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Organometallic Reagents

Deprotonative Metalation Using Ate Compounds: Synergy, Synthesis, and Structure Building**

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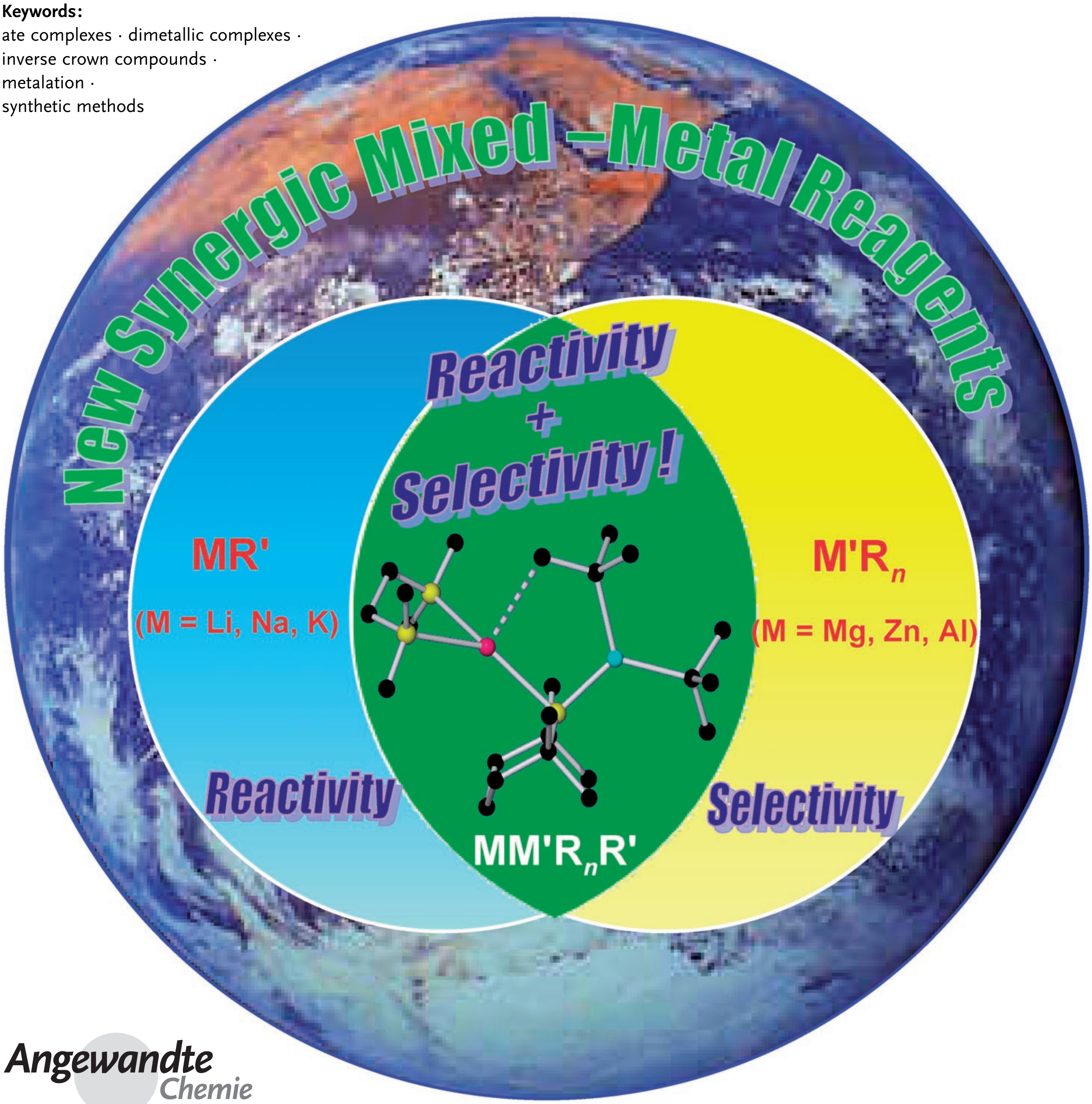
Keywords:
ate complexes · dimetallic complexes · inverse crown compounds · metalation · synthetic methods



Historically, single-metal organometallic species such as organolithium compounds have been the reagents of choice in synthetic organic chemistry for performing deprotonation reactions. Over the past few years, a complementary new class of metalating agents has started to emerge. Owing to a variable central metal (magnesium, zinc, or aluminum), variable ligands (both in their nature and number), and a variable second metallic center (an alkali metal such as lithium or sodium), "ate" complexes are highly versatile bases that exhibit a synergic chemistry which cannot be replicated by the homometallic magnesium, zinc, or aluminum compounds on their own. Deprotonation accomplished by using these organometallic ate complexes has opened up new perspectives in organic chemistry with unprecedented reactivities and sometimes unusual and unpredictable regioselectivities.

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1. Introduction

The deprotonative metalation of an aromatic ring is the transfer of a metal atom from an organometallic reagent or a metal amide to an aromatic substrate in exchange for a carbon-bound hydrogen atom. Schorigin first discovered this reaction mode in 1908 when he treated diethylmercury with sodium metal in benzene to induce reductive cleavage.[1] He happened to obtain phenylsodium as the reaction product, although the expected product was ethylsodium. Alkylpotassium reagents are also powerful enough for deprotonative metalation,[2] but organolithium compounds are unable to deprotonate benzene if no special activation is provided. Electropositivity of the metal employed is considered to be one of important factors for the activity of deprotonation. Organomagnesium reagents have been known not to participate in deprotonative metalation of benzene.

Since the pioneering work by Gilman[3] and Wittig,[4] the directed *ortho* metalation (DoM) reaction has been widely used as a powerful and efficient method for regioselective functionalization of aromatic compounds.[5] Various directing groups have been employed for facilitating the deprotonation of arenes, and various strong bases such as alkyl lithium or lithium dialkylamides have been employed. Among Group 1 organometallics, alkyl lithium reagents are most convenient to work with for synthetic chemists because the reagents are soluble in ethers or frequently also in alkanes, and many of them are already commercially available. Therefore, it has been of great practical importance to define the scope and limitation of alkyl lithium promoted deprotonative metalation reactions. Generally, only substrates with high C–H acidity enhanced by the directing functional groups are amenable to deprotonative lithiation. The ester group or cyano group has been regarded as an important and attractive directing group, however use has been limited because the deprotonation requires strictly controlled reaction conditions owing to the instability of intermediary aryl lithium species with the ester or cyano functionality. Lithium 2,2,6,6-tetramethylpiperidide (LTMP) has been used for directed *ortho* lithiation of aryl carboxylic esters, however unwanted condensation reactions between the aryl lithium and electrophilic directing groups have been known to occur during the metalation.[6] In situ trapping of the aryl lithium species by electrophiles during the deprotonation of aryl carboxylic esters has been reported, however bulkiness of the ester group is essential.[7] On the other hand, in 1989, Eaton et al. reported a selective magnesiation reaction of alkyl benzoate by using magnesium amides, thus suggesting the possibility of highly chemoselective conversion in the metalation chemistry.[8]

From a different viewpoint on the metalation, activation of alkyl lithium compounds has been also very important for deprotonative metalation chemistry and the following two methods are considered to be representative. One is the TMEDA-activated alkyl lithium reagent (TMEDA = N,N,N',N'-tetramethylethylenediamine) and the other is the

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[**] We acknowledge all the co-workers for their contribution to the development of this fascinating chemistry.

tert-butoxide-complexed alkyl lithium reagent (LIC-KOR superbase). The former has been employed to achieve site-selective deprotonation at the position different from the site deprotonated with the alkyl lithium reagent alone.[9] The latter superbase approach of a mixed-metal reagent was introduced by Schlosser, and the reagent shows enormous reactivity toward deprotonative metalation.[10] Ring protons of weakly activated or nonactivated benzene derivatives can be easily deprotonated by using the superbase, and in some cases unique site selectivities are observed. Conventional bases for the deprotonative metalation have been the simple organometallic compounds of Group 1 mentioned above. However, recently new chemistry for the deprotonative metalation of aromatic compounds has started to grow through the use of diverse multimetallic complexes such as ate complexes.

2. Selected Uses of Ate Compounds for Synthesis

Wittig introduced the term "ate" about 50 years ago when he realized that classes of such metallic compounds with anionic formulations could be developed.[11] The behavior of several mixed lithium metal ate compounds towards fluorene in diethyl ether was studied as a measure of the dissociation of the complex into the homometallic component compounds, and it was observed that dissociation varies in the following order: Ph_3BeLi (no dissociation) $< Ph_3ZnLi < Ph_7Zn_2Li_3 < Ph_3MgLi < Ph_3CdLi$. Abilities of these different ate complexes to deprotonate diphenylmethane were compared too, and prove to be in the order $Ph_3BeLi < Ph_3ZnLi < Ph_3CdLi < Ph_7Zn_2Li_3 \approx Ph_3MgLi$.

This pioneering work did not immediately open the way to a systematic study of ate compounds as deprotonating agents. Indeed, it is only relatively recently that this subject has attracted significant attention from chemists.

2.1. Deprotonation with Magnesiates

Since Wittig and co-workers introduced the first magnesiate, Ph_3MgLi, prepared by combination of diphenylmagnesium and phenyllithium, in 1951,[11] several structural studies of these compounds by X-ray crystallography have been carried out,[12] but the synthetic applications of magnesiate reagents remained seldom explored until 2000.

Richey and King observed that addition of macrocyclic coordinating agents accelerates metalation of acidic hydrocarbons ZH (fluorene, indene, etc.) by diorganomagnesium compounds R_2Mg, forming solutions of $[RMg(macrocycle)]^+Z^-$.[13] The authors proposed magnesium ate complexes such as R_3Mg^- as possible deprotonating species.

A particularly striking demonstration of a crown ether activation was published in 1991 by Bickelhaupt and co-workers.[14] Deprotonation of 5-bromo-1,3-xylylene-([15]crown-4) (**1**) was observed by using bis(4-*tert*-butylphenyl)magnesium in diethyl ether at room temperature (Scheme 1), a reaction that could occur via a transient magnesiate species generated after initial 1:1 complexation between the crown ether **1** and the organometallic reagent.

Robert E. Mulvey received his BSc Honours degree in 1981 at the University of Strathclyde and obtained his PhD there in 1984 with the late Ron Snaith. Following two years as a postdoctoral researcher with Ken Wade at the University of Durham, he returned to Strathclyde in 1986 to begin his fully independent research career. Appointed to a professorship in 1995, he has a long-standing fascination with alkali-metal organometallic chemistry.

Masanobu Uchiyama obtained his PhD (1998) from The University of Tokyo (Japan) with Prof. K. Shudo, Prof. T. Sakamoto, and Prof. Y. Kondo. He worked as an assistant professor at Tohoku University (1995–2001) and The University of Tokyo (2001–2003), and was promoted to lecturer (2003–2006). From 2001 to 2004, he served concurrently a three-year PRESTO project of JST. He became Associate Chief Scientist at RIKEN in April 2006. His research interests are in the area of synthetic organic chemistry with emphasis on organometallic, physical, and computational chemistry.

Florence Mongin obtained her PhD in organic chemistry in Rouen (France) under the supervision of Prof. G. Quéguiner. From 1995 to 1997 she worked with Prof. M. Schlosser at the Institute of Organic Chemistry of Lausanne (Switzerland). In 1997 she returned to Rouen as a Lecturer at the University (habilitation in 2003). She became Professor at the University of Rennes in September 2005. Her main research topic is deprotonation with bimetallic bases.

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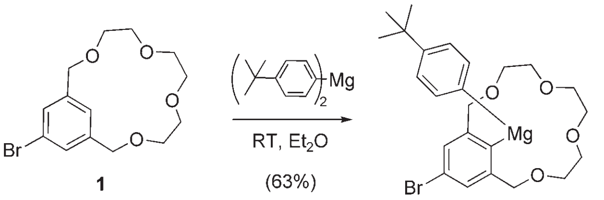

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Scheme 1. Deprotonation of **1** with bis(4-*tert*-butylphenyl)magnesium.

Even if magnesiates can be formed by addition of macrocyclic coordinating agents to diorganomagnesium compounds or Grignard reagents,[15] drawbacks including the high cost of this process lowered their synthetic development. Magnesiates generated by other preparation modes were preferred for this purpose.

In the following paragraphs we deal with lithium magnesiates, which are ate derivatives that contain two different s-block metals.

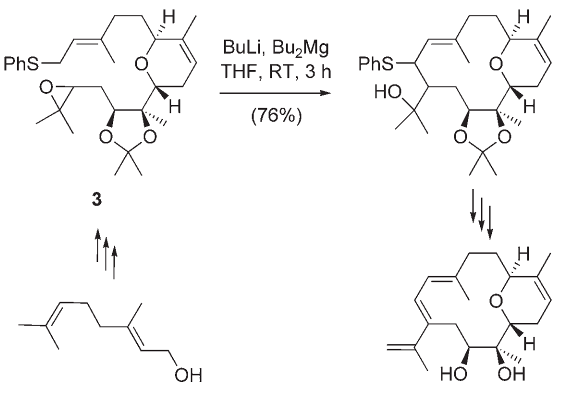
In spite of the various preparation modes developed to access lithium trialkyl and lithium tetraalkyl magnesiates—either by mixing diorganomagnesium and organolithium compounds in a 1:1 or 1:2 ratio,[11,16] by mixing an organolithium compound and a magnesium halide in a 3:1 or 4:1 ratio,[17] or even by reduction of dialkylmagnesium with lithium[18]—the synthetic applications of magnesiate reagents remained seldom explored[19] until recently.

Oshima and co-workers reported in 2000 the efficiency of lithium triorganomagnesiates in halogen–metal exchange reactions. Iodine–magnesium and bromine–magnesium permutations using these reagents were described for the preparation of phenyl-,[20] naphthyl-,[20a,c] alkenyl-,[20a,c,21] alkyl-,[20c] azulenyl-,[22] thienyl-,[20c,d] pyridyl-,[20c,d] diazinyl-,[23] quinolyl-,[24] and indolylmagnesium derivatives.[20f]

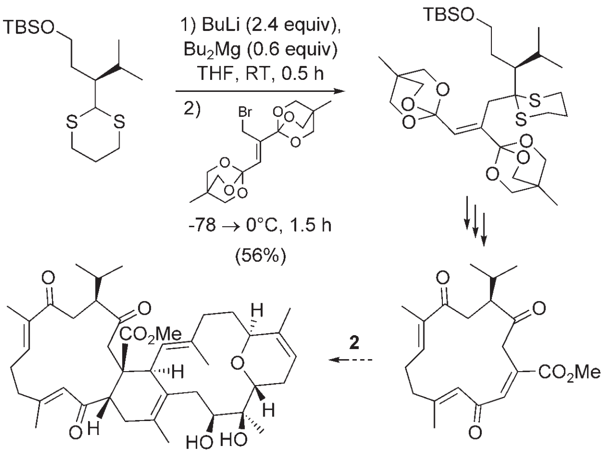
Lithium organomagnesiates first proved to be useful as deprotonating agents in modifying the reactivity of deprotonated substrates. Nakata and co-workers thus documented in 1997 a BuLi–Bu$_2$Mg-mediated Ito–Kodama cyclization. This reaction, which features intramolecular coupling of a phenylthio-stabilized allylic anion with epoxide, was originally performed using a mixture of butyllithium and DABCO in tetrahydrofuran (THF),[25] and next improved by varying the lithium chelating additive (HMPA, etc.).[26] The enantiospecific synthesis of the diol **2** used as the key step a BuLi–Bu$_2$Mg-mediated reaction starting from the phenyl sulfide **3** (Scheme 2).[27]

Intermolecular reactions of 2-substituted 1,3-dithianes were next studied.[28] The BuLi–Bu$_2$Mg-mediated dithiane coupling was for example efficiently used as the key step of the recently described asymmetric total synthesis of methyl sarcoate (**4**), a marine natural product (Scheme 3).[29] The 14-membered unit **2** and methyl sarcoate (**4**) are assumed to be the diene and dienophile, respectively, of a biosynthetic Diels–Alder reaction forming methyl sarcophytoate (**5**), a compound isolated from the Okinawan soft coral *Sarcophyton glaucum*.

Given that dibutylmagnesium cannot deprotonate alone, it seems that magnesiates would be the active species. The formation of lithium ate complexes (dimeric triple ions [R-Li-R]$^-$//Li$^+$) being favored in the presence of coordinating agents of lithium such as HMPA and DABCO,[30] they could be possible reactive intermediates in the alternative methods.



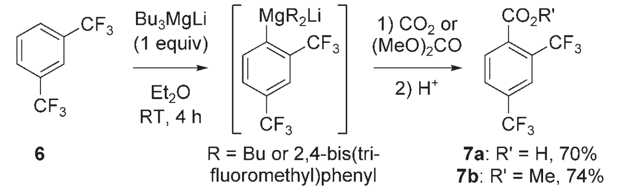
Scheme 2. Modified Ito–Kodama cyclization step in the synthesis of the 14-membered unit **2** of methyl sarcophytoate.



Scheme 3. Dithiane coupling step of the synthesis of methyl sarcoate (**4**).

The first use of a magnesiate as a deprotonating agent for aromatic compounds was reported in 1992.[31] Castaldi and Borsotti claimed the metalation of activated substrates such as (trifluoromethyl)benzene derivatives bearing a second group (*N*,*N*-dimethylamino, methoxy, or trifluoromethyl) at C3 with lithium magnesiates. The example of 1,3-bis(trifluoromethyl)benzene (**6**) was detailed. Treatment with one equivalent of lithium tributylmagnesiate in diethyl ether at room temperature resulted in the regioselective deprotonation of the substrate at the 4-position, as demonstrated by intercepting the aryl magnesiate with dry ice and dimethylcarbonate to afford the acid **7a** and ester **7b** in 70 and 74% yield, respectively (Scheme 4). When compared to previously documented lithium-base-mediated reactions,[32] deprotonations using lithium magnesiates tolerate higher temperatures and give higher yields. Nevertheless, the presence of two wasted butyl ligands reduces the interest of the method.

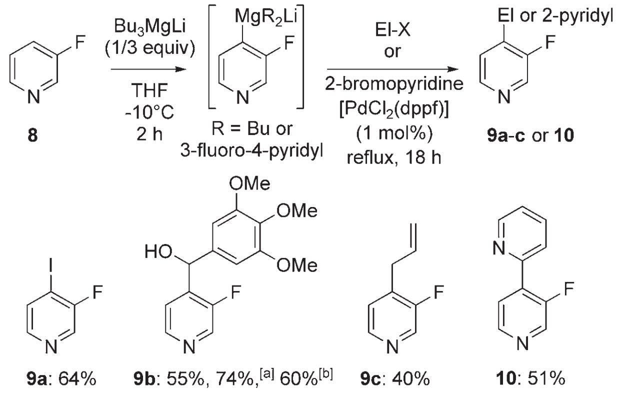
The preparation of functional heterocycles is an important synthetic goal because of the multiple applications of these



Scheme 4. Deprotonation of **6** with Bu_3MgLi and subsequent trapping.

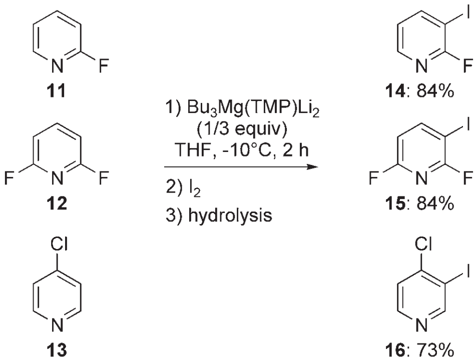
molecules. Richey and Farkas obtained 4- and 2-ethylpyridine by treating pyridine in diethyl ether at room temperature with solutions prepared by mixing diethylmagnesium and ethyllithium;[33] lithium trimethylmagnesiate was supposed to be responsible for the observed addition reactions. Deprotonation turned out to be possible on more acidic substrates such as fluoro-[34] and chloropyridines[35] using lithium magnesiates in THF.

The reaction of 3-fluoropyridine (**8**, Scheme 5) was achieved at −10 °C using lithium tributylmagnesiate (1/3 equiv). Upon addition of electrophiles, the 4-substituted compounds **9** were isolated in moderate yields (40–64 %). Adding TMEDA (1/3 equiv) to lithium tributylmagnesiate enhanced its reactivity; the yield with 3,4,5-trimethoxybenzaldehyde as the electrophile indeed reached 74 %, as opposed to 55 % with Bu_3MgLi alone. In strong contrast to the corresponding lithiopyridine, which decomposes between −60 and −20 °C,[36] the intermediate pyridylmagnesiate did not decompose through 3,4-pyridyne formation at −10 °C. Owing to its relative stability, it was successfully used in a palladium-catalyzed cross-coupling reaction with 2-bromopyridine to give **10**, a reaction normally problematic from the corresponding lithiopyridine.



Scheme 5. Deprotonation of **8** with Bu_3MgLi and subsequent electrophilic trapping. [a] With Bu_3MgLi and TMEDA (1/3 equiv). [b] With BuLi–TMEDA (1 equiv), −75 °C.

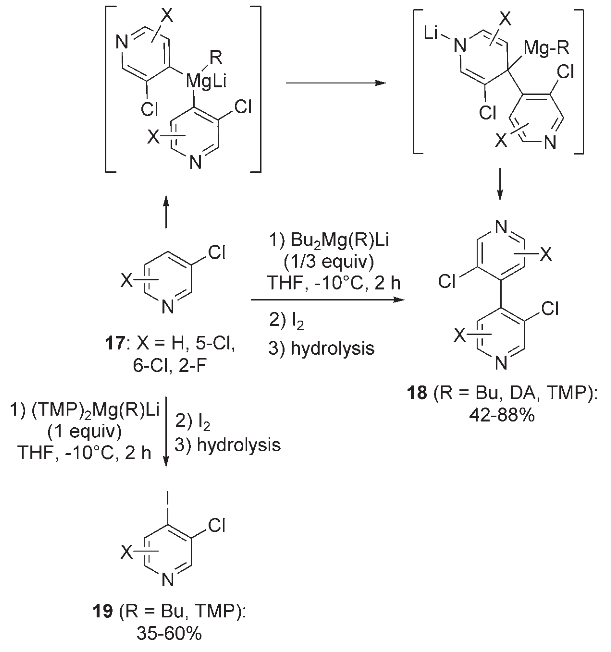
Turning to highly coordinated magnesiates and using the greater migratory aptitude of the 2,2,6,6-tetramethylpiperidino (TMP) group over alkyl groups, other fluoro- and chloropyridine compounds were deprotonated. The pyridylmagnesiates formed from 2-fluoro-, 2,6-difluoro-, and 4-chloropyridine (**11**–**13**) using $Bu_3Mg(TMP)Li_2$ (1/3 equiv) were quenched with iodine to give the corresponding 3-iodo derivatives **14**–**16** in good yields (Scheme 6).



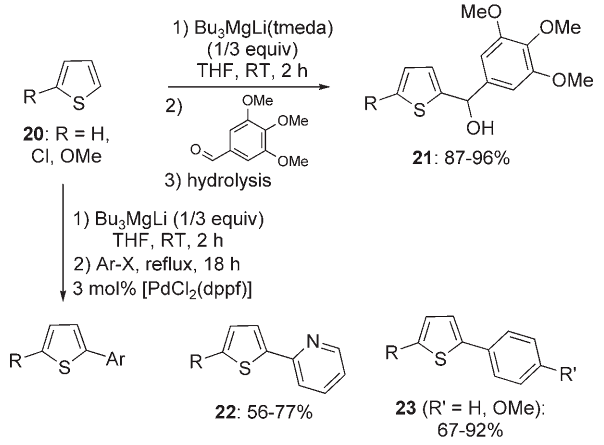
Scheme 6. Deprotonation of **11**–**13** with $Bu_3Mg(TMP)Li_2$.

The behavior of the arylmagnesiates coming from 3-chloropyridine compounds **17** is surprising. Thus, lithium magnesiate-induced (1/3 equiv) reactions of these substrates and subsequent interception with iodine provided the 4,4′-dimers **18** as the main products. Their formation was explained by a deprotonation at C4 giving a sterically congested 4-pyridylmagnesiate, which is stabilized through 1,2-migration. That the 4,4′-dimers are formed by an intramolecular process was suggested by the results of the reactions conducted with larger amounts of base. Indeed, when 3-chloropyridines **17** were subjected to the reaction with one equivalent of lithium magnesiate, the 4-iodo derivatives **19** were obtained in acceptable yields ranging from 35 to 60 % (Scheme 7).

The behavior of thiophenes[37] and furans[38] toward lithium organomagnesiates was also investigated. The thiophenes **20** underwent hydrogen–magnesium permutation next to the sulfur atom on treatment with 1/3 equivalent of lithium tributylmagnesiate in THF at room temperature (Scheme 8).



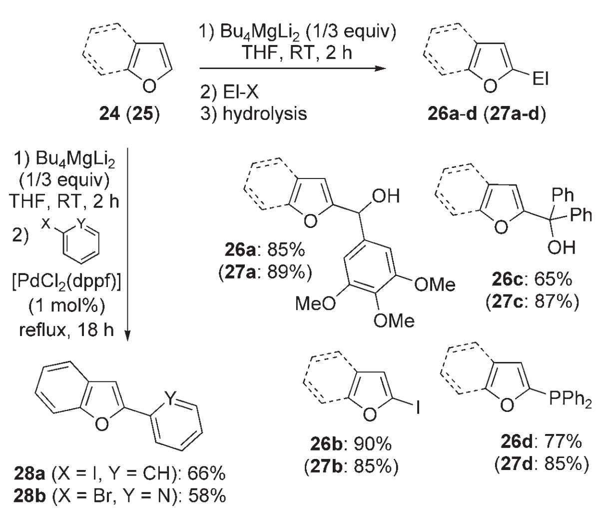
Scheme 7. Deprotonation of **17** with R_3MgLi (1/3 equiv or 1 equiv); DA = $i\mathrm{Pr}_2N$.



Scheme 8. Deprotonation of **20** with lithium tributylmagnesiates.

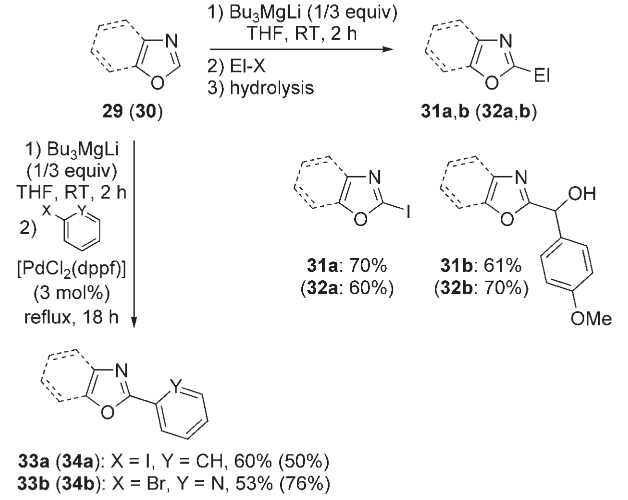
Monitoring the reaction by NMR spectroscopy revealed the quantitative formation of the expected lithium tri(2-thienyl)-magnesiates within 30 min when TMEDA was present. To make this reaction of preparative interest, electrophilic trapping by 3,4,5-trimethoxybenzaldehyde was performed to afford the corresponding alcohols **21** in excellent yields. More importantly, cross-couplings with various aromatic bromides or iodides furnished the functionalized products **22** and **23** in satisfactory yields.

Furan (**24**) was similarly α-deprotonated when submitted to lithium tributylmagnesiate (1/3 equiv) in THF at room temperature, but less rapidly. Monitoring the reaction by NMR spectroscopy showed the 2-magnesiated furan was more efficiently prepared using the highly coordinated lithium magnesiate Bu_4MgLi_2 (95% conversion within 1.5 h; Scheme 9). The method was very nicely transposed to benzofuran (**25**). Trapping reactions with 3,4,5-trimethoxybenzaldehyde, iodine, benzophenone, and chlorodiphenylphosphine were successfully used to get the products **26** and **27** in good yields. In the presence of a catalytic amount of $[PdCl_2(dppf)]$, reactions of the higher-order benzofurylmagnesiate with iodobenzene or 2-bromopyridine produced the coupled products **28**.



Scheme 9. Deprotonation of **24** and **25** with Bu_4MgLi_2.

The behavior of oxazoles **29** and **30** (Scheme 10) toward lithium magnesiates was studied to gain greater understanding of the nature of the species in solution after the deprotonation step.[39] Indeed, 2-lithiooxazoles resulting from the action of alkyl lithium reagents on the heterocycles are stabilized as lithium 2-(isocyano)enolates, with the open counterparts predominating at room temperature.[40] Deprotonation of oxazole (**29**) and benzoxazole (**30**) was achieved using lithium tributylmagnesiate (1/3 equiv) in THF at room temperature (Scheme 10). It was found by NMR spectroscopy that the 2-deprotonated species very rapidly and completely isomerized to the corresponding 2-(isocyano)enolates. Interestingly, 2-substituted oxazoles **31** and **32** were nevertheless isolated in satisfying yields after electrophilic trapping by iodine or 4-anisaldehyde, a result that could be interpreted by a intramolecular Passerini-type reaction, involving the α addition of the electrophilic site and the nucleophilic oxygen atom of the enolate to the isocyanide carbon atom. The intermediate magnesiates of oxazoles **29** and **30** were involved in reactions with aromatic halides under palladium catalysis too. The use of iodobenzene and 2-bromopyridine led to the coupled products **33** and **34** in moderate yields.



Scheme 10. Deprotonation of oxazole (**29**) and benzoxazole (**30**) with Bu_3MgLi.

Knochel and co-workers recently found that the addition of lithium chloride to alkyl magnesium chlorides enhances the reactivity of the latter for bromine–magnesium exchange reactions by producing highly active reagents of the type $[RMgCl_2]^-Li^+$.[41]

The corresponding mixed amide (TMP)MgCl·LiCl, which was prepared by reacting commercial *i*PrMgCl·LiCl with 2,2,6,6-tetramethylpiperidine, was used for the magnesiation of various aromatic and heteroaromatic compounds.[42] Starting from isoquinoline, 2,6-dichloropyridine, furan, thiophene, and benzothiophene, the reaction was successfully performed in THF at room temperature, as evidenced by subsequent trapping (with I_2, DMF, PhCHO, etc.) to give the functionalized heterocycles in high yields (Table 1, entries 1–5). Deprotonation of functionalized substrates such as aromatic esters (Table 1, entries 6 and 7), and other heterocycles such as 2-chloropyrimidine (entry 8), 5-bromopyrimidine (entry 9), 3-bromoquinoline (entry 10), 3,5-dibromopyridine (entry 11), thiazole (entry 12), and benzothiazole (entry 13) was also found to be possible, provided the temperature is reduced, to give the functionalized derivatives. Interestingly, 2-phenylpyridine (entry 14) was functionalized at the phenyl ring by using an excess of base at 55 °C.

As functionalization of aromatic heterocycles is a challenging synthetic goal, this method is anticipated to lead to important developments. These early results demonstrate the unexpectedly large potential of mixed lithium–magnesium bases in organic synthesis.

2.2. Deprotonation with Zincates

Dating back to 1858,[43] alkali-metal zincates represent one of the oldest classes of ate compounds in history. Underemployed for long periods, they started to emerge recently as versatile tools for synthetic chemists.

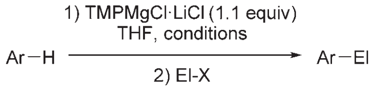
Since zinc belongs to the transition group and is consequently less electropositive than magnesium, deprotonation abilities of zincates are difficult to predict from the results observed with magnesiates.

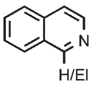
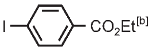
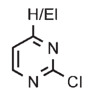
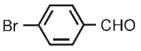
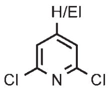
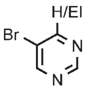
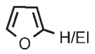
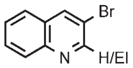
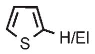
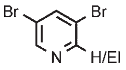
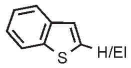
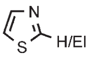
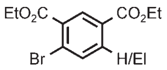
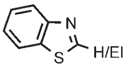
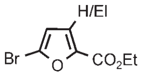
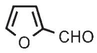
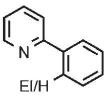
As for magnesiates, Richey and King observed in 2000 that the presence of coordinating agents allowed the Et_2Zn-mediated deprotonation of hydrocarbons such as indene, fluorene, and 1,2,3,4-tetraphenylcyclopentadiene in benzene or in some more polar solvents.[13b] The result was attributed to small amounts of organozincates (e.g. R_3Zn^-).

Lithium zincates can adopt two possible formulations:[44] R_3ZnLi and R_4ZnLi_2. Few years before the synthesis of Ph_3ZnLi by Wittig and co-workers in 1951,[11] Hurd succeeded in isolating Me_4ZnLi_2 by adding methyllithium to dimethylzinc in diethyl ether.[45] It was the first lithium zincate to be structurally characterized.[12,46]

Mobley and Berger observed that the equilibrium between Me_3ZnLi and Me_4ZnLi_2 lies far to the side of the ordinary zincate.[47] The efficiency of reactions using lithium zincates is nevertheless generally greater when "highly coordinated" R_4ZnLi_2 derivatives are used in place of ordinary R_3ZnLi,[48] the reactive species probably being the higher-energy tetracoordinated zincates.

Table 1: Deprotonation of aromatic compounds with (TMP)MgCl·LiCl.

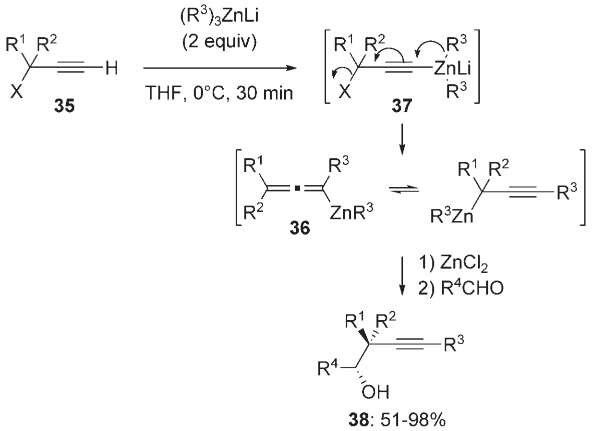


Entry	ArH/ArEl	*T* [°C], *t* [h]	ElX	El, yield [%]	Entry	ArH/ArEl	*T* [°C], *t* [h]	ElX	El, yield [%]
1		25, 2	I_2 PhCOCl[a] [b]	I, 92 COPh, 86 4-$C_6H_4CO_2Et$, 82	8		−40, 2	MeSSO$_2$Me 	SMe, 75 CH(OH)-4-C_6H_4Br, 68
2		25, 0.1	I_2 DMF PhCHO	I, 93 CHO, 90 CH(OH)Ph, 84	9		−40, 2	I_2	I, 67
3		25, 24	DMF	CHO, 81	10		−25, 0.3	I_2 DMF	I, 87 CHO, 91
4		25, 24	DMF	CHO, 90	11		−25, 0.5	I_2 DMF	I, 89 CHO, 85
5		25, 24	DMF	CHO, 93	12		0, 0.1	PhCHO	CH(OH)Ph, 94
6		−25, 0.5	I_2	I, 88	13		0, 0.1	I_2	I, 98
7		−25, 0.5		CH(OH)-2-furyl, 83	14		55, 24	I_2	I, 80

[a] A transmetalation with CuCN·2 LiCl (0.2 equiv) was performed. [b] Obtained by Pd-catalyzed cross-coupling after transmetalation with $ZnCl_2$.

The behavior of Ph$_3$ZnLi toward fluorene was studied in Et$_2$O and reported in 1951; quenching with CO$_2$ after 10 days, followed by acidic work up, afforded diphenyleneacetic acid in a low yield of 16%, as opposed to 47% with Ph$_3$MgLi.[11]

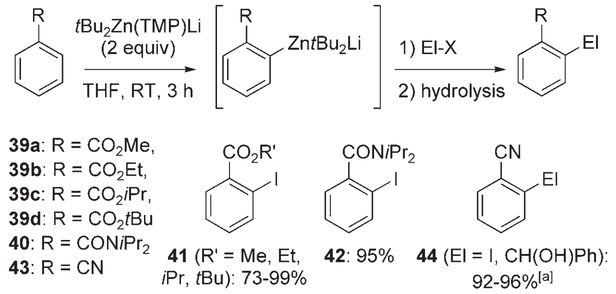
Owing to their softness, lithium zincates have first been used as halogen–metal exchange reagents. Iodine–zinc and bromine–zinc permutations with these reagents were described for the preparation of alkenyl-,[49] alkyl-,[49d,50] phenyl-,[48a,b,51] and indolylzinc derivatives.[52] Despite the early availability of preparation modes to access lithium organozincates,[53] deprotonation using them has been developed only recently. Harada and co-workers described the reaction of the propargylic substrates **35** ($X = MeSO_2O$, Cl; $R^1 = C_8H_{17}$, c-C_6H_{11}, Me, $PhCH_2CH_2$, $(MeO)_2CH(CH_2)_4$, $(CH_2)_5$; $R^2 = H$, –), with a variety of triorganozincates ($R^3 =$ alkyl, alkenyl, aryl) to generate the allenyl zinc reagents **36** (Scheme 11) through the facile 1,2-migration of the intermediate alkynyl zincates **37**; trapping by aldehydes occurred regioselectively at the γ positions to furnish the homopropargylic alcohols **38** in good yields.[54]



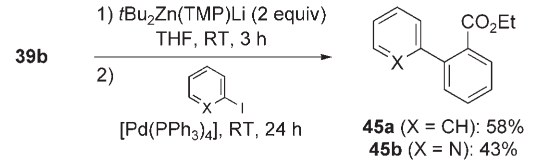
Scheme 11. Deprotonation of the propargylic substrates **35** with trialkyl zincates and subsequent trapping with aldehydes.

Kondo and co-workers reported in 1999 the synthesis of lithium di-*tert*-butyl(tetramethylpiperidino)zincate (TMP–zincate) from di-*tert*-butylzinc and LTMP. This heteroleptic deprotonating agent was chemoselectively used in the functionalized arenes series.[55] Various alkyl benzoates **39** and *N*,*N*-diisopropylbenzamide (**40**) were successively treated with TMP–zincate (2 equiv, in THF at room temperature for 3 h; Scheme 12) and iodine to afford the corresponding 2-iodo derivatives **41** and **42** in yields ranging from 73 to 99%. With benzonitrile (**43**), the amount of base could be reduced to one equivalent, as shown by intercepting the intermediate aryl zincate with iodine and benzaldehyde to give the functionalized compounds **44** in excellent yields.

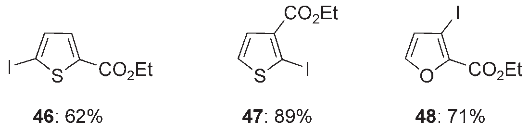
In contrast to the corresponding aryl lithium compound, which undergoes unwanted intermolecular condensation reactions with the electrophilic directing group during the metalation with LTMP,[6] the aryl zincate species derived from ethyl benzoate (**39b**) was treated with iodobenzene or 3-iodopyridine in the presence of [Pd(PPh$_3$)$_4$] at room temperature to give the coupled products **45** (Scheme 13).[56] Various heteroaromatic compounds were similarly deprotonated. Ethyl 2- and 3-thiophenecarboxylate, and ethyl 2-furancarboxylate provided the 5-, 2-, and 3-iodo derivatives **46**–**48**, respectively, after treatment of the intermediate zincates with iodine (Scheme 14).



Scheme 12. Deprotonation of the functionalized arenes **39**, **40**, and **43** using TMP–zincate and subsequent electrophilic trapping. [a] With one equivalent TMP–zincate.

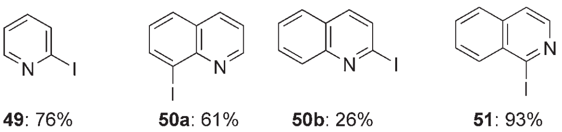


Scheme 13. Deprotonation of **39b** with TMP–zincate and subsequent cross-coupling.



Scheme 14. Deprotonation of ethyl 2- and 3-thiophenecarboxylate and ethyl 2-furancarboxylate with TMP–zincate and subsequent trapping with iodine yields **46**–**48**.

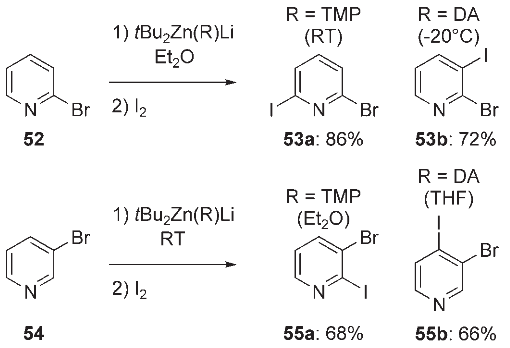
Interestingly, bare π-deficient heteroaromatic compounds were readily deprotonated. With TMP–zincate as a base and conducting the reactions at room temperature, pyridine was α-metalated, a result evidenced by intercepting the lithio derivative with iodine to provide **49** (Scheme 15). Under the same reaction conditions, quinoline was deprotonated at both C2 and C8 to give the derivatives **50a** and **50b** in a 70:30 ratio whereas isoquinoline was deprotonated selectively at C1 to



Scheme 15. Deprotonation of pyridine, quinoline, and isoquinoline with TMP–zincate and subsequent trapping with iodine yields **49**–**51**.

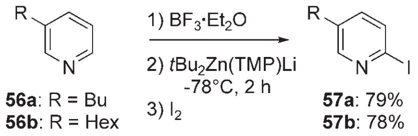
afford the iodide **51**. These results are of particular interest since such substrates can hardly be deprotonated by using lithium bases, owing to facile nucleophilic addition to the C=N bond.[36]

In ether solvents the *tert*-butyl group in the zincate is less susceptible to migration than the amido group, and this difference was exploited in the deprotonation of bromopyridines. Optional regioselectivities were obtained by varying the zincate amido group and the solvent.[57] The treatment of 2-bromopyridine (**52**) with TMP–zincate in Et$_2$O at room temperature mainly resulted in the deprotonation at the 6-position to afford, after trapping, the iodide **53a** in high yield (Scheme 16). In contrast, when lithium di-*tert*-butyldiisopropylaminozincate (DA–zincate) was employed at −20 °C, the reaction preferentially occurred at the 3-position to give the 3-iodo isomer **53b**. It was found for 3-bromopyridine (**54**) that reaction with TMP–zincate in Et$_2$O at room temperature occurred at the 2-position exclusively, as shown by the product **55a** that was obtained after trapping with iodine, whereas DA–zincate reacted predominantly at the 4-position in THF to give **55b**. It is noteworthy that formation of pyridyne was never suspected during these reactions, even at room temperature.



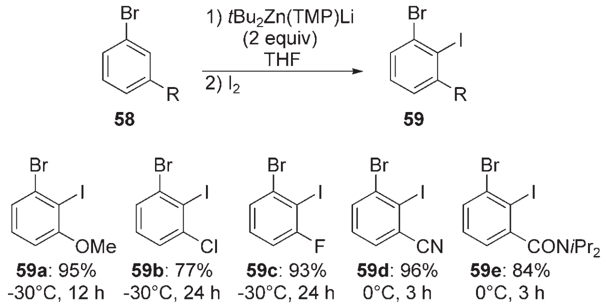
Scheme 16. Deprotonation of **52** and **54** with amido zincates and subsequent trapping with iodine.

Michl and co-workers reported in 2002 the use of TMP–zincate (2 equiv) for the regioselective metalation of 3-alkyl pyridine·BF$_3$ complexes **56** (Scheme 17).[58] The reaction occurred at the less hindered of the two reactive positions, a result evidenced by trapping the pyridyl zincates with iodine to afford the 2-iodo-5-alkyl pyridine derivatives **57** in good yields. The method proved to be superior to the use of LTMP/TMEDA, provided that two equivalents of zincate are used.

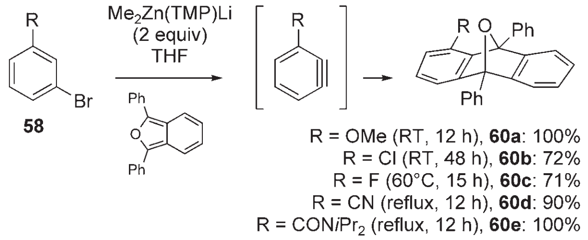


Scheme 17. Deprotonation of **56** with TMP–zincate and subsequent trapping with iodine.

The deprotonative zincation of various 3-substituted bromobenzene derivatives **58** (R = OMe, Cl, F, CF$_3$, CN, CON*i*Pr$_2$, CO$_2$Et, CO$_2$*t*Bu) was investigated by focusing on the nature of TMP–zincates.[51g,59] For bromobenzene derivatives **58** bearing OMe, Cl, F, CN, or CON*i*Pr$_2$ at the 3-position, the reaction with *t*Bu$_2$Zn(TMP)Li took place chemo- and regioselectively at C2 to give the corresponding 2-iodo derivatives **59** (Scheme 18). The nature of alkyl ligands on the zincates turned out to influence dramatically the reactivities of the resultant aryl zincates. Indeed, when Me$_2$Zn(TMP)Li was used instead of *t*Bu$_2$Zn(TMP)Li to deprotonate the same 3-substituted bromobenzenes, the benzyne formation could not be avoided. Raising the temperature of the reaction mixtures in the presence of 1,3-diphenylisobenzofuran resulted in the formation of the Diels–Alder adducts **60** from the intermediate substituted benzynes in high yields (Scheme 19). The method using Me$_2$Zn(TMP)Li is particularly useful for the synthesis of functionalized benzynes, since the conventional methods require highly substituted benzenes, and hardly tolerate electrophilic substituents.[60]



Scheme 18. Deprotonation of 3-substituted bromobenzenes **58** with *t*Bu$_2$Zn(TMP)Li and subsequent trapping with iodine.



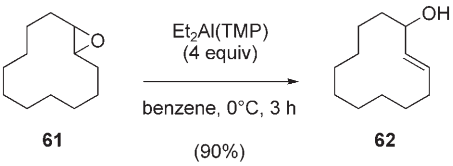
Scheme 19. Deprotonation of 3-substituted bromobenzenes **58** with Me$_2$Zn(TMP)Li in the presence of 1,3-diphenylisobenzofuran.

This drastic change of reaction modes dependent on the alkyl-ligation environment is a feature of zincates that is interesting and potentially useful from the synthetic viewpoint.

2.3. Deprotonation with Aluminates

Organoaluminum compounds have been widely used both in industrial and laboratory synthetic chemistry,[61] serving as polymer synthesis catalysts,[62] Lewis acid reagents,[63] and organic synthetic building blocks.[64] As demonstrated by recent developments,[65] organoaluminum species have become extremely important synthetic intermediates and reagents in the formation of carbon–carbon and carbon–heteroatom bonds, especially in aliphatic chemistry.

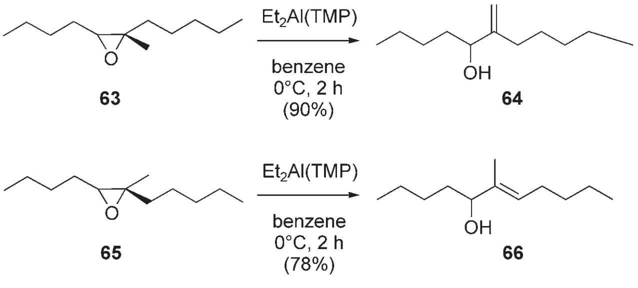
Yamamoto and co-workers originally reported in 1974 the use of $Et_2Al(TMP)$ as a new type of base for the regiospecific deprotonation of epoxides.[66] $Et_2Al(TMP)$ can be prepared in situ from diethylaluminum chloride and LTMP (1:1 ratio) in benzene at 0 °C for 30 min. Deprotonation of (*E*)-cyclododecene oxide (**61**) with $Et_2Al(TMP)$ (4 equiv) in benzene proceeded smoothly at 0 °C to afford (*E*)-2-cyclododecen-1-ol (**62**) in 90 % yield (Scheme 20).



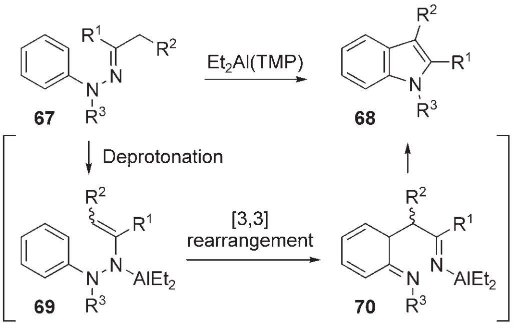
Scheme 20. Deprotonation of (*E*)-cyclododecene oxide (**61**) with Et_2Al(TMP).

Several oranoaluminum reagents were studied in their ability to deprotonate by using **61** as a model substrate under fixed conditions (0 °C, 1 h): $Et_2Al(NEt_2)$ less than 5 %, $Et_2Al(NcHex_2)$ 36 %, $Et_2Al(NiPr_2)$ 45 %, $Et_2Al(TMP)$ 80 %. It should be noted that LTMP itself was an unsatisfactory reagent for this transformation under the same reaction conditions (less than 5 % of **62** and greater than 70 % of the starting oxido compound **61** was recovered). Regioselectivity of this deprotonation with $Et_2Al(TMP)$ was very high. The deprotonation of *Z* epoxide **63** with $Et_2Al(TMP)$ produced the disubstituted allylic alcohol **64** in 90 % yield, whereas the reaction with *E* epoxide **65** gave the trisubstituted *E* allylic alcohol **66** as the predominant product (Scheme 21).

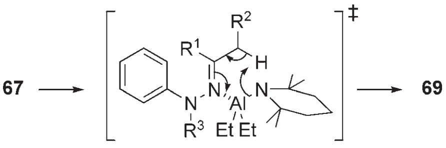
In 1993, Yamamoto and co-workers reported that Et_2Al(TMP) is also highly effective for the Fischer indole synthesis (Scheme 22).[67] Regiospecificity of the $Et_2Al(TMP)$-mediated indole synthesis from aryl hydrazones of unsymmetrical ketones turned out to be generally high, and hence the superiority of $Et_2Al(TMP)$ as a regioselective agent over previously known catalysis is apparent. This observation clearly supports regioselective enehydrazine formation by preferential abstraction of the α-methylene hydrogen atom *anti* to the hydrazone by $Et_2Al(TMP)$, as shown for **71** (Scheme 23).



Scheme 21. Regioselectivity of the deprotonation reaction with $Et_2Al(TMP)$.



Scheme 22. $Et_2Al(TMP)$-promoted Fischer indole synthesis.



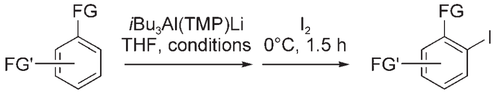
71

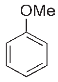
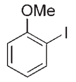
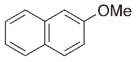
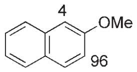
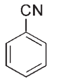
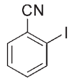
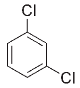
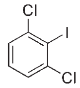
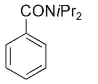
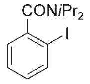
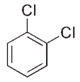
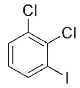
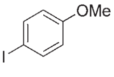
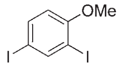
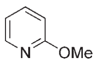
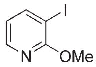
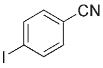
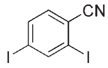
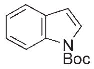
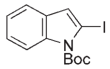
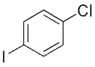
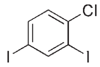
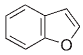
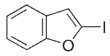
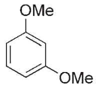
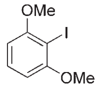
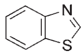
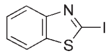
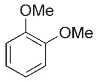
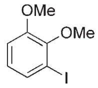
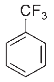
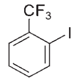
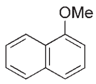
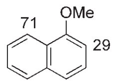
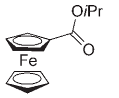
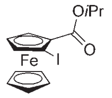
Scheme 23. $Et_2Al(TMP)$-promoted regioselective deprotonation.

In contrast to aliphatic aluminum chemistry, aromatic aluminum chemistry had not been well-developed, simply because of the poor synthetic availability of these systems. A conventional preparative method for aromatic aluminum compounds has been the transmetalation of aryl lithium or aryl Grignard reagents.[68] This method, however, suffers from the limited compatibility of functional groups on aromatic rings with intermediary ArLi or ArMgX species, or their precursors (alkyl lithium or alkyl Grignard reagents), which are too highly reactive towards various electronegative functional groups (such as halogen, amide, and cyano groups) and π-deficient heterocycles.[6] Hydro- or carboalumination, which is known to be a powerful preparative method in aliphatic chemistry,[69] is ineffective for aromatic compounds because of the structural limitations of benzene rings.[60c] In addition, neither oxidative addition nor halogen–metal exchange reactions of aluminum on aromatic rings have been realized to date. Thus, the deprotonative alumination of functionalized benzene derivatives would be more attractive and advantageous to generate (multi)functionalized aromatic aluminum compounds from the viewpoint of the availability of precursors. However, tricoordinated aluminum reagents including $Et_2Al(TMP)$ are ineffective for the directed *ortho* alumination of functionalized benzene derivatives.

Uchiyama and co-workers reported in 2004 lithium triisobutyl(tetramethylpiperidino)aluminate (TMP–aluminate) from triisobutylaluminum and LTMP.[70] This heteroleptic deprotonating agent was chemoselectively used in the functionalized arenes series (Table 2). This deprotonative alumination was found to be regioselective and tolerant of both electron-donating groups (such as OMe) and electron-withdrawing groups. Notably, deprotonative alumination

Table 2: Deprotonative alumination of functionalized aromatic rings using $i\mathrm{Bu}_3\mathrm{Al(TMP)Li}$.[a]



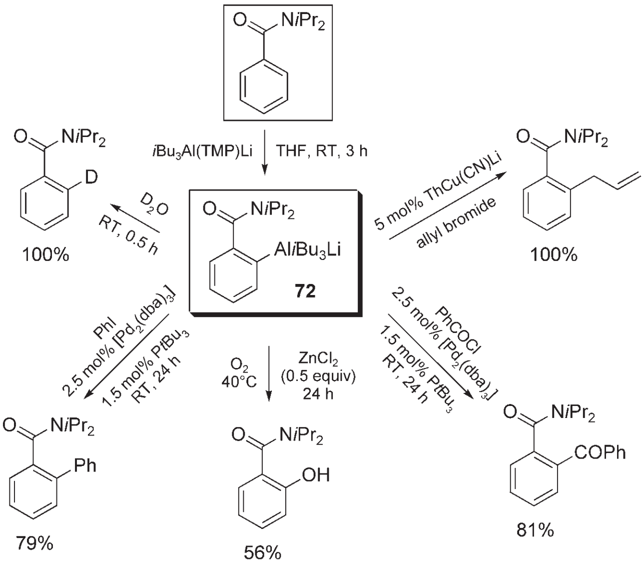
Entry	Substrate	Product	Yield [%][b] (conditions)	Entry	Substrate	Product	Yield [%][b] (conditions)
1			99 (RT, 3 h)	10			84 (RT, 3 h)
2			100 (−78 °C, 2 h)	11			74 (−78 °C, 12 h)
3			94 (RT, 3 h)	12			72 (−78 °C, 5 h)
4			83 (RT, 3 h)	13			82 (−78 °C, 1 h)
5			90 (−78 °C, 2 h)	14			64 (100)[c] (−78 °C, 5 h)
6			100 (−78 °C, 2 h)	15			88 (RT, 2 h)
7			92 (0 °C, 4 h)	16			86 (0 °C, 2 h)
8			74 (0 °C, 4 h)	17			40 (0 °C, 7 h)
9			68 (RT, 3 h)	18			37 (−78 °C, 2 h)

[a] The deprotonative alumination was carried out by using $i\mathrm{Bu}_3\mathrm{Al(TMP)Li}$ (2.2 equiv) and substrate (1.0 equiv) in THF. [b] Yield of isolated product. [c] Value in parenthesis is the yield of the 2-deuterated product (quenched with D_2O).

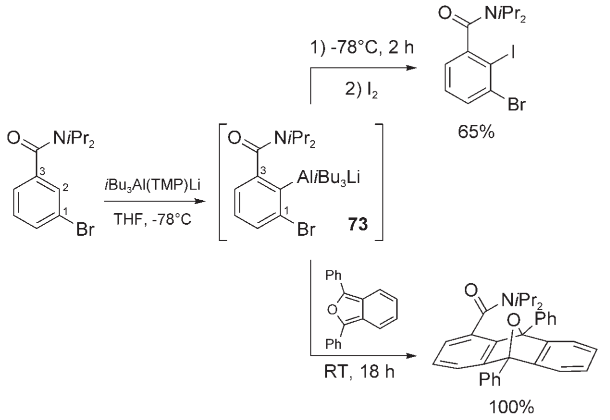
occurred with suppression of nucleophilic addition to carbonyl and CN groups (Table 2, entries 2, 3, and 5) or benzyne formation with halogens (entries 4–6 and 11–12), and halogen–metal exchange of iodine substituents (entries 4–6). Such chemoselectivity is considered to be unique to this aluminate agent, because neither conventional metal bases (such as RLi and Grignard reagents) nor even TMP–zincates can coexist with the aryl iodide.[55] Heteroaromatics such as pyridine, indole, benzofuran, and benzoxazole rings were similarly applicable substrates (Table 2, entries 13–16). The functionalized aryl aluminate intermediate **72** (as a typical intermediate of this metalation) can be utilized as an aryl anion equivalent (Scheme 24).

The chemo- and regioselective zincation of *meta*-functionalized haloaromatics and the generation of 3-substituted benzynes could be controlled by utilizing the drastic ligand effects seen in these zincates.[51g] In the case of the aluminum ate base, generation of benzynes could be controlled by changing the reaction temperature (Scheme 25). The intermediate **73**, generated by the deprotonative alumination of *N*,*N*-diisopropyl-3-bromo-2-iodobenzamide, could be trapped with an electrophile (I_2) at low temperature, while the generation of a 3-functionalized benzyne proceeded smoothly at room temperature, and this reacted with 1,3-diphenylisobenzofuran to give the corresponding Diels–Alder adduct in quantitative yield.

$i\mathrm{Bu}_3\mathrm{Al(TMP)Li}$ is also effective for direct generation of the functionalized allylic aluminum compounds, whereby the one-pot regioselective transformation can be realized under mild conditions (Table 3).[70b]



Scheme 24. Electrophilic trapping of the functionalized aryl aluminate intermediate **72**; Th = thienyl.



Scheme 25. Thermally controlled generation (bottom) and suppression (top) of a 3-functionalized benzyne.

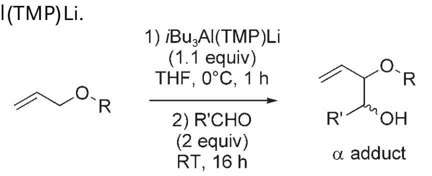
3. Synergy and Structure Building

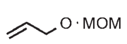
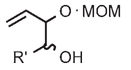
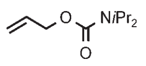
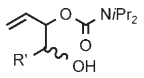
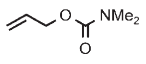
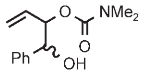
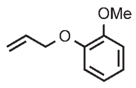
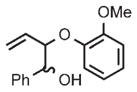
To this point, this Review has been largely focused on key synthetic applications of magnesiates, zincates, and aluminates from the point of view of transforming an organic starting material into a final organic product, which is usually accomplished by strategies involving metalation and subsequent electrophilic interception. Synthetic chemists can dedicate their working lives to perfecting such transformations. The final organic products are all important, but to synthesize them with maximum efficiency, to employ the best metalating reagent for the task, and to enable the rational design of future syntheses, one must build up a portfolio of knowledge about the intermediate chemistry taking place prior to the formation of the final organic product. Specifically, this portfolio should include information on the composition and structure of the ate reagent itself, and of the metalated organic derivatives it forms prior to any electrophilic interception step. This information is particularly germane in the case of heteroleptic (mixed-ligand) ate complexes, for which ligand-transfer selectivity can become an issue (for example, in TMP–zincates, either the amido ligand or the alkyl ligand can function as the Brønsted base). Accumulating valuable information of this type can also have positive results extending beyond the confines of synthetic organic chemistry, such as the discovery of a new unprecedented class of structure or molecular architecture that one would be more likely to find in the realm of macrocyclic/supramolecular chemists.

Accordingly, this section of our Review deals with representative examples of deprotonative applications of magnesiates, zincates, and to a lesser extent, aluminates, for which there exists a well-defined and revealing structural chemistry. Much of this synthetic and structural chemistry has a synergic element to it, in the sense that compounds with a heterobimetallic (ate) combination of an alkali metal (usually Li, Na, or K) and magnesium or zinc or aluminum, can effect (often surprising) reactions which cannot be replicated by the corresponding homometallic (non-ate) alkali-metal, magnesium, zinc, or aluminum compounds. This special synergic chemistry will be emphasized throughout this section. The terms alkali-metal-mediated magnesiation (AMMM), alkali-metal-mediated zincation (AMMZ), and alkali-metal-mediated alumination (AMMA) seem appropriate to describe these and the other synergic deprotonative metalations recorded in this Review.

One possible manifestation of this synergy is in “inverse crowns”,[71] which formally comprises cationic “host” rings and anionic “guests”. The term inverse crown was coined because of the mutual interchange between Lewis acidic (metallic) and Lewis basic (anionic) sites compared to that

Table 3: Deprotonative alumination of functionalized allylic compounds using iBu$_3$Al(TMP)Li.



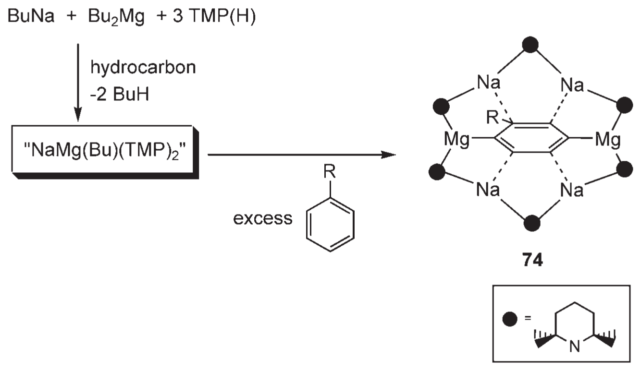
Entry	Substrate	R′	Product	Yield[a]	α/γ
1		Bu		97	> 99:1
2		Ph		77	97:3
3		Bu		70	> 99:1
4		Ph		96	85:15
5		Ph		63	79:21
6		Ph		82	> 99:1

[a] Yield of isolated product. Diastereomeric ratio of α products (*erythro*/*threo*): entry 1 (87:13), entry 2 (56:44), entry 3 (not determined), entry 4 (82:17), entry 5 (58:42), entry 6 (99:1). *E*/*Z* ratios of γ products were not determined. MOM = methoxymethyl.

found in conventional crown ether complexes of the alkali metals (Lewis basic rings with Lewis acidic guests). This section will therefore also highlight the most interesting cases in which synergic deprotonative metalation has led to the construction of an inverse crown.

Inverse crown compounds with alkoxide, hydride, oxide, or peroxide guests are known which have in common eight-membered $(MNMgN)_2$ host rings (M = Li, Na, or K).[72] As these mixed-metal compounds either arise from deprotonative metalation reactions for which regioselectivity is not an issue (for example, as in the case of alkoxo inverse crown compounds, which are formed by deprotonation of a strongly acidic OH group of an alcohol[73]) or do not arise from deprotonative metalation at all (for example, as in the case of hydrido inverse crown compounds, which are proposed to be formed by β-hydride elimination from an *i*PrN unit of a diisopropylamido ligand[74]), they need not be discussed further here.

Regioselectivity is important in deprotonation reactions of the arenes toluene (always) and benzene (when two or more hydrogen atoms are removed). AMMM of benzene and toluene via the monoalkyl–bisamido base "NaMg(*n*Bu)(TMP)$_2$" (Scheme 26), prepared nonstoichiometrically by reaction of butylsodium, dibutylmagnesium, and three molar equivalents of TMPH (one equivalent resists metalation) produces twofold deprotonation at equivalent aromatic ring sites (that is, the 1,4-positions in benzene and the 2,5-positions in toluene).[75]



Scheme 26. Synthesis of arenediide inverse crown compounds **74**.

For electronic and steric reasons the regioselectivity of the former dimetalation may not seem that surprising as 1,4-disubstitution maximizes the distance between the negative charges on the ring and concomitantly between the Mg atoms bonded to it. However, the fact that benzene can be directly magnesiated at all, let alone twofold magnesiated, is in itself a major surprise given that conventional magnesium reagents such as Grignard or dialkylmagnesium reagents are inert towards benzene. Conversely the latter regioselectivity is unexpected as the most acidic hydrogen (by several pK_a units) belongs to the methyl arm of toluene, which makes it the target of conventional organometallic bases in generating benzyl ($PhCH_2^-$) products.

In both cases twofold deprotonation is manifested in isostructural 12-membered inverse crown ring products of the formula $[Na_4Mg_2(tmp)_6(arene{-}2H)]$ (**74**, where arene−2H is C_6H_4 or $C_6H_3CH_3$; Figure 1). A salient feature is the near coplanarity of the Mg atoms to the arene ring plane in filling the cleaved H sites, indicative of Mg–C σ bonding. Linking these Mg atoms are five-membered NNaNNaN bridges, the Na atoms of which are positioned nearly perpendicular to the arene ring plane, indicative of Na–(π-arene) electrostatic interactions. This σ- and π-bonding distinction, which reflects to an extent the predominance of covalency and ionicity in Mg–C and Na–C bonds, respectively, has become a signature feature of arene-based inverse crown compounds and related (nonmacrocyclic) mixed-metal structures.[72]

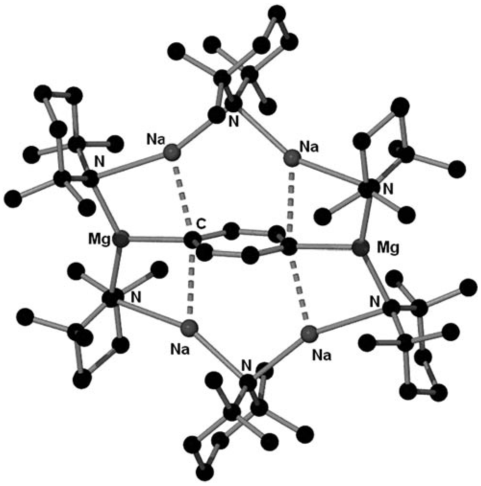
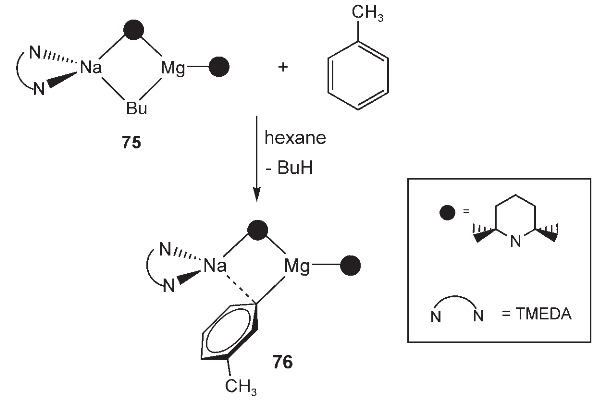


Figure 1. Molecular structure of arenediide inverse crowns **74**.

Implicating a stepwise mechanism (successive deprotonations) as opposed to a simultaneous templation through an arene dianion, toluene is monodeprotonated uniquely in the *meta* position (i.e., the "5"-position) by the TMEDA embodiment of this monoalkyl–bisamido system, namely [(tmeda)Na(μ-Bu)(μ-tmp)Mg(tmp)] (**75**).[76,77] X-ray crystallographic characterization of the reactant base **75** and the product [(tmeda)Na(μ-$C_6H_4CH_3$)(μ-tmp)Mg(tmp)] (**76**) enables this monodeprotonative reaction to be depicted in lucid structural terms (Scheme 27). The species **75** functions as an alkyl (as opposed to an amido) base in generating the (*meta*-C)–Mg bond, the Mg atom of which still carries the {(μ-tmp)Na(tmeda)} and terminal TMP units. The alkyl basicity of **75** also extends to reactions with the aromatic heterocycle furan and the transition-metal π-arene complexes bis(benzene)chromium and bis(toluene)chromium.

Furan undergoes AMMM exclusively at the α position, an ordinary result in terms of selectivity (α lithiation is common)[78] but extraordinary in being manifested in the novel 12-membered $(NaOCMgCO)_2$ inverse crown structure of $[\{\{(thf)_3Na_2\}\{(tmeda)Mg_2\}(2\text{-}C_4H_3O)_6\}_\infty]$ (**77**, Figure 2). Illustrating beautifully the synergic σ–π bonding signature of inverse crown compounds, this structure is homoleptic in having clearly distinguishable sets of α-furyl anions, four in



Scheme 27. Synthesis of the mixed-metal sodium–magnesium synergic base **76**.

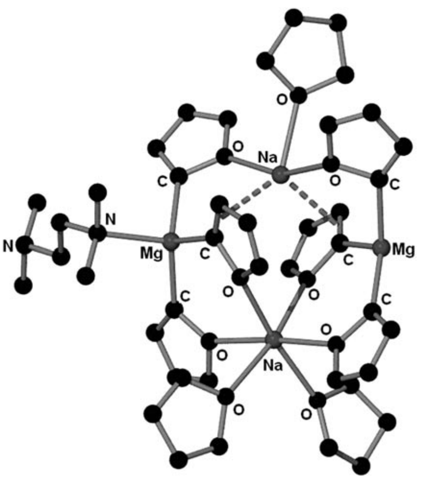
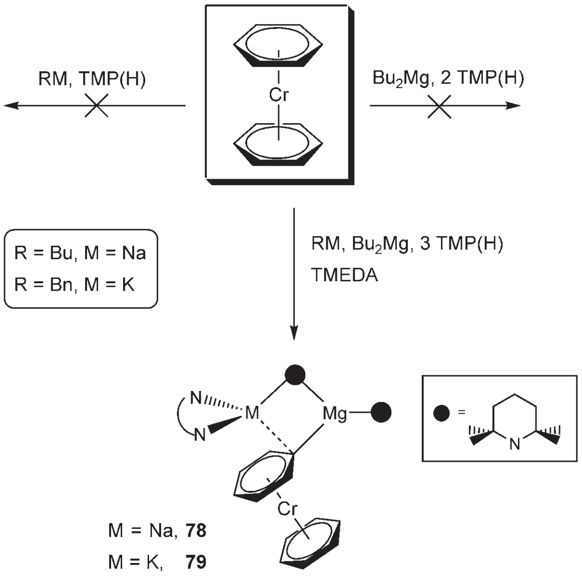


Figure 2. Molecular structure of **77**.

the "host" ring and two in "guest" positions. The latter set supplements the coordinative requirements of one Na cation through the C=C π system.

Conversely, AMMM of bis(benzene)chromium[79] and bis(toluene)chromium[80] does not promote the construction of inverse crown ring structures but does bring about special synergic selectivities. Deprotonation occurs exclusively on one arene ring only (*para*-directed in the case of toluene) and stops at monodeprotonation even when the mixed-metal base is administered in excess. This contrasts with the poor selectivity associated with conventional lithiation, which produces a mixture of monodeprotonation and dideprotonation (one deprotonation at each ring) products when bis(benzene)chromium is treated with one molar equivalent of TMEDA-activated butyllithium.[81]

Emphasizing the synergy of the AMMM method (note here that AM can be Na or K), corresponding homometallic reactions involving butylsodium or benzylpotassium or dibutylmagnesium with TMPH/TMEDA mixtures fail to similarly promote metalation of these chromium π-arene complexes (Scheme 28).



Scheme 28. Synergic monodeprotonation reactions of bis(benzene)chromium; Bn = benzyl.

The molecular structures of the products of the AMMM method, $[(\text{tmeda})\text{AMMg}\{\text{Cr}(C_6H_4R)(C_6H_5R)\}(\text{tmp})_2]$ (**78**, AM = Na, R = H; **79**, AM = K, R = H; **80**, AM = Na, R = *para*-CH_3) are essentially the same (Figure 3). The Mg atom occupies the coordination site of the cleaved H atom in the plane of the arene ring still carrying the {(μ-tmp)Na(tmeda)} and terminal TMP unit of the reactant base **75** (in the cases of **78** and **80**), while the Na and K atoms adopt a nearly perpendicular disposition to this plane in engaging with its π face. Interestingly, the tolyl rings of the chromium complex **80** adopt an almost eclipsed disposition (i.e., one Me group in line with the other). DFT calculations indicate that the alkali-metal···(π-arene) interactions are significant in the *para* selectivity of the magnesiation with **80**.[80] Why compounds **78**–**80** appear to be resistant to further AMMM and do not undergo twofold deprotonation (or higher) remains an open question, though twofold deprotonation seems feasible sterically on the basis of molecular models, so the problem must be electronic in origin.

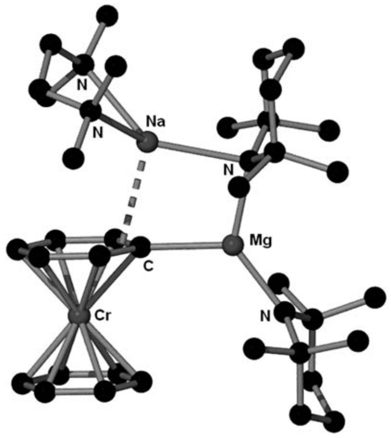
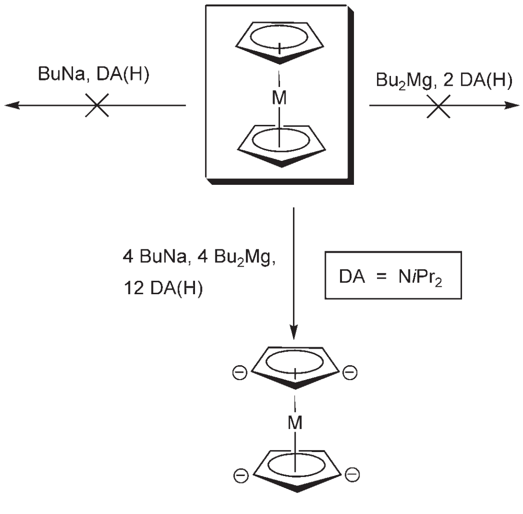


Figure 3. Molecular structure of **79**.

Higher deprotonation is, in contrast, easily achievable when AMMM is applied to metallocene substrates. Thus, subjecting ferrocene, ruthenocene, or osmocene to the synergic amide base sodium–magnesium tris(diisopropylamide) generates a remarkable Group 8 homologous series of fourfold-deprotonated metallocenes of general formula $[\{M(C_5H_3)_2\}Na_4Mg_4(da)_8]$ (**81**; M = Fe, Ru, or Os; da = iPr$_2$N; Scheme 29).[82,83] This tetramagnesiation is manifested in a remarkable inverse crown structure, comprising a 16-membered $\{(NaNMgN)_4\}^{4+}$ host ring and a metallocene tetraanion $\{M(C_5H_3)_2\}^{4-}$ guest core (Figure 4), which remains intact in arene solution.

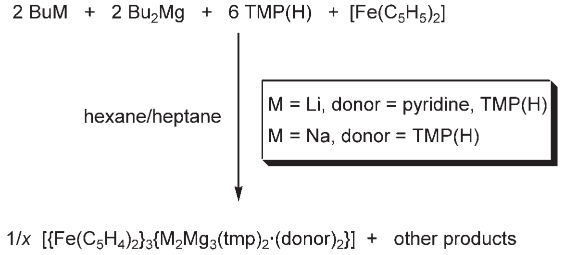


Anion of **81**

Scheme 29. Synergic tetradeprotonation reactions of Group 8 metallocenes (M = Fe, Ru, or Os).

The fourfold deprotonation is selective with Mg atoms substituting for the cleaved H atoms in the 1-, 1′-, 3-, 3′-positions. Such controlled, regioselective polymetalation of metallocenes is beyond the capabilities of conventional organometallic bases (notably organolithium reagents which are limited to effecting mono- or dilithiation). Even more significantly, direct magnesiation (let alone tetramagnesiation) of these metallocenes is not possible using conventional organomagnesium bases (Grignard reagents or bisalkyl reagents). Mediation by the alkali metal (sodium) is therefore the crucial factor in switching on the synergy (sodium diisopropylamide on its own is also ineffectual in metalating ferrocene) that powers the polymagnesiation.

When the amide component of the synergic base is changed from DA to TMP in "NaMg(nBu)(TMP)$_2$", the deprotonating power diminishes in that now only two H atoms can be cleaved from ferrocene (in the 1,1′-positions, the usual regioselectivity observed in dilithiation reactions).[84] But in terms of structure building this is another remarkable reaction (Scheme 30) because it leads to the construction of multinuclear ferrocenophane bisamide complexes of the general formula $[\{Fe(C_5H_4)_2\}_3\{M_2Mg_3(tmp)_2(donor)_2\}]$ (**82**; M = Li, donor = pyridine or TMP(H); M = Na, donor = TMP(H); Figure 5). The reduction in (poly)basicity of "NaMg(nBu)(TMP)$_2$" compared to that of "NaMg(DA)$_3$" is thought to be steric in origin.



82

Scheme 30. Synergic synthesis of the trinuclear ferrocenophanes **82**.

In AMMM, the alkali-metal component not only enhances the magnesiating power of the synergic base, it also assumes the role of a chemical architect in directing (or helping to direct) the molecular structure of the magnesiated organic substrate. This is illustrated most vividly in the spectacular ring expansion that takes place upon substituting

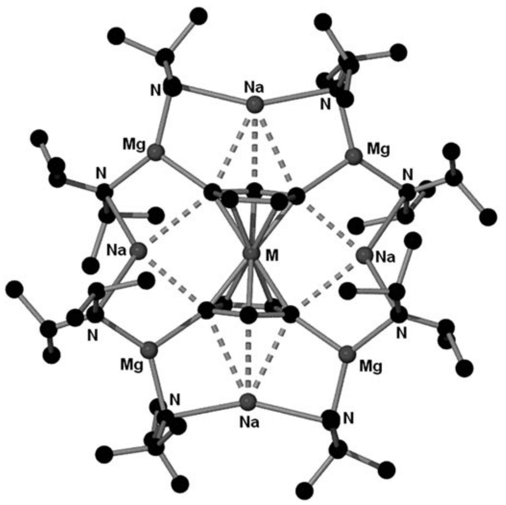


Figure 4. Molecular structure of the metallocenyl inverse crowns **81**.

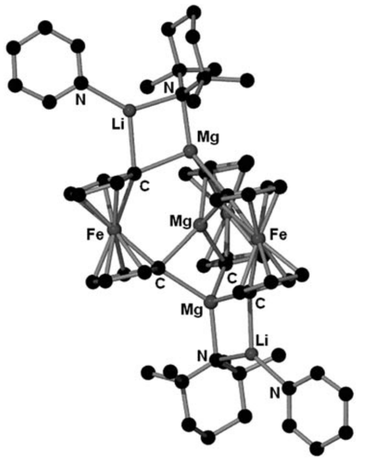


Figure 5. Molecular structure of **82** (with M = Li and donor = pyridine).

sodium by potassium in the arene deprotonation reactions that yield **74** (see Scheme 26).[85]

The 12-membered host ring of **74** is now replaced by the largest inverse crown synthesized to date, a 24-membered hexapotasssium–hexamagnesium dodecaamide ring, which acts as a polymetallic cyclic host to six onefold-deprotonated arene anions in products of the general formula $[K_6Mg_6(tmp)_{12}(arene{-}1H)_6]$ (arene = benzene or toluene; Figure 6).

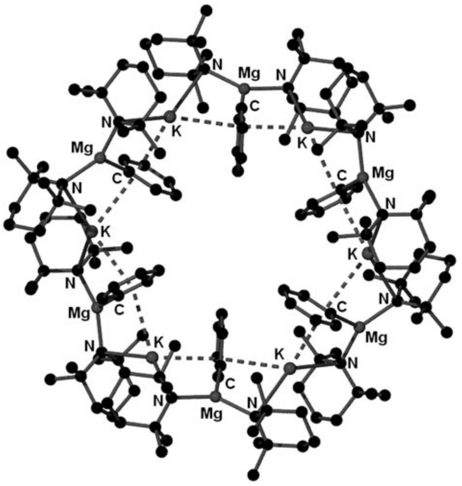


Figure 6. Molecular structure of $[K_6Mg_6(tmp)_{12}(arene{-}1H)_6]$.

As in the sodium structures, the encapsulated arene anions receive dual (σ and π) stabilization from the Mg and K atoms, respectively. It must be emphasized that in the potassium reaction only onefold deprotonation takes place, whereas with sodium twofold deprotonation takes place. This runs counter to the general convention in homometallic chemistry that organopotassium compounds are orders of magnitude more reactive than organosodium congeners. Hence, this is another demonstration of how the synergic effect of the mixed-metal partnership can reverse normal orders of reactivity.

Combining the alkali metal with zinc instead of magnesium can also lead to a reversal in the expected order of reactivity. Zinc is usually considered to be less reactive than magnesium but when dressed as the ate complexes "$KZn(HMDS)_3$" and "$KMg(HMDS)_3$", the former smoothly deprotonates toluene to give the benzyl product $[\{KZn(hmds)_2(CH_2Ph)\}_\infty]$,[86] whereas the latter is inert under the same conditions. This opening example of AMMZ exhibits the same synergic σ- and π-bonding distinction that is a signature feature of the deprotonated arene products of AMMM, but as the K···Ph π contacts occur intermolecularly as opposed to intramolecularly, structurally this is manifested in an open polymeric chain arrangement (Figure 7) as opposed to a closed inverse crown cycle. The origin of this deprotonation is also synergic as neither KHMDS nor $Zn(HMDS)_2$ are capable of deprotonating toluene on their own.

Benzene can be similarly synergically zincated (and even twofold zincated) by AMMZ.[87,88] In this reaction (Scheme 31), the structurally defined sodium TMP–zincate reagent [(tmeda)Na(μ-*t*Bu)(μ-tmp)Zn(*t*Bu)] **83** functions as an alkyl base in contrast to the amido (TMP) basicity exhibited by "$LiZn\textit{t}Bu_2(TMP)$" in the aforementioned studies from Kondo and Uchiyama.[55] It may be significant that in the former case the bulk solvent was apolar hexane, whereas in the latter case polar THF was employed, though the organic substrates deprotonated are also dissimilar.

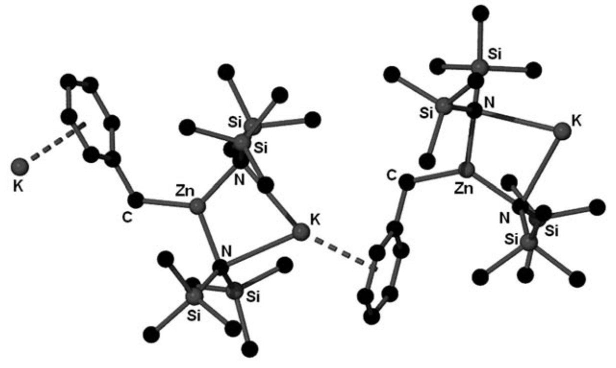
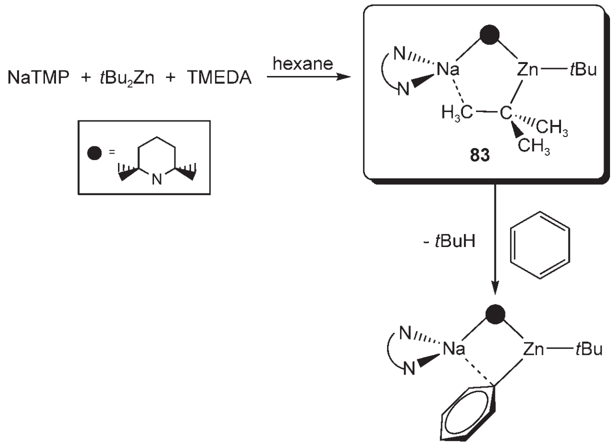


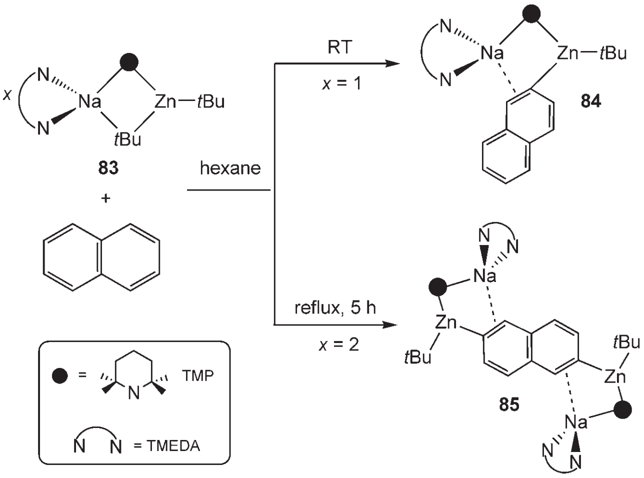
Figure 7. Section of the infinite chain structure of $[\{KZn(hmds)_2(CH_2Ph)\}_\infty]$.



Scheme 31. Synthesis of the sodium TMP–zincate **83** and its 1:1 reaction with benzene.

Structurally this AMMZ of benzene represents the isomorphous replacement of a *t*Bu ligand (with a strong σ bond to Zn and a weak agostic interaction with Na) by a Ph ligand (with a strong σ bond to Zn and a weak π bridge to Na), as the {(tmeda)Na(μ-tmp)Zn(*t*Bu)} arch-shaped remainder of the structure remains intact. Looking for a reactivity hot spot within **83**, one is immediately drawn to the weak agostic $Na{\cdots}Me(CMe_2)$ contact, which can be envisaged to break under Lewis basic (in this case, π-arene) attack on the Na atom to open up the NaNZnC(C) ring. In both **83** and its phenyl derivative, the architectural ambitions of the Na atom in building larger, aggregated structures like that realized in magnesiates such as **74** are thwarted by the electronic and steric stabilization provided by the chelating tmeda ligand.

Polycyclic aromatic hydrocarbons can also undergo AMMZ, effected by the sodium TMP–zincate reagent **83**. Thus, naphthalene can be transformed to zincated derivatives not directly accessible with mainstream organozinc reagents. These AMMZ reactions (Scheme 32)[89] exhibit a high degree of stoichiometric control as mixtures of naphthalene and **83** (again functioning as an alkyl base) in 1:1 ratios produce the monozincated complex $[(\text{tmeda})\text{Na}(\mu\text{-tmp})(\mu\text{-2-C}_{10}\text{H}_7)\text{Zn}(t\text{Bu})]$ (**84**), whereas 1:2 ratios produce mainly the dizincated complex $[(\text{tmeda})_2\text{Na}_2(\mu\text{-2,6-C}_{10}\text{H}_6)\text{Zn}_2(t\text{Bu})_2]$ (**85**). The associated deprotonations leading to their formation are therefore regioselective at the 2- and 2,6-positions, respectively, which is a marked improvement on naphthalene metalation reactions performed by BuLi[3] or superbasic LIC–KOR[90] as they produce nonselective mixtures of 1- and 2-monosubstituted isomers as well as all ten possible disubstituted isomers. Consistent with the view that the metalation process leading to the formation of **84** is an AMMZ and not a sodium addition, the Zn atom occupies the deprotonated 2-position and lies in the naphthyl ring plane, while the Na atom engages in a long η^2 interaction at the 1- and 2-positions (Figure 8).



Scheme 32. Regioselective monozincation and dizincation of naphthalene with **83**.

The centrosymmetric molecular structure of **85** (Figure 9) closely resembles that of **84** but with an additional $[(\text{tmeda})\text{Na}(\mu\text{-tmp})\text{Zn}(t\text{Bu})]^+$ cationic unit grafted onto the 6-position where the second proton was cleaved. In keeping with the centrosymmetry, the residues occupy sterically minimizing transoid positions on opposite sides of the naphthalenediide ring plane. This pair of synergically zincated naphthalene structures thus maintain the in-plane (σ-based) and out-of-plane (π-based) bonding pattern between the deprotonated aromatic substrate and the zinc and sodium atoms, respectively, though again the voluminous tmeda ligand at sodium prevents aggregation into an inverse crown or other type of supramolecular architecture.

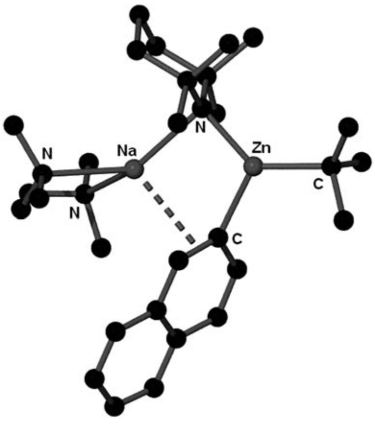


Figure 8. Molecular structure of **84**.

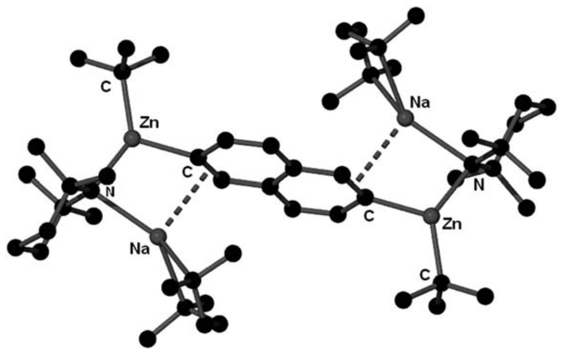
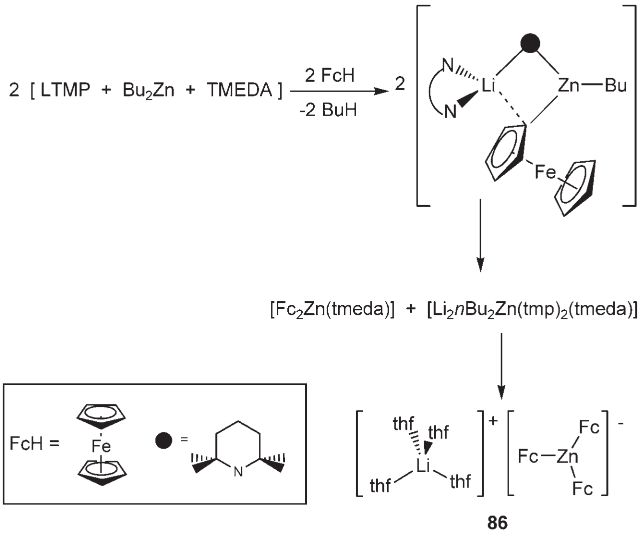


Figure 9. Molecular structure of **85**.

AMMZ has also made possible the first direct zincation of a metallocene.[91] In this reaction (Scheme 33) ferrocene is ultimately converted to the tris(ferrocenyl)zincate $[\text{Li}(\text{thf})_4]^+[(\text{Fc})_3\text{Zn}]^-$ (**86**; $\text{Fc} = \text{C}_5\text{H}_5\text{FeC}_5\text{H}_4$). Here mediation is achieved by lithium via an in situ mixture of LTMP, Bu_2Zn, and TMEDA, the deprotonative reactivity of which is synergic since neither LTMP nor Bu_2Zn on their own are capable of metalating ferrocene even in the presence of TMEDA.

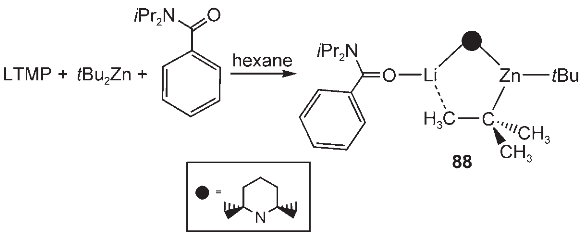


Scheme 33. Synthesis of the tris(ferrocenyl)zincate **86**.

In the absence of ferrocene, this in situ mixture in hexane solution affords the crystalline lithium TMP–zincate $[(\text{tmeda})\text{Li}(\mu\text{-}n\text{Bu})(\mu\text{-tmp})\text{Zn}(n\text{Bu})]$ (**87**). In terms of composition and structure, **87** belongs to the same family as **83** with lithium substituted for sodium, an *n*-butyl ligand substituted for a *tert*-butyl ligand, and a long-range, weak Li⋯$CH_2(CH_2CH_2CH_3)$ contact substituted for a Na⋯CH_3-(CMe_2) contact.

By analogy with the related magnesiates used in AMMM, one would expect sodium zincate reagents to be more powerful synergic bases than lithium zincate reagents. This is borne out by the reactions of **83** with ferrocene, which, depending on the stoichiometry used, can inflict single, twofold, or even fourfold deprotonation of the metallocene.[92]

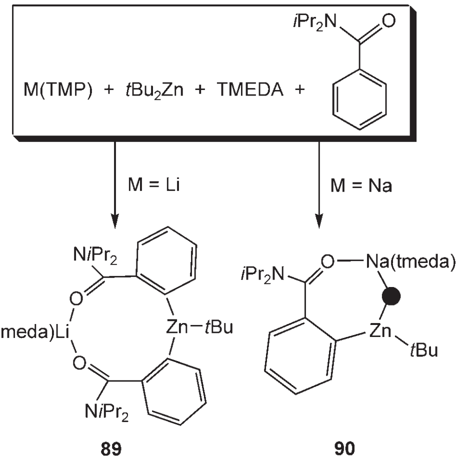
As discussed earlier in this Review, alkali-metal zincate reagents are excellent tools for effecting directed *ortho* metalation (DoM) of various aromatic substrates. Studies gleaning structural insights at both the premetalation and postmetalation stages into how AMMZ can effect directed *ortho* zincation (DoZ) of the tertiary aromatic amide *N*,*N*-diisopropylbenzamide have also been reported.[93,94] At the premetalation stage, a synergic lithium zincate mixture of LTMP and $t\mathrm{Bu}_2\mathrm{Zn}$ in hexane reacts with the amide to generate the 1:1 donor–acceptor complex [{(*i*Pr)$_2$NC(Ph)(=O)}Li(μ-tmp)(μ-*t*Bu)Zn(*t*Bu)] (**88**; Scheme 34). Highlighting the kinetic advantage of lithium-mediated zincation over conventional lithiation, the enhanced stability of the mixed-metal approach means that this reaction can be performed at room temperature without provoking deprotonation, when organolithium reagents such as BuLi rapidly effect *ortho* deprotonation of this amide at subambient temperatures.



Scheme 34. Synthesis of the novel donor–acceptor complex **88**.

The structure of **88** establishes that the first point of coordination of the benzamide is the alkali metal (as it is in conventional directed *ortho* lithiation), through a short Li–O dative bond (and a much weaker Li⋯Me(CMe_2) agostic bridge). In the presence of TMEDA, the components of **88** react to effect DoZ, manifested in the bis(benzamide) derivative [(tmeda)Li{2-[1-C(O)N(*i*Pr)$_2$]C_6H_4}$_2$Zn(*t*Bu)] (**89**; Scheme 35).

Here the synergic lithium TMP–zincate reagent functions as a dual alkyl–amido base with the coproducts of the *ortho* zincation *tert*-butane and TMPH. Demonstrating another alkali-metal effect, the corresponding sodium TMP–zincate reagent **83** utilizes only one of its Brønsted basic arms (*t*Bu) in deprotonating the benzamide at the *ortho* position to generate the bis(benzamide) derivative [(tmeda)Na(tmp){2-[1-C(O)N(*i*Pr)$_2$]C_6H_4}Zn(*t*Bu)] (**90**; Scheme 35). The TMP arm of **83** remains intact within **90**. Therefore, although the same pattern of chemoconnectivity (O atom to alkali-metal center; *ortho*-C atom to Zn atom) accompanies these DoZ reactions, zincation is executed within a 10-membered [Li(OCCC)$_2$Zn] ring in **89**, but within a seven-membered, five-element (NaNZnCCCO) ring in **90** (Figure 10).



Scheme 35. Contrasting ring structures **89** and **90**, formed upon treating lithium and sodium TMP–zincates, respectively, with *N*,*N*-diisopropylbenzamide.

This comparison again emphasizes the added value of isolating and characterizing reactive metallic intermediates, for if normal electrophilic quenching protocols were followed, this distinction in chemical architecture (which has uncovered a stoichiometric preference for employing the lithium base over the sodium base) would be otherwise lost.

When separated from an alkali-metal copartner, $t\mathrm{Bu}_2\mathrm{Zn}$ is incapable of directly zincating tertiary aromatic amides; hence, these DoZ applications clearly fall within the category of synergic (AMMZ) reactions.

Structural and mechanistic information have also been collected from an investigation of the use of AMMZ to

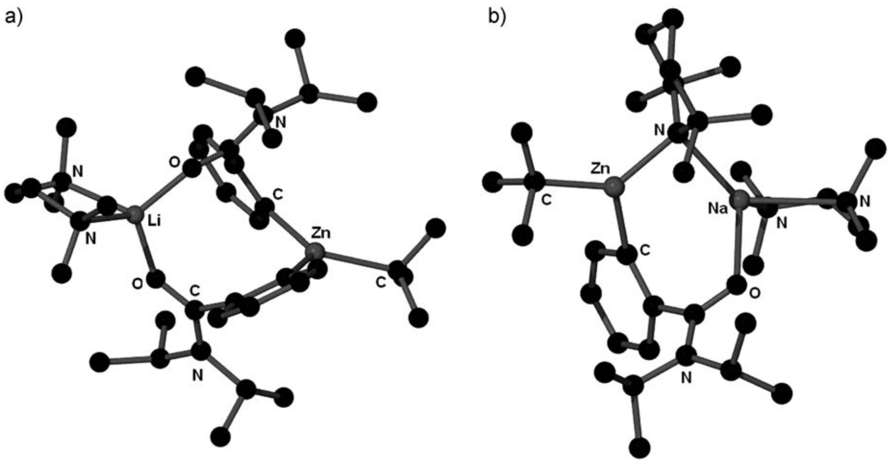
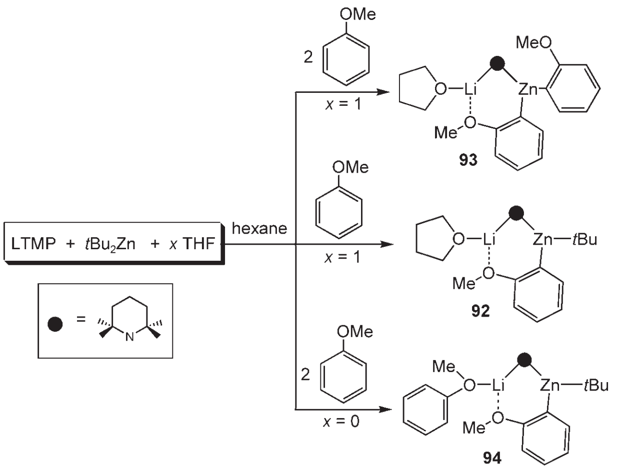


Figure 10. Molecular structures of **89** (a) and **90** (b).

perform DoZ on the aromatic ether anisole.[95] Employing the structurally defined lithium TMP–zincate [(thf)Li(μ-tmp)(μ-*t*Bu)Zn(*t*Bu)] (**91**) as the AMMZ reagent, one and 0.5 molar equivalents, respectively, react with anisole to give the mono(*ortho*-deprotonated anisole) complex [(thf)Li(μ-tmp)(μ-*o*-C_6H_4OMe)Zn(*t*Bu)] (**92**) and the bis(*ortho*-deprotonated anisole) complex [(thf)Li(μ-tmp)(μ-*o*-C_6H_4OMe)Zn(*o*-C_6H_4OMe)] (**93**), respectively (Scheme 36).

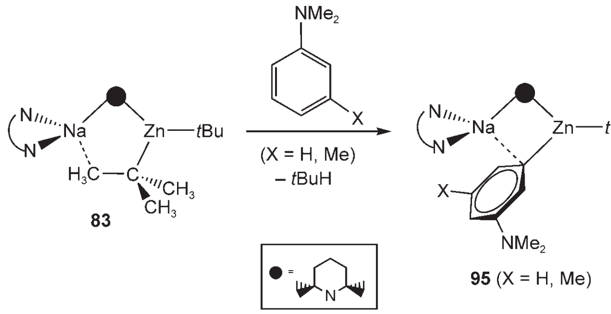


Scheme 36. Stoichiometric reactions of lithium TMP–zincate with anisole.

As the TMP bridge is retained in both products, the zincate **91** functions as a monobasic and dibasic alkyl-transfer reagent, respectively. This is in marked contrast to the reported DoM chemistry of in situ prepared **91** with a variety of aromatic and heteroaromatic substrates (see Section 2.2.), whereby it functions exclusively as an amido (TMP) base. Exemplifying the tunable nature of the lithium TMP–zincate reagent, this change in ligand-transfer selectivity appears to be triggered by the bulk solvent selection (hexane in the former cases, THF in latter).

Interestingly, when a THF-free hexane solution of LTMP and *t*Bu_2Zn is treated with one or two equivalents of anisole (Scheme 36), the isolable product is [{Ph(Me)O}Li(μ-tmp)(μ-*o*-C_6H_4OMe)Zn(*t*Bu)] (**94**), which contains one *ortho*-deprotonated and one neutral (Lewis basic) anisole ligand. The formation of **94** with its 2:1 stoichiometry of “anisole” and “base” from a 1:1 reaction mixture hints that the rate of anisole metalation is faster than the rate of formation of the mixed-metal reagent, presumably in the absence of THF “[(anisole)Li(μ-tmp)(μ-*t*Bu)Zn(*t*Bu)]”, and that this intermediate, once formed, reacts with noncoordinated anisole to generate **94**.

Within the context of *directed* metalation, however, the most eye-catching AMMZ results thus far have come in the area of aniline metalation.[96] Carrying a weak *ortho*-directing dialkylamino substituent, *N*,*N*-dimethylaniline undergoes *ortho* metalation with PhLi in poor yield,[97] and BuLi in good yield.[98] However, changing the metalation agent from these conventional organolithium compounds to the sodium TMP–zincate **83** remarkably diverts the orientation of the deprotonation to the *meta* position, as manifested in the crystalline complex [(tmeda)Na(μ-Ar*)(μ-tmp)Zn(*t*Bu)] (**95**; Ar* = 3-$C_6H_4NMe_2$). The same *meta* regioselectivity is observed upon subjecting 3-methyl-*N*,*N*-dimethylaniline to **83** (Scheme 37). Direct zincation of a tertiary aniline is not possible at any ring position when using mainstream alkyl zinc reagents, so the unprecedented carbon–hydrogen to carbon–zinc transformation taking place in both of these reactions can be attributed to the mixed-metal synergy inherent in AMMZ. In the molecular structure of **95** (Figure 11), the zinc center fills the *meta*-hydrogen void, essentially in the plane of the aryl ring, with sodium weakly bound to this *meta*-C atom lying almost orthogonal to this plane. A {(μ-tmp)Na(tmeda)} unit and a terminal *t*Bu ligand are carried over during these zincation processes, thus indicating that **83** again functions as an alkyl base through loss of *t*BuH.



Scheme 37. *meta* Metalation of *N*,*N*-dimethylanilines with sodium TMP–zincate **83**.

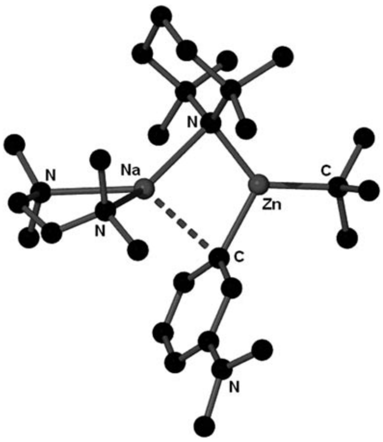


Figure 11. Molecular structure of **95**.

DFT calculations on model regioisomers of **95** with deprotonation of the anilide at the *ortho*, *meta*, *para*, or methyl positions, support the experimental findings that the *meta* isomer is the minimum-energy structure. With the nitrogen lone pair impaired for metal coordination owing to its conjugation with the aromatic π system, the electrostatic Na···(π-Ar*) contacts are implicated as a major factor in the *meta* selectivity.

The final reaction type in this series is alkali-metal-mediated alumination (AMMA). While the structural chemistry of general alkali-metal aluminates has been widely studied over the years,[12] to date there has been only one specific report (in 2006)[99] providing structural insights of alkali-metal TMP–aluminates and the metallic intermediates they form upon deprotonation of an organic substrate. Thus, the sodium TMP–aluminate [(tmeda)Na(μ-tmp)(μ-*i*Bu)Al(*i*Bu)$_2$] (**96**), synthesized straightforwardly by mixing its three constituent parts (NaTMP, *i*Bu$_3$Al, and TMEDA), features a planar, four-element NaCAlN ring with a mixed *i*Bu–TMP bridging ligand set, and its structure is completed by two terminal *i*Bu ligands on the Al center and a tmeda ligand on the Na atom (Figure 12).

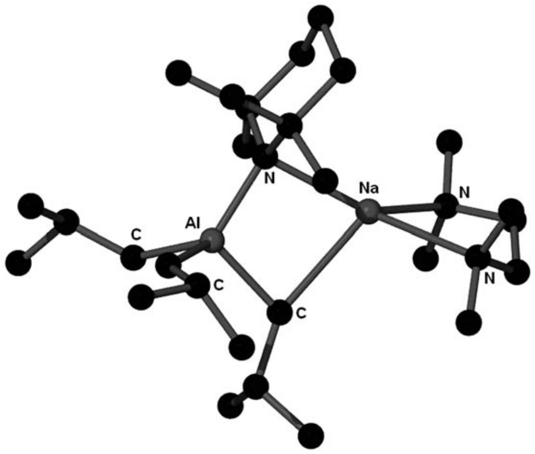
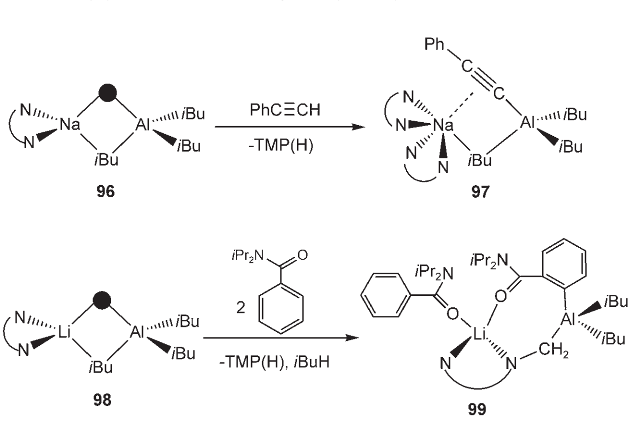


Figure 12. Molecular structure of **96**.

Disregarding the valency distinction between Al and Zn which necessitates an additional anionic ligand (here a terminal *i*Bu group) on the Al center, the structure of **96** bears a close resemblance to the TMP–zincate **83**. However, the similarity does not seemingly carry over to their metalation chemistry, for while **83** usually functions as an alkyl base in bulk hexane solution, **96** reacts with phenylacetylene in the same solvent to generate crystalline [(tmeda)$_2$Na(μ-*i*Bu)(μ-C≡CPh)Al(*i*Bu)$_2$] (**97**) with elimination of TMPH, not *i*BuH (Scheme 38).

The fact that the Na atom in **97** is heavily embraced by donors (by two tmeda ligands) may be a factor in this preferred TMP basicity. A notable feature of the molecular structure of **97** is the contrasting near-linearity of the C≡C-Al bond angle and the near perpendicularity of the C≡C-Na bond angle, which mirrors the situation in the aforementioned magnesiates and zincates: While the divalent metal (Mg or Zn) participates preferentially in σ bonding, the alkali metal participates in cation–π-type bonding.



Scheme 38. Synthesis of the novel aluminate species **97** and **99**.

The same paper reports that the congeneric lithium TMP–aluminate [(tmeda)Li(μ-tmp)(μ-*i*Bu)Al(*i*Bu)$_2$] (**98**), which exists as an oil, exhibits dual alkyl–amido basicity in its reaction with *N*,*N*-diisopropylbenzamide to form the novel heterobimetallic–heterotrianionic complex [{PhC(=O)N*i*Pr$_2$}Li{2-[1-C(=O)N*i*Pr$_2$]C$_6$H$_4$}{Me$_2$NCH$_2$CH$_2$N(Me)-CH$_2$}Al(*i*Bu)$_2$] (**99**; Scheme 38). Determination of the molecular structure of **99** (Figure 13) reveals a complicated combination of an *ortho*-deprotonated benzamide ligand (confirmation of a directed *ortho* alumination), a methyl-deprotonated tmeda ligand, and a neutral benzamide molecule that is ligated through Li–O coordination. From a structural design viewpoint, its salient feature is an irregularly shaped 11-membered (LiNCCNCAlCCCO) ring.

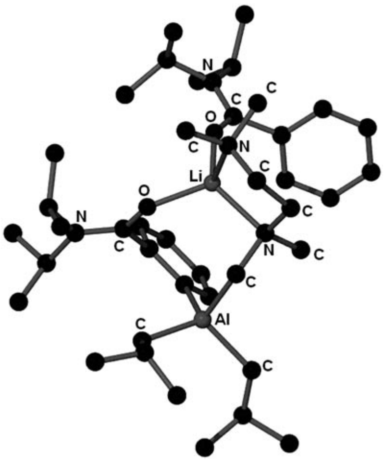


Figure 13. Molecular structure of **99**.

On its own, *i*Bu$_3$Al is too weak of a base to metalate a tertiary aromatic amide or TMEDA, so the two distinct deprotonations of this reaction appear to be synergic in origin, as the coordinated Li atom appears to activate the TMP and *i*Bu bases at the Al center. This work also establishes that normal patterns of reactivity can be reversed by using AMMA, for although *N*,*N*-diisopropylbenzamide is significantly more acidic than TMEDA, TMEDA deprotonation is favored over that of a second benzamide molecule.

4. Summary and Outlook

Alkyl lithium compounds and modifications thereof (for example, TMEDA-activated complexes and *tert*-butoxide-complexed LIC–KOR superbases), and lithium amides, have hitherto been the reagents of choice in synthetic chemistry for performing deprotonative metalations (lithiations). By pulling together many representative recent examples, this Review has demonstrated that new organometallic ate formulations that combine an alkali metal with either magnesium, zinc, or aluminum offer the synthetic chemist an even wider choice of metalating agents. Furthermore, the often milder conditions required for these magnesium–hydrogen, zinc–hydrogen, or aluminum–hydrogen exchange reactions, which makes them more tolerant of a wider range of functional groups and of aromatic heterocycles, has opened up new perspectives in synthetic and structural chemistry. This improvement can be used for the elaboration of complex organic molecules. Commonly these ate reagents exhibit a synergic chemistry which cannot be replicated by the homometallic magnesium, zinc, or aluminum compounds on their own, hence their deprotonation reactions are best regarded as alkali-metal-mediated magnesiations, zincations, or aluminations. Often these reactions are marked by unusual regioselectivities and/or polydeprotonations. The metalated organic substrates, the intermediates formed prior to any electrophilic interception step, often have special structures such as "inverse crown" ring compounds and other types of supramolecular architecture.

Owing to an adjustable metal center (the active metalating source: magnesium, zinc, aluminum), an adjustable alkali metal (the mediator of the metalation reaction), and adjustable ligands (amides, alkyls, etc.) as well as adjustable coligands (tmeda, thf, other amines, ethers, etc.), the scope for developing new reagents of this type is potentially enormous, as is the future role of alkali-metal-mediated metalation in synthesis.

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