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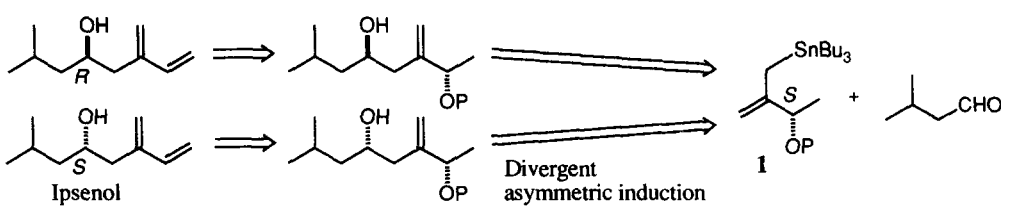
Optically Active Allylic Tin Reagent as an Enantio-divergent Synthon of Isoprenoids via Remote and Divergent Asymmetric Induction

Yutaka Nishigaichi,* Hiroki Kuramoto and Akio Takuwa

Department of Chemistry, Faculty of Science, Shimane University, Matsue 690, Japan

Abstract : (*S*)-2-(1-Hydroxymethyl)allyltin (**1a**) can be prepared in high enantiomeric purity. When its methylated and acetylated derivatives are allowed to add to aldehydes with the help of *i*-PrOTiCl$_3$ and SnCl$_4$, *syn*- and *anti*-homoallylic alcohols are stereoselectively obtained, respectively, via 1,4-asymmetric induction. These reactions are applied to the synthesis of the both enantiomers of a pheromone constituent, ipsenol, from a single enantiomer of **1a**.

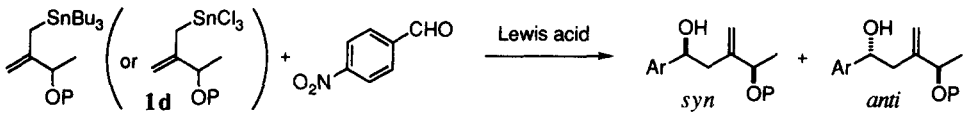
Efficient synthesis of optically active compounds is one of the most important issues in the organic chemistry.[1] Among various methods for it, asymmetric induction from optically active substrates is a promising way, where one enantiomeric source usually induces a new chiral center of one configuration, *R* or *S*. Therefore we need both enantiomers to prepare the both enantiomeric products. On the other hand, if a single enantiomer can induce both *R*- and *S*-stereocenters separately (divergent asymmetric induction), this will be a practically useful method for the asymmetric synthesis. In this communication, we describe the preparation of optically active allylic tin reagents **1** as chiral isoprenyl synthons, and preliminary results of their application to the divergent asymmetric induction realized by the synthesis of the both enantiomers of ipsenol, a constituent of the sex pheromone of the bark beetle. Scheme 1 shows the retrosynthetic pathways.



Scheme 1.

The success of the divergent stereoinduction must depend upon the new type of 1,4-remote asymmetric induction from the allylic tin reagents[2,3] in a divergent way. Therefore, we first examined the reactions of racemic **1** toward *p*-nitrobenzaldehyde. After trying several protecting groups (P) and Lewis acids as a reaction promoter (Table 1), we found that two methods were promising. One is the use of *i*-PrOTiCl$_3$ as a Lewis acid in the reaction of **1b** (P = Me) (entry 4), and the other is the use of SnCl$_4$ as a transmetallating reagent in the reaction of **1c** (P = Ac) (entry 10), where the actual reacting species was allylic trichlorotin **1d**. Interestingly, the major products for the two reaction methods had the opposite stereochemistries: the **1b**/*i*-PrOTiCl$_3$-system gave the *syn*-adduct and the **1c**/SnCl$_4$-system gave the *anti*-adduct. Protecting groups and Lewis acids applied other than Me and Ac, and *i*-PrOTiCl$_3$ and SnCl$_4$ were ineffective. The reason for the present stereoselection is not clear enough now, but the coordinating abilities of the Lewis acids may affect. As indicated in the previous report,[2a] the reaction of entry 4 (P = Me, Lewis acid = *i*-PrOTiCl$_3$) also proceeded via the Ti-bridged cyclic transition state (Scheme 2). The SnCl$_4$-promoted reaction (entry 10) did via the 6-membered cyclic transition state consisting of transmetallated allylic trichlorotin **1d**[4] which was characterized by its intramolecular coordination (Scheme 3).

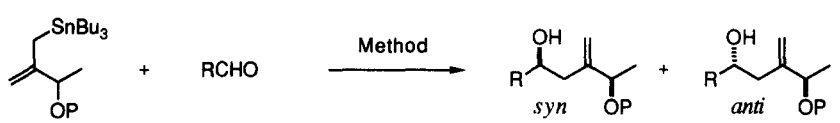
Table 1. Effect of Protecting Groups and Lewis Acids on Stereoselectivity



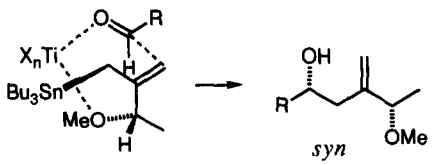
Entry	Protecting group P	Lewis acid (2 equiv.)	Product ratio *syn*	Product ratio *anti*	Total yield %
1	Me	BF_3·OEt_2	36	64	82
2	Me	$SnCl_4$[a]	45	55	75
3	Me	$TiCl_4$-Et_2O	47	53	66
4	Me	*i*-PrOTiCl_3	88	12	85
5	CH_2OMe	*i*-PrOTiCl_3	57	43	90
6	CH_2Ph	*i*-PrOTiCl_3	43	57	81
7	$SiMe_2Bu$-*t*	*i*-PrOTiCl_3	53	47	quant
8	COMe	BF_3·OEt_2	53	47	97
9	COMe	*i*-PrOTiCl_3	34	66	79
10	COMe	$SnCl_4$[a]	21	79	74
11	COPh	$SnCl_4$[a]	32	68	77
12	COBu-*t*	$SnCl_4$[a]	47	53	85

[a] Reaction was carried out via transmetallation accompanying the formation of **1d**.

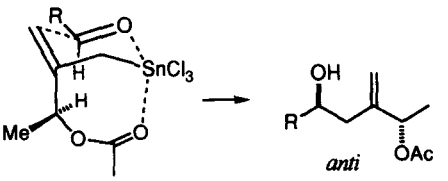
Table 2. Divergently Stereocontrolled Reaction



Entry	P (Method)	Aldehyde R	Product ratio *syn*	Product ratio *anti*	Total yield %
1	Me (**1b**)	*p*-$MeO_2CC_6H_4$	91	9	98
2	(*i*-PrOTiCl_3, -78 – 0°C)	*p*-ClC_6H_4	94	6	88
3		C_6H_5	98	2	53
4		*p*-MeC_6H_4	96	4	93
5		*p*-$MeOC_6H_4$	47	53	30
6		*n*-C_7H_{15}	77	23	92
7		*c*-C_6H_{11}	96	4	58
8		*t*-Bu	73	27	44
9	Ac (**1c**)	C_6H_5	21	79	74
10	($SnCl_4$, 0°C	*p*-MeC_6H_4	28	72	68
11	transmetallation)	*n*-C_7H_{15}	26	74	86
12		Et_2CH	23	77	63



Scheme 2. Lewis acid (Ti)-bridged transition state

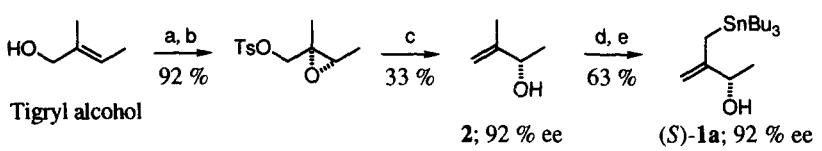


Scheme 3. Intramolecularly coordinated 6-membered cyclic transition state

We also examined the generality of the divergent stereoinduction by applying to various aldehydes (Table 2). High to moderate selectivity appeared in most aliphatic and aromatic cases. Only *p*-anisaldehyde (entry 5) showed very low selectivity and yield. This indicates that the tin reagents are more generally applicable than the corresponding silane reagents.[2a] In addition, the tin reagents have the advantage of undergoing transmetallation.[4]

We therefore applied the present divergently stereocontrolled reaction to the synthesis of the both enantiomers of ipsenol.[5] The key point of our strategy is one enantiomeric chiral source **1** can induce the separate formation of both *R*- and *S*-stereocenters by applying appropriate protecting groups and Lewis acids. Thus, one enantiomer of the allylic tin reagent will be an enantio-divergent synthon of isoprenoids. (Scheme 1)

As a starting material, we required an optically active alcohol, 3-methyl-3-buten-2-ol (**2**). We could obtain it as the *S*-enantiomer from tigryl alcohol via 3 steps in 30% of overall yield (Scheme 4).[6] Its enantiomeric purity was determined to be 92% ee by the NMR spectrum of its (*S*)-*O*-methylmandelate. Conversion from **2** to the optically active allylic tin compound, (*S*)-3-(tributylstannylmethyl)-3-buten-2-ol (**1a**), was readily realized following Trost's method.[7] It was confirmed as above that the optical purity was completely retained while under strongly basic conditions. The alcoholic hydroxyl group was then protected by two ways in high yields affording (*S*)-**1b**[8] and (*S*)-**1c**[9] (Scheme 5).



Scheme 4.[10] a) Ti(OPr-*i*)$_4$, (+)-DIPT, *t*-BuOOH, CH_2Cl_2, -20°C; b) TsCl, Et_3N; c) NaI, Zn(Cu), $HOCH_2CH_2OH$, 80°C; d) *n*-BuLi, TMEDA, Et_2O-THF; e) Bu_3SnCl

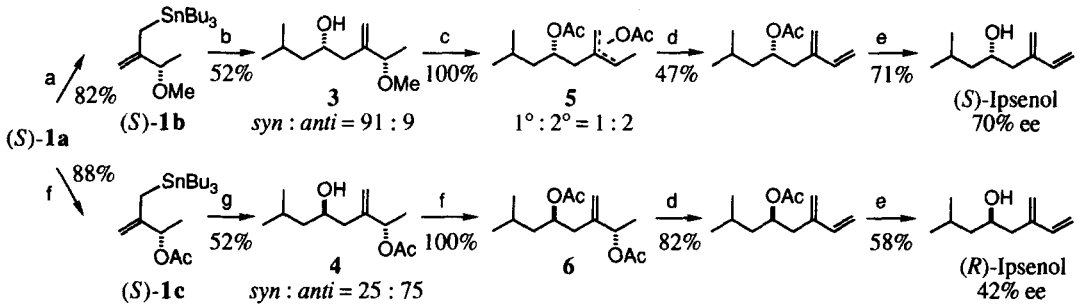
As the first step, 3-methylbutanal was subjected to the above reactions with (*S*)-**1b** and (*S*)-**1c**. The diastereomeric ratios (*syn*/*anti*) of the products were 91/9 and 25/75, respectively, which are similar results to those mentioned above. The next step was the conversion of the allylic ether and ester to the isoprenyl group by the elimination of methanol and acetic acid from **3** and **4**, respectively.

As the most straightforward way, we initially tried Pd-catalyzed elimination of acetic acid from hydroxy acetate **4**, but ipsenol was obtained in only poor yield by the use of both Pd(0) and Pd(II) catalysts.[11] Finally, we found that Pd(II)-catalyzed reaction of the diacetate **6** at 100°C successfully gave acetate of ipsenol.

On the other hand, elimination of hydroxy methyl ether **3** was more troublesome, because direct elimination of methanol is difficult in the presence of a hydroxyl group. At this stage, the following procedure is most successful: acidic treatment of the methyl ether in acetic anhydride afforded a regioisomeric mixture of the corresponding diacetates (**5**; primary acetate : secondary acetate = 1 : 2), of which Pd(II)-catalyzed reaction as above gave acetate of ipsenol in a moderate yield. This rather low yield may be attributed to the lower reactivity of the regioisomer (primary acetate) toward the elimination.

Hydrolysis of the acetate readily afforded ipsenol, of which enantiomeric purity was determined by ^{1}H NMR spectroscopy of its (*S*)-*O*-methylmandelate. Ipsenol from (*S*)-**1b** was the (*S*)-isomer of 70% ee, while one from (*S*)-**1c** was the (*R*)-isomer of 42% ee. This means that the single enantiomer of the reagent **1a** can afford

the both enantiomers of ipsenol. Thus, we can formally use **1a** as a dual enantiogenic synthon of the isoprenyl nucleophile. Synthetic improvement and further application of **1** are now in progress.



Scheme 5.[10] a) NaH, MeI, DMF-THF; b) 3-methylbutanal, *i*-PrOTiCl$_3$, CH_2Cl_2, -78 – 0°C; c) Ac_2O, $HClO_4$; d) $Pd(OAc)_2$, Ph_3P, dioxane, 100°C, 3h; e) NaOH, MeOH; f) AcCl, pyridine, CH_2Cl_2; g) $SnCl_4$, CH_2Cl_2, 0°C, then 3-methylbutanal, 0°C.

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8. **1b**: ^{1}H NMR ($CDCl_3$) 0.74-1.00 (m, 15H), 1.24 (d, J = 6.4 Hz, 3H), 1.25-1.37 (m, 6H), 1.43-1.55 (m, 6H), 1.63 (d, J = 12.2 Hz, 1H), 1.78 (d, J = 12.2 Hz, 1H), 3.24 (s, 3H), 3.61 (q, J = 6.4 Hz, 1H), 4.63 (s, 1H), 4.73 (s, 1H). ^{119}Sn NMR (CCl_4) -16.0. IR (neat) 2950, 1630, 1460, 1370, 1100, 870, 660 cm^{-1}. $[\alpha]_D$ = +4.5° (*c* = 1.3, $CHCl_3$).
9. **1c**: ^{1}H NMR ($CDCl_3$) 0.76-1.00 (m, 15H), 1.21-1.40 (m, 6H), 1.32 (d, J = 6.6 Hz, 3H), 1.43-1.54 (m, 6H), 1.70 (d, J = 12.0 Hz, 1H), 1.81 (d, J = 12.0 Hz, 1H), 2.05 (s, 3H), 4.62 (s, 1H), 4.77 (s, 1H), 5.19 (q, J = 6.6 Hz, 1H). ^{119}Sn NMR (CCl_4) -14.8. IR (neat) 2950, 1740, 1630, 1460, 1370, 1240, 1050, 870, 660 cm^{-1}. $[\alpha]_D$ = -4.2° (*c* = 1.4, $CHCl_3$).
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