Lithiation

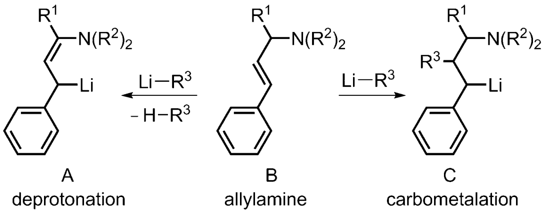
International Edition: DOI: 10.1002/anie.201702377
German Edition: DOI: 10.1002/ange.201702377

The Reactivity of Benzyl Lithium Species is Regulated by Intermediate Structures

*Ulrike Kroesen, Lena Knauer, and Carsten Strohmann**

Abstract: *The reaction of benzyl lithiums is an important aspect in organic and organometallic synthesis. Reported herein are detailed insights into the reactivity of benzyl lithiums as regulated by intermediate structures. By discussing the carbometalation of allylamines and the reaction of the formed benzyl-lithium compounds with electrophiles, the influence of the metal as well as the solvent on the electronic structure of the intermediate is described. This molecular structure strongly influences the reactivity of these intermediates. By choosing the appropriate reaction conditions, the regioselectivity of reactions with electrophiles can be regulated. With trimethylchlorosilane in n-pentane a selective reaction at the para-position takes place. In contrast, selective reaction at the benzylic position, with trimethylchlorostannane in tetrahydrofuran (THF) as a solvent, is accomplished.*

Allylamines are often used as important building blocks in the synthesis of pharmaceuticals, for example Terbinafine.[1] The deprotonation of allylamines with organometallic bases and their use as homoenolate equivalents has already been widely investigated.[2] By using the Lochmann–Schlosser base, allylamines can be easily deprotonated and functionalized at the γ-position.[3] In contrast, allylamines offer a second reactivity with organolithiums, as carbometalation of the double bond is possible (Scheme 1).[4] This type of reaction is relatively unknown and leads to the intermediates described in the present paper.



Scheme 1. The two possible reaction pathways: deprotonation and carbometalation of allylamines by organolithium compounds.

During our studies on the carbometalation of allylamines we observed a selective carbometalation in *n*-pentane when using *tert*-butyllithium and will now describe the conversion of the benzyl-lithium compound with electrophiles. A formal negative charge at the benzylic position is formed. The reaction of benzyl anions with electrophiles is well established as the main reaction, whereas the reaction in the aromatic *para*-position is only observed as a side reaction.[5] The position of the lithium within the carbometalated product is affected by the solvent and strongly influences the intermediate electronic structure. Thus there is an impact on the reactivity with added electrophiles (Figure 1).

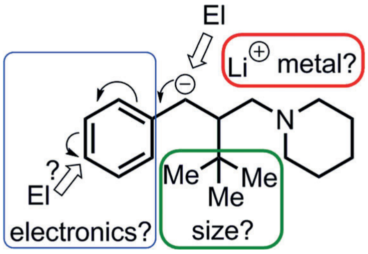
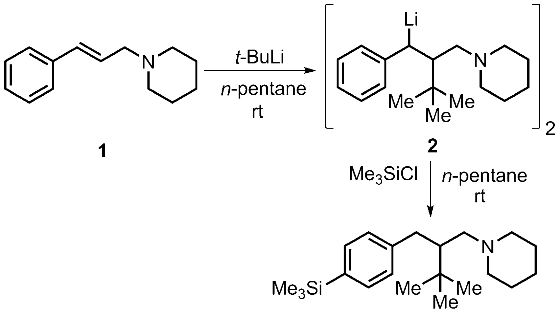


Figure 1. Factors affecting the reaction of electrophiles at either the benzylic or *para* position of benzyl-lithiums.

Herein we present a possible pathway to perform the reaction with electrophiles at the *para*-position as the main reaction. In a first experiment the carbometalation reaction of the piperidinoallylamine **1** in *n*-pentane was carried out with *tert*-butyllithium, followed by reaction with trimethylchlorosilane. After a proton transfer, the *para*-substituted product **3** was obtained in an isolated yield of 82 % (Scheme 2).

It was of special interest to identify the intermediate structure of the organolithium compound to explain the outcome of this reaction. The structure of the intermediate



3 82%

Scheme 2. Carbolithiation of the piperidinoallylamine **1** with *tert*-butyllithium and further reaction with trimethylchlorosilane at the *para*-position in *n*-pentane.

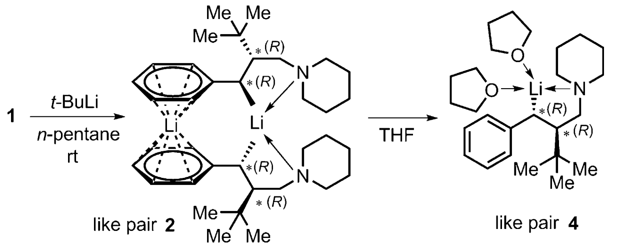
---

[*] U. Kroesen, L. Knauer, Prof. Dr. C. Strohmann
Anorganische Chemie, Technische Universität Dortmund
Otto-Hahn-Straße 6, 44227 Dortmund (Germany)
E-mail: carsten.strohmann@tu-dortmund.de

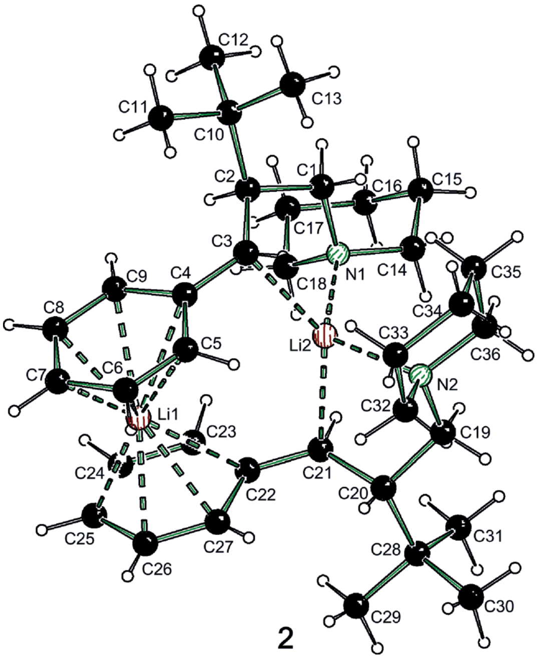
Supporting information and the ORCID identification number(s) for the author(s) of this article can be found under: https://doi.org/10.1002/anie.201702377.

carbometalated species in *n*-pentane was successfully isolated and characterized (Scheme 3).

The solvent-free carbolithiated piperidinoallylamine crystals were monoclinic, space-group $P2_1$, and consisted of two similar dimers in the asymmetric unit. It is homochiral, but only the like diastereomer can be found in the crystal, and the lithium is positioned *trans* to the *tert*-butyl group (Figure 2). One of the lithium centers (Li1) is η^6-coordinated by the phenyl groups of two monomers while the other lithium (Li2) is coordinated in a η^1-coordination mode by the benzylic carbon atoms of the monomers, as evidenced by the short carbon–lithium distances [C3-Li2 2.301(9) Å, C21-Li2 2.294(7) Å]. Li2 is also coordinated by the two nitrogen centers of the piperidine rings. This structure is unique, as only few examples of lithium cations coordinated by π-systems, instead of carbanions, are known in literature.[6] Also it should be highlighted that there are two lithium atoms in the same molecule, but in different chemical environments.[7] This molecular structure is, to the best of our knowledge, the first example for an alkyl lithium compound with one lithium–π-system contact and one lithium–carbanion contact in a single molecule.



Scheme 3. Formation of two intermediate carbolithiated structures **2** and **4**.



2

Figure 2. Molecular structure of **2** in the crystal.[8] One of two molecules of the asymmetric cell is described. Selected bond lengths [Å]: C2–C3 1.500(6), C3–C4 1.398(7), C4–C5 1.435(6), C5–C6 1.370(6), C4–C9 1.455(6), C8–C9 1.376(6), C3–Li2 2.301(9), C20–C21 1.517(6), C21–C22 1.392(7), C22–C23 1.445(6), C23–C24 1.389(6), C22–C27 1.458(6), C26-C27 1.377(6), C21–Li2 2.294(7).

As a second step, the influence of the solvent on the structure as well as on the reactivity was investigated. By adding tetrahydrofuran (THF) as a polar solvent, the structure in the crystal as well as in solution changed. Single crystals of the carbolithiated product coordinated by THF were obtained as triclinic crystals (space group $P\bar{1}$). The asymmetric unit contains one monomer with a lithium coordinated by the benzylic anion, the piperidine nitrogen center, and two THF molecules (Figure 3). The benzylic group is less shielded than in the solvent-free dimer and the negative charge is more concentrated on the carbanionic center.

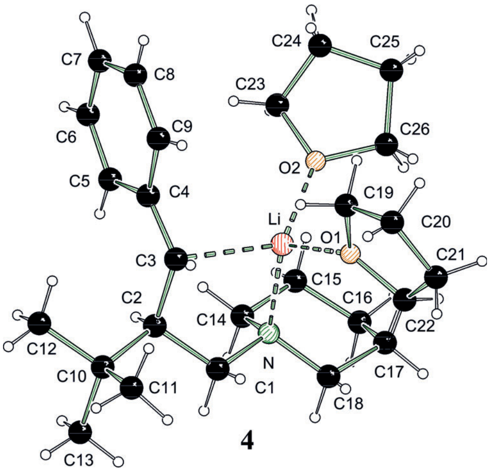


Figure 3. Molecular structure of **4** in the crystal.[8] Selected bond lengths [Å] and angles [°]: C2–C3 1.418(2), C3–C4 1.425(3), C4–C5 1.418(2), C5–C6 1.374(3), C4–C9 1.419(2), C8–C9 1.380(3), N–Li 2.134(3), C1–Li 2.424(3), C3–Li 2.297(3), Li–O1 1.935(3), Li–O2 1.975(3); C2-C3-C4 125.3(2).

To compare the molecular structure in the solid state with the solution structure, NMR measurements were carried out. In the ^{7}Li NMR spectrum, with THF as a solvent, only one signal at $\delta = 0.8$ ppm was observed. Furthermore the ^{1}H NMR and ^{13}C NMR spectra show signals corresponding to a monomeric species. Crystals of the solvent-free carbolithiated piperidinoallylamine had poor solubility in nonpolar solvents. As the ^{1}H and ^{13}C NMR spectra in benzene show, more than one stereoisomer exists in solution. The ^{7}Li NMR spectrum shows two different signals, one broad signal from $\delta = -1.3$ to -4.2 ppm in the benzylic region as well as one sharp signal at $\delta = -7.3$ ppm, which is indicative of a lithium cation in between two π-systems.[10] This data suggests that in solution a dimer is formed, where two different lithium cations exist, one in between the two phenyl groups, and one in a benzylic environment.

The structure in the solid state matched the solution-state NMR data. To strengthen these results, quantum chemical calculations of the NMR chemical shifts were performed using DFT-methods at the B3LYP/6-311+G(2d,p)//B3LYP/6-31+G(d) level.[10] For the monomeric species a ^{7}Li chemical shift of $\delta = 1.2$ ppm was calculated, and fits well to the measured data. For the dimeric species the calculations result in chemical shifts of $\delta = 0.7$ and -5.7 ppm. The calculations are in accordance with the observed ^{7}Li NMR measurements, most notably the chemical shift of $\delta = -7.3$ ppm is an explicit sign of a lithium–aryl sandwich complex in solution.[9]

To underline the crystallographic results and provide insight into the influence of the intermediate structure on possible reactions with electrophiles, quantum chemical calculations were conducted. The Connolly surface was calculated to show the accessibility of reactive centers in the examined intermediates (Figure 4). The electrostatic potential of the solvent-free structure shows good accessibility at the *para*-position and also underlines that the benzylic position is relatively shielded. A bulky electrophile such as trimethylchlorosilane can only react in the less shielded *para*-position. The intermediate structure in the solid state as well as the corresponding quantum chemical calculations indicate clearly that the electronic structure can lead to the *para*-substituted product as the main product of the reaction of the benzyl-lithium compound with electrophiles.

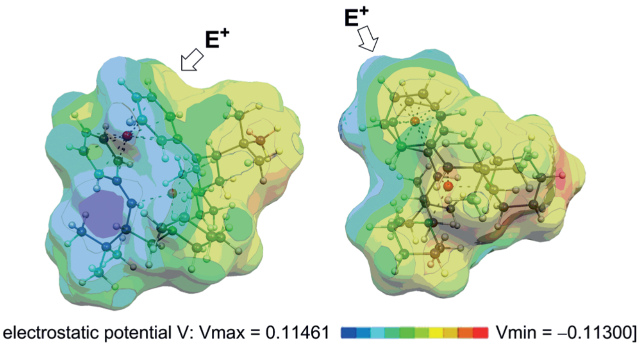
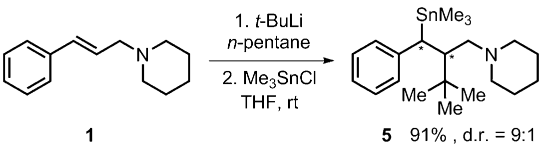


Figure 4. Visualization of the electrostatic potential of **2** from the sideview (left) and frontview (right) [MEP (Connolly surface, probe-radius 1.6 Å); B3LYP/6-31+G(d).[10]

Additional calculations of the NBO charges on the B3LYP/6-31+G(d) level complete these results. In the dimeric molecule NBO charges are −0.589 and −0.601 at the benzylic positions and −0.420 and −0.417 at the *para*-positions. As the benzylic position is shielded and the charges do not differ significantly, a reaction in the benzylic position is hindered in comparison to the reaction in the *para* position. In the case of the monomeric molecule, the benzylic position is less shielded in comparison to the dimeric structure. The NBO charge in the benzylic position amounts to −0.669 in comparison to −0.353 in the *para*-position, thus making a reaction of electrophiles at the benzylic position more probable.

In general benzyl lithiums react, in less polar solvents, by undergoing inversion from a backside attack, as we have demonstrated in our studies on α-lithiated benzylsilanes.[11] In the presented example the backside of the molecule is significantly shielded by the *tert*-butyl group. Furthermore, there is only one intramolecular handle (the piperidino group) and, in a polar solvent such as THF, the lithium cation can be detached from the carbanionic center. These arguments show that the known reaction path with inversion of the configuration might be energetically disfavored and other competing reaction paths might become more relevant.

In experimental studies the influence of the intermediate structure on the reactivity was examined. After the carbometalation reaction in *n*-pentane, THF was added and the reaction with the electrophile was carried out. As the reaction with trimethylchlorosilane showed a 1:1 mixture of the benzyl-substituted and the *para*-substituted product, the experiment gives first hints that the changing structure, depending on the solvent, has an essential influence on the reactivity. In comparison to trimethylchlorosilane, an experiment with trimethylchlorostannane was carried out. By adding THF we have been able to show a selective reaction at the benzylic position with a yield of 91% of **5** and a diastereomeric ratio of 9:1 (Scheme 4).[12] The experiment shows that it is possible to control the regioselectivity of the reaction by knowing the behavior of the intermediate structure. Also, the experiment shows a high diastereoselectivity (9:1). In further experiments the influence of the metal, the solvent, and the electrophile on the diastereoselectivity will be examined.



Scheme 4. Carbolithiation of the piperidinoallylamine and further reaction with trimethylchlorostannane in THF.

In conclusion, our studies on the carbometalation of allylamines have revealed the importance of the choice of solvent and its influence on the intermediate structure of benzyl-lithium compounds. We also showed the effect that structure has on the reactivity of the metalated species. Depending on the solvent and electrophile we carried out a selective reaction at either the benzylic position or the *para*-position of the phenyl group. Calculations together with experimental results lead to well-grounded explanations for the reactivity of these benzyl-lithium compounds. The intermediate structure strongly influences the reaction mechanism pathway of electrophilic addition and therefore results in the regioselectivity of this reaction. Additionally, the solvent-free intermediate structure represents one of only a handful of lithium structures with two nonequivalent lithium cations, one of which is part of a lithium–aryl sandwich complex. It is the first known example of an alkyl lithium compound having one lithium–aryl sandwich complex and one lithium coordinated by a carbanionic center.

Acknowledgments

We thank the Deutsche Forschungsgemeinschaft (DFG) for financial support. U.K. thanks the FCI for a Chemiefonds Fellowship.

Conflict of interest

The authors declare no conflict of interest.

Keywords: allylic compounds · lithiation · regioselectivity · structure-activity relationships · X-ray diffraction

---

[1] B. Sigurgeirsson, S. Billstein, T. Rantanen, T. Ruzicka, E. di Fonzo, B. J. Vermeer, M. J. Goodfield, E. G. Evans, *Br. J. Dermatol.* **1999**, *141*, 5 – 14.

[2] a) H. Ahlbrecht, U. Beyer, *Synthesis* **1999**, 365 – 390; b) F. Haeffner, M. A. Jacobson, I. Keresztes, P. G. Williard, *J. Am. Chem. Soc.* **2004**, *126*, 17032 – 17039.

[3] a) H. Ahlbrecht, A. Kramer, *Chem. Ber.* **1996**, *129*, 1161 – 1168; b) L. Lochmann, J. Pospísil, D. Lím, *Tetrahedron Lett.* **1966**, *7*, 257 – 262; c) M. Schlosser, *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 701 – 706; *Angew. Chem.* **1974**, *86*, 751 – 756.

[4] a) S. Klein, I. Marek, J. F. Poisson, J. F. Normant, *J. Am. Chem. Soc.* **1995**, *117*, 8853 – 8854; b) S. Norsikian, I. Marek, S. Klein, J. F. Poisson, J. F. Normant, *Chem. Eur. J.* **1999**, *5*, 2055 – 2068; c) C. Unkelbach, C. Strohmann, *J. Am. Chem. Soc.* **2009**, *131*, 17044 – 17045.

[5] a) S. G. Koller, U. Kroesen, C. Strohmann, *Chem. Eur. J.* **2015**, *21*, 641 – 647; b) C. Strohmann, K. Lehmen, K. Wild, D. Schildbach, *Organometallics* **2002**, *21*, 3079 – 3081; c) M. G. Davidson, D. Garcia-Vivo, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, *Chem. Eur. J.* **2011**, *17*, 3364 – 3369; d) D. R. Armstrong, M. G. Davidson, D. Garcia-Vivo, A. R. Kennedy, R. E. Mulvey, S. D. Robertson, *Inorg. Chem.* **2013**, *52*, 12023 – 12032; e) C. Mück-Lichtenfeld, H. Ahlbrecht, *Tetrahedron* **1999**, *55*, 2609 – 2624.

[6] Examples for lithium cations coordinated by a π-system: a) S. Kohrt, S. Dachwitz, C. G. Daniliuc, G. Kehr, G. Erker, *Dalton Trans.* **2015**, *44*, 21032 – 21040; b) C. Üffing, R. Koppe, H. Schnöckel, *Organometallics* **1998**, *17*, 3512 – 3515; c) M. I. Arz, D. Gei, G. Schnakenburg, A. C. Filippou, *J. Am. Chem. Soc.* **2016**, *138*, 4589 – 4600; d) S. Horchler, E. Parisini, H. W. Roesky, H.-G. Schmidt, M. Noltemeyer, *J. Chem. Soc. Dalton Trans.* **1997**, 2761 – 2763; e) F. Lips, J. C. Fettinger, P. P. Power, *Polyhedron* **2014**, *79*, 207 – 212.

[7] Molecular structures with two different lithium cations, one of them coordinated by a π-system: a) Q. F. Mokuolu, P. A. Duckmantion, P. B. Hitchcock, C. Wilson, A. J. Blake, L. Shukla, J. B. Love, *Dalton Trans.* **2004**, 1960 – 1970; b) B. Eichhorn, H. Noth, T. Seifert, *Eur. J. Inorg. Chem.* **1999**, 2355 – 2368; c) R. Bomparola, R. P. Davies, S. Hornaeur, A. J. P. White, *Dalton Trans.* **2014**, *43*, 14359 – 14367.

[8] CCDC 1530477 (**2**) and 1530478 (**4**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

[9] R. H. Cox, H. W. Terry, *J. Magn. Reson.* **1974**, *14*, 317 – 322.

[10] Detailed information on the used theoretical methods see: a) V. H. Gessner, S. G. Koller, C. Strohmann, A.-M. L. Hogan, D. F. O'Shea, *Chem. Eur. J.* **2011**, *17*, 2996 – 3004; b) K. Götz, V. H. Gessner, C. Unkelbach, M. Kaupp, C. Strohmann, *Z. Anorg. Allg. Chem.* **2013**, *639*, 2077 – 2085.

[11] H. Ott, C. Däschlein, D. Leusser, D. Schildbach, T. Seibel, D. Stalke, C. Strohmann, *J. Am. Chem. Soc.* **2008**, *130*, 11901 – 11911.

[12] NOE-experiments were ambiguous because of the equal size of substituents. Crystallization of the product structure to determine the main diastereomer has not succeeded.

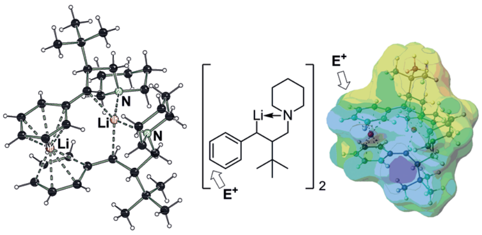
Manuscript received: March 6, 2017
Revised: March 23, 2017
Final Article published: ■■ ■■, ■■■■

Communications

Lithiation

U. Kroesen, L. Knauer,
C. Strohmann* ____________ ■■■■–■■■■

The Reactivity of Benzyl Lithium Species is Regulated by Intermediate Structures



A benzyl-lithium complex, with non-equivalent environments for its two lithium centers, leads to unexpected regioselective reactions with electrophiles (E^+) at the *para*-position. By changing the solvent to tetrahydrofuran, a monomer is formed and electrophiles react at the benzylic position.