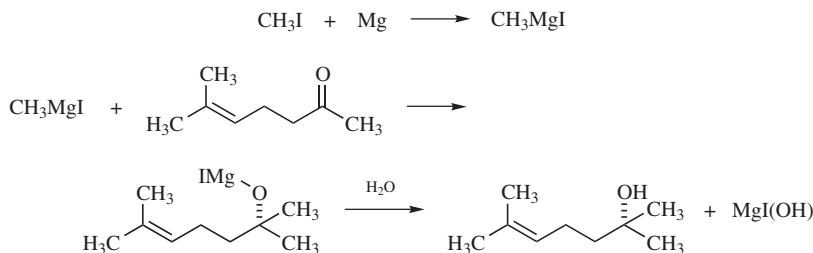# GRIGNARD REACTIONS

1. Introduction

A Grignard reagent is prepared by first adding magnesium and a partial charge of solvent to the reactor, followed by the addition of RX, in the remaining solvent, to the reaction flask. In spite of its industrial use for many years, the commercial-scale production of Grignard reagents has not been extensively described. The Grignard reaction has been commercially important for a number of 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 Grignard reagent: (*1*) magnesium metal, (*2*) the halide, (*3*) the solvent, (*4*) the substrate, and (*5*) disposal of the by-products. Reactions and applications of Grignard reagents include asymmetric syntheses using Grignard reagents, Grignard reactions with inorganic chlorides, Grignard reagents as bases, metal-assisted modified Grignard reactions, intramolecular Grignard reactions, Grignards as methacrylate polymerization catalysts, and Grignard reagents as supports for the Ziegler-Natta process.

Of all the "name reactions" in chemistry, there is arguably none better known than the "Grignard reaction". It is hardly an exaggeration to say that virtually every chemist, at some time or another in his or her professional life, has carried out a Grignard reaction.
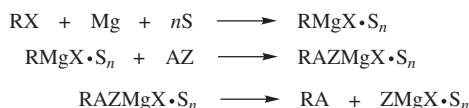
The term Grignard reaction refers to both the preparation of a class of organomagnesium halide compounds and their subsequent reaction with a wide variety of organic and inorganic substrates. As such it has had a wide and profound influence on synthetic chemistry since its first elucidation by Victor Grignard at the beginning of the twentieth century.

Barbier reported (1) in 1899 that a mixture of methyl iodide, a methyl ketone, and magnesium metal in diethyl ether produced a tertiary alcohol. Detailed studies by his student Victor Grignard are documented in his now classical doctoral thesis, presented in 1901. Grignard established (2) that the reaction observed by Barbier could be separated into three distinct steps: Grignard reagent formation, reaction of the intermediate organomagnesium compound with a substrate, and product formation by hydrolysis.

$$CH_3I + Mg \longrightarrow CH_3MgI$$

As a consequence, the general nature of this sequence can be used to prepare an extraordinary variety of new compounds. For this Grignard was awarded the Nobel Prize in Chemistry in 1912 at the age of 39.

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:

$$RX + Mg + nS \longrightarrow RMgX \cdot S_n$$
$$RMgX \cdot S_n + AZ \longrightarrow RAZMgX \cdot S_n$$
$$RAZMgX \cdot S_n \longrightarrow RA + ZMgX \cdot S_n$$

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.

For many years the Grignard reaction was viewed as a generally useful synthetic method only for research (gram or kilogram scale). The drawbacks were the perceived cost limitations of the organic halides and magnesium metal, the well-known difficulties encountered with diethyl ether as a solvent, and the widespread belief that the reaction was inherently hazardous. The development of improved industrial procedures, including the substitution of tetrahydrofuran (THF) (3) for diethyl ether and the demonstration that the less reactive, but significantly less expensive, vinyl and aryl chlorides (4–7) 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.

For convenience and economy of text, the molecular formula of a Grignard reagent is typically written as RMgX. Grignard himself proposed this general formula. The actual structures of the reagents in solution are considerably more complex. The colligative properties of Grignard reagents led Schlenk and Schlenk (8) to propose the equilibria

$$2\ RMgX \rightleftharpoons R_2Mg + MgX_2$$
$$R_2Mg + MgX_2 \rightleftharpoons R_2MgMgX_2$$
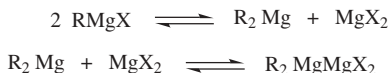
In fact, the use of dioxane to precipitate MgX_2 from solutions of Grignard reagents is a standard method of preparation for solutions of diorganomagnesium

compounds. Numerous methods have been used to establish the nature of Grignard reagents in solution and this work has been reviewed (9,10).

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). A brief but by no means all-inclusive list of typical reactions is given in Table 1. The richness of

Table 1. **Reaction of RMgX with Various Reactant**[a]

Entry[b]	Reactant	Product
1	H_2O	RH
2	O_2/H_2O	ROH
3	CO_2/H_2O	RCOOH
4	I_2	RI
5	R′X	R–R′
6[c]	MX_n	MR_n
7[d]	$COCl_2$	R_3COH
8		
9[e]		
10[f]		
11[e]		
12[e]		
13		

Table 1 (*Continued*)

Entry[b]	Reactant	Product
14	R'–C(=O)–N(R'')–R''	R'–C(=O)–R
15	R'–C(=O)–O–C(=O)–R''	R'–C(=O)–R
16	R'–N=C=O	R–C(=O)–N(H)–R'
17	R'–C(=O)–O–OC(CH₃)₃	(CH₃)₃C–O–R
18	(cyclohex-2-enone)	(1-R-2-cyclohexen-1-ol, HO, R)
19[g]	(cyclohex-2-enone)	(3-R-cyclohexanone)
20[e]	(γ-butyrolactone with R')	R–C(OH)(R)–CH₂–CH₂ ... R'–C(H)(OH)
21	R'₂C=C=O	R'–CH(R')–C(=O)–R
22	R'–S(=O)–O–R''	R'–S(=O)–R
23[e]	R'SSR'	RSR'
24	S	RSH
25[e]	S	RSR

Table 1 (*Continued*)

Entry[b]	Reactant	Product
26	CS_2	$\underset{R}{\overset{\displaystyle S}{\overset{\|}{\underset{}{C}}}}\!\!-\!SH$
27	SO_2	$\underset{R}{\overset{\displaystyle O}{\overset{\|}{\underset{}{S}}}}\!\!-\!OH$
28	$R'\!-\!N\!=\!C\!=\!S$	$R'\!-\!\underset{NH}{}\overset{\displaystyle S}{\overset{\|}{C}}\!-\!R$
29	$R'\!-\!N\!=\!C\!=\!O$	$R'\!-\!\underset{NH}{}\overset{\displaystyle O}{\overset{\|}{C}}\!-\!R$
30	$R'\!-\!C\!\equiv\!N$	$R'\!-\!\overset{\displaystyle O}{\overset{\|}{C}}\!-\!R$
31	$R'\!-\!\underset{R'}{\overset{\displaystyle NH}{\overset{\|}{C}}}$	$\underset{R'}{\overset{H_2N}{}}\,C\,\underset{R'}{\overset{R}{}}$
32	$\underset{R'}{\overset{R'}{}}\!\!-\!\triangle\!\!-\!O$ (epoxide)	$HO\,\underset{R'\;\;R'}{\overset{R}{}}C\!-\!CH_2$
33	$CH_2\!=\!CH$-epoxide	$R\!-\!CH_2\!-\!CH\!=\!CH_2\,CH_2\!-\!OH$
34	$R'\!-\!C\!\equiv\!C\!-\!H$	$R'\!-\!C\!\equiv\!C\!-\!MgX$

[a] Refs. 10 and 11.
[b] The reactant specified reacts with 1 mol of RMgX without catalyst unless otherwise specified.
[c] n RMgX.
[d] 3 RMgX.
[e] 2 RMgX.
[f] Catalyst.
[g] CuI $< -40°C$.

Grignard chemistry is illustrated by the fact that the reaction conditions permit the choice of converting an ester to either a tertiary alcohol (Table 1 entry 9) or a ketone (Table 1 entry 10). Likewise, the reaction of a Grignard reagent with cyclohexenone can result in either a 1,2-addition yielding a substituted cyclo-hexanol (Table 1 entry 18) or a 1,4-addition to give a three-substituted cyclohex-anone (Table 1 entry 19). The historical background in the classic volume by Kharasch and Reinmuth (11) has been superceded by the more recent *Handbook*

of Grignard Reagents (10) as a reference volume for both the theoretical and practical aspects of Grignard chemistry.

2. Preparation of Grignard Reagents

A Grignard reagent is prepared by first adding magnesium and a partial charge of solvent to the reactor (10−12), followed by the gradual addition of RX, in the remaining solvent, to the reaction. Initiation should occur within the first 10 wt% addition of the RX mixture. Evidence for the initiation is a large exotherm. Many chemists look for turbidity or change of color, but this can be misleading if the agitation is strong enough to abrade the magnesium. A milky appearance in the solution often indicates water contamination. Until initiation has been confirmed, no more than 20 wt% of the RX charge should be added to the reactor. Otherwise, there is a risk of initiation after all of the RX has been added. This is especially dangerous, because the resulting exotherm could cause a release of the reactor contents into the atmosphere, and possibly result in a fire. Most incidents with Grignard processing are related to problems with initiation.

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.

2.1. 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. If the H_2O content is >0.02 wt%, then the reaction of Mg and RX does not initiate, except for an extremely reactive RX species, such as benzyl bromide. However, ultrasonic treatment has been used to initiate Grignard reagent formation in wet ether (13). Although adventitious O_2 does not retard the initiation process, the O_2 reacts with the Grignard reagent to form a $RMgO_2X$ peroxo species. Furthermore, upon hydrolysis, the oxidized Grignard reagent forms a ROH species that may cause purification problems.

The peroxo species can oxidize other reactants, liquids, catalyst, or final product in the subsequent coupling reaction. One example of such oxidation is observed in the preparation of triphenylphosphine (14,15). If this reaction is hydrolyzed in air instead of an inert N_2 atmosphere, then the amount of triphenylphosphine oxide increases from <1 wt% to >15 wt%.

$$Cl_3P \ + \ 3\ C_6H_5MgCl \ \xrightarrow{\text{air}} \ 0.15\ (C_6H_5)_3PO \ + \ 0.85\ (C_6H_5)_3P$$
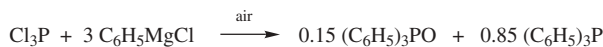
Other considerations for the solvent are the solubility of the Grignard reagent, the temperatures required for initiation and adventitious reactions of the Grignard with the solvent (16−19). Based on these three considerations, the best general solvent for the preparation of a Grignard reagent is THF. 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. Most commercially available Grignard reagents are supplied in diethyl ether or THF.

2.2. Magnesium Preparation.   A surface coating resulting from the oxidation or hydration of the metal surface is the principal problem encountered from the magnesium component. This coating prevents initiation of the Grignard reaction. Fortunately, there are numerous methods to remove the inert coating, thus activating the magnesium (11,20–24). These methods include addition of I_2, $BrCH_2CH_2Br$, activated Mg (20,24), and ultrasound. However, for industrial use, the best method is using freshly chipped Mg turnings with a small quantity of the desired Grignard added to the reactor before addition of RX (10). The nature of the surface oxide coating has recently been examined by several surface-specific techniques such as Auger electron spectroscopy (AES), low energy electron diffraction (LEED) and X-ray photoelectron spectroscopy (XPS) (25).

2.3. The Organohalogen Component.   Just as for Mg and the solvent, the organic halide must be dry (<0.02 wt% of H_2O) and free of O_2 for the reasons previously discussed. Occasionally, RX may be contaminated with residual HX. Often, this can be remedied by passing the neat halide through molecular seives. Care should be taken with the specifications of RX.

The relative reactivity of the halogens is reflected in the rate of disappearance of Mg, which follows the general order $I > Br > Cl \gg F$. Unfotunately, 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.

The general effect of R on the rate of formation of RMgX is allyl, benzyl > 1°alkyl > 2°alkyl, cycloalkyl = 3°alkyl, aromatic > vinyl. Again, the more reactive R is, the more probable the formation of homocoupled product. Another important consideration for the R group is the compatibility of functional groups in the organic halide. Because of the reactivity of the Grignard reagent, noncompatible functional groups need to be protected.

2.4. Other Methods.   There are several alternative methods for making Grignard reagents. Metal-exchange reactions are straightforward and MgR$_2$ can easily be prepared by this route (26–30). This method is typically used when Grignard reagent formation is difficult to initiate or a diorganomagnesium reagent is desired:

$$R_nM \ + \ n\,MgCl_2 \ \longrightarrow \ n\,RMgCl \ + \ MCl_n$$

where M = Na, Li, or Hg. Acid–base preparation (10,21) works only if RH is more acidic than R′H. This method is typically used to make Grignard reagents of terminal alkynes:

$$R-C{\equiv}CH \ + \ R'MgX \ \longrightarrow \ R-C{\equiv}CMgX \ + \ R'H$$

Hydromagnesation reactions allow for the preparation of a Grignard from an olefin (31–35).
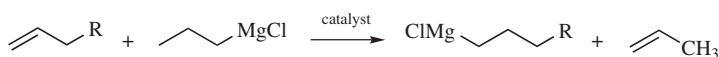
This method provides an economic advantage if the olefin is significantly less expensive than the corresponding organic halide. Interestingly, when MgH_2 reacts with an alkyne in the presence of a Cu catalyst, only the cis-alkene Grignard reagent is formed (10).

3. Industrial Manufacturing Process

In spite of many years of industrial use, the commercial-scale production of Grignard reagents has not been extensively described. The general features of a small production unit have been reported (36) and a pilot-size operation suitable for pharmaceutical applications has been described (37). A continuous system, practical for small- or medium-scale production, was patented by Hoffman-La Roche (38) and pilot scale production of silanes using a continuous reactor have been studied in detail by Klokov and Andrianov in Russia (39). However, 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. A simplified schematic diagram is shown in Figure 1.

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 vessels throughout. All vessels must be supplied with an inert gas (nitrogen or argon) for purging and blanketing and are vented to release off-gases. It is imperative that the reaction vessel be protected with a rupture disk.

3.1. Formation of the Grignard Reagent. In the classical methodology for the start-up of a batch process (Fig. 1), magnesium turnings or chips are charged to vessel R-2. After thorough purging with an inert gas, a portion of the solvent is then added, followed by a fraction of the halide charge from vessel R-1. The chief hazard associated with the manufacture of Grignard reagents occurs at this stage in connection with the difficulty in initiating the reaction. If the addition of the halide is continued before initiation, then the presence of excess halide suddenly initiating generates such a large exotherm that the cooling system may be overwhelmed. This may result in a dangerous pressure buildup and a potential explosion.

To minimize the effects of this difficulty, an initiator is frequently employed. Among the numerous suggestions in the literature, the most satisfactory industrial procedure is to retain a portion of the Grignard from the preceding batch and to add this portion to the initial ether charge. The purpose of this procedure is to eliminate residual water and to clean the magnesium surface. Once this initiator has been added, the halide is added at a rate determined by the temperature and the pressure in the reaction vessel.

The solvent volume required is determined by the maximum solubility of the Grignard reagent—typically $1–3\ M$. Since it is often desirable to have a homogeneous solution of Grignard, as opposed to a slurry, reaction volumes (and space yields) are greatly influenced by the concentration of the Grignard.
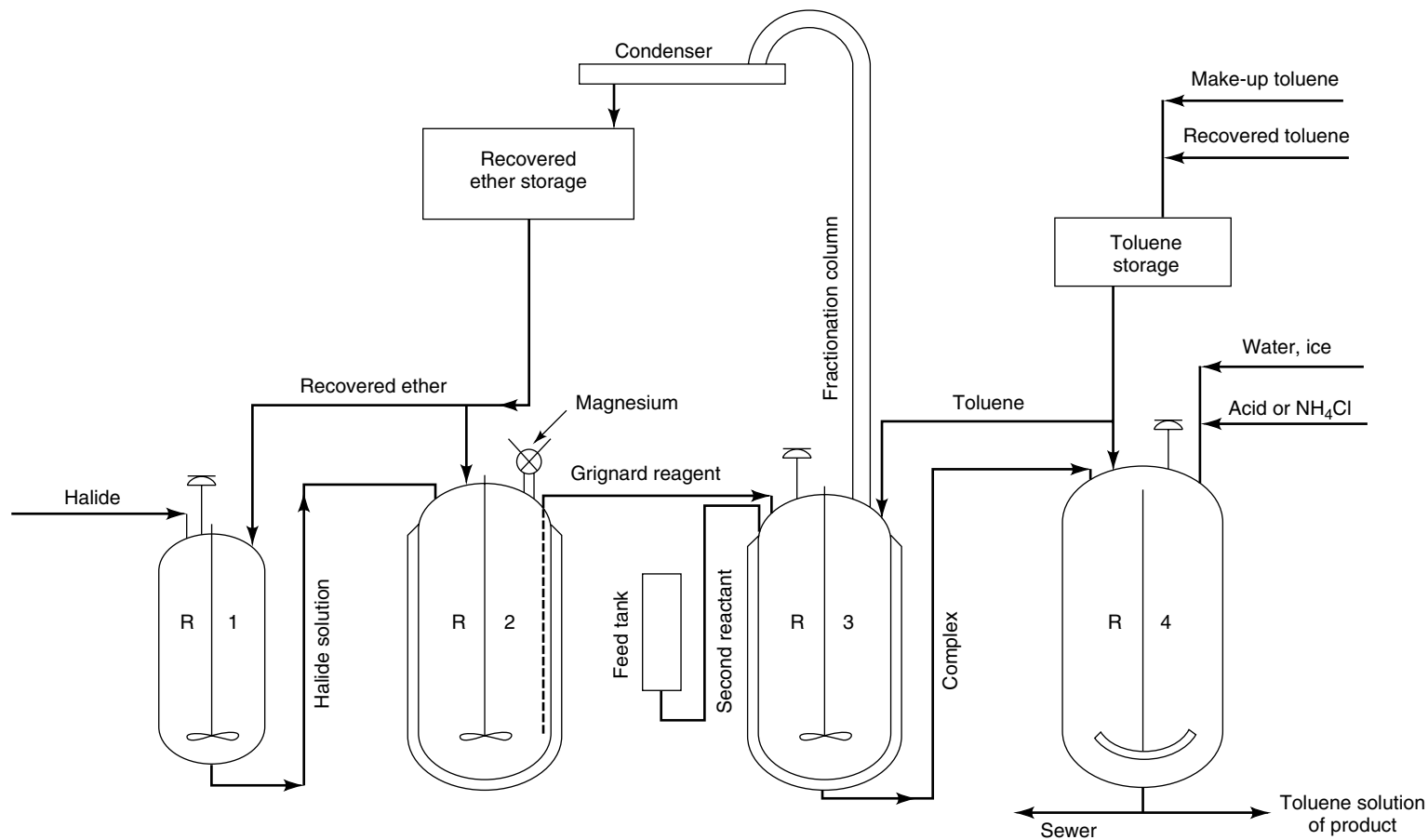
Fig. 1. Flow diagram of a Grignard plant.

Cooling is routinely applied, either with ambient process water if THF is the solvent or with chilled brine if diethyl ether is used. Since Grignard reagents are particularly reactive with water, liquid hydrocarbon coolants may be preferred, to eliminate the risk that could arise from a cooling-system leak. Recently, an on-line infrared method has been developed to monitor the formation and utilization of Grignard reagents (40).

Filtration of a Grignard reagent solution will result in the isolation of finely divided, black magnesium particles. These black particles are highly activated and will react vigorously with air or any source of acidic protons including water (*vide infra*, Fire Hazards).

3.2. Reaction of the Grignard Reagent with a Substrate.

For the process represented in Figure 1, the Grignard reagent is usually transferred from the reaction vessel R-2 to the coupling vessel R-3 for the reaction with the substrate. In most cases, it is advisable to remove particles of residual magnesium by filtration. The substrate, dissolved in an ether or hydrocarbon solvent, is then added slowly from the feed tank (with cooling of the reaction vessel). The addition can also be reversed, ie, via addition of the Grignard reagent slowly from vessel R-2 to a solution of the substrate in vessel R-3. The choice of direct or reverse addition is dictated by several factors and is usually established by suitable process and pilot-plant studies before reaching the plant stage. After the reaction is complete, most of the ether is removed by distillation, with or without the addition of enough hydrocarbon to R-3 to maintain adequate agitation. At this point the contents of R-3 are pumped to R-4 for further processing.

3.3. Hydrolysis of the Reaction Mixture.

Apart from the reaction of Grignard reagents with organic or inorganic halides, the reaction gives a complex that requires a quench step to release the desired product. Water has sufficient acidity to hydrolyze the complex, but the basic magnesium salts formed in this reaction generate a gel. This can be overcome through the addition of a stronger acid to neutralize the basic salts and produce water-soluble magnesium salts. Sulfuric and hydrochloric acids are commonly employed, but may lead, particularly in the case of some tertiary alcohols, to dehydration. In these cases, the use of weaker acids such as acetic acid or ammonium chloride permits the recovery of the desired alcohol. After the hydrolysis step is complete, the aqueous phase is separated from the organic phase and the product is then isolated.

Hydrolysis of reaction mixtures involving Grignards containing alkyl magnesium halide, where the alkyl group is C-4 or lower (eg, methyl, ethyl, butyl) may result in the release of gaseous by-products resulting from the protonation of excess Grignard during hydrolysis. Proper venting should be provided for in these instances. As an example, a 200 L (55 gal) drum of 3 M methyl magnesium chloride has the potential to release up to 600 mol (13,440 L) of methane when hydrolyzed!

In those cases where hydrolysis is not required, the metathetical reaction leads directly to the product (plus magnesium halide) in the solvent. Volatile products may be removed by direct distillation or the solid magnesium halide may be removed by filtration, before solvent evaporation. If the final product is not water sensitive, water-washing of the final reaction product mixture usually removes the salts conveniently.

4. Analysis of Grignard Reagents

There are three potential problems that may occur during Grignard reagent preparation: (*1*) oxidation by O_2, (*2*) hydrolysis by H_2O, or (*3*) homocoupling during the addition of alkyl or aryl halide. All three of these reactions decrease the active Grignard reagent while maintaining the same equivalents of base. Consequently, the concentration of a Grignard reagent should not be assumed, based on the reactants. The disadvantages of not analyzing the Grignard reagent are improper stoichiometry, potentially deleterious side reactions, highly exothermic quenching processes, phase splits, waste disposal, and cost problems. The analytical technique must be able to differentiate between active Grignard and total basicity.

Many methods are available to measure the active Grignard (41–50), ranging from titration to electrophilic quenching followed by gas chromatography (gc) analysis. Potentiometric titration (41,42) using 2-butanol (42) 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. Standard titration techniques (43,44), using 2-butanol as the titrant, have greater error (3 standard deviations = 1–5% of value), but in most cases this is still acceptable.

Electrophilic quench followed by gc analysis can give the accuracy and precision of a potentiometric titration (46–50). 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. The activity divided by the total basicity should be >90%. If it is not, then the Grignard reagent should be checked for unreacted alkyl or aryl halide, homocoupled product, hydrolysis products, and oxidation products.

Spectroscopic techniques such as nuclear magnetic resonance (nmr) and crystallography have been employed in structure elucidation (40,51–63). The nmr data are extremely dependent on the solvent, steric bulk of the organic group, temperature, and concentration. Typically, to observe the Schlenk equilibrium, low temperatures are required ($-70°C$), but it has been observed at ambient temperature with the bulky *tert*-butylmagnesium chloride (58,59) in THF. The high field resonance arises from R_2Mg and the low field resonance from RMgX. Similar findings have also been observed by ^{25}Mg-nmr (60).

Crystal structures of Grignard reagents do not necessarily correspond to their structure in solution. In general, the crystal structures (61–64) indicate the reagents are ligated with THF or diethyl ether and are frequently observed to be dimers. The Mg atoms in the dimers do not have a Mg–Mg bond; instead the dimers are typically held together by a halide bridge.

5. 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

Table 2. **Comparison of Commercial Organometallic Reagents**[a]

Parameter	R3Al	RMgX	RLi
solvents	neat, hydrocarbons	ethers, hydrocarbons, amines	hydrocarbons, amines
possible R groups	butyl, octyl, ethyl	numerous alkyl or aryl groups including those with substituents	methyl, butyl, hexyl, phenyl
relative cost per mole of R transferred[b]	1	2	9

[a] Available in commercial (ie, metric ton) quantities.
[b] Calculations are based on R = butyl.

construct various element–carbon bonds. Compared with other organometallic reagents, organomagnesium compounds offer considerably greater flexibility, efficiency, and degree of reactivity resulting from the choice of solvent and organic halide. The range of commercially available organoaluminum or organolithium compounds is limited to simple alkyl and aryl groups (methyl, butyl, hexyl, and phenyl for lithium; *n*-Butyl and *n*-octyl for aluminum). Grignard reagents, by contrast, can tolerate a wider range of substituents on the carbon framework (Table 2). Recent developments with activated forms of magnesium metal have allowed the preparation of a large range of Grignard reagents with various functional groups on the organic substituent including halides and cyclic ethers [65]. Activated magnesium is also now commercially available.

For reasons of cost, the organic chloride is preferred as a starting material over the corresponding bromide or iodide, in spite of its generally lower reactivity. With the development of THF as a substitute for diethyl ether and the use of active magnesium powder, many Grignard reagents can be made from the corresponding chlorides in high yield.

There are five components to the cost of using a Grignard reagent: (*1*) magnesium metal, (*2*) the halide, (*3*) the solvent, (*4*) the substrate, and (*5*) disposal of the by-products. The price of magnesium in mid-2004 was $6.40/kg (99.98% purity), having risen from $3.20/kg (99.95%) in 1992. Prices for THF and diethyl ether, the two most commonly used solvents, have also increased (Table 3) in the same period. The cost of the halide depends on its structure, but as a general rule the order of cost is chloride < bromide < iodide.

There is often a choice of two or more different substrates that can give rise to the same product with different Grignard reagents. As an example, 1,1-diphenyl-ethanol [599-67-7] can be prepared by three different routes, as shown

Table 3. **Costs of Components of Grignard Reagents, U.S. $/kg**[a]

Component	1970	1979	1992	2004
magnesium	1.36	2.90	3.20	6.40
tetrahydrofuran	0.81	1.65	2.30	2.27
diethyl ether	0.38	0.70	1.15	1.78
toluene	0.08	0.34		0.68

[a] Bulk pricing, 2004.
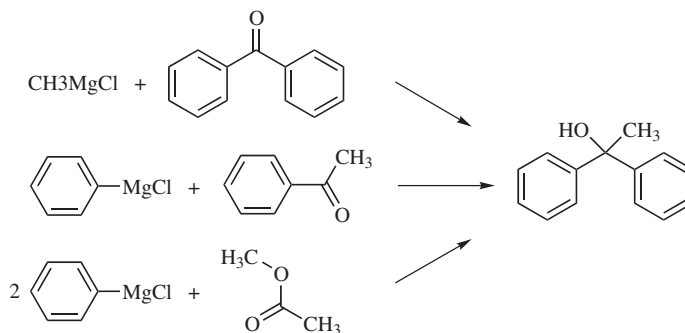
Fig. 2.   Preparation of 1,1-diphenylethanol from methylmagnesium chloride and benzo-phenone, phenylmagnesium chloride and acetophenone, or phenylmagnesium chloride and methyl acetate.

in Figure 2. The choice depends on the yield and ease of purification as well as the cost of the substrate and the Grignard reagent.

Aqueous work-up of the typical Grignard reaction gives a mixed magnesium hydroxide–halide solution or suspension, which must be disposed of. The cost of disposal of the acidic aqueous waste in accordance with local wastewater treatment regulations must also be considered. One limiting factor inherent in the use of Grignard reagents is the sacrificial nature of the magnesium metal used to mediate the coupling of the organic group to the substrate. By its very nature, and like the Wittig reaction, Grignard chemistry is not inherently atom-efficient.

Nonaqueous work-up of a Grignard reaction will almost always result in the formation of insoluble magnesium salts that are difficult to filter. These circumstances can arise where a Grignard adduct is water or acid sensitive and must be isolated from the reaction mixture by filtration or distillation without hydrolysis. This step should be carefully planned, prior to scale-up, to resolve the issue of dealing with the salts.

For many fine chemical producers, including pharmaceutical manufacturers, using a Grignard reagent is often a make-or-buy decision, the choice depending on (*1*) the possibility of more cost-effective uses for the equipment being used to generate the Grignard reagent, (*2*) the facility for solvent recovery, and (*3*) waste disposal. For these reasons, custom synthesis by a company specializing in Grignard chemistry is often an option. In the past decade a growing number of companies have begun to offer Grignard reagents on a commercial scale in multi-ton lots. The reagent can be supplied either in 55-gal drums or in bulk containers. Table 4 lists several common Grignard reagents commercially available in 2004, together with typical pricing. Literally hundreds of other Grignards are offered by catalogue or specialty houses and in most cases these can also be produced in bulk. The commercial synthetic chemist should not be dissuaded from considering using a Grignard reaction for an industrial process simply because the requisite Grignard reagent may not appear to be commercially available.

Table 4. **Prices for Selected Commercially Available Grignards**[a]

Reagent	Solvent	Concentration, mol/kg	Selling price, $/kg of solution
CH_3MgCl	THF	3.0	10.95
CH_3MgBr	diethyl ether	3.0	13.95
C_2H_5MgCl	diethyl ether	2.0	13.85
C_6H_5MgCl	THF	2.0	10.40
$CH_2=CHMgBr$	THF	0.7	16.45
$(CH_3)_3CMgCl$	diethyl ether	2.0	19.10

[a]Available in 2004.

6. Health and Safety Factors

6.1. Fire Hazards.   The hazards associated with the manufacture, transport, and use of Grignard reagents are related to the flammability of the solvents employed and the exothermic reactions involved in their preparation and use. Historically, diethyl ether was the common solvent used in the preparation of Grignard reagents. Commercially, however, its use is limited by its extreme flammability and relatively low boiling point, which preclude its use in reactions with higher working temperatures. Starting in the 1950s, there began a widespread adoption of THF in commercial-scale production. THF is a cyclic ether with a boiling point $30°C$ higher than that of diethyl ether and a flash point of $-17°C$, compared with $-45°C$ for diethyl ether.

Because of the exotherm, Grignard reactions are carried out in jacketed, glass-lined steel reactors equipped with cooling, explosion-proof electrical wiring, explosion disks, and inert atmosphere for purging and blanketing. To control the heat of reaction when THF solvent is employed, ambient cold water may suffice. For reactions using diethyl ether, chilled water or brine is required to keep the reaction mass below the boiling point. Since Grignard reagents are particularly reactive with water, liquid hydrocarbon coolants, eg, kerosene, may be substituted to eliminate the risk of a water leak. Similar precautions apply for the use of commercial Grignard reagents.

Spills of Grignard reagents should be contained with inert absorbent material (such as soda ash) and transferred with nonsparking bronze, brass, or plastic tools. Because Grignard reagents are highly reactive; fire extinguishers containing carbon dioxide, chlorinated hydrocarbons, or water must not be used. Dry chemical fire extinguishers and full personal protective clothing, including self-contained breathing apparatus, are recommended.

For Grignards made on a commercial scale, there are also important safety issues with handling the magnesium. Unreacted magnesium heels and filter residue are highly reactive and represent a serious fire hazard. Many producers of Grignard reagents find that careful hydrolysis of the residual magnesium is preferable to storage or solids disposal.

6.2. Toxicology.   Because of their high reactivity, there is little meaningful information on the health hazards of Grignard reagents per se. Rather, consideration needs to be given to the reagents employed, including the solvents and the products (or by-products) of the reaction. Some starting materials, such

as organic halides (notably methyl bromide and vinyl chloride), are particularly toxic. Hydrolysis of a phenylmagnesium halide produces benzene. By-products of the decomposition of Grignard reagents are an additional concern. As with flammable organic halides, there is a potential for the release of hazardous hydrogen halide vapors (HCl, HBr).

In general, exposure of living tissue to a Grignard solution will result in a vigorous reaction with water in the tissue, resulting in thermal and caustic burns. Subsequent ignition of the solvent is also a possible risk. Water that has been in contact with a Grignard reagent should be considered caustic and appropriate precautions taken with its handling and disposal.

6.3. 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. Table 5 gives the CAS Registry Numbers of those currently listed in the U.S. and the corresponding status in selected other countries.

Providing Grignard reagents to persons with the intent to produce controlled substances, with reckless disregard toward their illegal use, is specifically prohibited under the Comprehensive Methamphetamine Act of 1996 and providers are subject to civil penalties. Organomagnesium compounds are specifically mentioned (including phenyl magnesium bromide and ethyl magnesium bromide) in the Special Surveillance List, promulgated by the U.S. Drug Enforcement Agency (64 FR 50541).

6.4. Handling, Shipping, and Storage.   Merchant Grignard reagents are supplied commercially in 55-gal (200 L) 16-gauge stainless steel tighthead drums (DOT-17C in the United States, IATA IA2 internationally), with double-welded top and body seams. Heads with a minimum convexity of 3/8 in., but not extending beyond the level of the chimes, are required in the United States. Threaded metal plugs are required and must engage at least three threads with a gasket in place. Thin gauge drums are prone to "triangulation" when diethyl ether Grignard solutions are allowed to get cold in transit or storage. Proprietary designs also exist for returnable, refillable bulk containers suitable for shipment of Grignard reagents.

Classified as "flammable-when wet" liquids, Grignard reagents in the United States must bear a red U.S. Department of Transportation label. The appropriate international designation of Grignard reagents is UN-1993. Container size restrictions apply for ocean shipment of Grignard reagents that generate gaseous by-products (C-1−C-4 hydrocarbons) upon hydrolysis. Shippers of Grignard reagents should be aware that the ship's captain often has the final word about whether or not the ship will accept a Grignard container. Air freight shipment of Grignard solutions is limited to 1-L-containers. Some shippers limit services to ground shipment only.

As with any potentially flammable material, the best storage facility is a well-ventilated, fire-resistant building suitable for flammable chemicals. Because of the limited solubility of Grignard reagents in the solvents typically used, special storage considerations are required in cold weather. Most Grignard reagents are formulated to remain soluble at temperatures $>20°C$. During cold seasons, Grignard reagents must be shipped in heated containers and stored at $>15°C$.

Table 5. **Grignard Reagents Listed on the U.S. EPA Toxic Substances Control Act (TSCA) List and Other Governmental Regulatory Listings**

Name	RMgX formula	CAS Registry number	Canada	EU (EINECS #)	Japan	Others
methylmagnesium chloride	CH_3MgCl	[676-58-4]	X	211-629-7	ENCS (2)-3469 ISHL 1-(2)-152	Philippines Australia
methylmagnesium bromide	CH_3MgBr	[75-16-1]	X	200-844-1	ENCS (2)-3468 ISHL 1-(2)-153	Philippines
methylmagnesium iodide	CH_3MgI	[917-64-6]	X	213-031-1	ISHL 1-(2)-154	
ethylmagnesium chloride	CH_3CH_2MgCl	[2386-64-3]	X	219-206-9	ENCS (2)-3469 ISHL 1-(2)-201	
Ethylmagnesium bromide	CH_3CH_2MgBr	[925-90-6]	X	213-127-3	ENCS (2)-3468 ISHL 1-(2)-10	Australia
n-propylmagnesium chloride	$CH_3CH_2CH_2MgCl$	[2234-82-4]	X	218-785-5	ENCS (2)-3469	
iso-propylmagnesium chloride	$(CH_3)_2CHMgCl$	[1068-55-9]	X	213-947-1	ENCS (2)-3469	
n-butylmagnesium chloride	$CH_3CH_2CH_2CH_2MgCl$	[693-04-9]		211-739-5	ENCS (2)-3001 ISHL 1-(2)-130	
sec-butylmagnesium chloride	$CH_3CH_2CH(CH_3)MgCl$	[15366-08-2]	X	239-403-3	ENCS (2)-3001 ISHL 1-(2)-130	
sec-butylmagnesium bromide	$CH_3CH_2CH(CH_3)MgBr$	[79722-38-6]	X	239-403-3	ENCS (2)-3001 ISHL 1-(2)-130	
tert-butylmagnesium chloride	$(CH_3)_3CMgCl$	[677-22-5]		211-638-6	ENCS (2)-3001 (2)-3793 ISHL 1-(2)-130	
n-pentylmagnesium bromide	$CH_3(CH_2)_4MgBr$	[693-25-4]	X	211-747-9	ENCS (2)-3001 ISHL 1-(2)-144	
cyclo-pentylmagnesium bromide	C_5H_9MgBr	[33240-34-5]	X	251-420-8		
n-hexylmagnesium bromide	$CH_3(CH_2)_5MgBr$	[3761-92-0]	X		ENCS (2)-3468	
n-octylmagnesium bromide	$CH_3(CH_2)_7MgBr$	[17049-49-9]	X		ENCS (2)-3468 ISHL 1-(2)-26	

Table 5 (*Continued*)

Name	RMgX formula	CAS Registry number	Canada	EU (EINECS #)	Japan	Others
vinylmagnesium bromide	$CH_2=CHMgBr$	[1826-67-1]	X	217-375-3	ENCS (2)-3439 ISHL 1-(2)-113	Korea (KE-03717)
allylmagnesium chloride	$CH_2=CHCH_2MgCl$	[2622-05-1]	X	220-067-1	ISHL 1-(2)-210	China
phenylmagnesium bromide	C_6H_5MgBr	[100-58-3]	X	202-867-2	ENCS (2)-2206 ISHL 1-(2)-120	
phenylmagnesium chloride	C_6H_5MgCl	[100-59-4]	X	202-868-8	ENCS (3)-3903 ISHL 1-(2)-119	Australia China Switzerland (G-2729)
1-naphthylmagnesium bromide	$1-C_{10}H_7MgBr$	[703-55-9]	X			
benzylmagnesium chloride	$C_6H_5CH_2MgCl$	[6921-34-2]	X	230-039-0	ISHL 1-(2)-142	
p-tolylmagnesium bromide	$4-CH_3C_6H_4MgBr$	[4294-57-9]	X			
o-tolylmangesium chloride	$2-CH_3C_6H_4MgCl$	[33872-80-9]	X	251-709-9		

[a] For Canada, items listed on either the Domestic Substance List (DSL) or Non-Domestic Substance List (NDSL).

[b] For the European Union, items listed on the European Inventory of Existing Commercial Substances (EINECS).

[c] For Japan, items listed on either the list of Existing and New Chemical Substances (ENCS) or the Industrial Safety and Health Law list (ISHL).

[d] For Australia, items listed on the Australian Inventory of Chemical Substances (AICS).

[e] For China, items listed on the China Inventory of Existing Chemical Substances (IECSC).

[f] For Switzerland, items listed on the Switzerland Consolidated Inventory.

[g] For Korea, items listed on the Korea Existing Chemicals Inventory (KECI).

[h] For the Philippines, items listed on the Philippine Inventory of Chemicals and Chemical Substances (PICCS).

Containers must not be allowed to sit outside or in cold conditions such as un-
heated warehousing, to avoid precipitation of magnesium salts. Certain solvents,
such as 1,4-dioxane and dimethoxyethane, complex with the magnesium halide,
MgX_2, leading to precipitation. While such precipitation does not irreparably
harm the reagent, it does alter its composition by affecting the Schlenk equili-
brium. If this situation is encountered, the original composition can usually be
reestablished by gentle warming with agitation.

7. Reactions and Applications of Grignard Reagents—Recent Developments

There are several reviews and books that discuss the general chemistry of
Grignard reagents (10,66,67). The focus here is the specific commercial growth
areas in Grignard chemistry.

8. Activated Magnesium

In 1972, Rieke and Hudnall first reported the preparation of highly reactive mag-
nesium powders by reducing metal salts in ethereal or hydrocarbon solvents
using alkali metals as reducing agents (68). Subsequent elaboration of these stu-
dies and improvements in methods have created a general approach to producing
a wide range of active metals useful for synthesis (69). One of the most notable
reactions is the conversion of p-fluorotoluene to the corresponding Grignard re-
agent in 1 h in refluxing THF (70). In the subsequent 30 years, literally thousands
of novel reagents and fine chemical products have been produced, many of which
are unattainable by standard methods. Use of the so-called Rieke magnesium
allows for the formation and reaction of Grignard reagents at temperatures of
$-78°C$ or lower (71)

9. Alkyl Cross-Coupling Reactions

Grignard reagents can be made to undergo several types of transition metal cat-
alyzed coupling reactions. Until recently, catalyzed alkyl coupling was generally
unavailable owing to the tendancy 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 (72) and nickel
(73) catalysts or with stoichiometric amounts of cuprates (74).

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 (75).

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