• A large part of organic chemistry involves building more complex molecules from smaller ones using a designed sequence of reactions, i.e. chemical synthesis. Especially in more complex cases, synthetic problems are often best solved BACKWARDS in a process known as retrosynthetic analysis.

**BUT FIRST...............**

### How to Ride a Bicycle

#### 1.1 Parts of the bicycle
- It is important to understand bicycle nomenclature
- We will not cover IUPAC bicycle nomenclature in this case

![Bicycle parts diagram](image)

#### 1.2 Bicycle Safety
**Question?** Which of the following are essential SAFETY ITEMS when riding a bicycle

- helmet
- brakes
- reflector

![Bicycle safety diagram](image)

#### 1.3 Physics of Bicycle Riding
- You MUST understand the relevant forces involved, without this understanding you can NOT ride a bicycle!

![Bicycle physics diagram](image)

• Review sessions on Saturday
• Chad's Review on Bicycle Riding
• Kahn Academy lectures on Bicycle riding
1. Summary of First Semester Reactions Useful in Synthesis

1.1 Synthesis of Halides, Reactions that MAKE Bromides

- Bromides are very useful functional groups that do many reactions because they are good leaving groups

1.2 Synthesis of Alkenes, Elimination Reactions that MAKE Alkenes

- In a synthesis context we try to avoid reactions that involve carbocation rearrangements if at all possible
- Therefore, use E2 elimination of ALKYL BROMIDES rather than E1 to AVOID carbocation intermediates

- Use a STRONG BULKY base with a 2° halide (to avoid SN2) to form the Saytzeff (or Zatisev, spell it any way you like!), more substituted alkene product

- SN2 is not possible for a 3° bromide, therefore use a NON-bulky base with a 3° halide to get the Saytzeff/Zaitsev (spell this name anyway you like!) alkene product

- Use a BULKY base with a 3° halide to get the ANTI-Saytzeff (also called the Hofmann) least substituted alkene product
1.3 Synthesis of Alcohols

Addition reactions we know that form alcohols:

- In the context of synthesis, we try to avoid reactions that involve carbocation intermediates.
- Therefore, to do Markovnikov addition of water to a C=C bond, we will use the Lewis acid catalyzed method with mercuric acetate (Hg(OAc)₂) rather than Bronsted acid catalysis using, for example, H₂SO₄.

Substitution reactions we know that form alcohols: SN2

- Required for further synthesis of alkynes (see later).

1.4 Synthesis of Dibromides

- Required for further synthesis of alkynes (see later).

- NOTE: This addition is ANTI-, even though there is no possibility of cis-trans-isomers in this reaction. We can still tell that the addition is ANTI- and our answer MUST include this.
- This reaction forms a pair of (R)/(R) and (S)/(S) enantiomers, and we need to distinguish these from the (R)/(S) diastereomer (the meso compound) that is NOT formed.

1.5 Synthesis of Alkanes

- More useful than it looks!

- Other catalysts you may see include Raney Ni or Pt.

1.6 SN2 Reactions

- Useful in many reactions that require addition of a substituent or formation of a new bond.
Example:

You will need to be able to use these reactions forwards and backwards!

2. Multi-Step Synthesis

- multi-step chemical synthesis involves building larger or more complex molecules from smaller ones using a designed series of reactions
- this involves putting a series of reactions together in sequence (multiple steps)
- here we will look at some simple examples
- to do these problems you need to KNOW THE REACTIONS, and PRACTICE, practice, practice......

Example Problem 1: Synthesize the molecule on the right from the one on the left. This cannot be done in one reaction. Give reagents and conditions and the intermediate molecules at each step.

- the FIRST REACTION WORKING BACKWARDS must have an alkene as the product
- alkenes can be formed by elimination from halides or alcohols
- of these two we choose the halide reaction, because the halide can be made from the starting structure more easily than the alcohol, completing the problem
- NOTE: the first bromination is of an alkane, EITHER Br₂/light or NBS/light can be used, if we were brominating in an allylic position only NBS/light could have been used
- then E2 elimination, which is the standard way to make an alkene avoiding cation intermediates

Example Problem 2: Synthesize the molecule on the right from the one on the left. This cannot be done in one reaction. Give reagents and conditions and the intermediate molecules at each step.

Retrosynthesis : Page 4
The first bromination is of an alkane, EITHER Br₂/light or NBS/light can be used
• Br₂/light cannot be used for the last bromination of the alkene, we need to avoid Br₂ addition to the C=C bond
• It may be a good idea to always use NBS and for all radical brominations then you don't have to remember
  which bromination reagent works best in which case, this one works in all cases
• E2 with a BULKY BASE, which is the standard way to avoid SN2 to make an alkene, then brominate again in the
  allylic position (same reagents)
• Formation of an alkene in the last step is NOT a good idea, there is more than one leaving group, double
  eliminations may occur, or the C=C bond may be formed in the wrong place with respect to the other bromine

Example Problem 3:

• We need to add Br at a position that is not possible by direct bromination, the obvious way is by addition of HBr
  to an alkene Anti-Markovnikov, so first, make an alkene as usual

• We have two ways to make an alcohol, SN2 or water addition to an alkene, the best thing to "do" with the
  starting alcohol is make an alkene, which decides for us which alcohol synthesis method to use

3. Retrosynthetic Analysis : The Synthon

The most important concept from First Semester Organic Chemistry:

• Lewis Acid/Base reactions explains bond formation
• The Lewis Base provides the electrons and the Lewis Acid accepts the electrons to make the bond

• Lewis acid base theory is extremely useful in PREDICTING the products of organic reactions
• Although it works as a fundamental theory, we will find that occasionally we have to just "know" some reagents,
  the same will apply for reaction in reverse, next…….
• LEWIS ACID BASE THEORY HELPS US TO UNDERSTAND THE PRODUCTS OF REACTIONS
• Lewis acid/base theory helps us to generate the product of a reaction when we are provided with the reactants

New concept: the SYNTHON, explains bond formation from reactants, Lewis acid/base theory in REVERSE
• SYNTHON THEORY HELPS US TO UNDERSTAND WHERE THE PRODUCTS CAME FROM
• Synthony theory helps us to figure out what Lewis acid/base reaction to DO to form a bond
• Retrosynthetic analysis helps us to generate the reactants when we are provided with the product
• Synthons indicate where the electrons come from to make the bond, they help us to identify which fragment is the Lewis base and which fragment is the Lewis acid do make the desired bond
• Synthons DON’T EXIST, they are the products of a THOUGHT EXPERIMENT, they need to be converted into "real" reactants, or synthetic equivalents
• One synthon must carry the electron pair (LB), the other accepts the electrons to make the bond (LA)
• Somewhat counter-intuitive is that the synthon with the electrons (LB) is usually the one where the ELECTRONS WOULD BE MOST STABLE (lowest in energy)
• The idea here is that the synthon that carries the electrons would be most useful if it could be kept "in a bottle", if the electron pair is very high in energy then that synthon may be impossible to make and the retrosynthetic strategy would fail
• Very often, even putting the electrons where they are most stable results in one or more of the synthons being so unstable, and they have to be used in the form of "synthetic equivalents" or "actual reagents", these are stable chemicals that react in the same way as the synthons.

Example 1:
• disconnect the O-C bond and "put" the electrons on the synthon where they would be most "temporarily" stable


• NEXT, ask the following question about each synthon "can it be put into a bottle (with an appropriate counter ion)?", if the answer is yes then the synthon is also the reagent, if the answer is no, then we need to convert the synthon into an actual useable reagent, i.e. a synthetic equivalent
• reacting the synthetic equivalents makes the required alcohol


Retrosynthesis : Page 6
Example 2:
• disconnect the indicated C-C bond
• one of the carbons must carry the electron pair, one the leaving group, which is best?

Example 3: disconnect the indicated bond (this is a reaction you have not yet seen)

Example 4: a more realistic application
• synthons and **retrosynthetic strategy** is an advanced organic chemistry concept
• however, we **don't** analyze every forward reaction in terms of Lewis acid/base, we don't have time, we just **know the reactions forwards**
• similarly, we **won't** analyze every reverse reaction in terms of synthons, we won't have time, we **will** just **know the reactions backwards**
• it sometimes takes experience and practice to recognize how to convert the synthons into synthetic equivalents, so you should expect to find some of these difficult to do at first
• we will return to synthons as we work our way through the semester

**Summary of Synthetic Equivalents**
• The hardest part of retrosynthetic analysis using synthons is knowing exactly which synthons are stable and are already synthetic equivalents, and which need to be “translated” into synthetic equivalents, A summary of the ones we have come across so far is given below
• Do NOT try to memorize these, instead, learn them by using them, refer to this table when solving synthesis problems so that you learn by using!

<table>
<thead>
<tr>
<th>positive synthon</th>
<th>synthetic equivalents</th>
</tr>
</thead>
<tbody>
<tr>
<td>R—CH₂</td>
<td>alkyl halide</td>
</tr>
<tr>
<td>R—CH₂—Br</td>
<td>aldehyde/ketone</td>
</tr>
<tr>
<td>R—CH₂=O</td>
<td>aldehyde/ketone</td>
</tr>
<tr>
<td>R—C=O—H</td>
<td>epoxide</td>
</tr>
<tr>
<td>R—C=O—H</td>
<td>epoxide</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>negative synthon</th>
<th>synthetic equivalents</th>
</tr>
</thead>
<tbody>
<tr>
<td>R—O</td>
<td>R—O—Na</td>
</tr>
<tr>
<td>R—C≡C</td>
<td>R—C≡C—Na</td>
</tr>
<tr>
<td>N≡C</td>
<td>N≡C—Na</td>
</tr>
<tr>
<td>R—CH₂</td>
<td>R—CH₂—Li</td>
</tr>
</tbody>
</table>

• Later we will find out why sp³ hybridized carbons as negative synthons require a lithium metal rather than a sodium metal counter ion and why we draw a covalent bond in this case
• We will return to these synthons and retrosynthetic analysis throughout the course, repeated exposure will also facilitate learning
4. SN2 Reactions Revisited : Practice Doing Reactions in Reverse

How would you make the following molecules using the SN2 reaction?

- The emphasis is on recognizing which bond you can make, and identifying the synthons and thus reactants...

**Example 1:**

- **3° halide**
  - No SN2 here
  - **3° halide**

- **1° halide**
  - SN2 allowed, thus better synthons, only way to do the reaction

**Example 2:**

- **2° bromide**
  - Preferred method

- **1° bromide**
  - Preferred method

**Example 3:**

- SN2 not possible at sp² carbon

- **must be 2° again,**
  - better use tosylate
  - best leaving group
Example 4:

- you can “make up” your own SN2 reaction, just look for obvious bond to make, do reaction “backwards” to get the synthons and reactants

An Example in Synthesis:

- We can’t add -OMe to an alkane, so we need to a LEAVING group at that carbon
- An SN2 reaction works well to make the required C-O bond
- Going backwards from there, back to the starting structure, involves simple reactions we have used previously

5. Putting it all Together: A Retrosynthesis Strategy

- look for the reactant “in” the target molecule
- identify the required Functional Group Interconversions (FGI) and C–C (C–X) bond making reactions
- generally, try to make C–C (C–X) bonds first, or do an FGI that will allow you to do so
- if your first route doesn’t work, go back a step and change the approach
- DON’T look at the starting material (at first), it doesn’t help you!
- You MUST know the reactions forwards and backwards, and practice, practice, practice......

The Problems: Synthesize the (target) molecule on the right from the starting molecule the left. This cannot be done in one reaction. Give reagents and conditions and the intermediate molecules at each step. Do not show any mechanisms or transient intermediates.

Example 1:
• look for the starting structure in the target molecule
• identify the new C-C band that has to be made, do this first (going backwards, so step 3!)
• identify the FGI that you can and need to do, in this case make the bromide (step 2)
• identify the FGI you can and need to do, in this case dehydration of an alcohol to make an alkene (step 1)

Example 2:

• look for starting structure in target molecule and for any new C-C bonds
• **make the C-C bond (backwards) first if possible** (as in this case)
• identify FGIs, in this case making an allylic bromide is the obvious one
• making an alkene must be next step
• making the bromide must be the first step

Example 3:

• there will sometimes be more than one correct way of solving these problems
• note the bulky base with the tertiary halide gives the least substituted non-Sayetzeff alkene
• note the NON-bulky base with the tertiary halide gives the most substituted Sayetzeff alkene

Example 4:
6 Retrosynthesis: Summary of Reactions

Do NOT start studying by trying to memorize the reactions here!

Work as many problems as you can, with this list of reactions in front of you if necessary, so that you can get through as many problems as you can without getting stuck on eth reagents/conditions, and so that you can learn and practice solving reaction problems. Use this list AFTER you have worked all of the problems, and just before an exam. By then you will have learned a lot of the reagents/conditions just by using them and you will only have to memorize what you haven't learned yet. Then do the following:

• Cover the entire page of reagents/conditions with a long vertical strip of paper, see if you can write down the reagents/conditions for each reaction, check to see which you get correct, if COMPLETELY correct, circle Y, if incorrect or even slightly incorrect, circle N. In this way you keep track of what you know and what you don't know.
• Keep coming back to this list and so the same thing only for those reactions you circled N, until all are circled Y.

Knowing the reagents/conditions on this page is INSUFFICIENT to do well on an exam since you will ALSO need to recognize how to use and solve reaction problems in different contexts, this page ONLY helps you to learn the reagents/conditions that you have not YET learned by working problems.

Obviously we like to minimize memorization in a class that is designed to help you understand organic chemistry, but you can't work everything out from first principles, and there is nothing wrong with a little bit of memorization. There is a reason that it is useful to "just know" some material. Material that you just know can be used more quickly and accurately than material you have to "work out". This is why we memorize multiplication tables, for example.
The image contains a page from a document, showing chemical reactions and structures. The text is as follows:

- CH_2=CH_2 + HBr + ROOR → Y/N
- Cyclic compound + H_2 + Pd/C (or Pt or Raney Ni) → Y/N
- Cyclic compound + Na^+ − CN → Y/N

This is a generic SN2 reaction. You will generally need to work out the reagents for SN2 reactions.

- PhBr + Na^+ − O-t-Bu → Y/N
  2° halide requires bulky base to avoid SN2, gives Sayetzeff alkene

- Cyclic compound + Na^+ − OMe → Y/N
  3° halide with NON-bulky base gives Sayetzeff alkene

- Cyclic compound + t-BuO^− + K → Y/N
  3° halide with BULKY base gives Anti-Sayetzeff (Hoffman) alkene