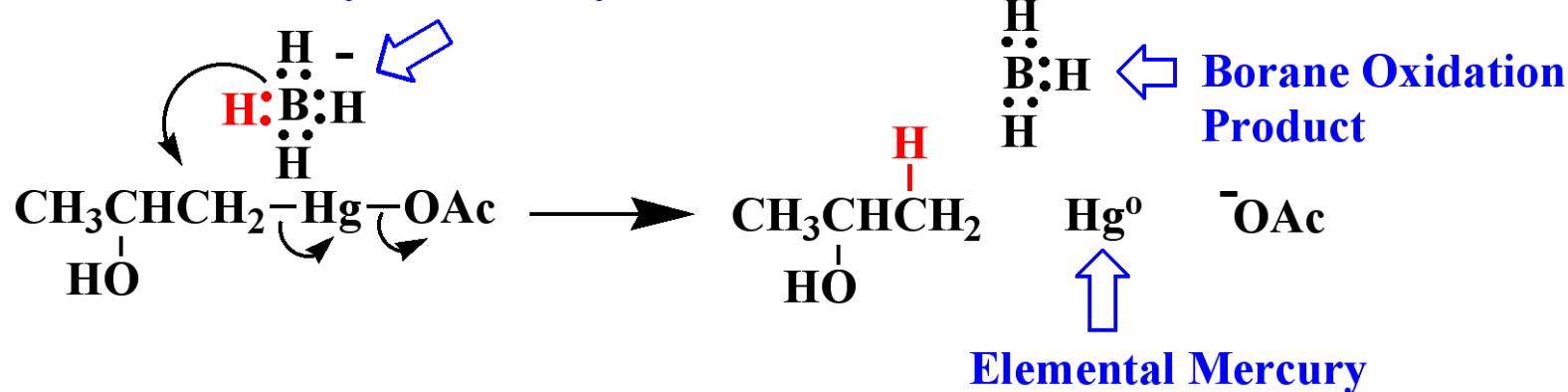
- Organomercury compound can be isolated but is normally reacted with NaBH_4



stable organomercury compound

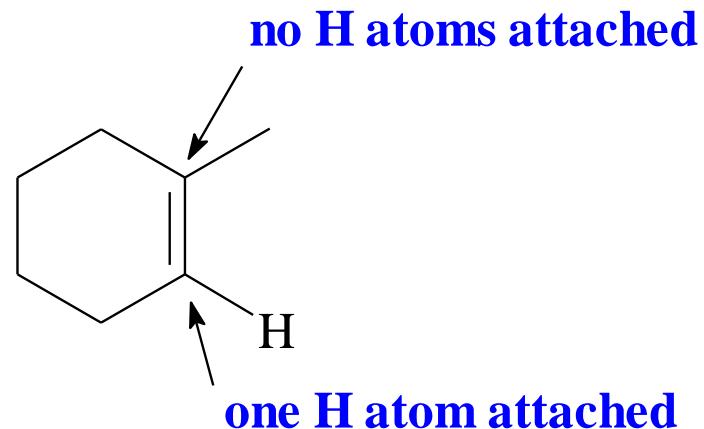
Reduction Mechanism:

Borohydride is a hydride donor:



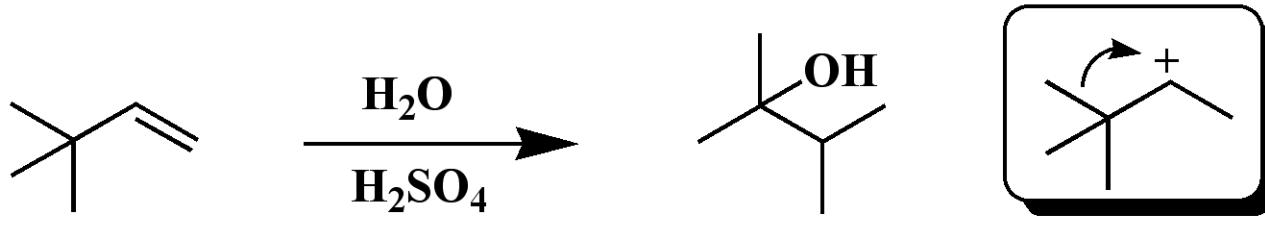
Hydration By Oxymercuration (4)

- Why termed Markovnikov addition?
- **H** has added to the (alkene) carbon that has the **most** hydrogens attached to it (“**them that has, gets**”)
- **OH** adds to the (alkene) carbon that has the **least** hydrogens attached to it

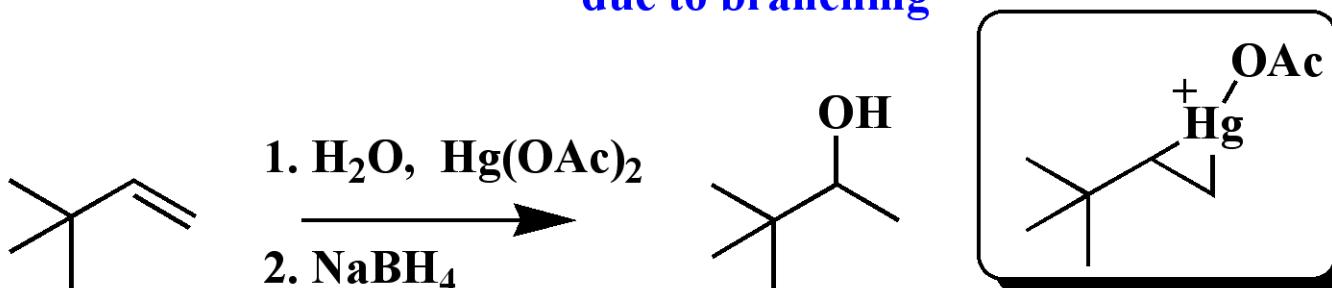


The Oxymercuration-Demercuration Reaction

A means of avoiding rearrangements
AND
getting Markovnikov product



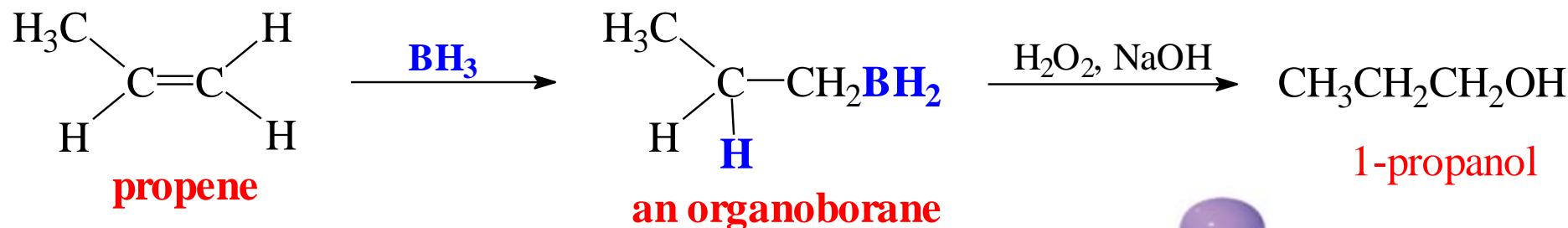
Rearranged product
due to branching



No rearrangement due to cyclic
mercurium ion intermediate.

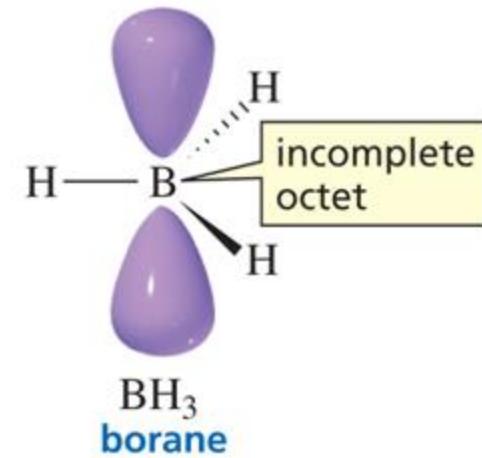
Hydration By Hydroboration (1)

- Formally the **Anti-Markovnikov** addition of water



Hydroboration is a two-step process:

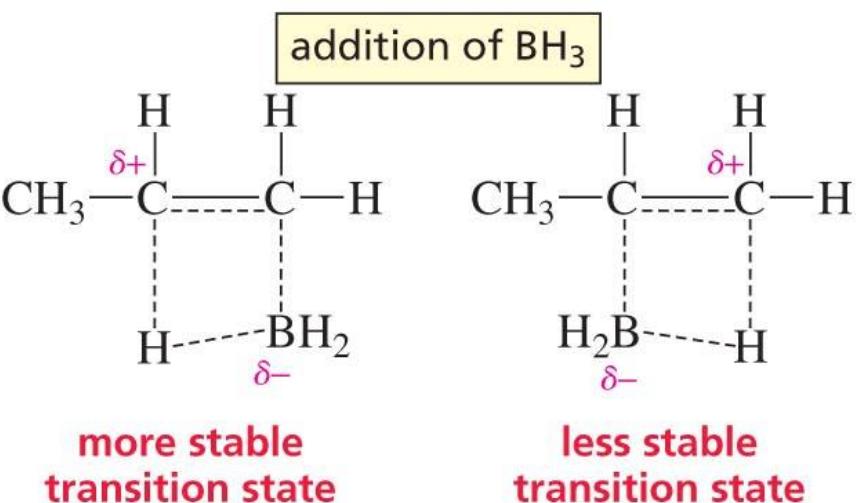
- Trialkylborane formation
- Hydroperoxide and base treatment



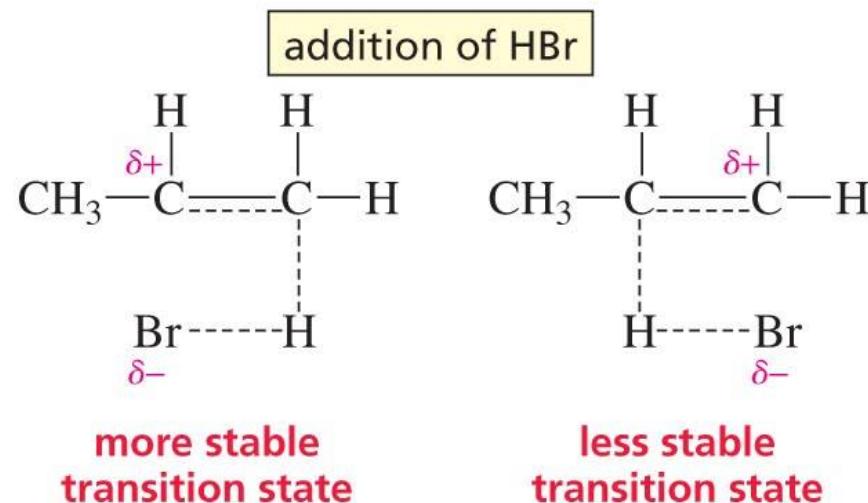
- BH_3 = borane, 6 valence electrons, very reactive, electrophile
- Overall **H** has added to the C with the **least** H attached

Hydroboration Mechanism

Regioselectivity due to four membered cyclic transition state and steric interaction between borane and the alkene substituents :



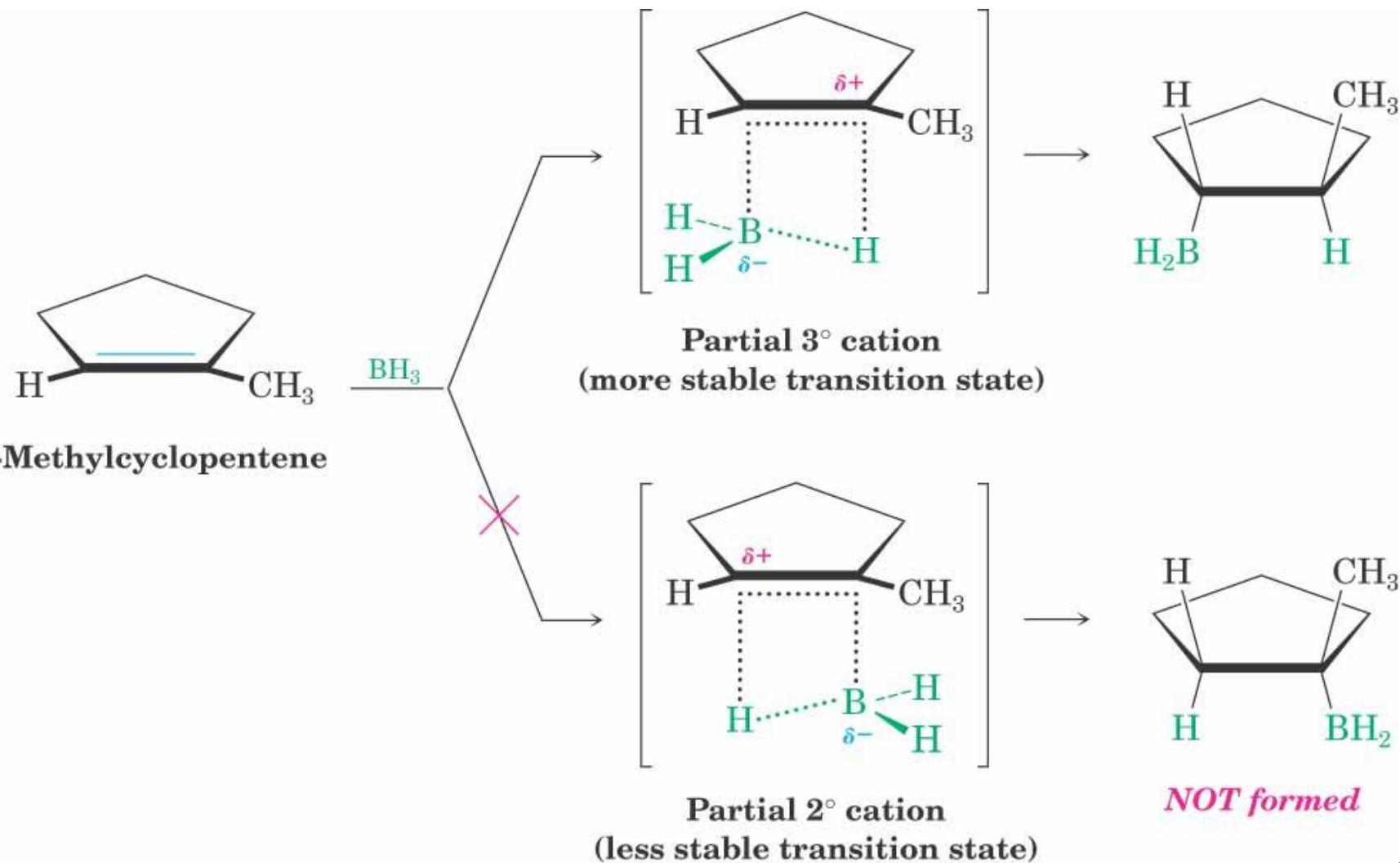
VS



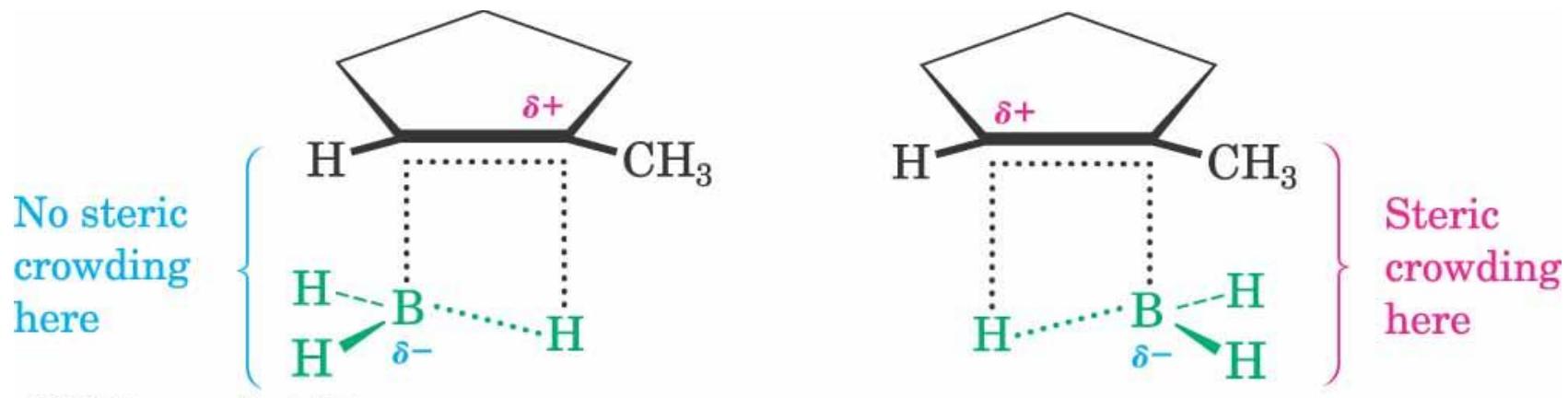
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Transition state is **sterically** and **electronically** more favourable for anti-Markovnikov addition 34

Hydroboration Mechanism



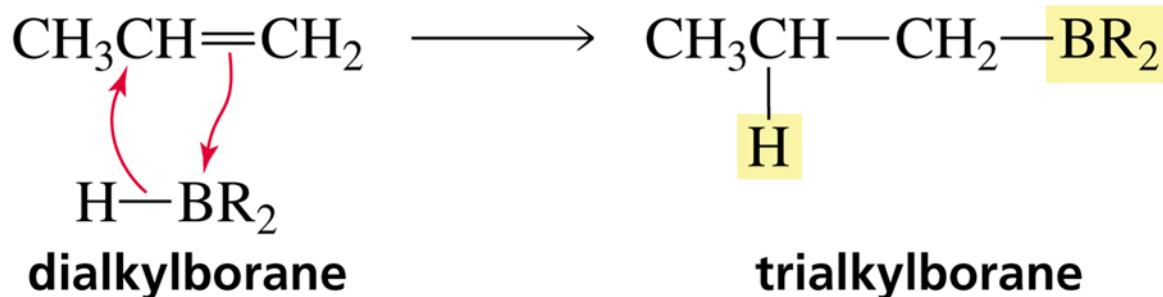
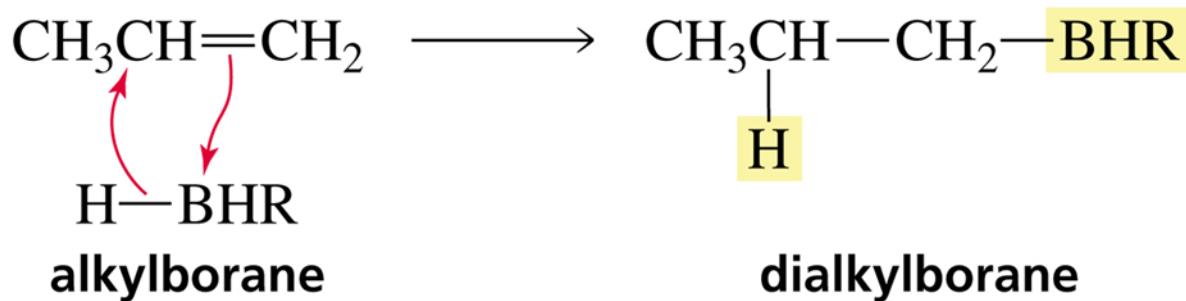
Hydroboration Mechanism



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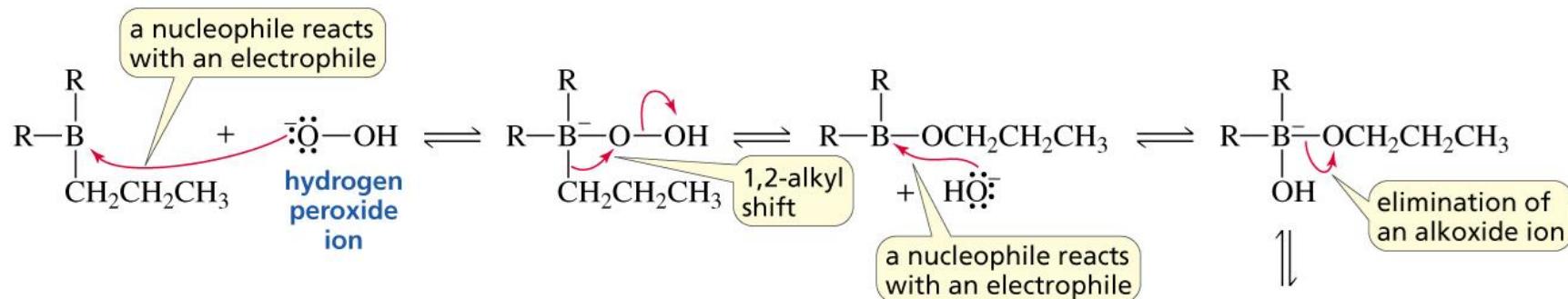
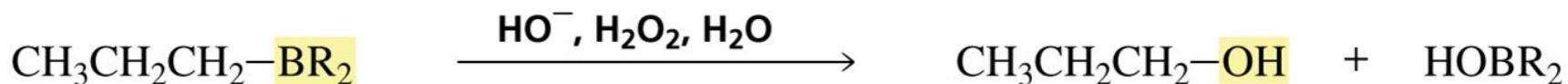
- In transition state, new C-B and C-H bonds form on the **SAME** face at the **SAME** time (**SYN** addition)
- Why anti-Markovnikov addition? - reaction proceeds via lower energy (more stable) transition state
- Transition state is **sterically** and **electronically** more favourable for anti-Markovnikov addition

Borane Has Three Potential Hydride Ions, so a Dialkylborane and a Trialkylborane Can Be Formed

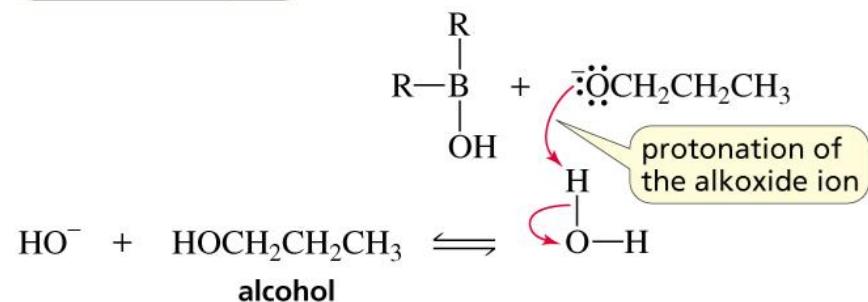


Hydroboration is Followed by Oxidation

In the oxidation reaction, OH replaces BR_2

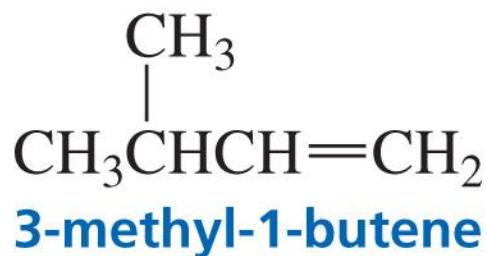


For reference ONLY; *DON'T NEED
TO KNOW OXIDATION
MECHANISM*

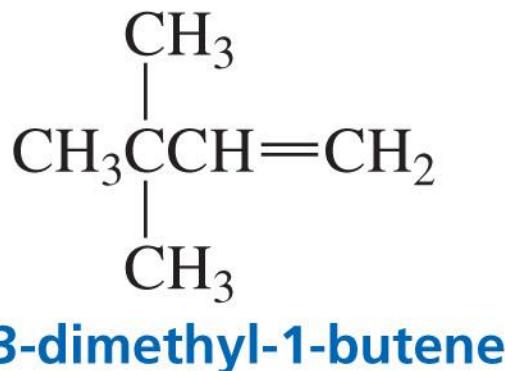


It is an oxidation reaction because the number of C—O bonds increases.

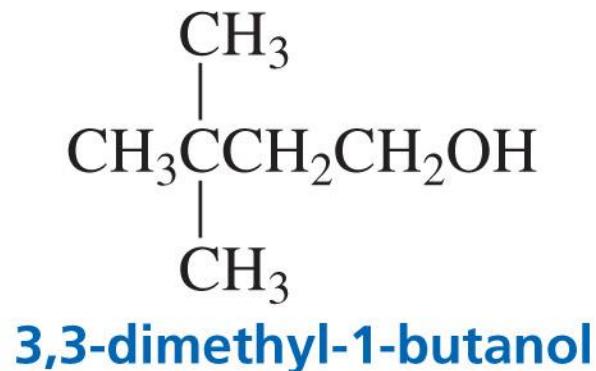
No Carbocation Rearrangements



$\xrightarrow{\begin{array}{l} \text{1. BH}_3/\text{THF} \\ \text{2. HO}^-, \text{H}_2\text{O}_2, \text{H}_2\text{O} \end{array}}$

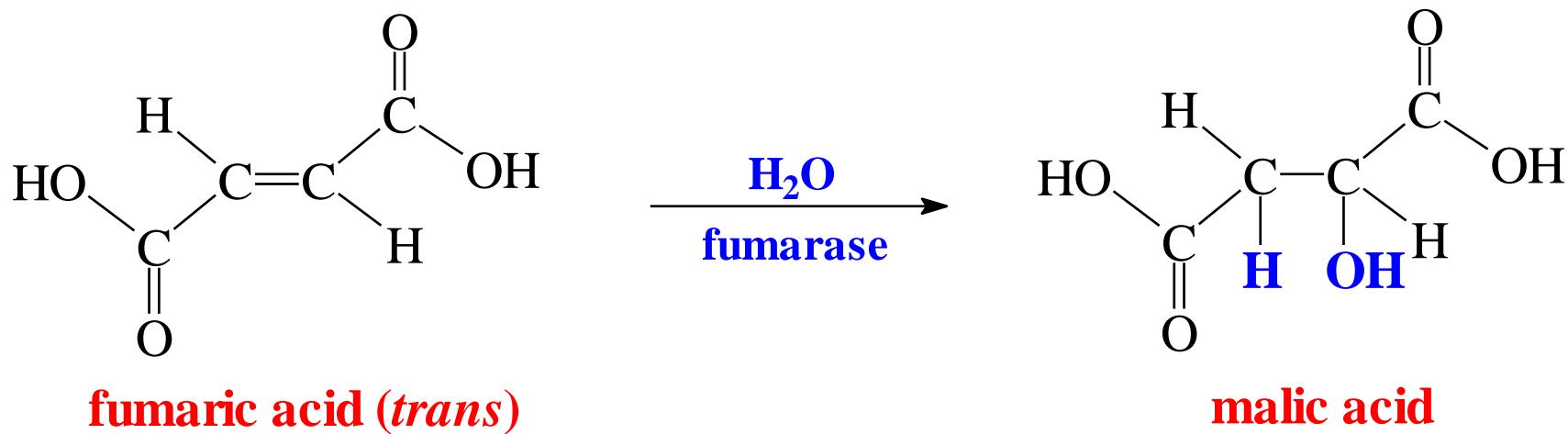


$\xrightarrow{\begin{array}{l} \text{1. BH}_3/\text{THF} \\ \text{2. HO}^-, \text{H}_2\text{O}_2, \text{H}_2\text{O} \end{array}}$



Biological Alkene Hydration

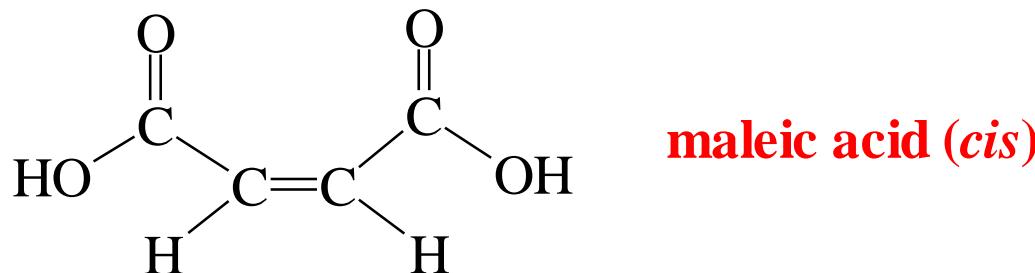
- Alkene hydration is achieved using **enzymes** in living organisms



- Fumarase (enzyme) catalyzes hydration of fumaric acid to malic acid

Biological Alkene Hydration

- This is significant in the **CITRIC ACID** cycle - involved in food metabolism
- Fumarase **will not** catalyze hydration of the *cis* stereoisomer of fumaric acid (maleic acid)

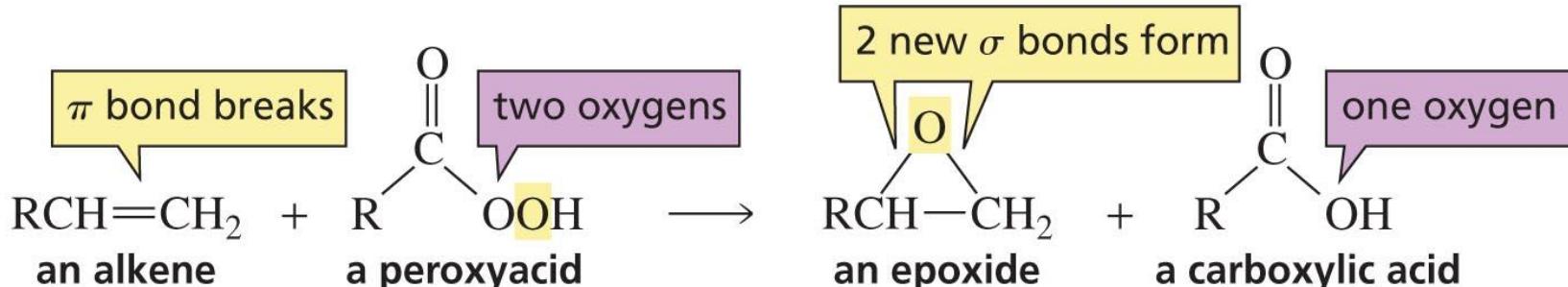


- Enzymes are said to be **“substrate specific”**

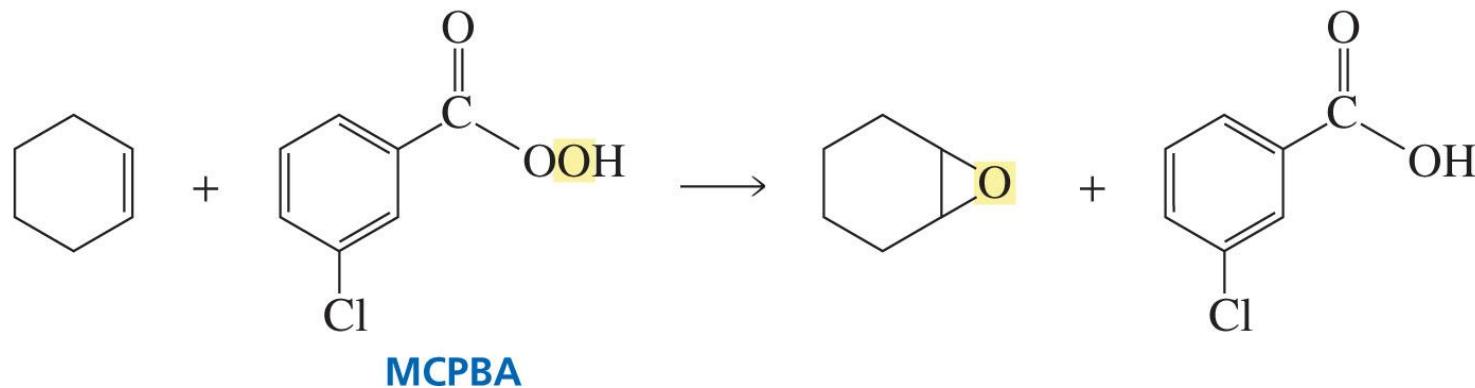
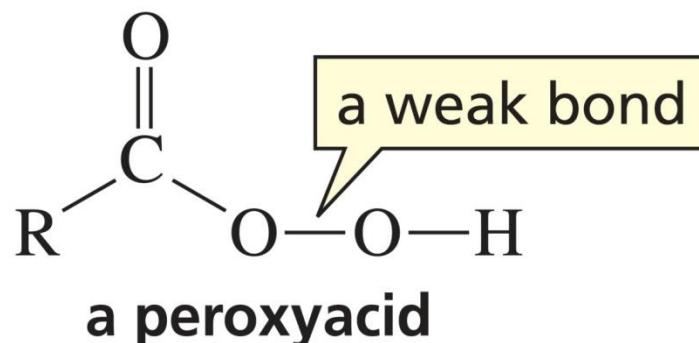
Alkene addition reactions summary

| Reagent | Syn/Anti | Markovnikov |
|-------------------------------------------------------------------------------------|----------|-------------|
| HBr | - | yes |
| Br ₂ | Anti | - |
| Br ₂ /H ₂ O | Anti | yes |
| H ₂ O, H ⁺ | - | yes |
| H ₂ O, Hg(OAc) ₂ | - | yes |
| H ₂ O, BH ₃ , H ₂ O ₂ , OH ⁻ | Syn | no |

Alkene Epoxidation



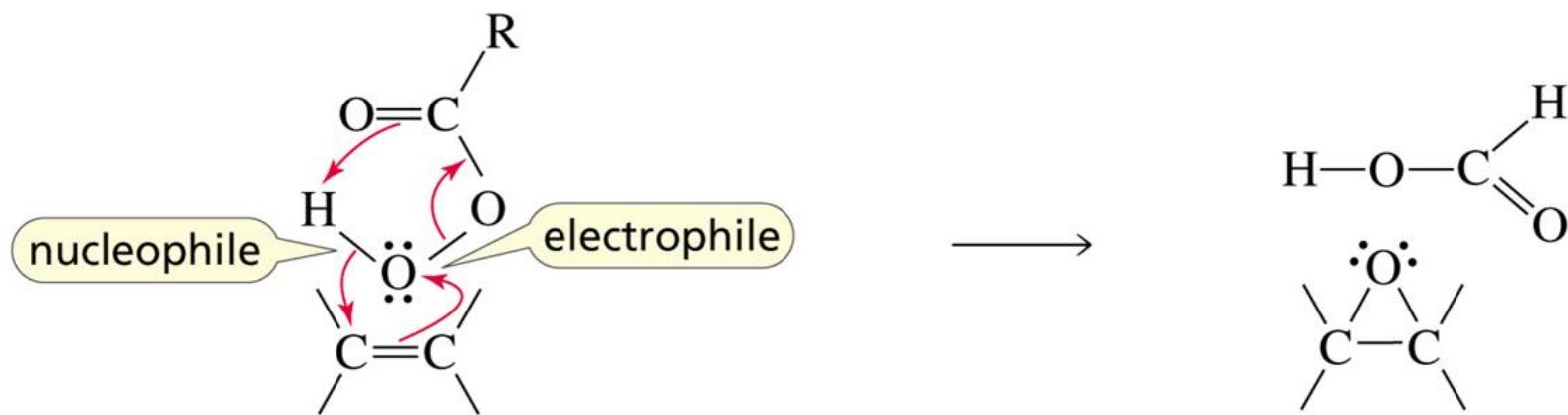
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- 1) Non-polar solvents (i.e. CH₂Cl₂) used; so formation of ions or charged species unlikely
- 2) No free rotation around sigma bond even though pi bond broken: due to reaction being stereospecific

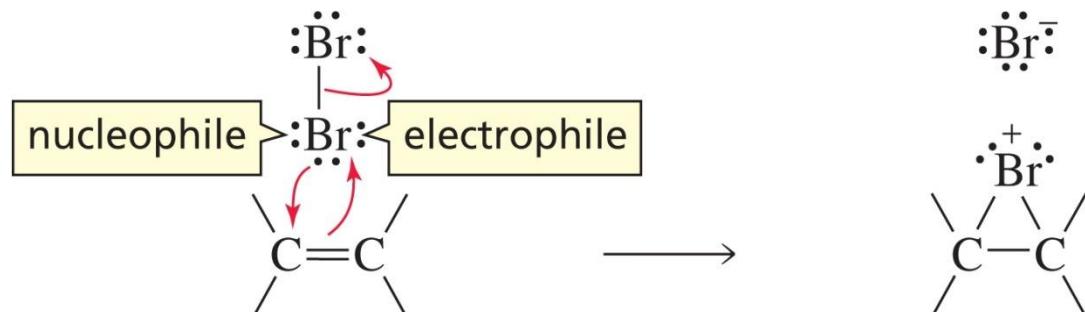
So.....mechanism must be consistent with these observations.....

Mechanism: cyclic and concerted



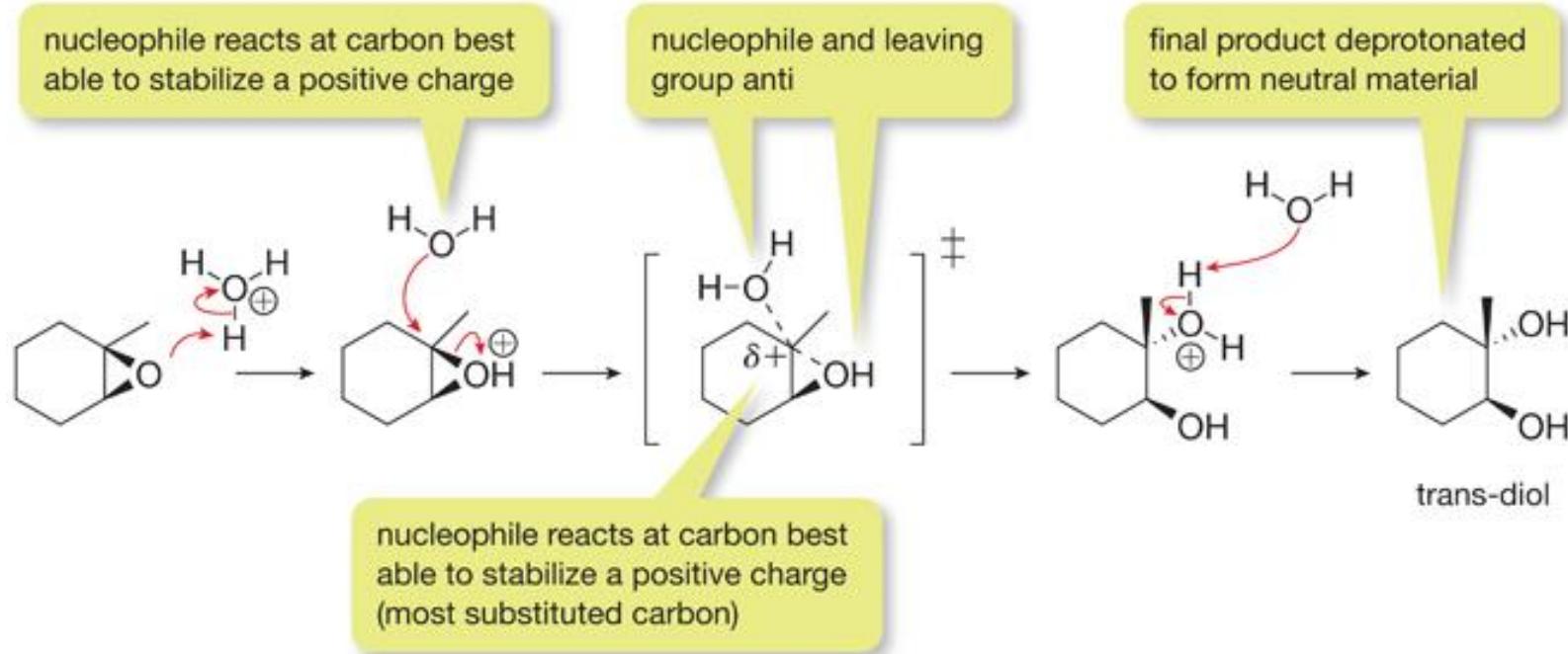
Reaction Stereospecific: stereochemistry of product depends on stereochemistry of alkene

the mechanism is similar to that for the addition of Br₂



Reactions of epoxides

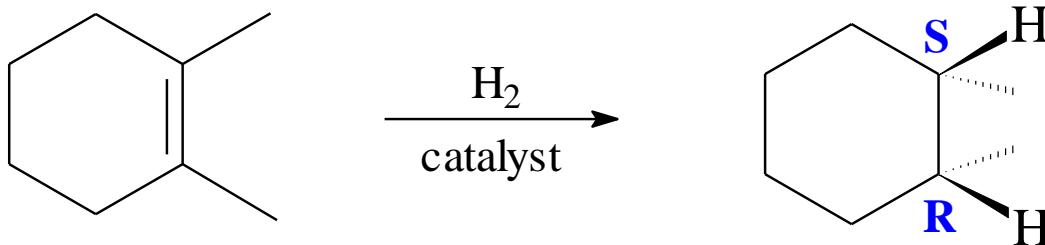
Acid Conditions:



Base Conditions:

Hydrogenation (Reduction)

- Addition of H_2 gas to alkene C=C, forms a **(cyclo)ALKANE**

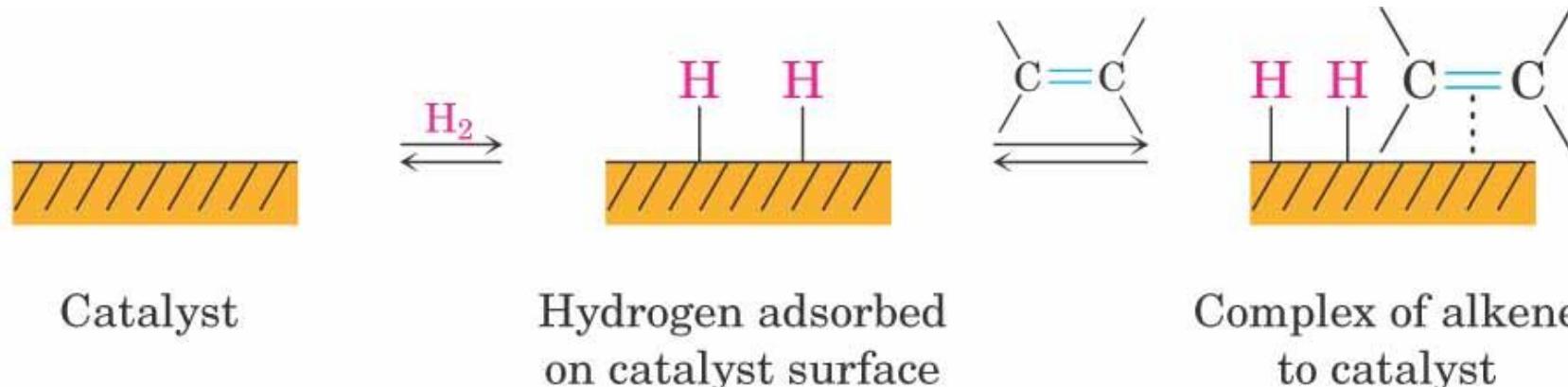


1,2-dimethylcyclohexene

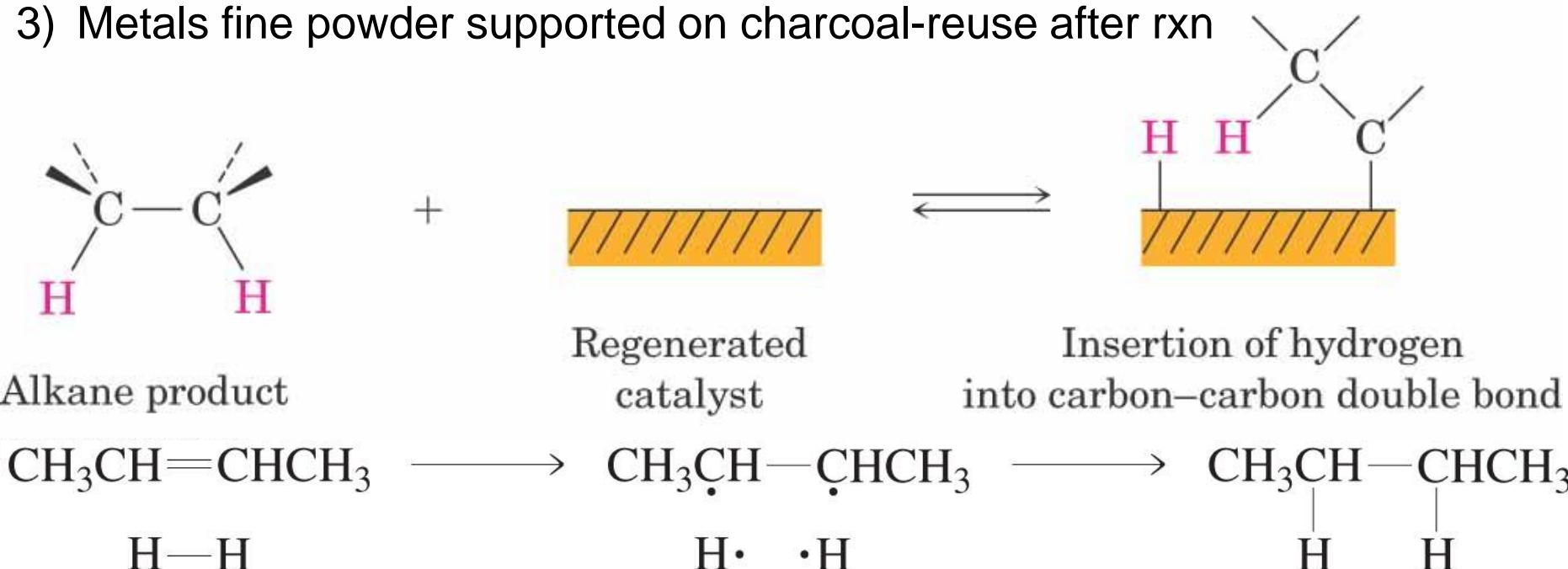
meso compound (achiral)

- Both H atoms add to the _____ face of the ring (
_____ ADDITION again)
- Catalyst: often Pd/C, Pt/C, Ni, Rh or PtO_2 (Adams catalyst)
- Reaction _____: different stereoisomers give different stereoisomeric products

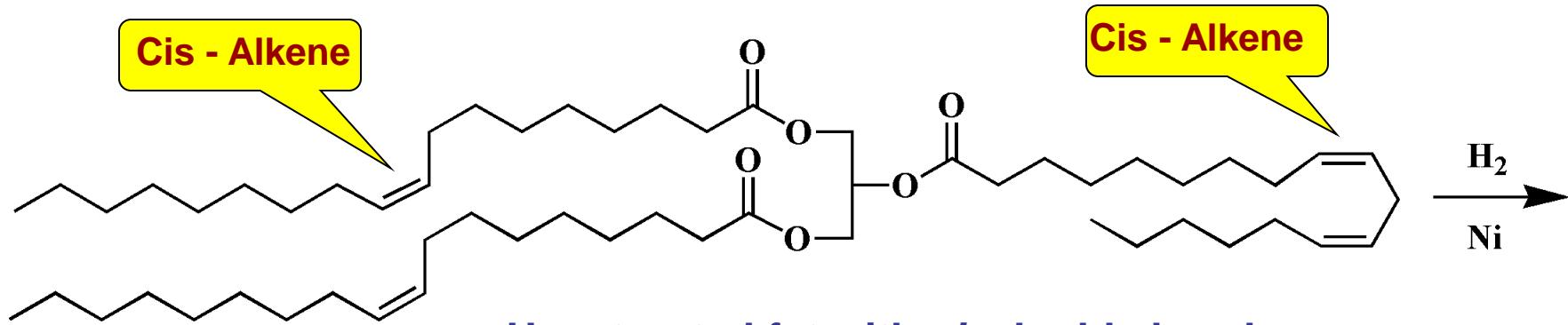
Hydrogenation (1)



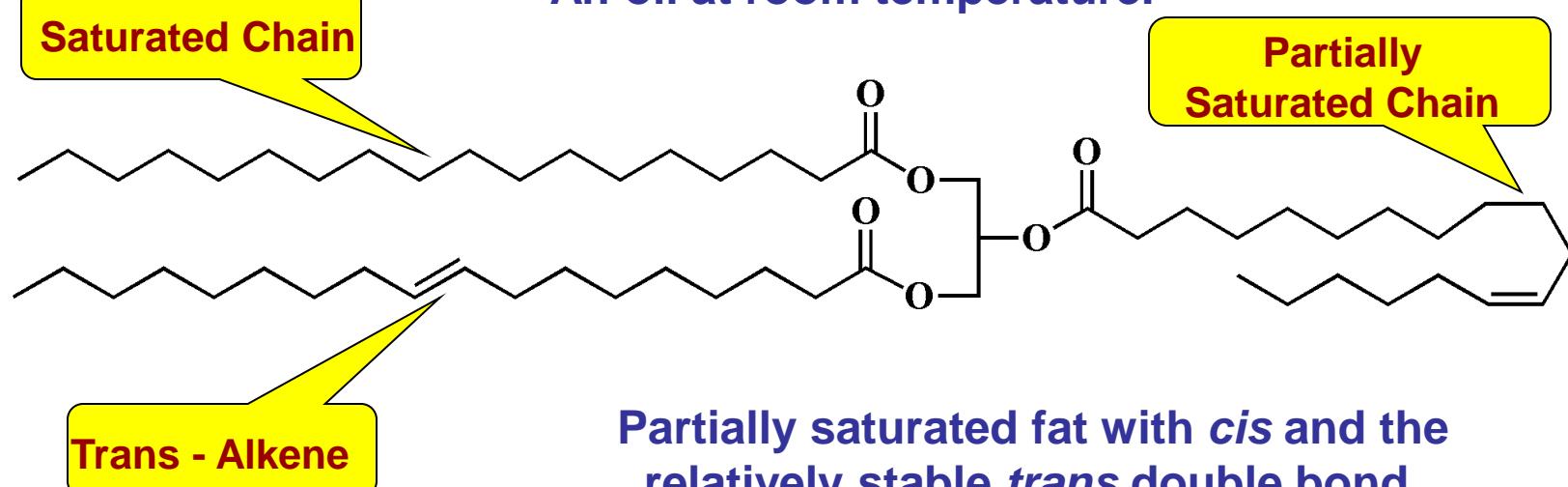
- 1) “Heterogenous catalyst” (both solid and solution)
- 2) 100% SYN addition to give “cis” product
- 3) Metals fine powder supported on charcoal-reuse after rxn



Partial Hydrogenation



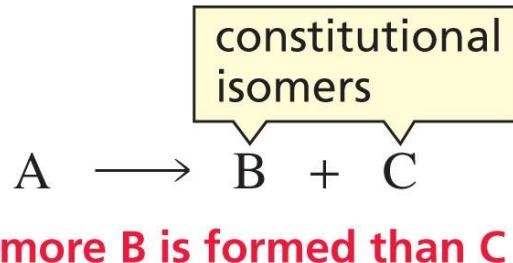
Unsaturated fat with *cis* double bonds.
An oil at room temperature.



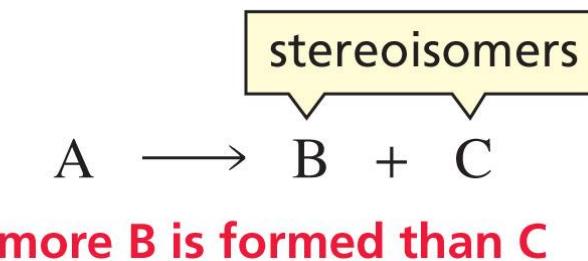
Partially saturated fat with *cis* and the
relatively stable *trans* double bond.
A butter-like solid at room temperature.

Regioselective, Stereoselective and Stereospecific Reactions

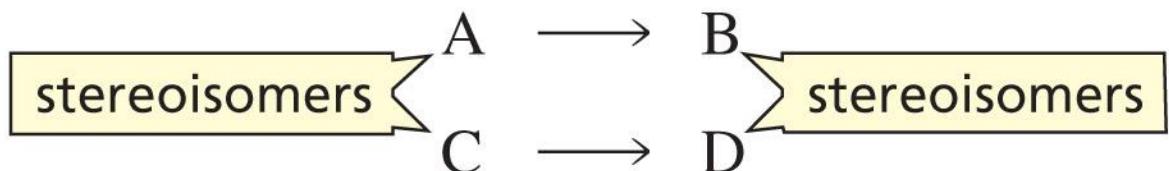
a regioselective reaction



a stereoselective reaction



stereospecific reactions

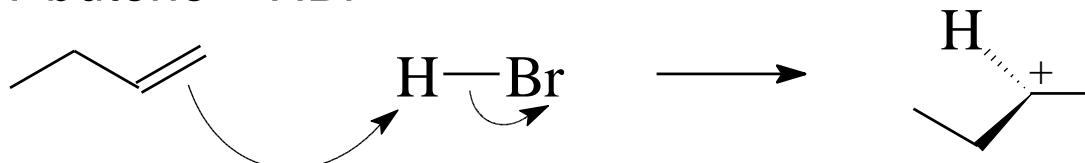


Stereoselective and Stereospecific Syntheses

- ❖ **Stereoselective reactions** are reactions that lead to a preferential formation of one stereoisomer over other stereoisomers that could possibly be formed
 - **enantioselective** – if a reaction produces preferentially one enantiomer over its mirror image
 - **diastereoselective** – if a reaction leads preferentially to one diastereomer over others that are possible
- ❖ **Stereospecific reaction:** each stereoisomeric reactant forms a different stereoisomeric product or a different set of stereoisomeric products
 - All stereospecific reactions are stereoselective
 - Not all stereoselective reactions are stereospecific

Stereochemistry of Electrophilic Addition Reactions (Formation of One Chiral Center)

- Consider 1-butene + HBr



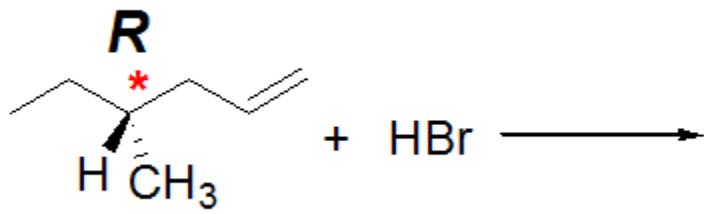
planar carbocation

- Carbocation is **planar**, can be attacked by Br^- equally well from either face
- Will see a **RACEMIC MIXTURE** of products formed (50% *R*, 50% *S*)
- Both reactants (1-butene and HBr) are **ACHIRAL** and optically **INACTIVE**, product is optically inactive also and racemic mix

If the reactant does not have an **asymmetric center** and the reaction forms a product with an **asymmetric center**, the product will be a **racemic mixture**.

Stereochemistry of Reactions: Addition of HBr to a Chiral Alkene (Formation of NEW chiral centers)

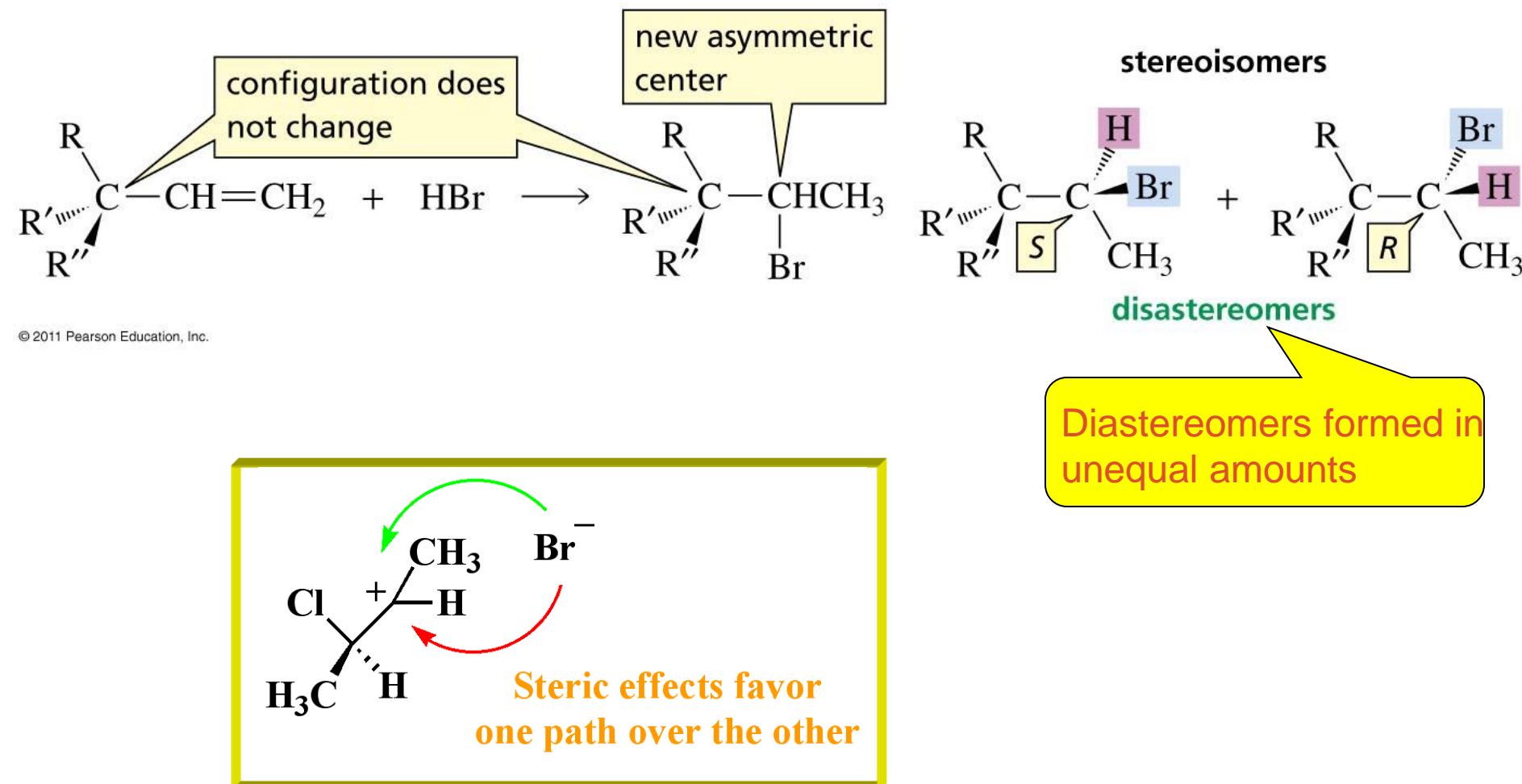
- Addition reaction creating new asymmetric center in reactant with an existing stereocenter gives a pair of diastereomers in unequal amounts.
- Facial approaches are different in energy and stability due to diastereomeric transition state



General Rule:

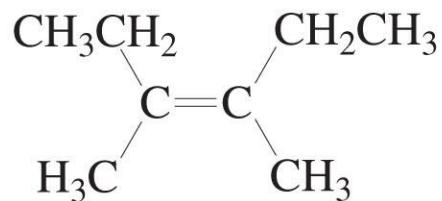
Chiral reactant (single enantiomer) + achiral reactant = Unequal amounts of diastereomeric products

- The presence of an asymmetric center near a reacting center will result diastereoselectivity.

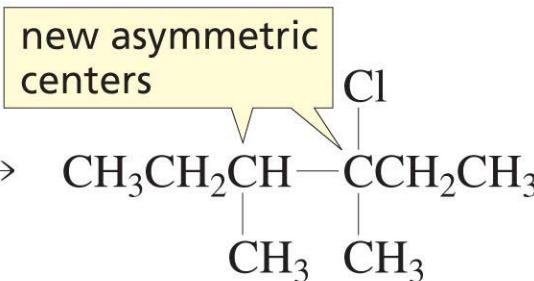


Stereochemistry of Reactions: Addition of HX and formation of **TWO** chiral centers)

Addition reactions that form products with two asymmetric centers



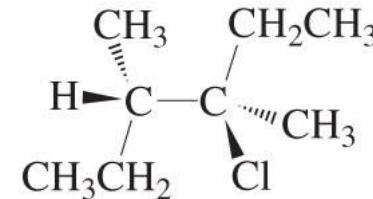
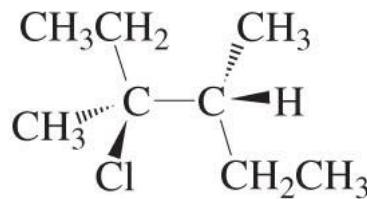
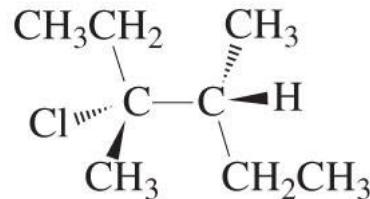
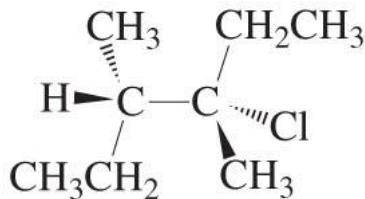
cis-3,4-dimethyl-3-hexene



3-chloro-3,4-dimethylhexane

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All four possible stereoisomers result:



perspective formulas of the stereoisomers of the product

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Stereospecific Reaction: Bromine Addition (SYN)

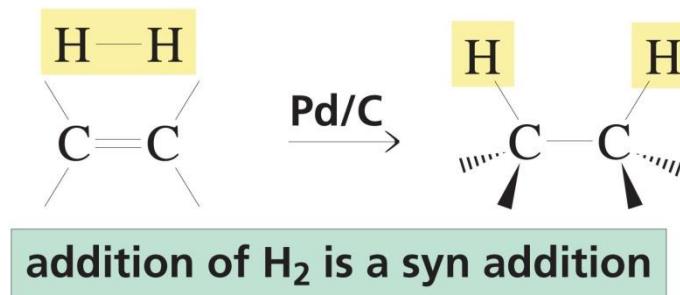
- Stereospecific
 - IF reactant can exist as stereoisomers, each stereoisomer of reactant forms different stereoisomer of product
- Br₂ addition to *cis*-2-butene forms two **threo** enantiomers:

The stereoisomers obtained as products depend on the mechanism of ₅₅ the reaction.

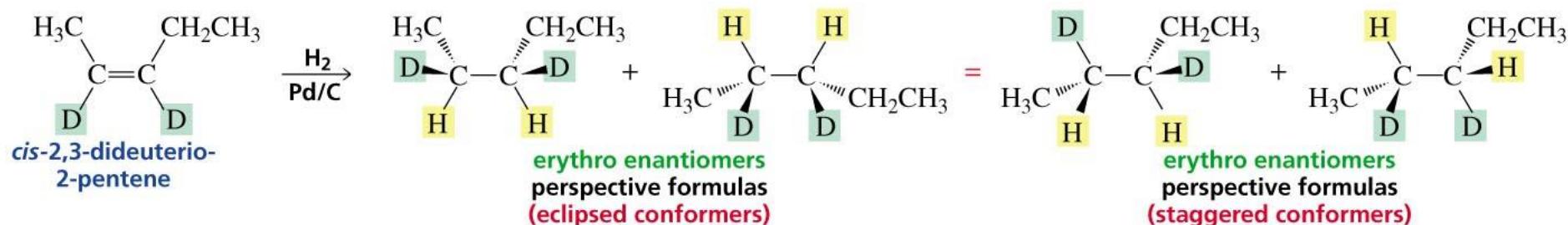
Stereospecific Reaction: Bromine Addition (SYN)

- Br_2 addition to *trans*-2-butene forms *meso* product
- If *non-symmetrical trans-alkene*: form *erythro* enantiomers
- All stereospecific rxns are also stereoselective.

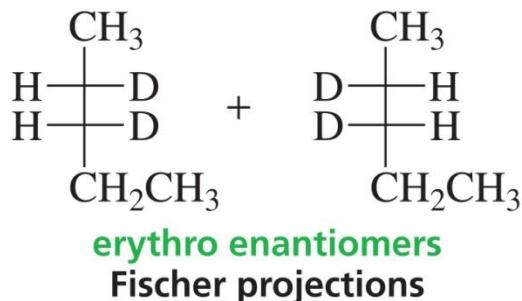
The Stereochemistry of Hydrogen Addition (SYN): a stereospecific reaction



Exclusive Formation of Erythro Enantiomers:

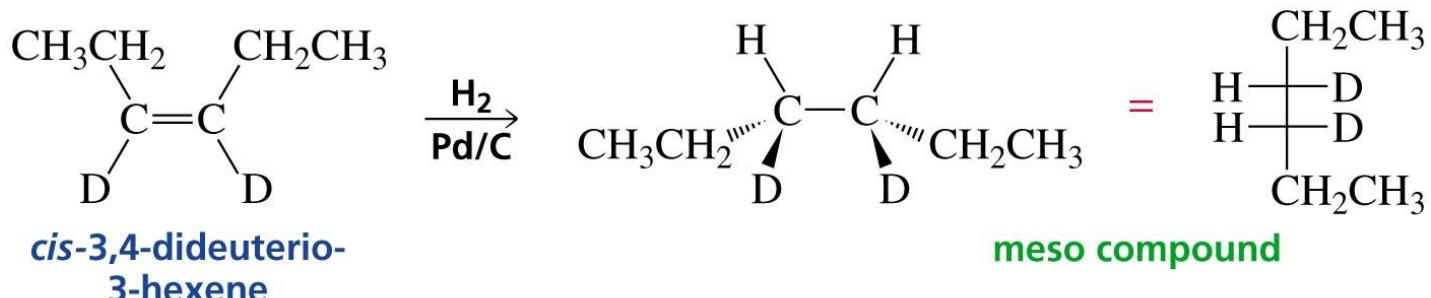


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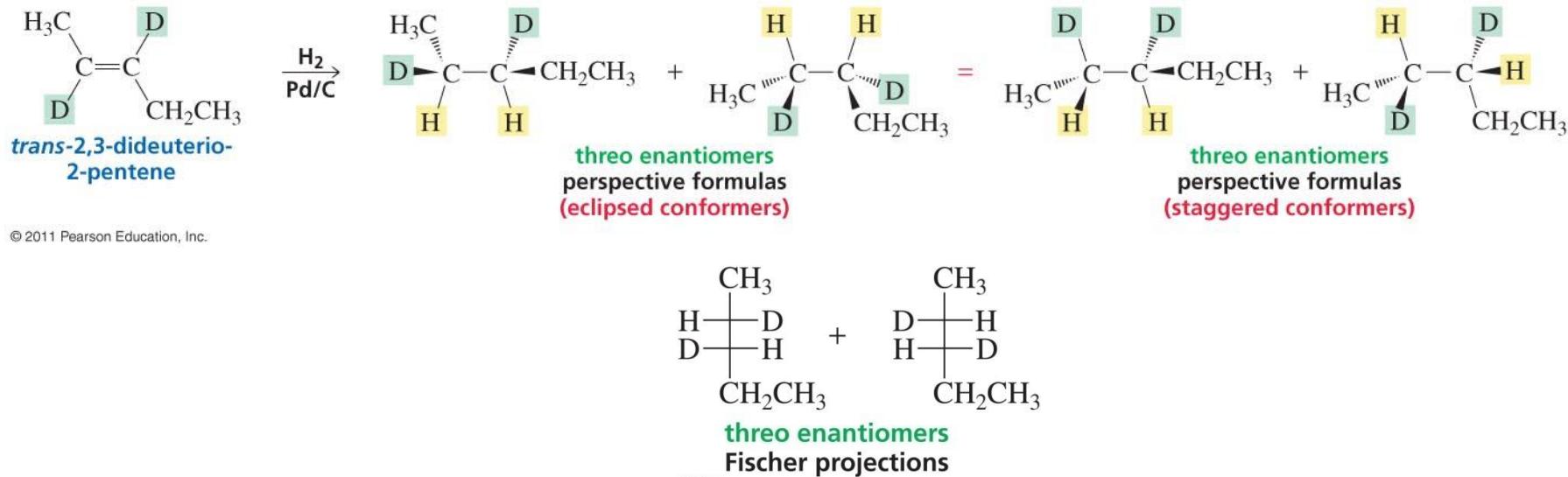
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Exclusive Formation of Meso Stereoisomer:



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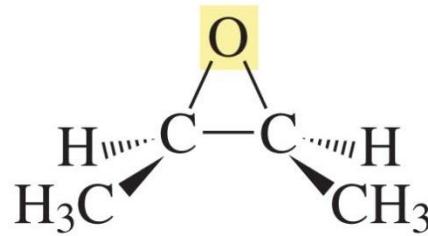
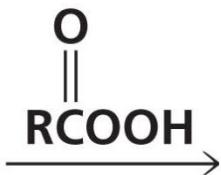
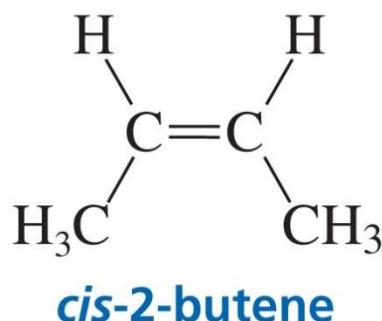
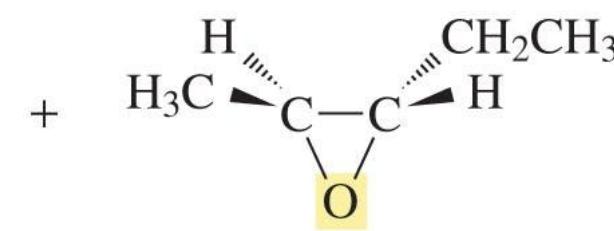
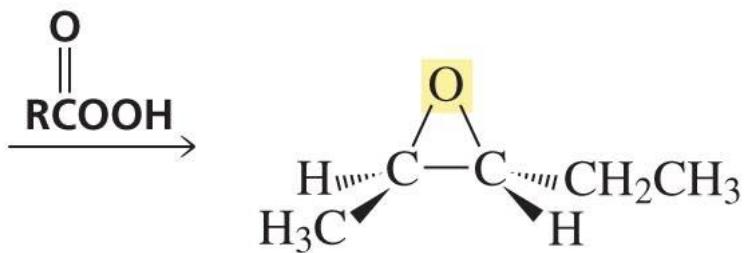
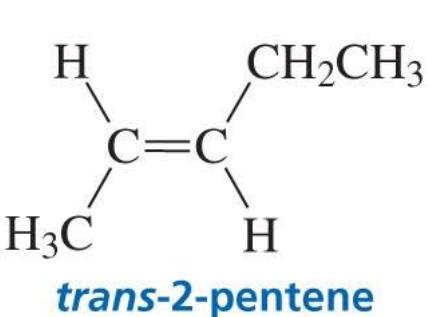
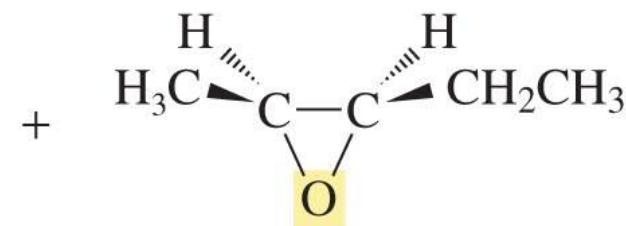
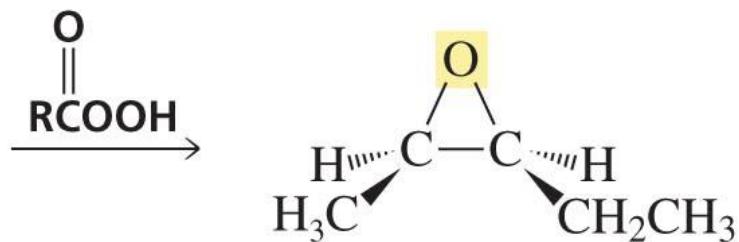
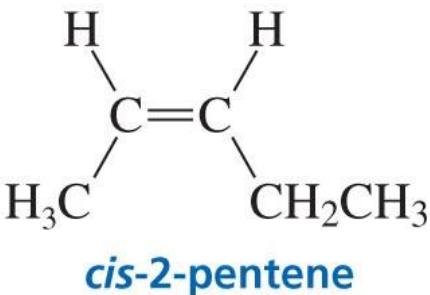
Exclusive Formation of Threo Enantiomers:



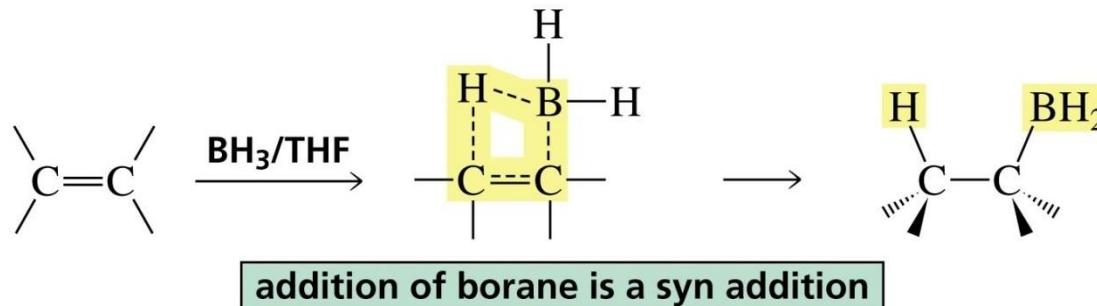
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The Stereochemistry of Epoxidation (SYN)

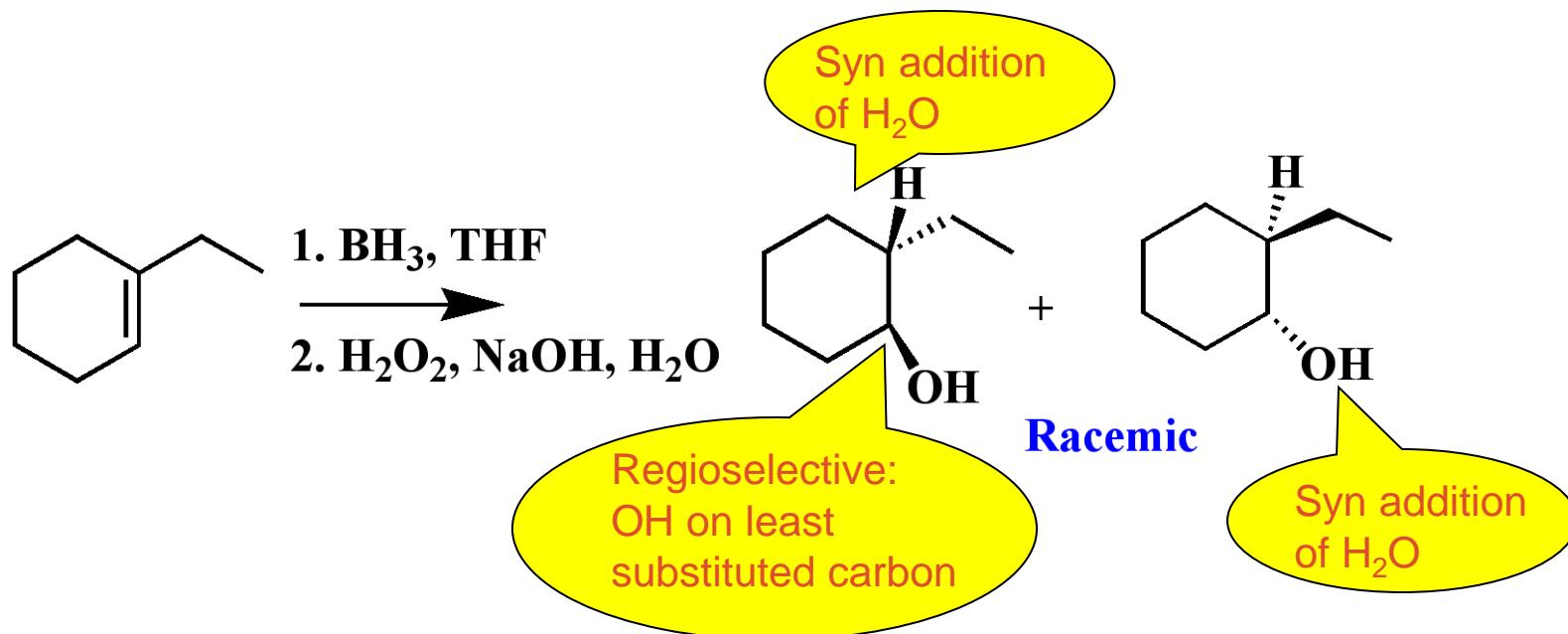
The addition of a peroxyacid to an alkene to form an epoxide is a concerted reaction. Orientation of alkyl substituents remain unchanged.



The Stereochemistry of Hydroboration–Oxidation (SYN)



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Stereochemistry of Alkene Addition Reactions

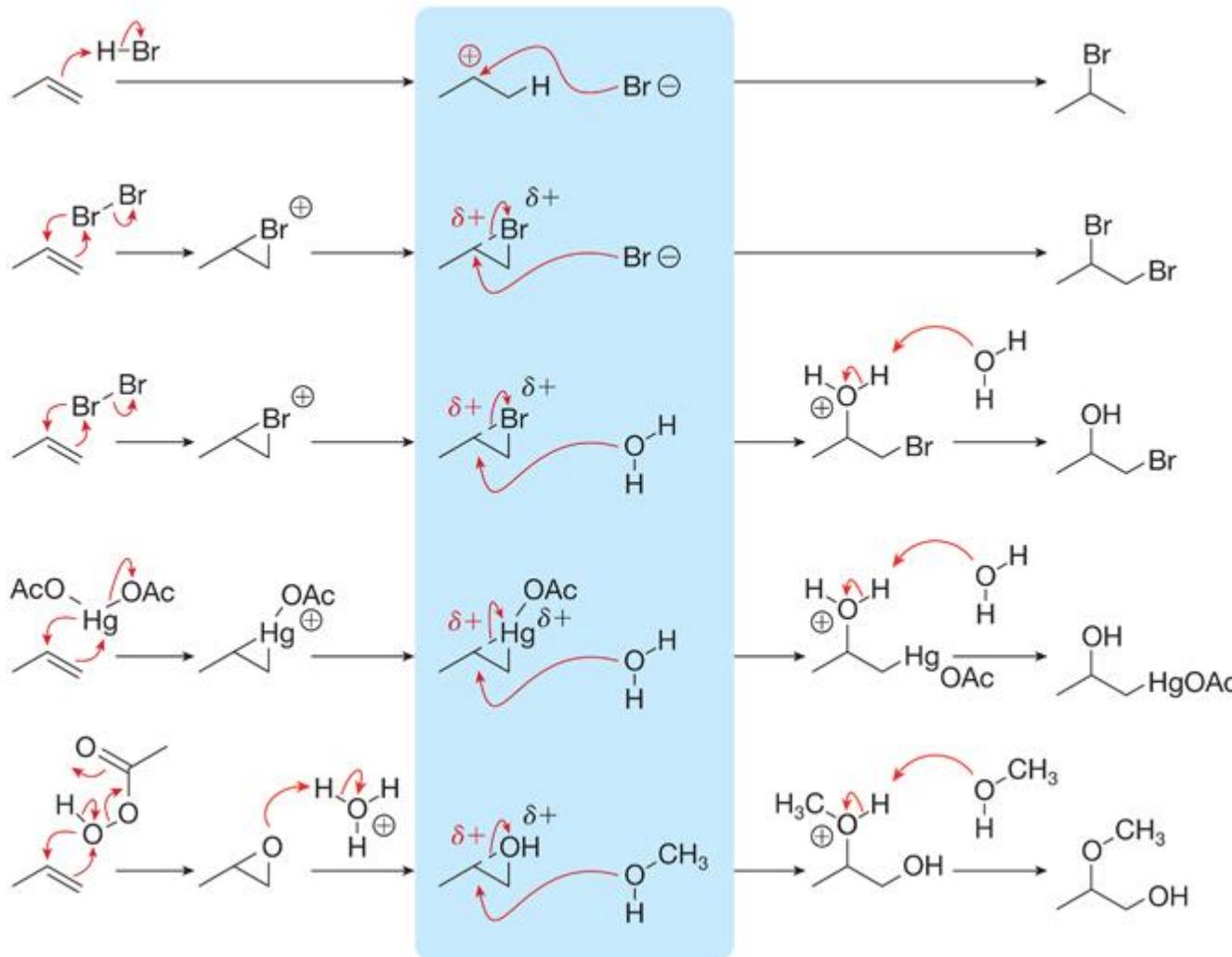
CIS - SYN - (ERYTHRO or CIS)

Table 5.3 Stereochemistry of Alkene Addition Reactions

| Reaction | Type of addition | Stereoisomers formed |
|-------------------------------------------------------------------------------------------------------------------------------------------------------|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Addition reactions that create one asymmetric center in the product | | <ol style="list-style-type: none"> If the reactant does not have an asymmetric center, a racemic mixture will be obtained. If the reactant has an asymmetric center, unequal amounts of a pair of diastereomers will be obtained. |
| Addition reactions that create two asymmetric centers in the product | | |
| Addition of reagents that form a carbocation intermediate | syn and anti | Four stereoisomers will be obtained (the cis and trans isomers form the same products). |
| Addition of H ₂ | syn | cis → erythro or cis enantiomers* |
| Addition of borane | | trans → threo or trans enantiomers |
| Addition of a peroxyacid | | |
| Addition of Br ₂ , Br ₂ + H ₂ O, Br ₂ + ROH (any reaction that forms a cyclic bromonium ion intermediate) | anti | cis → threo or trans enantiomers trans → erythro or cis enantiomers* |

* If the two asymmetric centers have the same substituents, a meso compound will be obtained instead of the pair of erythro enantiomers.

Mechanistic patterns: Cyclic intermediates



Key Concepts

- Alkenes undergo **electrophilic addition reactions**. Electrophile adds to the sp^2 carbon bonded to the greater number of hydrogen atoms and a **nucleophile** adds to the other sp^2 carbon of the alkene double bond.
- **HX and $\text{H}^+/\text{H}_2\text{O}$ addition to alkenes lead to alkyl halide and alcohol formation:** form **carbocation** intermediates. **Order of stability:** tertiary > secondary > primary > methyl cation. Carbocations can rearrange via **1,2-hydride shifts, 1,2-methyl shifts and ring expansions**.
- **Oxymercuration, alkoxymercuration, and X_2 addition to alkenes form alcohols, ethers and vicinal dihalides:** form cyclic intermediates; concerted reaction mechanisms.
- **Hydroboration of alkenes forms alcohols:** concerted reaction mechanism with no intermediate formed.
- **Oxidation:** increases number of C-O, C-N, or C-X bonds and decreases number of C-H bonds
- **Reduction:** decreases number of C-O, C-N, or C-X bonds and increases number of C-H bonds
- Some addition reactions **regioselective:** preferentially form one constitutional isomer over another.
- **Hammond postulate:** relates the structure of intermediates with energy: transition state more similar in structure to species to which it is more similar to in energy. More stable product = more stable transition state = major product of reaction
- **Hydrogenation of alkenes forms alkanes:** addition of H_2 to alkene. Heat of hydrogenation used to determine stability of alkenes. Smaller heat of hydrogenation = greater stability of alkene
- **Order of alkene stability:** tetra-substituted > tri-substituted > di-substituted > mono-substituted
- Trans alkenes more stable than cis alkenes due to less steric hindrance

Key Concepts

- **Regioselective reaction:** forms a particular constitutional isomer in preference to another or in a higher ratio than the other possible isomer in a reaction
- **Stereoselective reaction:** forms a particular stereoisomer in preference to another or in a higher ratio than the other possible stereoisomer in a reaction
- **Stereospecific reaction:** when each stereoisomer of reactant forms a different or different set of stereoisomers
- **Syn addition:** substituents add to the same side of a double bond
- **Anti addition:** substituents add to the opposite sides of a double bond
- **H₂ addition to alkene:** syn addition
- **X₂ addition to alkene:** anti addition
- **Peroxy acid addition to alkene:** syn addition of O atom
- **Hydroboration-oxidation of alkene:** overall syn addition of H₂O
- Enzymes usually catalyze reaction of only one stereoisomer and form only one stereoisomer