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The use of organomagnesium compounds in preparative organic chemistry

Nobel Lecture, December 11, 1912

It is not without some apprehension that I acknowledge the great honour which has been done me by giving an account of a subject so specialized in its essence, so vast in its applications, as that on which I have been engaged for the past twelve years and more.

If I had to speak to you only on my own research into organic magnesium compounds my task would be fairly simple, but, since my original discovery, so much other work has been done independently of and parallel with mine that now I cannot very well leave out any one brick from the edifice if I am to enable you to see it in its true perspective.

But alas! I should have to survey the entire subject of organic chemistry, with its complicated formulae and with its forbidding names - which are liable to daunt even the initiated. To do this would certainly be to abuse the kindness of the eminent audience around me and I shall do my best not to be guilty of such discourtesy.

My learned colleague, Professor Sabatier, has just shown you how certain metals can serve momentarily as a carrier for an element such as hydrogen in order to transform it into an organic compound. Now, there are other metals which can serve as carriers for a complete organic radical and enable it to be transferred to another molecule.

Such compounds, which result from the union of a metal with one or more organic radicals, are called organometallic compounds. These, with a fairly large number of metals, have been known for a long time, though they do not all lend themselves equally readily to the practical application that I have just mentioned. Some of them, those of the alkaline metals sodium and potassium, are very active but very unstable and difficult to prepare directly - in short they are unsuitable for practical application. Others, such as those of mercury, err in the other direction - they are too stable and will react in only a small number of cases. In fact, throughout the second half of last century chemists had at their disposal only a single group of organometallic compounds, namely the organic zinc compounds.

Typical of these substances, which were discovered by Frankland in 1849, is zincdimethyl, $Zn(CH_3)_2$. They make possible several excellent methods of synthesizing hydrocarbons, secondary and tertiary alcohols, ketones and hydroxy acids. However, they were still very far from satisfying all requirements of the chemist. There are, in fact, very few organic zinc compounds; only the first members of the series, which correspond to the simplest organic radicals, can be prepared without too much difficulty, but they have the disadvantage of being spontaneously inflammable in air and are consequently very dangerous to handle. Apart from this, the reactions which they give do not lend themselves to wide use, as some of them take several weeks or even months to complete, and then the yields are very often unsatisfactory.

It was therefore natural that we should seek to replace the zinc compounds by other more numerous ones, easier to prepare and handle and with greater reactive capacities.

The one metal to which our thoughts inevitably turned was magnesium, in view of its analogy with zinc and of its much greater reactivity due to its appreciably lower atomic weight. However, it could not be studied properly from the point of view with which we are concerned until it could be prepared in a suitably pure state.

It was then that the researches conducted by Lohr, Fleck and Waga at the Lothar Meyer Laboratory during the years 1891 to 1894 showed that symmetrical organic magnesium compounds were not liquid, like those of zinc, but solid, almost insoluble in all neutral solvents and spontaneously inflammable, not only in air but also in carbon-dioxide gas. Thus it was difficult to show their reactive capacities, and the results obtained were rather discouraging.

These compounds therefore seemed destined to fall back into oblivion, when in 1898 my eminent chief, Professor Ph. Barbier of Lyons, hit upon the idea of trying out on magnesium the method which Saytzeff had successfully adapted to zinc in a certain number of cases. With this method the organometallic compound no longer has to be prepared in advance; all that is necessary is to bring the two reactants together in the presence of the metal. Professor Barbier thus succeeded in causing a reaction between a ketone with a $-COCH_3$ group, the natural methylheptenone, and methyl iodide. Now this reaction was completely impossible with zinc. It therefore revealed that magnesium possesses special properties and a study of it was made at the Laboratory although the results obtained were so erratic that Professor Barbier confined himself to publishing the preceding reaction.

Almost two years later my chief advised me to resume this study in order to perfect his reaction, but I soon came up against the same difficulties, and it was then that I abandoned this procedure, which lacked flexibility, and went back to preparing the organic magnesium compounds in advance, but this time not by Löhr's method, which experience had shown to be unsatisfactory, but by a method which had formerly been tried by Frankland and by Wanklyn for organic zinc compounds. By heating the methyl iodide with the zinc in the presence of anhydrous ether these scientists had obtained compounds of the form $Zn(CH_3)_2 \cdot O(C_2H_5)_2$ which displayed more or less the same properties as the non-ethereal compound; unfortunately, the need to heat in a sealed tube and then to distil the solid mass produced by the reaction robbed these new compounds of any practical value.

I thought that with magnesium, which is more electropositive than zinc and has greater reactivity, the same reaction would be easier and more complete. And this in fact was the case, for I found that magnesium in the presence of anhydrous ether attacks alkyl halides at ordinary temperature and pressure and that this reaction, which is more or less total, gives a compound which is completely soluble in ether. This was the fundamental discovery which placed in the hands of the chemist quite an important series of new organometallic compounds, and it is these compounds, together with their principal applications, which I am going to attempt to describe to you.

As I have just said, the preparation of organic magnesium compounds is very simple. There is only one essential precaution to take; the operation must be carried out in a medium free from moisture and atmospheric oxygen.

The apparatus consists of a spherical flask surmounted by a good reflux condenser and a bulb with a tap. Let us assume that we are preparing the first member of these compounds. One gram-atom of magnesium (24 g), for instance, is placed in the flask, and one molecule of methyl iodide is dissolved in an equalvolume of anhydrous ether. By means of the tap 25-30 cubic centimetres of this solution are allowed to drop from the bulb on to the magnesium. Almost immediately there is a very intense reaction, which is moderated by adding, all at once, 200-250 cubic centimetres of anhydrous ether to the flask; it is then maintained by allowing the rest of the reaction mixture to drip on to the magnesium. The operation is completed by heating for a few moments, if necessary. Under these conditions all the magnesium disappears and we finally get a perfectly fluid and colourless liquid, although at first it shows a slate-coloured cloudiness due to extremely minute particles of iron from a slight impurity in the magnesium used.

The compound prepared in this way presents all the characteristics of an organometallic compound: water decomposes it with violence; it fixes oxygen and carbon dioxide gas, and it reacts vigorously with almost all the functional groups of organic chemistry. But it already possesses one advantage over the organic zinc compounds, namely that it can be exposed to air without igniting. It is therefore no more dangerous to handle than ether itself.

When prepared in this way we can use it without making any alteration to the apparatus; in fact it is usually sufficient to allow the substance which has to be brought into reaction, or rather its ethereal solution, to drip from the bulb. Then, if necessary, the reaction is completed by allowing the materials to stand in the cold or by heating them for some hours in a water-bath.

However, before studying the results which we can obtain in this way we must take a look at the reagents - from the point of view of their form and their variety - which we shall be using.

Whereas the zinc compounds are symmetrical, i.e. the metal, by its two valences, has fixed two identical radicals to give $Zn(CH_3)_2$, $Zn(C_2H_5)_2$, etc., this apparently is not the case with the organic magnesium compounds. Experience shows, in fact, that the halogen, which was originally joined to the organic radical, still accompanies this latter in all the compounds which the organic magnesium compound forms by addition; it therefore appears to be intimately linked with it.

Moreover, when an organic zinc compound gives an addition compound with an aldehyde molecule, for example, only one of the two radicals becomes always fixed to the organic molecule; the other remains attached to the metal and is lost to the reaction. With an organic magnesium compound, on the other hand, the whole of the organic radical can be transported to the other molecule. For these two reasons I thought it necessary to adopt for these reagents the general formula:

$$RMgX$$

in which R is an organic radical and X is a halogen; and in view of this constitution I have called these compounds *mixed organic magnesium compounds.*

Experience then showed that these compounds did not simply dissolve in ether but combined with one or even two ether molecules (Tschelinzeff), this probably resulting from the fact that the oxygen of the ether can become tetravalent; these are therefore oxonium compounds (A. Baeyer). This moreover agrees with the fact that the nitrogen atom of the tertiary amines may, by becoming pentavalent, also serve as a carrier for the organic magnesium compounds (Tschelinzeff).

Let us see what freedom we have in our choice of R and X. We observe here that magnesium is greatly superior to zinc. Whereas, generally speaking, zinc reacts suitably only with the first members of the alkyl iodides, with magnesium it is possible to use bromides, iodides and in many cases chlorides. These latter halides may sometimes even be more suitable, especially where the alkyl halide tends to lose a molecule of halogenated acid to give an ethylenic hydrocarbon, for instance, for tertiary butyl chloride and for pinene hydrochloride.

With regard to the choice of R one might almost say that the only limit is the number of monohalides themselves, at least in so far as saturated, aliphatic, cycloalkane or phenolic monohalides are concerned. But the reaction is generally easier and more regular with the primary than with the secondary and still more so than with the tertiary derivatives.

Moreover, we can go still further, for in a certain number of cases the existence of another functional group in the molecule does not prevent the reaction from being normal, which is usually the case with the ethers of alcohols or of phenols and in some other particular instances.

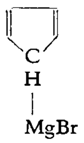
The presence of a double bond is no obstacle either, except in the case where it is in the vicinity of the halogen, as in the derivatives of allyl alcohol. The difficulty here is that this double bond increases the reactive capacities of the organometallic compound ; this can be obviated by using the same procedure as for zinc, i.e. the Barbier method.

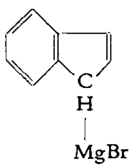
But this is not all. Organic compounds exist in which a hydrogen atom, joined to the carbon, acquires acid properties as a result of the proximity of certain functional groupings. The most sharply characterized of these substances are the true acetylenic hydrocarbons, which react with the organic magnesium compounds by double decomposition; for instance:

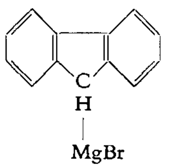
$$CH_3-C\equiv C-H + C_2H_5MgBr \rightarrow C_2H_6 + CH_3-C\equiv C-MgBr$$

We thus get, as Jotsitsch has shown, acetylenic magnesium compounds which possess all the properties of ordinary organic magnesium compounds.

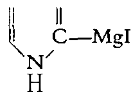
I for my part have shown that two double bonds suitably situated can also give to a hydrogen atom sufficient mobility to produce the above reaction; this is what happens with cyclopentadiene and the derivatives of its ring system, indene and fluorene, which give organic magnesium compounds (V. Grignard and Ch. Courtot).



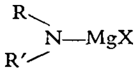




Finally B. Oddo established that the same also applies to the compounds possessing the pyrrole bond and that by the same mechanism these give magnesium compounds of the following type:



On the other hand, the primary or secondary amino compounds also react through the hydrogen combined with the nitrogen and give compounds of the general formula



$$\mathrm{(R)(R')N{-}MgX}$$

which have similar properties to those of the preceding compounds. These are the amino magnesium compounds of L. Meunier.

This is already a considerable range of reagents; but there are still more.

The question arose, whether it would not be possible to produce the organometallic functional group twice, starting from a dihalogenated derivative. I first tried (Tissier and Grignard) ethylene bromide and trimethylene bromide, but in these two cases a single atom of magnesium removes the two atoms of bromine by liberating the divalent hydrocarbon radical. It could nevertheless be predicted that the normal reaction would become possible if the two halogen atoms were sufficiently far away. I was more successful, in fact, with 1,5-dibromopentane (V. Grignard and G. Vignon), then with dipentene dihydrochloride (Ph. Barbier and V. Grignard), which gave me the expected dimagnesium compounds. Such compounds are-now known from position 1-4 to position 1-11 (Blaise, Hamonet, Braun).

Finally, acetylene itself usually gives a dimagnesium compound by Jotsitsch's reaction.

It should not be thought, however, that all these reactions give quantitative yields. In reality, more or less important secondary reactions occur in a number of cases. The most consistent of these is that which results from removal of the halogen, simultaneously from two organic halide molecules, by a magnesium atom, accompanied by joining of the two radicals; this is the same reaction as that discovered by Wurtz, using sodium:

$$2RX + Mg \rightarrow MgX_2 + R\text{–}R$$

This reaction is insignificant with the first members, but it increases with the molecular weight, at least in the aliphatic series.

Another secondary reaction results from elimination of a molecule of halogen acid with production of a double bond. This reaction sometimes occurs with the secondary and especially the tertiary halides, but it can generally be attenuated, as I have already said, by using the chloride rather than bromides or iodides.

Let us now see how all these reactions can be applied. As I have just mentioned, they react with almost all the functional groups and if I mentioned every case I should try your patience by presenting formula upon formula. I shall therefore do no more than outline the principal results.

The reactions of organic magnesium compounds are of two kinds - reactions of substitution and reactions of addition.

It is in this way that these compounds react with substances containing one or more atoms of reactive hydrogen, irrespective of whether this hydrogen is joined to the carbon, as we have already seen, or to the nitrogen, as in ammonia, the primary and secondary amines, the amides, etc., or again to the oxygen as in alcohols, phenols, acids and pseudoacids, etc. The organic radical is then released as hydrocarbon, the volume of which, if one is careful to take one of the first members, can be used for making a very accurate determination of the reactive hydrogen (Tschugaeff, B. Oddo, Zerewitinoff).

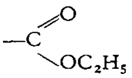
The action of water, in particular, can be used for preparing hydrocarbons (Tissier and Grignard).

The organic halogenated derivatives and, more specifically, the allyl halides (Tiffeneau), the chloromethyl esters (Hamonet), readily react, accompanied by joining of the organic radicals, to give hydrocarbons or ethers.

The reactions of addition take place with a divalent element such as oxygen, which gives alcohols or phenols, and sulphur which results in mercaptans, thiophenols, etc. ; but they are of more special importance with the functional groups in which two atoms are united by a multiple bond. Such are:

$$(C{=}O)'' \qquad (C{=}S)'' \qquad (C{\equiv}N)' \qquad (N{=}O)' \text{ or }''' \qquad (S{=}O)''$$

In all these cases one of the bonds in the functional group is broken, whilst the radical R becomes fixed to the element of maximum valence and MgX becomes fixed to the other. However, the organic magnesium compounds do not become fixed to an ethylenic or acetylenic bond. Finally, with certain more complex functional groups, such as the ester group



addition to the CO and substitution of the OC_2H_5 group, which is replaced by R, may take place simultaneously. But owing to the exceptional activity of the organic magnesium reagents it is somewhat difficult to separate these two phases and to prevent the reaction from continuing until it is complete.

What are the results of these two reaction processes?

The aldehydes give secondary alcohols, except for formaldehyde which gives primary alcohols. The ketones result in tertiary alcohols.

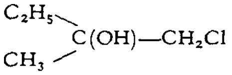
Esters will usually give tertiary alcohols, except in the case of formic esters, which give secondary alcohols.

The position is the same, generally speaking, with acid chlorides and acid anhydrides.

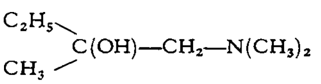
The presence of double bonds in the aldehyde, ketone or ester molecule does not normally disturb the reaction.

Thus, for instance, with terpene aldehydes, such as citral and citronellal, it has been possible to produce a series of alcohols used in perfumery.

The reaction is still normal despite the presence of halogens; thus with ethyl-magnesium bromide monochloracetone produces alcohol:

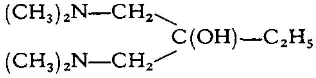


which is easily transformed into a tertiary amine:



which is the parent substance of *stovaine* (Fourneau).

Likewise, starting with dichloracetone, we arrive in a similar manner at the diamino alcohol:



$$\begin{matrix}(CH_3)_2N{-}CH_2\searrow & \\ & C(OH){-}C_2H_5 \\ (CH_3)_2N{-}CH_2\nearrow & \end{matrix}$$

the parent substance of *alypine* (Farben Fabr. vorm. Fr. Bayer).

These two artificial alkaloids are useful substitutes for cocaine, possessing the same anaesthetic properties but with less toxicity.

The many alcohols which can be prepared by the above methods can, in turn, be used as *raw* materials for the preparations of ethylenic hydrocarbons.

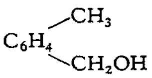
Some of these alcohols, especially the tertiary alcohols, lose a molecule of water spontaneously during the reaction; but in other cases thiseffect can be induced by means of an excess of organic magnesium compound or by other methods (Klages).

It should be mentioned that isoprene and hydrocarbons of the same type which yield rubbers by polymerization have been prepared by the magnesium methods.

An important series of hydrocarbons is particularly interesting from the theoretical point of view - these are hydrocarbons obtained from magnesium compounds of cyclopentadiene, indene and fluorene. Owing to their constitution, all these hydrocarbons are coloured, from pale yellow to dark red. They have thus become much more easily accessible and in much larger numbers than was the case with Thiele's method (V. Grignard and Ch. Courtot).

A much more curious characteristic than spontaneous splitting-off of water is the following:

If we try to apply the formaldehyde method to benzyl magnesium chloride, $C_6H_5\text{-}CH_2\text{-}MgCl$, a transposition phenomenon occurs and we get the orthotoluenic alcohol



$$C_6H_4\begin{matrix}\nearrow CH_3 \\ \searrow CH_2OH\end{matrix}$$

(Tiffeneau and Delange).

I succeeded in getting round this dificulty by causing bromobenzene magnesium to react with ethylene monocblorohydrin:

$$C_6H_5MgBr + ClCH_2{-}CH_2OH \rightarrow C_6H_5{-}CH_2{-}CH_2OH$$

I thus obtained primary phenylethyl alcohol, a fundamental constituent of attar of roses, which had previously been nothing but a laboratory curiosity, and at the same time I established the first method whereby in aromatic compounds a halogen, and consequently another functional group, can be introduced at the end of a side-chain containing more than one carbon atom.

The technique of organic chemistry laboratories has for some years been enriched by many methods of aldehyde synthesis, to which the organic magnesium compounds have made a large contribution. These compounds can in fact be obtained:

(1) By the action of formic esters at a temperature of -50°C, which limits the reaction to the first phase (Gattermann and Maffezzoli).

(2) By means of orthoformic ester, which results in readily hydrolysable acetals (Bodroux, Tschitschibabin).

(3) By decomposition, with dry oxalic acid, of ethers of α-glycols which themselves are prepared by the action of the organic magnesium compounds on phenoxyacetic ester, $C_6H_5O \cdot CH_2CO_2C_2H_5$; ethoxyacetic ester, $C_2H_5O \cdot CH_2CO_2C_2H_5$; and ethoxyacetones with the general formula $C_2H_5OCH_2\text{-}CO\text{-}R$ (Behal and Sommelet).

(4) By the action of disubstituted formamides, for instance diethylformamide $(C_2H_5)_2N\text{-}COH$ (Bouveault).

(5) By means of ethoxymethylene aniline $C_2H_5OCH{=}N\text{-}C_6H_5$ (Monier-Williams).

Likewise for the production of ketones we now have several methods :

The action on nitriles (Blaise) and amides (Beis) as well as the gradual reaction, at low temperature, with acid chlorides (Darzens) or with acid anhydrides (Fournier).

The nitriles themselves can be obtained by means of cyanogen chloride and cyanogen (Grignard). -This latter method is even the only regular one for the cycloalkane series.

Finally, acids are easily and very widely prepared by the action of carbon dioxide (Grignard).

When the oxygen is replaced by sulphur the character of the reaction remains the same: carbon disulphide gives dithiocarboxylic acids $R \cdot CS \cdot SH$ (Houben), whilst carbonyl sulphide gives thiolic acids $R\,CO.SH$ (Weigert).

The position is still the same when the carbon itself is replaced by sulphur; sulphur dioxide, by the same mechanism, gives sulphinic acids $R \cdot SO \cdot OH$ (Rosenheim and Singer).

The non-carbon functional groups can also give interesting results. Thus, nitrogenous ethers and nitro derivatives give disubstituted hydroxylamines (Moureu).

But we can go still further by working on molecules of complex function.

If a molecule has two identical functions the reaction will normally affect the two functions simultaneously. For example, diketones give ditertiary glycols, except in the case of β -diketones which react only through their enolic hydroxyl function (Valeur, Zelinsky).

Among the diketones the quinones must be mentioned separately. Benzoquinone does not react, but its higher homologues react through one CO only (Bamberger and Blangey).

The pseudoquinones can react through their two groups, and anthraquinone, in particular, has given important results (Haller, Guyot).

The di-esters likewise lead to ditertiary glycols (Valeur).

Cyanoacetic ester reacts only through its nitrile function and gives ketonic acids (Blaise).

But in other cases, where the two functions are different, I have shown that by reversing the usual procedure, that is to say, by allowing the magnesium compounds to fall little by little into the solution of the compound with which it has to react, it is possible to induce the two functional groups to react successively, starting, of course, with the more negative.

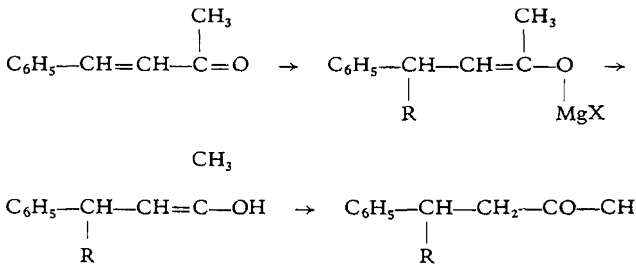
Thus the ketonic esters gradually lead to acid alcohols, then to ditertiary glycols. Here again the β -ketonic esters are a special case because they react in the enol form.

Likewise ethyloxalyl chloride gives α -hydroxy acids, then ditertiary glycols.

With regard to ketonic esters I must mention a new group of very interesting syntheses, namely asymmetrical syntheses. When we transform a ketonic group into a tertiary alcohol group it often happens that the carbon of the carbinol becomes asymmetrical, but it is very clear that under normal conditions there is no reason why one of the optical isomers should predominate over the other; thus we get the racemic mixture. But if we create temporary asymmetry in the molecule the reaction of the magnesium compound can itself become asymmetrical and cause the two enantiomorphs to have different proportions. This is what Mc Kenzie did. He esterified benzoylformic, pyruvic and laevulic acids by *l*-menthol, and he caused the organic magnesium compound to react with the CO of each of these active esters. Then by saponifying the products obtained in order to eliminate the menthol he obtained slightly laevorotatary alcohol acids.

Finally, the organic magnesium compounds can produce in certain cases a phenomenon of apparent fixing to an ethylene bond. This will happen when the double bond is near a functional group with a multiple bond, in position α–β, called a "conjugated position".

I observed this phenomenon for the first time in the case of ethylidene-acetylacetic ester and it has since been met with by several chemists (Hailer and Bauer, Blaise and M. Courtot, etc), but the main systematic study of it was made by Kohler and his pupils. Kohler's experiments clearly demonstrated the mode of fixing which I had assumed in the case of ethylidene-acetylacetic ester: the magnesium compound is never added to the ethylenic double bond but to the two extreme atoms of the conjugated system, i.e. at 1-4. For instance, under suitable conditions, with benzylidene-acetone, we get:



$$C_6H_5-CH{=}CH-\overset{CH_3}{C}{=}O \rightarrow C_6H_5-\underset{R}{CH}-CH{=}\overset{CH_3}{C}-\underset{MgX}{O} \rightarrow$$

$$C_6H_5-\underset{R}{CH}-CH{=}\overset{CH_3}{C}-OH \rightarrow C_6H_5-\underset{R}{CH}-CH_2-CO-CH_3$$

And the final result is the same as if the magnesium compound had become fixed to the ethylene bond without involving the CO.

At the same time, the normal reaction with the CO takes place. These two reactions are independent and can occur in very variable proportions depending on the working conditions, the nature of the unsaturated compound and the nature of the magnesium compound.

To complete this survey of the most important reactions I must also mention the substitution reactions produced by the metallic or metalloidal derivatives, and in particular the halogen derivatives. A large number of organometalloidal and organometallic compounds have been prepared in this way.

Of all this research I shall mention only, in the first group, that with the halogen derivatives of silicon (Dilthey, Kipping) and with orthosilicic ester (Khotinsky and Seregenkoff), which has made a substantial contribution to organic silicon chemistry.

In the second group, among the organometallic compounds, we must mention in particular the mixed organic zinc compounds which Blaise obtained by the action of anhydrous zinc chloride:

$$RMgX + ZnCl_2 \rightarrow RZnCl + MgXCl$$

This is the only method at present known of producing organic zinc aromatics.

Such, ladies and gentlemen, are the principal syntheses which we are able to carry out by means of magnesium; there are in fact other less important ones which I have had to pass over in silence.

The organic magnesium compounds have indeed given rise, in organic chemistry laboratories, to an enormous amount of work at present spread among more than seven hundred papers. As a result, zinc has to a large extent been dispossessed of its preserves. It still has the Saytzeff and Reformatsky reactions, although it also shares these with magnesium; following the research conducted by Blaise, however, it appears to be the metal of choice for the synthesis of ketones by Freund's method, i.e. by means of acid chlorides.

And now a question arises!

With this extraordinary faculty of being able to adapt itself to the most varied chemical molecules, might magnesium not be capable of playing a very active part in the natural syntheses of organized matter?

Willstatter in fact recognized that this metal accumulates, so to speak, in a substance possessing considerable catalytic activity, namely chlorophyll. He isolated from the most varied chlorophylls compounds containing up to 3.5% magnesia. And from his studies he concluded that compounds analogous to the organic magnesium compounds must form and that the absorption of carbon dioxide gas by chlorophyll would in every way be comparable to the Grignard reaction. He thus came to compare the chlorophylls of leaves with the haemoglobin of animals; hence for living matter there would apparently be two transformation cycles - life due to synthesis by means of magnesium and life due to oxidation by means of iron.

However, it remains to be discovered in what form magnesium can adapt itself to these reactions in such an environment, an environment so different from that in which we are accustomed to seeing it triumphant.

This is the problem for tomorrow!