On 1,4-Diastereoselectivity in the Chiral Allylsilane Addition to Chiral α–Substituted Aldehydes.

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Abstract: Chiral allylsilane 2 reacted with chiral α–substituted aldehydes to afford the corresponding 1,4-*syn*-products with good diastereoselectivities. The best selectivities are observed when the reactions are carried out by transmetallation of allylsilane using Tin (IV) chloride in CH_2Cl_2, at -78°C, before addition of the aldehydes.
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The reaction of allylic organometallic reagents with aldehydes has emerged as one of the more synthetically useful methods for acyclic stereoselection.[1] Lewis acid promoted allylation reactions of chiral α–substituted aldehydes have been extensively studied and continue to be an active area of research.[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. Many methods can be used to control the configurations of stereogenic centers that are close to each other.[2,3] However relatively few methods are available for control of the stereochemistry of more remote stereogenic centers.[4,5]

We describe herein a divergently stereocontrolled reaction between chiral α–substituted aldehydes and a chiral allylsilane bearing an ethereal functionality, whose coordination to the Lewis acid was found to play a very important role. These allylsilanes undergo Lewis acid promoted reactions with chiral aldehydes with efficient 1,4-asymmetric induction, independent of the aldehyde absolute stereochemistry, affording the 1,4-*syn* isomer as the major product.

The allylsilane functionality is introduced by cerium mediated trimethylsilylmagnesium chloride addition on the ester group, applying the method of Bunnele and Narayanan.[6] Treatment of ester 1[7] with the reagent prepared from 3 equivalents each of trimethylsilylmagnesium chloride and carefully prepared $CeCl_3$ in THF at -78°C to rt over 6h, followed by work-up with NH_4Cl and SiO_2 chromatography, reproducibly gave allylsilane 2 in 70% yield (Equation 1).[8]
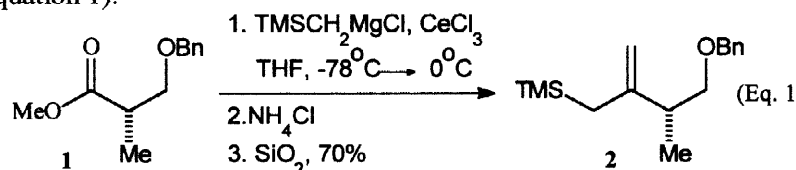
Aldehydes **3-6** were prepared from methyl 3-hydroxy-2-methylpropionate, both enantiomers of which are commercially available.[9] For these aldehydes, chelation is presumably prevented by use of bulky silyl protecting groups, since with few exceptions, silyl ethers are recognized generally for their poor coordinating and chelating abilities.[10a,11]

All of the studies were carried out on aldehydes **3-6** and allylsilane **2** with $SnCl_4$ as the Lewis acid. Tin(IV) chloride promoted reactions of chiral allylsilane **2** with chiral α–methyl aldehydes **3-6** were carried out at 4 different conditions: **1.**Aldehyde and $SnCl_4$ were mixed for 5 min. before the addition of allylsilane; **2.**Allylsilane and $SnCl_4$ were mixed for 1h before the addition of a solution of the aldehyde; **3.**$SnCl_4$ was added to a mixture of allylsilane and aldehyde

in CH_2Cl_2 at -78°C; **4.**Allylsilane and $SnCl_4$ were mixed for 1h at -78°C before the addition of a solution of the aldehyde pre-mixed with $SnCl_4$ at -78°C.

Under these conditions allylsilane **2** reacted with aldehydes **3-4** to give a mixture of 1,4-*syn* and 1,4-*anti*-diastereomers with useful diastereoselectivities, favoring the 1,4-*syn*-isomer with *anti*-Felkin addition (Scheme 1).[10b] It should be noted that this reaction affords a very important subunit with different protecting groups at both termini. Results of reactions of **2** with (S)-aldehydes **3-4** are summarized in Table I.
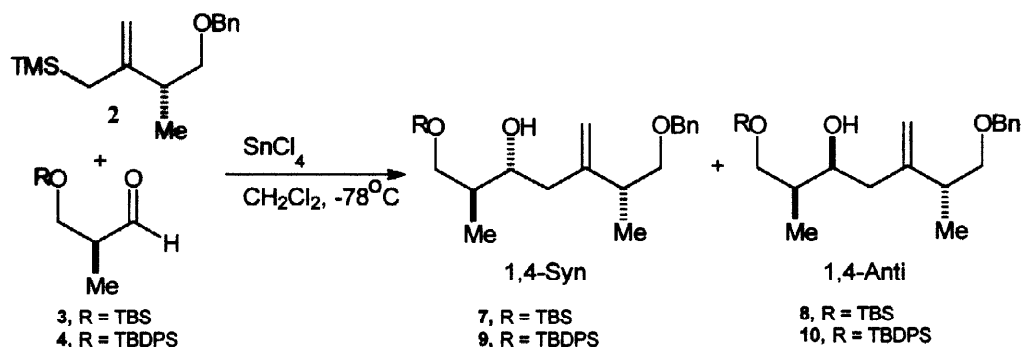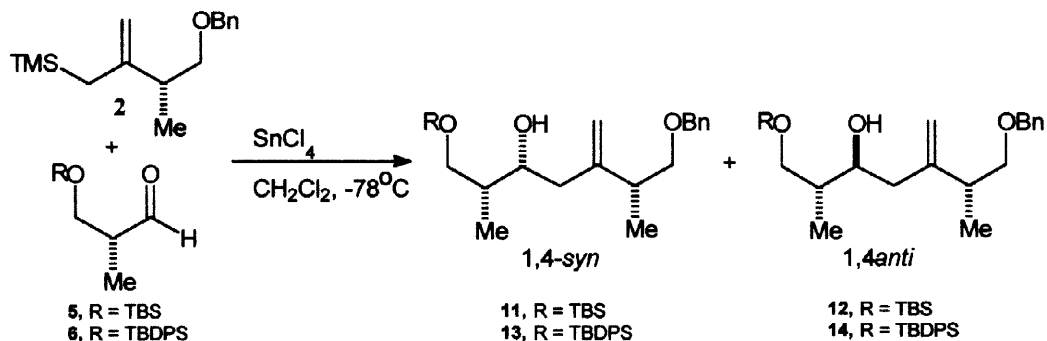
Scheme 1

Table I: Tin(IV) Chloride-Promoted Additions of Chiral Allylsilane **2** to (S)-aldehydes.

Condition[a]	R = TBS[b,c] 1,4-*syn*(**7**) : 1,4-*anti*(**8**)	Yield (%)[d]	R = TBDPS[b,c] 1,4-*syn*(**9**) : 1,4-*anti*(**10**)	Yield (%)[d]
1	52 : 48	80	85 : 15	61
2	90: 10	70	82 : 18	35
3	83 : 17	87	90 : 10	72
4	84 : 16	75	54 : 46	40

a.Reactions were carried out in dichoromethane at -78°C using molar equivalents of allylsilane, $SnCl_4$ and aldehyde. **b.**The ratios were determined by ^{1}H and ^{13}C-NMR spectroscopic analysis of the purified product mixture after protection with TMS-imidazol. Protection as the secondary TMS ether is necessary since the allylsilane reaction afforded mixtures of the secondary silylated (TMS) and non-silylated products. The 1,4-*syn* and *anti*-products could not be separated and were characterized as mixtures; **c.** Averages of at least three runs with ratios +/- 3%. **d.**Combined yields of products isolated chromatographically (SiO_2).

Under the same conditions as described above, allylsilane **2** reacted with the enantiomers of aldehydes **3,4** to give 1,4-*syn*-products with Felkin addition (Scheme 2 and Table II).[10b,11]

Scheme 2

Table II: Tin(IV) Chloride-Promoted Additions of Chiral Allylsilane **2** to (R)-aldehydes.

Condition[a]	R = TBS[b,c] 1,4-*syn*(11) : 1,4-*anti*(12)	Yield(%)[d]	R = TBDPS[b,c] 1,4-*syn*(13) : 1,4-*anti*(14)	Yield(%)[d]
1	75 : 25	90	91 : 09	54
2	90: 10	92	92 : 08	90
3	85 : 15	95	89 : 11	83
4	68 : 32	66	72 : 28	36

The stereoselectivity of the tin(IV)chloride promoted reactions of allylsilane with aldehydes is consistent with a mechanism involving transmetallation of the allylsilanes to give an intermediate allyltin trichloride which is stabilized by tin-oxygen interaction, and which then reacts with the aldehyde via a chair-like six-membered ring transition state in which the aldehyde approaches the complex opposite to the methyl group. 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, independent of the aldehyde absolute configuration (Scheme III).

Scheme III

(S)-aldehyde (*anti*-Felkin addition)   (R)-aldehyde (Felkin addition)
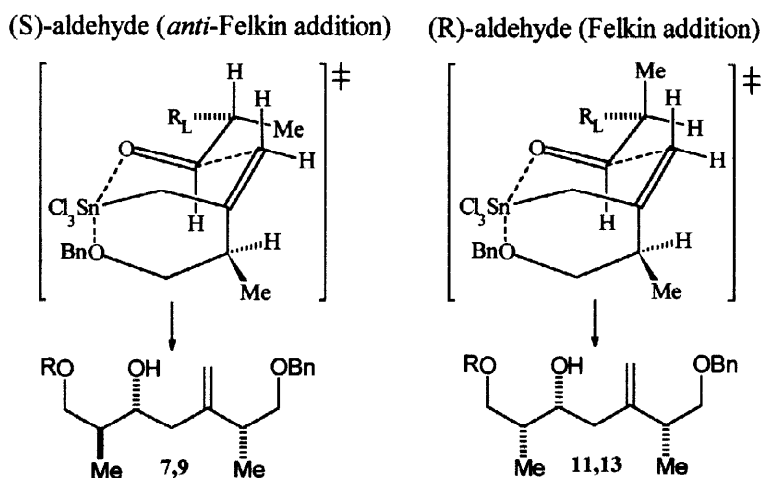
The 1,4-syn relationship in adducts **7,9** and **11,13** was ascertained by spectroscopic analysis of the corresponding acetonides. The indicated vicinal coupling constant data for the benzylidene acetals unambiguously established the configuration of the newly formed stereocenter of the anti-felkin adducts **7,9** and the Felkin adducts **11,13**. Average coupling constants of 11 Hz indicate that protons Ha-Hc in **16** are on opposite faces of the heterocyclic ring, and therefore the acetonide is derived from an anti adduct. In contrast, coupling constants of 1-3 Hz for Ha-Hc in **15** are characteristic of protons residing on the same face of the ring, indicative of a syn product. In some instances the relative ring stereochemistry was further supported by 1H-1H NOE difference measurements. The illustrated NOE measurements on benzylidene acetal established the syn relationship between the newly formed hydroxyl and adjacent methyl bearing stereocenter, thereby securing the stereochemical assignment of these adducts. 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.

Scheme IV

a. TBAF,THF, r.t., 75%; b. CSA(cat.), CH_2Cl_2, 4-methoxybenzaldehyde dimethylacetal, 78%
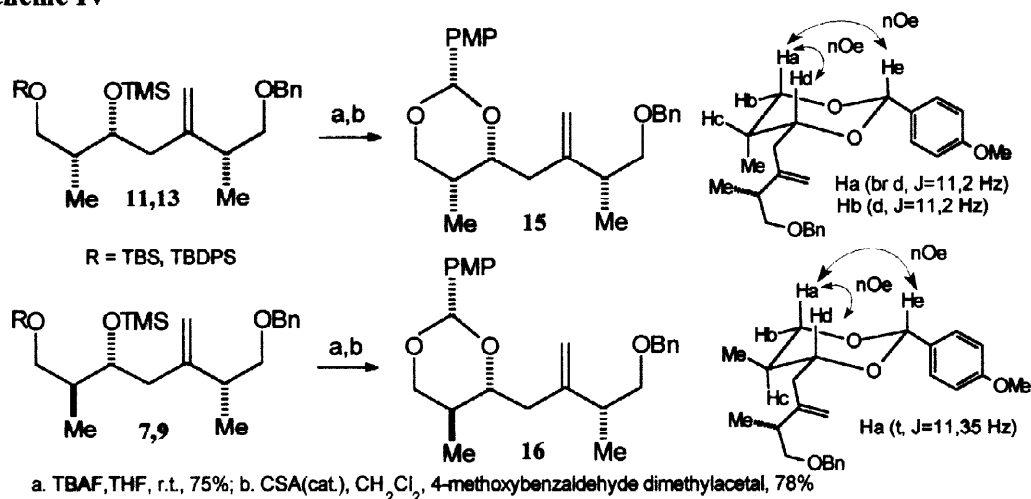
The examples shown that the levels of π–facial selection are independent of the absolute stereochemistry of the aldehydes. The data support the notion that the stereocenter in allylsilane is primarily responsible for the observed diastereoselection. Other Lewis acids should be tested in this reaction in order to improve yields and selectivities and to reduce the amount of racemization in these aldehydes. We believe that this chemistry is truly significant in the context of acyclic diastereoselection and will prove to be exceptionally useful in the synthesis of complex organic molecules like polypropionate and polyacetate-derived natural products. Further exploration of these reagents and their applications is now underway in our laboratory.

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9.Standard literature methods were employed. The final step in each case was Swern oxidation of the corresponding alcohol. Attempts to purify aldehydes 3-6 by silica-gel chromatography resulted in partial racemization. Since the diastereoselectivity of the reactions of these aldehydes with allylsilane 2 depends on their enantiomeric purity, crude aldehydes were used in all of the studies described in the text. It should be noted that partial racemization probably is occurring during reaction since we observed small peaks at δ 1.0-1.2 ppm.

10.(a) Schreiber, S.L.; Shambayati, S.; Blake, J.F.; Wierschke, S.G.; Jorgensen, W.L. *J. Am. Chem. Soc.* **1990**, *112*, 697-703. (b) All new compounds were isolated as chromatographically pure materials and exhibited acceptable ¹H-NMR, ¹³C-NMR, IR, MS, and HRMS spectral data.

11.**Condition 2:** To a solution of 2.5 mmol of allylsilane 2 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 1 h when 2.7 mmol of aldehyde in 2 mL of CH_2Cl_2 was added. This mixture was stirred at -78°C for 30 min 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 (2x5 mL). The combined organic layer was dried ($MgSO_4$), filtered, and concentrated *in vacuo*. Purification by flash chromatography on silica gel (30% EtOAc/hexanes) afforded the corresponding homoallylic alcohols.