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Synthesis and Reactivity of Conformationally Locked α-Aminoorganostannanes and α-Aminoorganolithiums. Discovery of a Surprising Configurational Requirement for Transmetalation

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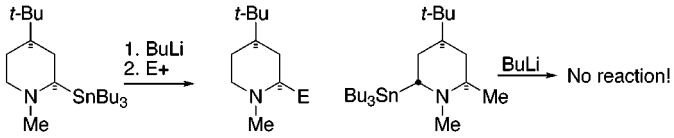
ABSTRACT



2-Tributylstannyl-*N*-methylpiperidines that are conformationally locked by a 4-*tert*-butyl substituent were evaluated in transmetalations (Sn–Li exchange) and reactions with electrophiles. When the tin is equatorial, transmetalation occurs smoothly as does reaction with carbonyl electrophiles. Alkyl halides seem to undergo single electron transfer reactions, affording nonselective alkylation products, along with products of radical disproportionation. In a surprise, an axially oriented tin failed to transmetalate, suggesting that a synclinal relationship between the nitrogen lone pair and the carbon–tin bond is a requirement for transmetalation.

α-Amino organolithiums have received a significant amount of interest over the past two decades because of their configurational stability and synthetic versatility.[1] In 1993, we reported the synthesis of *N*-methyl-2-lithiopyrrolidine and -piperidine from the corresponding *N*-methyl-2-tri-*n*-butylstannylpyrrolidine and -piperidine through tin−lithium exchange with *n*-butyllithium, to produce organolithium species having extraordinary configurational stability.[2] The lithiated species were then reacted with different electrophiles to provide 2-substituted *N*-methyl pyrrolidines and piperidines in good to excellent yields. The steric course[3] of these reactions was found to depend on the type of electrophile:[2b] ketones, aldehydes, and esters react with retention while alkyl halides react with inversion. Reducible electrophiles such as benzyl bromide, ethyl bromoacetate, and benzophenone give complete racemization.

All of our previous studies evaluated the steric course of reactions where the only stereocenter was the metal-bearing carbon of enantiopure organolithiums. In this report, we disclose the results of an investigation into the transmetalation and electrophilic quench of diastereomeric, conformationally locked, racemic piperidines. During the course of these studies, we were surprised to find a severe stereoelectronic requirement for tin−lithium exchange.

(1) Reviews: (a) Beak, P.; Reitz, B. D. *Chem. Rev.* **1978**, *78*, 275. (b) Beak, P.; Zajdel, W. J.; Reitz, B. D. *Chem. Rev.* **1984**, *84*, 471. (c) Gawley, R. E.; Rein, K. S. In *Comprehensive Organic Synthesis*; Trost B. M., Fleming, I., Eds.; Pergamon: Oxford, 1991; Vol. 3, Chapter 1.2. (d) Gawley, R. E. *Curr. Org. Chem.* **1997**, *1*, 71.

(2) (a) Gawley, R. E.; Zhang, Q. *J. Am. Chem. Soc.* **1993**, *115*, 7515. (b) Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5763. (c) Gawley, R. E.; Zhang, Q. Z. *Tetrahedron* **1994**, *50*, 6077.

(3) Gawley, R. E. *Tetrahedron Lett.* **1999**, *40*, 4297.

(4) Gössinger, E. *Monatsh. Chem.* **1982**, *113*, 339.

(5) (a) Beak, P.; Lee, W.-K. *J. Org. Chem.* **1990**, *55*, 2578. (b) Beak, P.; Lee, W.-K. *J. Org. Chem.* **1993**, *58*, 1109.

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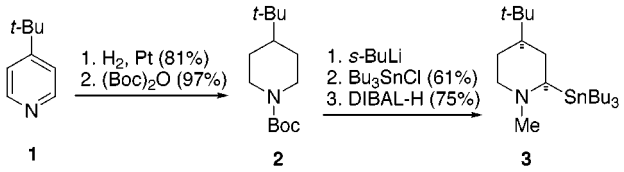
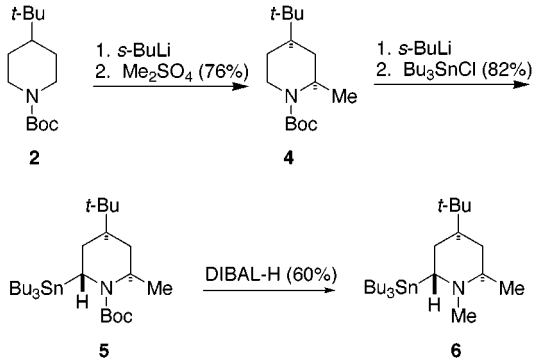
Because of the variability of the steric course of S_E2 substitution in unsubstituted heterocyclic rings, our plan was to evaluate reactivities of conformationally restricted 4-*tert*-butyl-*N*-methylpiperidines having a 2-tri-*n*-butylstannyl group in both the axial and equatorial positions. To this end, piperidines **3** (Scheme 1) with an equatorial stannyl group

Scheme 1



and **6** (Scheme 2) with an axial stannyl group were prepared for this study. As shown in Scheme 1, 4-*tert*-butylpyridine **1** was hydrogenated, in the presence of a catalytic amount of platinum oxide,[4] in an ethanol/chloroform solvent mixture

Scheme 2

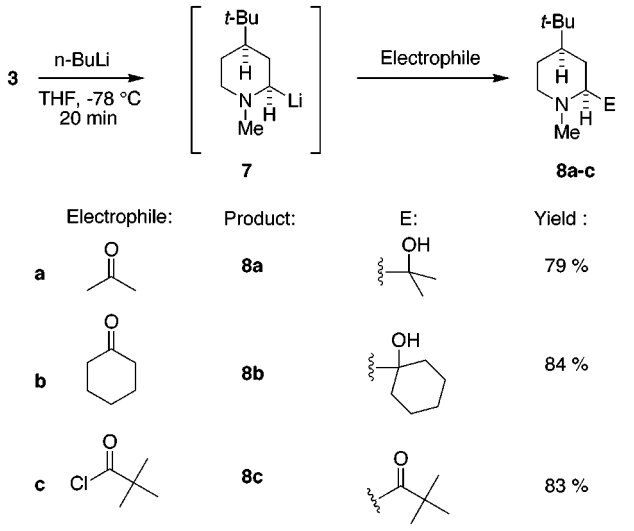


to afford 4-*tert*-butylpiperidine in 81% yield. Protection of the amine functional group was done with di-*tert*-butyl dicarbonate in dichloromethane to give carbamate **2** in 97% yield. Deprotonation of **2** with *sec*-butyllithium in the presence of TMEDA in diethyl ether at −78 °C, as reported by Beak,[5] and alkylation with tri-*n*-butylstannyl chloride (in 61% yield) was followed by reduction of the BOC group with diisobutylaluminum hydride to give **3** in 75% yield (36% from **1**). The equatorial position of the tri-*n*-butylstannyl group was assigned on the basis of NMR analysis.[6]

For comparison with (cis) **3**, we would have liked to examine the trans stereoisomer, having an axial tin, but several attempts at introduction of an axial tin using iminium ion chemistry[7a,b] or reduction of enamides[7c] were unsuccessful. Knowing that 2,6-dimethyls could be introduced in a trans orientation by a lithiation strategy,[5] we followed the route shown in Scheme 2, to obtain axial stannane **6**, which also has an equatorial methyl in the 6-position. Carbamate **2** was deprotonated and methylated with dimethyl sulfate to obtain carbamate **4** in 76% yield. Stannylation of **4** with tri-*n*-butylstannyl chloride afforded stannyl carbamate **5** in 82% yield. Reduction of the carbamate moiety with excess diisobutylaluminum hydride afforded *N*-methyl piperidine **6** in 60% yield. The relative configuration was assigned on the basis of literature precedent[5] and ^{1}H NMR spectroscopy.[6]

Piperidine **3** was transmetalated by treatment with *n*-butyllithium for 20 min at −78 °C in THF (Scheme 3), and

Scheme 3

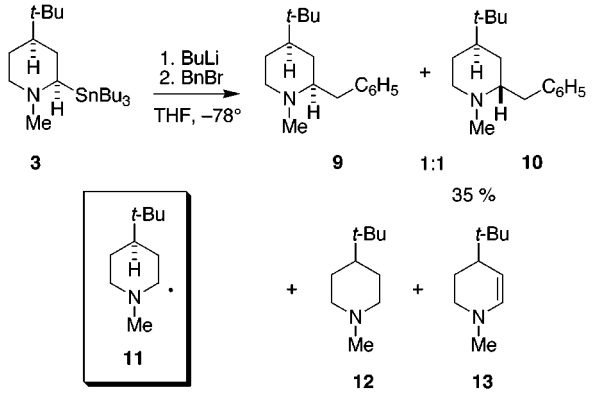


the resulting 2-lithiopiperidine **7** was allowed to react with various carbonyl electrophiles to afford *N*-methyl piperidines **8a**−**c** in excellent yields. As we found previously in the unsubstituted case,[2b] deprotonation of cyclohexanone or acetone does not compete effectively with addition to the carbonyl. The percentage yields of educts **8a**−**c** are similar to the yields obtained with unsubstituted α-lithiopiperidine, and the steric course at the carbanionic carbon was similar to that observed in the unsubstituted series: retention (S_E2ret).

With benzyl bromide as electrophile (Scheme 4), the yield of substitution product was lower, and the steric course was random. With enantiopure organolithiums unsubstituted in the 4-position, we also found stereorandom substitution[2] and believe that the reason is a radical mechanism involving initial single electron transfer (SET).[8] In this case, SET from organolithium **7** to benzyl bromide would produce radical **11** after loss of bromide. This reaction mixture also yielded a mixture of **12** and a compound tentatively identified as **13**. The former was prepared independently (vide infra), the latter appeared as a nearby peak in the GC-MS trace, with a molecular weight and fragmentation pattern consistent with this structure. These two compounds would result from disproportionation of **11**, again consistent with an SET mechanism with this electrophile.

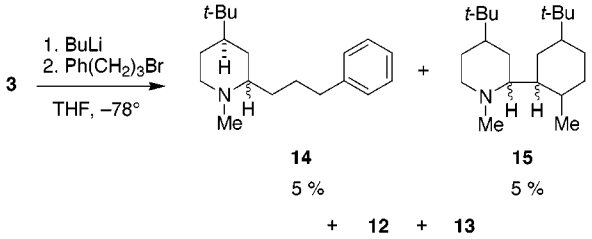
(6) Gawley, R. E.; Low, E.; Chambournier, G. *Org. Lett.* **1999**, *1*, 653.
(7) (a) Meyers, A. I.; Shawe, T. T.; Gottlieb, L. *Tetrahedron Lett.* **1992**, *33*, 867. (b) Gottlieb, L.; Meyers, A. I. *Tetrahedron Lett.* **1990**, *33*, 4723. (c) Wilkinson, T. J.; Stehle, N. W.; Beak, P. *Org. Lett.* **2000**, *2*, 155.
(8) Gawley, R. E.; Low, E.; Zhang, Q.; Harris, R. *J. Am. Chem. Soc.* **2000**, *122*, 3344.

Scheme 4



Finally, the same reaction was repeated with phenylpropyl bromide (Scheme 5) as the electrophile. With enantiopure

Scheme 5



4-unsubstituted piperidines, this electrophile afforded complete inversion (S_E2inv) of configuration in 75−76% yield.[2b] Since the lithium in **7** is formally equatorial (it is probably bridged to the nitrogen, distorting a perfect chair), invertive substitution should be severely inhibited. In the event, the product of electrophilic substitution (**14**) was isolated in only 5% yield as a mixture of diastereomers. In this case, we found a dimer (**15**) of unknown relative configuration, and probable disproportionation products **12** and **13**. All of these products are consistent with the intervention of an SET mechanism. Dimers were observed in the reaction of lithiopyrrolidine with benzyl bromide, which is thought to proceed by an SET mechanism.[8] Only polar pathways are followed for this electrophile in unsubstituted piperidines, so it appears that when the preferred pathway for electrophilic substitution, here S_E2inv, is unlikely or impossible, SET can intervene as a competitive pathway. The reasons for mechanistic variations between retentive or invertive polar substitutions and SET reactions have not been completely clarified but are the subject of ongoing investigation.[8]

It was of interest to investigate the corresponding axial organolithium, since we anticipated that S_E2inv would be more easily accommodated with a formally axial lithium. Much to our surprise, treatment of **6** with *n*-butyllithium did not trigger any tin−lithium exchange to **16**: only starting material (**6**) was detected after workup (Scheme 6). This surprising observation was confirmed in side-by-side experiments in which the transmetalations of piperidines **3** and **6** were followed by methanol quench. The crude mixtures were analyzed by GC-MS after workup, and the traces were compared to those of piperidines **12** and **17** which were synthesized independently from **2** and **4**, as shown in Scheme 6. The trace of the crude mixture from the transmetalation of **3** compared favorably with independently prepared **12** while the trace coming from the transmetalation of **6** showed no trace of **17**! Seemingly, an *equatorial* tri-*n*-butylstannyl group is required for the tin−lithium exchange to occur in these species. This failure may provide a clue to the explanation of other tin−lithium exchange failures reported in the literature.[9]

Using the Karplus relationship between $^3J_{Sn-C}$ coupling constants and torsion angles,[10] we recently showed that equatorial stannane **3** and its analogue lacking the *tert*-butyl exist as half-chairs in solution.[6,11] Axial stannane **6** shows couplings to C-4 of 17.4 Hz and to C-6 of 21.8 Hz; however, the Karplus relationship allows two solutions: $50 \pm 5°$ or $115 \pm 5°$ to C-4 and $49 \pm 5°$ or $120 \pm 5°$ to C-6. The ∼50° solution is a slightly distorted chair; the ∼115−120° implies a half-chair, since the anticlinal angle is approaching the eclipsing value of 120°, as observed with the equatorial stannanes.[6,11] Although the solution conformation of **6** cannot be determined from the present data with certainty, we are working under the hypothesis that it is in a relatively undistorted chair. If it was a half-chair, it would be difficult to explain the differences in reactivity between **3** and **6**.

In conclusion, we have shown that conformationally rigid 4-*tert*-butyl-2-lithio-*N*-methylpiperidines having an equatorial lithium react stereoselectively with carbonyl electrophiles (S_E-2ret) in excellent yields. Stereorandom alkylation in modest yield was observed with benzyl bromide, consistent with a change in mechanism, most likely SET. However, unlike unsubstituted 2-lithiopiperidines, equatorially lithiated **7** does not react well with unactivated alkyl halides, apparently due to the intervention of SET processes. This could be due to the fact that the preferred mode of alkylation is S_E2inv,

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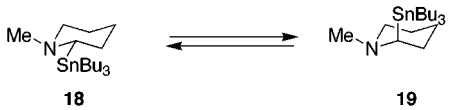
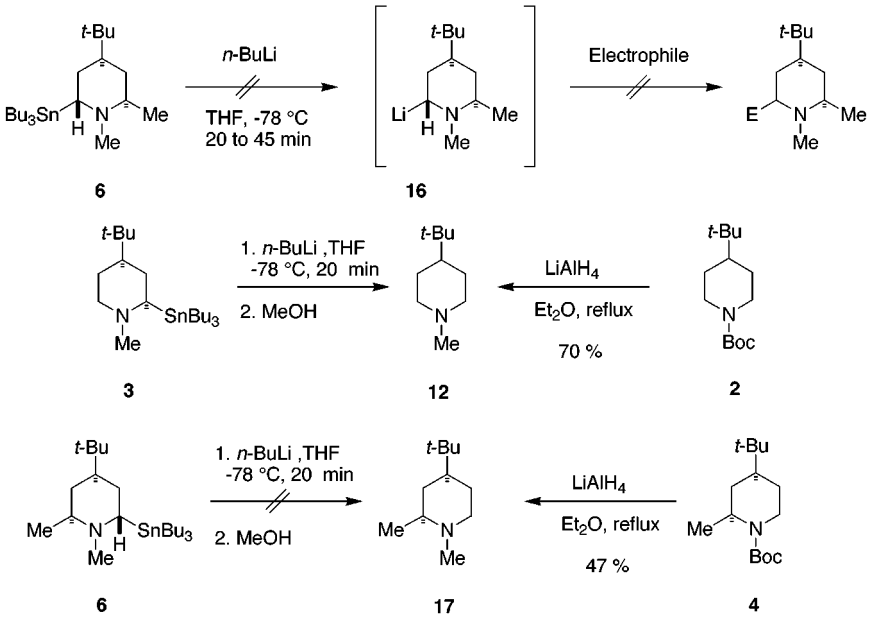
(10) (a) Kitching, W.; Olszowy, H.; Waugh, J.; Doddrell, D. *J. Org. Chem.* **1978**, *43*, 898. (b) Kitching, W.; Olszowy, H. A.; Harvey, K. *J. Org. Chem.* **1982**, *47*, 1893.

(11) Stannane conformers **18**/**19** could be observed as well-resolved, unique conformers below −60 °C.[6] For the equatorial conformer **18**, the $^3J_{Sn-C}$ coupling to carbon-6 is 24.6 Hz, corresponding to possible torsions of 45° or 123°, according to the two possible solutions to Kitching's Karplus-like relationship.[10] For *tert*-butylpiperidine **3**, *J* values suggest that the corresponding torsion is either 42° or 126°. Because of the 4-*tert*-butyl group, a 42° torsion requires a boat conformation with the Bu_3Sn group in a flagpole orientation. Since this orientation would be of extraordinarily high energy, the 123°/126° torsions are more likely. This angle is close to an eclipsing angle of 120°, suggesting a flattened ring (half-chair). For **19**, the solutions to the Kitching/Karplus equation correspond to possible torsions of 64° or 107°. Previously, we interpreted these data in terms of a relatively undistorted chair with an axial tin, but the 107° value cannot be completely ruled out.



18 19

Scheme 6



difficult when the lithium is equatorial. In a surprise, we found that when the tin is trans to the *tert*-butyl group, transmetalation fails completely. In these piperidines, a requirement for transmetalation appears to be a synclinal relationship between the C−Sn bond and the nitrogen lone pair. It is possible that this effect is relevant to the failure or reluctance of certain other (acyclic) α-aminoorganostannanes to transmetalate.[9]

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Supporting Information Available: Experimental details for the preparation and characterization of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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