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Crotylation of Aldehydes by Crotyltins: Discrimination between Mechanisms Involving Transmetallation or Simple Lewis Acid Assistance through the Consideration of the Stereochemistry of the Corresponding Homoallylic Alcohols

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Dedicated to Professor Jan-Erling Bäckvall on the occasion of his 60th birthday

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In the reaction of crotyltins with aldehydes in the presence of metal salts, the double consideration of the *syn*/*anti* ratio of the branched homoallylic alcohols and the *Z*/*E* ratio of their linear regioisomers is proposed as a way to discriminate between a reaction mechanism involving a transmetallation step and a reaction mechanism involving simple Lewis acid activation of the aldehyde. The formation of branched *syn* isomers along with Z-linear isomers as major compounds is considered to be indicative of a reaction occurring under Lewis acid assistance, whereas preference for the branched *anti* isomers together with *E*-linear isomers is considered to be indicative of a transmetallation step prior to crotylation. For reactions performed in the presence of $CeCl_3 \cdot 7H_2O$/NaI, the Lewis acid assistance was shown to be the exclusive or highly prevalent pathway. Moreover, in regards to the selectivity, the regiopreference depends on the nature of the crotyltin. Whereas soluble crotyltin preferentially leads to Z-linear adducts, polymer-supported crotyltin affords the *syn*-branched adducts probably due to a lower 1,3-metallotropy. For reactions performed in the presence of InX_3, simple Lewis acid assistance and transmetallation appear to be competitive processes; the first one is favoured with aromatic aldehydes especially in dichloromethane, whereas transmetallation appears to be prevalent with poorly reactive aldehydes especially with $InBr_3$ in acetonitrile.

Introduction

The allylation of aldehydes by using γ-substituted allyltins, which is a versatile synthetic method for the preparation of homoallylic alcohols, has been extensively investigated[1] due to the usefulness of these products, which are important building blocks for the synthesis of many natural products and pharmaceuticals.[1,2] The mechanism of this reaction is considered to occur through a six-membered transition state under thermic[3] and high pressure[4] conditions and shown to be easier when increasing the Lewis acid character of the tin centre.[5] Alternatively, open transition states are considered when this reaction is achieved with [γ-substituted-allyl] triorganotins in the presence of a Lewis acid like $BF_3 \cdot OEt_2$. In this case, an antiperiplanar transition state is generally accepted in unhindered systems as a result of the lower steric interactions between the R group of the aldehyde and the γ-alkyl group of the allyltin.[6] However, synclinal transition states can be favoured for instance in intramolecular allylstannations of aldehydes[7] or when γ-alkoxyallyltins containing a bulky α substituent are engaged (Figure 1).[8]

In every case, this condensation of γ-substituted allyltins with aldehydes is an intriguing subject with respect to its regioselectivity (linear α adducts/branched γ adducts) and its stereoselectivity (*E*/*Z* ratio in α adducts or *syn*/*anti* ratio in γ adducts).

It is noteworthy that the open transition states (Figure 1) have to be considered when the Lewis acid is unable to transmetallate the allyltin. This situation can be strongly modified, in terms of both regioselectivity (α/γ) and stereo-

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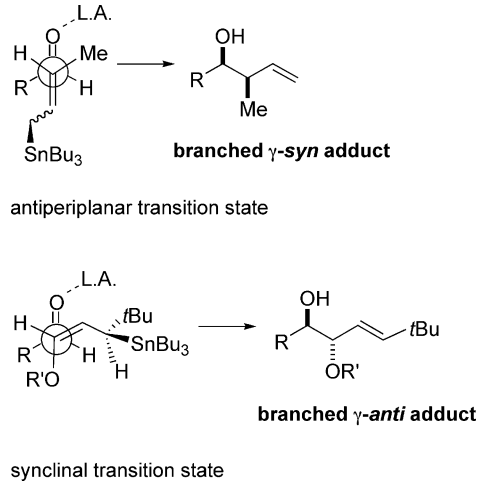
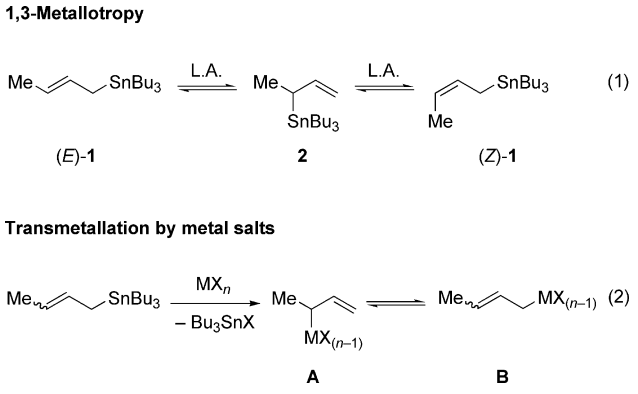


Figure 1. Reaction of γ-substituted allyltins with aromatic aldehydes in dichloromethane at low temperature (–78 °C) in the presence of $BF_3{\cdot}OEt_2$.

selectivity (*E*/*Z*, *syn*/*anti*), when the Lewis acids are metal salts potentially able to transmetallate the Sn–C bond (for instance $TiCl_4$, $SnCl_4$, InX_3).[1,7d,9] In this last case, several parameters including the nature of both the solvent and the aldehyde, as well as experimental conditions (temperature, order for the addition of the reagents, ...), may strongly affect the nature of the effective allylation reagent.[1,7d,9a,10] Accordingly, in the crotyltin series, the effective species can be crotyltin **1** initially added or its isomer **2** formed after a 1,3-metallotropy [Scheme 1, Equation (1)], but also a new allylmetal species (**A** or **B**) obtained after transmetallation [Scheme 1, Equation (2)].



Scheme 1. Isomerisation and transmetallation of crotyltins.

The result is the possible formation of branched and linear adducts with a stereochemistry that is directly dependent on the nature of the involved mechanism: whereas (*E*)-**1**, (*Z*)-**1** and **2** are likely to react through open transition states in the presence of Lewis acids, allylmetal halides **A** and **B**, owing to the higher acidity of the metal centre, are likely to react through a six-membered transition state.

Recently, we decided to investigate more thoroughly this complex and intriguing subject because we needed to discriminate between a simple Lewis acid assistance and a transmetallation occurring in reactions involving allyltins anchored onto a polymeric support. Indeed, we have shown that allylation of aldehydes with these polymer-supported reagents in the presence of either $CeCl_3$ or InX_3 (X = Cl or Br) is reasonably convenient and environmentally friendly, as pollution by tin residues was measured under 5 ppm, whereas cerium pollution appeared under 1 ppm in the final products.[11]

However, as a result of the fact that the reaction can proceed either by simple Lewis acid assistance of the metal salt on the aldehyde or through a preliminary transmetallation process between allyltins and cerium or indium salts, it was of importance to discriminate between these two mechanisms. In fact, the real usefulness of polymer-supported allyltins might be questionable if the effective organometallic species was a soluble allylcerium or a soluble allylindium resulting from transmetallation. Herein, we would like to describe how the analysis of diastereomeric distribution on both the branched γ adducts (ratio *syn*/*anti*) and the linear α adducts (ratio *Z*/*E*) can be used to achieve a primary discrimination between a transmetallation and a simple Lewis acid assistance in the crotyltin series.

Results and Discussion

Our investigation of this problem was focused on the careful analysis of the regio- and stereocontrol observed in the addition of the soluble crotyltri-*n*-butyltin **1** and the polymer-supported analogue **3** (*Z*/*E*, 30:70) to a series of aromatic and aliphatic aldehydes under various experimental conditions. In a typical procedure, the aldehyde and the Lewis acid were successively added to either a solution of crotyltri-*n*-butyltin or to a mixture of polymer-supported crotyltri-*n*-organotin in solvents such as acetonitrile or dichloromethane, and the reaction was stirred for 1 to 48 h. These solvents are those used in our previous work involving polymer-supported reagents, and furthermore, they are known to have different behaviour in their ability to facilitate transmetallation reactions. Unless mentioned otherwise, the reactions were conducted on the diastereomeric mixture of crotyltins (*Z*/*E*, 30:70). Good yields were uniformly obtained whatever the nature of the aldehydes and the Lewis acids used as promoters. The diastereomeric distributions were carefully analysed by gas chromatography after complete characterisation of the corresponding alcohols by NMR spectroscopic analysis. The obtained results are given in Tables 1 and 2.

Regio- and Stereoselective Control in Reactions Involving Crotyltri-*n*-butyltin 1

In reactions involving the soluble crotyltri-*n*-butyltin **1** with aldehydes, the following statements or observations can be considered meaningful:

(1) The reaction of crotyltri-*n*-butyltin with benzaldehyde in dichloromethane in the presence of $BF_3{\cdot}OEt_2$, a Lewis acid unable to give transmetallation, was considered as the

reference for the allylation reaction mediated by simple Lewis acid assistance. In fact, it is well known that crotyltri-*n*-butyltin in the presence of $BF_3{\cdot}OEt_2$ reacts with aldehydes through an open transition state leading to the exclusive branched γ adducts with a high *syn* preference regardless of the geometry of the tin reagent (Table 1, Entry 1).[6]

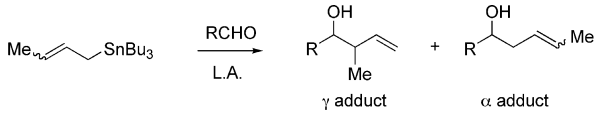
(2) Reactions performed in the presence of $CeCl_3{\cdot}7H_2O$/NaI in acetonitrile produced the linear α adducts as the major products with a strong preference for the *Z* configuration as previously reported by Bartoli.[12] Otherwise, the minor branched γ adducts were obtained as a mixture of *syn*/*anti* isomers, which was highly dependent on the nature of the aldehydes (*syn* preference with aromatic aldehydes and *anti* preference with both cyclic and aliphatic aldehydes).

(3) In experiments using $InCl_3$ as a promoter, the two regioisomers were isolated with a poor regioselectivity, whatever the nature of the aldehydes and of the solvents (Table 1, Entries 6–13). However, aromatic and aliphatic aldehydes distinguished between themselves by exhibiting opposite stereochemistry in the corresponding branched γ adducts: *syn* selectivity with aromatic aldehydes (Table 1, Entries 6–9) and *anti* selectivity with aliphatic aldehydes (Table 1, Entries 10–13). On the other hand, all of the corresponding linear α regioisomers were obtained with a strong preference for the *Z* configuration especially when reactions were carried out in dichloromethane.

(4) Interestingly, when $InBr_3$ was used as a promoter, we observed a great influence of the solvent on the regiocontrol of the allylation. A highly prevalent formation of the branched γ adduct was observed when the allylation was carried out in acetonitrile with both aromatic and aliphatic aldehydes. Moreover, in regards to the diastereoselectivity, we found that the stereopreference mainly depends on the nature of the aldehydes. Whereas aromatic aldehydes preferentially led to branched *syn* adducts (Table 1, Entries 14 and 16), aliphatic aldehydes afforded the branched *anti* isomers (Table 1, Entries 18 and 20). Interestingly, when the allylation was carried out in dichloromethane, the linear α adducts largely prevailed, whatever the nature of the aldehydes (Table 1, Entries 15, 17, 19 and 21), but the stereoselectivity was shifted from a *Z* preference (Table 1, Entries 15, 17, 21) to an *E* preference with the cyclohexanecarbaldehyde (Table 1, Entry 19).

(5) Finally, as isomerisations of homoallylic alcohols have been previously reported in the presence of metal salts or acids,[13] we also checked that the composition of the isomeric mixture of homoallylic alcohols remains un-

Table 1. Crotylation of aldehydes with soluble crotyltin **1** promoted by Lewis acids.



Entry	Lewis acid	Solvent	Aldehyde[a]	Product distribution		Overall yield
				γ adduct [%] (***syn***/***anti***)[b]	α adduct [%] (***Z***/***E***)[b]	[%][c]
1	$BF_3{\cdot}OEt_2$	CH_2Cl_2	PhCHO	**100** (**82**:18)	0	91
2	$CeCl_3{\cdot}7H_2O$ (10% NaI)	CH_3CN	PhCHO	20 (**75**:25)	**80** (**99**:01)	89
3	$CeCl_3{\cdot}7H_2O$ (10% NaI)	CH_3CN	*p*-$NO_2(C_6H_4)CHO$	6 (**70**:30)	**94** (**99**:01)	69
4	$CeCl_3{\cdot}7H_2O$ (10% NaI)	CH_3CN	*c*-$C_6H_{11}CHO$	7 (21:**79**)	**93** (**95**:05)	73
5	$CeCl_3{\cdot}7H_2O$ (10% NaI)	CH_3CN	*n*-$C_7H_{15}CHO$	6 (42:**58**)	**94** (**97**:03)	79
6	$InCl_3$	CH_3CN	PhCHO	**60** (**84**:16)	40 (**60**:40)	79
7	$InCl_3$	CH_2Cl_2	PhCHO	**63** (**99**:01)	37 (**65**:35)	72
8	$InCl_3$	CH_3CN	*p*-$NO_2(C_6H_4)CHO$	**57** (**63**:37)	43 (**95**:05)	82
9	$InCl_3$	CH_2Cl_2	*p*-$NO_2(C_6H_4)CHO$	**57** (**69**:31)	43 (**95**:05)	91
10	$InCl_3$	CH_3CN	*c*-$C_6H_{11}CHO$	**59** (15:**85**)	41 (21:**79**)	63
11	$InCl_3$	CH_2Cl_2	*c*-$C_6H_{11}CHO$	**54** (02:**98**)	46 (**89**:11)	84
12	$InCl_3$	CH_3CN	*n*-$C_7H_{15}CHO$	**59** (40:**60**)	41 (**55**:45)	93
13	$InCl_3$	CH_2Cl_2	*n*-$C_7H_{15}CHO$	**69** (27:**73**)	31 (**93**:07)	90
14	$InBr_3$	CH_3CN	PhCHO	**94** (**59**:41)	6 (**50**:50)	79
15	$InBr_3$	CH_2Cl_2	PhCHO	22 (**95**:5)	**78** (**84**:16)	72
16	$InBr_3$	CH_3CN	*p*-$NO_2(C_6H_4)CHO$	**95** (**69**:31)	5 (**75**:25)	43
17	$InBr_3$	CH_2Cl_2	*p*-$NO_2(C_6H_4)CHO$	43 (**80**:20)	**57** (**80**:20)	60
18	$InBr_3$	CH_3CN	*c*-$C_6H_{11}CHO$	**80** (14:**86**)	20 (23:**77**)	96
19	$InBr_3$	CH_2Cl_2	*c*-$C_6H_{11}CHO$	21 (01:**99**)	**79** (34:**66**)	94
20	$InBr_3$	CH_3CN	*n*-$C_7H_{15}CHO$	**75** (43:**57**)	25 (34:**66**)	72
21	$InBr_3$	CH_2Cl_2	*n*-$C_7H_{15}CHO$	5 (39:**61**)	**95** (**63**:37)	88

[a] The allylation reactions of aldehydes (1 equiv.) by crotyltri-*n*-butyltin (*E*/*Z*, 70:30; 1.1 equiv.) were carried out in the presence of either $CeCl_3{\cdot}7H_2O$ (1 equiv.) and NaI (0.1 equiv.) or InX_3 (1 equiv., X = Cl or Br). [b] The regioisomeric and stereoisomeric ratios were determined by GC after assignment of the structures by ^1H NMR spectroscopy. [c] Isolated yield of the mixture of homoallylic alcohols after column chromatography on silica gel.

changed in our experimental conditions. For this purpose, mixtures of branched and linear homoallylic alcohols in dichloromethane or acetonitrile solution were stirred with metal salts ($CeCl_3 \cdot 7H_2O$, 10% NaI; $InCl_3$ or $InBr_3$) for 24 h at 20 °C. Fortunately, as previously observed by Zhao for crotylations performed in protic acids,[14] no isomerisation of γ adducts into α adducts was noticed, and the obtained mixtures of regio- and diastereomers can be seen as a reflection of kinetic control.

Regio- and Stereoselective Control in Reactions Involving Polymer-Supported Crotyltin 3

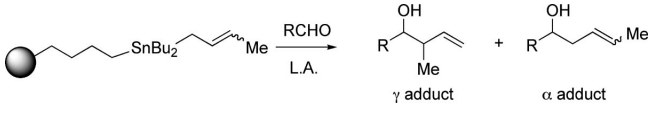
Before attempting to rationalise the regio- and stereocontrol observed in the addition of soluble crotyltri-*n*-butyltin **1** to aldehydes, we wish to report the set of results obtained in the crotylation of aldehydes with polymer-supported crotyltin **3**. For this purpose, the supported reagent **3** was prepared according to the procedure described for the synthesis of polymer-supported allyltins[11] and treated with a series of aromatic and aliphatic aldehydes. In a typical procedure, reactions were conducted at room temperature for 18 h by stirring the reaction mixture containing resin **3**, the aldehyde and the metal salt in the appropriate solvent (in suitable tubes for parallel synthesis equipment). Good GC conversions were obtained, whatever the nature of the aldehydes and experimental conditions (Table 2).

The following statements or observations in reactions involving addition of supported crotyltin **3** to aldehydes can be considered meaningful:

(1) Reactions performed in the presence of $CeCl_3 \cdot 7H_2O$/NaI at 60 °C in acetonitrile afforded the branched γ adducts as the major products, whatever the nature of the aldehydes. It is noteworthy that a reversed regioselectivity was obtained in comparison to the reaction carried out with soluble crotyltri-*n*-butyltin **1** (Table 1, Entries 2–5). Moreover, the stereocontrol in the γ adducts was strongly dependent on the nature of the aldehydes: *syn* preference with benzaldehyde, *anti* preference with cyclohexanecarbaldehyde and broadly a 1:1 mixture of the two diastereomers with octanal (Table 2, Entries 1, 2, 3). For the minor linear α adduct, a high *Z* preference was obtained, whatever the nature of the aldehydes.

(2) Surprisingly, when $InCl_3$ was used as the promoter, a high preference for linear α adducts was observed for benzaldehyde and octanal, whereas the branched γ adduct was the major product in the crotylation of cyclohexanecarbaldehyde. In terms of stereochemistry, whereas aromatic aldehydes afforded mainly branched *syn*-γ adducts and *Z*-linear α adducts, octanal and cyclohexanecarbaldehyde exhibited a preference for branched *anti*-γ adducts and a poor stereoselectivity in linear α adducts, which was shifted from a slight *Z* preference in dichloromethane to a slight *E* preference in acetonitrile.

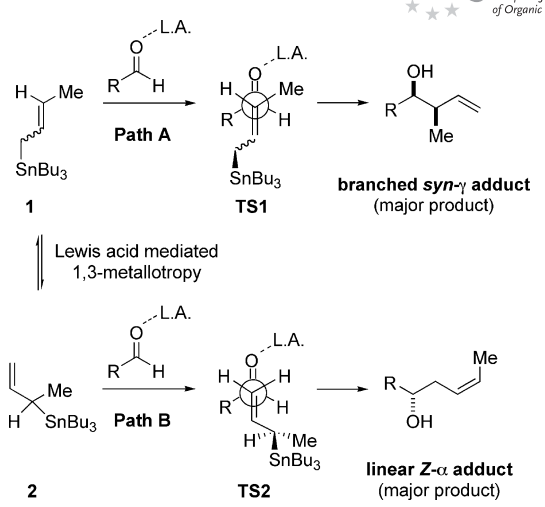
Table 2. Crotylation of aldehydes with the polymer-supported crotyltin **3** promoted by InX_3.



Entry	Lewis acid	Solvent	Aldehyde[a]	Product distribution		Overall conversion rate[c] [%]
				γ adduct [%] (***syn***/*anti*) [b]	α adduct [%] (***Z***/*E*) [b]	
1	$CeCl_3 \cdot 7H_2O$ (10% NaI)	CH_3CN	PhCHO	**85** (**99**:01)	15 (**99**:01)	70
2	$CeCl_3 \cdot 7H_2O$ (10% NaI)	CH_3CN	*c*-$C_6H_{11}CHO$	**88** (28:**72**)	12 (**99**:01)	80
3	$CeCl_3 \cdot 7H_2O$ (10% NaI)	CH_3CN	*n*-$C_7H_{15}CHO$	**86** (**51**:49)	14 (**94**:06)	75
4	$InCl_3$	CH_3CN	PhCHO	12 (**99**:01)	**88** (**72**:28)	72
5	$InCl_3$	CH_2Cl_2	PhCHO	22 (**60**:40)	**78** (**72**:28)	80
6	$InCl_3$	CH_3CN	*c*-$C_6H_{11}CHO$	**68** (16:**84**)	32 (25:**75**)	90
7	$InCl_3$	CH_2Cl_2	*c*-$C_6H_{11}CHO$	**82** (12:**88**)	18 (**54**:46)	98
8	$InCl_3$	CH_3CN	*n*-$C_7H_{15}CHO$	17 (40:**60**)	**83** (44:**56**)	65
9	$InCl_3$	CH_2Cl_2	*n*-$C_7H_{15}CHO$	25 (42:**58**)	**75** (**57**:43)	95
10	$InBr_3$	CH_3CN	PhCHO	**60** (**66**:34)	40 (**70**:30)	65
11	$InBr_3$	CH_2Cl_2	PhCHO	**52** (**98**:02)	48 (**68**:32)	93
12	$InBr_3$	CH_3CN	*c*-$C_6H_{11}CHO$	37 (18:**82**)	**63** (19:**81**)	76
13	$InBr_3$	CH_2Cl_2	*c*-$C_6H_{11}CHO$	**69** (18:**82**)	31 (44:**56**)	71
14	$InBr_3$	CH_3CN	*n*-$C_7H_{15}CHO$	46 (49:**51**)	**54** (49:**51**)	80
15	$InBr_3$	CH_2Cl_2	*n*-$C_7H_{15}CHO$	35 (45:**55**)	**65** (**66**:34)	75

[a] The allylation reactions of aldehydes (1 equiv.) by polymer-supported crotyltin **3** (*E*/*Z*, 70:30; 1.1 equiv.) were carried out in the presence of either $CeCl_3 \cdot 7H_2O$ (1 equiv.) and NaI (0.1 equiv.) or InX_3 (1 equiv., X = Cl or Br). [b] The regioisomeric and stereoisomeric ratios were determined by GC after assignment of the structures by ^1H NMR spectroscopy. [c] Conversion rates into homoallylic alcohols determined by GC.

(3) In the case of reactions carried out in the presence of $InBr_3$, a mixture of branched and linear adducts was obtained with a poor selectivity, whatever the nature of the aldehydes. In terms of stereochemistry, the addition of **3** to benzaldehyde gave the two regioisomers with a strong preference for the branched *syn*-γ adduct and for the linear *Z*-α adduct (Table 2, Entries 10 and 11), whereas the addition of **3** to cyclohexanecarbaldehyde exhibited a poor regioselectivity with a preference for branched *anti*-γ adducts and a slight preference for linear *E*-α adduct. In the case of octanal, the stereochemical trends appeared less clear: the branched γ adduct was obtained with a very poor stereoselectivity, whatever the nature of the solvent, whereas the linear α adduct was formed with a *Z* preference in dichloromethane but without stereoselectivity in acetonitrile.

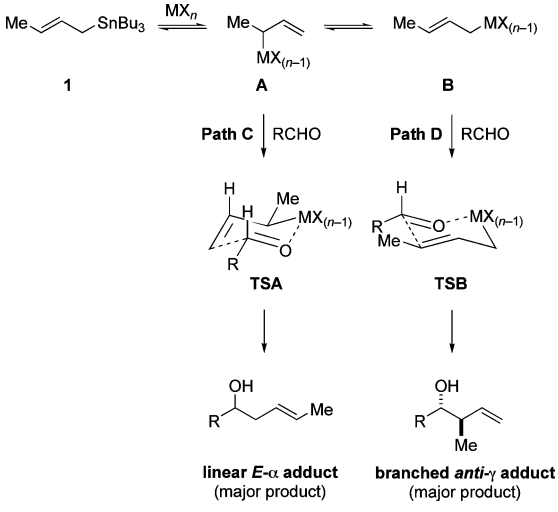


Scheme 2. Simple Lewis acid assistance for the crotylation of aldehydes.

Mechanistic Considerations

In spite of the relative complexity of the obtained results, a primary rationalisation of the results was attempted by taking into account the possible isomerisation of the crotyltin species through a 1,3-metallotropy process [Scheme 1, Equation (1)] and the possible transmetallation of crotyltin species by metal salts [Scheme 1, Equation (2)]. With this in mind, we can reasonably expect an open transition state when crotyltin is the effective allylation reagent by assuming that the metal salt acts as a simple Lewis acid on the carbonyl functionality. In this case, the formation of homoallylic alcohols can be rationalised through open transition states involving Lewis acid assistance according to Scheme 2. Thus, when the crotyltin species are preserved, an antiperiplanar transition state (TS1) is usually invoked according to Yamamoto[1,6] because of the minimisation of steric interactions between the R group of the aldehyde and the γ-methyl group of **1**, which leads to the predominant formation of the branched *syn* adduct, regardless of the geometry of the crotyltin unit. The *Z* geometry of the linear adducts can also be explained through an antiperiplanar transition state involving the less stable, but more reactive, 3-tri-*n*-butylstannylbut-1-ene (**2**), which results from the isomerisation of crotyltri-*n*-butyltin **1** in the presence of the Lewis acid (1,3-metallotropy).[15] In this case, the approach of **2** should occur through TS2 (Scheme 2, path B) in order to accommodate the methyl substituent in the less-hindered position (as far as possible from the R group of the aldehyde). In these open transition states, the tri-*n*-butylstannyl group is orthogonal to the allyltin double bond in agreement with the higher stability of the allyltins in this conformation: the minimisation of the molecular energy is about 1.7 kcal mol^{-1}.[16]

In contrast, when a transmetallation process is involved, the primary obtained allylmetal species **A** can react with the aldehyde to afford the linear *E*-α adduct through a six-membered cyclic transition state (TSA), in which the methyl group of the crotyl moiety and the R group of the aldehyde adopt a pseudoequatorial position (Scheme 3, path C). However, as a result of the poor stability of allylmetal species **A**, their rearrangement into the more stable crotyl species **B** can occur before addition to aldehydes. Thus, when crotyl species **B** are the effective crotylation reagents of aldehydes, the branched *anti* adducts are obtained through a cyclic transition state (TSB) (Scheme 3, path D).[1]



Scheme 3. Lewis acid transmetallation reaction.

Accordingly, the regiochemical outcome of the reaction will be dependent on kinetic parameters involved in these competitive reactions and more exactly on the nature of the effective allylmetal species **1**, **2**, **A** and **B**. In fact, even if organometallic species **2** and **A** are highly unstable relative to **1** and **B**, they are expected to be more reactive due to their lower steric requirements in the transition states where they are involved. Thus, both the reactivity/stability of the organometallic species and the nature of the Lewis acid–aldehyde complex should be taken into account to explain the observed regio- and stereoselectivities. With Schemes 2 and 3 as general guidelines, the regio- and sterecontrol observed in theses crotylation reactions can be reasonably explained.

Reactions in the Presence of Cerium Trihalides

The exclusive formation of the branched γ adduct with a strong preference for the *syn* adduct in the reaction carried out with soluble crotyltri-*n*-butyltin **1** in the presence of $BF_3{\cdot}OEt_2$ can be considered as a reference reaction and rationalised according to the antiperiplanar transition state (TS1) of Yamamoto.[6]

The formation of the linear *Z*-homoallylic alcohols as the major adducts when crotylation is achieved with crotyltri-*n*-butyltin **1** in the presence of $CeCl_3{\cdot}7H_2O$/NaI in acetonitrile is consistent with Lewis acid assistance on the aldehydes. In these cases, the initial step of the sequence involves the isomerisation of **1** (*Z*+*E*) into its unhindered isomer **2**, which then adds to aldehydes faster than **1**. This in turn leads mainly to linear *Z* adducts according to path B (Scheme 2). The formation of branched γ adducts (obtained as minor regioisomers) can also be explained by an open antiperiplanar transition state according to path A (Scheme 2) in the case of benzaldehyde (*syn* preference) or according to an open synclinal transition state when the *anti* isomer is preferred (case of octanal or cyclohexanecarbaldehyde). This possibility is often neglected but not impossible due to favourable secondary orbital interactions.[7b,c,d,17] The occurrence of a transmetallation reaction can be ruled out in these reactions because of the high *Z* selectivity observed on the linear adducts (vide supra). It is worth noting that the transmetallation of crotyltins by $CeCl_3{\cdot}7H_2O$ has been previously excluded on the basis of spectroscopic analyses.[12]

When the same reactions were carried out with polymer-supported crotyltin **3**, the stereochemical trends were maintained (high *Z* selectivity for linear α adducts and *syn* or *anti* preference for the branched γ adducts in function of the nature of the aldehyde), but the regioselectivity of the reaction is strongly modified with a high preference for the branched γ adducts, as previously observed for crotylation of aldehydes in the presence of the $CeCl_3{\cdot}7H_2O$/NaI system immobilised on alumina.[12b] In our case, this change is probably due to lower kinetics for the 1,3-metallotropy, which allows isomerisation of **3** into its rearranged isomer, a result which might be seen as a matrix effect on the 1,3-metallotropy.

In summary, the mechanism of the crotylation involving $CeCl_3{\cdot}7H_2O$/NaI as a promoter can be reasonably explained by simple Lewis acid assistance, whatever the nature (soluble or insoluble) of the crotyltin involved in this reaction. This trend appears to be similar with those encountered with other metal salts used in the presence of water, as for instance PbI_2/$n$$Bu_4NBr$.[18]

Reactions Involving Indium Trihalides and Crotyltri-n-butyltin

For crotylations performed with soluble crotyltri-*n*-butyltin **1** in the presence of $InCl_3$, the situation appears quite similar with those observed in the presence of cerium salts in spite of a lower and reversed regioselectivity. The double preference for the branched *syn*-γ adduct and linear *Z*-α adduct in the case of benzaldehyde is consistent with a reaction occurring mainly under Lewis acid assistance according to paths A and B (Scheme 2). With nonaromatic aldehydes, the involved mechanisms are less clear. Whereas the formation of branched γ adducts with a strong preference for the *anti* isomer might suggest a transmetallation reaction leading to crotylindium species able to react with aldehydes through a cyclic transition state (TSB) (path D Scheme 3), the high *Z* selectivity observed on the minor linear α adducts, especially in dichloromethane, is well accounted by the acyclic antiperiplanar transition state TS2 (Path B, Scheme 2). Because of this high *Z* selectivity, the whole set of experiments involving $InCl_3$ and crotyltri-*n*-butyltin can be more reasonably explained by the occurrence of open transition states but with a preference for antiperiplanar ones with aromatic aldehydes and synclinal ones with nonaromatic aldehydes.

Finally, the use of indium tribromide as a promoter of the crotylation of aldehydes by soluble crotyltri-*n*-butyltin exhibits quite different results in terms of regioselectivity, which appears to be solvent dependent (preference for the branched γ isomers in acetonitrile and for the linear α isomers in dichloromethane). In regard to the stereochemical aspects, with aromatic aldehydes, the *Z* preference for linear α adducts combined with a *syn* selectivity for the γ adducts is once again indicative of simple Lewis acid assistance as a main pathway. In contrast, the double preference for the branched *anti*-γ adduct and for the linear *E*-α adduct in the case of the crotylation of cyclohexanecarbaldehyde is consistent with a mechanism involving a transmetallation step as shown in Scheme 3. For octanal, the poor observed stereoselectivities suggest competitive processes involving mainly transmetallation in acetonitrile and Lewis acid assistance in dichloromethane. This trend in favour of an easier transmetallation in acetonitrile has been previously mentioned in the literature.[19] Thus, in our set of experiments, we can reasonably assume that with less reactive aldehydes, the transmetallation can be easier than direct reaction on the aldehyde–Lewis acid complex. This is true for indium tribromide promoted crotylations, but such a pathway can also be considered (at least in part) for reactions achieved in the presence of indium trichloride when acetonitrile is used as the solvent.

Reactions Involving Indium Trihalides and Polymer-Supported Crotyltriorganotins

When reactions involving $InCl_3$ or $InBr_3$ were carried out with polymer-supported crotyltin **3**, the double preference for the major linear *Z*-α adduct and the minor branched *syn*-γ adduct observed in the case of benzaldehyde is still consistent with a reaction occurring mainly under Lewis acid assistance according to path **A** and **B** (Scheme 2).

For less reactive nonaromatic aldehydes, the competing processes envisaged for crotyltri-*n*-butyltin have still to be invoked with a slower direct addition on the aldehyde–Lewis acid complex. The result is a higher extent of both the isomerisation by 1,3-metallotropy (with concomitant obtaining of linear adducts as major products in the case of benzaldehyde) and the transmetallation process, which

is probably mainly involved with cyclohexanecarbaldehyde with both $InBr_3$ and $InCl_3$ when acetonitrile is used as a solvent. The case of octanal seems to be an intermediate situation with an overlapping of several pathways and a higher rate of transmetallation when the promoter is $InBr_3$. When reactions were carried out in dichloromethane, the minor formation of branched *anti*-γ adducts along with the major linear α adducts (with a slight preference for the *Z* configuration) seems indicative of open transition states with Lewis acid assistance on the aldehyde, but the situation remains questionable in this case and requires further investigation. For this reason, we have attempted to elucidate the nature of the effective organometallic species through NMR spectroscopic studies performed with polymer-supported crotyltin **3** and $InCl_3$ in CD_2Cl_2. The spectra were taken after 2, 4 and 24 h, respectively, and no evidence of crotylindium species could be found in solution by ^1H NMR spectroscopy. Furthermore, the ^{119}Sn MAS-NMR resonance for the recovered resin appeared as two signals at –14 and –18 ppm, which are typical of (*E*)- and (*Z*)-crotyltin without observable signal in the range of the triorganotin chloride. These results were found to be inconsistent with the transmetallation hypothesis for reactions carried out with $InCl_3$ in dichloromethane and suggest simple Lewis acid assistance under these experimental conditions.

Conclusions

In function of the reactivity of the aldehyde, the nature of the Lewis acid and the solvent, we can obtain: (1) a direct addition to aldehyde, which leads to branched *syn*- or *anti*-γ adducts through an open antiperiplanar or synclinal transition state; (2) a rearrangement of the crotyltin by 1,3-metallotropy before addition to aldehyde, which gives linear *Z*-α adducts through an open transition state; (3) a transmetallation of the crotyltin by the metal salts and subsequent reaction with aldehydes through a cyclic transition state, either through immediate reaction of the new branched allylmetals to afford linear *E*-α adducts or after further isomerisation of these branched allylmetals into more stable crotylmetals, whose reaction with aldehyde afford mainly branched *anti*-γ adducts.

With these possibilities in mind, the consideration of the regioisomeric ratio together with the configuration of the obtained homoallylic alcohols (including minor ones) can be used to discriminate between reaction mechanisms involving simple Lewis acid assistance (open transition states) from those including a transmetallation step (cyclic transition states) when one of these pathways is exclusive or highly prevalent.

In terms of synthetic interest, the consideration of this general sequence should allow to choose the appropriate experimental conditions in order to control the formation of the desired homoallylic alcohols with a high *syn* or *anti* preference for branched isomers, but also with a high *Z* or *E* preference for linear adducts. Furthermore, when the transmetallation can be avoided, the use of polymer-supported allyltins should allow access to the desired targets (sometimes with a reversed regioselectivity when compared to the reactions performed in solution), with the benefits of the allyltin reactivity but without the drawbacks of the organotin pollution.

Experimental Section

General: Commercially available organic and inorganic compounds, as well as solvents, were purchased and used without further purification. Crotyltri-*n*-butyltin **1** was prepared from tri-*n*-butyltin chloride by using an already described procedure,[20] and polymer-supported crotyltin **3** was obtained similarly in a Barbier mode as previously achieved for other supported allyltins.[11] ^1H and ^{13}C NMR spectra were recorded with a Bruker Avance 300 spectrometer operating at 300 MHz for ^1H and 75.5 MHz for ^{13}C in $CDCl_3$ solution. Chemical shifts (δ) are expressed in ppm downfield to tetramethylsilane (TMS) as the internal standard and coupling constants (*J*) are expressed in Hertz. Solid-state MAS-NMR experiments were performed at room temperature with a Bruker Avance 500 spectrometer operating at 186.5 MHz for ^{119}Sn by using a 4-mm double-bearing Bruker probehead. ^{119}Sn MAS spectra were acquired with ^1H TPPM decoupling during acquisition and a MAS frequency of 10 kHz. Repetition time was set to 20 s for quantitative purpose, as $^{119Sn}T_1$ were measured to be of the order of 3 s. Spectra were referenced to Me_4Sn using Ph_4Sn as a secondary reference (δ = –121.15 ppm). GC analyses were performed with an HP 6890 apparatus (FID, carrier gas N_2, split: 98:2) by using a methyl/phenyl silicone capillary column (Macherey–Nagel, Optima δ^3: 30 m, 0.25 mm, 25 μm). The flow rate was 1.3 mL min^{-1} and the same programme was used for every required analyses of homoallylic alcohols: initial temperature: 80 °C (1 min) then 12 °C min^{-1} until 250 °C.

General Procedure for the Crotylstannation of Aldehydes in the Presence of $BF_3{\cdot}OEt_2$: To a solution of aldehyde (1.7 mmol) in dry CH_2Cl_2 (11 mL) was added, under an atmosphere of argon, crotyltri-*n*-butyltin (1.1 mmol) and, dropwise at –78 °C, a solution of $BF_3{\cdot}Et_2O$ (6.8 mmol). The reaction mixture was stirred at –78 °C for 1 h and then quenched with a mixture of THF/H_2O, 1:1. After extraction with Et_2O, the organic layer was washed with brine (50 mL), dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by chromatography on silica gel.

General Procedure for the Crotylstannation of Aldehydes in the Presence of $CeCl_3{\cdot}7H_2O$/NaI

Method A. With Crotyltri-*n*-butyltin 1: To a solution of $CeCl_3{\cdot}7H_2O$ (1.0 mmol) and NaI (0.1 mmol) in acetonitrile (10 mL) was added aldehyde (1 mmol) and crotyltri-*n*-butyltin (1.1 mmol). The reaction mixture was stirred 18 h at room temperature. The reaction was then quenched with HCl (0.1 M, 10 mL) and extracted with Et_2O (3 × 20 mL). The organic layer was then washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The crude product was used for GC analyses and purified by chromatography on silica gel for NMR spectroscopic determination.

Method B. With Polymer-Supported Crotyltin 3: To a suspension of polymer **3** (1.0 g, 1.1 mmol) in acetonitrile were added aldehyde (1.0 mmol), $CeCl_3{\cdot}7H_2O$ (1.0 mmol) and NaI (0.1 mmol). The reaction mixture was stirred for 18 h at 60 °C and then quenched with HCl (0.1 M, 10 mL). The polymer was filtered and then washed with diethyl ether (6 × 30 mL) and then THF (6 × 30 mL). The filtrate was extracted with diethyl ether and washed with brine

(50 mL), dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by chromatography on silica gel.

General Procedure for the Allylstannation of Aldehydes with InX_3

Method A. With Crotyltri-*n*-butyltin 1: To a solution of aldehyde (1 mmol) in CH_2Cl_2 (or MeCN; 10 mL) was added crotyltri-*n*-butyltin (280 μL, 1.1 mmol) and InX_3 (1 mmol). The reaction mixture was stirred at 25 °C and monitored by TLC. After consumption of the aldehyde, the reaction was quenched with HCl (0.1 M, 10 mL) and extracted with diethyl ether (3 × 20 mL). The organic layer was then washed with brine, dried with $MgSO_4$ and concentrated in vacuo. The crude product was purified by chromatography on silica gel.

Method B. With Polymer-Supported Crotyltin 3: To a suspension of polymer (1.0 g, 1.1 mmol) in CH_2Cl_2 (or MeCN; 10 mL) were added aldehyde (1.0 mmol) and InX_3 (1.0 mmol). The reaction mixture was stirred for 18 h at 25 °C and then quenched with HCl (0.1 M, 10 mL). The polymer was filtered and washed with diethyl ether (6 × 30 mL) and then with THF (6 × 30 mL). The filtrate was extracted with diethyl ether and washed with brine (50 mL), dried with $MgSO_4$ and concentrated in vacuo.

Products Distribution in Homoallylic Alcohols: The homoallylic alcohols were firmly characterised on the basis of their ^1H NMR spectra in agreement with the literature[9d,13c,14,21] and their isomeric distribution was determined by GC analysis. GC (homoallylic alcohols derived from benzaldehyde): t_R = 7.03 (*anti*), 7.16 (*syn*), 7.81 (*E*), 7.96 (*Z*) min. GC (homoallylic alcohols derived from *p*-nitrobenzaldehyde): t_R = 12.60 (*anti*), 12.66 (*syn*), 13.06 (*E*), 13.24 (*Z*) min. GC (homoallylic alcohols derived from cyclohexanecarbaldehyde): t_R = 6.77 (*anti*), 6.90 (*syn*), 7.64 (*E*), 7.74 (*Z*) min. GC (homoallylic alcohols derived from octanal): t_R = 7.25 (*anti*), 7.34 (*syn*), 7.89 (*E*), 8.01 (*Z*) min.

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[1] For review articles, see: a) Y. Yamamoto, N. Asao, *Chem. Rev.* **1993**, *93*, 2207–2293; b) Y. Nishigaichi, A. Takuwa, Y. Naruta, K. Maruyama, *Tetrahedron* **1993**, *49*, 7395–7426; c) J. A. Marshall, *Chem. Rev.* **1996**, *96*, 31–47; d) E. J. Thomas, *Chem. Commun.* **1997**, 411–418; e) J. A. Marshall in *Lewis Acids in Organic Synthesis* (Ed.: H. Yamamoto), Wiley-VCH, Weinheim, **2000**, vol. 1, pp. 453–522; f) J. A. Marshall, *Chem. Rev.* **2000**, *100*, 3163–3185; g) S. E. Denmark, N. G. Almstead in *Modern Carbonyl Chemistry* (Ed.: J. Otera), Wiley-VCH, Weinheim, **2000**, pp. 299–401; h) S. E. Denmark, J. Fu, *Chem. Rev.* **2003**, *103*, 2763–2793; i) E. J. Thomas, *Chem. Rec.* **2007**, *7*, 115–124; j) J. A. Marshall, *J. Org. Chem.* **2007**, *72*, 8153–8166.

[2] a) W. R. Roush in *Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic Chemistry* (Eds.: B. M. Trost, I. Fleming), Pergamon Press, Oxford, **1991**, vol. 2, pp. 1–53; b) Y. Yamamoto, *J. Org. Chem.* **2007**, *72*, 7817–7831.

[3] a) C. Servens, M. Pereyre, *J. Organomet. Chem.* **1972**, *35*, C20–C21; b) V. J. Jephcote, A. J. Pratt, E. J. Thomas, *J. Chem. Soc., Chem. Commun.* **1984**, 800–802; c) J.-P. Quintard, G. Dumartin, B. Elissondo, A. Rahm, M. Pereyre, *Tetrahedron* **1989**, *45*, 1017–1028.

[4] a) Y. Yamamoto, K. Maruyama, K. Matsumoto, *J. Chem. Soc., Chem. Commun.* **1983**, 489–490; b) N. S. Isaacs, R. L. Marshall, D. J. Young, *Tetrahedron Lett.* **1992**, *33*, 3023–3024.

[5] a) A. Gambaro, D. Marton, V. Peruzzo, G. Tagliavini, *J. Organomet. Chem.* **1981**, *204*, 191–196; b) A. Gambaro, D. Marton, V. Peruzzo, G. Tagliavini, *J. Organomet. Chem.* **1982**, *226*, 149–155; c) A. Gambaro, P. Ganis, D. Marton, V. Peruzzo, G. Tagliavini, *J. Organomet. Chem.* **1982**, *231*, 307–314.

[6] a) Y. Yamamoto, H. Yatagai, Y. Naruta, K. Maruyama, *J. Am. Chem. Soc.* **1980**, *102*, 7107–7109; b) Y. Yamamoto, H. Yatagai, Y. Ishihara, N. Maeda, K. Maruyama, *Tetrahedron* **1984**, *40*, 2239–2246.

[7] a) S. E. Denmark, E. J. Weber, *J. Am. Chem. Soc.* **1984**, *106*, 7970–7971; b) S. E. Denmark, T. Wilson, T. M. Willson, *J. Am. Chem. Soc.* **1988**, *110*, 984–986; c) S. E. Denmark, E. J. Weber, T. M. Wilson, T. M. Willson, *Tetrahedron* **1989**, *45*, 1053–1065; d) G. E. Keck, S. M. Dougherty, K. A. Savin, *J. Am. Chem. Soc.* **1995**, *117*, 6210–6223.

[8] S. Watrelot-Bourdeau, J.-L. Parrain, J.-P. Quintard, *J. Org. Chem.* **1997**, *62*, 8261–8263.

[9] a) G. E. Keck, D. E. Abbott, E. P. Boden, E. J. Enholm, *Tetrahedron Lett.* **1984**, *25*, 3927–3930; b) A. Boaretto, D. Marton, G. Tagliavini, P. Ganis, *J. Organomet. Chem.* **1987**, *321*, 199–207; c) R. L. Marshall, D. J. Young, *Tetrahedron Lett.* **1992**, *33*, 2369–2370; d) J. A. Marshall, K. W. Hinkle, *J. Org. Chem.* **1995**, *60*, 1920–1921; e) J. A. Marshall, K. W. Hinkle, *J. Org. Chem.* **1996**, *61*, 105–108; f) T. Miyai, K. Inoue, M. Yasuda, A. Baba, *Synlett* **1997**, 699–700; g) J. Becker, R. Frölich, K. Salorinne, D. Hoppe, *Eur. J. Org. Chem.* **2007**, 3337–3348.

[10] Y. Yamamoto, N. Maeda, K. Maruyama, *J. Chem. Soc., Chem. Commun.* **1983**, 742–743.

[11] J.-M. Chrétien, F. Zammattio, D. Gauthier, E. Le Grognec, M. Paris, J.-P. Quintard, *Chem. Eur. J.* **2006**, *12*, 6816–6828.

[12] a) G. Bartoli, M. Bosco, A. Giuliani, E. Marcantoni, A. Palmieri, M. Petrini, L. Sambri, *J. Org. Chem.* **2004**, *69*, 1290–1297; b) G. Bartoli, A. Giuliani, E. Marcantoni, M. Massaccesi, P. Melchiorre, S. Lanari, L. Sambri, *Adv. Synth. Catal.* **2005**, *347*, 1673–1680.

[13] a) J. Nokami, L. Anthony, S.-I. Sumida, *Chem. Eur. J.* **2000**, *6*, 2909–2913; b) S.-I. Sumida, M. Ohga, J. Mitani, J. Nokami, *J. Am. Chem. Soc.* **2000**, *122*, 1310–1313; c) J. Nokami, K. Nomiyama, S. Matsuda, N. Imai, K. Kataoka, *Angew. Chem. Int. Ed.* **2003**, *42*, 1273–1276; d) K.-T. Tan, S.-S. Chng, H.-S. Cheng, T.-P. Loh, *J. Am. Chem. Soc.* **2003**, *125*, 2958–2963.

[14] G.-L. Li, G. Zhao, *J. Org. Chem.* **2005**, *70*, 4272–4278.

[15] J. A. Marshall, G. S. Welmaker, B. W. Gung, *J. Am. Chem. Soc.* **1991**, *113*, 647–656.

[16] a) T. I. Moder, C. K. Hsu, F. R. Jensen, *J. Org. Chem.* **1980**, *45*, 1008–1010; b) G. Dumartin, J.-P. Quintard, M. Pereyre, *J. Organomet. Chem.* **1983**, *252*, 37–46.

[17] a) G. E. Keck, K. A. Savin, E. N. K. Cressman, D. E. Abbott, *J. Org. Chem.* **1994**, *59*, 7889–7896; b) Y. Nishigaichi, A. Takuwa, *Tetrahedron Lett.* **1999**, *40*, 109–112.

[18] I. Shibata, N. Yoshimura, M. Yabu, A. Baba, *Eur. J. Org. Chem.* **2001**, 3207–3211.

[19] M. Yasuda, T. Miyai, I. Shibata, A. Baba, R. Nomura, H. Matsuda, *Tetrahedron Lett.* **1995**, *36*, 9497–9500.

[20] T. Carofiglio, D. Marton, G. Tagliavini, *Organometallics* **1992**, *11*, 2961–2963.

[21] A. N. Thadani, R. A. Batey, *Org. Lett.* **2002**, *4*, 3827–3830.

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