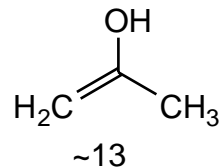
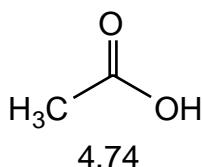
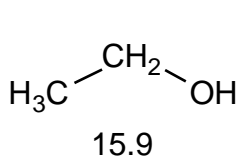


1. (3 minutes) Give approximate pK_a values for the following compounds (no explanations required):



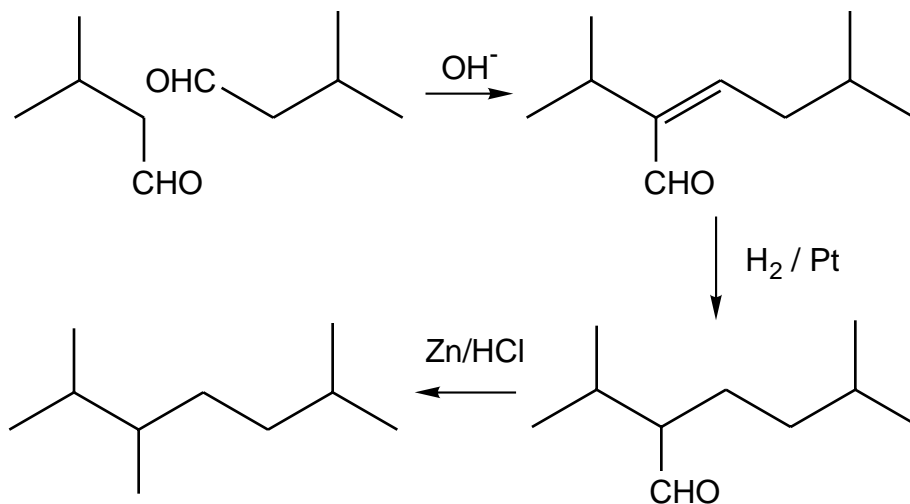
[2 points for each within ± 1 unit; 1 point for each within ± 2 units. Note that 19 is the pK_a of acetone. The enol here is less stable than acetone, thus more acidic in giving the same anion. Clearly the acidity of an enol should fall between those of an alcohol and a carboxylic acid.]

2. (3 minutes) What lesson about the design of a synthesis is taught by the practical preparation of $(\text{CH}_3)_3\text{C}-\text{NH}-\text{NH}_2$?

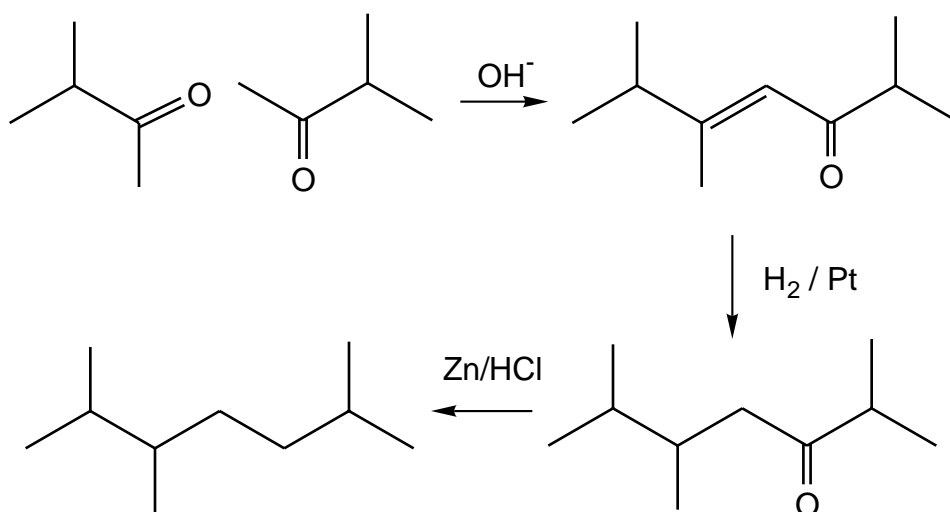
The main lesson is that even a reaction that gives very low yield ($t\text{-BuCl} + \text{H}_2\text{NNH}_2$ gives only 5% S_N2) can still be quite practical, if the starting materials are cheap and the desired product is easily purified (the predominant product is a gas, and the desired hydrochloride salt is easily to purify by crystallization). *The method recommended in the chemical literature was expensive and cumbersome with many steps, several of them low-yield, just to avoid the admittedly low-yield S_N2 reaction.*

3. (6 minutes) Show a sequence of reagents and intermediate products that would allow preparation of the following 10-carbon alkane in good yield. You may use any reagents you wish, but **all carbons must come from a single 5-carbon compound**. No mechanisms or curved arrows are necessary, just reagents and intermediates.

[This is problem 6:2f, from the assigned set. It also appeared on a previous exam. Note the bold-face restriction that both 5-carbon units come from the same molecule, suggesting aldol.]



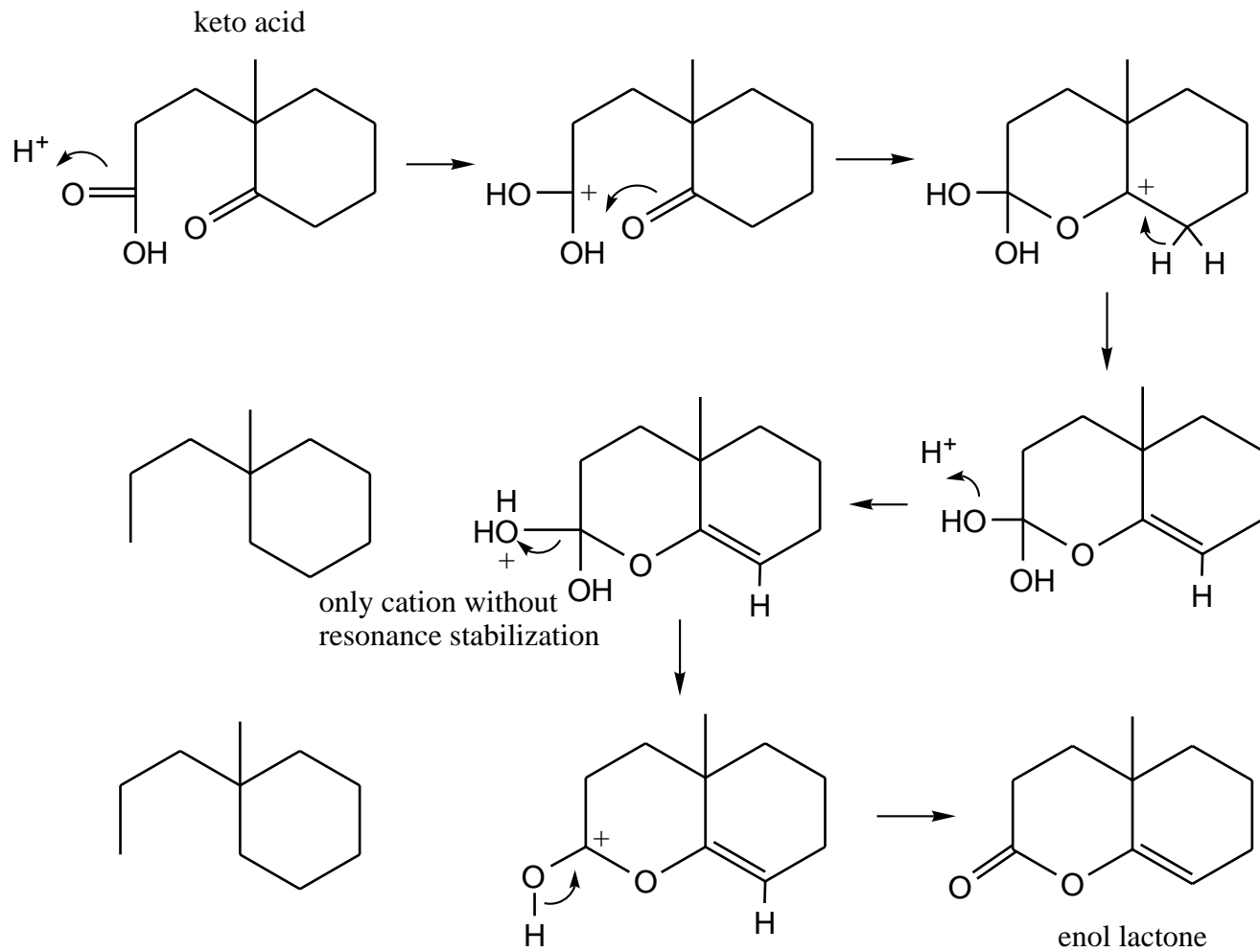
There are many other schemes for reducing the two double bonds. One could also begin the aldol-dehydration sequence with methyl isopropyl ketone:



4. (8 minutes) One reaction in Woodward's synthesis of cortisone involved acid-catalyzed conversion of a keto acid to an enol lactone. Add necessary atoms, bonds, and arrows to the following structures to show every step involved in this conversion. **Draw only one curved arrow in each structure.** You will probably not need all of the structures.

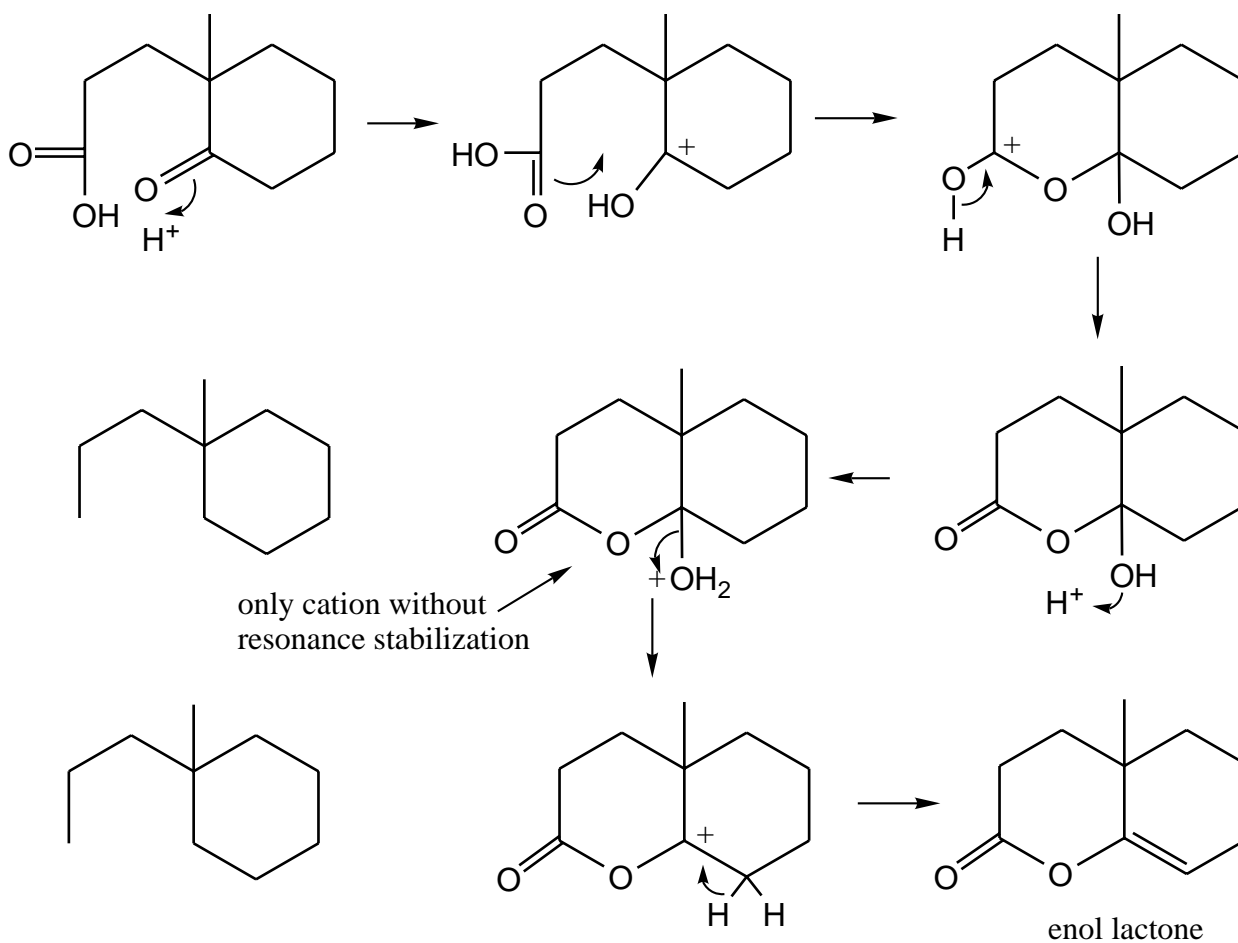
Three possibilities are shown below. As we'll see in Ch. 19, it is slightly easier to protonate the carbonyl of an acid than of a ketone, but it is not obvious which mechanism is best, and probably all contribute to some extent. Isotopic labeling with ^{18}O might allow some distinctions, if independent loss of ^{18}O is not too rapid. At any rate, a correct answer should show a reasonable sequence involving low-energy cationic intermediates. Direct protonation of the OH group of COOH and loss of water to generate the cation R-C=O^+ can occur, but only when the normal Fischer protonation of the C=O group cannot lead to product (as we'll see shortly). Many papers ignored the instruction to draw one curved arrow in each structure.

I. Initial protonation and ultimate loss of acid oxygen:

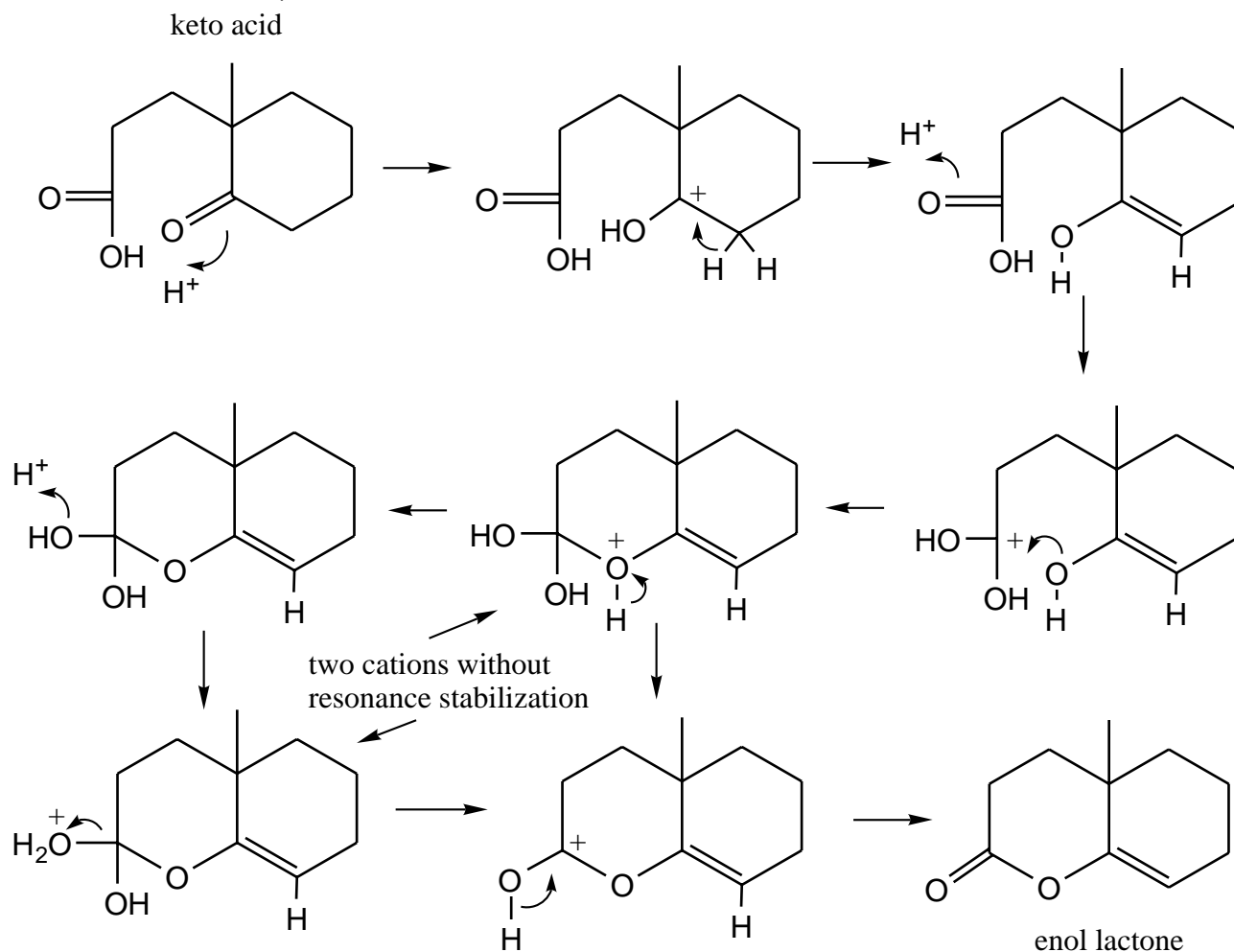


II. Initial protonation and ultimate loss of ketone oxygen.

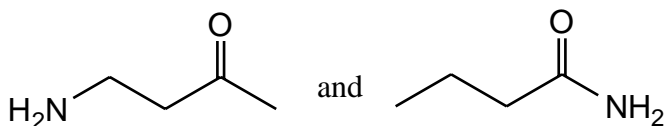
keto acid



III. Initial protonation of ketone, subsequent protonation and loss of acid oxygen (Fischer esterification of enol):



5. (6 minutes) Explain where you would look in the IR spectra to distinguish between the two compounds in each of the following pairs. Be as specific as you can. [Continued on following page]



Both compounds will show a strong C=O stretching absorption in the 1700/cm region. Because of resonance stabilization involving C-O single bond character (mixing N lone pair with σ^* of C=O), the amide absorption will come at lower frequency (~1685 vs. ~1715/cm).

[RCOOR and RCOCl have higher frequencies because of triple bond resonance structures, but for the amide the $H_2N^+=C-O^-$ contribution is more important.]

heptane and octane

Since these compounds have identical groups, the only reliable way to distinguish their IR spectra would be by comparison of the fingerprint region (800-1400/cm) with spectra of authentic samples.

[It is true that there are more CH bonds (per molecule) in octane, but there are not more CH bonds per unit weight, so unless you knew the molecular weight the CH intensity would be useless. and if you knew the molecular weight, you'd already know which is which. At any

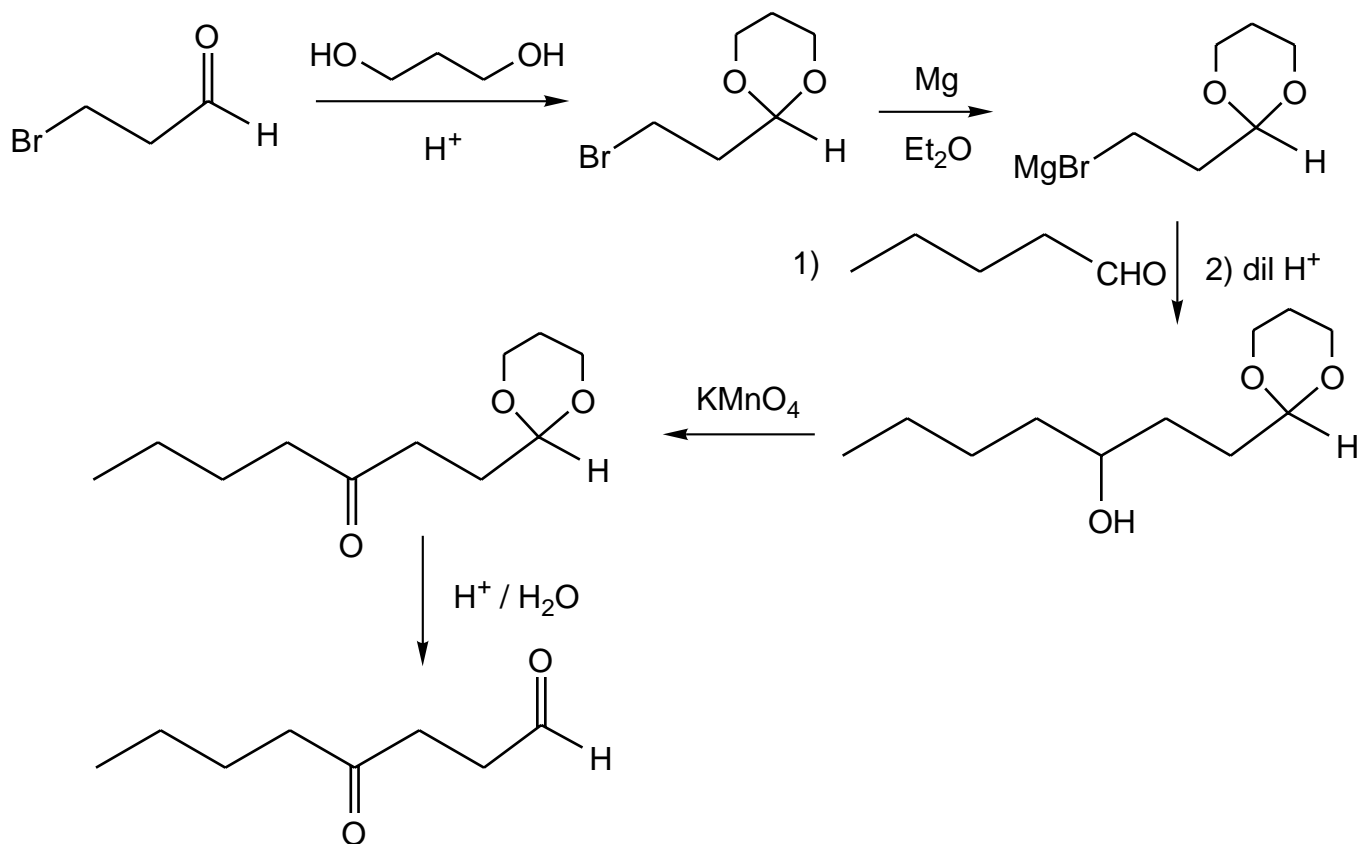
rate, peak intensities are very hard to interpret in the IR, so forget the idea of measuring C-H intensities. The idea that centrosymmetry of the even-numbered chain would make some of its peaks disappear is a very clever one, but the reduction due to symmetry would be balanced by an increase due to number of atoms, and anyway the bands would be hard to count, because they overlap.]

EtOH and EtSH

The OH bond is stronger than the SH bond (111 vs. 83 kcal/mole), and therefore the characteristic O-H stretch comes at higher frequency (3600 vs /cm) than that of the S-H stretch (2600/cm). [Note that the mass difference between S and O has very little influence - the frequency is proportional to the square root of $(m_1+m_2)/m_1m_2$, which is about equal to 1 for an X-H bond whatever the mass of X. The mass factors differ by only 1.5% between OH and SH.]

6. (6 minutes) Describe a high-yield preparation of the following compound from starting materials containing **five or fewer carbons**. No mechanisms are required, just show reagents and intermediate products.

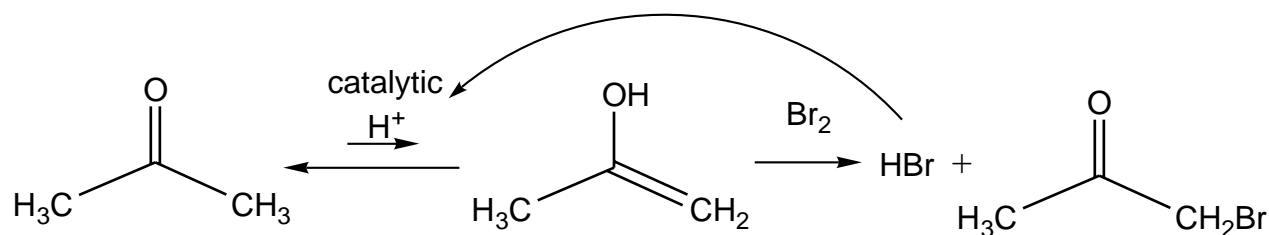
[This is problem 6:6b from a problem set. Of course there are a large number of possible syntheses, but most must address the problem of using a protecting group during the C-C bond-forming reaction, since neither hydroxyl nor carbonyl can be tolerated within a Grignard (or other carbanionic) reagent.]



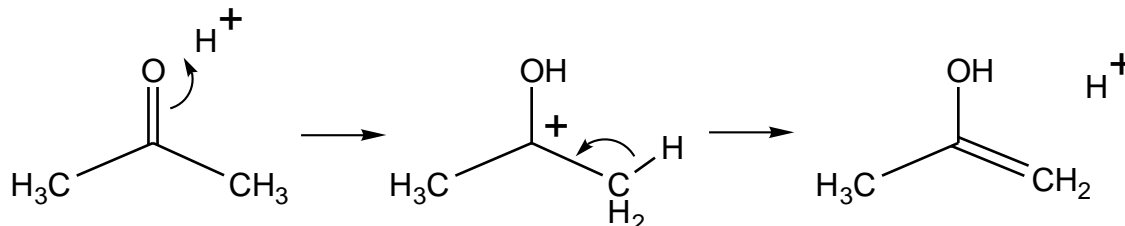
7. (8 minutes) Explain why reaction in the dark between Br₂ and acetone (2-propanone) starts slowly and then accelerates.

In the dark there is no important free-radical bromination (even in the light it is minor, because the ionic reaction is easy and gets faster as HBr is formed by either mechanism). Ionic bromination can be either base-catalyzed (via enolate) or acid-catalyzed (via enol). The inorganic product of the reaction is HBr, which would destroy base catalyst, so the reaction

via enolate would slow down. The system in this question must start neutral, so that creation of HBr, an acid catalyst, explains the acceleration.



Note that in acid the enol is formed by initial protonation, not via the enolate:



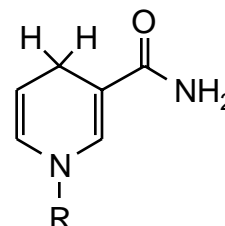
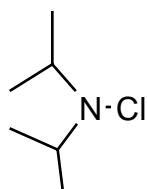
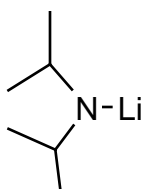
8. (10 minutes) Show practical reactions to illustrate the use of five of the following seven reagents. Be as specific as you can. **Choose only 5 of the 7.**

$\text{Br}_2 / \text{PBr}_3$

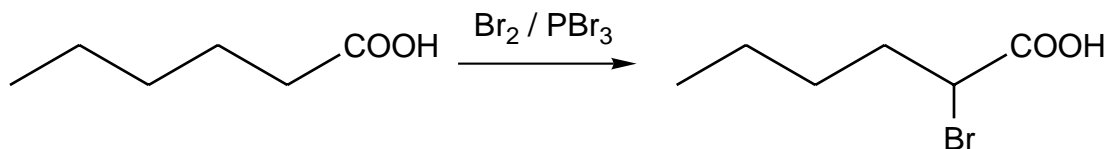
CH_2N_2

$\text{H}_2\text{NNH}_2 / \text{strong base}$

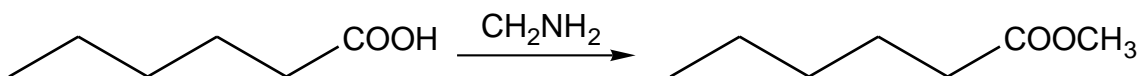
a peroxy acid



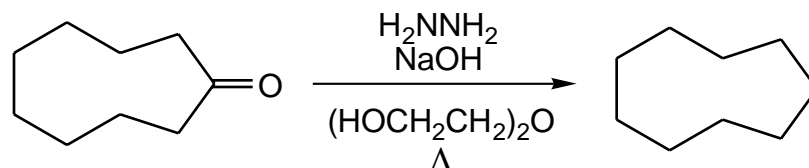
$\text{Br}_2 / \text{PBr}_3$ [Hell-Volhard-Zelinsky α -bromination of carboxylic acid]



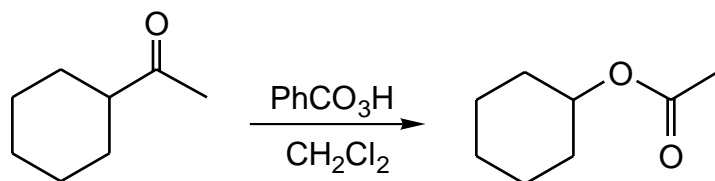
CH_2N_2 [Diazomethane, clean formation of methyl ester from carboxylic acid]



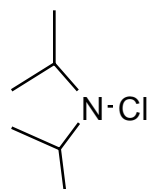
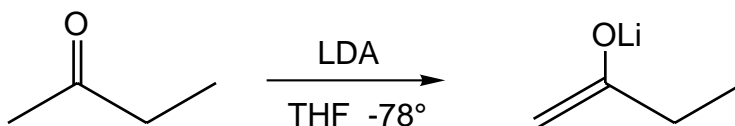
$\text{H}_2\text{NNH}_2 / \text{Strong Base}$ [Wolf-Kishner reduction of ketone or aldehyde]



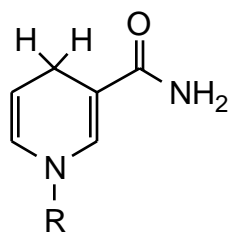
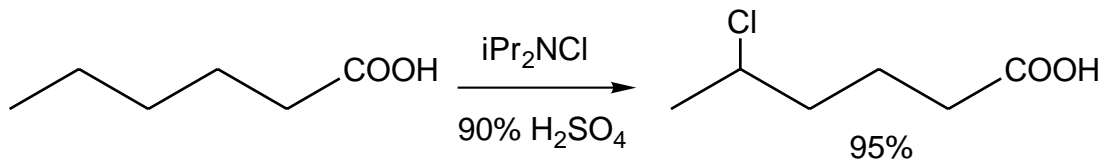
Peroxy Acid [Baeyer-Villiger oxidation of ketone to ester, or aldehyde to acid]



[lithium diisopropyl amide - LDA - quantitative enolate formation for mixed aldol]



[chlorodiisopropylamine - gives cationic radical for selective chain chlorination]



[NADH, or NADPH, hydride source for enzymic reduction of carbonyl]

