

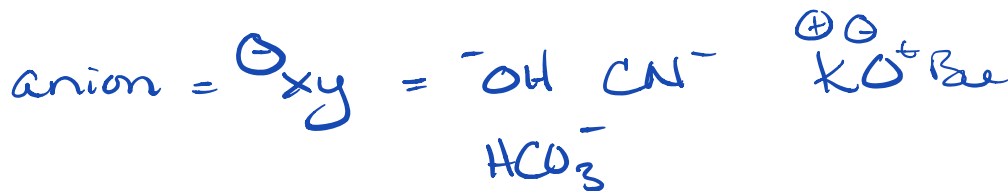
NUCLEOPHILIC SUBSTITUTION AND ELIMINATION

The question is how do we discern when substitution is favored versus 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° > 2° → 3° α-haloketone, α-haloester, α-halonitrile	3° > 2° > 1°
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
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	S_N1	E1
substrate	3° > 2°	3° > 2° > 1°
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

lesser nucleophiles



Better nuc

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)

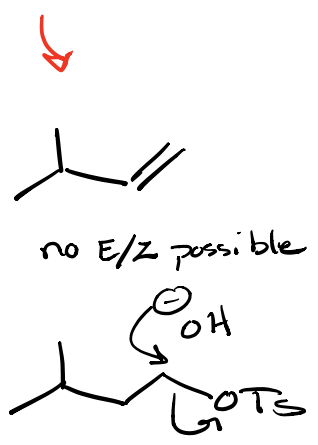
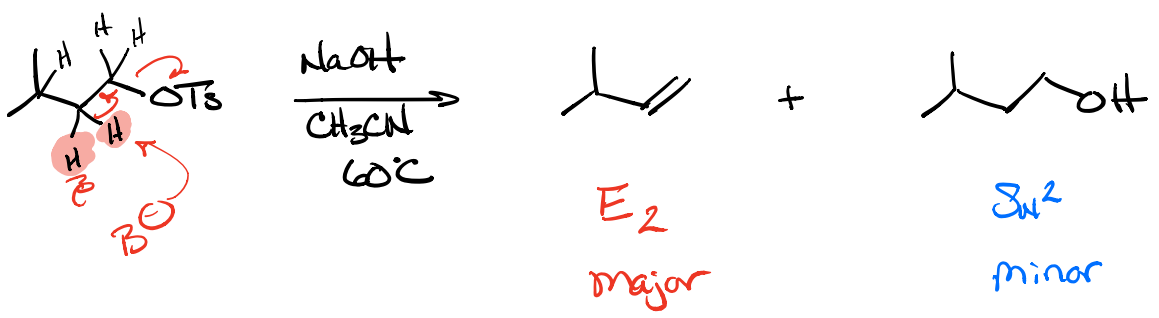
Increasing nucleophilicity (solvolysis) ↑

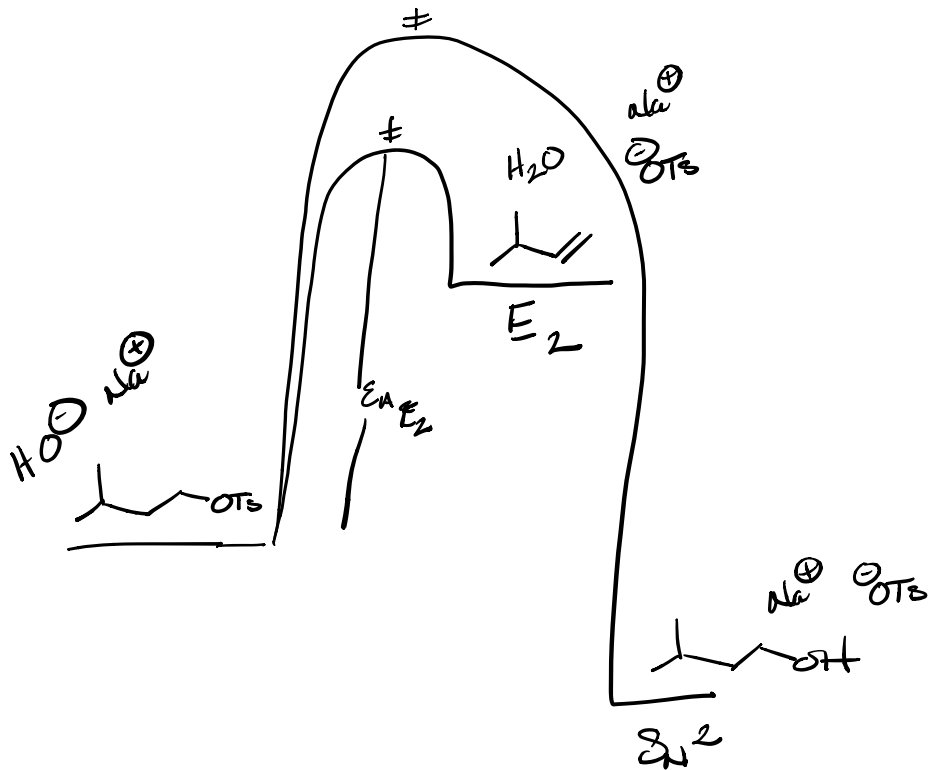
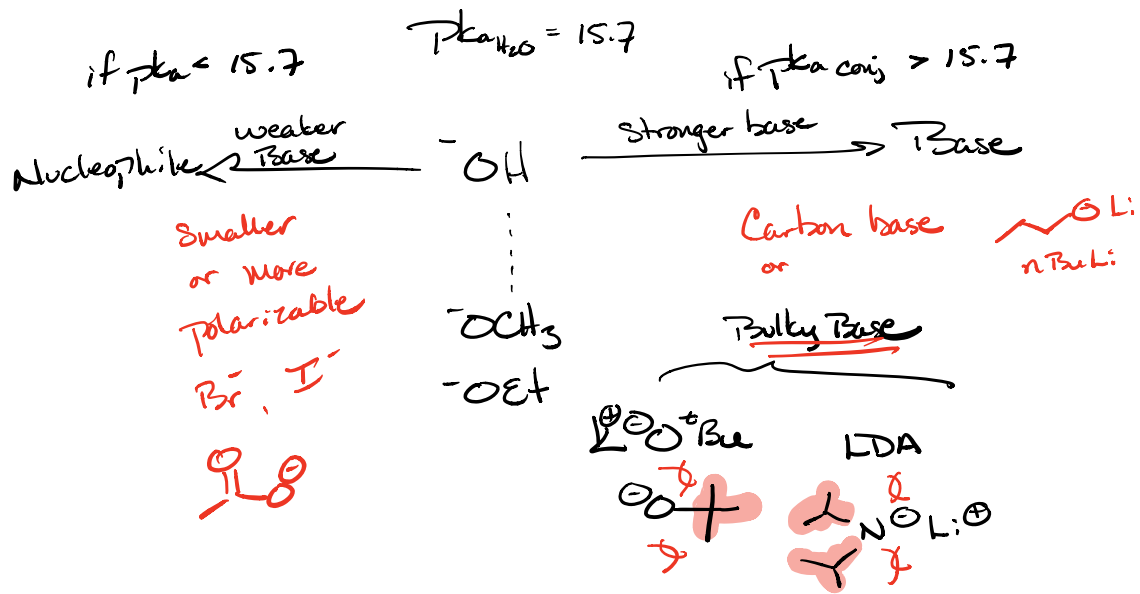
Ethanol
Methanol
50% Aqueous Ethanol
Water
Acetic Acid
Formic Acid
Trifluoroethanol
Trifluoroacetic acid

Handwritten structures: CH_3COOH , $HCOOH$, CF_3COOH , CF_3CH_2OH

↑ Substrate most important
 { nuc/base
 LG
 Solvent
 temp

Not Rigid
 Priorities change w/ each
 problem.







Substrate $1^\circ \Rightarrow \text{S}_\text{N}2$

LG = Cl^- ok LG

nuc/base = $\text{OCH}_3^- \approx \text{OH}^- \Rightarrow$ base E_2/E_1

Solvent = MeOH protic $\Rightarrow \text{S}_\text{N}1/\text{E}_1$ C^+

Temp = $25^\circ\text{C} \Rightarrow$ low temp relative to ok LG (Cl^-)
 $\text{S}_\text{N}1/\text{S}_\text{N}2$

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Increasing nucleophilicity (solvolysis) \uparrow
 Ethanol
 Methanol
 50% Aqueous Ethanol
 Water
 Acetic Acid
 Formic Acid
 Trifluoroethanol
 Trifluoroacetic acid