ORGANOMETALLIC CHEMISTRY

Sandro Cacchi,
Dipartimento di Studi di Chimica e Tecnologia delle Sostanze Biologicamente Attive, *Università degli Studi "La Sapienza", P. le A. Moro 5, 00185 Rome, Italy*

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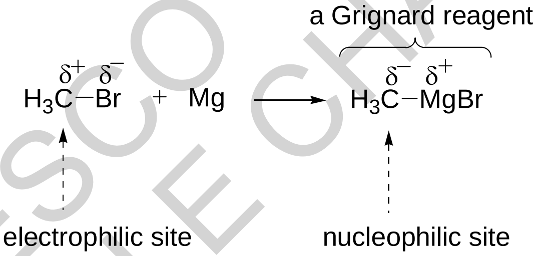
Contents

Summary

This chapter deals with the utilization of some selected organometals in organic synthesis and the rationale behind the most significant reactions presented. In particular, the first part of the chapter treats the reactions involving the utilization of organometallic reagents containing highly electropositive metals such as lithium and magnesium and zinc. Then, organometallics involving transition metals such as copper and palladium are discussed and, in the final part, the focus is on the chemistry of organoboranes, containing a highly electronegative metalloid.

1. Introduction

The origin of organometallic chemistry dates back to the mid of 1800, when Frankland discovered the methyl and ethyl derivatives of mercury, tin and zinc. However, it was the successful introduction of the organomagnesium reagents by Victor Grignard around 1900 that provided a real breakthrough in the utilization of organometallics in organic synthesis. The discovery that an alkyl halide could be readily converted into an organomagnesium compound via reaction with metallic magnesium, Mg(0), and that such a transformation could turn the electrophilic carbon originally bound to the halide into a nucleophilic center (Scheme 1) made it possible to develop unprecedented chemistry. The Grignard reaction provided an extremely powerful tool in organic synthesis, overcoming some of the limits of classical organic synthesis.



Scheme 1

Since then, an ever-increasing number of organic transformations have been based on organometallic compounds. The reactivity of a wide range of organometallic starting materials, intermediates and catalysts have been investigated and a huge number of new and efficient synthetic transformations involving their utilization have been developed. The way organic chemists design and realize synthetic processes has been deeply and irreversibly influenced by the use of organometallics. An important part of many synthetic processes both in academic and industrial laboratories are presently based on organometallic compounds. Nowadays, the arsenal of the practicing synthetic chemist can make use of a wide range of organometallic compounds involving alkali metals, magnesium, boron, zinc, copper, nickel, palladium, platinum and many other metals.

The aim of the present chapter is to provide a brief overview of the synthetic potential of a few, arbitrarily selected organometallics in organic synthesis. The author preferred to limit the number of organometallics described, leaving room to the rationale behind the most significant reactions presented, rather then providing a long “aseptic” list of synthetic applications of a wider range of organometals. In this context, although the term "organo-metallic compound" can be taken to include any species made up of an organic fragment and one or more metals (hence not only organometallics containing carbon-metal bonds but also, for example, metal alkoxides as well as diverse families of important coordination compounds), in general the discussion will be limited to substances having carbon-metal bonds.

In particular, the first part of the chapter (Section 2) will treat the reactions involving the utilization of organometallic reagents containing highly electropositive metals such as lithium and magnesium, the most important organometallics of the groups IA and IIA from a synthetic point of view, and zinc, a metal of the group IIB. The second part (Section 3) will discuss organometallics involving transition metals such as copper and palladium. Finally (Section 4), the chemistry of organometals containing boron, a highly electronegative metalloid, will be discussed. Of course, many other organometallics containing metals such as, for example, sodium, potassium, cadmium, aluminum, manganese, nickel, rhodium, cobalt, indium, platinum, and lanthanides such as cerium, just to name a few, have been successfully used in organic synthesis. Though their applications are remarkable in many cases (for example, Cr and Mn have been widely used in oxidation reactions; Rh and Ru have used in hydrogenations; etc.), in general their synthetic scope appears to be more limited compared with lithium, magnesium, copper, palladium and boron organometals. Other metals, such as mercury and thallium, have known significant developments which have provided a number of interesting and useful synthetic methodologies but their use is presently restricted because of severe toxicity problems. Anyhow, for all the organometals not discussed in this chapter, the reader can refer to the large number of specific books and/or reviews available.

2. Organometallic Compounds of the Group IA and IIA

2.1. Organolithium Compounds

Lithium is a strongly electropositive element and the carbon-lithium bond is polarized so as to place high electron density on the carbon. Therefore, organolithium compounds are strong bases and nucleophiles. They are usually designed as RLi, which is a useful but incomplete representation of their composition in solution where they exist as more complex structures. For example, simple organolithium reagents exist mainly as tetramers in ethers and as hexameric structures in hydrocarbons. Their degree of aggregation as well as their reactivity can be modified by the addition of chelating ligands such as tetramethylenediamine (TMEDA) or strong donor molecules such as *N*,*N*-dimethylpropyleneurea (DMPU) and hexamethylphosphorictriamide (HMPA) (Figure 1).

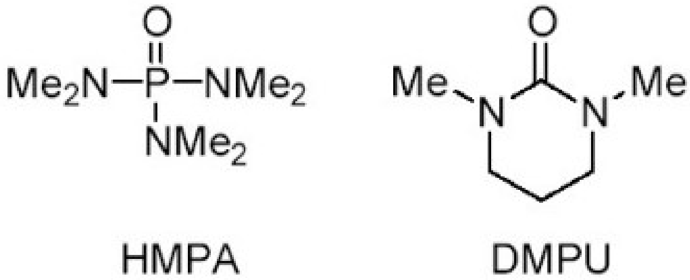


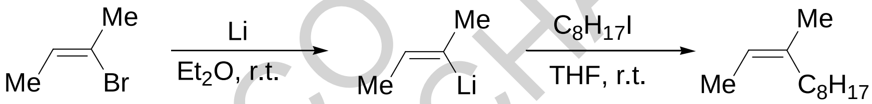
Figure 1: Some donor molecules used to modify the degree of aggregation as well as reactivity of organolithium compounds

2.1.1. Preparation of Organolithium Compounds

Simple organolithium compounds are usually prepared by reaction of lithium metal with an appropriate organic halide (Scheme 2). With alkyl halides, loss of stereochemical integrity at the site of reaction is usually observed. With vinyl halides, the configuration of the double bond is generally preserved (Scheme 3).

$$RX + 2\,Li \longrightarrow RLi + LiX$$

Scheme 2

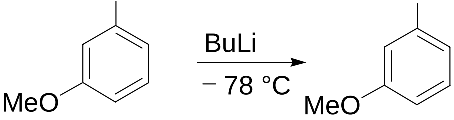


Scheme 3

Organolithium reagents can also be prepared via a metal-halogen exchange process involving an organo halide and an alkyl lithium (Scheme 4). The reaction proceeds in the direction favoring the formation of the organolithium reagent derived from the more acidic compound. Thus, the greater stability of sp^2 carbanions in comparison with that of sp^3 carbanions is the driving force of the conversion of vinyl or aryl halides into the corresponding lithium derivatives in the presence of alkyl lithium reagents (Scheme 5).

$$RX \xrightarrow{R^1Li} RLi$$

Scheme 4



Scheme 5

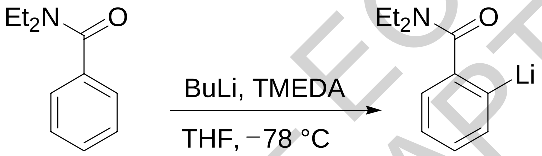
Another general method which is very useful for the preparation of organolithium compounds is the hydrogen-metal exchange or metalation (Scheme 6).

$$\mathrm{RH} \xrightarrow{\mathrm{R^1Li}} \mathrm{RLi}$$

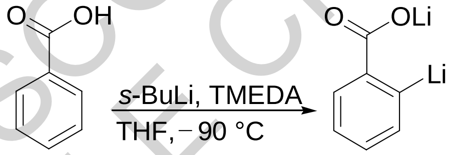
Scheme 6

The directing effect of the substituents in the substrate and the acidity of the available hydrogens influence the position of lithiation. The latter factor, of course, plays an important role even in determining the basic strength of the organolithium reagent required to perform the exchange reaction. Examples of this method are shown in Schemes 7-11.

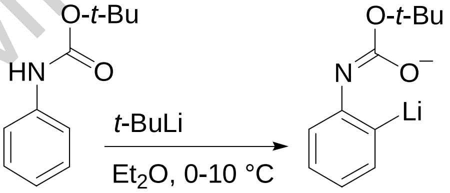
Scheme 7



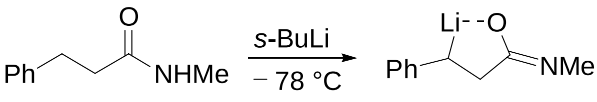
Scheme 8



Scheme 9



Scheme 10

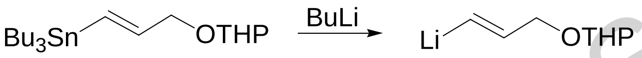


Scheme 11

Organolithium reagents can also be prepared through a metal-metal exchange process involving an alkyl lithium and an organometallic compound (Scheme 12). The reaction proceeds so as to favor the formation of the organometallic derivative with the more stable carbanion bound to the more electropositive metal. An example of this exchange chemistry applied to a vinyltin compound and an alkyl lithium - a type of metal-metal exchange particularly useful synthetically - is outlined in Scheme 13.

$$\mathrm{RM} \xrightarrow{\mathrm{R^1Li}} \mathrm{RLi}$$

Scheme 12



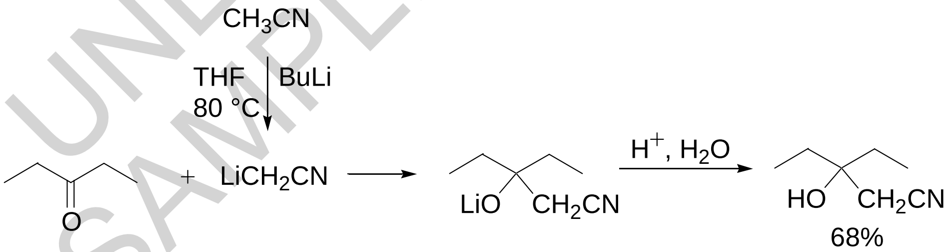
Scheme 13

2.1.2. Reactions of Organolithium Compounds

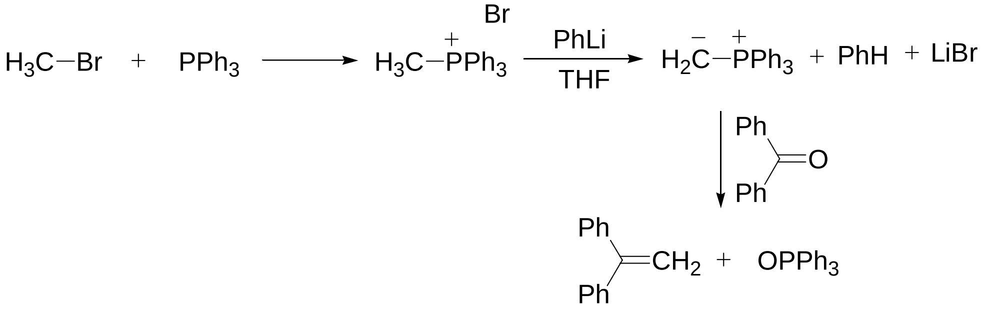
Organolithium compounds have been widely used to generate anions from other acids, in general carbon acids, and in carbon-carbon bond-forming reactions. In the latter case, carbon-carbon bonds have been formed via reaction with alkylating agents and with carbonyl compounds.

2.1.2.1. Reactions with Carbon Acids

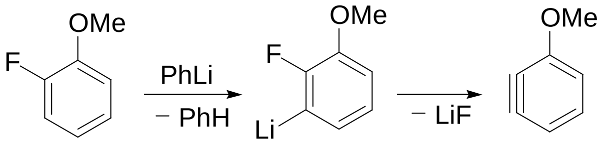
Examples of the utilization of organolithium compounds to generate anions have been reported in Schemes 14-16. Scheme 15 shows the formation of an ylide intermediate in the Wittig reaction and Scheme 16 describes the utilization of phenyllithium in the preparation of a benzyne derivative.



Scheme 14



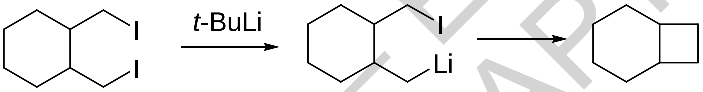
Scheme 15



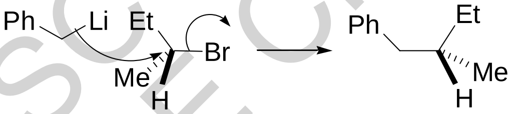
Scheme 16

2.1.2.2. Reactions with Alkylating Agents

Good results have been usually obtained in alkylation reactions with primary alkyl iodides and methyl iodide in intermolecular and intramolecular (Scheme 17) processes. Secondary alkyl bromides can be used as alkylating agents with benzyllithium and allyllithium reagents. Interestingly, with enantiomerically pure secondary alkyl bromides, a high degree of inversion can be observed (Scheme 18). Examples of alkylations by allylic halides have also been described. Radical reactions due to electron transfer processes can complicate alkylation reactions.

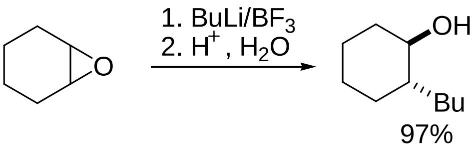


Scheme 17



Scheme 18

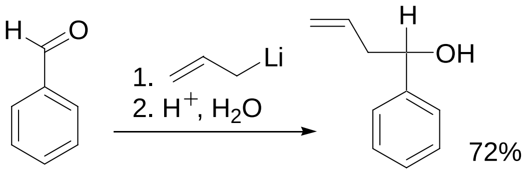
The reaction of organolithium compounds with epoxides, another class of saturated carbon electrophiles, leads to the formation of alcohol derivatives via opening of the epoxide ring (Scheme 19).



Scheme 19

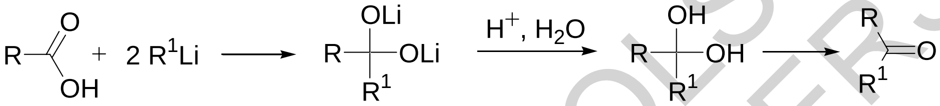
2.1.2.3. Reactions with Carbonyl Compounds

Organolithium compounds react with aldehydes and ketones to afford alcohols (Scheme 20).



Scheme 20

The reaction with carboxylic acids represents a useful method for the synthesis of ketones (Scheme 21). This reaction - quite efficient with organolithium reagents but poor for organomagnesium reagents - involves the formation of a dilithio adduct, the stability of which against elimination and a second addition step is crucial for the success of the reaction. Ketones have also been prepared via the reaction of organolithium compounds with acid anhydrides, acyl chlorides, and *N*-methoxyamides.



Scheme 21

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Biographical Sketch

Sandro Cacchi was born in Macerata (Marche), Cacchi Sandro began his university training at the University of Camerino where he obtained a Laurea degree in Chemistry in 1968. He directly moved to the University of Bologna where he worked under the direction of Professor Caglioti as temporary assistant professor. After doing his national service (October 1968 - December 1969), he went back to the University of Bologna and was promoted permanent assistant professor in 1970. In 1972, maintaining his academic position at the University of Bologna (till 1982), he joined the University "La Sapienza", Rome, where he was temporary professor. From 1973 to 1976 he was temporary professor at the University of Camerino and, from 1977 to 1982, at the University "La Sapienza", Rome. At the University "La Sapienza" he became Associate Professor of Organic Chemistry in 1983 and, subsequently (1986), full Professor of Organic Chemistry.

Dr. Cacchi made a contribution early in his career with the development of new, selective synthetic procedures directed towards the functionalization or preparation of complex molecules, with particular emphasis on the chemistry of molecules of biological interest. In that period he was also the co-author of a book (*Chimica delle Sostanze Naturali*, 1971) and wrote a monograph (*Principi di Bio-organica*, 1977) on the chemistry of natural substances.

In the late seventies, however, he moved to the exciting new field of palladium chemistry and the utilization of palladium catalysis in organic synthesis became a major goal that he pursued in many ways, with the search for new and selective methodologies being a major thrust even in this area.

His scientific contributions have involved the introduction of organotriflates in the Heck reaction and other palladium-catalyzed reactions such as carbonylation, reduction, Heck-Sonogashira-Cassar coupling of terminal alkynes; the development of oxy- and aminopalladation/reductive elimination protocols for the construction of functionalized heterocycles; pioneering work on the capture of carbopalladation adducts with nucleophiles which led to the development of hydroarylation and hydrovinylation reactions of alkenes and alkynes; the development of various domino coupling/cyclization and vinylic substitution/cyclization procedures for the synthesis of heterocycles.

The development of environmentally friendly processes is also one of his main current scientific interests and some of his recent studies investigated the utilization of unusual media, such as supercritical carbon dioxide and ionic liquids, in palladium-catalyzed reactions.

Dr. Cacchi's work has been described in about 180 publications and 7 patents. Dr. Cacchi also authored 5 books and several monographies. He has presented about 150 talks throughout academia and industry and at numerous national and international meetings, as well as serving as a frequent reviewer. Recently, he was member of the Editorial Board of the “Handbook of Organopalladium Chemistry for Organic Synthesis”, Ed. Negishi, E. John Wiley & Sons, New York, 2002.