exo Adduct **4**: 4-(3-Furyl)pyridine hydrochloride (80 mg, 0.44 mmol) [14] was added to a solution of 4-(maleimidomethyl)pyridine (80 mg, 0.43 mmol) in distilled toluene (10 mL). The suspension was stirred with potassium carbonate for 2 h at room temperature and filtered. The resulting solution of **2** and **3** was flushed with argon and heated at 60 °C in the dark for 5 d. The crystals of *exo* adduct that formed were then collected by filtration. Yield: 65 mg (41 %) ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.02 (d, J = 8 Hz, 1 H), 3.08 (d, J = 8 Hz, 1 H), 4.68 (s, 2 H), 5.47 (d, J = 3 Hz, 1 H), 5.65 (s, 1 H), 6.92 (d, J = 3 Hz, 1 H), 7.19 (d, J = 6 Hz, 2 H), 7.27 (d, J = 6 Hz, 2 H), 8.55 (d, J = 6 Hz, 2 H), 8.66 (d, J = 6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.5, 47.5, 48.8, 81.3, 82.7, 119.7, 122.4, 133.1, 150.3, 150.8, 175.0, 175.2. Anal. calcd for $C_{19}H_{15}N_3O_3$: C 68.46, H 4.54, N 12.61. Found: C 68.37, H 4.57, N 12.62. Neither the mass spectrum nor melting point could be obtained owing to rapid reverse Diels–Alder reaction on ionization or heating.

endo Adduct **5**: An identical reaction mixture to that above was kept at room temperature in the dark for 10 d. White crystals of **4** were removed by filtration, and **5** was separated from the filtrate by preparative thin-layer chromatography (7% methanol in chloroform). Yield: 5 mg (3 %) ^{1}H NMR (250 MHz, $CDCl_3$): δ = 3.75 (m, 2 H), 4.29 (s, 2 H), 5.43 (m, 1 H), 5.62 (m, 1 H), 6.22 (s, 1 H), 6.84 (d, J = 6 Hz, 2 H), 6.94 (d, J = 6 Hz, 2 H), 8.27 (d, J = 6 Hz, 2 H), 8.52 (d, J = 6 Hz, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 41.1, 46.3, 47.4, 80.2, 81.7, 120.0, 123.5, 130.8, 149.8, 150.1. Neither the mass spectrum nor melting point could be obtained owing to rapid reverse Diels–Alder reaction on ionization or heating.

Received: July 22, 1994 [Z 7157 IE]
German version: *Angew. Chem.* **1995**, *107*, 223

Keywords: Diels–Alder reactions · enzyme models · host–guest chemistry · kinetics · porphyrinoids

[1] W. J. Albery, J. R. Knowles, *Biochemistry* **1976**, *15*, 5627.
[2] J. M. Avis, A. R. Fersht, *Biochemistry* **1993**, *32*, 5321; K. Johnsson, R. K. Allemann, H. Widmer, S. A. Benner, *Nature (London)* **1993**, *365*, 530.
[3] H. L. Anderson, J. K. M. Sanders, *J. Chem. Soc. Chem. Commun.* **1989**, 1714.
[4] C. J. Walter, H. L. Anderson, J. K. M. Sanders, *J. Chem. Soc. Chem. Commun.* **1993**, 458.
[5] R. P. Bonar-Law, L. G. Mackay, C. J. Walter, V. Marvaud, J. K. M. Sanders, *Pure Appl. Chem.* **1994**, *66*, 803.
[6] L. G. Mackay, R. S. Wylie, J. K. M. Sanders, *J. Am. Chem. Soc.* **1994**, *116*, 3141; T. R. Kelly, G. J. Bridger, C. Zhao, *ibid.* **1990**, *112*, 8024; J. S. Nowick, Q. Feng, T. Tjivikua, P. Ballester, J. Rebek, Jr., *ibid.* **1991**, *113*, 8831; W. L. Mock, T. A. Irra, J. P. Wepsiec, M. Adhya, *J. Org. Chem.* **1989**, *54*, 5032.
[7] H.-J. Schneider, R. Kramer, J. Rammo, *J. Am. Chem. Soc.* **1993**, *115*, 8980.
[8] D. Hilvert, K. W. Hill, K. D. Nared, M.-T. M. Auditor, *J. Am. Chem. Soc.* **1989**, *111*, 9261; A. C. Braisted, P. G. Schultz, *ibid.* **1990**, *112*, 7430; V. E. Gouverneur, K. N. Houk, B. de Pascual-Teresa, B. Beno, K. D. Janda, R. A. Lerner, *Science* **1993**, *262*, 204.
[9] F. Fringuelli, A. Taticchi, *Dienes in the Diels-Alder Reaction*, Wiley, Chichester, **1990**.
[10] The kinetics of a thiazolium-cyclophane which mimics the reversible benzoin condensation of thiamine pyrophosphate have also been studied in both directions: F. Diederich, H.-D. Lutter, *J. Am. Chem. Soc.* **1989**, *111*, 8438.
[11] It is difficult to extract directly experimental values for the rate of the forward *exo* reaction within the cavity, because the binding equilibria in this system are very complicated. This is often the case for enzyme mimics that have not had the benefit of millions of years of evolution to optimize their catalytic abilities [7]. A general computer model of the binding and kinetics has been developed in this laboratory (R. S. Wylie, J. K. M. Sanders, *Tetrahedron* **1994**, in press) and may well allow more direct access to such rate constants in the near future.
[12] A. J. Kirby, *Adv. Phys. Org. Chem.* **1980** *17*, 183.
[13] S. Anderson, H. L. Anderson, J. K. M. Sanders, *Acc. Chem. Res.* **1993**, *26*, 469.
[14] P. Ribereau, G. Queguiner, *Can. J. Chem.* **1983**, *61*, 334.

The Formation of a Mixed Organolithium Aggregate $Li_4R_2nBu_2$ during the Heteroatom-Assisted Lithiation of 1,3-Bis(dimethylaminomethyl)-2,4,6-trimethylbenzene (R = 2,6-$(CH_2NMe_2)_2$-3,5-$Me_2C_6HCH_2$)

Peter Wijkens, Ernout M. van Koten, Maurits D. Janssen, Johann T. B. H. Jastrzebski, Anthony L. Spek, and Gerard van Koten*

Dedicated to Professor Ekkehard Lindner on the occasion of his 60th birthday

In the course of our studies into the organometallic chemistry of the potentially tridentate monoanionic 2,6-bis(dimethylaminomethyl)phenyl ligand, compounds having special properties and reactivities were obtained:[1, 2] 1) metals stabilized in unusual oxidation states,[3] 2) stabilized reactive intermediates,[4] and 3) species showing catalytic activity.[5] Such organometallic compounds have related structures in which two five-membered M-C-C-C-N chelate rings share a common M–C bond.

In order to fine-tune the metal environment, we decided to investigate the properties of compounds in which the two five-membered chelate rings are extended to six-membered ones having an M-C-C unit in common. Heteroatom-assisted lithiation is, especially when the heteroatom belongs to a tertiary amino group, a valuable reaction for the synthesis of heteroatom-containing organolithium compounds, and usually provides products of high purity with excellent yield.[6, 7] We therefore started our investigations with the attempted metalation of 1,3-bis(dimethylaminomethyl)-2,4,6-trimethylbenzene (**1**) at the 2-methyl group.

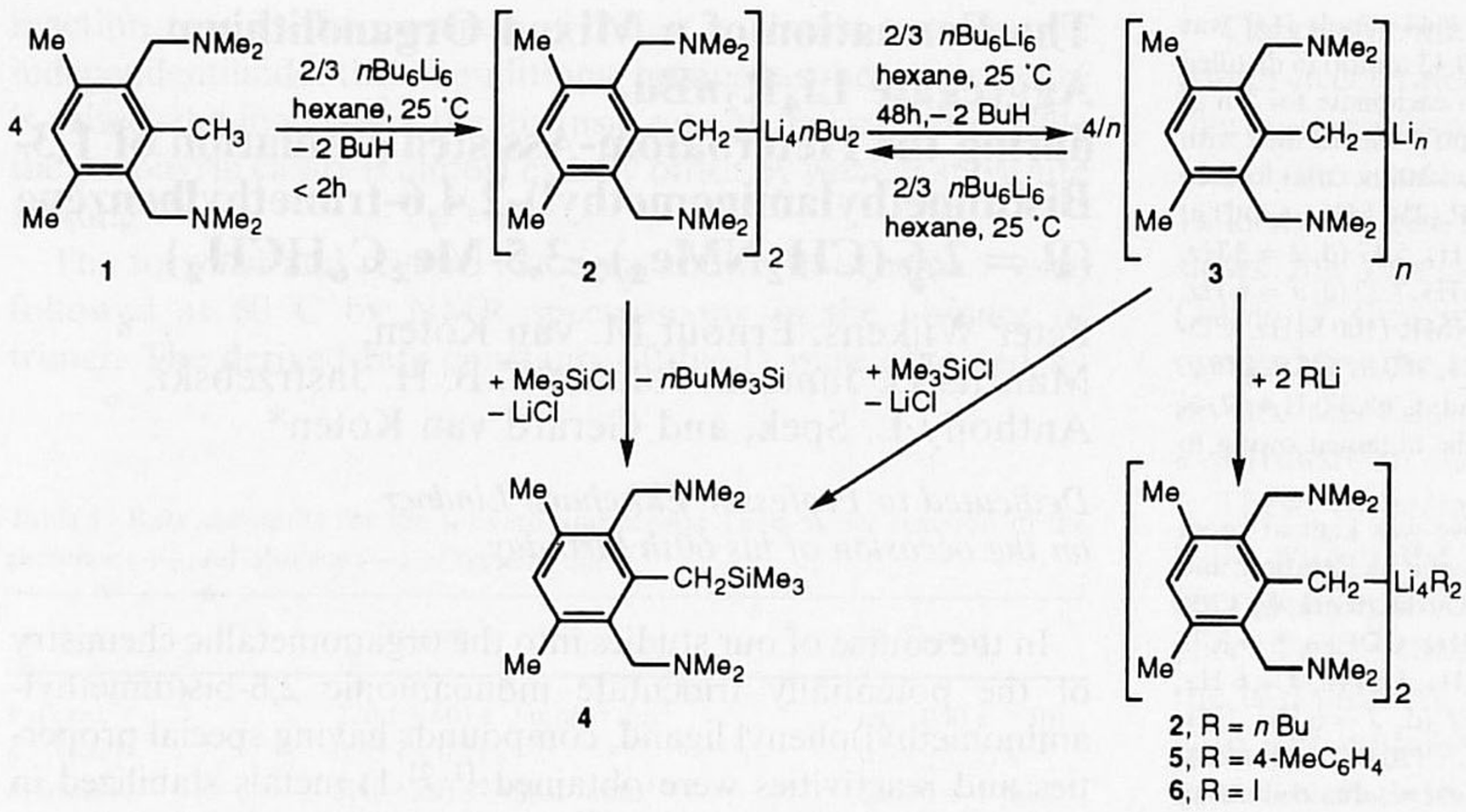
The lithiation of **1** with *n*BuLi in a 1:1 molar ratio at room temperature afforded a white, crystalline precipitate within two hours. According to its ^{1}H NMR spectrum this precipitate appeared to be a unique aggregate **2** of the parent lithiated ligand and unreacted *n*BuLi in a 1:1 ratio (Scheme 1).[8] Compound **2** was characterized by elemental analysis, ^{1}H, ^{13}C, and ^{6}Li NMR spectroscopy, and an X-ray crystal structure determination.[9]

Prolonged reaction times (two days) afforded a yellow compound **3**, tentatively assigned the structure of the pure lithiated ligand. Its insolubility in both apolar and polar solvents hampered characterization of **3**. Alternatively, **3** could be prepared in high yield within two hours by the reaction of **1** with *t*BuLi in a 1:1 molar ratio (see *Experimental Procedure*). According to the ^{1}H NMR and mass spectra (see *Experimental Procedure*), reaction of both **2** and **3** with D_2O afforded exclusively the α-monodeuteriobenzyl derivative; this indicated that quantitative regioselective lithiation at the 2-methyl group had occurred. This was furthermore confirmed by the exclusive formation of the α-trimethylsilylbenzyl derivative **4** from the reaction of both **2** and **3** with Me_3SiCl (Scheme 1). Moreover, reaction of **2** with Me_3SiCl afforded the α-trimethylsilylbenzyl derivative and $nBuMe_3Si$ in a 1:1 molar ratio, while the same reaction of **3** afforded only trace amounts (<1 %) of $nBuMe_3Si$. That **2** may

[*] Prof. Dr. G. van Koten, P. Wijkens, E. M. van Koten, M. D. Janssen, Dr. J. T. B. H. Jastrzebski
Debye Institute, Department of Metal-Mediated Synthesis
Utrecht University
Padualaan 8, NL-3584 CH Utrecht (The Netherlands)
Telefax: Int. code +(30) 523-615

Dr. A. L. Spek
Bijvoet Center for Biomolecular Research
Laboratory of Crystal and Structural Chemistry, Utrecht University

  0570-0833/95/0202-0219 $ 10.00+.25/0



Scheme 1.

be regarded as an intermediate in the heteroatom-assisted lithiation of **1** to give **3** became evident from the initially surprising observation that reaction of pure **3** with one equivalent of *n*BuLi led to selective re-formation of **2**.

An X-ray crystal structure determination of **2** revealed an overall structural geometry based on a central, almost regular Li_4 tetrahedron.[9] Two of the four Li_3 faces of the Li_4 tetrahedron are each bound to an anionic tridentate ligand ($\overset{\frown}{CN_2}$) through the benzylic carbon atom in a four-center two-electron (4c–2e) interaction (C–Li 2.319(7) Å, mean value). The two butyl groups are likewise 4c–2e-bound through the α-carbon atom (C–Li 2.215(7) Å, mean value) to the other two Li_3 faces (Fig. 1).[10] Coordinative saturation for each lithium atom is achieved by intramolecular coordination of the four nitrogen atoms (N–Li 2.079(7) Å, mean value), two from each of the heteroatom-containing ligands. The two tridentate anionic ligands may be arranged in two different ways at the faces of the Li_4 tetrahedron, and two enantiomeric aggregates thus exist. As a consequence of the crystal space-group symmetry, both are present in the unit cell.

The bonding of the benzylic group to the Li_3 face is slightly asymmetric, as is reflected by the three different C–Li distances (2.204(6), 2.348(7), and 2.407(7) Å). However, there seems to be no significant interaction between the aromatic C1 atom attached to C_α and one of the Li atoms (shortest C1–Li distance 2.782 Å). This conclusion seems to be corroborated by the angle of 113° between the C1–C7 bond and the center of the plane defined by Li1, Li2, and Li4. This points to a tetrahedral geometry around the benzylic carbon atom. These structural features of **2** are rather surprising since numerous X-ray crystal structure determinations have shown that aggregated benzyllithium compounds have planar benzyl ligands in which both the benzylic C_α and the aromatic C(*ipso*) atoms interact with lithium, as in $[PhCH_2Li(N(CH_2CH_2)_3N)_2]_n$[11] and $[PhCH_2Li(Et_2O)]_n$.[12] Only in monomeric $[PhCH_2Li(tmeda)(thf)]$ (tmeda = *N,N,N′,N′*-tetramethylethylenediamine)[13] and $[PhCH(SPh)Li(thf)_3]$[14] is the benzylic group η^1-bound.

The overall structural geometry of **2** is closely related to that found for other tetranuclear alkyl- and aryllithium aggregates:[15] each of the organic groups is 4c–2e-bound to a Li_3 face of the central Li_4 tetrahedron; the fourth coordination site of each lithium atom is occupied by either an intramolecularly coordinating substituent (i.e., a well-positioned solvent molecule)[16, 17] or an additional donor molecule.[18, 19]

The ^1H, ^{13}C, and ^6Li NMR spectra of **2**, recorded in solution ([D_8]toluene) and at low temperature (−30 °C), are consistent with a structure in solution analogous to that found in the solid state. Furthermore, the molecular weight of 587 measured by cryoscopy in benzene agrees with this tetranuclear aggregation state (calcd 608). Below −10 °C the ^1H NMR spectrum of **2** shows four resonances for the two NMe_2 groups, two AB patterns for the two CH_2N groups, and two resonances for the two Me substituents; the H4 resonance is, on the other hand, a singlet (Table 1). These results indicate the lack of a symmetry plane perpendicular to the plane of the aryl ring that also contains C(benzyl)–C4 as well as the lack of a symmetry plane containing the aryl ring. Accordingly, the CH_2NMe_2 substituents are diastereotopic as are the methyl groups in each NMe_2 group. This diastereotopicity also indicates that the N–Li coordination is nonfluxional on the NMR timescale at this temperature. A similar conclusion can be drawn from ^{13}C NMR data obtained at −20 °C. Moreover, the ^6Li NMR spectrum at −20 °C shows two distinct resonances at $\delta = 1.36$ and 1.44, respectively, in a 1:1 intensity ratio; this indicates the presence of two magnetically inequivalent lithium atoms in the Li_4 tetrahedron (the two benzylic ligands and the two butyl groups are enantiotopic as a result of twofold axial symmetry).

At higher temperatures (20 °C) a process becomes operative on the NMR timescale that generates a virtual symmetry plane perpendicular to the plane of the aryl ring; in

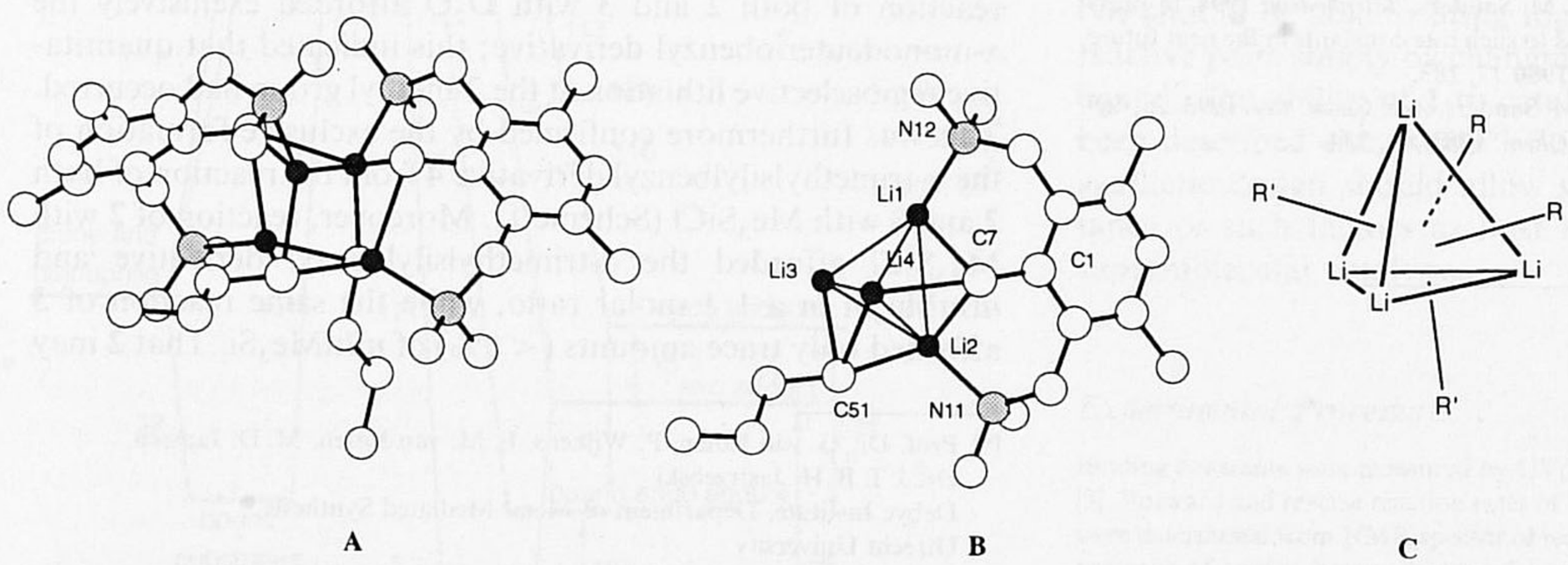


Fig. 1. A: crystal structure of **2**; B: part of the structure of **2** (one of the benzylic ligands and one of the butyl groups are omitted for clarity) with the adopted numbering scheme; C: schematical representation showing the orientation of the two different groups R ($\overset{\frown}{CN_2}$) and R′ (*n*Bu) over the Li_4 tetrahedron. Important bond lengths [Å]: Li1-Li2 2.544(8), Li2-Li3 2.582(9), Li1-Li4 2.571(8), Li2-Li3 2.585(8), Li2-Li4 2.510(8), Li3-Li4 2.494(8), C7-Li1 2.204(6), C7-Li2 2.348(7), C7-Li4 2.407(7), C51-Li1 2.198(8), C51-Li2 2.338(6), C51-Li3 2.211(7), N11-Li2 2.123(6), N12-Li1 2.045(7).

  0570-0833/95/0202-0220 $ 10.00+.25/0

Table 1. Relevant ^{1}H and ^{13}C NMR data in [D$_8$]toluene for [D]-**1**, **2**, **4**, **5**, and **6** (in [D$_8$]toluene).

Cmpd.	T [°C]	$\delta(^1H)$ 3,5-ArMe$_2$	NMe$_2$	CH$_2$N	$\delta(^{13}C)$ 3,5-ArMe$_2$	NMe$_2$	CH$_2$N	ArCH$_2$X
2	−20	2.24, 2.26	2.00, 2.11, 2.19, 2.26	3.15, 3.40 [a]; 3.15, 3.50 [a]	21.7, 22.1	44.0, 44.4, 47.9, 48.7	59.4, 59.9	24.5 [b]
2	25	2.22	2.06, 2.25	3.18, 3.49 [a]	21.8	44.2, 48.3	59.7	24.3 [b]
2	100	2.15	2.08	3.30				
5	−20	2.15, 2.35	1.50, 1.60, 1.88, 2.35	2.98, 3.52 [a]; 3.15, 3.71 [a]	22.0, 22.3	43.7, 44.3, 45.3, 49.3	58.6, 60.0	23.3 [b]
5	25	2.17	1.72, 2.00	3.14, 3.64 [a]	21.7	43.9, 47.8	59.4	23.2[b]
5	100	2.11	1.95	3.35				
6	25	2.35	2.07, 2.19	3.19, 3.51 [a]	22.0	44.7, 49.4	59.1	26.0 [b]
[D]-**1**	25	2.34	2.11	3.34	20.5	44.9	57.6	15.7 [c]
4	25	2.31	2.11	3.35	20.7	44.9	57.9	19.3 [d]

[a] ^2J(HH) = 12 Hz. [b] X = Li, the line width of 80 Hz, due to coupling of three lithium atoms with carbon, corresponds to an average $^1J(^{13}C^7Li)$ of about 9 Hz. [c] X = D, ^1J(CD) = 19 Hz. [d] X = SiMe$_3$.

the ^{1}H NMR spectrum there is one AB pattern, two NMe resonances, and one Ar–CH$_3$ resonance. A possible explanation might be a process involving the pairwise exchange of coordinating nitrogen atoms. Finally, at elevated temperatures (above 100 °C) there is also coalescence of the AB pattern and the two NMe resonances coalesce to single lines. The ^{6}Li NMR spectrum shows a single resonance; this indicates that the Li atoms have become equivalent. These observations are probably explained by process involving fast scrambling of the organic groups over the Li$_3$ faces of the Li$_4$ tetrahedron (alternatively interaggregate exchange may occur). Similar process have been proposed for other tetranuclear organolithium compounds in which the organic group contains one heteroatom substituent.[16, 17]

Previously we suggested a possible mechanism for the heteroatom-assisted lithiation of substituted *N,N*-dimethylbenzylamines with *n*BuLi that involves the successive replacement of *n*Bu groups on the Li$_3$ faces of the solvated Li$_4$(*n*Bu)$_4$ aggregate. The first step was the anchoring of the substrate through its heteroatom to a vertex of the Li$_4$ tetrahedron.[20] Based on chemical evidence Li$_4$(*n*Bu)$_2$(C$_6$H$_4$-2-CH$_2$NMe$_2$)$_2$ was proposed to be a stable intermediate in the lithiation reaction of C$_6$H$_5$CH$_2$NMe$_2$ with *n*BuLi.[21, 22] The isolation of **2** provides additional evidence for the mechanism outlined above. The conversion of **2** to **3** proceeds much slower than that of **1** to **2**, since, in order to anchor the substrate, the reaction beyond **2** requires cleavage of the intramolecular Li–N bond.

This reasoning points the way for the rational construction of mixed organolithium clusters by design of organic ligands, that is to say, the two benzylic diamine anions in **2** stabilize a dicationic Li$_4$ tetrahedron [($\overset{\frown}{CN_2}$)$_2$Li$_4$]$^{2+}$ that can bind two monodentate anions R$^-$. The selective synthesis of the [(C$\overset{\frown}{N_2}$)$_2$Li$_4$X$_2$] aggregates with X = *n*Bu (**2**), or *p*Tolyl (**5**), or halide (**6**) (Scheme 1 and *Experimental Procedure*) is proof of the potential of this method. Recent examples of this exciting area in organolithium chemistry is the selective synthesis of RLi$_2$X aggregates in which R is the pentadentate monoanionic organic group [C$_6$H$_3$-2,6-(CH$_2$N(Me)CH$_2$CH$_2$NMe$_2$)$_2$]$^-$.[23]

Owing to the presence of two different organic groups in **2**, this material is obviously not well suited as a starting material for the synthesis of other organometallic compounds, and it has already been shown that its reaction with Me$_3$SiCl affords two products. For the synthesis of organometallic compounds containing the [1,3-bis(dimethylaminomethyl)-4,6-dimethylphenyl)methyl tridentate monoanionic ligand, compound **6** (which may be regarded as a soluble modification of **3**) seems to be a better choice. This topic will be the subject of a forthcoming study.

Experimental Procedure

2: A hexane solution (16 mL) of 1.6 M *n*BuLi (25.6 mmol) was added at room temperature to a solution (30 mL) of **1** [24] in hexane. After 1 h the clear yellow solution was concentrated to ca. 20 mL. After 2 h pale yellow crystals were formed. These were isolated by centrifugation, washed with pentane, and dried in vacuo to afford **2** (2.56 g, 70% yield). Relevant ^{1}H and ^{13}C NMR data are given in Table 1 [26]. Reaction of **2** with Me$_3$SiCl afforded **4** and BuMe$_3$Si in a 1:1 molar ratio according to ^{1}H and ^{13}C NMR, and GCMS analysis.

3: A pentane solution (6.2 mL) of 1.5 M *t*BuLi (9.3 mmol) was added at −50 °C to a solution (20 mL) of **1** in pentane. The reaction mixture was stirred at room temperature for 1 h, during which time a yellow solid material was formed. This solid material was isolated by centrifugation, washed with pentane, and dried in vacuo to afford **3** (1.92 g, 87% yield). Reaction of a suspension of **3** in D$_2$O afforded, according to ^{1}H and ^{13}C NMR, and GCMS analysis, exclusively 1,3-bis-(dimethylaminomethyl)-4,6-dimethyl-2-monodeuteriomethylbenzene. Reaction of a suspension of **3** with Me$_3$SiCl afforded exclusively **4**.

Reaction of a suspension of **3** in benzene or diethyl ether with *n*BuLi, 4-MePhLi, and LiI (1:1 molar ratio) afforded **2**, **5**, and **6**, respectively. All compounds were characterized by elemental analysis, and ^{1}H and ^{13}C NMR spectroscopy. Relevant ^{1}H and ^{13}C NMR data are given in Table 1 [26].

Received: July 23, 1994 [Z 7164 IE]
German version: *Angew. Chem.* **1995**, *107*, 239

Keywords: chelate ligands · lithium compounds · metalation

[1] G. van Koten, *Pure Appl. Chem.* **1989**, *61*, 1681.
[2] G. van Koten, *Pure Appl. Chem.* **1990**, *62*, 1155.
[3] A. de Koster, J. A. Kanters, A. L. Spek, A. A. H. van der Zeijden, G. van Koten, K. Vrieze, *Acta Crystallogr. Sect. C* **1985**, *41*, 893.
[4] J. A. M. van Beek, G. van Koten, W. J. J. Smeets, A. L. Spek, *J. Am. Chem. Soc.* **1986**, *108*, 5010.
[5] D. M. Grove, G. van Koten, A. H. M. Verschuren, *J. Mol. Catal.* **1988**, *45*, 169.
[6] H. W. Gschwend, H. R. Roderiguez, *Org. React.* **1979**, *26*, 1.
[7] J. T. B. H. Jastrzebski, G. van Koten, *Inorg. Synth.* **1989**, *26*, 150.
[8] With this knowledge in mind, it is obvious that reaction of **1** with 2 equiv of *n*BuLi would afford **2** in quantitative yield (see *Experimental Procedure*).
[9] X-ray crystal structure data for **2**: C$_{38}$H$_{68}$Li$_4$N$_4$, monoclinic, space group $P2_1/c$, a = 10.8476(7), b = 16.5638(11), c = 22.3064(12) Å, β = 101.525(5)°, V = 3927.1(4) Å^3, ρ_{calcd} = 1.030 g cm^{-3}, μ(Mo$_{K\alpha}$) = 0.5 cm^{-1}, Z = 4, 8946 unique reflections ($1.5 < \theta < 27.4$), 3800 with $F_0 > 4.0\sigma(F_0)$. Enraf-Nonius CAD4T rotating anode diffractometer, graphite monochromated Mo$_{K\alpha}$ radiation, λ = 0.71073 Å, T = −123 °C. Solution by direct methods (SHELXS86), refinement of F^2 with SHELXL-93 converged at R_1 (wR_2) = 0.088 (0.242), $w = 1/(\sigma^2(F_o^2) + (0.1124P)^2)$ for 416 refined parameters (anisotropic temperature factors for the nonhydrogen atoms). Hydrogen atoms were included at calculated positions (C–H = 0.98 Å), riding on their carrier atoms. Further details of the crystal structure investigation are available on request from the Cambridge Crystallographic Data Centre, University Chemical Laboratory, 12 Union Road, Cambridge CB2 1EZ (UK), on quoting the full journal citation.
[10] The two benzylic and the two butyl groups are crystallographically inequivalent and afford slightly but not significantly different bond lengths and angles.
[11] S. P. Patterman, I. L. Karle, G. D. Stucky, *J. Am. Chem. Soc.* **1970**, *92*, 1150.
[12] M. A. Beno, H. Hope, M. M. Olmstead, P. P. Power, *Organometallics* **1985**, *4*, 2117.
[13] W. Zarges, M. Marsch, K. Harms, G. Boche, *Chem. Ber.* **1989**, *122*, 2303.

  0570-0833/95/0202-0221 $ 10.00+.25/0

[14] W. Zarges, M. Marsch, K. Harms, W. Koch, G. Frenking, G. Boche, *Chem. Ber.* **1991**, *124*, 543.
[15] E. Weiss, *Angew. Chem.* **1993**, *105*, 1565; *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1501.
[16] G. W. Klumpp, *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 1.
[17] J. T. B. H. Jastrzebski, G. van Koten, M. Konijn, C. H. Stam, *J. Am. Chem. Soc.* **1982**, *104*, 5490.
[18] H. Köster, D. Thoenes, E. Weiss, *J. Organomet. Chem.* **1978**, *160*, 1.
[19] H. Hope, P. P. Power, *J. Am. Chem. Soc.* **1983**, *105*, 5320.
[20] The kinetic intermediates are most likely smaller aggregates. The tetranuclear lithium aggregates are the thermodynamically most stable species.
[21] G. van Koten, J. T. B. H. Jastrzebski, *Tetrahedron* **1989**, *45*, 569.
[22] However, in the case of the present benzylic diamine chelate the $Li_4Bu_2(\overset{\frown}{CN_2})_2$ aggregate is further stabilized, since the two $\overset{\frown}{CN_2}$ groups effectively cap the four Li atoms and prevent further attack by the free benzylic diamine ligands.
[23] I. C. M. Wehman-Ooyevaar, G. M. Kapteijn, D. M. Grove, A. L. Spek, G. van Koten, *J. Organomet. Chem.* **1993**, *452*, C1.
[24] Obtained in almost quantitative yield by reaction of 1,3-bis(bromomethyl)-2,4,6-trimethylbenzene [25] with 4 equiv of Me_2NH; characterized by ^1H and ^{13}C NMR spectroscopy and GCMS.
[25] A. W. van der Made, R. H. van der Made, *J. Org. Chem.* **1993**, *58*, 1262.
[26] Detailed ^1H, ^{13}C, and ^6Li NMR data are available upon request from the authors.

Carbon–Carbon Bond Cleavage with Inversion of Configuration: Conversion of (*R*)-(+)-1-Methoxytetrafluoropropionic Acid to (*S*)-(−)-1,2,2,2-Tetrafluoroethyl Methyl Ether

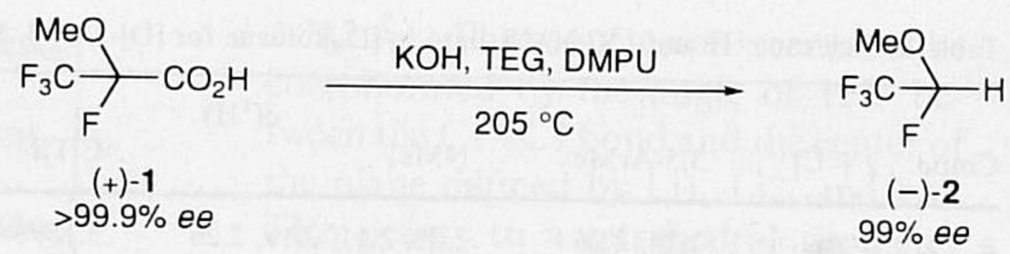
Keith Ramig,* Linda Brockunier,
Patrice W. Rafalko, and Leonid A. Rozov

Dedicated to Professor Theodore Cohen on the occasion of his 65th birthday

Asymmetric synthesis of pharmaceuticals is of increasing interest, because in many cases only one enantiomer of a chiral drug may be effective. In the field of inhalational anesthetics differences in the pharmacological profiles of enantiomers have been noted.[1] However, access to these small, highly fluorinated compounds in optically active form has been limited owing to the scarcity of suitable synthetic methods.[2] Enantiomeric separation of some of these compounds on a preparative scale has only recently been accomplished.[3]

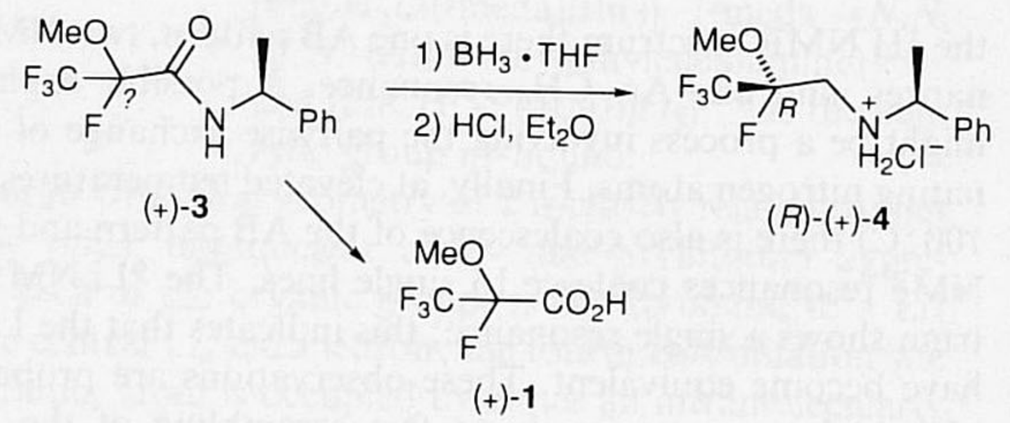
A recent report[4] has detailed the asymmetric synthesis of 1,2,2,2-tetrafluoroethyl methyl ether (**2**),[5] an intermediate in the synthesis of the anesthetic compounds 1,2,2,2-tetrafluoroethyl difluoromethyl ether (desflurane, Suprane, **6**),[6] and 1,2,2,2-tetrafluoroethyl chlorofluoromethyl ether.[7] The key reaction was stereospecific decarboxylation of enantiomerically pure 1-methoxytetrafluoropropionic acid (**1**),[8] yielding ether **2** with 99% enantiomeric excess (*ee*) (Scheme 1). Important data lacking in that paper were the absolute configurations of the starting material and the product. We wish to report that we have determined the absolute configurations of both acid **1** and ether **2**. This data, which will establish the stereochemical direction of C–C bond cleavage, is important if these types of reactions are to become viable in asymmetric synthesis.

[*] Dr. K. Ramig, L. Brockunier, Dr. L. A. Rozov
Ohmeda Pharmaceutical Products Division Inc.
100 Mountain Avenue, Murray Hill, NJ 07974 (USA)
Telefax: Int. code +(908) 771-6161
P. W. Rafalko
BOC Group Technical Center, Murray Hill, NJ (USA)



Scheme 1. Decarboxylation of acid **1** [4]. TEG = triethylene glycol, DMPU = dimethylpropylene urea = 1,3-dimethyl-3,4,5,6-tetrahydro-1*H*-2-pyrimidinone.

The absolute configuration of acid **1** is established by an X-ray crystallographic structure determination of a derivative. Amide (+)-**3** (>99.9% diastereomeric excess),[4] an intermediate in the optical resolution of acid (±)-**1**, is treated sequentially with $BH_3 \cdot THF$ complex[9] and ethereal HCl, affording amine salt (+)-**4**[10] (Scheme 2). The X-ray crystal structure[11]



Scheme 2. Establishment of the absolute configuration of acid **1**.

(Fig. 1) shows that the chiral fluorine-bearing carbon atom has the (*R*) configuration. Thus, it is established that acid **1** has the (*R*)-(+) configuration.

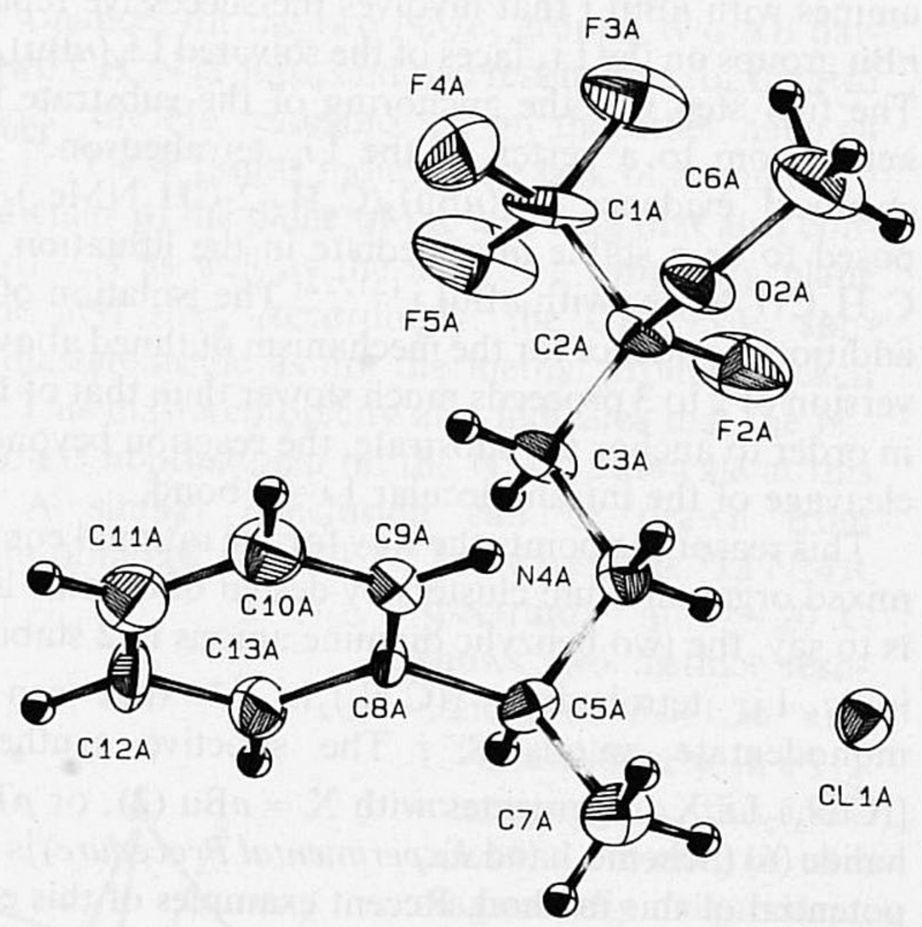


Fig. 1. ORTEP drawing of one of the two (*R*)-(+)-**4** molecules [11] in the asymmetric unit.

Establishment of the absolute configuration of ether **2** relies upon its conversion to a compound of known absolute configuration (Scheme 3). Trichlorination of the methoxy group of ether (−)-**2**[4] with Cl_2/incandescent light followed by difluorination with SbF_3/Br_2[12] gives chloroether (−)-**5** (bp 22–24 °C, $[\alpha]_D^{25} = -33$ ($c = 1$ in $CHCl_3$)). Chloroether (−)-**5** is converted to the anesthetic (−)-desflurane ((−)-**6**) by the action of Na in MeOH. According to ^1H and ^{19}F NMR analyses, the reaction results in a 1.5:1 mixture of chloroether **5** and desflurane. Chiral

  0570-0833/95/0202-0222 $ 10.00+.25/0