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Allyltrichlorostannane additions to chiral aldehydes

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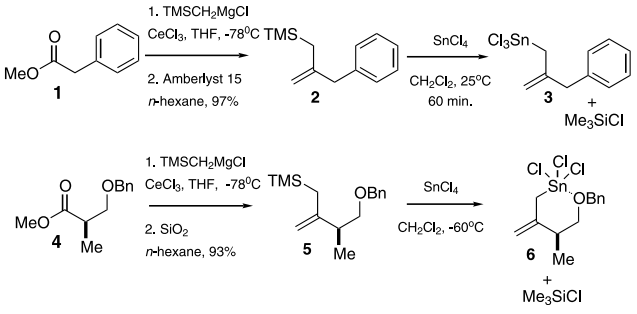
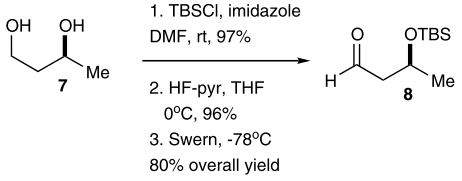
This paper is dedicated to Professor Albert James Kasheres on the occasion of his 60th birthday and also to the Brazilian Chemical Society (SBQ)

Abstract—Chiral and achiral allyltrichlorostannanes reacted with chiral β-alkoxy and *syn* and *anti* α-methyl-β-alkoxy aldehydes to give the corresponding homoallylic alcohols with moderate to high diastereoselectivities.

The Lewis-acid mediated reaction of allylsilanes and allylstannanes with aldehydes is a well-known procedure for the preparation of homoallylic alcohols.[1] Chiral allylmetal reagents may be thought of as acetate–enolate equivalents for diastereoselective construction of stereochemically well-defined homoallylic alcohols. Because these reactions complement the aldol reactions, allylsilanes and allylstannanes are among the most important groups of organometallic reagents available for the control of acyclic stereochemistry.[2]



Scheme 1.



Scheme 2.

We recently communicated that in situ prepared chiral allyltrichlorostannanes react with chiral α-methyl aldehydes to give 1,2-*syn* homoallylic alcohols that are key intermediates for the preparation of polyacetate and polypropionate-derived natural products.[3–5] We have described also that chiral and achiral allyltrichlorostannanes react with *N*-Boc-α-aminoaldehydes to give 1,2-*syn* *N*-Boc-α-aminoalcohols that are key intermediates for the preparation of hydroxyethylene dipeptide isosteres.[6–9]

We wish to describe here a divergently stereocontrolled reaction between chiral β-alkoxy and α-methyl-β-alkoxy aldehydes with achiral and chiral allyltrichlorostannanes to give homoallylic alcohols with moderate to high diastereoselectivities.[10] This study details our efforts to understand the double stereodifferentiating stereocontrol elements involved in chiral allyltrichlorostannane additions to chiral β- and α,β-disubstituted aldehydes.[3–9] In this part of the investigation, we have examined the interplay between 1,2-(Felkin–Anh), 1,3- and 1,4-asymmetric induction in allyltrichlorostannane reactions with α-methyl-β-alkoxy aldehydes under conditions that preclude internal chelation with the aldehyde β-alkoxy substituent.

Achiral allylsilane **2** was prepared from phenylacetic acid methyl ester **1**, while chiral allylsilanes (*R*)-**5** and (*S*)-**5** were prepared from methyl 3-hydroxy-2-methyl-

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propionate **4**, both enantiomers of which are commercially available (Scheme 1).[9,11] According to previously established experimental procedures, allylsilanes **2** and **5** and $SnCl_4$ were mixed before the addition of a solution of the aldehyde in order to promote the ligand exchange reaction leading to the corresponding allyltrichlorostannanes **3** and **6**, respectively (Scheme 1).[4,5]

Aldehyde (*S*)-**8** was prepared in excellent yields from (3*S*)-1,3-butanediol **7** by a sequence that involved full protection as its bis-TBS ether, selective removal of the primary TBS protecting group and Swern oxidation under standard conditions (Scheme 2).

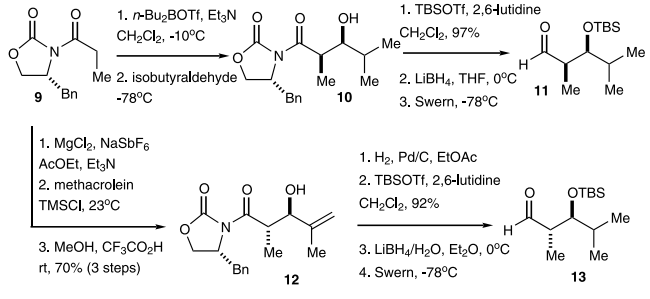
The 1,2-*syn* and 1,2-*anti* aldehydes **11** and **13** were easily prepared from oxazolidinone **9** by using *syn*[12] and *anti*[13] selective aldol reactions, respectively, as the key steps (Scheme 3).

These substrates have been selected to be representative of the complex fragments that might be coupled in polyacetate and polypropionate-derived aldol-type reactions.[14] For these aldehydes, internal chelation is presumably prevented by use of bulky silyl protecting groups since, with few exceptions, silyl ethers are recognized generally for their poor coordinating and chelating abilities.[15]

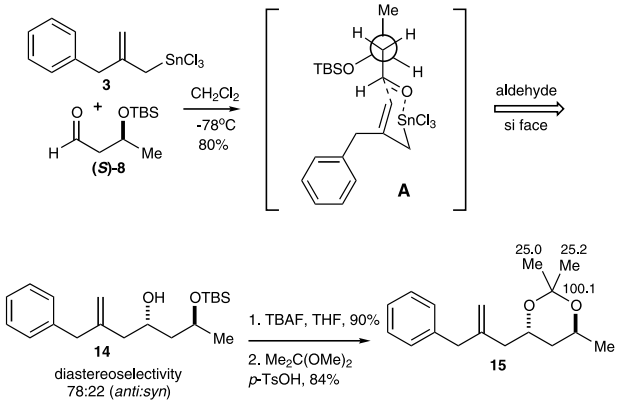
In order to check the facial selectivity of aldehyde (*S*)-**8** we reacted it with achiral allyltrichlorostannane **3** (Scheme 4).[16]

Achiral allyltrichlorostannane **3** reacted with chiral β-alkoxy aldehyde (*S*)-**8** in CH_2Cl_2 at −78°C to give the corresponding 1,3-*anti* product **14** as the major product in good yield and with 78:22 diastereoselectivity favoring the 1,3-*anti* isomer (Scheme 4).[17] The stereoinduction observed in this reaction indicates that the intrinsic facial bias imposed by the resident β-OTBS substituent results in preferential formation of the 1,3-*anti* diastereomer, with a preference for aldehyde *Si*-face attack.[16,17]

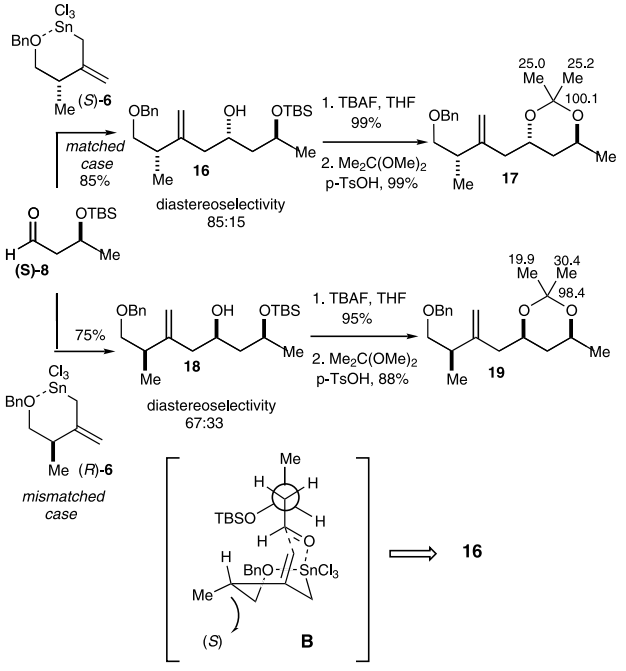
In the proposed transition state conformation (**A**), steric interactions are expected to be reduced when the β-Me substituent in this aldehyde is placed *anti* to the Cα-C=O bond (Scheme 4).[16] In this conformation we might also expect minimization of destabilizing dipole interactions since the β-OTBS group and C=O are



Scheme 3.



Scheme 4.



Scheme 5.

oriented in opposite directions. A chair-like transition state (**A**) with the alkyl group of the aldehyde in an equatorial position and with attack to the *Si*-face of the aldehyde, explains the observed sense of induction.

The relative stereochemistry for homoallylic alcohol **14** was ascertained on the basis of the ^{13}C NMR analysis of the corresponding acetonide **15** (Scheme 4).[18] Treatment of **14** with TBAF at rt effected smooth deprotection of the silyl ether to provide the corresponding diol that was treated with $Me_2C(OMe)_2$ in the presence of *p*-TsOH to give acetonide **15** in 73% overall yield. ^{13}C NMR resonances at 25.0, 25.2 and 100.1 are characteristic of a 1,3-*anti*-acetonide.[19]

Under the same conditions allyltrichlorostannane (*S*)-**6** reacted with aldehyde (*S*)-**8** to give 1,3-*anti*-1,4-*syn* product **16** as the major product (85:15 diastereoselectivity) (Scheme 5).[17] As we know from previous

work,[3–9] the facial bias of this chiral allyltrichlorostannane is dominated by the α-methyl stereocenter and tends to give the 1,4-*syn* isomer with *Si*-face attack. This is an example of a *matched* reaction.

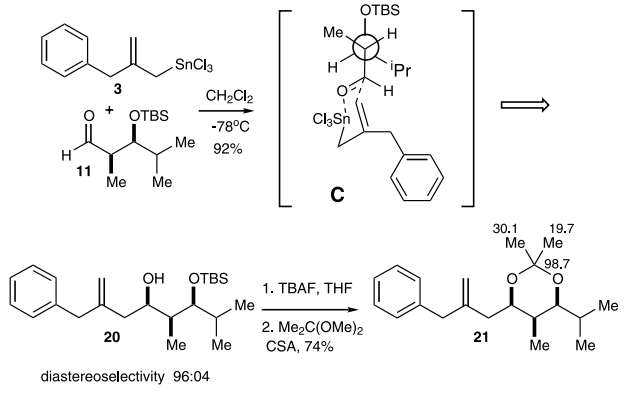
Addition of the enantiomeric allyltrichlorostannane (*R*)-**6** to aldehyde (*S*)-**8** led to a 67:33 mixture favoring the 1,4-*syn*-1,3-*syn* product **18**, in a *mismatched* case (Scheme 5).[17]

The stereoselectivity of these reactions is consistent with an intermediate allyltin trichloride which is stabilized by tin–oxygen interaction (boat-like), and which then reacts with the aldehyde via a chair-like six-membered ring transition state (**B**) in which the aldehyde approaches the boat-like complex opposite to the methyl group (Scheme 5). A boat-like arrangement is proposed, as it avoids steric interactions between the aldehyde substituents and the axial methyl group α to the double bond in the chair structure. The preference of the alkyl group of the aldehyde to adopt an equatorial position controls the aldehyde facial selectivity, resulting in the favored 1,4-*syn* stereochemistry in the adduct.

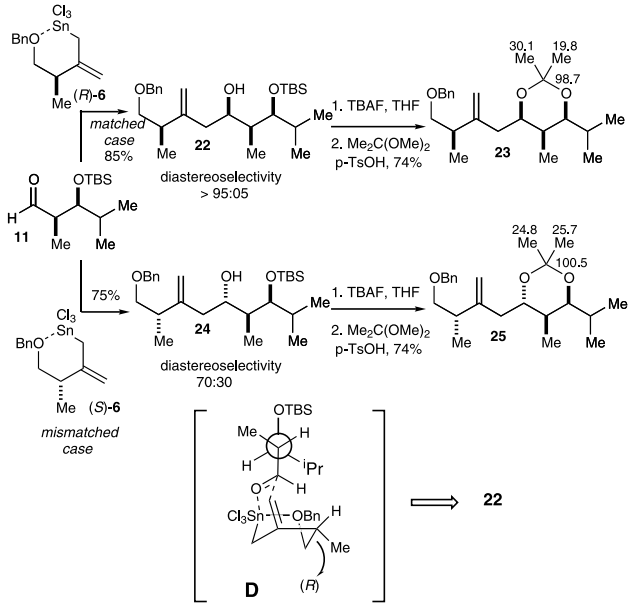
The relative stereochemistry for homoallylic alcohols **16** and **18** was unambiguously established on the basis of the ^{13}C NMR analysis of their respective acetonides **17** and **19** (Scheme 5).[18,19] Treatment of **16** and **18** with TBAF at rt followed by treatment of the corresponding diols under acidic conditions with 2,2-dimethoxypropane gave acetonides **17** (99%) and **19** (83%), respectively. Observed ^{13}C NMR resonances at 25.0, 25.2 and 100.1 for **17** are characteristic of an *anti-1,3-diol*-acetonide and ^{13}C NMR resonances at 19.9, 30.4 and 98.4 for **19** are consistent with a *syn-1,3-diol*-acetonide.[19]

We next examined the stereochemical impact of both α and β-aldehyde substituents with chiral-*syn* and *anti* disubstituted α-methyl-β-alkoxy aldehydes.

Achiral allyltrichlorostannane **3** reacted with chiral *syn*-α,β-disubstituted aldehyde **11** to give the corresponding 1,2-*syn-1,3-syn* product **20** in 92% yield and with 96:04 diastereoselectivity (Scheme 6).[17]



Scheme 6.



Scheme 7.

This example shows that a 1,2-*syn* aldehyde has a preference to give the product with Felkin addition as well as 1,3-*syn* addition.[20] In the presence of an α-methyl stereocenter, 1,3-asymmetric induction imposes an intrinsic facial bias on the carbonyl that results in the formation of the 1,3-*syn*-dioxygen relationship.

In the proposed transition state conformation (**C**), steric interactions are expected to be reduced when the β-OTBS substituent is placed *anti* to the Cα-C=O bond (Scheme 6).[16] In this conformation we might also expect minimization of destabilizing dipole interactions since the β-OTBS group and C=O are oriented in opposite directions. A chair-like transition state (**C**) with attack to the *Re*-face of the aldehyde (Felkin addition), explains the observed induction direction.[20]

The stereochemical assignment of compound **20** was determined by analysis of the ^{13}C NMR spectra of acetonide **21**. ^{13}C NMR resonances at 19.7, 30.1 and 98.7 are characteristic of a *syn-1,3-diol*-acetonide.[18,19]

The reaction of chiral allyltrichlorostannane (*R*)-**6** with aldehyde **11** gives homoallylic alcohol **22** (*all-syn* product) as the major isomer (Felkin addition, *matched case*)[17,20] (Scheme 7).

The stereoselectivity of this reaction is consistent with a chair-like six-membered ring transition state (**D**) in which the aldehyde approaches the boat-like allyltin complex opposite to the methyl group (Scheme 7). The preference of the alkyl group of the aldehyde to adopt an equatorial position controls the aldehyde facial selectivity, resulting in the favored 1,4-*syn* stereochemistry in the adduct.

Allyltrichlorostannane (*S*)-**6** reacted with aldehyde **11** to give a 70:30 ratio favoring isomer **24**, in a *mis-*

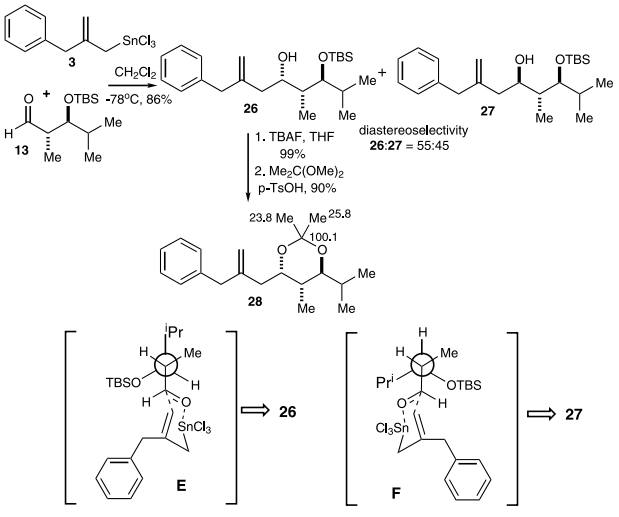
matched case (Scheme 7).[17,20] In this latter case, the α-methyl stereocenter in allyltrichlorostannane (propensity for 1,4-*syn* addition) exerts a dominant influence on aldehyde facial selectivity, by overriding the intrinsic bias imposed by the α and β stereocenters in the aldehyde, to give the 1,3-*syn* product.

The stereochemical assignment of compounds **22** and **24** was again determined by ^{13}C NMR analysis of acetonides **23** and **25**, respectively (Scheme 7). ^{13}C NMR resonances at 19.8, 30.1 and 98.7 for **23** are characteristic of a *syn-1,3-diol*-acetonide and ^{13}C NMR resonances at 24.8, 25.7 and 100.5 observed for **25** are consistent with an *anti-1,3-diol*-acetonide.[18,19]

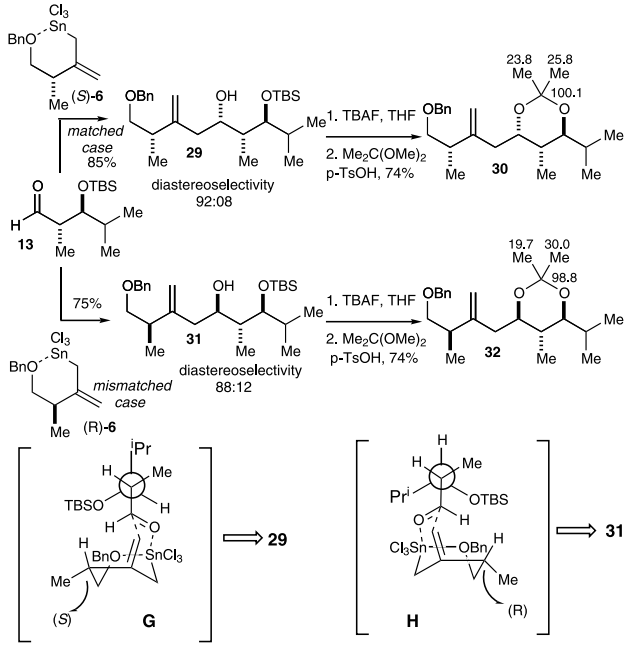
Before starting the study described in Scheme 8, we expected that under conditions that preclude internal chelation, the carbonyl facial bias of *anti*-disubstituted aldehyde **13** should be highly predictable, since the factors which favors both 1,2- and 1,3-asymmetric induction mutually reinforce nucleophilic addition to give 1,2-*syn*-1,3-*anti* diastereomer.[16] We have observed that this is not the case under the reaction conditions described here.

Achiral allyltrichlorostannane **3** additions to chiral *anti*-α,β-disubstituted aldehyde **13** gave the corresponding 1,2-*syn*-1,3-*anti*-product **26** as the major product in good yields, although with only 55:45 diastereoselectivity (Scheme 8).[17,20]

This example shows that an *anti* aldehyde has no facial preference under these conditions, since the Felkin addition to give 1,2-*syn* isomer competes with the β-alkoxy stereocenter to give the 1,3-*syn* isomer. We believe that in this case, the corresponding transition states should be very similar in energy, with conformer **E** (which gives the 1,2-*syn* isomer) being destabilized by the *gauche* interaction $^{i}Pr/Me$ while conformer **F** (which gives the 1,2-*anti* isomer) being destabilized by the $^{i}Pr/C{=}O$ and Me/OTBS gauche interactions (Scheme 8).



Scheme 8.



Scheme 9.

Under the same conditions described before allyltrichlorostannane (*S*)-**6** reacted with aldehyde **13** to give 1,2-*syn*-1,3-*anti* isomer **29** with 92:08 diastereoselectivity (Scheme 9).[17,20]

The reaction of allyltrichlorostannane (*R*)-**6** with aldehyde **13** gave homoallylic alcohol **31** as the major isomer in 88:12 diastereoselectivity (*anti*-Felkin addition, partially *matched case*).[17,20]

The results described in Scheme 9 can be rationalized with dominant acyclic 1,4-asymmetric induction from the chiral allyltrichlorostannane. These are examples of partially *matched* reactions, with the chiral allyltrichlorostannanes (*S*)-**6** and (*R*)-**8** being responsible for the control of the observed diastereoselectivities, through transition states analogous to **G** and **H**, respectively (Scheme 9). This reaction with 1,2-*anti* β-OTBS aldehydes is characterized by poor levels of diastereoselectivity only when an achiral allyltrichlorostannane is used. This attenuated 1,3-*anti* selectivity for 1,2-*anti* aldehydes with the TBS protecting group appears to be general, as similar trends were observed for titanium and boron aldol reaction variants.[16] One might project that the transition states of these reactions exhibit less charge separation than the aldol processes, and are accordingly less subject to the electrostatic influence of the β-OTBS function.

As before, the relative stereochemistry for compounds **29** and **31** was determined by analysis of the ^{13}C NMR of the corresponding acetonides **29** and **31**, respectively (Scheme 9). ^{13}C NMR resonances at 23.8, 25.8 and 100.1 observed for **30** are characteristic of an *anti-1,3-diol*-acetonide and ^{13}C NMR resonances at 19.7, 30.0 and 98.8 for **32** are characteristic of a *syn-1,3-diol*-acetonide.[18,19]

The examples presented in this work show that the levels of π-facial selection are dependent on the absolute stereochemistries of the aldehydes as well as of the allyltrichlorostannane.

The results from these experiments suggest that the stereochemical relationships between the α and β aldehyde substituents may confer either a reinforcing (*matched*) or opposing (*mismatched*) facial bias on the carbonyl moiety. In this complex scenario, the chiral allyltrichlorostannane may adopt either a reinforcing or nonreinforcing relationship. One possible reason for this result could be attributed to the involvement of energetically similar chair and twist-boat pericyclic transition states which lead to diastereomeric product formation. Another possibility to consider in these reactions is that nonbonded interactions between the allyltrichlorostannane and aldehyde α substituents may not be significant in pericyclic transition states leading to either Felkin or *anti*-Felkin addition products.[20] We believe that this chemistry is truly significant in the context of acyclic diastereoselection and will prove to be useful in the synthesis of more complex molecules like polyacetate and polypropionate-derived natural products.[21,22]

Acknowledgements

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17. (a) The ratios were determined by ^{1}H and ^{13}C NMR spectroscopic analysis of the purified product mixture; (b) The *syn* and *anti*-products could not be separated and were characterized as mixtures. We have been able to separate both *syn* and *anti* diols originating from homoallylic alcohols **18** and **24** and they were characterized individually; (c) All of the percentage values represent data obtained from three individual trials.
18. Having confirmed the relative (*syn* or *anti*) relationship between allylsilane derived stereogenic centers, the absolute stereochemistry of the newly formed hydroxyl substituent was determined by ascertaining its relationship to the stereocenter originating from the aldehydes, which are of known configuration.
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21. All new compounds were isolated as chromatographically pure materials and exhibited acceptable ^{1}H, ^{13}C NMR, IR, MS, and HRMS spectral data.
22. **General procedure for allyltrichlorostannane coupling reactions**: To a solution of 2.5 mmol of allylsilane **6** in 7 mL of dry CH_2Cl_2 at −78°C was added 2.5 mmol of $SnCl_4$. The resulting solution was stirred at −78°C for 30 min

when 2.7 mmol of aldehyde in 2 mL of CH_2Cl_2 was added. This mixture was stirred at −78°C for 1 h and quenched by the slow addition of 0.2 mL of Et_3N, followed by 10 mL of saturated NH_4Cl solution. The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2×5 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (30% EtOAc/hexanes) gave the corresponding homoallylic alcohols.