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The Tri-*n*-butyltin Group as a Novel Stereocontrol Element and Synthetic Handle in the Aza-[2,3]-Wittig Sigmatropic Rearrangement

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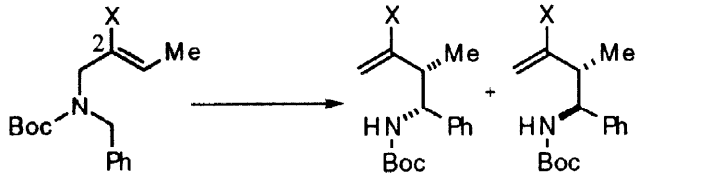
Abstract: The stereoselective *trans* hydrostannation of a non terminal alkynyl benzyl amine is described which furnished a tri-*n*butyltin substituted aza-[2,3]-Wittig sigmatropic rearrangement precursor. Anionic rearrangement afforded a vinyl stannane product, in 71% yield, with near complete control of diastereoselectivity. Subsequent transition metal catalysed carbon-carbon bond forming reactions gave potential precursors to novel unnatural amino acids in good to moderate yields.

Despite the tremendous advances made with the familiar oxy-[2,3]-Wittig rearrangement and its widespread use in organic synthesis,[1] the development of the corresponding aza process had remained elusive. It was clear from the literature that the conquering of this problem was not as simple as just changing an oxygen atom to a nitrogen.[2] The incorporation of a nitrogen atom into the system confers its own unique properties: nitrogen is less electronegative than oxygen so the thermodynamic driving force for the process is diminished and the atom is trivalent as opposed to divalent. The relief of ring strain in 2-azetidinones[3] and vinyl aziridines[4] had been used to provide a thermodynamic driving force for the formation of cyclic products with good stereocontrol. Through rational design we independently characterised the first acyclic example of this rearrangement (**a**, Scheme 1).[5] We know that the Boc protecting group is essential to facilitate metallation of the more acidic benzylic position[6] and we believe stabilises the nitrogen anion formed from the rearrangement, thus increasing the thermodynamic driving force for the reaction. This simple rearrangement was unselective and few other migrating groups were tolerated.



Scheme 1 Bu^nLi, Et_2O/HMPA (4:1). **a**, X = H, -78 to -40 °C, 14 h, 82%; **b**, X = $SiMe_3$, -78 °C. 10 m, 88%

The oxy [2,3]-Wittig process is extremely facile at sub-ambient temperatures and inherently diastereoselective. The lower electronegativity of nitrogen clearly affects the driving force of the reaction and because of comparitively longer bonds to those in the oxygen system we believe the transition state is looser and so cannot transmit stereochemical information as well. Our unique solution to these problems was to incorporate an anion stabilising group at the central C-2 vinylic carbon atom of the allylic amine precursors (**1b**, Scheme 1). This has the dual effect of lowering the energy of the transition state and controlling the sense of

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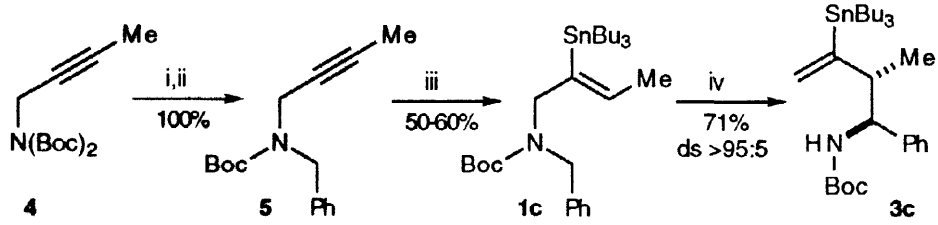
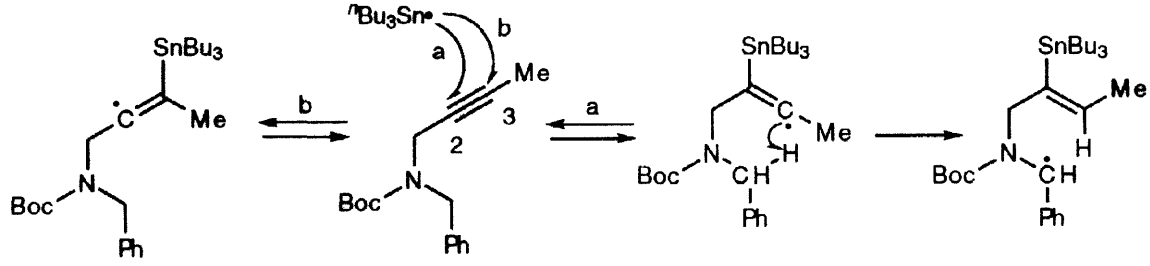
diastereoselection.[7,8] The excellent diastereocontrol is good evidence that this is a pericyclic process. During the course of our investigation two other acyclic investigations have appeared.[9,10] We are using our products as precursors to α- and β-amino acids, but to expand this methodology we were interested in a C-2 vinyl substituent that could be used as a synthetic handle to provide more diverse structures from the stereodefined homoallylic amine products **3**. We reasoned that a C-2 tributyltin substituent (**1c**) may be able to promote the rearrangement in much the same way as silyl substituents.[8] The resultant vinyl tin products (**2/3 c**) could themselves be used further in transition metal catalysed coupling reactions to form new carbon-carbon bonds.

Aza-[2,3]-Wittig precursor **1c** was most easily prepared from the alkynyl amine **5**, in turn derived from the readily available di-*N*-Boc protected alkyne **4**.[11] Monodeprotection with TFA and benzylation under standard conditions led to **5** in quantitative yield (Scheme 2).[12,13]



Scheme 2 i) 1.9 equiv. TFA, CH_2Cl_2, 1 h; ii) 1.3 equiv. KH, 0 °C, 1.2 equiv. BnBr, 0 °C to rt, THF, 16 h; iii) 20 mol% ACN, 1.1 equiv. Bu_3SnH, PhMe, 110 °C, 22 h; iv) 1.3 equiv. LDA, THF/HMPA (4:1), -78 to -40 °C, 20 h.

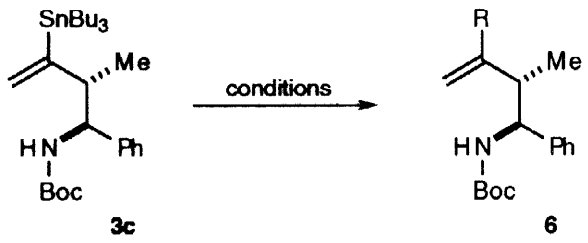
The *trans* addition of tri-*n*-butyltin hydride across non-terminal actelylenes had no exact precedent. Hydrostannation of ethyl *N*-acetyl-*D,L*-propargylglycinate under palladium catalysed or free radical conditions gave mainly *syn* addition products.[14] However the *trans* addition of tri-*n*-butyltin hydride across non-terminal propargylic alcohols gave predominantly the *Z* isomer.[15] Thus treatment of **5** with tri-*n*-butyltin hydride with catalytic azo-biscyclohexanecarbonitrile (ACN)[16] in refluxing toluene gave the desired rearrangement precursor **1c** in a clean isolable yield of 50-60% after chromatography. The structure of **1c** was verified primarily by 1H NMR. That the methyl group was geminal to a proton was evidenced by the methyl resonance appearing as a doublet (δ1.68, J=6.4Hz) and the *trans* relationship of the tin and proton by the magnitude of the ^{119}Sn-H coupling constant (δ6.02, J=130 Hz).[14] In addition the 1H NMR spectrum of the destannylated material, formed by treatment with MeLi, was identical to that prepared unambiguously.[5] We speculate that the *Z*-diastereoisomer is formed preferentially due to the vinyl radical formed at C-3 (path a, Scheme 3) intramoleculary abstracting a proton (1,5 relationship) from the stable benzylic position. In comparison the addition of the tin radical to C-3, to give a vinyl radical at C-2 (path b, Scheme 3), would require a not so favourable 1,4 H abstraction to reach a more stable benzyl radical intermediate. The resultant benzylic radical then carries on the chain by reaction with tri-*n*-butyltin hydride.



Scheme 3

Treatment of **1c** with LDA in THF/HMPA (4:1) at -78 °C and then warming to -40 °C overnight furnished the homoallylic amine **3c** in 71% yield, essentially as one diastereoisomer judged by 1H NMR.[17] This diastereoisomer exhibited a characteristic chemical shift for its allylic methyl group (δ0.57, d, J=7.0Hz) similar to those of the silicon analogues.[7,8] In addition we were able to compare the destannylated material, formed by treatment with MeLi, with our first rearrangement products. The stereochemical identity of the latter having been unambiguously determined by comparison to a natural product.[5] The diastereoselection is in accord with our transition state model for this rearrangement and it is clear that the tri-*n*-butyltin group controls the diastereoselectivity, but does not accelerate the rearrangement as silicon does.[7]

Elaboration of the vinyl stannane under standard conditions gave a series of diverse structures **6a-e** in good to moderate yield. The small decrease in yield for the preparation of **6a-c**, compared to similar elaborations on a γ-tri-*n*-butylstannaneallylglycine derivative,[14] probably reflects the additional steric effect of the allylic methyl substituent in this work. The carbonylation product **6e** was formed in excellent yield and represents a structure unobtainable by rearrangement of an aza-[2,3]-Wittig precursor containing a phenyl ketone at the C-2 position in **1**. These products represent novel precursors to unnatural amino acids.[5]



3c **6**

6	R	Yield/%
a	$-CH_2CH=CH_2$	57
b	$-CH_2C_6H_5$	62
c	$-C_6H_5$	53
d	-I	52
e	-CO.Ph	75

Figure 1 conditions for **a** 2 equiv. allyl bromide, 5 mol% Pd_2dba_3, 40 mol% Ph_3As, THF, 67°C, 36 h; **b** 1.5 equiv. benzyl bromide, 5 mol% Pd_2dba_3, 40 mol% Ph_3As, THF, 67 °C, 21 h; **c** 1.3 equiv. iodobenzene, 4 mol% Pd_2dba_3, 32 mol% Ph_3As, THF, 67 °C, 21 h; **d** 1.1 equiv. I_2, CH_2Cl_2, rt, 30 min.; **e** 1.5 equiv. iodobenzene, 5 atm. CO, $Cl_2Pd(PPh_3)_2$, THF, rt, 21 h.

We have shown that the tri-*n*-butyltin group can control the diastereoselection of an aza-[2,3]-Wittig sigmatropic rearrangement in high yield and could no doubt be used in the rearrangement of related congeners. The products are useful for further elaboration, especially transition metal catalysed coupling reactions to form new carbon-carbon bonds. These novel compounds may find use in the preparation of new unnatural amino acid structures, studies which are currently underway.

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12. Satisfactory 1H- and 13C-NMR, IR, MS, HRMS and/or analysis were obtained for all new compounds.

13. Attempted rearrangement of this compound under a variety of different conditions only gave *tert*-butoxycarbonylbenzylamine as biproduct. This product has been detected before in the attempted rearrangement of a *Z*-crotyl amine derivative (see ref. 5).

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16. Conventional AIBN was found to give lower yields.

17. Use of *n*-BuLi or MeLi as base caused destannylation and then rearrangement to give **2/3a** (2:1) in 32 and 55% yield respectively with ~20% destannylated starting material.