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Unveiling the Structural Complexity of Lithium Organozinc Alkoxo Clusters and their Applications to Enantioselective Michael Addition Reactions

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Dedicated to Professor Robert E. Mulvey on the occasion of his 65th birthday

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Abstract: We report three novel lithium zincate alkoxo clusters, which can be accessed through a convenient co-complexation reaction of the corresponding dialkylzinc derivatives with lithium alkoxides of the formula $[\text{LiO}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2]$, or via a deprotonation process mediated by the higher-order zincate Li_2ZnEt_4 and dimethylethanolamine. These complexes have been isolated as colourless crystalline solids and characterised by multinuclear magnetic resonance spectroscopy, elemental and single-crystal X-ray diffraction analysis. XRD analysis of the crystal structures, combined with ^1H DOSY NMR experiments, was crucial for understanding the chemistry behind these complexes. Furthermore, complexes obtained by mixing ZnEt_2 with a chiral nonracemic lithium alkoxide generated from (1*R*,2*S*)-*N*-methylephedrine have been explored in promoting an enantioselective Michael addition reaction towards *trans*- β -nitrostyrene, with the corresponding nitroalkane isolated in up to 37.3% enantiomeric excess.

Introduction

In recent times, heterobimetallic compounds that combine an alkali metal with a less electropositive metal (also known as *ates*) have emerged as powerful reagents, finding widespread application in both stoichiometric and catalytic transformations.^[1,2] These main-group heterobimetallic systems have shown enormous potential for arene functionalisation via deprotonative metalation^[3] and metal-halogen exchange.^[4] Within catalysis, alkali-metal magnesiates and aluminates have been successfully employed in hydroelementation^[5] and cyclisation^[6] reactions, demonstrating enhanced catalytic power, selectivities, and functional group tolerance compared to their monometallic counterparts. The isolation and trapping of organometallic intermediates involved in these reactions has been key to advancing the mechanistic understanding of how these bimetallic

systems operate and how their reactivity can be finely tuned by adding different additives.^[1a,7]

Amongst these family of compounds, alkali-metal zincates are well-established reagents in modern organometallic synthesis, finding extensive applications in a myriad of fundamental organic transformations such as zinc-halogen exchange,^[4a,c,8] epoxide ring openings,^[9] nucleophilic additions,^[10] and deprotonative metalation,^[11] to name but a few. Showcasing the enhanced nucleophilic power of these reagents, our groups have recently shown that tetraorganozincates Li_2ZnR_4 (R= alkyl,aryl) can efficiently promote conjugate additions to nitroolefins, yielding a wide range of synthetically valuable nitroalkanes. These reactions proceed with excellent yields (up to 98%) in a chemoselective manner under mild reaction conditions (0 °C, 30 min) without the need for transition metal catalysis or the use of additives.^[12]

Building on these studies, we wondered whether the enhanced nucleophilicity and unique chemoselectivity displayed by these higher-order zincates^[13] could be enriched with enantioselectivity when combined with chiral nonracemic alkoxy ligands. To date, only a few studies involving chiral ate complexes capable of promoting enantioselective nucleophilic additions have been reported in the literature. For instance, Harrison-Marchand *et al.* developed a methodology enabling the enantioselective nucleophilic 1,2-addition to ketones by using chiral lithium amido zincates.^[14,15] In this regard, previous work by Hevia and Knochel has shown that mixed alkyl/alkoxide lithium zincates, obtained by co-complexation of lithium alkoxides with dialkylzinc reagents, can be used for the functionalisation of a wide range of bromoarenes containing sensitive functional groups such as nitro, ketone and aldehyde groups via direct Zn-Br exchange reactions.^[16] This alkoxide-activating effect has also been applied to other heterobimetallic systems combining a group 1 metal alkoxide with a group 1 or group 2 metal alkyl reagent.^[17]

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The results included in this work: (i) assess the feasibility of synthesizing higher-order dialkoxy dialkyl zincate species characterised through an extensive structural study using a racemic ligand as the alkoxide precursor, and (ii) explore the potential of chiral lithium zincates as powerful nucleophiles, both in terms of reactivity and enantioselectivity, using a chiral nonracemic ligand as the alkoxide precursor and nitroolefins as electrophiles.

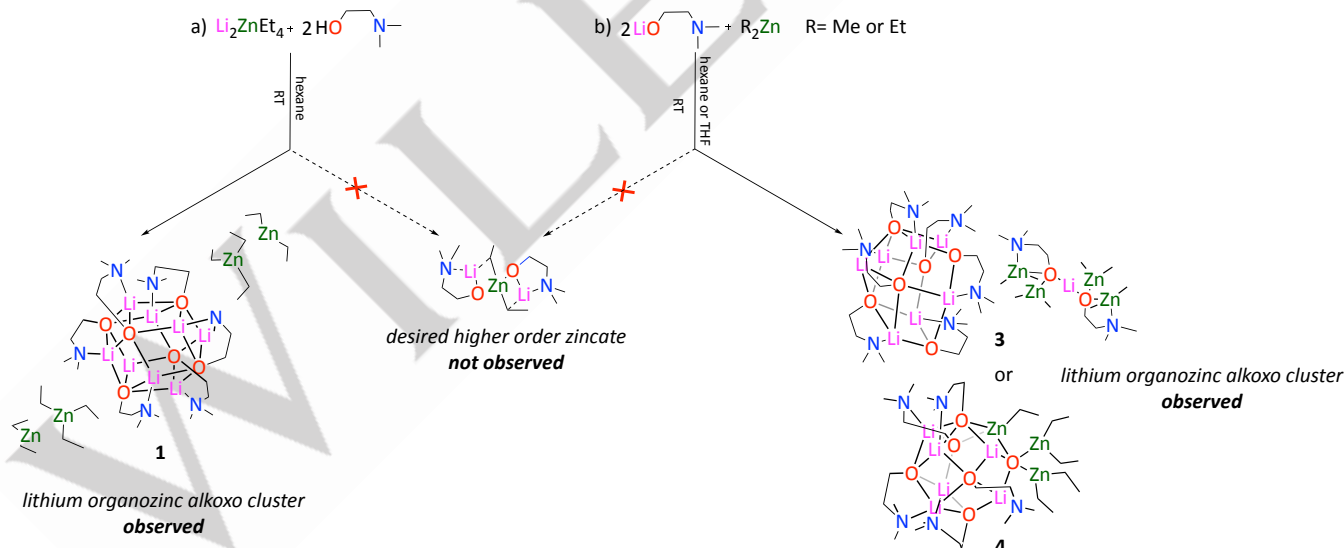
Results and Discussion

We began our study by investigating the deprotonative capability of the well-structurally defined^[12] higher-order zincate Li_2ZnEt_4 towards two equivalents of the racemic amino alcohol DMEA (dimethylethanolamine) in hexane. We selected this alcohol because of its pendant NMe_2 Lewis basic site, which we thought could contribute to the overall stabilisation of the alkali-metal.^[16,18] However, the ^1H NMR spectrum of the reaction crude was rather complex, suggesting the presence of several species in solution. Upon cooling this solution, colourless crystals of the complex lithium zincate $[\{\text{Li}_8(\text{OR})_6\}^{2+}\{\text{ZnEt}_3\}^-] \cdot 2\text{ZnEt}_2$ (**1**) ($\text{R} = \text{C}_2\text{H}_4\text{NMe}_2$) were obtained in a 24% isolated yield (Scheme 1a and Figure 1).

X-ray crystallographic studies established the pseudo-solvent-separated ion pair (SSIP) structure of **1**, which comprises a novel octanuclear lithium cage dication $[\{\text{Li}_8(\text{OR})_6\}^{2+}$ and two $\{\text{ZnEt}_3\}^-$ anions. This compound also co-crystallises with two

equivalents of ZnEt_2 (see ESI for details). The unusual complex Li dication present in **1** forms a cage containing 14 vertexes and 12 square Li_2O_2 faces, with Li-O bond distances ranging from 1.927(4) to 1.990(4) Å. Every oxygen atom binds to four lithium centers, and two distinct Li environments are present. Six lithium atoms bind to three alkoxide groups and complete their distorted tetrahedral coordination by chelation with the NMe_2 group of one these alkoxide ligands (see Figure 1). The two remaining Li atoms in the cage (Li_{33} in Figure 1) bind to three alkoxide groups and form a long electrostatic interaction with the methylene group of the $\{\text{ZnEt}_3\}^-$ anion [$\text{Li}_{33}\text{-C}_{16}$, 2.483(4) Å]. Similar interactions have been previously noted in alkali-metal zincate chemistry.^[19] The zinc anion present comprises a trigonal planar zinc center bonded to three ethyl groups, [mean Zn-C bond length 2.050 Å]. This motif has also been described for other zincate complexes exhibiting SSIP structures.^[20]

Compound **1** was further characterised in deuterated benzene solutions using multinuclear ^1H , ^{13}C and ^7Li magnetic resonance spectroscopy. The most distinct signal in the ^1H NMR was a quartet at 0.47 ppm for the Zn- CH_2 groups. Consistent with the increased anionic character, this resonance is significantly shielded compared to that observed for ZnEt_2 (0.11 ppm).^[21] The ^7Li NMR spectrum showed a single signal at 0.67 ppm. ^1H DOSY NMR studies also confirmed the retention of the SSIP constitution of **1** in solution, as indicated by the different diffusion coefficients observed for the resonances of the Et and $\text{OCH}_2\text{H}_4\text{NMe}_2$ groups (see Supporting Information for details).



Scheme 1. Adopted approaches for the synthesis of lithium dialkyl dialkoxy zincates by deprotonative approach (a), and a co-complexation approach in hexane or THF (b).

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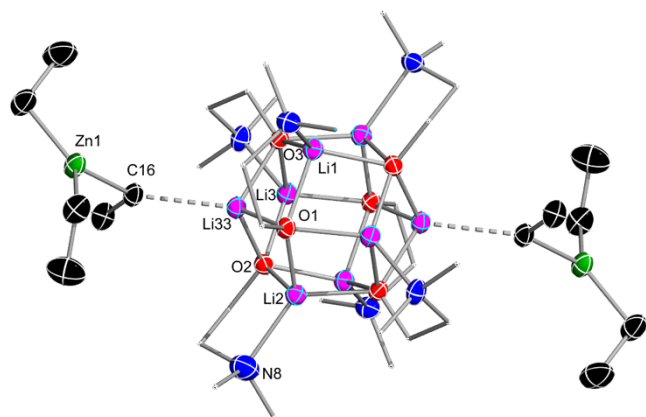


Figure 1. Molecular structure of $[(\text{Li}_8(\text{OR})_6)^{2+}\{\text{ZnEt}_2\}_2]\cdot 2\text{ZnEt}_2$ (**1**). H atoms, disordered components and ZnEt_2 fragments are omitted, and C atoms on the alkoxide groups are drawn as wire frames for clarity. Symmetry transformations to generate symmetrical atoms: 1-x, 1-y, 1-z. Thermal ellipsoids are set at 30% probability.

While formation of **1** may be favoured by the crystallisation conditions and only represents one of the possible products present in the reaction crude, its formation can be the result of a redistribution process of a putative $[\text{Li}_2\text{ZnEt}_2(\text{OR})_2]$. The complexity of **1** contrasts with the structure established for related mixed alkyl/alkoxide $[(\text{LiZnEt}_2(\text{OR}')_2)]_2$ ($\text{R} = \text{R} = \text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)\text{CH}_2\text{CH}_2\text{N}(\text{CH}_3)_2$), which exhibits a dimeric contacted ion pair structure.^[16] This compound was prepared by co-complexation of ZnEt_2 with the relevant LiOR'. Inspired by this work we decided to try a similar approach using DMEA. We first prepared the lithium alkoxide by deprotonating DMEA, with *n*-BuLi in hexane, leading to the formation of a white solid. The latter could be recrystallised at -30°C using a 1:1 mixture of hexane/THF, furnishing the lithium alkoxide $[(\text{Li}(\text{OC}_2\text{H}_4\text{NMe}_2)_2)]_8$ (**2**) in a 50% isolated yield. X-ray crystallographic studies confirmed that **2** exhibits an octameric structure motif (Figure 2), as already reported by P. C. Andrews and co-workers in 2002.^[22a] This motif is reminiscent of that described for other lithium alkoxides such as lithium *tert*-butoxide.^[22b] It consists of alternating Li and O (as part of the alkoxide ligand) atoms forming an eight-membered ring prism. The presence of an internal Li–O bond [Li1–O3, 1.994(2) Å] makes this structure resemble a fused hexagonal prism and a cubane. The Li–O distances range from 1.899(2)–1.994(2) Å. Each lithium in the structure displays a distorted tetrahedral geometry, bonding to three oxygens and being further stabilised by the coordination of the pendant NMe_2 group from one of the alkoxide groups [average Li–N bond distance, 2.161 Å]. ^1H DOSY NMR studies suggest that some deaggregation of this octameric structure occurs in C_6D_6 solutions, as indicated by the estimated molecular weight ($M_w = 447 \text{ g mol}^{-1}$), which is consistent with the presence of pentamer/tetramer equilibrium in solution (error 9%).

Compound **2** was reacted with one and two molar equivalents of ZnEt_2 . By carefully comparing ^1H , ^{13}C and ^7Li NMR spectra of both putative species ($\text{LiOR}\cdot\text{ZnEt}_2$ and $2\text{LiOR}\cdot\text{ZnEt}_2$; $\text{R} = \text{OC}_2\text{H}_4\text{NMe}_2$) with those of their starting materials (LiOR and Et_2Zn), it can be proposed that both homometallic components have undergone co-complexation. This conclusion is supported by significant changes in the chemical shifts in the ^1H NMR

spectrum (see ESI for details) of relevant resonances from the alkoxide and Et groups. However, it should be noted that similar spectra were recorded for $\text{LiOR}\cdot\text{ZnEt}_2$ and $2\text{LiOR}\cdot\text{ZnEt}_2$. Attempts to isolate a pure complex by crystallisation were unsuccessful.

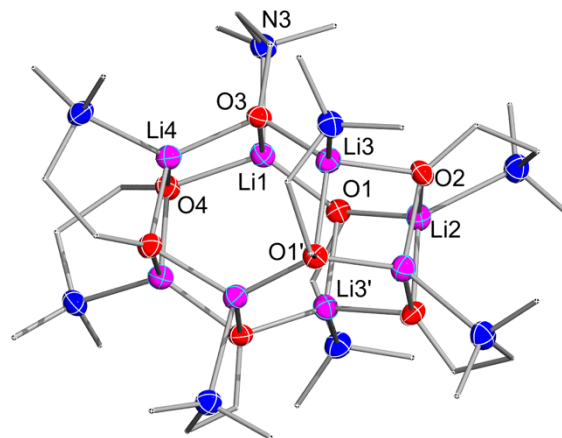


Figure 2. Molecular structure of $[\text{Li}(\text{CH}_2)_2\text{N}(\text{CH}_3)_2]_8$ (**2**). H atoms are omitted, and C atoms are drawn as wire frames for clarity. Symmetry transformations to generate symmetrical atoms: -x, y, 1/2-z. Thermal ellipsoids are set at 50% probability.

We then turned our attention to using ZnMe_2 as a precursor, which was reacted with 0.5 equiv of LiOR. This reaction yielded colourless crystals of $[(\text{Li}_7\text{OR}_6)^+\{(\text{LiZn}_4(\text{OR})_2(\text{Me})_8)^-\}]$ (**3**), whose structure in the solid state was established by X-ray crystallographic studies (Scheme 1b and Figures 3a,b). Exhibiting a polymeric chain structure, compound **3** comprises a heptanuclear lithium alkoxide $\{\text{Li}_7(\text{OR})_6\}$ cation and a novel heteroleptic zincate $[(\text{LiZn}_4(\text{OR})_2(\text{Me})_8)^-]$ anion, which are connected by medium-strength Li...Me electrostatic interaction [Li1–C18, 2.492(11) Å]. These type of interactions are responsible for the propagation of the polymeric structure (Figure 3c).

Interestingly, the Li:Zn and OR:Me ratios in this structure are consistent with the overall stoichiometry employed $\{2\text{LiOR}\cdot\text{ZnMe}_2\}_4$; however, the constitution of this complex is very unique. It can be envisaged as an intermediate between the structure of the homometallic species and those of other related alkali-metal organyl(alkoxide) compounds^[21,11b] where a discrete $\{\text{Zn}(\text{OR})_2(\text{R})_2\}^{2-}$ is formed. Thus, the octameric structure of LiOR (**2**) is cleaved, eliminating a $\{\text{Li}(\text{OR})_2\}^-$ fragment that has been sequestered by four equivalents of ZnMe_2 . The Li5 center adopts a linear geometry, being bonded to two alkoxide ligands [Li5–O4, 1.846(2) Å, O4Li5O4' angle, 180.0°]. Each oxygen also coordinates to two ZnMe_2 fragments, with one of the Zn centers receiving further stabilisation by the coordination of the NMe_2 group of the alkoxide backbone, closing a four-membered $\{\text{ZnOCN}\}$ ring. On the other hand, the heptanuclear lithium cation present in **3** forms a cage structure, where six lithium atoms are further stabilised by coordination to the NMe_2 of the alkoxide backbone, whereas the remaining Li (Li1 in Figure 3) interacts with the Me group of the zincate anion. The ^1H NMR spectrum of **3** in C_6D_6 shows relatively broad signals, indicative of some fluxionality present in solution. A distinct singlet at -0.36 ppm is observed, which can be assigned to the methyl groups of the zincate anion. ^1H DOSY NMR studies reveal that the mixed-

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metal/mixed-ligand constitution of the complex is retained in solution, with the methyl and alkoxide group signals exhibiting similar diffusion coefficients (see SI for details). Furthermore, the ^7Li NMR at room temperature shows three different signals at 0.88, 0.78 and 0.70 ppm, which is consistent with the presence of different chemical environments for Li, and aligns with the structure of **3** in the solid state.

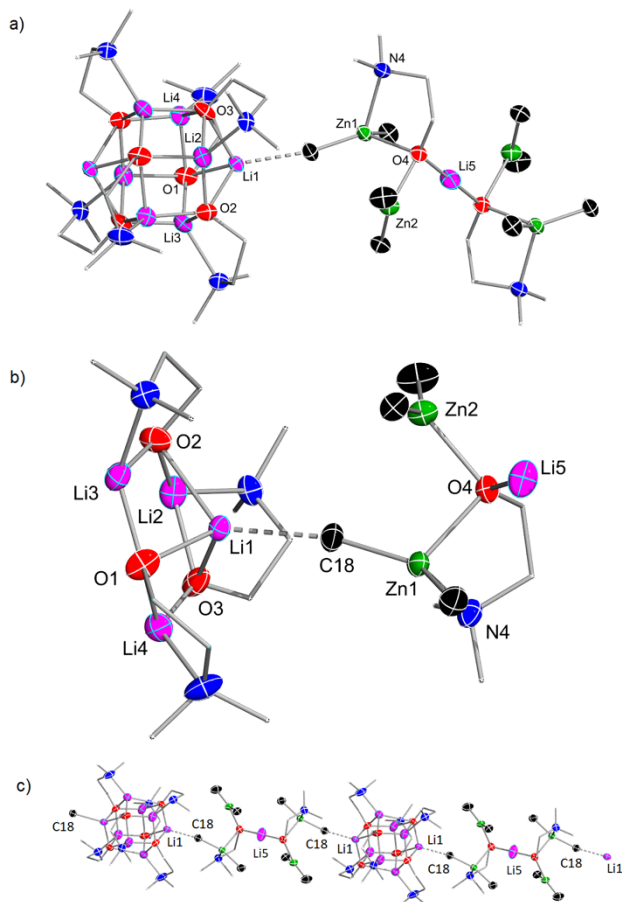


Figure 3. (a) Structure of $[\{\text{Li}_7(\text{OR})_6\}^+[\{\text{LiZn}_4(\text{OR})_2(\text{Me})_6\}^-]]$ (**3**). H atoms, disordered components are omitted, and C atoms are drawn as wire frames (except for Me groups of the zinc moiety) for clarity. (b) Asymmetric unit of compound **3**. (c) Polymeric chain structure of **3**. Symmetry transformations to generate symmetrical atoms: $-x+1, -y+1, -z+1; -x+2, -y+2, -z+2$. Thermal ellipsoids are set at 30% probability.

We next pondered whether changing the donor ability of the solvent could also influence the outcome of these co-complexation reactions. Swapping hexane by THF, a 2:1 mixture of LiOR and ZnEt_2 was stirred at room temperature for 2 h. Upon cooling to -5°C , colourless crystals of $[\text{Li}_6(\text{OR})_5\text{OZn}_3\text{Et}_3]$ (**4**) were obtained in a modest 10% yield. X-ray crystallographic studies revealed a new motif for this heterobimetallic complex (Scheme 1b and Figure 4). Exhibiting a contacted ion pair structure, **4** comprises a heptanuclear cluster made up of six Li atoms and one zinc center. The metal centers are interconnected by either bridging alkoxide ligands or one oxo anion (O4 in Figure 4). The latter coordinates to two Li atoms and Zn1 [Li6-O4, 1.901(5) Å, Li5-O4, 1.988(6) Å and Zn1-O4, 1.970(2) Å] within the cluster, as well as two additional ZnEt_2 fragments [Zn2-O4, 2.036(2) Å; Zn3-

O4, 2.031(2) Å]. Zn1 completes its distorted tetrahedral geometry by binding to a terminal Et group. Li6 in the cluster binds to only three O atoms, including O4, while the remaining Li atoms exhibit distorted tetrahedral environments, binding to three alkoxide groups, with one of them acting as a chelating ligand via its NMe₂ backbone [Li-O distances ranging from 1.897(6) to 2.170(6) Å].

Interestingly, the formation of **4** suggests that in THF, the highly aggregated cage structure of **2** is partially retained, forming a co-complex with ZnEt_2 . The incorporation of oxygen into the cage could be due to adventitious presence of moisture in the reaction media or traces of air.^[23] While the synthesis of **4** is reproducible, it should be noted that its formation likely occurs during the crystallisation process, as the ^1H NMR analysis of a 2:1 mixture of ZnEt_2 and LiOR in C_6D_6 solutions showed no evidence of this compound.

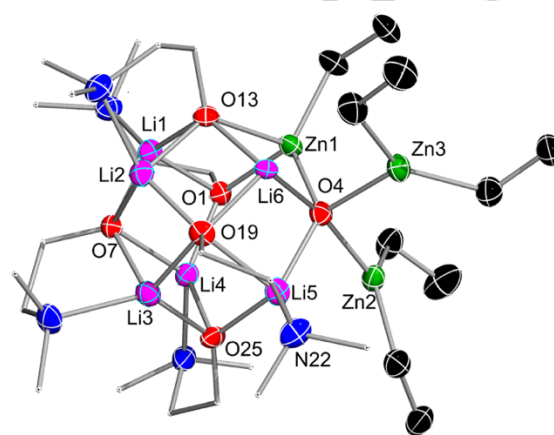
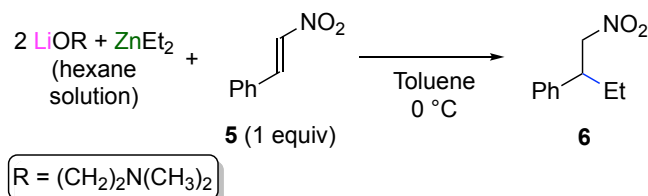


Figure 4. Molecular structure of $[(\text{LiOR})_5\text{LiOEt}_3\text{Zn}_3]$ (**4**). H atoms, disordered components are omitted, and C atoms are drawn as wire frames (except for alkyl groups of the zinc moiety). Thermal ellipsoids are set at 50% probability.

After conducting these structural investigations, we turned our attention to the reactivity of mixed-metal alkyl/alkoxide combinations. To explore this, we tested a 2:1 mixture of LiOR (R = $\text{C}_2\text{H}_4\text{NMe}_2$) and ZnEt_2 with nitroolefin **5** (Scheme 2). The *in-situ* formed 2LiOR: ZnEt_2 mixture (1 mmol) was added dropwise to a toluene solution (3 mL) containing *trans*- β -nitrostyrene (0.149 g, 1 mmol) at 0°C . The resulting yellow solution was stirred for 1 h. After removing the solvent carefully, the residual oil was analysed by NMR spectroscopy. The ^1H NMR of the reaction crude indicated almost complete conversion of the substrate, with residual signals from DMEA. The ^{13}C NMR spectrum confirmed the presence of the desired adduct, with the CH_3 group being significantly shielded at -2.9 ppm, likely due to the close proximity of the zinc atom. Additionally, the ^7Li NMR spectrum showed only one resonance corresponding to a single lithium species. The deshielding observed [0.81 vs 0.7 of $\text{Et}_4(\text{OR})_2\text{ZnLi}_2$] was probably due to the coordination of the nitro group. The corresponding nitroolefin **6** was isolated by column chromatography in 70% yield. This result demonstrates that, even though the desired higher-order zincate species was not formed, the transfer of the ethyl group mediated by the organozinc alkoxo complex proceeded smoothly. This aligns with recent findings showing that lithium alkoxides can enhance the reactivity of certain type of

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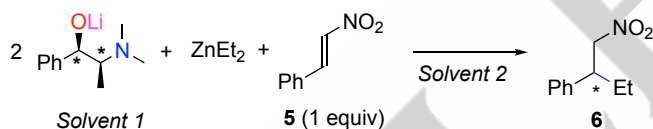
organometallic compounds.^[17] Thus, after confirming that the *in situ* prepared lithium organozinc alkoxo complex 2LiOR·ZnEt₂ was effective in promoting a Michael addition reaction with nitrostyrene **5** (Scheme 2), we aimed to further develop a chiral version of this transformation.



Scheme 2. Addition of 2LiOR·ZnEt₂ to nitroolefin **5**.

Inspired by the Brückner's work on the asymmetric sulfonylation of ephedrine-modified organozincates,^[24] we focused on developing an enantioselective protocol for the reaction described earlier, using the lithium alkoxide derived from the chiral amino alcohol (1*R*,2*S*)-*N*-methylephedrine (LiOR*). The results of our systematic investigations, which involved varying parameters such as temperature and solvent, are summarised in Table 1. Initially, we mixed LiOR* and Et₂Zn in hexane at RT in a 2:1 ratio. This mixture was then added to a toluene solution of nitrostyrene **5**, which had been pre-cooled to -50 °C. The solution was stirred at this temperature for 2 h before being quenched with water. The resulting product was obtained in a 90% isolated yield, but was essentially racemic (enantiomeric excess, ee: 5%) (Table 1, entry 1).

Table 1. Addition of 2LiOR*·ZnEt₂ to nitroolefin **5** under different conditions.



Entry	T (°C) ^[a]	Solvent 1	T (°C) ^[b]	Solvent 2	Yield of 6 (%)	ee (%)
1	RT	hexane	-50	Tol ^[c]	90	5
2	-50	hexane	-78	THF ^[d]	89	19
3	-50	THF	-78	THF ^[e]	80	1.8
4	-50	hexane	-78	THF ^[f]	75	30
5	-50	hexane	-78	THF ^[g]	70	37.3

[a] Co-complexation reaction. [b] Nucleophilic addition. [c] Tol: toluene [d] Molarity of the nitroolefin solution: 0.5 (0.25 mmol in 0.5 mL of THF); [e] Molarity of the nitroolefin solution: 0.25 (0.25 mmol in 1 mL of THF); [f] Molarity of the nitroolefin solution: 0.125 (0.125 mmol in 0.5 mL of THF); [g] Molarity of the nitroolefin solution: 0.125 (0.0625 mmol in 0.5 mL of THF). All reactions were quenched after 2 h. Yields of isolated product Enantiomeric excess (ee) determined by chiral GC according to the literature.^[25]

Notably, replacing toluene with THF under these conditions, increased the ee to 19%, indicating that the enantioselectivity was influenced by the solvent (Table 1, entry 2). Building on this finding, we replaced the hexane solution of the organometallic compound with an equivalent volume of THF. Under these conditions, however, the ee dramatically decreased to 1.8% (Table 1, entry 3). To optimise the reaction, we halved the molar equivalents of the substrate, while maintaining the same volume of THF (0.125 mmol in 0.5 mL of THF). This adjustment resulted

in an increase in ee by 10% (Table 1, entry 4). When we further reduced the substrate amount to 0.0625 mmol in 0.5 mL of THF (Table 1, entry 5), the ee improved to 37.3%. Despite these moderate ee values, they are significant, given that the formation of the zincate species was only partial, as by co-complexation studies of the achiral lithium alkoxide. Further investigations into the aggregation effects of LiOR are planned for future works.

Conclusion

In summary, by exploring the constitution of mixed alkoxide/alkyl complexes, a new series of heterobimetallic complexes has been isolated and structurally characterised. Co-complexation methods between LiOR and ZnR₂ have proven more effective than the deprotonative approach mediated by Li₂ZnEt₄ in relation to the aminoalcohol DMEA. The breakdown of the LiOR cluster has contributed to the formation of the complex. Although these findings suggest reasons why the formation of the desired higher-order zincate species Et₂OR₂ZnLi₂ did not occur or occurred only partially, novel type of organozincates with unprecedented architectures have been isolated, offering promising new applications.^[26]

Complexes between ZnEt₂ and a chiral nonracemic lithium alkoxide derived from ephedrine have been investigated for promoting an enantioselective Michael addition reaction to *trans*-β-nitrostyrene, with the corresponding adduct isolated in up to 37.3% ee. Further extension of this bimetallic chemistry to its asymmetric version is being pursued in our laboratories, and results will be reported in due course.

Supporting Information

Additional references cited within the Supporting Information.^[27-32]

Acknowledgements

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Conflict of Interest

The authors declare no conflict of interest.

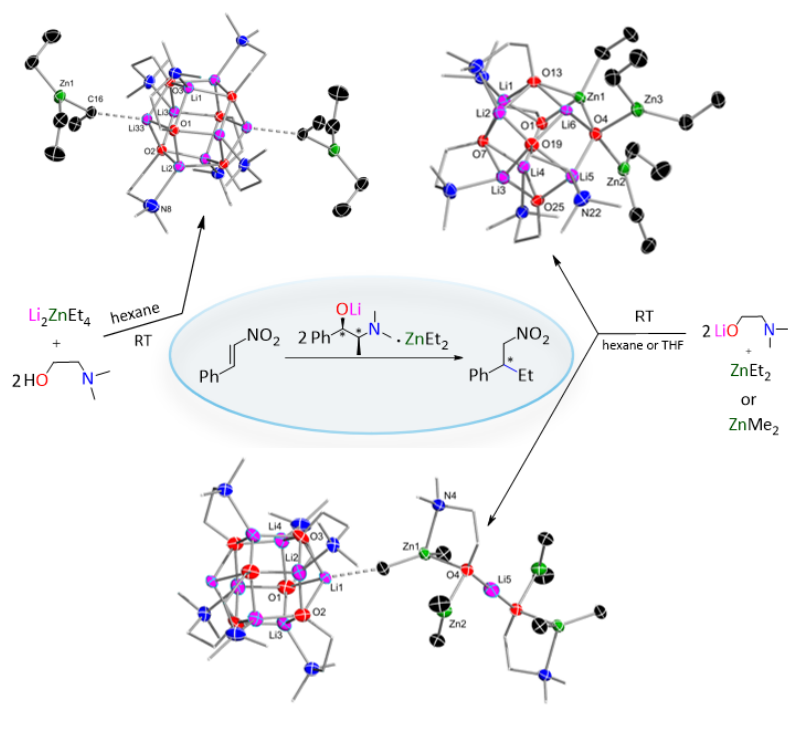
Keywords: aggregation • alkali metals • lithium • zinc • ate complexes

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RESEARCH ARTICLE

Entry for the Table of Contents



Novel structural motifs in alkali-metal zincate chemistry have been uncovered through co-complexation reactions of dialkylzinc derivatives with lithium alkoxides or via a deprotonative approach involving the higher-order zincate Li_2ZnEt_4 and dimethylethanolamine. Additionally, the effectiveness of complexes between ZnEt_2 and a chiral nonracemic alkoxide derived from (1*R*,2*R*)-*N*-methylephedrine in promoting enantioselective Michael addition reactions to *trans*- β -nitrostyrene has been investigated.

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