2-Lithio-*N*-methylpiperidine and 2-Lithio-*N*-methylpyrrolidine: Configurationally and Chemically Stable Unchelated α-Aminoorganolithiums

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The past 10–15 years has seen a surge of interest in the use of functionalized organolithiums in organic synthesis.[1] An important category of such systems includes α-heteroatom-substituted organolithiums, especially when the heteroatom is oxygen or nitrogen. α-Alkoxyorganolithiums rose to prominence after it was demonstrated[2] that they are configurationally stable at low temperature, making them useful intermediates in asymmetric synthesis.[3] α-Aminoorganolithiums have also found an important place in asymmetric synthesis, but most examples[4] involve dipole-stabilized systems[5] in which the carbanionic carbon is benzylic or allylic and epimerizes rapidly, even at low temperature.[6] Recently, information about the configurational stability of nonconjugated, acyclic dipole-stabilized α-aminoorganolithiums has been obtained which reveals configurational lability, except at very low temperature (Figure 1a and b).[7,8] A cyclic system appears to be more configurationally stable at −78 °C in the presence of TMEDA (Figure 1c),[9] and a chelated but not dipole-stabilized acyclic α-aminoorganolithium showed configurational stability only at −95 °C (Figure 1d).[10] The effect of TMEDA is inconsistent in the above examples, as it accelerates epimerization of the acyclic systems (Figure 1a and 1b) and retards epimerization of the lithio-BOC-pyrrolidine (Figure 1c).

It has been over 20 years since Peterson introduced transmetalation as a means of preparing nonchelated 1° α-aminoorganolithiums (R_2NCH_2Li).[11] To our knowledge, however, there are no examples of tin/lithium transmetalations to 2° α-aminocarbanions *that are not stabilized by chelation or a dipole or both*. In fact, we are aware of two reports indicating the failure of the transmetalation approach to acyclic α-aminoorganolithiums.[10,12] In light of this, we were somewhat surprised to find that *N*-methyl-2-(tributylstannyl)piperidine and pyrrolidine undergo rapid transmetalation in ether or THF in the presence or absence of TMEDA to produce 2-lithiopiperidines and 2-lithiopyrrolidines, which show remarkable chemical and configurational stability in the presence of TMEDA.

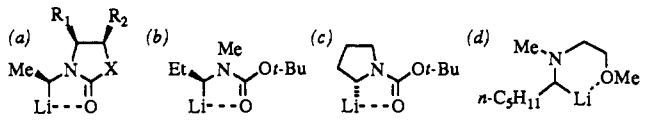
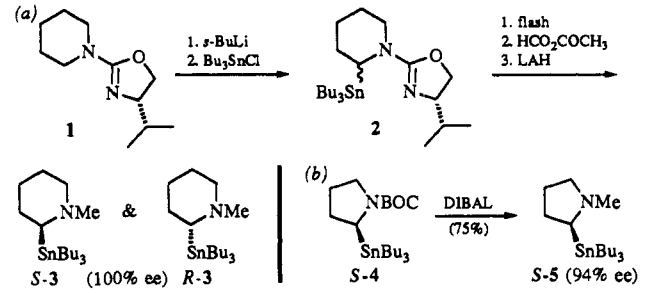
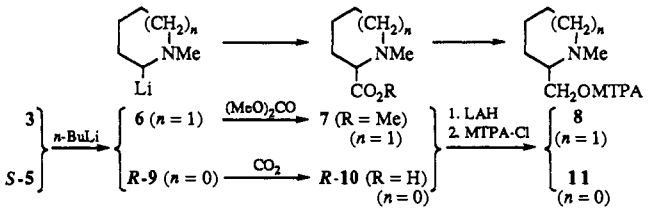


Figure 1. (a) X = O, epimerizes in 5 min −78 °C; X = NMe, epimerizes in 45 min at −78 °C (ref 7). (b) Configurationally stable at ≤ −95 °C (ref 8). (c) Configurationally stable at −78 °C in the presence of TMEDA (ref 9). (d) Configurationally stable at ≤ −95 °C (ref 10).

Scheme I



Scheme II



Synthesis of the stannanes is outlined in Scheme I. Piperidinooxazoline **1**[13] was alkylated to a separable mixture of stannanes **2** in 90% yield. After separation of the diastereomeric stannanes **2** by flash chromatography, the oxazoline was removed by formylation and reduction.[14] Both enantiomers of the 2-(tributylstannyl)-*N*-methylpiperidine were obtained in this way.[15a] Pyrrolidinylstannane *S*-**5** was obtained in 75% yield by DIBAL reduction of *S*-**4**.[16] The enantiomeric excess of *S*-**4** is presumed to be 94% on the basis of the reported enantioselectivity.[15b]

Scheme II outlines the transmetalation, electrophilic quench, and Mosher analysis[17] of the piperidine and pyrrolidine systems. The transmetalation of **3** was complete in less than 5 min at −80 °C, as judged by quenching with dimethyl carbonate. The configurational stability of **6** was evaluated in both ether and THF, with and without added TMEDA, at temperatures from

(1) For numerous reviews, see: Trost, B. M.; Fleming, I., Eds. *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vols. 1 and 3.

(2) (a) Still, W. C. *J. Am. Chem. Soc.* **1978**, *100*, 1481–7. (b) Still, W. C.; Sreekumar, C. *Ibid.* **1980**, *102*, 1201–2.

(3) For example, see: (a) Chan, P. C.-M.; Chong, J. M. *Tetrahedron Lett.* **1990**, *31*, 1985–8. (b) Chong, J. M.; Mar, E. K. *Tetrahedron* **1989**, *24*, 7709–7716. (c) Chong, J. M.; Mar, E. K. *Tetrahedron Lett.* **1990**, *31*, 1981–4. (d) Marshall, J. A.; Welmaker, G. S.; Gung, B. W. *J. Am. Chem. Soc.* **1991**, *113*, 647–56, and references cited therein.

(4) Reviews: (a) Gawley, R. E.; Rein, K. S. In *Comprehensive Organic Synthesis*; Trost, B. M., Fleming, I., Eds.; Pergamon: 1991; Vol. 3, chapter 1.2. (b) Highsmith, T. K.; Meyers, A. I. In *Advances in Heterocyclic Natural Product Synthesis*; Pearson, W. H., Ed.; JAI: Greenwich, CT, 1991.

(5) (a) Beak, P.; Reitz, D. B. *Chem. Rev.* **1978**, *78*, 275. (b) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471–573.

(6) (a) Rein, K.; Goicoechea-Pappas, M.; Anklekar, T. V.; Hart, G. C.; Smith, G. A.; Gawley, R. E. *J. Am. Chem. Soc.* **1989**, *111*, 2211–7. (b) Meyers, A. I.; Guiles, J.; Warmus, J. S.; Gonzalez, M. A. *Tetrahedron Lett.* **1991**, *32*, 5505–6.

(7) (a) Pearson, W. H.; Lindbeck, A. C. *J. Am. Chem. Soc.* **1991**, *113*, 8546–8. (b) Pearson, W. H.; Lindbeck, A. C.; Kampf, J. W. *Ibid.* **1993**, *115*, 2622–36.

(8) Chong, J. M.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220–2.

(9) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708–10.

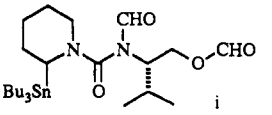
(10) Burchat, A. F.; Chong, J. M.; Park, S. B. *Tetrahedron Lett.* **1993**, *34*, 51–4.

(11) (a) Peterson, D. J. *J. Organomet. Chem.* **1970**, *21*, P63–4. (b) Peterson, D. J. *J. Am. Chem. Soc.* **1971**, *93*, 4027–31. (c) Peterson, D. J.; Ward, J. F. *J. Organomet. Chem.* **1974**, *66*, 209–17.

(12) Tsunoda, T.; Fujiwara, K.; Yamamoto, Y.; Itô, S. *Tetrahedron Lett.* **1991**, *32*, 1975–8.

(13) Gawley, R. E.; Hart, G. C.; Bartolotti, L. J. *J. Org. Chem.* **1989**, *54*, 175–81.

(14) Other methods for removal of the oxazoline (hydrazinolysis or LAH reduction) either were ineffective or destroyed the stannane. Previously (Gawley, R. E.; Smith, G. A. *Tetrahedron Lett.* **1988**, *29*, 301–2) we had discovered that acetic formic anhydride removed the oxazoline and replaced it with a formyl group. Treatment of **2** with acetic formic anhydride afforded a compound tentatively identifed as **i**, on the basis of NMR and MS analysis. Reduction of **i** with LAH afforded **3**.



(15) Satisfactory analytical data (^1H and ^{13}C NMR, MS, and combustion analysis) were obtained for compounds **2**, **3**, and **5**. (a) (+)-**3**: $[\alpha]_D$ +52.7 (*c* = 0.75, chloroform); (−)-**3** $[\alpha]_D$ −55.2 (*c* = 0.75, chloroform); (b) *S*-(+)-**5**: $[\alpha]_D$ 97.4 (*c* = 1.25, hexanes), presumed to be 94% ee.

(16) No rotation was reported for *S*-**4**.[9] We obtained $[\alpha]_D$ +137 (*c* = 1.75, hexanes).

(17) (a) Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543–9. (b) Dale, J. A.; Mosher, H. S. *J. Am. Chem. Soc.* **1973**, *95*, 512–9.

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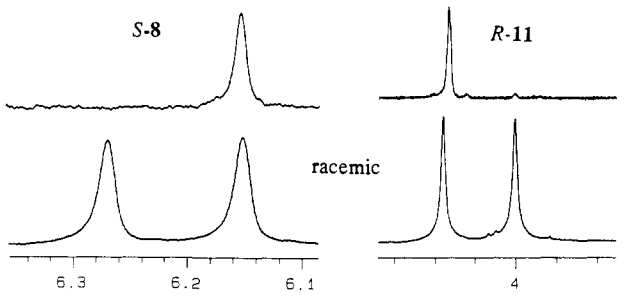

Figure 2. ^{19}F NMR of (*R*)-Mosher esters of *N*-methylpiperidine methanol (left, 0.5% trifluoroethanol in $CDCl_3$) and *N*-methylpyrrolidine methanol (right, 0.5% trifluoroacetic acid in $CDCl_3$). Control experiments indicated that 0.5% of *R*-**8** would have been detected for the piperidines.

Table I. Configurational and Chemical Stability of 2-Lithiopiperidine **6**

solvent	*t*, (°C)	*T* (min)	yield of **7** (%)	ee (%)
THF	−80	15	71	99
THF	−80	45	73	99
THF	−80	75	70	99
THF/TMEDA	−80	45	84	99
ether/TMEDA	−80	45	83	99
THF	−60	15	68	99
THF	−60	45	45	95
THF	−60	75	10	93
THF/TMEDA	−60	45	74	99
ether/TMEDA	−60	45	50	99
THF/TMEDA	−40	45	60	99
THF/TMEDA	−20	15	38	28
THF/TMEDA	0	15	0	

−80 to 0 °C, for up to 75 min. Proton or fluorine NMR analysis of Mosher ester **8** (Figure 2) yielded the data listed in Table I. Lithiopiperidine **6** is both configurationally and chemically stable at −80 °C for at least 75 min. At −60 °C, **6** decomposes in the absence of TMEDA, but even under these conditions the remaining material retains its configuration. Addition of TMEDA stabilizes **6** such that it is configurationally stable up to −40 °C for at least 45 min albeit with some loss in yield.

Similar properties were observed for *S*-**5**, which was transmetalated to *R*-**9** (Scheme II), quenched with carbon dioxide, and analyzed similarly (Figure 2).[18] The data in Table II indicate that *R*-**9** is also configurationally stable up to −40 °C. Since the absolute configuration of the stannylpyrrolidine **5** is known to be *S*,[9] obtention of *R*-**10** indicates that transmetalation and quenching

(18) Reaction of **9** with dimethyl carbonate was not a clean reaction.

Table II. Configurational and Chemical Stability of 2-Lithiopyrrolidine (R-**9**)

solvent	*t*, (°C)	*T* (min)	yield of R-**10** (%)	ee (%)
THF	−80	45	20	94
THF/TMEDA	−80	15	83	94
THF/TMEDA	−80	45	82	94
THF/TMEDA	−80	75	83	94
THF/TMEDA	−60	45	67	94
THF/TMEDA	−40	45	54	94
THF/TMEDA	−20	15	34	80
THF/TMEDA	0	15	0	

with CO_2 occurred with net retention of configuration. Since tin–lithium exchange usually occurs with retention, it appears that the carboxylation of **9** also occurs with retention.

The absolute configuration at C-2 of **2** and **3** are not known. By analogy with **5** (assuming that both transmetalation and acylation of **3** occur with retention), we can tentatively assign the *S* configuration to the dextrorotatory enantiomer of **3**.[19]

In summary, 2-lithio-*N*-methylpiperidines and pyrrolidines are chemically and configurationally stable for up to 45 min, at temperatures up to −40 °C, in the presence of TMEDA. This is 40–55 °C higher temperature than that required to stop racemization of the chelated α-aminoorganolithiums studied previously (Figure 1, especially d). Three factors may be involved in the remarkable stability of **6** and **9**: (i) bridging of the lithium across the carbon–nitrogen bond[20] (probably more important in the absence of chelation) may significantly raise the barrier to inversion; (ii) chelation may actually *facilitate* racemization by "holding" the cation nearby as the carbanion inverts; or (iii) the added barrier of a ring flip that accompanies the inversion may slow the process compared to acyclic systems. To our knowledge, these are the first α-aminoorganolithiums lacking any stabilization other than that provided by the nitrogen atom to be so characterized.

Acknowledgment. This work was partially supported by the National Institutes of Health. Q.Z. also thanks the University of Miami for a fellowship.

(19) This corresponds also to the configuration/sign of rotation of *S*-(+)-**5**. Uncertainty still exists, however: theory predicts that carboxylation of methyllithium occurs with retention (Kaufman, E.; Sieber, S.; Schleyer, P. v. R. *J. Am. Chem. Soc.* **1989**, *111*, 4005–8). Acylation of a configurationally stable benzyllithium with dimethyl carbonate occurs with retention, but carboxylation of the same organolithium occurs with inversion (Hoppe, D.; Carstens, A.; Kramer, T. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1424–5).

(20) Schleyer, P. v. R.; Clark, T.; Kos, A. J.; Spitznagel, G. W.; Rohde, C.; Arad, D.; Houk, K. N.; Rondan, N. G. *J. Am. Chem. Soc.* **1984**, *106*, 6467–75.