

The heterolysis of AZ is dependent on the substrate and does not always occur. The final isolation of the product usually involves a hydrolysis step.

The development of improved industrial procedures, including the substitution of tetrahydrofuran (THF) for diethyl ether and the demonstration that the less reactive, but significantly less expensive, vinyl and aryl chlorides could be successfully used, has greatly expanded the commercial possibilities of this reaction. In the flavor, fragrance, pharmaceutical, and fine chemical industries, its use can generally be regarded as routine. Tens of thousands of metric tons of Grignard reagents are produced annually for captive use or merchant sale.

The great value of the Grignard reaction to the synthetic chemist is its general applicability as a building block for an impressive range of structures and functional groups. The Grignard reagent can act both as a prototypical carbon nucleophile that can undergo addition and substitution reactions and as a strong base that can deprotonate acidic substrates, resulting in the conjugate base or in some cases elimination reactions. Grignard reagents react with most functional groups containing polar multiple bonds (eg, ketones, nitriles, sulfones, and imines), highly strained rings (epoxides), acidic hydrogens (eg, alkynes), and certain highly polar single bonds (eg, carbon-halogen and metal-halogen).

PREPARATION OF GRIGNARD REAGENTS

A Grignard reagent is prepared by first adding magnesium and a partial charge of solvent to the reactor, followed by the gradual addition of RX, in the remaining solvent, to the reaction. The quality of the solvent, magnesium, and RX can have a marked and often deleterious effect on the preparation of the Grignard reagent. Some of the problems are homocoupled product, formation of RMgO_2X , and noninitiated reaction of RX with Mg. Therefore, proper preparation and handling of each component must be carried out.

Solvent Preparation

The most critical aspect of the solvent is that it must be dry (<0.02 wt% of H_2O) and free of O_2 .

Other considerations for the solvent are the solubility of the Grignard reagent, the temperatures required for initiation and adventitious reactions of the Grignard with the solvent. Based on these three considerations, the best general solvent for the preparation of a Grignard reagent is THF. However, other solvents that are commonly used are diethyl ether, methyl *tert*-butyl ether, di-*n*-butyl ether, glycol diethers, tertiary amines, toluene, dioxane (for the preparation of R_2Mg), and hexane.

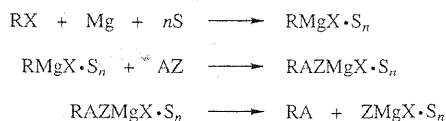
Magnesium Preparation

A surface coating resulting from the oxidation or hydration of the metal surface is the principal problem encountered from the magnesium component. Fortunately, there are numerous methods to remove the inert coating, thus activating the magnesium. For industrial use, the best

GRIGNARD REACTIONS

The term Grignard reaction refers to both the preparation of a class of organomagnesium halide compounds and their subsequent reaction with a wide variety of organic and inorganic substrates. Of all the "name reactions" in chemistry, there is arguably none better known than the "Grignard reaction".

The general sequence of the reactions is now embodied in the following generic forms, where RX = an organic halide (most typically a chloride or bromide, although fluorides can be induced to react); S = a coordinating solvent (such as an ether or an amine); and AZ = a substrate with an electronegative group, Z:



method is using freshly chipped Mg turnings with a small quantity of the desired Grignard added to the reactor before addition of RX.

The Organohalogen Component

Just as for Mg and the solvent, the organic halide must be dry (<0.02 wt% of H₂O) and free of O₂. The relative reactivity of the halogens is reflected in the rate of disappearance of Mg, which follows the general order I > Br > Cl ≫ F. Unfortunately, the rate of disappearance of Mg does not always correlate with the formation of active Grignard. Typically, the more reactive the RX, the higher the probability of forming a homocoupled product. Therefore, when choosing X, the rate of reactivity, product selectivity, and cost must be taken into account.

Other Methods

There are several alternative methods for making Grignard reagents. Metal-exchange reactions are straightforward and MgR₂ can easily be prepared by this route.

Hydromagnesation reactions allow for the preparation of a Grignard from an olefin.

INDUSTRIAL MANUFACTURING PROCESS

In spite of many years of industrial use, the commercial-scale production of Grignard reagents has not been extensively described. The only practically important method is the batch method described by Grignard in 1900, namely, formation of the Grignard reagent, reaction with a substrate, followed by hydrolysis of the reaction mixture.

The equipment can be constructed of carbon steel except for the hydrolysis vessel, which is usually glass-lined to avoid corrosion by aqueous acids. It is desirable to use stainless steel or, preferably, glass-lined ves-

using 2-butanol as the titrant is recommended as the general method for determining the activity of Grignard reagents. The advantages of this method are that it does not titrate Mg-OH or Mg-OR, results are reproducible (3 standard deviations = 0.6% of value), analysis of the solution is direct, and analysis takes <10 min.

Electrophilic quench followed by gc analysis can give the accuracy and precision of a potentiometric titration. However, each Grignard reagent and its product must be calibrated vs a gc standard, which is time consuming. Also, these methods typically take a minimum of 1 h from the start of the quench procedure to obtaining the final chromatogram. The advantage of the gc method is that a direct measurement of the homocoupled product, oxidized Grignard, hydrolyzed Grignard, and unreacted alkyl or aryl halide can all be made.

Total basicity is measured by standard acid-base titration techniques.

Spectroscopic techniques such as nuclear magnetic resonance (nmr) and crystallography have been employed in structure elucidation. The nmr data are extremely dependent on the solvent, steric bulk of the organic group, temperature, and concentration.

Crystal structures of Grignard reagents do not necessarily correspond to their structure in solution. In general, the crystal structures indicate the reagents are ligated with THF or diethyl ether and are frequently observed to be dimers.

ECONOMIC ASPECTS

The Grignard reaction has been commercially important for >50 years, and for certain industrial processes it remains the favored (or only) practical route to construct various element-carbon bonds.

There are five components to the cost of using a

from titration to electrophilic quenching followed by gas chromatography (gc) analysis. Potentiometric titration

such as organic halides (notably methyl bromide and vinyl chloride), are particularly toxic.

Regulatory Considerations

Commercial use of a Grignard reagent in the United States requires that it appear on the Environmental Protection Agency (EPA) list of Chemical Substances in Commerce. A corresponding registration exists for the European Community, Japan and a number of other countries.

REACTIONS AND APPLICATIONS OF GRIGNARD REAGENTS—RECENT DEVELOPMENTS

Reactions and applications of Grignard reagents include asymmetric syntheses, reactions with inorganic chlorides, reagents as bases, metal-assisted modified reactions, intramolecular reactions, as methacrylate polymerization catalysts, and reagents as supports for the Ziegler-Natta process.

There are several reviews and books that discuss the general chemistry of Grignard reagents. The focus here is the specific commercial growth areas in Grignard chemistry.

ALKYL CROSS-COUPLING REACTIONS

Grignard reagents can be made to undergo several types of transition metal catalyzed coupling reactions. Until recently, catalyzed alkyl coupling was generally unavailable owing to the tendency for β -elimination or low reactivity. However, several recent reports in the literature describe Grignard-related systems that not only perform alkyl couplings, but do so with inexpensive iron and nickel catalysts or with stoichiometric amounts of cuprates.

Aryl chlorides, alkyl bromides, and various aryl and alkyl iodides have all demonstrated excellent selectivity, often in the presence of sensitive functional groups such as esters and nitriles. For the commercial synthetic chemist there is significant value in reaction systems that avoid the protection/deprotection "gymnastics" frequently required in complex multistep syntheses.

M. Fieser and L. Fieser, *Reagents for Organic Synthesis*, John Wiley & Sons, Inc., New York, 1967, p. 415.

V. Grignard, *Compt. Rend.* **130**, 1322 (1900).

G. Silverman and P. Rakita, *Handbook of Grignard Reagents*, Marcel Dekker, Inc., New York, 1996.

PHILIP E. RAKITA
Armour Associates, Ltd.