

THE INFLUENCE OF (ORGANO)METALLICS “METAL-TUNING” ON STEREO- AND REGIO-CHEMICAL CONVERGENCE IN REACTIONS OF ALLYLIC CARBANIONS WITH ALDEHYDES

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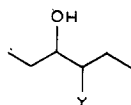
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Summary

Although the reaction of heterosubstituted allylic carbanions (**2**) with aldehydes generally produces a mixture of the γ - and α -adducts (**4** and **3**), *syn*-**3** and *anti*-**3** can be prepared either exclusively or predominantly by the proper choice of the organometallic compound added.

The structural unit like **1** is frequently encountered in many important natural products. For the synthesis of such compounds, it is essential to control



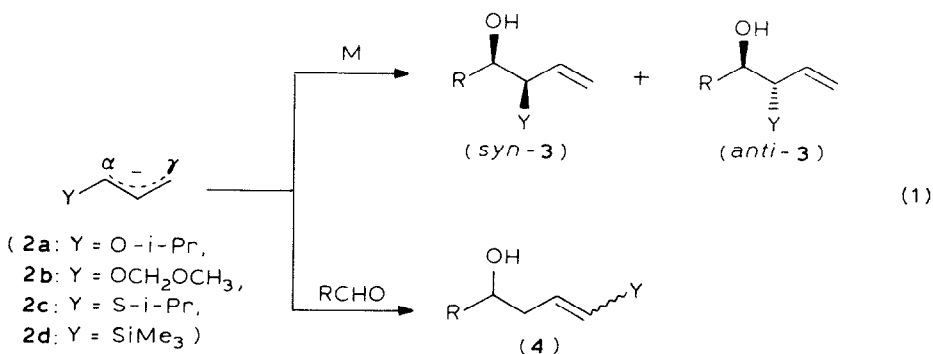
(**1a**: Y = C,
1b: Y = O,
1c: Y = S)

the relative stereochemistry between the two adjacent substituents [1]. We intended to control such stereochemistry via the reaction of aldehydes with heterosubstituted allylic carbanions (**2**), eq. 1 [2]. For this approach, it is necessary to control both regio- and stereo-chemical selectivities; i the regioselective reaction at the α -position of **2** and ii the stereoselective formation of either *syn*-**3** or *anti*-**3**. In this paper, we report that such stereo- and regio-chemical [3] convergence can be realized by metal tuning and either the *syn* or *anti* diastereomer can be obtained by the appropriate choice of “M”.

TABLE 1
REACTION OF **2a** AND **2b** WITH BENZALDEHYDE

Entry	2	Additive M	Product ratio			Total yield(%) isolated
			<i>syn</i> -3	<i>anti</i> -3	4	
1	2a	Bu ₃ SnCl/BF ₃	100	—	—	89
2	2a	 BCl	89	11	—	76
3	2a	EtAlCl ₂	84	16	—	70
4	2a	Cp ₂ ZrCl ₂	27	73	—	88
5	2b	Et ₃ Al	92	8	—	80
6	2b	Et ₂ AlCl	41	10	49	31
7	2b	Cp ₂ ZrCl ₂	37	63	—	80
8	2b	Cp ₂ ZrCl ₂ ^a	48	52	—	73
9	2b	Cp ₂ TiCl ₂ ^a	18	82	—	32

^a 0.5 eq. of M was used.

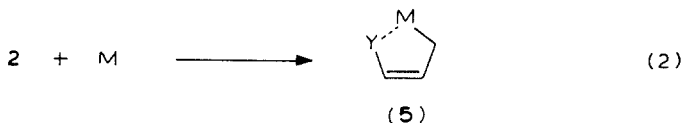


Results and discussion

Stereochemical convergence for Y = O

The reaction of **2a** and **2b** with benzaldehyde in the presence of M was investigated and the results are summarized in Table 1. By using Sn as M, *syn*-**3a** was obtained exclusively in high yield (entry 1). Presumably, Bu₃SnCl reacts at the γ -position of **2** to produce 3-isopropoxy-2-propenyltributylstannane. Although isolation of the intermediate was not tried, previous studies on the alkylation reaction of **2a** suggested regioselectivity [4], in fact this type of an allylic stannane was isolated in the reaction of **2c** and **2d**. Therefore, the *syn(erythro)* selectivity in entry 1 can be explained by an acyclic transition state proposed previously [5].

Boron and aluminium exhibit *syn(erythro)* selectivity, though the degree of selectivity is not so high as for tin (entries 2, 3, and 5). In these cases, ClBLn and ClALn presumably attack the γ -position of **2** to produce the *Z*-allylmethyl 5 owing to the strong coordination ability of the oxygen atom toward B and Al (eq. 2).



Therefore, the *syn* isomer is produced predominantly through the six-membered

TABLE 2
REACTION OF **2c** WITH ALDEHYDES

Entry	RCHO	Additive M	Product ratio			Total yield(%) isolated
			<i>syn</i> - 3	<i>anti</i> - 3	4	
1	PhCHO	Bu ₃ SnCl/BF ₃	90	10	—	78
2	(CH ₃) ₂ CHCHO	Bu ₃ SnCl/BF ₃	100	—	—	89
3	PhCHO	Ph ₃ SnCl/BF ₃	85	15	—	80
4	PhCHO	Et ₃ Al	63	37	—	90
5	(CH ₃) ₂ CHCHO	Et ₃ Al	55	45	—	92
6	PhCHO	Et ₂ AlCl	75	25	—	94
7	PhCHO	EtAlCl ₂	55	34	11	78
8	PhCHO	Et ₃ B	52	48	—	69
9	PhCHO	 -BCl	60	29	11	72
10	PhCHO	n-Bu-9-BBN	65	10	25	69
11	PhCHO	Cp ₂ ZrCl ₂ ^a	10	90	—	83
12	(CH ₃) ₂ CHCHO	Cp ₂ ZrCl ₂ ^a	20	80	—	90

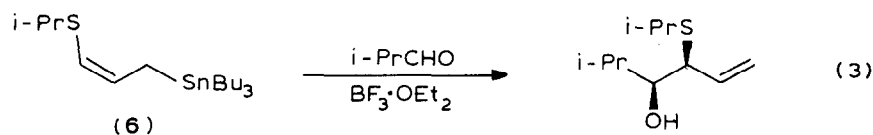
^a 0.5 eq of M was used.

cyclic transition state [1,6]. The *syn*-selectivity of B and Al is in marked contrast with the *anti*-selectivity of the carbon analogues (crotyl-boron and -aluminum).

On the other hand, Zr and Ti [7] exhibit *anti*-selectivity as reported earlier (entries 4, 7–9). In the simple crotyl system, the direction of the selectivity is always the same with B, Al, Zr, and Ti [1]. It seems that the steric bulk of the two Cp ligands prevents intramolecular coordination as in **5** and hence the double bond is in *E*-geometry. This is confirmed for **2c** and will be discussed later.

Stereochemical convergence for Y = S

The reaction of **2c** with aldehydes in the presence of M was examined and the results are summarized in Table 2. Here again, use of Sn produces the *syn* isomer either exclusively or predominantly (entries 1–3). The intermediate **6** was isolated and treatment of **6** with isobutyraldehyde in the presence of BF₃·OEt₂ produced *syn*-**3c** exclusively (eq. 3).



Al and B exhibit low *syn*-selectivity (entries 4–10). The degree of the *syn*-selectivity is lower than that shown in Table 1, cf. entry 7 of Table 2 vs. entry 3 of Table 1 and entry 9 of Table 2 vs. entry 2 of Table 1. The relatively low coordination ability of S toward B and Al, in comparison with the high ability of O, make it difficult to adopt a *Z* geometry as in **5**.

Zr exhibits *anti*-selectivity (entries 11 and 12) [8]. Here again the steric bulk of the two Cp ligands may force the double bond to be in *E* geometry. Irrespective of the

TABLE 3
REACTION OF **7** WITH BENZALDEHYDE

Entry	Additive M	RCHO	Product ratio ^a		Total yield(%) isolated
			<i>syn</i> - 8 (Z/E)	<i>anti</i> - 8 (Z/E)	
1	Cp ₂ ZrCl ₂	PhCHO	18 (–/100)	82 (1/1)	64
2	Cp ₂ TiCl ₂	PhCHO	16 (–/100)	84 (1/4)	50
3	Cp ₂ ZrCl ₂	PhCHO·BF ₃ ^b	69 (1/3)	31 (1/1)	62
4	Cp ₂ ZrCl ₂	PhCHO(BF ₃) ₂ ^b	78 (2/3)	22 (1/1)	60

^a Ratio of Z- to E-olefin. 0.5 eq of M was used. ^b Mixture of PhCHO and BF₃·OEt₂ was added.

tivity from *anti* and *syn* (entries 3 and 4). This inversed stereoselectivity is presumably a reflection of reversal of the transition state from the cyclic six-membered chair to acyclic geometry [9].

Stereochemical convergence for Y = Si

Finally we examined metal tuning in the reaction of **2d** with aldehydes and the results are summarized in Table 4. Here again, use of Sn enables **2d** to react with aldehydes in *syn* manner (entries 1 and 2). Isolation of *syn*-**3** in the pure form was difficult owing to the presence of BF₃·OEt₂ which induced deoxysilylation.

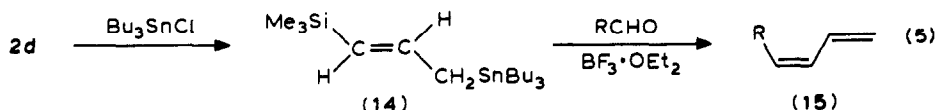


TABLE 4
REACTION OF **2d** WITH ALDEHYDES

Entry	RCHO	Additive M	Product ratio			Total yield(%) isolated
			<i>syn</i> - 3	<i>anti</i> - 3	4	
1	PhCHO	Bu ₃ SnCl/BF ₃	100	–	–	77 ^a
2	n-C ₉ H ₁₉ CHO	Bu ₃ SnCl/BF ₃	100	–	–	85 ^a
3	PhCHO	EtAlCl ₂	4	88	7	66
4	n-PrCHO	EtAlCl ₂	–	100	–	52
5	CH ₃ CH=CHCHO	EtAlCl ₂	14	86	–	46
6	PhCHO	Et ₂ AlCl	–	58	42	40
7	i-PrCHO	BCl	–	100	–	60
8	PhCHO	BCl	15	79	6	33
9	PhCHO	BCl	–	71	29	62 ^b
10	PhCHO	BCl ₂	–	100	–	10
11	PhCHO	n-Bu-9-BBN	2	96	2	6

^a The total yield isolated refers to the Z-diene (**15**). ^b The boron reagent and PhCHO were added at –30°C, though they were normally added at –78°C.

TABLE 5
 METAL TUNING IN **2**

Y	M			
	Sn	Al	B	Ti, Zr
C ^b	S ^a	A	A	A
Si	S	A-A	A-A	A
S	S	S	S	A
O	S	S-S	S-S	A

S: high *syn*-selectivity. A: high *anti*-selectivity. S: *syn*-selectivity. A: *anti*-selectivity.

^b Ref. 1.

The intermediate **14** was isolated and treatment with aldehydes in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ produced the *Z*-diene **15** (eq. 5) [10].

B and Al generally give the *anti* isomer predominantly and in some cases produce *anti*-**3** exclusively (entries 4 and 7). Although the *anti*-selectivity is very high with cyclopentylidichloroborane and *n*-Bu-9-BBN, the total yield is disappointing (entries 10 and 11).

In conclusion, the metal tuning in **2** is summarized in Table 5. Irrespective of heteroatoms (Y), Sn- BF_3 always produces *syn*-**3**, while Ti and Zr give *anti*-**3**. Al and B exhibit *anti*-selectivity for Y = C and Si, while they exhibit *syn*-selectivity for Y = S and O. The variation in selectivity is explained through three types of transition state models; the acyclic model, the cyclic six-membered chair with *Z*-geometry, and the cyclic six-membered chair with *E*-geometry.

Experimental

General information concerning instrumental and materials was described previously [11]. Bu_3SnCl , Ph_3SnCl , Cp_2ZrCl_2 , Cp_2TiCl_2 , EtAlCl_2 in hexane, and Et_2AlCl in hexane were purchased from Aldrich Chem. Co. and used as provided. Dicyclopentylboron chloride and cyclopentylboron dichloride were prepared according to the reported procedure through BH_2Cl and BHCl_2 , respectively [12].

Reaction of **2a** and **2b** in the presence of M

The general procedure for the preparation of **2** was described previously [3]. To an ether solution of **2a** (1 mmol) or to a THF solution of **2b** (1 mmol), cooled to -78°C , M (1 mmol) was added and the resulting mixture was stirred at this temperature. Benzaldehyde (1 mmol) was added and the mixture allowed to warm to 0°C , except in the case of entry 1. If Bu_3SnCl was used, $\text{BF}_3 \cdot \text{OEt}_2$ (1 mmol) was added immediately after the addition of benzaldehyde. The reaction was quenched at 0°C by slow addition of water, except in the case where a borane derivative was used as additive, in which the recovered borane was oxidized with $\text{H}_2\text{O}/\text{NaOH}$. The organic layer was separated and the aqueous layer twice extracted with ether. The combined organic layer was dried over anhydrous MgSO_4 . The product ratio was determined by GLPC analysis (DC 550, 5%, 3 m) and/or ^1H NMR spectroscopy. Isolation of the products was carried out by a short silica gel column. For the spectroscopic data and structure determination of 1-phenyl-2-isopropoxy-3-butenol and 1-phenyl-2-(methoxymethoxy)-3-butenol, see ref 3. 1-Phenyl-4-(methoxy)meth-

oxy-3-butenol: b.p. 115°C/2 Torr (Kugelrohr); ^1H NMR (CDCl_3): δ 2.80–3.00 (m, 2), 3.36 (s, 3), 3.40 (br-s, 1), 3.68 (s, 2), 3.84 (t, 1, J 7.0 Hz), 5.80–6.20 (m, 2), 7.20 (s, 5) ppm; IR (CCl_4): 3560, 1600, 1120, 1040 cm^{-1} ; MS: m/e (M^+) 208. Anal. Found: C, 69.40; H, 7.82. $\text{C}_{12}\text{H}_{16}\text{O}_3$ calcd.: C, 69.21; H, 7.75%.

Reaction of **2c** in the presence of **M**

To an ether solution of **2c** cooled to -78°C was added an equivalent amount of **M**. The aldehydes were added and workup was carried out as described above. The structure determination of 1-phenyl-2-(isopropylthio)-3-butenol (**8**) and 3-(isopropylthio)-4-hydroxy-5-methylhexene (**9**) was carried out previously [3]. 1-Phenyl-4-(isopropylthio)-3-butenol: b.p. 125°C/2 Torr (Kugelrohr); ^1H NMR (CDCl_3): δ 1.25 (d, 6, J 7.0 Hz), 2.01 (br-s, 1), 2.40 (m, 2), 2.91 (septet, 1, J 7.0 Hz), 4.40 (t, 1, J 6.0 Hz), 5.40–5.90 (m, 2), 7.20 (s, 5) ppm; IR (CCl_4): 3480, 1635, 1600, 1450, 1385, 1250 cm^{-1} ; MS: m/e (M^+) 222. Anal. Found: C, 70.45; H, 8.02. $\text{C}_{13}\text{H}_{18}\text{OS}$ calcd.: C, 70.23; H, 8.16%. 3-(Isopropylthio)-2-propenyltributylstannane (**6**) was isolated in 92% yield through a short silica gel column; ^1H NMR (CCl_4): δ 0.70–2.00 (m, 33), 1.84 (d, 2, J 8.0 Hz), 3.01 (septet, 1, J 7.0 Hz), 5.62 (d, 1, J 10.0 Hz), 5.80 ppm (td, 1, J 8.0 and 10.0 Hz); MS: m/e (M^+) 405.

Reaction of **2d** in the presence of **M**

To a THF solution of **2d** cooled at -78°C was added an equivalent amount of **M**, and then the aldehydes were added. A similar workup procedure was employed. The structure determination of 1-phenyl-1,3-butadiene, 1-phenyl-2-(trimethylsilyl)-3-buten-1-ol, 1-phenyl-4-(trimethylsilyl)-3-buten-1-ol, 3-(trimethylsilyl)-4-hydroxy-1-heptene, and 3-(trimethylsilyl)-4-hydroxy-5-methyl-1-hexene was carried out as previously described [3]. 3-(Trimethylsilyl)-4-hydroxy-1,5-heptadiene; ^1H NMR (CCl_4) *anti* isomer: δ 0.09 (s, 9), 1.22 (dd, 1, J 8.0 and 5.0 Hz), 1.70 (d, 3, J 4.5 Hz), 2.48 (br-s, 1), 4.12 (m, 1), 4.74 (dd, 1, J 16.5 and 2.0 Hz), 4.86 (dd, 1, J 10.0 and 2.0 Hz), 5.36–5.52 (m, 2), 5.80 ppm (ddd, 1, J 10.0, 10.0, and 16.5 Hz); MS: m/e (M^+) 184. Anal. Found: C, 65.04; H, 11.08. $\text{C}_{10}\text{H}_{20}\text{OSi}$ calcd.: C, 65.15; H, 10.94%. The *syn* isomer was not isolated in the pure form, so structure determination was ambiguous but was carried out through extrapolation from the other examples. *Z*-Trideca-1,3-diene; ^1H NMR (CDCl_3): δ 1.05 (t, 3, J 7.0 Hz), 1.55 (m, 14), 1.95 (m, 2), 4.75 (d, 1, J 9.0 Hz), 4.86 (d, 1, J 18.0 Hz), 5.40 (dt, 1, J 7.0 and 9.0 Hz), 5.81 (dd, 1, J 9.0 and 9.0 Hz), 6.05 ppm (ddd, J 9.0, 9.0, and 18.0 Hz); IR (CCl_4): 990, 910 cm^{-1} ; MS: m/e (M^+) 180. Anal. Found: C, 86.77; H, 13.50. $\text{C}_{13}\text{H}_{24}$ calcd.: C, 86.59; H, 13.41%. 3-Trimethylsilyl-2-propenyltributylstannane (**14**) was isolated in 70% yield from **2d**; ^1H NMR (CCl_4): δ 0.10 (s, 9), 0.80–1.70 (m, 27), 1.81 (d, 2, J 8.0 Hz), 5.15 (d, 1, J 18.0 Hz), 5.97 ppm (td, 1, J 8.0 and 18.0 Hz); MS: m/e (M^+) 403.

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