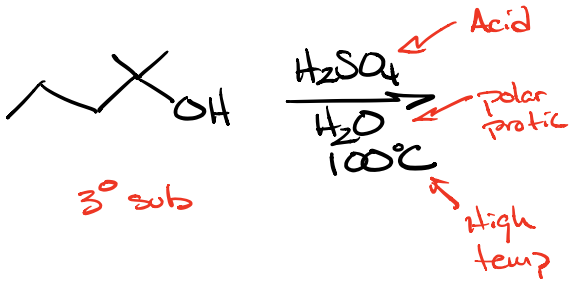
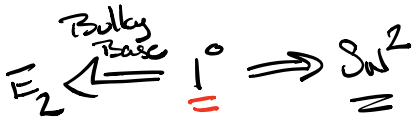
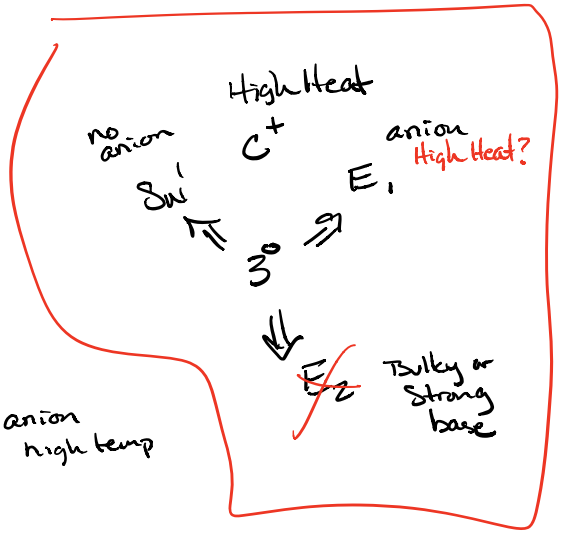
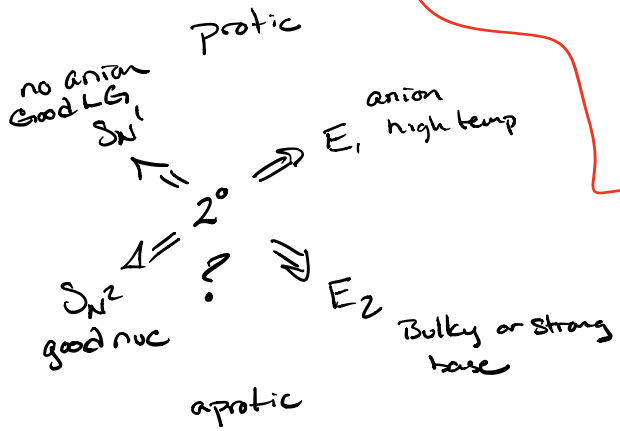
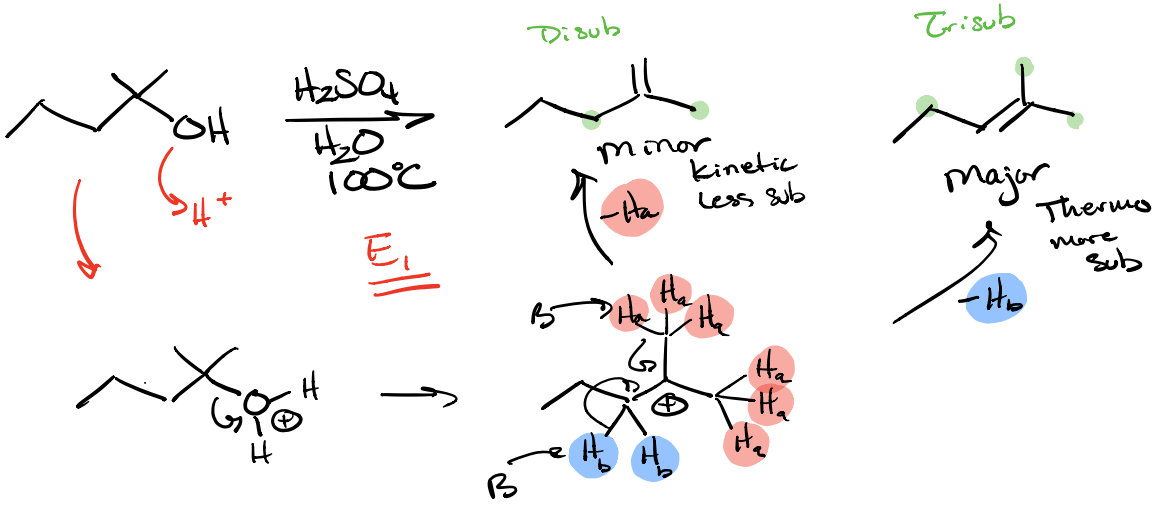

Acid
$H_2SO_4$
$H_2O$
100°C
polar protic
High temp
OH
3° sub
no good LG OH

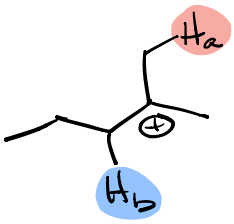
$E_1$

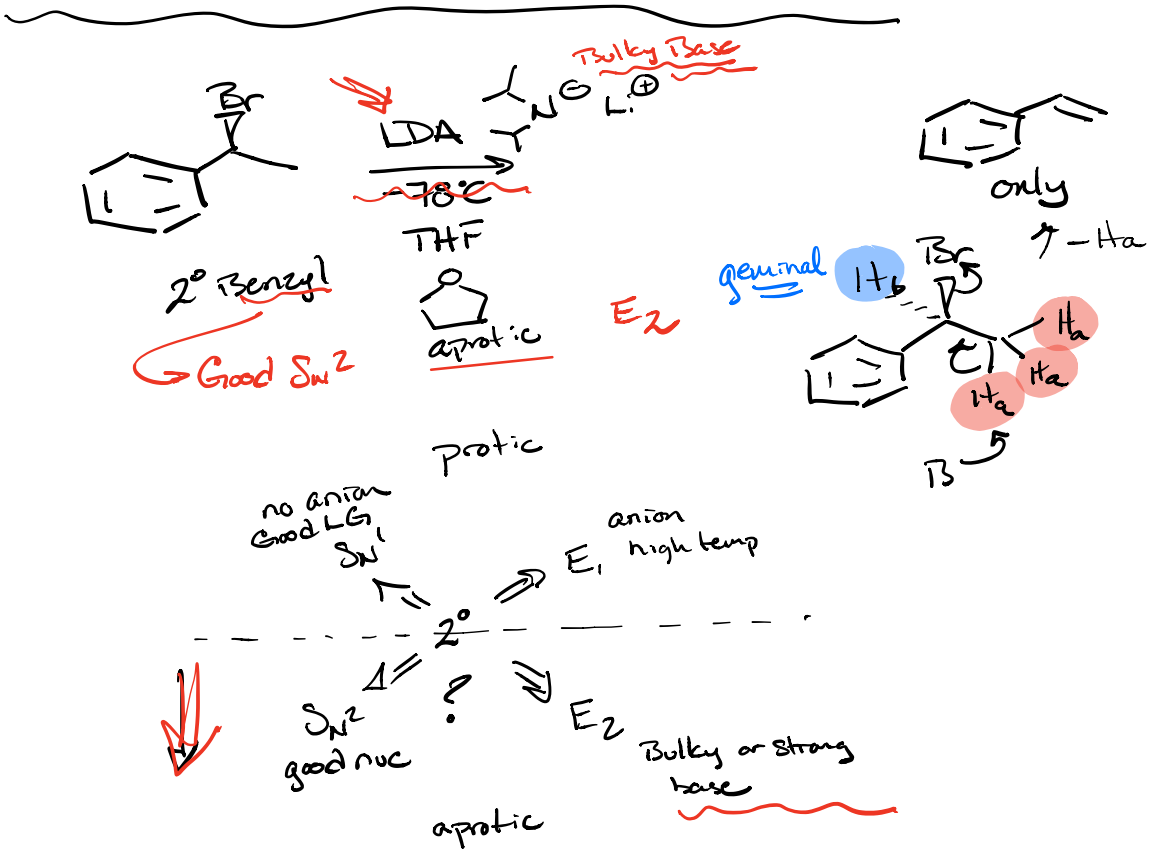

Bulky Base
$E_2$
1°
$S_N2$


High Heat
no anion
$C^+$
anion
High Heat?
$S_N1$
$E_1$
3°
$E_2$
Bulky or Strong base

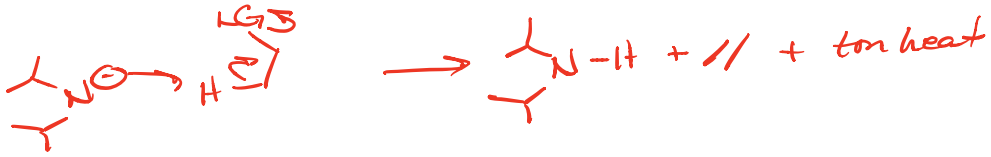

protic
no anion
Good LG
$S_N1$
$E_1$
anion
high temp
2°
?
$S_N2$
good nuc
$E_2$
Bulky or Strong base
aprotic


$H_2SO_4$
$H_2O$
100°C
$E_1$
$H^+$
Disub
minor
kinetic
less sub
$-H_a$
Trisub
major
Thermo
more
sub
$-H_b$
B
$H_a$
$H_b$




-78°C ⇒ Cold LDA to Control Exothermic Rxn




-30°C ⇒ Cold KO$^t$Bu to control heat

## NUCLEOPHILIC SUBSTITUTION AND ELIMINATION

The question is how do we discern when substitution is favored verse elimination? The answer is found partly in how we should think about reactions of alkyl halides.

> *The characteristic reaction of alkyl halides (or alkyl tosylates) with a Lewis base is **elimination**, special conditions are required to promote substitution.*

Given here is a set of guidelines (not absolutes) that can be used to arrive at the probable solution to nucleophilic substitution/elimination problems.

| | Substitution | Elimination |
|---|---|---|
| | $S_N2$ | E2 |
| substrate | benzyl = allyl > Me > $1^o$ > $2^o$<br>α-haloketone, α-haloester, α-halonitrile | $3^o$ > $2^o$ > $1^o$ |
| solvent | polar aprotic | polar aprotic |
| nucleophile | good nuc (weaker base than $OH^-$) | bulky or strong base >= $OH^-$ |
| leaving group | sulfonate > $I^-$ > $Br^-$ > $Cl^-$ | sulfonate > $I^-$ > $Br^-$ > $Cl^-$ |
| Temp | low | high |
| | $S_N1$ | E1 |
| substrate | $3^o$ > $2^o$ | $3^o$ > $2^o$ > $1^o$ |
| solvent | polar protic | polar protic |
| nucleophile | weak nuc (no anions!) | any anionic base |
| leaving group | sulfonate > $I^-$ > $Br^-$ > $Cl^-$ | sulfonate > $I^-$ > $Br^-$ > $Cl^-$ |
| Temp | low | high |

## Classification of Nucleophiles

| | |
|---|---|
| Very good nucleophile | $I^-$, $HS^-$, $RS^-$ |
| Good nucleophile | $Br^-$, $OH^-$, $RO^-$, $CN^-$, $N_3^-$ |
| Fair nucleophile | $NH_3$, $Cl^-$, $F^-$, $RCO_2^-$ |
| Weak nucleophile | $H_2O$, ROH |
| Very weak nucleophile | $RCO_2H$ |

LDA  $KO^tBu$ $KOH$ Bulky Base

Nucleophilic Constants of Various Nucleophiles

| Nucleophile | $n_{CH_3I}$ | p$K_a$ of conjugate acid |
|---|---|---|
| $CH_3OH$ | 0.0 | -1.7 |
| $F^-$ | 2.7 | 3.45 |
| $CH_3CO_2^-$ | 4.3 | 4.8 |
| $Cl^-$ | 4.4 | -5.7 |
| $NH_3$ | 5.5 | 9.25 |
| $N_3^-$ | 5.8 | 4.75 |
| $C_6H_5O^-$ | 5.8 | 9.89 |
| $Br^-$ | 5.8 | -7.7 |
| $CH_3O^-$ | 6.3 | 15.7 |
| $OH^-$ | 6.5 | 15.7 |
| $(CH_3CH_2)_3N$ | 6.7 | 10.70 |
| $CN^-$ | 6.7 | 9.3 |
| $I^-$ | 7.4 | -10.7 |
| $(CH_3CH_2)_3P$ | 8.7 | 8.69 |
| $C_6H_5S^-$ | 9.9 | 6.5 |

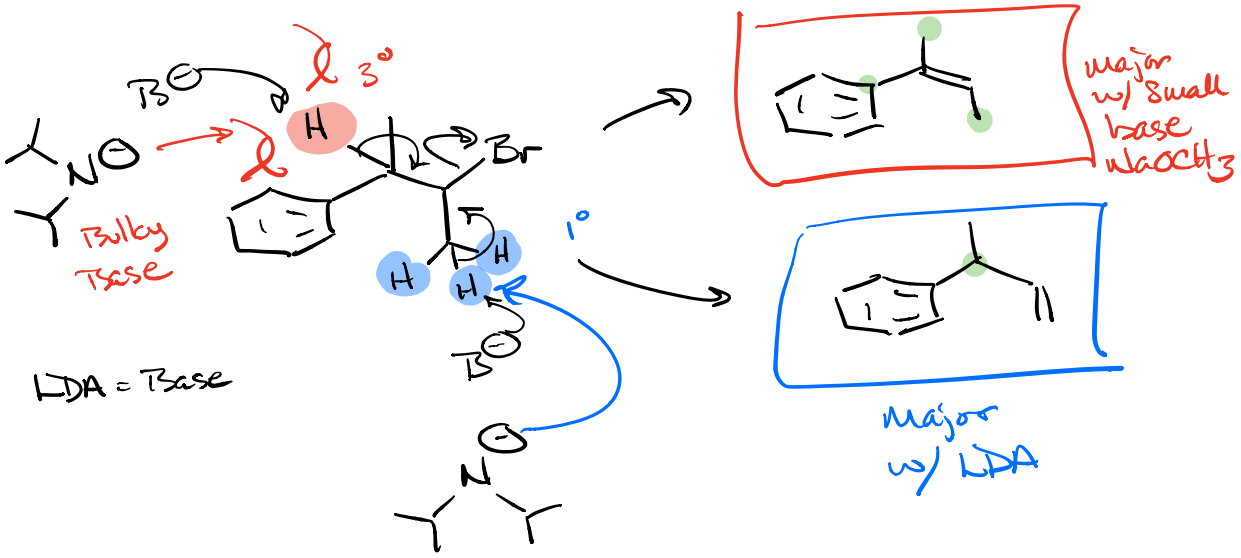
Solvents Which Promote $S_N2$/E2 (bimolecular)

Acetone
Dimethyl sulfoxide (DMSO)
*N*,*N*-Dimethylformamide (DMF)
Acetonitrile
Hexamethylphosphoramide (HMPA)
Tetrahydrofuran (THF)

Solvents Which Promote $S_N1$/E1 (Unimolecular/Ionizing)

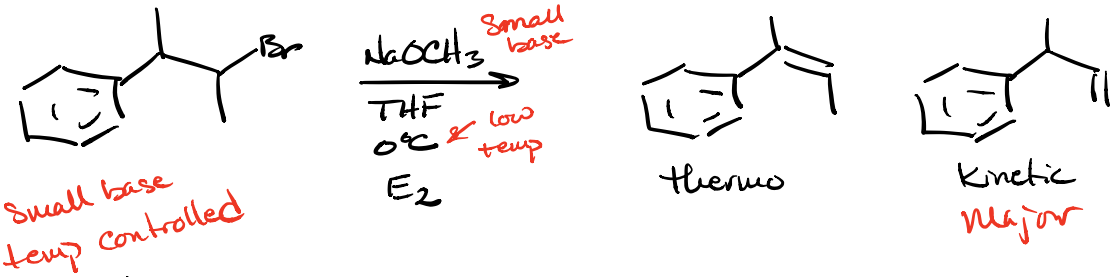
Increasing nucleophilicity (solvolysis)

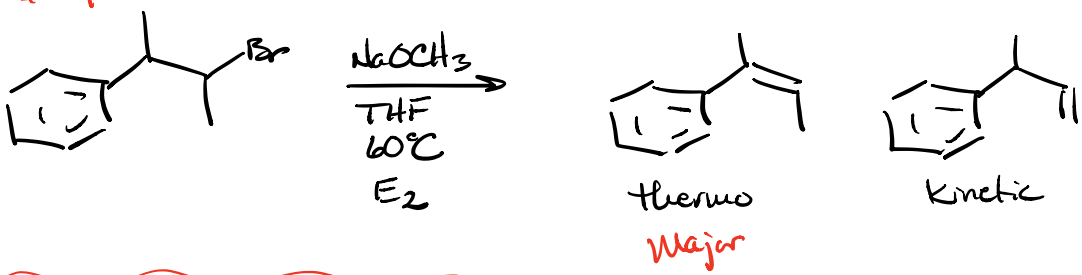
Ethanol
Methanol
50% Aqueous Ethanol
Water
Acetic Acid
Formic Acid
Trifluoroethanol
Trifluoroacetic acid

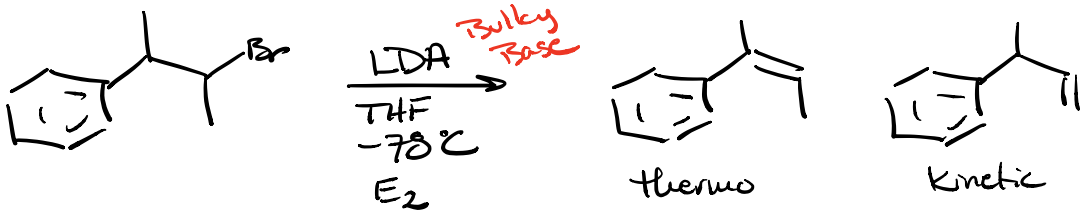


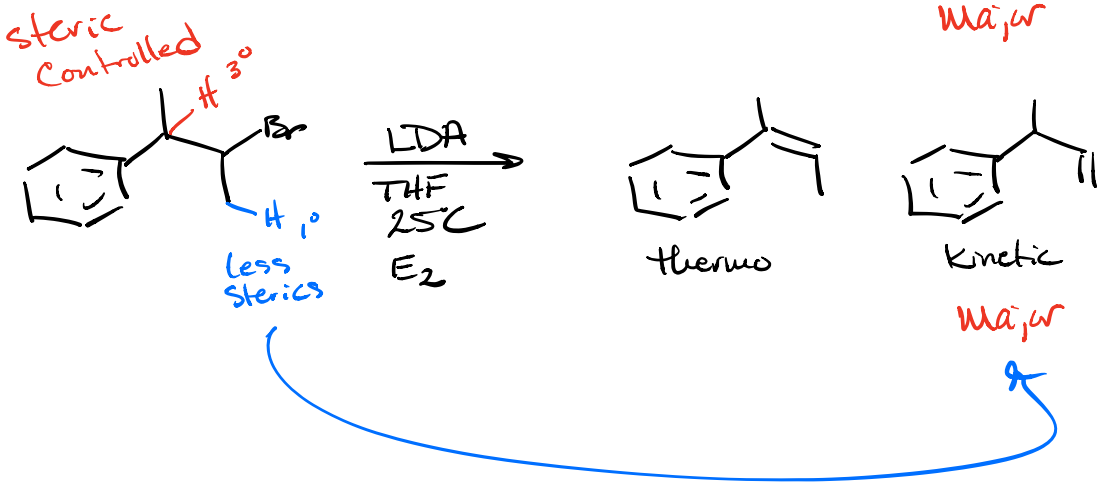

LDA = Base

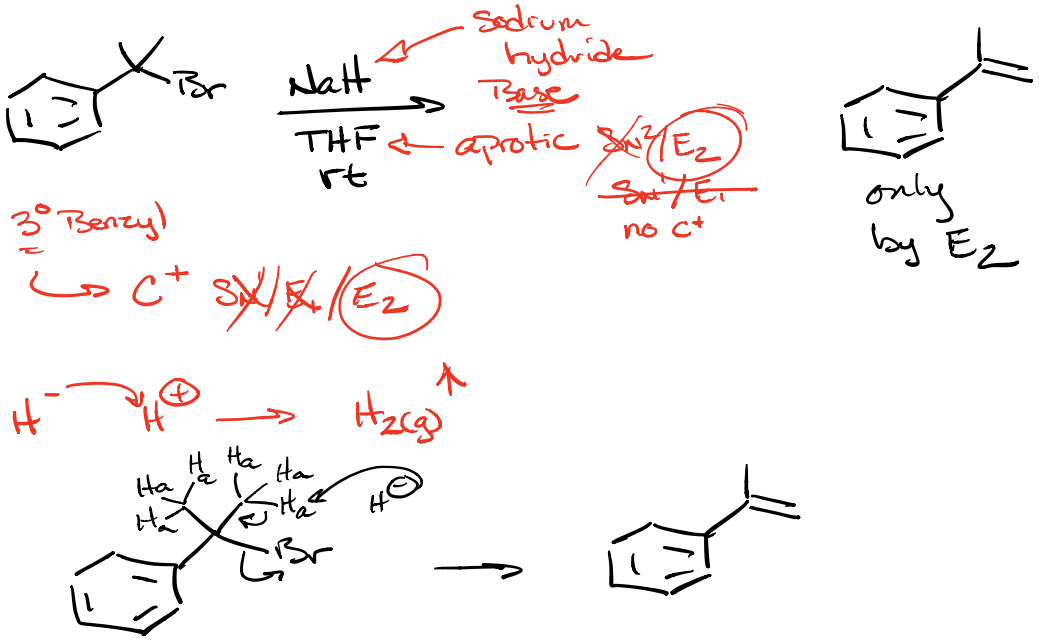
Base = $NaOCH_3$
small

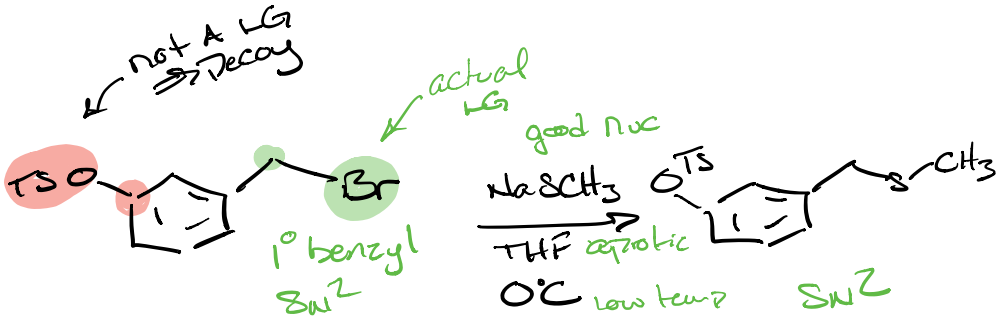

Br
NaOCH3
Small base
THF
0°C
low temp
E2
Thermo
Kinetic
Major
small base
temp controlled


Br
NaOCH3
THF
60°C
E2
Thermo
Major
Kinetic


Br
LDA
Bulky Base
THF
-78°C
E2
Thermo
Kinetic
Major

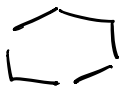

steric Controlled
H 3°
Br
H 1°
less sterics
LDA
THF
25°C
E2
Thermo
Kinetic
Major



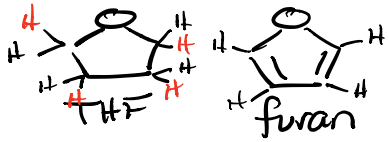

Question about Rings ⟹ do they React?

aromatic
all C are $sp^2$
Not Reactive

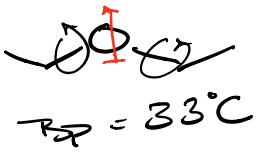


Cyclohexane
most C are $sp^3$
yes reactive

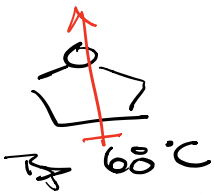
$S_N1$ $S_N2$ $E_1$ $E_2$
on $sp^3$ Carbons
⟹ Never Sp or $Sp^2$




Tetrahydrofuran

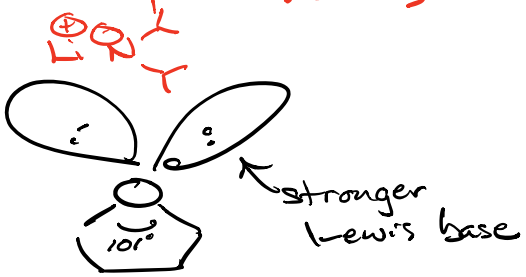


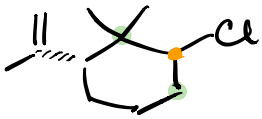
bp = 33°C

bp 60°C

better at solvating nucleophile $NaOCH_3$



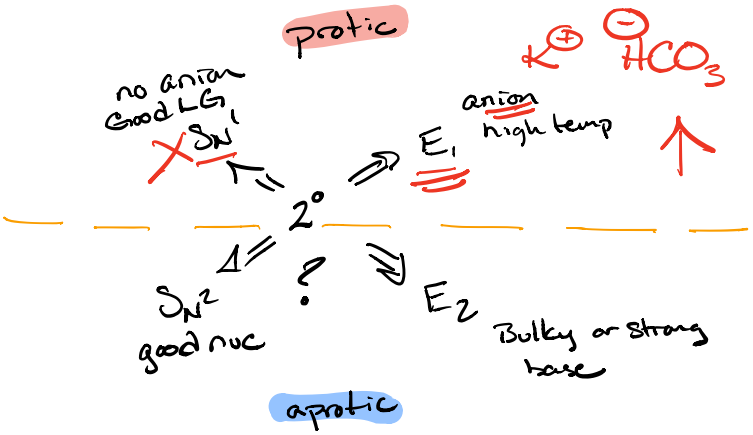


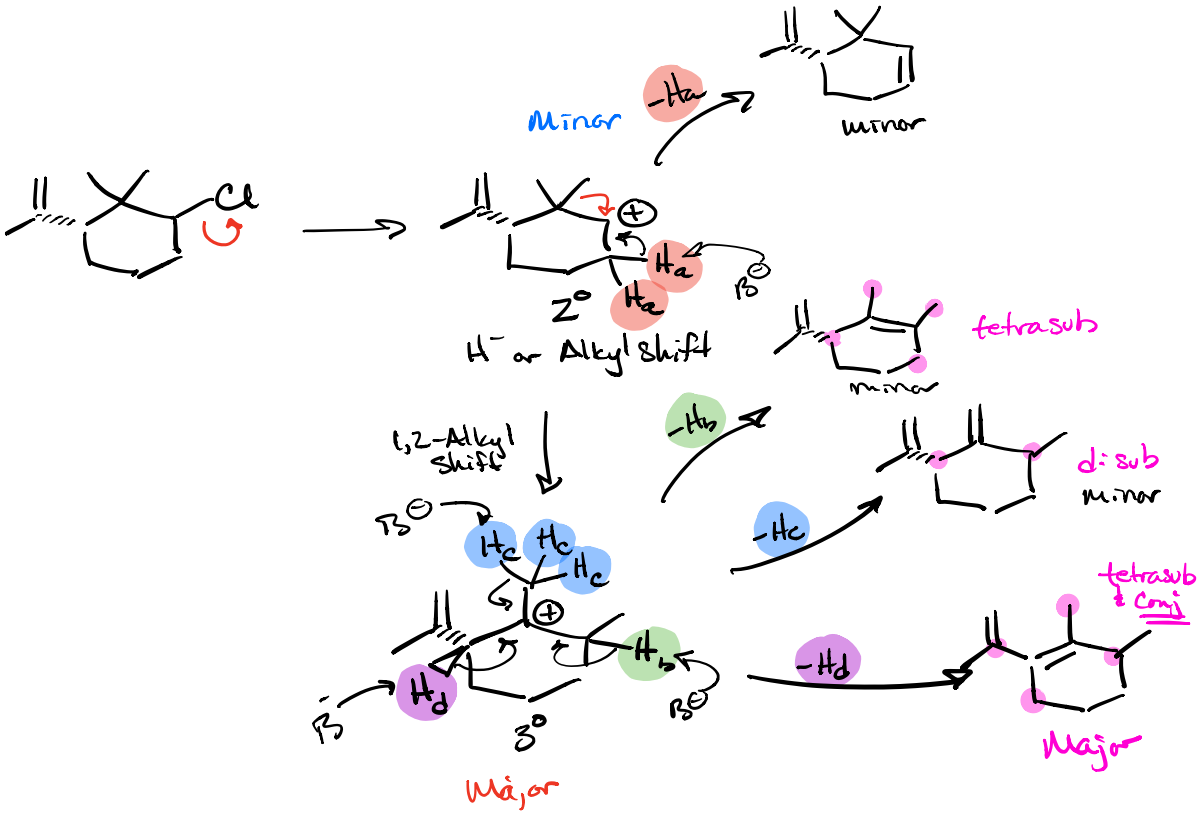
$KHCO_3$
MeOH
60°C

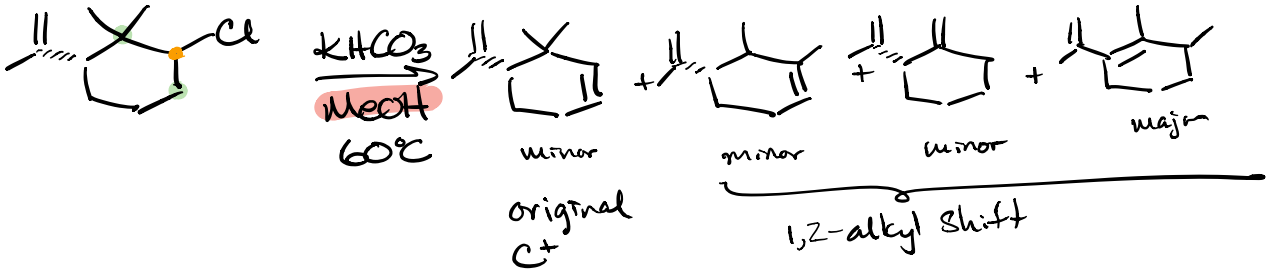
2° chloride

High temp ⇒ Thermo E1

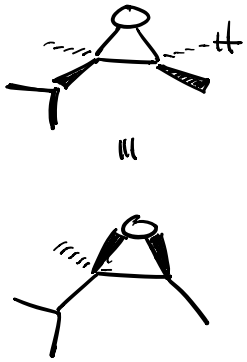
LG = $Cl^-$ okay LG






$E_1$



III

Bulky Base

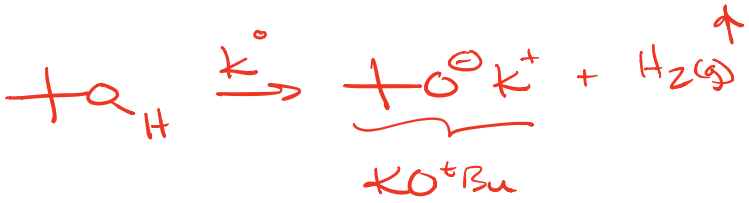
$KO^tBu$

~~$^tBuOH$~~

0°C

~~$E_1$~~ or $E_2$

$E_2$

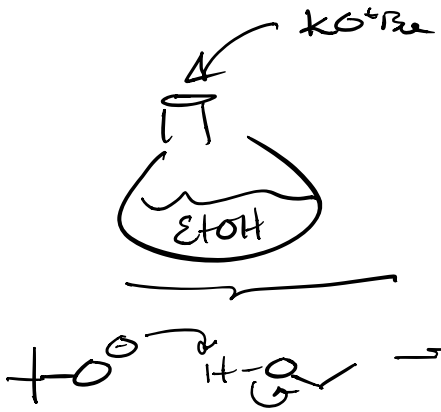


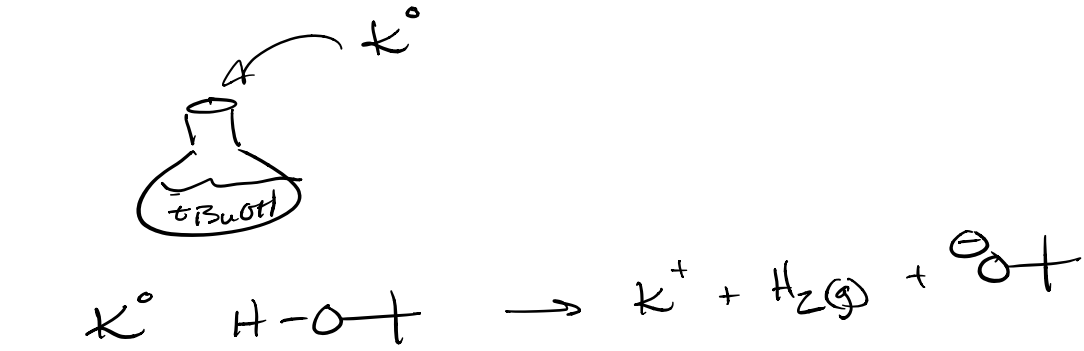

**$E_1$**

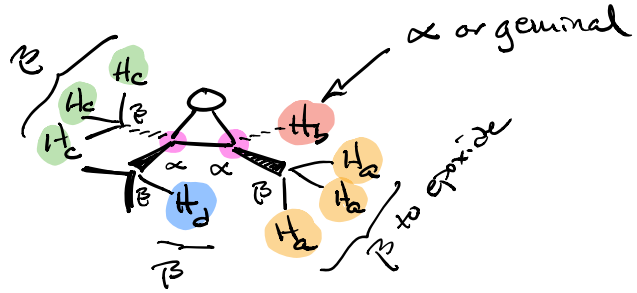
- ionizing solvent
- requires $H^+$
- Higher Heat
- weaker base

~~**$E_2$**~~

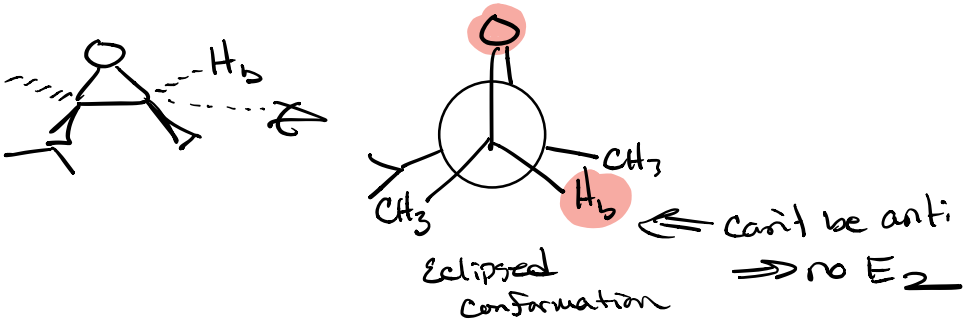
- Strong Base ⇒ Bulky Base
- Any Solvent protic or aprotic
- Cold or Hot
- Does not require $H^+$
  - ↳ can't have acid

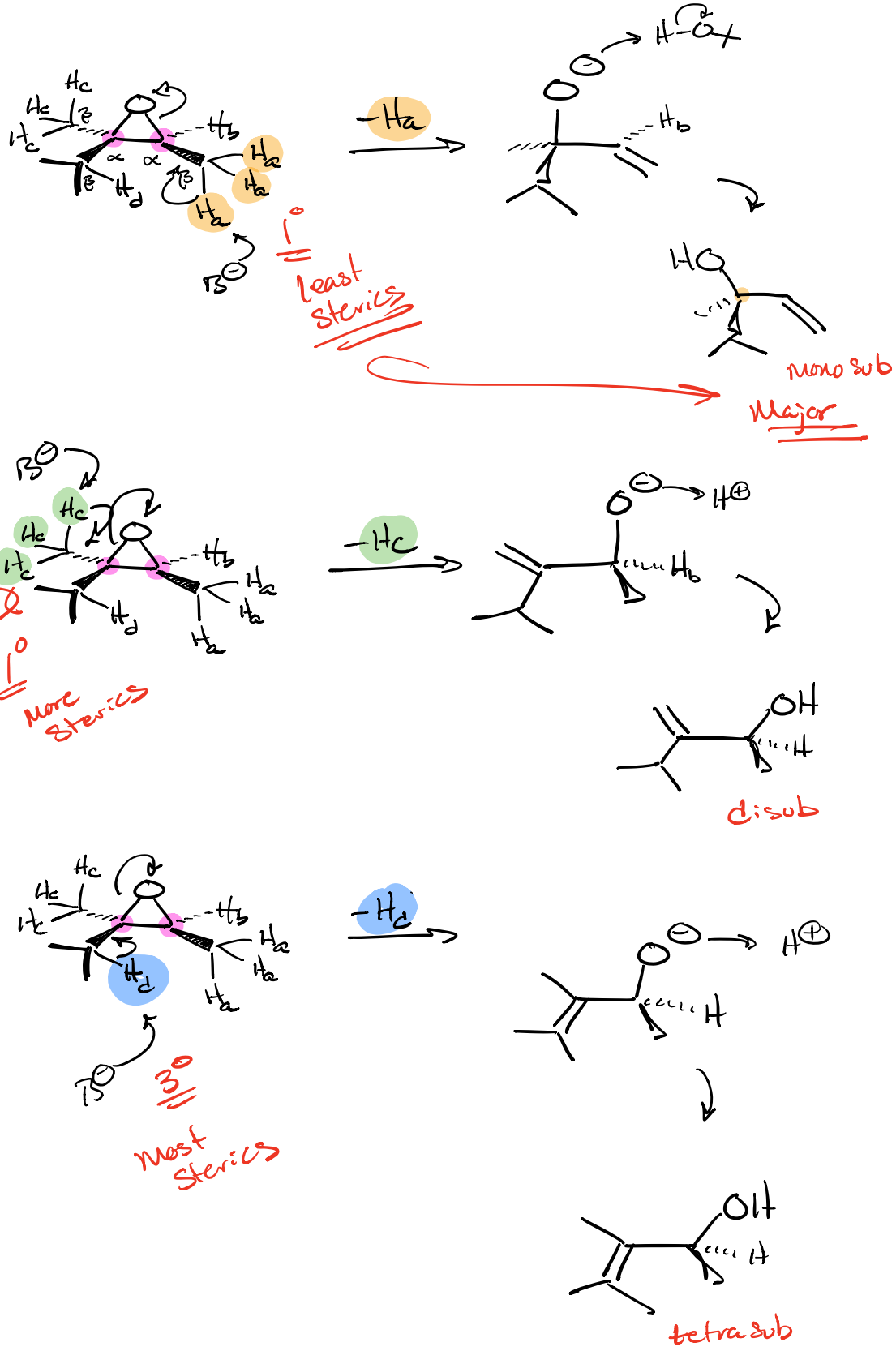


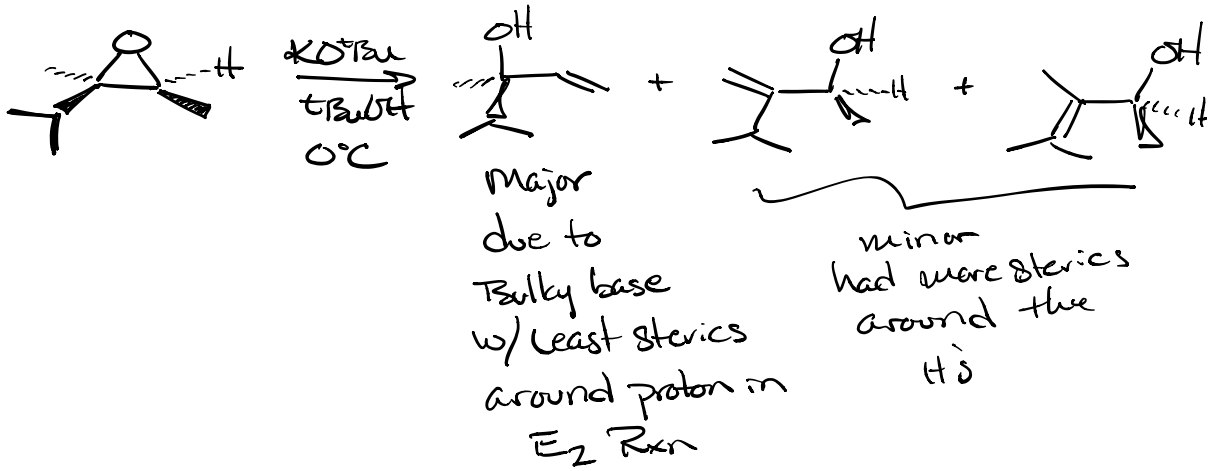




$H_b$ α or geminal $E_2$ Requires pulling anti to LG

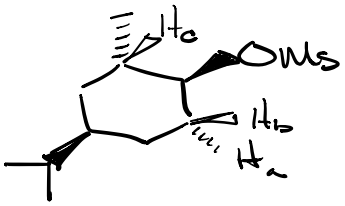



-Ha
1°
least sterics
mono sub
Major
-Hc
2°
more sterics
disub
-Hd
3°
most sterics
tetra sub




Major due to Bulky base w/ least sterics around proton in $E_2$ Rxn

minor had more sterics around the H

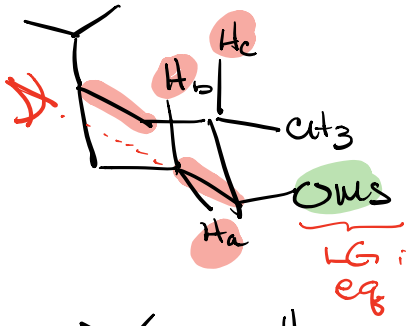


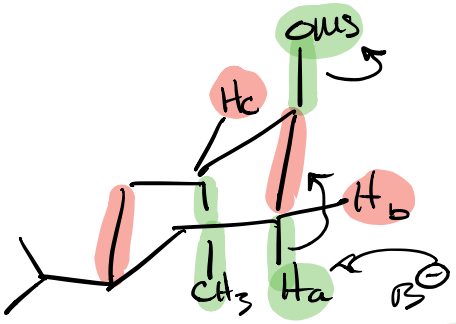

$E_2$

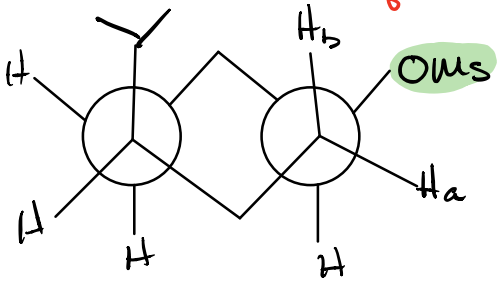
$KO^tBu$

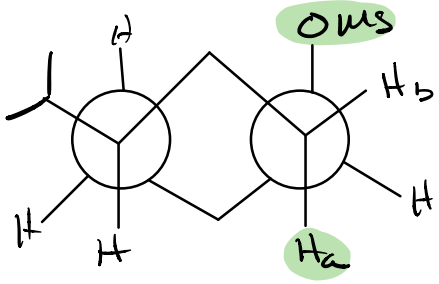
$^tBuOH$

40°C



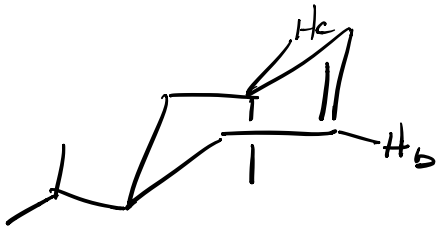



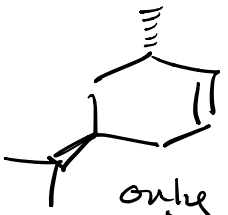

Both $H_a$ & $H_b$ gauche to LG ⇒ no $E_2$

$E_2$ allowed

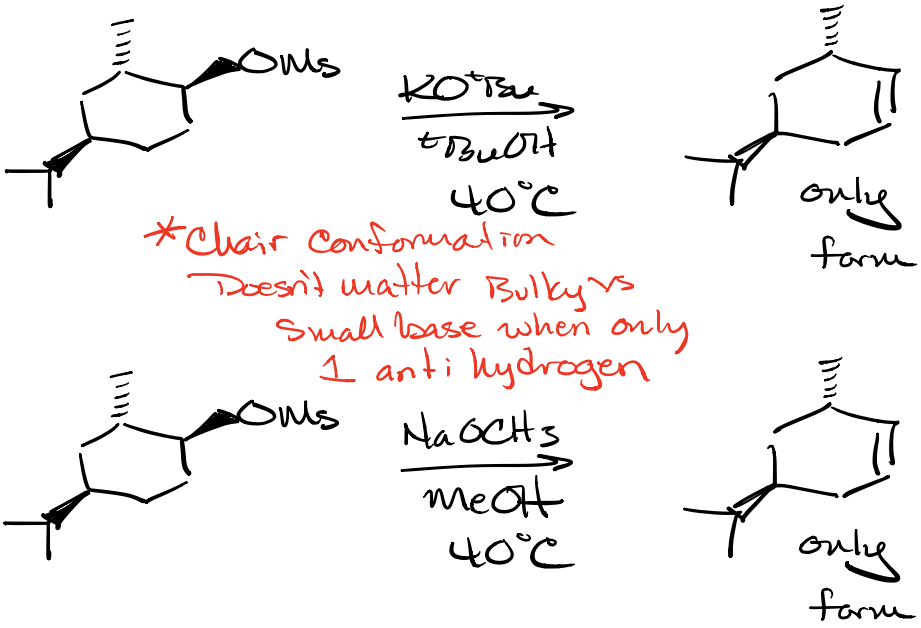
* when a LG is eq on ring no anti H ⇒ no $E_2$ Rxn




III

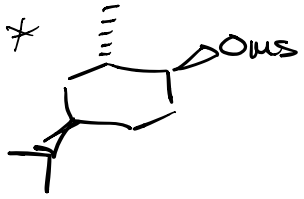


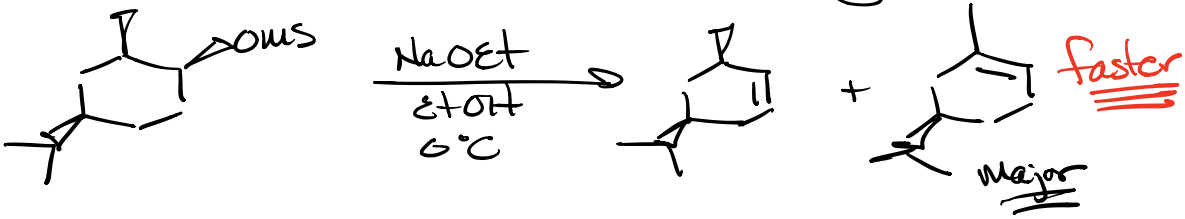
only form

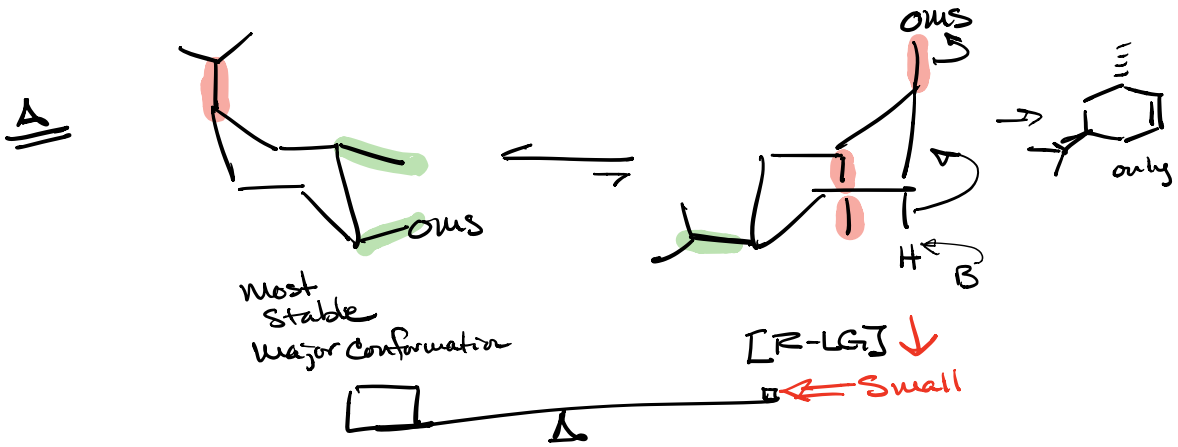


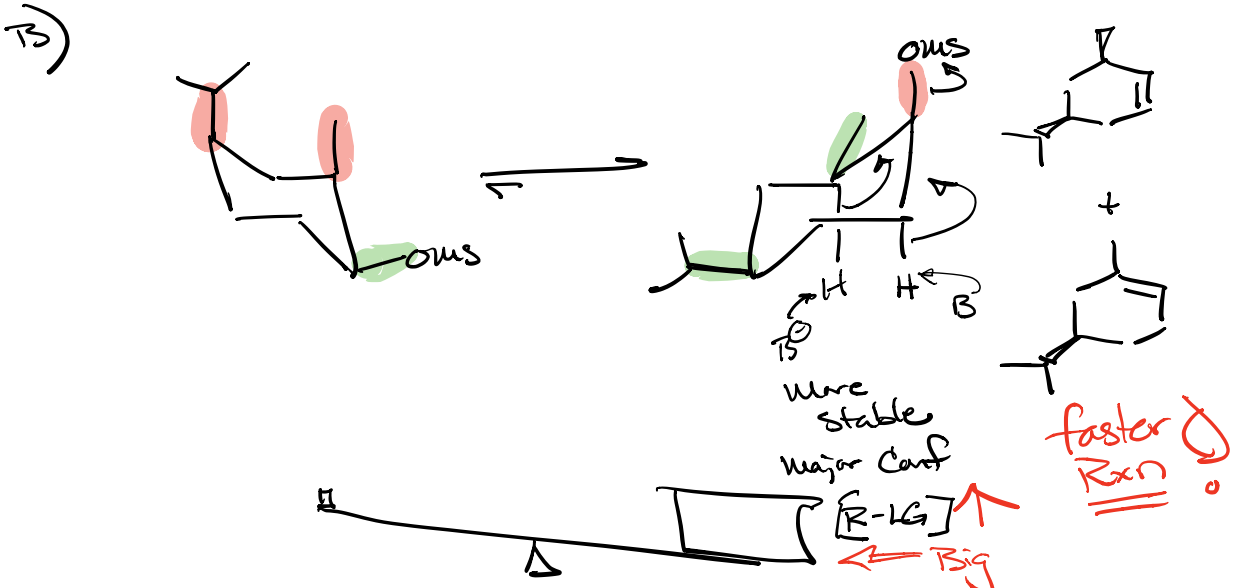

*Chair Conformation
Doesn't matter Bulky vs
Small base when only
1 anti hydrogen

which Rxn is faster?
Explain & give products for both.

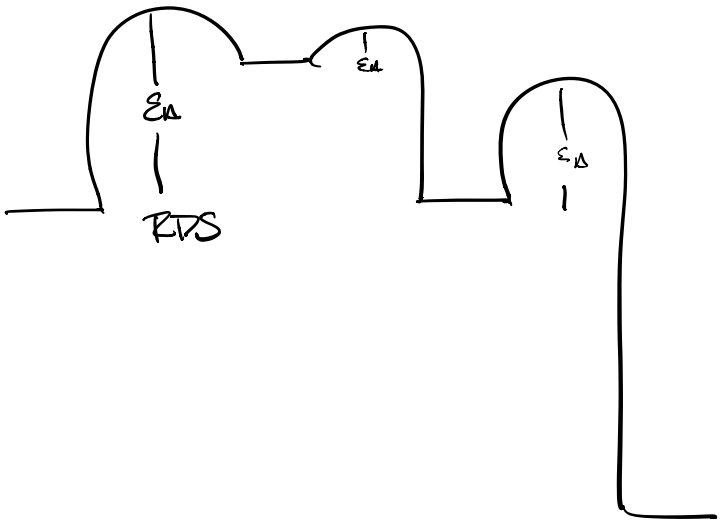
A 


B 


A 

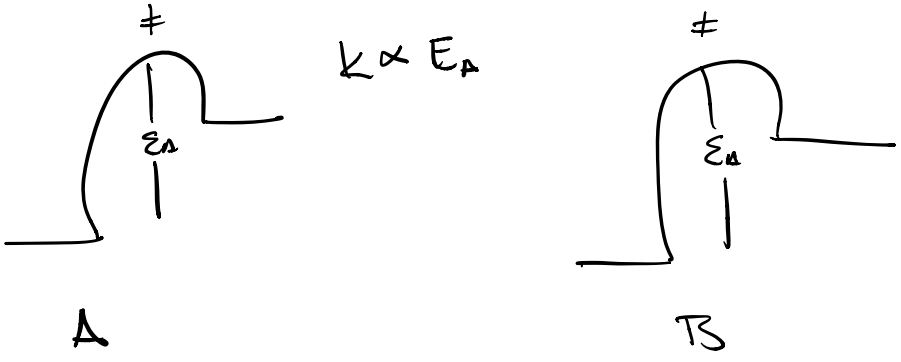

B) 


$$R_{E2} = k[R\text{-}LG][Base]$$




$$\text{Rate} = k[\text{R-LG}][\text{Base}]$$

$k \propto E_a$

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