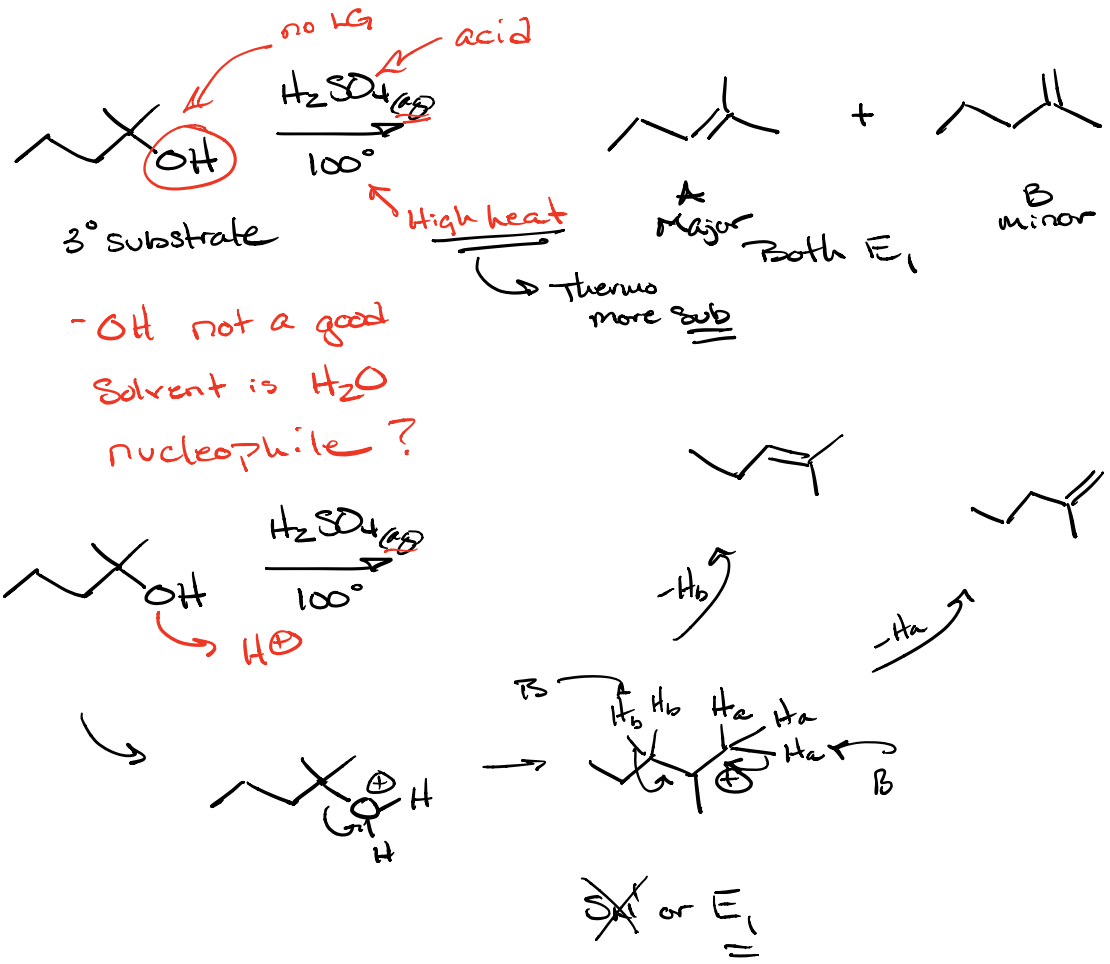
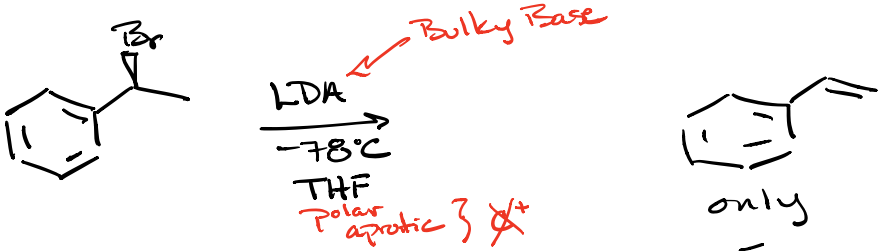

no LG
acid
H_2SO_4 (aq)
100°
OH
3° substrate
High heat
Thermo
more sub
A
Major
+
B
minor
Both E_1
-OH not a good
solvent is H_2O
nucleophile ?
H_2SO_4 (aq)
100°
$H^{\oplus}$
$-H_b$
$-H_a$
B
H_b
H_a
S_N1 or E_1

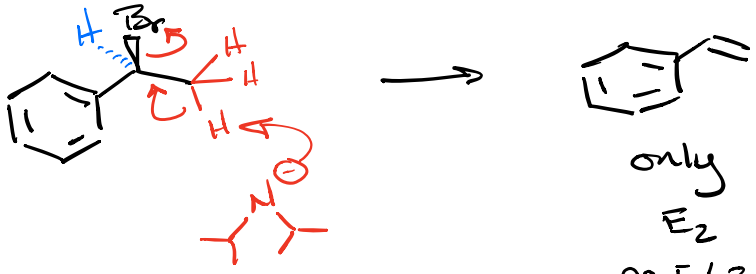


2° Benzyl bromide

LDA  Bulky Base

functions as base ⇒ not a nucleophile

~~SN2~~ ~~SN1~~ E_2, ~~E1~~



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 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

Nucleophilic Constants of Various Nucleophiles

Nucleophile	n_{CH_3I}	pK_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

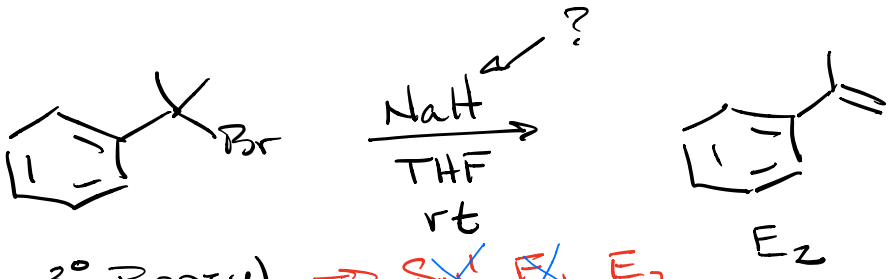
Solvents Which Promote S_N2/E2 (bimolecular)

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

Solvents Which Promote S_N1/E1 (Unimolecular/Ionizing)

Increasing nucleophilicity (solvolysis) ↑

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

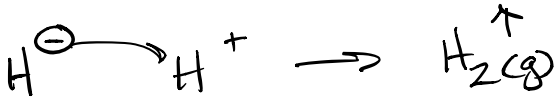


3° Benzyl ⇒ ~~S_N1~~ ~~E1~~ E_2

Br^- LG good LG

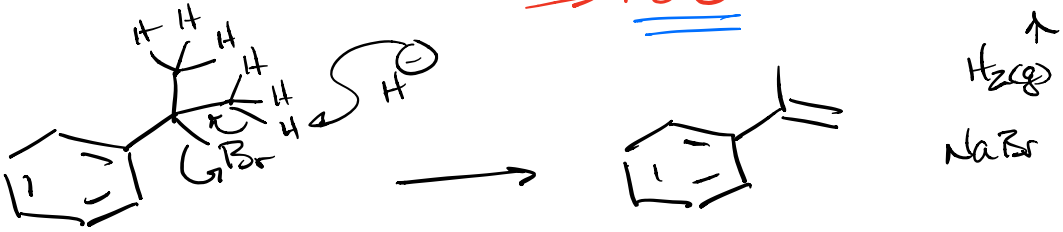
Base/nuc NaH = $^{\ominus}H$ small hard anion

Sodium hydride

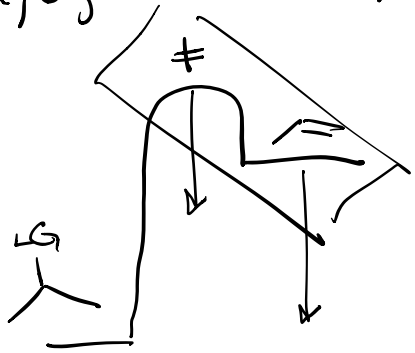


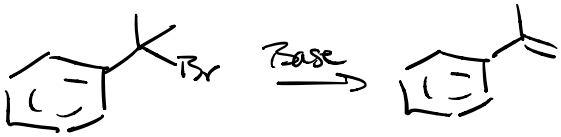
Solvent THF  polar aprotic

↳ no C^+

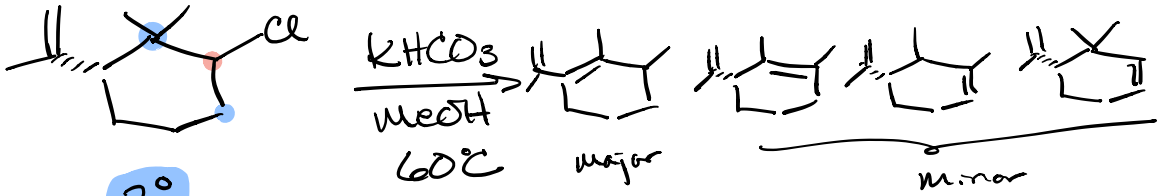


Elimination Rxns EA lowered by Conjugation in product





Highly Conjugated



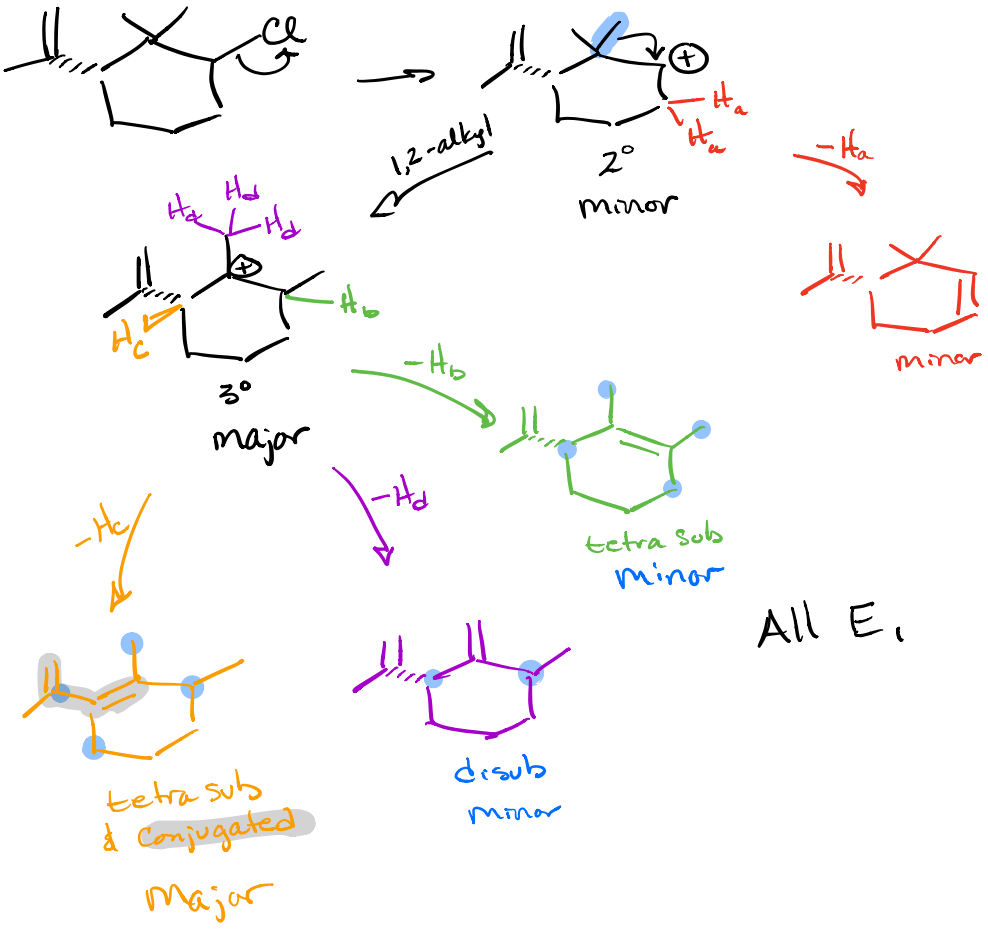
2°

LG = Cl^-

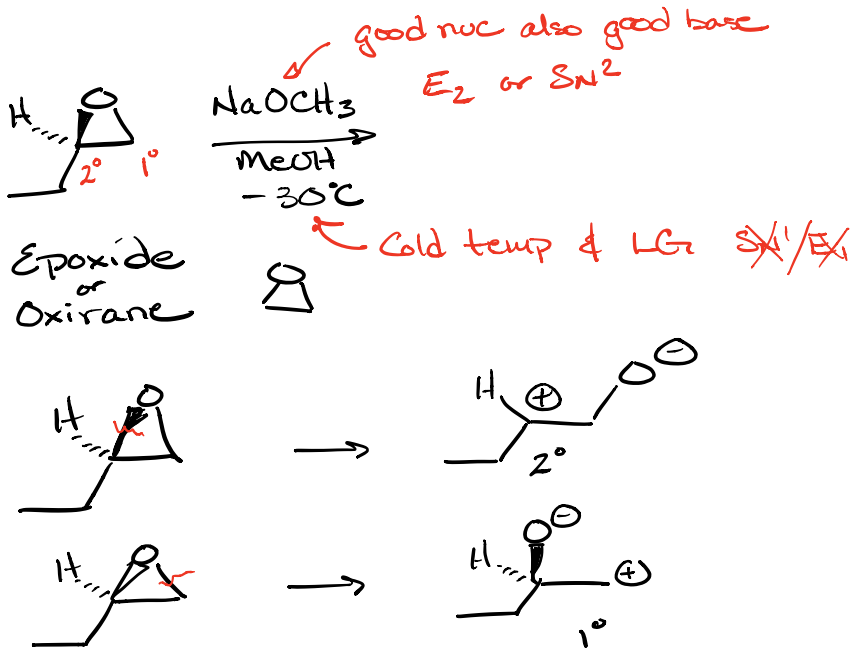
Solvent = MeOH protic ⇒ C^+

Temp = 60°C High

Nuc/Base = K^+ HCO_3^- Base ⇒ E_1 E_2



All E_1

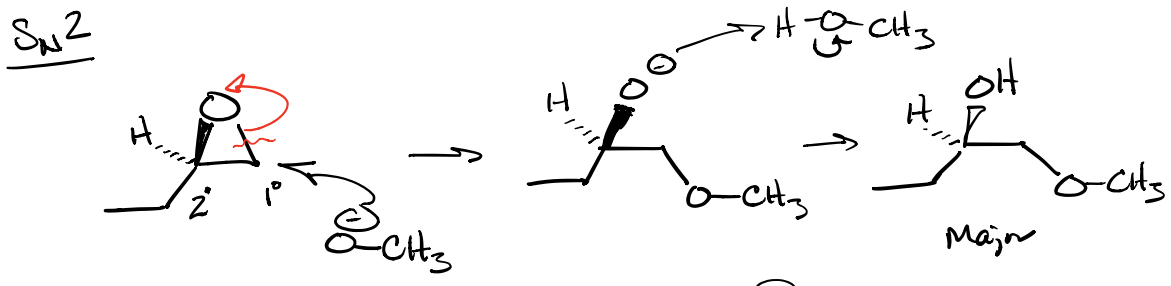


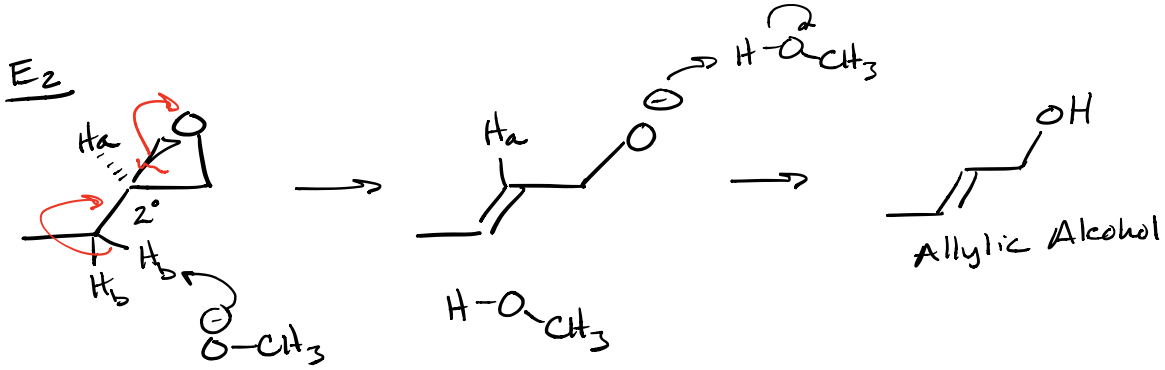
Low temp $\Rightarrow S_N2$

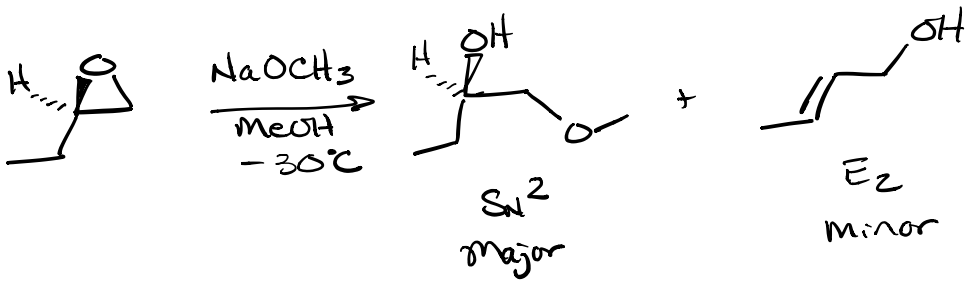
1° sub $\Rightarrow S_N2$

good nuc $\Rightarrow S_N2$ } Major

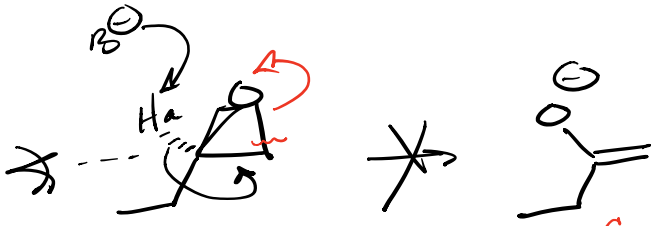
Also have strong E_2 mina





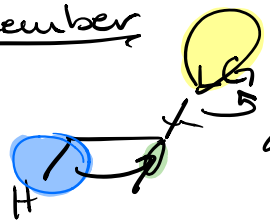


low heat
↑ substrate
good nuc

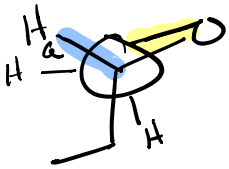


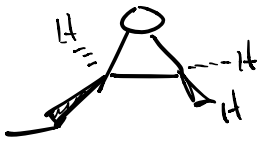
Geometry of bond does not allow Ha to go E2

Remember

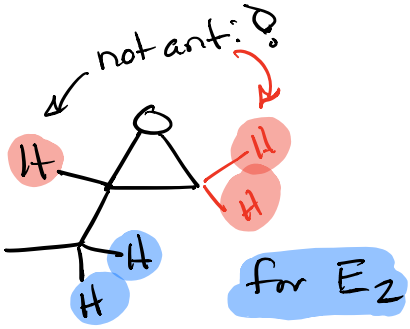


anti to one another for E2

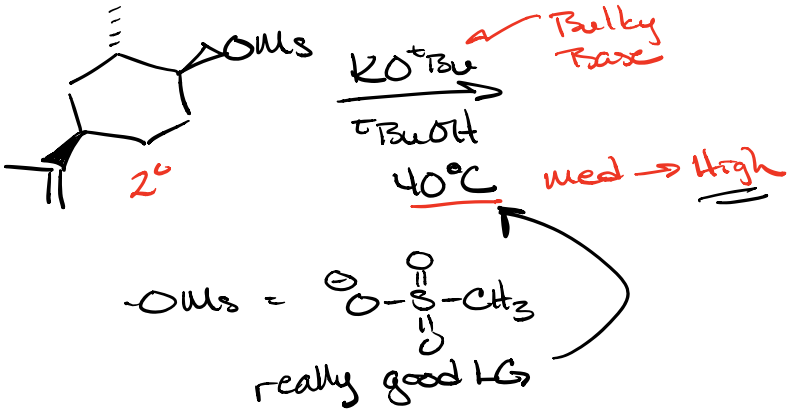


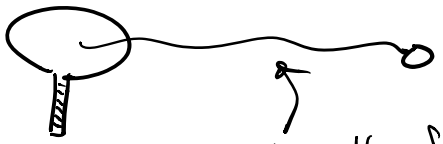


Ha is not anti to LG



for E2

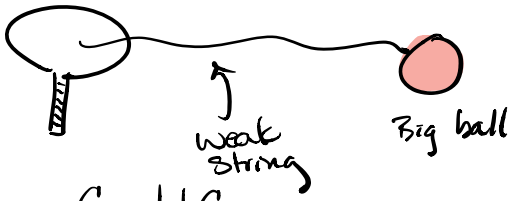




strength of bond ∝ how good LG is

Temperature

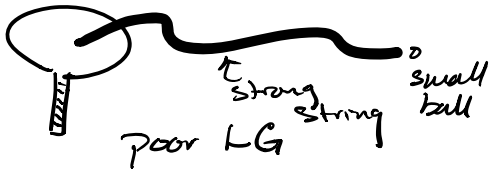
High vs Low Relative to LG



Good LG

Low temp ~ 25°C might actually be high

High > 25°C
low < 25°C

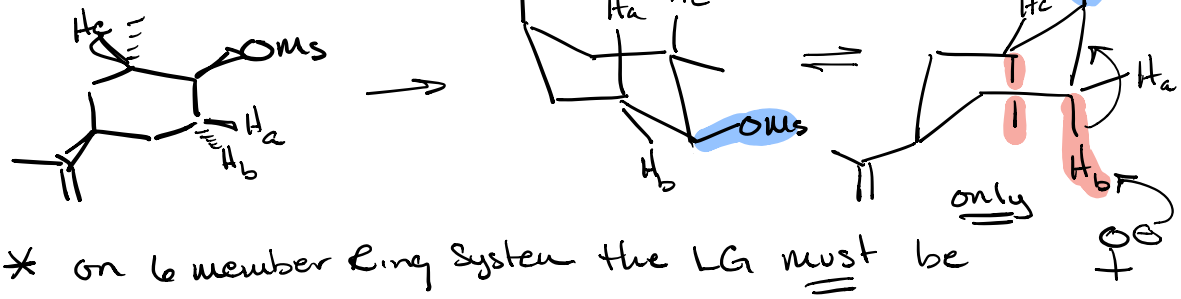


poor LG

High temp Δ or > 100°C

low < 100°C

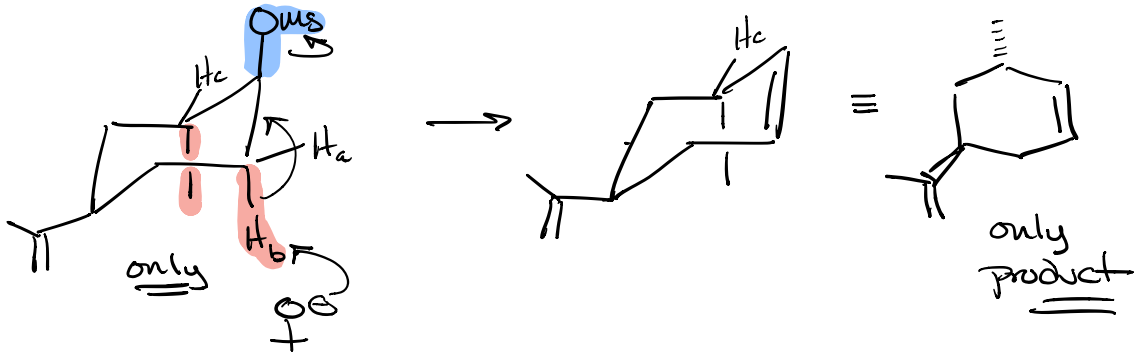
E_2 major

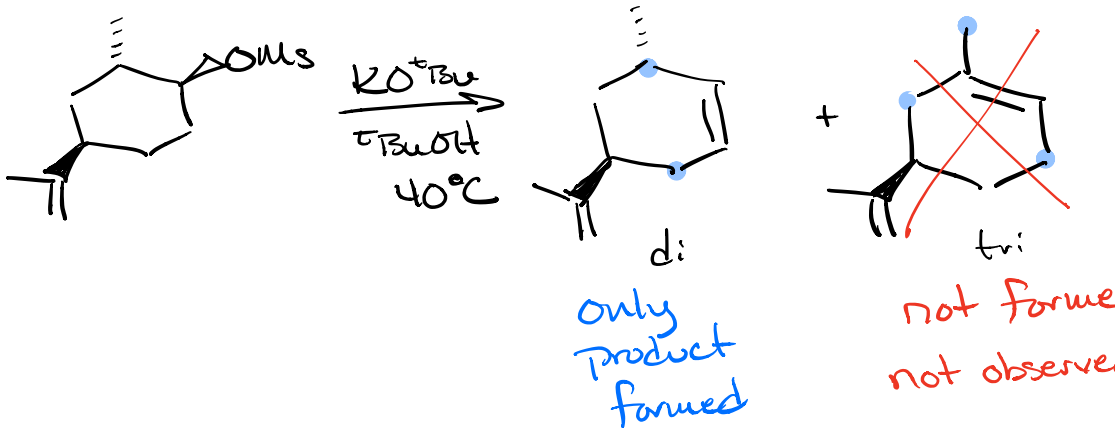


* on 6 member ring system the LG must be axial to have a anti hydrogen.

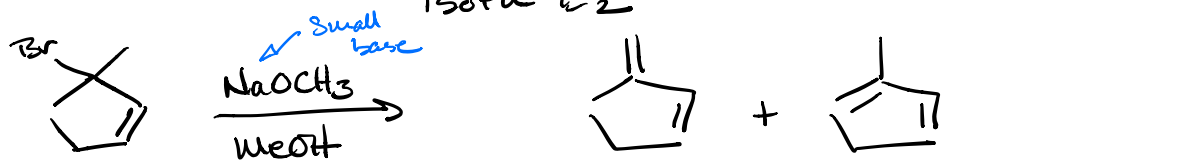
⇒ LG cannot be equitorial and go E_2

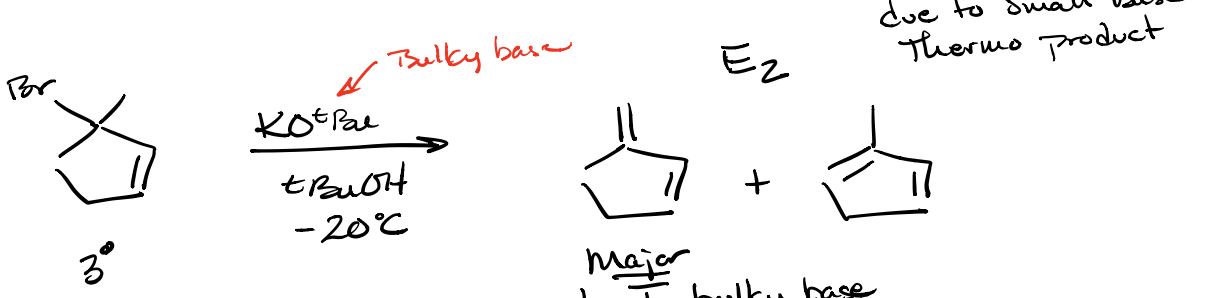
⇒ no anti H in eq orientation

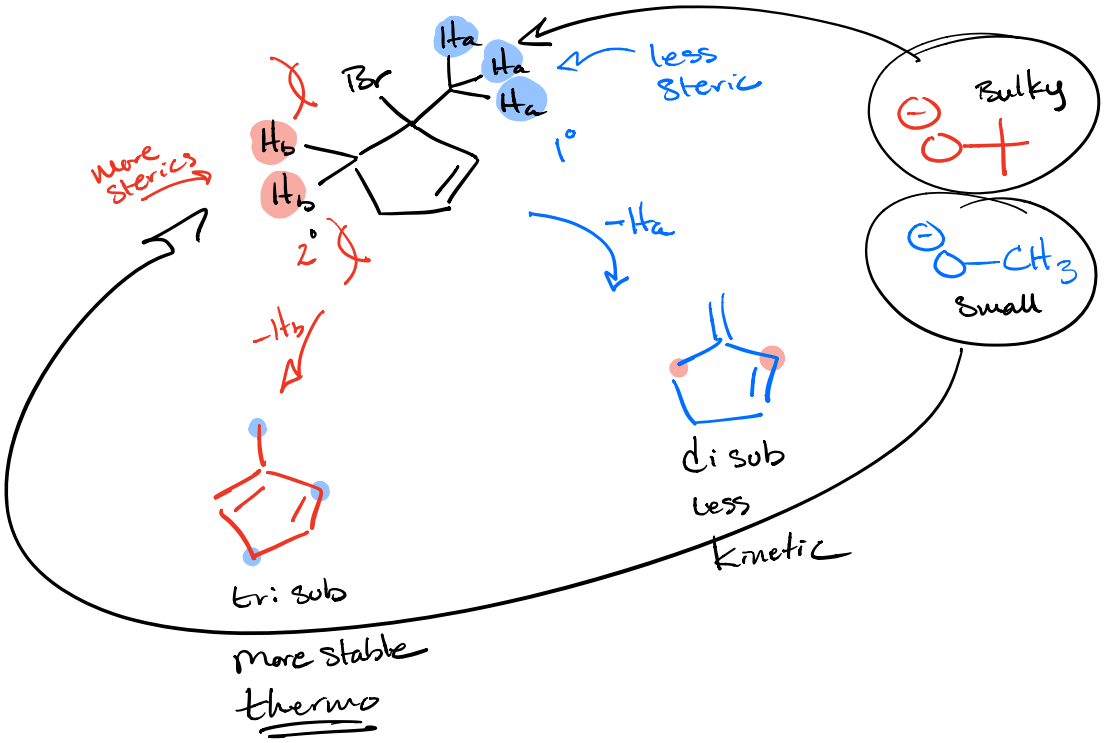

OMs
Hc
Ha
Hb
only
Hc
≡
only
product


OMs
KO^{t}Bu
^{t}BuOH
40°C
di
tri
only
product
formed
not formed
not observed

Both E_2


Br
small base
NaOCH3
MeOH
60°C
+
major
due to small base
Thermo product

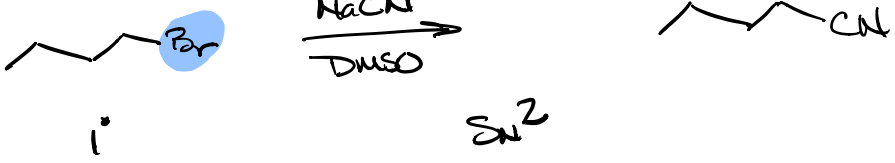

Br
3°
Bulky base
KO^{t}Bu
^{t}BuOH
-20°C
E_2
+
major
due to bulky base
preference to pull less steric hindered
proton



* Bulky Base w/ Choice of Protons
  ⟹ less sterically Hindered

Small Base
  ⟹ more Sub double bond

which rxn is faster ? ← good nuc



1° S_N2

faster Rxn ⇒ Better LG

1. Decide mechanism
2. find difference
3. Decide which Rxn faster base on differences.