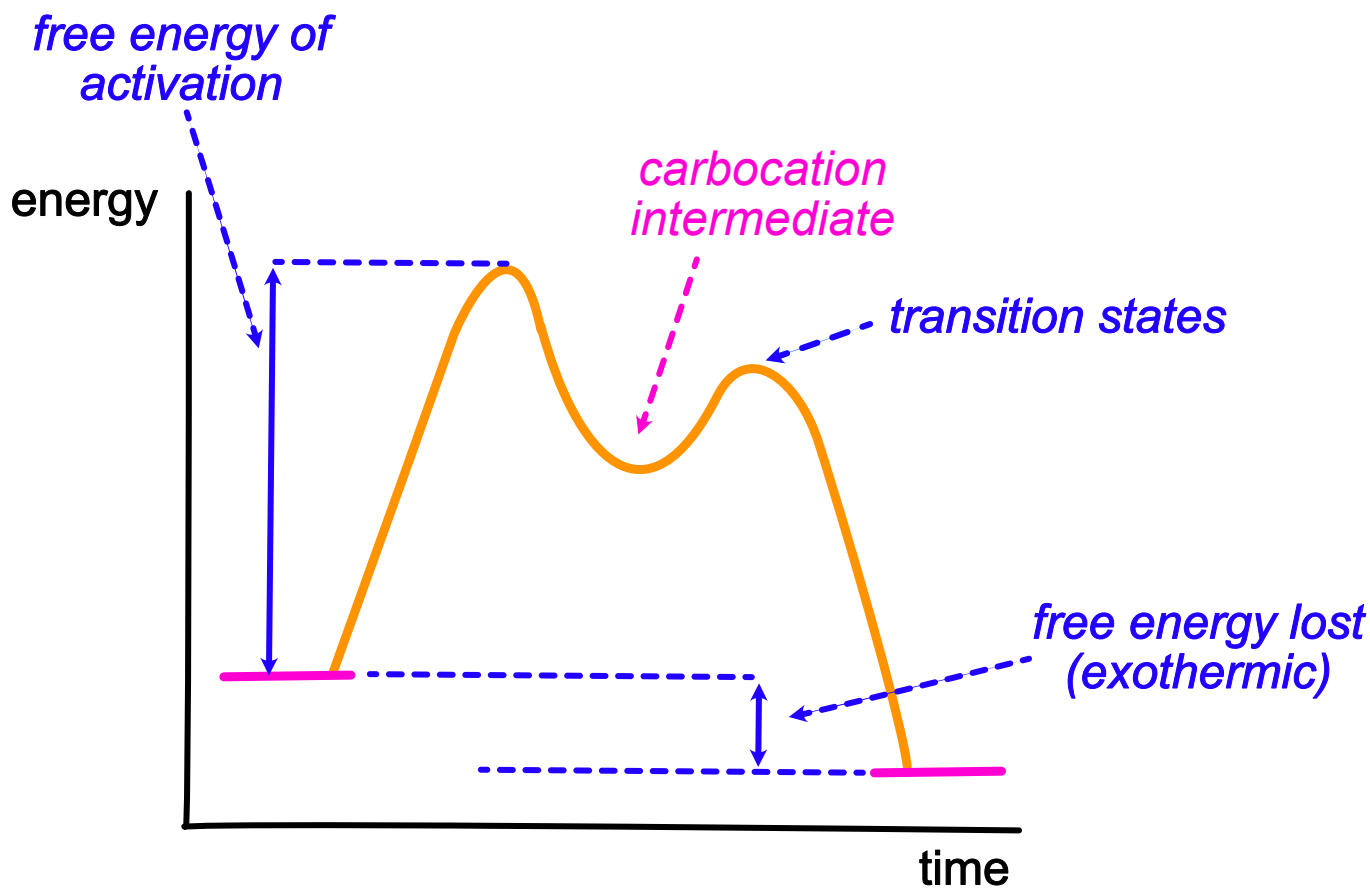
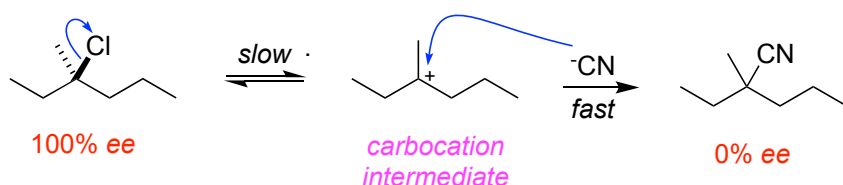


1. S_N1 Displacement At sp³ Centers

from chapter(s) _____ in the recommended text

A. Introduction

B. Fundamentals



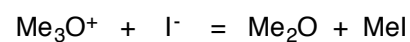
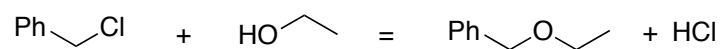
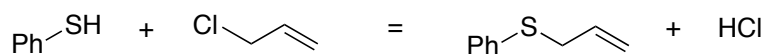
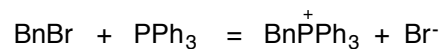
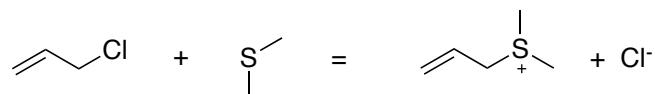
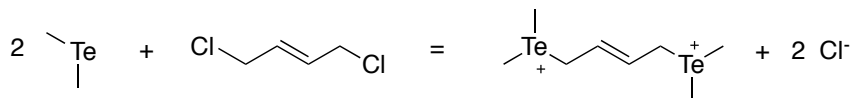
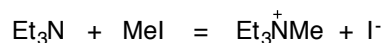
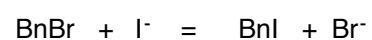
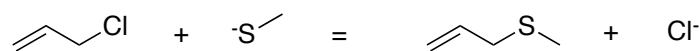
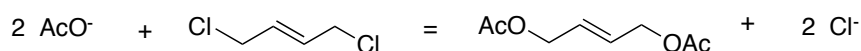
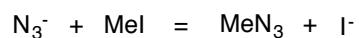
n = number of
chiral centers

2^n stereoisomers possible

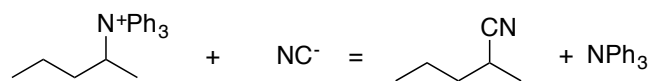
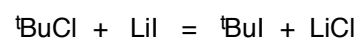
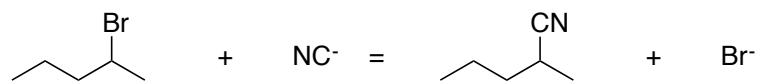
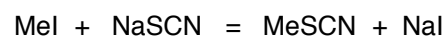
$$2^2 = 4$$

C. Charges On Nucleophiles And Leaving Groups

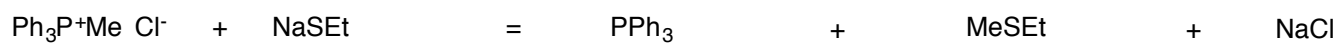
Nucleophiles



Leaving Groups



(intramolecular)



D. S_N1 Slow Formation Of Carbocations

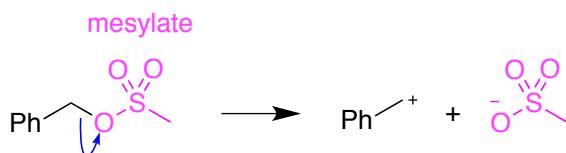
Key Steps

Substitution describes reactions in which one group *replaces another*.

S_N1 stands for substitution by a nucleophile *with first order kinetics*.



carbocation and bromide



*benzyl carbocation
and -OMs*

formation of a carbocation *is* the rate limiting step.





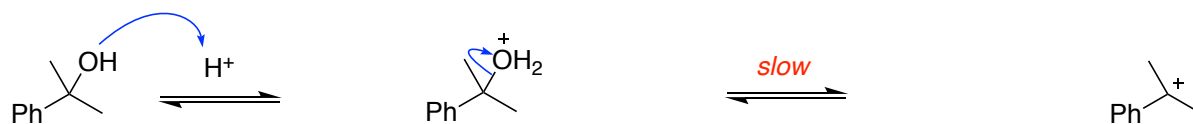
carbocation and hydroxide



carbocation and water

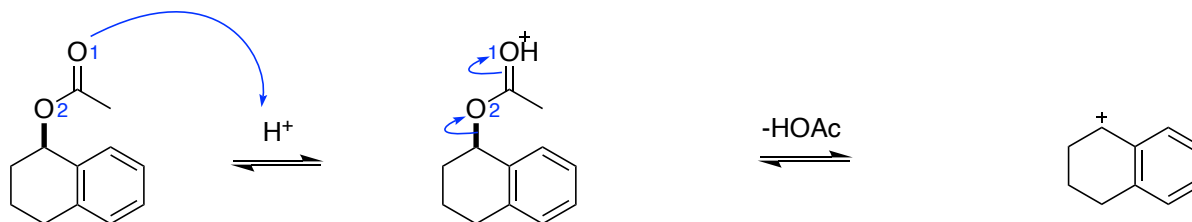
Water is a much *better* leaving group than hydroxide
 pathway on the *right* is more favorable
 the one on the *left* does not proceed at all.

Some poor *leaving groups* can be converted into better ones by protonating them: *true*



protonated intermediate

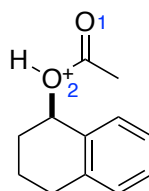
carbocation intermediate



protonated intermediate

carbocation intermediate

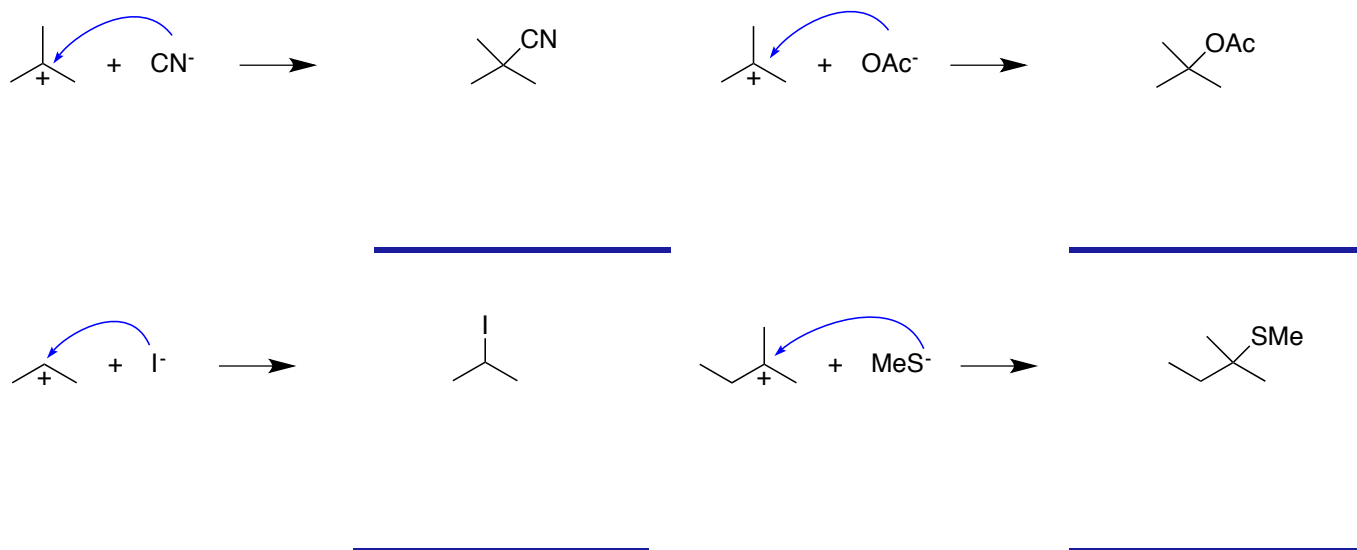
only protonation of O^1 is stabilized by resonance from the other oxygen.



*this cannot be
 stabilized by resonance*

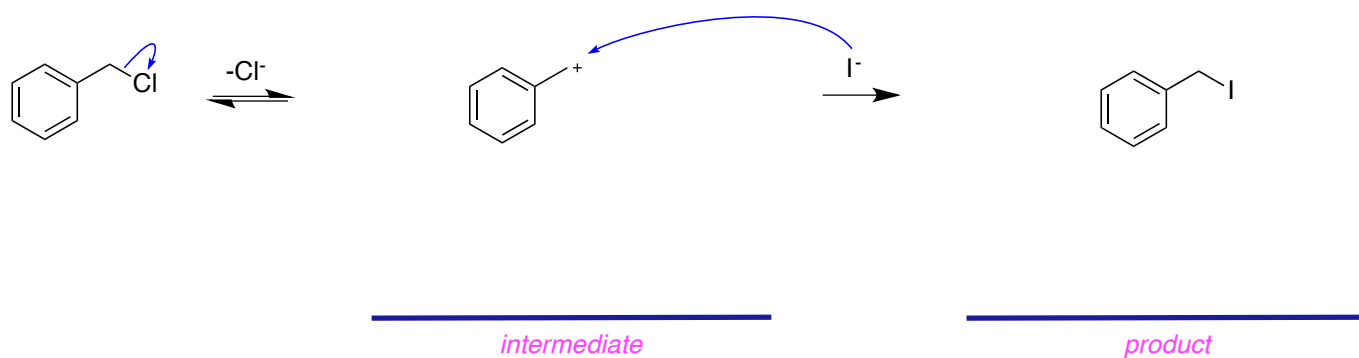
E. SN1 Fast Combination Of Cations With Nucleophiles

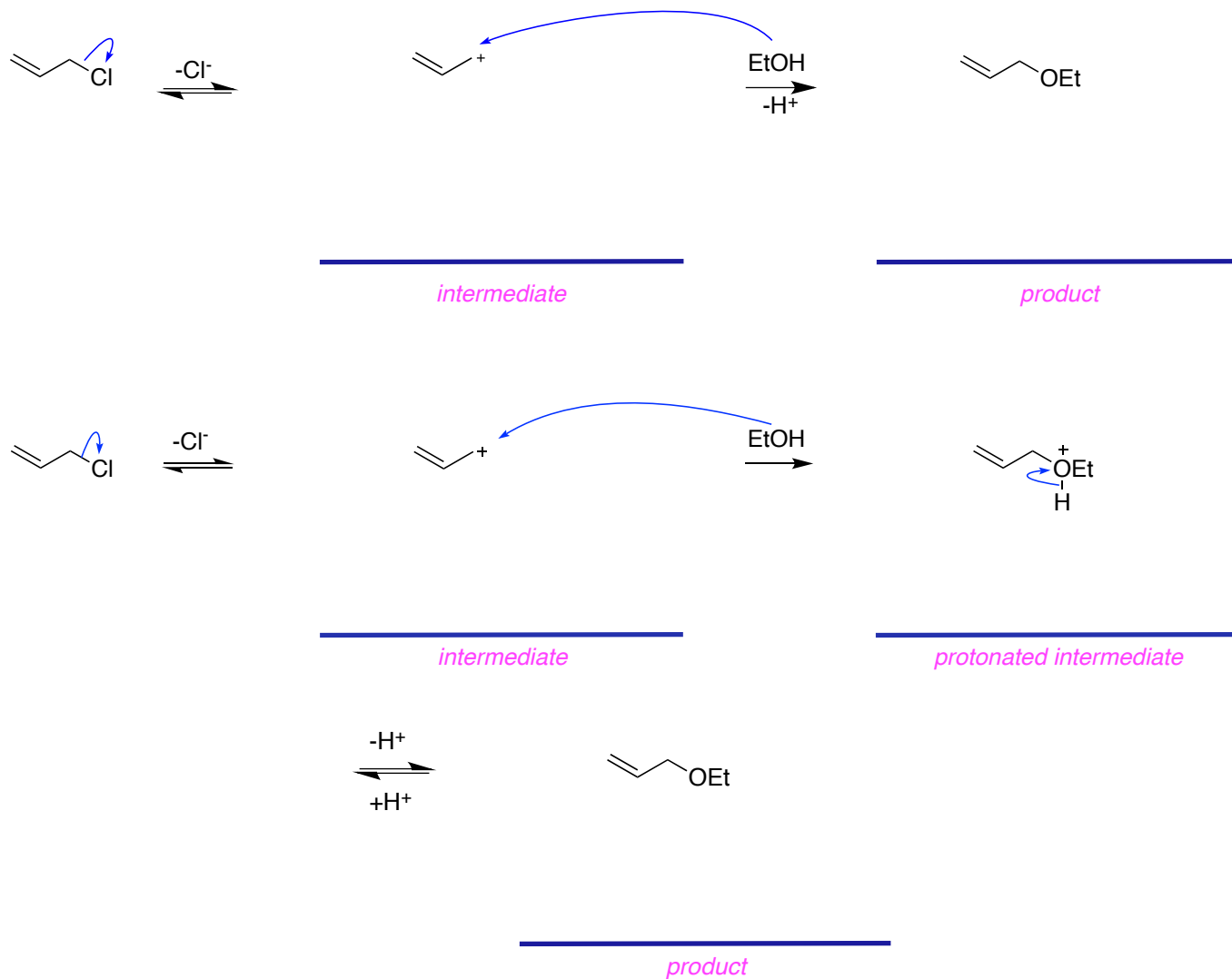
Carbocations *can* combine with negatively charged nucleophiles to produce neutral molecules.



When carbocations combine with *neutral* nucleophiles they form *cations*

the products will be *racemic*, because the intermediate, sp^2 -hybridized carbocations, are *flat*

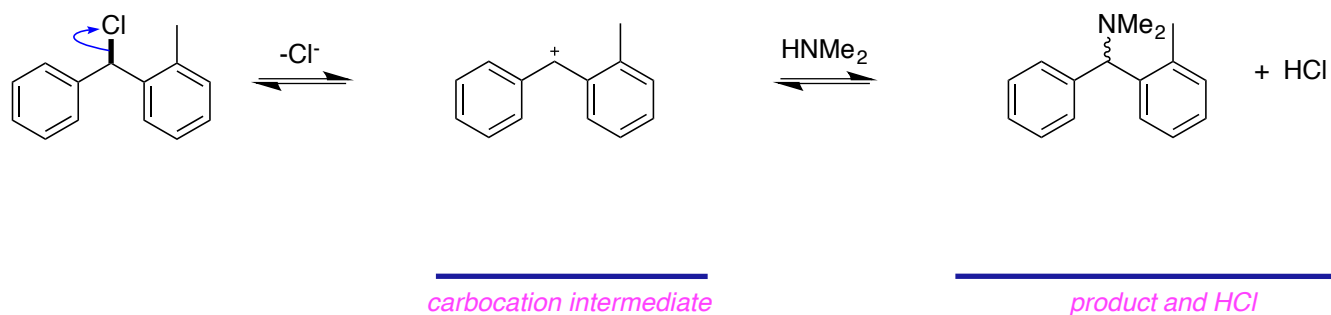




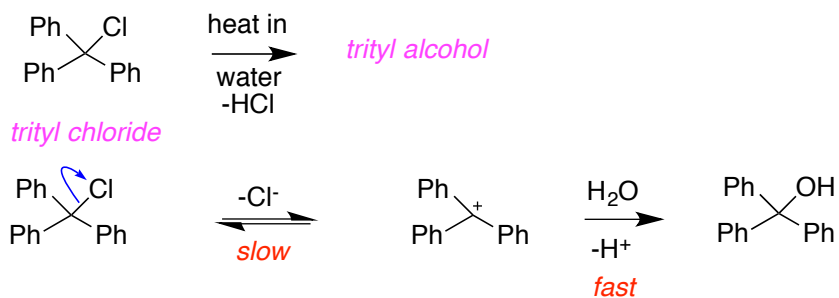
S_N1 reaction of *tert*-butyl chloride with water involves *two* intermediates.

S_N1 reaction of *tert*-butyl bromide with acetate (MeCO_2^-) involves *one* intermediate.

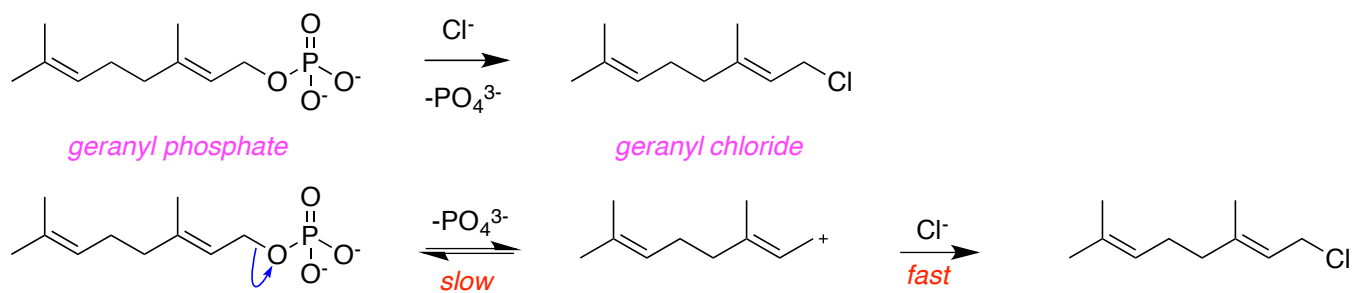
S_N1 reaction of bromide with allyl chloride involves *one* intermediate.

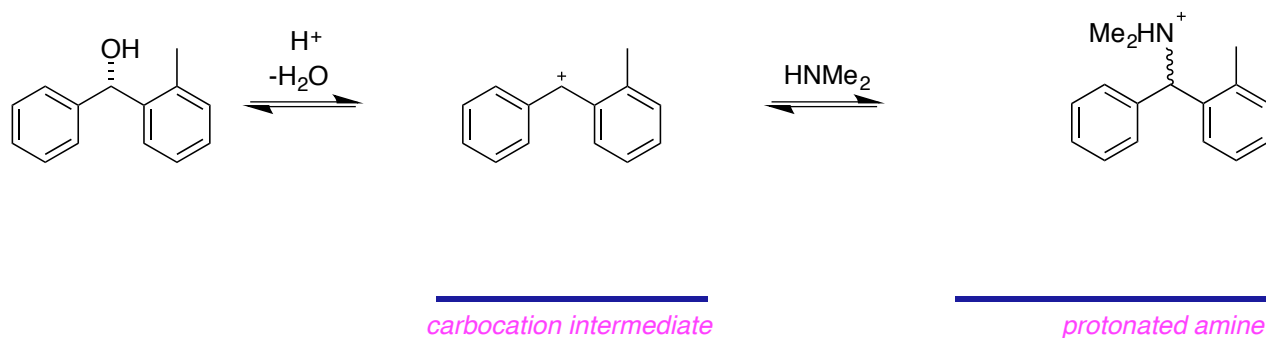


a

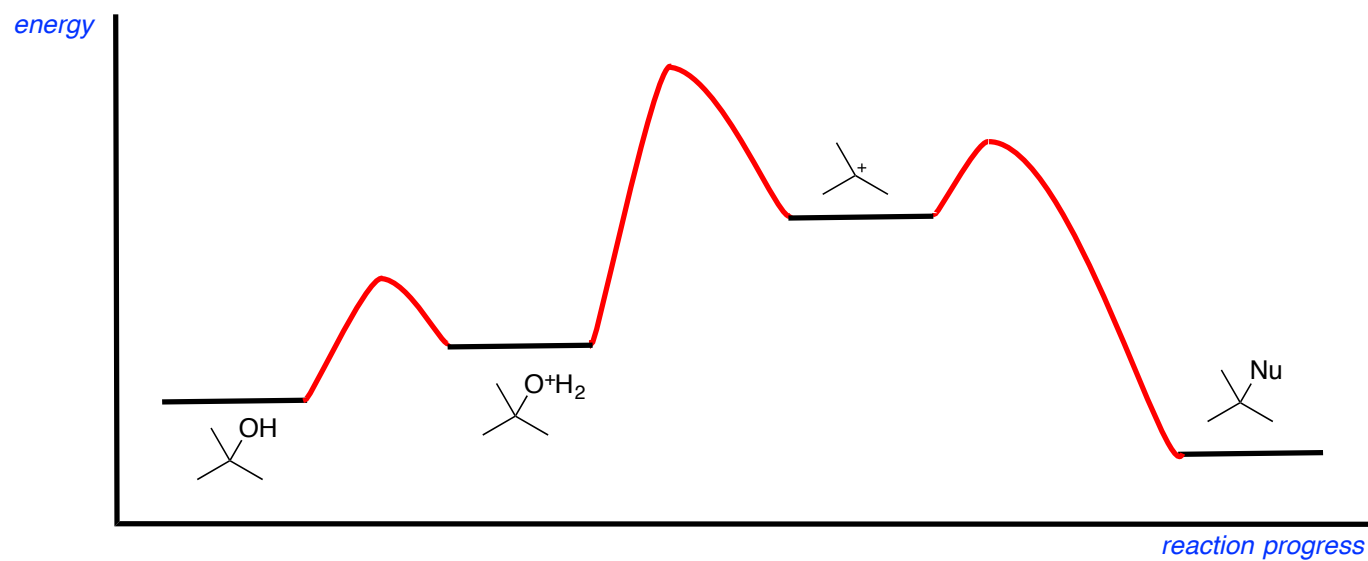
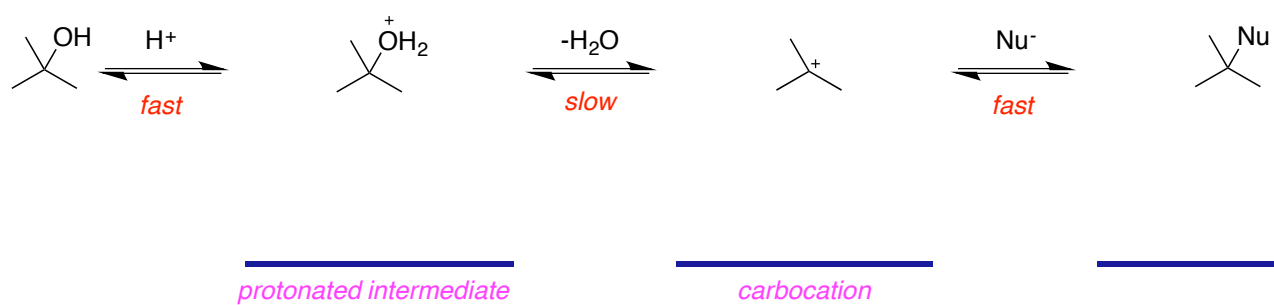


b



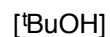


F. S_N1 Kinetics



the rate of the reaction above *is* proportional to the concentration

rate is proportional to



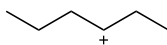
rate =



triphenylmethyl chloride with sodium cyanide proceeds *at the same rate* the if the concentration of the cyanide salt is doubled

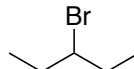
G. Carbocation Stabilities Govern SN1 Rates

Rates of S_N1 reactions tend to *increase* with stabilities of carbocation intermediates.



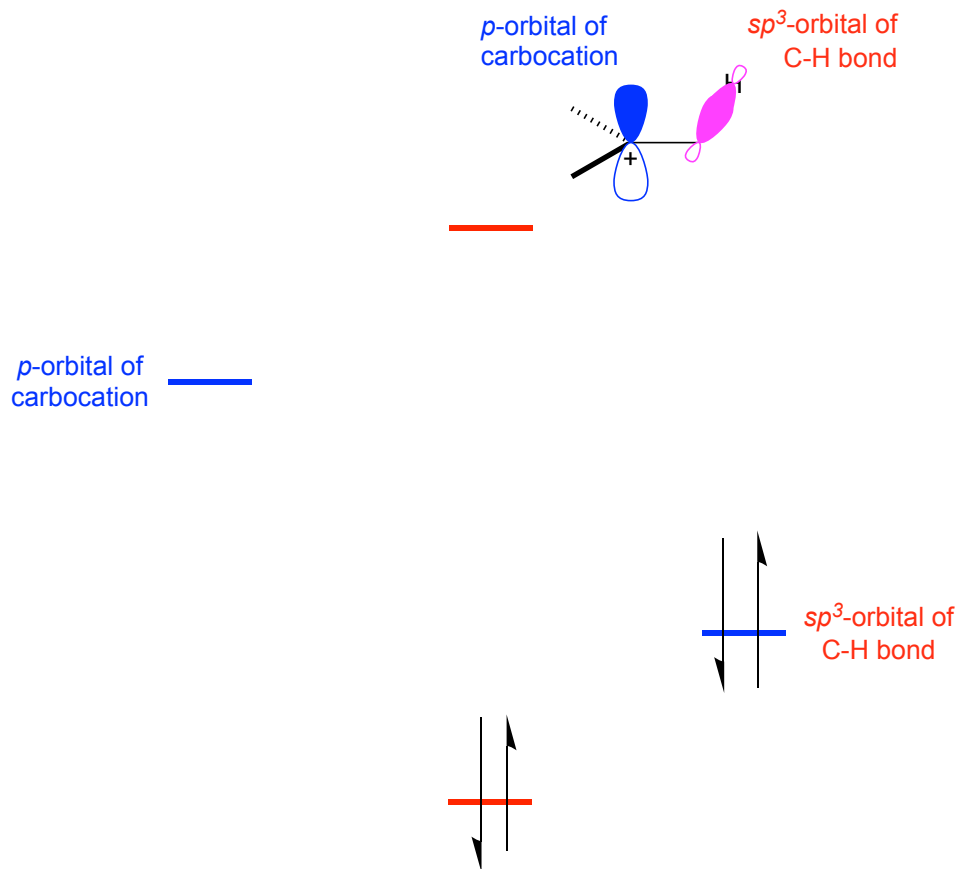
most stable

least stable



fastest

slowest



There are **3** times more of these interactions in the ^tBu cation than in Me⁺.

In Et⁺ the sp³ orbitals of the methyl group are tilted a bit *away from* the empty p-orbital of the cation, thus the overlap, and therefore the stabilization, is *less* than a situation in which the orbitals were completely parallel.

system overall is *greater* than that from hyperconjugation in Et⁺.

Allyl cations are *more* stable than many other primary carbocations.

secondary molecular orbital interactions between an *empty* p-orbital and appropriately aligned C-H σ-orbitals

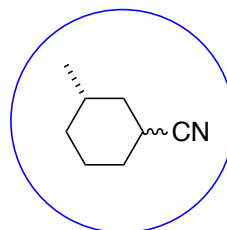
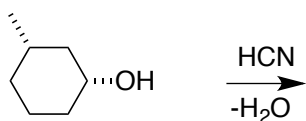
*show 3°, 1°, 2°, Me
on top of line*

	Me	1°	2°	3°
<i>least stable</i>	0	1	2	3
<i>most stable</i>	0	1	2	3

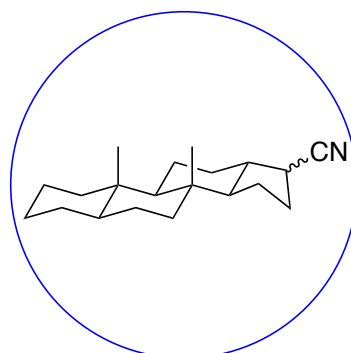
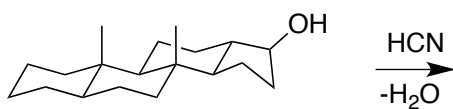
*on bottom of line
show number of p-to-σ interactions*



circle if optically active



circle if optically active



circle if optically active

2. S_N2

from chapter(s) _____ in the recommended text

A. Introduction

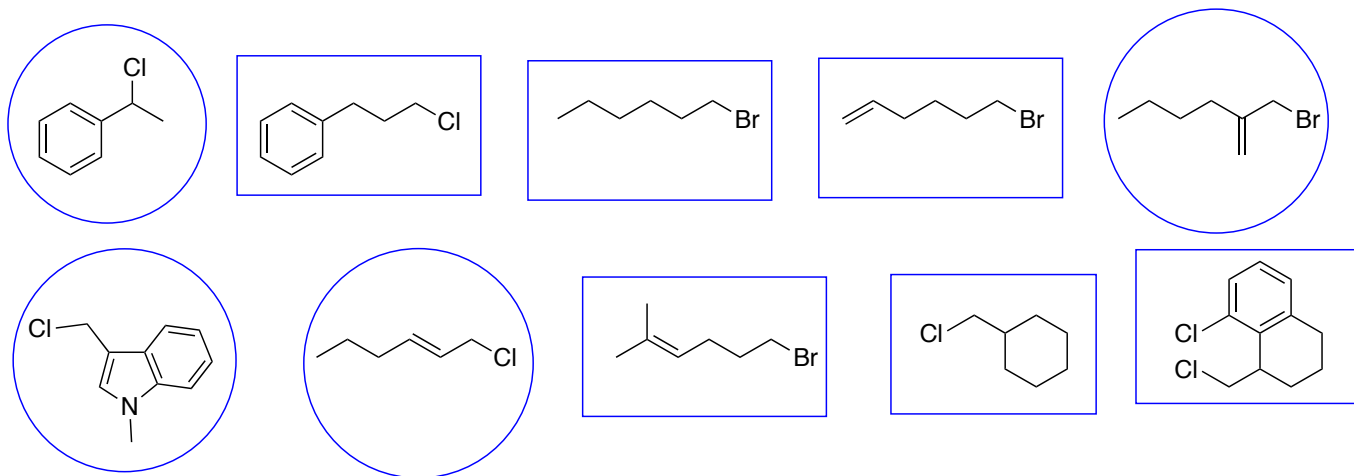
B. Differentiating S_N1 and S_N2

S_N2 describes reactions in which one *replaces another* and *with second order kinetics*.

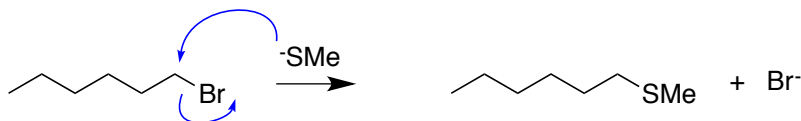
Inversion of configuration is observed in S_N2 processes whereas S_N1

unstable carbocations tend to proceed via S_N2 pathways.

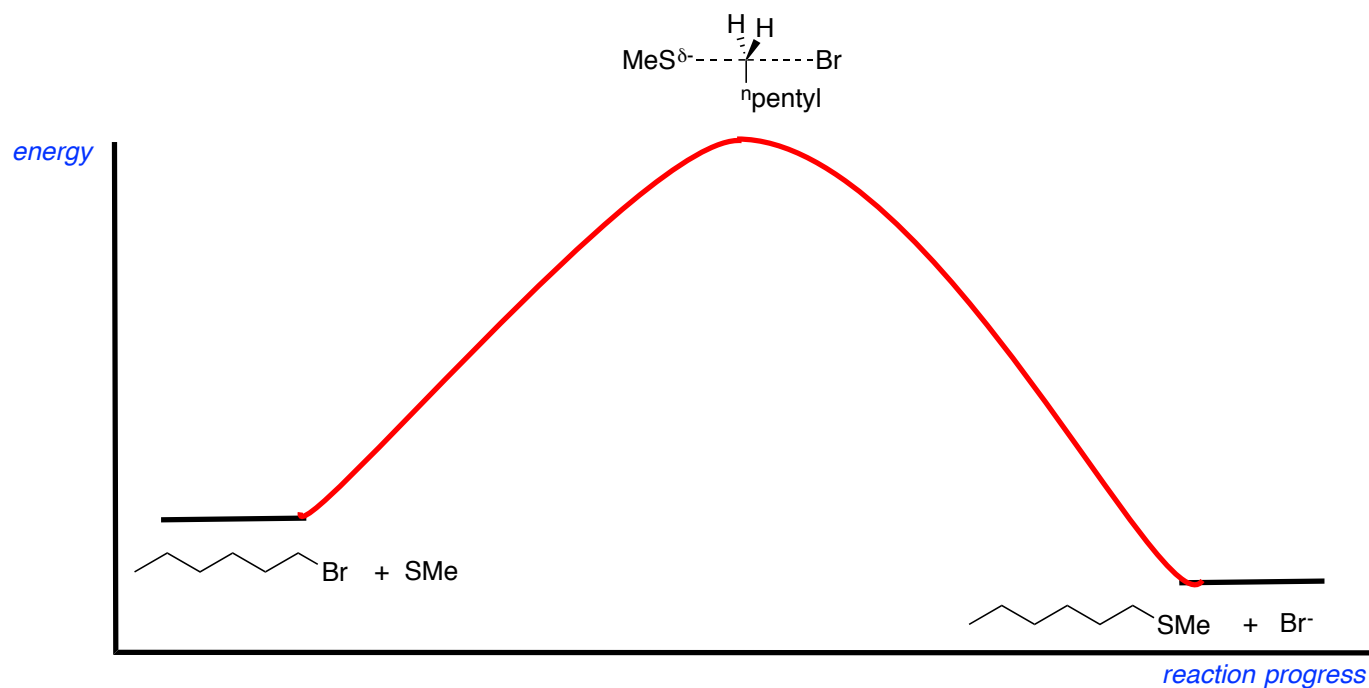
tertiary carbocations often proceed via S_N1 mechanisms.



C. S_N2 Kinetics



product plus by-product



Note: This process does not include an intermediate, and the simultaneous substitution is the slow or rate determining step.

concentration of the nucleophile *doubles*

Reaction of methyl iodide with azide is *accelerated*

A substrate that might react via both S_N1 and S_N2 pathways is *more*

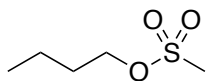
The transition state in a S_N2 reaction is *less*

D. S_N2 Stereochemistry

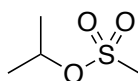
Conversion Of Alcohols Into Leaving Groups

Hydroxyl groups *are not* good leaving groups

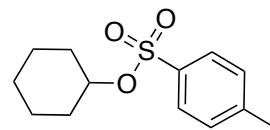
tosylates or mesylates makes them into much *better*



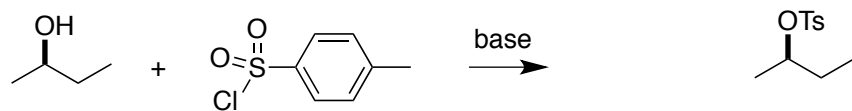
*n*butyl mesylate



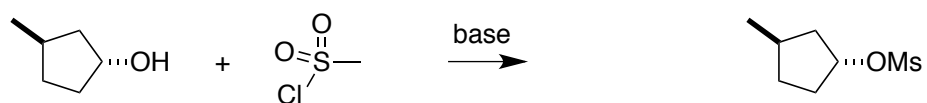
*i*propyl mesylate



cyclohexyl tosylate



^sbutyl tosylate



Mesyl is an $-S(O)_2Me$ group, and mesylate is $-O-SO_2Me$.

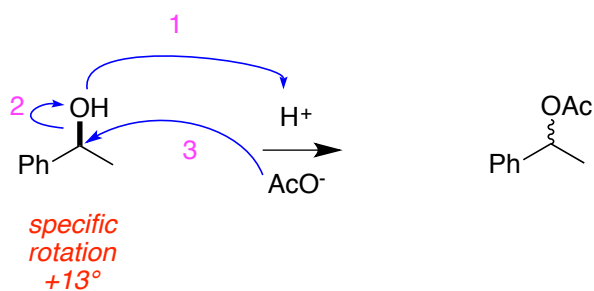
Tosyl is an $-S(O)_2Ar$ group, and tosylate is $-O-SO_2Ar$ (where Ar is $-C_6H_4-4-Me$).



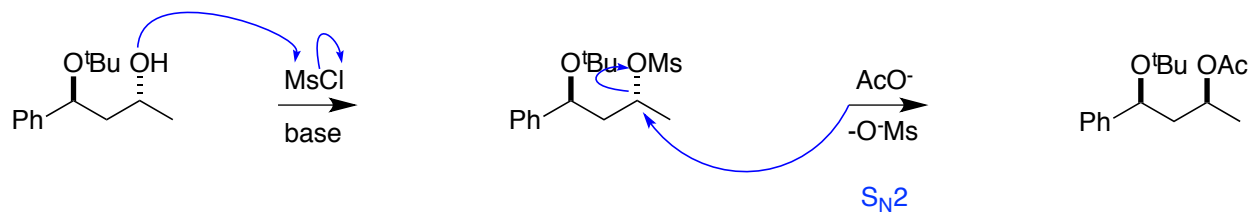
Mesylates and tosylates are *better* leaving groups than hydroxide formed with *retention* of configuration
 S_N2 processes with complete *inversion* stereochemistry.

Interconversions Of Enantiomers And Diastereomers

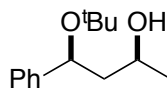
The first reaction is most like S_N1 .

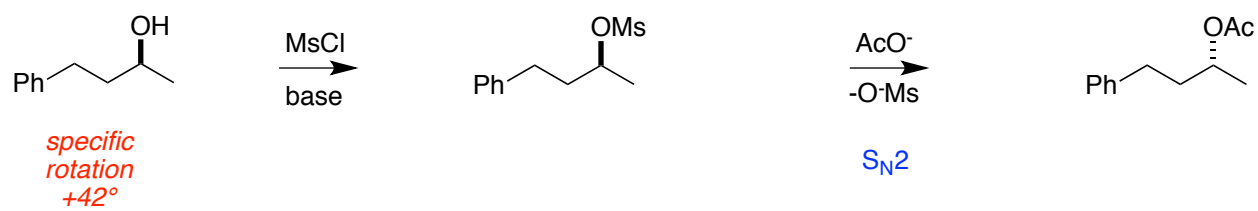


specific rotation $= 0^\circ$

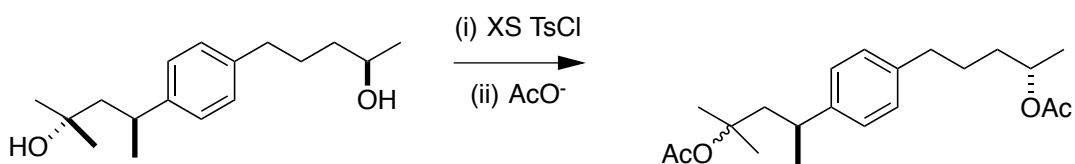
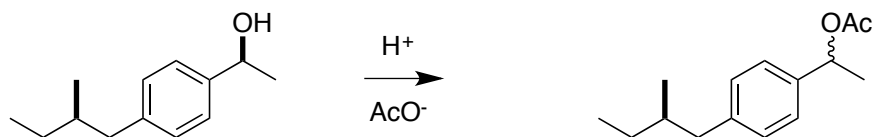


hydrolysis





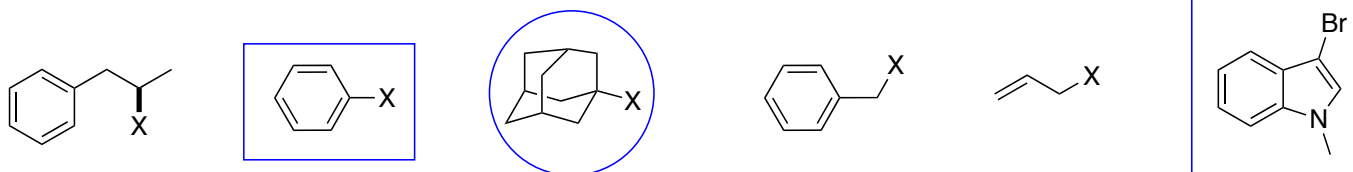
specific rotation = -42°



product of one $\text{S}_{\text{N}}1$ and one $\text{S}_{\text{N}}2$ reaction

E. Stereoelectronic Effects

S_N2 reactions occur via approach of a nucleophile in a trigonal bipyramidal *transition state* cannot readily undergo bimolecular nucleophilic



S_N1 displacements involve interaction of a LUMO on the substrate with a nucleophile *HOMO*.

In S_N1 reactions the LUMO is *the empty p-orbital of the carbocation*.

S_N2 displacements involve interaction of a LUMO on the substrate with a nucleophile *HOMO*.

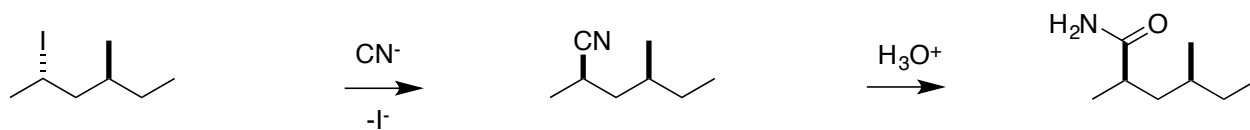
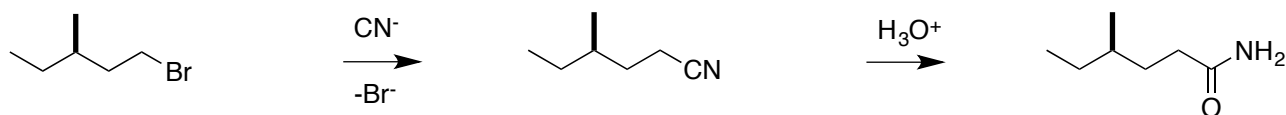
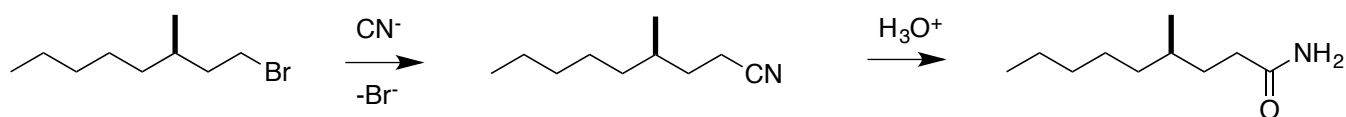
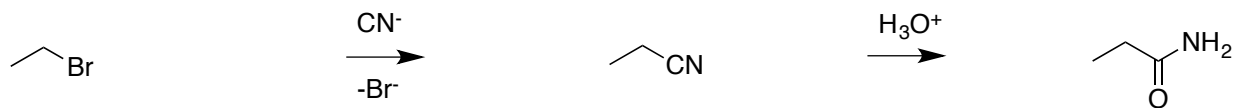
In S_N2 reactions the LUMO is a σ^* orbital.



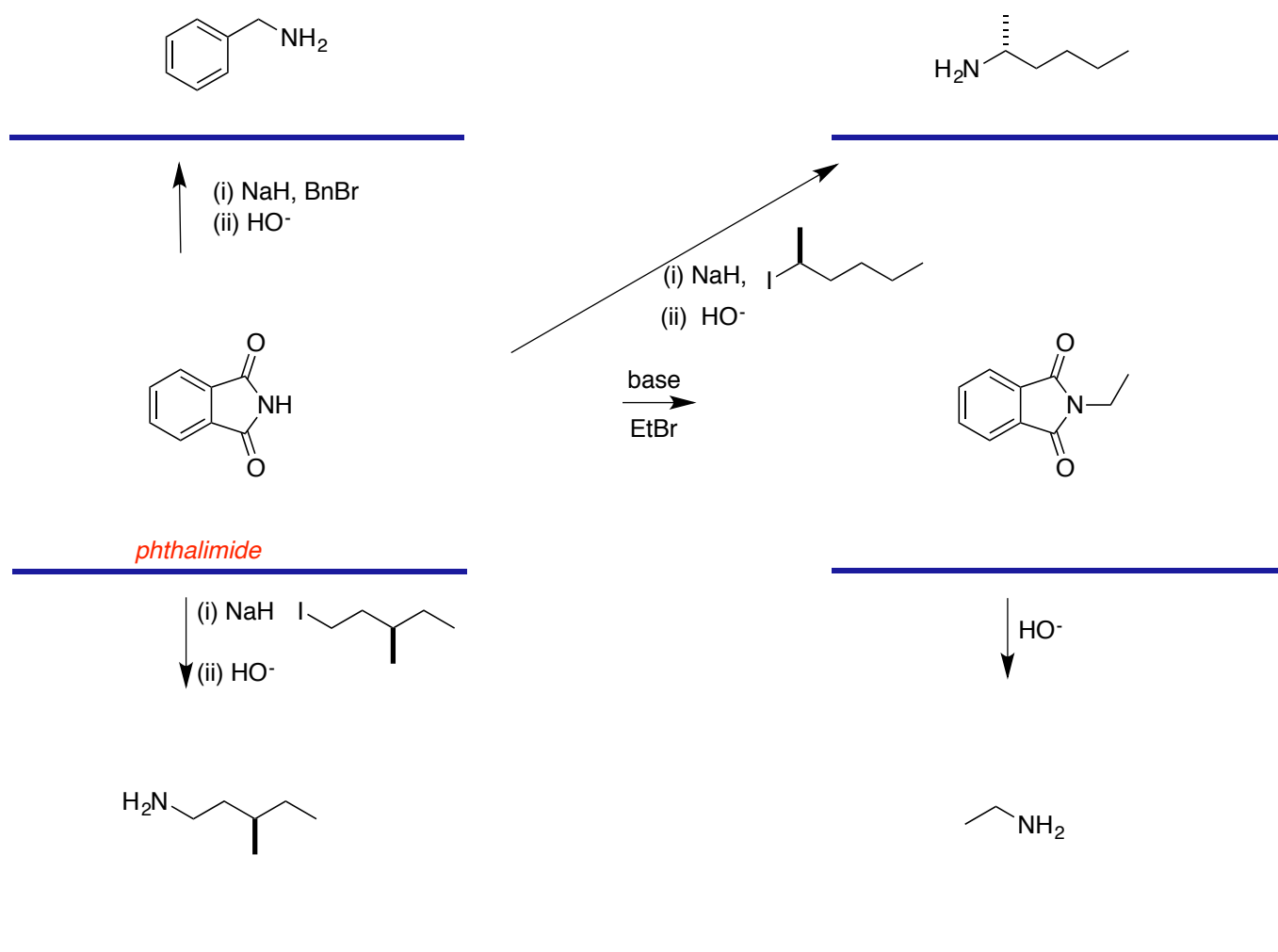
draw C - I σ^ -orbitals and orientation of S_N2 displacement by CN^-*

F. S_N2 Reactions Applied To Make Amides And Amines

Cyanide: A Useful C-Nucleophile



Phthalimide: Useful *N*-Nucleophile For Syntheses Of Primary Amines



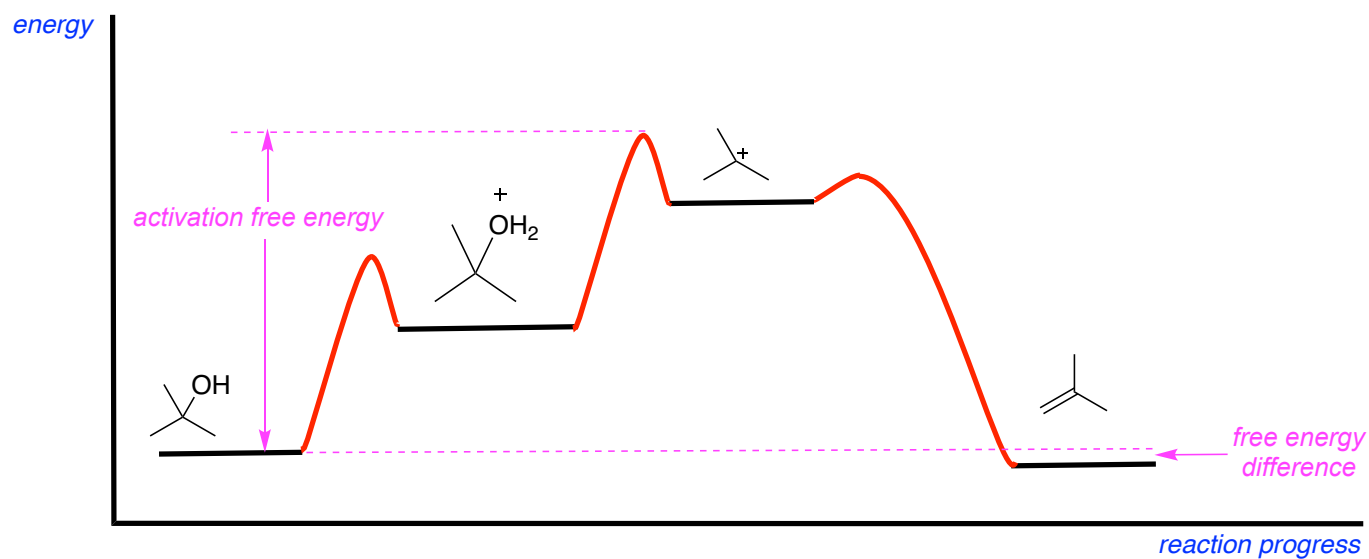
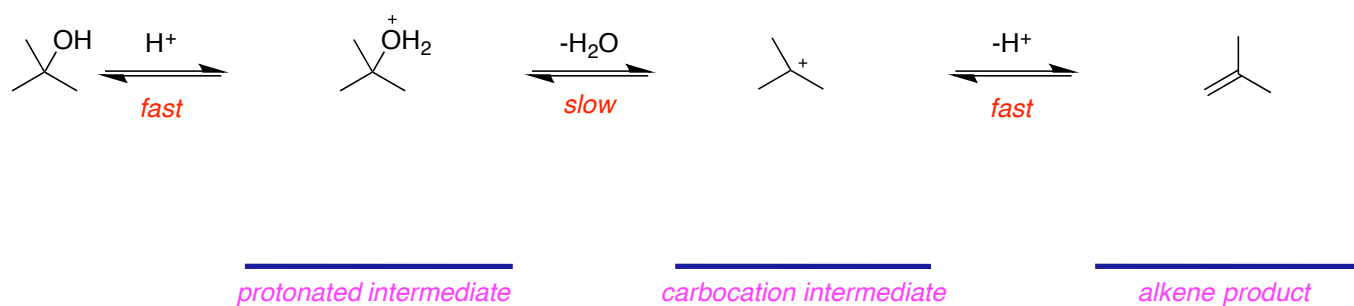
Using this reaction it is possible to make *primary amines*
 This so called *Gabriel* synthesis is a *better*

3. Eliminations

from chapter(s) _____ in the recommended text

A. Introduction

B. E1 Mechanisms



C. E1 Kinetics

the rate of the reaction above *is* proportional to starting material

rate is proportional to



rate =



Mathematically, the rate of a reaction is approximately given by which of the following equations **C and D**.

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$$

A

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ$$

B

$$k = A e^{-E_a/RT}$$

C

$$\ln k = \ln A - E_a/RT$$

D

Using a reference text, define the following terms:

ΔG^\ddagger = Gibbs energy of activation units kiloJoules (kJ)

ΔS^\ddagger = entropy of activation units Joules*(Kelvin)⁻¹ (J/K)

ΔH^\ddagger = enthalpy of activation units kiloJoules (kJ)

ΔG° = Gibbs free energy per mole of reaction at standard conditions (298 K, 100 kPa, 1M Reactant/Product) units kiloJoules (kJ)

ΔS° = Entropy per mole of reaction at standard conditions units Joules*(Kelvin)⁻¹ (J/K)

ΔH° = Enthalpy per mole of reaction at standard conditions units kiloJoules (kJ)

T = absolute temperature measured in Kelvin

R = universal gas constant units Joules*(Kelvin)⁻¹*(moles)⁻¹

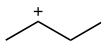
A = pre-exponential factor which is a constant representing the empirical relationship between rate coefficient and temperature unique to the chemical reaction

E_a = activation energy for the reaction

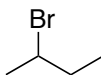
The difference between ΔG^\ddagger and E_a is E_a is more analogous to ΔH^\ddagger which considers the thermodynamic form of the rate equation, while ΔG^\ddagger is the difference between the ground state of reactant and transition peak with respect to both ΔS^\ddagger and ΔH^\ddagger .

Influence Of Carbocation Stabilities

Rates of E1 reactions tend to increase



most stable

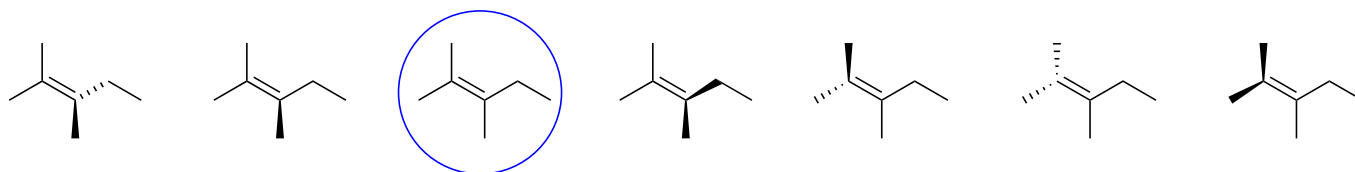


least stable

fastest

slowest

Bredt's Rule

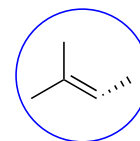
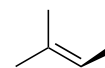
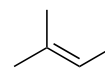
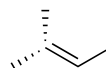
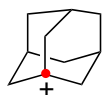


adamantane below is sp^3 -hybridized so it has ideal dihedral angles of $\sim 109^\circ$

All the carbons in adamantane have *the same* hybridization states.

the adamantane carbocation shown involves *more* ring and bond strain.

resembles the configuration around the alkene in *adamantene*; this *is not* a stable conformation.



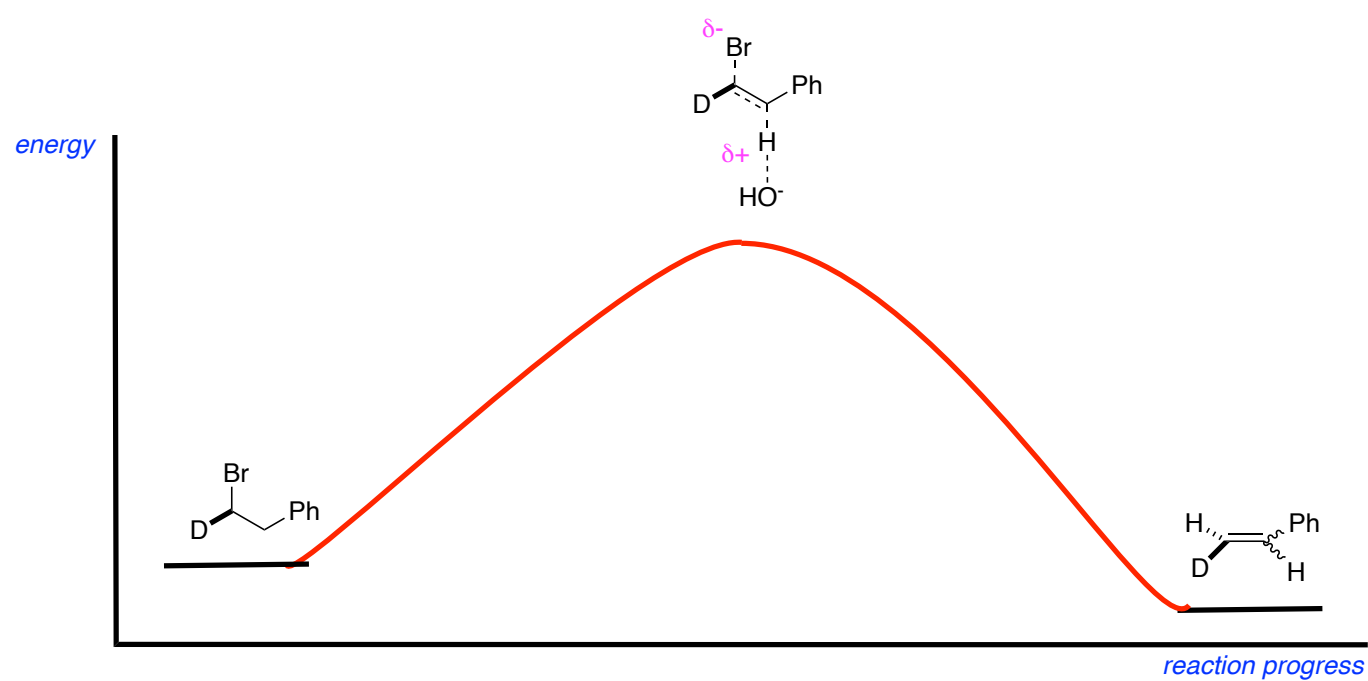
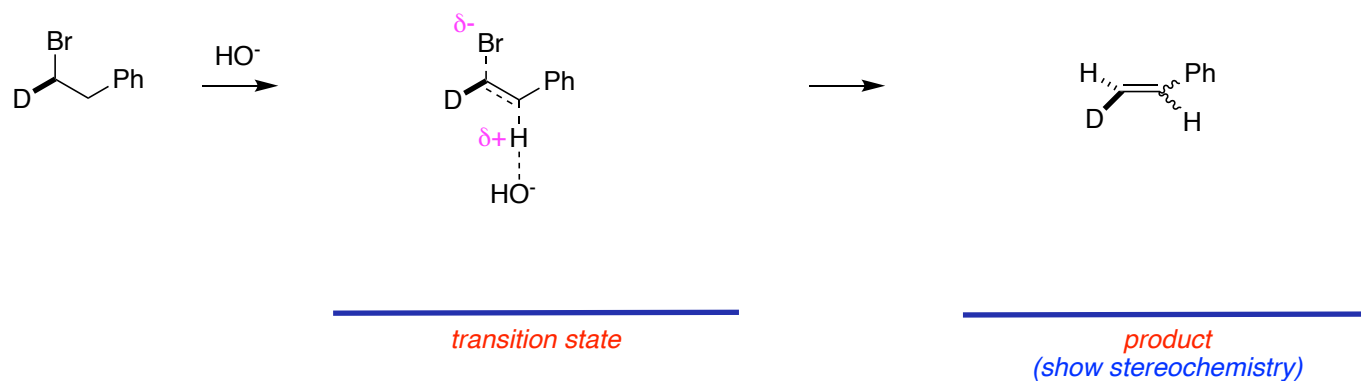
adamantane

adamantane
cation

adamantene

E1 eliminations that result in formation of adamantene *are not* favorable.

D. E2 Mechanisms



E. E2 Kinetics

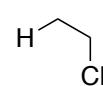
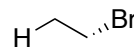
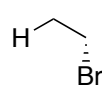
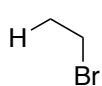
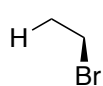
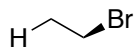
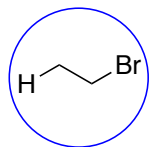
rate is proportional to $[\text{DCHBrCH}_2\text{Ph}] [\text{OH}^-]$

rate = $k [\text{DCHBrCH}_2\text{Ph}] [\text{OH}^-]$

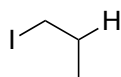
Doubling the amount of base *doubles* rates of E2 eliminations.

F. E2 Stereoelectronics

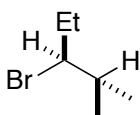
that puts two substituents on *different* sides and *perpendicular*.



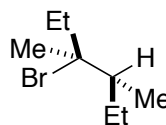
syn-periplanar
EtCl



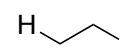
anti-periplanar
1-iodopropane



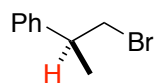
anti-periplanar
EtBrHCCHMe2



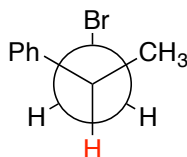
anti-periplanar
EtMeHCCBrMeEt



anti-periplanar
ethyl iodide

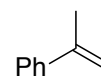


..... can be represented as

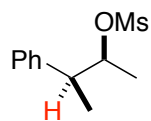


complete Newman projection

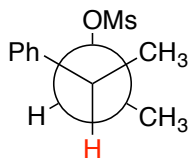
base
→



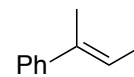
show alkene product



..... can be represented as

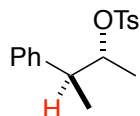


base
→

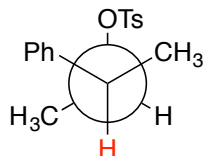


complete Newman projection

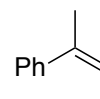
show alkene product



..... can be represented as

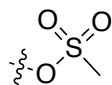


base
→

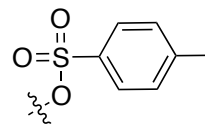


complete Newman projection

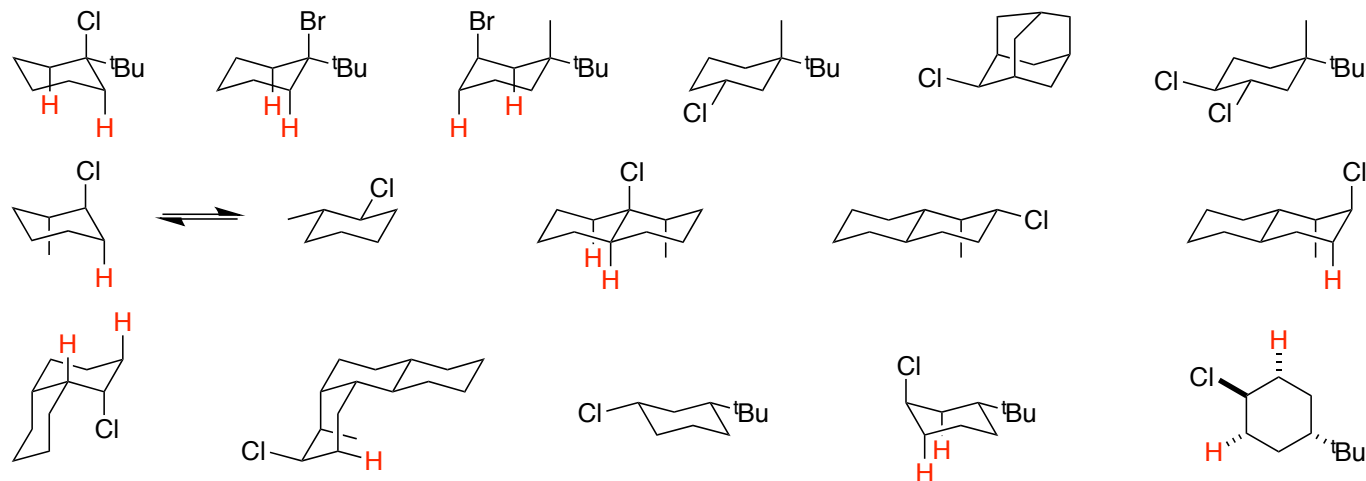
show alkene product



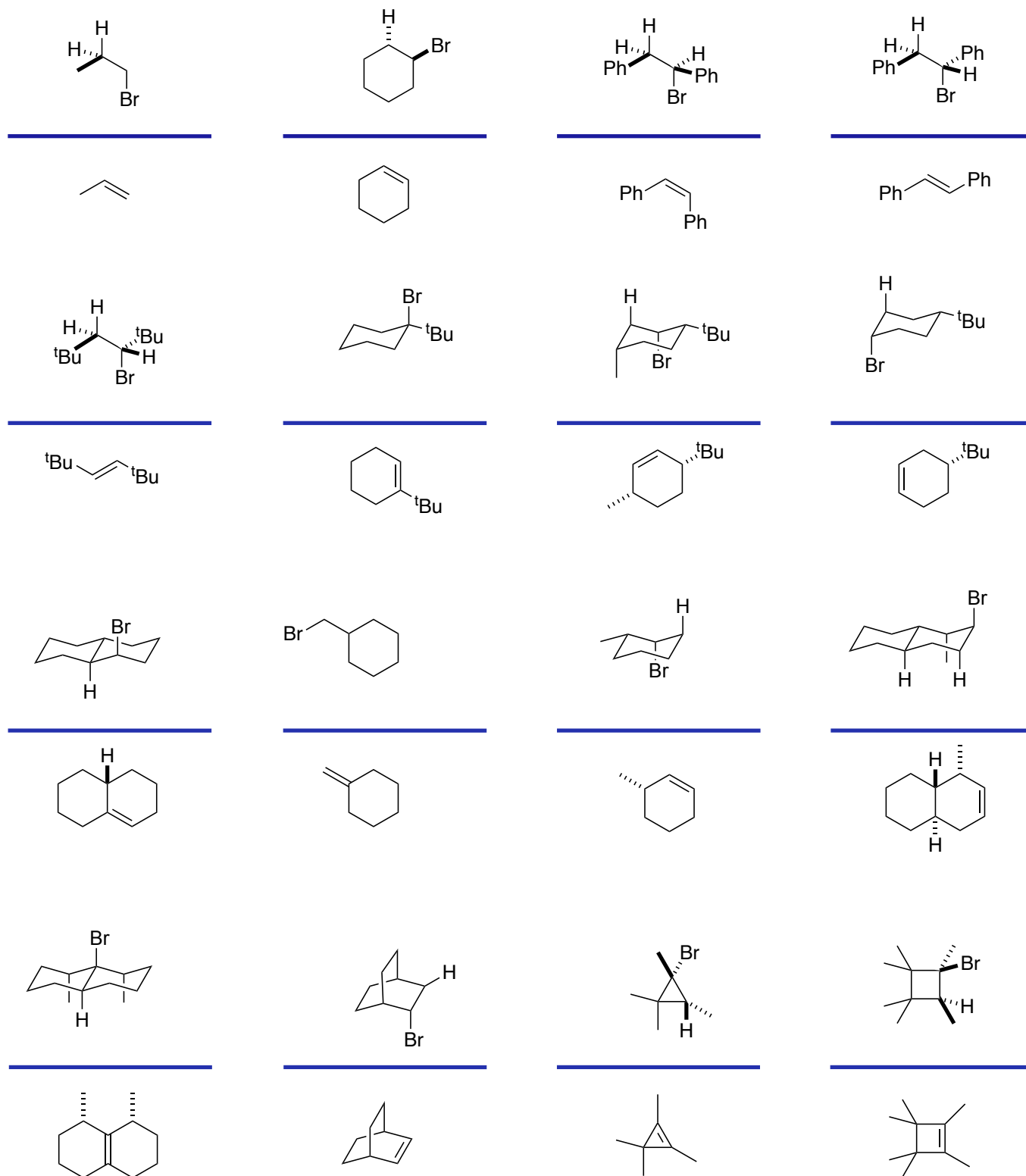
mesyl group, -OMs



tosyl group, -OTs



hydrogen that is being deprotonated and the leaving group are *anti*-periplanar.



G. Factors That Favor E1, E2, S_N1, or S_N2

Basicity vs Nucleophilicity

- (i) strongly basic character of Y⁻ will increase the rate of E2 relative to E1 reactions and it will tend to favor E2 over nucleophilic substitution reactions;
- (ii) weakly basic character of Y⁻ will retard the rate of E2 relative to E1 reactions and it will tend to favor E1 over nucleophilic substitution reactions;
- (iii) less basic character of Y⁻ will not affect the rate of E1 eliminations, but it will not favor E2 over E1 mechanisms; and,
- (iv) strongly nucleophilic character of Y⁻ will increase the rate of S_N2 relative to S_N1 reactions and it will tend to increase the rates of S_N2 over elimination reactions.

the likelihood of preferential E2 *increases* with the base strength.

Nucleophilicity

- (i) S_N1 relative to S_N2 reactions; and,
- (ii) E1 over E2

- (i) S_N2 relative to S_N1 reactions;
- (ii) E2 over E1 reactions.

The following order is approximate. It varies with the HOMO/LUMO match of the nucleophile with the electrophile.

N ₃ ⁻	CN ⁻	I ⁻	MeO ⁻	NH ₃	H ₂ O	Cl ⁻
<i>most nucleophilic</i>			<i>least nucleophilic</i>			
NH ₂ ⁻	HO ⁻	PhO ⁻	NH ₃	H ₂ O	Cl ⁻	
<i>most basic</i>			<i>least basic</i>			

because HCl the strongest acid, then H₃O⁺ then NH₄⁺ then PhOH (marginally) then H₂O then NH₃

Temperature And Entropy

$$\Delta G^\ddagger = \Delta H^\ddagger - T\Delta S^\ddagger$$

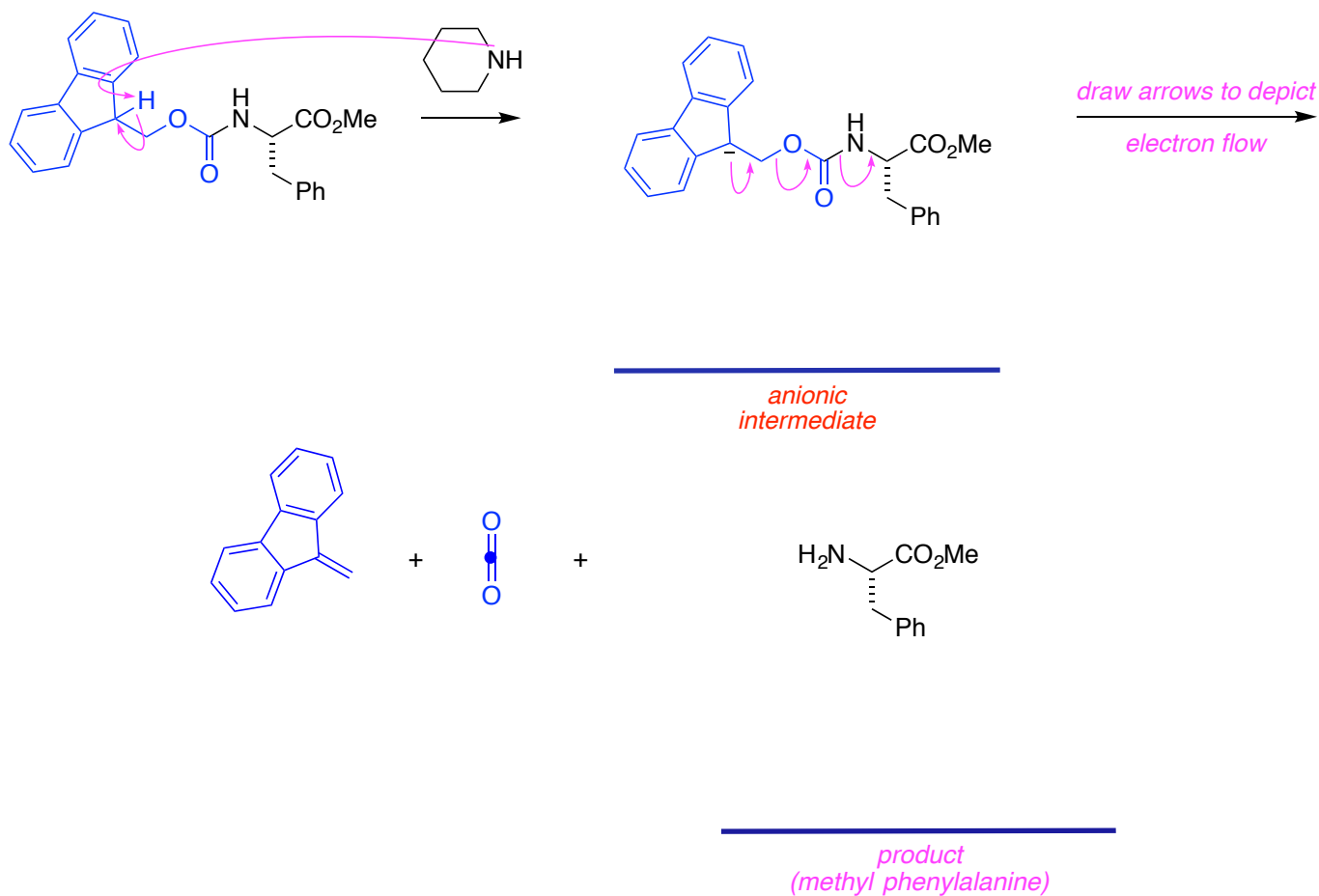
rate determining transition states in *E2* and *S_N2* over *E1* and *S_N1* reactions.

Low temperatures therefore tend to favor *E2* and *S_N2* over *E1* and *S_N1* reactions.

High temperatures therefore tend to *E1* and *S_N1* over *E2* and *S_N2* reactions.

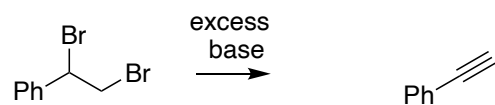
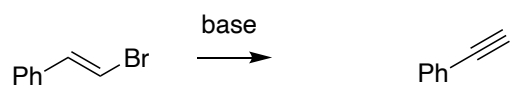
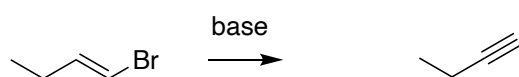
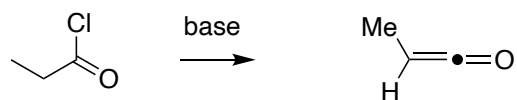
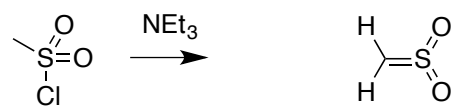
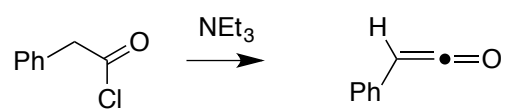
H. E1cB

removal of 9-fluorenyloxymethyl groups, *ie* *Fmoc* used to protect amines as *carbamates*.



Fluorenyl anions formed in this protection process have **14** π e, and are therefore *aromatic*.

I. Eliminations To Give Allenes, Alkynes, Ketenes And Sulfenes



ketene

sulfene

ketene

alkyne

alkyne

alkyne

4. Reactions Of Alkenes Via Protonation

from chapter(s) _____ in the recommended text

A. Introduction

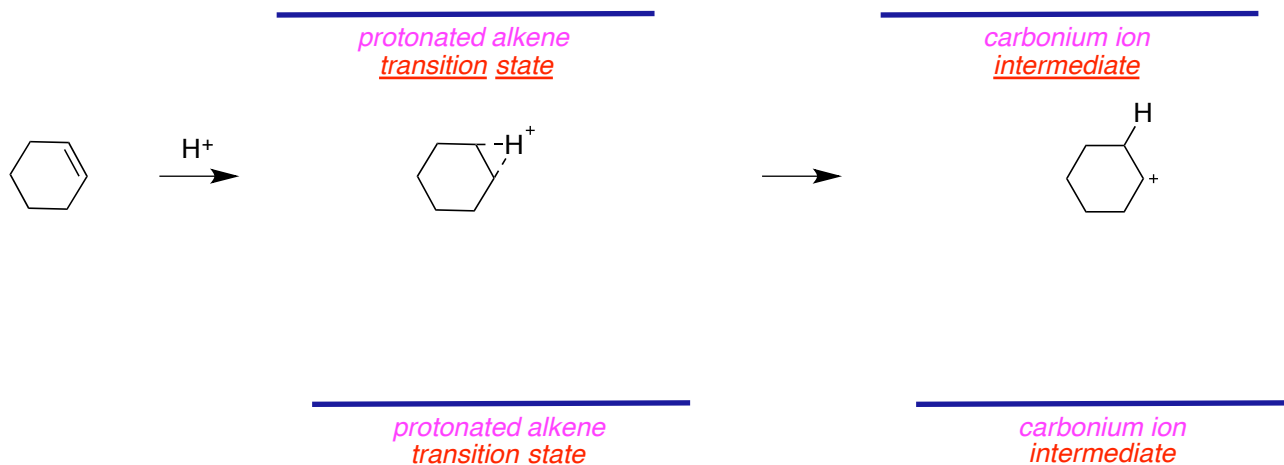
B. Protonation Of Alkenes: forms most stable carbocation

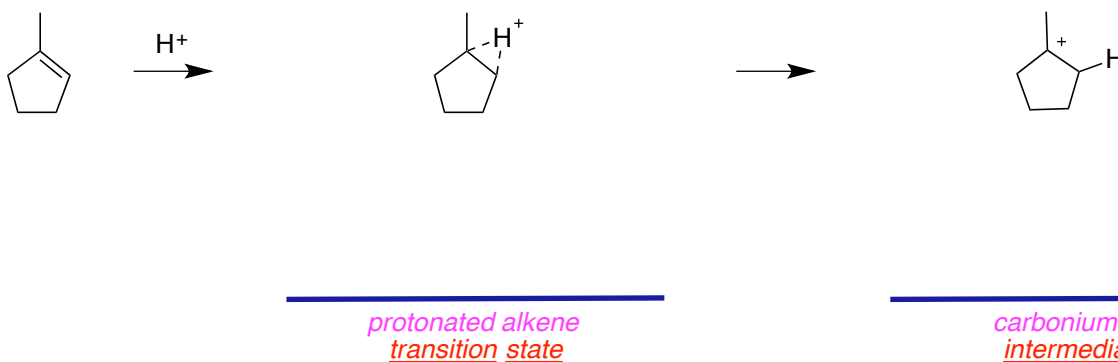
Generation Of Carbocations Via Protonation

Protons are the *simplest* of all electrophiles.

attacks from either side of the alkene or the other, giving one neutral *sp³-hybridized* carbon and a *sp²-hybridized*

Alkenes oriented perpendicular to a proton represent a *transition* while the carbonium ion is an *intermediate*.



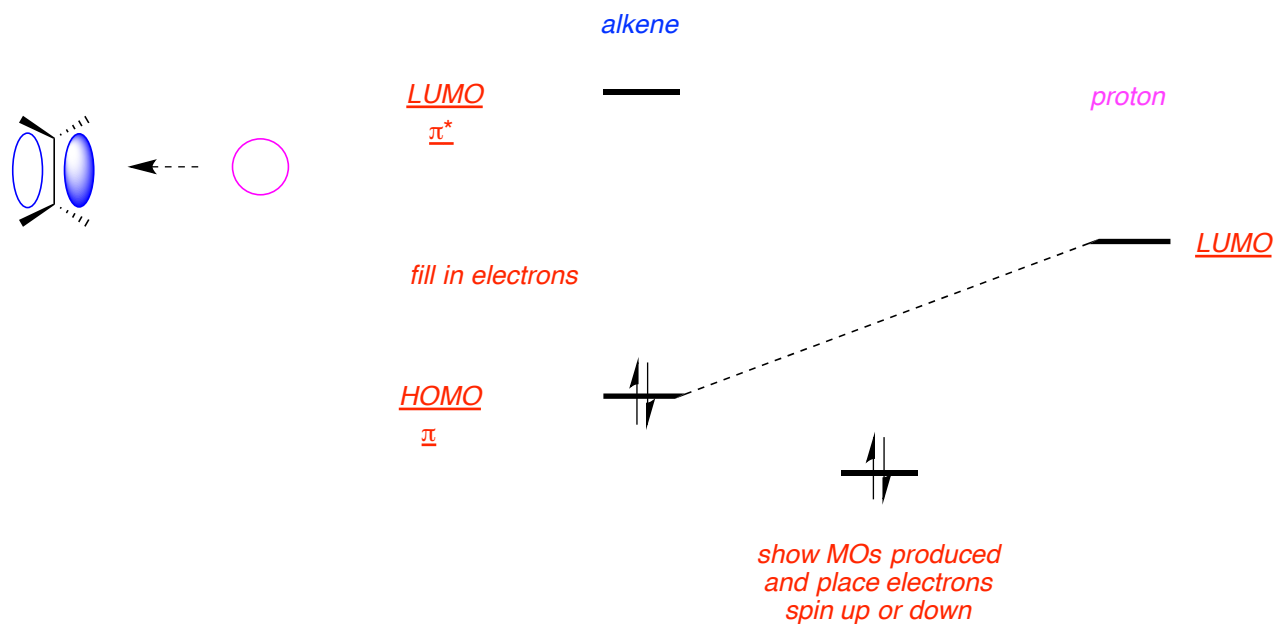


while other trajectories give more stabilization of the developing sp^3 -hybridized carbon.

A Molecular Orbital Picture Of Alkene Protonation

and when that lower-energy orbital is *more* populated with electron density

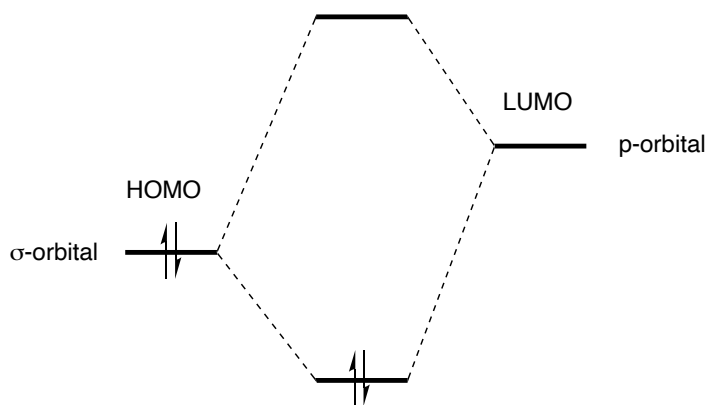
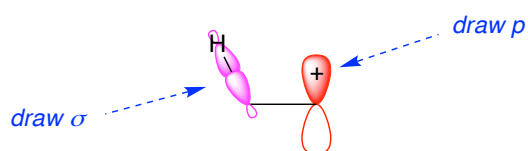
A proton *does not* have a highest occupied molecular orbital (HOMO), so only the **LUMO**
Thus the **LUMO** of a proton and the **HOMO** of an alkene should be considered when a proton



Perpendicular approach of a proton to a symmetrical π -cloud is net *stabilizing*.

C. Carbocation Stabilities

Valence bond and molecular orbital approaches are *alternative theories to explain bonding in general*.
 methyl cation due to mixing of the empty p-orbital (*LUMO*)
 the filled σ -bonding orbital of a C-H bond on the adjacent methyl (*HOMO*).



The σ -orbital brings **2** electrons into the interaction, whereas the p-orbital bears **0** e⁻, thus the total number of electrons to place in the new molecular orbitals is **2**;

C-H bond on the adjacent methyl can only occur when the orbitals *are in the same plane*.

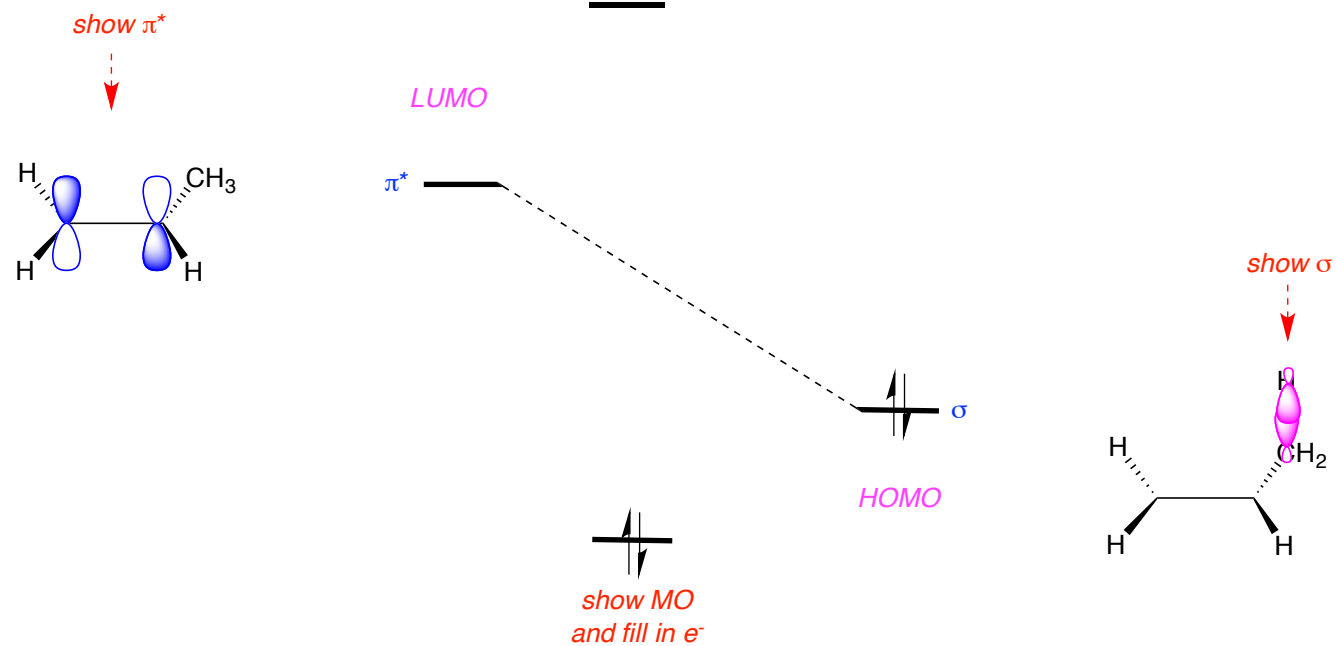
any instant because the other two *cannot achieve significant orbital overlap*.

A secondary propyl cation has **2** adjacent methyl groups, and therefore **2** filled σ - C-H bonds
 Secondary propyl cations are *more* stable than ethyl or methyl cations because of this

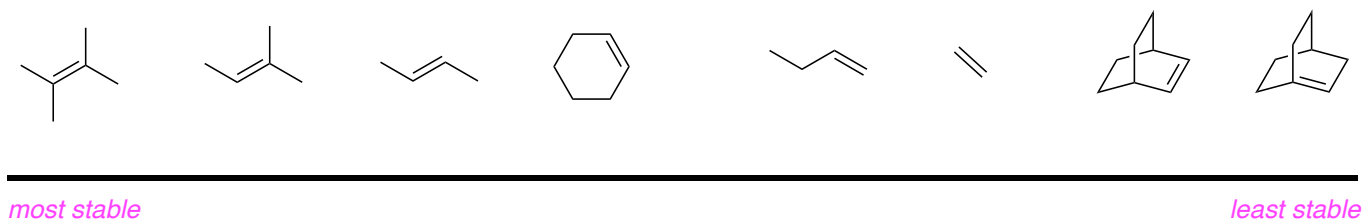
A *tert*-butyl cation has **3** adjacent methyl groups, and therefore **3** filled σ - C-H bonds that can stabilize by molecular orbital interactions. ^tBu-cations are *more* stable than ethyl or methyl cations because of this.

D. Alkenes Stabilities

Stabilities of most alkenes *increase with* the number of substituents.



Alkenes can only have the *stabilizing* interactions (above) if they have allylic C – H bonds. Interactions like this explain why more substituted alkenes have *enhanced* stabilities.



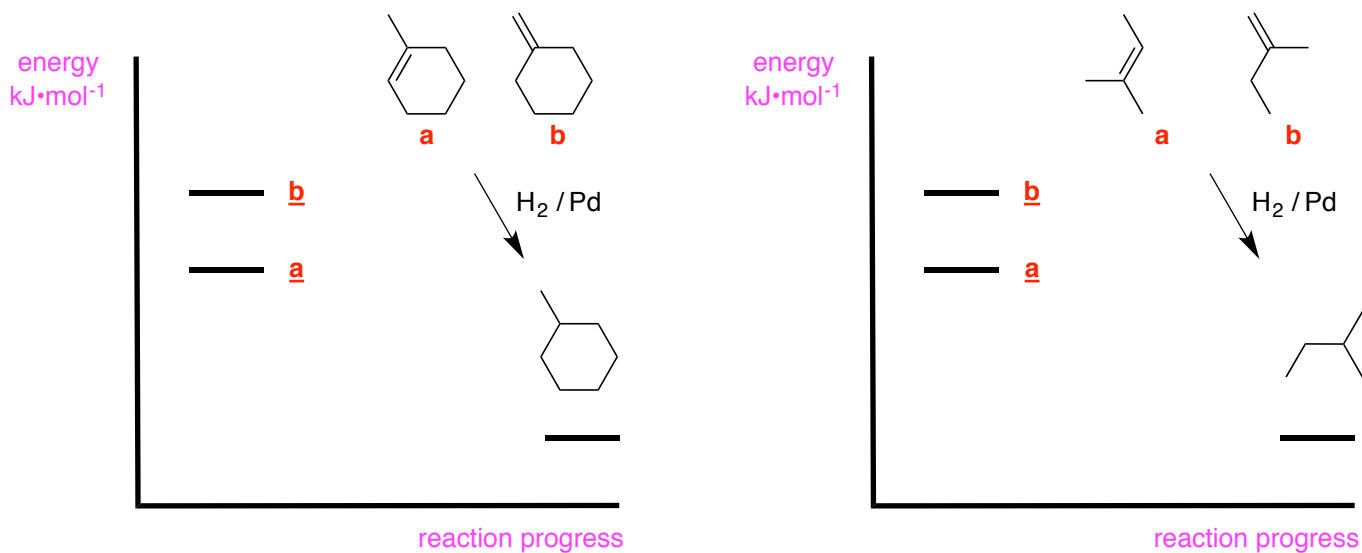
Heats Of Hydrogenation

Energy is *liberated* when hydrogen is added across a C=C bond.

Energies involved in such processes are called heats of *hydrogenation*.

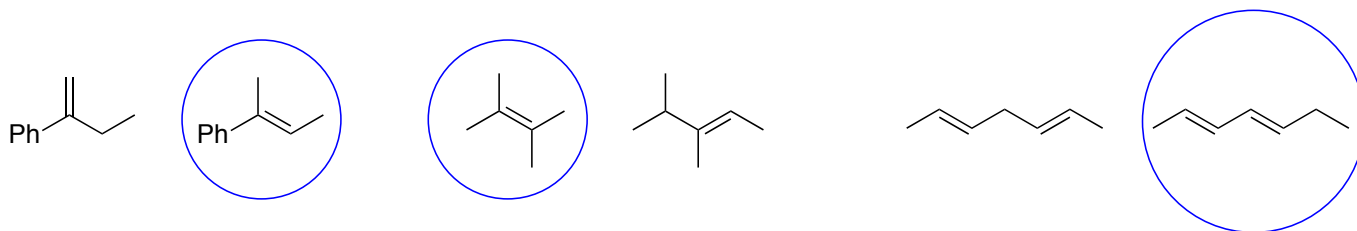
more stable alkenes will have *lower* heats of hydrogenation than less stable ones.

give the same or very similar products *can* be used to gauge the relative stabilities



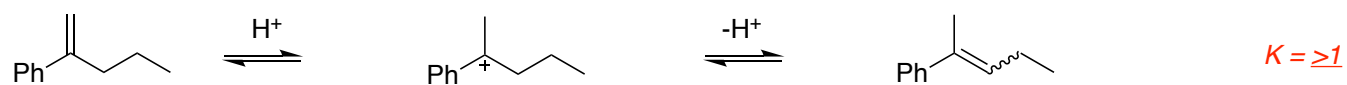
a has the higher heat of hydrogenation, while in the diagram on the right it is **b**.

E. Acid-mediated Alkene Isomerization



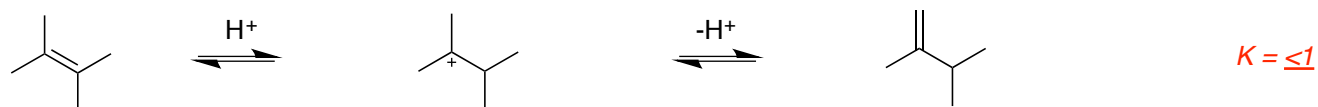
then lose a proton *from a different carbon* to give a different alkene that *is* an isomer of the first.

This reaction may be driven to form the most stable alkene, *ie* by *thermodynamics*.



carbocation

alkenes (cis + trans)



carbocation

alkene

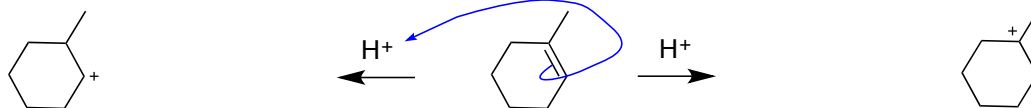


carbocation

alkene

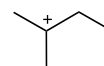
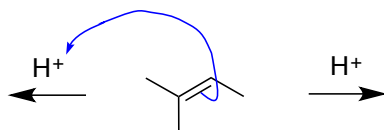
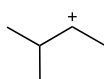
It is *conceivable* that carbocations can shift groups to isomerize faster than they can lose protons

the most possible carbocation *intermediates* formed by protonation of the following alkenes



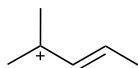
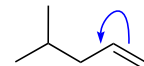
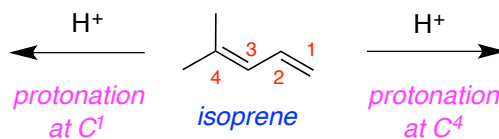
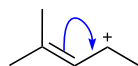
least favorable
2° carbonium ion

most favorable
3° carbonium ion

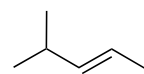


least favorable
2° carbonium ion

most favorable
3° carbonium ion



show resonance
stabilized forms

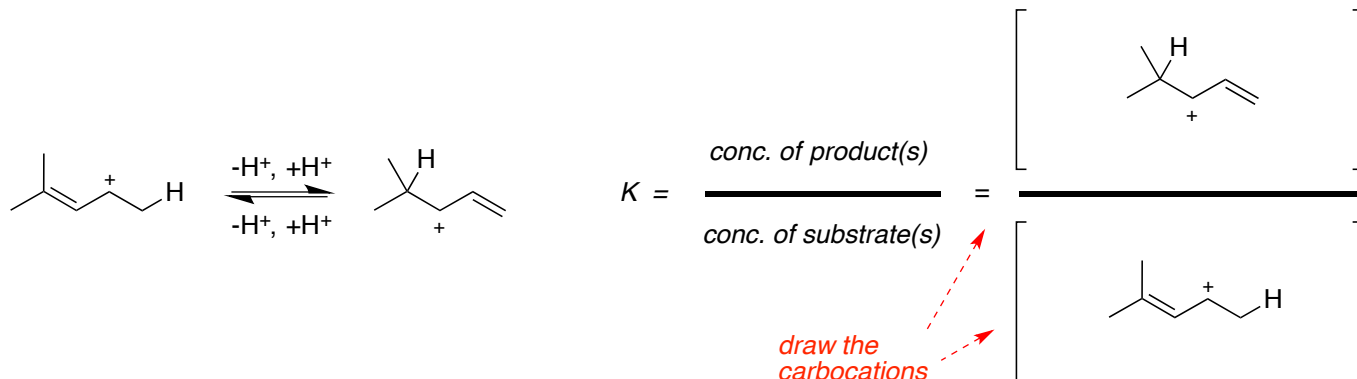


most favorable
3° carbonium ion

least favorable
1° carbonium ion

Protonation of isoprene at the diene termini (C¹ and C⁴) *gives* a cation stabilized by allylic resonance protonation at the internal positions (C² and C³) *does not*.

Free energy change for this reaction involves a *small* entropy factor because the number of starting materials *equals* the number of products.



The equilibrium constant featured above is *less than* one.

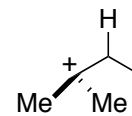
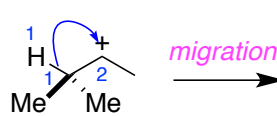
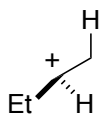
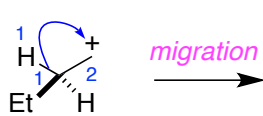
F. Carbocation Rearrangements

Hydride Shifts

two electrons this is called a *hydride* migration because a proton and two electrons is a *hydride anion*.

preferred one may be predicted by considering the relative stabilities of the carbocations produced: *true*.

Draw curly arrows to describe the following 1,2-hydride migration reactions, and predict the products.





collisions of protons with *unsymmetrical* alkenes are *most* thermodynamically favorable

Alkyl Shifts

positive charge appears to shift in the *opposite*

Carbocation rearrangements are favorable if the cation formed is *more* stable than the original one.

tend to undergo rearrangements if the products are *secondary / tertiary* carbocations

secondary ones tend to only migrate to form *tertiary* carbocations.

Show curly arrows for the *1,2*- migration reactions shown below



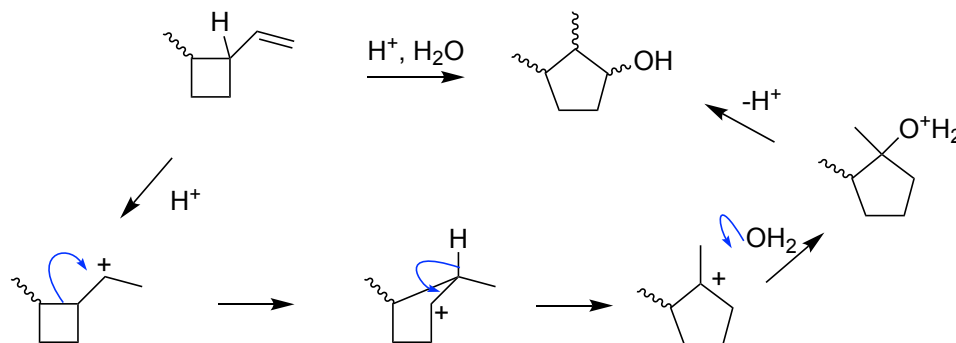
draw curly arrows

*draw curly arrows
and product*



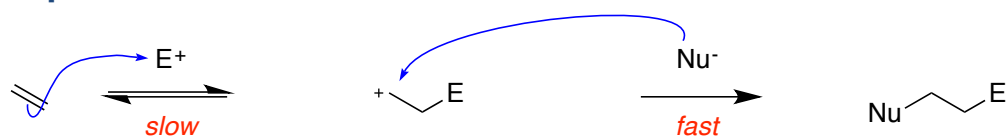
If the migrating group is an alkyl then these processes can be called *alkyl shift* reactions.

1,2-migration then it is the one *most* able to support a positive charge that shifts preferentially (Me because methyl cations are *less* stable than Et^+ (though it does not actually shift as a complete carbocation, the shift involves a developing positive $\text{Et}^{\delta+}$; the group most able to support a positive charge shifts preferentially)).



see: <https://youtu.be/FsQb6o510EY>

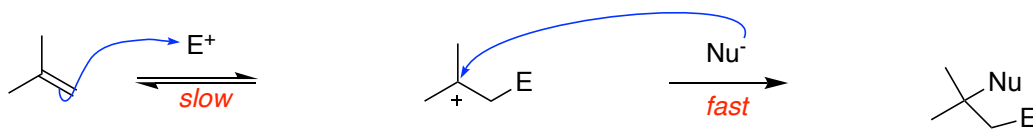
G. Electrophilic Addition Mechanisms



carbocation intermediate

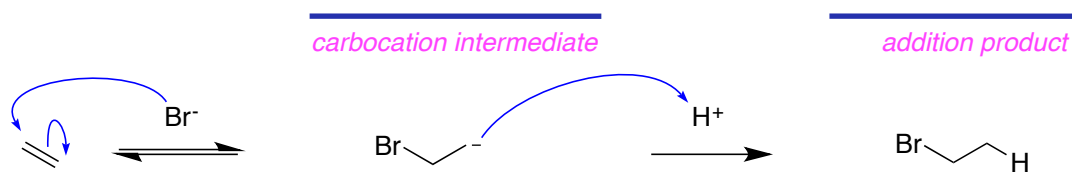
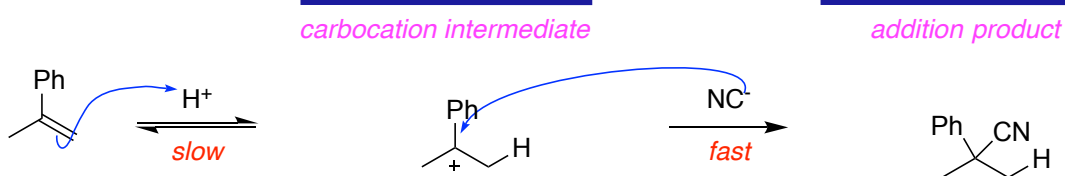
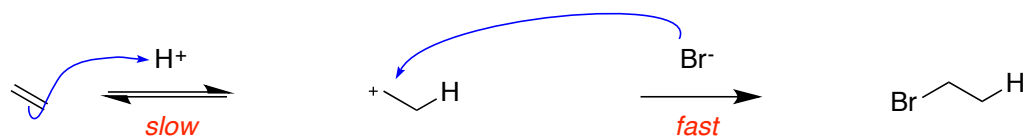
addition product

then the first step will be relatively *slow* compared with the second.



carbocation intermediate

addition product



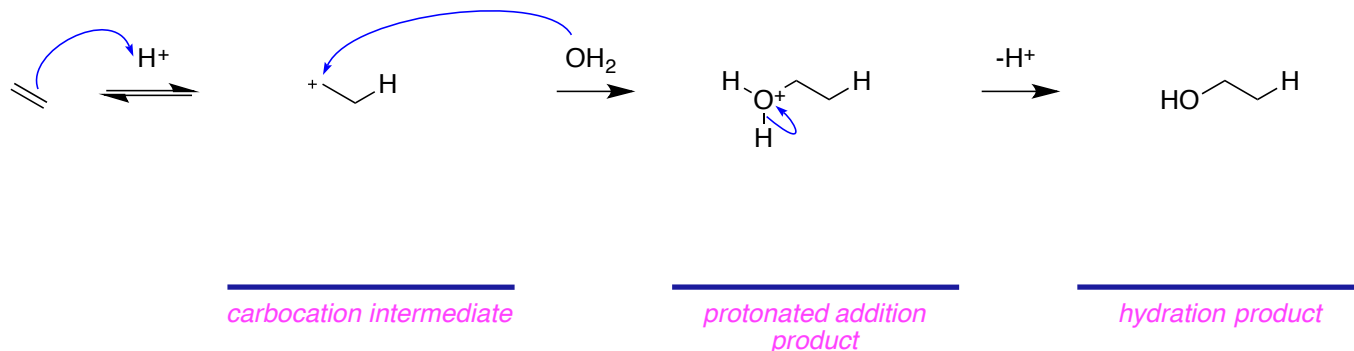
carbanion intermediate

addition product

Addition of HBr to ethene *does not* proceed in this way.

- bromide, being negatively charged, is repelled by electrons in the alkene π -bond

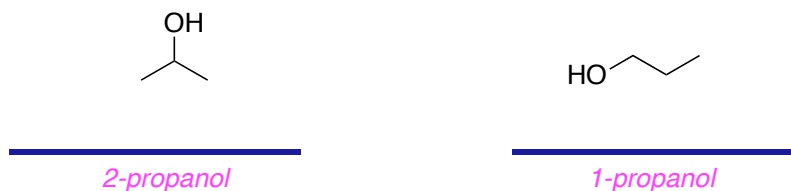
so a positively charged entity, usually a *proton*, must be lost to give a neutral addition product.



H. Acid-mediated Hydration Of Alkenes

less favorable than for most other alkenes because the carbocation formed 1° .

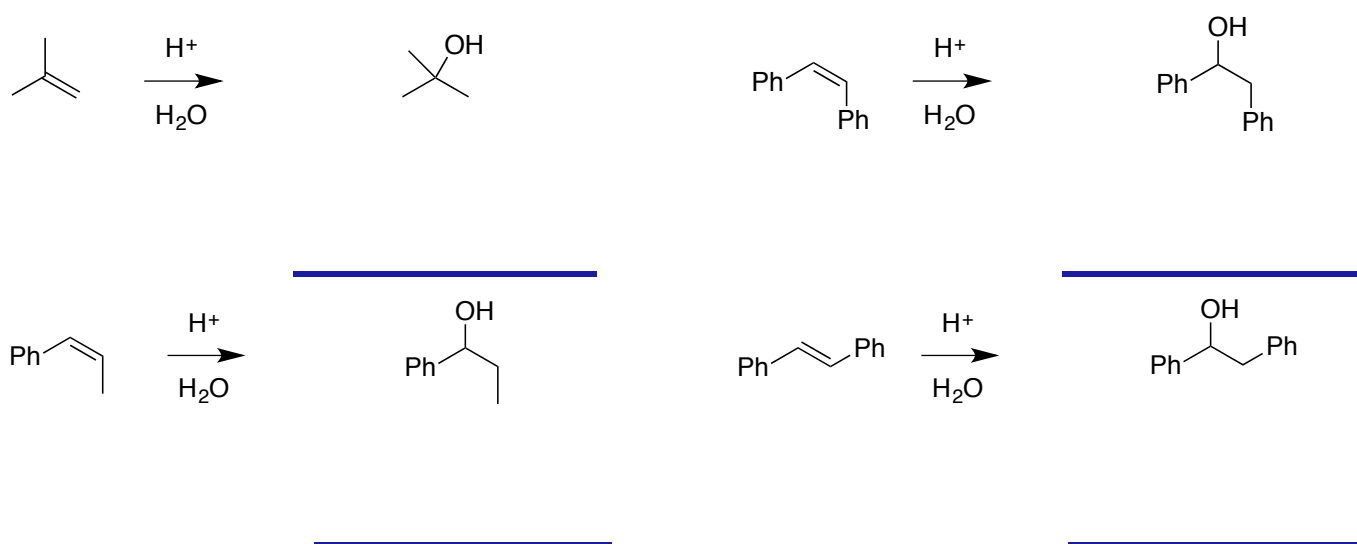
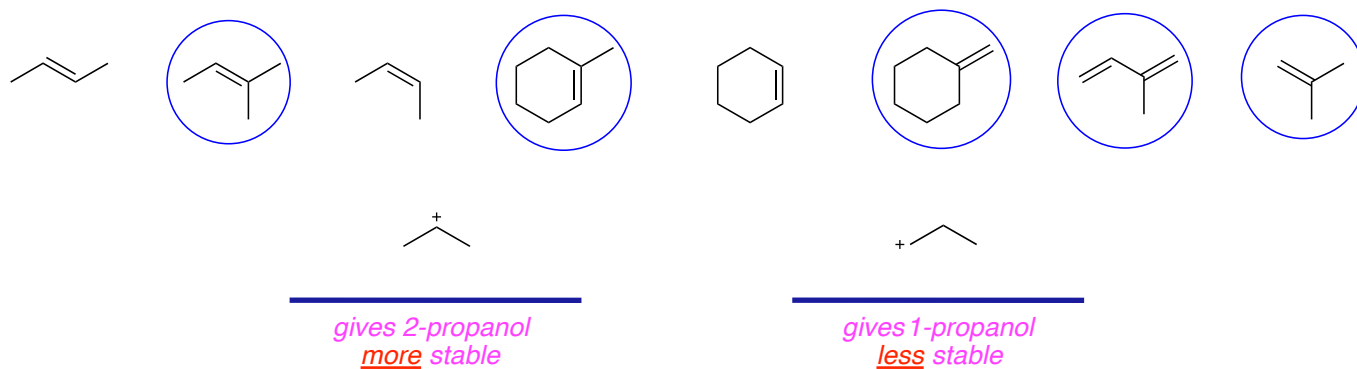
Hydration of propene could give *two* possible hydration products in which the *H* and *OH* groups become attached to different carbon atoms, *ie regioisomers*;



Reactions which form one regioisomer selectively are called *regioselective*.

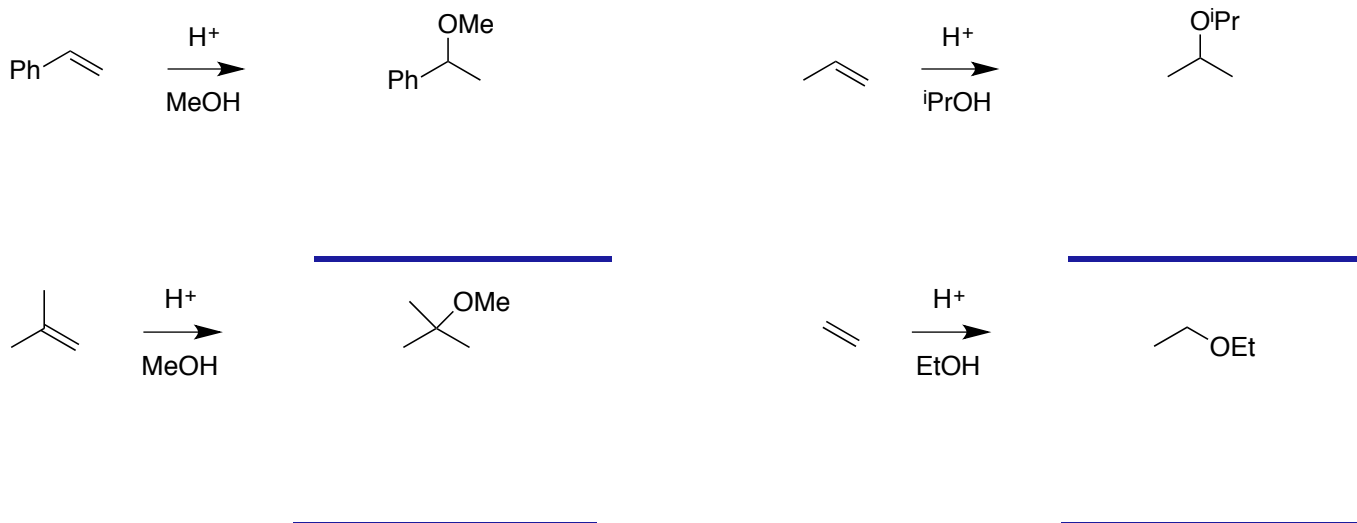
one chemical functional group in preference to others are called *chemoselective*.

one enantiomer in preference to another, and preferential formation of one diastereomer: *enantioselective* and *diastereoselective*

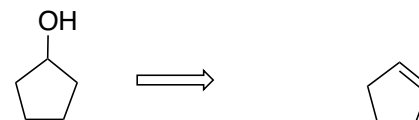
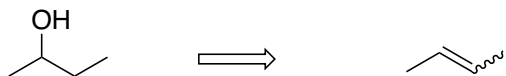
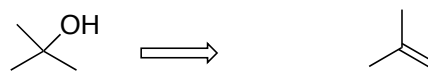
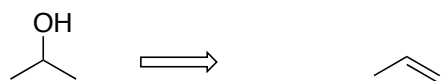


In the absence of water the reverse reaction (alcohol to alkene) would occur via a(n) *E1* pathway.

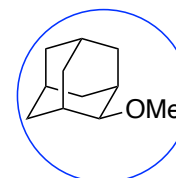
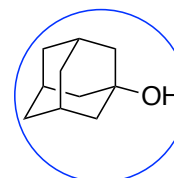
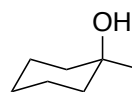
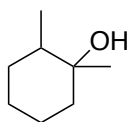
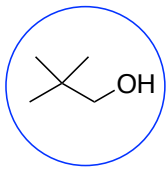
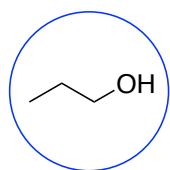
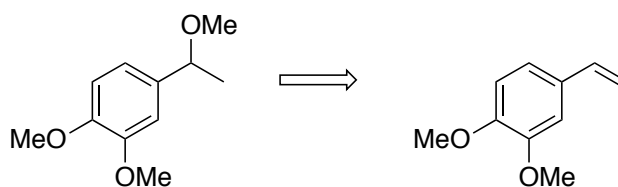
Predict the products of the following reactions to form *ethers*.



The reactions above *are not* hydration reactions, but they are mechanistically similar.



1-butene would give mixtures of alcohol regioisomers



5. Oxidation States, Hydrogenation, And Hydrogenolysis

from chapter(s) _____ in the recommended text

A. Introduction

B. Oxidation States Of Functional Groups

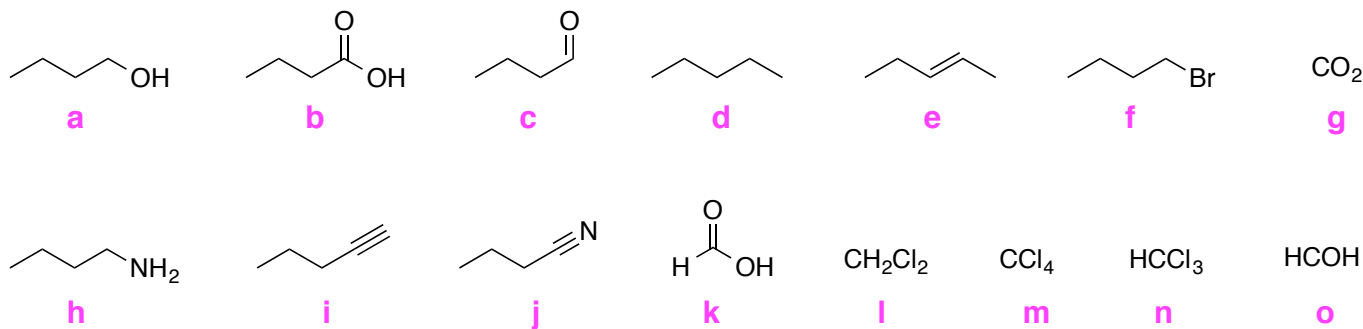
Reduction is *addition* of electrons from the substrate, and *loss* from the reducing agent.
Oxidation is *e⁻addition* from the oxidizing agent and *loss* from the substrate.

more

less

less

more



lowest oxidation state

d

one level higher

a, e, f, h

one more level higher

c, i, l, o

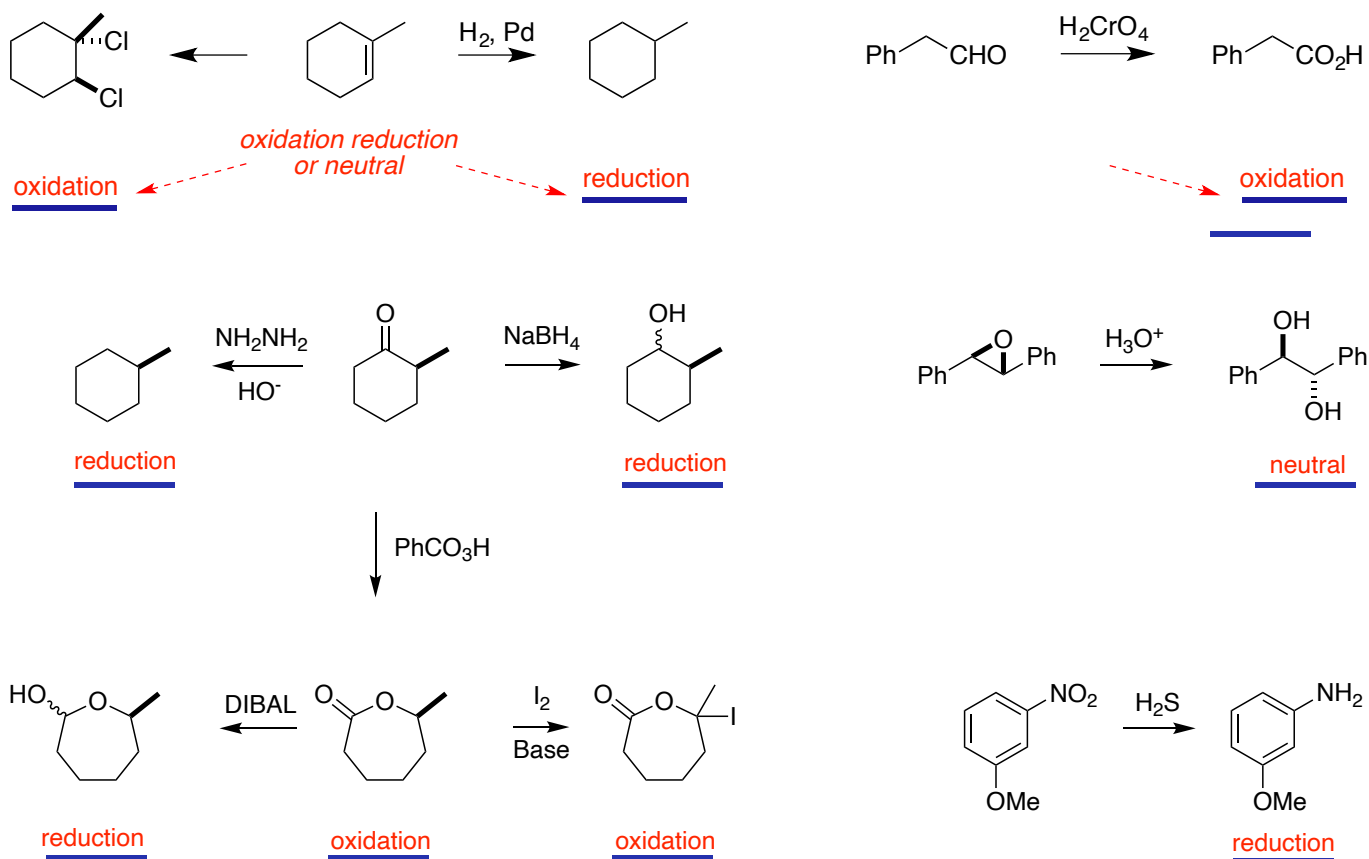
still another level higher

b, j, k, n

highest oxidation state

g, m

Cyclohexane is at a *higher* oxidation state than hexane.



C. Dihydrogen Additions

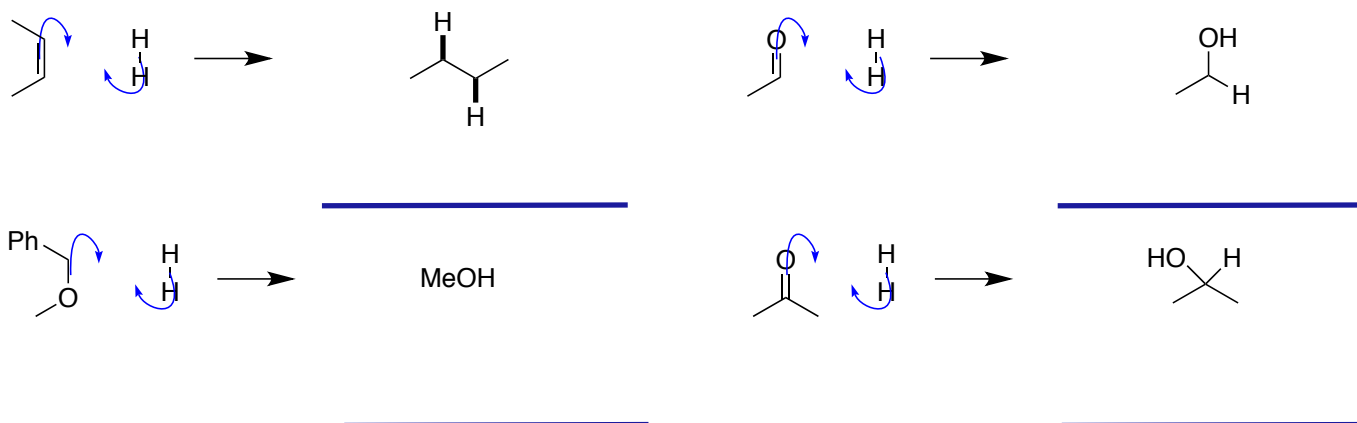
Hydrogenations And Hydrogenolyses Are Different: How?

Hydrogenation involves addition of H_2 across an unsaturated bond without cleaving

Hydrogenolysis involves addition of H_2 across a single bond with cleavage.

Addition of hydrogen to an alkene or an aldehyde can be thought of as proceeding via: (i) *homolytic* cleavage of H_2

Hydrogenolysis is closer to a *radical* mechanism, than a *ionic* one.

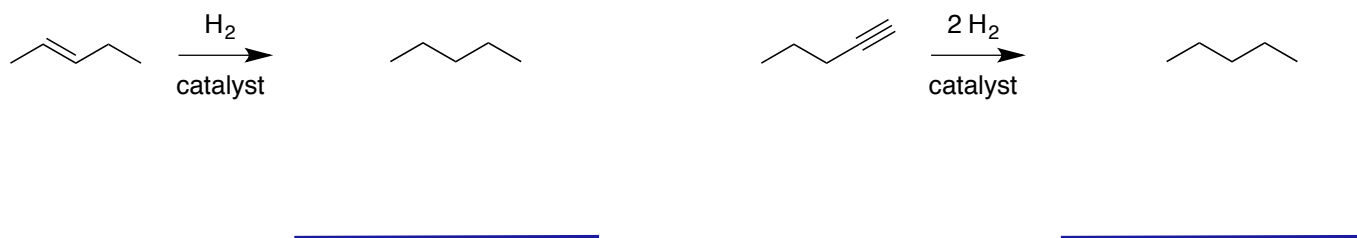


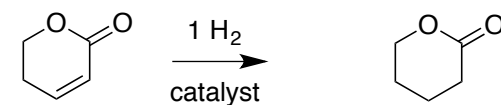
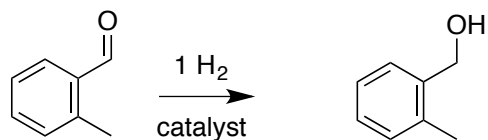
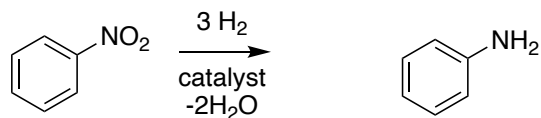
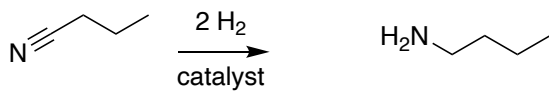
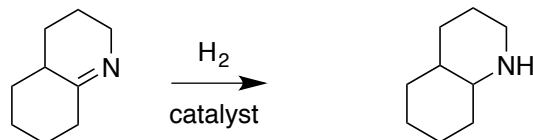
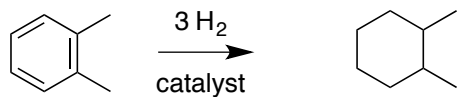
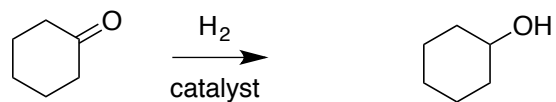
hydrogen adds to are inclined to *stabilize* a single electron.

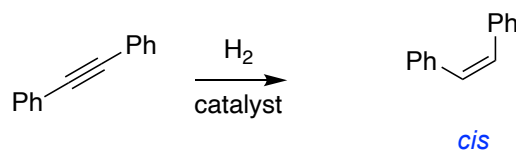
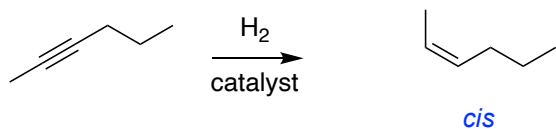
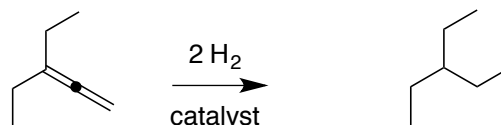
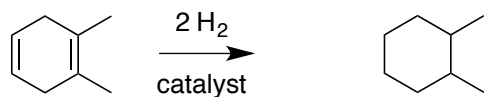
hydrogenolysis of benzyl ethers favorable, because the *benzyl* radical is stabilized by resonance.

Aromatic aldehydes, ketones, and esters are *more* easily hydrogenated than similar aliphatic

Hydrogenations

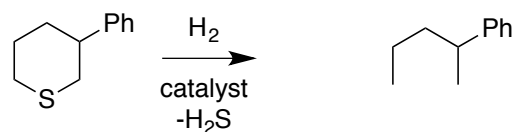
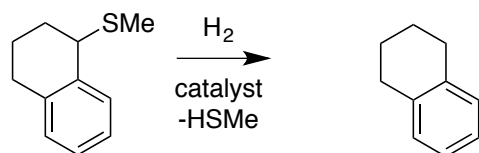


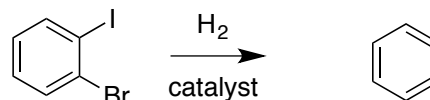
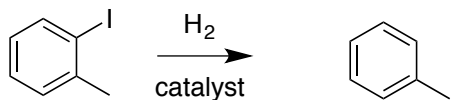
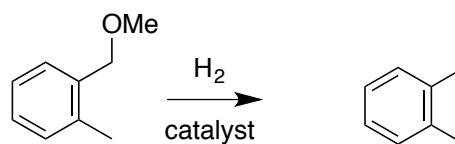
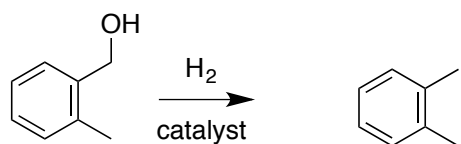




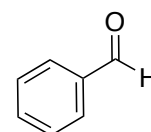
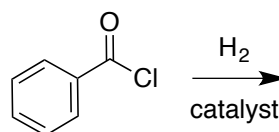
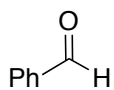
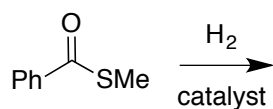
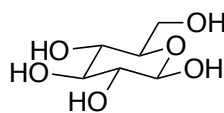
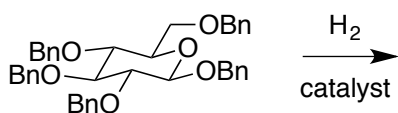
Hydrogenolyses

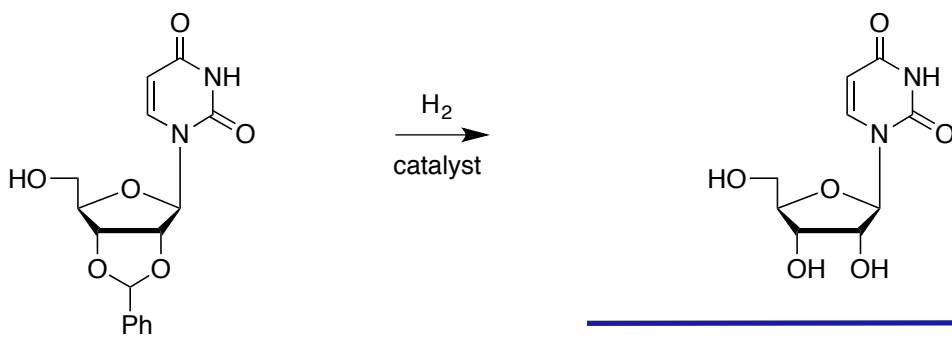
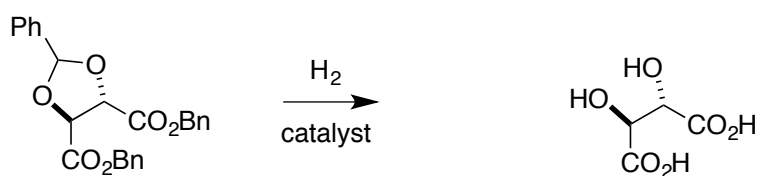
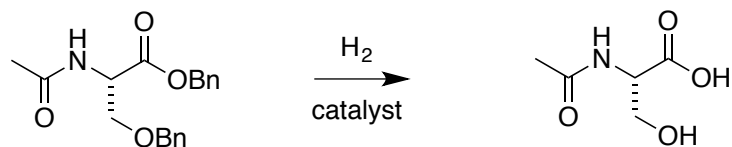
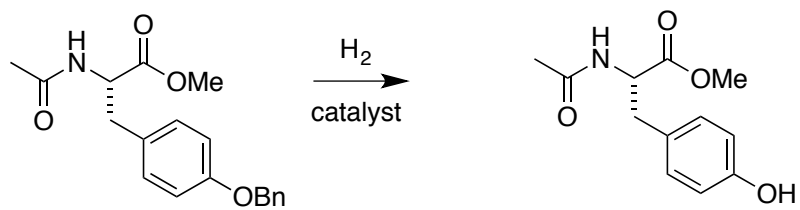
Hydrogenolysis refers to addition across *single* bonds.



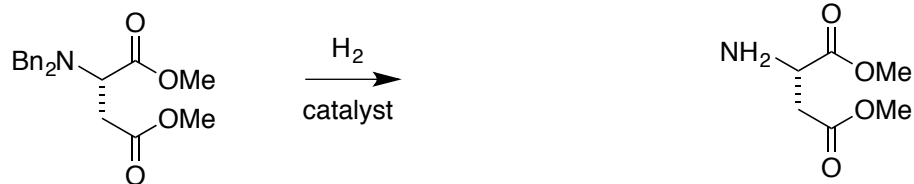


Note: further hydrogenolysis of these products to alcohols is possible, and these may undergo hydrogenolysis to toluene.



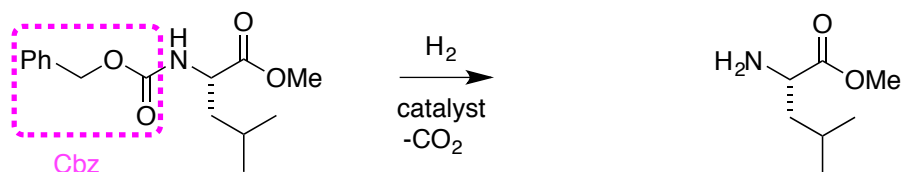


does not reduce the base



It tends to be *harder* to remove benzyl groups from amines than from alcohols

benzyl group is connected to the oxygen of a carbamate, *ie* benzyloxycarbonyl or *Cbz*.



D. Double Bond Equivalents

convert ethene and ethyne into ethane requires *1* and *2* molecules of H₂

Conversion of benzene to hexane would require *4* molecules of H₂

For hydrocarbons containing *n* carbon atoms, the DBE *can* be calculated

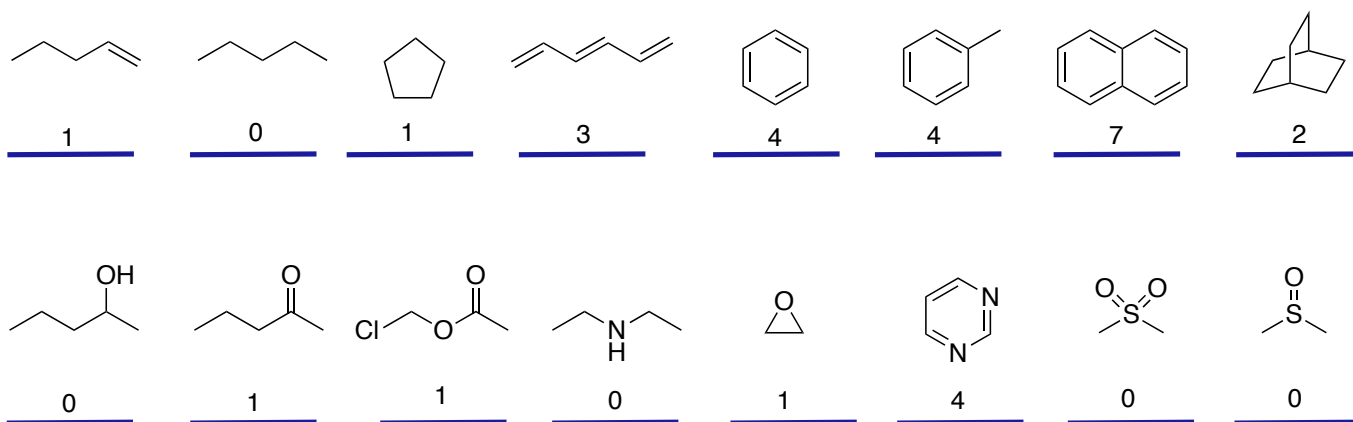
halogenated hydrocarbons containing n carbon atoms, *can* be calculated by replacing the halogen atoms

DBEs of acetone and *cis*-1,2-cyclohexandiol are **1** and **1**, respectively.

may be ignored to calculate the DBE, eg acetone C_3H_6O may be considered to be C_3H_6 . (**True**, check

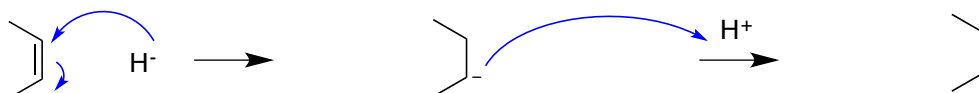
DBEs of 3-aminopropene and pyridine are **1** and **4**

calculating the DBE, eg ethylamine C_2H_7N (DBE = **0**) may be considered to be C_3H_6 . (**True**, check

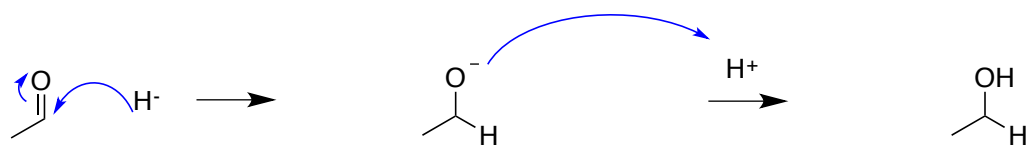


They **do not** apply when calculating unsaturation between two atoms not including carbon but addition of O and S obviously changes oxidation state but **does not** change DBEs.

E. Hydridic Reductions Are Stepwise



hard



easy

6. Halogenation Of Alkenes

from chapter(s) _____ in the recommended text

A. Introduction

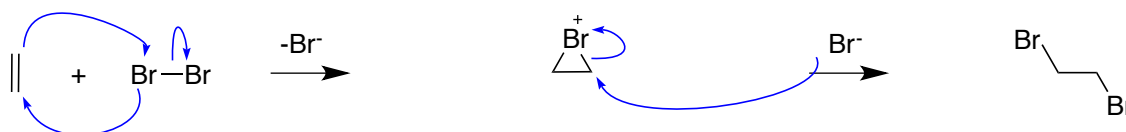
B. Halonium Intermediates

Like protons, halogens (X_2) tend to approach alkenes or alkynes *perpendicular* to the π -bond and an $X-X$ bond to become *polarized* until *halide* (X^-) and a halonium ion formed.

Halonium ions are *positively* charged; the *-ium* suffix in that name *is* indicative

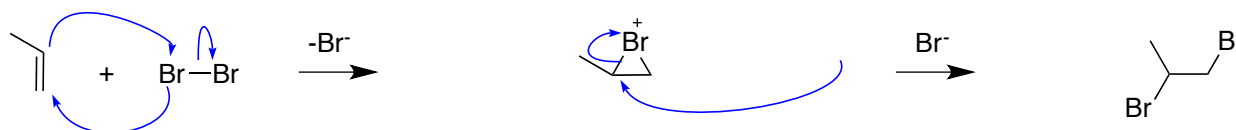
Chlorination and Bromination: Valence Bond Description

featuring halonium ion *intermediates*.



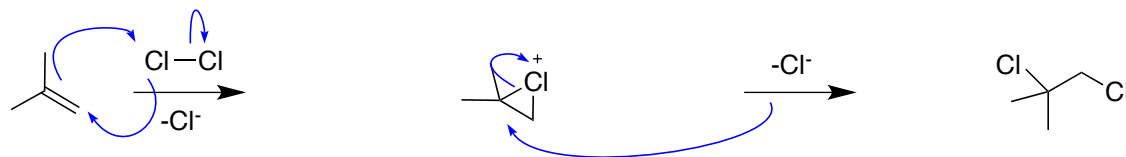
bromonium ion

1,2-dibromide



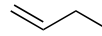
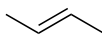
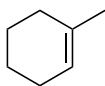
bromonium ion

1,2-dibromide



Halogen (X_2) are *electrophiles* while, because of their π -clouds, alkenes are *nucleophiles*. Bromine, for instance, is an *electrophile* because it *becomes polarized in the presence of high electron density*.

halogenation of alkenes involves rate-limiting *electrophilic* attack of the halogen
 this is *nucleophilic* attack of the alkene on the bromine.
 React *faster* than ones that have less or electron withdrawing substituents.

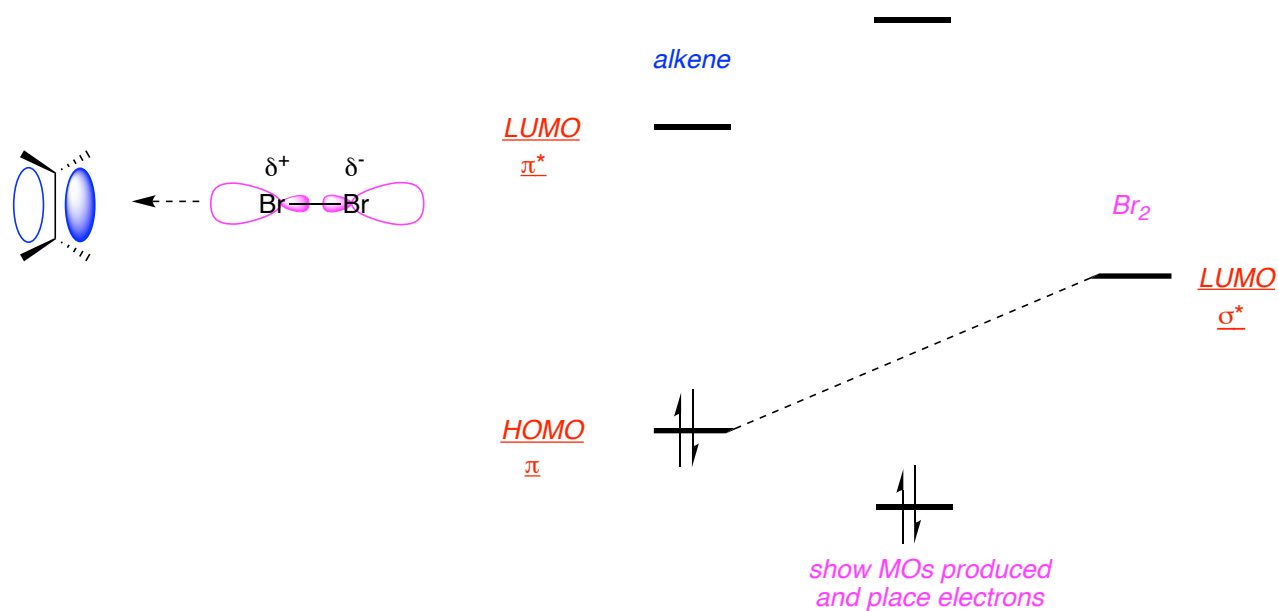


fastest bromination

slowest bromination

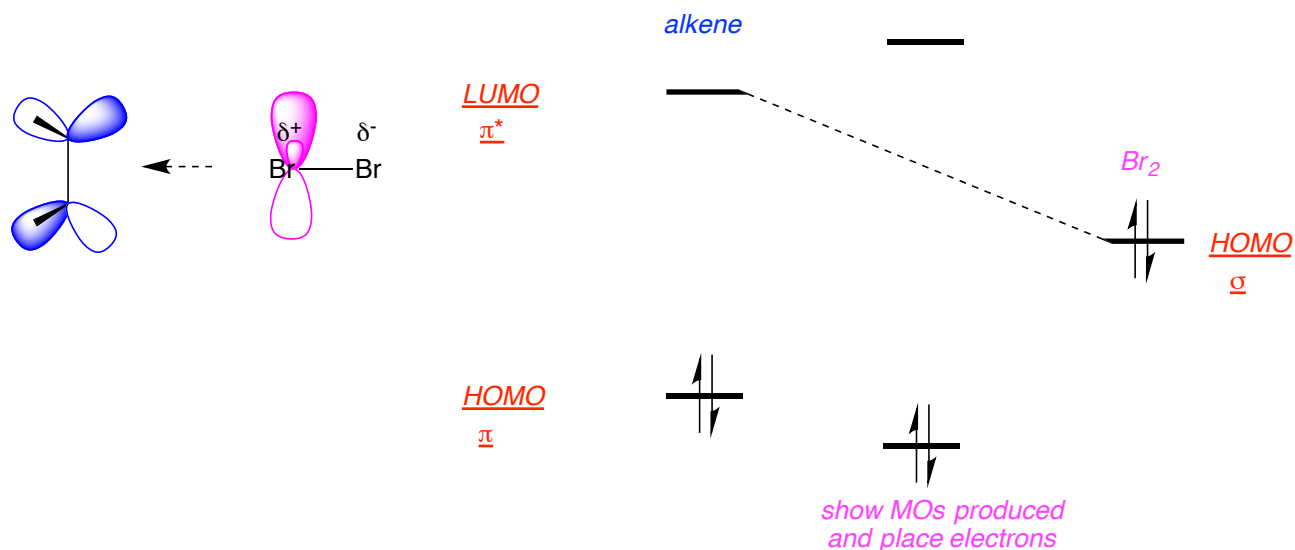
Halogenation of alkenes are *addition* reactions involving bonding of one X-

Chlorination and Bromination: MO Description



Perpendicular approach of halogens (X_2) to a symmetrical π -cloud is net *stabilizing*,
 halogenation is the most important orbital overlap so this is called the *primary* interaction.

Halogenation of alkenes is further stabilized by a *secondary orbital interaction* between the π^* -orbitals



Secondary interactions as shown above *do not* favor formation of bromonium ions.

C. Stereospecificities

Cyclic Alkenes

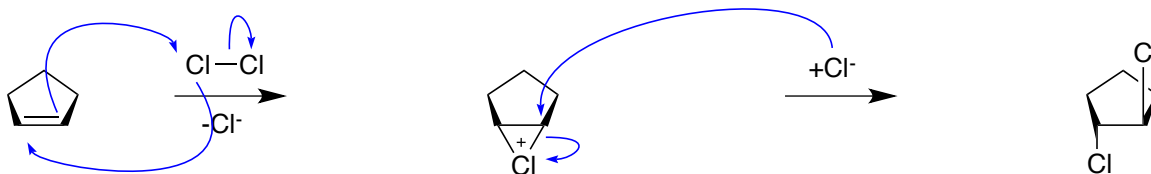
Bromonium ions in bromination of alkenes, tend to be opened by S_N2 attack of bromide

Nucleophilic attack on halonium ions occurs *anti* to the halogen atom
alkenes within a ring (*ie endocyclic* ones) give *trans*--dihalide products.

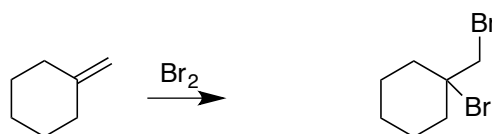
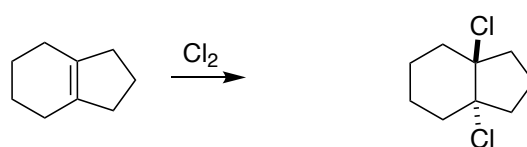
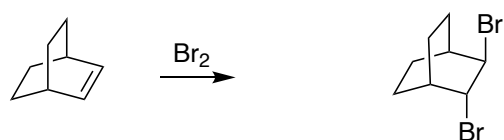
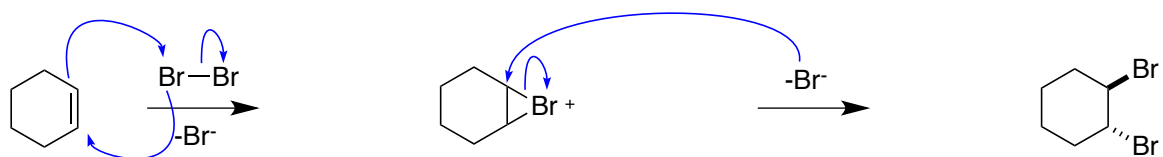
Bromination of cyclohexene *mostly* affords the *trans*--1,2-dibromocyclohexane

bromonium ion must occur from the *opposite* face of the bromine atom.

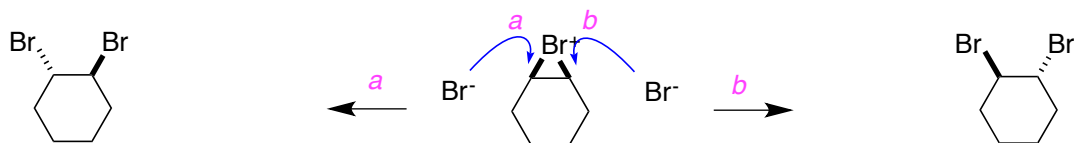
halogenation of *cis*-endocyclic alkenes is therefore *stereospecifically-trans*, meaning it *always* gives the *trans*-product.



Of course, if the product is chiral then a racemate is formed.



Nucleophilic attack on the following bromonium ion gives *enantiomers*.



S,S

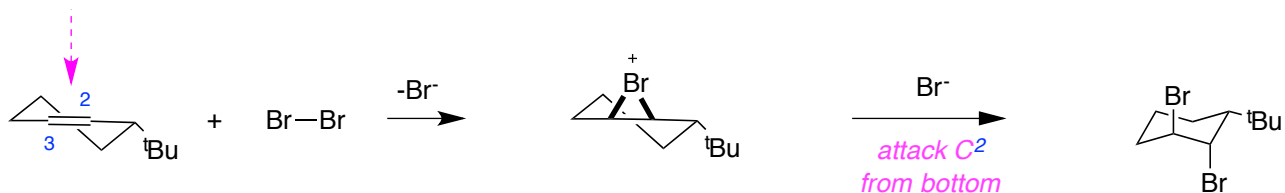
R,R

the ratio of the two enantiomers formed will be *equal*, ie the product will be *a racemate*

It *is not* possible to form *meso*-stereomers in this reaction.

other one is formed in *equal* amounts; this is true

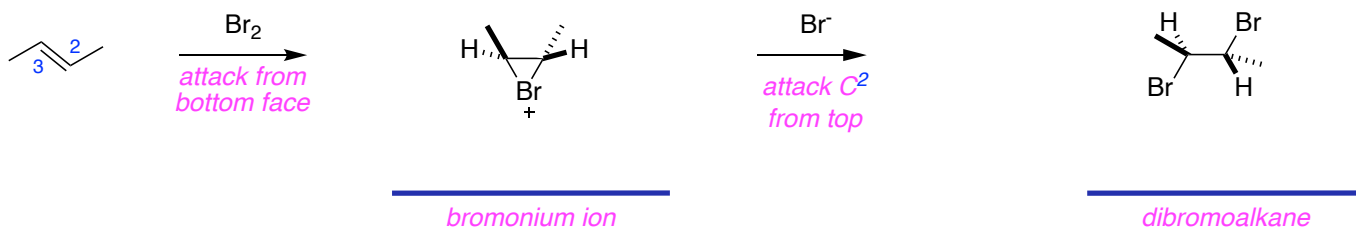
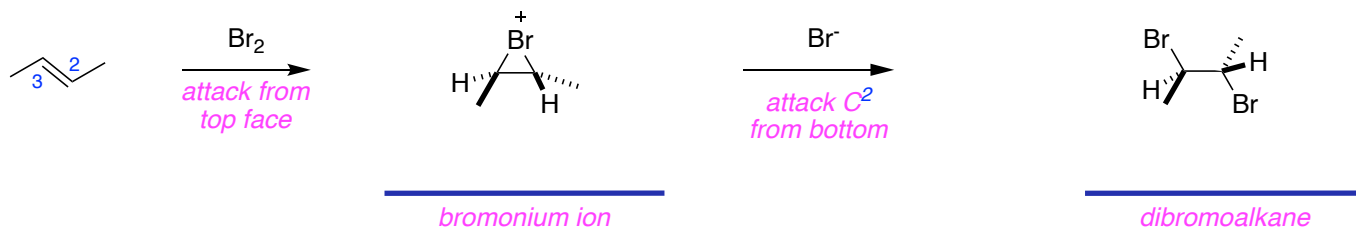
bromonium ion formation



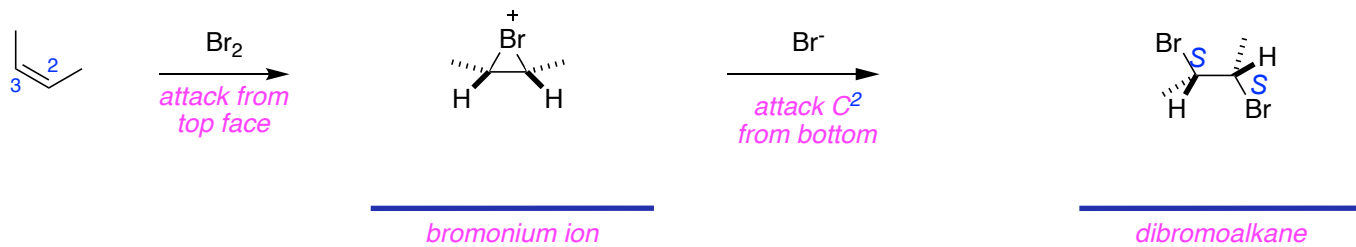
bromonium ion

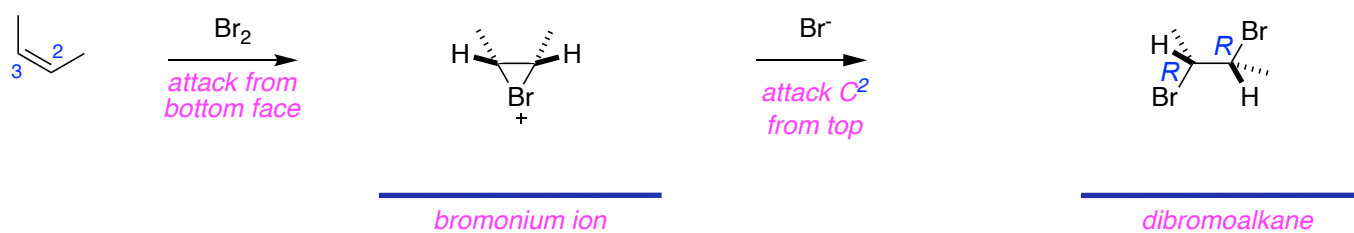
1,2-dibromide

Acyclic Alkenes

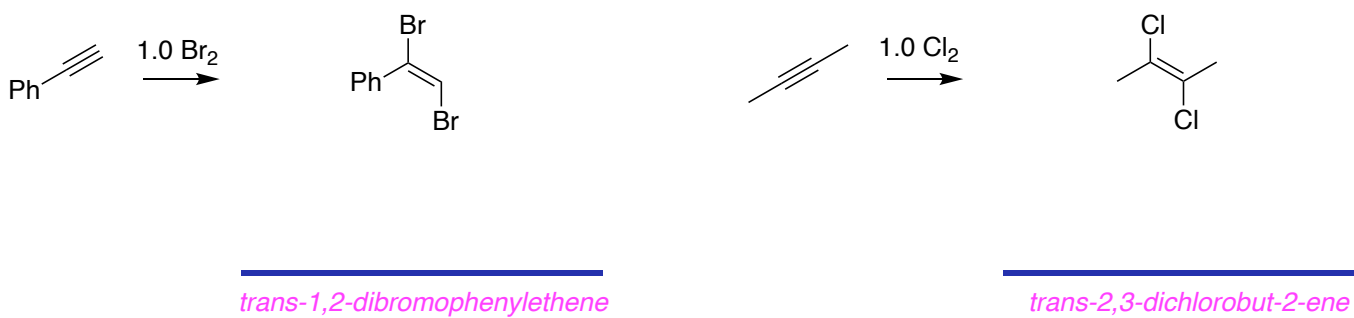
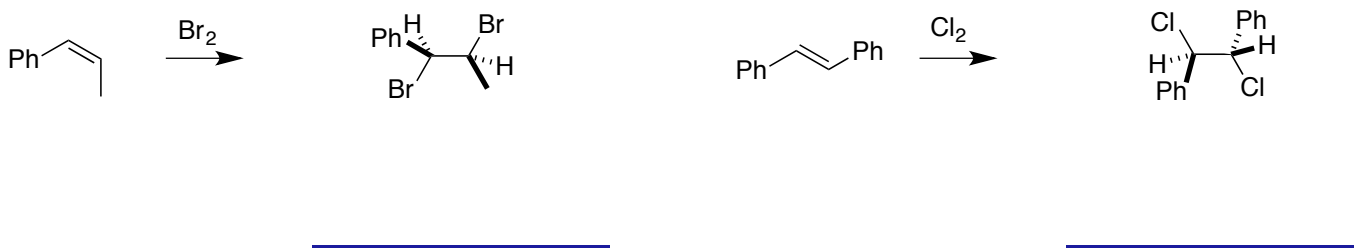
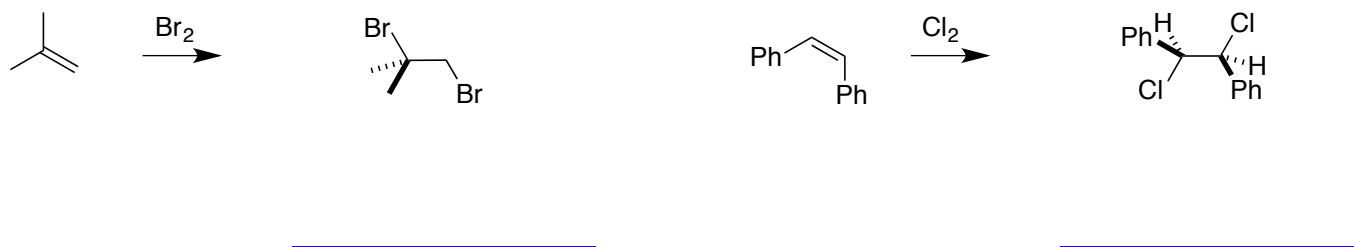


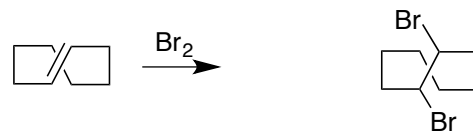
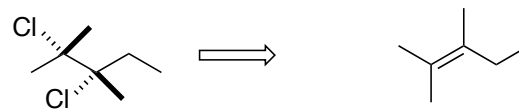
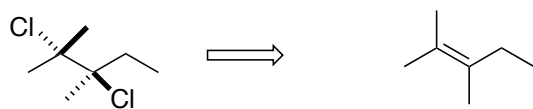
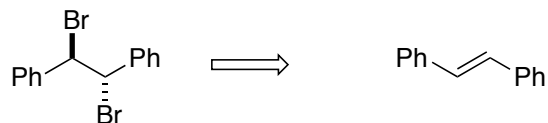
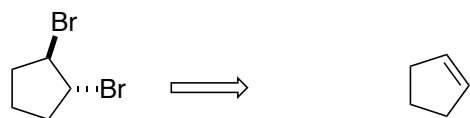
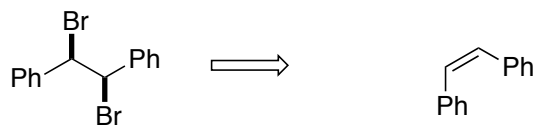
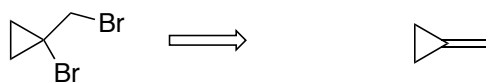
The products from these two reaction pathways are *identical*.





When *E*- and *Z*-2-butene react with bromine, the products are racemic *enantiomers*.

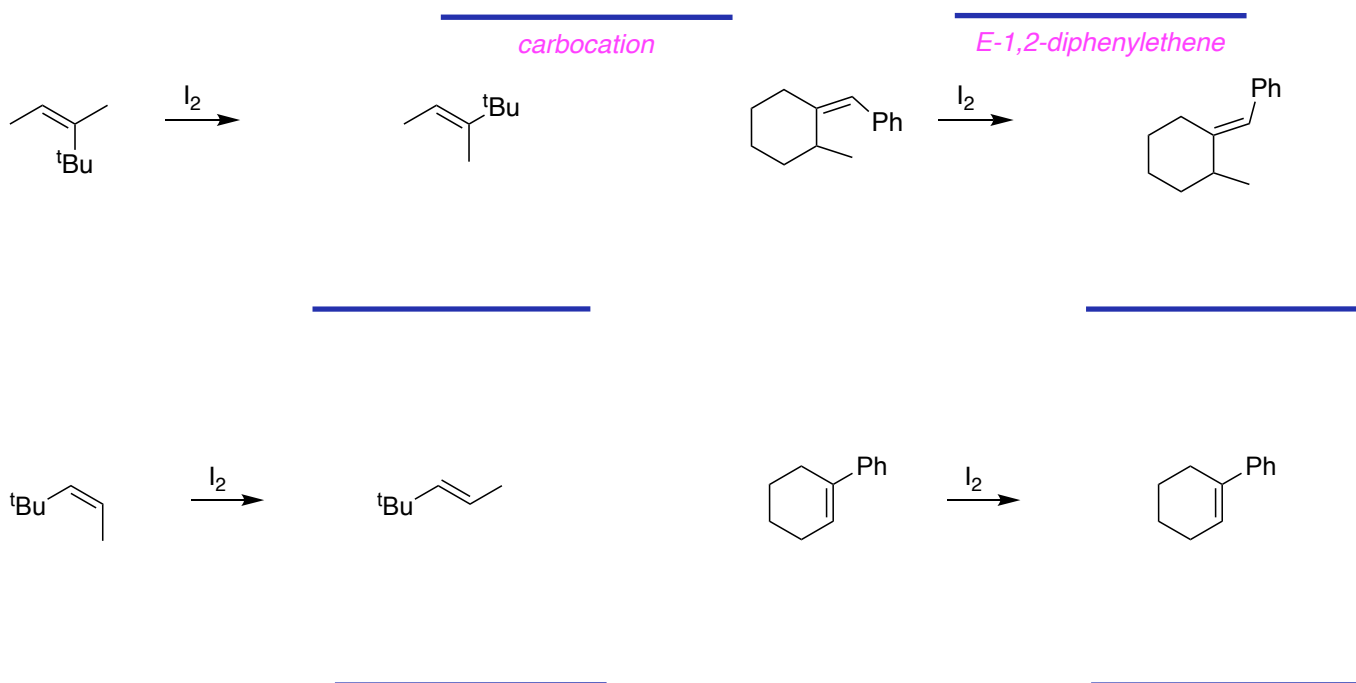
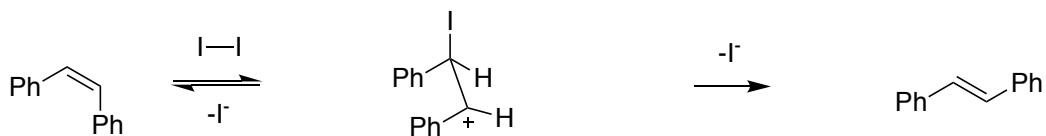


trans-cis-

D. Iodination

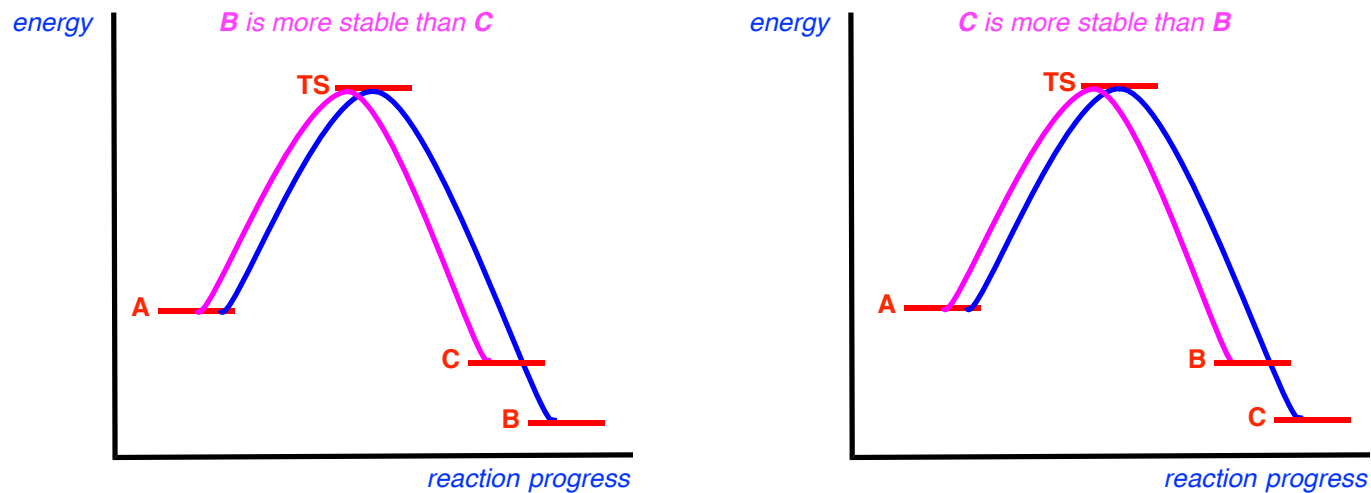
Impact of Reversibility

iodination does not give product because *the product is thermodynamically unstable relative to ethene and iodine*.



E. Kinetic And Thermodynamic Control

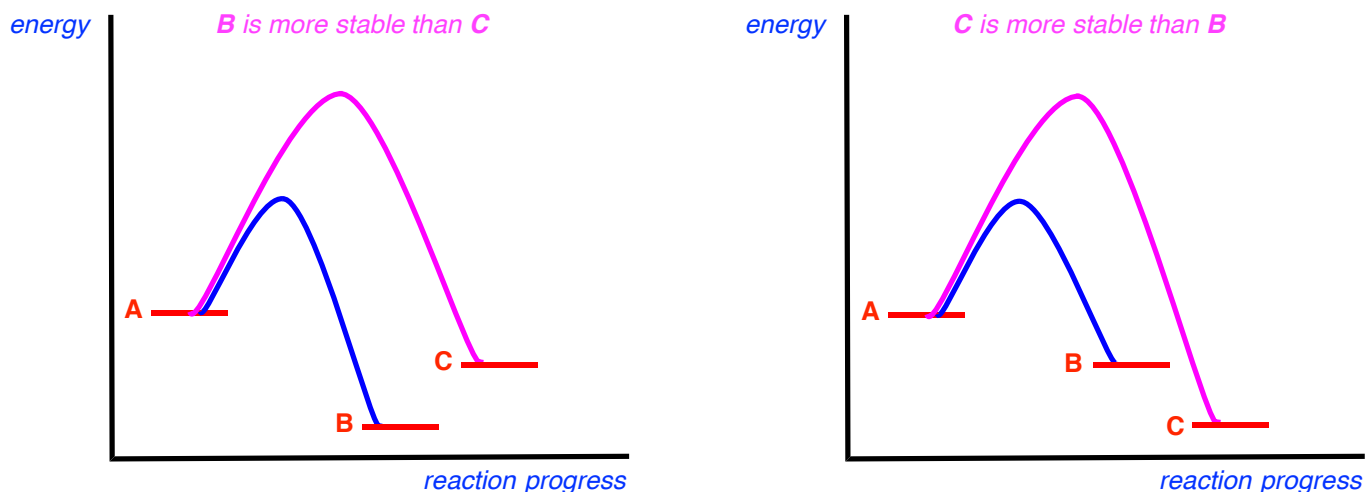
Kinetic Control



In both diagrams, **B** and **C** must be *lower* energy than **A** and the products *cannot* surmount the energy barrier

The rate of formation of **B** and **C** in this reaction *is not* dependent on the stabilities it *is* dictated by the energy barrier

B:C product ratio will be *1*, and when **C** is more stable than **B** it will be *1*.



B:C ratio will be determined by their relative *rates of formation*, and it will *be invariant*. In this case the **B:C** ratio is a *kinetic* one.

Thermodynamic Control

Both Products Equilibrate With Starting Material

A under the reaction conditions, *ie* the process is *reversible* and **B** and **C** have *different energies*. **B:C** will be *>1*, and *will* change as the reaction progresses.

$$K_B = [B] / [A] \quad \text{and} \quad K_C = [C] / [A]$$

At equilibrium, the K_B / K_C ratio *is* another constant, K_{BC} , where

$$K_{BC} = [B] / [C]$$

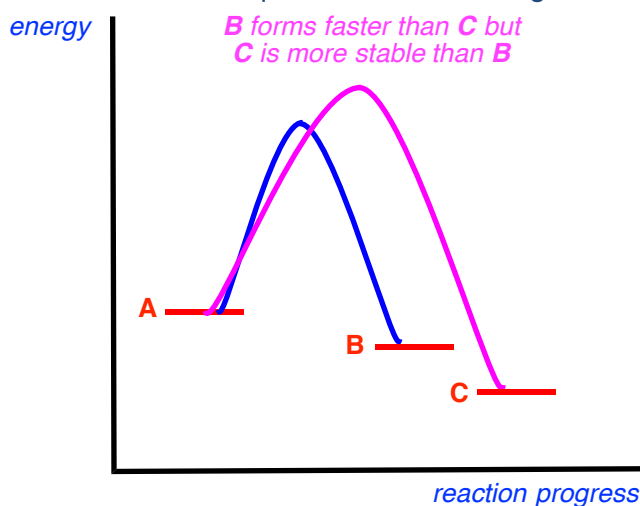
and the **B:C** ratio is *independent of* the concentration of **A**.
kinetic and thermodynamic controls are *coincident* insofar as they both

B:C ratio is determined by the relative *activation energy barriers* but at the end it is governed by the relative *stabilities of the products*.

These ratios are *different* but they both favor the same product.

Non-coincident Kinetic And Thermodynamic Control

Least Stable Product Forms Faster and Both Equilibrate With Starting Material

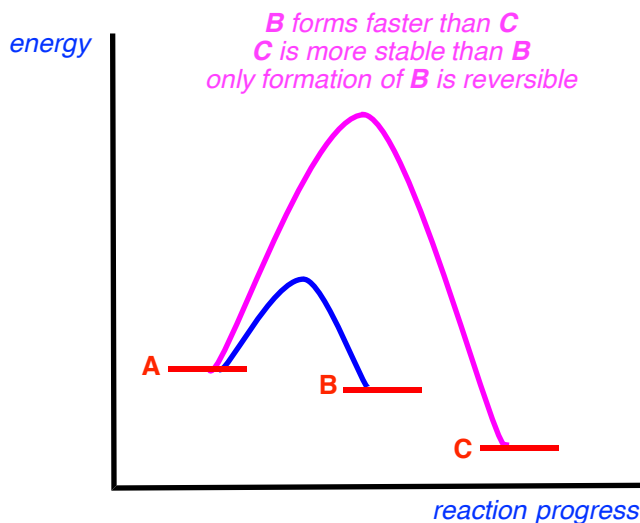


Least Stable Product Forms Faster and It Alone Equilibrates With Starting Material

B forms faster than **C** so it is the *kinetic* product; it forms *reversibly*.

C is the *thermodynamic* product; it forms *reversibly*.

product **B** would *be disfavored* because it will revert as the reaction proceeds and *reversibly* forms **C**.



B forms faster than **C** so it is the *kinetic* product; only **B** forms *reversibly*.

C is the *thermodynamic* product; it forms *irreversibly*.

product **B** would *not be observed* because it will revert as the reaction proceeds and *irreversibly* forms **C**.

kinetic and thermodynamic control a *kinetic* product would form preferentially in the early stage transformed into a different *thermodynamically* controlled product later.

F. Bromination 1,3-Butadiene

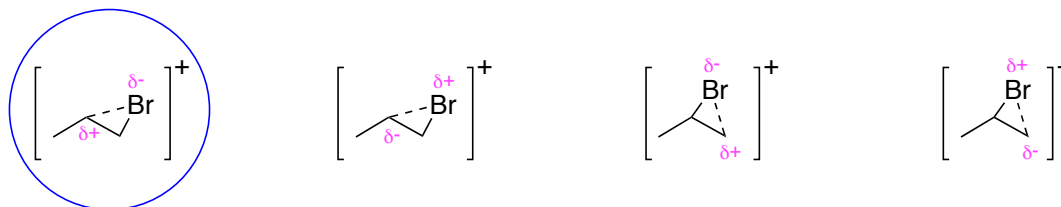
1,2-dibromide forms quickly in the early stages of the reaction, *ie* it is the *kinetic* product.

The amount of 1,2-dibromide *decreases* as the reaction time is extended, and the concentration of 1,4-dibromide *increases*.

the alkene products: *1,4-dibromide has two groups substituted on the alkene product while 1,2-isomer has only one group.*

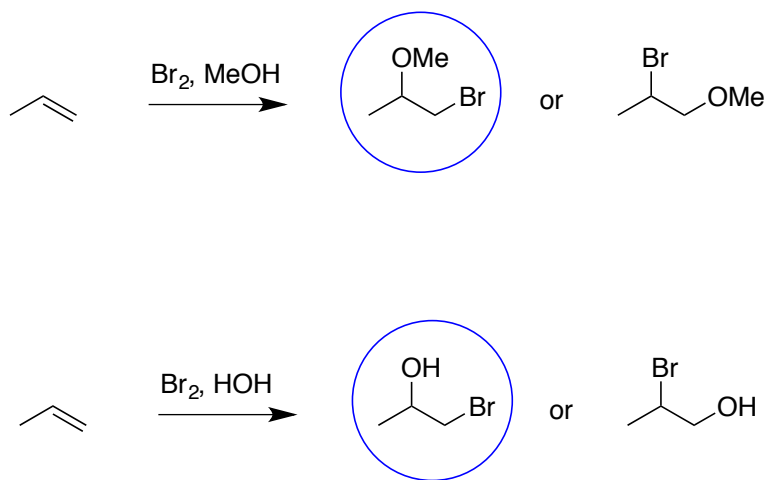
Nucleophilic attack on alkenes tends to be much *less* favorable than electrophilic attack it *does not* proceed unless there are electron-withdrawing groups

G. Halogenations In Nucleophilic Solvents



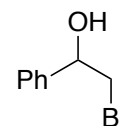
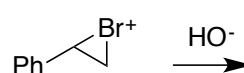
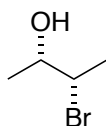
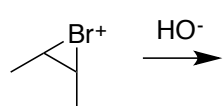
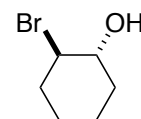
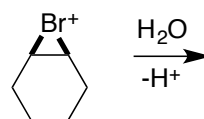
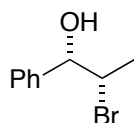
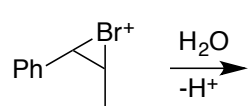
Nucleophiles add to the carbon of an unsymmetrical halonium ion that is *best* able to support

Regio--selectivity is important when bromination of unsymmetrical alkenes bromide because the reaction can produce different *regioisomers*.



Opening of bromonium or chloronium ions by water is called a *halohydrin* reaction.

the halogen on the carbon least able to support a negative charge because *this is the precursor to the most stable cation*.



Considerations regarding potential carbocation stabilities *are* likely to apply to ring opening of epoxides.

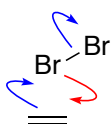
7. Epoxidation And Regioselectivity

from chapter(s) _____ in the recommended text

A. Introduction

B. Reagents And Mechanism

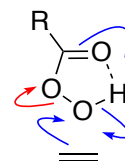
Bromination of alkenes can be drawn as loss of bromide *pushing* electrons away



bromination



*epoxidation
general
X is leaving group*

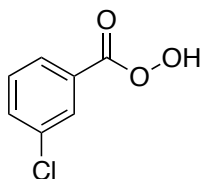


*epoxidation
with peracid*

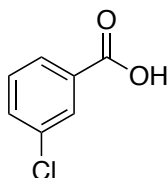
Epoxides are **3** membered rings containing oxygen.

agents for epoxidation possess a leaving group that *pushes* electrons away becomes more polarized and *electrophilic* as it adds to an alkene.

Reagents



mCPBA



*product after donation
of oxygen*



dimethyldioxirane



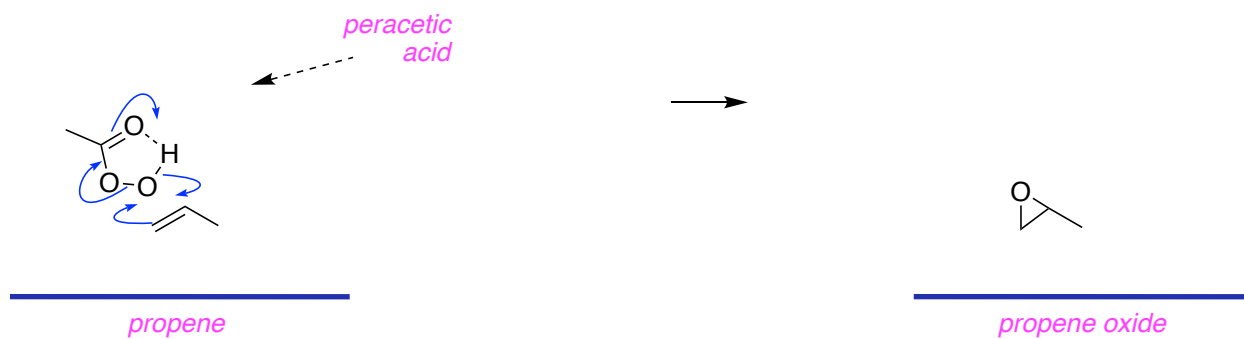
*product after donation
of oxygen*

Epoxidation usually involves *electrophilic* attack of an oxidant on an alkene therefore acts as an *electrophile*.

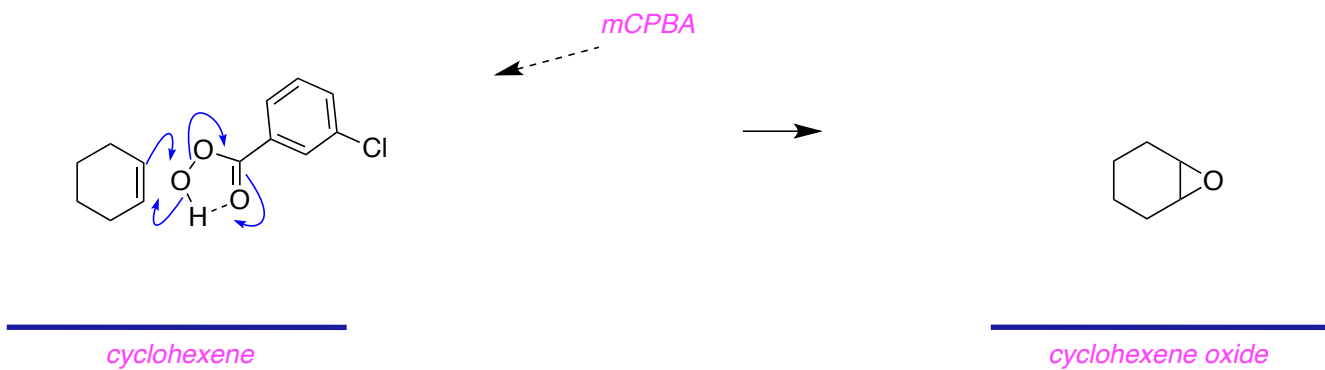
Epoxidation of alkenes is an *addition* reaction.

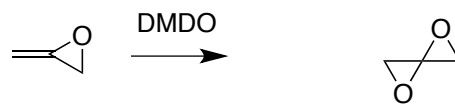
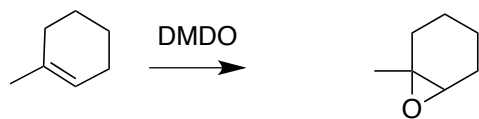
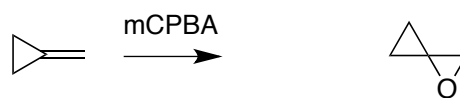
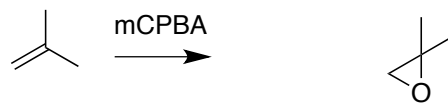
Mechanisms

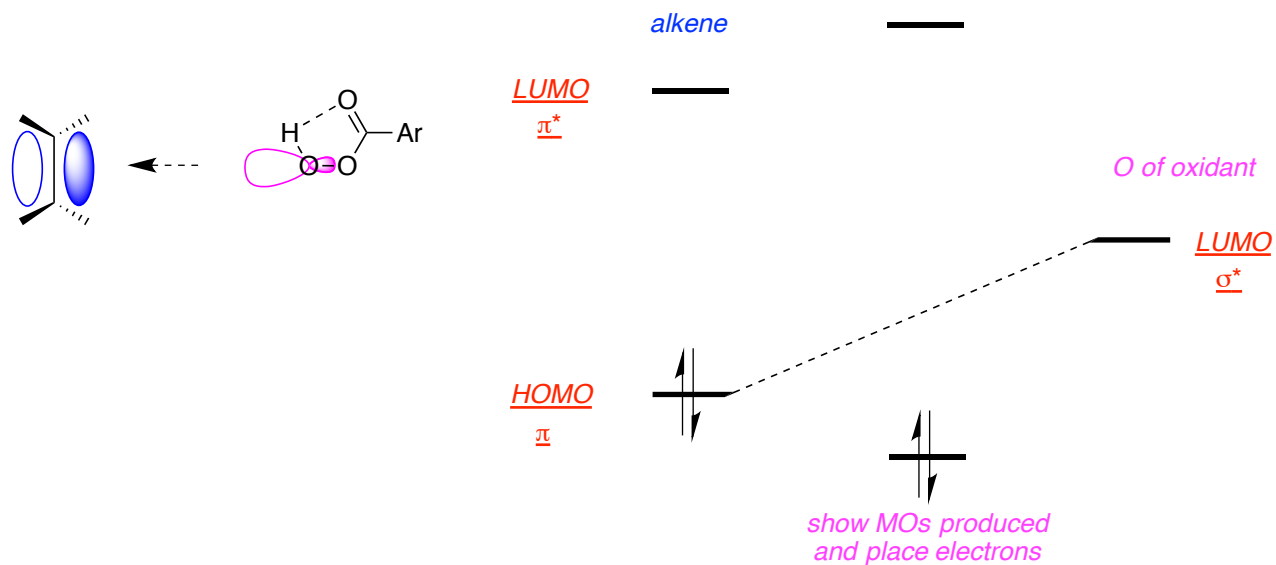
Epoxidation With Peracetic acid



Epoxidation With *m*-Chloroperbenzoic acid







C. Epoxidation Rates

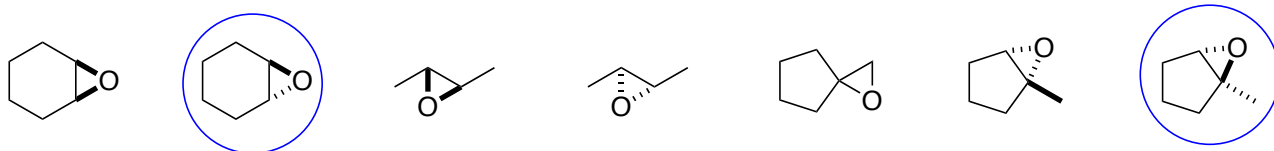
Epoxidation of these alkenes involves *electrophilic* attack of the agent on the alkene, so alkenes that are *more* electron rich react fastest.

Electron densities around alkenes tend to *increase* with the number of alkyl substituents.

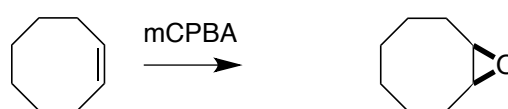


D. Stereospecificities

Cyclic Alkenes

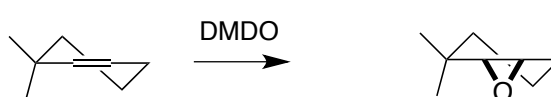
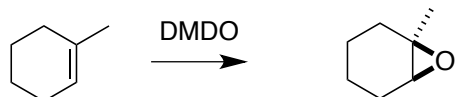


the geometry of the double bond is 100 % *conserved* in epoxidation reactions mediated by



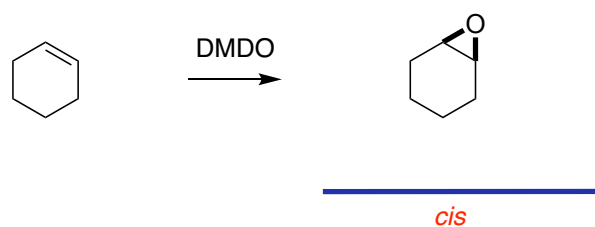
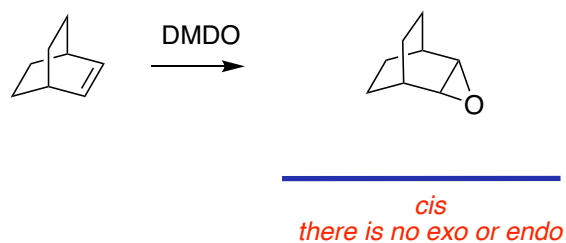
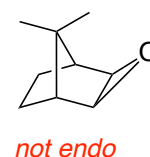
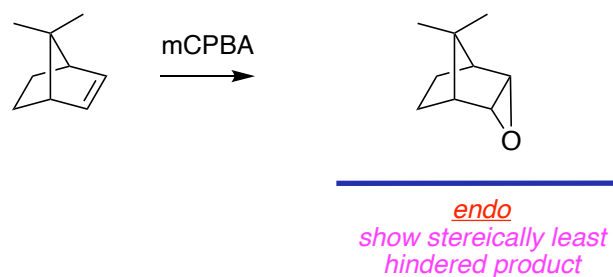
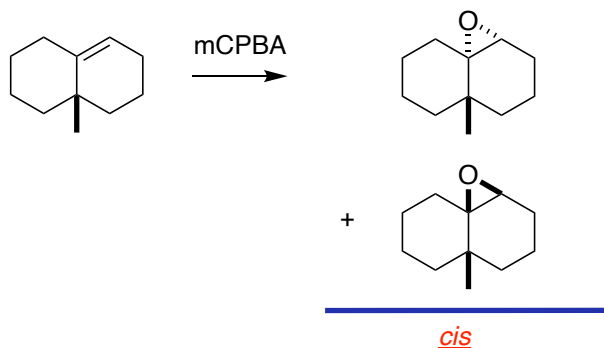
cis

cis



cis

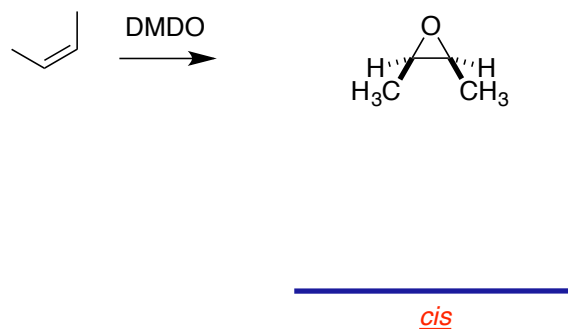
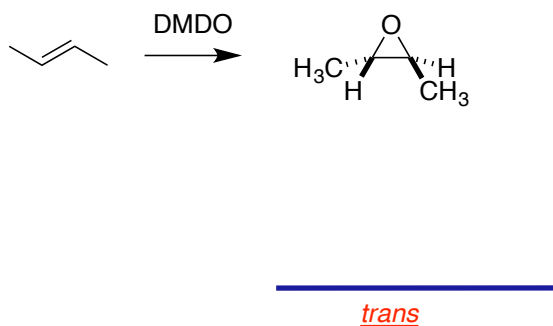
cis

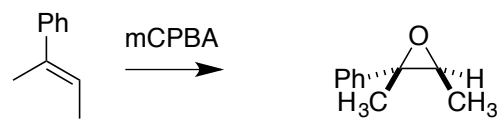
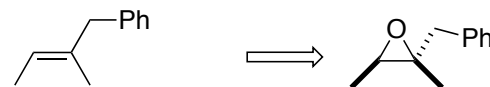
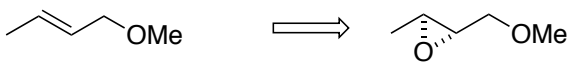
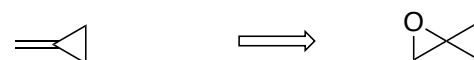
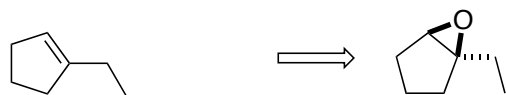


In general, epoxidations *cis*-alkenes *always* like those above give the products of *syn*-addition.

Acyclic Alkenes

substituents attached to the epoxide *does* reflect the geometry of the alkene in these reactions, because they are also formed via *syn*- stereospecific additions.

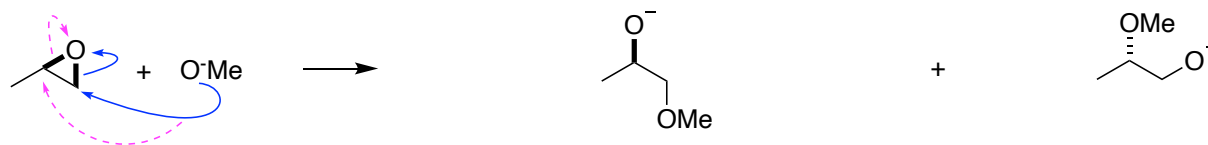


cistrans

E. Regioselectivity Of Epoxide Ring Opening Reactions

Neutral Or Basic Conditions

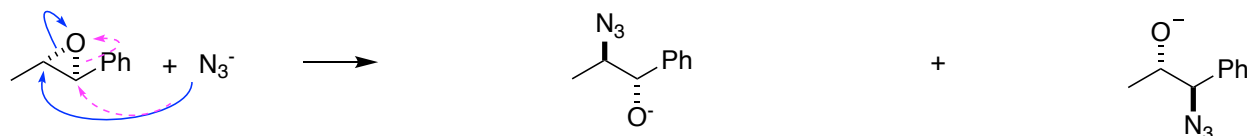
at least two *regioisomeric* products
it is largely dictated by *steric* factors.



major *minor*



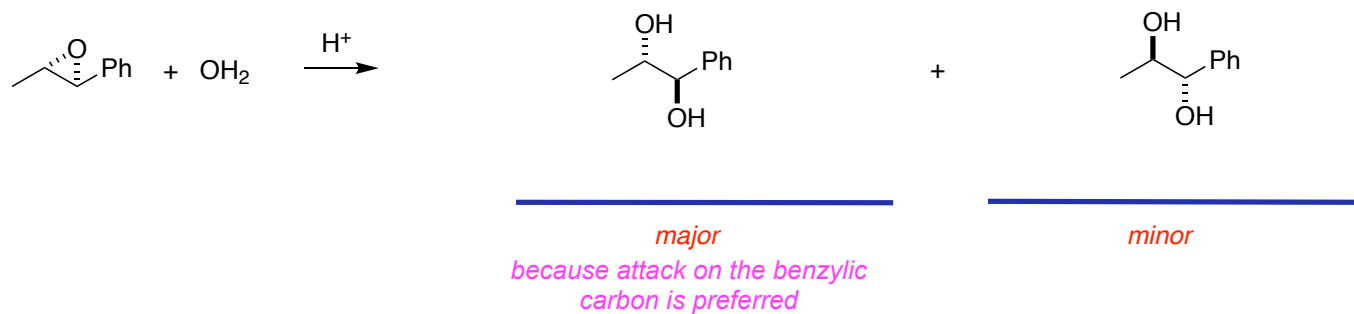
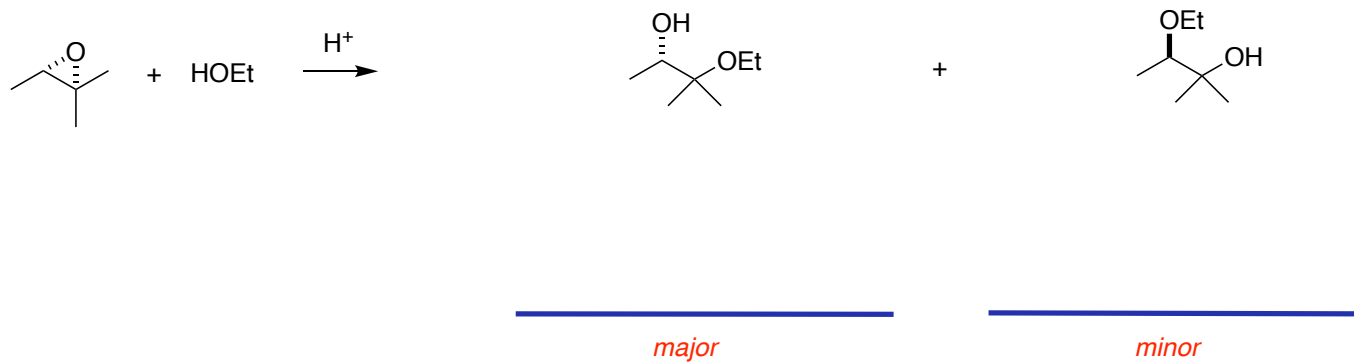
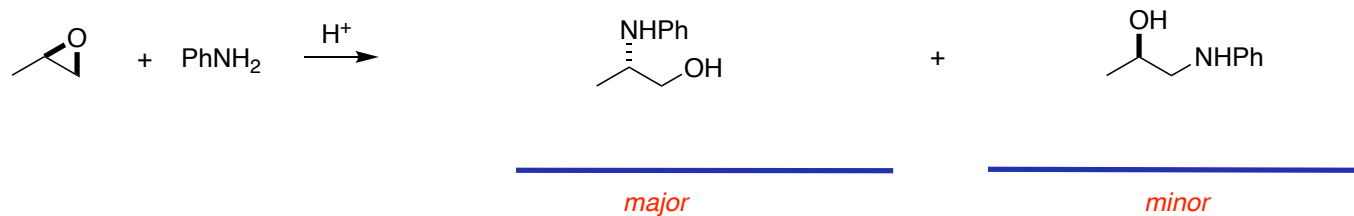
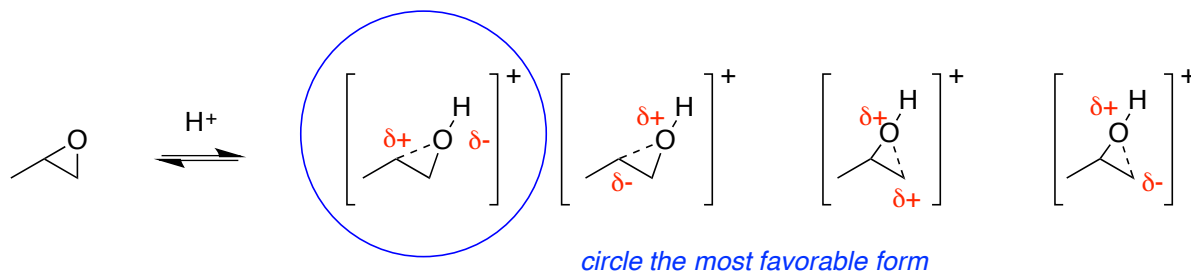
major *minor*

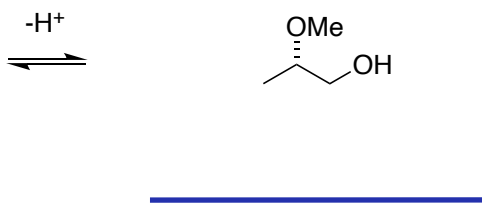
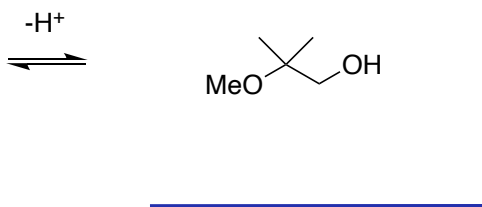
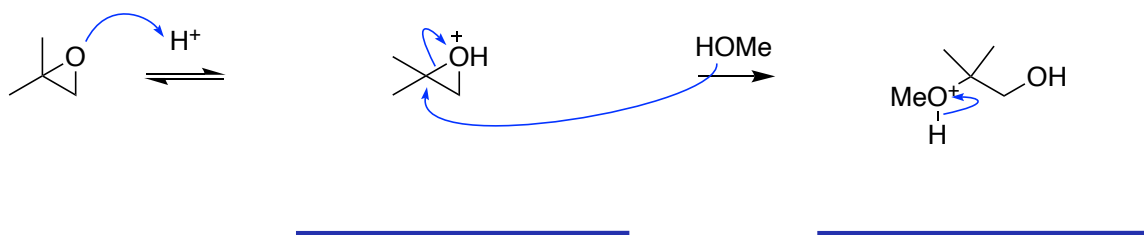


major *minor*

so they are *regioselective* and not *regiospecific*.

Acidic Conditions





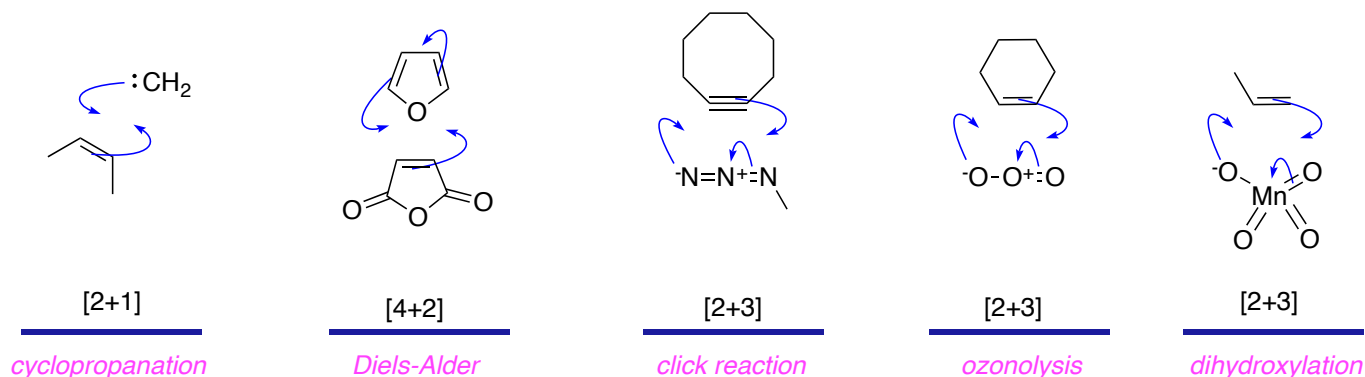
8. Cycloadditions To Alkenes And Alkynes

from chapter(s) _____ in the recommended text

A. Introduction

B. Cycloaddition Nomenclature

can only be [2 + 1] processes, and [3 + 2] / [1 + 4] leads to five-membered rings



C. Carbene Additions [2 + 1] (Cyclopropanations)

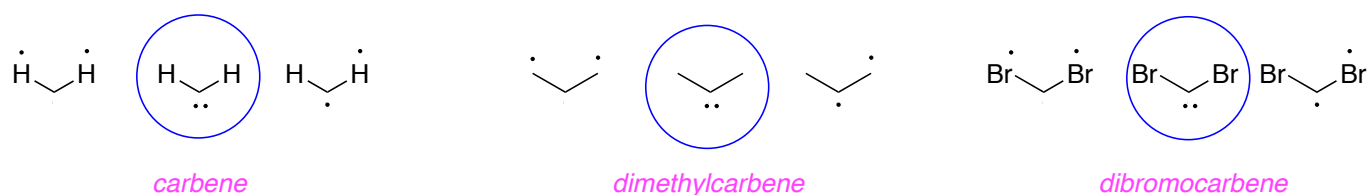
Reagents that contribute one atom to a ring in cycloadditions must be able to expand their valency by two: *true*.

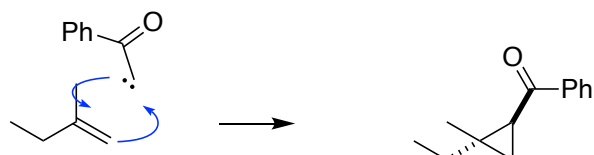
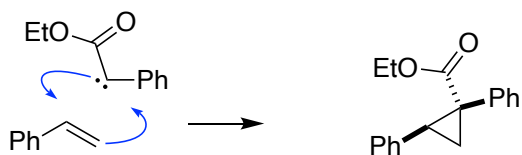
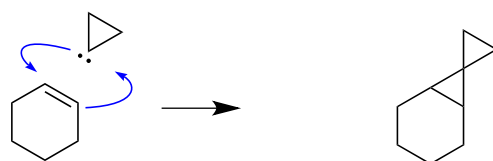
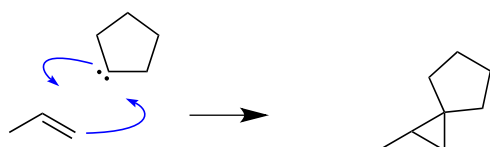
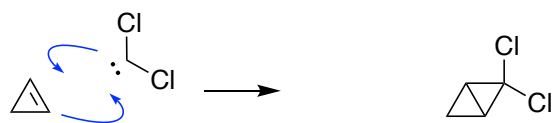
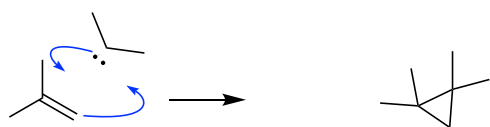
Carbenes have only **6** electrons in the valence shell of carbon.

expanding the valency of the carbon to **4**.

A leaving group *is not* required in cyclopropanations featuring carbenes.

Carbenes can be sp² hybridized with *an empty p-orbital*, ie *singlet* forms
sp³ hybridized with *a diradical structure*, ie *triplet*





show only trans-product

show only trans-product

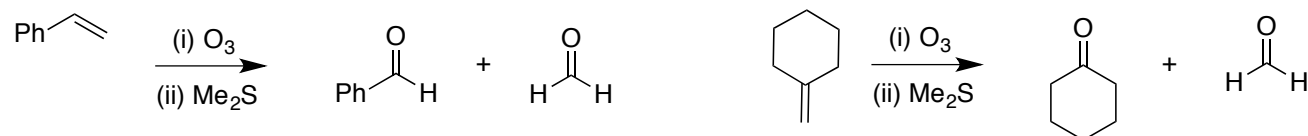
Substances that have two rings sharing a single carbon are called *spiro*.

D. Ozonolysis [2 + 3]

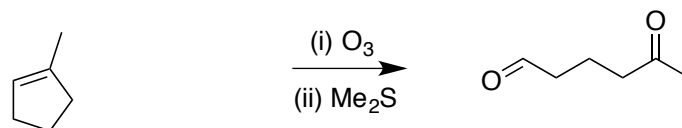
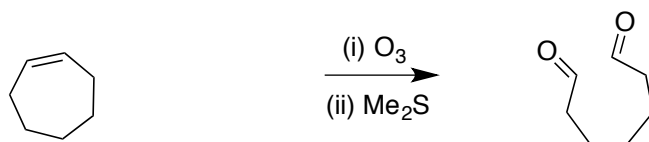
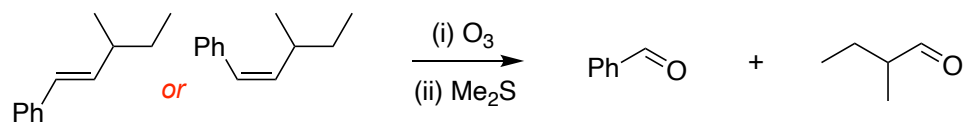
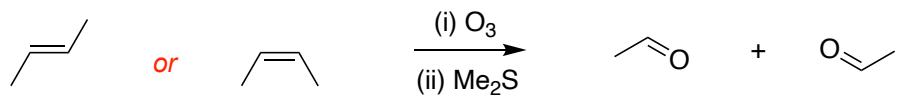
It smells like *a sea breeze / don't smell it, it's highly toxic*

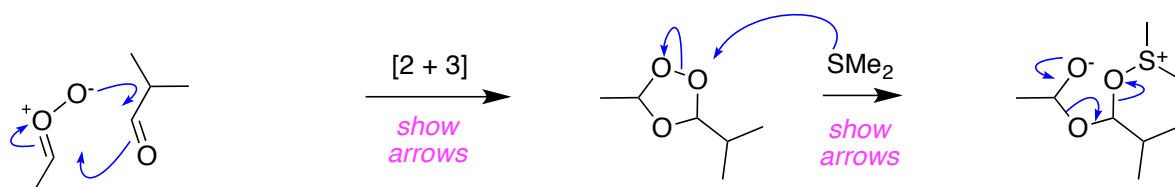
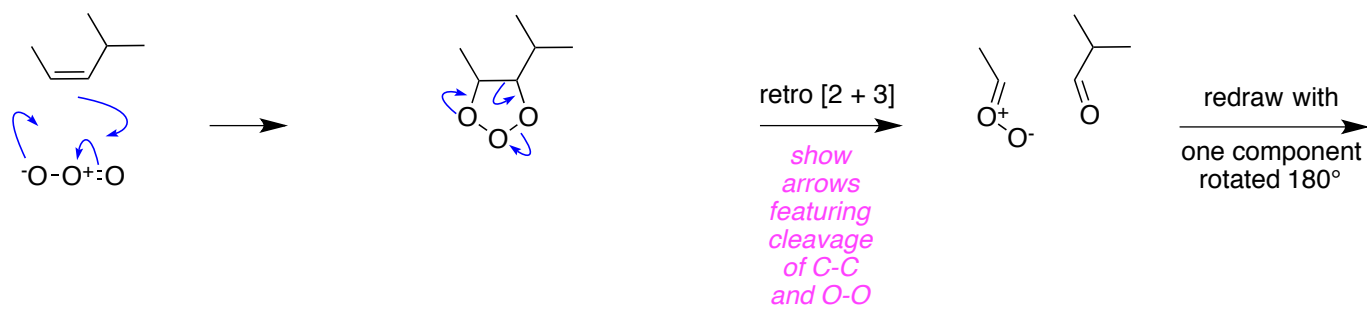
Treatment with ozone, *ie ozonolysis*, then quenching the produce with a mild reducing agent cleaves alkenes to give *aldehydes / ketones* at either terminus

This reducing agent can be *Me₂S / PPh₃ / Zn dust* (dimethyl sulfate cannot be a reducing agent)



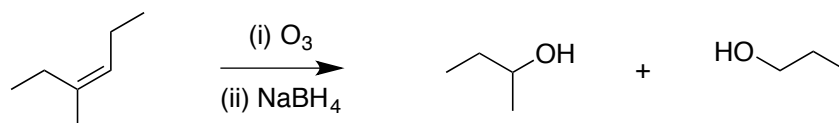
A retro-[2 + 3] is a *ring cleavage to 2 and 3 atoms components*.

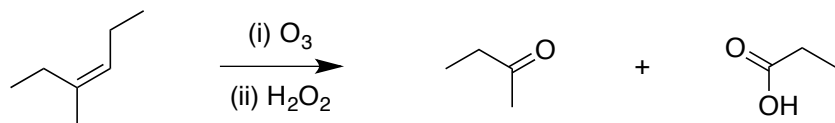




DMSO is Me_2SO

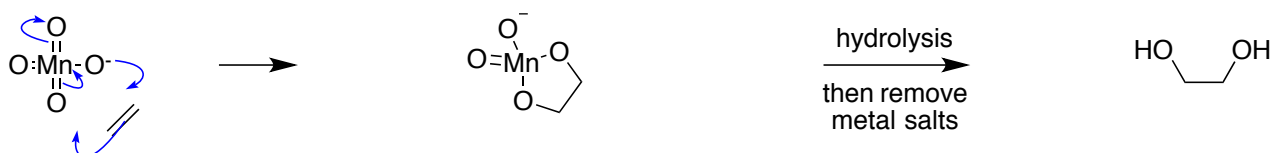
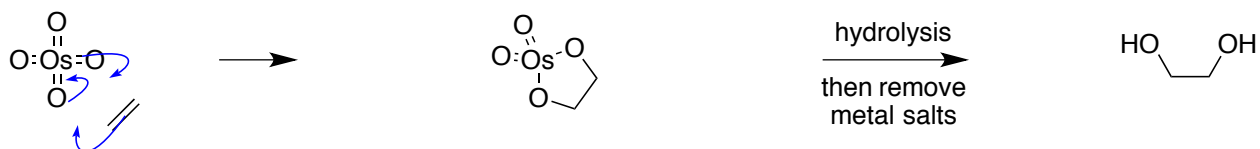
ozonolysis reactions may be *reduced* to alcohols if the mixture is treated with sodium borohydride, or *oxidized* to acids if treated with hydrogen peroxide.



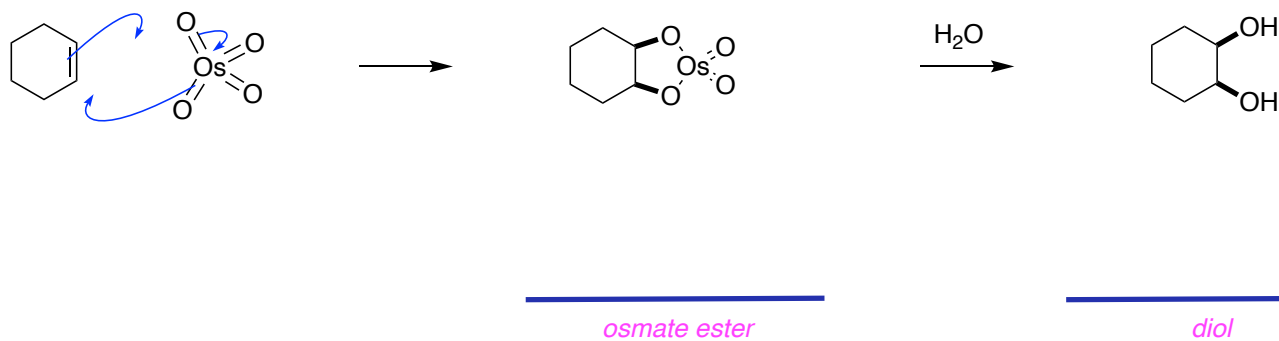


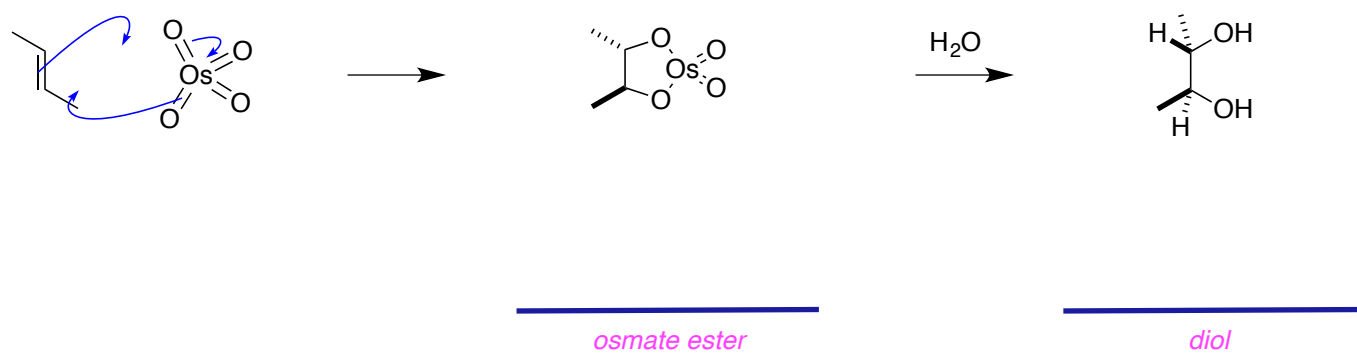
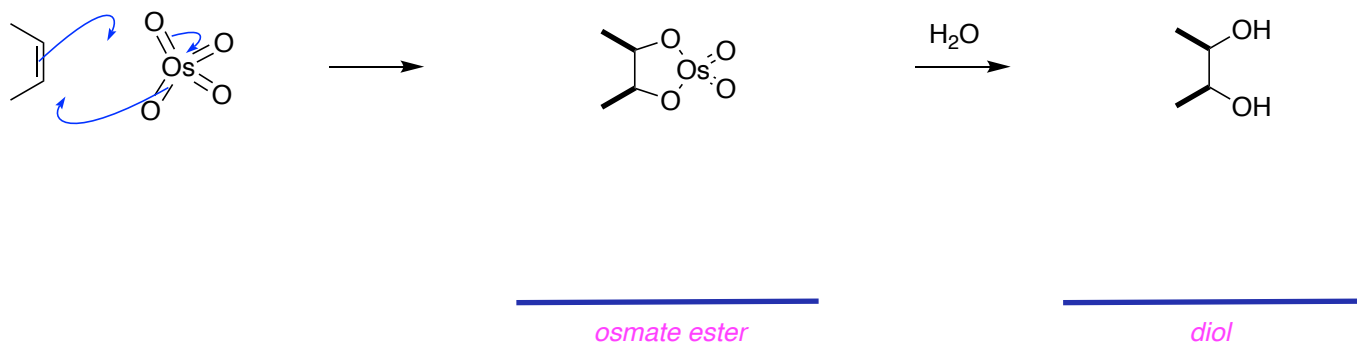
E. *syn*-Dihydroxylation [2 + 3]

A dihydroxylation adds 2 hydroxyl groups to an alkene.



metal oxides to alkenes occur with *syn* face specificity.

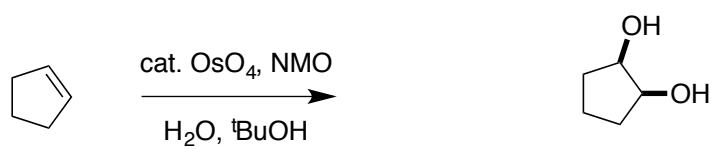


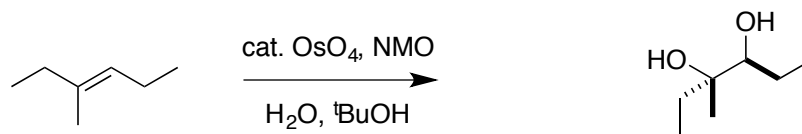


Dihydroxylation with osmium tetroxide is stereospecifically *syn*

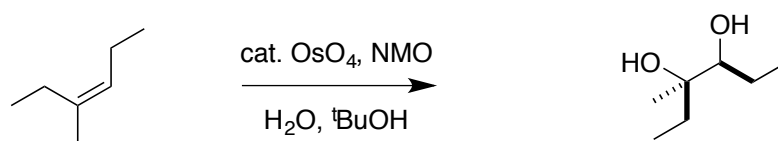
This is *unlike* generation of diols via epoxidations which gives net *anti* addition







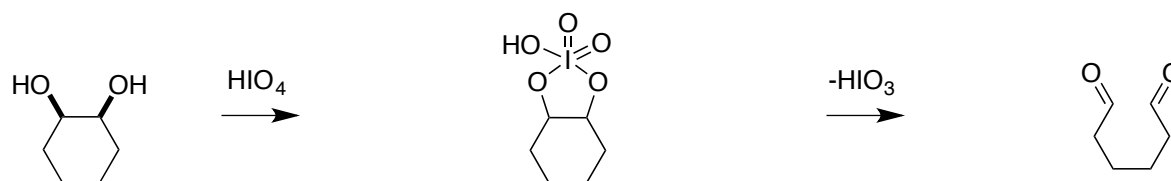
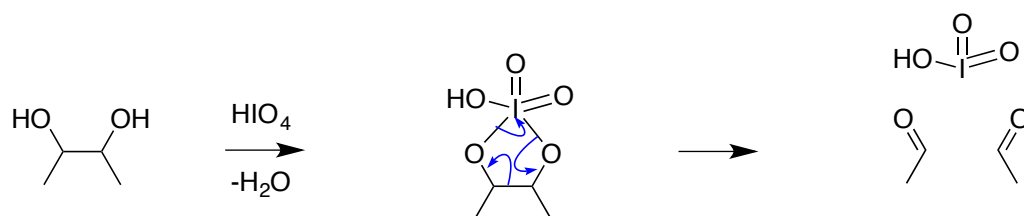
(Of course, both enantiomers form in both the problems shown on this page.)



The products of the two reactions above are *diastereomers*

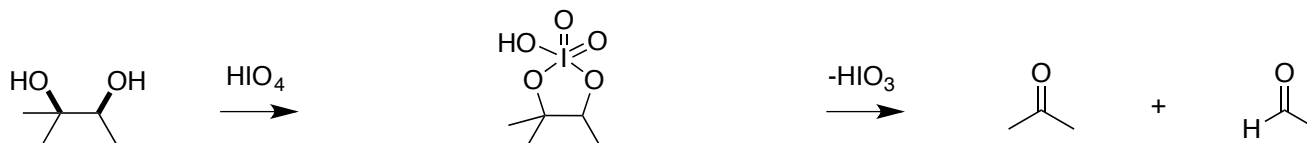
Periodate Cleavage

The iodine of periodic acid (HIO_4) is in the **+7** oxidation state; it is **reduced** in this reaction to HIO_3 which is in the **+5** oxidation state.



periodate intermediate

products



periodate intermediate

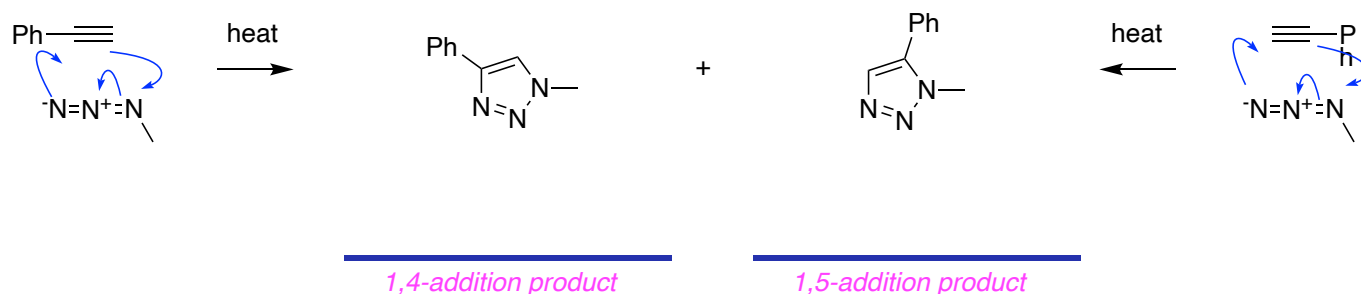
products

F. Azide-Alkyne “Click Reactions” [2 + 3]

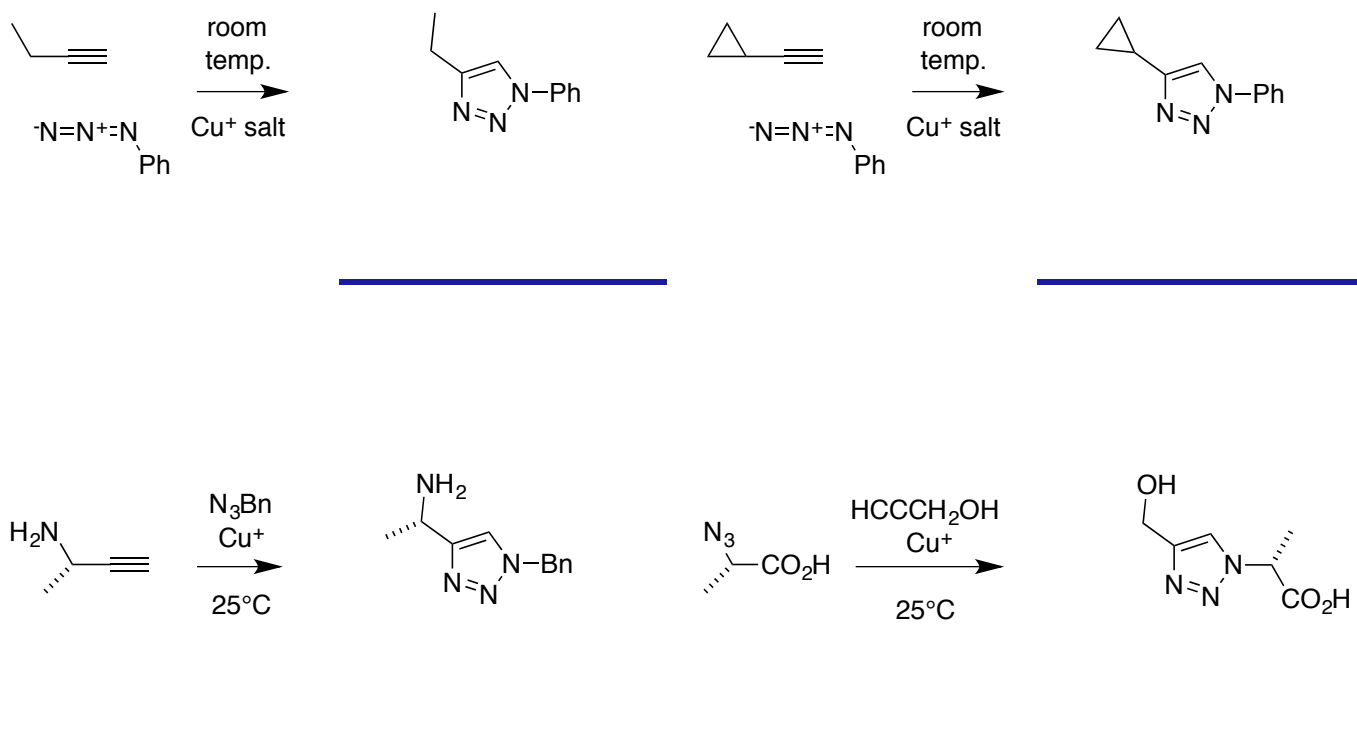
A terminal alkyne is a C – C triple bond *at the end of a chain*.

Heating organic azides and terminal alkynes together causes them to undergo [3 + 2]

Two *regioisomers* are always formed in this reaction, *ie* it is *regioselective*.



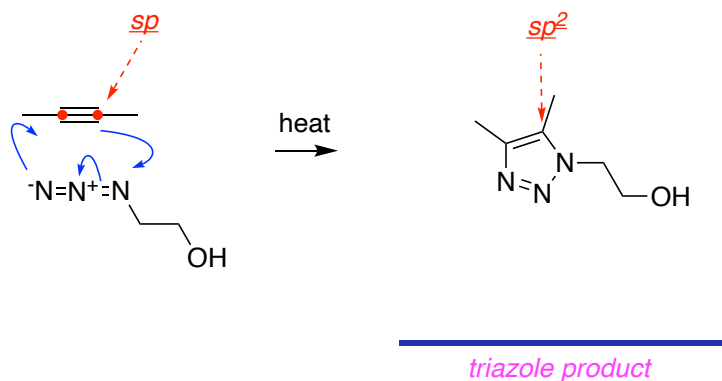
1,4-cycloaddition product, *ie* the reaction becomes 100% *regiospecific*



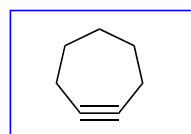
many different organic functionalities, but *none* of them react quickly with azides or with alkynes.

ie this type of click reaction is *chemoselective*.

copper ions are cytotoxic, and cells are *less* stable



the ideal geometry around the “red dot carbons” is 180° , whereas in the triazole product it is 120° .



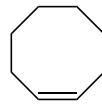
cycloheptyne

3



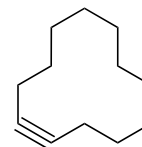
cyclopropyne

4



cyclooctyne

2



cycloundecyne

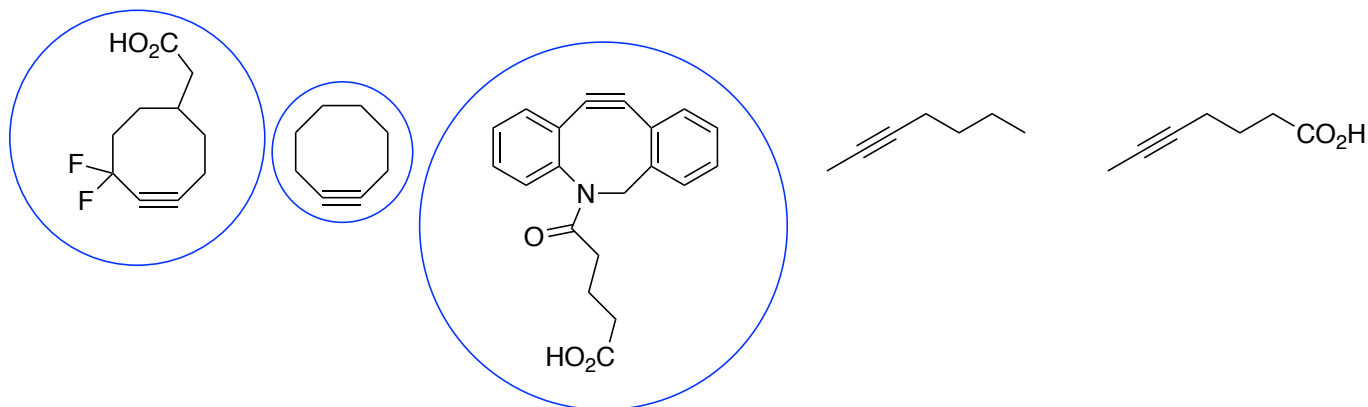
1

and this is called the heat of *hydrogenation* for that substrate.

liberates most heat in this reaction is the *most* strained, ie cyclopropyne.

changes alkyne sp -hybridized carbons to sp^3 , thereby making those carbon atoms *more* able to fit

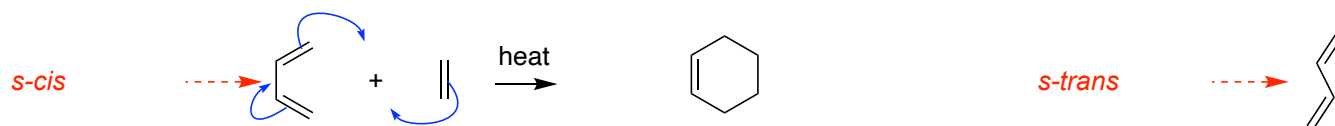
alkyne sp -hybridized carbons to sp^2 , thereby making those carbon atoms *more* able to fit



Reactions like these *do not* need copper salts to proceed at room temperature

on the cell surface, can be observed using *confocal microscopy*.

G. Diels Alder Reactions [4 + 2]

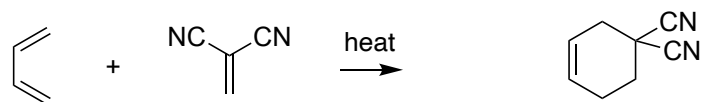


When dienes undergo [4 + 2] cycloadditions, they must be in *s-cis* conformations. conformation about the σ -bond that connects the π -bonds.

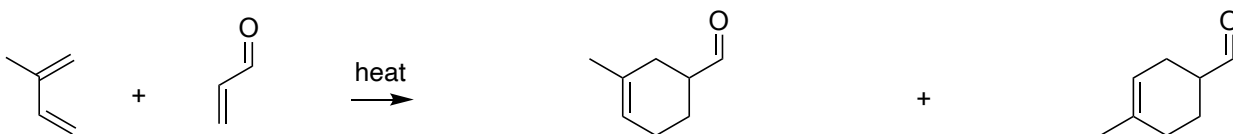
s-cis and *s-trans* conformations *are* in rapid equilibrium at room temperature.

the monoalkene is called the *dienophile* meaning it *loves* dienes.

ie the dienophile adds to *the same* face(s) of the *s-cis* diene conformation. This is called *suprafacial*.

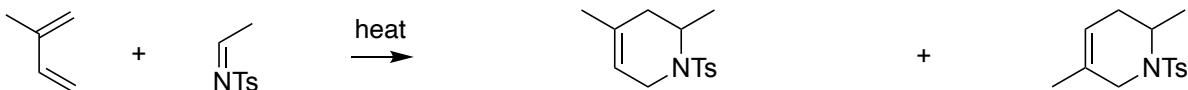


“4,4-dicyanocyclohexene”



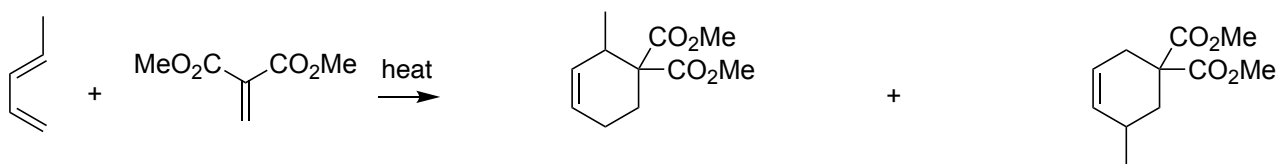
regioisomer 1

regioisomer 2



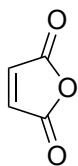
regioisomer 1

regioisomer 2

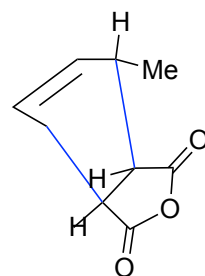
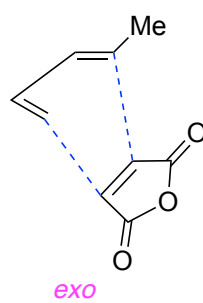


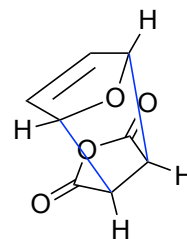
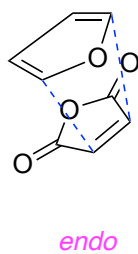
regioisomer 1

regioisomer 2

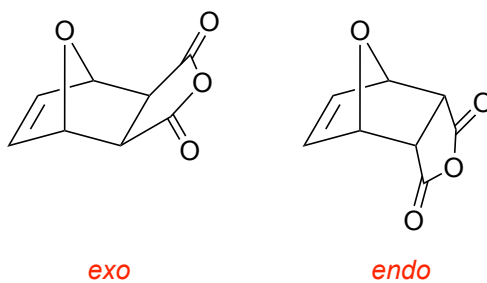
exo- and endo-Additions

maleic anhydride

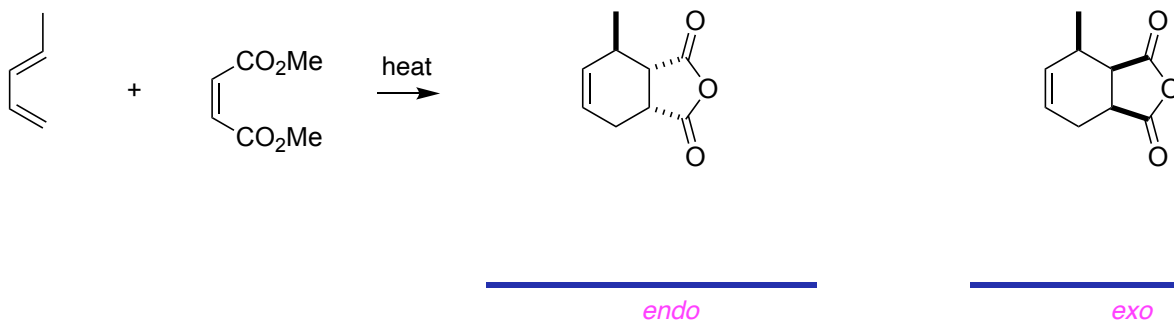
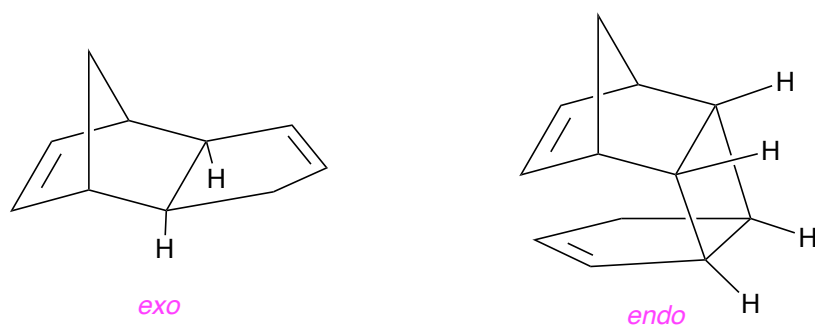
furan

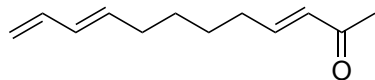
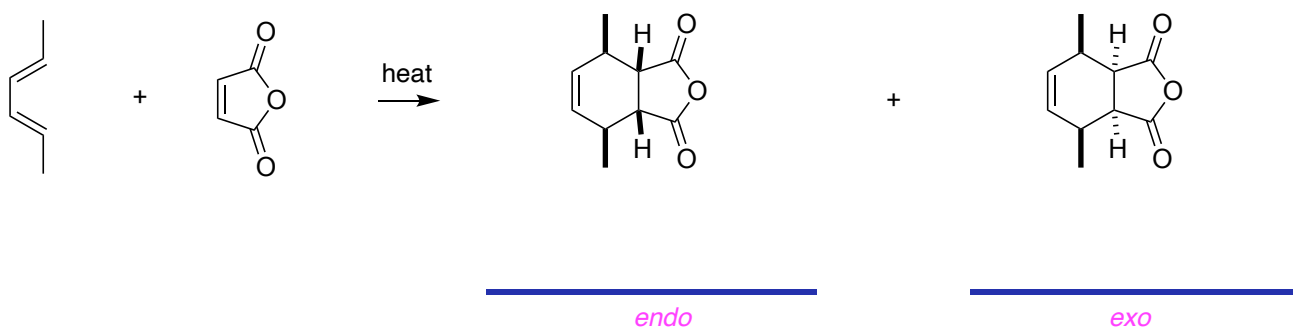
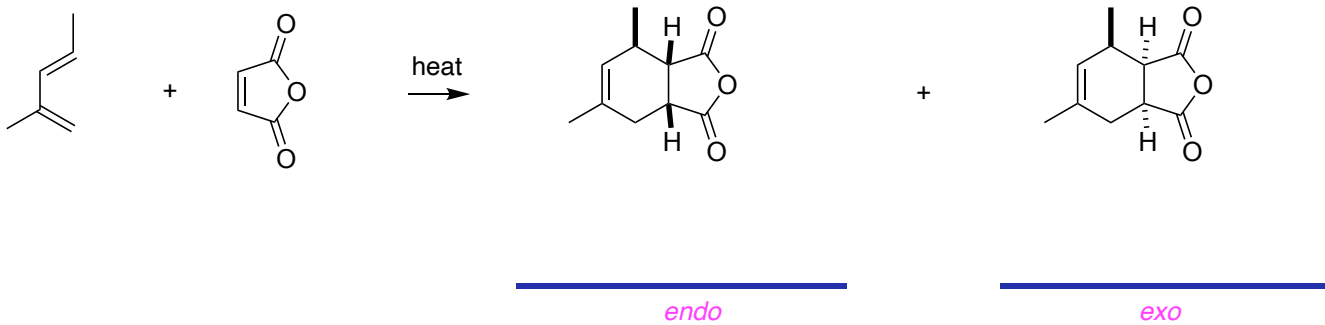
product of exo addition

product of endo addition

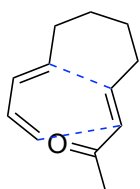


Consequently, the *endo*-isomer is the *kinetic* product, and the *exo*- will predominate at extended reaction
 pure isomer can be isolated in the *late* stages of the reaction and the equilibrium is adjusts to *favor*

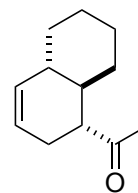




is equivalent to

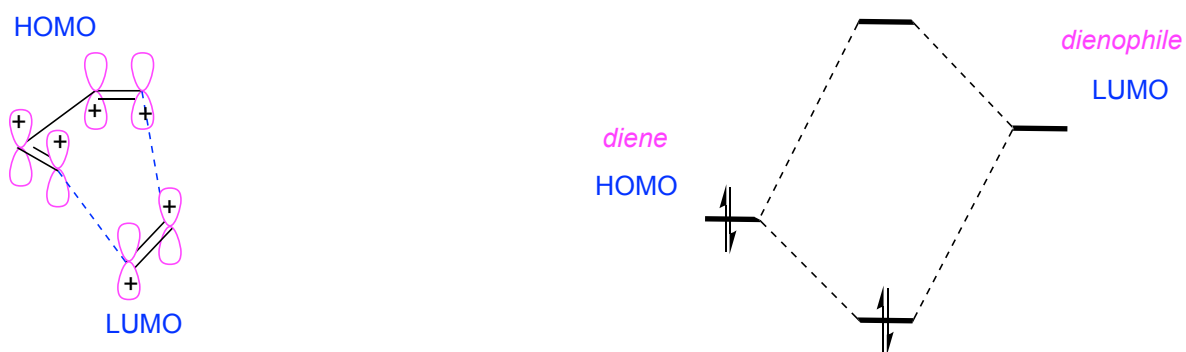


heat



draw in a suitable conformation

1,3-butadiene gives 4 molecular orbitals of which the lowest energy 2 are filled with two electrons each.



HOMO-LUMO overlap such as that shown above are called *frontierorbital* interactions.

Charge in the *HOMO* redistributed to compensate for the lack of it in the *LUMO* drives these reactions to occur.