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A Highly Diastereomerically Enriched Benzyllithium Compound: The Molecular Structure and the Stereochemical Course of Its Transformations†

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*Summary: The solid state structure of the lithiated [(benzylsilyl)methyl]amine Me$_2$Si{[R]-[CHLiPh]}(CH$_2$-SMP) [(R,S)-**2**] {SMP = 1-[(S)-2-(methoxymethyl)pyrrolidinyl]} and the absolute configuration at the metalated carbon center of this alkyllithium compound, which is highly diastereomerically enriched in solution, were determined by single-crystal X-ray diffraction methods. The stereochemical course of an integral sequence of transformations, starting from unmetalated [(benzylsilyl)methyl]amine **1**, was experimentally clarified. For the selective reaction of [(R,S)-**2**] with MeI, inversion of the configuration at the metalated carbon center was found.*

The synthesis of enantiomerically or diastereomerically enriched alkyllithium compounds, in which the metalated carbon center is the stereogenic center, has been intensively studied for the last 20 years.[1] Among these are several enantiomerically enriched benzyllithium compounds.[1−4] The determination of the absolute configuration at the metalated stereogenic center and the clarification of the stereochemical course of further transformations are most important. However, this is often difficult to realize on the basis of experimental evidence. Instead, stereochemical assumptions are made, which are not always generally applicable. Furthermore, many aspects of the reaction mechanisms have not been understood so far.

In 1989, Chan and co-workers reported the lithiation of 1-[(benzyldimethylsilyl)methyl]-(*S*)-2-(methoxymethyl)pyrrolidine (**1**) and further substitution reactions with alkyl halides, which showed very high diastereomeric ratios.[3] A significant solvent effect on the diastereomeric ratios (d.r.) of the transformations with methyl iodide was observed when the reaction was carried out in THF (d.r. = 75:25) and diethyl ether (d.r. ≥ 98:2). Due to the absence of knowledge of the solid state structure for 1-{[(*R*)-(lithiomethylphenyl)dimethylsilyl]methyl}-(*S*)-2-(methoxymethyl)pyrrolidine [(*R*,*S*)-**2**], the authors had to deduce the absolute configuration at the metalated stereogenic center from the absolute configurations of the trapping product (*S*,*S*)-**3**, which is formed "presumably with retention of stereochemistry",[3a] and by comparison of product **5** of the Si−C cleavage reaction with a purchased authentic sample.[3a,c]

By dynamic ^{13}C NMR spectroscopy, Fraenkel and coworkers were able to show that the benzyllithium compound (*R*,*S*)-**2** exists as a monomeric single diastereomer in THF solution between −93 and +27 °C.[4] This is in agreement with the results of the trapping reactions at variable temperatures performed by Chan and our research group (see Experimental Section) which prove a stability of configuration on at least the time scale of the reaction.

The amazingly high selectivity of reactions of the title compound and the apparent stability of configuration make a closer look at the stereochemical course of its transformations necessary. Thus, it was of great interest to determine the structure (and the absolute configuration) of lithium alkyl (*R*,*S*)-**2** in the crystal. Furthermore, beginning with a *known* absolute configuration at the metalated carbon center, we have examined experimentally and explained the stereochemical course of an integral sequence of transformations, starting from the unmetalated silane **1**.

The lithiation of silane **1** was carried out with *tert*-butyllithium at −90 °C in toluene/*n*-pentane (Scheme 1).[5] At −30 °C, yellow-colored needles of the metalated product (*R*,*S*)-**2** could be isolated as single crystals in 80% yield. The stereochemical course of further transformations with the metalated silane is not affected by crystallization and isolation of the product. Reactions starting with the product as prepared and maintained in solution give the same d.r. values. After dissolving the solid (*R*,*S*)-**2** in pure toluene, the trapping reaction with methyl iodide was carried out at −90 °C and the

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† Dedicated to Professor Waldemar Adam on the occasion of his 65th birthday.

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(1) Basu, A.; Thayumanavan, S. *Angew. Chem., Int. Ed. Engl.* **2002**, *41*, 716−738, and literature therein.

(2) For examples see: (a) Stratmann, O.; Kaiser, B.; Fröhlich, R.; Meyer, O.; Hoppe, D. *Chem. Eur. J.* **2001**, *7*, 423−435. (b) Beak, P.; Anderson, D. R.; Curtis, M. D.; Laumer, J. M.; Pippel, D. J.; Weisenburger, G. A. *Acc. Chem. Res.* **2000**, *33*, 715−727. (c) Weisenburger, G. A.; Faibish, N. C.; Pippel, D. J.; Beak, P. *J. Am. Chem. Soc.* **1999**, *121*, 9522−9530. (d) Pippel, D. J.; Weisenburger, G. A.; Wilson, S. R.; Beak, P. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 2522−2524. (e) Hoppe, D.; Kaiser, B.; Stratmann, O.; Froehlich, R. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 2784−2786. (f) Ahlbrecht, H.; Harbach, J.; Hoffmann, R. W.; Ruhland, T. *Liebigs Ann.* **1995**, 211−216. (g) Boche, G.; Marsch, M.; Harbach, J.; Harms, K.; Ledig, B.; Schubert, F.; Lohrenz, J. C. W.; Ahlbrecht, H. *Chem. Ber.* **1993**, *126*, 1887−1894. (h) Marsch, M.; Harms, K.; Zschage, O.; Hoppe, D.; Boche, G. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 321−323.

(3) (a) Chan, T. H.; Pellon, P. *J. Am. Chem. Soc.* **1989**, *111*, 8737−8738. (b) Chan, T. H.; Lamothe, S. *Tetrahedron Lett.* **1991**, *32*, 1847−1850. (c) Chan, T. H.; Nwe, K. T. *J. Org. Chem.* **1992**, *57*, 6107−6111.

(4) (a) Fraenkel, G.; Duncan, J. H.; Martin, K.; Wang, J. *J. Am. Chem. Soc.* **1999**, *121*, 10538−10544. (b) Fraenkel, G.; Martin, K. *J. Am. Chem. Soc.* **1995**, *117*, 10336−10344.

(5) In a Schlenk flask, a solution of 1.00 g (3.60 mmol) of **1** in toluene (5 mL) was cooled to −90 °C and 2.12 mL of *t*-BuLi (solution in pentane, c = 1.7 mol·L^{-1}) (3.60 mmol) was added. The solution was warmed slowly to rt. After 12 h at −30 °C, yellow crystals (needles) of (*R*,*S*)-**2** were obtained in 80% yield (816 mg, 2.88 mmol). They were washed with *n*-pentane, and all volatile components were removed.

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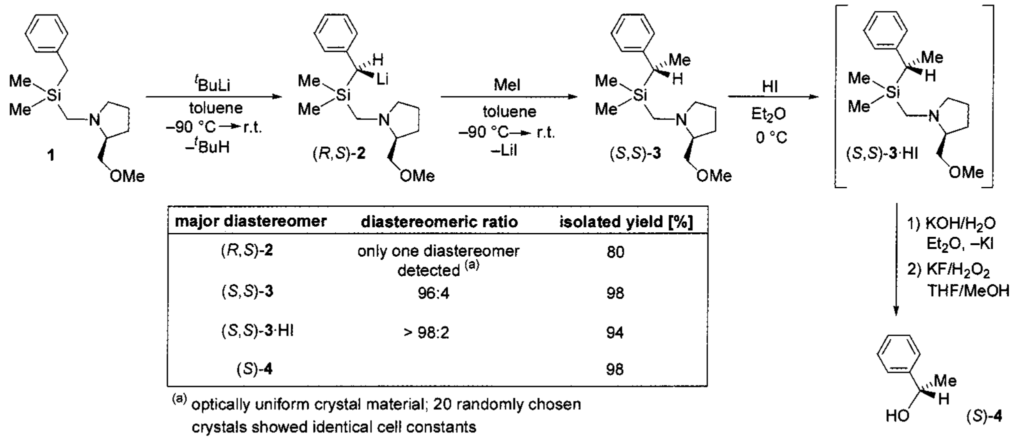
Scheme 1



major diastereomer	diastereomeric ratio	isolated yield [%]
(*R*,*S*)-2	only one diastereomer detected [(a)]	80
(*S*,*S*)-3	96:4	98
(*S*,*S*)-3·HI	> 98:2	94
(*S*)-4		98

[(a)] optically uniform crystal material; 20 randomly chosen crystals showed identical cell constants

reaction mixture subsequently was warmed to room temperature. Methylated silane (*S*,*S*)-**3**/(*R*,*S*)-**3** was formed in 98% yield and was found to have a diastereomeric ratio d.r. [(*S*,*S*)-**3**:(*R*,*S*)-**3**] = 96:4.[6]

Only for the determination of the absolute configuration of the major diastereomer of silane (*S*,*S*)-**3**, the hydrogen iodide adduct (*S*,*S*)-**3**·HI was formed by reacting the compound with anhydrous hydrogen iodide (solution in diethyl ether) at 0 °C.[7] Colorless needles of (*S*,*S*)-**3**·HI were obtained as single crystals from CH$_2$Cl$_2$/*n*-pentane. The Si−C cleavage reaction with KF/H$_2$O$_2$ was effected using the method of Chan et al. in a mixture of THF and methanol at 50 °C to give benzyl alcohol (*S*)-**4**.[3c]

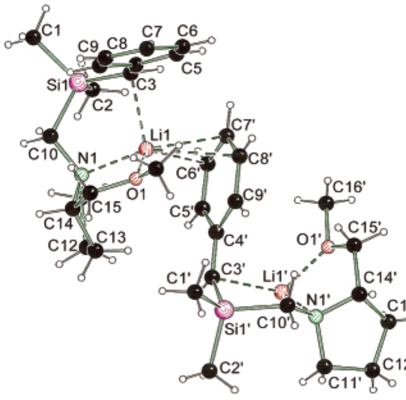


Figure 1. Molecular structure and numbering scheme of compound (*R*,*S*)-**2** (molecule A) in the crystal (Schakal plot).[8] Selected bond distances (Å) and angles (deg) [compared to selected bond distances (Å) and angles (deg) of compound (*S*,*S*)-**3**·HI in brackets]: Li(1)−C(3) 2.27(1), Si(1)−C(3) 1.797(7) [1.914(9)], Si(1)−C(10) 1.914(7) [1.910(7)], C(3)−Si(1)−C(10) 107.9(3) [104.2(3)], N(1)−C(10)−Si(1) 111.5(4) [119.2(5)], N(1)−Li(1)−C(3) 97.0(5), O(1)−Li(1)−N(1) 83.2(5), C(3)−C(4)−C(5)−C(9) 180(1) [179(1)], Si(1)−C(3)−C(4)−C(5) 9(1) [93.1(8)], C(9)−C(4)−C(3)−Si(1) 9(1) [87.9(9)], Si(1)−C(3)−C(4)−H(3) 174(5) [110(6)], Li(1)−C(3)−C(4)−C(5) 85.6(7), Li(1)−C(3)−C(4)−C(9) 94.4(7).

Compound (*R*,*S*)-**2** crystallized from toluene in the hexagonal crystal system, space group $P3_2$.[9,10] Three crystallographically independent molecules were found in the asymmetric unit, each building up infinite chain structures of (*R*,*S*)-**2** in the solid state (due to the similarity of the structural parameters, only molecule A is discussed and shown in Figure 1). The chains are formed by π-interactions between a lithium center and the phenyl group of an adjoining silane molecule. As predicted by Chan and Fraenkel,[3a,4] the lithium center Li(1) of the metalated α-carbon center is coordinated by the two donor groups N(1) and O(1) of the (aminomethyl) ligand, transferring the stereochemical information onto the metal fragment. The coordination sphere of Li(1) is completed by contacts to the three aromatic carbon centers C(6)′, C(7)′, and C(8)′ of the adjoining silane molecule. The benzylic carbon atom C(3) is almost planar, but is nevertheless a stereogenic center due to the C(3)−Li(1) contact. The least-squares plane that includes Si(1), C(3), C(4), and H(3) shows an rms deviation of only 0.019 Å, and the largest deviation from the plane is 0.03(2) Å for C(3). This is underlined

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(6) In a Schlenk flask, a solution of 500 mg (1.72 mmol) of (*R*,*S*)-**2** in toluene (4 mL) was cooled to −90 °C and 243 mg (1.72 mmol) of MeI was added. The reaction mixture was warmed slowly to rt. After separation of LiI all volatile components were removed. Purification by Kugelrohr distillation gave (*S*,*S*)-**3**/(*R*,*S*)-**3** as a colorless oil in 98% yield (491 mg, 1.69 mmol). The d.r. value was determined by ^{1}H NMR spectroscopy. Anal. Calcd for $C_{17}H_{29}NOSi$: C, 70.04; H, 10.03; N, 4.80. Found: C, 69.69; H, 9.95; N, 5.08. ^{1}H NMR (400.1 MHz, CDCl$_3$): δ −0.07 (s, 3H, SiC*H*$_3$), 0.08 (s, 3H, SiC*H*$_3$), 1.41 (d, $^3J_{H,H}$ = 7.3 Hz, 3H, CHC*H*$_3$), 1.54−1.64, 1.66−1.80, 1.85−1.97, 2.06−2.12, 2.29−2.36 (m, 6H, CC*H*$_2$C, NC*H*$_2$C), 1.69, 2.49 (AB-system, $^2J_{A,B}$ = 14.4 Hz, 2H, SiC*H*$_2$N), 2.32 (q, $^3J_{H,H}$ = 7.6 Hz, 1H, C*H*CH$_3$), 3.02−3.05 (m, 1H, NC*H*C), 3.25−3.27, 3.39−3.44 (m, 2H, C*H*$_2$O), 3.37 (s, 3H, OC*H*$_3$), 7.08−7.12 (m, 3H, aromat. H), 7.20−7.28 (m, 2H, aromat. H). ^{13}C NMR (100.6 MHz, CDCl$_3$): δ −4.5 (Si*C*H$_3$), −4.4 (Si*C*H$_3$), 14.9 (CH*C*H$_3$), 23.2 (*C*H$_2$), 28.3 (*C*HCH$_3$), 28.4 (*C*H$_2$), 43.7 (Si*C*H$_2$N), 57.4 (*C*H$_2$), 59.0 (O*C*H$_3$), 67.6 (*C*HCH$_2$O), 76.4 (*C*H$_2$O), 124.2 (*C*-p), 127.2, 127.8 (*C*-o, *C*-m), 145.7 (*C*-i). ^{29}Si NMR (59.6 MHz, CDCl$_3$): δ 2.04 ppm.

(7) To a solution of 1.00 g (3.43 mmol) of (*S*,*S*)-**3** in Et$_2$O was added a solution of anhydrous HI in Et$_2$O (1.72 mL, 3.43 mmol) at 0 °C. After 5 min of stirring at rt all volatile components were removed. A colorless solid was obtained in 94% yield (1.35 g, 3.22 mmol) and recrystallized from CH$_2$Cl$_2$/*n*-pentane to give colorless crystals (needles) after 12 h at −30 °C. The d.r. value was determined by ^{1}H NMR spectroscopy.

(8) Keller, E. *SCHAKAL99*; Freiburg, Germany, 1999.

(9) Crystallographic data for (*R*,*S*)-**2** (yellow needles from toluene, 0.40 × 0.30 × 0.30 mm^3) (soft crystals with disadvantageous scattering properties): $C_{16}H_{26}LiNOSi$, M = 283.41, hexagonal, space group $P3_2$ (no. 145), a = 16.144(2) Å, c = 16.777(3) Å, U = 3786.4(11) Å^3, Z = 9, D_c = 1.119 Mg/m^3. Type of radiation: Mo Kα, λ = 0.71073 Å, μ = 0.134 mm^{-1}. Measurements: Stoe IPDS diffractometer, T = −100 °C. The structure was solved using direct and Fourier methods; 49 707 reflections measured with θ in the range 2.52−25°, 8883 unique reflections; 8338 with $I > 2\sigma(I)$; refinement by full-matrix least-squares methods (based on F_o^2, SHELXL-97); anisotropic thermal parameters for all non-H atoms in the final cycles; H atoms treated by a mixture of independent and constrained refinement; R = 0.0935 [$I > 2\sigma(I)$], $wR(F_o^2)$ = 0.2525 (all data), absolute structure parameter 0.1(2) [larger displacement parameter of C(36) in the direction of the C(35)−C(36) bond in molecule C; higher standard deviations and less reliable bond lengths and angles for this part of the molecule].

(10) Sheldrick, G. M. *SHELXTL 6.10*; Bruker AXS Inc: Madison, WI.

by the average Si(1)−C(3)−C_{ipso}−C_{ortho} torsion angle around the C(3)−C(4) bond, which is 9(1)°. Furthermore, the sum of the angles around C(3) is 360(3)°. The average Li(1)−C(3)−C_{ipso}−C_{ortho} torsion angle around the C(3)−C(4) bond, which is 90.0(7)°, shows that the lithium−carbon bond Li(1)−C(3) is almost orthogonal to the C(3)−C(4)−C(5) plane. So provided that the *S* configuration at the stereogenic carbon center of the (aminomethyl) substituent remains unchanged during the metalation, the absolute configuration at metalated C(3) is *R*. In contrast to the expectations of Chan and Fraenkel,[3a,4] the phenyl substituent and the methoxymethyl substituent are pointing in the same direction, showing no steric interactions. In agreement with the well-known fact that silicon centers have a stabilizing effect on α-carbanionic centers, the C(3)−Si(1) bond of (*R*,*S*)-**2** is shortened by this polarization effect [compared to the value in the unmetalated compound (*S*,*S*)-**3**·HI]:[10,11] 1.797(7), 1.818(7), and 1.825(7) Å (for molecules A, B, and C, respectively) compared to 1.914(9) Å. The C(3)−C(4) single bond is influenced by the metalation of C(3) as well: C(3)−C(4) = 1.419(9), 1.431(9), and 1.37(1) Å[9] (for molecules A, B, and C, respectively) compared to 1.49(1) Å for (*S*,*S*)-**3**·HI. In the related lithiated benzyl(piperidinomethyl)silane, whose synthesis and crystal structure were reported recently,[12] the corresponding bond lengths Si(1)−C(3) = 1.821(3) and C(3)−C(4) = 1.453(4) Å are of comparable values, indicating analogous stabilizing effects by the silicon center and the phenyl group.

In the literature, both the *R*,*S* and the *S*,*S* diastereomer of lithium alkyl **2** have been proposed as the major diastereomer.[3a,4a] On the basis of these predictions, both retention and inversion of the configuration at C(3) have been postulated for the reactions of (*R*,*S*)-**2** with alkyl halides.[3] Our X-ray structural analysis of (*R*,*S*)-**2** shows that *R* configuration at the metalated carbon center and inversion of configuration (for the reaction of (*R*,*S*)-**2** with methyl iodide in toluene) are in fact the case. A look in the literature reveals that both retention and inversion of the configuration have been observed for the reactions of lithiated benzylic and related systems with various electrophiles.[13] In most cases no solid state structure of the corresponding lithium alkyl could be determined to confirm the absolute configuration of the stereogenic metalated carbon center. The stereochemical course of the reaction of our lithium alkyl with the electrophile methyl iodide in toluene can be understood on the basis of the solid state structure of compound (*R*,*S*)-**2**, which was crystallized from the same solvent used in the substitution reaction with the alkyl iodide, in combination with computational studies.

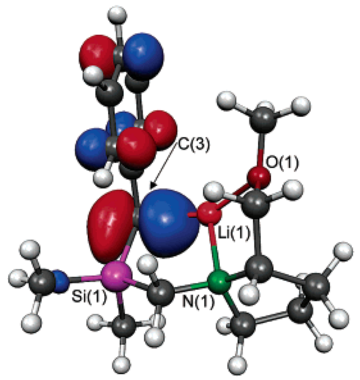

Figure 2. B3LYP/6-31+G(d)-optimized structure of monomeric (*R*,*S*)-**2** and visualization of the HOMO (Molekel plot[14]).

The modeling of monomeric (*R*,*S*)-**2** [B3LYP/6-31+G(d)][15] indicates that the highest occupied molecular orbital (HOMO) is chiefly located at the metalated carbon center and the aromatic ring system (Figure 2). It can be deduced from the calculated orbital coefficients that both inversion and retention of configuration are almost equally likely to result from electrophilic attack. Only the fact that the site opposite the lithium center is sterically accessible to attack by electrophiles (the coordination polymer of the solid state structure should be broken up in solution) makes it possible for (*R*,*S*)-**2** to react selectively with inversion of configuration at C(3) under kinetic control in nonpolar solvents.

It is now of interest to determine whether the results of our investigation may be of use in understanding the stereochemistry of benzyllithium systems in general, or if investigations of systems like (*R*,*S*)-**2** are too specialized to set up common rules for the stereochemistry of this class of compounds.

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Supporting Information Available: Details on the crystal structure determinations and the DFT calculation are available free of charge via the Internet at http://pubs.acs.org.

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(11) Crystallographic data for (*S*,*S*)-**3**·HI (colorless needles from CH_2Cl_2/*n*-pentane, 0.20 × 0.20 × 0.10 mm^3): $C_{17}H_{30}INOSi$, $M = 419.41$, monoclinic, space group $P2_1$ (no. 5), $a = 12.079(3)$ Å, $b = 7.717(1)$ Å, $c = 21.597(4)$ Å, $\beta = 91.61(3)°$, $U = 2012.4(7)$ Å^3, $Z = 4$, $D_c = 1.384$ Mg/m^3, Type of radiation: Mo Kα, $\lambda = 0.71073$ Å, $\mu = 1.651$ mm^{-1}. Measurements: Stoe IPDS diffractometer, $T = -100$ °C. The structure was solved using direct and Fourier methods; 19 897 reflections measured with θ in the range 2.50−26°, 7917 unique reflections; 7084 with $I > 2\sigma(I)$; refinement by full-matrix least-squares methods (based on F_o^2, SHELXL-97); anisotropic thermal parameters for all non-H atoms in the final cycles; H atoms treated by a mixture of independent and constrained refinement; $R = 0.0518$ [$I > 2\sigma(I)$], $wR(F_o^2) = 0.1359$ (all data), absolute structure parameter 0.01(3).

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