NUCLEOPHILIC ADDITION TO CARBONYL-CONTAINING COMPOUNDS
GRIGNARD REACTION

Carbonyl-containing compounds, such as aldehydes, ketones, carboxylic acid and acid anhydrides, possess an electophilic carbon center, which can be attacked by various nucleophiles (Figure 1). Electrophilicity of the carbon-center can be further enhanced via a coordination of the carbonyl's oxygen with an electrophilic species, such as Lewis acids, including proton, aluminum trichloride, zinc bromide, etc.

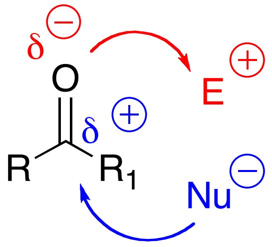
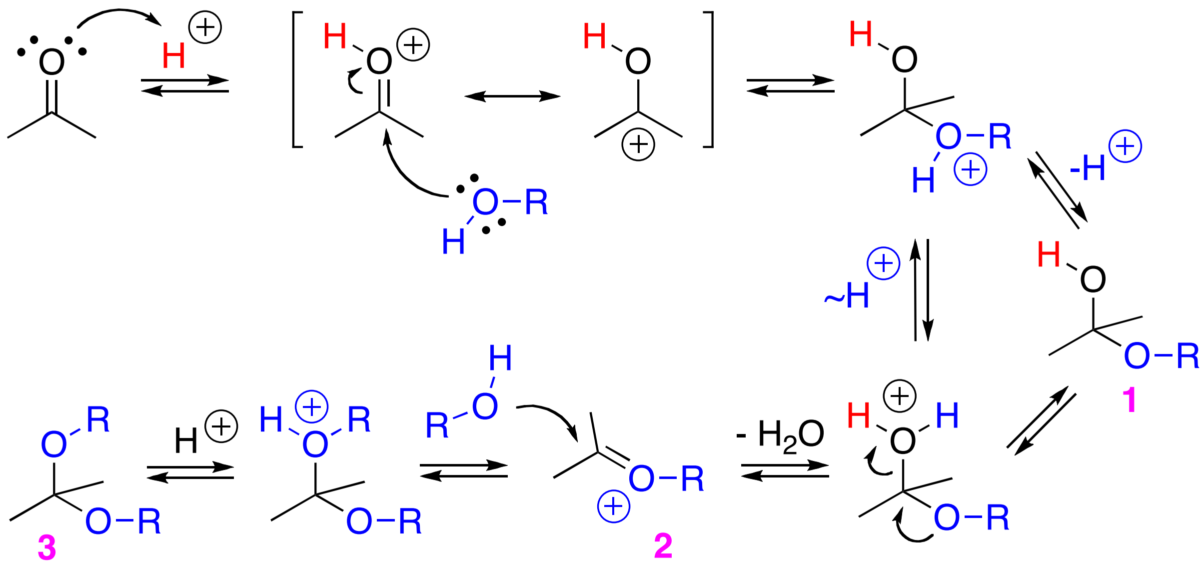


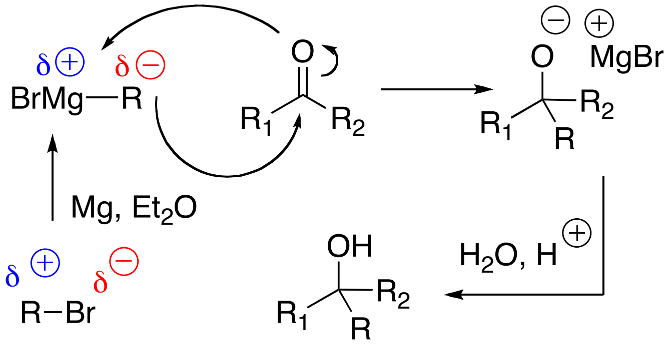
Figure 1

Under certain circumstances, in the presence of catalytic amount of acid, the oxygen atom of alcohols (ROH) can act as a nucleophile towards ketones and aldehydes (Scheme 1). Proton coordinates with the oxygen of the carbonyl moiety, which increases with electrophilicity of the carbonyl's carbon. Subsequently, nucleophilic attack by the alcohol leads to the formation of the hemiacetal **1** after the loss of a proton from the protonated hemiacetal **1**. Next, a series of proton transfer steps results in the loss of water and yields **2**, which also has an electrophilic carbon suitable for a nucleophilic attack by another molecule of the alcohol. The sequence affords the acetal **3**.



Scheme 1

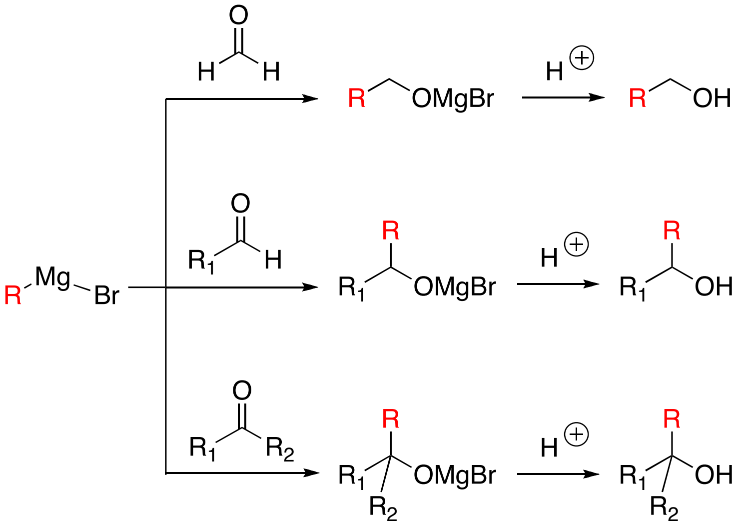
Various alkyl halides (primarily bromides and iodides) can react with magnesium (Mg) to produce an organometallic species, so-called Grignard reagents (Scheme 2). These compounds are completely soluble in ether and tetrahydrofuran (typical solvents for the Grignard reactions). Hence, the formation of a homogeneous solutions (dissolution of Mg) will be indicative of the Grignard reagents.



Scheme 2

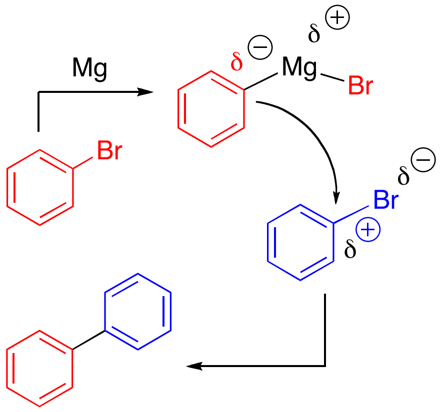
Notably, in the initial halide, the carbon center is partially positively charged, due to the presence of electronegative halide atom; the same carbon in the Grignard reagent has a full negative charge. Thus, Grignard reagents are nucleophilies; and the carbon atom is the nucleophile, which attacks the electophilic carbon of the carbonyl's compound. This produces the magnesium-containing salt, which becomes insoluble in the organic media (ether or tetrahydrofuran). Thus, the overall progress of the reaction could be monitored simply by observing the transition from heterogeneous to transparent to cloudy to heterogeneous mixture. Subsequent acidification of the reaction mixture will produce an alcohol.

This reaction is extensively used in the synthesis of various structurally and functionally diverse classes of compounds. For example, reaction of an alkyl magnesium bromide with a set of aldehydes and ketones produces various primary, secondary and tertiary alcohols (Scheme 3).



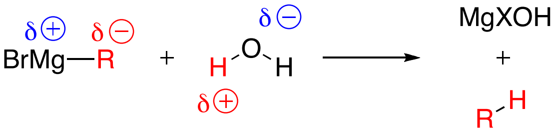
Scheme 3

It might be easy to recognize that Grignard reagent will act as a nucleophile not only towards carbonyl's carbon, but also towards any electrophilic center. For example, nitriles, CO_2, epoxides and halides are suitable electrophilic partners. Noteworthy, is the case of halides. This reaction is important for the proper preparation of the Grignard reagents from alkyl or aryl halides. It follows that excess of the halide leads to formation of side products (Scheme 4; formal arrow movement; this is not an S_N2 process; the reaction proceed via a radical mechanism). Therefore, bromide should be added slowly dropwise to the Mg. At any given time, the excess of Mg should be present in the reaction mixture.



Scheme 4

In addition to the nucleophilic nature of the Grignard reagents, they can also act as bases (Scheme 6). Therefore, the use of compounds with a reactive hydrogen, including H_2O, ROH and RNH_2, should be avoided. This reaction leads to the formation of C-H bond, and can be viewed as a dehalogenation reaction. Furthermore, if deuterated water, D_2O, is used instead of H_2O, this reaction maybe a convenient way to produce deuterated compounds (these compounds are important for various structural and mechanistic studies). Given reaction with water (Scheme) represents a side reaction, which decreases the efficiency of the formation of the Grignard reagent. Thus, water (and moisture) should be excluded the Grignard reaction.

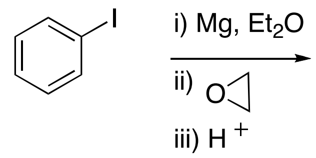


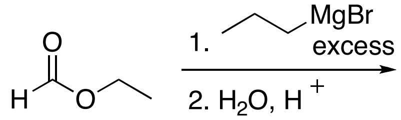
Scheme 5

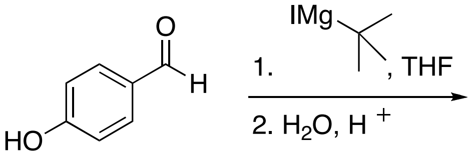
PROBLEMS

Some questions are based on the material covered in the lecture

1. Provide the products for the following reactions:







2. Is ROH a possible product (even in a small amount) in the reaction of the Grignard reagent (RMgBr) with water? Support your answer with reaction/mechanism scheme.
3. Why the glassware should be thoroughly dried for the preparation of a Grignard reagent?
4. The Grignard reagent is air-sensitive; thus a drying tube or inert atmosphere, such as N_2 gas, has to be applied. Yet, in some cases, mostly when Et_2O is used as a solvent, no inert atmosphere or a drying tube is required for the reaction to take place. Speculate on why does the reaction still work?
5. Using a Grignard reagent as one of the reagents, suggest as many synthetic routes to triphenylmethanol from common starting materials as you can.
6. Sometimes when the formation of a Grignard reagent is slow, a crystal of iodine is added to jump start the reaction. Propose the reaction mechanism for this reaction, and suggest a few reasons why I_2 is used for this purpose, and not any other halides.
7. Suggest a product for the reaction of methylmagnesium iodide and propyne. If there is no reaction, suggest a reason.