Module 2

E1, S_N1, E2, S_N2

Elimination and Substitution reactions

Learning objectives

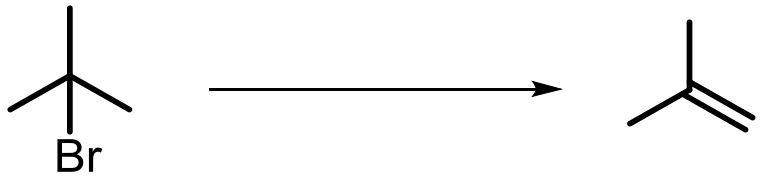
1. Identify: Leaving group, α-carbon, base, nucleophile, and solvent in a given reaction
2. Decide if a reaction proceeds via E1/S_N1, E2, or S_N2 mechanism
3. Draw mechanisms for E1, S_N1, E2, and S_N2 reactions
4. Understand reaction coordinate diagrams for E1, S_N1, E2, S_N2 reactions
5. Predict major product(s) of the reaction, including stereochemical and regiochemical considerations
6. Appreciate the orbital interactions in each reaction

Learning objectives

- [ ] 7. Rank leaving groups based on their rate of reaction
- [ ] 8. Rank substrates based on their rate of a given reaction
- [ ] 9. Be able to convert OH into a better leaving group (2 ways)
- [ ] 10. Draw a mechanism for an alcohol oxidation reaction (a type of E2 reaction)
- [ ] 11. Design a retrosynthesis and synthesis involving elimination, substitution and CHM 1321 reactions.

Elimination: examples

1)



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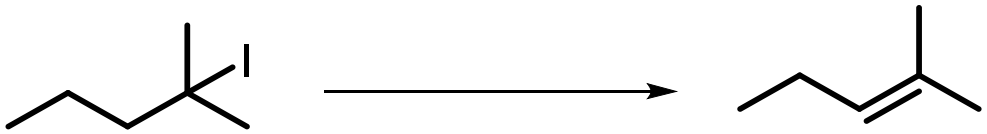

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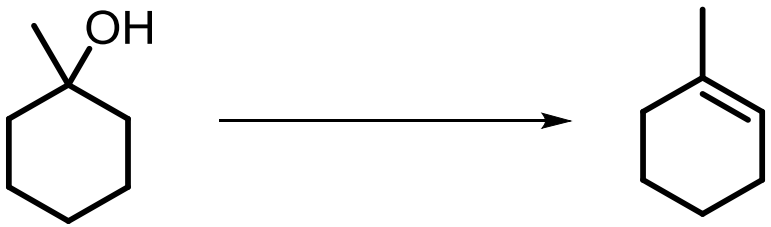
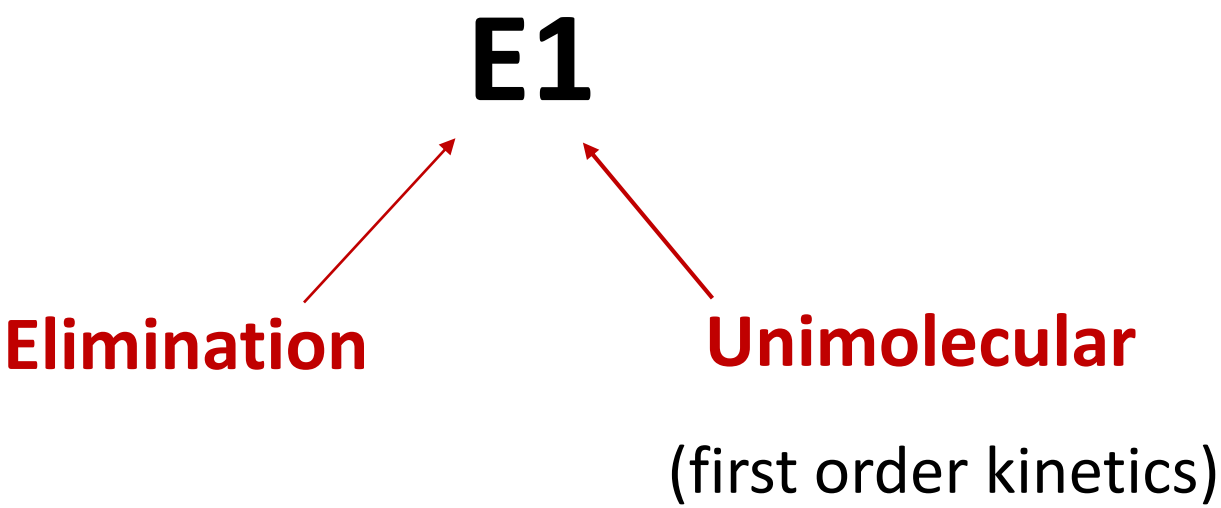


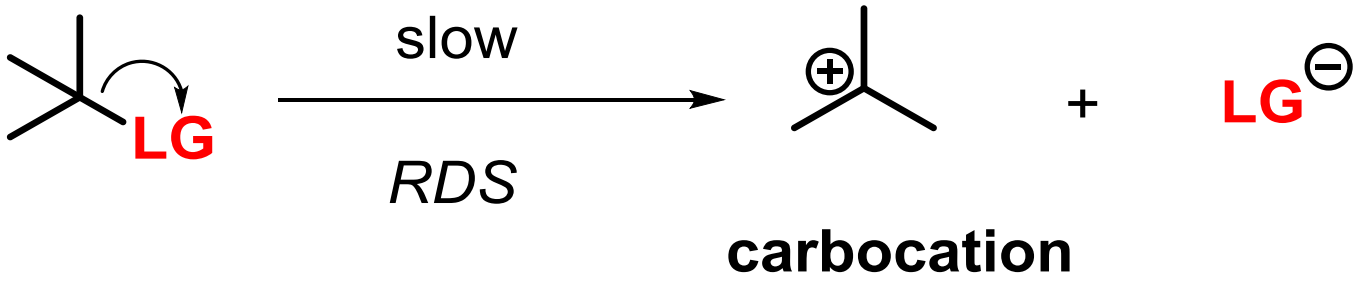
LG and H were *eliminated*

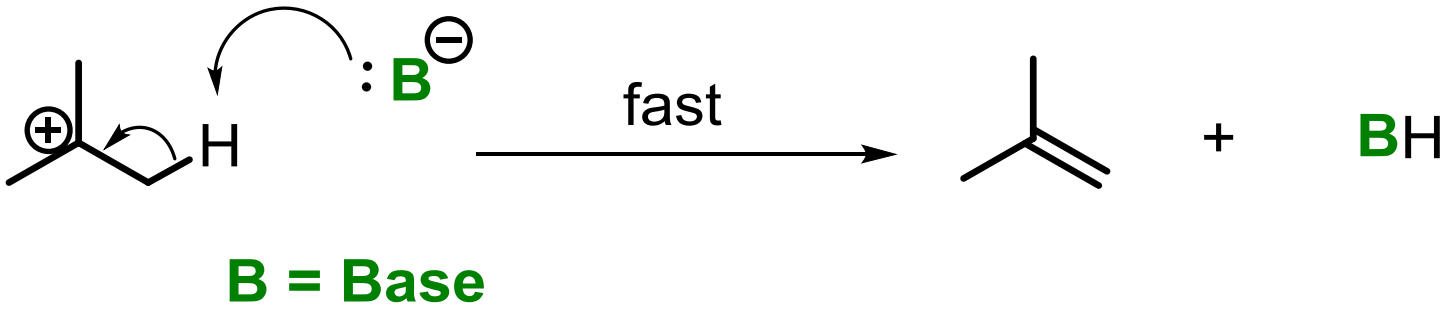
E1: general mechanism



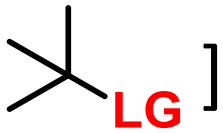
Rate = k[starting material]

E1: general mechanism

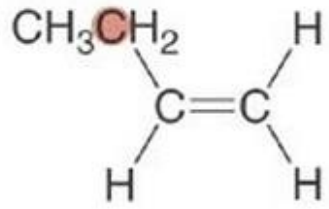




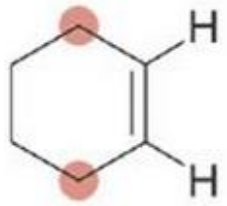
B = Base

Rate = k[] therefore *unimolecular*

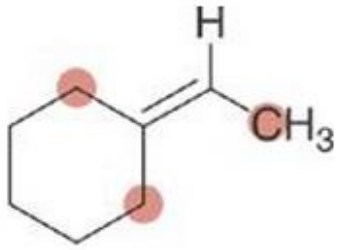
E1 regiochemistry: most substituted alkene



monosubstituted



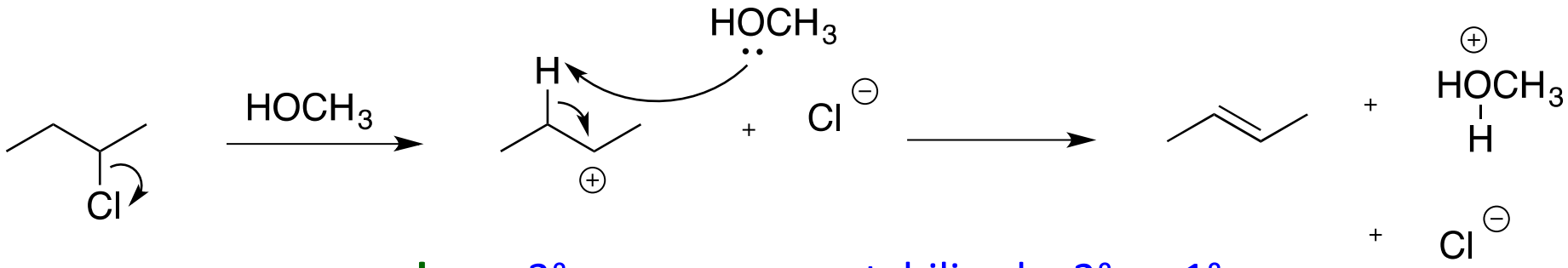
disubstituted



trisubstituted

More substituted = More stable

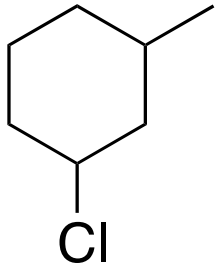
E1: Summary



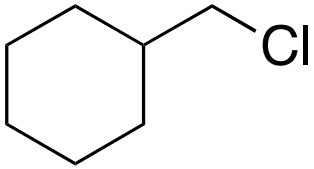
- **α-carbon**: 3° or resonance-stabilized > 2° >> 1°
- **Leaving group**: good LG is weakly basic
- **Base**:
  - Weak bases favour E1
  - Often solvent = base
- **Solvent**:
  - Polar, protic
  - Stabilize the TS of the RDS
- **Regiochemistry**: get most substituted (stable) alkene
- **Stereochemistry (E/Z)**: get most stable alkene
- Watch out for **rearrangements**

Problem 1: α-carbon

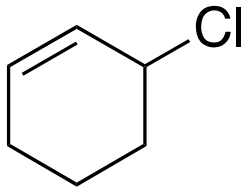
For which of the following would an **E1**-type reaction occur the *slowest*?



A

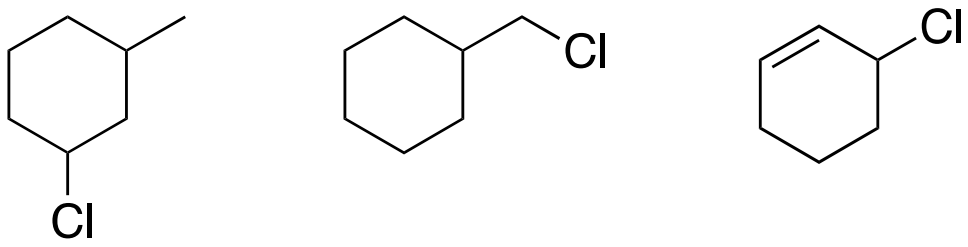


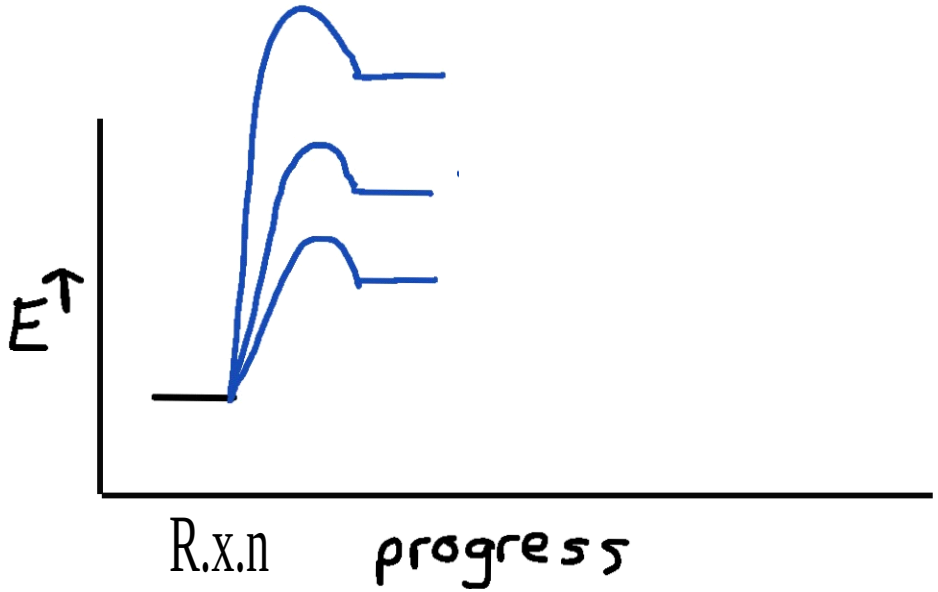
B



C

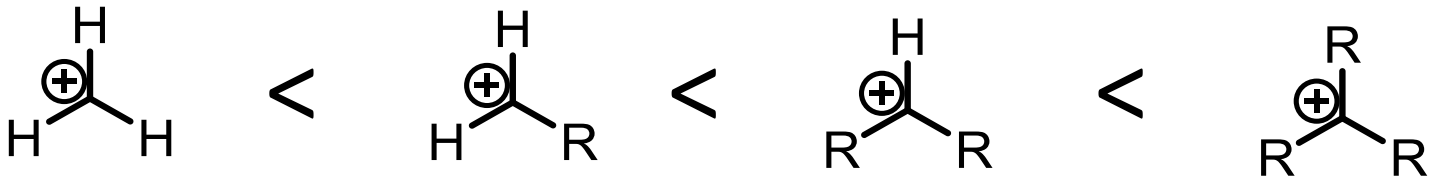
Hint: Focus on **E1** rate-determining step (r.d.s.)


Cl
Cl
Cl


E↑
R.x.n
progress

Carbocation stability

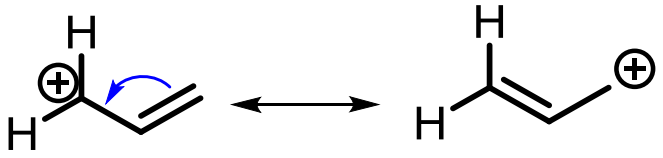
Least stable **Most stable**



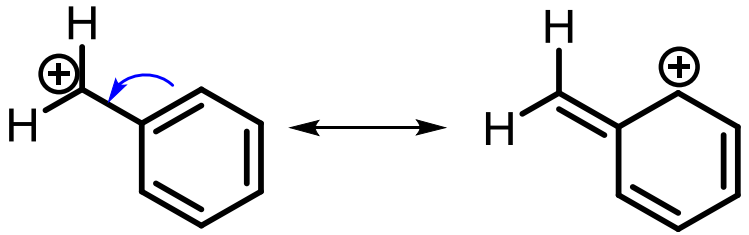
1° 2° 3°

Resonance -stabilized:

Allyl



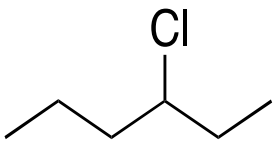
Benzyl



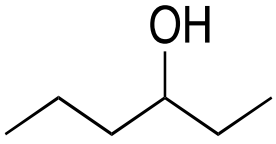
etc.

Problem 2: Leaving groups

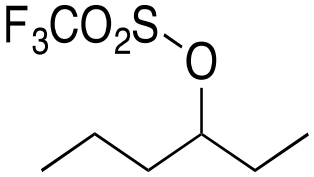
Which has the best leaving group?



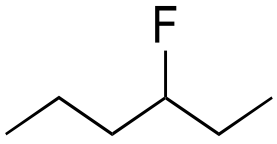
A



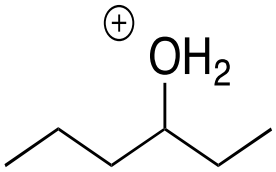
B



C

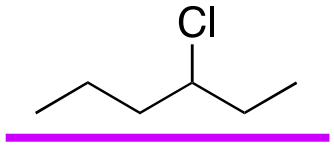


D

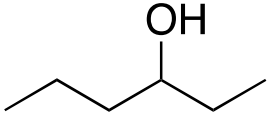


E

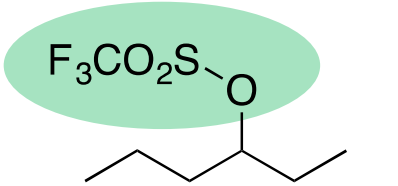
	A	B	C	D	E
LG:	Cl^-	OH^-	$CF_3SO_3^-$	F^-	H_2O
CA:	HCl	H_2O	CF_3SO_3H	HF	H_3O^+
pK_{aH}:	-7	15.7	-14	3.2	-1.7



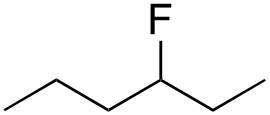
A



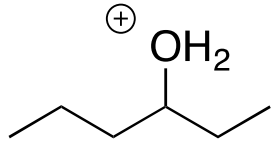
B



C



D



E

LG: Cl^- OH^- $CF_3SO_3^-$ F^- H_2O

CA: HCl H_2O CF_3SO_3H HF H_3O^+

pK_{aH} : -7 15.7 -14 3.2 -1.7

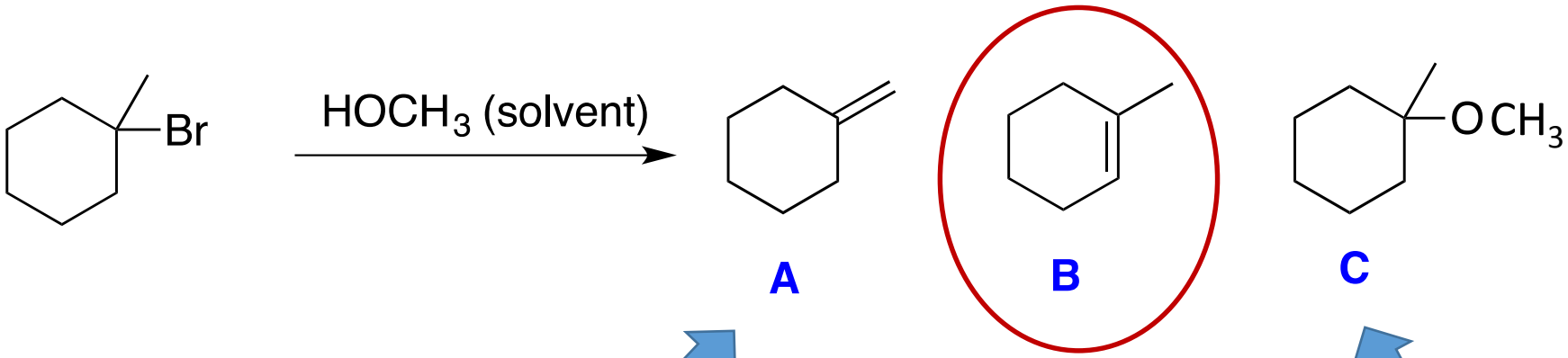
Need: $pK_{aH} < 0$ (usually)

CF_3SO_3H or **TfOH** (triflic acid)

$CF_3SO_3^-$ or **TfO^-** (triflate)

Problem 3

Choose the major *elimination* product:



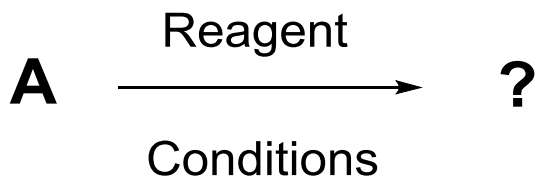
Only disubstituted (minor)

Most substituted alkene

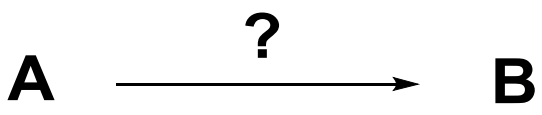
Not an elimination product

Problem types

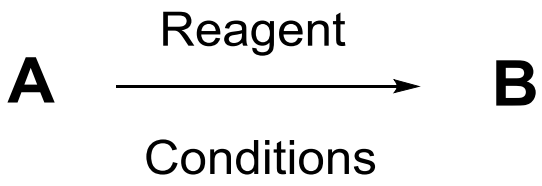
Predict the product(s):



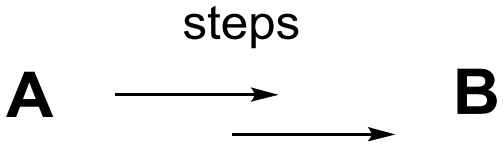
Provide reagents/conditions:



Draw the mechanism:

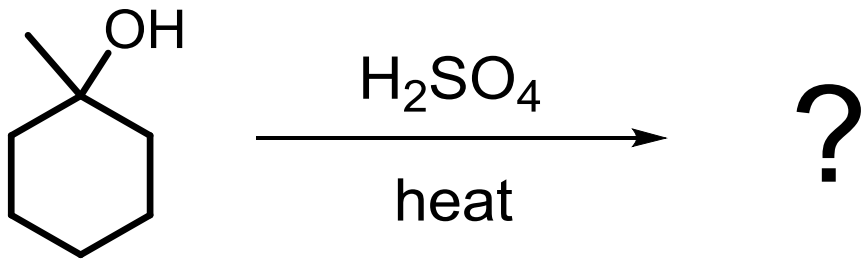


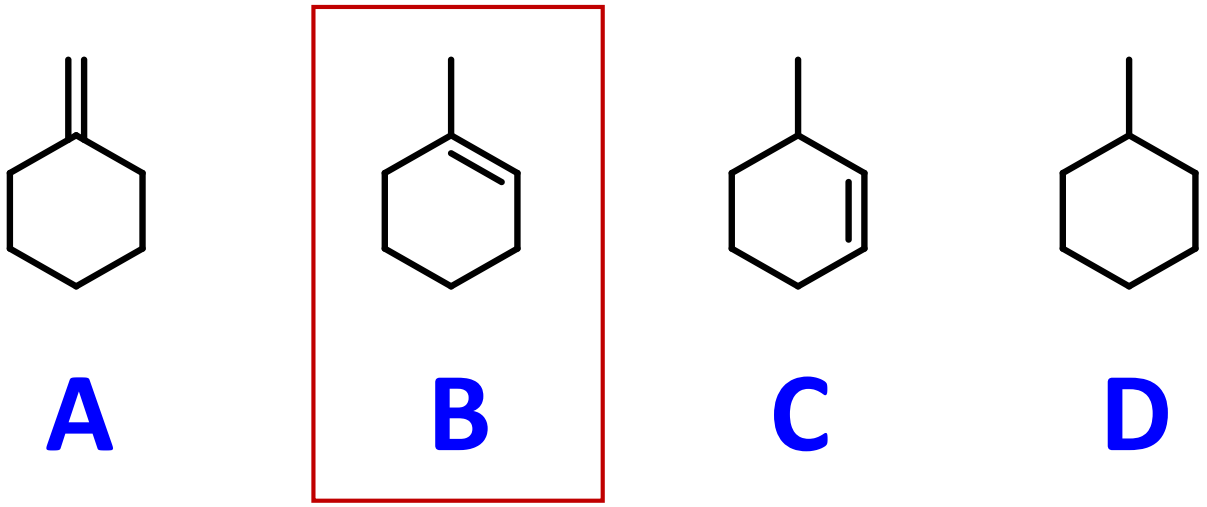
Propose a synthesis:



Problem 4

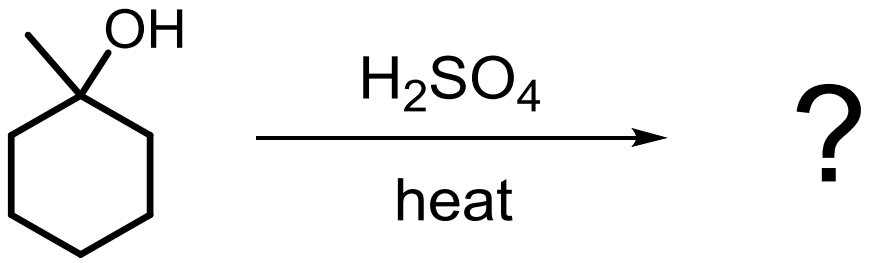
Predict the major product:





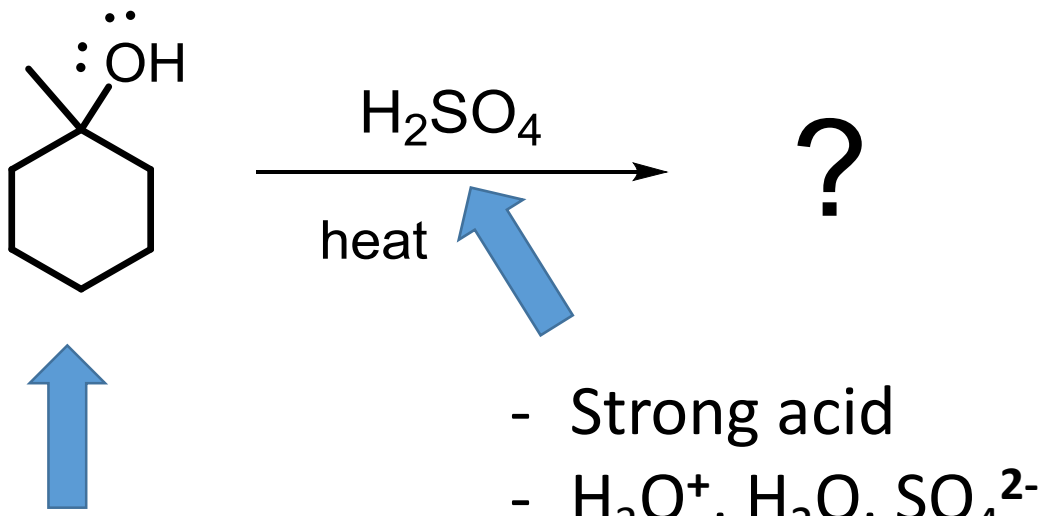
Problem 4 - strategy

Predict the major product:



- Scan the given info
- Identify the role of each component
- Identify the *type* of problem

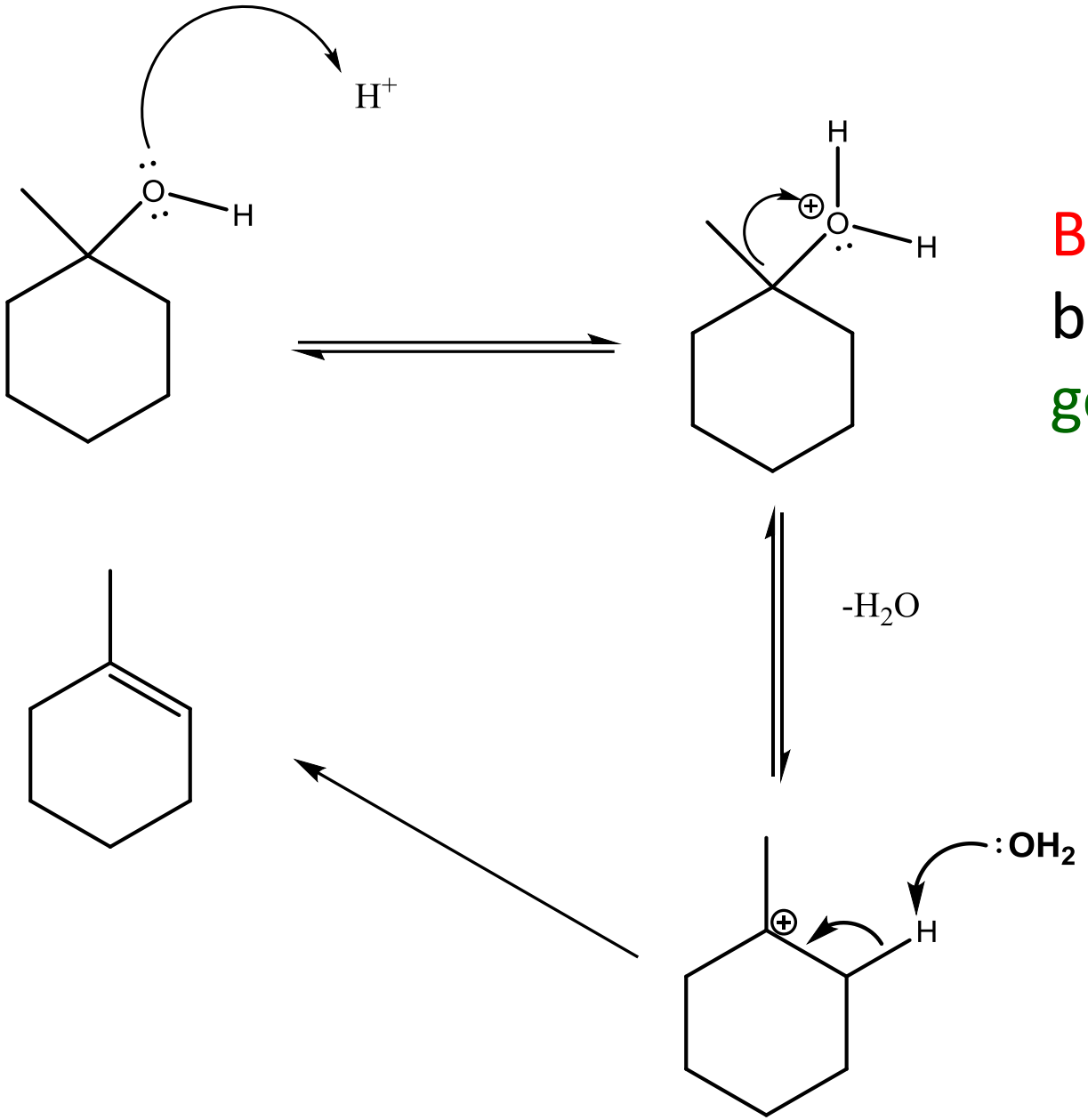
Problem 4 - analysis



- Strong acid
- H_3O^+, H_2O, SO_4^{2-}

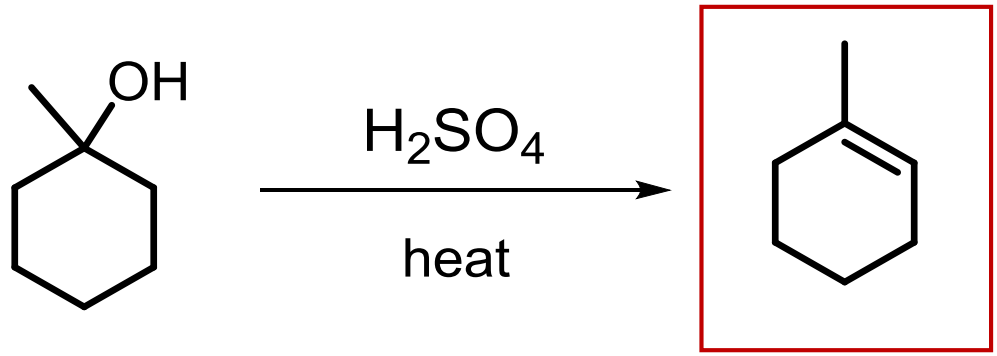
- Alcohol
- Tertiary (3˚)
- OH = poor LG

Ask: How may the starting material interact with the reagent?



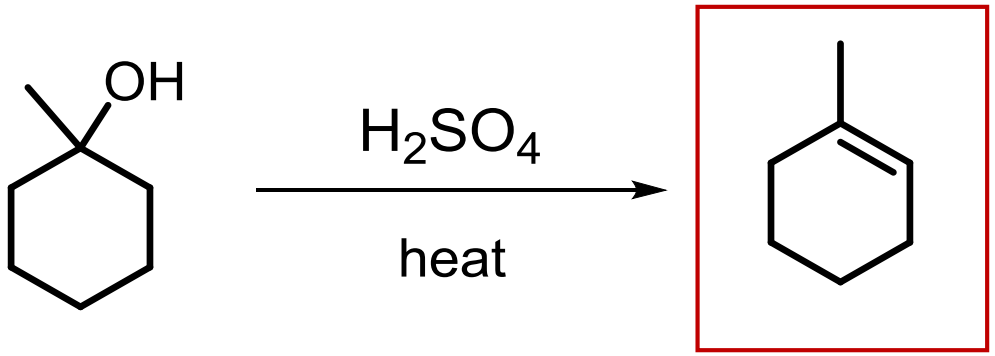
Bad LG has become a good LG

Problem 4 - essentials



1. Determine the role of each component
2. Recognize the type of reaction
3. Use your knowledge of **E1** to complete the problem

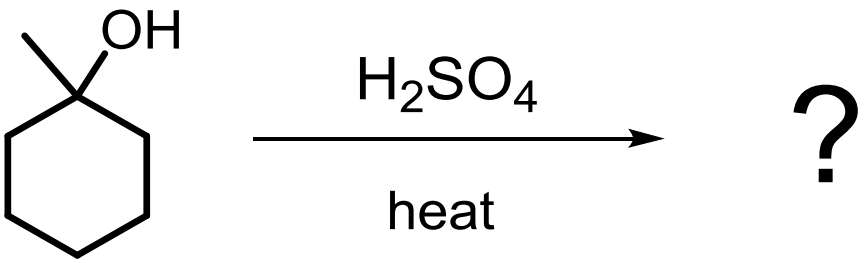
Problem 4 - concepts



Concepts: Acid-base, theory of E1

Difficulty level: **2** (in class), **3** (exam)
(1 – 10)

Problem 4 - Clues

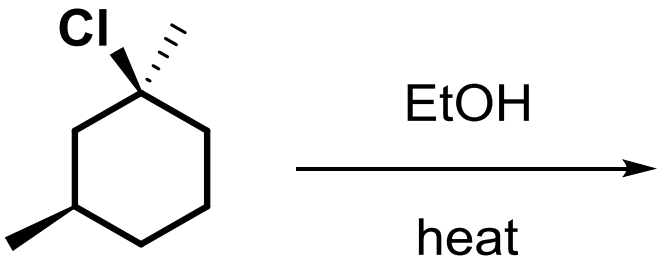


Clues: Tertiary α-carbon, strong acid, polar protic environment

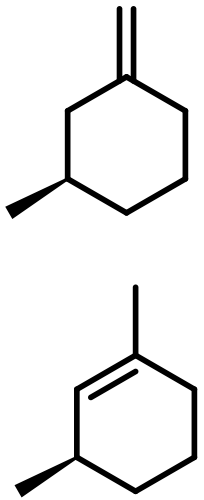
- Logical analysis of problem
- Intuition / pattern recognition

Problem 5

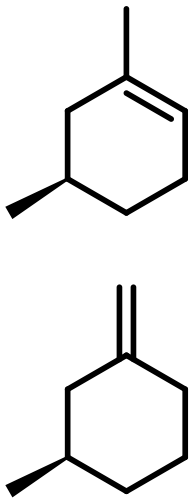
Predict the major elimination product(s):



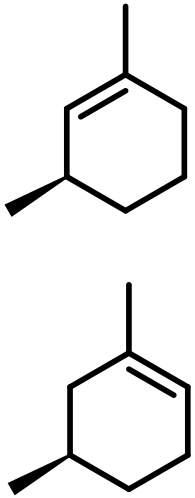
A



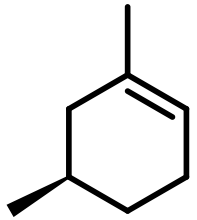
B



C



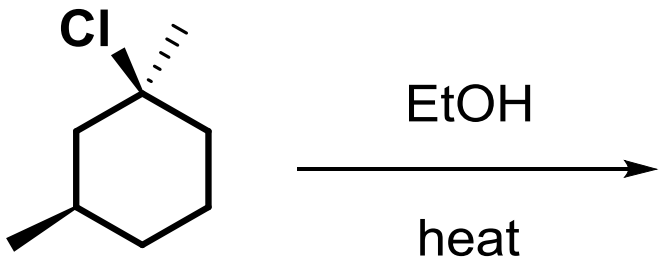
D



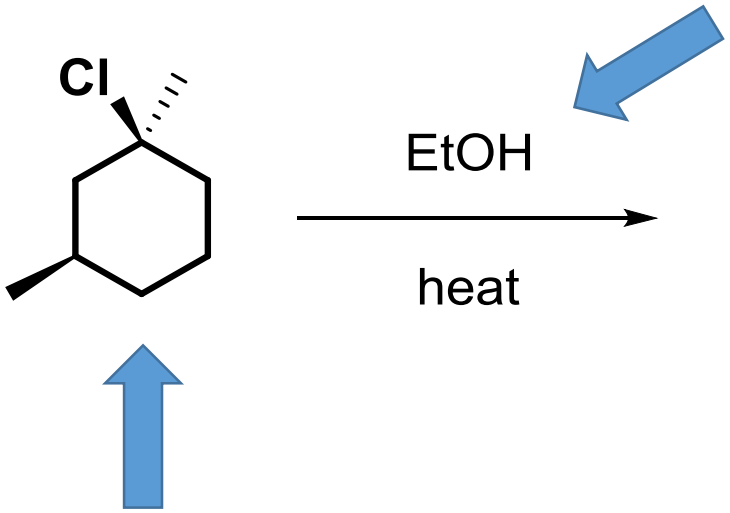
only

Problem 5 (difficulty: 3)

Predict the major elimination product(s):



- Scan the given info
- Identify the role of each component
- Identify the *type* of problem

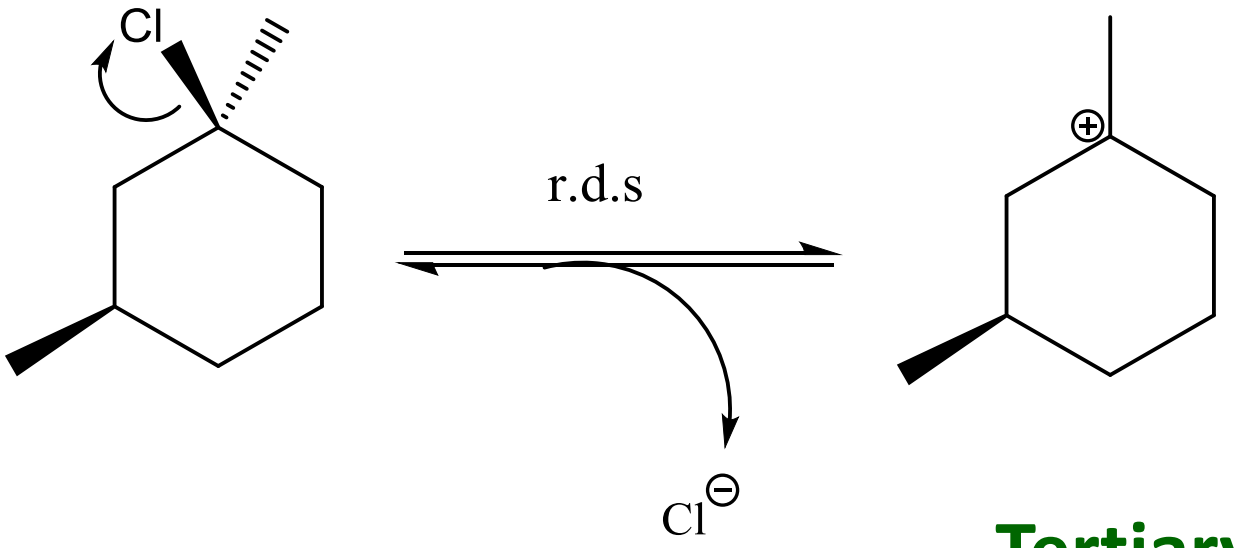


- Polar protic solvent
- Weak base

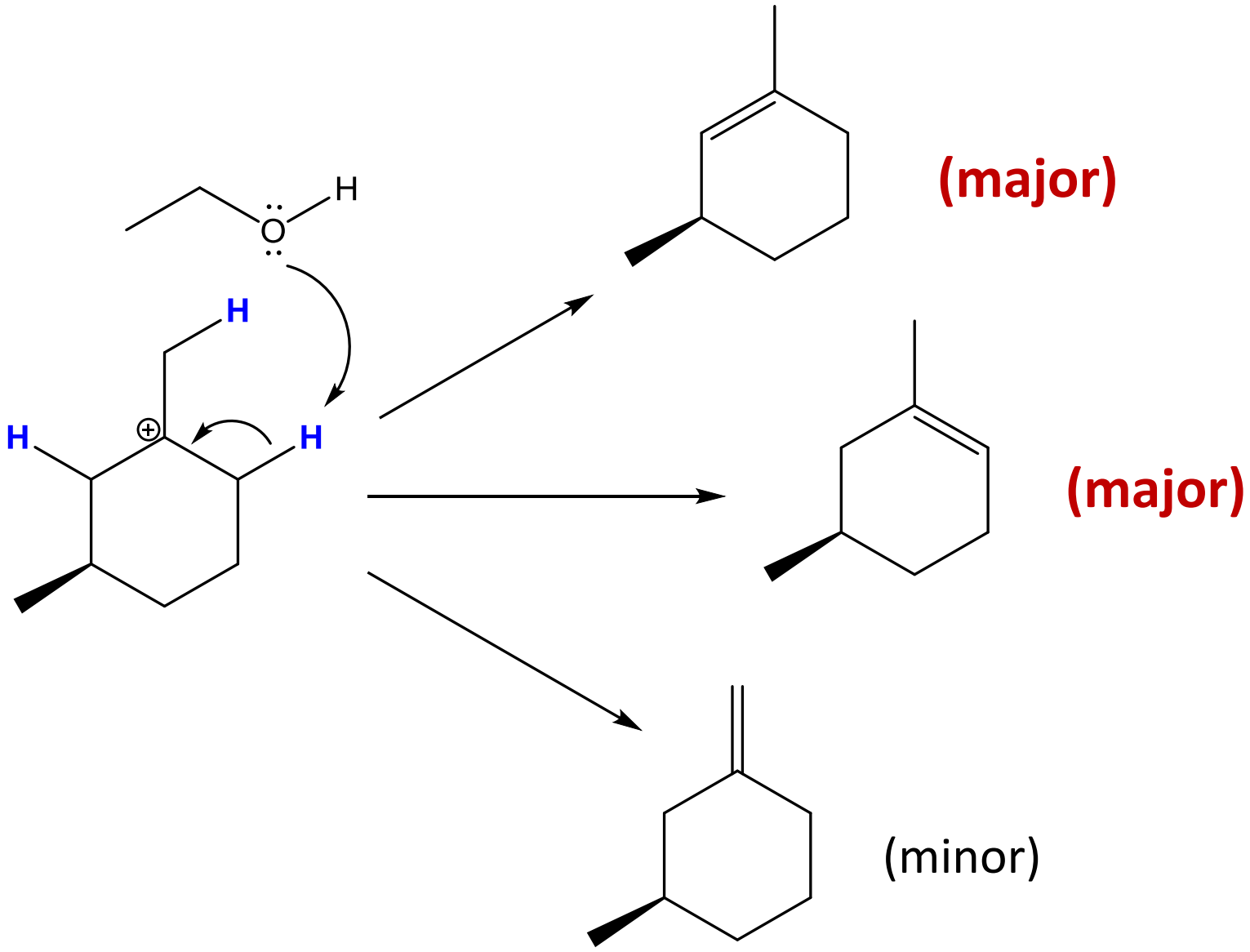
- 3˚ halide
- Cl = good LG

Ask: How may the starting material interact with the solvent/reagent?

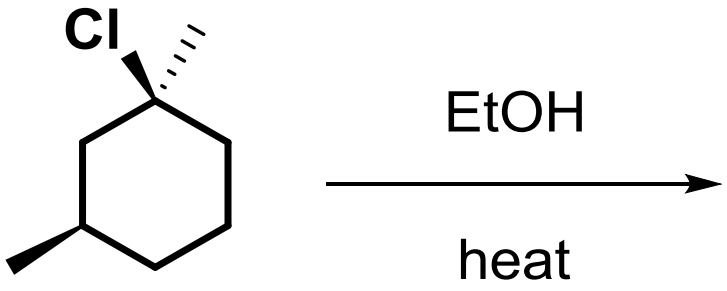
Problem 5: First step



Tertiary carbocation

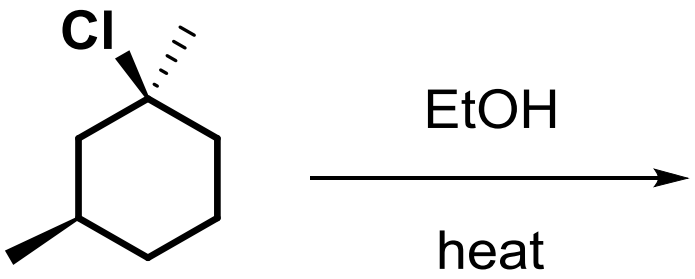

H
O
H
H
H
H
(major)
(major)
(minor)

Problem 5 - strategy



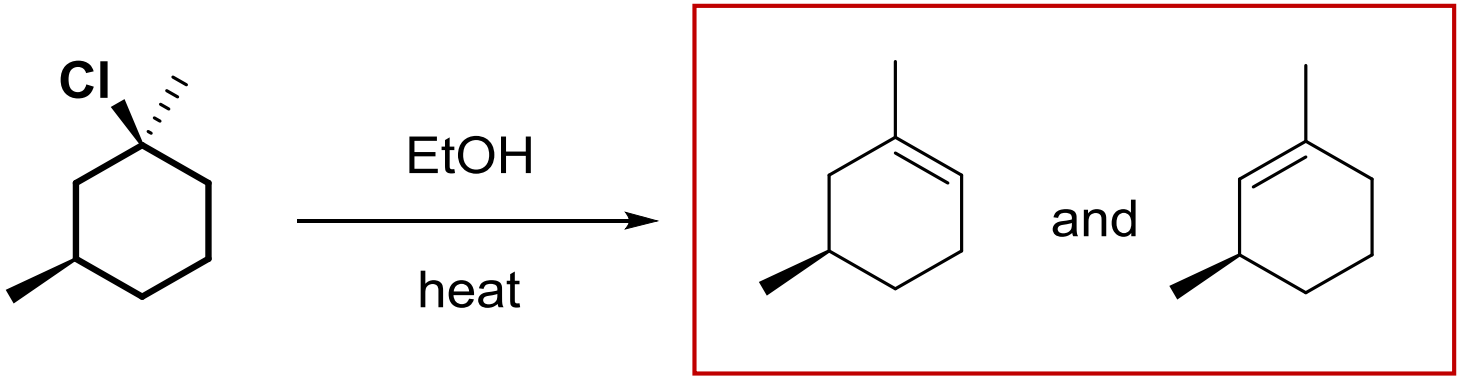
1. Determine the role of each component
2. Recognize this as an **E1** reaction
3. Use your knowledge of **E1** theory to determine the products

Problem 5 - strategy



1. Tertiary halide, polar protic solvent/weak base
2. Consider **E1** as a possibility
3. Work through **E1** mechanism to see outcome

Problem 5 - solution

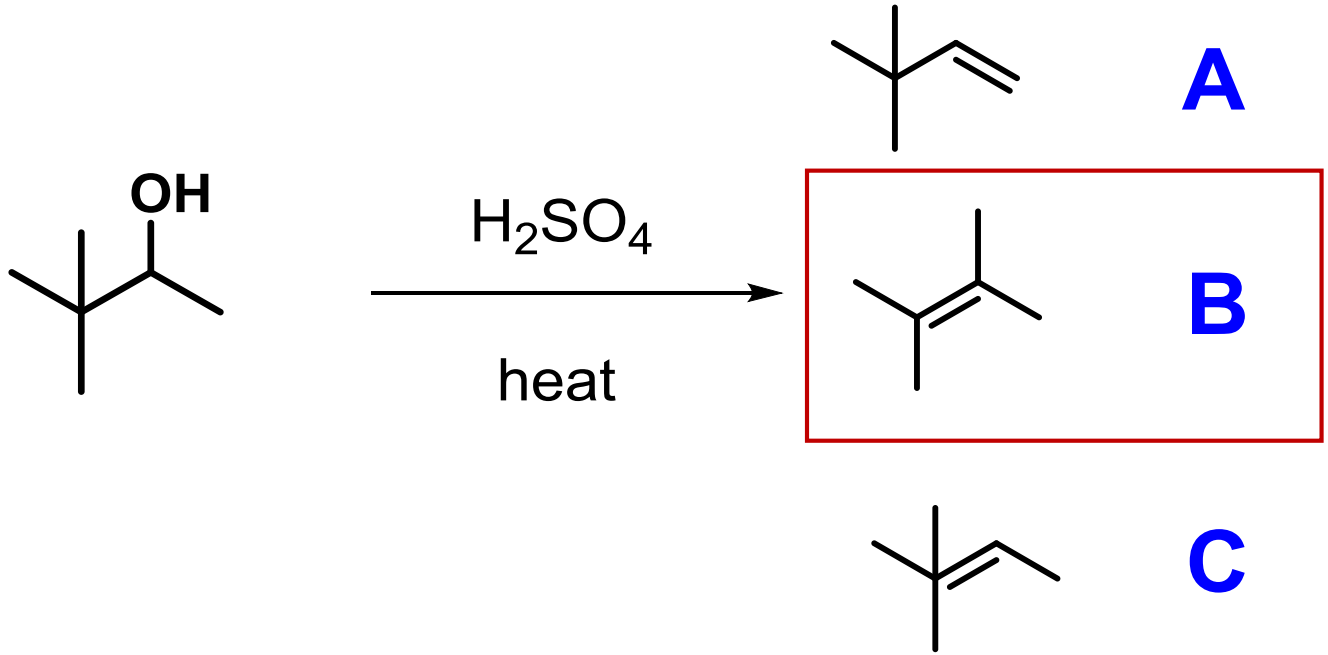


Clues: Tertiary α-carbon, good LG, polar protic environment

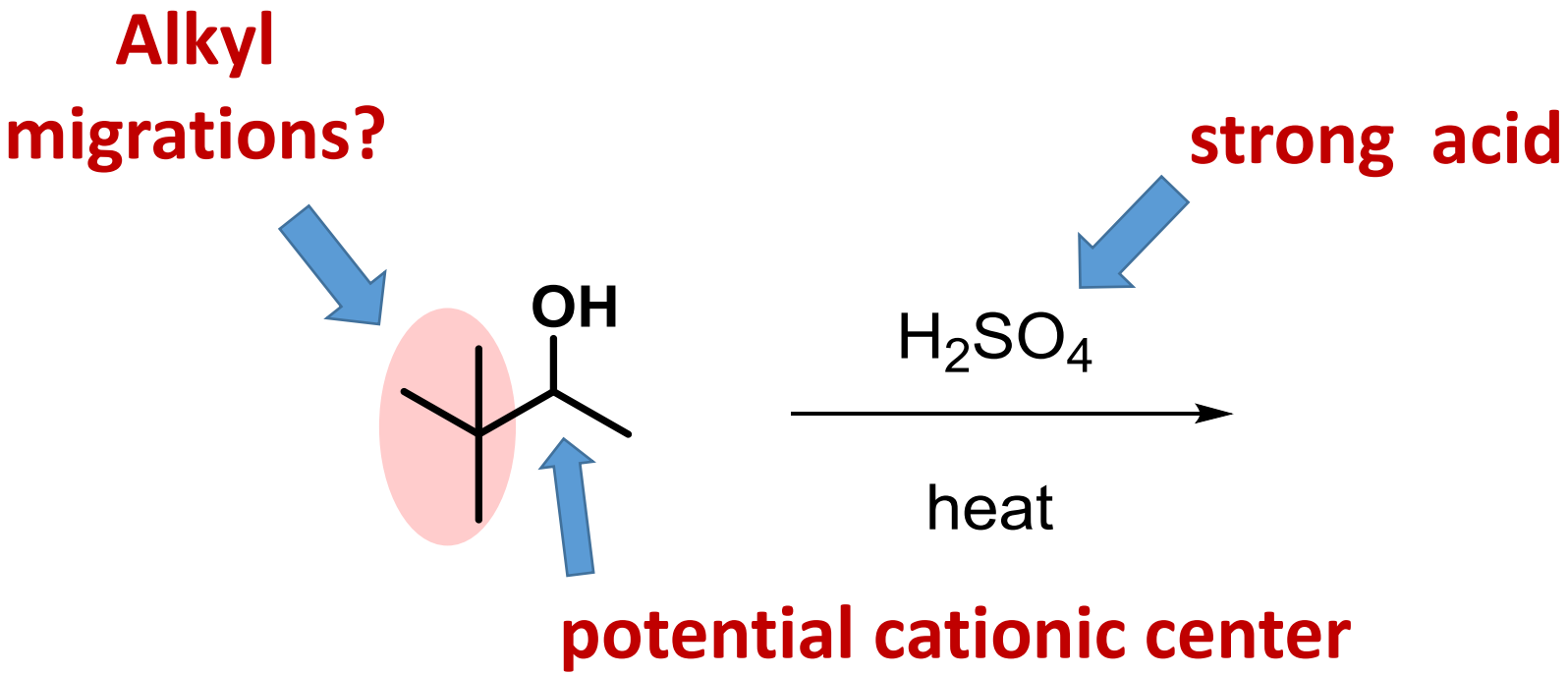
- Logical analysis of problem
- Intuition / pattern recognition

Problem 6

Predict the major product:

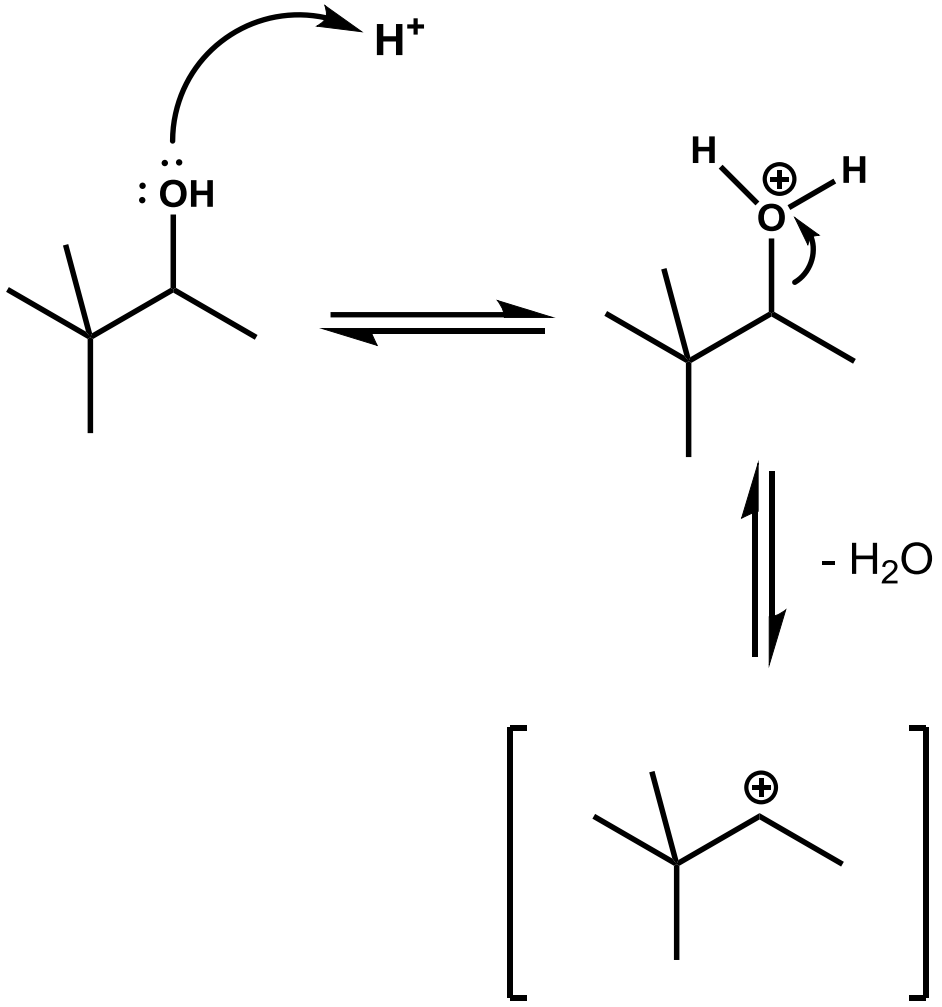


Problem 6 - clues

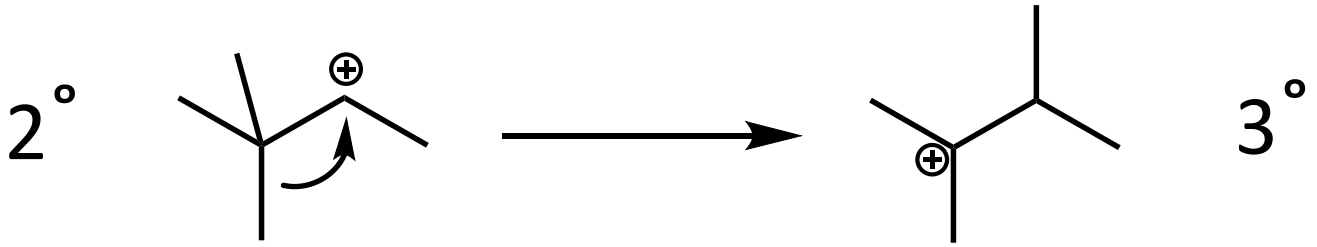


Clues: Secondary α-carbon, strong acid, polar protic environment

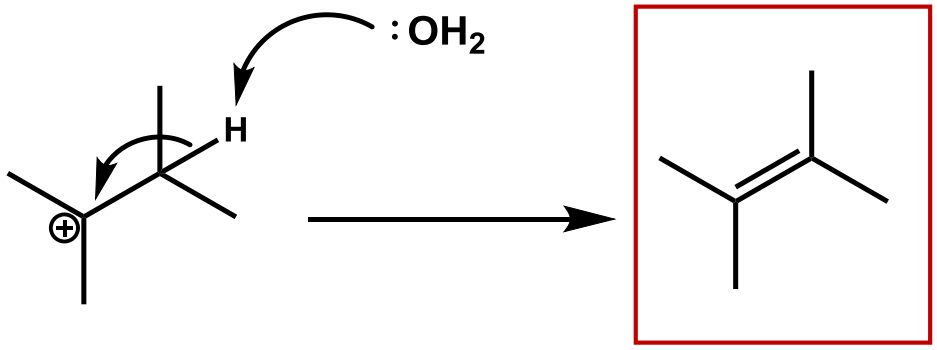
Problem 6 - mechanism



Bad LG
becomes
good LG

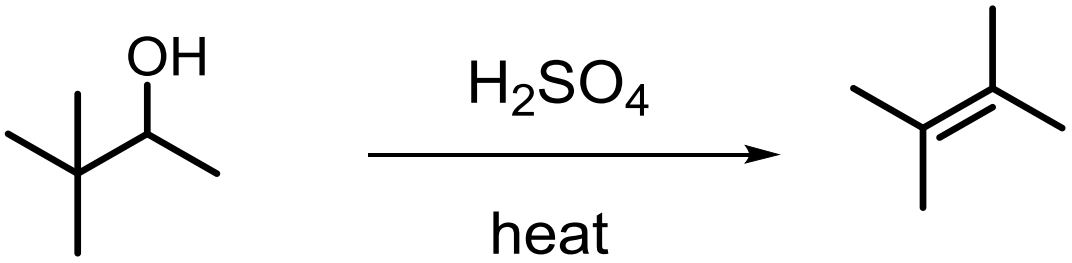


Caution: Watch out for cation rearrangements! (1,2-alkyl migrations)



Problem 6 - solution

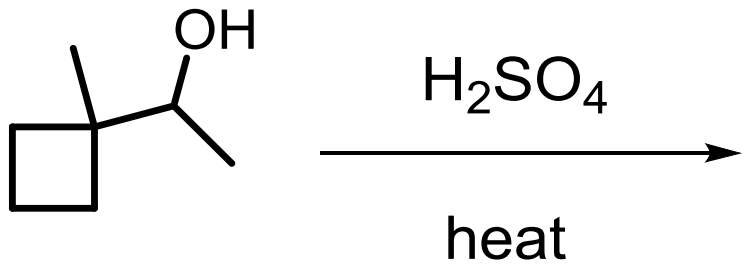
Predict the major product:

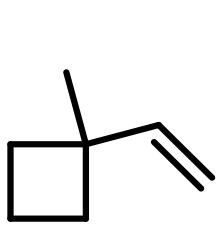


1. Secondary alcohol, strong acid, polar protic environment
2. Consider **E1** reaction
3. Work through **E1** mechanism and realize the possibility of carbocation rearrangement

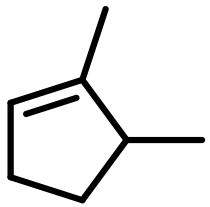
Problem 7

Predict the major product and propose a mechanism:

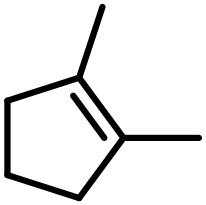




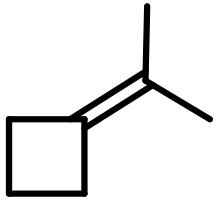
A



B

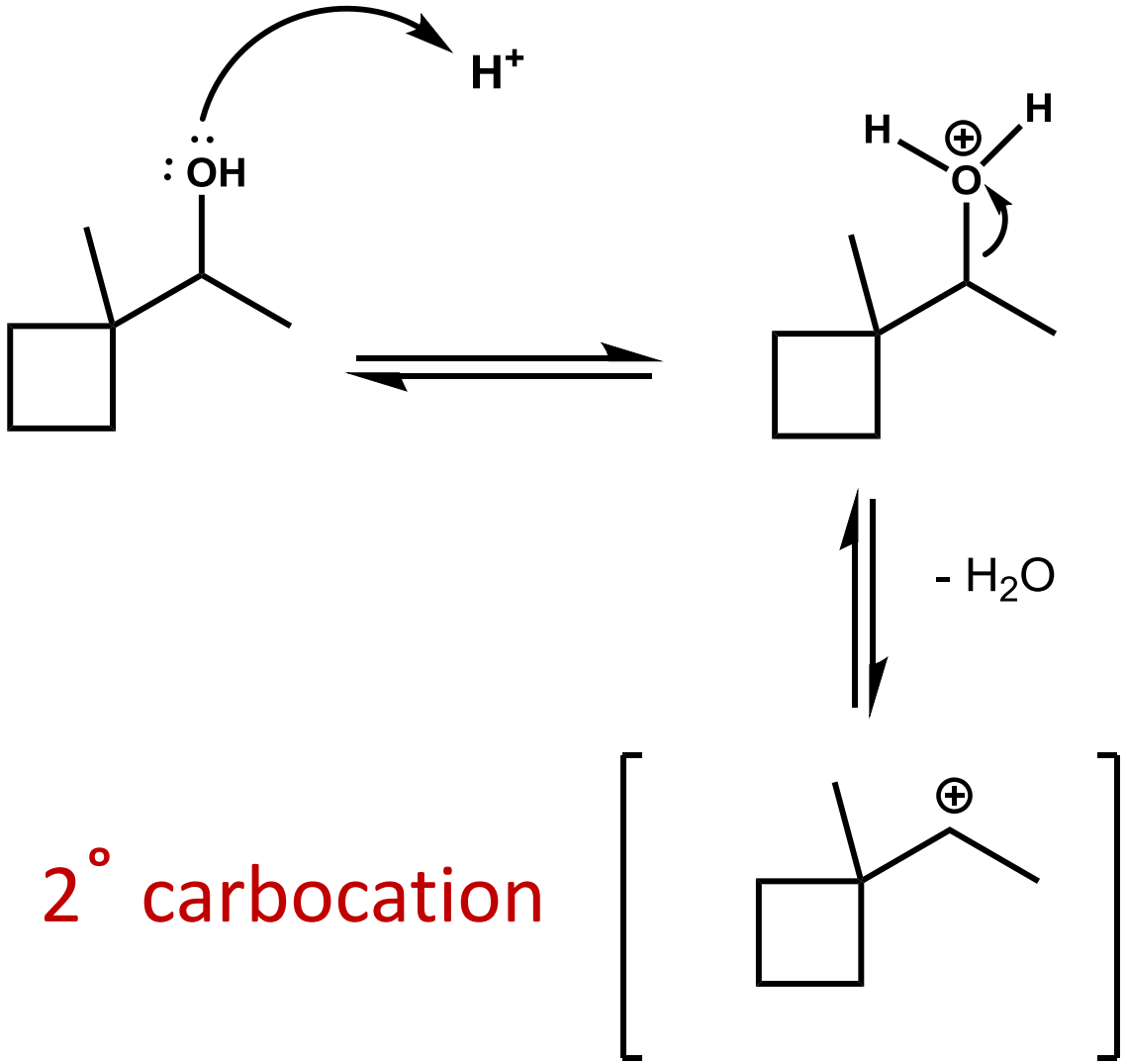


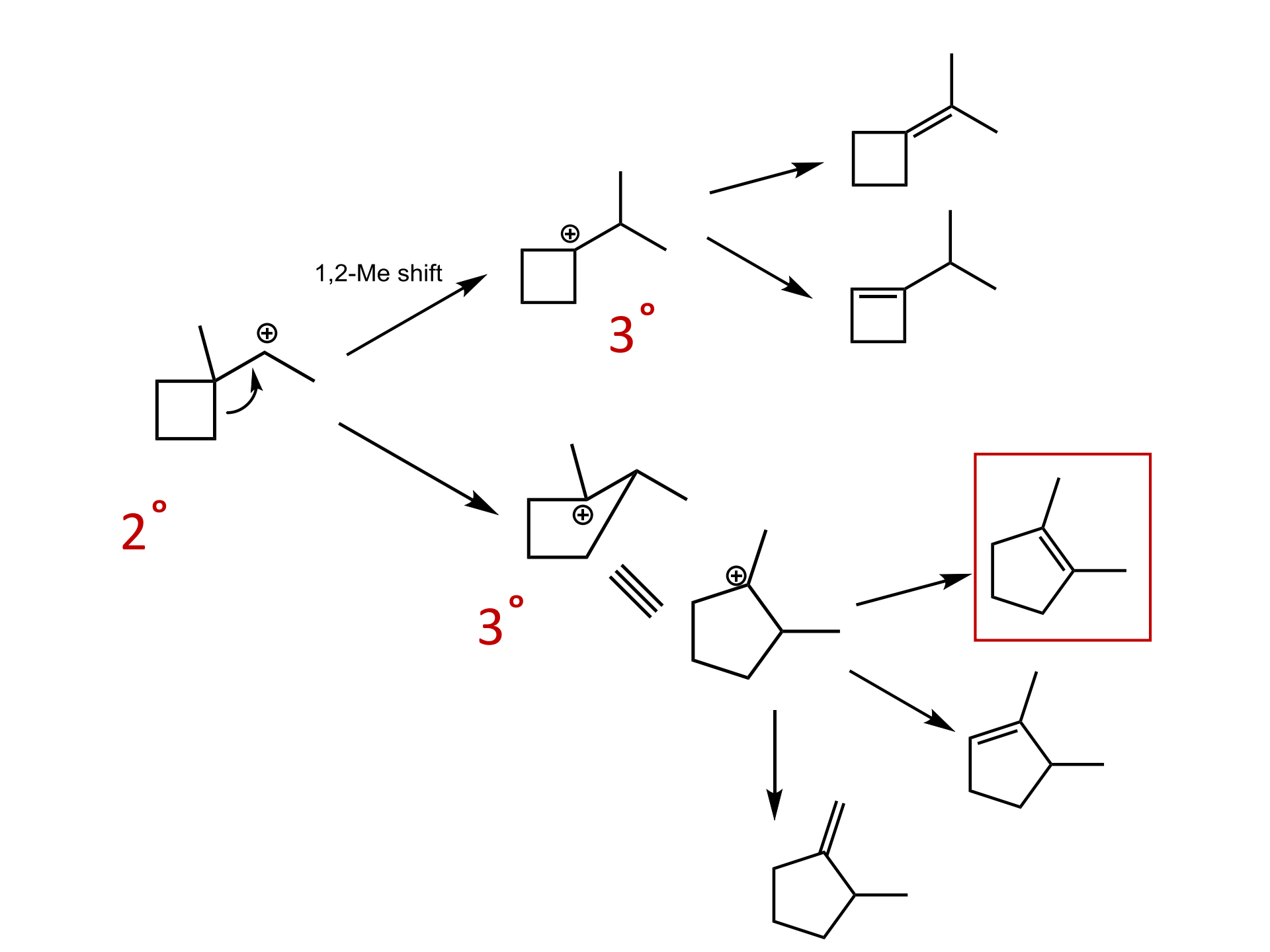
C



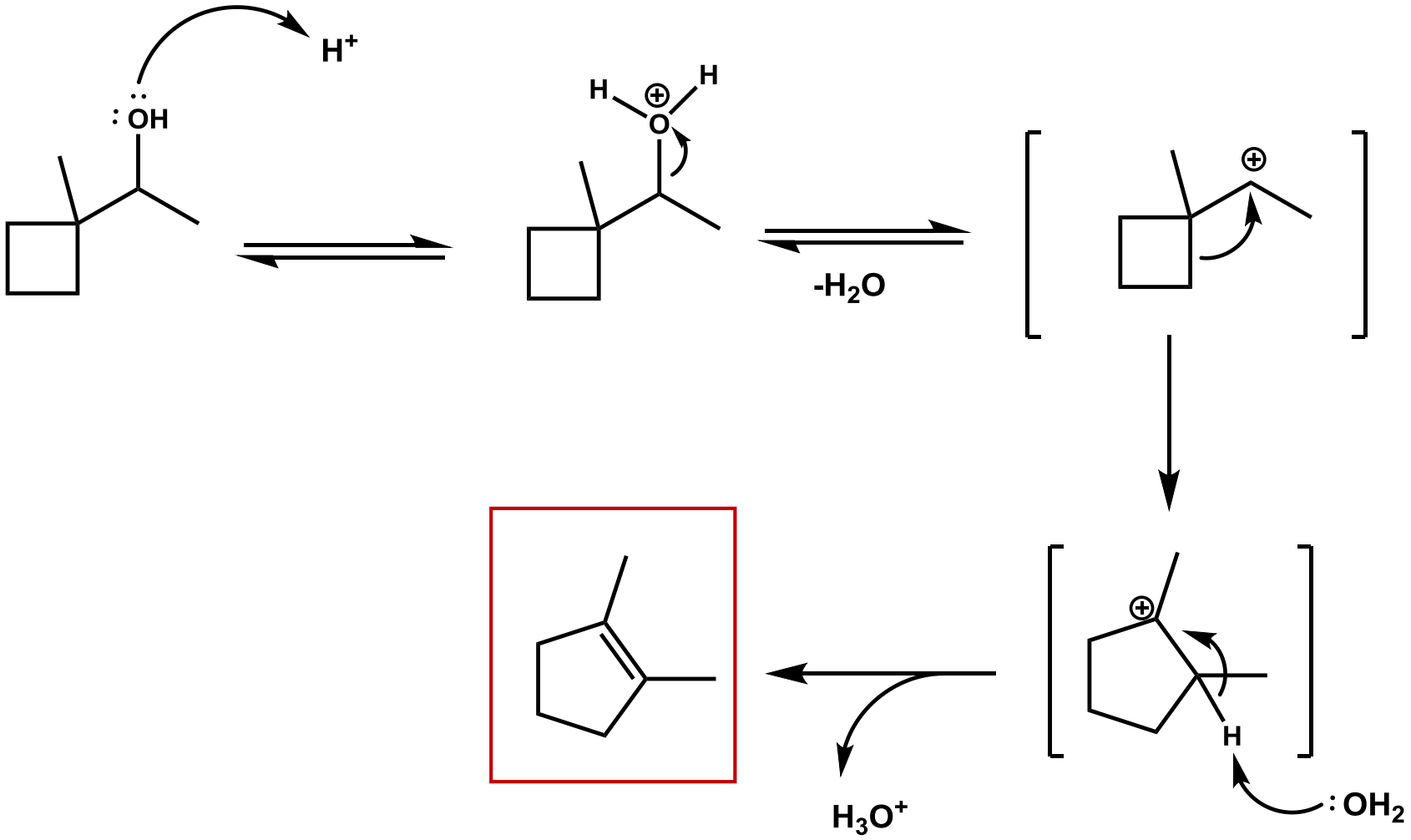
D

Mechanism

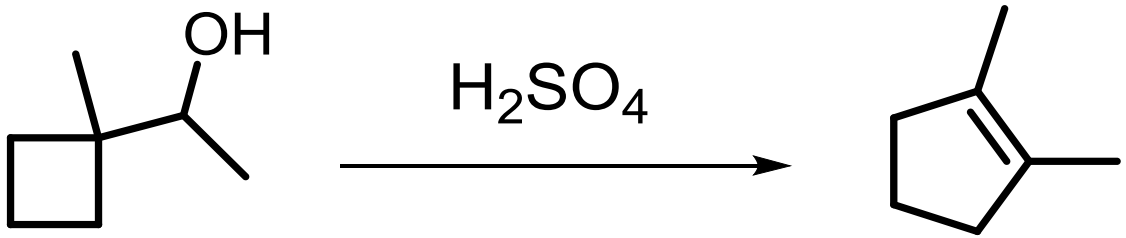



1,2-Me shift
2°
3°
3°

Problem 7 - Solution



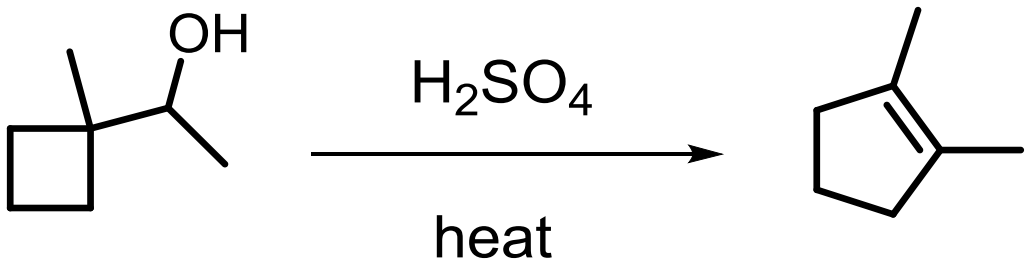
Problem 7 - Concepts



- Acid-base
- E1 reactions/mechanism
- Carbocation rearrangement
- Ring strain
- Ring expansion

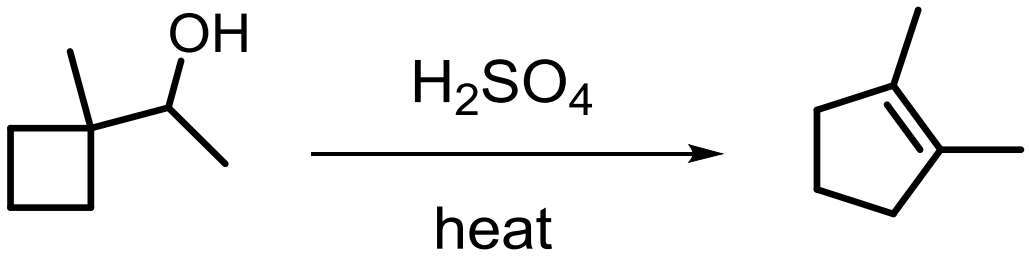
Problem 7b (product given)

Propose a mechanism for:



- Much easier problem
- Initial and final structures given

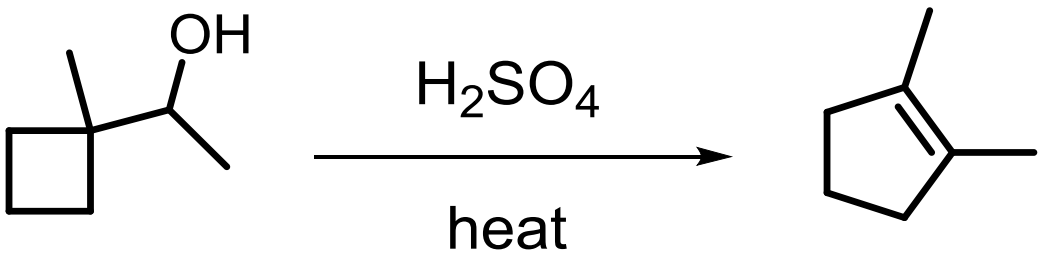
Problem 7b - strategy



1. Look at key *differences* between starting material and product

2. Try out a mechanism… here, you *know* when you're on a wrong path!

Problem 7b - analysis

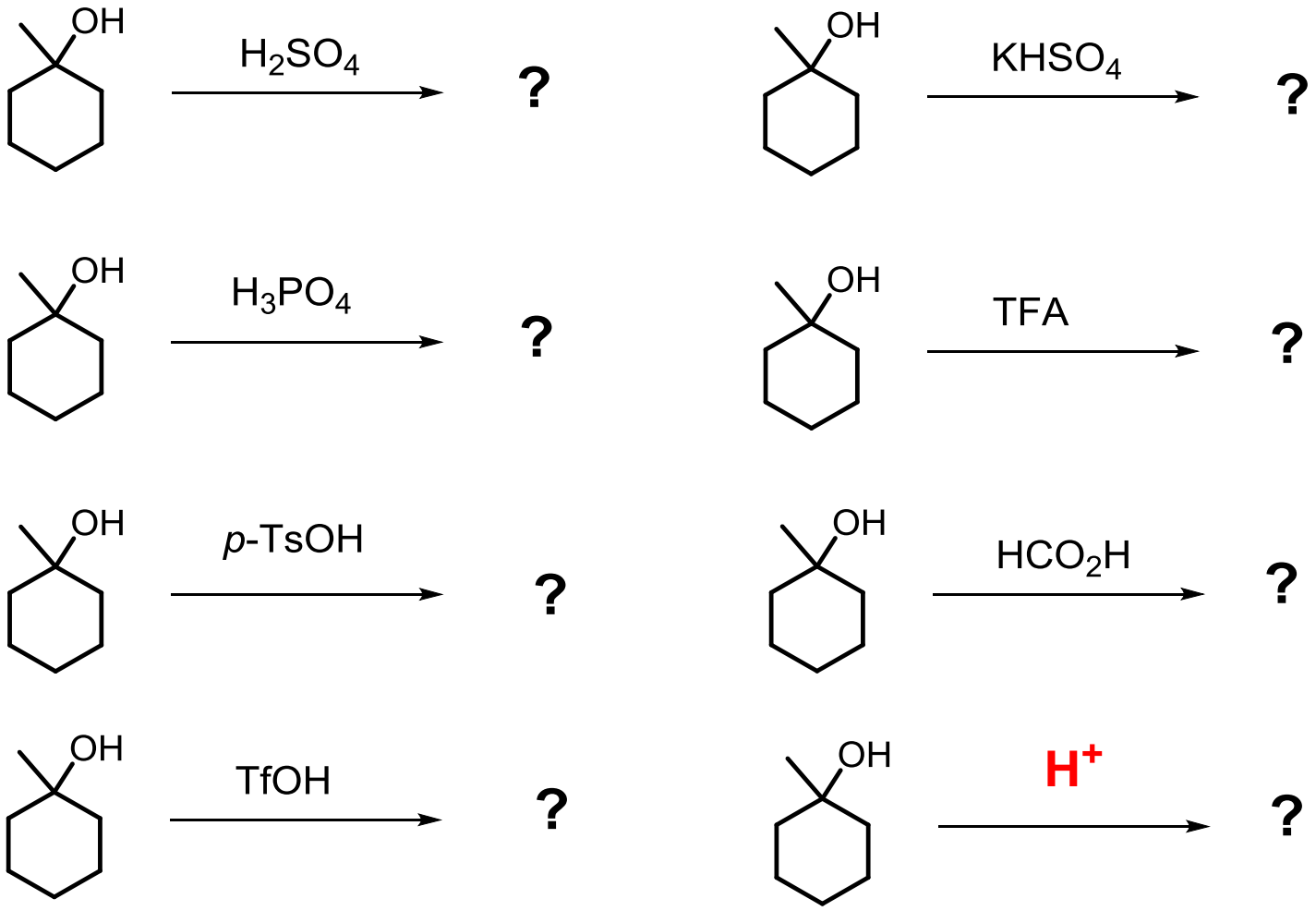


- Count atoms - lose/gain anything?
- Carbon skeleton

Differences:

- Lost **H** and **OH**, i.e. elimination
- **4**-membered to **5**-membered

The ‘unfamiliar’ reagent



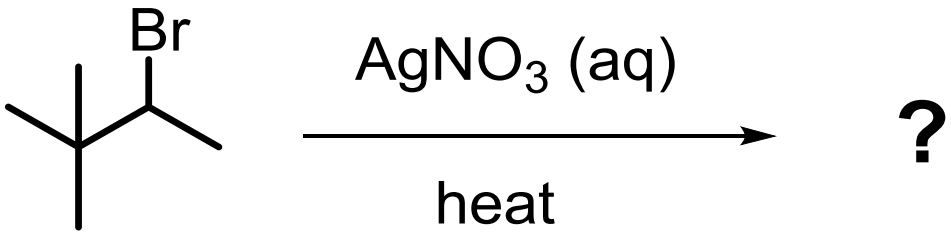
The ‘unfamiliar’ reagent

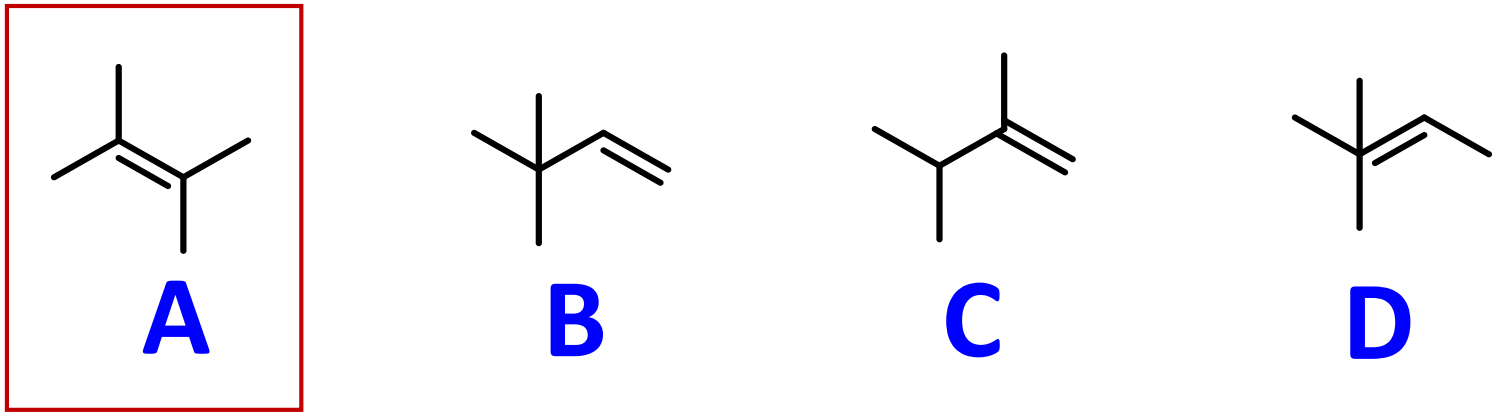
Tips:

- *Don’t panic*
- Analyze the reagent’s role
- What type of reagent?
- What are its constituents?
- What would it do to the starting material?

Problem 8

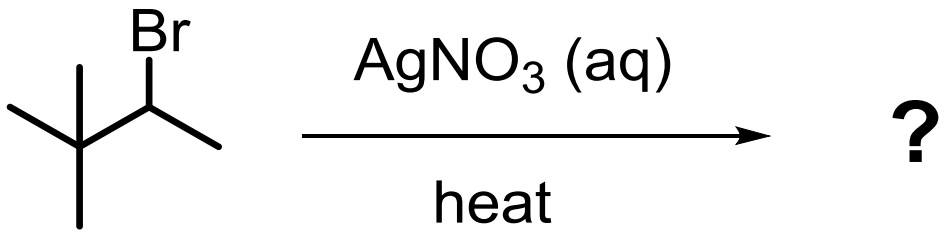
Predict the major product(s):





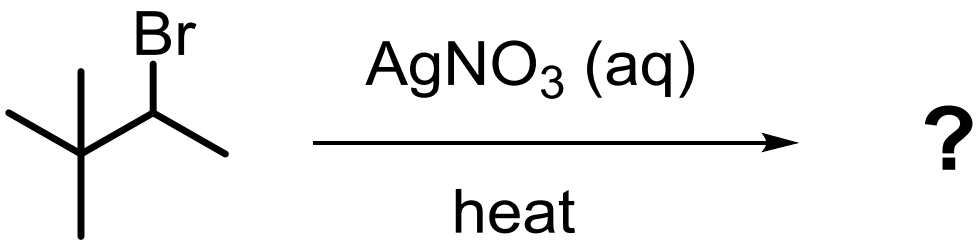
Problem 8

Predict the major product(s):



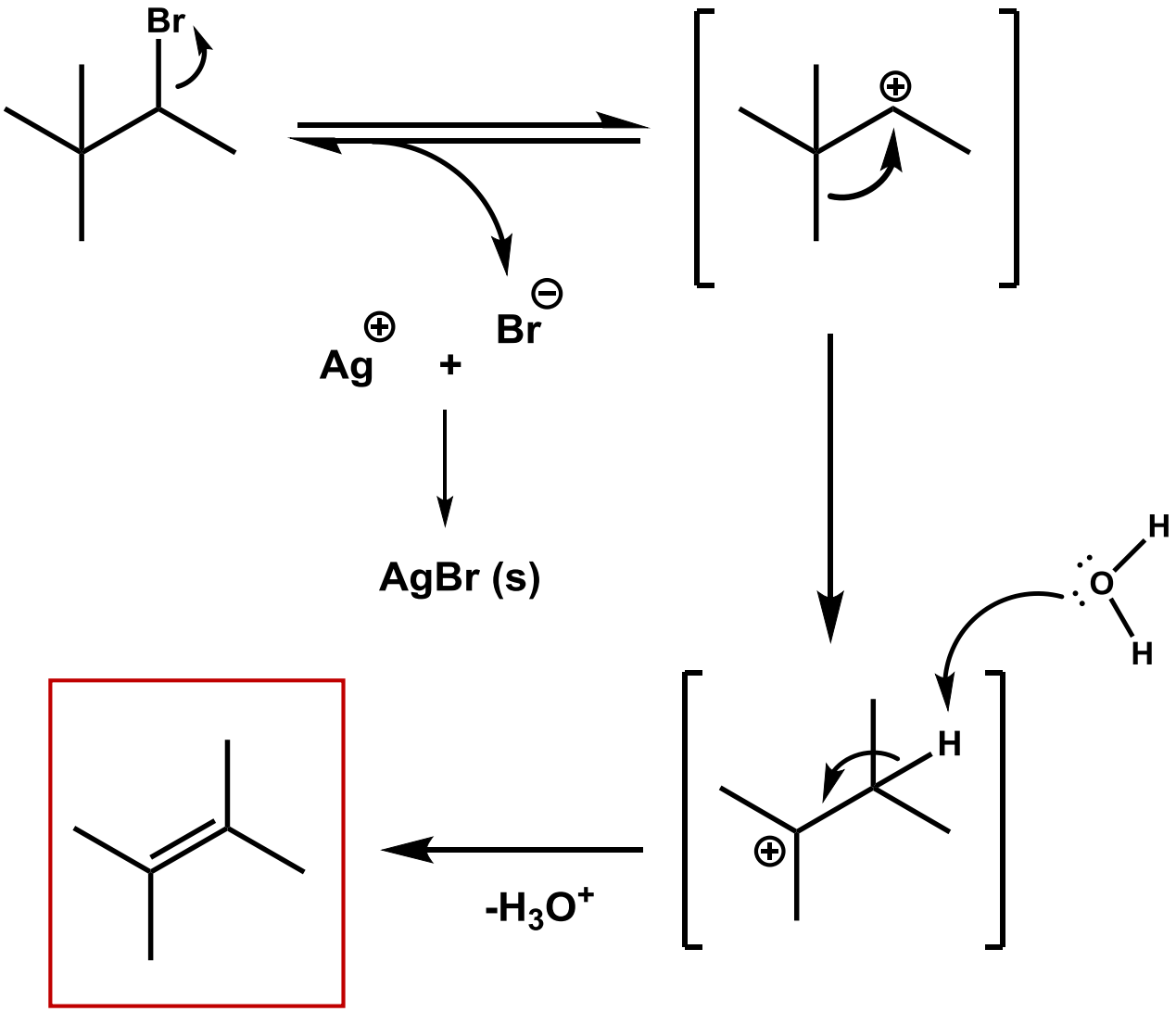
- Scan the given info
- Identify the role of each component
- Identify the *type* of problem

Problem 8 - analysis



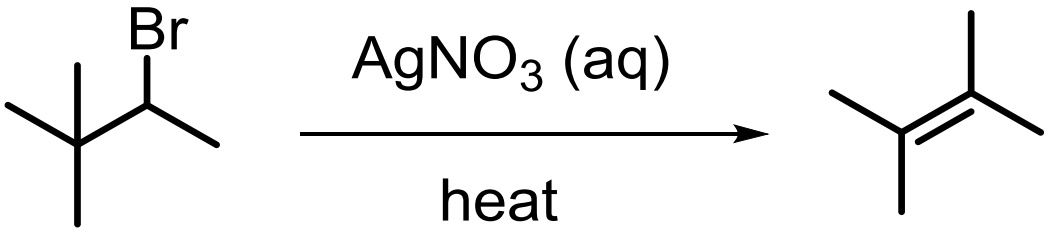
- Secondary halide, Br = good LG
- $AgNO_3(aq)$: H_2O, Ag^+, NO_3^-
- Polar protic solvent, weak base

Mechanism

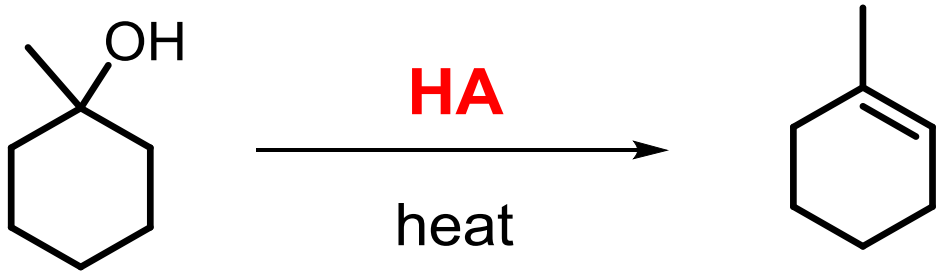


Problem 8 - Solution

Predict the major product(s):

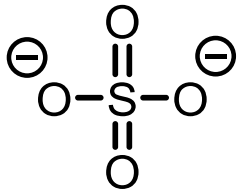


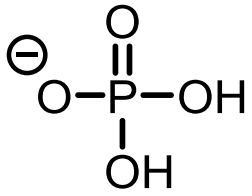
Tip: When faced with an 'unfamiliar' reagent, logically analyze its role. *Don't* *panic!*

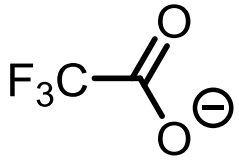


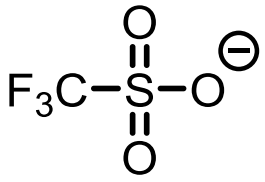
E1 product

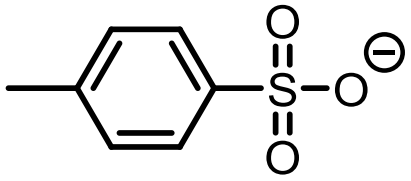
A =





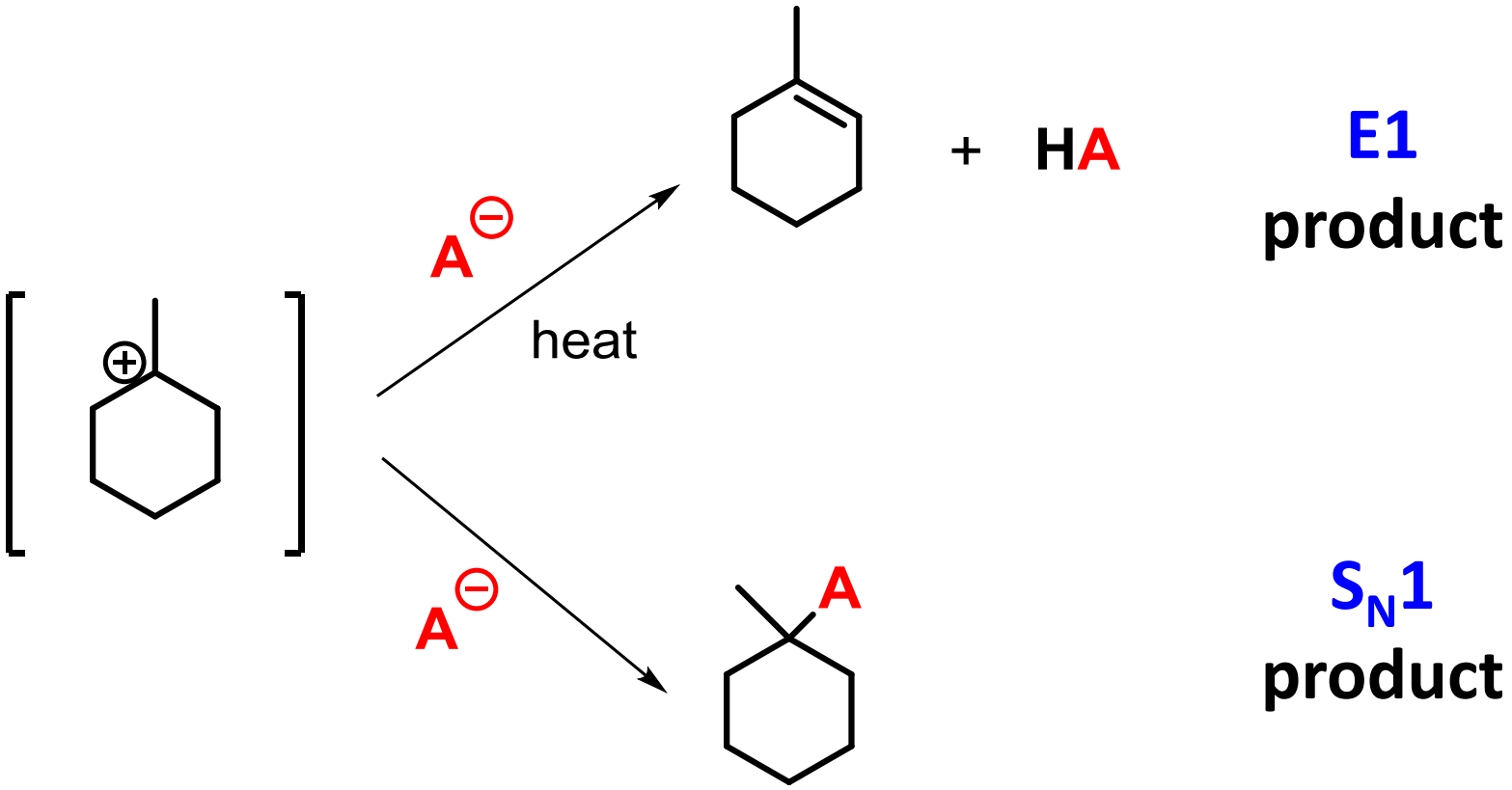






Very weak nucleophiles

E1 vs. S_N1 competition



http://www.masterorganicchemistry.com/2012/09/10/elimination-reactions-are-favored-by-heat/