Enantiomerically Enriched *t*-BOC-Protected α-Aminoorganolithiums: Preparation and Configurational Stability

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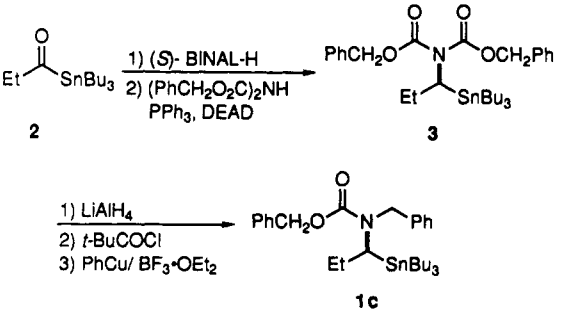
Summary: Enantiomerically enriched *t*-BOC-protected α-aminoorganolithiums, generated by Sn–Li exchange, are configurationally stable at −95 °C and may be trapped with complete retention of configuration.

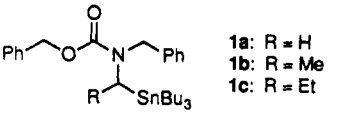
α-Aminoorganolithiums are synthetically useful reagents.[1] Most commonly, they have been generated by deprotonation of suitably activated amine derivatives.[2-7] They have also been generated by Sn–Li exchange.[8-10] Enantiomerically enriched α-aminoorganostannanes could be useful for the preparation of chiral, nonracemic amines (such as β-amino alcohols and α-amino acids). However, useful methods for asymmetric synthesis based on α-aminoorganostannanes will be dependent upon (a) reasonable preparations of such compounds in high enantiomeric excess, (b) retention of configuration upon transmetalation, (c) the configurational stability of the organolithiums formed, and (d) retention of configuration upon electrophilic quench. It is known that *α-alkoxy*-organostannanes undergo Sn–Li exchange to generate organolithiums that (a) are configurationally stable at low temperature and (b) react with electrophiles with complete retention of configuration.[11,12] Enantiomerically enriched α-alkoxyorganostannanes have been shown to be useful for the preparation of a variety of optically active alcohol derivatives.[13] Unfortunately, very little is known about Sn–Li exchange in, and the configurational integrity of organolithiums derived from, α-aminoorganostannanes.[9]

The question of configurational stability of α-aminoorganolithiums is particularly interesting. The configurational stabilities of other α-heteroatom-stabilized carbanions have been studied.[14] Chiral, nonracemic nonconjugated[15] α-aminocarbanions have been described but each case has been biased by conformational constraints[4a,4b] or small-ring strain.[16,17] For example, Pearson has very recently described chiral, nonracemic acyclic nitrogen-substituted carbanions where the nitrogen is part of a cyclic urea or oxazolidinone.[9b] Diastereomeric carbanions were formed, and it was shown that the less stable diastereomer rapidly epimerized (within 40 min at −78 °C) while the more stable diastereomer did not isomerize. Hence, it seems that the configurational stability (or lability) of these carbanions is dramatically influenced by the relative stabilities of diastereomers. We now report the first examples of enantiomerically enriched acyclic α-nitrogen-stabilized carbanions *free of diastereomeric biases* and the first experimental evidence for the extent of their configurational stability.

Scheme I



It has recently been shown that (racemic) carbamates **1a** and **1b** readily undergo tin–lithium exchange and that the resulting organolithiums may be trapped with electrophiles in good yields; the benzyl groups may be removed by hydrogenolysis, and thus the carbamatostannanes are useful synthetic equivalents of primary α-amino anions.[9a]



1a: R = H
1b: R = Me
1c: R = Et

Since enantiomerically enriched α-hydroxystannanes are readily available by asymmetric reduction of acylstannanes[18] or via enzymic esterification,[13d] the former

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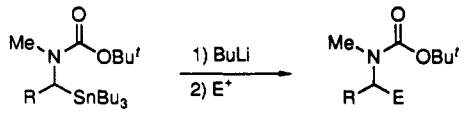
Table I. Transmetalation/Trapping Reactions of *N*-Methyl-*t*-BOC Carbamates 9



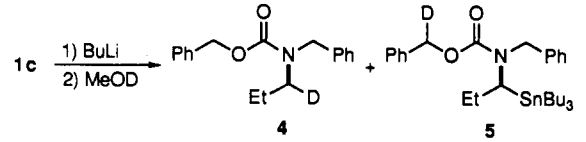
9a-d

entry	stannane	R	E$^+$	yield[a] (%)
1	**9a**	Et	CO_2	97
2			PhCHO	92[b]
3			$PhCH_2Br$	45
4	**9b**	*i*-Pr	CO_2	89
5	**9c**	*n*-C_5H_{11}	CO_2	95
6			cyclohexanone	84[c]
7	**9d**	c-C_6H_{11}	CO_2	92
8			CH_3CH_2CHO	91[b]

[a] Isolated yields. [b] Isolated as a ~1:1 mixture of diastereomers. [c] Protonated material (E = H, 10% yield) was also isolated.

compounds were attractive precursors to enantiomerically enriched carbamates **1**. Carbamate (*S*)-**1c** (~90% ee) was readily prepared from acylstannane **2** (Scheme I). Reduction of **2** followed by treatment of the resulting alcohol with dibenzyl iminodicarbonate[19] under Mitsunobu conditions[20] afforded iminodicarbonate **3**. Selective monoreduction followed by conversion of the *N*-(hydroxmethyl)carbamate to a pivalate and treatment of the pivalate with $PhCu/BF_3{\cdot}OEt_2$[21] furnished carbamate **1c**.

When **1c** was subjected to typical transmetalation/carboxylation conditions (1 equiv of *n*-BuLi, THF, −78 °C then CO_2) the expected acid was isolated in only ~40% yield. This result was rather unexpected since **1a** and **1b** had been reported to undergo transmetalation/electrophilic trapping in good yields.[9a] A comparative experiment with **1b** gave an excellent (90%) yield of acid. The cause of the lower yield in the case of **1c** was shown by a transmetalation/deuteration experiment: The expected deuterated compound **4** (51% yield) was isolated along

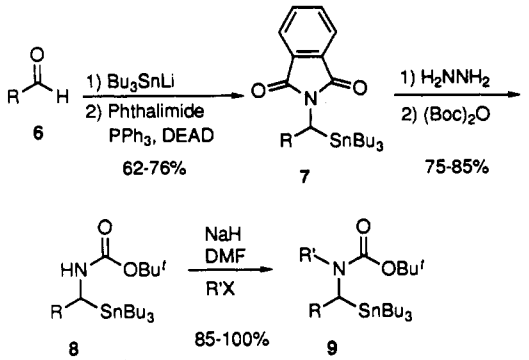


4 **5**

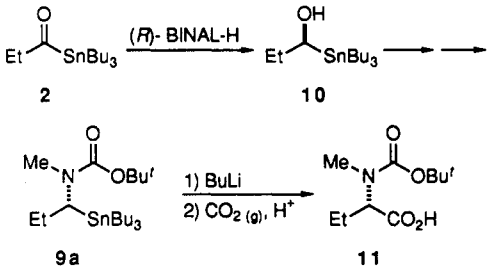
with **5**[22] (35% yield). Hence, it seems that deprotonation of the benzyl carbamate in **1c** (but not **1b**) is competitive with Sn–Li exchange. This difference may be due to subtle increased steric hindrance to transmetalation in **1c** compared to **1a** or **1b**. This result suggests that the synthetic utility of benzyl carbamates **1** is limited (to R = H and CH_3).[23]

To circumvent the problem of competing deprotonation, *t*-BOC derivatives **9** were prepared (Scheme II). The *t*-BOC group has previously been used as an activating group for the α′-lithiation of carbamates,[6] but there are no reported examples of stannanes **9** (or **7** or **8**). The sequence shown in Scheme II proceeded uneventfully, and

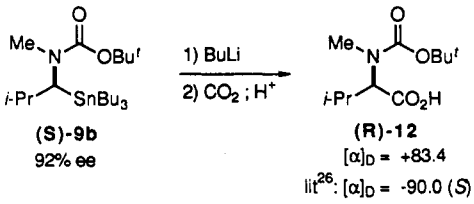
Scheme II



Scheme III



stannanes **9** could be isolated in good (40–65% from aldehyde **6**) overall yields.



On treatment with *n*-BuLi (THF, −78 °C), *N*-methylcarbamates **9a–d** underwent clean transmetalation[24] and the resulting α-lithiocarbamates could be trapped with electrophiles in good to excellent yields (Table I). Especially noteworthy is that the use of CO_2 as electrophile provides *t*-BOC-protected *N*-methylamino acids in excellent yields (89–97%). The latter materials may be useful in the synthesis of peptides containing *N*-methylamino acids.[25] With aldehydes, excellent yields of β-amino alcohols were isolated (entries 2, 8) but with essentially no diastereoselectivity. Only a mediocre yield of alkylated product was obtained using $PhCH_2Br$ (entry 3), a result consistent with those obtained in alkylations of α-alkoxyorganolithiums.[12]

To examine the configurational stability of *t*-BOC-protected α-aminoorganolithiums, stannane **9a** was prepared in enantiomerically enriched form (Scheme III). Thus, acylstannane **2** was reduced with (*R*)-BINAL-H to (*S*)-**10** (96% ee) which was subsequently manipulated (Scheme II) into (*R*)-**9a** (94% ee, 42% from **2**). The absolute configuration of **10** has been established previously;[18a] that of **9a** was assumed based on inversion of configuration under Mitsunobu conditions. Treatment of **9a** with *n*-BuLi followed by CO_2 afforded acid **11**. The enantiomeric purity of **11**, determined by HPLC analysis of the derived α-

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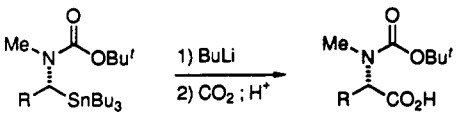
(22) The position of deuteration is clearly revealed by comparing the ^{13}C NMR spectrum (50 MHz, C_6D_5Br, 100 °C) of **1c** which shows a signal at δ 67.92 attributable to $PhCH_2O$– with that of **5**, wherein a 1:1:1 triplet (δ 67.62, J_{C-D} = 22.7 Hz) is observed.

(23) When the organolithium derived from **1c** was allowed to react with benzaldehyde, a 2:1 mixture of diastereomeric alcohols (50% isolated yield) was formed. The major diastereomer was of 88% ee, suggesting little or no loss of enantiomeric purity.

(24) Transmetalations of the corresponding *N*-allyl and *N*-benzyl carbamates were also clean but proceeded to only ~65% completion with 1 equiv of *n*-BuLi; complete (>95%) transmetalation was observed with 1.3–2 equiv of *n*-BuLi.

(25) See, for example: Hunt, S. In *Chemistry and Biochemistry of Amino Acids*; Barrett, G. C., Ed.; Chapman and Hall: London, 1985; p 55.

Table II. Configurational Stability of Organolithiums Derived from Enantiomerically Enriched 9a and 9b[a]



9a: R = Et
9b: R = *i*-Pr

11: R = Et
12: R = *i*-Pr

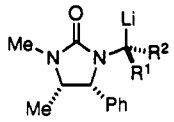
entry	R	temp (°C)	time (min)	yield[b] (%)	ee[c] (%)
1	Et	−55	120	69	24
2		−78	10	93	92
3		−78	180	76	80
4[d]		−78	180	54	68
5[e]		−78	180	50	0
6		−95	10	97	94
7		−95	180	75	92
8	*i*-Pr	−55	120	72	33
9		−78	180	72	83
10		−95	10	75	92

[a] All reactions were run in THF (0.2 M) with 1.05 equiv of *n*-BuLi unless otherwise noted. **9a** was of 94% ee with the absolute configuration depicted; **9b** was of 92% ee with the opposite stereochemistry. [b] Isolated yields of acid. [c] Determined by HPLC (silica) analysis of the derived (*S*)-α-phenylethylamides. [d] DME was used as solvent. [e] HMPA (2 equiv) was added 5 min after the addition of *n*-BuLi.

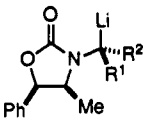
phenylethylamide, was used as an assay for the enantiomeric purity of the intermediate α-aminoorganolithium. Results are tabulated in Table II.

Under Sn–Li transmetalation conditions typically used (THF, −78 °C, 10 min) there was a slight loss of enantiomeric purity (entry 2). However, on prolonged standing at −78 °C (entry 3), there was clearly noticeable racemization; as expected, racemization was considerably faster at −55 °C (entry 1). Very significantly, transmetalation occurs very rapidly (within 10 min) at −95 °C, and the resulting carbanion may be trapped with complete retention of configuration (entry 6). Decreased yields of **11** after aging of the organolithium (entries 1, 3–5, 7) may indicate that the latter species is slowly decomposing.

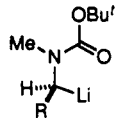
It is interesting to note that urea-stabilized organolithium **13a** has been reported by Pearson[9b] to epimerize to the more stable diastereomer **13b** over about 40 min (THF, −78 °C) while the carbamate-stabilized organolithium **14a** isomerized completely to the more stable diastereomer **14b** within 5 min under the same conditions.



13a: R^1 = H, R^2 = Me
13b: R^1 = Me, R^2 = H



14a: R^1 = Me, R^2 = H
14b: R^1 = H, R^2 = Me



15

The difference in configurational stability was ascribed to "the poorer lithium-ligating ability of a carbamate carbonyl oxygen versus a urea carbonyl oxygen."[9b] The carbamate-stabilized organolithiums **15** described here isomerize much more slowly than **14a**, exhibiting <2% isomerization after 10 min (in THF at −78 °C). This very different configurational stability may be due, at least in part, to the absence of a diastereomeric bias in **15**; in other words, organolithium **14a** is less configurationally stable than **15** because of an inherent diastereomeric bias which favors **14b**. In fact, the inversion processes observed are formally different in that **14a** undergoes epimerization while **15** undergoes racemization.

The effect of solvent was briefly investigated. When the better coordinating solvent DME (instead of THF) was used only slightly faster racemization was observed (compare entries 3 and 4). However, HMPA dramatically increased the rate of racemization (entry 5), and completely racemic material was isolated under conditions that afforded material of 80% ee when THF alone was used as solvent. Hence, it seems that intramolecular coordination (which could be disrupted by HMPA) plays a very important role in stabilizing these α-aminoorganolithiums. The effect of HMPA is in accord with Pearson's observation that TMEDA has a detrimental effect on the configurational stability of **13a**.[9b]

A similar set of experiments using carbamate **9b** (92% ee, R = *i*-Pr) gave comparable numbers (entries 8–10). Carbamate **9b** was also used for confirming assignments of absolute configuration since the acid derived from **9b** is the known *t*-BOC-*N*-methylvaline (**12**). Thus, (*S*)-**9b** (prepared as shown in Scheme III but using (*S*)-BINAL-H as the reducing agent) was converted (*n*-BuLi, THF, −95 °C then CO_2, H^+) to **12** of 92% ee which showed $[\alpha]_D$ = +83.4 (*c* 0.42, EtOH). Since (*S*)-**12** (derived from (*S*)-valine) exhibits $[\alpha]_D$ = −90.0 (*c* 0.5, EtOH),[26] the acid derived from (*S*)-**9b** must be *R* and the transmetalation-trapping sequence must have occurred with net retention of configuration.

The above results clearly show that *t*-BOC-protected α-aminoorganolithiums are configurationally more labile than their MOM-protected alkoxy counterparts (which show no detectable racemization at −78 °C and seem to be configurationally stable up to −30 °C).[11] However, since carbamates **9** undergo rapid Sn–Li exchanges at −95 °C and racemization is very slow at that temperature, such α-aminoorganolithiums may be generated and trapped with complete retention of configuration. Hence, enantiomerically enriched *t*-BOC-protected α-aminoorganostannanes (prepared from α-hydroxystannanes or via other routes) may be useful for the preparation of chiral nonracemic amines.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support and a postgraduate scholarship (to S. B.P.).

Supplementary Material Available: Experimental procedures and spectral (IR, ^{1}H NMR, ^{13}C NMR, MS) data for all new compounds reported (23 pages). Ordering information is given on any current masthead page.

(26) Cheung, S. T.; Benoiton, N. L. *Can. J. Chem.* **1977**, *55*, 906.