Metal-Template Electrophilic Substitution on Phenols: Synthesis and Crystal Structure of Bromomagnesium Phenolate and Its Reactive Complex with *para*-Isopropylbenzaldehyde

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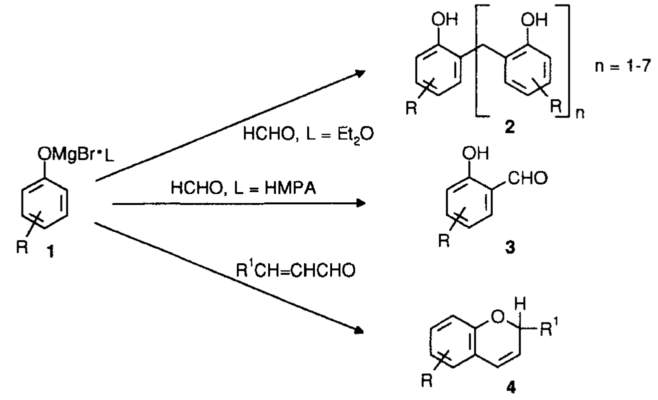
Dedicated to the memory of Professor Giuseppe Casnati on the 4th anniversary of his death

Abstract: The crystal structures of the bromomagnesium phenolate **5** and its complex **7** with *para*-isopropylbenzaldehyde are reported; for the first time it has been possible to demonstrate that the reactive complex **7**, responsible for the complete *ortho*-regioselective control in the alkylation of phenoxymagnesium bromides with aldehydes, is not obtained by simple replacement of the ethereal ligand but by expansion of the metal coordination sphere from 4 (usual tetrahedral configuration) to 5. We infer from ^{1}H NMR studies that the magnesium coordination of complex **7** in solution is analogous to that shown in the solid state, with a complexed ethereal molecule.

Keywords
crystal structure · electrophilic aromatic substitutions · magnesium · regioselectivity · template synthesis

Introduction

Non-transition-metal phenolates have found numerous applications in organic synthesis; one especially important class of reactions is the *ortho*-regioselective metal-template electrophilic substitution.[1] This reaction gives a variety of products depending upon the nature of the electrophile involved, the metal, its ligand and the solvent utilised. A typical set of products obtained from the reaction of aldehydes with bromomagnesium phenolates coordinating a convenient ligand is shown in Scheme 1.[2] This depicts how *ortho*-methylene-linked polyphenols **2** or salicylic aldehydes **3** can be synthesised with complete selectivity by reacting bromomagnesium phenolates **1** with formaldehyde in the presence of a soft (Et_2O) or hard (HMPA) donating ligand in a nonpolar solvent such as toluene. Moreover, flavenes and chromenes **4** are obtained from the reaction with α,β-unsaturated aldehydes.



Scheme 1. Products obtained from the reaction of aldehydes with bromomagnesium phenolates. R = H, alkyl, OMe, Cl, aryl; R^1 = alkyl, aryl.

Results and Discussion

Even though the synthetic applications of the reaction types in Scheme 1 are now well established, the mechanism by which they occur has never been fully elucidated. For example, a mechanism based on the initial metal-template electrophilic substitution process, which produces the intermediate **8**, has been invoked to rationalise the formation of product **9** by reaction of **5** and **6** in dry toluene at 100 °C (Scheme 2). An early step in this reaction is the interaction between the bromomagnesium phenolate **5** and the aldehyde **6** to give an active oriented complex **7** in which the metal atom serves as a link between the reaction partners. This interaction probably has two main consequences: the simultaneous activation of both reaction partners (the aldehyde by increasing electrophilicity owing to the coordination with the metal atom and the phenol by enhancing nucleophilicity of the nucleus itself owing to the weakening of the magnesium–phenolic oxygen bond with consequently more electron availability on the aromatic ring) and orientation with close contact of partners, enabling the aldehyde to approach the *ortho*

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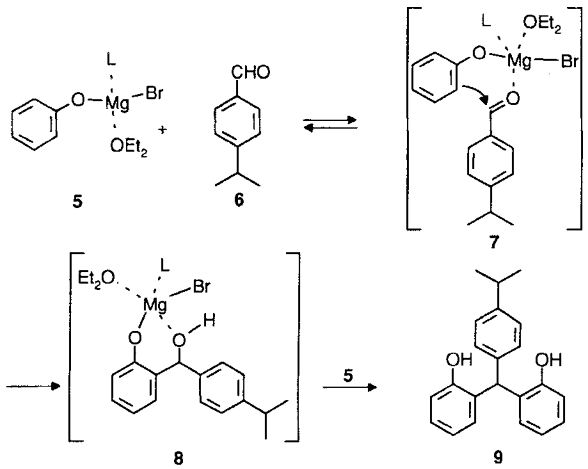

Scheme 2. The proposed metal-template electrophilic substitution mechanism.

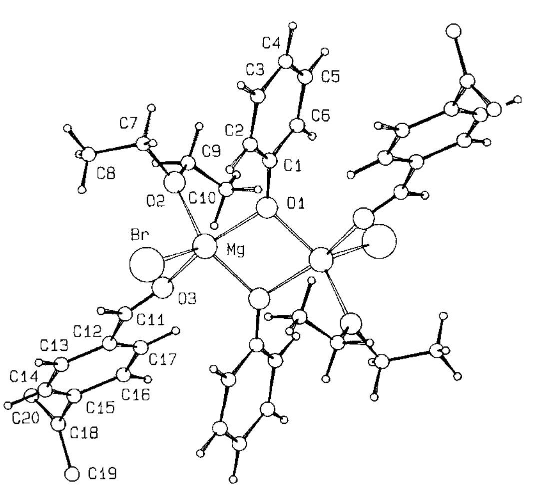

Figure 2. The X-ray crystal structure of complex **7** with arbitrary numbering scheme.

Table 1. Selected bond lengths (Å) and bond and torsion angles (°) of compounds **5** and **7**.

	Compound **5**	Compound **7**		Compound **5**	Compound **7**
Br–Mg	2.391(3)	2.502(5)	O3–C11	–	1.191(19)
Mg–O1	1.942(7)	2.005(10)	C7–C8	1.440(40)	1.468(46)
Mg–O2	1.971(8)	2.079(13)	C9–C10	1.390(41)	1.378(56)
Mg–O3	–	2.125(11)	C16–C17	–	1.406(28)
O1–C1	1.368(13)	1.322(22)	C18–C19	–	1.370(34)
O2–C7	1.524(29)	1.450(33)	C18–C20	–	1.321(42)
O2–C9	1.462(20)	1.356(32)			
Br-Mg-O3	–	96.4(3)	Mg-O1-C1	132.2(5)	129.0(10)
Br-Mg-O2	111.4(2)	106.4(3)	Mg-O2-C9	122.3(11)	127.8(18)
Br-Mg-O1	119.9(2)	110.6(3)	Mg-O2-C7	123.1(11)	122.6(15)
O2-Mg-O3	–	83.4(4)	C7-O2-C9	114.4(13)	108.1(22)
O1-Mg-O3	–	152.7(4)	Mg-O3-C11	–	137.5(10)
O1-Mg-O2	110.9(3)	92.5(4)			
Br-Mg-O2-C7	19.2(15)	27.1(18)	O1-Mg-O2-C9	–29.8(12)	79.1(23)
Br-Mg-O2-C9	–166.2(11)	–168.5(22)	Mg-O1-C1-C2	64.6(23)	24.9(14)
Br-Mg-O1-C1	64.1(8)	–64.1(13)	Mg-O1-C1-C6	–118.3(16)	–155.9(8)
O1-Mg-O2-C7	155.6(14)	–85.2(18)			

position of the phenol ring easily. The formation of similar oriented complexes has already been proposed by us and other authors to explain *ortho*-specific electrophilic substitution involving metal phenolates,[2a, 2b, 3] anilides[4] and benzyl–metal derivatives.[5]

Spectroscopic evidence for the formation of a 1:1 complex between 2,4,6-trimethylphenoxymagnesium bromide and 2-methylpropanal from ^1H and ^{13}C NMR investigations of different mixtures of the two reagents in diethyl ether has been described by Ungaro and coworkers.[6] Considerable efforts have been devoted to the identification of the structure of these and similar magnesium complexes[7] but crystals suitable for X-ray analyses have only rarely been isolated. Consequently our attention was drawn to the structural characterisation of phenoxymagnesium complexes **5** and **7** in order to explain the nature of their association and of their structural properties and to provide more information about the reaction mechanism (Scheme 2).

Crystals of complexes **5** and **7** were obtained by cooling their toluene solutions (see Experimental Section). The molecular structures of the two complexes are shown in Figures 1 and 2; Table 1 shows selected bond lengths, bond and torsion angles of compound **5** and **7**. The crystal data and pertinent details of the experimental conditions are reported in the Experimental Section.[8] In the solid state both the compounds are dimeric, forming four-membered square Mg_2O_2 rings. Consequently the O1 and O1′ oxygen atoms are three-coordinate and adopt a trigonal arrangement, while the magnesium atoms are four- and five-coordinate in complexes **5** and **7**, respectively. In both cases the phenyl oxygens show an enhanced donor capability and act as a bridging group between two metals.

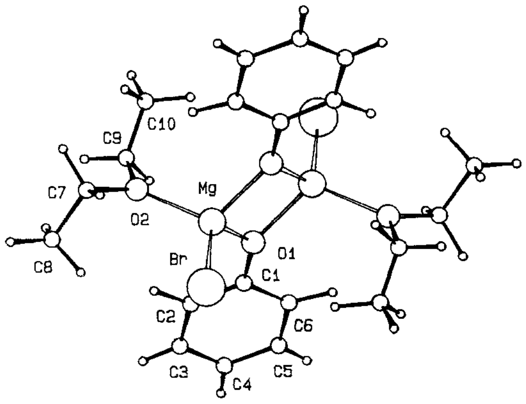

Figure 1. The X-ray crystal structure of complex **5** with arbitrary numbering scheme.

In complex **5** the distorted tetrahedral environment of the metals consists of two phenyl oxygens, one bromine atom and one OEt_2 group. The bond angles at the metal are far from the normal tetrahedral value, the smallest being within the four-membered ring. This distortion may be attributed both to the participation in the four-membered ring and to the difference in size of the atoms bonded to the magnesium atom. Metal coordination geometry rather similar to that in complex **5** has already been observed in $[C_2H_5MgBr\cdot O(i\text{-}C_3H_7)_2]_2$,[9] $[C_7H_{13}OMgBr\cdot O(C_4H_9)_2]_2$[10] and $[C_4H_9OMgBr\cdot O(C_4H_9)_2]_2$.[11]

In complex **7** the magnesium atom is five-coordinate with two phenolic oxygens, the OEt_2 and $OHCC_6H_4CH(CH_3)_2$ molecules and one bromine atom. This distorted pyramidal arrangement shows the O 1, O 1′, O 2 and O 3 atoms lying approximately in a plane, with bromine and magnesium atoms 3.06 and 0.58 Å out of this plane, respectively. While there are a number of systems solvated with diethyl ether in which the Mg atom is four-coordinate, there are very few with a five-coordinate Mg atom and a diethyl ether group: $[C_2H_5Mg_2Cl_3(OC_4H_{10})]_2$,[12] $[OMg_4Br_6(OC_4H_{10})_4]$.[13]

The Mg–Br bond lengths (2.391(3) and 2.502(5) Å) are significantly different in the two complexes, and while the latter compares well with the value predicted for covalent bond length,[14] the former is, as far as we know, shorter than any other value observed in similar molecular fragments[11, 15] and thus implies a strongly bonded molecule.

In both the complexes the Mg–O bond lengths (ranging from 1.942(7) to 2.079(13) Å) are near the sum of the ionic radii of Mg^{2+} and O^{2-}. Interpolation between the value for six coordination (0.86 Å) and that for four coordination (0.71 Å) by means of Shannon's procedure[16] gives a Mg–O separation of 2.01 Å. The reduction of the fivefold coordination of the magnesium atom to four is consistent with the decrease in the Mg–O bond lengths, which are significantly shortened in complex **5** with respect to those of **7**. In the two complexes the maximum deviation of oxygen atoms of the ether systems from the least-squares plane of their three attached atoms is 0.11 Å, while among the atoms attached to the phenyl oxygens this deviation has a maximum of 0.03 Å. In other words, these oxygens are practically coplanar with their attached atoms; this trigonal coordination may influence the differences in the Mg–O bond lengths. Probably because of the soft character and low decomposition temperatures of the crystals, the structure determinations could not pinpoint the positions of the ethyl groups of ether fragments and of the isopropyl groups satisfactorily and left considerable freedom of motion for the atoms. This explains the marked deviations of the bond lengths in these groups from the normal C–C single bond length. At the same time, any attempts to elucidate the ordering of these atoms over two or more positions failed. These differences have already been observed in a large number of similar molecular fragments.[9, 11, 17]

The lattice structures are such that the molecules are connected by normal Van der Waals interactions.

The unexpected coordination number in **7** clearly shows the importance of this structure determination, since initially it was assumed that complexation of the reagent occurred by simple replacement of the ethereal ligand. It appears, however, that the coordination number is increased from four (normal tetrahedral configuration) to five. We think that the coordination of magnesium of **7** in solution is analogous to that in the solid state. Indeed, the ^{1}H NMR spectrum in $CDCl_3$ of the crystals of **7** (used for X-ray structure determination) showed the presence of a complexed ethereal molecule, evidenced by the downfield shift of the methylene signal in comparison with that of free ether ($\Delta\delta \approx 0.1$).

To conclude, this paper has elucidated the metal-template mechanism of the *ortho*-regioselective electrophilic substitution involving aryloxymagnesium bromide and benzaldehydes, which occurs by expansion of the metal coordination sphere.

Experimental Section

Bromomagnesium phenolate **5** was prepared by reaction of ethyl magnesium bromide (20 mmol) and phenol (20 mmol, 1.9 g) in dry ether (80 mL). Upon removal of the solvent under reduced pressure and addition of dry toluene (80 mL) a solution was obtained from which white crystals of **5** could be recovered on cooling. Moreover, addition of *para*-isopropylbenzaldehyde (20 mmol, 3.0 g, 3.0 mL) in dry toluene (20 mL) to the phenolate **5** solution and storage of the resulting solution in the cold for several days resulted in a crop of crystals of **7** suitable for X-ray structure determination, making it possible to directly compare the structures of the bromomagnesium phenolate **5** and its reactive complex with an aromatic aldehyde **7**. Further, we verified that compound **9** was obtained in 87% yield by heating the toluene solution of **5** and **6** (molar ratio 2/1) at 100 °C for 5 h.

2,2′-Dihydroxy-4″-isopropyltriphenylmethane (9): Pale yellow solid, m.p. 135–136 °C; ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): $\delta = 1.2$ (d, ^3J(H,H) = 7 Hz, 6 H; 2 CH_3), 2.9 (q, ^3J(H,H) = 7 Hz, 1 H; CH), 5.1 (s, 2 H; 2 OH), 5.9 (s, 1 H; CH), 6.8 (d, ^3J(H,H) = 8 Hz, 2 H; H-3 and H-3′ or H-6 and H-6′), 6.9 (t, ^3J(H,H) = 8 Hz, 2 H; H-4 and H-4′ or H-5 and H-5′), 6.9 (dd, ^3J(H,H) = 8 and 2 Hz, 2 H; H-6 and H-6′ or H-3 and H-3′), 7.1 (d, ^3J(H,H) = 8 Hz, 2 H; H-2″ and H-6″ or H-3″ and H-5″), 7.1 (dt, ^3J(H,H) = 8 and 2 Hz, 2 H; H-5 and H-5′ or H-4 and H-4′), 7.2 (d, ^3J(H,H) = 8 Hz, 2 H; H-3″ and H-5″ or H-2″ and H-6″); IR (KBr): $\tilde{\nu} = 3451$ (OH); MS (70 eV): *m/z* (%): 318 (63) [M^+], 275 (100) [$C_{19}H_{15}O_2^+$], 181 (44) [$C_{13}H_{9}O^+$]; anal. calcd for $C_{22}H_{22}O_2$ (318.4): C 82.99, H 6.96; found C 82.68, H 7.10.

Crystal structure analyses:[8] Specimens of both the complexes, sealed in Lindemann capillaries under a nitrogen atmosphere, were mounted on Siemens AED diffractometer equipped with a IBM PS 2/30 personal computer.[18] Data collection was at room temperature with $Cu_{K\alpha}$ radiation. Decomposition of 23% and 27% occurred during the data collection time for the complexes **5** and **7**, respectively. Corrections for decomposition, Lorentz and polarisation effects were applied. Both the structures were solved with automated Patterson methods with XFPS90[19] and refined with the CRYSRULER package[20] by means of SHELX76.[21] Most H atoms were found in a DF map, the remaining ones (those of the ethyl groups) were put in their calculated positions and refined isotropically. The absorption correction was performed with the program DIFABS.[22]

Complex 5: $C_{10}H_{15}O_2BrMg$, monoclinic, space group $P2_1/n$, $M = 271.4$, $a = 13.480(2)$, $b = 11.843(2)$, $c = 8.239(2)$ Å, $\beta = 105.58(2)°$, $V = 1267.0$ Å^3, $F(000) = 552$, $\rho_{calc} = 1.42$ g cm^{-3}, $\mu = 47.57$ cm^{-1}, $Z = 4$, crystal size = 0.06 × 0.10 × 0.17 mm, θ range = 3–55°, absorption correction: $\phi\mu_{min/max} = 0.59/1.41$, $\theta_{min/max} = 0.99/1.36$. 307 variables refined with 1162 independent reflections observed [$I > 3\sigma(I)$] of 2411 total; $R = 0.068$.

Complex 7: $C_{20}H_{27}O_3BrMg$, monoclinic, space group $P2_1/c$, $M = 419.64$, $a = 13.496(3)$, $b = 11.034(2)$, $c = 14.997(3)$ Å, $\beta = 100.04(5)°$, $V = 2199.1$ Å^3, $F(000) = 872$, $\rho_{calc} = 1.27$ cm^{-3}, $\mu = 29.49$ cm^{-1}, $Z = 4$, crystal size = 0.09 × 0.13 × 0.21 mm, θ range = 3–60°, absorption correction: $\phi\mu_{min/max} = 0.70/1.31$, $\theta_{min/max} = 0.57/1.07$. 187 variables refined with 1177 independent reflections observed [$I > 1.5\sigma(I)$] of 3265 total; $R = 0.067$.

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