Pure Appl. Chem., Vol. 78, No. 11, pp. 2015–2028, 2006.
doi:10.1351/pac200678112015

Alternatives to allylstannanes for remote stereocontrol*

Matthew Booth, Christopher Brain, Pilar Castreno, Sam Donnelly, E. Kate Dorling, Olivier Germay, Lindsay Hobson, Naresh Kumar, Nathaniel Martin, Christopher Moore, Devendra Negi, Eric J. Thomas‡, and Anna Weston

The School of Chemistry, The University of Manchester, Manchester, M13 9PL, UK

Abstract: Allylstannanes with remote heteroatom substituents are transmetallated by tin(IV) halides to give allyltin trihalides which react with aldehydes with useful levels of remote stereocontrol; the use of this chemistry is exemplified by syntheses of several natural products. However, organotin starting materials are toxic and lead to residues which are difficult to remove and to dispose of. Studies are therefore underway to find procedures to carry out these and analogous reactions without the use of organotin reagents. Following mechanistic studies into allylstannane transmetallation, the use of allylsilicon and germanium reagents was investigated, with the allylgermanium reagents being viable alternatives to allylstannanes. In addition, investigations of reactions of allylstannanes mediated by bismuth(III) iodide led to the development of reactions of allyl bromides with aldehydes promoted by the low-valency species formed by treatment of bismuth(III) iodide with zinc powder. These reactions proceed with useful complementary 1,5-stereocontrol.

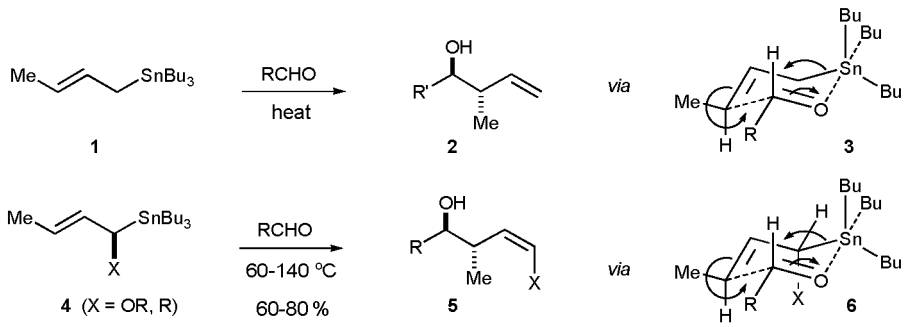
Keywords: synthesis; stereoselectivity; allylmetals; bismuth; organostannane.

APPLICATIONS OF REMOTE STEREOCONTROL USING ALLYLSTANNANES

Reactions of allylstannanes with aldehydes have been studied for many years. The original studies of the stereoselectivities of noncatalyzed reactions showed that (*E*)-but-2-enylstannanes **1** react with aldehydes to give the 1,2-*anti*-products **2** via the chair-like, six-membered, cyclic, transition structure **3** [1]. Subsequently, it was shown that analogous reactions of 1-substituted (*E*)-but-2-enylstannanes **4** give the (*Z*)-1,2-*anti*-products **5** with excellent stereoselectivities, even at the high temperatures, ≥100 °C, which are required for nonactivated aldehydes [2]. In these cases, it would appear that there is a marked preference for the 1-substituent next to the tin to adopt an axial position in transition structure **6**, perhaps because of the strong steric interaction between an equatorial 1-substituent and the apical substituent on the tin, see Scheme 1. Lewis acid-promoted reactions of allylstannanes with aldehydes are also useful in synthesis and are known to take place by transmetallation or by activation of the aldehyde by coordination of the Lewis acid [3,4].

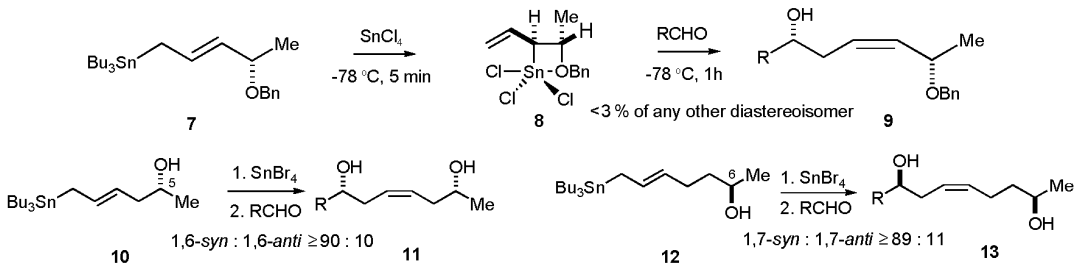
*Paper based on a presentation at the Second International Symposium on Green/Sustainable Chemistry, 10–13 January 2006, Delhi, India. Other presentations are published in this issue, pp. 1971–2050.

‡Corresponding author



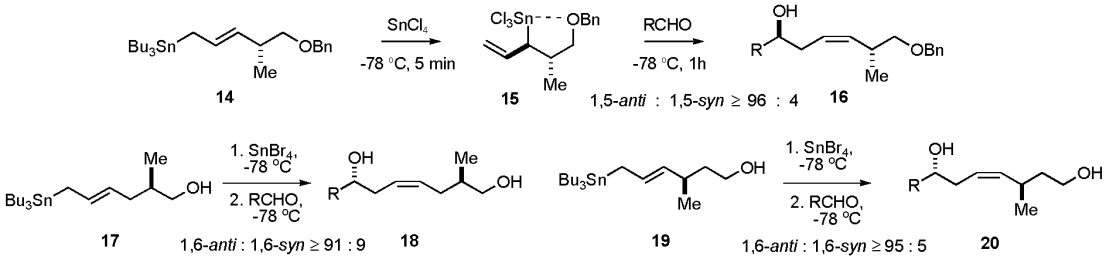
Scheme 1 Noncatalyzed reactions between but-2-enylstannanes and aldehydes.

During investigations of the chemistry of the 4-alkoxypent-2-enylstannane **7**, it was discovered that transmetallation at –78 °C with tin(IV) chloride generated an intermediate, believed to be the allyltin trichloride **8**, which reacted with aldehydes to give the (*Z*)-1,5-*syn*-hex-3-en-1-ols **9** with overall, 1,5-stereocontrol, see Scheme 2 [5,6]. Using tin(IV) bromide, the 5-hydroxyhex-2-enyl- and 6-hydroxyhept-2-enyl-stannanes **10** and **12** generated intermediates which reacted with aldehydes with useful 1,6- and 1,7-stereocontrol [7,8].



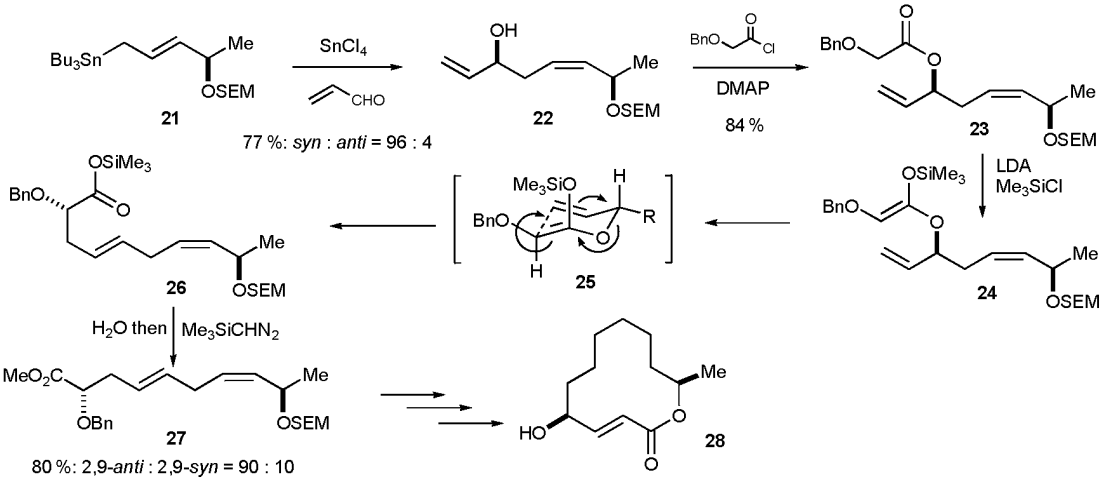
Scheme 2 Remote stereocontrol using 4-, 5-, and 6-alkoxy- and -hydroxyalk-2-enylstannanes.

On treatment with tin(IV) chloride, the 5-alkoxy-4-methylpent-2-enylstannane **14** gave an intermediate, believed to be the allyltin trichoride **15**, which reacted with aldehydes to give the (*Z*)-1,5-*anti*-products **16** [9], and similar reactions, albeit using tin(IV) bromide, were observed for the allylstannanes **17** and **19**, see Scheme 3 [10,11]. Analogous reactions were observed for N- and S-substituted allylstannanes and for tin(IV) halide-promoted reactions of functionalized allylstannanes with imines [6,12].



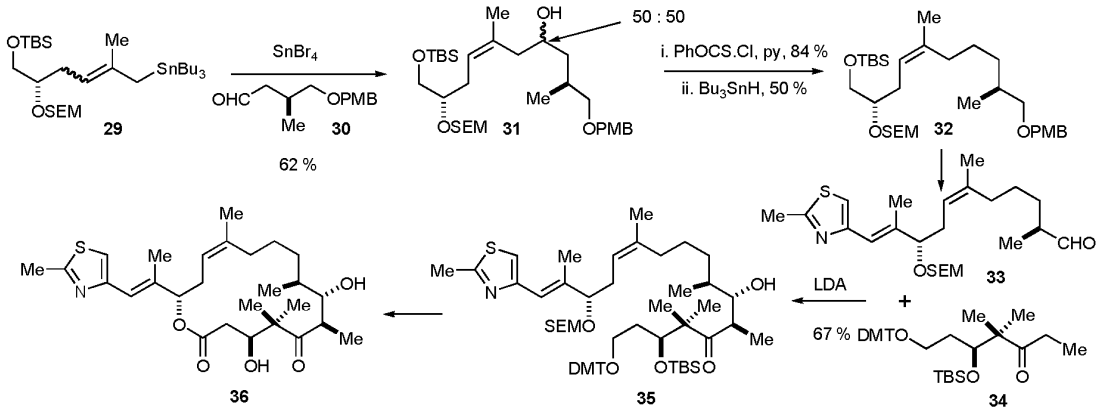
Scheme 3 Further examples of remote stereocontrol using allylstannanes.

The usefulness of this chemistry has been demonstrated in natural product synthesis. Patulolide C **28** is a simple macrolide characterized by the presence of two stereogenic centers in a 1,8-relationship. A diastereoselective synthesis of racemic patulolide has been completed in which the allylstannane (±)-**21**, following transmetallation with tin(IV) chloride, gave the 1,5-*syn*-product **22** on reaction with acrolein [13]. This was taken through to the ester **27**, using an Ireland–Claisen rearrangement of the benzyloxyacetate **23** via the ketene acetal **24**, involving the chair-like transition structure **25**, and hydrolysis of the intermediate silyl ester **26** with conversion to the methyl ester **27**, see Scheme 4. Ester **27** was taken through to patulolide C **28** using standard chemistry [13].



Scheme 4 A stereoselective synthesis of (±)-patulolide **28**.

This synthesis shows that the synthesis of even racemic compounds with remote stereogenic centers can be accomplished diastereoselectively from a single chiral starting material using the allyltin chemistry, but this approach is linear rather than convergent. In a synthesis of epothilone D **36**, the allyltin chemistry was applied to complete a stereoselective synthesis of the C(7)-C(17) fragment **33** [14]. In this case, the use of 1,6-stereocontrol followed by an Ireland–Claisen rearrangement resulted in a rather long synthesis. However, a shorter synthesis was completed using the allyltin chemistry to assemble the 12,13-double-bond stereoselectively, see Scheme 5.

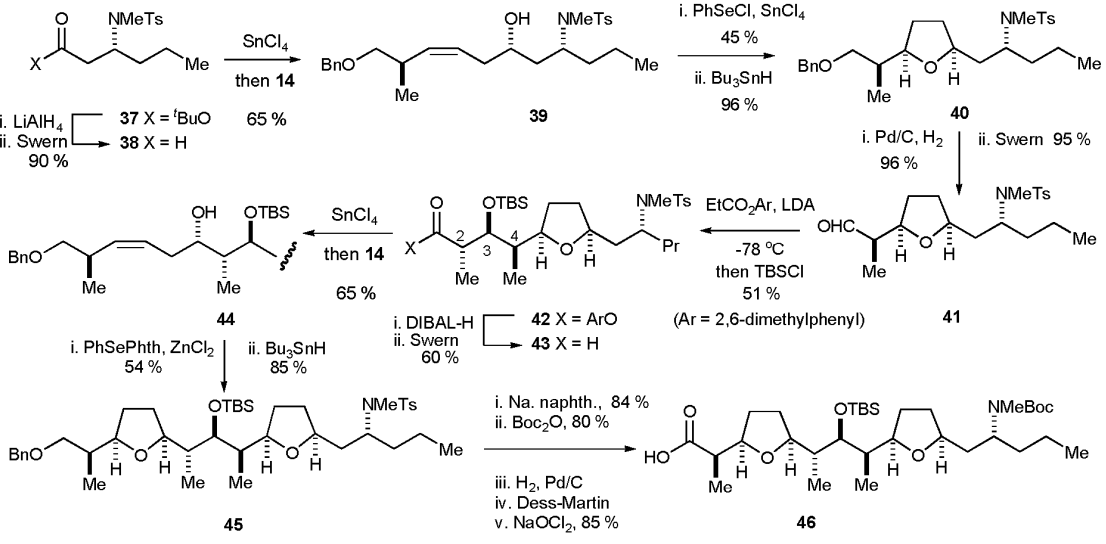


Scheme 5 A synthesis of epothilone D **36**.

The reaction of the bis-functionalized hex-2-enylstannane **29** with the enantiomerically enriched aldehyde **30** gave homoallylic alcohol **31** as mixture of epimers, but was highly stereoselective for the introduction of the required (*Z*)-double-bond. Deoxygenation then gave the alkene **32** which was taken through to the C(7)-C(17)-fragment **33**. Following an aldol condensation with the ethyl ketone **34**, protection, selective deprotection, oxidation, cyclization, and deprotection gave epothilone D **36** [14].

A synthesis of pamamycin 607 **54** has also been completed using the allyltin chemistry [15]. In this case, the key sequence involved the synthesis of 1,5-*anti*-products using the 4-methyl-5-benzyloxypent-2-enylstannane **14** followed by regio- and stereoselective cyclization using phenyl selenenyl chloride or phthalimide in the presence of ca. 20 % of a Lewis acid, typically tin(IV) chloride. In our hands, cyclizations of these slightly sterically hindered (*Z*)-alkenols induced by iodine as the electrophile were less efficient, and the use of a Lewis acid as a promoter improved the yields and rates of the reactions.

The C(1)-C(18) fragment **46** of pamamycin 607 was prepared as outlined in Scheme 6. Ester **37** was prepared by the enantioselective addition of lithium *N*-(*R*)-1-phenylethyl(*N*-phenylmethyl)amide to *tert*-butyl (*E*)-hex-2-enoate followed by transfer hydrogenolysis [16], *N*-tosylation and *N*-methylation. Reduction–oxidation gave the aldehyde **38**, which provided the 1,5-*anti*-homoallylic alcohol **39** on treatment with the stannane **14** and tin(IV) chloride under the usual conditions. Cyclization of the alkenol **39** using phenyl selenenyl chloride in the presence of tin(IV) chloride (20 mole %) and removal of the phenyl selenenyl substituent using tributyltin hydride gave the 2,6-*cis*-disubstituted tetrahydrofuran **40** with excellent stereoselectivity, although the yield of the cyclization was only modest because of competing participation of the nitrogen substituent. An aldol condensation of the aldehyde **41**, prepared from the benzyl ether **40** by hydrogenolysis and oxidation, with the lithium enolate of 2,6-dimethylphenyl propanoate [17] gave the 2,3-*anti*-3,4-*syn*-adduct as the major product, which was isolated as its *tert*-butyldimethylsilyl (TBS) ether **42** in an overall yield of 51 % from **41**.

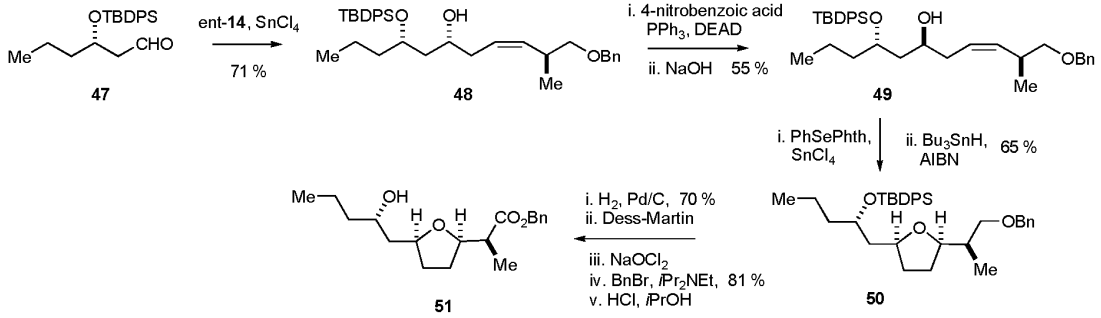


Scheme 6 Synthesis of the C(1)-C(18) fragment of pamamycin.

The ester **42** was converted into the aldehyde **43**, which gave the 1,5-*anti*-alcohol **44** using stannane **14** and tin(IV) chloride. Cyclization of the alcohol using phenyl selenenyl phthalimide–zinc(II) chloride gave the bis-tetrahydrofuran **45** as the dominant stereoisomer after reduction of the phenyl selenenyl group using tributyltin hydride. Removal of the *N*-tosyl group and reprotection of the nitro-

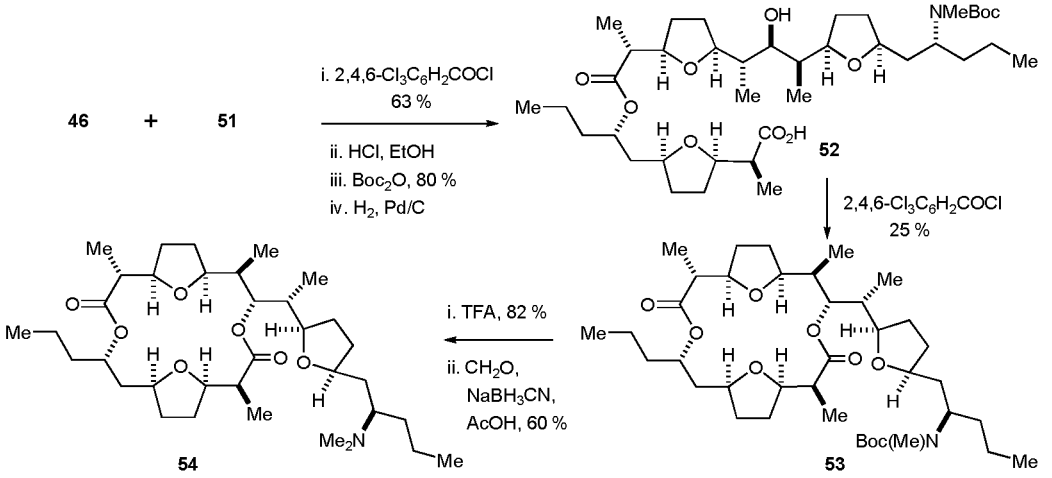
gen as its *tert*-butoxycarbonyl (Boc) derivative followed by selective deprotection and oxidation gave the acid **46** which corresponds to the C(1)-C(18) component of pamamycin 607, see Scheme 6.

Analogous chemistry was used to prepare the C(1')-C(11')-fragment **51** of pamamycin 607 as outlined in Scheme 7 [15]. The stannane ent-**14** was used to convert aldehyde **47** into the 1,5-*anti*-product **48**, and a Mitsunobu inversion and saponification gave the 1,5-*syn*-product **49**. Cyclization using phenylselenenyl phthalimide and tin(IV) chloride followed by reduction then gave the 2,5-*cis*-disubstituted tetrahydrofuran **50** which was converted into the hydroxy-ester **51** by hydrogenolysis, oxidation, conversion to a benzyl ester and removal of the *tert*-butyldiphenylsilyl group using acid. In this case, the cyclization, although stereoselective in favor of the all-*cis* tetrahydrofuran, gave small amounts, ca. 10 %, of other diastereoisomers.



Scheme 7 Synthesis of the C(1')-C(11') fragment of pamamycin 607.

Coupling acid **46** and alcohol **51** followed by removal of the TBS group under acidic conditions, reinstatement of the *N*-Boc group and hydrogenolysis of the benzyl ester gave the hydroxy acid **52**. Cyclization using a modified Yamaguchi procedure then gave the macrodiolide **53**, which was converted into pamamycin 607 **54** by removal of the Boc group and N-methylation, see Scheme 8 [15].

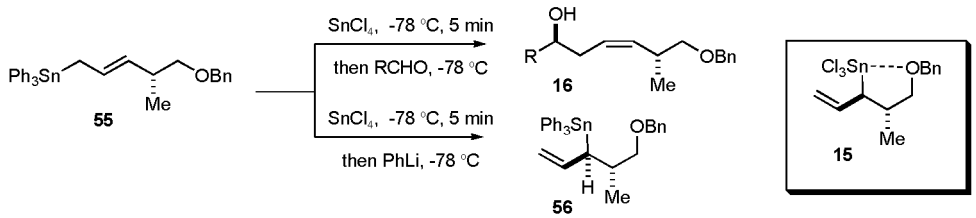


Scheme 8 Completion of a synthesis of pamamycin 60 **54**.

REACTION PATHWAYS OF REMOTE STEREOCONTROL USING ALLYLSTANNANES

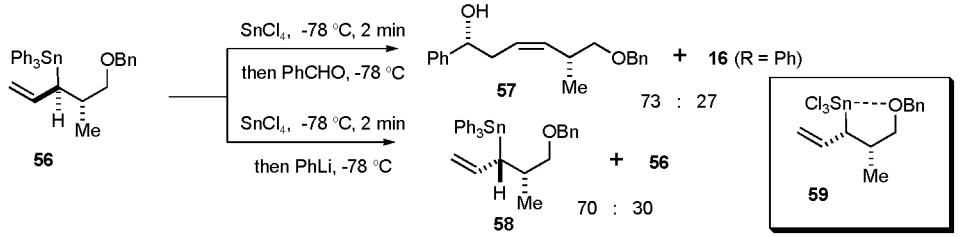
These syntheses of patulolide C, epothilone D, and pamamycin 607 demonstrate novel synthetic strategies based on remote stereocontrol using functionalized allylstannanes, but the widespread application of these reactions is limited by the use of organotin starting materials viz. the formation of tributyltin chloride as a side-product of the initial transmetallation step. However, before studying alternative procedures, it was necessary to get information about the mechanisms of these reactions.

The initial premise had been that a stereoselective transmetallation of the allylstannane by the tin(IV) halide to give an allyltin trihalide, e.g., **8** or **15**, Schemes 2 and 3, was taking place before addition of the aldehyde, the allyltin trihalide then reacting with the aldehyde via a six-membered, chair-like transition structure [6]. To confirm the stereoselectivity of these transmetallations, the pent-2-enyl(triphenyl)stannane **55**, which also gave the *anti*-1,5-products **16** with aldehydes under the usual conditions, was treated with tin(IV) chloride at –78 °C and phenyllithium was added to the reaction mixture, still at –78 °C, 5 min after the addition of the tin(IV) chloride. The *anti*-5-benzyloxy-4-methylpent-1-en-3-yl(triphenyl)stannane **56** was the only product isolated from this reaction, its structure being confirmed by X-ray crystallography of a derivative, see Scheme 9 [18]. This result was consistent with the *anti*-allyltin trichloride **15** being the dominant species in solution 5 min after transmetallation of the allylstannanes **14** and **55** by tin(IV) chloride at –78 °C.



Scheme 9 Trapping the allyltin trichloride **15** generated from the pent-2-en-1-ylstannane **55**.

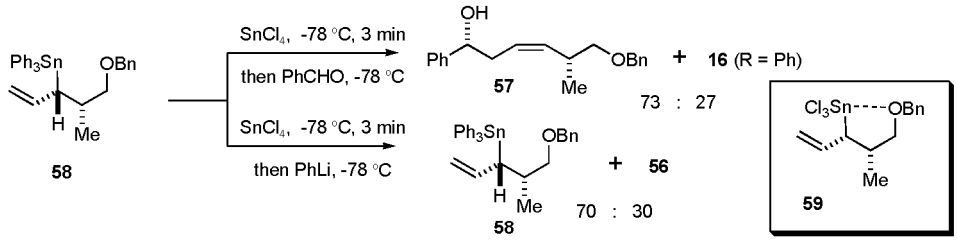
To probe the equilibration of allyltin trichlorides in dichloromethane at –78 °C, transmetallation of the pent-1-en-3-ylstannane **56** was examined, see Scheme 10. In this case, if benzaldehyde was added to the reaction mixture at –78 °C 2 min after the tin(IV) chloride, the major product was the 1,5-*syn*-product **57**, the ratio of the 1,5-*syn*- and 1,5-*anti*-products **57** and **16** (R = Ph) being ca. 80:20. However, this ratio was reduced to 60:40 if 5 min was left before addition of the aldehyde and was reversed to 80:20 in favor of the 1,5-*anti*-product **16** (R = Ph) if the mixture was left 15 min before addition of the aldehyde. Addition of phenyllithium after 2 min transmetallation gave the *syn*-pent-1-en-3-yl(triphenyl)stannane **58** as the major product, **58**:**56** = 70:30 [18].



Scheme 10 Trapping the allyltin trichloride **59** generated from the *anti*-pent-1-en-3-ylstannane **56**.

The predominant formation of the *syn*-products **57** and **58** from these reactions is consistent with the *syn*-allyltin trichloride **59** being the major product formed on transmetallation of stannane **56**. Moreover, as the two allyltin trichlorides **15** and **59** give different product distributions, they cannot be undergoing significant equilibration under our reaction conditions. Therefore, the highly stereoselective formation of the *anti*-allyltin trichloride **15** after 5 min of transmetallation of the pent-2-enylstannane **55** (and **14**) must be due primarily to kinetic control, although it would appear that on standing at –78 °C, the *syn*-allyltin trichloride **59** begins to isomerize to its *anti*-isomer **15**.

The formation of the internal *syn*-allyltin trichloride **59** on transmetallation of the pent-1-en-3-yl-stannane **56** was unexpected since such transmetallations usually proceed via SE2' pathways. However, transmetallation of the *syn*-pent-1-en-3-yl(triphenyl)stannane **58** using tin(IV) chloride also gave the *syn*-allyltin trichloride **59** as indicated by the formation of the *syn*-alcohol **57** as the major product when benzaldehyde was added to the reaction mixture after 3 min transmetallation, **57**:**16** = 73:27, and the *syn*-pent-1-en-3-ylstannane **58** was the major product if the reaction was quenched by phenyllithium, see Scheme 11. Thus, transmetallation of the *anti*-pent-1-enylstannane **56** took place with inversion of configuration, whereas transmetallation of the *syn*-isomer **58** involved retention [18].

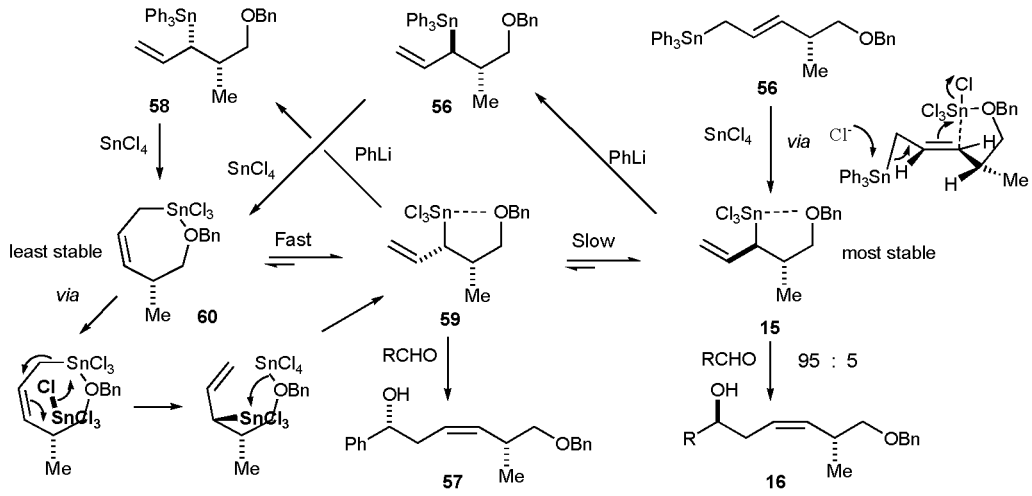


Scheme 11 Trapping the allyltin trichloride **59** generated from the *syn*-pent-1-en-1-ylstannane **58**.

Based on these data, a fuller pathway for the generation and trapping of the allyltin trichlorides **15** and **59** is given in Scheme 12. It is suggested that the stereoselective formation of the *anti*-pent-1-en-3-yltin trichloride **15** from the pent-2-enyl(triphenyl)stannane **56** is due primarily to kinetic control perhaps via an antarafacial process, with the 4-methyl substituent preferring to adopt the less hindered outside position, so controlling the facial selectivity of the transmetallation. The *anti*-allyltin trichloride **15** can then be trapped by aldehydes to give the 1,5-*anti*-products **16** or by phenyllithium to give the *anti*-pent-1-en-3-yl(triphenyl)stannane **56** [19].

Since transmetallations of both the *anti*- and *syn*-pent-1-en-3-yl(triphenyl)stannanes **56** and **58** give the *syn*-allyltin trichloride **59**, it is suggested that these reactions actually proceed via the initial formation of the pent-2-en-1-yltin trichloride **60**, which undergoes a rapid and stereoselective isomerization to the *syn*-isomer **59**. This selective isomerization may involve approach of tin(IV) chloride to the less hindered face of the coordinated pent-2-enyltin trichloride **60** followed by an SE' reaction as shown. The *syn*-pent-1-en-3-yltin trichloride **59** can then be trapped by the rapid addition of an aldehyde or phenyllithium to give the 1,5-*syn*-products **57** or the *syn*-pent-1-en-3-yl(triphenyl)stannane **58**, or it can slowly isomerize to the more stable *anti*-isomer **15**.

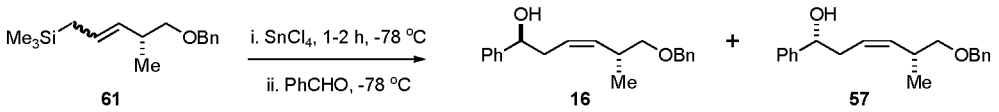
This work indicates that kinetic control determines the high stereoselectivity observed for the tin(IV) chloride promoted reactions of the pentenylstannanes **14** and **56**, providing the intermediate allyltin trichloride **15** is trapped within minutes at –78 °C.



Scheme 12 Outline reaction pathways for the isomeric pentenyltin trichlorides **15**, **59**, and **60**.

DEVELOPMENT OF TIN-FREE PROCEDURES FOR REMOTE STEREOCONTROL

Allylsilanes are known to be transmetallated using tin(IV) chloride [20]. However, transmetallation of the (*Z*)- and (*E*)-pent-2-enyl(trimethyl)silanes (*Z*)-**61** and (*E*)-**61** using tin(IV) chloride required 1–2 h at –78 °C, and the overall reaction with benzaldehyde showed only modest stereoselectivity in favor of the 1,5-*anti*-products **16**, although slightly better stereoselectivity was observed for the (*Z*)-isomer (*Z*)-**61**, see Scheme 13. Similar results were found with other aldehydes and for the analogous phenyl(dimethyl)allylsilanes, and are consistent with equilibration of the pent-1-enyltin chlorides **15** and **59** during the slow transmetallation step [20].

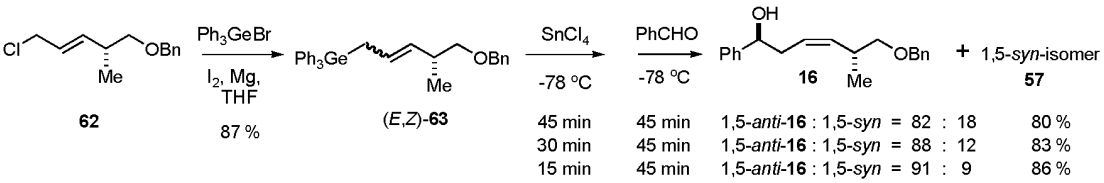


Scheme 13 Remote stereocontrol using allylsilanes.

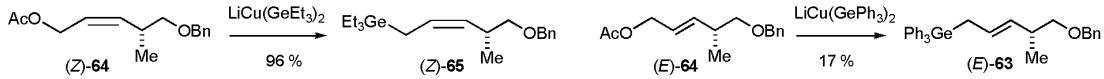
Since allylgermanes are between allylstannanes and allylsilanes in reactivity, it was of interest to investigate the rate and stereoselectivity of transmetallation of allylgermanes using tin(IV) chloride [21]. Interestingly, the overall stereoselectivity of transmetallation of the pentenyl(triphenyl)germane **63** [a ca. 50:50 mixture of (*E*)- and (*Z*)-isomers prepared from the allyl chloride **62** using the Barbier procedure] with tin(IV) chloride, and reaction of the allyltin trichloride so formed with benzaldehyde, was found to depend on the time allowed for the transmetallation step. With a transmetallation time of 45 min, only modest stereoselectivity, 82:18, was observed in favor of the 1,5-*anti*-product **16**, but this improved to 91:9 if the transmetallation time was only 15 min, see Scheme 14. If the aldehyde was added more quickly than this, transmetallation was incomplete, and branched side-products were formed by reaction of the allylgermane with the Lewis acid-coordinated aldehyde.

Reactions of the (*E*,*Z*)-pentenyl(triphenyl)germane (*E*,*Z*)-**63** with other aldehydes with transmetallation using tin(IV) chloride were studied, and the results are shown in Table 1. In addition, the (*Z*)-pent-2-enyl(triethyl)germane (*Z*)-**65** and the (*E*)-pentenyl(triphenyl)germane (*E*)-**63** were prepared from the acetates (*Z*)-**64** and (*E*)-**64** by treatment with the lithium bis(triethylgermyl)- and bis-(tri-

phenylgermyl)-cuprate, see Scheme 15, and their tin(IV) chloride-promoted reactions with aldehydes were investigated. The results of these studies are also shown in Table 1 [21].

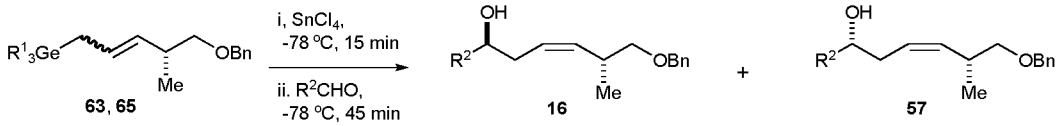


Scheme 14 Effect of time on allylgermane transmetallation.



Scheme 15 Preparation of the allylgermanes (*Z*)-**65** and (*E*)-**63**.

Table 1 Remote stereoselectivity in tin(IV) chloride-promoted reactions of allylgermanes **63** and **65**.

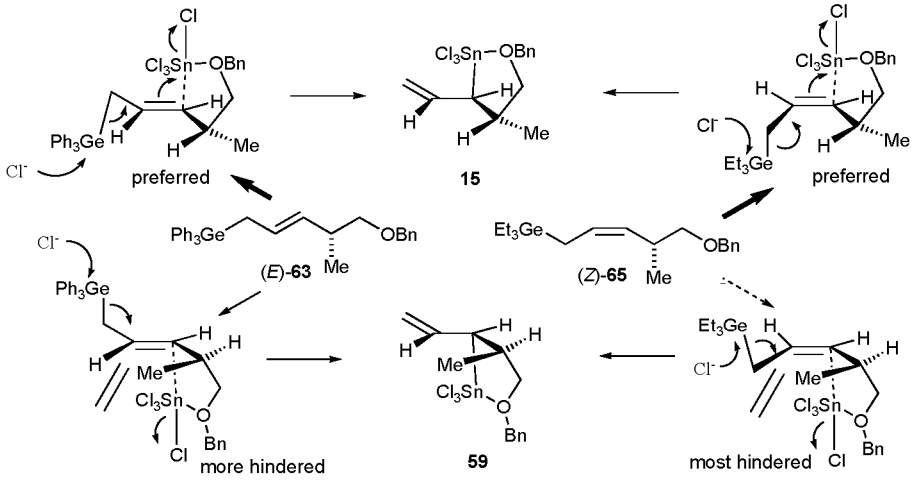


Pent-2-enyl-germane	Aldehyde R^2	Isolated yield (%)	Ratio 1,5-*anti*-**16**:1,5-*syn*-**57**
(*E*,*Z*)-**63**	Ph	58(86)[a]	91:9
"	4-$O_2NC_6H_4$	88	90:10
"	4-ClC_6H_4	56	99:1
"	$(CH_3)_2CH$	66(78)[a]	99:1
"	$CH_3(CH_2)_2$	(67)[a]	98:2
"	(*E*)-CH_3CH=CH	(86)[a]	97:3
"	(*E*)-PhCH=CH	(67)[a]	95:5
(*Z*)-**65**	Ph	100	98:2
"	4-$O_2NC_6H_4$	(85)[a]	98:2
"	4-ClC_6H_4	(84)[a]	99:1
"	$(CH_3)_2CH$	(57)[a]	99:1
"	$CH_3(CH_2)_2$	74	99:1
(*E*)-**63**	Ph	(86)[b]	91:9

[a]For the reactions in parenthesis, 3 equiv of aldehyde were used relative to the germane. For all other reactions, the mole ratio of germane to aldehyde was 1:1.
[b]The transmetallation time in this case was 7 min.

The tin(IV) chloride-promoted reactions of the allylgermanes **63** and **65** were stereoselective in favor of the 1,5-*anti*-products **16**. Reactions of the (*Z*)-pent-2-enyl(triethyl)germane (*Z*)-**65** were particularly stereoselective, with the ratio of the 1,5-*anti* : 1,5-*syn*-products being ≥98:2 in all cases. It may be that the geometry of the double-bond is important here since the transition structure leading to the *syn*-allyltin trichloride **59** from the (*Z*)-4-methylpentenylgermane (*Z*)-**65** would require the 4-methyl group to adopt the inside position with a severe steric interaction with the *cis*-orientated 1-methylene group, see Scheme 16. The transition structure for formation of the *syn*-allyltin trichloride **59** from the

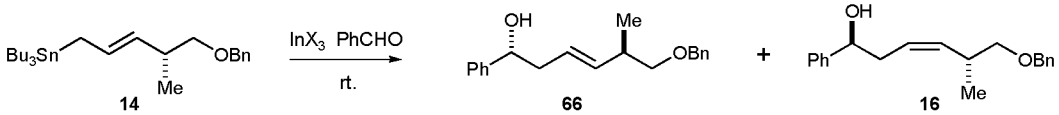
(*E*)-4-methylpentenylgermane (*E*)-**63** is less hindered since only the hydrogen on the double-bond is *cis*-disposed to the inside methyl group, although in both cases the methyl group prefers the less hindered outside position, leading to formation of the *anti*-allyltin trichloride **15** [21,22].



Scheme 16 Stereoselectivity of transmetallation of (*E*)- and (*Z*)-4-methylpent-2-enylgermanes.

The above results show that allylgermanes can be used in place of allylstannanes for remote stereocontrol at least for the formation of the 1,5-*anti*-products **16**. At this point, it was decided to see whether other reactive allylmetal reagents could be generated from allylstannanes, which react with useful stereoselectivity with aldehydes. It might then be possible to access these intermediates from non-metallic organo-starting materials.

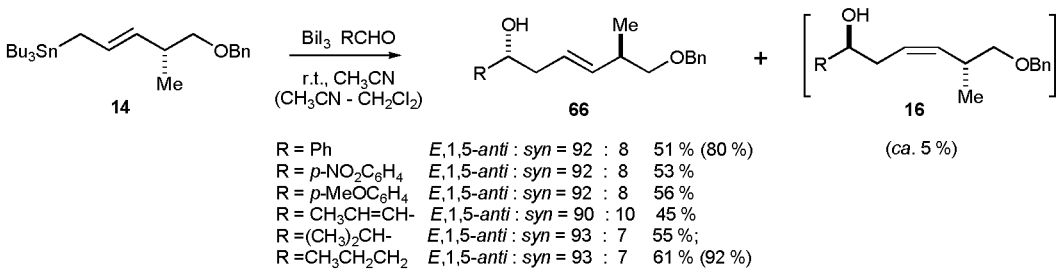
Transmetallation of the pent-2-enylstannane **14** using indium(III) halides was carried out at room temperature in the presence of benzaldehyde [23,24]. However, the major product was the 1,5-*anti*-(*E*)-hexenol (*E*)-**66**, see Scheme 17. This product had the opposite configuration at the newly formed stereogenic center from that in the 1,5-*anti*-(*Z*)-products **16** obtained using tin(IV) halides. However, the stereoselectivity was only modest, although it did improve along the series $InCl_3 < InBr_3 < InI_3$ [23].



$InCl_3$ CH_2Cl_2	*E*, 1,5-*anti* : *syn* = 70 : 30 (72 %)	10 %
$InBr_3$ CH_3CN	*E*, 1,5-*anti* : *syn* = 78 : 22 (66 %)	5 %
InI_3 CH_3CN	*E*, 1,5-*anti* : *syn* = 80 : 20 (42 %)	5 %

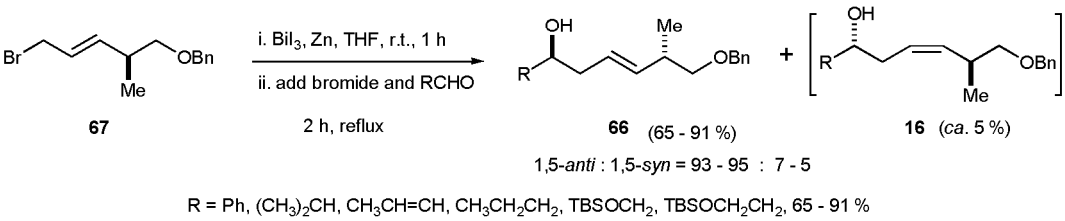
Scheme 17 Indium(III) halide-promoted reactions of pent-2-enylstannane **14** with aldehydes.

Better stereoselectivity in favor of the 1,5-*anti*-(*E*)-products **66** was observed, however, using bismuth(III) iodide, also at room temperature in the presence of the aldehyde, with better yields being obtained using a mixed acetonitrile-dichloromethane solvent system [23]. Under these conditions, less than 5 % of the 1,5-*anti*-(*Z*)-products **16** were obtained with better than 90:10 selectivity in the (*E*)-product manifold for the 1,5-*anti*-isomers **66**, see Scheme 18.



Scheme 18 Bismuth(III) iodide-promoted reactions of pent-2-enylstannane **14** with aldehydes.

Bismuth(III) iodide has been reduced using zinc powder to give a black solid, believed to be bismuth(0), which promoted the reaction of prop-2-enyl bromide, with aldehydes giving homoallylic alcohols [25]. Therefore, it was of interest to investigate the stereoselectivity of analogous reactions of 5-benzyloxy-4-methylpent-2-enyl bromide **67**. In the event, the bromide **67** and aldehydes when added in tetrahydrofuran to the suspension of the intermediate generated by reduction of bismuth(III) iodide with powdered zinc, gave the *anti*-(*E*)-isomers **66** as the major products, with stereoselectivities very similar to those obtained in the bismuth(III) iodide-promoted reactions of pentenylstannane **14** and aldehydes, see Scheme 19 [26].

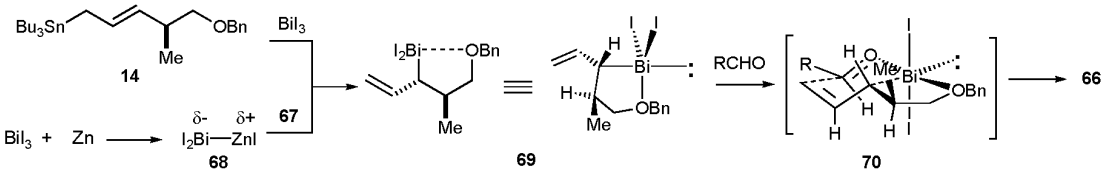


Scheme 19 Bismuth(III) iodide–zinc-promoted reactions of pentenyl bromide **67** with aldehydes.

These reactions of bromide **67** are of interest in that they provide tin-free 1,5-stereocontrol. Moreover, good yields and stereoselectivities were obtained with a range of aldehydes, both aliphatic and aromatic. The reactions are experimentally easy to carry out with the precipitated bismuth species simply being filtered off at the end of the reaction. The less polar, minor (*Z*)-isomers **16** can be separated from the major (*E*)-isomers **66** by column chromatography.

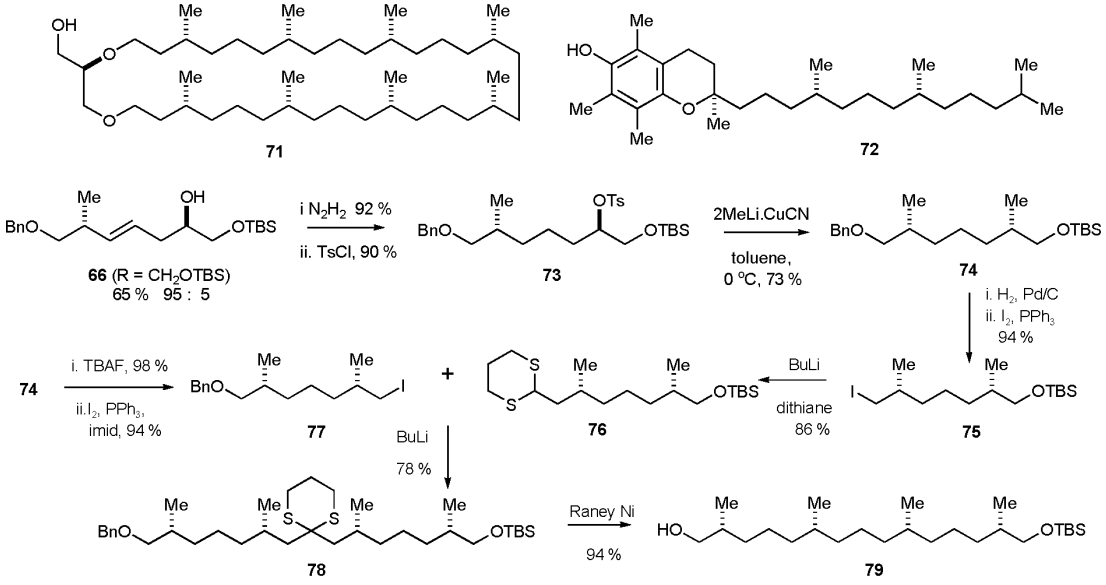
The mechanisms of these bismuth-mediated reactions have not yet been investigated. However, as the stereoselectivities of the bismuth(III) iodide-promoted reactions of the pentenylstannane **14** with aldehydes are very similar to those observed for the bismuth(III) iodide–zinc-promoted reactions with aldehydes of the pentenyl bromide **67**, it is likely that similar intermediates are involved. One possibility is that transmetallation of the pentenylstannane **14** by the bismuth(III) iodide is generating the pent-1-en-3-ylbismuth di-iodide **69**, see Scheme 20. In this intermediate, the bismuth could be trigonal with the lone-pair on bismuth and the carbon-bismuth bond apical [27]. Equatorial attack of the aldehyde *anti* to the oxygen substituent, proximal to the vinyl group, would then generate an octahedral complex which could react via the transition structure **70** to give the observed (*E*)-1,5-*anti*-products **66** [28]. Although bismuth(0) has been suggested as the intermediate generated in the reaction between bismuth(III) iodide and zinc [25], an alternative explanation is that a bimetallic zinc–bismuth species is formed, for example, **68** in which the zinc has inserted into a bismuth iodine bond. The zinc–bismuth bond in this species would be polarized so that the bismuth could behave as a nucleophile. This nucle-

ophilic bismuth species could then react with the pentenyl bromide **67** to give the allylbismuth di-iodide **69** either by a nucleophilic displacement or carbenoid-like insertion process.



Scheme 20 Possible reaction pathways for the bismuth-mediated reactions.

These mechanistic speculations are just hypothetical at present. The reaction conditions are very different from those used for the transmetallation of allylstannanes with tin(IV) halides, and so thermodynamic rather than kinetically controlled processes may be involved. Nevertheless, this chemistry should be useful in synthesis since it avoids the use of organotin reagents. To demonstrate its potential for stereoselective natural product synthesis, it has been applied to develop a stereoselective approach to aliphatic compounds with 1,5-*syn*-orientated methyl groups, e.g., the *Archaea* bacteria membrane component **71** [29] and vitamin E **72**. Thus, the hept-4-enol **66** (R = CH_2OTBS) was prepared from 2-*tert*-butyldimethylsilylethanal using the bromide **67** as outlined above. Following removal of the double-bond using diimide, activation of the hydroxyl group as its toluene *p*-sulfonate and treatment with lithium dimethylcuprate gave the *syn*-2,6-dimethylheptane **74**. Selective deprotection and conversion of the free hydroxyl group into the corresponding primary iodide gave the iodides **75** and **77**, which were used to alkylate dithiane, giving the dialkylated dithiane **78**. Reaction with Raney nickel then gave the open-chain alcohol **79**, which has four 1,5-*syn*-orientated methyl groups, see Scheme 21 [25].



Scheme 21 Synthesis of aliphatic compounds with *syn*-orientated 1,5-methyl substituents.

SUMMARY AND CONCLUSIONS

This work has demonstrated the scope and some applications of remote stereocontrol in reactions of functionalized allylstannanes with aldehydes. However, because of the difficulties in handling organotin reagents it was of interest to develop alternative procedures to carry out this kind of transformation. Using mechanistic studies as a guide, two complementary organotin-free procedures have been developed, namely, the use of allylgermanium compounds for the synthesis of 1,5-*anti*-(*Z*)-hex-3-enols **16** and allylic bromides-zinc/bismuth(III) iodide for the synthesis of *anti*-(*E*)-hex-3-enols **66**. The present work is concerned with establishing the scope of these reagents for synthesis and in probing mechanistic aspects of the organobismuth chemistry.

ACKNOWLEDGMENTS

We thank the EPSRC, AstraZeneca, Pfizer, and Novartis for support and Prof. Natsume, Department of Biological Science, Tokyo University of Agriculture and Technology, for a sample of authentic pamamycin C.

REFERENCES AND NOTES

1. C. Servens, M. Pereyre. *J. Organomet. Chem*. **35**, C20 (1972).
2. (a) A. J. Pratt, E. J. Thomas. *J. Chem. Soc., Perkin Trans. 1* 1521 (1989); (b) V. J. Jephcote, A. J. Pratt, E. J. Thomas. *J. Chem. Soc., Perkin Trans. 1* 1529 (1989).
3. (a) Y. Nishigaichi, A. Takuwa, Y. Naruta, K. Maruyama. *Tetrahedron* **49**, 7395 (1993); (b) G. E. Keck, D. E. Abbott, E. P. Boden, E. J. Enholm. *Tetrahedron Lett*. **25**, 3927 (1984).
4. Y. Yamamoto, H. Yatagai, Y. Ishihara, N. Maeda, K. Maruyama. *Tetrahedron* **40**, 2239 (1984).
5. A. H. MacNeill, E. J. Thomas. *Synthesis* 322 (1994).
6. E. J. Thomas. *J. Chem. Soc., Chem. Commun*. 411 (1997).
7. J. C. Carey, E. J. Thomas. *Tetrahedron Lett*. **34**, 3935 (1993).
8. J. Carey, E. J. Thomas. *J. Chem. Soc., Chem. Commun*. 283 (1994).
9. J. S. Carey, E. J. Thomas. *Synlett* 585 (1992).
10. S. J. Stanway, E. J. Thomas. *Tetrahedron Lett.* **36**, 3417 (1995).
11. S. MacCormick, E. J. Thomas, *J. Organometal. Chem*. **691**, 1437 (2006).
12. D. J. Hallett, E. J. Thomas. *J. Chem. Soc., Chem. Commun*. 657 (1995).
13. E. K. Dorling, E. J. Thomas. *Tetrahedron Lett.* **40**, 471 (1999).
14. N. Martin, E. J. Thomas. *Tetrahedron Lett*. **42**, 8373 (2001).
15. O. Germay, N. Kumar, E. J. Thomas. *Tetrahedron Lett*. **42**, 4969 (2001).
16. S. G. Davies, I. A. S. Walters. *J. Chem. Soc., Perkin Trans. 1* 1129 (1994).
17. M. C. Pirrung, C. H. Heathcock. *J. Org. Chem*. **45**, 1727 (1980).
18. R. Beddoes, L. A. Hobson, E. J. Thomas. *J. Chem. Soc., Chem. Commun*. 1929 (1997).
19. The reaction between the allyltin trichlorides and aldehydes may involve a six-membered transition structure with an octahedral tin. Alternatively, the aldehyde may displace the oxygen substituent from the tin followed by a metallo-ene type process via a transition structure with the group α to tin in the axial position, cf. transition structure **6**. This process explains the strong preference for *cis*-alkene formation in all cases.
20. C. T. Brain, E. J. Thomas. *Tetrahedron Lett.* **38**, 2387 (1997).
21. P. Castreno, E. J. Thomas, A. Weston. *Tetrahedron Lett*. Submitted for publication.
22. (*E*)-Alk-2-enylstannanes have usually been used in tin(IV) halide-promoted reactions with aldehydes and useful stereoselectivities obtained, vide supra. However, it may be that even better stereoselectivities would have been observed had (*Z*)-alk-2-enylstannanes been used.
23. S. Donnelly, E. J. Thomas, E. A. Arnott. *J. Chem. Soc., Chem. Commun*. 1460 (2003).

24. W. Miao, W. Lu, T. H. Chan. *J. Am. Chem. Soc*. **125**, 2412 (2003).
25. M. Wada, H. Ohki, K.-Y. Akiba. *Bull. Chem. Soc. Jpn*. **63**, 1738 (1990).
26. S. Donnelly, M. Fielding, E. J. Thomas. *Tetrahedron Lett*. **45**, 6779 (2004).
27. The X-ray structure of methylbismuth di-iodide shows the bismuth to be square pyramidal with the Bi-C and lone-pair *anti* to each other, see S. Wang, D. B. Mitzi, G. A. Landrum, H. Genin, R. Hoffmann. *J. Chem. Soc., Dalton Trans*. 2837 (1999).
28. The different stereoselectivities for the tin(IV) halide- and bismuth(III) iodide-promoted reactions of allylstannanes indicate that different mechanisms are involved. In Scheme 20, a cyclic transition structure **70** is proposed for the reaction between the alkenylbismuth di-iodide **69** and an aldehyde. However, an open-chain process, e.g., one involving an antiperiplanar arrangement of the terminal allylbismuth di-iodide **69** and the aldehyde carbonyl group, which is antarafacial with respect to the allylbismuth di-iodide, would also be compatible with the observed stereoselectivity. Alternatively, a bismuthate species might be involved which would have to react via an open-chain process. As the stereoselectivities of more allyllic bromides in this reaction are investigated, it may be possible to decide between cyclic and open-chain processes.
29. E. Montegro, B. Gabler, G. Paradies, M. Seemann, G. Helmchem. *Angew. Chem., Int. Ed*. **42**, 2419 (2003).