

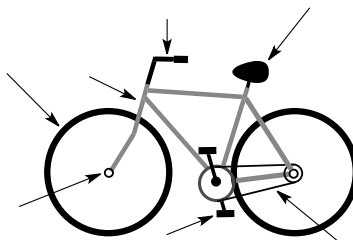
• A large part of organic chemistry involves building more complex molecules from smaller ones using a designed **sequence** of reactions, i.e. chemical synthesis. Especially in more complex cases, synthetic problems are often best solved BACKWARDS in a process know as retrosynthetic analysis

BUT FIRST.....

How to Ride a Bicycle

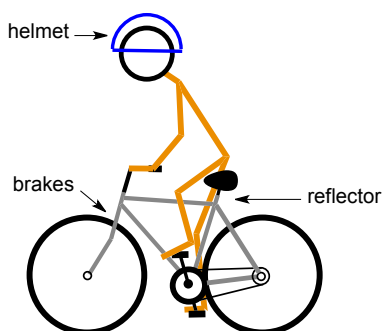
1.1 Parts of the bicycle

- It is important to understand bicycle nomenclature
- We will not cover IUPAC bicycle nomenclature in this case



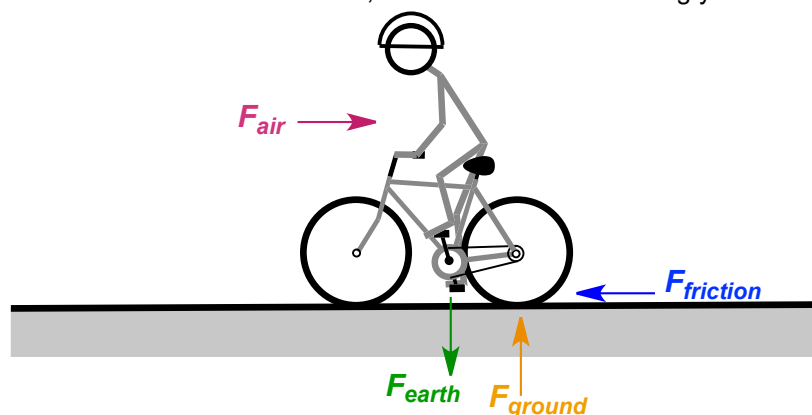
1.2 Bicycle Safety

Question? Which of the following are essential SAFETY ITEMS when riding a bicycle



1.3 Physics of Bicycle Riding

- You MUST understand the relevant forces involved, without this understanding you can NOT ride a bicycle!

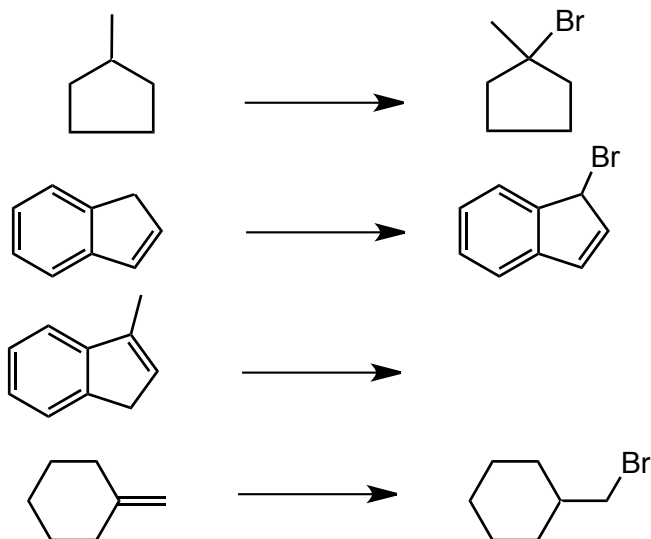


- Review sessions on Saturday
- Chad's Review on Bicycle Riding
- Kahn Academy lectures on Bicycle riding

1. Summary of First Semester Reactions Useful in Synthesis

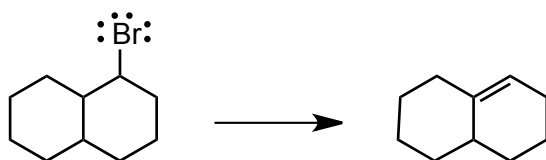
1.1 Synthesis of Halides, Reactions that MAKE Bromides

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

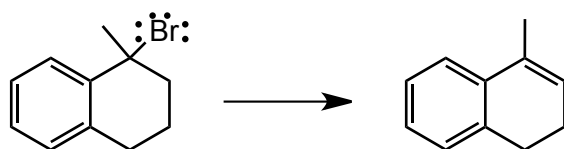


1.2 Synthesis of Alkenes, Elimination Reactions that MAKE Alkenes

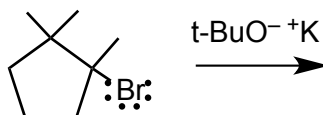
- In a synthesis context we try to avoid reactions that involve carbocation rearrangements if at all possible
- Therefore, use **E2 elimination of ALKYL BROMIDES** rather than E1 to AVOID carbocation intermediates



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



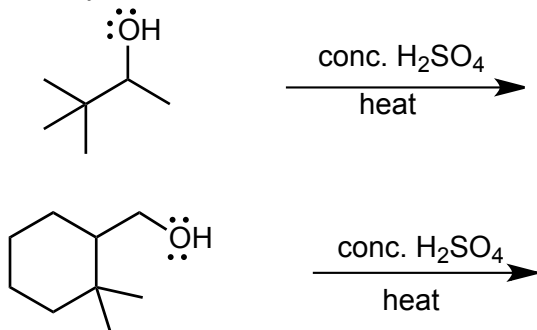
- SN2 is not possible for a 3° bromide, therefore use a **NON-bulky** base with a **3° halide** to get the **Saytzeff/Zaitsev** alkene product



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

Elimination of ALCOHOLS:

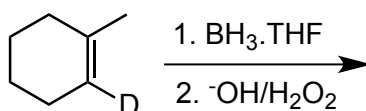
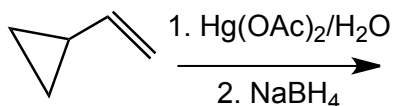
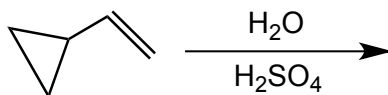
- In synthesis we try to avoid reactions that involve carbocation rearrangements, but sometimes that isn't possible



- Elimination of alcohols occurs via the E1 mechanism for secondary and tertiary alcohols, which involves carbocation intermediates which can, and usually will rearrange.
- Corresponding elimination of primary alcohols occurs by the E2 mechanism, which avoids carbocation intermediates in the elimination step, but these reactions are usually followed up by protonation/deprotonation steps (carbocation again) that results in overall rearrangement.

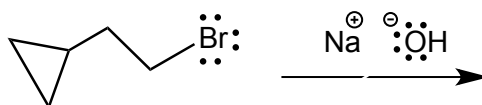
1.3 Synthesis of Alcohols

Addition reactions we know that form alcohols



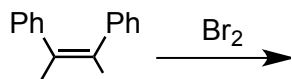
- In the context of synthesis we try to avoid reactions that involve carbocation intermediates
- THEREFORE, to do Markovnikov addition of water to a C=C bond will use the Lewis acid catalyzed method with mercuric acetate ($\text{Hg}(\text{OAc}_2)$) rather than Bronsted acid catalysis using, for example, H_2SO_4

Substitution reactions we know that form alcohols: **SN2**



1.4 Synthesis of Dibromides

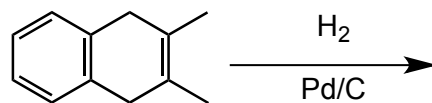
- Required for further synthesis of alkynes (see later)



- 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!

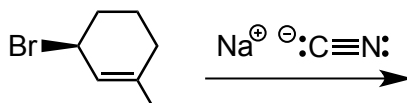


- Other catalysts you may see include Raney Ni or Pt

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

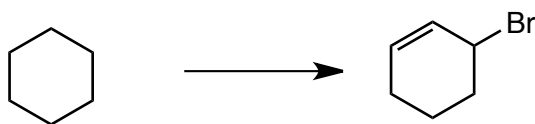
- multi-step chemical synthesis involves building larger or more complex molecules from smaller ones using a designed **series** of reactions
- this involves putting a series of reactions together **in sequence** (multiple steps)
- here we will look at some simple examples
- to do these problems you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



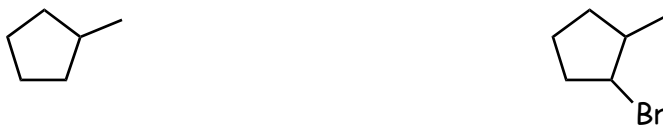
- the **FIRST REACTION WORKING BACKWARDS** must have an alkene as the product
- alkenes can be formed by elimination from halides or alcohols
- of these two we choose the halide reaction, because the halide can be made from the starting structure more easily than the alcohol, completing the problem
- **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.



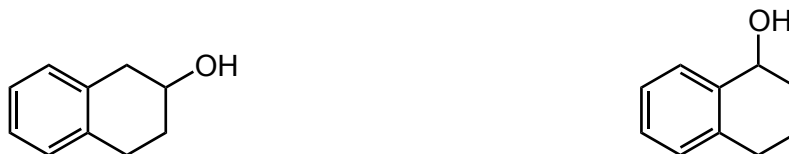
- The first bromination is of an alkane, EITHER Br₂/light or NBS/light can be used
- Br₂/light can NOT be used for the last bromination of the alkene, we need to avoid Br₂ addition to the C=C bond
- it may be a good idea to always use NBS and for all radical brominations then you don't have to remember 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

Example Problem 4:



- 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