Addition of α-Substituted (γ-Alkoxyallyl)tins on Aldehydes: The Dramatic Influence of the Size of the α-Substituent on the Diastereoselection

Sandrine Watrelot-Bourdeau, Jean-Luc Parrain,[§] and Jean-Paul Quintard*

Laboratoire de Synthèse Organique, UMR 6513 du CNRS, Faculté des Sciences et des Techniques de Nantes, 2 rue de la Houssinière, BP 92208, 44322-Nantes Cedex 3, France

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Introduction

The addition reaction of allyltins to aldehydes has been widely studied and used for the selective synthesis of homoallylic alcohols, as reported in books and review articles.[1−6] Compared to other allylmetals,[3] the allyltins offer an interesting chemical and configurational stability associated with a versatile reactivity which can be monitored by the choice of appropriate experimental conditions.[1−6]

According to pioneers in this field, under thermal conditions, without catalyst, the stereochemistry is directly dependent on the geometry of the allyltin reagent and is explained on the basis of a six-membered transition state,[7] while in the presence of a Lewis acid, the stereochemical course of the reaction might be much more dependent on the experimental conditions.

When the Lewis acids are able to give transmetalation reactions, new allylmetals able to react according to a six-membered transition state can be obtained as transient species. The stereochemical trends have been justified according to this general scheme when titanium tetrachloride,[8] tin polyhalides[6,9] or indium trichloride[10,11] have been used as Lewis acids. On the other hand, when the Lewis acid has no chance to undergo a transmetalation reaction (boron trifluoride), allyltins react with the complexed aldehyde to give the syn adducts irrespective of the geometry of the allyltin reagent. This result disclosed by Yamamoto in the crotyltin series was explained through an antiperiplanar open transition state.[12] Since most of the studies have been performed on crotyltins or minimally substituted allyltins, this explanation was often used to justify stereochemical trends in this type of reactions, even though the possible occurrence of a synclinal transition state was shown for intramolecular allylstannation of aldehydes.[13]

With the increasing number of studies related to substituted allyltins and with the use of chiral allyltins, the occurrence of a competition between antiperiplanar and synclinal open transition states is now usually considered to explain the stereochemical trends in this type of reaction,[3−5,14] although theory is far from giving reliable predictions in this field.

Obviously, the steric requirements in the transition state appear to be a driving force for the balance between the syn or anti adducts since it has been recently shown that substituents on the allyl unit have a great influence on the kinetics of the reaction[15] and that bulky substituents such as *tert*-butyl or triorganosilyl on the 2-position of *Z*-allyltins induce a higher preference for the anti isomer.[16,17]

The case of (α-alkoxyallyl)tins and (γ-alkoxyallyl)tins, compounds of interest for the stereocontrolled synthesis of polyhydroxylated compounds and sugars,[5,6,11] has to be considered with similar arguments, and examples of stereocontrol under thermal conditions[18] or in the presence of Lewis acids have been also extensively described.[1−6] For the reactions performed in the presence of Lewis acids, a large substituent in 2-substituted allyltins disfavors once more the syn preference,[17,19] but the effect of the α-substituent in (γ-alkoxyallyl)tins has not been systematically studied in terms of diastereoselection, even though lower syn/anti selectivities have been sometimes observed by Marshall as the size of the α-substituent increased.[20,21]

Results and Discussion

Taking advantage of our versatile preparation of *Z*-(α-substituted-γ-alkoxyallyl)tins,[22] we decided to examine the effect of the α-substituent on the stereochemical course of the reaction. For this purpose α-substituted (γ-ethoxyallyl)tributyltins **1a**−**h** (2 equiv) were added to benzaldehyde in methylene chloride at −78 °C in the presence of $BF_3{\cdot}Et_2O$ (1.1 equiv) (Scheme 1).

In every case, α-glycol monoethers were obtained in high yields with an *E*-configuration for the double bond and with a progressive shift from a syn preference to an

* Tel: (33) 2 40 37 30 29. Fax: (33) 2 40 74 50 00. E-mail: quintard@chimie.univ-nantes.fr.

§ Current address: Laboratoire de Synthèse Organique associé au CNRS, CP D12, Faculté des Sciences de Saint Jérôme, Avenue Escadrille Normandie-Niemen, 13397−Marseille, France.

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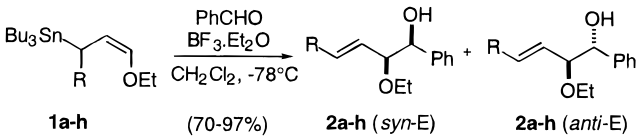
Scheme 1



1a-h (70-97%) **2a-h** (*syn*-E) **2a-h** (*anti*-E)

Table 1. Reaction of α-Substituted (γ-Ethoxyallyl)tributyltins with Benzaldehyde in the Presence of Boron Trifluoride Etherate

	allyltin [a]		homoallylic alcohols[b]		
entry	no.	R	yield	no.	syn-*E*/anti-*E*
1	**1a**	H	70	**2a**	93/7
2	**1b**	Me	95	**2b**	93/7
3	**1c**	Et	92	**2c**	72/28
4	**1d**	*n*-Bu	97	**2d**	70/30
5	**1e**	*i*-Pr	97	**2e**	19/81
6	**1f**	*t*-Bu	82	**2f**	3/97
7	**1g**	Me_3SiCH_2	85	**2g**	28/72
8	**1h**	$PhMe_2SiCH_2$	97	**2h**	18/82

[a] (γ-Ethoxyallyl)tins were obtained mainly or exclusively as *Z*-isomers (*E*/*Z* = 20/80 to 0/100). [b] Reactions were performed in methylene chloride at −78 °C; the allyltin (2 equiv.) was added to the mixture of aldehyde (1 equiv.) and boron trifluoride etherate (1.1 equiv.) (cf. typical experimental procedure).

anti preference with the increase of the steric hindrance due to the α-substituent (Table 1).

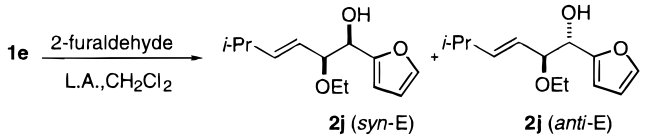
Entries 1 and 2 are extracted from previous work with (α-ethoxyallyl)tributyltin[23] and (α-ethoxycrotyl)tributyltin[24] but these reagents are known to react in the presence of $BF_3{\cdot}Et_2O$ after isomerization into (γ-alkoxyallyl)tins.[20] For these two compounds a high syn selectivity was obtained (syn/anti ~ 93/7). This syn selectivity decreases when *n*-alkyl substituents at the α-position are involved (syn/anti = 70/30 for R = Et or *n*-Bu) to reach a high anti preference with secondary or tertiary alkyl groups (syn/anti = 19/81 for R = *i*-Pr and syn/anti = 3/97 for R = *t*-Bu; cf. entries 5 and 6). Also of interest is the anti preference when R = CH_2SiMe_3 (syn/anti = 28/72) or R = CH_2SiMe_2Ph (syn/anti = 18/82) because of the possible subsequent use of the allylsilane functionality.

Furthermore, as with benzaldehyde, the ability of an α-substituent to induce an anti preference has been also observed with 3-methylcrotonaldehyde, which gave a mixture (syn/anti = 30/70) of the expected α-glycol monoether **2i** in reaction with **1g** under similar experimental conditions.

In the case of the allylstannation of 2-furaldehyde using **1e**, the stereochemical course of the reaction was shown to be highly dependent on the nature of the Lewis acid, specifically on its ability to give single or double coordination with oxygen(s) (Scheme 2).

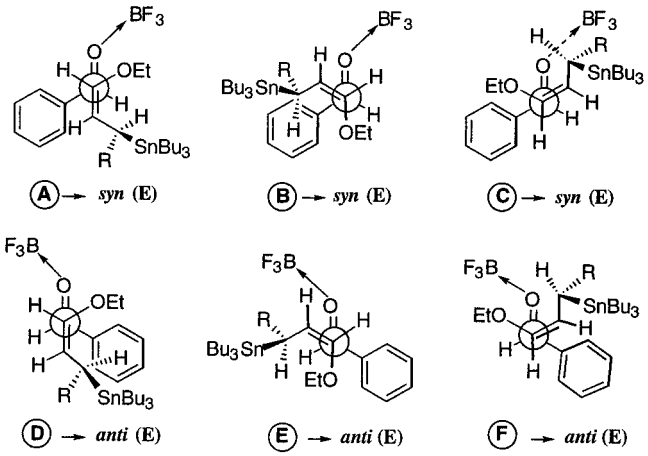
This last result demontrates a higher anti selectivity when 2-furaldehyde was used instead of benzaldehyde in boron trifluoride promoted reactions (cf. entry 5, Table 1). Reversed selectivity was observed when magnesium bromide was used as Lewis acid. On the basis of previous reports,[25] this last point can be reasonably explained by a chelated transition state when magnesium bromide is used.

Scheme 2



		2j (*syn*-E)	**2j** (*anti*-E)
$BF_3.Et_2O$ (1.1eq), -78°C	(91%)	8	92
$MgBr_2$ (2eq), -23°C	(32%)	78	22

Scheme 3



The evolution in the diastereoselectivity of the reaction of α-substituted (γ-ethoxyallyl)tins with benzaldehyde−boron trifluoride complex requires further comments since it is clear that the shift from a syn selectivity to an anti selectivity is dependent on the size of the α-substituent. If one refers to the work of Yamamoto[12] and Denmark,[13] open transition states are involved and the possible interactions due to the α-substituent must be considered both for antiperiplanar and synclinal transition states.

Taking into account the exothermic character of the reaction (which is performed at −78 °C), "reactant-like" transition states have to be considered. This implies an anti geometry for the benzaldehyde−boron trifluoride complex because of a higher stability compared to the syn complex.[26] Furthermore the allyltins must be considered to have a *Z*-configuration (*Z*/*E* = 80/20 to 100/0) with the Sn−C_{allyl} bond orthogonal to the double bond of the allyl unit to take into account the $\sigma \rightarrow \pi$ hyperconjugative stabilization in such a conformation.[27]

According to these initial remarks, six possible transition states (**A**−**F**) can be drawn for the approach of (*S*)-(α-alkyl-γ-ethoxyallyl)tins on the anti-benzaldehyde−boron trifluoride complex (Scheme 3) and similarly six other transition states are possible for the (*R*)-enantiomer.

Although there are many possible conformations that could be considered for open (nonchelated) transition states for the Lewis acid mediated addition of allylstannanes to aldehydes, usually the only ones that need to be considered are antiperiplanar transition states **A** and **D**[3] and low-energy synclinal transition states **C** and **E**,[3,28] because they both place the R group away from the

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phenyl. Synclinal transition state **B** has too much steric hindrance and is too high in energy to be considered, but synclinal transition state **F** remains questionable since steric hindrance can be counterbalanced by a geometry allowing a favorable interaction between the HOMO of the allyltin and the LUMO of the benzaldehyde.[14,29] When R is small (**1a** and **1b**), the comparison will be between the two low-energy antiperiplanar transition states **A** and **D**, with **A** strongly preferred on the basis of the steric effects. As R becomes larger (**1c**−**h**) both antiperiplanar transition states **A** and **D** become disfavored due to the steric interactions between R and the phenyl group, and synclinal transition states are involved. In the comparison between the synclinal transition states **C** and **E**, **E** is favored over **C** because the steric interactions between R and Lewis acid are less in **E** than in **C**. Thus, the shift from the antiperiplanar transition states **A** and **D** to the synclinal transition states **C** and **E** (or **F**, *vide supra*) as the R group becomes larger can completely explain the shift from the high syn preference (via **A**) to the high anti preference (via **E** or **F**)[30] as reported in Table 1.

Conclusion

Boron trifluoride promoted allylstannation of benzaldehyde (solvent CH_2Cl_2, −78 °C) with α-substituted (γ-ethoxyallyl)tributyltins appears to be highly dependent on the size of the α-substituent, the diastereoselectivity being progressively shifted from a high syn preference (R = H, Me) to a nearly exclusive anti preference (R = *t*-Bu). More generally, this result means that in the stereocontrolled synthesis of polyhydroxylated compounds, α-substituted (γ-alkoxyallyl)tins with appropriate alkoxy groups can offer an interesting possibility to obtain either syn or anti products using similar experimental conditions (with the same Lewis acid).

Experimental section

General. NMR Spectra were recorded for $CDCl_3$ solutions at 200.13 or 400.13 MHz (^{1}H NMR), 50.32 MHz (^{13}C NMR) or 149.21 MHz (^{119}Sn NMR) using tetramethylsilane (^{1}H, ^{13}C) or tetramethylstannane (^{119}Sn) as standards. Mass spectra were obtained in the GC/MS mode (EI, 70 eV). The GC separations of syn and anti isomers **2a**−**j** were performed on a CPwax 52 CB capillary column (l = 25 m; d = 0.25 mm; film = 0.2 μm). α-Substituted (γ-ethoxyallyl)tins were obtained according to previously described procedures: **1a**,[23] **1b**,[24] **1c**−**h.**[22]

Reaction of Allyltins with Aldehydes. BF_3 Promoted Reactions. In a Schlenk tube containing 0.5 mmol of aldehyde in dry CH_2Cl_2 (4 mL) cooled at −78 °C were successively added (syringe method) 0.55 mmol of boron trifluoride etherate and, after 15 min of stirring at −78 °C, 1 mmol of allyltin in CH_2Cl_2 (1 mL). After stirring during 1 h at −78 °C, the reaction mixture was hydrolyzed with an aqueous solution of $NaHCO_3$. After dilution with ether (10 mL) and warming up to room temperature, the reaction mixture was extracted with ether. After washing of the organic phase with aqueous NaCl solution, drying over magnesium sulfate, and removal of the solvents, the crude product was chromatographed (eluent, hexane/AcOEt/Et_3N = 88/10/2) on alumina deactivated by water (5%).

$MgBr_2$ Promoted Reactions. Magnesium bromide was first obtained in a Schlenk tube from reaction of magnesium with dibromoethane (2 mmol) in ether. After removal of ether, CH_2Cl_2 (4 mL) was added and the reaction mixture was cooled at −23 °C before addition of aldehyde (0.5 mmol). After 15 min of stirring, allyltin (0.75 mmol in 1 mL of CH_2Cl_2) was added at −23 °C and allowed to react for 2 h at this temperature before warming up to room temperature (4 h). Subsequent hydrolysis, treatments, and purification of the products were conducted as previously described for BF_3 promoted reactions.

Characterization of the Obtained Compounds. (γ-Ethoxyallyl)tins. While allyltins **1a**−**g** have been already described,[22,24] compound **1h** (*Z*-isomer) was obtained similarly in 58% yield mixed with 1,2-bis(dimethylphenylsilyl)ethane (∼30%).

3-(Tributylstannyl)-1-ethoxy-4-(dimethylphenylsilyl)-but-1-ene (1h). IR (film): 1655, 1590. ^{1}H NMR δ: 0.23 (s, 6H), 0.77 (d, 2H, J = 7.9), 0.80−1.00 (m, 15H), 1.10−1.70 (m, 15H), 2.59 (m, 1H), 3.70 (q, 2H, J = 7.0), 4.30 (dd, 1H, J = 6.1, 11.0, $^3J_{Sn-H}$ = 20), 5.63 (dd, 1H, J = 6.1, 0.75, $^4J_{Sn-H}$ = 22.4), 7.40−7.55 (m, 3H), 7.28−7.38 (m, 2H). ^{13}C NMR δ: −1.2 (2C), 8.8 (3C, $^1J_{Sn-C}$ = 277/290), 13.6 (3C), 15.4, 16.9 ($^1J_{Sn-C}$ = 297/311), 19.6 ($^2J_{Sn-C}$ = 27), 27.5 (3C, $^3J_{Sn-C}$ = 50/53), 29.2 (3C, $^2J_{Sn-C}$ = 19.5), 67.0, 113.5 ($^2J_{Sn-C}$ = 43.5), 127.4 (2C), 128.7, 133.5 (2C), 139.4 ($^3J_{Sn-C}$ = 46.5/48), 140.5. ^{119}Sn NMR δ: -15.8.

α-Glycol Monoethers. Compounds **2a** and **2b** have been already described.[23,24] For compounds **2c**−**j**, the *E*-configuration of the double bond was established on the basis of the vicinal coupling constant through the double bond ($^3J_{HH}$ ∼ 16 Hz), and the syn or anti configuration of the α-glycol monoethers was assigned on the basis of the value of the vicinal coupling constant $^3J_{H1H2}$ in the 2-ethoxy alcohols ($^3J_{H1H2}$ ∼ 8 Hz for the syn isomer and $^3J_{H1H2}$ ∼ 4.5 Hz for the anti isomer).

2-Ethoxy-1-phenyl-hex-3-en-1-ol (2c, syn/anti = 72/28). MS *m*/*z*: 114 (14), 113 (100), 107 (8), 105 (6), 85 (55), 79 (11), 77 (14), 67 (22), 57 (26), 43 (34), 41 (17), 29 (17). IR (film): 3455, 1667, 1605. Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.31; H, 9.16. Found: C, 75.96; H, 9.23.

***anti*-2c.** ^{1}H NMR δ: 0.94 (t, 3H, J = 7.5), 1.18 (t, 3H, J = 7.0), 2.03 (qdd, 2H, J = 7.5, 6.3, 1.5), 2.65 (d, 1H, J = 3.7), 3.36 and 3.59 (2dq, 2H, J = 9.4, 7.0), 3.83 (dd, 1H, J = 8.1, *4.3*), 4.80 (dd, 1H, J = 3.7, *4.3*), 5.32 (ddt, 1H, J = 15.5, 8.1, 1.5), 5.60 (dt, 1H, J = 15.5, 6.3), 7.20−7.40 (m, 5H). ^{13}C NMR δ: 13.4, 15.2, 25.3, 63.8, 75.7, 84.4, 124.8, 126.9 (2C), 127.2, 127.8 (2C), 138.1, 140.6.

***syn*-2c.** ^{1}H NMR δ: 0.88 (t, 3H, J = 7.5), 1.25 (t, 3H, J = 7.0), 1.96 (qdd, 2H, J = 7.5, 6.4, 1.5); 3.35 (d, 1H, J = 1.8), 3.39 and 3.67 (2dq, 2H, J = 9.4, 7.0), 3.67 (bt, 1H, J = *7.8*), 4.50 (dd, 1H, J = *7.8*, 1.8), 5.21 (ddt, 1H, J = 15.5, 7.8, 1.5), 5.46 (dt, 1H, J = 15.5, 6.4), 7.20−7.40 (m, 5H).^{13}C NMR δ: 13.3, 15.2, 25.2, 63.9, 76.9, 85.5, 125.4, 127.4 (2C), 127.6, 127.9 (2C), 137.7, 140.1.

Other α-glycol monoethers have been similarly characterized (cf. Supporting Information).

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Supporting Information Available: Tabulated MS, IR, ^{1}H NMR, and ^{13}C NMR data for compounds *syn*- and *anti*-**2c**−**j** (4 pages). This information is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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(30) In agreement with Fleming[28] and Keck,[14] we consider that further discussion is speculative until no more is known about the theoretical aspect of the problem.