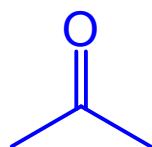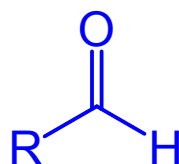# 12. Aldehydes & Ketones (text 13.1 – 13.11)

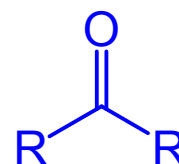## A. Structure and Nomenclature

- The carbonyl group is present in aldehydes and ketones and is the most important group in bio-organic chemistry.
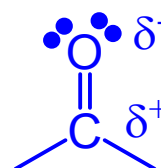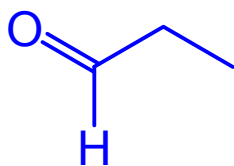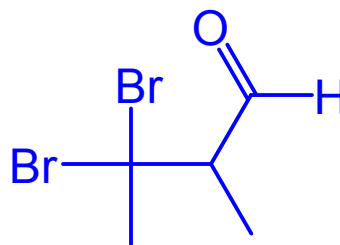
carbonyl group   aldehyde   ketone

- Both the C and O are sp^2, and their *p* orbitals overlap to form a π bond. Angles are 120°. Most importantly, the C=O is a polar double bond. It can react with both electrophiles and nucleophiles.

- In IUPAC nomenclature, for a compound named as an aldehyde, the C=O is always position #1 (takes precedence over other groups) and the suffix al is used.
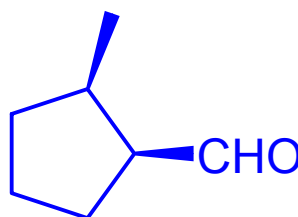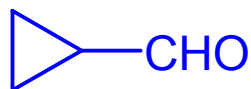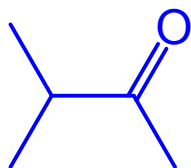
propanal   3,3-dibromo-2-methylbutanal

- When the one-carbon aldehyde group –CHO is a substituent on a ring, the suffix carbaldehyde is added to the ring name, and the point of attachment is given #1.
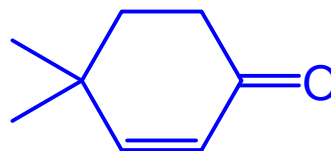
cyclopropanecarbaldehyde

cis-2-methylcyclopentanecarbaldehyde

- In ketones, the C=O is given the lowest possible number in the carbon chain and the suffix one is added.

3-methyl-2-butanone   4,4-dimethyl-2-cyclohexenone
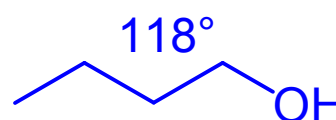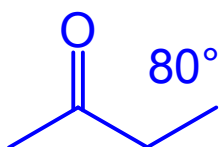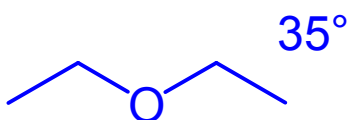
- In compounds with two or more functional groups, it may be necessary to name the carbonyl group as an ordinary substituent using oxo.
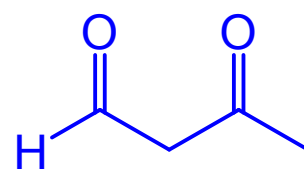
3-oxobutanal

- Carbonyl compounds don't have a δ^+ hydrogen, so intermolecular hydrogen bonding is not possible. However, the polar carbonyl group results in higher BP than ethers, but lower than that of alcohols.

35°   80°   118°

B. Preparation

- Aldehydes and ketones are prepared from the oxidation of primary and secondary alcohols (Chapter 8).

$$R-\underset{\underset{H}{|}}{\overset{\overset{OH}{|}}{C}}-R' \xrightarrow{[O]} \underset{R}{\overset{O}{\diagup}}\overset{\parallel}{\diagdown}{R'}$$
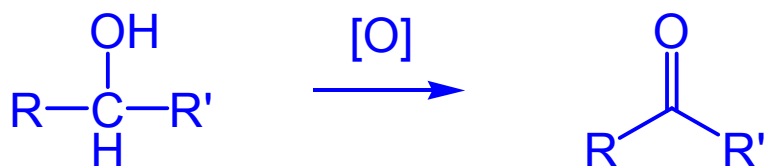
C. Spectroscopy

- In IR spectroscopy, the carbonyl group has a strong, distinctive absorption between $1705 – 1780$ cm^{-1}. (As we'll see later, the C=O stretch appears in all functional groups containing the C=O bond, including acids and derivatives).
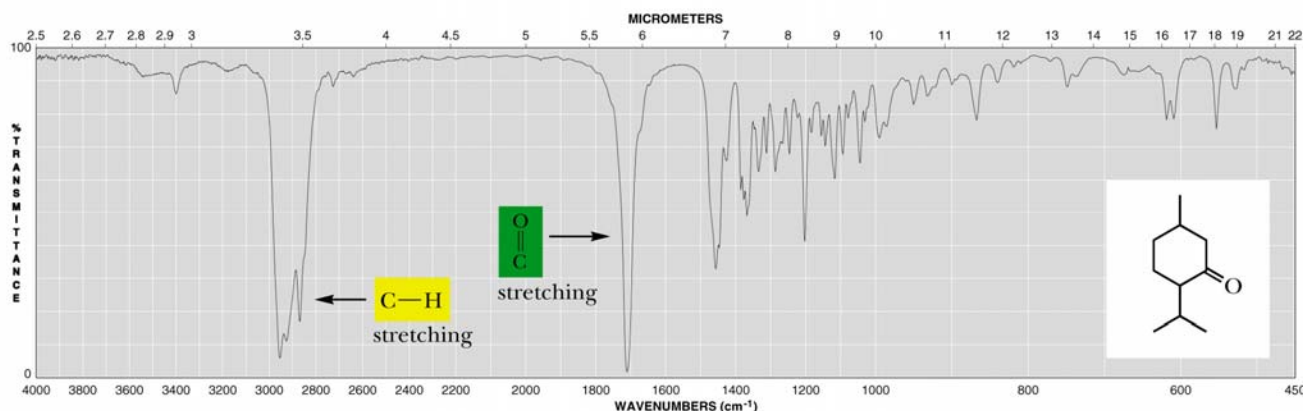
- In proton NMR, the H atom of aldehydes is shifted far downfield to about 9.5 – 10 ppm.

(300 MHz, CDCl₃)

Butanal

closely-spaced triplet

Chemical Shift (δ)

- Although the carbonyl H (**d**) splits (and is also split by) the two H atoms **c**, the splitting is very small. Thus, **d** looks like a singlet. Similarly, the signal for **c** looks like it is split only by the H atoms **b**.
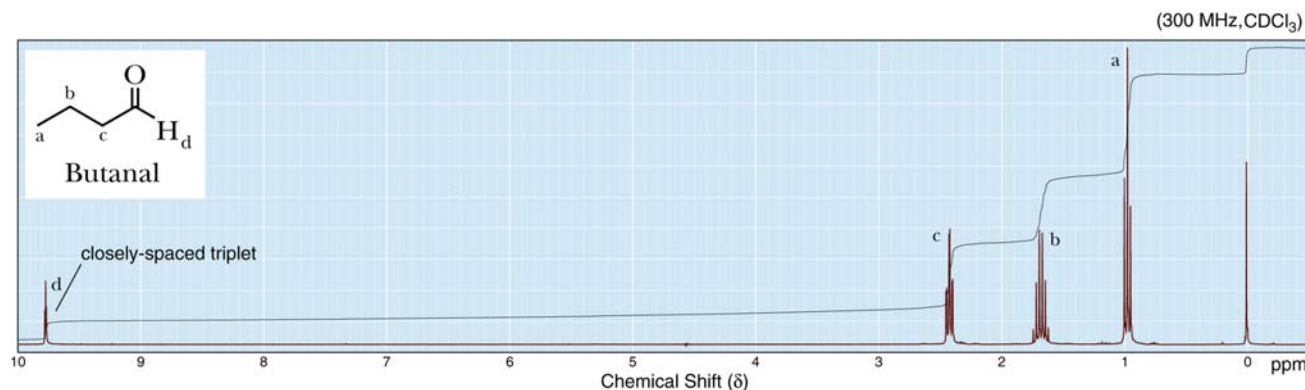
- Note that ketones do not have an H on the C=O, so the peak near 9.5 – 10 ppm does not appear.

D. Reactions

- Nucleophilic addition reactions are the defining reactions of carbonyl compounds.
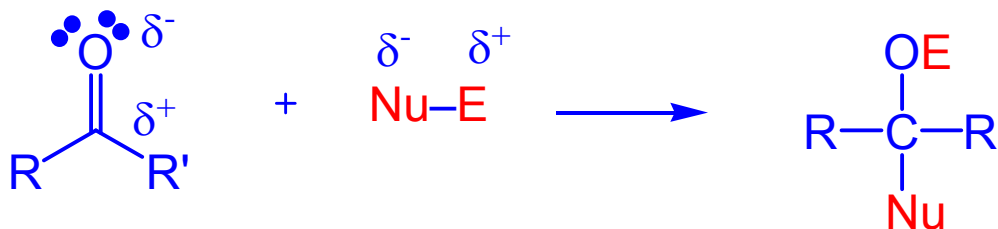
- The reaction is somewhat similar to alkene addition, but it is simpler because only one regioisomer is formed. The Nu always adds to the C, and the electrophile to the O.

- In basic solution, where anions exist, the mechanism is:
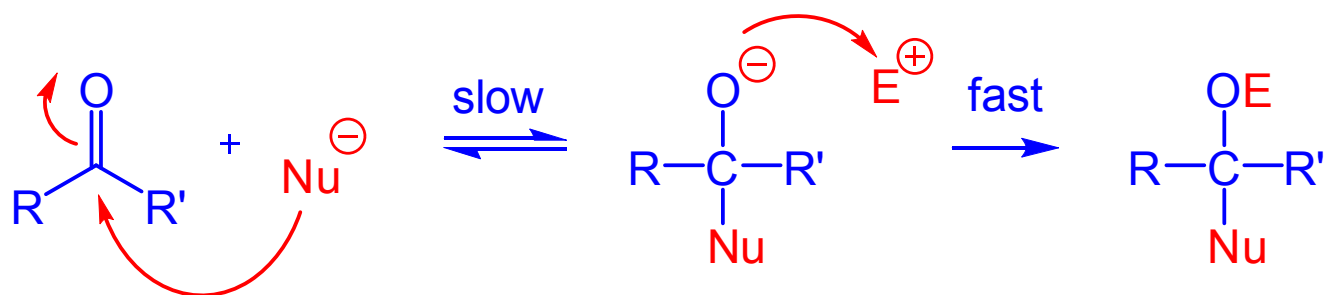
- Whereas, in acidic solutions, where cations exist, protonation occurs prior to the addition of the Nu:

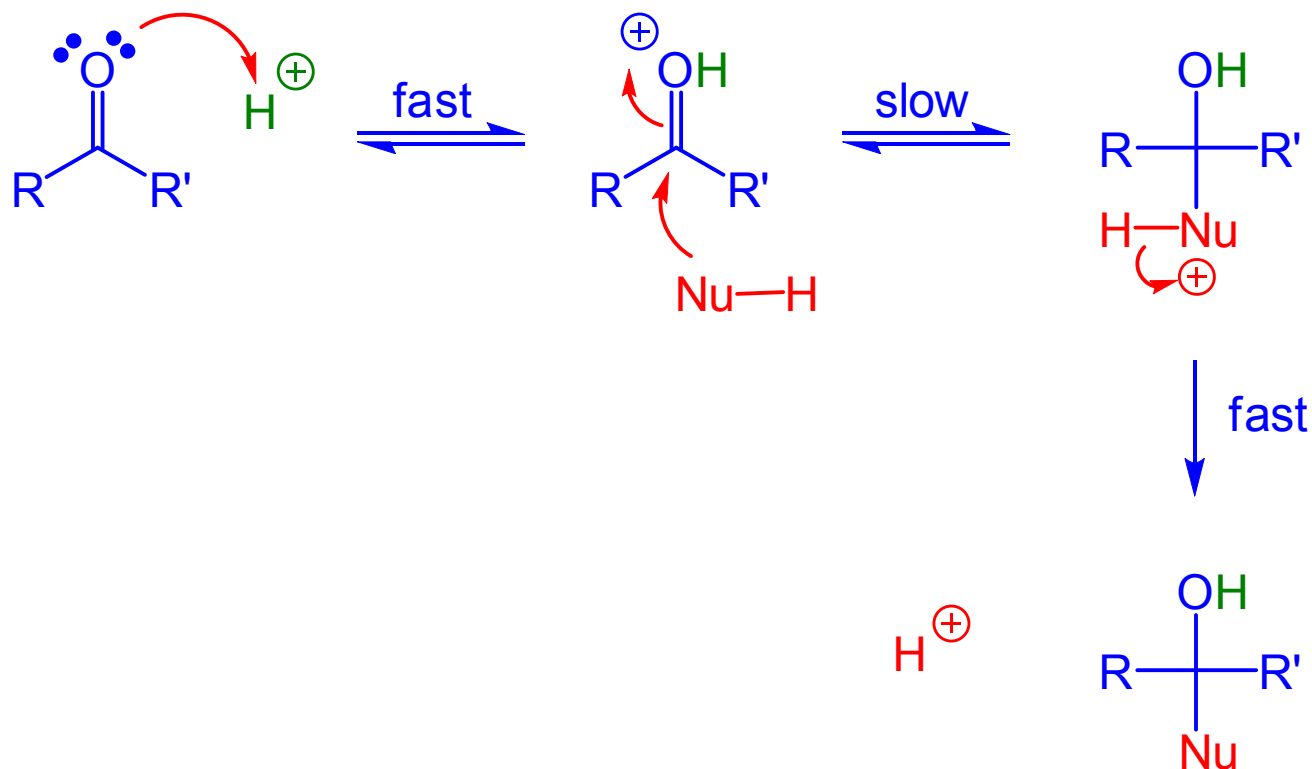- These are termed nucleophilic addition reactions because the RDS is the breaking of the π bond by Nu.

- As in alkene reactions, an sp^2 changes to sp^3, and a stereocentre may be formed. Both enantiomers will be formed in equal amounts (racemic mixture).

- Carbonyl reactions are not as exothermic as alkene reactions, so the reaction is easily reversed (this is a very useful biochemical property).

- Aldehydes (less hindered) react faster than ketones.

1. Addition of primary amines

- Results in imines, as the addition product is not stable.


an imine
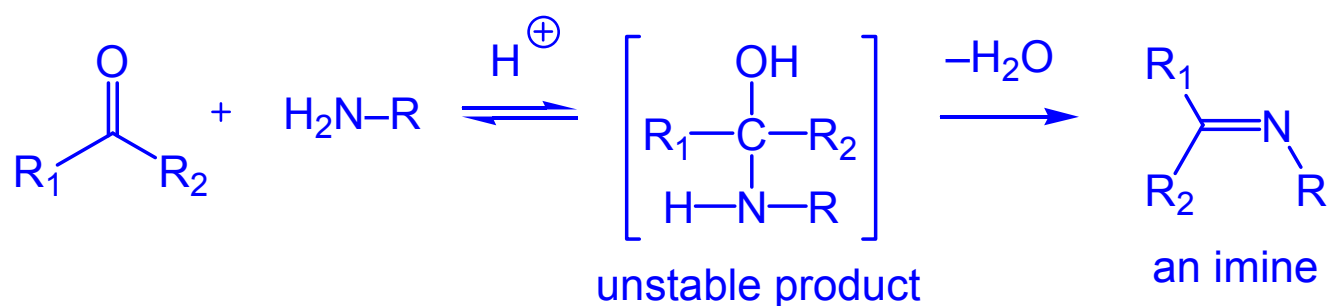
- The amine is a source of both Nu and E. Both the positive and negative portions add to C=O.

$$\overset{\delta^+}{H} \!-\! \overset{\delta^-}{NHR}$$

- Note that the O on the C=O is replaced by the N and everything attached to it.

- Reaction is acid-catalyzed, and the catalyst also promotes the elimination of water (like the elimination of water from alcohols to form alkenes) to form a C=N imine.

- Imines can be converted back to their parent carbonyl and amine compounds in the presence of water and acid.
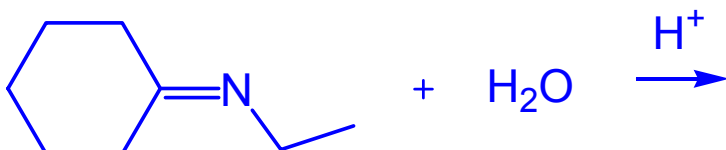

- Imines are often found in biomolecules. Retinal (the aldehyde form of retinol) is bonded to the opsin protein by an imine bond to form rhodopsin (textbook page 380).

- Like alkenes, imines can be reduced.
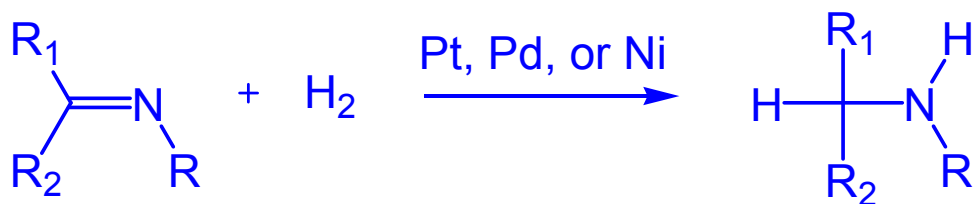
- The reaction of a carbonyl compound with an amine, followed by reduction of the imine, converts a carbonyl to a saturated amine. This is called reductive amination.

2. Addition of alcohols to form hemiacetals and acetals

- An alcohol has a polar OH bond, provides both Nu and E for the addition.

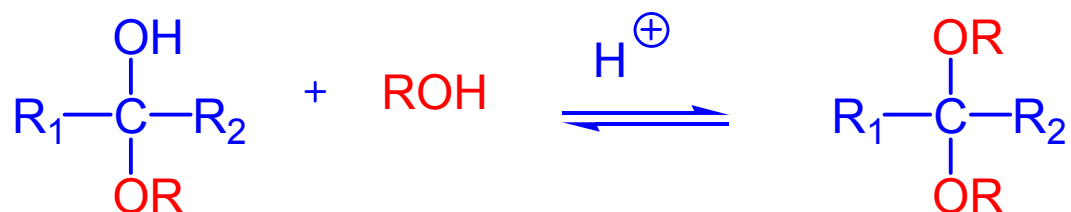- Addition occurs to both aldehydes and ketones:
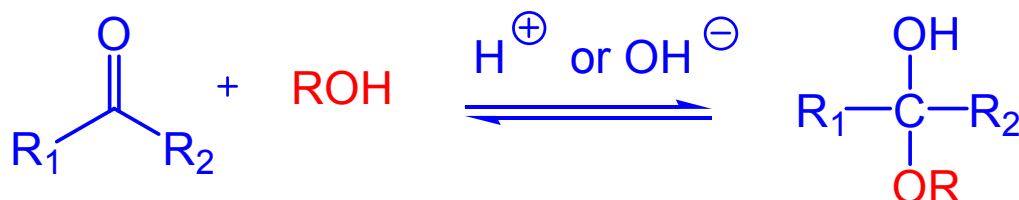
- The product of the reaction contains both OR and OH bonded to the same C, and is called a hemiacetal.

- Hemiacetal formation is either acid- or base-catalyzed and is reversible, so the hemiacetal is only stable in neutral solution. Exposure to acid or base reforms the carbonyl compound and alcohol.

- Note that the presence of *either* acid *or* base is necessary:

  - The C=O is a relatively weak electrophile. Protonating it gives it a positive charge, making it a better electrophile that can attract even weak nucleophiles (ROH)

  - Alcohols are poor nucleophiles. Deprotonating it makes it a good nucleophile that can attack electrophiles that are relatively weak (unprotonated C=O).

  - That is, acid makes the C=O more reactive, while base makes the ROH more reactive.

- The cyclic form of monosaccharides contains a hemiacetal.

β-D-Glucopyranose   α-D-Glucopyranose
(β-D-Glucose)   (α-D-Glucose)
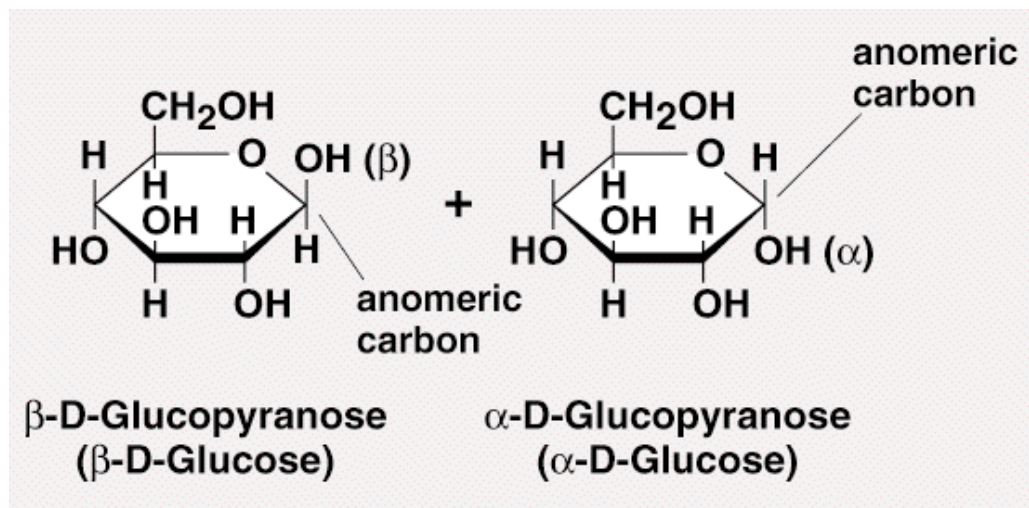
- In acid, hemiacetals react further with alcohols by an S_N1 reaction to yield a C bonded to two OR groups, an acetal.

$$R_1-\underset{\underset{OR}{|}}{\overset{\overset{OH}{|}}{C}}-R_2 \quad + \quad ROH \quad \underset{}{\overset{H^{\oplus}}{\rightleftharpoons}} \quad R_1-\underset{\underset{OR}{|}}{\overset{\overset{OR}{|}}{C}}-R_2$$

- Recognize the acetal formation is a S_N1. Acid protonates OH, making it an excellent leaving group (water). The Nu in the substitution is the alcohol.

- The acid-catalyzed formation of an acetal is reversible, but in basic solution it is stable.
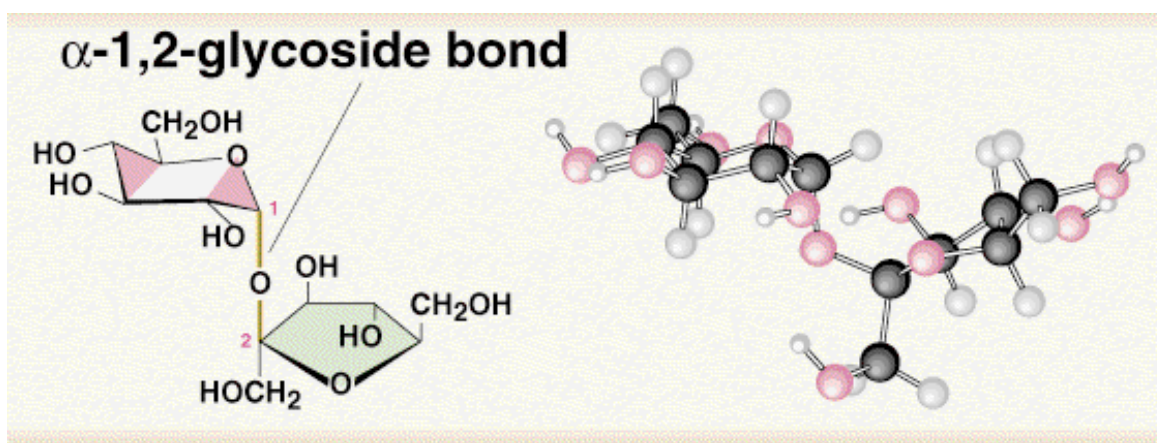
- Mechanism of acid-catalyzed hemiacetal formation:

- Acetal formation (S_N1) continues from the hemiacetal:

- Hemiacetal and acetal formation is very favourable when five- or six-membered rings are formed.
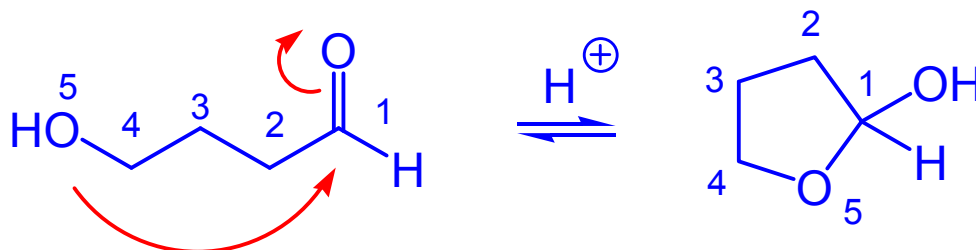
- Sucrose is a disaccharide that has acetal groups on both of its two rings, linking them together.

α-1,2-glycoside bond

- Because acetals are formed by a series of reversible steps in acidic solution, the acetal can revert back to the starting aldehyde and alcohol. Acetals are base-stable.


acetal   hemiacetal
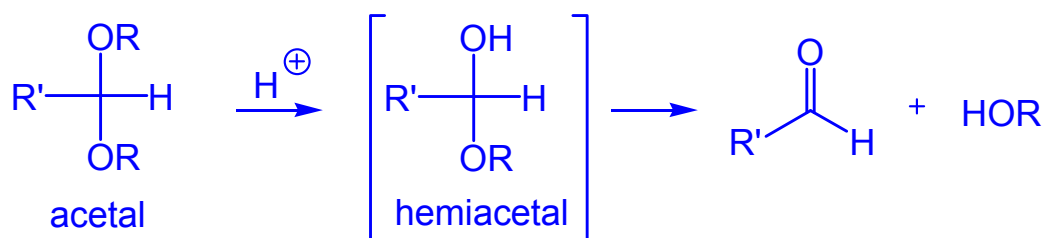
- In the reversal, note that the C bonded to the two O becomes the carbonyl, and the two O atoms become OH groups on the alcohol (text question 13.24).
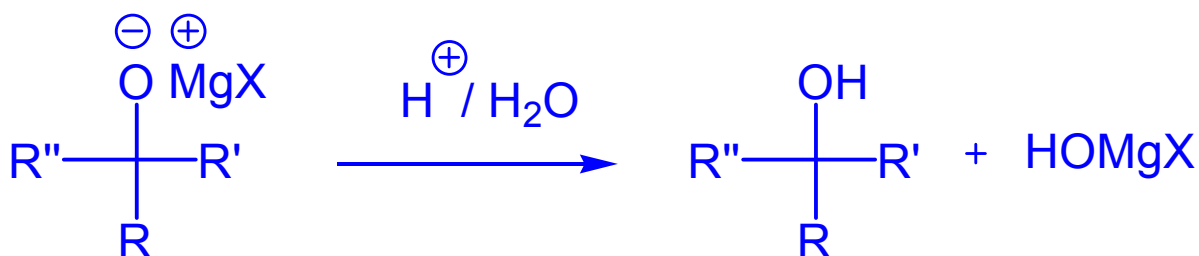
3. The Grignard reaction

- In the late 19th century, Victor Grignard discovered that alkyl halides reacted with Mg to form a very polar (almost ionic) C–Mg bond. The halide can be Cl, Br, or I.

$$\overset{\delta^+\ \ \delta^-}{R-X} \ + \ Mg \ \xrightarrow{\text{ether}} \ \overset{\delta^-\ \ \delta^+}{R-MgX}$$

- These organomagnesium compounds are known as Grignard reagents.

- It contains a C with a partial negative charge, which is only possible when C is bonded to something left of it on the periodic table. Grignard reagents are prepared in ether.

- *Grignard reagents behave like a negatively charged carbon.* They are nucleophiles, but they are also destroyed by the presence of compounds that can act as acids.
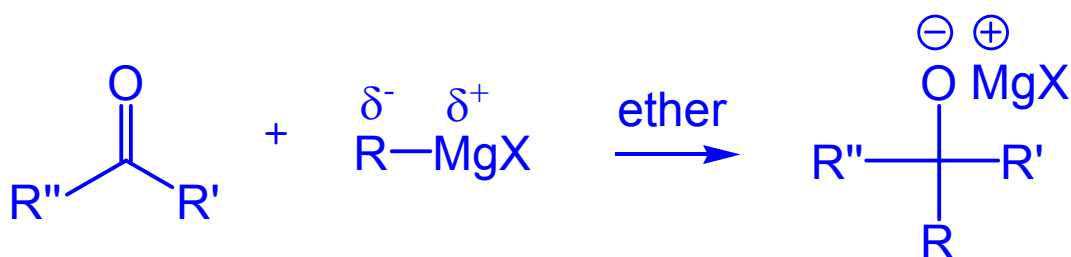

- The ionic product is easily converted to an alcohol using some sort of proton donor, such as acid in water.
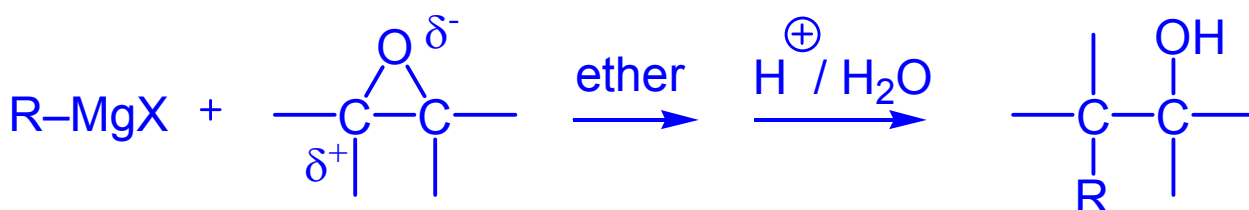
- The Grignard reaction is one of the most useful ways to create new C–C bonds. The starting materials (carbonyl compounds and alkyl halides) are readily available, and the product is formed in good yield.

- Two R groups come from the carbonyl compound, and one from the alkyl halide. It doesn't matter which R are from the carbonyl compound or from the alkyl halide.

- Sample Grignard reaction
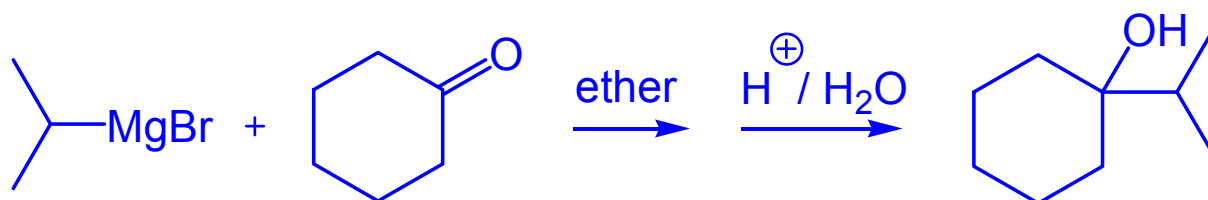
- Show two ways to make
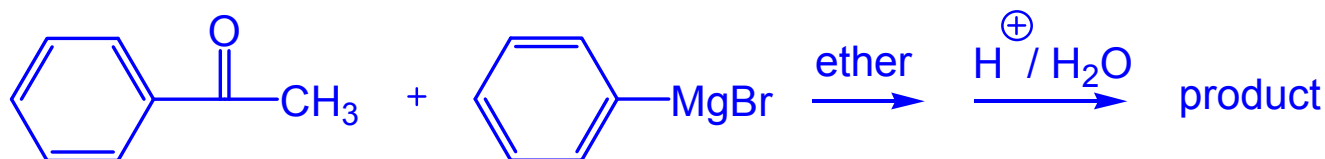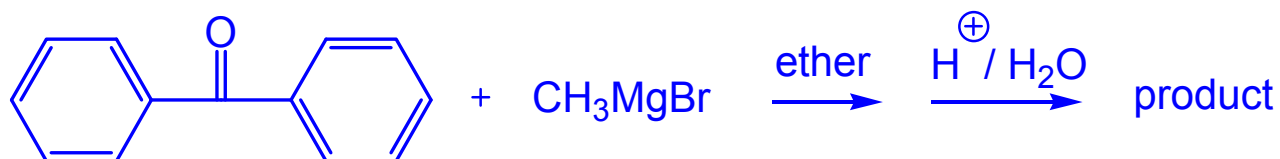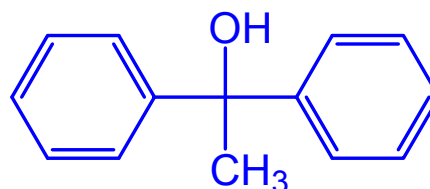
- Grignard reagents even react with carbon dioxide, to yield carboxylic acids, and with epoxides, to give alcohols.

- Reaction with epoxides occurs because of the polar C–O bond in addition to the reactivity of the strained 3-atom ring.

$$R\text{–}MgX \quad + \quad O{=}C{=}O \quad \xrightarrow{\text{ether}} \quad \xrightarrow{\overset{\oplus}{H}/H_2O} \quad \underset{RCOH}{\overset{O}{\parallel}}$$

$$R\text{–}MgX \ + \ \text{epoxide} \quad \xrightarrow{\text{ether}} \quad \xrightarrow{\overset{\oplus}{H}/H_2O} \quad \text{product}$$

4. Oxidation of aldehydes

- Aldehydes are easily oxidized to carboxylic acids using common reagents such as H_2CrO_4 or $KMnO_4$.

$$\underset{R\quad\quad H}{\overset{O}{\parallel}} \quad \xrightarrow{[O]} \quad \underset{R\quad\quad OH}{\overset{O}{\parallel}}$$
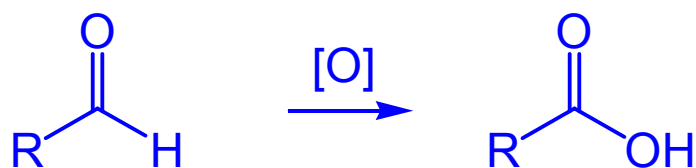
- The Tollen's Test for aldehydes relies on their easy oxidizability (Expt 5). The oxidizing agent is Ag^+ found in Tollens' reagent $Ag(NH_3)_2OH$.

- When Ag^+ oxidizes the aldehyde, it is reduced to Ag^0, which precipitates in the form of metallic silver. This is often observed in the form of a silver mirror on the glass.

- Another test for aldehydes is the Purpald® test, which forms a purple colour in the presence of aldehydes (Expt 5).

- Ketones are resistant to common oxidizing agents. This is the principal difference between aldehydes and ketones.

5. Reduction of aldehydes and ketones

- Both aldehydes and ketones can be reduced to alcohols.
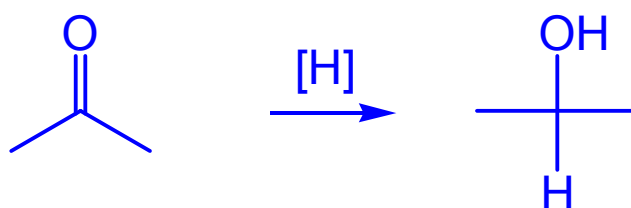
- The first method is catalytic hydrogenation, H_2 with Pt, Pd, or Ni, similar to the hydrogenation of C=C.

- The second is the use of metal hydrides, either one of:

  o Weaker: $NaBH_4$ in alcohol solvent (ROH), then by H_2O
  o Stronger: $LiAlH_4$ in ether solvent, followed by H_2O

- Metal hydrides are useful: they behave as H⁻ and they DO NOT reduce C=C. (H⁻ attacks a polar C=O bond)
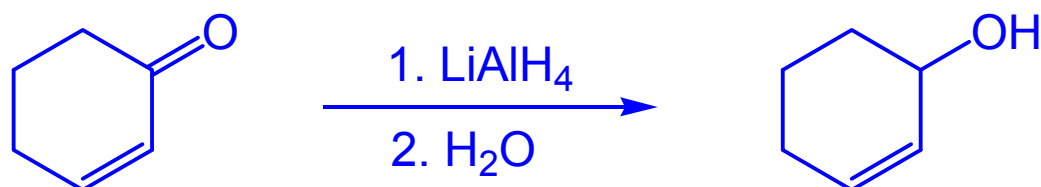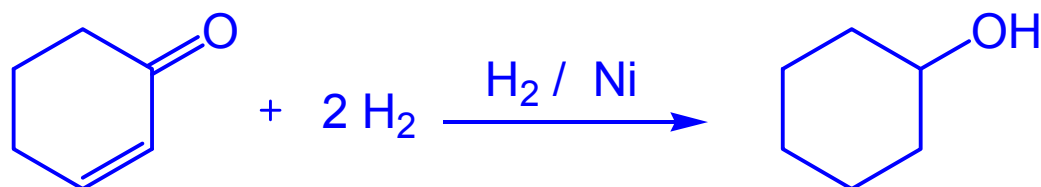
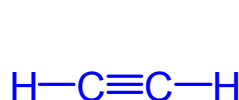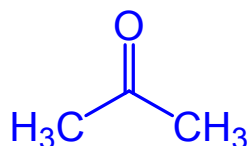# 6. Reaction at the α-carbon

- A carbon atom directly attached to a carbonyl group is termed an α-carbon. H attached to α-carbon is more acidic than normal due to resonance stabilization of the anion.
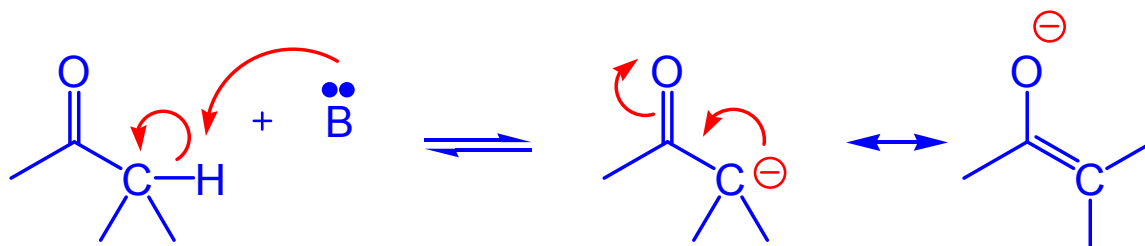
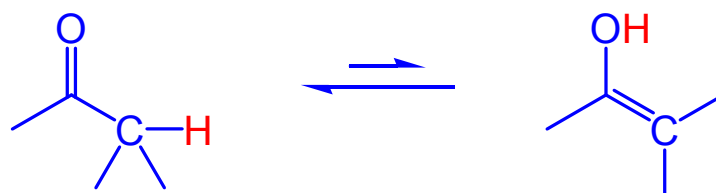- Resonance makes the α-hydrogens of carbonyl compounds more acidic than H on *sp* carbon atom.

H—C≡C—H	H_3C C CH_3	CH_3CH_2OH
pKa = 25	pKa = 19	pKa = 16

- A result of the acidity of α-hydrogens is that all aldehydes and ketones exist in solution as an equilibrium mixture of keto and enol forms.


keto form (more stable)   enol form (less stable)

- Keto-enol intercoversion involves **only** the movement of H from one atom to another. This change in molecular configuration is called tautomerism. The two forms are referred to as tautomers.

- Enol tautomers are always present, even though they may exist in very low concentrations; e.g. for acetaldehyde (ethanal), 1 molecule in 1.7×10^6.

  - Keto-enol tautomerism is important in the chemistry of nucleic acids, where the nucleobases of DNA can adopt enol forms. This is important from a biological perspective, as it allows of proper base pairing.

- If the α-carbon is a stereocentre, one enantiomer is slowly converted to a racemic mixture by enol formation. This racemization is accelerated by a little acid or base.
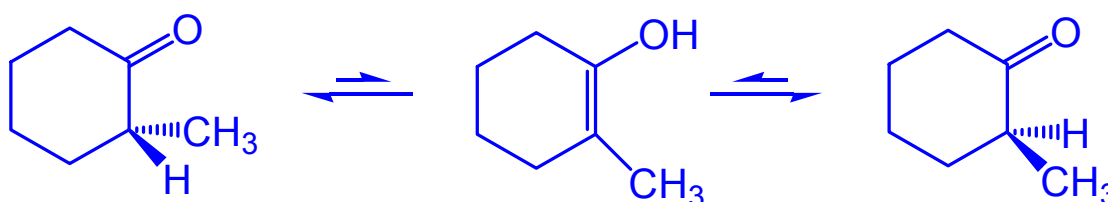

- A visual test for *methyl ketones*, called the iodoform test (Expt 5), relies on α-hydrogen acidity. These react with I_2 in base to give a carboxylic acid salt and the yellow ppt CH_3I.
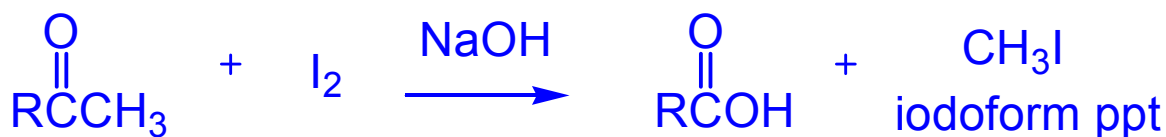

- Pages covered: Chap 13, 365-391.

- Text problems: 13, 15, 20-24, 29, 33, 35, 37, 39, 40, 44, 46.

- 2005: 38 – 40   2006: 35 – 38
 2007: 34 – 39   2008: 35 – 39

- Past test questions: Which one of the following Grignard reactions gives the product shown in good yield?
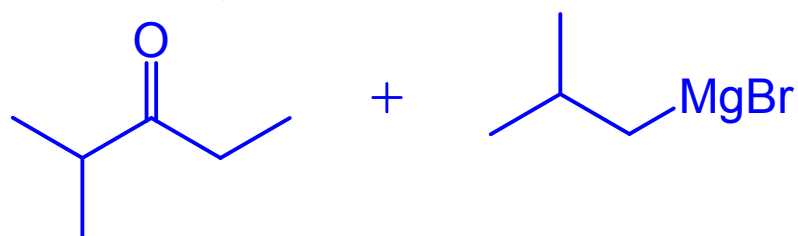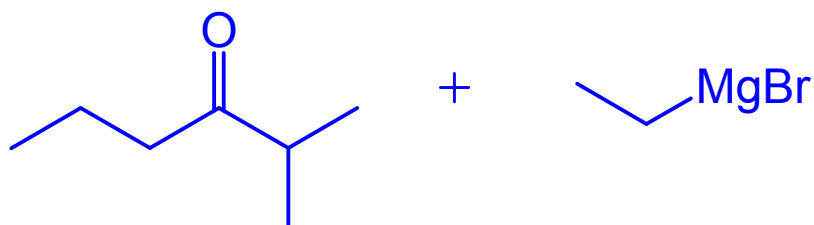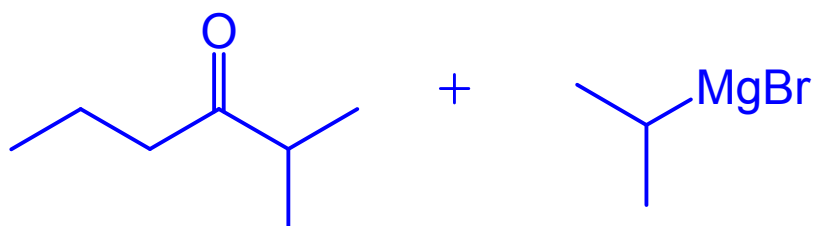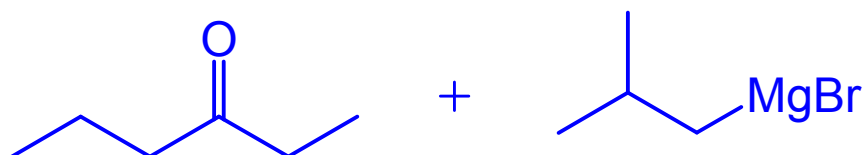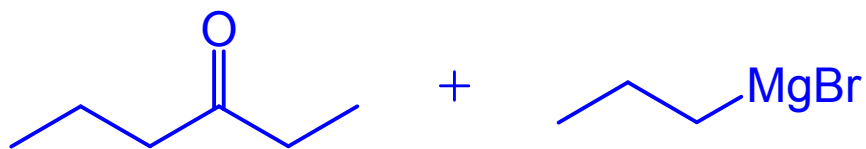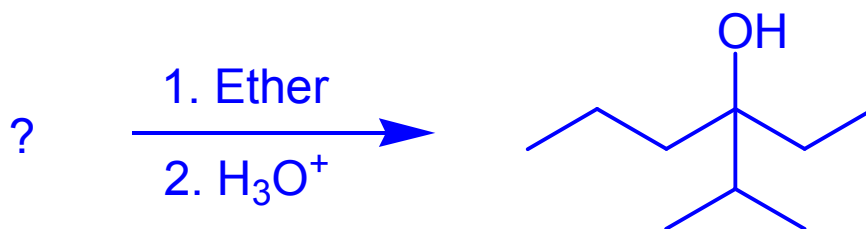
- What is a correct IUPAC name for benzyl isopropyl ketone?
  - o 3,3-dimethyl-1-phenylpropan-2-one
  - o 3-methyl-1-phenylbutan-2-one
  - o 2-methyl-1-phenylpropan-1-one
  - o 2-methyl-4-phenylpropan-3-one
  - o 1-phenylisopentanone

- Which one of the following compounds is an acetal?
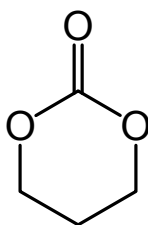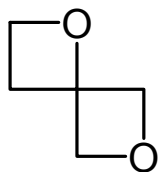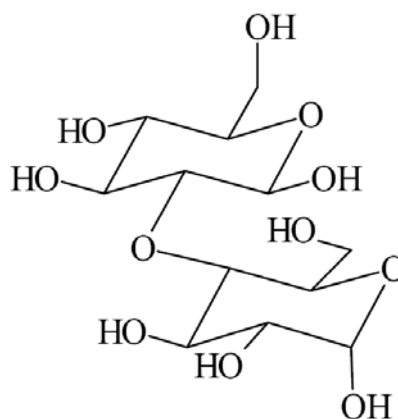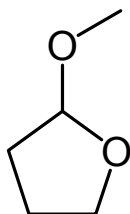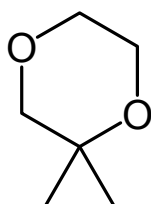
- During the course of the following multi-step process, the change in hybridization of the indicated atom is most accurately described as…
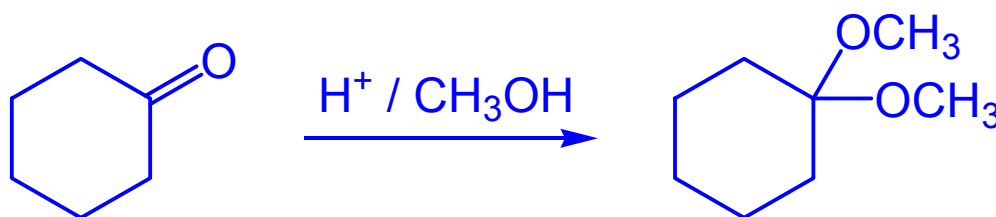
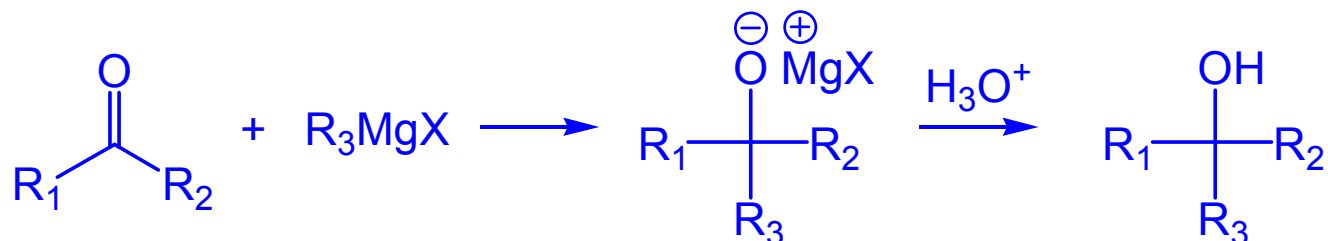

- $sp^2 \rightarrow sp \rightarrow sp^3 \rightarrow sp^2$
- $sp^2 \rightarrow sp^3 \rightarrow sp^2$
- $sp^3 \rightarrow sp \rightarrow sp^3$
- $sp^2 \rightarrow sp^3 \rightarrow sp^2 \rightarrow sp^3$
- $sp^2 \rightarrow sp \rightarrow sp^3$

- MCAT questions: What reagents could be used to synthesize this acetal?
  - 1-butanol with methanal
  - Butanal with methanol
  - 1,1-dibutanol with water
  - Propanal with methanol
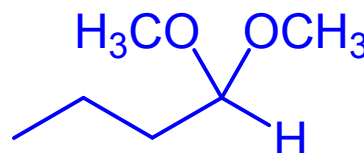
- Use this Grignard reaction to answer the following questions:

- o In the Grignard reaction, the Grignard reagent is a…
  - Strong nucleophile
  - Weak nucleophile
  - Strong electrophile
  - Weak electrophile

- o If 2-pentanone is reacted with phenyl magnesium bromide, what is true about the product?
  - The product has a chiral centre and the solution is optically active
  - The product has a chiral centre and the solution is not optically active
  - The product has no chiral centre and the solution is not optically active
  - The product is a meso compound

- o The Grignard reaction is a(n)
  - Electrophilic elimination
  - Aromatic substitution
  - Nucleophilic addition
  - Nucleophilic substitution