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A convenient route to *N*-alkyl-2-tributylstannyl-pyrrolidines involving reductive amination

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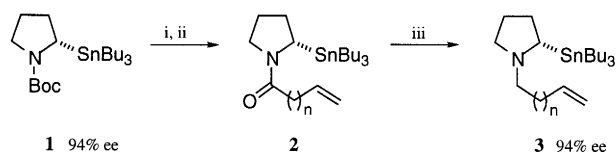
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Abstract

A new and convenient method for the formation of *N*-alkyl-2-tributylstannyl-pyrrolidines from *N*-Boc-2-tributylstannyl-pyrrolidine has been developed. The procedure uses *N*-Boc deprotection, followed by rapid base wash and reductive amination with an aldehyde and NaBH₃CN in nitromethane. © 2000 Elsevier Science Ltd. All rights reserved.

α -Amino-trialkylstannanes are important reagents in organic synthesis that allow the formation, by transmetalation, of the corresponding reactive α -amino-organolithium species, capable of effecting a wide variety of transformations.^{1–3} The *N*-Boc-2-tributylstannyl-pyrrolidine **1** is readily available in highly enantiomerically-enriched form,⁴ and therefore its direct conversion to the corresponding *N*-alkyl derivatives is highly desirable. Currently, this transformation is limited to the *N*-methyl (by reduction)^{1b} and *N*-allyl^{2b} derivatives, the latter by *N*-Boc deprotection of **1** with *B*-bromo-catecholborane,⁵ to give the secondary amine, which can be alkylated efficiently only with reactive electrophiles. We have prepared the *N*-but-3-enyl⁶ and *N*-pent-4-enyl compounds **3**, $n=1,2$ by a two-step route (Scheme 1) using *N*-Boc deprotection then addition of NaOH_(aq) and an acid chloride to give the amides **2**. Reduction of the amides **2** with LiAlH₄ gave the required α -amino-stannanes **3**.



Scheme 1. Reagents and conditions: (i) *B*-bromo-catecholborane, CH₂Cl₂, 10 min; (ii) 2 M NaOH_(aq), CH₂=CH(CH₂)_nCOCl, 18 h, $n=1$, 76%, $n=2$, 82%; (iii) LiAlH₄, Et₂O, 30 min, $n=1$, 89%, $n=2$, 92%

Although this route gave the desired *N*-alkyl compounds in good yield, the necessity to prepare the appropriate acid chlorides limited the synthetic utility of this procedure for more complex substrates.

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We, therefore, sought an alternative route to *N*-alkyl-2-tributylstannyl-pyrrolidines using the more readily available aldehydes, with in situ reduction. After screening a variety of solvents and reducing agents, it was found that *N*-Boc deprotection of stannane **1** with *B*-bromo-catecholborane,⁵ followed by rapid washing with 2 M NaOH_(aq), concentration in vacuo, and subsequent treatment with 4 Å molecular sieves, NaBH₃CN and the aldehyde, in nitromethane,⁷ gave the required stannanes **4** (Table 1).

Table 1
Synthesis of *N*-alkyl-2-tributylstannyl-pyrrolidines **4**



i, *B*-bromo-catecholborane, CH₂Cl₂, 10 min; ii, NaOH_(aq) wash; iii, MeNO₂, 4Å molecular sieves, NaBH₃CN, RCHO, 15 min.

| Entry | R | Yield 4 (%) [*] | Product | [α] _D ²⁰ (c, CHCl ₃) |
|-------|--|---------------------------------|-----------|--|
| 1 | -(CH ₂) ₃ CH ₃ | 64 | 4a | +64.3 (2.8) |
| 2 | -CH(CH ₃) ₂ | 62 | 4b | +72.3 (1.3) |
| 3 | -CH ₂ Ph | 50 | 4c | +67.3 (2.0) |
| 4 | -(CH ₂) ₂ CH=CH ₂ | 62 | 4d | +66.0 (1.3) |
| 5 | <i>E</i> -(CH ₂) ₂ CH=CHSPH | 72 | 4e | +55.3 (1.1) |
| 6 | <i>Z</i> -(CH ₂) ₂ CH=CHSPH | 69 | 4f | +46.0 (1.0) |
| 7 | -(CH ₂) ₂ C≡CSPH | 57 | 4g | +56.9 (1.1) |
| 8 | -(CH ₂) ₃ CO ₂ CH ₃ | 50 | 4h | +51.0 (2.5) |

^{*}Yield after chromatography on basic alumina.

Both linear and branched alkyl aldehydes (entries 1–3) reacted efficiently to give the corresponding stannanes **4** in good yield. The transformation was tolerant of various functional groups (entries 4–8). In all cases the *N*-alkyl derivatives **4**, derived from substrate **1** (94% ee),⁴ had large values for the optical rotation. The enantiomeric purity of a number of the products was checked using the two-step route (Scheme 1), which has been shown to be enantiospecific;⁶ in all cases the value for the optical rotation was in good agreement.⁸

In conclusion, we have shown that acid-sensitive, enantioenriched *N*-alkyl-2-tributylstannyl-pyrrolidines **4** may be prepared rapidly and efficiently by *N*-Boc deprotection, followed by in situ reductive amination in nitromethane. This procedure should be amenable to other unstable, acid-sensitive amines.

Acknowledgements

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References

1. Quench with external electrophiles: (a) Burchat, A. F.; Chong, J. M.; Park, S. B. *Tetrahedron Lett.* **1993**, *34*, 51; (b) Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5763.

2. 2,3-Sigmatropic rearrangement: (a) Coldham, I. *J. Chem. Soc., Perkin Trans. I* **1993**, 1275; (b) Gawley, R. E.; Zhang, Q.; Campagna, S. *J. Am. Chem. Soc.* **1995**, *117*, 11 817.
3. Anionic cyclizations: (a) Coldham, I.; Fernández, J.-C.; Snowden, D. J. *Tetrahedron Lett.* **1999**, *40*, 1819; (b) Coldham, I.; Hufton, R. *Tetrahedron* **1996**, *52*, 12541.
4. Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231.
5. Boeckman, R. K.; Potenza, J. C. *Tetrahedron Lett.* **1985**, *26*, 1411.
6. Coldham, I.; Hufton, R.; Snowden, D. J. *J. Am. Chem. Soc.* **1996**, *118*, 5322.
7. To a stirred solution of stannane **1** (250 mg, 0.54 mmol) in CH₂Cl₂ (5 mL) was added *B*-bromo-catecholborane (2.2 mL, 0.3 M in CH₂Cl₂). After 10 min at 22°C, the solution was washed rapidly with NaOH_(aq) (2 M, 3×5 mL), dried over MgSO₄ and concentrated in vacuo. Nitromethane (2.5 mL), 4 Å molecular sieves, NaBH₃CN (126 mg, 2.0 mmol) and 4-pentenal (92 mg, 1.1 mmol) were added and after 15 min the reaction was absorbed onto basic alumina. Chromatography (basic alumina, 10% EtOAc/pet.) gave the stannane **4d** (143 mg, 0.33 mmol, 62%) as an oil.
8. For example, the two-step route (Scheme 1) gave the stannanes **4b** and **4d**, [α]_D²⁰ +73.7 (*c* 1.2, CHCl₃) and [α]_D²⁰ +67.5 (*c* 1.2, CHCl₃), respectively.