

## &lt;&lt; Alcohols &amp; Thiols as Brønsted Acid &amp; Base

## → Acidity of Alcohols &amp; Thiols

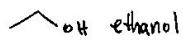
&gt; alkoxide - conjugate base of alcohol

• alcohol &amp; thiol are weak acids,

• acidity: thiol &gt; alcohol (element effect)

• alcohol &amp; water similar acidity (similar structure)

&gt; mercaptide / thiolate - conjugate base of thiol



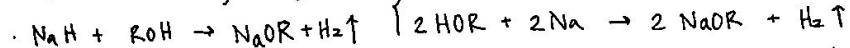
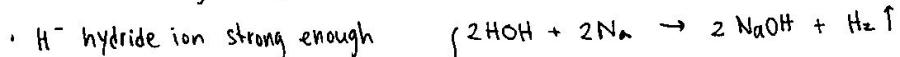
## NAMING

acid	conj. base	naming
alcohol	-oxide	common
	-ate	substitutive

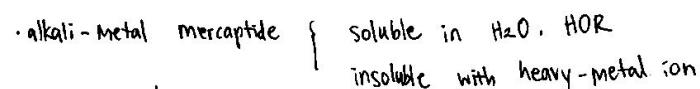
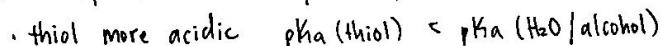
  

thiol	mercaptide	common
	-thiolate	substitutive

## → Formation of Alkoxides &amp; Mercaptides

• alcohol cannot fully dissociate in base  $\text{OH}^-$ •  $\text{OH}^-$  not strong enough base to convert alcohol to conj.-base alkoxide

• thiol can fully dissociate in hydroxide, alkoxide



## → Polar Effects on Alcohol Acidity

• induction effect -  $\uparrow$  acidity,  $\uparrow$   $\epsilon_{\text{neg}}$  halogen• distance effect -  $\uparrow$  acidity,  $\uparrow$  near  $-\text{OH}$ 

## → Solvent Effect on Alcohol Acidity

## ↑ acidity

## gas phase (no solvent)

•  $\uparrow$  alky sub,  $\uparrow$  acidity

• alky sub stabilizes negative charge at O atom

## in solution

•  $\downarrow$  alky sub,  $\uparrow$  acidity• alky sub prevent solvation of conjugate base,  $\downarrow$  stability of conj. base,  $\downarrow$  acidity

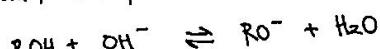
• Any alcohol in solution is more acidic in gas phase

## → Basicity of Alcohol &amp; Thiol

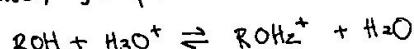
• Alcohol, like water, accept protons, becomes very basic

• Thiol accept proton, but much less basic than alcohol

• As weak acid, loss proton

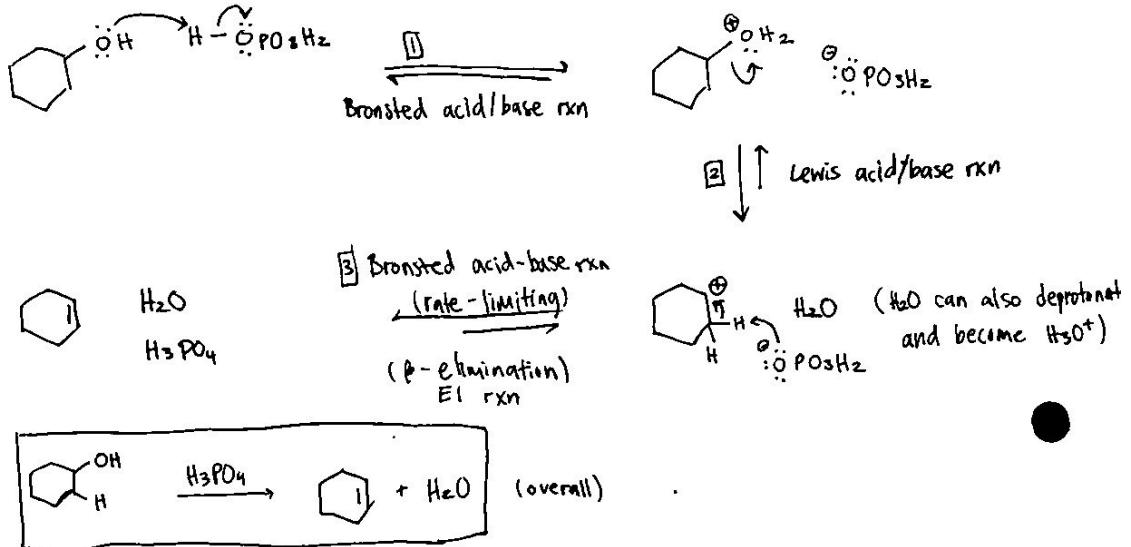


• As weak base, gain proton



### Dehydration of Alcohol

- > dehydration - elements of water lost from starting material
- Acid catalyst converts poor leaving group  $\text{-OH}$  to good leaving group  $\text{-O}^+ \text{H}_2$
- Acid-base reaction with carbocation intermediate



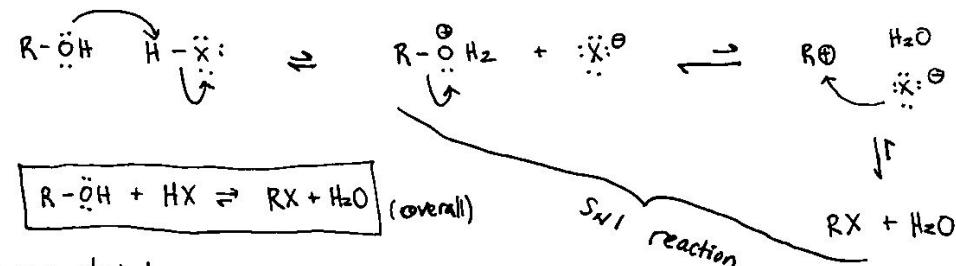
- An acid & its conj. base act in tandem in mechanism
- No  $\text{OH}^-$  needed, even  $\text{H}_2\text{O}$  is enough for the carbocation.
- alcohol dehydration is
  - E1 reaction
  - reverse of hydration of alkenes (fwd & reverse rxns)
  - microscopic reversibility
    - same rate limiting step
    - same catalyst accelerates both directions
- Rate of alcohol dehydration
  - $\uparrow$  alkyl sub,  $\uparrow$  rate (tertiary  $\gg$  secondary  $\gg$  primary)
- if there's more than one type of  $\beta$ -H, mixture of product produced.
  - product with  $\uparrow$  branch at double bond is major product
- carbocation intermediate allows rearrangement.

## Reactions of Alcohol with HX

- alcohol + hydrogen halide  $\rightarrow$  alkyl halide
- $K_{eq}$  is not large, use le Chatelier's principle to increase  $K_{eq}$
- $\rightarrow$  Tertiary alcohol (Secondary)

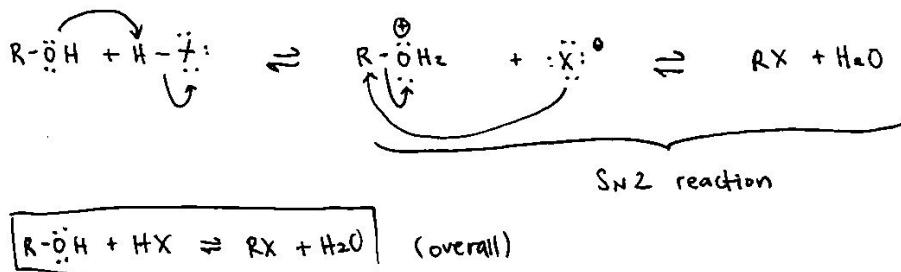
$\left. \begin{array}{l} \cdot \text{heat } (\uparrow \text{ temp}) \\ \cdot \text{separate } (\downarrow) \text{ product} \\ \cdot \text{add } (\uparrow) \text{ reactant} \end{array} \right\}$

- $S_N1$  reaction with  $H_2O$  as leaving group (have carbocation intermediate)



$\rightarrow$  Primary alcohol

- $S_N2$  reaction with  $H_2O$  as leaving group

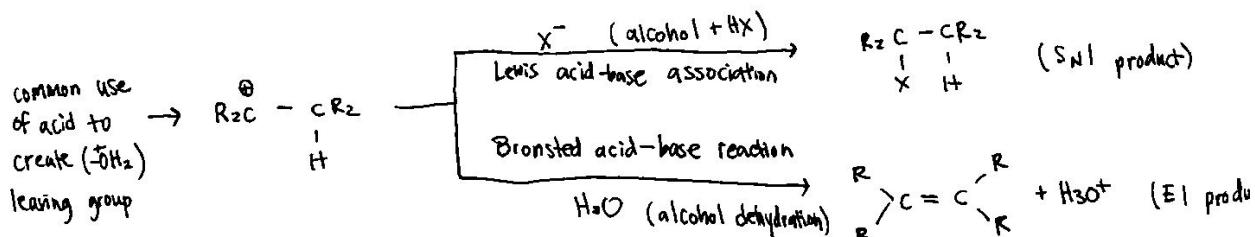


## Rate of reaction

- $\uparrow$  alkyl sub,  $\uparrow$  rate (heat needed for primary alcohol)

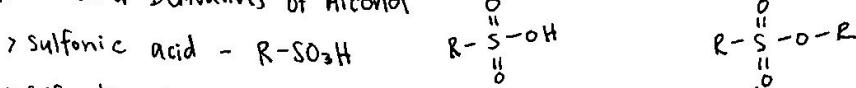
Secondary alcohol react in  $S_N1$  fashion.

Alkyl halide formation and dehydration to alkenes are alternative branches of common mechani of alcohol



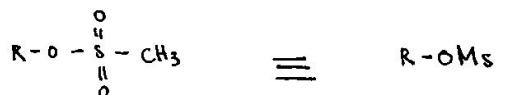
## << Alcohol -Derived Leaving Groups

→ Sulfonate Ester Derivatives of Alcohol

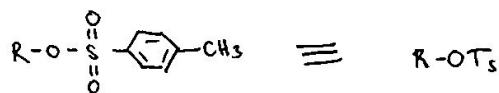
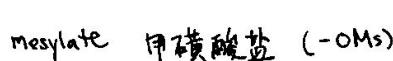


> Sulfonate ester - acid H of sulfonic acid replaced by alkyl / aryl group

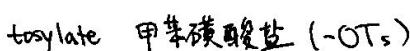
## → Abbreviation.



### methane sulfonate

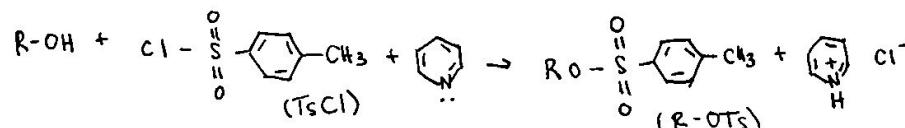


*p*-toluenesulfonate



## → Preparation of Sulfonate Esters

- alcohol + sulfonyl chloride + pyridine  $\rightarrow$  alkyl sulfonate + pyridine<sup>+</sup> + chloride<sup>-</sup>



## → Reactivity of Sulfonate Ester

- Sulfonate ester have approx same reactivity as corresponding alkyl bromide

### In Sub & elim rxn

- Sulfonate anions are good leaving groups, weak bases

consequence { primary & secondary sulfonate ester can  $S_N2$

Sul-EI in polar protic solvent

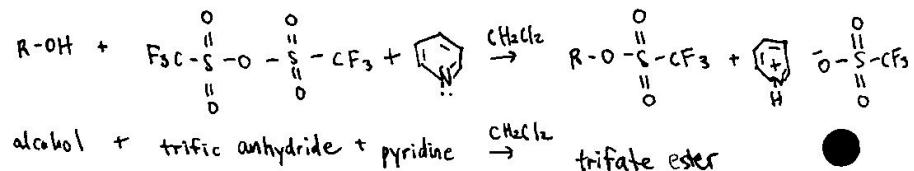
> trifluoromethanesulfonate ester - triflate ester (-OTf)



- very acidic, more acidic than  $(-\text{OMs})(-\text{OTs})$ , very reactive

- triflate anion (the conj. base) is very weak base, a good leaving group

→ Preparation of triflate ester



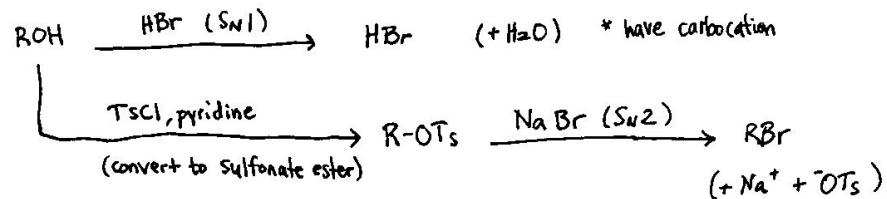
## &lt;&lt; Alcohol-Derived Leaving Groups

→ Sulfonate Ester Derivatives of Alcohol (Cont.)

→ Reactivity of Sulfonate Ester

• Sulfonate ester can undergo  $S_N2$  reaction

• serves as alternative path from alcohol to alkyl halide w/o carbocation intermediate

• Sulfonate ester can undergo  $E2$  reaction• Summary: alcohol → sulfonate ester →  $S_N2/E2$  (w/o carbocation)

• sulfonate ester ≈ alkyl halide

## → Alkylating Agents

→ alkylated - nucleophile receiving an alkyl group from sub rxn with alkylating agent

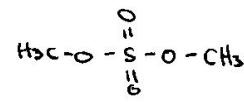
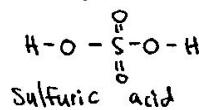
• like "protonated" by strong acid

→ alkylating agent - compound with good leaving groups that reacts rapidly with nucleophile in  $S_N2/S_N1$  reactions. (e.g. alkyl halide, sulfonate ester)

## → Ester Derivatives of Strong Inorganic Acid

• ester of strong inorganic acid is also alkylating agent

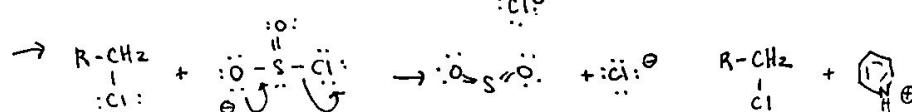
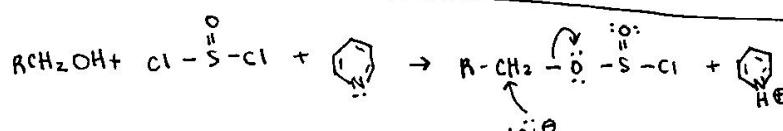
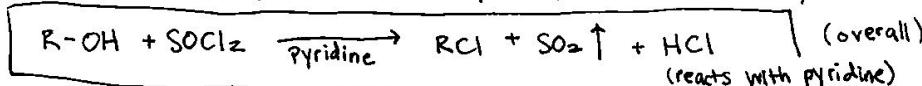
• leaving group is very weak base



good leaving group  
weak base

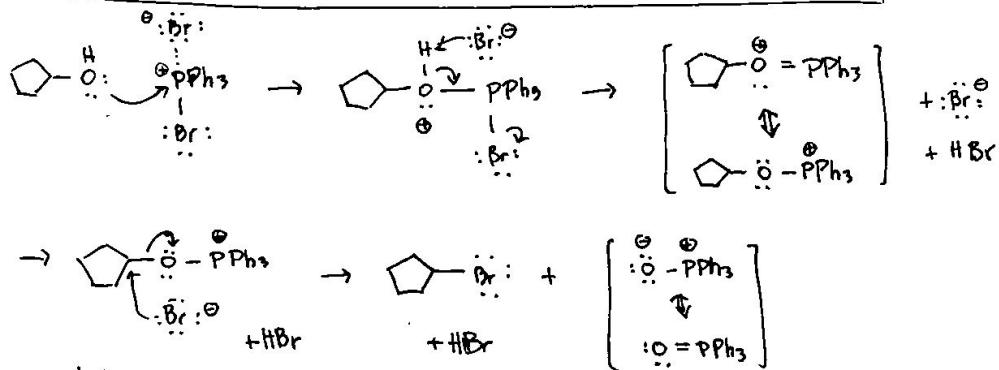
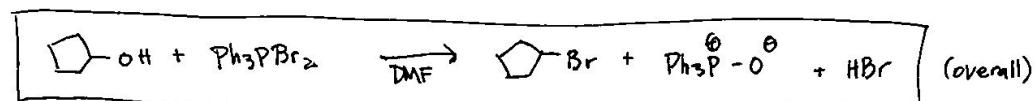
→ Reactions of Alcohol with Thionyl Chloride and Triphenylphosphine Dibromide ( $\text{Ph}_3\text{PBr}_2$ )

• produce primary alkyl halide from primary alcohol (secondary ok)



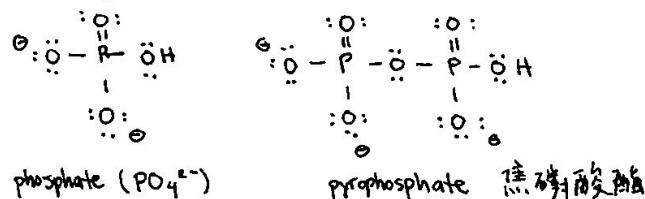
<< Alcohol-Derived Leaving Group

→ Alcohol +  $\text{Ph}_3\text{PBr}_2$  (Triphenylphosphine Dibromide)



- weak base, good leaving group
- $\text{S}_{\text{N}}2$  Rxn
- $\text{Br}^-$  attack intramolecular
- used for prepare  $2^\circ$  bromide
- $\text{Ph}_3\text{PCl}_2$  for  $2^\circ$  chloride

→ Biological Leaving Groups



- pyrophosphate ester is alkylating agent
- > farnesylation - biological alkylation involving pyrophosphate leaving group

- pyrophosphate poor leaving group (basic)
- but! pyrophosphate bond to enzyme with  $\text{Mg}^{2+}$ , neutralizing its charge, being more like pyrophosphoric acid
- weak bonding, ↑ leaving group ability

Conversion of Alcohol to RX

$\rightarrow$  1° Alcohol

- 1° + HBr  $\rightarrow$  RBr
  - 1° + Ph<sub>3</sub>PBr  $\rightarrow$  RBr
  - 1° + HI + (KI)  $\rightarrow$  RI
  - 1° + SOCl<sub>2</sub>  $\rightarrow$  RCl
  - 1° + ( )  $\rightarrow$  sulfonate ester + X<sup>-</sup>  $\rightarrow$  RX
- $\left. \begin{array}{l} \\ \\ \\ \\ \end{array} \right\}$  SN2  
alcohol with bulky alkyl sub.  
doesn't react (sterics)

$\rightarrow$  2° Alcohol

- 2° + SOCl<sub>2</sub>  $\rightarrow$  RCl (has rearrangement)
- 2° + ( )  $\rightarrow$  sulfonate ester + X<sup>-</sup>  $\rightarrow$  RX (polar, aprotic solvent) SN2
- 2° + ( )  $\rightarrow$  triflate ester + X<sup>-</sup>  $\rightarrow$  RX SN2
- 2° + HBr  $\rightarrow$  RBr (has rearrangement) SN1
- 2° + Ph<sub>3</sub>PBr<sub>2</sub>  $\rightarrow$  RBr SN2
- 2° + Ph<sub>3</sub>PCl<sub>2</sub>  $\rightarrow$  RCl SN2

$\rightarrow$  3° Alcohol

- 3° + HCl  $\rightarrow$  RCl
- 3° + HBr  $\rightarrow$  RBr } SN1

$\rightarrow$  Principles of Reactions

- -OH cannot be leaving group, OH<sup>-</sup> too basic
- -OH need conversion to good leaving group
- protonation - dehydration to alkene, alcohol + HX  $\rightarrow$  RX
- conversion to ester leaving group - esters sulfonate or alkyl halide

## &lt;&lt; Oxidation &amp; Reduction

→ Half Rxn

- > oxidation - loss  $e^-$  (LEO)
- > reduction - gain  $e^-$
- > half reaction - only show oxidation or reduction
  1. use  $H_2O$  balance O
  2. use  $H^+$  balance H
  3. use  $e^-$  balance charge

→ Oxidation Number

- oxidation number of C
  - every bond to less electroneg element or neg charge : -1
  - every bond to carbon or unpaired  $e^-$  : 0
  - every bond to more electroneg element or pos charge : +1
- $Nox = \text{add all the values}$
- if :
 

$Nox(\text{prod}) > Nox(\text{reactant})$	: oxidation
$Nox(\text{prod}) < Nox(\text{reactant})$	: reduction
$Nox(\text{prod}) = Nox(\text{reactant})$	: no redox
- $Nox(\text{prod}) - Nox(\text{reactant}) = \Delta Nox$

→ Oxidizing & Reducing Agent

> oxidizing agent - the reagent causes oxidation, it's reduced.

> reducing agent - the reagent causes reduction, it's oxidized.

→ Oxidation States of Functional Groups

↑ oxidation number →					
methane :	$CH_4$	$H_3C-OH$ $H_3C-X$	$H_2C=O$ $H_2CX_2$	$H-C(OH)=O$ $H-CX_3$	$O=C=O$ $CX_4$
$1^\circ C :$	$R-CH_3$	$R-CH_2-OH$ $R-CH_2-X$	$R-CH=O$ $R-CHX_2$	$R-C(OH)=O$ $R-CX_3$	
$2^\circ C :$	$R-CH_2-R$	$R-CH(OH)-R$ $R-CH-X-R$	$R-C(O)=O$ $R-CX_3$		
$3^\circ C :$	$R-CH-R$ $R$	$R-C(OH)=O$ $R-C-X$			

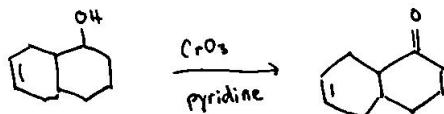
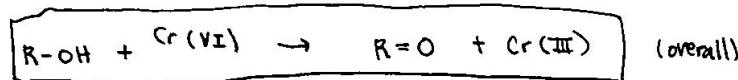
## ... Oxidation of Alcohol

→ Oxidation to Aldehyde &amp; Ketone

→ 2° alcohol

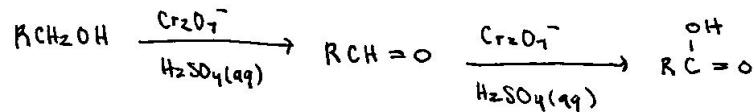
- reagent with Cr(VI) oxidize alcohol to ketone

- chromate  $\text{CrO}_4^{2-}$
- dichromate  $\text{Cr}_2\text{O}_7^{2-}$
- chromium trioxide  $\text{CrO}_3$   
(used with pyridine)

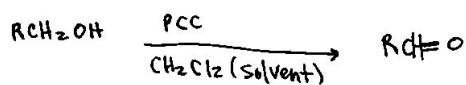
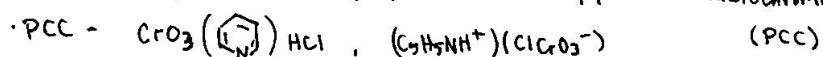


→ 1° alcohol

- Cr(VI) reagent oxidize 1° alcohol to aldehyde
- $\text{H}_2\text{O}$  oxidize aldehyde to carboxylic acid



• to get aldehyde only, anhydrous preparation uses pyridinium chlorochromate

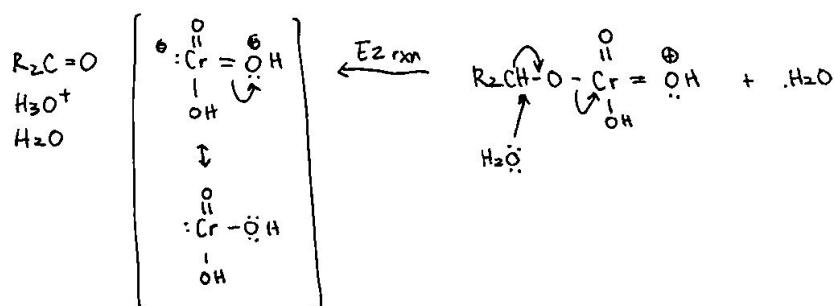
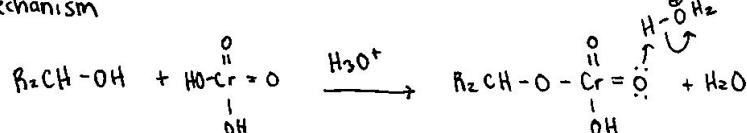


→ 3° alcohol

• 3° alcohol not oxidized under usual conditions

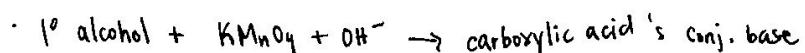
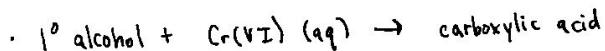
• α-carbon has no H.

→ Mechanism

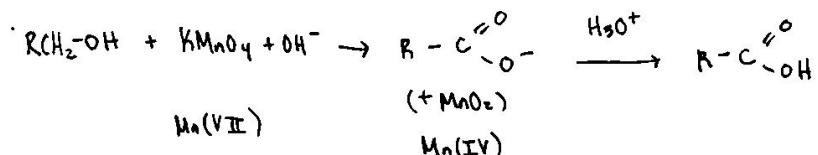


<< Oxidation of Alcohol

→ Oxidation to Carboxylic Acid



- potassium permanganate KMnO<sub>4</sub>

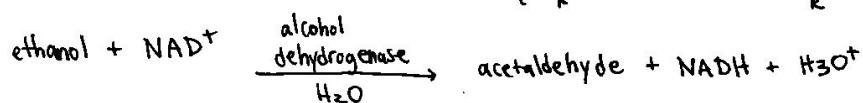
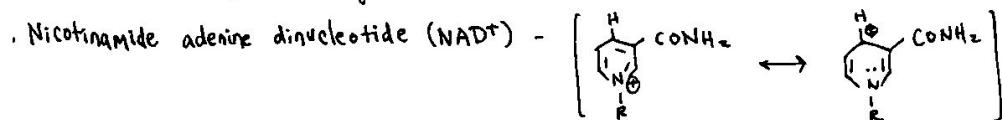


- KMnO<sub>4</sub> not used for alcohol with double/triple bond

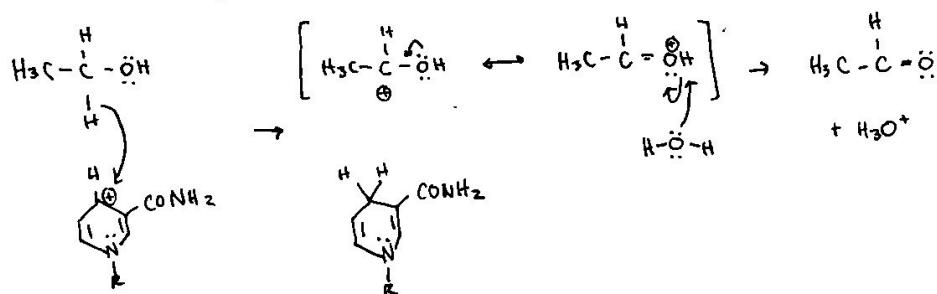
- KMnO<sub>4</sub> not used for 2° alcohol to ketone (ketone reacts with it)

<< Biological Oxidation of Ethanol

> coenzyme - molecules required, along with enzymes, for certain bio reaction to occur



→ Mechanism of NAD<sup>+</sup> rxn



## &lt;&lt; Chemical Equivalence &amp; Nonequivalence

- > chemical equivalent (group) - behave exactly the same toward a reagent } compare within a molecule
- > chemical nonequivalent - behave differently }
- constitutional equivalence
- > constitutionally equivalent - groups have the same connectivity relationship to all other atoms in the molecule
- constitutionally nonequiv groups are chemically nonequiv.
- constitutionally equiv groups can be { chem equiv } need stereochemical chem nonequiv relationship

> substitution test - determine stereochem relation for const. equiv. groups

- Substitute const. equiv. group with fictitious group
- Compare relationship of resulting molecules

> homotopic - groups that give identical molecule

- chemically equivalent at all times

> enantiotopic - groups that give enantiomers

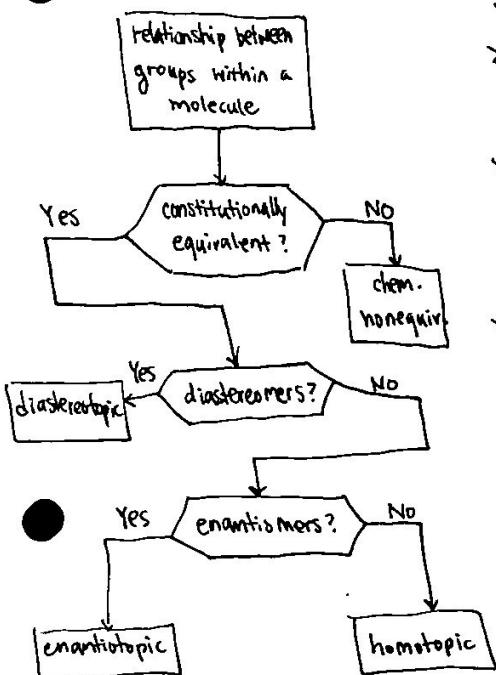
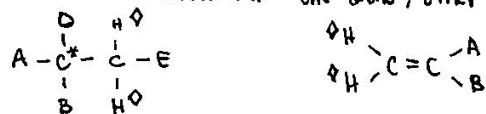
- chem. nonequiv toward chiral reagent

· chem equiv toward achiral reagent

> diastereotopic - groups that give diastereomers

- chemically nonequivalent at all times

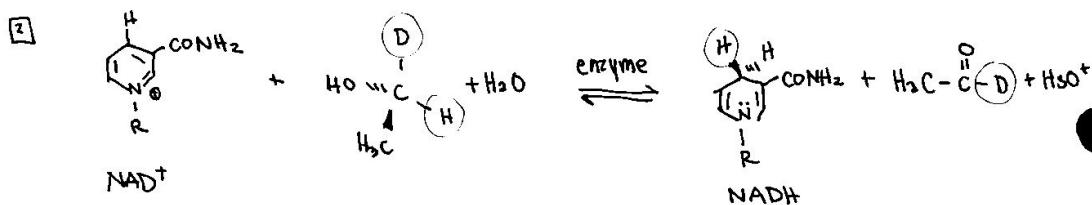
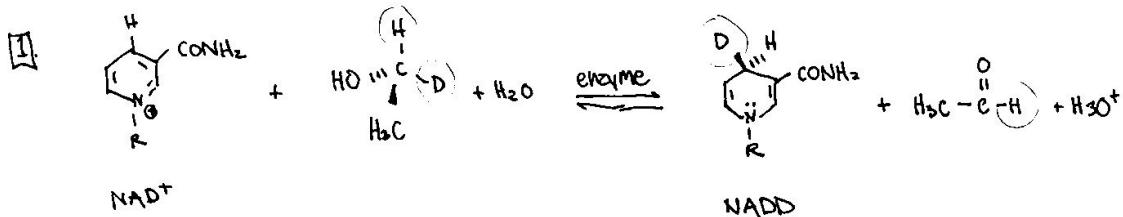
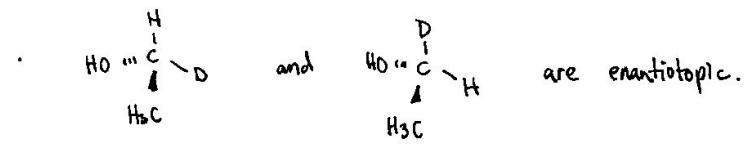
· molecules with asym. C (doesn't need to be near group)  
groups on one side of double bond the same, other diff.



→ Summary

- const. nonequiv → chem. nonequiv all times
- const. equiv {
  - homotopic → chem equiv. all times
  - enantiotopic →
    - chem equiv to achiral reagent
    - chem nonequiv to chiral reagent
- diastereotopic → chem nonequiv all times

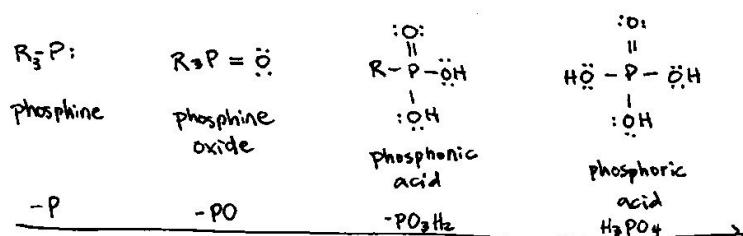
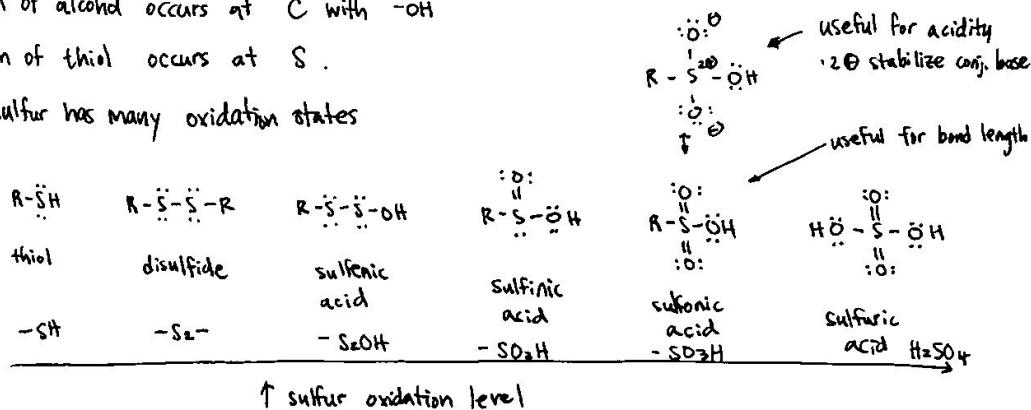
<< Stereochemistry of Alcohol Dehydrogenase Rxn



- enzyme is chiral
- enantiotopic molecule's groups react diff with chiral enzyme.
- microscopic reversibility requires reverse rxn to not scramble H and D

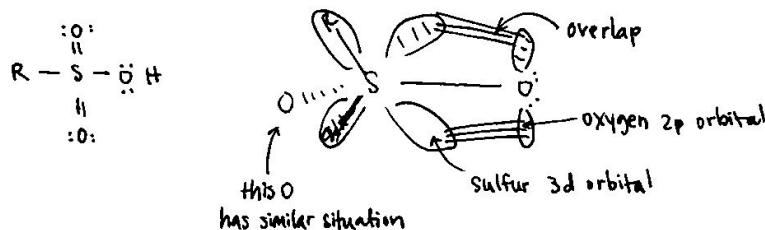
## &lt;&lt; Octet Expansion of Sulfur

- oxidation of alcohol occurs at C with  $-OH$
- oxidation of thiol occurs at S.
- Sulfur has many oxidation states

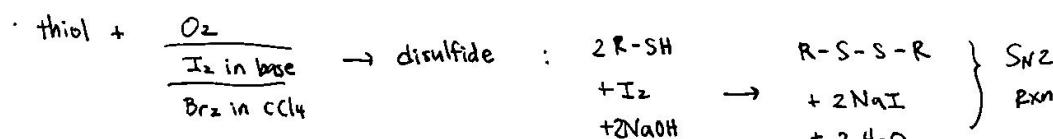
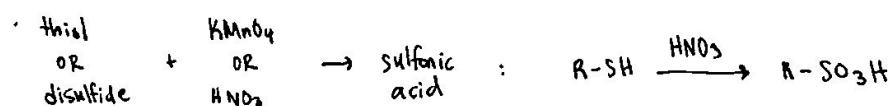


> octet expansion - atom surrounded by more than an octet of  $e^-$

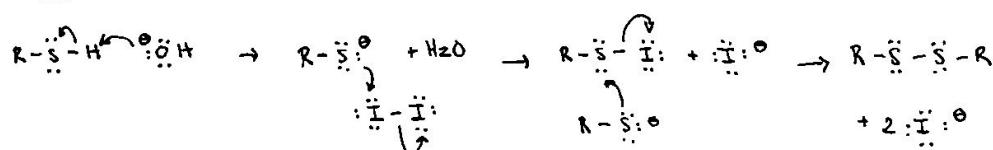
- elements with period  $\geq 3$
- unoccupied 3d orbital of rel low energy overlap with oxygen  $e^-$  pair



## &lt;&lt; Oxidation of Thiols



mechanism :



when thiol & disulfide both present, equilibrium of them stabilities.

## &lt;&lt; Synthesis of Alcohol

> organic synthesis - preparation of organic  $\text{w/o}$  compounds from other organic compound by the use of  $\text{i}^{(+)}$  rxn.

1. Hydroboration - oxidation of alkene
2. Oxymercuration - reduction of alkene
3. Acid - catalyzed hydration of alkene

## &lt;&lt; Retrosynthetic analysis

> multistep synthesis - synthesis involve a sequence of several rxns

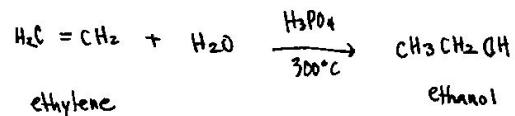
> target molecule - molecule to be synthesized

> work backward from target toward starting material

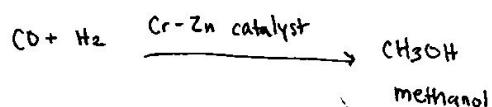
> retrosynthetic analysis - process of working backward from target

## &lt;&lt; Production &amp; Use of Ethanol &amp; Alcohol

→ Ethanol

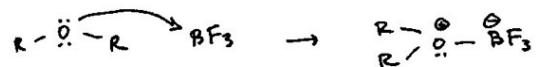


→ Methanol

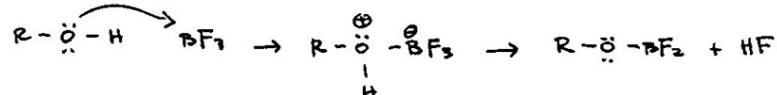


### Basicity of Ethers & Sulfides

- ethers are not acidic; ethers are weakly basic as alcohol
- sulfides are less basic than ether (element effect: S-H bond weaker than O-H)
- ethers are Lewis base, can solvate Grignard reagent & others



- water & alcohol are Lewis base, but can't solvate Lewis acid. they react.

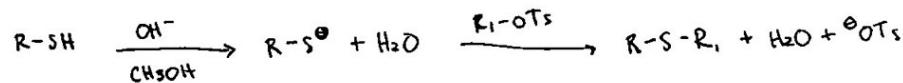
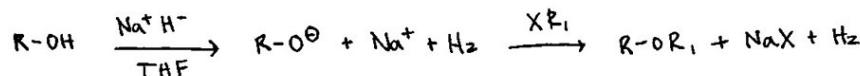


### Synthesis of Ethers and Sulfides

→ Williamson Ether Synthesis

→ preparation of ether by alkylation of an alkoxide

(sulfide by alkylation of a thiolate)



→ Mechanism

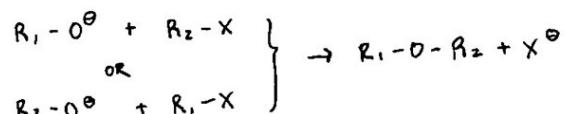
- $\text{S}_{\text{N}}2$  rxn
- only work with  $1^\circ$  alkyl halide ( $\text{S}_{\text{N}}2$ )



→ Choosing synthesis reactants

• two ways to get same result

• choose alkyl halide with greater  $\text{S}_{\text{N}}2$  reactivity



ether

<< Synthesis of Ester & Sulfide

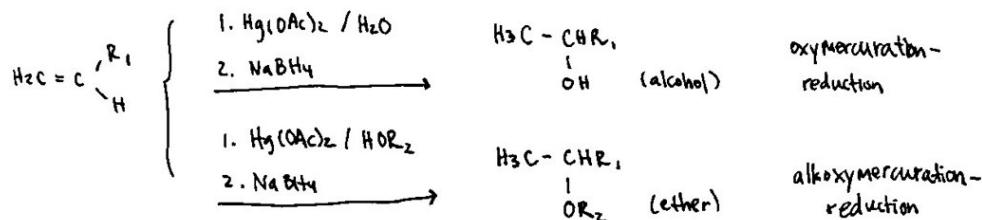
→ Alkoxymercuration - reduction of alkene

• same as oxymercuration-reduction, replace  $H_2O$  with alcohol  $ROH$ .

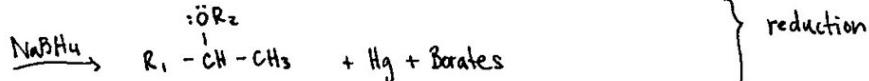
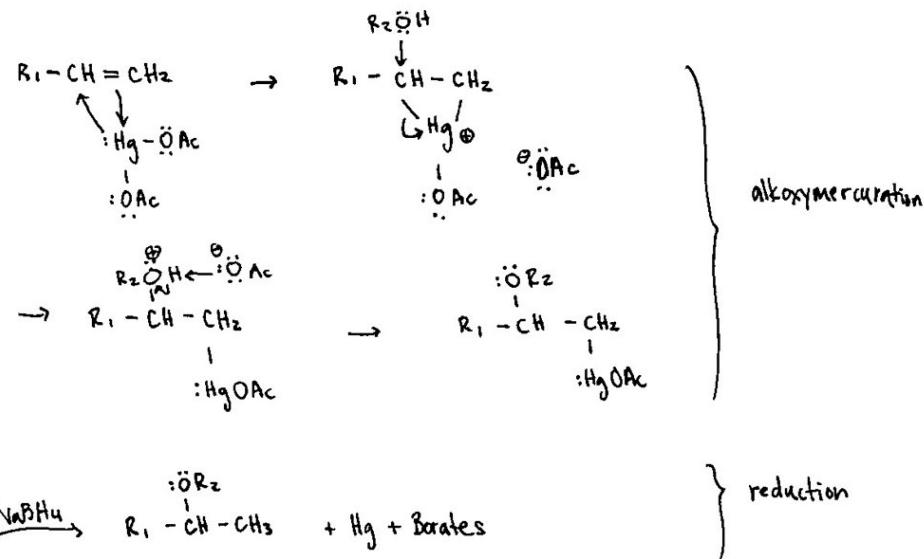
Markov.'s rule (CHEM 237)

$OH$  add to more alkyl

$H$  add to less alkyl



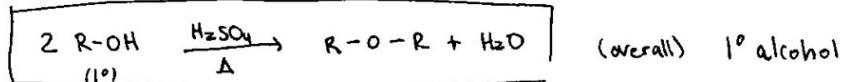
→ Mechanism



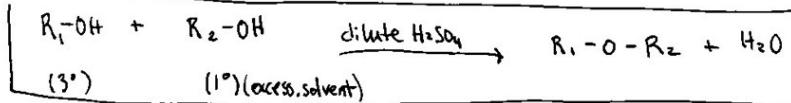
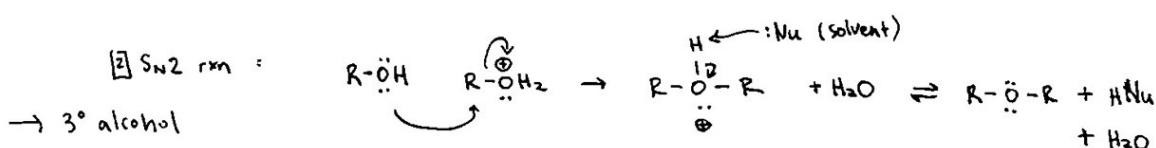
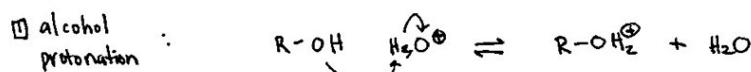
→ Ethers from Alcohol Dehydrations

→  $1^\circ$  alcohol

- 2  $1^\circ$  alcohol + acid + heat → sym. ether + water



•  $S_N2$  rxn for alcohol dehydration

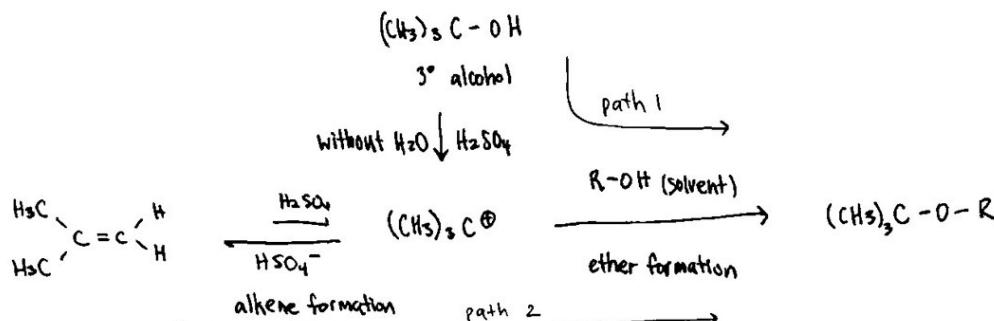


•  $3^\circ$  alcohol forms carbocation more readily than  $1^\circ$  alcohol (alkyl stabilize)

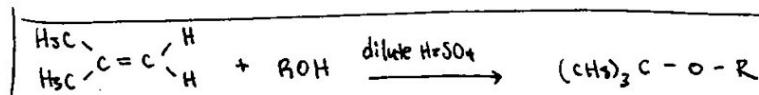
## &lt;&lt; Synthesis of Ether &amp; Sulfide

→ Ethers from Alkene Addition (3° alcohol)

- ether formation from 3° alcohol and dehydration of 3° alcohol are alternative branches of common mechanism.



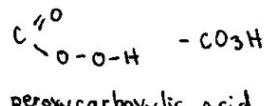
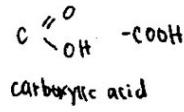
- ether can be formed from alkene, acid catalyst, and excess alcohol.



## &lt;&lt; Synthesis of Epoxide

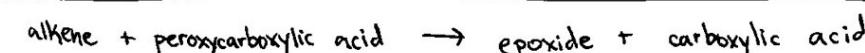
→ Oxidation of Alkenes with Peroxycarboxylic Acid

- peroxycarboxylic acid - carboxylic acid with  $-\text{OOH}$  instead of  $-\text{OH}$



- e.g. MCPBA, MMPP

- unstable

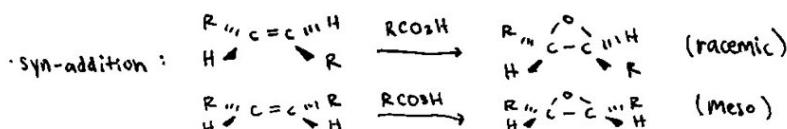
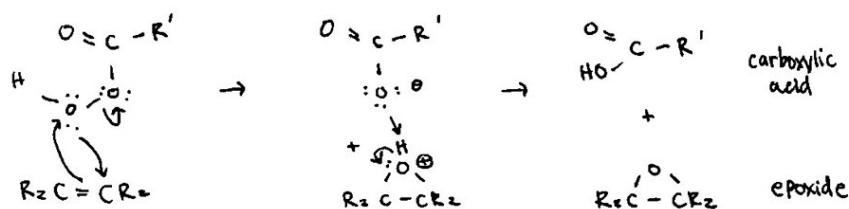


(overall)

- concerted electrophilic addition

- syn-addition

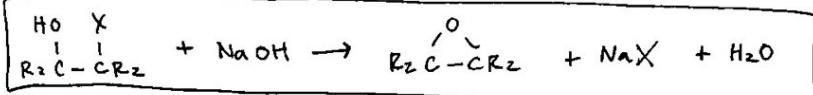
→ Mechanism



## Synthesis of Epoxide

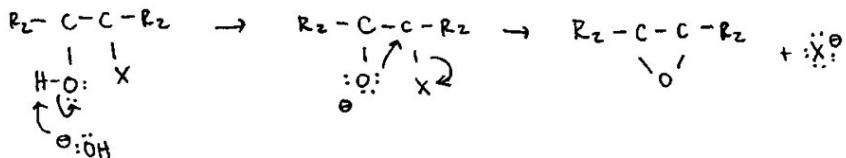
## → Cyclization of Halohydrins

• halohydrin + base → epoxide + water



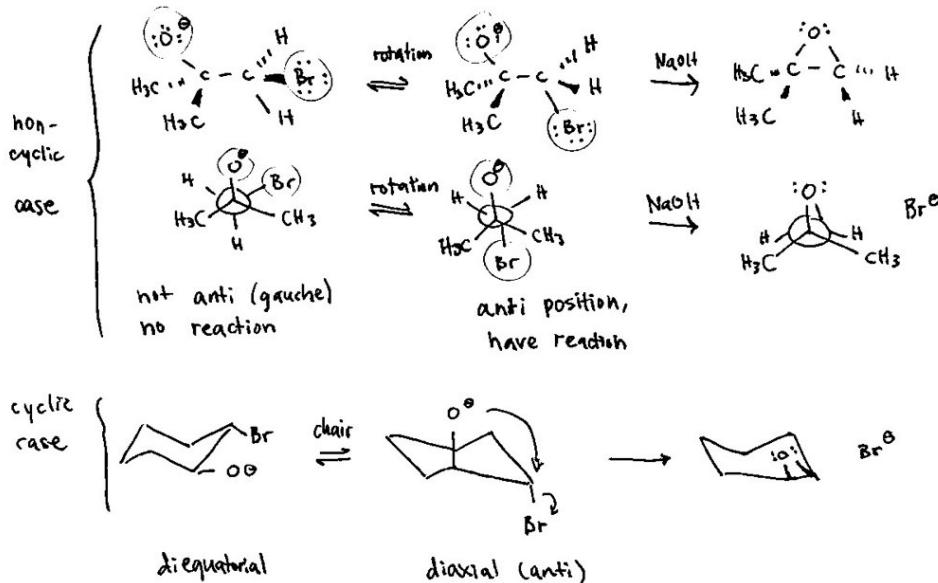
## → Mechanism

#### Intramolecular Williamson Ester synthesis



• Opposite-side substitution

• O and X must be anti (anti-periplanar), both axial in cyclic compound



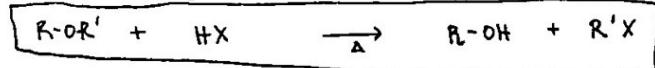
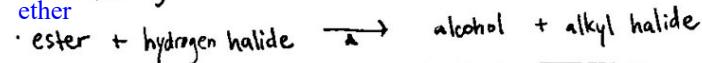
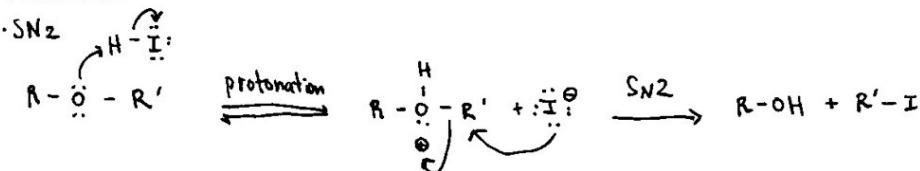
e<sup>-</sup>c cleavage of Ester ether

- ester nonreactive, used as solvent

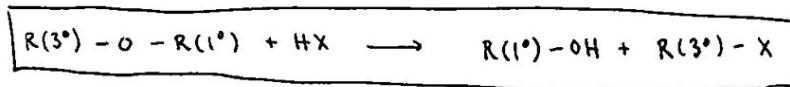
- no nucleophilic rxn since alkoxide is very basic  $\rightarrow$  bad leaving group
- ester do not react with base

 $\rightarrow$  1° Ester cleavage

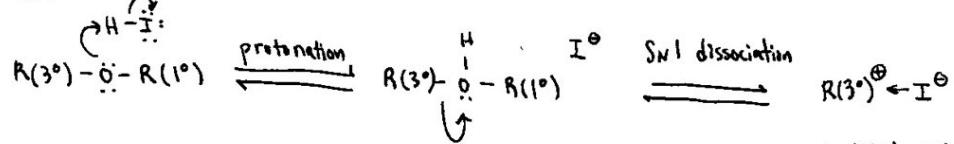
ether

 $\rightarrow$  Mechanism $\rightarrow$  3° Ester cleavage

ether

 $\rightarrow$  Mechanism

SN1



- tertiary carbocation more stable

- tertiary alkyl halide forms

- primary alcohol forms

« Nuc. Sub. rxn of Epoxide

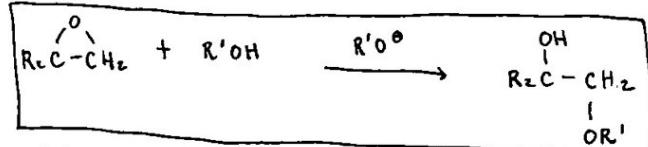
→ Ring-Opening Rxn under Basic Conditions

- S<sub>N</sub>2 rxn

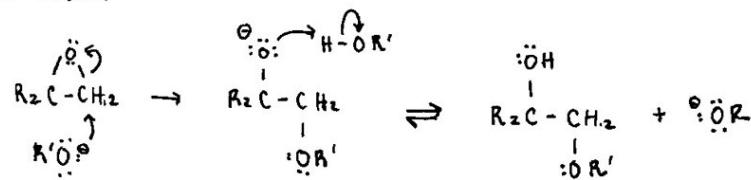
- epoxide oxygen as leaving group

- alkoxide as nucleophile (base)

- epoxide + alcohol (solvent)  $\xrightarrow{\text{alkoxide}}$  product with ester & alcohol group



→ Mechanism



- epoxide is a type of ether

- ring opening rxn is ether cleavage. (which doesn't occur in base for regular ester).

- epoxide can since it has angle strain → weak bond

- regioselectivity

- nucleophile attack less substituted C. (S<sub>N</sub>2 sterics)

- product -OH group at more alkyl sub.

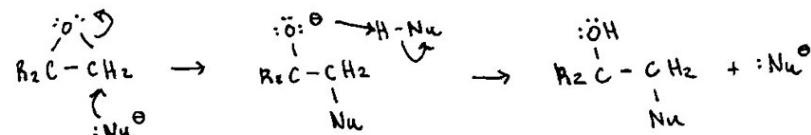
- stereochemistry

- inversion of config - opposite side substitution (S<sub>N</sub>2)

→ General Rxn

- can have any nucleophile

- can have asym. ester (regioselectivity applies)

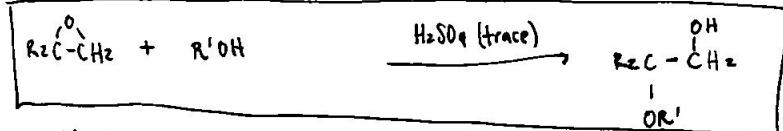


« Nuc. Sub. Rxn of Epoxide

→ Ring-Opening Rxn under Acidic Conditions

- epoxide very reactive, small amount of acid is enough

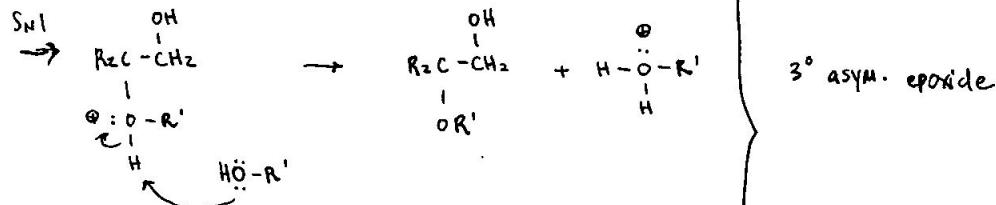
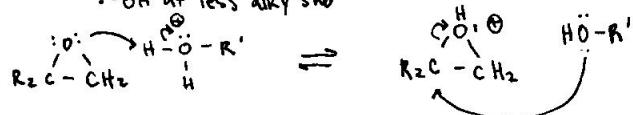
- epoxide + alcohol (solvent)  $\xrightarrow{\text{acid (trace)}}$  product with ether & alcohol group



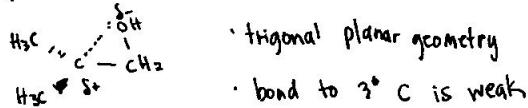
→ Mechanism

→ Regioselectivity

- nucleophile attacks more alkyl sub
- -OH at less alkyl sub



- 3° epoxide behave like 3° carbocation



• trigonal planar geometry

• bond to 3° C is weak

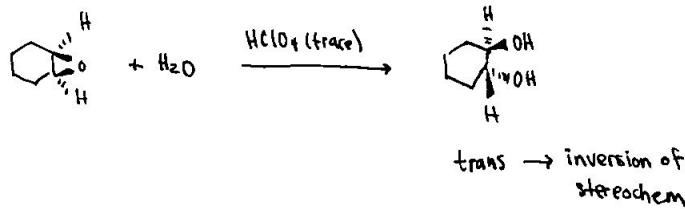
- S<sub>N</sub>1 with inversion of stereochemistry

- 2° epoxide give mixture of product

- favor -OH at more alkyl sub

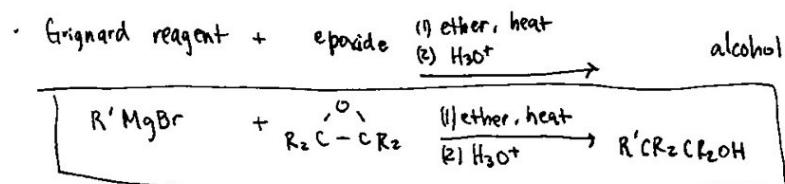
$\left. \right\} 2^\circ \text{ asym. epoxide}$

→ Glycol preparation

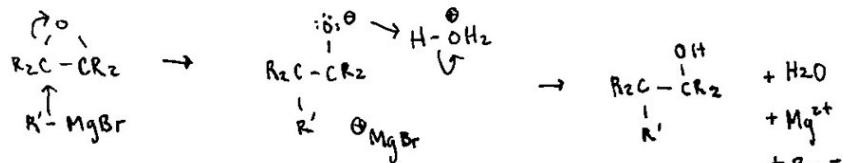


<< Nuc. Sub. Rxn of Epoxide

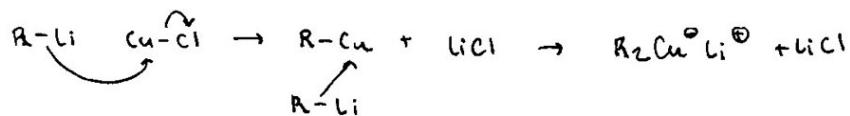
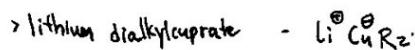
→ Rxn of Epoxides with Organometallic Reagents



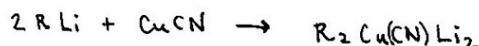
→ Mechanism



→ Organocuprate

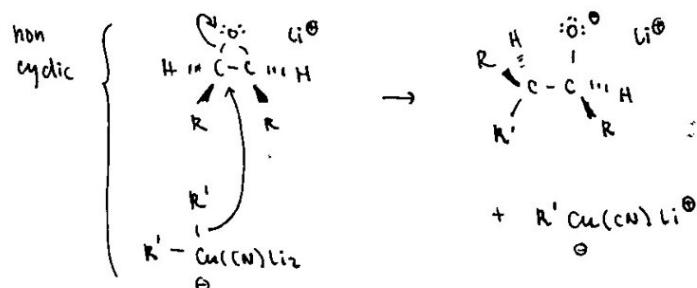
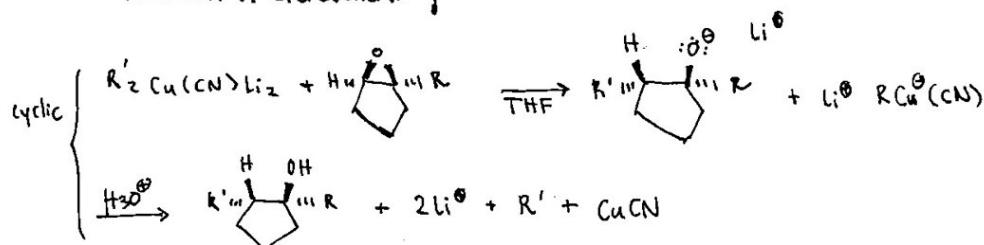


> higher-order organocuprate



→ Rxn Mechanism

- organocuprate attack less alkyl sub
- inversion of stereochemistry

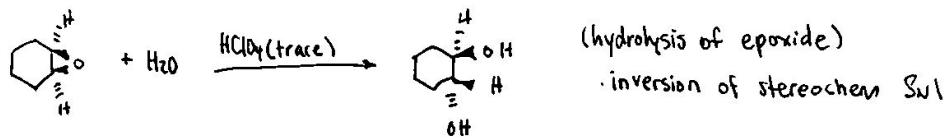


### Preparation of Glycols

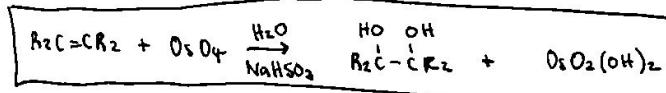
↳ glycol - compounds contain -OH group on diff C atoms.

↳ vicinal diol - diol which two -OH groups are at adjacent C.

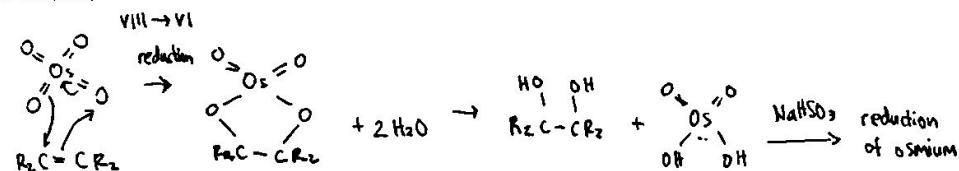
→ ring-opening of epoxide in acidic condition



→ oxidation of alkenes with osmium tetroxide ( $\text{OsO}_4$ )



→ Mechanism



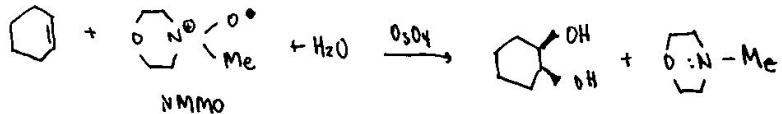
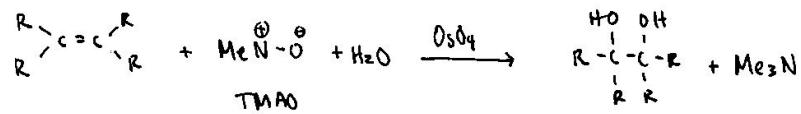
→ Drawback & Soln

•  $\text{OsO}_4$  toxic, expensive

• solution: recycle  $\text{OsO}_4$  using amine oxide ( $\text{R}_2\text{N}-\text{O}^\bullet$ ) during rxn

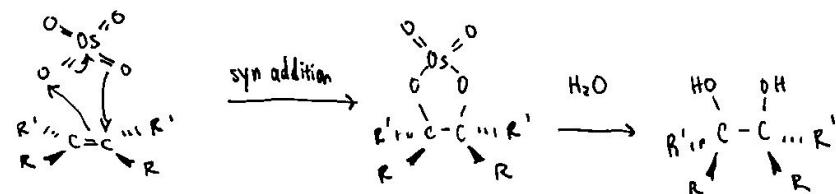


• reaction:



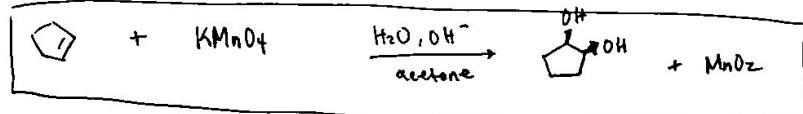
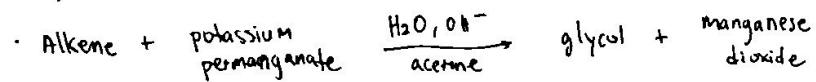
→ Stereochemistry

• syn addition, concerted



## Preparation of Glycol

$\rightarrow \text{KMnO}_4 + \text{alkene}$

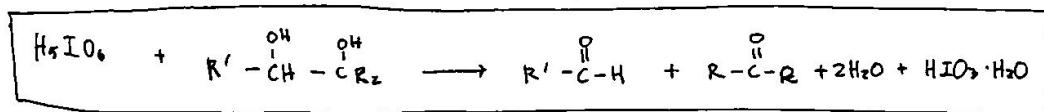


- syn-addition ( $\text{OsO}_4$  mechanism)

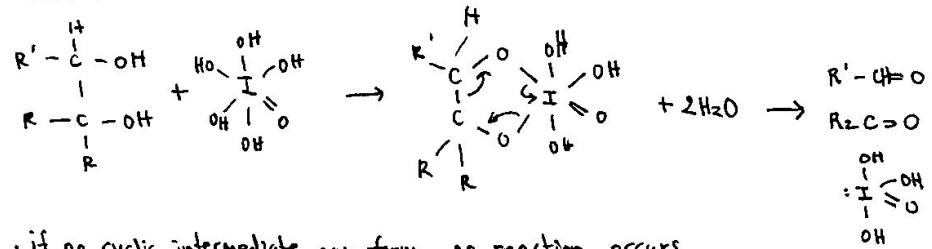
- cheap, but over-oxidation occurs

## Oxidative Cleavage of Glycol

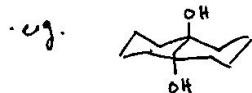
- periodic acid + glycol  $\xrightarrow{\text{dilute HOAc}}$  aldehyde + ketone +  $2\text{H}_2\text{O} + \text{HIO}_3 \cdot \text{H}_2\text{O}$



### Mechanism



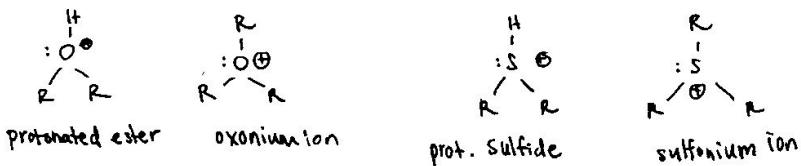
- if no cyclic intermediate can form, no reaction occurs



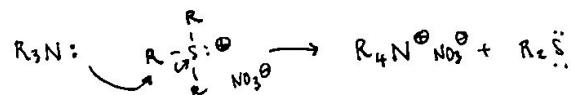
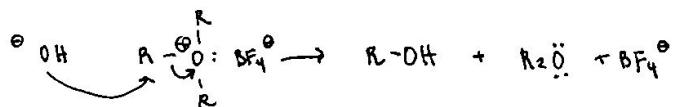
## Oxonium & Sulfonium Salt

- oxonium salt - compound where acidic H of protonated ether is replaced by alkyl group

- sulfonium salt - compound where acidic H of protonated sulfide is replaced by alkyl group



- Oxonium, sulfonium salt react with nucleophile in  $\text{S}_{\text{N}}2$  rxn



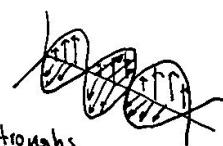
- Oxonium salt is very reactive alkylating agent

- Sulfonium salt less reactive.

## &lt;&lt; Intro to Spectroscopy

## → Electromagnetic Radiation

- perpendicular oscillating  $\vec{E}$  and  $\vec{B}$



- wavelength  $\lambda$  - distance between successive peaks / troughs

- frequency  $v$  - # of wavelength pass through a point per unit time

$$c = v\lambda = 3 \times 10^8 \text{ m/s}$$

$$T = \frac{1}{v}$$

- photon - light particle

$$E = hv = \frac{hc}{\lambda}$$

- electromagnetic spectrum - total range of em radiation

## → Absorption Spectroscopy

- absorption spectroscopy - absorption of em radiation is determined.

- spectrophotometer (Spectrometer) - instrument to perform abs spectroscopy.

- spectrum - graph of  $T$  vs  $\lambda$ , or  $I$  vs  $v$

- spectroscopy for structure determination.

- IR - functional group

- NMR - #, connectivity, functional group envir. of H, C

- UV-Vis - types of  $\pi - e^-$  system present.

## &lt;&lt; Infrared Spectroscopy

## → Infrared Spectrum

- wavenumber  $\tilde{\nu}$  - inverse of wavelength

$$\tilde{\nu} = \frac{1}{\lambda}$$

$$v = \frac{c}{\lambda} = c\tilde{\nu}$$

$$E = hv = \frac{hc}{\lambda} = hc\tilde{\nu} \quad (\text{SI unit})$$

- unit convention
 
$$\left. \begin{array}{l} \lambda : \mu\text{m} = 10^{-6} \text{ m} \\ \tilde{\nu} : \text{cm}^{-1} = 10^{-2} \text{ m}^{-1} \end{array} \right\}$$

$$\tilde{\nu} (\text{cm}^{-1}) = \frac{10^4 \text{ pm cm}^{-1}}{\lambda (\mu\text{m})}$$

- transmittance - ratio of intensity of transmitted light to intensity of incident light

$$\tau (\mu\text{m}) = \frac{10^4 \text{ pm cm}^{-1}}{\tilde{\nu} (\text{cm}^{-1})}$$

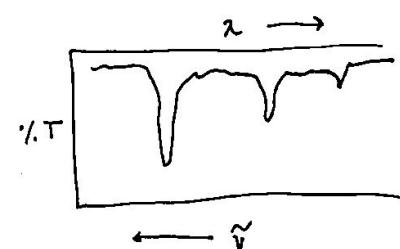
$$T = \frac{I}{I_0}$$

- absorbance - negative log of transmittance

$$A = -\log T = -\log\left(\frac{I}{I_0}\right) = \log\left(\frac{I_0}{I}\right)$$

$$A = \epsilon cl$$

$$[\epsilon] = \text{M}^{-1} \text{cm}^{-1}$$



### << Infrared Spectroscopy

→ Physical Basis of IR Spec.

- > bond vibration - bond undergo oscillatory stretching & bending motion
- > radiation transfer energy if freq of radiation match freq of vibration.

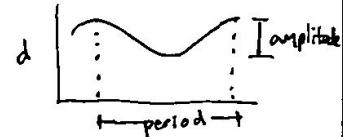
- > energy absorbed → vibrate in ↑ freq, ↑ amplitude
- > frequency doubles
- > energy is quantized

$$E_{hv} = E_1 - E_0$$

$$\Delta E = h\nu_0$$

$$h\nu_0 = \Delta E$$

← freq radiation = freq vibration



- > bonds vibrate with characteristic frequencies

### << Infrared Absorption & Chemical Structure

- > In all compounds, given functional group absorbs in same region of IR spectrum

- > 1000-1600 cm⁻¹ is fingerprint region - distinct, but hard to interpret

→ Factors determine IR Absorption Position

→ bond strength

$$\tilde{\nu} = \frac{1}{2\pi c} \sqrt{\frac{k}{\mu}} \quad \text{, where } \mu = \frac{M_1 M_2}{M_1 + M_2}$$

- > ↑ bond strength, ↑ k, ↑ bond dissociation E, ↑  $\tilde{\nu}$

→ Mass of atom

$$\tilde{\nu} = \frac{1}{2\pi c} \sqrt{\frac{k}{m}} \quad \text{, where } M \gg m$$

- > ↑ mass, ↓ vibration, ↓  $\tilde{\nu}$

- > lower mass atoms determine vibration freq.

→ type of vibration

- > stretching vibration - along line of chem. bond

- > bending vibration - not along line of chem. bond

- > bending at ↓  $\tilde{\nu}$ , ↓ E.

→ Factors Determine IR Intensity

- > ↑ # molecules (conc.) , ↑ intensity (↑ absorbing groups)

- > dipole moment determines the raise of IR signal

> infrared - inactive - vibration that occur but do no rise IR absorption. (no bond dipole)

> infrared - active - vibration that give rise to IR absorption. (has bond dipole)

> inactive { · symmetric molecule, no permanent bond dipole O=O } no net dipole

· symm. molecule, has bond dipole, but sym. stretch O=C=O,

> active { · nonsym. molecule, has bond dipole C-O }

· symm. molecule, has bond dipole, but unsym. stretch O=C=O } has net dipole

light interacts with polar bonds (but not nonpolar) b.c. its  $E$  exerts force on system of moving charges (vibrating bond dipole). When their freq. match, bond dipole gain energy, light absorbed (loss energy).

## << Functional Group Infrared Absorption

alkane	C-H	$2850 - 2960 \text{ cm}^{-1}$	Refer to cheatsheet
alkyl halide	C-X	(mass spec / NMR)	
alkyl fluoride	C-F	$1000 - 1100 \text{ cm}^{-1}$	
alkene	C=C	$1690 \text{ cm}^{-1}$	
alkenyl stretch	=C-H	$3000 \text{ cm}^{-1}$	
alkenyl bend	=C-H	$900 \text{ cm}^{-1}$	
alcohol	-OH	$3400 - 3600 \text{ cm}^{-1}$ (broad)	
alcohol ether	C-O	$1050 - 1200 \text{ cm}^{-1}$	

## Obtaining Infrared Spectrum

> infrared spectrometer - instrument of IR spectroscopy

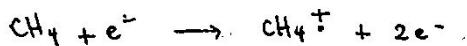
## Mass Spectrometry

## → Electron-Ionization Mass Spectra (Overview)

→ Mass spectrometer - instrument to obtain mass spectra

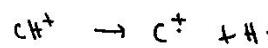
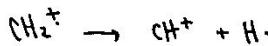
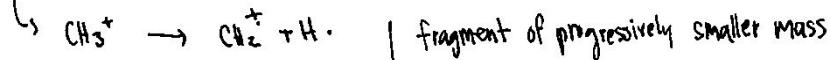
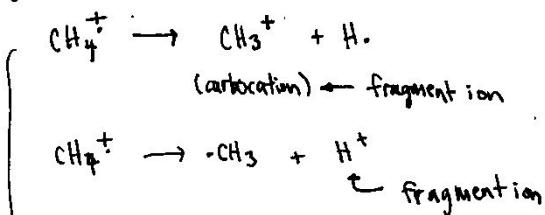
> Electron-Ionization Mass spec - compound vapoized and bombarded with e<sup>-</sup>

> radical cation - molecule lost an  $e^-$ , being both radical & cation



> fragmentation rxn - radical cation decomposes

> fragmentation - ionic product of fragmentation rxn



> mass-to-charge ratio - m/z (charge usually unit charge)

> Mass spectrum - graph of rel amount of each ion vs. mass/charge

> relative abundance - rel amount of each ion

> EI mass spectrum - Mass spec where ions are produced by e<sup>-</sup> ionization

## &lt;&lt; Mass Spectrometry

## → EI Mass Spec (cont.) (Overview)

- only ions are detected ; neutral molecule/radical not detected.

- only for molecules that can vaporize in vacuum.

- purpose
  - determine molecular mass
  - determine partial structure (by fragment ion analysis)
  - confirm structure of compounds with suspected structure

ionization w/o fragmentation  
↑

> molecular ion - ion derived from  $e^-$  ejection before fragmentation takes place  
(M)

- molecular ion occurs at  $\frac{M}{2}$  value equal to molecular mass of sample molecule (except for isotopes)

> base peak - ion of greatest rel abundance in mass spec.

- aka largest peak
- assigned 100%.

## → Isotopic Peaks

- isotopes of atoms may have diff mass
- Each isotopic compound contributes a peak with rel abundance  $\propto$  to its amount
- Amount of isotopic compound  $\propto$  natural abundance.
- rel abundance  $\propto$  amount  $\propto$  natural abundance

$$\text{rel abundance of isotopic compound} = \frac{\text{abundance of isotope compound}}{\text{abundance of main compound}} = \left( \frac{\# \text{ of atoms of that element in compound}}{\text{abundant}} \right) \cdot \left( \frac{\text{nature abun of isotope}}{\text{nature abun of main}} \right)$$

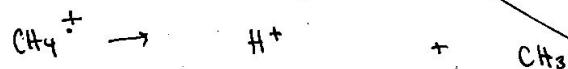
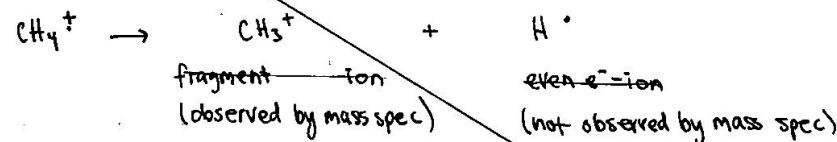
- Isotopic enrichment help determine fate of specific atom in mechanisms

## → Fragmentation

→ fragment ion - cation product of fragmentation rxn

→ even-electron ion - radical product (with frag. ion of cation with no unpaired  $e^-$ )

→ odd-electron ion - neutral molecule product (with frag. ion of radical cation of molecular ion)

→ Fragmentation with even- $e^-$  ion product

## << Mass Spectrometry

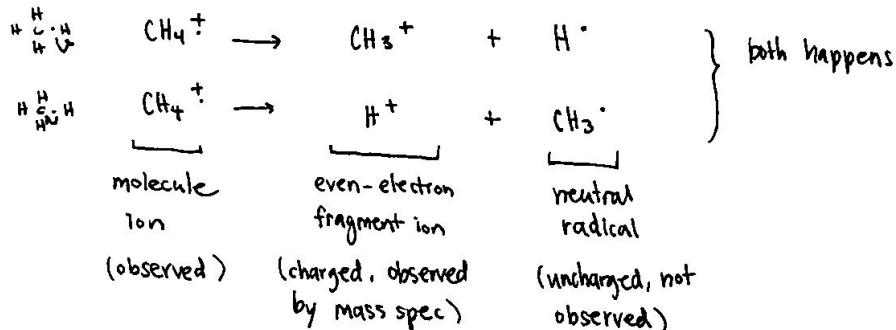
→ Fragmentation

→ fragment ion - cation product of fragmentation rxn

> even-electron ion - cation with no unpaired  $e^-$  (other product: radical)

> odd- $e^-$  ion - radical cation (other product: neutral molecule)

→ Fragmentation producing even- $e^-$  ion



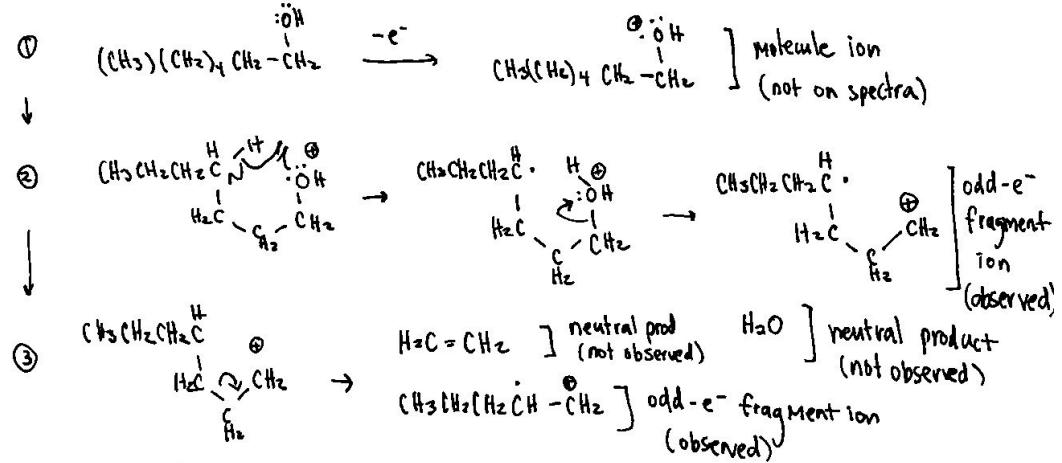
- molecule ion present in spectra
  - both product present in spectra

- both product present in spectra, since  $e^-$  can go either way

→ Fragmentation producing odd- $e^-$  ion

- molecule ion NOT present in spectra (fast rxn)

- only one ion present in spectra (the other neutral)



## → Spectra Analysis

- If molecule only has C, H, O, X { even- $e^-$  ion has odd mass  
odd- $e^-$  ion has even mass

- Height of peak determined by ion stability

- ↑ peak, ↑ abundance, ↑ stability (use carbocation stability analysis)  
(instability → decomposition)

- for molecular ion, { only has C, H, O → even mass  
                  + even N      → even mass  
                  + odd N      → odd mass

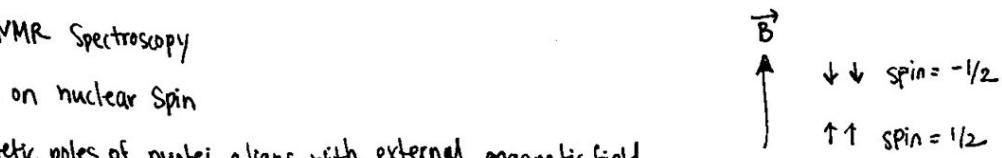
## &lt;&lt; Overview of Proton NMR Spectroscopy

- proton NMR ( $^1\text{H}$  NMR) detects proton by spin
- > operating frequency ( $\nu_0$ )
- > resonance, absorption, line - peaks in NMR
- > chemical shift - position of peaks
- > reference - tetramethylsilane (TMS)  $\text{Si}(\text{CH}_3)_4$
- > NMR spectrum of compounds has separate resonance for each chemically nonequiv. ~~nuclei~~ nuclei ( $\text{H}$ )
- chem shift determined by nearby group
- size of peak proportional to # proton contributing to absorption
- splitting of peak determines # proton on adjacent C.

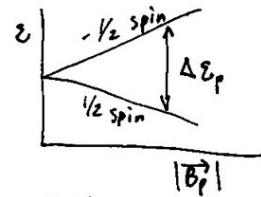
NMR Solvents

- chloroform-d
- acetone-d<sub>6</sub>
- deuterium oxide

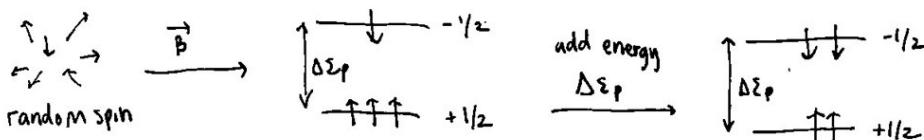
## &lt;&lt; Physics of NMR Spectroscopy



- based on nuclear Spin
- Magnetic poles of nuclei aligns with external magnetic field .
- diff spin has diff energy
  - $+1/2$  has lower E than  $-1/2$  , under  $\vec{B}$
- > fundamental eq of NMR:  $\Delta \varepsilon_p = \frac{\hbar \gamma_H}{2\pi} |\vec{B}_p|$ 
  - h - Planck's constant  $= 3.99 \times 10^{-34} \text{ J s mol}^{-1}$
  - $|\vec{B}_p|$  - magnetic field at proton (magnitude)
  - $\gamma_H$  - gyromagnetic ratio of proton  $= 26753 \text{ rad gauss}^{-1}\text{s}^{-1}$
  - $\Delta \varepsilon_p$  - energy diff of two spin states of proton
  - If  $|\vec{B}_p| = 0$ ,  $\Delta \varepsilon_p = 0$
  - $|\vec{B}_p| \uparrow$ ,  $\Delta \varepsilon_p \uparrow$



> nuclear magnetic resonance (NMR) -  $+1/2$  proton absorb  $\Delta \varepsilon_p$  to invert spin to  $-1/2$



> NMR Spectrometer - absorption spectrometer detecting NMR

> NMR Spectroscopy - study of NMR absorption

- frequency of absorption -  $v_p = \frac{E_p}{h} = \frac{\Delta \varepsilon_p}{h} = \frac{\gamma_H}{2\pi} |\vec{B}_p| \Rightarrow \text{radiowaves}$

## Chemical Shift in NMR Spectra

shift caused by two types of proton in  $\vec{B}_p$  absorbs diff freq.

Effective local  $\vec{B}_p$  for proton  $\neq$  external  $\vec{B}_0$  provided

$$\vec{B}_p < \vec{B}_0$$

$e^-$  has their magnetic field

> shielding - reduction of local magnetic field by nearby  $e^-$

atom  $e^-$  neg  $\downarrow$ ,  $e^-$  at proton  $\uparrow$ ,  $e^-$  shielding  $\uparrow$  (Si)

atom  $e^-$  neg  $\uparrow$ ,  $e^-$  at proton  $\downarrow$ ,  $e^-$  shielding  $\downarrow$  (D, Cl)

$$B_p(e^- \text{ neg} \downarrow) < B_p(e^- \text{ neg} \uparrow)$$

$$B_p(e^- \text{ neg} \downarrow) < B_p(e^- \text{ neg} \uparrow)$$

$$\nu(e^- \text{ neg} \downarrow) < \nu(e^- \text{ neg} \uparrow) \quad (\nu_p \propto B_p)$$

$$\nu(e^- \text{ neg} \downarrow) - \nu(\text{TMS}) < \nu(e^- \text{ neg} \uparrow) - \nu(\text{TMS})$$

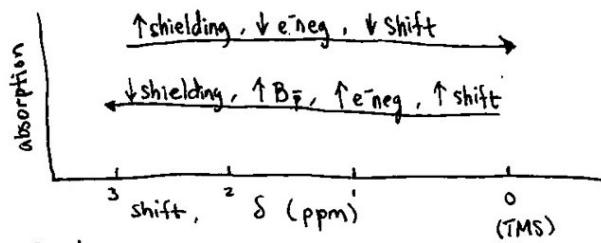
$$\Delta\nu(e^- \text{ neg} \downarrow) < \Delta\nu(e^- \text{ neg} \uparrow)$$

$$\boxed{\text{shift of } e^- \text{ neg} \downarrow < \text{shift of } e^- \text{ neg} \uparrow}$$

> shift - frequency diff from reference TMS in Hz.

$$\frac{\Delta\nu(e^- \text{ neg} \downarrow)}{\nu_0} = \frac{\Delta\nu(e^- \text{ neg} \uparrow)}{\nu_0}$$

$$\boxed{\delta(e^- \text{ neg} \downarrow) < \delta(e^- \text{ neg} \uparrow)} \quad (\text{ppm})$$



→ Shift Scale

shift in Hz is proportional to  $B_0$  of spectrometer

$\delta$  scale is independent of spectrometer

$$\delta(\text{ppm}) = \frac{\Delta\nu \text{ in Hz}}{\nu_0 \text{ in MHz}}$$

## &lt;&lt; Chemical Shift &amp; Structure

- shift affected by e<sup>-</sup>neg nearby groups

→ Factors affecting Chemical Shift

- ↑ shift, ↑ e<sup>-</sup>neg of near groups

- ↑ shift, ↑ # of e<sup>-</sup>neg near groups

- ↑ shift, ↓ distance between proton & e<sup>-</sup>neg near groups

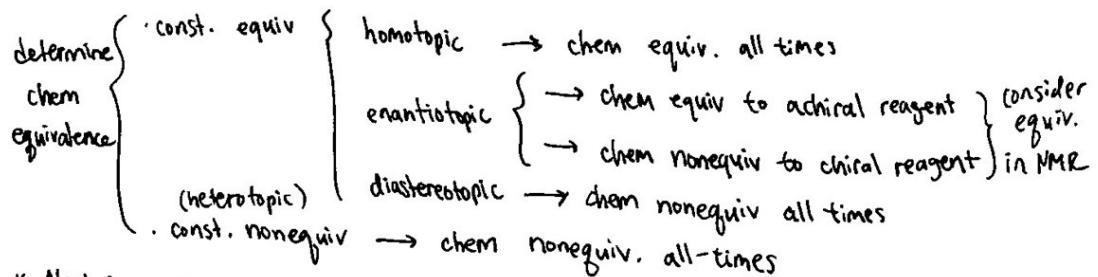
→ General Observations

- methyl protons (-CH<sub>3</sub>) - at lower end of shift
- methylene proton (-RCH<sub>2</sub>) - to higher than methyl → +0.1 δ
- methine proton (-R<sub>2</sub>CH) - to higher than methylene → +0.1 δ

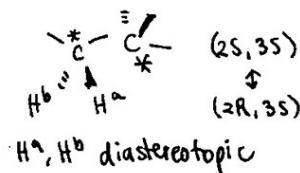
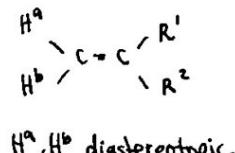
- shift of proton affected by both groups nearby if 1<sup>+</sup> functional group present.

## &lt;&lt; Number of Peaks

- diff shift ⇔ diff chem environment ⇔ chem. nonequiv. proton



\* Alert:



## &lt;&lt; Integration

> integration - total area under peak

- relative height ∝ # proton contributing to peak

- only gives ratio of # proton

## << Spin-Spin Splitting

> Split - NMR for a set of equiv. nuclei appears as more than one line

### → Splitting Rule

- $n$  adjacent protons cause NMR of observed proton split into  $n+1$  lines
- splitting is mutual

> Coupled - two sets of protons split each other

- splitting not observed between chem equiv. proton.

- with saturated C, splitting not observed between protons on nonadjacent C.

> coupling constant ( $J$ ) - spacing between adjacent peaks of a splitting pattern in Hz  
 • two coupled protons must have same  $J$ .

- $J$  does not vary with operating freq.  $\nu_0$

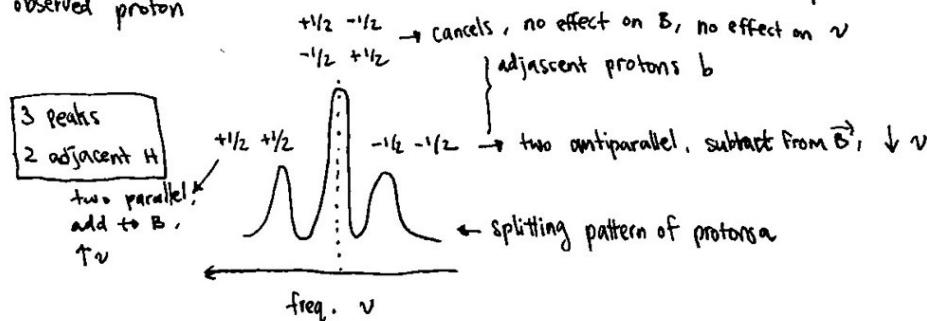
- chem shift read as midpoint of splitting

### → Relative Intensity of Lines in Splitting

# equiv. adjacent H	# lines in splitting ( $n+1$ )	Relative line intensity
0	1 singlet	1
1	2 doublet	1 1
2	3 triplet	1 2 1
3	4 quartet	1 3 3 1
4	5 quintet	1 4 6 4 1
:	:	:

### → Reason of Splitting

- magnetic field caused by spin of neighboring proton affects total field experienced by observed proton



- + spin add to  $\vec{B}$ ,  $\uparrow \nu$

- - spin subtract from  $\vec{B}$ ,  $\downarrow \nu$

- + and - cancels.

} splitting gives connectivity

## &lt;&lt; Solving Structures from NMR Spectra

- abbreviation :  $\delta$  [chemical shift] ( [integration] , splitting , coupling constant)  
e.g.  $\delta$  1.67 (3H, t,  $J = 7.2\text{ Hz}$ )

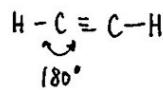
→ Method

1. molecular formula → unsaturation number  
functional groups , rings
2. # absorption peaks → # chem nonequiv H
3. total integration  
molecular formula } → # integration / proton
4. integration → # H in each set
5. shift → functional groups nearby
6. splitting → # adjacent nonequiv. H

## &lt;&lt; Structure &amp; Bonding in Alkyne

• alkyne - hydrocarbon with  $C \equiv C$  triple bond

•  $C \equiv C$  shorter than  $C=C$ ,  $C-C$

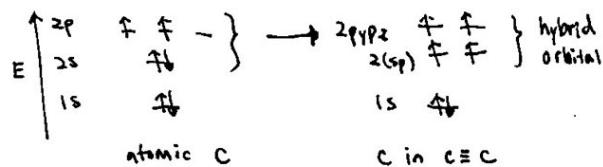


• linear - bond angle  $180^\circ$

• no cis-trans isomer

• no cycloalkynes smaller than cyclooctyne

•  $sp$  hybridization



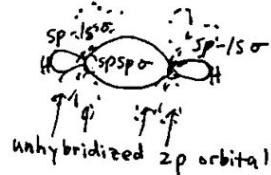
•  $e^-$  closer to nucleus  
than  $sp^2$ ,  $sp^3$

• shorter, stronger  $C \equiv C$ ,  $C-H$  bond

•  $sp-sp$  or bond ( $C \equiv C$ )

•  $sp-1s$  or bond ( $C-H$ )

} more s-character,  $\downarrow E$



• left-over  $2p$  orbitals

• 2  $\pi$  bonds

• mutually perpendicular - surrounds the molecule

• less stable

•  $\uparrow \Delta H_f^\circ$

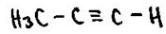
• less stable than isomeric alkene

• less stable if  $C \equiv C$  at the end

## &lt;&lt; Nomenclature of Alkynes

→ Common Name

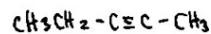
• named as derivative of parent compound acetylene.



methylacetylene

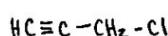


dimethylacetylene



ethylmethylacetylene

• named as derivative of propargyl group  $HC \equiv C-CH_2-$

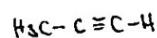


propargyl chloride

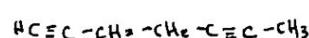
→ IUPAC

• use "-yne"

• use lowest double/triple bond first



propane

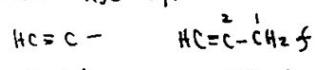


1,5-heptadiyne

• if ambiguous, then use double

bond first

• substituent use "-yl"



ethynyl

2-propynyl

## &lt;&lt; Physical Properties of Alkynes

## → Boiling Points &amp; Solubilities

- boiling pt similar to analog alkene & alkane
- lower density than H<sub>2</sub>O
- not soluble in H<sub>2</sub>O

## → IR Spectroscopy

- 2100-2200 cm<sup>-1</sup> (need asymmetry to be obvious)
- symmetric alkyne has weak signal
- ↑ bond strength, ↑ ν, up field
- ≡C-H at 3300 cm<sup>-1</sup>

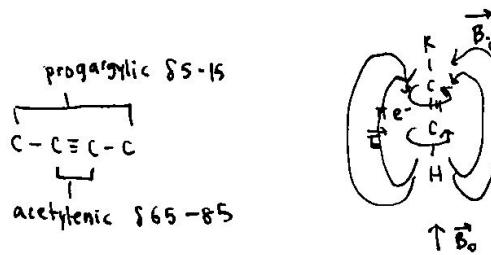
## → NMR Spectroscopy

→ <sup>1</sup>H NMR

- acetylenic δ 1.7-2.5 -C≡C-H (vinylic for C=C δ 4.9-5.5)
- propargylic δ 1.8-2.2 -C≡C-C-H (allylic for C=C δ 1.8-2.2)
- have small chem shift ∵ induced B<sub>i</sub> by π e<sup>-</sup> opposes B<sub>o</sub>, so C≡C-H in the axis has reduced local B.

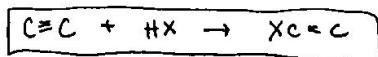
→ <sup>13</sup>C NMR

- δ 65-85, lower than alkene (acetylenic)
- δ 9-15, propargylic



## &lt;&lt; Addition Reaction of the Triple Bond

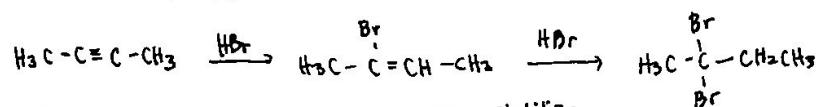
- alkyne + HX → alkene halide



- regioselectivity: Markov
- Br to alkyl
- reversed in presence of peroxide (free radical rxn)

• kinetics: slower than alkene

• second addition to substituted alkene can happen, but slower

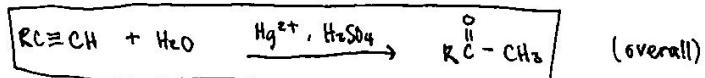
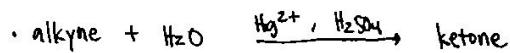


• add to C with Br since resonance stabilize

• slower ∵ polar effect of Br destabilize carbocation

Conversion of Alkynes to Aldehyde & Ketone

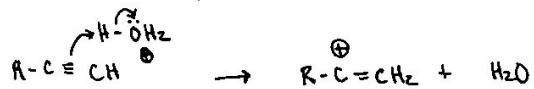
Hydration of Alkynes



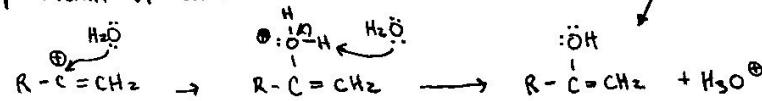
• alkyne hydration is irreversible.

→ Mechanism (Acid-Catalyzed Hydration)

① production of vinyl cation



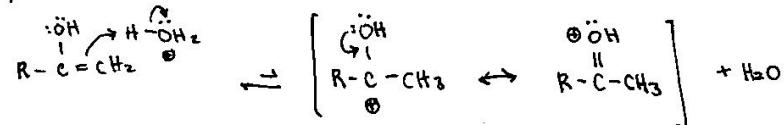
② production of enol



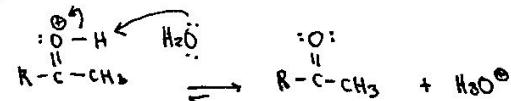
• enols are converted to ketone by  $K_{eq} \gg 1 \rightarrow$  irreversible

• enol is stable, but ketone is even more stable : C=O more stable than C=C

③ protonation of enol



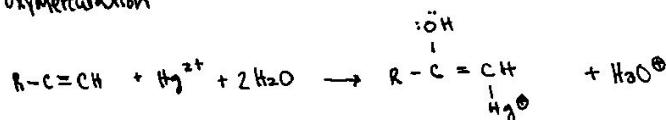
④ production of ketone



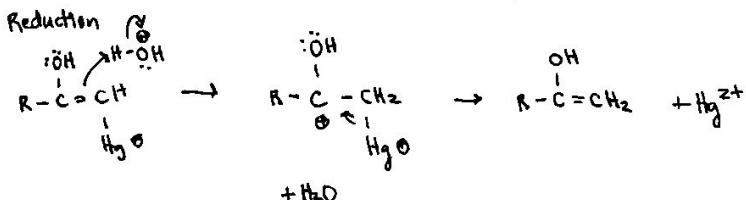
→ Mechanism (Hg<sup>2+</sup>-catalyzed hydration)

• like oxymercuration-reduction

① Oxymercuration

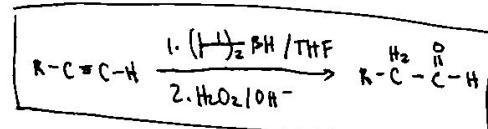
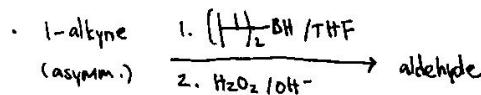
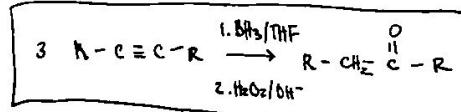
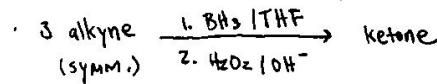


② Reduction

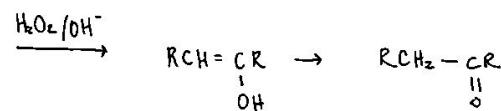
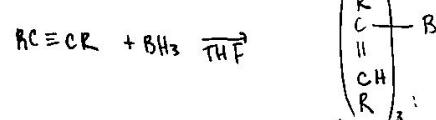


## << Conversion of Alkyne to Aldehyde & Ketone

### → Hydroboration - Oxidation of Alkyne



→ Mechanism with  $\text{BH}_3$

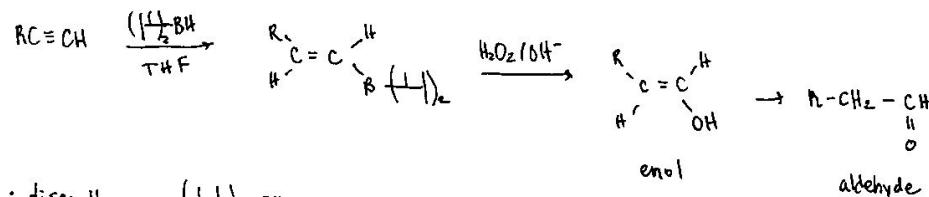


- second addition of  $\text{BH}_3$  to this is possible.

- less controlled

Addition to 1-alkyne (asym.) cannot be prevented unless change reagent.

→ Mechanism with  $R_2B\text{H}$

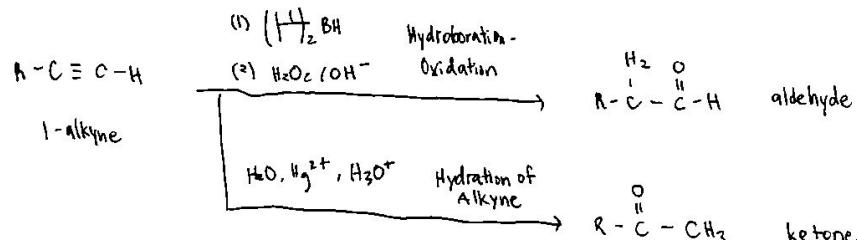


- disiamylborane  $(\text{H})_2\text{BH}$  is highly branched
    - steric effect interfere with second addition.
  - regiochemistry

- $B \rightarrow$  less sub
- $H \rightarrow$  more sub

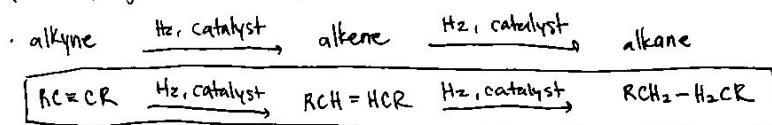
## → Conclusion

→ Complementary Methods to prepare Aldehyde & Ketone



## &lt;&lt; Reduction of Alkyne

→ Catalytic Hydrogenation of Alkyne (cis-alkene produced)

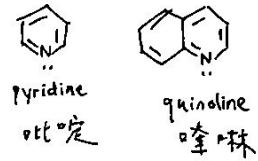


> catalyst poison - disturbs action of catalyst

- stops reaction with alkene for isolation

• e.g.  $\text{Pb}^{2+}$ , pyridine, quinoline

> Lindlar catalyst - prepared by  $\text{Pd/CaCO}_3 + \text{Pb(OAc)}_2$

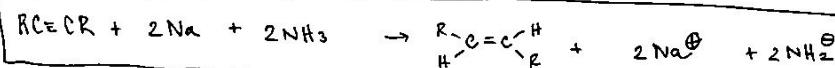


## • Regioselectivity

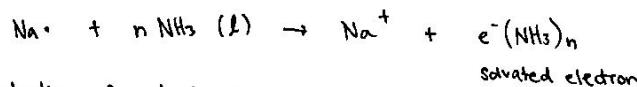
- syn-addition, gives cis-alkene

→ Reduction of Alkyne with Na in Liquid Ammonia ( $\text{NH}_3$ ) (trans-alkene produced)

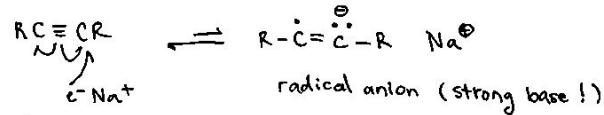
- alkyne + sodium + ammonia → trans-alkene + sodium ion



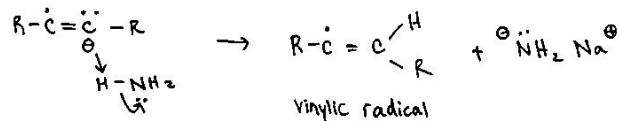
## → Mechanism

① Solvation of  $e^-$ 

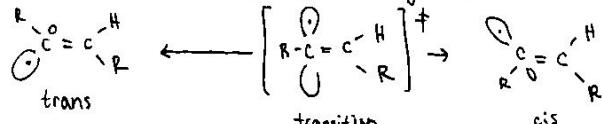
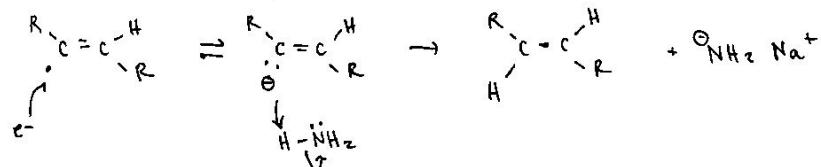
## ② production of radical anion



## ③ production of vinylic radical



## ④ Rapid interconversion favors trans config due to sterics effect

⑤ Accept  $e^-$ , form anion, protonate

## &lt;&lt; Acidity of 1-Alkyne

## → Acetylenic Anion

> carbanion - conjugate base of hydrocarbon, a carbo cation

• formed by reacting with strong base



> alkyl anion - conj. base of alkane



less acidic

> vinylic anion - conj. base of alkene



(all strong bases)

> acetylenic anion - conj. base of alkyne

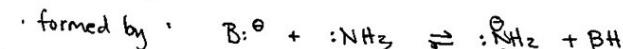


more acidic

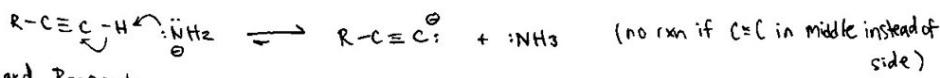
• alkyl & vinylic anion not formed ∵ not acidic

• acetylenic anion form ∵ weakly acidic

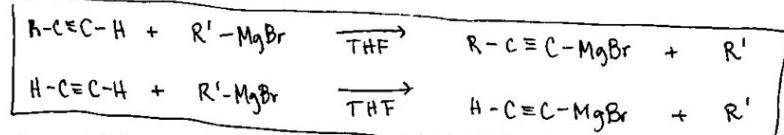
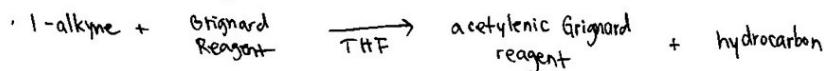
• react with strong base sodium amide (sodamide)  $\text{NaNH}_2$



• reaction highly favorable



## → Acetylenic Grignard Reagent



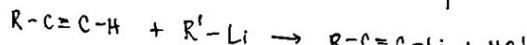
> transmetalation - a rxn that metal is transferred from one carbon to another

• rxn is acid-base in nature.

•  $\text{R}'^{\ominus}$  is a stronger base than  $\text{R-C}\equiv\text{C}^{\ominus}$

• rxn favors weaker base

• organolithium reagent can be prepared similarly

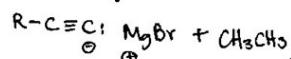
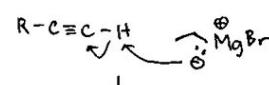


→ Factors affecting acidity of hydrocarbon

• ↑ bond order, ↑ bond strength, ↑ bond dissociation E (not major factor of acidity)

• ↑ bond order, ↑ s character, ↓ nuclear screening, ↑ e<sup>-</sup> neg., ↑ H acidity

/ view rxn as ionic:



• similar trend hold for nitrogen



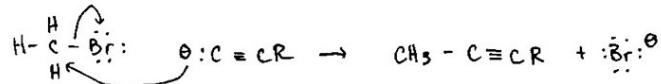
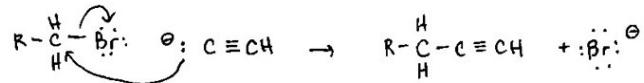
↔ acidity

<< Acidity of 1-Alkyne

→ Acetylenic Anion as Nucleophile

• acetylenic anion is strong base, but still less basic to alkyl anion / vinylic anion.

• good base → good nucleophile → S<sub>N</sub>2 rxn



• Makes new C-C bond!

... Structure & Stability of Diene

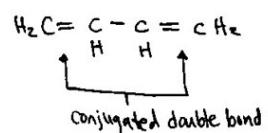
> diene - compounds with two C=C

> conjugated diene - two double bond separated by a single bond

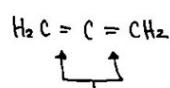
> conjugated double bond - C=C in conjugated diene

> cumulene - one carbon participate in two carbon-carbon double bond

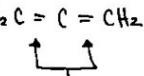
> cumulated double bond - C=C in cumulene



conjugated diene



cumulene

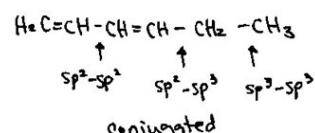
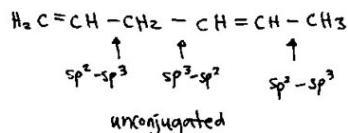


cumulated double bond

→ Stability of Conjugated Diene

• conjugation provides extra stability

•  $\sigma$  bond with more s character → ↑ stability (with tradeoff)

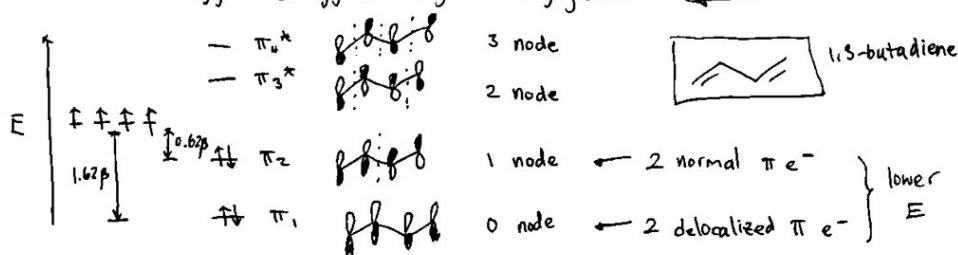


• MO theory: conjugated  $\pi$  system

> beta ( $\beta$ ) - negative energy unit (positive value = less E = More Stable)

> delocalized - e<sup>-</sup> in orbital spread across entire molecule

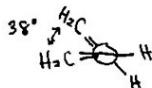
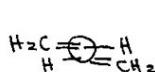
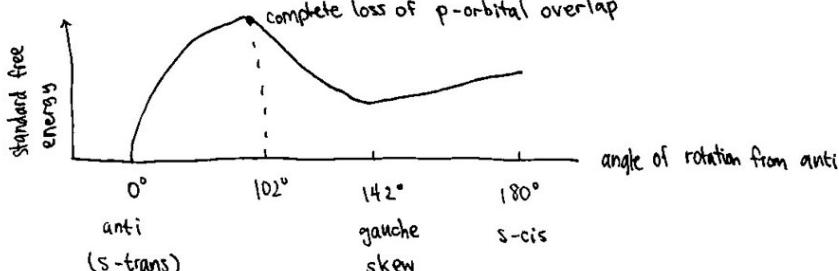
> delocalization energy - energy advantage of conjugation



→ Structure of Conjugated Diene

• ↑ s character, ↑ bond strength, ↓ bond length

complete loss of p-orbital overlap



coplanar p orbital

Vander Waals sterics

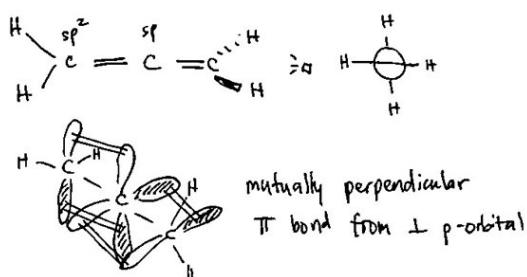
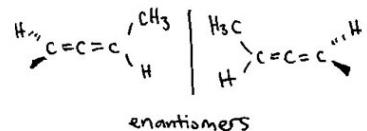
## << Structure & Stability of Diene

### → Structure & Stability of Cumulated Diene

- sp-hybridized ( $180^\circ$ ) of C with two double bond

- two  $\pi$  bond are perpendicular
  - does NOT overlap
  - p orbitals are perpendicular

- can be chiral without asym. C



- cumulated diene is least stable.

## << UV-Vis Spectroscopy (Electronic Spec)

> UV-Vis spectroscopy - in ultraviolet & visible range (200-750 nm)

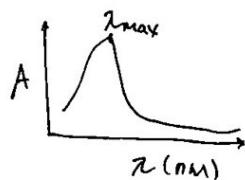
### → UV-Vis Spectrum

- Wavelength in nm on x axis
- Absorbance on y axis  $A = \log \left( \frac{I_0}{I} \right)$

### > Beer's law

$$A = \epsilon \ell c$$

- $\epsilon$  [ $M^{-1}cm^{-1}$ ] molar extinction coefficient ( $10^4$ - $10^5$  for conj. molecule)
- c [M] concentration
- $\ell$  [cm] path length



### → Physical Basis

- $\pi e^-$  & unshared e- pair absorb UV-Vis radiation
  - conjugated  $\pi e^-$  has higher  $\lambda_{max}$  than normal  $\pi e^-$

- UV-Vis spec diagnoses conjugated double & triple bond

> Chromophore - structural feature of a molecule responsible for its UV-Vis Absorption.

- absorption mechanism -  $\pi \rightarrow \pi^*$  transition for conj. molecule (ground  $\rightarrow$  excited)

### → Conjugated Alkenes

- $\uparrow$  length of conj.  $\pi$  system  $\cdot \uparrow \lambda_{max}$

$$\Delta E = h\nu = \frac{hc}{\lambda}$$

• HOMO  $\rightarrow$  LUMO transition

•  $\downarrow \Delta E$  gap,  $\uparrow$  length of conj.  $\pi$  system ( $\#$   $\pi$  bond)

- conformation of diene unit about central single bond

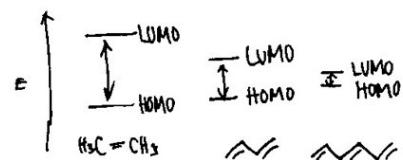
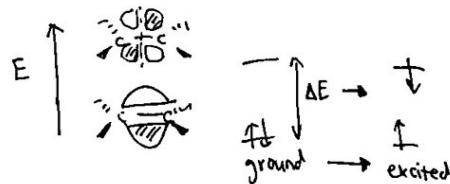
• s-cis,  $\uparrow \lambda_{max}$ ,  $\downarrow \epsilon$

• s-trans,  $\downarrow \lambda_{max}$ ,  $\uparrow \epsilon$

- alkyl substitution at double bond

•  $\uparrow$  alkyl sub,  $\uparrow \lambda_{max}$

• 5nm / alkyl group



## &lt;&lt; Fluorescence

> fluorescence - emission of light in visible range from compounds that absorb UV light.

- light emission to loss extra energy from HOMO  $\rightarrow$  LUMO

- emitted light has lower  $\downarrow E$ , higher  $\uparrow \lambda$  than absorbed

> Stokes shift - wavelength shift of emitted light from absorbed

- $\pi \rightarrow \pi^*$  transition cause change to optimal bond length

- bond start to stretch & compress to the optimal length

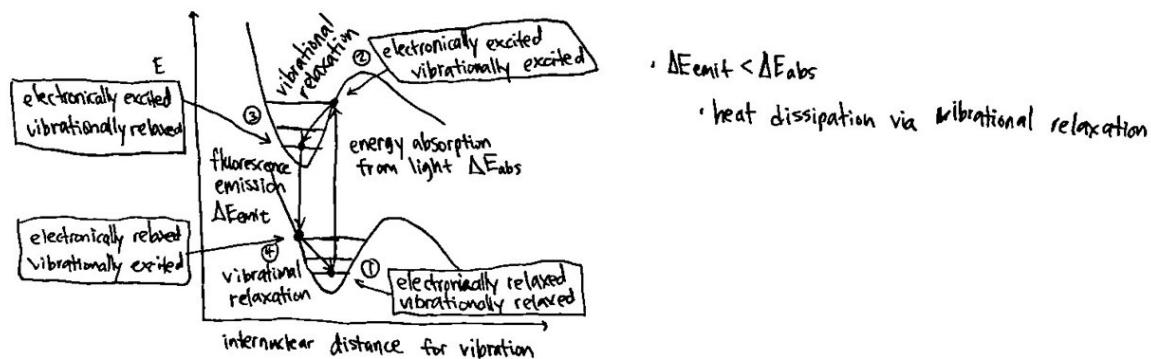
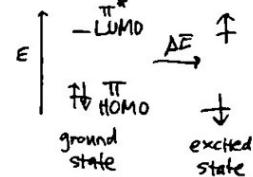
- vibrationally excited!

- short time

- energy (some) dissipate as heat

- Energy lost is less than energy gained  $\rightarrow \lambda_{\text{emit}} * > \lambda_{\text{absorb}}$

? quantum yield - efficiency of fluorescence, fraction of excited states that return to ground state by fluorescence.



## &lt;&lt; Diels-Alder Rxn

> Diels-Alder rxn - rxn between conjugated diene and an alkene

> cycloaddition rxn - addition rxn that results in formation of a ring

> conjugate (1,4-) addition - addition that occurs across the outer carbons of the diene.

- results in formation of double bond at 2C-3C (relative location)

> dienophile - the alkene that reacts with diene

> pericyclic rxn - a concerted rxn that involves a cyclic flow of  $e^-$

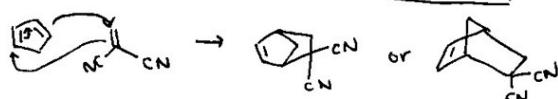
- $\boxed{\text{diene} + \text{alkene (dienophile)} \rightarrow \text{ring}}$  ring formation!

$\rightarrow$  Mechanism



- alkene with ester (-CO<sub>2</sub>R), nitrile (CN), unsaturated, c<sup>-</sup>neg group,  $\uparrow$  rxn rate

- $\boxed{\text{cyclic diene} + \text{alkene} \rightarrow \text{bicyclic product}}$



- diene + diene, alkene + alkene  $\rightarrow$  no rxn!

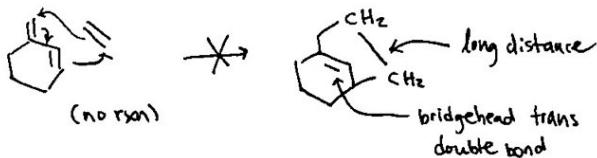
## Diels-Alder Rxn

→ Effect of Diene Conformation on Rxn

- s-trans diene - no rxn

- locked s-trans diene has no rxn

- s-trans single bond becomes a trans bridgehead double bond, bad!



- s-cis diene - more reactive

- locked s-cis diene more reactive than noncyclic diene



- noncyclic dienes have s-trans conformation

- E low

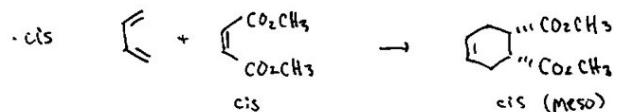
- have E barrier to change to s-cis to react

- cyclic locked s-cis diene doesn't have such E barrier

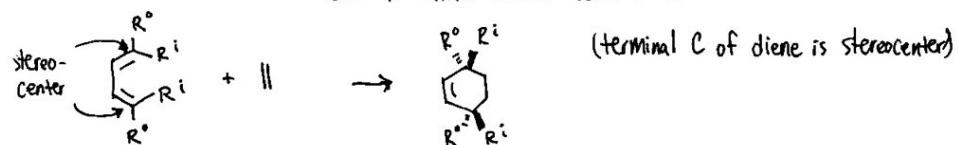
- sterics need to be considered for E/Z diene's conformation change from trans → cis

→ Stereochemistry

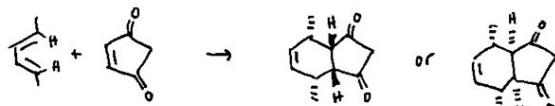
- concerted, syn addition - add to one face of π system



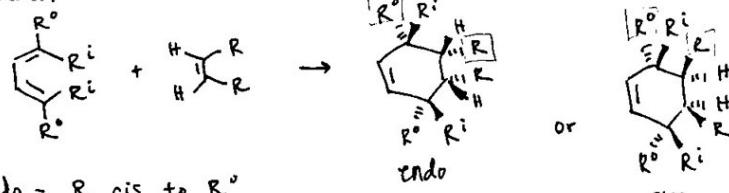
- inners are cis;outers are cis; inner-outer are trans



- if both terminal C of diene and C of dienophile are stereocenter, the H at ring junction are cis.



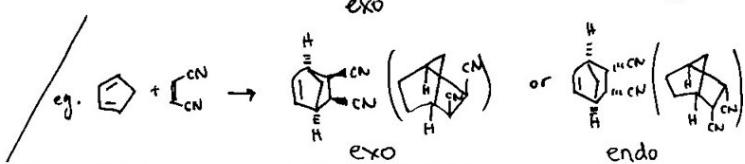
→ Conclusion



> endo - R° cis to R°

> exo - R° trans to R°

> endo usually faster than exo



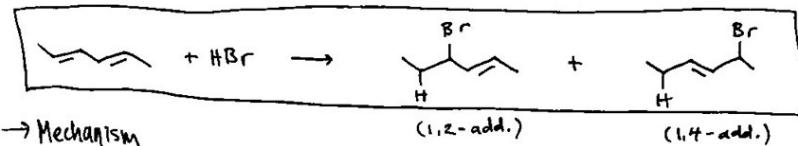
## Addition of HX to Conjugated Diene

→ 1,2 - and 1,4 - Addition

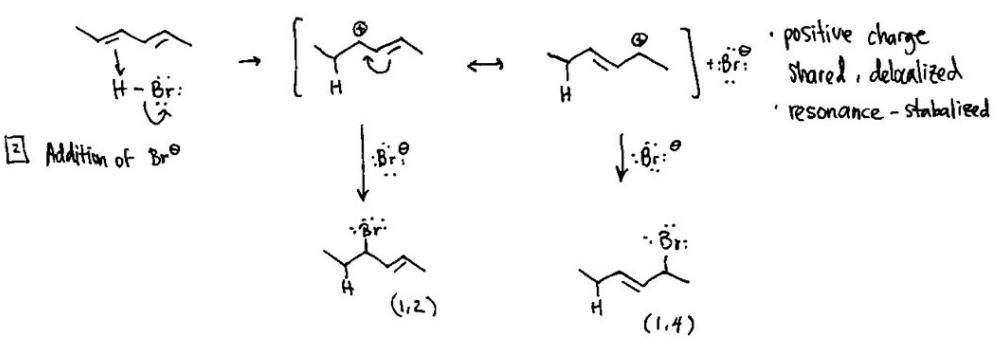
- $\text{HX} + \text{conj. diene}$  gives { 1,2-addition product (Major)  
1,4-addition product (minor)

→ 1,2-Addition - addition occurs at adjacent carbon

> 1,4-Addition - addition to carbon that have 1,4-relationship (relative) (conjugate addition)

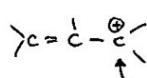


#### protonation of double bond p: resonance

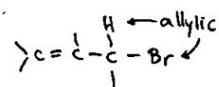


→ Allylic carbocation: resonance & stability

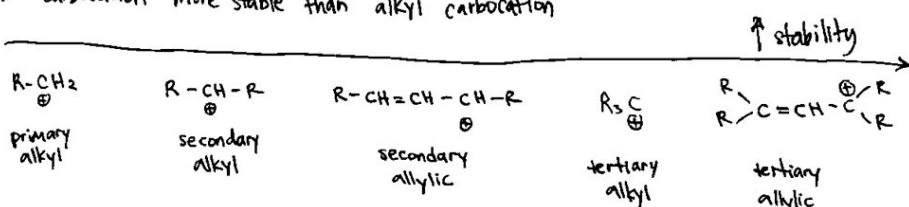
> allylic carbocation - carbocation where  $\oplus$ -charged,  $e^-$ -deficient C is adjacent to double bond



allylic carbocation



• allylic carbocation more stable than alkyl carbocation



- resonance structure provides a device to show  $e^-$  delocalization with Lewis structure
  - resonance  $\rightarrow e^-$  delocalization  $\rightarrow \downarrow E$  bonding  
 $\rightarrow$  stabilization
  - resonance energy - energy advantage of  $e^-$  delocalization
  - $e^-$  delocalize throughout ( $\pi_1$ , bonding MO)
  - positive charge only on two C, not on central C
    - if  $e^-$  present, it occupies  $\pi_2$  nonbonding MO  $\rightarrow$  has node at central C
    - the positive charge = absent  $e^-$   $\rightarrow$  not at central C

↔ Addition of HX to Conjugated Dienes

→ Kinetic & Thermodynamic Control

- > kinetically controlled - products of rxn do not come to equilibrium under rxn condition
  - relative ratio of product controlled by relative rate

- > thermodynamically controlled - products of rxn come to equilibrium under the rxn condition

- kinetically controlled rxn can have similar product ratio than thermo controlled

- thermo controlled rxn cannot have similar ratio than kinetically controlled

→ Addition of HX to Conj. Diene

- kinetically controlled

- 1,2-addition is major, but less stable

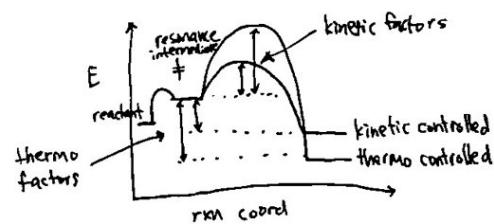
- 1,4-addition is minor, but more stable

alkene with double bond inside is  
more stable

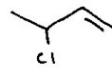
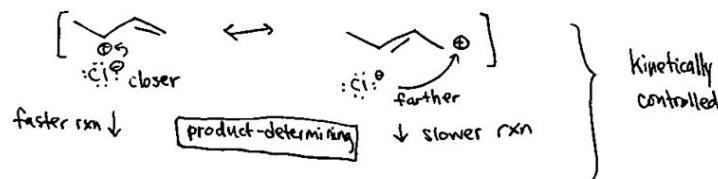
- 1,2-addition has faster rxn → Major } not in equilibrium

- 1,4-addition has slower rxn → Minor } (kinetic control)

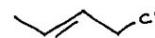
- kinetically controlled rxn product ratio determined by relative free energy of transition state of product determining step (energy barrier), but not  $\Delta G$  of product.



↓ [rate-limiting]



major, yet  
less stable

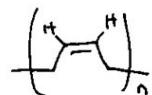


minor, yet  
more stable

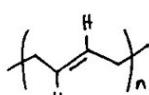
/ kinetic cares  
transition/intermediate  
→ rate ; thermo cares  
product stability /

↔ Diene Polymers

· 1,3-butadiene polymerizes to polybutadiene



1,4-addition  
cis double bond



1,4-addition  
trans double bond

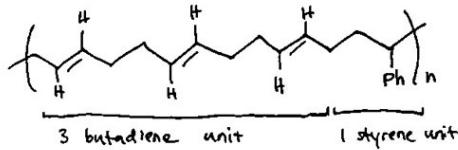


1,2-addition

· Mixed with various  
proportion

> copolymer - polymer produced by simultaneous polymerization of  $\text{Z}^{(+)}$  polymers

· 1,3-butadiene polymerizes with styrene ( $\text{H}_2\text{C}=\text{CH}-\text{Ph}$ ) in 3:1 ratio to form  
styrene-butadiene rubber (SBR)



## ↔ Resonance

→ Drawing Resonance Structure

- show delocalization of  $e^-$

- arrow pushing without moving any atoms - describe single molecule

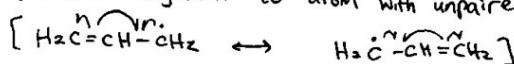
1. double bond, triple bond, atom with unshared  $e^-$  pair adjacent to  $e^-$ -deficient atom



2. double / triple bond adjacent to atom with unshared  $e^-$  pair



3. double / triple bond adjacent to atom with unpaired  $e^-$



4. double bond can be moved in a cycle around a 6-membered ring

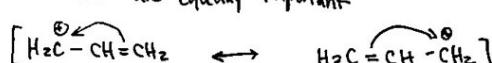


→ Evaluating Relative Importance of Resonance Structures

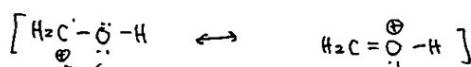
- Evaluate structure as if they are separate molecule

- more stable structure → more important

1. Identical structures are equally important

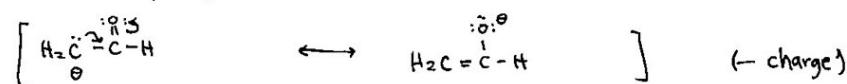
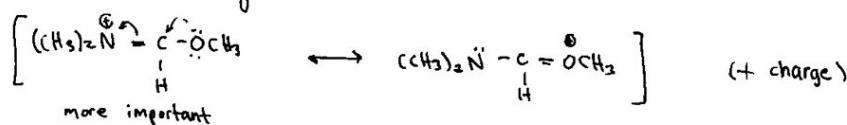


2. Structures have complete octet are more important (octet is more important than charge!)

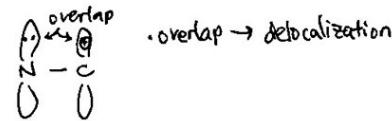
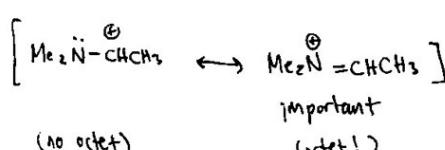
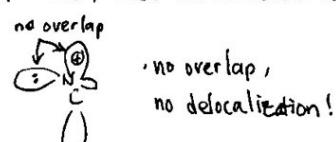
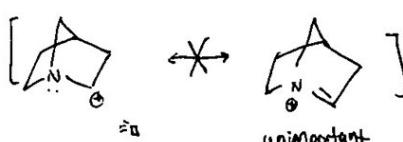


3. Structures with appropriate charge placement are more important

- $\oplus$  charge on  $e^-$  positive atom
- $\ominus$  charge on  $e^-$  negative atom } relatively



4. If orbital overlap suggested by the structure is impossible, then the structure is not important



## << Resonance

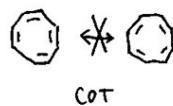
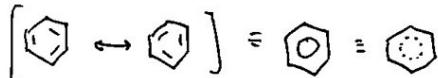
### → Using Resonance Structure

- All other things being equal, the molecule with greater # of important structures is more stable.
- Resonance-stabilized molecules are more stable than...
  - their individual contributing structures
  - other isomeric molecules without resonance
- Resonance can be used to analyze reactivity
  - More reactive intermediates are more stable react faster (↑ rate)
- When predicting products, we can treat each resonance structure as separate compounds
  - predict structure of product

## << Aromatic Compounds

### → Structure of Benzene

- benzene ring is inert to rxn
- benzene has C-C bond order of "1.5"
  - one single type of bond instead of separate single & double bond
- all C are  $sp^2$ , so they are coplanar
  - allows overlapping of  $2p$  orbitals
- compare to 1,3,5,7-cyclooctatetraene (COT)
  - COT has diff single & double bond length
  - COT can react with HBr
  - COT is not coplanar, having  $sp^2, sp^3$ 
    - no resonance



### → Stability of Benzene

> empirical resonance energy - experimental estimate of how much special stability is implied by resonance structure.

- $\Delta H_f^\circ$  (benzene) = 82.93 kJ/mol
- empirical resonance E = 141 kJ/mol ← how much benzene is stabilized, the energy that benzene "doesn't have"

### → Aromaticity (Hückel 4n+2 rule)

> aromatic follows all Hückel 4n+2 rule:

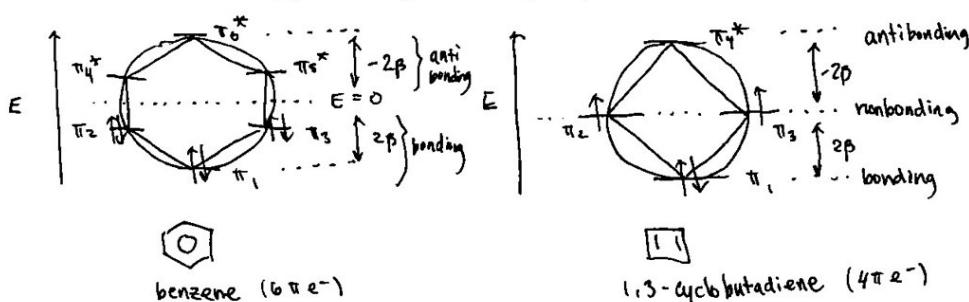
1. compound contains  $(^{+})$  rings that have cyclic arrangement of p orbital
2. every atom of an aromatic ring has a p orbital
3. ring is planar
4. cyclic arrangement of p orbital contain  $4n+2\pi e^-$

n	0	1	2	3	4
$\pi e^-$	2	6	10	14	18

## &lt;&lt; Aromatic Compounds

→ Frost Circle

1. For cyclic conj. hydrocarbon / ion with  $j$  sides ( $j$  overlapping  $2p$  orbitals)
  - inscribe a regular polygon of  $j$  sides within a circle of  $2\beta$  radius
  - one vertex of the polygon in vertical position
2. Place one MO energy level at each vertex ( $j$  MOs)
3. Draw a horizontal line that bisects the polygon.
  - MO above the line are antibonding
  - MO below the line are bonding
  - MO on the line are nonbonding
4. Lowest energy level is  $2\beta$  at lowest vertex. Other levels calculated by trigonometry
5. Add  $\pi e^-$  to energy levels by Pauli's principle & Hund's rule



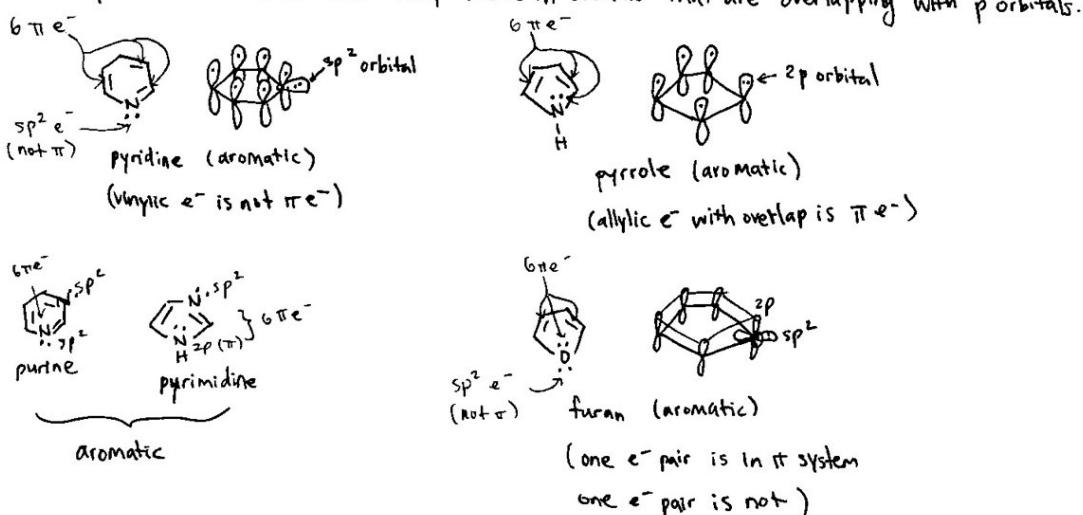
&gt; degenerate - orbitals have the same energy

- Cyclic conj. molecules / ions with  $4n+2 \pi e^-$  have exactly the right # of  $e^-$  to fill bonding MO.
- The bonding MO in cyclic conj. molecule have very low  $\downarrow E$ . ( $\uparrow$  resonance  $E$ )

→ Aromatic Heterocyclics

- vinylic  $e^-$  are not counted as  $\pi e^-$ .

- allylic  $e^-$  are  $\pi e^-$  when they reside in orbitals that are overlapping with  $p$  orbitals.



## ↔ Aromatic Compounds

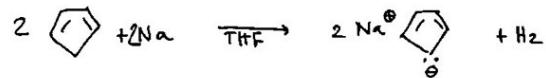
→ Aromatic Ions

→ Anion

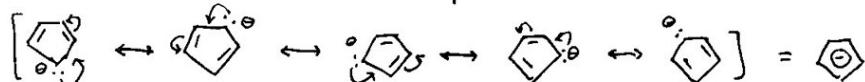
- 2H-cyclopentadien-1-ide anion is aromatic



- formed by rxn with sodium

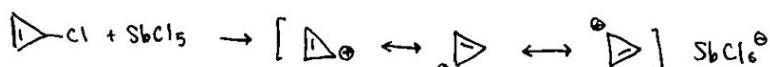


- very stable = basic = conj. acid very acidic



→ Cation

- cyclopropenyl cation is aromatic



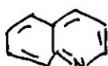
- atoms with empty p orbitals are part of the  $\pi-e^-$  system, but contribute no  $e^-$  to the  $\pi-e^-$  count.

## → Aromatic Polycyclic Compounds



naphthalene

(two fused benzene rings)



quinoline

(fused benzene & pyridine)



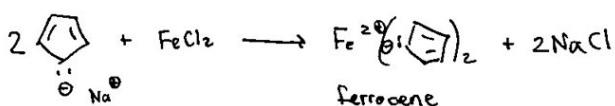
indole

(fused benzene & pyrrole)

- graphite, graphene, fullerene

## → Aromatic Organometallic Compound

- ferrocene has aromatic rings



ferrocene



top view

## → Antiaromatic Compounds

- antiaromatic - planar continuous ring of  $4n \pi e^-$

- highly unstable

- no resonance energy (2  $\pi e^-$  in nonbonding MO)



- Hund's rule - two nonbonding MO half occupied → double free radical

- angle strain



$[\text{C}_4\text{H}_4^-]_2$  is stable  $\because$  Fe donates 2  $e^-$  to let it have 6  $\pi e^-$ , being aromatic



## &lt;&lt; Noncovalent Interactions of Aromatic Rings

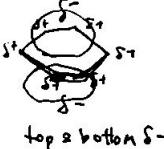
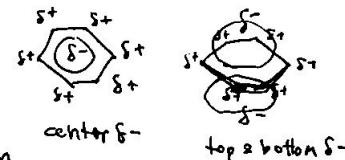
- aromatic ring has  $\pi e^-$  density at center, top, bottom.

- benzene has zero net dipole  $\therefore$  symmetry

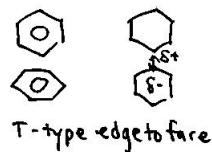
$\rightarrow$  Aromatic Ring + Aromatic Ring

- > offset stacking - center of rings have stacking interaction  
that offset to avoid juxtaposition of like charges

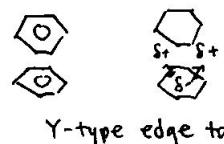
- > edge-to-face - planes of rings are perpendicular  
• more stable



offset stacking



T-type edge to face



Y-type edge to face

- enthalpy driven

- aromatic ring can interact with polarizable nonpolar groups via Van der Waals attraction

$\rightarrow$  Aromatic Ring + Cation

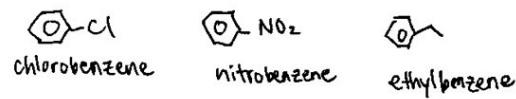
- > pi-cation interaction - interaction between aromatic ring & cation

 $\pi$ -cation interaction

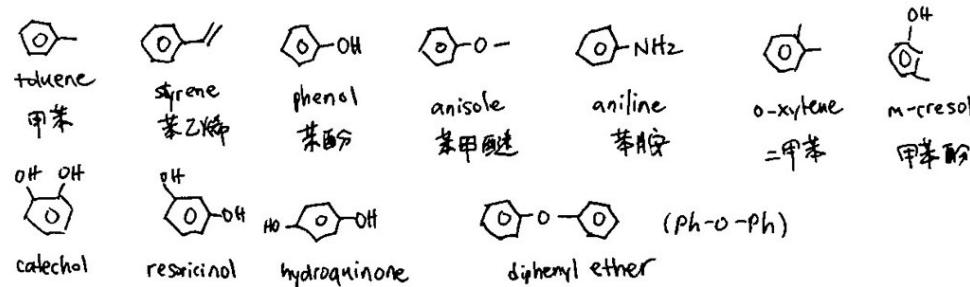
- ↓ entropy, ↓ΔG

## &lt;&lt; Benzene Nomenclature

## • substitutive naming

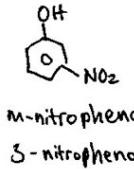
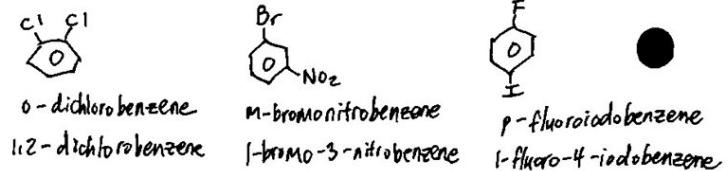


## • common name



## • positional prefix (old system)

- ortho (o) - 1,2 relationship
- meta (m) - 1,3 relationship
- para (p) - 1,4 relationship



## • groups

- > aryl group - benzene ring or substituted benzene ring cited as substituent
- > phenyl group - unsubstituted benzene ring as substituent (-Ph)
- > benzyl group - Ph-CH<sub>2</sub>f

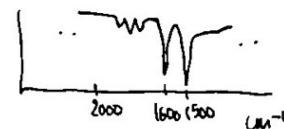
## &lt;&lt; Physical Properties of Benzene Derivatives

- boiling point of benzene deriv. are similar to those with similar shape & mass
- cyclic is higher than linear ∵ symmetry
- para has higher than meta, ortho ∵ symmetry
- benzene deriv. less dense than H<sub>2</sub>O, more dense than linear
- benzene insoluble in H<sub>2</sub>O ∵ H-bonding

## &lt;&lt; Spectroscopy of Benzene Derivative

## → IR Spectroscopy

- $1600\text{cm}^{-1}$ ,  $1500\text{cm}^{-1}$ ,  $\text{C}=\text{C}$  stretch, large
- $1660\text{-}2000\text{cm}^{-1}$ , overtone & combination bands, small



## → NMR Spectroscopy

- NMR absorption at larger chemical shifts are typical of most benzene derivatives

- benzene, singlet,  $\delta 7.4$

- ring current - circulation of  $\pi\text{e}^-$  around the ring

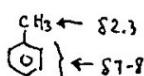
- $\vec{B}_0$  induces ring current  $\rightarrow$  induces  $\vec{B}_i$

- $\vec{B}_0$  adds to  $\vec{B}_i$  outside the ring

- net B field higher

- ring current is characteristic of aromatic compounds

- benzylic proton,  $\delta 2\text{-}3$



- -OH in phenol,  $\delta 5\text{-}6$

→  $^{13}\text{C}$  NMR Spectroscopy

- aromatic  $\text{C}=\text{C}$ ,  $\delta 110\text{-}160$

- benzene,  $\delta 128.5$

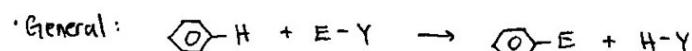
## → UV Spectroscopy

- $\lambda_{\text{max}} \sim 210\text{nm}$

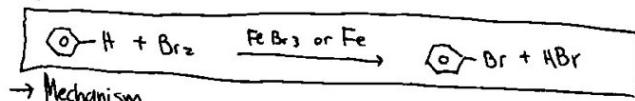
- $\lambda_{\text{weak}} \sim 260\text{nm}$

## &lt;&lt; Electrophilic Aromatic Substitution Rxn of Benzene

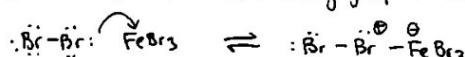
- > hydrogen of an aromatic ring is substituted by an electrophile (Lewis acid)



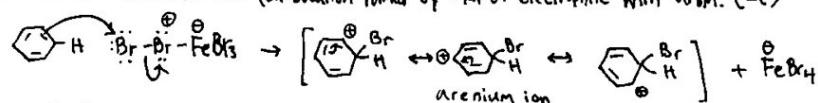
## → Halogenation of Benzene



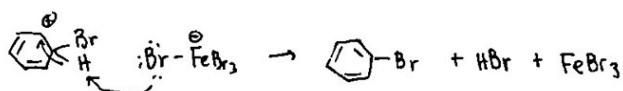
[1] Formation of Complex for better leaving group ( $e^-$ -acceptor) → show benzene very unreactive



[2] Formation of arenium ion (carbocation formed by rxn of electrophile with arsm.  $\text{C}=\text{C}$ )



[3] Removal of ring proton H

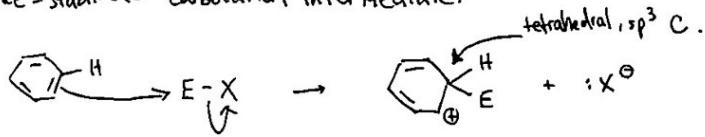


Electrophilic Aromatic Substitution Rxn of Benzene

→ Mechanistic Steps

① Generation of an electrophile.

② Nucleophilic rxn of the  $\pi e^-$  of the aromatic ring with the electrophile to form a resonance-stabilized carbocation intermediate.

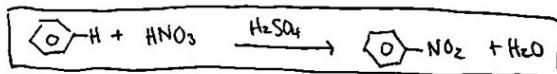


③ Loss of a proton from the carbocation intermediate to form substituted aromatic compound.



→ Nitration of Benzene

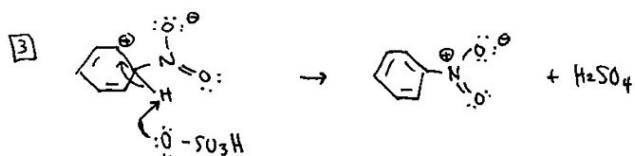
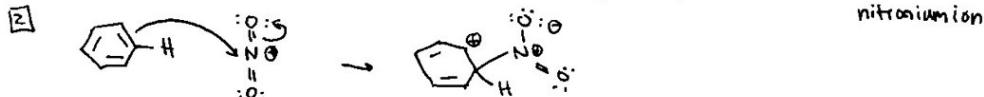
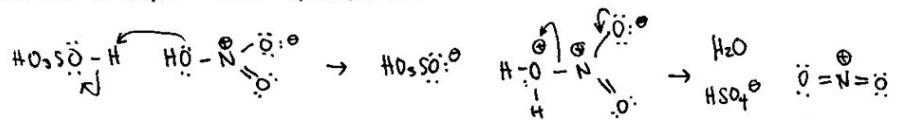
· nitro group  $-NO_2$  substitute H.



benzene + nitric acid → nitrobenzene

→ Mechanism

① Generate electrophile  $NO_2^+$  nitronium ion

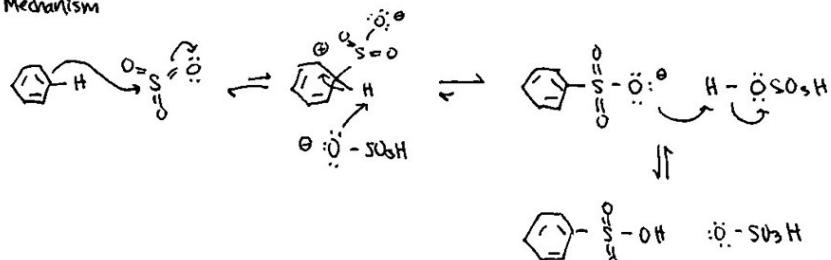


→ Sulfonation of Benzene

· benzene + sulfur trioxide  $\xrightarrow{H_2SO_4}$  benzenesulfonic acid



→ Mechanism



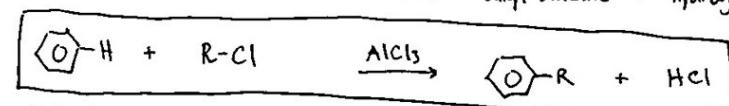
↔ Electrophilic Aromatic Substitution Rxn of Benzene

→ Friedel-Crafts Alkylation of Benzene

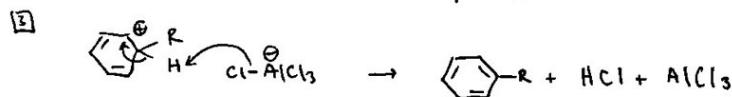
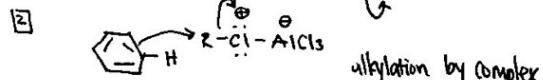
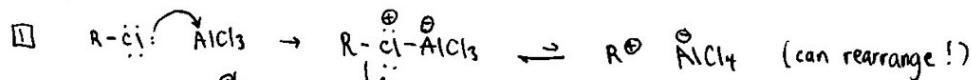
> Friedel-Crafts alkylation - alkyl group transferred to an aromatic ring with acid catalyst present.

• have carbocation rearrangement

• benzene + alkyl chloride  $\xrightarrow{\text{AlCl}_3}$  alkyl benzene + hydrogen chloride



→ Mechanism

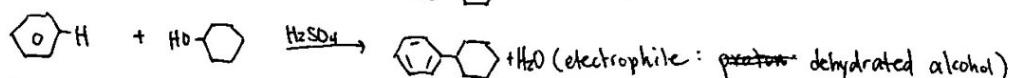
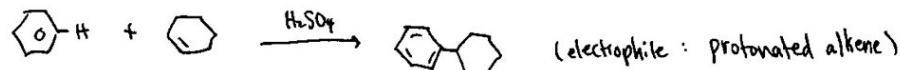


+ rearrangement possible!

• alkylbenzene can undergo further rxn

• to get purer product, need excess of reactant

• can also use alkene & alcohol as electrophile

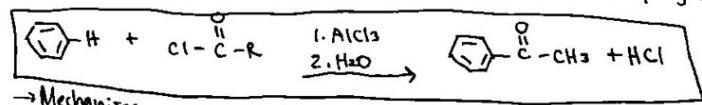


→ Friedel-Crafts Acylation of Benzene

> acylation rxn - acyl group ( $\text{R}-\overset{\oplus}{\text{C}}=\text{O}$ ) transferred from one group to another

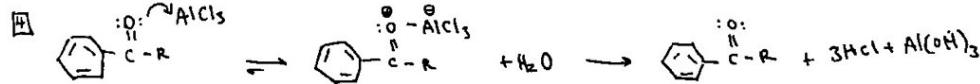
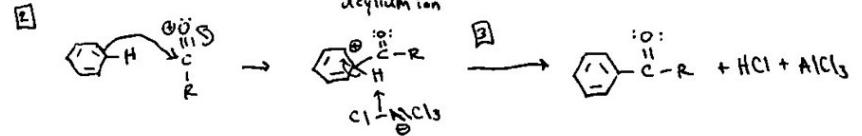
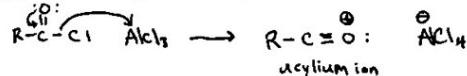
> Friedel-Crafts acylation - acyl group from acid chloride introduced into aromatic ring

• benzene + acyl chloride  $\rightarrow$  ketone + hydrogen chloride



→ Mechanism

① Generate electrophile of acylium ion

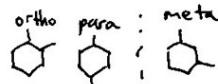


• can react intramolecularly - faster ∵ proximity effect

Electrophilic Aromatic Substitution Rxn of Substituted Benzenes

→ Directing effects of substituents

rxn of monosub. benzene is regioselective



> Ortho-para-directing group - original substituent that undergoes further substitution at the ortho and para positions

> Meta-directing group - original sub that undergoes further sub at meta position

A substituent is either ortho-para-directing or meta-directing

reason: kinetic!

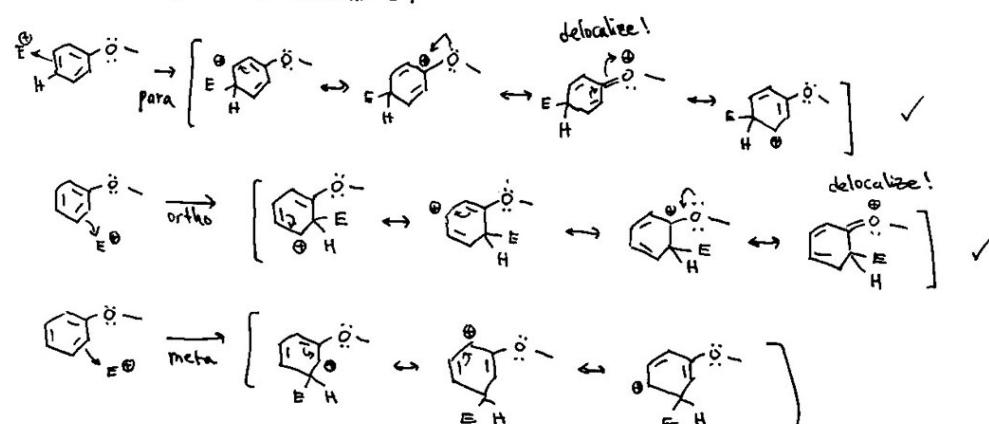
sub rxn at one position is much faster than another - in competition

→ Ortho-Para-Directing Groups

mostly alkyl groups & groups with unshared e<sup>-</sup> pair on atom attached to benzene ring

ortho & para locations form four resonance structure, but meta forms three.

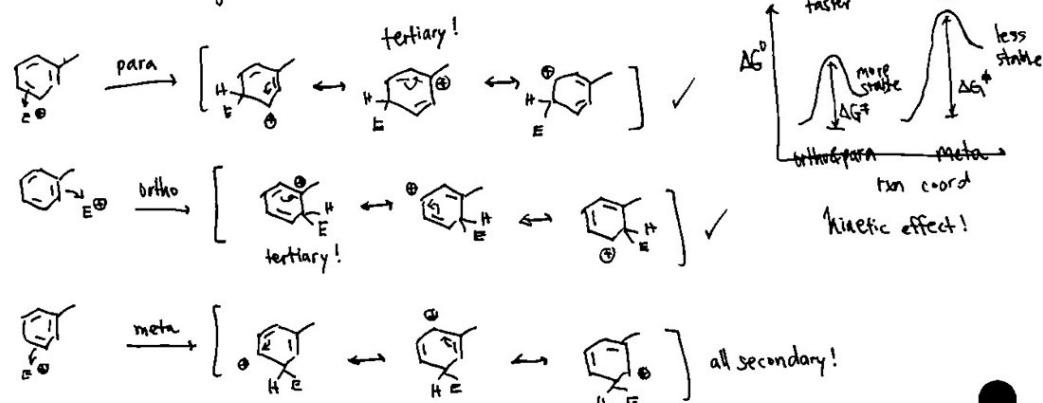
unshared e<sup>-</sup> pair on substituent provides extra delocalization for adjacent e<sup>-</sup>-deficient C.



ortho & para → delocalize e<sup>-</sup> → ↑ # resonance structure → ↑ stability

→ ↑ rate of rate-limiting carbocation formation → ↑ more product observed

for alkyl groups, ortho & para locations form one tertiary carbocation, but meta forms all secondary.



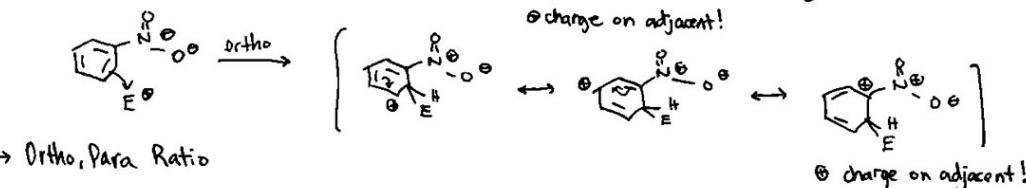
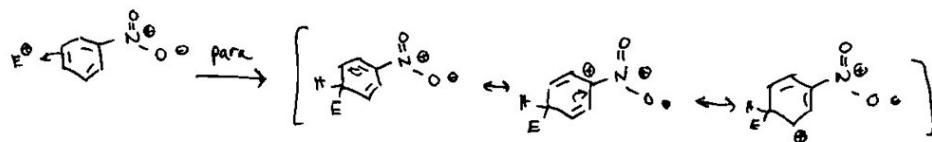
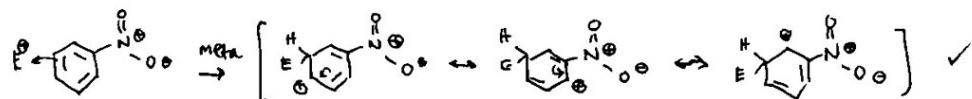
ortho & para → stable tertiary cation → ↑ rate

## &lt;&lt; Electrophilic Aromatic Substitution Rxn of Substituted Benzenes

→ Directing effects of Substituents (cont.)

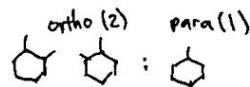
→ Meta-Directing Groups

- mostly polar groups that do not have an unshared  $e^-$  pair on atom adjacent to benzene ring
- they have partial positives  $\delta^+$
- ortho & para have  $\delta^+$  charge close at adjacent atoms  $\text{rxn}$ 
  - $\uparrow E$ ,  $\downarrow$  stability,  $\downarrow$  rate
- meta doesn't have close like charges
  - $\downarrow E$ ,  $\uparrow$  stability,  $\uparrow$  rate



→ Ortho, Para Ratio

- vary from case to case
- Friedel-Crafts acylation of toluene
  - all para, no ortho
  - ortho has van der Waals repulsion
- Nitration of toluene
  - ortho  $>$  para
  - $2 : 1$
  - both positions are fast, so the ratio is the relative probability



→ Activating & Deactivating Effect of Substituent

- activating group - sub. benzene deriv.  $\text{rxn}$  more rapidly than benzene (donate  $e^-$ )
  - deactivating group - sub. benzene derivative that react more slowly than benzene (withdraw  $e^-$ )
  - a substituent is either activating or deactivating in all electrophilic aromatic sub. rxn.
  - deactivating - halogen, all meta-directing groups
  - activating - all ortho-para-directing groups EXCEPT halogens
- { directing effect - rel. rate of rxn of same compound (meta vs. ortho-para)
- { activating/deactivating effect - rel. rate of rxn of diff. compounds (sub. benzene vs. benzene)

## << Electrophilic Aromatic Substitution Rxn of Substituted Benzenes

→ Activating & Deactivating Effects of Substituents (cont.)

→ Resonance Effect Stabilize

> resonance effect - ability of the sub to stabilize carbocation intermediate by delocalization of  $e^-$  from substituent into the ring.

→ Polar Effect Destabilize

> polar effect - tendency of sub to pull  $e^-$  away from ring by  $e^-$  neg.

• destabilize by inducing positive charges

→ Substituent Analysis

• methoxy group - ortho-para, activating

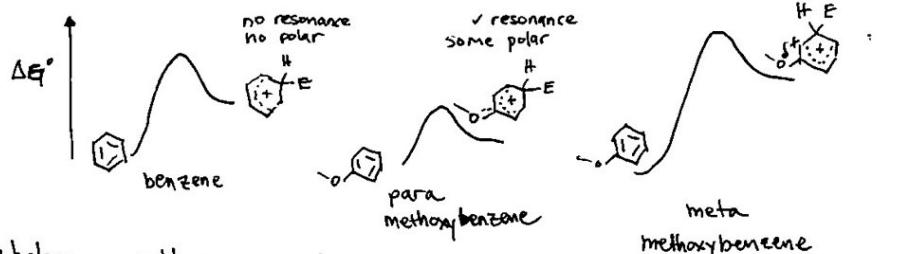
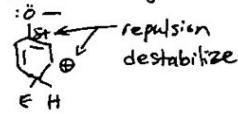
• with methoxy - resonance > polar

• without methoxy (benzene) - no resonance → activating at ortho-para

• meta is deactivating

• no resonance at meta

• polar effect in place



• halogen - ortho-para, deactivating

• have polar effect  $\because e^-$  neg

• less effective resonance effect

$\because 2p-3p$  overlap ineffective overlap

• para-ortho 4 resonance structure

• meta 3 resonance structure

} deactivating

$\xrightarrow{\text{resonance effect}}$  ortho-para

• alkyl group - ortho-para, activating

• no resonance

• have "anti"-polar effect  $\because e^-$  positive } activating

, stabilizing!

• nitro group - meta, deactivating

• no resonance

• have polar effect  $\because e^-$  neg } deactivating

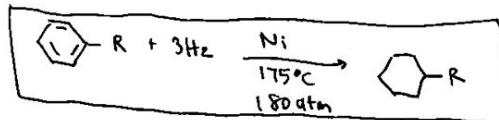
## &lt;&lt; Electrophilic Aromatic Substitution Rxn of Substituted Benzenes

→ Applications in Organic Synthesis

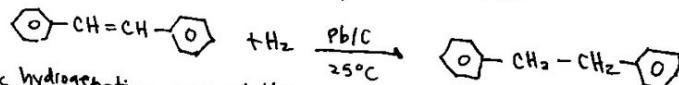
- activating/deactivating effect & directing effect determine order of reactant used
- if directing effect of two sub agree, then no problem
  - Note hindrance of steric
- if directing effect of two sub disagree,
  - if one is more stronger than the other, then override
  - if equally strong, then both can happen → mixture of product
- activating subed. benzene undergo rxn with milder conditions than benzene
- activating subed benzene → fast rxn → mixture of additional sub
- deactivating subed benzene → slow rxn → less additional sub.

## &lt;&lt; Hydrogenation of Benzene Derivatives

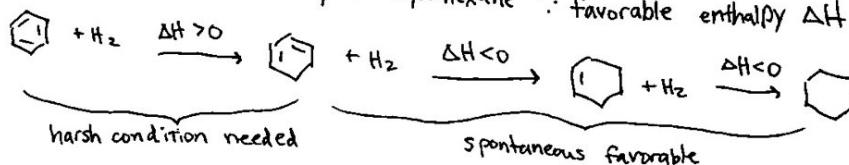
- harsh conditions needed to hydrogenate benzene derivative



without harsh conditions, benzene ring doesn't react:

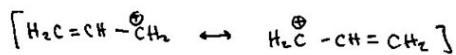


catalytic hydrogenation goes all the way to cyclohexane ∵ favorable enthalpy  $\Delta H$ .

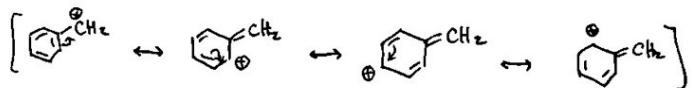


## &lt;&lt; Rxn Involving Allylic &amp; Benzylic Carbocation

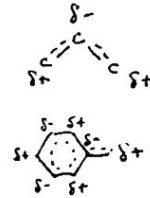
- > allylic group - a group on a carbon adjacent to C=C double bond
- > benzylic group - group on a carbon adjacent to a benzene ring / subst. benzene ring.
- they are both resonance stabilized in carbocation form
  - delocalized  $\pi e^-$  and  $\sigma^-$  deficiency ( $\delta^+$  charge)



allyl cation



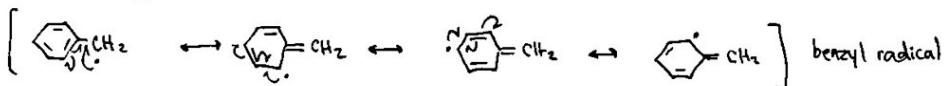
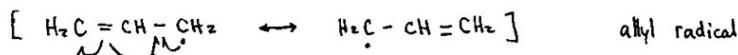
benzyl cation



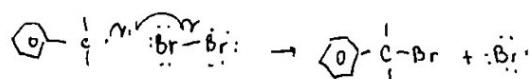
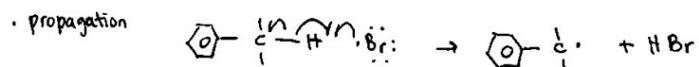
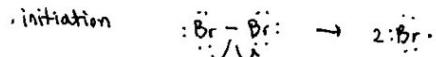
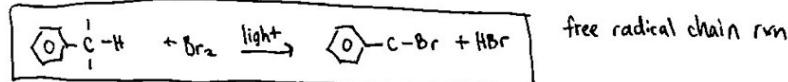
- rxn rate higher for allylic / benzylic carbocation than otherwise
  - resonance-stabilized carbocation
- rxn rate even higher for those that have activating substituent
  - even more resonance structures  $\rightarrow$   $\uparrow$  stability
  - e.g. allylic / benzylic alcohol  $\rightarrow$  faster rxn
- more than one product can be formed with allylic / benzylic carbocation
  - shared, delocalized  $\delta^+$  charge
  - nucleophilic attack have diff locations
  - have to take stability into account

## &lt;&lt; Rxn Involving Allylic &amp; Benzylic Radicals

- > allylic radical - has unpaired  $e^-$  at allylic position
- > benzylic radical - has unpaired  $e^-$  at benzylic position
- they are both resonance stabilized

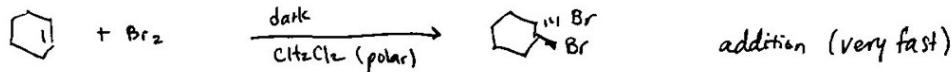


- more stable than nonallylic/nonbenzylic radicals
- form radical intermediate more readily
- bromination of cumene

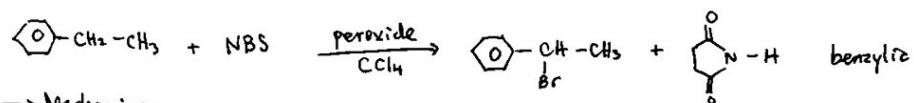
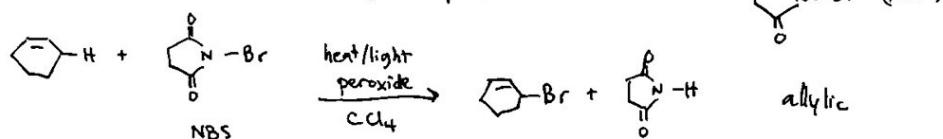


## &lt;&lt; Rxn Involving Allylic &amp; Benzylic Radicals

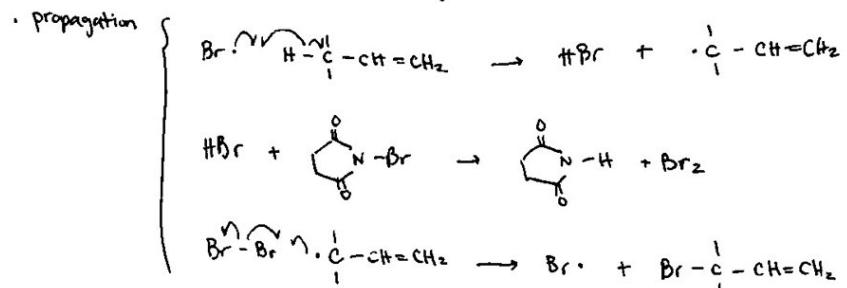
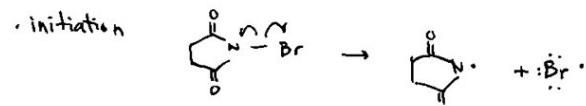
- allylic radical is stable enough to compete with bromination
- rxn condition can be chosen carefully



• NBS (*N*-bromosuccinimide) <sup>slowly, conc. low</sup>  
can speed up substitution of Br.

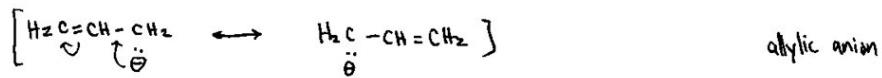


→ Mechanism



## &lt;&lt; Rxn Involving Allylic &amp; Benzylic Anions

- they're resonance-stabilized



• More stable than nonallylic/nonbenzylic anion { resonance effect  
polar effect - eneg of  $\text{sp}^2$ -C }

- As conj. base, they're stable → their acid are more acidic

## Rxn Involving Allylic & Benzylic Anions

## → Allylic Grignard Reagents

• allylic Grignard reagent resembles carbanions

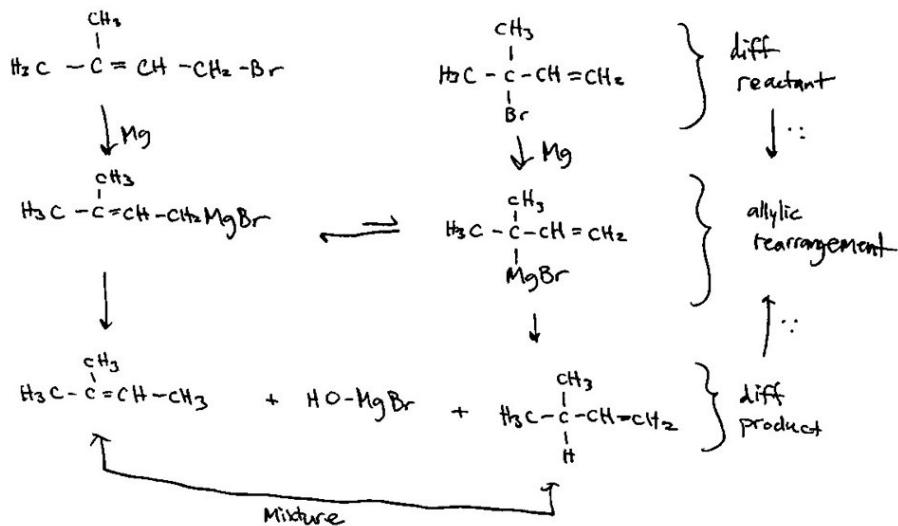


• allylic rearrangement - simultaneous movement of a group G and a double bond



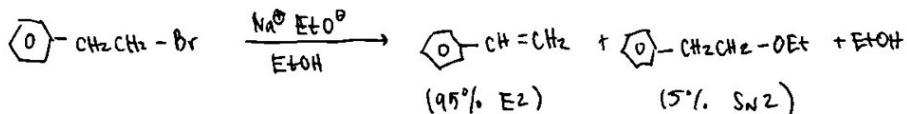
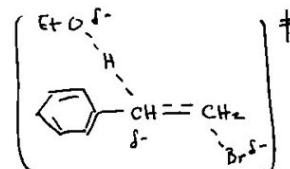
- Ge is any group
- can be Mg Br  $\rightarrow$  Grignard
- not resonance!
- isomers in equilibrium

- can be formed from diff reactants
  - can form diff product } :: allylic rearrangement



→ E2 Elimination with Allylic/Benzylic ~~two~~ hydrogens

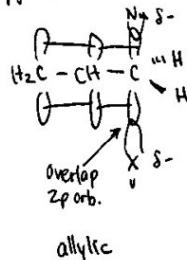
- higher acidity of  $\beta$ -H  $\uparrow$  rate of E2
    - allylic/benzylic H has  $\uparrow$  rate of E2
    - transition state has carbocation character at  $\beta$ -C



## Aromatic & Benzylic SN2 Rxn

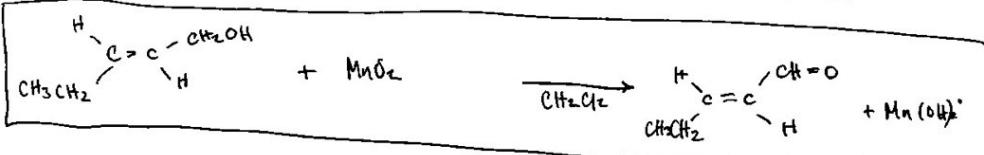
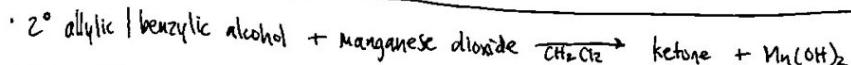
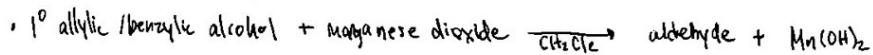
- they're faster than nonallylic / nonbenzylic

- energy of transition state reduced by  $2p$ -orbital overlap

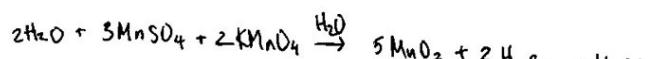


## "Allylic & Benzylic Oxidation"

→ Oxidation of Allylic Benzylic Alcohol with MnD<sub>2</sub>

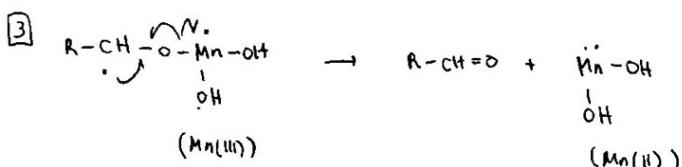
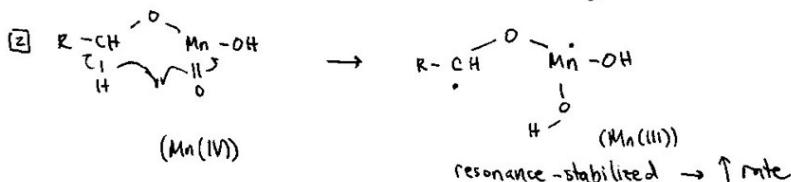
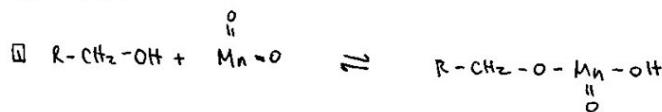


MnO<sub>2</sub> formed from KMnO<sub>4</sub> and dried



MnO<sub>2</sub> gives selective rxn to allylic/benzylic -OH.

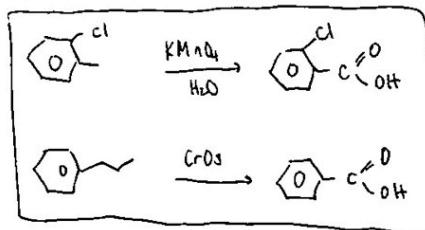
→ Mechanism



## $\longrightarrow$ Benzylic Oxidation of Alkylbenzene

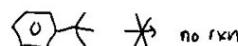
• Alkyl sidechain on benzene (regardless of length) is converted to carboxylic acid ( $-COOH$ )

Condition :  $\text{Cr(VI)} : \text{Na}_2\text{Cr}_2\text{O}_7 / \text{CrO}_3$   
 $\text{Mn(III)} : \text{KMnO}_4$   
 $\text{O}_2 + \text{catalyst}$

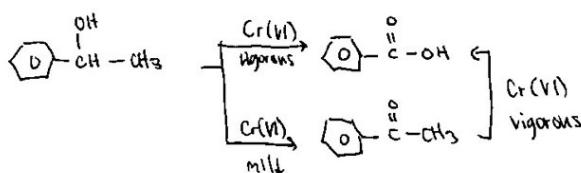


, must have benzylic H

- t-butyl group no rxn



• with milder condition,  $2^{\circ}$  alcohol first to ketone



## Biosynthesis of Terpenes

→ biosynthesis - synthesis of chemical compounds by living organisms  
→ isoprene rule

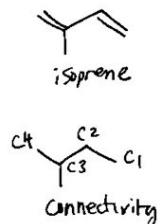
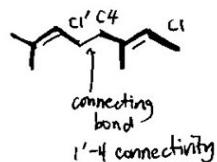
essential

**essential oil** - substance that possesses a key characteristic (odor/flavor) of the natural material from which it comes.

> terpene - natural product with  $C:H = 5:8$   
 • satisfies isoprene rule

> isoprene rule - terpenes consists of repeating units of 5-C diene isoprene's connectivity

- ignores double bond, substituent
  - only consider connectivity
  - terpene can have 1'-4 or 1'-1 connectivity



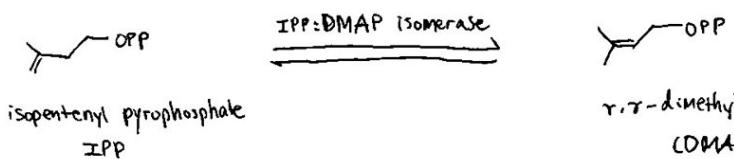
> Monoterpene - terpene with 10 C

> sesquiterpene - terpene with 15 C

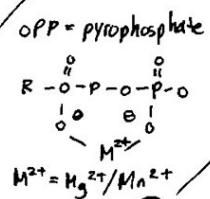
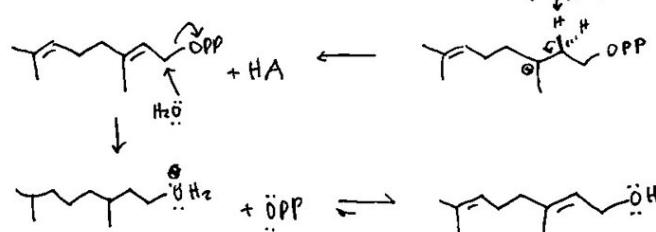
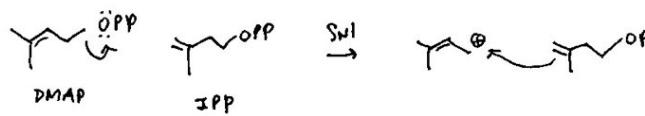
> diterpene - terpene with 20C

→ biosynthesis of terpene

- reactants: IPP, DMAP

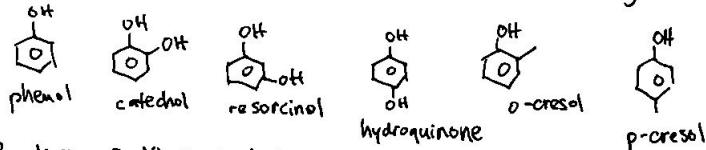


• held in prenyl transferase



## &lt;&lt; Introduction

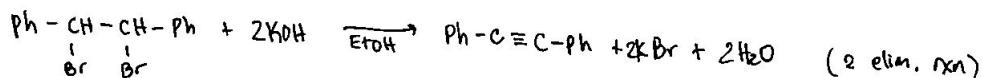
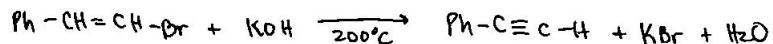
- > aryl halide - compound that halide is bound to carbon of aromatic ring (like benzene)
- > vinylic halide - halogen bound to carbon of double bond
- > allylic halide - halogen bound to carbon adjacent to double bond
- > phenol - hydroxyl group (-OH) bound to an aromatic ring

<< Lack of Reactivity of Vinylic & Aryl Halide under S<sub>N</sub>2 Conditions

- vinylic & aryl halide do not undergo S<sub>N</sub>2 rxn
- vinylic halide would have sp-hybridized transition state, ↑ E, ↓ rate
- vinylic halide has van der Waals repulsion for S<sub>N</sub>2 mechanism, ↑ E, ↓ rate
  - can't opposite-side attack
  - can't in same plane } sterics
- aryl halide also has sterics problem
- aryl halide with inversion of stereochem (for S<sub>N</sub>2), ↑ E, ↓ rate

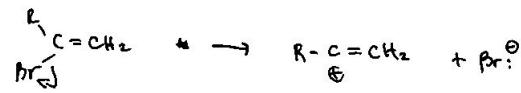
## &lt;&lt; Elimination of Vinylic Halide

- Vinylic halide can have elimination rxn with harsh conditions

<< Lack of Reactivity of Vinylic & Aryl Halide Under S<sub>N</sub>1 Conditions

- Vinylic & aryl halide do not undergo S<sub>N</sub>1 rxn

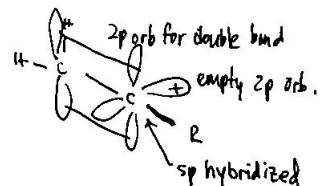
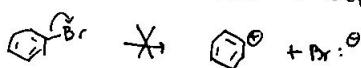
> vinylic cation - carbocation which e<sup>-</sup>-deficient C is part of double bond



- sp hybridized, ↑ E, ↓ stability
- empty 2p orbital not in π system, + on C=C unfavorable
- overall, unstable!

> Vinylic C-X bond is stronger ∵ sp<sup>2</sup>-hybridized (rather than sp<sup>3</sup>)

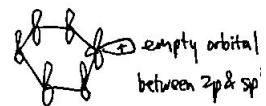
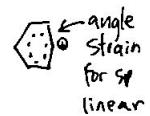
> aryl cation - carbocation which e<sup>-</sup>-deficient C is part of aromatic ring



- sp linear geometry creates angle strain

- empty orbital is between 2p and sp<sup>2</sup>, having ↑ high E.

- overall, unstable!

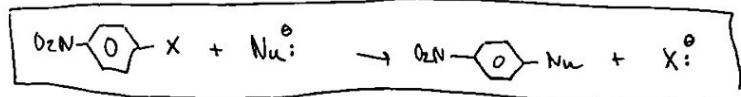


... Nucleophilic Aromatic Substitution Rxn of Aryl Halide

- aryl halide undergo no S<sub>N</sub>1, S<sub>N</sub>2 rxn

- aryl halide with 1<sup>(+)</sup> nitro group (NO<sub>2</sub>) ortho / para to halogen undergo nucleophilic sub. rxn

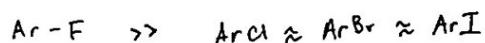
> nucleophilic aromatic substitution - substitution at C of an aromatic ring by nucleophilic mechanism.



→ Reactivity trend

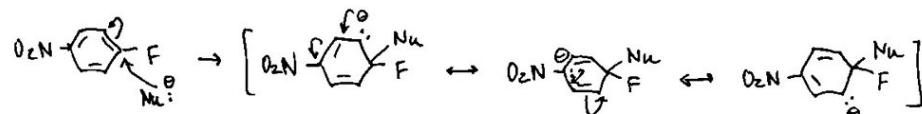
- ↑ # -NO<sub>2</sub> group, ↑ rate (ortho/para to X)

- Aryl fluoride most reactive, ↑ rate

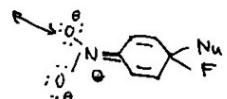


→ Mechanism

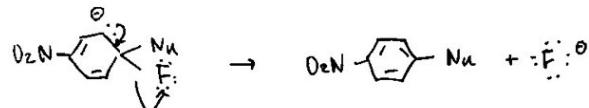
① Formation of Meisenheimer complex (resonance-stabilized), rate limiting



[a] the complex can also have e<sup>-</sup> delocalize on nitro group



② Loss of halide as leaving group



- no inversion of stereochemistry

Intro Transition Metal Catalyzed Rxn

→ Transition Metals & Complexes

> transition metal - elements in the "d block"

· fill n level s orbital, (n-1) level d orbital

· ns and (n-1)d has similar E, all considered as valence e<sup>-</sup>

> ligand - groups that surrounds transition metal

> coordination complex - compounds containing transition metals surrounded by ligands  
(transition-metal complex) (could be ions)

→ Classification of Ligands

· ligands are Lewis base

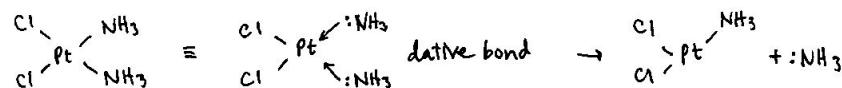
> L-type ligand - neutral molecule after dissociation from metal with e<sup>-</sup> pair.

> X-type ligand - anion after dissociation from metal with e<sup>-</sup> pair.

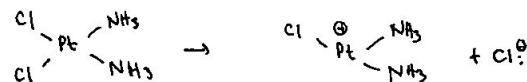
· bonding e<sup>-</sup> on L-type ligand are considered to "belong" completely to the ligand

· convention - e<sup>-</sup> pair in L-type ligand is completely assigned to the ligand

> dative bond - leaving bonding e<sup>-</sup> pair on ligand



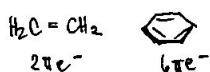
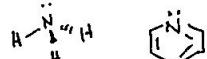
· bonding e<sup>-</sup> on X-type ligand is one to ligand, one to metal



### L-type

· lone pairs / π bond

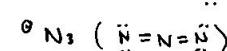
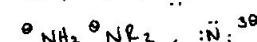
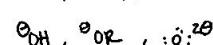
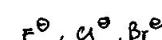
· neutral



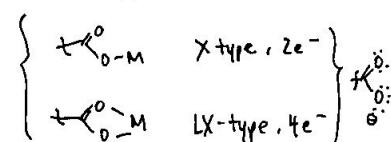
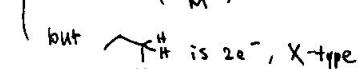
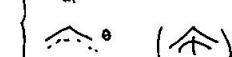
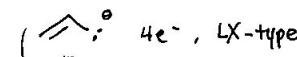
### X-type

· lone pairs

· anion



### Combined L & X



← Intro Transition Metal Catalyzed Rxn

→ Oxidation State &  $d e^-$

- Metal Oxidation State = (Total Molecular charge) -  $\sum$  (ligand charge)

- L-type ligand doesn't contribute to metal ox. state

- $\# d e^- = (\text{Group number}) - (\text{oxidation state})$   
(metal valence  $e^-$ )

→ Electron Counting

- total  $e^-$  count =  $\# d e^- + 2(\# \text{ ligand lone pair} / \pi \text{ bond})$

- $e^-$  count follow 18  $e^-$  rule

- have exceptions

- typically  $\leq 18 e^-$ , rarely  $> 18 e^-$

Workflow

1. metal oxidation state

2.  $\# d e^-$

3. total  $e^-$  count

← Fundamental Rxns of Transition Metal Complex

→ Ligand Dissociation - Association

- oxidation state unchanged

- total  $e^-$  count changed

→ Ligand Substitution

- dissociation of a ligand accompanied with association of another

- X-type sub. X-type

- L-type sub. L-type

- oxidation state no change

- total  $e^-$  count no change

→ Oxidative Addition

- Add two X-type ligand

- oxidation state  $\uparrow +2$

- $d e^-$  count  $\downarrow -2$

- total  $e^-$  count  $\uparrow +2$

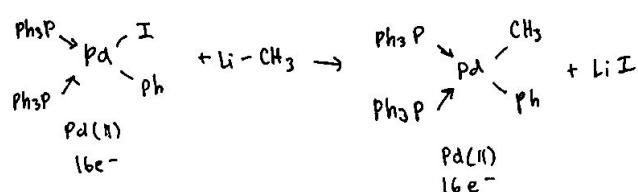
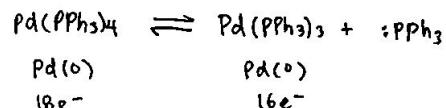
→ Reductive Elimination

- lost two X-type ligand

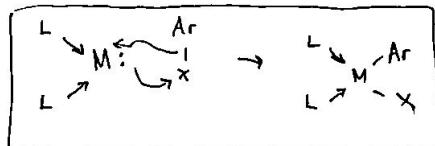
- oxidation state  $\downarrow -2$

- $d e^-$  count  $\uparrow +2$

- total  $e^-$  count  $\downarrow -2$

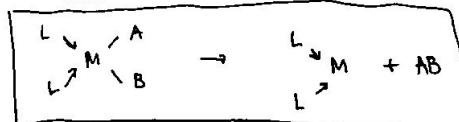


retention of stereochem



(equivalently,  
add metal into  
Ar-X bond)

retention of stereochem



(equivalently,  
remove metal  
into AB)

## &lt;&lt; Fundamental Rxns of Transition Metal Complex

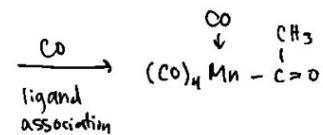
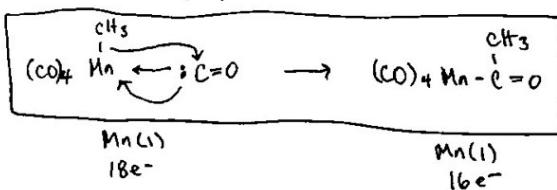
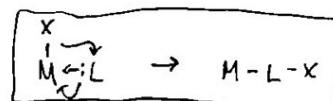
## → Migratory Insertion

→ ligand insert into metal-ligand bond:  $L-MR \rightarrow M-L-R$ 

→ 1:1 insertion

→ new bond formed at same atom that was bound to metal

• metal oxidation state no change

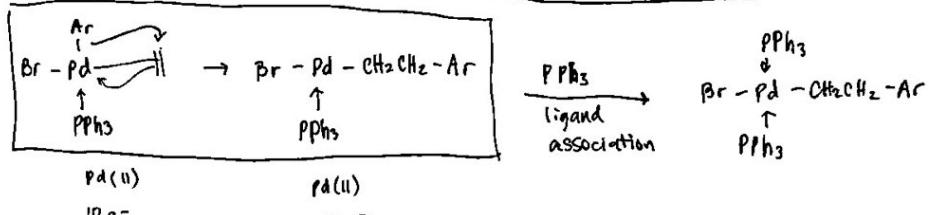
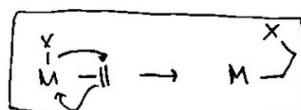
• total e<sup>-</sup> count  $\downarrow -2$ • coord #  $\downarrow -1$ 

• product can further associate

## → 1:2 insertion

→ migrating group move to atom adjacent to the one bound to metal

• oxidation state no change

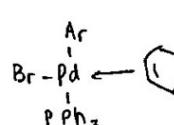
• total e<sup>-</sup> count  $\downarrow -2$ • coord #  $\downarrow -1$ 

• product can further associate

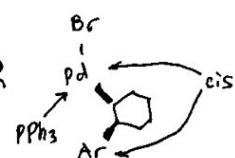
## → Stereochemistry

• syn-addition

• intramolecular



syn 1:2-insertion



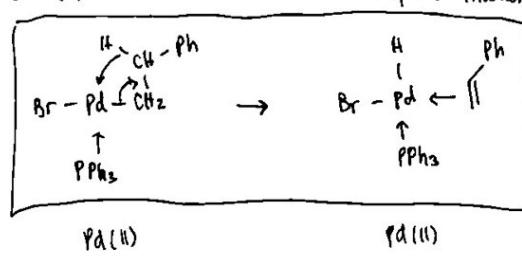
## → β-Elimination

→ a group β to the metal migrates with its bonding e<sup>-</sup> pair to metal

• oxidation state no change

• total e<sup>-</sup> count  $\uparrow +2$ • coord #  $\uparrow +1$ 

• syn-elimination

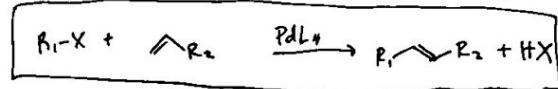
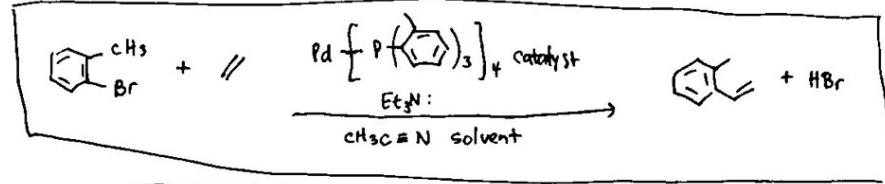


ligand association

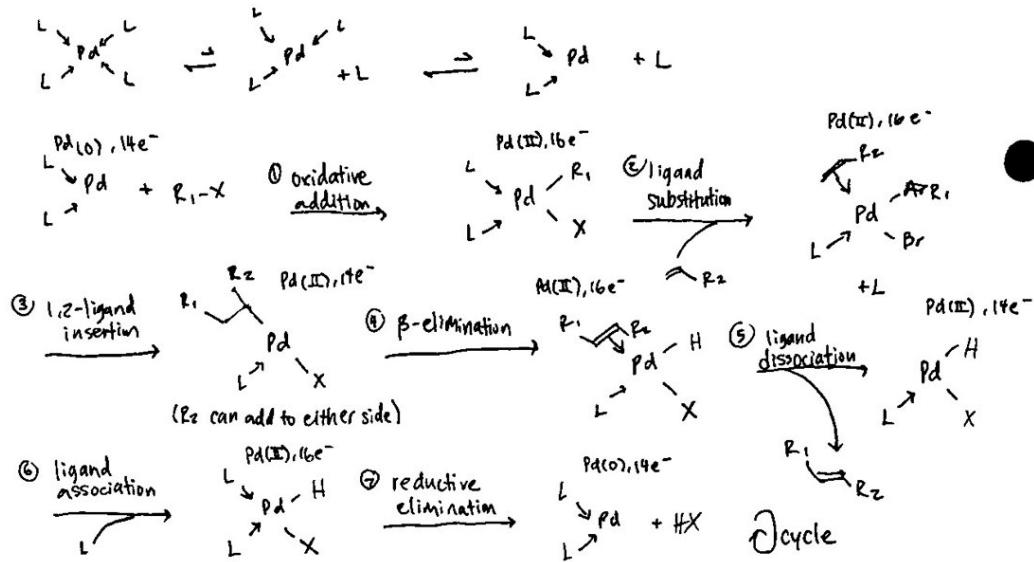
Examples of Transition Metal-Catalyzed Rxn

→ Heck Rxn

Heck rxn - an alkene coupled to an aryl bromide/iodide under Pd(0) catalyst

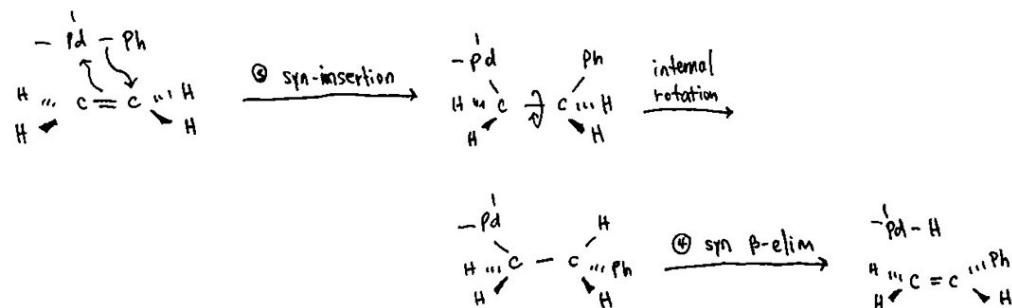


→ Mechanism



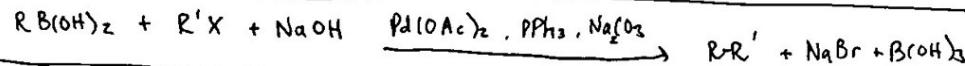
Pd(0) is the catalyst (e.g. Pd(OAc)<sub>2</sub>)

Step ③, ④ require syn stereochem



<< Example of Transition Metal-Catalyzed Rxn

→ Suzuki Coupling



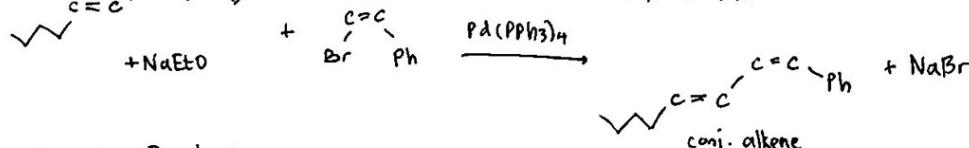
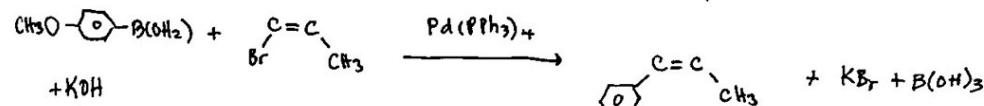
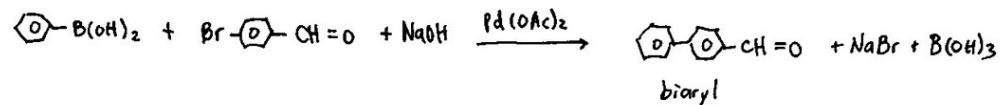
- R = aryl/vinylic group

- R-R' can be biaryl or aryl-substituted alkene, conjugated alkene

  - biaryl - compound in which two aryl rings are connected by a single bond or

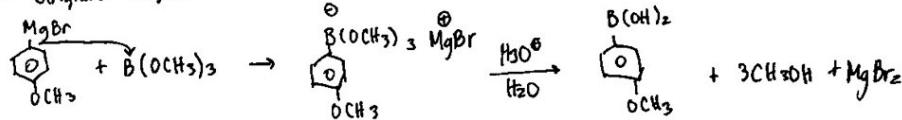
  - catalyst is Pd(0) (e.g.  $\text{Pd(OAc)}_2$ ,  $\text{Pd(PPh}_3)_4$ )

→ Examples

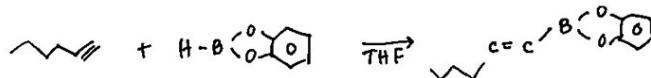


→ Preparing Reactants

① From Grignard reagent

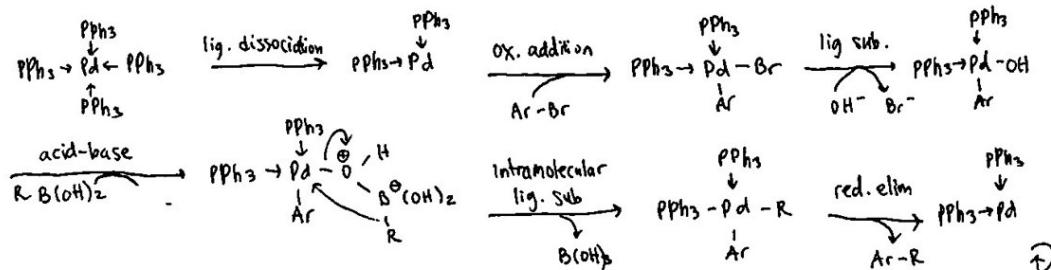


② From Catecholborane



→ Mechanism

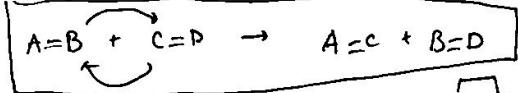
- retention of stereochemistry



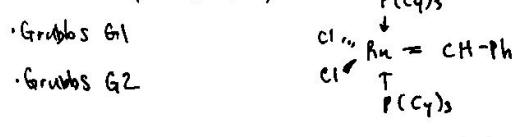
<< Examples of Transition Metal Catalyzed Rxn

→ Alkene Metathesis

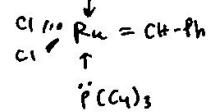
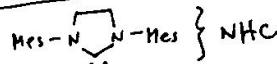
→ alkene metathesis = alkenes slice apart and reassemble  
(olefin metathesis)



• Ruthenium catalyst Ru (IV)

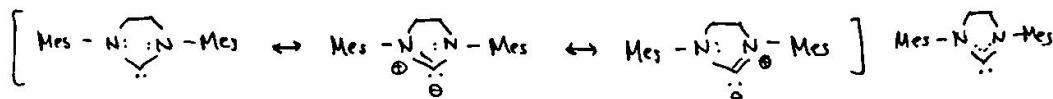


G1 catalyst



G2 catalyst

• NHC is resonance-stabilized



• useful for ring closing



→ Mechanism

- retention of stereochem
- no self-metathesis ∵ sterics

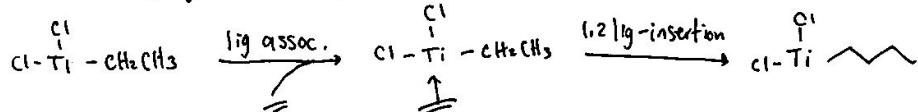
→ Other Rxns

→ Ziegler-Natta polymerization

• produce polyethylene

• catalyst  $\underbrace{\text{TiCl}_2(\text{CH}_2\text{CH}_3)}$  formed from  $\text{TiCl}_3$ ,  $(\text{CH}_3\text{CH}_2)_2\text{AlCl}$

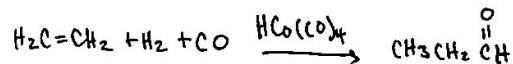
Ziegler-Natta catalyst



→ Hydroformylation

• form aldehyde from alkene

• tetracarbonylhydridocobalt (I) catalyst:  $\text{HCo}(\text{CO})_4$



• 1,2 insertion of ethylene

• 1,1,1-insertion of CO.

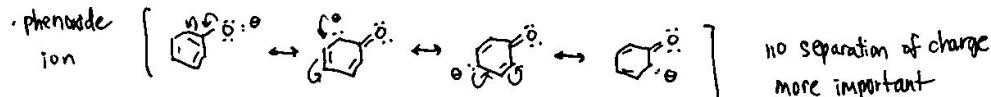
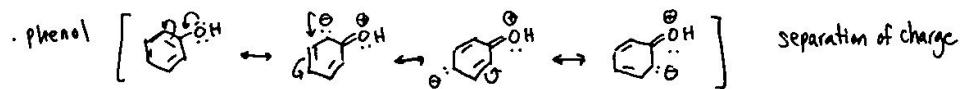
## &lt;&lt; Acidity of Phenol

→ Resonance &amp; Polar Effect

- phenol ionize to form phenoxide ion



- both phenol & phenoxide ion are resonance stabilized

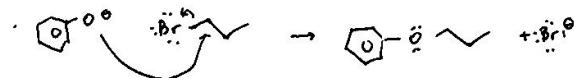


- phenoxide ion more stabilized → phenol more acidic than alcohol
- polarize effect of benzene ring further stabilize phenoxide ion

- ortho, para nitro groups ( $\text{NO}_2$ ) has more resonance structure
  - $e^-$  delocalized to N
  - more stable conj. base
  - more acidic

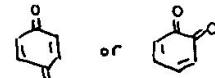
→ Formation &amp; Use of Phenoxides

- NaOH converts  $\text{Ph-OH}$  completely to  $\text{Ph-O}^-$
- equilibrium to the right  $K_{\text{eq}} = 10^6$
- $\text{NaOH} + \text{Ph-OH} \rightleftharpoons \text{Ph-O}^- + \text{H}_2\text{O} + \text{Na}^+$
- $\text{Ph-O}^-$  is soluble in water
- used to separate compounds
- $\text{Ph-O}^-$  acts as nucleophile



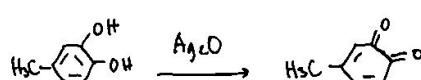
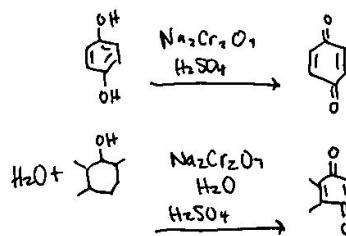
## &lt;&lt; Quinones &amp; Semiquinones

→ quinone - compound containing



- oxidation of phenol gives quinone

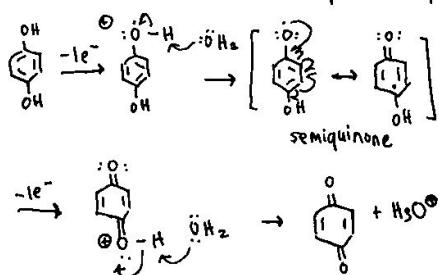
• o-quinone less stable than p-quinone



• bond dipole close to each other

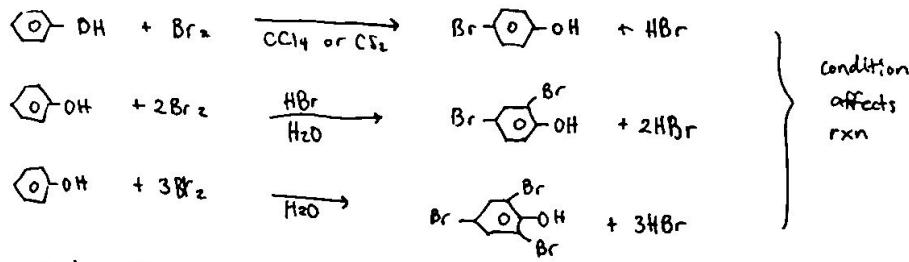
• oxidation of hydroquinone

→ semiquinone - one-e<sup>-</sup> oxidation product of hydroquinone



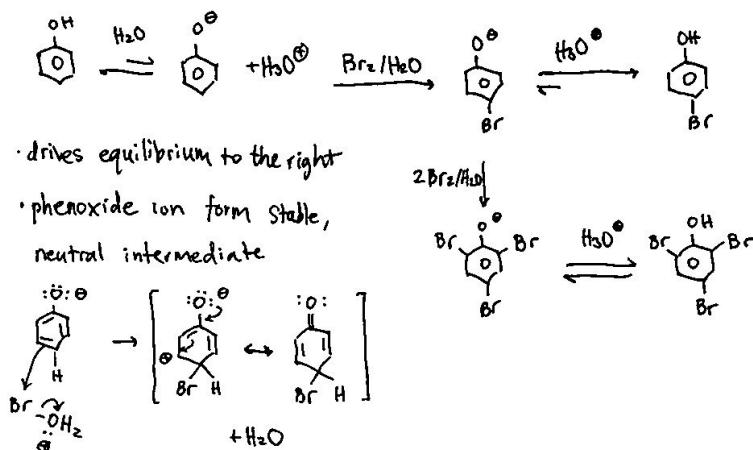
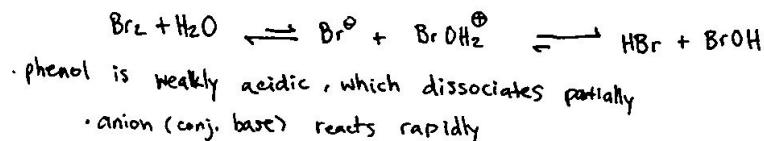
## Electrophilic Aromatic Substitution Rxn of Phenol

### Bromination of Phenol



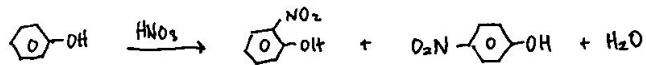
### Factors affecting rxn rate

- Br<sub>2</sub> reacts with water to generate better electrophile BrOH<sup>+</sup>

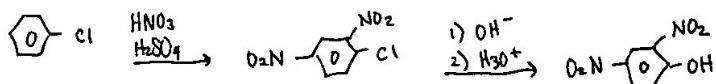


### Nitration of Phenol

- nitration can only do once for electrophilic sub

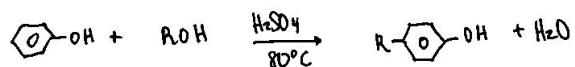


- di-/tri-substituted phenol is by nucleophilic sub

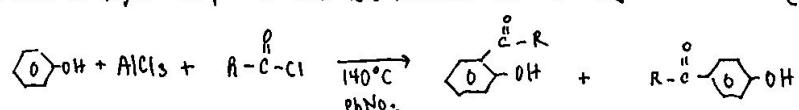


### Friedel-Crafts Alkylation / Acylation

- alkylation at high temp



- acylation at higher temp ∵ less less reactive adduct



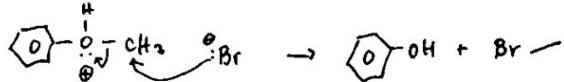
## &lt;&lt; Reactivity of Aryl-Oxygen Bond

→ No S<sub>N</sub>1, S<sub>N</sub>2 for Aryl-Oxygen bond

· same reasoning as aryl halide

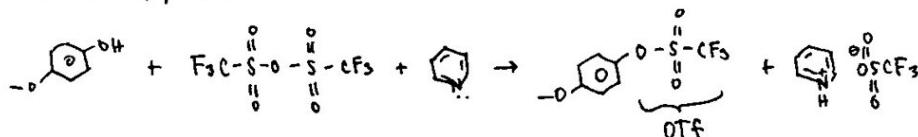
· for any  $\text{O}-X$

· used to select ether cleavage product

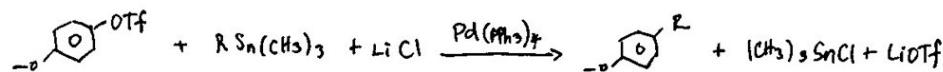


→ Stille Rxn: Substitution at Aryl-Oxygen Bond

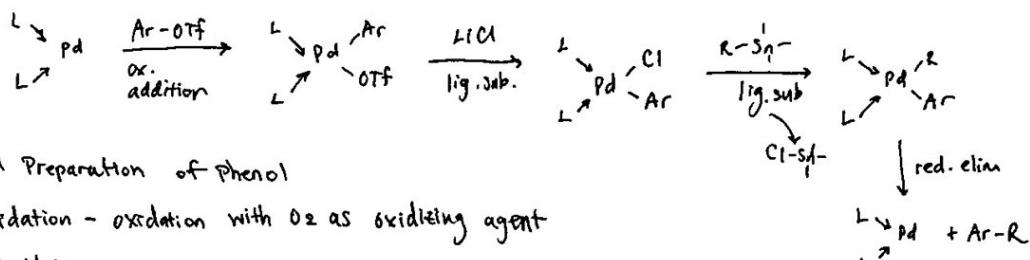
1 Formation of aryl triflate



2 Transition Metal Catalysis



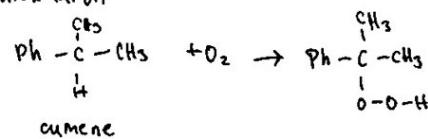
→ Mechanism



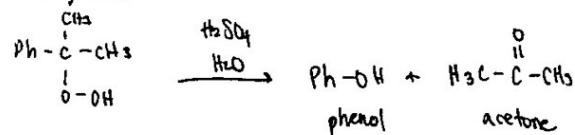
## &lt;&lt; Industrial Preparation of Phenol

> autoxidation - oxidation with O<sub>2</sub> as oxidizing agent

1 Autoxidation



2 Rearrangement



→ Mechanism

