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Communication

1,5-Induction in Reactions Between 2-Alkoxy-(2-tributylstannylethylidene)cyclohexanes and Aldehydes

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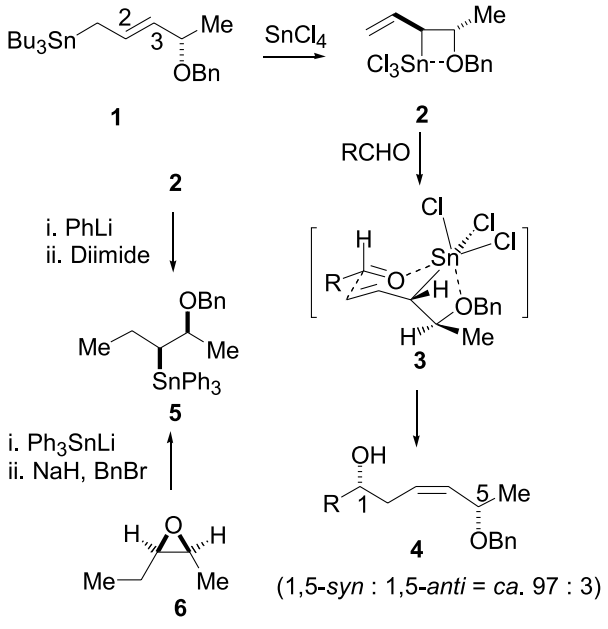
2-Metoxi(2-tributilestaniletilideno)cicloexano **16** sofre transmetalação estereosseletiva sob tratamento com tetracloreto de estanho (IV) para gerar o tricloreto de alilestanho **19** que reage com aldeídos fornecendo (*Z*)-(3-hidroxialquilideno)-2-metoxicicloexanos **17a-g** com excelente estereocontrole 1,5.

2-Methoxy(2-tributylstannylethylidene)cyclohexane **16** undergoes stereoselective transmetalation on treatment with tin(IV) chloride to generate the allyltin trichloride **19** which reacts with aldehydes to give the (*Z*)-(3-hydroxyalkylidene)-2-methoxycyclohexanes **17a-g** with excellent 1,5-stereocontrol.

Keywords: allylstannane, stereocontrol.

Introduction

Alk-2-enylstannanes with heteroatom substituents at the 4-, 5- and 6-positions undergo stereoselective transmetalation on treatment with tin(IV) halides to generate allyltin trihalides which react with aldehydes with useful levels of 1,5-, 1,6- and 1,7-asymmetric induction[1]. For example, transmetalation of the 4-benzyloxypent-2-enylstannane **1** with tin(IV) chloride generates the allyltin trichloride **2** which reacts with aldehydes, *via* the transition structure **3**, to give the 1,5-*syn*-(*Z*)-products **4**, 1,5-*syn* : 1,5-*anti* =96 : 4[2]. The stereoselectivity of transmetalation is due to kinetic control[3]. The relative configuration of the two stereogenic centres in the intermediate allyltin trichloride **2** has been confirmed by trapping with phenyllithium which gave the 2-benzyloxy-3-pentyl (triphenyl)stannane **5**, the structure of which was established by comparison with a sample prepared from the epoxide **6**[4] (Scheme 1).



Scheme 1.

In order to delineate the scope of these reactions, it was necessary to establish whether the chemistry is compatible with the presence of substituents at C(2) and C(3) in the allylstannane. It has been found that the stereoselectivity is not significantly affected by substituents at C(2); indeed it is slightly enhanced. For example, the 2-methylpent-2-enyl(tributyl)stannane **7**, as an (*E*)/(*Z*)-mixture, reacts with aldehydes on transmetalation with tin(IV) chloride with excellent 1,5-stereoselectivity[5] (Scheme 2.)

However, the effect of a substituent at C(3) is difficult to predict, and has not yet been investigated. Indeed transmetalation of a 3,4-disubstituted alk-2-enylstannane **9** would generate an intermediate *tertiary* allyltin trichloride **10**, and the stability of such an intermediate, e.g. towards elimination of a tin alkoxide, is very uncertain. We now report aspects of the chemistry of the 3,4-disubstituted

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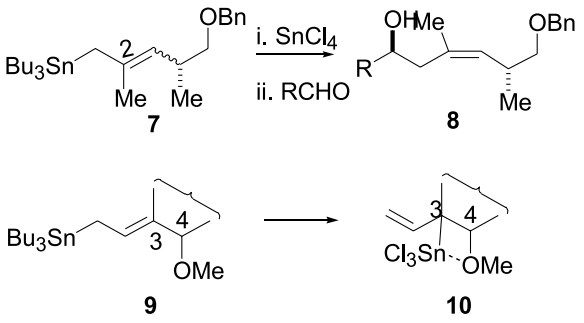
allylstannane **16**. This was found to undergo highly stereoselective transmetalation with tin(IV) chloride giving an intermediate allyltin trichloride which is stable under our reaction conditions and which undergoes usefully stereoselective reactions with aldehydes.

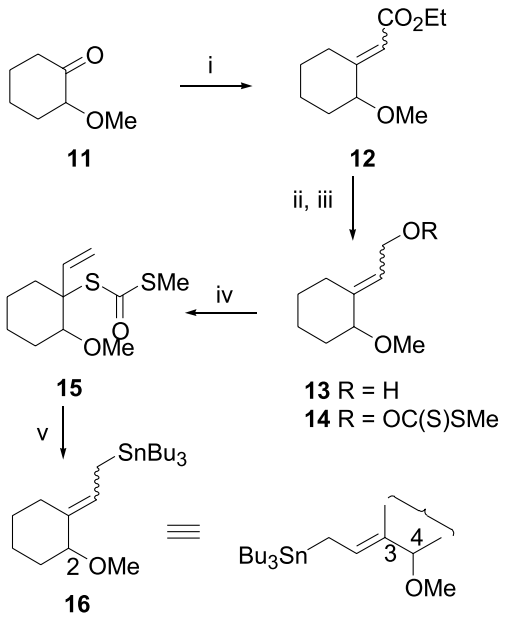


Scheme 2.

Results and Discussion

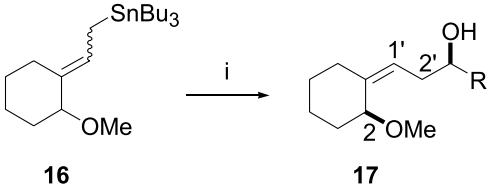
The 2-methoxy(2-tributylstannylethylidene) cyclohexane **16** was prepared as outlined in Scheme 3. The condensation between racemic 2-methoxycyclohexanone **11** and triethyl phosphonoacetate gave the unsaturated ester **12** in an 87% yield as a 60 : 40 mixture of (*E*)- and (*Z*)-isomers. Interestingly, the corresponding Peterson reaction using ethyl trimethylsilylacetate gave more of the (*Z*)-isomer, (*E*) : (*Z*) = 20 : 80, albeit in a lower yield (47%). The (*E*)- and (*Z*)-isomers could be readily distinguished by ^{1}H NMR, for example 2-H for the (*Z*)-isomer, at δ 5.26, was significantly more deshielded than 2-H for the (*E*)-isomer, observed at δ 3.59. After reduction of the ester, the allylic alcohol **13** was converted into the xanthate **14** with good yields being obtained if the deprotonation of the alcohol was completed by heating in toluene under reflux prior to the addition of the carbon disulfide. The xanthate, still as a 60 : 40 mixture of (*E*)- and (*Z*)-isomers, was converted into the dithiocarbonate **15** by heating in toluene under reflux. This rearrangement was quite stereoselective giving an 87 : 13 mixture of diastereoisomers. It is believed that the major product has the vinyl and methoxy groups *cis*-disposed about the six-membered ring, but this stereochemical assignment was not confirmed. Instead the mixture of dithiocarbonates was taken through to the allylstannane **16** as an 85 : 15 mixture of (*E*)- and (*Z*)-isomers, by treatment with tributyltin hydride under free-radical conditions, the stereochemical assignment being made on the basis of strong nOe effects between H-2 and the vinylic proton for the major, but not for the minor isomer.

Reactions between the stannane **16** and aldehydes were carried out by treatment of the allylstannane with tin(IV)



Scheme 3. *Reagents and conditions:* i) NaH, $(EtO)_2P(O)CH_2CO_2Et$, THF (87%; *E* : *Z* = 60 : 40); ii) DIBAL-H, THF (96%); iii) NaH, PhMe, reflux 30 min, then CS_2, 0 °C – rt, 1 h, followed by MeI, rt, 30 min (88%); iv) PhMe, reflux, 4 h (100%; 87 : 13 mixture of diastereoisomers); v) Bu_3SnH, AIBN, PhH (81%; *E* : *Z* = 85 : 15).

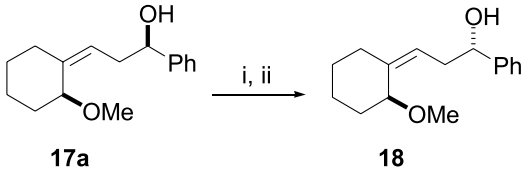
chloride at –78 °C for 5 min followed by addition of the aldehyde. After a further 45 min at –78 °C the reactions were quenched to give, after chromatography, the products indicated in Scheme 4[6].



Scheme 4. *Reagents and conditions:* i) $SnCl_4$, -78 °C, 5 min, then RCHO, -78 °C, 45 min (R = Ph, **17a**, 52%; 2-naphth., **17b**, 62%; *p*-BrC_6H_4, **17c**, 61%; *p*-$O_2NC_6H_4$, **17d**, 63%; MeCH=CH, **17e**, 50%; *n*-Pr, **17f**, 70%; *i*-Pr, **17g**, 45%).

In all cases the reactions appeared to be highly stereoselective with only one product being detected by ^{1}H and ^{13}C NMR (>95 : 5). In order to confirm that the 1,5-diastereoisomers were distinguishable, the benzaldehyde derived product **17a** was converted into its diastereoisomer **18** by inversion using a Mitsunobu reaction followed by saponification (Scheme 5). Although the isomers **17a** and **18** were inseparable by TLC, their ^{1}H NMR spectra were quite different, e.g. 2-H and OCH_3 were at δ 4.08 and 3.23 for **17a** and at δ 4.20 and 3.17 for **18**, respectively. Close examination of the crude reaction mixture from the reaction

between benzaldehyde and the stannane **16** indicated that only a trace, <5% of **18** was present.

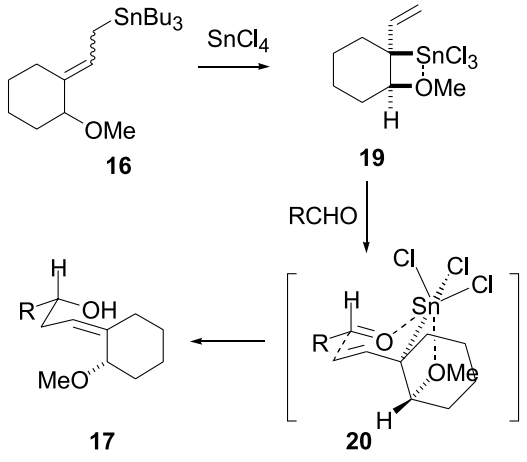


17a **18**

Scheme 5. *Reagents and conditions:* i) Ph_3P, $EtO_2C.N{=}N.CO_2Et$, *p*-$O_2NC_6H_4CO_2H$, PhMe, rt (51%); ii) NaOH, MeOH, rt (93%).

The geometry of the double-bonds in the products **17** was confirmed by nOe studies. For example, for **17a** and **b** significant enhancement of 2'-H_2 but no enhancement of 1'-H was observed on irradiation of 2-H.

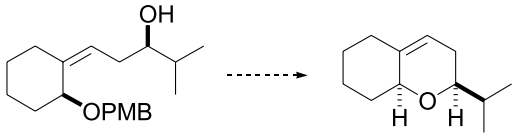
The regioselectivity of the aldehyde-stannane reactions, and the selective formation of the (*Z*)-products, are consistent with transmetalation of the allylstannane **16** on reaction with tin(IV) chloride to give the intermediate allyltin trichloride **19**. Reaction with aldehydes through the chair-like transition structure **20** would then give the 1,5-*syn*-(*Z*)-products **17** (Scheme 6). This stereoselectivity has precedent in the reactions of aliphatic allylstannanes, e.g. **1**[1]. The relative configurations assigned to the stereogenic centres in the products **17** were finally confirmed by an X-ray crystal structure of the *p*-nitrobenzoate ester of the product **17d**[7].



16 **19** **17** **20**

Scheme 6. Proposed pathway for formation of products **17.**

This work has shown that a 3-alkyl substituent does not disrupt the transmetalation using tin(IV) chloride of a 4-alkoxyalk-2-enylstannane and that the allyltin trichlorides generated from 3,4-disubstituted alk-2-enylstannanes can react with aldehydes with excellent stereocontrol. Further work will explore the chemistry of the products, e.g. **21**, obtained using related stannanes, and their application to the synthesis of fragments of natural products, e.g. **22** (Scheme 7).



21 **22**

Scheme 7.

Acknowledgements

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6. *General procedure for the reactions of the stannane **16** with aldehydes:* Tin(IV) chloride (1 M in dichloromethane, 0.56 cm^3, 0.56 mmol) was added dropwise to a stirred solution of the allylstannane **16** (200 mg, 0.466 mmol) in dichloromethane (5 cm^3) at –78 °C and the mixture stirred for 5 min. A solution of *p*-bromobenzaldehyde (104 mg, 0.56 mmol) in dichloromethane (2 cm^3) at –78 °C was added and the mixture left to stir for an additional 45 min at –78 °C. Saturated aqueous sodium hydrogen carbonate (2 cm^3) was added and the mixture allowed to warm to room temperature then poured into water (10 cm^3) and extracted with dichloromethane (2 x 10 cm^3). The combined organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Flash chromatography of the residue, eluting with ether-light petroleum-triethylamine (100 : 300 : 3) gave (*Z*,2*SR*,3'*RS*)-(3-hydroxy-3-*p*-bromophenylpropylidene)-2-methoxycyclohexane **17c** (93 mg, 61%), as a colourless oil. HRMS-found: $M^+ + NH_4$, 342.1060;

calc. for $C_{16}H_{25}{}^{79}BrNO_2$: 342.1068. IR (film) $\nu_{max/}cm^{-1}$ 3399, 1592, 1486, 1444, 1403, 1196, 1143, 1070, 1010, 943 and 823. ^{1}H-NMR (300 MHz; $CDCl_3$) δ 7.50 and 7.25 (br d, *J* 8.5, each 2 H, ArH), 5.36 (br t, *J* 7.5, 1 H, 1'-H), 4.66 (m, 1 H, 3'-H), 4.06 (m, 1 H, 2-H), 3.22 (s, 3 H, OCH_3), 2.53 (m, 3 H, 2'-H_2 and OH), 2.30 (m, 1 H, 6-H), 1.97 (m, 2 H, 6-H' and 3-H) and 1.82-1.06 (m, 5 H, 3-H', 4-H_2 and 5-H_2). ^{13}C-NMR (75 MHz; $CDCl_3$): δ 143.1, 141.7, 131.3, 127.6, 121.1, 120.8, 73.8, 73.3, 55.1, 37.0, 32.7, 31.7, 27.9 and 20.6. MS (CI): *m/z* 344 (M^+ + 18, 12%), 342 (M^+ + 18, 15), 312 (96), 310 (96), 295 (17), 293 (23), 277 (37), 275 (40), 201 (44) and 199 (53).

7. Details of the X-ray crystal structure will be reported elsewhere.

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