JOC Notes

Absolute Configuration of 2-(Tributylstannyl)pyrrolidine by Anomalous Dispersion X-ray Analysis

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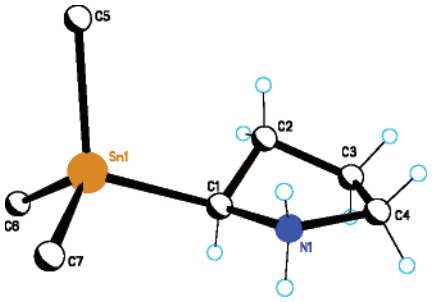
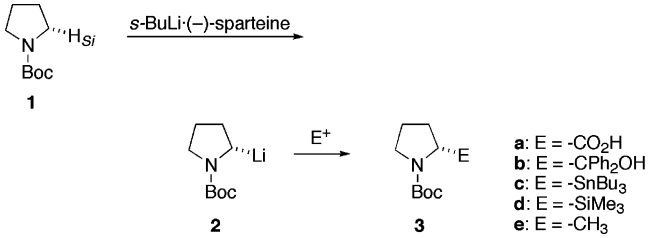


Enantiopure 2-(tributylstannyl)pyrrolidine hydroiodide may be prepared in excellent yield by TMSI treatment of the corresponding *N*-Boc compound, which is in turn prepared by asymmetric deprotonation (*s*-BuLi·sparteine) and stannylation, as described in the literature. Crystals of the hydroiodide salt suitable for X-ray analysis were obtained, and although there is some disorder about the butyl groups, analysis using anomalous dispersion establishes the absolute configuration as *S*.

Much of the progress in the chemistry of chiral organolithium compounds over the past 15 years, described in several recent monographs, involves asymmetric deprotonation through the use of butyllithium·sparteine complexes as a chiral base.[1] The specific case of enantioselective removal of the H_{Si} proton of *N*-Boc pyrrolidine, **1**, was reported by Kerrick and Beak in 1991.[2] In this paper, the absolute configuration of two examples of electrophilic substitution, **3a**,**b**, was established by comparison with compounds derived from L-proline; the configurations of **3c**−**e** were assigned by analogy. Although the number of electrophiles that react with this chiral organolithium is somewhat limited, the stannylation to produce **3c** (E = $SnBu_3$) works well.



In the intervening years, a considerable body of work has ensued and is based on the configurational assignment of the 2-(tributylstannyl)pyrrolidine that was made "by analogy". For example, reduction of the Boc to a methyl affords a class of compounds that show excellent reactivity with a variety of electrophiles[3] and extraordinarily high configurational stability.[4,5] In 1994, we reported the synthesis of enantiopure 2-(tributylstannyl)-*N*-methylpiperidines and assigned the absolute configuration by comparison of specific rotations of the homologous 5- and 6-membered heterocycles.[5] Later, we showed that the steric course of electrophilic substitutions of 2-lithiopyrrolidines and 2-lithiopiperidines were dependent on the electrophile.[3] Moreover, the steric course of a [2.3]-sigmatropic rearrangement[6] and an anionic cyclization[7] is predicated on the configuration of **3c**. Tin−lithium exchange of **3c**, followed by a second transmetalation with copper salts, produces a scalemic organocuprate that sometimes behaves differently from the same cuprate obtained after asymmetric deprotonation/cupration.[8] Because the absolute configuration of stannane **3c** is central to all of the applications mentioned above, we sought to place the absolute configuration on a firmer foundation.

Several applications of α-aminoorganolithium chemistry involve removal of the Boc group from 2-(tributylstannyl)pyrrolidine **3** and replacement with another group such as allyl, benzyl, or isobutyl. We have used two reagents to remove the Boc group from **3c**: *B*-bromocatechol borane and trimethylsilyl iodide. The amine product obtained using *B*-bromocatechol borane is rather unstable, perhaps because of traces of boron impurities. Herein, we report a reliable procedure to remove the Boc group to afford the crystalline hydroiodide salt in quantitative yield (85% after recrystallization). The fragile needles crystallized in the $P2_1$ (#4) space group. These crystals are thermally stable for at least 6 months in air at room temperature.

Curiously, four molecules appeared in the unit cell, whereas this space group usually has only two. However, they each pack in chains made by the screw axes along b, with the ammonium ions associated with the iodides (NH−I distances of 2.53 and 2.54 Å may be a little long to be considered hydrogen bonds). The butyl groups show

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(2) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708−9710.
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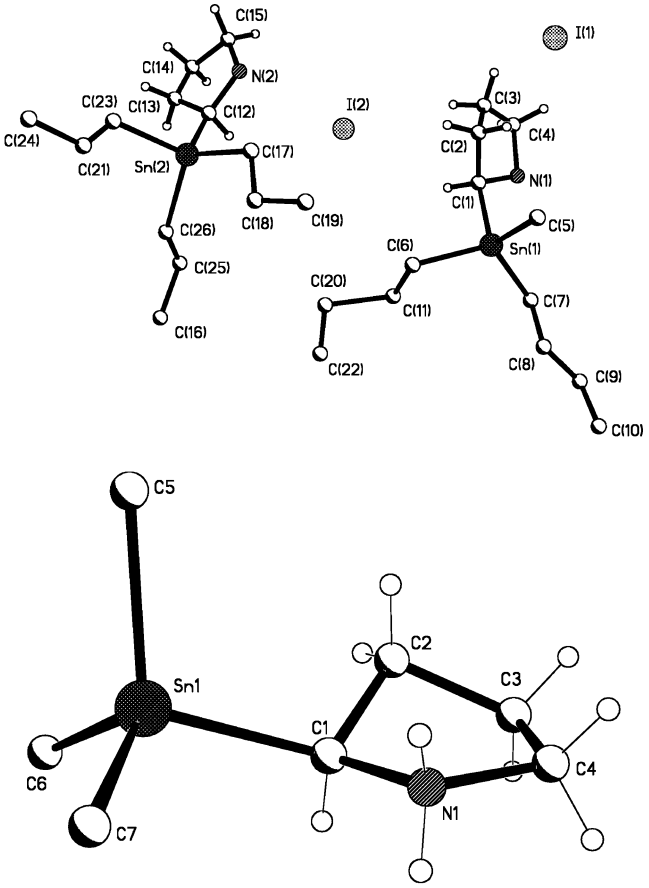

FIGURE 1. Title compound, showing (top) only the atoms that were refined in the final model (see the Supporting Information for details). The other atoms of the butyl groups were disordered and could not be accurately modeled. On the bottom are shown only the critical atoms establishing the absolute configuration.

considerable disorder, and a satisfactory model of the disorder could not be obtained. Despite the fact that the majority of the unaccounted for electron density appears where the remainder of the butyl group carbon atoms are anticipated to occupy, only the carbon atoms of the butyl groups that did not show disorder were included in the final refinement. Nine of the strongest 11 residual electron density peaks are in the tributyltin cone (with the other two near the heavy atoms of iodine and tin), and when attempts were made to fully model the butyl groups, stable positions for the remaining carbon atoms could not be found. Attempts at modeling different orientations of the butyl groups using the SHELX "PART" command did not lead to a meaningful model, nor did the use of standard restraints on bond lengths and angles. Data were collected on two different crystals, but neither afforded complete refinement of the butyl groups. Nevertheless, the atoms of the pyrrolidine ring, the tin, and several carbons attached to tin showed no disorder (Figure 1). The final R value of 9.7% is relatively low considering all of the C's are isotropic. The Sheldrick least-squares refinement gave a Flack x parameter = 0.1 with esd = 0.1. The expected values are 0 (within 3 esd's) for correct and +1 for incorrect absolute configuration. Analysis of the Flack parameters using the R configuration confirmed the S configuration in our crystal.

In conclusion, a high yield procedure is reported for removing the Boc group from 2-(tributylstannyl)pyrrolidine to give crystalline hydroiodide, and anomalous dispersion single-crystal structure analysis establishes clearly that the absolute configuration assigned by Kerrick and Beak[2] was correct.

Experimental Part

***(S)*-2-(Tributylstannyl)pyrrolidine Hydroiodide.** To a solution of *(S)*-*N*-Boc-2-(tributylstannyl)pyrrolidine[2] (275 mg, 0.60 mmol) in dry CH_2Cl_2 (5 mL) was added slowly TMSI (100 μL, 0.77 mmol) at room temperature (during the TMSI addition color changes to yellow and then colorless). After 30 min, water (1 mL) was added slowly at room temperature followed by dichloromethane (20 mL). The layers were separated, and the organic layer was washed with water (2 × 5 mL) and satd NaCl (5 mL), dried over $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure to give a white solid. The product was purified by recrystallization (CH_2Cl_2/hexane) to give crystalline product (246 mg, 84%): mp 89−90 °C; $[\alpha]^{23}_D$ +19.5 (c 1.102, $CHCl_3$); IR (hexane mull) 2957, 1460, 757 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 0.90 (t, J = 7 Hz, 9H), 1.19(m, 6H), 1.34(m, 6H), 1.65 (m, 6H), 1.86 (m, 2H), 2.07 (m, 1H), 2.27 (m, 1H), 2.80 (m, 1H), 3.33 (m, 2H), 8.20 (br, s, 1H), 8.75 (br, s, 1H) ppm; ^{13}C NMR (67 MHz, $CDCl_3$) δ 10.6, 13.8, 24.4, 27.5, 29.1, 30.2, 44.6, 45.6; MS (m/z) 362.1 ($M-I^+$). Anal. Calcd for $C_{16}H_{36}INSn$: C, 39.37; H, 7.43. Found: C, 39.44; H, 7.55.

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Supporting Information Available: Proton and carbon NMR spectra of the title compound and details of the X-ray analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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