The alkali metals (Li, Na, K etc.) and the alkaline earth metals (Mg and Ca, together with Zn) are good reducing agents, the former being stronger than the latter. Sodium, for example, reduces elemental chlorine to chloride anion (sodium is oxidized to its cation), as do the other metals under varying conditions. In a similar fashion these same metals reduce the carbon-halogen bonds of alkyl halides. The halogen is converted to halide anion, and the carbon bonds to the metal (the carbon has carbanionic character). Halide reactivity increases in the order: Cl < Br < I. The following equations illustrate these reactions for the commonly used metals lithium and magnesium (R may be hydrogen or alkyl groups in any combination). The alkyl magnesium halides described in the second reaction are called Grignard Reagents after the French chemist, Victor Grignard, who discovered them. The other metals mentioned above react in a similar manner, but the two shown here are the most widely used. Although the formulas drawn here for the alkyl lithium and Grignard reagents reflect the stoichiometry of the reactions and are widely used in the chemical literature, they do not accurately depict the structural nature of these remarkable substances. Mixtures of polymeric and other associated and complexed species are in equilibrium under the conditions normally used for their preparation.

\[ \text{R}_3\text{C}-\text{X} + 2\text{Li} \rightarrow \text{R}_3\text{C-Li} + \text{LiX} \quad \text{An Alkyl Lithium Reagent} \]

\[ \text{R}_3\text{C}-\text{X} + \text{Mg} \rightarrow \text{R}_3\text{C-MgX} \quad \text{A Grignard Reagent} \]

The metals referred to here are insoluble in most organic solvents, hence these reactions are clearly heterogeneous, i.e. take place on the metal surface. The conditions necessary to achieve a successful reaction are critical.

- **First**, the metal must be clean and finely divided so as to provide the largest possible surface area for reaction.
- **Second**, a suitable solvent must be used. For alkyl lithium formation pentane, hexane or ethyl ether may be used; but ethyl ether or THF are essential for Grignard reagent formation.
- **Third**, since these organometallic compounds are very reactive, contaminants such as water, alcohols and oxygen must be avoided.

These reactions are obviously substitution reactions, but they cannot be classified as nucleophilic substitutions, as were the earlier reactions of alkyl halides. Because the functional carbon atom has been reduced, the polarity of the resulting functional group is inverted (an originally electrophilic carbon becomes nucleophilic). This change, shown below, makes alkyl lithium and Grignard reagents unique and useful reactants in synthesis.

Reactions of organolithium and Grignard reagents reflect the nucleophilic (and basic) character of the functional carbon in these compounds. Many examples of such reactions will be encountered in future discussions, and five simple examples are shown below. The first and third equations demonstrate the strongly basic nature of these compounds, which bond rapidly to the weakly acidic protons of water and methyl alcohol (colored blue). The nucleophilic carbon of these reagents also bonds readily with electrophiles such as iodine (second equation) and carbon dioxide (fifth equation). The polarity of the carbon-oxygen double bonds of CO\(_2\) makes the carbon atom electrophilic, shown by the formula in the shaded box, so the nucleophilic carbon of the Grignard reagent bonds to this site. As noted above, solutions of these reagents must also be protected from oxygen, since peroxides are formed (equation 4).

Another important reaction exhibited by these organometallic reagents is **metal exchange**. In the first example below, methyl lithium reacts with cuprous iodide to give a lithium dimethylcopper reagent, which is referred to as a Gilman reagent. Other alkyl lithiuns give similar Gilman reagents. A useful application of these reagents is their ability to couple
with alkyl, vinyl and aryl iodides, as shown in the second equation. Later we shall find that Gilman reagents also display useful carbon-carbon bond forming reactions with conjugated enones and with acyl chlorides.

$$2 \text{CH}_3\text{Li} + \text{CuI} \rightarrow (\text{CH}_3)_2\text{CuLi} + \text{LiI} \quad \text{Formation of a Gilman Reagent}$$

$$(\text{C}_3\text{H}_7)_2\text{CuLi} + \text{C}_6\text{H}_5\text{I} \rightarrow \text{C}_6\text{H}_5\text{-C}_3\text{H}_7 + \text{LiI} + \text{C}_3\text{H}_7\text{Cu} \quad \text{A Coupling Reaction}$$

The formation of organometallic reagents from alkyl halides is more tolerant of structural variation than were the nucleophilic substitutions described earlier. Changes in carbon hybridization have little effect on the reaction, and 1º, 2º and 3º-alkyl halides all react in the same manner. One restriction, of course, is the necessary absence of incompatible functional groups elsewhere in the reactant molecule. For example, 5-bromo-1-pentanol fails to give a Grignard reagent (or a lithium reagent) because the hydroxyl group protonates this reactive function as soon as it is formed.

$$\text{BrCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} + \text{Mg} \rightarrow \{ \text{BrMgCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OH} \} \rightarrow \text{HCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{OMgBr}$$

Exchange metalation is particularly useful when it can be directed to specific sites in a molecule. One such case is the directed ortho metalation of aromatic rings bearing a suitable directing group.

Contributors