

The Importance of (Intramolecular) Solvation in Organomagnesium Chemistry*

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While in the 'normal' coordination behaviour of organomagnesium compounds tetra-coordination of magnesium seems to be dominant, higher coordination numbers as well as unusual reactivity can be achieved by the introduction of (poly)ether functionality which is capable of intramolecular 'solvation'. Thus, (i) penta- or hexa-coordinated magnesium has been found in aryl Grignard reagents **1** with one polyether side arm; (ii) during the formation of **1** or of the crown ether Grignard compounds (2-bromomagnesium-1,3-xylene)-15-crown-4 (**4**) and (2-bromomagnesium-1,3-xylene)-18-crown-5 (**5**) from the corresponding aryl bromides and magnesium, ether cleavage occurred and furnished valuable insight into details of the formation mechanism; and (iii) under rather mild conditions, diphenylmagnesium or phenylmagnesium bromide underwent reactions which are normally restricted to much more reactive organometallic compounds such as organolithiums: halogen–metal exchange, metalation of an aromatic carbon–hydrogen bond, or cleavage of an arylalkyl ether bond.

Structures and coordination modes of organomagnesium reagents

The formation of the famous Grignard reagents, i.e. alkyl- or aryl-magnesium halides, from organic halides and metallic magnesium,¹ is traditionally presented² as described in eqn. (1).



Taken at face value, the formulation as R–Mg–X would imply that magnesium is divalent and dicoordinate. If so, these species are expected to be linear, and this prediction is independent of their description in terms of sp-hybrid-

ization,³ VSEPR theory, or *ab initio* calculations.⁴ Indeed, the few experimental data available all reveal linear structures (Table 1).

There are two reasons why experimental data on simple monomeric magnesium compounds are so scarce. In the first place, owing to their highly polar character, they have low volatility; organomagnesium compounds in particular tend to decompose before attaining an appreciable vapour pressure, so that gas-phase electron diffraction measurements are not possible. On the other hand, structure determination in the solid state is difficult because unsolvated organomagnesium compounds are usually polymeric and, with one exception,⁶ microcrystalline or amorphous.⁷ The few available data suggest that most of these compounds occur as polymeric chains composed of four-membered rings; these are connected in a spiro fashion at the tetra-coordinated magnesium atoms which are bridged by the organic group through a 3-center-2-electron bond. Those magnesium–carbon bond distances are about 2.25 Å (Scheme 1).

However, simple as the above-mentioned structures may be, they are exotic in the sense that organomagnesiums do not normally exist in the unsolvated state. Rather, as is well

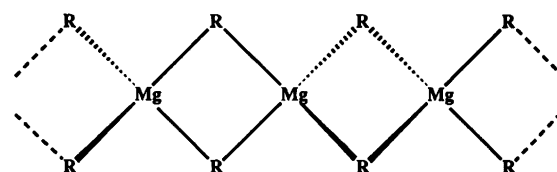
Table 1. Bond distances in unsolvated, monomeric, linear (organo)magnesium compounds MgX₂.⁵

| Phase | Compound X–Mg–X | <i>d</i> (Mg–X)/Å |
|---------|---|--------------------|
| Gas | Br–Mg–Br | 2.34 |
| | I–Mg–I | 2.52 |
| | Cp–Mg–Cp ^a | 2.339 ^b |
| | Np–Mg–Np ^c | 2.126 |
| Crystal | (Me ₃ Si) ₃ C–Mg–C(SiMe ₃) ₃ | 2.116 |

^aCp = cyclopentadienyl. ^b*d*[Mg–Cp(centroid)].

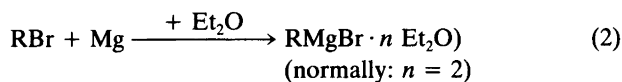
^cNp = neopentyl.

* Presented as a plenary lecture at the third European Symposium on Organic Reactivity, July 7–12, 1991 in Göteborg, Sweden.



Scheme 1.

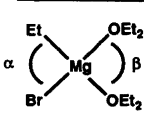
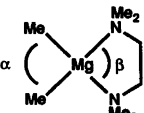
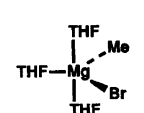
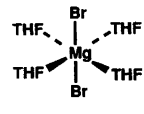
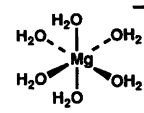
known since the initial discovery of Victor Grignard,¹ they are prepared in a Lewis basic solvent, mostly diethyl ether or tetrahydrofuran (THF); the solvent not only is required for a smooth (and often close to quantitative) reaction, but it also forms an integral part of the organomagnesium reagent once it is formed [eqn. (2)].

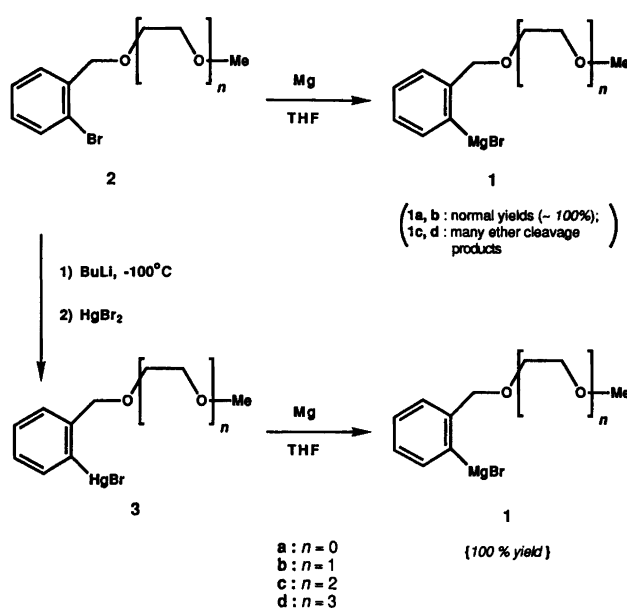


In the vast majority of cases, magnesium is tetracoordinated. In dilute solutions and in many crystal structures, the Grignard reagents RMgX or diorganomagnesiums R_2Mg form monomeric units which complete the tetra-coordination by two molecules of Lewis base ($n = 2$) as illustrated by the first two typical entries in Table 2.

In view of this preponderance of tetracoordination, one may raise the question of whether in these reagents magnesium is electronically saturated, or if other factors prevent higher coordination states. The existence of a number of compounds with penta- or hexa-coordination, all having small ligands and/or high charge on the central magnesium (see the lower three entries in Table 2), suggested that in organomagnesium chemistry it is not so much electronic saturation but rather steric hindrance that dictates the coordination mode.

Table 2. Selected crystal structure data on tetra- and higher-coordinated magnesium compounds.¹⁰

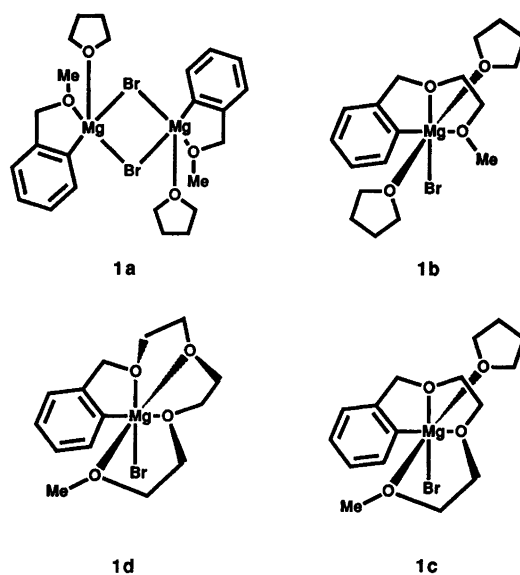
| | Bond length/Å | | | | Bond angle/° | |
|---|---------------|-------|-----------|------|--------------|---------|
| | C-Mg | Mg-Br | C-O | C-N | α | β |
|  | 2.15 | 2.48 | 2.04 | — | 125 | 101 |
|  | 2.17 | — | — | 2.24 | 130 | 82 |
|  | — | 2.5 | 2.04–2.28 | — | — | — |
|  | — | 2.63 | 2.16 | — | — | — |
|  | — | — | 2.07 | — | — | — |



Scheme 2.

In order to address this problem, we decided to investigate organomagnesium reagents with intramolecular coordination of the Lewis base, because removal of the steric repulsion between the normal, rather bulky intermolecular ether ligands L in $\text{RMgX} \cdot L_2$ by formation of chemical bonds as in polyethers of type 1 (Scheme 2) was envisaged to favour higher coordination numbers if steric hindrance really was a decisive factor.

This expectation was fully borne out by the X-ray crystal structures of 1.⁸ Even in 1a, which has only one intramolecular ether oxygen available, the coordination number of magnesium is increased from 4 to 5 in a bromine-bridged dimeric structure with one additional molecule of THF per magnesium (Scheme 3). When two intramolecular ether



Scheme 3.

oxygens are available, as in **1b**, hexacoordinated magnesium is encountered in a monomeric structure which includes *two* external Lewis bases (i.e. THF molecules); this illustrates, in a rather spectacular way, the space-saving effect of intramolecular coordination. In **1c**, the coordination number of magnesium is not further increased, but the polyether chain wraps around the central atom to replace one of the external ethers. This process goes on for **1d** which exists as a 'solvent-free', but hexacoordinated Grignard reagent!

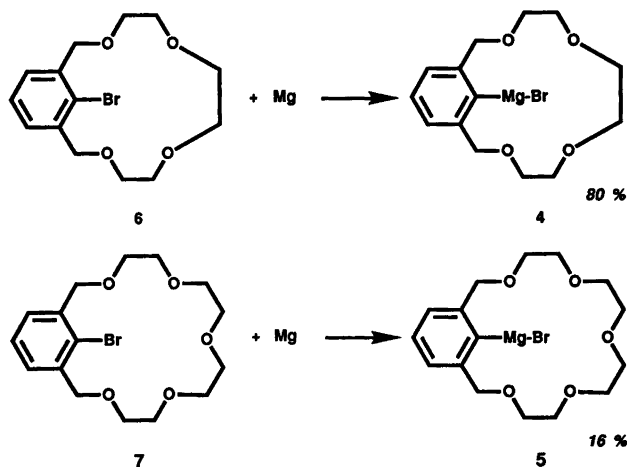
Unusual reactions: formation of the Grignard reagent

Intramolecular coordination leads not only to unusual structures, but, in consequence, also to unusual reactions. A first indication may be found in Scheme 2: whereas **1a** and **1b** are formed from the corresponding aryl bromides **2** in practically quantitative yield, the more efficiently coordinated **1c** and **1d** gave (too many) side products by cleavage of the polyether side chain; this is uncommon, because, as stated above, normal Grignard reagents, including **1a** and **1b**, are obtained in ethereal solvents without ether cleavage and in high yields. Therefore, in order to prepare **1c** and **1d** in pure form, it was necessary to take a detour via the organomercury compounds **3** as indicated in Scheme 2.

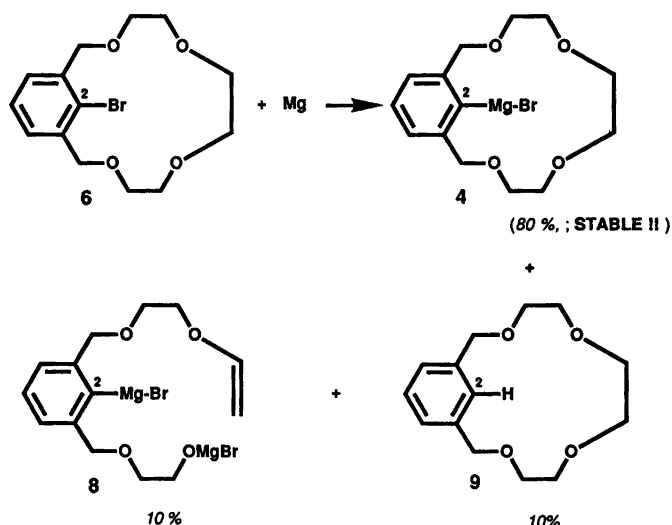
We had previously encountered, and, in more depth, investigated, this phenomenon of intramolecular ether cleavage while studying the crown ether Grignard reagents **4** and **5-10** (Scheme 4).

Their formation from the corresponding aryl bromides **6** and **7**, respectively, had also given lower than normal yields owing to cleavage of the crown ether bridge. As this cleavage was particularly simple and specific in the case of **4**, as shown in Scheme 5, it will be used to illustrate the unusual chemistry involved.

Note that (a) **4**, **8** and **9** account for 100 % of the product formation, i.e. there are *no other side products*; for instance, there was no cleavage at the inherently more reac-



Scheme 4.



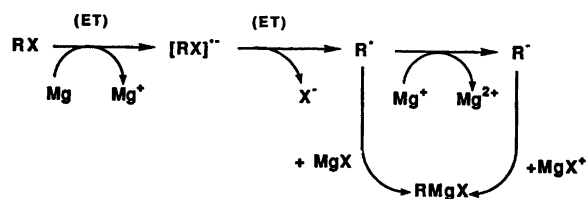
Scheme 5.

tive benzylic ether position; (b) **8** and **9** are formed in a 1 : 1 ratio; (c) only in **8**, is position 2 between the bridges functionalized, whereas in **9**, it carries a hydrogen which, as shown by deuterium labeling, is not derived from the solvent THF; (d) compound **4**, once formed, is *stable* for months in THF solution and does *not* form **8** and **9**; (e) **8** and **9** are formed when bromobenzene and magnesium are added to **4** in a THF solution and do react to give phenylmagnesium bromide, while **4** is inert to preformed phenylmagnesium bromide; (f) ether cleavage *does not occur* when bromobenzene and magnesium are added to a THF solution of **9**.

Taken together, all these experimental observations lead to the conclusion that both the occurrence and the specificity of the ether cleavage require at the same time the magnesium function at position 2 and a reactive species which is present only *during* the process of Grignard formation.

In principle, there are two intermediates which are sufficiently reactive to be candidates for effecting such a cleavage. It should be recalled that in contrast with the as such correct, but deceptively simple overall stoichiometry of eqn. (1), it has long been recognized that the formation of Grignard reagents is a complicated multistep process, the essential features of which are shown in Scheme 6.

According to this scheme, one of the highly reactive intermediates to be considered is the radical R^{\cdot} formed from the organic halide $R-X$ by electron transfer (ET). There is general agreement on the existence of R^{\cdot} as an



Scheme 6.

intermediate, although the modalities of its behaviour are still a matter of some controversy.^{6,7,9-11} Less well documented is the intermediacy of the carbanion R^- , but we wish to point out that apart from its possible involvement in the present context, there is completely independent evidence for its occurrence.⁷

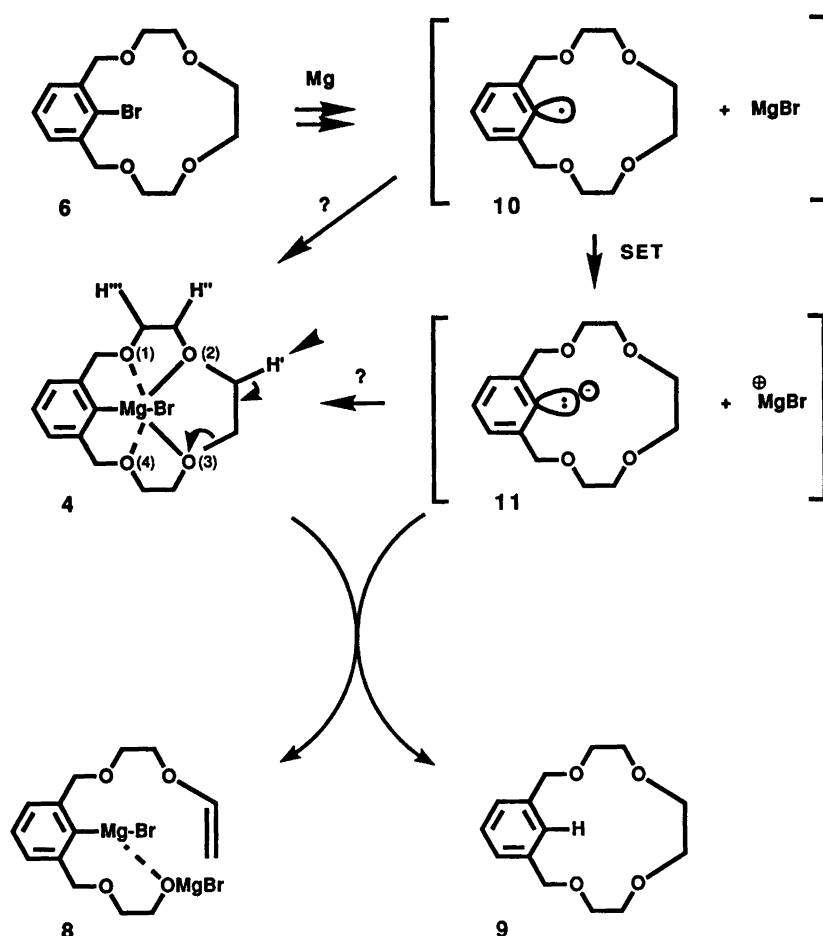
We feel that the peculiar ether cleavage reactions of **1**, **4** and **5** can only be understood, as illustrated for **4** in Scheme 7, as the action of the carbanion R^- (in the present case **11**) on (previously formed) **4**. This process is an E2 reaction with **11** as the attacking base and oxygen O3 as the leaving group. It requires the activating influence of magnesium coordination at O2 and O3, which has the double effect of making the indicated proton H' next to O2 more acidic and O3 a better leaving group; note the dotted line between O3 and the carbon-bound magnesium bromide in **8** which, in a purely formal way, indicates the outcome of this interaction. Without this activation, e.g. with **9** as a substrate, attack by **11** does not occur. The specific coordination of magnesium to O2 and O3, first postulated to rationalize the cleavage reaction, has been corroborated by the X-ray structure of **4**,⁹ which shows two types of magnesium-oxygen distance: two short ones [Mg-O2, 2.13(1) Å; Mg-O3, 2.112(1) Å], and two weaker ones [Mg-O1, 2.33(1) Å; Mg-O4, 2.49(1) Å].

The same specificity of attack on **4** would be difficult to explain for the intermediate radical R^\cdot (*in casu* **10**), which, if anything, would probably prefer attack at the (doubly activated!) benzylic CH_2 group. In a similar fashion,⁸ the cleavage of **5** can be rationalized, the difference being that owing to the additional ethyleneoxy unit of **5**, O2 and O3 are no longer equivalent, so that several modes of cleavage can and do occur. The higher proportion of cleavage for **5** (84%) compared with that for **4** (20%) must be due to the precipitation of the sparingly soluble **4** during the formation reaction, whereby it is protected against attack by R^- ; the more soluble **5** stays in solution and is largely consumed.

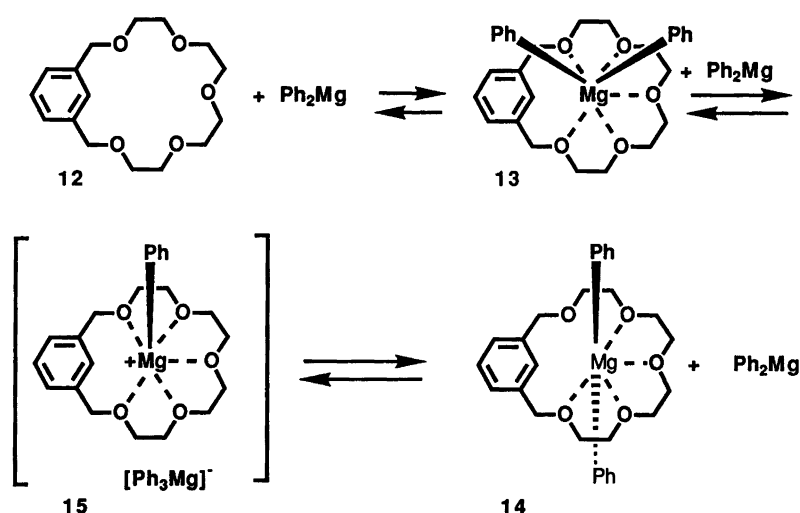
It should be emphasized again that the unexpected side reactions in the formation of the Grignard reagents described here form a strong indication for the occurrence of the evasive carbanion as an intermediate.

Unusual reactivity: organolithium-type behaviour of organomagnesium compounds

Organolithium compounds are much more reactive than their organomagnesium counterparts owing to the more strongly developed carbanion character of the former. In connection with the investigations described in the previous



Scheme 7.



Scheme 8.

paragraph, we encountered crown ether/organomagnesium combinations which approach organolithiums in reactivity; related observations in comparable systems have been published by the group of Richey, Jr.¹²

When 1,3-xylylene-18-crown-5 (**12**) is added to a solution of diphenylmagnesium in diethyl ether, no particular interactions are discernible. In toluene-*d*₈ solution, however, ¹NMR spectroscopy reveals the occurrence of an equilibrium between two species **13** and **14**¹³ (Scheme 8); their identity follows from the similarity of the spectral data of **13** to those of related side-on complexes of magnesium¹⁴ and zinc,¹⁰ while that of **14** was established by a crystal structure determination.¹³

Apart from the remarkable rotaxane structure of **14**, an intriguing question is how the diphenylmagnesium is 'threaded' through the cavity of **12**. This cavity is much too small to permit the direct penetration of a bulky benzene ring as can be judged from the crystal structure of **12**,¹⁵ especially in the space filling presentation (Fig. 1). This holds *a fortiori* for the formation of the analogous rotaxane from **12** and di-(*p*-*tert*-butylphenyl)magnesium;¹⁰ certainly the *tert*-butyl group is barred from passing through the crown ether cavity!

We therefore suggest that one of the phenyl groups of the side-on complex **13** is 'carried around' to the other side via the intermediate ate-complex **15**; while **15** was not observable directly, there are precedents for the formation of stable ate-complexes from organomagnesiums and crown ethers.¹²

For **9**, the lower homolog of **12**, an analogous rotaxane formation was not to be expected as the cavity of **9** is definitely too small. Instead, and to our surprise, the interaction between **9** and diphenylmagnesium in toluene at 80 °C gave, besides one equivalent of benzene, the metalation product **16** (Scheme 9), the structure of which has been shown by X-ray diffraction to be completely analogous to that of **4**.¹⁶ Compound **16** is, incidentally, one of the very few stable organomagnesium compounds with *two different organic* groups; it is in fact the first one with two different *aryl* groups! The analogous treatment of **9** with phenylmagnesium bromide gave – with a slower conversion rate – **4** which was identical with the product previously obtained from **6** and magnesium (Schemes 4 and 5).

Such easy metalations of aromatic carbon–hydrogen bonds are without precedent, but the halogen–metal exchange reaction of **6** and diphenylmagnesium proceeded

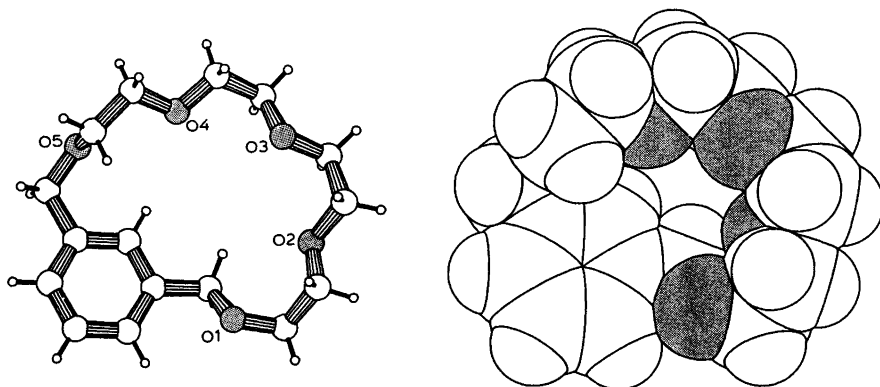
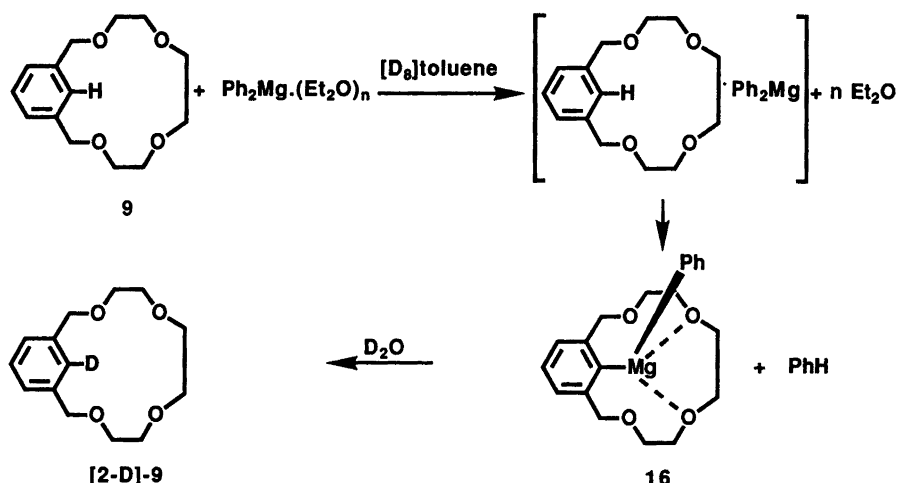
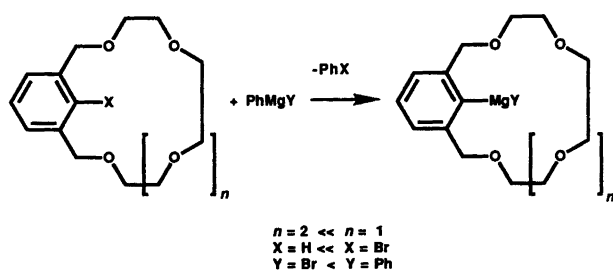


Fig. 1. X-Ray crystal structure of **12**: PLUTO drawing (left) and space-filling presentation (right).



Scheme 9.

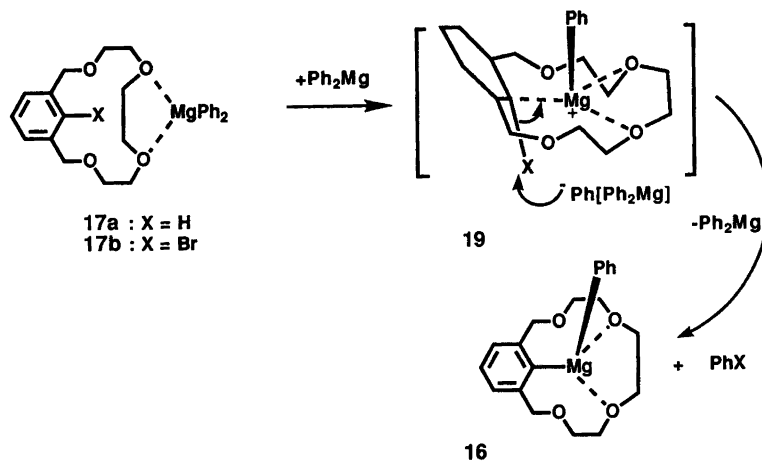


Scheme 10.

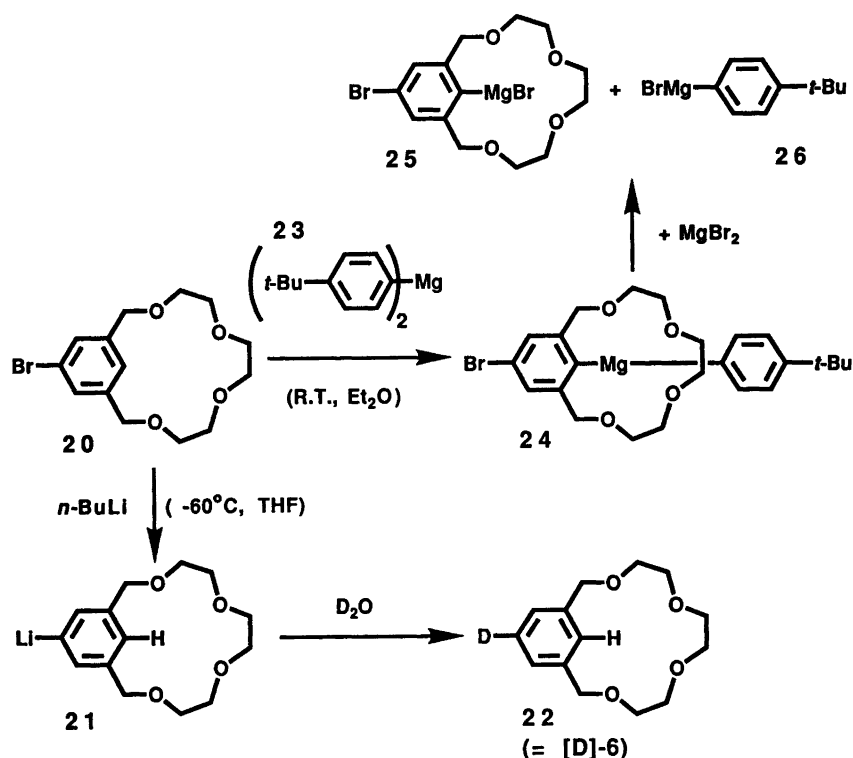
even more easily: at room temperature in toluene, the reaction was complete within 24 h. The larger crown ethers were clearly less reactive: **12** gave no reaction, but formed the rotaxane **14** (*vide supra*), and **7** underwent slow bromine–lithium exchange to give the *phenylmagnesium* analog of **5**. Thus, as summarized in Scheme 10, the crown-ether-promoted reactions proceed with increasing ease in the order 18-crown-5 < 15-crown-4; Grignard reagent < diorganylmagnesium; and hydrogen < bromine.

Both the direct metalation and the halogen–metal ex-

change of an aromatic compound are unknown for organomagnesium compounds;¹⁷ rather, they are typical for organolithium reagents, although it should be pointed out that even *n*-butyllithium metalates benzene very slowly, so that activation by bases such as *N,N,N',N'*-tetramethylethylenediamine is required.¹⁸ We therefore rationalize the unusual activation encountered here by complex formation between the crown ether and the organomagnesium reagent as illustrated for the formation of **16** (Scheme 11). In the initial side-on complex **17**, cleavage of the magnesium–phenyl bond is facilitated by stabilization both of the Ar–Mg⁺ moiety in the crown ether cavity and of the phenyl anion by a second molecule of diphenylmagnesium; the resulting ate-complex **18** (not shown, but analogous to **15** in Scheme 8) leads to the related transition state **19**, in which we postulate a dual activation: the (stabilized) phenyl anion of the triphenylmagnesate unit performs the (probably decisive) nucleophilic attack on X (X = H: **9**; X = Br: **6**), but the simultaneous electrophilic attack of the positively charged magnesium at the *ipso*-carbon C2 undoubtedly is also of importance.



Scheme 11.



Scheme 12.

The dominant role of crown ether complexation for the enhanced reactivity of the organomagnesium reagents is nicely demonstrated by the surprising difference in selectivity of organolithiums and organomagnesiums in their reaction with the crown ether **20** which offers both a bromine functionality – residing outside of the crown ether region of the molecule – for an inherently fast halogen–metal exchange, and a proton – within the crown ether cavity – for the inherently slower metalation (Scheme 12).

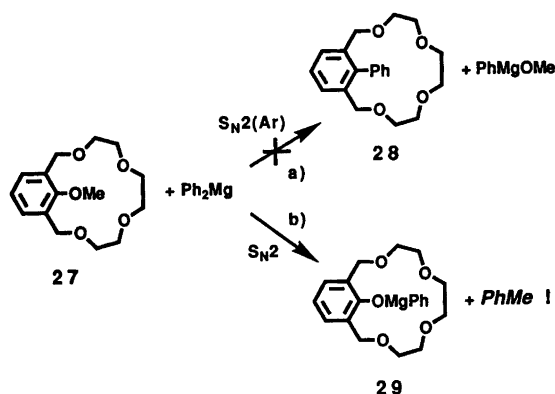
It turned out that butyllithium leads to bromine–lithium exchange and furnishes **21** which was characterized by deuteration to **22**. Obviously, the organolithium reagent does not possess a strong affinity for crown ether coordination and expectedly chooses the normally faster reaction pathway. Bis-(*p*-*tert*-butylphenyl)magnesium (**23**), on the other

hand, being inherently too unreactive to attack an aryl bromide, experiences extraordinary activation through the crown ether, and thus it leaves the bromide alone and quantitatively metalates the proton in the cavity. The resulting **24** – another stable unsymmetrical diarylmagnesium – on addition of magnesium bromide quantitatively undergoes Schlenk equilibrium disproportionation to the crown ether Grignard reagent **25** and *p*-*tert*-butylphenylmagnesium bromide (**26**), presumably because in **25**, the coordination of the (more positive!) magnesium is favoured, and steric congestion is reduced.

Unusual reactivity: cleavage of aryl ethers

Another functional group which, under normal conditions, is inert to organomagnesium compounds is the aryl alkyl ether function. Like most other ethers, anisole and similar ethers are completely stable and can serve as solvents for the organomagnesium reagent; only under rather forcing conditions (e.g. heating for hours to 100–200 °C, depending on the type of reagent¹⁹) does ether cleavage occur.

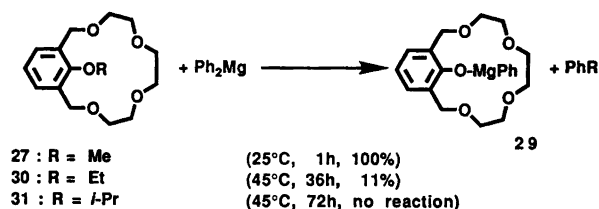
Initially, we considered two modes of reaction between diphenylmagnesium and **27**, a crown ether analog of anisole; both of them involve activating coordination of magnesium at the ether oxygen, but they differ in the point of concomitant attack of the phenyl anion (Scheme 13): (a) attack of the phenyl anion at the *ipso*-carbon C2, formally an $S_N2(\text{Ar})$ reaction, would lead to **28**; or (b) attack of the phenyl anion at the methyl carbon, formally an S_N2 reaction, would lead to **29** (and toluene!).



Scheme 13.

Experimentally, ether cleavage via pathway (b) was the only reaction observed, and it occurred with remarkable ease.²⁰ The addition of **27** to a solution of diphenylmagnesium in diethyl ether resulted in the formation of a white precipitate; presumably, it was a side-on complex **32** (*vide infra*, Scheme 15), because immediate hydrolysis gave only 2% each of toluene and of the phenol **33**; after an hour at room temperature, the conversion was practically quantitative. The same reaction occurred with phenylmagnesium bromide, but here again it was much slower.

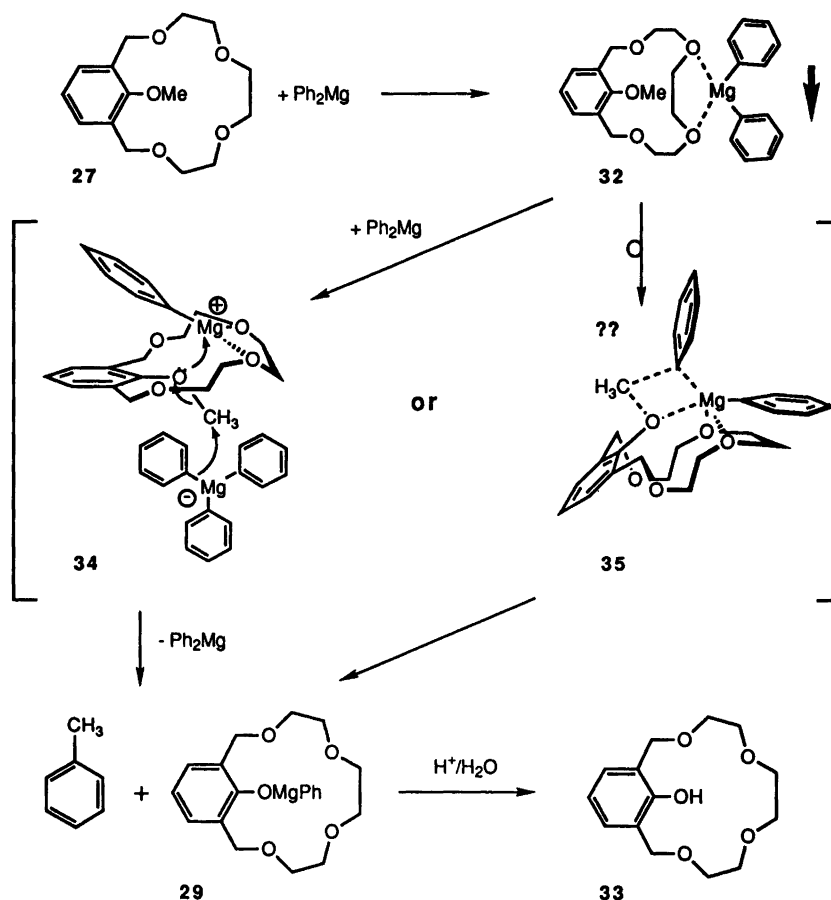
Of different conceivable mechanisms, the S_N2 process is the most likely one as no other mechanism would explain the strong rate retardation when the ethyl or the isopropyl ether, **30** and **31**, respectively, were substituted for the methyl ether **27** (Scheme 14). By analogy with earlier schemes, we assume that double activation of the methyl



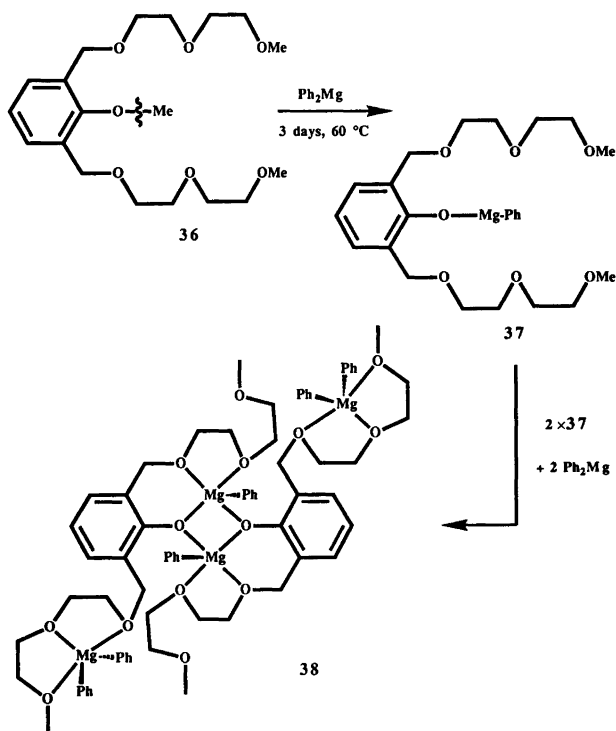
Scheme 14.

ether function is the cause of its easy cleavage (Scheme 15): the specific coordination of the organomagnesium reagent facilitates dissociation to an ate/ RM^+ complex with the aid of an additional diphenylmagnesium. This develops into a transition state **34** which permits a linear arrangement as required for an S_N2 transition state. This is not the case for the alternative transition state **35** which might have seemed attractive because without additional diphenylmagnesium, it can be formed just by conformational changes of **32**. It is important to point out that, in THF, reaction does not occur, presumably because this strongly basic solvent successfully competes with **27** for diphenylmagnesium and thus prevents the prerequisite formation of **32**.

Does only a crown ether such as **27** meet the structural conditions for this type of unusual enhancement of reactivity? The answer is no, but the degrees of freedom were found to be rather limited. Thus, methyl ether cleavage did not occur when diphenylmagnesium was reacted with the one-armed polyethers analogous to **2** with OMe instead of Br. However, the two-armed polyether **36** was cleaved in a heterogenous, sluggish, and incomplete reaction; after 3 days at 60°C, some crystals of **38** separated from the solution and were identified by X-ray crystal structure determination¹⁴ to be composed of two molecules of the expected cleavage product **37** and two additional molecules of



Scheme 15.



Scheme 16.

unchanged diphenylmagnesium (Scheme 16). The two phenoxide functions of 37 bridge the two phenylmagnesium cations to form a central four-membered ring; each of these two magnesiums is pentacoordinate, making use of two of the three oxygens of one side arm. The other side arms are wrapped with all three oxygens around the additional, pentacoordinated diphenylmagnesiums.

Conclusions

By judicious choice of intramolecular ether functions, it is possible to achieve unusually high coordination numbers for magnesium in organomagnesium compounds, and to demonstrate the occurrence of reactions under mild conditions which are normally reserved for much more reactive organometallic compounds.

Acknowledgements. I am very grateful to my colleagues and coworkers whose names are cited in the references.

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