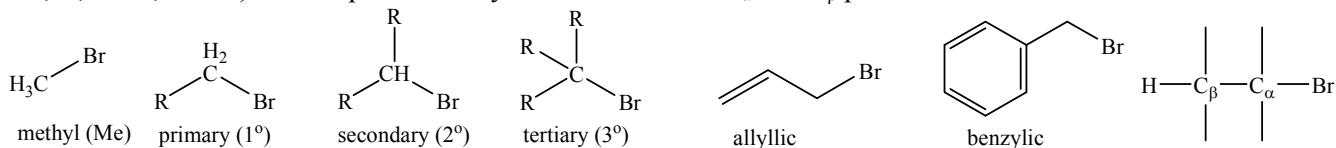


Summary of features to examine to decide what mechanism is in operation, suggested strategy

1. Look at the reaction conditions first. A strong base/nucleophile favors the bimolecular processes ($S_N2, E2$). We will simplistically view strong electron pair donation as coming from anions of all types leading to S_N2 (always backside attack) and $E2$ reactions (always "anti" $C_\beta-H/C_\alpha-X$ bond orientations, for us). A weak base/nucleophile favors the unimolecular processes ($S_N1, E1$). Weak electron pair donors will typically be neutral solvent molecules, usually water (H_2O), alcohols (ROH), or simple carboxylic acids that are liquid (RCO_2H , methanoic = formic acid or ethanoic = acetic acid), leading to S_N1 and $E1$ reactions (usually $S_N1 > E1$). See more details in the chart, just below.
2. Next, look to the reactant structures ($CH_3X, 1^\circ RX, 2^\circ RX, 3^\circ RX$, allylic, benzylic), ($X = \text{good leaving group} = -Cl, -Br, -I, -OTs, -OH_2^+$). It's important that you understand the C_α and C_β positions.



a. CH_3X (methyl) =

- i. bimolecular conditions – only reacts in S_N2 reactions with strong nucleophiles (negative charge in our course, neutral sulfur and phosphorous are exceptions) no other reactions
- ii. no unimolecular reactions ($S_N1 / E1$) due to the high energy of $^+CH_3$.

a. $1^\circ RX$ (primary) =

- i. bimolecular conditions – mainly S_N2 , some $E2$, exception = mainly $E2$ with potassium t-butoxide
- ii. no unimolecular reactions ($S_N1 / E1$) due to the high energy of $1^\circ R^+$.

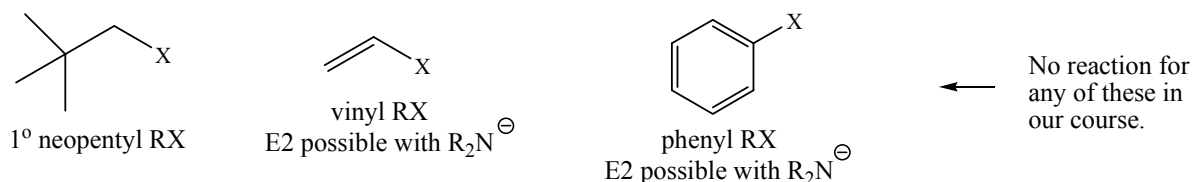
b. $2^\circ RX$ (secondary) =

- i. bimolecular conditions - both S_N2 and $E2$ are usually observed. In our course we will assume mostly S_N2 , except for stronger, sterically bulky bases and bulky bases, (see chart below) where $E2$ becomes the major product.
- ii. unimolecular conditions - generally S_N1 more than $E1$, except $E1$ is major with $ROH/H_2SO_4/\Delta$. (see chart below)


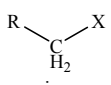
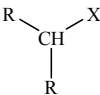

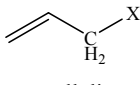
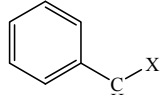
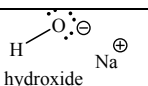
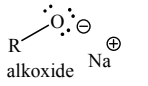
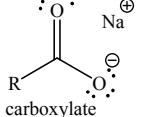
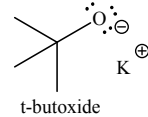
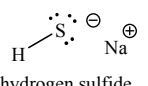
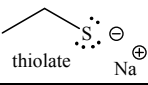
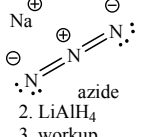
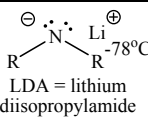
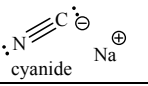
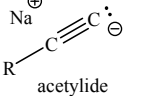
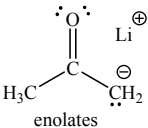
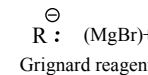
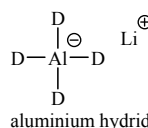
c. $3^\circ RX$ (tertiary) =

- i. bimolecular condition - only $E2$, most stable alkene is the major product, $3^\circ RX$ is too sterically hindered for S_N2 reactions to compete.
- ii. unimolecular conditions - generally $S_N1 > E1$, except $E1$ is the major product with $ROH/H_2SO_4/\Delta$.

d. Unreactive R-X patterns include: 1° neopentyl RX, vinyl RX and phenyl RX – No reaction



Simplified, generic rules for our course.

typical strong base nucleophiles are: (for our course)	 methyl	 primary	 secondary	 tertiary	 allylic	 benzylic
 hydroxide	only S _N 2	S _N 2 > E2	E2 > S _N 2 more basic	only E2	only S _N 2	only S _N 2
 alkoxide	only S _N 2	S _N 2 > E2	E2 > S _N 2 more basic	only E2	only S _N 2	only S _N 2
 carboxylate	only S _N 2	S _N 2 > E2	S _N 2 > E2 less basic	only E2	only S _N 2	only S _N 2
 t-butoxide	only S _N 2	E2 > S _N 2 exception (bulky & basic)	only E2	only E2	not discussed in our course	not discussed in our course
 hydrogen sulfide	only S _N 2	S _N 2 > E2	S _N 2 > E2 less basic	only E2	only S _N 2	only S _N 2
 thiolate	only S _N 2	S _N 2 > E2	S _N 2 > E2 less basic	only E2	only S _N 2	only S _N 2
 azide 2. LiAlH ₄ 3. workup	only S _N 2	S _N 2 > E2	S _N 2 > E2 less basic	only E2	only S _N 2	only S _N 2
 LDA = lithium diisopropylamide	not discussed in our course	only E2 exception (bulky & basic)	only E2	only E2	not discussed in our course	not discussed in our course
 cyanide	only S _N 2	S _N 2 > E2	S _N 2 > E2 less basic	only E2	only S _N 2	only S _N 2
 acetylide	only S _N 2	S _N 2 > E2	E2 > S _N 2 more basic	only E2	only S _N 2	only S _N 2
 enolates	only S _N 2	S _N 2 > E2	S _N 2 > E2 less basic	only E2	only S _N 2	only S _N 2
 Grignard reagents	Not generally useful with RBr in our course.	Not generally useful with RBr in our course.	Not generally useful with RBr in our course.	Not generally useful with RBr in our course.	Not generally useful with RBr in our course.	Not generally useful with RBr in our course.
 aluminium hydride	only S _N 2	S _N 2 > E2	S _N 2 > E2 less basic	only E2	only S _N 2	only S _N 2

NaH, KH and NaNR₂ react only as bases in our course. Grignard reagents, RMgBr, do not undergo useful reactions with RBr compounds.

Reaction Templates - sideways and vertical perspectives (either one will work)

$S_N2/E2$ (HO^- or CH_3O^-) always backside for S_N2 and usually anti $C_\alpha-H/C_\beta-X$ attack for E2

$S_N1/E1$ (H_2O / CH_3OH) - attack from either face of R^+ for both reactions (S_N1 and E1)

2° RX = all mechanisms are possible

Name: butane, pentane, hexane, heptane, ...

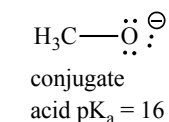
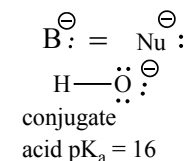
X = -Br, -D = deuterium

Substitution = (2,3), (3,4), (4,5), ...

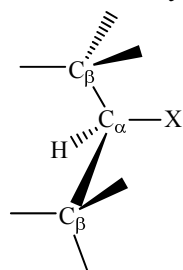
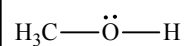
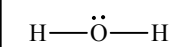
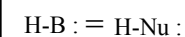
Stereochemistry = R / S

isotopes of hydrogen
H = protium (proton)
D = deuterium
T = tritium

Strong (S_N2 / E2)



Weak (S_N1 / E1)



2R-bromo-3R-deuteriohexane
2R-bromo-3S-deuteriohexane
2S-bromo-3R-deuteriohexane
2S-bromo-3S-deuteriohexane

3R-bromo-2R-deuteriohexane
3R-bromo-2S-deuteriohexane
3S-bromo-2R-deuteriohexane
3S-bromo-2S-deuteriohexane

R = H

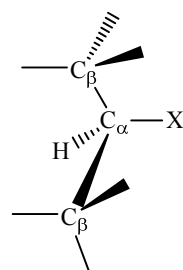
E2 = 1 product, (no E/Z, C=CH₂)

E1 = 1 product, (no E/Z, C=CH₂)

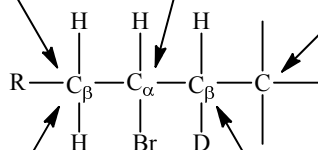
S_N2 = 1 product (inversion)

S_N1 = 2 products (racemization)

Who cares?



conditions?



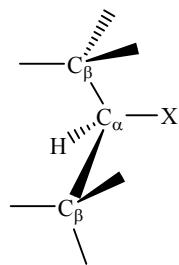
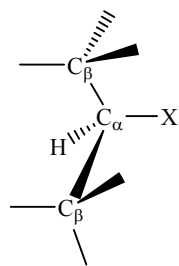
R = carbon

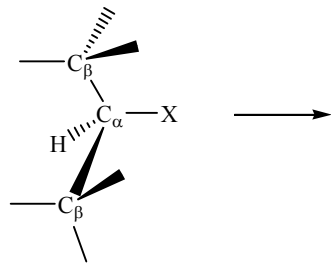
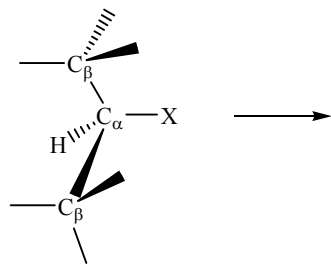
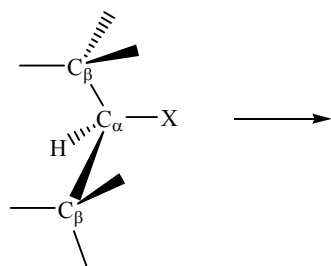
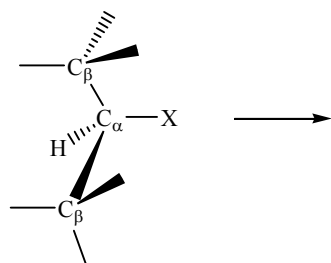
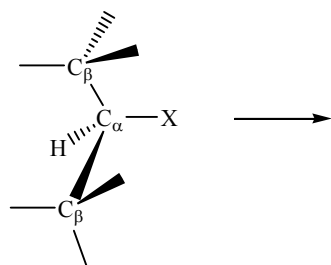
E2 = 2 products (E and Z)

E1 = 2 products (E and Z)

E2 = 2 products (E or Z with or without D)

E1 = 4 products (both E & Z, with H and with D)




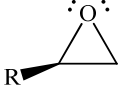
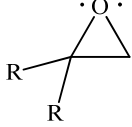
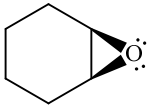
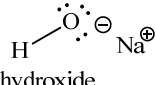
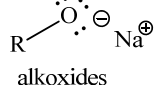
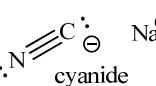
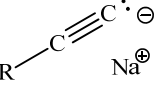
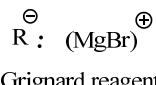
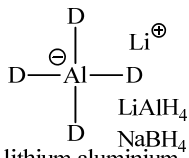


Carbonyl Patterns (C=O) - Simple Examples For Our Course. Most of these reactions require a final workup step (protonation of the alkoxide anion).

weak electrophiles when neutral strong base/nucleophile	$\begin{array}{c} \text{:O:} \\ \\ \text{H}-\text{C}-\text{H} \end{array}$ methanal formaldehyde	$\begin{array}{c} \text{:O:} \\ \\ \text{H}_3\text{C}-\text{C}-\text{H} \end{array}$ ethanal acetaldehyde aldehydes	$\begin{array}{c} \text{:O:} \\ \\ \text{H}_3\text{C}-\text{C}-\text{CH}_3 \end{array}$ propanone acetone ketones	$\begin{array}{c} \text{:O:} \\ \\ \text{H}_3\text{C}-\text{C}-\text{O}-\text{C}-\text{CH}_3 \\ \\ \text{H}_2 \end{array}$ ethyl ethanoate ethyl acetate esters
$\text{H}-\ddot{\text{O}}^- \text{Na}^+$ hydroxide	carbonyl addition (hydration)	carbonyl addition (hydration)	carbonyl addition (hydration)	acyl substitution (ester hydrolysis) base hydrolysis saponification
$\text{R}-\ddot{\text{O}}^- \text{Na}^+$ alkoxides	carbonyl addition (hemi-acetal)	carbonyl addition (hemi-acetal)	carbonyl addition (hemi-ketal)	not discussed in our course
$\text{:N}\equiv\text{C}^- \text{Na}^+$ cyanide	carbonyl addition (cyanohydrin)	carbonyl addition (cyanohydrin)	carbonyl addition (cyanohydrin)	not discussed in our course
$\text{R}-\text{C}\equiv\text{C}^- \text{Na}^+$ terminal acetylides	carbonyl addition (propargyl alcohol)	carbonyl addition (propargyl alcohol)	carbonyl addition (propargyl alcohol)	not discussed in our course
$\text{R}^- \text{Mg}^+ \text{Br}$ Grignard reagents made from RBr + Mg	carbonyl addition (1° alcohol)	carbonyl addition (2° alcohol)	carbonyl addition (3° alcohol)	reacts twice 1. carbonyl substitution 2. carbonyl addition (3° alcohol)
$\begin{array}{c} \text{D} \\ \\ \text{D}-\text{Al}^- \text{Li}^+ \\ \\ \text{D} \end{array}$ lithium aluminium deuteride (hydride)	carbonyl addition (methanol)	carbonyl addition (1° alcohol)	carbonyl addition (2° alcohol)	reacts twice 1. carbonyl substitution 2. carbonyl addition (1° alcohol)

Mechanisms:

Epoxide Compounds - Simple Examples For Our Course. Most of these reactions require a final workup step (protonation of the alkoxide anion).

weak electrophiles when neutral strong base/nucleophile	 ethylene oxide	 monosubstituted epoxide	 geminal substituted epoxide	 cyclohexene oxide
 hydroxide	epoxide addition with nucleophilic attack at less hindered carbon	epoxide addition with nucleophilic attack at less hindered carbon	epoxide addition with nucleophilic attack at less hindered carbon	epoxide addition with nucleophilic attack at less hindered carbon
 alkoxides	epoxide addition with nucleophilic attack at less hindered carbon	epoxide addition with nucleophilic attack at less hindered carbon	epoxide addition with nucleophilic attack at less hindered carbon	epoxide addition with nucleophilic attack at less hindered carbon
 cyanide	epoxide addition with nucleophilic attack at less hindered carbon	epoxide addition with nucleophilic attack at less hindered carbon	epoxide addition with nucleophilic attack at less hindered carbon	epoxide addition with nucleophilic attack at less hindered carbon
 terminal acetylides	epoxide addition with nucleophilic attack at less hindered carbon	epoxide addition with nucleophilic attack at less hindered carbon	epoxide addition with nucleophilic attack at less hindered carbon	epoxide addition with nucleophilic attack at less hindered carbon
 Grignard reagents made from RBr + Mg	epoxide addition with nucleophilic attack at less hindered carbon	epoxide addition with nucleophilic attack at less hindered carbon	epoxide addition with nucleophilic attack at less hindered carbon	epoxide addition with nucleophilic attack at less hindered carbon
 lithium aluminium deuteride (hydride)	epoxide addition with nucleophilic attack at less hindered carbon	epoxide addition with nucleophilic attack at less hindered carbon	epoxide addition with nucleophilic attack at less hindered carbon	epoxide addition with nucleophilic attack at less hindered carbon

Mechanisms:

S_N1 / E1 Tendencies - Simplified, generic rules for our course.

typical weak base nucleophiles are: (for our course)	$\text{H}_3\text{C}-\text{X}$ methyl	$\begin{array}{c} \text{R} \\ \\ \text{C}-\text{X} \\ \\ \text{H}_2 \end{array}$ primary	$\begin{array}{c} \text{R} \quad \text{X} \\ \diagdown \quad / \\ \text{CH} \\ \\ \text{R} \end{array}$ secondary	$\begin{array}{c} \text{R} \quad \text{X} \\ \diagdown \quad / \\ \text{C} \\ \\ \text{R} \end{array}$ tertiary
$\text{H}-\ddot{\text{O}}-\text{H}$	no reaction	no reaction	S _N 1 > E1 (makes alcohols)	S _N 1 > E1 (makes alcohols)
$\text{R}-\ddot{\text{O}}-\text{H}$	no reaction	no reaction	S _N 1 > E1 (makes ethers)	S _N 1 > E1 (makes esters)
$\begin{array}{c} \text{:O:} \\ \\ \text{C} \\ \\ \text{O}-\text{H} \\ \text{:} \end{array}$	no reaction	no reaction	S _N 1 > E1 (makes ethers)	S _N 1 > E1 (makes esters)

Useful ROH Reactions - Not enough time to discuss these in our course. Simplified, generic predictions.

alcohol reactions in strong acid: (for our course)	$\text{H}-\text{X}$ (X = Cl, Br or I)	PBr ₃	1. TsCl 2. NaBr	CrO ₃ pyridine (PCC)	CrO ₃ H ₂ O/H ₃ O ⁺ (Jones)	others not discussed
$\text{H}_3\text{C}-\text{OH}$ methyl	S _N 2 make RBr	S _N 2 make RBr	not needed	E2 aldehydes	E2 x 2 carboxylic acids (C=O hydrate)	Fischer Ester Synthesis H ₂ SO ₄ (cat.) ROH + RCO ₂ H (-H ₂ O)
$\begin{array}{c} \text{R} \\ \\ \text{C}-\text{OH} \\ \\ \text{H}_2 \end{array}$ primary	S _N 2 make RBr	S _N 2 make RBr	not needed	E2 aldehydes	E2 x 2 carboxylic acids (C=O hydrate)	Acetal / Ketal Synthesis TsOH (cat.) 2 x ROH + R ₂ CO (-H ₂ O)
$\begin{array}{c} \text{R} \quad \text{OH} \\ \diagdown \quad / \\ \text{CH} \\ \\ \text{R} \end{array}$ secondary	S _N 1 make RBr	S _N 1 make RBr	1. acyl-like substitution 2. S _N 2 make RBr (avoids rearrangements)	E2 ketones	E2 ketones	Imine Synthesis TsOH (cat.) RNH ₂ + R ₂ CO (-H ₂ O) R ₂ NH + R ₂ CO (-H ₂ O)
$\begin{array}{c} \text{R} \quad \text{OH} \\ \diagdown \quad / \\ \text{C} \\ \\ \text{R} \end{array}$ tertiary	S _N 1 make RBr	S _N 1 make RBr	not discussed	no reaction	no reaction	Alkoxide Synthesis NaH + ROH E1 Alkene Synthesis ROH + H ₂ SO ₄ Δ (-H ₂ O) Others, but no room