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CHEMO, REGIO AND STEREOSELECTIVITY IN THE REACTION OF p-BROMOBENZALDEHYDE WITH α-ETHOXYCROTYLTRIBUTYLTIN

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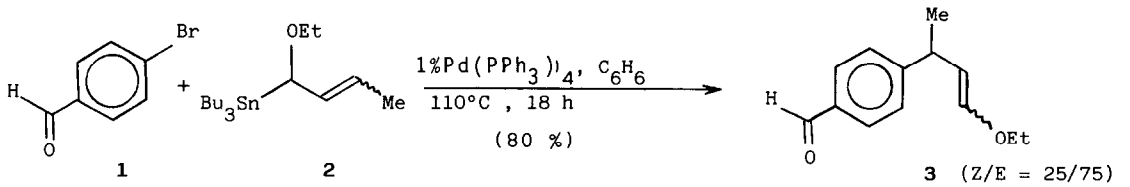
Abstract : *The reaction of p-bromobenzaldehyde* ***(1)*** *with α-ethoxycrotyltributyltin* ***(2)*** *has proved amenable to control in terms of chemo, regio and stereochemistry, using appropriate experimental conditions, namely* $Pd(PPh_3)_4$ *catalysis,* $BF_3.Et_2O$ *catalysis or simple heating. In the latter case, a dramatic kinetic effect has been observed :* ***2E*** *has been proved to be much more reactive (and much more stereoselective) than* ***2Z.***

The versatility of allyltin derivatives in organic synthesis has been widely demonstrated during the last decade (1) and one of the most interesting trends is the use of functionnalized allyltins. We have already examined some aspects of the reactivity of α-ethoxyallyltin derivatives (2, 3, 4) and in this paper, we wish to report some striking results concerning the control of chemo, regio and stereoselectivity in a model reaction involving parabromobenzaldehyde **(1)** and α-ethoxycrotyltributyltin **(2)** as a function of the experimental conditions and of the geometry of the crotyl unit.

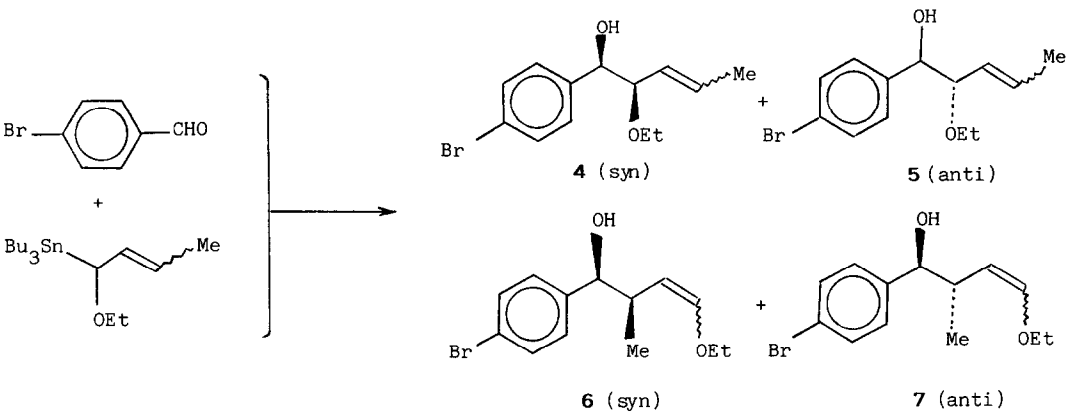
In the presence of tetrakistriphenylphosphine palladium, α-ethoxycrotyltributyltin reacts as a d^3 propionaldehyde synthon equivalent at the bromine atom to give the corresponding vinylethers **(3)** uncontaminated by products of addition on the aldehyde function :



1 **2** **3** (Z/E = 25/75)

This reaction provides an efficient route to monoprotected dialdehydes and underlines once more the ability of palladium-complex catalysts to guide the chemoselectivity of the reaction towards the halogen site when competition is possible with a carbonyl function (1, 5).

When a reversed chemoselectivity is desired, the propensity of the aldehyde to react with allyltins drives the reaction to homoallylic alcohols under Lewis acid catalysis or heating (in the absence of $Pd(PPh_3)_4$) (1, 6).



Our results are given in the table. When α-ethoxycrotyltributyltin **(2)** is allowed to react with p-bromobenzaldehyde **(1)** at -78°C in methylene chloride in the presence of boron trifluoride etherate (entries a, b) the α-glycol monoethers **4** and **5** are obtained in 95 % yield with a high syn preference (**4/5** = 93/7) and a clean E-configuration for the double bond irrespective of the configuration of **2**. This result is rationalized by an initial isomerization of **2** into the more stable γ-ethoxyallyltin derivative as already shown in the case of α-ethoxyallyltributyltin (2-4). Subsequently, the reaction occurs with a syn preference (irrespective of the geometry of the allyl unit) in full agreement with the results obtained by YAMAMOTO with unsubstituted crotyltributyltin (6, 7) or YAMAMOTO and ourselves in the case of heterosubstituted allyltributyltin derivatives (2, 4, 6, 8). This syn selectivity for $MgBr_2$ or BF_3-promoted addition of γ-alkoxyallyltin on aldehydes has been recently rediscovered and investigated by two other groups (9, 10).

The regioselectivity obtained for Lewis acid promoted additions (obtention of α-glycols monoethers **4** and **5**) can be strongly modified when the reaction is performed under heating (without catalyst) (1) as illustrated in the table (entries c-j). In these cases the major isomers are homoallylic alcohols bearing a vinylic ether function (masked aldehyde group) **6** and **7** obtained usually contaminated with **4** and **5**. However, on decreasing the temperature of the reaction from 150°C to 100°C, a dramatic difference appears in the reactivity of the two α-ethoxycrotyltributyltin isomers. The E isomer **2E** is much more reactive than the Z isomer **2Z**, and, using appropriate experimental conditions, it is possible to obtain almost exclusive reaction of the E isomer starting from an equimolar mixture of **2E** and **2Z** (entry h). In such circumstances the reaction appears to be highly regio and stereoselective ; the anti adduct **7** is obtained with high preference (**6/7** = 2/98), almost exclusively in the Z configuration (Z/E = 98/2). This result is in agreement with the stereochemical behaviour of (E) α-(alkoxy-methoxy)crotyltributyltins (11-13) but

TABLE : Reaction of p-bromobenzaldehyde (1) with α-ethoxycrotyltributyltins (2)

Entry	Allyltins 2Z/2E	Stoichiometry 2/1	Experimental conditions	Overall yields	Products distribution				Remaining 2 (Z/E)
					4 (syn)	5 (anti)	6 (syn)	7 (anti)	
a	80/20	1,5	BF_3Et_2O, CH_2Cl_2, -78°C→ 0°C	95 %	93 (Z/E = 0/100)	7 (Z/E = 0/100)	0	0	nd
b	50/50	1,5	BF_3Et_2O, CH_2Cl_2, -78°C→ 0°C	80 %	94 (Z/E = 0/100)	6 (Z/E = 0/100)	0	0	nd
c	82/18	1	120°C, 120 h, neat	50 %	4.4 (Z/E = 47/53)	13.6 (Z/E = 84/16)	43.9 (Z/E = 58/42)	38.1 (Z/E = 70/30)	nd
d	82/18	1	150°C, 24 h, neat	75 %	9.1 (Z/E = 21/79)	10.9 (Z/E = 76/24)	53.4 (Z/E = 54/46)	26.6 (Z/E = 53/47)	nd
e	50/50	1	150°C, 24 h, neat	80 %	10.5 (Z/E = 5/95)	8.5 (Z/E = 82/18)	37.5 (Z/E = 53/47)	43.5 (Z/E = 59/41)	(Z/E = 58/42)
f	50/50	2	150°C, 24 h, neat	100 %	1.8 (Z/E ≃ 11/89)	4.2 (Z/E = 77/23)	20.5 (Z/E = 66/34)	73.5 (Z/E = 83/17)	(Z/E = 75/25)
g	82/18	1	100°C, 6 h, neat	22 %	2 (Z/E ≃ 5/95)	1 (Z/E ≃ 70/30)	22 (Z/E = 57/43)	75 (Z/E = 94/6)	(Z/E = 100/0)
h	50/50	2	100°C, 6 h, neat	50 %	0	0	2 (Z/E = 60/40)	98 (Z/E = 98/2)	(Z/E = 68/22)
i	100/0	1	100°C, 6 h, neat	8 %	0	0	59 (Z/E = 67/33)	41 (Z/E = 79/21)	(Z/E = 100/0)
j	100/0	1	100°C, 6 h, EtOH (5 eq)	10 %	7.3 (Z/E = 44/56)	22.7 (Z/E = 76/24)	30 (Z/E = 65/35)	40 (Z/E = 85/15)	(Z/E = 100/0)

the present result demonstrates that a good selectivity is accessible even with a mixture of allyltins isomers. Furthermore such a difference in kinetics allows access to pure **2Z** isomer after an hexane/acetonitrile partition of the reaction mixture obtained in attempt (g). The organotin isomer **2Z** extracted in the hexane phase has been subsequently allowed to react with 1 (6 h, 100°C) to give regioselectively **6** and **7** with a slight preference for the Z configuration and for the syn isomer (**6**/**7** = 59/41). In order to avoid further complication which might be due to retroallylstannation (14), we have performed this reaction in ethanol expecting that the initial adducts might be trapped by transalkoxylation. The disappointing result (mixture of all regio and stereoisomers - entry j) is probably due to an initial isomerization of **2Z** in its three allylic isomers (**2E** and two γ-ethoxyallyltin derivatives) in the presence of ethanol (15).

In conclusion, under moderate heating (100°C neat reagents), the reaction of **1** with **2** is easily amenable to regioselective control. Furthermore the high reactivity of isomer **2E** (compare with **2Z**) allows us to stereospecifically obtain monoprotected hydroxyaldehyde as an anti Z isomer **(7)** even in the presence of **2Z**. When **2Z** is used as a sole reagent, the syn Z isomer **6** is obtained with poor stereoselectivity. Work is now in progress to improve this last point.

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16 - **Products analysis :** While GC/MS gives very similar patterns for compounds **4-7**, their configurationnal analysis has been carried out using 200 MHz ^{1}H NMR. The NMR parameters were obtained by examination of different fractions isolated by liquid chromatography using selective proton decoupling when necessary. According to this route Z or E configuration at the double bond were easily assigned and the following coupling constants were obtained for ^{3}JHH at the syn or anti junction : **4E** (7.9 Hz), **4Z** (∿ 8.8 Hz ; incomplete set of NMR parameters), **5E** (4.8 Hz), **5Z** (4.3 Hz), **6E** (5.2 Hz), **6Z** (5 Hz), **7E** (7.9 Hz), **7Z** (7.9 Hz).

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