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ARTICLE

Structural and Reactivity Insights in Mg-Zn Hybrid Chemistry: Zn-I Exchange and Pd-Catalysed Cross-Coupling Applications of Aromatic Substrates

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Expanding the synthetic potential of Mg-Zn hybrid organyl reagents (generated via transmetallation reactions), this study uncovers a versatile approach, involving a sequence of direct Zn-I exchange and Pd catalysed cross-coupling reactions which grants access to a wide range of asymmetric bis(aryls). By combining X-ray crystallography with ESI-MS and non-deuterium NMR spectroscopic studies, new light is shed on the heterobimetallic constitution of the intriguing organometallic species [(THF)₄MgCl₂Zn(*t*Bu)Cl] (**1**) and [$\text{Mg}_2\text{Cl}_3(\text{THF})_6$]⁺[Zn(*t*Bu)₃]⁻ (**2**), formed through transmetallation of *t*BuMgCl with *n* equivalent amounts of ZnCl₂ (*n* = 1 and 3 respectively). Operating by cooperative effects, alkyl-rich hybrid **2** can effectively promote direct Zn-I exchange reactions with aromatic halides in short periods of time at room temperature in THF solution. The structural elucidation of key organometallic intermediates involved in some of these Zn-I exchanges, provides new reactivity insights into how these bimetallic systems operate. Thus, while the reaction of **2** with 3 equivalents of 2-iodoanisole (**3b**) gives magnesium dizincate [$\text{Mg}(\text{THF})_6$]²⁺[Zn(*o*-C₆H₄-OMe)₃]²⁻ (**4**) which demonstrates the 3-fold activation of the *t*Bu groups attached to Zn in **2**, using 2-iodobenzonitrile (**3i**), only two *t*Bu groups react with the substrate, affording [(THF)₄MgCl(NC-*o*-C₆H₄)ZnI(*o*-C₆H₄-CN)(THF)] (**7**). In **7** Mg and Zn are connected by an aryl bridge, suggesting that the formation of contacted ion-pair hybrids may have a deactivating effect on the outcome of the Zn-I exchange process. A wide range of homoleptic tris(aryl) zincate intermediates have been prepared *in situ* and used as precursors in Pd catalysed cross-coupling reactions, affording bis(aryls) **6a-s** in excellent yields under mild reaction conditions without the need of any additive or polar cosolvent such as NMP or DMI.

Introduction

The reactivity of any organometallic reagent is inherently linked to its structure or structures in solution.¹ For example, it is well known, that the composition of organomagnesium reagents (Grignard reagents) in solution is best described in terms of the Schlenk equilibrium.² Similar equilibria have also been proposed and reported for organozinc and organoaluminium reagents.³ In addition, a multitude of structural, spectroscopic and reactivity studies in organolithium chemistry have exposed the rich structural diversity exhibited by these reagents.⁴ All these polar compounds are used daily worldwide in synthetic laboratories and industrial processes and have found numerous applications.⁵ Many of these important reagents (often depicted by a single simple formula such as RM, RMX; M = Li, Mg, Zn, Cu; X = halide) are, in fact, *dynamic multi-component mixtures* in solution which can contain one, or more reactive organometallic

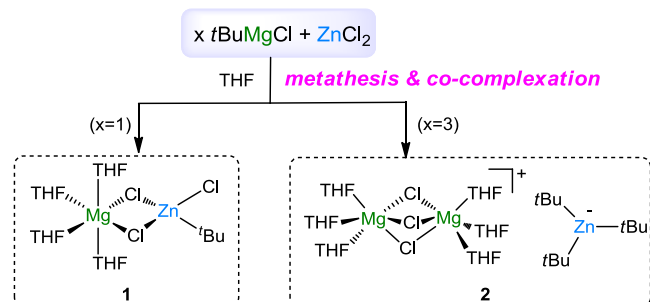
species, in different aggregated and/or solvated states.⁶ Thus, understanding and controlling the complex constitution of these reagents, not only in the solid state but even more importantly, in solution, is crucial since structural variations such as solvation and aggregation can often finely tune their reactivity and selectivity.⁷

Adding a new level of complexity to this area, recent studies have revealed that in many cases the reactivity of these compounds can be greatly affected by the synthetic method chosen for their preparation. For example, magnesium reagents prepared by oxidative metal insertion react generally poorer in Pd-catalysed cross coupling reactions, than the same reagent, prepared by an iodine/magnesium exchange reaction.⁸ Lei has reported a dramatic reactivity difference for arylzinc ArZnCl reagents in Ni-catalysed homo-coupling reactions, depending on whether they are prepared by a transmetallation reaction from

lithium-, or from magnesium reagents.⁹ A similar effect has been noticed by Bedford in iron-catalysed cross-coupling reactions of bis(aryl)zinc reagents with benzyl halides.¹⁰ Furthermore, Knochel has shown that zinc reagents prepared by a transmetallation reaction starting from organomagnesiums, are generally more nucleophilic towards carbonyl functionalities, than zinc reagents, prepared by oxidative insertion of zinc powder.¹¹

In-situ metathesis (or transmetallation) approaches, where a metal ionic salt (such as MgX_2 , ZnX_2 , AlX_3 ; X = halide) is reacted with a high polarity organometallic reagent (commonly RLi or $RMgX$) constitute common methodologies to prepare low polarity organometallic reagents.¹² These reactions are favoured by the concomitant formation of LiX or MgX_2 ionic species which in solution should coexist with the newly generated organometallic species. Although their presence in the reaction media has often been overlooked, a flurry of recent reports has highlighted that, far from being mere spectators, these salts can greatly influence the constitution and reactivity of the newly formed organometallic reagent.¹³ Some of these studies propose the involvement of mixed-aggregates, resulting from the co-complexation of the low-polarity organometallic reagent and the salt byproduct (in a metastable molecular form distinct from the precipitated ionic lattice form), as a plausible explanation for the observed salt-effects.¹⁴ Notwithstanding, it should be noted that tangible proof on the formation of these mixed-metal species is limited and little information is available regarding their constitutions (either in solution or in the solid state).¹⁵

Shedding some light on this intriguing area, in a preliminary report studying the seemingly straightforward metathesis reactions of $ZnCl_2$ with $tBuMgCl$, we disclosed the formation of novel mixed-metal salt intermediates, Mg-Zn hybrids.¹⁶ Depending on the reaction stoichiometry employed bimetallic species $[(THF)_4MgCl_2Zn(tBu)Cl]$ (**1**) and $[\{Mg_2Cl_3(THF)_6\}^+\{Zn(tBu)_3\}^-]$ (**2**) could be isolated and structurally defined (Scheme 1).



Scheme 1 Synthesis of Mg-Zn hybrids **1** and **2** via salt-metathesis reactions

In the solid state, tris(alkyl)zincate **2** exists as a solvent-separated ion pair (SSIP). However, NMR spectroscopic analysis of redissolved crystals of **2** in d_8 -THF revealed that this compound appears to be in equilibrium with at least two other organometallic species, which were assigned to the single metal components tBu_2Zn and $tBuMgCl$. Preliminary reactivity studies showed that THF solutions of **2** undergo a metal-iodine exchange reaction with 4-iodotoluene allowing the isolation of a

magnesium tris(aryl)zincate intermediate resulting from a three-fold activation of all the *t*Bu groups present in hybrid **2**.

Building on these preliminary findings, here we provide a comprehensive study, exploring the synthetic applications of Mg-Zn-hybrid reagents, generated via salt-metathesis (transmetallation) reactions in metal-halogen exchange and Pd catalysed cross-coupling processes. Considering the complex composition of **2** in THF solutions, where at least three main species can be detected (tBu_3Zn^- , tBu_2Zn and $tBuMgCl$), this study assesses which of these components could be responsible for the exchange reaction, or, in other words, whether the process taking place is a genuine halogen-zinc exchange or alternatively a halogen-magnesium exchange reaction (followed by a transmetallation step). Seeking an answer to this fundamental question and in order to get a more detailed picture of the organometallic species participating in such transmetallation mixtures, a series of comparative reactivity studies have been undertaken, in combination with multinuclear NMR spectroscopic and electrospray ionization (ESI) mass spectrometric (MS) analysis.

Furthermore, we present a new synthetically useful protocol, allowing a stepwise sequence of *transmetallation* (generation of Mg-Zn hybrid **2 in situ**), *iodine/zinc exchange* with an aryl iodide (formation of a tris(aryl) intermediate) and Pd catalysed *cross-coupling* reactions to be carried out. The scope and limitations of this new iodine/zinc exchange, as well as trapping and characterization of key reactions intermediates, which provide new reactivity insights into how these bimetallic systems operate, are also presented in this article.

Results and Discussion

Assessing the reactivity of n equivalent $RMgCl/ZnCl_2$ (n = 1, 3) combinations in metal-iodine exchange processes

Different stoichiometric ratios of freshly titrated, commercially available $tBuMgCl$ solution and $ZnCl_2$ (1:1 and 3:1) were prepared in THF and the resulting organometallic mixtures were tested in the halogen-metal exchange reaction using 4-iodoanisole (**3a**) as typical model substrate. Alkyl magnesium compounds are known to undergo halogen-metal exchange reactions.¹⁷ In accordance with this, $tBuMgCl$ showed some reactivity in the exchange reaction with **3a**, although this exchange proceeded slowly at 0–20 °C and after 24 h only 27% of 4-iodoanisole was consumed. No exchange reaction was observable within the first 30 minutes (Figure 1, **A**). Interestingly, on adding 1 equivalent of $ZnCl_2$ to $tBuMgCl$, this limited (but observable) exchange reactivity was completely suppressed. Similarly, a 1:1 mixture of $iPrMgCl$ and $ZnCl_2$ showed no reactivity with **3a**, whereas $iPrMgCl$ on its own reacts efficiently with this substrate at 0 °C within only 5–10 minutes. These findings suggest that under these conditions the transmetallation reaction between the two alkyl magnesium reagents ($RMgCl$; R = *t*Bu, *i*Pr) and $ZnCl_2$ must be complete forming halide-rich Mg-Zn hybrid **1**, a contacted ion pair (CIP)

structure, which is not reactive enough for the desired transformation (Figure 1, B).

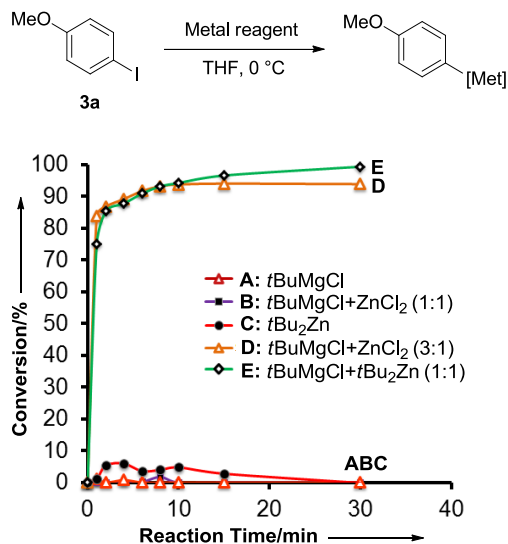


Figure 1. Reaction of 4-iodoanisole (**3a**, 3 mmol) with A: *t*BuMgCl (3 mmol); B: *t*BuMgCl (3 mmol) + ZnCl₂ (3 mmol); C: *t*Bu₂Zn (1.5 mmol); D: *t*BuMgCl (3 mmol) + ZnCl₂ (1 mmol); E: *t*Bu₂Zn (1.5 mmol) + *t*BuMgCl (1.5 mmol); Conversions have been determined by GC-analysis of hydrolyzed reaction aliquots using an internal standard (tetradecane) monitoring the depletion of **3a**. The error is estimated to be ± 3%.

Halide-free *t*Bu₂Zn (purified by sublimation)¹⁸ did not undergo any halogen-zinc exchange reaction (Figure 1, C). Also, combining *t*Bu₂Zn with 2 molar equivalents of anhydrous MgCl₂ did not facilitate the exchange-reaction. In contrast, on treating **3a** with a 3:1 mixture of *t*BuMgCl/ZnCl₂ (presumably forming tris(alkyl) hybrid **2** as a major species in solution) a rapid exchange reaction took place leading to almost full conversion to the corresponding aryl organometallic product, within only 10-15 minutes at 0 °C (Figure 1, D). Comparing these exchange rates, the 3:1 mixture reacted approximately 500 times faster with 4-iodoanisole than did *t*BuMgCl.¹⁹ Tris(alkyl)zincate **2** can also be obtained by the combination of *t*Bu₂Zn with one molar equivalent of *t*BuMgCl. In fact, such mixtures displayed the same high reactivity in the exchange reaction (Figure 1, E). Interestingly, a similar accelerating effect upon addition of ZnCl₂ was observed for other simple alkyl Grignard reagents (Table 1). Reactions of **3a** with RMgCl (where R = Me, Et, Bu, *i*Pr), as well as the corresponding 3:1 mixtures of RMgCl:ZnCl₂ were studied under the same conditions. Primary alkylmagnesium reagents (RMgX; R = Me, Et, Bu) are generally inefficient exchange reagents. In contrast, the mixing of these magnesium reagents with ZnCl₂ in the aforementioned 3:1 stoichiometry prior to the addition of **3a**, led in all three cases to a faster exchange reaction (19-100%, Table 1, Entries 1-3). The secondary alkylmagnesium reagent *i*PrMgCl is a well-known halogen-magnesium exchange reagent.²⁰ Even in the case of an electron rich aromatic iodide (**3a**) a conversion of 86% was readily achieved after 10 min reaction time. Nevertheless, the combination of *i*PrMgCl with ZnCl₂ (3:1) led again to an accelerated exchange, affording complete conversion of **3a** in the same time (Table 1, Entry 4).

These findings revealed that the *in situ* formed ate complexes (presumably [$\{Mg_2Cl_3(THF)_6\}^+\{R_3Zn\}^-$]) are significantly more reactive in halogen-metal exchange processes than the corresponding Grignard reagents from which they are derived. The effect is most pronounced in the case of the tertiary alkylmagnesium reagent *t*BuMgCl where the greatest acceleration is observed (Table 1, Entry 5).

Table 1. Direct comparison of the reactivity of Grignard reagents (RMgX) and the corresponding salt-metathesis mixtures RMgCl/ZnCl₂ (3:1) in the halogen/metal exchange reactions with **3a**.

Entry	R ^a	RMgCl ^b	RMgCl/ZnCl ₂ (3:1) ^{b,c}
1	Me	2%	19%
2	Et	40%	80%
3	<i>n</i> Bu	12%	>95%
4	<i>i</i> Pr	86%	>95%
5	<i>t</i> Bu	0%	>95%

^a Commercially available THF solutions of alkylmagnesium reagents were used, as obtained. ^b Conversion (depletion) of 4-iodoanisole determined by GC-analysis of hydrolysed reaction aliquots with an internal standard (tetradecane). ^c The exchange reagent was prepared *in situ* by mixing RMgCl (3.0 mmol) and ZnCl₂ (1.0 mmol) in THF.

NMR Spectroscopic Studies

To acquire a deeper understanding of the constitution of the organometallic species involved in these transmetallation reactions multinuclear (¹H and ¹³C) studies on *t*BuMgCl/ZnCl₂ mixtures were undertaken. Previously we have shown that when isolated crystals of [$\{Mg_2Cl_3(THF)_6\}^+\{Zn*t*Bu_3\}^-$] (**2**) are dissolved in deuterated THF, this Mg-Zn hybrid is in dynamic equilibrium with its homometallic components.¹⁶ It should be noted that although **2** is the dominant species present in solution, this equilibrium is highly sensitive to its concentration in these THF-d₈ solutions and under diluted conditions, the disproportionation of **2** into *t*BuMgCl and *t*Bu₂Zn becomes much more favourable.²¹ A solvent effect has also been noticed. Thus in non-polar deuterated benzene, **2** exists as a single species displaying one signal in its ¹H NMR for the *t*Bu groups (δ 1.12 ppm) along with two multiplets at 1.38 and 3.69 ppm corresponding to the THF ligands bonded to Mg. The ¹H and ¹³C-NMR spectra of crystalline **2** in THF-d₈ solution and a freshly prepared mixture of *t*BuMgCl and ZnCl₂ in a 3:1 stoichiometry proved to be almost identical, showing that Mg-Zn hybrid **2** is the main component in solution and is not only formed during crystallization.

In order to obtain further knowledge of the species in solution, the constitution of these *t*BuMgCl/ZnCl₂ mixtures was also studied by collecting their NMR spectra in non-deuterated THF (No Deuterium-NMR).²² This approach avoids the tedious removal and replacement of the solvent by expensive THF-d₈ which could potentially alter or influence the composition of the organometallic species present in solution (see Supporting

Information for details). ^1H and ^{13}C NMR spectra of $t\text{BuMgCl}$ (0.86M in THF) show two sets of *tert*-butyl resonances (see Table 2) consistent with the presence of two different aggregates in solution.²³ On adding 1 molar equivalent of ZnCl_2 , both spectra simplify substantially, showing a single *t*Bu-containing species (Table 2, Entry 3). The ^{13}C NMR spectrum shows an informative resonance at 21.8 ppm assignable to the quaternary C of the *t*Bu group, which is further downfield than those observed in the related Grignard precursor (15.4 and 14.8 ppm) but comparable with that found in neutral $t\text{Bu}_2\text{Zn}$ (25.1 ppm, Table 2, Entry 2). These spectra are consistent with a complete transmetallation reaction, forming hybrid $[(\text{THF})_4\text{MgCl}_2\text{Zn}(t\text{Bu})\text{Cl}]$ (**1**) which in solution retains its bimetallic constitution.²⁴ Interestingly, when a 3:1 $t\text{BuMgCl}:\text{ZnCl}_2$ mixture is studied using NoD NMR experiments, the ^1H and ^{13}C spectra are almost identical to those previously discussed in deuterated THF solutions, with tris(*tert*-butyl) zincate **2** co-existing in solution with its two single metal components (Table 2, Entry 4). Following a similar trend to that observed for **1**, the $\{\text{ZntBu}_3\}^-$ anion shows a singlet at 0.82 ppm in the ^1H NMR spectrum whereas the quaternary C of the *t*Bu groups resonates at 23.3 ppm.

Table 2. Chemical shifts (ppm) of the ^1H and $^{13}\text{C}\{^1\text{H}\}$ NMR spectra of $t\text{BuMgCl}$, $t\text{Bu}_2\text{Zn}$ and mixtures n eq $t\text{BuMgCl} + \text{ZnCl}_2$ ($n = 1$ and 3) in THF solutions.

Entry	RM ^a	δ ^1H (Me) ^b	δ ^{13}C (M-C) ^c	δ ^{13}C (Me) ^c
1	$t\text{BuMgCl}$	0.86, 0.85	15.4, 14.8	35.5 34.8
2	$t\text{Bu}_2\text{Zn}$	0.97	25.1	32.5
3	$t\text{BuMgCl} + \text{ZnCl}_2$	0.95	21.8 (br)	33.5
4	3 $t\text{BuMgCl} + \text{ZnCl}_2$	0.88, 0.82 ^d , 0.80(br)	24.8, 23.3 ^d , 15.0, 14.5	35.9 ^d , 35.2, 34.4, 32.5

^a The *in situ* mixtures were prepared by mixing freshly titrated $t\text{BuMgCl}$ with ZnCl_2 in THF in the indicated ratio. ^b δ /ppm, 500 MHz, 27 °C, downfield THF resonance (3.62) was used as a reference. ^c δ /ppm, 125 MHz, 27 °C, downfield THF resonance (68.03) was used as a reference. ^d Resonances belonging to Mg/Zn hybrid **2**, which is the major species present in solution.

The presence of these three different organometallic species in equilibrium poses the question whether the reaction of this mixture with 3-iodoanisole (**3a**) is a genuine Zn-I exchange process, or alternatively, is the result of a Mg-I exchange reaction, to form an arylmagnesium intermediate which in turn can undergo transmetallation with $t\text{Bu}_2\text{Zn}$ or unreacted ZnCl_2 . However, considering the comparative reactivity studies shown above (Figure 1 and Table 1, Entry 1), this last scenario appears to be very unlikely, as the *in situ* generated zincate complex **2** is significantly more reactive in the halogen-exchange process than $t\text{BuMgCl}$. This higher reactivity should affect the position of the above-mentioned equilibrium towards the production of bimetallic **2** which can subsequently react with more substrate.

ESI Mass Spectrometric Studies

Complementary insight into the nature of species involved in these reaction mixtures was obtained from ESI-mass spectrometry. Contrasting with NMR spectroscopy, this technique selectively probes the charged components present in solution.²⁵ Some of our previous studies have shown that ESI-MS can be a useful tool for the detection of solvent-separated organozincate anions present in THF solutions.^{26,14d} Thus, mixtures of n $t\text{BuMgCl}$ ($n = 1$ and 3) and ZnCl_2 in THF were prepared, and diluted aliquots (~ 25 mM) were introduced into the ESI-MS spectrometer (refer to Supporting Information for experimental details).²⁷

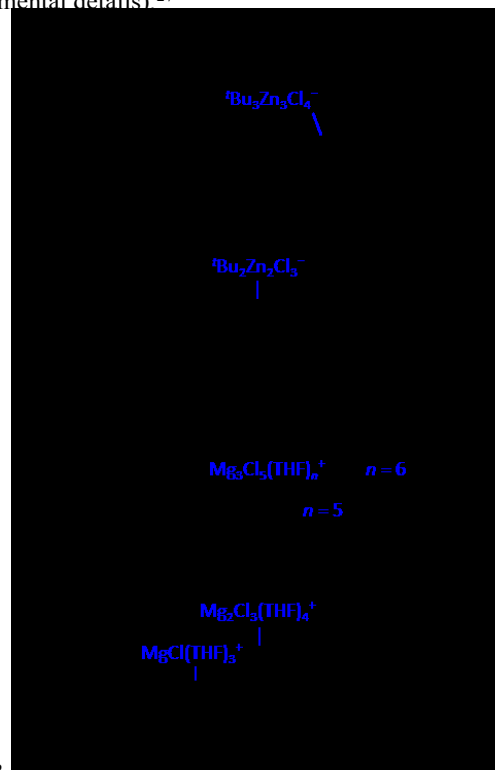


Figure 2. Negative ion mode (top) and positive ion mode (bottom) ESI mass spectra of a 25-molar solution of ZnCl_2 and $t\text{BuMgCl}$ in THF.

$t\text{BuMgCl}/\text{ZnCl}_2$ in a 1:1 ratio. Upon addition of 1 equivalent of ZnCl_2 to a solution of $t\text{BuMgCl}$ in THF, the formation of *tert*-butyl zincate anion $\{t\text{Bu}_3\text{Zn}_3\text{Cl}_4\}^-$ is observed (Figure 2) as the predominant species as well as $\{t\text{Bu}_2\text{Zn}_2\text{Cl}_3\}^-$ ($m/z = 351$) and $\{t\text{BuZnCl}_2\}^-$ ($m/z = 195$, off-scale in Figure 2).²⁸ The formation of $\{t\text{Bu}_2\text{Zn}_2\text{Cl}_3\}^-$ can be rationalized as the stepwise complexation of $t\text{BuZnCl}$ to $\{t\text{BuZnCl}_2\}^-$, with the equilibrium lying on the side of the higher aggregate (note that the concentration enrichment during the ESI process supposedly shifts the equilibrium toward higher aggregation states compared to the situation in the sample solution). The detection of these zincate anions²⁹ contrasts with our previous studies on THF solutions of neutral zinc species RZnCl ($\text{R} = \text{Bu}, \text{Bn}, \text{Ph}$) which afforded only trace amounts of alkyl or arylzincate anions upon negative-ion mode ESI,^{14d} indicating that spontaneous disproportionation of RZnCl in neat THF is not favourable. These results provide further support for the presence of mixed-metal species (Mg/Zn hybrids) in the seemingly simple metathetical reactions between RMgCl and ZnCl_2 . Furthermore,

highlighting the complexity of these reactions, a comparison with the spectra obtained for transmetalation mixtures of lithium alkyl *t*BuLi and ZnCl₂ in a 1:1 ratio, revealed that although in both cases zincate anions are detected, the composition of the latter is more complicated, containing several mononuclear and dinuclear species including {ZnCl₃}⁻ and {*t*Bu₂LiZn₂Cl₄}⁻ which are absent in the *t*BuMgCl/ZnCl₂ mixture.^{26a} These significant differences in the compositions of these salt-metathesis mixtures (which at a superficial understanding would be expected to generate *t*BuZnCl along with either MgCl₂ and LiCl), illustrate the important role that inorganic salts can play in controlling the overall constitution of the newly formed organometallic reagent. Moreover, they also contribute to understanding the different reactivities noted in the literature for RZnX reagents depending on the organometallic source (RMgX or RLi) employed in their preparation.^{9,30}

Turning to the positive ion mode spectra, several THF-solvated magnesium ions ([MgCl(THF)₃]⁺, [Mg₂Cl₃(THF)₄₋₅]⁺ and [Mg₃Cl₅(THF)₅₋₆]⁺) were detected in solution (Figure 2, bottom). Such Mg-cations have been reported before in the solid state, as well as in solution.^{6d,31} The series of cations can be rationalized by stepwise co-complexation of neutral MgCl₂ and the [MgCl]⁺ cation and it is reasonable to assume that they might exist in a dynamic equilibrium in solution. Interestingly, no zinc cations, or cations containing *t*Bu-groups, have been detected though zinc cationic species are known.³²

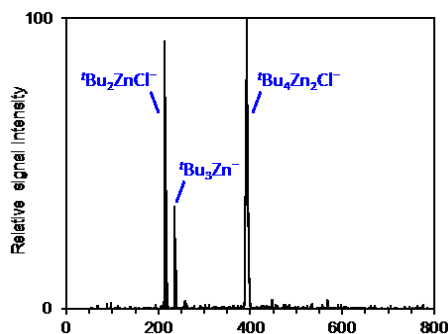


Figure 3. Negative-ion mode ESI mass-spectrum of a 25-mmolal solution of ZnCl₂ and 3 *t*BuMgCl in THF.

***t*BuMgCl/ZnCl₂ in a 3:1 ratio** The negative-ion mode ESI mass spectrum of an *in-situ* prepared THF-solution of 3 equivalents of *t*BuMgCl and ZnCl₂ revealed the presence of three new zincate species {*t*Bu₂ZnCl}⁻, {*t*Bu₃Zn}⁻ and {*t*Bu₄Zn₂Cl}⁻ (*m/z* = 213, 235 and 392 respectively, Figure 3). All these zincate anions are consistent with a higher degree of alkylation and it should be noted that none of them occur in the 1:1 mixtures. The spectra recorded for a crystalline sample of isolated **2** proved to be identical to that shown in Figure 3 (see Figure S15, Supporting Information), which is consistent with the same reactivity observed in the Zn-I exchange reactions with **3a** for the 3:1 *in situ* mixture and the isolated Mg/Zn hybrid **2**. Interestingly, although the tris(alkyl)zincate anion is not the major species present in solution, the equilibrium can be shifted towards its almost exclusive formation by introducing an additional

equivalent of *t*BuMgCl making four in total (see Figure S16, Supporting Information).

Applying Mg-Zn hybrids to direct Zn-I exchange and Pd-catalysed cross-coupling reactions: Structural authentication of key reaction intermediates

Encouraged by the reactivity studies with **3a** (*vide infra*) which show that the metal-halogen exchange process occurs almost quantitatively when treated with a *t*BuMgCl/ 0.33 ZnCl₂ mixture (Figure 1, D), the isolation of the organometallic intermediate previous to the hydrolysis step was attempted, upon cooling the reaction mixture. While this led to the successful isolation of a microcrystalline solid unfortunately it could not be employed for an X-ray crystallographic study. Notwithstanding, the same approach, changing the organic halide to the related 2-iodoanisole (**3b**), led to the isolation of novel tris(aryl) Mg-Zn hybrid [{Mg(THF)₆ }²⁺ {Zn(*o*-C₆H₄-OMe)₃ }₂⁻] (**4**) in an isolated 28% yield whose structure was determined by X-ray crystallography (Figure 4).

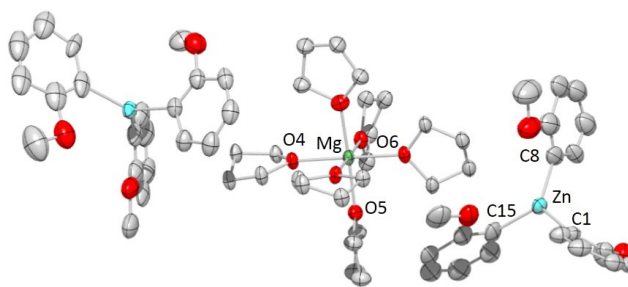


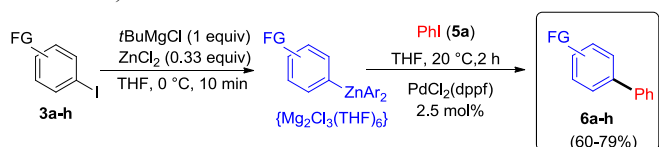
Figure 4. Molecular structure of [{Mg(THF)₆ }²⁺ {Zn(*o*-C₆H₄-OMe)₃ }₂⁻] (**4**) with 30% probability ellipsoids. Hydrogen atoms and minor THF disorder components have been omitted for clarity.

Reinforcing the results gleaned from the reactivity and spectroscopic studies, the structural elucidation of **4** provides further confirmation of the occurrence of a Zn-I exchange process, where each *tert*-butyl group of Mg-Zn hybrid **2** reacts with one equivalent of the aromatic substrate, to generate a new tris(aryl) zincate intermediate. Revealing a new structural modification, **4** comprises an octahedral magnesium dication solvated by six molecules of THF, balanced by two tris(aryl) zincate anions. Interestingly, MgCl₂ is not included in the constitution of this bimetallic intermediate, despite being present in solution as well as being a component of **2**. A plausible explanation could be the presence of several cationic species in equilibrium in THF solution (as hinted by the positive ion-mode ESI-MS spectra, see for example, Figure 2, bottom), with the homoleptic dication {Mg(THF)₆ }²⁺ crystallising preferentially in the case of **4**.³³ Although the isolated yield of **4** is modest (28%), ¹H NMR monitoring of the reaction of isolated crystals of **2** with three equivalents of **3b** in deuterated THF at room temperature showed the almost quantitative formation of **4** (>90% conversion) along with *t*BuI within 20 minutes.³⁴ The high atom economy of this transformation (employing all three *t*Bu arms of **2**) contrasts with previous studies using related lithium zincates [LiZn*t*Bu₃] and [Li₂Zn*t*Bu₄], where equimolar

amounts of the organic halide and the mixed-metal reagent are required.³⁵ Under substoichiometric conditions these mixed Li-Zn species are sluggish to react, which is attributed to their degradation, due to the competing reaction of the *t*Bu groups on the zincate with the generated *t*BuX to form isobutene.³⁶ Also Knochel has shown that ZnAr₂ intermediates can be prepared *in situ* by adding substoichiometric amounts of lithium acetylacetonate, Li(acac), to ZnⁿPr₂ in the presence of several functionalised aromatic iodides (Ar-I); however the use of a highly polar combination of solvents (Et₂O/NMP in a 1:10 ratio; NMP= *N*-methylpyrrolidone) is required to favour the reactions.³⁷

Since the Mg-Zn hybrid approach grants access to homoleptic tris(aryl) zincates in an efficient manner, under mild reaction conditions (room temperature, short reaction times, in the absence of additives), we then tested their applications as precursors in Pd-catalysed Negishi cross-coupling reactions, one of the most powerful methods for C(*sp*²)-C(*sp*²) bond formation in synthesis.³⁸ Informative mechanistic studies on this fundamental process have revealed that the transmetallation of the substituent in the organozinc precursor to the Pd catalyst may be the rate-determining step of the catalytic cycle.³⁹ Interestingly, Organ has recently shown that mixed-halide-alkyl zincates are much more efficient transmetallating reagents in these processes than neutral RZnX reagents, although the solvent choice also plays a major role in these processes and without polar NMP or DMI the couplings do not take place.⁴⁰

To explore the scope of our Mg-Zn hybrid-mediated approach, several aryl iodides (**3**) were treated with a 3:1 mixture of *t*BuMgCl/ZnCl₂ in THF for 2 h, before adding iodobenzene (**5a**) as an organic electrophile, in the presence of 2.5 mol% of PdCl₂(dppf) (dppf = 1,1'-bis(diphenylphosphino)ferrocene).⁴¹ The preliminary cross-coupling results proved very promising as several biphenyls could be isolated in good yields (60-79%) under non-optimized reaction conditions (Scheme 2, Table 3, Entries 1-8).



Scheme 2. Synthesis of asymmetric bis(aryls) **6a-h** by sequential direct Zn-I exchange and Pd-catalysed Negishi cross-coupling reaction with PhI (**5a**).

In general, the substitution pattern of the aryl iodide did not show any significant influence on the efficiency of the iodine/zinc exchange or the cross-coupling conditions. Thus, *p*-, *o*- and *m*-iodoanisole (**3a-c**) furnished the corresponding phenyl-substituted anisole derivatives **6a-c** smoothly in a similar yield (76-79%; Table 3, Entries 1-3). Similarly, *o*-, *m*- and *p*-iodotoluene derivatives (**3d-f**) afforded asymmetric biphenyls **6d-f** in 60-65% yield after successful cross-coupling with iodobenzene (**4a**, Entries 4-6). In the case of iodotoluene derivatives, the isolated yields were lower due to the formation of biphenyl as side product arising from a homo-coupling process. Generally, during the exchange reactions, the use of

electron-rich substrates (iodotoluene, iodoanisole) seemed to favor this competing process; whereas no homo-coupling products were detected when aromatic iodides bearing electron-withdrawing substituents were used.

Nitriles are important synthetic building blocks and the iodine/zinc exchange is perfectly compatible with the cyano group of iodobenzonitriles (**3g-h**). Illustrating the functional group tolerance of this approach, despite its enhanced reactivity, tris(alkyl)zincate **2** did not attack the nitrogen containing unsaturated functional group under the employed reaction conditions and the cross-coupling with iodobenzene (**5a**) provided the coupling products (**6g-h**) in good yields (71-75%, Entries 7-8).^{42,43} Interestingly, when this method was applied to 2-iodobenzonitrile (**3i**), the relevant coupling product **6i** could only be obtained in a modest 31% yield. ¹H NMR monitoring of the reaction of isolated crystals of Mg-Zn hybrid **2** with three equivalents of **3i** revealed that only two of three alkyl groups on the zincate are active towards the Zn-I exchange with this substrate (see Figures S31 and S32, in Supporting Information). This reduced reactivity of **2** towards **3i** is rather surprising as in general aromatic substrates containing strongly electron-withdrawing groups are more activated towards metal-halogen exchange processes, especially if the substitution of the halide is at the *ortho* position of these groups.⁴⁴ Furthermore, after 2 hours at room temperature, the remaining *tert*-butyl group attached to zinc starts to be consumed by reaction with the generated *t*BuI furnishing the bimetallic intermediate [(THF)₄MgCl(NC-*o*-C₆H₄)ZnI(*o*-C₆H₄CN)(THF)] (**7**), along with concomitant release of isobutene (Scheme S1 in Supporting Information).

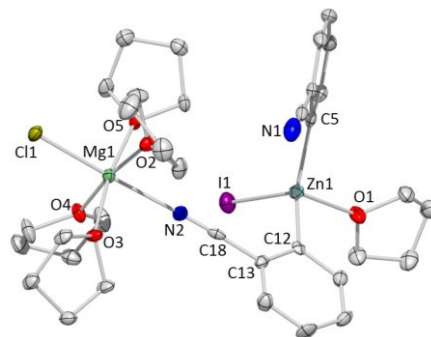


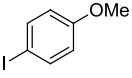
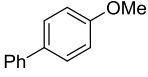
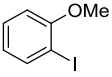
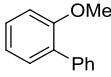
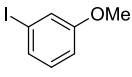
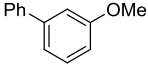
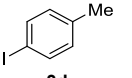
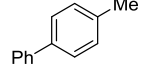
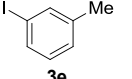
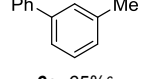
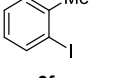
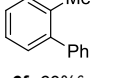
Figure 5. Molecular structure of [(THF)₄MgCl(NC-*o*-C₆H₄)ZnI(*o*-C₆H₄CN)(THF)] (**7**) with 50% probability ellipsoids. Hydrogen atoms have been omitted for clarity.

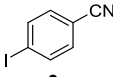
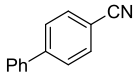
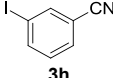
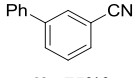
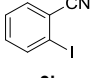
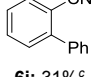
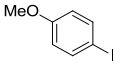
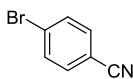
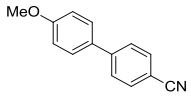
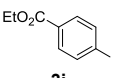
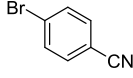
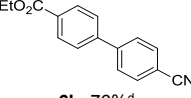
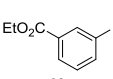
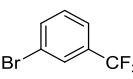
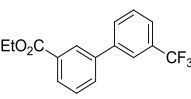

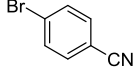
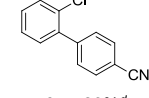
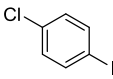
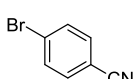
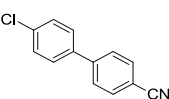
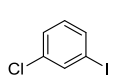
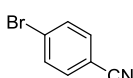
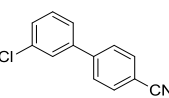
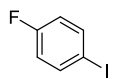
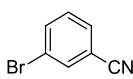
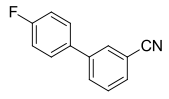
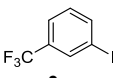
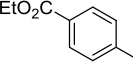
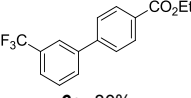
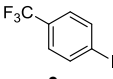
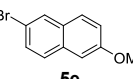
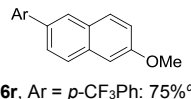

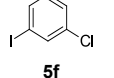
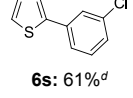
X-ray crystallographic studies established the contacted ion pair (CIP) structure **7** (Figure 5) where both metals are connected by an *ortho*-metallated benzonitrile fragment which coordinates unsymmetrically to the bimetallic system, bonding through its *ortho*-C (C12 in Figure 5) to Zn and through its N atom (N2 in Figure 5) to Mg. Magnesium completes its distorted octahedral coordination by binding to a Cl atom and to four THF molecules whereas distorted tetrahedral Zn binds to a terminal *ortho*-metallated benzonitrile fragment, an iodine atom and a solvating THF molecule. The CIP structure of this hybrid contrasts sharply with the SSIP structures previously determined for precursor **2** and also the Zn-I exchange intermediate **4**.

This structural feature could shed some light on the lack of activation observed for the third *tert*-butyl group present in **2** when reacted with **3i**. A recent theoretical study into Zn-I exchange reactions of lithium tris(alkyl)zincates (LiZnR_3) revealed that in the most energetically favoured pathway the first step of the reaction is coordination of the substrate through its iodine atom to lithium, activating the C-I bond of the arene which facilitates the Zn-I exchange reaction.⁴⁵ If a similar mechanism could be taking place for Mg-Zn hybrid **2**, **3i** would initially coordinate to the cationic Mg centre, allowing anionic $\{\text{Zn}t\text{Bu}_3\}^-$ to react with the activated C-I bond. Assuming that the Zn-I exchange reactions of the three *tert*-butyl groups in **2** occur in a sequential manner, after the successful exchange of two of the alkyl groups, the formation of a putative CIP intermediate $[(\text{THF})_4\text{MgCl}(\text{NC}-o\text{-C}_6\text{H}_4)\text{Zn}(t\text{Bu})(o\text{-C}_6\text{H}_4\text{-CN})(\text{THF})]^{46}$ may hinder the coordination of the third molecule of substrate to magnesium. Furthermore, even if the remaining equivalent of **3i** was able to bind to Mg, the less flexible CIP structure of this intermediate may prevent the approach of the remaining *tert*-butyl ligand close enough to the C-I bond for the exchange reaction to occur.

A similar rationale could also explain the complete lack of reactivity observed for CIP zincate $[(\text{THF})_4\text{MgCl}_2\text{Zn}(t\text{Bu})\text{Cl}]$ (**1**) when reacted with **3a** (*vide supra*) as well as the previously reported use of highly polar cosolvents,³⁷ since the latter should favour the formation of more reactive SSIP species.

Table 3. Iodine/zinc exchange reaction using various aryl iodides (**3**) and subsequent cross-coupling reactions with electrophiles (**5**) using Pd-catalysis, leading to bis(aryls) of type **6**.

	Substrate	Electrophile ^a	Product/Yield ^b
1	 3a	PhI (5a)	 6a : 79% ^c
2	 3b	PhI (5a)	 6b : 76% ^c
3	 3c	PhI (5a)	 6c : 76% ^c
4	 3d	PhI (5a)	 6d : 65% ^c
5	 3e	PhI (5a)	 6e : 65% ^c
6	 3f	PhI (5a)	 6f : 60% ^c

7	 3g	PhI (5a)	 6g : 71% ^c
8	 3h	PhI (5a)	 6h : 75% ^c
9	 3i	PhI (5a)	 6i : 31% ^c
10	 3a	 5b	 6j : 81% ^c
11	 3j	 5b	 6k : 76% ^d
12	 3k	 5c	 6l : 86% ^d
13	 3l	 5b	 6m : 89% ^d
14	 3m	 5b	 6n : 86% ^d
15	 3n	 5b	 6o : 0% ^{d,e}
16	 3o	 5d	 6p : 75% ^d
17	 3p	 5j	 6q : 80%
18	 3q	 5e	 6r , Ar = <i>p</i> -CF ₃ Ph: 75% ^d
19	 3r	 5f	 6s : 61% ^d

^a 0.9-1.0 equivalent of electrophile was used. ^b Isolated yield of product estimated to be of >95% purity according to GC and ¹H-NMR analysis. ^c 2.5 mol% of PdCl₂(dppf) was used. ^d 0.9 mol% of PEPPSI-*i*Pr was used. ^e No reaction was observed even after heating to 50 °C for 24 h.

Regarding the scope of this approach to prepare asymmetric bis(aryls), it was found that aryl bromides could also be used as electrophiles. A cross-coupling reaction occurred smoothly between **3a** and 4-bromobenzonitrile (**5b**) utilizing three different commonly used Pd-catalysts (PEPPSI-*i*Pr,⁴⁷ Pd(OAc)₂/S-Phos,⁴⁸ PdCl₂dppf⁴¹). No significant reactivity differences were observed between the employed catalyst systems and the biaryl **6j** was isolated in 57-81% yield (Entry 10). Upon treatment with hybrid **2** the ester functionalized aryl iodide **3j** could be readily converted to a zinc reagent and subsequent Negishi cross-coupling afforded **6j** in 76 % yield (Entry 11).⁴⁹ Ethyl 3-iodobenzoate (**3k**) reacted in a similar way and cross-coupling with 3-bromo-benzotrifluoride (**5c**) furnished the functionalized biaryl in 86% yield (Entry 12). Contrastingly ethyl 2-iodobenzoate was compatible with the halogen/zinc exchange, but reacted only sluggishly in cross-coupling reactions with PEPPSI-*i*Pr (1.5 mol%) as catalyst.⁵⁰ Interestingly, the 1,2-dihalo-substituted benzene derivative (**3l**) proved to be stable after successful halogen/metal exchange and did not undergo elimination forming an aryne under the present reaction conditions. Whereas *ortho*- and *para*-chloro-iodobenzene (**3l**, **m**) could be readily transformed into zinc reagents and used for further functionalization (Entries 13-14), the zinc reagent derived from *m*-chloro-iodobenzene (**3n**) was reluctant to undergo cross-coupling reactions, even after prolonged heating to 50 °C (Entry 15).⁵¹ Fluorine-containing aromatic compounds play an important role in pharmaceutical science.⁵² Thus, the reactions of different fluorine-containing aromatic iodides (**3o-q**) were tested under these reaction conditions. Pleasingly these substrates could be readily converted to the zincate reagent and used efficiently in cross-coupling reactions affording products **6p-r** in excellent yields (75-80%, Entries 16-18). Furthermore, the heterocyclic substrate 2-iodothiophene (**3r**) reacted in an exchange reaction furnishing a heterocyclic zincate reagent. Its reaction with 3-chloro-iodobenzene (**5f**) furnished the functionalized thiophene **6s** in 61% yield after column chromatographical purification (Entry 19).⁵³

Conclusions

By combining transmetallation reactions with metal-halogen exchanges processes we report an efficient and versatile method which grants access to magnesium tris(aryl) zincate reagents. Firstly, combining X-ray crystallography with NMR spectroscopic and ESI MS studies, we have shed some new light on the complex constitution of the organometallic intermediates involved in the transmetallation reactions of Grignard reagents with variable amounts of ZnCl₂. In all cases mixed-metal magnesium zincates (Mg-Zn hybrids) are formed. Focussing on metal-halogen exchange reactions, a fundamental tool for the functionalisation of aromatic substrates, we report thatSSIP hybrid [$\{Mg_2Cl_3(THF)_6\}^+ \{Zn^+tBu_3\}^-$] (**2**) can effectively

promote direct Zn-I exchange reaction of aromatic halides in short periods of time at room temperature in THF without the need of polar solvent additives. By switching on cooperative effects, the three *t*Bu groups attached to Zn are active towards the exchange, accessing synthetically valuable tris(aryl)zincate anions. Contrastingly, under similar reaction conditions described neither homometallic component *t*BuMgCl or Zn*t*Bu₂ undergo M-I exchange. *In situ* studies, using a range of RMgCl reagents, reveal that in all cases the transmetallation step is faster than the magnesium-iodine exchange process. Contrastingly, using a CIP halide-rich alkyl Mg-Zn hybrid [(THF)₄MgZn(*t*Bu)Cl₃](**1**), the metal-halogen exchange process is totally suppressed.

No Deuterium-NMR and ESI-MS spectroscopic studies probing the organometallic intermediates in these transmetallation mixtures show that in THF solutions, mixed Mg-Zn compounds are the dominant species present, although in the case of *t*BuMgCl/ 0.33 equivalents of ZnCl₂, it appears that hybrid **2** is in equilibrium with its homometallic counterparts. Notwithstanding, considering that neither *t*BuMgCl or Zn*t*Bu₂ can promote M-I exchange reactions, it can be expected that when these mixtures are confronted with the aromatic substrate, this equilibrium will lie toward the formation of **2**. Structural evidence for the success of this reaction was gained by the isolation of the magnesium dizincate intermediate [$\{Mg(THF)_6\}^{2+} \{Zn(o-C_6H_4-OMe)_3\}_2^-$] (**4**), which in agreement with the reactivity studies demonstrates the high atom economy of the Zn-I exchange process. Interestingly, using 2-iodobenzonitrile (**3i**), only two *t*Bu groups react with the substrate, affording [(THF)₄MgCl(NC-*o*-C₆H₄)ZnI(*o*-C₆H₄-CN)(THF)] (**7**), where Mg and Zn are connected by a bridging aryl ligand. These findings suggest that the formation of contacted ion-pair intermediates may have a detrimental effect on the efficiency of the Zn-I exchange process.

Expanding the synthetic utility of these heterobimetallic systems, we have applied this approach to a wide range of substituted aromatic substrates, generating homoleptic tris(aryl) zincate intermediates which in turn can react efficiently in Negishi cross-coupling reactions under mild reaction conditions without the need of a polar co-solvent.

Experimental Section

Typical procedure for the iodine/zinc exchange using *in situ* generated **2** and subsequent cross-coupling reaction

A Schlenk flask was charged with freshly titrated *t*BuMgCl solution (0.96M in THF, 3.12 mL, 2.99 mmol) and a solution of ZnCl₂ in THF (1.0M, 1.0 mmol, 1.0 mL) was added via a syringe at 0 °C. The resulting clear solution was stirred for 5 min at 0 °C before 4-iodoanisole (**3a**, 702 mg, 2.99 mmol) was added. The mixture was stirred for 30 min at 0 °C and subsequently 4-bromobenzonitrile (**5b**, 546 mg, 2.99 mmol) and PdCl₂dppf (54 mg, 0.075 mmol) were added. After stirring for 2 h at 20 °C the reaction was quenched by addition of aq. HCl (2M, 5 mL), the phases separated and the aqueous phase was extracted three times with ethyl acetate. The combined organic extracts were dried with MgSO₄ and the solvent was removed *in vacuo*. The crude product was subjected to column-chromatographic purification (SiO₂, hexane/EtOAc = 10:1) furnishing **6j** as an off-white solid (505 mg, 81%). For analytical data see Supporting Information.

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† Electronic Supplementary Information (ESI) available: [full experimental details, X-ray crystallographic data and copies of the NMR and ESI-MS spectra]. See DOI: 10.1039/b000000x/

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