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ARTICLE

TMP (2,2,6,6-Tetramethylpiperidide)-Aluminate Bases: Lithium-Mediated Almination or Lithiation/Alkylaluminium-Trapping Reagents?

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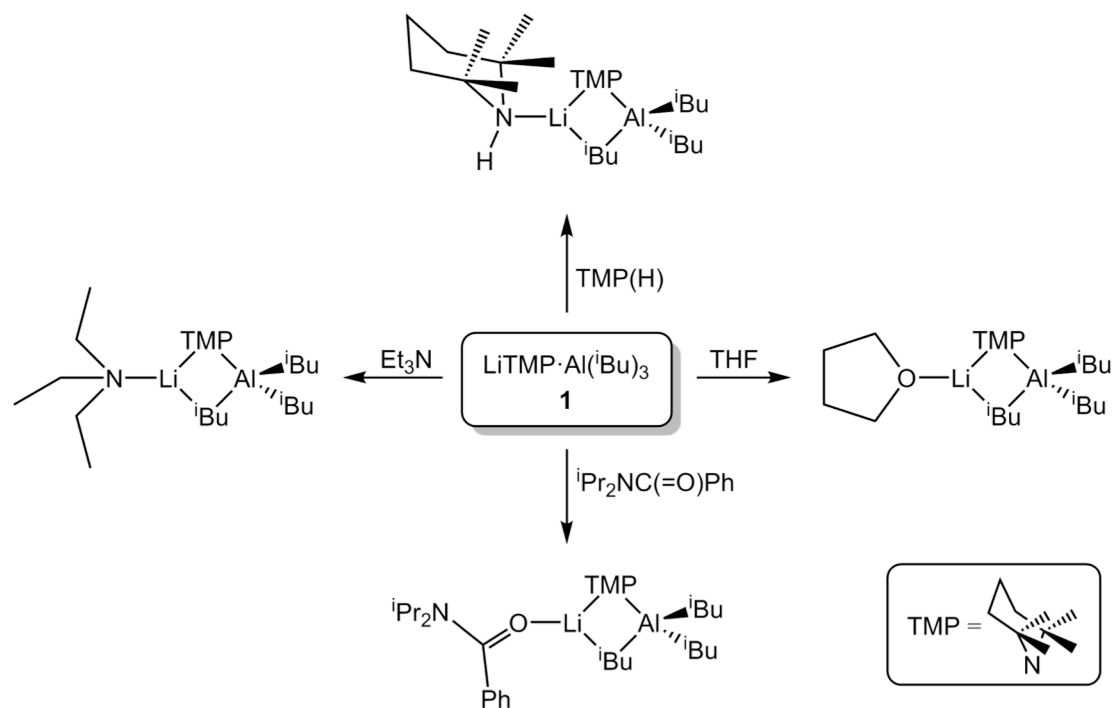
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The lithium TMP-aluminate bases "LiTMP·Al(^tBu)₃" **1** and "LiTMP·Al(TMP)(^tBu)₂" **2**, where TMP is 2,2,6,6-tetramethylpiperidide, have recently come under the spotlight as "alminating" reagents in that they can perform aluminium-hydrogen exchange on a wide variety of aromatic substrates. Previous studies have intimated that **1** existed as a single species in THF solution formulated as [(THF)·Li(μ-TMP)(μ-^tBu)Al(^tBu)₂] **1**·THF, having a contacted ion pair structure as evidenced by an X-ray crystallographic study of isolated crystals. But here using anisole as a case substrate it is revealed that pre-crystallised **1**·THF cannot deprotonate anisole at all whether in hexane or THF solution contradicting earlier *in situ* applications of **1** which revealed near quantitative metallation of anisole. NMR spectroscopic studies of **1** made *in situ* in THF solution ascribe this reactivity distinction from **1**·THF to complex equilibria involving five major species in LiTMP·THF, Al(^tBu)₃·THF, [(Li(THF)₄)⁺{Al(TMP)(^tBu)₃}⁻] **1**·(THF)₄, [(THF)Li(μ-TMP)(μ-OC₆H₇)Al(^tBu)₂], **4**, and (TMP)Al(^tBu)₂·THF. Reagent **2** in contrast is found to exist as only two separated homometallic species in LiTMP·THF and (TMP)Al(^tBu)₂·THF in THF solution. The constitutions of **1** and **2** in non-polar hexane solution are also revealed. With the aid of DFT calculations, discussion focuses on the fact that none of the aluminate species present in THF solutions of **1** or **2** can deprotonate/metallate anisole, instead the metallation processes appear to be LiTMP lithiations followed immediately by trapping by an alkylaluminium complex, in a metal exchange which drives the reaction to the product (arylaluminated) side.

Introduction

The changing landscape of metallation over the past decade or so has seen the growth of a forest of new metallating agents. Now metals such as magnesium, zinc, and aluminium, in particular, and copper and manganese to a lesser extent, stand tall beside lithium as capable of executing metal-hydrogen exchange on a myriad of aromatic and heteroaromatic substrates. Moreover these fundamentally important reactions of this new set of metal reagents can often offer general advantages (most significantly, improved functional group tolerance, milder reaction conditions, greater compatibility with tandem transition metal catalysed bond forming strategies) over those executed by long established lithium alkyl¹ and lithium amide² reagents. Less electropositive than lithium, these other metals form less polar and consequently less reactive organometallic compounds than organolithium reagents so activation is required to adapt them for metallation applications. Two types of activation are common. Stoichiometric lithium

chloride can be added to fashion mixed organometallic-salt systems typified by the turbo-Hauser reagent (TMP)MgCl·LiCl (TMP is 2,2,6,6-tetramethylpiperidide).³ Though salt additive effects have long been recognised, Knochel has masterminded a remarkable row of reagents of this type based upon them.⁴ Activation can also be realised through mixed organometallic-organometallic systems where one metal is an alkali metal and the second is one of the aforementioned nominally less reactive metals.⁵ Amido-alkyl combinations typified by LiTMP·Zn(^tBu)₂⁶ and (TMEDA)Na(ⁿBu)·Mg(TMP)₂⁷ which can also be regarded as ates (zincate and magnesiate respectively) have proved the best metallating agents in this category – note all-alkyl combinations show a greater tendency for nucleophilic addition.⁸ While in metallation reactions the efficiency and scope of these new activated systems have generally been well studied, by comparison definite information on them in their own right has been rather thin on the ground prompting some to be likened to black box reagents.⁹



Scheme 1. Lewis base mediated co-complexation reactions of LiTMP and Al(ⁱBu)₃ in bulk hexane solution.

A particularly attractive branch of this multicomponent ate chemistry is alkali-metal-mediated aluminations (AMMAI) due to the high abundance, comparative cheapness, low toxicity and recycling opportunities of the group 13 metal as well as the documented halogen tolerance of lithium aluminates.¹⁰ It was in the course of comparing the two reagents that dominate AMMAI chemistry, Uchiyama and Wheatley's "LiTMP·Al(ⁱBu)₃" **1**¹¹ and our own bis-TMP version "LiTMP·Al(TMP)(ⁱBu)₂" **2**¹² in reactions with polydentate Lewis bases,¹³ and stimulated further by Knochel's intriguing report of the turbo-Hauser base analogue "TMPMgCl·LiCl·AlEt₃",¹⁴ that we had cause to revisit these key reagents in their own right. Though both have been studied previously the direct comprehensive comparison between them made here through new NMR (including DOSY) spectroscopic studies, reactivity observations and DFT calculations uncovers several remarkable and surprising findings that provide a more complete picture of these complicated multicomponent base mixtures. Specifically doubt is cast on *in situ* **1** being a single species in THF solution and on the existence of **2** as a mixed-metal species either in hexane or THF solution. The most extraordinary revelation from this work is that neither **1** nor **2** appears capable of "aluminating" substrates in THF solution through a lithium aluminate species, so calling into question the term alkali-metal-mediated aluminations (AMMAI) to describe their metallation applications in this medium. Instead evidence points to these being lithiation reactions, the generated carbanions of which are rapidly trapped by alkylaluminium species to form aluminate products.¹⁵

Results and Discussion

Has the active base of **1** been crystallographically characterised?

In the original preparation of **1** reported by Uchiyama in 2004,^{11a} LiTMP prepared *in situ* by the action of *n*-butyllithium on TMP(H) at -78°C was subsequently treated with triisobutylaluminium and the mixture was warmed to 0°C. The bulk solvent employed was THF (in an approximate 25 molar excess on a 2 mmol scale reaction) though the mixture also contained hexane from the lithium and aluminium reagent solutions employed. Evidence that LiTMP and triisobutylaluminium can interact with each other under the mediation of a Lewis base L to forge co-complexes of the type [L·Li(μ-TMP)(μ-ⁱBu)Al(ⁱBu)₂] came from our crystallographic characterisation of three examples where L is *N,N*-diisopropylbenzamide, TMP(H) or triethylamine (Scheme 1).¹⁶ Going one step better, Naka, Uchiyama and Wheatley subsequently crystallographically characterised an aluminate compound containing all the components of the base reaction mixture **1** in the mono-THF complex [(THF)·Li(μ-TMP)(μ-ⁱBu)Al(ⁱBu)₂] **1**·THF (Scheme 1).^{11b} These Lewis base stabilised aluminates have in common contacted ion pair structures where Li and Al connect through ligand bridges. Significantly the crystals of all of these compounds were grown in bulk hydrocarbon solutions. The most experimentally relevant set of **1**·THF were crystallised from a bulk hexane solution containing a stoichiometric deficiency of THF [0.625 mmol per 1 mmol of "LiTMP·Al(ⁱBu)₃"].¹⁷ However the base mixture **1** is prepared and utilised in a vast excess of THF in its

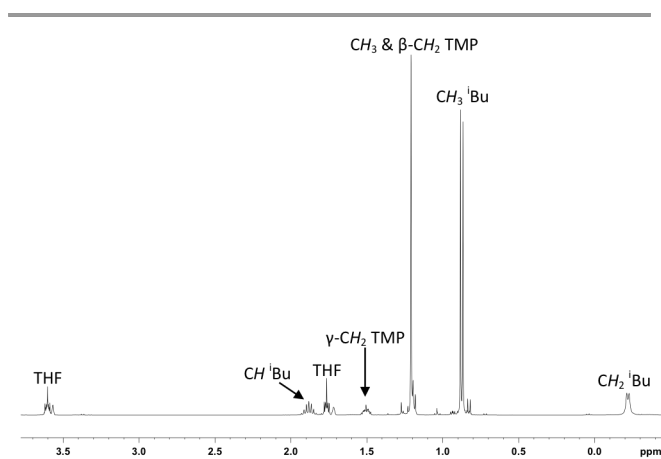


Figure 1. ^1H NMR spectrum of crystalline $\text{THF}\cdot\text{LiTMP}\cdot\text{Al}(\text{iBu})_3$ **1**·**THF** in d_8 -THF solution in which it forms solvent-separated $[\{\text{Li}(\text{THF})_4\}^+\{\text{Al}(\text{TMP})(\text{iBu})_3\}^-]$ **1**·(**THF**)₄.

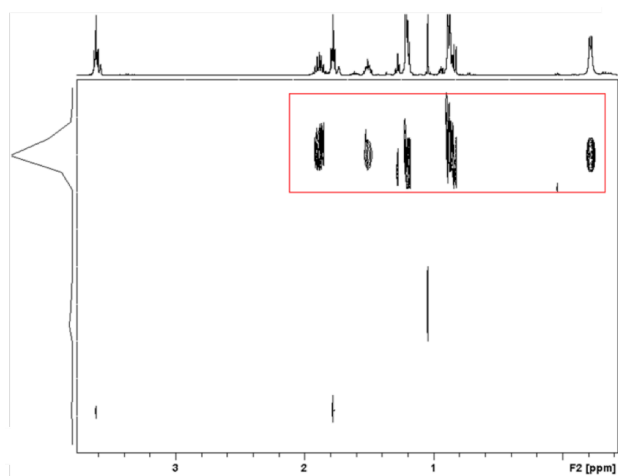
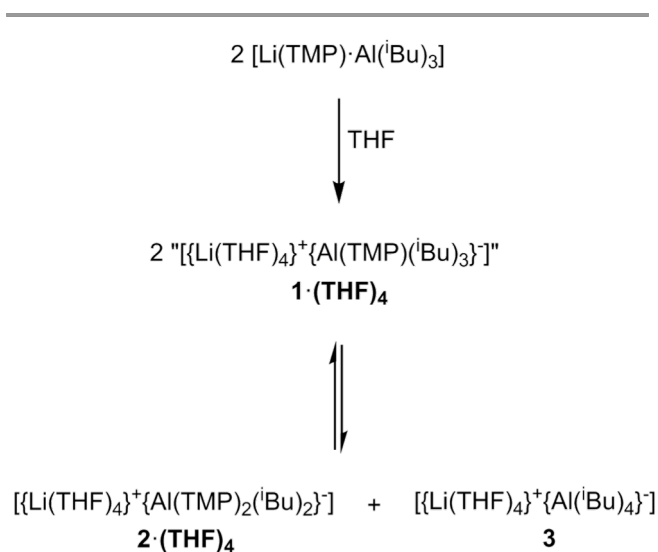


Figure 2. DOSY ^1H NMR spectrum of crystalline $\text{THF}\cdot\text{LiTMP}\cdot\text{Al}(\text{iBu})_3$ **1**·**THF** in d_8 -THF solution. Note that a trace amount of $\text{TMP}(\text{H})$ is evident at 1.04 ppm.

synthetic applications so the question requiring an answer is “does **1**·**THF** represent the experimental base in the THF solution mixture of **1**?”

Towards answering this question in this new study we prepared **1**·**THF** in crystalline form following the aforementioned literature procedure and dissolved it in neat d_8 -THF to replicate the environment it is employed in during successful AMMAI applications. Recording the ^1H NMR spectrum at ambient temperature revealed a simple pattern showing one set of ^1Bu and TMP resonances consistent with a single solution species (Figure 1). Supporting this single species assignment, the ^7Li NMR spectrum shows a sharp single resonance at 1.21 ppm. Re-running the ^1H NMR spectra at elevated temperatures (from 300 to 330 K) did not change this pattern. A DOSY ^1H NMR 18 spectrum (Figure 2) of this d_8 -THF solution of crystalline **1**·**THF** showed that all of the resonances of the aluminate moiety (that is ^1Bu , CH_2 , -0.22 ppm; CH_3 , 0.88 ppm; CH , 1.88 ppm; TMP , CH_3 , 1.21 ppm; $\beta\text{-CH}_2$, 1.20 ppm; $\gamma\text{-CH}_2$, 1.51

ppm) lie along the same line on the y-axis with essentially the same diffusion coefficient ($6.95 \times 10^{-10} \pm 0.09 \times 10^{-10} \text{ m}^2/\text{s}$) implying that the two distinct ligands belong to the same compound/structure. Only the THF resonances (at 1.78 and 3.61 ppm) of the **1**·**THF** formulation lie outside of this line. The obvious explanation is that THF is labile and hence could be undergoing a metal-attached coordinative, metal-free decoordinative equilibrium in d_8 -THF solution. These resonances appear lower down the y-axis as the THF has a smaller molecular weight and thus a higher diffusion coefficient ($2.05 \times 10^{-9} \pm 0.01 \times 10^{-10} \text{ m}^2/\text{s}$) than the “ $\text{LiTMP}\cdot\text{Al}(\text{iBu})_3$ ” portion of crystalline **1**·**THF**. The obvious assignment for this single species in a vast pool of excess THF is the solvent-separated ion pair $[\{\text{Li}(\text{THF})_4\}^+\{\text{Al}(\text{TMP})(\text{iBu})_3\}^-]$ **1**·(**THF**)₄. Supporting this assignment a comparatively broad resonance at 139.8 ppm is found in the ^{27}Al NMR spectrum in d_8 -THF solution consistent with an asymmetrical $[\{\text{Al}(\text{TMP})(\text{iBu})_3\}^-]$ ion and as aforementioned its ^7Li NMR spectrum shows a singlet resonance at 1.21 ppm which coincides exactly with the ^7Li NMR spectrum of the ate compound $[\{\text{Li}(\text{THF})_4\}^+\{\text{Al}(\text{iBu})_4\}^-]$ implying that the separated $\{\text{Li}(\text{THF})_4\}^+$ cation is common to both ates [note though that the chemical shift for the $\{\text{Li}(\text{THF})_4\}^+$ cation is highly sensitive to changes in concentration – see Figure S1(b) in ESI for an example]. It is well known that low local symmetry around Al centres in general,¹⁹ and indeed specifically in TMP attached systems leads to broad signals [in $(\text{TMP})_2\text{AlX}$ systems they can be hundreds or even thousands of Hz broad].²⁰



Scheme 2. The previously postulated dismutation of putative $\text{LiTMP}\cdot\text{Al}(\text{iBu})_3$ **1** in bulk THF solution.

Intriguingly these NMR spectroscopic results from d_8 -THF solutions of crystalline **1**·**THF** are in discordance with our earlier studies of “ $\text{LiTMP}\cdot\text{Al}(\text{iBu})_3$ ” prepared *in situ* in bulk THF solution.²¹ A combination of ^1H , ^7Li and ^{13}C NMR data pointed strongly to the existence of a dismutation process (Scheme 2) in contrast to the single species implicated in the

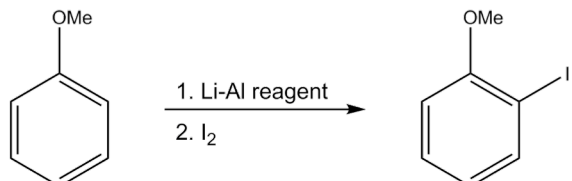
d_8 -THF solution of crystalline **1**·THF. The key piece of evidence towards this dismutation was the characterisation of the tetraalkylaluminumate $[\{Li(THF)_4\}^+\{Al(iBu)_4\}^-]$, **3** a solvent-separated ion pair structure though this was the only species unequivocally identified from the mixture. Arrived at by simply balancing the stoichiometry of the equilibrium reaction, the putative co-product “ $[\{Li(THF)_4\}^+\{Al(TMP)_2(iBu)_2\}^-]$ ”, **2**·(THF)₄ inspired us to the idea of employing the bis-TMP species “LiTMP·Al(TMP)(iBu)₂”, **2** in AMMAI reactions (see later). Knochel's subsequent discovery that a closely related equilibrium may be operating in THF solution mixtures of TMPMgCl·LiCl and Al(Et)₃ leading to the tetraalkylaluminumate “MgCl·Al(Et)₄” (characterised in part by a sharp resonance at 159 ppm in ²⁷Al NMR spectra) and the alkylaluminium amide (TMP)Al(Et)₂·THF¹⁴ motivated us to revisit in greater detail the comparison between the THF solutions of crystalline **1**·THF and its *in situ* form **1**. Our findings detailed below were unexpected.

Comparative reactivity studies of *in situ* **1** and crystalline **1**·THF with anisole

A pivotal molecule in the development of directed *ortho* metallation (DoM) chemistry²² in the classical studies of Wittig²³ and Gilman,²⁴ anisole is a benchmark substrate for measuring the performance of metallating agents. Hence there are numerous reports of the *ortho* metallation of anisole by different metallating reagents. Lithium mono-TMP aluminumate **1** is included in this number as in fact anisole was utilised as the model substrate by Uchiyama when this reagent was first introduced.^{11a} This original study found that a THF solution of *in situ* **1** gave a 99% yield of *o*-iodoanisole following quenching of the metallated intermediate with iodine (Table 1: this table gives the yields of the reactions of anisole with various Li-Al and Al reagents mentioned in this paper). This “AMMAI” was carried out at room temperature for three hours and most significantly the base:anisole stoichiometry employed to achieve this yield was 2.2:1.0 molar equivalents, that is the base was in a slightly greater than twofold excess. Hence this implies that at least 50% of the base **1** is inactive towards anisole under the conditions studied. For comparison in this

work we repeated this original reaction but this time using a 1:1, base:anisole stoichiometry in bulk THF solution. That *in situ* **1** could deprotonate anisole effectively was confirmed by this repeat reaction though significantly the yield of deprotonated anisole observed in a ¹H NMR spectrum of a d_6 -benzene solution of the reaction mixture only approached 50% conversion of anisole starting material. This loss of about 50% of base activity is explicable if the dismutation equilibrium in Scheme 2 lies to the right hand side and if one of the two components, the tetrabutyl aluminumate **3** was inactive towards anisole. Previously we had reported that **3** failed to react with *N,N*-diisopropylbenzamide²¹ which carries a much stronger *ortho*-deprotonating directing group than the methoxy substituent of anisole so it was anticipated that **3** would be inert towards anisole in bulk THF solution and a control reaction between them confirmed this view. Moreover we found that **3** even failed to deprotonate the acidic *N-H* bond of TMP(H), the co-product obtained when the TMP anion functions as a base. Further proof that tetrabutylaluminumate **3** is a major component of *in situ* **1** came from the observation of a sharp resonance at 152.5 ppm in its ²⁷Al NMR spectrum in d_8 -THF solution that matches that of an authentic sample of **3**. The sharpness of this resonance is consistent with the high degree of symmetry in the tetrahedral Al centre in **3**. This sharp resonance (reported at 153.4 ppm)²⁵ appears to have been wrongly assigned as belonging to putative contacted ion-pair “LiTMP·Al(iBu)₃” **1** in an earlier paper.^{11b} A highly asymmetrical $[Al(TMP)(iBu)_3]^-$ centre would give rise to a broader resonance which as mentioned earlier appears in our spectrum at 139.8 ppm. Note as mentioned above that a similar ²⁷Al chemical shift is found in the related highly symmetrical tetraethylaluminumate “ $[(MgCl)^+(AlEt_4)]^-$ ” (at 159 ppm) as reported by Knochel.¹⁴ Interestingly when we repeated the original reaction carried out by Uchiyama using a 2.2:1.0 stoichiometric ratio of *in situ* **1** to anisole in THF solution and recorded the NMR spectrum of the metallated intermediate in d_8 -THF solvent we see lithiated anisole (confirmed by comparison to a spectrum of an authentic sample) as well as aluminated anisole through diagnostic doublet of doublet resonances for the anisole *meta* C-*H* adjacent to the *ortho* site of metallation at 7.65 and 7.48 ppm

Table 1. Comparative reactivities of various Li-Al or Al reagents towards anisole.



Metal reagent	Solvent	Yield (%)
LiTMP·Al(iBu) ₃ (1) (<i>in situ</i> 2.2 equiv)	THF	99
LiTMP·Al(iBu) ₃ (1) (<i>in situ</i> 1 equiv)	THF	50
(THF)LiTMP·Al(iBu) ₃ (1 ·THF) (crystals)	THF or hexane	0
(THF)LiTMP·Al(iBu) ₃ (1 ·THF) (<i>in situ</i> 1 equiv)	hexane	0
(THF)LiTMP·Al(TMP)(iBu) ₂ (2 ·THF) (<i>in situ</i> 1 equiv)	hexane	77
$[\{Li(THF)_4\}^+\{Al(iBu)_4\}^-]$ (3)	THF	0
Al(iBu) ₃	THF	0

respectively in an appropriate 1:4 ratio (Figure 3). This provided the first strong hint that the reactions of *in situ* **1** are not merely, if at all, aluminium-hydrogen exchange reactions.

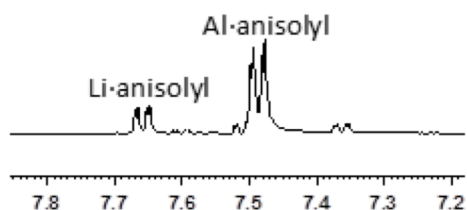


Figure 3. Part of the aryl region of the ^1H NMR spectrum of the reaction of *in situ* $\text{LiTMP}\cdot\text{Al}(\text{iBu})_3$ **1** with anisole in d_8 -THF solution showing both lithiated anisole and aluminated anisole.

Surprisingly, contrasting with the previous straightforward metallation of anisole using *in situ* prepared **1**, on dissolving crystalline $\mathbf{1}\cdot\text{THF}$ in THF solution mixed with anisole and stirring the mixture for several hours to replicate the reaction with *in situ* **1** no reaction was observed to take place (Table 1) as determined from the recovered anisole seen in NMR spectra. The implication of this finding is that once the aluminate structure of $\mathbf{1}\cdot\text{THF}$, presumably as $[\{\text{Li}(\text{THF})_4\}^+\{\text{Al}(\text{TMP})(\text{iBu})_3\}^-]$, $\mathbf{1}\cdot(\text{THF})_4$, is formed all deprotonative reactivity of the mixture is lost. To probe this idea further $\mathbf{1}\cdot\text{THF}$ was also prepared *in situ* in hexane solution by combining its component compounds [$\text{Al}(\text{iBu})_3$, LiTMP and THF in a 1:1:1 ratio] but even this mixture proved inert towards anisole. Under these poorly solvating conditions the aluminate

will almost certainly be in its contacted ion pair form $[(\text{THF})\cdot\text{Li}(\mu\text{-TMP})(\mu\text{-iBu})\text{Al}(\text{iBu})_2]$, $\mathbf{1}\cdot\text{THF}$. On the basis of these pieces of evidence we can conclude with some certainty that $\mathbf{1}\cdot\text{THF}$ is not the active experimental base in the solution mixture **1**, that crystalline $\mathbf{1}\cdot\text{THF}$ does not undergo a dismutation equilibrium in the THF solution akin to that shown for *in situ* **1** in Scheme 2 but remains as the solvent-separated species $\mathbf{1}\cdot(\text{THF})_4$, and in answer to the question posed the actual active base of **1** has therefore seemingly not been crystallographically characterised or more accurately $[(\text{THF})\cdot\text{Li}(\mu\text{-TMP})(\mu\text{-iBu})\text{Al}(\text{iBu})_2]$ $\mathbf{1}\cdot\text{THF}$ is not the active base (but see qualification later).

Towards solving the puzzle of “ $\text{LiTMP}\cdot\text{Al}(\text{TMP})(\text{iBu})_2$ ”

For reasons that will become clear later in the discussion we have been unsuccessful in our several attempts to isolate a solid form let alone a crystalline form of “ $\text{LiTMP}\cdot\text{Al}(\text{TMP})(\text{iBu})_2$ ”, **2**, the putative co-product of the hypothesised dismutation portrayed in Scheme 2. However it was the postulated presence of **2** in a THF solvated form $\mathbf{2}\cdot(\text{THF})_n$ within this equilibrium having the attraction of seemingly possessing extra TMP power (as it is the single TMP ligand in **1** that is its active base component) that encouraged us to make a reagent of this twofold TMP stoichiometry. To begin the study of **2** here, we recorded the ^1H NMR spectra of its individual constituent compounds LiTMP²⁶ and $(\text{TMP})\text{Al}(\text{iBu})_2$,¹² **2** itself, as well as a 1:1 mixture of **2** and THF in d_{14} -hexane solution (Figure 4). Interestingly this comparison revealed that LiTMP and $(\text{TMP})\text{Al}(\text{iBu})_2$ remain separated as homometallic species.

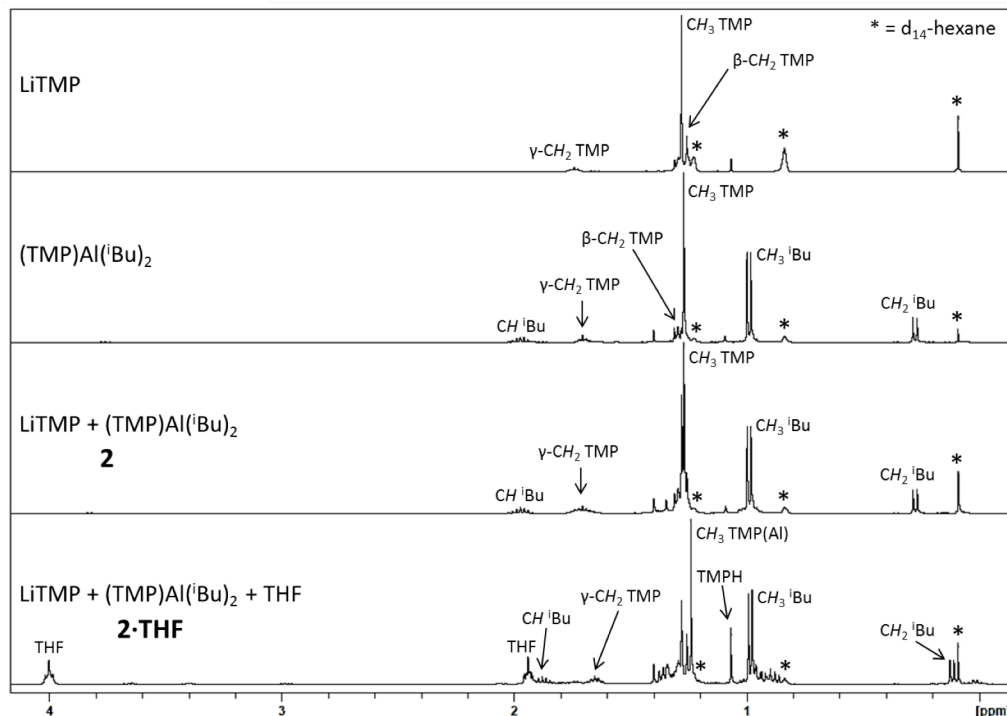
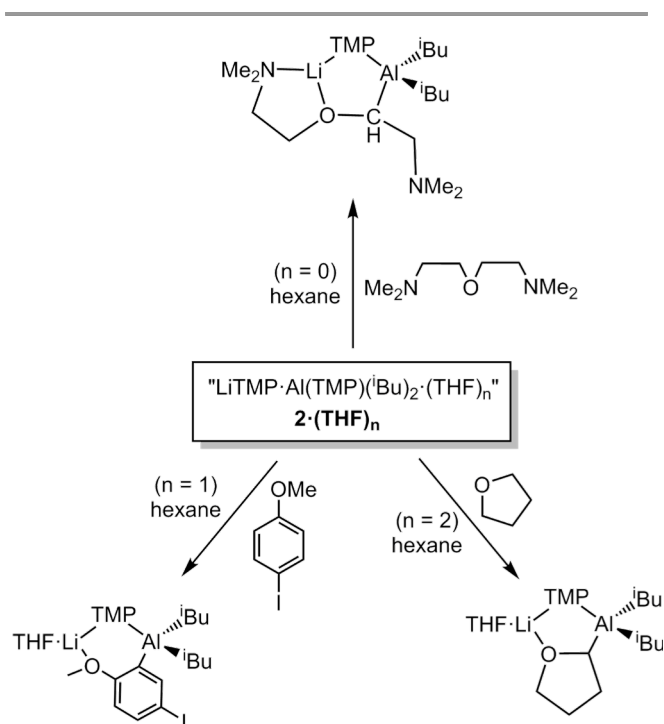


Figure 4. Overlay of ^1H NMR spectra of **2** and its component parts in d_{14} -hexane solution.

When stoichiometric THF is introduced it appears to interact preferentially with the Al reagent to afford $[(\text{TMP})\text{Al}(\text{iBu})_2 \cdot \text{THF}]$ which we have previously characterised²⁷ as the chemical shifts of the ¹Bu resonances move (most diagnostically the CH₂ attached to the metal moves from 0.28 to 0.15 ppm) together with those for the TMP anion; whereas those of LiTMP remain unchanged. While these species appear to stay separated, it should be noted that there is a precedent for donor-free co-complexation in polymeric $[\{\text{Li}(\text{TMP})\text{AlMe}_3\}_\infty]$,²⁸ though significantly this crystalline compound was formed under much harsher reflux conditions in toluene than the room temperature conditions of our NMR comparison coupled with the fact that its alkyl groups are much smaller than those in **2**.

Turning to reactivity issues, earlier studies showed $2 \cdot (\text{THF})_n$ was an effective base as it executed AMMAI on a range of organic substrates (Scheme 3).¹³ Most significantly, $2 \cdot (\text{THF})_1$ was found to metallate THF in bulk hexane solution as evidenced by the slow appearance of resonances attributed to *ortho*-deprotonated THF (*o*-OC₄H₇⁻), while addition of a second THF molecule led to the formation of $[(\text{THF}) \cdot \text{Li}(\mu\text{-TMP})(\mu\text{-OC}_4\text{H}_7)\text{Al}(\text{iBu})_2]$, **4**, which was crystallographically authenticated (See ESI, Figure S9).²⁹ Anisole was similarly *ortho*-aluminated by $2 \cdot (\text{THF})_1$ to generate crystalline $[(\text{THF}) \cdot \text{Li}(\mu\text{-TMP})(\mu\text{-C}_6\text{H}_4\text{OMe})\text{Al}(\text{iBu})_2]$, **5**, which in turn could be intercepted by the electrophile iodine to produce *o*-iodoanisole in a 77% yield (Table 1).¹² As mentioned previously this behaviour contrasts with that of *in situ* **1**·THF, which fails to metallate anisole at all in hexane solution under the conditions studied.

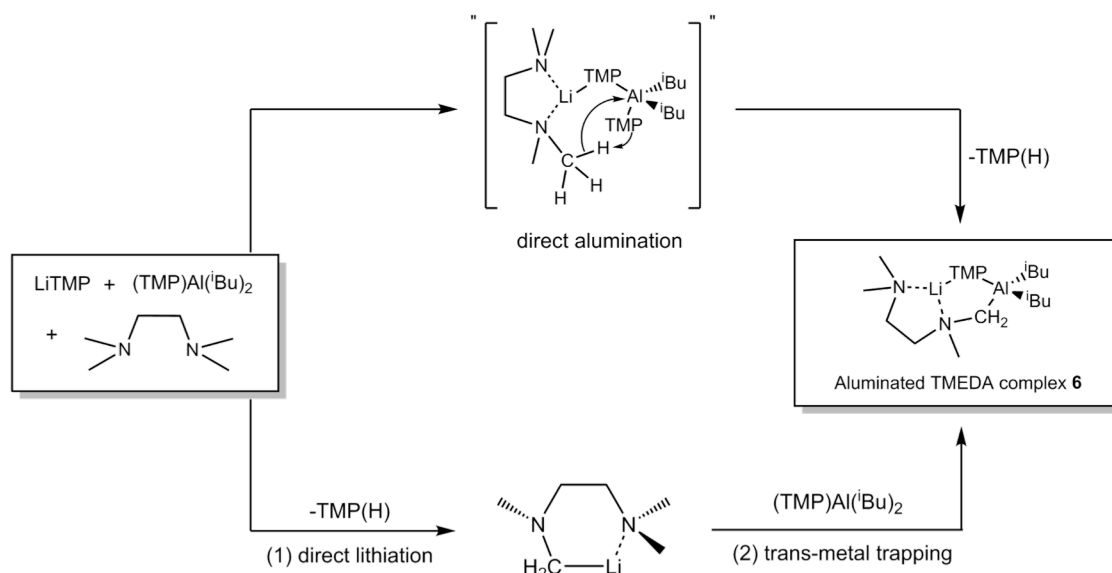


Scheme 3. Selection of deprotonation reactions executed by bis-TMP reagent $2 \cdot (\text{THF})_n$.

Since the diamine TMEDA (*N,N,N',N'*-tetramethylethylenediamine), the methyl groups of which are only weakly acidic, could also be “aluminated” at one of these terminal methyl sites by *in situ* **2** in hexane solution we originally proposed an intramolecular mechanism through a contacted but open structure as depicted in Scheme 4.³⁰ However DFT calculations performed here (see below) indicate that such a twofold TMP structure would be unstable with the Al bound TMP ligand under geometry optimisation moving across to the Li centre in a non-solvated $(\text{TMP})\text{Li}(\mu\text{-TMP})\text{Al}(\text{iBu})_2$ structure which breaks apart to the homometallic components THF·LiTMP³¹ and $(\text{TMP})\text{Al}(\text{iBu})_2$ on addition of a single THF ligand. It is therefore envisioned that LiTMP does the metallation (lithiation) of TMEDA to give $\text{Li}[\text{CH}_2\text{N}(\text{Me})\text{CH}_2\text{CH}_2\text{NMe}_2]$, the reduced steric profile of which compared to that of LiTMP allows its trapping via co-complexation (trans-metal-trapping is probably more apt here, see later) with carbophilic $(\text{TMP})\text{Al}(\text{iBu})_2$ to generate the observed heterobimetallic product $\text{Li}[\text{CH}_2\text{N}(\text{Me})\text{CH}_2\text{CH}_2\text{NMe}_2](\text{TMP})\text{Al}(\text{iBu})_2$ (**6**) (Scheme 4).

If the trans-metal-trapping by the aluminium reagent is not 100% efficient then lithiated substrates could persist, which might explain the presence of lithiated anisole as well as aluminated anisole in the aforementioned reaction with *in situ* **1** and anisole (this inefficient trapping was proven directly by mixing lithiated anisole and the salt $[\{\text{Li}(\text{THF})_4\}^+ \{\text{Al}(\text{iBu})_4\}^-]$, **3**, in d₈-THF solution and recording the ¹H NMR spectrum which revealed no reaction had taken place – in contrast to the neutral species $(\text{TMP})\text{Al}(\text{iBu})_2$ which proved an excellent trapping reagent for the lithiated anisole, as detailed below). Applying this same train of thought to the failure of **1**·THF to likewise metallate anisole in hexane solution can be attributed to the lack of available LiTMP in the reaction mixture as it would be locked within a closed contacted structure with a strong $\text{Li}(\mu\text{-TMP})(\mu\text{-iBu})\text{Al}$ bridge less sterically congested than an unstable $\text{Li}(\mu\text{-TMP})_2\text{Al}$ bridge. Interestingly our initial empirical reasoning that installing two TMP ligands within $2 \cdot \text{THF}$ would boost reactivity levels compared to that of the mono-TMP base **1**·THF appears correct but for the wrong reason: in no example yet has $2 \cdot \text{THF}$ functioned as a di-TMP reacting species, instead it appears to be the “free” LiTMP present in the hexane solution mixture that boosts its reactivity compared to that of **1**·THF. Unlike other bimetallic reagents which can show unusual regioselective orientations, the regioselectivities observed here for $2 \cdot \text{THF}$ are the same as those found for LiTMP (but in improved yields through the subsequent generation of Al-C bonds which lead to greater stability).

Until the present study no comparable reactivity study of **2** had been carried out in bulk THF solution. Therefore we dissolved the components of **2**, LiTMP and $(\text{TMP})\text{Al}(\text{iBu})_2$ in THF solution at room temperature and added one molar equivalent of anisole then stirred the mixture for several hours. A ¹H NMR spectrum of the reaction mixture in d₆-benzene solution confirmed that **2**, as anticipated, also deprotonates anisole in this bulk polar medium.



Scheme 4. Previously hypothesised open ring structure pathway for intramolecular AMMAI reaction of TMEDA (top) and new proposed two-step mechanism for formation of “aluminated” TMEDA complex $\text{Li}[\text{CH}_2\text{N}(\text{Me})\text{CH}_2\text{CH}_2\text{NMe}_2](\text{TMP})\text{Al}(\text{iBu})_2$ (**6**) (bottom).

What about the reactivity of **2** in bulk THF solution in the absence of anisole? As mentioned above, previously we established that **2** readily deprotonates a stoichiometric quantity of THF in bulk hexane solution to afford the crystalline THF anion ($\text{C}_4\text{H}_7\text{O}^-$) contact ion pair complex **4** in a novel example of “cleave and capture chemistry”.³² Here in this work we allowed **2** on its own to be stirred in THF solution for 24 hours at room temperature before recording a ^1H NMR spectrum of the resulting mixture in d_8 -THF solution. Resonances characteristic of the deprotonated but intact THF ring were observed (e.g., at 2.90, 3.42 and 3.74 ppm, see Figure S14 in ESI) consistent with **4**, but significantly these were only visible on magnifying the spectrum. A substantially larger resonance was seen for $\text{TMP}(\text{H})$ at 1.06 ppm, much greater in relative integration terms than could be accounted for by the TMP^- consumed in generating the trace amount of **4** witnessed in the spectrum. While hydrolysis can never be ruled out completely as a contributing factor (though we scrupulously dried the THF solvent before employing it in the reaction), it seems more likely that the generated THF anion ($\text{C}_4\text{H}_7\text{O}^-$) is unstable in the bulk polar medium. It could exist initially either as the lithium derivative $[(\text{THF})_x(\text{LiOC}_4\text{H}_7)_n]$ or the solvent-separated aluminate $[\{\text{Li}(\text{THF})_4\}^+\{\text{TMP}(\text{OC}_4\text{H}_7)\text{Al}(\text{iBu})_2\}^-]$ (contrast this with the bimetallic-stabilised contacted ion pair form **4** found in hexane solution)²⁹ but would then decompose presumably via a [3+2] cycloreversion to the enolate of acetaldehyde and ethene.³³ To investigate what effect this formation and break down of **4** would exert on the Brønsted basic properties of **2** we stirred a THF solution of **2** for 24 hours before introducing anisole as the metallation probe. As expected no metallation of anisole took place as a ^1H NMR spectrum of the reaction mixture revealed free anisole as well as THF anions and a substantial amount of $\text{TMP}(\text{H})$. From these observations we conclude that if left to stir for a period of

time in THF solution, **2** will deprotonate THF releasing $\text{TMP}(\text{H})$ and be consumed. To check whether all base activity is lost under such circumstances, we crystallised **4** from hexane solution, isolated it and dissolved it in bulk THF solution. Anisole was added subsequently and the solution was stirred for 24 hours. NMR analysis of the resulting mixture revealed that again no metallation of anisole had occurred confirming that aluminate **4**, probably present in the modified solvent-separated form $[\{\text{Li}(\text{THF})_4\}^+\{\text{TMP}(\text{OC}_4\text{H}_7)\text{Al}(\text{iBu})_2\}^-]$ is inactive as a base even though it contains a TMP^- ligand. Curious about the constitution of **2** in THF solution we compared its ^1H NMR spectrum with those of its constituent parts LiTMP and $(\text{TMP})\text{Al}(\text{iBu})_2$ (see composite spectra in Figure 5). Close examination of these spectra show that the principal resonances of LiTMP (Me of TMP at 1.07 ppm) and $(\text{TMP})\text{Al}(\text{iBu})_2$ (Me of TMP at 1.21 ppm; CH_2 of iBu at 0.03 ppm) match almost exactly with corresponding resonances in **2** (1.04, 1.21 and 0.03 ppm, respectively) though it is noticeable that the resonances associated with LiTMP are extremely sensitive to even small changes in concentration. Therefore it appears certain that under the conditions studied [longer periods of time lead to the deprotonation/decomposition of THF] LiTMP and $(\text{TMP})\text{Al}(\text{iBu})_2$ exist as separate species each solvated by THF. This viewpoint is supported by a DOSY spectrum, which shows a significant difference in the diffusion

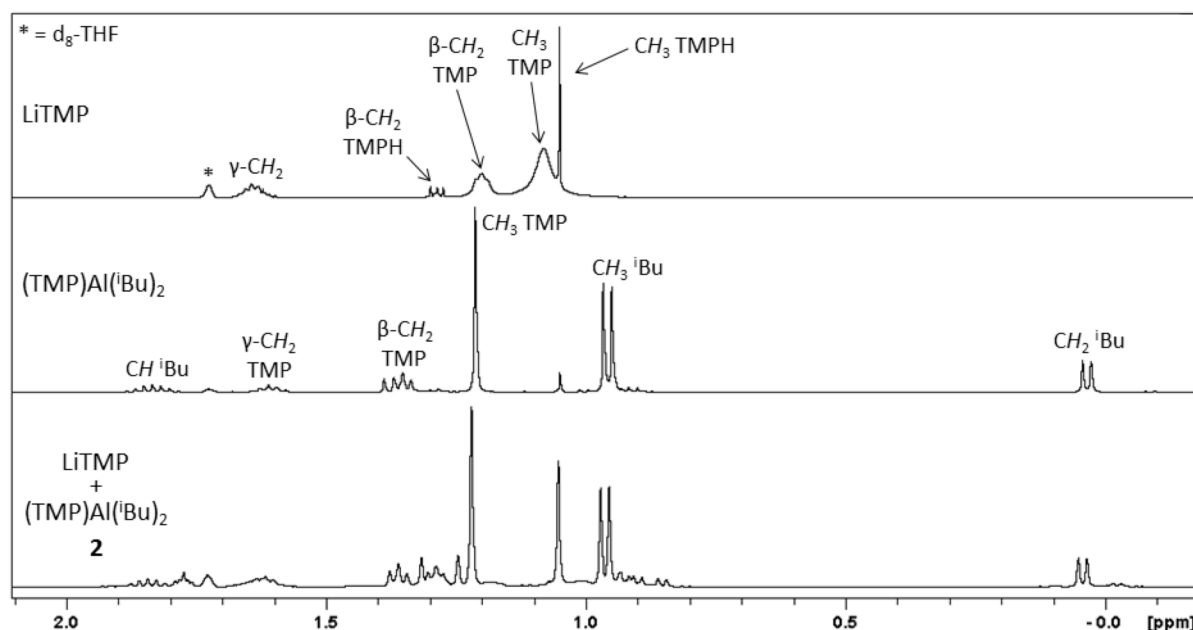


Figure 5. Overlay of ^1H NMR spectra of **2** and its component parts in d_8 -THF solution.

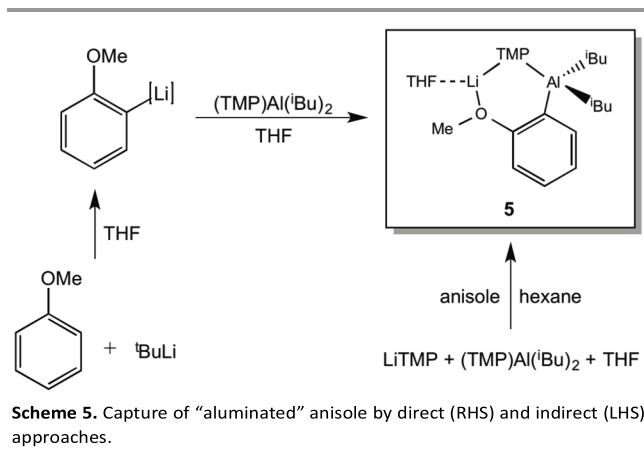
coefficients for each compound [$\text{LiTMP} = 1.22 \times 10^{-9} \text{ m}^2/\text{s}$; $(\text{TMP})\text{Al}(\text{iBu})_2 = 8.37 \times 10^{-10} \text{ m}^2/\text{s}$]. Thus clearly whether in hexane or THF solution there is no interaction between LiTMP and $(\text{TMP})\text{Al}(\text{iBu})_2$ due to a formidable steric barrier, but once LiTMP metallates a substrate (e.g., THF or anisole) the new lithiated substrate species being of reduced steric profile and greater nucleophilicity through Li-C bond formation can join together (be trapped) with the neutral aluminium complex. Evidence that such fragments can join together comes from the previously reported crystal structures of $[(\text{THF})\cdot\text{Li}(\mu\text{-TMP})(\mu\text{-OC}_4\text{H}_7)\text{Al}(\text{iBu})_2]$, **4**,²⁹ and $[(\text{THF})\cdot\text{Li}(\mu\text{-TMP})(o\text{-C}_6\text{H}_4\text{OMe})\text{Al}(\text{iBu})_2]$, **5**,¹² respectively (see also the DFT study detailed below).

Taking stock of these findings the picture of **2** in bulk THF solution emerging now is that only LiTMP (solvated by THF), $(\text{TMP})\text{Al}(\text{iBu})_2$ (solvated by THF), and depending on the age and history of the solution variable amounts of the THF degradation products **4** (presumably in its THF-separated form $[\{\text{Li}(\text{THF})_4\}^+\{(\text{OC}_4\text{H}_7)(\text{TMP})\text{Al}(\text{iBu})_2\}^-]$), $[(\text{THF})_x(\text{LiOC}_4\text{H}_7)_n]$, $[(\text{THF})_n\text{LiO-C}=\text{CH}_2]$ ³⁴ and ethene are observable by this NMR spectroscopic interrogation. Significantly we can find no evidence for a bimetallic cocomplex “ $\text{LiTMP}\cdot\text{Al}(\text{TMP})(\text{iBu})_2$ ” **2** which falls into line with our DFT computational analysis (see below) that questions the thermodynamic feasibility of such a di-TMP contacted or solvent-separated bimetallic structure.

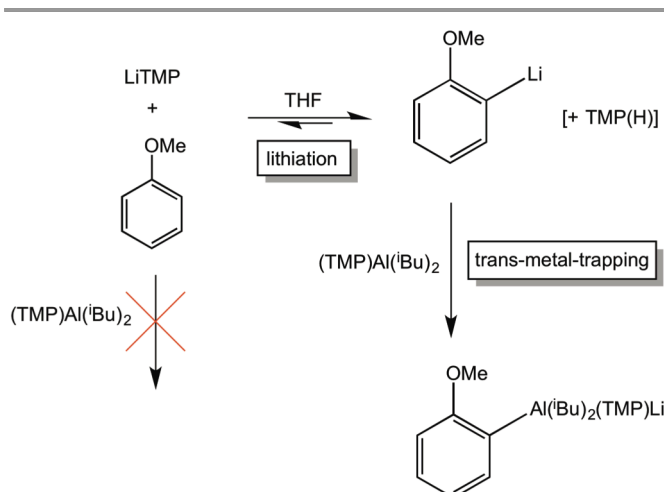
Having tested all of the metal species within this **2** mixture for their metallating ability the only possible candidate to emerge is the aforementioned LiTMP , which in bulk THF solution exists in solvated form as deduced by Renaud and Fox who observed both dimeric and monomeric forms through ^7Li NMR

spectroscopic studies.³⁵ Wheatley *et al* confirmed these assignments in a later paper.^{11b}

To establish whether LiTMP was the active Brønsted base component in **2** we dissolved freshly prepared LiTMP in d_6 -benzene solution in an NMR tube to which a few drops of THF were added. A ^1H NMR spectrum of this mixture was recorded after 30 minutes and again after 24 hours (see Figure S17 in ESI). Ethene was revealed in both spectra through a resonance at 5.25 ppm, which increased with time, consistent with the metallation, ring opening and cleavage of THF. Significantly when **2** is left to stir in bulk THF solution for 24 hours a small amount of aluminate **4** is observed as mentioned previously, the implication being that LiTMP is lithiating THF to generate “ $\text{C}_4\text{H}_7\text{O}^-$ ” anions a small amount of which is trapped by $(\text{TMP})\text{Al}(\text{iBu})_2$ to generate $[(\text{OC}_4\text{H}_7)(\text{TMP})\text{Al}(\text{iBu})_2]^-$ while the remainder decompose to ethene and lithium enolate. We also examined the lithiation of anisole (Scheme 5). Uchiyama, Mongin *et al* previously reported that subjecting anisole to one molar equivalent of LiTMP in THF solution over two hours produced after iodine quenching only 9% of *ortho*-iodoanisole.³⁶ To ascertain how much lithiated anisole was present prior to any quenching step we reacted LiTMP with anisole in the same stoichiometry in THF solution, but found the reaction afforded only about a 5% yield of lithiated anisole. Hence LiTMP can definitely metallate/lithiate anisole, unlike any of the other species identified within the mixture of **2**, albeit in a meagre yield. Since **2** furnishes excellent yields of metallated anisole following iodine quenching the implication is that once formed any lithiated anisole will be quickly trapped by the strongly carbophilic $(\text{TMP})\text{Al}(\text{iBu})_2$. This was established unequivocally by taking a 1:1 mixture of lithiated anisole (prepared separately by reaction of anisole and $^t\text{BuLi}$ in



THF at 0°C)³⁷ and (TMP)Al(ⁱBu)₂ in d₈-THF solution in an NMR tube and recording the ¹H and ¹³C spectra (see Figures S11 and S12 in ESI). The most diagnostic resonance in the former, the *meta* C-H adjacent to the metallated C-M, shows a significant upfield shift (from 7.66 to 7.49 ppm) signifying the attached metal M has switched from Li to Al; with a similar shift seen in the ¹³C spectra for the metallated C-M atom from 159.2 to 154.4 ppm [note that Uchiyama reported a similar but not identical upfield Li to Al shift on treating lithiated anisole with ^tBuLi with the C-Al resonance appearing at 152.91 ppm, the main distinction being the trapping Al reagent used was Al(ⁱBu)₃]. From integration ratios this trans-metal trapping of the anisoyl carbanion by (TMP)Al(ⁱBu)₂ seems essentially quantitative. As depicted in Scheme 6, this insertion of the aluminium reagent into the Li-C(anisoyl) bond should drive the equilibrium between anisole and lithiated anisole towards the lithiated species thus increasing the overall metallation yield of the reaction. We established that such an equilibrium exists between lithiated anisole and LiTMP by taking a freshly prepared sample of the former and mixing it with an equimolar amount of TMP(H) in d₆-benzene solution and stirring the solution for 10 minutes. At this point LiTMP was observed via a ¹H NMR spectrum. It is worthy of comment that (TMP)Al(ⁱBu)₂, though not a metallating agent itself, contributes to the success of the metallation reactions of **2** in two key ways: firstly, it traps the lithium carbanion and stabilises the carbanion moiety by reducing the polarity of the metal-carbon bond; secondly, by not engaging at all with LiTMP on the left hand side of the equation (Scheme 6) the equilibrium can shift towards the desired anisoyl aluminium product. This hypothesis of non-cocomplexed LiTMP and (TMP)Al(ⁱBu)₂ homometallic species swimming separately in a pool of THF runs counter to any thinking that a "LiTMP·Al(TMP)(ⁱBu)₂" cocomplex was responsible for these "AMMAI" reactions. Therefore the weight of evidence from this work suggests these reactions are not in fact direct aluminations (aluminium-hydrogen exchanges) at all but rather two step lithiation/trans-metal-trapping processes (trans-metal-trapping seems a more apt description here than the usual applied "transmetallation" for although aluminium is replacing



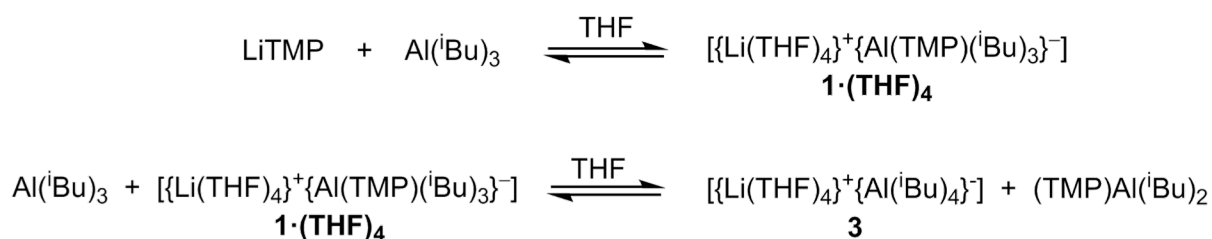
Scheme 6. Proposed two-step pathway for the "aluminum" of anisole.

lithium in binding to the carbanion C atom the lithium may not necessarily leave the aluminium system but could remain part of a contacted ion pair or solvent separated ion pair compound). Similar reactivities to this one have recently been reported for the homoleptic bimetallic mixtures of LiTMP and Zn(TMP)₂³⁸ or Cd(TMP)₂³⁹ as they appear not to be "LiZn(TMP)₃" or "LiCd(TMP)₃" tris-TMP ates, but instead remain separated components in which LiTMP is also the active metallating base.^{9, 40}

Despite this evaluation of the reactions of **2** in bulk THF solutions not being AMMAIs the essential point remains the same that these reactions are still synergistic in origin (for efficiency but not for any special selectivity) for without participation of the aluminium reagent, quenching of the lithiated substrates with electrophiles E⁺ would be unsatisfactory leading to poor yields of the desired E⁺(substrate)⁻ products. This reflects the non-selective nature of iodine quenching as it would quench both lithiated anisole and LiTMP to prevent the equilibrium in Scheme 6 shifting towards lithiated anisole; whereas the aluminium reagent selectively targets lithiated anisole and ignores the bulkier LiTMP.

Re-evaluating the composition and active base component of *in situ* **1** in THF solution.

Now that the picture of **2** in THF solution is much more transparent following these new findings, the composition of **1** in THF solution needs to be re-considered. Taking into account the surprising discovery that LiTMP is the active base component within **2** we can propose a more complete composition for **1** (Scheme 7). Far removed from the original idea that it existed as a single species of formula [(THF)·Li(TMP)(ⁱBu)Al(ⁱBu)₂], in this proposal **1** contains no less than five species in two interconnected equilibria including most significantly the separated monometallic species LiTMP, which we have already established can perform metallation of a substrate. Convincing evidence for the second equilibrium came from mixing authentic samples of the salt [Li(THF)₄]⁺[Al(ⁱBu)₄]⁻, **3**, and (TMP)Al(ⁱBu)₂ in d₈-THF



Scheme 7. Re-evaluated composition of "single-species" THF·Li(TMP)·Al(iBu)₃ showing its existence as two connected equilibria involving five distinct species.

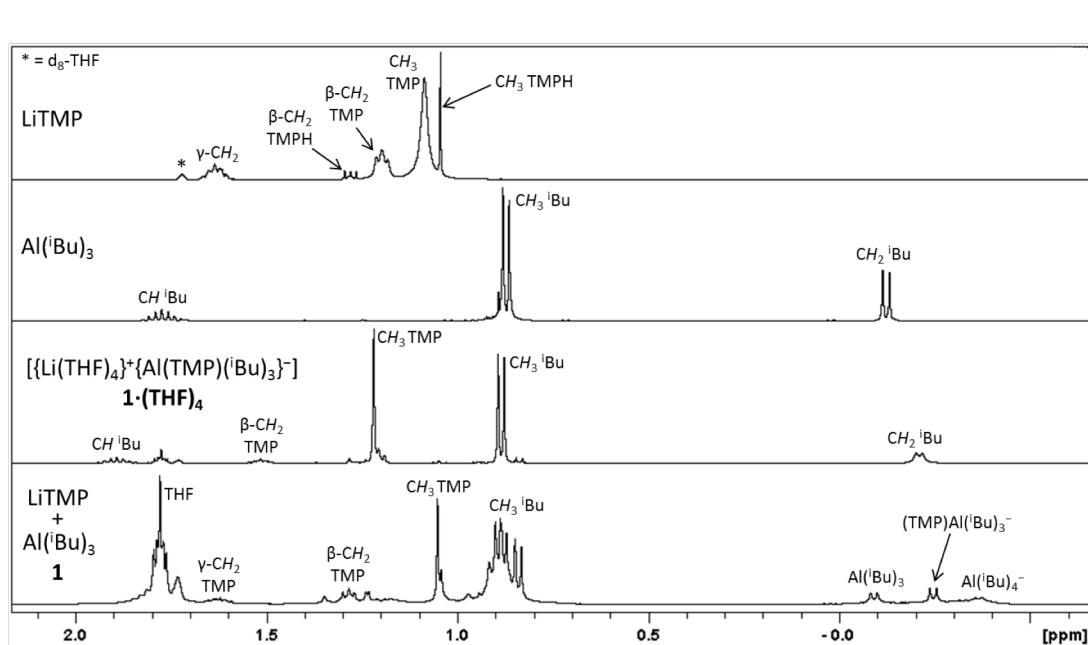


Figure 6. ¹H NMR spectrum of (TMP)Al(iBu)₂ + [Li(THF)₄]⁺[Al(iBu)₄]⁻ **3** in d₈-THF solution.

solution and recording the ¹H NMR spectrum at room temperature (Figure 6). The low frequency region about 0 ppm is extremely informative as each species exhibits a well-defined Al-CH₂(iBu) resonance within it. Four such resonances observed at (0.02, -0.10, -0.22 and -0.37 ppm) can be assigned to (TMP)Al(iBu)₂, Al(iBu)₃, [Li(THF)₄]⁺[Al(TMP)(iBu)₃]⁻ and [Li(THF)₄]⁺[Al(iBu)₄]⁻ respectively. Four CH₃(iBu) resonances were also observed for the four distinct species though the doublet of doublets for Al(iBu)₃ and [Li(THF)₄]⁺[Al(TMP)(iBu)₃]⁻ overlap. All assignments were verified by comparison with the spectra of authentic samples of the individual components. The trialkyl-amido aluminate [Li(THF)₄]⁺[Al(TMP)(iBu)₃]⁻ was prepared by reacting neutral (TMP)Al(iBu)₂ with an equimolar amount of iBuLi in THF solution (Figures S20 and S21 in ESI, note the corresponding resonance for iBuLi comes more upfield at -0.98 ppm) and this aluminate gave an identical spectrum to that of crystalline **1**·THF dissolved in d₈-THF solution, which we discovered was inactive as a base. It is also significant that no LiTMP was found in the spectrum of the [Li(THF)₄]⁺[Al(iBu)₄]⁻, **3**, and (TMP)Al(iBu)₂ mixture as evidenced by the absence of a Me resonance at 1.05 ppm. When

TMP is attached to Al this Me resonance moves downfield to 1.21 ppm in (TMP)Al(iBu)₂ and 1.20 ppm in [Li(THF)₄]⁺[Al(TMP)(iBu)₃]⁻ though these signals cannot be differentiated in the combined spectrum. Since the equilibrium under these ambient temperature conditions greatly favours (TMP)Al(iBu)₂ its Me(TMP) resonance is much larger than that of [Li(THF)₄]⁺[Al(TMP)(iBu)₃]⁻. Measurement of the relative integrals of [Li(THF)₄]⁺[Al(TMP)(iBu)₃]⁻ and Al(iBu)₃ is hampered by the broadness of the Al-CH₂(iBu) resonance of the former species. Note that the corresponding resonance for the homoleptic ate [Li(THF)₄]⁺[Al(iBu)₄]⁻ is similarly broad.²¹ In both cases the broadness can be attributed to the quadrupolar effect of the ²⁷Al centre (spin 5/2). In the symmetrical species [Li(THF)₄]⁺[Al(iBu)₄]⁻ the Al-CH₂(iBu) resonance is a doublet due to coupling with the adjacent CH but this is further split by the Al into a doublet of sextets though as the environment is not perfectly symmetrical some merging of the lines occurs and the resonance observed appears wide and broad (see Figures S24 and S25 in the ESI for decoupling and 2D [¹H,²⁷Al] HSQC and HSQC-TOCSY experiments which support the Al and iBu assignments within **1**·(THF)₄ and **3**). The equilibria are also implicated on mixing

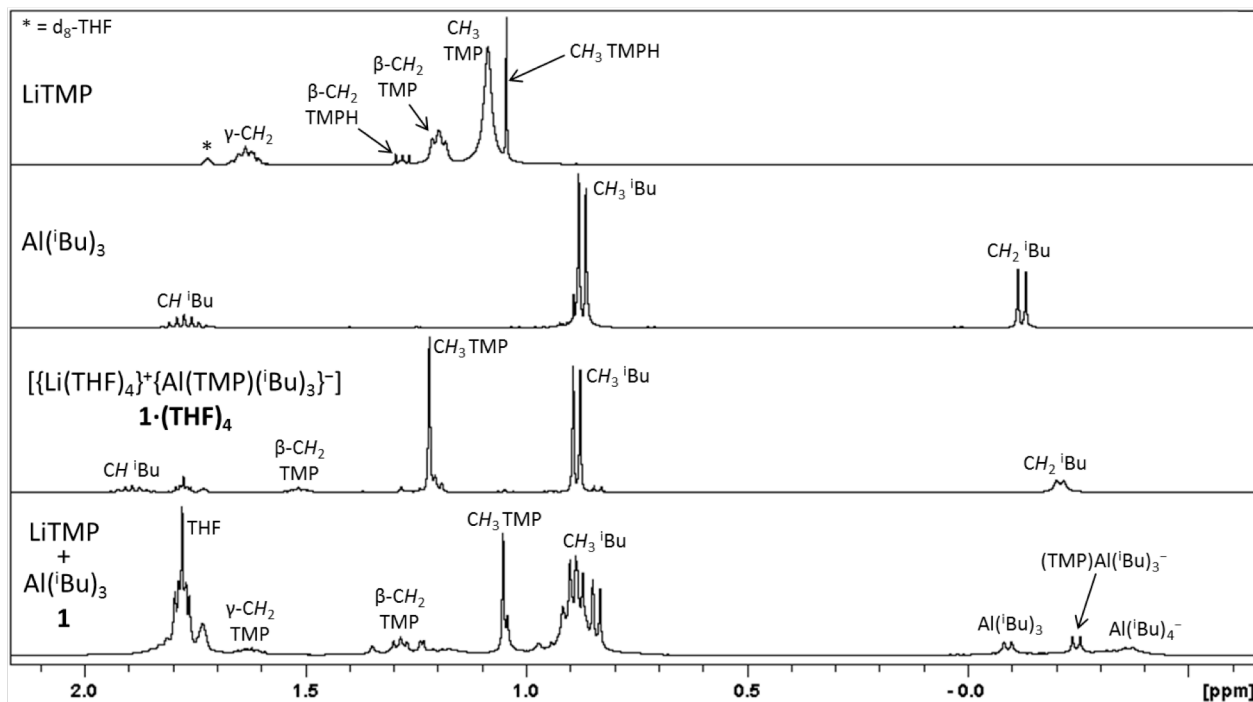


Figure 7. Overlay of ^1H NMR spectra of LiTMP, $\text{Al}(\text{iBu})_3$, $[\{\text{Li}(\text{THF})_4\}^+\{\text{Al}(\text{TMP})(\text{iBu})_3\}^-]$ and $[\text{LiTMP} + \text{Al}(\text{iBu})_3]$ in d_8 -THF solution.

equimolar proportions of LiTMP and $\text{Al}(\text{iBu})_3$ in d_8 -THF solution (see the spectra comparison in Figure 7). On recording this ^1H NMR spectrum at 0°C , the resonances for LiTMP (most diagnostically the Me resonance at 1.05 ppm, though this overlaps with a TMPH resonance the presence of which is unavoidable due to attack of THF by LiTMP) and $\text{Al}(\text{iBu})_3$ (at -0.25 ppm) are the most prominent. A smaller extremely broad resonance for $[\{\text{Li}(\text{THF})_4\}^+\{\text{Al}(\text{iBu})_4\}^-]$ is clearly seen too. The presence of $[\{\text{Li}(\text{THF})_4\}^+\{\text{Al}(\text{iBu})_4\}^-]$ is also clearly distinguishable in the Me region of the ^1Bu group as a doublet at 0.84 ppm, though the analogous doublets for the other ^1Bu containing species overlap into a complex multiplet at about 0.89 ppm consistent with there being multiple species present rather than simply $\text{Al}(\text{iBu})_3$. Due to the fact that we are seeing some metallation in the solution due to the presence of TMPH then it is possible that the amount of $(\text{TMP})\text{Al}(\text{iBu})_2$ in solution is being decreased as this species will trap any carbanion formed upon metallation (see earlier discussion of efficient trapping of anisoly anions by $(\text{TMP})\text{Al}(\text{iBu})_2$). Clearly the $(\text{iBu})\text{Me}$ region at 0.80-0.95 ppm in containing more than the four overlapping species you would expect in the equilibrium proposed supports this suggestion. Other ates of formula $(\text{TMP})\text{Al}(\text{iBu})_2\text{X}$ where X is for example $\text{C}_4\text{H}_7\text{O}^-$ or $\text{C}_2\text{H}_3\text{O}^-$ formula could also be present. To check whether LiTMP was participating in an equilibrium with the salt $[\{\text{Li}(\text{THF})_4\}^+\{\text{Al}(\text{iBu})_4\}^-]$ we added both to a d_8 -THF solution and monitored it by ^1H NMR spectroscopy. The spectra revealed that the resonances associated with the two individual compounds remain unchanged. We thus conclude that these

two species are not in equilibrium with each other. Neither is LiTMP in equilibrium with $(\text{TMP})\text{Al}(\text{iBu})_2$ as we established through the aforementioned studies of $2\cdot\text{THF}$.

Based on these new observations we can find no evidence at all for a species of composition “ $[\{\text{Li}(\text{THF})_n\}^+\{\text{Al}(\text{TMP})_2(\text{iBu})_2\}^-]$ ” that we had originally presumed in the dismutation process shown in Scheme 2. DFT calculations (see below) support the non-existence of such a heteroleptic aluminate species. It transpires that $1\cdot\text{THF}$ is much more complicated existing in at least five distinct species in THF solution. The complexity can be attributed to the lability of $\text{Al}(\text{iBu})_3$ which can add a TMP ligand to generate $[(\text{TMP})\text{Al}(\text{iBu})_3]^-$ and gain or lose an ^1Bu group to form $[\text{Al}(\text{iBu})_4]^-$ or $[\text{Al}(\text{iBu})_2]^+$ containing species; whereas by comparison the solution chemistry of $2\cdot\text{THF}$ is much simpler due to the relative poor lability of $(\text{TMP})\text{Al}(\text{iBu})_2$ and specifically its inability to form a co-complex with LiTMP on steric grounds. Where $1\cdot\text{THF}$ and $2\cdot\text{THF}$ do coincide is in the fact that the active base ingredient in both mixtures in THF solution is LiTMP. Ironically, revisiting the original question, “has the active base of **1** been crystallographically characterised?”, the revised answer is yes, as LiTMP has been crystallographically characterised in two different polymorphic forms²⁶ as well as in a THF-solvated form.³¹ $2\cdot\text{THF}$ is the strongest base because it would always have the largest proportion of LiTMP present in a solution of the same molarity; whereas in $1\cdot\text{THF}$ some LiTMP will always be lost due to the equilibria in operation. This last point is in agreement with the excess of $1\cdot\text{THF}$ (2.2 molar equivalents) used by Uchiyama *et*

al in their synthetic applications to ensure maximum yields of the metallated/quenched substrates were obtained. Moreover **1**·THF is never going to be a good base in hexane solution for if the LiTMP:Al(ⁱBu)₃ ratio in the starting mixture is exactly 1:1 there will be no free LiTMP available to perform the metallation. However, there are at least two qualifications. First, at higher temperatures the contacted ion pair structure of **1**·THF could break up and release LiTMP making metallations of suitably thermally stable substrates a possibility. In contrast free LiTMP is always available in hexane solutions of **2**·THF. Second, Lewis bases can coordinate to the Lewis acidic lithium centre and generate a contacted ion pair aluminate with Al(ⁱBu)₃ that can subsequently metallate a C-H bond in the Lewis base in a genuine example of alkali-metal-mediated alumination. This possibility has already been demonstrated in the formation of [Li{Me₂NCH₂CH₂N(Me)CH₂}₂Al(ⁱBu)₂] (**6**) by reaction of **1** with two equivalents of TMEDA in hexane solution.³⁰

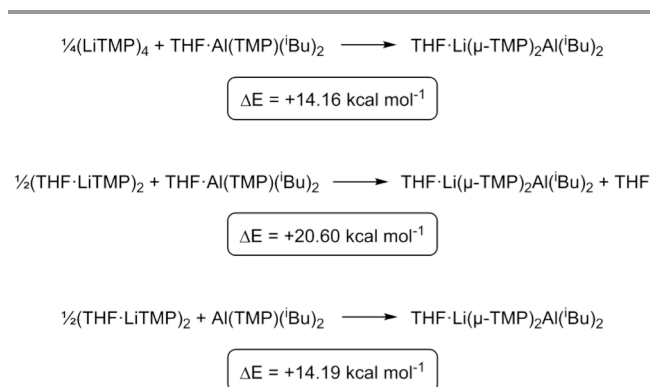
DFT Calculations

Theoretical calculations

The structure of **1** “LiTMP·Al(ⁱBu)₃” was previously interrogated by DFT calculations using the B3LYP/6-31+G* level of theory.^{11b} This comprehensive theoretical study by Naka, Uchiyama, and Wheatley *et al* was performed on [S·LiNMe₂·Al(Me)₃] (where S = the donor solvent Me₂O) for calculational simplicity and its metallation reaction with anisole was modelled. Rigorous in its detail and broad in scope, this study uncovered possible intermediates and transition states along the reaction coordinate as well as quantifying the energy differences involved. However, its starting point of a contacted ion pair structure [S·Li(μ-Me)(μ-NMe₂)·Al(Me)₂] and the subsequent pre-metallation complex it forms with anisole [Ph(Me)O·Li(μ-Me)(μ-NMe₂)·Al(Me)₂], a dative coordination leading to an energy saving of -15.8 kcal mol⁻¹, are, on the basis of the new information established here, not relevant to the actual experimental reagent **1** employed in bulk THF solution. This is because all the mixed lithium-aluminium species present in bulk THF solution are solvent separated and so the Li cannot cooperate with Al by providing the anisole with a coordination point adjacent to the amido ligand attached to the Al. In other words no complex induced proximity effect would be possible. We confirmed this experimentally by showing that the solvent-separated aluminate [Li(THF)₄]⁺[Al(TMP)(ⁱBu)₃]⁻ **1**·(THF)₄ is incapable of metallating anisole in bulk THF solution.

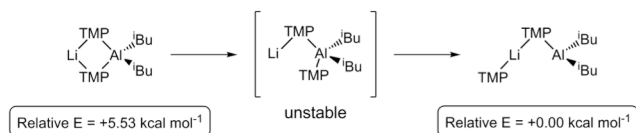
In earlier work, we also performed DFT calculations considering the feasibility of a structure of putative **2**·THF of formula [THF·Li(μ-TMP)₂Al(ⁱBu)₂].¹² These calculations used the Gaussian 03 package with geometry optimisation using the B3LYP density functionals and the 6-311(d, p) basis set with zero point energy corrections. While this study confirmed the most energetically stable arrangement of **2**·THF has two bridging TMP ligands with the two terminal ⁱBu ligands on Al,

significantly it also exposed the relative instability of **2**·THF with respect to either its homometallic components LiTMP and (TMP)Al(ⁱBu)₂ or THF solvates thereof. Depending on the homometallic components employed this instability ranged from +14.16 to +20.60 kcal mol⁻¹ (Scheme 8).

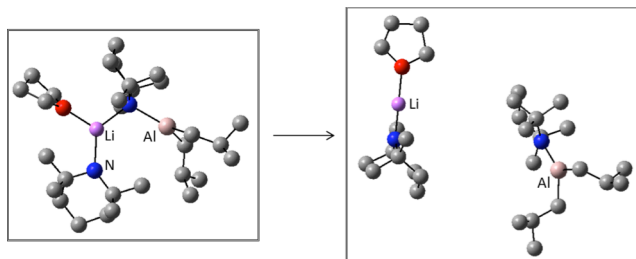


Scheme 8. Energies obtained from DFT calculations for the possible reactions in which putative THF·Li(μ-TMP)₂Al(ⁱBu)₂ is formed.

To shed more light on **2** having accrued much more knowledge on the experimental system through this study we have carried out additional calculations using the same parameters. To start we modelled a THF-free version of **2**, Li(μ-TMP)₂Al(ⁱBu)₂, **2**_{closed}, having a closed four-membered (LiNAIN) ring, comparing it against an open version **2**_{open}, to ascertain the effect that relaxing the steric strain by opening the ring might have on the stability of **2** (Scheme 9). Our first model of **2**_{open} was derived by breaking one of the Li-N(TMP) bonds in **2**_{closed} to leave a single Li-N(TMP)-Al bridge with the remaining three ligands bonded solely to Al. However, under geometry optimisation this 1-coordinate Li/4-coordinate Al model rearranged through the migration of the terminal Al-attached TMP ligand to a terminal position on Li to generate a more realistic 2-coordinate Li/3-coordinate Al structure, isoelectronic with crystallographically characterized (TMEDA)Li(μ-TMP)Li(TMP)⁴¹ and (PMDETA)Na(μ-TMP)Li(TMP).⁴² Relieving the steric strain by opening the LiNAIN ring in this way does indeed increase the stability with **2**_{open} being -5.53 kcal mol⁻¹ more stable than **2**_{closed}. That notwithstanding, on introducing a THF ligand to the lithium centre to mimic the experimental stoichiometry of **2**·THF, the structure fragmented under geometry optimisation into the homometallic components THF·LiTMP and (TMP)Al(ⁱBu)₂ (Scheme 10). The energy given by the sum of these two separated homometallic components is -1614.811704 a.u. compared to -1614.805526 a.u. for **2**_{closed}·THF, equating to the former being more stable by -3.87 kcal mol⁻¹ [or by a more realistic -14.19 kcal mol⁻¹ if the dimeric aggregation of (THF·LiTMP)₂ is taken into account]. Collectively these results suggest that a THF solvate of the contacted ion pair LiTMP·Al(TMP)(ⁱBu)₂, whether in a closed or open ring arrangement would be too high in energy to exist, supporting the experimental NMR investigations which failed to detect any such species.



Scheme 9. ChemDraw representation of the rearrangement of $\text{Li}(\mu\text{-TMP})_2\text{Al}(\text{i-Bu})_2$ **2**_{closed} into $(\text{TMP})\text{Li}(\mu\text{-TMP})\text{Al}(\text{i-Bu})_2$ **2**_{open} as predicted by DFT calculations.

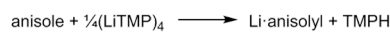


Scheme 10. Fragmentation of $(\text{THF})(\text{TMP})\text{Li}(\mu\text{-TMP})\text{Al}(\text{i-Bu})_2$ into its homometallic components as predicted by DFT calculations.

We have also modelled the reaction of LiTMP with anisole, which experimentally produced less than 10% of either lithiated anisole or its 2-iodo derivative following quenching with iodine. In the calculations where lithiated anisole was modelled somewhat unrealistically as an unsolvated monomer or a mono-THF-solvated monomer where the Li atoms have low coordination numbers the ΔE values for the reactions were highly endergonic (Scheme 11). However even when the lithiated anisole was modelled more realistically as a tetramer⁴³ or tri-THF-solvated monomer starting from $(\text{LiTMP})_4$ or $(\text{THF}\cdot\text{LiTMP})_2$ respectively as the base, the reactions are close to thermoneutral (ΔE is $+1.73 \text{ kcal mol}^{-1}$ or $-1.18 \text{ kcal mol}^{-1}$ respectively) though the latter one is marginally exergonic. The thermodynamics changed significantly when $(\text{TMP})\text{Al}(\text{i-Bu})_2$ was introduced to the lithiated anisole. Depending on what form of lithiated anisole (tetramer, mono-THF-solvated monomer or tri-THF-solvated monomer) was employed the ΔE values ranged from $-9.39 \text{ kcal mol}^{-1}$ to $-28.45 \text{ kcal mol}^{-1}$, so in all three cases the reaction proved exergonic (Scheme 11). These calculations are therefore fully consistent with our experimental observations that LiTMP can lithiate anisole to only a limited extent, but that introducing the aluminium trapping reagent makes the C-H to C-metal transformation much more favourable.

Conclusions

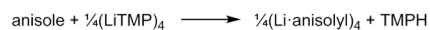
This study has examined in detail the constitutions of the two most important alkali metal aluminate reagents made to date in “ $\text{LiTMP}\cdot\text{Al}(\text{i-Bu})_3$ ” **1** and “ $\text{LiTMP}\cdot\text{Al}(\text{TMP})(\text{i-Bu})_2$ ” **2**. In contrast to previous investigations that viewed **1** as a single species in THF solution, this study uncovers five distinct species, which appear to exist simultaneously in two connected equilibria in THF solution. Scheme 12 gives a pictorial summary of the species that exist in both hexane and THF



$$\Delta E = +30.48 \text{ kcal mol}^{-1}$$



$$\Delta E = +17.60 \text{ kcal mol}^{-1}$$



$$\Delta E = +1.73 \text{ kcal mol}^{-1}$$



$$\Delta E = -1.18 \text{ kcal mol}^{-1}$$



$$\Delta E = -18.71 \text{ kcal mol}^{-1}$$



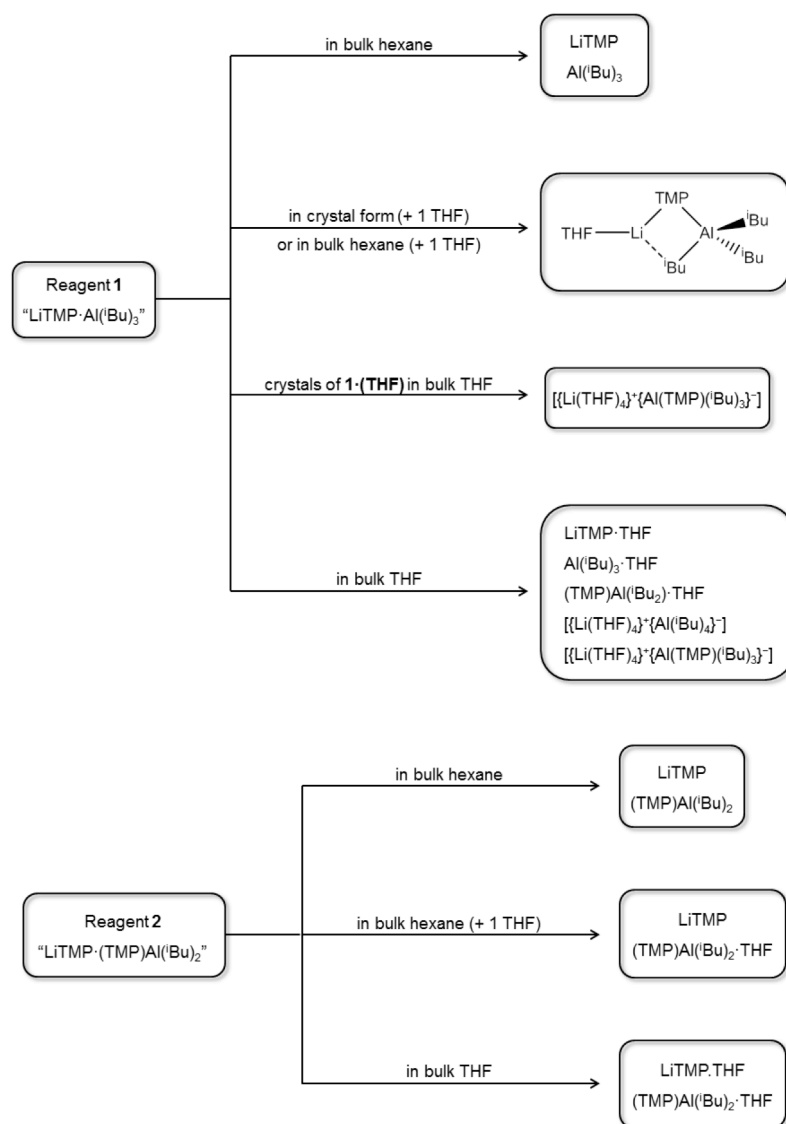
$$\Delta E = -28.45 \text{ kcal mol}^{-1}$$



$$\Delta E = -9.39 \text{ kcal mol}^{-1}$$

Scheme 11. Energies of the modelled metallations and subsequent trapping reactions of anisole.

solution as well as those of **2** in the same media. One striking observation is that the single species previously identified in crystal form $[(\text{THF})\cdot\text{Li}(\mu\text{-TMP})(\mu\text{-i-Bu})\text{Al}(\text{i-Bu})_2]$, **1**·**THF**, is not an active base in either hexane or THF solution using anisole as a test Brønsted acid. We confirmed that these crystals do indeed form a single species when dissolved in THF solution in the solvent-separated modification $[\{\text{Li}(\text{THF})_4\}^+\{\text{Al}(\text{TMP})(\text{i-Bu})_3\}^-]$ **1**·**(THF)**₄. Remarkably, however, on making up **1** *in situ* by adding LiTMP and $\text{Al}(\text{i-Bu})_3$ to THF solution, four other species in addition to $[\{\text{Li}(\text{THF})_4\}^+\{\text{Al}(\text{TMP})(\text{i-Bu})_3\}^-]$ **1**·**(THF)**₄ are produced as identified from NMR data. Preparing authentic samples of all of these species and testing them all individually with anisole, we found that only the lithium amide LiTMP was capable of metallating anisole. Though the yield of lithiated anisole was low, it can be quickly trapped by an alkylaluminium species (we term this trans-metal-trapping), which drives the reaction forward to a high yield of “aluminated” anisole. Reagent **2** is more simple in solution remaining as its added components LiTMP and $(\text{TMP})\text{Al}(\text{i-Bu})_2$ in hexane or as THF solvates thereof when stoichiometric THF is added or in bulk THF solution. The lack of complexity can be attributed to the extra bulk of $(\text{TMP})\text{Al}(\text{i-Bu})_2$ compared to $\text{Al}(\text{i-Bu})_3$ which prevents its association with LiTMP and thus preventing the complicated equilibria witnessed for **1**. On the basis of these findings one must advise caution against assuming that a crystalline bimetallic species grown from solution is the active reagent in



Scheme 12. Summary of the compositions of "aluminate" reagents 1 and 2. Note depending on the age of solutions, THF degradation products will also be present.

AMMAI reactions; but on the other hand, it was only through the isolation of such a metallo intermediate that its inactivity as a base could be unequivocally exposed. Looking more generally, while the complexities apparent in alkali-metal-mediated metallation reactions have recently been cause to tag them as "black box chemistry", shafts of light are now becoming visible through it. In this specific case the message seems to be that unless these aluminate species are in contacted ion pair form where the alkali metal can act as a Lewis acidic coordination point for an incoming substrate to closely approach the anionic aluminium moiety, AMMAI will not generally occur; otherwise any observed metallation may be effected by the separated lithium reagent followed by rapid trapping of the newly formed lithium carbanion via an alkylaluminium reagent.

Experimental Section

General methods

All reactions and manipulations were carried out under a protective dry pure argon atmosphere using standard Schlenk techniques. Products were isolated and NMR samples prepared within an argon-filled glovebox. Hexane was dried by heating to reflux over sodium-benzophenone and distilled under nitrogen prior to use. *n*BuLi (1.6 M in hexanes) and Al(*i*Bu)₃ (1.0 M in hexanes) were purchased from Aldrich and used as received. *i*BuLi (1.6 M in heptane) was purchased from ACROS and used as received. TMP(H) was obtained from Aldrich and dried over 4 Å molecular sieves prior to use. LiTMP^{26b} and Al(TMP)(*i*Bu)₂¹² were prepared according to

literature procedures. NMR spectra were recorded on a Bruker AVANCE 400 NMR spectrometer, operating at 400.13 MHz for ^1H , 155.50 MHz for ^7Li , 104.25 MHz for ^{27}Al and 100.62 MHz for ^{13}C . All ^{13}C NMR spectra were proton decoupled. ^1H and ^{13}C spectra were referenced to the appropriate solvent signal, ^7Li NMR spectra were referenced against LiCl in D_2O at 0.00 ppm and ^{27}Al NMR spectra were referenced against AlCl_3 in D_2O at 0.00 ppm.

Theoretical Calculations

DFT calculations were performed using the Gaussian ⁴⁴ computational package G03. In this series of calculations the B3LYP ⁴⁵ density functional and the 6-311(d,p) ⁴⁶ basis set were used. After each geometry optimization a frequency analysis was performed. The energy values quoted include the zero point energy contribution.

Synthesis of $[\{\text{Li}(\text{THF})_4\}^+\{\text{Al}(\text{tBu})_4\}^-]$ (**3**)

*n*BuLi (3.13 mL, 1.6 M in hexanes, 5 mmol) was added to a mixture of THF (4 mL) and TMPH (0.85 mL, 5 mmol) at -78°C and the mixture was stirred for 10 min at 0°C . $\text{Al}(\text{tBu})_3$ (5 mL, 1 M in hexanes, 5 mmol) was then added at -78°C and the mixture stirred for 30 min at 0°C to give a pale yellow solution and a white solid. The reaction mixture was then heated to refluxing temperature to obtain a clear solution and subsequent bench cooling of this solution afforded colourless crystals of **3** (0.55 g, 20%). ^1H NMR (C_6D_6 , 400.13 MHz, 300 K): δ 3.46 (m, 16H, OCH_2 THF), 2.37 (sept, 4H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 1.38 (d, 24H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$), 1.32 (m, 16H, CH_2 THF), 0.07 ppm (d, 8H, $\text{CH}_2\text{CH}(\text{CH}_3)_2$); ^{13}C NMR (C_6D_6 , 100.62 MHz, 300 K): δ 67.75 (OCH_2 THF), 29.55 ($\text{CH}_2\text{CH}(\text{CH}_3)_2$), 28.03 ($\text{CH}_2\text{CH}(\text{CH}_3)_2$), 25.48 ppm (CH_2 THF) [note that the resonance for $\{\text{CH}_2\text{CH}(\text{CH}_3)_2\}$ could not be observed in either C_6D_6 or $[\text{D}_8]\text{THF}$ solution however its existence was confirmed by a ^1H - ^{13}C HSQC experiment (see Figures S21 and S22 in ESI)]; ^7Li NMR (C_6D_6 , 155.50 MHz, 300 K): δ -1.19 ppm.

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Notes and references

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