Simultaneous Control of Regio- and Stereochemistries in the Reaction between α-Alkoxyaldehydes and Pentadienyltin. Selective Preparations of the Four Regio- and Diastereoisomers

Yutaka Nishigaichi,* Yasushi Hanano, and Akio Takuwa
Department of Chemistry, Faculty of Science, Shimane University, 1060 Nishikawatsu-cho, Matsue 690

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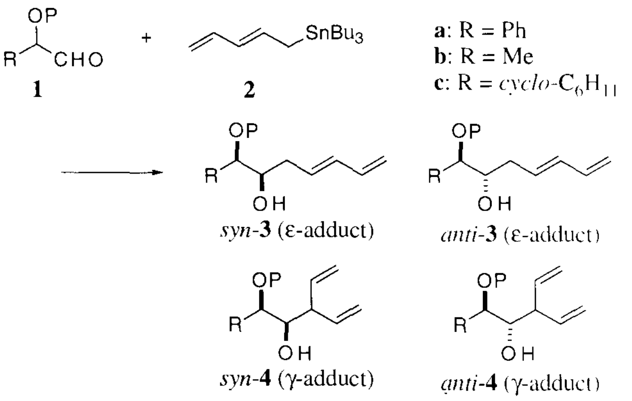
In the reaction between α-alkoxyaldehydes and pentadienyltin, each of the possible four regio- and stereoisomers, *syn*-γ-, *anti*-γ-, *syn*-ε-, and *anti*-ε-adducts, was selectively synthesized by the use of an appropriate combination of alkoxyl groups, Lewis acids, and solvents applied.

Allylic tin reagents are recognized to be useful for their wide utility in synthetic organic chemistry.[1] They are stable enough to handle usually and yet can be employed to various reactions. Among them, Lewis acid-mediated reaction toward electrophiles is one of the most useful ones due to its reactivity and selectivity.[2] One remarkable example is the work made by Keck and coworkers; diastereoselective reaction of allylic tin reagents toward oxygenated aldehydes.[3] The choice of the Lewis acid applied and the protecting group of the hydroxyl group was the critical point to control the selectivity.

As an allylic tin homologue, 2,4-pentadienyltin is also interesting which has an extended conjugate system. It has been reported to show divergent regioselectivity,[4] i.e. it can react at both γ and ε positions depending on the Lewis acid applied, though most of pentadienylmetals[5,6] show only one regioselectivity.



Scheme 1.

Along these lines, we get interested in the selective preparation of the each isomer in the reaction betweeen α-oxygenated aldehydes (**1**) and tributylpentadienyltin (**2**) as shown in Scheme 1. There are possibly four regio- and stereoisomers **3** and **4** except for *E/Z* isomerism. ε-Adduct **3** has a conjugate diene moiety which would undergo the Diels-Alder reaction and other addition reactions.[7] γ-Adduct **4** has a non-conjugated 1,4-diene moiety which is also a synthetically important building block.[6a,8]

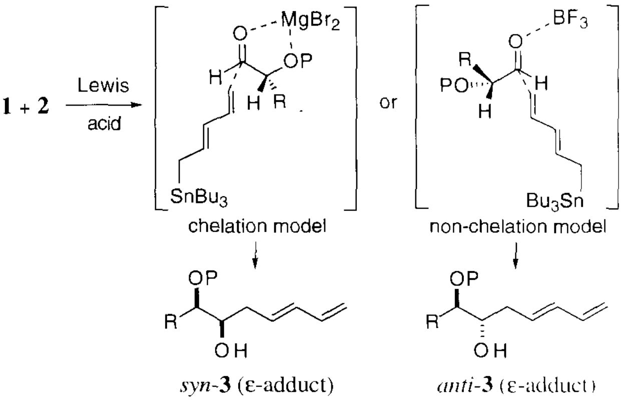
Because $MgBr_2 \cdot OEt_2$ and $BF_3 \cdot OEt_2$ are known as suitable Lewis acids for *syn*- and *anti*-diastereoisomers, respectively, in the reaction of allylic tins when combined with the protecting groups of an α-oxygenated aldehyde such as benzyl (Bn), methoxymethyl (MOM), and *tert*-butyldimethylsilyl (TBS) groups,[3a,b] these Lewis acids were also applied to the reaction between **1a** and **2**.[9]

Table 1. Reaction between **1a** and **2**

entry	**1a** P	Lewis acid/solvent[a]	selectivity[b] γ / ε	 *syn*/*anti*[c]	yield[d] %
1	Bn	$MgBr_2 \cdot OEt_2/CH_2Cl_2$	12/88	>99/1	70
2	MOM	$MgBr_2 \cdot OEt_2/CH_2Cl_2$	6/94	97/3	93
3	TBS	$BF_3 \cdot OEt_2/CH_2Cl_2$	<1/99	20/80	80
4	Bn	$ZnCl_2/Et_2O$	77/23	>99/1	80
5	Bn	$SnCl_4/CH_2Cl_2$	>99/1	>99/1	72
6	Bn	$InCl_3/CH_3CN$	>99/1	>99/1	76
7	MOM	$SnCl_4/CH_2Cl_2$	>99/1	>99/1	62
8	TBS	$ZnCl_2/Et_2O$	86/14	75/25	77
9	TBS	$InCl_3/CH_2Cl_2$	>99/1	78/22	78
10	TBS	$InCl_3/CH_3CN$	>99/1	43/57	73
11	TBS	$InCl_3/EtOH$	>99/1	25/75	70

[a] For reaction conditions, see note 9. [b] Determined by ^1H NMR. [c] Stereoselectivity of the major regioisomer. [d] Total yield of the products.

As shown in Table 1, $MgBr_2 \cdot OEt_2$ and $BF_3 \cdot OEt_2$ were again successfully employed to the present reaction with high ε-regioselectivity to give preferentially *syn*-**3** (entries 1 and 2) and *anti*-**3** (entry 3), respectively. These selectivities can be explained by acyclic transition state models, chelation model for the *syn*-adduct and non-chelation model for the *anti*-adduct (Scheme 2). Judging from the regioselectivity here, tributylpentadienyltin itself should be the actually reacting species.



Scheme 2.

As for the γ-selective pentadienylation of aldehydes using pentadienyltin reagents, a couple of methods have been reported: the use of a coordinating substituent on pentadienyltin,[10] the use of (*Z*)-pentadienyltin,[11] and the $ZnCl_2$-mediated reaction.[4] From the viewpoint of generality of the reaction, the regiocontrol by Lewis acids would be better.

First, $ZnCl_2$-mediated reaction[4] was tried with the benzyl-protected **1a** (Table 1, entry 4). Unfortunately, the regioselectivity was moderate in spite of high *syn*-stereoselectivity of the γ-adduct. Thus, we searched more suitable Lewis acids.

Consequently, $SnCl_4$[2] and $InCl_3$[12] were found to give only one isomer, *syn*-γ-adduct (Table 1, entries 5 and 6), in the reaction with benzyl-protected **1a**. As for the solvent in the $InCl_3$-mediated reaction, various ones could be used from aprotic non-polar one to protic polar one, among which CH_3CN gave the best results: high yield, high regio- and stereoselectivities, and high reaction rate (see Table 2, entries 4-6 and note 9c). Methoxymethyl group was also a suitable protecting group for this purpose (Table 1, entry 7).

Table 2. Reaction between **1b** and **2**

entry	**1b** P	Lewis acid/solvent[a]	selectivity[b] γ / ε	*syn*/*anti*[c]	yield[d] %
1	Bn	$MgBr_2·OEt_2/CH_2Cl_2$	17/83	>99/1	81
2	TBS	$BF_3·OEt_2/CH_2Cl_2$	<1/99	55/45	80
3	Bn	$SnCl_4/CH_2Cl_2$	>99/1	>99/1	70
4	Bn	$InCl_3/CH_2Cl_2$	>99/1	93/7	87
5	Bn	$InCl_3/CH_3CN$	>99/1	98/2	95
6	Bn	$InCl_3$/EtOH	>99/1	95/5	93
7	TBS	$InCl_3$/EtOH	>99/1	12/88	88

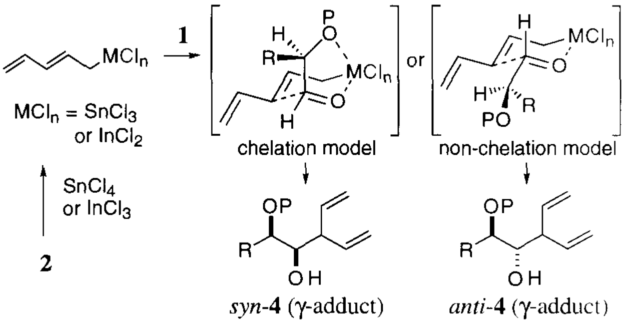
For footnotes, see Table 1.

Table 3. Reaction between **1c** and **2**

entry	**1c** P	Lewis acid/solvent[a]	selectivity[b] γ / ε	*syn*/*anti*[c]	yield[d] %
1	Bn	$MgBr_2·OEt_2/CH_2Cl_2$	4/96	>99/1	99
2	TBS	$BF_3·OEt_2/CH_2Cl_2$	<1/99	12/88	87
3	Bn	$InCl_3/CH_3CN$	>99/1	>99/1	99
4	TBS	$InCl_3$/EtOH	>99/1	22/78	91

For footnotes, see Table 1.

Both of these Lewis acids are known to perform transmetallation with allylic tin reagents,[2,12,13] so the actually reacting species here are supposed to be trichloropentadienyltin[13] and dichloropentadienylindium, which should react via chelation-controlled and 6-membered cyclic transition state as shown in Scheme 3.[3,14] It is noteworthy that the diastereoselectivity here is different from the results in the allylbromide/In powder/water-THF system reported by Paquette and co-workers.[14]



Scheme 3.

For the selective formation of the *anti*-γ-adduct, TBS group was selected as the protecting group considering the previous results.[3] $ZnCl_2$-mediated reaction was disappointing again (Table 1, entry 8). Though the reason is still unexplained, $SnCl_4$-mediated reaction did not proceed with TBS-protected **1a**. Therefore, $InCl_3$-mediated reaction was investigated using various solvents (Table 1, entries 9-11). Interestingly, ethanol was the most *anti*-selective (non-chelation controlled; Scheme 3) in this case (entry 11). The combination of ethanol and TBS-protection was critical, because the reaction of benzyl-protected **1b** was highly *syn*-selective (chelation controlled) even in ethanol (Table 2, entry 6). Cooperation of ethanol and TBS group inhibited the coordination of the ethereal oxygen of the aldehyde to the indium atom.

Thus, each of the four regio- and stereoisomers was able to be obtained by employing an appropriate combination of Lewis acids, protecting groups, and solvents. Next, these methods were applied to other α-oxygenated aldehydes, **1b** (R = Me) and **1c** (R = *cyclo*-hexyl). As summarized in Tables 2 and 3, similar selectivity was realized except for entry 2 in Table 2. These results mean that the present methodology can be applied widely to synthetic use. This work also elucidates the characteristic property of pentadienylindium reagent, diverse selectivity depending upon the solvent and the functionality of the substrate.

References and Notes

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9 Reaction conditions. a) $MgBr_2$-mediated reaction: to a stirred CH_2Cl_2 solution (5 ml) of **1** (0.2 mmol) and $MgBr_2·OEt_2$ (0.4 mmol) was added **2** (0.4 mmol) at -23 °C under nitrogen. After 4.5 h, aqueous HCl solution (2 mol/l) was added to the reaction mixture. The ethereal extract was washed with KF solution (10%), dried over Na_2SO_4, and condensed. Products were isolated by TLC. b) BF_3-mediated reaction: same conditions were employed except temperature (-78 °C) and reaction time (2 h). c) $InCl_3$-mediated reaction: same conditions were employed except solvent (as indicated in Tables), temperature (room temperature), and reaction time (0.5 h in CH_3CN or 12 h in CH_2Cl_2 and ethanol). d) $SnCl_4$-mediated reaction: to a stirred CH_2Cl_2 solution of **2** (0.4 mmol) at -78 °C were added a CH_2Cl_2 solution of $SnCl_4$ (0.4 mmol) and then a CH_2Cl_2 solution of **1** (0.2 mmol). Totally, 5 ml of CH_2Cl_2 was used. The reaction was worked up as above after 2 h. e) $ZnCl_2$-mediated reaction: a mixture of **1** (0.2 mmol), **2** (0.3 mmol), and $ZnCl_2$ (0.7 mmol) was diluted with dry ether (1 ml) and stirred vigorously at room temperature for 12 h. The reaction was worked up as above.

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