

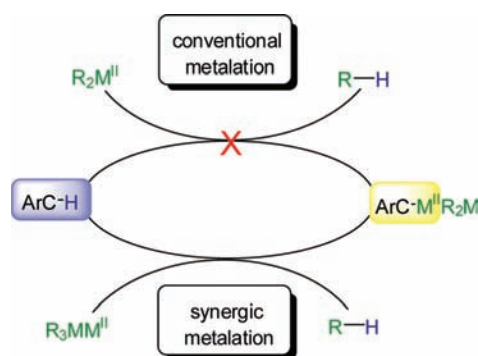
Avant-Garde Metalating Agents: Structural Basis of Alkali-Metal-Mediated Metalation

ROBERT E. MULVEY

WestCHEM, Department of Pure and Applied Chemistry,
University of Strathclyde, Glasgow G1 1XL, U.K.

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CONSPECTUS



Metalation, one of the most useful and widely used synthetic methodologies, transforms a relatively inert carbon–hydrogen bond to a more labile carbon–metal bond. Until recently, most organometallic reagents that facilitate this process have combined strongly electropositive metals, such as lithium, with organic reagents to form highly polar and, by implication, highly reactive carbon–metal bonds. For example, the alkyllithium reagents and bulky lithium amides that are commonly employed for this purpose can suffer from low functional group tolerance. Lithio-products of these reactions generally have low kinetic stabilities.

More recently, several groups around the world have pioneered alternative metalation reagents, complex metalators, which can be interpreted as composite molecules or mixtures made up of two or more distinct compound types. Several examples include magnesiate complexes, Lochmann–Schlosser superbases, Kondo and Uchiyama’s 2,2,6,6-tetramethylpiperidine (TMP)–zincate complexes, and Knochel’s turbo-Grignard and related salt-supported reagents.

This Account describes our rational development of novel complex metalators based on existing structural templates and designed to execute alkali-metal-mediated metalations (AMMMs). By changing the nonalkali metal in these structures, we have produced tailor-made dianionic–dicationic structures such as [(TMEDA) · Na(μ-TMP)(μ-ⁿBu)Mg(TMP)], [(TMEDA) · Na(μ-TMP)(μ-ⁿBu)Zn(ⁿBu)], and [(TMEDA) · Li(μ-TMP)Mn(CH₂SiMe₃)₂] (TMEDA = *N,N,N',N'*-tetramethylethylenediamine). These compounds can perform unprecedented magnesiations, zincations, or manganations on aromatic substrates that are generally inert toward conventional Mg, Zn, or Mn(II) reagents. Although the alkali metal is an essential component of these new complex metalators, interestingly, the less electropositive, less polar nonalkali metal [Mg, Zn, or Mn(II)] actually carries out the deprotonation. We view this unique behavior as a mixed-metal synergic effect: intramolecular communication through metal–ligand–metal bridges directs special regioselectivities or polydeprotonations.

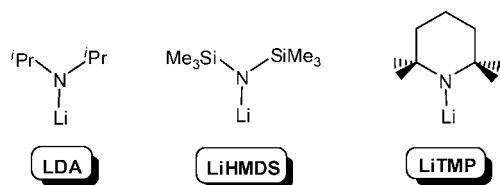
We demonstrate structurally defined alkali-metal-mediated magnesiations (AMMMg), zincations (AMMZn), and manganations [AMMMn(II)] of representative aromatic substrates (including benzene, toluene, anisole, and ferrocene). In addition, we present remarkable *meta*-orientated metalations of toluene and *N,N*-dimethylaniline. We also review 2-fold metalations of arenes, in which an arenediide guest is encapsulated within a 12-atom polymetallic cationic (NaNNaMgN)₂ host ring to form inverse crown structures. Furthermore, using X-ray crystallography of a turbo-Grignard reagent, we establish a link between our complex metalators and turbo-Grignard reagents.

Armed with this accruing knowledge of complex metalators, we think rapid progress in “low polarity metalation” should now be possible. The greatest remaining challenge is to develop methodologies that shift these processes from stoichiometric reactions into more economical catalytic ones.

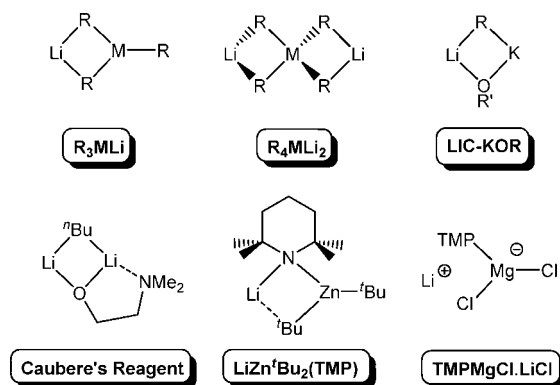
Introduction

Eighty years ago Schlenk (the father of organolithium chemistry) and Bergmann sowed the seeds of the concept of metalation (metal–hydrogen exchange; usually lithium–hydrogen exchange) reporting that ethyllithium reacts with fluorene to produce fluorenyllithium.¹ Today metalation is one of the world's most practiced synthetic methodologies. Supreme players in this art of proton abstraction from organic substrates are organolithium reagents (commonly *n*-butyllithium) closely followed by sterically demanding amides of lithium (of which, diisopropylamide, LDA; 1,1,1,3,3,3-hexamethyldisilazide, LiHMDS; and 2,2,6,6-tetramethylpiperidide, LiTMP, are at the forefront, see Scheme 1). Ziegler first introduced lithium dialkylamide bases in 1932,² and they were subsequently developed as reagents for the enolization of carbonyl compounds. Independent investigations of the lithiation of anisole led Gilman³ and Wittig⁴ to the recognition that heteroatom-containing ring substituents directed the metalation (lithiation) of an aromatic ring to an adjacent (*ortho*) position. DoM (directed *ortho*-metalation) was thus up and running and has continued to advance at a furious pace with major contributions by Beak, Meyers, and Snieckus among others.⁵ These “simple”, in the sense of having monoanionic–monocationic formulations, organolithium and lithium amide reagents are still the reagents of choice (certainly the first ones synthetic practitioners test) for many metalation purposes, but far from all. They suffer from generic faults and limitations. Prominent among these are attacks upon sensitive functional groups, low stabilities of the developing lithioaromatic intermediates, competition from nucleophilic addition (especially in the case of alkyl lithium reagents) and other alternative reaction pathways, and a general requirement for subambient temperature conditions. Abstracting hydrogen from a carbon–hydrogen bond and substituting with a metal to form a new labile carbon–metal bond may appear a trivial exercise to the uninitiated, but in reality metalation chemistry is a complicated jungle, and it is often difficult to predict which reagent will follow the desired path especially when confronted with multihydrogen-containing substrates.

SCHEME 1. The Popular Utility Amides of Lithium



SCHEME 2. Simplistic Representations of a Selection of Complex Metalators



“Complex” Metalators: Ates, Mixed-Metal Superbases, Unimetal Superbases, and Turbo-Grignard Reagents

The fundamental importance of the metalation reaction to modern chemistry has stimulated researchers to continually add to the choice of reagents capable of selectively abstracting hydrogen from organic substrates. Improvements on the performances of existing organolithium and lithium amide bases are sought both for general utilization over a broad range of applications and for specific applications of special significance. Depending on the particular metalation reaction, the requirements of the base may differ, but in general, high reactivity (optimally at ambient temperature), high selectivity (especially an ability to deprotonate at positions inaccessible via other reagents), and high functional group tolerance (both before and after metal–hydrogen exchange) are essential. Through the years, the new reagents introduced for this purpose have become more elaborate than their simple monoanionic–monocationic forerunners. Scheme 2 shows a selection of the best known such “complex metalators”. Their empirical formulas reveal that in common they have composite compositions, made up of two or more distinct families of compounds. Ates, for example, commonly found as “ R_3MLi ” or “ R_4MLi_2 ”, can be regarded in this context as 1:1 and 2:1 mixtures, respectively, of an organolithium compound “ RLi ” and an organometallic compound “ R_2M ” of a divalent metal (e.g., Mg, Zn). Among his many seminal contributions to chemistry, Wittig pioneered ate compounds appreciating the originality of these multicomponent species vis-à-vis their single-component precursors in deprotonation reactions of diphenylmethane.⁶ Whereas these representative common “ R_3MLi ” and “ R_4MLi_2 ” ate formulations can be designated monoanionic–dicationic, the leading Lochmann–Schlosser reagent, LIC–KOR, constitutes a dianionic–dicationic modification, pairing *n*-butyllithium with potassium *t*-butoxide.⁷ On

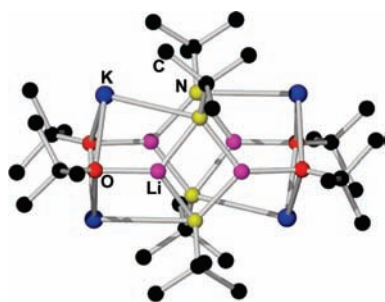
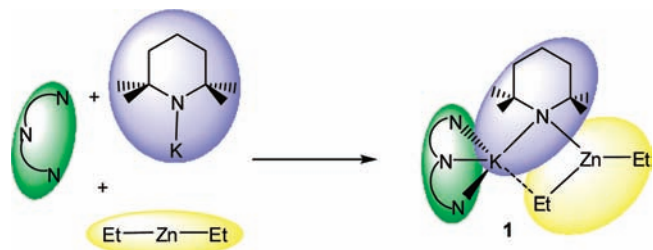


FIGURE 1. Molecular structure of the mixed lithium–potassium amide alkoxide superbases $[(^t\text{BuN}(\text{H}))_4(^t\text{BuO})_4\text{Li}_4\text{K}_4 \cdot (\text{C}_6\text{H}_6)_n]$.

a comparative, qualitative scale of basicity, LIC–KOR occupies an intermediate position higher than *n*-butyllithium but lower than *n*-butylpotassium. The popular description of LIC–KOR as a “superbase” derives from this enhanced reactivity over the former, and while it is less reactive than the latter, its reactivity is generally more controllable kinetically and thus more utilizable than the aggressive unimetal potassium alkyl. Schlosser remarks in elaboration that “the symbiotic action of two different metals (lithium and potassium) suppresses erratic side reactions”.⁷ In contrast to that available on its separate components, definite structural information on the heavily utilized LIC–KOR reagent still proves elusive. Only the lithium primary amide–potassium alkoxide composite $[(^t\text{BuN}(\text{H}))_4(^t\text{BuO})_4\text{Li}_4\text{K}_4 \cdot (\text{C}_6\text{H}_6)_n]$, which displays fused, dimeric $(\text{LiN})_2$ and $(\text{KO})_2$ rings in an attractive carousel arrangement (Figure 1), appears representative of a structurally characterized bona fide superbases, though its synthetic use is extremely limited.⁸ Complementing the mixed-metal LIC–KOR superbases is a series of unimetal superbases⁹ generally of the dianionic–monocationic genre, established by Caubère. Best known is the complex alkyllithium–lithium aminoalkoxide, $^t\text{BuLi}–\text{Me}_2\text{N}(\text{CH}_2)_2\text{OLi}$ (“Caubère’s reagent”) introduced by Caubère and developed further by Gros and Fort.¹⁰ In an excellent thought-provoking review,⁹ which brings out explicitly the intertangled complexity of unimetal superbases and other compounds exhibiting “aggregative activation”, Caubère concedes that “the actual nature of the reactive moiety of superbases are generally inaccurately known or completely unknown”. Though 15 years of further investigation have elapsed since this statement, relatively little disentanglement has been achieved with respect to understanding the structural mechanics of superbasicity. This contrasts with the significant synthetic progress made with metalated pyridines using Caubère’s reagent.¹⁰ Arguably, the avant-garde complex metalators are those in which an alkali metal is an essential component but where the actual metalation is performed by a second metal cocomponent. This is the core principle of

our own research, the details of which are summarized in the next subsection. Ates can be reintroduced into the discussion at this point because they intrinsically fall into this category provided the cocomponent metal is not from group 1. Though the literature contained many precedented examples of specific ate-induced metalations, in 1999 Kondo and Uchiyama reported a notable systematic study of this mixed-metal ate approach.¹¹ Utilizing the monoamido-dialkyl zincate reagent “ $\text{LiZn}^t\text{Bu}_2(\text{TMP})$ ”, a dianionic–dicationic amalgamation, as a complex zincator, they carried out deprotonation reactions of high levels of chemo- and regioselectivity on a series of functionalized aromatics. No structural details of the zincate reagent or of any metalated intermediates were reported in these initial studies. In a creative play on semantics, the super in superbases has been replaced by turbo in “turbo-Grignard” reagents to denote, as with the former, greatly enhanced reactivities, this time in comparison to that of conventional Grignard reagents. Sensitive arenes and heteroarenes previously inert to magnesiation (from conventional Grignard reagents) can now be readily magnesiated by these turbo complex magnesiators.¹² Pioneered by Knochel, the magic potions that effect these unlikely regioselective magnesiations have formulas such as $\text{TMPMgCl} \cdot \text{LiCl}$ (dianionic–dicationic) or $(\text{TMP})_2\text{Zn} \cdot 2\text{MgCl}_2 \cdot 2\text{LiCl}$ (dianionic–tricationic), but when they are utilized in situ in THF solution, details of how their different components interact with each other are sketchy. Mongin has also reported success in direct magnesiation applications of furans with more standard ate formulations (for example, Bu_4MgLi_2).¹³

From this brief survey, the key to finding new improved metalating agents appears to lie in mixing together two or more distinct components to combine different anions with the same cation, different cations with the same anion, or a combination of different anions and different cations. It is said that “l’union fait la force” (“union makes strength”), and in the examples discussed here, this certainly applies as the union of components produces stronger metalators. However, nearly all of these complex metalators have been discovered experimentally through trial-and-error approaches, albeit with logic behind the choice of specific components. For the rational design of tailor-made metalating devices, one should have detailed knowledge of how these different components fit together within a new composite molecule (or molecules) and be able to correlate this structural modification with any enhancement (or diminishment) in reactivity compared with that of its separated components. We have attempted to adopt this combined structural/reactivity strategy in our own studies. As a result we have successfully built structural templates

SCHEME 3. Cocomplexation Synthesis of Potassium Zincate **1**


that are primed for executing alkali-metal-mediated metalation (AMMM). By changing the metal cocomponent within these templates, we have the capacity to tune them to carry out enhanced magnesiations, zincations, or manganations, where *M* is Mg, Zn, or Mn(II).

Alkali Metals: From Laborers to Foremen. When searching for new metalating agents, one must ponder the vast ocean of possibilities available within what is loosely termed “ate chemistry”. Comparatively the collective number of reported, well-characterized ate complexes with well-defined reactivity profiles known to date is but a drop in this ocean. Think about it this way. In theory, every organolithium compound can be transformed into ate complexes of every other metal in the periodic table. Taking into account, the valency of the other metal (for example, the trivalency of aluminum) leads to an exponential increase in the number of possible distinct ate formulations (for example, LiAlR_4 , $\text{LiAlR}_3\text{R}'$, $\text{LiAlR}_2\text{R}'_2$, LiAlRR'_3 , $\text{LiAlR}_2\text{R}'\text{R}''$, $\text{LiAlRR}'_2\text{R}''$, $\text{LiAlRR}'\text{R}''_2$, etc., where R, R', and R'' can be almost any organocarbon, organoelement, or inorganic anion, etc.). This number can be multiplied many times over when adding stoichiometric variants (for example, LiZnR_3 , Li_2ZnR_4 , LiZn_2R_5 , etc.) to the count. Thus, the permutations appear almost infinite, and this is only for organolithium ates; similar hordes of compounds will exist for organosodium ates and organopotassium ates, etc. Such a huge population of mixed-metal compounds must contain a large, diverse range of reactivities and structures, proportionately greater than that of organolithium compounds, which are themselves renowned for their chemical and structural variety. For this reason, to group all these mixed metal compounds together under the designation “ate”, in effect relegating them to a single type of functional group and implying a general chemical profile, seems wholly inadequate. The term “compound” would be only marginally more uninformative. Clearly compounds belonging to ate chemistry need more differentiation and discrimination.

Conceptually, we view the reactions that produce our particular brand of complex metalators as “cocomplexations”. Scheme 3 depicts an example from potassium zincate chem-

istry.¹⁴ Three distinct components of the reaction KTMP , Et_2Zn , and PMDETA interlock to generate the “cocomplex” **1**. KTMP functions dualistically as a K atom Lewis acid toward one Et arm of the zinc alkyl and as an N Lewis base toward zinc; the zinc alkyl functions dualistically in a vice versa manner to the potassium amide, while PMDETA completes the cocomplex by functioning as a tridentate (N_3) Lewis base to the alkali metal. Cocomplex appears more appropriate than “aggregate” because it immediately conveys to the reader a compound with more than one molecular component, whereas aggregate often refers to the association of a single molecular component, such as in hexameric $[(\text{BuLi})_6]$. In fact, aggregation should be avoided when designing the perfect complex metalator as larger (aggregated) molecules are significantly less reactive kinetically than smaller (nonaggregated) counterparts. Molecules that undergo complicated intermolecular equilibria in solution (for example, tetramer–dimer interconversions) may also be problematic as different components may react differently with the organic substrate to generate unwanted mixtures of products. More appealing is a single molecule with a well-defined structure. As now outlined, we have directed our studies toward building such ideal molecules rationally using a combined bimetallic–bi(bulky)ligand approach, which appears to suppress aggregation and reduce the extent of any intermolecular processes.

Alkali-Metal-Mediated Magnesiation (AMMMg). Belonging to the dianionic–dicationic category of compounds, the five-component sodium–magnesium monoalkyl-bisamido cocomplex $[(\text{TMEDA}) \cdot \text{Na}(\mu\text{-TMP})(\mu\text{-}^i\text{Bu})\text{Mg}(\text{TMP})]$, **2**, is an effective complex magnesiator.¹⁵ Several of its reactions have been structurally framed in the sense that a picture can be pieced together of the molecular transformation taking place by having available the structure of both the base **2** and the product containing the deprotonated substrate as well as NMR solution spectra of both species. Given the complicated solution chemistry of organomagnesium compounds epitomized by Grignard reagents, this X-ray crystallographically painted picture cannot be all revealing, but at the very least, it provides a useful guide to possible solution structures (which can be probed by NMR spectroscopy) and an ideal starting point with which to construct model molecules for computational analysis and, at the very most, defines exactly the ground-state structures of the bimetallic base and metalated product. Reaction of **2** with benzene yields $[(\text{TMEDA}) \cdot \text{Na}(\mu\text{-TMP})(\mu\text{-Ph})\text{Mg}(\text{TMP})]$, **3**.¹⁵ Structurally this reaction represents replacement of an alkyl Bu^- by an aryl Ph^- with essentially retention of the rest of the base molecule (Figure 2). Benzene with a $\text{p}K_a$ of about 43 is not easy to deprotonate due to its

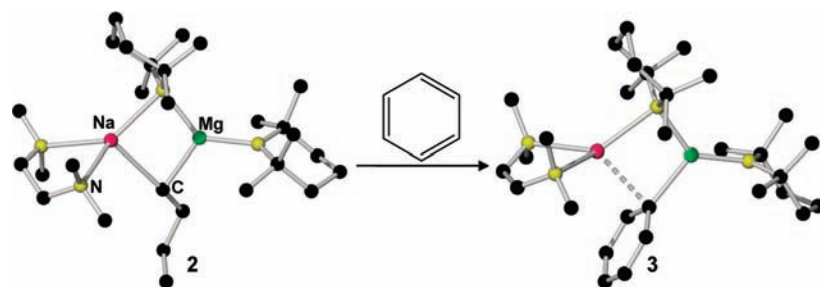


FIGURE 2. AMMMg of benzene via **2**.

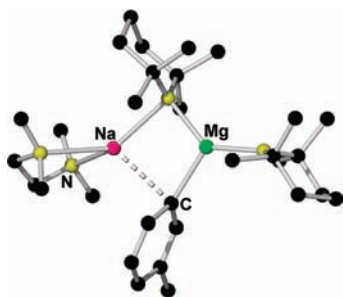


FIGURE 3. Molecular structure of **4**.

lack of activating electron-withdrawing substituents, and it is conspicuous that neither NaTMP nor ^tBuMgTMP, homometallic components of **2**, can accomplish its deprotonation to any significant extent. With heterobimetallic **2**, benzene is easily magnesiated. Magnesiation of toluene, where regioselectivity becomes an issue, also proves straightforward with **2**, producing [(TMEDA) · Na(μ-TMP)(μ-*m*-C₆H₄CH₃)Mg(TMP)], **4**, in a crystalline yield of 58%.¹⁶ The surprising bonus of this magnesium–hydrogen exchange reaction, seen in the molecular structure of **4** (Figure 3) and by NMR spectroscopy, is its *meta*-orientation. Lateral metalation of the methyl group to generate resonance-stabilized benzyl carbanions is the usual deprotonation. Hence, not only does **2** show enhanced magnesiative reactivity toward arenes (Grignard reagents are generally inert toward benzene or toluene), it can also deliver special regioselectivities, beyond the scope of conventional organometallic reagents such as ^tBuLi. Both areneide bridges in **3** and **4** exhibit similar bonding patterns: lying almost coplanar with the arene ring, Mg engages with the deprotonated C atom (*meta* in the case of **4**) primarily through σ -bonding, whereas Na lies near perpendicular to this ring interacting mainly with its π -system. This 2-fold σ - and π -stabilization of the deprotonated aromatic substrate by the linked nonalkali metal and alkali metal, respectively, is a signature feature of AMMM chemistry. In conventional (nonsynergic) chemistry, organosodium reagents are orders of magnitude more reactive (carbanion releasing) than organomagnesium reagents, but in these cocomplexes, it is the “less reactive” magnesium that executes deprotonation (concomitant with the

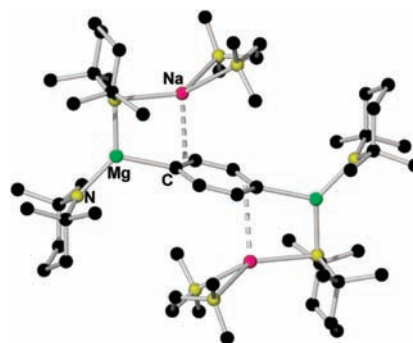
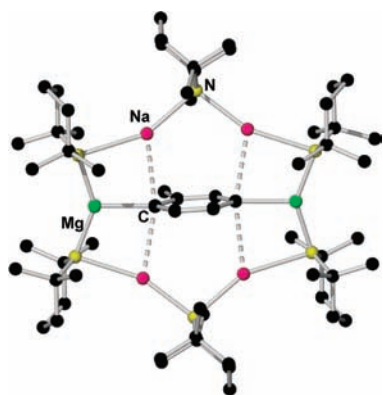
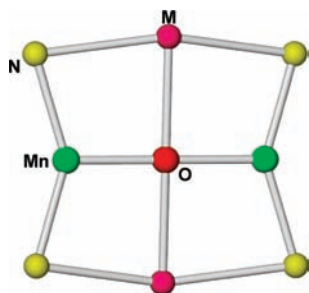


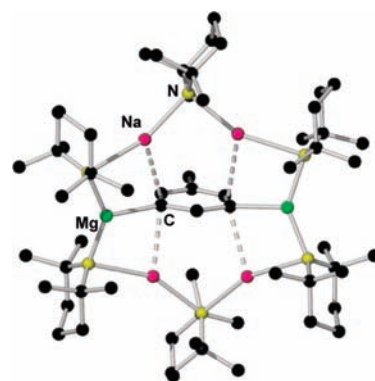
FIGURE 4. Molecular structure of “open inverse crown” **5**.

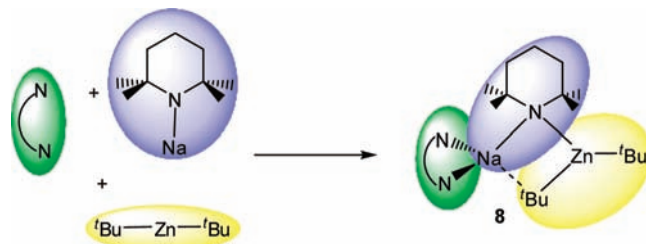
development of a new magnesium–carbon σ -bond), while sodium, although essential for execution of the deprotonation, takes on only a watching (foreman) brief. Benzene can also be stoichiometrically 2-fold deprotonated by the action of a *t*-butyl variant of **2**. Thus subjecting benzene to two molar equivalents of a NaTMP/^tBuMgTMP/TMEDA mixture produces [1,4-((TMEDA) · Na(μ-TMP)Mg(TMP))₂C₆H₄], **5** (Figure 4).¹⁷ Dimagnesiation occurs regioselectively at the sterically optimum 1,4-positions of the areneide ring, which as in **3** and **4** engages in a σ - and π -manner with Mg and Na, respectively.

TMEDA performs an aggregation-blocking role in **3** and **4**, but it can also perform other roles in AMMM chemistry. Crucially, it is sometimes needed to initiate cocomplexation. As outlined later, NaTMP and ^tBu₂Zn do not form a cocomplex in hexane solution, but on addition of TMEDA the powerful zincator [(TMEDA) · Na(μ-TMP)(μ-^tBu)Zn(^tBu)] is formed.¹⁸ TMEDA can also sometimes have a deactivating effect on bimetallic mixtures. Its participation in **2** limits the reactivity toward benzene or toluene to a single deprotonation, whereas in its absence the same bimetallic mixture, NaMg(^tBu)(TMP)₂, can achieve their 2-fold deprotonation. Bypassing the acidic Me substituent, the base dimagnesiates toluene at the 2,5 (*ortho*, *meta*)-positions producing a 2-fold deprotonated arene captured within a 12-atom tetrasodium-dimagnesium amide ring in the extraordinary host–guest molecule [(TMP)₆Na₄(2,5-Mg₂C₆H₃CH₃)], **6** (Figure 5).¹⁹ Note that its 2:1 Na/Mg stoichiometry in deviating from the 1:1 reactants ratio can be accounted for by elimination of a Mg(TMP)₂ molecule during


 FIGURE 5. Molecular structure of inverse crown **6**.

 FIGURE 6. Common molecular motif of manganate oxo inverse crowns $[M_2Mn_2(NR_2)_4(O)]$.

formation of **6**. Comprising an anionic (2⁻) core and a surrounding polymetallic cationic (2⁺) ring, albeit that the primary connection between them is two predominately covalent Mg–C(aryl) bonds, the structure of **6** is an inverse crown.²⁰ The name inverse crown derives from the mutual interchange of Lewis basic (anionic; here, the C₆H₃CH₃²⁻ guest) and Lewis acidic [cationic; here, the (Na₄Mg₂N₆)²⁺ host ring] sites compared with their dispositions in conventional crown ether complexes (host rings containing O atoms, Lewis basic; core guest metal cations, Lewis acidic). In this area, the name was originally used to describe the inverse crown “ether” arrangements that possess core oxygen-based guests, the newest members of which are amido(oxo)manganates $[M_2Mn_2(NR_2)_4(O)]$, where M = Li, NR₂ = TMP and M = Na, NR₂ = HMDS (Figure 6).²¹ The working deprotonating base unit of heteroleptic NaMg(ⁿBu)(TMP)₂ forming **6**, the ⁿBu⁻ ligand, is eliminated as butane. This base activity can be deduced from the observation that changing the alkyl component but keeping the other components of the synergic bimetallic mixture the same can alter the regioselectivity of the magnesiation reaction. Thus, changing ⁿBu for the silyl-stabilized, heteroneopentyl ligand Me₃SiCH₂ within NaMg(CH₂SiMe₃)(TMP)₂ instigates 3,5 (*meta*, *meta*) 2-fold deprotonation of toluene, manifested in the inverse crown [(TMP)₆Na₄(3,5-Mg₂C₆H₃CH₃)], **7** (Figure 7).²² The byproduct of the reaction is Me₄Si. The formation of these


 FIGURE 7. Molecular structure of inverse crown **7**.

 SCHEME 4. Cocomplexation Synthesis of Complex Zincator **8**


alternative regioisomeric inverse crowns **6** and **7** demonstrates that such synergic bases can be tuned to metalate arenes selectively at different positions depending on the identity of the basic alkyl component. Structurally **6** and **7** both have a puckered 12-atom [(NaNNaMnN)₂] host ring that encapsulates a toluenediide guest through a combination of Mg–C σ-bonds and Na–π arene interactions.

Alkali-Metal-Mediated Zincation (AMMZn). With its reactivity centered on its s² valence electrons, the stability of its +2 oxidation state, and an ability to form trigonal planar ate geometries, zinc in many ways could be considered a twin of magnesium. As family traits extend to structural chemistry, the design of the molecular structure of the complex magnesiator **2** can be used to construct similar complex zinc bases. Kondo had already demonstrated that the then structurally opaque lithium zincate LiZn^tBu₂(TMP) could metalate aromatic substrates,¹¹ so giving confidence that such fabricated zinc molecules would possess the required high reactivity (higher than conventional diorganozinc reagents) to perform direct zinc–hydrogen exchange (AMMZn) reactions. Thus, cocomplexation of NaTMP, ^tBu₂Zn, and TMEDA in hexane solution produced the dianionic–dicationic device [(TMEDA) · Na(μ-TMP)(μ-^tBu)Zn(^tBu)], **8** (Scheme 4).¹⁸ TMEDA facilitates cocomplexation for without it the NaTMP/^tBu₂Zn mixture is insoluble in hydrocarbon media. Structurally, zincate **8** (Figure 8) adheres closely to the template design of magnesiate **2** but with the distinction of a bisalkyl-monoamido formulation rather than a monoalkyl-bisamido formula-

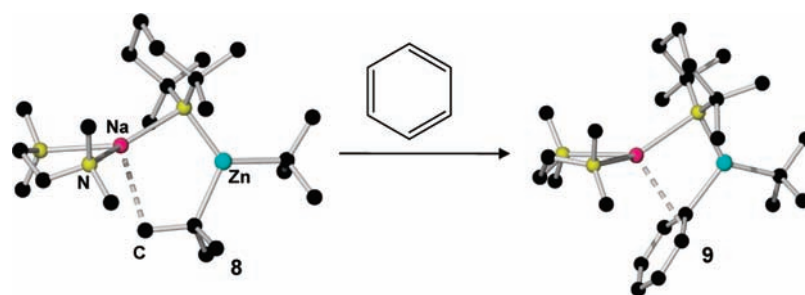
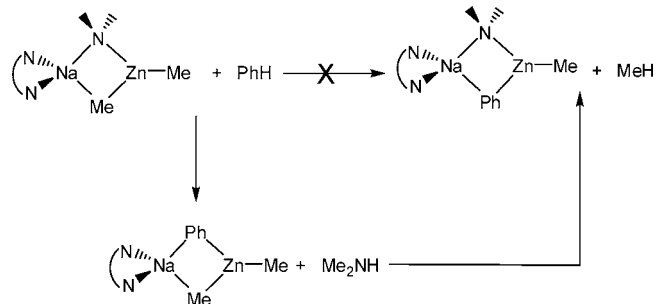


FIGURE 8. AMMzincation of benzene via **8**.

SCHEME 5. Proposed Two-Step Mechanism of Amidozincates Bases

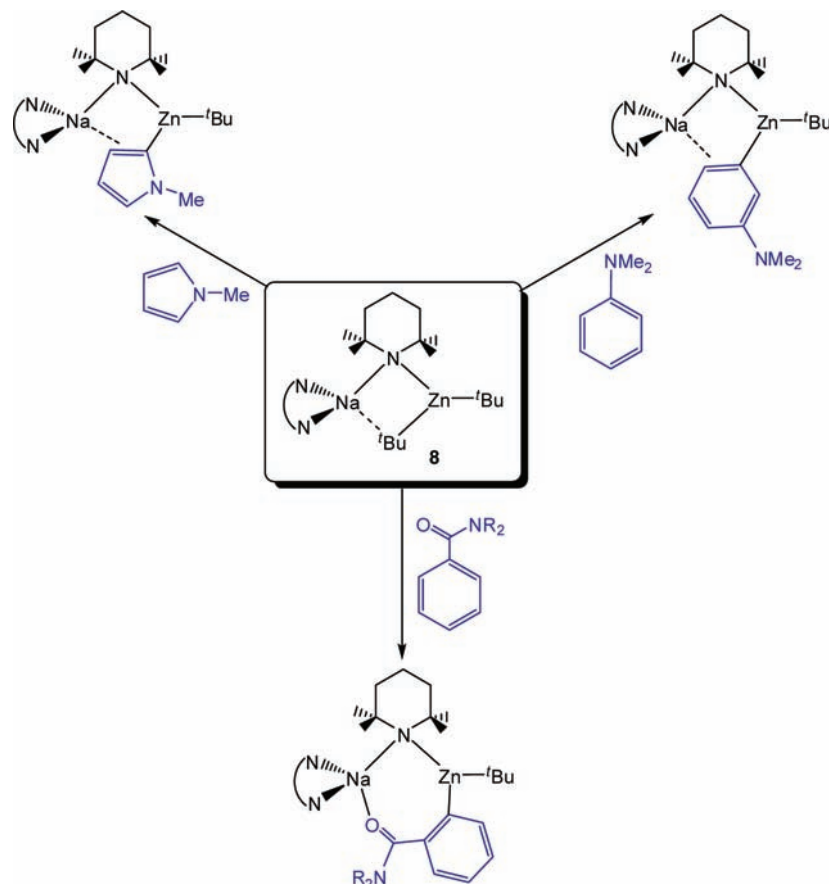


tion. While this stoichiometry of **8** is by design here since it matches that of the reactants, the strong carbophilicity of zinc often dictates this 2:1, organo-C/organon-N ratio in its heteroleptic ate formulations even when the stoichiometry of the reactants differs. Benzene is easily zincated by **8** to afford heterotrileptic $[(\text{TMEDA}) \cdot \text{Na}(\mu\text{-TMP})(\mu\text{-Ph})\text{Zn}(\text{tBu})]$, **9**.¹⁸ Structurally mapping this reaction by X-ray crystallography (Figure 8) establishes its overall alkyl basicity; thus, the deprotonated substrate Ph occupies the bridging site left by the expelled tBu, with $\text{Na} \cdots \text{Ph} \pi$ contacts replacing $\text{Na} \cdots \text{Me}$ agostic contacts. However, what this crystallographically drawn map cannot show is any chemical change taking place between these structural limits, that is, kinetic events prior to the production of the thermodynamic product **9**. DFT calculations by Nobuto and Uchiyama exploiting the structures elucidated by X-ray crystallography nicely complement this work by filling this gap in the structural map.²³ Thus, using the simplified models of $[(\text{TMEDA}) \cdot \text{Na}(\mu\text{-NMe}_2)(\mu\text{-Me})\text{Zn}(\text{Me})]$ for **8** and $[(\text{TMEDA}) \cdot \text{Na}(\mu\text{-NMe}_2)(\mu\text{-Ph})\text{Zn}(\text{Me})]$ for **9**, they compute that from relative activation energies the reaction is more favorable in two steps than in one (Scheme 5). Thus, the amido ligand is the kinetic base first abstracting a hydrogen from benzene to generate a bisalkyl–monoaryl intermediate $[(\text{TMEDA}) \cdot \text{Na}(\mu\text{-Me})(\mu\text{-Ph})\text{Zn}(\text{Me})]$, which then attacks evolved Me_2NH to afford the final products of the reaction, $[(\text{TMEDA}) \cdot \text{Na}(\mu\text{-NMe}_2)(\mu\text{-Ph})\text{Zn}(\text{Me})]$ and methane. This stepwise mechanism adds strong support to our interpretation of such reactions as AMMzincation(s), since in addition to the two metals being con-

nected by a bridging atom (C or N) throughout the whole process, the second step is mediated through sodium forming a dative bond with the returning amine molecule in an intermediate complex. Exporting this idea to the real experimental heteroleptic **8** marks TMP and tBu, respectively, as its kinetic and thermodynamic base components.

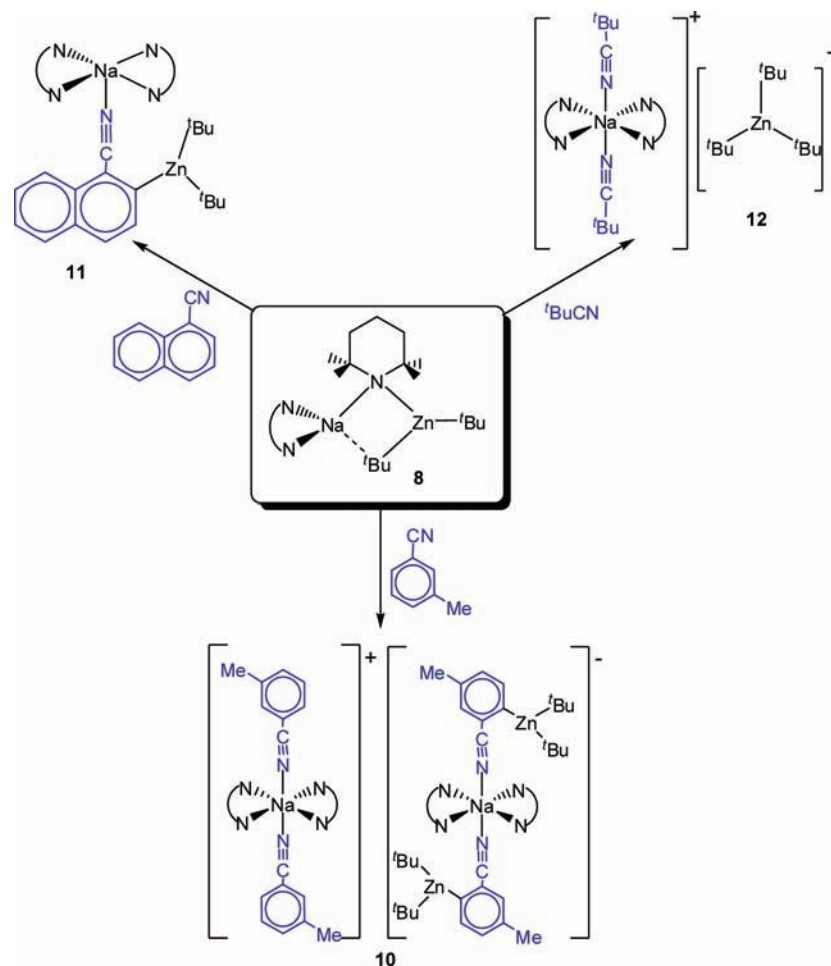
Structurally mapped reactions with a series of organic substrates have established the credentials of **8** as a powerful and versatile complex zincator (Scheme 6). Again acting as an overall alkane base (tBu releasing) with retention of the remainder of its molecular structure, **8** regioselectively monozincates *N,N*-diisopropylbenzamide at the *ortho* position,²⁴ 1-methylpyrrole at the α position,²⁵ *N,N*-dimethylaniline at the *meta* position,²⁶ and naphthalene at the 2-position.²⁷ Stoichiometric 2,6-dizincation of naphthalene is also accomplished. The results with *N,N*-dimethylaniline and naphthalene are particularly special because *ortho* not *meta* selectivity would be expected for the former and probably no zincation at all, let alone selective mono- and dizincation, for the unactivated substituent-free polycyclic aromatic hydrocarbon. Note that in all these reactions, with TMP retained in the final (isolated, crystalline) product, overall a new Zn–C bond has formed over an existing Zn–C bond. These are also likely to be two-step reactions.

While the DFT study exposed the limitations of the X-ray crystallographic mapping approach, a series of reactions between **8** and a variety of nitrile substrates emphasizes emphatically its immense usefulness (Scheme 7).²⁸ *m*-Tolunitrile is zincated *ortho* to its electron-withdrawing nitrile substituent, not an unexpected regioselectivity, but how this is manifested was surprising and without X-ray crystallography would have been exceptionally difficult to decipher. Thus the zincated product has the extraordinary ion-pair structure (Figure 9) of $[(3\text{-Me-C}_6\text{H}_4\text{CN})_2\text{Na}(\text{TMEDA})_2]^+[(6\text{-Zn}(\text{tBu})\text{-3-Me-C}_6\text{H}_3\text{CN})_2\text{Na}(\text{TMEDA})_2]^-$, **10**, which can be interpreted as a “sodium sodiumdizincate”. The anionic moiety contains two *ortho*-zincated nitrile ligands, while the cationic moiety contains two neutral, nonzincated nitriles, with each moiety built

SCHEME 6. A Selection of AMMZn Reactions by **8**


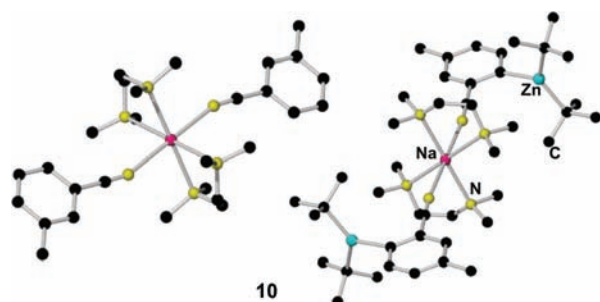
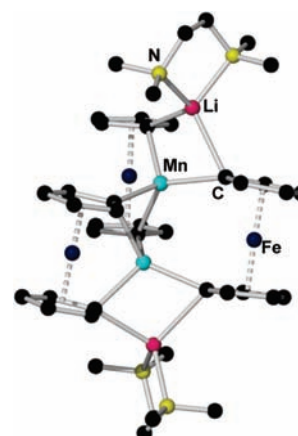
upon an octahedral sodium platform having a pair of equatorial TMEDA ligands. TMP(H) was detected in the reaction filtrate confirming that **8** functions as a kinetic amido base in forming **10**, which retains both alkyl groups on zinc. 1-Cyanonaphthalene is also zincated *ortho* to the nitrile substituent; however the product is not an ionic zincate but the discrete molecular species [(TMEDA)₂Na{2-Zn(^tBu)₂-1-N≡C-C₁₀H₆}], **11**. TMP basicity is again implicated with retention of the Zn(^tBu)₂ unit. Complicating the picture more, studied as a nonacidic model nitrile to shed light on structural maneuvers prezincation, trimethylacetone nitrile ^tBuC≡N reacts with **10** to afford the trialkylzincate [(^tBuCN)₂Na(TMEDA)₂]⁺(^tBu₃Zn)⁻, **12**. Though ionic like **10**, **12** is a simple monozincate, not a dizincate, and surprisingly its anion is not heteroleptic [^tBu₂(TMP)Zn]⁻, which would signify a straightforward scission of **8**, but homoleptic [^tBu₃Zn]⁻, indicative of a dismutation. Three different nitrile substrates with the same complex zincator give three different types of product (!); clearly this study raises the bar of complexity of structural zincate chemistry in general and TMP-zincate chemistry specifically and demands that much more work is practiced before they can be mastered.

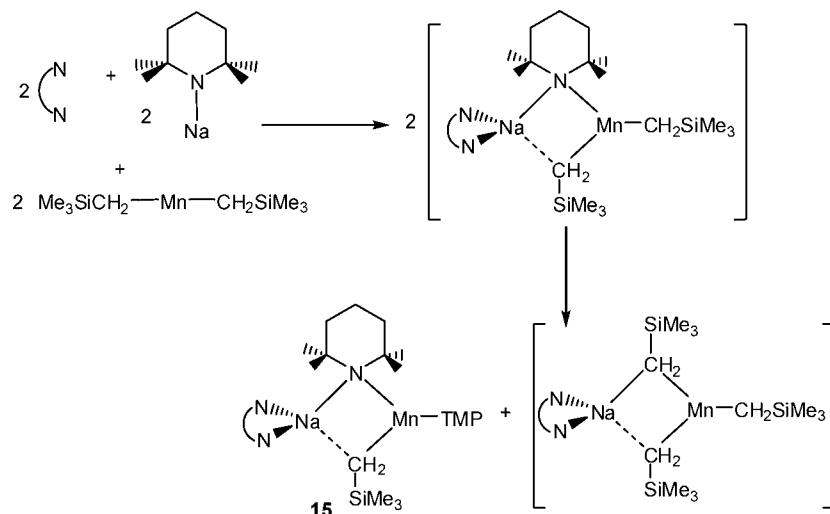
Alkali-Metal-Mediated Manganation (AMMMn). The template design for a complex metalator is extendable to Mn(II) with judicious choice of ligand. Prone to β -hydride elimination on attachment to the transition metal, the ⁿBu ligand used in magnesiator **2** is best avoided and instead trimethylsilylmethyl, Me₃SiCH₂⁻, is preferred. Free of β -hydrogen atoms, this ligand has long been utilized as an entry to stabilized transition metal-alkyl σ bonds, the dichotomy of which is that bisalkyl Mn(CH₂SiMe₃)₂ is generally inert toward *CH* deprotonation of aromatic substrates. However, built into the template structure of [(TMEDA)·Li(μ -TMP)Mn(CH₂SiMe₃)₂], **13**, its manganating ability is boosted significantly. This AMMMn was demonstrated with ferrocene, which, inert to Mn(CH₂SiMe₃)₂, is 1,1' 2-fold deprotonated by **13** in the guise of the dilithium-dimanganese(II) trinuclear ferrocenophane [(TMEDA)₂Li₂Mn₂{Fe(C₅H₄)₂}]₃, **14** (Figure 10).²⁹ Toluene, in contrast, resists deprotonation/manganation by the lithium manganate **13**. Substituting sodium for lithium produces a stronger complex manganator in [(TMEDA)·Na(μ -TMP)(μ -CH₂SiMe₃)Mn(TMP)], **15**.³⁰ Note that this alternative monoalkyl-bisamido composition (compare, vice versa in **13**) is not imposed by the reactants stoichiometry but is favored even in

SCHEME 7. Reactions of **8** with Different Nitrile Substrates

2:1 alkyl/amido mixtures through dismutation (Scheme 8). This change could be viewed as a symbiotic effect of the more ionic sodium (compared with lithium) exporting more ionic character onto Mn(II). The structurally framed reaction with benzene (Figure 11) demonstrates the effectiveness of **15** as a Mn(II) base operating through its alkyl ligand. AMMMn also occurs with the substituted benzenes, anisole, and *N,N*-diisopropyl benzamide, producing *ortho*-manganation (Scheme 9).³¹ Here, however, **15** acts as an alkyl base for the former, but as an amido base for the latter generating [(TMEDA) · Na(TMP)(*o*-C₆H₄OMe)Mn(TMP)], **16**, and [(TMEDA) ·

Na(TMP){*o*-[C(O)N-^{*i*}Pr₂]C₆H₄}Mn(CH₂SiMe₃)], **17**, respectively. This ambibasic behavior must have its roots in kinetic/thermodynamic factors though the sample of AMMMn reactions is presently too small to make any correlations with substituent effects. Manganates **16** and **17** were successfully cross-coupled with iodobenzene under [PdCl₂(dppf)] catalysis to

FIGURE 9. Ion pair structure of **10**.FIGURE 10. Molecular structure of ferrocenophane **14**.

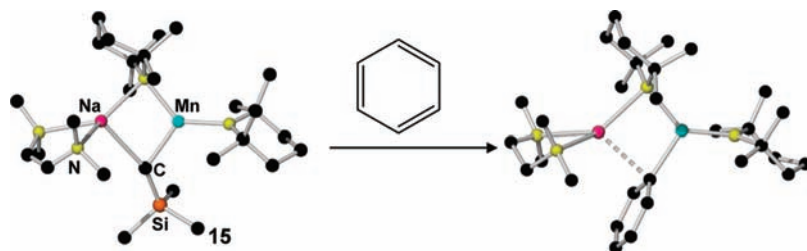
SCHEME 8. Dismutation Process Leading to **15**


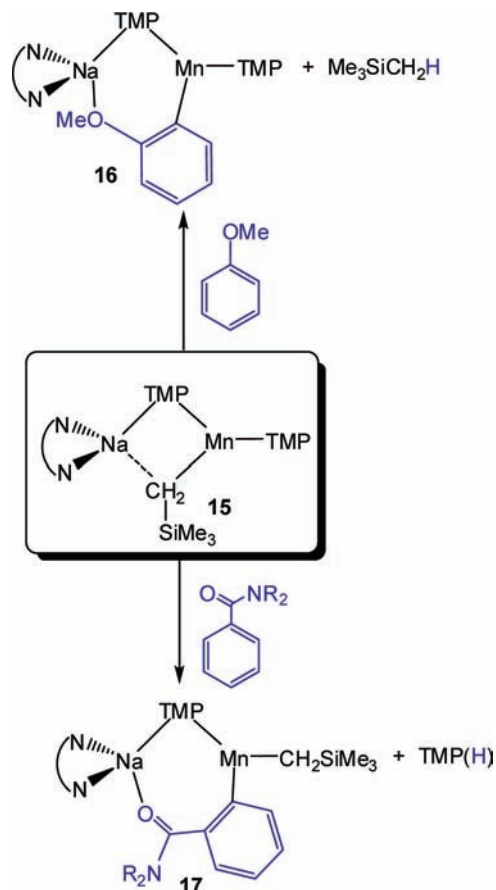
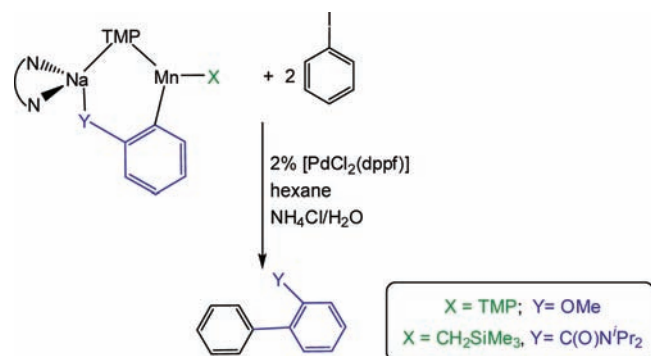
generate unsymmetrical biaryl compounds in yields of 98.8% and 66.2%, respectively (Scheme 10).

Demonstrating the first direct (that is, not made indirectly by a transmetalation approach) dimanganation of an arene, benzene is 1,4 2-fold deprotonated by an in situ mixture of $[\text{Na}_4\text{Mn}_2(\text{TMP})_6(\text{CH}_2\text{SiMe}_3)_2]$ (Scheme 11).³⁰ Mimicking a previous reaction with magnesium, the stoichiometry of the complex base was designed to manifest the double manganese–hydrogen exchange process in the form of an inverse crown and was successful, affording $[(\text{TMP})_6\text{Na}_4(1,4\text{-Mn}_2\text{C}_6\text{H}_4)]$, **18**. This compound represents the first inverse crown in which a transition metal features in the host ring and the first magnetic inverse crown. Variable-temperature magnetization measurements showed **18** to be antiferromagnetic in nature with a magnetic exchange interaction of -0.70 cm^{-1} . Applying the same complex base mixture to toluene produced the *meta*–*meta* deprotonated guest inverse crown $[(\text{TMP})_6\text{Na}_4(3,5\text{-Mn}_2\text{C}_6\text{H}_3\text{CH}_3)]$, **19**, which is isostructural to the magnesium inverse crown **7** (Figure 7), and a pseudoregioisomer to the magnesium *ortho*–*meta* deprotonated guest inverse crown **6**. Switching the substitution pattern on the arene guest from 1,4- Mn_2 in **18** to 2,5- Mn_2 in **19** reduces the magnetic exchange interaction between the two paramagnetic Mn(II) centers to -0.1 cm^{-1} .

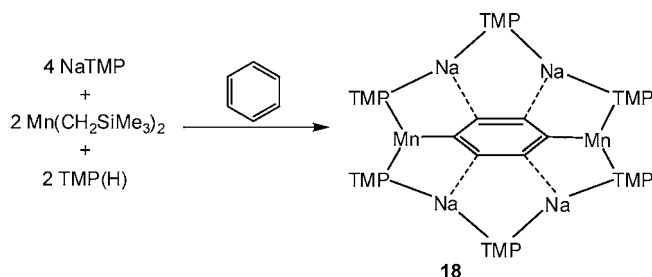
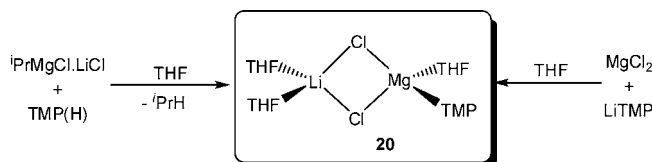
Looking under the Hood of a Turbo-Grignard Reagent.

The brilliant metalation work of the Knochel team in developing “turbo-Grignard” chemistry might be considered a special subcategory of AMMMg. Cocomplexes such as “ $\text{TMPMgCl} \cdot \text{LiCl}$ ” exhibit enhanced reactivity compared with “ TMPMgCl ” and perform regioselective magnesium–hydrogen exchange on a wide variety of functionalized aromatic substrates that appears to be mediated by an alkali metal (in the form of lithium chloride). While their synthetic development is powering ahead at great speed, the structural understanding of these hybrid organometallic–saltlike molecules has hardly left the starting grid. However, recently the first inroads toward finding a structural rationalization for their exceptional magnesiating ability has come from X-ray crystallographic elucidation of $\text{TMPMgCl} \cdot \text{LiCl}$ (or at least one component of its reaction mixture). Synthesized either by Knochel’s recipe of ${}^i\text{PrMgCl} \cdot \text{LiCl}$ with TMP(H) or the new alternative recipe of MgCl_2 and LiTMP , both in THF solution, the isolated crystalline product is in fact the tris(THF) solvate, $[(\text{THF})_2\text{Li}(\mu\text{-Cl})_2\text{Mg}(\text{THF})\text{TMP}]$, **20** (Scheme 12).³² Linked via Cl bridges, the two metal atoms form a nonplanar (LiClMgCl) ring in the molecular structure (Figure 12). Terminal TMP and THF ligands complete the distorted tetrahedral Mg center, while two THF ligands do likewise for Li. Appearing ready to disintegrate into


FIGURE 11. AMMMn of benzene via **15**.

SCHEME 9. AMMMn Reactions of **15** with Substituted BenzenesSCHEME 10. Cross-Coupling Applications of **16** and **17** with Iodobenzene

TMPMgCl and LiCl on thermodynamic grounds, cocomplex **20** is clearly a metastable product, whose existence owes much to the stabilization provided by the three THF ligands. What can we infer from this structure about the workings of TMP-based turbo-Grignard reagents? (1) They are molecular species, not saltlike; (2) their active TMP base binds to Mg, not to Li (hence justifying the inclusion of their reactions under the AMMMg designation); (3) the Mg–N(TMP) bond is terminal; thus only one bond needs to cleave to release the active base; (4) labile THF ligands may facilitate the precoordination of the

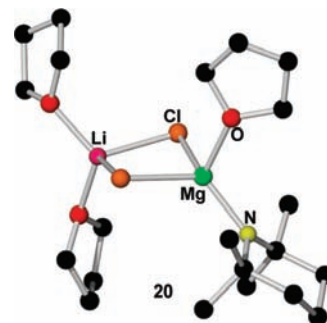
SCHEME 11. Synthesis of the Manganese Arenediide Inverse Crown **18**SCHEME 12. Synthesis of the Structurally Defined Turbo-Grignard Reagent **20**

aromatic substrate prior to its magnesiation; (5) due to their ate “Li⁺MgR₃[−]” constitutions, the anionic electron availability on Mg is high and must be a key factor in their boosted magnesiating power.

Finally, it is evident that the structure of **20** is not far off the template design of **2**. Both are bimetallic dianionic–dicationic devices with a mixed terminal/bridging ligand set on Mg. The main distinction, the additional (fourth) ligand on Mg in **20**, is a consequence of reduced steric factors.

Conclusions and Outlook

The past decade has witnessed a remarkable reassessment of metalation chemistry with a catalog of important advances made in different laboratories across the world. Previously held convictions about the scope and limitations of this globally practiced metal–hydrogen exchange reaction have been shattered by this research. In particular, perceived wisdom used to be that low polarity metals (Mg, Mn, Zn, Al, etc.) were too kinetically unreactive to *directly* metalate aromatic compounds. However, this is now achievable using the assortment of complex metalators mentioned in this Account. Our contribution through a predom-

FIGURE 12. Molecular structure of turbo-Grignard reagent **20**.

inantly inorganic structural focus, which complements nicely the much larger organic literature in the area, has pinpointed bimetallic ligand structural templates that can execute these low polarity metalations (magnesiations, manganations, etc.). The other areas of complex metalators less structurally defined probably involve structures not dissimilar to these templates. Rapid progress should now be possible by permutating different combinations of basic ligands (and ancillary structure supporting ligands) with different combinations of metals in these structural templates. Thus in the future, metalation should not be the domain of a few, select high polarity metals but should also be accessible to many other lower polarity metals through custom-made bimetallic (or higher metallic) reagents. Transforming stoichiometric metalations to catalytic processes will be the next big challenge.

I am deeply indebted to a highly talented group of co-workers and collaborators whose names appear in the relevant references. Financial support from the EPSRC and the Royal Society is also gratefully acknowledged.

BIOGRAPHICAL INFORMATION

Robert Emmet Mulvey was born in Glasgow (Scotland) in 1959, where he received his B.Sc. (Hons) in 1981 from the University of Strathclyde. He obtained his Ph.D. from the same institution in 1984 under the direction of Dr. Ron Snaith. Following a two year postdoctoral fellowship with Prof. Ken Wade at the University of Durham, he returned to Strathclyde in 1986. Promoted to Professor in 1995, he has long been mesmerized by the chemistry of polar organometallic compounds.

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