N-Boc-2-stannyloxazolidines Derived from (*R*)-Phenylglycinol: Preparation, Transmetalation, and Use as Precursors of Enantioenriched (α-Aminoalkyl)triorganostannanes

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Summary: Upon transmetalation with n-butyllithium (THF, −78 °C, 30 min), 2-(triorganostannyl)oxazolidines afforded the corresponding 2-lithiooxazolidine species, which were proved to be configurationally stable under these experimental conditions. When 2-(triorganostannyl)oxazolidines were involved in reactions with organocuprates promoted by boron trifluoride, the oxazolidine ring was opened to give stereoselectively the enantioenriched N-Boc (α-aminoalkyl)triorganostannanes whose absolute configuration of the major isomer was determined by an X-ray analysis.

Enantioenriched (α-aminoalkyl)triorganostannanes are compounds of great interest because of their potential ability to give enantioenriched chiral α-aminoalkyl anions, whose synthetic potential has been recently reviewed.[1] Indeed, in achiral series, the transmetalation of (α-aminomethyl)- or (α-aminobenzyl)tributylstannanes with *n*-butyllithium has been proved to be possible[2−5] as well as cross-coupling with acyl halides.[6] Subsequently, transfer of chiral α-aminoalkyl units via (aminoalkyl)lithium reagents was described, making these organostannane precursors promising tools for the enantioselective synthesis of compounds of biological interest such as *β*-amino alcohols,[7−9] α-amino ketones,[10] and unusual α-amino acids[11,12] by trapping the organolithium species with appropriate electrophiles.

Enantioenriched (α-aminoalkyl)stannanes were initially obtained from chiral carbamates or ureas by reaction of (α-iodoethyl)tributylstannane with the N−H function of the above-mentioned derivatives followed by separation of diastereomers[13] or by substitution of the *N*-alkylsulfonyl derivatives with stannyl anions.[14] Simultaneously, an enantioselective synthesis involving the BINAL-H reduction of acylstannanes and further transformation of the α-stannyl alcohol through a Mitsunobu reaction was reported.[7,11]

Although efficient, these methods can be challenged by the metalation of *N*-protected piperidines or pyrrolidines (deprotonation by *s*-butyllithium or isopropyllithium). The asymmetric induction can be brought about by the protective group (for instance, the chiral 2-oxazolinyl group)[15,16] or by carrying out the metalation reaction of the *N*-Boc derivatives in the presence of the commercially available (−)-sparteine.[17−21] This last route appears to be more attractive in terms of workup but is practically limited to the synthesis of one enantiomer, due to the poor availability of (+)-sparteine.[22,23] In addition, this route suffers from strong limitations, both in reactivity and in enantioselectivity for the piperidine series.[24] Synthesis of both enantiomers by this way usually requires appropriate transmetalation/trapping sequences[25] or use of the recently described (+)-sparteine surrogate derived from (−)-cytisine.[26] However, even though they are useful for synthesis, such approaches reflect the configurational stability of

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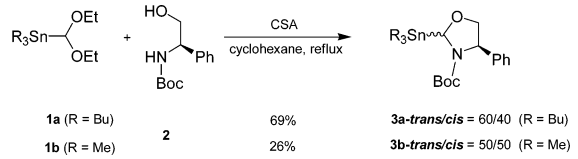
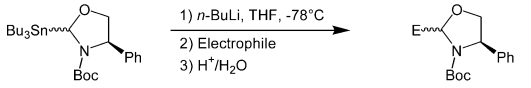
Scheme 1. Preparation of *N*-Boc-2-(triorganostannyl)oxazolidines



1a (R = Bu) 69% **3a-*trans*/*cis*** = 60/40 (R = Bu)
2
1b (R = Me) 26% **3b-*trans*/*cis*** = 50/50 (R = Me)

Scheme 2. Transmetalation of *N*-Boc-2-(tributylstannyl)oxazolidines



3a-*trans*	**3b-*trans*** (E = Me_3Sn)	58%
3a-*cis*	**3b-*cis*** (E = Me_3Sn)	58%
3a-*trans*	**3c-*trans*** (E = Ph_3Sn)	83%
3a-*cis*	**3c-*cis*** (E = Ph_3Sn)	67%
3a-*trans*	**3d-*trans*** (E = *c*-C_6H_{10}(OH))	69%
3a-*cis*	**3d-*cis*** (E = *c*-C_6H_{10}(OH))	75%

the organolithium reagent−diamine complex and not the intrinsic stability of the α-aminoalkyl reagent.

In this context, it seems of great interest to extend the Lewis acid promoted opening of chiral α-stannylacetals by nucleophiles[27−29] to the chiral 2-stannyloxazolidine series, since these compounds can be readily obtained under mild experimental conditions. For instance, the norephedrine- and camphor-derived *N*-Boc-2-stannyloxazolidines have been prepared by Colombo and used as chiral formyl anion equivalents.[30−32] We extended this method to the synthesis of *N*-Boc-2-stannyloxazolidines derived from commercially available (*R*)-phenylglycinol through transacetalization of the readily available (diethoxymethyl)triorganostannanes (Scheme 1)[33−36] (cf. the Supporting Information).

This reaction affords two diastereomers, defined as *trans* and *cis*, depending on the relative positions of the Ph and the R_3Sn moieties on the cycle. After separation by liquid chromatography on silica gel (eluent 95/5 hexanes/AcOEt) the diastereomers **3a-*trans*** and **3a-*cis*** were fully characterized for the first time by multinuclear NMR, MS, elemental analysis, and $[\alpha]_D^{20}$ values. These two diastereomers were separately submitted to transmetalation by *n*-butyllithium (1.6 M in hexanes) at −78 °C in THF over 30 min before trapping with a solution of trimethyltin or triphenyltin chloride, added dropwise at −78 °C (Scheme 2). The expected 2-(triorganostannyl)oxazolidines were obtained with a complete retention of the configuration, as attested by NMR analysis (cf. the Supporting Information).[37,38]

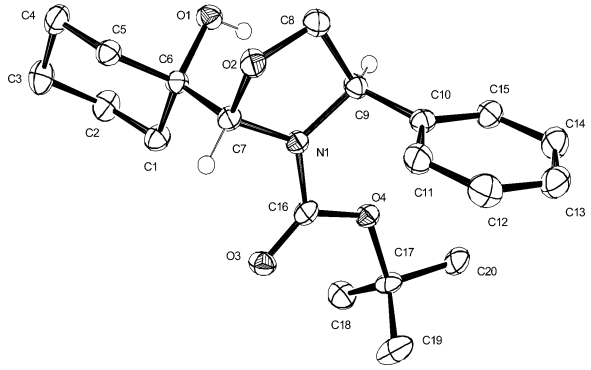


Figure 1. ORTEP view of **3d-*trans*** with thermal ellipsoids drawn at the 50% probability level.

This result demonstrates that 2-lithio-*N*-Boc-oxazolidines derived from (*R*)-phenylglycinol are configurationally stable at −78 °C in THF, at least for 30 min (in the limits of the NMR detection), and allows an improved preparation of **3b** in comparison to the transacetalization reaction. It is also worth noting that these 2-lithiooxazolidines can also be trapped by other electrophiles such as cyclohexanone with retention of their configuration (75% yield in **3d-*cis*** with *cis*-lithiooxazolidine and 69% yield in **3d-*trans*** with *trans*-lithiooxazolidine). In each case the adducts **3d-*cis*** and **3d-*trans*** were unambiguously identified on the basis of their NMR spectra using appropriate sequences (cf. the Supporting Information). Furthermore, the X-ray structure of **3d-*trans*** (mp 160 °C) confirms the NMR determination (Figure 1 and the Supporting Information).

Not surprisingly, on the basis of previous reports involving norephedrine- and camphor-derived *cis*-2-lithiooxazolidines,[30−32] the present series of transmetalation/electrophilic trapping sequences demonstrates unambiguously for the first time, through the use of *both diastereomers*, the configurational stability of these anionic species.

The second point of interest of this contribution is the access to (α-aminoalkyl)triorganostannanes by using reagents able to prevent transmetalation reactions. For instance, when Me_2CuLi was allowed to react with pure **3a-*cis*** or with pure **3a-*trans*** in the presence of $BF_3{\cdot}Et_2O$, the same diastereomeric mixture of alcohols was obtained, **4a**/**5a** = 84/16, and obviously the reaction behaves similarly when the thermodynamic mixture of *cis*- and *trans*-2-(tributylstannyl)oxazolidines was used (Scheme 3). Under the same experimental conditions, similar results were obtained with **3b** (*cis* + *trans*) but not with **3c** (R_3Sn = Ph_3Sn). This lack of reactivity of **3c** with Me_2CuLi in the presence of $BF_3{\cdot}Et_2O$ might be explained by the steric hindrance caused by the phenyl groups around tin.

At this point, it was important to assign the configuration of the obtained diastereomers. For this purpose, the transformation of **4a** and **5a** into crystallized dini-

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(37) The assignment of the *cis* or *trans* configuration of the 2-stannyloxazolidines was firmly established on the basis of nOe experiments and Karplus type relationships for ^3J(HH) and ^3J(SnC). The nOe effect might give ambiguous results, but the use of ^3J(Sn−C−N−C) and ^3J(Sn−C−O−C) allows a determination of the shape of the ring and further measurement of ^3J(H−C−C−H) is indicative of the slight torsion arising in the ring, giving unambiguous assignment when combined with nOe experiments. NMR data are reported in the Supporting Information.

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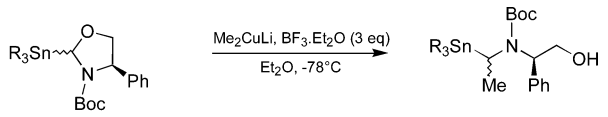
Scheme 3. Ring Opening of *N*-Boc-2-(triorganostannyl)oxazolidines



R = Bu : ***3a*** (*cis* or *trans*)	69%	**4a**/**5a** = 84/16
R = Me : ***3b*** (*cis* or *trans*)	47%	**4b**/**5b** = 55/45

trobenzoate derivatives failed (the obtained products remaining oily compounds). However, after separation of the trimethylstannyl derivatives **4b** and **5b**, colorless crystals of the major component **4b** were obtained without any derivatization (mp 64 °C). The molecular structure of **4b** was obtained by an X-ray analysis, and its *S* configuration at the new stereogenic center was unambiguously determined both on the basis of the relative configuration of the two stereogenic centers and also in terms of absolute configuration, on the basis of a value of 0.1(2) for the Flack parameter[39] (Figure 2 and the Supporting Information).

To our knowledge, this structural analysis demonstrates for the first time on the basis of a crystal structure the occurrence of a chelation between the tin center and the carbonyl group of the carbamate in a *N*-Boc-(α-aminoalkyl)triorganostannane. The value of the Sn−O1 bond length (2.99 Å instead of 3.51 Å for a simple van der Waals contact) and those of the angles around tin show a distorted-trigonal-bipyramidal environment around tin. In addition, compound **4b** was shown to be homologous with **4a** on the basis of the NMR spectra and the $[\alpha]_D^{19}$ values.[40]

On the basis of previously published results in closely related series, compounds **4** and **5** should be valuable precursors to examine the configurational stability of α-amino carbanions.[9,41−45] The interest of these enantioenriched chiral α-aminoorganostannanes was recently underlined by two contributions reporting new preparations: one is based on a S_N2 displacement of an α-stannyl mesylate by an appropriate amide salt,[46] and the second one involves the addition of (tributylstannyl)-lithium to chiral *tert*-butanesulfinimines.[47]

Conclusion. The preparation of *N*-Boc-2-stannyloxazolidines such as **3a-*cis*** and **3a-*trans*** and further transmetalation with *n*-butyllithium demonstrate the configurational stability of the *N*-Boc-2-lithiooxazolidines at −78 °C in THF for at least 30 min. Furthermore, these 2-(triorganostannyl)oxazolidines allow a possible access to enantioenriched (α-aminoalkyl)triorganostannanes, which can be considered as storable

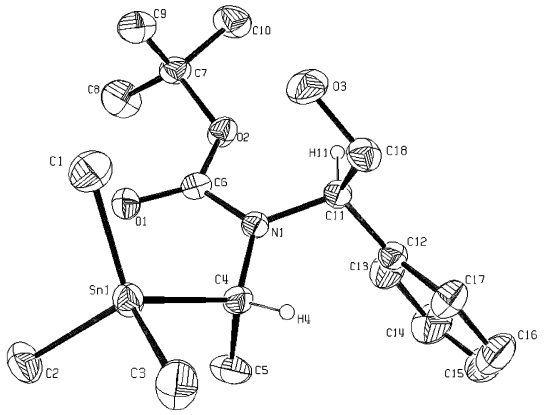


Figure 2. ORTEP view of compound **4b** with thermal ellipsoids drawn at the 30% probability level (except for chiral centers, hydrogens were omitted for clarity). Selected bond lengths (Å): Sn(1)−C(1) = 2.142(5), Sn(1)−C(4) = 2.172(4), O(1)−C(6) = 1.241(4), N(1)−C(6) = 1.344(5), N(1)−C(4) = 1.471(5), N(1)−C(11) = 1.481(5), Sn(1)−O(1) = 2.99. Selected angles (deg): C(1)−Sn(1)−C(2) = 111.6-(2), C(1)−Sn(1)−C(3) = 110.0(2), C(1)−Sn(1)−C(4) = 114.53-(19), C(3)−Sn(1)−C(4) = 99.55(18), C(6)−N(1)−C(4) = 119.3(3), N(1)−C(4)−Sn(1) = 116.7(3), O(1)−C(6)−N(1) = 123.4(3), Sn(1)−O(1)−C(6) = 98.52, O(1)−Sn(1)−C(1) = 77.47, O(1)−Sn(1)−C(2) = 82.12, O(1)−Sn(1)−C(3) = 161.59, O(1)−Sn(1)−C(4) = 62.32.

potential α-amino anion equivalents. For the last transformation, the stereoselectivity should be improved in order to avoid the separation of diastereomers **4** and **5**. For instance, the use of another soft nucleophile/Lewis acid pair and/or the use of another protective group on nitrogen might bring such improvements, as suggested by preliminary experiments involving reaction of an *N*-Tos analogue of **3a-*trans*** with $Me_2CuLi/BF_3{\cdot}Et_2O$ (dr > 95/5; over 75% yield).

A comprehensive study of the mechanisms involved both in the preparation and in the stereochemical aspects of the Lewis acid promoted opening of 2-stannyloxazolidines by soft nucleophiles will be reported in due course.

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Supporting Information Available: Text giving experimental details relative to the preparation of *N*-Boc-2-(tributylstannyl)oxazolidines, the transmetalation of *N*-Boc-2-(tributylstannyl)oxazolidines, the reaction of *N*-Boc-2-(triorganostannyl)oxazolidines with Me_2CuLi in the presence of $BF_3{\cdot}Et_2O$ and X-ray analysis data (excluding atomic coordinates, bond distances, bond angles, and anisotropic displacement parameters). This material is available free of charge via the Internet at http://pubs.acs.org. Further details concerning crystallographic data of the structures have been deposited with the Cambridge Crystallographic Data Center as Supplementary Publication Nos. CCDC 221824 for **3d-*trans*** and CCDC 183110 for **4b**. Copies of the data can be obtained, free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, U.K. (fax, +44(0)-1223-336033; e-mail, deposit@ccdc.cam.ac.uk).

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