Available online at www.sciencedirect.com
SCIENCE DIRECT®
Tetrahedron Letters 45 (2004) 1759–1761
Tetrahedron Letters

Nucleophilic synthesis of enantiopure 2-(tributylstannyl)pyrrolidines and piperidines ☆

Robert E. Gawley,[a,b,*] Graciela Barolli,[a] Sachin Madan,[b] Michele Saverin[a] and Sean O'Connor[a]

[a]*Department of Chemistry, University of Miami, Coral Gables, FL 33124, USA*
[b]*Department of Chemistry and Biochemistry, University of Arkansas, Fayetteville, AR 72701, USA*

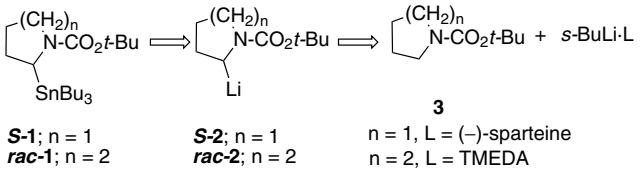
Received 25 November 2003; revised 11 December 2003; accepted 12 December 2003

Abstract—*trans*-Cumylcyclohexanol (TCC) is used as a chiral auxiliary for the stereoselective addition of tributyltinlithium to *N*-acylpyrrolidinium/piperidinium ion with 70–80% diastereoselectivity at 0 °C. After removal of the minor diastereomer by radial chromatography, enantiopure *N*-methyl-2-(tributylstannyl)pyrrolidine and piperidine were produced by reductive removal of the auxiliary.

Stannylpyrrolidines have become important tools for asymmetric synthesis, primarily via tin–lithium exchange, and sometimes tandem transmetalations such as Sn → Li → Cu or Pd.[1] Tin–lithium exchange[2] is the most common method to generate an unstabilized α-aminoorganolithium. For example, scalemic 2-(tributylstannyl)pyrrolidines are precursors of unstabilized α-aminoorganolithiums that have been used for enantioselective alkylation, anionic cyclizations, and sigmatropic rearrangements.[1] On the other hand, scalemic stannylpiperidines have not enjoyed similar success because of the difficulty in making them.[3]

Following earlier work from the Hoppe group in α-alkoxy systems,[4] Kerrick and Beak made the important discovery that the *s*-BuLi·sparteine complex enantioselectively deprotonated *N*-Boc pyrrolidine **3** (Eq. 1), and that the resultant organolithium *S*-**2** could be stannylated to afford *S*-**1** in up to 97:3 enantiomer ratio (er).[5] Subsequently, we showed that reduction of the *N*-Boc to a methyl gave a precursor to α-aminoorganolithium compounds that possess exceptional configurational stability, and exhibit broadened reactivity with electrophiles when compared to the lithiated *N*-Boc heterocycles.[3,6]

A significant bottleneck to further development and implementation of 2-(stannyl)pyrrolidines in asymmetric synthesis is the dearth of methods for synthesis. *To date, only deprotonation/stannylation routes have been reported for the preparation of these compounds*. Asymmetric deprotonation is the only route to enantioenriched 2-(metalated)pyrrolidines (maximum er = 97:3), but this route fails with piperidines![7] So far, (−)-sparteine is the only commercially available chiral ligand suitable for this reaction, although (+)-sparteine can be made by total synthesis,[8] and O'Brien has reported a (+)-sparteine surrogate that selectively produces *R*-**2** in a similar deprotonation.[9] Deprotonation and stannylation of piperidines equipped with a chiral oxazoline auxiliary affords a 50:50 dr; separation of diastereomers is tedious, and removal of the auxiliary requires two steps.[3,6]



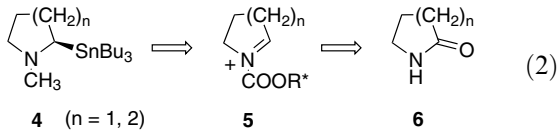
(1)

We asked whether it would be possible to generate 2-(tributylstannyl) heterocycles, **4**, from lactams by

Keywords: (Stannanyl)pyrrolidines; TCC; *N*-Acyliminium ion; Asymmetric synthesis.
☆ Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2003.12.080
* Corresponding author. Tel.: +1-479-575-6933; fax: +1-479-575-5178; e-mail: bgawley@uark.edu

0040-4039/$ - see front matter © 2003 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2003.12.080

nucleophilic addition of tributylstannyllithium to chiral *N*-acyliminium ion **5** (Eq. 2). Herein, we report a method for the synthesis of enantiopure (*S*) or (*R*) *N*-methyl-2-(tributylstannyl)pyrrolidines and piperidines from lactams **6**.



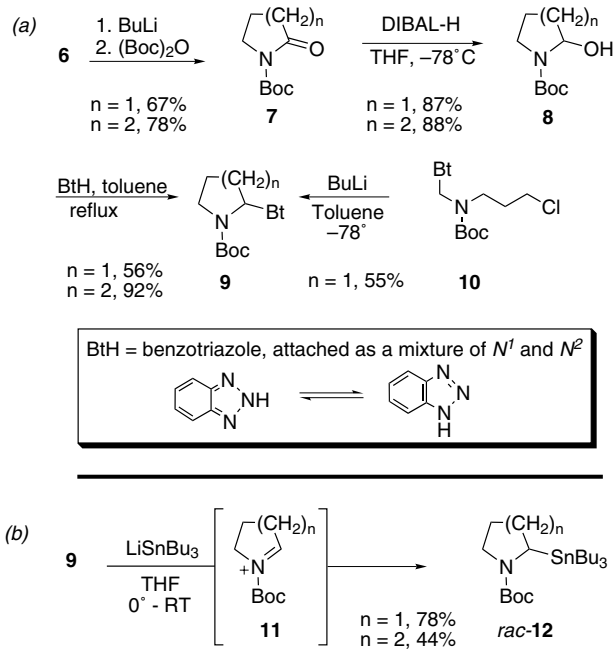
4 (n = 1, 2) **5** **6** (2)

Initial viability of the plan was explored using *N*-Boc lactams **7**, as shown in Scheme 1a. Deprotonation of lactam **6** with butyllithium and N-acylation with Boc anhydride afforded *N*-Boc lactams **7** in 67% yield for the pyrrolidinone and 73% for the piperidinone after distillation. DIBAL-H reduction to aminal **8**, followed by treatment with benzotriazole gave benzotriazolyl heterocycles **9** in excellent overall yield after recrystallization. We investigated several leaving groups to generate the *N*-acyl iminium ion, but found the benzotriazole methodology of Katritzky and Pearson, reported some years ago, to be the most efficient.[10,11] Boc benzotriazole **9** is also available in 55% yield by deprotonation and cyclization of **10**.[11] Treatment of benzotriazole **9** with tributyltin lithium afforded *N*-Boc stannylpyrrolidine **12** in 40–50% yield, via *N*-acyliminium ion **11**, as shown in Scheme 1b.

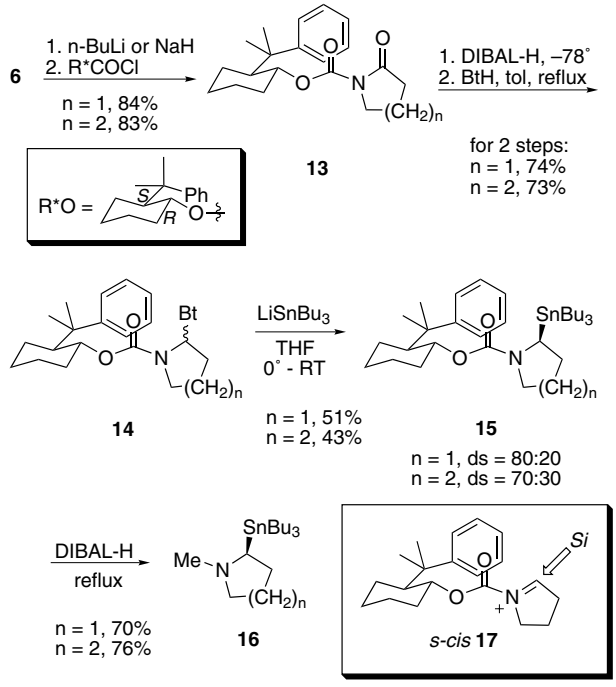
Having established the viability of a nucleophilic synthesis of racemic stannyl heterocycles **12**, we sought to render the process enantioselective through the use of a carbamate chiral auxiliary in place of the Boc group. A menthol-based auxiliary afforded neither selectivity in the addition nor separability of diastereomers, so we turned to *trans*-cumylcyclohexanol (TCC), extensively developed by Comins for nucleophilic additions to *N*-acylpyridiniums.[12] As shown in Scheme 2, acylation of lactams **6** with 1*S*,2*R* TCC chloroformate afforded urethanes **13** in excellent yield. The procedure has been carried through with the 1*R*,2*S* enantiomer as well. DIBAL-H reduction at −78 °C and treatment with benzotriazole afforded **14**, as a mixture of constitutional and stereoisomers, in 73–74% overall yield. Treatment with tributyltinlithium then gave 2-(tributylstannyl)pyrrolidine carbamate **15** in 80–85% ds and moderate yield. Stannyl heterocycles **15** are available as a single diastereomer by radial or short column chromatography.

The absolute configuration of the carbon bearing the tin was established by reduction to the versatile reagent (*S*)-*N*-methyl-2-(tributylstannyl)pyrrolidine and piperidine **16** in good yield after column chromatography, and comparison to an authentic sample.[3] The steric course of the reaction appears to involve preferential addition to the *Si* face of iminium ion **17** (Scheme 2, inset). It is likely that the reason for the modest selectivity is the presence in solution of the *s-cis* iminium ion shown, as well as the *s-trans* conformer.

In summary, we have demonstrated a nucleophilic, asymmetric synthesis of *N*-methyl-2-(tributylstannyl)pyrrolidine and -piperidine, via a chiral *N*-acyliminium ion generated from a lactam. The method affords either enantiomer in higher enantiomeric purity than is possible by asymmetric deprotonation (for the pyrrolidines), and that is not available at all by asymmetric deprotonation of Boc-piperidine (Fig. 1). The availability of racemic or enantiopure 2-(tributylstannyl)pyrrolidines from lactams and acyclic amines expands the applicability of α-aminoorganolithium



Scheme 1.



Scheme 2.

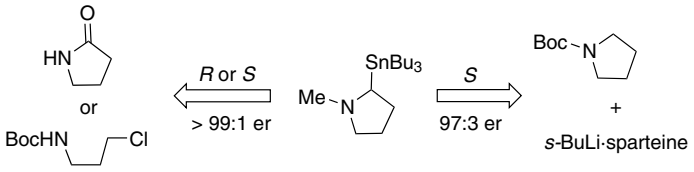


Figure 1.

chemistry to synthetic plans not amenable to a deprotonation strategy.

Supplementary data. Experimental details, NMR spectra, and SFC chromatograms of crude and pure diastereomers **15**, are available online with the paper in ScienceDirect.

Acknowledgements

This work was supported by the National Institutes of Health (GM 56271), and by core facilities funded by NSF (CHE 0077679 at UM), NIH (P20 R15569 at UA), and the Arkansas Biosciences Institute.

References and notes

1. Review: Gawley, R. E.; Coldham, I. In *The Chemistry of Organolithium Compounds (Patai Series)*; Rappoport, Z., Marek, I., Eds.; Wiley: Chichester, 2003.
2. (a) Peterson, D. J.; Ward, J. F. *J. Organomet. Chem.* **1974**, *66*, 209–217; (b) Peterson, D. J. *J. Organomet. Chem.* **1970**, *21*, 63–64; (c) Peterson, D. J. *J. Am. Chem. Soc.* **1971**, *93*, 4027–4031.
3. Gawley, R. E.; Zhang, Q. *J. Org. Chem.* **1995**, *60*, 5763–5769.
4. Hoppe, D.; Hintze, F.; Tebben, P. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 1422–1423.
5. (a) Kerrick, S. T.; Beak, P. *J. Am. Chem. Soc.* **1991**, *113*, 9708–9710; (b) Beak, P.; Kerrick, S. T.; Wu, S.; Chu, J. *J. Am. Chem. Soc.* **1994**, *116*, 3231–3239.
6. (a) Gawley, R. E.; Zhang, Q. *J. Am. Chem. Soc.* **1993**, *115*, 7515–7516; (b) Gawley, R. E.; Zhang, Q. *Tetrahedron* **1994**, *50*, 6077–6088.
7. Bailey, W. F.; Beak, P.; Kerrick, S. T.; Ma, S.; Wiberg, K. B. *J. Am. Chem. Soc.* **2002**, *124*, 1889–1896.
8. Smith, B. T.; Wendt, J. A.; Aubé, J. *Org. Lett.* **2002**, *4*, 2577–2579.
9. Dearden, M. J.; Firkin, C. R.; Hermet, J.-P. R.; O'Brien, P. *J. Am. Chem. Soc.* **2002**, *124*, 11870–11871.
10. (a) Katritzky, A. R.; Chang, H.-X.; Wu, J. *Synthesis* **1994**, 907–908; (b) Pearson, W. H.; Stevens, E. P. *Synthesis* **1994**, 904–906.
11. Katritzky, A. R.; Luo, Z.; Fang, Y. *Tetrahedron Lett.* **2000**, *41*, 9691–9693.
12. Comins, D. L. *J. Heterocycl. Chem.* **1999**, *36*, 1491–1500.