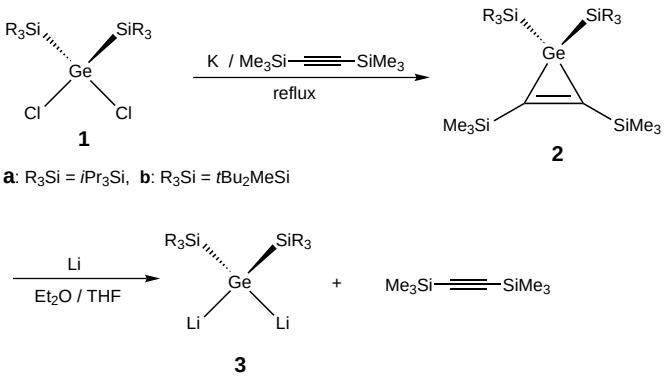
The First Isolable 1,1-Dilithiogermane and Its Unusual Dimeric Structure—An Effective Reagent for the Preparation of Double-Bonded Derivatives of Group 14 Elements**

Akira Sekiguchi,* Rika Izumi, Shinji Ihara, Masaaki Ichinohe, and Vladimir Ya. Lee

Organolithium derivatives are among the most important organometallic compounds in organic chemistry.[1] The organolithium compounds are well investigated, however, our knowledge of lithium derivatives of heavier Group 14 elements is still very limited. Among the most intensively studied are silyllithium compounds,[2] whereas very little experimental work on germyllithium derivatives has been published.[3]

1,1-Dilithiogermane derivatives (R_2GeLi_2) are of interest in view of their synthetic utility, structure, and reactivity. However, there are few reports of dilithiogermane compounds, because of the lack of a useful synthetic method.[4] In 1999, we reported the unexpected reaction of silacyclopropene with lithium to form a dilithiosilane derivative.[5] As part of this study, we have examined the reaction of the persilyl-substituted germacyclopropene with lithium and have found the clean formation of $[R_2GeLi_2]$ and bis(trimethylsilyl)acetylene by cleavage of the two Ge–C bonds in the three-membered ring. We herein report the synthesis and isolation of the first stable 1,1-dilithiogermane derivative, its unexpected crystal structure, and its use in the preparation of double-bonded derivatives of heavier Group 14 elements.

As a precursor for 1,1-dilithiogermane, we first prepared germacyclopropenes, from which the generation of the 1,1-dilithiogermane was expected upon reduction with lithium. To date, only six examples of stable germacyclopropenes have been described,[6] with five of them being structurally characterized. We employed a new method for the preparation of germacyclopropenes, in which the germylene was generated in situ by reduction of the corresponding dichlorogermane **1** with molten potassium, in the presence of bis(trimethylsilyl)acetylene, without solvent (Scheme 1). After 19 h under reflux, the starting chlorogermanes **1a** and **1b** were completely consumed and the corresponding germacyclopropenes, 1,1-bis(triisopropylsilyl)-2,3-bis(trimethylsilyl)-1-germacycloprop-2-ene (**2a**; 83%) and 1,1-bis(di-*tert*-butyl(methyl)silyl)-2,3-bis(trimethylsilyl)-1-germacycloprop-2-ene (**2b**; 81%), were formed. The germacyclopropenes **2a** and **2b** were isolated by recrystallization from pentane as air-stable colorless crystals. The crystal structures of both **2a** and **2b**



Scheme 1. Synthesis of germacyclopropenes and dilithiogermanes.

were determined by X-ray analysis and show isosceles-triangle cores with the shortest endocyclic C=C double bond lengths of all germacyclopropenes known to date: 1.317(3) Å for **2a** and 1.317(2) Å for **2b**.[6,7]

The reduction of both germacyclopropenes **2** with excess lithium in diethyl ether/tetrahydrofuran at room temperature quickly produced a red-brown reaction mixture containing the desired bis(triisopropylsilyl)dilithiogermane (**3a**) and bis(di-*tert*-butyl(methyl)silyl)dilithiogermane (**3b**). After the removal of lithium, the solvent, and the bis(trimethylsilyl)-acetylene, the oily residue was washed with dry pentane to give 1,1-dilithiogermanes **3a** and **3b** as extremely air- and moisture-sensitive pale yellow powders (Scheme 1). Such 1,1-dilithiogermane derivatives **3** have been isolated as stable compounds for the first time, although the formation of 1,1-dilithiogermanes was proposed some time ago.[4]

The crystal structure of **3b** was determined by X-ray diffraction analysis (Figure 1).[7] This structure is rather

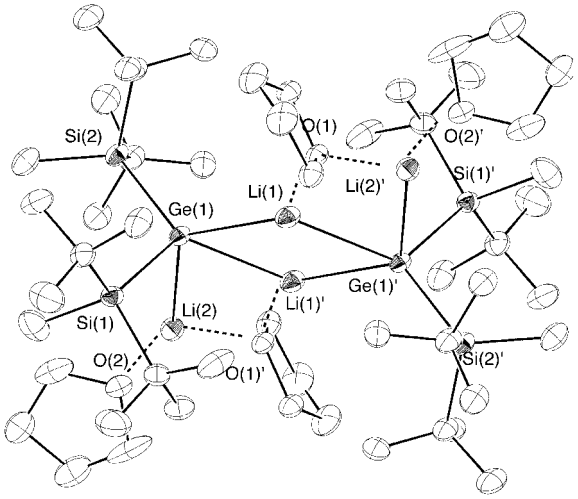


Figure 1. Structure of **3b** (ORTEP plot, thermal ellipsoids set at the 30% level; hydrogen atoms omitted for clarity). Selected interatomic distances [Å] and angles [°]: Ge(1)-Si(1) 2.4026(11), Ge(1)-Si(2) 2.4145(10), Ge(1)-Li(1) 2.664(6), Ge(1)-Li(2) 2.649(6), Li(1)···O(1) 2.092(6), Li(2)′···O(1) 2.041(7), Li(2)···O(2) 1.955(6), Li(2)···O(1)′ 2.041(7); Si(1)-Ge(1)-Si(2) 109.42(4), Si(1)-Ge(1)-Li(2) 88.61(14), Si(2)-Ge(1)-Li(2) 101.18(15), Si(1)-Ge(1)-Li(1) 104.94(15), Si(2)-Ge(1)-Li(1) 125.81(14), Li(2)-Ge(1)-Li(1) 120.46(19), Si(1)-Ge(1)-Li(1)′ 122.52(14), Si(2)-Ge(1)-Li(1)′ 123.96(14), Li(2)-Ge(1)-Li(1)′ 63.23(18), Li(1)-Ge(1)-Li(1)′ 60.8(2), Ge(1)-Li(1)-Ge(1)′ 119.2(2).

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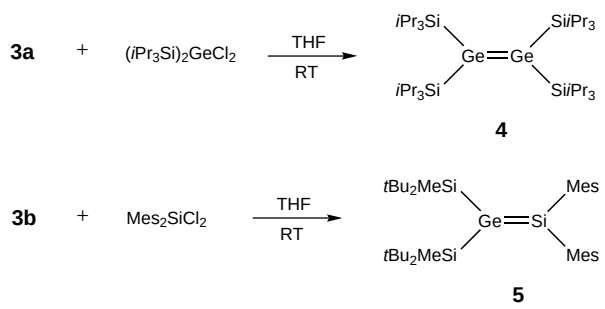
unusual and shows a dimeric molecule, in which the two lithium atoms Li(1) and Li(1)′ are shared by the two Ge atoms, to form an almost regular rhombus Ge(1)-Li(1)-Ge(1)′-Li(1)′ (Ge(1)-Li(1) = 2.664(6), Ge(1)-Li(1)′ = 2.709(6) Å). This arrangement is in sharp contrast to that of the monomeric and symmetrical 1,1-dilithiosilane.[5] The geometry of the Ge atom in **3b** is far from the ideal tetrahedral: both Ge atoms are pentacoordinated and bound to the three Li atoms (Li(1), Li(1)′, and Li(2) for Ge(1); Li(1), Li(1)′, and Li(2)′ for Ge(1)′). Both Li(1) and Li(1)′ atoms have one coordinated THF molecule, whereas each Li(2) and Li(2)′ atom is coordinated by two THF molecules. The Si–Ge bond lengths of 2.4026(11) and 2.4145(10) Å, as well as the Ge–Li bond lengths of 2.664(6), 2.649(6), and 2.709(6) Å, lie in the normal range (2.38 – 2.46 Å for Si–Ge bond lengths,[8] and 2.61 – 2.76 Å for Ge–Li bond lengths).[3d]

As we expected, the 1,1-dilithiogermanes **3** are highly reactive. The most important examples of the reactivity of **3** are their coupling reactions with dihalogermane or dihalosilane to form the corresponding digermene or germasilene. Thus, the reaction of **3a** with dichlorobis(triisopropylsilyl)-germane cleanly gave the tetrakis(triisopropylsilyl)digermene (**4**).[9] Reaction of dichlorodimesitylsilane with **3b** allowed us to prepare unsymmetrically substituted 2,2-bis(di-*tert*-butyl-(methyl)silyl)-1,1-dimesitylgermasilene (**5**) as a red-brown solid in 77 % yield (Scheme 2).[10, 11]



Scheme 2. Synthesis of double bonded derivatives of Group 14 elements; Mes = 2,4,6-trimethylphenyl.

Experimental Section

Compound **2b**: Dichlorobis(di-*tert*-butyl(methyl)silyl)germane (3.7 g, 8.1 mmol) was heated under reflux with an excess of potassium (2.2 g, 57 mmol) in bis(trimethylsilyl)acetylene (120 mL) for 19 h. After removal of the inorganic salts by filtration and removal of the solvent in vacuo, the residue was recrystallized from pentane to give **2b** as colorless crystals (3.7 g, 81 %). M.p. 125 – 127 °C (dec.); ^{1}H NMR (300 MHz, [D$_6$]benzene, TMS): $\delta = -0.02$ (s, 6H), 0.38 (s, 18H), 1.15 (s, 36H); ^{13}C{^{1}H} NMR (75.5 MHz, [D$_6$]benzene, TMS): $\delta = -4.9$, 1.2, 22.1, 30.1, 165.3 (C=C); ^{29}Si{^{1}H} NMR (59.6 MHz, [D$_6$]benzene, TMS): $\delta = -9.6$, 23.9; HRMS *m*/*z*: calcd. for $C_{26}H_{60}GeSi_4$: 558.2989, found: 558.2992.

Compound **3b**: The germacyclopropene **2b** (55 mg, 0.1 mmol) was treated with an excess of lithium (15 mg, 2.2 mmol) in a dry, oxygen-free mixture of Et_2O (1.6 mL) and THF (0.4 mL) at room temperature for 2.5 h, to give a red-brown reaction mixture. After the reaction was complete, the solvents and bis(trimethylsilyl)acetylene were removed in vacuo. Then dry toluene (1.5 mL) was added to the solid residue and excess lithium was removed by filtration in a glovebox. After evaporation of toluene, the residue was washed with pentane to give a pale yellow powder **3b** (39 mg, 71 %). ^{1}H NMR (300 MHz, [D$_8$]THF, TMS): $\delta = 0.12$ (s, 6H), 1.03 (s, 36H); ^{13}C{^{1}H} NMR (75.5 MHz, [D$_8$]THF, TMS): $\delta = -1.4$, 21.9, 26.5; ^{29}Si{^{1}H} NMR (59.6 MHz, [D$_8$]THF, TMS): $\delta = 24.0$.

Spectral data for **3a**: ^{1}H NMR (300 MHz, [D$_8$]THF, TMS): $\delta = 0.80 - 1.08$ (m, 6H), 1.09 (d, $J = 7.7$ Hz, 36H), ^{13}C{^{1}H} NMR (75.5 MHz, [D$_8$]THF, TMS): $\delta = 17.0$, 22.1; ^{29}Si{^{1}H} NMR (59.6 MHz, [D$_8$]THF, TMS): $\delta = 31.1$.

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[7] Crystal structure analysis of **3b**: Single crystals for X-ray analysis were obtained by recrystallization from benzene. Diffraction data were collected at 150 K on a MacScience DIP2030 K Image Plate Diffractometer with graphite-monochromated $Mo_{K\alpha}$ radiation ($\lambda = 0.71070$ Å). Crystal data: $[\{tBu_2MeSi)_2GeLi_2(THF)_2\}_2] \cdot C_6H_6$, $C_{58}H_{122}Ge_2Li_4O_4Si_4$, $M_r = 1168.86$, monoclinic, space group = $P2_1/c$, $a = 11.2220(8)$, $b = 18.699(1)$, $c = 16.886(1)$ Å, $\beta = 102.550(4)$, $V = 3458.7(4)$ Å^3, $Z = 2$, $\rho_{calcd} = 1.122$ g cm^{-3}, GOF = 1.024. The final *R* factor was 0.0607 ($R_w = 0.1743$ for all data) for 8186 reflections with $I_o > 2\sigma(I_o)$. Crystal data for **2b** at 120 K: $C_{26}H_{60}GeSi_4$, $Mr = 557.69$, monoclinic, space group = $P2_1/c$, $a = 19.3030(6)$, $b = 11.0260(5)$, $c = 18.1070(7)$ Å, $\beta = 118.032(2)^\circ$, $V = 3401.1(2)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.089$ g cm^{-3}, GOF = 1.040, $R = 0.0632$, $R_w = 0.0861$. The structure was solved by the direct method and refined by the full-matrix least-squares method using the SHELXL-97 program. CCDC-173500 for **2a**, CCDC-173501 for **2b**, and CCDC-173502 for **3b** contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB2 1EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).

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[10] Spectral data for **5**: red-brown solid; m.p. 92–93 °C; ^{1}H NMR (300 MHz, [D$_6$]benzene, TMS): $\delta = 0.15$ (s, 6H), 1.17 (s, 36H), 2.06 (s, 12H), 2.81 (s, 6H), 6.73 (s, 4H); ^{13}C{^{1}H} NMR (75.5 MHz, [D$_6$]benzene, TMS): $\delta = -3.2$, 22.5, 25.8, 30.3, 30.6, 128.8, 139.1, 139.2, 143.6; ^{29}Si{^{1}H} NMR (59.6 MHz, [D$_6$]benzene, TMS): $\delta = 31.4$, 146.9 (*Si*=Ge); HRMS *m*/*z*: calcd for $C_{36}H_{64}GeSi_3$: 654.3536, found: 654.3531; UV/Vis (hexane) $\lambda_{max}(\varepsilon)$: 237 (31700), 289 (8700), 430 nm (5300).

[11] We recently reported stable germasilenes: a) 2-disilagermirene: V. Ya. Lee, M. Ichinohe, A. Sekiguchi, N. Takagi, S. Nagase, *J. Am. Chem. Soc.* **2000**, *122*, 9034; b) 1,2-disila-3-germacyclopenta-2,4-diene: V. Ya. Lee, M. Ichinohe, A. Sekiguchi, *J. Am. Chem. Soc.* **2000**, *122*, 12604; c) (tBu$_2$MeSi)$_2$Si=GeMes$_2$: M. Ichinohe, Y. Arai, A. Sekiguchi, N. Takagi, S, Nagase, *Organometallics* **2001**, *20*, 4141.

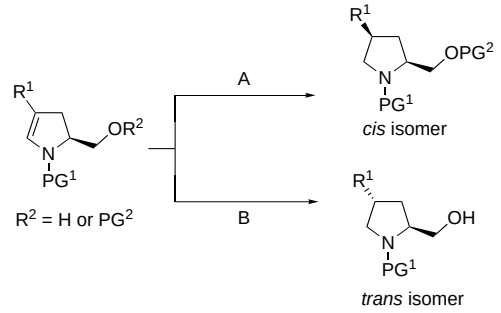
Stereoselective Synthesis of Boc-Protected *cis* and *trans*-4-Trifluoromethylprolines by Asymmetric Hydrogenation Reactions**

Juan R. Del Valle and Murray Goodman*

The effect of the proline residue on peptide conformation[1–3] has been the impetus for the design of various unnatural substituted prolines. These amino acid surrogates have featured in a number of biologically active[4–7] and highly ordered peptides.[8, 9] Prolines substituted at the 4-position have been shown to enhance the thermal stability of collagen-mimetic triple helices, with *trans*-4-fluoroproline yielding the most striking results.[10–12] The nature of the functional group and the steric constraints imposed by the C4 substituent can greatly influence the conformation of the pyrrolidine ring, as well as the rate of *cis*–*trans* isomerization about the amide bond.[13–15] For these reasons, the preparation of 4-substituted prolines is an attractive goal in peptidomimetic chemistry.

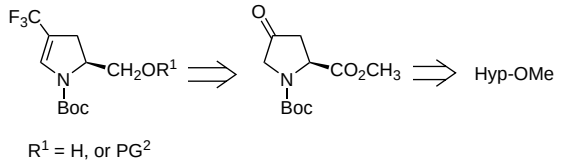
The synthesis of *cis*-4-phenylproline by a hydrogenolysis reaction, which starts from hydroxyproline was recently described by Hruby and co-workers.[16] In addition, Nevalainen et al. reported a preparation of Fmoc-*trans*-4-methylproline (Fmoc = 9-fluorenylmethoxycarbonyl) by asymmetric hydrogenation, which yields the desired isomer in a 6:1 diastereomeric ratio before purification.[17] Although these and other syntheses of 4-substituted prolines are in the literature,[18–21] a number of desirable targets continue to pose a synthetic challenge. In particular, several *trans*-substituted prolines have been difficult to synthesize with high stereoselectivity. In connection with our studies on bioactive and highly ordered peptides, we undertook the synthesis of both stereoisomers of 4-trifluoromethyl-L-proline. These building blocks are expected to have profound conformational effects on their host structures, which arise from the electronegative nature of the trifluoromethyl group.

Our strategy for the preparation of the title compounds employs asymmetric hydrogenation of the pyrrolines shown in Scheme 1. For the synthesis of the *cis* isomer, the facial



Scheme 1. Strategies for the asymmetric hydrogenation of pyrroline intermediates. A = Sterically directed hydrogenation, B = hydroxy-directed hydrogenation.

selectivity of the hydrogenation was expected to depend on steric factors, which result from protection of the hydroxy functionality as an ether or ester moiety. We were unable to find previous syntheses of *trans*-substituted prolines that exploit the potential for hydroxy-directed hydrogenation of pyrroline intermediates. We envisioned this as a viable route towards the *trans*-proline isomer as well as related analogues. The retrosynthesis in Scheme 2 shows Boc-4-prolinone (Boc = *tert*-butoxycarbonyl) as a precursor to the desired pyrrolines.



Scheme 2. Retrosynthesis of Boc-4-trifluormethyl-L-proline; Hyp = hydroxyproline.

The synthesis of Boc-4-trifluoromethyl-L-proline (Scheme 3) begins with the methyl ester of commercially available and inexpensive *trans*-4-hydroxyproline (**1**). Boc-protection was carried out under normal conditions, followed by oxidation using trichloroisocyanuric acid and catalytic 2,2,6,6-tetramethyl-1-piperidinoxyl (free radical; TEMPO)[22] to give ketone **3**.

With the protected prolinone in hand, the trifluoromethyl group was introduced by treatment of **3** with trimethyl(trifluoromethyl)silane, in the presence of a fluoride initiator[23, 24] to afford the tertiary alcohol **4** in 56% yield. Compound **4** was a single diastereomer which we presumed to be the 2*S*,4*S* isomer from the steric implications of the reaction.

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