Lecture 6

Addition Reactions of Alkenes, Alkynes

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  - 多步合成
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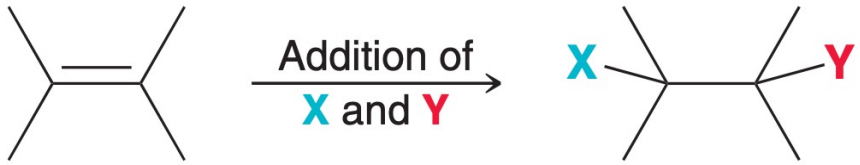
    - 改变π键的位置
  - 烷烃、烯烃、炔烃的转化

Addition Reactions of Alkenes

Hydrohalogenation, Hydration, Hydrogenation, Halogenation,

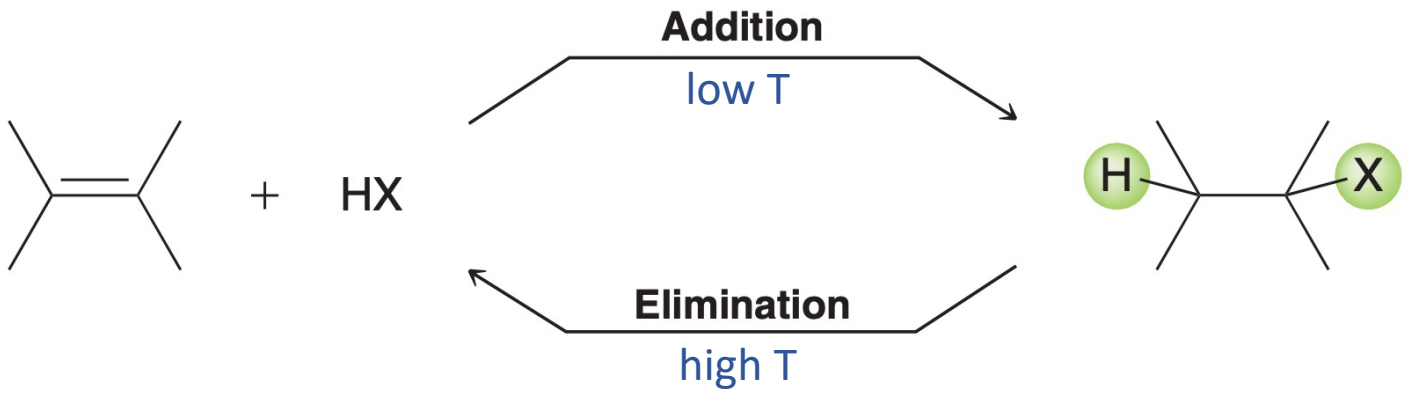
Halohydrin Formation, Dihydroxylation, Oxidative Cleavage

- 烯烃的加成反应



TYPE OF ADDITION REACTION	NAME
Addition of H and X → H–C–C–X	*Hydrohalogenation* (X = Cl, Br, or I)
Addition of H and OH → H–C–C–OH	*Hydration*
Addition of H and H → H–C–C–H	*Hydrogenation*
Addition of X and X → X–C–C–X	*Halogenation* (X = Cl or Br)
Addition of OH and X → HO–C–C–X	*Halohydrin formation* (X = Cl, Br, or I)
Addition of OH and OH → HO–C–C–OH	*Dihydroxylation*

- 加成反应vs消除反应



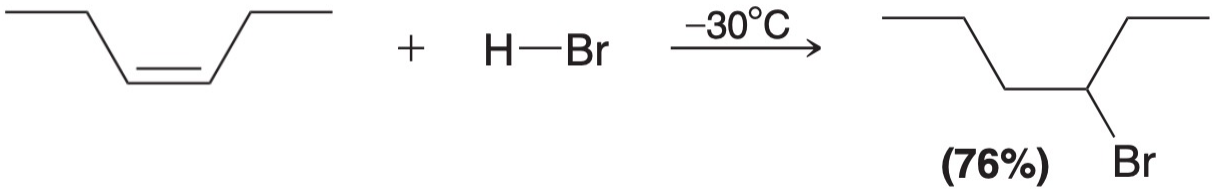
$$\Delta G = \underbrace{(\Delta H)}_{\text{Enthalpy term}} + \underbrace{(-T\,\Delta S)}_{\text{Entropy term}}$$

⊖ ⊕

加成反应在相对低温进行

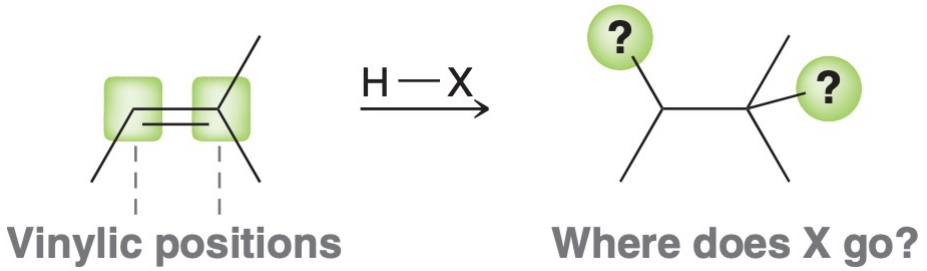
加热可以促进**消除**反应的发生

- **氢卤化**

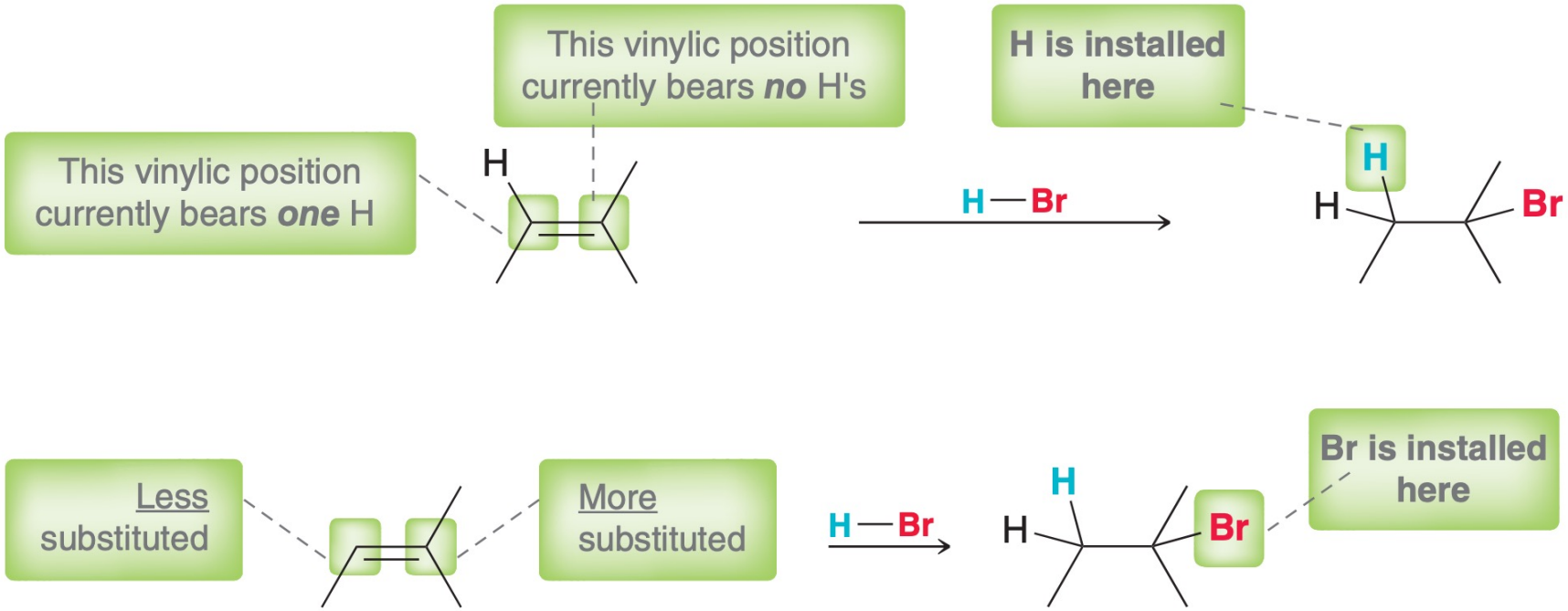


this is symmetric…

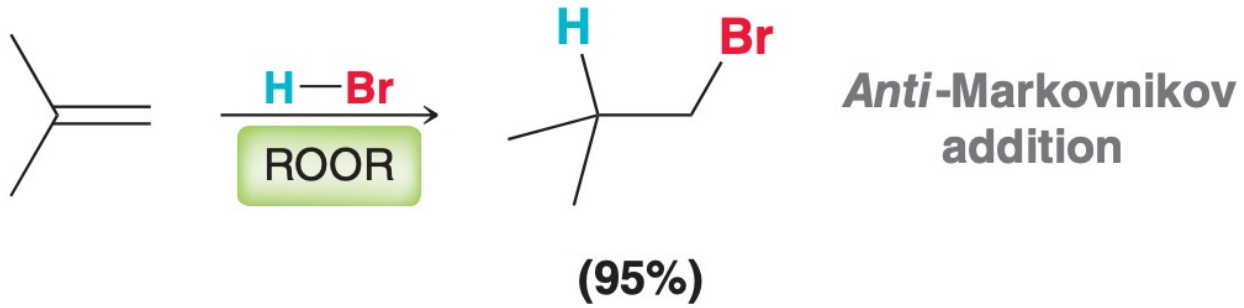
for this asymmetric alkene…



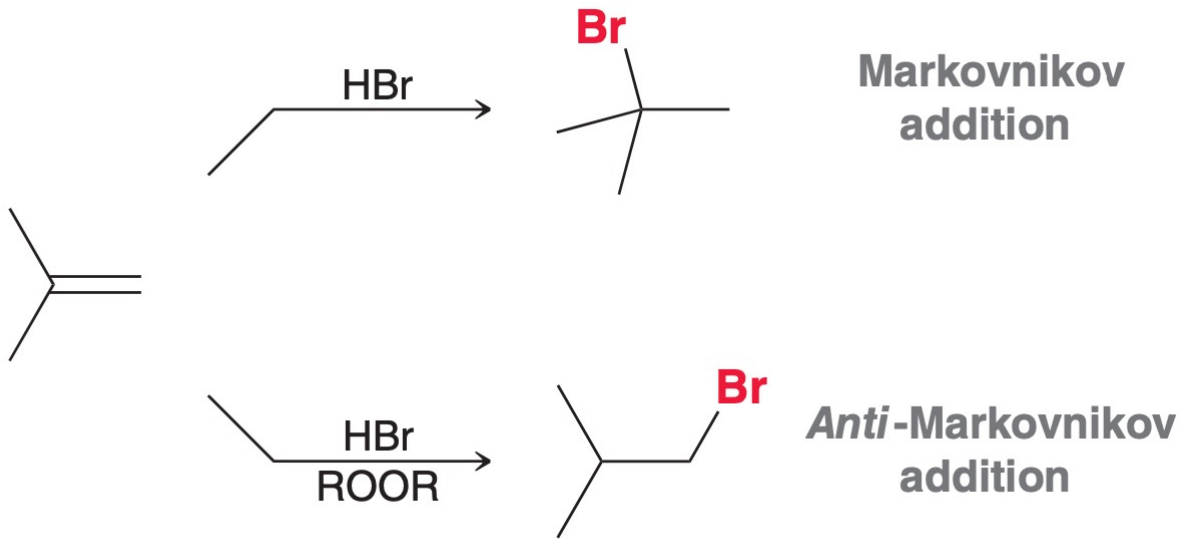
- 马氏规则(Markovnikov's rule)：氢多加氢



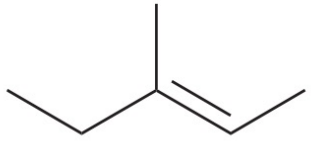
- 反马规则(*anti*-Markovnikov's rule)：氢少加氢

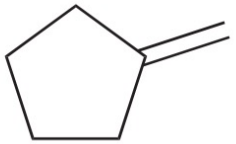


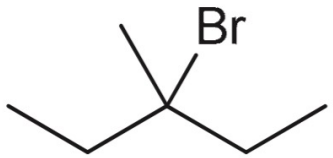
- 氢卤化的区域选择性

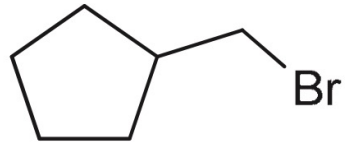

HBr
Br
Markovnikov addition
HBr
ROOR
Br
Anti-Markovnikov addition

- Practice: draw the expected major product for each of the following reactions:

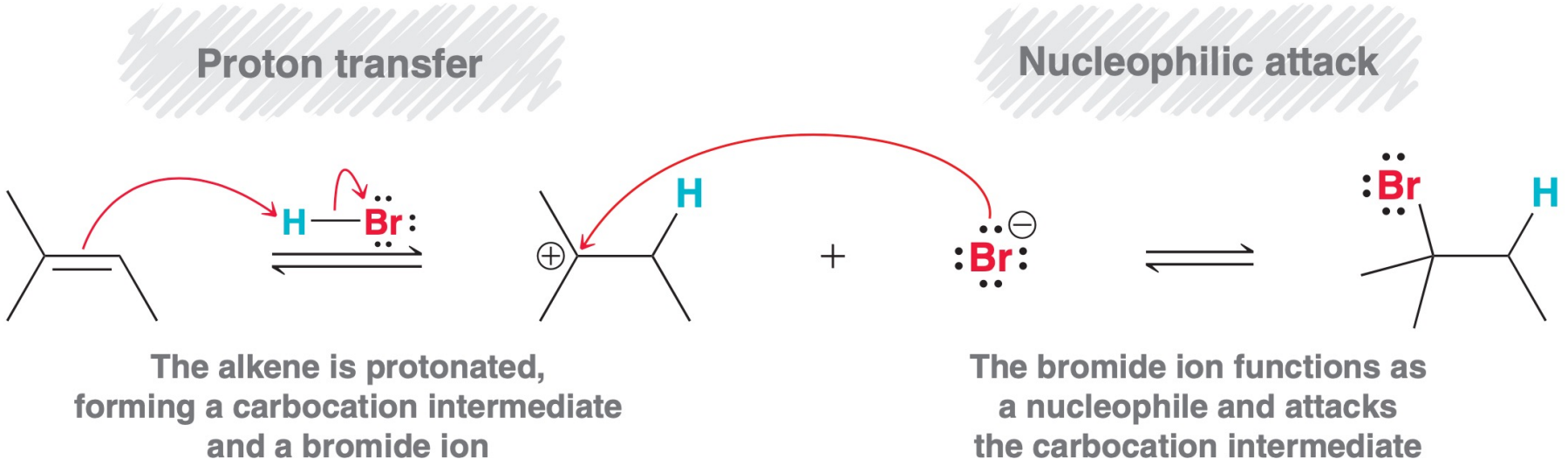
(a)  HBr → ?

(b)  HBr, ROOR → ?

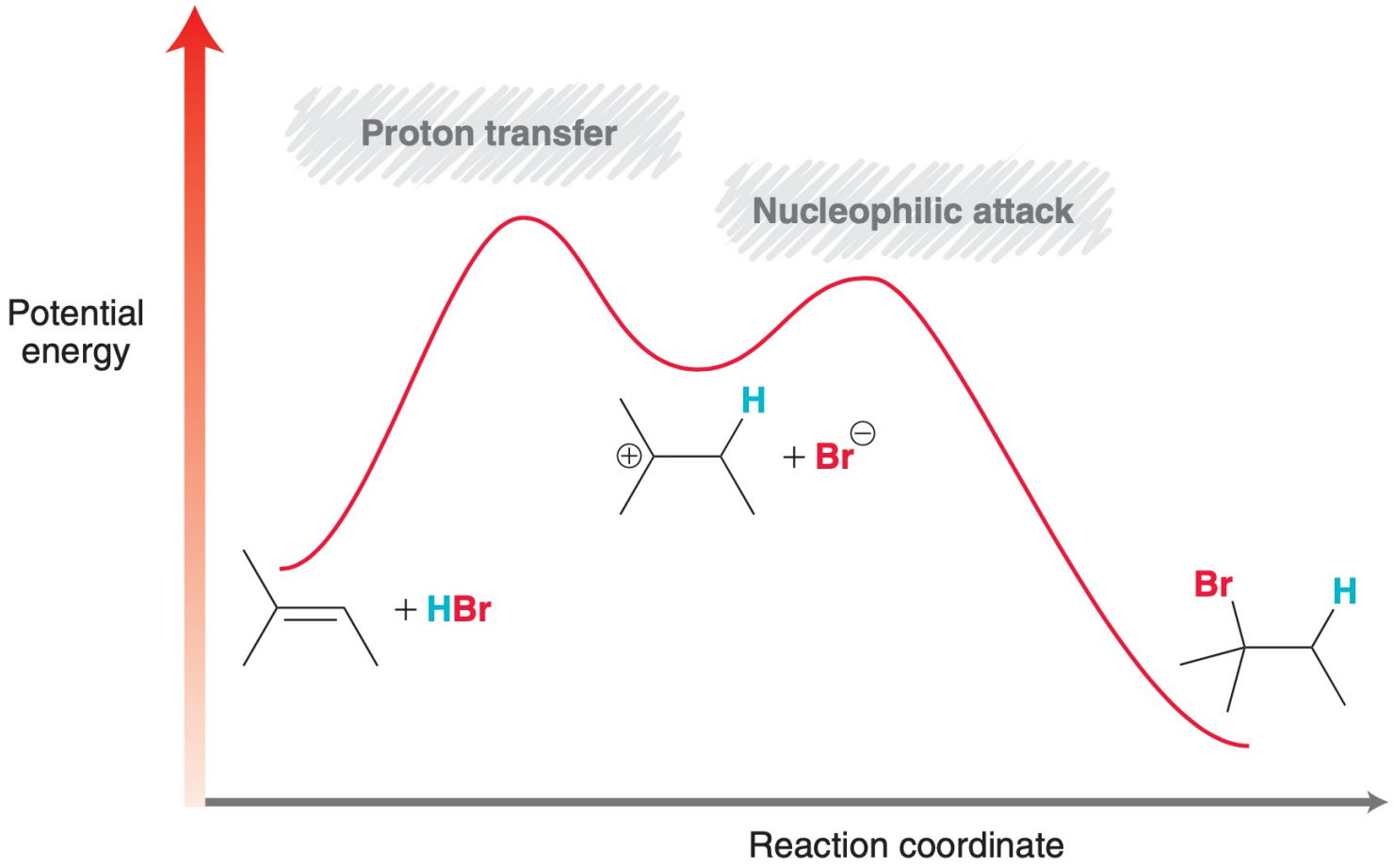




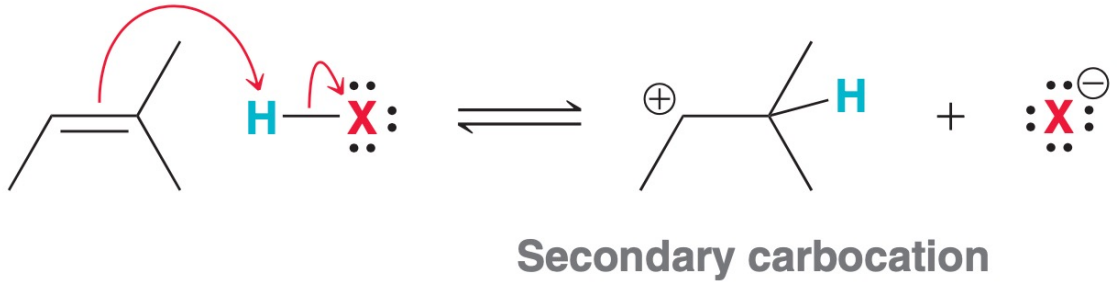
- **The Mechanism of Hydrohalogenation**



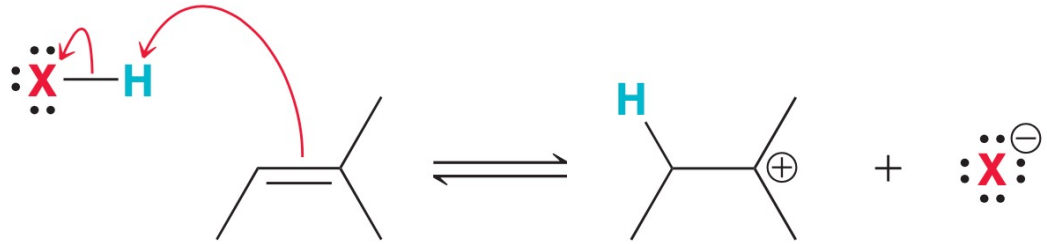
- 反应历程


Proton transfer
Nucleophilic attack
Potential energy
H
+ Br
+ HBr
Br
H
Reaction coordinate

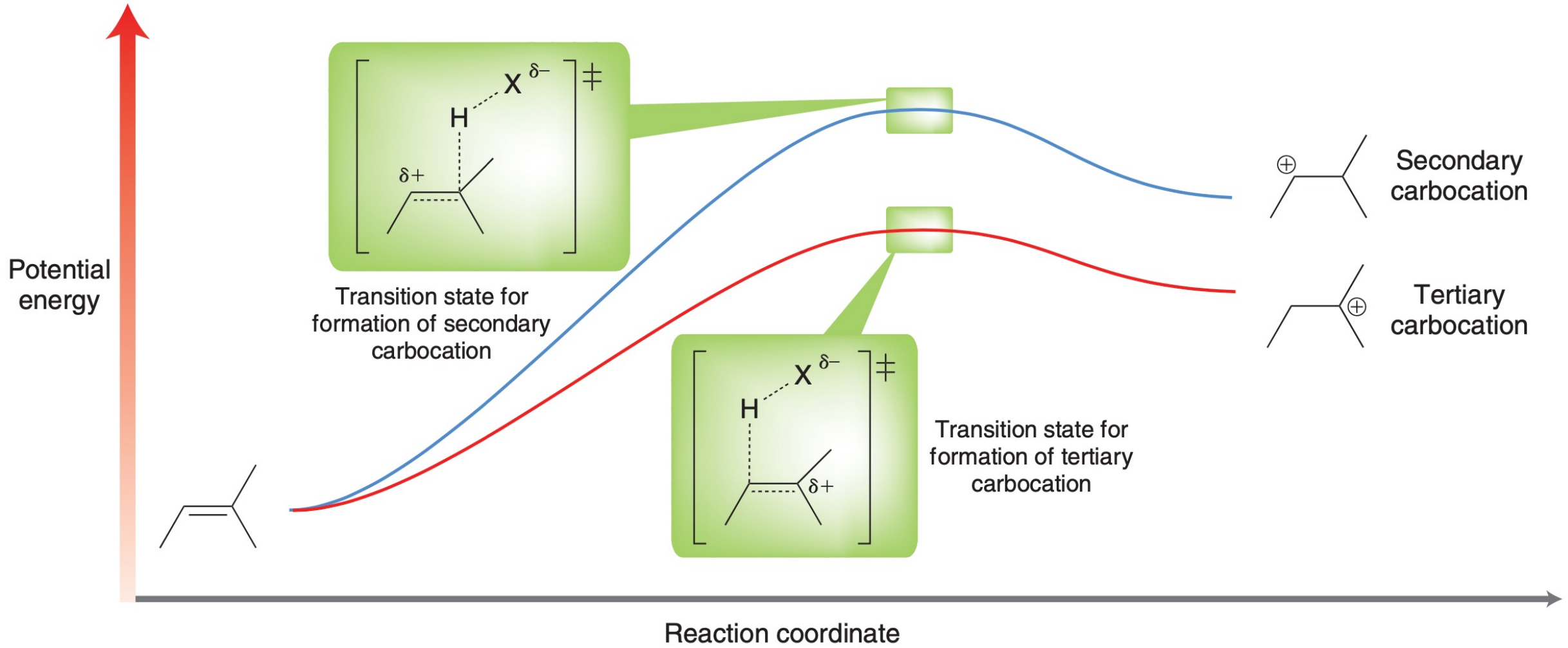
- 形成多取代的碳正离子更稳定



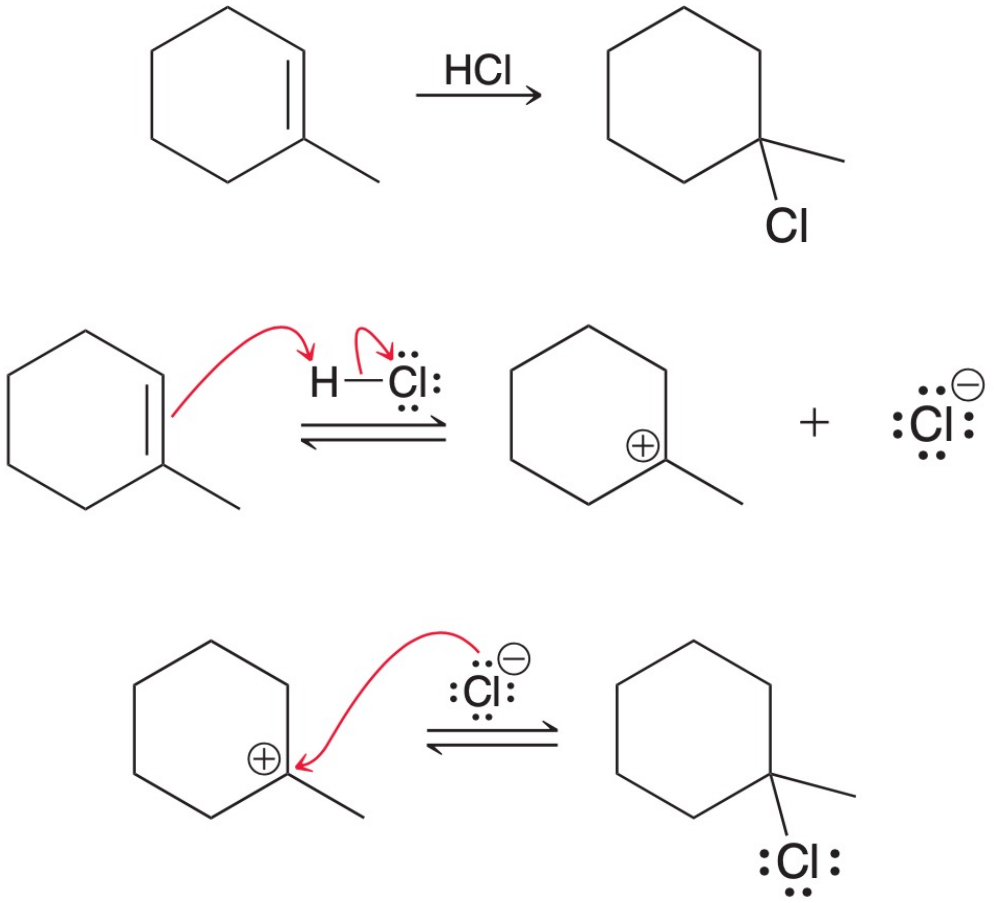
Secondary carbocation



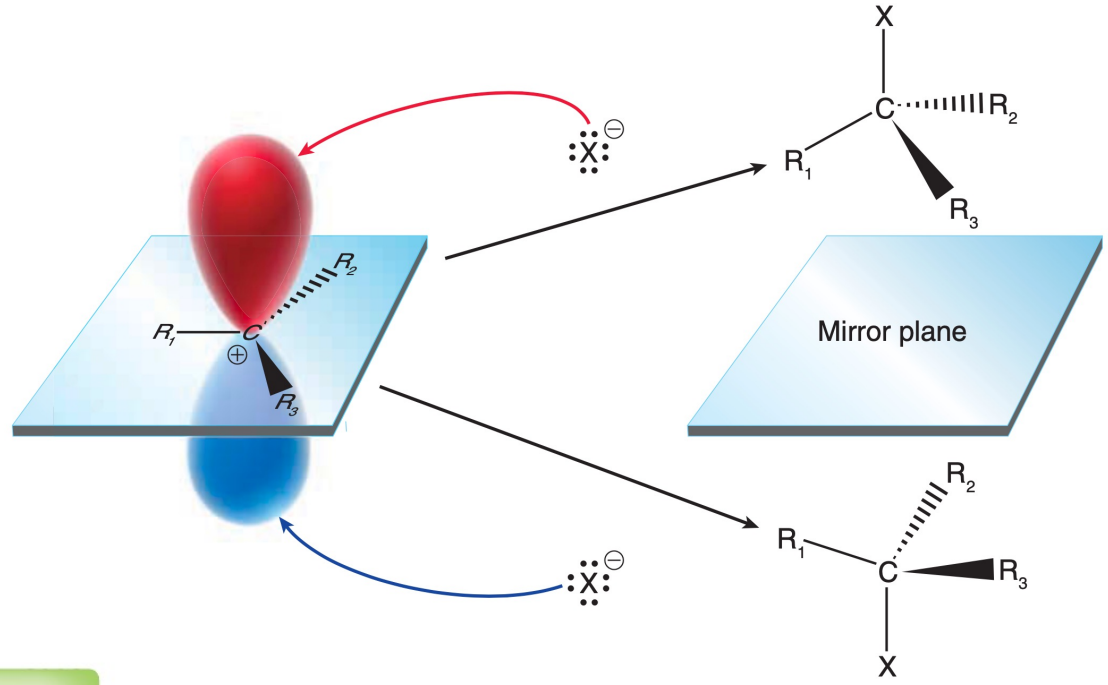
Tertiary carbocation

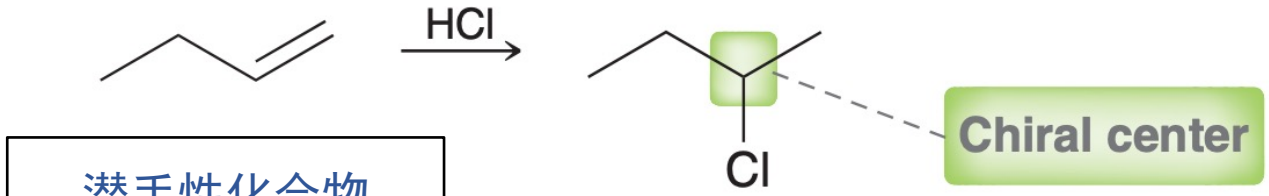

Potential energy
Reaction coordinate
X δ−
H
δ+
Transition state for formation of secondary carbocation
Transition state for formation of tertiary carbocation
Secondary carbocation
Tertiary carbocation

- Practice: draw a mechanism for the following transformation:



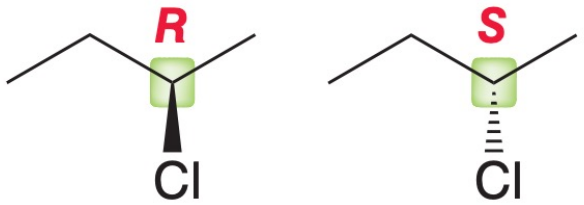
- 氢卤化的立体化学特征



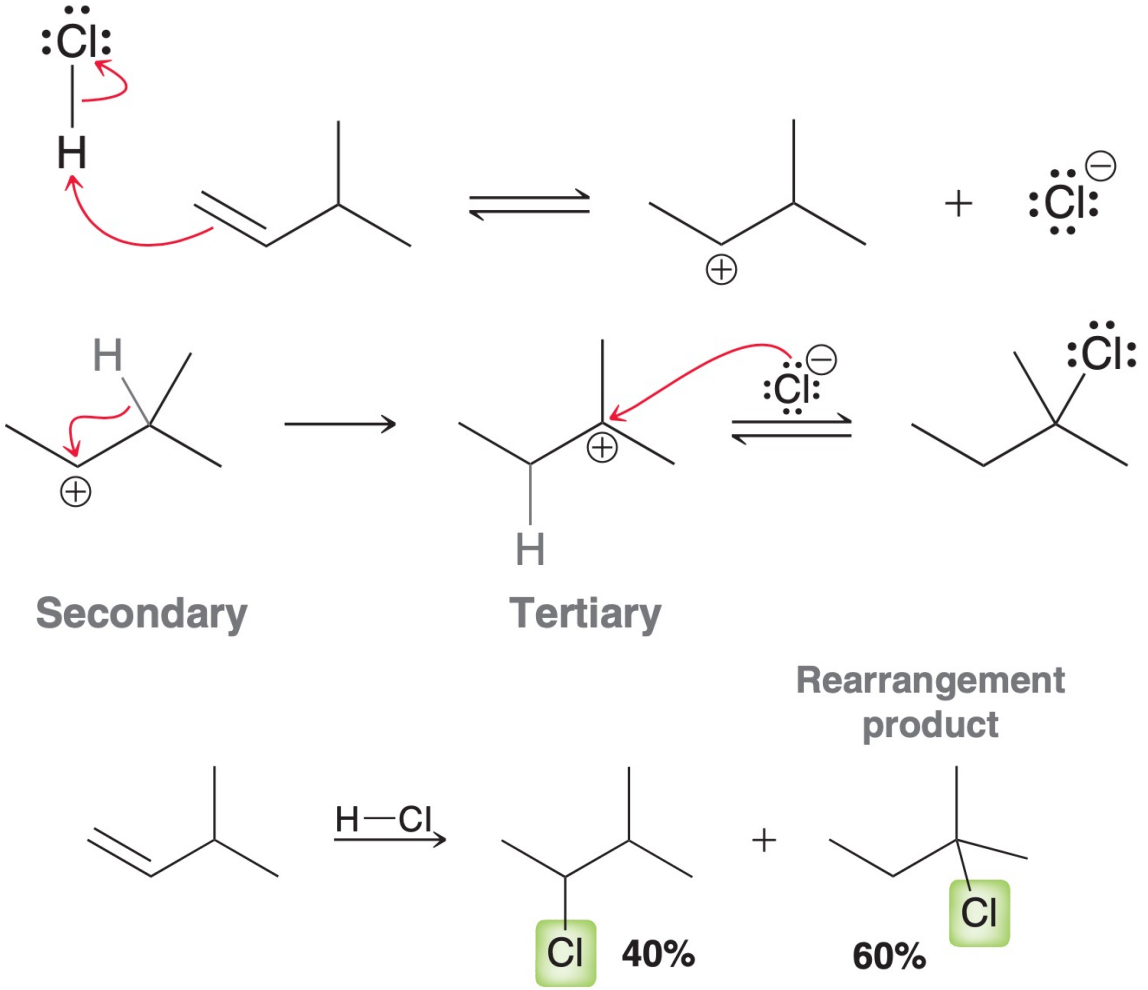


潜手性化合物

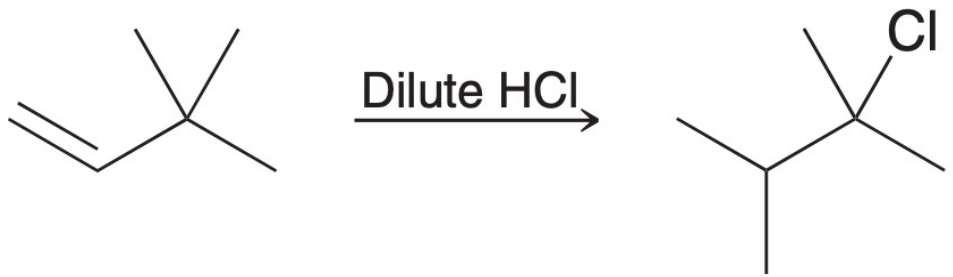
prochiral compound

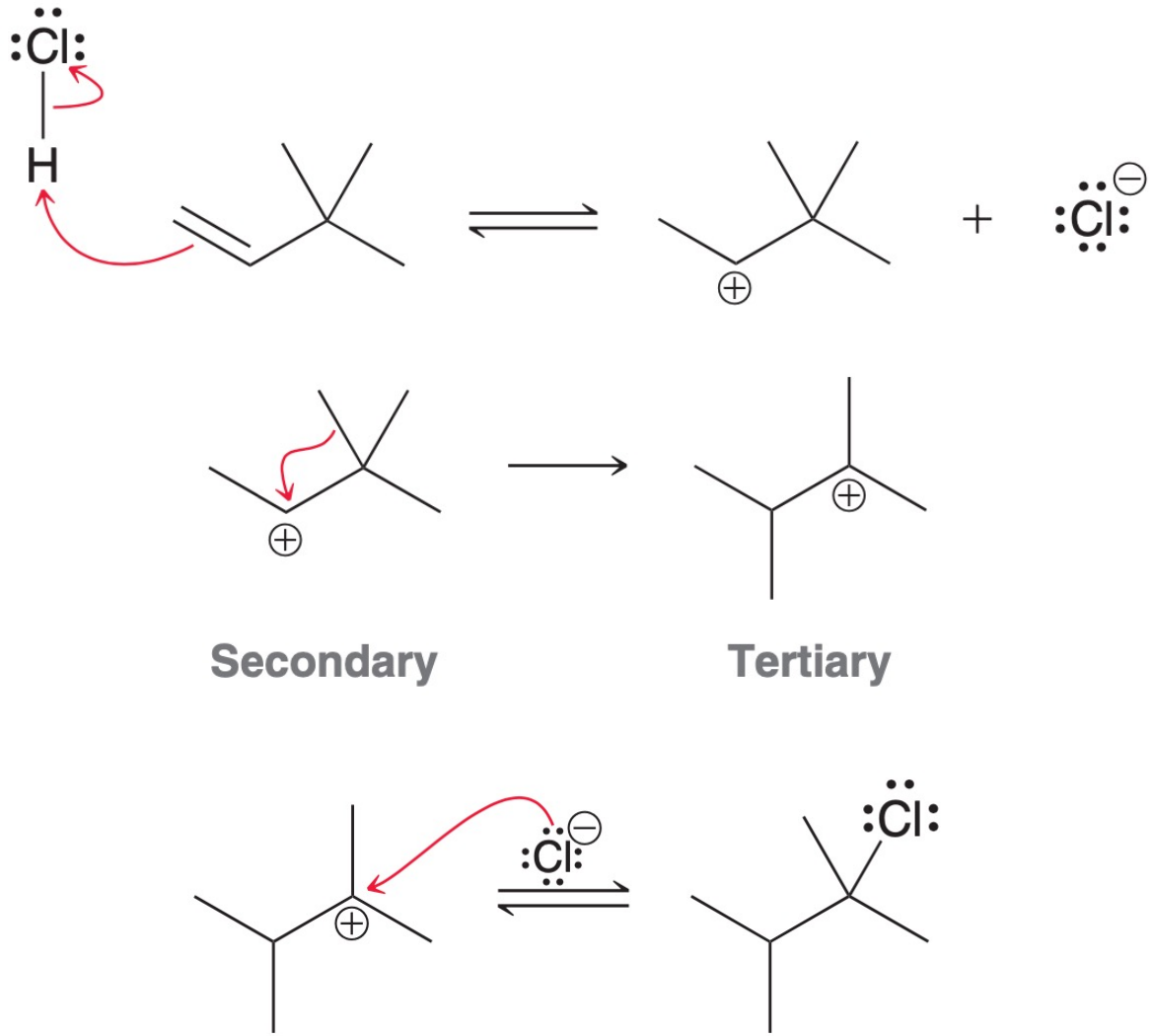


- 氢卤化过程中的碳正离子重排

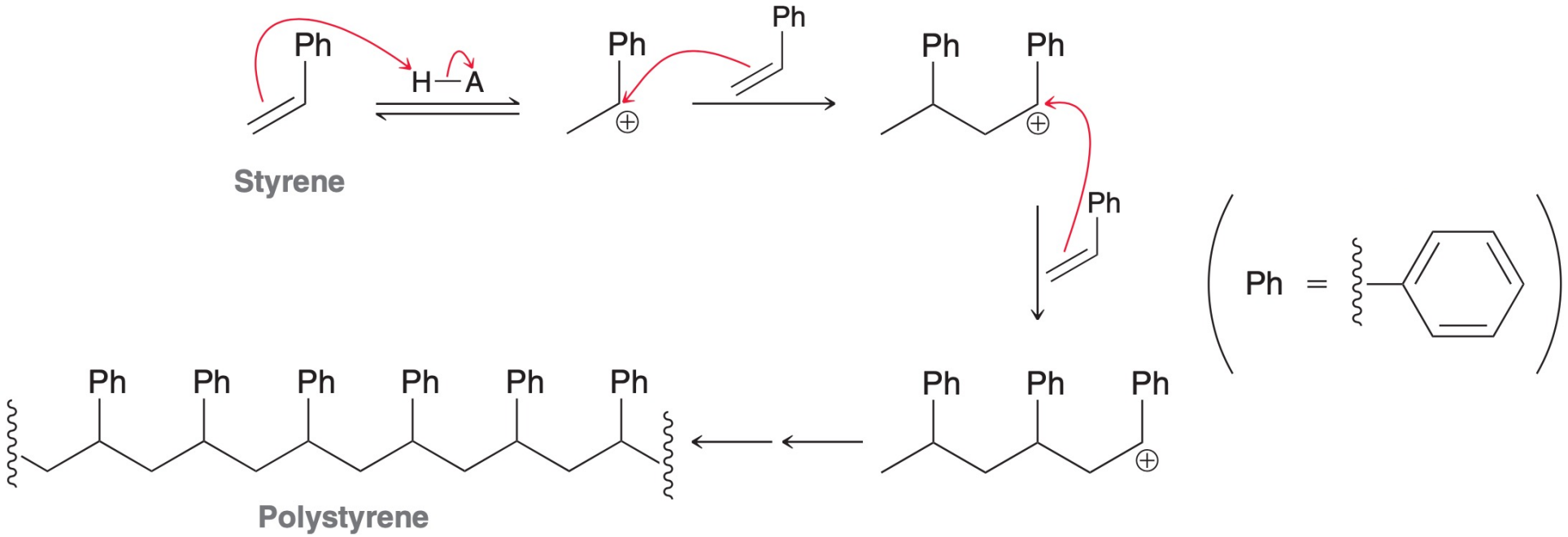


- Practice: draw a mechanism for the following transformation:

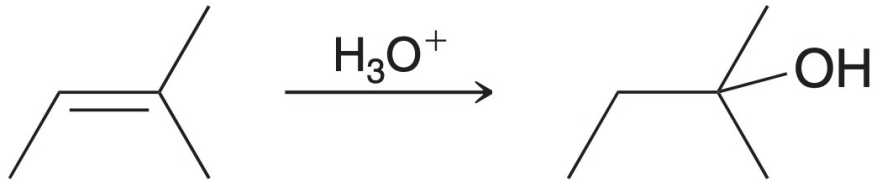



Secondary
Tertiary

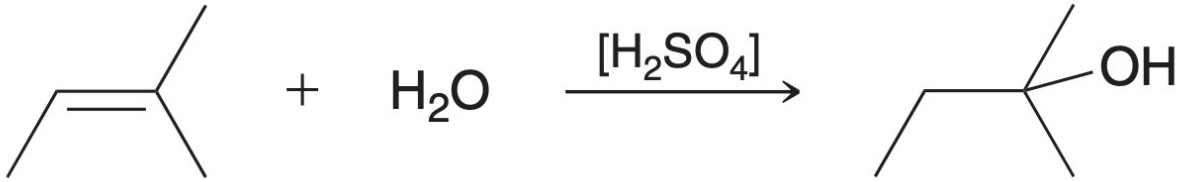
- Cationic polymerization and polystyrene



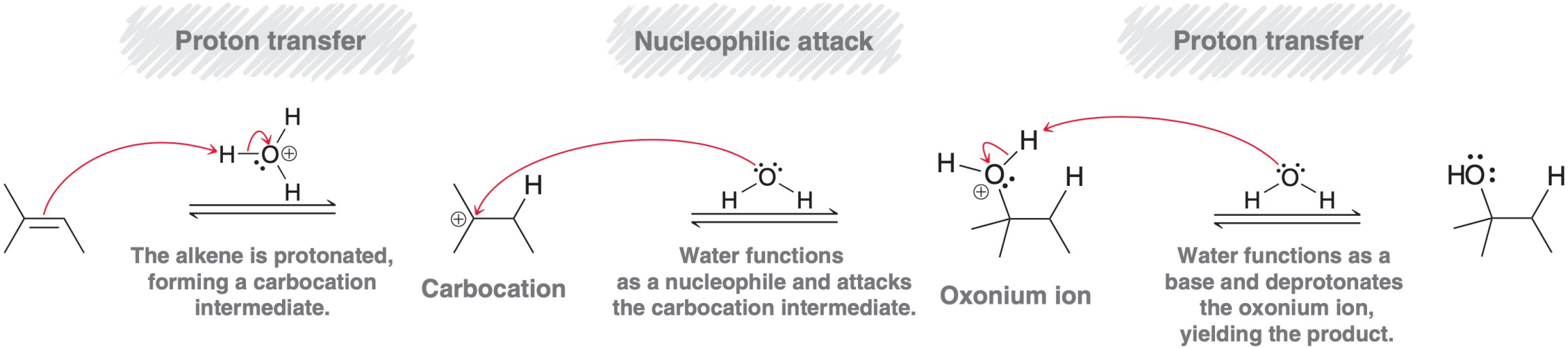
- **酸催化的水合反应**



(90%)

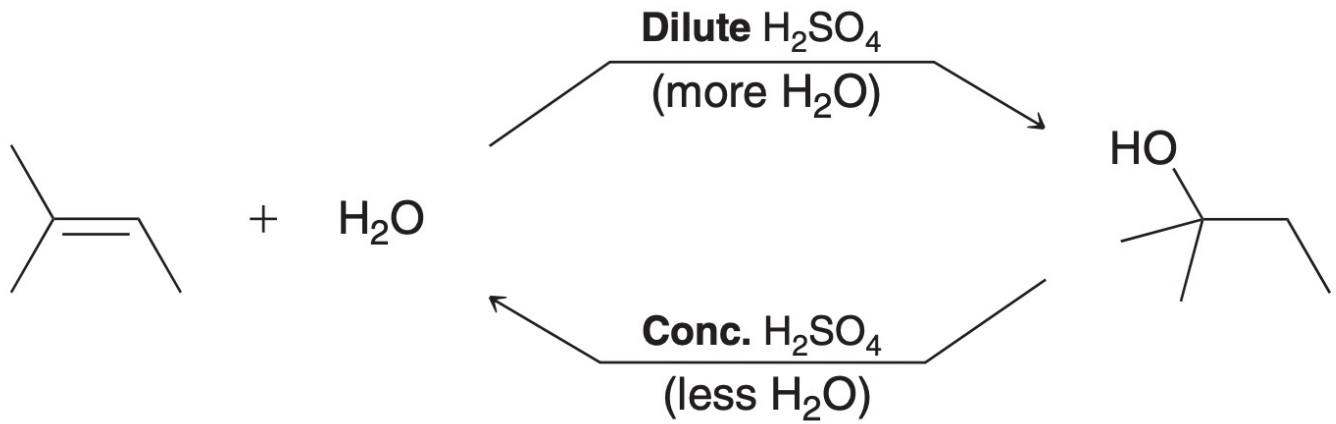


- **The Mechanism of Acid-Catalyzed Hydrohalogenation**

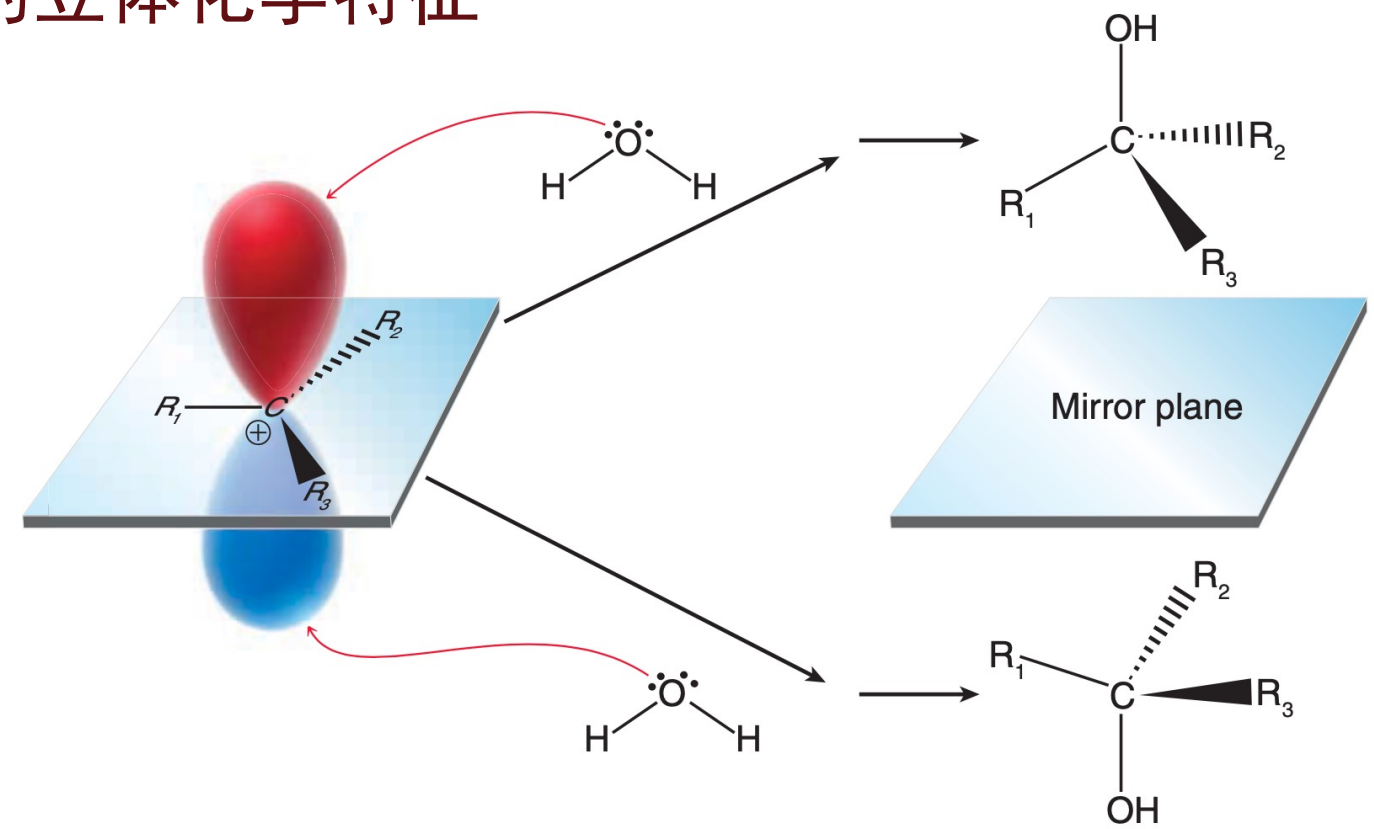


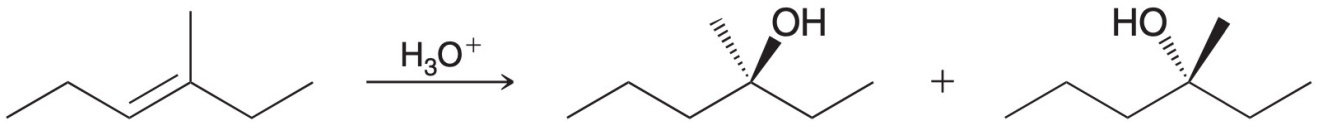
存在碳正离子中间体——马氏加成

- 硫酸的浓度控制反应的方向



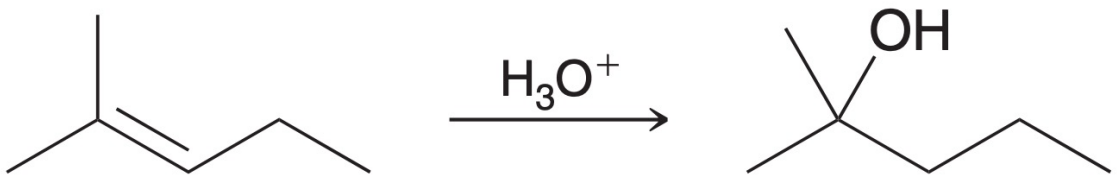
- 烯烃水合的立体化学特征



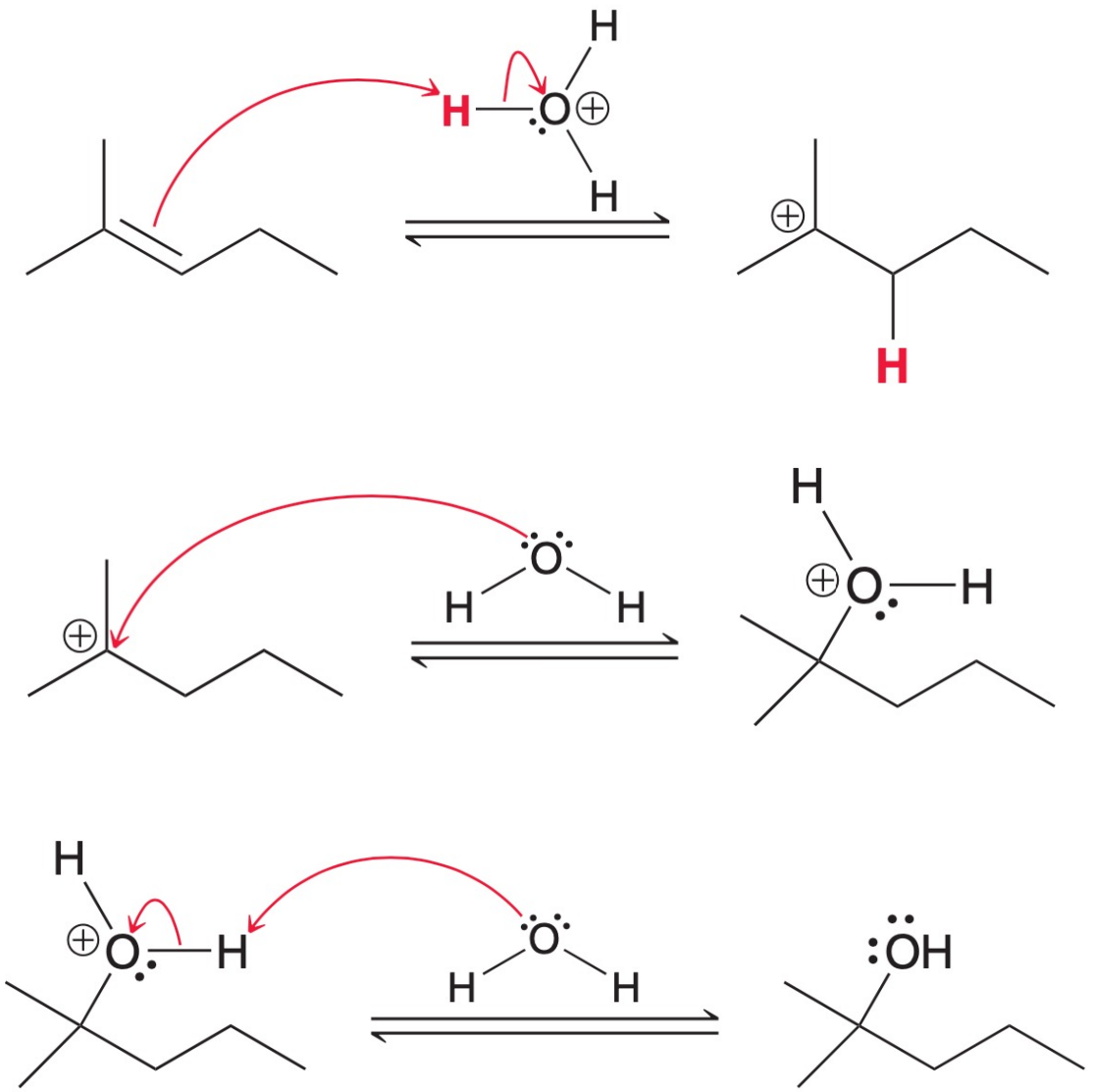


生成消旋的产物

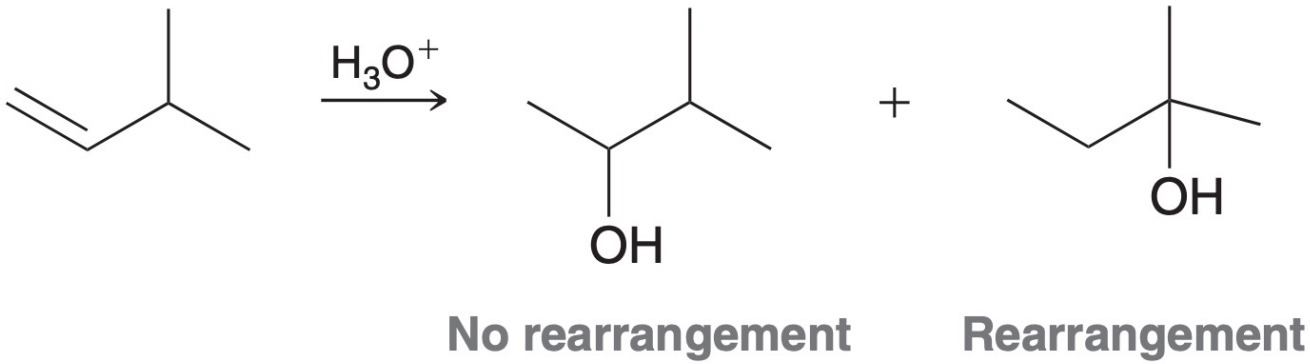
- Practice: draw a mechanism for the following transformation:



Acid-Catalyzed Hydration

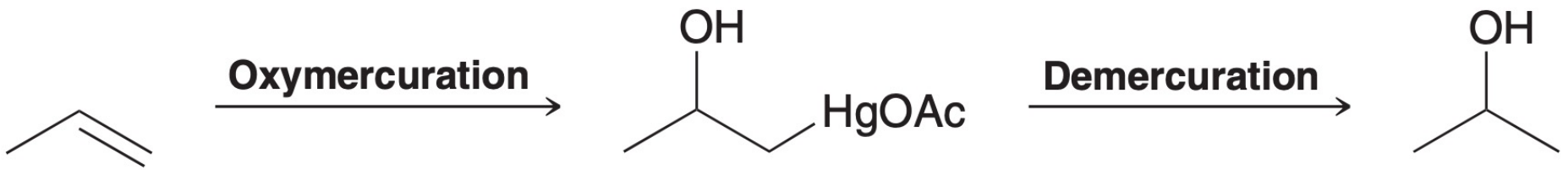


- 酸催化的水合反应存在重排的现象



反应较为低效！

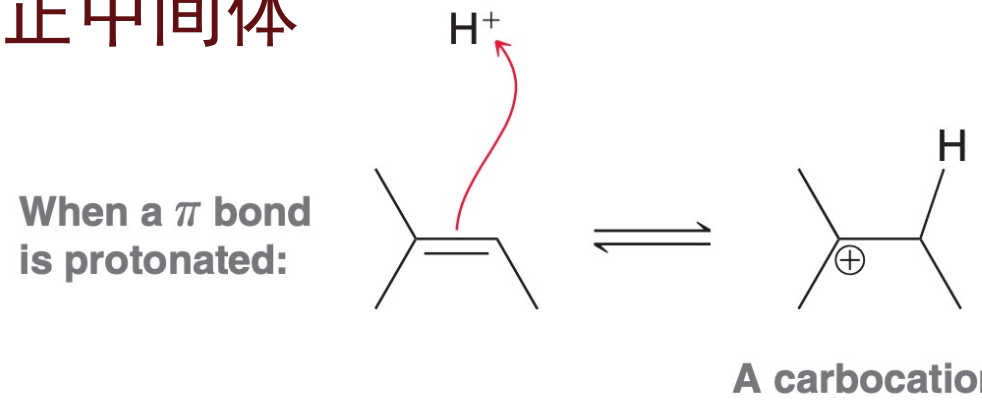
- **氧化羟汞化-脱汞**

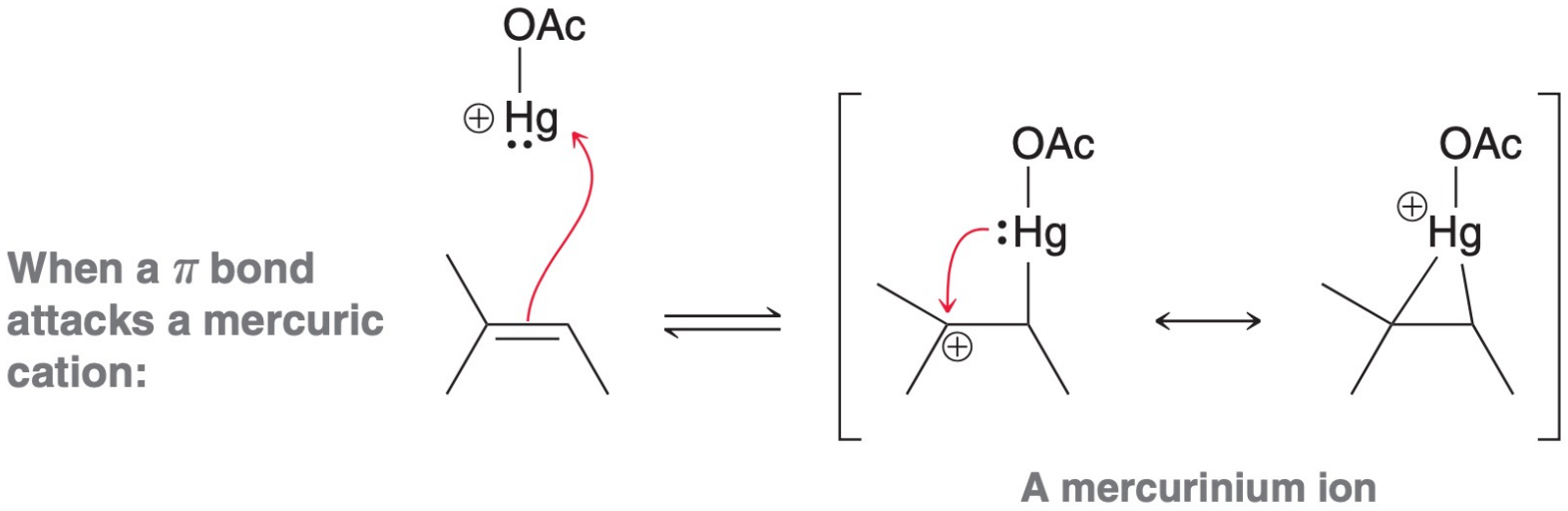


- 有机汞试剂

Mercuric acetate　　Mercuric cation

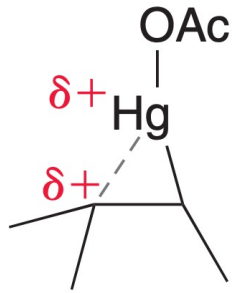
- 羟汞化不形成碳正中间体



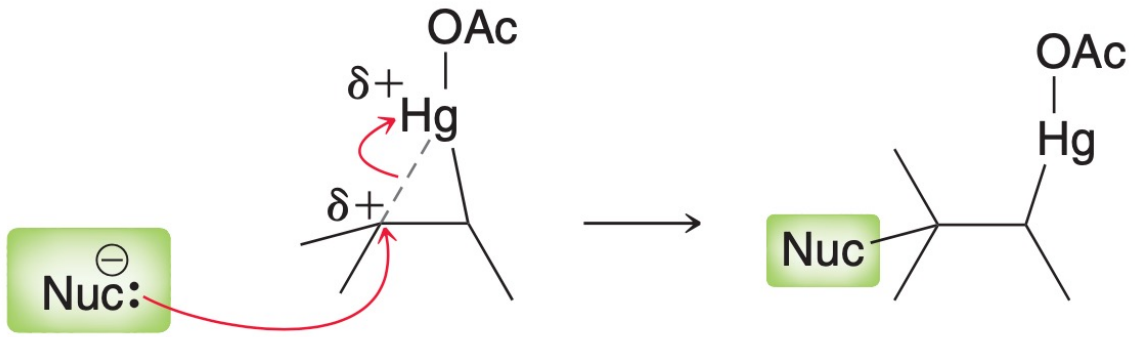


汞鎓(wēng)离子

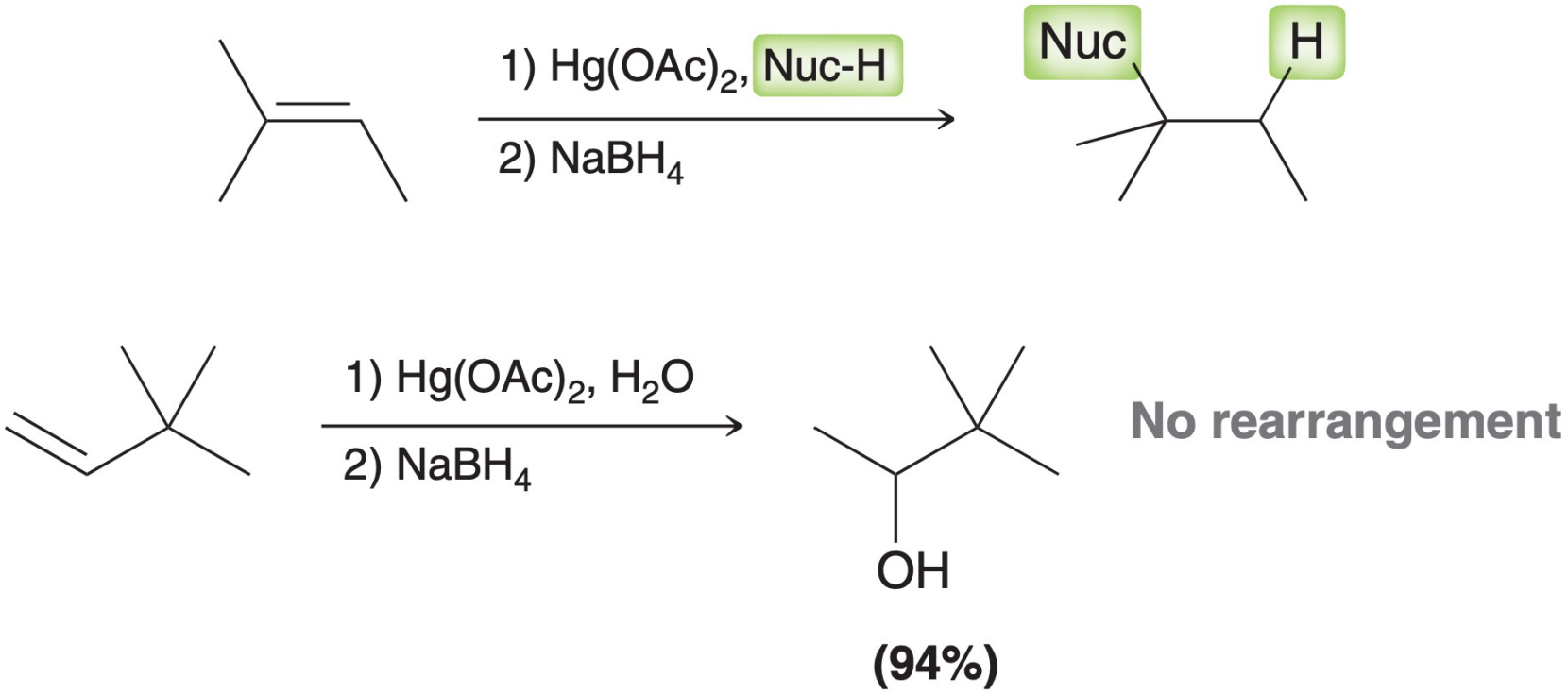
- 汞鎓(wēng)离子的反应



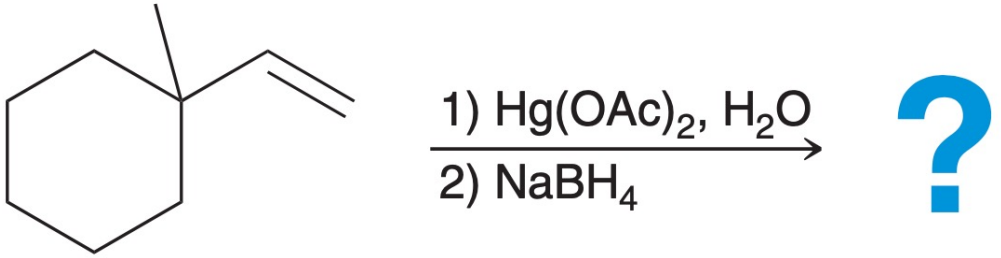
Mercurinium ion

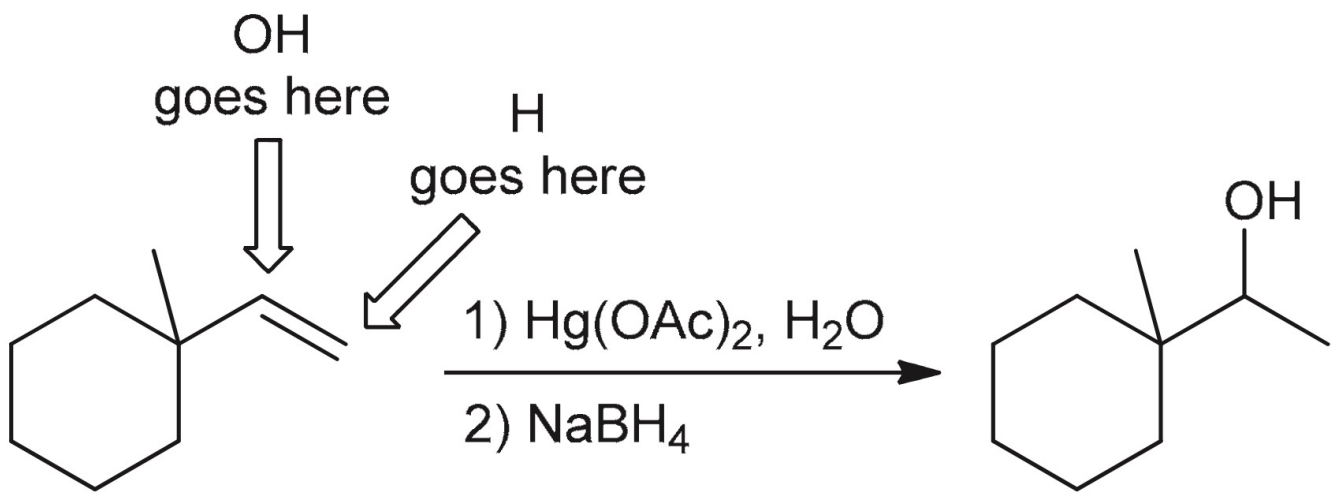


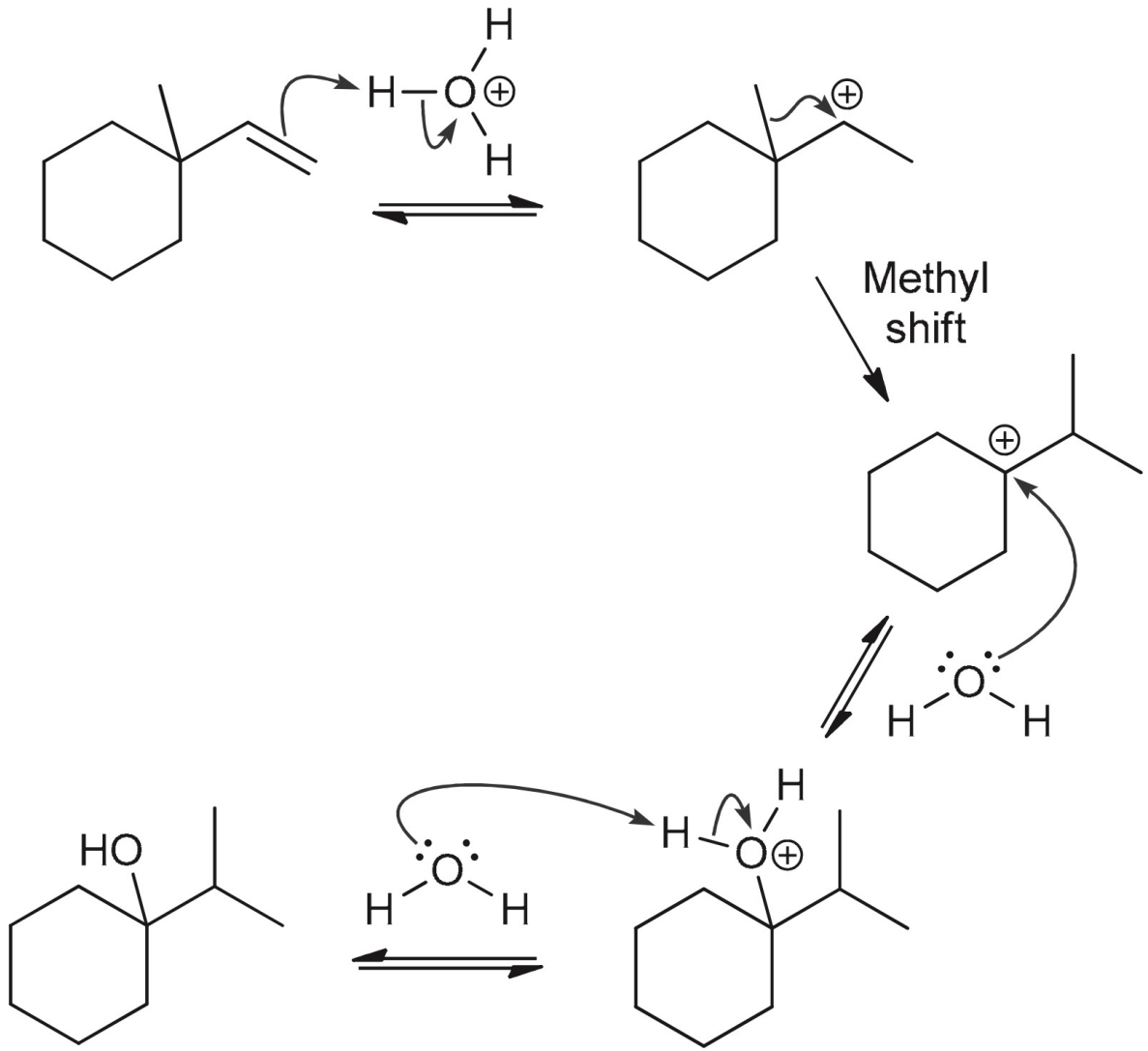
- 脱汞化


1) Hg(OAc)2, Nuc-H
2) NaBH4
Nuc
H
1) Hg(OAc)2, H2O
2) NaBH4
OH
(94%)
No rearrangement

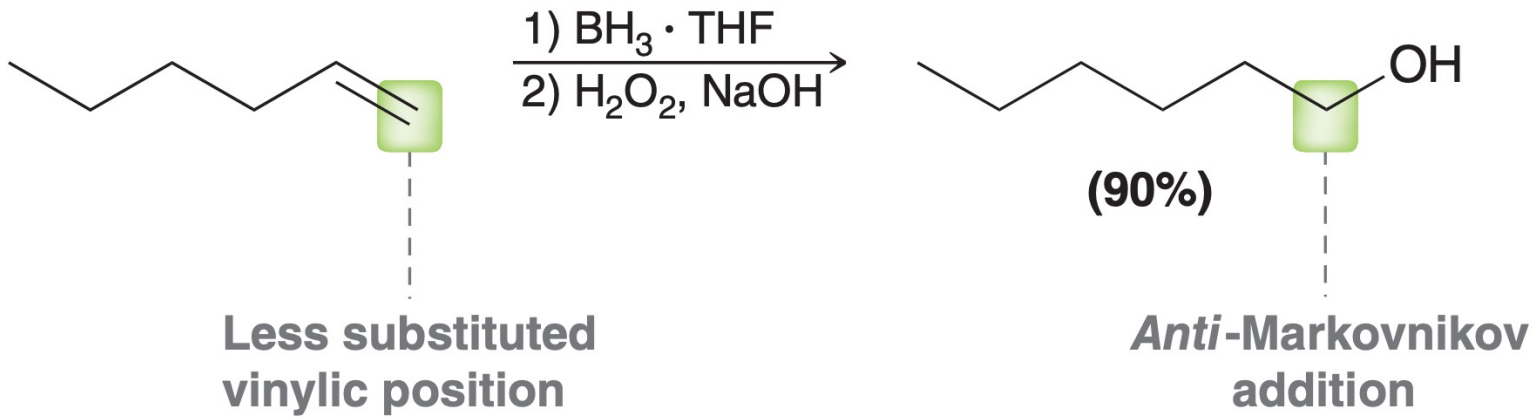
- Practice: predict the product for the reaction, and predict the products if an acid-catalyzed hydration had been performed rather than an oxymercuration-demercuration:




OH
goes here
H
goes here
1) Hg(OAc)2, H2O
2) NaBH4
OH


H
H—O⊕
H
Methyl
shift
HO
H
O
H
H
H
O⊕

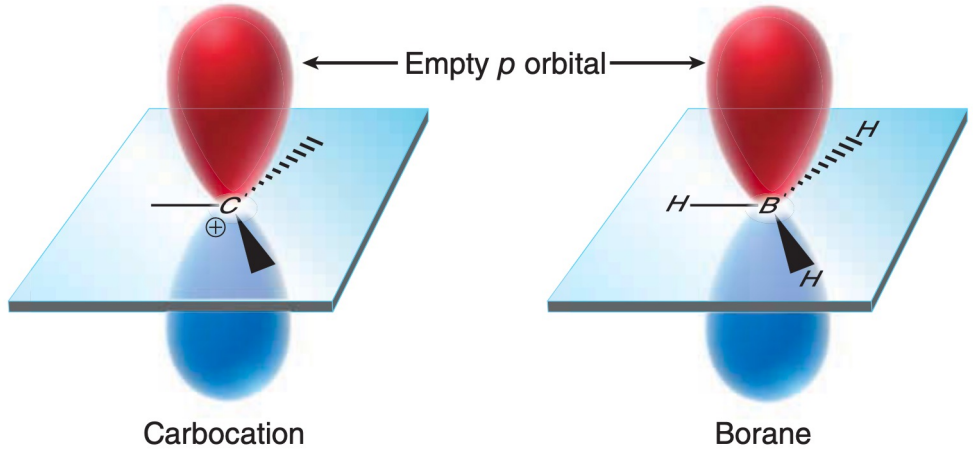
- **硼氢化-氧化**

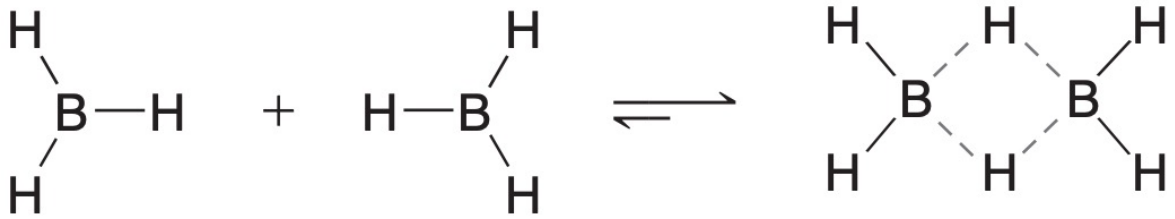


不同于酸催化水合和羟汞化的马氏加成

硼氢化-氧化为**反马加成**

- 硼烷

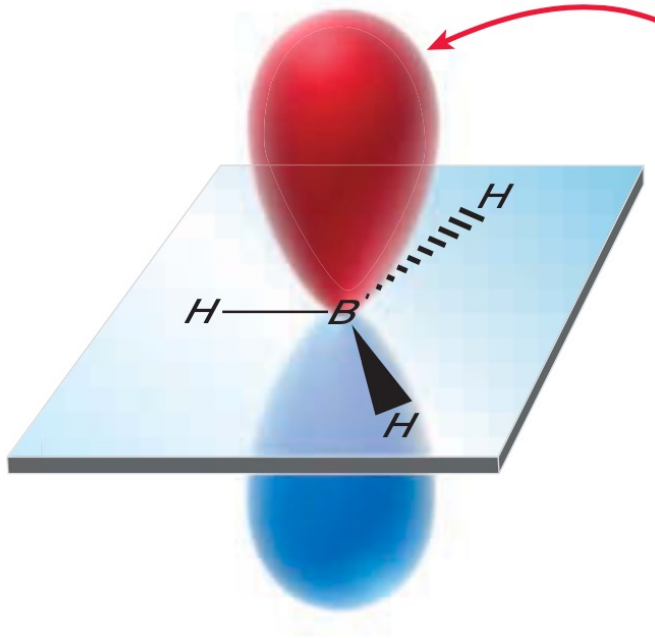


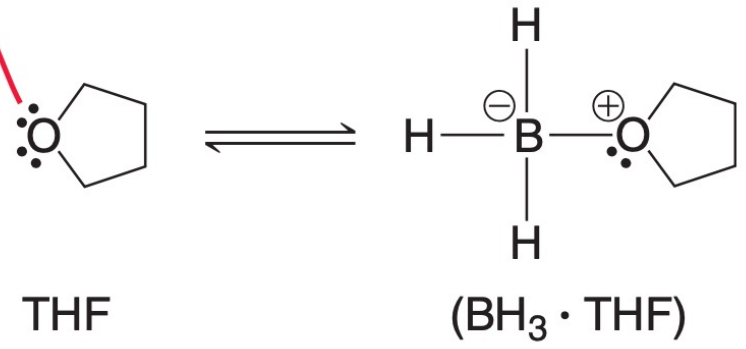


Borane　　Diborane

甲硼烷易以二聚体的形式存在

- 使用四氢呋喃(THF)作配体稳定甲硼烷





THF

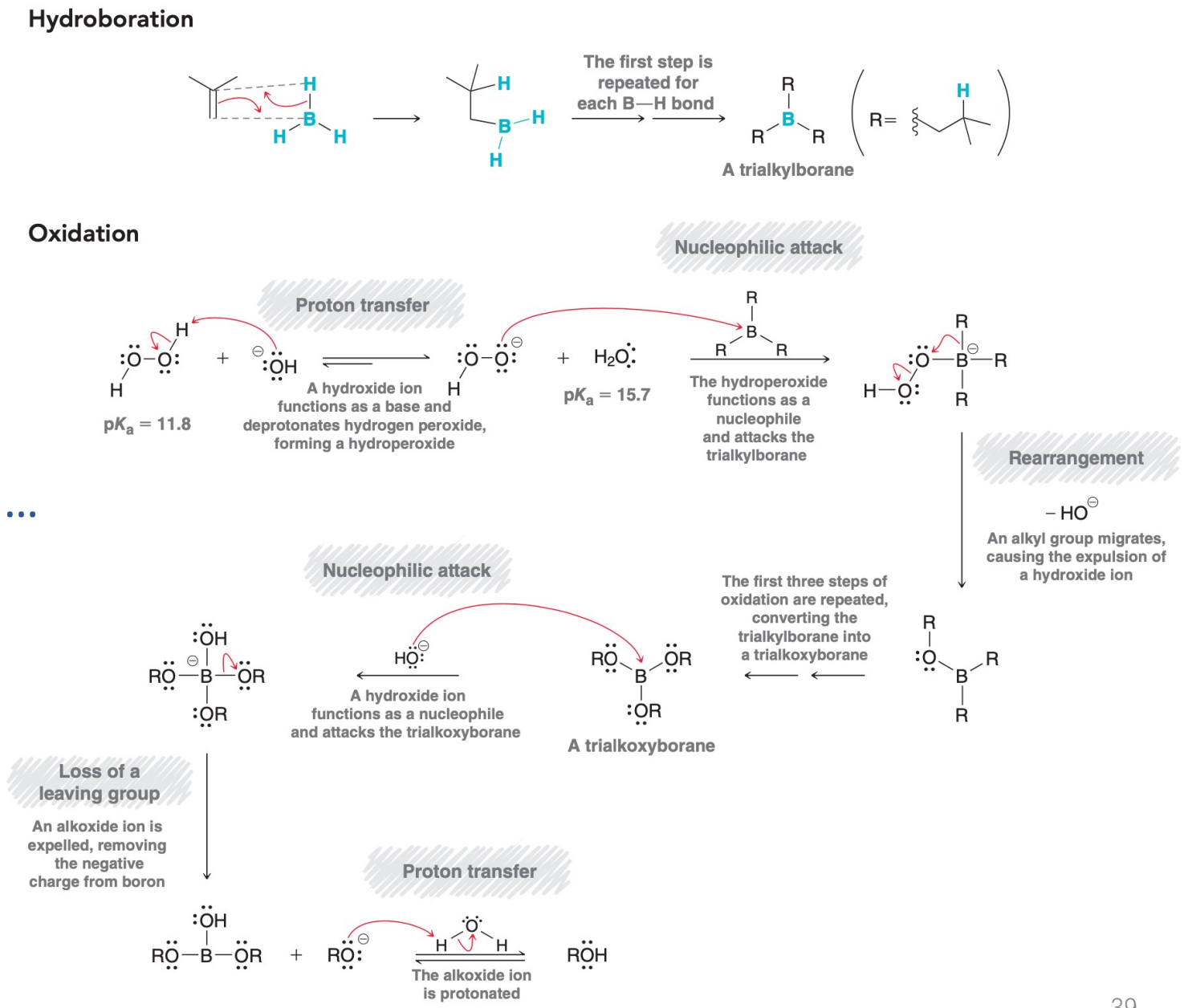
$(BH_3 \cdot THF)$

tetrahydrofuran

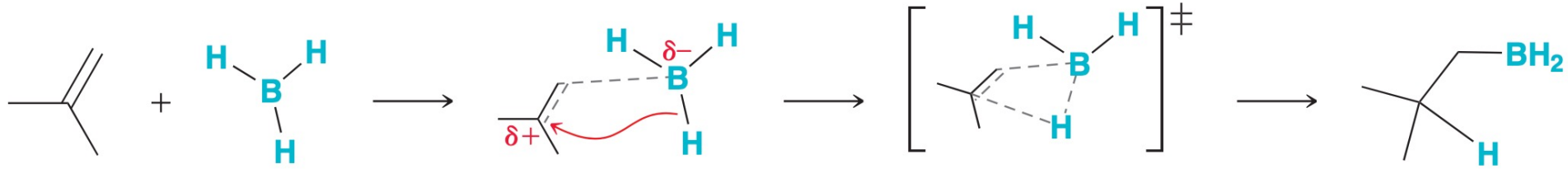
四氢呋喃

- 反应机理

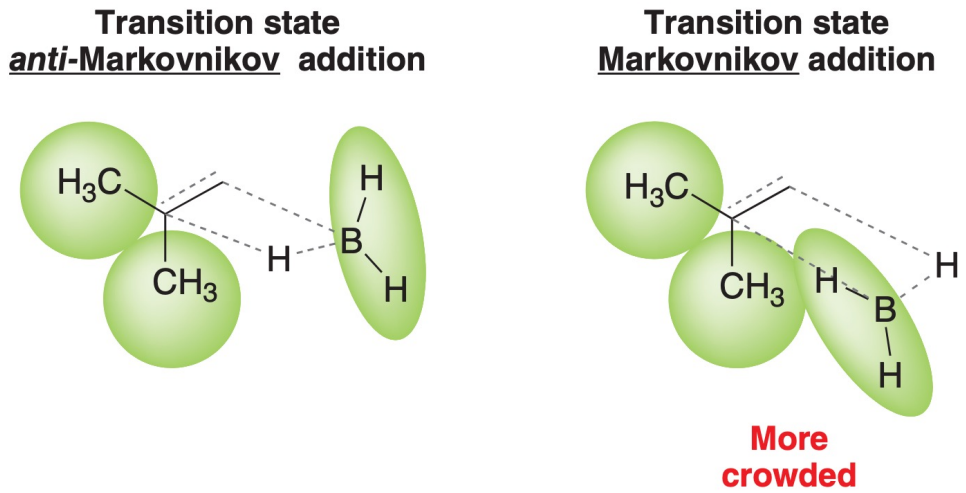
a very complicated mechanism…



- 硼氢化的区域选择性与立体选择性

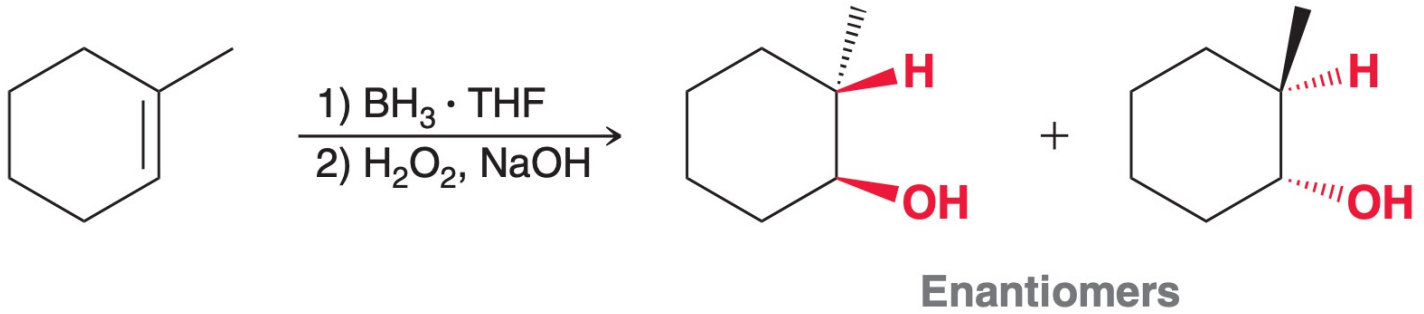


电子效应：多取代碳原子能够稳定正电荷

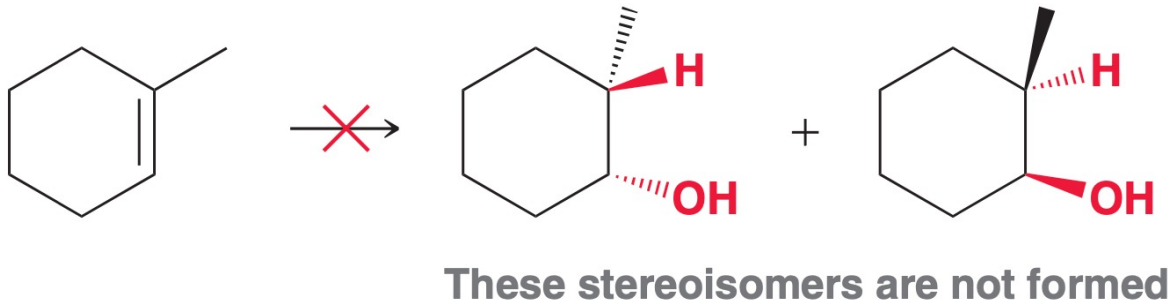


位阻：反式构型位阻更小，更稳定

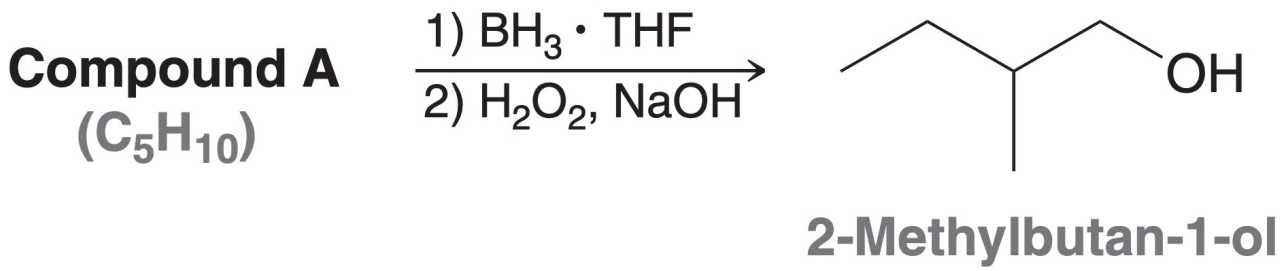
- 硼氢化-氧化的立体专一性

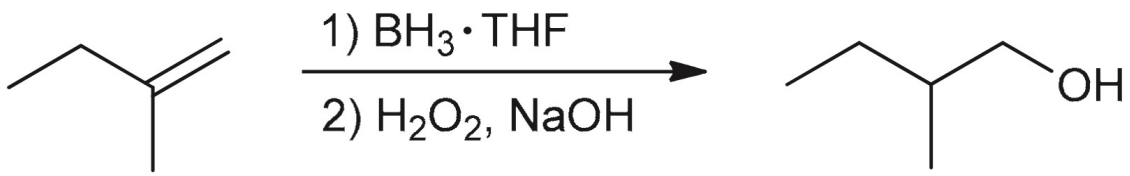


***syn* addition**

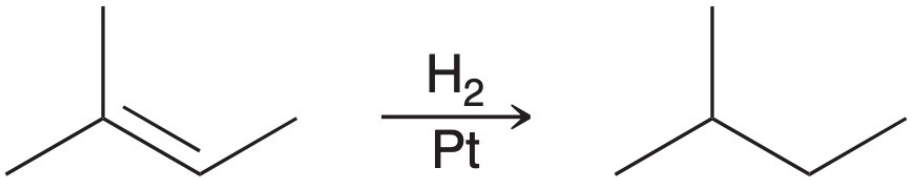


- Practice: compound **A** has the molecular formula C_5H_{10}. Hydroboration-oxidation of compound **A** produces 2-methylbutan-1-ol. Draw the structure of compound **A**:



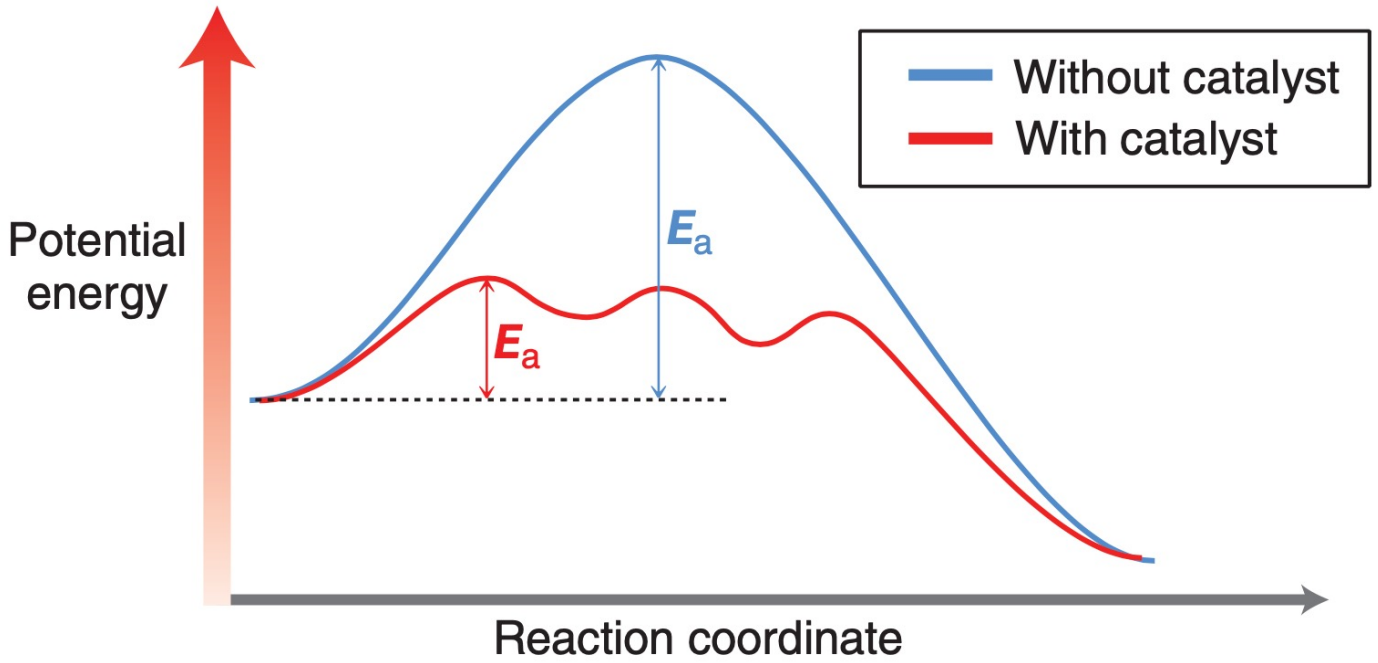


- **表面催化氢化**

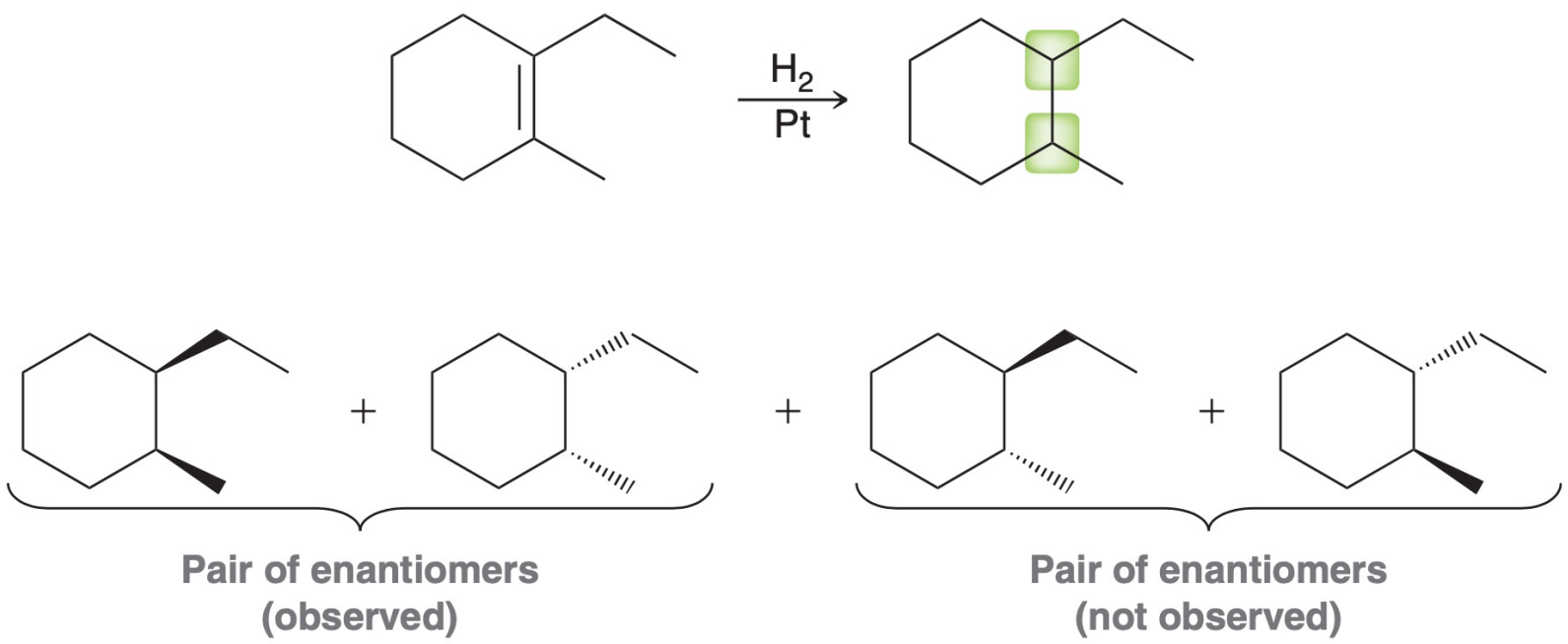


(100%)

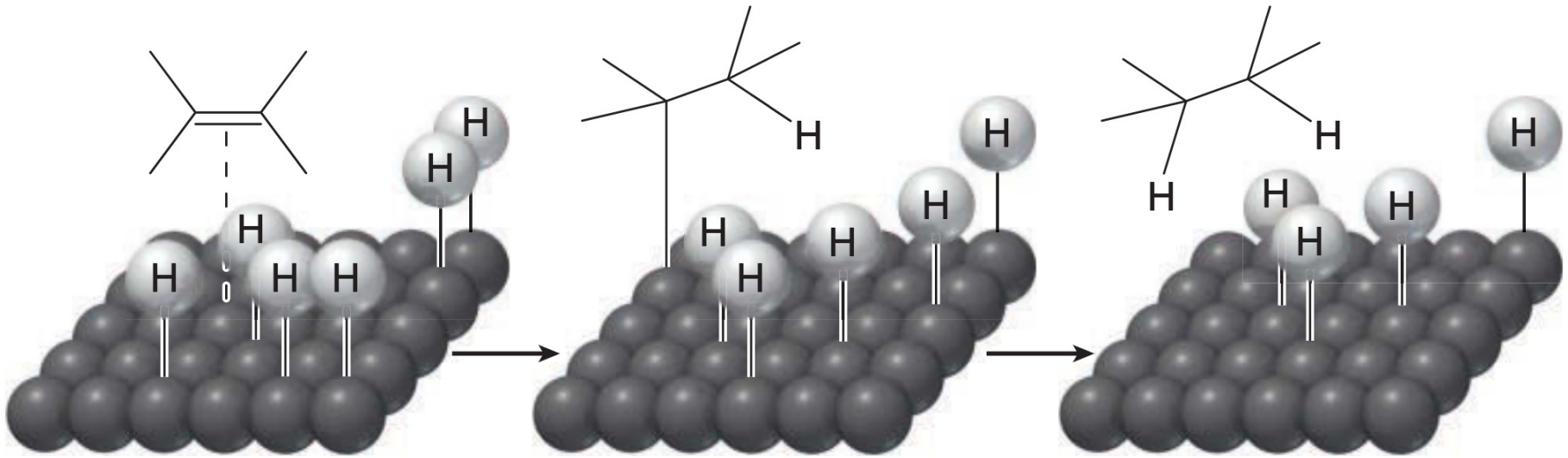
- 催化剂降低反应活化能


Without catalyst
With catalyst
Potential energy
E_a
E_a
Reaction coordinate

- 表面催化氢化的立体专一性



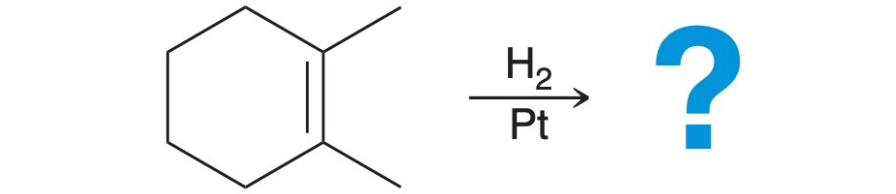
- 表面催化机理



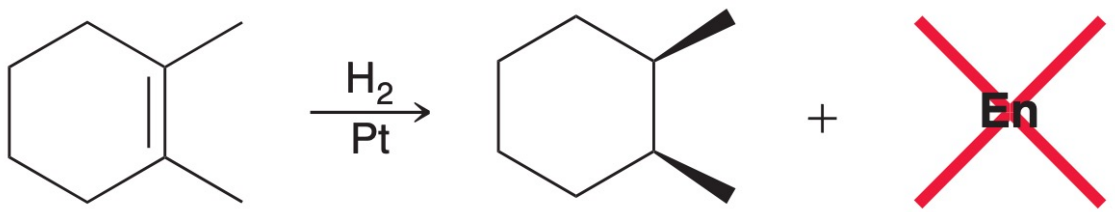
- 判断加成后的产物是否存在手性

Zero chiral centers	*Syn* requirement is not relevant. Only one product formed.
One chiral center	Both possible enantiomers are formed.
Two chiral centers	The requirement for *syn* addition determines which pair of enantiomers is obtained.

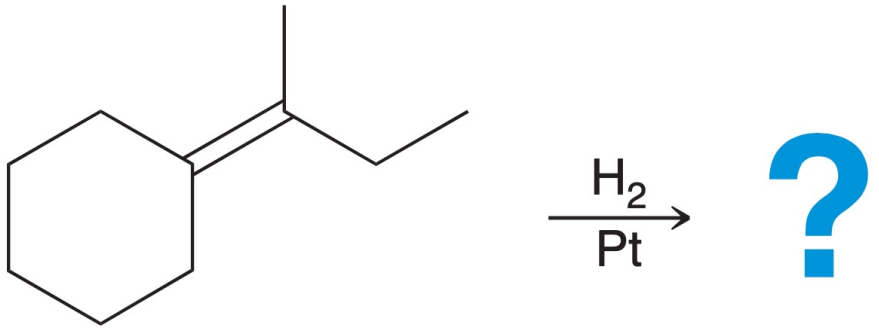
- 生成内消旋化合物时不用加En.

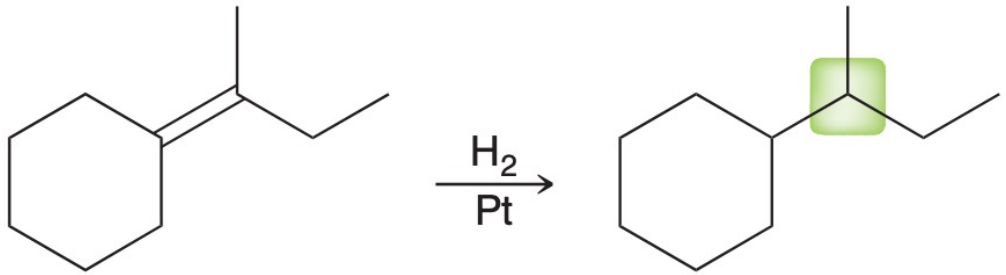


***Syn* addition produces only only one product:**
a *meso* compound

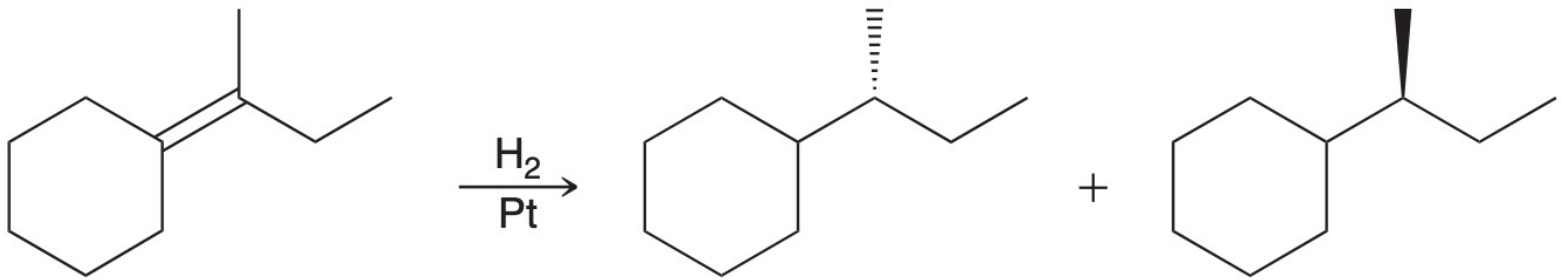


- Practice: predict the products of each of the following reactions:

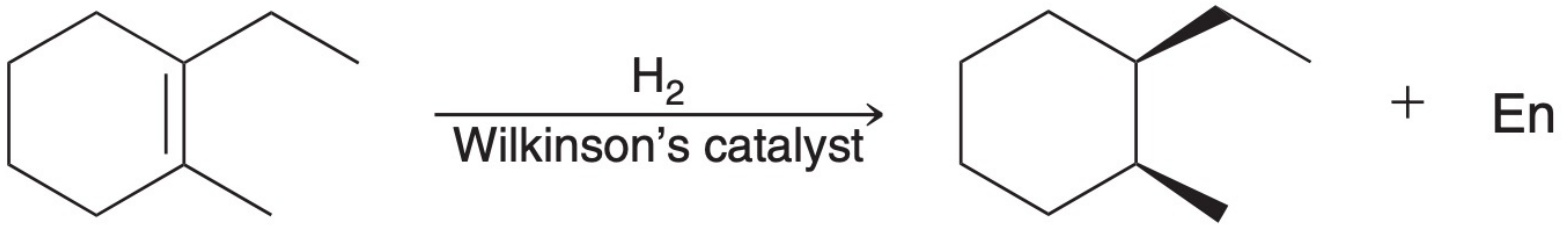


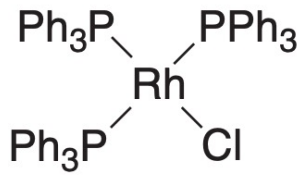


One chiral center



- 均相催化(homogenous catalysis)



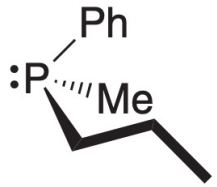


Wilkinson's catalyst

均相催化剂：与反应物处于同一相内

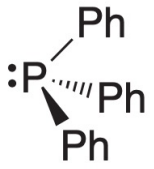
- **手性催化氢化**

使用手性膦(lìn)配体

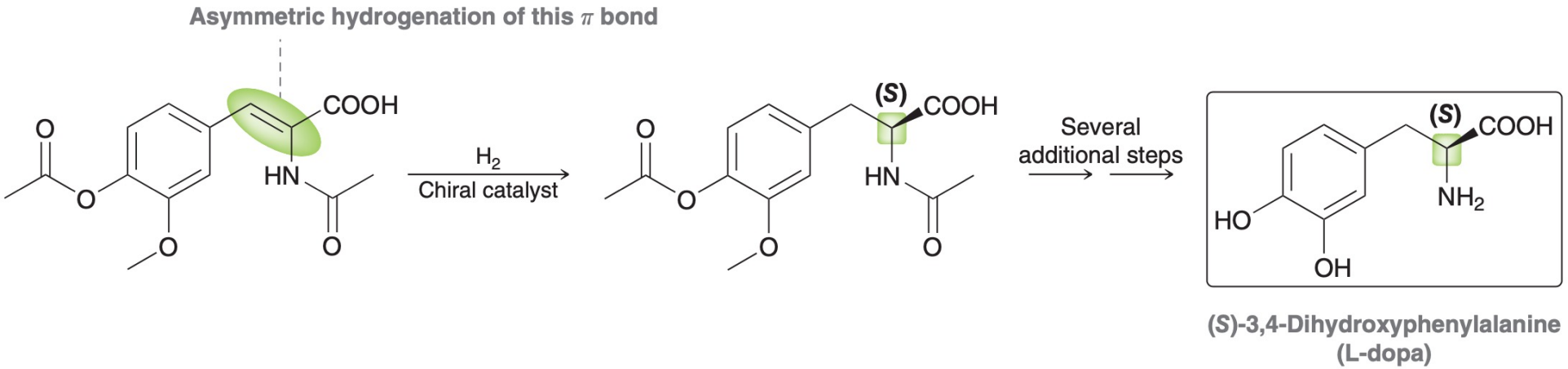


Chiral phosphine ligand

rather than

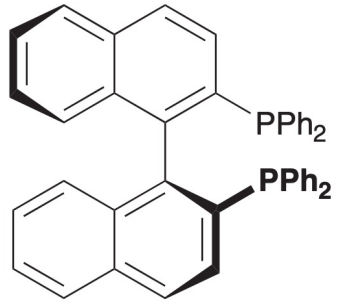


Symmetrical phosphine ligand

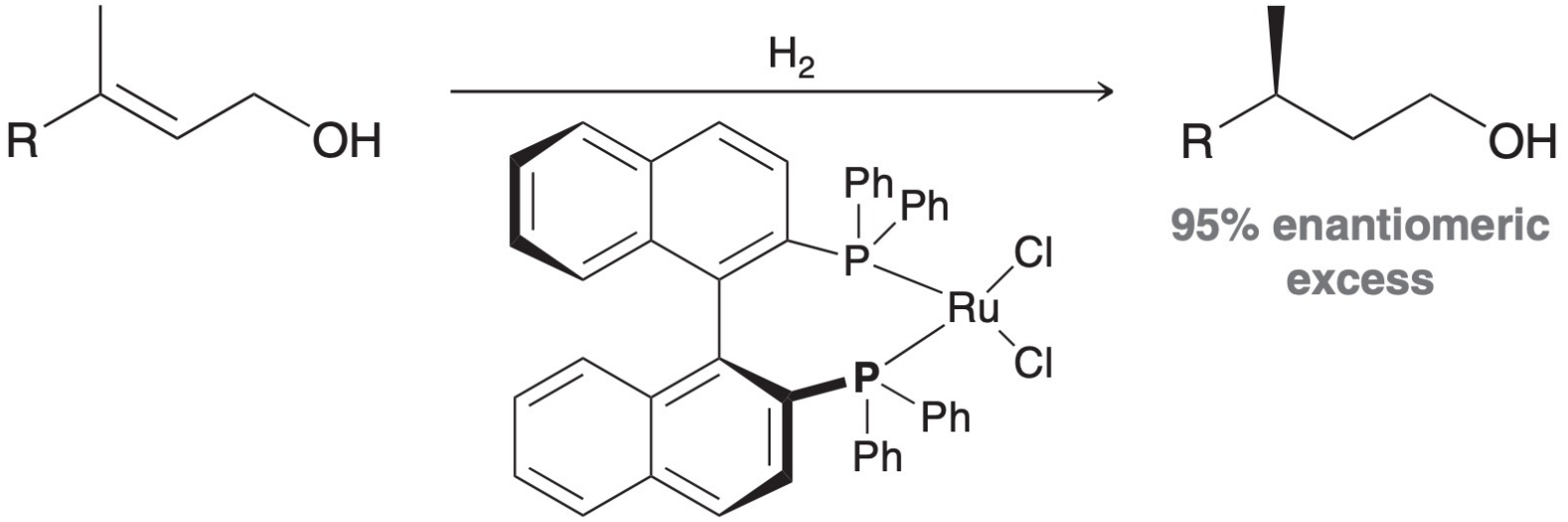


(*S*)-3,4-Dihydroxyphenylalanine (L-dopa)

- 手性配体



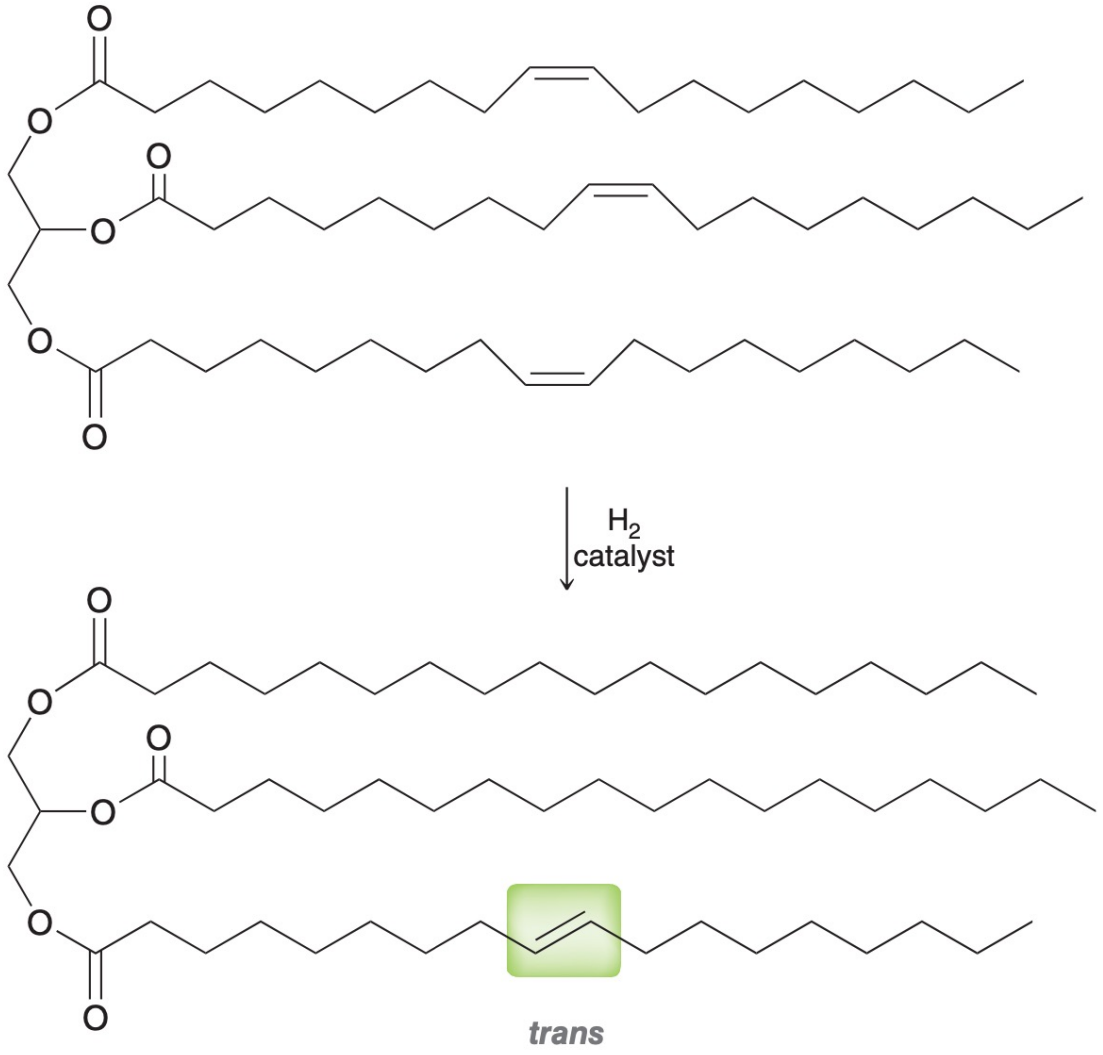
(*S*)-(–)-BINAP
(*S*)-2,2′-Bis(diphenylphosphino)-1,1′-binaphthyl



95% enantiomeric excess

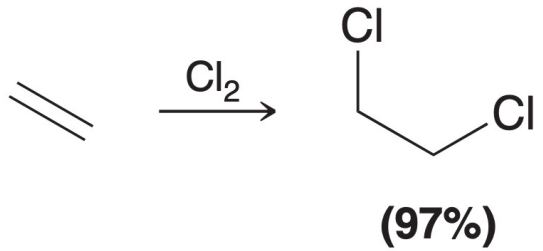
$Ru(BINAP)Cl_2$

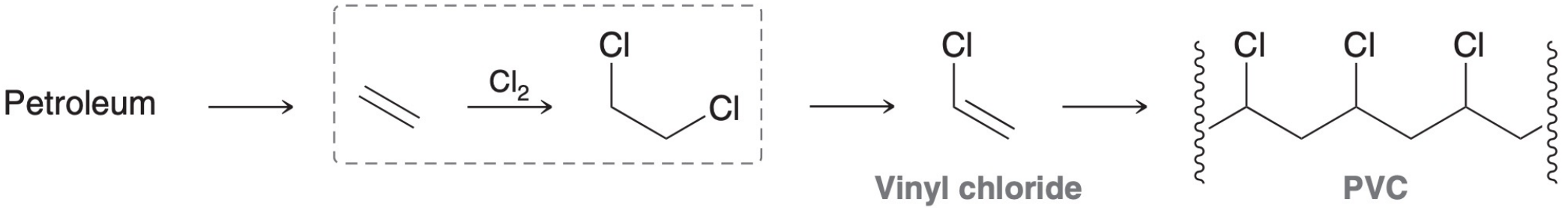
- 油脂的催化氢化



可能产生反式双键

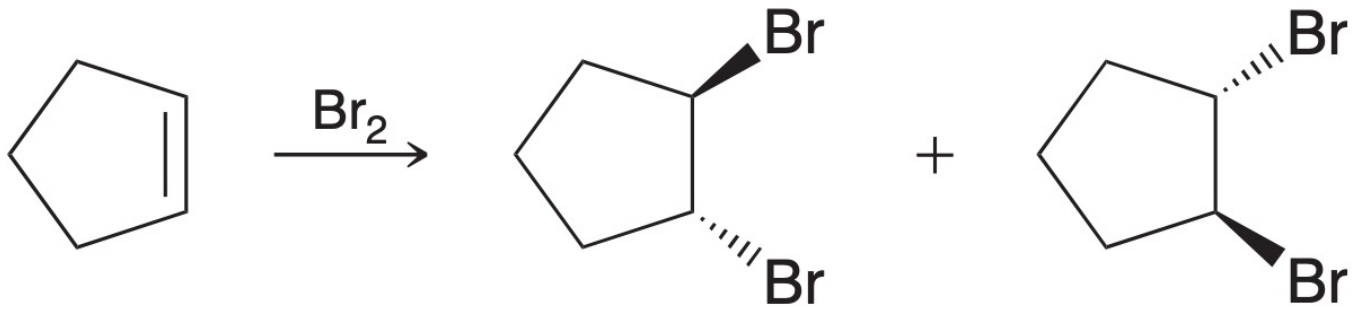
- **双卤化**

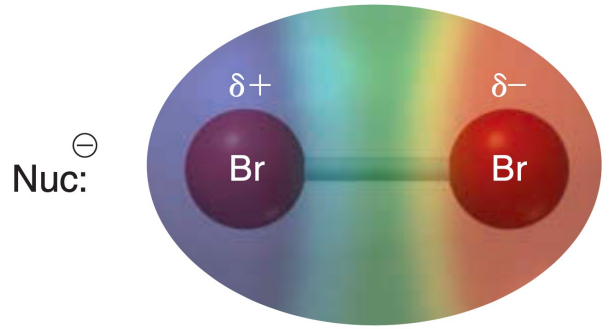




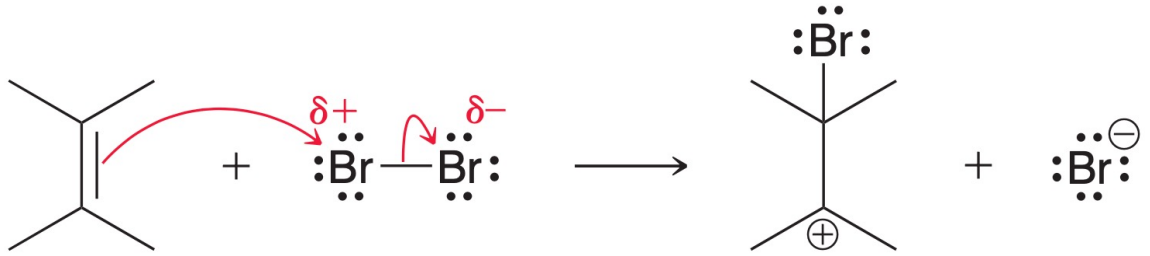
双卤化产物可用于生产PVC塑料

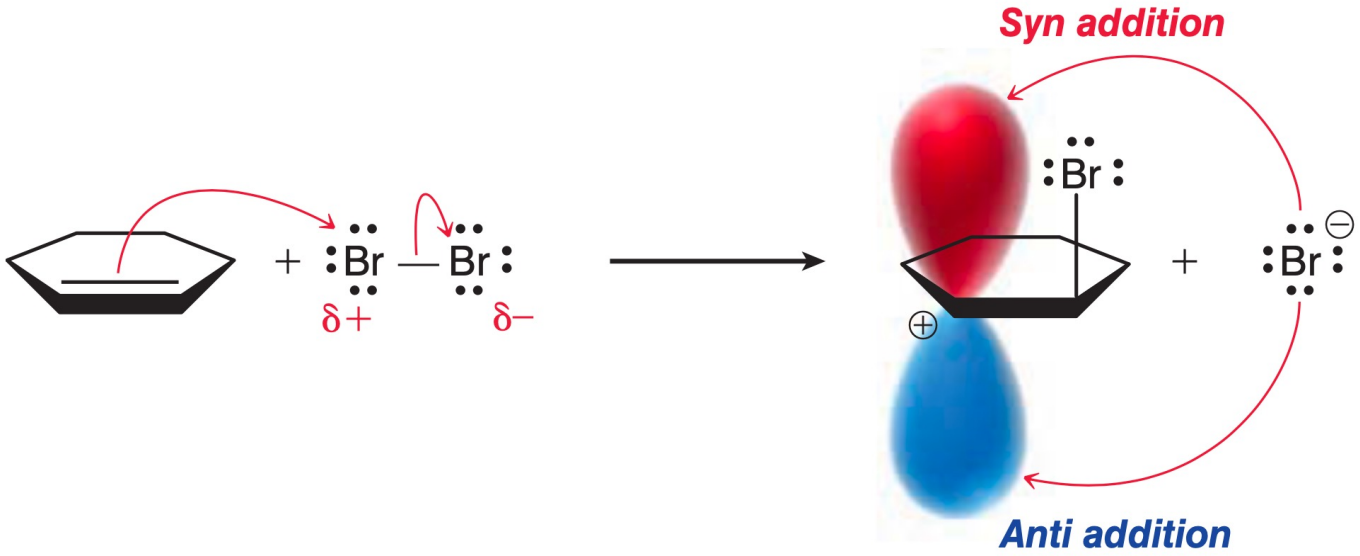
- 立体专一性：双卤化为反式加成





- 可能的反应机理……?



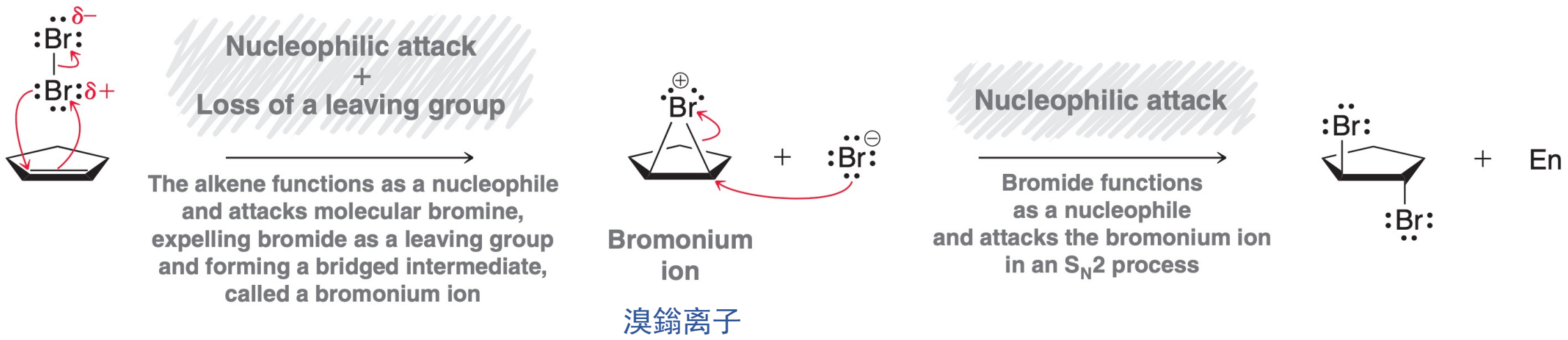


发生顺式和反式加成的机会均等...

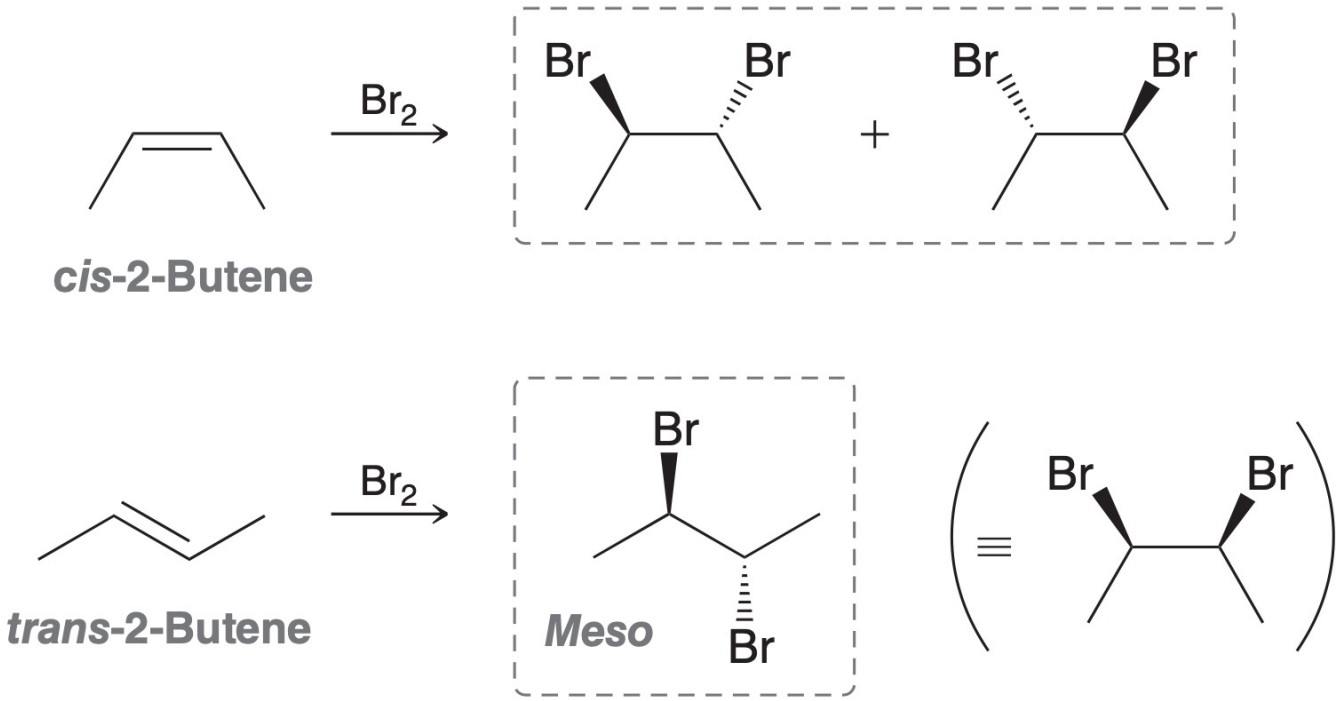
然而.....

与实际产物的立体构型不符！

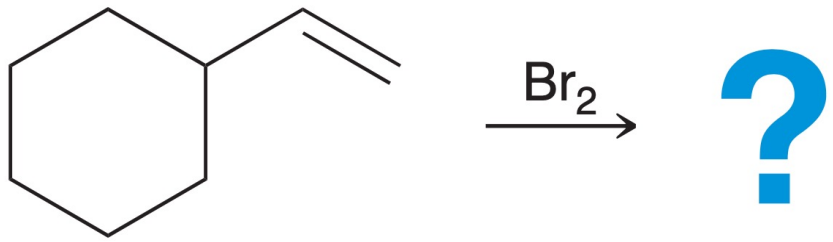
- **The Mechanism of Halogenation**



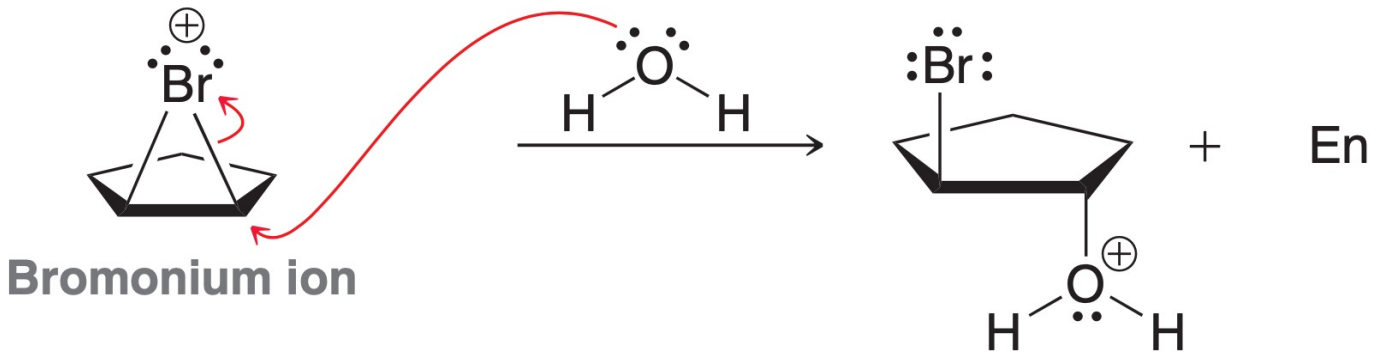
- 注意内消旋化合物的生成



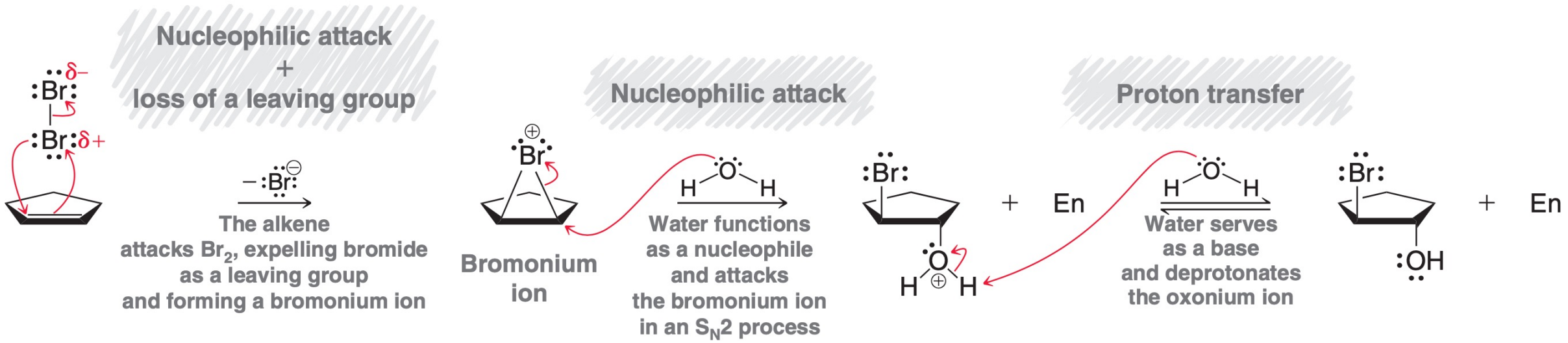
- Practice: propose a mechanism, and predict the major product(s) for the following reaction:



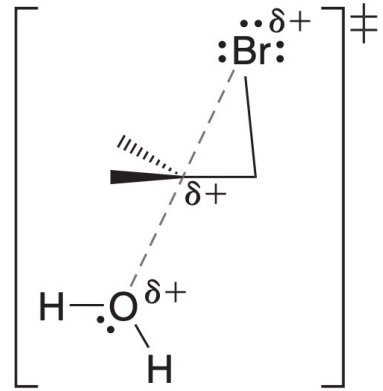
- **羟卤化**



- **The Mechanism of Halohydrin Formation**

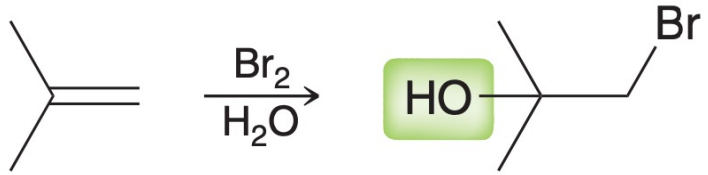


- 羟卤化的区域选择性

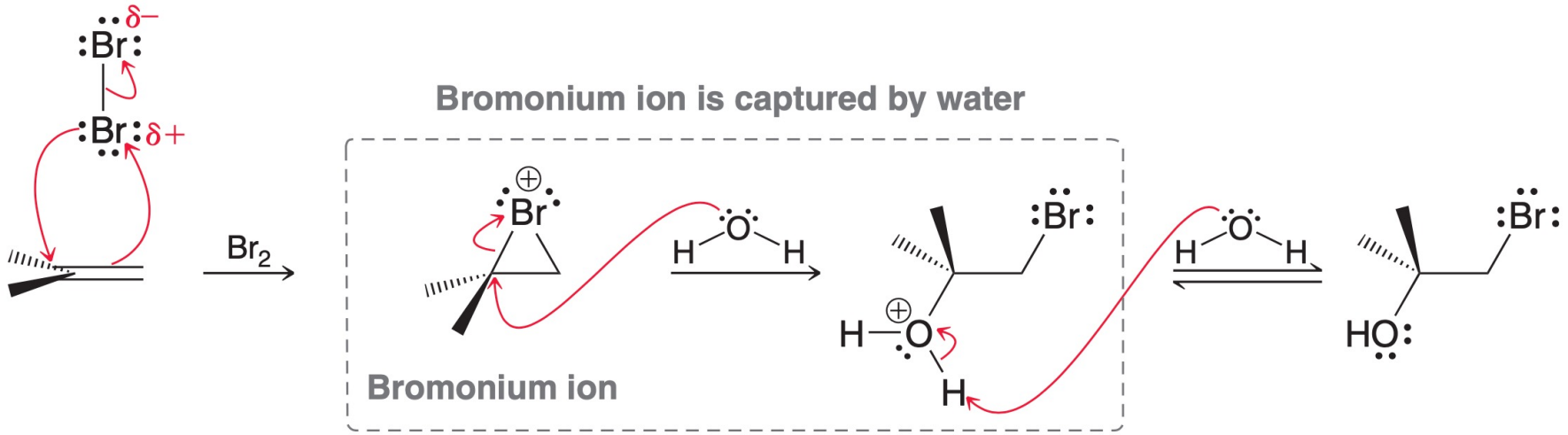


过渡态具有部分碳正离子的性质

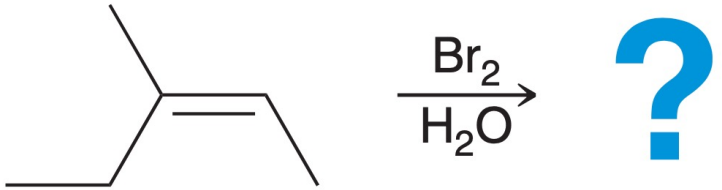
正电荷位于多取代的碳上更稳定

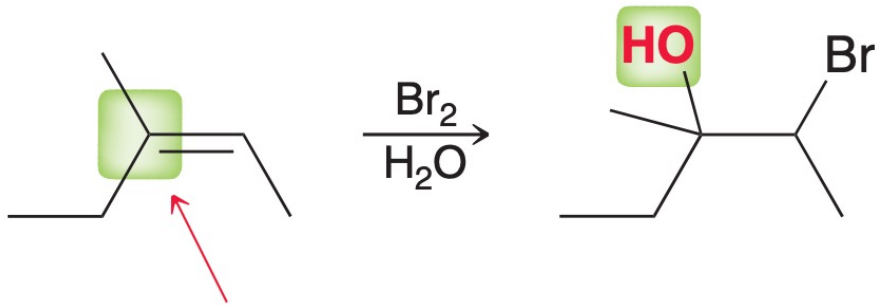


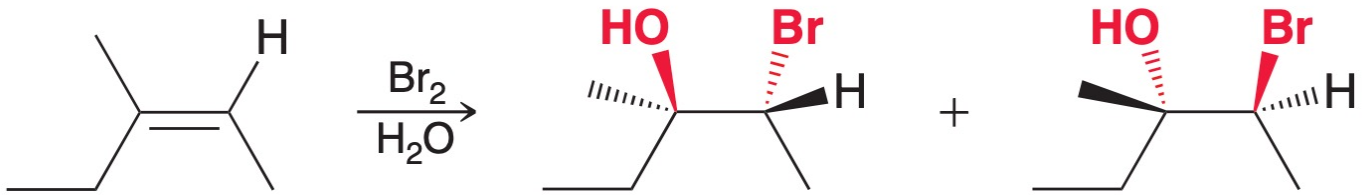
羟基加成在多取代的碳上



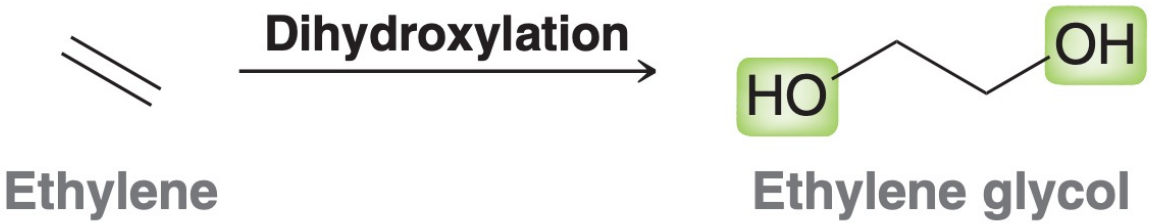
- Practice: predict the major product(s) for the following reaction:



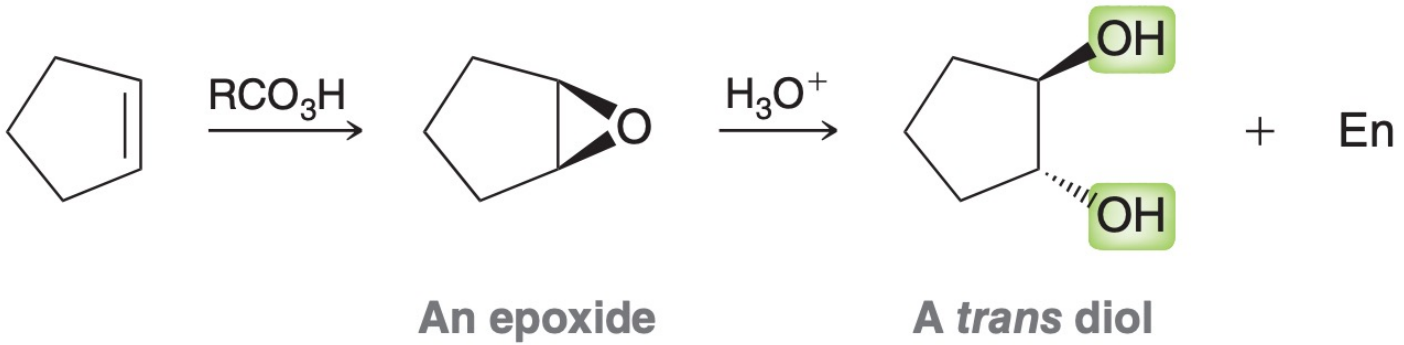

HO
Br
Br_2
H_2O
OH group is placed here
at the more substituted position


H
Br_2
H_2O
HO
Br
H
+
HO
Br
H

- **双羟化**

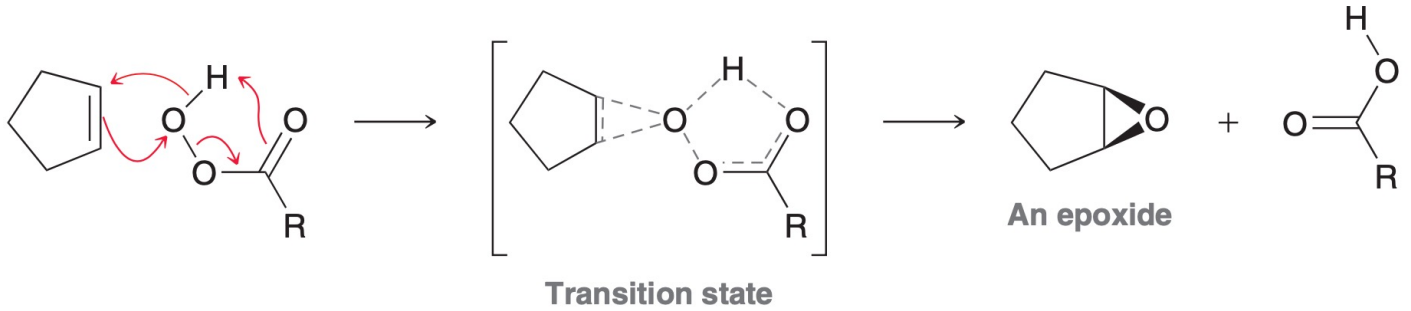


- 反式双羟化：环氧化

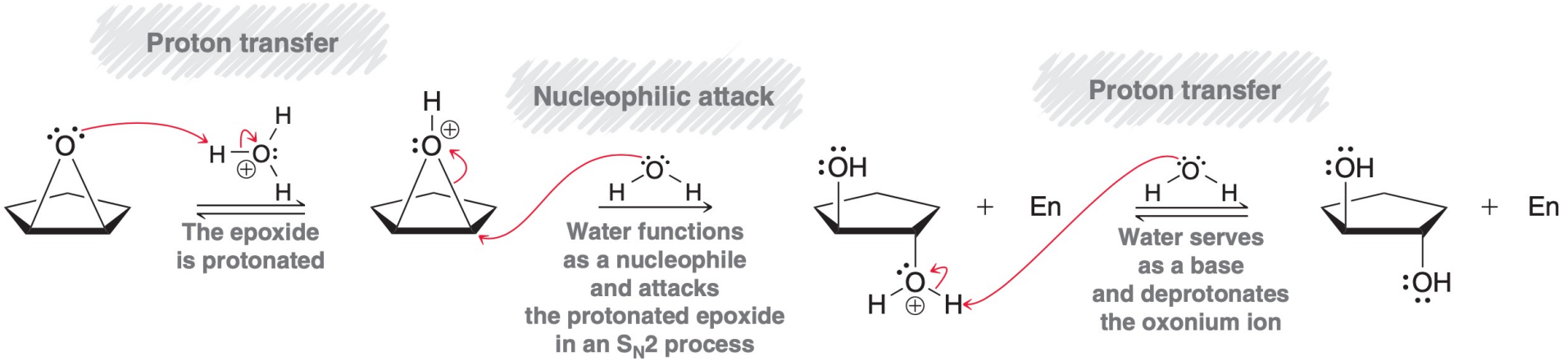


- The Mechanism of *anti*-Dihydroxylation

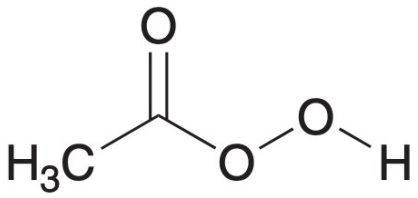
Formation of an epoxide



Acid-catalyzed opening of an epoxide

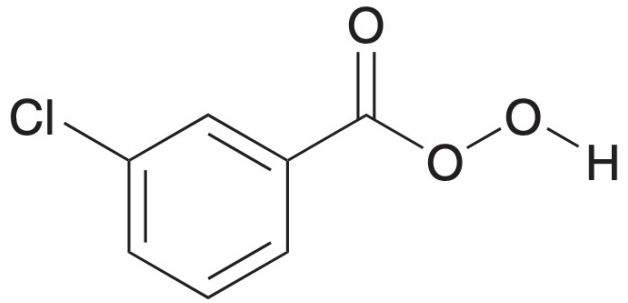


- 常见的过氧酸



Peroxyacetic acid

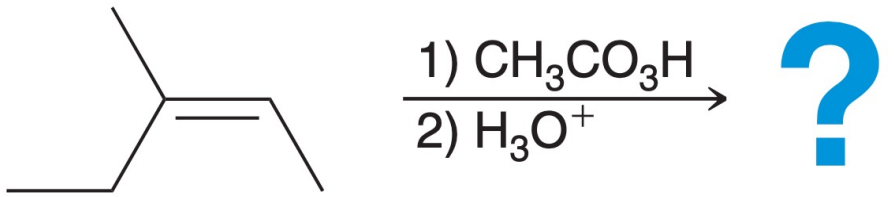
过氧乙酸

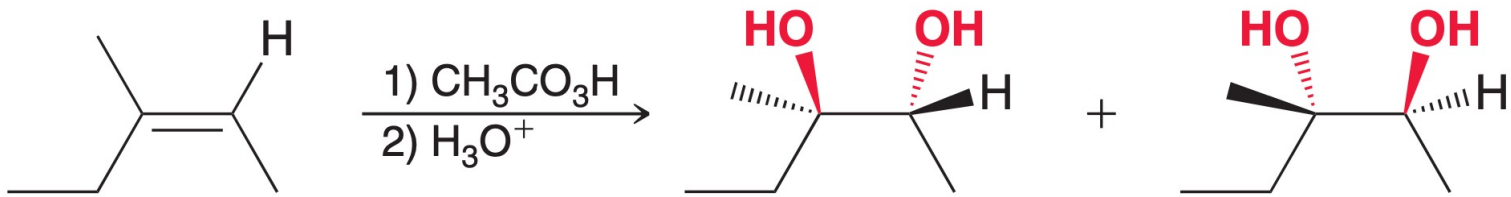


***meta*-Chloroperoxybenzoic acid (MCPBA)**

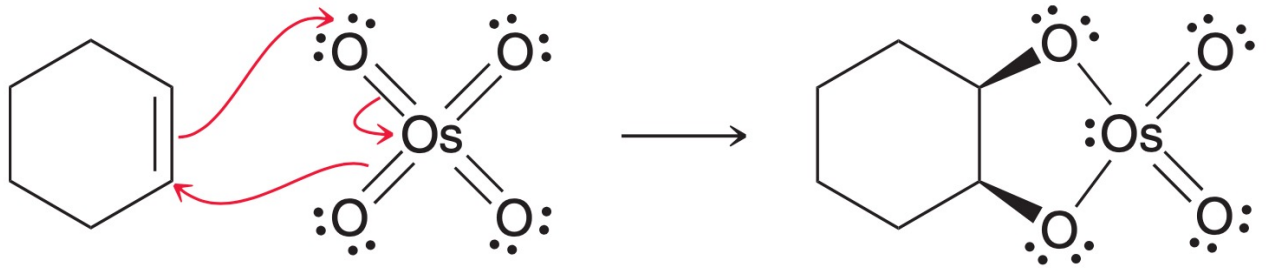
间氯过氧苯甲酸

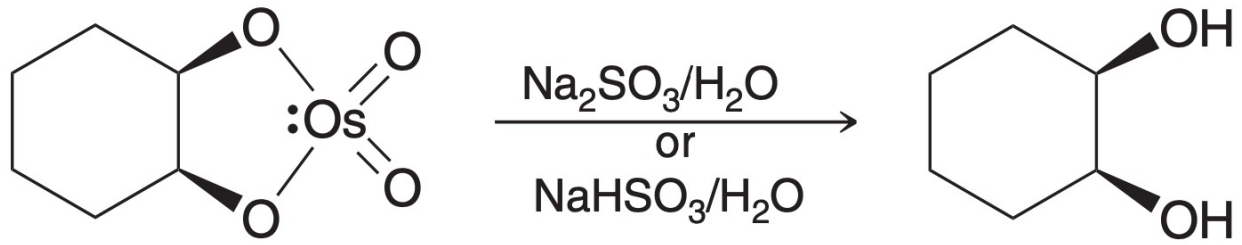
- Practice: predict the major product(s) for the following reaction:



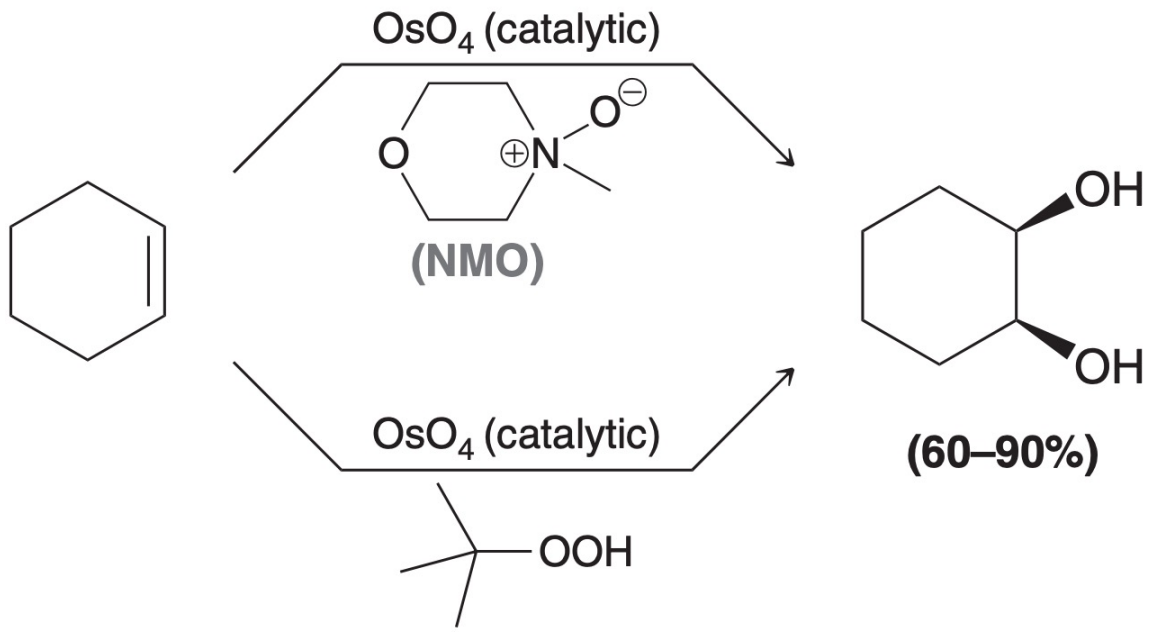


- 顺式双羟化：OsO_4





- 使用共氧化剂(co-oxidant)使OsO_4再生

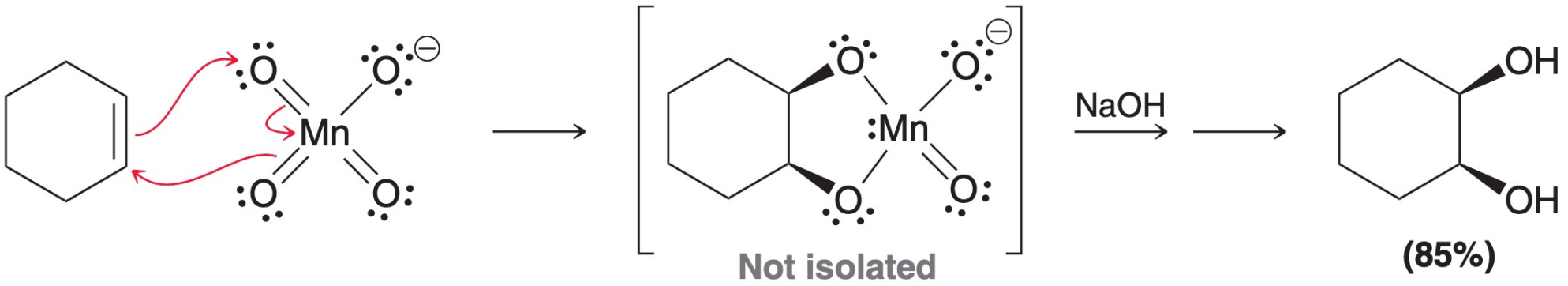


OsO_4剧毒，且价格昂贵

使用共氧化的方法可将OsO_4变为催化剂

大大减少OsO_4的用量，安全且经济

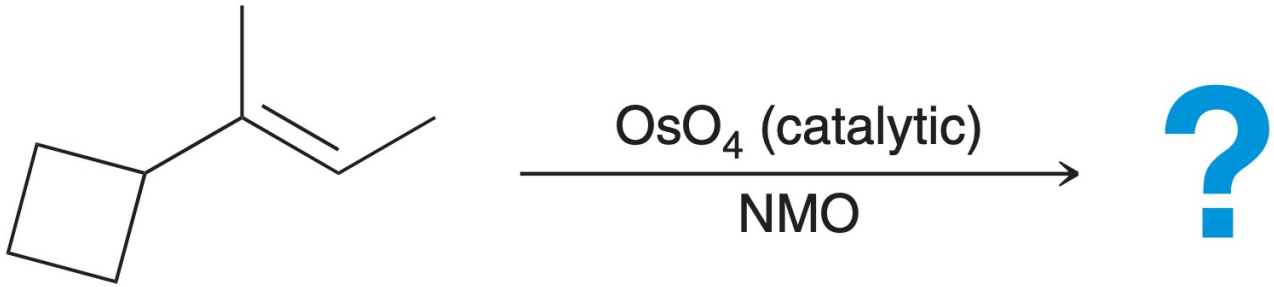
- $KMnO_4$也能进行顺式双羟化

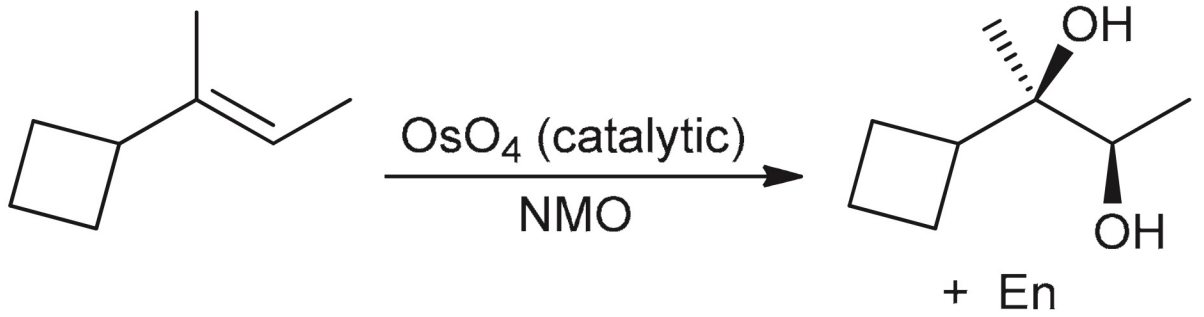


$KMnO_4$氧化性过强，易使产物进一步氧化

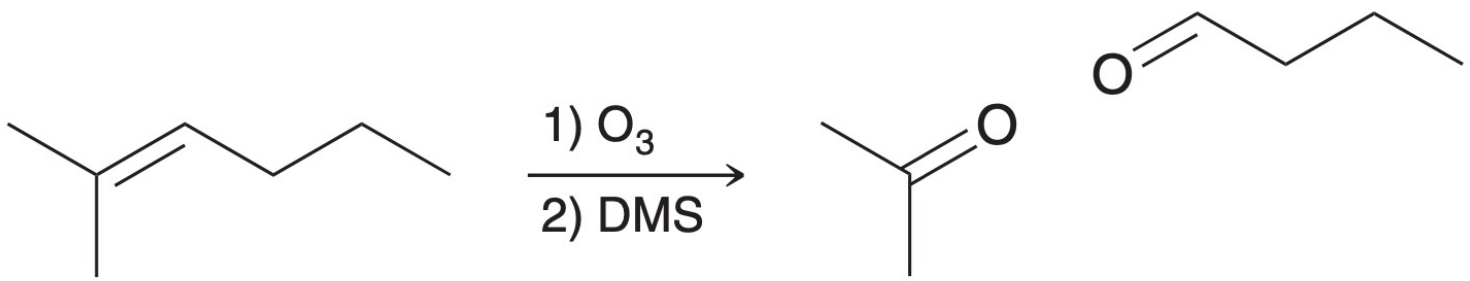
需使用冷、稀的碱性$KMnO_4$溶液进行反应

- Practice: predict the product(s) for the reaction. Make sure to consider the number of chiral centers being formed.

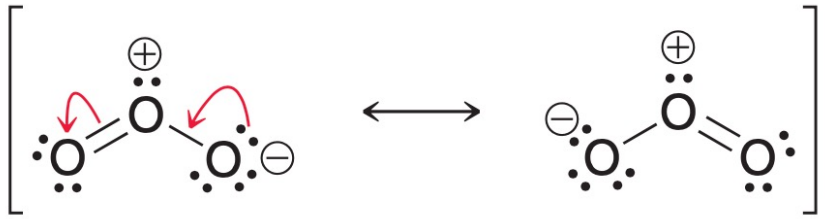


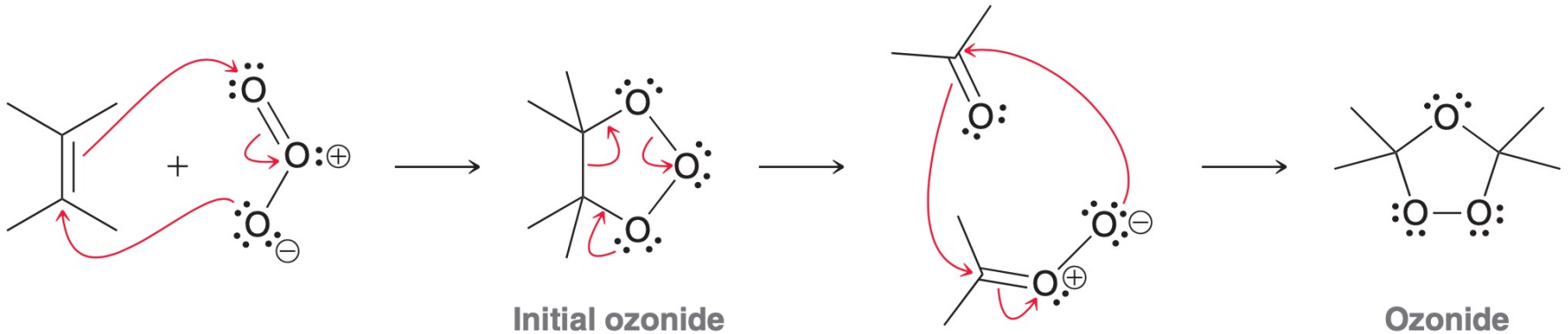


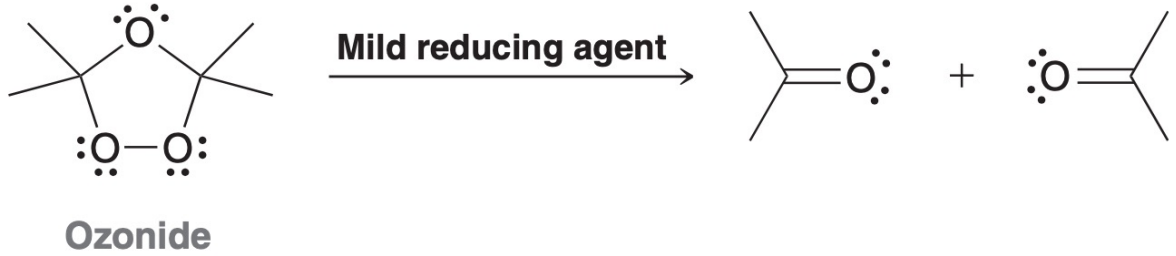
- 臭氧化(ozonolysis)



- 反应机理

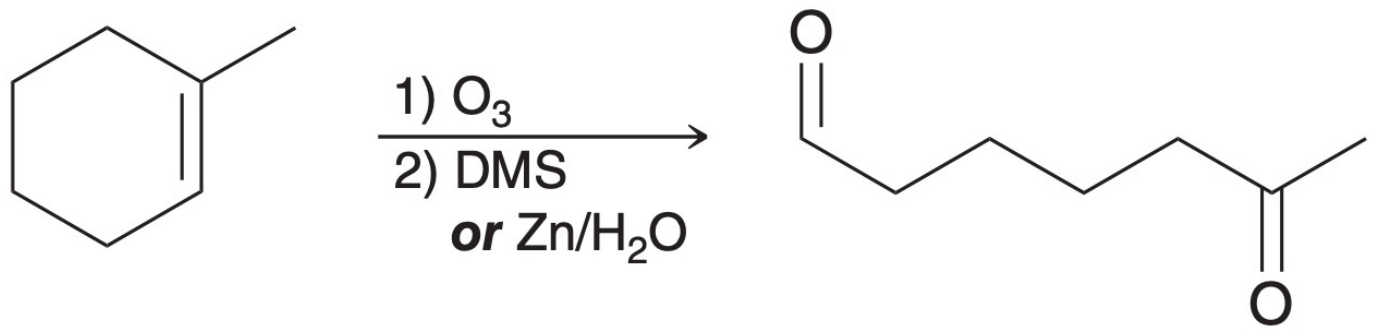



Initial ozonide
(molozonide)
Ozonide

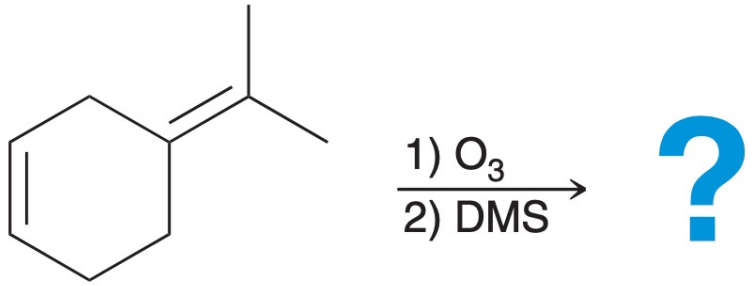

Mild reducing agent
Ozonide

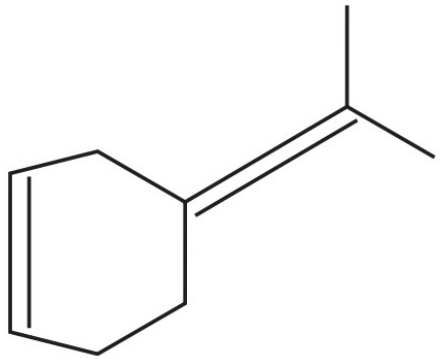
- Example

为什么是mild reducing agent?

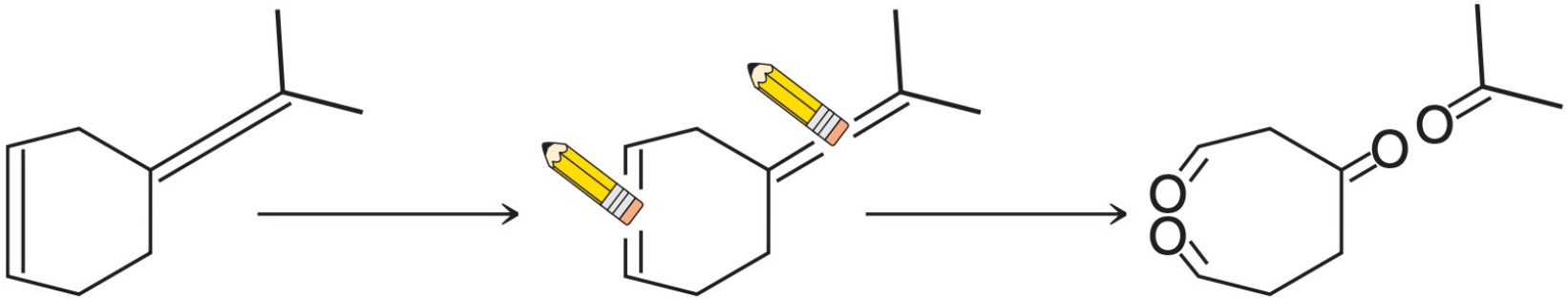


- 快速写出臭氧化产物的方法



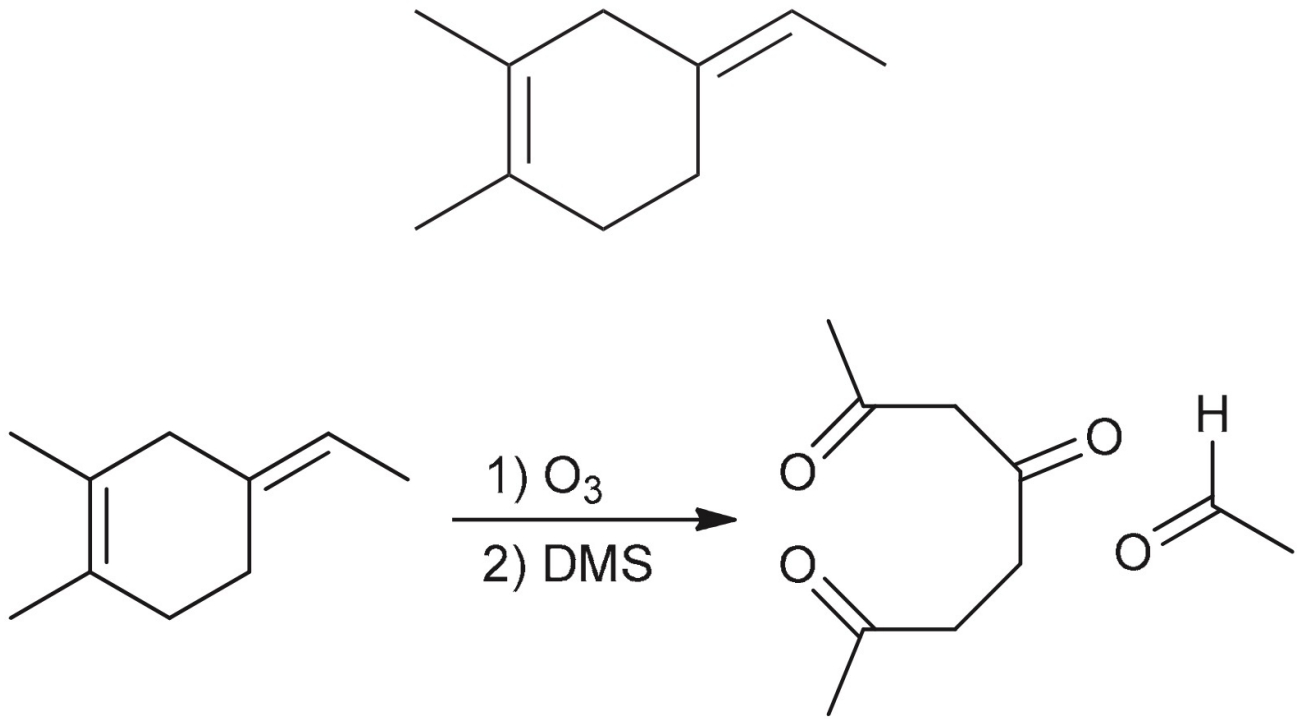


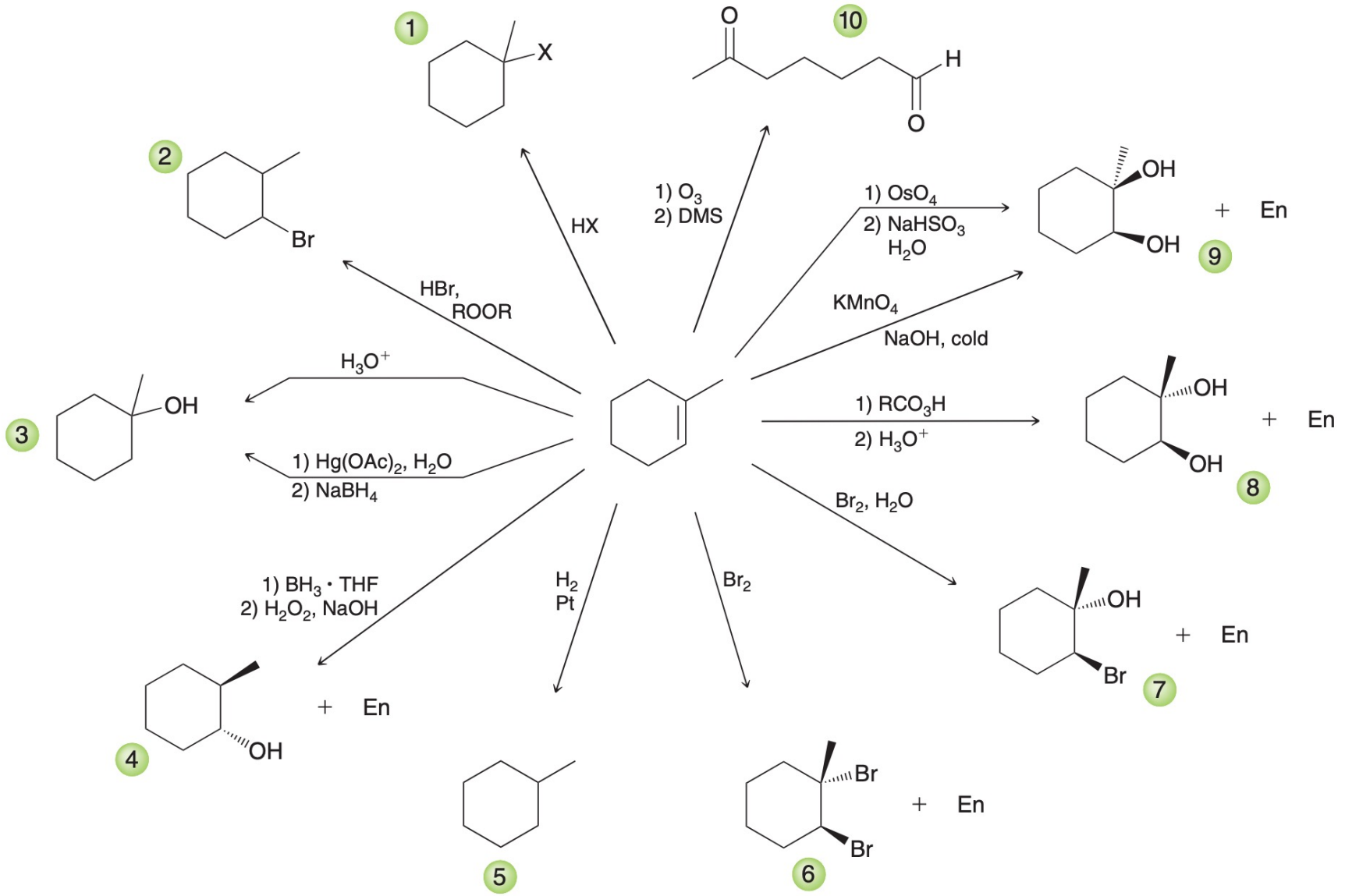
首先，拉长反应物中的双键



擦掉双键，在两侧加上羰基

- Practice: predict the products that are expected when the following alkene is treated with ozone followed by DMS:



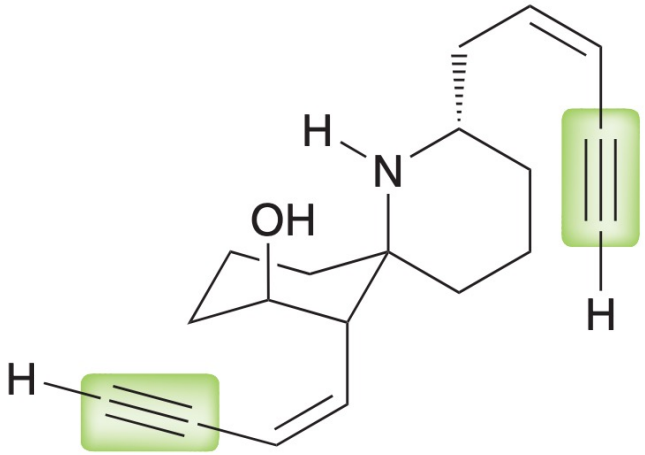


1. Hydrohalogenation (Markovnikov)
2. Hydrohalogenation (*anti*-Markovnikov)
3. Acid-catalyzed hydration and oxymercuration-demercuration
4. Hydroboration-oxidation
5. Hydrogenation
6. Bromination
7. Halohydrin formation
8. *Anti* dihydroxylation
9. *Syn* dihydroxylation
10. Ozonolysis

Alkynes

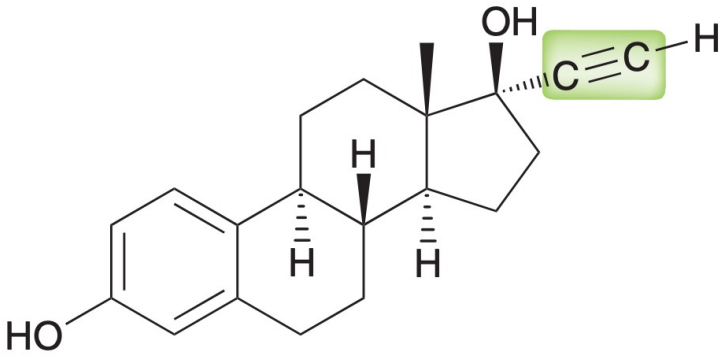
Nomenclature of Alkynes, Basic Physical & Chemical Properties, Preparations, Reactions of Alkynes

乙炔焊接



Histrionicotoxin

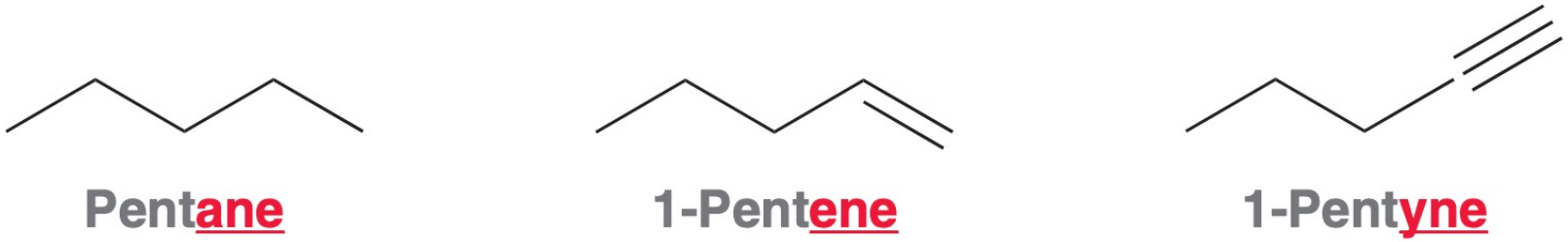
箭毒蛙毒素



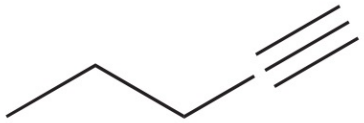
Ethynylestradiol

乙炔雌二醇

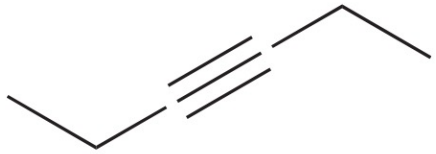
- 炔烃的命名
  - 与烯烃大致相同
  - 将后缀换为-yne



- 端炔和内炔

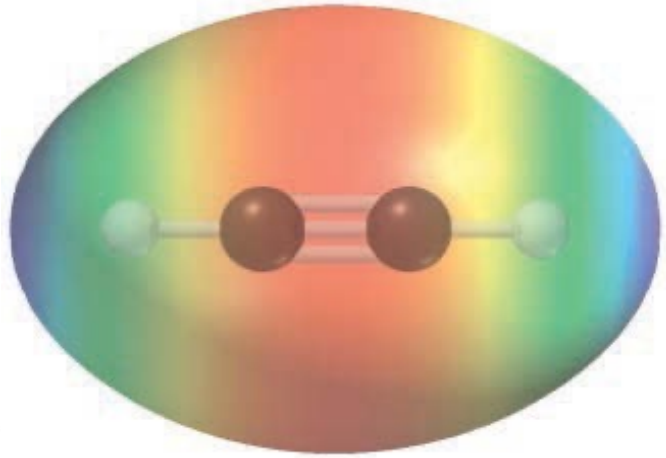


Terminal

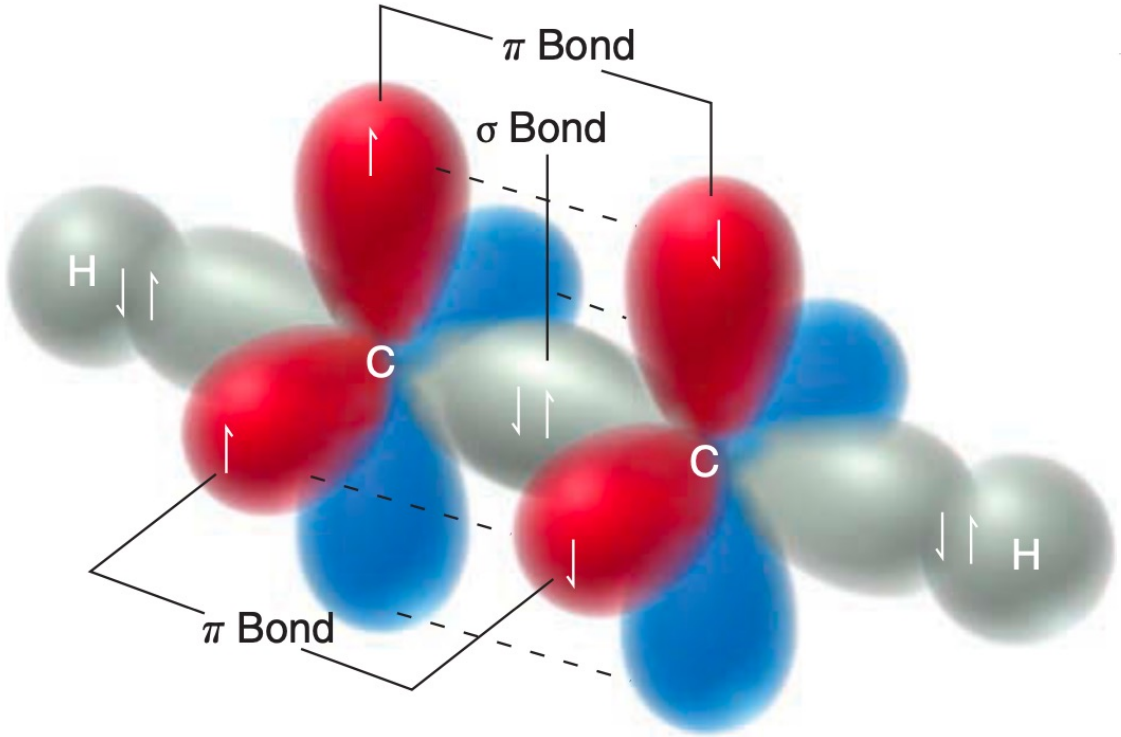


Internal

- 炔烃的结构特征



三键的电子密度很高



炔烃的碳呈sp杂化

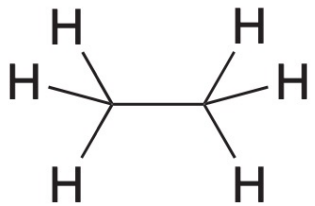
- 最小的环炔烃为九元环

Cyclononyne

然鹅它在室温也很容易分解
所以说 环炔烃真的很不稳定啊╮(╯▽╰)╭

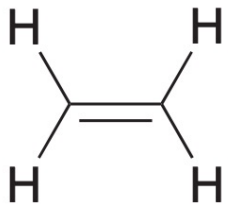
- 端炔的酸性

Ethane



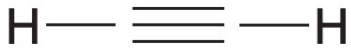
$pK_a = 50$

Ethylene



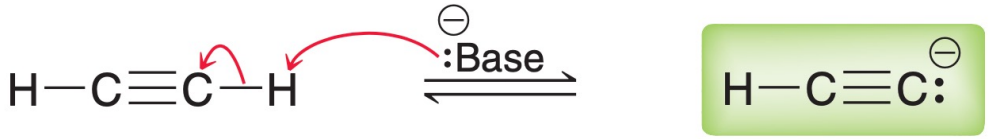
$pK_a = 44$

Acetylene

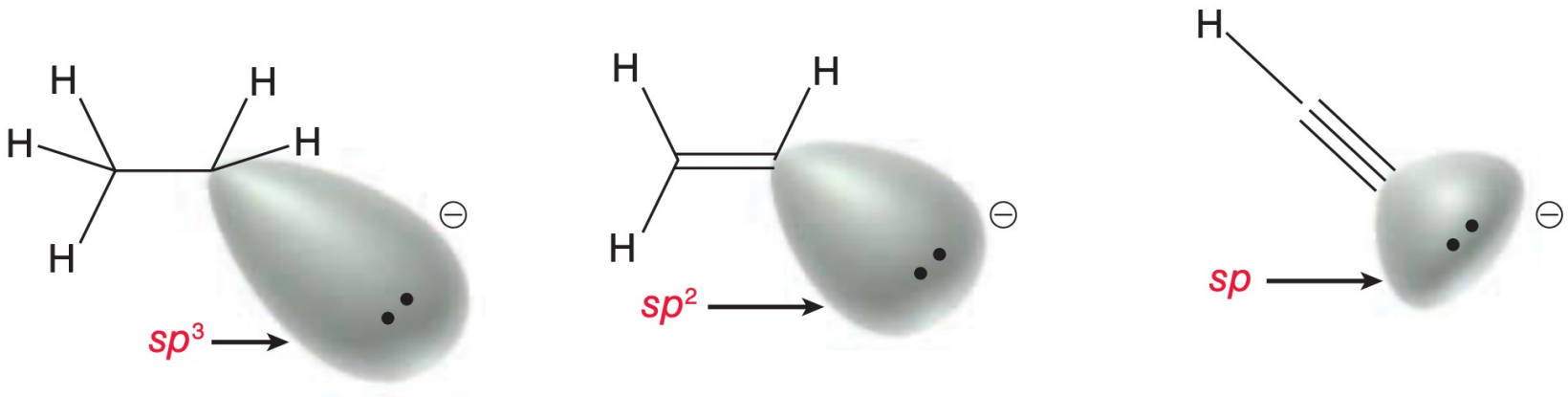


$pK_a = 25$

- 端炔负离子较稳定



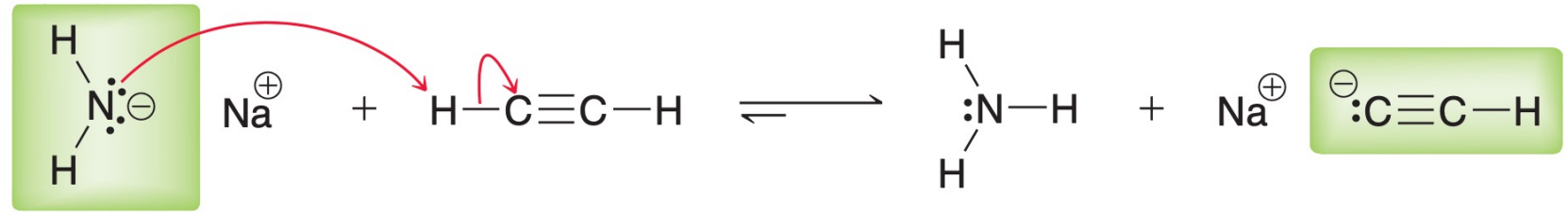
Acetylene　　Acetylide ion



sp杂化的电子云较为收束

负电荷更集中

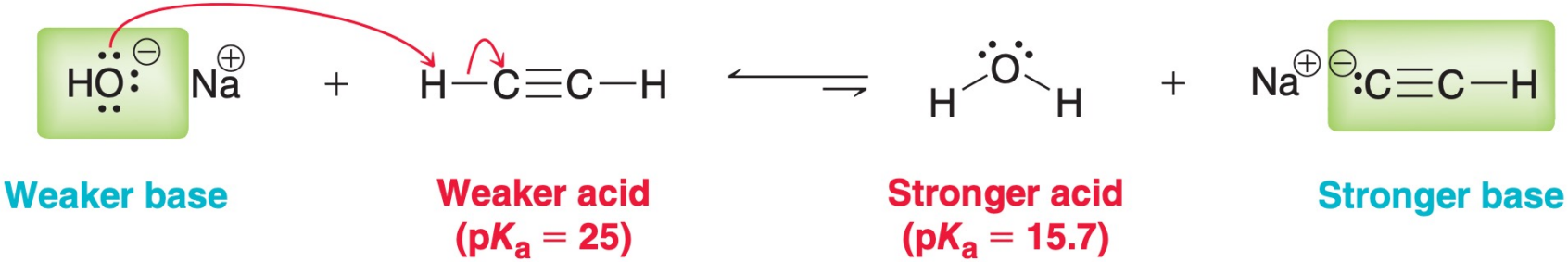
- 强碱可攫(júe)取端炔的质子



$NaNH_2$

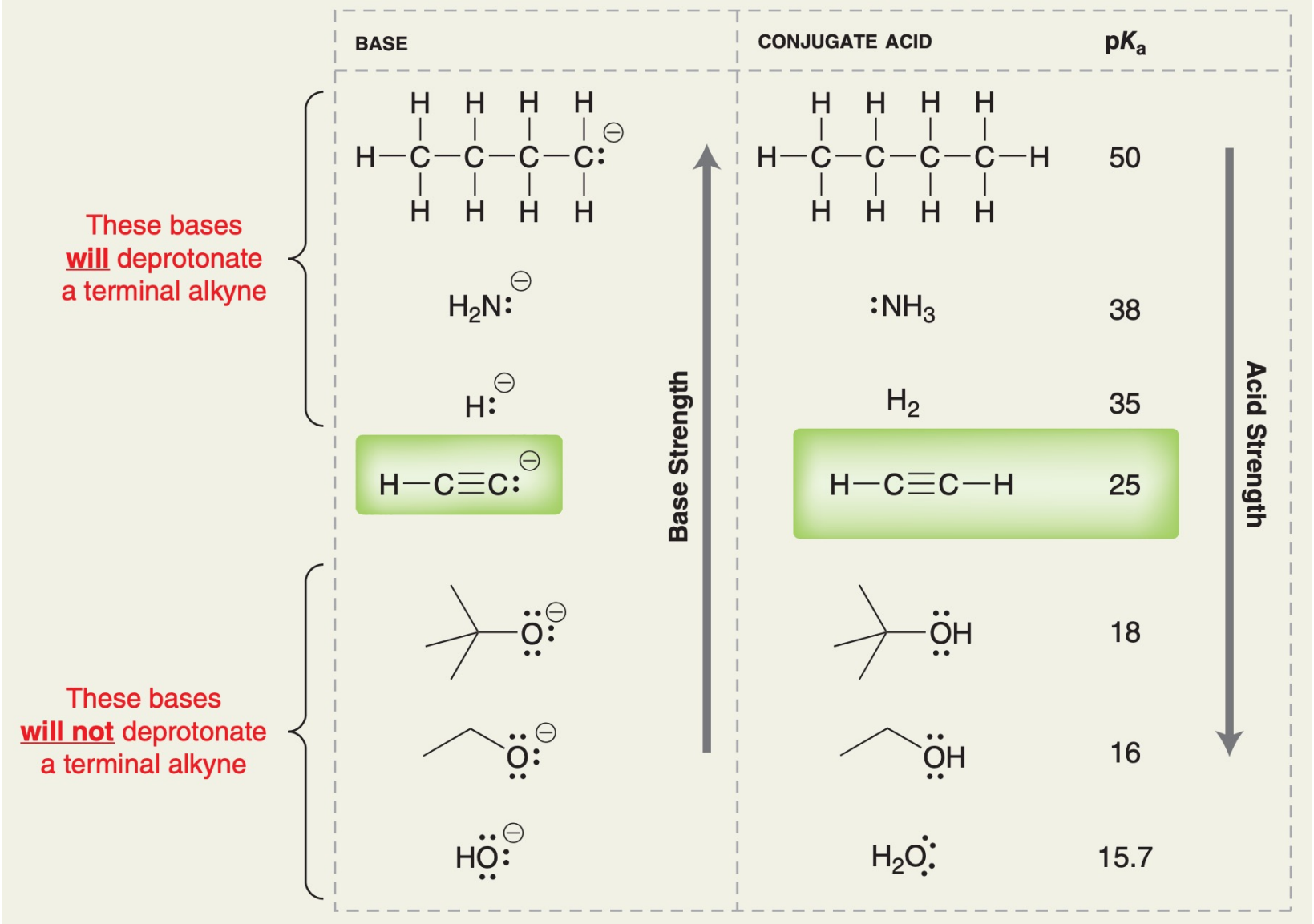
氨基钠

Equilibrium favors formation of weaker acid and weaker base



Equilibrium favors the weaker acid and weaker base

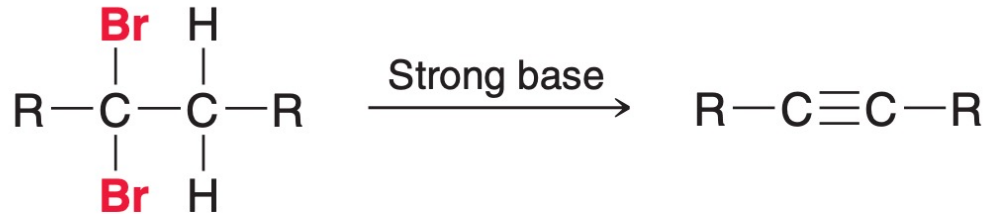
- 酸性的比较


BASE
CONJUGATE ACID
pKa
These bases will deprotonate a terminal alkyne
These bases will not deprotonate a terminal alkyne
Base Strength
Acid Strength
50
38
35
25
18
16
15.7

- 使用偕二卤代烃和邻二卤代烃制备炔烃(E2 mechanism)

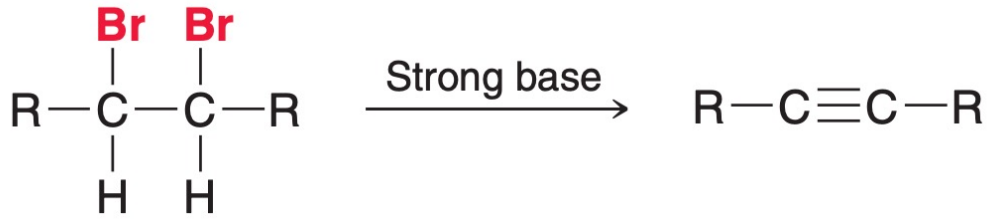
geminal dihalide

偕二卤代烃

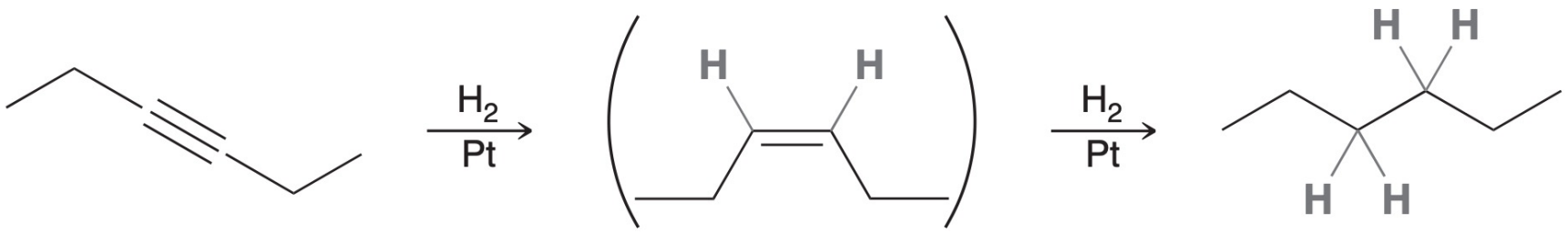


vicinal dihalide

邻二卤代烃



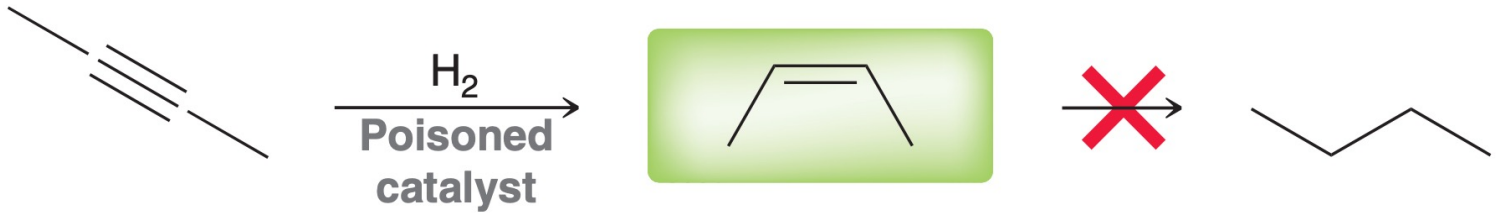
- 炔烃的催化氢化还原（顺式）

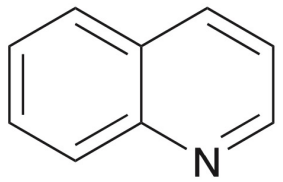


如想还原到烯烃就停止...

烯烃中间体不易分离！

- 选择性还原



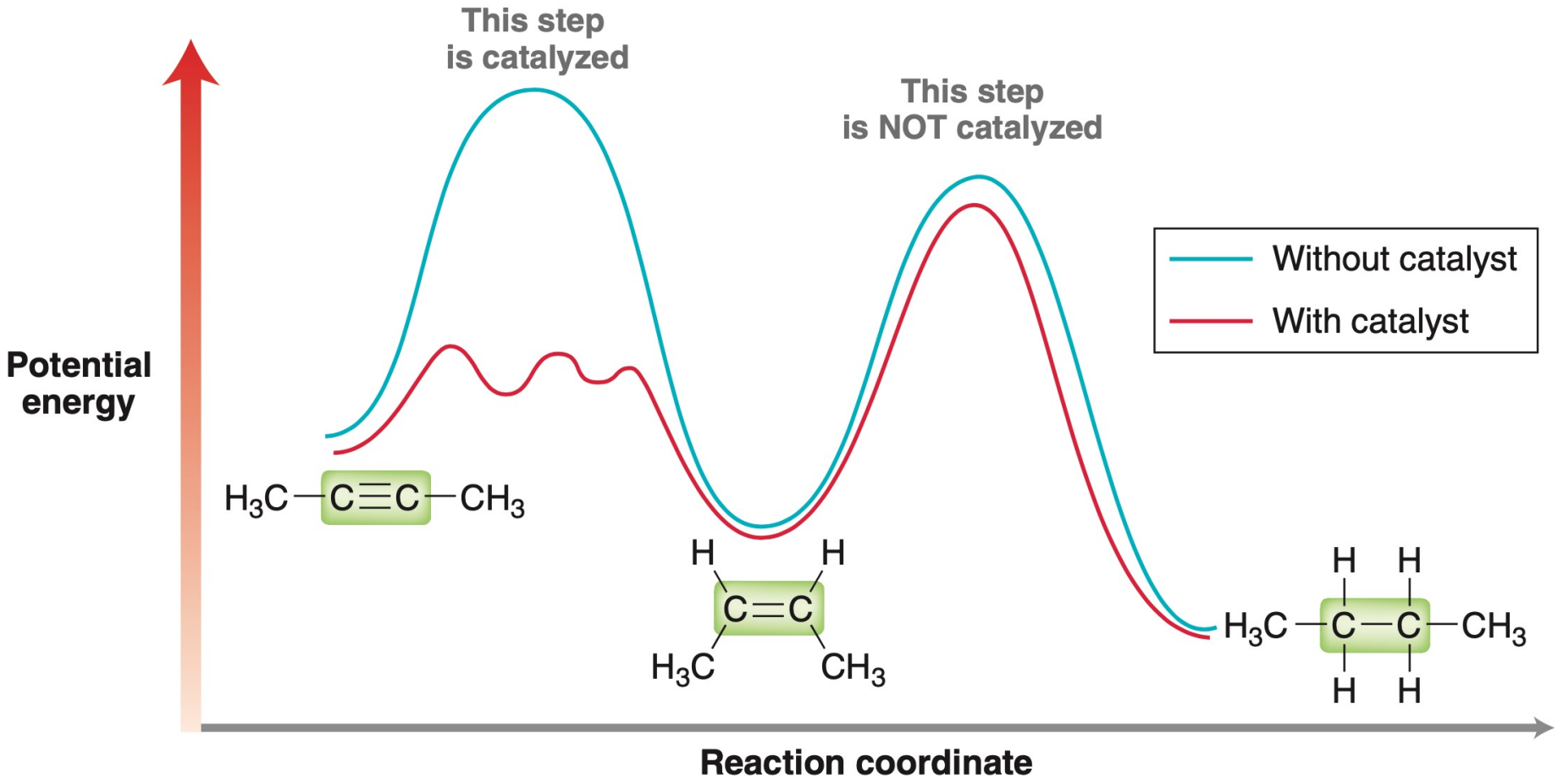
常见的中毒催化剂：1. Lindlar's catalyst = 

, Pd / $BaSO_4$, CH_3OH

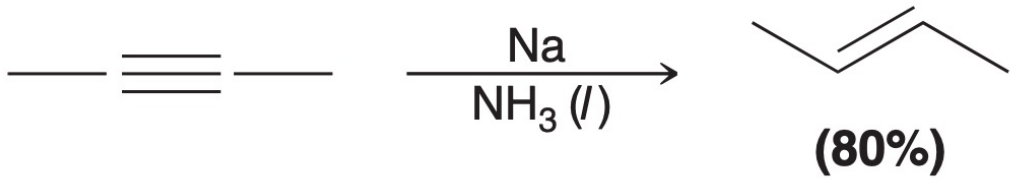
Quinoline

2. nickel-boron complex (Ni_2B)

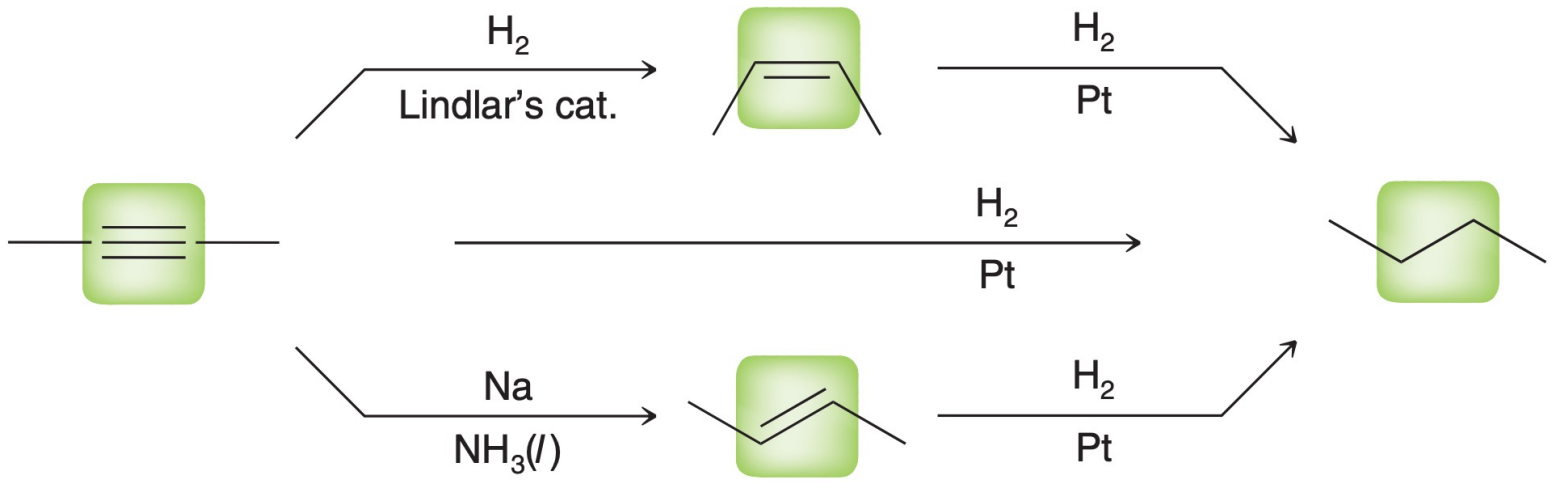
- 反应历程


This step
is catalyzed
This step
is NOT catalyzed
Without catalyst
With catalyst
Potential
energy
Reaction coordinate
H3C—C≡C—CH3
H
H
C=C
H3C
CH3
H
H
H3C—C—C—CH3
H
H

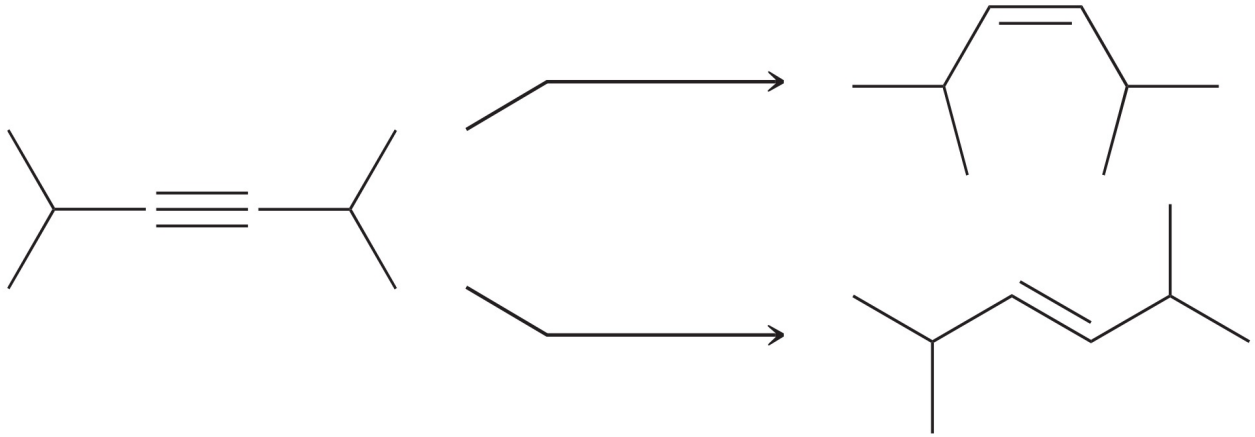
- 使用金属溶液进行还原（反式）



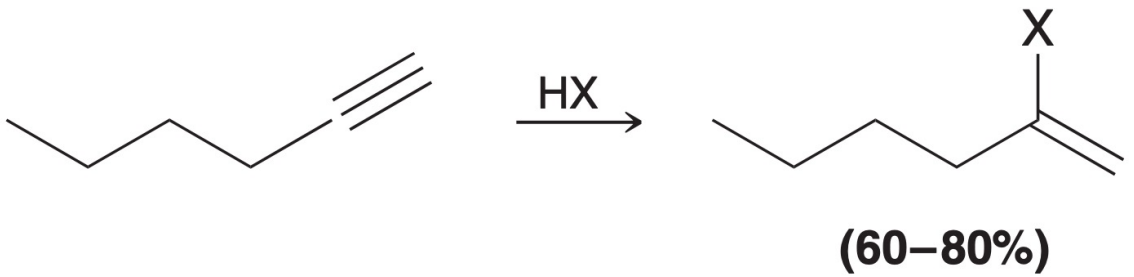
- 几种还原的对比



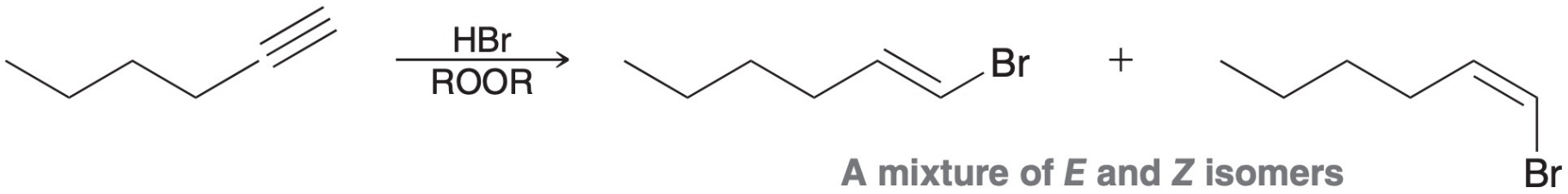
- Practice: identify reagents that you could use to achieve each of the following transformations:



- 炔烃氢卤化（马氏加成）

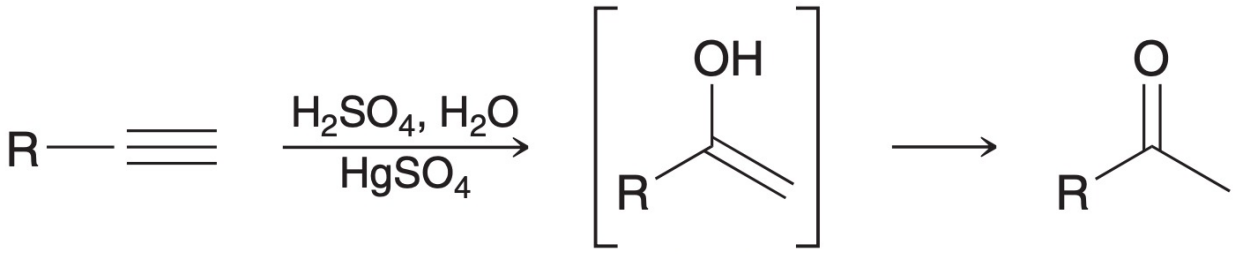


- 炔烃氢卤化（反马加成）

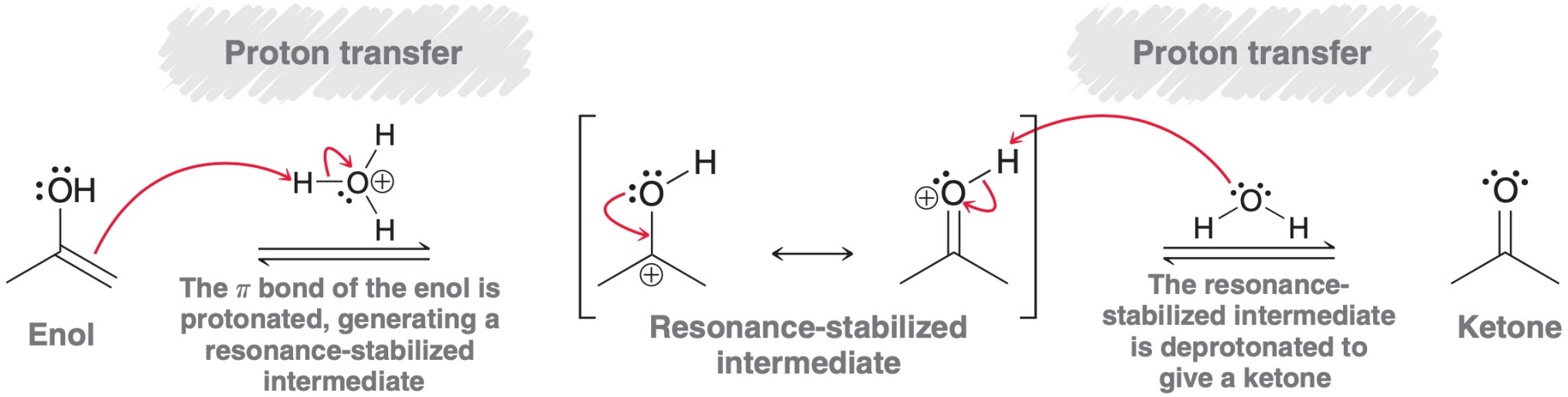


得到E/Z两种构型的混合物

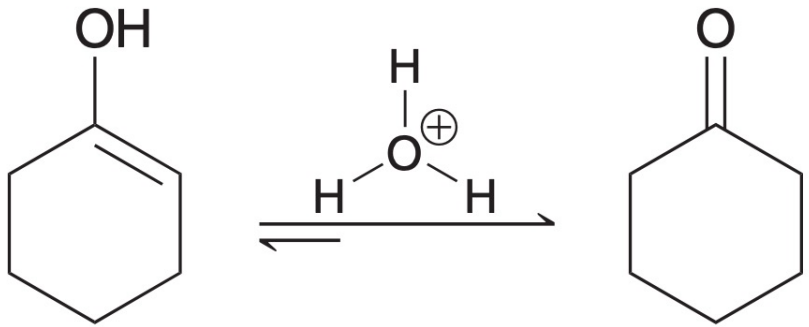
- 炔烃的水合



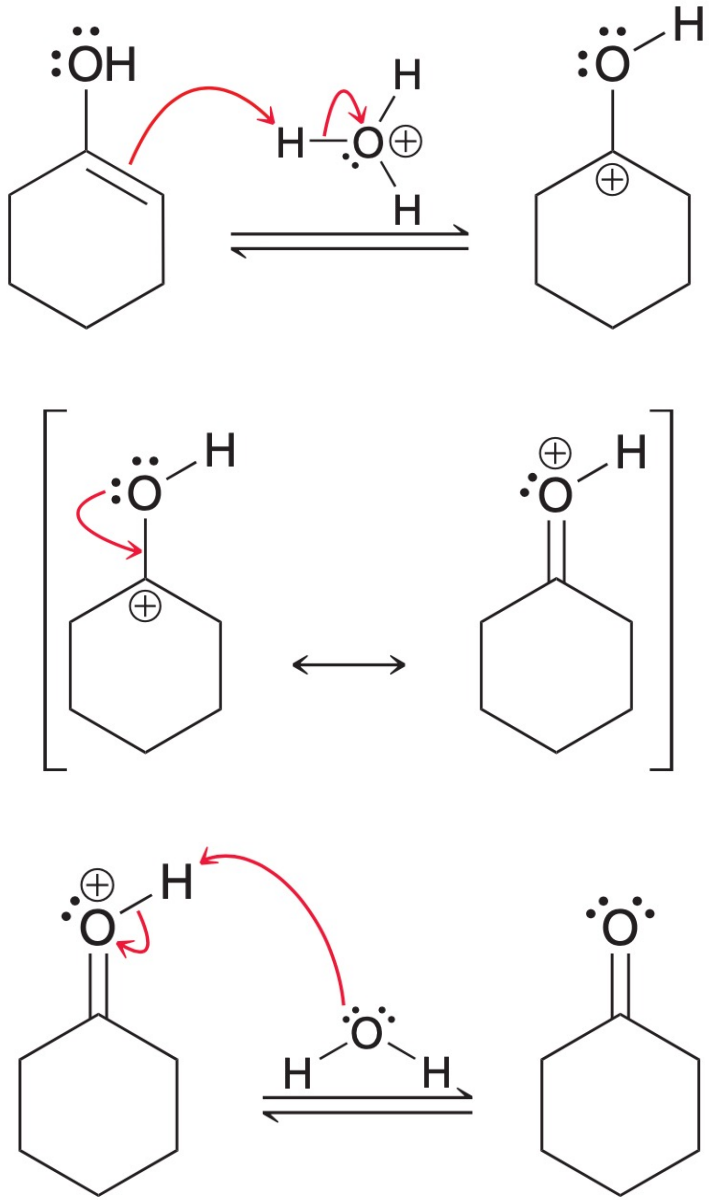
- **Mechanism: Acid-Catalyzed Tautomerization**



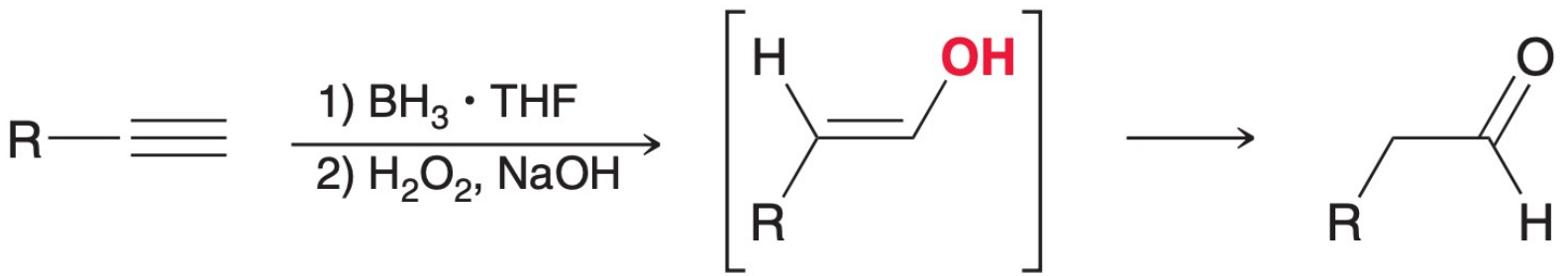
- Practice: under normal conditions, 1-cyclohexenol cannot be isolated or stored in a bottle, because it undergoes rapid tautomerization to yield cyclohexanone. Draw a mechanism for this tautomerization:



Keto-enol Tautomerization



- 炔烃硼氢化-氧化

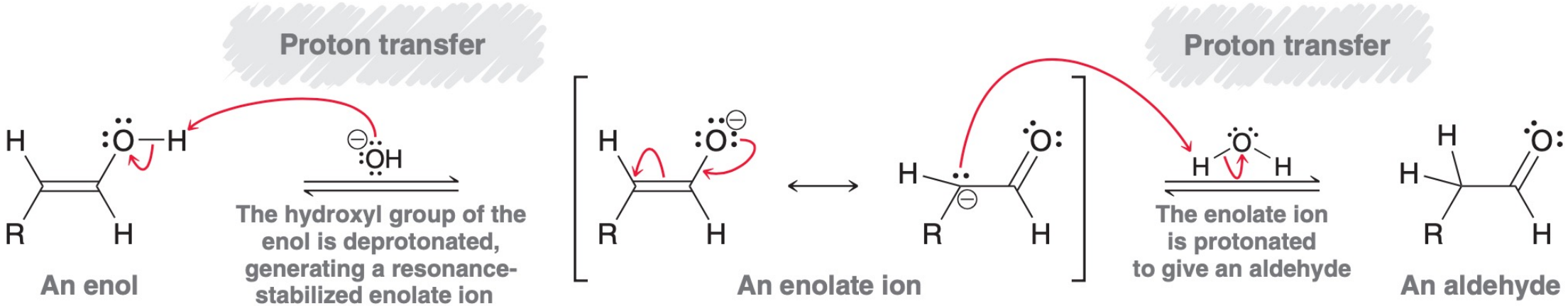


醛

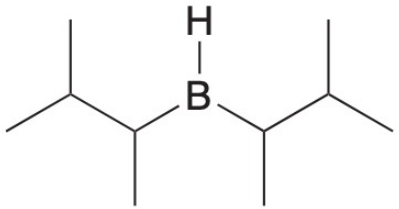
碱性条件

如何完成烯醇重排？

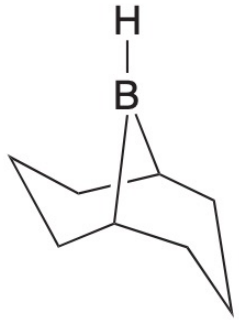
- **Mechanism: Base-Catalyzed Tautomerization**



- 利用改性硼烷试剂完成炔烃硼氢化

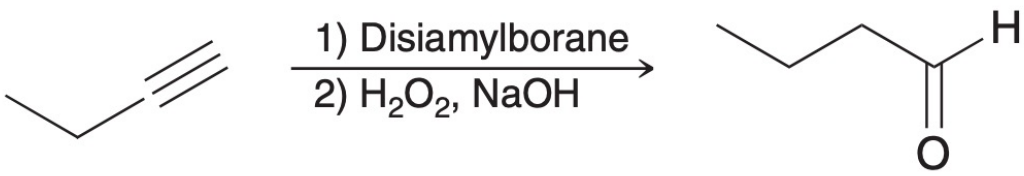


Disiamylborane

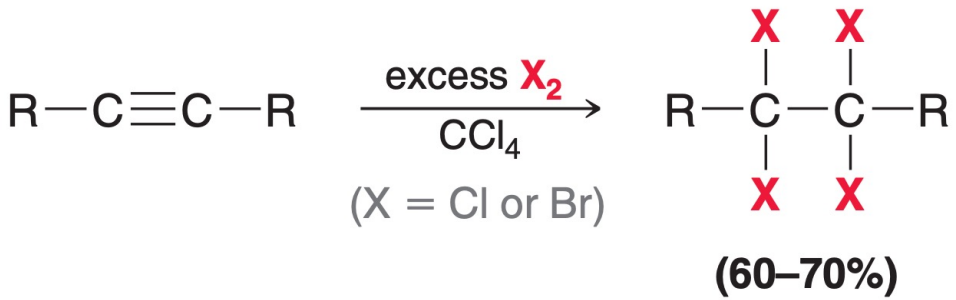


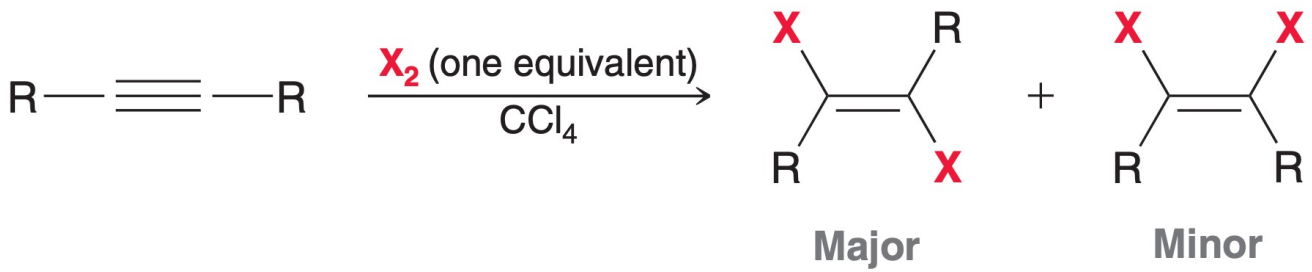
9-BBN
(9-Borabicyclo[3.3.1]nonane)

位阻效应显著——避免二次加成

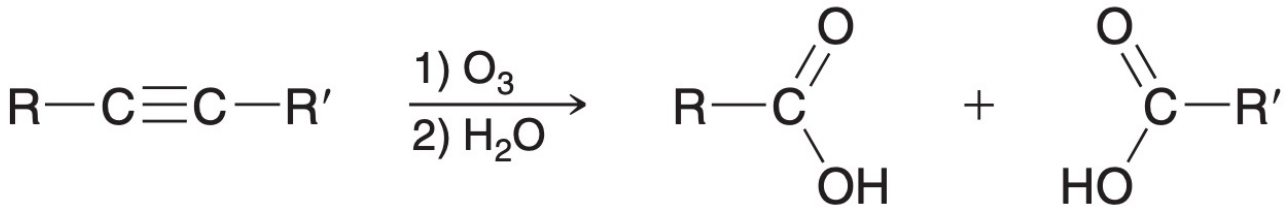


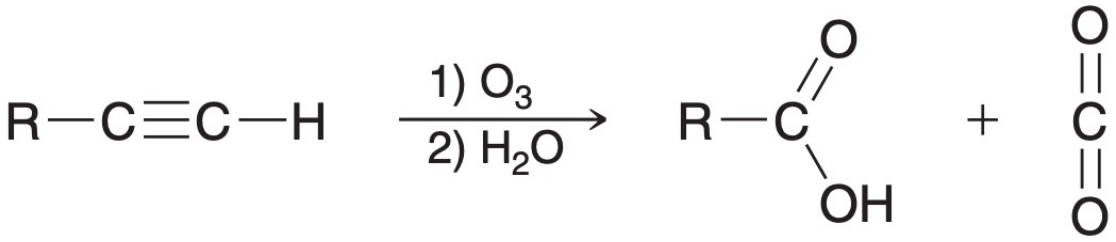
- 炔烃的卤化


R—C≡C—R
excess X2
CCl4
(X = Cl or Br)
X X
R—C—C—R
X X
(60–70%)

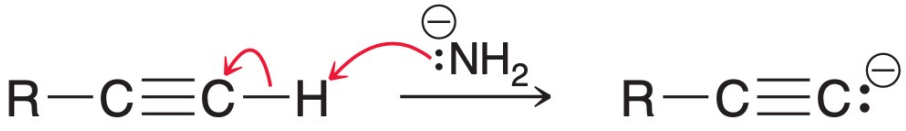

R—≡—R
X2 (one equivalent)
CCl4
X R
R X
+
X X
R R
Major
Minor

- 炔烃臭氧化

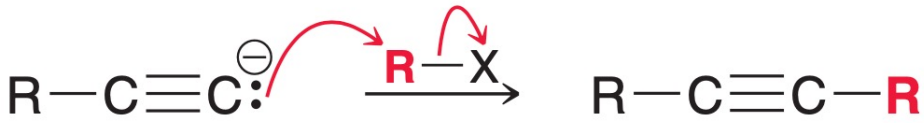


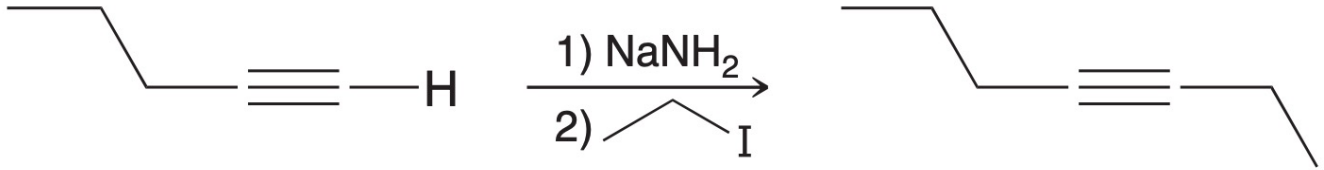


- 端炔烷基化



An alkynide ion

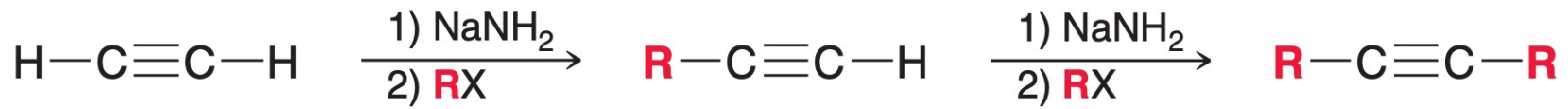


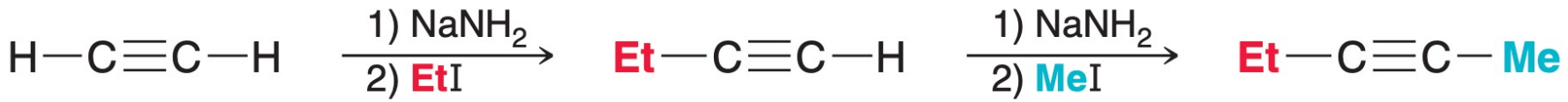


This process is only efficient with methyl or primary alkyl halides.

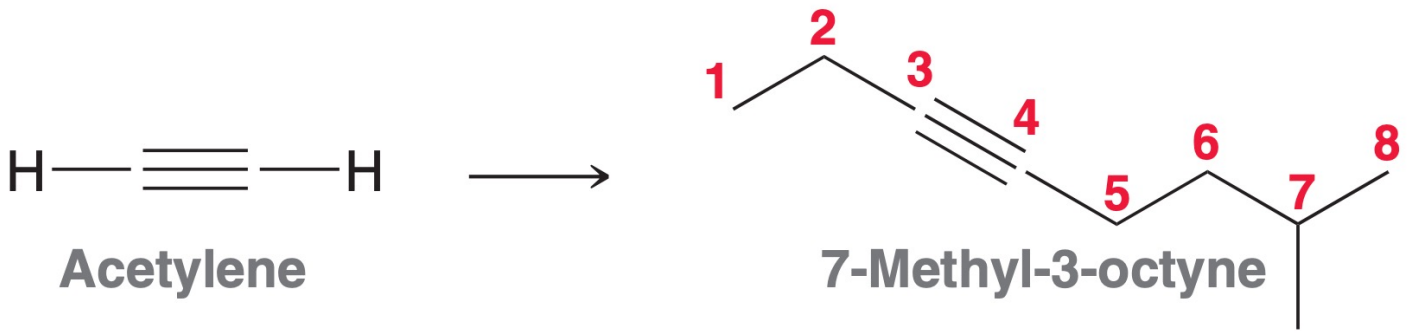
二、三级卤代烃与炔基负离子反应时，易发生消除反应

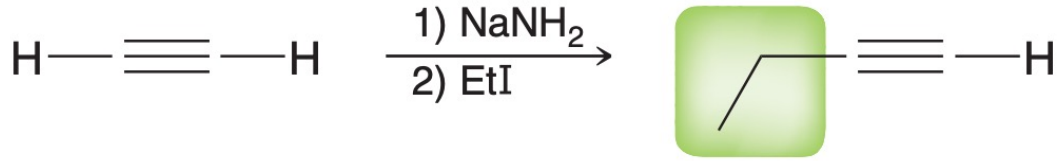
- 乙炔的双烷基化

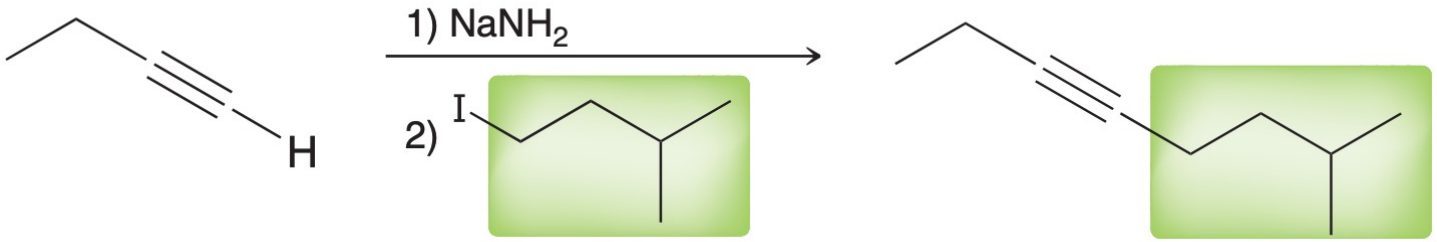

H—C≡C—H
1) NaNH2
2) RX
R—C≡C—H
1) NaNH2
2) RX
R—C≡C—R

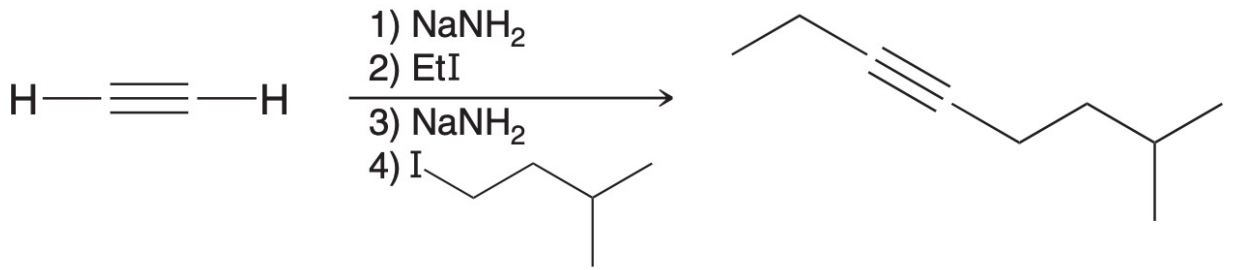

H—C≡C—H
1) NaNH2
2) EtI
Et—C≡C—H
1) NaNH2
2) MeI
Et—C≡C—Me

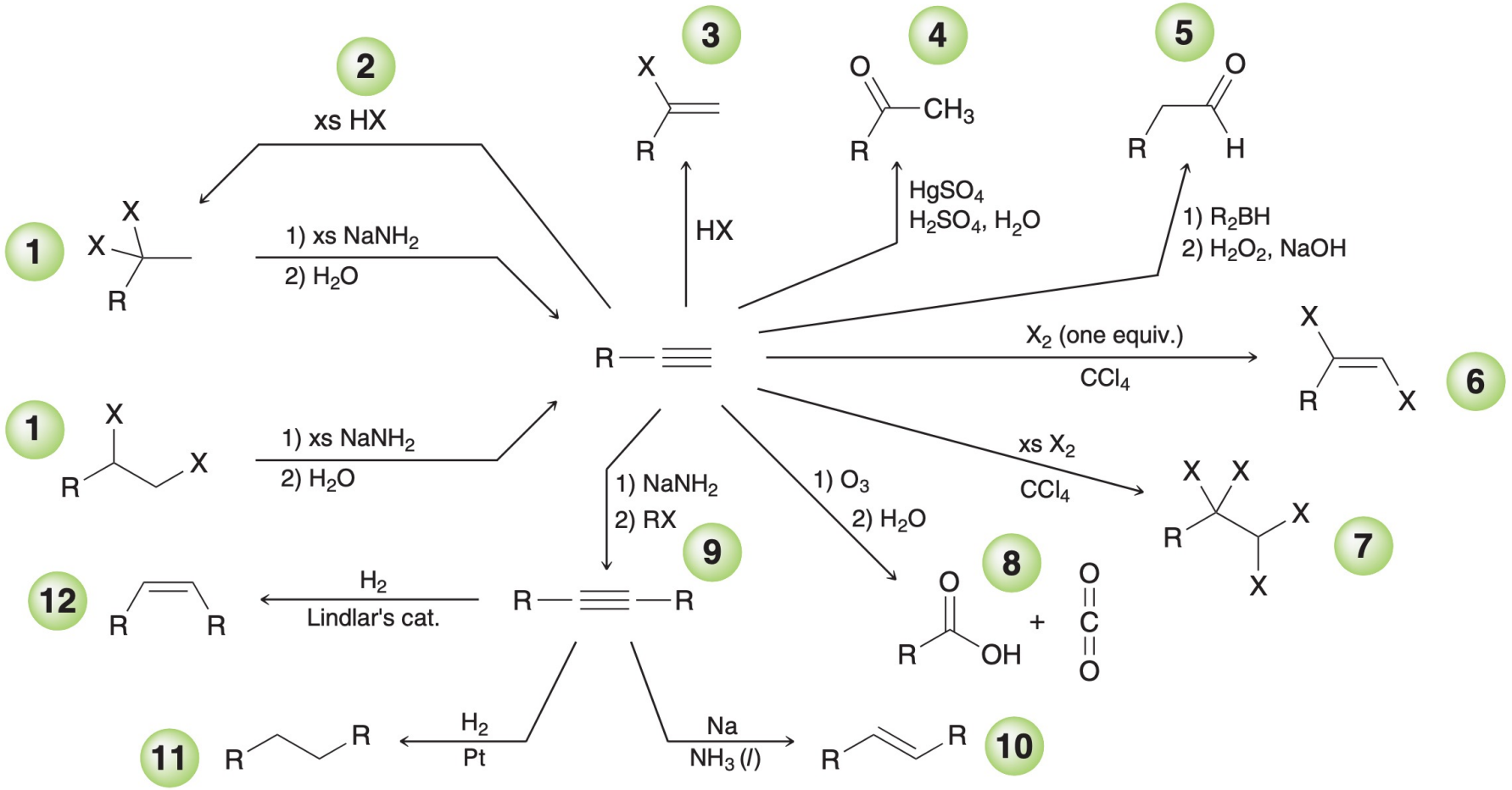
- Practice: identify reagents that can be used to convert acetylene into 7-methyl-3-octyne.




H
H
1) NaNH2
2) EtI
H


H
1) NaNH2
2)
I


H
H
1) NaNH2
2) EtI
3) NaNH2
4)
I

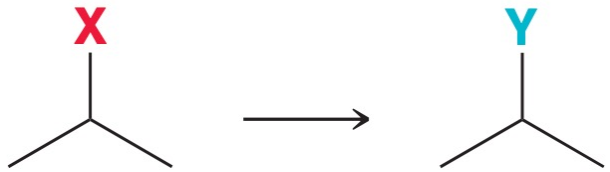


1. Elimination
2. Hydrohalogenation (two equivalents)
3. Hydrohalogenation (one equivalent)
4. Acid-catalyzed hydration
5. Hydroboration-oxidation
6. Halogenation (one equivalent)
7. Halogenation (two equivalents)
8. Ozonolysis
9. Alkylation
10. Dissolving metal reduction
11. Hydrogenation
12. Hydrogenation with a poisoned catalyst

Synthesis Route Design

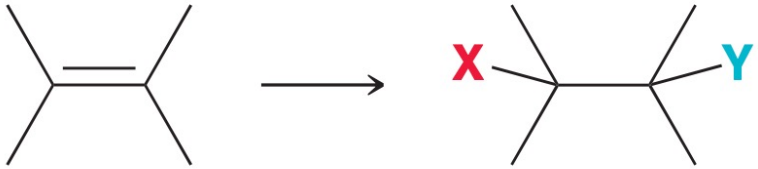
One-Step Transformation, Multiple-Step Transformation, Transformation of Hydrocarbons

Substitution reactions

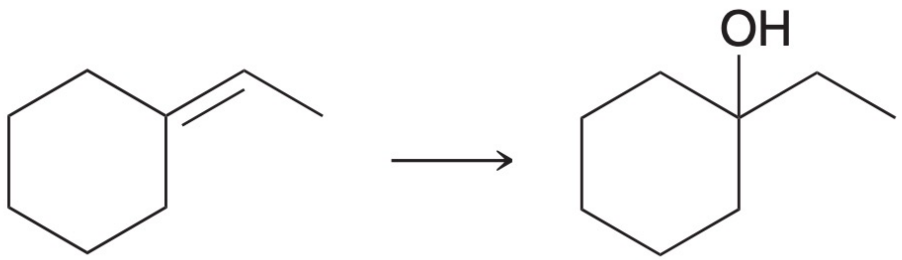


Elimination reactions

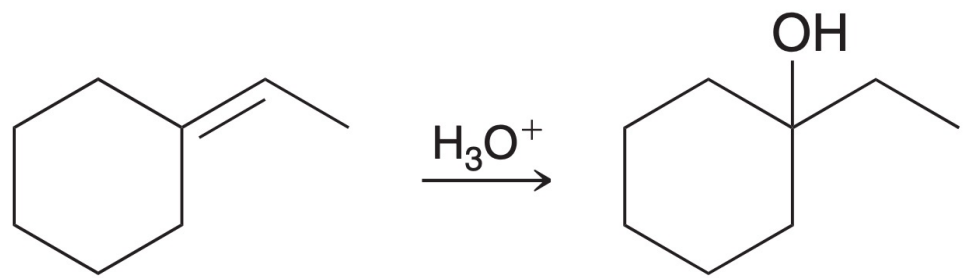
Addition reactions



- Practice: identify the reagents that you would use to accomplish the following transformation:

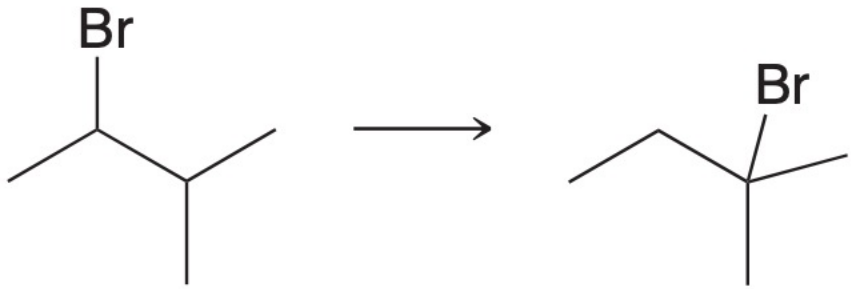


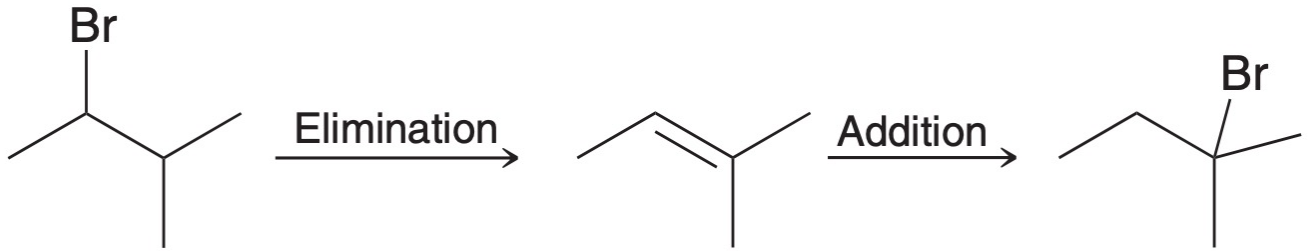
1. Which two groups are being added across the double bond?—H and OH.
2. What is the regioselectivity?—Markovnikov addition.
3. What is the stereospecificity?—Not relevant (no chiral centers formed).



If rearrangement were possible, then oxymercuration-demercuration would have been the preferred route.

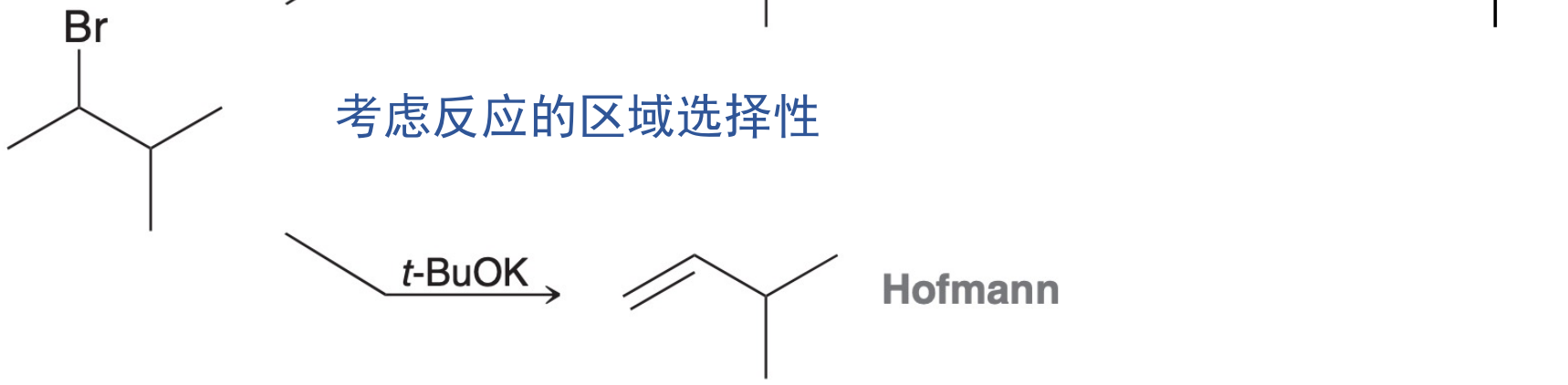
- 改变LG的位置



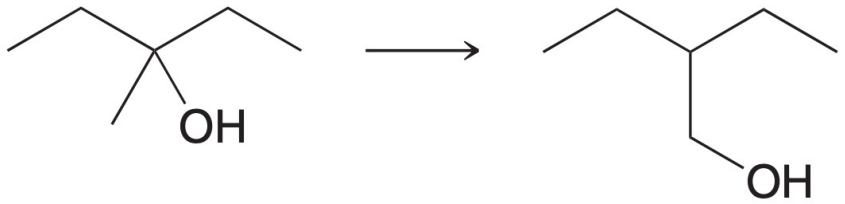


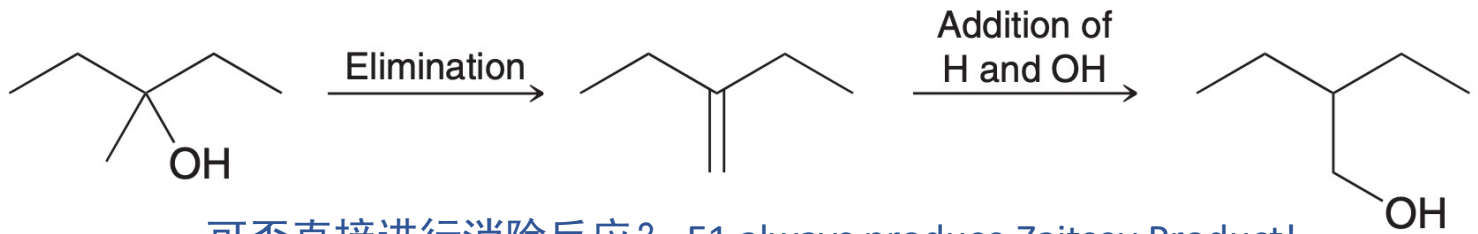
二级底物

$E2 > S_N2$

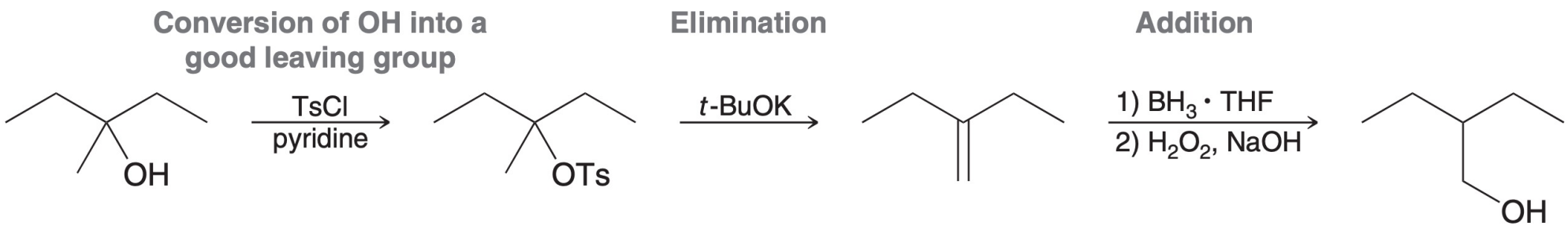


考虑反应的区域选择性

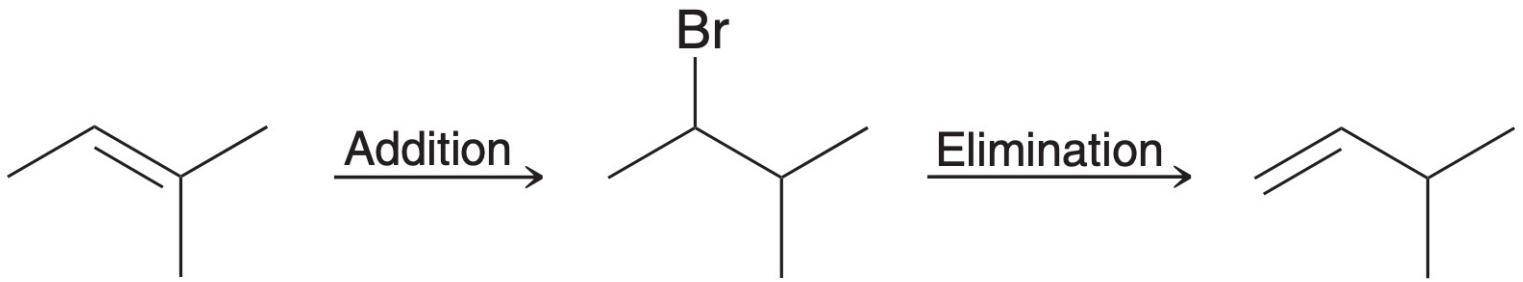




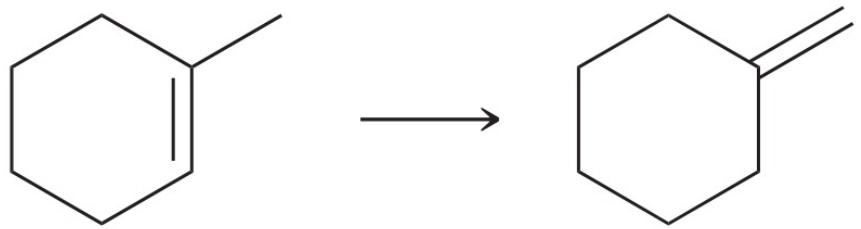
可否直接进行消除反应？ E1 always produce Zaitsev Product!

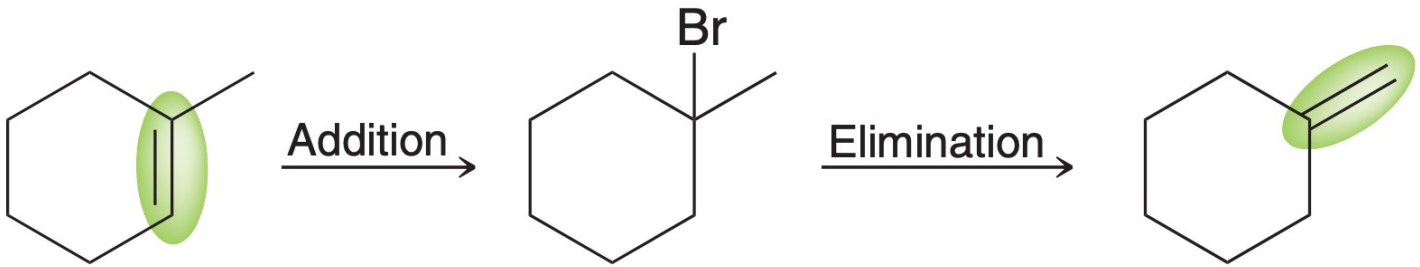


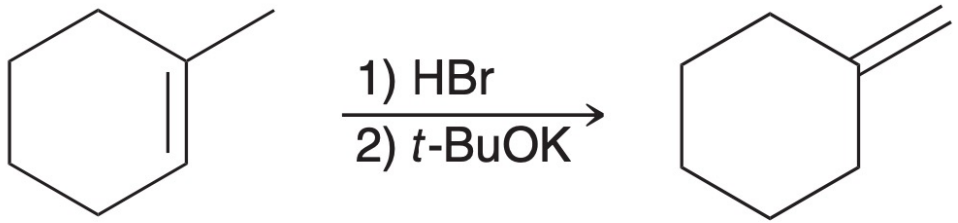
- 改变π键的位置



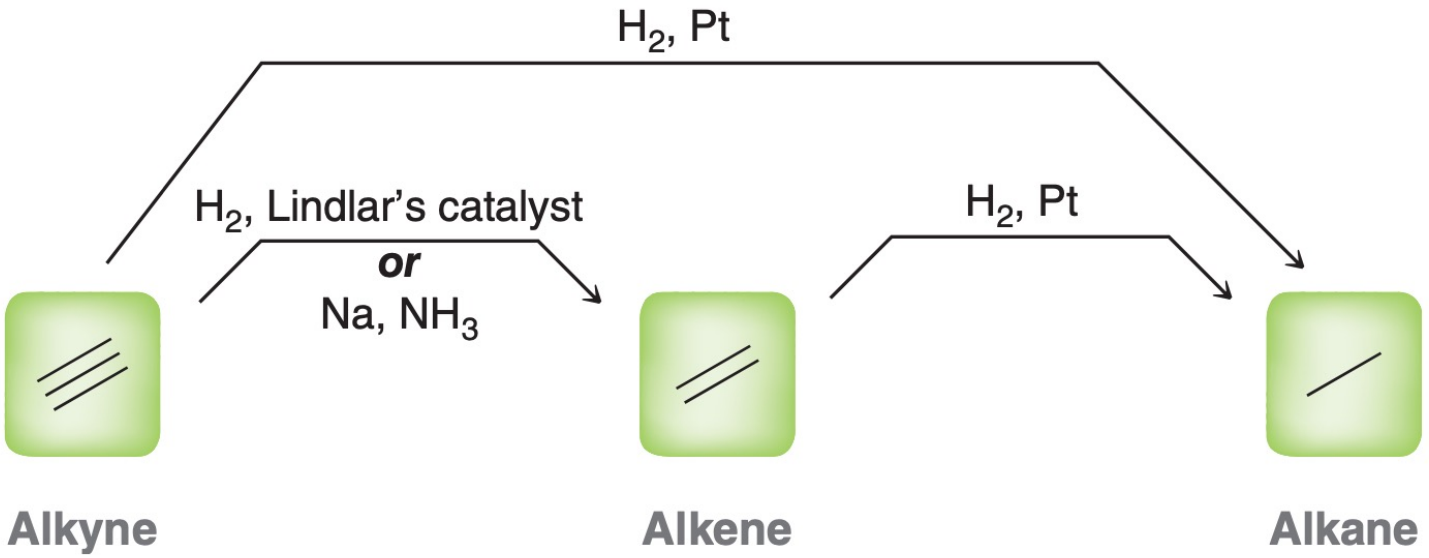
- Practice: identify the reagents you would use to accomplish the following transformation:



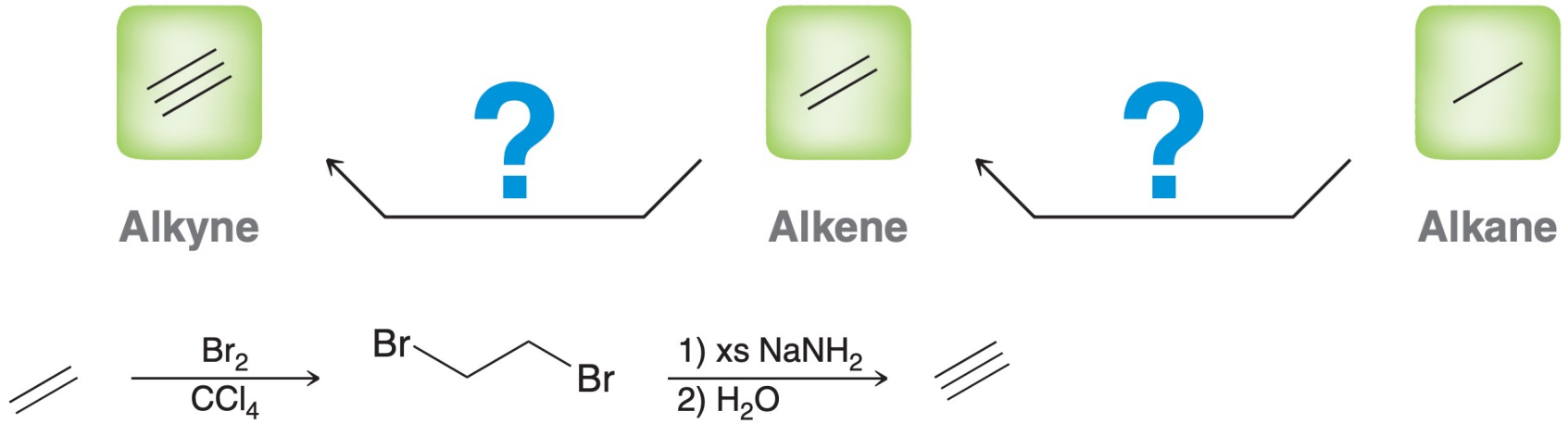

Br
Addition
Elimination


1) HBr
2) t-BuOK

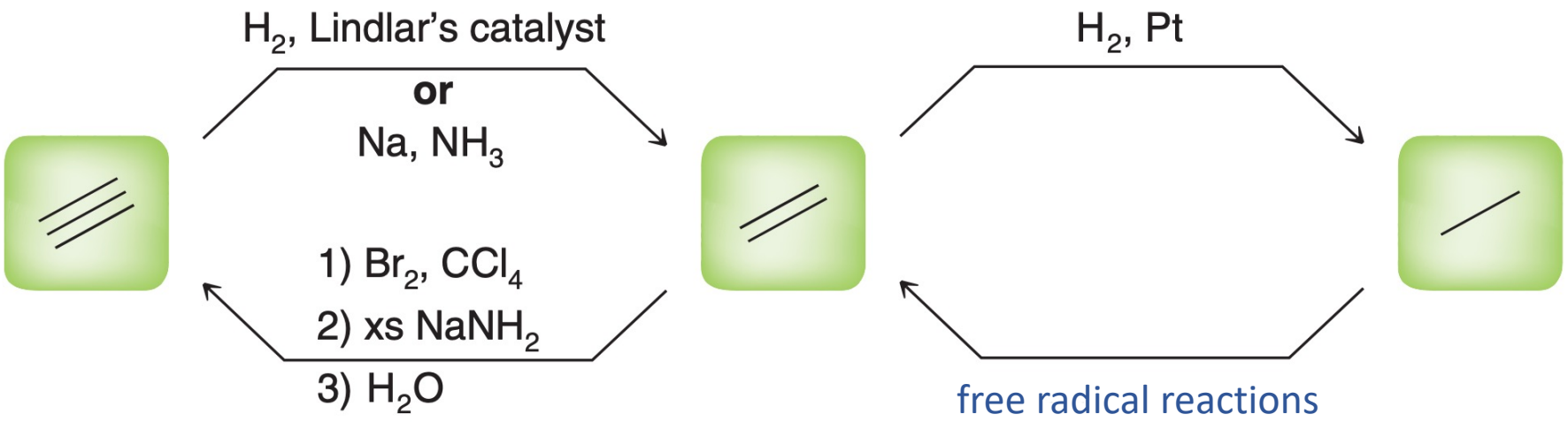
- 不饱和烃向饱和烃转化


H2, Pt
H2, Lindlar's catalyst
or
Na, NH3
H2, Pt
Alkyne
Alkene
Alkane

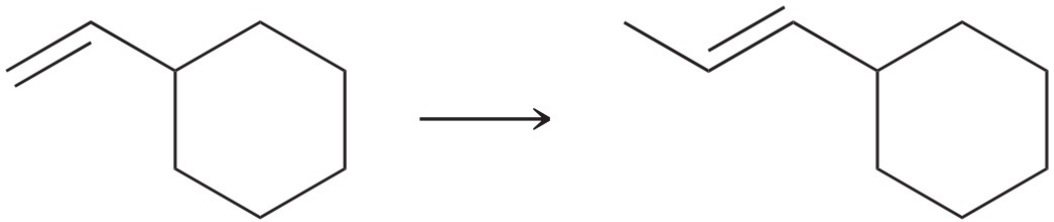
- 饱和烃向不饱和烃转化

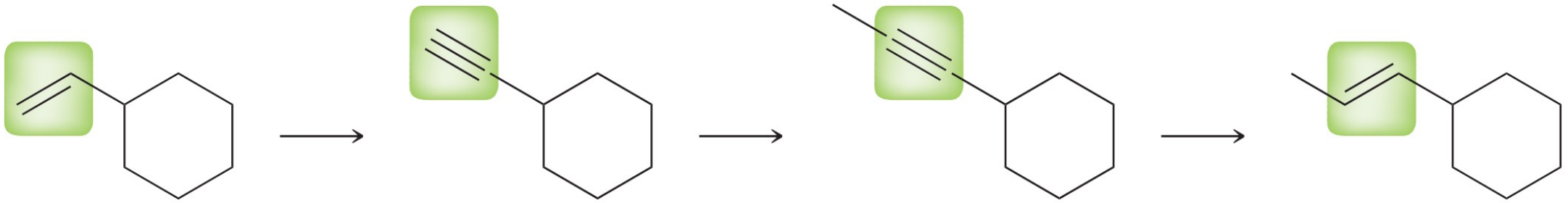


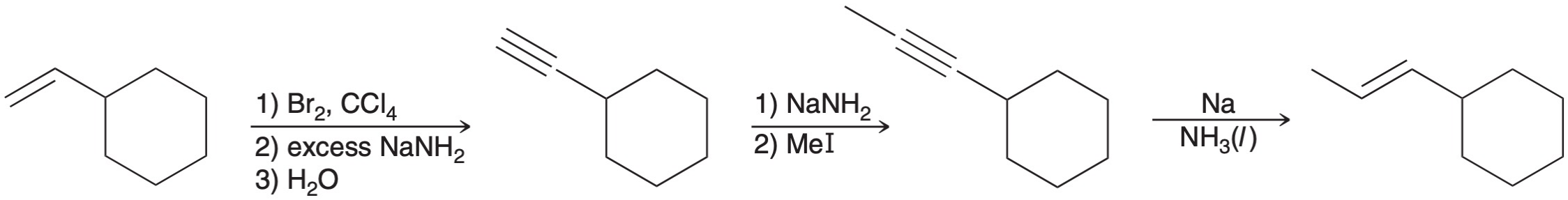
- 饱和烃向不饱和烃转化


H2, Lindlar's catalyst
or
Na, NH3
1) Br2, CCl4
2) xs NaNH2
3) H2O
H2, Pt
free radical reactions

- Practice: propose an efficient synthesis for the following transformation:






1) Br_2, CCl_4
2) excess $NaNH_2$
3) H_2O
1) $NaNH_2$
2) MeI
Na
$NH_3(l)$