

Grignard Reagents

(For Semester-III)

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1.0 Organometallic Reagents

Organometallic compounds are those compounds which have metal-carbon bond. Due to the significant difference in electronegativity between metals and carbon, they are highly polar in nature. However, this definition is not quite explicit as many reagents deemed to be organometallic in nature do not possess a metal carbon bond. Wilkinson catalyst, $(\text{RhCl}_2(\text{PPh}_3)_2)$, a popular organometallic catalyst for hydrogenation reaction does not possess a metal-carbon bond. Thus, the above definition may be modified to include compounds containing metal- electronegative atom bonds in the gambit of organometallic compounds.

Li											C	N	O		
0.98											2.55	3.04	3.44		
Na	Mg										Al	Si	P		
0.93	1.31										1.61	1.9	2.19		
K					Fe	Co	Ni	Cu	Zn						
0.82					1.83	1.88	1.91	1.9	1.65						
					Ru	Rh	Pd		Cd						
					2.2	2.28	2.2		1.69						
					Os	Ir	Pt		Hg						
					2.2	2.2	2.28		2.0						

Fig 1: Elements commonly involved in formation of organometallic compounds. (Elements highlighted in blue are the source of most common organometallic reagents used for organic synthesis)

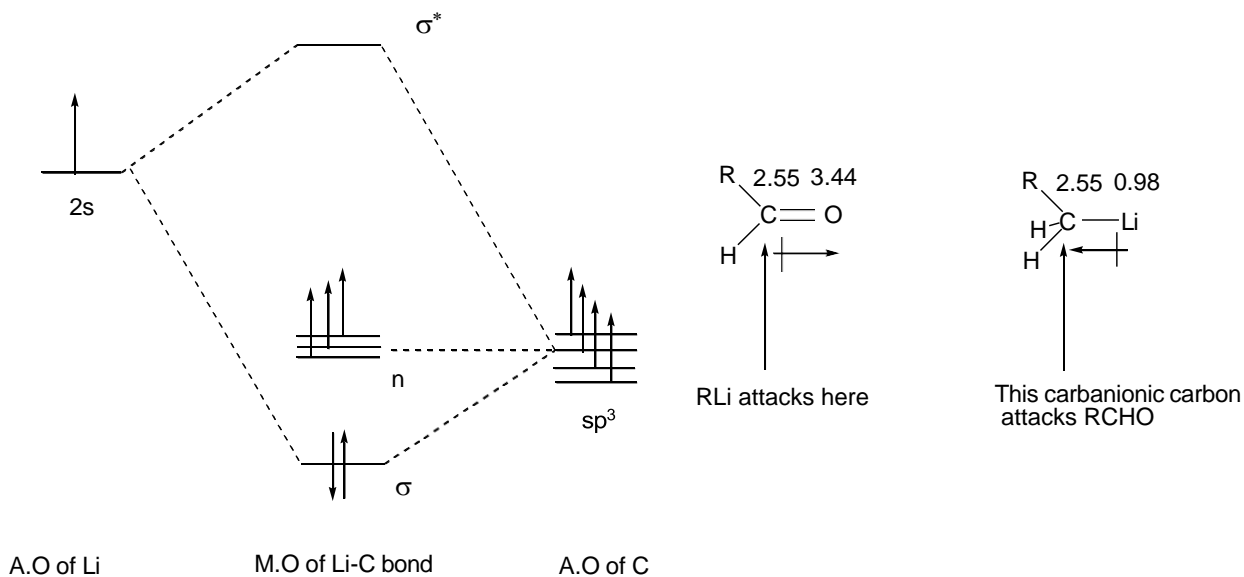
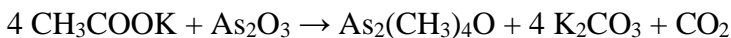


Fig 2 : M.O diagram of C-Li bond showing the high degree of polarization.

The high polarity of the metal-carbon bond is responsible for the high ionic nature of the organometallic compounds (Fig 2). As such these reactions mostly involve nucleophilic attack of the carbanion on the electrophilic center of an organic molecule.

The first organometallic compound was synthesized by French Chemist Louis Claude Cadet de Gassicourt in 1760 by the reaction of potassium acetate with arsenic trioxide. This red coloured liquid is called Cadet's Fuming Liquid in his honour.

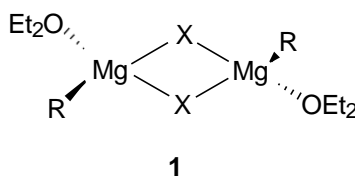


1.1 Classification of Organometallic Compounds

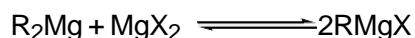
Organometallic compounds may be classified in different ways. They may be classified according to the type of metal-carbon bond or according to the metal center involved in these compounds. For our convenience we will follow the latter classification throughout this text.

1.1 Grignard Reagents

Grignard reagents are organometallic compounds having Mg-C bond. Magnesium can form two covalent bonds with carbon. Of the various organomagnesium compounds possible, organomagnesium halides and to a lesser extent dialkyl magnesium compounds are widely used for synthesis. Although the Grignard reagents are usually formulated as RMgX, but in reality they are a mixture of a variety of species. The ratio of the species in solution varies with the organic group, the halogen, the solvent, the concentration and the temperature. It is believed that in case of organomagnesium chlorides (RMgCl) in diethyl ether, the predominant species over a wide range of concentrations is a solvated, halogen-bridged dimer **1**. The degree of association varies as the halide is changed to Br or I.

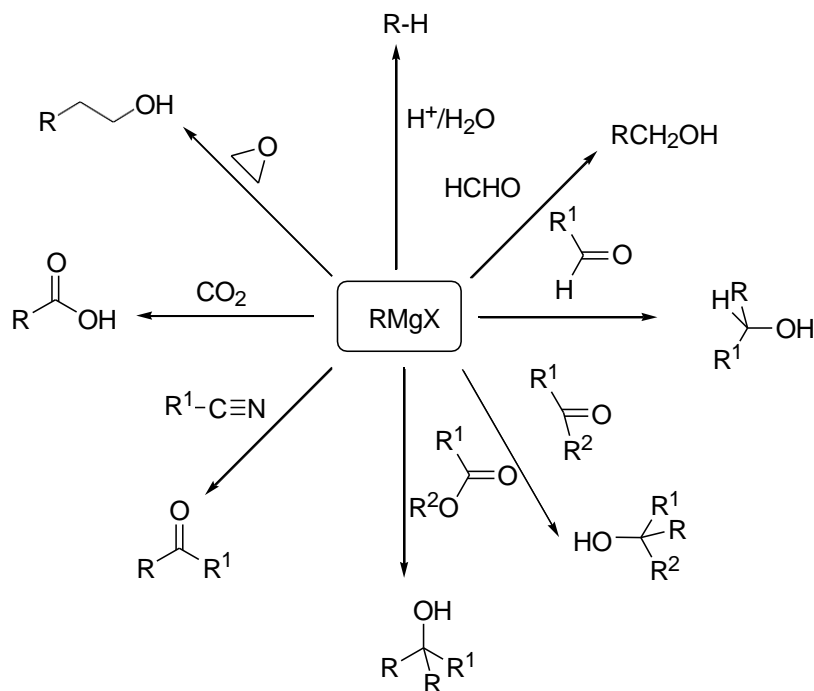


However, in case of THF, due to the highly coordinating nature of the solvent, there is a lesser degree of association. Therefore, monomeric species dominate in THF, however, there are significant concentrations of R_2Mg , MgX_2 and $RMgX$ in equilibrium.



1.2 Addition of Grignard Reagents to Carbonyl Groups

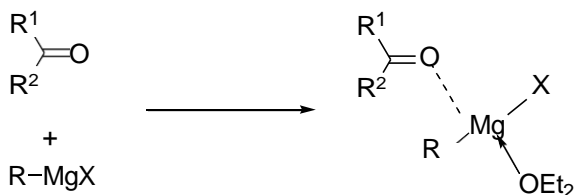
The addition of Grignard reagents to carbonyl group is one of the most important methods for carbon-carbon bond formation. Though the overall reaction is quite simple but it is highly susceptible to a number of side reactions. The reactivity of Grignard reagents towards different carbonyl group containing compounds also varies thus giving rise to different end products depending on reactants (Scheme 1).



Scheme 1

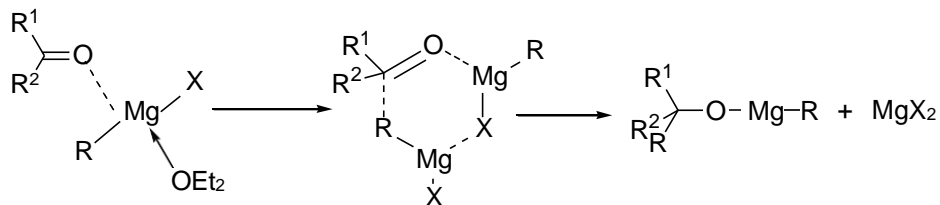
The mechanism of this reaction is usually depicted to consist of the following steps-

- Complexation of the organomagnesium species with the substrate (Scheme 2).



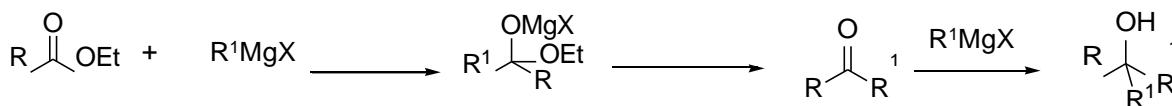
Scheme 2

- The next step involves nucleophilic attack of organic moiety of Grignard reagent on the electron deficient carbon of carbonyl group *via* a molecular complex (Scheme 3).



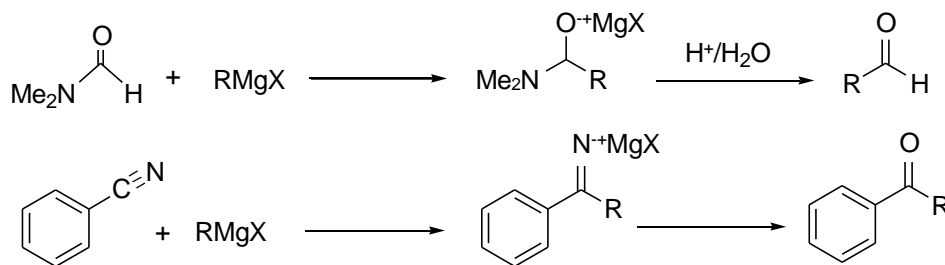
Scheme 3

- The intermediate formed in the above step is hydrolyzed to give a tertiary alcohol. However, if the carbonyl group is attached with a leaving group (i.e., if $\text{R}^1 = \text{OR}$) then the tetrahedral adduct can break down to regenerate a $\text{C}=\text{O}$ group that undergoes a fast second addition step (Scheme 4).



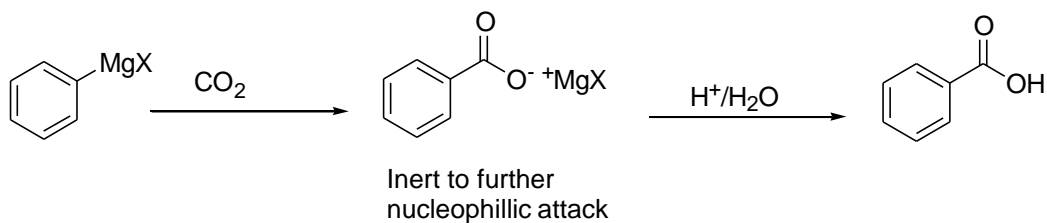
Scheme 4

However, a number of methods have been devised to stop the reaction at the aldehyde or ketone stage. Such protocols involve the formation of a masked carbonyl compound, which releases the desired compound on hydrolysis (Scheme 5).



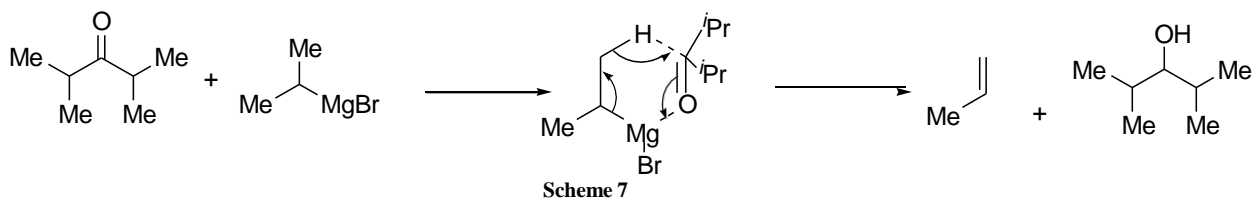
Scheme 5

In case of reaction of Grignard reaction with carbon dioxide, the reaction stops at the carboxylate (RCO^{2-}) stage as it is resistant to further nucleophilic attack (Scheme 6)



Scheme 6

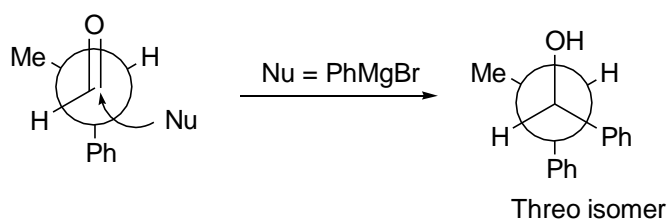
Grignard reactions are prone to undergo side reactions. The reaction of a sterically hindered ketone with a Grignard reagent having a β -H shows a tendency towards reduction of the carbonyl group (Scheme 7).



Scheme 7

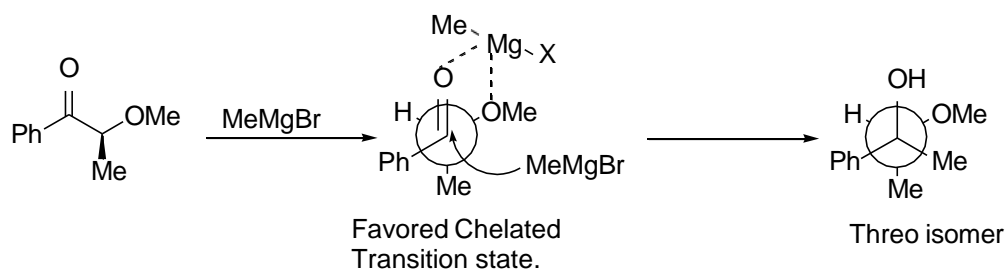
3. The Stereochemistry of Grignard Reaction

The stereochemical outcome of Grignard reaction can be predicted on the basis of Cram's rule. To apply Cram's rule we designate the groups on the carbon adjacent to the carbonyl group as small (S), medium (M) and large (L). The preferred conformation of 2-phenyl-propanaldehyde has carbonyl group staggered between methyl group (M) and hydrogen atom (S). Now according to Cram's rule, the nucleophilic attack by phenylmagnesium bromide will take place from the least hindered position between methyl group and hydrogen atom (Scheme 8).



Scheme 8

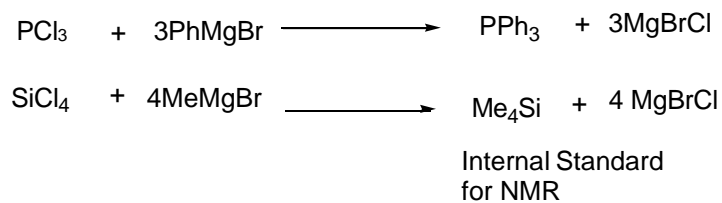
In the case of the Grignard addition to chiral substrates that possess a heteroatom in the α - or β - position, a modification in the application of the Cram's rule is required. In the reaction of (*S*)-2-methoxy-1-phenylpropanone with methyl magnesium bromide, a cyclic structure where the methoxy group is synperiplanar to carbonyl group is formed. This results in the restriction in the freedom of the diastereoselective transition state and thus the attack takes place from the least hindered side having the methyl and the methoxy groups (Scheme 9).



Scheme 9

4. Other Uses of Grignard Reagents

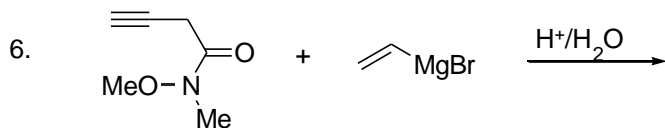
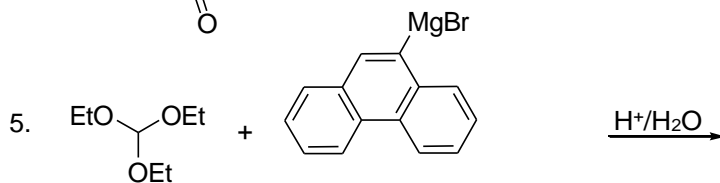
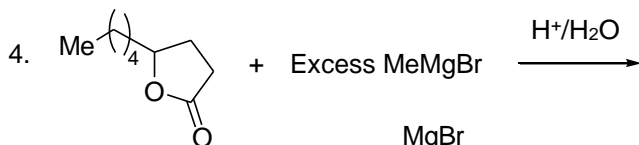
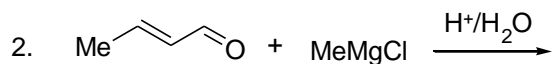
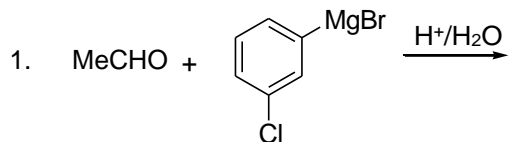
Grignard reagents are not only useful reagents for organic transformation but they are also useful in the synthesis of other useful organometallic reagents such as organosilicon and organophosphorus reagents. For example, the reaction of Grignard reagents with SiCl_4 and PCl_3 gives triphenylphosphine and tetramethylsilane, respectively (Scheme 10).



Scheme 10

Problems

Predict the major products of the following reactions.



Text Book

M. B. Smith, *Organic Synthesis*, 2nd Ed., McGraw Hill, Singapore, 2004.