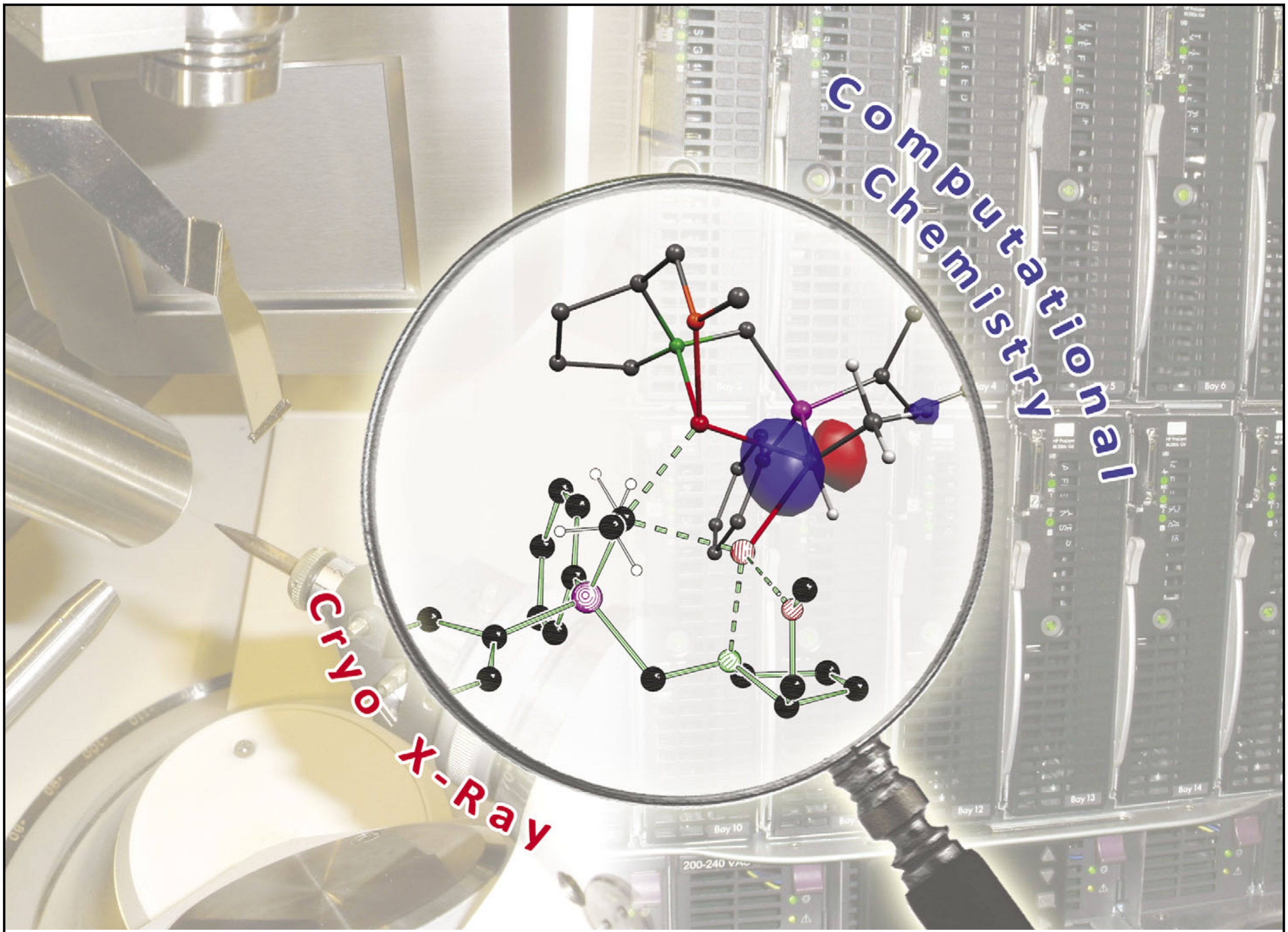

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A diastereomerically enriched, dimeric organolithium compound and the stereochemical course of its transformations

The diastereoselective α-lithiation of a chirally functionalised ethylsilane is reported which furthermore reveals the lithiated product to possess a novel dimeric structure with defined configurations at the two metalated carbon centres. Quenching of the dimeric species with Me_3SnCl proceeds under inversion with a d.r. of up to 97:3.

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COMMUNICATION

A diastereomerically enriched, dimeric organolithium compound and the stereochemical course of its transformations†

Christian Unkelbach, Bors C. Abele, Klaus Lehmen, Daniel Schildbach, Benedikt Waerder, Kerstin Wild and Carsten Strohmann*

Received 21st September 2011, Accepted 4th November 2011
DOI: 10.1039/c1cc15872d

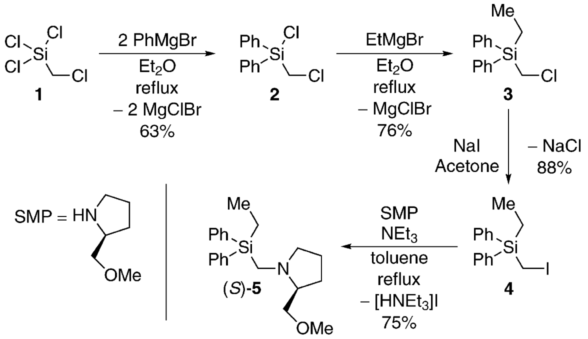
A dimeric α-silylated ethyllithium compound is presented featuring stereogenic metalated carbon centres with defined configurations. It can be generated by diastereoselective deprotonation of the corresponding ethylsilane. Reaction with Me_3SnCl proceeds under inversion and the transfer of the stereoinformation is possible with dr's of up to 97 : 3.

Highly stereomerically enriched organolithium compounds are versatile and sought-after synthetic intermediates in stereoselective syntheses.[1] A silicon centre next to the metalated carbon centre plays an important role in stabilizing its configuration and can serve as a synthetic break point in the later steps of a synthetic protocol.[2] In the past, α-silylated highly diastereomerically enriched organolithiums have been reported which have been successfully employed in the transfer of the chiral information on the metalated carbon centre in further transformations.[3] The synthetic potential of silicon-substituted organolithium reagents so far has been limited to diastereoselective deprotonation reactions of silanes which bear a second stabilizing group besides the silicon centre next to the methylene group undergoing metalation, *i.e.* allyl-, benzyl- or trimethylsilylmethyl silanes.[4] However, alkylsilanes other than methylsilanes have not been successfully subjected to metalation attempts in the past. Thus, our initial investigations concerned the question whether an ethylsilane as the most basic example for an alkylsilane with a longer side-chain could be readily metalated next to the silicon centre.

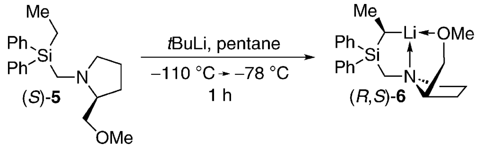
Starting compound (*S*)-**5** was obtained in a four-step synthesis using standard procedures in an overall yield of 32% (Scheme 1).

Using *tert*-butyllithium as the base, the lithiation of (*S*)-**5** can be conducted at low temperatures in pentane yielding α-lithiated product **6** after a reaction time of 1 h (Scheme 2).

In addition, the resulting lithiated species can be successfully crystallised from pentane/toluene. In contrast to previously published structures of silyl-substituted optically active alkyllithiums which are exclusively monomeric,[5] (*R*,*S*)-**6** forms a dimeric aggregate in the solid state (Fig. 1).



Scheme 1 Synthesis of optically active ethylsilane (*S*)-**5**.



Scheme 2 Deprotonation of (*S*)-**5** with *tert*-butyllithium.

(*R*,*S*)-**6** crystallises from pentane/toluene in the monoclinic crystal system, space group *C*2. The asymmetric unit contains one molecule which then forms the C_2-symmetric dimer $[(R,S)\text{-}\mathbf{6}]_2$. Each lithium centre shows contacts to both metalated carbon centres as well as to the nitrogen and oxygen donors of their respective SMP moiety. The central structural motif of the dimer is a four-membered C–Li ring formed by the two metalated carbon and the two lithium atoms. This ring exhibits a slight kink which is reflected by an angle of 10.2° between the C1–Li–C1′ and the C1–Li′–C1′ planes' normals. Despite nominally possessing five contacts each, the configuration at the metalated carbon centres can be unambiguously assigned as *R* since the angle between each carbon and the two lithium centres is only 65.7°.[6] The metalated carbon centres of each moiety are distinctly pyramidalised with a sum of the angles around each carbanionic unit (consisting of C1, C2, H1 and Si) of 330.4°. This grade of pyramidalization is remarkably close to a tetrahedral environment and considerably more eminent than in monomeric silyl-substituted organolithiums or in comparable, centrosymmetric dimeric α-silylated secondary alkyllithiums.[4,7]

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† Electronic supplementary information (ESI) available: Experimental, computational and crystallographical data. CCDC [836557 and 836558]. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1cc15872d

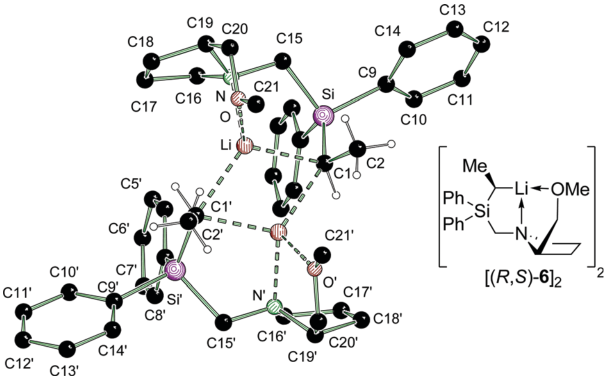
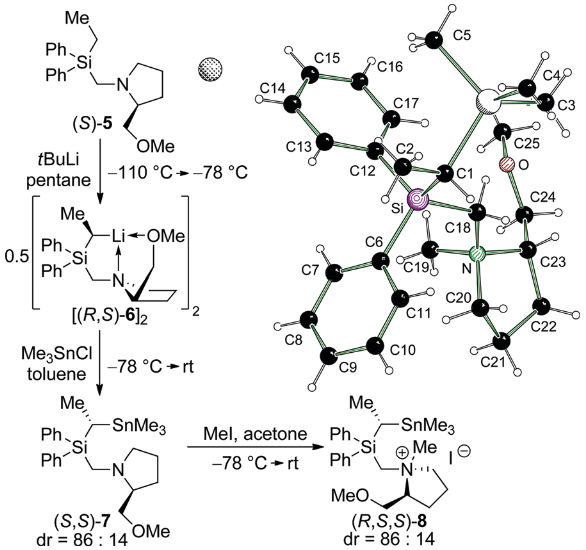


Fig. 1 Molecular structure and numbering scheme of $[(R,S)\text{-}\mathbf{6}]_2$ (some hydrogen atoms omitted for clarity).[6] Selected bond lengths (Å) and angles (°): Si–C1 1.827(2), Li–C1 2.281(3), Li–C1′ 2.305(4), Li–Li′ 2.488(6), Li–C1–Li′ 65.7(1), C1–Li–C1′ 113.6(1), C2–C1–Si 113.0(2), H1–C1–C2 114.0(1), H1–C1–Si 118.7(3).

Quenching of (*R*,*S*)-**6** was performed using Me_3SnCl at −78 °C to ensure an immediate and stereoselective reaction under mild conditions. Respective stannylated compound (*S*,*S*)-**7** was afforded in 91% yield and a dr of 86 : 14 (determined *via* ^1H NMR). The absolute configuration of the major stereoisomer which is formed could be determined after quaternization of the SMP nitrogen centre with iodomethane and crystallization of the resulting ammonium iodide species (*R*,*S*,*S*)-**8** (Scheme 3).

It was observed that the major stereoisomer obtained in the experiment exhibits (*S*)-configuration at the stannylated carbon centre. This corresponds to a reaction of the lithiated species with the chlorostannane under inversion of the configuration at the metalated carbon centre. This stereochemical reaction course is known *e.g.* for benzyl- or allyllithium species with a planarized "carbanionic" centre without free coordination sites at the lithium.[1,3,8] While the latter is also fulfilled in the dimeric species $[(R,S)\text{-}\mathbf{6}]_2$—both lithium centres exhibit four contacts and are sterically shielded by the organic hull—the lithiated stereogenic carbon centres are tetrahedral rather than planar.



Scheme 3 (left) Lithiation/quenching sequence towards (*S*,*S*)-**7** and subsequent quaternization of SMP nitrogen with iodomethane. (right) Molecular structure and numbering scheme of (*R*,*S*,*S*)-**8** exhibiting (*R*)-configuration at the quaternary nitrogen and (*S*)-configuration at the metalated carbon centre.

Table 1 Influence of the temperature on the stereoselectivity of the lithiation/Me_3SnCl quenching sequence of (*S*)-**5** to obtain (*S*,*S*)-**7**

Entry	Solvent	$T_{\text{lithiation}}$/°C	$T_{\max}{}^{a}$/°C	$T_{\text{quenching}}$/°C	dr
1	Pentane	−110	−78	−78	86 : 14
2	Pentane	−78	−78	−78	73 : 27
3	Pentane	−40	−40	−78	66 : 34
4	THF	−78	−40	−78	—[b]
5	Pentane	−90	20	−78	86 : 14
6	Pentane	−40	20	−78	66 : 34
7	Pentane/THF[c]	−40	−20	−78	91 : 9
8	Pentane/TMEDA[c]	−40	−20	−78	97 : 3

[a] Highest temperature to which the reaction mixture was allowed to warm prior to quenching. [b] No lithiation of (*S*)-**5** detected. [c] THF and TMEDA added at −20 °C.

The α-deprotonation of (*S*)-**5** was also investigated using theoretical methods: computations conducted using the M052X method[9] and 6-31 + G(d) basis set reveal a barrier of 63 kJ mol^{-1} for the abstraction of the *pro-R* α-proton by *tert*-butyllithium corresponding to a slow, controlled deprotonation at low temperatures as demonstrated in the experiment. In comparison, the abstraction of the *pro-S* proton is 67 kJ mol^{-1}. The small difference of 4 kJ mol^{-1} between the two diastereo-differentiating transition states reflects the tendency of the stereoselectivity under kinetic conditions (86 : 14) which disallow for an epimerization of the configuration at the metalated carbon centre. Consecutively, we found that the dr observed in the experiment was governed by the initial temperature at which the deprotonation was performed (Table 1, entries 1–3).

Warming the reaction mixture to 20 °C for at least 1 h prior to quenching with Me_3SnCl at −78 °C had no effect on the dr (*cf.* Table 1, entries 5 and 6). This indicates a remarkable stability of the configuration at the metalated carbon centers of $[(R,S)\text{-}\mathbf{6}]_2$ in the absence of epimerization processes even at room temperature. However, once a coordinating component like TMEDA or THF is added to a reaction mixture containing $[(R,S)\text{-}\mathbf{6}]_2$ and the mixture allowed to warm to −20 °C, an alteration of the resultant dr of up to 97 : 3 ensued (Table 1, entries 8 and 9). This indicates the occurrence of an epimerization with a further enrichment of the diastereoisomer which is obtained preferentially under kinetic reaction conditions. It can be assumed that an intermediary cleavage of $[(R,S)\text{-}\mathbf{6}]_2$ and the other possible diastereomeric dimers to monomeric THF or TMEDA solvates takes place which decreases the barrier for an interconversion of the diastereomers into each other so that the epimerization towards the most stable dimeric species, $[(R,S)\text{-}\mathbf{6}]_2$, can proceed at −20 °C, resulting in a further enrichment of $[(R,S)\text{-}\mathbf{6}]_2$ and improved dr's in the quenching experiment. It should be noted that even from reaction mixtures containing both $[(R,S)\text{-}\mathbf{6}]_2$ and stoichiometric amounts of THF or TMEDA, only the former, dimeric species could be isolated rather than solvates or other hetero- or homochiral dimers.[10] As such, we assume that it is the dimeric species which is responsible for the observed stereoselectivity with Me_3SnCl even in the presence of coordinating additives. The HOMO of the dimeric species $[(R,S)\text{-}\mathbf{6}]_2$ was computed to examine the possibility of an electrophilic attack under inversion as proposed after the experimentally determined stereoselectivities of the quenching reactions

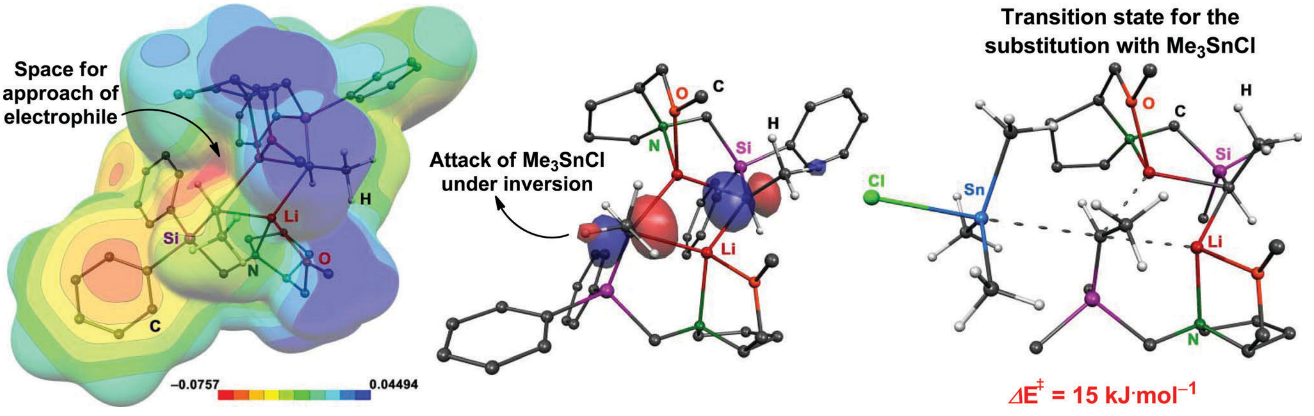


Fig. 2 M052X/6-31G(d)-optimised structure of [(*R*,*S*)-**6**]$_2$ (some hydrogen atoms omitted for clarity). (left) Conolly surface (probe radius 1.4 Å) mapped with electrostatic potential. (middle) Visualization of the HOMO of [(*R*,*S*)-**6**]$_2$ (Molekel representation;[10] surface cut-off = 0.065). (right) Transition state of the substitution reaction of simplified[11] [(*R*,*S*)-**6**]$_2$ with Me_3SnCl.

(Fig. 2). It was found that, despite the considerable pyramidalization of the carbanionic centres, the orbital coefficients located at their backside are still significant and comparable in size to those coefficients located in the central C–Li four-membered ring, thereby making the backside attack of the carbanionic centre of [(*R*,*S*)-**6**]$_2$ to an electrophile like Me_3SnCl feasible. This is also reflected in the electrostatic potential map of the compound which shows a considerable negative potential at the backside of the carbanionic centres and furthermore supported by the computation of the transition state for the substitution reaction of [(*R*,*S*)-**6**]$_2$[11] with Me_3SnCl. With an activation energy of merely 15 kJ mol^{-1}, the reaction of the aggregate with the electrophile can readily and selectively proceed even at low temperatures.

In summary, we herein present the optically active ethylsilane (*S*)-**5** which undergoes stereoselective α-deprotonation in pentane with *tert*-butyllithium at low temperatures. The product persists as a dimeric species which proved to be configurationally stable in apolar solvents at room temperature for at least 1 h. Stereoisomer [(*R*,*S*)-**6**]$_2$ is preferentially obtained under kinetic conditions and can be further enriched by epimerization in the presence of coordinating additives. It exhibits well-defined configurations at the stereogenic metalated carbon centres and both experiments and calculations support the preference of the formation of this stereoisomer. Furthermore, the reaction of [(*R*,*S*)-**6**]$_2$ with trimethyltin chloride proceeds under inversion of the configuration at the metalated carbon centres and with good diastereoselectivities. The stereochemical outcome of the reaction could be elucidated and rationalised by a combination of crystallographic and computational means.

This publication is dedicated to the occasion of the retirement of Prof. Dr. Bernhard Lippert. The authors gratefully acknowledge the German Research Foundation DFG for financial support.

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5 "Optically active alkyllithiums" in this case refers to alkyllithium species bearing a stereogenic lithiated carbon centre, a class of compounds for which—to the best of our knowledge—at the time of submission no dimeric example has been reported in the literature.

6 Upon formal separation of [(*R*,*S*)-**6**]$_2$ into two monomeric species, no matter which of the two lithiums is attributed to the carbanionic centre, the same configuration—*R*—ensues.

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10 For additional information on [(*R*,*S*)-**6**]$_2$ and computations regarding other diastereomeric species see the ESI†.

11 The computation of the transition state was accomplished by simplifying the dimer *via* substitution of the $SiPh_2$ for $SiMe_2$ groups.