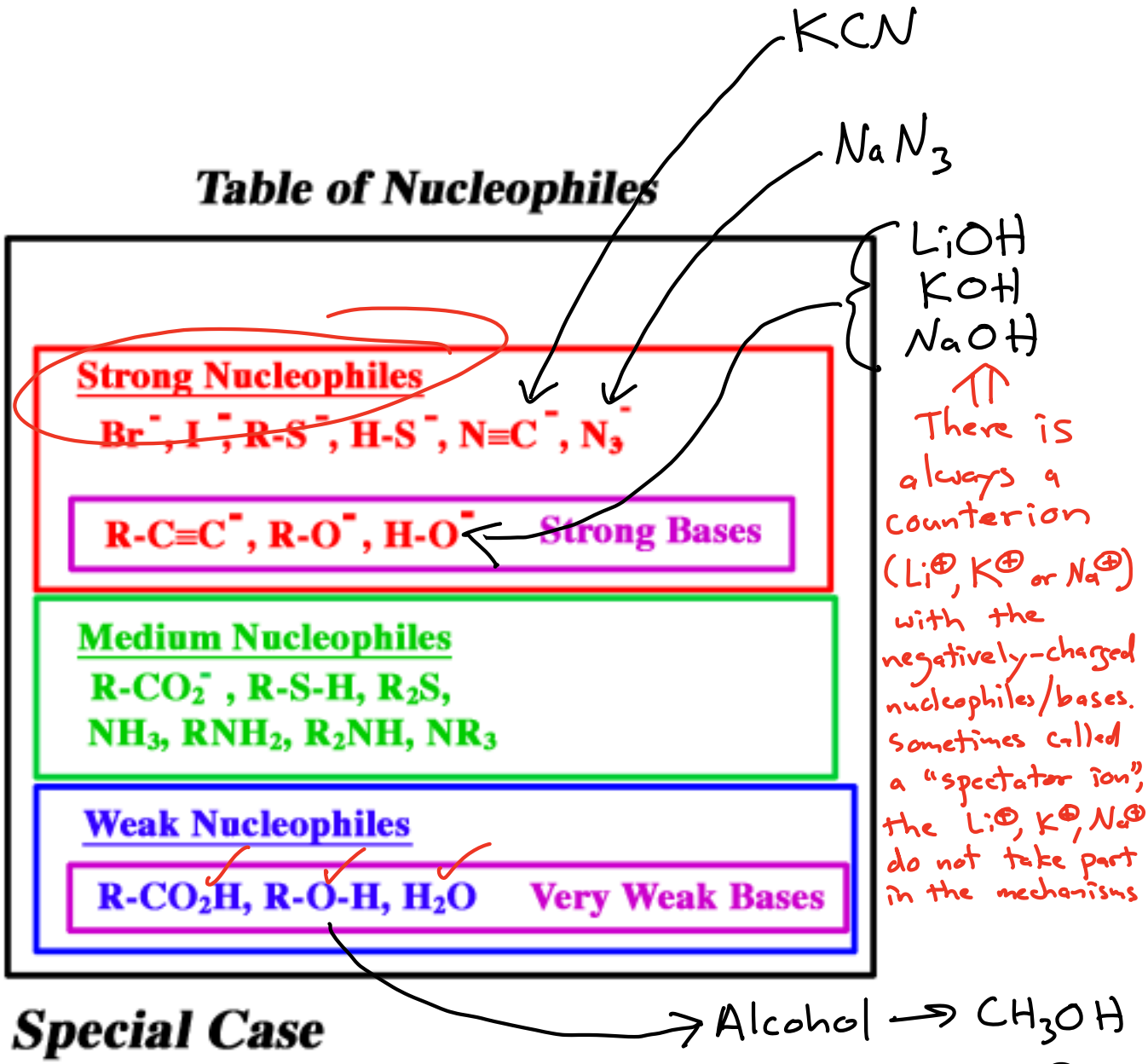
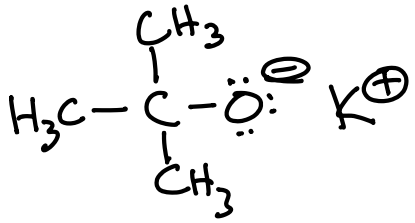
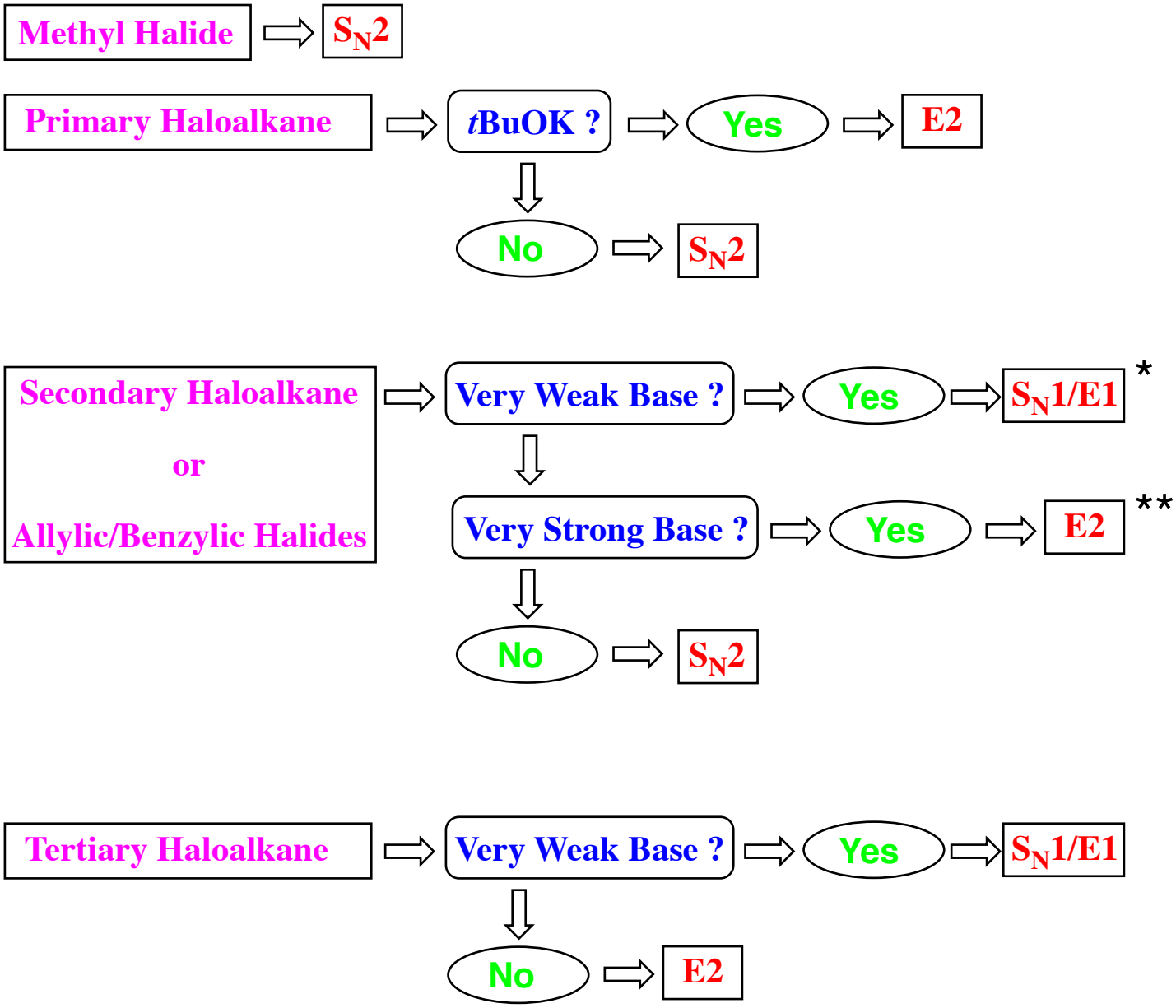




"KOtBu" or "tBuO⊖"

Substitution/Elimination Decision Map



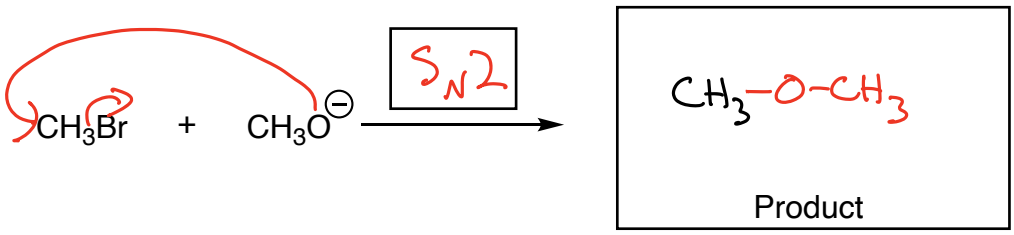
For S_N2 Remember Chiral Center InVERSiON
For E2 Remember anti-periplanar and Zaitsev
For S_N1 Remember Chiral Center Scrambling
For E1 Remember Zaitsev

* Note: With Very Weak Bases, SN2 can compete here, but for the purposes of this class, assume SN1 / E1 predominate

** Note: If tBuOK is the very strong base, an appreciable amount of a non-Zaitsev product can be formed because the bulky tBuOK will tend to react with the most accessible H atom.

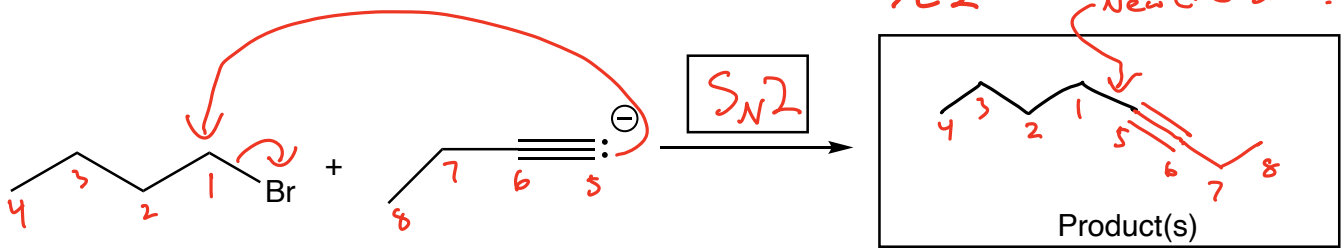
Substitution vs. Elimination Examples:

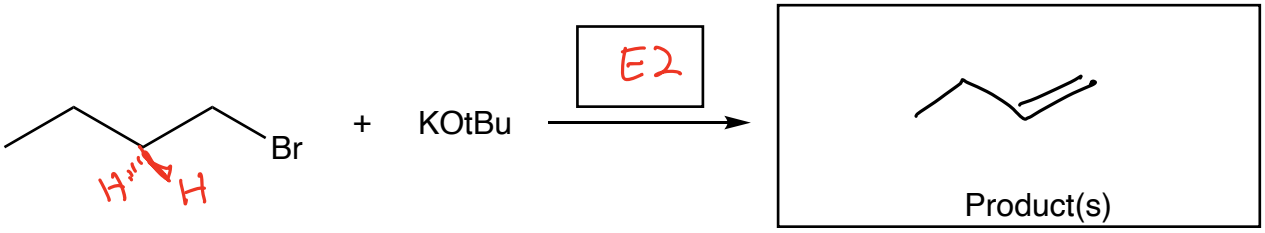
Methyl Haloalkanes (CH_3X) → Only S_N2 is possible



Primary (1°) Haloalkanes

S_N2 with all but KOtBu ($tBuO^{\ominus}K^{\oplus}$) → E2

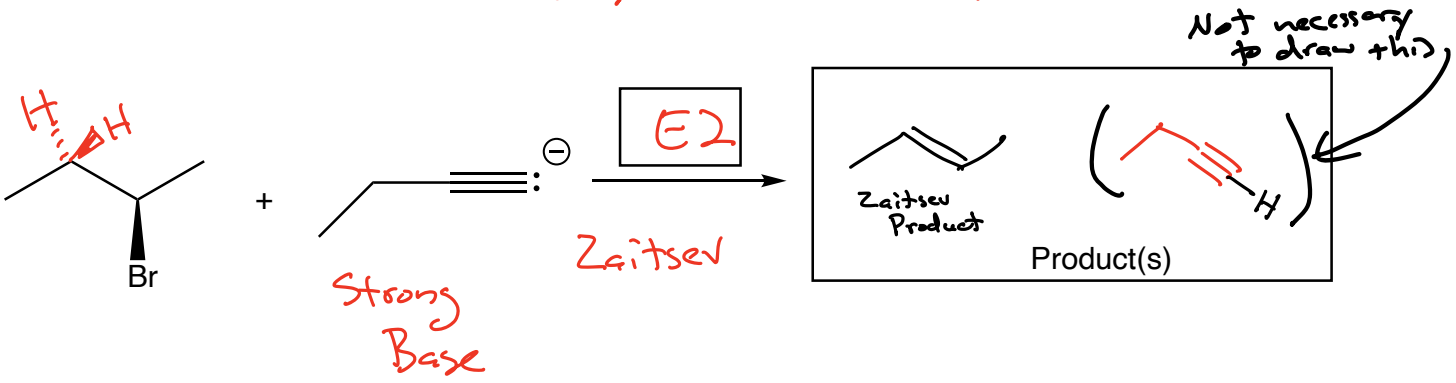


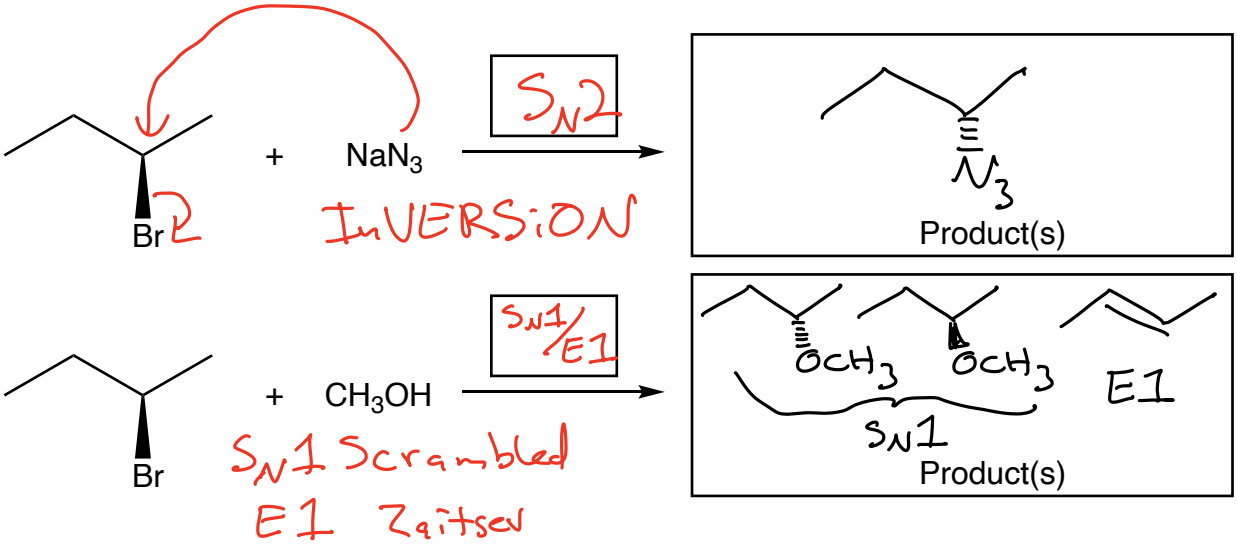


Secondary (2°) Haloalkanes → S_N2 with all but strong bases or very weak bases

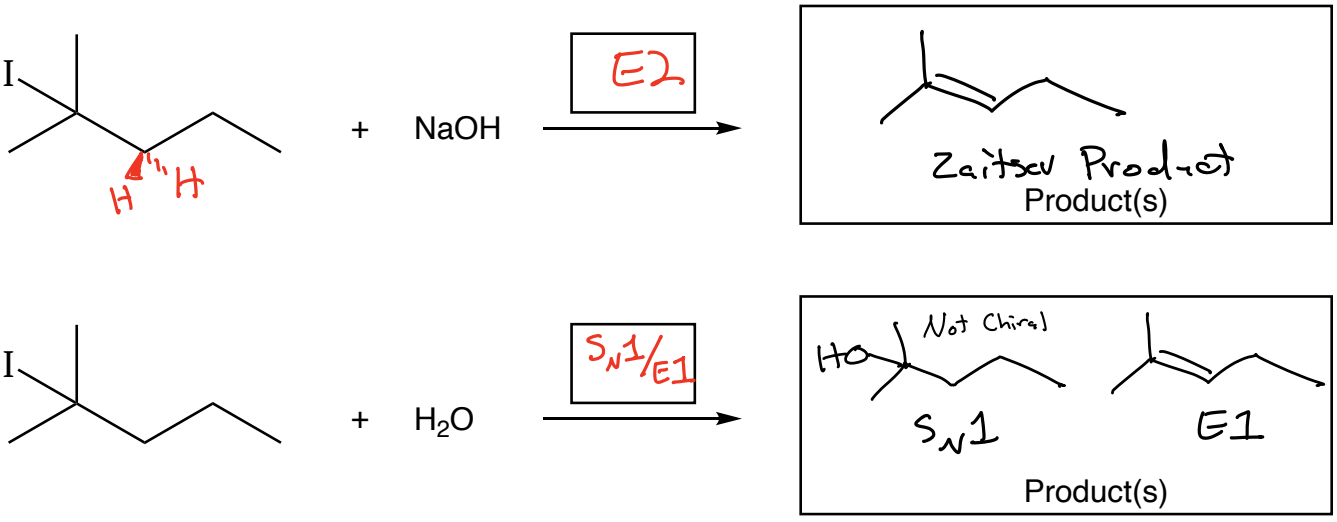
→ E2 with strong bases

→ S_N1/E1 with very weak bases

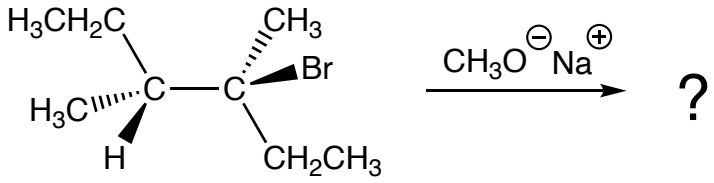




Tertiary (3°) Haloalkanes

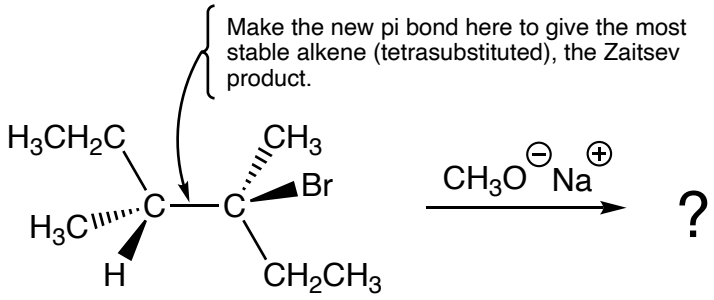


E2 Reaction Considerations:



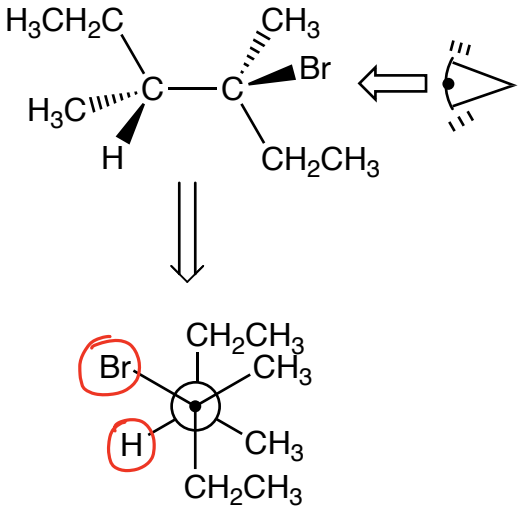
When analyzing highly substituted haloalkanes for a possible E2 reaction:

1. **You need to identify the most stable possible alkene (most highly substituted, *trans* over *cis*) that could be made (Zaitsev product).**



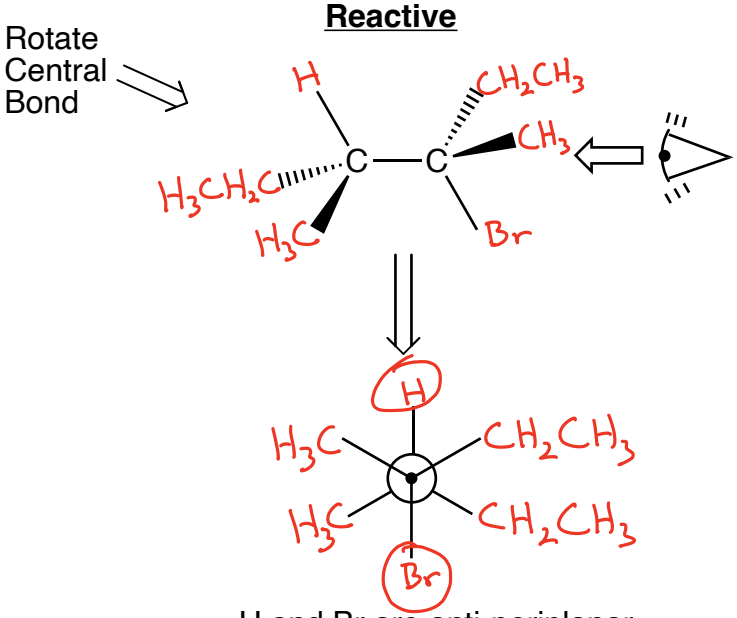
2. **Given the Zaitsev product you have identified, verify which anti-periplanar H atom(s) can be removed during the reaction to determine whether the product is E or Z.**
3. **You often need to rotate bonds to identify the particular H atom and configuration that reacts to give the alkene product.**

Not Reactive



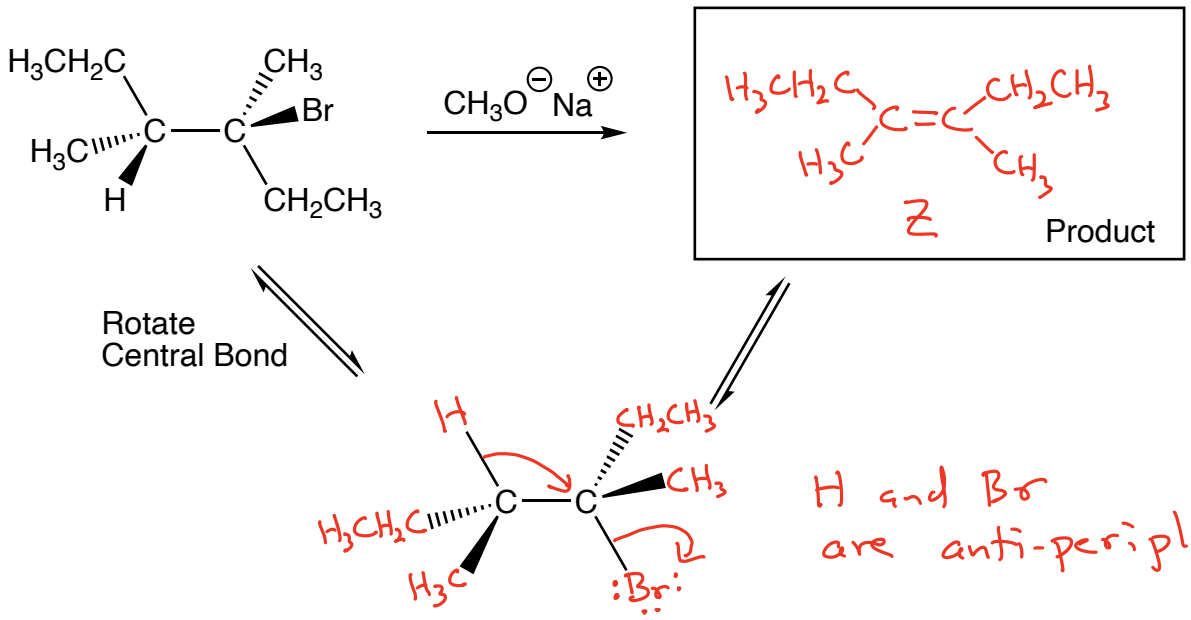
H and Br **not** anti-periplanar

Reactive

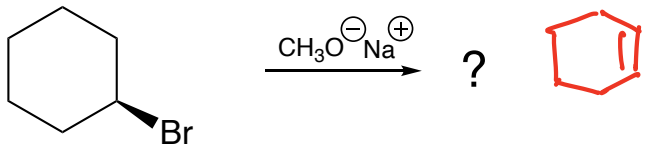


H and Br are anti-periplanar

Putting it all together:

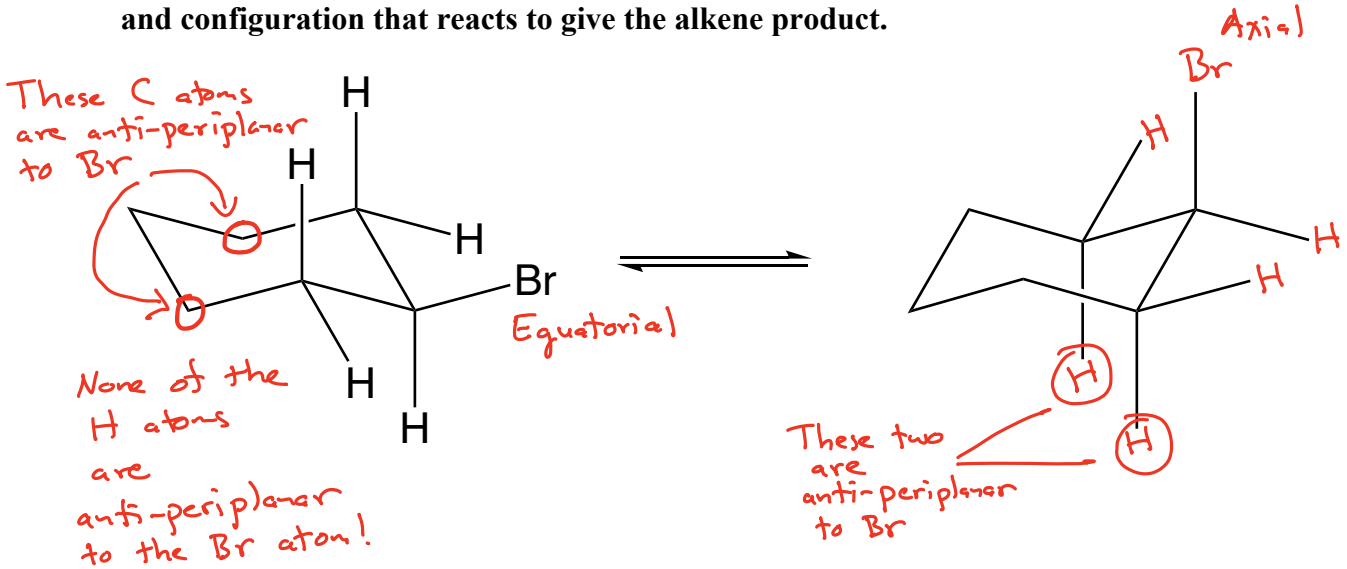


E2 Reaction of cyclohexane derivatives:



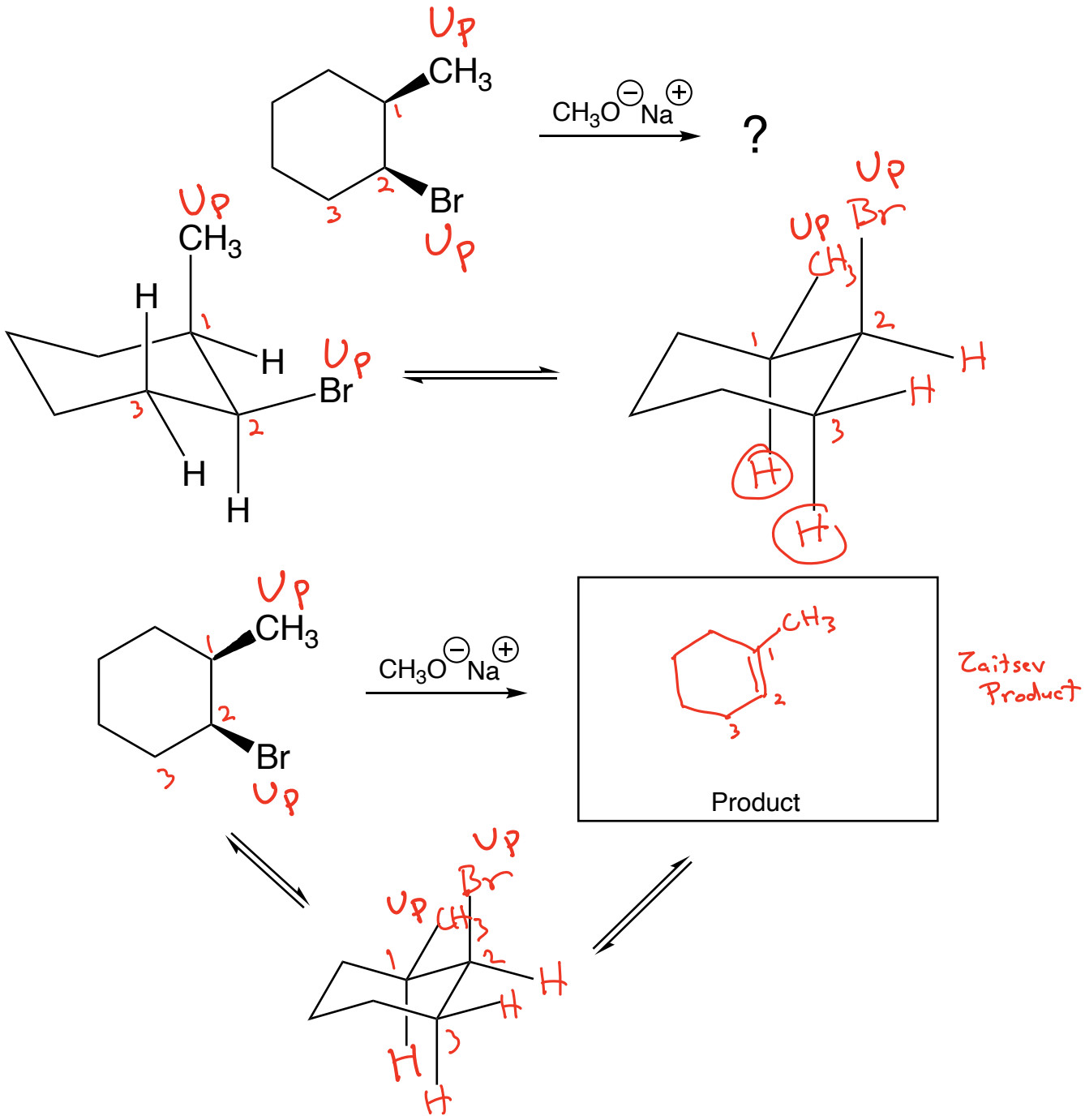
When analyzing highly substituted haloalkanes for a possible E2 reaction:

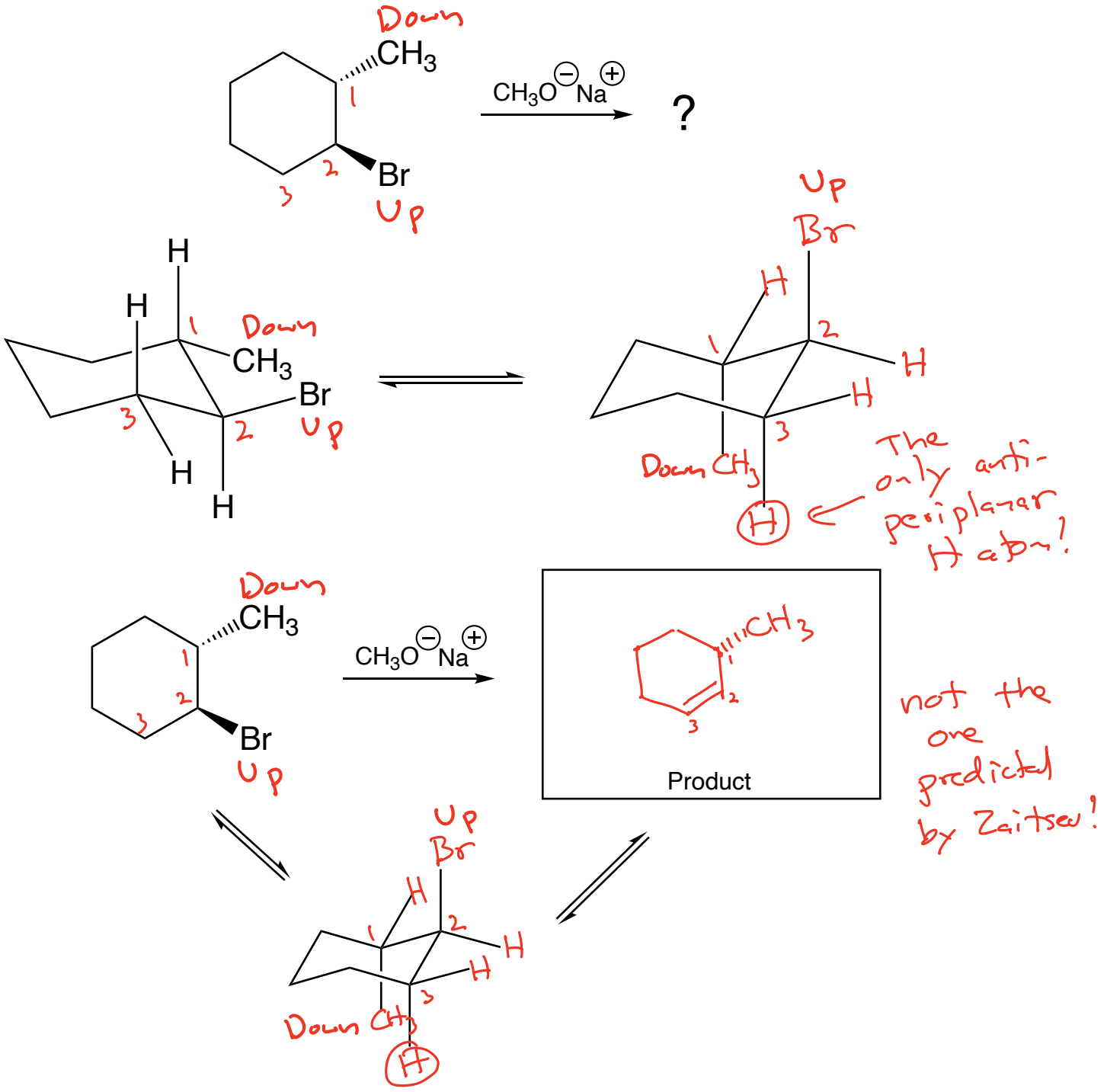
1. **You need to identify the most stable possible alkene (most highly substituted, *trans* over *cis*) that could be made (Zaitsev product).**
2. **Given the Zaitsev product you have identified, verify which anti-periplanar H atom(s) can be removed during the reaction to determine if that product can be made.**
3. **You often need to flip chairs in cyclohexane derivatives to identify the particular H atom and configuration that reacts to give the alkene product.**



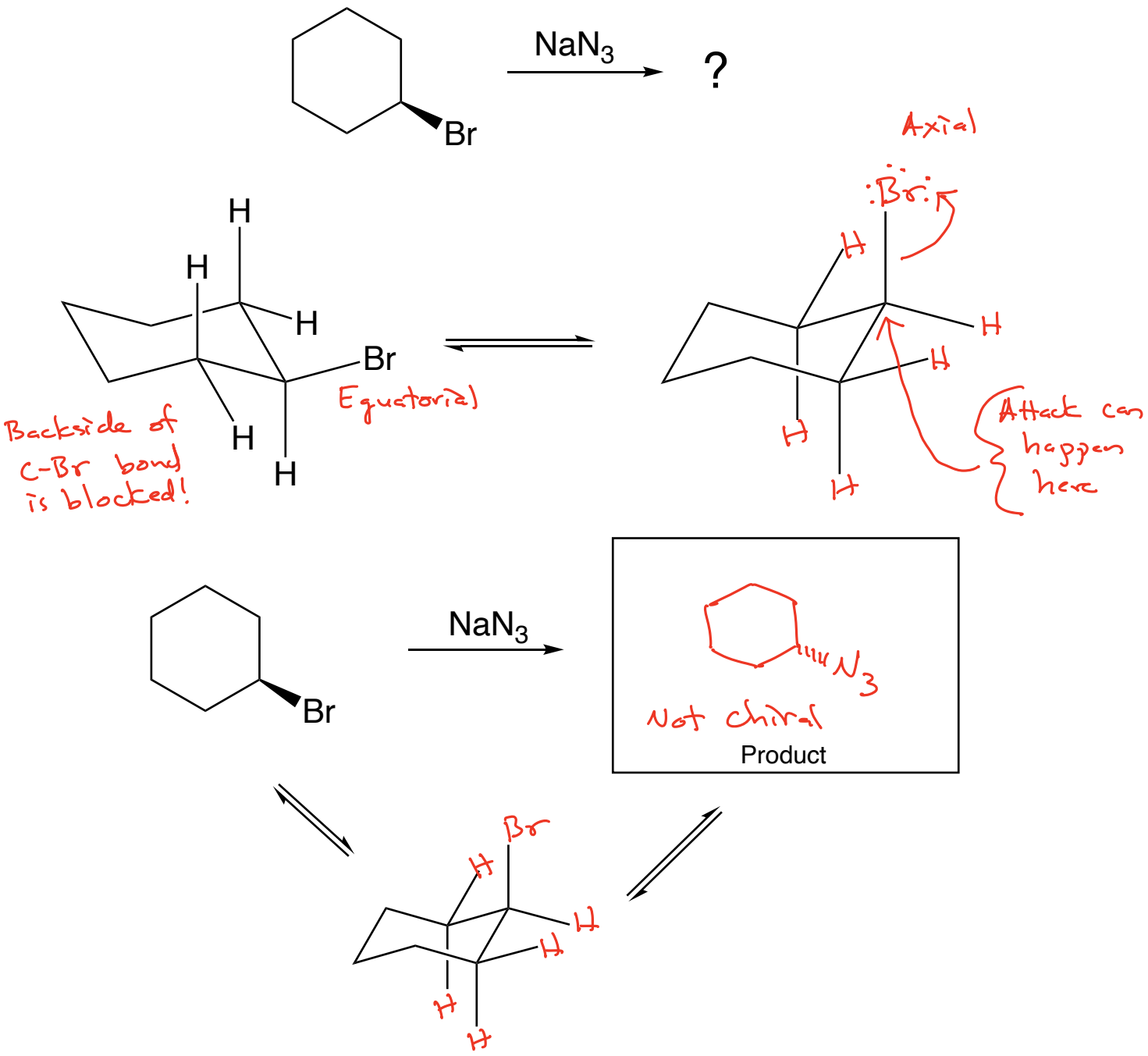
Rule: The halogen must be axial to react via E2 in cyclohexane derivatives

Classic Examples:




Down
CH3
1
2
3
Br
Up
CH3O Na
?
H
H
1
Down
CH3
Br
Up
3
2
H
H
Up
Br
H
1
2
H
H
3
Down CH3
H
The only anti-periplanar H atom!
Down
CH3
1
2
3
Br
Up
CH3O Na
CH3
1
2
3
Product
not the one predicted by Zaitsev!
Up
Br
H
1
2
H
H
3
Down CH3
H

S_N2 Reactions of Cyclohexanes:



Rule: The halogen must be axial to react in an S_N2 mechanism in a cyclohexane derivative.

Geminal
Dihaloalkanes

Vicinal
Tetrahaloalkanes

Alkynes

Aldehydes/Ketones

Vicinal
Dihaloalkanes

Vicinal
Diols

Alkenes

Alcohols

Halohydrins

Haloalkanes

Alkanes

Geminal Dihaloalkanes

Vicinal Tetrahaloalkanes

Alkynes (DFW)

Aldehydes/Ketones

R-C≡C-H Terminal 1) 3 $NaNH_2$ 2) H_2O, H_2O

R-C≡C-R Internal 2 $NaNH_2$

Double E2

Vicinal Dihaloalkanes (Waco)

Vicinal Diols

X_2 (Br_2, Cl_2) Anti 3-membered ring

Alkenes (ATX)

Alcohols

Adsorption on metal surface Pt^0, Pd^0, Ni^0 H_2

$Na^\bullet$ NH_3 Radical E product

Lindlar Catalyst Z product H_2 syn

Adsorption on metal surface Pt^0, Pd^0, Ni^0 H_2 syn

H-X (Cl, Br, I) Markovnikov, Mixed, Carbocation

H-Br ROOR hv or heat non-Markovnikov, Radical

Strong Base E2 Anti-periplanar TS Zaitsev's Rule

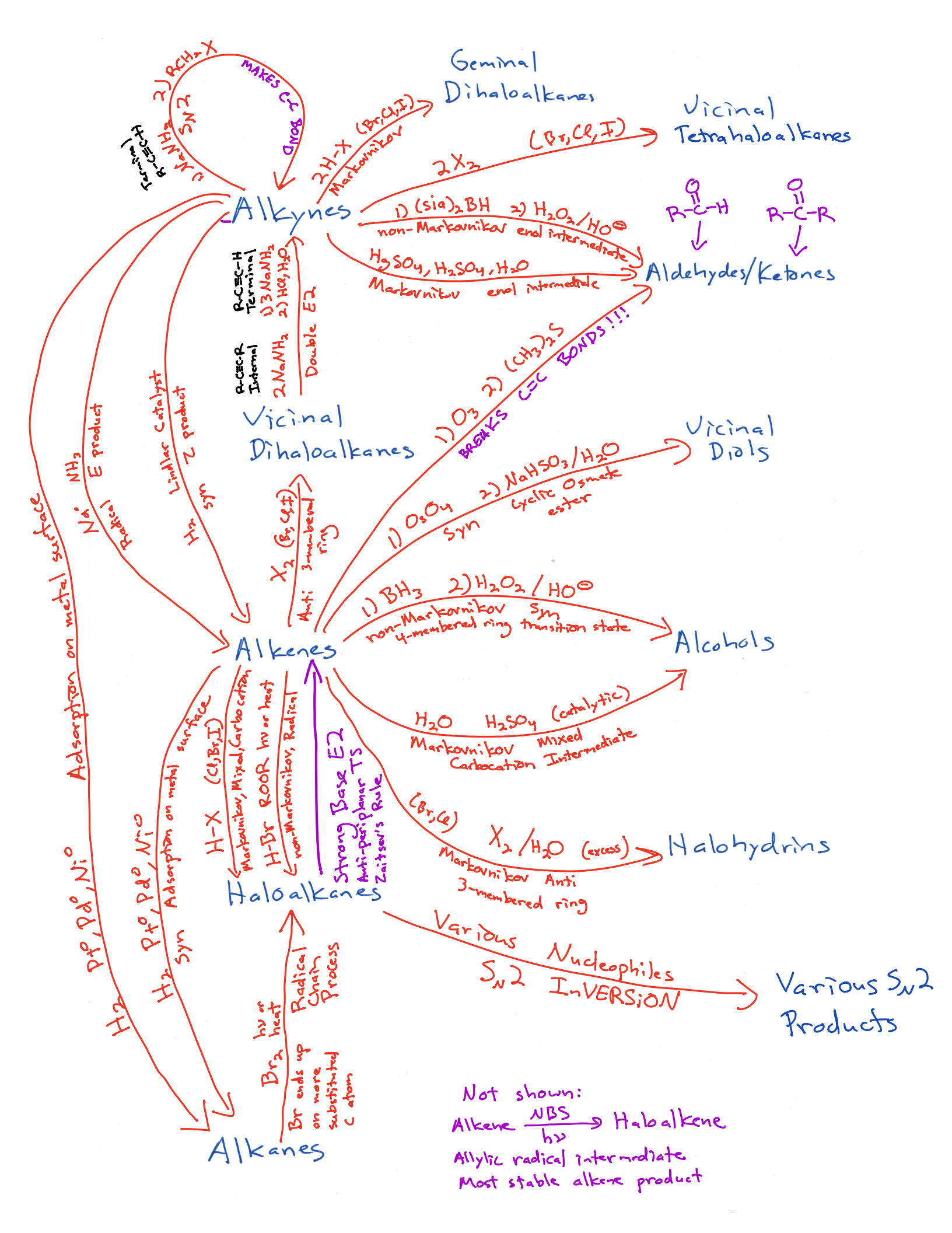
Halohydrins

Haloalkanes (S.M., N.B.)

Br_2 hv or heat Radical Chain Process Br ends up on more substituted C atom

Various S_N2 Products

Alkanes (San Antonio)


Terminal R-C≡C-H
1) NaNH2
2) RCH2-X
SN2
MAKES C-C
ANOG
Alkynes
2H-X (Br,Cl,I)
Markovnikov
Geminal Dihaloalkanes
2X2 (Br,Cl,I)
Vicinal Tetrahaloalkanes
1) (sia)2BH 2) H2O2/HO⊖
non-Markovnikov enol intermediate
H2SO4, H2SO4, H2O
Markovnikov enol intermediate
Aldehydes/Ketones
R-C(=O)-H
R-C(=O)-R
R-C≡C-H Terminal
1) 3 NaNH2
2) H⊕, H2O
R-C≡C-R Internal
2 NaNH2
Double E2
Vicinal Dihaloalkanes
1) O3 2) (CH3)2S
BREAKS C=C BONDS!!!
1) OsO4
Syn
2) NaHSO3/H2O
cyclic Osmate ester
Vicinal Diols
X2 (Br,Cl,I)
Anti
3-membered ring
Alkenes
1) BH3 2) H2O2/HO⊖
non-Markovnikov
4-membered ring transition state
Syn
Alcohols
H2O H2SO4 (catalytic)
Markovnikov
Mixed Carbocation Intermediate
(Br,Cl)
X2/H2O (excess)
Halohydrins
Markovnikov Anti
3-membered ring
Adsorption on metal surface
Pt°, Pd°, Ni°
H2
Syn
Adsorption on metal surface
Pt°, Pd°, Ni°
H2
Syn
Radical
Na° NH3
E product
Lindlar Catalyst
Z product
H2 syn
H-X (Cl,Br,I)
Markovnikov, Mixed Carbocation
H-Br ROOR hv or heat
non-Markovnikov, Radical
Strong Base E2
Anti-periplanar TS
Zaitsev's Rule
Haloalkanes
Various Nucleophiles
SN2
INVERSION
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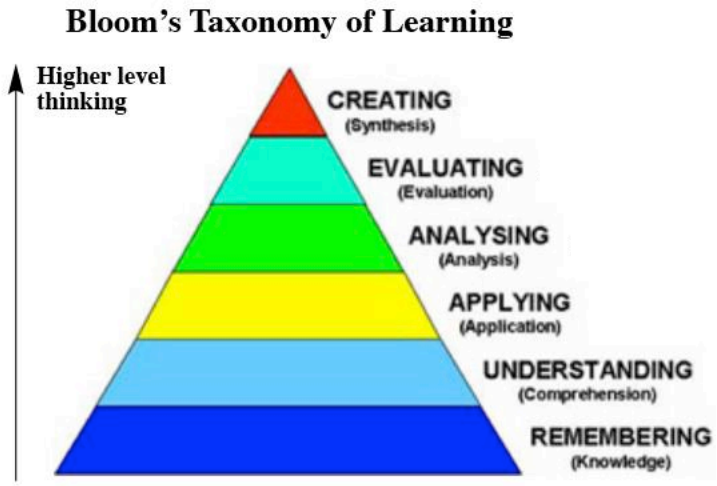
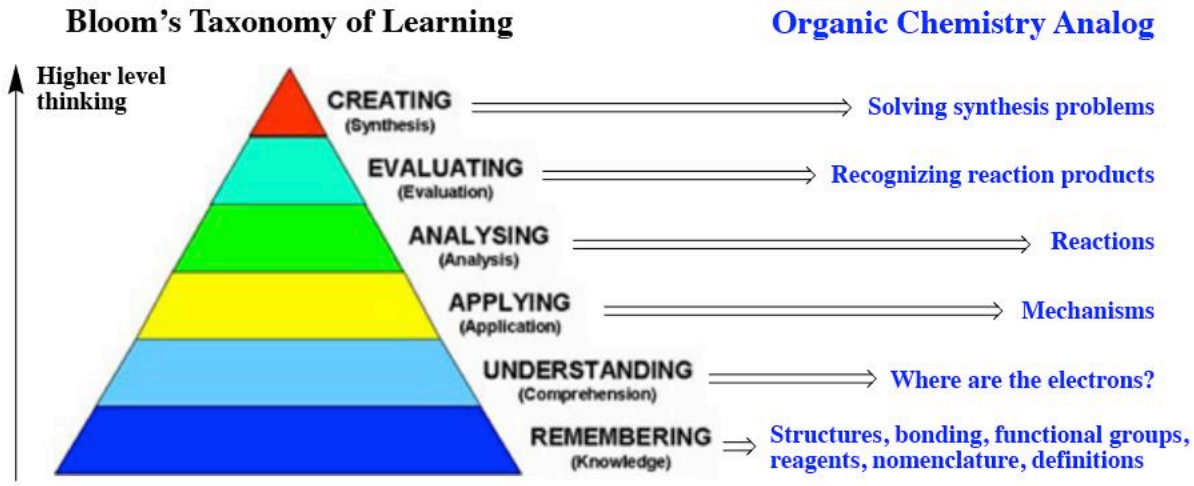
Br2
hv or heat
Radical Chain Process
Br ends up on more substituted C atom
Alkanes
Not shown:
Alkene NBS / hν → Haloalkene
Allylic radical intermediate
Most stable alkene product





A) **You must have your entire roadmap learned** so you can recite the NIRRS parameters for each reagent, i.e. Nature of overall transformation ("locations" on the roadmap), the Intermediate or transition state (carbocation, anti-periplanar etc.), the Reagents and how to designate them, as well as any Regiochemistry (Markovnikov, etc.) and any appropriate Stereochemistry (syn, anti, InVERSiON, scrambled, etc).

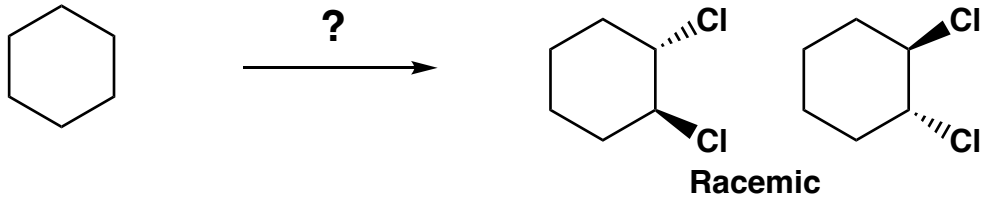
B) **Work backwards** (learn to RECOGNIZE the appropriate reagents and starting materials by looking at the products) from the final product. DO NOT try to work forward from the starting materials. Please trust me on this.

C) **Count carbons** in the starting material(s) and product(s) to see if any carbon-carbon bonds need to be broken or made, thereby zeroing in on key steps. This will be far more important next semester, so you should get used to doing this now.

D) **Pretty much all synthesis problems in OChem 1 involve traveling "north or south" on the so-called "I-35"** reactions (alkanes SA, haloalkanes NB/SM, alkenes ATX, vicinal dihaloalkanes Waco, alkynes DFW) at least part way at some point during the synthesis. This is not a promise or a rule, just an observation.

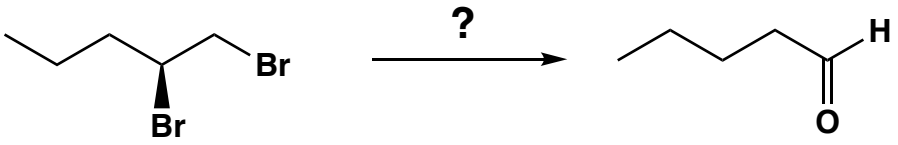
20. These are synthesis questions. You need to show how the starting material can be converted into the product(s) shown. You may use any reactions we have learned provided that the product(s) you draw for each step is/are the predominant one(s). Show all the reagents you need. Show each molecule synthesized along the way and be sure to pay attention to the regiochemistry and stereochemistry preferences for each reaction. You must draw all stereoisomers formed, and use wedges and dashes to indicate chirality at each chiral center. Write racemic when appropriate. **All the carbons of the product must come from carbons of the starting material.**

A) (7 pts)



Racemic

B) (4 pts)



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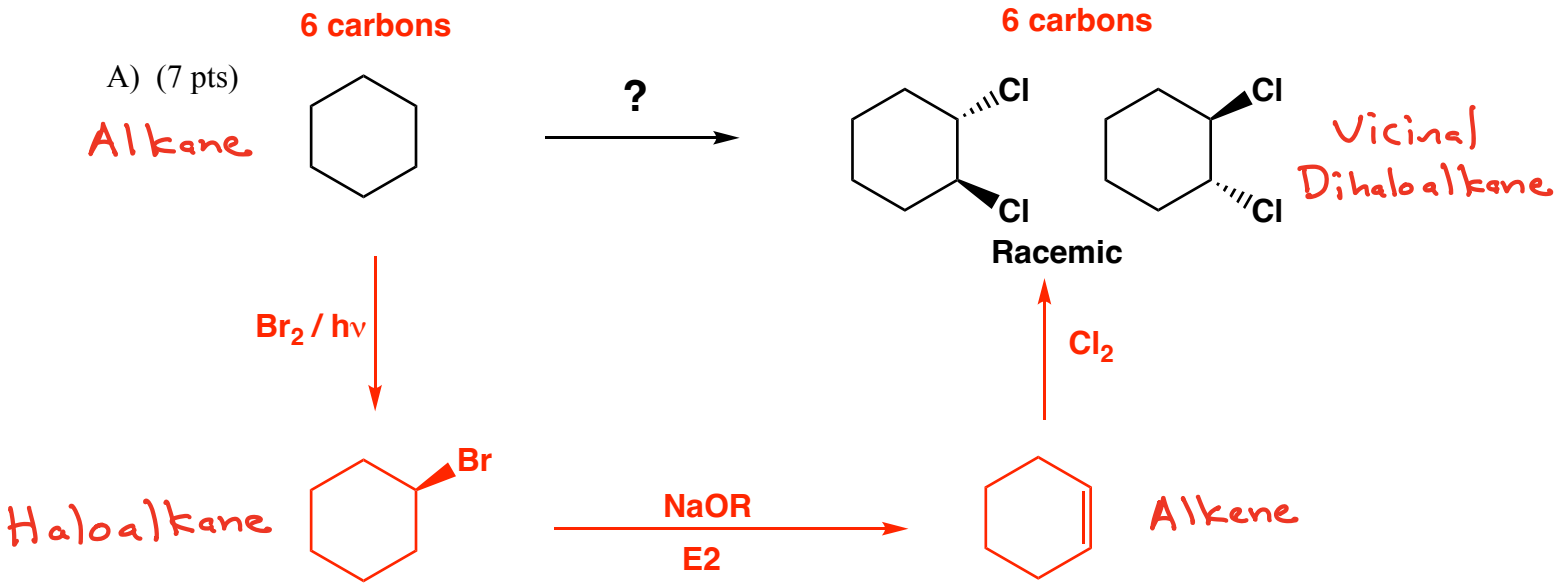
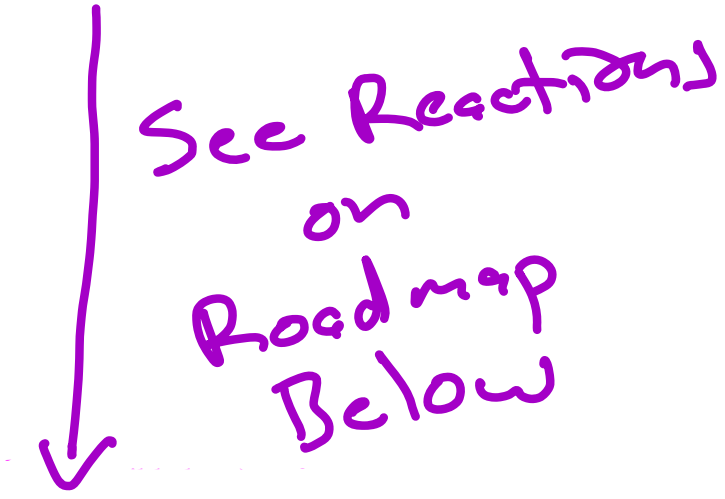
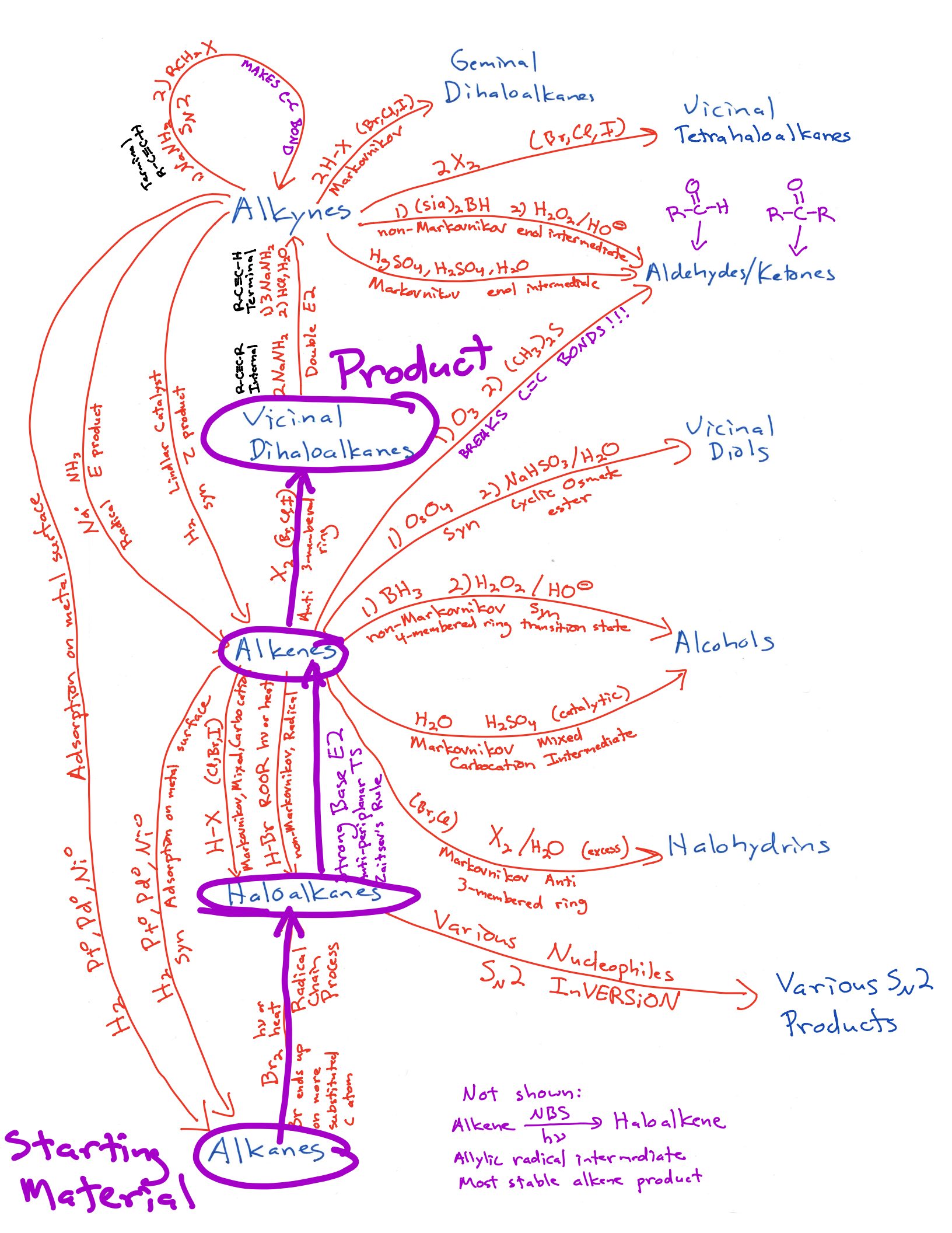


Recognize: The product is a *trans* dichlorocyclohexane tht must result from the reaction of an alkene (cyclohexene) with Cl_2. **Recognize**: The cyclohexene comes from the usual "I-35" combination of halogenation of an alkane with light (the only reaction that uses an alkane starting material) followed by an E2 in strong base such an alkoxide (NaOR).




Terminal R-C≡C-H
1) NaNH2
2) R-CH2-X
SN2
MAKES C-C BONDS
Alkynes
Geminal Dihaloalkanes
2 H-X (Br, Cl, I)
Markovnikov
Vicinal Tetrahaloalkanes
2 X2 (Br, Cl, I)
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Markovnikov enol intermediate
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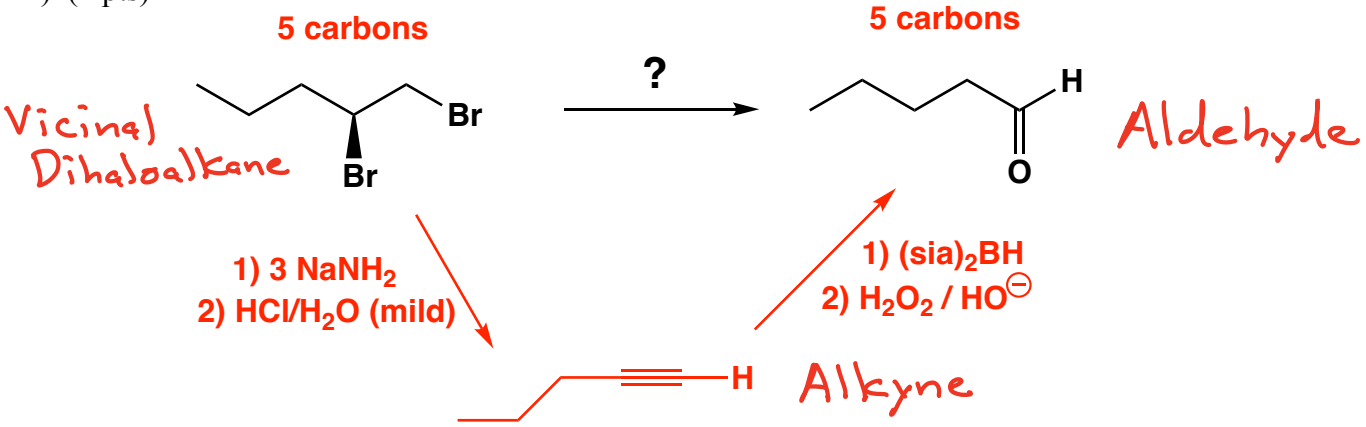
R-C(=O)-H
R-C(=O)-R
R-C≡C-H Terminal 1) 3 NaNH2 2) H⊕, H2O
R-C≡C-R Internal 2 NaNH2
Double E2
Product
Vicinal Dihaloalkanes
1) O3 2) (CH3)2S
BREAKS C=C BONDS!!!
1) OsO4 2) NaHSO3/H2O
Syn
cyclic Osmate ester
Vicinal Diols
X2 (Br, Cl)
Anti
3-membered ring
1) BH3 2) H2O2/HO⊖
non-Markovnikov Syn
4-membered ring transition state
Alcohols
Alkenes
H2O H2SO4 (catalytic)
Markovnikov Mixed Carbocation Intermediate
(Br, Cl) X2/H2O (excess)
Markovnikov Anti
3-membered ring
Halohydrins
H-X (Cl, Br, I)
Markovnikov, Mixed, Carbocation
H-Br ROOR hv or heat
non-Markovnikov, Radical
Strong Base E2
Anti-periplanar TS
Zaitsev's Rule
Haloalkanes
Various Nucleophiles
SN2 INVERSION
Various SN2 Products
Br2 hv or heat
Radical Chain Process
Br ends up on more substituted C atom
Alkanes
Starting Material
H2 Pt°, Pd°, Ni°
Adsorption on metal surface
Syn
Na° NH3
E product
Radical
H2 Pt°, Pd°, Ni°
Adsorption on metal surface
Lindlar Catalyst
Z product
Syn
Not shown:
Alkene NBS / hν → Haloalkene
Allylic radical intermediate
Most stable alkene product

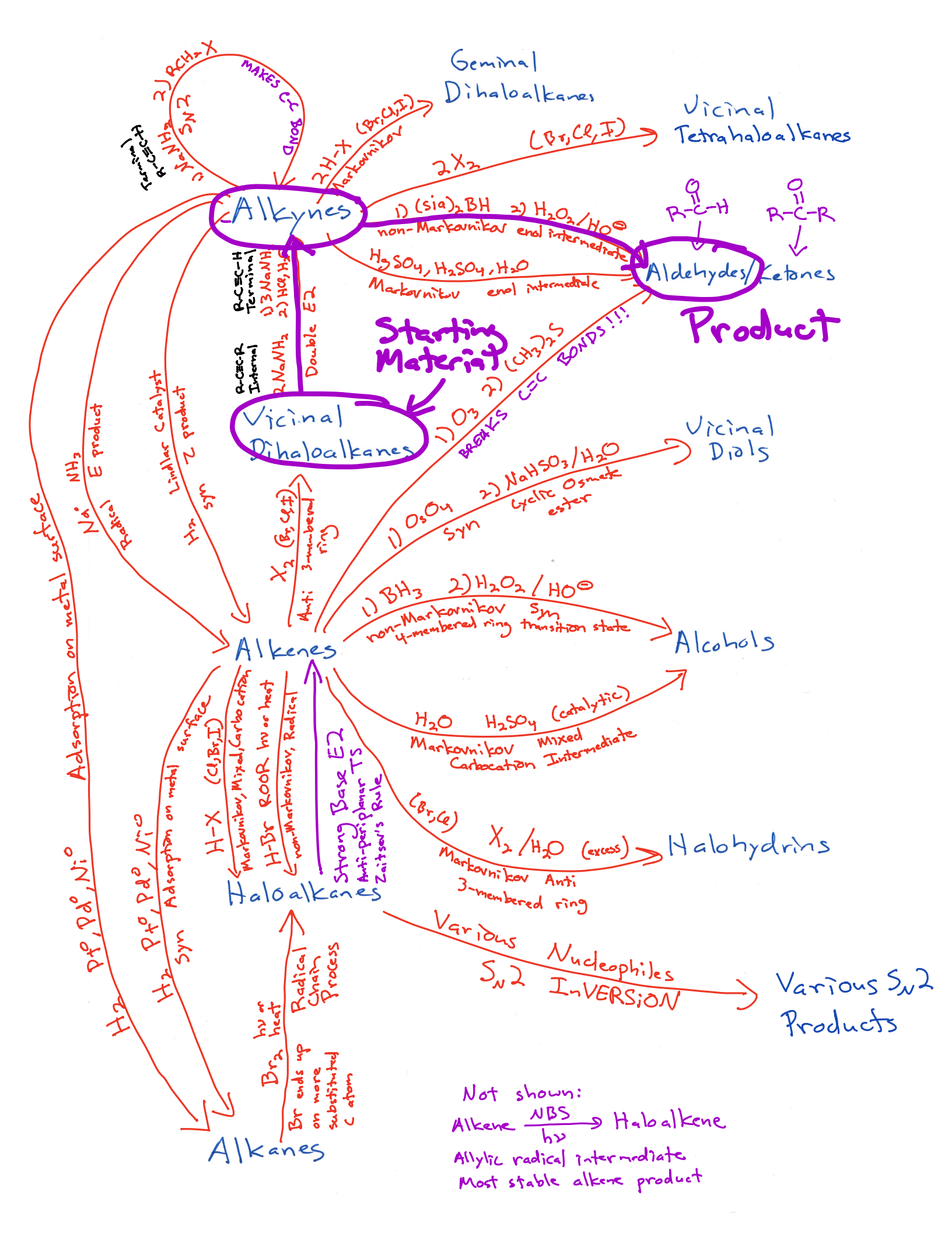
20. These are synthesis questions. You need to show how the starting material can be converted into the product(s) shown. You may use any reactions we have learned provided that the product(s) you draw for each step is/are the predominant one(s). Show all the reagents you need. Show each molecule synthesized along the way and be sure to pay attention to the regiochemistry and stereochemistry preferences for each reaction. You must draw all stereoisomers formed, and use wedges and dashes to indicate chirality at each chiral center. Write racemic when appropriate. **All the carbons of the product must come from carbons of the starting material.**

B) (4 pts)



Recognize: The product is an aldehyde that can be made from a primary alcohol, ozonolysis of an alkene (breaks carbon-carbon bond so not possible here) or from an alkyne. Choose the latter because an alkyne can be made from the starting vicinal dihaloalkane using base, in this case three equivalents of $NaNH_2$ followed by mild acid workup because the product is a terminal alkyne.

See Reactions on Roadmap Below


Alkynes
Terminal R-C≡C-H
1) NaNH2
2) RCH2-X
SN2
MAKES C-C
DOES NOT
R-C≡C-R Internal
1) 3 NaNH2
2) H2O, H3O+
Double E2
Geminal Dihaloalkanes
2 H-X (Br, Cl, I)
Markovnikov
Vicinal Tetrahaloalkanes
(Br, Cl, I)
2 X2
1) (sia)2BH 2) H2O2/HO⊖
non-Markovnikov enol intermediate
H2SO4, H2SO4, H2O
Markovnikov enol intermediate
Aldehydes/Ketones
Starting Material
Product
Vicinal Dihaloalkanes
1) O3 2) (CH3)2S
BREAKS C=C BONDS!!!
1) OsO4 2) NaHSO3/H2O
Syn
cyclic Osmate ester
Vicinal Diols
X2 (Br, Cl, F)
Anti
3-membered ring
Alkenes
1) BH3 2) H2O2/HO⊖
non-Markovnikov
4-membered ring transition state
Syn
Alcohols
H2O H2SO4 (catalytic)
Markovnikov
Mixed Carbocation Intermediate
(Br, Cl)
X2/H2O (excess)
Markovnikov
Anti
3-membered ring
Halohydrins
H-X (Cl, Br, I)
Markovnikov, Mixed, Carbocation
H-Br ROOR hv or heat
non-Markovnikov, Radical
Strong Base E2
Anti-periplanar TS
Zaitsev's Rule
Haloalkanes
Various Nucleophiles
SN2
INVERSION
Various SN2 Products
Br2
hv or heat
Radical Chain Process
Br ends up on more substituted C atom
H2
Pt°, Pd°, Ni°
Adsorption on metal surface
Syn
Alkanes
Na°
NH3
E product
Radical
Lindlar Catalyst
Z product
H2
syn
Not shown:
Alkene —NBS, hν→ Haloalkene
Allylic radical intermediate
Most stable alkene product