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Asymmetric Synthesis of 3-Hydroxy-pyrrolidines via Tin–Lithium Exchange and Cyclization

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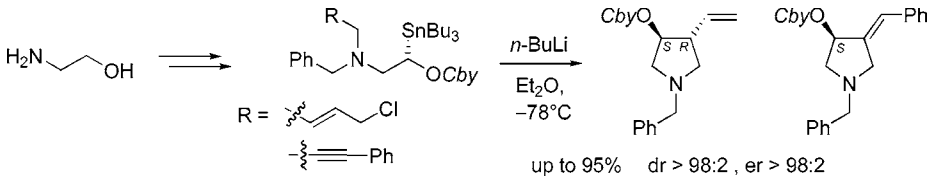
ABSTRACT



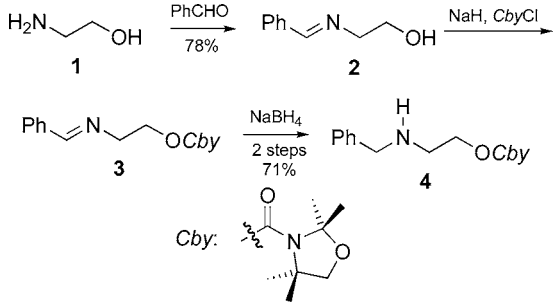
We report a method for the synthesis of chiral pyrrolidines using tin–lithium exchange and cyclization reactions. The precursors are formed readily from simple starting materials and undergo tin–lithium exchange by treatment with *n*-butyllithium. Subsequent intramolecular carbolithiation is stereoselective to give highly enantiomerically enriched pyrrolidines in excellent yields.

The synthesis of chiral pyrrolidines has attracted much interest in the past few years due to the presence of this ring system in natural products[1] and as chiral ligands and promotors in organocatalysis.[2]

Recently, we reported a powerful route to 2-substituted cyclopentanols via tin−lithium exchange and intramolecular cycloalkylation.[3] This type of cyclization makes use of chiral α-lithio carbamates and has also served well in the synthesis of vinylpyrrolidines.[4] We report herein a further extension of this methodology to form enantiomerically enriched 3-hydroxy-pyrrolidines.

We planned to prepare the desired enantioenriched α-lithio carbamate using a *s*-butyllithium/(−)-sparteine-mediated deprotonation of the alkyl carbamate **4** (Schemes 1 and 2).[5] Subsequent substitution with tributyltin chloride would give the highly enantioenriched stannane **7** as a stable carbanion equivalent.[6] The cyclization precursors would then be obtained from **7** by simple N-alkylation.

Scheme 1. Synthesis of Alkyl Carbamate **4**



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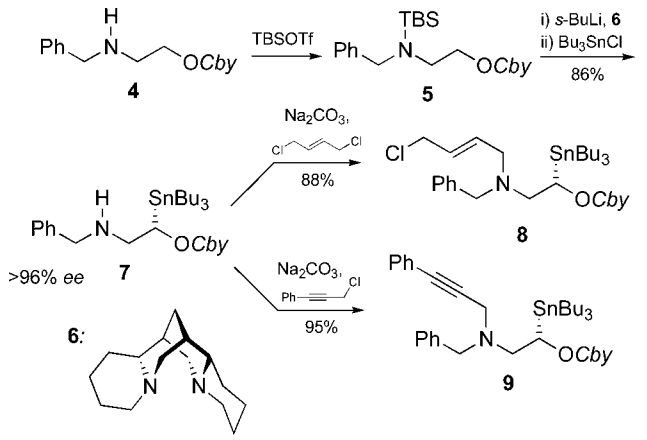
The chemistry proceeded smoothly, and the cyclization precursors were obtained readily by standard transformations. Imine formation of 2-amino-ethanol (**1**) with benzaldehyde, carbamoylation with CbyCl, and subsequent sodium borohydride reduction gave the alkyl carbamate **4** in 55% overall yield (Scheme 1).

Scheme 2. Synthesis of Cyclization Precursors **8** and **9**

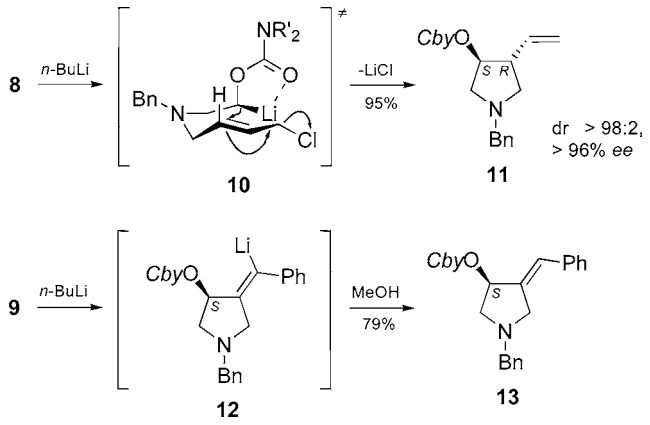


It was found necessary to protect the nitrogen atom of the secondary amino function of **4** prior to introduction of the tin group. After trying various possibilities, we found that *N*-silyl protection[7] with *tert*-butyldimethylsilyl triflate (TBSOTf) and NEt_3 gave the precursor **5** (Scheme 2) which underwent successful enantioselective *s*-butyllithium/(−)-sparteine (**6**) mediated deprotonation. Although hydrolytically labile, the N−Si bond of **5** survived short aqueous workup. Trapping with tributyltin chloride after deprotonation afforded the enantiopure stannane (*S*)-**7** in 86% yield. The enantiomeric ratio of stannane **7** was determined to be greater than 98:2 by chiral HPLC of the methyl carbamate derivative, obtained by treatment of **7** with methyl chloroformate. The absolute configuration of **7** is assigned as (*S*) on the basis of the known stereoselectivity preference for such stannylation reactions with related *O*-alkyl carbamates.[5]

With the enantioenriched stannane **7** in hand, we were then able to convert this into suitable cyclization precursors. The compounds **8** and **9** were chosen and could be formed readily from **7** by alkylations of the secondary amino function (Scheme 2).

Treatment of stannane **8** with *n*-butyllithium led to the five-membered heterocycle **11** (Scheme 3). The tin−lithium

Scheme 3. Cyclization to Pyrrolidines **11** and **13**



exchange was rapid, and subsequent 5-exo-*trig* cycloalkylation was stereoselective.[8] The trans-configured pyrrolidine (3*S*,4*R*)-**11** was isolated in enantio- and diastereomerically pure form in essentially quantitative yield.[9]

When the substrate **9** was treated with *n*-butyllithium, a 5-exo-*dig* intramolecular carbolithiation of the intermediate α-lithio carbamate with the alkyne moiety was achieved.[10] Protonation of the lithiated intermediate **12** with methanol yielded the 3-benzylidene-pyrrolidine **13** as a single diastereomer. The (*E*)-configuration of the double bond is the result of a *syn* addition onto the triple bond. The *cis* position of the phenyl group and the 5-methylene group is supported by the strong downfield shift by 1 ppm of one of the diastereotopic protons.

The enantiomeric excess of the pyrrolidine (2*S*,3*R*)-**11** was determined by derivatization into the corresponding (*R*)-Mosher ester **15** (Scheme 4). Following established protocols, the Cby group was removed to give the enantiomerically pure alcohol **14** in 84% yield. The Mosher ester **15** was obtained by acylation of the alcohol **14** with (*R*)-2-methoxy-2-phenyl-3,3,3-trifluoropropanoyl chloride in pyridine.[11]

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(9) **Representative Cyclization Procedure.** A solution of the allyl chloride **8** (114 mg, 0.17 mmol) in dry Et_2O (3 mL) under an atmosphere of argon in a flame-dried flask, sealed with a rubber septum, was cooled to −78 °C. *n*-Butyllithium (0.10 mL, 0.25 mmol, 1.5 equiv; 2.5 M in hexanes) was added dropwise, and the mixture was stirred for 2 h. After quenching with MeOH (0.2 mL) and H_2O (0.1 mL) at −78 °C, the mixture was allowed to warm to room temperature, dried (Na_2SO_4), filtered, and concentrated in vacuo. Flash chromatography (silica gel, Et_2O/petroleum ether = 1:4 to 1:1) afforded the product **11** as a colorless oil (57 mg, 0.16 mmol, 95%; $[\alpha]_D^{20} = -39.0$ ($c = 1.18$, $CHCl_3$)).

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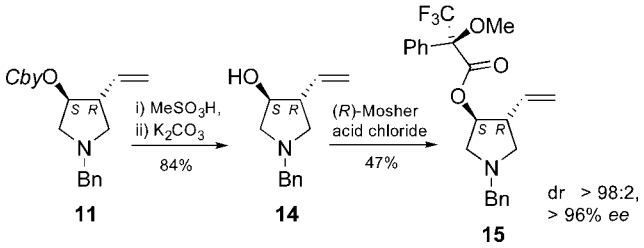
Scheme 4. Structure Elucidation of Cyclization Product **11**



The diastereomeric ratio of the pyrrolidine **15** was determined by ^{19}F NMR spectroscopy to be higher than 98:2, consequently leading to an enantiomeric excess of higher than 96% ee. The trans configuration of **11** was determined by NOE spectroscopic experiments. On the basis of literature precedent, the tin−lithium exchange and subsequent cyclization are assumed to occur with retention of configuration at the carbanion center.[1−5,8]

The enantiomeric excess of pyrrolidine **13** could not be determined. However, it is expected that the product **13** would have been formed with high enantioselectivity because the precursor **7** is highly enantioenriched and there is high selectivity in the formation of the product **11**. The product **13** was found to have a significant value for its specific rotation, $[\alpha]_D^{20} = -25.4$ ($c = 0.41$, CH_2Cl_2).

In summary, we have demonstrated that *s*-butyllithium/(−)-sparteine (**6**) can be used to prepare the enantioenriched stannane **7** by stereoselective deprotonation of a *N*-silyl-protected *β*-aminoalkyl carbamate. This compound acts as a stable carbanion equivalent. Tin−lithium exchange and intramolecular cyclization lead to the formation of enantiomerically and diastereomerically pure 3-hydroxy-pyrrolidines. The enantiomerically pure compound **7** may serve as a versatile key intermediate for the synthesis of further hydroxy-pyrrolidines or other chiral amines.

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Supporting Information Available: Additional descriptions and characterizations and spectroscopic data of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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