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Remote stereocontrol using allylstannanes: reversal in stereoselectivity using indium(III) and bismuth(III) halides as promoters

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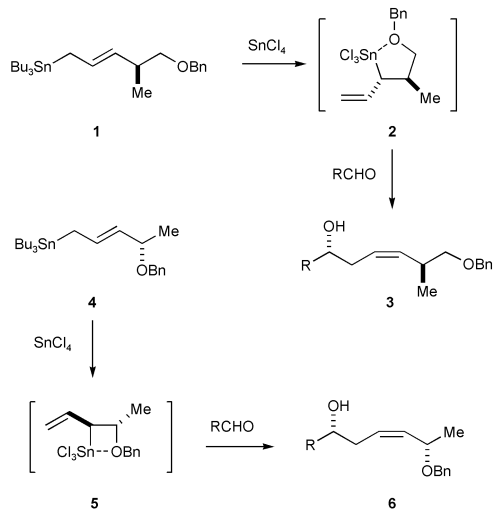
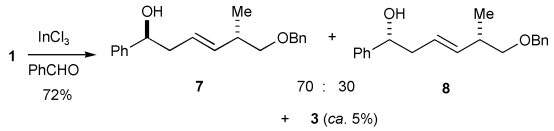
Allyl-indium(III) and -bismuth(III) dihalides, generated by transmetallation of 5-benzyloxy-4-methylpent-2-enyl(tributyl)stannane 1, react with aldehydes with useful levels of 1,5-stereocontrol, a 93 :7 ratio of 1,5-epimers in favour of the 1,5-*anti*-(*E*)-stereoisomers 7 and 11 typically being obtained using bismuth(III) iodide. The 4-benzyloxypent-2-enylstannane 4 similarly gives the 1,5-*syn*-(*E*)-hex-3-enols 13 also with *ca*. 93 :7, stereoselectivity.

Control of the relative configuration of remote stereocentres is a topic of considerable interest at present.[1] In this context, transmetallation of allylstannanes with heteroatom functionality at the 4-, 5- and 6-positions using tin(IV) halides has been shown to be stereoselective generating reactive allyltin trihalides which react with aldehydes and imines with useful levels of 1,5-, 1,6- and 1,7-stereocontrol.[2] For example, the 5-benzyloxy-4-methylpent-2-enyl(tributyl)stannane **1** gives the allyltin trichloride **2** on treatment with tin(IV) chloride which reacts with aldehydes to give 1,5-*anti*-(*Z*)-6-benzyloxy-5-methylhex-3-en-1-ols **3** with ≥96 :4 1,5-stereoselectivity,[3] and the 4-benzyloxypent-2-enylstannane **4** similarly gives the 1,5-*syn*-(*Z*)-5-benzyloxyhex-3-en-1-ols **6** *via* the allyltin trichloride **5**.[4] This chemistry has been used to complete several complex natural product syntheses.[5]



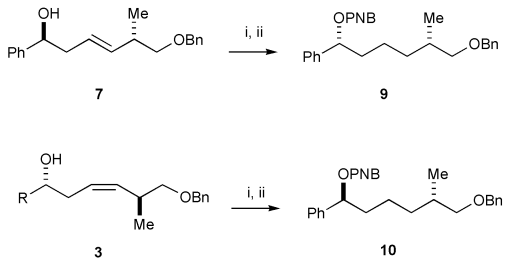
Transmetallation of allyl and allenylstannanes with indium(III) chloride has been widely investigated and stereoselective reactions of the intermediate organo-indium species developed into useful syntheses of 1,2-*anti*-products.[6] Although configurationally stable, the intermediate allyl and alkynyl indium dihalides have been shown to undergo rapid 1,3-rearrangement to give the more stable regioisomers, even in the presence of the aldehyde substrates.[6a] Transmetallation of allenylstannanes with bismuth(III) bromide has been disclosed, although the intermediate organobismuth species were not found to be configurationally stable under the reaction conditions,[7] and a procedure catalytic in bismuth triflate has been published.[8] We now report that transmetallation of the allylstannanes **1** and **4** with indium and bismuth trihalides generates intermediates which react with aldehydes with useful stereoselectivity which is complementary to that observed using tin(IV) chloride.

Reactions between the (racemic) allylstannane **1** and benzaldehyde were carried out by adding the stannane[3] to a solution of the aldehyde and indium(III) chloride at room temperature and led to the formation of a mixture of the 1,5-*anti* and 1,5-*syn*-(*E*) products **7** and **8**, ratio 70 : 30, respectively, together with *ca*. 5% of the (*Z*)-product **3**. Similar results were obtained in either acetone, dichloromethane or acetonitrile as the solvent, and better yields were obtained at room temperature, for example the 72% yield obtained in dichloromethane dropped to *ca*. 25% at −78 °C.



The (*E*)-geometry of the products **7** and **8**, which could not be separated, was established by ^{1}H NMR of the ketone formed in a 78% yield by oxidation of the mixture of **7** and **8** using the Dess Martin periodinane. The relative configuration at the newly formed stereogenic centre in **7** was established by correlation with the *anti*-(*Z*)-isomer **3**,[3] see Scheme 1. Thus the *p*-nitrobenzoate ester **9** obtained by esterification with inversion of the alcohol **7** using the Mitsunobu protocol followed by reduction of the double-bond by diimide was found to be diastereoisomeric with the ester **10** prepared from the alcohol **3** using the same procedures.

Although perhaps of interest mechanistically, the 70 : 30 diasteroselectivity obtained in these reactions is inadequate from a practical point of view. A slightly reduced stereoselectivity, 67 : 33, was obtained using indium(III) triflate in acetonitrile, but indium(III) bromide and iodide led to stereoselectivities of 78 : 22 and 80 : 20. Since better stereoselectivities had been obtained in allylstannane transmetallations when bulkier Lewis acids were used,[2] it was decided to see whether bismuth(III) salts[9] gave improved selectivity. Indeed, with bismuth(III) bromide in acetonitrile, the ratio of **7** to **8** was 90 : 10 (58%) and this increased to 92 : 8 when bismuth(III) iodide was used, see Table 1.



Scheme 1 *Reagents and conditions:* i, Ph_3P, DEAD, 4-$O_2NC_6H_4CO_2H$ (62–68%); ii, *p*-$TsNHNH_2$, NaOAc, DME, H_2O, heat under reflux (50–68%).

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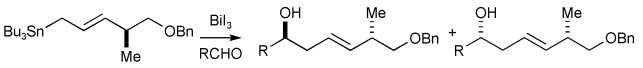
Table 1 Bismuth(III) iodide promoted reactions between aldehydes and the allylstannane **1**



1 7, 11 8, 12

R	Solvent	Yield (%)[a]	Products[b]	Product ratio[c]
Ph	MeCN	51(66)	**7**, **8**	92 : 8
Ph	$MeCN/CH_2CH_2$	80	**7**, **8**	92 : 8
p-$O_2NC_6H_4$	MeCN	53	**11a**, **12a**	95 : 5
p-$MeOC_6H_4$	MeCN	56	**11b**, **12b**	92 : 8
MeCH=CH	MeCN	45	**11c**, **12c**	90 : 10
Me_2CH	MeCN	55	**11d**, **12d**	93 : 7[d]
n-Pr	MeCN	61(82)	**11e**, **12e**	93 : 7[e]
n-Pr	$MeCN/CH_2CH_2$	92	**11e**, **12e**	93 : 7

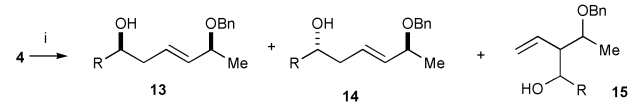
[a] Ratio of stannane : aldehyde : BiI_3 = 1 : 3 : 1 with yields based on stannane. Yields in parenthesis are based on the aldehyde and refer to reactions where the ratio of stannane : aldehyde : BiI_3 = 1.3 : 1 : 1.4. [b] In all cases, *ca.* 5% of *anti*-(*Z*)-alkenols analogous to **3** were obtained.[c] Determined from integration of the CH*Me* peaks. [d] Ratio estimated by glc.[e] Stereochemistry confirmed by correlation with the product prepared using the tin(IV) chloride promoted reaction of stannane **1**, *cf.* Scheme 1.

This stereoselectivity, in favour of the *anti*-(*E*)-stereoisomers **11**, was found for a selection of aldehydes, see Table 1. Initially the reactions were run in acetonitrile as solvent, but later it was found that better yields (*ca*. 90%) were obtained when a mixed solvent system of acetonitrile and dichloromethane (50 : 50) was used. All reactions were carried out by adding the stannane to a solution of the aldehyde and a suspension of the bismuth(III) iodide in the solvent at room temperature, and were quenched after 30 min. Other solvents, tetrahydrofuran, dimethyl sulfoxide and *N*,*N*-dimethyl formamide, gave lower yields and reactions at lower temperatures also gave lower yields with no improvement in stereoselectivity.

Bismuth(III) iodide promoted reactions of the racemic 4-benzyloxypent-2-enylstannane **4** with aldehydes gave the *syn*-(*E*)-isomers **13** with useful stereoselectivity, ratio **13** : **14** = *ca*. 93 : 7, together with minor amounts (*ca*. 5%) of branched products **15**, but the yields of **13** and **14** were only modest even in the optimised acetonitrile–dichloromethane solvent system, see Scheme 2.[10]

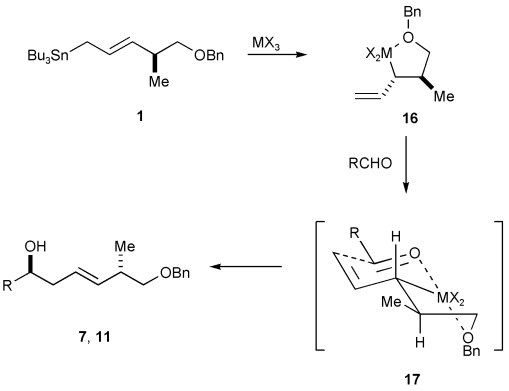
These bismuth(III) and indium(III) halide promoted reactions of the stannanes **1** and **4** are of interest since they give products complementary to those obtained from the analogous reactions using tin(IV) halides.[3] In particular, the configuration of the stereogenic centre bearing the hydroxyl group depends on the reaction conditions and so both diastereomeric series are now directly available.

The mechanisms of these new reactions have not been investigated. However, the regioselectivity and stereoselectivity observed are consistent with transmetallation to give internal allyl metal dihalides **16** which react with aldehydes possibly *via* six-membered transition structures, *e.g.* **17**, in which the group next to the metal adopts the equatorial orientation so leading to the overall 1,5-stereocontrol and introduction of the (*E*)-double-bond, see Figure 1.[11] As allyl indium dihalides are known to undergo rapid 1,3-equilibration to give the terminal allyl metal isomers,[6a] co-ordination of the metal by the benzyloxy group needs to be invoked to explain the observed regioselectivity.



13 14 15

Scheme 2 *Reagents and conditions:* i, RCHO, BiI_3, $MeCN–CH_2Cl_2$, r.t. 30 min (R = Ph, 56%; **12a** : **13a** = 93 : 7: R = *n*-Pr, 62%; **12b** : **13b** = 92 : 8: *ca*. 5% **15** in both cases).



1 16 7, 11 17

Fig. 1 Possible reaction pathway for the formation of products **7** and **11**.

Allenyl organobismuth dihalides are not configurationally stable,[6b] and so it is likely that the preferred intervention of the intermediate **16** (MX_2 = BiI_2) in which the methyl and vinyl groups are *trans*-disposed across the five-membered ring involves pre-equilibration of isomeric allylmetal species.[12]

Further work will investigate the use of this chemistry in synthesis and the development of analogous procedures which do not require allylstannanes as starting materials.

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