

Expanding Mg–Zn Hybrid Chemistry: Inorganic Salt Effects in Addition Reactions of Organozinc Reagents to Trifluoroacetophenone and the Implications for a Synergistic Lithium–Magnesium–Zinc Activation

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Abstract: Numerous organic transformations rely on organozinc compounds made through salt-metathesis (exchange) reactions from organolithium or Grignard reagents with a suitable zinc precursor. By combining X-ray crystallography, NMR spectroscopy and DFT calculations, this study sheds new light on the constitution of the organometallic species involved in this important synthetic tool. Investigations into the metathesis reactions of equimolar amounts of Grignard reagents (RMgX) and ZnCl₂ in THF led to the

isolation of novel magnesium–zinc hybrids, [(thf)₂Mg(μ-Cl)₃ZnR]₂ (R = Et, *i*Bu, *n*Bu or *o*-OMe-C₆H₄), which exhibit an unprecedented structural motif in mixed magnesium–zinc chemistry. Furthermore, theoretical modelling of the reaction of EtMgCl with ZnCl₂ reveals that formation of the mixed-

Keywords: addition reactions • cooperative effects • Grignard reaction • magnesium • salt effect • zincates

metal compound is thermodynamically preferred to that of the expected homometallic products, RZnCl and MgCl₂. This study also assesses the alkylating ability of hybrid **3** towards the sensitive ketone trifluoroacetophenone, revealing a dramatic increase in the chemoselectivity of the reaction when LiCl is introduced as an additive. This observation, combined with recent related breakthroughs in synthesis, points towards the existence of a trilateral Li/Mg/Zn synergistic effect.

Introduction

Organozinc compounds are amongst the most valuable and versatile low polarity organometallic reagents in synthesis.^[1] Boasting exceptional functional group tolerance, they play pivotal roles in many key organic transformations, including Negishi cross-couplings,^[2] enantioselective alkylations,^[3] oxidative cross-couplings,^[4] carbometallations^[5] and so forth. An important and widely used synthetic route to prepare organozinc compounds is in situ salt metathesis, in which ZnCl₂ is reacted with a more polar organometallic reagent (commonly RLi or RMgX). This well-established methodology is energetically driven by the formation of coproduced LiCl or MgCl₂ ionic lattices. More often than not the pres-

ence of these inorganic salts in the reaction media and their possible effects on the overall performance of the newly generated organozinc reagent is not studied or even considered. However, recent reports have highlighted the fact that far from being innocent spectators they can play a major role in the final outcome of organozinc reactions. Thus, for example, studies on the catalytic asymmetric arylation of aldehydes have revealed that although salt-free ZnPh₂ allows the isolation of benzylic alcohols with high levels of enantioselectivity (89–94% *ee*), if the arylzinc reagent is generated in situ by reacting PhM (2 equiv; M = Li, MgCl) with ZnCl₂ only racemic alcohols are obtained. These low enantioselectivities have been attributed to the presence of LiCl or MgCl₂ in the reaction mixture, which promote the background addition reaction faster than the catalytic asymmetric addition.^[6]

Adding a new level of complexity to these methods of performing metathesis reactions, it has been claimed that the behaviour of the organozinc reagent can be largely dictated by the organometallic source employed for its preparation. Thus, Lei and Marder et al. reported that in Ni-catalysed oxidative homocoupling reactions of ArZnX compounds there is a dramatic difference in the product yield and kinetics of the reactions depending on whether an aryl-Grignard or aryllithium reagent is used to generate the relevant arylzinc species (a quantitative 100% yield is obtained by using PhMgCl versus a modest 13% when PhLi is employed).^[7] Similarly, Breit and Studte have reported that

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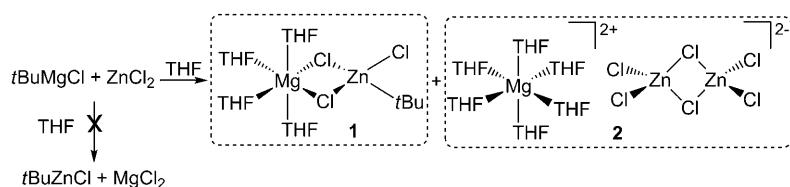
Supporting information for this article is available on the WWW under <http://dx.doi.org/10.1002/chem.201100866>.

substoichiometric additions of ZnCl_2 to Grignard reagents promote enantiospecific $\text{sp}^3\text{--sp}^3$ cross-coupling reactions with α -hydroxy esters, in which the presence of magnesium salts (resulting from metathesis) seems to be critical, since the use of organolithium reagents instead of RMgX inhibits the coupling process.^[8]

Closely related to this topic, recent advances in organic synthesis have shown that the reactivity of organomagnesium and organozinc compounds can be greatly enhanced by using inorganic salts as additives.^[9] Major contributors to this area are the Knochel Turbo-Grignard reagents, $\text{RMgCl}\cdot\text{LiCl}$ ($\text{R} = i\text{Pr}$ or 2,2,6,6-tetramethylpiperidide (TMP)). Unlike conventional monometallic Grignard reagents, these allow direct magnesianation of a myriad of functionalised aromatic molecules through magnesium–halogen or magnesium–hydrogen exchange, without the need for energy wasting cryogenic conditions.^[10]

Within the context of organozinc chemistry, LiCl promotes the direct insertion of elemental Zn into C--X bonds,^[11] as well as mediating alkyl–alkyl Negishi cross-coupling^[12] and carboxylation reactions.^[13] Furthermore, the addition of stoichiometric amounts of MgCl_2 to organozinc reagents has been shown to greatly accelerate their addition to aldehydes, ketones and CO_2 .^[14] Generally, the enhanced zincating power of these $\text{RZnX}\cdot\text{MX}$ mixtures is rationalised in terms of the formation of mixed-metal (zincate) species and the synergic partnership^[15] between the high polarity hard metal (Li or Mg) and the soft Zn . The general acceptance of the bimetallic constitution of these species (formed by co-complexation of the monometallic components)^[16] is somewhat paradoxical when compared with the aforementioned conventional approaches to metathesis, in which the formation of mixed-metal species is rarely invoked even though the newly generated organozinc compound must co-exist in solution with the concomitantly produced inorganic salt (LiX or MgX_2) unless its precipitation is observed.

To shed light on this apparent dichotomy, we have recently investigated the seemingly simple metathesis reaction of equimolar amounts of $t\text{BuMgCl}$ and ZnCl_2 , which revealed a more complex reality for this fundamental synthetic tool, involving the formation of the novel magnesium zincate $[(\text{thf})_4\text{MgZn}(t\text{Bu})\text{Cl}_3]$ (**1**; Scheme 1). Furthermore, a second magnesium–zinc species, homoleptic $[\{\text{Mg}(\text{thf})_6\}^{2+}\{\text{Zn}_2\text{Cl}_6\}^{2-}]$ (**2**; Scheme 1), was identified as a co-product of the reaction, which greatly affects the overall yield of **1** by reducing the amount of ZnCl_2 available to exchange with the Grignard reagent.^[17]

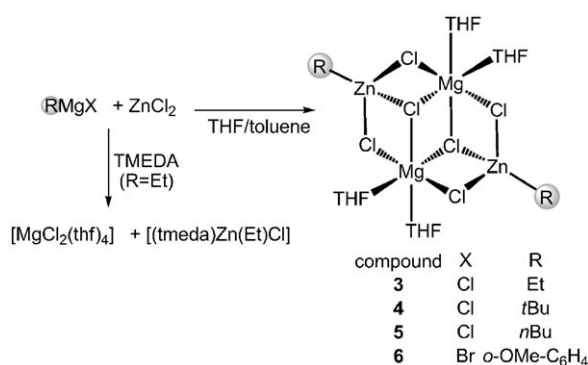


Scheme 1.

Building on these preliminary findings, we extend our studies into salt-metathesis reactions, herein, between Grignard reagents and ZnCl_2 by using them as a new vehicle to prepare mixed magnesium–zinc compounds (Mg--Zn hybrids). Furthermore, with the aid of DFT calculations, we reveal that the formation of these bimetallic species is thermodynamically preferred over the formation of the relevant homometallic products. We also evaluate the ability of these hybrids to function as alkylating agents towards ketones by using the sensitive ketone trifluoroacetophenone as a case study. The chemoselective alkylation of trifluoromethyl ketones is a powerful methodology for accessing trifluoromethyl-substituted tertiary alcohols, which are important subunits in many natural products and pharmaceutical compounds.^[18] However, this approach is compromised by the tendency of these ketones to undergo reduction when reacted with polar organometallic reagents (even when soft organozinc reagents are employed),^[19] which results from a competing β -hydride elimination reaction that is favoured by the presence of the highly electron-withdrawing CF_3 group.^[20] We also report interesting findings after investigating the alkylation activity towards trifluoroacetophenone of several bi- and trimetallic mixtures that combine an organometallic reagent (EtMgCl or EtZnCl) with one or two inorganic additives (LiCl , MgCl_2 or ZnCl_2) and reveal that greater levels of chemoselectivity are obtained when trimetallic combinations are employed, which hints at the existence of a trilateral synergistic effect.

Results and Discussion

Synthesis of new magnesium–zinc hybrids through salt-metathesis reactions: Initially, to assess whether the metathesis/co-complexation reaction shown in Scheme 1, which led to the isolation of magnesium–zinc compound **1**, was a general occurrence, we screened the salt-metathesis reactions of equimolar amounts of ZnCl_2 with a series of different Grignard reagents (EtMgCl , $t\text{BuMgCl}$, $n\text{BuMgCl}$ and $o\text{-OMe-C}_6\text{H}_4\text{MgBr}$; Scheme 2) by using THF as the solvent. In all cases, we observed the almost immediate precipitation of a white solid, which was removed by filtration. Addition of toluene to the remaining solutions allowed the crystallisation of the new magnesium–zinc hybrids, $[(\text{thf})_2\text{Mg}(\mu\text{-Cl})_2\text{ZnR}]_2$ ($\text{R} = \text{Et}$, **3**; $t\text{Bu}$, **4**; $n\text{Bu}$, **5**; $o\text{-OMe-C}_6\text{H}_4$, **6**; Scheme 2) in isolated yields ranging from 24 to 34% (see the Experimental Section for details). As previously observed for the formation of **1**, the relatively modest yields of these bimetallic species can be attributed to the precipitation of magnesium halozincate $[\{\text{Mg}(\text{thf})_6\}^{2+}\{\text{Zn}_2\text{Cl}_6\}^{2-}]$ (**2**; Scheme 1) as a white solid, resulting from the competing co-complexation reaction of ZnCl_2 with MgCl_2 (the latter present in the reaction media due to



Scheme 2.

the Schlenk equilibrium,^[21] which RMgCl reagents undergo in solution). Furthermore, the formation of zinc chloride rich compound **2** is favoured by its low solubility and significantly diminishes the amount of ZnCl₂ available for the metathesis reaction.^[22] Remarkably, when these metathesis reactions were performed by using poorly coordinating toluene as the bulk solvent, magnesium–zinc hybrids **3–6** were obtained in similar yields to those observed when employing neat THF.

In contrast, a dramatic effect on the course of these reactions was observed in the presence of the chelating diamine *N,N,N',N'*-tetramethylethylenediamine (TMEDA). Thus, the reaction of equimolar amounts of the crystalline solvate ZnCl₂·TMEDA^[23] with EtMgCl in neat THF occurs without formation of an insoluble product, affording a colourless solution that, on cooling, deposits colourless crystals. X-ray crystallographic and NMR spectroscopic studies revealed them to be a mixture of the two expected monometallic products of a classical metathesis reaction, namely, TMEDA-solvated alkylzinc chloride [(tmeda)Zn(Et)Cl]^[24] and the magnesium chloride THF solvate [MgCl₂(thf)₄] (Scheme 2), showing that the presence of TMEDA inhibits the formation of mixed magnesium–zinc species (not only metathesis intermediate **3**, but also the insoluble homoleptic species **2**); this illustrates the major role that coordinating solvents can play in bimetallic chemistry.^[25,26]

The bimetallic constitution of magnesium zincates **3–6** was established by X-ray crystallographic studies (Figure 1 and the Supporting Information). Contact ion-pair structures **3–6** display a new structural motif in magnesium–zinc mixed-metal chemistry,^[27] featuring dimeric arrangements that comprise two metal-chloride-connected {(thf)₂MgCl₃ZnR} units. Each magnesium–zinc pair and both magnesium atoms are connected by two bridging chlorines, giving rise to face-fused double heterocubane structures with two missing corners. Alternatively, by using the Mulvey inverse-crown nomenclature for bimetallic ring structures,^[28] **3–6** can be envisaged as [(ZnClMgCl)₂] cationic eight-membered rings hosting two chloride anion guests. The *exo*-disposed R groups coordinate terminally to the distorted tetrahedral zinc atoms, whereas each magnesium centre completes its octahedral coordination by bonding to

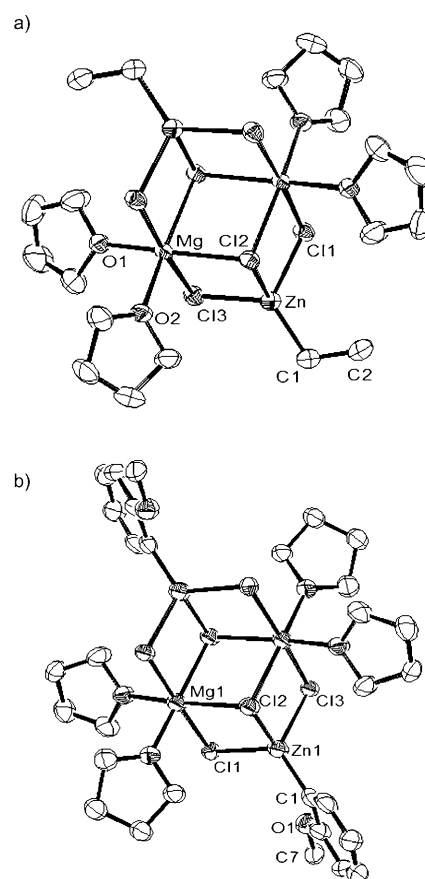


Figure 1. Molecular structures of a) **3** and b) **6** with 40% probability displacement ellipsoids. Hydrogen atoms and minor disorder components are omitted for clarity. Selected geometrical parameters (separations [Å] and angles [°]) for a) **3**: Zn–Cl1 2.3452(6), Zn–Cl2 2.5085(7), Zn–Cl3 2.3265(6), Zn–Cl1 1.967(3), Mg–Cl1 2.4780(10), Mg–Cl2 2.5632(9), Mg–Cl3 2.512(3), Cl1–Zn–Cl2 89.75(2), Cl1–Zn–Cl3 103.38(2), Cl1–Zn–Cl1 120.16(8), Cl2–Zn–Cl3 91.00(2), Cl2–Zn–Cl1 117.76(9), Cl3–Zn–Cl1 125.87(8) and b) **6**: Zn1–Cl1 2.347(2), Zn1–Cl2 2.504(2), Zn1–Cl3 2.3495(19), Zn1–Cl1 1.944(8), Mg1–Cl1 2.524(3), Mg1–Cl2 2.563(3), Mg1–Cl3 2.4912(10), Cl1–Zn1–Cl1 126.7(2), Cl1–Zn1–Cl3 123.6(2), Cl1–Zn1–Cl3 104.31(7), Cl1–Zn1–Cl2 107.0(2), Cl1–Zn1–Cl2 91.94(7), Cl3–Zn1–Cl2 91.90(7).

two mutually *cis* THF solvent ligands. A comparison of the principal dimensions within **3–6** (see Table S2 in the Supporting Information) revealed very little difference between them, including between the Zn–C bond lengths, which cover the narrow range 1.944(8) to 1.982(3) Å. Similar to **1**, magnesium zincates **3–6** can be envisaged as adducts of the two expected homometallic products of the metathesis reaction, MgCl₂ and RZnCl (Scheme 2), in which the inorganic magnesium salt is trapped within the molecular framework of a zincate species before it can aggregate to form an insoluble lattice. The structures of these hybrids, although unprecedented in mixed magnesium–zinc chemistry, bear a close resemblance to those found for the homometallic Grignard reagents [(RMg₂Cl₃(thf)₃)₂] (R = Et, CH₂Ph)^[29] and recently Campora et al. have reported a structurally related mixed magnesium–manganese complex as a side-product in

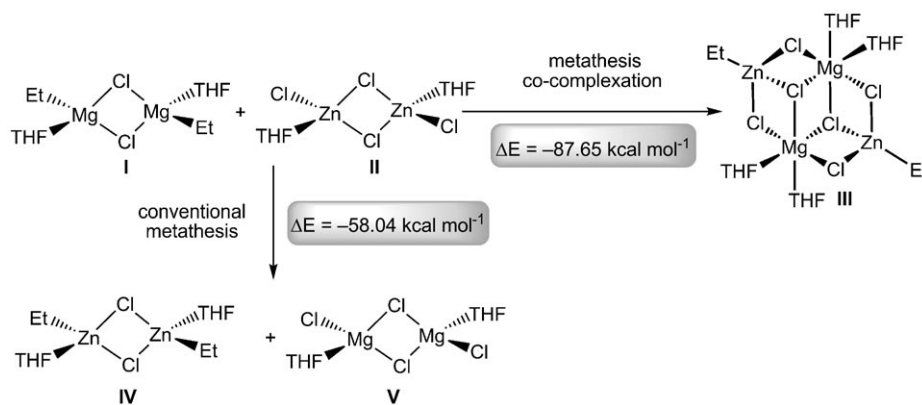
the metathesis reaction of di-benzylmagnesium with MnCl_2 .^[30]

Magnesium zincates $[\{(\text{thf})_2\text{Mg}(\mu\text{-Cl})_3\text{ZnR}\}_2]$ (**3–6**) were also characterised as solutions in $[\text{D}_8]\text{THF}$ by using ^1H and ^{13}C NMR spectroscopy (see the Experimental Section and Supporting Information for full details). Their spectra displayed a single set of resonances for the relevant R group and for free protic THF (displaced by the large excess of the $[\text{D}_8]\text{THF}$ solvent).^[31] The simplicity of these room-temperature NMR

spectra contrasts with the intricate constitution that Grignard reagents RMgX exhibit in solution, in which complex mixtures of different aggregates and organometallic species can be present.^[21a,29b] Remarkably, the chemical shifts displayed in the ^1H and ^{13}C NMR spectra for the R groups present in **3–6** differ significantly from those found for their Grignard precursors (RMgX ; see Table S3 in the Supporting Information), exhibiting values closer to those observed for related monometallic organozinc species. Thus, for example the ^1H NMR spectrum of **3** showed a quartet at 0.06 ppm corresponding to the CH_2 group of the Et fragment, which is similar to that observed for the same group in $[(\text{tmeda})\text{ZnEt}_2]$ (−0.15 ppm) but shifted significantly downfield compared to that in EtMgCl (−0.84 ppm). In the same way, the ^{13}C NMR spectrum of **3** displayed a resonance for the CH_2 group at 1.0 ppm, compared to 1.7 ppm for that in $[(\text{tmeda})\text{ZnEt}_2]$ and −2.4 ppm for that in EtMgCl , reflecting that the Et group in **3** retains most of its zinc character in solution and is less carbanionic than in the Grignard reagent.

To gain a greater understanding of the energetics involved in the formation of these bimetallic hybrids, a theoretical study of the reaction of EtMgCl and ZnCl_2 was also carried out. Firstly, exploratory ab initio calculations at the Hartree Fock (HF) level were performed by using the 6-31G* basis set (for full details see the Supporting Information). The resultant optimised geometries were subjected to a frequency analysis and then refined further by density functional theory (DFT) calculations utilising the B3LYP functionals and the 6-311G** basis set. The total energy taken from the DFT calculation was adjusted by inclusion of the zero point energy value from the HF calculation, modified by a factor of 0.91.^[32]

We evaluated the energies of the reactions of the homometallic reagents $[\{(\text{thf})\text{EtMgCl}\}_2]$ (**I**) and $[\{(\text{thf})\text{ZnCl}_2\}_2]$ (**II**; modelled as THF-solvated dimers, see Scheme 3 and the Supporting Information). Strikingly, the formation of the magnesium–zinc hybrid $[\{(\text{thf})_2\text{Mg}(\mu\text{-Cl})_3\text{ZnEt}\}_2]$ (**III**), obtained through a metathesis co-complexation approach is much more thermodynamically favoured (by 29.61 kcal



Scheme 3. DFT study of the energies of the reactions of the model systems $[\{(\text{thf})\text{EtMgCl}\}_2]$ (**I**) and $[\{(\text{thf})\text{ZnCl}_2\}_2]$ (**II**).

mol^{-1}) than the resulting homometallic products from the classical salt-metathesis reaction, namely, $[\{(\text{thf})\text{EtZnCl}\}_2]$ (**IV**) and $[\{(\text{thf})\text{MgCl}_2\}_2]$ (**V**; Scheme 3). The geometrical optimisation of Mg–Zn hybrid **III** was performed by sequential addition of THF molecules to the solvent-free model $[\{\text{ClMg}(\mu\text{-Cl})_2\text{ZnEt}\}_2]$ (**VIB**),^[32] in which the four metals adopt a linear chain $\text{Zn}\cdots\text{Mg}\cdots\text{Mg}\cdots\text{Zn}$ disposition (which was found to be 11.36 kcal mol^{-1} more stable than its cyclic isomer **VIA**, Figure 2a).

Remarkably when four molecules of THF were introduced (as found in the X-ray structure of **3**), the relative energies of these two theoretical models transposed and, in agreement with our experimental findings, cyclic inverse-crown **IIIA** (in which each Mg centre binds to two THF molecules) becomes the minimum energy theoretical structure (Figure 2b), followed by pseudo-linear chain **IIIB** (at 11.84 kcal mol^{-1}) and then cyclic **IIIC** (at 15.73 kcal mol^{-1} ; in these two models a single THF molecule is coordinated to each metal). Theoretical model **IIID**, resulting from the mere co-complexation of the monometallic components $[\{(\text{thf})\text{EtMgCl}\}_2]$ (**I**) and $[\{(\text{thf})\text{ZnCl}_2\}_2]$ (**II**), is the least stable structure of the four by a significant margin (72.46 kcal mol^{-1}). This energy gap is even more remarkable considering that **IIID** exhibits an almost isostructural motif to that calculated for **IIIA**, in which Mg and Zn have swapped positions and the ethyl group remains bound to Mg, showing that the metathesis (ligand-exchange) reaction is largely thermodynamically driven, without necessarily invoking the formation of a highly ionic lattice (i.e., MgCl_2 here or LiCl in other reactions).

In addition, it should be mentioned that comparison of the calculated bond lengths in the minimum energy theoretical structure **IIIB** with the relevant experimental values taken from the X-ray crystallographic study of **3** (see Table S4 in Supporting Information) show excellent agreement. Collectively, these theoretical studies not only support our experimental findings, but also underline the fact that the presence of mixed-metal species of this type in synthetic methodologies that employ salt-metathesis reactions may be much more common than perhaps initially considered, since

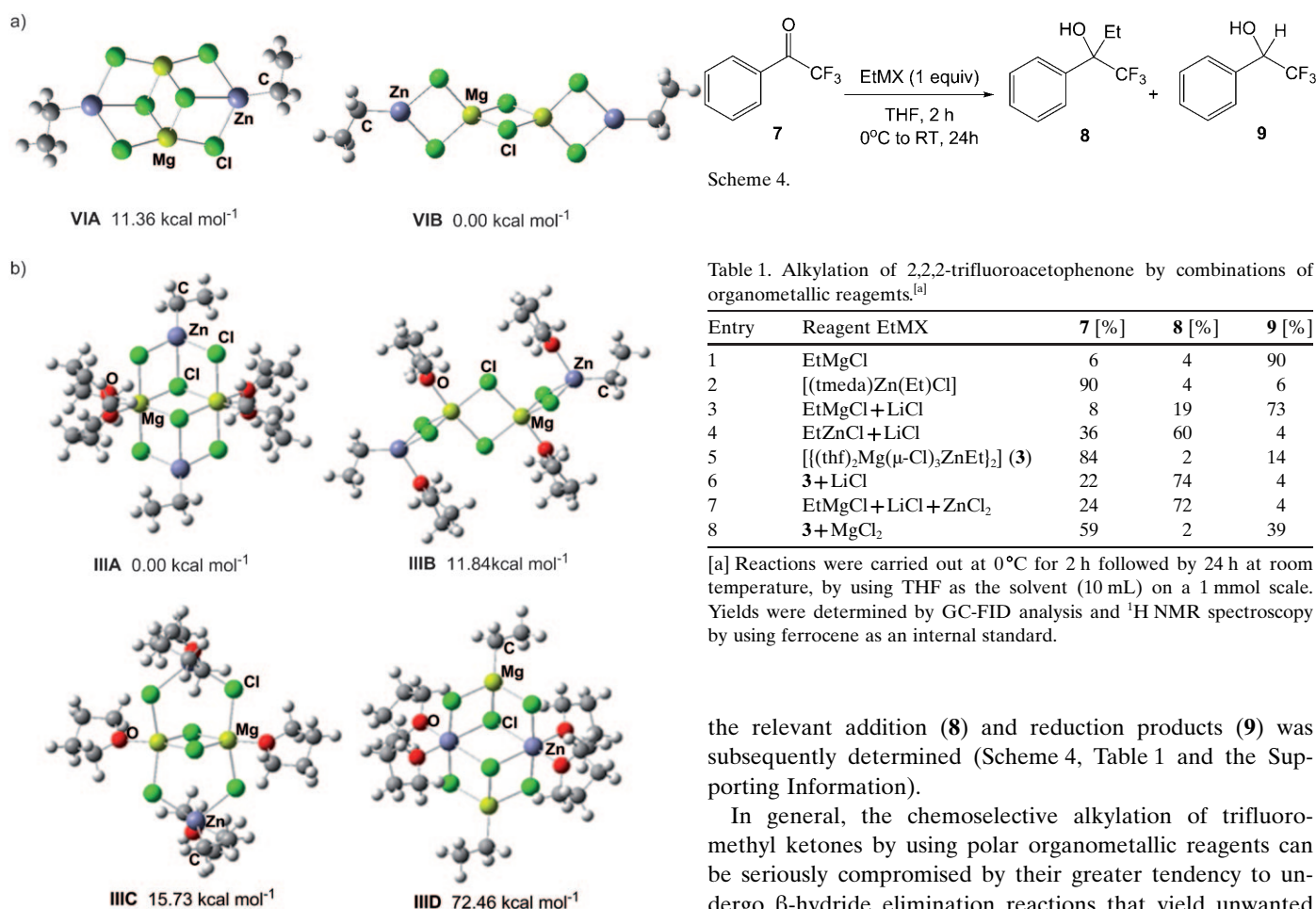


Figure 2. a) Modelled structures and relative energies of solvent free Mg–Zn hybrid **VI** in its two isomeric forms. b) Modelled structures and relative energies of **IIIA–D**.

their formation appears to be not only kinetically favoured, but also strongly thermodynamically driven.

Alkylation studies of trifluoroacetophenone (7): As previously mentioned, Knochel et al. have recently shown that the addition of stoichiometric amounts of MgCl₂ to functionalised organozinc reagents greatly accelerates their (otherwise kinetically retarded) addition to a wide range of ketones, aldehydes and CO₂.^[14] A similar effect has been noted for the Ni-catalysed oxidative homocoupling of ArZnCl, suggesting that mixed magnesium–zinc organometallic compounds might be the actual active species executing these surprisingly efficient reactions.^[7] Building on these recent advances, and in order to assess whether bimetallic species **3–6** could be involved in this type of reaction, we next compared the alkylation ability of the ethyl system [[{(thf)₂Mg(μ-Cl)₂ZnEt]₂] (**3**) towards trifluoroacetophenone (**7**) with that observed for other ethyl-based organometallic combinations (Scheme 4 and Table 1). These reactions were carried out in THF at 0°C for 2 h and then by allowing them to stand at room temperature for 24 h. The conversion of ketone **7** into

the relevant addition (**8**) and reduction products (**9**) was subsequently determined (Scheme 4, Table 1 and the Supporting Information).

In general, the chemoselective alkylation of trifluoromethyl ketones by using polar organometallic reagents can be seriously compromised by their greater tendency to undergo β-hydride elimination reactions that yield unwanted reduction products (**9**).^[20] Thus, the alkylation reaction of **7** with the homometallic reagents EtMgCl or [(tmeda)Zn(Et)Cl] were ineffective, yielding tertiary alcohol **8** in very low yields (4% in both cases, Table 1, entries 1 and 2). Notably, illustrating the marked polarity difference between organomagnesium and organozinc reagents, when EtMgCl was employed a large amount of undesired reduction product **9** (90%) was obtained, whereas the reaction with [(tmeda)Zn(Et)Cl] led to the recovery of the majority of starting material **7** and only 6% secondary alcohol **9** was observed (Table 1, entries 1 and 2). The addition of LiCl as an additive to both monometallic reagents was also examined, revealing a remarkable effect, the enhancement of both the reactivity and the chemoselectivity of EtZnCl (60% yield of **8**, Table 1, entry 4) and, although the reduction product **9** is still the major product (73%), there is a slight increase in the amount of alkylation product **8** (19% versus 4% in the absence of LiCl, Table 1, entries 1 and 3) when using the turbo Grignard reagent combination EtMgClEt·LiCl. Next, the alkylation ability of isolated crystals of magnesium–zinc hybrid **3** was examined, revealing the formation of only trace amounts of tertiary alcohol **8** (2% yield), along with a 14% yield of secondary alcohol **9** and unreacted starting material **7** (84%, Table 1, entry 5). These results are comparable to those observed for [(tmeda)Zn(Et)Cl] (Table 1, entry 2).

The modest alkylating ability of **3** (prepared by mixing equimolar amounts of ZnCl_2 and EtMgCl) contrasts somewhat with the high yields obtained for the relevant tertiary alcohols (up to 78%) when ketone **7** is reacted with Grignard reagents in the presence of substoichiometric amounts of ZnCl_2 (30 mol %).^[33] This significant difference in reactivity can be rationalised in terms of the different constitution of the mixed magnesium–zinc hybrids involved in the reactions.^[34] By using substoichiometric amounts of ZnCl_2 , magnesium trialkylzincates (empirically formulated as R_3ZnMgCl and also formed through a salt-metathesis reaction) have been proposed as the active alkylating species and can be expected to exhibit an enhanced nucleophilicity compared to that of monoalkyl species, such as $[(\text{thf})_2\text{Mg}(\mu\text{-Cl})_3\text{ZnEt}]_2$ (**3**), which are obtained under stoichiometric metathesis conditions. This highlights the importance of the amount of inorganic salts used as additives, since this can give rise to the in situ formation of completely different mixed-metal organometallic species, possessing different reactivity/selectivity patterns.

The poor conversions displayed by **3** contrast even more with those reported by Knochel et al. for the addition reactions of several functionalised RZnX reagents with **7** (60–87%) in the presence of equimolar amounts of MgCl_2 .^[14] Intrigued by this seemingly markedly different reactivity, we then noticed that these functionalised organozinc reagents are generated in the presence of one molar equivalent of LiCl . To probe whether LiCl could also be actively involved in these alkylation reactions, we then studied the alkylation of **7** by magnesium–zinc hybrid **3** with LiCl (one molar equivalent) as an additive (Table 1, entry 6), which gave rise to a dramatic increase in the formation of tertiary alcohol **8** (74% yield). Furthermore, a similarly high conversion was observed when an in situ mixture, combining equimolar amounts of the three distinct metal reagents EtMgCl , LiCl and ZnCl_2 , was employed (Table 1, entry 7).

Intriguingly, in contrast to the beneficial effect of LiCl in these reactions, when the stronger Lewis acid MgCl_2 was employed as an additive, magnesium–zinc hybrid **3** failed to promote the alkylation of **7** (Table 1, entry 8). Although the mechanistic implications of the presence of LiCl on these alkylation reactions can be considerably complex, the chemoselectivity observed could be triggered by the generation of a new trimetallic reagent, in which LiCl has been incorporated within magnesium–zinc hybrid **3**. In this regard, excellent reactivity, structural, theoretical and spectroscopic studies have established that the addition of LiCl (under stoichiometric or catalytic conditions) to monometallic reagents (such as RLi or RMgX) greatly affects their structure and chemical properties through the formation of unique mixed aggregates.^[35,10,16]

In contrast, to the best of our knowledge, the role that LiCl may play when added to bimetallic (ate) reagents (which, by analogy, could potentially lead to trimetallic species) has not been explicitly studied, although the in situ formation of mixed three-component Li/Mg/Zn reagents has already been speculated upon. Thus, Ishihara et al. have re-

ported highly effective alkylation and arylation reactions of ketones by Grignard reagents by using stoichiometric amounts of LiCl and ZnCl_2 as the catalyst. The presence of LiCl seems to be critical to promote these addition reactions and trimetallic $[\text{R}_3\text{Zn}]^-[\text{Li}]^+ [\text{MgX}_2]_m [\text{LiCl}]_n$ is purported to be the active species.^[36] Closely related metallation studies reported by Knochel et al. have revealed that the complex base $[(\text{tmp})_2\text{Zn}] \cdot 2\text{MgCl}_2 \cdot 2\text{LiCl}$ (prepared in situ by the addition of ZnCl_2 to the Turbo mixture $(\text{TMP})\text{MgCl} \cdot \text{LiCl}$) allows the selective direct zincation of sensitive aromatic substrates,^[37] whereas, in the absence of either MgCl_2 or LiCl , the reactions were sluggish and solubility problems were encountered.^[37a]

Similarly, in our studies, we found that when LiCl is present in solution during the metathesis reaction of EtMgCl with ZnCl_2 , the formation of the insoluble magnesium halozincate side-product $[\{\text{Mg}(\text{thf})_6\}^{2+} \{\text{Zn}_2\text{Cl}_6\}^{2-}]$ (**2**) is inhibited, giving rise to homogenous solutions. Remarkably, the NMR spectra of an aliquot of these solution mixtures in deuterated THF showed only one set of resonances for an ethyl group and for free protic THF, suggesting the presence of a single organometallic compound in solution and not a mixture of products under the conditions studied. Furthermore, the chemical shifts observed for the $\text{M}-\text{CH}_2$ group (at -0.03 and 1.8 ppm in the ^1H and ^{13}C NMR spectra, respectively) differ noticeably from those observed for **3** (at 0.06 and 1.0 ppm, respectively) and are distinct from those found for the Grignard reagent EtMgCl ($\text{M}-\text{CH}_2$ at -0.81 and -2.4 ppm, respectively) and for the Turbo Grignard mixture $\text{EtMgCl} \cdot \text{LiCl}$ (at -0.76 and -1.6 ppm, respectively). Remarkably, almost identical NMR spectra to those of in situ formed mixtures were recorded when equimolar amounts of isolated crystals of magnesium–zinc hybrid **3** and LiCl were dissolved in deuterated THF.^[38] This, coupled with our reactivity studies, hints at the possible formation of a trimetallic multicomponent reagent in solution.

Attempts to grow crystals of this putative trimetallic species by decreasing the temperature or adding non-coordinating solvents, such as hexane, to these solutions in THF were unsuccessful and only led to the isolation of THF-solvated inorganic salts. Intriguingly, and in contrast to the relatively large number of alkali-metal magnesiates and alkali-metal zincates that have been structurally characterised, a search of the Cambridge Crystallographic Database revealed that there is no precedent for structures combining these three specific key metals in organometallic synthesis, namely, Li , Mg and Zn . Our ongoing work will aim to synthesise and structural characterise trimetallic species of this type.

Conclusion

By trapping and structurally defining key organometallic intermediates of salt-metathesis reactions that involve equimolar amounts of different Grignard reagents with ZnCl_2 , we expose some of the hidden complexity of this widely used transformational tool. This evidence shows the forma-

tion of mixed-metal magnesium zinc species (Mg–Zn hybrids) of general formula $[(\text{thf})_2\text{Mg}(\mu\text{-Cl})_3\text{ZnR}]_2$.

Furthermore, a DFT computational study of these reactions reveals that these hybrids are significantly more energetically favourable than the “expected” homometallic products (MgCl_2 and RZnCl) of a metathesis reaction that has gone to full completion. These results support the view that mixed-metal compounds of this type can, in fact, be involved in or even responsible for reactivities previously attributed to conventional monometallic organozinc species. Furthermore, by assessing the alkylation reactions of several organometallic combinations towards 2,2,2-trifluoroacetophenone, we established that greater conversions and levels of chemoselectivity are accomplished when the three metals Li, Zn and Mg (accompanied by Cl and alkyl ligands) are present in the reaction mixture, which supports a trilateral-multicomponent partnership that adds a further level of sophistication and intrigue to these reactions. Collectively, we believe these findings provide important structural, theoretical and reactivity insights into the non-innocent role of inorganic salts in organic reactions that involve polar organometallic reagents and should raise awareness when in situ salt-metathesis methodologies are employed to generate the latter. Further investigations into the complicated (but fascinating) role that LiCl can play when added to bimetallic compounds, which can include the modification of not only their structures but also their chemical profiles, are in progress in our laboratory.

Experimental Section

General conditions: All reactions were performed under a protective argon atmosphere by using standard Schlenk techniques. Toluene 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 , 150.32 MHz for ^7Li and 100.62 MHz for $^{13}\text{C}\{^1\text{H}\}$ NMR spectroscopy. Grignard reagents were standardised by using a 1 M solution of 2-butanol in *p*-xylene and *N*-phenyl-1-naphthylamine as an indicator. Single-crystal X-ray diffraction data were recorded on Oxford Diffraction (now Agilent Technologies) Gemini diffractometers by using $\text{MoK}\alpha$ and $\text{CuK}\alpha$ radiation ($\lambda = 0.71073$ and 1.54180 Å, respectively; see the Supporting Information for a table of selected crystallographic data). The structures were solved by direct methods and refined on all unique F^2 values.^[39] Some minor disorder in THF ligands was resolved in the structure of **4**. CCDC-817989 (**3**), 817990 (**4**), 817991 (**5**) and 817992 (**6**) 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.

Synthesis of $[(\text{thf})_2\text{Mg}(\mu\text{-Cl})_3\text{ZnEt}]_2$ (3**):** ZnCl_2 (0.544 g, 4 mmol) was added to a solution of EtMgCl (2 mL, 2 M solution in THF, 4 mmol) in toluene (40 mL) and the resulting suspension was stirred at room temperature for 20 h. The solid was removed by filtration, the filtrate slowly concentrated in vacuo and left to stand at room temperature. After 24 h, a crop of colourless crystals of **3** was obtained (0.493 g, 33%). ^1H NMR (400.13 MHz, 298 K, $[\text{D}_8]\text{THF}$): $\delta = 3.61$ (m, 12H; OCH_2 (THF)), 1.76 (m, 12H; CH_2 (THF)), 1.12 (t, $J = 8.1$ Hz, 6H; CH_3 (Zn–Et)), 0.06 ppm (q, $J = 8.1$ Hz, 4H; CH_2 (Zn–Et)); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.62 MHz, 298 K, $[\text{D}_8]\text{THF}$): $\delta = 68.51$ (OCH_2 (THF)), 26.57 (CH_2 (THF)), 13.11 (CH_3 (Zn–Et)), 0.98 ppm (CH_2 (Zn–Et)).

Synthesis of $[(\text{thf})_2\text{Mg}(\mu\text{-Cl})_3\text{Zn}i\text{Bu}]_2$ (4**):** ZnCl_2 (0.680 g, 5 mmol) was added to a solution of $i\text{BuMgCl}$ (5 mL, 1 M solution in THF, 5 mmol) in toluene (45 mL) and the resulting suspension was stirred at room temperature for 20 h. The solid was removed by filtration, the filtrate slowly concentrated in vacuo and left to stand at room temperature. After 24 h, a crop of colourless crystals of **4** was obtained (0.524 g, 26%). ^1H NMR (400.13 MHz, 298 K, $[\text{D}_8]\text{THF}$): $\delta = 3.62$ (m, 13H; OCH_2 (THF)), 1.77 (m, 13H; CH_2 (THF)), 1.01 ppm (s, 18H; $\text{C}(\text{CH}_3)_3$ (Zn–*t*Bu)); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.62 MHz, 298 K, $[\text{D}_8]\text{THF}$): $\delta = 68.48$ (OCH_2 (THF)), 33.74 ($\text{C}(\text{CH}_3)_3$ (Zn–*t*Bu)), 26.60 (CH_2 (THF)), 22.01 ppm ($\text{C}(\text{CH}_3)_3$ (Zn–*t*Bu)).

Synthesis of $[(\text{thf})_2\text{Mg}(\mu\text{-Cl})_3\text{Zn}n\text{Bu}]_2$ (5**):** ZnCl_2 (0.272 g, 2 mmol) was added to a solution of $n\text{BuMgCl}$ (1 mL, 2 M solution in THF, 2 mmol) in THF (10 mL) and the resulting suspension was stirred at room temperature for 2 h. The solvent was then concentrated in vacuo to approximately 2 mL and toluene (30 mL) was then added. The resulting suspension was stirred for 1 h at room temperature and then the solid removed by filtration. The filtrate was slowly concentrated in vacuo and left to stand at room temperature. After 24 h, a crop of colourless crystals of **5** was obtained (0.197 g, 24%). ^1H NMR (400.13 MHz, 298 K, $[\text{D}_8]\text{THF}$): $\delta = 3.61$ (m, 12H; OCH_2 (THF)), 1.75 (m, 12H; CH_2 (THF)), 1.48 (m, 4H; Zn– $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 1.25 (m, 4H; Zn– $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.82 (t, $J = 7.3$ Hz, 9H; Zn– $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 0.14 ppm (t, $J = 7.8$ Hz, 4H; Zn– $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.62 MHz, 298 K, $[\text{D}_8]\text{THF}$): $\delta = 68.50$ (OCH_2 (THF)), 32.02 (Zn– $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 30.12 (Zn– $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 26.50 (CH_2 (THF)), 14.64 (Zn– $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$), 10.09 ppm (Zn– $\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_3$).

Synthesis of $[(\text{thf})_2\text{Mg}(\mu\text{-Cl})_3\text{Zn}(o\text{-C}_6\text{H}_4\text{OMe})]_2$ (6**):** ZnCl_2 (0.272 g, 2 mmol) was added to a solution of (*o*- $\text{C}_6\text{H}_4\text{OMe}$) MgCl (2 mL, 1 M solution in THF, 2 mmol) in THF (10 mL) and the resulting suspension was stirred at room temperature for 2 h. The solvent was then concentrated in vacuo to approximately 2 mL and toluene (30 mL) was added. The resulting suspension was stirred for 1 h at room temperature and then the solid removed by filtration. The filtrate was slowly concentrated in vacuo and left to stand at room temperature. After 24 h, a crop of colourless crystals of **6** was obtained (0.303 g, 34%). ^1H NMR (400.13 MHz, 298 K, $[\text{D}_8]\text{THF}$): $\delta = 7.39$ (d, $J = 6.8$ Hz, 2H; CH_{meta}), 7.01 (t, $J = 7.7$ Hz, 2H; CH_{para}), 6.73 (t, $J = 7.0$ Hz, 2H; CH_{meta}), 6.66 (d, $J = 8.1$ Hz, 2H; CH_{ortho}), 3.66 (s, 6H; OCH_3), 3.62 (m, 12H; OCH_2 (THF)), 1.75 ppm (m, 13H; CH_2 (THF)); $^{13}\text{C}\{^1\text{H}\}$ NMR (100.62 MHz, 298 K, $[\text{D}_8]\text{THF}$): $\delta = 166.76$ (C_{ipso}), 142.41 (C_{ortho}), 140.20 (C_{meta}), 127.92 (C_{meta}), 121.17 (C_{para}), 109.29 (C_{ortho}), 68.48 (OCH_2 (THF)), 55.38 (OCH_3), 26.53 ppm (CH_2 (THF)).

General procedure for alkylation studies with trifluoroacetophenone: The required metal salt(s) (1 mmol, MX, in which MX = LiCl (0.042 g), ZnCl_2 (0.136 g) or MgCl_2 (0.095 g)) and THF (10 mL) were added to a Schlenk tube and the resulting suspension was sonicated for 1 h to give a solution. The relevant organometallic species [1 mmol, RMX, in which $\text{RMX} = [(\text{thf})_2\text{Mg}(\mu\text{-Cl})_3\text{Zn}(\text{Et})(\text{Cl})]_2$ (**3**; 0.416 g), EtMgCl (0.5 mL, 1 M solution in THF) or EtLi (2 mL, 0.5 M solution in benzene/cyclohexane, 90:10)] was then added to this solution and the resulting solution stirred for 1 h at room temperature. The solution was then cooled to 0 °C and 2,2,2-trifluoroacetophenone (135 μL , 1 mmol) was then introduced. The reaction mixture was stirred for 2 h at 0 °C, then allowed to warm slowly to room temperature and stirred for a further 24 h. The resulting solution was then quenched with a concentrated NH_4Cl solution and the yields of the products and starting material were quantified by ^1H NMR spectroscopy and GC-FID of the crude reaction mixture, by using ferrocene (0.093 g, 0.5 mmol) as an internal standard.

Acknowledgements

We thank the Royal Society (University Research Fellowship to EH), the European Union (grant no. FP2010-RG-268329 to PGA), the Spanish MICINN (DELACIERVA-09-05 to PGA) and the EPSRC for their generous sponsorship of this research in both Strathclyde and Newcastle. We

also owe a debt of gratitude to Professor R. E. Mulvey for many helpful discussions.

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Received: March 21, 2011
Published online: June 7, 2011