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Structural studies of {^{6}Li} 2-lithiopyrrolidines using NMR spectroscopy

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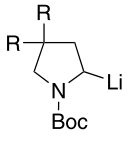
Abstract—A selection of *N*-substituted 2-lithiopyrrolidines were prepared and their structures were investigated by ^{6}Li and ^{13}C NMR spectroscopy. Evidence is presented for aggregation and dynamic solvation effects, depending on the nature of the *N*-substituent and substituents on the pyrrolidine ring. Studies were performed with *N*-Boc (coordinating carbonyl group), *N*-methoxyethyl (coordinating methoxy group) and *N*-alkyl (no coordinating group) heterocycles to represent three different classes of organolithiums: dipole-stabilized, unstabilized and chelated, and unstabilized.

1. Introduction

In addition to this Symposium-In-Print, three recent review monographs on organolithium chemistry attest to the importance of organolithium species in organic synthesis.[1] One of the more versatile such classes is α-aminoorganolithium compounds, which often carry a stereogenic carbon attached to the lithium.[2] When a chiral organolithium is enantioenriched either by deprotonation, transmetalation of scalemic stannanes, or by dynamic resolution, excellent enantioselectivities may be achieved. If chiral organolithium species are to find use in asymmetric synthesis then the organolithium species must either be generated enantioselectively and not lose its configurational stability (and must quench stereoselectively with retention or inversion of configuration) or it must be amenable to resolution (preferably dynamic) in the presence of a chiral ligand. In both cases, it is important to have knowledge of the rate of racemization of the organolithium species in question. This will be influenced by a number of factors, including its structure, the solvent and the temperature. In addition, the relative rate of reaction with the electrophile can influence the selectivity.

One class of compounds that have found use in asymmetric synthesis is 2-lithiopyrrolidines, which readily undergo electrophilic substitutions,[3,4] transition metal transmetalation and coupling,[5] sigmatropic rearrangements,[6] anionic cyclizations,[7–9] and dynamic resolutions.[10] The mechanism and steric course of these processes depend to some degree on the rate of racemization and on the solution structure.



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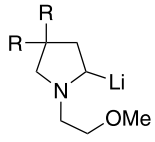
1b, R = Me



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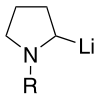

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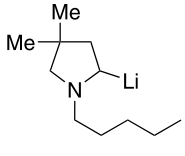

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In a preliminary communication, the solution structure of ^{6}Li-**3a** was deduced using ^{6}Li and ^{13}C NMR spectroscopy.[11] After transmetalation of 2-(tributylstannyl)-*N*-methylpyrrolidine with Bu^{6}Li, a single peak was observed in the ^{6}Li NMR spectrum and a pentet ($\delta = 66.3$, $^1J = 6.8$ Hz) was observed in the ^{13}C NMR spectrum, the latter corresponding

Keywords: Organolithium; Lithiation; Tin–lithium exchange; Lithiopyrrolidine; NMR spectroscopy.
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to the carbanionic carbon atom. When the pyrrolidine was enriched with ^{13}C at C-2, a triplet was observed in the ^{6}Li spectrum. These results show that two lithium atoms are attached to the carbanionic carbon atom, and conversely, that two carbon atoms are attached to the lithium atoms. Figure 1 shows the partial ^{13}C and full ^{6}Li spectrum of unlabelled *rac*-**3a** and the ^{6}Li NMR spectrum of (*S*)-**3a** enriched at C2 in ^{13}C.

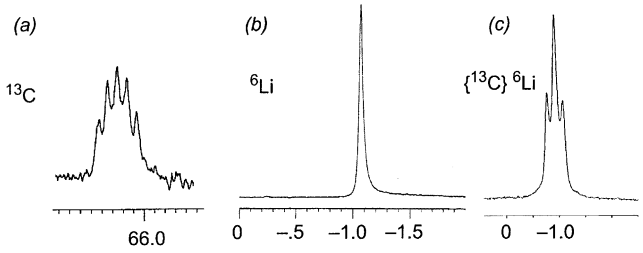
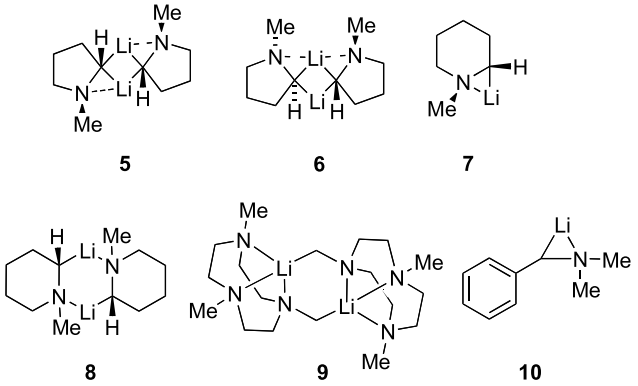
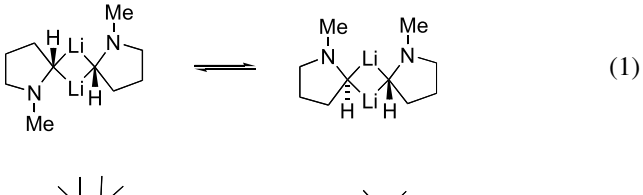


Figure 1. (a) Partial ^{13}C NMR and (b) ^{6}Li spectra of *rac*-^{6}Li-**3a**, 0.39 M in THF; (c) ^{6}Li spectrum of {^{13}C, ^{6}Li} (*S*)-**3a** (90:10 er, 0.39 M in THF; a ~0.05 M solution showed similar splitting). Temperature −100 °C.

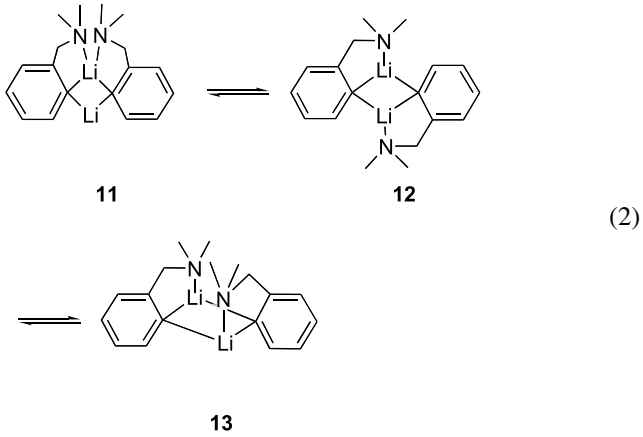
These data do not distinguish between a homochiral and a heterochiral dimer, but do indicate that, unless signals for the two dimers are coincidentally isochronous in both ^{13}C and ^{6}Li, both cannot be present (see below). If both heterochiral and homochiral dimers were energetically viable, a partly enantioenriched sample would show both. When the spectrum of ^{6}Li-**3a** of 90:10 er was recorded, only one ^{6}Li signal and one carbanionic carbon (a pentet) were observed. We therefore concluded that the dimer must be homochiral.[11] There are two possible homochiral dimeric structures that can be imagined for **3a**, namely **5** and **6**. Both have C_2 symmetry, and each should exhibit only one signal for the carbanionic carbon. However, since the two lithiums of **6** are nonequivalent, the conclusion was that **5** is the correct structure.[11] Note that the dashed lines between the lithiums and nitrogens indicate bonding that was not explicitly proven for **3a**, but was demonstrated in the homolog, 2-lithio-*N*-methylpiperidine **7**, which, we concluded, is monomeric. More recently, we found that the *N*-ethyl pyrrolidine **3b** may exist as a mixture of monomer and dimer.[12]



A referee has suggested that another structure for 2-lithio-*N*-methylpiperidine, that is also consistent with the observed ^{6}Li couplings to ^{13}C and ^{15}N, is **8**. Such a cyclic dimer is known in the solid state (**9**),[13] but this appears to be a rather special case where a triazacyclononane acts as a tridentate ligand and effectively competes with bridging of the lithium to the α-nitrogen. A more relevant example may be **10**, which shows lithium bridging to the nitrogen in the solid state.[14] Furthermore, note that the nitrogen atoms in both **7** and **8** are stereogenic. In the former, only one stereoisomer is possible due to the constraints of the 3/6 ring fusion. In the latter, four possible stereoisomers exist (epimeric at nitrogen only, not carbon), and one might reasonably expect to see more than one. However, only one set of signals was observed in the ^{6}Li, ^{15}N, and ^{13}C spectra, so we believe the conclusion is valid. The referee also noted that signals in the ^{13}C and ^{6}Li spectra of **5** and **6** might be coincidentally isochronous, or perhaps in equilibrium. Such an equilibrium might exist in the absence of Li–N bridging, by rotation of one heterocycle around the C···C axis of the C–Li–C–Li ring, as shown in Eq. 1. Such rotations are precedented.[15] A nitrogen-chelated example is shown in Eq. 2. Compound **11** has two nonequivalent lithiums, while in **12** and **13**, the two lithiums are equivalent. In this system, all three species could be observed in the ^{6}Li NMR spectrum at −135 °C. By −55 °C, all three had coalesced into a broad singlet. The *N*-ethyl analogs showed similar coalescence at temperatures around −100 °C. Note that the equilibrium between **12** and **13** involves loss of a solvent molecule (not shown), but rotation does not require breaking the N–Li bond. In contrast, if the lithium in **3a** is bridged to nitrogen as tentatively illustrated in **5**, such rotation would be expected to have a high barrier because it would entail breaking two N–Li bonds. Since we do not yet have evidence of lithium–nitrogen coordination in **3a**, structures such as those in Eq. 1 cannot be ruled out. At present, we are working under the hypothesis that **5** is the correct solution structure for **3a**. As we show below, unstabilized lithiopyrrolidines such as **3b** and **4** have much more complex solution behavior than does **3a**.



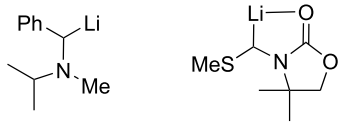
(1)



(2)

There are a number of methods by which configurational stability can be determined. These include using variable temperature NMR spectroscopy (with analysis of the coalescence of diastereotopic signals), using the Hoffmann test (as a qualitative measure by quenching with a chiral electrophile), or using electrophilic quench and analysis of

the enantiomer ratio of the products over different reaction times. In terms of gaining the most structural information, the use of NMR spectroscopy has considerable appeal. For example, benzylic α-aminoorganolithium **14** was studied by Ahlbrecht et al., and dipole stabilized organolithium **15** by Gaul et al.[16,17] Coalescence of the diastereotopic methyl groups of **14** occurred around 190 K and this equated to a barrier to inversion of about 9.0 kcal/mol at 190 K. This barrier increased slightly (to 10.0 or 10.5 kcal/mol) in the presence of the additives TMEDA or pentamethyldiethylenetriamine (PMDTA).[16] Line shape analysis of the coalescence of the H-5 signals of the lithiated *S*,*N*-acetal **15**, revealed activation parameters of $\Delta H^{\ddagger}=8.9\pm0.2$ kcal/mol and $\Delta S^{\ddagger}=-8.9\pm4.2$ cal/mol K ($\Delta G^{\ddagger}=10.8$ kcal/mol).[17]



14 **15**

It is clear from this discussion that some isolated information is known about the structures and the configurational stabilities of a few chiral α-amino-organolithium species. The importance of 2-lithiopyrrolidines in synthesis and our own studies in this area prompted us to compare a selection of *N*-substituted derivatives and to investigate their structures and relative stabilities. The *gem*-dimethyl compounds **1b**, **2b**, and **4** were prepared in the hope that DNMR could be used to evaluate their enantiomerization barriers. This was a reasonable expectation, since, in hexane–ether solvent mixtures, at least some *N*-alkyl lithiopyrrolidines are chemically stable at or near room temperature,[6,7] and dynamic resolution in the presence of a chiral ligand is possible at these temperatures.[10] However, such was not the case, and configurational stability had to be studied by aging, chemical trapping, and kinetic analysis of enantiomerization of **1a**, **2a**, and **3b**.[12] Herein we report details of our NMR spectral studies of three classes of ^{6}Li-labelled pyrrolidines: dipole stabilized **1a/b**, unstabilized and presumably chelated **2a/b**, and unstabilized **3b** and **4**.

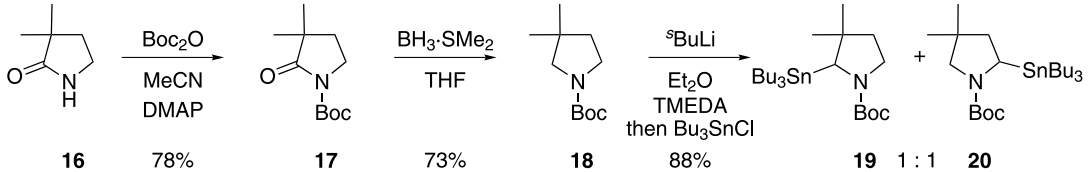
2. Results and discussion

We chose to study the structures of various *N*-substituted 2-lithiopyrrolidines by NMR spectroscopy. The *N*-substituted compounds **1**–**4** were selected to represent the different types of such compounds, containing coordinating carbonyl (**1**) or methoxy (**2**) groups, or non coordinating *n*-alkyl (**3**,**4**) groups.

In order to study these organolithiums by NMR, tin-lithium exchange from the corresponding 2-(tributylstannyl)-pyrrolidines was employed for their generation. These stannanes are typically prepared by deprotonation of *N*-Boc-pyrrolidine, addition of tributyltin chloride and replacement of the *N*-Boc substituent with another *N*-substituent as desired. We were interested to determine if this approach could be applied to the *gem*-dimethyl analog **18** (Scheme 1). This compound could undergo deprotonation with *sec*-BuLi at C-2 or at C-5 to give different regioisomeric products. The pyrrolidine **18** was prepared from the known lactam **16**.[18] Addition of Boc_2O gave imide **17**, which was reduced selectively to the pyrrolidine **18** using borane. No selectivity was obtained in the deprotonation of this compound under standard conditions (*sec*-BuLi, TMEDA) and an inseparable mixture of the stannylated products **19** and **20** was obtained. This lack of regioselectivity may be due to rotational restriction, and lithiation *syn* to the Boc carbonyl, as has been observed before.[19]

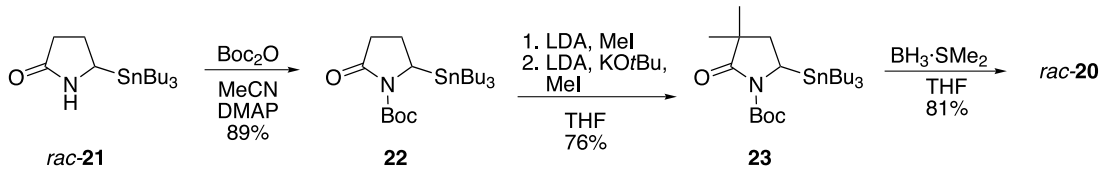
We therefore turned to an alternative route for the preparation of the dimethylpyrrolidines **1b**, **2b**, and **4**. The known lactam *rac*-**21**[20] was protected to give **22** and alkylated twice with iodomethane to give the lactam **23** (Scheme 2). The intermediate mono-methylated compound was used directly in the second methylation, which was found to be low-yielding using LDA but successful in the presence of potassium *tert*-butoxide (which is thought to give the base KDA[21]). Reduction of the lactam **23** with borane gave the desired pyrrolidine *rac*-**20**.

Deprotonation of the lactam **21** with sodium hydride and *N*-alkylation with bromopentane gave lactam **24** (Scheme 3). The base LDA was successful for both subsequent *C*-alkylations with iodomethane. The



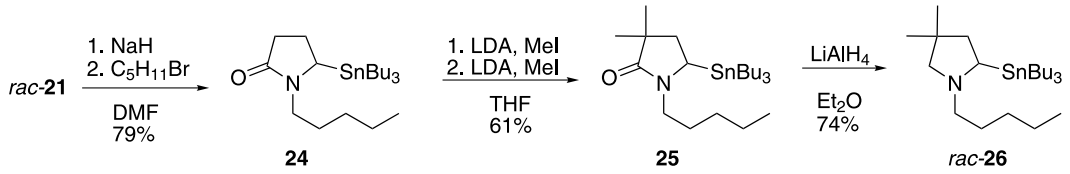
16 78% **17** 73% **18** 88% **19** 1 : 1 **20**

Scheme 1.



rac-**21** **22** **23**

Scheme 2.

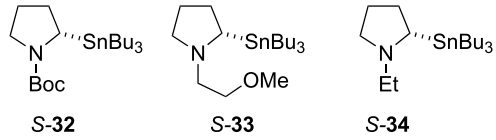


Scheme 3.

intermediate mono-methylated compound was found to be a single diastereomer and is likely to be the *trans* stereoisomer on the basis of related examples.[8,20,22] Reduction of the dialkylated lactam **25** to the pyrrolidine **26** was achieved using lithium aluminium hydride.

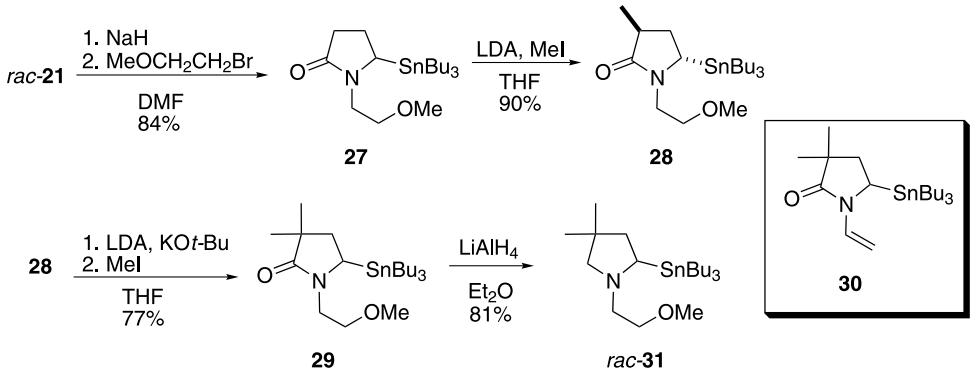
Alkylation of lactam **21** with bromoethyl methyl ether gave lactam **27** (Scheme 4). Mono-methylation gave **28** as a single diastereomer. Use of LDA as the base for the second methylation resulted in a mixture of products, including the desired compound **29** together with products such as **30**, resulting from deprotonation on the chain α- to the nitrogen atom and elimination of methanol. The base KDA however provided a good yield of the desired *gem*-dimethyl lactam **29** (together with **30**, 18%). Reduction of the lactam **29** gave the pyrrolidine **31**.

We now had the stannanes **20**, **26** and **31**, as well as the unsubstituted analogs that have previously been reported, *S*-**32**,[4] *S*-**33**,[23] and *S*-**34**[12] as precursors to the desired organolithium compounds **1**–**4**. The stannanes were treated with substoichiometric amounts of Bu^{6}Li in THF-d_8 at −80 °C in an NMR tube to give the organolithium species **1**–**4**.



2.1. Dipole-stabilized lithiopyrrolidines 1a,b (*N*-Boc)

The ^{6}Li and ^{13}C NMR spectra of the organolithium *S*-**1a** (95:5 er) in THF are shown in Figure 2. The lithium spectrum shows a single broad peak indicative of a species undergoing dynamic exchange of some sort. The carbon spectrum revealed only a single signal for the carbanionic carbon, but no coupling to ^{6}Li could be observed. The enantiomerization of **1a** is first order in organolithium, with a free energy barrier ($\Delta G^{\ddagger}$) of ~19–20 kcal/mol in ether and 4:1 hexane/ether solvent; in ether, $\Delta H^{\ddagger} = 19 \pm 3$ kcal/mol and $\Delta S^{\ddagger} = 40 \pm 8$ cal/mol K.[12] The proton NMR spectrum of lithiodimethylpyrrolidine **1b** is shown in Figure 3. At −20 °C, all the protons can be assigned, and there is no evidence of dynamic exchange of the *gem*-dimethyls. However, note that the broad AB quartet due to the H-5 protons at 2.72 ppm separates into a pair of doublets upon



Scheme 4.

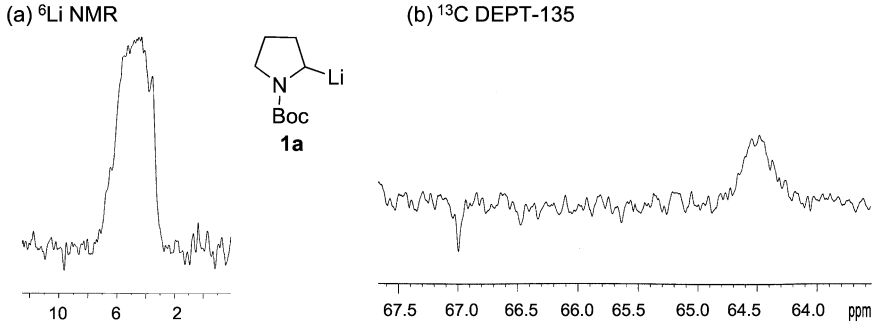


Figure 2. ^{6}Li and partial ^{13}C NMR spectra of *S*-**1a** in THF at −70 °C. The carbon spectrum was acquired using a DEPT-135 pulse sequence to suppress the THF-d_8 signal.

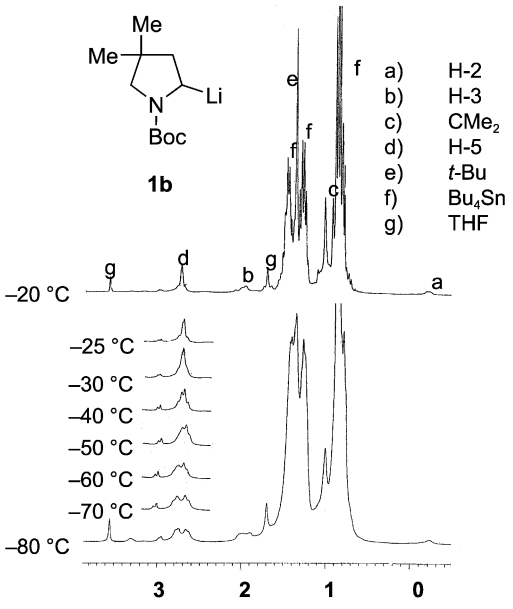


Figure 3. 300 MHz ^{1}H spectra of *rac*-**1b** in THF at varying temperatures.

cooling. At these temperatures, this dynamic phenomenon cannot be due to rotamers ($\Delta G^{\ddagger} \geq 15$ kcal/mol) or enantiomerization ($\Delta G^{\ddagger} = 20 \pm 3$ kcal/mol at -33 °C in ether or 4:1 hexane/ether[12]) as both would be slow on the NMR time scale. Instead, this may be an equilibrium between different aggregation states or, more probably, a solvation–desolvation phenomenon. The latter seems a more likely explanation since different aggregation states would be expected to show separate ^{6}Li signals at this temperature (see below). Although the ^{6}Li spectrum of **1b** was not recorded, the ^{6}Li spectrum of **1a** did show broadening indicative of a dynamic phenomenon, possibly of the same type as that observed in the proton spectrum **1b**. If this dynamic phenomenon is solvent exchange, it could be responsible for the large positive $\Delta S^{\ddagger}$ for enantiomerization of **1a**. Interestingly, Beak has reported that TMEDA accelerates the racemization of *S*-**1a** in ether, which could be due to a solvent/TMEDA exchange.[4,24]

2.2. Unstabilized, chelated lithiopyrrolidines 2a,b (*N*-methoxyethyl)

N-Methoxyethyl-2-lithiopyrrolidine *S*-**2a** ($\geq$95:5 er) showed one peak in its ^{6}Li spectrum, and a single signal in the carbanion region of the ^{13}C spectrum (Fig. 4). In the

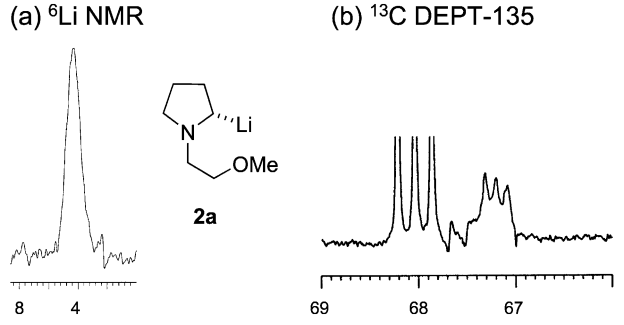


Figure 4. ^{6}Li and partial ^{13}C spectra of *S*-**2a** at -75 °C. The carbon spectrum was acquired using a DEPT-135 pulse sequence to suppress the THF-d_8 signal. The 1:1:1 triplet at 68.0 ppm is THF-d_7.

^{13}C spectrum, the signal is a 1:1:1 triplet, $\delta = 67.2$, $^{1}J\{^{13}C–^{6}Li\} = 14.4$ Hz, indicating a monomeric structure.[25] We did not anticipate observing coalescence due to enantiomerization on the NMR timescale, as *S*-**2a** is known to undergo racemization only slowly at -40 °C ($\Delta G^{\ddagger} = 20 \pm 3$ kcal/mol at 0 °C in THF or 4:1 hexane/ether).[12,23] The NMR spectrum of *rac*-**2b** showed one major peak in the ^{6}Li NMR spectrum, together with some minor signals, indicating that predominantly one species was present. The ^{13}C NMR spectrum of *rac*-**2b** did, however, give some useful information, revealing a triplet at $\delta = 68.2$, $^{1}J\{^{13}C–^{6}Li\} = 13.6$ Hz, corresponding to the carbon atom attached to the lithium atom (Fig. 5). In an experiment with a longer acquisition time, this signal lost its coupling information and appeared as an unresolved peak. No other signals were evident in this region. We infer that the major *rac*-**2b** species has only one lithium atom attached to the carbanionic carbon atom and is therefore likely to be a monomer in THF.[25] However, note that there are three possible monomeric structures that are consistent with this observation (**35**–**37**).

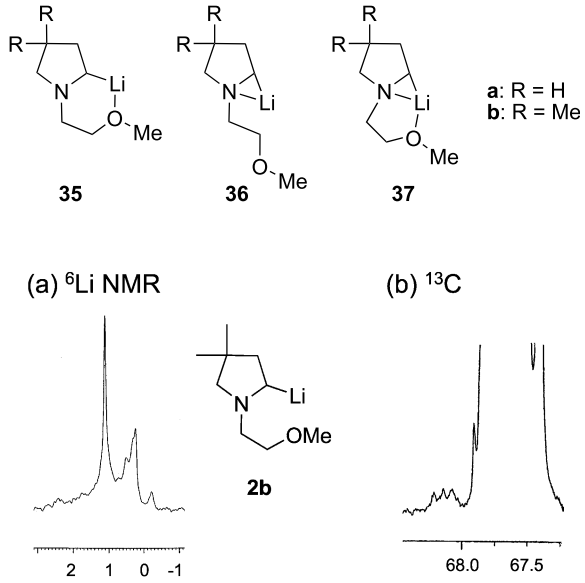


Figure 5. ^{6}Li and partial ^{13}C spectra of *rac*-**2b** at -80 °C in THF-d_8.

2.3. Unstabilized lithiopyrrolidines 3b, 4 (*N*-alkyl)

As reported elsewhere,[12] on one occasion we recorded a spectrum of *N*-ethyl-2-lithiopyrrolidine *S*-^{6}Li-**3b** in THF ($\geq$95:5 er) revealing two species in THF solution, one with a single attached lithium and one with two, probably monomeric and dimeric structures. At higher concentration (0.67 vs 0.27 M), as shown in Figure 6, four signals are discernable in the ^{6}Li NMR of *S*-**3b** ($\geq$95:5 er), as are four carbanionic carbons at 63.0, 64.1, 64.4, and 65.4 ppm. At this higher concentration, no monomer was detected. The signals at 63.0 and 64.1 ppm are clearly pentets indicative of dimers $^{1}J\{^{13}C–^{6}Li\} = 6.4$ and 6.8 Hz, respectively,[25] while the other two signals do not show resolved coupling. Also shown in Figure 6 are ^{6}Li and ^{13}C spectra of *S*-**3b** in the presence of one and two molar equivalents of PMDTA. Three of the four ^{6}Li signals appear to coalesce or merge, while a new 1:1:1 triplet appears near 69 ppm ($^{1}J\{^{13}C–^{6}Li\} = 14.2$ Hz), indicative of a monomer.[25]

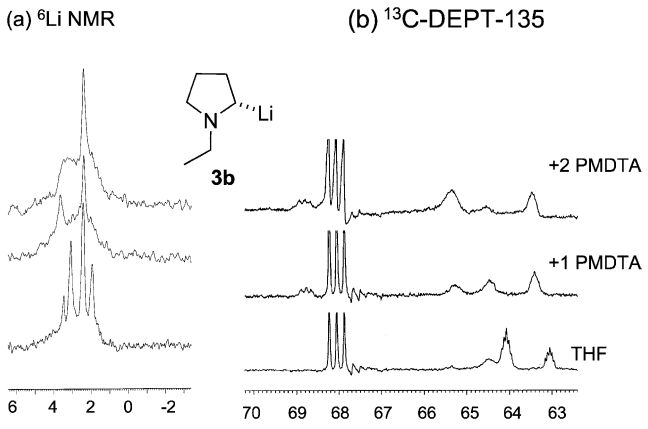
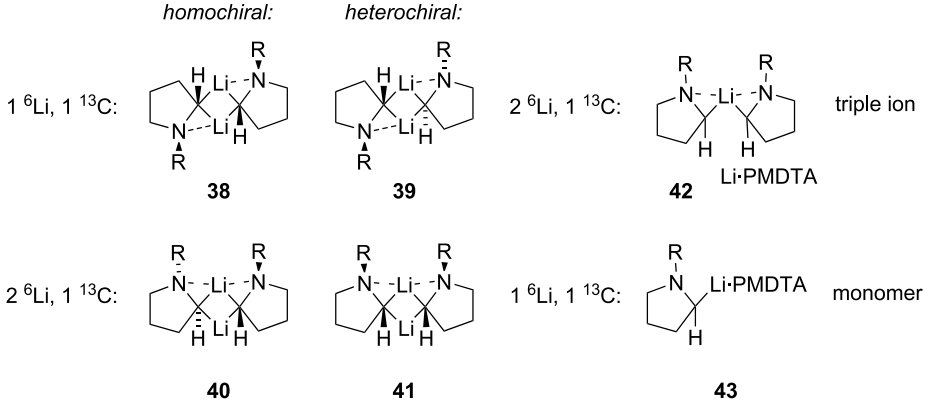


Figure 6. ^{6}Li and partial ^{13}C spectra of *S*-**3b** in the absence and presence of PMDTA at −75 °C. The carbon spectrum was acquired using a DEPT-135 pulse sequence to suppress the THF-d_8 signal. The 1:1:1 triplet at 68.0 ppm is THF-d_7.

Evident in the spectra recorded in the presence of PMDTA is a change in the relative ratios of the carbanionic species. In particular, the pentet at 64.1 ppm diminishes, while a peak at 65.0–65.2 ppm increases. Also, the upfield peak at 63.0 ppm loses its coupling information in the presence of PMDTA.

carbons, a pentet at $\delta = 65.4$, $^{1}J\{^{13}C–^{6}Li\} = 6.6$ Hz, and an unresolved peak at 63.7 of approximate equal intensity (Fig. 7). Thus, **4** exists in THF as a mixture of species, one of which is a dimer.

The unstabilized *N*-alkyl-2-lithiopyrrolidines show the greatest tendency toward structural diversity among the compounds studied. *N*-Methyl pyrrolidine *S*-**3a** or *rac*-**3a** appear to be homochiral dimers at 0.31–0.39 M in THF.[11] In contrast, *N*-ethyl pyrrolidine **3b** can exist as both a monomer and a dimer at 0.27 M. At higher concentrations, there is no evidence of monomeric *S*-**3b**, rather two distinct dimers and two other species are observed. Racemic **4** shows a dimeric structure as well as a second species. Structures **38**–**43** are possible monomers and dimeric aggregates. The dashed lines represent possible Li–N coordination. The number of lithium and carbon signals for each is indicated. For *S*-**3a**, the solution structure was established as **38** (R = Me; see also **5**), as described in Section 1.[11] Based on the similarity of chemical shifts, it is reasonable to assign a similar structure **38** (R = Et) to the *S*-**3b** dimer resonating at 63.0 or 64.1 ppm in the ^{13}C spectrum (Fig. 6). The other *S*-**3b** dimeric species (resonating at 63.0 or 64.1 ppm) may be **40** (R = Et). Together, these species would account for three of the four ^{6}Li resonances observed for **3b** (Fig. 6). In the



Transmetalation of the *N*-pentyl pyrrolidinylstannane *rac*-**26** with Bu^{6}Li in THF-d_8 gave the unstabilized organolithium *rac*-^{6}Li-**4**. The ^{6}Li NMR spectrum showed two large and several smaller signals, indicating several species in solution. The ^{13}C NMR spectrum showed two carbanionic

presence of PMDTA, a new signal appears at 69 ppm, in which only one ^{6}Li is in contact with the carbanionic carbon. In principle, this could be either triple ion **42** or monomer **43**, but since PMDTA is tridentate,[26] we assign it to monomer **43**. The unresolved resonance of **4** at 63.7 ppm

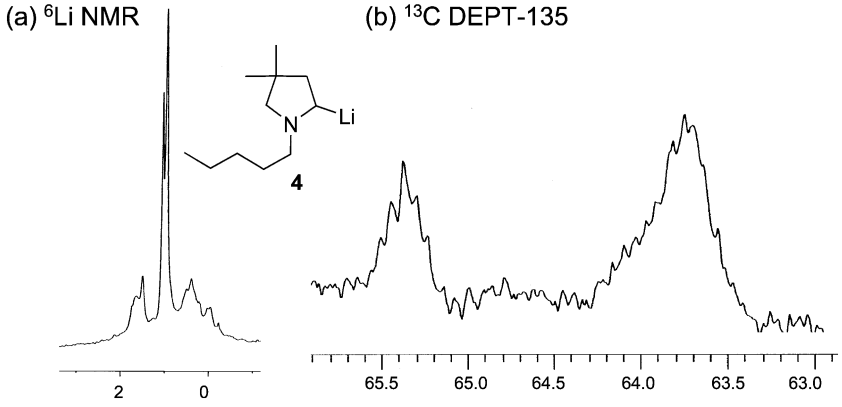


Figure 7. ^{6}Li and partial ^{13}C spectrum of *rac*-**4** at −75 °C. The carbon spectrum was acquired using a DEPT-135 pulse sequence to suppress the THF-d_8 signal.

(Fig. 7) has a chemical shift similar to the homochiral dimer of **3a**, so we assign it a similar structure, **38** (R=pentyl; dimethyls not shown). Based on the fact that there is only one other major ^{6}Li signal (Fig. 7), the signal resonating at 65.7 ppm is assigned to heterochiral dimer **39** (R=pentyl; dimethyls not shown).

In summary, we have shown that the solution structure of *N*-substituted-2-lithiopyrrolidines can vary from a single predominant species to a complex mixture of interconverting aggregates whose structure is influenced by a variety of effects, including chelation, enantiomer ratio, and concentration. It is interesting to note that, of the three structural types studied here and in a related work on the barrier to enantiomerization,[12] the class of lithiopyrrolidines with the most complex solution structure and the highest barrier to enantiomerization is also the only one that has been shown to undergo dynamic resolution in the presence of a chiral ligand.[10]

3. Experimental

3.1. General

NMR spectroscopy experiments with the organolithium species **1**–**4** were performed on 300, 400, or 500 MHz instruments. All manipulations were carried out under an argon atmosphere. Bu^{6}Li was prepared according to the procedure of Hilmersson and Davidsson,[27] as follows: ^{6}Li chunks (325 mg, 54.2 mmol) were cleaned with paper tissue, weighed, flattened between filter papers with a mallet, cut into thin strips, and contained under argon in a thick-walled tube with a rubber septum. Isopropanol (10 mL) was added and when the metal surface was clean, the solvent was removed by syringe. The lithium metal was washed four times with dry hexane, and then dry hexane (10 mL) was added followed by chlorobutane (2.83 mL, 27.1 mmol). The mixture was allowed to stand for 30 min, and then sonicated for 1 h. The mixture was allowed to stand overnight to settle. The clear solution of Bu^{6}Li was transferred by cannula to a flame-dried vacuum flask equipped with a vacuum tap and a magnetic stirrer bar. The solvent was removed carefully under high vacuum with vigorous stirring to give neat Bu^{6}Li as a viscous liquid determined to be ~8 M by titration. Samples in THF-d_8 were prepared either by addition of the neat Bu^{6}Li to a solution of the substrate in the NMR tube (the Bu^{6}Li solidified on the side of the tube and was carefully dissolved by intermittent removal of the tube from the cooling bath (−78 °C) and vigorous shaking for a few seconds), or by preparing the Bu^{6}Li solution in the NMR tube at low temperature in half of the solvent prior to addition of the substrate in the remainder of the solvent.

3.1.1. 1-*t*-Butoxycarbonyl-3,3-dimethyl-2-pyrrolidinone 17. To a solution of 3,3-dimethyl-2-pyrrolidinone **16**[18] (150 mg, 1.33 mmol) and Boc_2O (320 mg, 1.46 mmol) in MeCN (3.5 mL) was added 4-dimethylaminopyridine (DMAP) (7 mg, 0.06 mmol) at room temperature. After 16 h water (3 mL) and Et_2O (5 mL) were added and the organic phase was dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (50:1 to 10:1) gave the lactam **17** (222 mg, 78%) as an oil; R_f (petrol–EtOAc, 9:1) 0.15; ν_{max}(neat)/cm^{-1} 2975–2870 (C–H), 1780, 1750 and 1715 (C=O); δ_H(300 MHz, $CDCl_3$) 3.62 (2H, t, J=7 Hz, NCH_2), 1.81 (2H, t, J=7 Hz, NCH_2CH_2), 1.49 [9H, s, $C(CH_3)_3$], 1.15 [6H, s, $C(CH_3)_2$]; δ_C(75 MHz, $CDCl_3$) 179.0, 150.6, 82.7, 42.7, 42.2, 32.8, 28.0, 24.3; Found (ES) $[M+NH_4]^+$, 231.1710, $C_{11}H_{23}N_2O_3$ requires 231.1709; *m*/*z* (CI) 231 ($[M+NH_4]^+$, 5%), 175 (67), 131 (100) and 114 (92).

3.1.2. 1-*t*-Butoxycarbonyl-3,3-dimethyl-pyrrolidine 18. To a solution of the pyrrolidinone **17** (339 mg, 1.59 mmol) in THF (3 mL) was added $BH_3\cdot SMe_2$ (6.2 mL, 12.3 mmol, 2 M in THF) at room temperature. After 18 h MeOH (1 mL) was added dropwise with cooling, followed by water (3 mL) and $CHCl_3$ (10 mL). The aqueous phase was extracted with $CHCl_3$ (2×10 mL) and the organic phases were dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (1:0 to 10:1) gave the pyrrolidine **18** (232 mg, 73%) as an oil; R_f (petrol–EtOAc, 1:1) 0.70; ν_{max}(neat)/cm^{-1} 2965–2870 (C–H) and 1700 (C=O); δ_H(300 MHz, $CDCl_3$) 3.36 and 3.30 (2×1H, t, J=7 Hz, NCH_2CH_2, rotamers), 3.02 and 2.96 (2×1H, s, NCH_2C, rotamers), 1.60–1.50 (2H, m, NCH_2CH_2), 1.40 [9H, s, $C(CH_3)_3$], 0.99 [6H, s, $C(CH_3)_2$]; δ_C (75 MHz, $CDCl_3$) 154.6, 154.5, 78.8, 78.7, 58.8, 58.2, 45.1, 44.8, 39.3, 38.5, 38.2, 37.4, 28.5, 26.1; Found (EI) M^+, 199.1571, $C_{11}H_{21}NO_2$ requires 199.1572; *m*/*z* (EI) 199 (M^+, 9%) and 57 (100).

3.1.3. 1-*t*-Butoxycarbonyl-4,4-dimethyl-2-tributylstannyl-pyrrolidine and 1-*t*-Butoxycarbonyl-3,3-dimethyl-2-tributylstannyl-pyrrolidine, 19 and 20. To a solution of TMEDA (0.21 mL, 1.40 mmol) and the pyrrolidine **12** (232 mg, 1.17 mmol) in Et_2O (10 mL) at −78 °C was added ^{s}BuLi (1.08 mL, 1.40 mmol, 1.3 M in cyclohexane). After 6 h Bu_3SnCl (0.48 mL, 1.8 mmol) was added and the mixture was allowed to warm to room temperature. Water (5 mL) and petrol (10 mL) were added and the organic phase was separated, dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (1:0 to 20:1) gave stannanes **19** and **20** (503 mg, 88%) as an inseparable mixture (1:1), as an oil; R_f (petrol–EtOAc, 9:1) 0.55; ν_{max}(neat)/cm^{-1} 2965–2855 (C–H) and 1685 (C=O); δ_H(400 MHz, $CDCl_3$) 3.62–3.51 (0.6H, m, NCH), 3.46–3.35 (1.8H, m, NCH), 3.30–3.20 (1H, m, NCH), 3.16–3.09 (1.6H, m, NCH), 2.89 (1H, d, J=10.5 Hz, NCH), 1.78–1.20 [46H, m, $NCH(Sn)CH_2$, NCH_2CH_2, $C(CH_3)_3$ and $Sn(CH_2CH_2CH_2)_3$], 1.14–0.75 [42H, m, $CH_2C(CH_3)_2$ and $Sn(CH_2CH_2CH_2CH_3)_3$]; δ_C(100 MHz, $CDCl_3$) 154.4, 154.3, 78.4, 78.3, 60.3, 59.4, 45.5, 45.2, 44.3, 41.5, 41.4, 39.0, 29.2, 28.6, 28.5, 27.7, 27.6, 26.7, 26.5, 26.1, 25.7, 13.8, 13.7, 11.7, 10.1.

3.1.4. 1-*t*-Butoxycarbonyl-5-tributylstannyl-2-pyrrolidinone 22. To a solution of 5-tributylstannyl-2-pyrrolidinone **21**[20] (368 mg, 0.98 mmol) and Boc_2O (235 mg, 1.08 mmol) in MeCN (2.5 mL) and CH_2Cl_2 (0.5 mL) was added DMAP (6 mg, 0.05 mmol) at room temperature. After 16 h water (3 mL) and petrol (5 mL) were added and the organic phase was dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc

(50:1 to 20:1) gave the stannane **22** (413 mg, 89%) as an oil; R_f (petrol–EtOAc, 9:1) 0.40; ν_{max}(neat)/cm^{-1} 2960–2860 (C–H), 1755 and 1700 (C=O); δ_H(300 MHz, $CDCl_3$) 3.84 (1H, dd, J=8.5, 7 Hz, NCH), 2.60–2.20 (3H, m, CH^AH^{B}CH_2CO), 2.09–1.96 (1H, m, CH^AH^BCH$_2$CO), 1.60–1.38 [15H, m, C$(CH_3)_3$ and Sn$(CH_2CH_2CH_2)_3$], 1.31 [6H, sextet, J=7 Hz, Sn$(CH_2CH_2CH_2)_3$], 1.02–0.80 [15H, m, Sn$(CH_2CH_2CH_2CH_3)_3$]; δ_C(75 MHz, $CDCl_3$) 174.3, 151.6, 82.7, 47.8, 35.0, 29.0, 28.1, 27.5, 23.5, 13.7, 9.8; Found (ES) [M+H]$^+$, 476.2183, $C_{21}H_{42}NO_3^{120}Sn$ requires 476.2186; *m/z* (ES) 476 ([M+H]$^+$, 12%), 498 ([M+Na]$^+$, 100).

3.1.5. 1-*t*-Butoxycarbonyl-3,3-dimethyl-5-tributylstannyl-2-pyrrolidinone 23. To a solution of ^{i}Pr$_2$NH (89 μL, 0.74 mmol) in THF (1.5 mL) at 0 °C was added ^{n}BuLi (0.3 mL, 0.74 mmol, 2.5 M in hexanes). After 30 min the mixture was cooled to −78 °C and transferred via cannula to a −78 °C solution of lactam **22** (270 mg, 0.57 mmol) in THF (1.5 mL). After 20 min, MeI (0.1 mL, 1.6 mmol) was added and stirring was continued for 1 h at −78 °C. After warming to room temperature, water (2 mL) and hexane (10 mL) were added and the organic phase was separated, dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (1:0 to 10:1) gave the mono-methylated lactam (230 mg, 83%) as an oil, which was used directly in the second methylation:

To a solution of ^{i}Pr$_2$NH (75 μL, 0.63 mmol) and KO^{t}Bu (72 mg, 0.63 mmol) in THF (2 mL) at −78 °C was added ^{n}BuLi (0.25 mL, 0.63 mmol, 2.5 M in hexanes). After 10 min the mixture was transferred via cannula to a precooled (−78 °C) solution of the mono-methylated lactam (230 mg, 0.47 mmol) in THF (2 mL). After 10 min, MeI (0.25 mL, 4.0 mmol) was added and the mixture was allowed to warm to room temperature over 1 h. Water (5 mL) and petrol (40 mL) were added and the organic phase was separated, dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (1:0 to 50:1) gave the lactam **23** (215 mg, 91%) as an oil; R_f (petrol–EtOAc, 9:1) 0.42; ν_{max}(neat)/cm^{-1} 2965–2860 (C–H), 1755 and 1695 (C=O); δ_H (300 MHz, $CDCl_3$) 3.62 (1H, dd, J=10.5, 7.5 Hz, NCH), 2.03–1.83 (2H, m, NCHCH_2), 1.60–1.38 [15H, m, C$(CH_3)_3$ and Sn$(CH_2CH_2CH_2)_3$], 1.31 [6H, sx, J=7 Hz, Sn$(CH_2CH_2CH_2)_3$], 1.17 (3H, s, CH_3CCO), 1.15 (3H, s, CH_3CCO), 1.00–0.78 [15H, m, Sn$(CH_2CH_2CH_2CH_3)_3$]; δ_C(75 MHz, $CDCl_3$) 179.3, 152.2, 82.7, 43.3, 42.6, 38.4, 29.1, 28.0, 27.5, 24.8, 23.5, 13.7, 10.0; Found (ES) [M+H]$^+$, 504.2490, $C_{23}H_{46}NO_3^{120}Sn$ requires 504.2499; *m/z* (ES) 504 ([M+H]$^+$, 17%), 526 ([M+Na]$^+$, 60) and 549 ([M+2Na]$^+$, 100).

3.1.6. 1-*t*-Butoxycarbonyl-4,4-dimethyl-2-tributylstannyl-pyrrolidine 20. In the same way as lactam **17**, the lactam **23** (100 mg, 0.20 mmol) and BH_3·DMS (0.40 mL, 0.80 mmol, 2 M in THF) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (50:1) the pyrrolidine **20** (79 mg, 81%) as an oil; R_f (petrol–EtOAc, 9:1) 0.55; ν_{max}(neat)/cm^{-1} 2960–2855 (C–H), 1680 (C=O); δ_H(300 MHz, $CDCl_3$) 3.43 (1H, dd, J=11, 8 Hz, NCHSn), 3.12 (1H, d, J=10.5 Hz NCH^AH^B), 2.88 (1H, d, J=10.5 Hz, NCH^AH^B), 1.80–1.62 [2H, m, NCH(Sn)CH_2], 1.60–1.37 [15H, m, C$(CH_3)_3$ and Sn$(CH_2CH_2CH_2)_3$], 1.29 [6H, sextet, J=7 Hz, Sn$(CH_2CH_2CH_2)_3$], 1.08 (3H, s, NCH_2CCH_3), 1.01 (3H, s, NCH_2CCH_3), 0.96–0.74 [15H, m, Sn$(CH_2CH_2CH_2CH_3)_3$]; δ_C(75 MHz, $CDCl_3$) 154.3, 78.4, 59.4, 45.2, 44.3, 39.0, 29.2, 28.6, 28.5, 27.6, 26.5, 25.7, 13.8, 10.1; Found (FI) M$^+$, 489.2626, $C_{23}H_{47}NO_2^{120}Sn$ requires 489.2629; *m/z* (FI) 489 (M$^+$, 64%), 432 (100).

3.1.7. 1-Pentyl-5-tributylstannyl-2-pyrrolidinone 24. To a solution of lactam **21**[20] (430 mg, 1.15 mmol) in DMF (4 mL) at room temperature was added NaH (93 mg, 2.3 mmol, 60% in mineral oil) in one portion, and after 30 min, bromopentane (435 mg, 0.36 mL, 2.9 mmol) was added. After 2 h water (2 mL) and hexane (10 mL) were added and the organic phase was separated, washed with water (4×2 mL), dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (20:1 to 4:1) gave the lactam **24** (402 mg, 79%) as an oil; R_f (petrol–EtOAc, 1:1) 0.80; ν_{max}(neat)/cm^{-1} 2965–2855 (C–H), 1680 (C=O); δ_H(400 MHz, $CDCl_3$) 3.86 (1H, ddd, J=13.5, 8.5, 7.5 Hz, NCH^AH^B), 3.66 (1H, dd, J=8.0, 5.5 Hz, NCHSn), 2.54 (1H, ddd, J=13.5, 8.5, 4.5 Hz, NCH^AH^B), 2.44–2.24 (3H, m, NCOCH_2CH^CH^D), 2.08–2.01 (1H, m, NCOCH$_2$CH^CH^D), 1.65–1.20 [18H, m, NCH$_2$CH_2CH_2CH_2 and Sn$(CH_2CH_2CH_2)_3$], 0.99–0.84 [18H, m, N$(CH_2)_4CH_3$ and Sn$(CH_2CH_2CH_2CH_3)_3$]; δ_C(100 MHz, $CDCl_3$) 174.1, 48.2, 43.1, 32.3, 29.1, 29.0, 27.5, 27.2, 24.0, 22.5, 14.0, 13.6, 9.2; Found (ES) [M+H]$^+$, 446.2441, $C_{21}H_{44}NO^{120}Sn$ requires 446.2445; *m/z* (CI) 446 ([M+H]$^+$, 9%), 154 (100).

3.1.8. 1-Pentyl-3,3-dimethyl-5-tributylstannyl-2-pyrrolidinone 25. In the same way as lactam **23**, ^{i}Pr$_2$NH (0.14 mL, 1.14 mmol), BuLi (1.0 mL, 1.14 mmol, 1.15 M in hexanes), the lactam **24** (338 mg, 0.76 mmol) and MeI (0.12 mL, 1.9 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (20:1 to 4:1), the mono-methylated lactam (427 mg, 82%) as an oil; R_f (petrol–EtOAc, 1:1) 0.72; ν_{max}(neat)/cm^{-1} 2970–2860 (C–H), 1680 (C=O); δ_H(400 MHz, $CDCl_3$) 3.86 (1H, dt, J=13.5, 8.5 Hz, NCH^AH^B), 3.59 (1H, dd, J=9.5, 3.5 Hz, NCHSn), 2.54 (1H, ddd, J=13.5, 8.5, 4.5 Hz, NCH^AH^B), 2.36–2.24 [2H, m, NCOCH(CH$_3$)CH^CH^D], 1.98–1.90 [1H, m, NCOCH(CH$_3$)CH^CH^D], 1.55–1.38 [8H, m, NCH$_2$CH_2 and Sn$(CH_2CH_2CH_2)_3$], 1.38–1.22 [10H, m, NCH$_2$CH$_2$CH_2CH_2 and Sn$(CH_2CH_2CH_2)_3$], 1.20 (3H, d, J=6.5 Hz, NCOCHCH_3), 0.98–0.82 [18H, m, N$(CH_2)_4CH_3$ and Sn$(CH_2CH_2CH_2CH_3)_3$]; δ_C(100 MHz, $CDCl_3$) 175.9, 46.0, 43.0, 37.7, 33.0, 29.1, 29.0, 27.5, 27.1, 22.4, 16.0, 14.0, 13.7, 9.4; Found (ES) [M+H]$^+$, 460.2604, $C_{22}H_{46}NO^{120}Sn$ requires 460.2601; *m/z* (CI) 460 ([M+H]$^+$, 8%), 168 (100), which was used in the second methylation:

In the same way as above, the mono-methylated lactam (155 mg, 0.34 mmol), ^{i}Pr$_2$NH (61 μL, 0.51 mmol), ^{n}BuLi (0.20 mL, 0.51 mmol, 2.5 M in hexanes) and MeI (50 μL, 0.80 mmol) gave the lactam **25** (119 mg, 74%) as an oil; R_f (petrol–EtOAc, 1:1) 0.67; ν_{max}(neat)/cm^{-1} 2960–2860 (C–H), 1680 (C=O); δ_H(400 MHz, $CDCl_3$) 3.88 (1H, ddd, J=13.5, 9, 7.5 Hz, NCH^AH^B), 3.57 (1H, dd, J=10, 7 Hz, NCHSn), 2.57 (1H, ddd, J=13.5, 9, 5 Hz, NCH^AH^B),

2.08–1.89 [2H, m, NCH(Sn)CH_2], 1.58–1.20 [18H, m, NCH_2CH_2CH_2CH_2 and Sn(CH_2CH_2CH_2)$_3$], 1.15 (3H, s, NCOCCH_3), 1.09 (3H, s, NCOCCH_3), 1.00–0.84 [18H, m, N(CH_2)$_4$CH_3 and Sn(CH_2CH_2CH_2CH_3)$_3$]; δ_C(100 MHz, $CDCl_3$) 179.3, 43.7, 43.6, 40.8, 39.9, 29.2, 28.9, 27.4, 27.0, 25.0, 23.6, 22.4, 14.0, 13.6, 9.0; Found (ES) $[M+H]^+$, 474.2753, $C_{23}H_{48}NO^{120}Sn$ requires 474.2758; *m/z* (CI) 474 ($[M+H]^+$, 8%), 182 (100).

3.1.9. 1-Pentyl-4,4-dimethyl-2-tributylstannyl-pyrrolidine 26. To a suspension of $LiAlH_4$ (15 mg, 0.39 mmol) in Et_2O (0.5 mL) at 0 °C was added the lactam **25** (45 mg, 0.10 mmol) in Et_2O (1 mL). The mixture was warmed to room temperature, and after 1 h, re-cooled to 0 °C, quenched with MeOH (1 mL) and absorbed onto basic alumina. Purification by column chromatography on basic alumina, eluting with petrol then petrol–EtOAc (100:1 to 20:1) gave the pyrrolidine **26** (33 mg, 74%) as an oil; R_f (petrol–EtOAc, 1:1) 0.25; ν_{max}(neat)/cm^{-1} 2970–2780 (C–H); δ_H(400 MHz, C_6D_6) 2.97–2.88 (2H, m, NCH^AH^{B}CH$_2$ and NCH^CH^{D}CCH$_3$), 2.74 (1H, dd, J=10.5, 8.5 Hz, NCHSn), 2.17 (1H, ddd, J=12, 8.5, 4.5 Hz, NCH^AH^BCH$_2$), 1.94–1.38 [21H, m, NCH^CH^DC(CH$_3$)CH_2, NCH$_2$CH_2CH_2-CH_2 and Sn(CH$_2$CH_2CH_2)$_3$], 1.26 (3H, s, CCH$_3$), 1.17–0.98 [21H, m, CCH$_3$, N(CH$_2$)$_4$CH_3 and Sn(CH_2CH$_2$CH$_2$CH_3)$_3$]; δ_C(100 MHz, C_6D_6) 69.1, 58.0, 57.1, 45.8, 38.6, 30.6, 30.0, 29.6, 29.0, 28.8, 27.8, 22.9, 14.1, 13.7, 9.2; Found (ES) $[M+H]^+$, 460.2966, $C_{23}H_{50}N^{120}Sn$ requires 460.2965; *m/z* (CI) 460 ($[M+H]^+$, 1%), 170 (100).

3.1.10. 1-(2-Methoxy-ethyl)-5-tributylstannyl-2-pyrrolidinone 27. In the same way as lactam **24**, lactam **21** (1.40 g, 3.74 mmol), DMF (13 mL), NaH (302 mg, 7.48 mmol, 60% in mineral oil) and bromoethylmethylether (1.3 g, 0.88 mL, 9.4 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (20:1 to 1:1) the lactam **27** (1.36 g, 84%) as an oil; R_f (EtOAc) 0.45; ν_{max}(neat)/cm^{-1} 2965–2855 (C–H), 1685 (C=O); δ_H(300 MHz, C_6D_6) 4.02 (1H, dt, J=14.5, 6.0 Hz, CH), 3.77 (1H, t, J=6.5 Hz, CH), 3.56–3.40 (2H, m, 2×CH), 3.30 (3H, s, OCH$_3$), 2.80–2.70 (1H, m, CH), 2.45–2.00 (4H, m, CH$_2$CH$_2$CO), 1.56–1.40 [6H, m, Sn(CH$_2$CH_2)$_3$], 1.30 [6H, sextet, J=7.5 Hz, Sn(CH$_2$CH$_2$CH_2)$_3$], 0.98–0.79 [15H, m, Sn(CH_2CH$_2$CH$_2$CH_3)$_3$]; δ_C(75 MHz, C_6D_6) 173.6, 71.4, 58.4, 50.0, 43.5, 32.0, 29.5, 27.8, 24.5, 13.8, 9.5; Found (FI) M^+, 433.1997, $C_{19}H_{39}NO_2^{120}Sn$ requires 433.2003; *m/z* (FI) 433 (M^+, 100%).

3.1.11. 1-(2-Methoxy-ethyl)-3-methyl-5-tributylstannyl-2-pyrrolidinone 28. In the same way as lactam **23**, the lactam **27** (170 mg, 0.39 mmol), ^{i}Pr$_2$NH (68 μL, 0.57 mmol), ^{n}BuLi (0.49 mL, 0.57 mmol, 1.15 M in hexanes) and MeI (60 μL, 0.96 mmol) gave, after purification by column chromatography on silica gel, eluting with petrol–EtOAc (10:1 to 4:1), the lactam **28** (158 mg, 90%) as an oil; R_f (petrol–EtOAc, 1:1) 0.55; ν_{max}(neat)/cm^{-1} 2960–2855 (C–H), 1685 (C=O); δ_H(300 MHz, C_6D_6) 4.25–4.10 (1H, dt, J=14, 5 Hz, CH), 3.74 (1H, dd, J=9, 3 Hz, NCHSn), 3.38–3.21 (2H, m, 2×CH), 3.01 (3H, s, OCH$_3$), 2.75 (1H, ddd, J=14.5, 7, 4 Hz, CH), 2.34–2.21 (2H, m, NCHCH^AH^{B}CH), 1.92–1.76 (1H, m, NCHCH^AH^BCH), 1.55–1.34 [6H, m, Sn(CH$_2$CH_2)$_3$], 1.29 [6H, sextet, J=7.5 Hz, Sn(CH$_2$CH$_2$CH_2)$_3$], 1.18 (3H, d, J=6.5 Hz, NCOCHCH_3), 1.00–0.78 [15H, m, Sn(CH_2CH$_2$CH$_2$CH_3)$_3$]; δ_C(75 MHz, C_6D_6) 175.6, 71.8, 58.5, 48.2, 43.6, 37.6, 33.7, 29.6, 27.9, 16.3, 14.0, 9.9; Found (CI) $[M+H]^+$, 448.2234, $C_{20}H_{42}NO_2^{120}Sn$ requires 448.2238; *m/z* (CI) 448 ($[M+H]^+$, 24%), 156 (100).

3.1.12. 1-(2-Methoxy-ethyl)-3,3-dimethyl-5-tributylstannyl-2-pyrrolidinone 29 and 3,3-dimethyl-5-tributylstannyl-1-vinyl-2-pyrrolidinone 30. To a solution of ^{i}Pr$_2$NH (81 μL, 0.68 mmol) and KO^{t}Bu (77 mg, 0.68 mmol) in THF (3 mL) at −78 °C was added ^{n}BuLi (0.27 mL, 0.68 mmol, 2.5 M in hexanes). After 10 min a precooled (−78 °C) solution of the lactam **28** (200 mg, 0.45 mmol) in THF (3 mL) was added dropwise via cannula. The mixture was warmed to −40 °C and after 1 h, MeI (0.10 mL, 1.6 mmol) was added and the mixture was allowed to warm to room temperature. Water (5 mL) and petrol (20 mL) were added and the organic phase was separated, dried ($MgSO_4$) and evaporated. Purification by column chromatography on silica gel, eluting with petrol–EtOAc (20:1 to 4:1) gave the lactam **29** (159 mg, 77%) as an oil, R_f (petrol–EtOAc, 1:1) 0.65; ν_{max}(neat)/cm^{-1} 2960–2860 (C–H), 1685 (C=O); δ_H(300 MHz, C_6D_6) 4.26 (1H, dt, J=14, 5 Hz, CH), 3.76 (1H, t, J=8.5 Hz, NCHSn), 3.45–3.28 (2H, m, 2×CH), 3.08 (3H, s, OCH$_3$), 2.84 (1H, ddd, J=12, 7, 5 Hz, CH), 2.04–1.85 [2H, m, NCH(Sn)CH_2], 1.72–1.49 [6H, m, Sn(CH$_2$CH_2)$_3$], 1.41 [6H, sextet, J=7.5 Hz, Sn(CH$_2$CH$_2$-CH_2)$_3$], 1.33 (3H, s, COCCH$_3$), 1.20 (3H, s, COCCH$_3$), 1.06–0.92 [15H, m, Sn(CH_2CH$_2$CH$_2$CH_3)$_3$]; δ_C(75 MHz, C_6D_6) 179.1, 71.1, 58.5, 45.8, 44.2, 40.9, 40.7, 29.6, 28.0, 25.5, 23.9, 14.0, 9.4; Found (CI) $[M+H]^+$, 462.2392, $C_{21}H_{44}NO_2^{120}Sn$ requires 462.2394; *m/z* (CI) 462 ($[M+H]^+$, 19%), 170 (100); and the lactam **30** (35 mg, 18%) as an oil; R_f (petrol–EtOAc, 9:1) 0.38; ν_{max}(neat)/cm^{-1} 2965–2860 (C–H), 1705 (C=O), 1625 (C=C); δ_H(400 MHz, C_6D_6) 7.49 (1H, dd, J=15.5, 8.5 Hz, NCH=), 4.30 (1H, d, J=8.5 Hz, NCH=CH^AH^B), 4.17 (1H, d, J=15.5 Hz, NCH=CH^AH^B), 3.37 (1H, dd, J=8, 7 Hz, NCHSn), 1.95–1.80 [2H, m, NCH(Sn)CH_2], 1.57–1.45 [6H, m, Sn(CH$_2$CH_2)$_3$], 1.33 [6H, sextet, J=7 Hz, Sn(CH$_2$CH$_2$-CH_2)$_3$], 1.15 (3H, s, NCOCCH$_3$), 1.09 (3H, s, NCOCCH$_3$), 0.98–0.85 [15H, m, Sn(CH_2CH$_2$CH$_2$CH_3)$_3$]; δ_C(100 MHz, C_6D_6) 177.3, 130.7, 93.2, 41.8, 40.8, 38.3, 29.2, 27.6, 25.2, 24.5, 13.6, 10.4; Found (CI) $[M+H]^+$, 430.2134, $C_{20}H_{40}NO^{120}Sn$ requires 430.2132; *m/z* (CI) 430 ($[M+H]^+$, 100%).

3.1.13. 1-(2-Methoxy-ethyl)-4,4-dimethyl-2-tributylstannylpyrrolidine 31. To a suspension of $LiAlH_4$ (35 mg, 0.91 mmol) in Et_2O (1 mL) at 0 °C was added the lactam **29** (75 mg, 0.16 mmol) in Et_2O (1 mL). After 40 min at 0 °C MeOH (1 mL) was added and the mixture was absorbed onto basic alumina. Purification by column chromatography on basic alumina, eluting with petrol then petrol–EtOAc (50:1 to 10:1) gave the pyrrolidine **31** (58 mg, 81%) as an oil; R_f (petrol–EtOAc, 1:1) 0.20; ν_{max}(neat)/cm^{-1} 2960–2770 (C–H); δ_H(400 MHz, C_6D_6) 3.44 (2H, t, J=6 Hz, OCH$_2$), 3.17 (3H, s, OCH$_3$), 3.11 (1H, dt, J=12, 6 Hz, NCH^AH^{B}CH$_2$), 2.87 (1H, d, J=8.5 Hz, NCH^CH^{D}CCH$_3$), 2.67 (1H, dd, J=9.5, 8 Hz, NCHSn), 2.38 (1H, dt, J=12, 6 Hz, NCH^AH^BCH$_2$), 1.82–1.59 [9H, m, NCH^CH^DC(CH$_3$)-CH_2 and Sn(CH$_2$CH_2)$_3$], 1.43 [6H, sx, J=7 Hz, Sn(CH$_2$-CH$_2$CH_2)$_3$], 1.18 (3H, s, CCH$_3$) 1.08–1.03 [9H, m, CCH$_3$

and $Sn(CH_2)_3$], 0.96 [9H, t, $J=7$ Hz, $Sn(CH_2(CH_2)_2CH_3)_3$]; δ_C(100 MHz, C_6D_6) 72.6, 70.4, 58.8, 58.4, 56.8, 46.0, 39.4, 30.9, 30.0, 29.1, 28.2, 14.2, 9.5; Found (CI) $[M+H]^+$, 448.2611, $C_{21}H_{46}NO^{120}Sn$ requires 448.2601; *m/z* (CI) 448 ($[M+H]^+$, 4%), 156 (100).

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References and notes

1. (a) Clayden, J.; Organolithiums: Selectivity for Synthesis; Pergamon: Oxford, 2002; Vol. 23. (b) Hodgson, D. M., Ed.; Organolithiums in Enantioselective Synthesis; Springer: Heidelberg, 2003; Vol. 5. (c) Rappoport, Z., Marek, I., Eds.; The Chemistry of Organolithium Compounds; Wiley: New York, 2004.
2. Gawley, R. E.; Coldham, I. *The Chemistry of Organolithium Compounds (Patai Series)*; Rappoport, Z., Marek, I., Eds.; 2004, 997–1053.
3. (a) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708–9710. (b) Nikolic, N. A.; Beak, P.; Organic Syntheses, Coll; Wiley: New York, 1998; Vol. 9, pp 391–396; pp. 391-396. (c) Gawley, R. E.; Zhang, Q. *J. Am. Chem. Soc.* **1993**, *115*, 7515–7516. (d) Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5763–5769. (e) Gawley, R. E.; Campagna, S. In *ECHET96. Electronic Conference on Heterocyclic Chemistry*; Rzepa, H., Snyder, J., Eds.; Royal Society of Chemistry: London, 1996.
4. Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231–3239.
5. Dieter, R. K.; Dieter, J. W.; Alexander, C. W.; Bhinderwala, N. S. *J. Org. Chem.* **1996**, *61*, 2930–2931. (b) Dieter, R. K.; Li, S. *J. Org. Chem.* **1997**, *62*, 7726–7735. (c) Dieter, R. K.; Lu, K.; Velu, S. E. *J. Org. Chem.* **2000**, *65*, 8715–8724. (d) Dieter, R. K.; Alexander, C. W.; Nice, L. E. *Tetrahedron* **2000**, *56*, 2767–2778. (e) Dieter, R. K.; Topping, C. M.; Nice, L. E. *J. Am. Chem. Soc.* **2001**, *66*, 2302–2311. (f) Dieter, R. K.; Topping, C. M.; Chandupatla, K. R.; Lu, K. *J. Org. Chem.* **2001**, *123*, 5132–5133. (g) Dieter, R. K.; Oba, G.; Chandupatla, K. R.; Topping, C. M.; Lu, K.; Watson, R. T. *J. Org. Chem.* **2004**, *69*, 3076–3086. (h) Dieter, R. K.; Watson, R. T.; Goswami, R. *Org. Lett.* **2004**, *6*, 253–256.
6. Gawley, R. E.; Zhang, Q.; Campagna, S. *J. Am. Chem. Soc.* **1995**, *117*, 11817–11818.
7. Coldham, I.; Hufton, R.; Snowden, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5322–5323.
8. Coldham, I.; Fernandéz, J.; Price, K. N.; Snowden, D. J. *J. Org. Chem.* **2000**, *65*, 3788–3795.
9. (a) Coldham, I.; Vennall, G. P. *Chem. Commun.* **2000**, 1569–1570. (b) Coldham, I.; Hufton, R.; Price, K. N.; Rathmell, R. E.; Snowden, D. G.; Vennall, G. P. *Synthesis* **2001**, 1523–1531. (c) Ashweek, N. J.; Coldham, I.; Snowden, D. J.; Vennall, G. P. *Chem. Eur. J.* **2002**, *8*, 195–207.
10. (a) Coldham, I.; Dufour, S.; Haxell, T. F. N.; Howard, S.; Vennall, G. P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3887–3889. (b) Coldham, I.; Dufour, S.; Haxell, T. F. N.; Vennall, G. P. *Tetrahedron* **2005**, *61*, this issue, doi:10.1016/j.tet.2005.01.096.
11. Low, E.; Gawley, R. E. *J. Am. Chem. Soc.* **2000**, *122*, 9562–9563.
12. Ashweek, N. J.; Brandt, P.; Coldham, I.; Dufour, S.; Gawley, R. E.; Hæffner, F.; Klein, R.; Sanchez-Jimenez, G. *J. Am. Chem. Soc.* **2005**, *127*, 449–457.
13. Arnold, J.; Knapp, V.; Schmidt, J. A. R.; Shafir, A. *J. Chem. Soc., Dalton Trans.* **2002**, 3273–3274.
14. Boche, G.; Marsch, M.; Harbach, J.; Harms, K.; Ledig, B.; Schubert, F.; Lohrenz, J. C. W.; Ahlbrecht, H. *Chem. Ber.* **1993**, *126*, 1887–1894.
15. Reich, H. J.; Goldenberg, W. S.; Gudmundsson, B.Ö.; W. Sanders, A.; Kulicke, K. J.; Simon, K.; Guzei, I. A. *J. Am. Chem. Soc.* **2001**, *123*, 8067–8079. (b) Reich, H. J.; Goldenberg, W. S.; Sanders, A. W.; Jantzi, K. L.; Tzschucke, C. T. *J. Am. Chem. Soc.* **2003**, *125*, 3509–3521.
16. Ahlbrecht, H.; Harbach, J.; Hoffmann, R. W.; Ruhland, T. *Liebigs Ann.* **1995**, 211–216.
17. Gaul, C.; Arvidsson, P. I.; Bauer, W.; Gawley, R. E.; Seebach, D. *Chem. Eur. J.* **2001**, *7*, 4117–4125.
18. Ahn, Y.; Cardenas, G. I.; Yang, J.; Romo, D. *Org. Lett.* **2001**, *3*, 751–754.
19. (a) Coldham, I.; Copley, R. C. B.; Haxell, T. F. N.; Howard, S. *Org. Lett.* **2001**, *3*, 3799–3801. (b) Krow, G. R.; Herzon, S. B.; Lin, G.; Qiu, F.; Sonnet, P. E. *Org. Lett.* **2002**, 4.
20. Iula, D.; Gawley, R. E. *J. Org. Chem.* **2000**, *65*, 6196–6201.
21. (a) Raucher, S.; Koolpe, G. A. *J. Org. Chem.* **1978**, *43*, 3794–3796. (b) Gawley, R. E.; Termine, E. J.; Aubé, J. *Tetrahedron Lett.* **1980**, *21*, 3115–3118.
22. Pearson, W. H.; Stevens, E. P. *J. Org. Chem.* **1998**, *63*, 9812–9827.
23. Gawley, R. E.; Zhang, Q. *Tetrahedron* **1994**, *50*, 6077–6088.
24. Bertini Gross, K. M.; Beak, P. *J. Am. Chem. Soc.* **2001**, *123*, 315–321.
25. Bauer, W. In *Lithium Chemistry: A Theoretical and Experimental Overview*; Schleyer, P. v. R., Sapse, A.-M., Eds.; Wiley: New York, 1995; pp 125–172.
26. (a) Bauer, W.; Winchester, W. R.; Schleyer, P. v. R. *Organometallics* **1987**, *6*, 2371–2379. (b) Fraenkel, G.; Chow, A.; Winchester, W. R. *J. Am. Chem. Soc.* **1990**, *112*, 6190–6198. (c) Lappert, M. F.; Engelhardt, L. M.; Raston, C. L.; White, A. H. *J. Chem. Soc. Chem., Commun.* **1982**, 1323–1324.
27. Hilmersson, G.; Davidsson, O. *J. Organomet. Chem.* **1995**, *489*, 175–179.