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Stereocontrol in Nucleophilic Substitution Reactions at Silicon: The Role of Permutation in Generating Silicon-Centered Chirality

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Supporting Information

ABSTRACT: Intramolecular isomerization in pentacoordinate compounds can play an essential role for the adjustment of defined stereochemical information. Here, we present a conclusive mechanism of a stereocontrolled reaction on chiral dimethoxysilanes that opens new aspects in understanding the origin of creating silicon-centered chirality during a nucleophilic substitution process. By combining experimental, structural, and quantum chemical methods, we were able to disclose an interconversion process, based on consecutive Berry-type motions, as the most plausible mechanism for describing the stereochemical outcome in suchlike substitution reactions.

Pentacoordinate species have long been known as central intermediates in nucleophilic substitution reactions at silicon.[1] In case of substitutions at stereogenic centers, the stereochemical outcome of these reactions can strongly depend on the kinetics of intramolecular permutation that may occur in intermediate, higher-coordinate compounds.[2] In addition, also in transition-metal-mediated reactions, isomerization processes can play an important role.[3] This was impressively shown by Schrock and Hoveyda in asymmetric catalysis, where the dynamic behavior of molybdenum-based catalysts with metal-centered chirality is responsible for an exceptional efficiency and selectivity in homogeneous, enantioselective alkene metathesis.[4] In a profound, recently performed theoretical investigation, Couzijn et al. have demonstrated that the long-known Berry pseudorotation (BPR)[5] can be interpreted as the elemental mechanism for describing configurational stereomutations in pentacoordinate, trigonal-bipyramidal species (Figure 1).[6]

Figure 1. BPR as fundamental process for configurational changes in trigonal-bipyramidal compounds.[5] Axial substituents: blue; equatorial substituents: red.

In the meanwhile, the interest in synthesis and application of silicon-chiral silanes is continually growing, as can be seen on the great number of publications during the past few years.[7] Just a short while ago, we reported on a highly stereocontrolled reaction of chiral aminodimethoxysilanes with organolithium reagents.[8] Remarkable observations, such as the occurrence of stereoconvergency, and studies concerning the configurational stability of the substitution products gave first hints that the substitutions possibly follow a kinetically controlled, multistep mechanism.[8] Owing to the lack of asymmetric methods that apply nucleophilic substitution reactions for providing silicon-stereogenic molecules,[8,9] the mechanisms of transferring chiral information onto a silicon center are thus not really understood until now.

Therefore, in our present contribution, we examine in detail the intramolecular transfer of chirality in the course of a nucleophilic substitution reaction at a prochiral silicon center. Detailed mechanistic investigations have provided insight into the origin of creating a defined configuration at silicon. First structural data of a unique, inert precoordination compound have supported our drawn mechanistic picture of stereodifferentiation between two diastereotopic methoxy groups.

For our studies, we focused on a reaction system consisting of (trimethylsilyl)methyllithium and the cyclohexyldimethoxysilane (S_C)-**1** that was easily synthesized by our previously established procedure[10] from cyclohexyltrimethoxysilane and the lithium salt of (2*S*)-2-(methoxymethyl)pyrrolidine (SMP) in 94% yield (Table 1). Except for the SMP moiety and the silicon-bound methoxy groups, there are no additional coordination sites for an attacking nucleophile in the periphery of the substrate backbone of (S_C)-**1**. After the reaction had been first carried out in diethyl ether during slowly warming the mixture from −80 °C to room temperature, (S_C)-**1** was converted into (S_C,R_{Si})-**2** in 70% yield and with excellent stereoselectivity (d.r. = 98:2) (Table 1, Case I).[11] Astonishingly, the reaction proceeded with a distinct decrease in stereocontrol when performing in pentane under otherwise same reaction conditions. Now, the diastereomeric ratio only amounts to 70:30 (Table 1, Case II). It is worth mentioning that we even noticed a slight shift of the diastereomeric ratio (d.r. = 45:55) in favor of the S_{Si}-configured substitution product **2** after carrying out the reaction in pentane at 0 °C (Table 1, Case III). In another experiment in pentane solution, the reaction mixture had first been stirred for 48 h at −30 °C, before it was slowly warmed to room temperature afterward (Table 1, Case IV). Also in this case, (S_C,R_{Si})-**2** was obtained with only moderate stereochemical purity (d.r. = 74:26). In each case, the optical purity of compound **2** was verified by ^{1}H, ^{13}C, and ^{29}Si NMR spectroscopy. Already at this point, our investigation concerning the reactivity and selectivity suggests that the stereodetermining step needs to differentiate between activation barriers that differ only minimally in energy.

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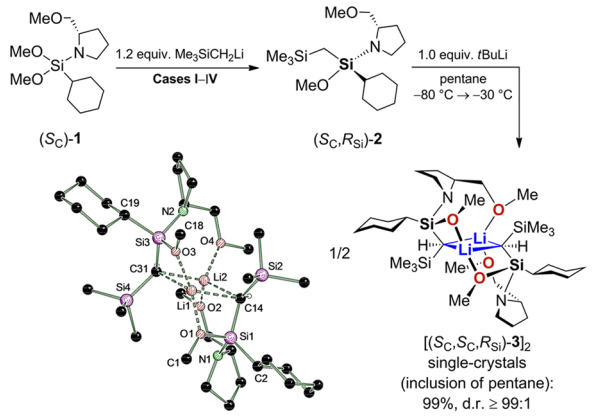
Table 1. Stereocontrolled Synthesis of (S_C,R_{Si})-2 and Determination of the Absolute Configuration at the Stereogenic Silicon Center



case	solvent	temperature	d.r.[c]
I[a]	diethyl ether	−80 °C → rt (20 h)	98:2
II[b]	pentane	−80 °C → rt (20 h)	70:30
III[b]	pentane	0 °C (15 min) → rt (20 h)	45:55
IV[b]	pentane	−80 °C → −30 °C (48 h) → rt	74:26

[a]70% yield of (S_C,R_{Si})-**2**. [b]Yields have not been determined. [c]The diastereomeric ratio of **2** has been determined by integration of baseline-separated ^{1}H NMR signals belonging to the two diastereomers.

In addition, the coordinating properties of diethyl ether seem to have a positive influence on the stereochemical outcome. The absolute configuration at the stereogenic silicon center could unambiguously be determined as R_{Si} by single-crystal X-ray diffractional analysis of the dimeric, α-lithiated compound $[(S_C,S_C,R_{Si})\text{-}\mathbf{3}]_2{\cdot}C_5H_{12}$ (Table 1).[12] The structural features are discussed in more detail in the Supporting Information.

In a next purpose, the initial nucleophilic attack at the silicon center of the reaction shown in Table 1 was calculated [M052X/6-31+G(d)].[13,14] Assuming that monomeric complexes are the acting species in the substitution mechanism, the monomeric, cyclohexyl-substituted precomplex ***syn*-Cy-E** was chosen as a plausible starting structure. In this way, the first and likewise rate-determining step of the reaction could be formulated (Figure 2). It is in fact a *syn*-type configuration of the initially formed complex (cyclohexyl group and coordinated nucleophile are situated at the same site) that passes through the energetically lowest transition state $[\mathbf{TS1}]^‡$ with an activation barrier of 45 kJ mol^{-1}, leading to the trigonal-bipyramidal key-intermediate **I1**.[15] In this pentacoordinate silicon species, the lithium cation is chelated by three donor atoms. As a result of this coordination, the nitrogen atom directly attached to silicon becomes also stereogenic with a fixed configuration. Another imaginable attack[16] at the silicon center out of an alternative *anti*-configured precomplex (***anti*-Cy-E**) via the transition state $[\mathbf{TS2}]^‡$ can unequivocally be excluded, considering the difference ($\Delta\Delta E^‡$) between $[\mathbf{TS1}]^‡$ and $[\mathbf{TS2}]^‡$ of 28 kJ mol^{-1} (Figure 2). The energetic preference of $[\mathbf{TS1}]^‡$ toward $[\mathbf{TS2}]^‡$ can be ascribed to a stereoelectronic effect (better HOMO|LUMO overlap in $[\mathbf{TS1}]^‡$); due to the quasi axial location of the silicon-bound OMe group in $[\mathbf{TS1}]^‡$, the extra electron density of the incoming carbanion might be better stabilized across the molecular framework.[17] The formation of **I1** through the energetically lowest barrier $[\mathbf{TS1}]^‡$ marks the first critical point for the stereochemical course of the reaction.

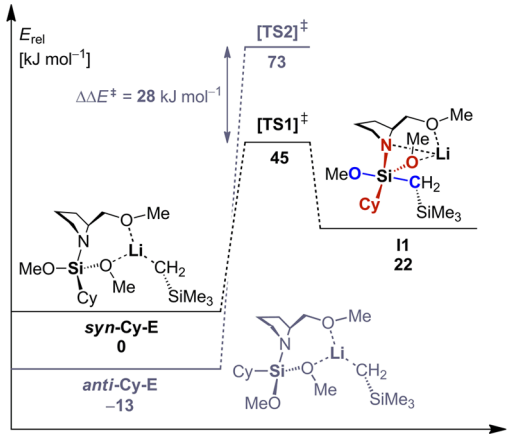


Figure 2. Activation barriers of the axial nucleophilic attack at silicon,[16] starting from the cyclohexyl-substituted reactants [M052X/6-31+G-(d)].[13] Numerical values in [kJ mol^{-1}]. Cy = cyclohexyl.

However, the question remains, in which step the final determination of the stereochemistry of the substitution product actually occurs. In case of an elimination of the methoxy group coordinated to lithium out of the pentacoordinate intermediate **I2** in which $[\mathbf{BPR1}]^‡$ had been turned the leaving OMe group in the axial position, the substitution product would feature the S_{Si} configuration (Figure 3, Path A). Hence, a direct liberation of the methoxy group as the predominant path appears unlikely. Instead, by the action of two Berry-type pseudorotations, **I1** can be interconverted via **I3** into the stereoelectronically most favored intermediate **I4**, in which the two Si−OMe groups are located in the axial position.[17] From that point, the liberation of the methoxy group (**I4** → **P2**) would terminate the substitution process under formation of the R_{Si}-configured product (Figure 3, Path B). In this mechanistic picture, the stereochemistry of the final product depends on a competition between the two diastereomorphic transition states $[\mathbf{BPR1}]^‡$ and $[\mathbf{BPR2}]^‡$ ($\Delta\Delta E^‡$ = 10 kJ mol^{-1}) belonging to Berry-type motions (Figure 3). The energetic preference of **I3** toward **I2** might be predominantly the result of a reduced repulsive interaction between the cyclohexyl and the pyrrolidine ring in **I3**, which is also expressed in the respective transition state $[\mathbf{BPR2}]^‡$ (for structural details, see the Supporting Information). In addition to this steric effect, the movement of the electronegative pyrrolidine moiety into the quasi axial position through $[\mathbf{BPR2}]^‡$ might also be taken into account for explaining the lower activation barrier for the conversion **I1** → **I3**.

Altogether, the impact of thermal variations on the diastereomeric ratio of the final product (Table 1, Cases II and III) should be the greater, the smaller the energy differences between stereodetermining transition states are. This corresponds nicely with our calculated permutational process.[18] The higher diastereoselectivity in Case 1 of Table 1 may be a consequence of additional solvent coordination to the lithium center, which could lead to a greater energetic difference between competing transition states.

Given our established experience in the field of structural elucidation of prelithiation complexes,[19] we attempted the isolation of an unreactive complex, comprising an amino-dimethoxysilane and an alkyllithium reagent, in order to give our proposed starting structures more significance on an experimental basis. Silanes bearing both silicon−nitrogen and silicon−oxygen bonds are suitable ligands, with the Si−OMe

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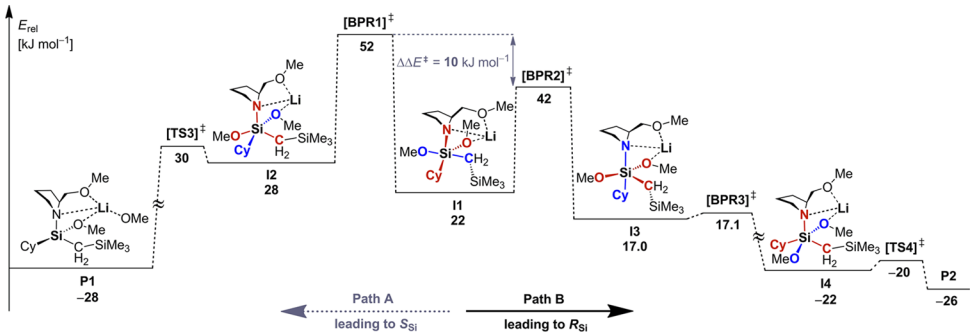
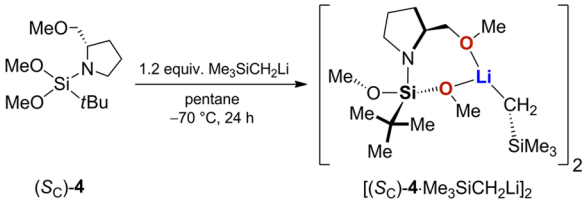


Figure 3. Stereodetermining differentiation between the two diastereomorphic permutational transition states [**BPR1**]‡ and [**BPR2**]‡ [M052X/6-31+G(d)].[13] Numerical values in [kJ mol^{-1}]. Cy = cyclohexyl. **P1** = [(S_C,S_{Si})-**2**·LiOMe], **P2** = [(S_C,R_{Si})-**2**·LiOMe].

group serving as an effective coordinating group for alkyllithium reagents.[20] To the best of our knowledge, presubstitution complexes that are formed prior to nucleophilic attack at silicon have not been observed nor experimentally characterized to date.[9]

The chance to form an inert complex of (trimethylsilyl)-methyllithium[21] and (S_C)-**1** seemed unpromising since the reaction already starts at low temperatures. However, the related *tert*-butyl-substituted compound (S_C)-**4** has been proved to be far less reactive concerning a nucleophilic substitution in our previous studies yet.[8] In fact, after we had exchanged the cyclohexyl by a *tert*-butyl group, the reactivity of the amino-dimethoxysilane toward a nucleophilic attack was diminished to the point that we finally succeded in isolating an unreactive, dimeric adduct of (S_C)-**4** and Me_3SiCH_2Li at −70 °C. This complex could be fully characterized by means of X-ray crystallography and NMR spectroscopy (Scheme 1 and Figure 4).

Scheme 1. Formation of the Inert Precomplex [(S_C)-4·Me_3SiCH_2Li]$_2$



The dimer[22] [(S_C)-**4**·Me_3SiCH_2Li]$_2$ crystallized in the form of colorless blocks in the tetragonal crystal system, space group $P4_12_12$ (Figure 4).[12] The lithium center is coordinated solely by the methoxymethyl side arm and the silicon-bound, *pro-S* methoxy group. The *tert*-butyl group shows a *syn*-type configuration with respect to complexed Me_3SiCH_2Li. The Li−O1 bond length [2.073(4) Å] is only slightly elongated, compared to Li−O3 [2.017(4) Å]. The ^{1}H NMR shifts ([d_6]-benzene) of the Si−OMe groups of the free compound (S_C)-**4** are at 3.41 and 3.47 ppm.[8] In [(S_C)-**4**·Me_3SiCH_2Li]$_2$, one of the two silicon-bound methoxy groups shows a ^{1}H NMR signal at higher field (3.35 ppm), with the other Si−OMe group almost remaining unchanged (3.50 ppm). The ^{7}Li NMR spectrum shows a singlet at 2.44 ppm. Also in solution, we can therefore assume the existence of a well-defined species, in which only one of the two diastereotopic Si−OMe groups is involved in coordination to the lithium center. Moreover, this structure supports our proposed mechanism of a nucleophilic attack out of

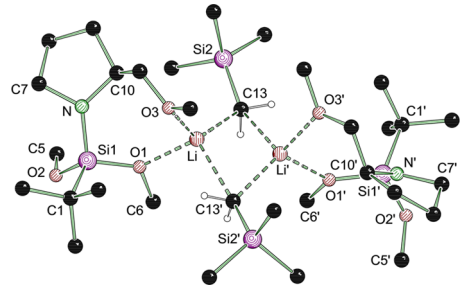


Figure 4. Molecular structure of [(S_C)-**4**·Me_3SiCH_2Li]$_2$ in the crystal.[12] The hydrogen atoms are omitted for clarity (except the hydrogen atoms bound to the metalated carbon atoms). Selected bond lengths [Å] and angles [°]: C5−O2 1.428(3), C6−O1 1.446(3), C13−Li 2.199(5), C13−Li′ 2.365(4), Li−O3 2.017(4), Li−O1 2.073(4), Li−C13′ 2.365(4), Li−Li′ 2.574(7), N−Si1 1.694(2), O1−Si1 1.6521(15), O2−Si1 1.6407(16), O3−Li−O1 96.28(17), Li−C13−Li′ 68.55(17), C13−Li−C13′ 107.38(16), C6−O1−Si1 120.95(14), C5−O2−Si1 122.98(16).

low molecular complexes with participation of the SMP OMe and one Si−OMe function.

We have also calculated the respective transition states of a nucleophilic attack at silicon out of the monomeric, *tert*-butyl-substituted complexes ***syn*-*t*Bu-E** and ***anti*-*t*Bu-E**. Again, the axial attack via the *syn*-configured transition state turned out to be the energetically most favored one ($\Delta\Delta E^‡$ = 36 kJ mol^{-1}). The remarkably higher activation barriers, compared to the cyclohexylsilane, reflect the observed inhibition of the reaction of (S_C)-**4** with Me_3SiCH_2Li (for details, see the Supporting Information).

In conclusion, we have shown for stereocontrolled nucleophilic substitution reactions on chiral aminodimethoxysilanes that stereomutation is of fundamental importance for creating silicon-centered chirality. The results of these studies might not only be of interest for the understanding of stereocontrolled reactions in heavy main group element chemistry; they might also bring light into transition-metal-mediated reactions in which high-coordinate intermediates play a crucial role.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures, characterization data, detailed structural information, quantum chemical calculations, and complete ref 13. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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REFERENCES

(1) (a) Chuit, C.; Corriu, R. J. P.; Reye, C.; Young, J. C. *Chem. Rev.* **1993**, *93*, 1371. (b) LaRonde, F. J.; Brook, M. A. *Tetrahedron Lett.* **1999**, *40*, 3507. (c) Cypryk, M.; Apeloig, Y. *Organometallics* **2002**, *21*, 2165. (d) Krouse, I. H.; Wenthold, P. G. *Organometallics* **2004**, *23*, 2573. (e) Mitzel, N. W.; Vojinovic, K.; Foerster, T.; Robertson, H. E.; Borisenko, K. B.; Rankin, D. W. H. *Chem.—Eur. J.* **2005**, *11*, 5114. (f) Gan, L.; Brook, M. A. *Can. J. Chem.* **2006**, *84*, 1416. (g) Gan, L.; Brook, M. A. *Organometallics* **2007**, *26*, 945. (g) Sohail, M.; Panisch, R.; Bowden, A.; Bassindale, A. R.; Taylor, P. G.; Korlyukov, A. A.; Arkhipov, D. E.; Male, L.; Callear, S.; Coles, S. J.; Hursthouse, M. B.; Harrington, R. W.; Clegg, W. *Dalton Trans.* **2013**, *42*, 10971.

(2) (a) Corriu, R. J. P.; Kpoton, A.; Poirier, M.; Royo, G.; Corey, J. Y. *J. Organomet. Chem.* **1984**, *277*, C25. (b) Stevenson, W. H., III; Wilson, S.; Martin, J. C.; Farnham, W. B. *J. Am. Chem. Soc.* **1985**, *107*, 6340. (c) Stevenson, W. H., III; Martin, J. C. *J. Am. Chem. Soc.* **1985**, *107*, 6352. (d) Holmes, R. R. *Chem. Rev.* **1990**, *90*, 17. (e) Holmes, R. R. *Chem. Rev.* **1996**, *96*, 927. (f) Pülm, M.; Tacke, R. *Organometallics* **1997**, *16*, 5664. (f) Kawachi, A.; Maeda, H.; Mitsudo, K.; Tamao, K. *Organometallics* **1999**, *18*, 4530. (g) Tacke, R.; Bertermann, R.; Biller, A.; Dannappel, O.; Pülm, M.; Willeke, R. *Eur. J. Inorg. Chem.* **1999**, 795. (h) Kost, D.; Kalikhman, I.; Krivonos, S.; Bertermann, R.; Burschka, C.; Neugebauer, R. E.; Pülm, M.; Willeke, R.; Tacke, R. *Organometallics* **2000**, *19*, 1083. (i) Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. L. *J. Am. Chem. Soc.* **2002**, *124*, 7920. (j) Kost, D.; Gostevskii, B.; Kocher, N.; Stalke, D.; Kalikhman, I. *Angew. Chem., Int. Ed.* **2003**, 1023. (k) Couzijn, E. P. A.; Schakel, M.; de Kanter, F. J. J.; Ehlers, A. W.; Lutz, M.; Spek, A. L.; Lammertsma, K. *Angew. Chem., Int. Ed.* **2004**, *43*, 3440. (l) Couzijn, E. P. A.; van den Engel, D. W. F.; Slootweg, J. C.; de Kanter, F. J. J.; Ehlers, A. W.; Schakel, M.; Lammertsma, K. *J. Am. Chem. Soc.* **2009**, *131*, 3741. (m) Bassindale, A. R.; Sohail, M.; Taylor, P. G.; Korlyukov, A. A.; Arkhipov, D. E. *Chem. Commun.* **2010**, *46*, 3274.

(3) (a) Heyde, T. A. D. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 823. (b) Brunner, H. *Angew. Chem., Int. Ed.* **1999**, *38*, 1194−1208.

(4) (a) Malcolmson, S. J.; Meek, S. J.; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008**, *456*, 933. (b) Marinescu, S. C.; Schrock, R. R.; Li, B.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 58. (c) Sattely, E. S.; Meek, S. J.; Malcolmson, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 943. (d) Klare, H. F. T.; Oestreich, M. *Angew. Chem., Int. Ed.* **2009**, *48*, 2085.

(5) Berry pseudorotation means the interconversion of axial and equatorial substituents in trigonal-bipyramidal systems via a square-pyramidal transition state [**BPR**]‡ with one of the five substituents remaining unchanged. See: (a) Berry, R. S. *J. Chem. Phys.* **1960**, *32*, 933. (b) Berry, R. S. *Rev. Mod. Phys.* **1960**, *32*, 447.

(6) (a) Couzijn, E. P. A.; Slootweg, J. C.; Ehlers, A. W.; Lammertsma, K. *J. Am. Chem. Soc.* **2010**, *132*, 18127. (b) Moberg, C. *Angew. Chem., Int. Ed.* **2011**, *50*, 10290.

(7) For some representative examples, see: (a) Schmidt, D. R.; ÒMalley, S. J.; Leighton, J. L. *J. Am. Chem. Soc.* **2003**, *125*, 1190. (b) Rendler, S.; Auer, G.; Oestreich, M. *Angew. Chem., Int. Ed.* **2005**, *44*, 7620. (c) Rendler, S.; Auer, G.; Keller, M.; Oestreich, M. *Adv. Synth. Catal.* **2006**, *348*, 1171. (d) Rendler, S.; Oestreich, M.; Butts, C. P.; Lloyd-Jones, G. C. *J. Am. Chem. Soc.* **2007**, *129*, 502. (e) Yasutomi, Y.; Suematsu, H.; Katsuki, T. *J. Am. Chem. Soc.* **2010**, *132*, 4510. (f) Xu, L.-W.; Li, L.; Lai, G.-Q.; Jiang, J.-X. *Chem. Soc. Rev.* **2011**, *40*, 1777. (g) Igawa, K.; Yoshihiro, D.; Ichikawa, N.; Kokan, N.; Tomooka, K. *Angew. Chem., Int. Ed.* **2012**, *51*, 12745. (h) Shintani, R.; Maciver, E. E.; Tamakuni, F.; Hayashi, T. *J. Am. Chem. Soc.* **2012**, *134*, 16955.

(8) Bauer, J. O.; Strohmann, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 720.

(9) (a) Kobayashi, K.; Kato, T.; Unno, M.; Masuda, S. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1393. (b) Tomooka, K.; Nakazaki, A.; Nakai, T. *J. Am. Chem. Soc.* **2000**, *122*, 408. (c) Igawa, K.; Takada, J.; Shimono, T.; Tomooka, K. *J. Am. Chem. Soc.* **2008**, *130*, 16132.

(10) Bauer, J. O.; Strohmann, C. *Chem. Commun.* **2012**, *48*, 7212.

(11) The inverse reactivity (substitution of the Si−N function) is true under acidic conditions, e.g., with alcohols and silanols. See: refs 8. and 10.

(12) CCDC 1019420 $[(S_C,S_C,R_{Si})$-**3**$]_2\cdot C_5H_{12}$ and CCDC 1019421 $[(S_C)$-**4**$\cdot Me_3SiCH_2Li]_2$ 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.

(13) Frisch, M. J. et al., *Gaussian 03*, revision E.01; Gaussian, Inc.: Wallingford, CT, 2004. For details, see the Supporting Information.

(14) For a profound comparison of different methods for calculations with alkyllithium species, see: Gessner, V. H.; Koller, S. G.; Strohmann, C.; Hogan, A.-M.; ÒShea, D. F. *Chem.—Eur. J.* **2011**, *17*, 2996.

(15) For some examples of isolated pentacoordinate compounds, see: (a) Laine, R. M.; Blohowiak, K. Y.; Robinson, T. R.; Hoppe, M. L.; Nardi, P.; Kampf, J.; Uhm, J. *Nature* **1991**, *353*, 642. (b) Tacke, R.; Burschka, C.; Richter, I.; Wagner, B.; Willeke, R. *J. Am. Chem. Soc.* **2000**, *122*, 8480. (c) Metz, S.; Burschka, C.; Platte, D.; Tacke, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 7006. (d) Nikolin, A. A.; Kramarova, E. P.; Shipov, A. G.; Baukov, Y. I.; Negrebetsky, V. V.; Korlyukov, A. A.; Arkhipov, D. E.; Bowden, A.; Bylikin, S. Yu.; Bassindale, A. R.; Taylor, P. G. *Organometallics* **2012**, *31*, 4988.

(16) A conceivable equatorial attack out of ***anti*-Cy-E** turned out to be energetically even less favorable than [**TS2**]‡ at 14 kJ mol^{-1}. For details, see the Supporting Information and also ref 17f.

(17) (a) Anh, N. T.; Minot, C. *J. Am. Chem. Soc.* **1980**, *102*, 103. (b) Kutzelnigg, W. *Angew. Chem., Int. Ed.* **1984**, *23*, 272. (c) Kaupp, M. *Angew. Chem., Int. Ed.* **2001**, *40*, 3534. (d) Tacke, R.; Bertermann, R.; Burschka, C.; Dragota, S.; Penka, M.; Richter, I. *J. Am. Chem. Soc.* **2004**, *126*, 14493. (e) Troegel, D.; Burschka, C.; Riedel, S.; Kaupp, M.; Tacke, R. *Angew. Chem., Int. Ed.* **2007**, *46*, 7001. (f) Bento, A. P.; Bickelhaupt, F. M. *Chem.—Asian J.* **2008**, *3*, 1783.

(18) A calculation of the energy differences on the basis of thermal free energies leads to the same conclusions (for details, see the Supporting Information).

(19) (a) Strohmann, C.; Gessner, V. H. *Angew. Chem., Int. Ed.* **2007**, *46*, 8281. (b) Gessner, V. H.; Strohmann, C. *J. Am. Chem. Soc.* **2008**, *130*, 14412. (c) Gessner, V. H.; Strohmann, C. *Organometallics* **2010**, *29*, 1858. (d) Gessner, V. H.; Däschlein, C.; Strohmann, C. *Chem.—Eur. J.* **2009**, *15*, 3320. (e) Carl, E.; Stalke, D. *Lithium Compounds in Organic Synthesis*; Luisi, R., Capriati, V., Eds.; Wiley-VCH: Weinheim, 2014; pp 3−31.

(20) Bauer, J. O.; Strohmann, C. *Angew. Chem., Int. Ed.* **2014**, *53*, 8167.

(21) (Trimethylsilyl)methyllithium exists as a hexamer in donor-free solvents and as a tetramer in ether solution: (a) Tecle, B.; Rahman, A. F. M. M.; Oliver, J. P. *J. Organomet. Chem.* **1986**, *317*, 267. (b) Tatic, T.; Meindl, K.; Pandey, S. K.; Stalke, D. *Chem. Commun.* **2010**, *46*, 4562.

(22) For other dimeric aggregates of Me_3SiCH_2Li, see: (a) Tatic, T.; Ott, H.; Stalke, D. *Eur. J. Inorg. Chem.* **2008**, 3765. (b) Tatic, T.; Hermann, S.; John, M.; Loquet, A.; Lang, A.; Stalke, D. *Angew. Chem., Int. Ed.* **2011**, *50*, 6666.

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