

# Grignard knowledge: Alkyl coupling chemistry with inexpensive transition metals

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## INTRODUCTION

The formation of a Grignard reagent is fascinating to watch. A heap of silvery magnesium turnings swirl in a clattering vortex around the bottom of a glass reaction vessel under a clear and colorless ethereal solvent. The silvery appearance soon changes as the mixture is treated with a clear and colorless organohalide (RX) in dropwise fashion. Soon the clear solution becomes turbid and the appearance of the magnesium begins to change. Over the course of the addition of RX, the magnesium becomes noticeably corroded. As the reaction begins to exotherm, the magnesium bits begin to dance on the convection currents and expanding gas bubbles in the refluxing solvent medium. As the solvent vapor pressure rises, the reflux condenser absorbs the vapors heat burden and returns condensed solvent back to the vessel. Over an hour or two, most of the magnesium metal has disappeared, indicating the reaction has gone to completion. What remains are perhaps a few stray bits of magnesium lying under a solution whose color may vary from amber to a turbid gray to the color of black tea. Neutral organic materials have somehow managed to digest the metallic magnesium.

For many chemists, the generation and use of a Grignard reagent was among the very first organic C-C bond-forming synthesis they performed as a college student. This reagent and its set of bond forming reactions are ubiquitous in the synthetic literature. The year 2001 marked the centennial of the publication by Grignard and (mentor) Barbier describing their now famous reaction mechanism. Victor Grignard went on to share the Nobel Prize for Chemistry with Sabatier in 1912. Throughout his career, Grignard continued to expand the scope

of the reaction chemistry, eventually ascending to the highest honorary status in chemistry - the rank of Named Reactions.

The formation and use of the Grignard Reagent is a nearly universal experience among synthesis chemists. However, the range of applications has advanced well past that described in most introductory texts, i.e., nucleophilic addition to carbonyl species or epoxides to form alcohols or carboxylic acids. The purpose of this article is to highlight the general considerations relating to Grignard technology and offer some interesting examples of bond-forming reactions of interest to the pharmaceutical community.

## THE GRIGNARD REAGENT AND ITS PROPERTIES

The Grignard Reagent is an organometallic species formed by the formal insertion of elemental magnesium ( $Mg^0$ ) into a carbon-halogen bond R-X ( $X = Cl, Br, I$ ) (1), affording an entity typically written as "RMgX". It is generally accepted that the metallation reaction consists of a stepwise path beginning with a rate determining single electron transfer (SET) from metallic magnesium to the  $\sigma^*$  orbital of the C-X bond of the organohalide (2). This transfer leads to a radical-anion/radical-cation pair at the surface of the magnesium (Figure 1). Transfer of halide anion to  $Mg^{+}$  to give  $XMg^+$ , followed by collapse of  $XMg^+$  and  $R^{\cdot}$  affords RMgX. The chance diffusion of  $R^{\cdot}$  from a neighboring site can lead to dimer (R-R) formation (3). This dimer formation is often generalized as a "Wurtz coupling."

Though it is tempting to accept it as the actual active species, the formula "RMgX" is merely a formalism that is useful in calculating stoichiometry and proposing

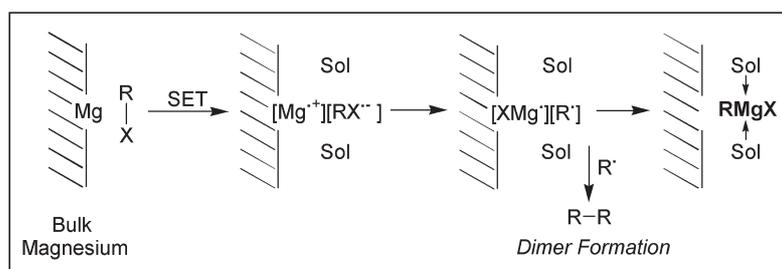
simple mechanisms. In reality, it is less than accurate in describing the solvated aggregate structure of the reactive species (4). Fortunately for Grignard users, large-scale industrial application occurs safely and reliably without detailed knowledge of the composition of the actual aggregate structure.

First and foremost, the Grignard species is a metallated carbanion and shares many of the properties of other metallated species. It is a nucleophile and a strong base, ranking third behind 1) RNa and 2) RLi in reactivity of the carbanion, based on electronegativity differences (5). Generally, the reactivity of a carbanionic reagent tends to increase  $\uparrow$  with increasing  $\uparrow$  p-character ( $sp < sp^2 < sp^3$ ) and increasing  $\uparrow$   $pK_a$  of the conjugate acid. As a nucleophile, a Grignard reagent bearing a localized (i.e., not resonance-stabilized) carbanion will generally behave as a hard nucleophile, offering higher relative reaction rates with hard electrophiles and 1,2-addition as opposed to conjugate addition. This behavior can be altered to that of a softer nucleophile by the addition of Cu(I) salts to form a cuprate species *in situ*. Certain Grignard reagents such as allylic or benzylic species may have an aptitude for conjugate or  $S_N2'$  addition *without* transmetalation additives.

Grignard reagents are strong bases and will react exothermically with a variety of Lewis and Brønsted acidic species. Carbon acids such as acetylene, chloroform, methylene chloride; and enolizable species, and oxyacids such as water, alcohols, carboxylic acids; and inorganic acids such as HX will react vigorously in contact with a Grignard reagent. An important point to consider is that Grignard reagents such as methyl-, ethyl-, propyl-, or butylmagnesium halides, when quenched with a proton, may lead to the rapid formation of methane, ethane, propane, and butane resulting in a rapid pressure buildup in a reactor or storage container. Care must always be taken to assure that a rapid quench leading to high vapor pressure products be avoided.

RMgX is very polar and consequently requires a coordinating solvent to keep it in solution. Ethers are most suitable owing to the availability of lone-pair electrons for coordination to the magnesium ion and resulting solubilization in organic media. Examples of common solvents include diethyl ether ( $Et_2O$ ), diisopropyl ether, dibutyl ether, tetrahydrofuran (THF), and butyldiglyme. Dimethoxyethane (DME) and 1,4-dioxane promote precipitation of  $MgX_2$  salts as a result of the Schlenk equilibrium (more on this later).

Figure 1 - Karasch-Reinmuth-Walvorsky mechanism leading to Grignard reagent formation



Reagent formation is usually, though not exclusively, carried out in ethereal solvent systems. The presence of hydrocarbon co-solvents can be tolerated to varying levels, especially at elevated temperature and pressure. A polarizable co-solvent like toluene can be used in a mixed solvent preparation of reagent. Furthermore, addition of an ethereal Grignard solution to a toluene solution of reactant is often well tolerated in terms of solubility. An attempt to dissolve a Grignard species in a hydrocarbon solvent will have a better chance for success if the Grignard species is solvated with an ether.

Grignard reagents are available from commercial suppliers in drums or cylinders and are typically offered as THF or diethyl ether solutions in the range of 1 to 3 Molar. As a practical consideration, the reagent concentration is limited by the solubility at temperatures the product is likely to encounter in transit and storage. Most Grignard reagents are formulated to remain soluble at temperatures above 20°C. The issue of solubility requires that during the cold season, Grignard reagents must be shipped in heated shipping containers and be stored at room temperature off the floor and on pallets. It is important for freight handlers to clearly understand that Grignard products must not be allowed to sit outside and cool on the loading dock or in unheated temporary warehousing. The result of cooling is precipitation of magnesium salts. While this does not irreparably harm the reagent, it does alter its composition by equilibration. The original composition is returned by simple dissolution of the reagent by warming with agitation.

When a Grignard reagent solution gets cold, solids precipitate and accumulate on the bottom of the storage container or vessel. This elementary fact is somewhat complicated by the Schlenk equilibrium (Figure 2). This equilibrium describes a disproportionation property of RMgX wherein factors that diminish solubility (i.e., lowered solvent polarity or low temperature) result in precipitation of the inorganic salt  $MgX_2$  from the organic solvent medium, thus driving the equilibrium to the right. Certain ethers such as DME and 1,4-dioxane drive the equilibrium to the right by virtue of the formation of stable coordination

complexes of the magnesium dihalide salt.

The predominant characteristic of a Grignard Reagent is the anionic aspect of the carbon attached directly to the magnesium ion. It is nucleophilic and usually quite basic in nature. These attributes - nucleophilicity and

basicity - while useful in bond forming reactions, in fact put some limits on the types of chemical moieties that can be present during the formation and use of a Grignard reagent.

Solvents with electrophilic sites such as acetonitrile, DMF, acetone, and ethyl acetate are unsuitable owing to their great (and irreversible!) reactivity with RMgX. Reactive moieties on the Grignard substrate such as aldehydes, ketones, esters, amides,  $SO_2X$ , nitriles, epoxides, hemiacetals, and most halogenated moieties (i.e., Si-Cl, P-Cl, etc.), must be protected or absent. Furthermore, the presence of hetero-atom acids such as water of hydration, phenols, alcohols, COOH, N-H,  $R_3N \cdot HCl$ , as well as carbon acids like terminal acetylenes and enolizable groups are quite incompatible with the formation of an RMgX functional group on a substrate.

In general, a Grignard reagent is prepared separately and combined with the reaction mixture as an ethereal solution. In some cases a Grignard reagent can be generated in the presence of the intended electrophile, which promptly undergoes addition. This is referred to as a Barbier reaction or colloquially as "Barbier conditions".

## SOME SYNTHETIC APPLICATIONS OF GRIGNARD REAGENTS

Although Grignard reactions trace back more than 100 years, the development of new reaction chemistry is far from static. Several relatively recent and noteworthy developments from the literature will be discussed. But before proceeding with reaction specifics, some basics are in order.

Figure 2 - The Schlenk equilibrium

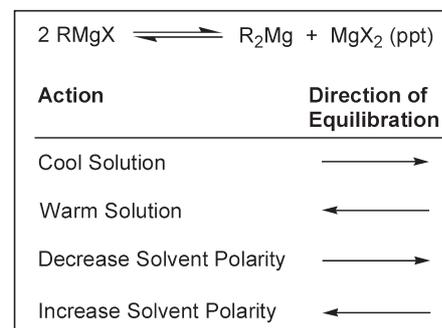
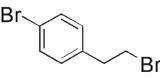
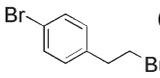


Figure 3 - Alkyl halide coupling with Grignard reagents

R-X	R'-MgX	R-R'	(% GC Yield)
n-C <sub>10</sub> H <sub>21</sub> Br	n-BuMgCl	n-C <sub>14</sub> H <sub>30</sub>	(100%)
	n-BuMgCl		(100 %)
n-C <sub>8</sub> H <sub>17</sub> Br	PhMgBr	PhC <sub>8</sub> H <sub>17</sub>	(90%)
n-BuOTs	n-BuMgCl	n-C <sub>8</sub> H <sub>18</sub>	(100%) <sup>a</sup>
n-C <sub>8</sub> H <sub>17</sub> Cl	n-BuMgCl	n-C <sub>12</sub> H <sub>26</sub>	(96%)

a) 100 mol % 1,3-butadiene

Kambe, et al., see Ref. 7

## Proposed Mechanism

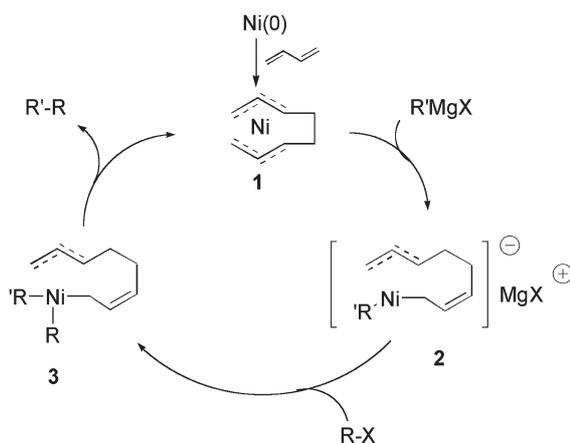
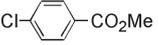
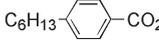
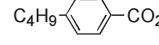
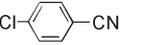
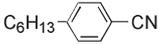
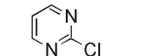
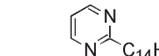
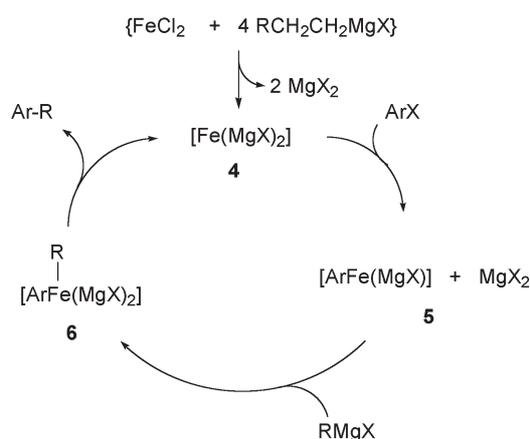


Figure 4 - Aryl chloride coupling with alkyl Grignard reagents

ArCl	R-MgX	Ar-R	(% GC Yield)
	n-C <sub>6</sub> H <sub>13</sub> MgBr		(>95 %)
	n-C <sub>4</sub> H <sub>9</sub> Li		(0 %)
	n-C <sub>6</sub> H <sub>13</sub> MgBr		(91 %)
	n-C <sub>14</sub> H <sub>29</sub> MgBr		(93 %)

Furstner, et al., see Ref. 8

## Proposed Mechanism



## Organometallic Mini-Tutorial

It is worth a reminder that the Grignard reagent is an electron rich species. Consequently it is capable of reducing some transition metal species to a lesser positive charge, a neutral state, or even negative charge. Some catalytic cycles depend on an *in situ* reduction of the transition metal in the process. Grignard reagents can transfer the R anion group of RMgX from the magnesium to catalyst M to afford a transient R-M<sup>(-)</sup> species. What happens next depends on the metal, its oxidation state, and what is attached to it. In the case of coupling reactions, the transition metal may undergo *oxidative* addition to form R-M-R' as a result of treatment with R'X. At this stage the R and R' groups are in close proximity and may form a carbon-carbon  $\sigma$ -bond and leave the vicinity of the metal as R-R' coupled product. Of the combined 4 electrons available in the R-M and R'-M  $\sigma$ -bonds, 2 stay with the metal and 2 are used in the R-R' bond of the coupled product - thus it is a *reductive* elimination from the metals perspective. There are a great variety of mechanisms and the order of addition of the R groups may vary with the system (6a).

## 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  $\beta$ -elimination or sluggish reactivity. However, several recent reports in the literature describe Grignard-related systems that not only perform alkyl couplings, but do it with inexpensive iron and nickel catalysts or with stoichiometric cuprates. Obviously, iron, nickel, and copper are inexpensive and not subject to erratic market price fluctuations that plague buyers of the platinum group metals. Additionally, the diverse connectivity and selective functional group transformations allowed by alkyl coupling reactions offers increased flexibility in the design of convergent syntheses. This is welcome news for the pharma scale-up chemist engaged in the eternal search for better process economics. We will examine a few of these reports.

Kambe and coworkers (7) have reported a nickel-catalyzed cross coupling in which aryl and alkyl Grignard reagents were coupled in moderate to high yields with alkyl

halides and tosylates. Thus, the reaction affords aryl-alkyl and alkyl-alkyl products (Figure 3).

The authors propose a mechanism wherein the Ni(II) is first reduced to Ni(0) by excess Grignard and then reacts with 2 equivalents of 1,3-butadiene to form the coupled bis- $\eta^3$ -octadienylnickel(II) complex 1. This complex undergoes nucleophilic addition of the Grignard reagent affording the anionic  $\eta^1, \eta^3$ -complex 2, which then undergoes oxidative addition of an alkyl halide to give intermediate complex 3. Reductive elimination affords R'-R as the system cycles back to complex 1.

The table in Figure 3 highlights the diverse connections made possible by this reaction. Primary alkyl bromides, chlorides, and tosylates are coupled with alkyl and aryl Grignards cleanly and in high yield by this system. In addition, an alkyl bromide moiety was coupled selectively in the presence of an aryl bromide group of 4-(2-bromoethyl)-bromobenzene.

An iron-based catalytic system for the coupling of alkyl Grignards to aryl chlorides has been reported recently by Fürstner and coworker (8). This system (Figure 4) offers considerable promise in expanding Grignard utility not only for the catalytic leverage, but also for the

extraordinary functional group tolerance that is evident.

The mechanism proposed by Fürstner invokes the generation of an Fe(-II) species **4** by the addition of 4 equivalents of a primary Grignard to FeCl<sub>2</sub>. This results in the reduction of Fe(II) to a formal -2 state with the concomitant generation of reduction, elimination, and coupling products from the Grignard reducing reagent. The proposed mechanism begins with the oxidative addition of ArX to electron rich [Fe(MgX)<sub>2</sub>] resulting in the addition complex **5** and the disproportionation of the Mg moiety. This is formally a 2 electron oxidation of Fe(-II) to Fe(0). The Fe(0) then undergoes an alkylation by a Grignard coupling reagent affording **6**, which upon reductive elimination of the coupling product, Ar-R, regenerates the [Fe(MgX)<sub>2</sub>] species.

What is striking about the Fürstner chemistry is the excellent selectivity. As seen in the table in Figure 4, in the presence of the [Fe(MgX)<sub>2</sub>] catalyst a Grignard reagent will react exclusively with the chloride moiety, leaving otherwise sensitive functional groups like esters and nitriles unchanged. In contrast to the success of numerous examples of alkyl Grignards, butyllithium failed to couple. Although not shown in the table, the reaction does favor electron deficient aryl chlorides. Electron rich aryl substrates containing alkoxy or alkyl substituents were shown to couple with the corresponding tosylate or triflate in good yield. For the scale-up chemist this selective coupling reaction affords the potential for greater convergence and less time spent in protection/deprotection gymnastics in the execution of a synthetic scheme.

A Cu(I)-mediated cross-coupling reaction of functionalized primary alkyl iodides with functionalized aryl cuprates (Figure 5) has been reported by Knochel and coworkers (9). This chemistry is notable for the generation and transmetalation of a Grignard in the presence of a labile functional group like ester. The overall strategy involved a Grignard species in two distinct ways. First, an aryl iodide **1** bearing a reactive Functional Group (FG<sub>1</sub>) was metallated with isopropylmagnesium halide at low temperature to afford ArMgX **2**. Second, Grignard **2** serves as a precursor for transmetalation with copper(I) for generation of a cuprate **3** (abbreviated as "Cu"). Cuprates are commonly generated by transmetalation of RMgX or RLi with Cu(I)X. Although many applications use catalytic quantities of Cu(I)X, the chemistry cited worked best at stoichiometric levels of Cu (i.e., 1 eq CuCN·LiCl).

Generation of a Grignard reagent by

treatment of a halide with magnesium turnings may be very slow at the required reaction temperature of -20°C. Accordingly, the authors chose to perform a transmetalation of the aryl iodide with commercially available isopropylmagnesium bromide to afford the aryl Grignard. It was found that the generation of the aryl Grignard by this method in the presence of trimethyl phosphite afforded little homocoupling.

The table in Figure 5 shows that esters and amides are tolerated in the coupling reactions. Of particular interest is the diallylaniline moiety. An olefin functional group might be expected to coordinate with many platinum group metal catalyst systems, possibly affording an altogether different manifold of product possibilities. A transition metal species that couples in the presence of esters, amides, and olefins is a useful thing. However, the requirement for an aryl iodide precursor is somewhat of a detraction from the process chemistry perspective, but, arguably, may be more than offset by the functional group tolerance shown by the chemistry.

In summary, a general case has been made for the continuing vitality of Grignard chemistry with some recent examples of unique bond forming reactions using nickel, iron, and copper catalysts and additives. It is worth considering that C-C bond forming

reactions based on the Grignard reagent may be economically advantageous owing to the low molar expense of magnesium and the general availability of halogenated precursors.

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Figure 5. Cu-Mediated cross-coupling of aryl iodides and alkyl iodides

