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AN ANOMALOUS CASE OF DIASTEREOFACIAL SELECTIVITY IN THE ADDITION OF CHIRAL ALLYLSTANNANES TO BENZALDEHYDE: IS THE "INSIDE ALKOXY" EFFECT INVOLVED?

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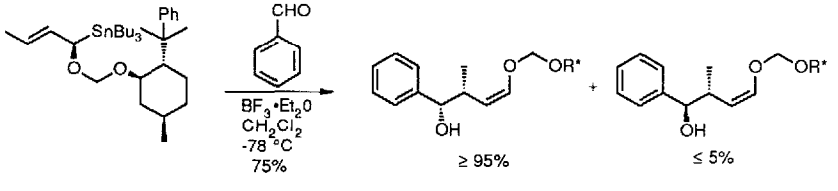
Summary: The "inside alkoxy" effect has been found to be important in the addition of α-(alkoxy) allylstannanes to aldehydes in the presence of BF_3•Et_2O.

Through studies of 1,3-dipolar addition to chiral alkenes and the ab initio MO method, Houk[2] has advanced a steric model for electrophilic reactions of chiral alkenes. Two characteristics of the model are: (1) the best electron-donor bond assumes the direction anti to the incoming electrophile to maximize electron donation to the electron deficient transition state; (2) the alkoxy (or an electron-withdrawing group) parallels the alkene double bond (so called "inside alkoxy") in the transition state to avoid withdrawing electrons. This hypothesis offers a rational for the stereochemical outcome of the 1,3-dipolar cycloaddition of nitrile oxide to chiral alkenes, and correctly predicts the same stereochemical outcome as Kishi's empirical model for hydroxylation of chiral alkenes.[3] McGarvey reported alkylations of chiral enolates that support the antiperiplanar approach.[4] However, Vedejs and coworkers[5] have reported that osmylation and epoxidation of the derivatives of 1-methylene-4-t-butylcyclohexane did not correlate with the "inside alkoxy" model. Franck and coworkers[6] also reported that certain Diels-Alder reactions did not correlate with the "inside alkoxy" theory. In this letter, we wish to report that a distinct electronic effect, which is best described as the "inside alkoxy" effect, has been revealed in the S_E' addition of the α-(alkoxy)allylstannanes to aldehydes in the presence of BF_3•Et_2O.

Recent studies by Marshall[7] have shown that in the presence of BF_3•Et_2O, α-(alkoxy)allylstannanes add to aldehydes at -78 °C yielding a mixture of diastereomers with the syn-(E) product predominant. In an effort to develop a new method of synthesizing enantiomerically pure allylstannanes, we have discovered that excellent diastereofacial selectivity between stannane **1** and benzaldehyde can be achieved under the Lewis acid conditions (BF_3•Et_2O, -78 °C), eq (1).

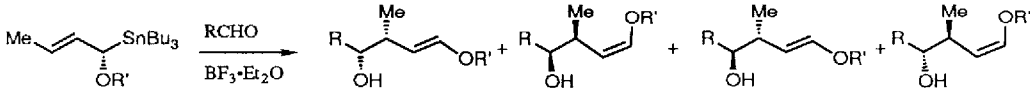


(1)

(R)-**1** (S,R)-**2** (R,R)-**3**

The new chiral allylstannane **1** was prepared according to the method of Thomas[8] except that the chiral auxiliary *8-(phenyl)menthyl* was employed. The separation of the diastereomers was achieved by careful column chromatography using silica gel with mixed solvent (CH_2Cl_2/hexanes = 1:4) as the eluent. The less polar allylstannane was determined to have the (R) configuration.[9] Likewise, the more polar stannane has the (S) configuration.[9]

Contrary to previous studies[7,10], which gave syn-(E) isomers as major products, the syn-(Z) and the anti-(Z) isomers were the only products detected in this study.[11] It appeared initially that the chiral auxiliary, which is five-bonds away from the reacting sp^2 carbon, had influenced the outcome of the reaction. Since no observation of this nature has been made in the past for these reactions, we extended the study with allylstannane **1** to aliphatic aldehydes, eq (2). Curiously, the diastereofacial selectivity decreased and the major

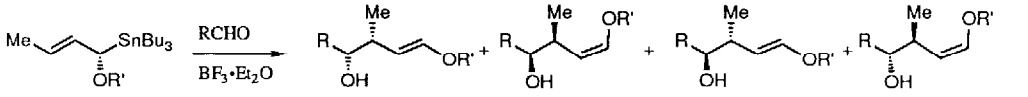


(2)

(S)-**1**	**4**	**5**	**6**	**7**
R'=(8-phenylmenthyl)oxymethyl	syn-(E)	syn-(Z)	anti-(E)	anti-(Z)
a R=n-hexyl	39	61	<1	<1
b =n-(E)-2-hexenyl	53	47	<1	<1
c =cyclohexyl	82	18	<1	<1
d = C_6H_5	<1	**95**	<1	5

products are syn-(E) isomers[11] for most aliphatic aldehydes. Furthermore the sense of facial selection is different for aromatic vs. aliphatic aldehydes.[11] Evidently, the chirality of the products depends on the allylic chiral center and aldehyde structure, but not on the chiral auxiliary.

We then investigated the reactions of allylstannane **8** with both aromatic and aliphatic aldehydes, eq. (3). The results agree with that from stannane **1**, i.e. all aromatic aldehydes produce syn-(Z) isomers.



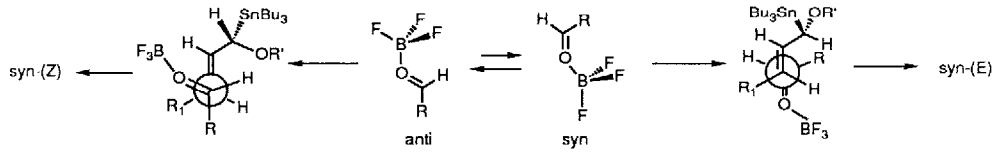
(3)

8	**9**	**10**	**11**	**12**
R'= (methyloxy)bzl	syn-(E)	syn-(Z)	anti-(E)	anti-(Z)
a R = C_6H_5	<1	**95**	<1	5
b =p-ClC_6H_4	<1	**95**	<1	5
c =p-$O_2NC_6H_4$	<1	**95**	<1	5
d =n-hexyl	55	45	<1	<1
e =cyclohexyl	80	20	<1	<1

The predominant formation of the (Z)-enol ether from the reactions of aromatic aldehyde and α-(alkoxy)allylstannanes cannot be interpreted on steric effects alone. A cyclohexyl group should be about the same steric size as a phenyl group. The fact that the syn-(Z) products predominate in the reactions with

aromatic aldehydes suggests that an electronic effect must be important in these reactions. We currently believe that the "inside alkoxy" effect advanced by Houk[2] for electrophilic additions to chiral alkenes might be involved.

It seems that this "inside alkoxy" effect dominates reactions with aromatic aldehydes, but not reactions with aliphatic aldehydes. While further investigation is planned, a possible cause is that the configuration of the BF_3•ArCHO complex plays a role in the outcome of the diastereofacial selectivity.[14] It is known that the BF_3•C_6H_5CHO complex mainly exists in the anti configuration in the crystal and in solution.[14] Therefore, as shown in Fig. 2, the "inside alkoxy" approach becomes the favored pathway because the alternative



synclinal, "inside alkoxy" antiperiplanar, "outside alkoxy"

Fig.2 Change in the configuration of the BF_3•aldehyde complexes leads to change of facial selection.

antiperiplanar arrangement would put the BF_3 directly over R_1. In cases where aliphatic aldehydes are concerned, the stability difference between the anti and the syn complexes might be small[15], or the rate of the interconversion between these two might be fast.[15] Therefore, the antiperiplanar approach, where the BF_3 is syn to R, is more favorable on steric grounds.[13] As far as we know, there is no experimental evidence concerning the constitution of the equilibrium mixture of anti/syn BF_3•aliphatic aldehyde complexes, although the anti configuration seems to be a general perception. Our speculation is based on our experimental results and the MNDO calculations performed by Reetze[14], which show ΔE = 2.5 kcal/mol for the difference between anti and syn BF_3•C_6H_5CHO, and 1.8 kcal/mol for the difference between anti and syn BF_3•CH_3CHO complexes. This speculation is also consistent with our recent proposal[10] that the antiperiplanar rotamer yields syn-(E) isomers and the synclinal arrangement leads to syn-(Z) diastereomers respectively. Further investigation of this matter is underway in our laboratories.

In summary, two new chiral allylstannanes have been prepared, and their absolute configurations have been determined.[9] Excellent diastereofacial selectivity has been observed for the reaction between aromatic aldehydes and the new allylstannanes. However, reactions with aliphatic aldehydes give the "normal" diastereofacial selection. The chirality of the products depends on the allylic chiral center and aldehyde structure, but not on the chiral auxiliary even when it has a strong diastereotopic bias.

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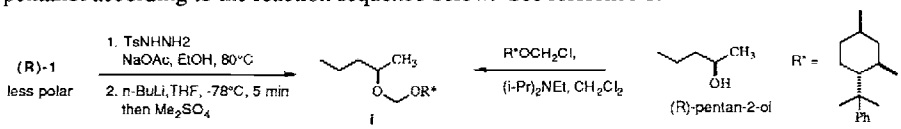
9. The absolute configurations of (R) and (S)-**1** were determined by correlation with (R)- and (S)-2-pentanol according to the reaction sequence below. See reference 8.



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11. The double bond geometry of the products was assigned from the vinylic ^{1}H NMR coupling constant: 6.2-6.4 Hz for (Z) enol ether double bond; and 12.2-12.5 Hz for (E) enol ether double bond. The syn and anti stereochemistry of the products was determined by ozonalysis of the enol ether double bond followed by a dimethyl sulfide work up producing the corresponding β-hydroxy aldehyde. Due to intramolecular hydrogen bonding the syn and anti diastereomers have characteristic proton coupling constant, Ja,b, respectively.[12] The syn stereochemistry obtained for all major products is consistent with literature precedents.[13] The absolute configuration of the carbinol carbons of the products was determined by the ^{1}H NMR spectra of their O-methyl mandelates.

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