

Chem 535-Synthetic Organic Chemistry

Synthesizing Synthesis/ The logic of polarity

Ideas for this lecture were taken from: The following sources:

1. Fuhrhop, J. Penzlin, G. "Organic Synthesis, Concepts, Methods, Starting Materials ed. 2" Chapter 3 "Retrosynthesis of Simple Organic Molecules" p. 171.

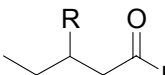
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1. What do I mean by the title of this lecture?!
 - 1.1. Synthesis means putting together or some act of assembly.
 - 1.2. Read the following definition of synthesis and you will get my meaning.

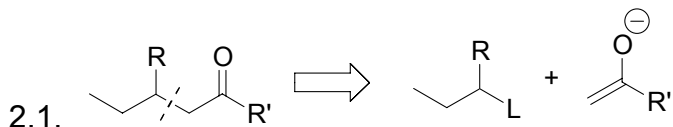
syn·the·sis [Pronunciation Key](#) (sĭn' thĭ-sĭs)

n. pl. **syn·the·ses** (-sĕz')

1.
 - a. The combining of separate elements or substances to form a coherent whole.
 - b. The complex whole so formed.
2. Chemistry. Formation of a compound from simpler compounds or elements.
3. Philosophy.
 - a. Reasoning from the general to the particular; logical deduction.
 - b. The combination of thesis and antithesis in the Hegelian dialectical process whereby a new and higher level of truth is produced.

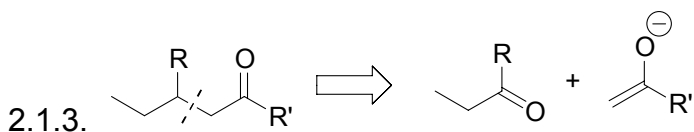
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- 1.3. Combining the chemical meaning of synthesis in 2 and the non-chemical meaning of synthesis in 1a you get my title.
 - 1.3.1. Organic synthesis will not make any sense to you unless you can combine it all together into one coherent body of knowledge. In this form the information in your head is also more useful.
 - 1.3.2. A logical thread that allows one to do this is polarity.
 - 1.3.3. Let me illustrate what I mean in the following example that we are going to do together.
 - 1.3.4. Let's retrosynthesize the following compound. Remember retrosynthesis involves more than one approach and a coherent choice of the best approach based on the efficiency by which a particular retrosynthetic analysis simplifies the target molecule.

2.  Let's ignore stereochemistry and make a racemic mixture.

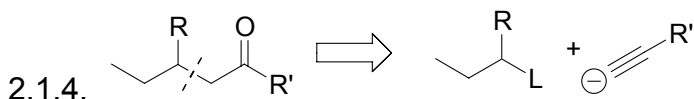


2.1.1. L is some leaving group.

2.1.2. Enolate alkylation

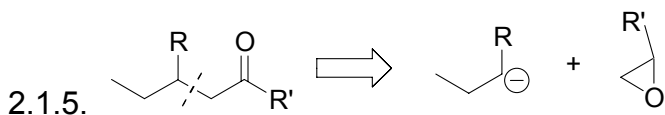


2.1.3.1. An aldol based disconnection that will involve reduction of an α,β -unsaturated ketone.



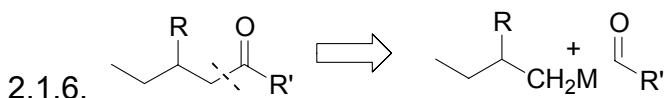
2.1.4.1. Will involve hydrolysis of the alkyne. Remember the regiochemistry of this hydrolysis can be controlled by hydroboration oxidation versus heavy metal catalyzed approaches.

2.1.4.2. Selectivity here will depend on R.

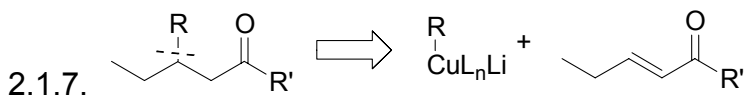


2.1.5.1. We can reverse the polarity of the general approach by using an epoxide.

2.1.5.2. In this case the fragment to the right is electron-rich instead of electron-poor. Electrophilic fragment in 1-3 become nucleophilic fragment in 4.



2.1.6.1.1. This will involve an oxidation of the secondary alcohol to the ketone. These are easy high-yielding reactions in general.



2.2. The approach you choose depends largely on what the R groups in the molecules are.

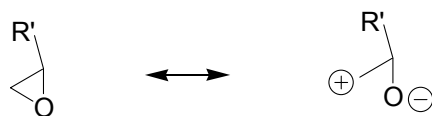
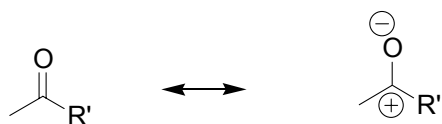
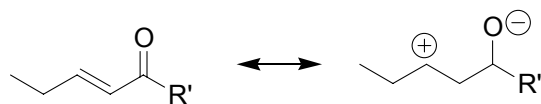
3. However you can surely see from the above examples that the way we retroanalyze molecules depends greatly on polarity.

3.1. and on extant functionality to optimize atom economy.

3.1.1. The carbonyl functionality stayed in place in the example above because we can't bothered to move it around much. This will cost us in steps. We want to make our synthesis as efficient as possible.

3.2. The carbonyl group is about in the middle of the molecule, keeping it in place optimized convergence.

3.3. In creating a solution to the synthetic problem above, and leaving the oxygen-atom functionality in place, we are thinking about polarity.

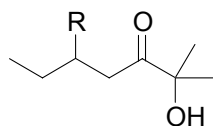


3.3.1.

3.4. This consideration guides our thinking.

3.4.1. After you have worked out how the polarity issues play in your analysis, the next question involves the details of which reagents to use.

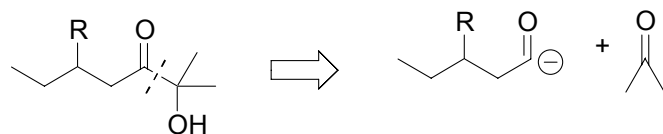
3.4.1.1. At this point you go to the literature.



4.

4.1. Similar considerations could be applied to the synthesis of this molecule with the caveat that the α -hydroxy group would need protection.

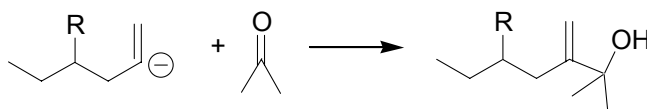
5. The approach below represents some deviation from those above because the 'use' of polarity in the carbonyl has been reversed.



5.1.

5.1.1. The anion in the scheme above is a synthon, an acylanion equivalent.

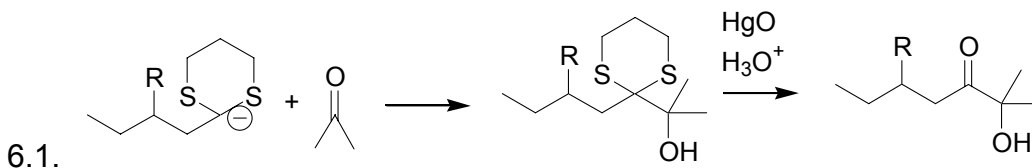
5.1.2. This might be accomplished in the following manner.



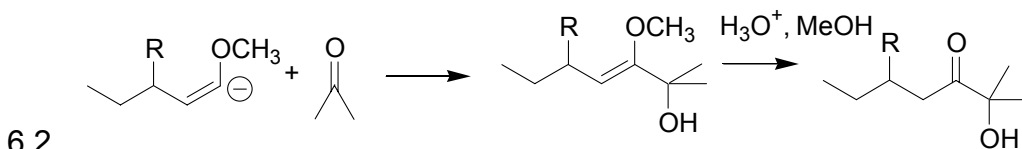
5.1.2.1.

5.1.2.2. The alkene would need to be oxidatively cleaved to the ketone.

6. There are more direct ways to use acylanion equivalents.

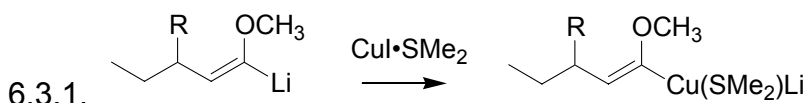
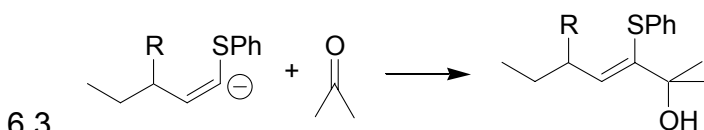


6.1.1. When the coupling of the electrophilic and nucleophilic partners is crowded as in the example above, this reaction does not work so well.

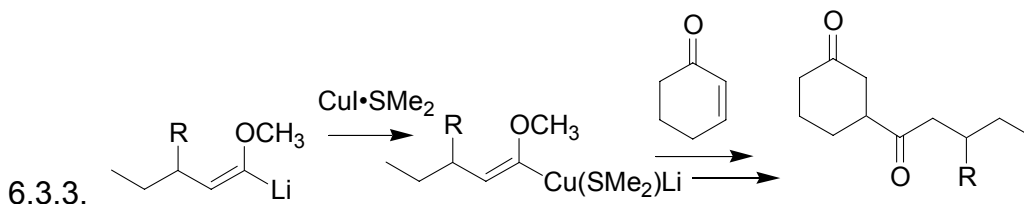


6.2.1. The anion can be generated from the enol ether and the very reactive organolithium reagent, *t*BuLi.

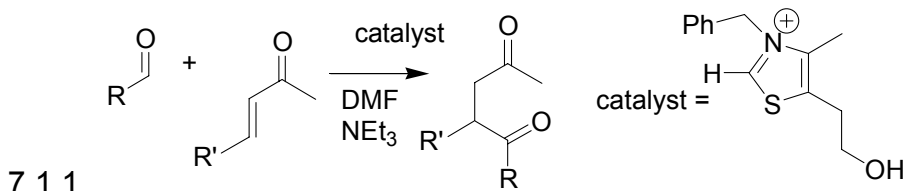
6.2.2. Generation of the nucleophile is somewhat easier when thioenolethers are used.



6.3.2. This reagent will perform 1,4-addition to α,β -unsaturated carbonyl compounds to yield, 1,4-diketones.

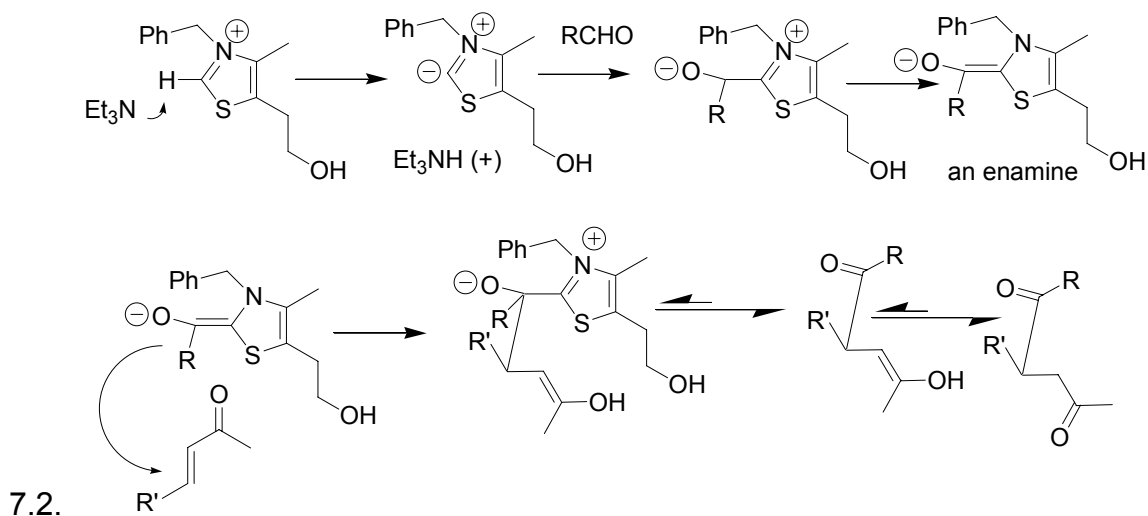


7. Another way to access acylanions as 1,4-addition reagents is by the Stetter reaction.



7.1.2. The hydrogen atom is shown in the catalyst because it is critical for the chemistry to run.

7.1.3. Stetter, H.; Kuhlmann, H. "The catalyzed nucleophilic addition of aldehydes to electrophilic double bonds." *Org. React. (N.Y.)* **1991**, *40*, 407.

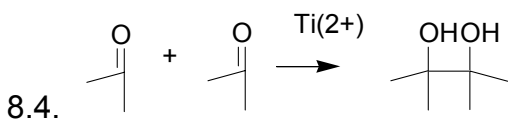


Ideas for the following were taken from:

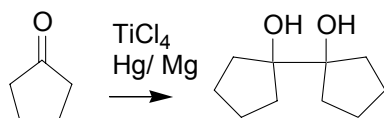
- Fuhrhop, J. Penzlin, G. "Organic Synthesis, Concepts, Methods, Starting Materials ed. 2" Chapter 3 "Retrosynthesis of Simple Organic Molecules" p. 53.
- Advance Organic Chemistry 3rd ed., J. March p. 949-964.

8. Pinacol Coupling

- 8.1. Consider the reaction below in which the ketone is reduced and coupled to another carbonyl.
- 8.2. In one partner the carbonyl is acting as an electron acceptor.
- 8.3. The other is acting as a nucleophile.
- 8.3.1. Not the usual polarity of the carbon atom alpha to the O atom of the carbonyl



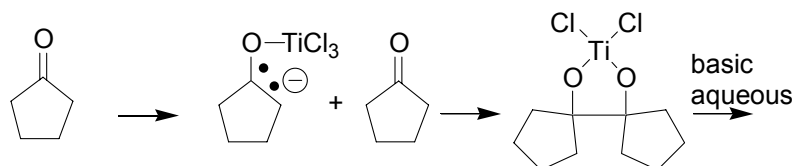
8.5. The reaction earns its name from the product, pinacol shown above.



8.6.

8.7. The low-valent metal is necessary because one of the carbonyl groups need to be reduced.

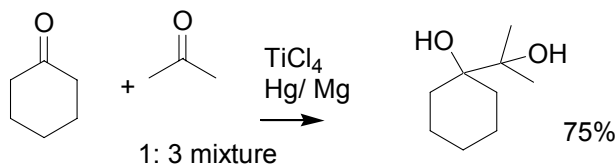
8.7.1. Titanium works well because Ti is oxophilic. It sits on the O atom preferentially after reduction.



8.7.2.

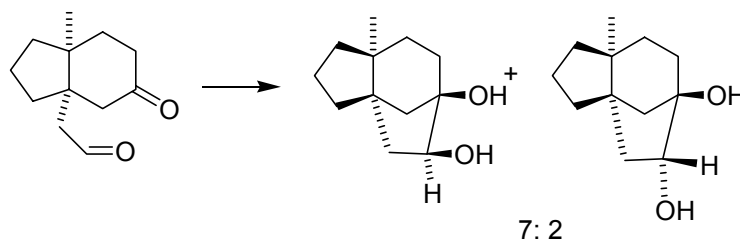
8.7.3. The basic aqueous work up followed by partitioning the mass into the organic phase yields the diol.

8.8. Intermolecular hetero pinacol coupling is more difficult to do than homocoupling.

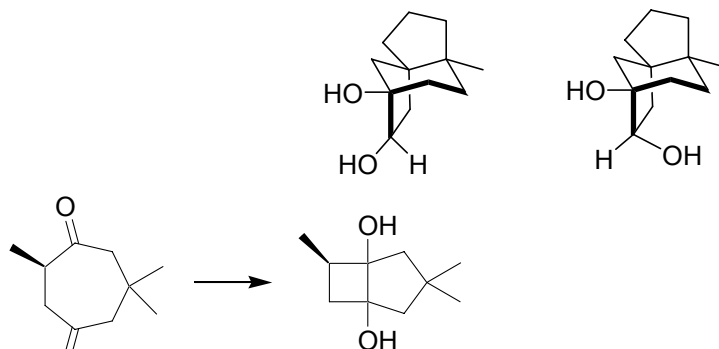


8.8.1.

8.9. However intramolecular heterocoupling is a facile process if the ketones approach each other during the normal thermal motions of the molecule.



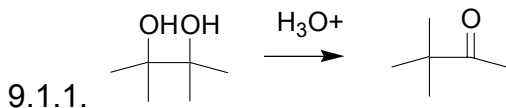
8.9.1.



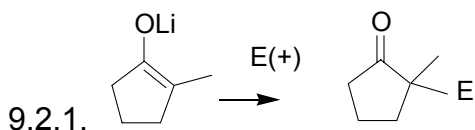
8.9.2.

9. Pinacol Rearrangement

9.1. Pinacol rearranges to pinacolone.

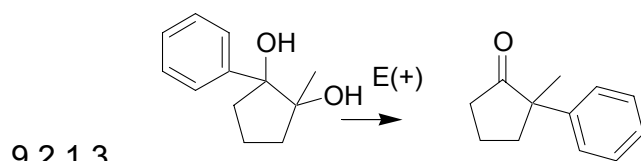


9.2. A good general way to make α -keto quaternary carbon centers.



9.2.1.1. If E is MeI, the reaction runs fine. If the electrophile gets more bulky yields decrease.

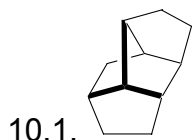
9.2.1.2. Furthermore E cannot be Ph-L (an aromatic group with a leaving group).

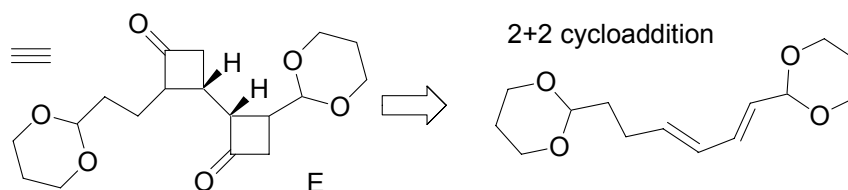
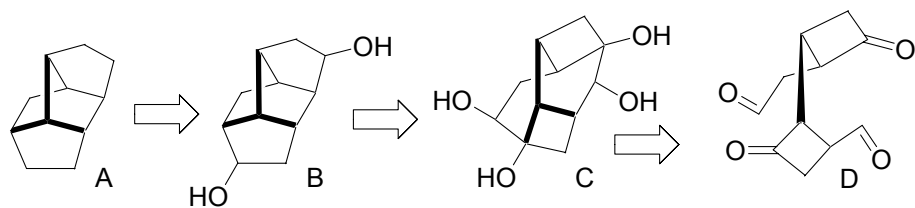


9.2.1.3.1. With the pinacol rearrangement, one can usually work out conditions in which aryl selectively 1,2-shifts.

9.3. The mechanism of this rearrangement involves protonation of the hydroxyl group and generation of a cation. The cation then rearranges.

10. Let's exercise with the pinacol reactions in the retrosynthetic analysis of the following polycyclic molecule.



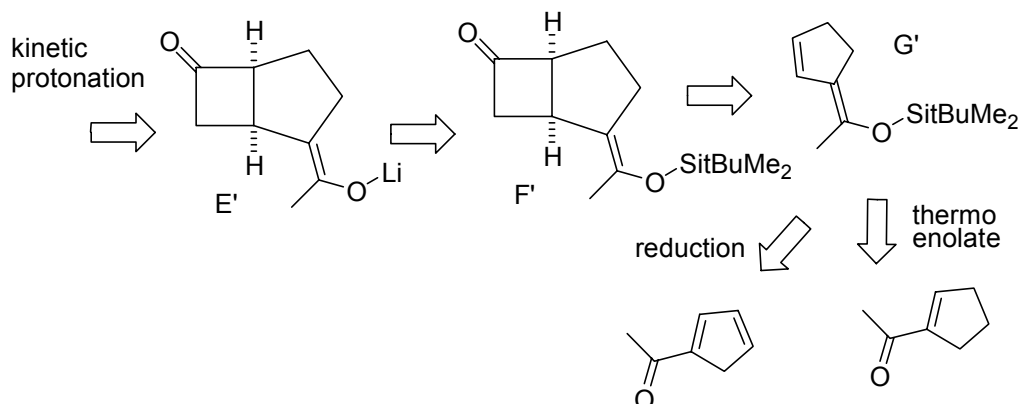
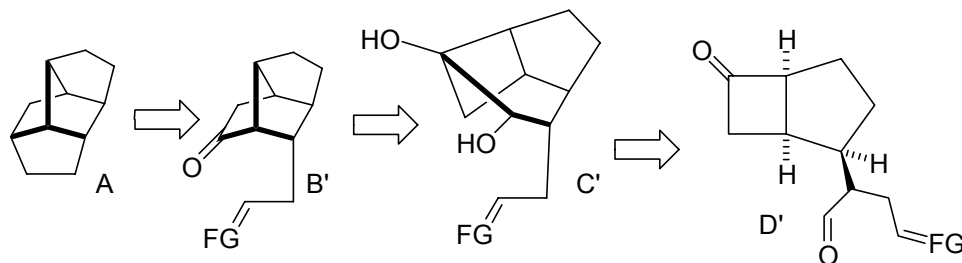


10.1.1.

10.1.2. D has the possibility of forming six or seven membered rings. The desired six-membered rings will probably prevail.

10.1.3. The 2+2 cycloaddition should be done one at a time.

10.1.4. A good method might be via **dichloroketene**. In the end game you are in the library looking through the literature for a possible 2+2 route to **E**.



10.2.

10.2.1. Another possibility. The kinetic protonation will be sketchy.

10.2.2. FG is a functional group with which you can perform the subsequent ring closure.

10.2.3. Regioselectivity of cycloaddition to F' will need to be looked up.