# Tool Box

Good Synthesis Strategy

1. Take inventory of the starting materials. Do you have the carbon fragments needed to make the target molecule? Starting materials are the compounds you are given to make the target molecule which is the molecule you are trying to make.

2. Describe how you will make the carbon-carbon bonds. Which reaction is most appropriate. For example, if you needed to make a six membered ring from a four carbon chain and a two carbon chain, one might consider a Diels-Alder reaction even if the chains were not in proper formation yet.

3. Remember that most functional groups can be interchanged, but it is hard to make carbon-carbon bonds. Do not fret if a functional group is not perfect for the carbon-carbon bond reaction you deam most important.

4. Make the carbon carbon bond formation, the centerpiece of your strategy.

5. Before or after making carbon-carbon bonds, if you have no functionality, think about halogenation reactions.   For students this is really the only reaction you know other than combustion (which is degradative) to get some reactivity in the molecule.
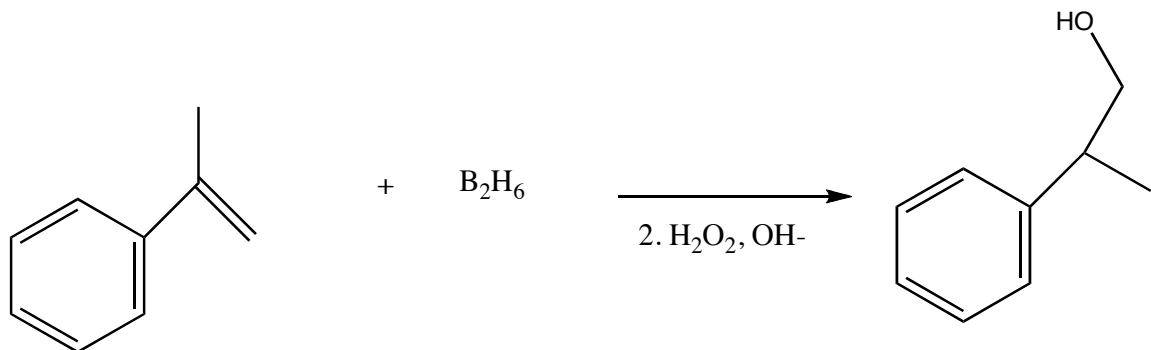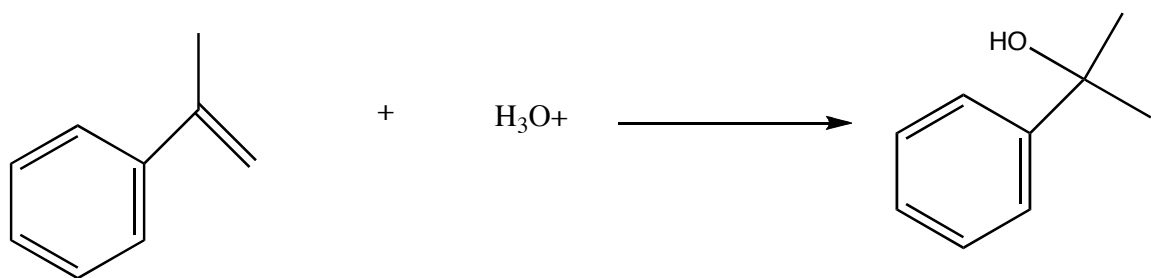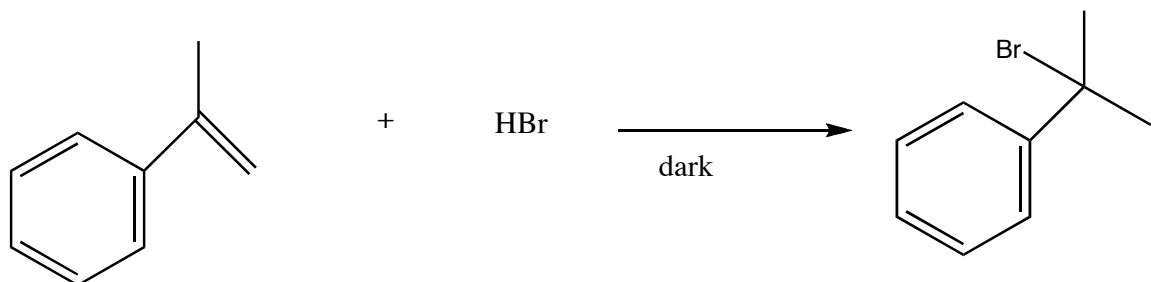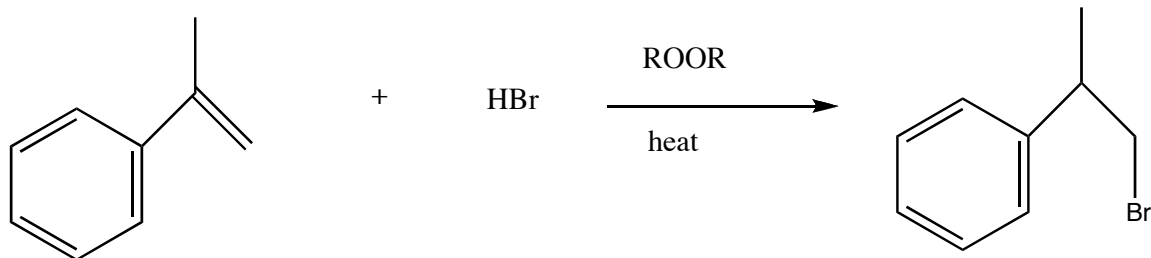
e.g.

free radical
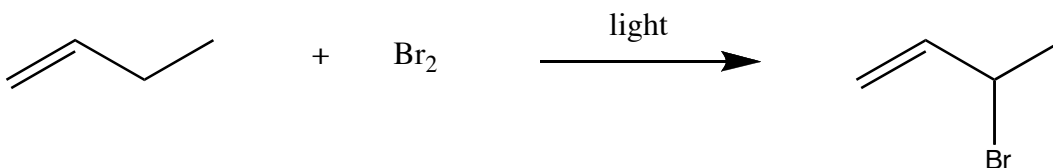


Electrophilic Aromatic Substitution
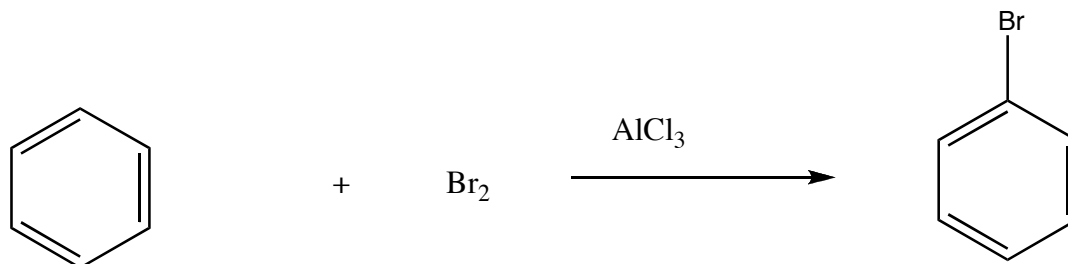
Note: you will normally have more regioselectivity with bromination than chlorination.

6. If you have a double bond, consider addition reactions. They are great because you have regiocontrol depending on which reaction you choose. You can place the functional group in the outer or inner position with the correct choice of a reaction.

e.g.

$+$ HBr $\xrightarrow[\text{heat}]{\text{ROOR}}$

$+$ HBr $\xrightarrow[\text{dark}]{}$

$+$ H_3O+ $\longrightarrow$

$+$ B_2H_6 $\xrightarrow[\text{2. } H_2O_2, \text{ OH-}]{}$

7. If you need to place a halogen in a chemically awkward position. For example, supposing it is benzylic, but you need it to be one more carbon out for chemical purposes. In this situation you can eliminate and then re-add using the regiochemistry from above. For example:
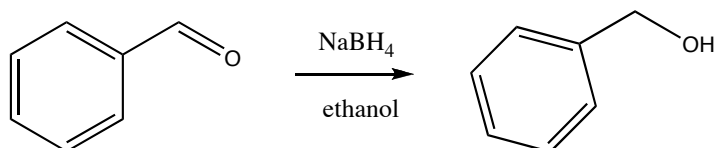

KOH

EtOH

heat

HBr
RooR
heat

Voila!!
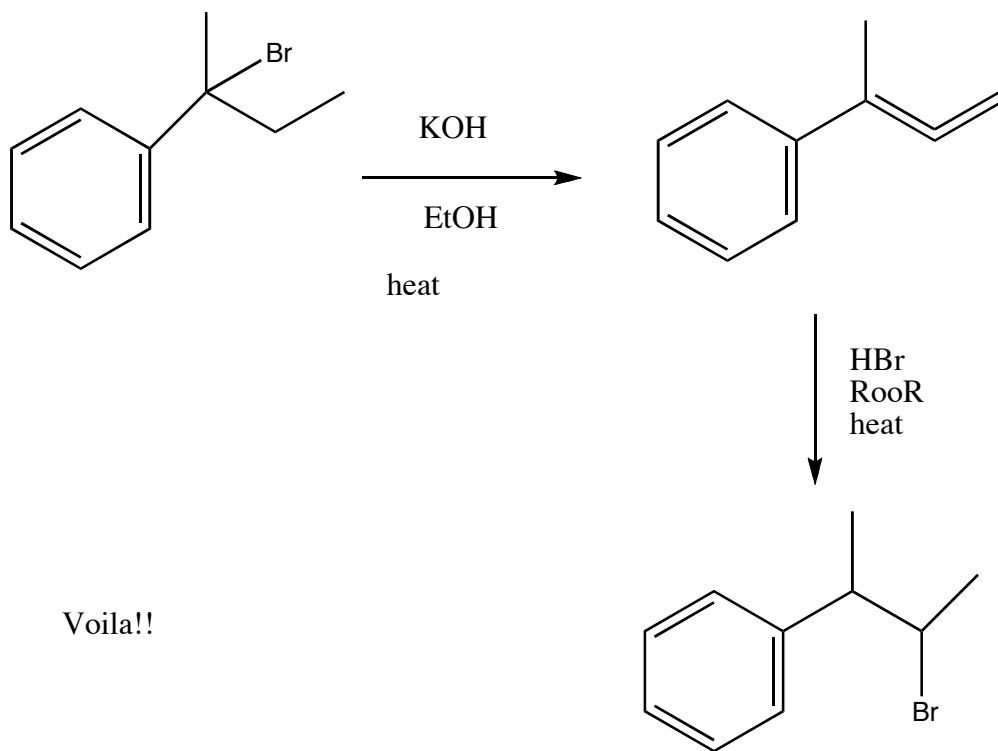
7. If you have an oxygen and it is in the wrong oxidation state. Do not despair!!! Just oxidize it or reduce it as needed. A hint about oxidizing and reducing agents. Most oxidizing agents have a lot of oxygen and most reducing agents have a lot of hydrogen (really hydride). For example.

oxidation
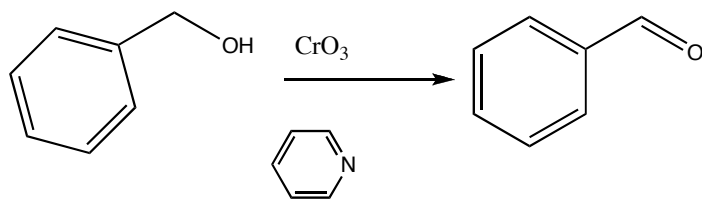
reduction

8 or 9 talk about overgeneralization. Don't go global.

The above are just two examples of oxidation and reduction, but realize you can adjust pretty much any oxygen into the functional group you need for a given synthesis.

Generally, it is good to learn reactions by the functional group they produce for synthesis. It is also important as shown above to know the reactions in interchangeable pairs and to know reactions that are complimentary in terms of regio- and/or stereochemistry as show above.   Finally, as indicated above it is very important to know the carbon-carbon bonding reactions and how to manipulate functional groups so you can get to the point where you can do the desired carbon-carbon bond forming reaction.

The following reactions are organized by the functional group they produce and carbon-carbon bond forming reactions are grouped together, regardless of the functional group produced.
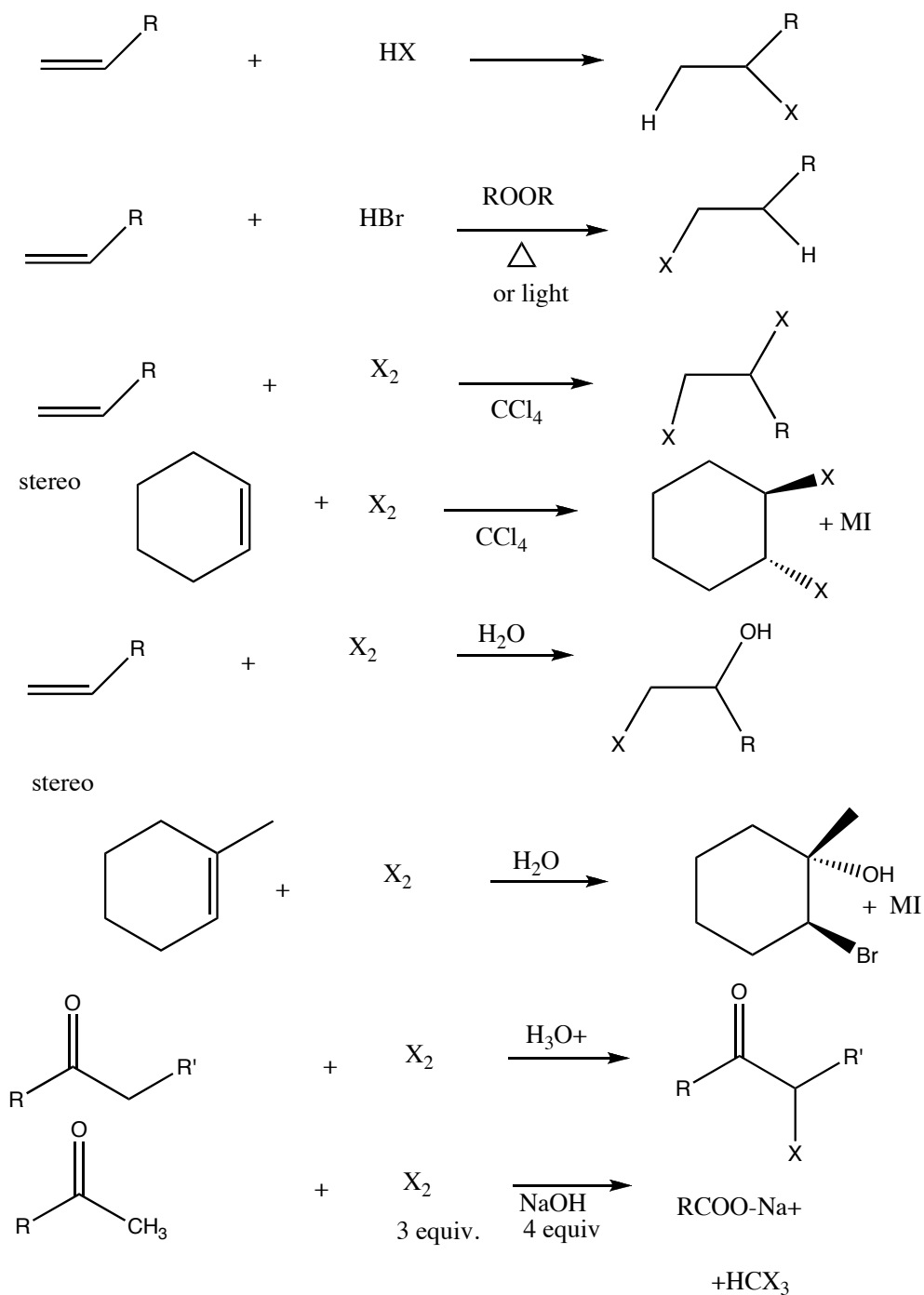
Reactions involving halogen and resulting in halogenated products. These reactions are the source of a great amount of confusion during both semesters of organic chemistry.

What should be noted first is the interchangeability of the addition of HX in the dark with no peroxides versus the addition of HBr in the light/peroxides.   The first reaction results in the Markovnikov addition of HX and different hydrohalogens (such as HCl and HBr) can be used. Markovnikov addition means the hydrogen aadds to the carbon with more hydrogens and the halogen to the carbon that is more substituted. The theory behind this will be covered in some depth in lecture. The complimentary, latter reaction is a free radical reaction. It is actually governed by similar principles, but it is the halide that adds first. Please note that the free radical reaction that results in "anti-Markovnikov addition only applies to HBr reactions.

Note the experimental implications. If you need the functional group on the terminal carbon of the molecule, the anti-Markovnikov, free radical is the one to choose.   If you need the functional group on the inner position (the number two position), use the normal ionic addition of HX (Markovnikov).   Please note the exercises given below the list.

The next four reactions demonstrate the addition of halogen to a double bond and the halohydrin reaction.   It should be noted that the addition of halogen is a stereospecific reaction giving at most two anti products that are typically enantiomers.   The halohydrin is what occurs when water is in the reaction. Rather than the halide anion being the nucleophile, the water serves at the nucleophile. All four reactions involve the formation of a "halonium ion" and the anti attack of the nucleophile which is the reason for the anti stereochemistry noted especially on rings.   It is also a Markovnikov addition. Again the water is the nucleophile and it attacks at the more substituted site. This theory will be covered in class.   Various halogens can be used in the reaction, though most reactions involved chlorine and bromine.

The last two reactions on the page involve the methods using both acid and base to add a halogen to an alpha carbon. This is a second semester reaction.

R + HX ⟶

R + HBr —ROOR, Δ or light⟶

R + X₂ —CCl₄⟶

stereo

+ X₂ —CCl₄⟶ + MI

R + X₂ —H₂O⟶ OH

stereo

+ X₂ —H₂O⟶ + MI

+ X₂ —H₃O+⟶

+ X₂ (3 equiv.) —NaOH (4 equiv)⟶ RCOO-Na+

+HCX₃

The following reactions are substitution reactions. The first reacton is the free radical substituion of an alkane. Synthetically speaking, this is the reaction to use when you are dead in the water – you have an alkane, have very little reactivity and need some polarity to get some chemistry going and build some structure. Really, the only other reaction of alkanes you learn is the reaction of alkanes with oxygen, which is combustion and is degradative, not generally a synthetic process. Please note that bromine is much less reactive and more selective than chlorine as shown

in the second reaction. If chlorine were used a substantial amount of chlorination would be obtained at all unique sites, but with bromine virtually all bromination is at the tertiary site.
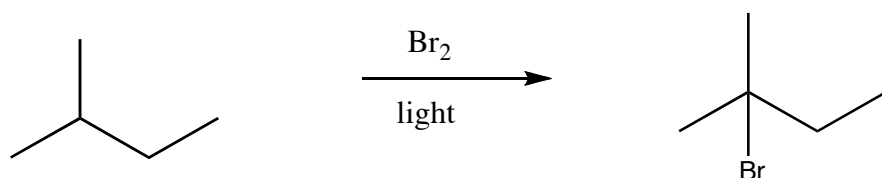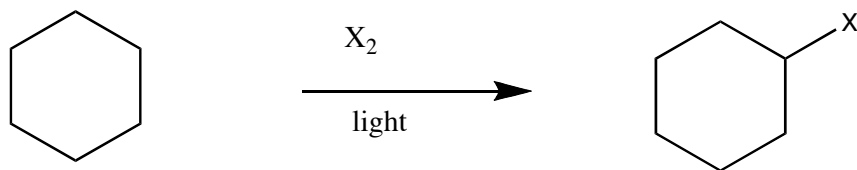

Note this reaction does not happen on vinylic positions or on aromatic rings.

There is a tendency of oeple to over-generalize reactions. Re – maybe put this up top.

The following are reactions that involve substitution reactions of a different variety. These reactions are either Sn2 or Sn1 reactions. The theory behind this will be discussed in lecture. The first reactions shown here are Sn2 reactions.
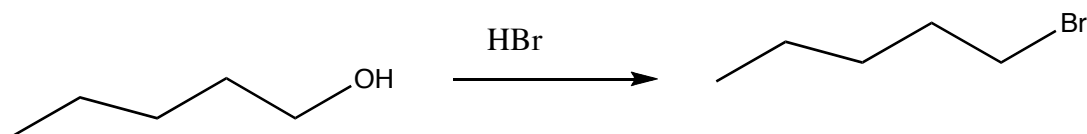

Because chlorine is a weak nucleophile, one cannot simply substitute Cl for water as shown in the above reaction. So you can't just interchange HCl for HBr. Instead, one has to use SOCl₂ as follows.
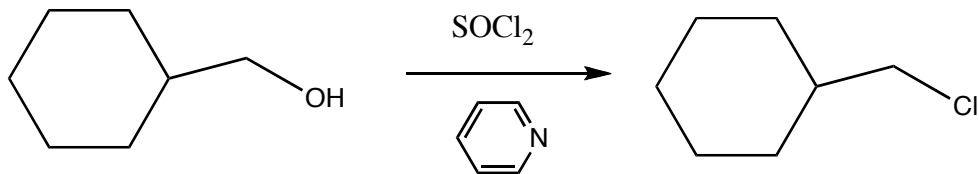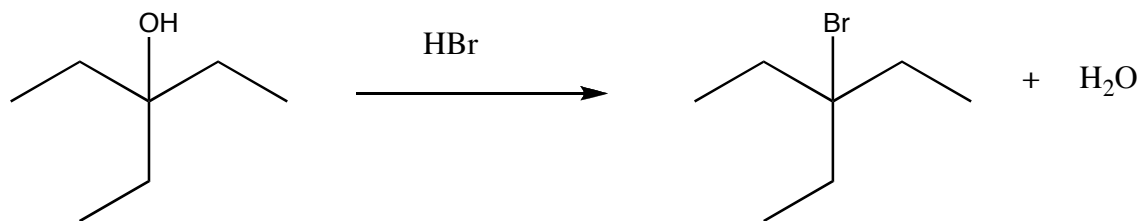

An alternative method for replacing an OH with bromine is as follows. There are analogous reagents using chlorine.
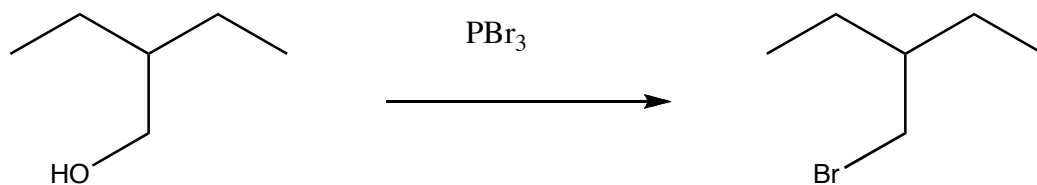
Lastly, halogens can be added by displacing really good leaving groups as shown below.
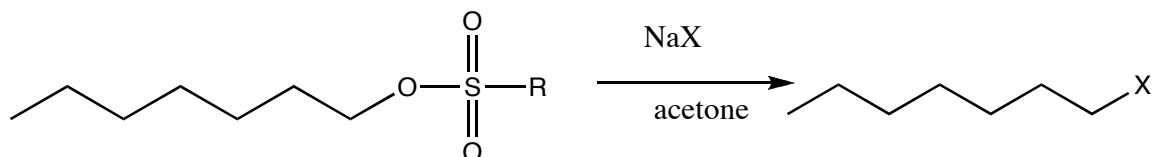
The following is an example of a Sn1 substitution.

On the next page are methods, largely electrophilic aromatic substitution for placing halogens on a aromatic rings. The first two reactions are about adding sulphonate groups to an aromatic ring along with a halogen. It is important to note that reactions involving aromatic rings are unique.
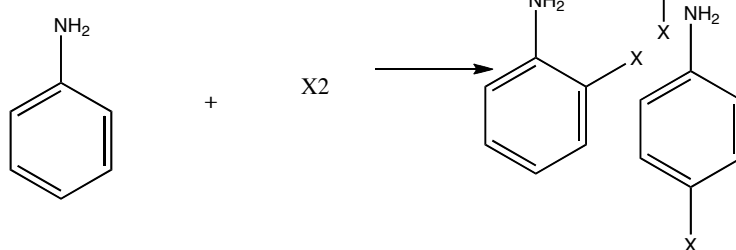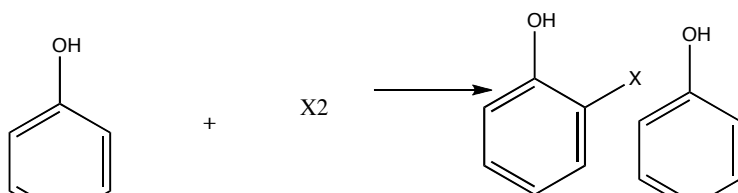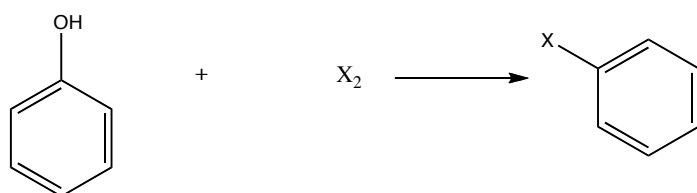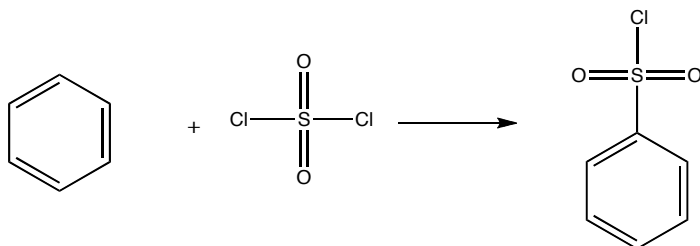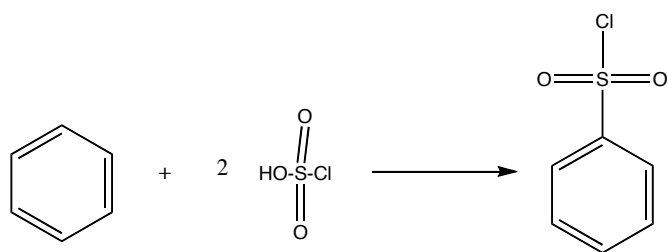
The following reactions involve the formation of Carbon-Carbon bonds. These reactions are extremely important to the formation of organic compounds. Obviously, because carbon-carbon bonds form the backbone of organic compounds. Often, a synthesis of a compound can easily worked out if one focuses on the carbon-carbon bond formation. I generally recommend when a student is looking at a synthetic target from a group of starting materials that one consider first which carbon-carbon bond forming reactions can be used in their formation. I will discuss this aspect with each reaction as I go through them.

The Diels Alder Reaction:

The need to make a six membered ring, would suggest the use of a Diels-Alder Reaction.
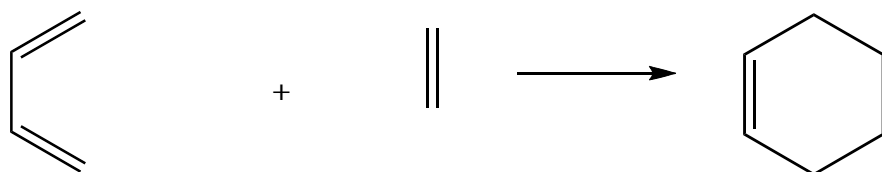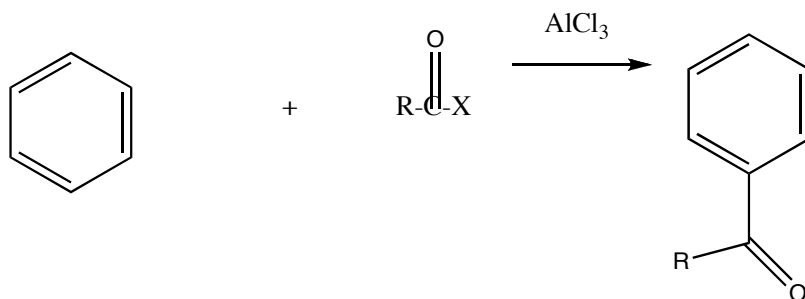

The Friedel Crafts alkylation Reaction:
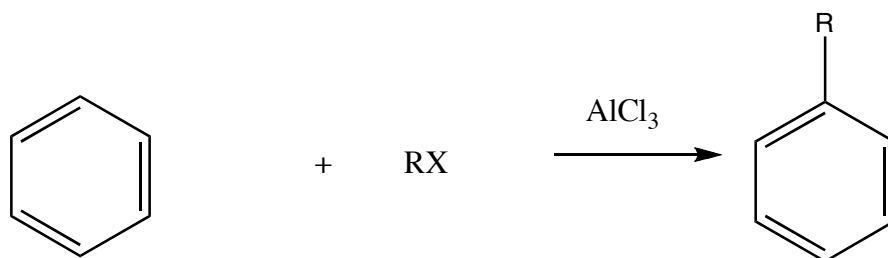
The need to make a carbon-carbon bond at the juncture to an aromatic ring would suggest the use of a Friedel-Crafts reaction. As you will read in your text this reaction has several synthetic problems, including polyalkylation and rearrangements of the side chain.

The Friedel-Crafts Acylaction reaction

This reaction would also be used in a situation where one wanted to make a C-C bond at the juncture to an aromatic ring. This reaction has the advantage of not being subject to rearrangement and polyacylation due to the deactivating effect of the acyl group to electrophilic aromatic substitution and the lack of rearrangement of acylium ions.   One should note that pretty much all functional groups can be interchanged. One should be primarily focused on linking up the carbons. The

oxygen can be removed through a variety of methods including the Wolf-Kishner reduction or the Clemmenson Reduction.
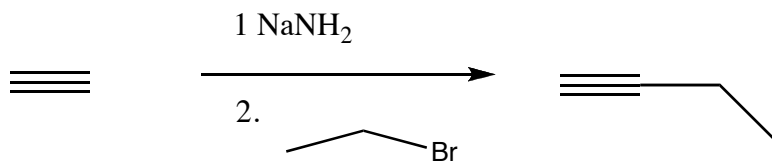

This reaction would be used when one want to make a straight chain. It takes advantage of the relative high acidity of acetylene hydrogens and the resulting nucleophilicity of the anion. The first step is just a Bronsted Acid – Base reaction and the second step is an SN2 reaction.
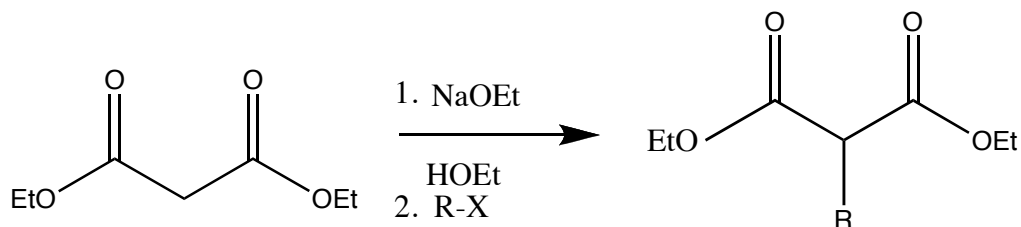
Addition of hydrogen cyanide

Alpha alkylation
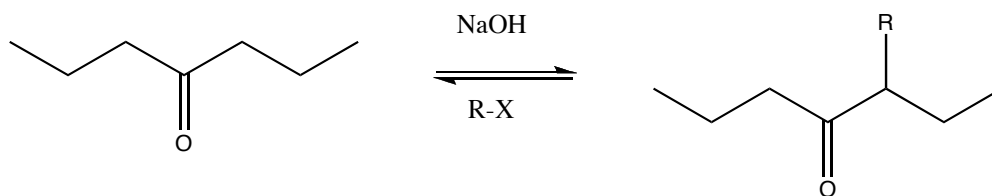
Problem: aldol -like condenstation will compete
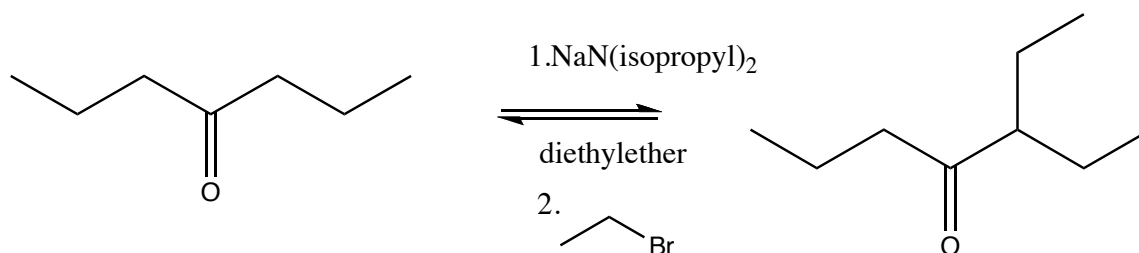
The strong, bulky base will completely remove the alpha hydrogen in the first step, eliminating the posibility for competing condensation.

The weaker, unbulky base will completely remove the alpha hydrogen because the alpha hydrogen is considerably more acidic due to the conjugation of the anion with the two carbonyl groups in the conjugate base. Try to draw the structures. The stabilized anion will undergo the substituion reaction with the alkylhalide.

The famous Grignard and organolithium.

The need to make a carbon-carbon bond at the carbon bearing an oxygen functionality (or something that can be converted to or from this functionality) suggests the use of a Grignard or organolithium reaction.

Aldol Reaction

I will not lie, the aldol reaction is my favorite reaction, partially because it is reaction that is prevalent in natural systems. Many natural products have the aldol structure which is what I call the 1, 2, 3 structure shown below. If you need to make a beta-hydroxy carbonyl compound or an alpha, beta unsaturated carbonyl compound, this suggests the use of the aldol reaction.   Note, the 3 position is the beta posistion with respect to the carbonyl, hence the second structure shown below is a beta hydroxy carbonyl compound.   The 2 and 3 positions respectively are the alpha and beta unsaturated positions in the third organic structure shown.

When thinking backwards to predict the aldol reagents, one needs to realize that the hydrogen is going to be pulled off position two and this enolate is going to attack position one of another molecule which will become position three in the final structure. Going backwards or thinking retrosynthetically is shown below for a specific aldol.

Self Aldol
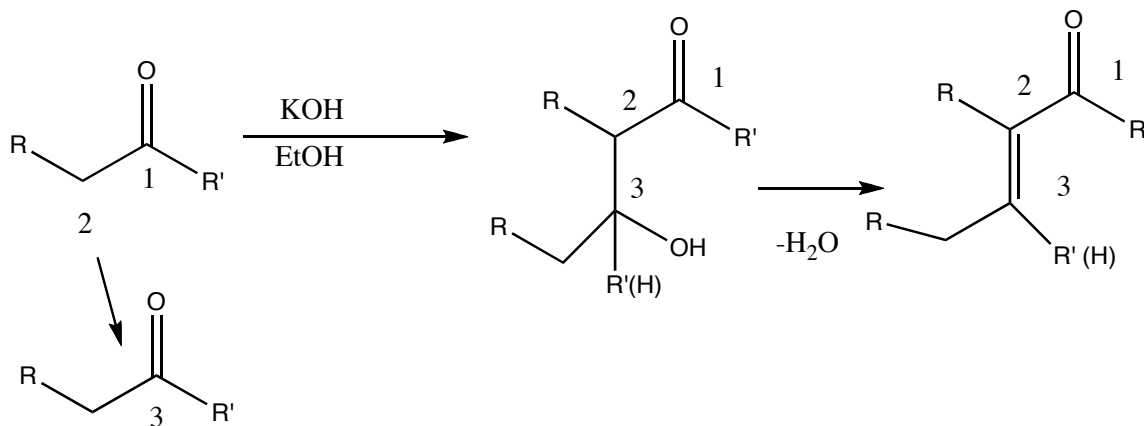
Super efficient tool box.

Reactions involving halogen and resulting in the incorporation of halogen into the compound.

stereo

stereo