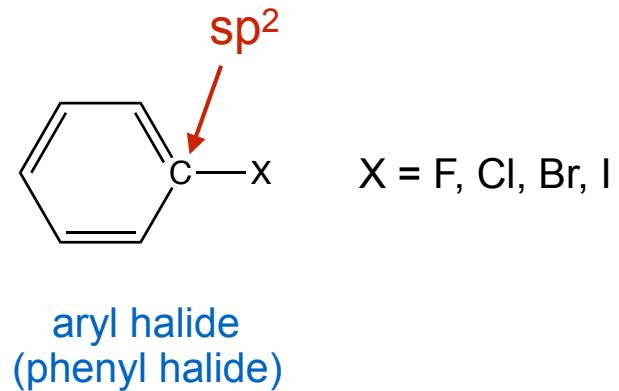
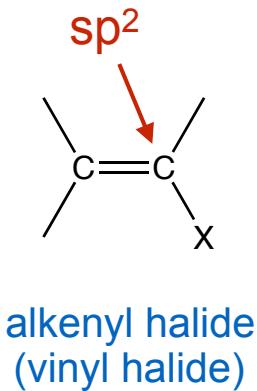
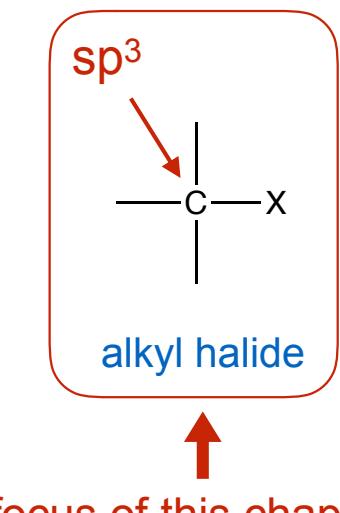
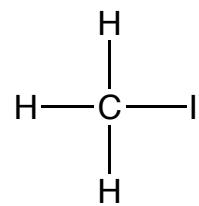


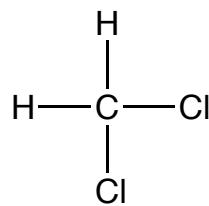
Chapter 6: Alkyl Halides - Nucleophilic Substitution



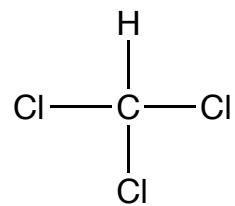
Ex: Common simple alkyl halides



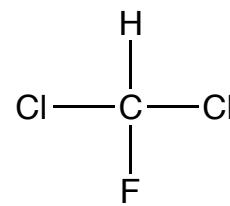
methyl iodide
iodomethane



methylene chloride
dichloromethane



chloroform
trichloromethane



Freon-22
dichlorofluoromethane

Q: Why study alkyl halides? Why are they important?

Petroleum! — Our Primary Source of Raw Organic Compounds



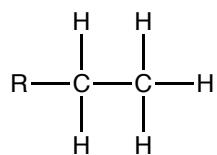
+



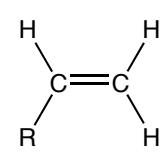
USA consumes
~ 7×10^6 barrels/day!



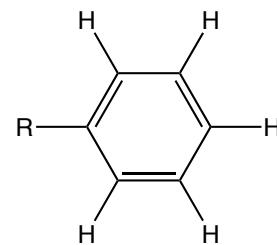
hydrocarbons - raw sources of carbon



alkanes



alkenes



arenes



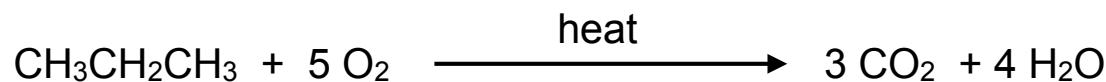
Q: What types of reactions do hydrocarbons undergo?

Q: How do we convert hydrocarbons into other useful starting materials?

Reactivity of hydrocarbons

Q: What types of reactions do hydrocarbons undergo?

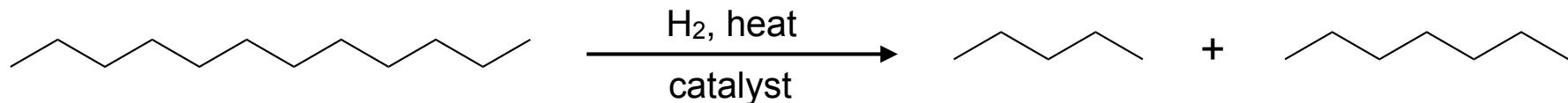
Ex: Combustion



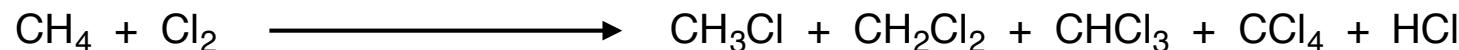
Ex: Catalytic cracking



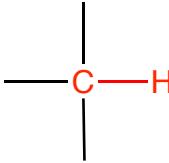
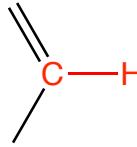
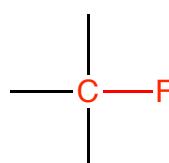
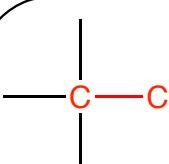
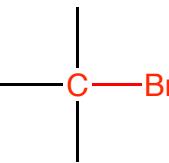
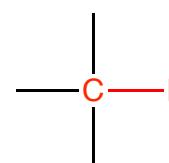
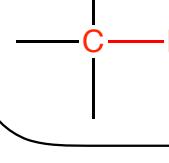
Ex: Catalytic hydrocracking



Ex: Halogenation



Q: Why are hydrocarbons so unreactive?

	bond strength (kJ/mol)	
	435	
		
	469	
		
	523	
		
	448	
		
	339	
		
	285	
		
	234	



C-X bonds on saturated carbon (sp^3) are significantly weaker than C-H bonds when X = Cl, Br, or I

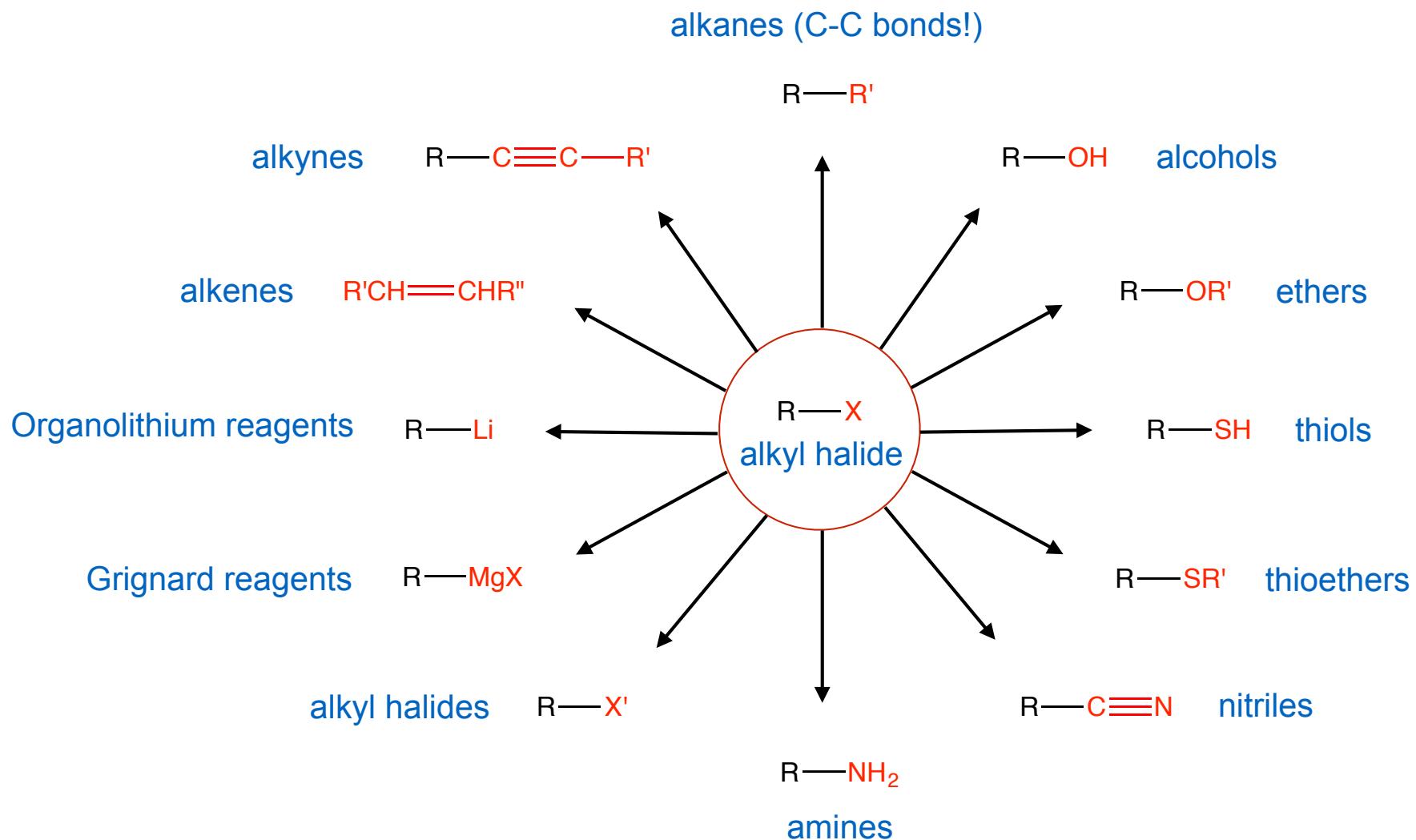
Q: Why?

Q: Significance of a weak bond?

→ Reactivity!!!

Utility of Alkyl Halides in Organic Synthesis

Q: What types of reactions do alkyl halides undergo?



Alkyl halides are incredibly useful as starting materials & chemical reagents!

Nomenclature of Alkyl Halides (6-2)

- Two ways to name alkyl halides

1. IUPAC - name as a **haloalkane** (an alkane with a **halo** substituent)

F-
fluoro

Cl-
chloro

Br-
bromo

I-
iodo

2. Common - name as an alkyl **halide**

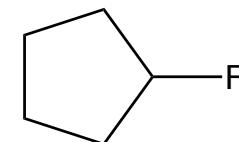
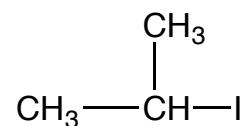
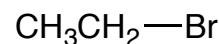
F
fluoride

Cl
chloride

Br
bromide

I
iodide

Ex:



IUPAC

bromoethane

2-iodopropane

fluorocyclopentane

Common

ethyl bromide

isopropyl iodide

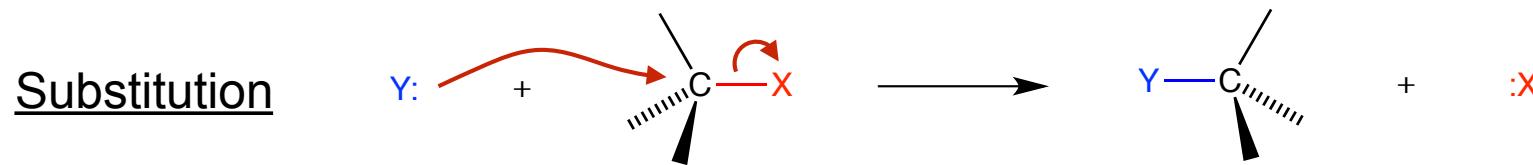
cyclopentyl fluoride

Common Uses of Alkyl Halides (6-3)

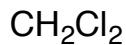
1. Reagents

Alkyl halides can be converted easily into many different functional groups due to the weak bond strength and polarity (high reactivity) of C-X bonds

Alkyl halides undergo two of the major classes of reactions



2. Solvents - Simple alkyl halides make good solvents



dichloromethane
methylene chloride



trichloromethane
chloroform

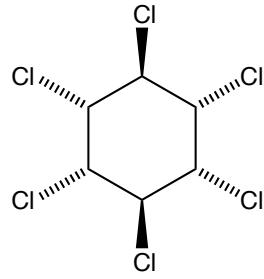


tetrachloromethane

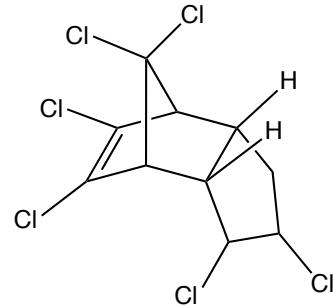
→ “Universal” solvents that dissolve many organic compounds

Q: Why are chlorinated alkanes good at dissolving organic compounds?

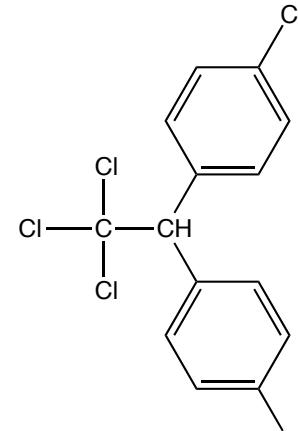
3. Pesticides - chlorinated hydrocarbons make up the majority of pesticides



lindane



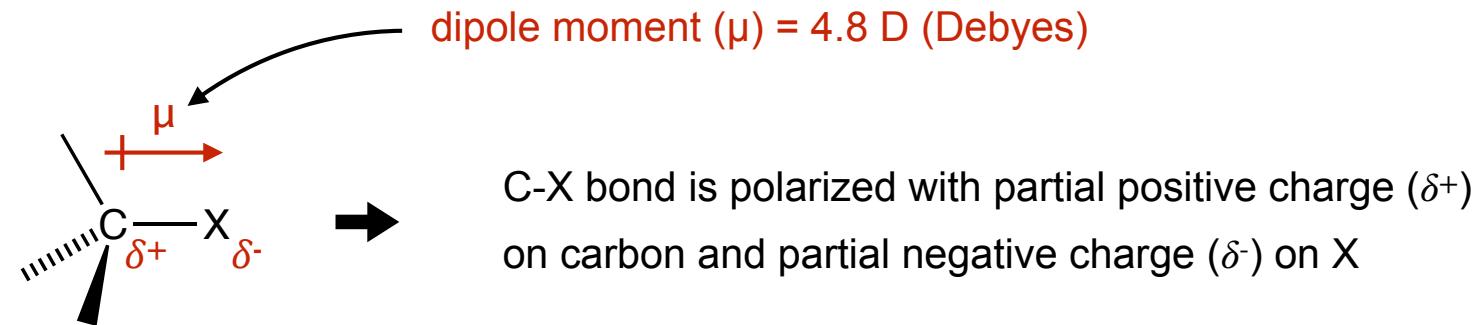
chlordan



DDT

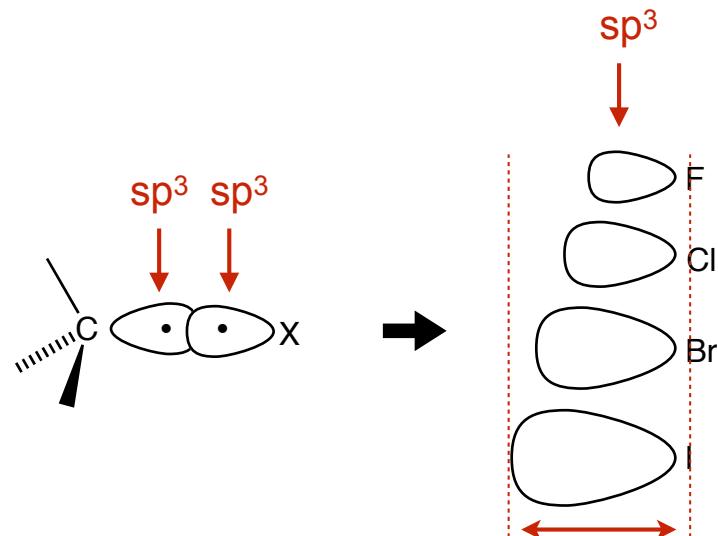
Q: Why do chlorinated organic compounds make such effective pesticides?

Structure of Alkyl Halides (6-4)



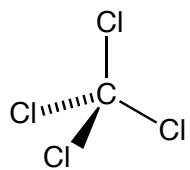
Electronegativity	F	Cl	Br	I	C	H
	4.0	3.2	3.0	2.7	2.5	2.1

bond	length (Å)	μ (D)	strength (kJ/mol)
C-F	1.3	1.51	456
C-Cl	1.78	1.56	351
C-Br	1.94	1.48	293
C-I	2.14	1.29	234
C-H	1.09	0.3	435
C-C	1.54	0	368



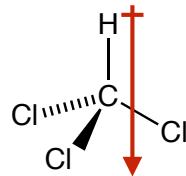
Q: Why do C-X bonds get longer and weaker moving down the periodic table?

Q: Effect of bond polarity on molecular polarity and properties?

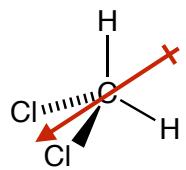


$$\mu = 0 \text{ D}$$

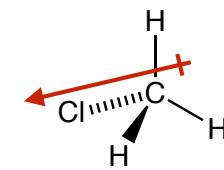
no molecular dipole



$$\mu = 1.03 \text{ D}$$



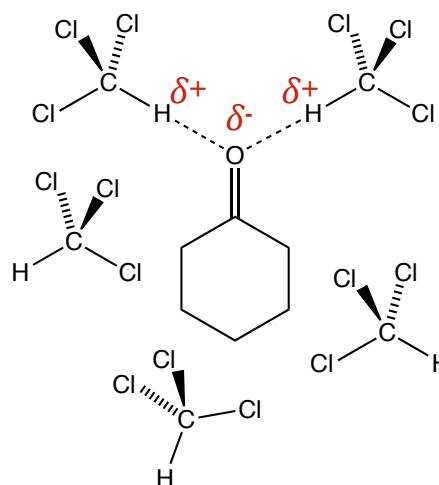
$$\mu = 1.60 \text{ D}$$



$$\mu = 1.94 \text{ D}$$

strong molecular dipole

polarity allows organic compounds with a wide range of polarity to dissolve in these solvents



Preparation of Alkyl Halides from Hydrocarbons (6-6)

Two general methods can be used to halogenate sp³-hydridized (saturated) carbon

1. Free-Radical Halogenation (We'll start here)

→ low selectivity where halogenation occurs

2. Allylic Bromination

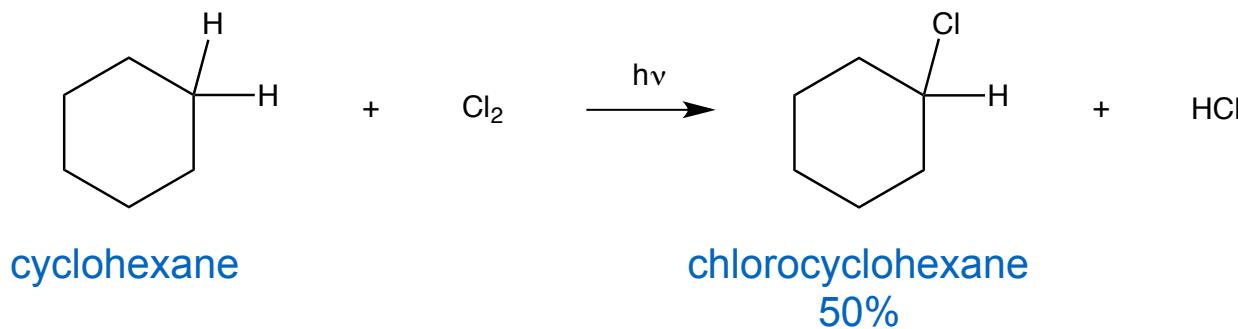
→ high selectivity where halogenation occurs

Note: Alkyl halides can be prepared from many other functional groups. We'll examine methods to convert other functional groups into alkyl halides later.

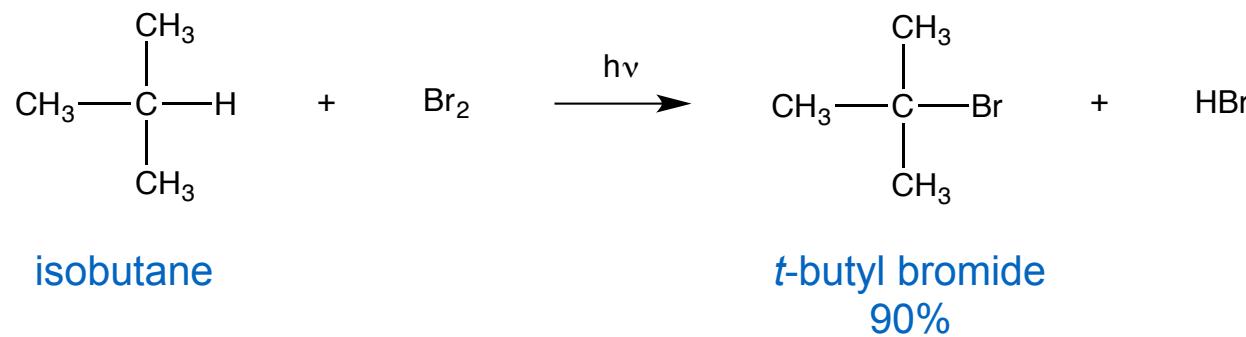
Free-Radical Halogenation

- Method to make alkyl chlorides and bromides
- Used widely in industry (chlorination is relatively inexpensive on a large scale)
- Produces mixtures of isomers (i.e., low selectivity)

Ex: Chlorination



Ex: Bromination



Q: How does free-radical halogenation work? What steps are involved?

Q: How do we study chemical reactions?

Read Chapter 4: The Study of Chemical Reactions

- Reaction mechanisms
 - Thermodynamics of reactions
 - Kinetics of reactions
- presented in the context of free-radical halogenation

Look closely at the material in these sections in Chapter 4

- 4-1: Introduction
- 4-2: Chlorination of methane
- 4-3: Free-radical chain reaction for chlorination
- 4-6: Bond dissociation enthalpies
- 4-7: Enthalpy changes in chlorination
- 4-13: Selectivity in halogenation
- 4-16: Reactive intermediates - stability of carbon radicals

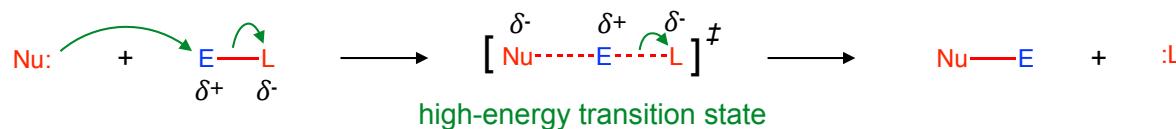
Q: How are bonds formed/broken in the majority of organic reactions?

1. Heterolytic Bond Formation (most reactions)

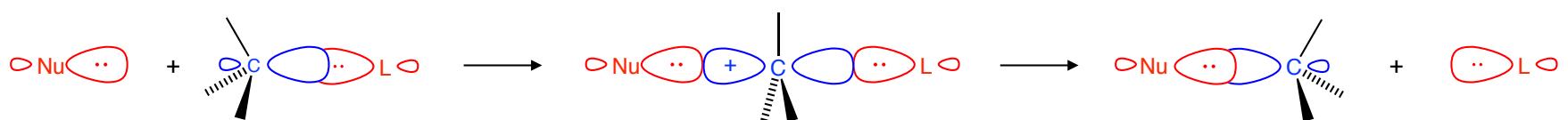
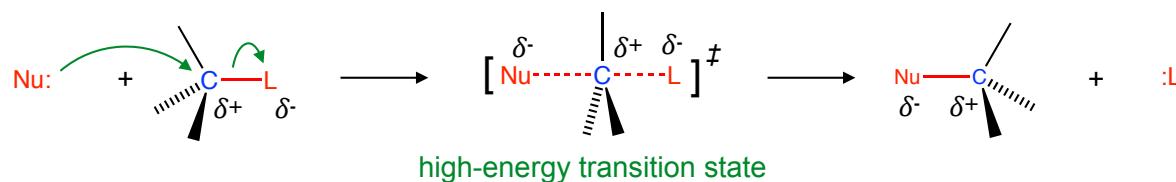
Nucleophile (Nu) - an electron-rich atom or group with a lone pair of electrons that can be donated to form a bond

Electrophile (E) - an electron-deficient atom or group that can accept a pair of electrons

Leaving Group (L) - an electron-rich atom or group that can stabilize a pair of electrons (a Nu that is weak)

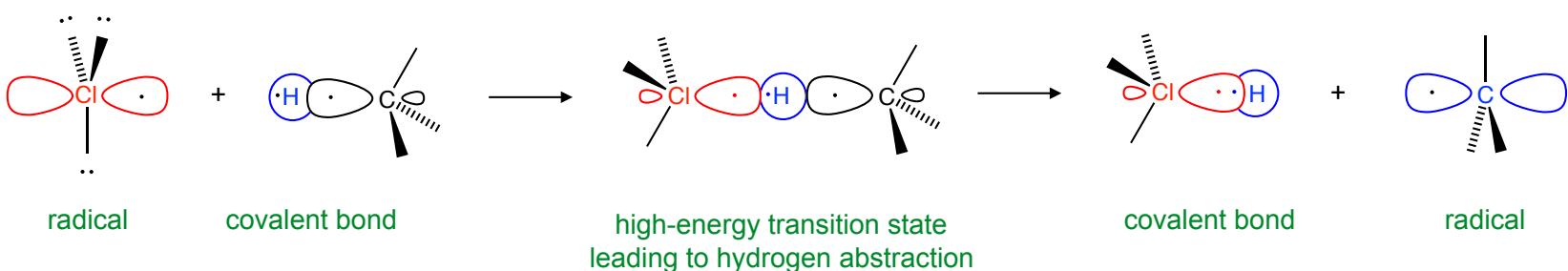
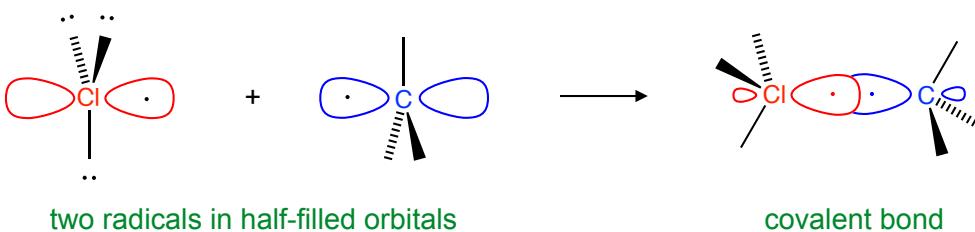
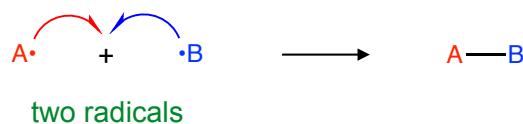


Q: How do we make carbon electron-deficient (electrophilic)?



2. Homolytic Bond Formation (less common—fewer reactions)

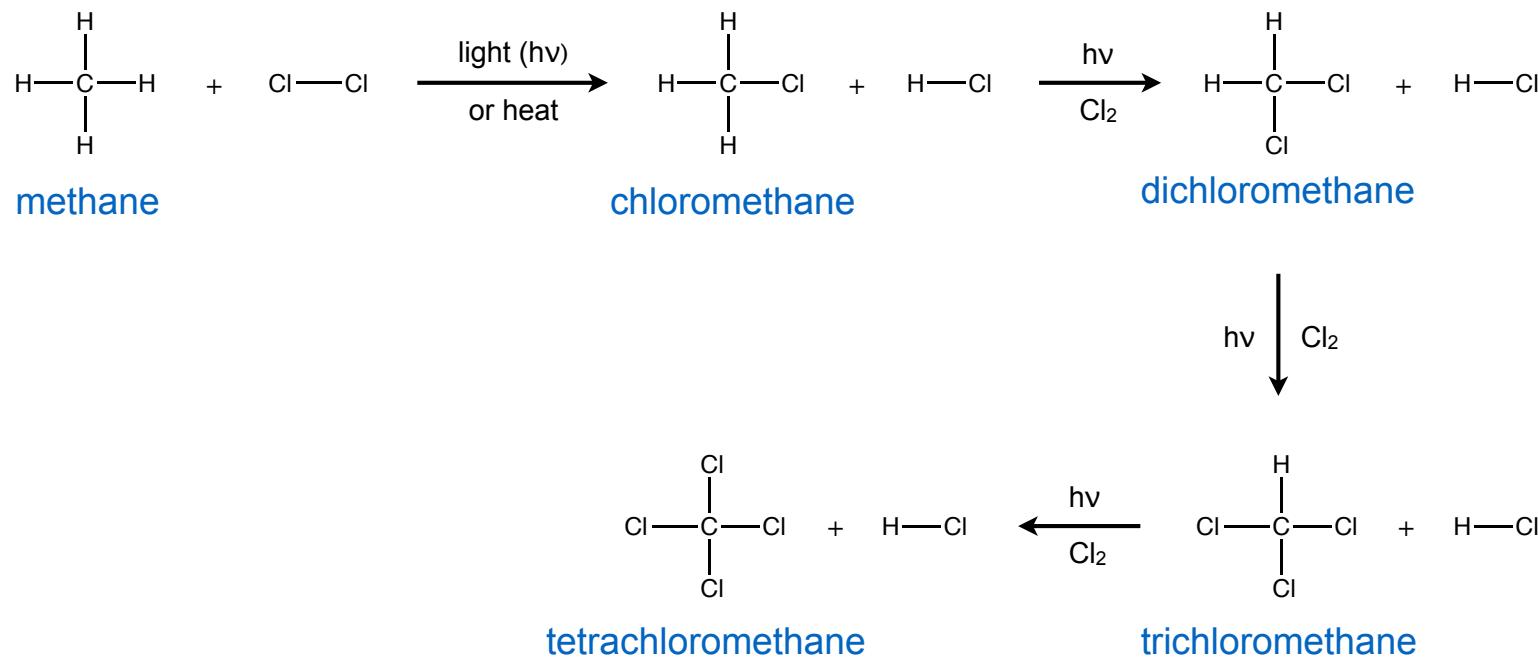
- Involves collisions between atoms or groups with a single, unpaired electron
- Use half-arrows to indicate the movement of single electrons



Preparation of Alkyl Halides from Hydrocarbons (6-6)

- See Chapter 4 sections 4-2, 4-3, 4-7, 4-10, 4-11, 4-12, and 4-13

Chlorination of methane (6-6A)

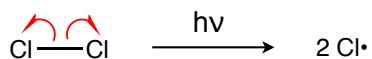


The reaction continues as long as Cl₂ and hν (or heat) are present

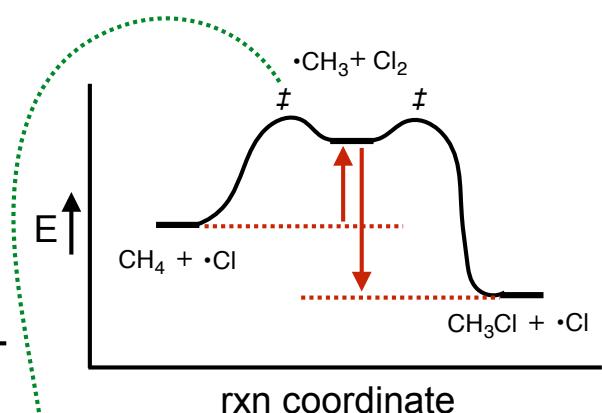
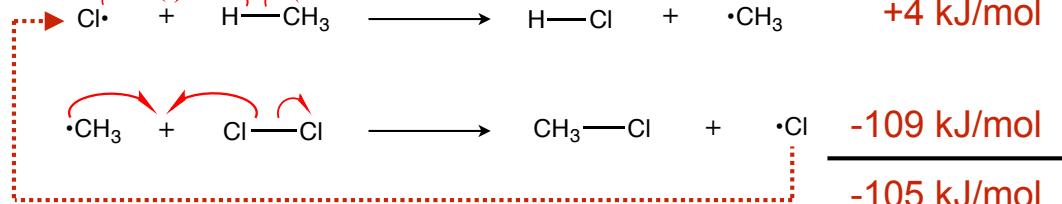
Q: How does the reaction work? Mechanism for bond making and breaking?

Mechanism for free-radical chlorination

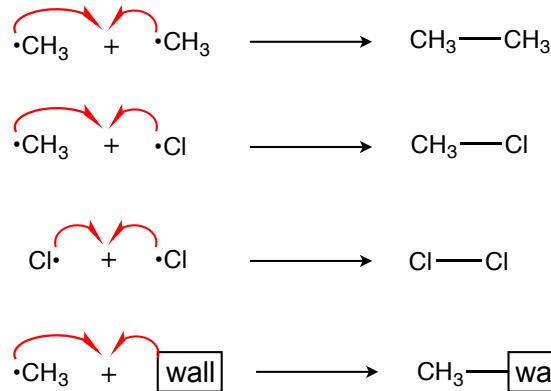
1. Initiation



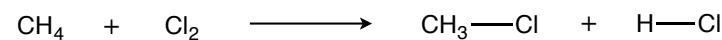
2. Propagation



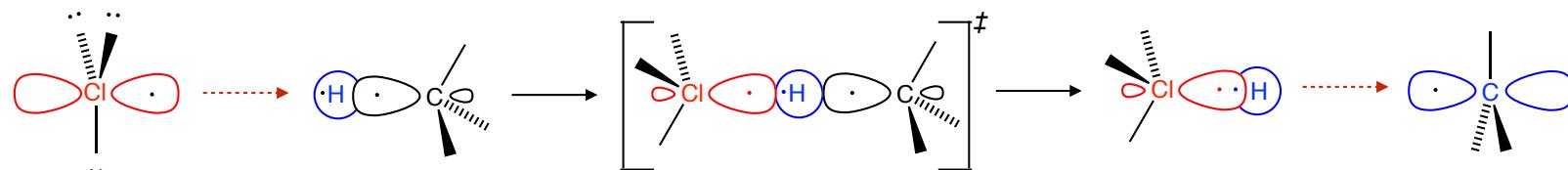
3. Termination



Net Rxn



Orbital picture of bond making & breaking during the first step of propagation



Cl· radical collides with H-C

transition state during collision

C· radical forms

Problem - The reaction doesn't stop after one step of halogenation

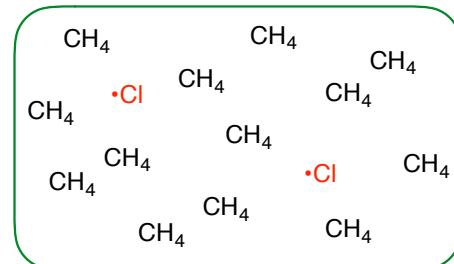


Q: How can polychlorination be prevented/minimized?

Stoichiometry!



Keep the concentration
of Cl_2 low relative to CH_4



Q: Why does chlorination happen in the first place?

Changes in Enthalpy During Chlorination

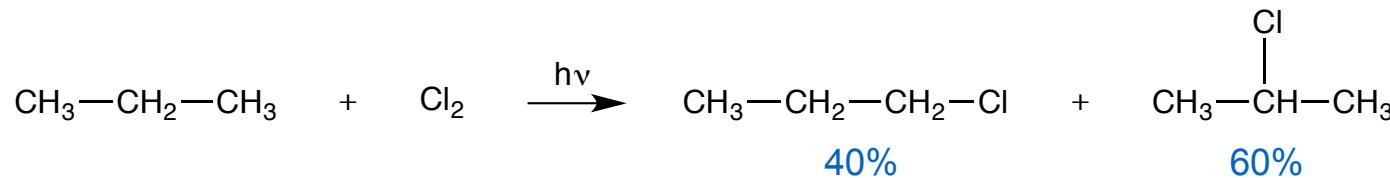
<u>Bonds Broken</u>	<u>ΔH (kJ/mol)</u>	<u>Bonds Formed</u>	<u>ΔH (kJ/mol)</u>
$\text{Cl}-\text{Cl} \longrightarrow 2 \cdot\text{Cl}$	+242	$\cdot\text{H} + \cdot\text{Cl} \longrightarrow \text{H}-\text{Cl}$	-431
$\text{CH}_3-\text{H} \longrightarrow \cdot\text{CH}_3 + \cdot\text{H}$	+435	$\cdot\text{CH}_3 + \cdot\text{Cl} \longrightarrow \text{CH}_3-\text{Cl}$	-351
$+677$			-782

$$\Delta H_{rxn} = \Delta H_{\text{bonds formed}} + \Delta H_{\text{bonds broken}} = (-782 \text{ kJ/mol}) + (+677 \text{ kJ/mol}) = -105 \text{ kJ/mol}$$

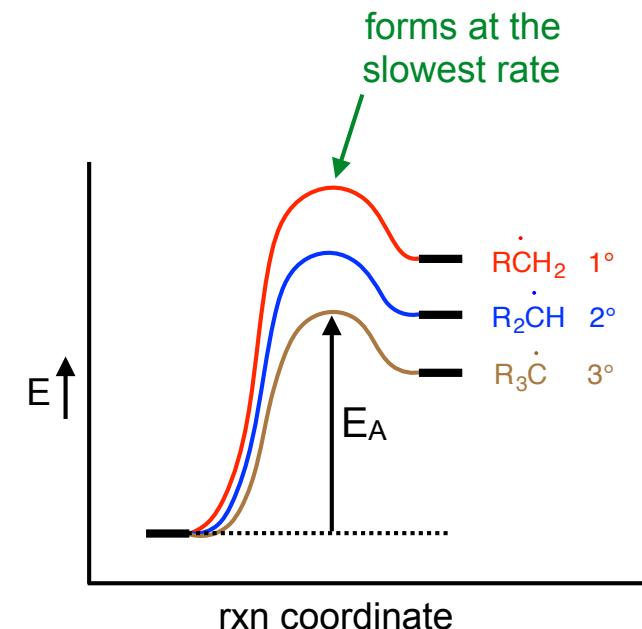
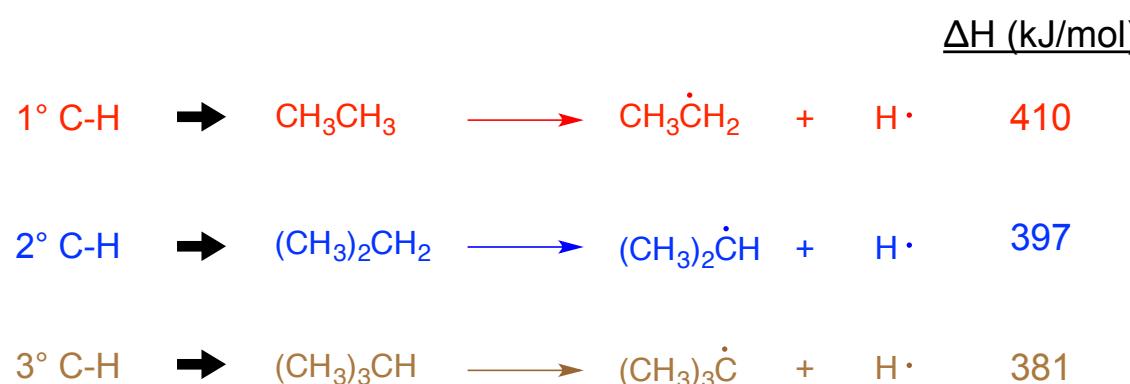


rxn is exothermic!

Ex: Chlorination of propane



Q: Why that distribution of products?

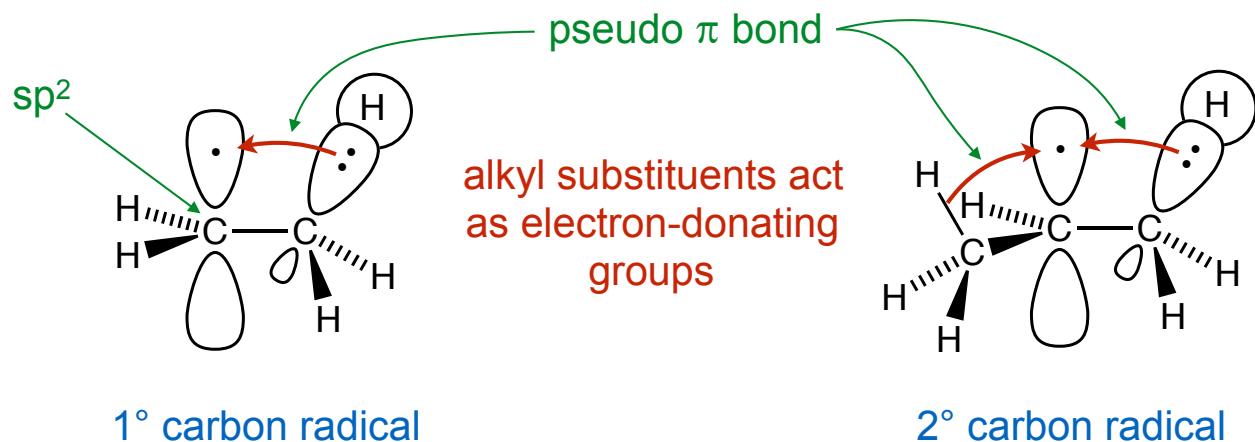


Relative rates of reactivity toward chlorination $\rightarrow \text{R}_3\text{CH} > \text{R}_2\text{CH}_2 > \text{RCH}_3$
5 3.5 1

Relative stabilities of carbon radical intermediates $\rightarrow \text{R}_3\dot{\text{C}} > \text{R}_2\dot{\text{C}}\text{H} > \dot{\text{RCH}}_2$
3° 2° 1°

Q: Why are more-substituted carbon radicals lower in energy (more stable)?

Q: Why are more-substituted carbon radicals lower in energy (more stable)?

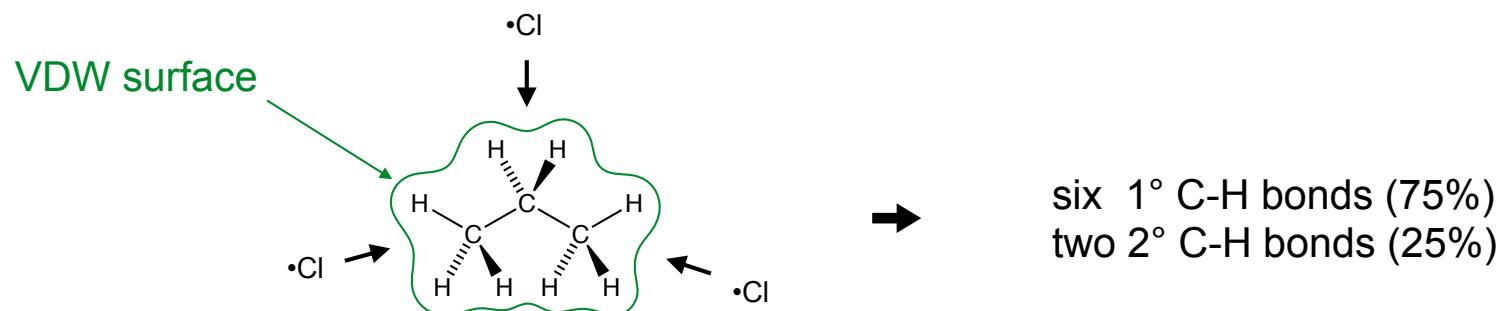


Hyperconjugation - weak donation of electron density from adjacent sigma bonds (sp^3 orbitals) into an empty or half-filled p orbital (a pseudo π bond) lowers the energy of a carbocation or radical intermediate

Note: We'll encounter hyperconjugation again when studying the stability of carbocation intermediates in electrophilic addition reactions of alkenes (Ch. 8), and **in all reactions with mechanisms involving formation of carbocation or radical intermediates**

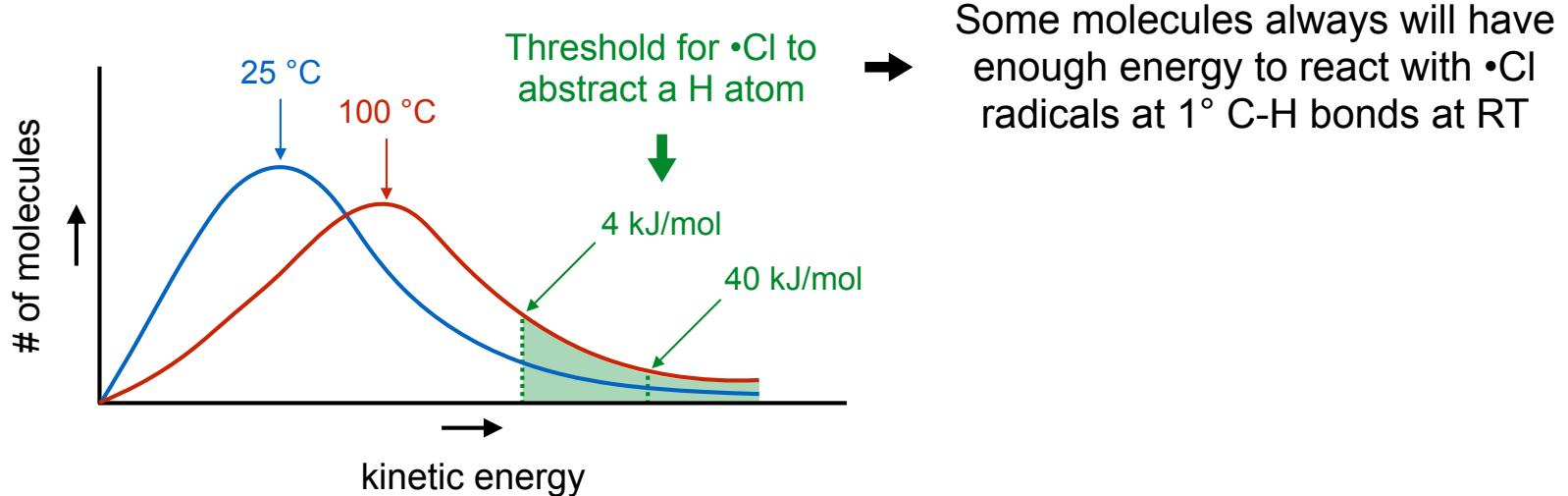
Q: Why does chlorination occur on the methyl groups of propane if 2° carbon radicals are lower in energy than 1° carbon radicals?

Q: Why does chlorination occur on the methyl groups if 2° carbon radicals are lower in energy than 1° carbon radicals?

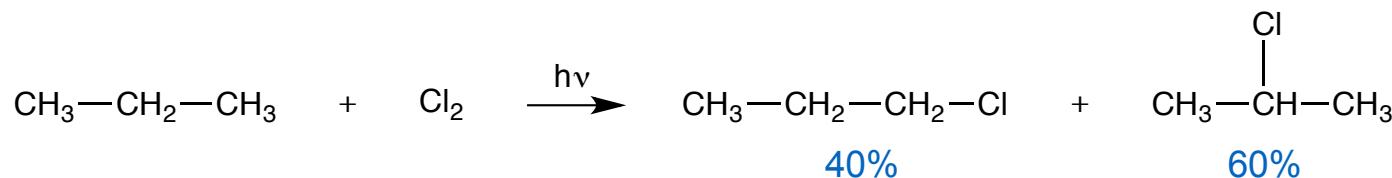


H atoms on 1° C-H groups are more accessible than on 2° C-H groups for collisions with •Cl radicals

Greater probability that a collision will occur at 1° C-H than 2° C-H

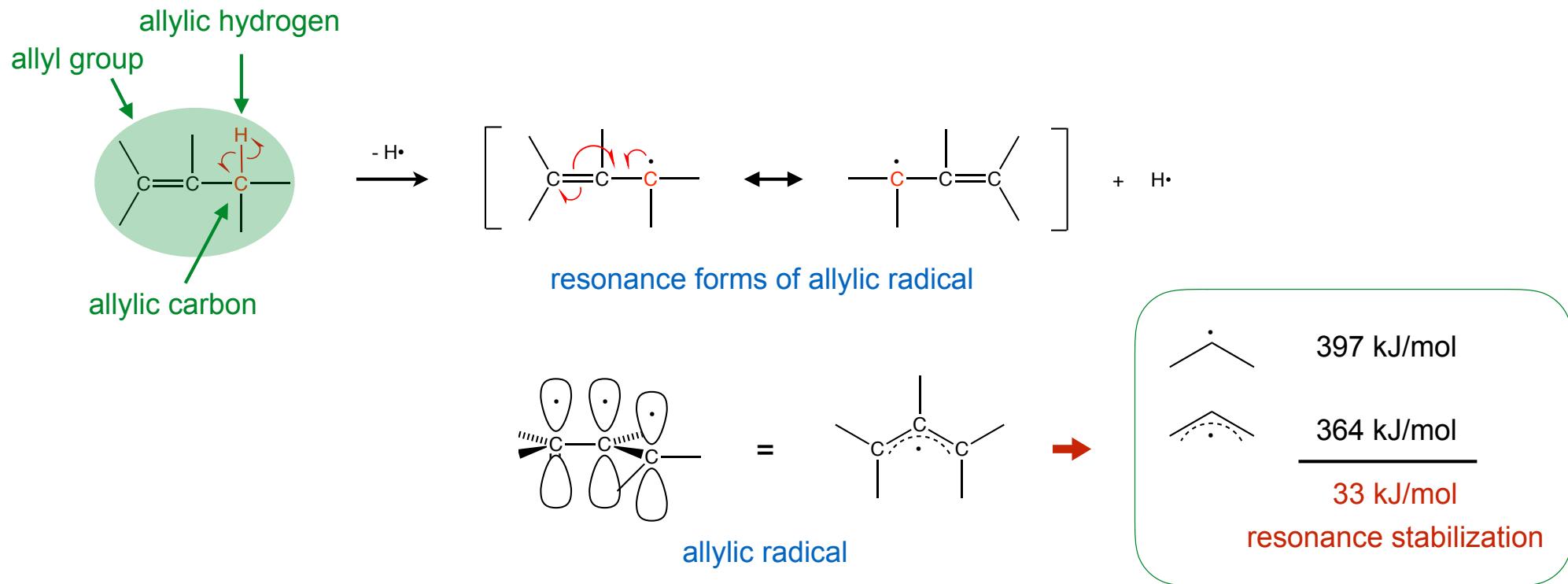


Q: Which is more important—stability of carbon radicals, or the # of H atoms (probability of collision)?



Allylic Bromination (6-6B)

- Free-radical halogenation (chlorination and bromination) generally is a poor synthetic method to prepare alkyl halides from **alkanes** due to low selectivity and polyhalogenation
- Free-radical bromination of alkenes can be carried out selectively at allylic positions on **alkenes**



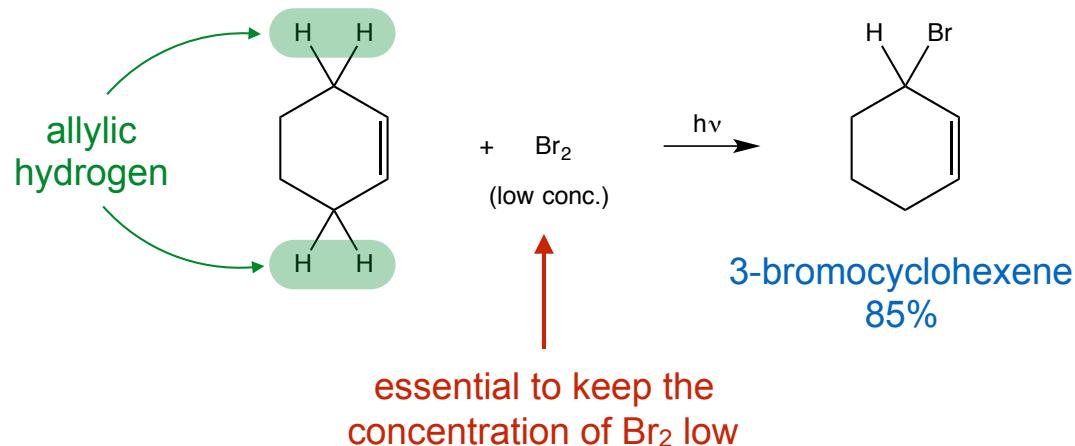
Resonance

- delocalization of π electrons between three or more than adjacent p orbitals (an extended π system)
- delocalization of π electrons lowers the energy of a π system compared to a π system where the electrons are localized (i.e., a C=C bond) → Resonance Stabilization

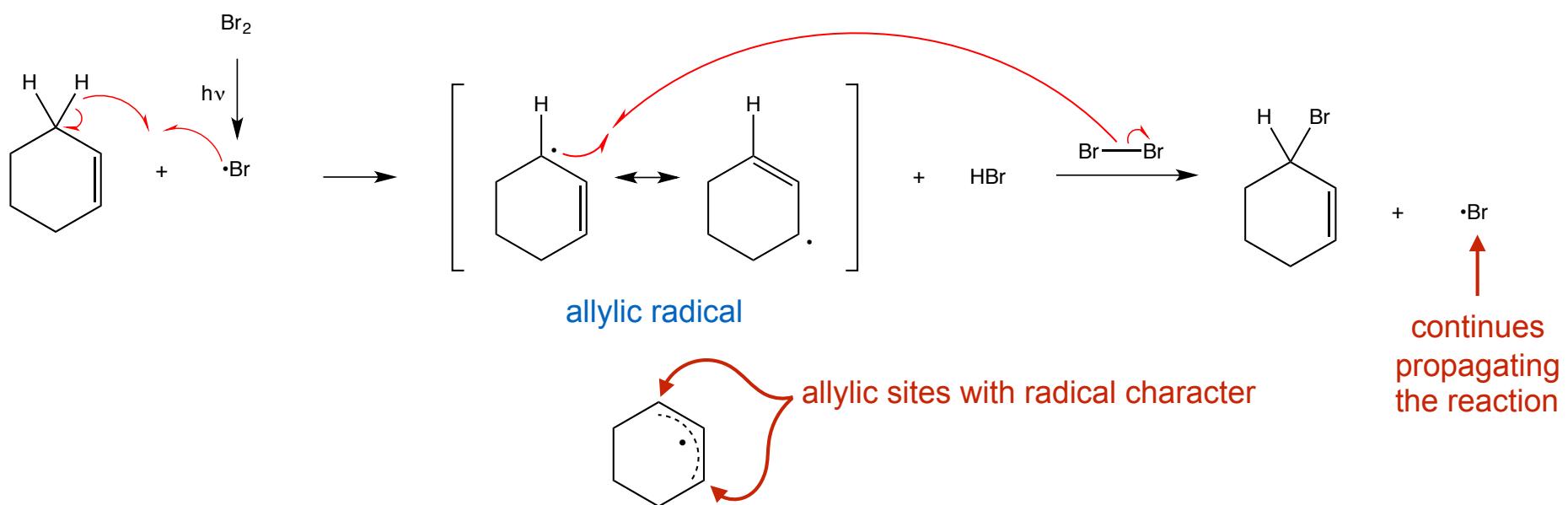
Q: Impact of having a saturated carbon next to a C=C bond (i.e., an allylic carbon)?

Q: Reactivity of allylic CH compared to saturated CH?

Ex: Allylic bromination of cyclohexene

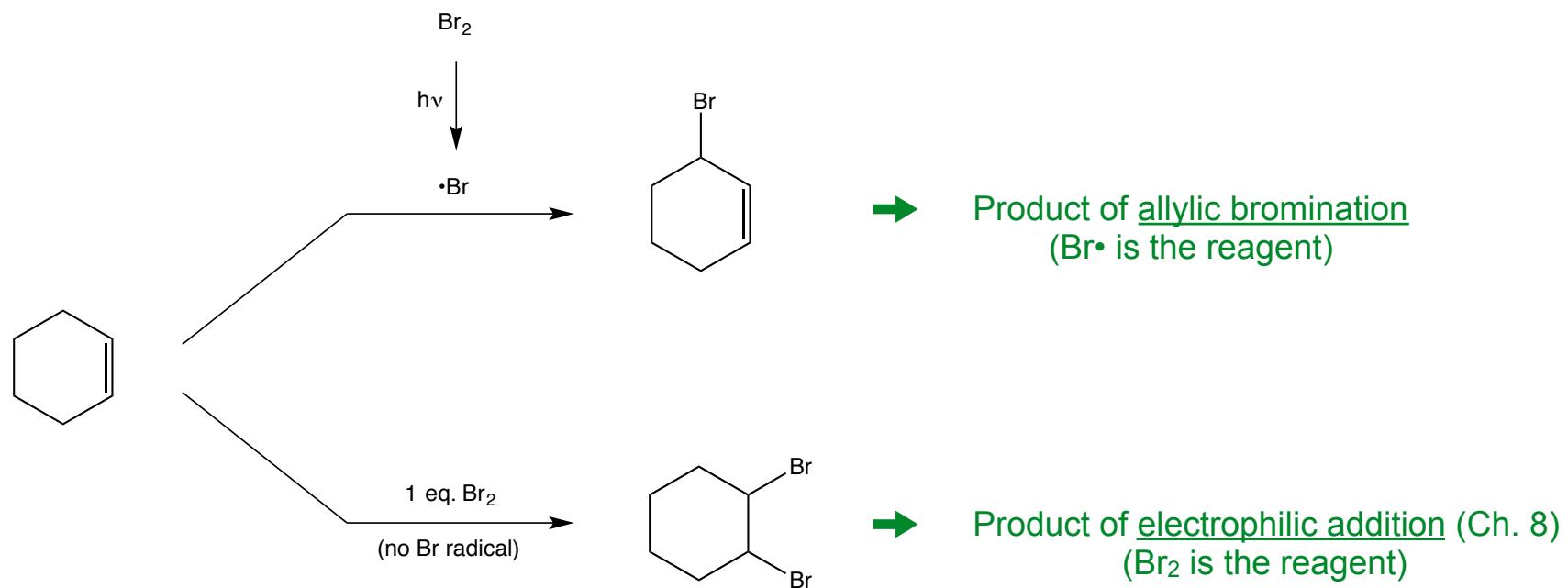


Mechanism

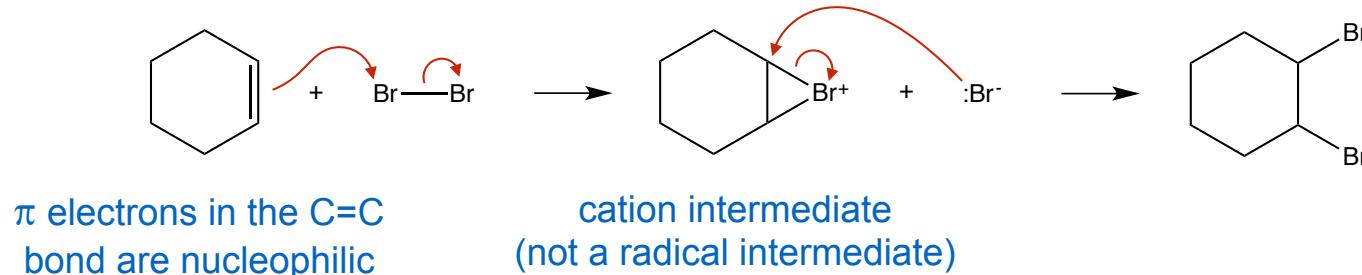


Q: Why doesn't •Br react with the other two saturated CH₂ groups?

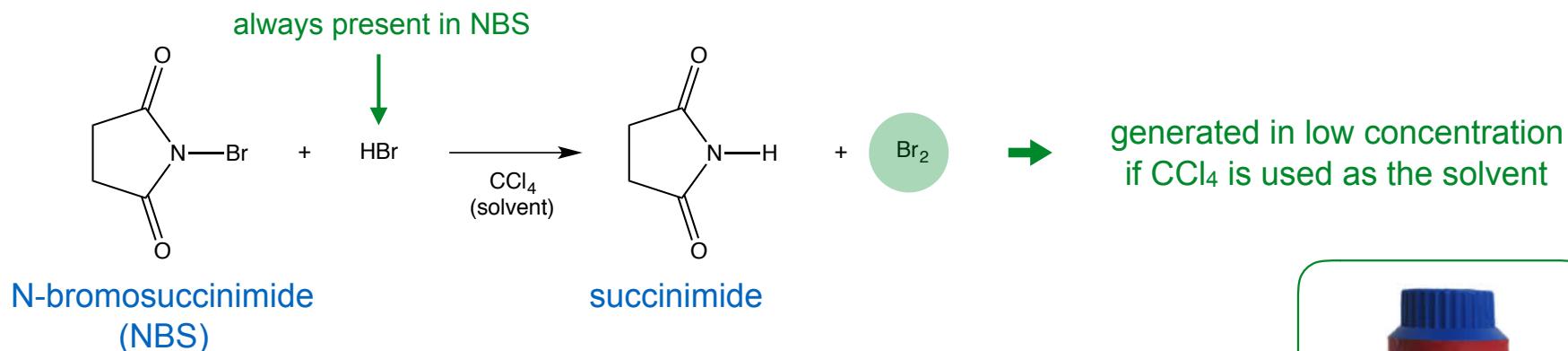
Q: Why is it necessary to keep the concentration of Br₂ low during allylic bromination?



Ex: Preview of electrophilic addition of bromine to alkenes (Ch. 8)



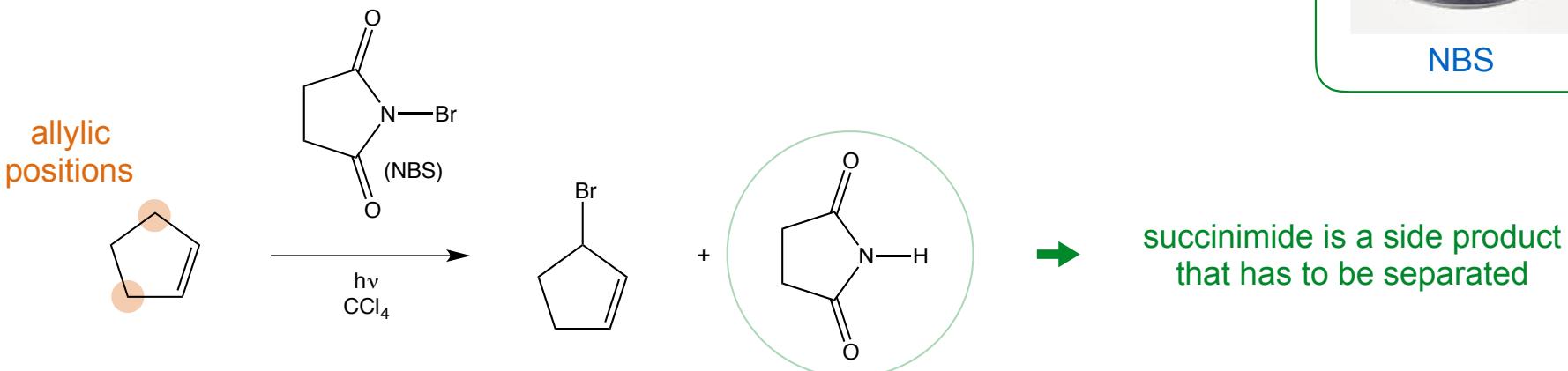
Q: How can the concentration of Br₂ be controlled to favor allylic bromination?



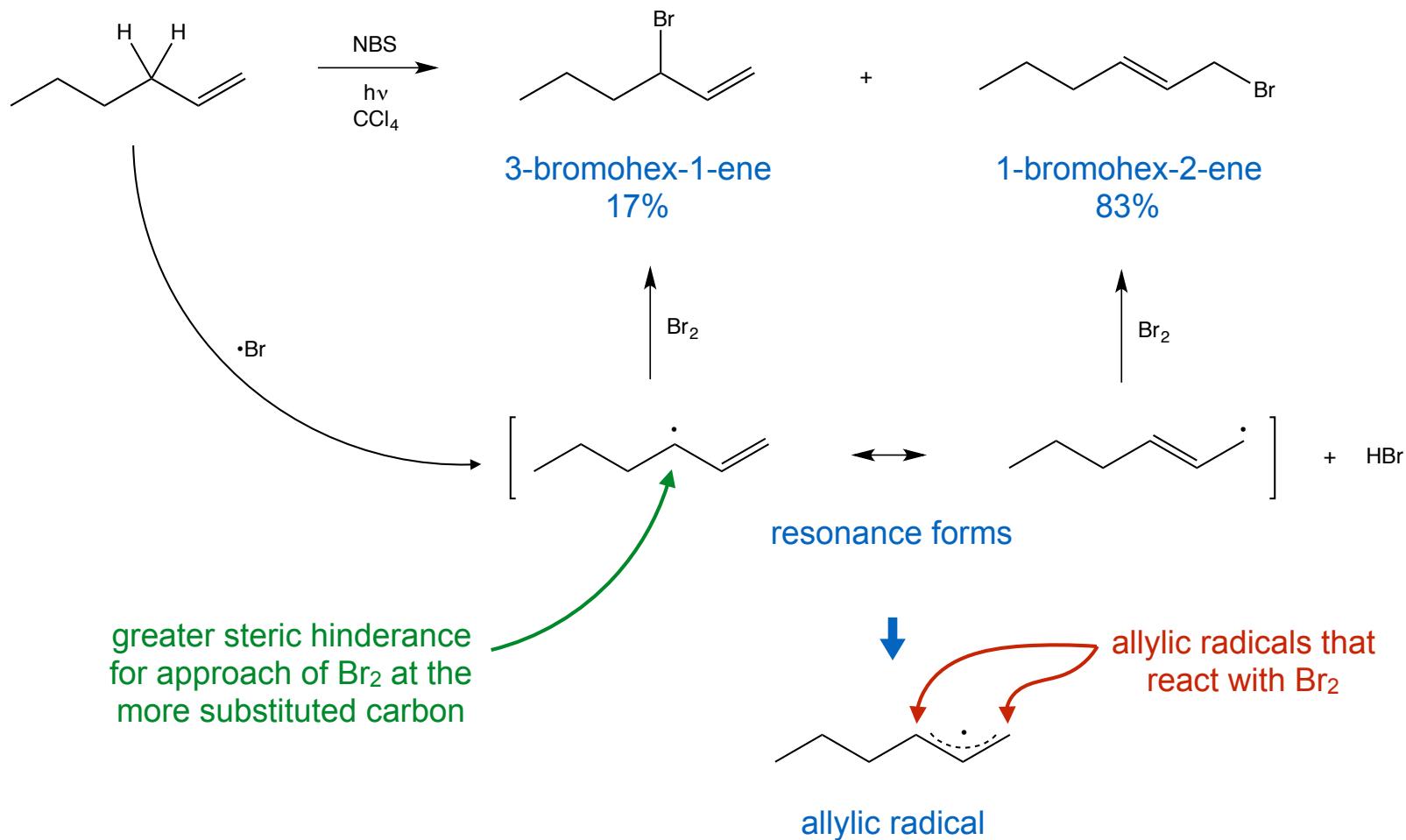
N-Bromosuccinimide (NBS)

- Source of Br₂
- Preferred reagent for carrying out allylic bromination
- Low solubility of NBS in CCl₄ (solvent used for rxns) keeps the concentration of Br₂ low

Ex:



Ex:



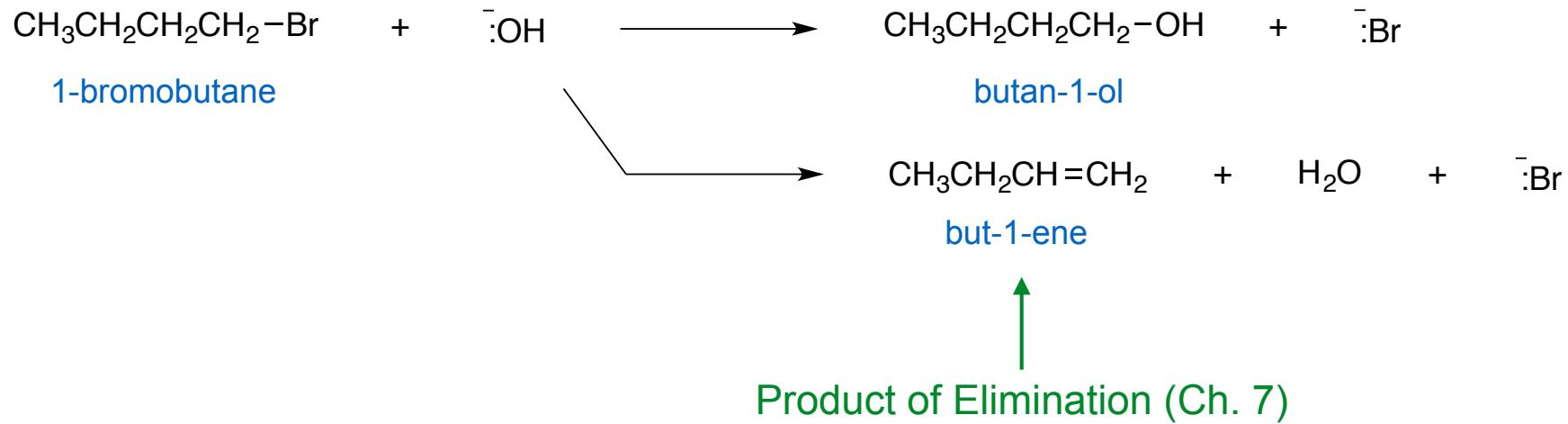
Rxns of Alkyl Halides: Nucleophilic Substitution & Elimination (6-7)

Now focus on reactions that alkyl halides undergo

Examine how alkyl halides can be converted into many other functional groups

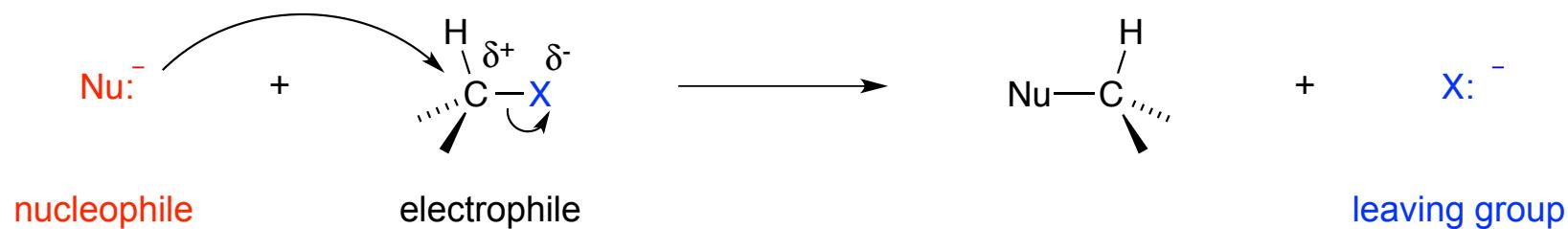
Product of Nucleophilic Substitution (Ch. 6)

Ex:

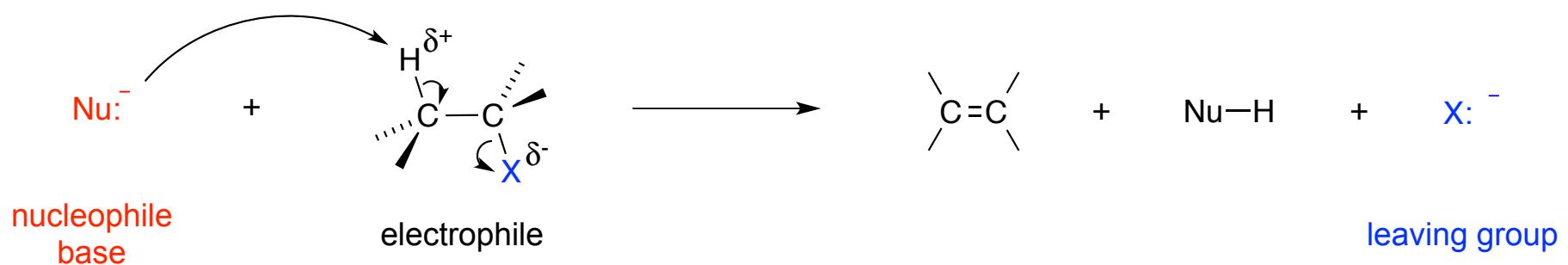


Q: How do the products differ from 1-bromobutane? Types of rxns?

Nucleophilic Substitution



Elimination



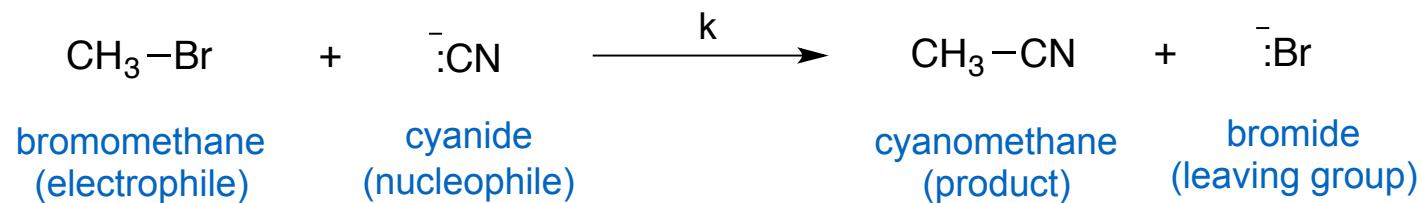
Nucleophile - an e⁻-rich atom that can donate a pair of e⁻s to form a bond (a Lewis base)

Electrophile - an e⁻-deficient atom that can accept a pair of e⁻s to form a bond (a Lewis acid)

Leaving group - an atom or group that can accept a pair of e⁻s from a bond and stabilize negative charge (a conjugate base of a strong acid)

Second-Order Nucleophilic Substitution: the S_N2 Rxn (6-8)

Ex: Cyanation of bromomethane



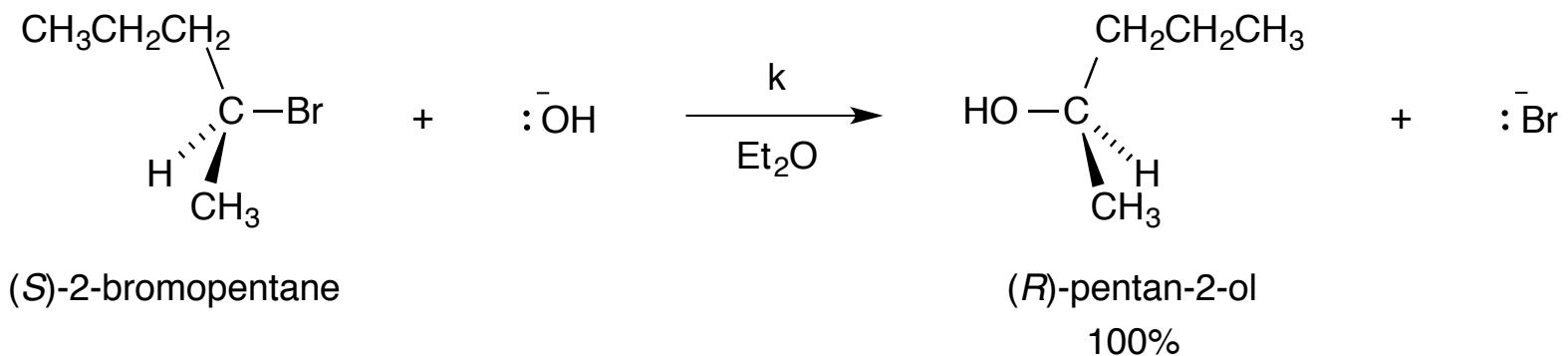
Experimental Observations

- When $[\text{CN}]$ is doubled \rightarrow rxn rate doubles
 - When $[\text{R-Br}]$ is doubled \rightarrow rxn rate doubles
- $\left. \right\} \text{Rxn rate} = k[\text{R-Br}][\text{CN}] \rightarrow \text{2nd-order rxn}$

S_N2 → Substitution, nucleophilic, 2nd-order

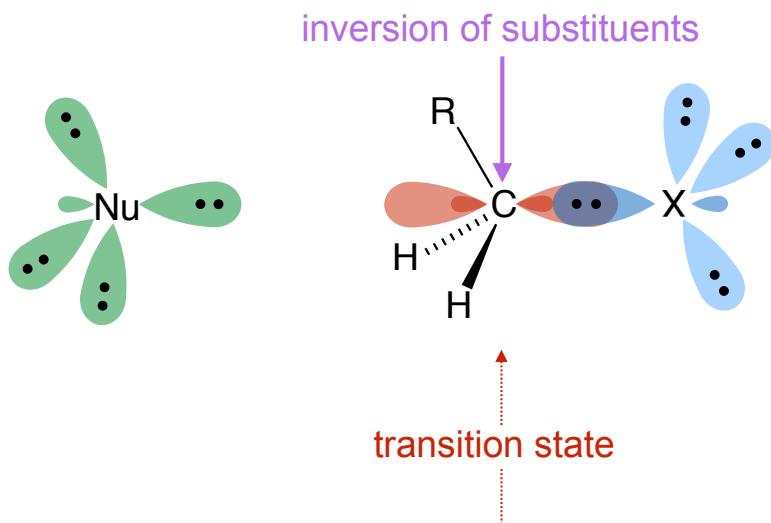
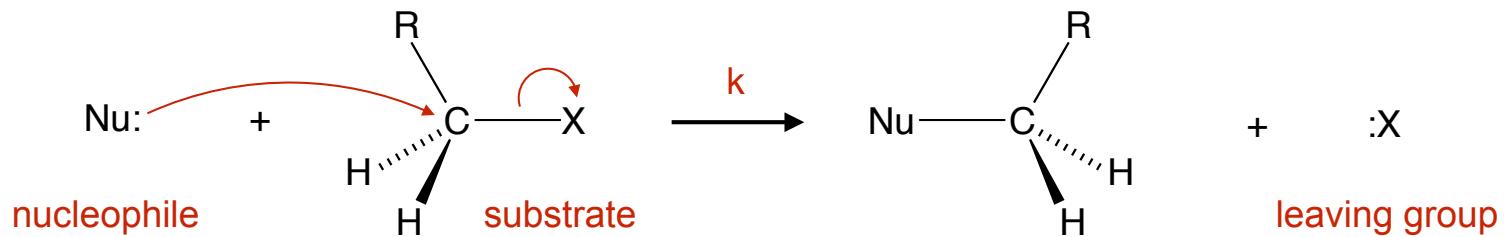
Stereochemistry: the S_N2 Rxn with a Chiral Alkyl Halide (6-12)

Ex:

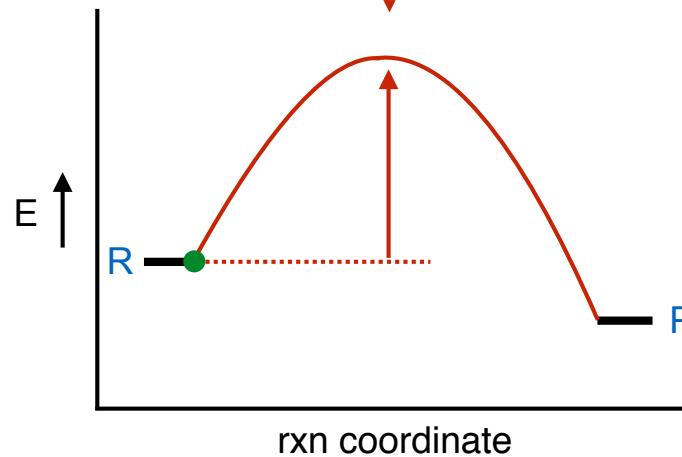


Q: Mechanism that explains inversion of configuration in the product?

Mechanism of the S_N2 Rxn



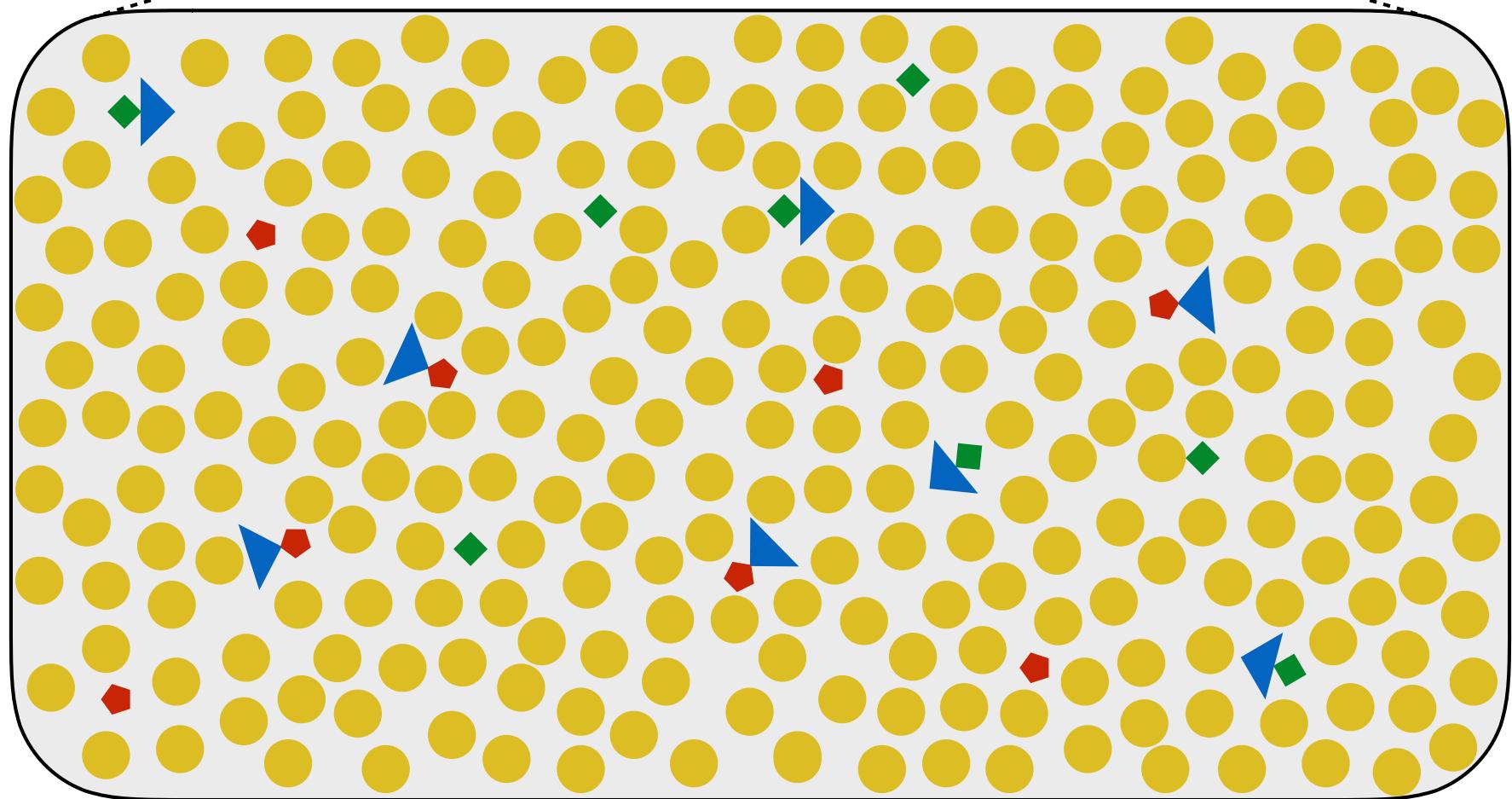
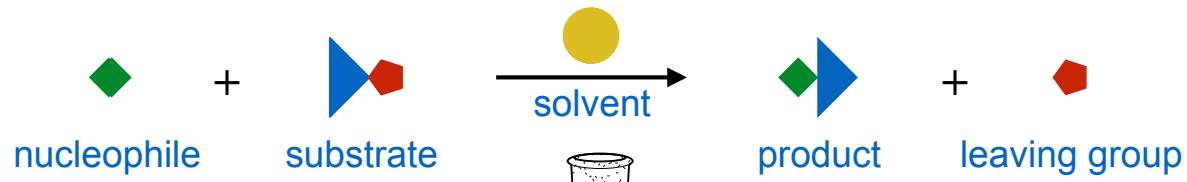
Concerted rxn - occurs in a single step that proceeds through a high-energy transition state with no rxn intermediate



$$\begin{aligned} \text{rxn rate} &= k[\text{substrate}][\text{nucleophile}] \\ &= k[R-X][\text{Nu}] \end{aligned}$$

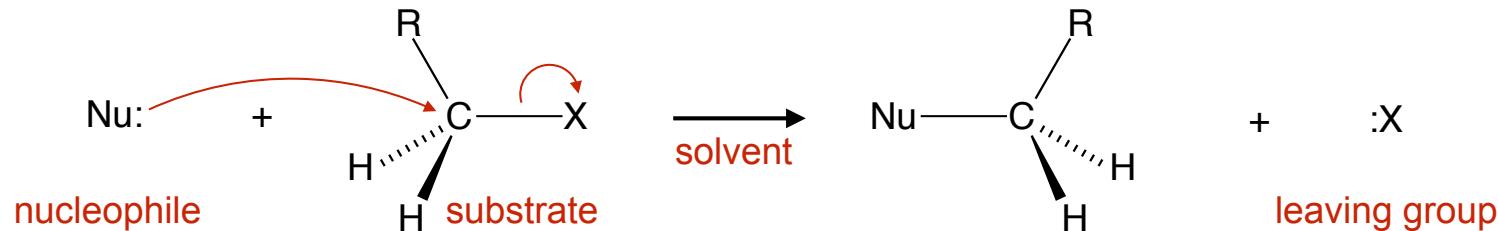
Q: How would you actually set up and carry out one of these reactions in the lab?

Q: What variables are involved in the reaction?



Q: How do the substrate, nucleophile, solvent, and leaving group affect the reaction?

Factors Affecting S_N2 Reactions



Factors influencing S_N2 Rxns

1. Substrate (R-L)

- The rates of S_N2 rxns depend on collisions between the nucleophile and alkyl halide, and that the carbon bearing the leaving group is sterically accessible to the nucleophile

2. Nucleophile (Nu:)

- The rates of S_N2 rxns depend on collisions between the nucleophile and alkyl halide, and the ability of the nucleophile to donate a pair of electrons to form a covalent bond

3. Leaving Group (:L)

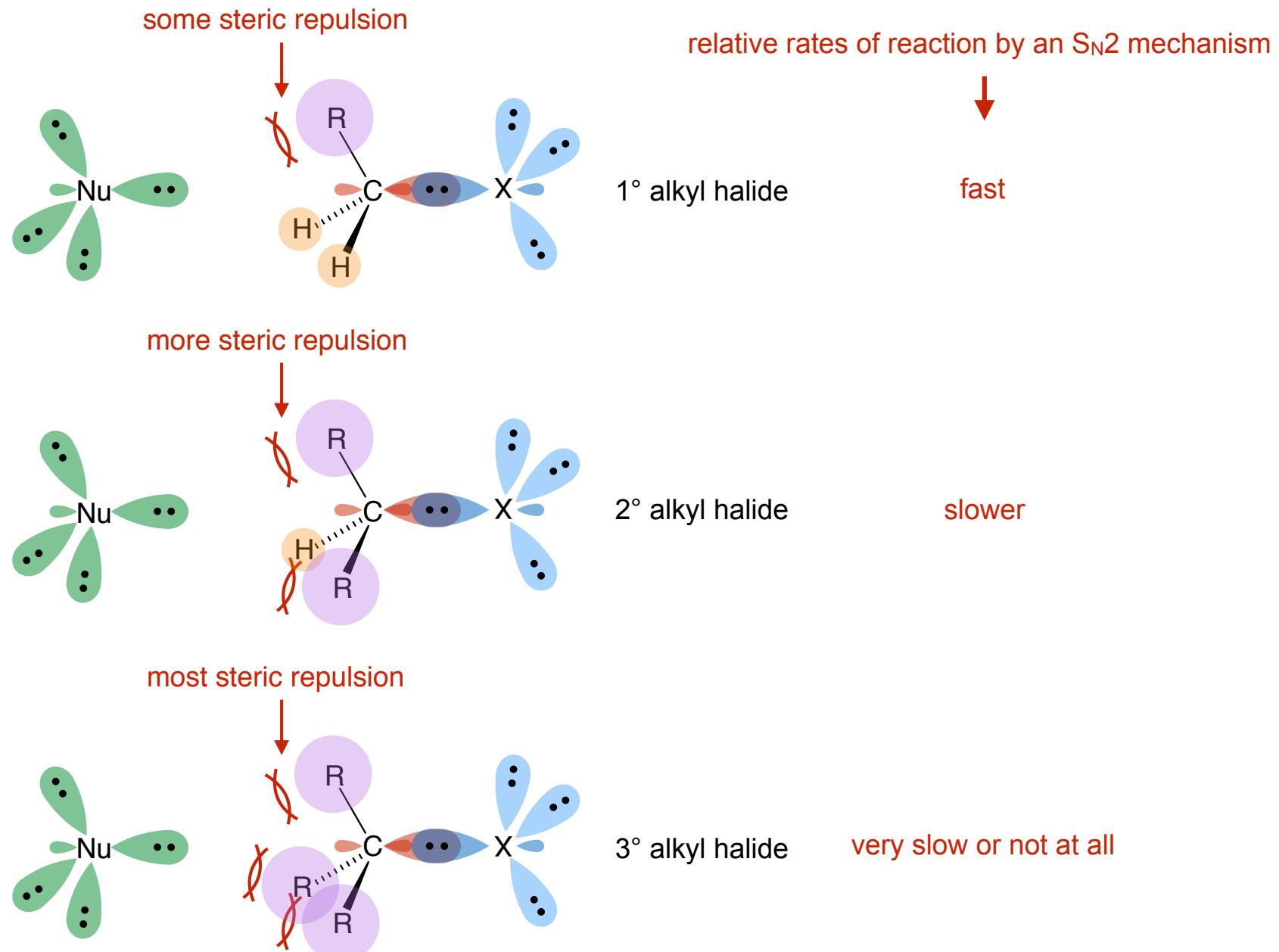
- S_N2 rxns require that the bond to the leaving group is weak, and that the leaving group stabilize the resulting negative charge (i.e., is the conjugate base of a strong acid) such that the leaving group is not a strong nucleophile

4. Solvent

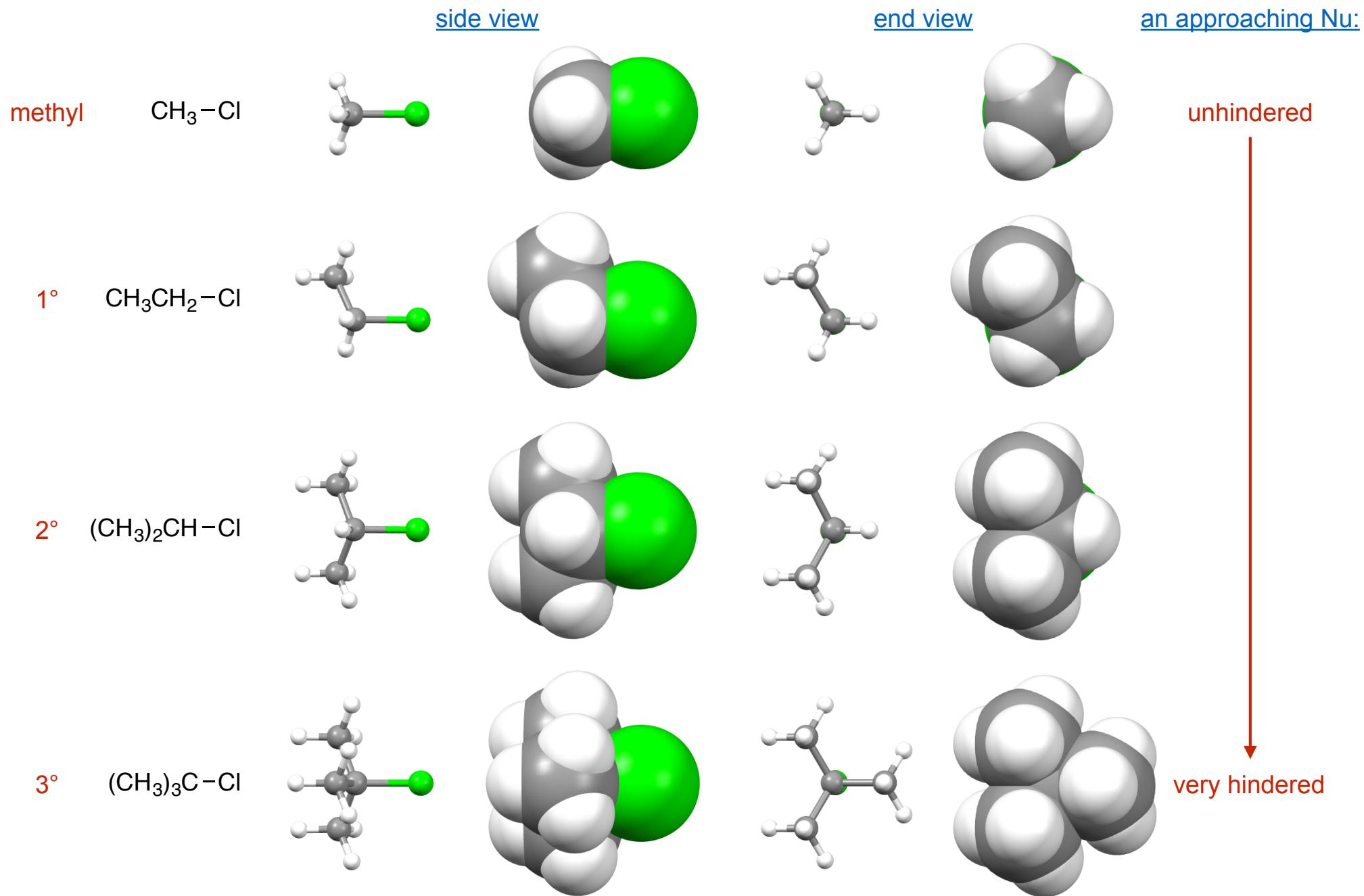
- Solvents that do not solvate the nucleophile enhance the rates of S_N2 rxns

Q: How do the *nucleophile, degree of substitution, leaving group & solvent* affect substitution via an S_N2 mechanism?

The Substrate: Steric Effect of Substituents on Rates of S_N2 Rxns (6-11)



Comparison of Steric Bulk of Alkyl Substituents



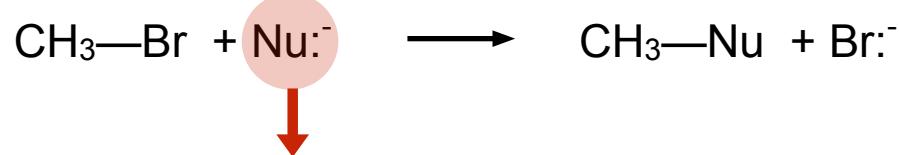
Nucleophiles (6-10)

Nucleophile - Any species with a lone pair of e⁻s that can be donated to an e⁻-deficient carbon atom to form a bond

Nucleophilicity - measure of the affinity of a species for a carbon atom in an S_N2 rxn



Ex:



HS ⁻	CN ⁻	I ⁻	CH ₃ O ⁻	HO ⁻	Cl ⁻	NH ₃	H ₂ O	1 ← Rel. rate
125,000	125,000	100,000	25,000	16,000	1000	700		

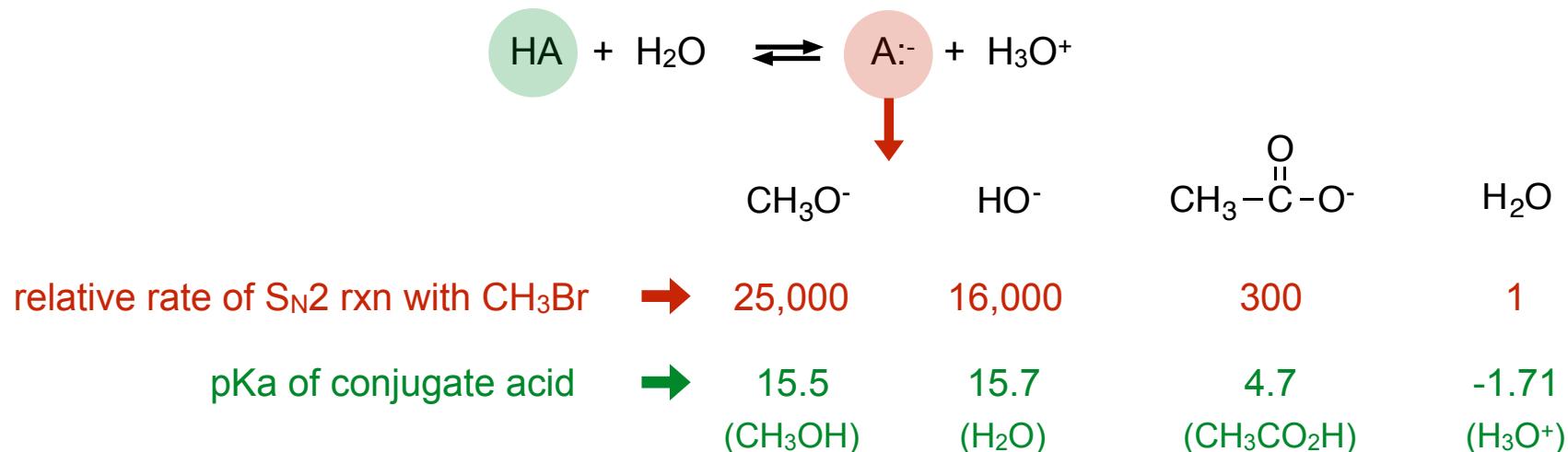
stronger Nu
more reactive

weaker Nu
less reactive

Q: What makes a nucleophile strong or weak?

Trends for Nucleophilicity

1. Nucleophilicity roughly parallels basicity for elements in the same row of the periodic table



$$K_{\text{eq}} = \frac{[\text{A}^-][\text{H}_3\text{O}^+]}{[\text{HA}][\text{H}_2\text{O}]}$$

$$K_a = K_{\text{eq}}[\text{H}_2\text{O}] = \frac{[\text{A}^-][\text{H}_3\text{O}^+]}{[\text{HA}]}$$

$$pK_a = -\log_{10} K_a$$

weaker acid

stronger acid

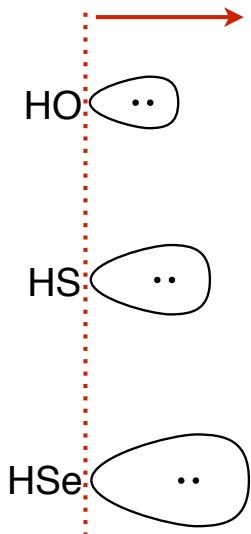
	pKa	acid	conj. base
	~50	CH ₄	$:\text{CH}_3^- + \text{H}^+$
	36	NH ₃	$:\text{NH}_2^- + \text{H}^+$
	16	H ₂ O	$:\text{OH}^- + \text{H}^+$
	3.5	HF	$:\text{F}^- + \text{H}^+$
	-7	HCl	$:\text{Cl}^- + \text{H}^+$
	-8	HBr	$:\text{Br}^- + \text{H}^+$
	-9	HI	$:\text{I}^- + \text{H}^+$

stronger base/Nu more reactive

weaker base/Nu less reactive

Trends for Nucleophilicity

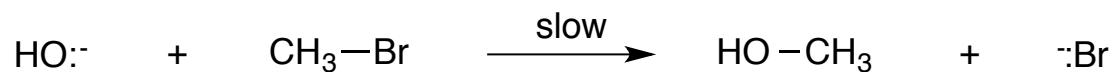
2. Nucleophilicity increases going down a family (column) in the periodic table



Valence e⁻s are farther from the nucleus

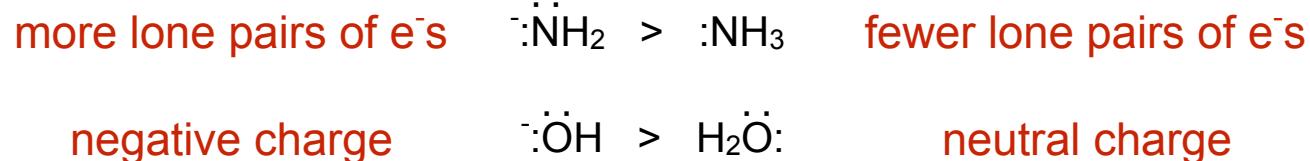
Valence e⁻s are more shielded from the nucleus and held less tightly (softer)

Ex:

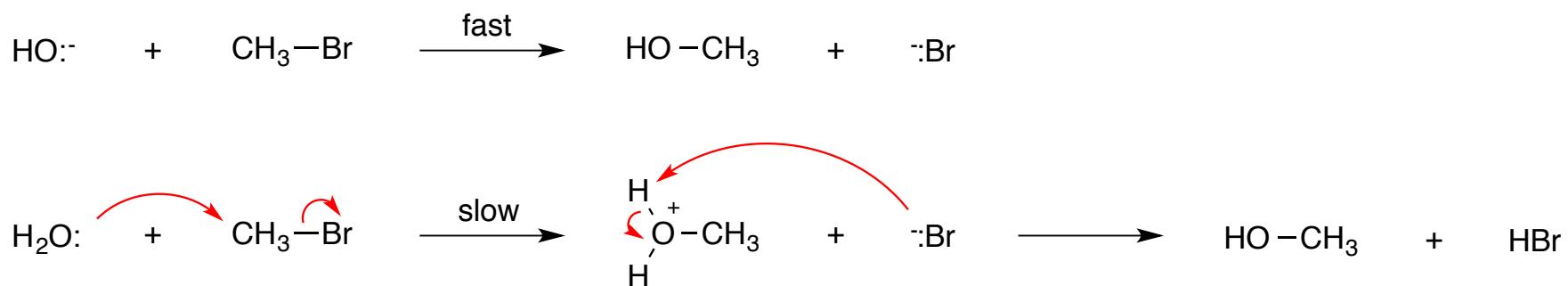


Trends for Nucleophilicity

3. Negatively charged Nu:⁻ are more reactive than the corresponding neutral Nu:

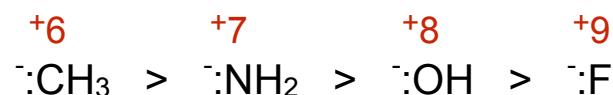


Ex:



Trends for Nucleophilicity

4. Nu: with lower nuclear charge in the same row of the periodic table are more reactive



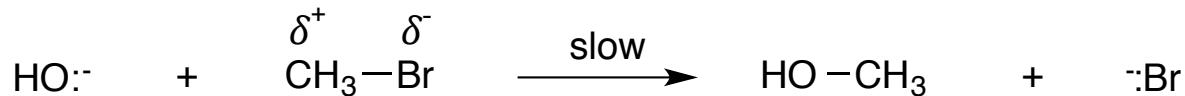
stronger Nu

weaker Nu

carbon 6 C 12.011	nitrogen 7 N 14.007	oxygen 8 O 15.999	fluorine 9 F 18.998
-----------------------------------	-------------------------------------	-----------------------------------	-------------------------------------

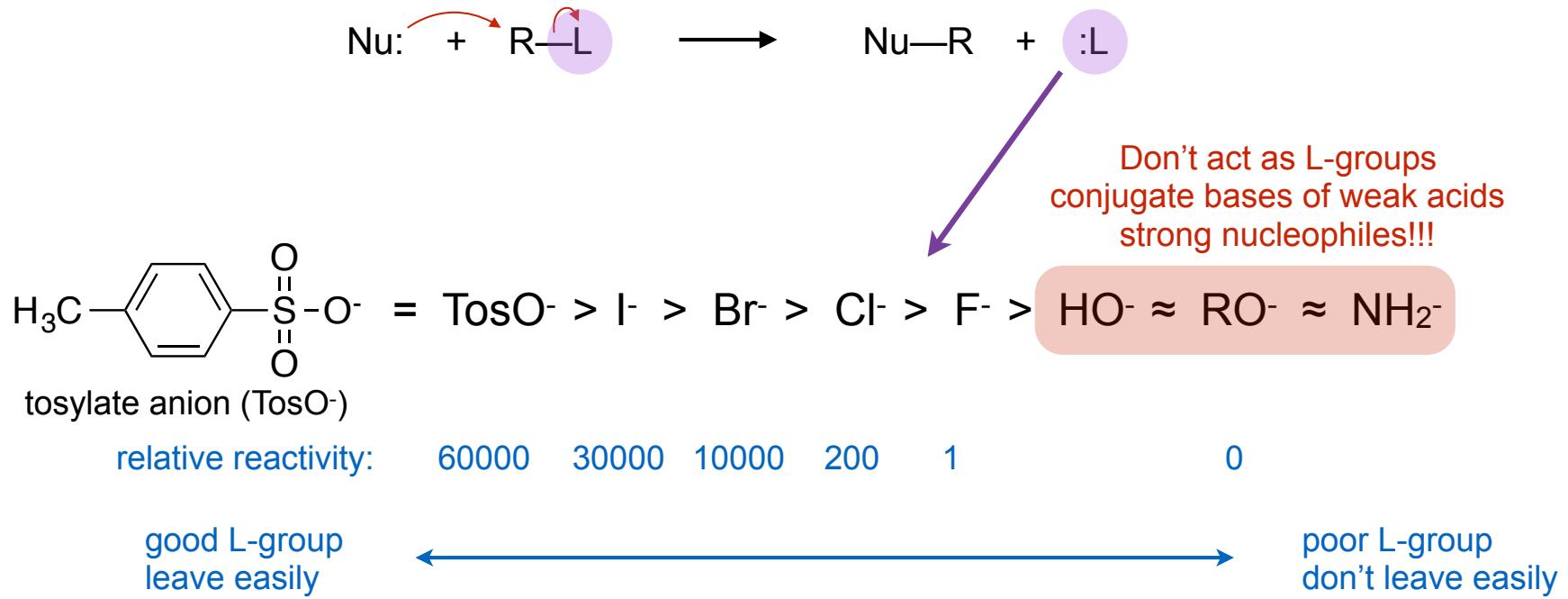
$$E_{\text{coul}} = k \frac{Q_1 Q_2}{d}$$

Ex:



Leaving Groups in S_N2 Rxns

Good leaving groups are conjugate bases of strong acids that can stabilize negative charge



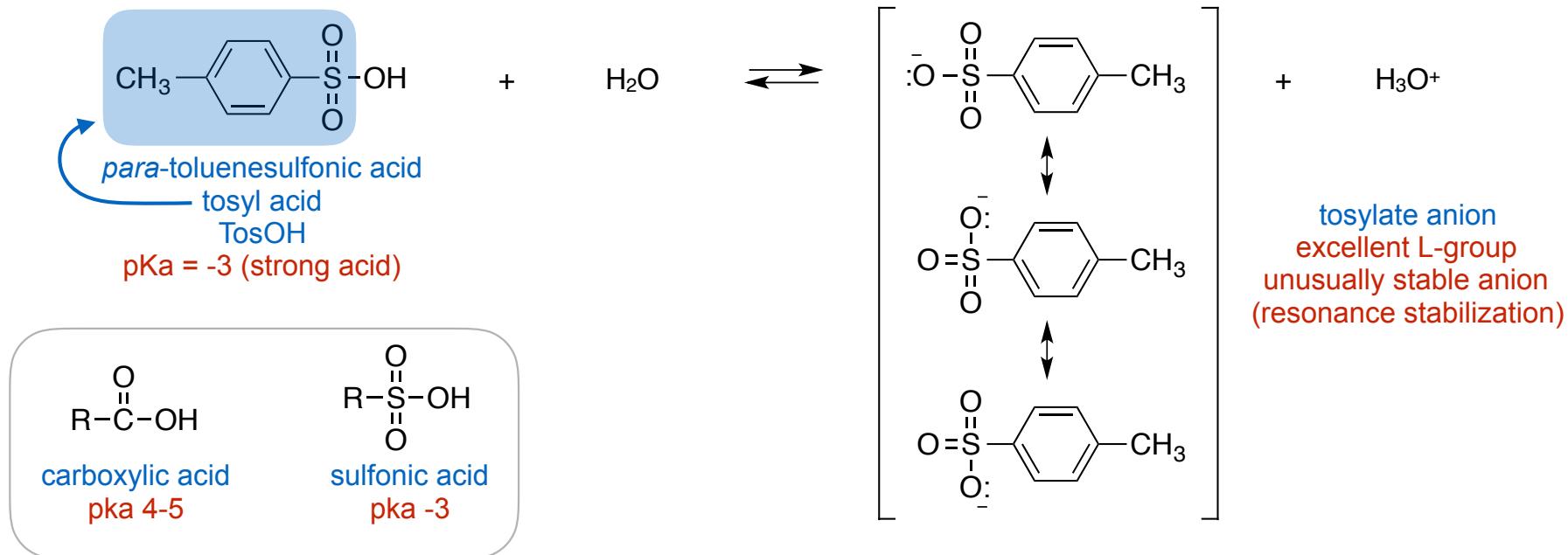
Acid	pKa
TosOH	-3
HI	-9
HBr	-8
HCl	-7
HF	3.5
H ₂ O	15.7
ROH	16-18
NH ₃	36



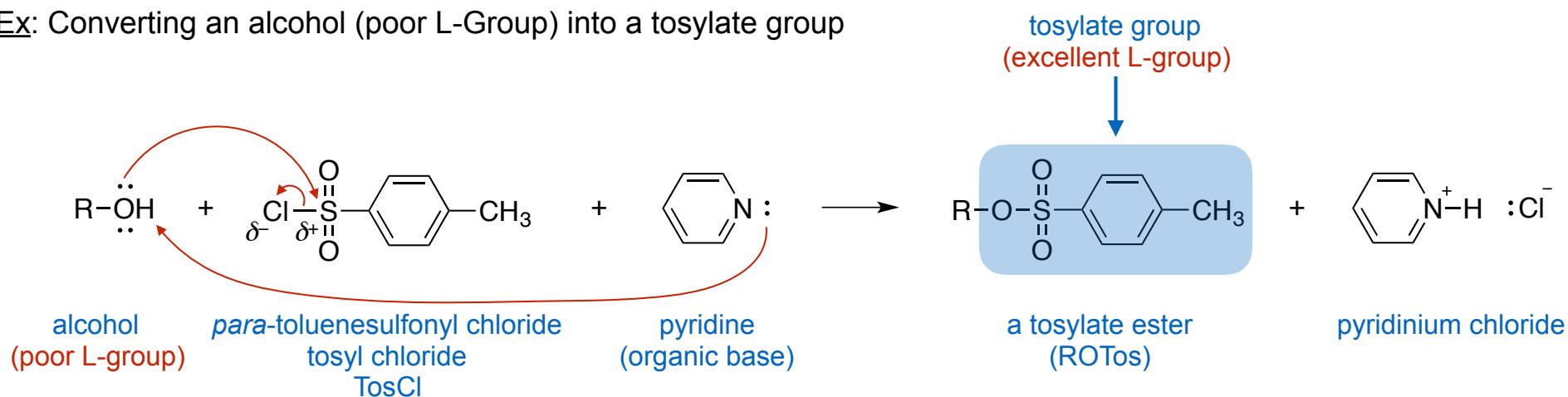
alcohols: R-OH
ethers: R-OR'
amines: R-NH₂

Don't undergo S_N2 rxns unless the functional groups are first converted into good leaving groups

Tosylate Anion Is An Excellent Leaving Group



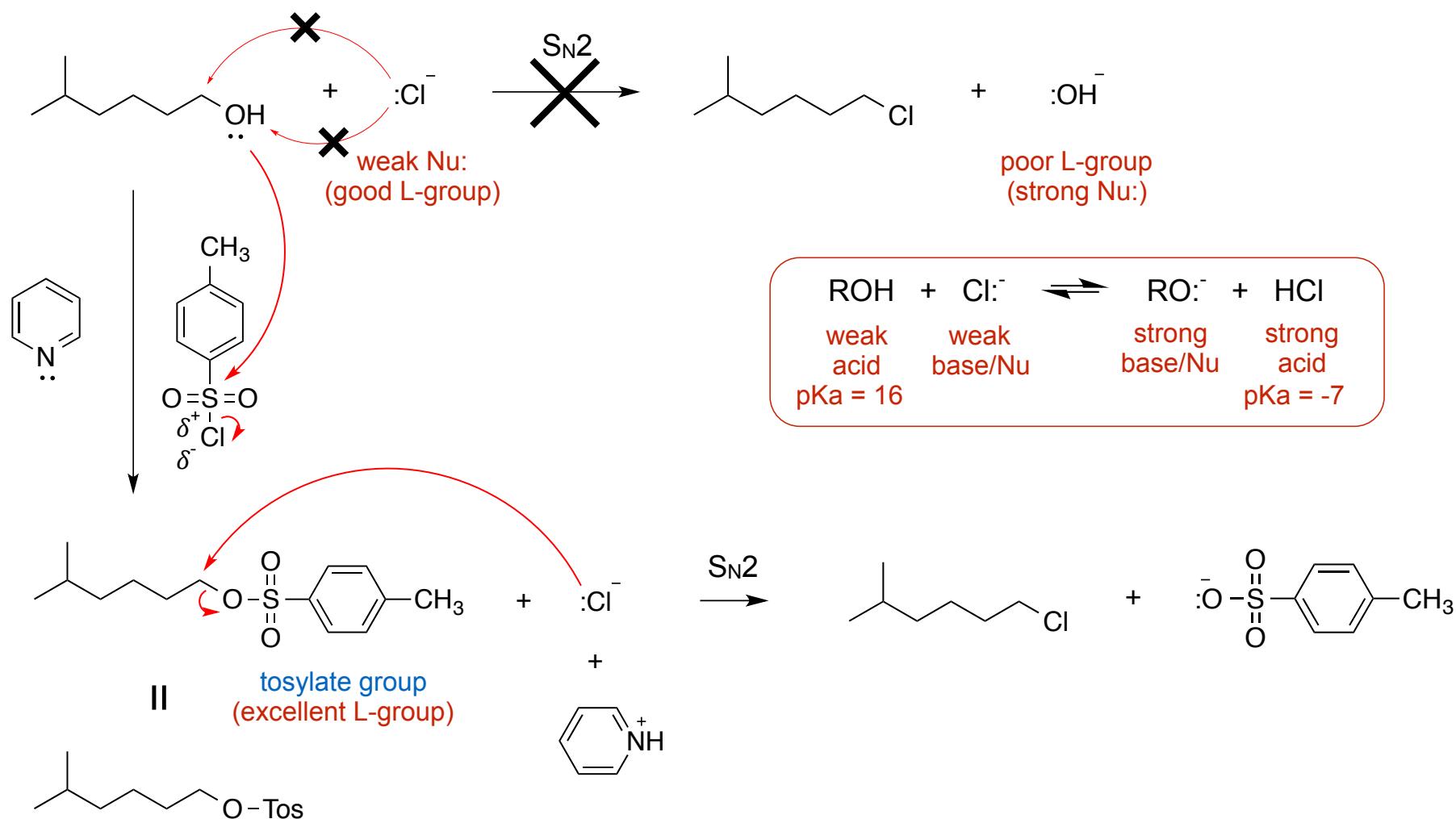
Ex: Converting an alcohol (poor L-Group) into a tosylate group



Tosylation is a good method to convert alcohols into excellent L-groups!

Q: How is converting an alcohol group into a good L-group via tosylation useful?

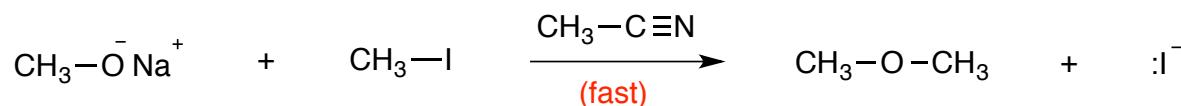
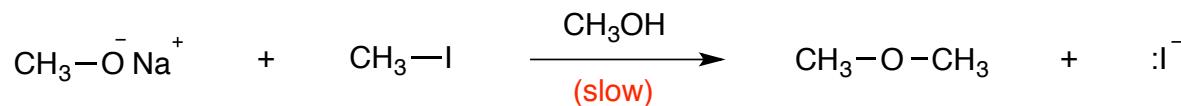
Ex:



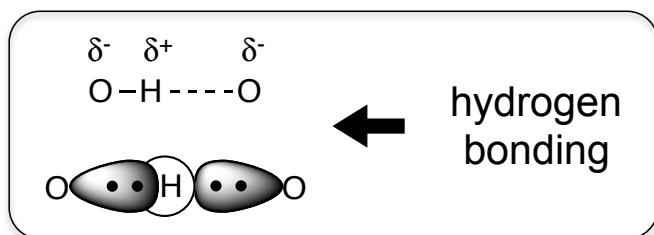
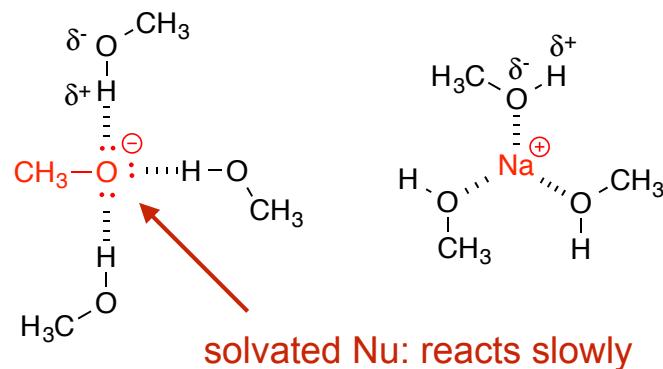
Tosylation is a good strategy to turn alcohols into excellent leaving groups that will undergo S_N2 reactions with weak nucleophiles

Influence of Solvent in S_N2 Rxns

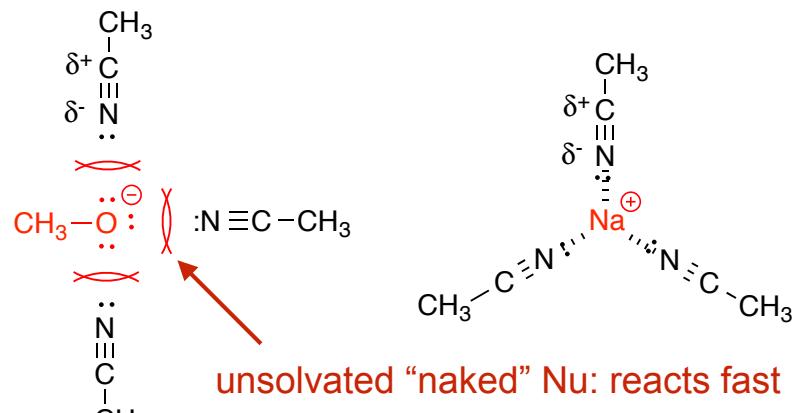
Ex:



polar solvents with an acidic proton bind to nucleophiles via hydrogen bonding & form a solvation shell that hinders nucleophilic attack



polar solvents with no acidic proton do not solvate nucleophiles due to electronic repulsion leaving nucleophile free to react unhindered



polar protic solvents decrease the relative rates of S_N2 rxns compared to polar aprotic solvents

Common Polar Solvents

Polar Protic Solvents - have an acidic proton



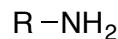
water



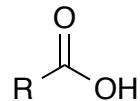
alcohols



ammonia

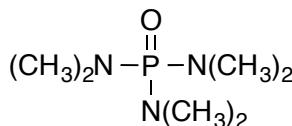


amines

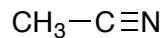


carboxylic acids

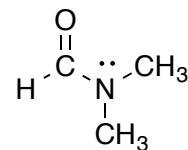
Polar Aprotic Solvents - have no acidic proton



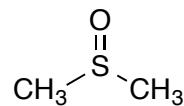
HMPA - hexamethylphosphoramide



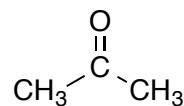
acetonitrile



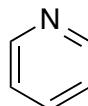
DMF - dimethylformamide



DMSO - dimethylsulfoxide



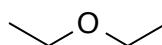
acetone



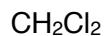
pyridine



THF - tetrahydrofuran



diethyl ether

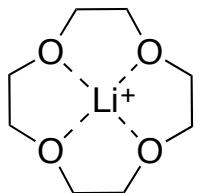


dichloromethane

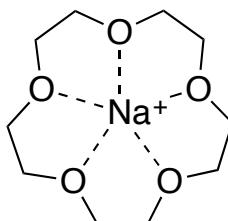
Q: Why not use nonpolar solvents?

Phase-Transfer Catalysts

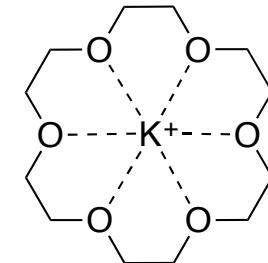
Phase-transfer catalysts such as crown ethers are used to make water-soluble nucleophilic reagents (e.g., ionic salts) soluble in organic solvents



12-crown-4
complexed to Li^+

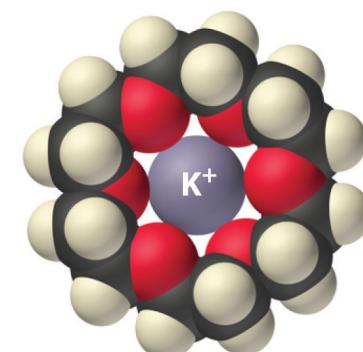
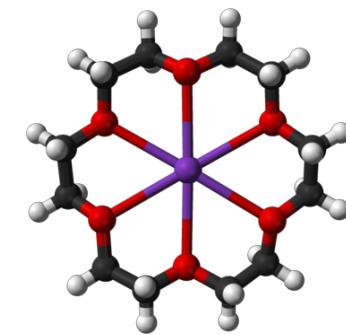
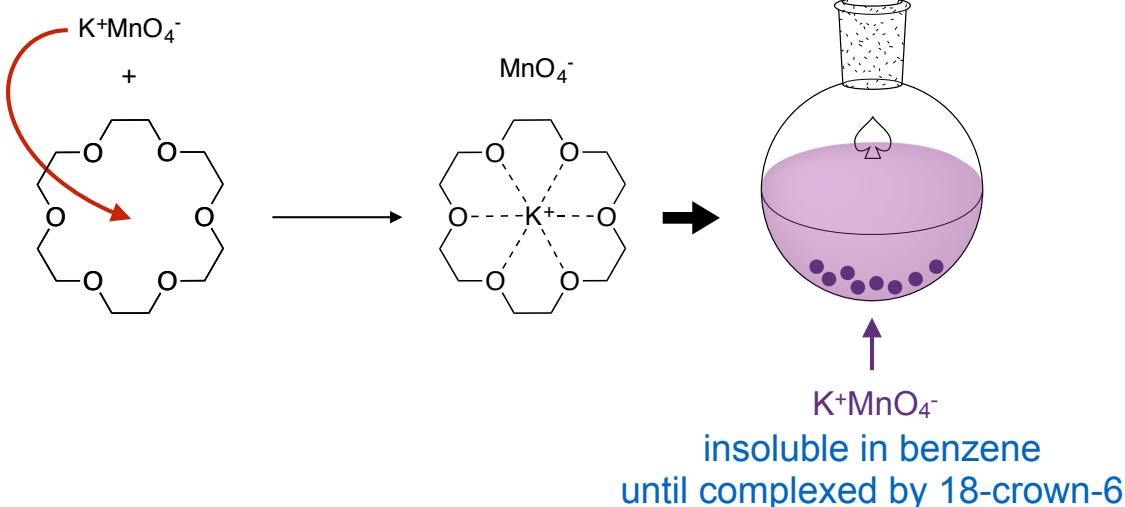
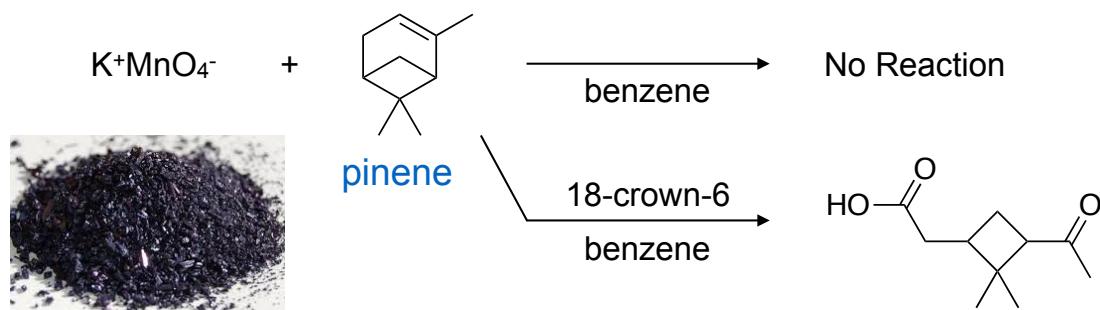


15-crown-5
complexed to Na^+

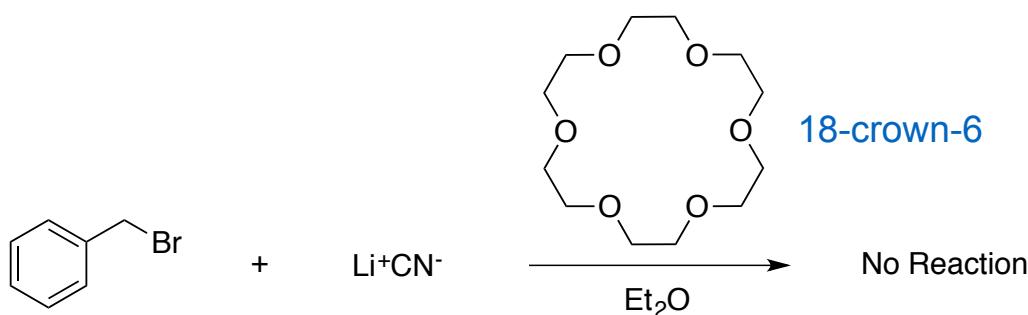
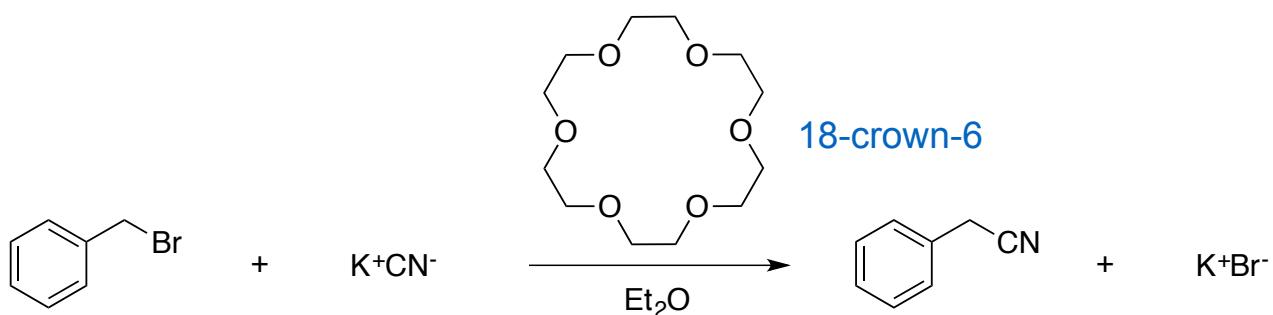


18-crown-6
complexed to K^+

Ex:

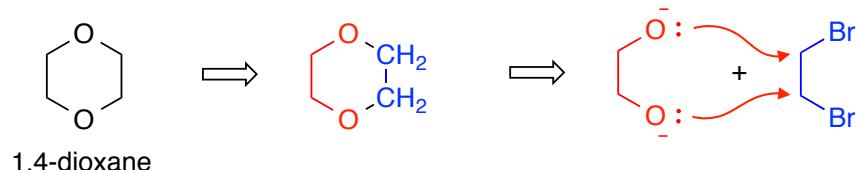
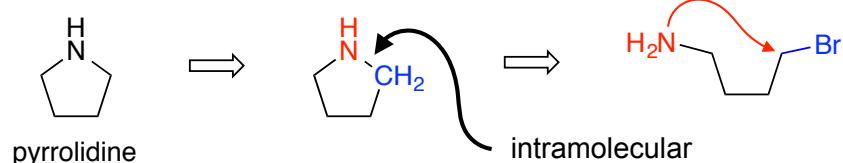
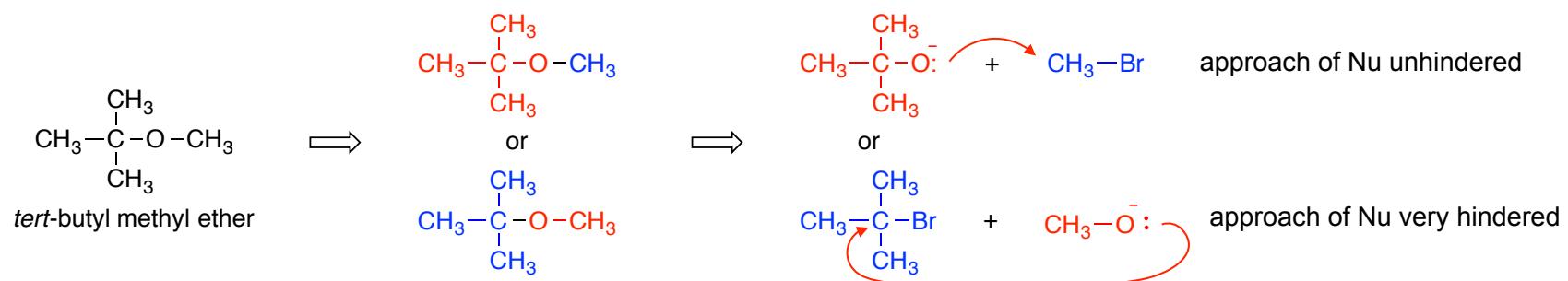
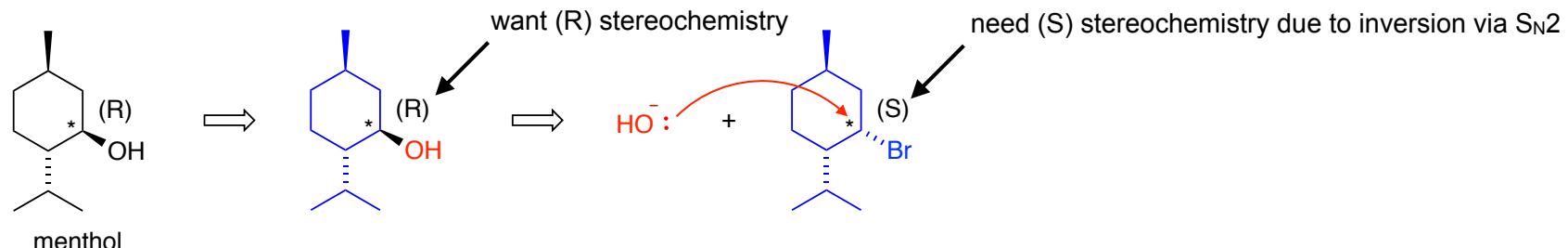
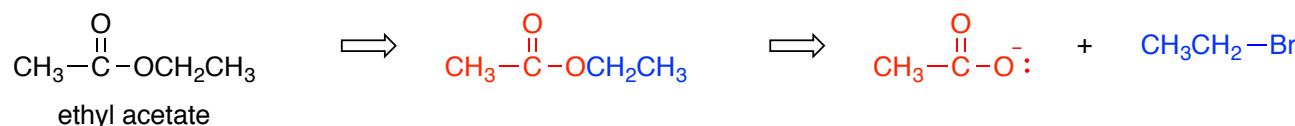
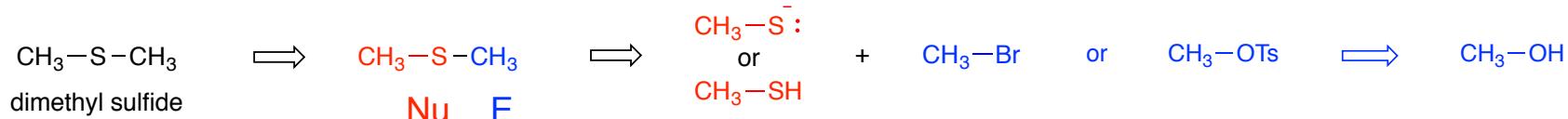


Ex:

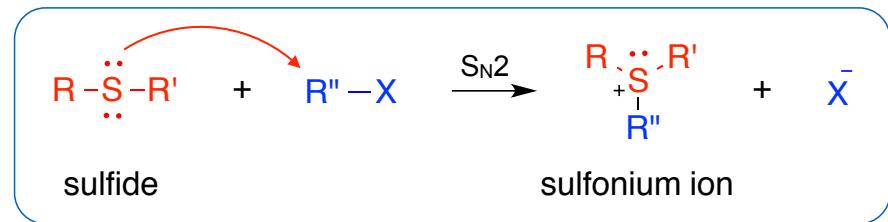


18-crown-6 selectively binds to K^+ (not Li^+ or Na^+) based on the size of the central cavity

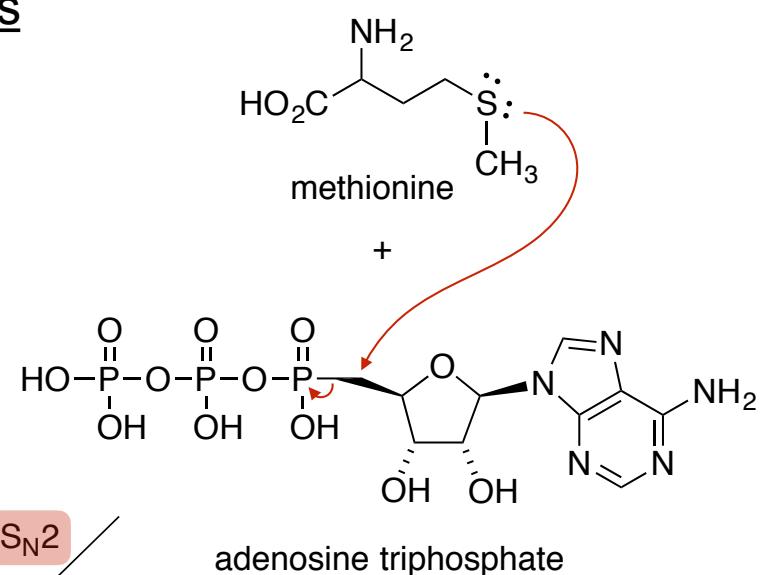
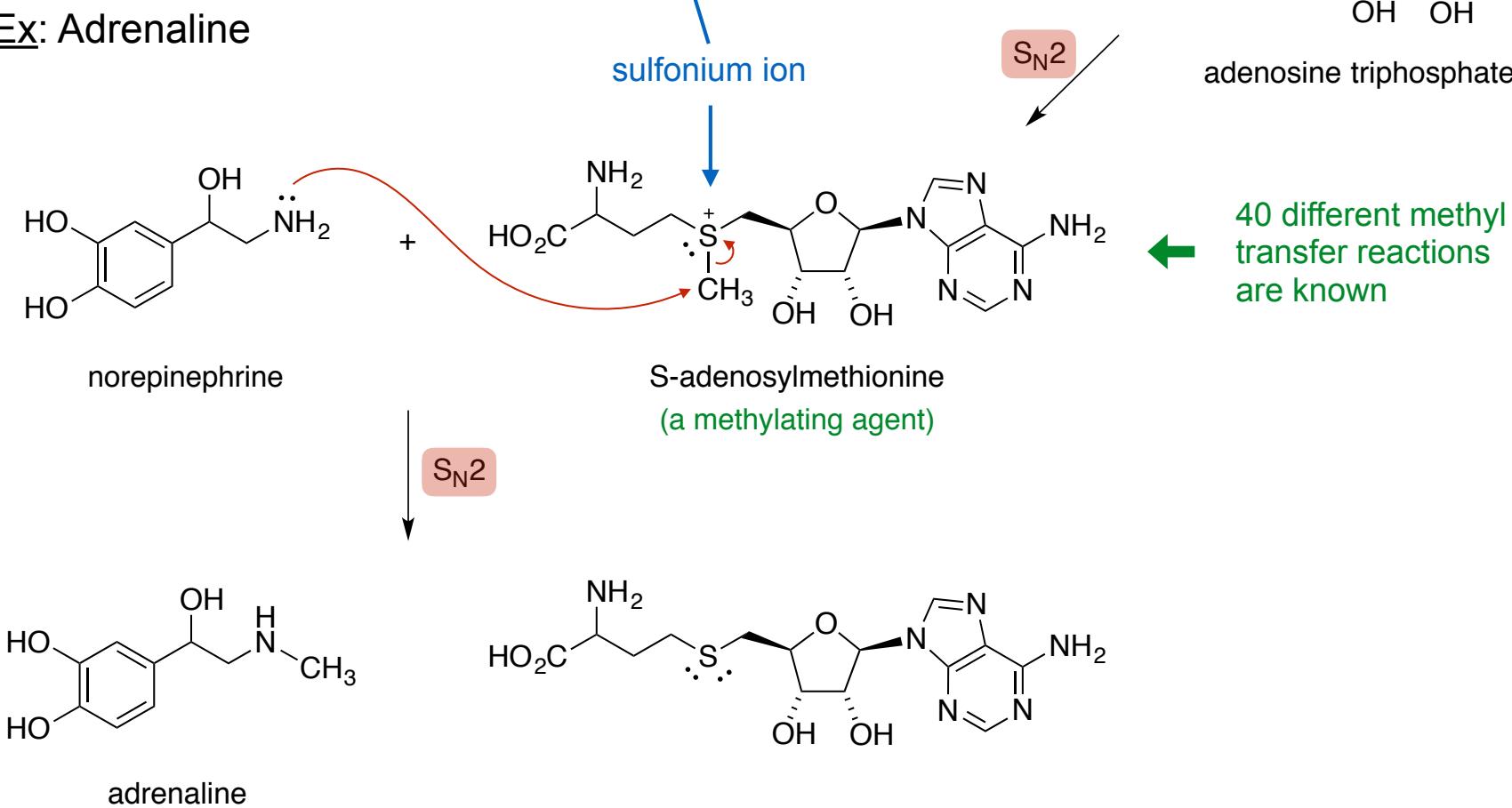
Q: How might the following be synthesized from an alkyl halide via S_N2 rxns?



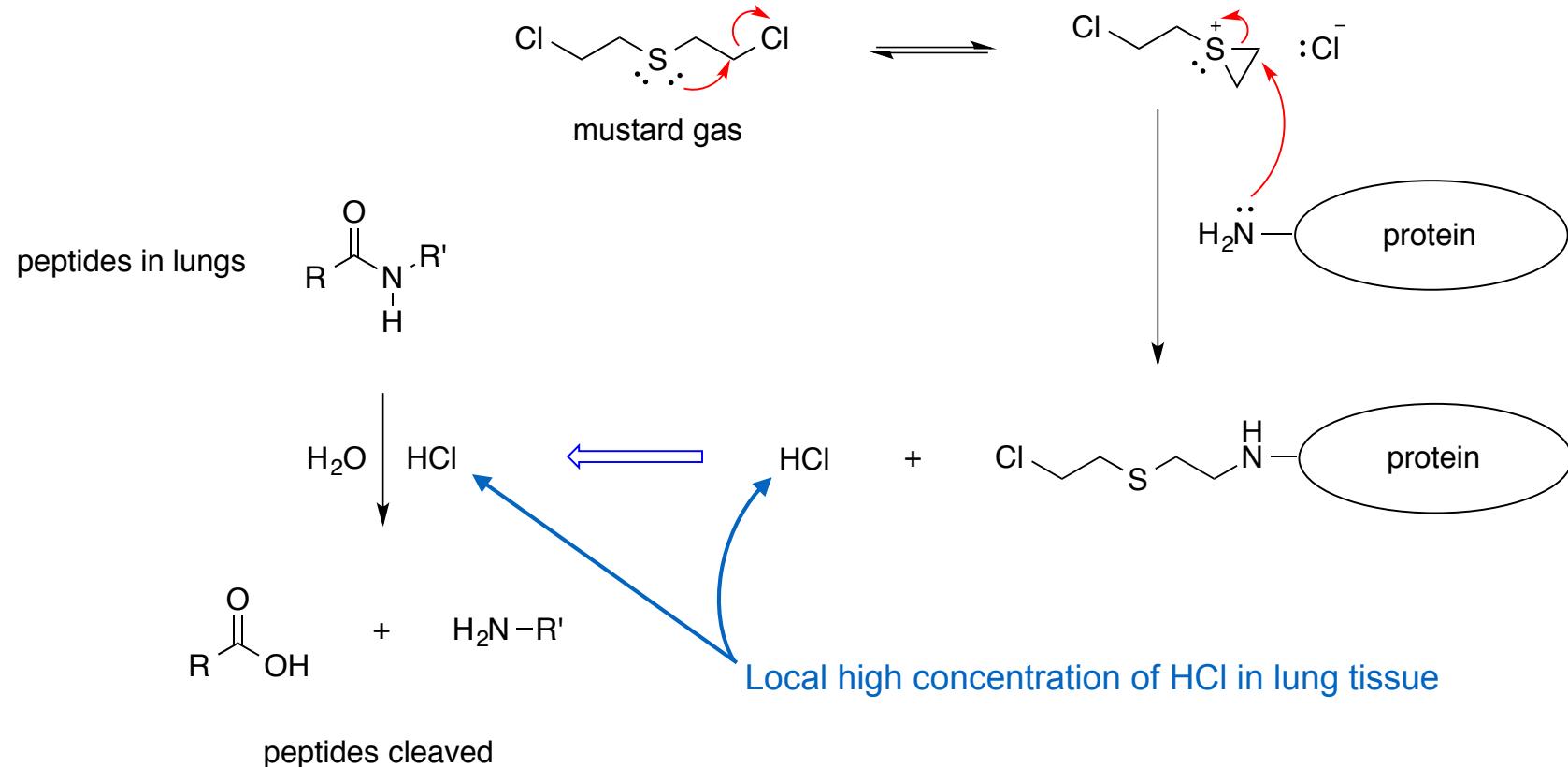
S_N2 alkylation rxns are common in biological systems



Ex: Adrenaline

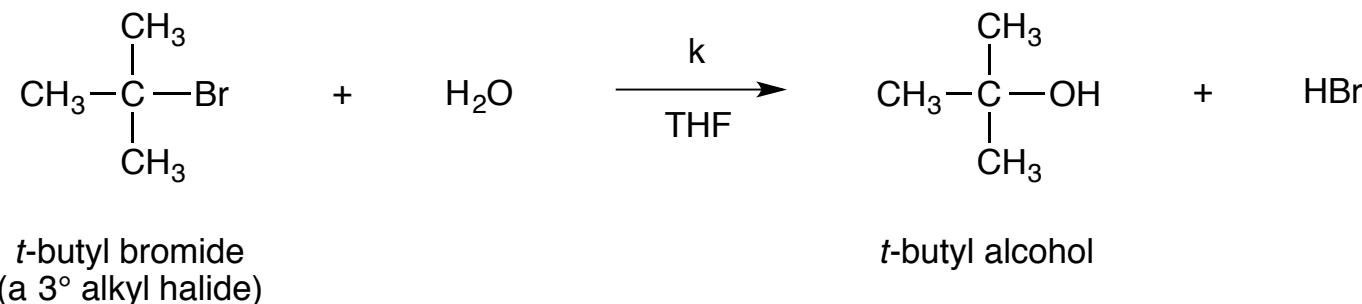


Ex: Mustard gas — alkylating agent used in WWII that caused $\sim 4 \times 10^5$ casualties



First-Order Nucleophilic Substitution: the S_N1 Rxn (6-13)

Ex:



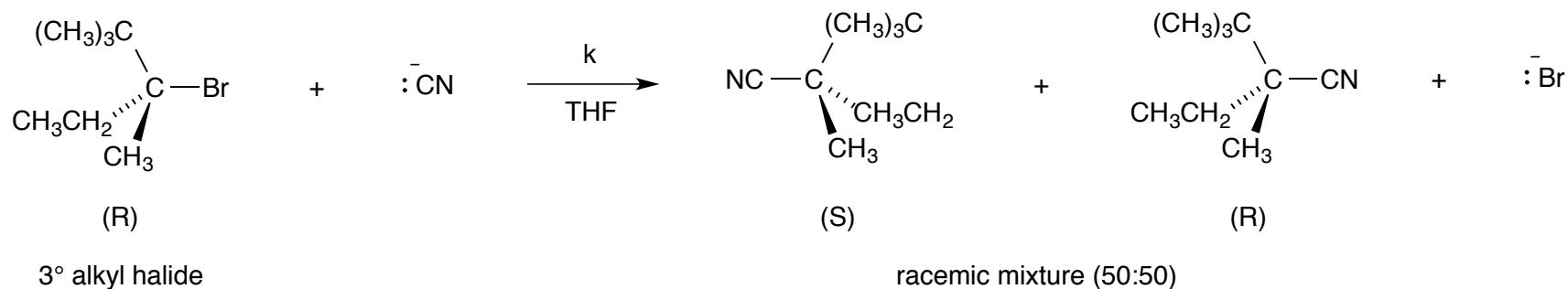
Experimental Observations

- When [H₂O] is doubled → rxn rate remains constant
 - When [R-Br] is doubled → rxn rate doubles
- $\left. \begin{array}{l} \text{Rxn rate} = k[\text{R-Br}] \rightarrow \text{1st-order rxn} \end{array} \right\}$

S_N1 → Substitution, nucleophilic, 1st-order

Stereochemistry: S_N1 Rxn with a Chiral Alkyl Halide (6-14)

Ex:

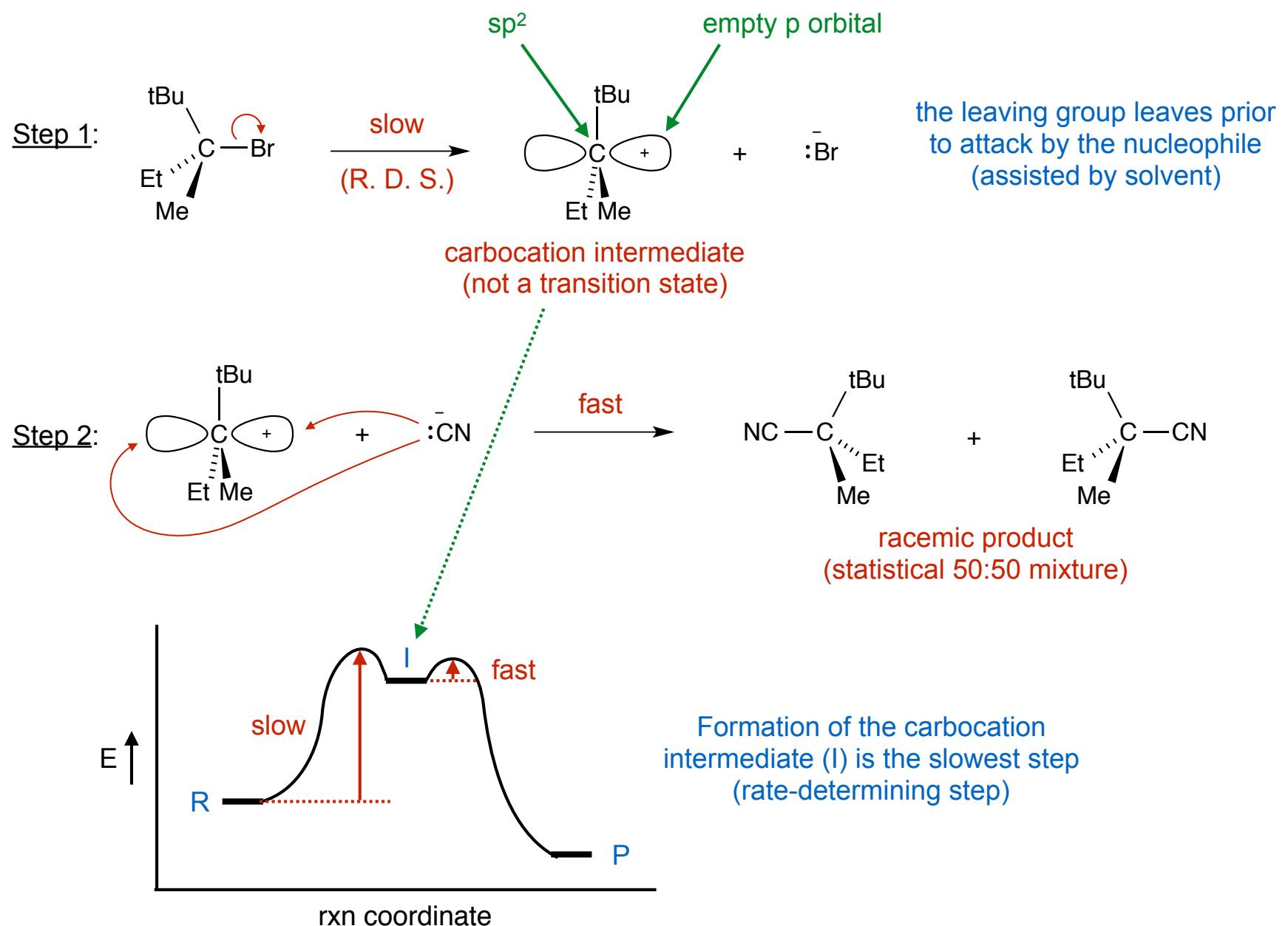


Evidence

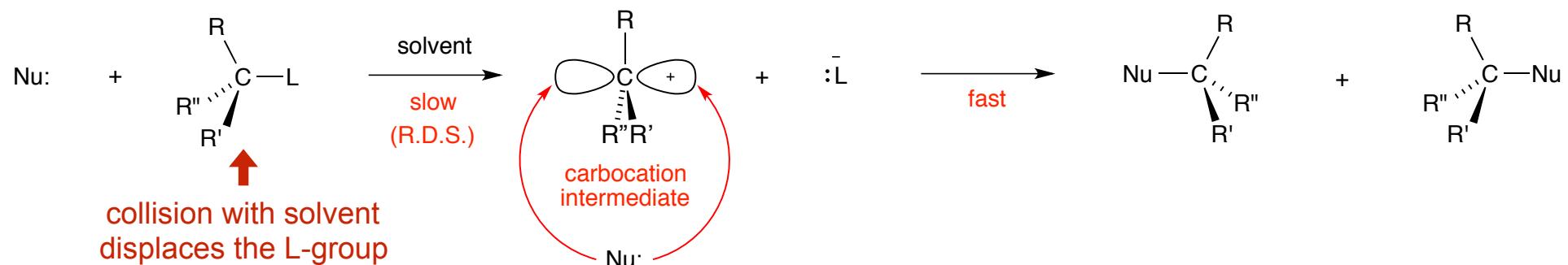
- When [CN] is doubled → rxn rate remains constant
 - When [R-Br] is doubled → rxn rate doubles
 - The product is a racemic mixture
- } Rxn rate = $k[R\text{-Br}] \rightarrow$ 1st-order rxn

Q: Mechanism that explains both racemization & dependence of rate only on the alkyl halide?

Q: Mechanism that can explain the observed rate dependence and racemic product?



General Rxn for S_N1

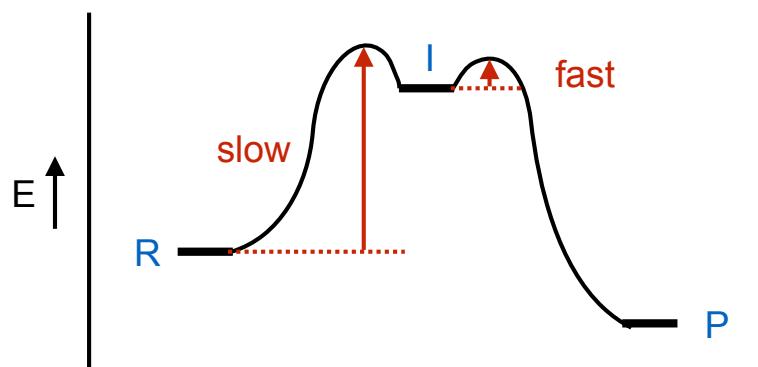


Q: How do the *nucleophile*, *degree of substitution*, *leaving group* and *solvent* affect substitution via an S_N1 mechanism?

Factors influencing S_N1 Rxns

1. Nucleophile

- Not a factor because there are two steps, where the rate depends on formation of the carbocation intermediate in the slow first step (RDS)



Formation of the carbocation intermediate (I) is the slowest step (rate determining step)

$$\text{Rxn rate} = k[\text{R}-\text{Br}] \rightarrow \text{1st-order rxn}$$

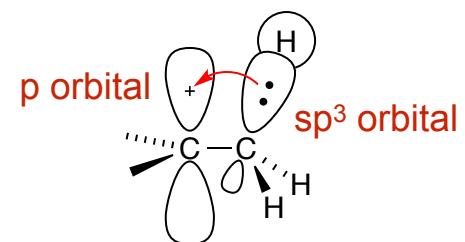
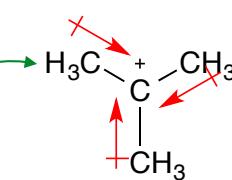
2. Substrate

- Rates of S_N1 rxns depend strongly on the stability of the carbocation intermediate
- Alkyl groups stabilize carbocations both inductively and via hyperconjugation

<u>carboxylic acid</u>	pKa
H—CO ₂ H	3.8
CH ₃ —CO ₂ H	4.8
CH ₃ CH ₂ —CO ₂ H	4.9

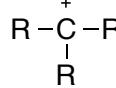
alkyl groups are e⁻-donating

e⁻-donation via induction
(through sigma bonding)

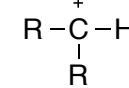


e⁻-donation via hyperconjugation
(through π-type bonding)

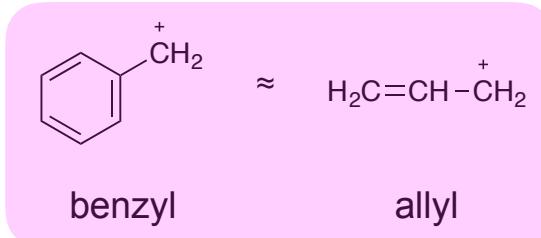
relative reactivity
via S_N1



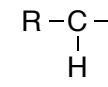
3°



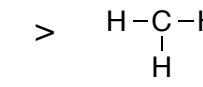
2°



don't react via S_N1



1°



methyl

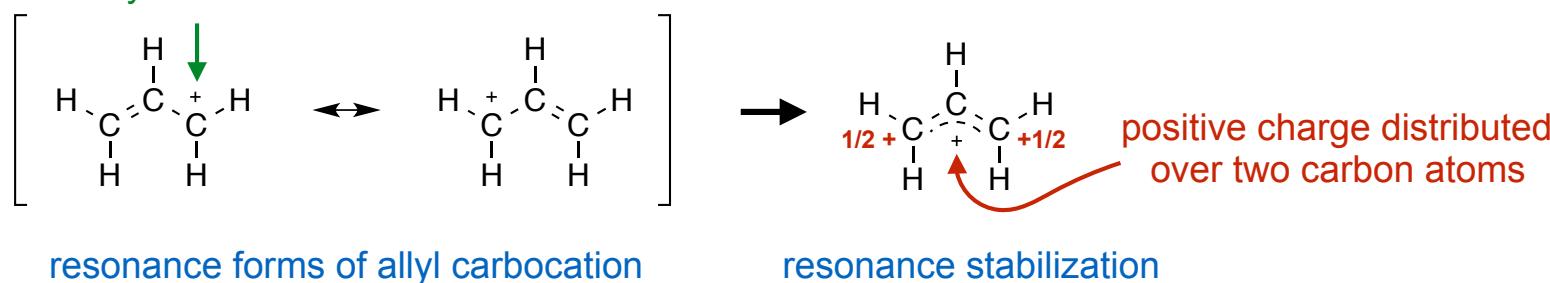
most reactive via S_N1
most stable
(lowest in E)

least reactive via S_N1
least stable
(highest in E)

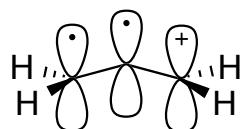
Q: Why are benzylic and allylic carbocations so stable?

Unusual Stability of Benzylic and Allylic Carbocations

allylic carbon

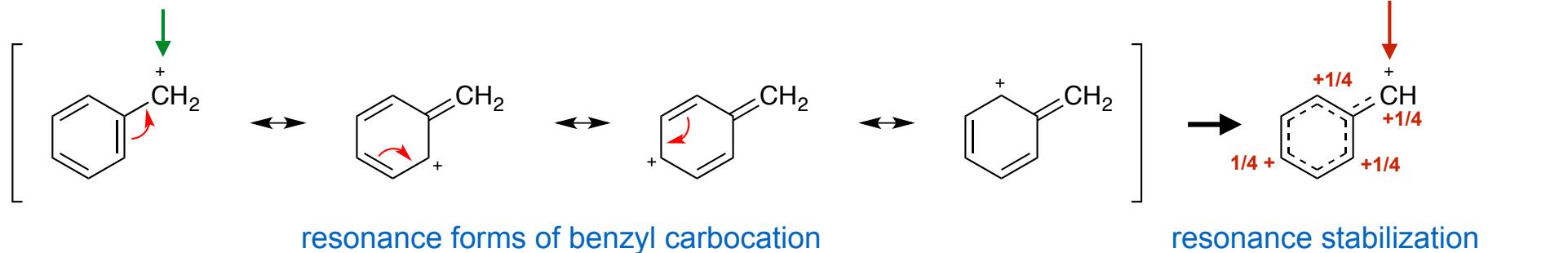


resonance stabilization

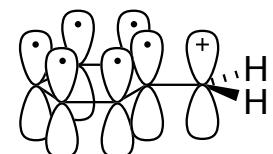


2π electrons
3 adjacent p orbitals

benzylic carbon



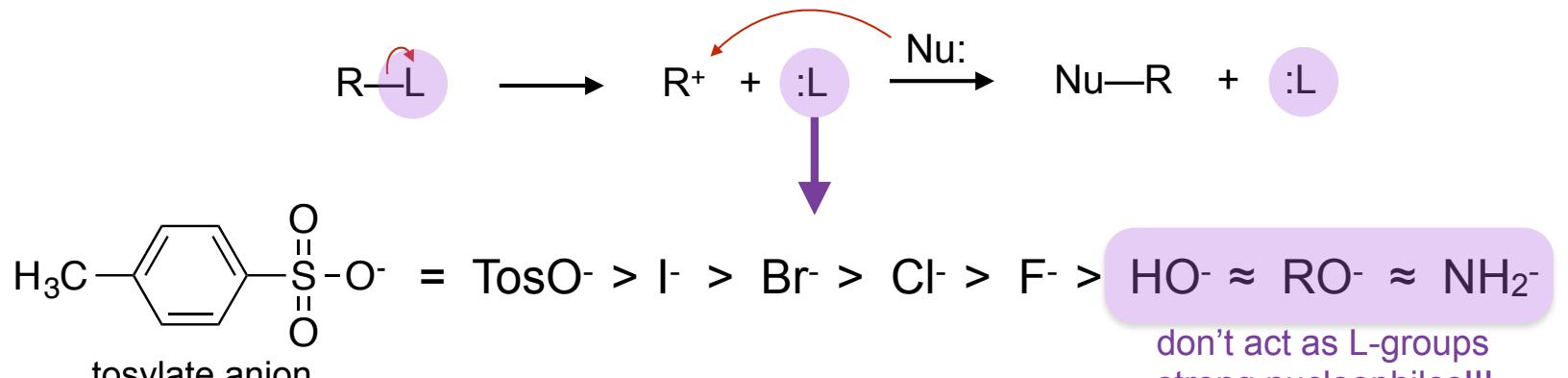
resonance stabilization



6π electrons
7 adjacent p orbitals

3. Leaving Groups

- L-groups are directly involved in forming the carbocation in the rate-determining step (R.D.S.)
- L-groups have the same order of reactivity for S_N1 rxns as for S_N2 rxns
- Good L-groups are conjugate bases of strong acids that can stabilize negative charge



relative reactivity: 60000 30000 10000 200 1 0

good L-group
leave easily

poor L-group
don't leave easily

Acid	pKa
TosOH	-3
HI	-9
HBr	-8
HCl	-7
HF	3.5
H ₂ O	15.7
ROH	16-18
NH ₃	36



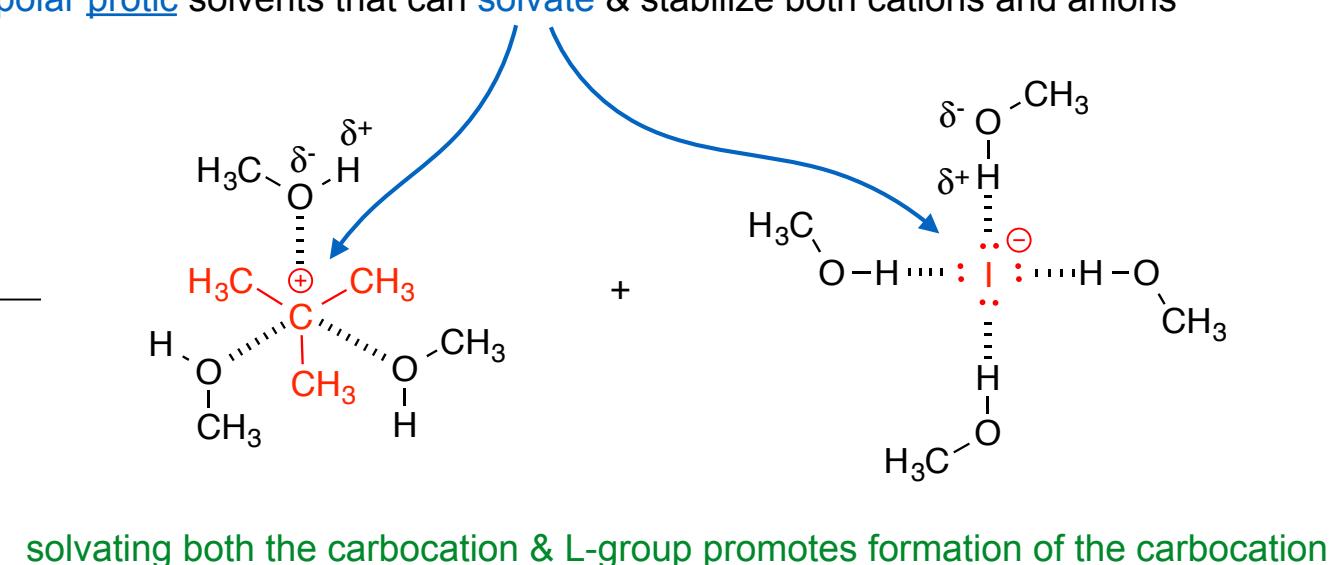
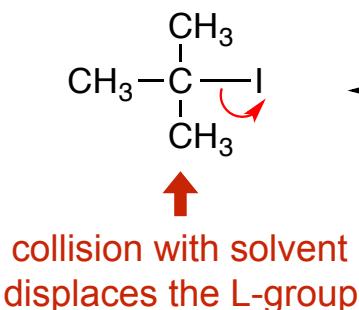
alcohols: R-OH
ethers: R-OR'
amines: R-NH₂

Don't undergo S_N2 rxns unless the functional groups are first converted into good leaving groups

4) Solvent

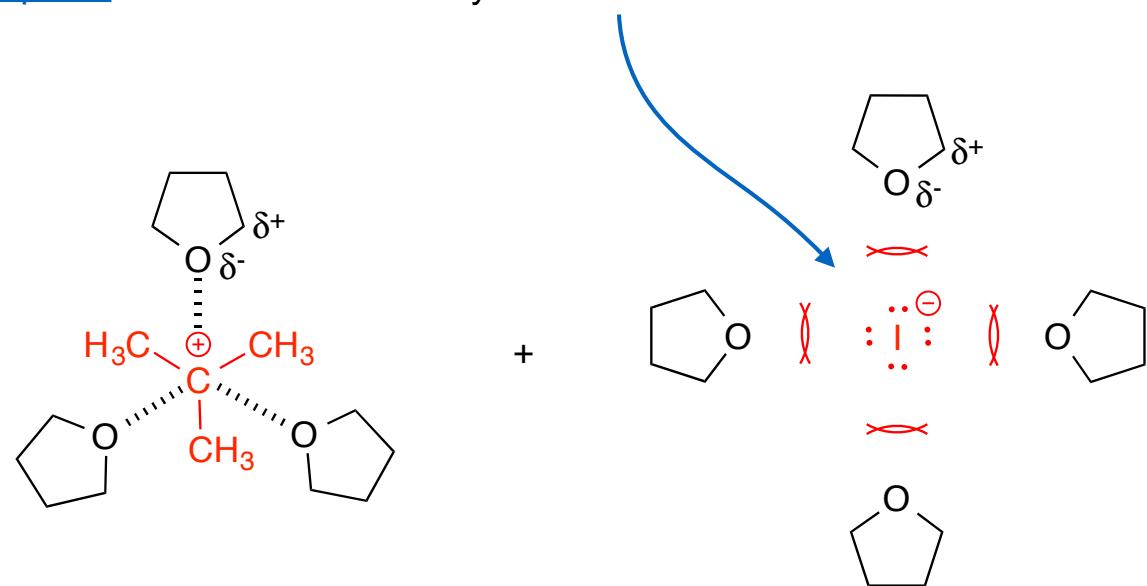
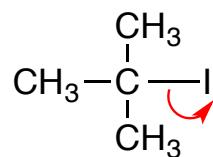
- Rates of S_N1 are faster in **polar protic** solvents that can **solvate** & stabilize both cations and anions

Ex:



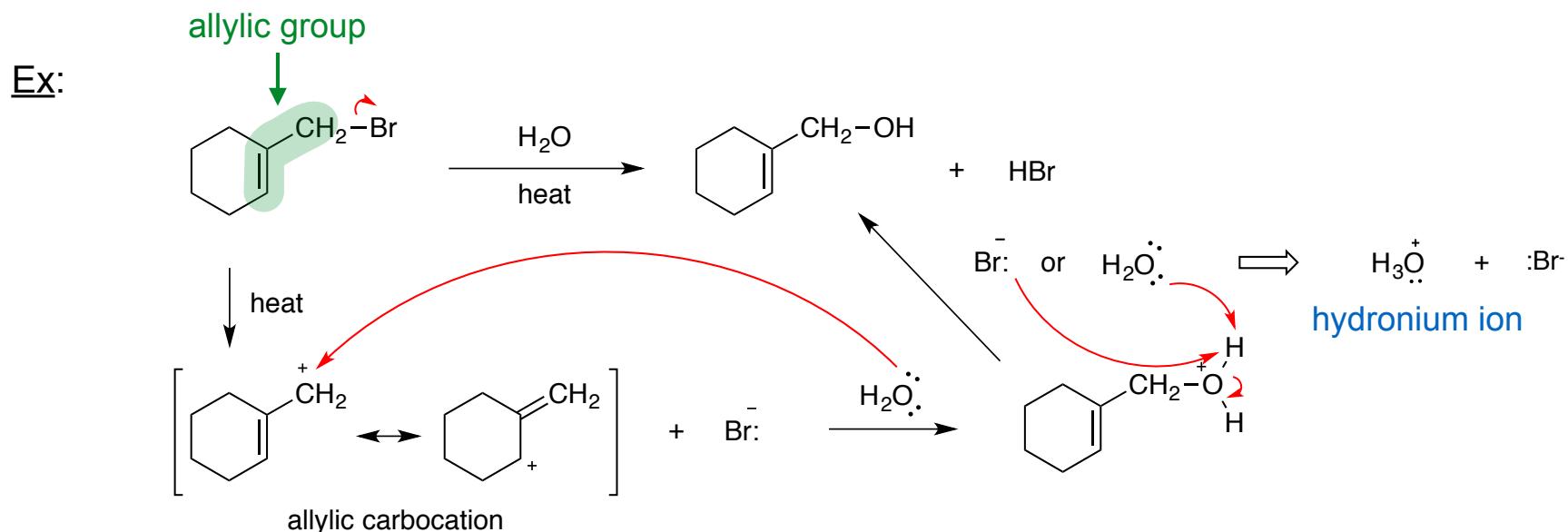
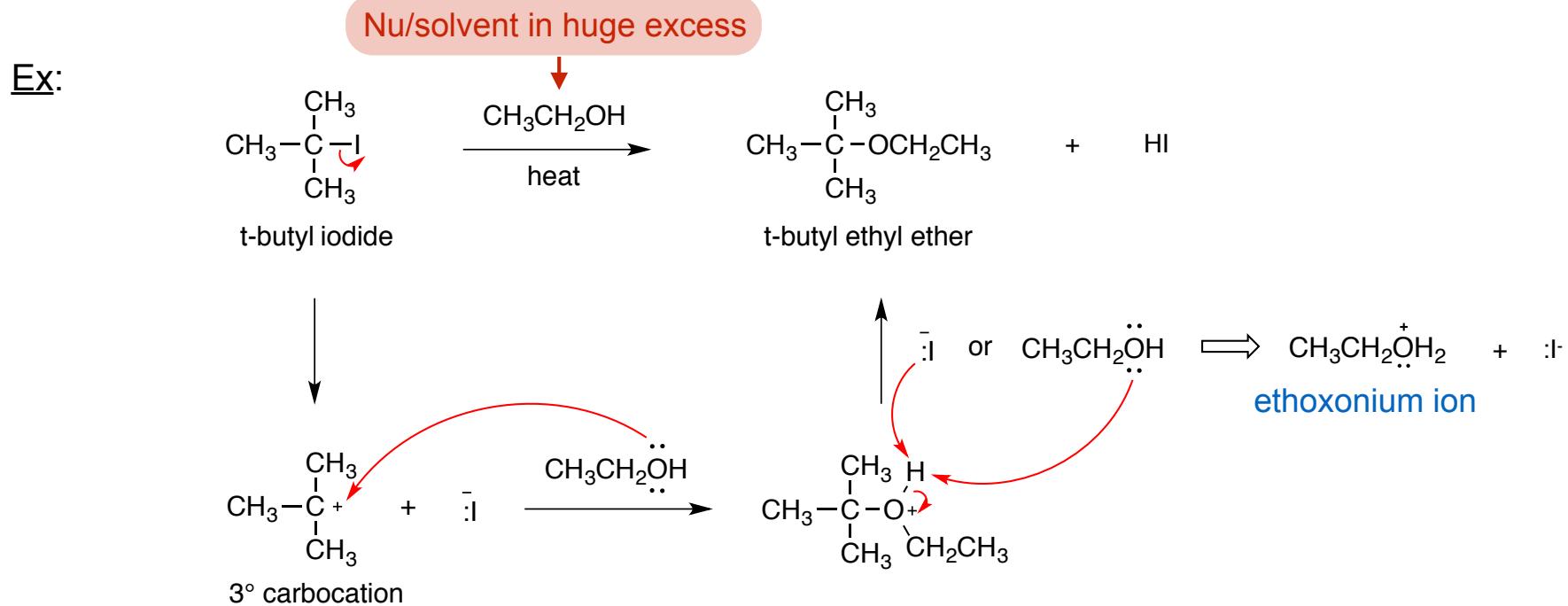
- Rates of S_N1 are slower in **polar aprotic** solvents because they **cannot solvate** & stabilize anions to assist departure of leaving groups

Ex:



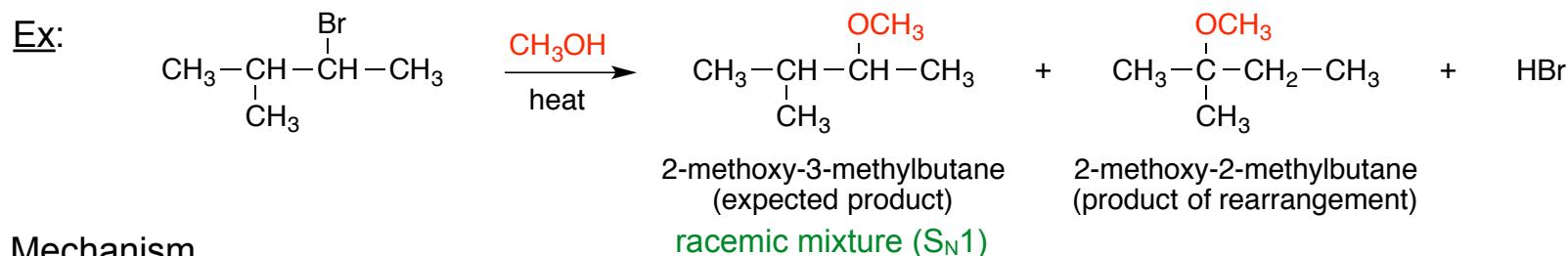
Solvolytic Rxns

S_N1 rxns where the solvent is also the nucleophile—very common for polar protic solvents (Why?)

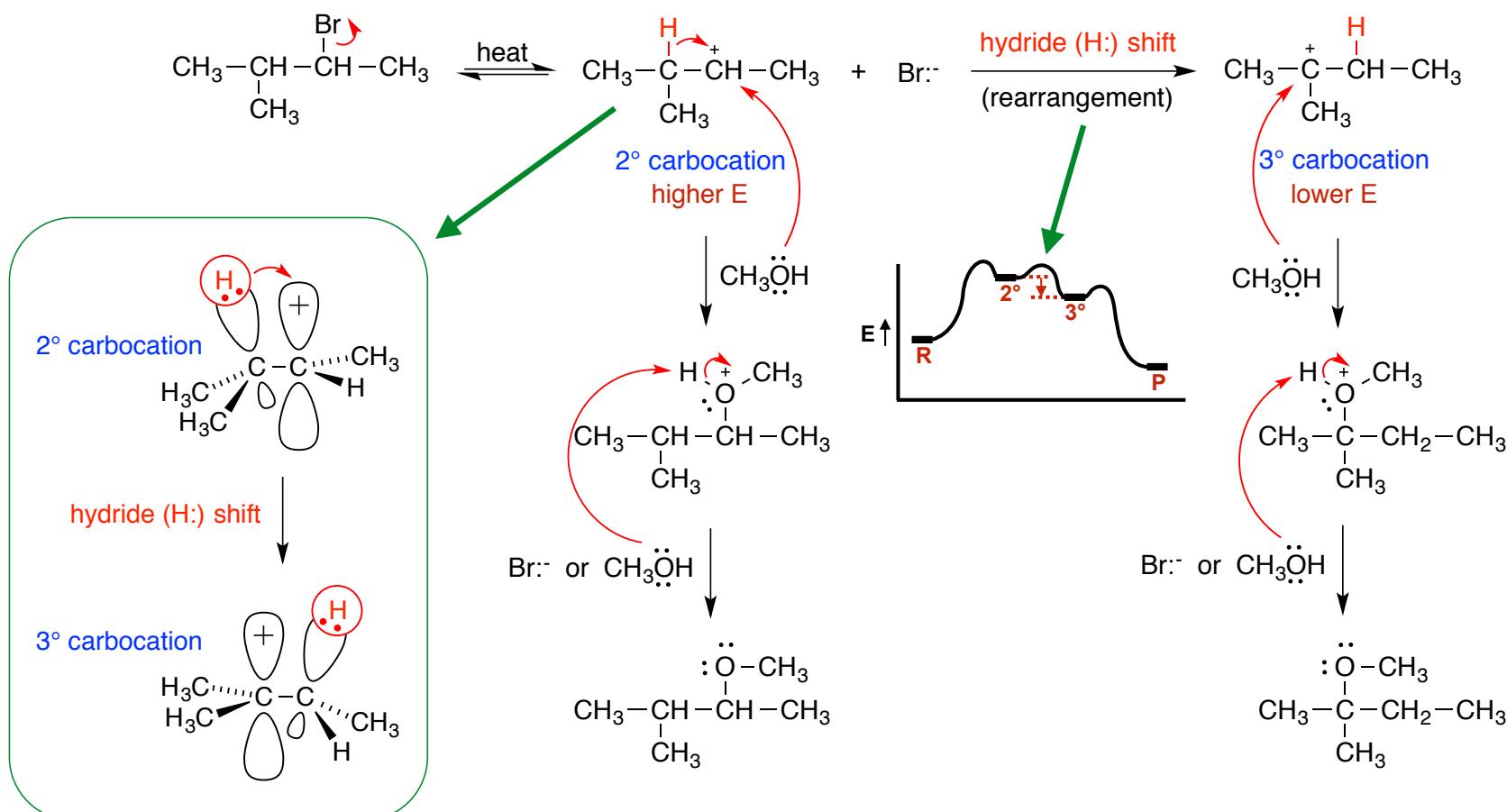


Carbocation Rearrangements in S_N1 Rxns (6-15)

1° & 2° carbocations can undergo rearrangement to form more stable 3° carbocations via hydride (H:) & alkyl (R:) shifts

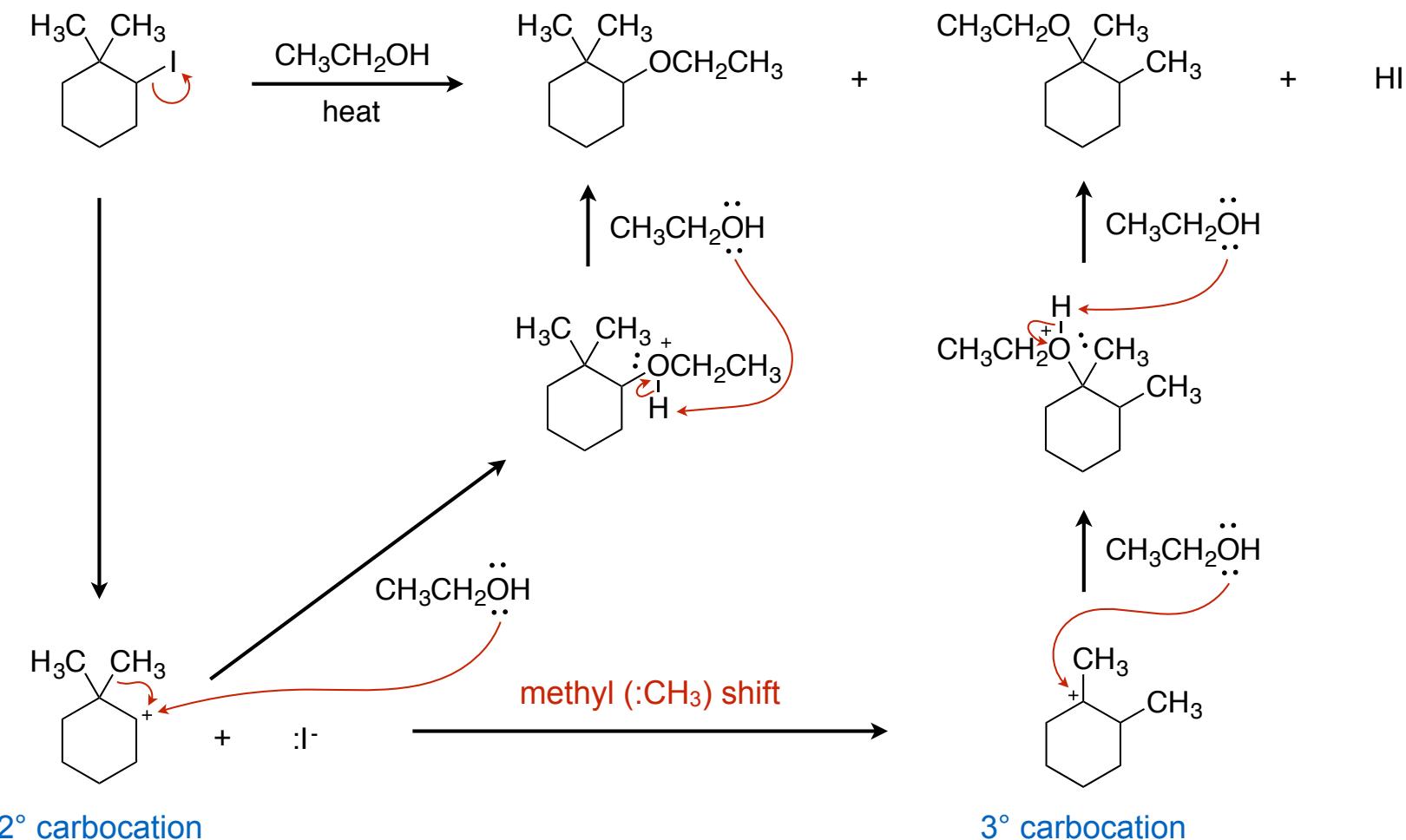


Mechanism



Note: 1° and 2° carbocations generally are prone to rearrangement if a hydride or alkyl shift from an adjacent carbon can generate a more substituted (more stable) carbocation

Ex: Carbocation rearrangement involving a methyl (alkyl) shift

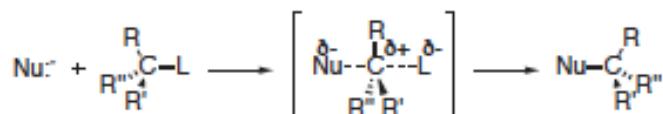


Note: rearrangement is the exception rather than the rule—but don't be surprised to if some rearrangement occurs with 2° alkyl halides under conditions that favor S_N1

Summary of S_N1 and S_N2 Rxns

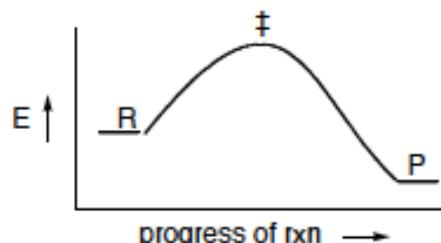
Rxn:

S_N2 Rxns (concerted – 1 step)

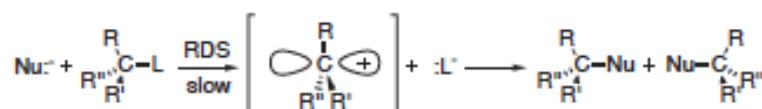


Kinetics:

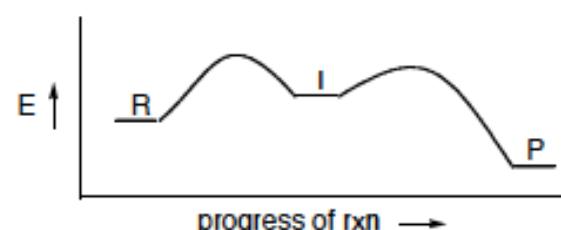
$$\text{Rate} = k[\text{Nu}][\text{R-L}] \quad (\text{2}^{\text{nd}}\text{-order rxn})$$



S_N1 Rxns (two steps)



$$\text{Rate} = k[\text{R-L}] \quad (\text{1}^{\text{st}}\text{-order rxn})$$



Energy Profile:

Substrate:
(alkyl halide)

$1^\circ > 2^\circ > 3^\circ$ Steric hinderance raises the energy of the transition state and slows the rate of rxn.

Nucleophile:

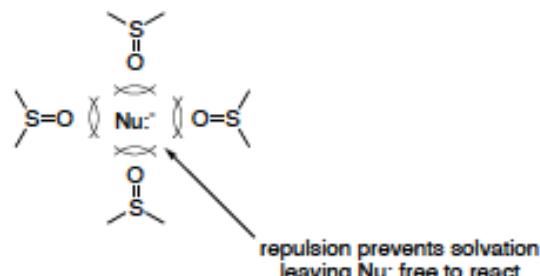
More reactive nucleophiles increase the rate of rxn. Good nucleophiles generally are negatively charged (e.g., OH⁻, RO⁻, RS⁻).

Leaving Group:

Good leaving groups lower the energy of the transition state and increase the rate of rxn. Good leaving groups are the conjugate bases of strong acids.

Solvent:

Polar aprotic solvents (e.g., DMSO, DMF, THF) increase the rate of rxn. These solvents leave the nucleophile unsolvated ("naked") and free to react with the substrate.

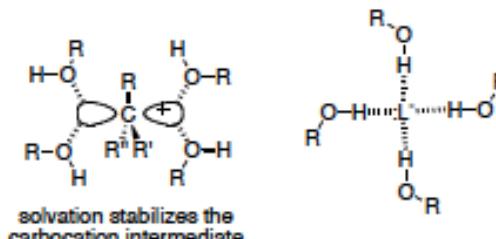


$3^\circ > 2^\circ \approx \text{allyl} \approx \text{benzyl} > 1^\circ$ Alkyl groups stabilize the carbocation. The more stable the carbocation intermediate, the faster the rate of rxn.

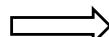
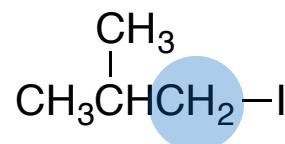
Nucleophiles are not involved in the rate determining (slow) first step. Neutral nucleophiles (e.g. H₂O, ROH) often are used for solvolysis, and to reduce E2 elimination.

Good leaving groups favor formation of a carbocation and increase the rate of reaction. Good leaving groups are the conjugate bases of strong acids.

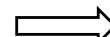
Polar protic solvents (e.g., H₂O, ROH, RCO₂H) increase the rate of rxn. These solvents solvate and stabilize both the carbocation intermediate and the leaving group.



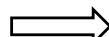
Q: Will these compounds react via an S_N1 or S_N2 mechanism?



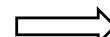
1°



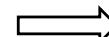
S_N2



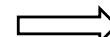
allylic



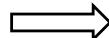
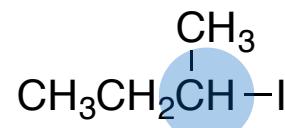
S_N1



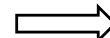
3°



S_N1

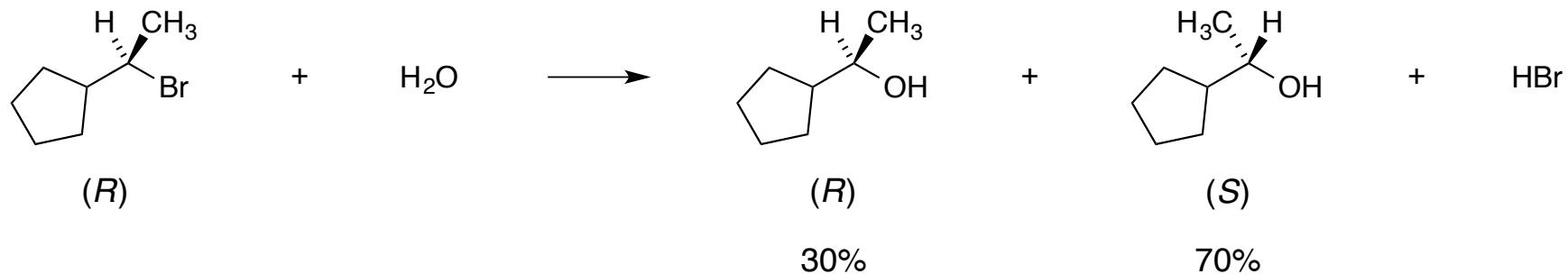


2°



$S_N1?$ or $S_N2?$

Ex: Explain these results



Q: Mechanism by which substitution occurs?

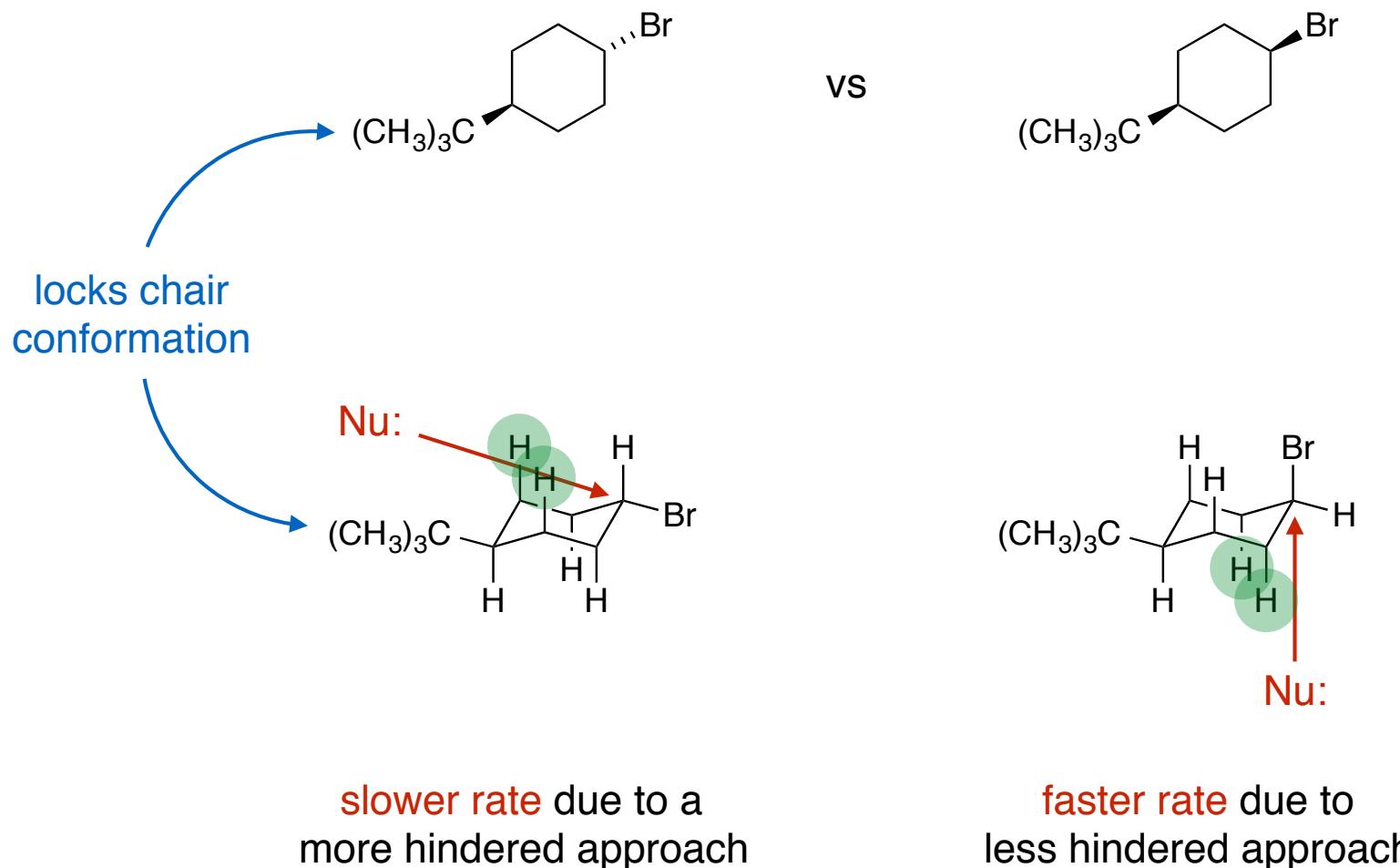
→ Both S_N1 (racemic product) and S_N2 (inverted product) mechanistic pathways!

Q: How could you bias the rxn to favor formation of more of the (S) stereoisomer?

Nu: → HO⁻ vs H₂O

Solvent → Et₂O (or another polar aprotic solvent) vs H₂O

Q: Which compound will react fastest via an S_N2 mechanism?



TECH SPACE

Scripps Research Institute scientists solve century-old chemistry problem

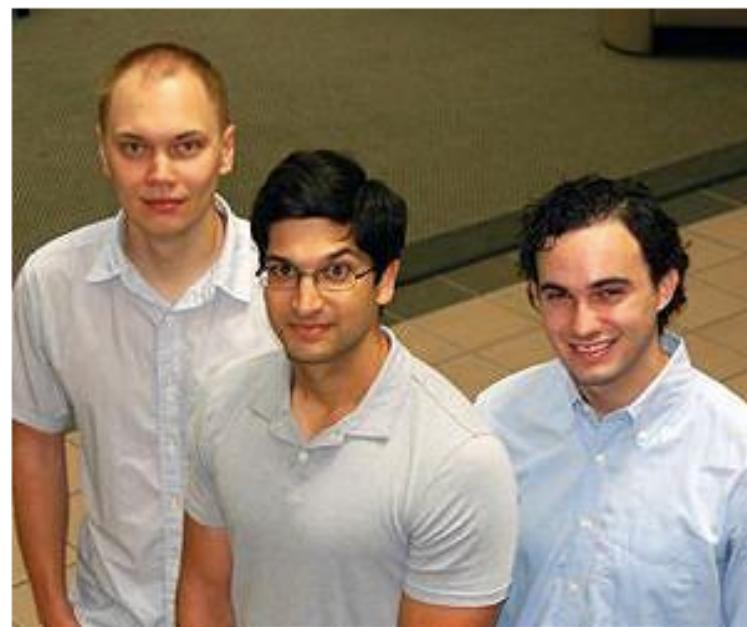
by Staff Writers

La Jolla CA (SPX) Sep 16, 2013

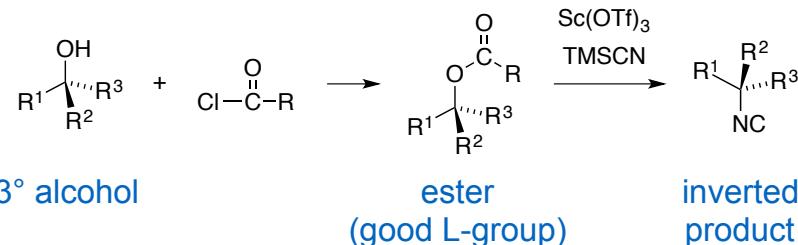
Chemists at The Scripps Research Institute (TSRI) have found a way to apply a "foundational reaction" of organic chemistry to a stubborn class of chemicals, in a transformation that has been thought impossible for a century.

The classic SN₂ reaction has enabled chemists to build and modify many pharmaceuticals as well as other useful organic molecules. While the reaction had been thought to exclude certain compounds, a paper in the September 12, 2013 issue of the journal Nature describes a new SN₂-like reaction that overcomes this limitation.

"We've widened the range of molecules that are responsive to this foundational technique; for example, we can now chemically synthesize a family of promising antimalarial and anticancer compounds that were previously off limits," said TSRI Assistant Professor Ryan A. Shenvi, who was the senior author of the paper.



Authors of the new Nature paper are TSRI assistant professor Ryan Shenvi (center), research associate Sergey Pronin (left) and graduate student Chris Reiher. Credit: Photo courtesy of The Scripps Research Institute.



Nature 2013, 501, 195-199

LETTER

Stereoinversion of tertiary alcohols to tertiary-alkyl isonitriles and amines

Sergey V. Pronin¹, Christopher A. Reiher¹ & Ryan A. Shenvi¹

The S_N2 reaction (bimolecular nucleophilic substitution) is a well-known chemical transformation that can be used to join two smaller molecules together into a larger molecule or to exchange one functional group for another. The S_N2 reaction proceeds in a very predictable manner: substitution occurs with inversion of stereochemistry, resulting from the 'backside attack' of the electrophilic carbon by the nucleophile. A significant limitation of the S_N2 reaction is its intolerance for tertiary carbon atoms: whereas primary and secondary alcohols are viable precursor substrates, tertiary alcohols and their derivatives usually either fail to react or produce stereochemical mixtures of products¹⁻³. Here we report the stereochemical inversion of chiral tertiary alcohols with a nitrogenous nucleophile facilitated by a Lewis-acid-catalysed solvolysis. The method is chemoselective against secondary and primary alcohols, thereby complementing the selectivity of the S_N2 reaction. Furthermore, this method for carbon–nitrogen bond formation mimics a putative biosynthetic step in the synthesis of marine terpenoids⁴ and enables their preparation from the corresponding terrestrial terpenes. We expect that the general attributes of the methodology will allow chiral tertiary alcohols to be considered viable substrates for stereoinversion reactions.

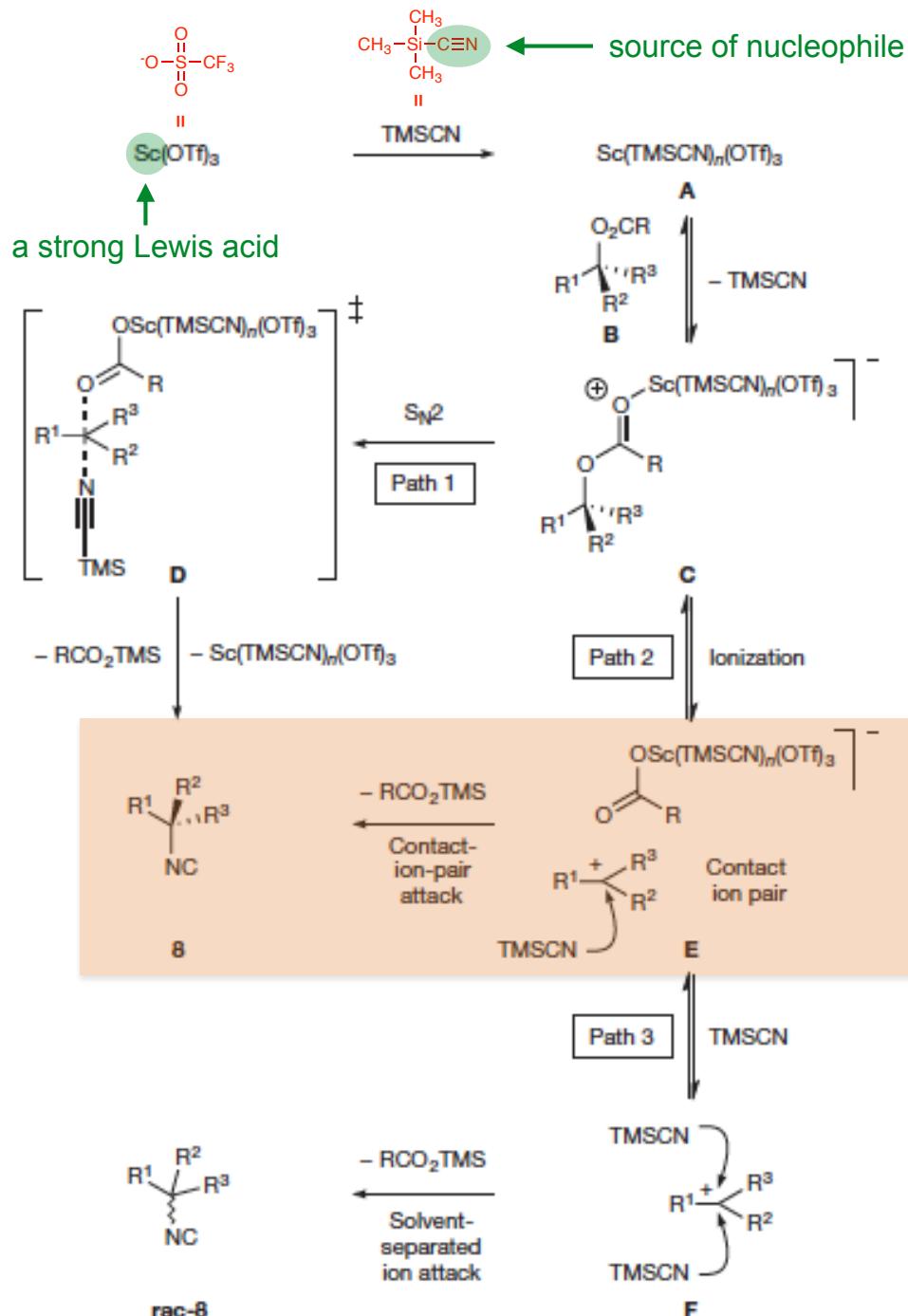


Figure 6 | Possible reaction pathways. A sketch of mechanistic possibilities according to experimental observation.