

# Massachusetts Institute of Technology

## Organic Chemistry 5.511

September, 2007  
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### Problem Set 1

## Functional Group Transformations Study Guide

The purpose of this three-part study guide is to assist you in mastering the key functional group transformations that you will need for the design of syntheses on problem sets and exams in 5.111 and 5.112. As a suggested course of study, I recommend that you might proceed as follows: (a) read the relevant chapter in the reading assignment in Carey & Sundberg and the appropriate section of the "Outline of Functional Group Transformations" handout; (b) attempt to answer the questions on that section of the problem set without reference to the textbook; (c) consult the text to check your answers and for help on any questions that you were unable to answer. Solutions to all questions will also be posted on the 5.512 website. Note that your aim is to become sufficiently conversant with this chemistry so that you can use these reactions in problem-solving without having to refer to the text or notes.

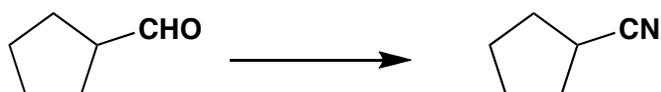
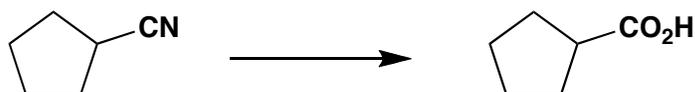
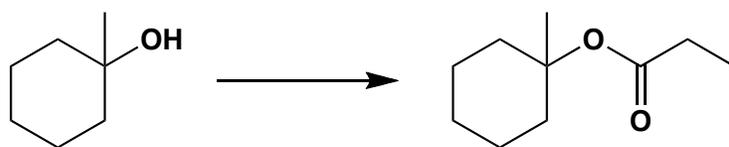
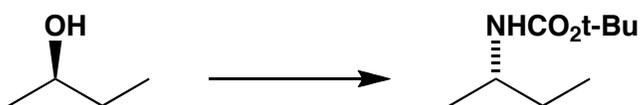
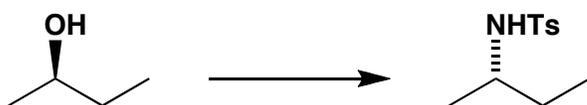
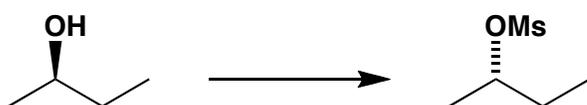
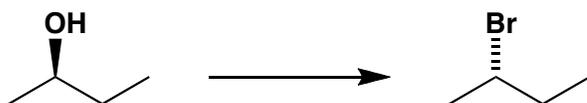
Each part of the Study Guide begins with questions that focus on mechanistic and stereochemical aspects of important functional group transformations. These deal with features of these reactions that are important to understand if you are to apply them in syntheses. This is followed in each part by a set of questions concerned with conditions for effecting specific transformations.

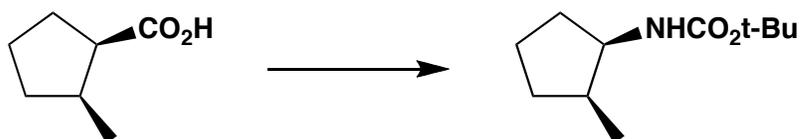
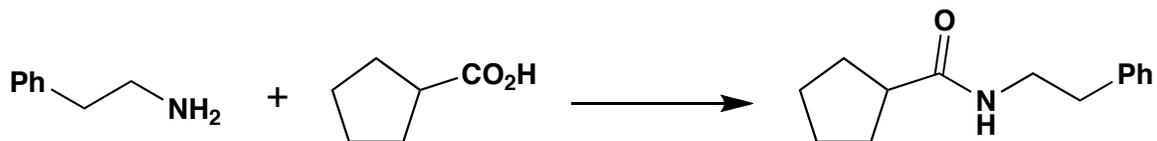
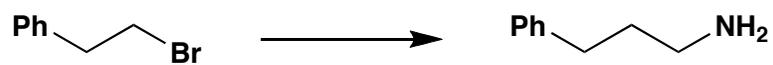
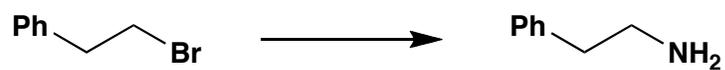
Problem Set 2 will consist of problems involving functional group transformations in the context of more complex molecules and will provide you with additional practice in this area.

### Part I - Functional Group Interconversions and Protective Group Chemistry

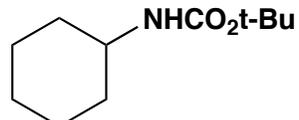
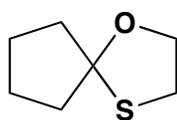
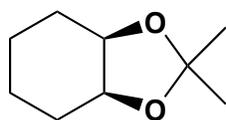
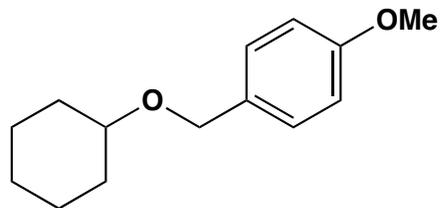
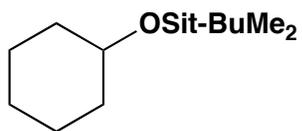
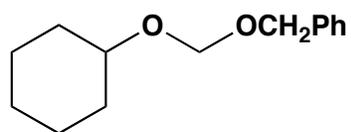
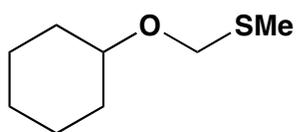
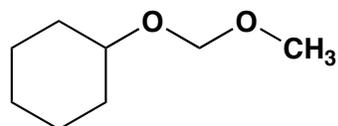
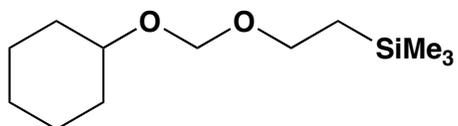
- (1) Preparing tosylates from tertiary alcohols is very difficult and generally is not possible in good yield due to side reactions such as elimination and rearrangement. On the other hand, mesylates can often be prepared in good yield since a different mechanism is involved. Provide detailed stepwise mechanisms for the conversion of cyclohexanol to the corresponding tosylate and mesylate under standard conditions (TsCl, pyr, CH<sub>2</sub>Cl<sub>2</sub> and MsCl, Et<sub>3</sub>N, CH<sub>2</sub>Cl<sub>2</sub>).
- (2) Explain why DMSO is generally superior to ethanol as a solvent for the conversion of primary alcohols to the corresponding nitriles.
- (3) Provide conditions for a mild method for converting a carboxylic acid to the corresponding acyl chloride under essentially neutral conditions. Suggest a mechanism for the key step.
- (4) Provide a mechanism for the DCC-based coupling of alcohols and carboxylic acids to form esters.
- (5) Why is it possible to convert phenols but not alcohols to the corresponding methyl ethers using diazomethane?
- (6) Provide a stepwise mechanism for the cleavage of anisole to phenol using BBr<sub>3</sub> in dichloromethane.
- (7) Provide a detailed stepwise mechanism for the cleavage of a PMB ether with DDQ.

Provide conditions for effecting each of the following transformations (more than one step may be necessary). In this and related problems in 5.511, you will be expected to indicate reagents, an appropriate solvent, and in cases where it is critical to the success of the reaction, the number of equivalents of reagents and the reaction temperature.



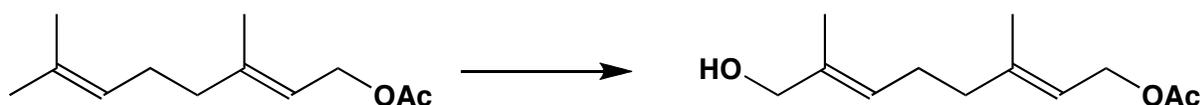


Provide conditions for the formation of each of the following protected functional groups and for their deprotection.

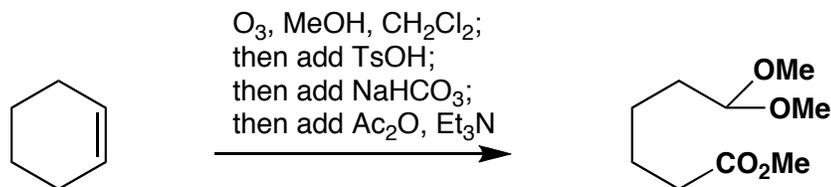
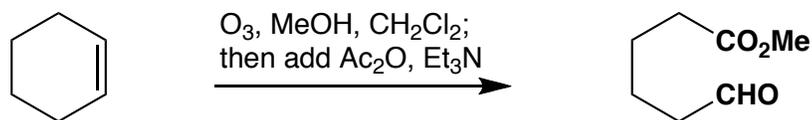
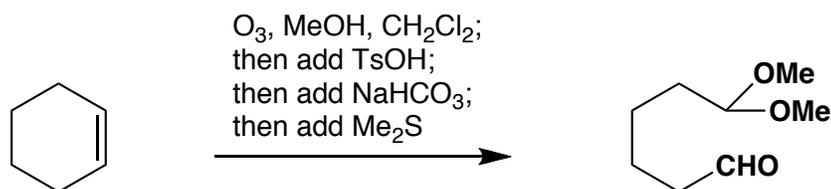


## Part II - Oxidation Methods

- (1) Provide a detailed stepwise mechanism for the Swern oxidation of a secondary alcohol.
- (2) Draw the transition state for the epoxidation of an alkene with a peracid.
- (3) Reaction of enol ethers with peracids such as *m*-CPBA (the "Rubottom Oxidation") produce  $\alpha$ -silyloxy ketones (usually hydrolyzed in situ or during workup to the  $\alpha$ -hydroxy derivatives). However, oxidation with DMDO often allows isolation of the epoxides. Provide a mechanism for each transformation and explain the different outcome of the reactions.
- (4) What is the composition of oxone?
- (5) Draw Lewis structures for the ground state of oxygen and the excited state "singlet oxygen."
- (6) What is a photosensitizer and what role does it play in the generation of singlet oxygen?
- (7) Provide a mechanism for the selenium dioxide oxidation of alkenes to allylic alcohols.

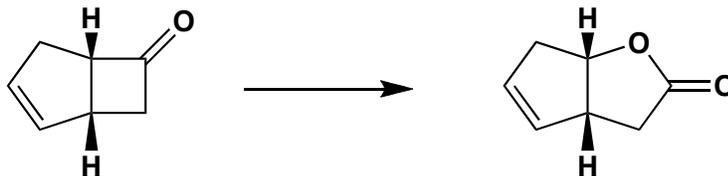


- (8) Provide a mechanism for the ozonolysis of a simple alkene in dichloromethane.
- (9) Provide a mechanism for each of the following ozonolyses (from *Org. Syn.* **1986**, 64, 150).

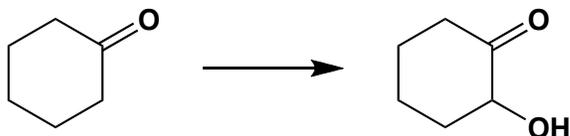
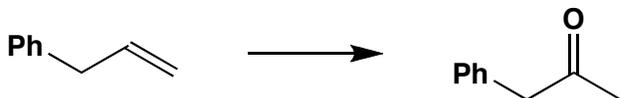
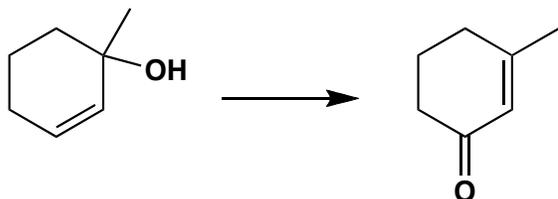
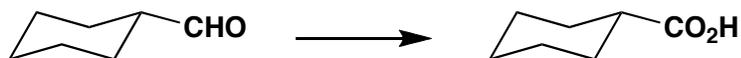


- (10) What is the migratory aptitude of typical groups in the Baeyer-Villiger oxidation? Explain
- (11) What is the structure of the Dess Martin reagent? IBX?

(12) Attempted Baeyer Villiger oxidation of the following compound with *m*-CPBA results in competing epoxidation at the alkene double bond. However, reaction with hydrogen peroxide provides the desired lactone. Explain why Baeyer Villiger oxidation of this ketone is possible under these conditions although most ketones such as cyclohexanone do not react with hydrogen peroxide.



Provide detailed conditions for effecting each of the following transformations (more than one step may be necessary).



### Part III. Reduction Methods

(1) What is the structure of “Crabtree's catalyst” and why is it especially useful for hydroxyl-directed hydrogenations?

(2) Provide a mechanism for the reduction of tertiary amides to amines with  $\text{LiAlH}_4$  and explain why amines and not alcohols are the products of the reaction.

(3) Explain why in reduction of ketones and aldehydes the reactivity order is  $\text{Zn}(\text{BH}_4)_2 > \text{NaBH}_4 > \text{NaBH}_3\text{CN}$ .

(4) Diborane reduces carboxylic acids to alcohols but reacts very slowly with carboxylic esters. Explain.

(5) Provide a mechanism to explain why DIBAL allows reduction of esters to aldehydes without over-reduction to alcohols.

(6) Esters react slowly with borane and alane ( $\text{AlH}_3$ ) but tertiary amides and lactams are reduced smoothly to amines. Explain.

(7) Suggest several reagents that effect selective 1,2-reduction of conjugated enones to produce allylic alcohols and explain why these reagents favor 1,2-reduction while the use of  $\text{NaBH}_4$  and  $\text{LiAlH}_4$  often leads to mixtures of 1,2 and 1,4-addition products.

(8) Provide a mechanism for the reduction of propargylic alcohols with Red-Al to (*E*)-allylic alcohols

(9) Indicate conditions that would be used for the conversion of cyclohexanol to cyclohexane via the Barton deoxygenation and provide a mechanism for each step.

(10) Provide conditions for the Birch reduction of anisole. Suggest a stepwise mechanism and explain the regiochemical course of the reaction.

Provide conditions for effecting the following transformations (more than one step may be necessary).

