Organometallic Reagents

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Structurally Engineered Deprotonation/Alumination of THF and THTP with Retention of Their Cycloanionic Structures**

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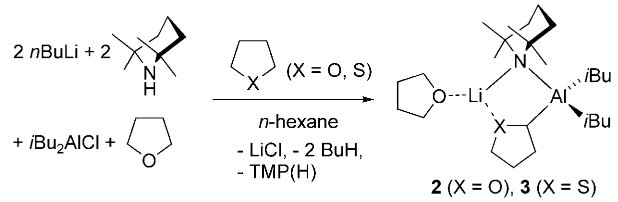
Dedicated to Professor Malcolm Chisholm on the occasion of his 65th birthday

Metalation has served well for over 80 years as a vehicle for transforming inert C–H bonds in organic compounds to reactive C–metal bonds.[1] Progress in metalation was accelerated greatly by the development of DoM (directed *ortho*-metalation),[2] pioneered by Snieckus, Beak, and others, a special type of lithiation (aromatic C–H to $C^{\delta-}$–$Li^{\delta+}$) reliant on the high polarity of carbon–lithium bonds in organolithium reagents. Many other metals could not engage in metalation due to the lower polarity/lower reactivity of their corresponding carbon–metal bonds. However, this obstacle has now been cleared by the recognition that when part of a mixed-metal system or other multicomponent mixture, these metals (for example, magnesium, zinc, aluminum or manganese) can exhibit greatly enhanced metalating properties often superior in terms of functional-group compatibility or reaction conditions to that of lithium. Interest in these new "low polarity" metalating agents is widespread with coverage in fundamental chemistry journals,[3] process chemistry journals,[4] interdisciplinary science journals,[5] and in news items in scientific media.[6] Knochel's turbo-Grignard reagents (e.g., (iPr)MgCl·LiCl)[7] are examples that have been commercialized. A spectacular demonstration of the special reactivity of bimetallic bases came with the α-zincation of tetrahydrofuran (THF) by the sodium dialkyl(amido)zincate [(TMEDA)Na(μ-TMP)(μ-CH_2SiMe_3)Zn(CH_2SiMe_3)] (TMEDA = *N,N,N′,N′*-tetramethylethylenediamine; TMP = 2,2,6,6-tetramethylpiperidine) to produce [(TMEDA)Na(μ-TMP)(μ-OC_4H_7)Zn(CH_2SiMe_3)].[5] Conventional metalation of THF invariably initiates decomposition by ring opening,[8] but in this low-polarity zincation the 5-atom ring of the sensitive α-deprotonated THF anion remains intact. However, this reaction is extremely slow (best yield was 52.7% after 2 weeks) and requires a massive stoichiometric excess of the cyclic ether (i.e., carried out in neat THF solvent). Here we report a vastly superior methodology to the cyclic THF α-anion, mediated by a lithium aluminate base with a higher amido content than the alkyl-rich zincate reagent. An analogous reaction with the sulfur analogue, tetrahydrothiophene (THTP), is also reported.

Empirically formulated as [(THF)Li(TMP)(TMP)Al(iBu)$_2$] (**1**), the base in question can be prepared straightforwardly by mixing commercially available nBuLi, TMP(H), iBu$_2$AlCl, and THF in a 2:2:1:1 stoichiometry in hexane with co-products butane and lithium chloride easily separated from the mixture. In contrast, zincate base [(TMEDA)Na(μ-TMP)(μ-CH_2SiMe_3)Zn(CH_2SiMe_3)] requires pre-preparation of the metal alkyls nBuNa and $(Me_3SiCH_2)_2Zn$, neither of which are commercially available. Aluminate base **1** cannot be isolated as a pure solid as it forms as an oil in hexane solution. Previously a modified version of it not containing THF was found to metalate TMEDA.[9] The potency of **1** as a base was obvious on standing as it begins to self-metalate, by deprotonating its THF ligand (evidenced by slow growth of resonances attributed to deprotonated THF, cf. complex **2**).[10] To accomplish the desired alumination of THF, only one molar equivalent of "reactant THF" was added to an in situ hexane solution of **1** which already contained one "ligand THF" molecule. The colorless crystalline product (isolated yield, 35%) was characterized by X-ray crystallography,[11] NMR spectroscopy, and elemental analysis as the lithium tetrahydro-2-furanylaluminate [(THF)Li(μ-TMP)(μ-OC_4H_7)Al(iBu)$_2$] (**2**; Scheme 1). Its comparative speed coupled to its stoichiometric nature marks this reaction as a major improvement over the zincation method.



2 (X = O), **3** (X = S)

Scheme 1. Synthesis of new complexes **2** (X = O) and **3** (X = S) through reaction of appropriate heterocycle with in situ generated **1**.

Crystalline **2** exists as a discrete molecular contacted ion pair structure as elucidated by X-ray crystallography (Figure S5 in the Supporting Information; see also Figure 1 for sulfur analogue). The structure displayed extensive disorder over all organic fragments, resulting in a detailed discussion of

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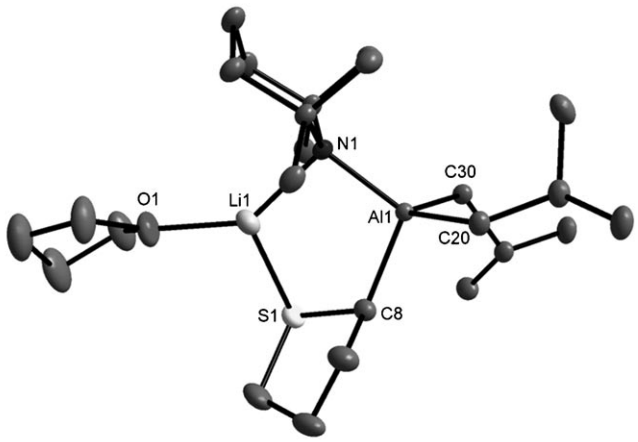

Figure 1. Molecular structure of **3** with hydrogen atoms omitted for clarity. Thermal ellipsoids are drawn at 50% probability. Selected bond lengths [Å] and angles [°] for **3**: Li1–O1 1.925(6), Li1–S1 2.413(3), Li1–N1 2.025(5), S1–C8 1.829(2), Al1–C8 2.054(2), Al1–N1 1.979(2); N1-Li1-O1 138.9(2), N1-Li-S1 111.3(2), O1-Li1-S1 108.5(2). Full geometric parameters for both **2** and **3** are included in the Supporting Information.

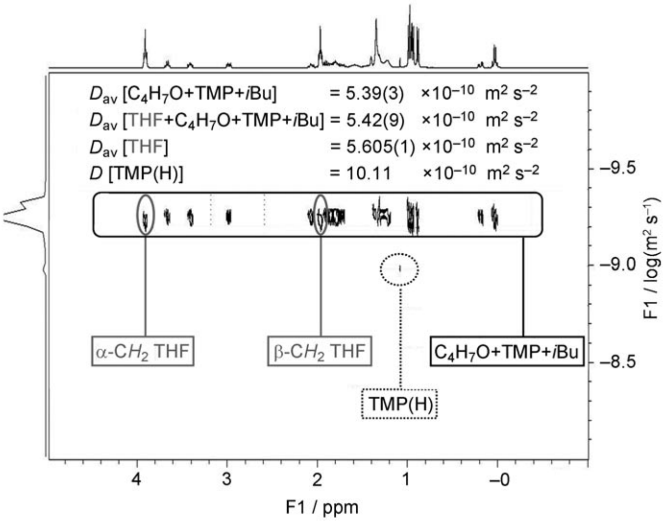

Figure 2. ^1H DOSY NMR spectrum of **2** (50 mg) at 300 K in C_6D_{12} (0.7 mL); *x* axis represents the ^1H chemical shift, *y* axis the diffusion dimension (log *D*).

specific bond parameters being unwarranted. However, it is clear that retention of the heterocyclic OC_4 ring of THF, deprotonated at the 2-position, is the salient feature. Stabilization of the sensitive cyclic ether anion occurs through both its O atom and deprotonated α-C atom, binding to lithium and aluminum, respectively. Though racemic overall, this α-C atom is rendered stereogenic on deprotonation as it bonds to four different atoms (Al, C, H, O). In addition to the THF anion bridge, lithium and aluminum are connected by the TMP N atom to complete a five-element (LiNAlCO) ring which fuses to the O–αC junction of the deprotonated THF molecule. Possessing a full complement of hydrogen atoms, a neutral, terminal THF ligand completes the distorted trigonal planar (1 × N; 2 × O) coordination of lithium, while two terminal *i*Bu ligands complete the distorted tetrahedral (3 × C; 1 × N) coordination of aluminum.

Aluminate **2** was also characterized in [D_{12}]cyclohexane solution by ^1H and ^{13}C NMR spectroscopy with all resonances easily assignable with the assistance of both COSY and HSQC spectra (see Experimental Section and Supporting Information for details). Of principal importance was the resonance of the hydrogen on the metalated C atom which is shielded by the metal ($\delta = 2.96$ ppm). For more solution structural elaboration **2** was also studied using diffusion-ordered NMR spectroscopy (DOSY).[12a] A ^1H DOSY NMR spectrum run at 300 K (Figure 2) reveals cross points for all ligand (THF, TMP, C_4H_7O, *i*Bu) resonances of **2** approximately in the same line of the second dimension (average diffusion coefficient, *D*, $5.42(9) \times 10^{-10}\,m^2 s^{-1}$). Consistent with all four ligands belonging to the same molecule, this observation implies the solid state structure of **2** is retained in this solution medium.[12b] Closer inspection of the DOSY NMR data hints at an equilibrium involving a fast decoordination–recoordination of the neutral THF ligand attached to Li as its *D* value ($5.605(1) \times 10^{-10}\,m^2 s^{-1}$) is slightly higher than the average *D* value of the other three ligands ($5.39(3) \times 10^{-10}\,m^2 s^{-1}$ for TMP, C_4H_7O and *i*Bu), a possibility supported by the broadness of the singlet in the ^7Li NMR spectrum. The fact that the D_{av} of neutral THF is far away from the diffusion coefficient expected for free THF (see in Figure 2 how a larger molecule than free THF, namely TMP(H), arising from a trace amount of hydrolysis, has a much higher *D* value of $10.11 \times 10^{-10}\,m^2 s^{-1}$), indicates how this equilibrium is strongly displaced to the retention of the solid state structure of **2** in solution. Further evidence for the predominant retention of the solid state structure of **2** in [D_{12}]cyclohexane solution came from ^1H–^7Li heteronuclear NOE (HOESY)[12c] experiments which show a good correlation between the H···Li distances in the crystal structure and the intensities of the ^1H–^7Li NOE responses (see Experimental Section and Supporting Information).

Sulfur heterocycle THTP was also smoothly aluminated by **1** with retention of its α-deprotonated anionic SC_4H_7 ring in the crystalline product [(THF)Li(μ-TMP)(μ-SC_4H_7)Al(*i*Bu)$_2$] (**3**). This was confirmed by ^1H and ^{13}C NMR spectroscopy which showed no evidence of deprotonated THF (cf. complex **2**) or "ligand" THTP. Mimicking the synthesis of **2**, this reaction (Scheme 1) was also stoichiometric, thus involving a 1:1 mixture of THF (present in in situ generated **1**) and THTP. The latter heterocycle is aluminated as seen through the crystallization of **3** (34%) and from NMR analysis of the reaction filtrate which suggested that the reaction was virtually quantitative. Contrary to the ease in which it is accomplished here, THTP is poorly reactive to metalation on account of the low kinetic acidity of its α-CH_2 atoms. Previously Glass and Liu reported[13] that metalation was possible with superbasic *n*BuLi/KO*t*Bu though the Li/K-metalated intermediate decomposed completely to a thioenolate and ethene at 5 °C. Magnesiation of THTP is also possible through [(TMEDA)Na(μ-TMP)(μ-CH_2SiMe_3)Mg(TMP)][14] but similar to the disadvantages of the aforementioned zincate base the components of this sodium magnesiate base *n*BuNa and Mg(CH_2SiMe_3)$_2$ have to be pre-

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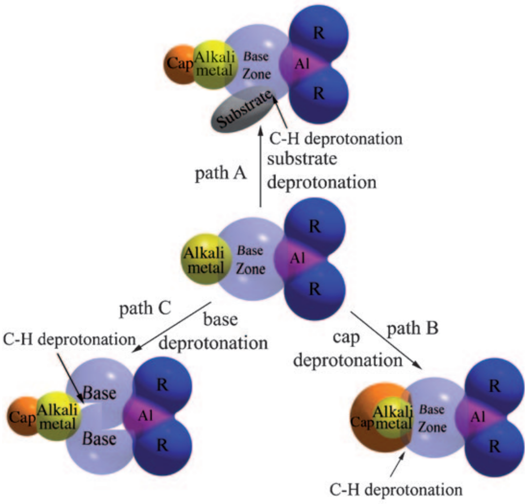
prepared. Aluminated tetrahydrothiophene **3** has been characterized by ^{1}H and ^{13}C NMR spectroscopy in [D$_{12}$]cyclohexane (see Experimental Section and Supporting Information). As with **2**, the proton bound to the aluminated carbon resonates upfield at $\delta = 1.75$ ppm. Determined by X-ray crystallography,[11] the molecular structure of **3** (Figure 1) is essentially identical to that of **2** with a Li–S dative bond instead of a Li–O dative bond closing its five-element (LiNAlCS) ring. The Li–S [2.414(4) Å] and Li–O [1.925(6) Å] bond lengths are in accord with those seen in an α-metalated 1,3-dithiane which also contains an S-coordinated Li(THF) fragment.[15]

Surveying recently reported structurally defined bis(TMP) aluminate reactions it is clear that the molecular design of the base (Scheme 2) can be tuned to effect special metalations in different ways. Small ligand caps on the alkali metal (AM) would enable a substrate to pre-coordinate to AM before being pushed into the base zone (path A) to undergo deprotonation and trapping. The new reactions disclosed herein probably come into this category. Alternatively (path B) a larger cap on a small AM can encroach into the base zone and become deprotonated itself. Combining TMEDA with lithium instigates this reactivity to trap a $Me_2NCH_2CH_2N(Me)CH_2^-$ ion.[9] Enlarging the size of AM can promote a third scenario (path C). Bulky base ligands can collide as the homometallic components approach each other, leading to novel C–H bond activations/cleavages with anions. The strong Brønsted base TMP$^-$ can be transformed to a Brønsted acid through deprotonation of a methyl sidearm by such action to generate a trapped N$^-$,C$^-$ dianion.[16] All of these structurally engineered deprotonations lead to heteroanionic aluminates. The next challenge will be to find the best ways to utilize them in C–C bond forming applications.[17]



Scheme 2. Tuning different selective deprotonations through an alkali metal aluminate motif.

Experimental Section

All reactions were carried out under a protective argon atmosphere using standard Schlenk techniques. Full details, including complete characterization, are given in the Supporting Information.

Synthesis of **2**: Hexane (10 mL) was introduced into an oven-dried Schlenk tube. Next, 1.6 M *n*BuLi (1.25 mL, 2 mmol) was added, followed by TMP(H) (0.34 mL, 2 mmol) at room temperature. The reaction mixture was left to stir for 10 min and then iBu$_2$AlCl (0.38 mL, 2 mmol) was injected into the Schlenk tube, producing a white suspension almost immediately. The reaction was left to stir for 1 h and was then filtered through Celite and glass wool, which was then washed with more hexane (10 mL). This solution was cannulated into a second Schlenk tube containing a solution of freshly prepared LiTMP in hexane (10 mL) [from a mixture of *n*BuLi (1.25 mL, 2 mmol) and TMP(H) (0.34 mL, 2 mmol)] to give a colorless solution. Finally, THF (0.32 mL, 4 mmol) was injected and the reaction mixture was left to stir overnight. Most of the solvent was removed under vacuum and the Schlenk tube was left in the freezer at −30 °C. A crop (0.302 g, 35 %) of colorless crystals formed which were suitable for X-ray crystallographic analysis.

Synthesis of **3**: The same procedure as described for **2** was employed until the final step where THF (0.16 mL, 2 mmol) and THTP (0.18 mL, 2 mmol) were injected and the reaction mixture was left to stir overnight. Upon cooling to −30 °C a crop (0.304 g, 34 %) of colorless crystals formed which were suitable for X-ray crystallographic analysis.

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parameters and 3146 independent reflections. Max/min residual electron density 0.531/−0.331 e Å^{-3}. Crystal data for **3**: $C_{25}H_{51}AlLiNOS$; a colorless block gave triclinic space group $P\bar{1}$, $a = 10.7592(8)$, $b = 11.0807(9)$, $c = 13.5715(11)$ Å, $\alpha = 90.902(7)$, $\beta = 104.045(7)$, $\gamma = 117.173(8)°$, $V = 1381.3(2)$ Å^3, $T = 123(2)$ K, $Z = 2$, $r_{\text{calcd}} = 1.076$ Mg m^{-3}, Mo$_{K\alpha}$ $\lambda = 0.71073$ Å, $R1 = 0.0475$ (for 4018 reflections with $I > 2\sigma(I)$) $wR2 = 0.1155$ and $S = 0.915$ for 307 parameters and 6844 independent reflections. Max/min residual electron density 0.465/−0.445 e Å^{-3}. Structures were solved and refined to convergence on F^2 (SHELXS and SHELXL-97; G. M. Sheldrick, *Acta Crystallogr. Sect. A* **2008**, *64*, 112). CCDC 788753 (**2**) and 788754 (**3**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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