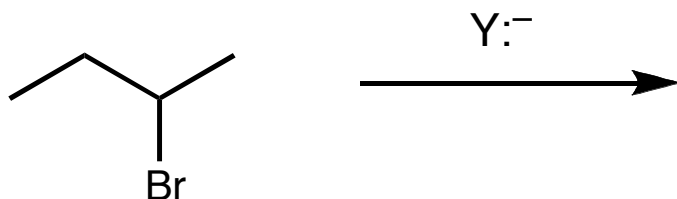


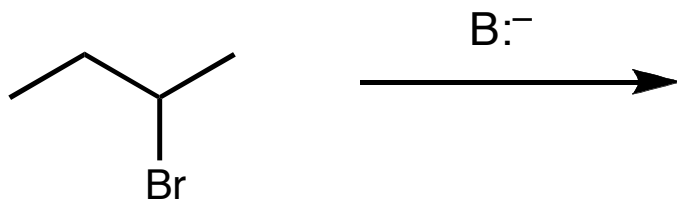
Alkyl Halides: Substitution and Elimination

- There are two particularly important reactions of alkyl halides:

Substitution involves replacing the halide with some other group:



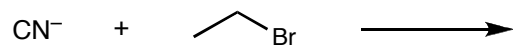
Elimination involves removing the halide **and** an adjacent hydrogen atom to yield an alkene:



Reading: Section 9.1

Nucleophilic Substitution: The S_N2 Reaction

- Can you predict the **product** and the **mechanism** of the following reaction:

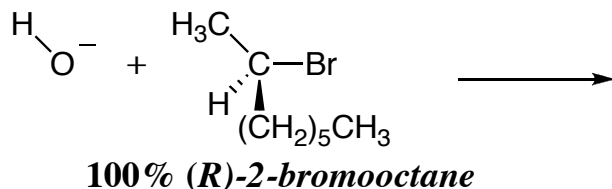


- What would be the **rate law** of this reaction? (Do you remember rate laws?)
- Why is this referred to as the **S_N2** reaction?

Reading: Section 9.4

Stereochemistry of the S_N2 Reaction

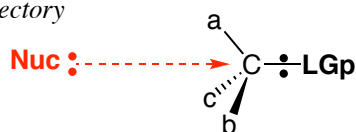
- Can you **predict** the product of the following reaction (including stereochemistry)?



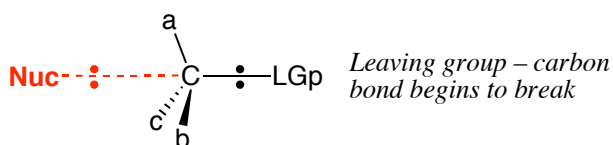
- Can you explain **why** that stereochemical result is observed for **all** S_N2 reactions?

- Let's take a look at the **transition state** for the S_N2 reaction:

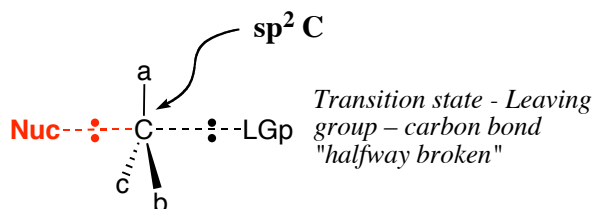
Nucleophile
approaches along
"proper" trajectory



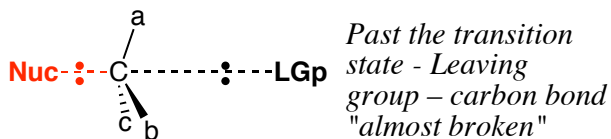
Nucleophile
begins to bond



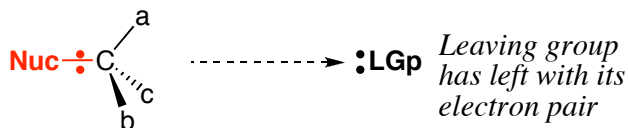
Transition state -
Nucleophile –
carbon bond
"halfway made"



Past the
transition state -
Nucleophile –
carbon bond
"almost complete"



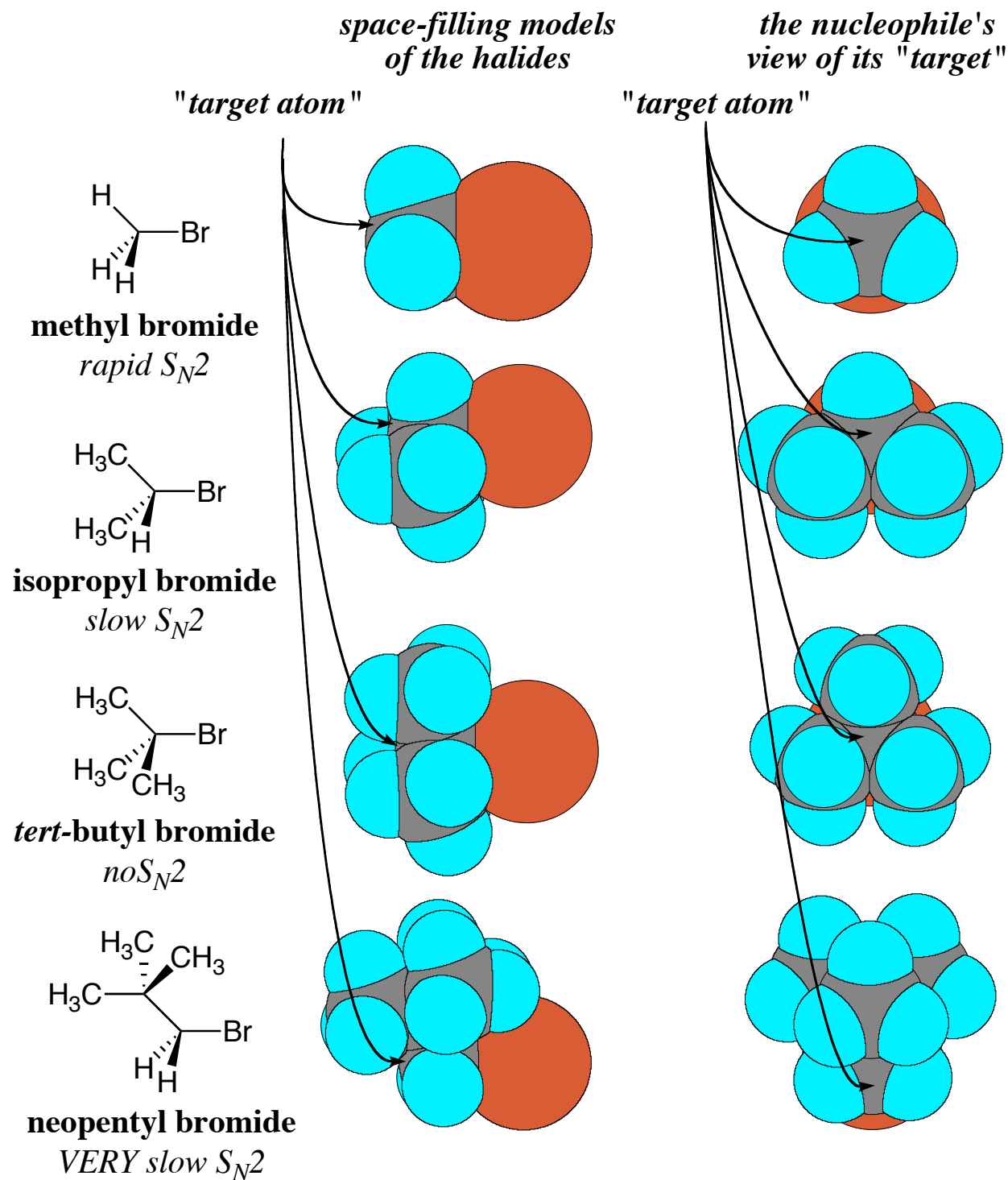
Nucleophile – carbon bond "complete" the nucleophile's electron pair now forms the new bond



Reading: Section 9.4

Steric Effects on S_N2 Reactions

- Because of the “backside attack” required for the S_N2 mechanism, these reactions are quite sensitive to **steric effects** (“crowding”). For example:



Reading: Section 9.4

Nucleophiles in the S_N2 Reaction

- Can you explain the relative **nucleophilicity** of the following nucleophiles in an S_N2 reaction?

Species	Name	Rel. Nucleophilicity
---------	------	----------------------

EXCELLENT NUCLEOPHILES

$\text{N}\equiv\text{C}^-$	cyanide	126,000
$\text{H}-\text{S}^-$	thiolate	126,000
I^-	iodide	80,000

GOOD NUCLEOPHILES

$\text{H}-\text{O}^-$	hydroxide	16,000
Br^-	bromide	10,000
$^-\text{N}=\text{N}^+=\text{N}^-$	azide	8,000
$\text{H}_3\text{N}:$	ammonia	8,000

MODERATE/POOR NUCLEOPHILES

Cl^-	chloride	1,000
CH_3COO^-	acetate	630
F^-	fluoride	80
$\text{H}_2\text{O}:$	water	1

Reading: Section 9.4

Leaving Groups in the S_N2 Reaction

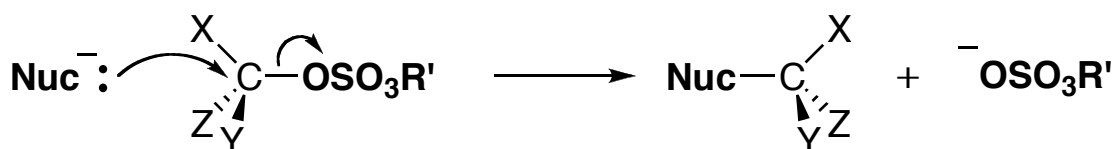
- What is the **leaving group** in an S_N2 reaction?
- Can you explain the relative **leaving group ability** of the following leaving groups?

Conjugate acid	pK _a	Leaving Group	Name
----------------	-----------------	---------------	------

GOOD LEAVING GROUPS

H—I	−10	I [−]	iodide
H—Br	−9	Br [−]	bromide
H—Cl	−7	Cl [−]	chloride
H—OSO ₂ R	−6.5	[−] OSO ₂ R	sulfonate*
H ₃ O ⁺	−1.7	H ₂ O	water

***NOTE:** Alkylsulfonic esters (**R—OSO₃R'**) react like alkyl halides towards nucleophiles (and bases).



POOR LEAVING GROUPS

H—F	+3.2	F [−]	fluoride
H ₂ S	+7	HS [−]	thiolate
H—C≡N	+9.2	[−] C≡N	cyanide
H ₂ O	+15.7	HO [−]	hydroxide
H—OR	+15 to 18	RO [−]	alkoxide

Reading: Section 9.4

Summary of Reactivity in S_N2 Reactions

- Mechanism:
- Stereochemistry:
- What makes for a **rapid** S_N2 reaction?

Steric Effects:

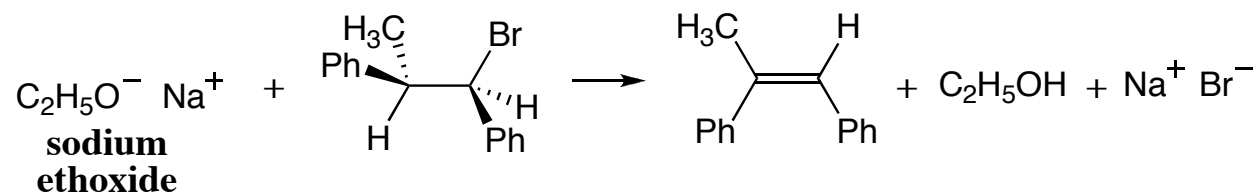
Nucleophilicity:

Leaving-Group Ability:

Reading: Section 9.4

Elimination: The E2 Reaction

- Here is an example of an E2 reaction. Can you draw a curved-arrow mechanism?

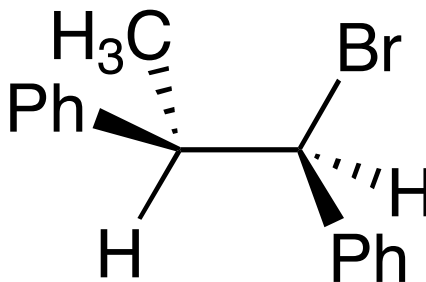


- Examine the **stereochemistry** of the above reaction. Why is this an example of *anti*-elimination?
- What transition state and product would lead to *syn*-elimination?
- What would be the *rate law* for this reaction?

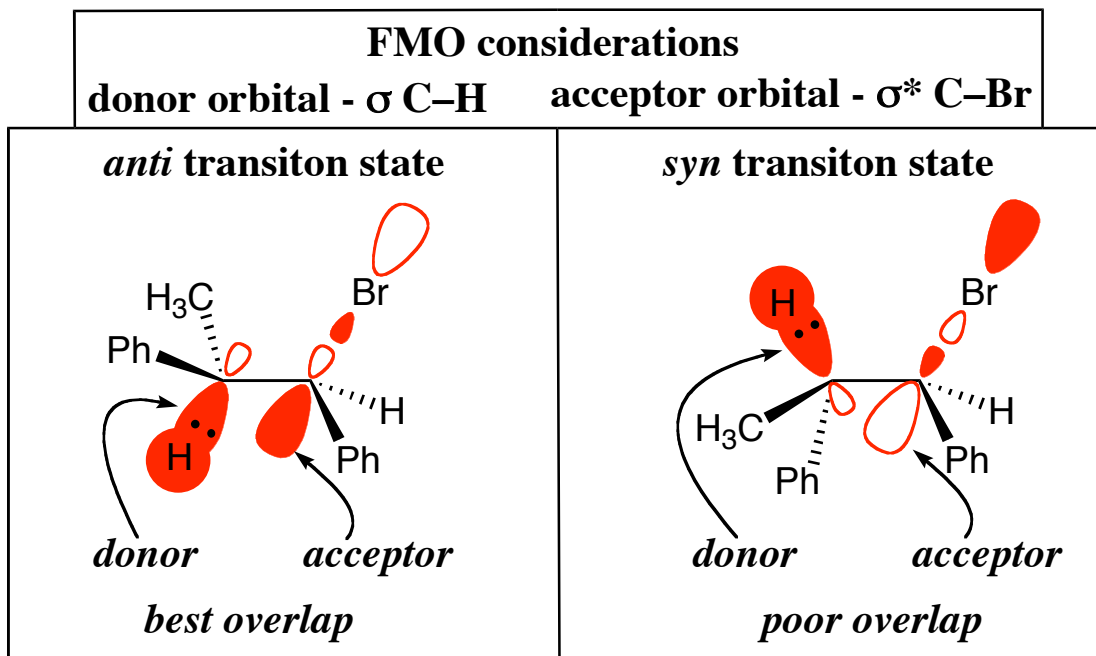
Reading: Section 9.5

Frontier Orbitals in the E2 Reaction

- Let's take a close look at the frontier orbitals involved in the E2 reaction. There are in fact **two** important interactions:



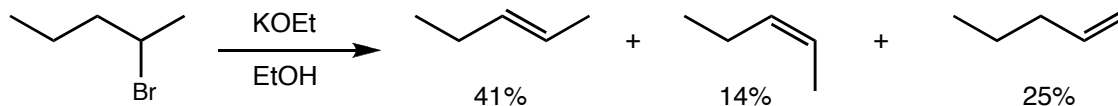
- Note the contrast between *anti*- and *syn*-elimination:



Reading: Section 9.5

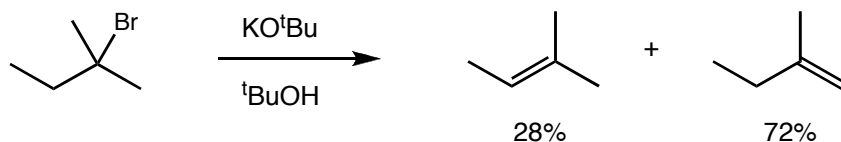
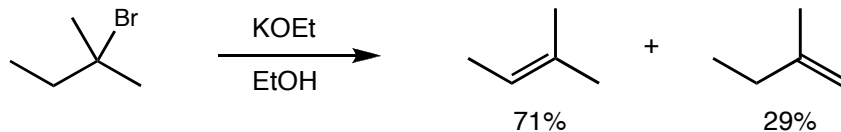
Alkene Isomers Formed by the E2 Reaction

- Many E2 reactions can give more than one possible isomer. Can you explain the distribution of products in the following reaction?



- You may notice that the above percentages do not add to 100%. What do you suppose is the *other* product that emerges from the above reaction?

- The choice of base can affect the distribution of products. For example:



Reading: Section 9.5

E2 vs. S_N2: The “GFP” Reaction Hierarchy

- To help decide which reaction will predominate, apply the “GFP” (good-fair-poor) reaction hierarchy. If *all else is equal*, choose the reaction that is at the top of the list:

1. S_N2 reactions: Require good steric interactions

Good if the halide is methyl or 1°

Fair if the halide is 2°

Poor if the halide is 3° **or** if the nucleophile is very bulky (e.g. ^tBuO[−])

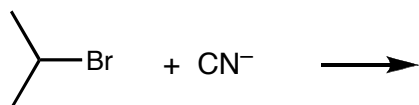
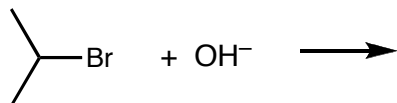
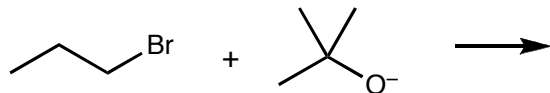
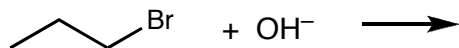
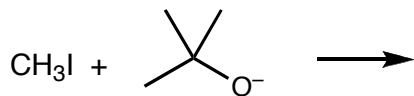
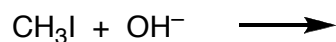
2. E2 reactions: Require a strong base

Good if the base is at least as strong as OH[−]

Fair if the base is between H₂O and OH[−] in strength

Poor if the base is weaker than H₂O

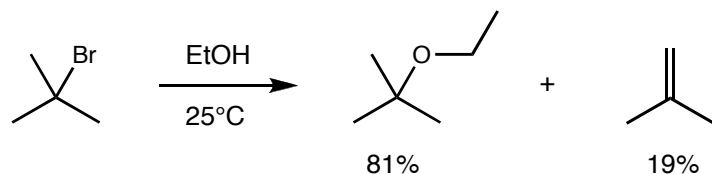
- Let's see some examples: Determine the *primary* product (and identify possible *secondary* products) for each of the following reactions:



Reading: Section 9.5

Reactions Involving Carbocations: S_N1 and E1

- Consider the following reaction. Why is it unlikely that this reaction proceeded by either an S_N2 or E2 mechanism?



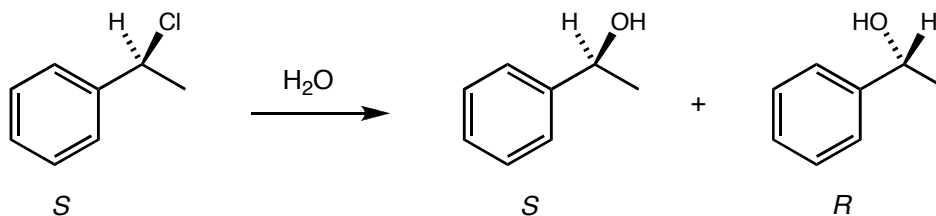
- Can you propose a mechanism for this reaction?
Hint: the *rate law* for this reaction is simply: $rate = k[tBuBr]$

- What do you suppose is a *requirement* for this reaction?

Reading: Section 9.6

The Stereochemistry of the S_N1 Reaction

- Given that the S_N1 mechanism proceeds through a carbocation intermediate, what would you expect to find when you subject the following alkyl halide to S_N1 conditions:



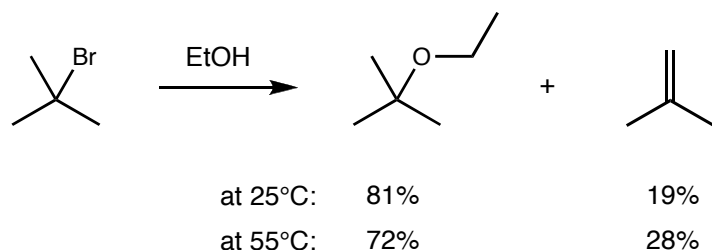
- In fact, the products are: 33% *S* and 67% *R*. How can we explain this observation?
- Can we make any generalizations about the stereochemical outcome of S_N1 reactions?

Reading: Section 9.6

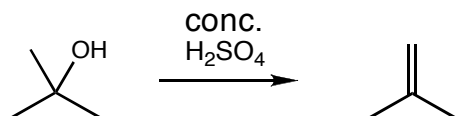
S_N1 vs. E1 Reactions

- In general, whenever S_N1 and E1 reactions take place, a mixture of both mechanisms is observed. Why might this be the case?

- It is often the case that higher temperatures favor elimination. For instance:



- One can ensure elimination by starting with an *alcohol*, instead of an alkyl halide, and treating it with concentrated sulfuric acid. Can you propose a mechanism for this reaction? Does this mechanism resemble any mechanism you have seen before?



Reading: Section 9.6

S_N1 / $E1$ / S_N2 / $E2$: The “GFP” Hierarchy Revisited

- We can now extend the hierarchy to include S_N1 and $E1$ reactions:

1. S_N2 reactions: Require good steric interactions

Good if the halide is methyl or 1°

Fair if the halide is 2°

Poor if the halide is 3° **or** if the nucleophile is very bulky (e.g. $^t\text{BuO}^-$)

2. $E2$ reactions: Require a strong base

Good if the base is at least as strong as OH^-

Fair if the base is between H_2O and OH^- in strength

Poor if the base is weaker than H_2O

3. S_N1 / $E1$ reactions: Require a stable carbocation

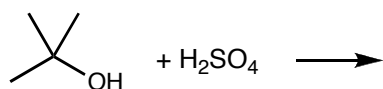
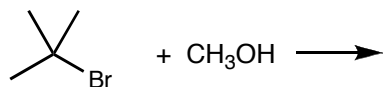
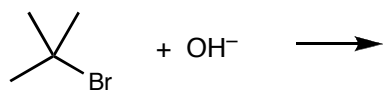
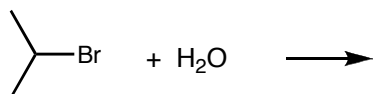
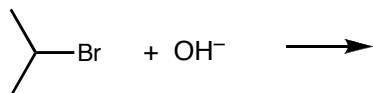
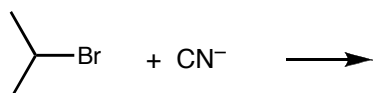
Good if the halide is 3°

Fair if the halide is 2°

Poor if the halide is methyl or 1°

(Note that S_N1 and $E1$ reactions almost always occur together, although you can ensure elimination by treating an alcohol with concentrated H_2SO_4 .)

- Use the hierarchy to determine the *primary* product (and identify possible *secondary* products) for each of the following reactions:



Reading: Section 9.7