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Stereochemical aspects of the chemistry of 2-[trialkyl(aryl)silyloxy]alkyl-4-alkoxyalk-2-enylstannanes

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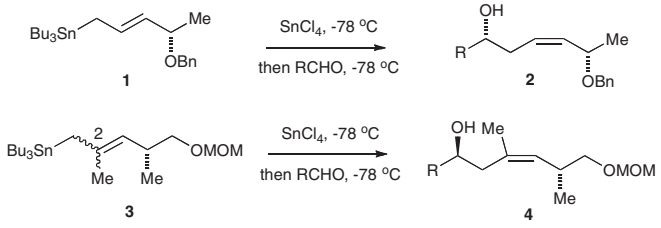
ABSTRACT

2-*tert*-Butyldimethylsilyloxymethyl-4-(methoxymethoxy)pent-2-enyl(tributyl)stannane, prepared predominantly as the (*Z*)-isomer, is transmetallated by tin(IV) chloride to generate an allyltin trichloride which reacts with aldehydes with excellent stereocontrol in favour of (*E*)-1,5-*syn*-3-*tert*-butyldimethylsilyloxymethyl-5-(methoxymethoxy)alk-3-en-1-ols. These were taken through to 3-[(*E*)-2-(methoxymethoxy) propylidenyl]-5-alkyl(aryl)tetrahydrofurans and used to prepare more complex 4-(methoxymethoxy) pent-2-enylstannanes.

Alkoxyalk-2-enylstannanes are transmetalled by tin(IV) halides to give allyltin trihalides which react with aldehydes with useful levels of remote stereocontrol;[1] for example, the 4-benzyloxypent-2-enylstannane **1** reacts with aldehydes to give (*Z*)-1,5-*syn*-hex-3-en-1-ols **2** containing less than 3% of any other stereoisomer.[2] Useful remote stereocontrol was also observed for analogous reactions of the 5-alkoxy-2,4-dimethylpent-2-enylstannane **3**, which gave the (*Z*)-1,5-*anti*-3,5-dimethylhex-3-en-1-ols **4** with excellent stereoselectivity showing that this chemistry is compatible with an alkyl substituent at C(2) in the stannane.[3]



It was of interest to see whether this chemistry was compatible with a functionalised alkyl group at C(2) in the stannane or whether such functionalisation would disrupt the remote stereocontrol. We now report aspects of the chemistry of 4-(methoxymethoxy)pent-2-enylstannanes with a trialkyl(aryl)silyloxyalkyl substituent at C(2).

The racemic 2-(*tert*-butyldimethylsilyloxy)methylpent-2-enylstannane **9** was synthesized as outlined in Scheme 1. Thus lithiation of the 2-(*tert*-butyldimethylsilyloxy)methylpropenyl-sulfone **6**, which is available from the alcohol **5**,[4] followed by addition of ethanal gave the hydroxyalkylsulfone **7** as a mixture of diastereoisomers. Treatment of this mixture with tri-*n*-butyltin hydride under free-radical conditions[5] gave the racemic (*Z*)-4-hydroxypent-2-enylstannane **8** together with a small amount of the (*E*)- isomer, (**2*Z***)-**8**:(**2*E***)-**8** = 90:10, and the alcohol **8** was converted into its methoxymethyl ether **9**.

The stereoselective formation of the (2*Z*)-isomer of the 4-hydroxypent-2-enylstannane **8** was established by ^{1}H NOE observations, for example, the significant enhancement of 3-H on irradiation of 2-CH_2 but not on irradiation of 1-H_2. This level of stereoselectivity, (2*Z*):(2*E*) = 90:10, was unexpected. Whether it was due to kinetic or thermodynamic control was not investigated but either way may be due to co-ordination of the hydroxyl group with the tributyltin moiety either during the tributyltin radical displacement of the phenylsulfonyl group or in the final product.

Tin(IV) chloride mediated reactions of the (2*EZ*)-pentenylstannane **9** with aldehydes were carried out under the usual conditions, that is, by stirring a mixture of the allylstannane and tin(IV) chloride at −78 °C for 5 min to generate the allyltin trihalide before addition of the aldehyde. After a further 30 min at −78 °C, and an aqueous work-up, the (*E*)-1,5-*syn*-homoallylic alcohols **10a–d** were obtained, see Scheme 2. In all cases the reactions proceeded with excellent stereoselectivity, less than 3% of any other diastereoisomeric product being detected by ^{1}H or ^{13}C NMR.[6,7]

The structures shown were assigned to the major products **10a–d** by analogy with the earlier work on remote stereocontrol using allylstannanes, for example, the formation of the 1,5-*syn*-products

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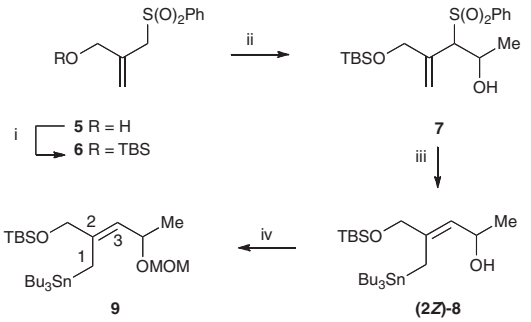
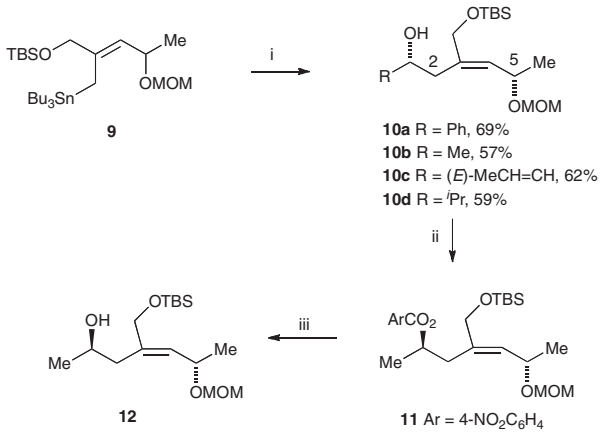


Scheme 1. Reagents and conditions: (i) TBSCl, imid., DCM, rt, 15 h (73%); (ii) LDA, THF, −78 °C, 45 min, ethanal, −78 °C, 30 min (68%, a 55:45 mixture of diastereoisomers); (iii) $^{n}Bu_3SnH$, AIBN (cat.), benzene, reflux, 2 h [69%; (**2*Z*)-8**:(**2*E*)-8** = 90:10]; (iv) $^{i}Pr_2NEt$, $MeOCH_2Cl$, DCM, 0 °C, rt, 15 h (82%).



Scheme 2. Reagents and conditions: (i) $SnCl_4$, DCM, −78 °C, 5 min, aldehyde, −78 °C, 30 min (57–69%); (ii) Ph_3P, 4-nitrobenzoic acid, DEAD, THF, rt, 2 h (79%); (iii) NaOH, MeOH, rt, 2 h (66%).

2 from reactions of the allylstannanes **1** with aldehydes.[1,2] To check that the 1,5-*syn*-products **10** were distinguishable from their 1,5-*anti*-epimers, the product **10b** from the reaction of the stannane **9** with ethanal was converted into the 1,5-*anti*-diastereoisomer **12** by reaction with 4-nitrobenzoic acid under Mitsunobu conditions and saponification of the resulting ester **11**. Although the 1,5-*syn*- and -*anti*-epimers **10b** and **12**, were indistinguishable by TLC, there were small but definite differences in their ^{1}H NMR spectra, for example, 3-H and 3-H′ were observed at δ2.18 and at 2.33 for the 1,5-*syn*-isomer **10b** and were coincident at δ2.28 for the 1,5-*anti*-isomer **12**. Examination of the ^{1}H NMR spectrum of the product **10b** from the reaction of stannane **9** with ethanal showed that only a small amount, less than 3%, of the 1,5-*anti*-epimer **12** was present. Similar minor products were detected at the <3% level in the ^{1}H NMR spectra of the products from the reactions of the other aldehydes with stannane **9**.

The (*E*)-geometry of the product **10a** from the reaction with benzaldehyde was confirmed by NOE observations, for example, a significant enhancement of the peak due to H-5 was observed on irradiation of 2-H_2. The geometry of the double-bond in the other products, **10a**, **10cd**, was assigned by analogy.

The selective formation of the homoallylic alcohols **10a**–**d** from the reactions of the allylstannane **9** with aldehydes is consistent with stereoselective transmetallation of the allylstannane, which is believed to be subjected to kinetic control,[8] to generate the allyltin trihalide **14** in which the vicinal methyl and propenyl groups are *trans* and pseudoequatorial with respect to the six-membered oxastannane ring.[9] The allyltin trichloride **14** can then react with an aldehyde via the six-membered, chair-like transition structure **15** to give the (*E*)-1,5-*syn*-product **10** after an aqueous work-up, see Figure 1.[1,2] Transition structure **15** involving a penta-co-ordinated tin is suggested by analogy with reactions of 1-substituted allylstannanes with aldehydes under high temperature, non-catalysed, conditions. These are believed to involve transition structures analogous to **15** in which the group next to tin adopts an axial position leading to the formation of *cis*-double-bonds in the product and relaying the stereochemical information from C(1) in the stannane to the hydroxyl bearing stereogenic centre in the product[10]

Having prepared the homoallylic alcohols **10**, it was of interest to study the aspects of their chemistry. Mesylation of the homoalcohols **10b** and **10d** gave the corresponding mesylates **16b**,**d**, which on desilylation using TBAF were converted into the (*E*)-3-alkylidenetetrahydrofurans **17b**,**d**, see Scheme 3. In a one-step procedure, the homoallylic alcohols **16a** and **16c** were treated with methane sulfonic anhydride for 18 h. Under these conditions, mesylation, desilylation and tetrahydrofuran formation occurred to give the 3-alkylidenetetrahydrofurans **17a** and **17c** directly, albeit only in modest, unoptimised yields.

The homoallylic alcohols **10** were also identified as precursors of more complex 2-substituted 4-alkoxypent-2-enylstannanes. Thus the monosilylated diol **10a** was converted into its regioisomer **21** by acetylation and fluoride induced desilylation of the resulting acetate **18** which was accompanied by migration of the acetyl group from the secondary to the primary alcohol to give the primary acetate **19**, see Scheme 4. Silylation of the secondary alcohol and saponification gave the secondary mono-silylated diol **21** which was converted into xanthate **22**. This rearranged on heating to give a mixture of the epimeric dithiocarbonates **23** and reaction of this mixture with tributyltin hydride under free-radical

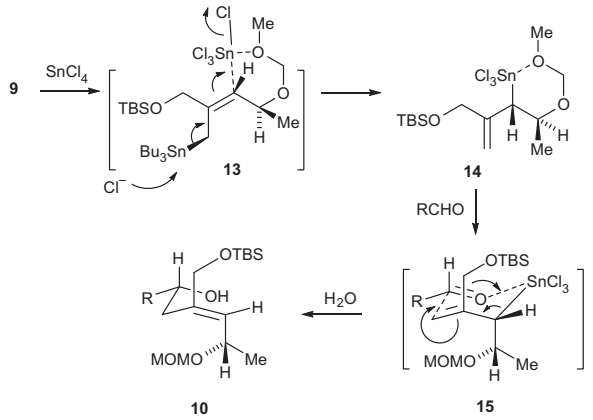
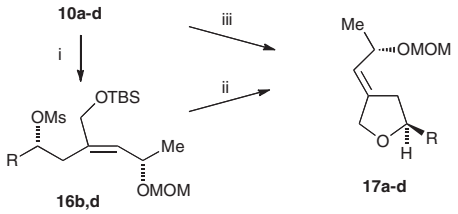
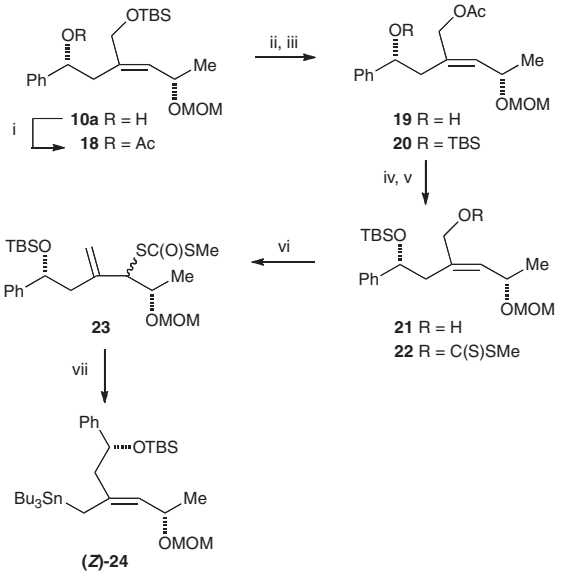


Figure 1. Outline of a mechanism that is consistent with the observed stereocontrol of tin(IV) chloride promoted reactions of allylstannane **9** with aldehydes.[8,9]



Scheme 3. Reagents and conditions: (i) Ms_2O, Et_3N, DCM, rt, 2 h (**16b**, 91%; **16d**, 37%); (ii) TBAF, THF, rt, 15 min (**17b**, 36%); **17d**, 43%); (iii) Ms_2O, Et_3N, DCM, rt, 18 h (**17a**, 33%; **17c**, 24%).

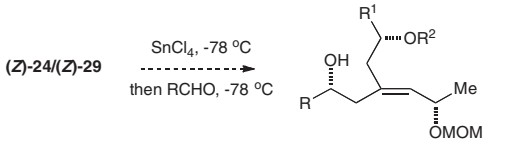


Scheme 4. Reagents and conditions: (i) Ac_2O, Et_3N, DMAP, DCM, rt, 1 h (94%); (ii) TBAF, THF, rt, 1 h (60%); (iii) TBSOTf, Et_3N, DCM, rt, 90 min (85%); (iv) NaOH, MeOH, rt, 1 h (96%); (v) NaH, toluene, rt, 90 min, CS_2, rt, 3 h, MeI, rt, 18 h (63%); (vi) toluene, heat, 6 h (ca. 100%); (vii) ^{n}Bu$_3$SnH, AIBN (cat.), toluene, heat, 90 min [58%; (*E*):(*Z*) = 6:94].

conditions gave the pent-2-enyl-stannane **24**, again predominately, 94:6, as the (*Z*)-isomer.

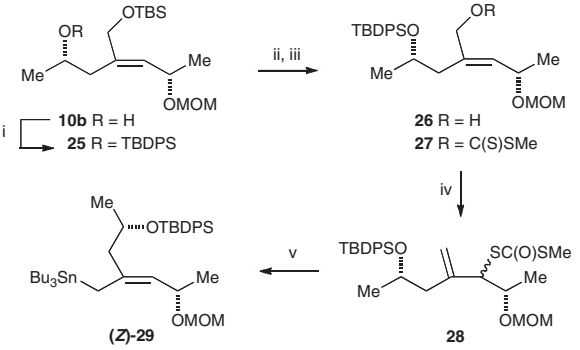
Stannane **29** was prepared from the monoprotected diol **10b** as outlined in Scheme 5. In this case, following protection of the secondary alcohol as it is *tert*-butyldiphenylsilyl ether **25**, selective removal of the *tert*-butyldimethylsilyl group gave the primary alcohol **26**. This was converted into xanthate **27** which rearranged to give the dithiocarbonates **28** on heating. These reacted with tributyltin hydride under free-radical conditions to give the pent-2-enylstannane **29**, again mainly as the (*Z*)-isomer.

However, preliminary studies of the tin(IV) chloride mediated reactions of the pent-2-enylstannanes **24** and **29** with aldehydes were not successful. Generally only complex mixtures of products were obtained and only in one case, the reaction of stannane **29** with ethanal, was a trace of the expected product **30** (R = R^1 = Me, R^2 = TBDPS) isolated.



30 R^1 = Ph, Me; R^2 = TBS, TBDPS

The difficulties in the tin(IV) chloride mediated reactions of the stannanes **24** and **29** with aldehydes contrasted with the results obtained using the pent-2-enylstannane **9** which gave the 1,5-*syn*-products **10** from tin(IV) chloride mediated reactions with aldehydes. One explanation for this dichotomy may be due to co-ordination of the electron deficient tin in the intermediate allyltin trihalides **14** and **31** by the silyloxy groups as well as by the MOM-ethers, see Figure 2. Perhaps the penta-co-ordinated allyltin trihalides **14a** and **31a** are in equilibrium with the hexa-co-ordinated species **14b** and **31b**. The latter would be unable to co-ordinate to, that is, to react with, aldehydes. For the allyltin trihalide **14** derived from stannane **9**, perhaps the equilibrium lies in favour of the more reactive allyltin trihalide **14a** whereas for the allyltin



Scheme 5. Reagents and conditions: (i) TBDPSCl, imid., DCM, rt, 18 h (83%); (ii) PPTS, EtOH, 40 °C, 4 h (72%); (iii) NaH, toluene, rt, 90 min, CS_2, rt, 2 h, MeI, rt, 18 h (70%); (iv) toluene, heat, 2 h (ca. 100%); (v) ^{n}Bu$_3$SnH, AIBN (cat.), benzene, rt, 1 h [77%, (*E*):(*Z*) = 30:70].

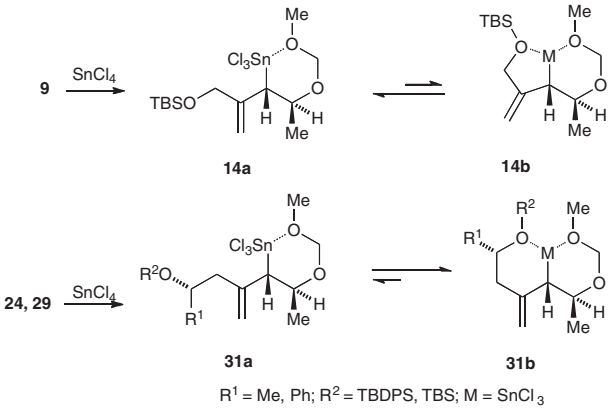


Figure 2. Options for co-ordination of the tin in allyltin trichlorides from transmetallation of pent-2-enylstananes.

trihalide **31** the equilibrium lies in favour of the less reactive hexa co-ordinated species **31b**. However, more work is required to delineate fully the reasons behind the differing reactivities of allylstannane **9** and the homologues **24** and **29**.

This work has shown that 4-alkoxypent-2-enylstannanes with functionality at the 2-position can undergo tin(IV) halide mediated reaction with aldehydes with remote stereocontrol. However the difference in reactivity between the 2-silyloxymethylpentenylstannane **9** and the 2-silyloxypropylpent-2-enylstannanes **24** and **29**, which may be due to additional co-ordination of the electron deficient tin in the intermediate allyltin trichlorides **31**, is of interest. Also of note in this work, is the stereoselective formation of the trisubstituted double-bonds of the (*Z*)-isomers of the stannanes **8**, **24** and **25** during the reactions of the sulfone **7** and dithiocarbonates **23** and **28** with tributyltin hydride under free-radical conditions. This may be due to thermodynamic control involving an interaction between the tin and the 5-heteroatom functionality in the products.

Acknowledgements

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6. The tin(IV) halide mediated reactions of 4-alkoxypent-2-enylstannanes with aldehydes give 1,5-*syn*-5-alkoxyalk-3-enols with excellent (*Z*)-stereoselectivity, for example, **1** → **2**. The geometry of the products **10** parallels this stereoselectivity but the products are designated as (*E*)-isomers simply because the *tert*-butyldimethylsilyloxymethyl group has priority according to IUPAC nomenclature over the hydroxyalkyl fragment.
7. *General procedure for reactions of the pent-2-enylstannane* **9** *with aldehydes: preparation of (1RS,5SR,3E)-3-tert-butyldimethylsilyloxymethyl-5-(methoxymethoxy)-1-phenylhex-3-en-1-ol* **10a**:
Tin(IV) chloride in dichloromethane (1 M, 2.8 ml, 2.8 mmol) was added to the pentenylstannane **9** (1.32 g, 2.345 mmol) in dichloromethane (25 ml) at −78 °C and the solution stirred for 5 min. Benzaldehyde (0.28 ml) in dichloromethane (5 ml) was added and the mixture stirred for 30 min at −78 °C. Saturated aqueous sodium hydrogen carbonate (2 ml) was added and the mixture allowed to warm to room temperature. Water (30 ml) was added and the aqueous phase extracted with dichloromethane (30 ml). The organic extracts were dried ($MgSO_4$) and concentrated under reduced pressure. Chromatography of the residue using ether/light petroleum (25:75 containing 1% triethylamine) gave the *title compound* **10a** (620 mg, 69%), as a colourless oil, R_F (ether:light petroleum = 1:3) 0.3 (Found: $M^+-CH_2OCH_3$, 336.2129; $C_{19}H_{31}O_3Si$ requires *M*, 336.2121); ν_{max} (film)/cm^{-1} 3427, 1673, 1603, 1471, 1463, 1453, 1255, 1156, 1098, 1029, 837, 777 and 700; δ_H (300 MHz; $CDCl_3$) 0.00 and 0.01 (each 3H, s, $SiCH_3$), 0.83 [9H, s, $SiC(CH_3)_3$], 1.12 (3H, d, *J* 6.3, 6-H_3). 2.36 (1H, dd, *J* 14.1, 9.8, 2-H), 2.50 (1H, dd, *J* 14.1, 3.5, 2-H′), 3.26 (3H, s, OCH_3), 3.84 (1H, br d, *J* 3.5, OH), 4.00 and 4.10 (each 1H, dd, *J* 12.5, 1.0, 3-CH), 4.40 (1H, dq, *J* 9.1, 6.3, 5-H), 4.44 and 4.58 (each 1H, d, *J* 6.8, OHC*H*O), 4.64 (1H, m, 1-H), 5.36 (1H, br d, *J* 9.1, 4-H), and 7.20 (5H, m, ArH); δ_C (75 MHz; $CDCl_3$) −5.41, −5.36, 18.30, 21.26, 25.86, 39.75, 55.15, 67.58, 67.62, 72.76, 93.59, 125.41, 127.15, 128.28, 130.53, 138.37 and 144.96; *m*/*z* (CI) 336 (M^+-45, 26%), 301 (15), 230 (19), 213 (60) and 187 (100).
8. (a) Beddoes, R.; Hobson, L. A.; Thomas, E. J. *J. Chem. Soc., Chem. Commun.* **1997**, 1929; (b) Hobson, L.; Vincent, M.; Thomas, E. J.; Hillier, I. H. *J. Chem. Soc., Chem. Commun.* **1998**, 899.
9. The intermediate allyltin trichloride **13** has been depicted as having a six-membered oxastannane ring involving co-ordination of the more remote oxygen of the methoxymethoxy substituent. There is always the possibility that the other oxygen of the methoxymethoxy group is involved in which a case a four-membered oxastannane ring would be formed. However, the preferred four-membered ring containing intermediate would still have the methyl and propenyl groups *trans*-disposed with respect to the oxastannane ring, that is, the same configuration at the tin bearing stereogenic centre relative to the configuration of the stereogenic centre bearing the methoxymethoxy substituent. The same overall stereochemical outcome would therefore be expected.
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