1,4-Asymmetric Induction from Chiral δ-Oxygenated Allylic Tin Reagents

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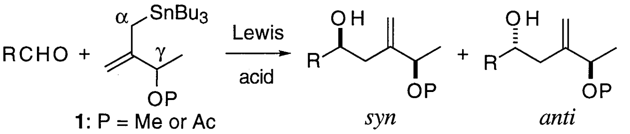
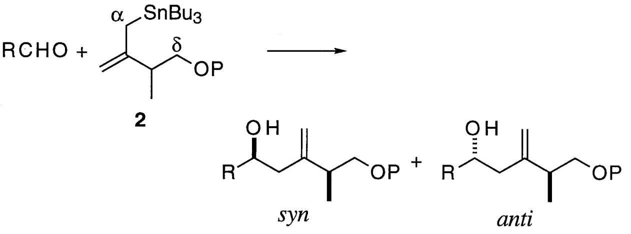
A new type of asymmetric induction from allylic tin reagents is developed. A chiral allylic tin which has an oxygen substituent (ether or ester) at its δ-position successfully induces a new chirality in a 1,4-induction mode in the reaction with aldehydes via the transmetallation with $SnCl_4$.

Allylic tin reagents are useful in organic synthesis especially in stereoselective synthesis.[1-3] Among them, Keck reported a decade ago that asymmetric induction from chiral aldehydes was successfully accomplished.[4] On the other hand, similar asymmetric induction from chiral substituents of allylic tins is not fully investigated.[1,2] With respect to asymmetric induction from β-substitutents, only a few reports appeared.[5-7]



Scheme 1.

In our previous report,[7] reagent **1** was found to exhibit successfully divergent stereoselectivity depending on the applied Lewis acid and the protecting group, P (Scheme 1). In this case, the coordinative oxygen functionality is located at the γ-position from the tin-connecting carbon and attatched directly to the chiral center. Thus, we have decided to extend this chemistry to the reaction of the allylic tin reagent **2**[8] with an oxygen fuctionality at the more remote δ-position and attatched indirectly to the chiral center (Scheme 2).[9,10]



Scheme 2.

As summarized in Table 1, the effects of protecting groups and Lewis acids were investigated in the reaction toward *p*-nitrobenzaldehyde. When the hydroxyl group of **2** was protected by methyl group (**2a**), ordinary Lewis acid-promoted reaction did not show high stereoselectivity (entries 1 and 2). In contrast, the transmetallation method[3] with $SnCl_4$ exhibited high *syn*-selectivity (entry 3). Methoxymethyl protection (**2b**) was found more effective for the *syn*-selectivity (entry 4). To our surprise, the reagent with a free hydroxyl group (**2c**) also showed high *syn*-selectivity and yield (entry 5).[10] However, acetyl protection (**2d**) turned out to show low selectivity via the transmetallation (entry 6). On the other hand, good *anti*-selectivity was found by the use of $TiCl_4$-Et_2O without transmetallation[11] (entry 7).

Table 1. Reaction of **2** toward *p*-nitrobenzaldehyde[a]

Entry	Allylic tin P	Lewis acid equiv.	Product ratio *syn*	*anti*	Yield %
1[b]	Me (**2a**)	$BF_3 \cdot OEt_2$ (2)	62	38	100
2[b]	Me	*i*-$PrOTiCl_3$ (2)	38	62	99
3[c]	Me	$SnCl_4$ (1.5)	93	7	100
4[c]	MOM (**2b**)	$SnCl_4$ (1.5)	100	0	100
5[c]	H (**2c**)	$SnCl_4$ (1.5)	98	2	84
6[c]	Ac (**2d**)	$SnCl_4$ (1.5)	66	34	100
7[b]	Ac	$TiCl_4$-Et_2O (1)	22	78	98

[a] All reactions were carried out in CH_2Cl_2 at -78 °C for 2 h. Yields and product ratios were determined by ^1H-NMR (270 MHz). [b] The allylic tin reagent **2** (1.5 equiv.) was added to the solution of the aldehyde and the Lewis acid. [c] The aldehyde was added to the premixed solution of **2** and $SnCl_4$.

Thus, two effective reagents, **2b** and **2c**, for the *syn*-product were applied to the reaction toward other aldehydes. The results are collected in Table 2. The selectivities were found to be generally high for both aromatic and aliphatic aldehydes, but the yield from **2b** were somewhat higher than from **2c**.

Table 2. Reactions via transmetallation with $SnCl_4$[a]

RCHO R	Product ratio (*syn/anti*) (Yield/%) from **2b**		from **2c**	
C_6H_5	93/7	(84)	90/10	(57)
p-$CH_3C_6H_4$	90/10	(75)	85/15	(42)
n-C_7H_{15}	86/14	(64)	89/11	(46)
$(C_2H_5)_2CH$	89/11	(62)	96/4	(53)

[a] See the footnotes *a* and *c* in Table 1.

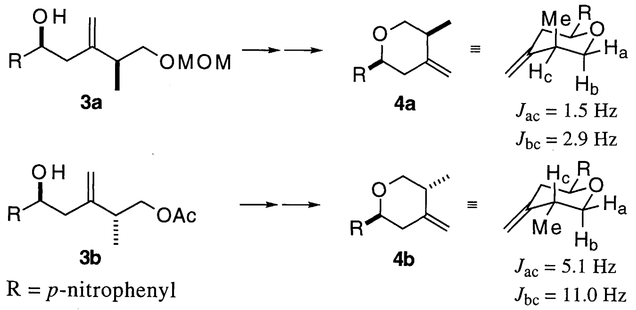
We also tried to apply the *anti*-selective reaction system, **2d** and $TiCl_4$-Et_2O (Table 3). The diastereoselectivity was found to remain *anti* for various aldehydes, though the product ratio decreased when the aldehydes were less reactive. In addition, while 0.5 equiv. of $TiCl_4$ was found to be much enough for high *anti*-selectivity and yield from reactive *p*-nitrobenzaldehyde, even 2.0 equiv. of $TiCl_4$ afforded only moderate to low yields from aliphatic aldehydes.

The stereochemistry of the products (R = *p*-nitrophenyl) was determined by transforming them to the cyclic derivatives (Scheme 3). Deprotection and tosylation were applied to the products **3a** and **3b** followed by cyclization under basic conditions to give the corresponding tetrahydropyrans **4a** and **4b**. The indicated coupling constants revealed that the methyl group of **4a** was located at axial and that of **4b** at equatorial. This concludes that **3a** has *syn*-configuration and **3b** has *anti*-configuration. Other products were also confirmed by comparing their ^1H-NMR specta with **3a** and **3b**.

Table 3. $TiCl_4$-Promoted reaction of **2d**[a]

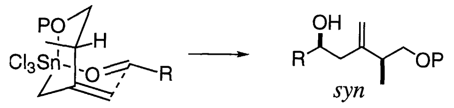
Entry	RCHO R	$TiCl_4$ equiv.	Product ratio *syn*	 *anti*	Yield %
1	p-$O_2NC_6H_4$	0.5	20	80	100
2	C_6H_5	1.0	31	69	65
3	p-$CH_3C_6H_4$	1.0	42	58	48
4	n-C_7H_{15}	2.0	34	66	31
5	$(C_2H_5)_2CH$	2.0	29	71	16

[a] See the footnotes *a* and *b* in Table 1.

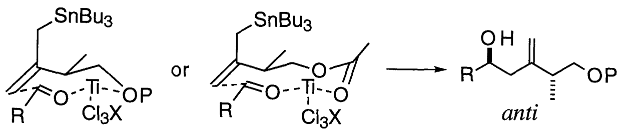


Scheme 3. Determination of the stereochemistry.

From these results, we can conclude that the selectivity is mainly controlled by the Lewis acid used; $SnCl_4$ afforded *syn*-products via transmetallation and $TiCl_3X$ did *anti*-ones. This different selectivity can be attributed to the difference of the transition states for the both reaction systems. An allylic tin trichloride given by the transmetallation favors a bicyclic transition state including both intra- and inter-molecular coordinations to the tin atom (Scheme 4). This conformation may avoid the allylic strain and the congestion with the reacting aldehyde to give the *syn*-product. On the other hand, $TiCl_3X$ accepts two intermolecular coordinations to afford a transition state in Scheme 5.[11] The methyl group at the chiral center should be located at the pseudo-equatorial position to afford the *anti*-product.



Scheme 4. Bicyclic transition state.



Scheme 5. Ti-bridged cyclic transition state.

As a conclusion, fairly high *syn*-stereoselectivity has been obtained in a new type of 1,4-asymmetric induction from β-substituted allylic tin reagents **2**, though *anti*-selectivity could not be controlled at a sufficiently high level. It is also noteworthy that an unprotected hydroxyl group on the allylic tin reagent did not seriously hamper the high *syn*-selectivity in the present reaction system.[10] Further improvement and non-racemic version[9] of the reaction are now being investigated.

References and Notes

1 Recent reviews: Y. Yamamoto and N. Asao, *Chem. Rev.*, **93**, 2207 (1993); Y. Yamamoto and N. Shida, in "Advances in Detailed Reaction Mechanisms," JAI Press (1994), Vol. 3, p. 1; J. A. Marshall, *Chem. Rev.*, **96**, 31 (1996).
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4 G. E. Keck and E. P. Boden, *Tetrahedron Lett.*, **25**, 265 (1984). G. E. Keck and E. P. Boden, *Tetrahedron Lett.*, **25**, 1879 (1984). G. E. Keck and D. E. Abbott, *Tetrahedron Lett.*, **25**, 1883 (1984). G. E. Keck, S. Castellino, and M. R. Wiley, *J. Org. Chem.*, **51**, 5478 (1986).
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6 M. Gruttadauria and E. J. Thomas, *J. Chem. Soc., Perkin Trans. 1*, **1995**, 1469.
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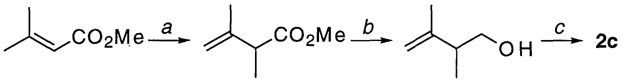
8 The reagent **2c** was prepared as depicted below. Appropriate protections of **2c** afforded **2a**, **2b**, and **2d**.



Reagents, conditions, and yields: [a] i) lithium diisopropylamide, HMPA, THF, -78 °C; ii) MeI, -78 °C; 66 %. [b] $LiAlH_4$, ether, 0 °C; 71 %. [c] i) n-BuLi, t-BuOK, hexane, 0 °C – r.t.; ii) n-Bu_3SnCl, THF, 0 °C; 89 %.

9 Similar type of products were given via the ene reaction of the silyl ether of optically pure 2,3-dimethyl-3-buten-1-ol, where the substrate applied was limited to glyoxylate. K. Mikami and A. Yoshida, *Tetrahedron Lett.*, **35**, 7793 (1994).
10 Similar substituents on the α- or γ-position of allylic tins are reported. J. S. Carey, T. S. Coulter, and E. J. Thomas, *Tetrahedron Lett.*, **34**, 3933 (1993). S. J. Stanway and E. J. Thomas, *Tetrahedron Lett.*, **36**, 3417 (1995).
11 The additive ether or an i-PrO ligand inhibited the transmetallation. See: Y. Nishigaichi, M. Fujimoto, K. Nakayama, A. Takuwa, K. Hamada, and T. Fujiwara, *Chem. Lett.*, **1992**, 2339. Also see Ref. 7.