## REMARKABLE INCREASE IN THE DIASTEREOFACIAL SELECTIVITY OF THE ADDITION OF $\beta$ -METHYL $\alpha$ -(ALKOXY)ALLYLSTANNANE TO ALDEHYDES: SUBSTITUENT EFFECTS ON DIASTEREOFACIAL SELECTIVITY

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Summary: Several new chiral allylstannanes were prepared and reacted with aldehydes. Excellent diastereofacial selectivity was observed for the reactions of allylstannane 1 with aldehydes in the presence of BF<sub>3</sub>•Et<sub>2</sub>O. This is in contrast to the results from other allylstannanes which do not bear a  $\beta$ -methyl group. These observations were rationalized based on a combination of steric and electronic effects.

The reaction of crotylstannanes with aldehydes in the presence of BF3•Et<sub>2</sub>O affords stereochemically defined building blocks for natural product synthesis.<sup>1</sup> A sufficient number of applications have appeared to provide good documentation for predicting a high syn-selective addition in these reactions<sup>2</sup>. Recent studies by Marshall on  $\alpha$ -(alkoxy)allylstannanes showed that asymmetric induction on achiral aldehydes can be realized by using enantiopure allylstannanes<sup>3</sup>. Unfortunately, although the simple diastereoselectivity (syn/anti) was high the diastereofacial selectivity was only modest. The factors that control the stereochemistry of the reactions between the two trigonal carbon atoms are not completely understood. In order to understand and control the diastereofacial selectivity in asymmetric S<sub>E</sub>2' reactions, we initiated a study of the substituents' effect in these reactions. Now we wish to communicate the results of our study and their implication on the transition state structure.

Allylstannanes 1, 2, 3 and 4 were prepared using the reported method<sup>3</sup> starting from tiglic aldehyde, cyclohexanecarboxaldehyde and crotonaldehyde respectively. Each allylstannane was allowed to react with a representative group of aldehydes in the presence of BF3•Et<sub>2</sub>O. The ratios of the diastereomers were determined by either <sup>1</sup>H NMR or GC/MS, and the chemical yields are in the range of 60-80%. In all cases studied, the highest diastereofacial selectivity was observed for allylstannane 1, eq (1). For example, aliphatic aldehydes



including primary (*n*-heptanal), secondary (cyclohexanecarboxaldehyde),  $\alpha$ ,  $\beta$ -unsaturated (*n*-2-heptenal), and propargyl (5-benzyloxy-2-pentynal) react with 1 at -78 °C in the presence of BF3\*Et<sub>2</sub>O smoothly producing a

uniformly high yield of syn-(E) isomers out of four possible diastereomers. It should be noted that allylstannane 1 fails to react with benzaldehyde under the same conditions.

Fair to good selectivities were observed for the reactions of allylstannanes 2, 3, and 4 with aliphatic aldehydes. However, excellent selectivity was observed with benzaldehyde, eq (2).<sup>4</sup>

R <sub>1</sub> SnBu <sub>3</sub>	$\frac{\text{RCHO}}{\text{BF}_3 \cdot \text{Et}_2 \text{O}} \xrightarrow{R} \bigvee_{\text{OH}}^{1}$		OH			q (2)
2 R1=Me, R'=CH <sub>2</sub> OBzl ∣	s a R=n-hexyl b = cyclohexyl c = phenyl	9 yn-(E) 32 80 <1	10 syn-(Z) 65 20 95	11 anti-(E) <1 <1 <1	12 anti-(Z) <1 <1 5	
3 R1=cyclohexyl R'=CH <sub>2</sub> OBzl	l, d R=n-hexyl e = cyclohexyl f = phenyl	83 58 3	13 42 91	<1 <1 <1	4 <1 6	
4 R1=cyclohexyl R'=CH <sub>2</sub> OMe	$ \begin{array}{ll} \mathbf{g} \ \mathbf{R} = \mathbf{n} - \mathbf{h} \mathbf{e} \mathbf{x} \mathbf{y} \mathbf{l} \\ \mathbf{h} &= \mathbf{c} \mathbf{y} \mathbf{c} \mathbf{l} \mathbf{h} \mathbf{e} \mathbf{x} \mathbf{y} \mathbf{l} \\ \mathbf{i} &= \mathbf{p} \mathbf{h} \mathbf{e} \mathbf{n} \mathbf{y} \mathbf{l} \end{array} $	81 80 11	12 20 61	1 <1 <1	6 <1 27	

The geometry of the enol ether double bond in the products, 9-12, was determined directly from the measurements of the <sup>1</sup>H NMR coupling constants of the vinyl protons.<sup>3</sup>, eq (3). The double bond geometry of the products, 5 and 6, was determined by nuclear Overhauser effect (NOE) measurements, eq (3).



The syn stereochemistry of the major products, although is in accord with literature precedent<sup>1-3</sup>, was further secured by a combination of chemical degradation followed by <sup>1</sup>H NMR spectroscopy analysis and molecular mechanics calculation. For example, ozonolysis of 5c followed by a dimethyl sulfide work-up gave  $\beta$ -hydroxy ketone, 13, whose <sup>1</sup>H NMR spectrum indicates the erythro configuration (i.e. Ja,b = 2.5 Hz), eq (4).



Molecular mechanics (MM2) calculations through multiconformer analysis<sup>5</sup> of 13 give global minimum conformations for the erythro and threo isomers as shown in Fig. 1. A coupling constant of 2.0 Hz was

calculated for the erythro isomer and 7.9 Hz for the threo isomer, which are in accord with the experimental result and literature precedent.<sup>6</sup>



Fig. 1 Global minimum conformations of 13 and its three isomer generated through MacroModel: (a) *erythro* isomer (Ja,b = 2.0 Hz); (b) *three* isomer (Ja,b = 7.9 Hz).

In summary, uniformly high diastereofacial selectivity was observed for the reactions of allylstannane 1 with aldehydes in the presence of  $BF_3$ ·Et<sub>2</sub>O; moderate facial selectivity was observed for allylstannanes 2, 3, and 4. Benzaldehyde reacts with 2, 3, and 4 yielding preferentially the (Z)-enol ether products.

To account for the increase in diastereofacial selectivity of stannane 1, the open transition state proposed by Yamamoto<sup>1</sup> in the crotyltin series is appropriate. A number of studies<sup>3,7</sup> have shown that the C-Sn bond is orthorgonal to the allylic system and anti to the incoming electrophile in the transition state. As depicted in Fig. 2, the relative position of the alkoxy group, OR', determines the facial selection. When the two trigonal carbons approach each other, three staggered rotamers are possible for each facial attack. Among the two antiperiplanar arrangements, rotamer A, which leads to (E) enol ether, is sterically favored since it avoids the repulsion between



Fig 2. Staggered rotamers of transition state conformation leading to Syn-(E) and Syn-(Z) products. R and OR' groups; the rotamer **B**, however, is favored electronically due to the "inside alkoxy" effect.<sup>8</sup> In the absence of a  $\beta$ -methyl group, a mixture of (E) and (Z) isomers are produced since neither the steric nor the electronic effect is dominant enough to overtake the other. In the presence of a  $\beta$ -methyl group, the "inside alkoxy" effect is diminished due to the donor ability of the methyl group, which stabilizes the developing positive charge at the carbon it attached to, eq. 5. Therefore, the steric effect alone determines the outcome of the



reactions. The electronic effects are much more important in the cases of the benzaldehyde, eq. 2. The anomalous nature of the reactions with aromatic aldehydes will be discussed in a separate paper.<sup>9</sup>

In summary, we have investigated the reactions of a few new  $\alpha$ -(alkoxy)allylstannanes with various aldehydes. A dramatic increase in the diastereofacial selectivity has been observed when the  $\beta$ -substituent of the allylstannane is changed from a hydrogen to a methyl group.

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