

C-N Bond Activation and Ring Opening of a Saturated N-Heterocyclic Carbene via Lateral Alkali-Metal-Mediated Metallation (AMMM)

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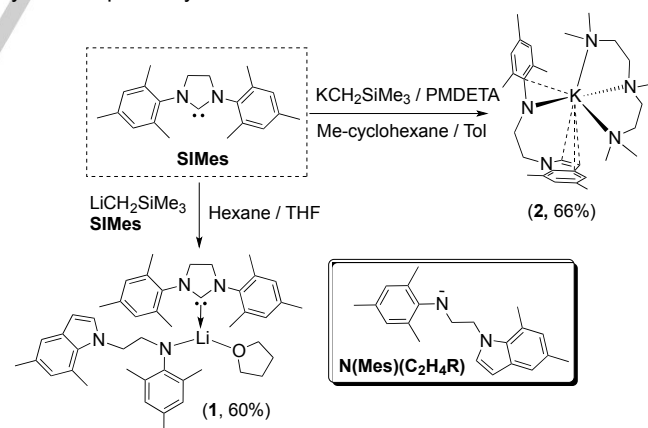
Abstract: Combining alkali-metal mediated metallation (AMMM) and N-heterocyclic carbene (NHC) chemistry, a novel C-N bond activation and ring-opening process is described for these increasingly important NHC molecules, which are generally considered robust ancillary ligands. Here, mechanistic investigations on reactions of saturated NHC **SIMes** (**SIMes** = $[\text{C}\{\text{N}(2,4,6\text{-Me}_3\text{C}_6\text{H}_2)\text{CH}_2\}_2]$) with group 1 alkyl bases suggest this destructive process is triggered by lateral metallation of the carbene. Exploiting co-complexation and trans-metal-trapping strategies with lower polarity organometallic reagents ($\text{Mg}(\text{CH}_2\text{SiMe}_3)_2$ and $\text{Al}(\text{TMP})/\text{Bu}_2$), key intermediates in this process have been isolated and structurally defined.

Since Arduengo's landmark isolation of the first N-heterocyclic carbene (NHC),^[1] an enormous amount of research activity has been devoted to advancing the applications of these special ligands, leading to important breakthroughs in transition-metal catalysis and organic synthesis^[2] as well as in main group chemistry.^[3] Many of these discoveries have been driven by the fine tunability, relative stability and robustness of these molecules as strong two electron sigma donors. Contrasting with the myriad of studies involving NHC-transition metal complexes,^[2] the use of these ligands in s-block metal chemistry has been limited to a few select investigations.^[4] Of these, key contributions from the groups of Arnold and Hill have demonstrated the excellent potential of NHCs for advancing s-block homogeneous catalysis,^[5] as well as for stabilizing novel Mg hydride clusters.^[6] Furthermore, the seminal work of Robinson^[7] on the deprotonation of **IPr** (1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene) at its C4 position (alkenic backbone) with *n*BuLi has pushed forward the applications of anionic NHCs,^[8] opening up a new construction point for the functionalization of these ligands. Other examples of direct C4-metallation of unsaturated NHCs have been reported using Na^[9] and K^[10] bases as well as mixed-metal systems such as sodium zincates^[11] or magnesiates.^[12] A novel example of this alkali-metal-mediated metallation (AMMM) involves the template base $[\text{Na}_2\text{Mg}_2(\text{TMP})_6(\text{nBu})_2]$ (TMP = 2,2,6,6-tetramethylpiperidine), which simultaneously deprotonates the backbone of **IPr** along with one Dipp (Dipp = diisopropylphenyl) substituent at its *para*-position.^[12] Related to that finding, Braunstein has also described the unexpected lateral lithiation of a $\text{CH}(\text{Me})_2$ wingtip

of a Dipp in a 4-amido-substituted NHC.^[13] Surprisingly, despite all this recent activity, the metallation of dihydro saturated NHCs, containing non-aromatic C_3N_2 rings has hardly been touched upon, probably as a dual consequence of being less robust than their unsaturated congeners and having reduced acidity of their backbone hydrogen atoms. This has been nicely illustrated for the contrasting reactivities of **IPr** and its saturated analog **SIPr** when treated with lithium metal, with the former undergoing C4 metallation whereas the latter affords a ring-cleaved amidinate complex, although the mechanism of this reaction is unknown.^[14]

Breaking new ground, here, in reporting the first metallation study between a saturated carbene and alkali-metal bases $[\text{MCH}_2\text{SiMe}_3]$ (M = Li, K), we disclose a novel s-block metal-mediated activation process. Moreover, structurally mapping these reactions using **SIMes** (**SIMes** = $[\text{C}\{\text{N}(2,4,6\text{-Me}_3\text{C}_6\text{H}_2)\text{CH}_2\}_2]$) as a case study, gives unique mechanistic insights into these transformations.

We started by reacting equimolar amounts of the silylalkyl reagents MR (M = Li, K R = CH_2SiMe_3) with **SIMes** at room temperature, which gave oily solids. Adding donor ligands (one extra equivalent of **SIMes** and THF for M = Li and tridentate N-donor PMDETA for M = K, Scheme 1) allowed isolation of complexes **1** and **2** as crystalline products in 61% and 66% yields respectively.



Scheme 1. Reactions of **SIMes** with $\text{MCH}_2\text{SiMe}_3$ (M = Li, K).

X-ray diffraction analysis of crystals of **1** and **2** revealed the presence of the same non-symmetrical amide ligand, containing mesityl and $\text{C}_2\text{H}_4\text{R}$ arms, where R is a 1-indolyl substituent (Fig. 1), presumably resulting from activation of neutral NHC **SIMes**. Reflecting the different coordination preferences of lithium and potassium, in **1** this amide ligand binds terminally to the metal via its amido N (N3 in Fig. 1). Contrastingly, in **2**, a chelating

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bonding mode is observed, where the K-N_{amide} bond is supported by a series of stabilizing π -electrostatic interactions with the indolyl C=C bonds, as well as with the C_{ipso} of the mesityl group. To engage in these π -contacts, K adopts a near perpendicular disposition to the planes defined by both aromatic rings. The coordination sphere of the alkali-metals is completed by a THF molecule and one neutral **SIMes** ligand for **1**, whereas in **2** K is chelated by tridentate PMDETA.

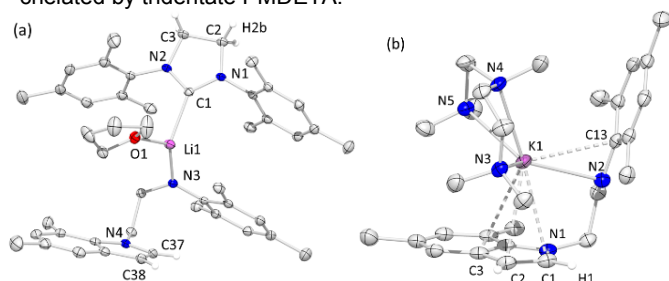
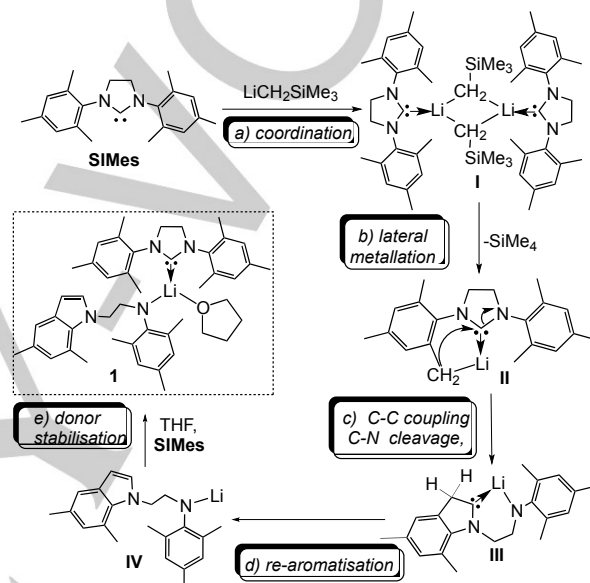


Figure 1. Molecular structures of **1** (a) and **2** (b) with thermal ellipsoids at 30% probability. Hydrogen atoms except for those attached to C37, C38, C2 and C3 in **1** and to C1 and C2 in **2** are omitted for clarity.

Although NHCs are generally accepted as robust spectator ligands, a number of studies have reported that when coordinated to transition metals they can undergo both C-H and C-N activation.^[15] To date, this reactivity has been missing in s-block chemistry, with the exception of Hill's^[16] work in the formal insertion of BeH₂ into a C-N bond of the unsaturated NHC **IPr** and the aforementioned reduction of **SIPr** with Li metal.^[14] The formation of **1** and **2** shows that under the conditions studied both alkali-metal MCH₂SiMe₃ reagents are able to promote the cleavage of the **SIMes** C-N bond, that is significantly different from the reactivity observed when potassium bis(trimethyl)silyl amide is treated with unsaturated NHCs, where only donor-acceptor coordination of the NHC to the K centre is observed.^[17] While as far as we can ascertain the activation of **SIMes** to give the anionic group present in **1** and **2** is unprecedented, it should be noted that investigations on other ring expanded carbenes containing N-mesityl substituents lead to the insertion of the carbene into one of their own *ortho*-methyl C-H bonds upon heating, furnishing N-alkyl indole products.^[18] Interestingly, the same studies have also reported the thermal resistance of **SIMes** to undergo insertion, even after prolonged periods of time (72h at 70°C).

In **1** and **2**, the transformation of **SIMes** into the anionic amide N(Mes)(C₂H₄R) can be rationalised assuming that lateral metallation of one *ortho*-Me of its mesityl group occurs (**II** in Scheme 2). This transformation is probably favoured by initial NHC pre-coordination to the alkali-metal alkyl complex (**I** in Scheme 2). This will not only activate the organometallic reagent by reducing its aggregation,^[19] but will also bring the *ortho*-Me into close proximity to the reactive alkyl group, akin to the complex-induced proximity effect (CIPE) in directed-*ortho* metallation.^[20] As mentioned above, lateral deprotonations in NHC chemistry are extremely rare with only two examples described for unsaturated NHCs.^[12,14] Notably, while these species are stable and can be structurally characterised, putative intermediate **II** must rapidly change to the ring open product **III** (Scheme 2), through the coupling of the benzylic CH₂

group of the mesityl substituent and the carbenic carbene, with subsequent cleavage of the C-N bond in the heterocycle to form **III**. This step resembles the mechanism proposed for ring expansion seen for NHC adducts of hydrosilanes and beryllium hydrides, where migration of anionic hydride to the electrophilic carbenic atom seems rate-limiting step.^[21] Having H substituents adjacent to its carbenic site, **III** will not be stable^[22] and it will undergo a typical 1,2-hydrogen shift process,^[23] rearomatising the five-membered ring, furnishing the N-alkyl indole fragment present in **1** and **2**. Donor stabilization of **IV** (which in the case of M= Li is an additional equivalent of **SIMes** and THF) should lead to the crystalline products **1** and **2** (when M= K) (Scheme 2).

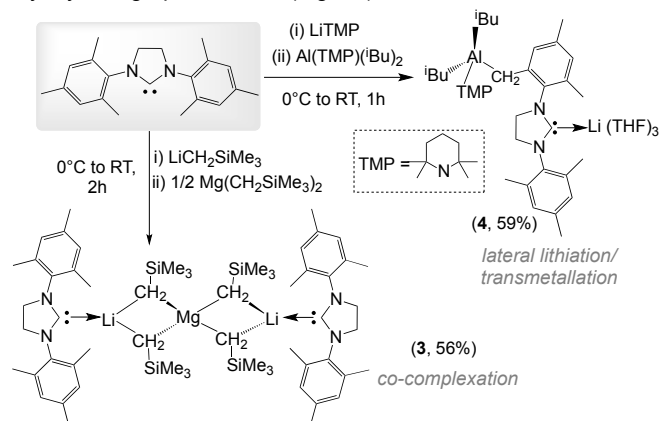


Scheme 2. Proposed mechanism for the formation of **1**

Attempts to isolate or even detect the postulated intermediates in Scheme 2 by reducing the temperature of the reaction were unsuccessful. Recently in collaboration with Mulvey we introduced the concept of trans-metal-trapping (TMT),^[24] where addition of low polarity organometallics such as Al or Ga species to lithiated substrates containing fragile anions allows stabilization and entrapment of these sensitive intermediates. Applying this approach to the lithiation of **SIMes**, we found that by using Mg(CH₂SiMe₃)₂ (0.5 equivalents) as an organometallic trap it is possible to intercept the postulated coordination adduct **I** (Scheme 2), which is isolated as the tetraorganomagnesiates **3** in a 56% yield (Scheme 3). X-ray crystallographic studies confirmed the bimetallic Weiss-motif^[25] constitution of **3** which can be envisaged as a co-complexation product of two equivalents of [SiMe₃Li(CH₂SiMe₃)] with one Mg(CH₂SiMe₃)₂ (Fig. 2a). Isolation of **3** implies that by forming a tetraalkylmagnesiates anion, containing significantly less polar and therefore less reactive metal-C bonds, the lateral metallation of **IMes** is inhibited.

In an attempt to trap the proposed metallated species prior to the ring-opening step we moved to the bimetallic combination LiTMP/Al(TMP)₂/Bu₂, where the steric mismatch between the two single-metal components precludes their co-complexation to form a lithium aluminate though they can still cooperate in a

sequential manner to promote aluminatation of aromatic molecules.^[24] ^1H NMR monitoring of the reaction of **SIMes** with LiTMP in deuterated THF^[26] demonstrated the formation of $\text{N}(\text{Mes})(\text{C}_2\text{H}_4\text{R})$ amide fragment resulting from activation of the C-N bond in the carbene. On the other hand performing the same reaction in the presence of the aluminium trap $[\text{Al}(\text{TMP})/\text{iBu}_2]$ furnished lithium aluminate **4** in a 59% yield (Scheme 3), whose molecular structure was determined by X-ray crystallographic studies (Fig. 2b).



Scheme 3. Trans-metal trapping (TMT) stabilizing strategies of reactive intermediates to give **3** and **4**.

Exhibiting a contacted ion pair structure, Li and Al are connected by an anionic **SIMes** ligand, which has been deprotonated at one *ortho*-Me of a mesityl ring, coordinating to Al via this benzylic C (C20 in Fig 2); whereas Li is attached to its normal carbenic position (C1 in Fig 2). The formation of **4** can be rationalised considering the fast transmetalation of the lateral lithiated intermediate **II** (Scheme 2) to the more carbophilic $[\text{Al}(\text{TMP})/\text{iBu}_2]$ fragment. Consistent with this interpretation, and illustrating the synergistic reactivity of this Li/Al bimetallic partnership, even when they operate in a non-synchronised manner, we found that on its own weak base $[\text{Al}(\text{TMP})/\text{iBu}_2]$ is unable to metallate **SIMes**. Notably, **4** is stable in C_6D_6 solutions at room temperature and no evolution to the C-N bond cleavage amide anion is observed over time.^[27] This stability can probably be attributed to the combination of the significantly greater covalent nature of the Al-C in **4** compared to the Li-C bond in the proposed lithium intermediate **II**, and the remote location of its benzylic position, sheltered by the bulky $[\text{Al}(\text{TMP})/\text{iBu}_2]$ fragment, with respect to the carbenic C [C20...C1, 3.701(5) Å], which should also disfavour a possible intramolecular C-C coupling step.

While this lateral metallation of **SIMes** is unprecedented, Aldridge has recently described intramolecular borylation at an *ortho*-Me group of an ancillary **IMes** ligand of an Ir complex using LiBH_4 as a boron source.^[15a] Interestingly, while from a mechanistic point of view, the formation of this C-H bond activation product is manifestly different to that of **4**, as it involves an oxidative addition step via an Ir intermediate (in our case the +1 oxidation state of the alkali metal is immutable), its structure shares several common features with that of **4**. Thus this work builds bridges between two key areas in synthesis,

namely transition-metal C-H activation and main group metal mediated metallation.

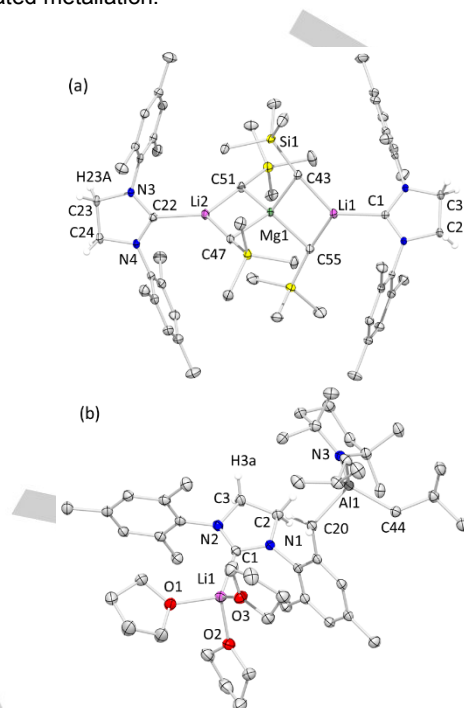
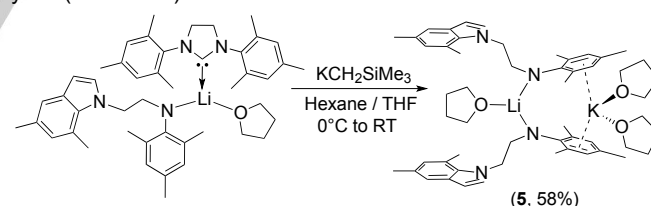


Figure 2. Molecular structures of **3** (a) and **4** (b) with thermal ellipsoids at 30% probability. Hydrogen atoms except those attached to C2, C3, C23 and C24 in **3** and to C2, C3 and C20 in **4** are omitted for clarity.

Since **1** still contains a neutral **SIMes** ligand coordinated to the Li centre, we pondered whether it could be also activated. While an excess of $\text{LiCH}_2\text{SiMe}_3$ does not seem to be effective, the reaction with the heavier alkali metal alkyl $\text{KCH}_2\text{SiMe}_3$, led to the isolation of the novel mixed lithium/potassium complex **5** in 58% yield (Scheme 4).



Scheme 4. Synthesis of potassium bis(amido) lithiate **5** via activation of the ancillary **SIMes** ligand of **1**.

The molecular structure of **5** displays two $\text{N}(\text{Mes})(\text{C}_2\text{H}_4\text{R})$ anions coordinated to the lithium centre via their N atoms, forming a novel potassium amidolithiate complex. Contrastingly, K forms a series of $\pi\text{-K}\cdots\text{C}$ interactions, engaging in a η^6 -fashion with the mesityl fragments of the two amido ligands. These well-defined distinct bonding modes of Li and K contrast with those found in other mixed lithium/potassium amides such as $[\text{LiK}(\text{TMP})_2(\text{PMDETA})]$ where both metals are bridged by amide N atoms.^[27] Potassium is further solvated by two molecules of THF while another THF completes the distorted trigonal planar geometry around Li (sum of the angles around Li, 359.8°), with a noticeably obtuse NLiN angle [133.3(4)°]. This distortion is

probably imposed by the formation of a coordination pocket for the $\{K(THF)_2\}^+$ cation with the mesityl rings. Structurally defined potassium lithiates are extremely rare, with a recent example of a potassium diboryllithiate reported by Nozaki^[28] in 2016, where similar Li-B/K-aryl interactions are observed.

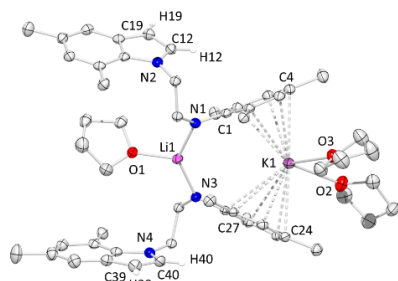


Figure 4. Molecular structure of **3** with thermal ellipsoids at 30% probability. Hydrogen atoms except for those attached to C12, C19, C39 and C40 are omitted for clarity.

In summary by describing the unprecedented metallation of the saturated NHC **SIMes** using Li and K alkyl bases, we have disclosed a novel alkali-metal-mediated C-N bond activation and ring opening process in NHC chemistry, which seems to be initiated by lateral metallation of the carbene. Exploiting co-complexation and trans-metal-trapping strategies with lower polarity organometallics reagents, potential key intermediates in this process, which otherwise would be too reactive to detect, have been isolated and structurally defined.

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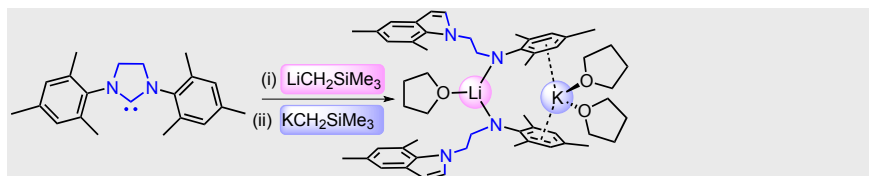
Keywords: alkali-metal, C-N activation, metallation, mixed-metal chemistry; N-heterocyclic carbenes

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COMMUNICATION



Co-lateral damage! Lateral metallation of saturated NHC **SiMes** triggers a destructive process, inducing C-N bond activation and ring opening of the five-membered heterocyclic ring.

Alberto Hernán-Gómez,* Alan R. Kennedy and Eva Hevia*

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