

We are meeting Tuesday and Thursday at 8:00 AM to learn about Synthetic Organic Chemistry.

A very important connection for you will be our homepage.

http://www.chem.uky.edu/courses/che535/ACG/535_AC.html

There you will find the syllabus and other goodies. I will try to post lectures at this url before I give them in class.

1. Various Text Sources

1.1. Note that I am not picking through any particular book.

1.2. Carey and Sundberg, *Advanced Organic Chemistry*, Part B Reactions and Synthesis.

1.3. R. C. LaRock *Comprehensive Organic Transformations*

1.4. J. March *Advanced Organic Chemistry*

1.5. MAJOR SOURCE

1.5.1. journal articles

1.5.2. I will guide you through the reading of the synthetic literature.

2. Learning objectives!

2.1. What is organic synthesis?

2.2. What steps should you take to master synthetic organic chemistry?

2.3. Terms:

2.3.1. functional group

2.3.2. defunctionalization

2.3.3. organic oxidation state (how does this relate to the two above?)

2.3.4. retrosynthetic analysis

2.3.5. molecular complexity

2.3.6. synthons

2.3.7. convergence in organic synthesis

2.4. How do I?:

2.4.1. present a synthetic plan on paper?

2.4.2. access the literature to aid in retrosynthesis?

- 2.4.3. use organic synthetic knowledge to convince others of the feasibility of my projects?
- 2.5. Read a published synthesis to understand the logic of the synthetic approach.
 - 2.5.1. cubane.

3. What is Organic Synthesis?

- 3.1. Cornforth's definition:
 - 3.1.1. Intentional construction of molecules by means of chemical reactions.
- 3.2. Cammers' 3-part definition
 - 3.2.1. **plan** intentional construction of molecules - retrosynthesis
 - 3.2.2. **convince** a funding agency or a supervisor that the work can be done and is worth doing
 - 3.2.3. **carry out** the laboratory work
 - 3.2.3.1. The last step does not happen until the first two do.
 - 3.2.3.2. The last step is very labor intensive (teams hard at work for years).
- 3.3. **The main focus of this course is on the planning and the convincing (2.1 & 2.2 above). We will not work in the laboratory.**
- 3.4. **If you have not guessed yet, the main purpose of this course is to get you to use the chemical literature as source of information.**

4. Synthesis involves

- 4.1. championship chess -> human against nature, the order in which you perform from steps is important
- 4.2. The profession of architecture -> economical construction with known methods
- 4.3. The profession of the law -> precedent is very important. Who did it before and how did they do it?
 - 4.3.1. Nature / Chemistry is difficult to predict. We need to find a similar published procedure and intellectually bridge the gap between it and what we want to accomplish.
 - 4.3.2. If you do our homework, this gap is small.
- 4.4. **Effectively convincing the reader of precedent for your plans is the key to writing winning problem sets.**

5. Human Limitations!

- 5.1. You can not learn all there is to know about organic synthesis in a lifetime. There certainly is too much for one semester.
- 5.2. We can only scratch the surface and you can take it from there.
 - 5.2.1. Edwin Vedejs (University of Wisconsin) told us when I was in your shoes taking this class, “you can't do it well without computers.”
 - 5.2.2. Luckily this time we have access to databases.
 - 5.2.2.1. Connectivity algorithm-Beilstein/ Sci-Finder Scholar

6. Teaching Style!

- 6.1. I will not talk about reaction after reaction usually used to accomplish some transformation.
- 6.2. The course is focused more toward getting you to use the library and learning chemistry. I hope you learn as much or more on your own in the library than from class sessions!
- 6.3. If you are relying entirely on the lectures and not reading the assignments given in class you are not doing enough.

7. What does it take to be a good synthetic chemist?

- 7.1. I have seen synthetic organic chemistry pursued at least two ways.
- 7.2. chemist ONE
 - 7.2.1.1. Read the literature and memorized particular transformations, know who did what when to which molecule.
 - 7.2.1.2. Keep a deck of index cards on interesting reactions
 - 7.2.1.3. Memorize which reactions to use for retrosynthetic transformations
- 7.3. chemist TWO
 - 7.3.1. Have a general interest in chemical transformations
 - 7.3.2. Care about how mechanisms are determined
 - 7.3.3. Know the principles of stereochemical control

7.3.4. Know something about biochemistry and why people make molecules in modern times.

7.3.5. Consider concepts like molecular strain and topology and what this means for reactivity.

7.4. Invariably synthetic chemist #2 is the better chemist

8. **Why do people synthesize organic molecules today?**

8.1. Expectations of the synthetic chemist have changed. Who is doing synthesis has changed.

8.1.1. Knowing how to make molecules is not enough just like knowing how to speak and write is not enough--you have to have something worth while about which to speak and/or write

8.1.1.1. To do this you need to know something about chemistry and science that can often times be far away from synthesis

8.1.1.2. Likewise engineers, microscopists, toxicologists and biologists are synthesizing molecules.

8.2. synthesis in the modern times is done to

8.2.1. Construct nanostructure

8.2.2. Apply or test a biological utility or theory

8.2.3. Gain enough synthetic knowledge of the molecular architecture of natural product x to be able to make analogues for drug testing

9. **Why did people synthesize organic molecules yesterday? 1930-1975**

9.1. Develop the field of organic chemistry- Prove the synthesis can be done

9.2. Prove structure of a natural product

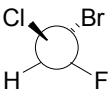
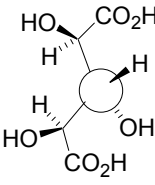
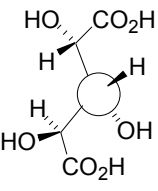
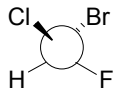
9.3. Test synthetic methodology

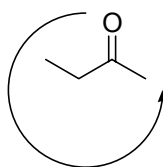
9.4. The above are worthwhile pursuits; however most of the above did not require a lot of knowledge in other fields.

10. **Some organic chemistry verbiage**

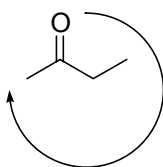
10.1.1. I will discuss the following terms and what they mean.

10.1.2. The table below was copied from *C&EN 1984, June 11, p. 21.* and the ideas of Prof. Kurt Mislow.

	chirotopic	achirotopic
stereogenic		
nonstereogenic		



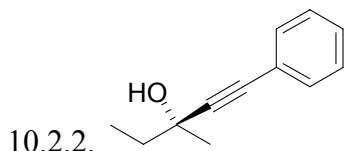
Si face



Re face

10.2. Re and Si. We use these adjectives when describing pro-stereogenic atomic centers.

10.2.1. These descriptors are relevant if we are considering a reaction at a carbonyl carbon.

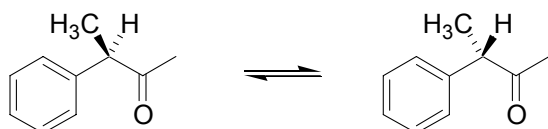


10.2.3. In this case we can state that the alkynyl anion added to the Si face fetches the R enantiomer.

10.2.4. *The absolute configuration of the product is just a name! It depended in this case on the priority (nomenclature, not chemistry) of the nucleophile.*

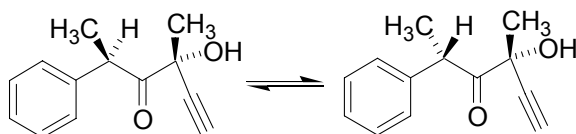
10.3. Review the Cahn, Ingold Prelog rules in an Organic Chemistry Textbook if you think this is necessary.

10.3.1. <http://www.vanderbilt.edu/AnS/Chemistry/Rizzo/chem220a/absolute.pdf>



10.4. The above process is *racemization* and involves the conversion of one enantiomer into another. Enantiomers can *racemize*. After they do we call the mixture optically impure or *racemic*.

10.4.1. The two structures above are enantiomers of each other.



10.5. The above process is *epimerization* and involves the conversion of one *diastereomer* into another.

10.5.1. The two structures above are *diastereomers* of each other.

10.5.2. Diastereomers describes two or more molecules that are stereoisomers but are not mirror images.

10.6. The two sets of molecules (11.4 and 11.5) above are fundamentally different can anyone tell me how?

10.6.1. I know one has two stereogenic centers and the other has one.

10.6.2. I know one is bigger than the other and the two molecules have different functional groups

10.6.3. But what is the other basic difference between the two pairs?

10.7. DISCUSSION FOLLOWS involving the following and the above molecules:

10.7.1. You are going to have to take your own notes here.

10.7.2. Kinetic Product/ Thermodynamic product/ Reaction Energy diagram/ The nature of asymmetry. Isomers, structural isomers, conformational isomers.

10.8. How are the following molecules related?

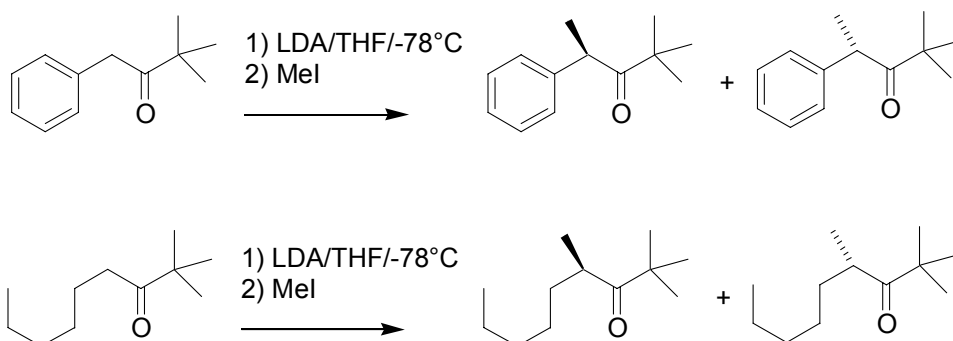


11. Before we talk about retrosynthesis we need to get a few other ideas about molecular structure down first. These are oxidation number and functional group.

11.1. **Functional groups** in organic molecules are molecular substructures that react similarly under similar conditions.

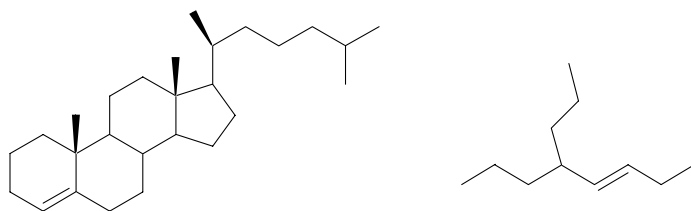
11.1.1. We can talk about the chemistry of ketones because ketones tend to behave like ketones from molecule to molecule.

11.1.2. For example:



11.1.3. We would expect the two molecules below to behave similarly. They both have the alkene functionality.

11.1.3.1. They should both react with Br₂



12. Divergent reactivity in functional groups could be explained by differences in alkene structure.

12.1. *cis* versus *trans*, cyclic versus acyclic

12.2. Consider *cis* and *trans* dienes with regard to the Diels-Alder reaction.

12.3. Likewise alcohols primary, secondary, and tertiary make up functional groups.

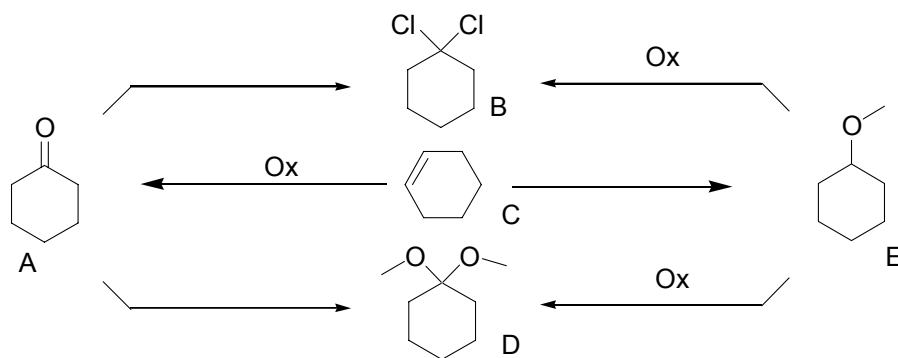
12.4. We would expect to be able to tosylate all primary alcohols in the presence of secondary and tertiary alcohols.

- 12.5. However we would not expect to be able to oxidize tertiary alcohols to ketones in the same way secondary alcohols are oxidized to ketones
- 12.6. Therefore with respect to oxidation the secondary alcohols and the tertiary alcohols need to be classified in separate functional groups
- 12.7. The above considerations are just language, the syntax of synthetic organic chemistry.

13. The nature of the conundrum.

- 13.1. We are trying to synthesize functional groups in complex molecules.
- 13.2. However these functional groups can change under the conditions that we used to synthesize other functional groups.
- 13.2.1. This is the reason why the order in which you do things is of a primary importance.
- 13.3. Some functional groups are orthogonal to other functional groups this means that group A will transform under conditions in which group B does not transform.
- 13.3.1. If it were not for this fact, synthetic chemists and life on earth would not be possible.

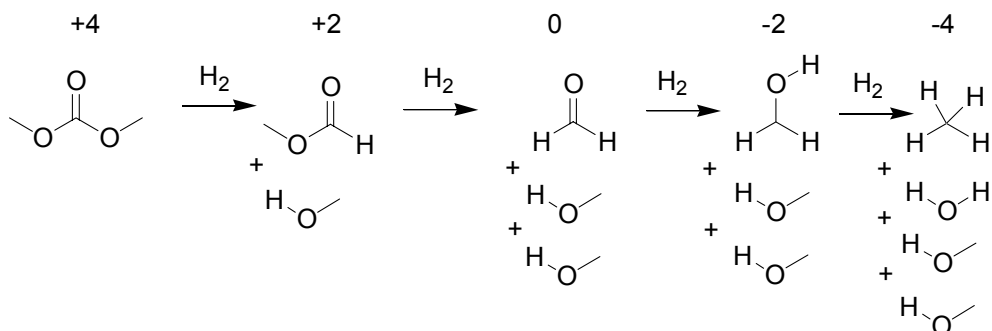
14. In the consideration of functional groups, oxidation/ reduction state in organic chemistry is an important concept.



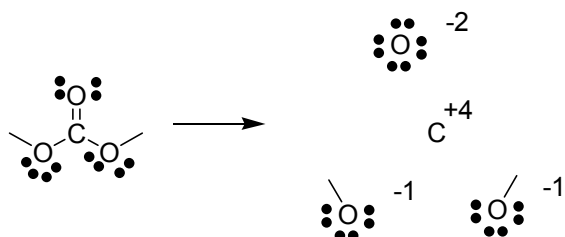
- 14.1. In the figure above, the ketone A, ketal D and geminal dichloride B belong to the same oxidation state. Whereas the alkene C and the ether E belong to the same oxidation state.
- 14.2. Consider the reactions above. Some arrows involve oxidation and others do not
- 14.3. How do you know which one's do?
- 14.4. *See J. March, Advanced Organic Chemistry, third edition, chapter 19, p. 1048. Or see the index for oxidation and reduction or the relevant sections in other editions.
- 14.5. The concept of Oxidation and Reduction in organic chemistry is not as straight forward as it is in other branches of chemistry that deal more frequently with metal centers.
- 14.6. In other branches of chemistry, oxidation is defined as the taking of electrons.
- 14.7. The oxidant gets reduced. In so doing it takes electrons.
- 14.8. Likewise the reducing agent gives up electrons and gets oxidized.
- 14.9. These reactions always have partners, oxidant and reducing agent.
- 14.10. Organic chemists are a bit more challenged when speaking of oxidation and reduction and oxidation numbers.
- 14.11. The principles still hold, but they are a little more difficult to apply.
- 14.12. Most mechanisms we write in organic chemistry do not involve the direct transfer of electrons from one molecule to another.
- 14.13. We could get real picky and talk about oxidation states of different carbons in molecules and assign increasing oxidation states to carbons bonded to more electronegative atoms.
- 14.14. Organic chemists traditionally have referred to the oxidation state of functional groups in a qualitative way to reflect their oxidation number.
- 14.14.1. We can put oxidation numbers on these functional groups.
- 14.14.2. In so doing we focus on a particular carbon atom.

14.15. In turn we define oxidation as the conversion from a functional group having a lower oxidation number to one having a higher oxidation number.

14.16. Consider the following:



Mnemonic to remember where to start, give the oxygen atoms or the halogen atoms all the bonded electrons.



etc. due to the relative electronegativities O and C versus C and H.

15. The alkane oxidation state is said to be defunctionalized

15.1. When the reactivity of alkanes can be accessed, often this reactivity is not selective.

15.1.1. On the other hand the alkene is considered a functional group.

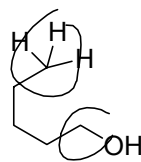
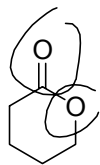
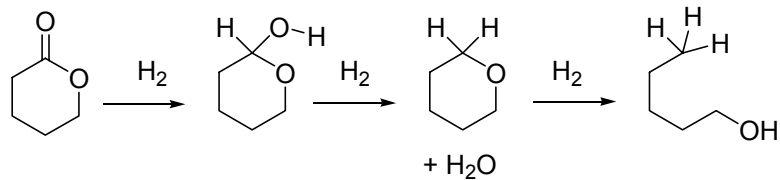
15.2. alkane \rightarrow alkene + $2e$ + $2H(+)$ is oxidation

15.3. alkene \rightarrow alkyne + $2e$ + $2H(+)$ is oxidation

15.4. However alkene + $(+)H$ + $(-)OH$ alcohol does not involve oxidation or reduction. The net result is merely adding a water molecule across the double bond.

16. If you can think about the change from one group to another in terms of addition or subtraction of H_2 then the change involves reduction/ oxidation.

16.1. Let's do this with the following ester.



16.2. In the hypothetical sequence above we added three H_2 molecules.

16.3. *Warning. Don't take the above reactions literally.* Adding 'H₂' to an ester is not necessarily the best way to transform it to a ketone, etc.