Restricted Stereochemistry of Solvation of Allylic Lithium Compounds: Structural and Dynamic Consequences

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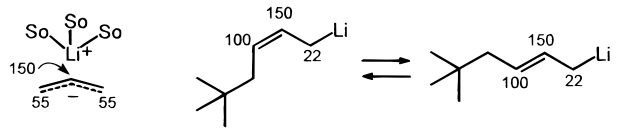
Abstract: Several 1-sila allylic lithium compounds have been prepared with potential ligands for Li substituted at the 2-position. They are [2-[[*cis*-2,5-bis(methoxymethyl)-1-pyrrolidinyl]methyl]-1-(trimethylsilyl)allyl]lithium (**22**), [2-[[*cis*-2,5-bis(methoxymethyl)-1-pyrrolidinyl]methyl]-1-(dimethylethylsilyl)allyl]lithium (**23**), [2-[[bis-(2-methoxyethyl)amino]methyl]-1-(dimethylethylsilyl)allyl]lithium (**24**), [2-[[bis(2-methoxyethyl)amino]methyl]-1-(*tert*-butyldimethylsilyl)allyl]lithium (**25**), and [2-[2-[bis(2-methoxyethyl)amino]-1,1-dimethylethyl](ethyl-dimethylsilyl)]allyllithium (**26**). Using diethyl ether or THF solutions all these compounds exhibited one bond ^{13}C, ^{7}Li spin coupling of ∼8 Hz, a 1:1:1:1 ^{13}C NMR pattern indicating monomeric structures; all show ligand resonances to be magnetically nonequivalent and reveal C_1, C_3 ^{13}C NMR shifts of about 40 and 75 δ which lie between those for model delocalized **1** and localized species **2**. These compounds are concluded to be examples of the heretofore missing folded, internally tridentately coordinated partially delocalized structures with small detectable C, Li covalence. The exception is **25** which, in diethyl ether, consists of a rapidly interconverting equilibrium mixture of localized and delocalized more solvated forms, the former prevailing at 300 K and progressively converting mainly to the latter by 180 K. NMR line shape analysis of the diastereotopic gem methylsilyl ^{13}C resonances as well as that due to the ligand carbons shows that all these line shape changes are due to the dynamics of inversion at lithium-bound carbon and that other ligand reorientation processes are slower than carbanide inversion; for inversion, $\Delta H^{\ddagger}$ is found to be 6−9 kcal·mol^{-1}, respectively. Averaging with increasing temperature of the ^{13}C, ^{7}Li spin coupling in **24** provides the dynamics of bimolecular carbon lithium bond exchange with $\Delta H^{\ddagger}$ of 12 kcal·mol^{-1}. Mechanisms are proposed on the basis of the data. We ascribe restricted stereochemistry of ligand lithium coordination to be responsible for these unusual internally coordinated structures.

Most solvated allylic lithium compounds adopt delocalized ion-paired structures,[1] some aggregated, as determined from spectroscopic,[2] X-ray crystallographic,[3] and supporting calculational studies.[4] Alternating ^{13}C NMR chemical shifts with shielding at the allyl termini, see **1** (shown without aggregation), is quite consistent with a delocalized anion[2]. A good model for an unsolvated allylic lithium, **2**, displayed ^{13}C shifts which resembled those for an alkene and are assigned to a localized structure.[5] Until recently there were no reports of spin coupling between ^{13}C and directly bonded ^{6}Li or ^{7}Li in any allylic lithium compound. Absence of the appropriate fine structure could be the result of fast ^{7}Li quadrupole-induced relaxation,[7] "relaxation of the second kind", fast intermolecular C, Li bond exchange,[8] or simply a very small coupling constant.



1 **2a** **2b**

At low temperatures, <180 K, unexpected nonequivalences seen among ^{13}C resonance in ion-paired allylic lithium com-

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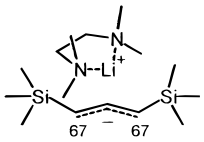
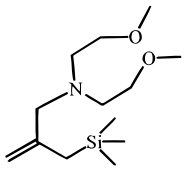
pounds,[9] for example, **3**, showed for the first time that



3

coordinated TMEDA was unsymmetrically sited with respect to the allyl loop and that ion pairs have energetically favored structures. Then, signal-averaging effects observed with increasing temperature were shown to result from the dynamics of reorientation of coordinated lithium with respect to the anion *within* the ion pair.[9,10]

Recently, a long anticipated, third general structure of allylic lithium compounds was reported that lies between the two reference compounds, **1** and **2**.[6,11] In experiments to slow down exchange of ions among ion pairs, to facilitate structure determination, it was proposed to encapsulate the ions by means of internal coordination to lithium using a pendant ligand. However, instead of producing such an ion pair, metalation of **4** produced a species that, from its NMR spectra, is best



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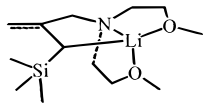


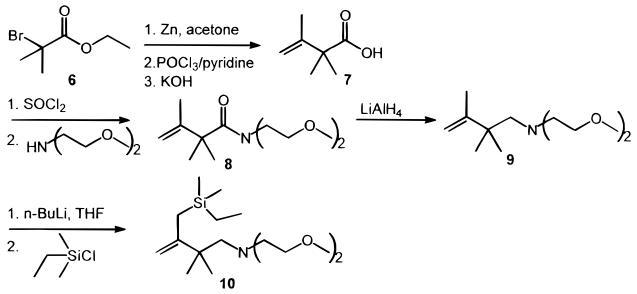
5

described as **5**, internally coordinated, partially delocalized with small detectable C, Li covalence. The allyl ^{13}C shifts lie between those for the two reference compounds **1** and **2**.[11] Compound **5** exhibits ^{13}C, ^{7}Li scalar coupling of 8 Hz, far below the 42 Hz common to many different monomeric organolithium compounds. Line shape analysis of NMR data obtained as a function of temperature provided dynamic information on inversion at carbon-bound lithium, C, Li bond exchange, and 1,3 lithium sigmatropic shifts.[11]

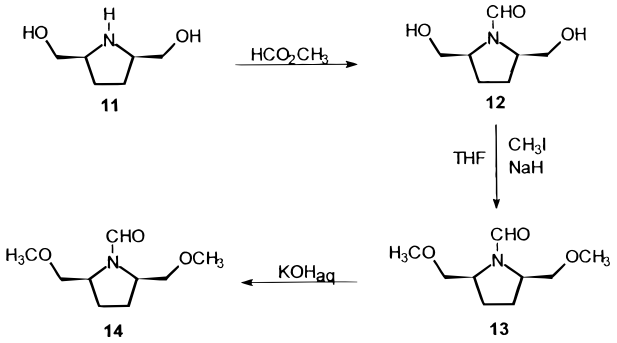
This article is addressed to the extent of the effects described above. Is the structure of **5** unique or is there a continuum of varying delocalization reflected by the ^{13}C NMR shifts and ^{13}C, lithium coupling constants? The latter should increase with decreasing delocalization. How would changing solvent, the attached ligand, and its tether and substitution on allyl affect the structure and dynamic behavior? Internally coordinated structures might be in equilibrium with others, for example, of general type **1**.

Results and Discussion

Following published procedures, ethyl-2-bromo-2-methylpropanoate was converted to 2,2,3-trimethyl-3-butenoic acid;[12−14] see **6** and **7**. Formation of the amide **8** followed by LAH reduction provided the required unsaturated amine, **9**. Allylic metalation and silylation to give **10** proceeded smoothly. In a

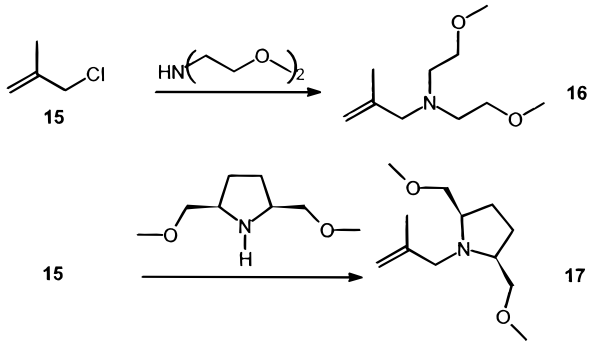


fashion similar to the chemistry of **4**, metalation of **10** is facilitated by the pendant ligand.[11] Diol **11**, which was prepared



in four steps[15−17] starting from adipic acid, was converted to *cis*-2,5-bis(methoxymethyl)pyrrolidine (**14**), following the procedure of Enders for transforming (*S*)-(−)-2-(hydroxymethyl)-pyrrolidine to the 2-methoxymethyl derivative;[18] see **11**−**14**.

Isobutenyl chloride (**15**), was conveniently aminated by both



bis(2-methoxyethyl)amine and *cis*-2,5-bis(methoxymethyl)pyrrolidine, the latter prepared as described above, forming, respectively, aminoalkenes **16** and **17**. Allylic metalation (*n*-butyllithium) of **16** and **17** followed by silylation provided our required starting materials, **18**−**21**. It is interesting that while metalation of allyl trimethylsilane is slow using *n*-butyllithum in THF and proceeds readily only with *sec*-butyllithium in THF,[9b] *n*-butyllithium readily deprotonates **16** and **17**. Preliminary studies of *N*-methyl-*N*,*N*-bis(2-methoxyethyl)amine as a catalyst for RLi metalation were disappointing;[19] it is inferior to TMEDA. Hence, the rapid metalations of **16** and **17** with *n*-butyllithium owe their facility to the *pendant* ligand, most likely due to its prior complexation with *n*-butyllithium thus directing base to the site of deprotonation.

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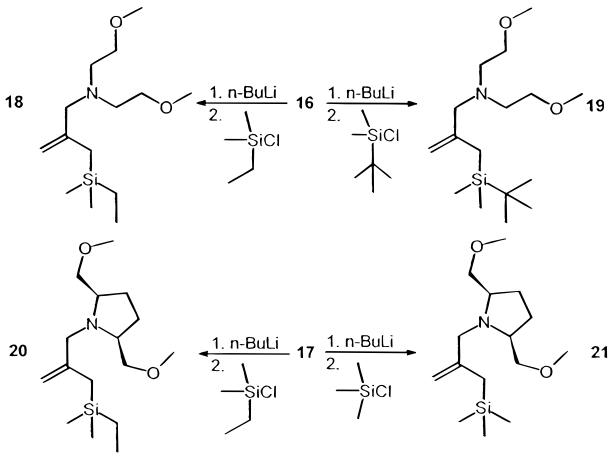
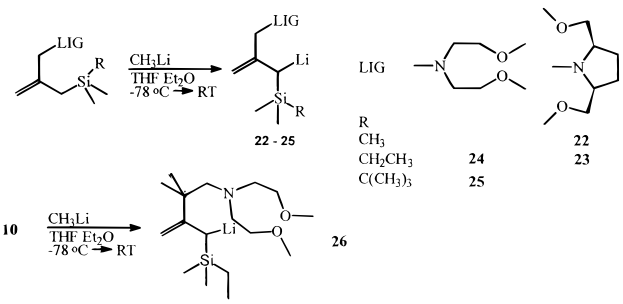


Allylsilanes **10**, **18**−**20**, and **2** are cleanly and exclusively metalated at allyl CH_2Si using methyllithium in THF/Et_2O[20] resulting in compounds **26** and **22**−**25**, respectively. Reaction



at allyl CH_2N is not detected. These compounds were transferred into diethyl ether-d_{10} or THF-d_8 for NMR study. Proton and ^{13}C chemical shifts for these species obtained at <180 K are listed around the structures in Table 1.

With the exception of **25** in diethyl ether, these samples gave no evidence for more than one species present over the entire temperature range investigated, 160−290 K.

As noted above, our model for a delocalized solvated (THF) allylic lithium compound is 1-(trimethylsilyl)lithium with ^{13}C NMR shifts for C_1, C_2, and C_3 of 53, 150, and 62 δ, respectively. This is the alternating pattern typical of a delocalized carbanion shielded at the termini due to negative charge.[9b] The shift values are consistent with the well-known linearity of the sp^2 ^{13}C shift with charge on carbon.[21] In contrast, the C_1, C_2, and C_3 shifts for unsolvated 3-(neopentylallyl)lithium are 22, 150, and 100 δ, respectively. These have the appearance of a 1-substituted alkene and are considered as representing a localized allylic lithium compound.[5a]

The allyl shifts for C_1, C_2, and C_3 of **22**−**26** lie between those for the model delocalized and localized **2** species described above and should therefore be regarded as partially delocalized. These shift values vary within a very narrow range. They appear not to depend significantly on changes in the structure of ligand from loose in **24** and **25** to constrained in **22** and **23** or with a change in tether, **26**.

In precursors to the allylic lithium compounds studied here, the two methoxyethyl moieties have the same ^{13}C NMR as do the two sides of *cis*-1,5-bis(methoxymethyl)pyrrolidine separated by its mirror plane. In contrast, all carbons in the attached ligands in **22**−**26** are magnetically nonequivalent at low temperature, 180 K.

The ^{13}C NMR data observed in this study also imply some detectable covalence between C_1 and lithium. The Fermi contact interaction[22] which is responsible for scalar coupling between directly bonded ^{13}C and ^{7}Li or ^{13}C and ^{6}Li requires some "s" character and degree of covalence associated with the bond. In fact, all the samples show evidence of one-bond ^{13}C, ^{7}Li spin coupling at low temperature, Table 2. ^{7}Li has $I = {}^3/_2$. ^{13}C NMR for C_1 of **23**−**26** consists of well-resolved equally spaced 1:1:1:1 quartets which establishes that ^{13}COH is bonded to one ^{7}Li, most likely in a monomer. The coupling constants are all ~7 ± 1 Hz. The splitting is only poorly resolved in the case of **22**, however;[11] its $^{13}C_1$ resonance width and shape is consistent with the conclusions for the other compounds. Note that ^{13}C, ^{7}Li coupling constants are averaged with increasing temperature due to intermolecular C, Li exchange and also progressively on cooling. The latter effect results from increasingly faster ^{7}Li nuclear electric quadrupole-induced relaxation. Due to these effects, ^{13}C, ^{7}Li coupling is sometimes not observed at all and often only manifested by selective broadening of the ^{13}C resonance for lithium-bound carbon within a narrow temperature range.[23]

Averaging of ^{13}C, ^{7}Li couplings due to ^{7}Li quadrupole-induced relaxation can be avoided by the use of samples enriched in ^{6}Li ($I = 1$) since the quadrupole moment of ^{6}Li is lower than that of ^{7}Li by a factor of 91.3.[24] However since the resonance ratio $\nu(^{7}Li)/\nu(^{6}Li)$ is 2.64, that puts $^{1}J(^{13}C,^{6}Li)$ at 2.5−3.0 Hz, which is easily missed in the case of viscosity broadening. This is difficult to use for NMR line shape analysis.

The ^{13}C, ^{7}Li coupling constants reported herein are very similar to those found for some benzylic lithium compounds.[25] These all hover around 6−8 Hz, much lower than the many ^{13}C, ^{7}Li coupling constants found for a wide variety of monomeric organolithium constants, which are uniformally 42 Hz.[26] The latter appear to be independent of the organic moiety. A rationalization of this unexpected uniformity, based on the treatment of Ramsey,[22] Karplus,[27] and Grant[28,29] and its accompanying approximations, then requires that the product of the "s" character and a function of the covalence, both associated with the C−Li bond, be a constant. Current NMR theory does not account for the failure of $^{1}J(^{13}C,^{7}Li)$ values for allylic[6,11] and benzylic[25] lithium compounds to conform to the common pattern found for most organolithium compounds.[26] Perhaps the conjugated nature of the former places them in a more ionic category than the latter.

Taken together, all these data are most consistent with the folded monomeric internally coordinated structures shown in Table 1. These are different from allylic lithium compounds described previously,[2,3] most likely due to the restricted options for stereochemistry of coordination of pendant ligand to lithium.

(20) Prior complexation of CH_3Li to pendant ligand must be implicated here also since CH_3Li fails to deprotonate allyltrimethylsilane under the same conditions.

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Table 1

^{13}C NMR Shifts, δ, Allylic Lithium Compounds **22**−**26**, THF-d_8 or Diethyl Ether-d_{10} Solution at Different Temperatures

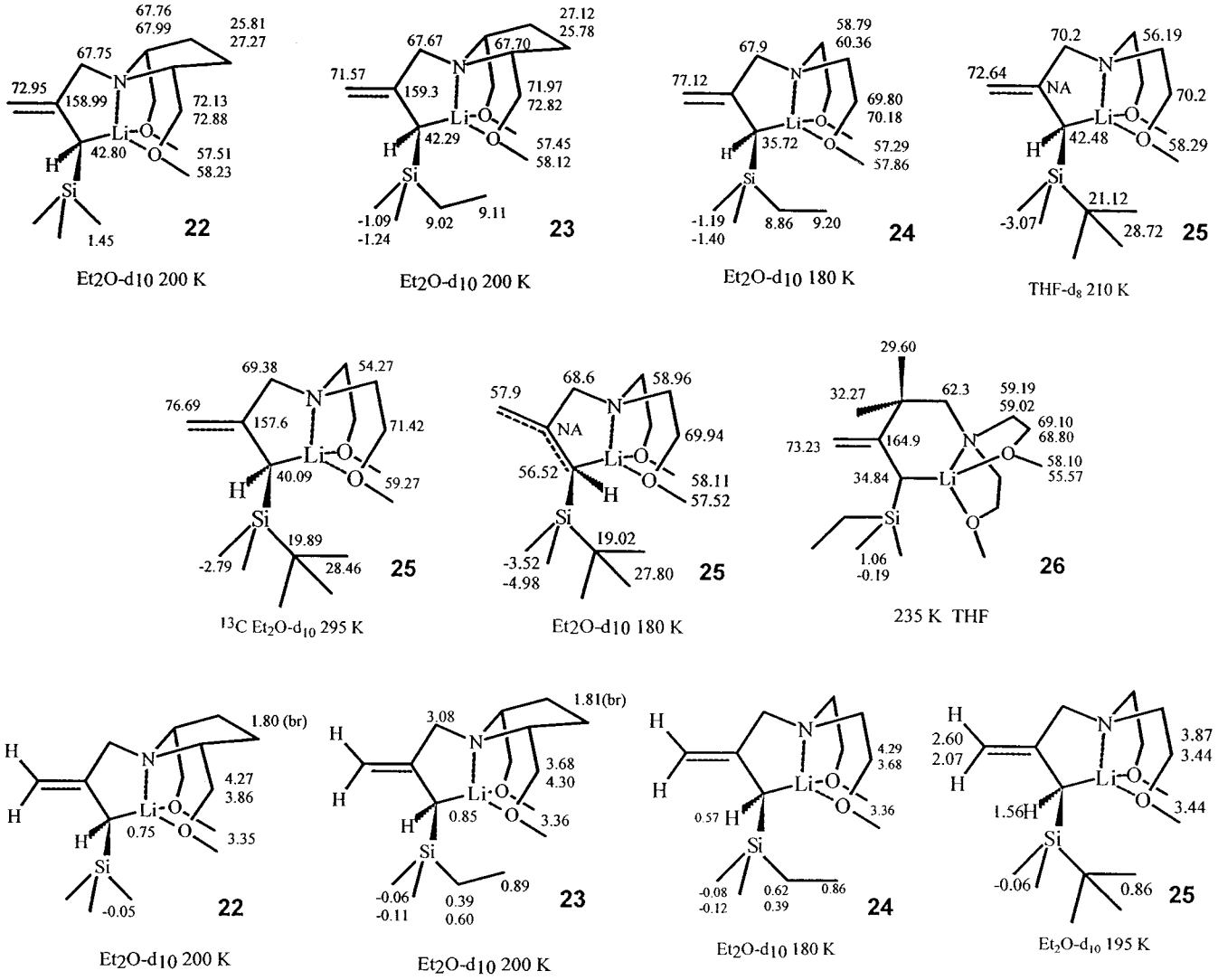

Table 2. $^1J(^{13}C,^7Li)$ (Hz) Values for Allylic Lithium Compounds

cpd	J (Hz)	solvent	T (K)
22	7.0[a]	Et$_2$O-d_{10}	240
23	7.0	Et$_2$O-d_{10}	235
24	7.8	THF-d_8	240
24	8.2	Et$_2$O-d_{10}	250
25	6.8	THF-d_8	245
26	6.0	THF-d_8	235

[a] Poorly resolved but line shape consistent with a monomer.

The only energetically favorable arrangement is with Li and N in or near the allyl plane and the oxygens on two sides and normal to this plane. Such an arrangement allows for "s" character associated with some covalency to the C−Li bond, hence detectable spin coupling. The published structures for solvated allylic lithium compounds have lithium normal to the allyl plane,[3] which minimizes the possibilities for ^{13}C, ^{7}Li spin coupling. Further, among our compounds internal coordination encapsulates lithium, reduces its exchange rate with lithium in other molecules compared to externally solvated allylic lithium compounds, and improves the liklihood of observing ^{13}C, ^{7}Li spin coupling should the value be large enough to resolve.

The $^{13}C_1$ NMR of **24** in diethyl ether-*d* solution provides just the changes needed to measure the intermolecular C, Li bond exchange and estimate the ^{7}Li quadrupole relaxation rate.[30] At low-temperature, one-bond $^{13}C_1$, ^{7}Li coupling is clearly seen. Since quadrupole relaxation is already slow enough at 260 K to reveal the ^{13}C, ^{7}Li coupling, it is unlikely to perturb the ^{13}C line shapes at higher temperatures. Besides, the contribution due to ^{7}Li quadrupole relaxation will also be taken into account; see below. The exchanging system, with ^{13}C in natural abundance is modeled as (eq 1) together with spin functions in

$$\begin{array}{ccccc} {}^{13}C^{7}Li + {}^{12}C^{7}Li^{*} & \rightleftharpoons & {}^{13}C^{7}Li^{*} + {}^{12}C^{7}l & & \\ \alpha\ell & m & \alpha m & \ell & \\ \beta\ell & m & \beta m & \ell & \end{array} \quad (1)$$

the product representation $\phi^{13}_C\phi^7_{Li}$, so that the quantum mechanics follows the chemistry. Here α, β are for ^{13}C ($I = {}^1/_2$), l and m for ^{7}Li ($I = {}^3/_2$). The ^{13}C transitions to be plotted are diagonal in ^{7}Li since this is a ^{13}C first-order spectrum and are listed as

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α ($^3/_2$) → β ($^3/_2$), α ($^1/_2$) → β ($^1/_2$), α ($-^1/_2$) → β ($-^1/_2$), and α ($-^3/_2$) → β ($-^3/_2$), where the states of ^{7}Li are indicated by their m_z eigenvalues. The required elements of the density matrix are

$$\langle \alpha\phi_{\mathrm{Li}}|\rho|\beta\phi_{\mathrm{Li}}\rangle = \rho^I \tag{2}$$

and are abbreviated as ρ^1, ρ^2, ρ^3, and ρ^4 for m_z of ^{7}Li, respectively, $^3/_2$, $^1/_2$, $-^1/_2$, and $-^3/_2$. Then, given the ρ^I elements, the absorption is given in (3).

$$\mathrm{Abs}(\nu) = -Im(\rho^1 + \rho^2 + \rho^3 + \rho^4) \tag{3}$$

The elements ρ^I are obtained by solving the four coupled first-order equations generated by taking the four elements of the density matrix equation (eq 4) whose states are connected by a

$$\langle \alpha\phi_{\mathrm{Li}}|l[\rho,H] - \rho/T + E\rho + R\rho|\beta\phi_{\mathrm{Li}}\rangle = 0 \tag{4}$$

^{13}C transition, where E and R are exchange and relaxation operators, respectively, $1/T$ is the ^{13}C line width in the absence of exchange, H is the Hamiltonian, and ρ is the density matrix. Elements of $E\rho$ are evaluated as follows. Consider the exchange process again, eq 1. Before exchange, an element of the density matrix of ^{13}C ^{7}Li is given by eq 5 since the trace of ρ is unity.

$$\rho^{\mathrm{CLi}}_{\alpha l,\beta l} = \rho^{\mathrm{CLi}}_{\alpha l,\beta l} \sum_m \rho^{\mathrm{Li}^*}_{m,m} \tag{5}$$

After exchange, switching Li* for Li (in C Li) and m for l in the spin products, we have eq 6. Since there are four spin states

$$\rho^{\mathrm{afterrex}}_{\alpha l,\beta I} = \sum_m \rho^{\mathrm{CLi}}_{\alpha m,\beta m}\, \rho^{\mathrm{CLi}}_{l,l}$$

$$= \sum_m \frac{1}{4}\rho^{\mathrm{CLi}}_{\alpha m,\beta m} \tag{6}$$

for ^{7}Li, each diagonal element is equal to $^1/_4$. Then, an element of $E\rho$ is given by eq 7 where k is the psuedo-first-order rate

$$[E\rho^{\mathrm{CLi}}]_{\alpha I,\beta I} = k\left(\frac{1}{4}\sum_m \rho^{\mathrm{CLi}}_{\alpha m,\beta m} - \rho^{\mathrm{CLi}}_{\alpha I,\beta I}\right)$$

$$= k\left(\frac{1}{4}\sum_{m\neq 1} \rho^{\mathrm{CLi}}_{\alpha m,\beta m} - \frac{3}{4}\rho^{\mathrm{CLi}}_{\alpha I,\beta I}\right) \tag{7}$$

constant.

Elements $(R\rho)_{\alpha l\beta l}$ have already been evaluated.[31] In the extreme narrowing approximation, $\tau\omega \ll 1$, the j_α are simply related and we are able to use a composite relaxation parameter, r, shown in eq 8, with q the electric field gradient, Q the

$$r = [(e^2qQ)/4I(2I-1)h]^2\tau \tag{8}$$

quadrupole moment, h Planck's constant, I the spin, and τ the correlation time.

Finally, we display the spin Hamiltonian in the rotating frame where ν_S is the resonance frequency of ^{13}C, ν is a point on the frequency axis, the operators have their usual meanings, and J_{CLi} is $^1J(^{13}\mathrm{C}^7\mathrm{Li})$, henceforth abbreviated as "J"; see eq 9.

$$H = 2\pi(\nu_s - \nu)I^z_{\mathrm{C}} + J_{\mathrm{C,Li}}I^z_{\mathrm{C}}\, I^z_{\mathrm{Li}} \tag{9}$$

The resulting four coupled equations (10), displayed in matrix form, are solved for the ρ elements as a function of the frequency

$$\begin{bmatrix} i2\pi(\Delta\nu-1.5J) - T^{-1} - 0.75k - 14.4r & 0.25k + 7.2r & 0.25k + 7.2r & 0.25k \\ 0.25k + 7.2r & i2\pi(\Delta\nu - 0.5J) - T^{-1} - 0.75k - 14.4r & 0.25k & 0.25k + 7.2r \\ 0.25k + 7.2r & 0.25k & i2\pi(\Delta\nu + 0.5J) - T^{-1} - 0.75k - 14.4r & 0.25k + 7.2r \\ 0.25k & 0.25k + 7.2r & 0.25k + 7.2r & i2\pi(\Delta\nu + 1.5J) - T^{-1} - 0.75k - 14.4r \end{bmatrix} \begin{bmatrix} \rho_1 \\ \rho_2 \\ \rho_3 \\ \rho_4 \end{bmatrix} = iC \begin{bmatrix} 1 \\ 1 \\ 1 \\ 1 \end{bmatrix} \tag{10}$$

and then summed as in (3) to give the NMR absorption. Use of trial values of k and r showed that ^{7}Li quadrupole-induced relaxation does not contribute detectably to the NMR line shapes above 260 K. Comparison of observed to calculated line shapes, Figure 1, provided the pseudo-first-order rate constants. Resulting activation parameters are $\Delta H^{\ddagger} = 12.5$ kcal·mol^{-1} and $\Delta S^{\ddagger} = 6.4$ eu; see Table 3.

At low temperature, ^{13}C NMR of the geminal methyls on Si in **22**−**26** in diethyl ether-d_{10} each give rise to a single 1:1 doublet. This splitting is not the result of slow interconversion of rotamers with nonequivalent methyls by rotation around the Si−allyl bonds since precursor propenes gave only a single line each for these methyl pairs in ^{13}C NMR at low temperature. Rather the geminal methyl doublets in our allylic lithium compounds are due to the chiral environments in these compounds. With increasing temperature these doublets progressively average to single lines at their respective centers. The line shapes are treated as due to two-site half-spin uncoupled equally populated exchanging systems.

The overall process responsible for these changes in line shapes is inversion at lithium-bound carbon; it must be first order since the appearance of the line shapes does not change with the concentration of the allylic lithium compound. Some proposals regarding the mechanism are made below. Comparisons of observed to calculated methylsilyl ^{13}C line shapes for **23** (^{1}H and ^{13}C) and **24** provided the first-order rate constants for inversion. The resulting activation parameters for all compounds studied are listed in Table 3.

As noted above, all carbons on the pendant ligands in **22**−**26** are magnetically nonequivalent. With increasing temperature, the equal ^{13}C NMR doublets due to CH_3O, CH_2O, and NCH_2C in **24**, for example, averaged to single lines at their respective centers; similar effects were found for the pyrrolidino ligand in **23**—doublets due to CH_3O, CH_2O, ring CH_2, and ring CH each undergo signal averaging with increasing temperature.

Phenomenologically these line shape changes are the result of ligand reorientation. Each doublet undergoing averaging was calculated as a separate two-site equally populated uncoupled exchanging system. Comparison of observed and calculated line shapes provided the reorientational rate constants. Since the line shapes were independent of concentration, the process responsible for the changes must be first order. Line shape analysis of the ligand ^{13}C resonances for **23** (CH_2CH_2 and CH_2O) and **24** (CH_2O and CH_3O) gave the activation parameters listed in Table 3.

In studies of allylic and benzylic lithium compounds[9,10] complexed to external ligands such as TMEDA, reorientational effects observed in NMR of the ligand were ascribed to rotation or flip-flopping of the complexed ligand on *one side* of the carbanionic plane (lateral motions), fast reversible N, Li dissociation accompanied by inversion at nitrogen and rotation around the NCH_2 bond, and transfer of coordinated lithium between two sides normal to the carbanionic face. Only the latter process results in inversion.

(31) A. Chow, M. S. Thesis, The Ohio State University, 1982.

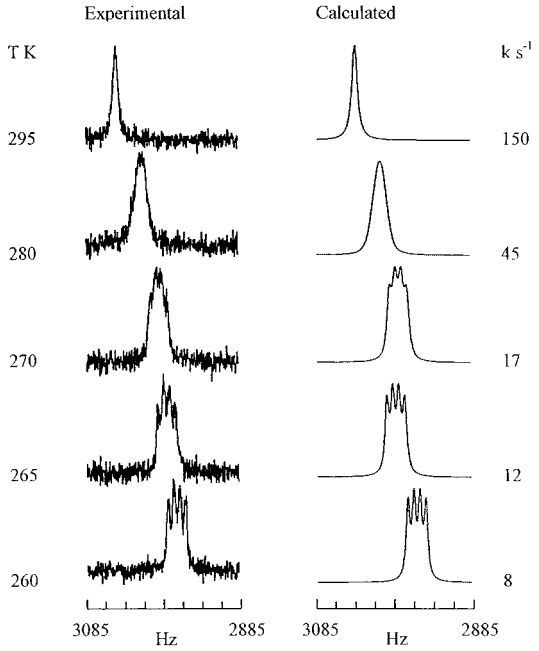


Figure 1. ^{13}C NMR of **24**, 0.25 M in diethyl ether-d_{10} (left) C_1 part, observed, different temperatures; (right) calculated, with rate constants.

Table 3. Activation Parameters for Allylic Lithium Compounds

cpd	process	resonance	$\Delta H^{\ddagger}$ (kcal/mol)[a]	$\Delta S^{\ddagger}$ (eu)[b]
22	inversion	OCH_3	9.3	−6.5
		CH_2	8.9	−8.0
23	inversion	$Si(CH_3)_2$	9.3	−7.3
		OCH_3	9.4	−6.2
		OCH_2	9.1	−8.1
		CH_2	9.4	−6.9
24	inversion	$Si(CH_3)_2$	6.1	−17.6
		OCH_3	5.9	−18.4
		OCH_2	6.2	−17.2
		$Si(CH_3)_2$ (^1H)	5.8	−15.8
	Li−C bond exchange	$^7Li-C_1$	12.5	−6.4
25	inversion	$Si(CH_3)_2$	8.5	-4.5
		OCH_3	8.9	−3.1
	ligand reorientation	NCH_2C	7.8	−21.0
		OCH_3	8.6	−15.0
26	inversion	$Si(CH_3)_2$	12.0	−2.0
		$C(CH_2)_2$	11.9	−8.0

[a] ±5%. [b] ±10%.

Due to the tridentate and attached nature of the ligand in **22**−**26**, ligand lithium dissociation would be a disfavored reorientation route compared to systems with external ligands. Further, with attached ligand, lateral motion would require a 1,3 lithium sigmatropic shift, already known to be slow[6] ($\Delta H^{\ddagger} = 18$ kcal·mol^{-1}), and would lead to thermodynamically unstable products. It is not surprising then that *all* the activation parameters determined for reorientation of the pendant ligands are essentially identical to inversion values that come from ^{13}C geminal methyl resonances, i.e., the other ligand reorientation processes must be much slower than inversion. The exception is **26** with the two-carbon tether. Possibly this is a looser bonding arrangement which might facilitate the dissociation reorientation process, hence ligand reorientation is considerably faster than inversion; see Table 3.

It might have been expected that the electronic structures of these internally solvated partially delocalized allylic lithium compounds would respond sensitively to changes in the ligand, its tether, substituent, and solvent. So far none of these modifications has shown significant influence on the degree of

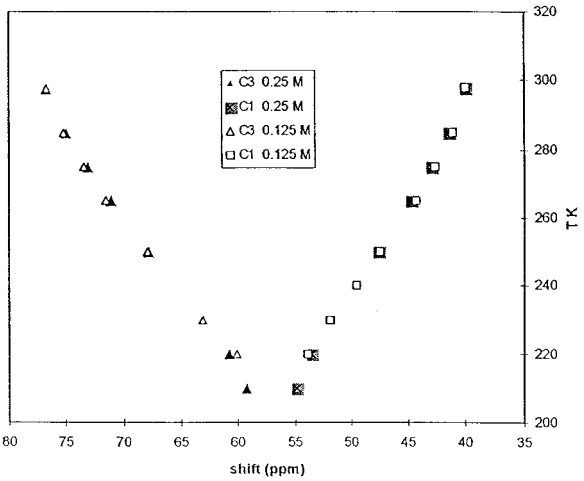


Figure 2. C_1 and C_3 ^{13}C NMR shifts of **25**, in diethyl ether-d_{10} at different concentrations, plotted versus temperature.

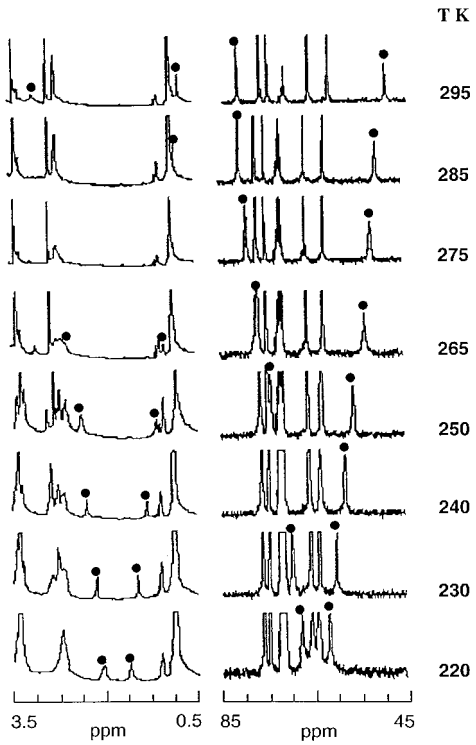


Figure 3. ^{13}C and ^1H NMR of **25** in diethyl ether-d_{-10} at different temperatures with $C_{(1)}H$ and $C_{(3)}H_2$ resonances indicated. (left) ^{13}C NMR; (right) ^1H NMR; $C_{(3)}H_2$ to left in each stack.

delocalization as evidenced by the C_1 and C_3 ^{13}C shifts. An exception is the behavior of **25**. In THF solution, **25** shows the same C_1, C_3 ^{13}C shifts as the other compounds largely independent of temperature between 180 and 290 K. In contrast, while the room-temperature ^{13}C NMR spectrum of **25** in diethyl ether was identical to that in the THF solution, on lowering the temperature, the C_1 and C_3 shifts approach each other, that of C_1 increasing and C_3 decreasing in almost linear fashion (see Figure 2). By 210 K, the C_1 and C_3 shifts resemble those for a typical ion-paired delocalized allylic metal compound such as [1-(trimethylsilyl)allyl]lithium.[9a] Similar results were observed in proton NMR, Figure 3. These observations were independent of concentration of **26**; see Figure 2. Within the entire temperature range over which **25** in diethyl ether was investigated, no more than one NMR spectrum was observed. The only reasonable explanation for these observations is that **25** in

diethyl ether consists of a rapidly interconverting equilibrium mixture of two or more species. The more covalent species) would prevail at higher temperatures, converting mainly to the ionic more delocalized species at lower temperatures.[32,33] Since the results appear to be independent of concentration, the aggregation of the different kinds of species must be the same.

Qualitatively the results for **25** have parallels in the extensive literature on equilibria between contact and solvent-separated ion-paired metal salts.[32,33] The latter are favored at lower temperatures due to exothermicity associated with coordinating extra ligand molecules to metal ion in the solvent-separated ion pairs, compared to the contact ion pairs.[32,33] The analogy is qualitative since the higher temperature form of **25** is regarded as a partially covalent species. Similar results have been observed for neopentylallyllithium, which interconverts rapidly between covalent and ionic forms with the latter predominant only at lower temperatures.[5a] Why **25** behaves in this way while the others described herein do not must be ascribed to the tertiary butyl group in silicon. Steric interactions between the tertiary butyl group in the (internally solvated) localized structure and the pendant ligand may be responsible for destablizing the higher temperature species.

It is also interesting that the rate of interconversion between the more covalent and more ionic forms of **25** is too fast to allow observation of NMR resonances due to the individual species. At the lowest temperature at which **25** in diethyl ether was investigated, being the slowest interconversion rate, only one species, the ionic one is present. Midrange at 260 K with similar concentrations of at least two species present, as evidenced by the observed shifts, still only one spectrum was observed.

As noted above, in the past allylic lithium compounds were reported to adopt two main structures, the delocalized ion-paired ones (see **1**), recognized by their alternating ^{13}C shifts with shielding at the termini, and the unsolvated species, for example, **2**, considered localized because their ^{13}C shifts resembled those for an alkene. In principle, one might expect there should be other structures between **1** and **2**; delocalized to different degrees, the less delocalized the greater the C, Li covalency. Two such structures reported recently[6,11] are favored only due to the strategic attachment of a coordinating ligand, which has the effect of severely restricting the stereochemistry of lithium coordination.

In the present study, we have investigated the extent of the structural and dynamic consequences of internal coordination of lithium by varying the nature of the ligand, its tether, and substitution.

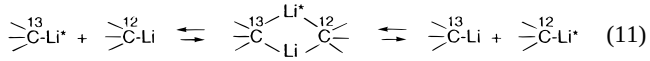
All the species reported here (except **25** at low temperature in diethyl ether) exhibit similar sets of allylic ^{13}C shifts, intermediate between those for reference localized and delocalized species. Extension of the tether from one to two carbons changes the shifts only a little. This applies also to the ligand carbon shifts. Similarly, replacing the floppy bis(2-methoxyethyl)amino ligand by the more constrained *cis*-2,5-bis(methoxymethyl)pyrrolidino moiety causes only minor changes in the ^{13}C allyl shifts. These changes are too small to interpret further.

Taken together, the shifts and ^{13}C, ^{7}Li spin coupling data for compounds studied here all support the folded partially delocalized internally coordinated structures with detectable C, Li covalence, proposed in structures **22**−**26**.

These compounds undergo several interesting fast equilibrium exchange and rearrangement processes—very fast ionic ⇄ covalent interconversions, inversion at carbon bound lithium measurable on the NMR time scale, and somewhat slower bimolecular C,Li bond exchange, the latter evidenced by averaging of the ^{13}C, ^{7}Li coupling constant for **24**. The system was simulated as in (1). The dynamic parameter, k, obtained

$$^{13}C^{7}Li + {}^{12}C^{7}Li^{*} \underset{k_2}{\rightleftharpoons} {}^{13}C^{7}Li^{*} + {}^{12}C^{7}Li \qquad (1)$$

from fitting the line shapes is the pseudo-first-order rate constant $k_2(^{13}C^{7}Li)$ as defined by Grunwald et al.[35] While there is no evidence for any particular mechanism, the process has to be second order in ground-state organolithium compound. Transition states dimeric with respect to ground state may resemble higher aggregated ground-state structures for many organolithium compounds.[3] Thus, C, Li bond exchange between monomers (the state of **24**) could be written, neglecting solvation, as (11) for a system with ^{13}C in natural abundance.



(11)

While ^{13}C NMR shifts for **22**−**26** do not vary much, there are differences among the dynamic results for inversion. Among compounds with a one-carbon tether, the reorientation parameters derived from the ^{13}C NMR ligand resonance are very similar to those from the geminal methyl pairs. Since the latter line shapes have to result from inversion, so must the line shape changes of the ligand resonances. In these cases, C_1 inversion is the fastest mode of ligand reorientation. The exception is **26** with a two-carbon tether wherein ligand reorientation is faster than inversion. Perhaps the complex in **26** is just weaker than in the other four compounds with a one-carbon tether. Ligand reorientation was found to be faster than inversion in cases of allylic lithium compounds complexed to external ligands.

Development of a mechanism for inversion in **22**−**26** requires taking into account the following observations. It is a first-order process. The results with the loose ligand bis(2-methoxyethyl)-amino compared to the constrained *cis*-2,5-bis(methoxymethyl)-pyrrolidino are not very different and in both cases ligand reorientation is driven by the inversion process. This suggests that fast reversible ligand lithium dissociation with nitrogen inversion is not a feature of the inversion process about C_1 (it is slower); i.e., lithium ligand coordination retains its integrity throughout inversion.

Inversion is slower than localized/delocalized allylic lithium interconversion and is much faster than rotation around the allylic bond, the latter with $\Delta H^{\ddagger}$ of 12−20 kcal·mol^{-1}.[2f] A mechanism for inversion consistent with the above observations involves (1) a 90° anticlockwise rotation of coordinated Li around C_1 with ionization and planarization, (2) transfer of coordinated Li^{+} between the two faces of the anion, and (3) 90° clockwise rotation with deplanarization around C_1. The overall result is inversion at C_1; see Figure 4. If step 1 and its reverse (2) are fast, that would account for the rapid localized/

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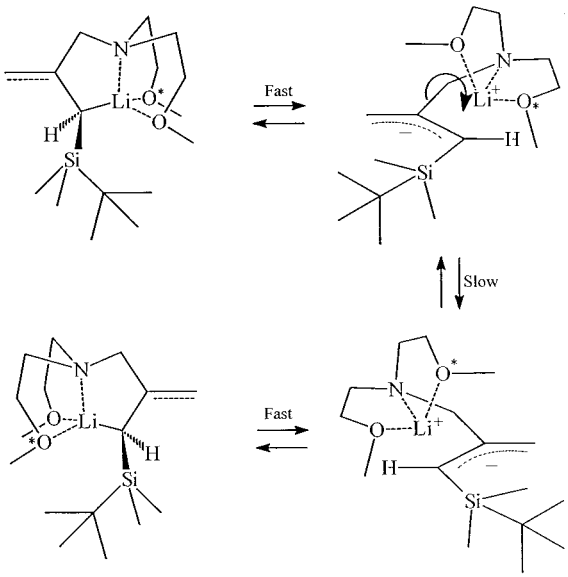

Figure 4. Proposed mechanism for inversion of allylic lithium compounds.

delocalized interconversion observed for **25** in diethyl ether. The rate determining step for inversion is (2), the transfer of coordinated Li^+ between two faces of the anion.

In sum, we have demonstrated the generality that our internally solvated allylic lithium compounds adopt partially delocalized structures with detectable C, Li covalence. They undergo fast inversion, the dynamics of which have been monitored using NMR line shape analysis as well as intermolecular C, Li bond exchange.

We attribute the unusual structures to the confined stereochemistry of lithium coordination and the encapsulated site of lithium.

Experimental Section

General Procedures. Solvents and common reagents were purchased from Ohio State University stores. Deuterated solvents were purchased from Cambridge Isotopes. Enriched ^{6}Li was purchased from Oak Ridge National Laboratory. Alkyllithiums (^{7}Li) and all other chemicals were purchased from the Aldrich Chemical Co.

Conventional FT-NMR spectra were recorded using a Bruker AC-200 spectrometer in the Chemistry Department or a Bruker Avance 300 spectrometer of The Ohio State University Central Campus Instrumentation Center (CCIC). Variable-temperature NMR spectra were recorded at the CCIC on a Bruker MSL 300 spectrometer or a Bruker Avance 300 spectrometer. Accurate mass spectra were obtained from a VG-250S or Kratos MS-30 mass spectrometer at the CCIC.

TMEDA was distilled from calcium hydride under argon and stored under argon in darkness. Diethyl ether, tetrahydrofuran, and pentane were freshly distilled from sodium benzophenone ketyl under industrial-grade argon. Reactions forming or using organolithium compounds were carried out under an argon atmosphere.

Handling of Organolithium Compounds. Organolithium compounds are very moisture and air sensitive. All glassware used for preparation or reaction of organolithium compounds was washed in a base bath, dried in an oven overnight, and then flame-dried under vacuum before flushing with argon. All syringes were dried in an oven overnight and flushed with argon while cooling before use.

Preparation of NMR Samples. All NMR tubes used for variable-temperature studies were sealed to a hard glass tube connected to a female 14/20 ground joint. This tube was then fitted with an adapter consisting of two male 14/20 joints joined by a 2-mm-straight bore glass stopcock. Caution was taken to avoid excess grease on all joints. A rubber serum stopper was fitted on the exposed end of the stopcock adapter and attached to a Schlenk line by a needle and Tygon tubing. The tube was flame-dried under vacuum and then flushed with argon three times consecutively. After the NMR tube cooled to room temperature, an aliquot of the prepared organolithium solution was syringed into it. The solvent was removed under vacuum, and the NMR tube was flushed with argon. The stopcock was closed and the stopper removed before the tube was attached to a high-vacuum line (10^{-6} Torr) trapped with liquid nitrogen. The side of the stopcock adapter that was open to the air during attachment to the high-vacuum line was allowed to pump down before the stopcock was opened to pump out the organolithium sample. After 0.5 h under high vacuum, the organolithium sample in the NMR tube was frozen in liquid nitrogen and deuterated solvent (0.8−1.0 mL) was vacuum transferred to the NMR tube. The contents were allowed to thaw and then were frozen again with liquid nitrogen before the NMR tube was sealed under vacuum at the hard glass portion. Samples thus prepared had a concentration of 0.25 M and were stored in dry ice before the low-temperature NMR studies.

Ethyl 2,2,3-Trimethyl-3-butenoate (7). Into a 250-mL three-necked flask were introduced Zn dust (4.0 g, 0.61 mol) and 50 mL of freshly distilled benzene. The mixture was heated to reflux, the heat source was removed, and a mixture of ethyl 2-bromoisobutyrate (10 g, 0.051 mol) and acetone (3.0 g, 0.051 mol) was added dropwise at a rate consistent with maintaining the reaction temperature at 80−85 °C. After addition was complete, the mixture was heated for 2 h and then cooled to room temperature.

Then, 60 mL of 12 N sulfuric acid was added. The resulting mixture was stirred vigorously for 1 h. After the two phases had separated, the lower aqueous layer was extracted with 50 mL of benzene. The combined benzene layers were washed with 100 mL of water, saturated $NaHCO_3$, and water again. The mixture was then dried over Na_2SO_4, evaporated to dryness in vacuo, and then distilled in vacuo to give 7.9 g of 3-hydroxy-2,2,3-trimethylbutyrate[12] in 89% yield: bp 40−45 °C/40 Torr; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.08 (q, 2H); 3.68 (s, 1H), 1.18 (t, 3H), 1.11 (s, 6H), 1.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 50.0 MHz) δ 178.3, 73.2, 60.5, 49.3, 24.9, 21.1, 13.9.

A mixture of 3-hydroxy-2,3,3-trimethylbutyrate (16.2 g, 0.093 mol) and 70 mL of pyridine was cooled to 0 °C in an ice bath. To the cooled solution was added slowly with vigorous stirring $POCl_3$ (14.2 g, 0.092 mol). White crystals formed almost immediately. The mixture was allowed to stand for 5 h at room temperature and was finally heated for 1.5 h using a heating mantle. It was then cooled to room temperature, treated with 100 mL of water, followed by 100 mL of diethyl ether, and stirred. After the layers were separated, the aqueous layer was extracted twice with 50 mL of ether. The ether layers were combined and washed with 2 × 100 mL of 2 N of HCl to remove pyridine, and excess HCl was removed by washing with 100 mL of water. The clear ether solution was dried over Na_2SO_4, and solvent was removed in vacuo. The residue was distilled to give 12.5 g of ethyl-3-chloro-2,3,3-trimethylbutyrate in 86% yield:[13] bp 100−105 °C/40 Torr; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.76 (m, 2H), 4.07 (q, 2H), 1.62 (q, 3H), 1.20 (s, 6H), 1.12 (t, 3H); ^{13}C NMR ($CDCl_3$, 50.0 MHz) δ 176.3, 147.7, 110.2, 60.4, 47.5, 24.4, 19.8, 13.9.

A mixture of ethyl 3-chloro-2,3,3-trimethylbutyrate (9.1 g, 0.058 mol) with 10 g of KOH in 15 mL of water and 50 mL of absolute ethanol was heated under reflux for 2 h and then cooled. Water (100 mL) was added, and the mixture was acidified by adding concentrated HCl dropwise. After 100 mL of ether was added, layers were separated. The aqueous layer was extracted twice with ether. The ether extracts were combined and washed with 50 mL of water and dried over Na_2SO_4. After removal of solvent in vacuo, the residue was distilled to give 6.0 g of the title compound,[14] **7**, in 81% yield:[13] bp 135−138 °C/40 Torr; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 11.0 (b, 1H), 4.92 (m, 2H), 1.77 (m, 3H), 1.40 (s, 6H); ^{13}C NMR ($CDCl_3$, 50.0 MHz) δ 183.2, 146.9, 111.1, 47.5, 24.3, 19.9.

***N,N*-Bis(2-methoxyethyl)-2,3,3-trimethyl-3-butenamide (8).** Thionyl chloride (5.2 mL, 0.071 mol) was added dropwise to **7** (6.0 g, 0.047 mol). The mixture was heated at 85 °C (water bath) for 1 h. Excess of thionyl chloride was removed by distillation, and the remaining mixture was cooled to 0 °C. Then, 14 mL of bis(2-methoxyethyl)amine (12.7 g, 0.12 mol) was added and the mixture was stirred for 3 h. At this point, 15 mL of water and 50 mL of ether were added. After separation, the aqueous layer was extracted with 2 × 30 mL portions of ether.

Ether layers were combined, washed with water, and dried over Na_2SO_4. After removal of solvent, the residue was distilled to give 8.3 g of title compound **4** in 73% yield: bp 108−112 °C/40 Torr; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.74 (m, 2H), 3.50 (t, 4H), 3.36 (t, 4H), 3.36 (t, 4H), 3.17 (s, 6H), 1.60 (m, 3H), 1.15 (s, 6H); ^{13}C NMR ($CDCl_3$, 50.0 MHz) δ 175.2, 149.6, 108.9, 70.8, 70.1, 58.5, 58.3, 47.9, 47.5, 46.2, 26.3, 19.5.

***N,N*-Bis(2-methoxyethyl)-2,3,3-trimethyl-3-butenylamide (9).** To a solution of $LiAlH_4$ (1.4 g, 0.036 mol) in 100 mL of THF was added **8** (8.0 g, 0.033 mol) in 15 mL of THF. The mixture was refluxed overnight. The excess $LiAlH_4$ was hydrolyzed by dropwise addition of 15 mL of 15% aqueous NaOH at 0 °C. The resulting precipitate was filtered. The solvent was removed in vacuo, and the residue was distilled to give 6.0 g of amine **9** in 80% yield: bp 83−84 °C/0.8 Torr; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.72 (m, 2H), 3.38 (t, 4H), 3.28 (s, 6H), 2.65 (t, 4H), 2.41 (s, 2H), 1.70 (m, 3H), 0.99 (s, 6H); ^{13}C NMR ($CDCl_3$, 50.0 MHz) δ 151.5, 110.0, 71.5, 65.4, 58.6, 55.6, 40.6, 25.4, 19.8.

3-[(Ethyldimethylsilyl)methyl]-*N,N*-bis(2-methoxyethyl)-2,2-dimethyl-3-butenylamine (10). Under an atmosphere of argon, a solution of amine **9**, (2.95 g, 0.013 mol) at 0 °C in 25 mL of THF was reacted with *n*-butylllithium (5.3 mL, 2.5 M, 0.013 mol) in pentane. The mixture was allowed to warm to room temperature and stirred for 2 h. After cooling the mixture to −78 °C, 1.82 mL (0.013 mol) of dimethylethylchlorosilane was added. The mixture was warmed to room temperature and stirred for 2 h after which 5 mL of water was added. THF was removed and 50 mL of ether was added. After separation of phases, the aqueous layer was extracted twice with 20 mL of ether. The combined ether layers were washed with 50 mL of water and dried over Na_2SO_4. After removal of solvent, the residue was distilled to give 1.6 g of product **10** in 39% yield: bp 120−125 °C/1.0 Torr; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.73−4.56 (m, 2H), 3.37 (t, 4H), 3.28 (s, 6H), 2.65 (t, 4H), 2.38 (s, 2H), 1.45 (m, 2H), 0.94 (s, 6H), 0.89 (t, 3H), 0.50 (q, 2H), −0.04 (s, 6H); ^{13}C NMR ($CDCl_3$, 50.0 MHz) δ 152.9, 108.1, 71.6, 65.6, 58.6, 55.8, 41.4, 25.2, 19.5, 7.69, 7.29, −2.88. GC indicated 50% of **9** (1.5 g) remained unreacted.

***N*-[2-[2-[Bis(2-methoxyethyl)amino]-1,1-dimethylethyl](ethyldimethylsilyl)]allyllithium (26).** To a solution of amine **10** (233 mg, 0.74 mmol) in 3.0 mL of THF was added methyllithium (0.65 mL, 1.4 M, 0.91 mmol) in ether at −78 °C. The mixture was then warmed to room temperature and stirred for 2 h.

An NMR tube with a ground joint connected to an adapter with a glass stopper was flame-dried under vacuum and flushed with argon. An aliquot of 1 mL of the above prepared solution was syringed into the NMR tube. The solvent was removed under vacuum, and the NMR tube was flushed with argon before it was transferred to a high-vacuum line (10^{-6} Torr) trapped with liquid nitrogen to remove all volatile impurities. After about 1 h, THF-d_8 (0.4 mL) was vacuum transferred to the NMR tube. While frozen with liquid nitrogen and under vacuum, the tube was sealed with a torch. This sample was stored in dry ice prior to NMR investigation.

***meso*-Diethyl 2,5-Dibromoadipate.** A 500-mL three-neck round-bottom flask was equipped with an addition funnel, a condenser, and an HCl/HBr trap. The flask was charged with adipic acid, (100 g, 0.68 mol) and thionyl chloride (122.6 mL, 1.68 mol). The mixture was then heated to 65−70 °C with a hot water bath for 2.5 h until the evolution of HCl gas was complete. Bromine (80.5 mL, 1.56 mol) was added to the addition funnel. After heating the solution to 85−95 °C, the bromine was added as fast as it would react while under irradiation from a flood lamp. After the addition was complete (5 h), the solution was maintained at 85−90 °C for 1 h and then allowed to cool to room temperature. Absolute ethanol (500 mL) in a 2-L beaker equipped with a magnetic stir bar was chilled in an ice bath. The reaction mixture was cautiously poured into the vigorously stirring ethanol and allowed to stir overnight in a fume hood, resulting in the formation of a large amount of crystals. The product was collected in a Buchner funnel and washed with a small amount of cold ethanol. The ethanolic mother liquor was then allowed to stir overnight in a fume hood for a second crop of crystals. The crystals were dissolved in diethyl ether, and the solution was washed with saturated $NaHSO_3$ (aqueous, 250 mL), H_2O (250 mL), saturated $NaHCO_3$ (aqueous, 2 × 250 mL), and saturated NaCl (aqueous, 250 mL). The solution was then dried over anhydrous Na_2SO_4. Filtration followed by rotary evaporation yielded the product as a waxy, colorless solid (129 g, 0.34 mol, 51%): mp 63−65 °C (lit.[15] mp 65−66 °C); ^{1}H NMR ($CDCl_3$, δ = 7.26 ppm) 4.21 (m, 6H), 2.15 (m, 4H), 1.28 (t, J = 7.0, 6H); ^{13}C NMR ($CDCl_3$, δ = 77.0) 169.13, 62.20, 44.66, 32.41, 13.91.

***cis*-2,5-Dicarbethoxy-*N*-benzylpyrrolidine.** A 1-L three-necked round-bottom flask was equipped with a condenser, an argon inlet, an addition funnel, and a magnetic stir bar. *meso*-Diethyl 2,5-dibromoadipate (129 g, 0.34 mol) was dissolved in benzene (400 mL) and heated to a gentle reflux. The heat was removed, and then benzylamine (129 mL, 1.18 mol) was added dropwise to maintain the reflux. After addition was complete, the mixture was refluxed overnight. Upon cooling to room temperature, the mixture was vacuum filtered to remove as much of the benzylamine hydrobromide salt as possible. To prevent isomerization, the product was not washed with base and some of the hydrobromide salt remained even after distillation due to sublimation as is evident in the NMR spectrum. The benzene was removed by rotary evaporation, and the product was distilled to give the product as a clear liquid in 74% (77.0 g, 0.25 mol): bp 170−174° C (2 Torr) (lit.[35] bp 145−148 °C/0.3 Torr); ^{1}H NMR ($CDCl_3$, δ = 7.24 ppm) 7.28 (m, 5H), 4.05 (m, 4H), 3.79 (s, 2H), 3.65 (m, 2H), 2.04 (m, 4H), 1.146 (m, 6H); ^{13}C NMR ($CDCl_3$, δ = 77.0 ppm) 173.36, 137.51, 129.48, 128.0, 127.16, 65.53, 63.43, 60.51, 57.77, 53.99, 28.6, 14.11.

***cis*-2,5-Dicarbethoxypyrrolidine.** *cis*-2,5-Dicarbethoxy-*N*-benzylpyrrolidine (23.6 g, 77.3 mmol) and absolute ethanol (100 mL) were introduced into the glass liner of a Parr high-pressure reactor. Palladium on carbon (10%, 2.36 g) was added and the reactor assembled. The reactor was flushed four times by filling with hydrogen to 400 psi and venting before finally being filled to 1200 psi. The reaction vessel was then heated at 40 °C overnight with vigorous stirring. The mixture was removed from the reactor and filtered through Celite to remove the catalyst. The filter cake was washed thoroughly with absolute ethanol. Rotary evaporation of the ethanol followed by distillation yielded the product (15.9 g, 73.4 mmol, 95%): bp 127−130 °C/2 Torr (lit.[36] bp 95−96 °C/0.3 Torr); ^{1}H NMR ($CDCl_3$, δ = 7.24 ppm) 4.10 (q, J = 7.10, 4H), 3.70 (m, br, 2H), 2.06 (m, br, 2H), 1.84 (m, br, 2H), 1.18 (t, J = 7.10, 6H); ^{13}C NMR ($CDCl_3$, δ = 77.0 ppm) 173.9, 60.82, 60.14, 29.68, 13.95.

***cis*-2,5-Bis(hydroxymethyl)pyrrolidine (11).** A 250-mL three-neck round-bottom flask was equipped with an addition funnel, a condenser, an argon inlet, and a magnetic stir bar. Lithium aluminum hydride (5.6 g, 0.148 mol) was charged into the flask, and *cis*-2,5-dicarbethoxypyrrolidine (12.75 g, 59 mmol) and diethyl ether (50 mL) were loaded into the addition funnel. The apparatus was flooded with argon and chilled to 0 °C before the addition of diethyl ether (50 mL) to the $LiAlH_4$ by syringe. The *cis*-2,5-dicarbethoxypyrrolidine solution was then added dropwise over a period of 20 min. The cooling bath was removed, and the mixture was stirred at room temperature for 1 h. Once again the mixture was cooled to 0 °C before quenching by extremely cautious incremented addition of H_2O (15 mL). The amount of water is very critical to the successful isolation of the product. Since the product is insoluble in diethyl ether, the ether was filtered off and the product and aluminum salts were collected on a Buchner funnel. The product was then washed from the aluminum salts by stirring the mixture in hot ethanol (100 mL) for 15 min and then filtering once again on a Buchner funnel. The process was repeated two additional times. The crude product (7.09 g, 54 mmol, 91%) was obtained by rotary evaporation in a tared 250-mL round-bottom flask and was not purified further before proceeding to the next step.

***cis*-2,5-Bis(hydroxymethyl)-*N*-formylpyrrolidine (12).** The synthesis of the title compound was based on the synthesis of (*S*)-(−)-1-formyl-2-(hydroxymethyl)pyrrolidine published by Kipphardt et al.[18] *cis*-2,5-Bis(hydroxymethyl)pyrrolidine (15.5 g, 0.118 mol) was transferred (by dissolving in ethanol followed by rotary evaporation to remove the ethanol) to a 250-mL three-neck round-bottom flask equipped with an argon inlet, an addition funnel, a reflux condenser, and a magnetic stir bar. The flask was cooled in an ice/water bath. Methyl formate (8.18 g, 0.136 mol) was then added dropwise. The mixture initially dissolves and then becomes viscous upon stirring

(36) O'Neil, B. T.; Watson, H. A. *J. Org. Chem.* **1990**, *55*, 2950.

overnight. The excess methyl formate and methanol were removed under vacuum to yield a foamy semisolid that was not purified further before proceeding to the next step.

***cis*-2,5-Bis(methoxymethyl)-*N*-formylpyrrolidine (13).** The synthesis of the title compound was based on the synthesis of (*S*)-(−)-1-formyl-2-(methoxymethyl)pyrrolidine published by Kipphardt et al.[18] The 250-mL three-neck round-bottom flask containing the crude *cis*-2,5-bis(hydroxymethyl)-*N*-formylpyrrolidine from the previous step was fitted with an argon inlet, a reflux condenser, and a magnetic stir bar. THF (150 mL) was added and the mixture cooled in a dry ice/acetone bath. *cis*-2,5-Bis(hydroxymethyl)-*N*-formylpyrrolidine was not very soluble in THF, but became brittle when cooled and was broken with a metal spatula to allow proper stirring. The cold bath was removed, and methyl iodide (24.0 mL, 0.386 mol) followed by sodium hydride (8.6 g, 0.356 mol) was added. The reaction was then allowed to warm slowly. At some point, large gray-brown clumps form in the solution. These clumps begin to break up with strong evolution of hydrogen at room temperature. It was necessary to control this reaction by occasionally cooling the flask in an ice bath. After the evolution of hydrogen abated, the mixture was refluxed for 20 min before the heat source was removed and the reaction was quenched by dropwise addition of 6 M HCl (26.5 mL). The THF was removed by rotary evaporation to yield the crude product in water. The product was not further purified before being carried on to the next step.

***cis*-2,5-Bis(methoxymethyl)pyrrolidine (14).** The synthesis of the title compound was based on the synthesis of (*S*)-(+)-2-methoxymethylpyrrolidine published by Kipphardt et al.[18] The aqueous solution containing the *N*-formyl-*cis*-2,5-bis(methoxymethyl)pyrrolidine from the previous step was transferred to a 500-mL Erlenmeyer flask. A solution of KOH (53 g, 0.94 mol) in water (210 mL) was added, and the mixture was stirred overnight. Potassium carbonate (150 g, 1.09 mol) was added causing precipitation of potassium salts which were removed from the solution by vacuum filtration on a Buchner funnel and washed with diethyl ether. The solution was extracted with diethyl ether (3 × 100 mL). The ether layers were combined and washed with saturated NaCl (aqueous, 50 mL) and dried over anhydrous Na_2SO_4 before removal of the ether by rotary evaporation. Distillation yielded the product (6.5 g, 41 mmol, 35% based on *cis*-2,5-bis(hydroxymethyl)-pyrrolidine): bp 65−70 °C/0.2 Torr; ^{1}H NMR ($CDCl_3$, δ = 7.26 ppm) 3.15 (m, 12H), 2.04 (s, 1H), 1.61 (s, br, 2H), 1.24 (s, br, 2H); ^{13}C NMR ($CDCl_3$, δ = 77.0 ppm) 76.74, 58.53, 57.59, 26.99.

2-[[Bis(2-methoxyethyl)amino]methyl]propene (16). Under an argon atmosphere, bis(2-methoxyethyl)amine (29.4 g, 220 mmol) and 2-methyl-3-chloropropene (10.0 g, 110 mmol) were introduced into a flame-dried 100-mL round-bottomed flask equipped with a magnetic stir bar and a reflux condenser. The mixture was heated to approximately 80 °C and stirred overnight. The mixture was cooled to room temperature resulting in precipitation of ammonium salts. After 50 mL of water was added, the mixture was poured into a separatory funnel and extracted with diethyl ether (3 × 50 mL). The ether layers were combined and washed with saturated aqueous sodium chloride solution and dried over sodium sulfate. After gravity filtration, the solvent was removed by rotary evaporation and the residue was fractionated to give 15.0 g of the title compound in 80% yield as a clear colorless liquid: bp 74−76 °C/4 Torr (lit.[16] bp 64 °C/2 Torr); ^{1}H NMR ($CDCl_3$, δ = 7.26 ppm) 4.82 (s, br, 1 H), 4.75 (s, br, 1H), 3.40 (t, J = 6.1 Hz, 4 H), 3.28 (s, 6 H), 2.98 (s, 2 H), 2.62 (t, J = 6.1 Hz, 4 H), 1.67 (s, br 2 H); ^{13}C NMR ($CDCl_3$, δ = 77.0 ppm) 143.90, 112.32, 71.24, 62.41, 58.56, 53.68, 20.50.

***cis*-2,5-Bis(methoxymethyl)-1-(2-methylallyl)pyrrolidine (17).** Under an argon atmosphere, *cis*-2,5-bis(methoxymethyl)pyrrolidine (15.6 g, 98 mmol) and 3-chloro-2-methylpropene (4.8 mL, 49 mmol) were introduced into a flame-dried 50-mL round-bottomed flask equipped with a magnetic stir bar and a reflux condenser. The mixture was heated to approximately 80 °C and stirred overnight. The mixture was cooled to room temperature resulting in a precipitate of ammonium salts. After 25 mL of water was added, the mixture was poured into a separatory funnel and extracted with diethyl ether (3 × 50 mL). The ether layers were combined and washed with saturated aqueous sodium chloride solution (25 mL) and dried over anhydrous sodium sulfate. After gravity filtration, the solvent was removed by rotary evaporation and the residue was fractionated to give the title compound (6.5 g, 30.5 mmol) in 62% yield as a clear colorless liquid: bp 110−115 °C/1 Torr; ^{1}H NMR ($CDCl_3$, δ = 7.26 ppm) 4.81 (s, br, 1H), 4.65 (s, br, 1H), 3.23 (m, 8H), 3.10 (s, 2H), 3.04 (m, 2H), 2.76 (m, 2H), 1.80 (m, 2H), 1.66 (s, 3H), 1.52 (m, 2H). ^{13}C NMR ($CDCl_3$, δ = 77.0 ppm) 145.35, 111.39, 77.08, 64.96, 62.75, 58.78, 27.91, 20.49; MS M^+/e calcd for $C_{12}H_{23}NO_2$ 213.172 889, obsd 213.172 637 9, base peak $C_{10}H_{18}NO^+$ 168.139 938 4.

2-[[Bis(2-methoxyethyl)amino]methyl]-1-(dimethylethylsilyl)propene (18). A 100-mL three-necked round-bottomed flask equipped with a magnetic stir bar, an argon inlet tube, a stopcock stopper, and a 25-mL addition funnel was flame-dried under vacuum and, after cooling to room temperature, was flushed twice with prepurified argon. Into the flask was introduced 2-[[bis(2-methoxyethyl)amino]methyl]propene (4.0 g, 21.4 mmol) and dry THF (20 mL) freshly distilled from sodium−benzophenone ketyl under argon. The mixture was cooled in a dry ice/acetone bath for 30 min, and *n*-butyllithium in hexanes (2.5 M, 8.6 mL, 22 mmol) was added dropwise via syringe. After stirring for 30 min at this temperature, the mixture was allowed to warm to room temperature and stirred for an additional 2 h, during which a bright yellow precipitate formed. The mixture was then cooled again in a dry ice/acetone bath and stirred for 30 min before the dropwise addition of chlorodimethylethylsilane (2.58 g, 21 mmol) from the addition funnel over 30 min, during which time the previously observed precipitate dissolved. On warming the mixture to room temperature and stirring for 3 h, a white precipitate of LiCl developed. The mixture was transferred to a 250-mL round-bottomed flask, and most of the solvent was removed by rotary evaporation. Saturated aqueous sodium chloride solution (75 mL) was added, and the mixture was transferred to a separatory funnel. The flask was washed with diethyl ether (75 mL), and the washings were added to the separatory funnel. The aqueous layer was additionally extracted with diethyl ether (2 × 75 mL) before the ether layers were combined and dried over anhydrous sodium sulfate. Solvent was removed by rotary evaporation before the residue was distilled under vacuum to afford 4.2 g of the desired title compound in 72% yield: bp 85−90 °C/0.7 Torr; ^{1}H NMR ($CDCl_3$, δ = 7.26 ppm) 4.79 (s, br, 1 H), 4.59 (s, br, 1 H), 3.42 (t, J = 6.0 Hz, 4 H), 3.29 (s, 6 H), 2.94 (s, 2 H), 2.65 (t, J = 6.0 Hz, 4 H), 1.55 (s, 2 H), 0.90 (t, J = 7.9 Hz, 3 H), 0.47 (q, J = 7.9 Hz, 2 H), −0.051 (s, 6 H); ^{13}C NMR ($CDCl_3$, δ = 77.00 ppm) 145.34, 109.63, 71.30, 62.79, 58.67, 53.80, 21.92, 7.14, 7.04, −3.62. MS M^+/e calcd for $C_{14}H_{31}NO_2Si$ 273.212 420, obsd 273.212 768 6, base peak $C_{12}H_{26}NOSi^+$ 228.175 445 6.

2-[[Bis(2-methoxyethyl)amino]methyl]-1-(*tert*-butyldimethylsilyl)-propene (19). A 100-mL three-necked round-bottomed flask equipped with a magnetic stir bar, an argon inlet tube, a stopcock stopper, and a 25-mL addition funnel was flame-dried under vacuum and, after cooling to room temperature, was flushed twice with prepurified argon. Into the flask was introduced 2-[[bis(2-methoxyethyl)amino]methyl]-propene (4.0 g, 21.4 mmol) and dry THF (20 mL) freshly distilled from sodium−benzophenone ketyl under argon. The mixture was cooled in a dry ice/acetone bath for 30 min, and *n*-butyllithium in hexanes (2.5 M, 8.6 mL, 22 mmol) was added dropwise via syringe. After stirring for 30 min at this temperature, the mixture was allowed to warm to room temperature and stirred for an additional 2 h, during which time a bright yellow precipitate formed. The mixture was then cooled again in a dry ice/acetone bath and stirred for 30 min before the dropwise addition of *tert*-butyldimethylsilyl chloride (3.17 g, 21 mmol) in THF (20 mL) from the addition funnel over 30 min, during which time the previously observed precipitate dissolved. The mixture was then warmed to room temperature and stirred for 3 h, during which time a white precipitate of LiCl formed. The mixture was transferred to a 250-mL round-bottomed flask and most of the solvent was removed by rotary evaporation. Saturated aqueous sodium chloride solution (75 mL) was added, and the mixture was transferred to a separatory funnel. The flask was washed with diethyl ether (75 mL) which was added to the separatory funnel. The aqueous layer was additionally extracted with diethyl ether (2 × 75 mL) before the ether layers were combined and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation before the residue was subjected to bulb-to-bulb distillation (3 Torr) to afford 2.03 g of the desired title compound in 31% yield: ^{1}H NMR ($CDCl_3$, δ = 7.26 ppm) 4.81 (s, br, 1 H), 4.62 (s,

br, 1 H), 3.44 (t, $J = 6.2$ Hz, 4 H), 3.31 (s, 6 H), 2.95 (s, 2 H), 2.67 (t, $J = 6.2$ Hz, 4 H), 1.58 (s, 2 H), 0.86 (s, 9 H), −0.04 (s, 6 H); ^{13}C NMR ($CDCl_3$, $\delta = 77.00$ ppm) 145.5, 109.9, 71.4, 62.7, 58.7, 53.8, 26.4, 19.1, 16.7, −5.983; MS M^+/e calcd for $C_{16}H_{35}NO_2Si$ 301.243 710, obsd 301.247 268 7, base peak $C_{14}H_{28}NOSi^+$ 256.182 830 8.

***cis*-2,5-Bis(methoxymethyl)-1-[2-[(dimethylethylsilyl)methyl]allyl]-pyrrolidine (20).** A 50-mL three-necked round-bottomed flask equipped with a magnetic stir bar, an argon inlet tube, a stopcock stopper, and a 25-mL addition funnel was flame-dried under vacuum and, after cooling to room temperature, was flushed twice with prepurified argon. Into the flask was introduced *cis*-2,5-bis(methoxymethyl)-1-(2-methylallyl)pyrrolidine (2.78 g, 13.0 mmol) and dry THF (5 mL) freshly distilled from sodium−benzophenone ketyl under argon. The mixture was cooled in a dry ice/acetone bath for 30 min, and butyllithium in hexanes (1.6 M, 10.6 mL, 17 mmol) was added dropwise via syringe. After stirring for 30 min at this temperature, the mixture was allowed to warm to room temperature and stirred for an additional 2 h, during which time a bright yellow precipitate formed. The mixture was then cooled again in a dry ice/acetone bath and stirred for 30 min before the dropwise addition of chlorodimethylethylsilane (1.91 g, 2.19 mL, 15.6 mmol) from the addition funnel over 30 min, during which time the previously observed precipitate dissolved. The mixture was then warmed to room temperature and stirred for 3 h. During this time, a white precipitate of LiCl developed. The mixture was transferred to a 250-mL round-bottomed flask, and most of the solvent was removed by rotary evaporation. Saturated aqueous sodium chloride solution (50 mL) was added, and the mixture was transferred to a separatory funnel. The flask was washed with diethyl ether (50 mL), and the washings were added to the separatory funnel. The aqueous layer was additionally extracted with diethyl ether (2 × 50 mL) before the ether layers were combined and dried over anhydrous sodium sulfate. After removal of solvent by rotary evaporation, the residue was distilled under vacuum to afford the desired title compound (1.40 g, 4.67 mmol) in 36% yield: bp 135−140 °C/0.8 Torr; ^{1}H NMR ($CDCl_3$, $\delta = 7.26$ ppm) 4.77 (s, br, 1H), 4.48 (s, br, 1H), 3.23 (m, 8H), 3.03 (m, 4H), 2.74 (m, 2H), 1.78 (m, 2H), 1.51 (m, 4H), 0.87 (t, $J = 7.8$ Hz, 3H), 0.43 (q, $J = 7.8$ Hz, 2H), −0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, $\delta = 77.0$ ppm) 146.67, 109.12, 77.20, 64.88, 63.43, 58.87, 27.98, 22.00, 7.29, 6.98, −3.67; MS M^+/e calcd for $C_{16}H_{33}NO_2Si$ 299.228 060, obsd 299.226 470 9, base peak $C_{14}H_{28}NOSi^+$ 254.194 351 2.

***cis*-2,5-Bis(methoxymethyl)-1-[2-[(trimethylsilyl)methyl]allyl]pyrrolidine (21).** A 50-mL three-necked round-bottomed flask equipped with a magnetic stir bar, an argon inlet tube, a stopcock stopper, and a 25-mL addition funnel was flame-dried under vacuum and, after cooling to room temperature, was flushed twice with prepurified argon. Into the flask was introduced *cis*-2,5-bis(methoxymethyl)-1-(2-methylallyl)pyrrolidine (2.65 g, 12.4 mmol) and dry THF (5 mL) freshly distilled from sodium−benzophenone ketyl under argon. The mixture was cooled in a dry ice/acetone bath for 30 min, and butyllithium in hexanes (1.6 M, 10.0 mL, 16 mmol) was added dropwise via syringe. After stirring for 30 min at this temperature, the mixture was allowed to warm to room temperature and stirred for an additional 2 h, during which a bright yellow precipitate formed. The mixture was then cooled again in a dry ice/acetone bath and stirred for 30 min before the dropwise addition of chlorotrimethylsilane (1.62 g; 1.89 mL; 14.9 mmol) from the addition funnel over 30 min. During this time, the previously observed precipitate dissolved. The mixture was then warmed to room temperature and during stirring over 3 h a white precipitate of LiCl formed. The mixture was transferred to a 250-mL round-bottomed flask, and most of the solvent was removed by rotary evaporation. Saturated aqueous sodium chloride solution (50 mL) was added, and the mixture was transferred to a separatory funnel. The flask was washed with diethyl ether (50 mL) which was added to the separatory funnel. The aqueous layer was additionally extracted with diethyl ether (2 × 50 mL) before the ether layers were combined and dried over anhydrous sodium sulfate. The solvent was removed by rotary evaporation before the residue was distilled under vacuum to afford the desired title compound (2.46 g, 8.6 mmol) in 69% yield: bp 130−140 °C/0.8 Torr; ^{1}H NMR ($CDCl_3$, $\delta = 7.26$ ppm) 4.77 (s, br, 1H), 4.47 (s, br, 1H), 3.23 (m, 8H), 3.03 (m, 4H), 2.76 (m, 2H), 1.79 (m, 2H), 1.52 (m, 4H), 0.045 (s, 9H); ^{13}C NMR ($CDCl_3$, $\delta = 77.0$ ppm) 146.63, 109.00, 77.14, 64.83, 63.33, 58.80, 27.89, 23.75, −1.44; MS M^+/e calcd for $C_{15}H_{31}NO_2Si$ 285.212 420, obsd 285.211 996 4, base peak $C_{13}H_{26}NOSi^+$ 240.177 795 4.

[2-[[*cis*-2,5-Bis(methoxymethyl)-1-pyrrolidinyl]methyl]-1-(trimethylsilyl)allyl]lithium (22). A 35-mL Schlenk tube equipped with a magnetic stir bar and an argon inlet tube was flame-dried under vacuum and then flushed with argon. Freshly distilled dry diethyl ether (2.15 mL) and *cis*-2,5-bis(methoxymethyl)-1-[2-[(trimethylsilyl)methyl]-allyl]pyrrolidine (0.200 g, 0.70 mmol) were introduced into the tube. After the solution was chilled to −78 °C with a dry ice/acetone bath under argon, a solution of methyllithium in diethyl ether (1.4 M, 0.65 mL, 0.92 mmol) was added slowly by syringe. The temperature was allowed to warm to room temperature, and then the mixture was stirred for 1 h.

An NMR sample with a concentration of 0.25 M was prepared as previously described: ^{1}H NMR (Et_2O-d_{10}, $\delta = 1.07$ ppm) 4.16 (d, $J = 3.2$ Hz, 1H), 4.13 (d, $J = 3.2$ Hz, 1H), 3.43 (s, 6H), 3.36 (m, 2H), 3.01 (s, 2H), 2.82 (s, br, 2H), 1.83 (m, br, 4H), 0.82 (s, 1H), −0.003 (s, 9H); ^{13}C NMR (Et_2O-d_{10}, $\delta = 14.5$ ppm) 158.82, 74.58, 69.13, 67.40, 58.81, 43.79, 27.69, 1.95.

[2-[[*cis*-2,5-Bis(methoxymethyl)-1-pyrrolidinyl]methyl]-1-(dimethylethylsilyl)allyl]lithium (23). A 35-mL Schlenk tube equipped with a magnetic stir bar and an argon inlet tube was flame-dried under vacuum and then flushed with argon. Freshly distilled dry diethyl ether (2.15 mL) and *cis*-2,5-bis(methoxymethyl)-1-[2-[(dimethylethylsilyl)-methyl]allyl]pyrrolidine (0.200 g, 0.67 mmol) were introduced into the tube. After the solution was chilled to −78 °C with a dry ice/acetone bath under argon, a solution of methyllithium in diethyl ether (1.4 M; 0.62 mL; 0.87 mmol) was added slowly by syringe. The temperature was allowed to warm to room temperature and then the mixture was stirred for 1 h.

An NMR sample with a concentration of 0.25 M was prepared as previously described: ^{1}H NMR (Et_2O-d_{10}, $\delta = 1.07$ ppm) 4.15 (d, $J = 3.4$ Hz, 1H), 4.12 (d, $J = 3.4$ Hz, 1H), 3.41 (s, 6H), 3.33 (m, 2H), 3.07 (s, 2H), 2.80 (s, br, 2H), 1.81 (m, 4H), 0.92 (t, $J = 7.9$ Hz, 3H), 0.51 (q, $J = 7.9$ Hz, 2H), −0.06 (s, 6H); ^{13}C NMR (Et_2O-d_{10}, $\delta = 14.5$ ppm) 159.09, 74.70, 73.76, 69.19, 67.35, 58.87, 42.80, 27.77, 10.36, 9.12, 0.50.

[2[[Bis(2-methoxyethyl)amino]methyl]-1-(dimethylethylsilyl)allyl]-lithium (24). A 35-mL Schlenk tube equipped with a magnetic stir bar and an argon inlet tube was flame-dried under vacuum and then flushed with argon. Freshly distilled dry THF (1.5 mL) and 2-[[bis(2-methoxyethyl)amino]methyl]-1-(dimethylethylsilyl)propene (0.200 g, 0.77 mmol) were introduced into the tube. After the solution was chilled to −78 °C with a dry ice/acetone bath under argon, a solution of methyllithium in diethyl ether (1.4 M, 0.66 mL, 0.92 mmol) was added slowly by syringe. The temperature was allowed to warm to room temperature, and then the mixture was stirred for 1 h. This procedure was also repeated using *n*-butyllithium (^{6}Li).

Samples were prepared using diethyl ether-d_{10} and THF-d_8 as solvents. This sample had a concentration of 0.25 M and was stored in dry ice prior to the NMR studies: ^{1}H NMR (Et_2O-d_{10}, $\delta = 1.07$ ppm) 3.29 (t, $J = 5.3$ Hz, 4 H), 3.04 (s, 6 H), 2.97 (s, 1 H), 2.93 (s, 1 H), 2.54 (s, 2 H), 2.41 (t, $J = 5.3$ Hz, 4 H), 0.60 (t, $J = 7.8$ Hz, 3 H), 0.33 (s, 1 H), 0.20 (q, $J = 7.8$ Hz, 2 H), −0.39 (s, 6 H); ^{13}C NMR (Et_2O-d_{10}, $\delta = 65.3$ ppm) 157.8, 76.00, 70.84, 69.24, 58.45, 56.74, 40.22, 10.41, 9.16, −0.52.

[2-[[Bis(2-methoxyethyl)amino]methyl]-1-(*tert*-butyldimethylsilyl)allyl]lithium (25). A 35-mL Schlenk tube equipped with a magnetic stir bar and an argon inlet tube was flame-dried under vacuum and then flushed with argon. Freshly distilled dry THF (1.5 mL) and 2-[[bis(2-methoxyethyl)amino]methyl]-1-(*tert*-butyldimethylsilyl)propene (0.232 g, 0.77 mmol) were introduced into the tube. After the solution was chilled to −78 °C with a dry ice/acetone bath under argon, a solution of methyllithium in diethyl ether (1.4 M, 0.66 mL, 0.92 mmol) was added slowly by syringe. The temperature was allowed to warm to room temperature, and then the mixture was stirred for 1 h.

NMR samples with a concentration of 0.25 M were prepared with THF-d_8 and Et_2O-d_{10} as previously described. Two other samples with concentrations of 0.50 and 0.125 M in Et_2O-d_{10} were also prepared: ^{1}H NMR (THF-d_8, $\delta = 1.73$ ppm) 3.59 (t, $J = 5.3$ Hz, 4 H), 3.35 (s,

6 H), 3.22 (s, br, 2 H), 2.84 (s, 2 H), 2.74 (t, $J = 5.3$ Hz, 4 H), 0.87 (s, 9 H), 0.85 (s, 1 H), −0.06 (s, 6 H); ^{13}C NMR (THF-d_8, $\delta = 67.4$ ppm) 158.3, 73.8, 70.9, 69.7, 68.3, 58.7, 56.1, 28.7, 20.6, −2.8.

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Supporting Information Available: Observed and calculated NMR line shapes and Eyring plots. See any current masthead page for ordering information and Web access instructions.

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