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Addition of Bu_3SnLi to *tert*-Butanesulfinimines as an Efficient Route to Chiral, Nonracemic α-Aminoorganostannanes

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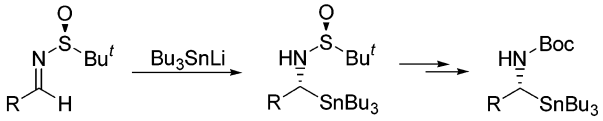
ABSTRACT



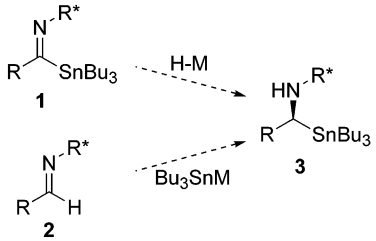
Addition of Bu_3SnLi to *tert*-butanesulfinimines proceeds with high diastereoselectivities to provide the expected adducts in excellent yields and typically with dr = >99:1. These adducts are readily converted to enantiomerically enriched *N*-Boc-protected α-aminoorganostannanes with complete retention of configuration.

α-Aminoorganostannanes have emerged as useful reagents for organic synthesis, particularly as precursors of α-aminoorganolithiums.[1] Access to enantiomerically pure α-aminoorganostannanes has thus far been limited to resolutions of diastereomeric derivatives,[2] enantioselective deprotonation/stannylation in select (cyclic[3] and allylic[4]/benzylic[5]) cases, or via enantiomerically enriched α-hydroxystannanes.[6,7] Routes from α-hydroxystannanes typically involve multiple steps, which detracts from their synthetic appeal.

In principle, facile entry to enantiomerically pure α-aminoorganostannanes might be realized by asymmetric reduction of imidoylstannanes or by asymmetric addition of a stannylmetallic reagent to an imine derivative (Scheme 1).

Imidoylstannanes (**1**) have been described in the literature, and their reduction to racemic α-aminoorganostannanes is known.[8] However, no asymmetric reductions have been reported, and we have found that diastereoselective reductions of chiral imidoylstannanes (**1**, R* = 1-phenylethyl or 1-naphthylethyl) proceeded with only modest selectivity (up to dr = 81:19). Furthermore, we were unable to efficiently remove the chiral auxiliary from adducts **3**.[9] Also, we were unable to find conditions to effect the addition of tributylstannylmetallics to simple imines such as **2** (R* = alkyl).

Scheme 1



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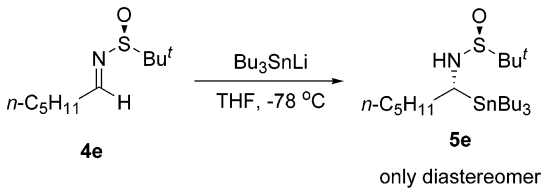
Recently, Ellman has shown that various organometallic reagents may be added to *tert*-butanesulfinimines with high diastereoselectivities.[10] Subsequent acidic cleavage of the *tert*-butanesulfinyl group affords amines with good enantiomeric purity. This chemistry has been extended for the preparation of 1,2-[11] and 1,3-amino alcohols,[12] α-amino acids,[13] and α-trifluoromethylamines.[14] Recent advances in the enantioselective preparation of *tert*-butanesulfinamide will undoubtedly stimulate more applications of this chiral auxiliary.[15,16] All of the additions to *tert*-butanesulfinimines thus far have been limited to carbon-based nucleophiles. Phosphorus-based nucleophiles have been added to other chiral sulfinimines,[17,18] but additions of heteroatom nucleophiles such as tributylstannylmetallics to *tert*-butanesulfinimines appear to be unknown. We now report that such additions are possible and, in fact, can serve as the basis for a short and reliable entry to enantiomerically pure α-aminoorganostannanes.

We anticipated that *tert*-butanesulfinimines, due to the electron-withdrawing sulfinyl moiety, would be more reactive than simple imines such as **2** toward stannylmetallics. However, initial results for the addition of Bu_3SnLi to aldimine **4e** under conditions similar to those previously reported for additions of Grignard reagents (−78 °C then warmed to 0 °C) to such imines were disappointing. Considerable amounts of Bu_3SnH and only traces of the desired adduct were isolated along with byproducts not containing a Bu_3Sn group. While Bu_3SnLi has been added to C═O functionalities (as a now routine method of preparing α-hydroxystannanes),[19] there have been no reports of successful additions to C═N groups. With aldehydes and ketones, additions of Bu_3SnLi are very rapid at −78 °C and reactions must be quenched at low temperatures to realize high yields. Also, the product α-hydroxystannanes are thermally unstable and must be handled carefully. We reasoned that perhaps addition of Bu_3SnLi to **4e** occurs at −78 °C, but at higher temperatures the initial adduct is unstable and decomposes to form the products observed. We were very satisfied to observe that when Bu_3SnLi and **4e** were admixed at −78 °C and the reaction was quenched (MeOH then aqueous NH_4Cl) at −78 °C, adduct **5e** could be isolated in good yield and, very significantly, as a single diastereomer by ^1H and ^{13}C NMR spectroscopy (Scheme 2).

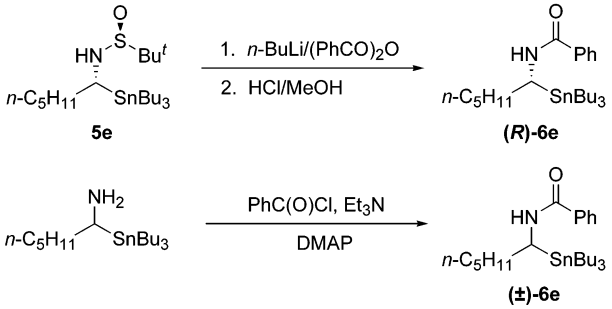
Scheme 2



As an additional bonus, stannylsulfinamide **5e** proved to be quite stable, surviving chromatography on silica gel and storage under ambient conditions for months.

To verify the high diastereoselectivity, adduct **5e** was benzoylated and then treated with HCl/MeOH to provide benzamide **6e** (Scheme 3). HPLC analysis of this benzamide

Scheme 3



on a ChiralCel OD column along with an independently prepared sample of racemic **6e** indicated the presence of only one enantiomer. Thus, adduct **5e** must have been formed with very high diastereoselectivity.

Other *tert*-butanesulfinimines were prepared and treated with Bu_3SnLi (Table 1). In all cases, good to excellent yields of adducts were obtained and diastereoselectivities were uniformly high. In most cases, only small (<1%) amounts of the minor enantiomer were detected by chiral HPLC analysis of the derived benzamides. Only in the case of aldimine **4a** with a relatively small methyl group was >1% of the minor enantiomer detected. The uniformly high selectivities observed with these Bu_3SnLi additions are quite remarkable since it is known that with typical organolithiums (RLi as opposed to Bu_3SnLi) selectivities are rather modest.[10c] In fact, even under optimal conditions (Grignard reagents in noncoordinating solvents) organometallics usually give selectivities in the 95:5 range.[10]

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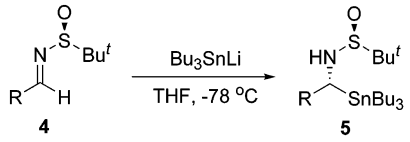
Table 1. Addition of Bu_3SnLi to Sulfinimines **4**

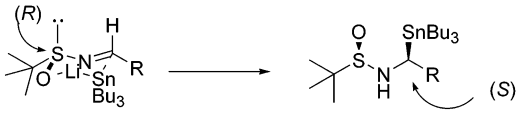


	aldimine **4**			adduct **5**			
entry	R	*R*/*S*	no.	no.	yield[a] (%)	dr[b]	*R*/*S*
1	Me	S_S	**4a**	**5a**	83	98.7:1.3	*R*
2	Et	S_S	**4b**	**5b**	92	99.2:0.8	*R*
3	*i*-Pr	S_S	**4c**	**5c**	96	99.3:0.7	*R*
4	*t*-Bu	S_S	**4d**	**5d**	94	>99:1[c]	*R*
5	*n*-C_5H_{11}	S_S	**4e**	**5e**	84	>200:1[d]	*R*
6	$BnO(CH_2)_7$	R_S	**4f**	**5f**	80	99.5:0.5	*S*
7	*c*-C_6H_{11}	S_S	**4g**	**5g**	89	99.5:0.5	*R*

[a] Percent isolated yields of chromatographed products. [b] Determined by HPLC analysis of derived benzamides with a Chiralcel OD column. [c] Only one diastereomer was observed by ^{13}C NMR spectroscopy. [d] Only one isomer was detected by HPLC.

The absolute configuration of the major adduct was determined by conversion to benzamides and comparison (HPLC elution times) with compounds of known absolute configuration prepared independently.[6] In all cases, the formation of the major isomer may be rationalized by invoking a six-membered-ring transition state as suggested by Ellman (for Grignard reagents, Scheme 4).[10c]

Scheme 4. Model To Rationalize the Stereochemistry of Bu_3SnLi Addition to *tert*-Butanesulfinimines



It is known that the sense of asymmetric addition to *tert*-butanesulfinimines may be reversed by changing the nature of the nucleophile. For example, Plobeck has shown that addition of aryl Grignard reagents to a series of imines gave diastereomeric ratios ranging from 80:20 to 97:3 while the corresponding aryllithiums gave ratios of 29:71 to 8:92.[20] In each case, the major diastereomer with the Grignard reagents could be rationalized on the basis of a six-membered transition state while the opposite isomers arising from aryllithium additions could be explained by a nonchelated open transition-state model. In our case, use of other tributylstannylmetallics afforded either no adduct ($Bu_3SnMgCl$) or the same diastereomer ($Bu_3SnZnEt_2Li$) as with Bu_3SnLi. Interestingly, it has been shown that $Bu_3SnZnEt_2Li$ gives opposite facial selectivity compared to Bu_3SnLi in conjugate additions to γ-alkoxy enoates.[21] With *tert*-butanesulfinimines, reversal of diastereoselectivity was never observed. Our inability to form the other diastereomer proved to be an inconvenience as it precluded determination of diastereomer ratios directly and derivatization of the adducts **5** was required. However, this is not a major drawback from a synthetic perspective since both enantiomers of *tert*-butanesulfinamide are readily available, and thus, either enantiomer of the desired α-aminoorganostannane should be accessible.

One of the big advantages of the *tert*-butanesulfinyl group (as opposed to other chiral sulfinyl auxiliaries) is that it can usually be readily removed by treatment with acid to provide free amines (as salts).[10] Unfortunately, with tributylstannyl-substituted sulfinamides **5**, treatment with protic or Lewis acids[22] under a variety of conditions gave only returned starting material or intractable mixtures. Our inability to directly remove the *tert*-butanesulfinyl group is likely due to the instability of α-stannylamines under acidic conditions and necessitated the development of alternative protocols to remove the *tert*-butanesulfinyl group.

Since we[2,6] and others[3] have previously shown that the *t*-Boc group is useful as a nitrogen protecting group for α-aminoorganostannanes and organolithiums, we looked for conditions wherein such a group could be introduced to the sulfinamides **5**. Selective removal of the *tert*-butanesulfinyl group would then give *t*-Boc-protected α-aminoorganostannanes directly. Many of the usual methods [e.g., $(Boc)_2O$ in combination with Et_3N/DMAP,[23] LDA,[24] *n*-BuLi,[25] or NaH[26]] for the introduction of *t*-Boc groups to amide-type functionalities[27] failed completely with the stannylsulfinamides, yielding intractable mixtures or returned starting material. Eventually, it was found that deprotonation of the sulfinamides with *n*-BuLi (THF, −78 °C) followed by treatment of the resulting anion with a premixed combination of $(Boc)_2O$ and DMAP (−78 °C to room temperature) could give the mixed imides **7** in reasonable yields. These mixed imides could be transformed into the desired Boc-protected amines **8** in high yields by selective cleavage of the sulfinyl group with MeLi (Table 2).

For amides **5** possessing an unbranched alkyl group, this two-step protocol worked very well. However, for compounds such as **5c**, with an isopropyl group, the Boc group could be introduced in only very low yields, likely due to steric crowding. Unfortunately, the instability of the intermediate (lithiated **5**, the same intermediate formed on initial addition to Bu_3SnLi to imines **4**) thwarted attempts to put the Boc group onto more hindered substrates as more forcing conditions lead to decomposition.

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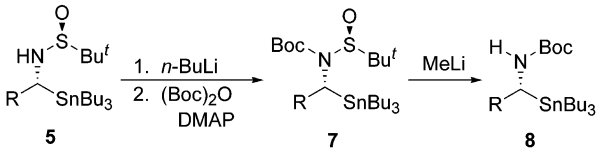
Table 2. Conversion of Sulfinamides **5** to Boc-Protected Stannanes **8**

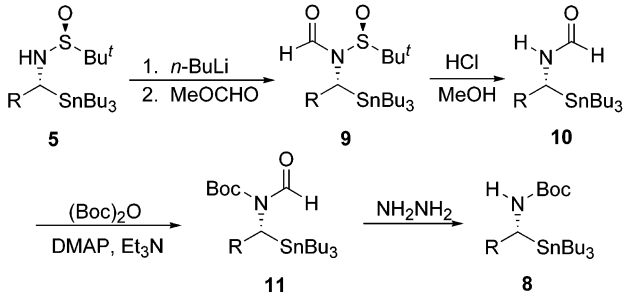


a: R = Me, **b**: R = Et, **e**: R = *n*-C_5H_{11}, **f**: R = $BnO(CH_2)_7$

entry	R	% yield[a] (**7**)	% yield[a] (**8**)
1	Me	69 (**7a**)	87 (**8a**)
2	Et	82 (**7b**)	94 (**8b**)
3	*n*-C_5H_{11}	80 (**7e**)	98 (**8e**)
4	$BnO(CH_2)_7$	73 (**7f**)	98 (**8f**)

[a] Percent isolated yields of chromatographed products.

Table 3. Conversion of Sulfinamides **5** Containing Branched Side Chains to Boc-Protected Stannanes **8**



c: R = *i*-Pr, **g**: R = *c*-C_6H_{11}

entry	R	% yield (**9**)	% yield (**10**)	% yield (**11**)	% yield (**8**)
1	*i*-Pr	59	100	96	100
2	*c*-C_6H_{11}	51	98	95	100

For compounds such as **5c** with a branched group, another protocol was developed to allow access to Boc-protected amines **8** (Table 3). Since a Boc group proved to be very difficult to introduce directly, the much smaller formyl group was initially introduced to give mixed imides **9** in moderate yields. Subsequent acidic cleavage of the *tert*-butanesulfinyl group, addition of the Boc group under standard conditions, and hydrazinolysis of the formyl group all proceeded in near-quantitative yields. This procedure with hindered substrates is not ideal because of its length but the steps are all operationally simple. Taken together with the two-step procedure developed earlier (Table 2), this chemistry should allow access to virtually any Boc-protected α-aminoorganostannane (**8**) with a primary or secondary alkyl side chain. It was not possible to acylate sulfinamide **5d**, containing a bulky *tert*-butyl group, under any of the conditions tried.

In summary, we have shown that addition of Bu_3SnLi to *tert*-butanesulfinimines proceeds with very high diastereoselectivities and a predictable sense of asymmetric induction. The sulfinamides thus formed are readily transformed to enantiomerically enriched Boc-protected α-aminoorganostannanes. This approach compares very favorably with other routes to stereodefined α-aminoorganostannanes and may become the method of choice for the preparation of such compounds. Work to examine other synthetic applications of sulfinamides **5** is in progress.

Acknowledgment. We thank the Natural Sciences and Engineering Research Council of Canada for financial support and a postgraduate scholarship (to K.W.K.). We are also grateful to Mr. Scott Wilkinson (Sepracor) for generous gifts of (*R*)- and (*S*)-*tert*-butanesulfinamide and synthetic precursors.

Supporting Information Available: Experimental details for the preparation of and spectral data for compounds **5** and **7**−**11**; details for the chiral HPLC separation of benzamides **6**; and details for determination of absolute configurations. This material is available free of charge via the Internet at http://pubs.acs.org.

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