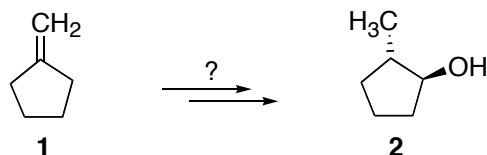


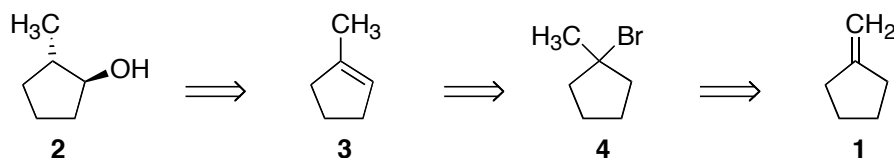
Introduction

The focus of exam three and the rest of this course will be on synthesis problems. These are particularly useful test items since they require you to put everything together, including reaction patterns, requisite conditions, stereochemical considerations and mechanisms, to develop a series of transformations that will convert a known set of starting materials to a synthetic target; it also happens that this is one of the most valuable skills required of any organic chemist. Undoubtedly, most of the students in this course are not pursuing careers in organic chemistry. For them, synthesis problems—and perhaps this course overall—represent an elaborate puzzle, one which requires you to know the language, rules and outcomes for a given set of conditions. Approach these problems then as you might an algebra problem, Sudoku puzzle or chess game. The number of molecules you can make with the chemical transformations you've learned so far is literally infinite, just as the number of possible Sudoku puzzles is infinite. Your challenge is to recognize what patterns and logic are operating that will allow you to convert one set of functional groups into another for seemingly different molecules. Like any puzzle or skill, practice makes perfect. I suggest that you attempt *all* of the synthesis problems that follow.

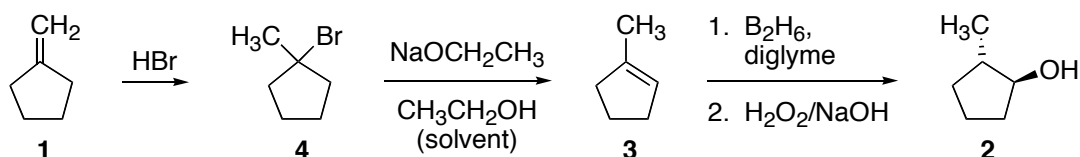
The most common mistake made when approaching a synthetic challenge is to begin with the starting material and try to “find a way” to the product through intense thinking and a lot of trial and error. Although this method may work for simple synthetic problems that require only one or two steps, it is inefficient and usually unsuccessful for more advanced problems. The key is to begin at the end; work backwards from the target, using your knowledge of chemical reactions, until you reach the starting material. This is called a retrosynthetic analysis. Let's work through the synthetic problem below as an example. At first glance you should recognize that there is no *one* chemical transformation that we've learned that is able to convert **1** into **2**; therefore, more than one step must be required.



Begin the retrosynthetic analysis by first drawing the target, in this case **2**. Then, draw the arrow shown below; this arrow is used to represent a retrosynthetic step (reverse thinking step). Each time you draw this arrow, you are asking the question, “What molecule can be converted into the molecule at the beginning of my retrosynthetic arrow using chemistry I know?” In this case the question is, “What molecule can be converted into a secondary alcohol that is *trans* to the adjacent methyl group in **2**?” Alcohols can be prepared from alkenes; specifically, hydroboration/oxidation of **3** is the best choice since this reaction is stereoselective. The –H and –OH groups are both added to the same face of the alkene, which puts the methyl group *trans* to the –OH group. This transformation is also regioselective and provides the least substituted alcohol (anti-Markovnikov addition). Hydration of **3** with H₂SO₄/H₂O to give **2** wouldn't work since that reaction proceeds through a carbocation intermediate and would provide a mixture of *cis* and *trans* alcohols. Hydration also provides the most substituted alcohol, which is not what is required. From **3** another retrosynthetic arrow is drawn and another question asked. From what molecule can the alkene in **3** be prepared? Alkenes can be prepared through a number of methods including dehydrohalogenation of alkyl halides. The tertiary alkyl bromide **4** is chosen rather than the secondary alkyl bromide because **4** can be prepared directly from our starting molecule **1** through Markovnikov addition of HBr. This completes the retrosynthetic analysis.



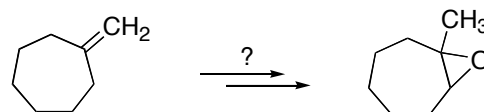
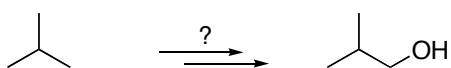
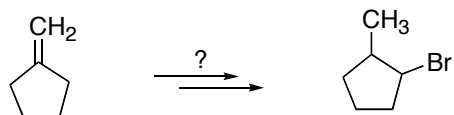
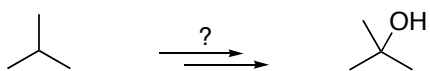
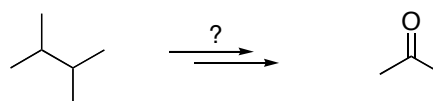
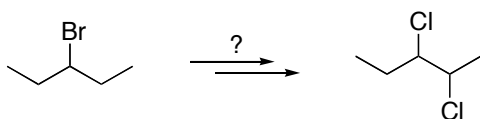
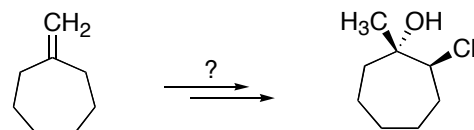
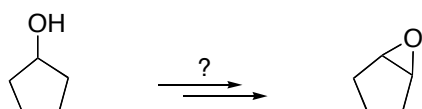
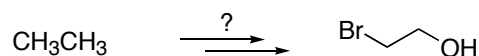
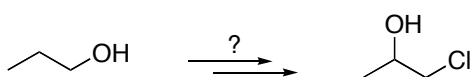
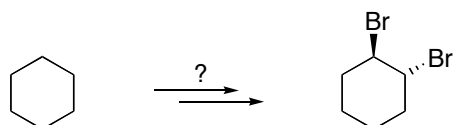
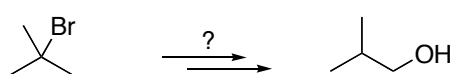
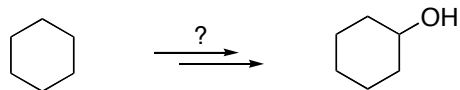
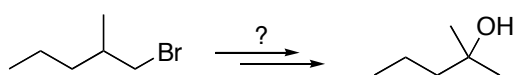
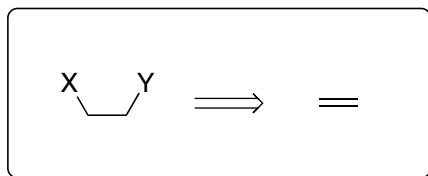
Once the retrosynthesis is complete, the forward reactions can be written including all the required conditions and reagents. Markovnikov addition of HBr across alkene **1** provides alkyl halide **4**. Although other conditions may be included such as solvents and temperatures, the most important reagent here is HBr. Dehydrohalogenation of **4** can be accomplished with a strong base. Typically, alkoxide bases such as NaOCH₂CH₃ or NaOC(CH₃)₃ are used. Zaitsev's rule predicts that the most substituted alkene will result from dehydrohalogenation. However, as we discovered in class large sterically hindered bases such as NaOC(CH₃)₃ may show a preference for deprotonation at the least sterically hindered site. In this case, that would revert **4** back to **1**. To avoid this complication, a smaller strong base such as NaOCH₂CH₃ is preferred. Finally, hydroboration of **3** with B₂H₆ followed by oxidation with H₂O₂/OH⁻ gives the target molecule, **2**. Other synthetic routes are certainly possible for our target, but this route appears to be the shortest.



Although you may never encounter this exact synthetic target again, you should recognize an important synthetic strategy in this example. Less substituted alkenes such as **1** can be converted into their more substituted isomers through a simple two step sequence: HX addition followed by dehydrohalogenation. This strategy is very powerful and can be used in several of the problems that follow. Look for important patterns and strategies in each of the problems you attempt. Doing so will dramatically increase the speed at which you are able to develop reasonable syntheses.

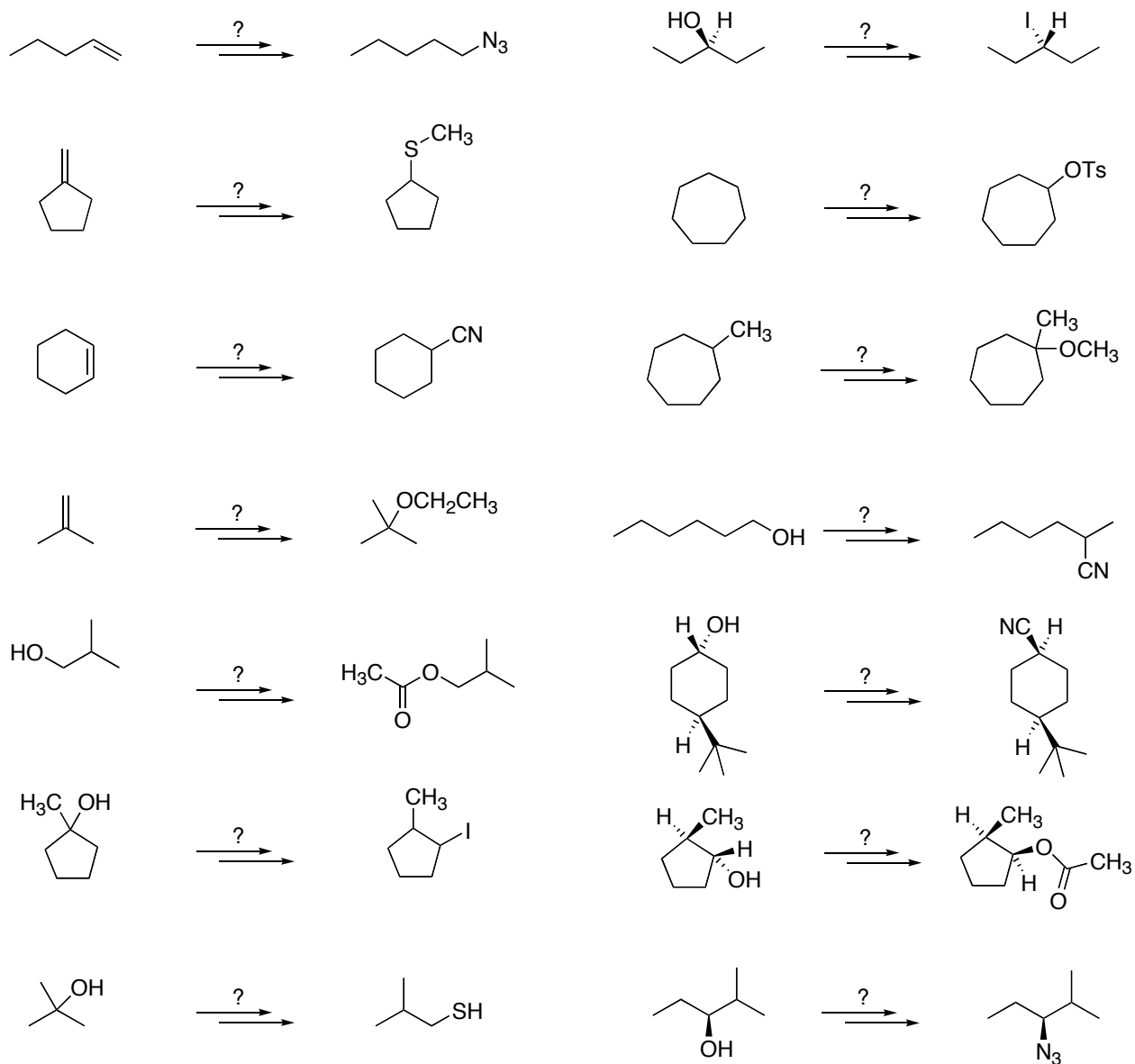
1. Syntheses Utilizing Addition Reactions of Alkenes

For each synthetic problem below, first write out a retrosynthetic analysis. Then, write the forward synthesis including all necessary reaction conditions and reagents for each transformation. All of the syntheses below utilize addition reactions to alkenes (e.g., hydration, halogenation, hydrogenation). The retrosynthetic step below, then, will be common to all of them.



2. Syntheses Utilizing Substitution Reactions.

For each synthetic problem below, first write out a retrosynthetic analysis. Then, write the forward synthesis including all necessary reaction conditions and reagents for each transformation. All of the syntheses below utilize either S_N1 or S_N2 . Pay particularly close attention to whether your synthesis must be stereoselective. S_N2 conditions are required (e.g., tosylate leaving groups on 1° or 2° carbons) if inversion of configuration is necessary.



3. Syntheses Utilizing Alkylation of Alkynes and Addition reactions to Alkynes

For each synthetic problem below, first write out a retrosynthetic analysis. Then, write the forward synthesis including all necessary reaction conditions and reagents for each transformation. Each synthesis involves an addition reaction to an alkyne (e.g., double halogenation, Hg^{2+} catalyzed hydration), alkylation of terminal alkynes, or both.

