# Alkynes and Organohalides

# Notes on Scheduling

- Review for Final Exam will be 6-9pm on Monday May 16th (during Lab hours) ***not*** Weds, May 18th. We will ***not*** have class (or lab) on Weds, May 18th.
- Final Exam will be in Snow Hall Monday, May 23 or Weds, May 25 - from 6-9pm.
- Vote to decide

# Outline

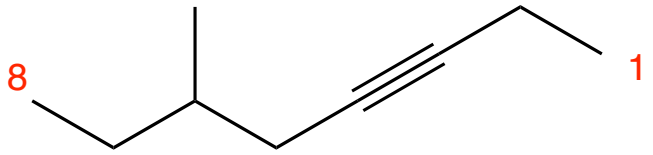
- Alkyne nomenclature
- Review of elimination reactions
- Zaitsev's rule
- Alkyne halogenations (HX and $X_2$)
- Alkyne preparation (from alkenes and alkyl halides)
- Alkyne oxidations (general, complimentary)
- Alkyne anions to make C-C bonds (pKa review)
- Organohalides (properties and reactions)
- Grignard chemistry
- Nucleophilic substitution (SN2) reaction mechanism
- Considerations for rate of reaction (nucleophile, leaving group, solvent effects)

# Naming alkynes

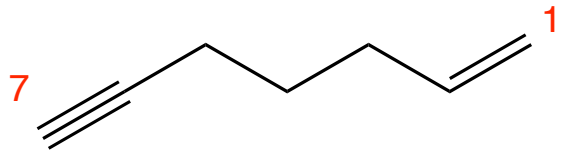
- Number starts from end nearest the first multiple bond (double or triple) so that bond receives the lowest possible number/priority

- When there's a choice: "lower bond gets lower number"

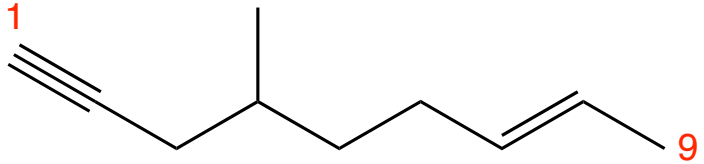
- Compound's suffix name corresponds to lowest number priority multiple bond – e.g. (*E*)-4-methyl-7-nonen-1-yne ***not*** (*E*)-4-methyl-1-nonyn-7-ene



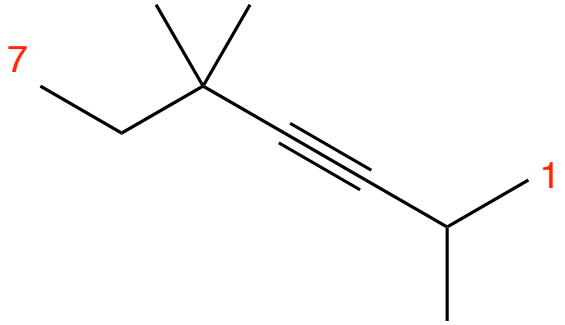

6-methyl-3-octyne




1-hepten-6-yne

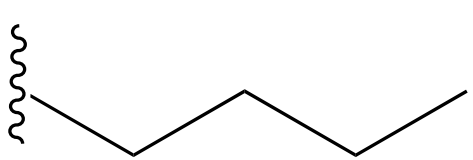



(*E*)- 4-methyl-7-nonen-1-yne

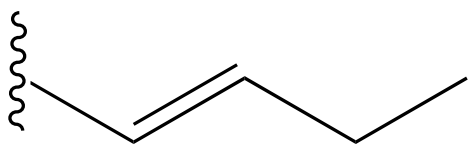



2,5,5-trimethylhept-3-yne

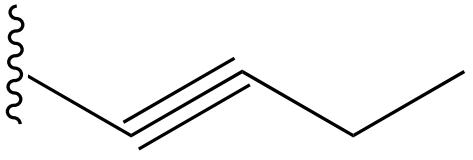
# Alkane, Alkene and Alkyne Functional Group Nomenclature



butyl group



butenyl group



butynyl group

*Alkenes*:

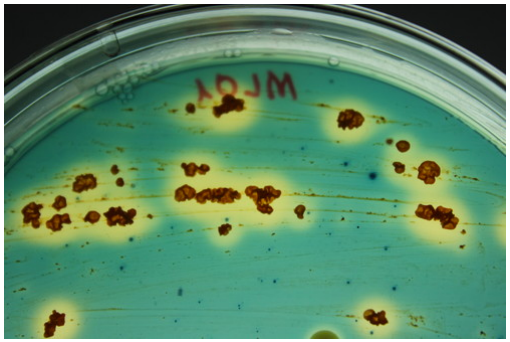
Dienes = 2 double bonds
Trienes = 3 double bonds
Tetraenes = 4 double bonds

*Alkynes*:

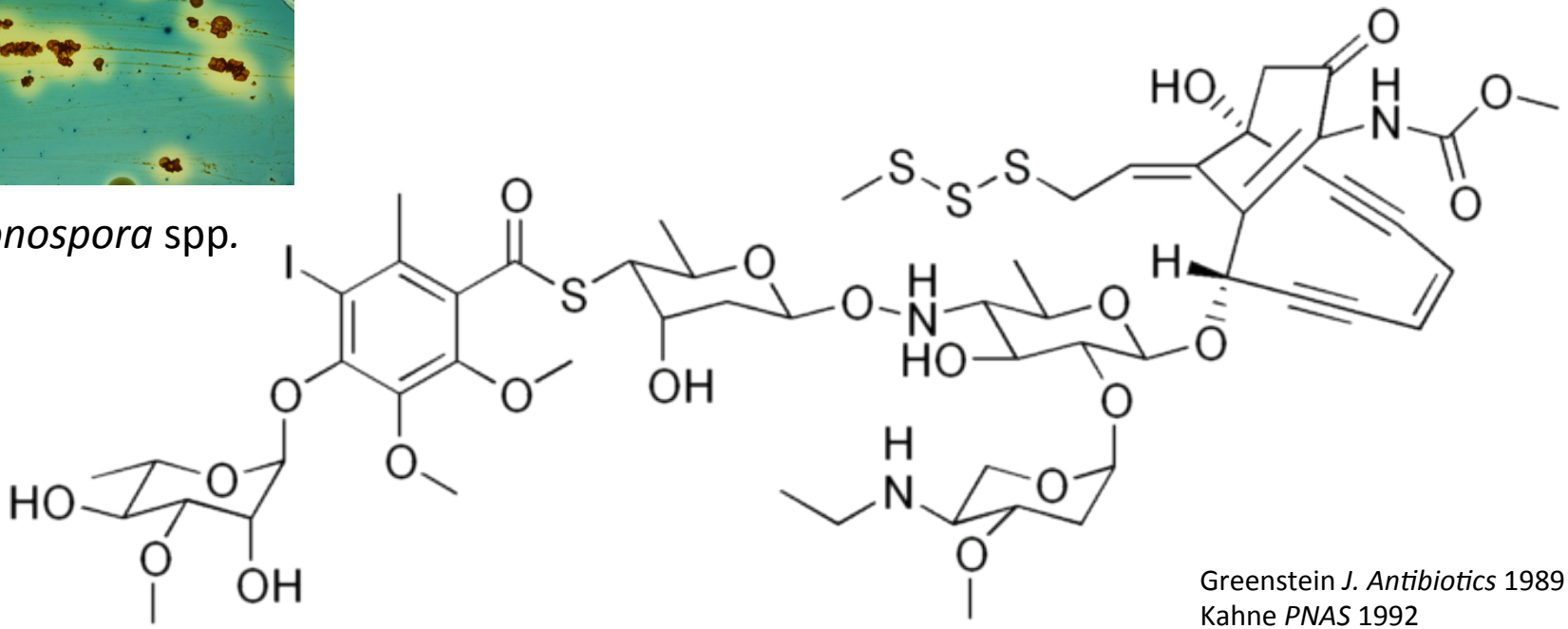
Diynes = 2 triple bonds
Triynes = 3 triple bonds
Tetraynes = 4 triple bonds

# ***Calicheamicin***: an "enediyne" antibiotic

- Isolated from Gram + bacterium *Micromonospora echinospora*
- *Caliche* clay soil in Texas by Lederle Labs (Pearl River)
- ***The most potent antibiotic known! MIC vs Staphylococcus aureus = ≤ 0.000031 μg/mL***
- Formed by a Bergman cyclization from a benzyl diradical



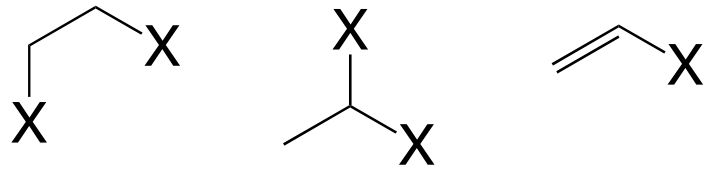
*Micromonospora* spp.




Greenstein *J. Antibiotics* 1989
Kahne *PNAS* 1992
Thorston, *Science* 2003

# Alkyne Preparation

- Alkene starting material forms:

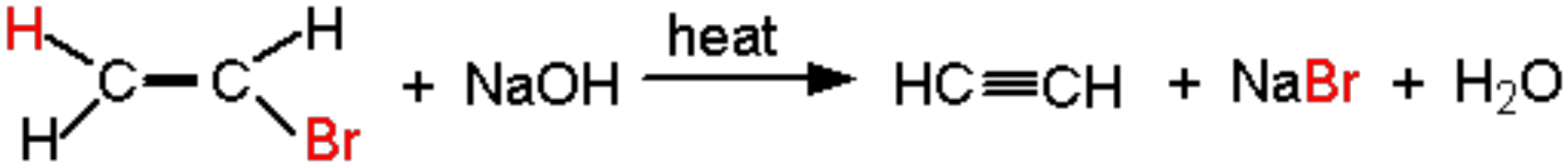



  - Vicinal dihalide (1, 2-dihaloalkane)
  - Geminal dihalide (1, 1-dihaloalkane)
  - Vinyl halides

- Alkynes formed *via* 1 and 2 step elimination reactions from dihalides

# Alkyne Preparation from Elimination of Vinyl Halide

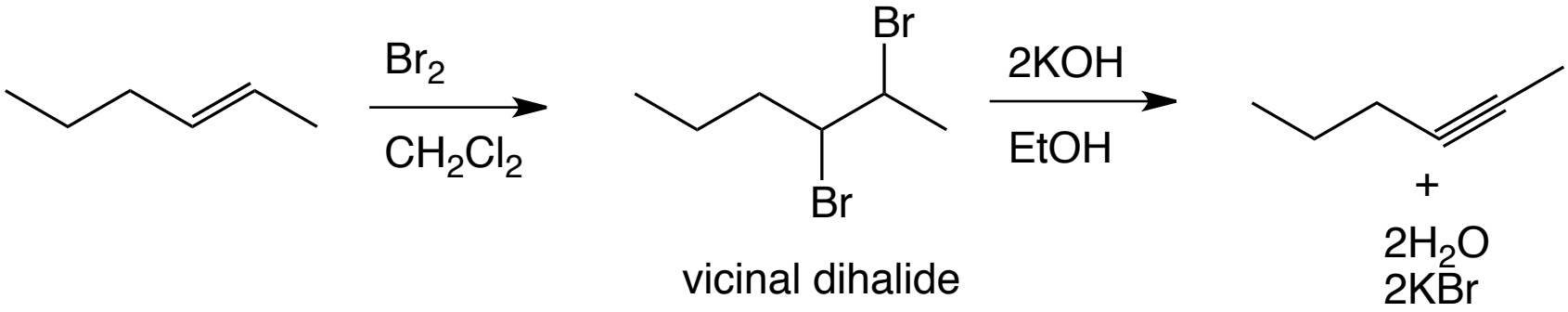
- Strong base required $NaNH_2$ or NaOH + heat
- Vinyl halides are intermediates in two-fold eliminations of vicinal and geminal dihalides
- Can occur via E1, E1CB or E2 elimination depending on structure of starting material




bromoethene
(vinyl bromide)

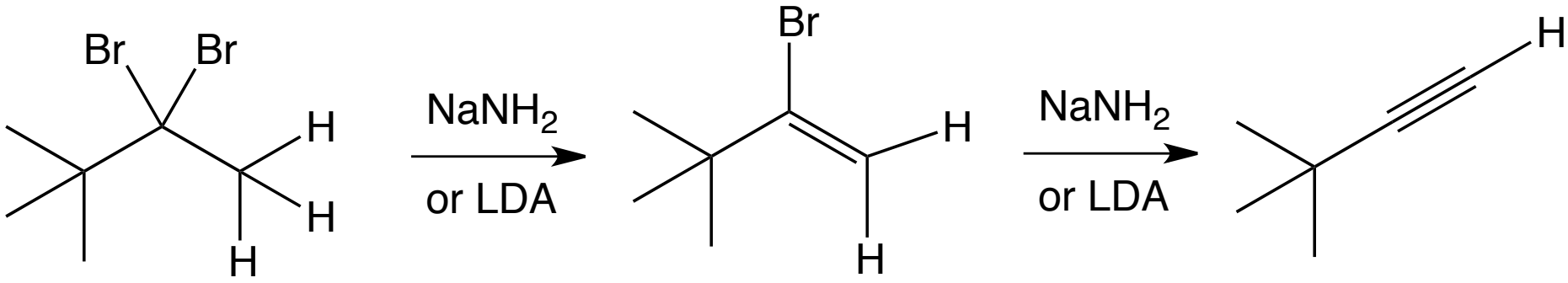
# Preparation of alkynes: Elimination of *vicinal* dihalides

- Similar base-catalyzed elimination reactions as for forming alkenes from alkyl halides
- Vicinal dihalides prepared from alkenes with $Br_2$ or $Cl_2$
- ***Overall reaction is alkene to alkyne***
- Two fold dehydrohalogenation with vinyl halide intermediate



# Alkyne synthesis from *geminal* dihalides or vinyl halides

- Sodium amide ($NaNH_2$) or LDA (lithium diisopropylamide) = ***strong base***
- $NH_2:^-$ anion is the conjugate base of ammonia ($NH_3$)
- Weaker acid = strong congugate base
- pKa $NH_3$ = 38 (i.e. very weak acid)



# Electrophilic Addition reactions of alkynes

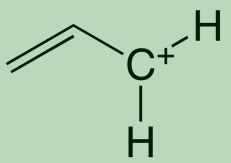
- Electron rich carbon-carbon triple bond is strong and short (965 kJ/mol, 120 pm)
- Alkynes react as nucleophiles with HX and $X_2$ electrophiles
- Mechanistically similar to electrophilic additions of alkenes

- ***Carbocation stability determines regiochemistry of addition***

- Typically proceed with *trans* stereochemistry

# Carbocation stability: Used to determine if a structure can appear in a mechanism

Yes



allyl

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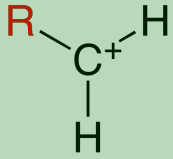

1° alkyl

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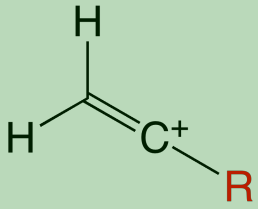

2° vinyl

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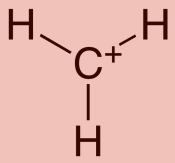
No



methyl

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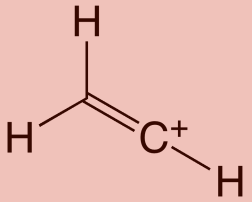
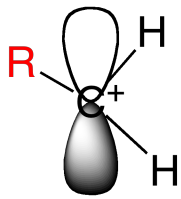


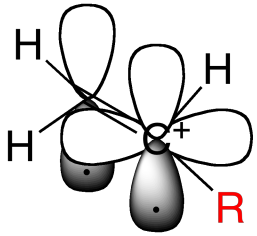
1° vinyl

sp2 hybridized carbocation

-0 π bond
-1 σ bond
-vacant p orbital
-only one R group



sp hybridized carbocation
*note linear geometry*
-1 π bond
-1 σ bond
-vacant p orbital
-only one R group



Vinyl (and aryl) carbocations cannot be stabilized by resonance because π electron clouds are perpendicular to vacant p orbital of carbocation. Resonance requires parallel orbitals for overlap

More stable → Less stable

=

More resonance structures

More hyperconjugation from attached R groups

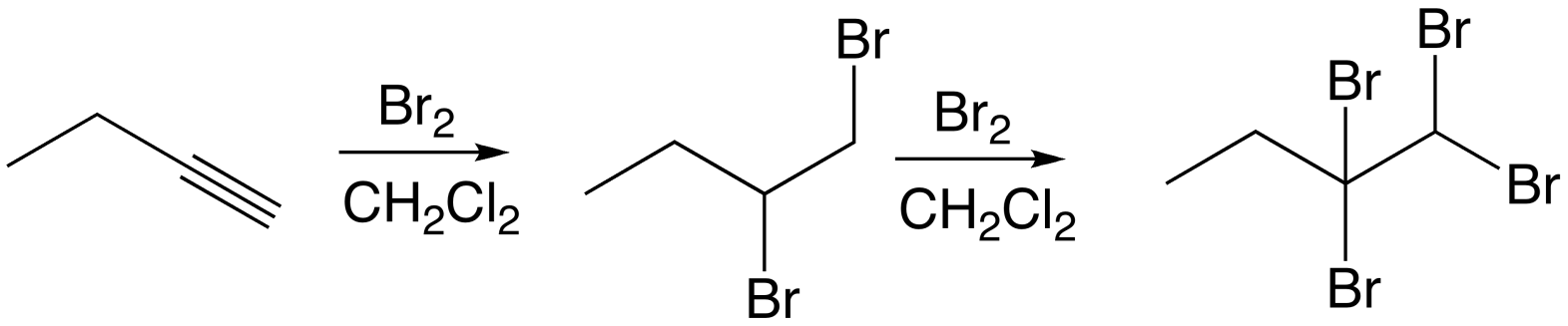
=

Less resonance structures

Less hyperconjugation from attached R groups

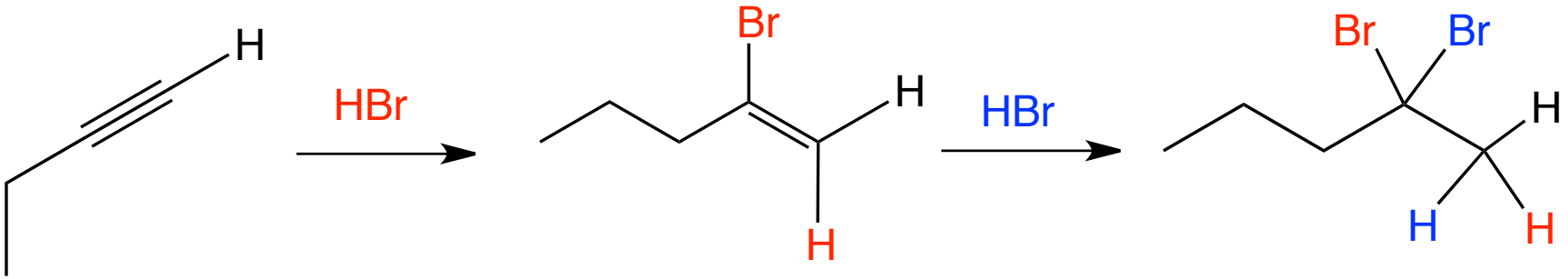
# Electrophilic addition of $X_2$ to alkynes

- Trans vicinal dihalides form first (1 eq of $X_2$)
- Tetrahalides are final (2 eq of $X_2$)



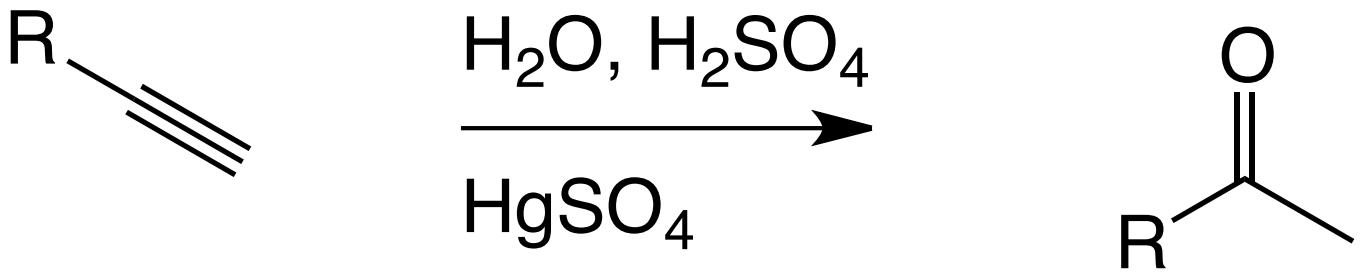
# Electrophilic addition of HX to terminal alkyne

- Vinyl halides form first from 1 eq of HX
- *This is due to carbocation stability ($2^o$ vs $1^o$ vinyl)*
- Geminal dihalides are final product (2 eq of HX)
- *Also due to carbocation stability ($3^o$ vs $1^o$ vinyl)*



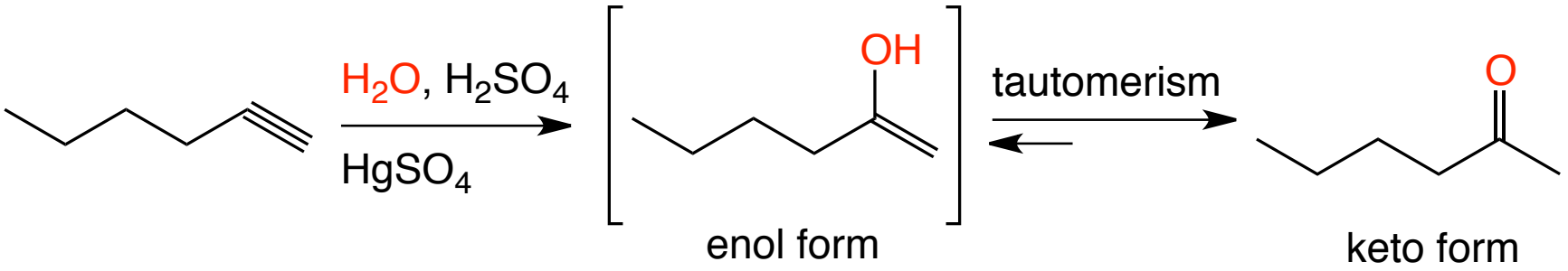
# Oxymercuration/Demercuration with Terminal Alkynes

- Terminal alkynes are best candidates for hydration because they produce a single product – methyl ketones

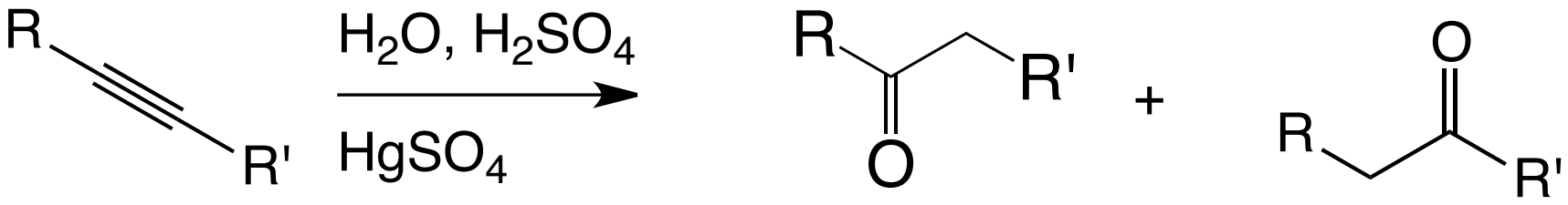


# Hydration of Alkynes *via* Oxymercuration/Demercuration

- Very similar to hydration of alkenes
- Markovnikov addition of water by Hg (II) ion gives product
- Keto-enol *tautomer* product (isomers that spontaneously interconvert by moving a electrons and a hydrogen atom)
- Unsymmetrical internal alkynes give mixtures of ketones
- Terminal alkynes give only methyl ketones



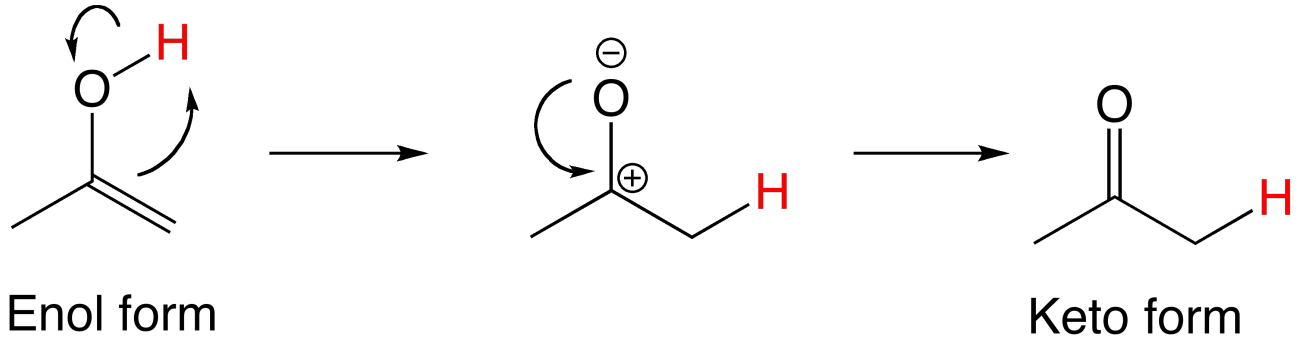
# Unsymmetrically substituted internal alkynes give a mixture of ketones

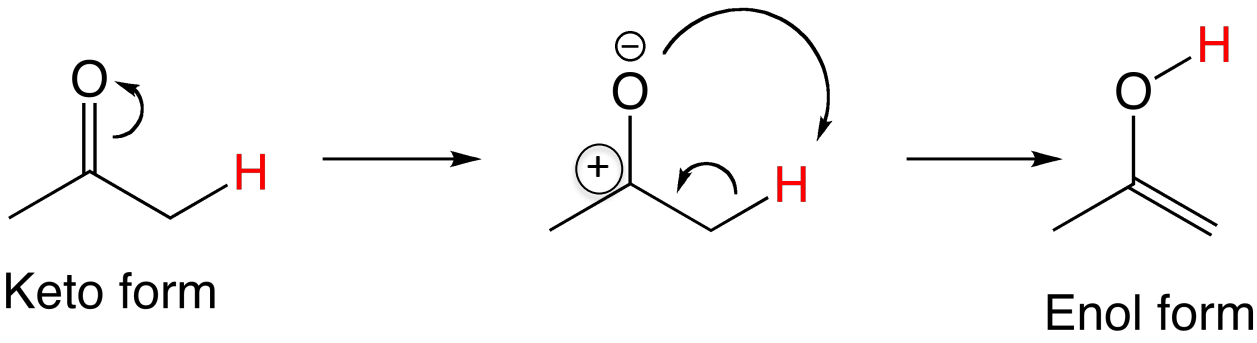



Since oxidation can occur at both ends of triple bond, 2 products result from unsymmetrical alkynes

# Keto-Enol Tautomers

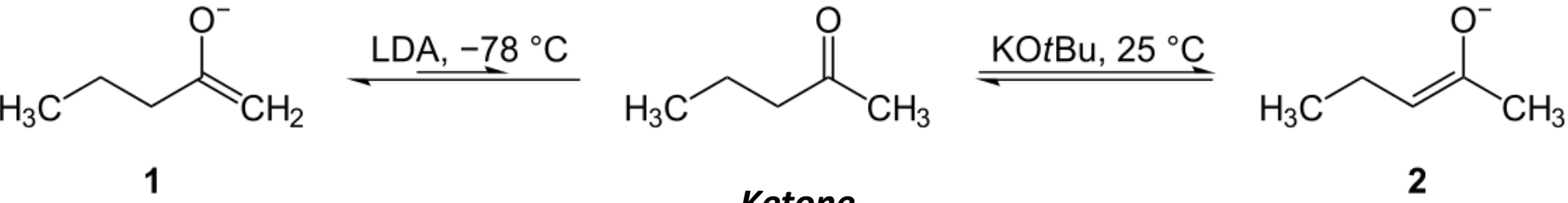
- Keto-enols are “tautomers”
- Tautomers are constitutional isomers that interconvert via migration of a proton
- Very important in mechanism of many reactions



# Enolates

- Enolates are formed from deprotonation of a keto-enol system
- Protons alpha to a carbonyl are slightly acidic
- Must form in Brønsted acid free conditions since they are very basic
- Can modulate regiochemistry with temperature and base selection




**1**

***Ketone***

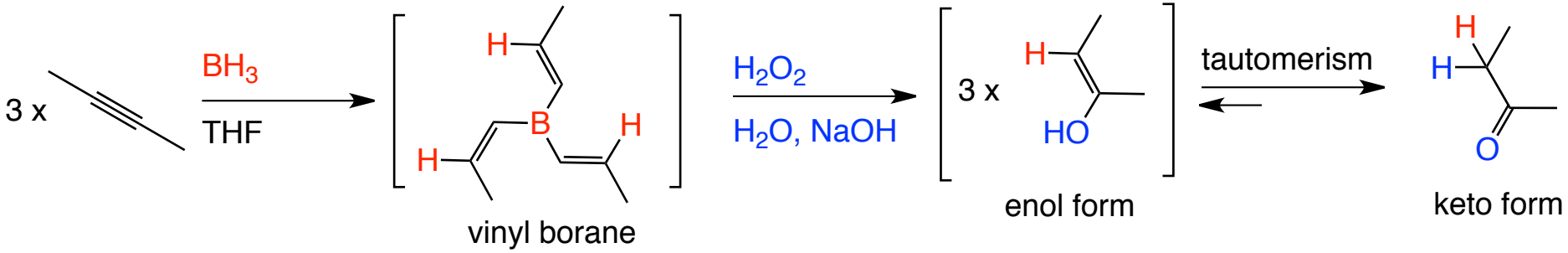
**2**

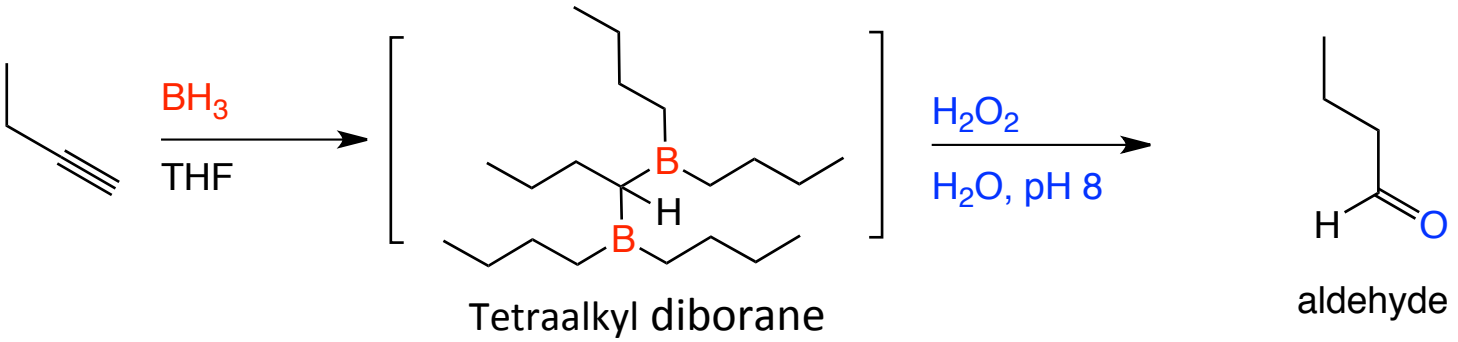
***Kinetic enolate***
(sterically most accessible proton
is removed with stronger base at low temps)

***Thermodynamic enolate***
(weaker base, higher temps
removes more "hindered"
proton)

# Hydroboration/Oxidation of Alkynes

- Borane adds rapidly to alkynes (mechanism similar to addition to alkenes)
- *Markovnikov rules are not applicable to internal alkynes*
- Internal alkynes give ketones (keto-enol tautomer product)
- *Terminal alkynes give aldehydes ("Anti-Markovnikov")*

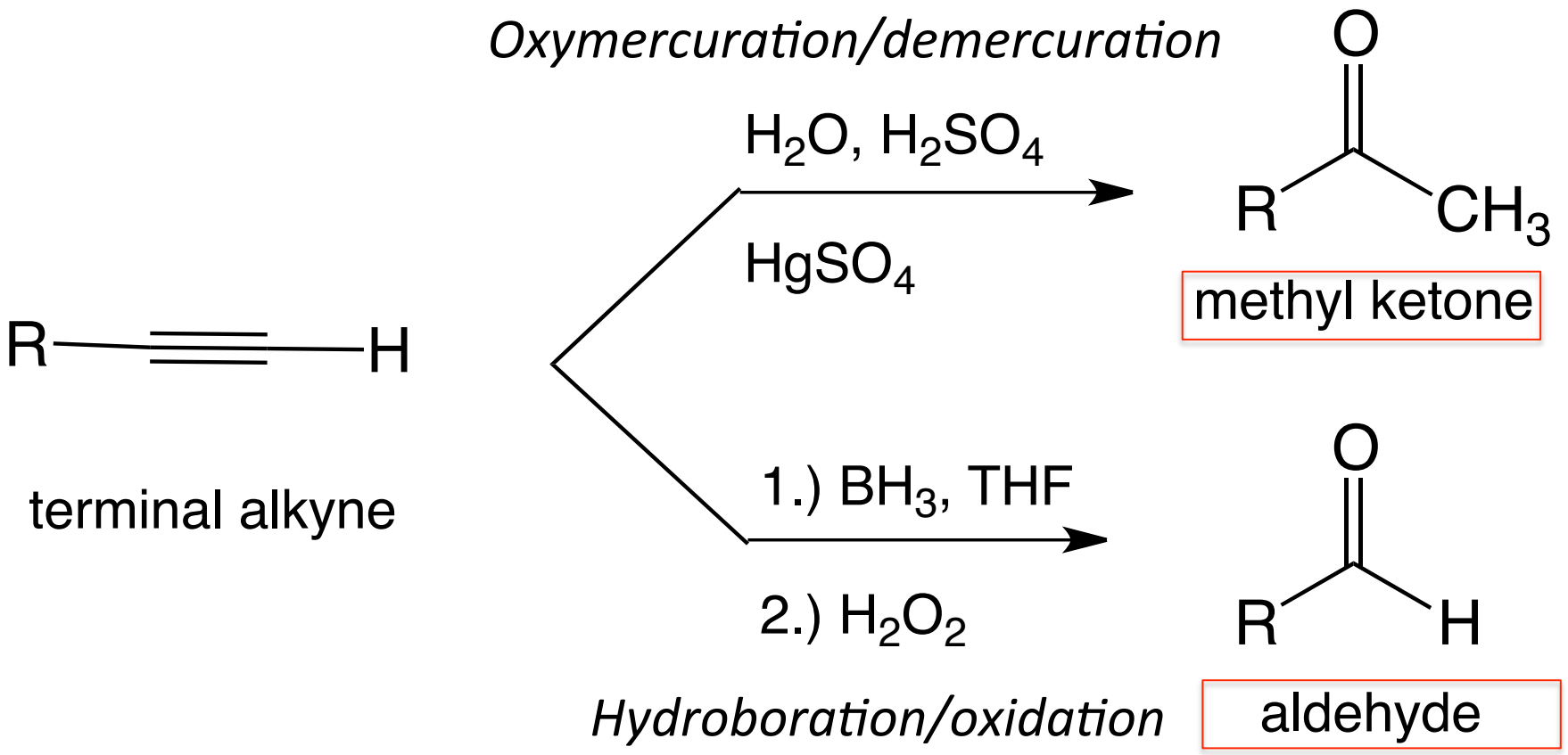


# Internal alkyne oxidation

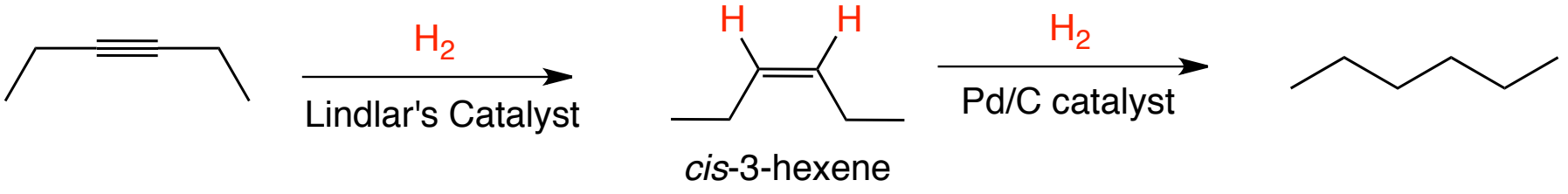
- Give ketone products using **either** oxymercuration/demercuration or hydroboration/oxidation
- If alkyne is symmetrically substituted = one ketone product results
- If alkyne is asymmetrically substituted = mixture of products

# Terminal alkyne oxidation: Complimentary procedures ☺

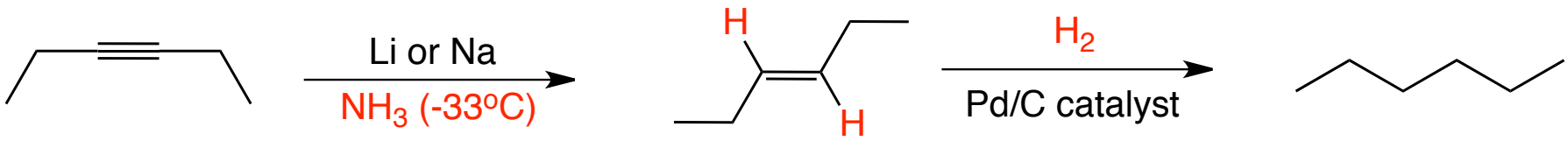


# Complimentary Alkyne Reduction to form *cis* or *trans* Alkenes and Alkanes

- ***Alkynes are reduced to alkenes and alkanes depending on catalyst selection***
- Two step, non-degenerate process involving $H_2$ with Lindlar's catalyst (-176 kJ/mol) followed by $H_2$ with Pd/C (-137 kJ/mol)
- Hydrogenation of alkynes occurs with *syn* stereochemistry to give *cis* alkene product using Lindlar catalyst
- Hydrogenation of alkynes occurs with *anti* stereochemistry to give *trans* alkene product using Li or Na catalyst with liquid ammonia as proton donor (radical anion mechanism with amide ion stabilized by metal)



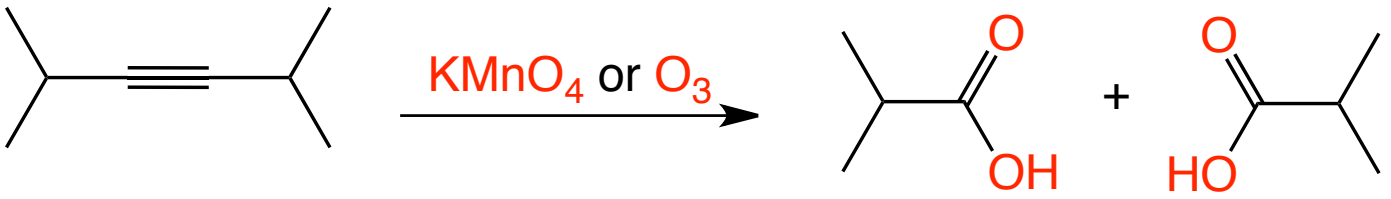

*cis*-3-hexene

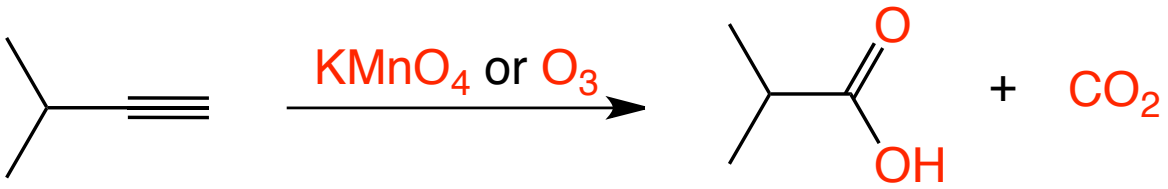



*trans*-3-hexene

# Oxidative Cleavage of Alkynes

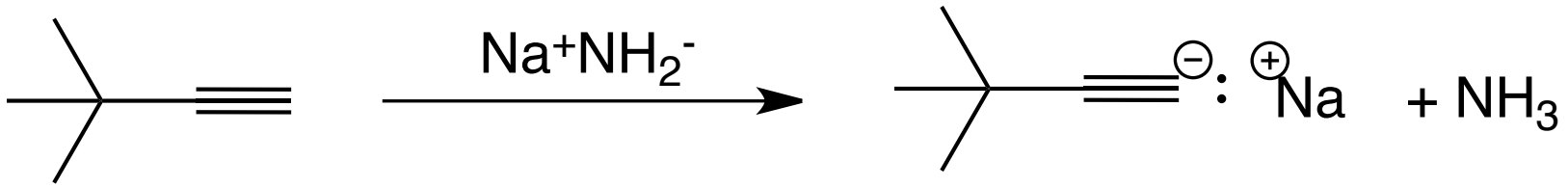
- ***Powerful oxidants such as $O_3$ and $KMnO_4$ can be used to cleave alkynes (similar to alkene mechanism)***
- Yields typically low due to alkyne stabilities
- *Internal alkynes give 2 carboxylic acids*
- *Terminal alkynes give 1 carboxylic acid + 1 $CO_2$*



# Alkyne Acidity: Formation of Acetylide Anions

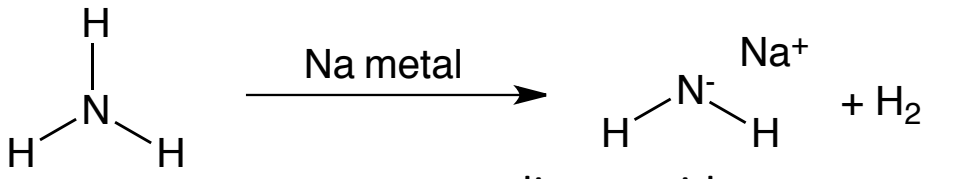
- ***As compared to alkenes, alkynes are relatively acidic***
- Treatment with strong base (i.e. sodium amide, $Na^+ :NH_2^-$) will remove terminal proton



# Review of p*K*a for use in Organic Reactions

- *An acid can be deprotonated by the conjugate base of another acid that has a larger pKa*

| Family | Example | *K*a | p*K*a |
|---|---|---|---|
| ***Alkyne*** | ***CHCH (acetylene)*** | ***$10^{-25}$*** | ***25*** |
| Alkene | $CH_2CH_2$ (ethylene) | $10^{-44}$ | 44 |
| Alkane | $CH_4$ (methane) | $10^{-60}$ | 60 |




***ammonia acid (pKa = 35)***

sodium amide, a very strong base
(conjugate base of ammonia)

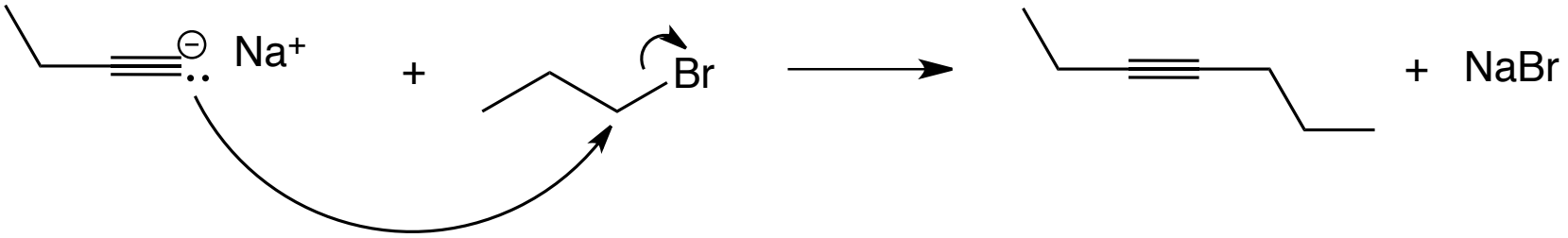
# Alkyne Acidity: Explained with Atomic Orbitals

- Acetylide anion has 50% "s-character"
- s-orbitals are physically closer to positively charged nucleus and lower in energy than p-orbitals
- Negative charge of anion thus has greater stability in an orbital with greater s-character because electrons are closer to nucleus and thus stabilized, lower energy

| Family | Example | Hybridization | % "s-character" |
|---|---|---|---|
| ***Alkyne*** | ***CHCH (acetylene)*** | ***sp*** | ***50*** |
| Alkene | $CH_2CH_2$ (ethylene) | sp2 | 33 |
| Alkane | $CH_4$ (methane) | sp3 | 25 |

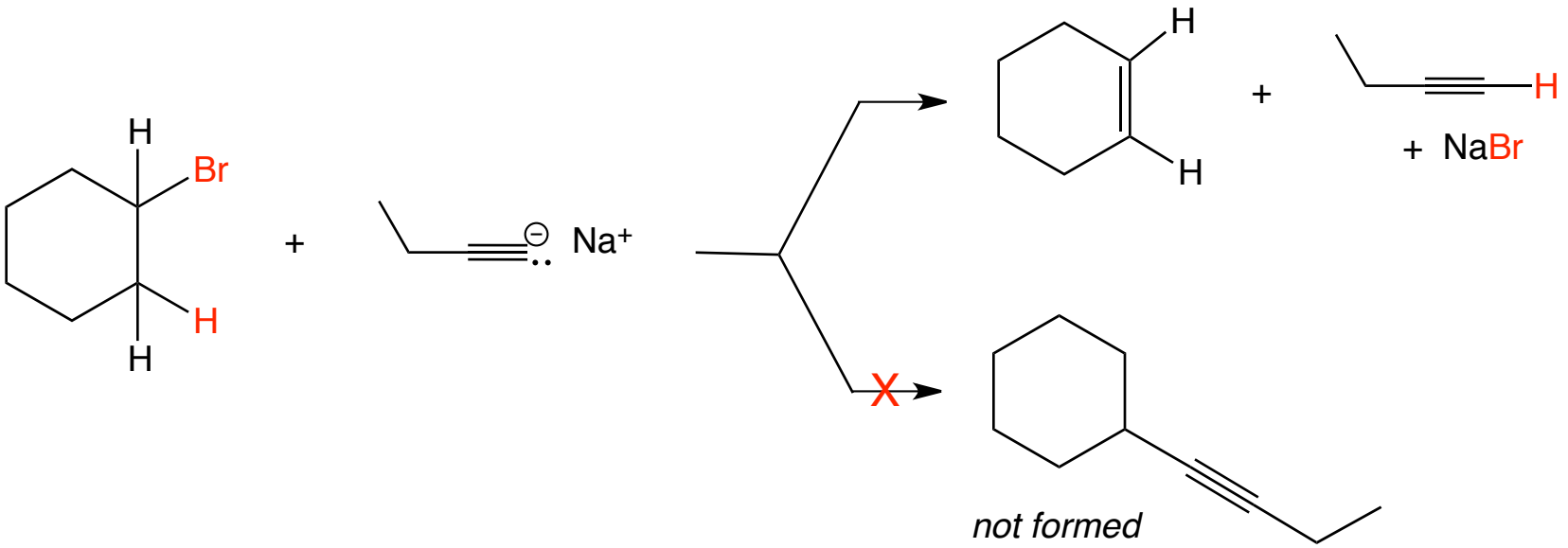
# Alkylation of Acetylide Anions

- Acetylide = Always terminal = linear unhindered geometry, negative charge and electron lone pair make alkyne anions great nucleophiles
- Can react with alkyl halide (electrophiles) to make new C-C bond!



# Limitations to Alkylation using an Alkyne Anion

- The reaction is limited to use with primary alkyl bromides and alkyl iodides
- Because of alkyne anion's basicity, it causes elimination with 2° and 3° alkyl halides



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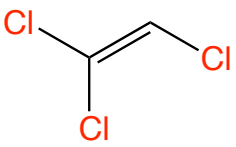
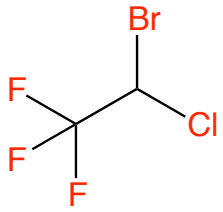
- Final Exam will be in Snow Hall Monday, May 23 or Weds, May 25 - from 6-9pm.
- Vote to decide

# Organohalides

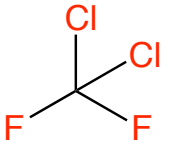
- Organic compounds with 1+ halogen atom
- Widespread in nature - over 5000 organohalides described
- Chloromethane (kelp, forest fires, volcanoes)
- Industrial use (solvents, anesthetics, refrigerants, pesticides)



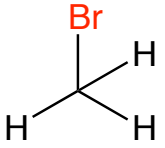

Trichloethylene
*(solvent)*



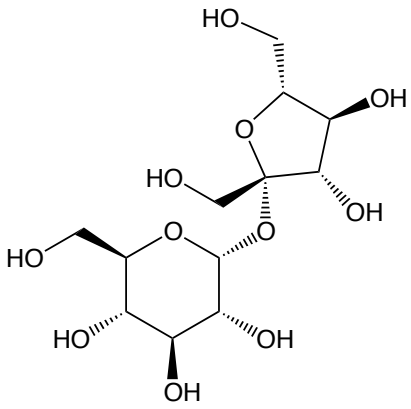

Halothane
*(inhaled anesthetic)*



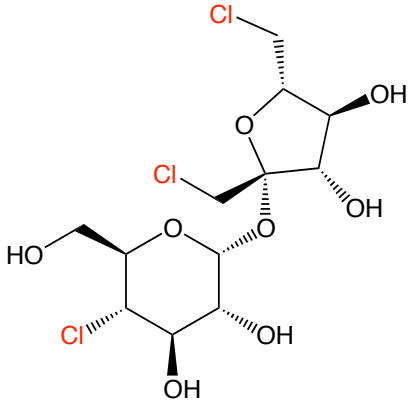

Dichlorodifluoromethane
*(refrigerant)*




Bromomethane
*(fumigant)*




sucrose
*(table sugar)*



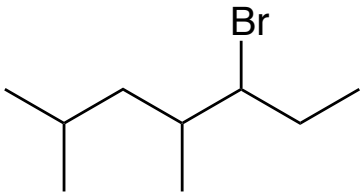

sucralose
***600 x sweeter than table sugar***
*(1 mg = 1 teaspoon)*

# Why Study Organohalides?

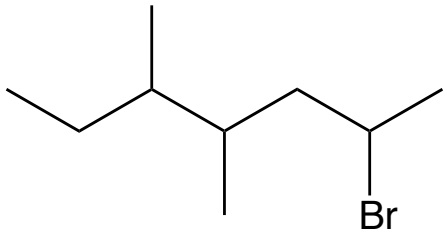
- Many alkynyl halides and alkenyl halides are known
- We are primarily concerned with alkyl halides because of the similarity in their reactivity (lab) as compared to alcohols (nature)
- Substitution and elimination reactions of alkyl halides thus provide a model for analogous biological reactions (occurring with alcohols)

# Naming Linear Alkylhalides

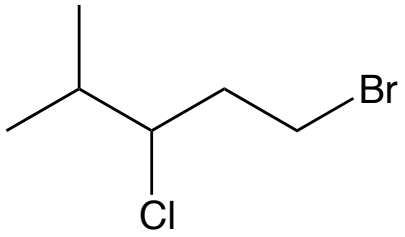
- Number longest chain starting at the end nearest the first substituent (either halo or alkyl)
- Name compound as a substituted alkane (i.e. bromo-methylheptane, not methyl-bromoheptane)




5-bromo-2,4-dimethylheptane



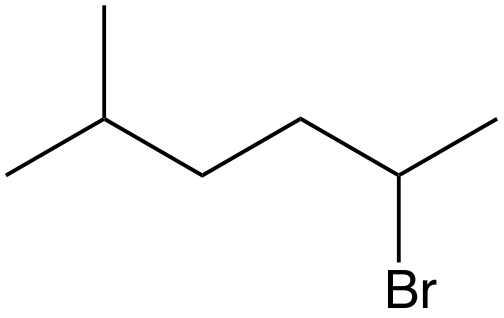

2-bromo-4,5-dimethylheptane




1-bromo-3-chloro-4-methylpentane

# Naming Linear Alkylhalides, cntd

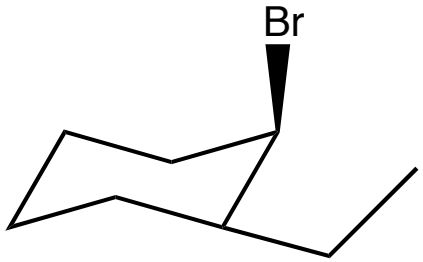
- If the parent chain can be properly numbered at either end, begin at the end nearer the substituent that has alphabetical priority



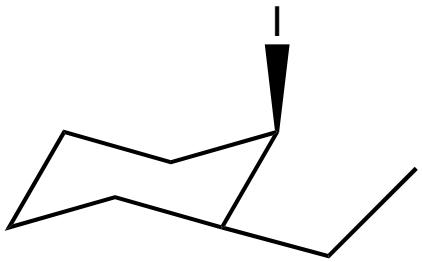

2-bromo-5-methylhexane
(not 5-bromo-2-methylhexane)

# Cyclic Alkyl Halide Nomenclature

- Name as “cycloalkane” which allows for movement of halide portion of name (it’s not always first)




(1*R*)-1-bromo-2-ethylcyclohexane




(2*R*)-1-ethyl-2-iodocyclohexane

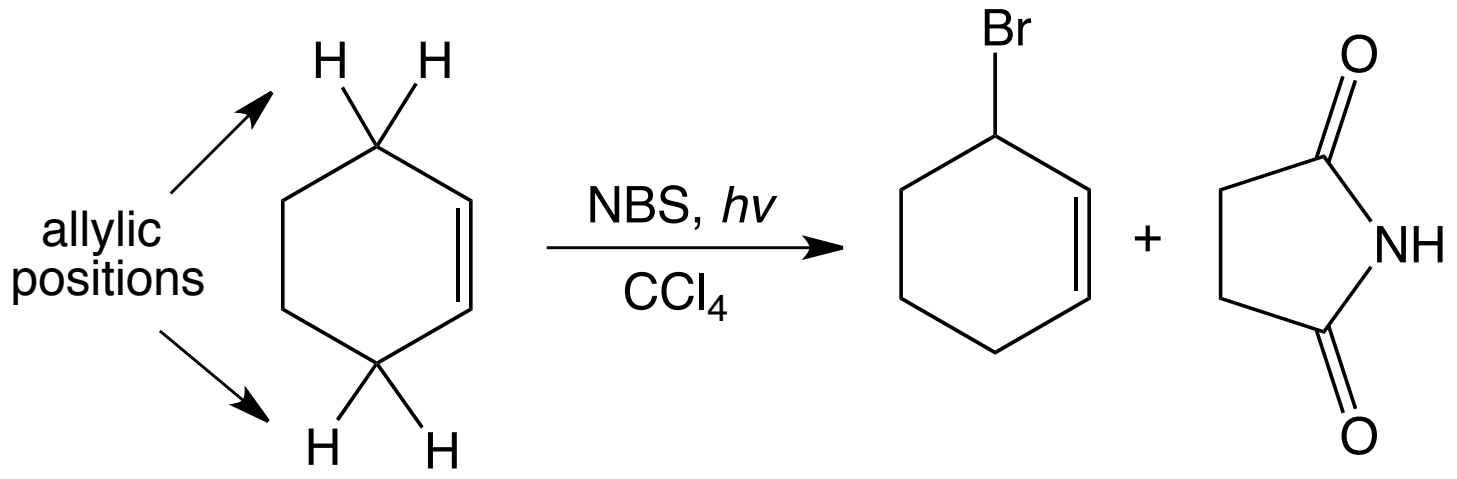
# Physical Properties of Alkylhalides

- Longer the bond length, the weaker the C-X bond
- Higher the dipole moment of C-X bond the better the electrophilicity of alkylhalide carbon atom
- The C-Br bond represents "best of both worlds"

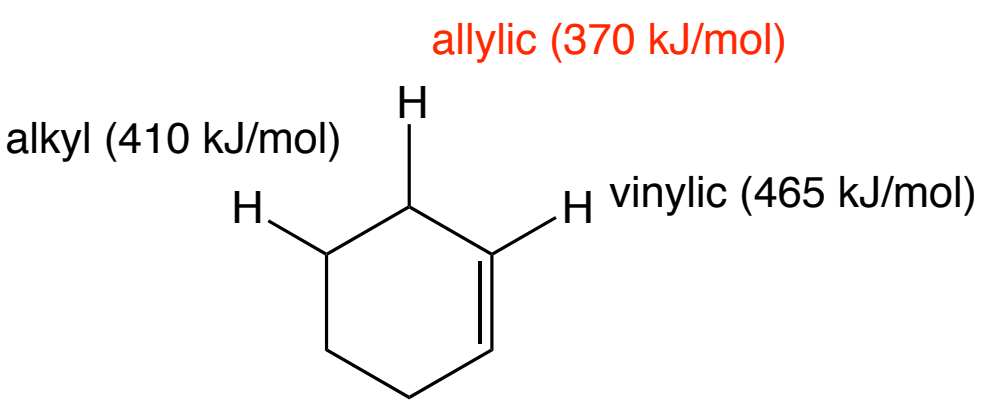
| Halomethane | Bond Length (pm) | Bond Strength (kJ/mol) | Dipole moment (*D*) |
|---|---|---|---|
| $CH_3F$ | 139 | 460 | 1.85 |
| $CH_3Cl$ | 178 | 350 | 1.87 |
| ***$CH_3Br$*** | ***193*** | ***294*** | ***1.81*** |
| $CH_3I$ | 214 | 239 | 1.62 |

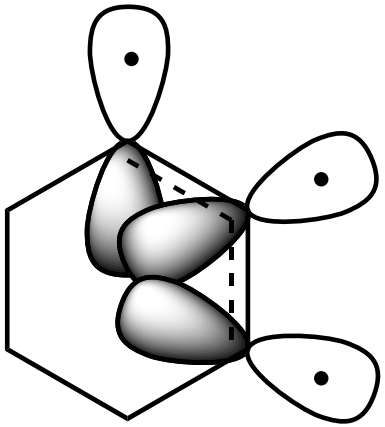
# Allylic Bromination

- Alkenes typically undergo *anti* addition with $Br_2$ (through halonium ion intermediates) to give *trans* products
- However, a free radical mechanism can give selective "allylic" bromination using NBS



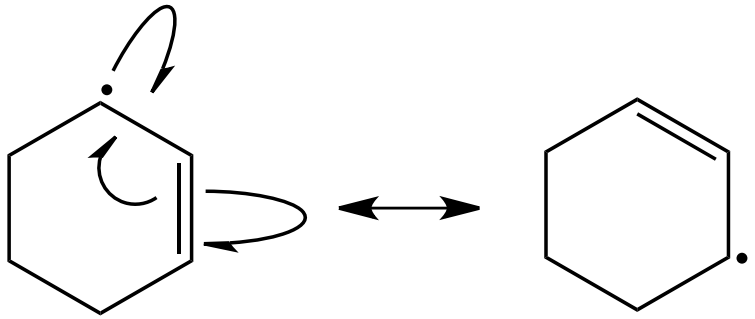
# Bond Dissociation Energy, Resonance and Resulting Stability of Allylic Radicals



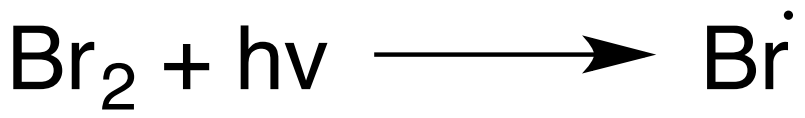



- All ***conjugated*** carbon atoms adopt $sp^2$ hybridization
- Leads to electronic symmetry and bonding electrons spread over more nuclei
- This increases molecule's stability
- However, electron ***delocalization*** leads to product mixtures…

resonance stabilization

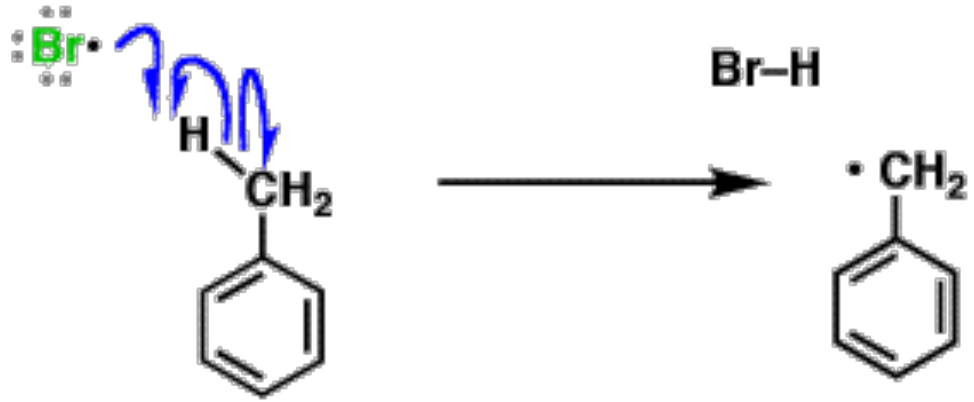


**Initiation** – Generate Br radical



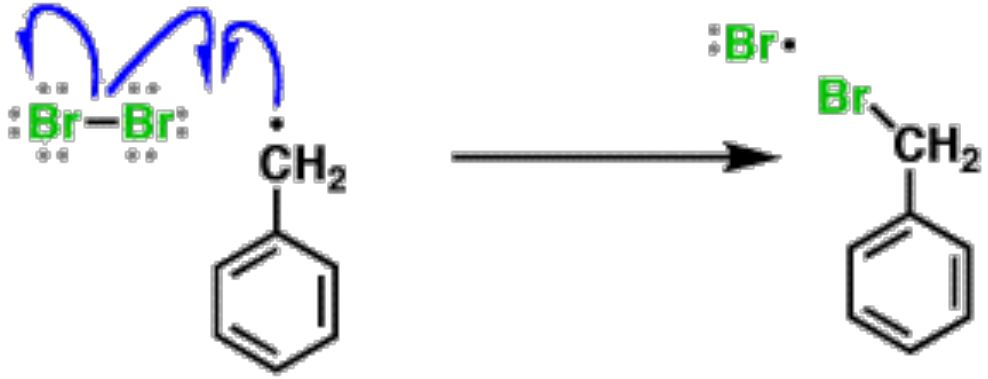

**Propagation Step 1**

| Form | Break |
|---|---|
| Br–H | C–H |

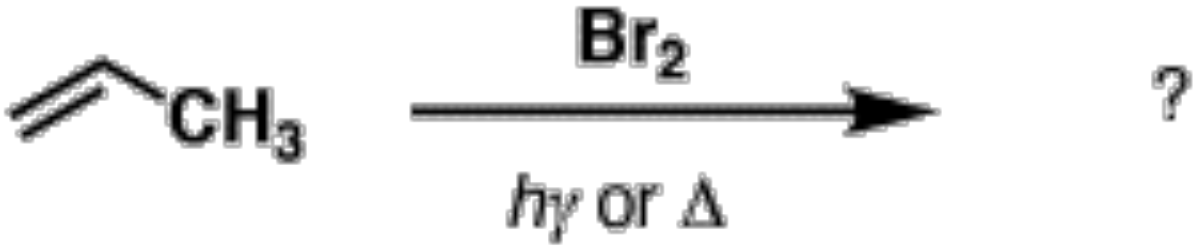



**Propagation Step 2**

| Form | Break |
|---|---|
| C–Br | Br–Br |

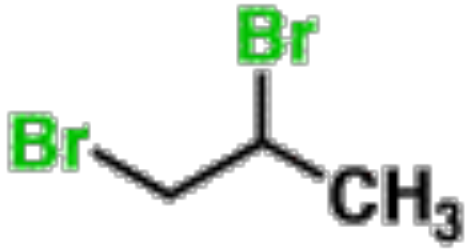


# Problem with excess $Br_2$

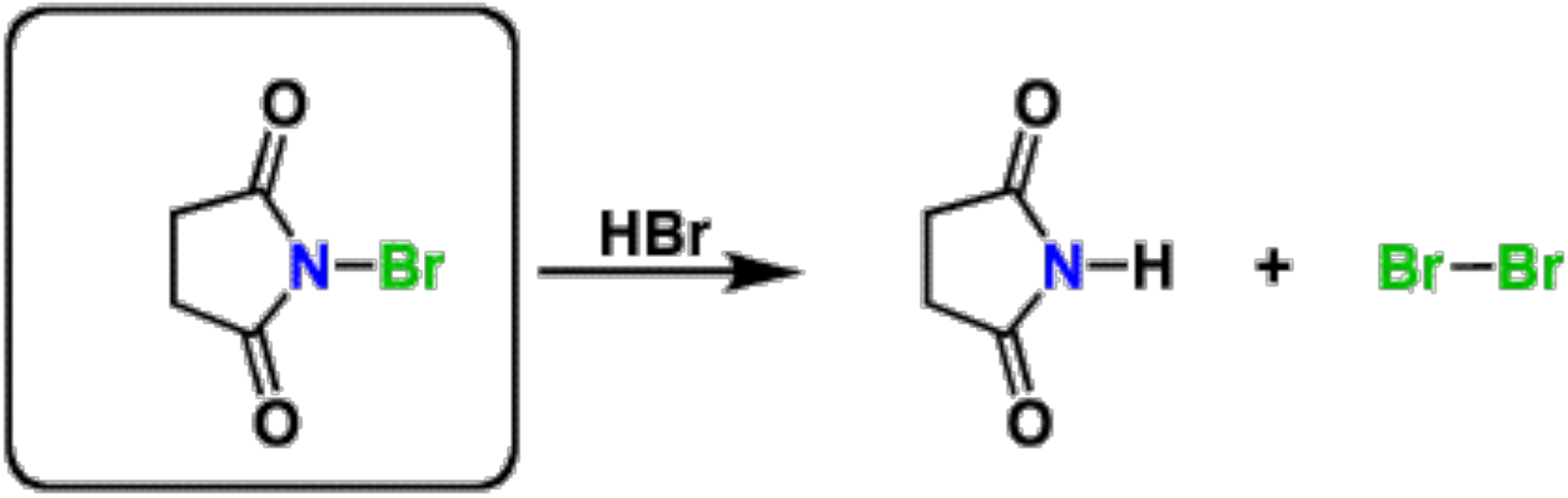



*Desired product*


*Actual product*

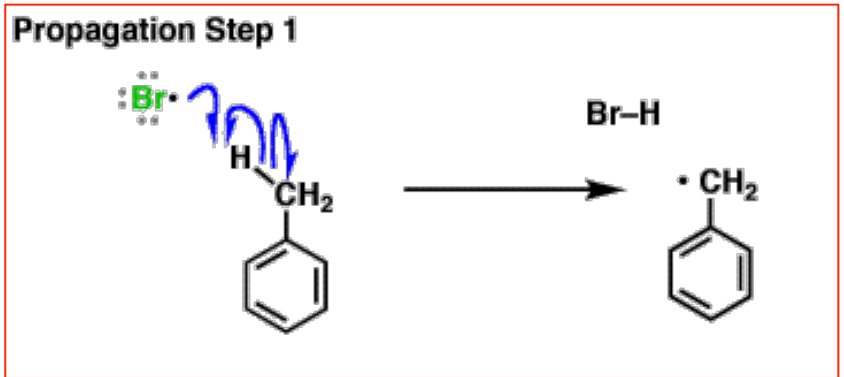


# NBS reacts with HBr product from Propagation Step 1 to form $Br_2$ effectively controlling the reaction rate



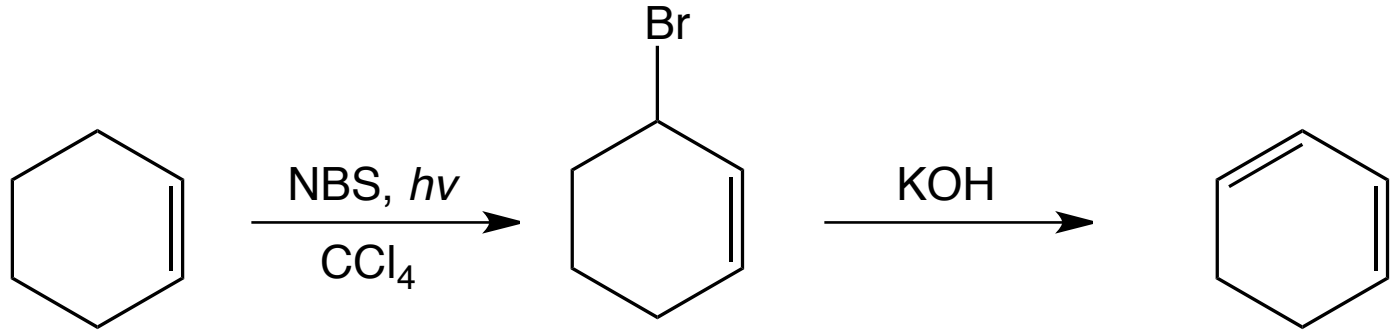

***N*-bromo succinimide (NBS)**

**Succinimide**

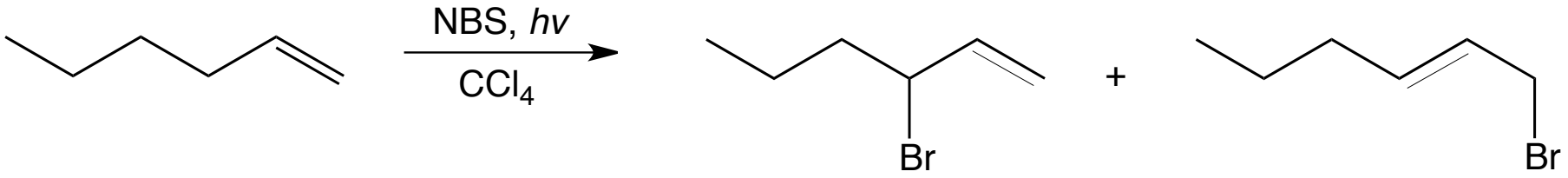


# Pros and Cons of Allylic Bromination

- Pros:  Products are useful for preparing dienes




- Cons: Unsymmetrical alkenes give product mixtures (*via* allylic rearrangement)



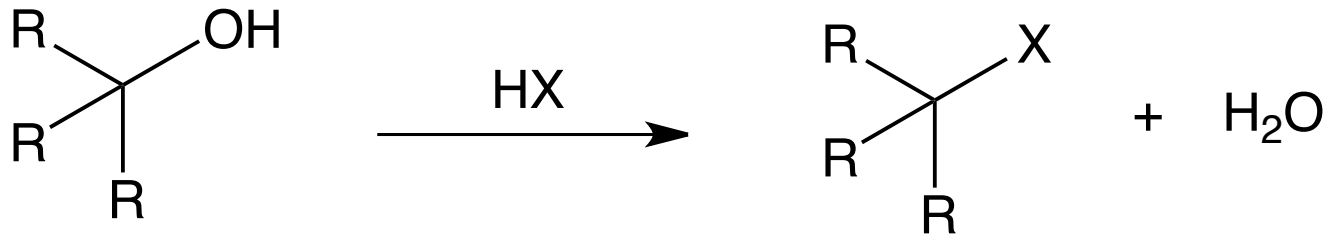
# Preparation of Alkyl Halides from Alcohols

- ***Converting alcohols to alkyl halides is important transformation***

- Order of alcohol reactivity:

  methyl (slowest) < 1° < 2° < 3° (fastest)

  *alkoxide anion is stabilized by induction from R groups*




R = H or alkyl

***Nucleophilic substitution mechanism:***

***- Methyl and 1° alcohols (SN1)***

***- 2° and 3° alcohols (SN2)***

# Milder Reagents for Alkyl Halide Preparation from Alcohols

***Less acidic and less likely to cause acid-catalyzed rearrangements:***

R-Cl = Thionyl chloride ($SOCl_2$) in pyridine

R-Br = Phosphorus tribromide ($PBr_3$) in ether at 35$^oC$

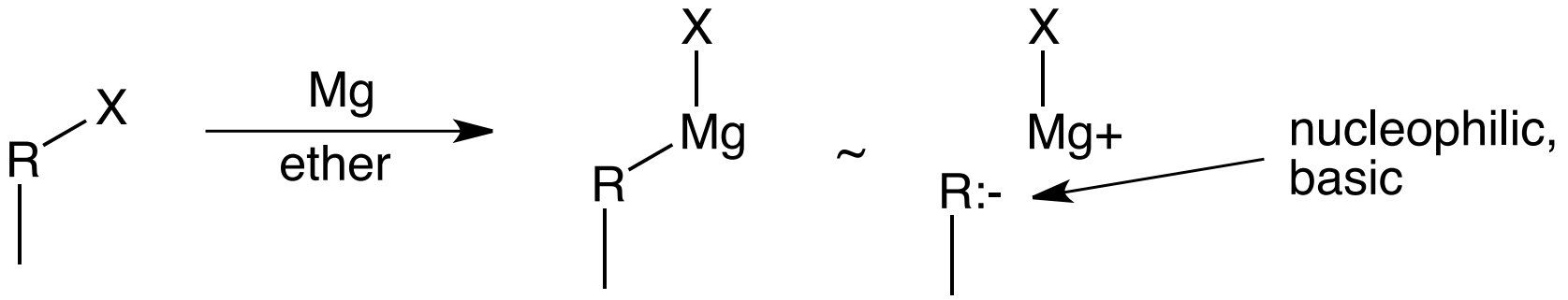
R-F = Hydrofluoric acid (HF) in pyridine

*Works with secondary and tertiary alcohols only*

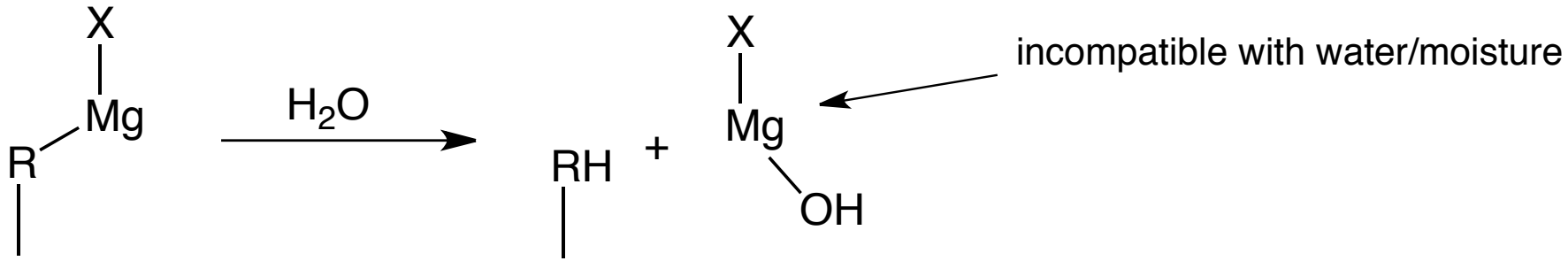
# Grignard Reagents for the Preparation of C-C Bonds

- Alkyl halides (RX) react with Mg metal in ether or THF to produce alkyl magnesium halides (RMgX).
- Product is a "Grignard Reagent" which is good nucleophile (it's a carbanion salt of $Mg^{+}$)
- Since the acidity of hydrocarbons so low (pKa = 44-60), the anions are strong conjugate bases
- Must be protected from moisture or will quickly convert back to hydrocarbon (thus the Grignard reaction has limited utility)
- Large scope of alkyl and halo substrates
  - $1^{o}$, $2^{o}$, $3^{o}$ alkyl, alkenyl, aryl
  - Cl (slow), Br, I

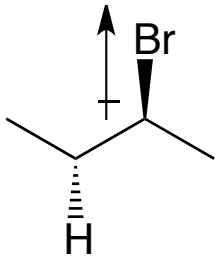
# The Grignard Reaction




R = 1º, 2º, 3º alkyl, alkenyl or aryl
X = Cl, Br or I

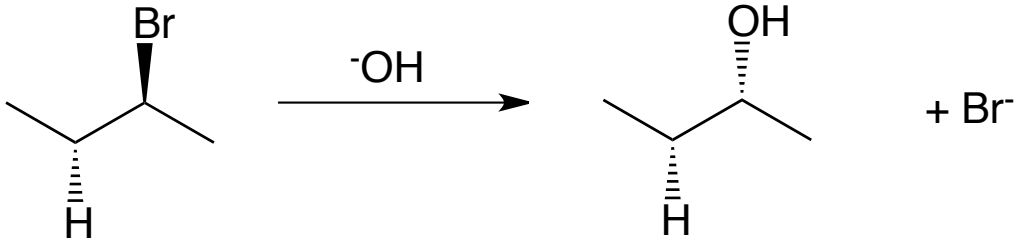


# Alkyl Halides are Electrophiles

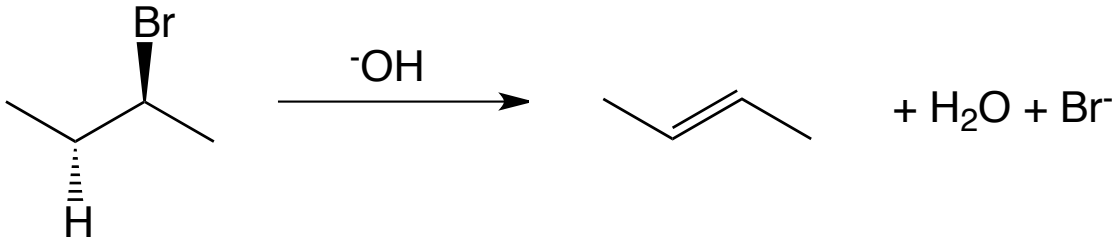



- Upon treatment with base or nucleophiles alkyl halides will undergo:

- Substitution




- and/or Elimination



# Two Types of Nucleophilic Substitution Reactions

## $S_N2$

Substitution

Nucleophilic

Bimolecular (2)

Rate = k [RX] [Nuc:]

*Complete inversion of configuration of electrophile* (concerted mechanism)

## $S_N1$

Substitution

Nucleophilic

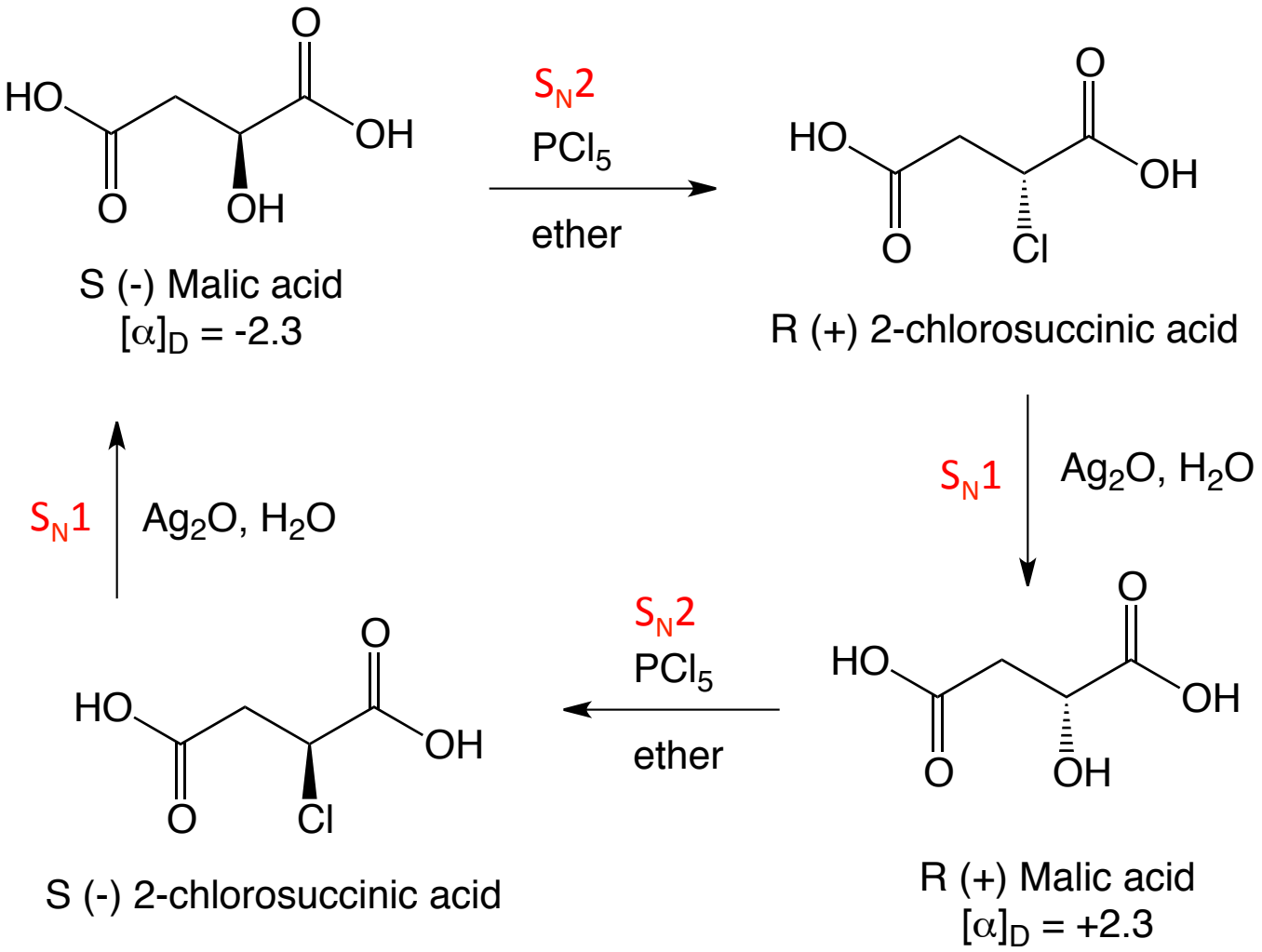
Unimolecular (1)

Rate = k [RX]

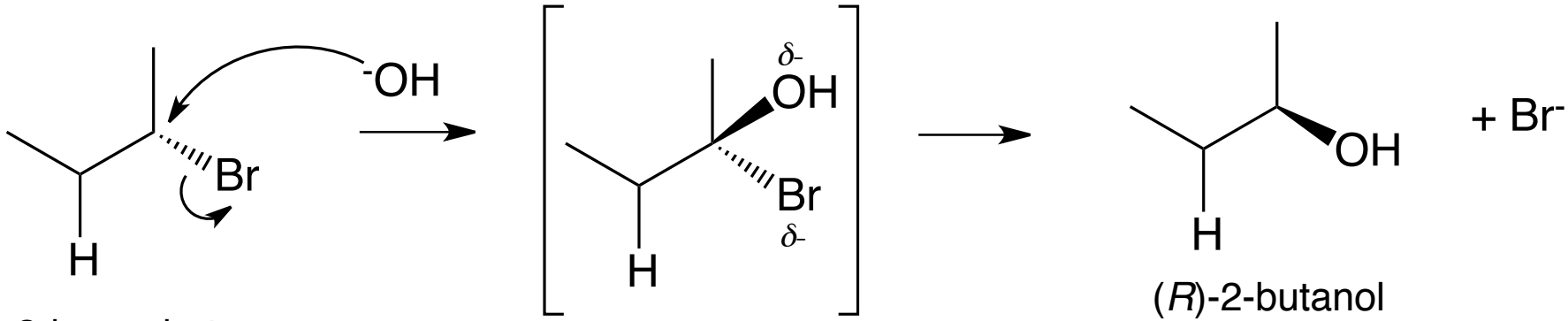
*Mixtures of stereoisomers produced* (planar carbocation intermediate)

# Nucleophilic Substitution Reaction

- Discovered by Paul Walden (1896) by observing SM and product optical rotations
- *Reactions occur with inversion of configuration*
- SN2 and SN1 reactions occuring



# The $S_N2$ Reaction Mechanism



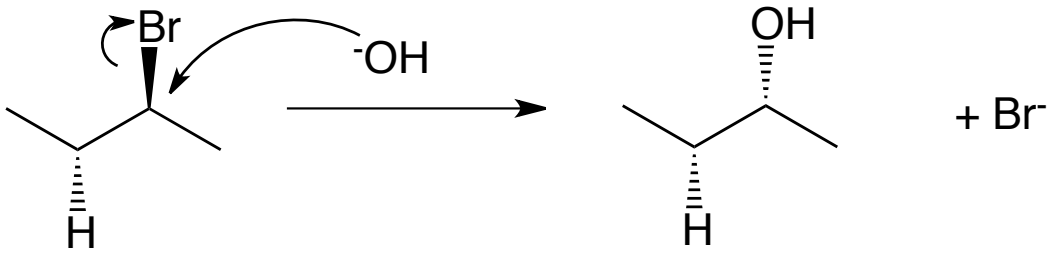

(*S*)-2-bromobutane

bimolecular transition state accounts for kinetics and stereochemical inversion

(*R*)-2-butanol

# Kinetics of Nucleophilic Substitutions

- Kinetics = Reaction Rate = how fast (or slow) reactants are converted to products
- Because reactions rely on molecular collisions, *rates are determined by reactant concentrations*




- At a given temperature and solvent:
  - If [$OH^-$] is doubled, the rate may double
  - If [alkyl bromide] is doubled, the rate may double

***$S_N2$ = Second order kinetics = when the rate has a linear dependence on two reactants***

# Mathematics of Kinetics

***Reaction rate*** = rate of disappearance of reactant (or appearance of products). This is what is measured/ determined experimentally

Rate = $k$ [RX] x [$OH^-$]

Units = Liter/mol x second

Where:

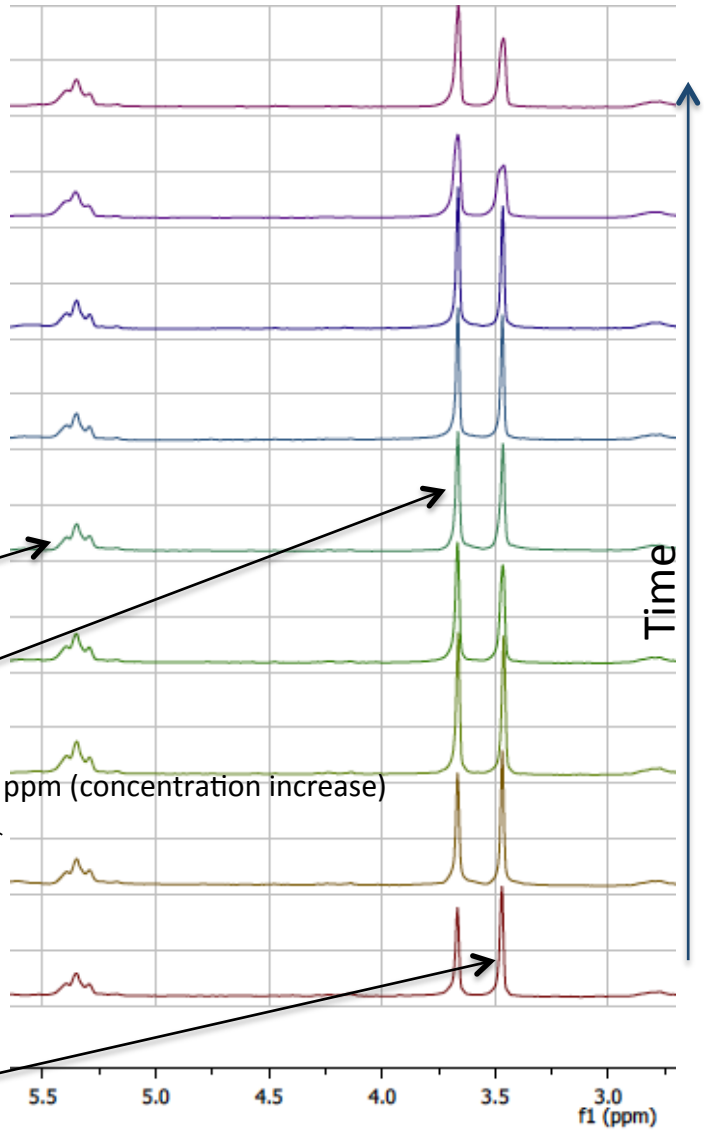
[RX] = Molar concentration of alkyl bromide electrophile

[$OH^-$] = Molar concentration of $OH^-$ nucleophile

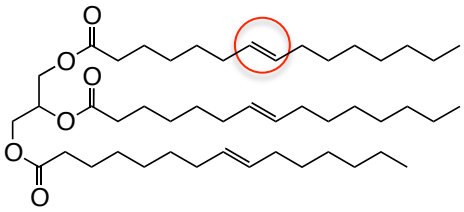
$k$ = rate constant

# Kinetics to Measure Biodiesel Production

Cool…




Olefin $CH_2$ 5.3 ppm (no concentration change)

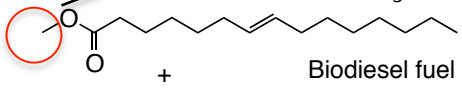


Fats and oils in recycled cooking oil

KOH

$CH_3OH$

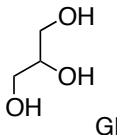
60°C, 60 min



Me ester $CH_3$ 3.7 ppm (concentration increase)

Biodiesel fuel

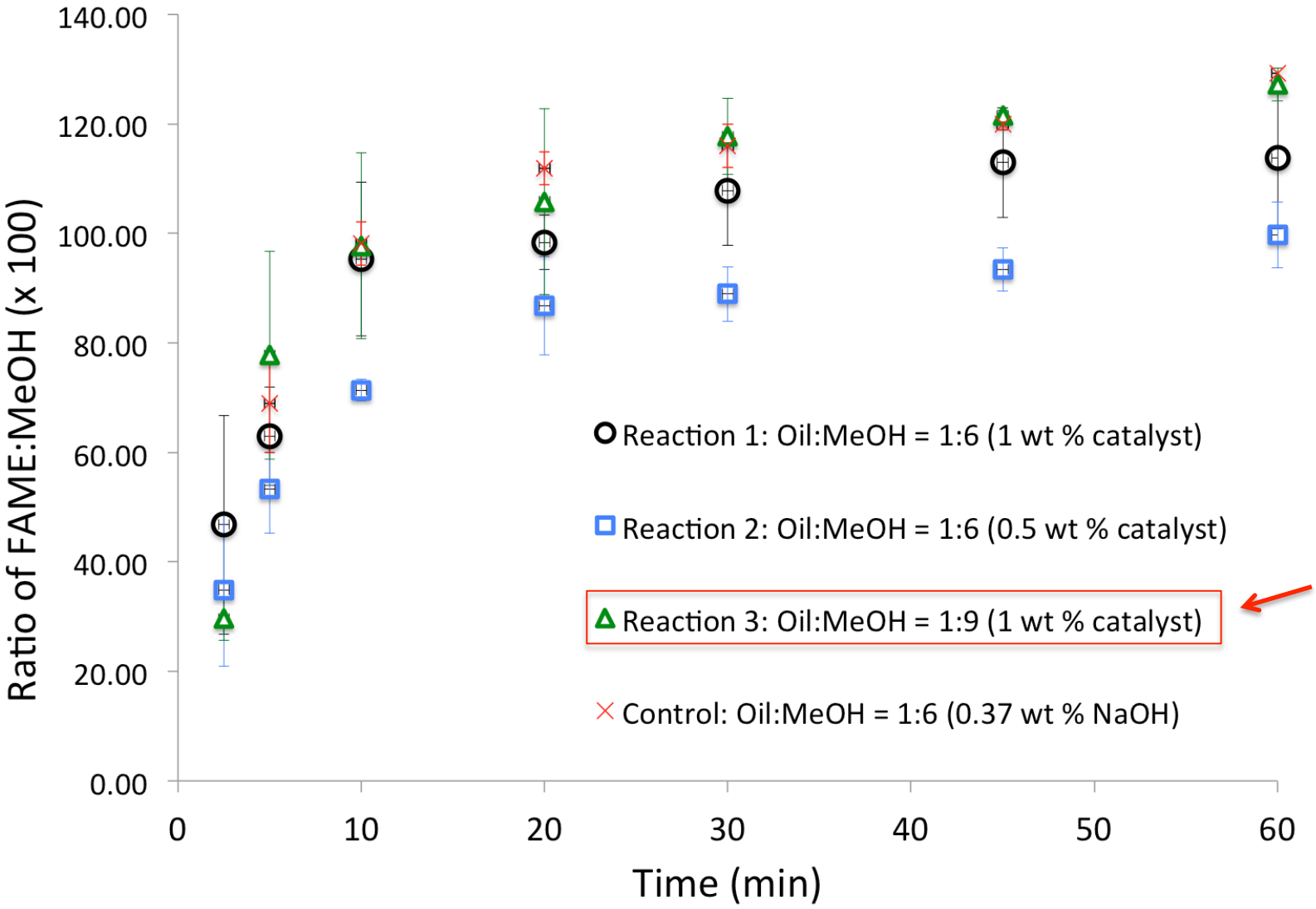
+



Glycerol (byproduct)

MeOH $CH_3$ 3.5 ppm (concentration decrease)

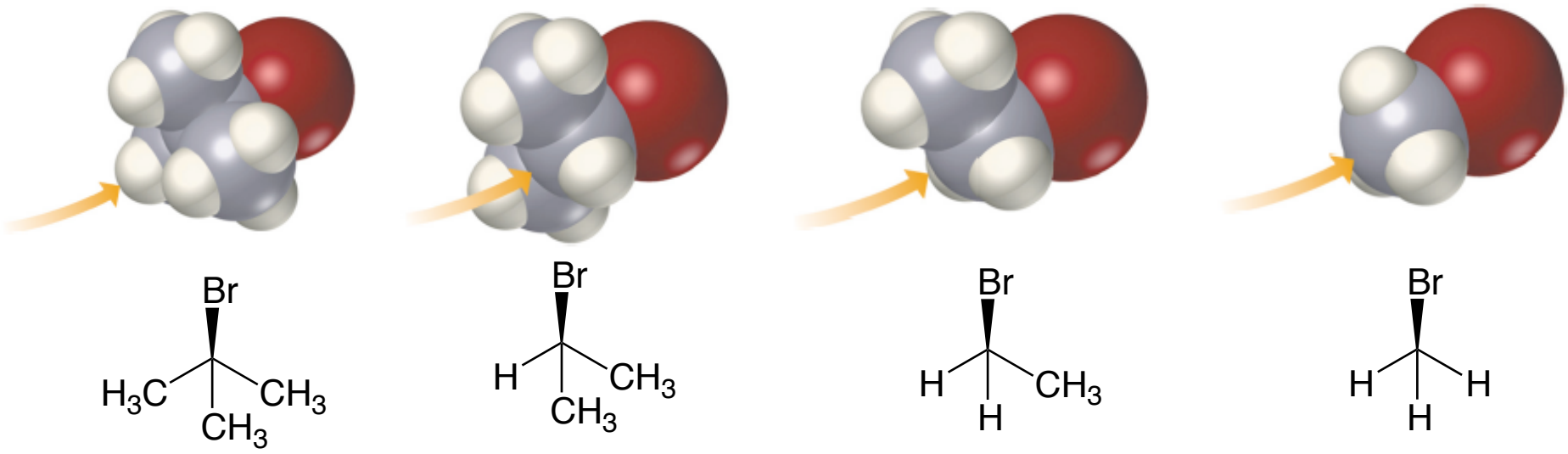
# 2nd Order Kinetics for Biodiesel Production



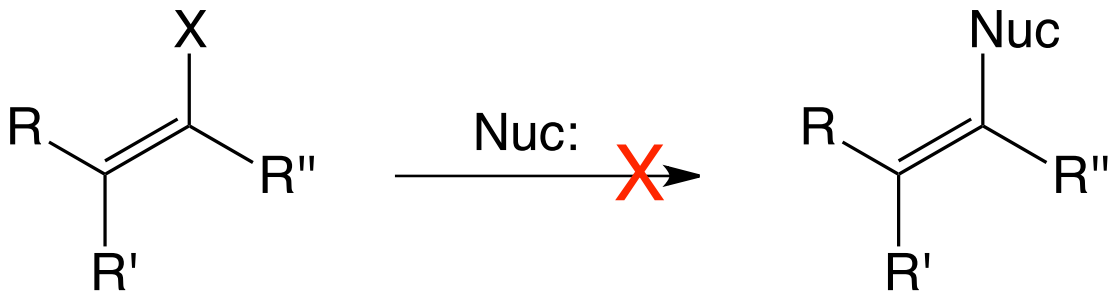

Rate dependence on [oil] and [methanol]

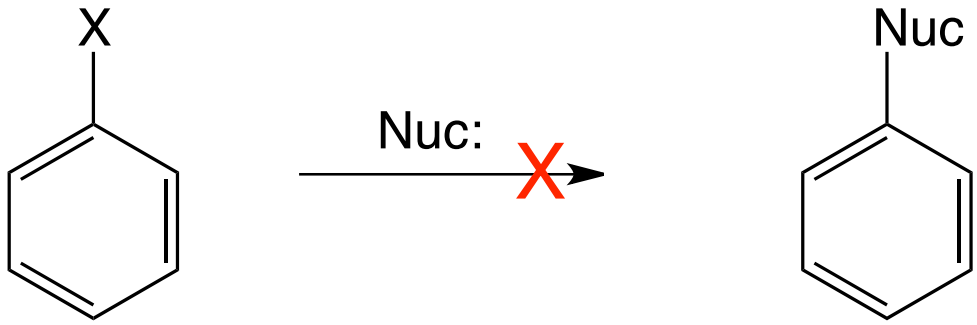
# Sterics Affect the Rate of $S_N2$ reactions

- Nucleophile approaches electrophilic carbon atom at 180° from the leaving group (i.e. backside attack)
- The rate of $S_N2$ reactions decrease with increasing substitution (steric hindrance) on electrophile
- Therefore, methyl and 1° alkyl halides are more common substrates for $S_N2$ reactions



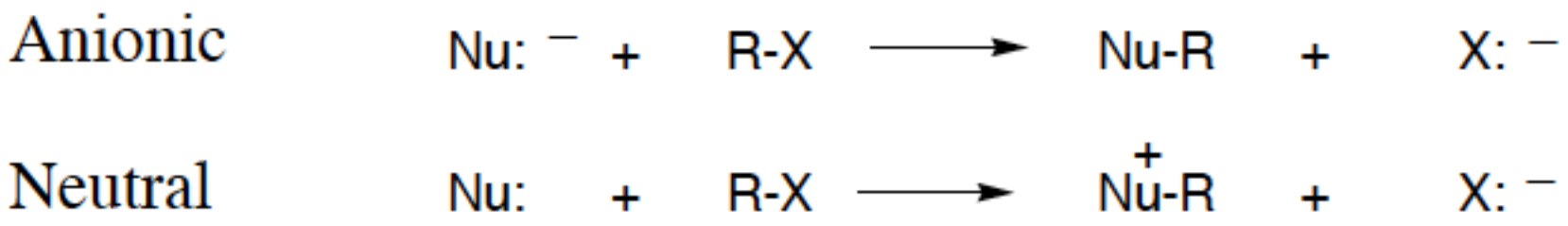
# Vinyl and Aryl Halides ***do not*** React *via* Nucleophilic Substitution



# Strength of Nucleophile Affects the Rate of $S_N2$ Reactions

- ***Nucleophilicity:***
  - Imprecise measurement
  - Charged nucleophiles (nuc:$^-$) are often more reactive than neutral nucleophiles (nuc:)



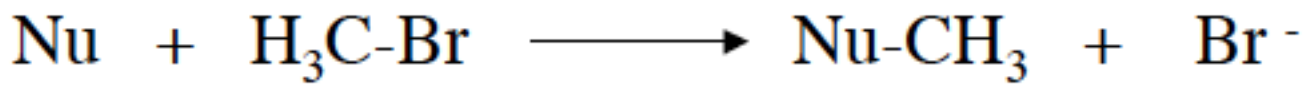
# Nucleophilicity and Basicity

- Nucleophiles are Lewis Bases (e- donors)
- Nucleophilicity parallels Brønsted basicity when comparing those with same attacking atom (stronger base = weaker conjugate acid)
- Nucleophilicity increases going down a column of the periodic table (larger $e^-$ cloud = $e^-$s less bound to nucleus) e.g. $HS^-$ is 7.8x more reactive of a nucleophile as compared to $HO^-$

| Nu: | $CH_3O^-$ | $HO^-$ | $CH_3CO_2^-$ | $H_2O$ |
|---|---|---|---|---|
| relative reactivity: | 25,000 | 16,000 | 500 | 1 |
| pKa of the conj. acid: | 15.5 | 15.7 | 4.7 | -1.7 |

Base strength

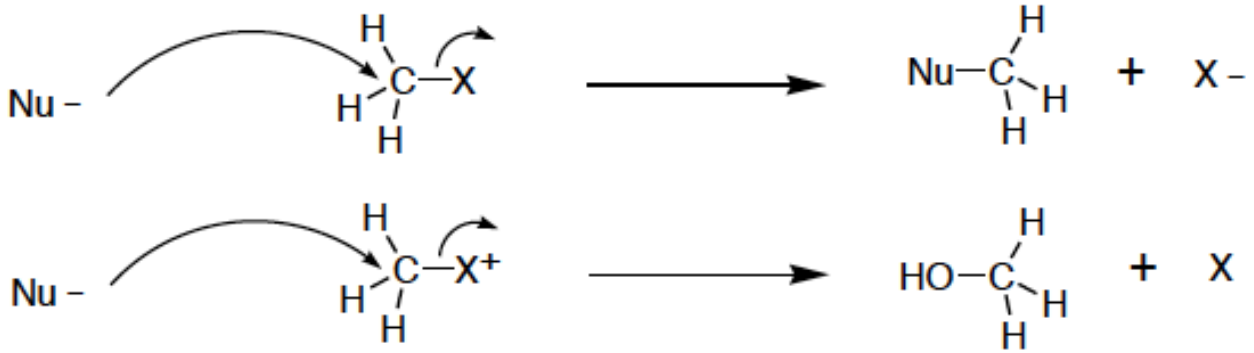
# Relative Reactivity of Selected Nucleophiles




| Nu = | | relative reactivity= |
|---|---|---|
| | $H_2O$ | 1 |
| | $CH_3CO_2^-$ | 500 |
| | $NH_3$ | 700 |
| | $Cl^-$ | 1,000 |
| | $HO^-$ | 16,000 |
| | $CH_3O^-$ | 25,000 |
| | $I^-$ | 100,000 |
| | $N\equiv C^-$ | 125,000 |
| | $HS^-$ | 125,000 |

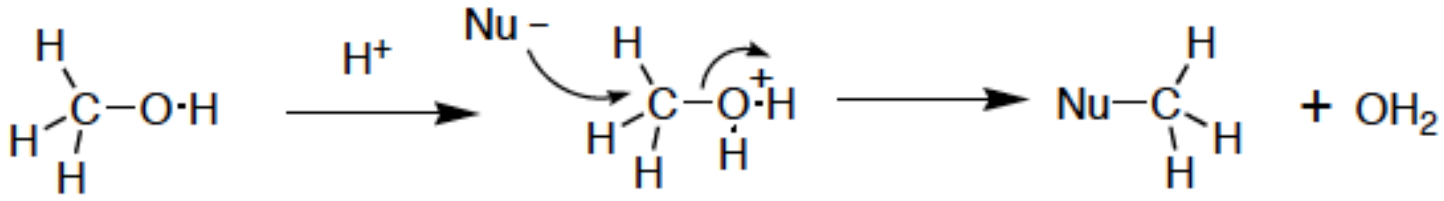
# The Role of the Leaving Group in $S_N2$ Reactions

- Leaving group is displaced by incoming nucleophile and can be neutral or carry a negative charge
- Best leaving groups are those that can stabilize the negative charge (i.e. *via* resonance)
- Good leaving groups are the weak conjugate bases of strong acids (e.g. $Cl^-$, $Br^-$, $I^-$, $TsO^-$).
- Poor leaving groups are strong conjugate bases of weak acids (e.g. $F^-$, $OH^-$, $OR^-$, $H_2N^-$) and must be chemically converted to better leaving groups (e.g. OH to OTos or OH to $OH_2^+$)



# Leaving Group Conversion

- Convert a poor leaving group to a good one with acid catalyst

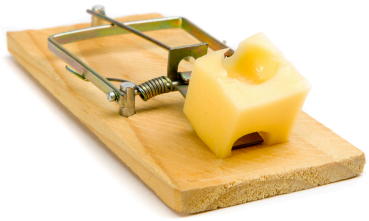



pKa of
$H_3O^+$ = -1.7
$H_2O$ = 15.7

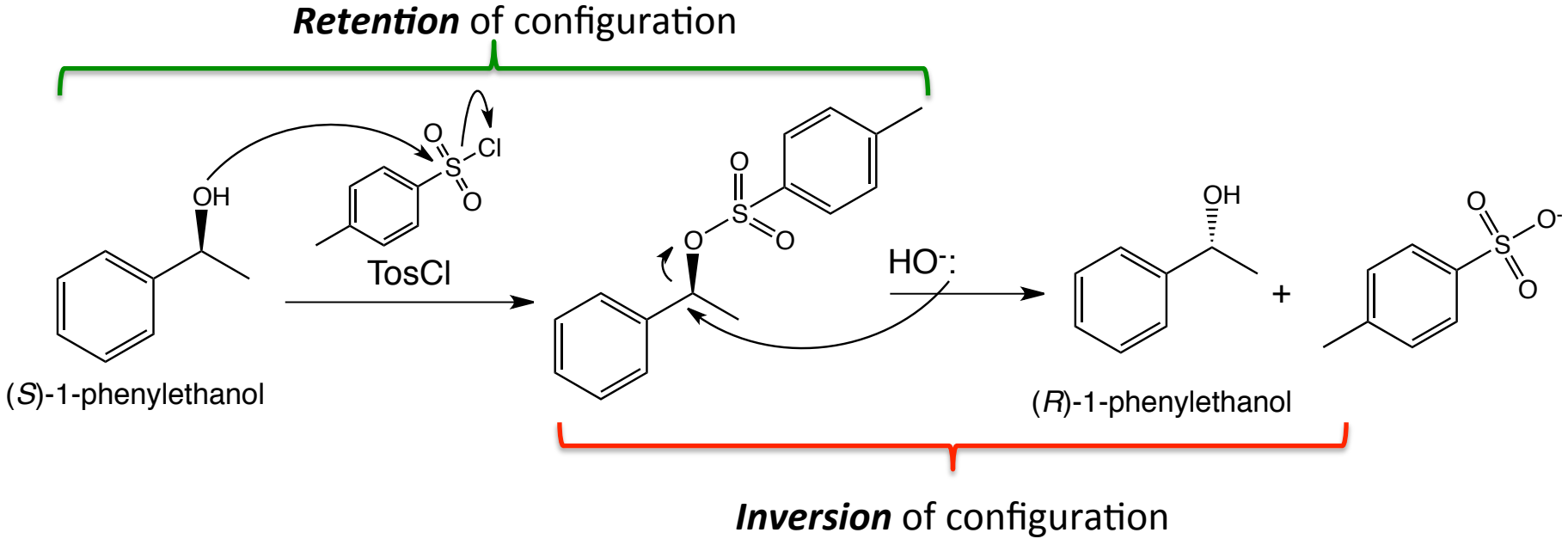
| LG: | $HO^-$, $H_2N^-$, $RO^-$ | $F^-$ | $Cl^-$ | $Br^-$ | $I^-$ | $TosO^-$ |
|---|---|---|---|---|---|---|
| Relative Reactivity: | <<1 | 1 | 200 | 10,000 | 30,000 | 60,000 |
| pKa: | >15 | 3.45 | -7.0 | -8.0 | -10 | -2.8 |

Increasing reactivity in $S_N2$ reaction

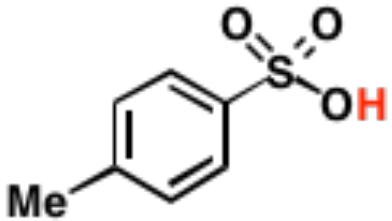
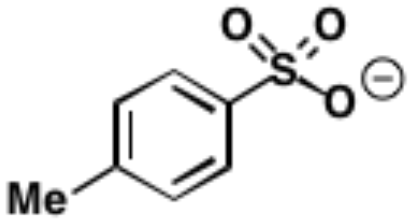
# Building a Better Electrophile



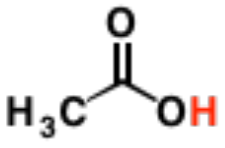
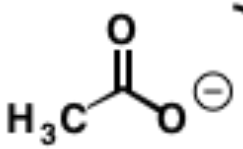
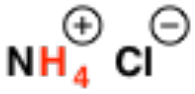
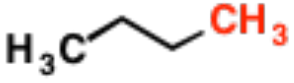
- *p*-toluenesulfonate esters or “tosylates” are prepared from alcohols
- They are excellent leaving groups for nucleophilic substitution reactions



**A pKa table is a handy guide to leaving groups**

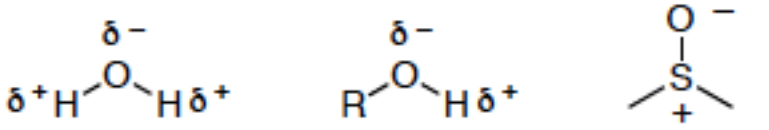
| Functional group / Example | | pKa | Conjugate base |
|---|---|---|---|
| Hydroiodic acid | HI | –10 | $I^{\ominus}$ |
| Hydrobromic acid | HBr | –9 | $Br^{\ominus}$ |
| Hydrochloric acid | HCl | –6 | $Cl^{\ominus}$ |
| Sulfuric acid | $H_2SO_4$ | –3 | $HSO_4^{\ominus}$ |
| Sulfonic acids |  (tosic acid) | –3 |  |
| Hydronium ion | $H_3O^{\oplus}$ | –1.7 | $H_2O$ |

*Excellent leaving groups (extremely weak bases)*

| | | | | |
|---|---|---|---|---|
| Hydrofluoric acid | H–F | 3.2 | $F^{\ominus}$ | **Exception:** $F^{\ominus}$ is typically an extremely poor leaving group (forms strong bonds) |
| Carboxylic acids |  | 4 |  | ***Moderate leaving groups (weak bases)*** |
| Protonated amines |  | 9-11 | $NH_3$ | |
| Water | HO–H | 16 | $HO^{\ominus}$ | ***Poor leaving groups (strong bases)*** |
| Alcohols | $CH_3O$–H | 16-18 | $CH_3O^{\ominus}$ | |
| Amine | $NH_3$ | ~35 | $NH_2^{\ominus}$ | ***Extremely poor leaving groups (very strong bases)*** |
| Hydrogen | H–H | 42 | $H^{\ominus}$ | |
| Alkane |  | ~50 |  | |

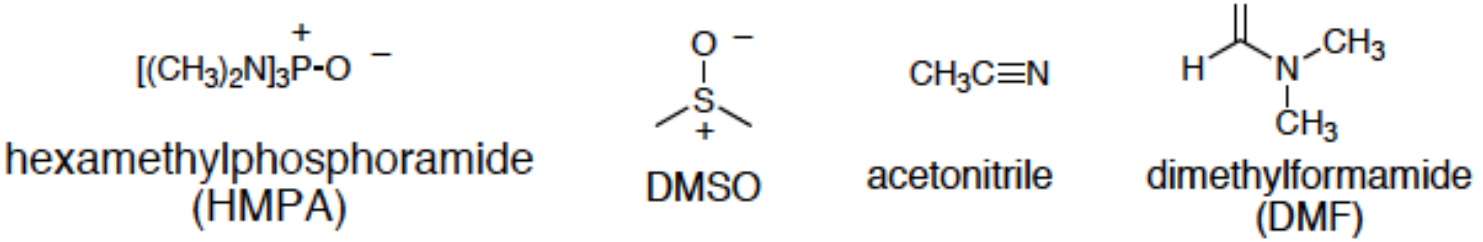
# Solvent's Role in $S_N2$ Reactions

- ***Polar vs. Non-Polar Solvents***
  - *Polar* = High dipole moment (water, alcohols, DMSO, etc.)




  - *Non-polar* = Low dipole moment (hexanes, dichloromethane, benzene, etc.)

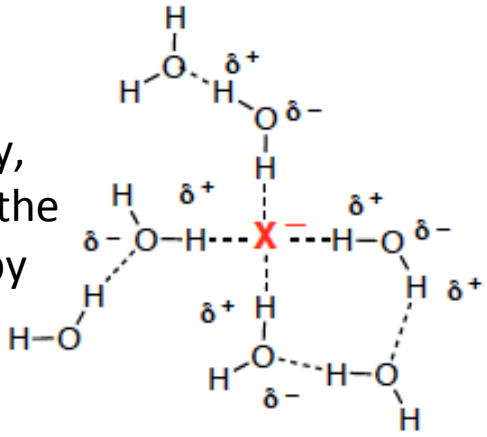
- ***Protic vs. Aprotic Solvents***
  - *Protic* = have acidic hydrogen atoms that form H-bonds (water, alcohols)
  - *Aprotic* = no acidic hydrogen atoms

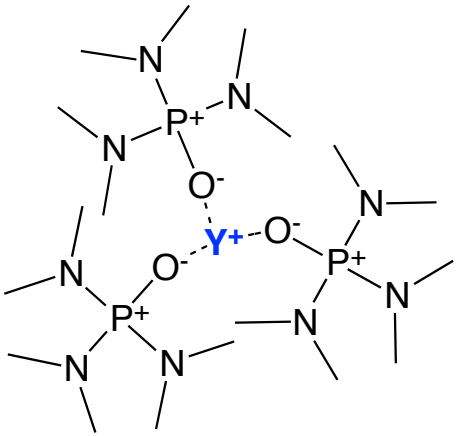


# Solvation in $S_N2$ Reactions

- *Solvent molecules form a "cage" around reactants and greatly influence their reactivity*
- **Protic Solvents:** Selectively solvate and stabilize anion (nucleophile) thus lowering its Free Energy (G) and raising the overall Activation Energy (ΔG‡) of the reaction. *Do not favor $S_N2$ reactions.*
- **Polar Aprotic Solvents:** Selectively solvate and stabilize cation (electrophile), allowing easier reaction with the nucleophile. . *Favor $S_N2$ reactions.*

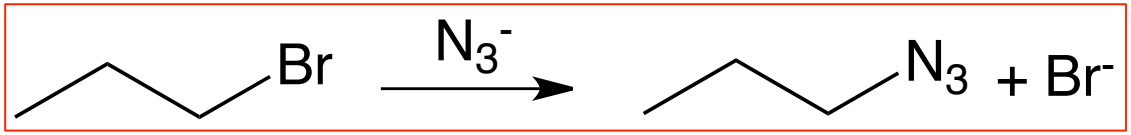
$H_3O^+$ lowering energy, and thus stabilizing, the anion (*nucleophile*) by H-bond donation



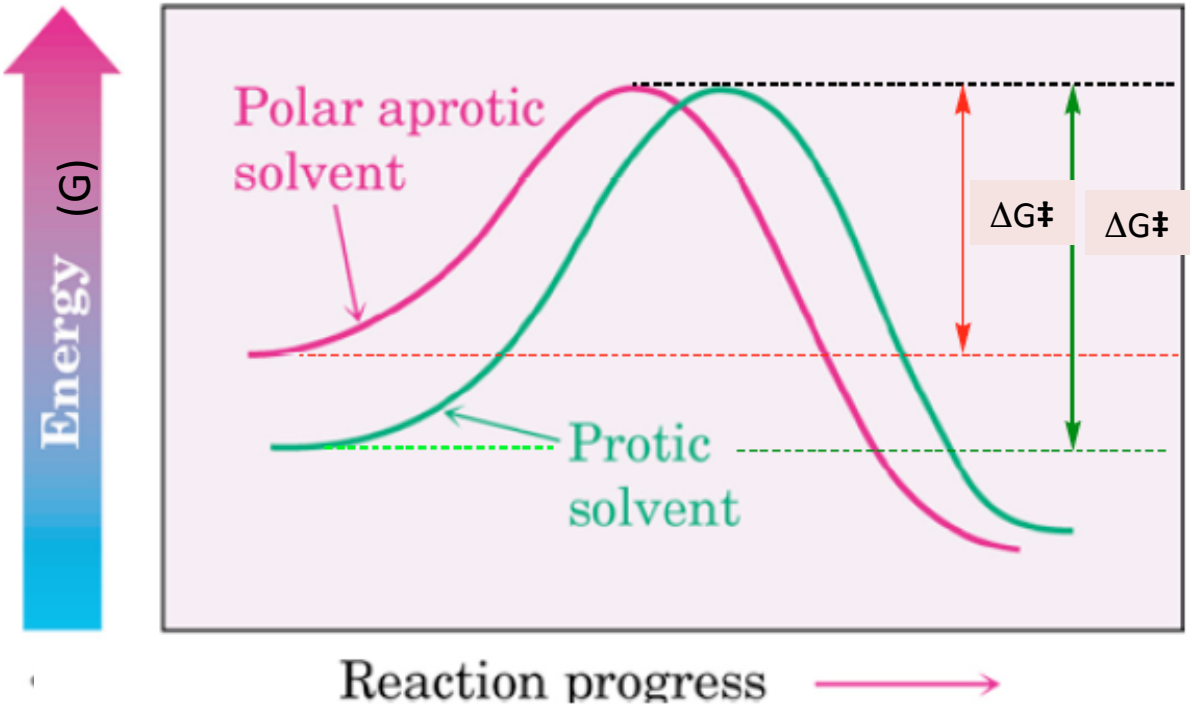


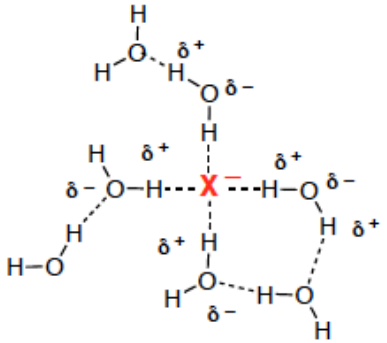
HMPA stabilizing charge of cation (*electrophile*), easing nucleophilic attack

# Solvent Effects on $S_N2$ Reaction

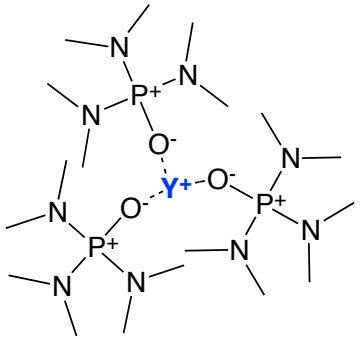



| Solvent: | $CH_3OH$ | $H_2O$ | DMSO | DMF | $CH_3CN$ | HMPA |
|---|---|---|---|---|---|---|
| relative reativity: | 1 | 7 | 1,300 | 2,800 | 5,000 | 200,000 |



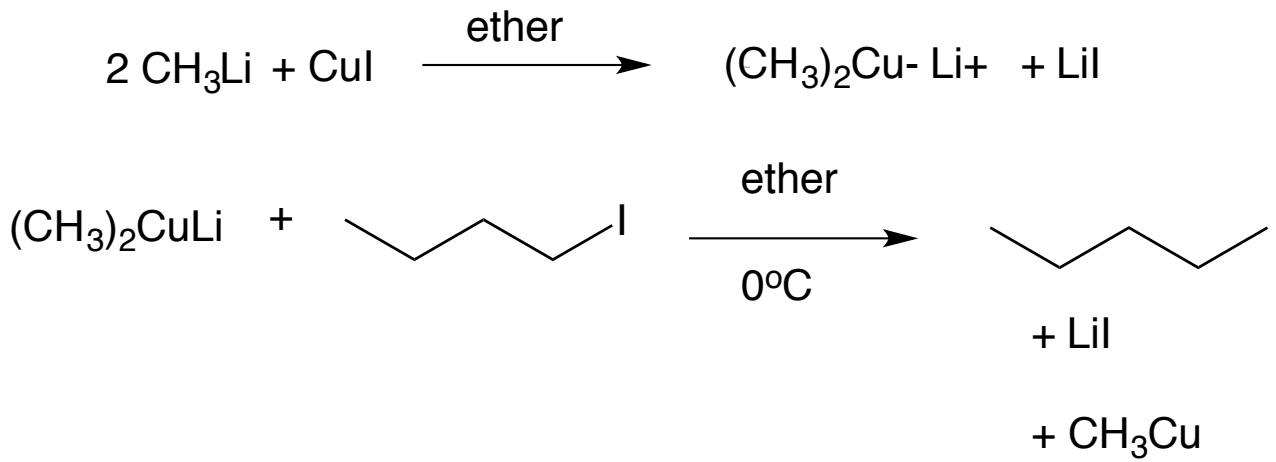
Protic solvents stabilize nuc



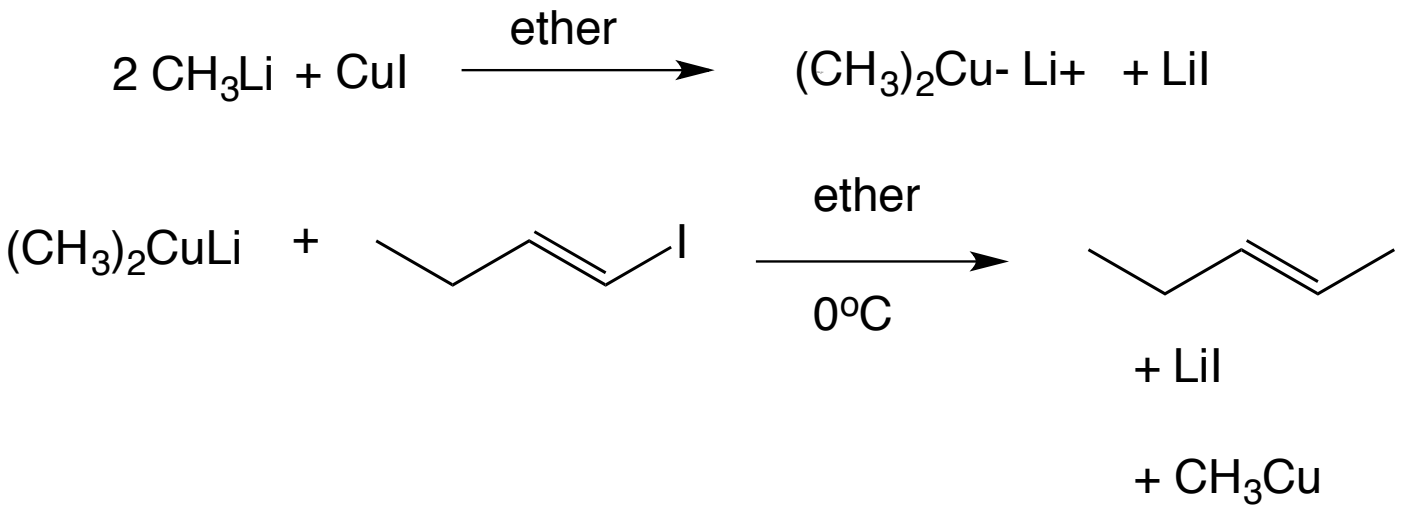
Polar aprotic stabilize electrophile

# Organometallic Reagents and Reactions

- Alkyl lithium Reagents
- Gilman Reagents
  - Vinyl coupling
  - Aryl coupling
- Suzuki-Miyuara coupling



# Gilman Reagents for Vinyl and Aryl Coupling



# Homework

- Chapter 9 (in chapter problems only):

1, 3, 4, 5, 6, 8, 9, 10, 11

- Chapter 10 (in chapter problems only):

1, 2, 4, 5, 6, 7, 8, 9, 10, 11

Chapter 11: 1, 2, 4, 5, 6, 7, 8, 9, 11, 12, 13, 15, 16, 17, 19, 20