

Objective 14. Develop synthesis strategies for organic synthesis.

You've been doing organic synthesis in organic lab this semester.

Organic synthesis strategies include:

- converting one functional group to another,
- moving a functional group from one carbon to an adjacent carbon,
- making a carbon-carbon bond to make a bigger molecule, and
- making a compound with two or more functional groups.

You want to identify the Reaction Type to accomplish your desired synthesis. Structural features help you figure out the reaction type. Identifying the structural feature as a nucleophile or electrophile tells you how the reaction occurs.

Table 1. Synthesis Strategies Summary

Structure Change	Reaction Type	Structural Features	What Happens
Make an acid or base	Proton transfer	Acid and base. See pKa table.	H <sup>+</sup> (only) is transferred from acid to base.
Make a better Leaving Group (LG)	Proton transfer	LG and Acid. See pKa table.	H <sup>+</sup> (only) is transferred from acid to base.
Make a C=C pi bond	Elimination	H bonded to beta C (or carbocation), LG, and Nu: <sup>-</sup>	Nu: <sup>-</sup> reacts at H, pi bond forms, LG leaves
Add atoms or groups to each atom in a pi bond	Electrophilic Addition	C=C pi bond Nu: <sup>-</sup> reacts with E <sup>+</sup>	Atoms or group add to each vinylic C.
	Nucleophilic Addition	C=O bond. Nu: <sup>-</sup> reacts at carbonyl C.	Atoms or groups add to carbonyl C and O.
Convert or exchange one functional group for another at one carbon	Nucleophilic Substitution	alpha carbon, LG, and Nu: <sup>-</sup>	Leaving group exchanges with another atom or group at alpha C.
	Nucleophilic Acyl Substitution	carbonyl C bonded to a LG, Nu: <sup>-</sup>	Leaving group exchanges with another atom or group at carbonyl C.
	Electrophilic Aromatic Substitution (addition/elimination)	aromatic pi bond and strong E <sup>+</sup>	H exchanges with another atom or group at aromatic C. See o, p vs. m directors.
Convert or exchange one functional group for another at one carbon	Oxidation/Reduction	Carbon-oxygen bond, carbon-nitrogen bond, nitrogen-hydrogen bond, nitrogen-oxygen bond	gain or loss of O or H at one C or N.

Structural features:

C=C pi bond (including conjugated diene and aromatic)

C-O, C-X, C-N compounds: alpha carbon, leaving group (HOH, ROH, NH<sub>3</sub>, X<sup>-</sup>), H bonded to beta carbon, epoxide

C=O compounds: carbonyl carbon, carbonyl oxygen, alpha carbon (C next to carbonyl C), beta carbon

TWO structural features:

β-hydroxy aldehyde/ketone (see enolates)

α,β-unsaturated aldehyde/ketone (see enolates)

β-keto ester (see ester enolates)

Table 2. Nucleophiles and Electrophiles by Atom Type

Atom Type	Nucleophile	Electrophile
hydrogen	Acid (H <sup>+</sup> , RCOOH, ROH, etc.) See pK <sub>a</sub> table.	Hydride (H <sup>-</sup> ), H bonded to beta carbon
carbon	CN <sup>-</sup> , acetylide, Grignard, enolate, ester enolate	Carbocation, carbonyl carbon, alpha carbon on LG
nitrogen	Lone pair N: NH <sub>3</sub> , NH <sub>2</sub> <sup>-</sup> , NRH <sub>2</sub> , NRH <sup>-</sup> , imine N	NH <sub>4</sub> <sup>+</sup> , NH <sub>3</sub> , ..
oxygen	Lone pair O: H <sub>2</sub> O, OH <sup>-</sup> , ROH, RO <sup>-</sup> , ROR, RCOO <sup>-</sup>	H <sub>2</sub> O, H <sub>3</sub> O <sup>+</sup> , ROH, ROH <sub>2</sub> <sup>+</sup> , ROHR <sup>+</sup> ,
X (Cl, Br, I)	X <sup>-</sup>	X <sub>2</sub>
Bond	C=C pi bond, C≡C bond pi bond	

Many organic reactions are reversible.

Table 3. Reversible Reaction Types

Forward Reaction	Example:	Reverse Reaction
Acid-Base	$\text{ROH} + \text{H}^+ \rightleftharpoons \text{ROH}_2^+$	Base-Acid
Substitution	$\text{ROH} + \text{HBr} \rightleftharpoons \text{RBr}$	Substitution
Addition	ethylene + HBr $\rightleftharpoons$ ethyl bromide	Elimination
Oxidation	$1^\circ \text{ROH} \rightleftharpoons \text{RCHO}$ or $\text{RCOOH}$	Reduction

Example: ethanol reacts in several ways:

Substitution with HX to form ethyl bromide. (Or substitution with RX to form ether.)

Elimination to form ethylene.

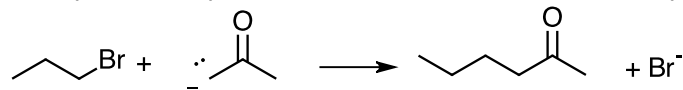
Oxidation to form acetic acid.

This means there are at least three ways to synthesize ethanol (look at reverse reaction).

1. Make a C-C bond. (Make a big molecule from a small molecule.)

See Table 1. What reaction types would you use to make a carbon-carbon bond? Give an example for each type. (Hint: there are at least 4 different reaction types.)

Example: Nucleophilic substitution.  $\text{RBr} + \text{carbon nucleophile}$ .



2. Move a functional group, e.g., -OH or pi bond, over one carbon.

See Table 1. What reaction type

a. To move a -OH or -X group over one carbon, you can use an elimination reaction to make a \_\_\_\_\_ followed by an addition reaction (2 step synthesis). Describe how you would make 2-propyl bromide from 1-propyl bromide.

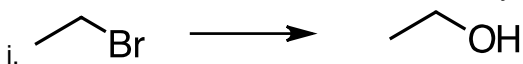
b. To move a pi bond over one carbon, you can use a \_\_\_\_\_ reaction reaction followed by a \_\_\_\_\_ reaction (2 step synthesis). Describe how you would make 2-butene from 1-butene.

c. To move a C=O bond over one carbon, you can convert the C=O to another group first. Then, do a 2 step synthesis from part a or b. Describe how you would make acetone from propanal.

3. Here is a method you can use to determine how to synthesize a target compound from a starting material.

- Draw the structures of the reactant (starting material) and product (target compound).
- How does the starting material differ from the target compound? At which atom does the reaction occur? Which bond breaks/forms?
- Is the number of carbons in the starting material the same as the number of carbons in the target compound? Does a C-C bond form? If yes, then you'll have to make a C-C bond by using a carbon Nu<sup>-</sup> (CN<sup>-</sup>, acetylide ion, RMgX, enolate ion). Or break a C-C bond by ozonolysis or decarboxylation.
- Identify the structural features in the starting material and target compound. Identify each structural feature as a nucleophile or electrophile. This tells you the possible reaction types.
- What is the reaction type?
- What reagent will accomplish this reaction and reaction type?

a. Describe how to make ethanol from ethyl bromide.



ii. Alkyl halide  $\rightarrow$  alcohol. Reaction occurs at alpha C. C-Br bond breaks. C-O bond forms.

iii. 2 carbons  $\rightarrow$  2 carbons. A C-C bond does not form.

iv. Br LG (Nu<sup>-</sup>), alpha C (E<sup>+</sup>), H bonded to beta C (E<sup>+</sup>)  $\rightarrow$  OH LG (Nu<sup>-</sup>), alpha C (E<sup>+</sup>), H bonded to beta C (E<sup>+</sup>), acidic H on O (E<sup>+</sup>), basic O (Nu<sup>-</sup>). Possible reaction types: substitution, elimination.

v. Reaction type = nucleophilic substitution. Don't want elimination because no pi bond forms.

vi. Use OH<sup>-</sup> as Nu<sup>-</sup> to react at alpha C to substitute OH for Br.

b. Describe how to make acetaldehyde from ethanol.

c. Describe how to make 2-butene from 1-butene.

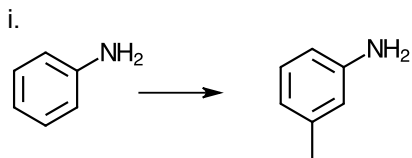
d. Describe how to make 2-propanol from 1-propanol.

e. Describe how to make isopropanol from acetaldehyde.

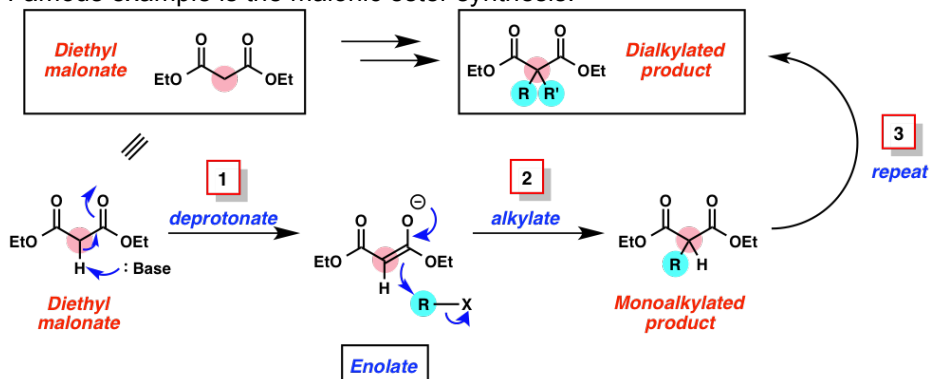
f. Describe how to make C<sub>4</sub>H<sub>10</sub> from C<sub>2</sub>H<sub>5</sub>Br.

g. Describe how to make C<sub>2</sub>H<sub>5</sub>COOH from C<sub>2</sub>H<sub>5</sub>Br.

h. Describe how to make



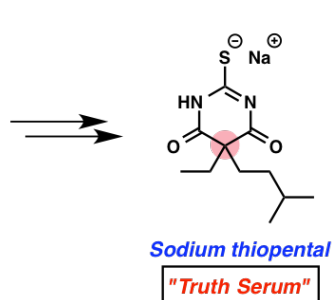
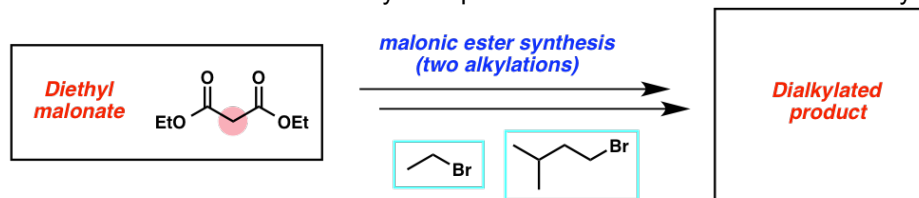
j. (From LearnBacon.com) Enolate alkylation  
Famous example is the malonic ester synthesis.



Malonic ester synthesis is used to make countless bioactive molecules, e.g., barbiturates (sedative-hypnotic drugs which can cause death by depressing the central nervous system).

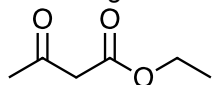
Famous barbiturate is sodium thiopental (used in psychiatry, lethal injections, truth serums).

Predict the structure of the dialkylated product formed in the malonic ester synthesis of sodium thiopental.

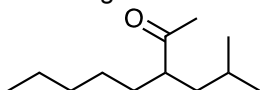


**CNS depressants**  
  
**BARBITURATES**  
 analgesics sedatives  
 3-4 billion doses prescribed per year

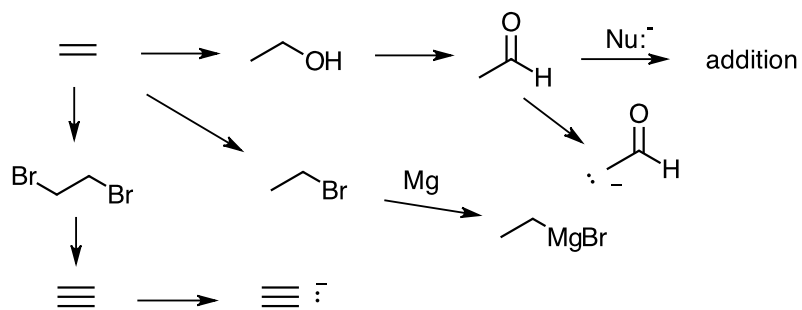
k. Starting from ethyl acetate, describe a synthesis of:



l. Starting from acetone,  $C_5H_{11}Br$ , and  $(CH_3)_2CHCH_2Br$ , describe a synthesis of:

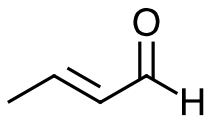


4. The chemical industry uses ethylene, acetylene, or benzene as the starting materials to make bigger molecules.  
Examples:

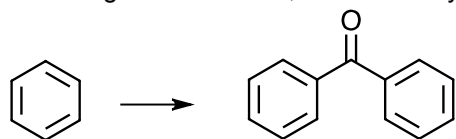


Note acetylide,  $\text{C}_2\text{H}_5\text{MgBr}$ , and the enolate ion are nucleophiles to make C-C bonds.

- Starting from ethylene, describe a synthesis of 1,3-butadiene.
- Starting from ethylene, describe a synthesis of acetone.
- Starting from ethylene, describe a synthesis of ethyl acetate.
- Starting from ethylene, describe a synthesis of:



- Starting from benzene, describe a synthesis of aspirin.
- Starting from benzene, describe a synthesis of benzophenone.



- Using toluene,  $\text{NaCN}$ , and  $\text{CO}_2$  as the sources of carbon atoms, describe a synthesis of:
  - phenylacetic acid
  - benzoyl chloride