

Shedding New Light on ZnCl_2 -Mediated Addition Reactions of Grignard Reagents to Ketones: Structural Authentication of Key Intermediates and Diffusion-Ordered NMR Studies

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Dedicated to Professor Víctor Riera on the occasion of his retirement, an inspirational mentor and a pioneer of organometallic chemistry in Spain

Abstract: Building on recent advances in synthesis showing that the addition of inorganic salts to Grignard reagents can greatly enhance their performance in alkylation reactions to ketones, this study explores the reactions of EtMgCl with benzophenone in the presence of stoichiometric or catalytic amounts of ZnCl_2 with the aim of furthering the understanding of the role and constitution of the organometallic species involved in these transformations. Investigations into the metathesis reactions of three molar equivalents of EtMgCl with ZnCl_2 led to the isolation and characterisation (X-ray crystallography and ^1H and ^{13}C NMR spectroscopy) of novel magnesium “zinc-rich” zincate $[(\text{THF})_6\text{Mg}_2\text{Cl}_3]^+[\text{Zn}_2\text{Et}_5]^-$ (**1**), whose complicated constitution in THF solutions was assessed by variable-tempera-

ture ^1H DOSY NMR studies. Compound **1** reacted with one equivalent of benzophenone to yield magnesium magnesiate $[(\text{THF})_6\text{Mg}_2\text{Cl}_3]^+[\text{Mg}_2(\text{OC}(\text{Et})\text{Ph}_2)_2\text{Cl}_3(\text{THF})]^-$ (**3**), whose structure was determined by X-ray crystallography. ^1H NMR monitoring of this reaction showed two equivalents of ZnEt_2 formed as a co-product, which together with the “magnesium only constitution” of **3** provides experimental insights into how zinc can be efficiently recycled in these reactions, and therefore used catalytically. The chemoselectivity of this reaction can be

rationalised in terms of the synergic effect of magnesium and zinc and contrasts with the results obtained when benzophenone was allowed to react with EtMgCl in the absence of ZnCl_2 , where the reduction of the ketone takes place preferentially. The reduction product $[(\text{THF})_5\text{Mg}_3\text{Cl}_4(\text{OC}(\text{H})\text{Ph}(\text{CF}_3)_2)]$ (**4**) obtained from the reaction of EtMgCl with 2,2,2-trifluoroacetophenone was established by X-ray crystallography and multinuclear (^1H , ^{13}C and ^{19}F) NMR spectroscopy. Compounds **3** and **4** exhibit new structural motifs in magnesium chemistry having MgCl_2 integrated within their constitution, which highlights the new role of this inorganic salt in providing structural support for the newly generated alkoxide ligand.

Keywords: addition reactions • Grignard reagents • mixed-metal chemistry • NMR spectroscopy • zincates

Introduction

Amongst the different synthetic tools available for the generation of new C–C bonds, the addition of polar organometallic reagents to carbonyl compounds constitutes one of the most fundamental methodologies in organic chemistry.^[1] En-

dowed with strong nucleophilic power coupled with their ready availability,^[2] Grignard reagents (RMgX) are usually the reagents of choice to perform these transformations.^[3] Nevertheless, on many occasions the desired addition products are obtained in mixtures along with the undesired reduction and/or enolisation products, resulting from competing β -hydride elimination and deprotonation reactions respectively.^[4] To overcome this contamination, several synthetic strategies have been developed with the aim of enhancing the nucleophilicity of the organomagnesium reagent as well as activating the carbonyl substrates. Thus, Ishihara has shown that the use of mixed lithium-magnesium reagents (empirically formulated as LiMgR_3), formed by reaction of Grignard reagents with organolithium compounds, allows the highly efficient alkylation of a wide range of enolizable ketones.^[5] The use of inorganic salts as additives can also have a beneficial effect on favouring these alkylation reactions, in particular using rare-earth metal salts, a methodology pioneered by Imamoto and co-workers^[6] and re-

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cently upgraded by Knochel et al. by using stoichiometric mixtures of lanthanide salts and lithium chloride, $\text{LnCl}_3 \cdot 2\text{LiCl}$ ($\text{Ln} = \text{La}, \text{Ce}, \text{Nd}$)^[7] compatible with the use of Grignard reagents bearing highly sensitive organic functional groups. A landmark in this evolving area has been Ishihara's practical ZnCl_2 -catalysed addition of Grignard reagents to ketones, which facilitates access to a wide range of tertiary alcohols in excellent yields using a simple, low-cost, environmentally friendly inorganic salt as a catalyst.^[8] By comparing stoichiometric^[9] and catalytic studies, the authors proposed magnesium zincates empirically formulated as R_3ZnMgCl (formed via salt metathesis reactions) as the active species performing the addition reactions.^[10] In closely related work, the addition of MgCl_2 to organozinc reagents has recently proved to greatly accelerate their (otherwise kinetically retarded) addition to aldehydes, ketones and CO_2 .^[11] In spite of these excellent organic studies, which draw attention to the participation of mixed magnesium–zinc compounds in addition reactions,^[12] to date these proposed intermediates have not been detected nor isolated from solution and little information is available regarding their constitutions (either in solution or in the solid state). Starting to fill this important gap of knowledge, we have recently investigated salt metathesis reactions between variable amounts of the homometallic species $i\text{BuMgCl}$ and ZnCl_2 ,^[13] which has allowed the isolation and characterisation of a series of novel magnesium zincates (which we have previously described as Mg–Zn hybrids).^[14,15] In sharp contrast with the lack of reactivity observed for conventional organozinc reagents, these mixed-metal modifications can efficiently promote direct Zn–I exchange reactions with aromatic halides^[13] as a consequence of the cooperative (synergic) effect of having both metals, magnesium and zinc, combined through ligands in the same molecule.^[16]

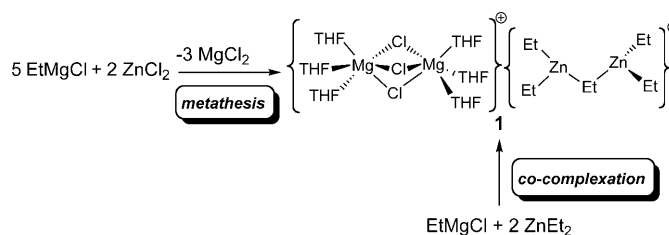
Building on these results, here we extend our studies on Mg–Zn hybrids to their application in alkylation reactions of ketones. Thus, investigating as a case study the reaction of benzophenone with EtMgCl in the presence of ZnCl_2 (under both stoichiometric and catalytic conditions), we provide new solid-state and solution insights (using a combination of X-ray crystallography with ^1H diffusion-ordered (DOSY) NMR spectroscopy) into the real composition of the key organometallic intermediates (including mixed magnesium–zinc species and relevant alkylation and reduction products) involved in this reaction prior to the hydrolysis step. We disclose that switching $i\text{BuMgCl}$ for EtMgCl has a profound effect not only on the reactivity of the mixed magnesium–zinc compound generated but also on its composition. Thus, aiming to advance understanding into how these mixed-metal systems operate and into the origins of their unique chemoselectivity, here we report $[(\text{THF})_6\text{Mg}_2\text{Cl}_3]^+ [\text{Zn}_2\text{Et}_5]^-$ (**1**), obtained by the reaction of three molar equivalents of EtMgCl with ZnCl_2 , which is, to the best of our knowledge, the first example of a structurally defined penta(alkyl) dizincate. Furthermore, as evidenced by ^1H NMR monitoring, **1** reacts with benzophenone, not only stoichiometrically but also catalytically, to yield the homo-

metallic “magnesium magnesiate” alkylation product $[(\text{THF})_6\text{Mg}_2\text{Cl}_3]^+ [\text{Mg}_2(\text{OC}(\text{Et})\text{Ph})_2\text{Cl}_3(\text{THF})]^-$ (**3**), which provides compelling experimental evidence that mixed magnesium–zinc compounds are the truly active species in this chemoselective transformation as well as providing useful information into how ZnEt_2 can be recycled into the catalytic cycle proposed by Ishihara.

Results and Discussion

Synthesis and characterisation of mixed magnesium–zinc species:

As previously mentioned, magnesium trialkyl zincates have been suggested as the active species in zinc-catalysed organic reactions of Grignard reagents.^[8,12] Thus, following the same metathetical approach that we previously employed successfully to prepare the magnesium trialkyl zincate $[(\text{THF})_6\text{Mg}_2\text{Cl}_3]^+ [\text{Zn}i\text{Bu}_3]^-$,^[13] we reacted three molar equivalents of ethylmagnesium chloride with ZnCl_2 using THF as a solvent, affording a colourless solution that deposited colourless crystals of a mixture of the novel magnesium penta(ethyl) zincate $[(\text{THF})_6\text{Mg}_2\text{Cl}_3]^+ [\text{Zn}_2\text{Et}_5]^-$ (**1**) and $[(\text{THF})_4\text{MgCl}_2]$. Magnesium zincate **1** could also be obtained as a crystalline pure solid in a 21 % yield when equimolar amounts of EtMgCl were reacted with commercially available Et_2Zn in THF (Scheme 1). This yield could be improved to 45 % when a 1:2 ratio of $\text{EtMgCl}/\text{ZnEt}_2$, matching that in the product, was employed.^[17]



Scheme 1. Synthesis of $[(\text{THF})_6\text{Mg}_2\text{Cl}_3]^+ [\text{Zn}_2\text{Et}_5]^-$ (**1**).

X-ray crystallographic studies established the solvent-separated ion-pair structure of **1**. This contains the same dinuclear magnesium-based cation $[(\text{THF})_6\text{Mg}_2\text{Cl}_3]^+$ previously found in the related magnesium zincate $[(\text{THF})_6\text{Mg}_2\text{Cl}_3]^+ [\text{Zn}i\text{Bu}_3]^-$ ^[13] and in the solid-state structures of other conventional Grignard reagents^[18] as well as the stoichiometrically unusual “zinc-rich” anionic $[\text{Zn}_2\text{Et}_5]^-$. Unfortunately, the anion of the structure is affected by a high degree of dynamic and/or static disorder involving the ethyl groups and Zn. A less disordered structure was obtained when the different Grignard reagent EtMgBr was employed as the ethyl source, which led to the isolation of the related trimagnesium dizincate $[(\text{THF})_6\text{Mg}_3(\text{Br})_3(\text{OEt})_2]^+ [\text{Zn}_2\text{Et}_5]^-$ (**2**), containing the same penta(ethyl) dizincate anion as **1** (Figure 1). Although there is still some disorder present which prevents a detailed discussion of the bond lengths and angles of **2**, its connectivity is definite. That notwithstanding,

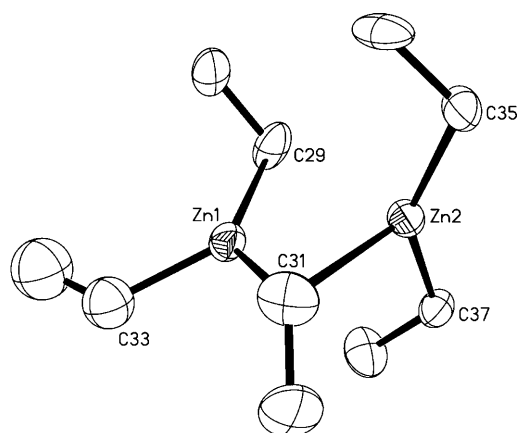


Figure 1. Structure of the anion $[Zn_2Et_3]^-$ present in **2** with 40% probability displacement ellipsoids. Hydrogen atoms and other disorder components are omitted for clarity.

this type of anion which comprises two distorted trigonal-planar zinc centres connected by an ethyl bridge and with two additional terminal Et groups is unprecedented in zincate chemistry.^[19] A close literature analogue is the sodium dizincate $[Na(THF)_6]^+[Zn_2(C_5H_5)_3]^-$, prepared by Carmo and co-workers^[20] using a similar metathetical route as described for **1** and **2**, by reacting sodium cyclopentadiene NaC_5H_5 with $ZnCl_2$ in a 5:2 stoichiometric ratio. Remarkably, by tuning the stoichiometry of this reaction the authors can prepare the corresponding sodium triorganozincate $[(THF)_2NaZn(C_5H_5)_3]$ which contrasts with our observations for the $EtMgCl/ZnCl_2$ system where both stoichiometries (3:1 and 5:2) led to the formation of **1**. Experimentally we found that, when we carried out the reaction of five molar equivalents of $tBuMgCl$ with two molar equivalents of $ZnCl_2$, only trialkyl zincate $[{(THF)_6Mg_2Cl_3}]^+[Zn_2Bu_3]^-$ is formed,^[13] suggesting that, in these metathesis reactions between $RMgCl$ and $ZnCl_2$, the steric demands of the R group play an important role in controlling the constitution of the resulting mixed magnesium–zinc species, overriding the stoichiometry of the starting materials.

We next studied the structure of **1** in $[D_8]THF$ solution [as **1** is sparingly soluble in non-polar solvents our reactivity studies (vide infra) have been carried out in this polar solvent] using NMR spectroscopy.^[21] The room-temperature 1H NMR spectrum showed a single set of resonances for the ethyl groups (a triplet at $\delta=1.09$ and a quartet at $\delta=-0.21$ ppm for the $Zn-CH_3$ and $Zn-CH_2$ groups, respectively) as well as two multiplets at $\delta=3.64$ and 1.76 ppm for free protic THF.^[22] In addition, the ^{13}C NMR spectrum displayed two signals at $\delta=0.8$ and 13.6 ppm that can be easily assigned to the $Zn-CH_2$ and $Zn-CH_3$ groups, respectively. These chemical shifts are similar to those observed in the 1H and ^{13}C NMR spectra of $[ZnEt_2(TMEDA)]$ ^[23] but differ significantly from those found in the spectra of $EtMgCl$,^[24] highlighting the marked “zinc-character” of the mixed-metal compound **1**. The simplicity of these NMR spectra contrasts with the intricate mixture of organometallic species ob-

served in $[D_8]THF$ solutions of $[{(THF)_6Mg_2Cl_3}]^+[Zn_2Bu_3]^-$ ^[13] where the mixed metal compound is in dynamic equilibrium with its monometallic components tBu_2Zn and $tBuMgCl$.^[25] Considering the structure of **1** in the solid state, if retained in solution, two different sets of signals are expected in the NMR spectra, differentiating bridging and terminal Et groups. A variable-temperature study was undertaken (from $25^\circ C$ to $-43^\circ C$) which revealed a dramatic change in the shape and the resolution of the $Zn-CH_2$ resonance (from a well-resolved quartet at room temperature to an extremely broad signal at $-43^\circ C$), hinting at the presence of a rapid dynamic process, which can be slowed-down as the temperature is decreased. To gain further understanding of the real constitution of **1** in solution we next studied its diffusion properties using diffusion-ordered NMR spectroscopy (DOSY).

This methodology can be used to identify different components present in solution as well as to estimate their sizes (which are inversely proportional to their diffusion coefficients, D).^[26] For example, seminal contributions by Williard and co-workers have shown that, using simple organic hydrocarbons as references, accurate hydrodynamic dimensions of several organolithium compounds can be established.^[27] Using a similar approach Mulvey et al.^[28] have recently disclosed the complex composition in THF solution of Knochel’s Turbo Hauser bases.^[29] 1H DOSY NMR spectra of **1** using internal standards^[30] were recorded at room temperature and at $-40^\circ C$.^[21] In both cases all the different components separate in the diffusion dimension according to their relative size (Figure 2). The methylene and methyl resonances of the ethyl groups in **1** show, as expected, a single cross-peak point with the same diffusion coefficient (D), although significantly distinct values were observed for the two different temperatures [$D(25^\circ C)=1.24(3) \times 10^{-9} m^2 s^{-1}$; $D(-40^\circ C)=2.69(1) \times 10^{-10} m^2 s^{-1}$] indicating that the constitution in solution of the anion present in **1** changed dramatically as the temperature decreases. Thus, at room temperature the relevant “Zn–Et” species has a similar size to that of 1-phenylnaphthalene ($D(PhN)=1.18(2) \times 10^{-9} m^2 s^{-1}$) (Figure 2a), whereas at lower temperatures ($-40^\circ C$) its relative size has considerably increased, now lying between those of PhN and TPhN (Figure 2b).

The good linear correlations observed between $\log D$ and $\log V$ (V =molar volume)^[31] of the internal standards^[32] provided two calibration curves (one for each temperature) which can be used to interpolate the relevant value of D observed for the Zn–Et species present in solution when crystals of **1** are dissolved in deuterated THF, providing an approximate value of its size (in terms of its V) and therefore a measure of its constitution in solution. Some important conclusions can be drawn from the comparison of the values obtained [$V(25^\circ C) = 160 cm^3 mol^{-1}$; $V(-40^\circ C) = 226 cm^3 mol^{-1}$] with the DFT optimised molecular volume of $\{Zn_2Et_3\}^-$ ($V = 232 cm^3 mol^{-1}$). Thus, whereas at $-40^\circ C$ the anion $\{Zn_2Et_3\}^-$ seems to be the most plausible species in solution (only 3% error), at room temperature the DOSY data clearly indicate that this anion is not the main species

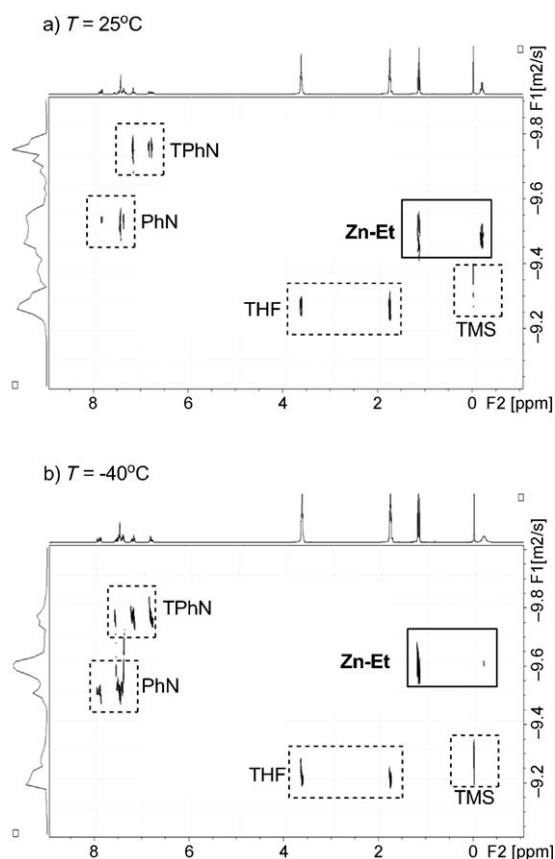


Figure 2. ¹H DOSY NMR experiment in [D₈]THF of **1** in the presence of three internal standards (TPhN: 1,2,3,4-tetraphenylnaphthalene; PhN: phenylnaphthalene; and TMS: tetramethylsilane) at a) 25 °C and b) -40 °C.

present and if it exists, it must be in equilibrium with smaller “Zn–Et” species, which overall have an average volume significantly smaller than that calculated for $\{\text{Zn}_2\text{Et}_3\}^-$ (which gives a ten-fold increase in error of 31%). Figure 3 charts some of these possible smaller aggregates with their respective calculated volumes (V) and the error calculated for every structure with respect to the average V predicted

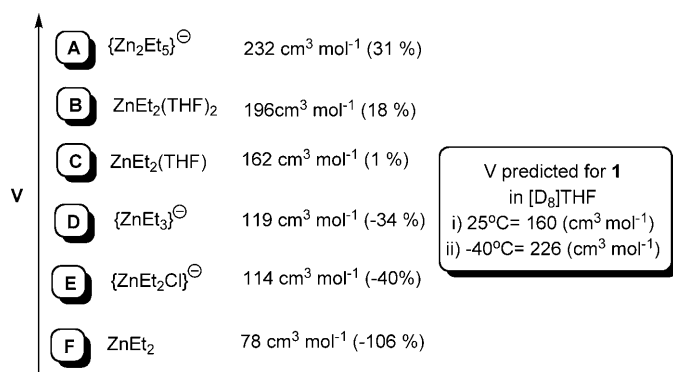
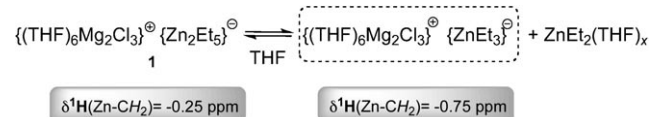


Figure 3. Possible species of the anion $\{Zn_2Et_5\}^-$ present in **1** in $[D_8]THF$ solution with errors (in parentheses) for every consideration with respect to the estimated V value predicted through the DOSY study at 25 °C.

through the room temperature DOSY study. Although this method is not able to establish absolutely the nature of the solution species at room temperature, a plausible situation could be the equilibrium of $\{\text{Zn}_2\text{Et}_3\}^-$ with triethylzincate $\{\text{ZnEt}_3\}^-$ and monomeric diethylzinc (probably solvated by 1 or 2 molecules of THF)^[33] (Scheme 2). Supporting this idea, we have recently reported a similar process for the “zinc-rich” zincate $[(\text{THF})_3\text{LiZn}_2(\text{Me})_3(\text{NAr})_2]$, which in solution is in dynamic equilibrium with triorganozincate $[(\text{THF})\text{LiZn}(\text{Me})(\text{NAr})_2]$ and ZnMe_2 .^[19]

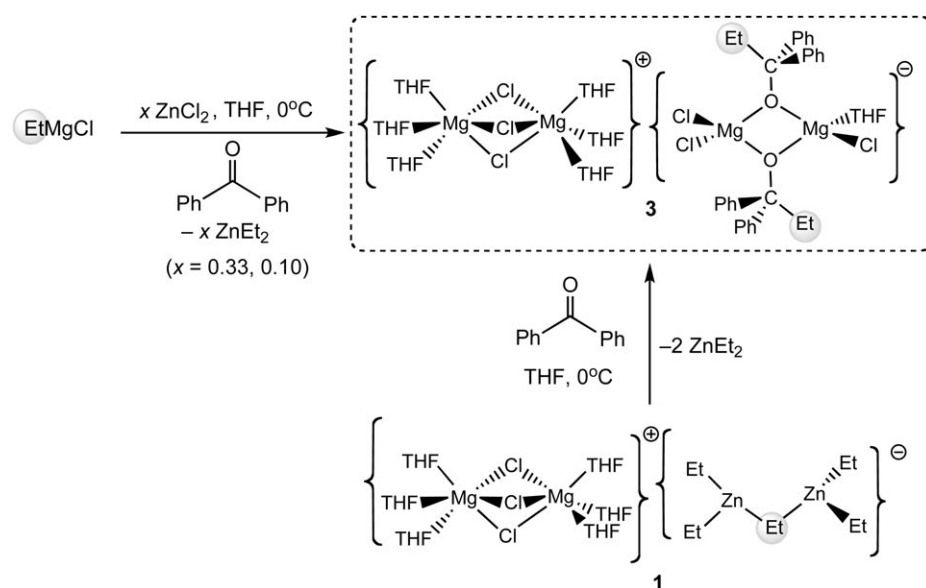


Scheme 2. Plausible temperature-dependent equilibrium process affecting **1** in THF solution.

To explore this idea further, taking advantage of the relatively high volatility of Et_2Zn , we dissolved 0.125 mmol of **1** in deuterated THF (0.5 mL) using ferrocene (0.062 mmol) as an internal standard. The ^1H NMR spectrum of this mixture displayed a quartet at $\delta = -0.25$ ppm for the $\text{Zn}-\text{CH}_2$ unit, the integration of which accounted for 10H (5 Et groups). This solution was then put under vacuum for an hour, affording an orange residue that was redissolved in deuterated THF. Its ^1H NMR spectrum still displayed a single set of resonances for the ethyl groups, significantly upfield in comparison to those in **1** (quartet at $\delta = -0.75$ ppm for $\text{Zn}-\text{CH}_2$) and with a lower relative integration of 6.3H (≈ 3 Et groups). This experiment confirms the presence of volatile ZnEt_2 (or a related THF solvate) as one species present in the THF solution of **1** at room temperature. Furthermore when “ ZnEt_2 ” is removed under vacuum, a new species is formed with a substantially higher carbanionic character (on the basis of $\delta(^1\text{H})$ of the Et groups) than **1**, consistent with the presence of the $\{\text{ZnEt}_3\}^-$ anion. Nicely complementing the DOSY study, these results provide further support for the presence of the equilibrium depicted in Scheme 2, highlighting the complexity of the solution constitution of these mixed-metal compounds.

Alkylation reactions with benzophenone: To investigate whether **1** can be an active species in the chemoselective alkylation reactions of ketones by Grignard reagents in the presence of ZnCl₂, we next pursued a study of its reactivity towards benzophenone. To a solution of **1** in THF cooled to 0°C one molar equivalent of benzophenone was added and the mixture was stirred for one hour.

The resulting solution was then placed in the freezer affording a crop of colourless crystals of the homometallic magnesium compound $[(\text{THF})_6\text{Mg}_2\text{Cl}_3]^+ [\text{Mg}_2(\text{OC}(\text{Et})\text{Ph}_2)_2\text{Cl}_3(\text{THF})]^-$ (**3**) (Scheme 3). For comparison, we also performed the in situ reaction of EtMgCl with variable amounts of ZnCl_2 ($x=0.33, 0.1$) under the same



Scheme 3. Benzophenone alkylation reactions.

conditions, finding that both reactions led to the formation of **3** in isolated yields of 20–25%.

Established by X-ray crystallographic studies the structure of **3** provided confirmation of the successful addition of an ethyl group from **1** to benzophenone. Exhibiting a solvent-separated ion pair structure, magnesium magnesiate **3** contains the same dinuclear cation $\{(THF)_6Mg_2Cl_3\}^+$ as **1**, whereas its anionic counterion is the novel dimagnesium mixed alkoxide–chloride $[Mg_2(OC(Et)Ph)_2Cl_3(THF)]^-$ (Figure 4). Surprisingly, the “magnesium-only” constitution of **3** contrasts with the mixed-metal nature of **1** and paradoxically it represents, to the best of our knowledge, the first example of a structurally defined reaction intermediate of the addition of a zincate to the C=O bond of a ketone.^[34] The structure of the anionic moiety in **3** is composed of two

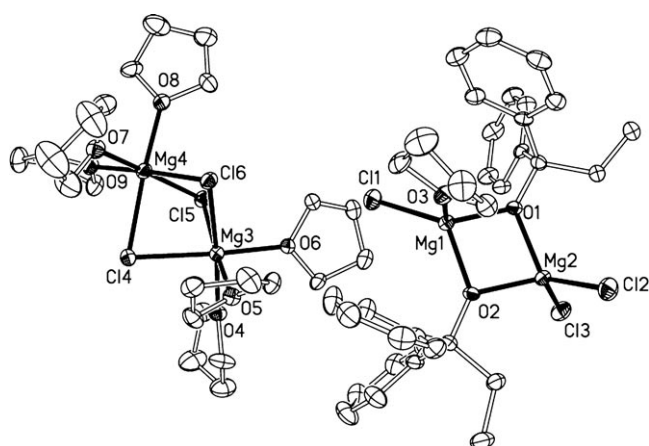


Figure 4. Ion pair structure of **3** showing cation (left) and anion (right) with 40% probability displacement ellipsoids. Hydrogen atoms and minor disorder components are omitted for clarity.

chemically distinct distorted tetrahedrally coordinated magnesium atoms [bond angles ranging from 82.82(7) to 124.66(7)°] connected by the two newly formed bridging alkoxide ligands $\{OC(Et)Ph\}$ (average Mg–O bond length, 1.968 Å). Although there are several examples of related magnesium alkoxides with a dinuclear arrangement,^[35] its non-symmetrical constitution, with Mg1 bonded to one chlorine atom and a THF molecule and Mg2 bonded to two chlorine atoms (Figure 4), is extremely rare.

Also noteworthy in **3**, is the fact that the desired resulting addition product, the alkoxide $\{OC(Et)Ph_2\}^-$ forms part of a magnesiate anion, instead of a

neutral magnesium compound,^[36] which can be an advantage to its further functionalisation, since, in general, magnesiates display an enhanced nucleophilicity than vis-a-vis relevant neutral species. The structural authentication of **3** also highlights the importance of the inorganic salt $MgCl_2$ (here provided by the alkylating reagent **1** but in other in situ methodologies, such as the one reported by Ishihara and co-workers, present in solution as a side product of the $RMgCl/ZnCl_2$ metathesis), which not only provides a solvation anchor for the benzophenone (due to its high Lewis acidity) that will activate it towards the nucleophilic attack of the zincate anion, but also supplies structural support for the resulting alkoxide product ($MgCl_2$ is not only part of the cation in **3** but it also participates in the anionic moiety).

Magnesium–magnesiate **3** was also characterised by 1H and $^{13}C\{^1H\}$ NMR spectroscopy, where the most diagnostic signals confirming the success of the alkylation reaction were a quartet and a triplet at $\delta=2.46$ and 0.74 ppm respectively in the 1H NMR spectrum belonging to the ethyl group adding across the ketone C=O bond. Moreover, the ^{13}C NMR spectrum showed a drastic change in the chemical shift of the carbon that has experienced the addition of **1**, which appears considerably more shielded (at $\delta=80.9$ ppm) than the carbonyl group of benzophenone ($\delta=195.9$ ppm) as a result of its hybridization change (see Experimental Section and Supporting Information for details).

$ZnCl_2$ -mediated addition of $EtMgCl$ to benzophenone: The isolation of the alkylation intermediate **3** prompted us to take a closer look at the reaction of benzophenone and mixed Mg–Zn compound **1** in $[D_8]THF$ solutions. 1H NMR monitoring of the reaction revealed that after 2 h at 0°C, benzophenone and **1** have been fully consumed, generating **3** along with another organometallic product containing ethyl groups whose chemical shifts (quartet and triplet at

$\delta = 0.02$ and 1.12 ppm respectively) are consistent with those of ZnEt₂·MgCl₂ (vide infra) (see Figure S8 in the Supporting Information).^[21] Also observed were small amounts of β -hydride elimination products: namely the relevant reduction alkoxide (whose most diagnostic resonance is a singlet at $\delta = 5.91$ ppm for the hydride that has added across the C=O bond) and ethylene (singlet at $\delta = 5.34$ ppm) (Figure S8).^[21] The relative integration of these species showed that 85 % of the ketone has reacted to yield **3** and only 10 % has experienced the competing β -hydride elimination reaction. The high chemoselectivity of the reaction is similar to that previously reported by Ishihara for the reaction of benzophenone with EtMgCl with 0.3 equivalents of ZnCl₂ (in terms of the ratio of the secondary and tertiary alcohol formed).^[9] By contrast, if the ketone is reacted with EtMgCl in the absence of ZnCl₂, the reduction product is the major product with a modest yield for the alkylation product of 16 %.^[8]

Since **1** possesses five potential alkylating arms the reaction was performed with a 2 molar excess of benzophenone, which showed that half of the ketone was transformed into **3** while the rest was left unreacted, demonstrating that only one of the five ethyl groups present in **1** participates in the alkylation reaction. At this point, it is noteworthy to mention that, DOSY studies have revealed that **1** exhibits a complicated constitution in THF solution. Thus, it is not possible to unequivocally establish whether the alkylation is carried out by the {ZnEt₃}[−] ion or by dizincate {Zn₂Et₅}[−], since both species coexist in dynamic equilibrium (Scheme 2), although it could be expected that a triethylzincate anion would be a stronger nucleophile than related {Zn₂Et₅}[−], where the negative charge is shared by two zinc atoms.^[37]

The high efficiency and chemoselectivity of these alkylation reactions can be rationalised in terms of the synergic alliance of Mg and Zn in **1**. Thus, in general, organozinc reagents are softer nucleophiles and less prone to undergo β -hydride elimination processes than Grignard reagents; however, they are reluctant to react with unactivated ketones due to their relatively low kinetic reactivity.^[38] Here, this kinetic hurdle is easily lowered by the formation of a zincate anion, which can now selectively transfer an Et group to benzophenone.^[39] Magnesium is also an important player in this reaction, as the cation {(THF)Mg₂Cl₃}⁺ (which if maintained in solution will be an even stronger Lewis acid than charge-neutral MgCl₂) will anchor the ketone, activating its carbonyl group through coordination and hence facilitating its nucleophilic attack by the zincate anion, as well as trapping the resulting alkoxide anion to yield **3**. Thus, recent reports have shown that this Mg-Zn partnership has proved successful not only in addition reactions^[8–10] but also in other fundamental organic processes such as nucleophilic substitutions,^[12a] metal-halogen exchange^[13] and coupling applications.^[14,12b]

Along with **3**, the reaction of **1** with benzophenone led to the formation of two equivalents of ZnEt₂ (Figure S8),^[21] which, coupled with the fact that **3** contains only magnesium and no zinc in its formulation, explains how zinc could be

recycled in a catalytic process (similar to the one reported by Ishihara using ZnCl₂ as catalyst),^[8] provided that the co-complexation reaction of the Grignard reagent EtMgCl with ZnEt₂ to form **1** is favoured over the reaction with the ketone (background reaction). Additional DOSY and NMR studies^[21,40] revealed that, in solution, this newly generated ZnEt₂ species interacts with MgCl₂. This is closely related to a recent report by Knochel and co-workers that shows that by adding stoichiometric amounts of MgCl₂ to organozinc reagents it is possible to remarkably accelerate and improve their reactivity towards carbonyl compounds. In our system we found that an equimolar mixture of ZnEt₂/MgCl₂ reacted very slowly with benzophenone (¹H NMR monitoring of the reaction showed 16 % conversion over 20 h at room temperature). Slightly better results were observed when the more activated ketone 2,2,2-trifluoroacetophenone was employed (showing conversions of 38 % and 46 % to the relevant alkylation and reduction products), which contrasts with the complete lack of alkylation reaction observed when homometallic ZnEt₂ is employed, where after 24 h, the relevant secondary alcohol is obtained in a 74 % yield.^[41] Therefore, adding to our previous findings,^[13] these results emphasise even more the significant role that inorganic salts such as MgCl₂ or LiCl (which on many occasions are present in solution due to the common use of in situ metathetical approaches) can play in organic synthesis, where far from being mere spectators, they can interact not only with the organic substrate but also with the organometallic species involved.

We next investigated if magnesium zincate **1** could act as a catalyst for the EtMgCl alkylation of benzophenone. The ¹H NMR spectrum of the reaction mixture of equimolar amounts of the Grignard reagent and the ketone in the presence of 10 mol % of **1** (Figure S8)^[21] showed the almost quantitative formation of **3** (90 % conversion) and only 10 % of the reduction product. This spectrum is reminiscent of that found for the stoichiometric reaction (Figure S8),^[21] with the obvious difference that the amount of ZnEt₂ generated is significantly smaller due to the use of substoichiometric quantities of **1**. The high conversion observed to the alkylated product **3** showed that the competing background reaction of EtMgCl with benzophenone, under these reaction conditions is overridden by the co-complexation with the in situ generated ZnEt₂, recycling the active species **1** that can in turn react with benzophenone. Remarkably, concentration studies have proved that the preference of EtMgCl to form mixed-metal species **1** under catalytic conditions over the reaction with the ketone to yield the reduction product is strongly dependent on the amount of solvent (THF) employed. To explain, contrasting with the excellent conversion results above mentioned, under dilute conditions (0.18 M solution of EtMgCl), the reduction product and **3** are obtained in an almost 1:1 ratio. In addition, mirroring Ishihara's methodology,^[8] the reaction of 1.3 molar equivalents of EtMgCl with benzophenone and 10 % mol of ZnCl₂ (Figure S8)^[21] displayed an identical ¹H NMR spectrum to that obtained when **1** was used as a catalyst, which strongly sug-

gests that mixed-metal (synergic) compounds such as **1** are the genuine alkylating active species in this versatile methodology. The cooperative behaviour of Mg and Zn in **1** in these catalytic processes can also be described in terms of combined Lewis acid-Lewis base activation, an idea widely used in organic chemistry within the context of catalysis,^[42] where magnesium being part of the cationic moiety in **1** acts as a Lewis acid (activating the substrate) whereas the alkylating species is the zincate anion $\{Zn_2Et_5\}^-$, which is a much more powerful nucleophile than charge-neutral ZnR_2 compounds (Lewis base activation).^[11]

Reduction products: One of the missing pieces in this intricate structural jigsaw of alkylation reactions of ketones is the constitution of the reduction co-products obtained as a consequence of competing β -hydride elimination processes. This type of reaction occurs marginally when the Mg–Zn hybrid **1** is employed stoichiometrically (vide supra), but it becomes more important under catalytic conditions, probably as a consequence of the presence of a large excess of Grignard reagent that can compete with zincate **1** to react with the ketone (background reaction). Thus, a 1H NMR spectrum of an aliquot taken from the reaction of $EtMgCl$ with benzophenone at room temperature showed that the alkoxide $\{OC(H)Ph_2\}$ reduction compound is the major product.^[21,43] Attempts to grow crystals of this β -hydride elimination intermediate suitable for X-ray diffraction were unsuccessful. However, when the same reaction was performed using 2,2,2-trifluoroacetophenone colourless crystals of the reduction product $[(THF)_5Mg_3Cl_4\{OC(H)Ph(CF_3)\}_2]$ (**4**) were obtained in a 24% isolated yield. The identity of **4** was confirmed by 1H , $^{13}C\{^1H\}$ and ^{19}F NMR spectroscopy (see Experimental Section) and its molecular structure determined by X-ray crystallography.

Contrasting with the solvent-separated ion pair structure of **3**, mixed magnesium-chloro-alkoxide **4** exhibits a contact ion pair structure with three magnesium centres, each of them in a distinct chemical environment (Figure 5). Distorted tetrahedral $Mg1$ is bonded to a THF molecule, a terminal chlorine and two bridging $\{OC(H)Ph(CF_3)\}^-$ alkoxide anions (resulting from hydride addition to the $C=O$ bond of the ketone)^[44] which connect it to $Mg2$. The latter completes a distorted octahedral geometry by binding to a THF molecule and three chlorines which bridge to distorted octahedral $Mg3$ which in turn is also coordinated by three further THF molecules. This mixture of bridging chloro and alkoxide ligands coupled with the different coordination geometries of the magnesium atoms must contribute significantly to the non-linearity of the $Mg\cdots Mg\cdots Mg$ vector $[134.64(4)^\circ]$. The trinuclear asymmetric structure of **4**; contrasts with the previous example of a reduction product containing magnesium reported by Henderson and co-workers, resulting from exposing benzophenone to the alkylmagnesium amide $[BuMgN(SiMe_3)_2]$, which exhibits a symmetric dimeric arrangement with each magnesium atom solvated by an unreacted ketone molecule.^[45]

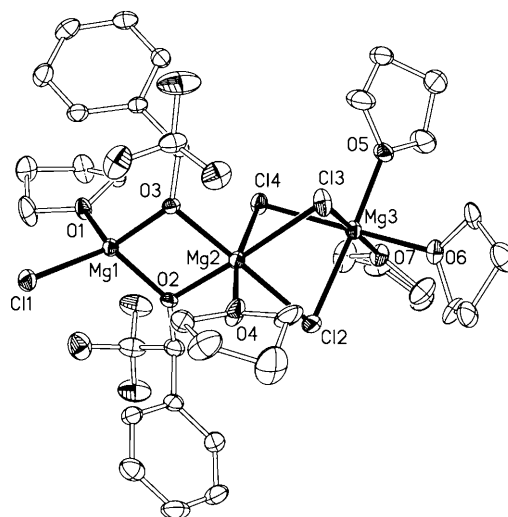


Figure 5. Molecular structure of **4** with 40% probability displacement ellipsoids. Hydrogen atoms and minor disorder components are omitted for clarity.

An alternative view of **4** is as a co-complex of $MgCl_2 \cdot (THF)_3$ (present in solution as a consequence of the Schlenk equilibrium which Grignard reagents can undergo)^[3] with the neutral heteroleptic dimer $[(THF)MgCl\{OC(H)Ph(CF_3)\}]_2$ (obtained by the β -hydride elimination of $EtMgCl$ with the ketone), showing that as in **3**, the inorganic salt is incorporated within the structure of the organometallic intermediate.

Conclusion

Despite the prominent organic studies available for the preparation of tertiary alcohols by reacting Grignard reagents with ketones in the presence of zinc salts, the true constitution of the organometallic species involved in this fundamental synthetic tool have remained unclear. Performed to attempt to advance the knowledge of these reaction intermediates by using an alternative approach rather than performing the reactions in situ followed by a hydrolysis workup, we have structurally defined novel magnesium penta(ethyl) zincate **1** as the mixed Mg–Zn species responsible for carrying out these alkylation reactions (both stoichiometrically and catalytically in the presence of an excess of $EtMgCl$). DOSY NMR studies have revealed the intricate constitution of **1** in THF solutions, which appears to be in a temperature-dependent equilibrium with a related triethyl-zincate species and charge-neutral $ZnEt_2 \cdot (THF)_x$ ($x=0-2$).

Studies of the reaction of **1** with benzophenone led to the isolation and structural authentication of the “magnesium-only” alkoxide-chloro complex **3** as well as to the formation of two molar equivalents of $ZnEt_2$ (detected by 1H NMR monitoring of the reaction) which provide new valuable clues into how zinc can be recycled in the catalytic process

previously reported by Ishihara for the ZnCl₂-catalysed alkylation of ketones using Grignard reagents.

These results highlight the complicated chemistry that magnesium–zincates display in solution as well as the profound influence that the inorganic salts, resulting as co-products of in situ metathetical approaches, may have in the final outcome of these alkylation reactions. Hence, here MgCl₂ does not only have a Lewis acid activating effect (by coordinating to the ketone and therefore enhancing its electrophilicity) but also is incorporated into the constitutions of both the mixed-metal alkylating reagent and the resulting alkylation/reduction products, in which the integrated MgCl₂ provides structural support to the newly formed magnesium-alkoxide species.

Finally we believe this study advances understanding of the addition reactions of Grignard reagents with ketones as well as defining the important role played by ZnCl₂ when it is used as an additive (either catalytically or stoichiometrically) acting as a precursor to the mixed magnesium–zinc species. The synergic partnership of both metals enables the chemoselective alkylation of the ketone, minimising the formation of undesired reduction products by simultaneously increasing the nucleophilicity (anionic component) and electrophilicity (cationic component) of the organometallic reagent, allowing further activation of the organic substrate (through coordination of the ketone to a magnesium-based Lewis acid cation). Collectively, these findings may contribute to further breakthroughs in this intriguing area of mixed-metal chemistry, in particular towards extending the scope of the applications of magnesium zincates to other key organic transformations.

Experimental Section

General conditions: All reactions were performed under a protective argon atmosphere using standard Schlenk techniques. Hexane and THF were dried by heating to reflux over sodium benzophenone ketyl and distilled under nitrogen prior to use. NMR spectra were recorded on a Bruker DPX 400 MHz spectrometer, operating at 400.13 MHz for ¹H, 376.36 MHz for ¹⁹F and 100.62 MHz for ¹³C[¹H]. Satisfactory elemental analysis of compounds 1–4 could not be obtained due to their highly air- and moisture-sensitive nature.

Synthesis of [(THF)₆Mg₂Cl₃]⁺[Zn₂Et₃][−] (1): A solution of ethylmagnesium chloride (5 mL of a 2 M solution in THF, 10 mmol) in THF (2 mL) was cooled to 0 °C, and zinc chloride (0.544 g, 4 mmol) was added, giving a suspension, which was stirred for 1 h at room temperature. The precipitate [(THF)₄MgCl₂] was then removed by filtration, and the filtrate concentrated in vacuo (to approx. 2 mL), hexane (1 mL) was added and then transferred to the freezer (−30 °C). After 48 h a crop of colourless crystals of [(THF)₄MgCl₂] and **1** was isolated. Compound **1** could also be prepared using an alternative co-complexation route by reacting EtMgCl (2.5 mL of a 2 M solution in THF, 5 mmol) with ZnEt₂ (5 mL of a 1 M solution in hexane, 5 mmol) using THF as a solvent (10 mL), which allowed the isolation of pure **1** (0.96 g, 21 %, maximum possible yield 50 %). Better yields could be obtained when the reaction was carried out using a 1:2 ratio of EtMgCl/ZnEt₂ (1.96 g, 45 %). ¹H NMR (400.13 MHz, 298 K, [D₈]THF): δ = 3.64 [m, 24H, OCH₂ THF], 1.76 [m, 24H, CH₂ THF], 1.09 [t, 15H, CH₃, Zn–Et], −0.21 ppm [q, 10H, CH₂, Zn–Et]; ¹³C[¹H] NMR (100.62 MHz, 298 K, [D₈]THF): δ = 68.47 [OCH₂, THF], 26.37 [CH₂, THF], 13.59, [CH₃, Zn–Et], 0.79 ppm [CH₂, Zn–Et].

Synthesis of [(THF)₆Mg₃(OEt)₂Br₃]⁺[Zn₂Et₃][−] (2): To a solution of ethylmagnesium bromide (2 mL of a 1 M solution in THF, 2 mmol) in THF (10 mL), diethylzinc (4 mL of a 1 M solution in hexanes, 4 mmol) was added dropwise. The resulting colourless solution was stirred for 1 h at room temperature, concentrated in vacuo (to ca. 3 mL) and then transferred to the freezer (−30 °C). After 24 h a crop of colourless crystals of [(THF)₄MgBr₂] were isolated (0.14 g, 0.3 mmol). The solvent was removed from the filtrate in vacuo, hexane (1 mL) and THF (1 mL) added, and then returned to the freezer (−30 °C). After 48 h a crop of colourless crystals of **2** were isolated (0.17 g, 24 %). Compound **2** could also be prepared using an alternative metathesis route by reacting EtMgBr (5 mL of a 1 M solution in THF, 5 mmol) with ZnCl₂ (0.272 g, 2 mmol), which allowed the isolation of a crop of colourless crystals of a mixture of **2** and [MgCl₂(THF)₄]. ¹H NMR (400.13 MHz, 298 K, [D₈]THF): δ = 3.81 [brs, 4H, OCH₂, Zn–OEt], 3.61 [m, 24H, OCH₂, THF], 1.77 [m, 24H, CH₂, THF], 1.19 [m, 9H, CH₃, Zn–OEt], 1.13 [t, 15H, CH₃, Zn–Et], −0.19 ppm [brs, 10H, CH₂, Zn–Et]; ¹³C[¹H] NMR (100.62 MHz, 298 K, [D₈]THF): δ = 68.22 [OCH₂, THF], 58.20 [OCH₂, Zn–OEt], 26.32 [CH₂, THF], 21.73 [CH₃, Zn–OEt], 12.56, [CH₃, Zn–Et], 1.93 [CH₂, Zn–Et]. The presence of two ethoxide groups in the cationic moiety of **2** is probably due to partial oxygen contamination of the Grignard reagent, which also explains the low yields obtained for **2**.

Synthesis of [(THF)₆Mg₂Cl₃]⁺[Mg₂(OC(=O)Ph)₂Cl₃(THF)][−] (3): To a solution of ethylmagnesium chloride (2 M solution in THF, 2 mL, 4 mmol) in THF (10 mL) was added zinc chloride (1 M solution in diethyl ether, 0.4 mL, 0.4 mmol). The resulting solution was stirred for one hour at room temperature, cooled to 0 °C in an ice bath, and then benzophenone (0.728 g, 4 mmol) was added, to give a deep pink/red solution which after stirring for 1 h at 0 °C turned light yellow. Approximately half of the solvent was removed in vacuo and hexane (2 mL) was then introduced. The resulting solution was transferred to a freezer (−30 °C). After 24 h a crop of colourless crystals of **3** was isolated (isolated yield = 0.611 g, 23 %). Compound **3** could alternatively be prepared by reacting isolated crystals of **1** (0.863 g, 1 mmol) with benzophenone (0.182 g, 1 mmol) in THF solution (3 mL). The reaction mixture was stirred for one hour at 0 °C, affording a light yellow solution which on cooling deposited a crop of crystals of **3** (isolated yield = 0.284 g, 41 %). ¹H NMR (400.13 MHz, 298 K, [D₈]THF): δ = 7.47 [d, 8H, H_{ortho}], 7.23 [t, 8H, H_{meta}], 7.13 [t, 4H, H_{para}], 3.61 [m, 28H, OCH₂ THF], 2.46 [q, 4H, CH₂, Zn–Et], 1.76 [m, 28H, CH₂ THF], 0.74 ppm [q, 6H, CH₃, Zn–Et]; ¹³C[¹H] NMR (100.62 MHz, 298 K, [D₈]THF): δ = 149.77 [C_{ipso}], 128.96 [C_{ortho}], 128.31 [C_{meta}], 126.85 [C_{para}], 80.79 [C–O], 68.36 [OCH₂, THF], 37.17 [CH₂, Et], 26.39 [CH₂, THF], 10.96 ppm [CH₃, Et].

Synthesis of {(THF)₃Mg₃Cl₄(OC(H)Ph(CF₃))₂} (4): To a solution of ethylmagnesium chloride (2 M solution in THF, 2 mL, 4 mmol) in THF (10 mL) was added 2,2,2-trifluoroacetophenone (0.56 mL, 4 mmol), affording a pale yellow solution. After stirring for 1 h at room temperature, the solvent was removed in vacuo. THF (8 mL) and hexane (1 mL) were then introduced. The resulting pale yellow solution was placed in a refrigerator (5 °C). After 24 h a crop of colourless crystals of **4** was obtained (0.459 g, 25 %). ¹H NMR (400.13 MHz, 298 K, [D₈]THF): δ = 7.74 [m (br), 2H, H_{ortho}], 7.25–7.38 [m (br), 3H, H_{meta} and H_{para}], 5.41 [m (broad), 1H, CH], 3.61 [m, 9H, OCH₂, THF], 1.77 ppm [m, 9H, CH₂, THF]; ¹³C[¹H] NMR (100.62 MHz, 298 K, [D₈]THF): δ = 140.57 [C_{ipso}], 130.11 [C_{ortho}], 128.93 [C_{meta}], 128.78 [C_{para}], 75.43 [C–O], 67.62 [OCH₂, THF], 25.42 ppm [CH₂, THF] (due to the moderate solubility of **4** in [D₈]THF and the relevant resonance for the CF₃ group could not be detected); ¹⁹F NMR (376.36 MHz, 298 K, [D₈]THF): δ = 77.3 [d, ³J_{H–F} = 80.8 Hz].

X-ray crystallography: Data were collected on Oxford Diffraction Xcalibur and Gemini diffractometers with MoK_α radiation. In all three structures disorder was resolved for some THF groups with the aid of restraints on geometry and/or displacement parameters; there is disorder also in the anion of **2**. H atoms were included as riding atoms in geometrically calculated positions. Programs were standard Oxford Diffraction control and data reduction software,^[46] programs of the SHELX family,^[47] and local programs.

Crystal data for 2: C₂₈H₃₈Br₃Mg₃O₈·C₁₀H₂₅Zn₂·C₄H₈O, *M*_r = 1183.6, monoclinic, space group *P*2₁/*n*, *a* = 11.9392(2), *b* = 19.2945(3), *c* =

24.3335(5) Å, $\beta = 101.850(2)^\circ$, $V = 5486.02(17) \text{ Å}^3$, $Z = 4$, $T = 123 \text{ K}$; 26334 reflections collected, 10766 unique, $R_{\text{int}} = 0.040$, 589 refined parameters, 34 restraints, $R(F, F^2 > 2\sigma) = 0.034$, $R_w(F^2, \text{all data}) = 0.066$, goodness of fit (all F^2) = 0.82, final difference map extremes 0.62 and -0.50 e Å^{-3} .

Crystal data for 3: $\text{C}_{24}\text{H}_{48}\text{Cl}_3\text{Mg}_2\text{O}_6 \cdot \text{C}_{34}\text{H}_{38}\text{Cl}_3\text{Mg}_2\text{O}_3 \cdot 2\text{C}_4\text{H}_8\text{O}$, $M_r = 1381.4$, triclinic, space group $P1$, $a = 12.2922(4)$, $b = 17.6084(9)$, $c = 18.4551(9) \text{ Å}$, $\alpha = 76.886(4)^\circ$, $\beta = 73.607(4)^\circ$, $\gamma = 73.777(4)^\circ$, $V = 3631.7(3) \text{ Å}^3$, $Z = 2$, $T = 150 \text{ K}$; 24263 reflections collected, 14588 unique, $R_{\text{int}} = 0.039$, 832 refined parameters, 1430 restraints, $R(F, F^2 > 2\sigma) = 0.046$, $R_w(F^2, \text{all data}) = 0.100$, goodness of fit (all F^2) = 0.80, final difference map extremes 0.50 and -0.37 e Å^{-3} .

Crystal data for 4: $\text{C}_{36}\text{H}_{52}\text{Cl}_4\text{F}_6\text{Mg}_3\text{O}_7$, $M_r = 925.5$, monoclinic, space group $P2_1/n$, $a = 12.7595(4)$, $b = 26.1757(8)$, $c = 13.4412(4) \text{ Å}$, $\beta = 98.802(3)^\circ$, $V = 4436.3(2) \text{ Å}^3$, $Z = 4$, $T = 150 \text{ K}$; 17079 reflections collected, 9102 unique, $R_{\text{int}} = 0.037$, 600 refined parameters, 593 restraints, $R(F, F^2 > 2\sigma) = 0.039$, $R_w(F^2, \text{all data}) = 0.079$, goodness of fit (all F^2) = 0.80, final difference map extremes 0.43 and -0.32 e Å^{-3} . CCDC-791203 (2), CCDC-791204 (3), CCDC-791205 (4), contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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- [24] ^1H NMR spectrum of EtMgCl in $[\text{D}_8]\text{THF}$: $\delta = 1.13$ (t, CH_3), -0.80 ppm (q, $\text{Mg}-\text{CH}_2$); $^{13}\text{C}\{^1\text{H}\}$ NMR spectrum of EtMgCl in $[\text{D}_8]\text{THF}$: $\delta = 14.0$ (CH_3), -2.42 ppm ($\text{Mg}-\text{CH}_2$).
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- [31] The logarithm of the diffusion coefficients can be correlated with the logarithm of the molecular weights (assuming that the size of a molecule is proportional to its FW). However, for the species involved in this study, which contain a single atom (Zn) considerably heavier than the rest of the atoms involved (C, H, Cl and O), the accuracy of this approximation can be compromised. In these cases more meaningful results can be obtained using the correlation of $\log D$ with $\log V$ (V = molar volume). This is nicely exemplified in the Supporting Information of this article where we report the ¹H DOSY experiment at 25°C in [D₈]THF of the well known compound [ZnEt₂(TMEDA)] using the same internal standards as for **1**. Thus, whereas a good fit is observed between its estimated V using DOSY NMR with its calculated V (error –9%), a much greater degree of inaccuracy is obtained between its estimated FW and its actual FW value (error –22%).
- [32] Volumes (cm³mol^{–1}) of the internal standards used and the possible species in [D₈]THF were obtained from their optimised geometries. DFT calculations were used to obtain the optimised geometries of the molecules and ions using the Gaussian G03 computational package. The B3LYP density functionals and the 6–311G** basis set were employed in this exercise. For each optimised species a frequency analysis was performed and no imaginary frequencies were obtained.
- [33] The Supporting Information includes a DOSY study of ZnEt₂ in deuterated THF solution which suggests that at room temperature a mixture of [(THF)_xZnEt₂] (x = 0, 1 and 2) species coexist in equilibrium. In addition, DOSY experiments of an equimolar mixture of ZnEt₂ and MgCl₂ in deuterated THF showed that both species interact in solution, as the estimated V value (175 cm³mol^{–1}) is significantly larger than the average volume predicted when the solution contains only ZnEt₂ (V = 131 cm³mol^{–1}). Thus the presence of heteroleptic species such as [ZnEt₂Cl][–] cannot be ruled out in the solution constitution of **1** at room temperature (see Supporting Information).
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