

Synthesis and Retrosynthesis

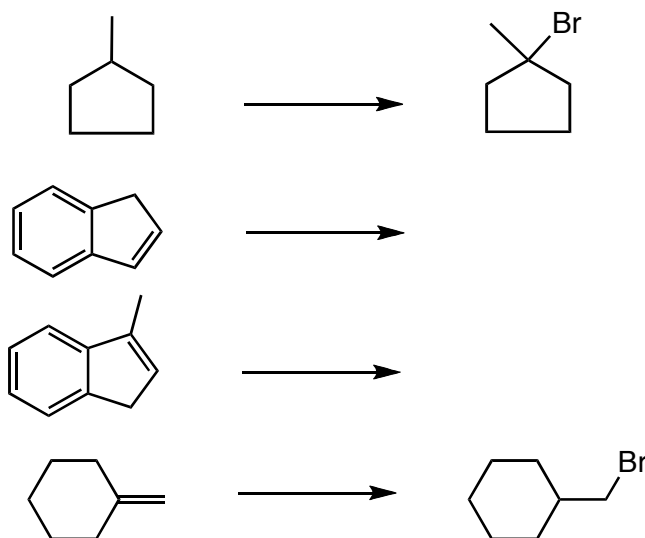
Putting Reactions Together

• 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 know as retrosynthetic analysis

1. Summary of First Semester Reactions Useful in Synthesis

1.1 Synthesis of Halides (Bromides)

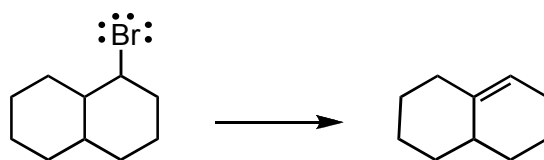
• Bromides are essential functional groups, easy to form, easy to remove as a leaving group



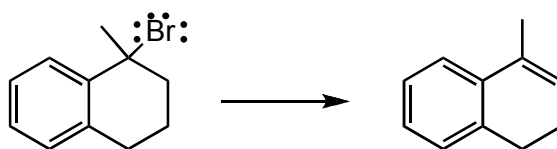
1.2 Synthesis of Alkenes

• E2 elimination **AVOIDS** CATION INTERMEDIATES

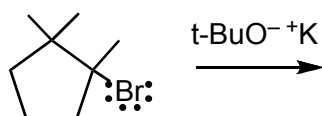
• **SUMMARY** of which bases to use under which circumstances



• Use a **BULKY** base with a **2° halide** to ensure no SN2, get **Saytzeff** (most substituted) alkene product



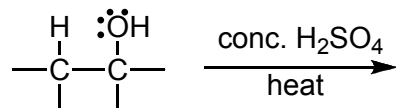
• Use a **NON-bulky** base with a **3° halide** (no SN2 not possible) to get the **Saytzeff** alkene product



• Use a **BULKY** base with a **3° halide** to get a **Non-Saytzeff** (Hoffmann, least substituted) alkene product

1.3 Alkenes from Alcohols (E1 and E2 elimination in a new context)

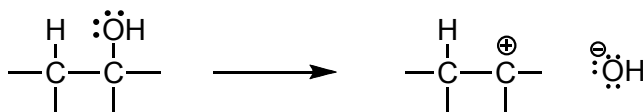
The reaction



- note a special kind of **SOLVENT EFFECT** here! In an aqueous medium, acid catalyzes water ADDITION to the alkene to make an alcohol. In conc. sulfuric acid medium, the acid helps to REMOVE water from an alcohol to make an alkene (the sulfuric acid DEHYDRATES the alcohol)
- Alternate reagents and conditions are H₂SO₄/P₂O₅, and others....

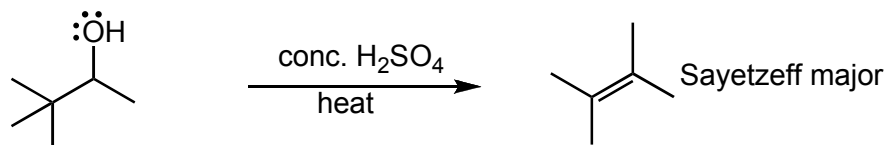
Mechanism: you already know it - either an E1 or an E2 elimination!

- in the mechanism, H₂O is the leaving group, ⁻OH is a poor leaving group (this is an important general principle that we will return to again later....)



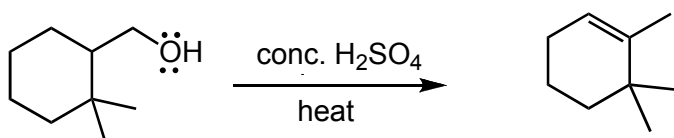
- in general, small neutral molecules such as water make excellent leaving groups, since they tend to contain low energy electrons, we will see thus again

Example



- With 3° and 2° alcohols the elimination mechanism is almost always E1, the protonated water is a very good leaving group, so good that E1 is quite fast even at a secondary carbon to make a secondary cation
- carbocation intermediates means rearrangements
- the sulfuric acid is the initial acid, the bisulfate anion is a likely base to deprotonate, recovering the acid catalyst
- The alkene formed will be the Saytzeff (Zaitzeff), there are no stereochemical constraints in the E1 mechanism and the most stable alkene will form

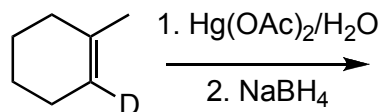
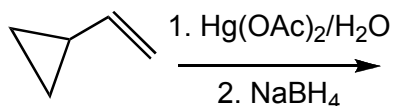
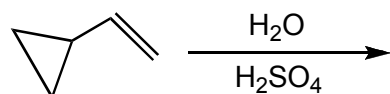
Example



- With a primary alcohol the mechanism is almost certainly E2
- Also, in the strong acid, protonation and deprotonation will occur, and if this can result in formation of a more stable alkene, then the more stable alkene will form
- the final product is the SAME as if the mechanism was E1 followed by carbocation rearrangement (although it doesn't, but you could work out the correct final product that way)

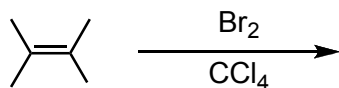
1.4 Synthesis of Alcohols

- Use reagents that avoid carbocation intermediates whenever possible



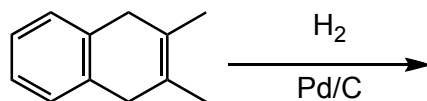
1.5 Synthesis of Dibromides

- Required for further synthesis of alkynes (see later)



1.6 Synthesis of Alkanes

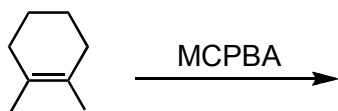
- More useful than it looks!



- Other catalysts you may see include Raney Ni or Pt

1.6 Synthesis of Epoxides

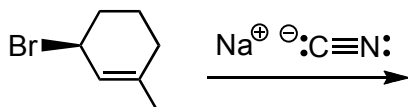
- Epoxides are important in carbon-carbon bond forming reactions (see later)



1.7 SN2 Reactions

- useful in many reactions that require addition of a substituent or formation of a new bond

Example

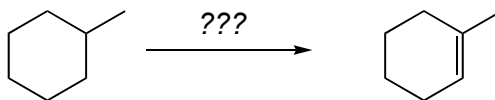


You will need to be able to use these reactions forwards and backwards!

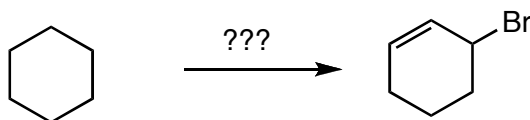
2. Multi-Step Synthesis

- 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, practice.....

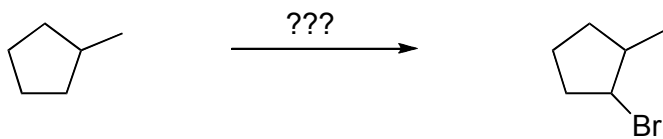
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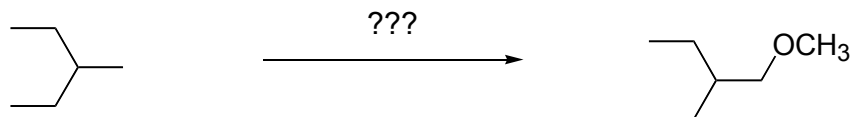
- brominate to get a functional group onto the alkene, then E2, which is the standard way to make an alkene



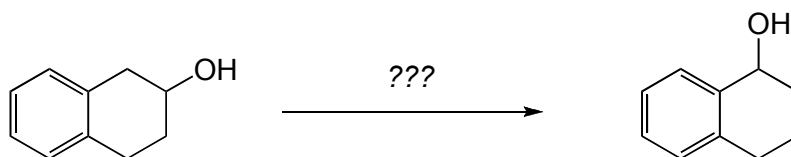
- brominate to get a functional group onto the alkane, then E2 with a BULKY BASE, which is the standard way to avoid SN2 to make an alkene, then brominate again in the allylic position (different reagents)



- 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



- can't add -OMe to an alkane, so we need to add a functional group, a LEAVING group at that carbon, once we recognize this then the strategy is same as previous problem



- 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 : Lewis Acid/Base reactions explains bond **formation**

- The Lewis Base **provides** the electrons and the Lewis Acid **accepts** the electrons to make the bond

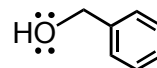
New concept : the SYNTHON, explains bond formation from **reactants**



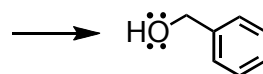
- synthons indicate where the electrons come from to make the bond (equivalent to Lewis base and Lewis acid)
- the synthons are often not "real" (can't be put into a bottle), and may need to be converted into "real" reactants
- one synthon must carry the electron pair (LB), the other usually needs a leaving group (LA)
- the synthon with the electrons (LB) is usually the one where the ELECTRONS WOULD BE MOST STABLE, the idea here is that the synthon that carries the electrons should be easy to make, if the electron pair is very high in energy then that synthon may be impossible to make and the retrosynthetic strategy would fail

Example 1

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

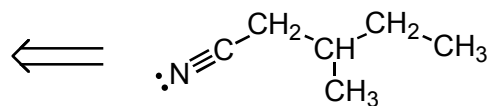


- convert to "real" reactants (synthetic equivalents) by adding a leaving group to the "positive" synthon, the negative synthon doesn't have to be converted into something more stable
- reacting the synthetic equivalents makes the required alcohol

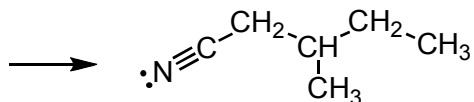


Example 2

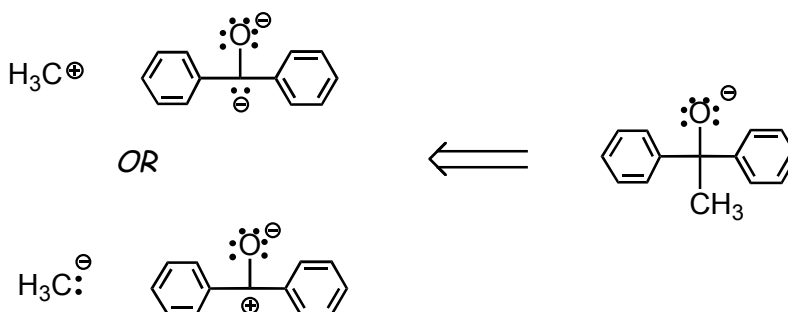
- disconnect the indicated C-C bond
- one of the carbons must carry the electron pair, one the leaving group, which is best?



- convert to "real" reactants (synthetic equivalents)



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



- convert to "real" reactants (synthetic equivalents)

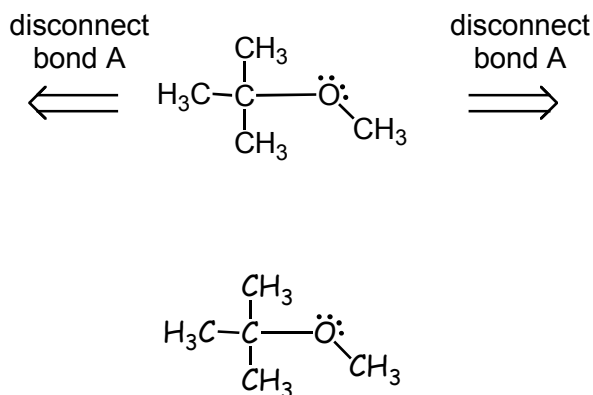


- in this case the "leaving group" is the C-O pi-bond
- synthon **retrosynthetic strategy** is an advanced organic chemistry concept
- however, we **don't** analyze every forward reaction in terms of Lewis acid/base, we don't have time, we just **know the reactions forwards**
- similarly, we **won't** analyze every reverse reaction in terms of synthons, we won't have time, we **will just know the reactions backwards**

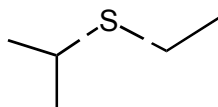
4. SN2 Reactions Revisited : Practice Doing Reactions in Reverse

- how would you make the following molecules using the S_N2 reaction??
- emphasis is on recognizing which bond you can make, and identifying the synthons and thus reactants...

Example 1

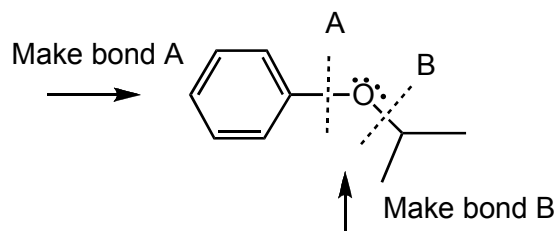


Example 2

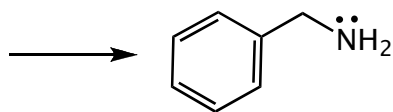


- 2° tosylate better than 2° halide, but still not as good as 1° anything!

Example 3



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

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, 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 bond 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 FGI's, 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

Retrosynthesis PROBLEMS

Identifying Synthons

In each case identify the best synthons for disconnection of the indicated bonds, AND the actual reagents (synthetic equivalents) required to do the reactions. Some of these are difficult, don't worry if you need to look at a lot of the answers, we did not cover all of these reactions in class.

1 (standard)		<u>Answer</u> Correct Y / N
2 (standard)		<u>Answer</u> Correct Y / N
3 (standard)		<u>Answer</u> Correct Y / N
4 (standard)		<u>Answer</u> Correct Y / N
5 (challenging)		<u>Answer</u> Correct Y / N
6 (challenging)		<u>Answer</u> Correct Y / N
7 (challenging)		<u>Answer</u> Correct Y / N
8 (challenging)		<u>Answer</u> Correct Y / N

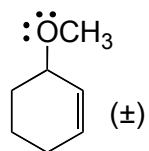
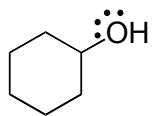
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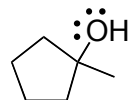
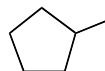
1. You do them in a group, someone else in the group gets to the answer before you, you understand why the answer is correct, you therefore assume you can do that problem, you check "Y"
2. You do them on your own, you are not sure about the answer, you check it to see if you are right, you are, you check "Y"
3. You do a problem, it is similar to the one you just did, you look at the answer, you understand the answer, you check "Y"
4. You can't do a problem, you ask for help, you understand the answer, you check "Y"
5. You do a problem, you get it mainly correct, but a little bit wrong, you understand what you did wrong, you check "Y"

UNDERSTANDING is different from DOING. In each of the above scenarios you have not proven that you can do the problem, rather you have proven that you CAN'T do the problem without help from others, or without "cheating" on the time it takes to do a problem, or without proving that you can do the problem 100% correct.

Example 3

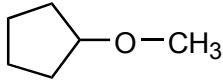
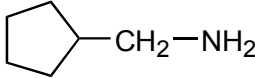
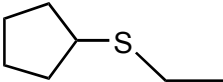


Example 4



- 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-Saytzeff alkene
- note the NON-bulky base with the tertiary halide gives the most substituted Saytzeff alkene

In each case identify the reactants that can be used with an alkyl halide in an SN2 reaction to synthesize the provided structure

1 (standard)	$\text{Me}-\text{O}-\text{Ph}$	<u>Answer</u> Correct Y / N
2 (standard)		<u>Answer</u> Correct Y / N
3 (standard)	$\text{H}_3\text{C}-\text{C}\equiv\text{C}-\text{CH}_3$	<u>Answer</u> Correct Y / N
4 (standard)	$\text{H}_3\text{C}-\overset{\text{O}}{\parallel}{\text{C}}-\text{O}-\text{CH}_2-\text{CH}=\text{CH}_2$	<u>Answer</u> Correct Y / N
5 (standard)		<u>Answer</u> Correct Y / N
6 (standard)		<u>Answer</u> Correct Y / N

Doing problems is the only way that you will learn organic chemistry. You should do problems in the notes, from the textbook and from problem sets.



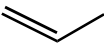
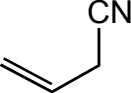
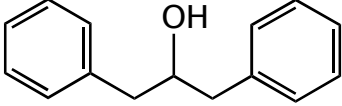
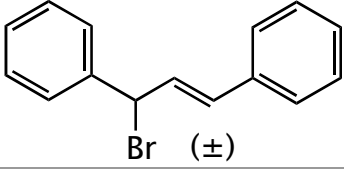
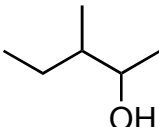
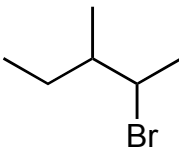
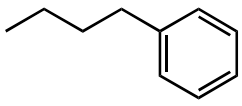
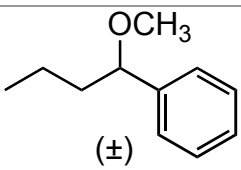
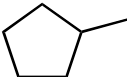
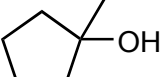
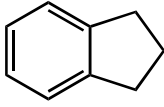
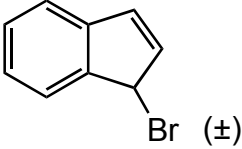

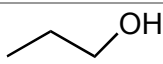
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4. You can't do a problem, you ask for help, you understand the answer, you check "Y"
5. You do a problem, you get it mainly correct, but a little bit wrong, you understand what you did wrong, you check "Y"

UNDERSTANDING is different from DOING. In each of the above scenarios you have not proven that you can do the problem, rather you have proven that you CAN'T do the problem without help from others, or without "cheating" on the time it takes to do a problem, or without proving that you can do the problem 100% correct.

Provide a synthesis of the target molecule on the right from the starting molecule on the left. This cannot be done in one reaction. Give reagents, conditions and intermediate molecules at each step. Do not show any mechanisms or transient intermediates

1 (easier)			<u>Answer</u> Correct Y / N
2 (easier)			<u>Answer</u> Correct Y / N
3 (easier)			<u>Answer</u> Correct Y / N
4 (easier)		<i>(ignore stereochemistry)</i> 	<u>Answer</u> Correct Y / N
5 (easier)			<u>Answer</u> Correct Y / N
6 (standard)			<u>Answer</u> Correct Y / N
7 (standard)			<u>Answer</u> Correct Y / N
8 (standard)			<u>Answer</u> Correct Y / N

It is CRITICAL that you keep track of what you know and what you don't know. Each notes problem has a "Correct Y / N" box. When you are PROPERLY CONVINCED that you can do a problem, circle "Y", if you can't do the problem circle "N". Keep coming back to those problems with the circled "N", until you can circle the "Y".