emerging.[19] We are convinced that fragment-based evolutionary design approaches like TOPAS that are able to optimize for several fitness functions in parallel—including predictions of metabolic and pharmacokinetic parameters—will lead to further significant progress in this area of computational chemistry and virtual screening.

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Chirally Modified *n*-Butyllithium: Tuning the Composition, Structure, and Enantioselectivity with Modular Fencholates**

Bernd Goldfuss,* Melanie Steigelmann, and Frank Rominger

This work is dedicated to Prof. Dr. Günter Helmchen on the occasion of his 60th birthday.

Chirally modified organolithium reagents are eminent as reagents in enantioselective syntheses[1] and as initiators in asymmetric–anionic polymerization.[2] The control of reactivity and selectivity by suitable moderators is crucial for successful application.[3] Studies in solution[4] and in the solid state[1a,g,h, 5] yield precious information on the nature of chiral organolithium systems[6] and open possibilities for a rational design of new reagents.[7] Although *n*-butyllithium (*n*BuLi) is among the most widely employed organolithium reagents and several X-ray diffraction studies have been performed on achiral *n*BuLi complexes,[8] there is little structural information on chirally modified *n*BuLi species.[5b,c, 9]

Recently, we reported the synthesis and the X-ray crystal structure of the enantiopure *n*BuLi lithium fencholate complex **1**.[9] Complex **1** forms spontaneously as a colorless precipitate on mixing anisylfenchole (**2**) and a solution of *n*BuLi in hexane and contains one equivalent of *n*BuLi as well as three lithium fencholate moieties **2**-Li (Figure 1).[9] The

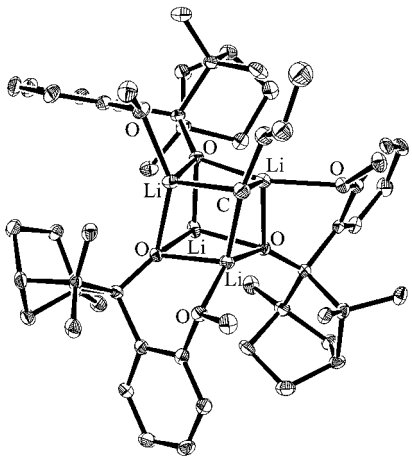

Figure 1. Molecular structure of **1**. The hydrogen atoms are omitted.

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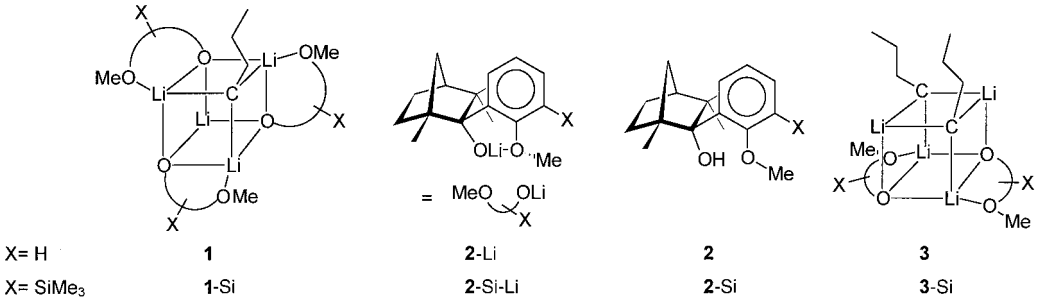
introduction of **2**-Si, which contains an $SiMe_3$ substituent *ortho* to the methoxy group, as a precatalyst increases (relative to **2**) both the reactivity and the enantioselectivity of diethylzinc additions to benzaldehyde.[10] Herein we show that **2**-Si is also capable of trapping *n*BuLi (→**3**-Si) and thus chirally modifying it. The $SiMe_3$ substituent in **2**-Si influences



the composition and the structure of the enantiopure *n*BuLi complex and also increases the enantioselectivities of *n*BuLi addition reactions to benzaldehyde.

Addition of *n*BuLi (in hexane) to **2**-Si results in the formation of a colorless precipitate which was identified, after recrystallization and single-crystal X-ray analysis, as the *n*BuLi fencholate complex **3**-Si (Figure 2).[11] Two *n*BuLi molecules and two lithium fencholate units form a distorted

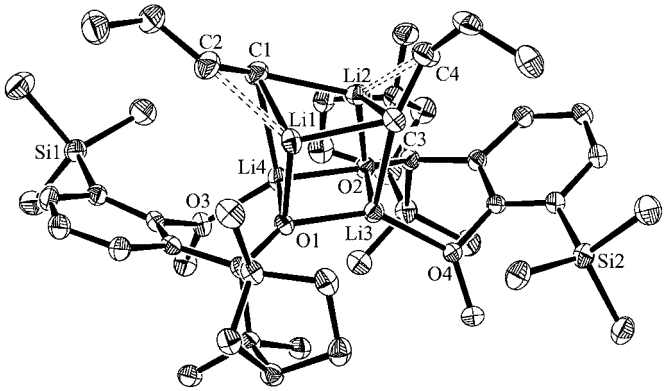
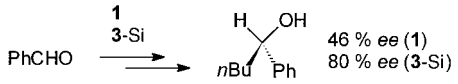


Figure 2. Molecular structure of **3**-Si. The hydrogen atoms and one *n*-hexane molecule are omitted. Selected bond lengths [Å] and angles [°]: C1-Li1 2.157(6), C1-Li2 2.172(6), C1-Li4 2.446(6), C3-Li1 2.192(6), C3-Li2 2.173(6), C3-Li3 2.450(6), O1-Li1 1.891(5), O1-Li3 1.926(5), O1-Li4 1.881(5), O2-Li2 1.919(5), O2-Li3 1.884(5), O2-Li4 1.896(5), C2-Li1 2.381(6), C4-Li2 2.359(6), O3-Li4 1.947(5), O4-Li3 1.974(5), Li1-H^a_{C2} 2.25, Li1-H^b_{C2} 2.32, Li2-H^b_{C4} 2.18, Li2-H^b_{C4} 2.31; Li1-C1-C2 78.5(2), Li2-C3-C4 77.0(2).

$Li_4C_2O_2$ cube in **3**-Si (Figure 2).[12] While in **1** lithium ions next to the *n*-butylide units are coordinated by methoxy groups,[9] no analogous Li–O bonds are apparent for Li1 and Li2 in **3**-Si. Instead, these lithium ions form short bonds to the β-CH_2 units of the *n*-butylide groups (Li1–C2: 2.381(6) Å, Li2–C4: 2.359(6) Å). Intraaggregate secondary Li–CH_2 interactions are also found in $(cC_6H_{11}Li)_6$,[13] $\{(cCHCMe_2CMe_2)CH_2Li\}_6$,[14] $(n\text{BuLi}\cdot\text{LiO}t\text{Bu})_6$,[8e] $(n\text{BuLi})_6$,[15] $(t\text{BuLi})_4$,[15] $(i\text{PrLi})_6$,[16] $(t\text{BuCH}_2\text{CH}_2\text{Li}\cdot\text{THF})_4$[17] as well as with cyclopropyl-ring edges.[18] These secondary Li–C interactions in **3**-Si clearly direct *trans* (at C1) and *gauche* (at C3) *n*-butylide units towards the Li–C edges of the $Li_4C_2O_2$ cube (Figure 2).

Like **2**, the trimethylsilyl derivative **2**-Si is also able to "trap" *n*BuLi, whereby an aggregate is formed, but not with a *n*BuLi:lithium fencholate ratio of 1:3 as found in **1** but with a ratio of 2:2. Both **1** and **3**-Si can butylate benzaldehyde, with however, different enantioselectivities (Scheme 1).[19] While **1** yields *(R)*-1-phenyl-1-pentanol in 46 % *ee*, **3**-Si affords, under analogous conditions, 80 % *ee*.[20]

To explore the origins of the increased *n*BuLi content (relative to **1**) in **3**-Si caused by $SiMe_3$ substitution, the energies of formation for the structurally characterized compounds **1** and **3**-Si as well



Scheme 1. In enantioselective additions to benzaldehyde complexes **1** and **3**-Si yield preferentially (*R*)-1-phenyl-1-pentanol.

as for the possible, but not observed, species **1**-Si and **3** were computed (ONIOM[21](B3LYP[22]/6-31 + G*:UFF[23]), Table 1, Equations (1) – (4)).[24] For ligand **2**-Li (X = H) the most exothermic energy of formation is computed for complex **1** with a *n*-butylide:fencholate ratio of 1:3 [Eq. (1), – 196.2 kcal mol^{-1}]. The formation of complex **3** from *n*BuLi

Table 1. Total energies *E* (ONIOM(B3LYP/6 – 31 + G*:UFF)) for the evaluation of the relative energies of formation of *n*BuLi lithium fencholates according to Equations (1) – (4).[a]

Compound	*E* [a.u.]	Compound	*E* [a.u]
*n*BuLi	– 47.40173	**1**	– 297.29345
2-Li	– 83.19300	**1**-Si	– 297.21014
2-Si-Li	– 83.19314	**3**	– 261.45943
		3-Si	– 261.40716

[a] All fully optimized structures (C_1 symmetry, with the exception of *n*BuLi(C_s)) were characterized as minima (NIMAG = 0) by frequency calculations. Zero-point energy corrections are not included.[21]

and **2**-Li in a ratio of 2:2 is, in comparison to **1**, less favored by 27 kcal mol^{-1} [Eq. (2), – 169.4 kcal mol^{-1}]. This explains the preferential formation of **1**.[9] The $SiMe_3$ substituent in **2**-Si supports the 2:2 composition more: the formation of **3**-Si with an *n*-butylide:fencholate ratio of 2:2 [Eq. (4), – 136.4 kcal mol^{-1}] is only 7 kcal mol^{-1} less favorable than the formation of **1**-Si with a 1:3 composition [Eq. (3), – 143.7 kcal mol^{-1}] and **3**-Si is formed experimentally.[25]

$$n\text{BuLi} + 3\,\mathbf{2}\text{-Li} \longrightarrow \mathbf{1} \qquad -196.2\ \text{kcal mol}^{-1} \qquad (1)$$

$$2\,n\text{BuLi} + 2\,\mathbf{2}\text{-Li} \longrightarrow \mathbf{3} \qquad -169.4\ \text{kcal mol}^{-1} \qquad (2)$$

$$1\,n\text{BuLi} + 3\,\mathbf{2}\text{-Si-Li} \longrightarrow \mathbf{1}\text{-Si} \qquad -143.7\ \text{kcal mol}^{-1} \qquad (3)$$

$$2\,n\text{BuLi} + 2\,\mathbf{2}\text{-Si-Li} \longrightarrow \mathbf{3}\text{-Si} \qquad -136.4\ \text{kcal mol}^{-1} \qquad (4)$$

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Equations 1 and 3 show a significant destabilization (53 kcal mol^{-1}) of **1**-Si relative to **1**, while more similar energies of formation difference 33 kcal mol^{-1}) are evaluated in Equations 2 and 4 for **3** and in **3**-Si.

Why **1**-Si is less stable than **1** is clearly shown in the computed structure of **1**-Si (Figure 3). The arrangement of three bulky trimethylsilylaryl moieties gives rise to repulsive interactions between the $SiMe_3$ groups and the *endo*-situated methyl groups of the bicyclo[2.2.1]heptane fragments (Figure 3). Similar repulsive interactions between *endo* methyl groups were identified as origin for the favored (*R*)-biaryl conformation in 2,2′-(bis-2-hydroxy-1,3,3-trimethylbicyclo-[2,2,1]hept-2-yl)-1,1′-biphenyl.[26]

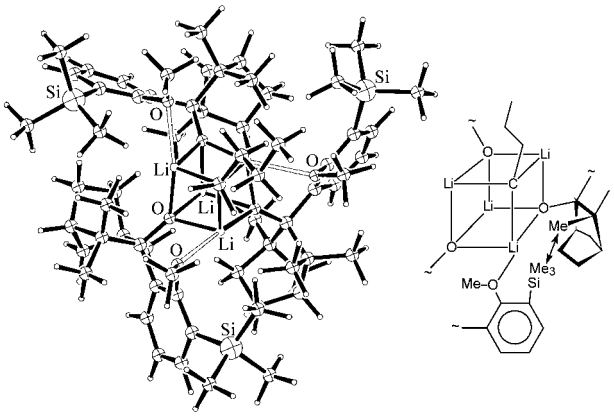

Figure 3. ONIOM(B3LYP/6–31 + G*:UFF) optimized structure of **1**-Si. The repulsive interactions between $SiMe_3$ and the *endo* methyl groups of the bicyclo[2.2.1]heptane fragments are shown schematically (right).

The stereochemical influence of $SiMe_3$ groups directs an increase in the *n*BuLi:lithium fencholate ratio from 1:3 in **1** to 2:2 in **3**-Si. Furthermore, agostic interactions are formed between the lithium ions and the β-CH_2 units in **3**-Si. These contacts offer a possible method to modify the reactivities (e.g. an increased propensity for β-hydride eliminations)[27] and selectivities of the mixed anionic aggregate **3**-Si, relative to **1**. Indeed higher enantioselectivities are observed in the reactions of **3**-Si with benzaldehyde than in that of **1** with benzaldehyde. Thus, the targeted variation of the *ortho* substituents X (e.g. H versus $SiMe_3$) of the anisylfencholate units provides many possibilities for tuning the compositions, structures, and selectivities of chirally modified *n*-butyllithium reagents.

Experimental Section

For the syntheses of **1** and **2**-Si see ref [9] and [10a].

Synthesis and crystallization of **3**-Si: *n*BuLi (1.0 mmol, 1.6 M in hexane, 0.63 mL) was added at 0 °C to **2**-Si (166 mg, 0.5 mmol) and the mixture was stirred at 25 °C for 30 min. Repeated cooling to −78 °C yielded a colorless, crystalline precipitate, which after recrystallization afforded single crystals of **3**-Si.[11]

Enantioselective butylation of **1** and **3**-Si: The complexes **1** or **3**-Si were prepared from **2** (3 mmol, 781 mg) or **2**-Si (2 mmol, 665 mg), respectively, with *n*BuLi (1.6 M, 4 mmol, 2.50 mL) in hexane. The reaction mixture was cooled to −78 °C and after 20 min benzaldehyde (for **1**: 1 mmol, 106 mg; for **3**-Si: 2 mmol, 212 mg) was added. After 2 h at −78 °C the mixture was warmed to 25 °C, stirred for 2 h and then hydrolyzed. After purification by chromatography (for **1**: silica gel, toluene:acetone = 29:1; for **3**-Si: petroleum ether:ethyl acetate = 9:1) the product *(R)*-1-phenyl-1-pentanol was obtained in a yield of 34% for **1** and 38% for **3**-Si, with 46 and 80% *ee*, respectively (GC, HPLC: DAICEL OB-H, isopropanol:hexanes = 0.8:99.2).

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[11] X-ray structure analysis of **3**-Si: SHELXTL V5.10, $C_{54}H_{94}Li_4O_4Si_2$, $M = 891.23$, $T = 200(2)$ K, $\lambda = 0.71073$ Å, monoclinic, space group: $P2_1$, $Z = 2$, $a = 10.3514(1)$, $b = 21.8005(3)$, $c = 12.3909(1)$ Å, $\beta = 98.703(1)^\circ$, $V = 2764.01(5)$ Å^3, density (calcd): 1.071 g cm^{-3}, reflections collected: 20901, independent reflections: 9020 ($R_{int} = 0.0343$), observed reflections: 7114 ($I > 2\sigma(I)$), absorption coefficient $\mu = 0.104$ mm^{-1}, absorption correction: semi-empirical from equivalents, max/min transmission: 0.96 and 0.71, refinement method: full-matrix least-squares on F^2, data/restrains/parameter: 9020/26/609, Flack parameter 0.10(11), final R indices ($I > 2\sigma(I)$), $R1 = 0.048$, $wR2 = 0.102$, largest differential peak and hole: 0.21 und -0.21 e Å^{-3}. Crystallographic data (excluding structure factors) for the structure reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-145225. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: (+44) 1223-336-033; e-mail: deposit@ccdc.cam.ac.uk).

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C–H Activation by Direct Borane – Hydrocarbon Dehydrogenation: Kinetic and Thermodynamic Aspects**

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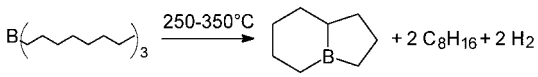
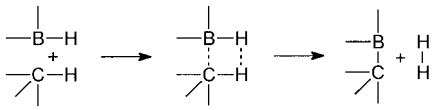
Dedicated to Prof. Manfred Regitz on the occasion of his 65th birthday

Selective C–H activations and functionalizations of hydrocarbons are challenging chemical processes with enormous synthetic potential.[1] Transition metal catalyzed[2, 3] and metal-free[4] C–H activations are being studied intensively.[5] Allylic C–H activations with organoborane reagents have been established as useful methods in organic synthesis.[6] Köster and Rotermund discovered in 1960 that the pyrolysis of triorganoboranes (e.g. tri-*n*-octylborane) yielded bicycloorganoborane, alkene, and molecular hydrogen (Scheme 1).[7] After further studies Köster et al. proposed a four-center mechanism for the observed cleavage of C–H and the formation of C–B bonds (Scheme 2).[8]



Scheme 1. Pyrolysis of tri-*n*-octylborane.



Scheme 2. The four-center mechanism of borane – hydrocarbon dehydrogenation reactions proposed by Köster.

Recently, similar intramolecular C–H activations of *tert*-butyl and phenyl groups in organoboranes in solution were reported[6e] without transition metal catalysts.[3] To analyze the factors influencing the reactivity and selectivity of these *direct*, uncatalyzed borane – hydrocarbon dehydrogenations, we have studied the kinetic and thermodynamic aspects by theoretical methods.

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