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Search for Configurationally Stable, Aracemic α-Amino Organolithiums

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Abstract: The search for configurationally stable α-amino carbanions has led to an interesting observation of differing reactivity of diastereomeric organolithiums and to the characterization of aracemic 2-lithio-*N*-methylpiperidine and 2-lithio-*N*-methylpyrrolidine as configurationally stable α-aminoorganolithiums. Details for the preparation of these and related α-lithioheterocycles, evaluation of their chemical and configurational stability, and a preliminary evaluation of the stereoselectivity of their reactions with electrophiles is presented.

Heteroatom-stabilized organolithiums are used extensively as selective reagents in organic synthesis.[1] Particularly noteworthy has been the development during the past 15 years of α-heteroorganolithiums in which the carbanionic carbon is stereogenic. For α-alkoxyorganolithiums, the seminal paper was Still's report[2] that α-alkoxyorganolithiums obtained by tin-lithium exchange are configurationally stable in THF solution[3] at temperatures of –30 °C for at least 15 minutes (Figure 1). In 1988, Chong reported that binaphthol-modified lithium aluminum hydride would reduce acyl stannanes enantioselectively,[4] an observation that paved the way for the use of α-alkoxyorganolithiums in enantioselective acylations,[5] carboxylations and carbomethoxylations,[6] 1,4-additions,[7] and macrocylizations.[8] Stereoselective 1,3-rearrangement of allylic α-alkoxystannanes led to the use of the resultant species in an enantioselective allylation of aldehydes.[4b] In 1990, Hoppe found that *O*-alkylcarbamates may be enantioselectively deprotonated by *sec*-butyllithium/sparteine,[9] which has led to the enantioselective synthesis of 2-hydroxyalkanoic acids,[9] secondary alcohols,[9] diols,[10] and *S*-1-methyldodecyl acetate.[11]

Although α-aminocarbanions have been known since 1965,[12,13] evidence that the carbanionic carbon of secondary α-aminoorganolithiums could be stereogenic (*i.e.*, tetrahedral sp^3 instead of trigonal sp^2) was not provided until Fraser[14] and Seebach[15] observed fundamental differences between the chemical behavior of metalated nitrosamines and amides (Figure 2). Specifically, the alkylation of a conformationally locked piperidine nitrosamine occured from the axial direction,[14,15] whereas a similar lithiated amide afforded the less stable[16,17a] equatorial substitution product.[15,17a]

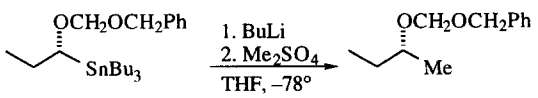


Figure 1

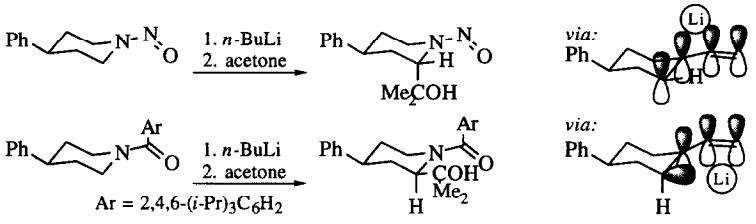


Figure 2

Since the equatorial isomer is the *less* stable product, it seems reasonable to assume that the carbanion is configurationally stable, and that the Li–C–N–C=O atoms lie in the approximate equatorial plane. Ab initio calculations also indicate that there is a strong stereoelectronic preference for the carbanion lone pair (10 - 20 kcal/mol, depending on geometry)[17b] to remain in the nodal plane of the amide π-system, with the carbanionic carbon clearly pyramidal. When a lithium atom is included, metalated esters[17a] and amides[17c] show an additional stabilization when the lithium is chelated to the carbonyl oxygen (13 kcal/mol for esters and 28 kcal/mol for amides). Two crystal structures have provided solid confirmation of these structural features of α-amino carbanions.[18, 49]

Applications of dipole-stabilized α-amino-organolithiums[19] to asymmetric synthesis have been numerous, emanating primarily from Meyers' laboratory.[20] However, virtually all of these synthetic applications have involved deprotonation of benzylic or allylic protons α to a formamidine nitrogen. Although the deprotonation of chiral formamidines[21] and the related oxazolines[22] is stereoselective and produces a pyramidal carbanion, it is now clear[21c,22] (Figure 3) that these benzylic organolithiums are capable of rapid epimerization at temperatures at or below –78 °C.[23]

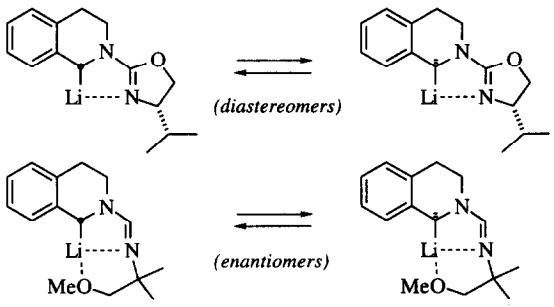


Figure 3

Activated piperidines. For α-aminoorgano-lithiums that are not allylic or benzylic, the kinetic barrier to deprotonation has made these systems less accessable. The nitrogen activating groups that have the most synthetic potential are the *N-t*-butylformamidino-[24] and *N-t*-butoxycarbonyl- (*N*-BOC-)[25] pyrrolidines and piperidines. As do the piperidine amides mentioned previously,[15,17a] rigid piperidinoformamidines alkylate equatorially, even giving *cis*-2,6- (diequatorial) substitution in conformationally rigid systems (Figure 4a).[24] Conformationally mobile 2-lithio-6-propylpiperidine formamides fail to alkylate, undergoing SET instead.[24a] 2-Methylpiperidinooxazoline (Figure 4b) gives *trans*-2,6-dimethylpiperidines (in addition to disproportionation via SET), which results from equatorial alkylation of the 6-methyl-axial conformer.[26] Rigid *N*-BOC-piperidines give trans 2,6-disubstitution products (Figure 4c).[25b] The BOC result has been interpreted as arising from an axial lithium on a chair conformation (Figure 4d).[24b,c] However, this structure appears to be less satisfactory than a planar carbanion on a twist-boat (Figure 4e) for two reasons: (i) it requires that the 'amide' portion of the urethane rotate out of planarity, which is likely to cost at least 15 kcal/mol;[27,28] (ii) the theoretical work mentioned above indicates a similarly costly price must be paid for placing the C–Li bond into conjugation with the amide (or nitrogen) π electrons. These energy costs are much

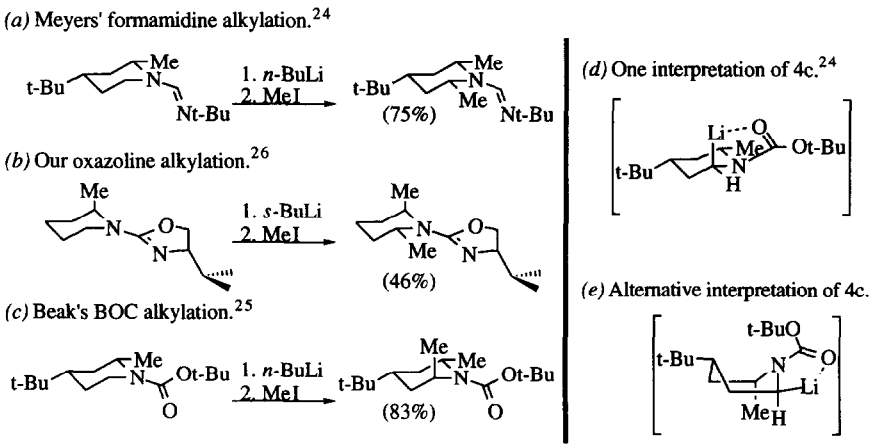


Figure 4

larger than the energy difference between a chair and boat conformation (5.6 - 8.5 kcal/mol for an unsubstituted cyclohexane[29]), or than that required to place a methyl group in an axial position (Figure 4b; note also the pseudo '1,3-diaxial' methyl-hydrogen interaction in Figure 4e). Whichever conformation is involved, it appears that all of these carbanions are configurationally stable, perhaps because of a diastereomeric bias.

Configurational stability of α-aminoorganolithiums. In 1986, we reported that aracemic piperidinooxazolines could be deprotonated and methylated highly selectively,[26] which is consistent with a stereoselective deprotonation and an α-aminoorganolithium that is configurationally stable (Figure 5a).[30] Although this was apparently the first aracemic, configurationally stable α-aminoorganolithium, the chemistry of this species is typified by single electron transfer reactions, limiting its synthetic utility. In 1991, Kerrick and Beak, following the lead of Hoppe[9] in the α-alkoxy series, found that *N*-BOC-pyrrolidines are enantioselectively deprotonated by the complex of *s*-butyllithium and sparteine.[31] Quenching the anion with tributylstannyl chloride afforded 2-tributylstannyl-*N*-BOC-pyrrolidine in 94% ee. Tin-lithium exchange in the presence of tetremethylethylene diamine (TMEDA) produced 2-lithio-*N*-BOC-pyrrolidine that was configurationally stable for at least 30 minutes at –78 °C, and probably much longer (Figure 5b).[32] Last year, Vedejs and Moss reported that *N*-trityl-2-lithioaziridines are configurationally stable because of the aziridine effect (Figure 5c).[33] These cyclic carbanions stand in contrast to three closely related acyclic carbanions. For example, Chong and Park[34] showed that the lithiated urethane in Figure 5d requires temperatures below –95° for configurational stability. Interestingly, this system is *less stable* in dimethoxyethane (DME) or in the presence of hexamethylphosphoramide (HMPA) (*cf.*, Figure 5b). Another acyclic dipole-stabilized α-amino carbanion was reported by Pearson and Lindbeck in 1991 (Figure 5e).[35] Here again, additives (in this case TMEDA) *accelerate* epimerization. Finally, the first enantiomerically enriched secondary α-aminocarbanion that is stabilized only by chelation (and not a dipole) was reported by Burchat, Chong and Park in 1993 (Figure 5f).[36] This system is slightly less configurationally stable than the related urethane chelate shown in Figure 5d, but it does not invert at temperatures below –95°. Two noteworthy trends appear in these examples: (i) carbanionic carbons in a ring (Figure 4 and 5a-c) appear to be more configurationally stable than the acylic examples (Figure 5d-f), and (ii) coordinating additives render cyclic anions less likely to invert and acylic ones more so.

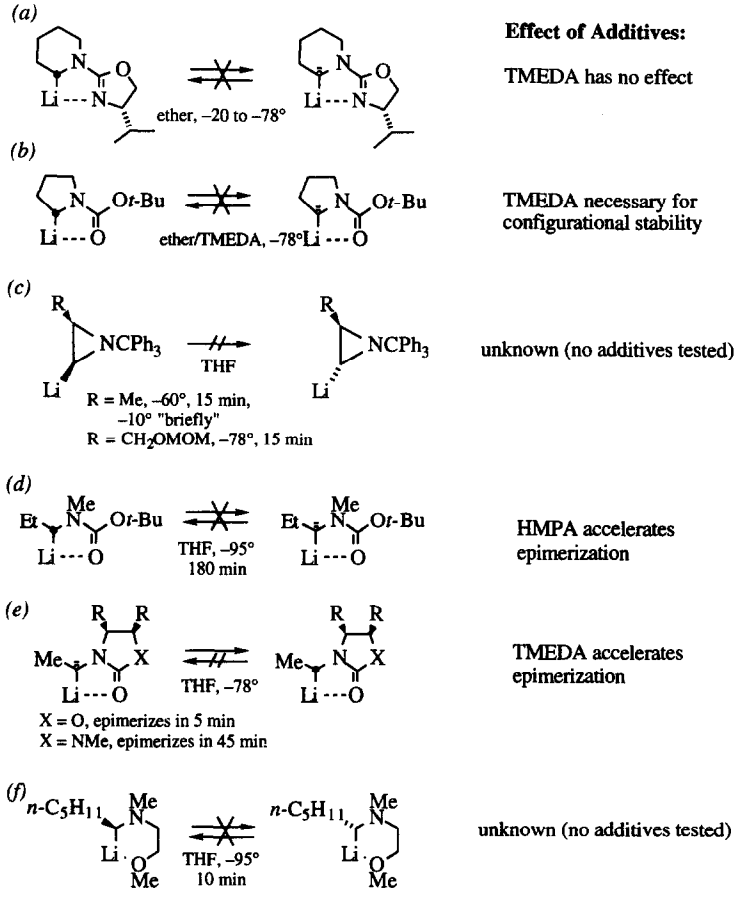


Figure 5

Reactivity of diastereomeric organolithiums. Piperidinooxazoline **1** (Figure 6a) is deprotonated[26] and alkylated in good yield (but no stereoselectivity) with tributyltin chloride. Flash chromatography separates the two diastereomers of **3**, providing *R*-(+)-**2** that is >99% pure by high pressure liquid chromatography (HPLC) (Figure 7). We have converted *R*-(+)-**2** and *S*- (–)-**2** to the corresponding *N*-methyl derivatives, and have compared the physical and chemical properties of these piperidines with the homologous pyrrolidine of known configuration (*vida infra*). On that basis, we assign the absolute configurations as shown. Having these two diastereomeric organostannanes in hand affords us the opportunity to examine the reactivity of the two derived diastereomeric organolithiums. Thus, *R*-**2** and *S*-**2** were transmetalated with butyllithium and alkylated with tributyltin chloride and methyl iodide. The results are surprising, and clearly indicate a differential reactivity of the two organolithiums. The *R* isomer affords a 1:1 mixture of stannane **2**, but a 6:1 ratio of methylated adducts **4** (86% retention of configuration, Figure 6b).[37] Conversely, the *S* isomer affords (Figure 6c) an 8:1 *S*/*R* ratio of **2** with tributyltin chloride (89% retention) and a 1:1 ratio of methyl adducts **4**. We had originally postulated[26b] that the organolithium derived by deprotonation has the *R*-configuration (*i.e.*, *R*-**3**), and we know[26b] that it methylates selectively (affording the *R* isomer)[38] and stannylates nonselectively. This assignment is consistent with the

alkylation experiments outlined in Figure 6b (and with the assignment of the illustrated configurations to **2**, assuming only that the Sn-Li exchange occurs with retention). It is also consistent with a configurationally stable organolithium, since equilibrating organolithiums would give the same product ratios for either *R*- or *S*-**2**. *Most interesting, however, is the clear difference in reactivity of these organolithium isomers: one is selective in its reaction with methyl iodide or tributyltin chloride, while the other is not, and vice versa.* We previously showed that the tendency of *R*-**3** to alkylate nonselectively is due to SET.[26b] Single electron transfer occurs when the appropriate combination of organometal oxidation potential and alkyl halide reduction potential are present.[39] The present results seem inconsistent with this notion, although it is conceivable that selective radical coupling (large tributyltin approaching anti to the isopropyl *vs* small methyl) might account for the results of Figure 6c.

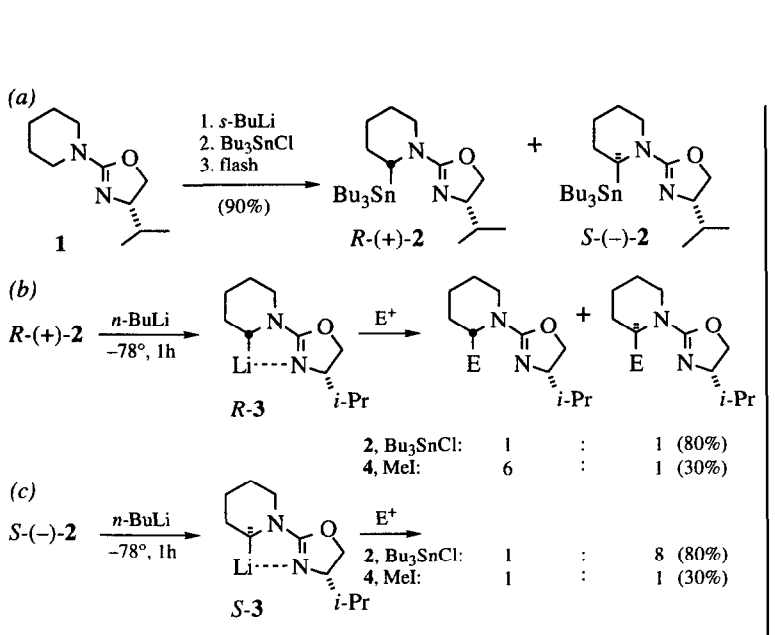


Figure 6

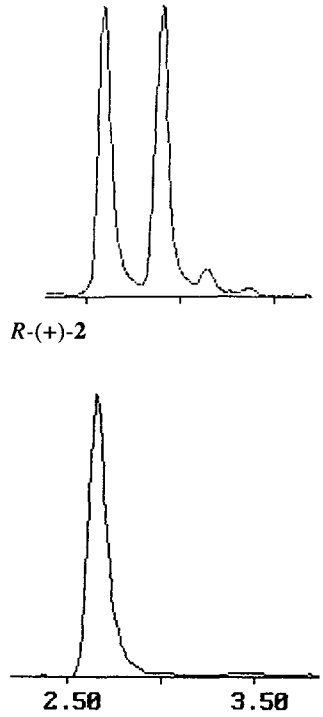


Figure 7

'Simple' α-aminoorganolithiums. Although it is possible to deprotonate the α-carbon of an unactivated tertiary amine,[12] it is not possible to do so enantioselectively. Because of the importance of α-aminocarbanions to organic synthesis in general, and because of the potential importance that a configurationally stable α-aminocarbanion could have (especially in heterocyclic chemistry), we decided to remove the oxazoline to obtain aracemic 2-stannylpiperidines lacking any chelating group. We also decided to examine the homologous pyrrolidines, that are available by asymmetric alkylation.[31] We hoped to examine the dynamics of the α-aminoorganolithiums (assuming they would transmetalate)[40] and survey their reactivity with electrophiles. Herein we report the results of our studies to date.[41]

Hydrazinolysis (the standard method for removing the oxazoline[26]) consumed **2**, but also destroyed the (presumed) aminostanne product. Lithium aluminum hydride reduction, which effectively removes the oxazoline from hydroxybenzylisoquinolyloxazolines,[42] failed to react with **2**. Previously, we had noticed that acetic formic anhydride converts isoquinolyloxazolines to *N*-formylisoquinolines.[43] With **2**, similar treatment afforded a ring opened *N,O*-diformyl compound, which was then reduced to **5** (Figure 8a). The similar rotations (of opposite sign) of the two enantiomers, and the high enantiomeric purity of alkylation products (*vide infra*) confirmed that there was little or no racemization in the conversion of **2** to **5**. To make the analogous pyrrolidine, *S*-(+)-**6**[31] was reduced to *S*-(+)-**7** in 75% yield with diisobutyl aluminum hydride (Figure 8b).

The absolute configuration of the two enantiomers of **5** were assigned by comparison of (+)- and (–)-**5** with *S*-(+)-**7**, whose configuration should be unchanged from that of *S*-(+)-**6**. Specifically, *S*-(+)-**7** affords *R*-(+)-*N*-methylprolinol (**8**) upon transmetalation, carboxylation, and reduction (net retention of configuration, Figure 8c). Similarly, (+)-**5** affords *R*-(+)-*N*-methylpiperidine-2-methanol **9**, independent of the electrophile used (Figure 8d).[44] Assuming only that similar mechanisms operate for the lithiopyrrolidine and lithiopiperidine, by analogy (of both rotation and stereochemistry) (+)-**5** is assigned the *S* configuration. By extension, the configurations for **2** noted previously and illustrated in Figure 6 are also established.

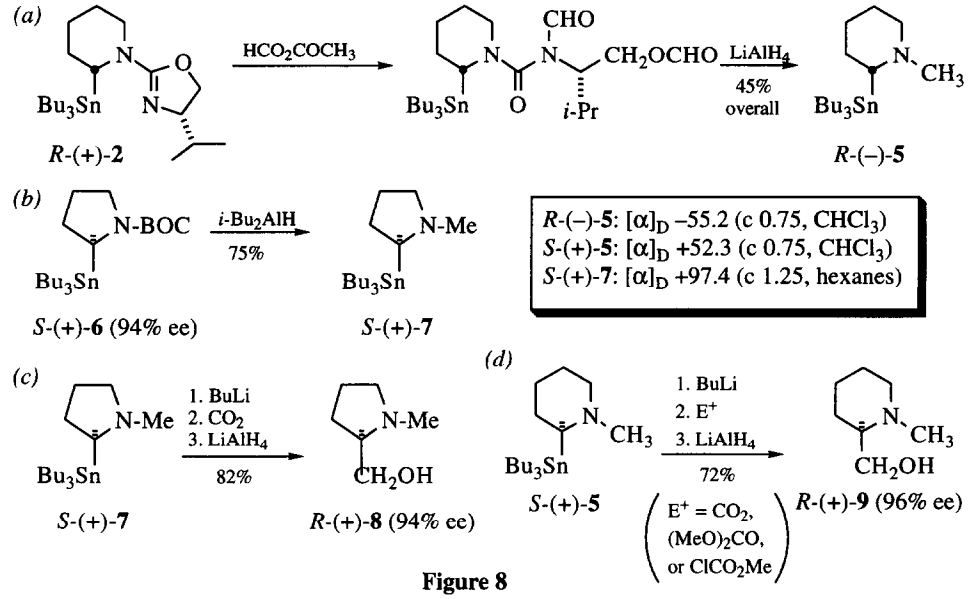


Figure 8

The stability of the *N*-methyl 2-lithiopyrrolidines and piperidines was evaluated by generating the organolithium by transmetalation, which was complete in less than five minutes at –78°, waiting varying intervals of time at various temperatures, and quenching with either carbon dioxide or dimethyl carbonate. Reduction and enantiomer analysis of the MTPA (methoxytrifluoromethylphenylacetic acid) ester (Mosher ester)[45] by ^{19}F NMR yielded the results outlined in Tables 1 (for 2-lithiopiperidine) and 2 (for 2-lithiopyrrolidine) and illustrated schematically in Figure 9.[46] It is worth noting in passing that the ^{19}F signal of the *u* diastereomer for both the pyrrolidine and piperidine methanols resonates at higher field than the *l* diastereomer.[47]

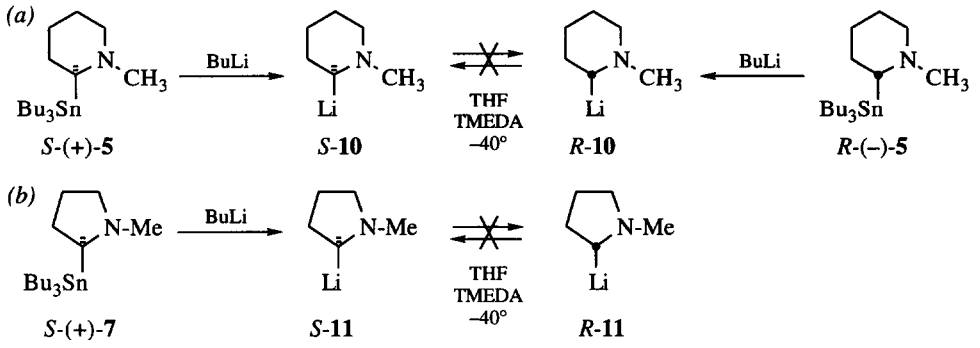


Figure 9

In light of the fragile configurational stability of most of the α-aminoorganolithiums shown in Figure 5, the stability of these species is surprising. Both 2-lithiopyrrolidines and piperidines resist racemization (in THF, in the presence of TMEDA) at temperatures as "high" as –40° for at least 45 minutes! The TMEDA seems to be more necessary for chemical stability (*cf.* Table 1, entries 5 & 7; Table 2, entries 1 & 2) than for configurational stability (*cf.* entries 1, 4, and 6). Ether also seems to be a compatible solvent. The dipole-stabilized organolithiums in Figures 5b and d require temperatures of –78° and –95° for configurational stability, respectively, considerably lower than what we observe for **10** and **11**, although the stabilizing effect of TMEDA on the cyclic organolithium (Figure 5b) is also observed here. The organolithium in Figure 5f is stabilized only by a 6-membered chelate (*i.e.*, no dipole), and also requires temperatures of –95° for configurational stability. Among the factors that may be responsible for this added stability are: (i) bridging of the lithium across the carbon-nitrogen bond,[48] which is probably more important in the absence of chelation; (ii) chelation could *facilitate* racemization by "holding" the cation nearby as the carbanion inverts; and (iii) the added barrier of a ring flip that accompanies the inversion may slow the process compared to acyclic systems. To probe this issue, we prepared *S*-(+)-2-tributylstannyl-*N*-methoxyethylpyrrolidine **16**, as shown in Figure 10. The configurational stability was evaluated by transmetalation, carboxylation, and reduction. The data are shown in Table 3.

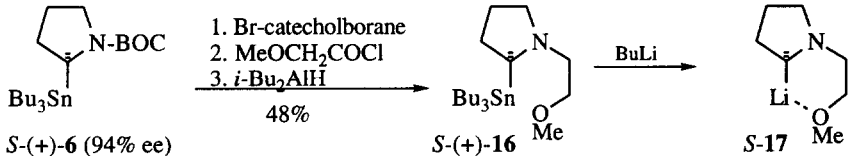
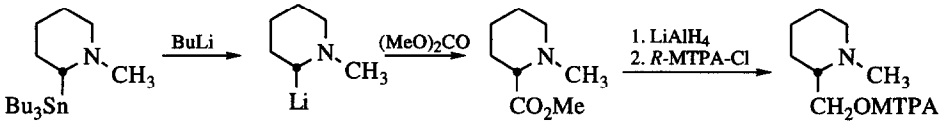


Figure 10

The chelated lithiopyrrolidine **17** exhibits an interesting TMEDA effect: at –78° the configurational stabiltity is retained for up to 75 minutes in THF (with or without TMEDA) or dimethoxyethane (Table 3, entries 1 - 4), but the chemical lifetime appears to be *shortened* in the presence of TMEDA (Table 3, entries 2 & 3). At –60°, the configurational stability is maintained in THF/TMEDA, albeit in significantly lower yield (entry 6). In the absence of TMEDA, racemization is faster, especially in dimethoxyethane (entries 5 & 7).

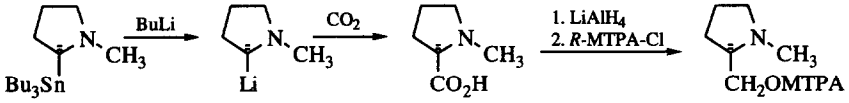
Table 1. Configurational and chemical stability of 2-lithiopiperidine *R*-**10**.



R-(–)-**5** (≥99% ee) *R*-**10** *S*-**12** *u*-**13**

Entry	Solvent	Temperature	Time (min)	Yield of 12	% de of 13
1	THF	–80°	75	70	99
2	THF/TMEDA	–80°	45	84	99
3	Ether/TMEDA	–80°	45	83	99
4	THF	–60°	15	68	99
5	THF	–60°	45	45	95
6	THF	–60°	75	10	93
7	THF/TMEDA	–60°	45	74	99
8	Ether/TMEDA	–60°	45	50	99
9	THF/TMEDA	–40°	45	60	99
10	THF/TMEDA	–20°	15	38	28
11	THF/TMEDA	0°	15	0	–

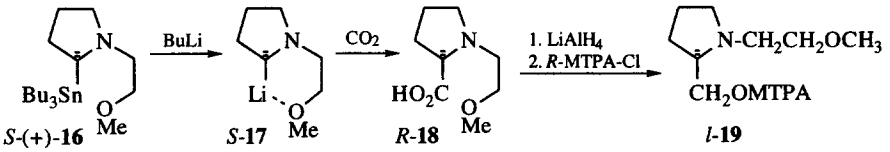
Table 2. Configurational and chemical stability of 2-lithiopyrrolidine *S*-**11**.[46]



S-(+)-**7** (94% ee) *S*-**11** *R*-**14** *l*-**15**

Entry	Solvent	Temperature	Time (min)	Yield of *R*-14	% de of 15
1	THF	–80°	45	20	94
2	THF/TMEDA	–80°	75	83	94
3	THF/TMEDA	–60°	45	67	94
4	THF/TMEDA	–40°	45	54	94
5	THF/TMEDA	–20°	15	34	80
6	THF/TMEDA	0°	15	0	–

Table 3. Configurational and chemical stability of 2-lithiopyrrolidine *S*-**17**.



S-(+)-**16** *S*-**17** *R*-**18** *l*-**19**

Entry	Solvent	Temperature	Time (min)	Yield of *R*-18	% de of 19
1	THF	–78°	10	76	92
2	THF	–78°	75	75	92
3	THF/TMEDA	–78°	75	50	92
4	$MeO(CH_2)_2OMe$	–78°	10	75	92
5	THF	–60°	45	73	86
6	THF/TMEDA	–60°	45	41	92
7	$MeO(CH_2)_2OMe$	–60°	45	39	0
8	THF	–40°	45	72	69
9	THF/TMEDA	–40°	34	34	84

Discussion. Comparing pyrrolidines **11** and **17** illustrates several differences. For example, in the presence of TMEDA, the *N*-methoxyethyl substituent promotes racemization to some extent (*cf.* Table 2, entry 4; Table 3, entry 9). It also decreases chemical stability (*cf.* Table 2, entry 3 & 4; Table 3, entry 6 & 9). In the *absence* of TMEDA, *chemical* stability of **17** is *increased* (*cf.* Table 2, entry 1 and Table 3, entry 2). It is also useful to compare **17** with its acyclic cousin shown in Figure 5f. The latter requires temperatures at or below –95° for configurational stability in THF, and racemizes at –78°.[36] In DME, it is almost completely racemized (27% ee) after 20 minutes at –78°,[36] whereas **17** is not appreciably racemized at –78° after 10 minutes (Table 3, entry 4).

At approximately the same time as our preliminary report,[41] Boche reported the crystal structures of two α-aminoorganolithiums: [α-(dimethylamino)benzyllithium·diethyl ether]$_2$, **20**, and *S*-α-(methylpivaloylamino)-benzyllithium·sparteine, **21** (Figure 11).[49] These structures have the common feature of a strongly pyramidalized carbanion, but differ markedly in that the lithium of **20** is bridged by the nitrogen, while the lithium of **21** is not. Chelation by the pivaloyl oxygen in **21** is consistent with previous structural theories regarding dipole-stabilized systems (*vide supra*), and the bridging in **20** is consistent with ab initio calculations.[48,49] Interestingly, **20** forms a heterochiral dimer. Note that the dimer would suffer severe crowding if it were homochiral (see **22**).

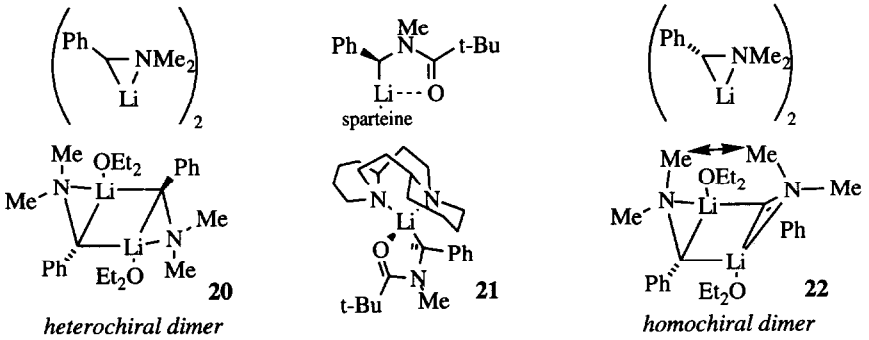


Figure 11

The aggregation states of **10**, **11**, and **17** are unknown. However, since these organolithiums are enantiopure (or nearly so), only a homochiral dimer may form (in appreciable quantities). But it is probably safe to assume that there is bridging in these compounds, similar to the Boche crystals of **20**. Bridging provides a simple explanation for the remarkable configurational stability of **10** and **11**, since both the carbanionic carbon *and* the nitrogen are stereogenic in the bridged species **23**, which is illustrated as a monomer for simplicity (Figure 12a). Inversion of configuration at the carbanionic carbon requires inversion at the 'quaternary' nitrogen, which is not possible unless both the C–Li and the N–Li bonds of **23** are broken simultaneously. Additionally, we may speculate on the effect of TMEDA on the chemical stability of **10** and **11** (*cf.* Table 1, entries 6 and 7, and Table 2, entries 1 and 2): TMEDA may chelate the lithium of a monomeric species and thereby stabilize it, perhaps by inhibiting aggregation to a crowded (unstable?) homochiral dimer.

Chelated lithiopyrrolidine **17** may be in equilibrium with a bridged species such as **24** (Figure 12b), but inversion of the carbanionic carbon of **17** may occur with the lithium still held by the methoxy. The acyclic counterpart to **17** is **25** (see Figure 5f), which racemizes much more easily. In addition to racemization by a path similar to **24**, an additional route is now available (Figure 12c). Bridging to **26** may be followed by inversion of the carbanionic carbon while the lithium is chelated by both nitrogen and oxygen (**26** → **27**), a path not possible

when the carbanion is in a ring, such as **24**. Thus the presence of the chelating methoxy accounts for the decreased configurational stability of **17** relative to **10** or **11**, while the presence of the ring explains the increased stability of **17** (**24**) over **25** (**26**). Based on these arguments, we can predict enhanced configurational stability of simple bridged but unchelated acyclic species such as **20** over chelated counterparts such as **25**.

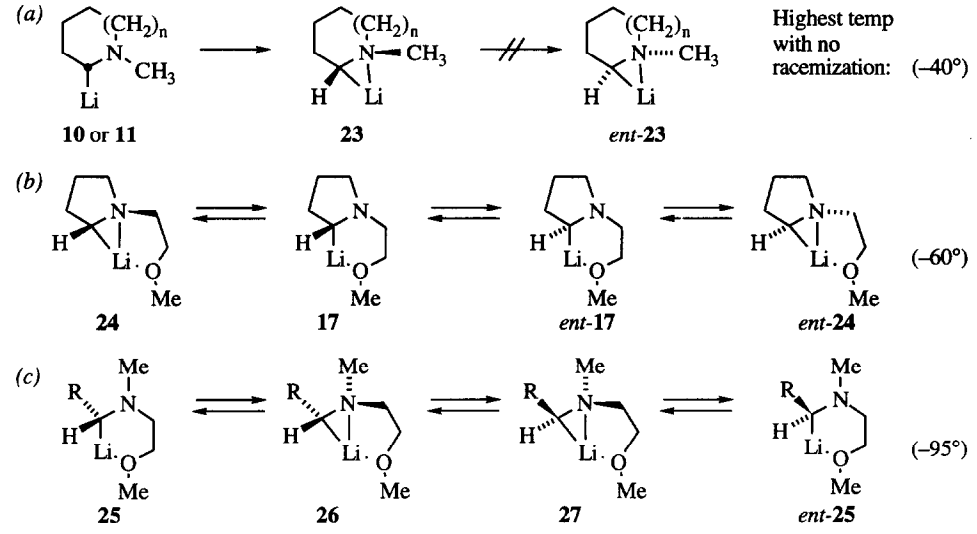


Figure 12

Reactions with other electrophiles. Clearly, the synthetic utility of aracemic α-aminoorganolithiums rests not only on their configurationally stability, but also on their abilty to add to other species without racemization. In this regard, it is worth remembering that lithiated piperidinoformamidines[24a] and oxazolines[26b] are prone to single electron transfer in their reactions with alkyl halides. Evaluation of the reactivity of **10** and **11** toward other electrophiles is incomplete at this time, but the following preliminary observations can be reported. We noted above (Figure 8) that lithiopiperidine **10** reacts with carbon dioxide, dimethyl carbonate, and methyl chloroformate with net retention of configuration. The same is true of **10** and tributyltin chloride (as indicated by rotation). Addition of **11** to benzaldehyde occurs with retention and to benzophenone with racemization; addition of **10** and **11** to cyclohexanone affords adducts that appear to be enantiopure (presumably with retention). The reaction of **10** and **11** with unactivated primary alkyl halides occurs with inversion of configuration.

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Experimental.

All proton NMR spectra were recorded at 300 or 400 MHz (400 MHz unless otherwise noted). ^{13}C spectra were recorded at 22.5 or 100 MHz. Mass spectra were measured in either DCI or FAB mode. Elemental analyses were performed by Atlantic Microlabs. All glassware was oven dried (120 °C) and cooled under a nitrogen atmosphere. Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl under N_2. Tetramethylethylene diamine (TMEDA) was distilled from calcium hydride under N_2. Commercial solutions of butyllithium in hexane and *s*-butyllithium in cyclohexane were titrated prior to use with 1,10-phenanthroline (monohydrate) as the indicator.

***N*-{(4*S*)-[4,5-Dihydro-4-(1-methylethyl)-2-oxazolyl]}-2-tributylstannylpiperidine (2).** Piperidinooxazoline 1[26] was dissolved in ether (0.5M) and cooled to –78 °C. *s*-BuLi (1.3 eq.) was added to this solution. The reaction was warmed to –25 °C and kept at –25 °C for one hour. The reaction was then cooled to –78 °C and tributyltin chloride (1.2 eq.) was added. The reaction was warmed to room temperature slowly and quenched with brine. The aqueous layer was extracted with ether three times. The combined organic layers were dried with $MgSO_4$. The product was obtained after removing the solvent in vacuo. The ratio of two isomers *R*- and *S*-2 was 1:1 and they were separated by column chromatography (hexanes:ethyl acetate 6:1) with a total 90% yield. The diastereomer excess for each diastereomer was determined by HPLC (hexanes:isopropanol 95:5, Bakerbond, DNBPG, Pirkle). 2-*R*-

(+)-**2**: $[\alpha]_D$ = +37.9 (c = 3.45, $CHCl_3$). ^1H NMR ($CDCl_3$) 0.9 (21 H, m), 1.3 (12 H, m), 1.7 (6 H, m), 1.9 (1 H, m), 3.0 (1 H, m), 3.75 (1 H, m), 3.85 (1 H, m), 3.9 (2 H, m, CH_2O), 4.2 (1H, m). ^{13}C NMR ($CDCl_3$) 10.9, 13.6, 17.8, 19.1, 25.2, 25.8, 27.5, 29.1, 29.9, 33.4, 46.8, 49.8, 70.3, 70.6, 161. IR (neat) 2840-2940, 1645 cm^{-1}. C, H Analysis calc. C 56.94, H 9.49 found C 57.07, H 9.60. MS (MH^+, ^{120}Sn) 487. 2-*S*-(–)-**2**: $[\alpha]_D$ = –80.61 (c = 3.95, $CHCl_3$). ^1H NMR ($CDCl_3$) 0.9 (21 H, m), 1.4 (12 H, m), 1.5 (6 H, m), 1.9 (1 H, m,), 3.0 (1 H, m), 3.6 (1 H, m), 3.75 (1 H, m), 3.85 (2 H, m), 4.2 (1 H, m). ^{13}C NMR ($CDCl_3$) 10.9, 13.6, 17.6, 19.2, 25.2, 25.6, 27.5, 29.1, 30.2, 33.2, 47.1, 49.4, 70.3 (2C), 160.9. IR (neat) 2820-2940, 1648 cm^{-1}. C, H Anal. calc. C 56.94, H 9.49 found C 56.93, H 9.80. MS (MH^+, ^{120}Sn) 487.

***N*-(4*S*)-[4,5-Dihydro-4-(1-methylethyl)-2-oxazolyl]-2-methylpiperidine (4).** *R* or *S*-**2** was dissolved in 9:1 ether-THF, and TMEDA (0.1 eq) was added to the solution. The mixture was cooled to –78 °C and treated with BuLi (1.3 eq., 1.24M in hexanes). After 1 h, MeI (1.4 eq.) was added to the solution. A white precipitate formed immediately. After 30 min, the reaction was quenched with brine and diluted with ether. The aqueous layer was extracted with ether twice. The combined organic layers were dried with $MgSO_4$ and concentrated in vacuo. The product was purified by flash chromatography (hexanes : AcOEt 2 : 1, followed by hexanes : AcOEt : EtOH 2 : 1 : 0.5) to remove 2,3-dehydro-**1**, which co-elutes with one of the methyl diastereomers on capillary GC. Spectral characteristics matched those reported previously.[26]

***N*-Methyl-2-tributylstannylpiperidine (5).** Piperidinooxazoline **2** (2.20 g, 4.50 mmol) was dissolved in THF (9 mL, 0.5M) with 1g of anhydrous Na_2CO_3. Acetic formic anhydride (15 eq.) was added to the solution slowly. The reaction was stirred at room temperature overnight. After concentration in vacuo, the residue was dissolved in ether, washed with saturated sodium bicarbonate solution twice and brine once. The ether solution was dried with $MgSO_4$ and concentrated in vacuo. For spectral characterization of this intermediate, the residue was purified by column chromatography (hexanes : ethyl acetate 10 : 1). For preparative purposes, the product of this step (2.58 g) was directly reduced by $LiAlH_4$ (0.44 g, 2.5 eq.) in THF (20 mL) at room temperature for 4 hours. After cooling to 0 °C, the reaction was quenched with water (1 mL), 20% sodium hydroxide (1 mL), and water (2 mL). After filtration, the cake was washed with ether (3x10 mL). The ether solution was dried with $MgSO_4$ and concentrated in vacuo. The product (0.8 g) was purified by column chromatography (hexanes : ethyl acetate 6 : 1) with overall 45% yield. ^1H NMR (C_6D_6) 0.9 (15 H, m), 1.4 (12 H, m), 1.8 (6 H, m), 2.2 (3 H, s), 2.4 (2 H, br), 2.9 (1 H, br). ^{13}C NMR (C_6D_6) 10.75, 13.6, 24.9, 26.2, 27.5, 29.3, 31.1, 47.9, 57.1, 61.4. IR (neat) 3000, 2940 cm^{-1}. C, H Anal. calc. C 55.71, H 10.60 found C 55.93, H 10.31. MS (MH^+, ^{120}Sn) 389. ***R*-(–)-*N*-Methyl-2-tributylstannylpiperidine** (*R*-(–)-**5**) was prepared from 2-*R*-(+)-**2**: $[\alpha]_D$ = –55.2 (c = 0.75, $CHCl_3$). ***S*-(+)-*N*-Methyl-2-tributylstannylpiperidine** (*S*-(+)-**5**) was prepared from 2-*S*-(–)-**2**. $[\alpha]_D$ = +52.7 (c = 0.75, $CHCl_3$).

***S*-(+)-*N*-Methyl-2-tributylstannylpyrrolidine (7).** *S*-(+)-*N*-BOC-Tributylstannylpyrrolidine (**6**, 3.02 g, 6.56 mmol) in 7.6 mL of THF was cooled to –78 °C, and treated dropwise with *i*-Bu_2AlH (neat, 4.67 mL, 26.2 mmol). The mixture was warmed to room temperature slowly and stirred for 75 h. The mixture was cooled to 0 °C and carefully quenched with ice water. After stirring for 1 h, the mixture was filtered and the cake was washed with ether three times. The filtrate was dried over $MgSO_4$, and concentrated to give crude product which was purified by flash chromatography on silica gel (hexane : EtOAc : EtOH 5 : 1 : 0.5) to give 1.86 g (75%) of **7** which was kept refrigerated. ^1H NMR (C_6D_6) 1.05 (15 H, m), 1.45 (6 H, m), 1.8 (6 H, m), 1.85 (2 H, m), 2.05 (2 H, m), 2.25 (2 H,m), 2.4 (3 H, m), 3.0 (1 H, m). ^{13}C NMR (C_6D_6) 58.6, 58.0, 43.2, 30.8, 29.8, 27.9, 25.7, 13.9, 9.3. IR (neat) 2950, 2920, 2860, 2840, 2750, 1452 cm^{-1}. MS (^{120}Sn) 376. C, H Anal. calc. C 54.59 H 4.45 found C 54.84 H 4.49. $[\alpha]_D$ = +97.4 (c = 1.25, hexanes), presumed to be 94% ee.[31]

General procedure for the transmetalations and electrophilic quench of 2-tributylstannylpiperidines and 2-tributylstannylpyrrolidines. Under nitrogen, the tributylstannyl compound in THF (0.1M) and TMEDA (1.3 eq) was cooled to –78 °C and treated with BuLi (1.6M in hexanes, 1.3 eq.). The yellow solution was stirred at –78 °C for 20 min. The electrophile was added and the reaction was kept at –78° for 1 h. The reaction was quenched with 2M HCl, and extracted with ether three times to remove any neutral compounds. The aqueous solution was basified with powdered Na_2CO_3 and extracted with ether four times. The combined ether solutions were dried with Na_2CO_3. After filtration, the solvent was removed *in vacuo*.

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