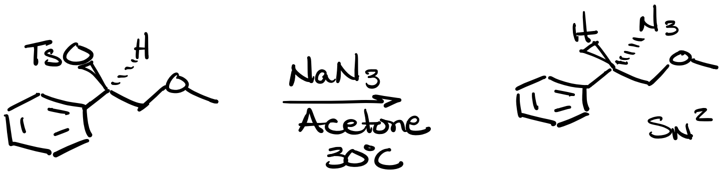
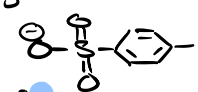
S_N1 / E_1 / S_N2 / E_2 Examples

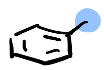
From last lecture



S_N2 major

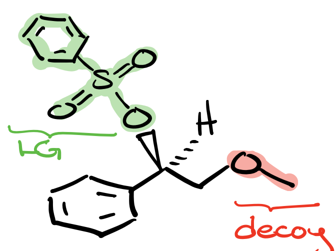
Good nuc N_3^- $\,^{\ominus}N=\overset{\oplus}{N}=N^{\ominus}$ — S_N2

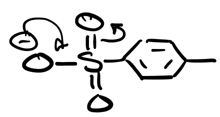
LG = OTs =  very good — S_N1, S_N2, E_1, E_2

⇒ Substrate - 2° benzylic  — S_N2

Solvent = polar aprotic — S_N2

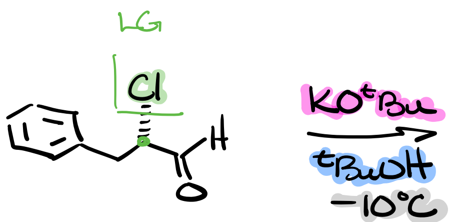
temp = mid



 For more stable as a LG

$^{\ominus}O-CH_3$ Poor LG not very stable

(2)



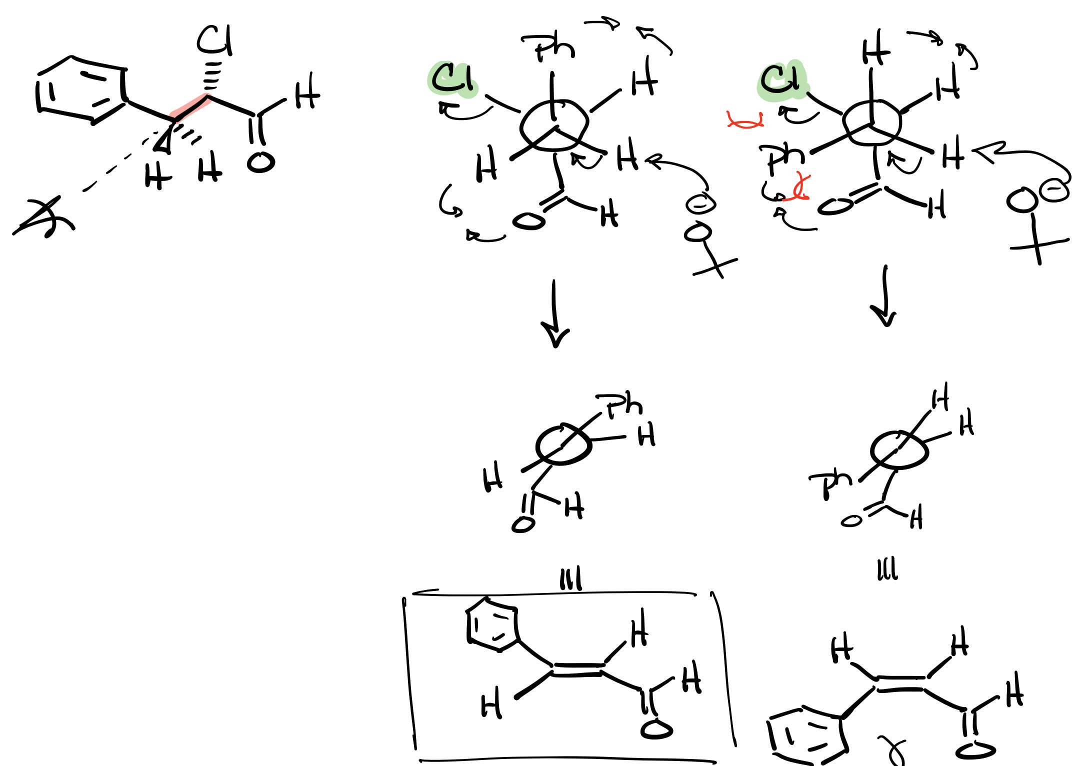
Substrate = α-halo aldehyde 2° ⇒ ~~S_N2~~

LG = $Cl^{\ominus}$ OK LG ~~E_1~~ / ~~S_N1~~ ~~S_N2~~ E_2

⇒ Nucleophile / Base = KO^{t}Bu = $K^{\oplus}\ ^{\ominus}O$–^{t}Bu = $\boxed{\text{Bulk Base, non-nucleophilic} \quad E_2}$

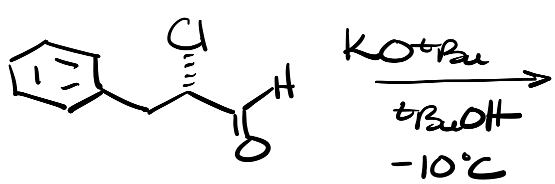
Solvent = ^{t}BuOH = polar protic ~~S_N1~~ / ~~E_1~~

Temp = −10°C → Low temp ~~S_N2~~ / ~~S_N1~~



(E) (Z)

Major Minor



Solvent → Why polar protic?

K° + ^{t}BuOH → KO^{t}Bu + $H_{2(g)}$↑

Solvent of Convience

Temp Low? KO^{t}Bu is very reactive
very exothermic

NUCLEOPHILIC SUBSTITUTION AND ELIMINATION

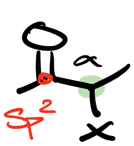
The question is how do we discern when substitution is favored verse elimination? The answer is found partly in how we should think about reactions of alkyl halides.

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

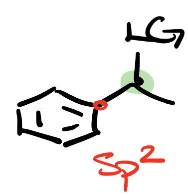
Given here is a set of guidelines (not absolutes) that can be used to arrive at the probable solution to nucleophilic substitution/elimination problems.

	Substitution	Elimination
	S_N2 (Sterics)	E2
substrate	benzyl = allyl > Me > 1^o > 2^o	3^o > 2^o > 1^o
Low sterics	{α-haloketone, α-haloester, α-halonitrile]	
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

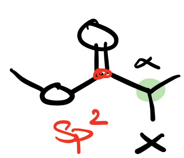
α-halo ketone



benzylic

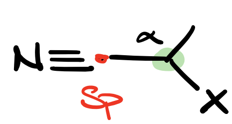


α-halo ester



Sp² & Sp Carbons have Low Sterics

α-halo nitrile



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

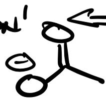
#3

E_1

major
50/50

Substrate = 3°   ~~S_N2~~ $E_1/S_N1/E_2$

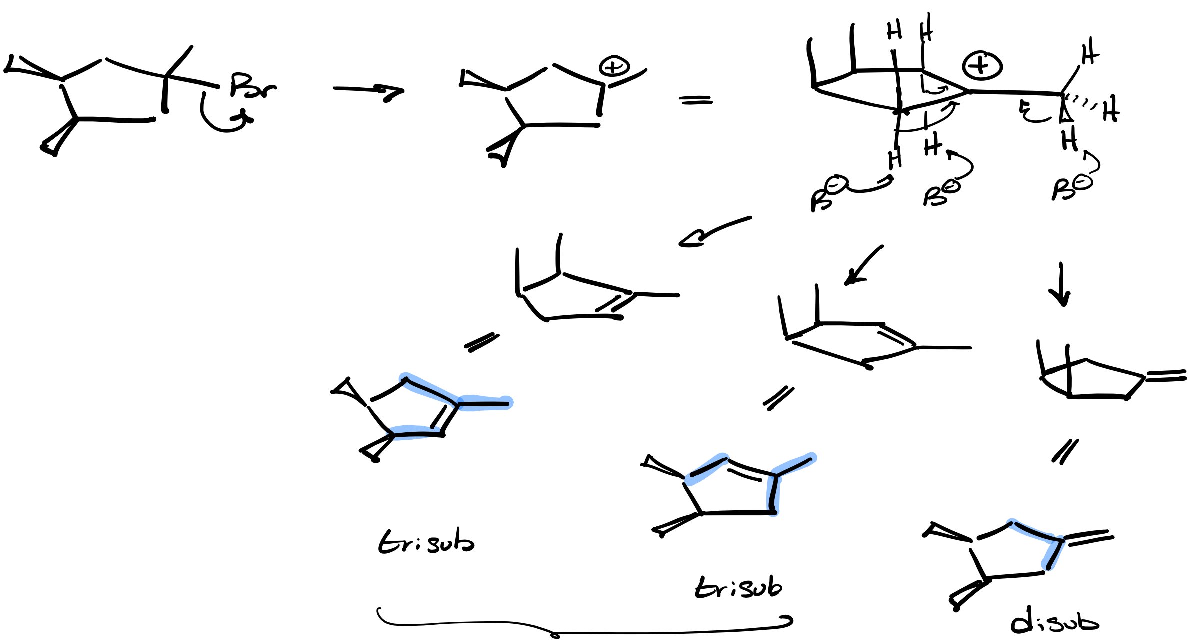
LG = Br^- good LG E_1/S_N1 ⇐ Elevated temp ⇒ $C^{\oplus}$

nuc/base = NaOAc = Na^+  weak base/poor nuc ~~S_N2~~/~~E_2~~/~~S_N1~~/E_1

Solvent = AcOH =  polar protic S_N1/E_1

temp = 40°C higher (elevated) E_1 / ~~E_2~~

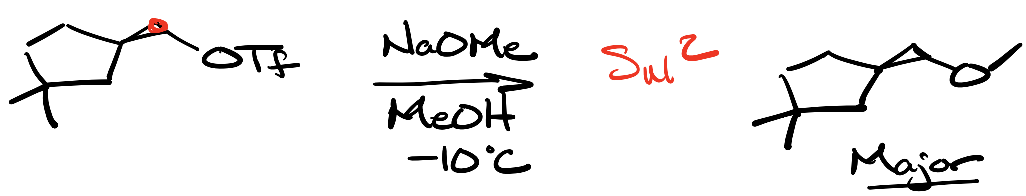
$\boxed{\text{Conclusion } E_1}$



Thermodynamic
Major

Kinetic

#4



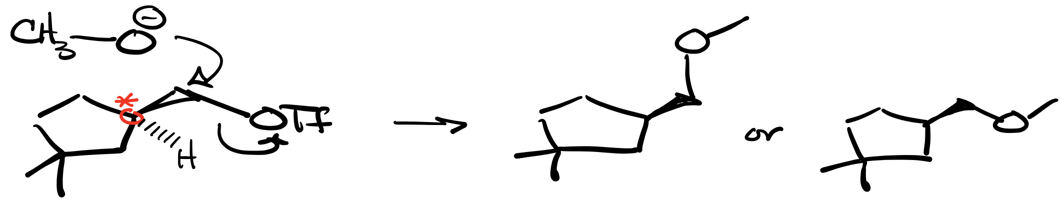
Substrate 1° ⇒ S_N2

LG = very good OTf = $^{\ominus}O-S(=O)_2-CF_3$ S_N2

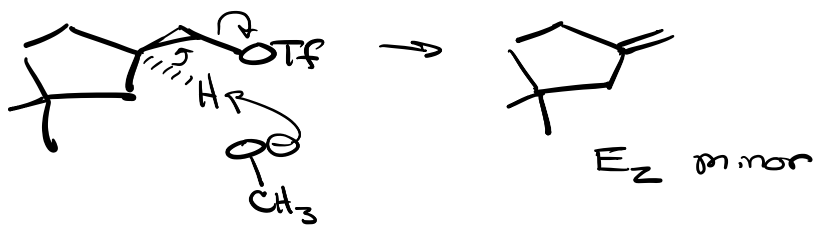
nuc/base = $^{\ominus}OCH_3$ strong base ≥ $OH^{\ominus}$ ~~Concerning~~? E_2

Solvent = polar protic S_N1/E_1 ?

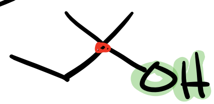
Temp = low S_N1/S_N2



Competing E_2



#5



$\xrightarrow[\text{Acetone, } 25°C]{NaOAc}$ No Reaction

Substrate 3° $S_N1/E_1/E_2$ ~~S_N2~~

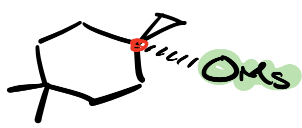
⇒ ~~LG~~ $OH^{\ominus}$ poor LG unless Acid (HCl, H_2SO_4, H_3PO_4)

nuc/base Na^+  poor nuc/weak base E_1

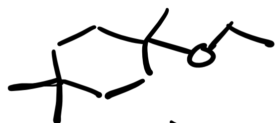
Solvent  polar aprotic S_N2/E_2

Temp 25°C Room temp middle

#6



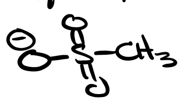
$\xrightarrow[40°C]{EtOH}$ (no nuc/base)



S_N1

major

⇒ Substrate 3° $E_1/S_N1/E_2$

⇒ LG OMs =  Good LG

⇒ nuc/base = None = Solvolysis = S_N1

⇒ Solvent = polar protic S_N1 / ~~E_1~~

⇒ Temp = 40°C Elevated ⇒ E_1 ⇒ C^+

} C^+ S_N1 / ~~E_1~~ (no anion)

Solvolysis