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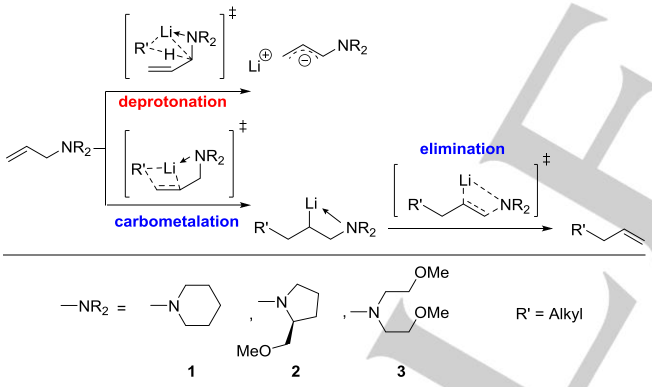
Controlling the coordination sphere of alkyllithiums results in selective reactions with allylic amines

Ulrike Kroesen, Christian Unkelbach, Daniel Schildbach and Carsten Strohmann*[a]

Abstract: In this communication, a selective way and a better understanding to control the reaction of allylic amines with metalorganic bases depending on the amine handle as well as the metalorganic base is presented. Depending on the number of coordinating groups within the amine handle either a selective carbometalation or deprotonation reaction can be performed. By changing the alkali metal within the base from lithium to sodium or potassium, a change of chemoselectivity takes place and the reaction of piperidinoallylamine can be controlled.

Alkali metalation reactions represent a versatile and important type of reaction in organic and metalorganic synthesis. They allow the creation of highly reactive molecular building blocks and further reaction with electrophiles.[1] One challenge is the synthesis via competing deprotonation and carbometalation of allylic amines and the understanding of metastable metalated species.[2] Especially non-substituted allylic amines are only sparsely studied as the concurrence of the two reactivities proved difficult to control.[3] The carbometalation results in a β-metalated alkylamine species which is usually not stable and will decompose via elimination yielding a lithium amide and an alkene species (Scheme 1).[4]

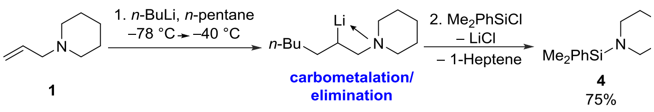


Scheme 1. Competing deprotonation and carbometalation with further decomposition of allylic amines.

Three different approaches are imaginable to control this concurrence. On the one hand, reactivities might be influenced by coordinating solvents. On the other hand, intramolecular donor groups can be incorporated in the allylic amines to benefit from complex-induced proximity-mediated reactivity tuning.[5] Thirdly, the change of the metal within in the metalorganic base might change the chemoselectivity. In this paper we put focus on the influence of intramolecular donating groups and in addition showed the influence of changing the alkali metal in one selected example. Quantum chemical calculations in combination with structural determination via X-ray diffraction explain this influence.

Three systems with different side arm properties and coordinating capacities have been investigated: Piperidine, optically active bidentate (*S*)-methoxypyrrolidine (SMP)[6] and tridentate bis(2-methoxyethylamine) (BMEA) were introduced in the amine side arm (scheme 1, compounds **1**, **2** and **3**). Irrespective of the solvent, a specific chemoselectivity could be determined depending on the number of coordinating groups (see SI). The experimental results show a carbometalation followed by an elimination of a lithium amide and an alkene species for the piperidine-substituted allylic amine (one coordinating centre). In presence of the SMP handle (two coordinating centres) and the BMEA group (three coordinating centres) a deprotonation could be observed.

Comparing these results of the three investigated allylic amines, a decisive influence of the amine side arm on the reaction behavior is shown. If only one coordinating side arm is present in the substrate, the degree of coordination is insufficient to facilitate α-deprotonation of the allyl moiety. This is regardless of introducing coordinating solvents like THF which have no influence on the observed chemoselectivity. Instead, the alkyl lithium approaches the electron richest position in the molecule, the double bond, and undergoes carbometalation. As the resulting charge is not sufficiently stabilized by the absence of a π-system within the molecule, an elimination of the lithium amide takes place and the corresponding alkene is formed (Scheme 2).[4]



Scheme 2. Carbometalation and elimination of the piperidine substituted allylic amine **1**.

In case of the tridentate BMEA side arm, a precisely opposite chemoselectivity is present. Due to the two additional coordinating groups, the alkyllithium reagent can be precoordinated intramolecularly and thus be brought into proximity with the proton to be abstracted. Independently of the solvent and the alkyllithium reagent used, a deprotonation of the allylic amine can be carried out selectively. The bidentate SMP-substituted amine has comparable reactivity and also undergoes

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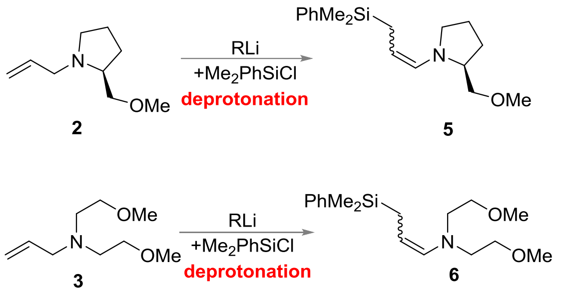
selective deprotonation (Scheme 3). Quenching of the lithiated species of **2** and **3** with chlorosilanes yields an E/Z mixture of the corresponding γ-silylated enamine species. The E/Z ratio depends on the solvent and is described in detail in the supporting information.[7]

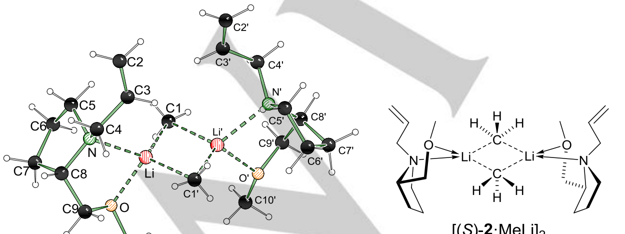


Scheme 3. Deprotonation of the allylic amines **2** and **3**.

To sum up, the chelation of the lithium by at least two donor atoms is essential for the deprotonation. The solvent affects exclusively the reactivity of the metallated species but has no influence on the chemoselectivity. Thus, it was not taken into account for further studies.

To understand and explain the experimental observations, additional quantum chemical calculations in the gas phase on the M062X/6-31+G(d) level of theory have been carried out.[8] Calculations have been performed for all three model systems for their reaction with ethyllithium. For obtaining a correct statement by quantum chemical calculations, the choice of an adequate model system is crucial. As the SMP-substituted allylic amine does not undergo any reaction with methyllithium, the reactive intermediate could be crystalized to find a suitable model system for the calculations.

Crystals of the bidentate allylic amine **2** with methyllithium could be obtained and investigated by X-ray structural analysis (Figure 1). The compound is a dimer in which the lithium centres are bridged by the two methyl anions and each lithium centre is chelated by the amino and ether function of the SMP group. While only few dimeric structures of methyllithium coordinated by diamine ligands are known in literature,[9] **7** represents the first structure of a N,O-coordinated methyllithium dimer.



[(*S*)-**2**·MeLi]$_2$
7

Figure 1. Molecular structure of **7** in the crystal.[10] (symmetry operations: −x+2, −y+2, z). Selected bond lengths [Å] and angles [°]: C1−Li‘ 2.190(2), C1−Li 2.246(3), C9−Li 2.778(3), Li−O 2.030(2), Li−C1‘ 2.190(2), Li−N, 2.201(2), Li−Li’ 2.423(4), L‘−C1−Li 66.22(10), C1‘−Li−N 118.86(12), C1‘−Li−C1 113.77(10).

Based on the species **7**, a dimeric model has been chosen for quantum chemical calculations for all three investigated allylic amines in their reaction with ethyllithium.

As shown in figure 2, the carbometalation barrier of the piperidine substituted allylic amine of 66 kJ/mol is 16 kJ/mol lower than the barrier of the deprotonation [82 kJ/mol].

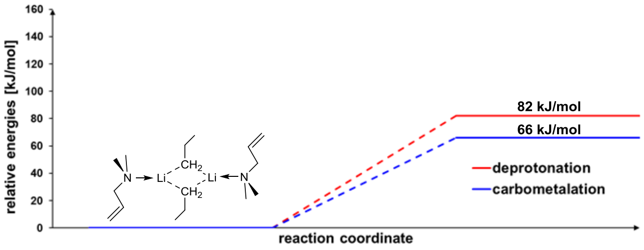


Figure 2. Competing carbometalation and deprotonation, M062X/6-31+G(d).

In contrast, for the SMP-substituted allylic amine a barrier of 129 kJ/mol is calculated for the addition of ethyllithium to the double bond (Figure 3). With only 93 kJ/mol the deprotonation barrier is 36 kJ/mol lower. The BMEA-substituted allylic amine shows barriers of 106 kJ/mol for the deprotonation and 139 kJ/mol for the carbometalation reaction (Figure 4). This is consistent with the experimental results.

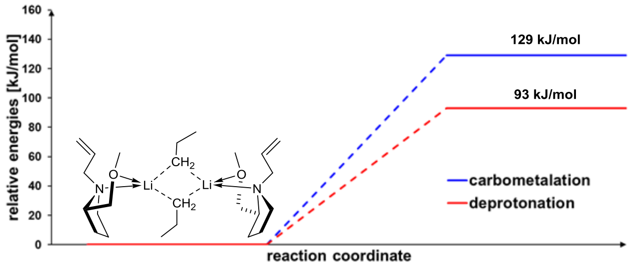


Figure 3. Competing carbometalation and deprotonation, M062X/6-31+G(d).

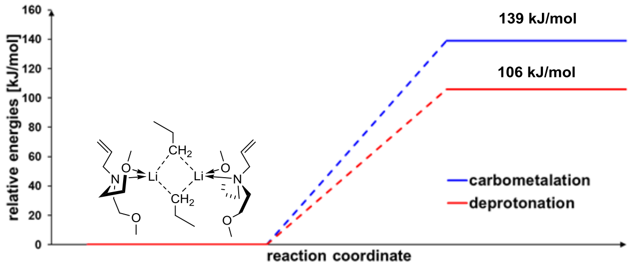
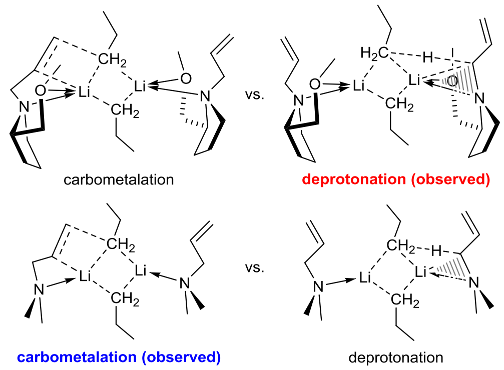


Figure 4. Competing carbometalation and deprotonation, M062X/6-31+G(d).

In order to understand the energetic differences, the geometry of the three optimized structures (starting material, two transition states) should be discussed in more detail. The largest difference is in the coordination sphere of the lithium cation. The analysis of the bond lengths in the transition states of the carbometalation shows a possible explanation for the high activation barrier in comparison to the deprotonation reaction in case of the amines with more than one coordinating group within the amine handle.



Scheme 4. Competing transition states of the carbometalation and deprotonation with the SMP-substituted allylic amine (top) and the piperidine-substituted allylic amine (bottom).

To allow an approximation of the alkyllithium to the double bond, one of the nitrogen centres of the coordinating handle is extended in its bond lengths to the lithium if two or more coordinating groups exist in one amine handle (Scheme 4). This way a lower coordination number can be made possible for the lithium, which is necessary for the carbometalation. To reach this, the preferred N-Li-coordination is weakened. For the piperidine-substituted allylic amine with only one coordinating group the nitrogen-lithium bond length is short for both the starting material as well as the transition state for the carbometalation. In contrast, in the transition state for the deprotonation, the formation of a highly strained three-membered Li-N-C ring is necessary to facilitate the abstraction of the α-hydrogen atom of the allyl moiety. For the allylic amines with a further coordinating group the oxygen coordination replaces the nitrogen coordination. Because of this lower ring tension exists and the deprotonation barrier is lowered (Figure 5). This phenomenon has already been observed in the reactivity of a PDMTA·(nBuLi)$_2$ dimer.[11]

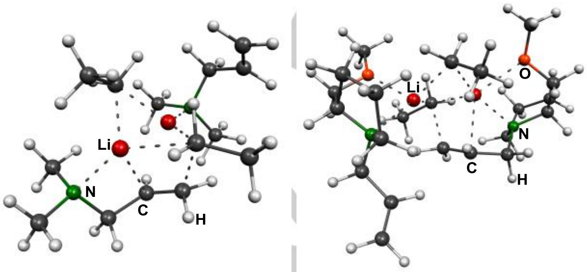
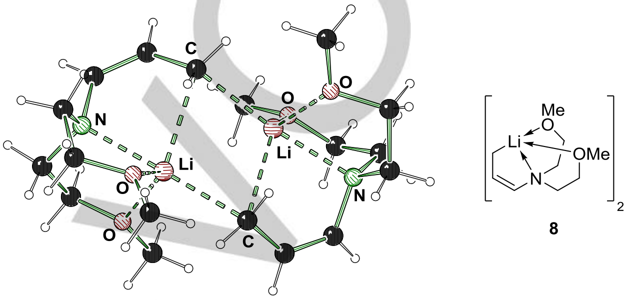


Figure 5. Transition states of the carbometalation with ethyllithium with one coordinating group (left) and two coordination groups (right).

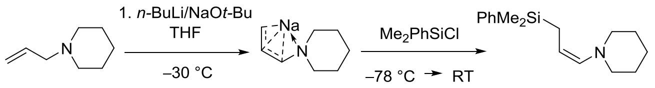
Single crystals of one of the deprotonation products could be obtained which underline the experimental and theoretical results (Figure 6). Compound **8** crystallizes from *n*-pentane/diethylether in the triclinic crystal system in the space group $P\bar{1}$. The asymmetric unit contains a complete molecule of the dimeric compound. This lithiated allylic amine can also be considered as an α-lithiated, *cis*-configured enamine. In addition to the two bridging carbanionic centres, each lithium atom also forms contacts to the three coordination sites of the BMEA handle.



8

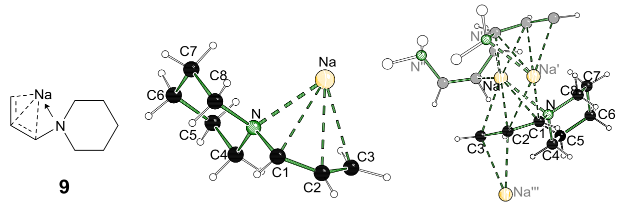
Figure 6. Molecular structure of **8** in the crystal.[10] Selected bond lengths [Å] and angles [°]: C7−C8 1.336(3), C8−C9 1.428(3), C16−C17 1.340(3), C17−C18 1.423(3), Li1−O2 2.037(4), Li1−N1 2.175(4), Li1−O1 2.227(4), Li1−C18 2.277(4), Li1−C9 2.426(4), Li2−O(4) 2.078(4), Li2−O(3) 2.150(4), Li2−N2 2.172(4), Li2−C9 2.261(4), Li2−C18 2.486(4), O2−Li1−N1 79.87(14), O1−Li1−C9 101.21(15), C18−Li1−C9 104.64(16), Li2−C9−Li1 73.39(14), Li1−C18−Li2 71.97(14).

In order to further study the possibility of prevention of the carbometalation of the piperidine substituted allylic amine, the influence of the alkali metal on the structure and reactivity was investigated. In case of using alkyllithium reagents, Li-C contacts are comparatively short. Thus, the concurrence of carbolithiation and deprotonation is strongly influenced by the coordination sphere of the lithium cation. Within the chemistry of alkyl sodium or alkyl potassium reagents, higher and more complex aggregates may be formed.[12] Less approximation of the metal to the carbanionic centre is needed, the coordination sphere of the alkali metal gets less important compared to organolithium chemistry and other reactive centres become accessible. By changing the metalating system from an alkyllithium reagent to a mixed-metal system containing eihter potassium *tert*-butoxide or sodium *tert*-butoxide, a deprotonation reaction could be observed and the silylated enamine was obtained in yields up to 73% (Scheme 5). No traces of carbometalation or elimination products were detected.



1 **9** **10**

Scheme 5. Selective deprotonation of the allylic amine **1** by using the sodium containing Schlosser's base.



9

Figure 7. Lewis formula (left), asymmetric unit of **9** in the crystal (middle)[10], as well as extended coordination environment of the sodium centres and the allyl moiety (right). Symmetry operations: #1 –x, y–1/2, –z+1/2, #2 –x, –y+2, –z, #3 –x, y+1/2, –z+1/2. Selected bond lengths [Å] and angles [°]: C1–Na 2.719(2), C2–Na 2.749(2), C3–Na 2.669(2), N–Na 2.4622(17), N–C1 1.445(3), C1–C2 1.373(3), C2–C3 1.387(3), N–C1–Na 64.20(10), C1–C2–C3 131.0(2), N–C1–C2 121.3(2).

Single crystals of the highly reactive intermediate could be obtained (Figure 7). Compound **9** crystallized in the monoclinic crystal system in the space group $P2_1/c$. The asymmetric unit contains a complete monomer of the solvent-free 2D coordination polymer. The sodium centre is intramolecularly coordinated in a η^3-mode by the cisoid allyl moiety.

The further reaction of **9** with electrophiles has been investigated. First results show that only the γ-substituted product is formed as it is the case when reacting the lithiated analogues of **2** and **3** with silanes. The ratio of the *cis* and *trans* isomers depends strongly on the electrophile used. For example, trimethylchlorosilane has a high favour of the *cis*-configured product whereas trimethylchlorostannane has a distinct preference for the *trans* product. Additional investigations will be performed in the future to clarify the preference of either the *cis* or the *trans* isomer.

Within this paper the strong influence of the amine handle as well as the metalating reagent, especially the alkali metal, on the structure and reactivity of allylic amines could be shown. Quantum chemical calculations deliver a good explanation for the solvent independent selective carbometalation and elimination for the allylic amine with only one coordinating handle. In contrast, allylic amines with two or more intramolecular coordinating groups perform a selective deprotonation. By isolating highly reactive intermediates the structure of metalated allylic amines could be well described. Also the sodiated structure shows clearly the influence of the alkali metal. Using the sodium containing Schlosser's base instead of alkyl lithium reagents delivers a nice solution to perform a deprotonation instead of a carbometalation of the piperidine-substituted allylic amine. In the future, further investigations on the formation of *cis* and *trans* substituted products will be performed.

Keywords: allylic compounds • lithiation • structure-reactivity relationships • X-ray diffraction • chemoselectivity

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[10] CCDC 1569697, CCDC 1569698 and CCDC 1569699 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. For details, see also the Supporting Information.

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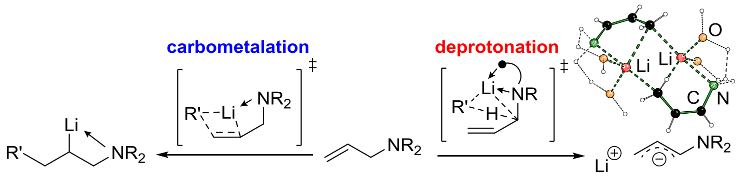

Either a selective carbometalation or deprotonation of allylic amines with alkyllithiums can be performed. The coordination sphere of the lithium centre in the corresponding reactions can be controlled depending on the number of coordinating groups within the amine handle.

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