CHEM 221 section 52

LECTURE #13 Thurs., April 03, 2008

ASSIGNED READINGS:

TODAY'S CLASS:

Ch. 9 Elimination rxns: loss of "H-LG" → alkene product
- E2 = concerted β-elimination
- E1 = step-wise elimination via C+ intermediate
- Regiochemistry, stereochemistry
- Competition between E1 & E2

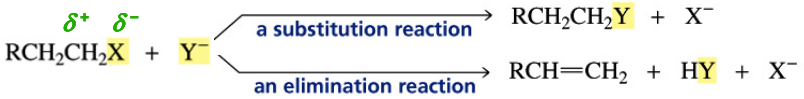
Competition between substitution & elimination

9.11 Synthesis – all specialized sections (4.12, 6.11…)

FINAL EXAM: Thurs. April 17th, 7-10 pm, CC-408

- cumulative; some MC, explanations, drawings, mechanisms, synthesis
- samples: http://faculty.concordia.ca/rogers, click Teaching, 221…

Ch.9: Elimination reactions of alkyl halides
Competition between substitution & elimination



Chapter Goals *Understand the two basic types of elimination rxns.*
Understand competition: substitution vs. elimination.

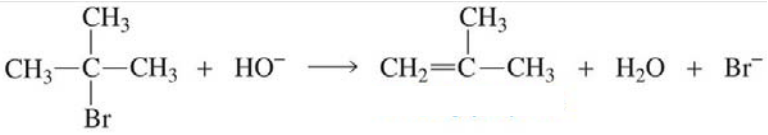
- Learn the mechanisms of E1 & E2 rxns – *including stereochemistry.*
- Predict/control competition between different reaction pathways.
- Apply these concepts to the synthesis of organic compounds.

Chapter Outline:

9.1-2	The E2 reaction: **a CONCERTED elimination rxn**
9.3	The E1 reaction: **a STEP-WISE elimination rxn**
9.4	Competition between E1 & E2
9.5-9.6	Stereochemistry: E1, E2 & importance for cyclic compounds
[9.7	*Kinetic isotope effect can help determine mechanism]*
9.8	Competition between substitution & elimination
9.9-9.12	Applications to organic synthesis

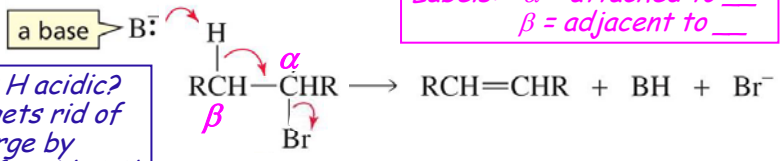
9.1 The E2 rxn: 1-step, bimolecular process

Dehydrohalogenation: Loss of HX from adjacent Cs



Concerted mechanism: B takes H⁺… π-bond forms… pushes off LG
"β-elimination" or "1,2-elimination"

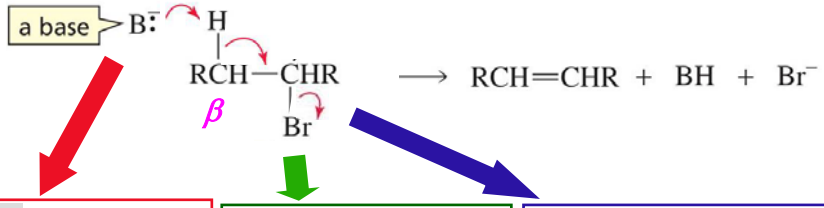
Labels: α = attached to ___
β = adjacent to ___



Why is β-C's H acidic?
- *conj.base gets rid of its -ve charge by pushing off stable LG!*

"ELIMINATION BIMOLECULAR" = "E2" rate = k [RX] [B]
└ RLS involves 2 molecules

Factors affecting E2 rxns: B, LG & Sterics



Base
- stronger B *OR* ↑ [B]
  ⇨ faster E2 rxn !

Leaving Group
- better LG
  ⇨faster E2 rxn !

Sterics: 3° > 2° > 1°
- more highly sub'd
  ⇨faster E2 rxn !

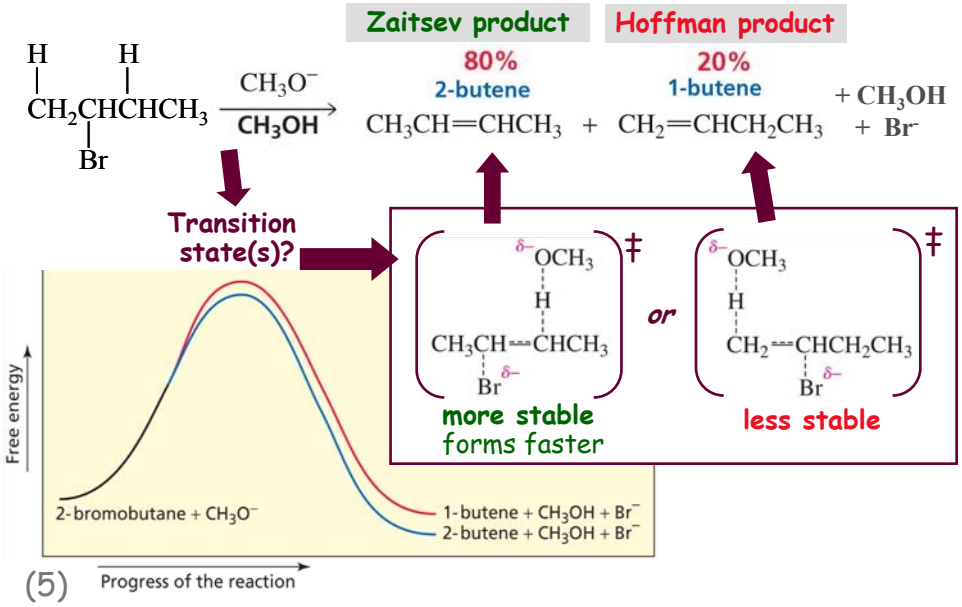
Why is E2 fastest for 3° > 2° > 1° ? *(Unlike S_N2…)*

- Steric hindrance not usually an issue: **BASE can easily reach Hs**
- **E2 transition state (‡) resembles ALKENE product**

more highly substituted
⇨ more stable

9.2 The E2 rxn is regioselective: most stable product dominates

Zaitsev's rule: major product = most substituted alkene



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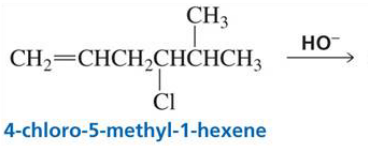
Identify the major & minor products of this E2 rxn
RULE: most stable alkene = major product



4-chloro-5-methyl-1-hexene

Be on the lookout for special cases of stabilization:
e.g., conjugation (*i.e.*, resonance delocalized π-systems)

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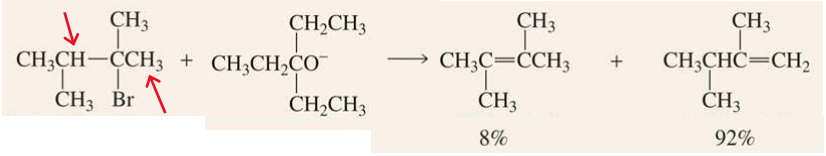
Exceptions: cases when less stable alkene is major…

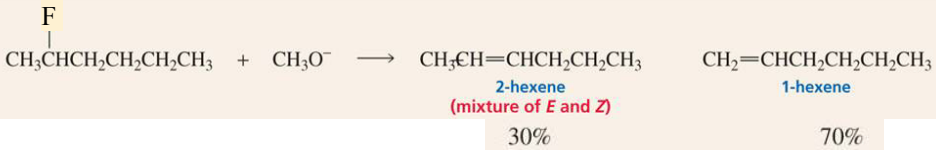
1.) Extremely bulky B: *e.g.,* Et_3CO^- — *a useful trick* (see Table 9.1)

- B cannot reach H on most-substituted β-C
- can get high yield of non-Zaitsev (Hoffman) product



2.) Very poor LG: *e.g.,* F^- — *not too common* (see Table 9.2)

- LG resists leaving ⇨ ‡ resembles C-, not alkene
- C-anions destabilized by EDGs (unlike C+…)



9.3 The mechanism of an E1 reaction

Carbocation ⇨ open shell ⇨ HIGHLY electrophilic !

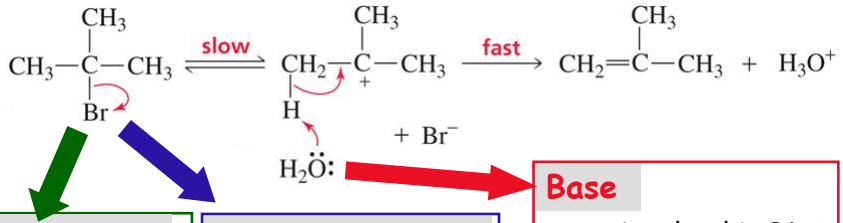
⇐ RATE-LIMITING STEP
- stable molecule falls apart!
- rxn shows 1st order kinetics
- rate = k [alkyl halide]

REGIOCHEMISTRY ?
- major = more stable alkene
- But: C+ may rearrange…

"ELIMINATION UNIMOLECULAR" = "E1"
└ RLS involves 1 molecule

1st step (SLOW): LG leaves (heterolytic C-X bond cleavage)
2nd step (FAST): B deprotonates β to C+ centre

Factors affecting E1 rxns: LG & sterics but not B



Leaving Group
- Better LG
  ⇨ ↑ C-X cleavage
  ⇨ faster E1 rxn !

(but always quite slow)

Sterics: 3° > 2° > 1°
- more substit'd
  ⇨ ↑ C+ stability
  ⇨ faster E1 rxn !

Base
- not involved in RLS
  ⇨[B] & strength have NO EFFECT
  (do affect E2…)

Remember: C+ intermediate
- Most stable one dominates: might rearrange before B attacks…

9.4 Competition between E2 & E1 rxns

Table 9.3 & 5

E2: predictable regio. & stereo.	**E1:** less control of regio./stereo.
A one-step mechanism	A stepwise mechanism that forms a carbocation intermediate ←
A bimolecular rate-determining step	A unimolecular rate-determining step
No carbocation rearrangements	Carbocation rearrangements ←

Reactivity order:
3° > 2° > 1° ~~> methyl~~ Cannot eliminate. (only 1 C atom!)

E1 & E2

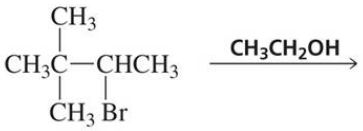
E2 only

As with substitutions: concerted rxn inherently faster, so…
- **Want E2 ?** SPEED UP E2 ⇦ strong base, aprotic solvent
- **Want E1 ?** SLOW DOWN E2 ⇦ weak base, protic solvent

Would this elimination occur via E1 or E2?
What would be the major & minor products?
Any idea about stereochemistry?

PROBLEM 10◆

(& p.406-7)



Elimination rxns are stereoselective (favour 1 stereoisomer product)

- if mechanism can form both E & Z isomers: major = the more stable one

Major product = most stable alkene → ① **REGIO?** most subst'd/conj'd → ② **STEREO?** cis *vs.* TRANS

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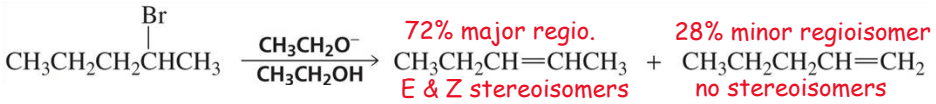
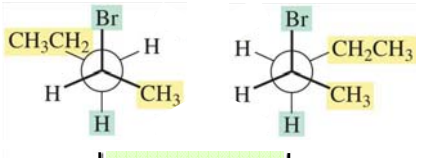
9.5 Elimination rxns are stereoselective (& E2 has 3D needs…)



3D REQUIREMENTS of E2 MECHANISM: major stereoisomer = ?

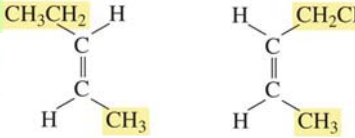
- staggered R-X conformations react (more stable ⇨ more common)
- via ANTI-PERIPLANAR elim'n of H-X (H-X coplanar ⇨ p-overlap…)
- major isomer: bulkier groups TRANS (more stable ‡ ⇨ faster rxn)

For major regioisomer:
2 β–H's on 2° *β*-C
⇨ 2 anti-H-X confo's
⇨ 2 stereoisomers form



alkene-like ‡

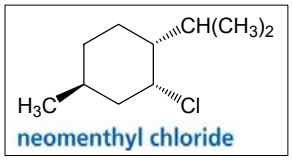
MAJOR STEREOISOMER
(*E*)-2-pentene
more stable



MINOR STEREOISOMER
(*Z*)-2-pentene
less stable

1 H on preferred *β*-C ⇨ 1 confo. to consider ⇨ 1 stereoisomer ONLY

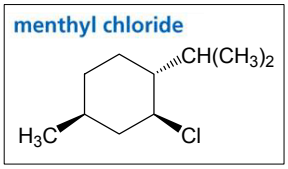
Which compound will undergo faster E2 elimination? (9.6)



neomenthyl chloride

E2's characteristics:
- need anti-periplanar H-X
- rate = k [B] [R-X]

⇨ How much R-X is in an E2-reactive conformation?



9.8 Competition: substitution *vs.* elimination

Think through factors to predict pathway: E *vs.* S_N

SUBSTRATE: __° & LG
LG likely to leave on its own? ⟶ favours step-wise mechanisms
Is steric hindrance an issue? ⟶ disfavours S_N2

↓

REAGENT: Nu or B
Strong enough to push off LG? ⟶ favours concerted mechanisms

↓

SOLVENT:
Polar enough to stabilize C+? ⟶ step-wise mech's less unfavourable

↓

TEMPERATURE:
Is rxn being run at high temp.? ↗ favours elimination over substitution
↳entropically favoured rxns
$\Delta G = \Delta H - T\Delta S$

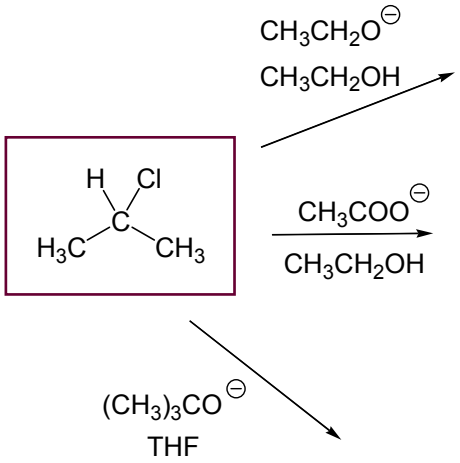
↓

Conclude: E vs S_N
and: mechanism type ↗ then determine regio- & stereochem. to identify major & minor products

Summary of competition: substitution *vs.* elimination

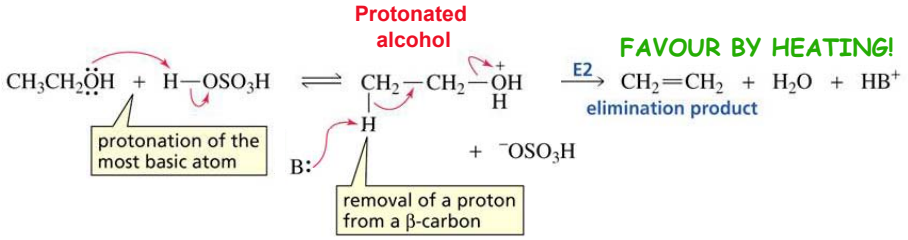
Substrate Table 9.6	S_N2 *vs.* E2 Concerted High [ ] of good Nu / strong B in aprotic solvent	*Control?*	S_N1 *vs.* E1 Step-wise Poor Nu / weak B in protic solvent
1° RX	Substitution	*Want E?* ⇨ *bulky B*	neither
2° RX	BOTH	*Want E?* ⇨ *bulky B, ↑ T*	BOTH *(no control)*
3° RX	Elimination		BOTH *(no control)*

Which pathways would occur under these conditions?

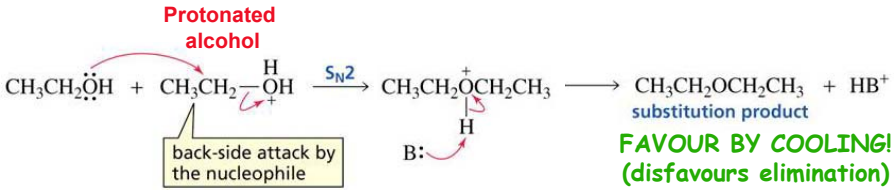


1° alcohol in acid: E2 dehydration *vs.* S_N2 solvolysis…

In acidic solution: -OH becomes good LG "H_2O"



Competing rxn = Alcohol (solvent) attacks as Nu instead of B



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9.9 Substitution & elimination rxns in synthesis

Classic use of S_N2 reaction: TO PREPARE ETHERS

Williamson ether synthesis

$$\underset{\text{alkyl halide}}{R{-}Br} + \underset{\text{alkoxide ion}}{R{-}O^-} \longrightarrow \underset{\text{ether}}{R{-}O{-}R} + Br^-$$

- **Alkoxides are easily & cleanly made by treating ROH with:**

  sodium metal: $ROH + Na \rightarrow RO^- + Na^+ + \frac{1}{2} H_2$ (redox rxn)

  OR

  sodium hydride: $ROH + NaH \rightarrow RO^- + Na^+ + H_2$ (acid-base rxn)

- **Versatile:** can use either of 2 combinations of alkyl halide & alkoxide whichever favours the desired S_N2 rxn more (over E2…)

$$\underset{\text{propyl bromide}}{CH_3CH_2CH_2Br} + \underset{\text{butoxide ion}}{CH_3CH_2CH_2CH_2O^-} \longrightarrow \underset{\text{butyl propyl ether}}{CH_3CH_2CH_2OCH_2CH_2CH_2CH_3} + Br^-$$

$$\underset{\text{butyl bromide}}{CH_3CH_2CH_2CH_2Br} + \underset{\text{propoxide ion}}{CH_3CH_2CH_2O^-} \longrightarrow \underset{\text{butyl propyl ether}}{CH_3CH_2CH_2OCH_2CH_2CH_2CH_3} + Br^-$$

More important if one alkoxide is bulkier… Poorer Nu…

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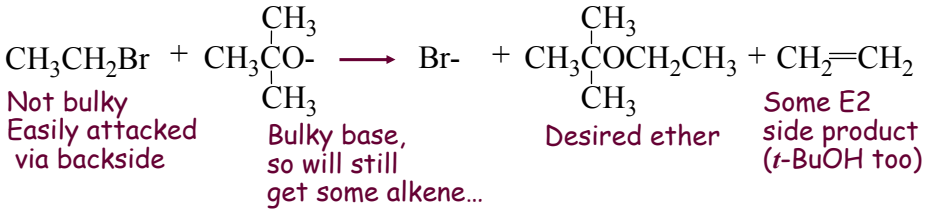
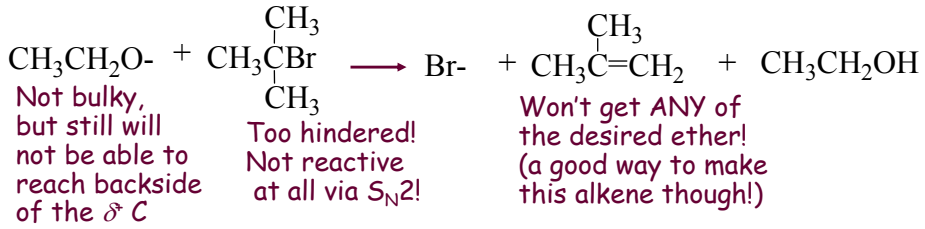
To synthesize an ether: see best results if…

- **provide the less hindered group via the alkyl halide**

use bulkier one as alkoxide; otherwise δ C's backside is too hindered…



Compare to results if do rxn the other way around:

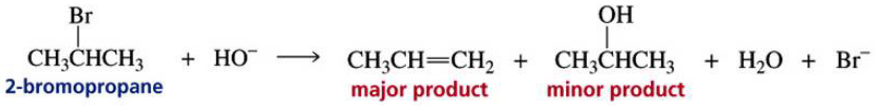


To efficiently synthesize an alkene via loss of HX:

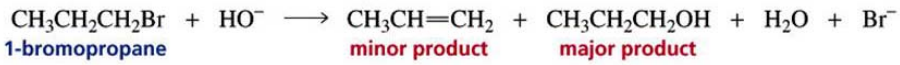
- **use the most hindered alkyl halide possible**

EXAMPLE: If we want to prepare propene in the lab: $CH_3CH{=}CH_2$
- Dehydrohalogenate 2-bromopropane ***or*** 1-bromopropane?

A good route to the alkene: (hindered halide, plus strong base
even better if use strong BULKY base)

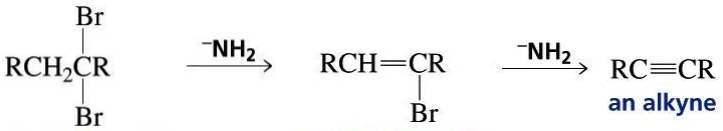


A good route to an alcohol: (less hindered halide, OH^- as Nu):



9.10 Consecutive E2 elimination reactions

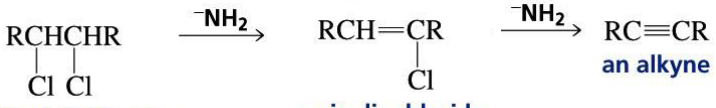
"geminal" = substituents on same *C*



a geminal dibromide — a vinylic bromide

A 2nd elimination can occur under same conditions!
⇨ the sp²-*C*'s H in vinylic halide would be more acidic than any sp3-*C*'s H's in molecule, due to:
1) EWG effect of LG &
2) higher electronegativity of sp²-*C*!

"vicinal" = substituents on adjacent *Cs*



a vicinal dichloride — a vinylic chloride

9.11: Designing a synthesis
(& 4.12, 6.12) **Synthetic planning & retrosynthetic analysis**

Syn·the·sis \ 'sin(t)-thə-səs \ noun [Gk, fr. *Syntithenai* to put together]

1.a the composition or combination of parts or elements so as to form a whole
b the production of a substance by the union of chemical elements, groups or simpler compounds or by the degradation of a complex compound
c the combining of often diverse conceptions into a coherent whole
2.a deductive reasoning…

"Starting material" = what you start with *"SM"*
"Target molecule" = desired compound

Is there an obvious sequence of rxns that could lead to this product?
- if starting material can only undergo 1 type of rxn: start there!
- remember the tools at your disposal (rxn types, & regio/stereochem)
- often convenient to:
  use substitution to switch functional groups
  use alkene intermediate to switch locations of groups

Playing with molecular building blocks

BASIC TYPES OF ORGANIC REACTIONS *(so far...more in Organic II)*

1. **Radical halogenation:**
   adds a functional group to alkanes *(unreactive!)*

2. **Substitution:**
   change to a different functional group

3. **Elimination:**
   create a π-bond

4. **Electrophilic addition:**
   use π-bond to add a new functional group
   (very helpful for switching funct'nl group positions!)

Mixing & matching these types of rxns can provide a variety of routes to our molecules of interest → versatility!
(use trial & error to find best pathway!)

(23) **MAKE A COMPREHENSIVE SUMMARY OF RXNS!**

Designing a synthesis: (4.12, 6.12, 9.11)
synthetic planning & retrosynthetic analysis

IDEAL GOAL: SYNTHESIZE THE TARGET MOLECULE USING…
- fewest # steps possible
- highest yield of desired product possible (intermediate steps too)
- simplest / safest / cheapest / fastest rxns possible

OUR GOALS FOR NOW (we are beginners…):
- use chemically reasonable sequence of rxns *(desired product = major)*
- if will get a mixture of products at any step, say so!
  ⇨ would have to purify the product before using in next step

PLANNING OUR SYNTHESIS:

1. **Compare the SM & target molecule**
   C skeleton: How do SM & target compare? Any clear "subunits"?
   Functional groups: Any new groups? Any groups present in both?
   Choose conditions that won't react with groups that remain unchanged.
2. **Is there an obvious set of reactions to get from SM to target?**
   - Try to add very reactive functional groups near the end.
3. **If there is no obvious forward plan: try to work backwards!**
   "RETROSYNTHETIC ANALYSIS"

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"Retrosynthetic analysis" (E.J.Corey, organic chemist - Nobel Laureate 1990)

Work backwards from the target molecule: *(see 6.12)*

→ **do you know any reactions that product that type of compound?**

e.g., a particular functional group:

an alcohol?	*Substitution, or hydration of alkene*
a nitrile?	*Substitution with Nu = CN^-*
a terminal alkyne?	*Substitution with Nu = $HC{\equiv}C^-$*

e.g., a particular regiochemistry or stereochemistry:

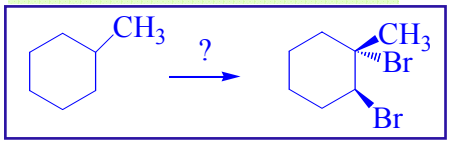
a primary alcohol adjacent to a 2° C?	*Alkene hydration – anti-Markov.*
vicinal dihalide with anti orientation?	*Alkene halogenation*
vicinal OH & X (= halohydrin)?	*Alkene halogenation in water*
a cyclic alkane with trans substituents (∴ cis H's!)?	*Alkene hydrogenation*

CONVENTIONAL WAY TO SHOW RETROSYNTHETIC ANALYSES:

→ **start with target & work backwards, 1 rxn at a time**
→ **use open arrows "⇒" to denote backwards steps**
→ **once you have a plan: write reactions in forward order & only THEN write in the reagents**

(NOTE: rxns don't need to balance, & don't include mechanistic details)

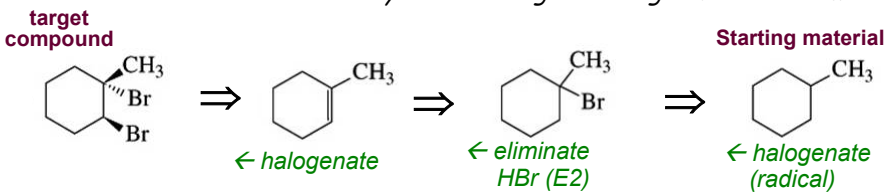
Design a synthesis for…



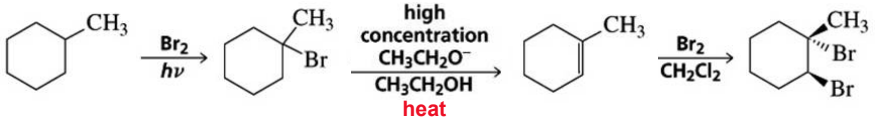
Can't do this in one step!
- SM = alkane (only rxn: halogenation)
- target = vicinal dihalide…

ANY IDEAS?

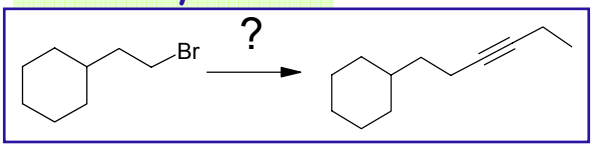
Retrosynthetic analysis: *(don't show reagents; helpful to note rxn types here, since you're thinking about regio & stereochem now!)*



Proposed synthetic route: *(show all reagents & conditions here)*



Another synthesis…

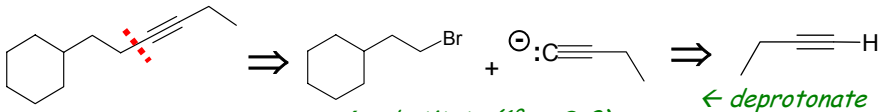


- SM = an alkyl halide
- target = an alkyne!

(so far: know RC≡C⁻ as Nu)

ANY IDEAS?

Retrosynthetic analysis: *(helpful to note rxn types – but not required)*

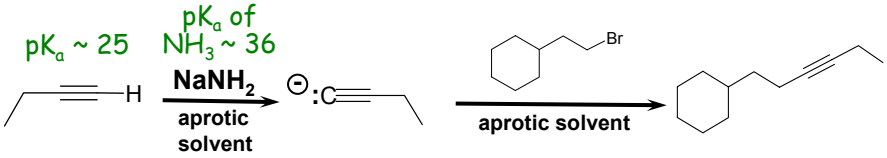


← substitute (1° ∴ S_N2) (avoid E2 competition? ok … S_N2 > E2 for 1°)

← deprotonate (need a base whose conjugate acid's pK_a > this)

pK_a ~ 25

Synthetic route: *(show all reagents & conditions)*



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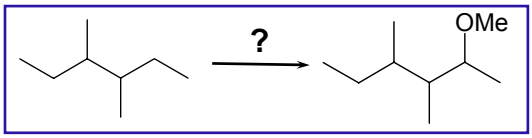
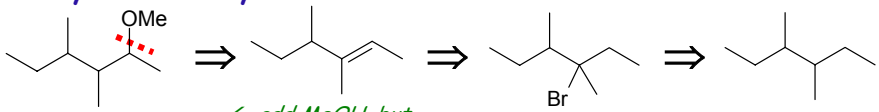
One last synthesis…

- SM = an alkane
- target = an ether
- same backbone…



Retrosynthetic analysis:

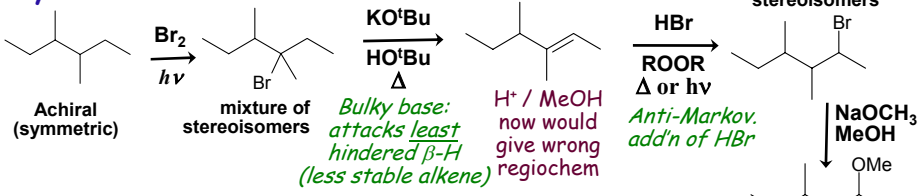


← add MeOH, but anti-Markovnikov??? Can't do this directly!

← eliminate HX, non-Zaitsev!

← brominate

Synthetic route:



Achiral (symmetric)

mixture of stereoisomers

Bulky base: attacks least hindered β-H (less stable alkene)

H⁺ / MeOH now would give wrong regiochem

Anti-Markov. add'n of HBr

mixture of stereoisomers (due to Br precursor)

Not the only possible route! *(can see a few more)*
e.g., from alkene: hydroboration → anti-Markov. ROH → deprotonate & react with CH_3I

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FINAL EXAM INFORMATION

Thurs. April 17th, 7-10 pm, CC-408

Exam room: allowed: models (prebuilt), calculator
forbidden: cell phones, e-dictionaries, *etc*

Cumulative: will drop midterm if do better on final exam

Format: a few: MC or T/F or circle correct word
mostly: explanations
drawings
predict products/reactants
mechanisms
synthesis

Samples: http://faculty.concordia.ca/rogers (Teaching, 221)