Pergamon

Tetrahedron Vol. 50, No. 20, pp. 6089-6096, 1994

0040-4020/94 $6.00+0.00

0040-4020(94)E0295-5

The Configurational Stability of Chiral Lithio α-Amino Carbanions. The Effect of Li-O *vs.* Li-N Complexation.

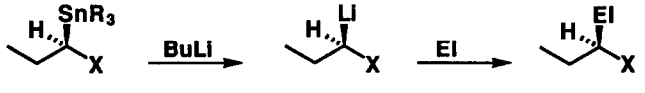
Todd R. Elworthy and A. I. Meyers*

Department of Chemistry, Colorado State University, Fort Collins, Colorado 80523, U. S. A.

Abstract: α-Lithio pyrrolidine, as its *N*-*t*-BOC or formamidine derivative, has been generated in high enantiomeric purity *via* Sn-Li exchange of the enantiomerically enriched (88-95%) α-tributylstannane derivative, **4**. The alkylation of these lithio carbanions gave 2-methyl pyrrolidines as well as providing a measure of their configurational stability. It was found that the α-lithio formamidines were configurationally more stable than the *t*-BOC derivatives and this is attributed to the stronger O-Li bond which weakens the adjacent C-Li bond, thus allowing configurational decay to occur more readily. This is the first report wherein a difference is observed between O-Li-C and N-Li-C configurational stability.

Carbanions adjacent to heteroatoms have been the subject of numerous reports in recent years. Although much of the effort has been directed [1] toward α-oxyanions **2a**, there is a considerable body of knowledge now available [2] on α-amino carbanions **2b**.

Recently there have been a number of studies dealing with the configurational stability of α-amino carbanions [3] **2b** which do not appear to possess the configurational stability exhibited by α-oxycarbanions **2a**. [1] These are usually generated from chiral non-racemic stannanes **1** and

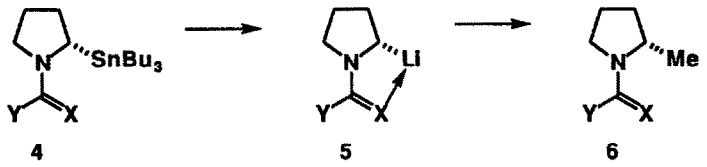


(+)-1 (+)2 (+)-3

a) X = OR, OCR (O)
b) X = NR_2, NCOR (O), $NCNR_2$ (O)

alkylated to products, **3**, having largely or completely retained their configuration. In general the α-oxo lithioanions **2a** are more stable, maintaining their configuration [1] at temperatures approximately -30° C whereas the α-amino lithio species **2b** generally lose [3,12] their configurational integrity in the temperature range of -50° C to -78° C.

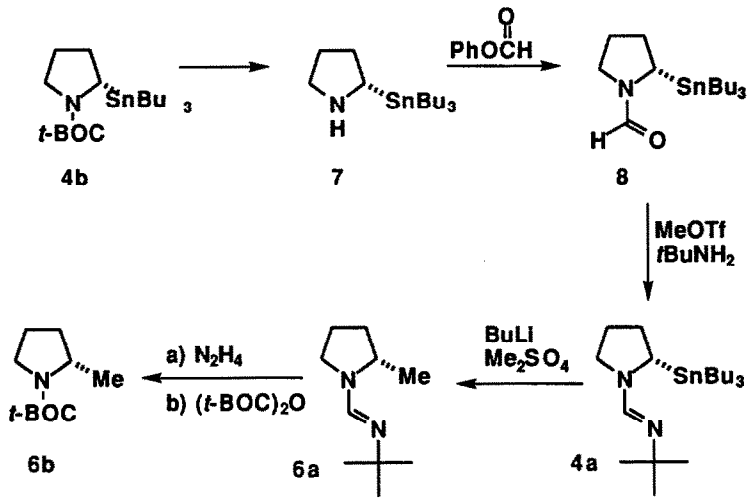
We wish to describe the behavior of a chiral lithio formamidine **5a**, where the stability of the C-Li bond configuration is significantly greater than others thus far described. When compared



4 **5** **6**

a) X = N-*t*-Bu, Y = H (Formamidine)
b) X = O, Y = O*t*-Bu (*t*-BOC)

directly with the known *t*-BOC anion **5b**, it is apparent that the nitrogen coordination in **5a** (X = NR) confers more configurational stability than the oxygen coordination in **5b** (X = O). In order to assess the relative stabilities of **5a/5b**, we have prepared the chiral non-racemic stannane **4a**. The latter was reached by initially preparing the *t*-BOC derivative **4b** according to the method of



4b **7** **8**

6b **6a** **4a**

Beak [3d] and then removing the *t*-BOC group. [4] The resulting unstable pyrrolidine **7** was immediately transformed to the *N*-formyl derivative **8** in 48% yield ($[\alpha]^{20}_D$ 205° c, 2.0 EtOH). The enantiomeric purity was assessed using chiral hplc analyses [5] and found to be 88-95% ee in good agreement with the value reported by Beak for **4b**. [3d]

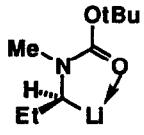
Treatment with methyl triflate and *t*-butylamine gave the desired chiral formamidine **4a** in 77% yield. [6] In order to assess the configurational stability of **5a**, excess butyllithium (2.5 equiv) was added to **4a** in ether at -78° C and stirred for 10 min. [7] Addition of dimethyl sulfate gave the enantiomerically enriched 2-methylformamidine **6a** in variable yields due to its sensitivity to silica gel during purification. Considerable decomposition of **6a** was noted although the crude material was present in much higher quantities. The lithiated formamidine **5a**, known from previous studies [3f] to be less stable than the corresponding lithiated carbamate **5b**, limited the time and temperature ranges that could be studied. Nevertheless, a series of experiments to probe the configurational stability of **5a** were successful and are tabulated in the Table. [8] As can be seen from the Table, the enantiomeric excess of **6a** is generally constant [9] between -78° C and -55° C

Conditions for the Transmetalation of Stannane 4a and Enantiomeric Purity of 6a.

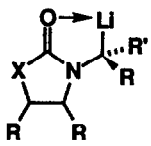
Entry	Metalation Temp [a] (**4a**)	Time (min)	**6a** (%) [b]	**6a** (ee) [c]
1	-78° C	0.5	30	86
2	-78° C	10	49	88
3	-78° C	30	29	88
4	-78° C	60	--[d]	--[d]
5	-55° C	10	36	82
6	-60° C	10	23	45 [e]

a) All metalations carried out in ether unless otherwise specified. b) Yield of isolated pure material *via* silica gel chromatography although crude yields were estimated (NMR) to be >80%. c) Determined by hplc as the *N*-*t*-BOC pyrrolidine **6b**. d) Complete decomposition of **5a** during this time interval. e) Transmetalation performed in 1,2-dimethoxyethane.

in THF (entries 1 - 5) thus verifying the configurational stability of its precursor, **5a**. This is in contrast to the configuration stability exhibited by acyclic anions **9** and **10** described by Chong [3b] and Pearson [3a] respectively. It was reported that **9** deteriorates to 24% of its original configuration



9



10 (X = NR, O)

at -55°C whereas **5a** is seen to maintain its configuration with virtually no loss in ee of product (Table, entry 5). Comparing **5a** to the *t*-BOC system **5b**, there was considerable enhancement of configurational stability for **5a**. The *N*-*t*-BOC lithiopyrrolidine **5b** showed 80% loss of optical activity [3d] after 30 min at -78° C whereas the lithio formamidine **5a** showed complete conservation of chirality (88% ee, entry 3, Table) under the same conditions. As observed by Chong, [3b] the use of DME as a solvent resulted in significant levels of racemization (Table, entry 6) and this may be attributed to the bidentate character of the DME or more efficient solvation of the lithium cation in **5a**, thus weakening the C-Li linkage.

What may be concluded from this study is that configurational stability relies heavily upon the ligands present to associate with the lithium ion. [12] It has long been known [10] that the reactivity of organolithiums is significantly altered by added external ligands and this is generally assumed to be the result of de-aggregation of the organolithium reagent. We believe that the harder oxygen atom in **5b**, generally agreed by most to bind strongly to lithium ion, actually may loosen the lithium-carbon attraction and allow carbanion inversion to occur more readily. Such an event has been suggested [10,11] to be responsible for the increase in basicity of organolithium reagents in an aggregate. The nitrogen ligand in **5a** may be a poorer donor of electrons to lithium ion, [11] which could allow the C-Li bonding to remain closely associated and therefore inhibiting carbanion inversion. [12] The ability of lithium to complex to either an external ligand or the sp^3-carbon anion provides the delicate balance between carbanion configurational stability or its loss. These experiments, comparing the two lithio species **5a** and **5b**, seem to present the first direct observation which allows a comparison of carbanion stability with regard to *O- vs. N*-ligands in two very closely related systems. This behavior appears to depend on several factors which are not completely understood, particularly the nature of the aggregates comprising **5a**, **5b**. Further insights into the mechanism of lithium carbon inversion (racemization) will undoubtedly be

required [12] and these are subjects for further study. It is noteworthy that Boche[13] has recently concluded, based on X-ray and computational studies, that the α-lithio amino carbanions do not appear to be carbenoid in nature, since the C-N bond is virtually unaltered. Thus, we may at this time still consider them to be carbanions. This is consistent with the observation made in this report.

Experimental.

General: (-)-Sparteine was liberated from its hydrosulfate salt (Aldrich) with 30% aqueous NaOH and extracted with CH_2Cl_2. The extract was washed with brine, dried (Na_2SO_4), and distilled by Kugelrohr at 0.7 mmHg, to collect the desired free amine at 115 - 120° C. The amine was stored as a 0.15 M ether solution at -30° under argon. Diethyl ether, tetrahydrofuran (THF), and 1,2-dimethoxyethane (DME) were distilled from sodium benzophenone ketyl. Dichloromethane (CH_2Cl_2) was distilled from CaH_2 prior to use. Methyl trifluoromethanesulfonate was used as received from Aldrich.

(*S*)-2-(Tri- butyltin)-*N*-(*tert*-butoxycarbonyl)pyrrolidine (4b)

This compound was prepared according to the procedure of Beak and Kerrick. [3] A 0.12 M solution (120 mL, 14.4 mmol, 1.25 equiv) of (-)-sparteine was cooled to -78°, treated with *sec*- BuLi (15.7 mL, 0.80 M in cyclohexane, 12.5 mmol, 1.10 equiv) and stirred for 15 min. After which time, the clouded solution was treated with *N-tert*-BOC-pyrrolidine (1.95 g, 11.4 mmol, 1.00 equiv), dissolved in Et_2O (7 mL). The resultant solution was stirred at -78° for 4 h, cooled to -90° and treated with tri-butyltin chloride (3.4 mL, 12.5 mmol, 1.10 equiv). This solution was stirred for 12 h and then allowed to warm to ambient temperature and the volatiles were removed with a rotary evaporator. The resulting residue was subjected to silica gel chromatography (80 g). Compound **4b** (4.17 g, 79%) was eluted with 5% EtOAc-hexanes: R_f (10% EtOAc-hexanes) 0.49; $[\alpha]^{25}_D$ +142° (*c*. 2.9, $CHCl_3$), lit; [3d] $[\alpha]^{30}_D$ +132° (*c*. 2.9, $CHCl_3$); IR (thin film) 2955, 2915, 2860, 1680, 1455, 1410, 1165, 1120 cm^{-1}.

(*S*)-2-(Tri- butyltin)-*N*-formylpyrrolidine (8)

The carbamate **4b** (4.3 g, 9.3 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (20 mL), cooled to ca. 10°, and treated with *B*-bromocatechol borane [7] (39 mL, 0.5 M in CH_2Cl_2, 19.5 mmol, 2.1 equiv). After stirring for 20 min, the solution was poured into 25 g of ice and 25 mL of 10% aqueous NaOH then extracted with CH_2Cl_2 (4 x 25 mL). The combined organic extracts were

immediately washed with brine, dried over Na_2SO_4, and filtered. The filtrate was immediately treated with phenyl formate (2.5 mL, 23 mmol, 2.5 equiv) and the volatiles were removed by rotary evaporation. The reaction vessel was briefly evacuated and refilled with argon at room temperature and the resultant yellow solution was stirred for 14 h at room temperature and then subjected to silica gel chromatography (75 g). The residue was initially eluted with 5% EtOAc-hexane and the eluant was graduated to 20% EtOAc-hexane at which concentration the desired compound, **8**, eluted (1.74 g, 48%) as a clear, colorless oil: R_f (20% EtOAc-hexane) 0.23; $[\alpha]^{25}_D$ +205.5° (*c.* 2.0, EtOH); ^{1}H NMR (300 MHz, C_6D_6) δ 0.80-1.19 (m, 15 H), 1.37 (m, 8H), 1.77 (m, 8H), 2.85 (m, 3H), 7.95 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 8.3 (minor), 9.0 (major), 10.0 (major), 12.4 (minor), 13.5 (major), 25.2 (minor), 25.9 (major), 27.2 (minor), 27.4 (major), 28.8 (major), 28.9 (minor), 43.6 (major), 43.7 (minor), 45.5 (minor), 46.4 (major), 158.9 (major), 159.9 (minor); IR (thin film) 2960, 2920, 2875, 1665, 1650, 1460, 1410, 1375, 1075 cm^{-1}; gas chromatograph/mass spectrum (GCMS) t_R = 11.7 min (oven program: 50° for 1 min, 20°/min to 280° for 5 min); MS(EI) *m/z* 389 (M^+ with ^{120}Sn, 2.7), 388 (M^+ with ^{119}Sn, 0.9), 387 (M^+ with ^{118}Sn, 2.2), 385 (M^+ with ^{116}Sn, 0.8), 336 (17), 332 (base), 331 (42), 330 (74), 328 (43), 218 (15), 179 (20), 177 (21), 98 (69). *Anal.* Calcd. for $C_{17}H_{35}NOSn$: C, 52.62; H, 9.03; N, 3.61. Found: C, 52.45; H, 9.06; N, 3.57.

(*S*)-2-(Tri- butyltin)-*N*-(*N'-tert*-butylformimide)pyrrolidine (4a)

In a 25-mL round bottom flask equipped with a reflux condensor, formamide **8** (639 mg, 1.64 mmol, 1.00 equiv) was dissolved in CH_2Cl_2 (3 mL) and treated with methyl trifluoromethanesulfonate (0.20 mL, 1.8 mmol, 1.1 equiv). The resulting clear, colorless solution was heated to reflux for 2.5 h at which time formamidine **6** could not be detected by TLC. The reaction vessel was cooled with a tap water bath (*ca.* 10°) and the solution treated with *tert*-butylamine (0.21 mL, 2.0 mmol, 1.2 equiv) and the resultant yellow solution was again heated to reflux. After 12 h, the solution was cooled and the volatiles removed by rotary evaporation. The residue was subjected to silica gel chromatography (50 g) (5% Et_3N-hexanes) to afford the desired formamidine **2** (563 mg, 77%) as a clear, colorless oil: R_f (5% Et_3N-20% EtOAc-hexanes) 0.27; $[\alpha]^{25}_D$ +209° (*c.* 1.0, CH_2Cl_2); ^{1}H NMR (300 MHz, C_6D_6) δ 1.05 (m, 16H), 1.29 (s, 9H), 1.46 (m with sextet overlap, J = 7.2 Hz, 8 H), 1.79 (m, 8 H), 2.98 (m, 2 H), 3.32 (t, J = 8.1 Hz, 1H), 7.45 (s, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 11.3 (t, $J_{C-^{118}Sn}$ = 150 Hz), 11.4, 26.7, 28.2 (t, $J_{C-^{118}Sn}$ = 26 Hz), 29.6, 29.8, 30.4, 31.9, 46.0, 48.5, 53.2, 146.0; IR (thin film) 2960, 2915, 2855, 2845, 1635, 1465,

1455, 1360, 1205 cm^{-1}; GCMS; the compound decomposed prior to elution from the GC column. *Anal.* Calcd for $C_{21}H_{44}N_2Sn$: C, 56.92; H, 9.94; N, 6.32. Found: C, 56.91; H, 9.97; N, 6.23.

A Typical Procedure for the Preparation of (*S*)-2-Methyl-*N*-(*N'*-*tert*-formimide) pyrrolidine (6a)

A 0.05 M ethereal solution of stannane **4a** (259 mg, 0.57 mmol, 1.00 equiv) was cooled to -78° C and the reaction vessel was evacuated (ca. 1 mmHg) for 3-5 min and purged with argon. BuLi (0.92 mL, 1.55 M in hexane, 1.43 mmol, 2.50 equiv) was added dropwise and the resulting light yellow solution was stirred for 10 min. Dimethyl sulfate (0.16 mL, 1.7 mmol, 3.0 equiv) was added and the solution was stirred an additional 5 min at -78° C. The volatiles were removed by rotary evaporation and the residue was chromatographed on silica gel (10 g). Tetrabutylstannane and **2** (14 mg, 0.030 mmol) were respectively eluted, with 5% Et_3N-hexanes. The desired compound, **3** (47 mg, 49%) was then eluted with 5% Et_3N-80% EtOAc-hexanes as a clear, colorless oil: R_f (7% Et_3N-25% EtOAc-hexanes) 0.05; $[\alpha]^{25}_D$ +29.8° (*c.* 1.0, CH_2Cl_2); ^1H NMR (300 MHz, C_6D_6) δ 0.99 (d, *J* = 6.3 Hz, 3 H), 1.11 (dq, *J* = 0.9, 4.8 Hz, 1 H), 1.33 (m with overlapped singlet, 10 H), 1.52 (m, 2 H), 3.30 (t, *J* = 5.7 Hz, 2 H), 3.47 (br q, *J* = 6.0 Hz, 1H), 7.53 (s, 1 H); ^{13}C NMR (75 MHz, C_6D_6) δ 21.4, 23.3, 31.7, 33.5, 46.7, 53.3, 53.5, 146.0; IR (thin film) 2965, 2870, 1645, 1460, 1370, 1215 1165 cm^{-1}; GCMS: t_R= 4.90 min (oven temp: 50° for 1 min, 20°/min to 280°); MS(EI) *m/z* 169 (M + 1, 7), 168 (M^+, 46), 154 (11), 153 (base), 111 (23), 84 (89), 70 (25).

2*S*-Methyl-*N*-(*tert*-butoxycarbonyl)pyrrolidine (6b)

Liquid chromatography (Chiralcel OD, [5] 100% hexane, 0.75 mL/min, 214 nm) t_R = 21.2 min for the 2*S*-isomer, percent area = 88.6; t_R = 25.6 min for the 2*R*-isomer, percent area = 8.6; R_f (15% EtOAc-hexanes) 0.27; $[\alpha]^{25}_D$ +27.9° (*c.* 2.45, $CHCl_3$), lit.[3] $[\alpha]^{20}_D$ +31.2° (*c.* 2.76, $CHCl_3$) which was determined to be 95% ee as (*R*)-Mosher amide; ^1H NMR (300 MHz, $CDCl_3$) δ 1.08 (d, *J* = 6.0 Hz, 3 H), 1.43 (m with overlapping singlet, 10 H),1.84 (m, 3H), 3.28 (br s, 2 H), 3.78 (br s, 1 H).

Acknowledgement. The authors are grateful to the National Science Foundation for support of this work. We also are grateful to Professor Peter Beak for helpful discussions.

References

1. a) Still, W. C.; Sreekumar, C. *J. Am. Chem. Soc.,* **1980**, *102*, 1201 and earlier references cited. b) Hutchinson, D. K.; Fuchs, P. L. *J. Am. Chem. Soc.* **1987**, *109*, 4930 and references cited

therein. c) Sawyer, J. S.; Kucerovy, A.; MacDonald, T. L.; McGarvey, G. J. *J. Am. Chem. Soc.* **1988**, *110*, 842. d) Sommerfeld, P.; Hoppe, D. *Synlett* **1992**, 764 and earlier work cited.

2. a) For early work see Peterson, D. J. *J. Am. Chem. Soc.* **1971**, *93*, 4027. b) Beak, P.; Zajdel, W. J.; Reitz, D. B. *Chem. Rev.* **1984**, *84*, 471. c) Gawley, R. E.; Rein, K. *Comprehensive Organic Synthesis Selectivity for Synthetic Efficiency* Vol. 3, Ch. 1, 2. d) Beak, P.; Lee, W.-K. *Tetrahedron Lett.* **1989**, *30*, 1197. e) Meyers, A. I. *Tetrahedron* **1992**, *48*, 2589.

3. a) Pearson, W. H.; Lindbeck, A. C. and Kampf, J. W. *J. Am. Chem. Soc.* **1993**, *115*, 2622. b) Chong, M. J.; Park, S. B. *J. Org. Chem.* **1992**, *57*, 2220. c) Burchat, A. F.; Chong, J. M.; Park, S. B. *Tetrahedron Lett.* **1993**, *34*, 51. d) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708. e) Zchage, O.; Hoppe, D. *Tetrahedron* **1992**, *48*, 5657. f) Meyers, A. I.; Guiles, J.; Warmus, J. S.; Gonzalez, M. A. *Tetrahedron Lett.* **1991**, *32*, 5505. g) See reference 12a.

4. Boeckmann, Jr., R. K.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411.

5. Performed on Chiralcel OD, Diacel Co., Tokyo, Japan. 0.5 - 1.0% EtOH in hexane visualized at 250 nm.

6. Physical data for **4a**: $[\alpha]_D$ 209°; (c 1.0 CH_2Cl_2); ^{1}H-NMR δ 0.98-1.12 (m, 16H), 1.29 (s, 9H), 1.36-1.55 (m), 1.60-1.98 (m, 8H) 2.93-3.04 (m, 2H), 3.32 (t, J = 8.1 Hz, 1H), 7.45 (s, 1H), ^{13}C-NMR (75 MHz C_6D_6) δ 11.3 (t, $J_{C\text{-}Sn}$ =150 Hz), 11.4, 26.7, 28.2 (t, $J_{C\text{-}Sn}$ = 26 Hz) 29.6, 29.8, 30.4, 31.9, 46.0, 48.5, 53.2, 146.0. **Anal Calcd** for C_{21} $H_{44}N_2Sn$: C, 56.92; H, 9.94; N, 6.32. Found: C, 56.91; H, 9.97; N, 6.23.

7. Use of 1.0-2.0 equiv of butyllithium gave incomplete transmetalation.

8. The absolute stereochemistry of **6a** was confirmed by transforming it to **6h** and comparison with the data reported in ref. 3d above. This was accomplished in two steps a) hydrazinolysis in EtOH-H_2O-HOAc; b) addition of t-BOC_2O to the pyrrolidine to afford **6h**. Pyrrolidine **6b** prepared from either route gave identical elution patterns on chiral hplc analysis.

9. The sensitivity of the lithio formamidines **5a** to temperatures above -60° C precluded our effort to allow the anions to age for longer times. Note the total loss of material after 1 hour at -78° C. The pathway that arises has already been described by us (Meyers, et al. *J. Am. Chem. Soc.* **1984**, *106*, 3270). Furthermore, use of highly reactive electrophiles (e.g. Me_2SO_4 allyl halides, etc.) leads to competing N-alkylation of **5a** thus giving lower yields, as seen in Table 1.

10. Hay, D. R.; Song, Z.; Smith, S. G.; Beak, P. *J. Am. Chem. Soc.* **1988**, *110*, 8145. These authors also suggest that the oxygen carbonyl of various amides donates electrons to the lithium cation thus increasing the observed reactivity of metalations.

11. Arnett, E. M.; Moe, K. D. *J. Am. Chem. Soc.* **1991**, *113*, 7068 suggests that Li-O bond is much stronger than Li-N bond in solution. See also McGarrity, J. F.; Ogle, C. A. *J. Am. Chem. Soc.* **1985**, *107*, 1805, 1810.

12. Gawley, R. E.; Zhang, Q. *J. Am. Chem. Soc.* **1993**, *115*, 7515.

13. Boche, G.; Marsch, M.; Harbach, J.; Harms, K.; Ledig, B.; Schubert, F.; Lohrenz, J. C. W.; Albrecht, H. *Chem. Ber.* **1993**, *126*, 1887.

(*Received* 22 *November* 1993)