Grignard reagent and Green Chemistry: Mechanistic studies to understand the molecular origins of selectivity in the formation of RMgX

Hassan Hazimeh, Jean-Marc Mattalia, Mireille Attolini, Nicolas Bodineau, Kishan Handoo
Caroline Marchi-Delapierre, Eric Pérale & Michel Chanon

Laboratoire AM3, Case 561, UMR CNRS 6178, Faculté des Sciences et Techniques de Saint-Jérôme, Université Paul Cézanne (Aix-Marseille III), 13397 Marseille Cedex 20, France
E-mail: michel.chanon@univ-u-3mrs.fr

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Controlling selectivity is one of the important keywords in the development of Green Chemistry. The mechanistic study of the formation of RMgX with the aim of understanding at which step(s) the selectivity is settled shows that there is room for basic research in a field too often considered as the simple development of new recipes. One of the most widely used reactions in synthetic studies still offers fascinating conundrums when one tries to answer the apparently simple question: at which step(s) does the formation of by-products coexisting with RMgX occur? Here the illustration of this statement is given by studying the patterns of reactivity of aliphatic and aromatic radical clock halides toward magnesium or potassium. The importance of using the concepts developed by electrochemists to rationalize the selectivity observed at cathodes or anodes for understanding selectivity observed in the reactive dissolution of metals is stressed.

Keywords: Green chemistry, Grignard reagent, mechanistic study

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Since its discovery more than a century ago, the Grignard reagent has played a central role in synthesis. March's treatise, a great classic of organic chemistry, connects RMgX with the preparation of the following classes of compounds: acetals, alcohols, aldehydes, alkenes, alkyl halides, arenes, amines, amides, boranes, carboxylic acids, enamines, esters, imides, mercaptans, oximes, etc. Even more striking is the "evergreen" character of this reaction. Table I selects some of the breakthroughs associated with this reagent over more than a century. This table is remarkable within the perspective of green chemistry. Some opponents to the importance of looking at synthetic chemistry under a greener perspective offer the argument: chemistry is a mature science, there is not much room left for improvements. If one searches in the Chemical Abstracts data bank at the keywords Grignard reagent one obtains 18319 answers. Despite the unavoidable conclusion that thousands of chemists performed this reaction, it clearly appears that one century was necessary to see the emergence of drastic innovations.

The situation of understanding the mechanism of formation of RMgX is along the same line. The first proposition that radical species could be involved as intermediates in this formation was done by Gomberg in 1927. Since this date several prestigious teams have invested much time and ingenuity to disentangle the complexities of this mechanism. The mechanism found in the textbooks of chemistry is reported in Scheme I.

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>1900</td>
<td>Grignard discovers the reagent</td>
</tr>
<tr>
<td>1934</td>
<td>Clement: enamin of aryl halides by alkyl halides MeC,MgBr</td>
</tr>
<tr>
<td>1953</td>
<td>Knott, Normant: THF as solvent for preparing PyMgBr, and vinyIMgBr</td>
</tr>
<tr>
<td>1967</td>
<td>Villieras: general approach to magnesium carbenoids by halogen magnesium exchange</td>
</tr>
<tr>
<td>1972</td>
<td>Rieke: highly reactive Mg metal: even Ph MgF may be directly obtained</td>
</tr>
<tr>
<td>1973</td>
<td>Kumada: cross coupling reactions of RMgX with RX</td>
</tr>
<tr>
<td>1985</td>
<td>Imamoto: cerium chloride for inducing selectively 1-2 addition of RMgX to ketones</td>
</tr>
<tr>
<td>2000</td>
<td>Knochel: halogen-magnesium exchange reaction for preparing functionalized RMgX</td>
</tr>
</tbody>
</table>
When $RX$ is an alkyl halide, the electron transfer is concerted with the cleavage of the C-X bond, whereas some aryl halides radical anions are long lived enough to be considered as intermediates rather than transition states. It is noteworthy that even recently this electron transfer mechanism has been challenged.

Even if logical, this scheme does not account directly for a certain number of observations. In terms of selectivity, one has to explain why the alkyl iodides which are the best acceptors in the halide series are generally the ones which give the lowest yields of RMgX. Among the same line the tertiary halides, which are the best acceptors in the series primary, secondary, tertiary provide the lowest yields of RMgX. For the aryl halides, one would guess that para nitro substituted halides are going to yield easily the corresponding ArMgX but they do not yield easily. One has to understand too, why very small amounts of selected compounds can inhibit the formation of RMgX under certain circumstances.

We will encounter, in the following, other observations which demand improvements or refinements of Scheme I.

Scheme II summarizes the principle of the tools that we have used throughout our studies. Radical clocks are specifically designed organic halides. The design includes an internal radical trap spatially disposed to trap intramolecularly as rapidly as possible a radical if this one is formed on the route going from the substrate (here organic halide) to the products (here RMgX). If this trapping occurs, a cyclized product will be formed as well as the main expected one which is linear. The presence of this cyclic product constitutes a proof that at least part of RMgX is formed via a route involving a radical. To render this proof compelling one has to show that another intermediate (carbanion or carbonium) would not produce the cyclic product under the conditions of experiment. On the other hand, the non observation of a cyclic product does not make it possible to directly discard the participation of the radical in the formation of the linear compound. It may simply occur that, at the bifurcation point, the rate constant of the step competing with the intramolecular trapping is high enough to prevent any production of cyclized product. For this reason, in the design of radical clocks, the searchers have designed structures in which the intramolecular trapping (or, more generally, rearrangement) displays rate constants as high as possible. This has been particularly true for the radical clocks designed to study biological problems. The label “radical clock” is associated with the structures in which the rate constant of cyclization (or rearrangement) may be precisely measured. In this case, the ratio cyclized/uncyclized U product tells also the rate at which the radical intermediate reacts to go toward the linear product. The intramolecular step which competes with the intramolecular trapping may be: coupling of the radical with another paramagnetic species, atom transfer reaction (bimolecular homolytic substitution), $\alpha$- or $\beta$-scission, addition on any double or triple bond, formation of an uneven bond (1e-bond by reaction with a Lewis acid or 3e-bond by reaction with a Lewis base, a special case of uneven bond being the bond between the radical and a diamagnetic metal surface), reductive or oxidative electron transfer.

In Scheme I, the intramolecular step supposed to compete with the intramolecular trapping is a coupling of the carbon centred radical with the MgX paramagnetic species situated either on the metal surface or in the solution. It should be clear that radical clocks provide information only about the steps which form by-products via a radical route. It is supposed that the alkyl halides studied here do not react with the formed RMgX under our experimental conditions. This supposition could no longer hold for benzyl or allylic halides. The limits of the radical clocks methodology to disentangle mechanistic complexities have been critically discussed.

The aim of this report is to extract information from mechanistic data to gain insights on some of the factors ruling the selectivity in the formation of RMgX. To do so, we will first show how the use of alkyl halide types of radical clocks led us to the study of aromatic halide types of radical clocks. The insights gained on these aromatic radical clocks will then provide fresh views to return to factors possibly playing a role in the selectivity of the Grignard reagent formation from alkyl halides. To accelerate
the reading of readers more interested into yields than into mechanisms, the parts specifically dealing with yields will be printed in italics.

Results and Discussion

Alkyl halides radical clocks

Bickelhaupt's group was the first group to use radical clocks in the study of Grignard reagent formation mechanism. Scheme III shows that cyclic products are indeed formed when the classical radical clock 6-bromo-1-hexene ($k_c = 2.3 \times 10^{-5} \text{s}^{-1}, 25 \degree \text{C}$) reacts with magnesium in THF. The amount of cyclized product is, however, drastically lower than the quantities observed when this radical clock reacts with Bu₃SnH. This very low amount was first taken as an evidence converging with the Kharasch-Walborsky hypothesis that the carbon centred radical (R' in Scheme I) is adsorbed on the metal surface as soon as it is formed. This adsorption on the metal surface would prevent the cyclization. The cyclized product would result from an equilibrium adsorbed versus "free" carbon centred radical generally shifted toward the adsorbed species. A variation of this representation would be in cage (the cage including the metal surface) versus out of cage reactivity. Another representation was later proposed by Garst. This author, extending the theoretical treatments of diffusion at the interface solid-liquid, showed that the observed small amount of cyclized and dimeric compounds do not demand the intervention of adsorption. The controversy on this problem is summarized in two Accounts and an useful discussion of this issue may be found in van Klink PhD. It is remarkable that the intervention or non intervention of adsorption of radical species on the metallic surfaces to rationalize the overall selectivity has given rise to the same kind of controversies. A good illustration of this point is provided by a look at some of the reports dealing with the mechanism of Kolbe reaction.

On our side, we synthesized a set of radical clocks displaying two characteristics: 1) they were cyclizing faster ($k_c = 10^{-3} \text{s}^{-1}, 65 \degree \text{C}$) than the 6-bromo-1-hexene one, 2) the series chloro, bromo, iodo was examined. The second point could have been considered as a waste of time. Indeed, if one returns to Scheme I, it appears that the competition intramolecular trapping of the radical versus its intermolecular reactions should not, at first sight, depend on the nature of X. Actually, the experimental results gathered in Scheme IV show that this expectation was not fulfilled. Everything was going on as if a kind of memory effect was operating.
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\[ \text{Scheme III} \]

\[
\begin{align*}
\text{DEE} & : \text{diethyl ether} & 0.19 \\
\text{THF} & : \text{tetrahydrofuran} & 0.39 \\
\end{align*}
\]

Yields are given in percents.

**Scheme IV**

Such a kind of memory effect had been reported in reactions involving electron transfer. The first case was the S_{RN1} mechanism\(^{63,64}\). Kornblum had observed that in a competition between the electron transfer route and the classical S_N2 displacement, for \textit{para} nitro-benzylic halides, the chloro substrate was yielding the highest amount of radical reaction\(^{65,66}\). The opposite order is shown in **Scheme IV**. The second case was reported by Bunnett and then conjointly studied by this author with Beckwith using aromatic centred radical clocks on reaction with the solvated electron (K/NH\textsubscript{2}/t-BuOH)\(^{67,68}\). Their results were later reinterpreted by Andrieux and Saveant\(^{69}\).

**Scheme V** shows that for this series of radical clocks the highest amount of cyclized product is obtained with the iodo substrate. With \(X = \text{Br}\) and \(I\), 17-18.5\% of the dimer of the cyclized radical are formed (not considered in **Scheme V**). This order fits with the order seen in **Scheme IV**.

As a working hypothesis, we first applied the concepts proposed by Andrieux and Saveant to rationalize the changes in selectivity reported in **Scheme IV**. To do so, one had to admit that, in THF, the magnesium surface was able to produce solvated electron\(^{70}\). The concentration of solvated electron would rapidly decrease from the metal surface to the bulk solution. There would, therefore, be a gradient of concentration for the solvated electron. When the...
halide radical clocks would approach the metal surface, the best electron acceptor (iodide) would be the first to react with the solvated electron. The poorest electron acceptor (chloride) would have to go nearer the metal surface to give birth to the carbon centred radical. This carbon centred radical being born in a medium richer in solvated electron would be transformed more rapidly into a carbanion than the radical produced by the iodo substrate. As the carbanion cyclizes far slower than the radical does, the apparent memory effect was rationalized. This explanation was not quite compelling. There was no precedent in the literature for the presence of solvated electron in the vicinity of a magnesium surface submerged in THF. We decided to study the pattern of reactivity displayed by the radical clocks studied by Bunnett and Beckwith when reacted with magnesium in THF.

Aryl halide radical clocks

Scheme VI shows an unexpected result. When the aryl halide radical clocks react with magnesium in THF almost no cyclized product is observed\(^7\). This is so for the three different halides. This result is unexpected for several reasons: the first one is that the aryl radical has been measured to cyclize at least 10 times faster \((k_{cy} = 4.0 \times 10^8 \text{ s}^{-1}, 30^\circ\text{C})\) than the alkyl radicals studied in the preceding paragraph (Scheme IV)\(^71,72\). If no other parameter intervenes one should expect a ratio cyclized/linear higher than the one shown in Scheme IV. These unexpected results were confirmed by Garst's team\(^72\). They found the same very low amount of cyclized product in THF; this amount increased slightly when the reaction was performed in diethyl ether. This team brought a quantitative plus in their report. Garst had been able to propose a model accounting for the observed selectivity in the reaction of Mg with 6-bromo-1-hexene. Applying this model to the aryl radical clocks he expected more than 70% of cyclized product formation.

Why so little cyclization? Returning to Scheme I the simplest explanation would be to suppose that aryl radicals have the possibility to react about 100 times faster than alkyl radicals with MgX radicals. Such a hypothesis has no special support from the literature. A more attractive explanation was offered by a discovery of Bickelhaupt's group\(^76\). To explain a consistent and extensive set of rearranged by-products when selected aromatic halides reacted with magnesium, this group had proposed that one of the reactions possibly competing with the intramolecular cyclization of the aryl radical was its reduction at the metal surface\(^31\). Aryl carbanions would then be on the route aryl halides to ArMgX. Aryl radicals are known to be far better oxidizing agent than alkyl ones\(^75\). Within Bickelhaupt's proposition, the reason why the aryl radical clocks are yielding so little cyclization could be that they accept an electron from the metal surface faster than they cyclize.

This was the explanation that we favoured\(^76\). For the same observation, Garst proposed another one. One important difference between aryl and alkyl halides is the average lifetime of their radical anions. This lifetime is definitely longer for aryl halide radical anions although some of them could cleave with rate constants in the range of those proposed for alkyl halides\(^77\). Based on this point, Garst proposed that these aryl radical anions are further reduced into dianions on the route toward ArMgX\(^73\). These dianions (intermediates or transition states) would then cleave into an aryl carbanion and a halide anion. We have discussed elsewhere the reasons why we do not find this proposition compelling\(^78\).

One of these reasons is that, among the numerous publications dealing with the reactivity of aryl halides at a cathode only one proposes that dianions could be involved\(^79\). Pulse radiolysis studies confirm this general trend\(^80\). Electrochemical studies of aryl halides provide, furthermore, a fresh view of the succession of events which rule the fate of an aryl radical formed in the vicinity of the cathode when aryl halides are electrolysed. Savéant and Amatore
proposed a detailed model to describe what occurs in the vicinity of a cathode when an aryl halide is submitted to electrolysis. The succession of steps is shown in Scheme VII.

The physical model partly overlaps with Garst's diffusion model. The aryl halides radical anions would be produced in a thin layer (about 10 Å) of liquid covering the electrode. Thanks to their lifetime, they could diffuse away toward the bulk. During this diffusion, they would cleave into aryl radicals and halide anion. The longest lived radical anions (chlorides) would cleave at the greatest distance from the metal surface; therefore they would have a smaller probability of diffusing back to the metal surface where they are transformed into carbanions. These carbanions reacting with MgX⁺ would yield RMgX⁻. The mechanism shown in Scheme I would therefore be replaced by the one shown in Scheme VIII.

Thus, in contrast with the solvated electron model described in the preceding paragraph, the aryl chloride radical clocks should yield the highest amount of cyclized product. Expressed in terms of yields of RMgX this means that when the radical by-products were expected to be more important for the alkyl iodides in the series of halides, the reverse should be true for the aryl halides. This statement could be weakened because subtle differences revert this order. The electrochemical model leads to a fresh view of the factors affecting the overall selectivity in the preparation of ArMgX. Because the fate of the aryl radical critically depends upon the distance from the magnesium surface where it is formed, the overall selectivity amounts to an averaged value of a series of little flasks. In every flask, a specific selectivity is settled as shown in Figure 1. For the aryl halides that we studied, the flask in close proximity to the surface weights the most in the average ruling the overall selectivity. This is because the radical anions of the studied radical clocks are short lived. Furthermore, we have shown that the reducing power developed in the vicinity of the surface (heterogeneous electron transfer) may be higher than the one obtained in the bulk (homogeneous electron transfer) even when the reducing reagent is the solvated electron. In short, the main reason why less cyclized products were formed with the aryl radical clocks than with the slower alkyl radical clocks seems to be the high oxidizing power of the aryl radical.

The mechanism proposed in Scheme VIII has several consequences in terms of yields of ArMgX although the description that we give here considerably oversimplifies the electrochemical model. The structure of the radical clock, the viscosity of the solvent, the rate of cyclization of the radical, play a role in ruling the ratio cyclized/linear compounds. We discuss these refinements in another report and a full treatment is given in Amatore's review.

Scheme VIII helps in understanding why ethers are the best solvents for preparing Grignard reagents. If naked carbanions are intermediates on the route toward RMgX, any species able to protonate them will compete with their reaction on MgX₂. Tables of pKₐ values show that among the available solvents, ethers are the rare ones with a donor number higher than alkanes displaying a very low acidity.

Several explanations were proposed to explain the effect of entrainment used to prepare ArMgX products which could not be obtained by the simple Grignard procedure. Garst provided an original one 60 years after the discovery of this effect. The addition of dibromoethane or any reactive alkyl halide to the medium would have, as main consequence, to enrich the medium in MgX₂. This salt would have several beneficial effects. One would be to increase the polarity of the medium which accelerates the electron transfer steps. The second would be to
This detail is: keep an excess of the MgX₂ salt with respect to the reducing alkali metal. This excess will, then, play its entrainment role in the step “preparation of the Grignard reagent”. Otherwise, some of the highly basic carbanion could abstract a proton from the medium. One remarkable feature of Rieke’s magnesium does not seem to be directly rationalized within the framework of Scheme VIII. This feature is the beneficial salt effect associated with the addition of potassium iodide to the solution. A tentative explanation could have to do with the corrosion model of Grignard reagent formation. In this model, the metal surface is divided into coupled anodic and cathodic sites. The anodic dissolution of magnesium could be catalyzed by IK in a way reminiscent of the solid-liquid phase transfer catalysis. This point deserves further study using radical clocks.

With this fresh view expressed in Scheme VIII and Figure 1 it is tempting to return to alkyl halide radical clocks and check if this scheme could be extended to these substrates.

Return to Alkyl Halide Radical Clocks

The cathodic reactivity of 6-bromo-1-hexene in THF was not reported in the literature. Collaboration with Combellas-Kanoufi group allowed filling this gap. The radical clock studied in the Grignard reagent formation by Bickelhaupt (Scheme III), when reduced at a carbon cathode in THF as a solvent, yields a slightly higher yield of cyclic product (9%). This hints at a certain similarity between the succession of events occurring near the cathode and near the magnesium surface. We discussed the limits of this similarity elsewhere. In the present
In this process, some of the carbanions formed in the vicinity of the cathode, could act as reducing agents toward the RX molecules diffusing from the bulk toward the cathode (step 3). The consequence of this autocatalytic process would be to increase the relative quantity of radicals. Such an increase would be associated with more cyclized products for alkyl halide radical clocks and more radical by-products in the preparation of the Grignard reagent of the corresponding alkyl halides. The best chances of having an efficient step 3 would be for R carbanions with good reducing properties and RX with good acceptor properties. On the side of carbanions, this condition discards aromatic carbanions with respect to alkyl ones. On the side of alkyl halides, the best acceptors are the iodides and, for the carbanions R involved in step 3, the best reducing carbanions would be the tertiary ones. This argument should be refined if one remembers that too different rates of steps 2 and 3 lower the turnovers. The systems leading to the best turnovers are expected to display the highest quantities of cyclized products for alkyl halide radical clocks and autocatalysis could contribute in explaining the leaving group effects shown in Scheme IV.

On the side of yields, the autocatalytic scheme could explain why alkyl iodides generally yield lower yields of RMgX than the corresponding chlorides. In the same line, tertiary halides give lower yields than primary ones. In a careful old work, Gilman’s group performed an interesting series of experiments. For a given halide, they would try to prepare RMgX according two procedures. In the first one, the alkyl halide was added very rapidly to a suspension of magnesium in diethylether; in the second, the halide was very slowly added to the same suspension. Clearly, the first procedure corresponds to a higher concentration of RX in the vicinity of the metal.

<table>
<thead>
<tr>
<th>Halide</th>
<th>Slow addition (%)</th>
<th>Fast addition (%)</th>
<th>Difference (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>EtBr</td>
<td>93</td>
<td>87</td>
<td>6</td>
</tr>
<tr>
<td>i-PrBr</td>
<td>84</td>
<td>79</td>
<td>17</td>
</tr>
<tr>
<td>t-BuBr</td>
<td>25</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>n-BuCl</td>
<td>91.2</td>
<td>90.6</td>
<td>1</td>
</tr>
<tr>
<td>n-BuBr</td>
<td>94</td>
<td>79</td>
<td>16</td>
</tr>
<tr>
<td>n-BuI</td>
<td>85.6</td>
<td>67.8</td>
<td>17.8</td>
</tr>
</tbody>
</table>

Difference = [(Slow addition – Fast addition)/Slow addition] x 100
first procedure favours the autocatalytic participation. These authors observed no significant difference in RMgX yields between the two procedures when the substrates were alkyl chlorides. In contrast, when an alkyl iodide was submitted to this set of experiments, a clear difference in yields was observed between the two procedures. In the series EtBr, n-BuBr, t-BuBr the largest difference was found for the third one (Table II). The convergence is rather striking. To be more compelling, one would have to check that the reported differences cannot be rationalized in the framework of a reaction between the starting substrates and RMgX, although it is generally accepted that, for the alkyl halides present in Table II, this reaction is slow, but it is known that in the S_n2-E2 competition, the importance of E2 elimination is in the order I>Br>Cl. Also, several examples of the Grignard reagent acting as a base have been reported.

**Conclusion**

We started this presentation with an apparently simple aim: establish connections between yields (selectivity) and the possible mechanisms for one of the most used reactions in organic chemistry. Even without going into the details some very general remarks emerge. The first one is that the science of reactions is a very slow science; it took respectively 34, 72, 100 years to pass i) from the alkyl halides to the aryl ones in the preparation of Grignard reagents, ii) from relatively active magnesium to a really reactive one, iii) from poorly functionalized substrates to functionalized ones. Grignard reaction is not an exception. Just consider the number of years which separate the discovery of the Diels Alder reaction and its first intramolecular extension to total synthesis. In the perspective of a Greener chemistry, it would be important to examine the question: How could we increase the pace of innovation in this field? The second one is that simple guesses, not supported by in depth experimental studies, may be hazardous. Seeing that aryl halides were, at first sight, less easy to transform into ArMgX than alkyl halides could have suggested that the yields of ArMgX would in general lag behind AlkylMgX. The reverse is probably true. If the autocatalytic hypothesis contributes in the explanation of higher quantities of radical by-products going from alkyl fluoride to alkyl iodides, one could again meet a counter-intuitive situation. The best yields of alkylMgX could be, after optimization, obtained from the fluoroalkyl.

The gap between the various components of chemical science is, one more time, illustrated by this presentation. To better understand the roots of selectivity of Grignard reagent formation, the tools were available in Electrochemistry since 1980, they were not used as such for more than 25 years. It is now clear that every progress done in the modelisation of the molecular events occurring in the vicinity of the cathode or the anode is relevant to the optimization of the yields of reactions involving the reactive dissolution of a metal in solution.

There is still a long way to reach a satisfactory understanding of this chemistry of reactive dissolutions. This is the reason why we finish with a series of question marks. What are the consequences of the corrosion-like approach of Grignard reagent formation? Why traces of inhibitors may stop a reaction which is not a chain reaction? Why the inhibitor dioxygen inhibits some Grignards but does nothing to others? What is the molecular representation of what is called active sites on the metal surface? Why do the shape and density of pits observed at the magnesium surface depends on the nature of X for various RX?

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