The competing reactions to consider with this group of nucleophiles/bases are SN2 and E2 (because all of the above nucleophiles are considered strong by us). 1, 5 and 7 you can use, as is. 2, 3, 4, 6, 8, 9 and 10 you will have to make according to "acid/base" procedures given below.

The secondary, tertiary, benzylic and allylic R-X compounds listed at the left can be made via free radical substitution at an sp3 C-H bond (Br2/hν). The primary R-X compounds are made by 1o ROH + HBr in an SN2 reaction on the protonated alcohol.

**SN2 reactions always go by inversion of configuration (backside attack)**

**E2 reactions always go by the anti Cβ−H/Cα-X conformation (in our course)**

**Some factors favoring SN2 are:**

1. less steric hindrance (at both the Cα position and the Cβ position), and
2. less basic nucleophile/base (judge this by the pKa of the conjugate acids, lower value)
3. allylic and benzylic R-X compounds react very fast via SN2 reactions

**The opposite of these favors E2 reactions**

1. more steric hindrance in the R-X compound and more steric hindrance in the nucleophile/base
2. more basic nucleophile/base (judge this by the pKₐ of the conjugate acids, higher value)

**Some Generalities**

1. methyl-X always reacts by SN2 with strong base/nucleophiles
2. primary R-X almost always reacts by SN2 > E2 with one exception (potassium t-butoxide reacts with E2 > SN2 because it is a sterically large base)
3. secondary R-X can react by both SN2 and E2 (this is the most ambiguous RX pattern to evaluate).
   a. When the base is stronger (higher pKₐ for its conjugate acid) the result is E2 > SN2 (hydroxide, alkoxides, terminal acetylides)
   b. When the base is weaker (lower pKₐ for its conjugate acid) the result is SN2 > E2 (carboxylates, cyanide, imidate, enolates, thiolate)
4. tertiary R-X only can react by E2 reactions with strong base/nucleophiles (but there has to be an anti Cβ−H to react)
5. allylic and benzylic R-X react very fast by SN2
6. neopentyl R-X does not react well by any of our mechanisms (SN2/E2 or SN1/E1)
7. vinyl R-X and phenyl R-X do not react by SN2/E2 or SN1/E1 reactions
Write a 3D structure of (3S,4S)-3-iodo-4-methoxyhexane.

1. **What is/are the expected product(s) of this compound with sodium cyanide in DMSO (dimethylsulfoxide is the solvent).** Show all mechanistic details clearly for how each of the possible products is formed (3D structures, curved arrows, lone pairs and formal charges).

**Possible Key**

1. **3D structure**

   (3S,4S)-3-iodo-4-methoxyhexane

2. **mechanisms and products**
Write a 3D structure for the given name. (2R,3S,4R) 2-deuterio-3-bromo-4-methylhexane

All variations are shown below, which are enantiomers, diastereomers?

How would the problem change if the bromine, deuterio and/or methyl were moved to another position?

What are the expected products if hydroxide is the electron donor? How would the expected products change if hydroxide were changed to ethoxide (?), water (?) or ethanol(?). Write a separate mechanism showing the formation of each possible product.

How to write a 3D structure for the given name. (2R,3S,4R) 2-deuterio-3-bromo-4-methylhexane

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What are the expected products if hydroxide is the electron donor? How would the expected products change if hydroxide were changed to ethoxide (?), water (?) or ethanol(?). Write a separate mechanism showing the formation of each possible product.

1. Draw \( C_\alpha = C_3 \) (in this problem) first in its proper configuration (R or S).

2. Add in groups on \( C_\beta \) carbons in any manner. If you are lucky, they will be in the correct configuration. If you are wrong, then switch two convenient groups.

3. If there is a strong nucleophile/base, then write out all of the \( S_N2/E2 \) possibilities. The \( S_N2 \) product will form only by inversion of configuration. Any \( E2 \) products require an anti \( C_\beta-H \) and \( C_\alpha-X \) conformation. You should draw every possible conformation and examine the predicted alkene that forms. This will determine the configuration of any alkene products. You must look at every possible \( C_\beta-H \) to determine all of the possible alkene products.

4. If there is a weak nucleophile/base, then write out all of the \( S_N1/E1 \) possibilities. The first step for both mechanisms is loss of the leaving group which forms a carbocation. If we ignore rearrangement possibilities, then there are two choices, \( S_N1 \) and \( E1 \), that can occur. For \( S_N1 \) products add the :Nu-H from the top and bottom. If \( C_\alpha \) is a chiral center, there will be two different products. It is also possible that there are two products in a ring with cis/trans possibilities and no chiral centers. You will also have to take off the extra proton via an acid/base reaction to get a neutral product. For \( E1 \) products you will have to remove any \( C_\beta-H \) (no anti requirement). Make a double bond between all different \( C_\beta-H's \). Switch the two groups on either of the carbons of each double bond to see if different stereoisomers are formed. The possible outcomes are that the switch produces no change or E/Z stereoisomers are formed. Any possible outcome is a predicted result in \( E1 \) reactions.
Available chemicals from the catalog

Possible Starting Hydrocarbons

CH₃   CH₃CH₃   H---C≡C---H

Additional starting structures available for now because we cannot make them - YET. Each will be eliminated as we learn how to make them.

OH  OH  OH  OH
H---COOH   H---COOH   H---COOH   t-butyl alcohol

Other commercially available chemicals and reagents - you can invoke these whenever you need them.

Br₂  Cl₂  HCl  HBr  HI  H₂SO₄  H₂O   Na  Na  Na  Na  Na  Li
=  =  =  =  =  =  =  =  =  =
  S---O   S---O   S---O   S---O   S---O   S---O
  H---N   H---N   H---N   H---N   H---N
sodium hydride (very strong base)  sodium amide (very strong base)  sodium hydride (very strong base)  potassium hydride (very strong base)  lithium aluminumhydride = LAH (very strong nucleophilic hydride)

= Ts-Cl (tosyl chloride) makes ROH into tosylates, with pyridine

pyridine = proton sponge

n-butyl lithium (very strong base)

Some useful acid/base reactions using the above reagents.

Synthesis of lithium diisopropyl amide, LDA. (acid / base reaction)

Think - sterically bulky, very basic that goes after weakly acidic protons.

Synthesis of carbanion nucleophiles with LDA. (acid / base reaction)

terminal acetylides are good nucleophiles at methyl, primary, allyl and benzyl RX, mostly E2 at secondary and only E2 tertiary RX
Ketone enolates are good nucleophiles at methyl, primary, secondary, allyl and benzyl RX, only E2 at tertiary RX.

Ester enolates are good nucleophiles at methyl, primary, secondary, allyl and benzyl RX, only E2 at tertiary RX.

Alkoxide enolates are good nucleophiles at methyl, primary, secondary, allyl and benzyl RX, mostly E2 at secondary and only E2 tertiary RX, they are also used as moderately strong bases.

Potassium t-butoxide, sterically bulky base that mostly does E2 reactions with RX compounds (except SN2 with CH3-X).

Carboxylates are good nucleophiles at methyl, primary, secondary, allyl and benzyl RX, making esters, only E2 at tertiary RX.

SN2 with acetate produces esters, then acyl substitution with hydroxide produces the alcohol, if desired.

Acetate is less basic than hydroxide and does more SN2 than E2 at 2° RX.
Synthesis of imidate and alkyl imide (precursor to 1° amines)

\[
\begin{align*}
K_{eq} &= \frac{K_{a1}}{K_{a2}} = \frac{10^{-8}}{10^{-16}} = 10^{8} \\
\text{resonance stabilized makes imidate less basic and a better behaved nucleophile}
\end{align*}
\]

Propose a synthetic plan for the following molecules starting from the above compounds. You should be able to show a reaction (reagent and product) for each step of your synthesis. You should also be able to write out a mechanism for each reaction you use. As you progress through organic chemistry, you will find there is often more than one synthetic approach. If we have covered it, you should be able to do it.

Group A (bromo compounds from free radical substitution at sp³ C-H positions)

Free Radical substitution at sp³ C-H

\[
\begin{align*}
\text{H}_3\text{C-Br} & \quad \text{R-H} + \text{Br}_2 & \quad \text{R-Br} + \text{H-Br} \\
\text{1} & \quad \text{2} & \quad \text{3} & \quad \text{4} & \quad \text{5} & \quad \text{6} & \quad \text{7} & \quad \text{8} & \quad \text{9} & \quad \text{10}
\end{align*}
\]

The usual preference for a hydrogen by a halogen atom is benzyl > allyl > 3° > 2° > 1° > methyl C-H
Group B (bromo compounds from given primary alcohols and H-Br via $S_N2$ reactions, $2^\circ$ and $3^\circ$ ROH react via $S_N1$, covered later) We need a reaction like this, for now, because $1^\circ$ C-H positions are less reactive in free radical substitution reactions.

Group C (alcohols from methyl and primary bromides and hydroxide via $S_N2$ reactions)

Group D (alcohols from secondary bromides and acetate via $S_N2$ reactions, followed by acyl substitution)

Synthesis of ethanoate (acetate) nucleophile with sodium hydroxide. (acid / base reaction)

We can't make these secondary alcohols using $S_N2$ reactions with hydroxide and RX because hydroxide is more basic and we get E2 $>$ $S_N2$. 

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Group E (ethers from methyl and primary bromides and alkoxides via $S_N$2 reactions, t-butoxide reacts mostly by E2, $2^o$ RX and $3^o$ RX mainly form E2 products too) See comments in C above.

Group F (esters from methyl, primary and secondary bromides and carboxylates (acetate, here) via $S_N$2 reactions, esters can be hydrolyzed to alcohols via acyl substitution with hydroxide, see Group D)
Group G (amines from methyl, primary and secondary bromides and conjugate base of phthalimide via $S_N2$ reactions, the alkyl imide can be hydrolyzed to primary amines via two acyl substitutions with hydroxide, see mechanism on page 3)

![Mechanism for Group G](image)

Group H (tosylates formed from alcohols and tosyl chloride/pyridine via acyl substitution reaction, converts "OH" from poor leaving group into a very good leaving group similar to iodide)

![Mechanism for Group H](image)

Group I (alkenes formed by E2 reaction with potassium t-butoxide and R-Br compounds)

![Mechanism for Group I](image)
Group J (alkynes from terminal acetylide and methyl or primary RX via $S_N^2$ reaction, reactions are possible in stepwise manner on both sides of ethyne, can put one or two “R” groups on, mostly E2 reaction at $2^\circ$ R-Br and only E2 at $3^\circ$ RX)

Group K (nitriles from cyanide and methyl, primary and secondary RX via $S_N^2$ reaction, reaction, only E2 reaction at $3^\circ$ R-Br)

Group L (thiols from hydrogen sulfide and methyl, primary and secondary RX via $S_N^2$ reaction, reaction, only E2 reaction at $3^\circ$ R-Br)
Group M (synthesis of ketones from 2-propanone (acetone) via $S_N2$ with propanone enolate at methyl, $1^\circ$, $2^\circ$ RX. Only E1 at $3^\circ$ RX. Make propanone enolate from propanone and lithium diisopropylamide = LDA at $-78^\circ$C, made from diisopropylamine and n-butyl lithium shown on page 2 under useful acid/base reactions.)

New bond at $C_\alpha$ carbon to carbonyl group.

Group N (synthesis of esters from ethyl ethanoate (ethyl acetate) via $S_N2$ using an ester enolate at methyl, $1^\circ$, $2^\circ$ RX. Only E1 at $3^\circ$ RX. Make ester enolate from ester and lithium diisopropylamide = LDA at $-78^\circ$C, made from diisopropylamine and n-butyl lithium shown on page 2 under useful acid/base reactions.)

Many other examples are possible.
A few possible answers: (Use a strip of paper 1/3 of the width of the page to cover up one of the columns below and quiz yourself about what should be there. By rotating through the different columns you test yourself about the starting materials, the reagents and the products.

1. Synthesis of R-Br (or R-Cl) from an sp³ C-H bond.

Free radical halogenation
1. initiation - forms 2 free radicals
2a CH abstraction by X•
2b X abstraction by R₃C•
3. termination - combines 2 free radicals

Br• is very selective for the weakest C-H bond available (benzylic = allylic > tertiary > secondary > primary > methyl). Cl• is less selective, but still follows the same overall order of reactivity.
2. Synthesis of R-OH from R-Br. (SN₂ = HO⁻ at methyl and 1° RX or SN₁ = H₂O at 2° and 3° RX)
Methyl and primary RX compounds react well with hydroxide, HO⁻ in SN₂ reactions. Hydroxide causes too much E2 product at secondary RX and only E2 product at tertiary RX so a different strategy must be used. Water, H₂O, can be used in SN₁ reactions, which are favored over E1 reactions at 2° and 3° RX.

3. Synthesis of R-Br from R-OH using H-Br, (SN₂ at CH₃OH and 1° ROH, SN₁ at 2° ROH and 3° ROH)
Methyl and primary carbocations are too energetically expensive to form in solution. We do not propose them in our course. These alcohols protonate and water is pushed off by bromide in an SN₂ reaction. Secondary and tertiary carbocations are formable in solution and we propose SN₁ in those examples. Allylic and benzylic carbocations are more stable (even if primary because of resonance) and SN₁ or SN₂ is reasonable.
4. Synthesis of R-OTs from R-OH using Ts-Cl / pyridine. Nucleophilic attack occurs by oxygen at electrophilic sulfur in an “acyl-like” substitution reaction. Pyridine acts as a proton sponge to neutralize the HCl formed. The tosylate group is very similar to a bromide or an iodide leaving group. 3° ROTs are prone to eliminate (E2).

\[
\begin{align*}
\text{H}_3 \text{C} &- \text{OH} & \text{Cl-S} &- \text{O} \text{O} \text{N} \\
\text{alcohols} & & \text{toluenesulfonyl chloride} & & \text{pyridine} & & \text{tosylates} \\
\text{Ts-Cl / pyridine} & & \text{acyl-like substitution} \\
\text{H}_3 \text{C} &- \text{O} \text{Ts} \\
\end{align*}
\]
5. Synthesis of alkenes. (E2 or E1 strategies, only E2 reactions are shown here.) Potassium t-butoxide is sterically bulky and very basic which favors E2 reactions even at primary RX centers. This is the only base shown in this section. Other strong bases will only form E2 product at tertiary RX centers and mainly form S_N2 product at primary RX centers. Secondary RX centers often react via both S_N2 and E2. More basic electron pair donors favor E2 reaction (for us = terminal acetylides, hydroxide, alkoxides) and less basic electron pair donors favor S_N2 reaction (for us = cyanide and acetate).

6. Synthesis of ethers. (S_N2 or S_N1 strategies, only S_N2 reactions are shown here.) Similar to #2 above, but using RO^- instead of HO^- or ROH instead of H_2O. The sodium alkoxide can be made from the alcohol and sodium hydride.

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SN₂ only works this way here

SN₂

H₃C—Br

or

H₃C—Br

or

H₃C—Br

or

H₃C—Br

or

H₃C—Br

or

H₃C—Br
7. Synthesis of esters. (S_N2 or S_N1 strategies, only S_N2 strategies shown here). The sodium acetate can be made from acetic acid and sodium hydroxide. Only E2 reaction at 3° RX.

8. Synthesis of nitriles. (S_N2 strategies, only S_N2 strategy). NaCN can be viewed as “carbanion in a bottle”. Only E2 at 3° RX. Less basic than terminal acetylides, so S_N2 > E2 at 2° RX.
9. Alternative synthesis of alkynes. (SN2 strategies). The terminal acetylide has to be made from an alkyne and Na\(^+\) / R\(_2\)N\(^-\). Terminal acetylides are more basic than cyanide, so E2 > SN2 at 2° RX.
10. Synthesis of R-SH (thiols). (S_N2 strategies) Sulfur, in general, is a very good nucleophile (S_N2) and fairly poor base (E2). S_N2 reactions are favored over E2 reactions except at 3° RX. We will assume that NaSH is commercially available. Its conjugate acid, H_2S, is a foul smelling, poisonous gas.
11. Synthesis of imides. (S_N2 strategies). See the overall strategy on page 3, at the top.
12. Synthesis of different ketones from 2-propanone (acetone). (Sn2 strategies at Me, 1°, 2° RX. Only E2 at 3° RX.)
13. Synthesis of different esters from ethyl ethanoate (ethyl acetate). \((S_N2\) strategies) Similar to ketone enolate reactions above (see ketone comments in #11).
SN2 = alkylation reaction

2 steps combined.
1. LDA (acid/base)
2.

2 steps combined.
1. LDA (acid/base)
2.

2 steps combined.
1. LDA (acid/base)
2.

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