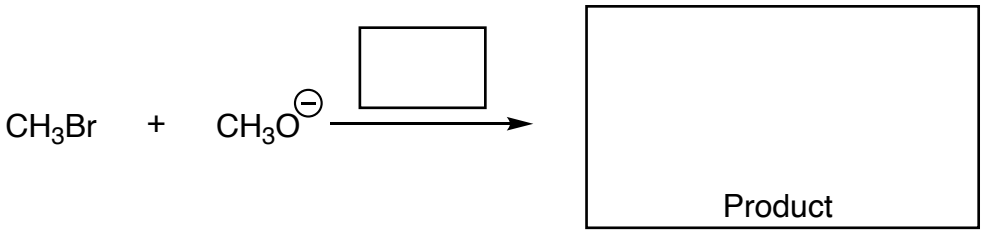
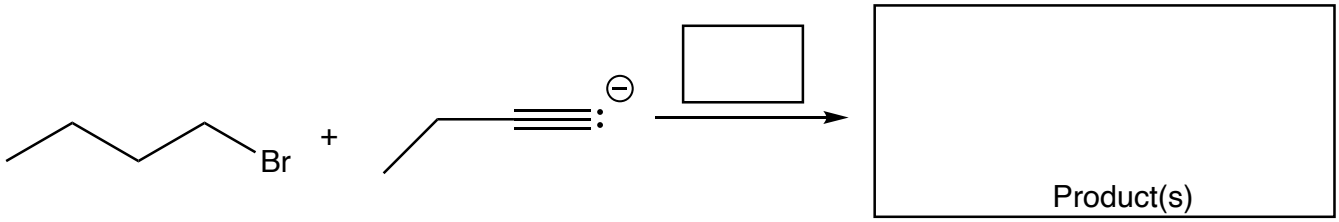
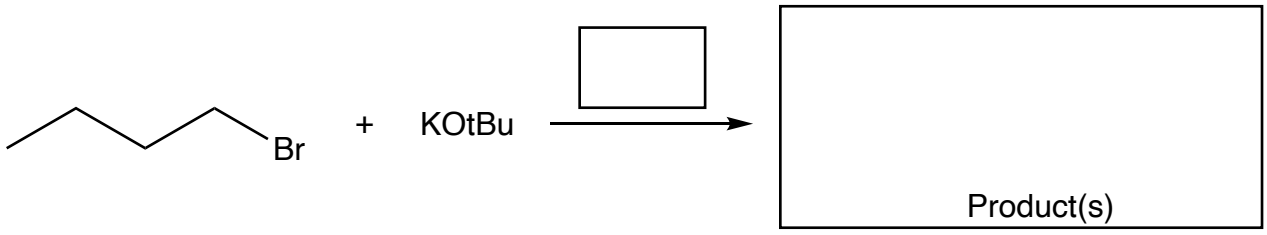
Substitution vs. Elimination Examples:

Methyl Haloalkanes (CH_3X)

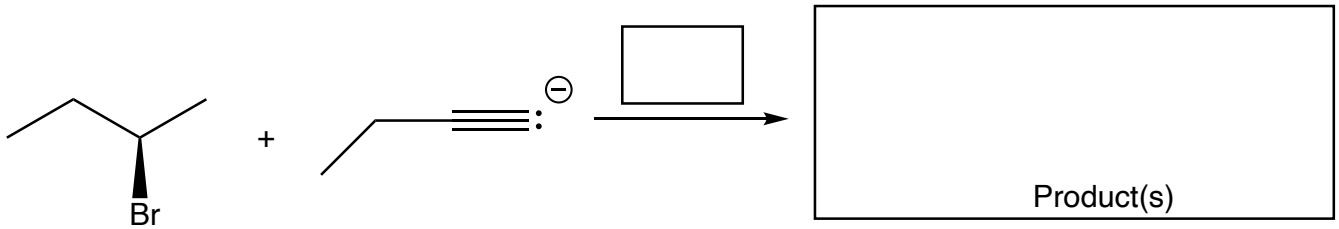


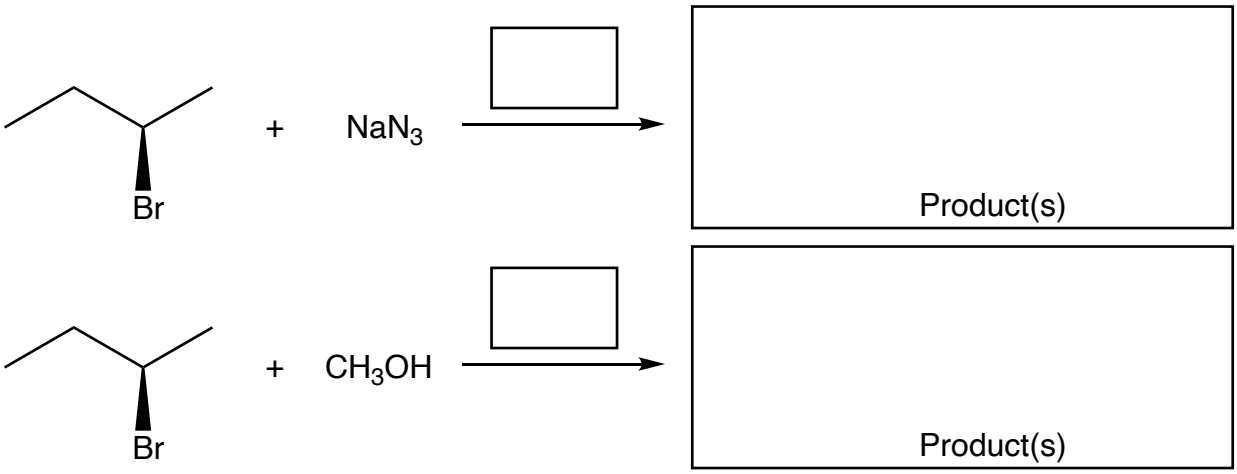
Primary (1°) Haloalkanes



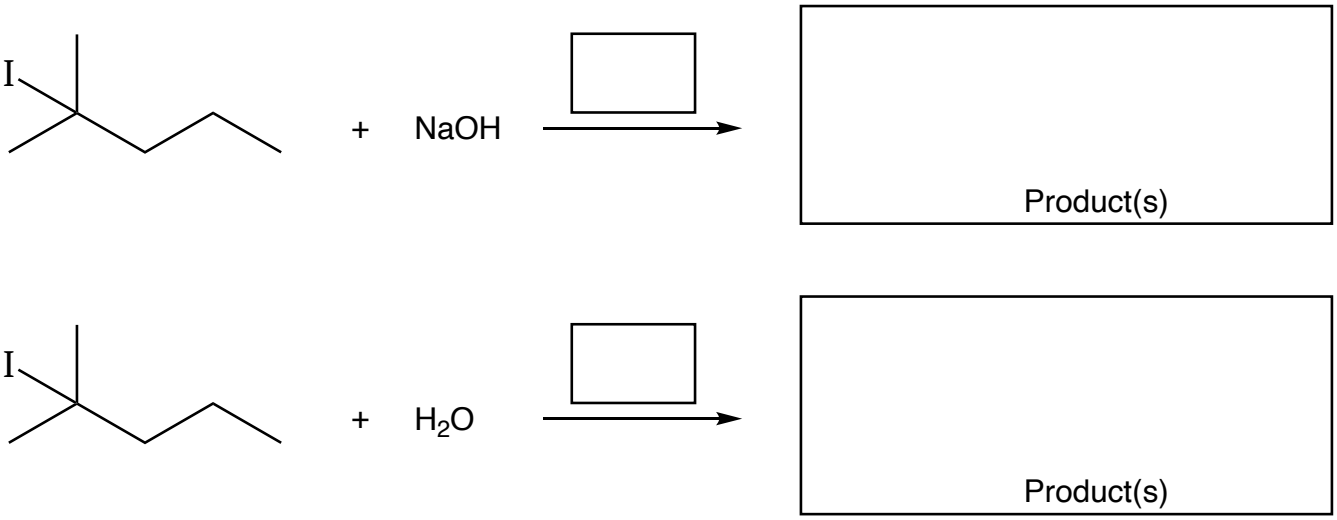


Secondary (2°) Haloalkanes

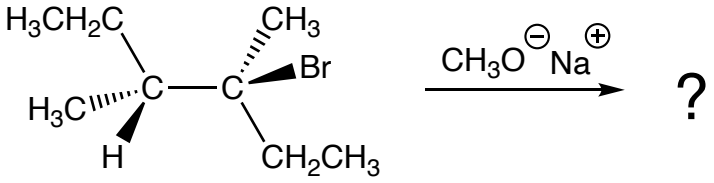




Tertiary (3°) Haloalkanes

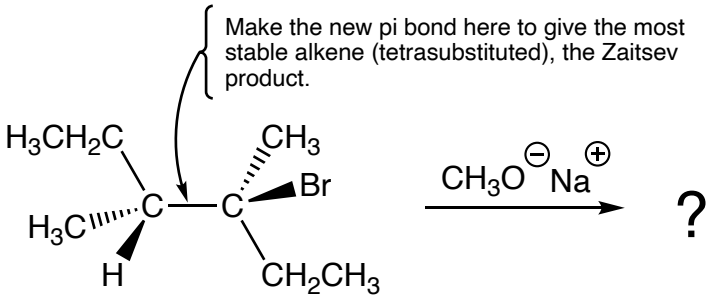


E2 Reaction Considerations:

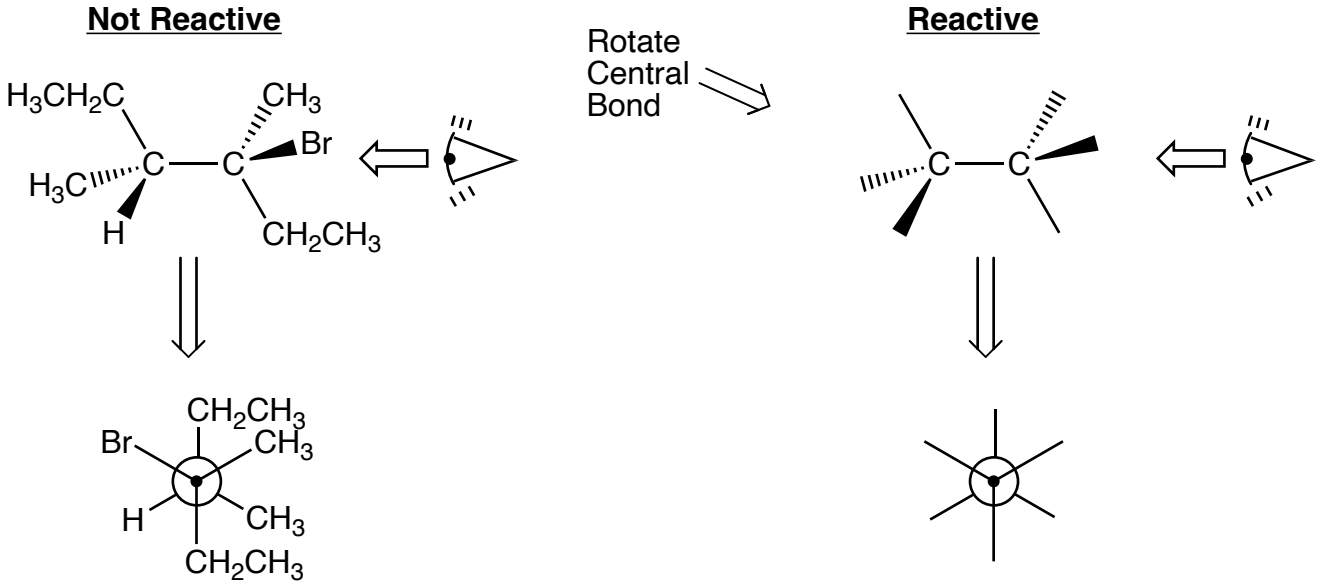


When analyzing highly substituted haloalkanes for a possible E2 reaction:

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



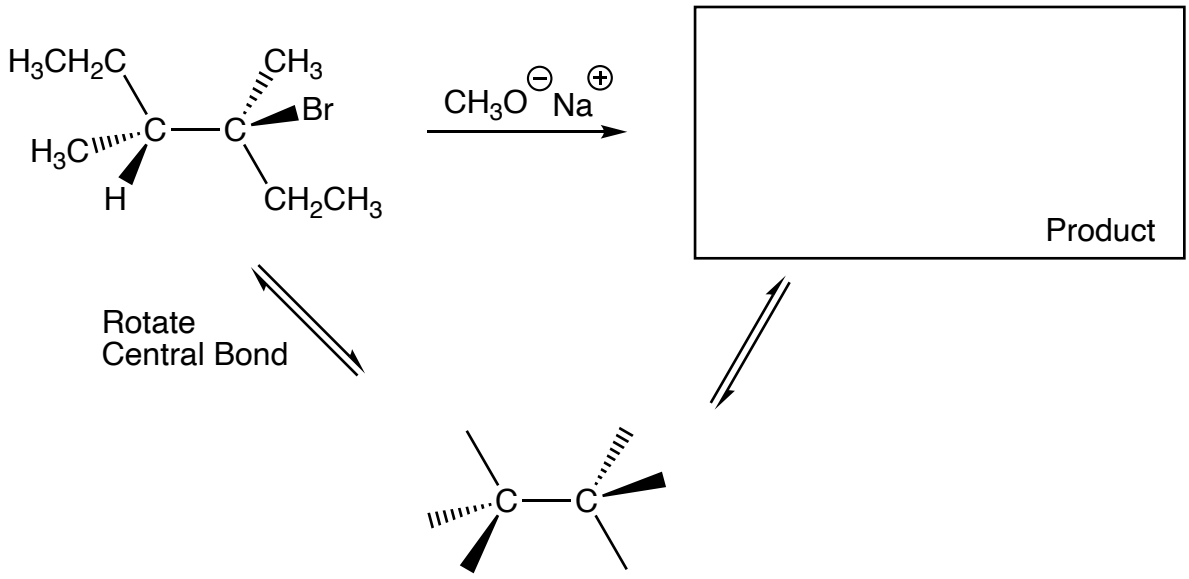
2. **Given the Zaitsev product you have identified, verify which anti-periplanar H atom(s) can be removed during the reaction to determine whether the product is E or Z.**
3. **You often need to rotate bonds to identify the particular H atom and configuration that reacts to give the alkene product.**



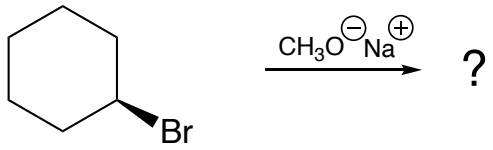
H and Br **not** anti-periplanar

H and Br are anti-periplanar

Putting it all together:

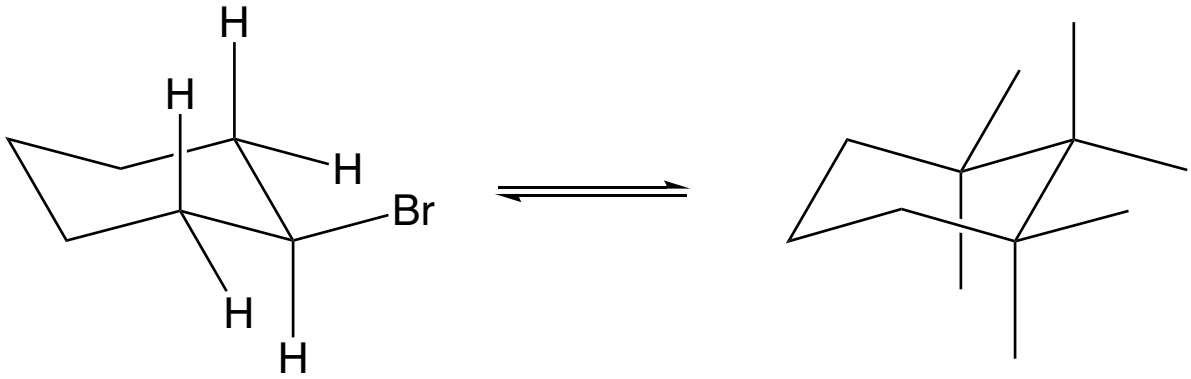


E2 Reaction of cyclohexane derivatives:



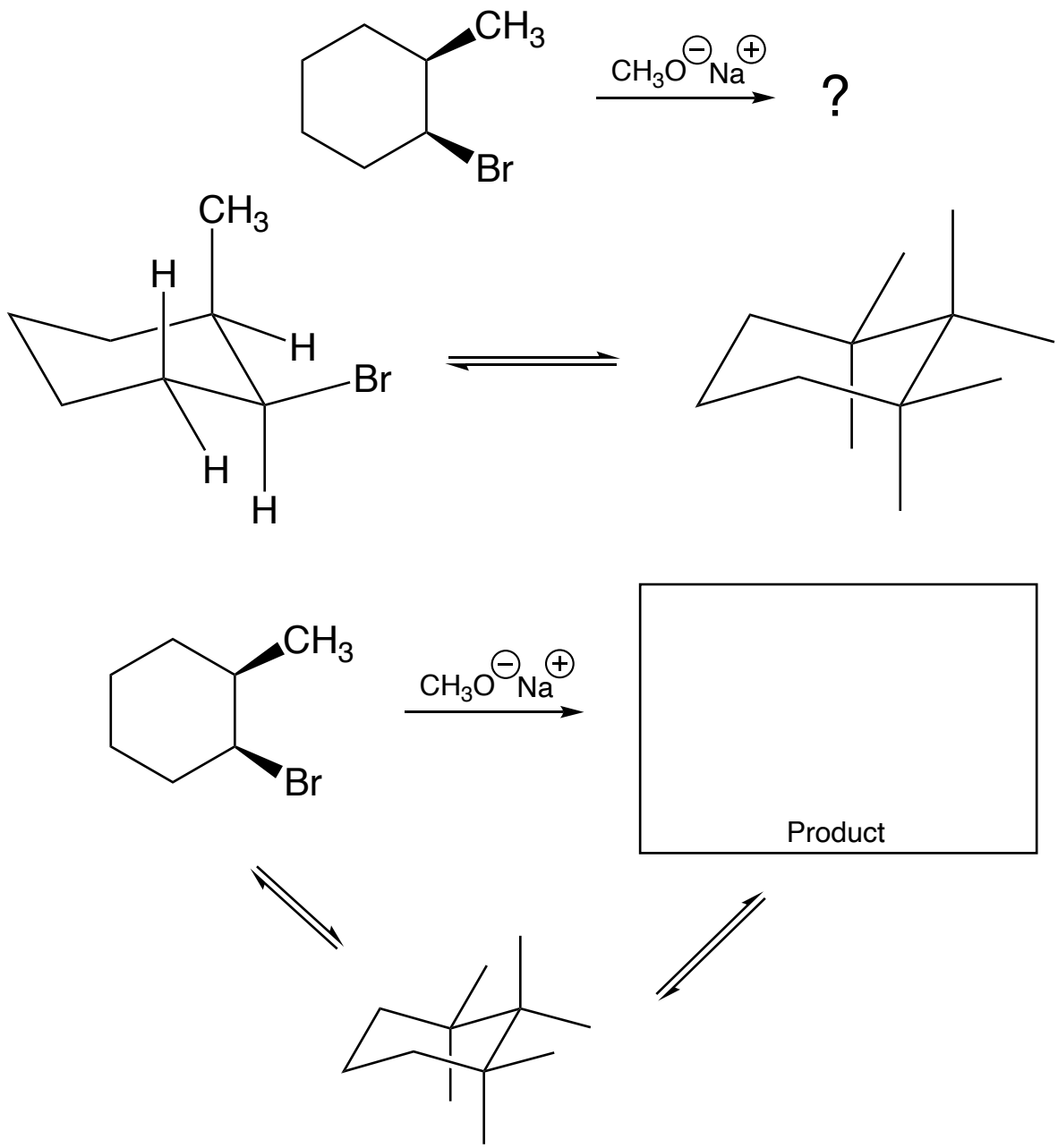
When analyzing highly substituted haloalkanes for a possible E2 reaction:

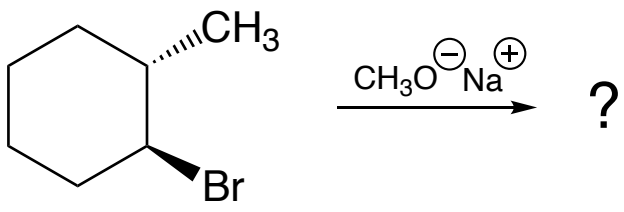
1. **You need to identify the most stable possible alkene (most highly substituted, *trans* over *cis*) that could be made (Zaitsev product).**
2. **Given the Zaitsev product you have identified, verify which anti-periplanar H atom(s) can be removed during the reaction to determine if that product can 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.**

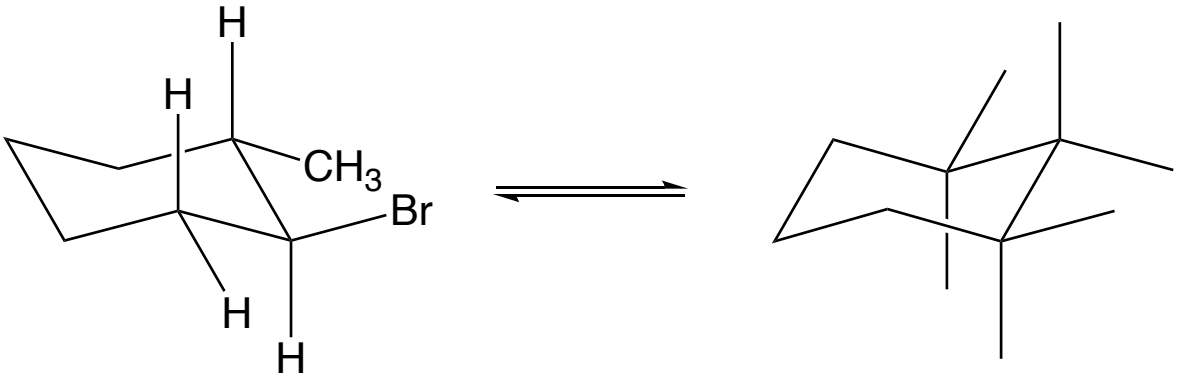


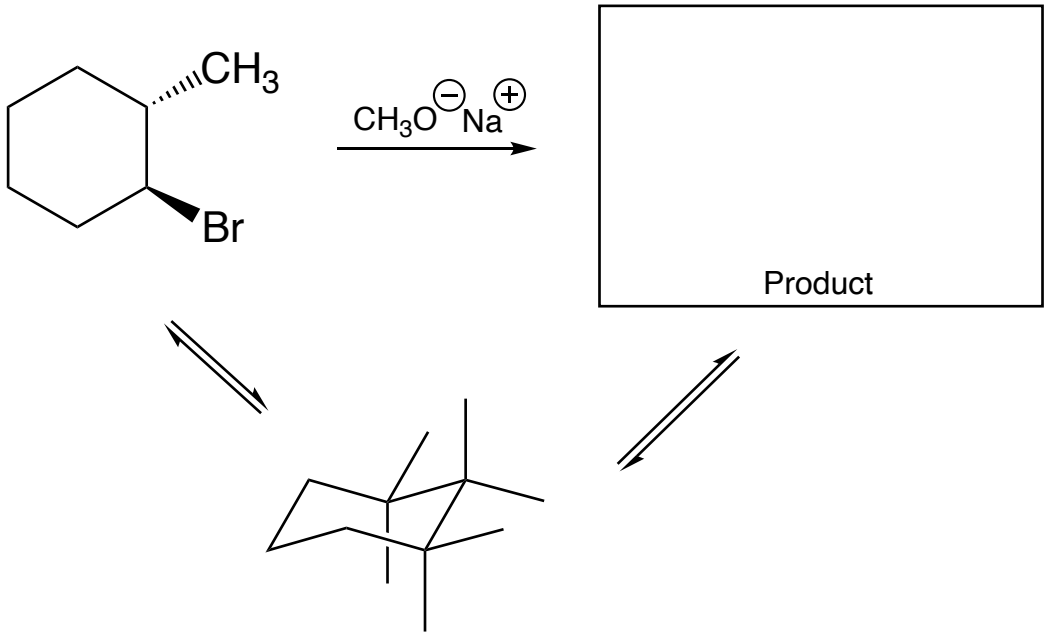
Rule:

Classic Examples:

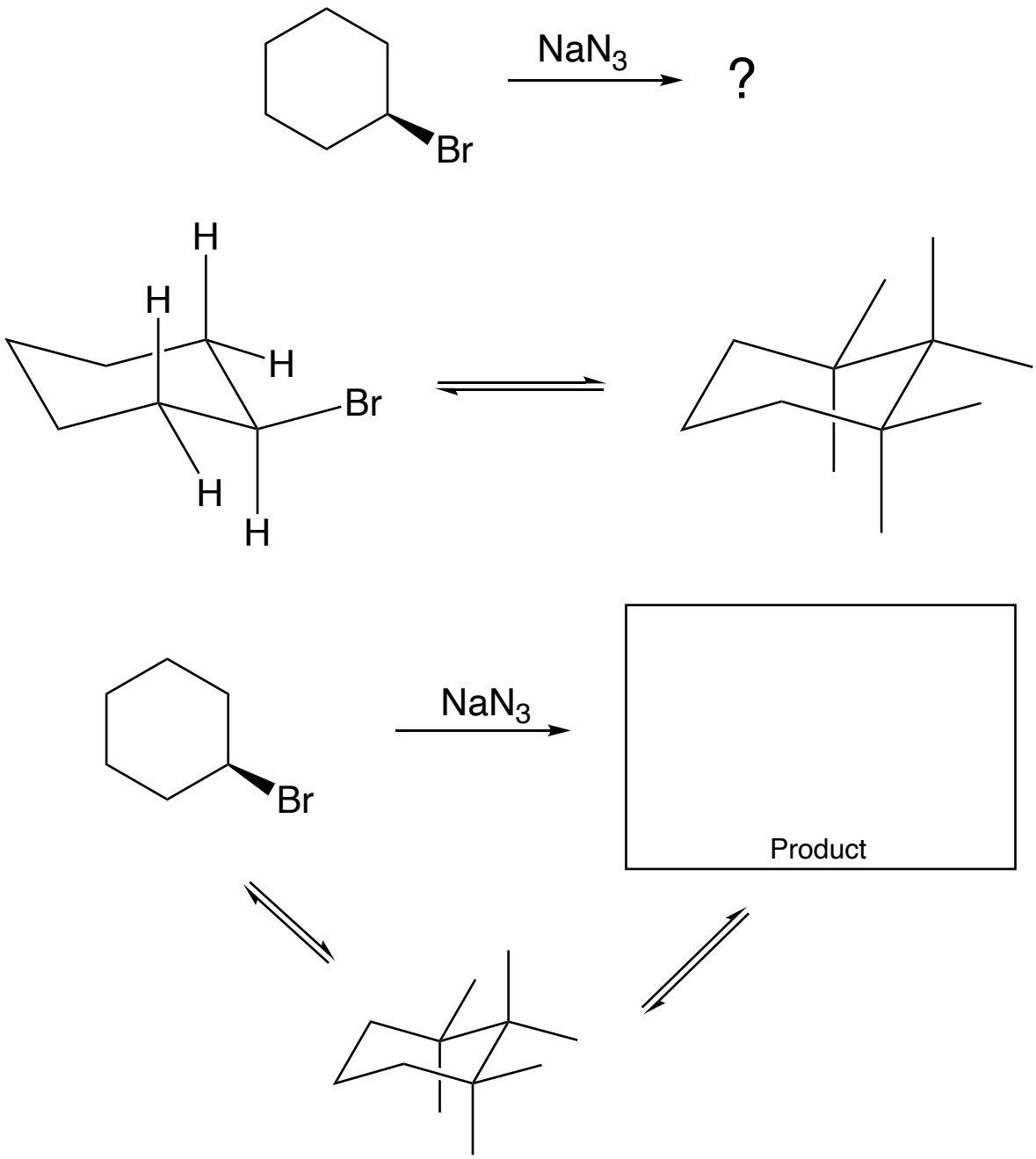



CH3
CH3O Na
Br
?


H
H
CH3
Br
H
H


CH3
CH3O Na
Br
Product

S_N2 Reactions of Cyclohexanes:



Rule:

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

Radical $Na^\bullet$ NH_3 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 hν or heat non-Markovnikov, Radical

Strong Base E2 Anti-periplanar TS Zaitsev's Rule

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

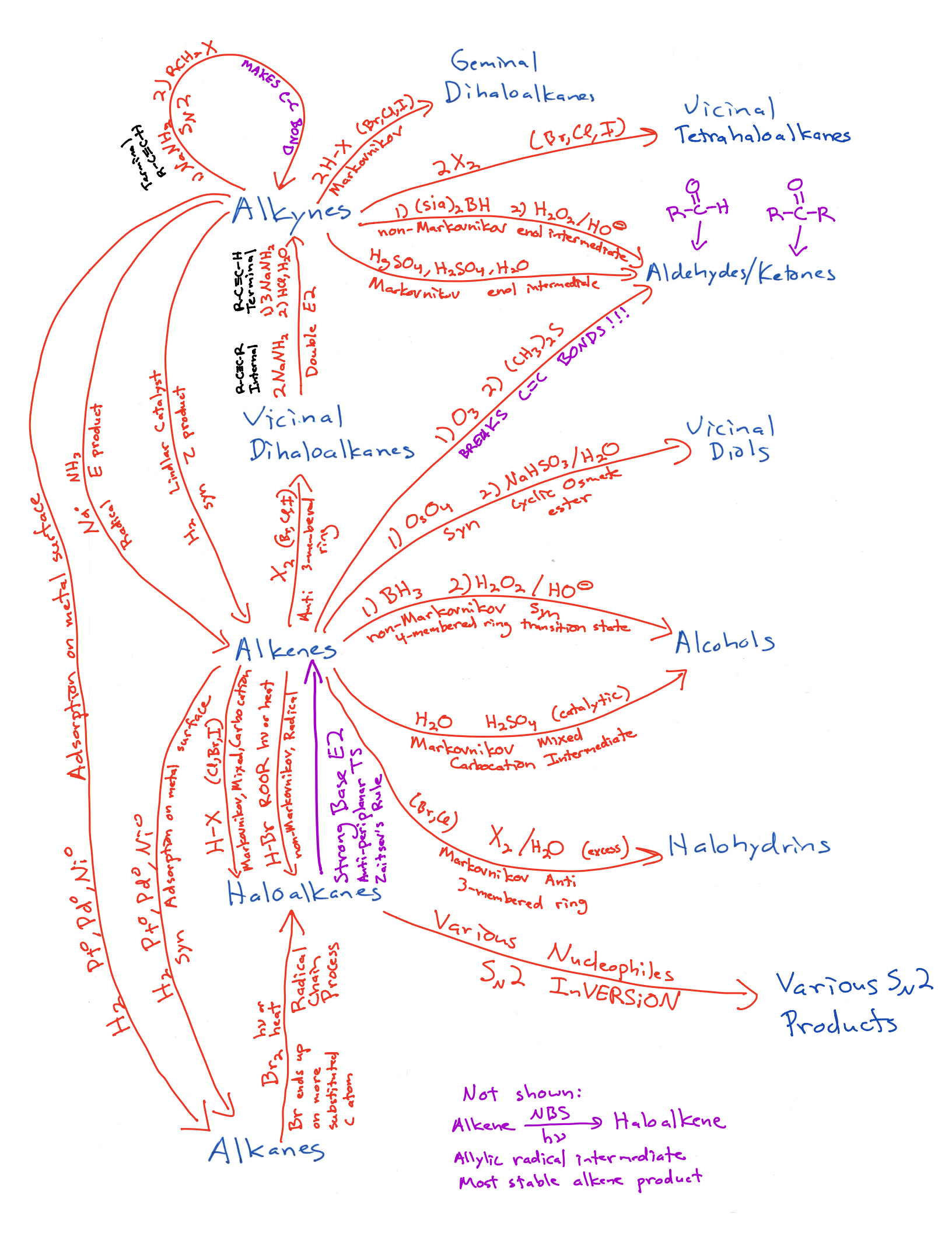
Halohydrins

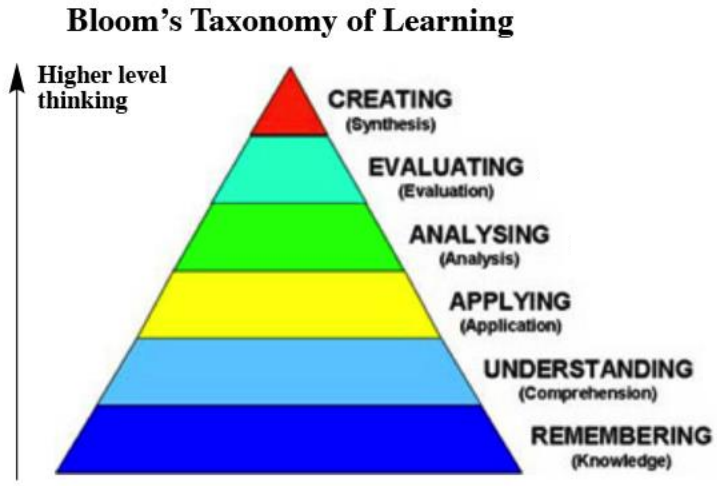
Br_2 hν or heat Radical Chain Process

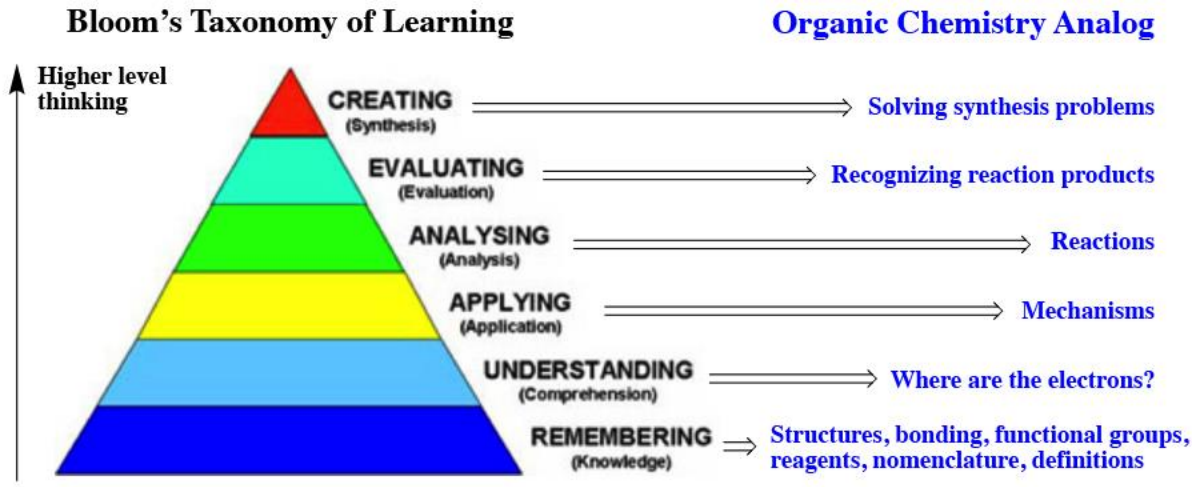
Br ends up on more substituted C atom

Various S_N2 Products

Alkanes (San Antonio)


Terminal RC≡CH
1) NaNH2
2) RCH2X
SN2
MAKES C-C
ANOTHER
Geminal Dihaloalkanes
2H-X (Br,Cl,I)
Markovnikov
Vicinal Tetrahaloalkanes
(Br,Cl,I)
2X2
Alkynes
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
RC≡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!!!
Vicinal Diols
1) OsO4
Syn
2) NaHSO3/H2O
cyclic Osmate ester
X2 (Br2, Cl2)
Anti
3-membered ring
Adsorption on metal surface
Na° NH3
E product
Radical
Lindlar Catalyst
Z product
H2 syn
Alkenes
1) BH3 2) H2O2 / HO⊖
non-Markovnikov Syn
4-membered ring transition state
Alcohols
H2O H2SO4 (catalytic)
Markovnikov Mixed Carbocation Intermediate
(Br,Cl)
X2 / H2O (excess)
Markovnikov Anti
3-membered ring
Halohydrins
Pt°, Pd°, Ni°
H2
Adsorption on metal surface
Syn
H-X (Cl,Br,I)
Markovnikov, Mixed, Carbocation
H-Br ROOR hν or heat
non-Markovnikov, Radical
Strong Base E2
Anti-periplanar TS
Zaitsev's Rule
Haloalkanes
Various Nucleophiles
SN2
INVERSION
Various SN2 Products
Br2
hν 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).

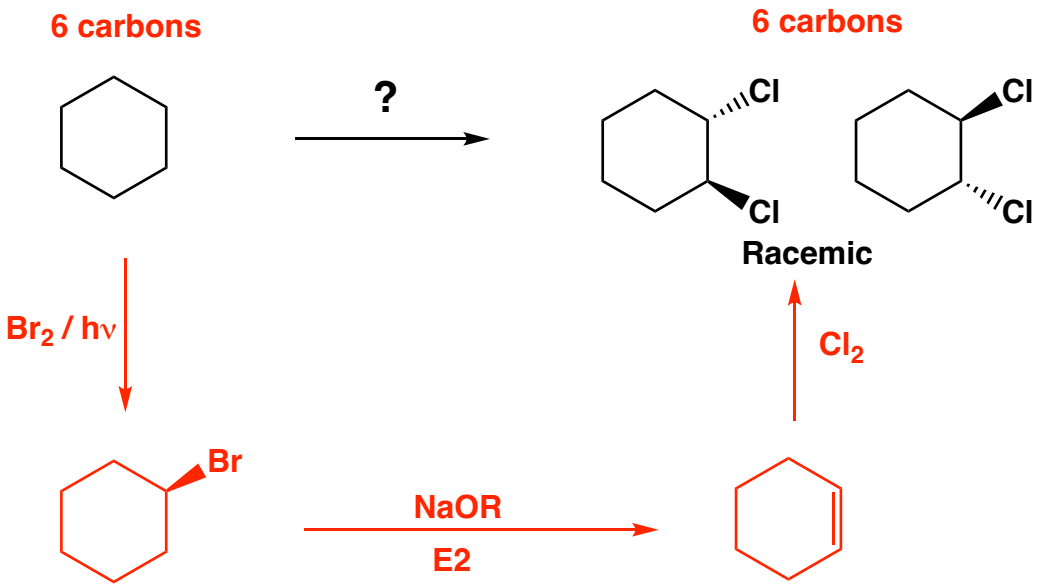
B) **Work backwards** (learn to RECOGNIZE the appropriate reagents and starting materials by looking at the products) from the final product. DO NOT try to work forward from the starting materials. Please trust me on this.

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.

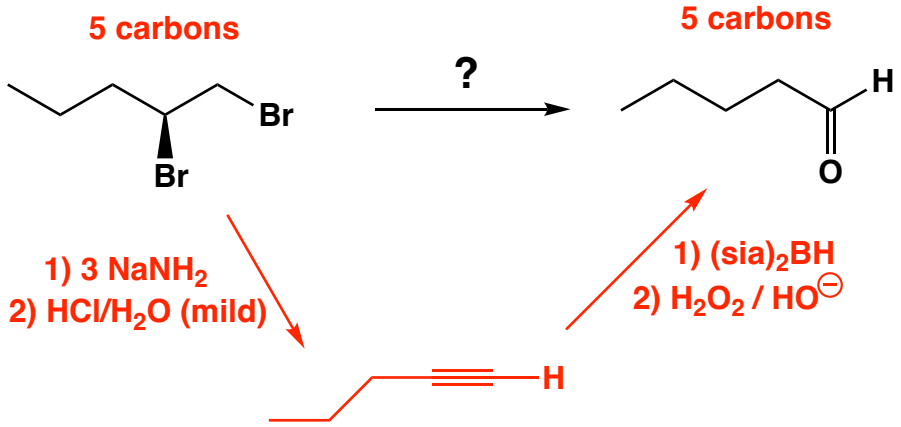
20. These are synthesis questions. You need to show how the starting material can be converted into the product(s) shown. You may use any reactions we have learned provided that the product(s) you draw for each step is/are the predominant one(s). Show all the reagents you need. Show each molecule synthesized 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)



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).

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.

Table 10.1 **Boiling Points and Solubilities in Water of Five Groups of Alcohols and Hydrocarbons of Similar Molecular Weight**

Structural Formula	Name	Molecular Weight (g/mol)	Boiling Point (°C)	Solubility in Water
CH_3OH	Methanol	32	65	Infinite
CH_3CH_3	Ethane	30	−89	Insoluble
CH_3CH_2OH	Ethanol	46	78	Infinite
$CH_3CH_2CH_3$	Propane	44	−42	Insoluble
$CH_3CH_2CH_2OH$	1-Propanol	60	97	Infinite
$CH_3CH_2CH_2CH_3$	Butane	58	0	Insoluble
$CH_3CH_2CH_2CH_2OH$	1-Butanol	74	117	8 g/100 g
$CH_3CH_2CH_2CH_2CH_3$	Pentane	72	36	Insoluble
$HOCH_2CH_2CH_2CH_2OH$	1,4-Butanediol	90	230	Infinite
$CH_3CH_2CH_2CH_2CH_2OH$	1-Pentanol	88	138	2.3 g/100 g
$CH_3CH_2CH_2CH_2CH_2CH_3$	Hexane	86	69	Insoluble

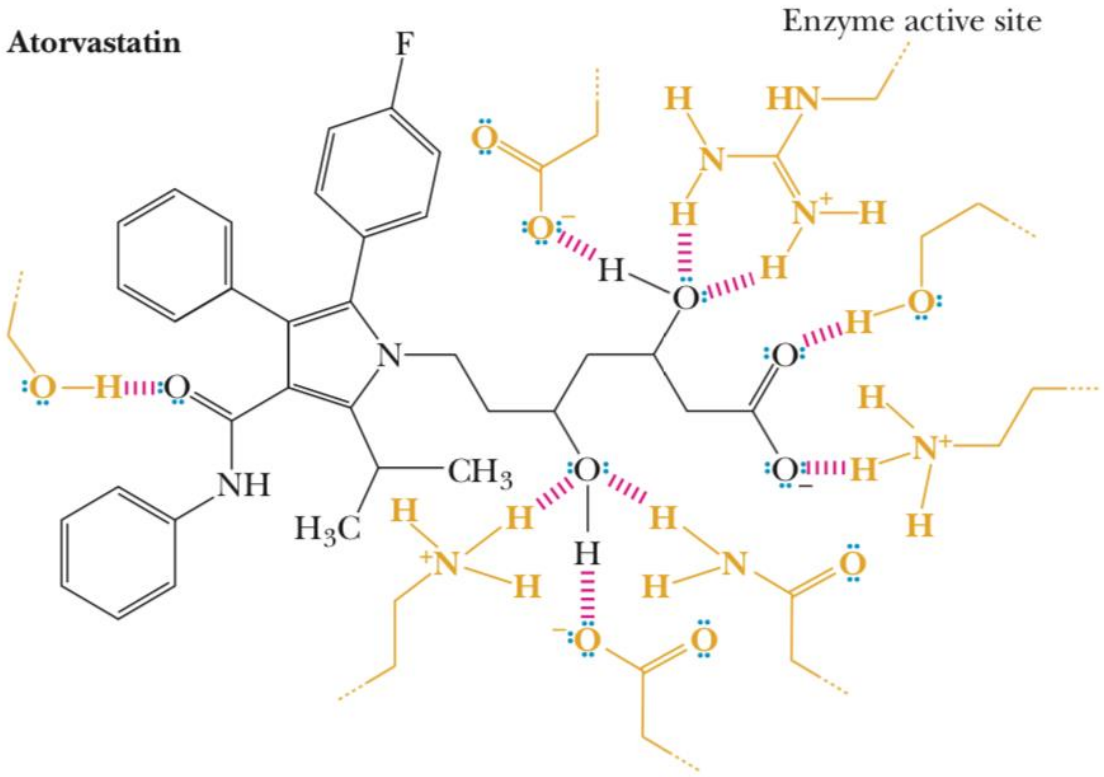


Figure 2

Hydrogen bonding (shown in red) between atorvastatin and the functional groups at the active site of the enzyme HMG-CoA reductase. The nine hydrogen bonds (shown in red), many of which involve hydroxyl groups on atorvastatin or the enzyme surface, help to provide the specificity that directs the binding of the drug to its target enzyme.

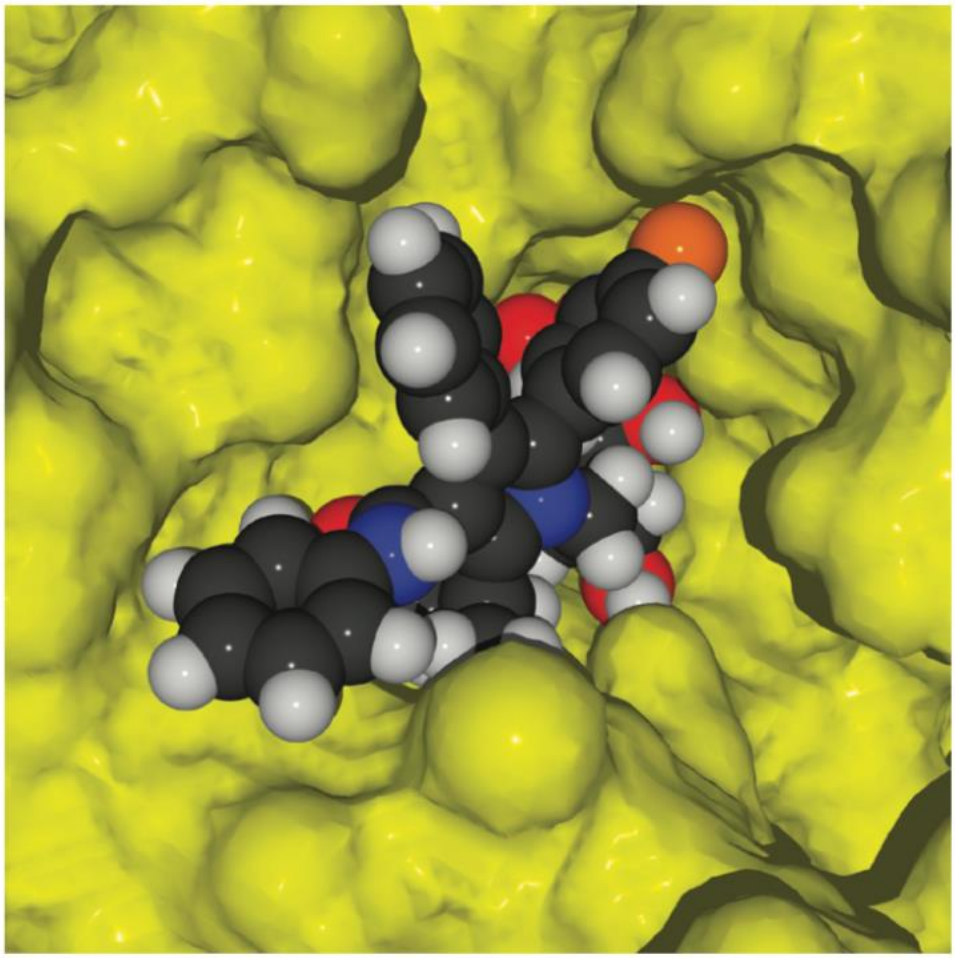
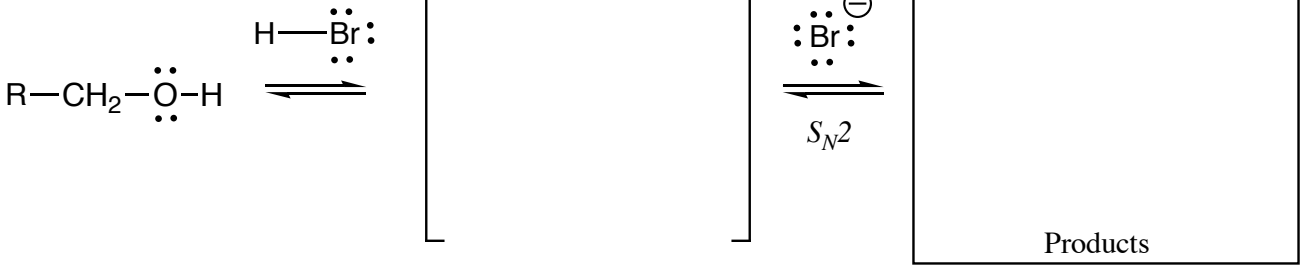


Figure 1

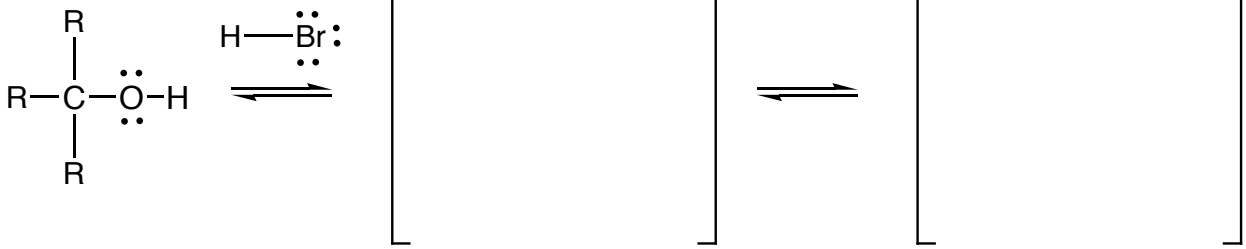
A space-filling model of the cholesterol-lowering drug atorvastatin (Lipitor) bound to the active site of its enzyme target HMG-CoA reductase (shown as a yellow surface). The shape of the drug is complementary to the active site of the enzyme.

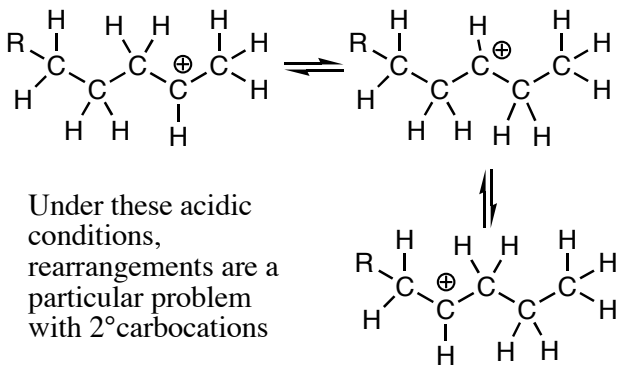
Alcohols + H-X

1° Alcohols: S_N2



2°/3° Alcohols: S_N1





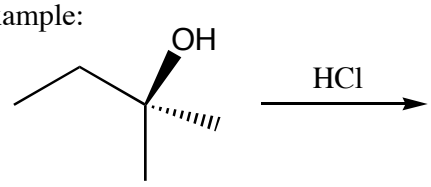
Under these acidic conditions, rearrangements are a particular problem with 2°carbocations

Summary:

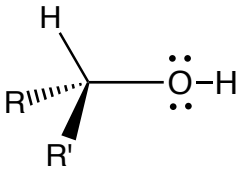
Regiochemistry:

Stereochemistry:

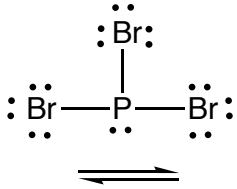
Example:

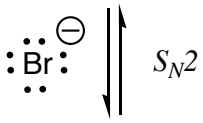


Alcohols + PBr_3



1° or 2° Alcohols





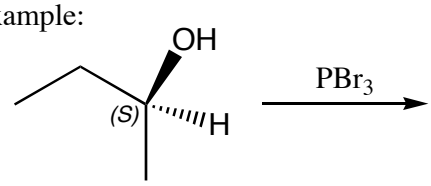
Products

Summary:

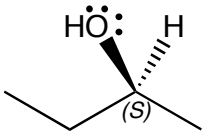
Regiochemistry:

Stereochemistry:

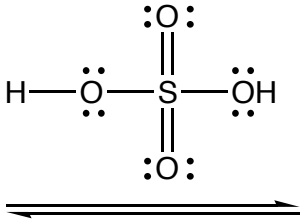
Example:

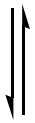


2° or 3° Alcohol Dehydration

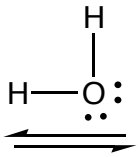


2° or 3° Alcohols





Products



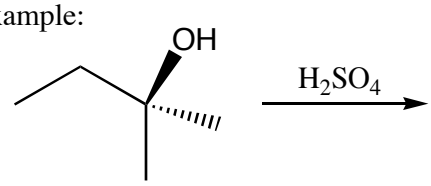
E1

Summary:

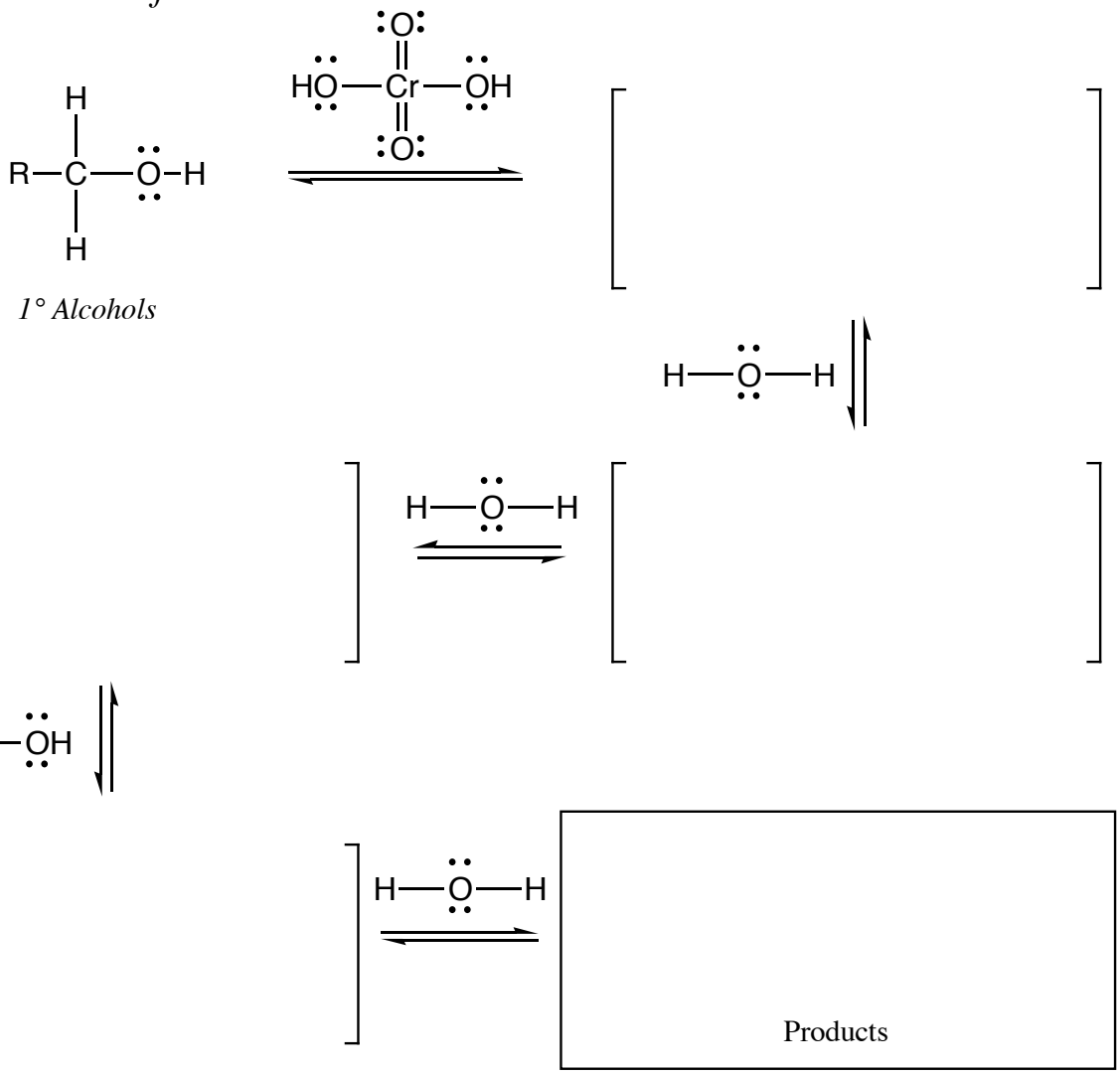
Regiochemistry:

Stereochemistry:

Example:



Chromic Acid Oxidation of Alcohols



Summary:

Regiochemistry:

Stereochemistry:

Example: