Synthesis of *anti*-Homoallylic Alcohols and Monoprotected 1,2-Diols through $InCl_3$-Promoted Addition of Allylic Stannanes to Aldehydes

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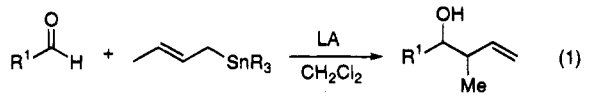
Additions of crotyltrialkylstannanes to aldehydes lead to *syn* adducts selectively through an acyclic transition state in the presence of Lewis acid promoters such as BF_3·OEt_2, $MgBr_2$, and the like (eq 1).[1]

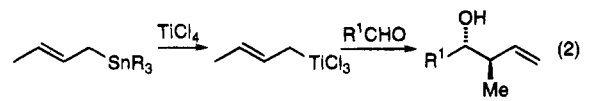


(1)

R = Me or Bu

LA = 1 equiv. of BF_3·OEt_2 or $MgBr_2$ or ZnI_2 or $SnCl_4$ or $TiCl_4$

In 1984, Keck and co-workers found that premixing the stannane with 2 equiv of $TiCl_4$ prior to addition of the aldehyde resulted in a strong preference for the *anti* adduct.[2] It was surmised that this latter reaction involves transmetalation to a crotyltitanium species which reacts with the aldehyde through a cyclic transition state (eq 2).[2,3]



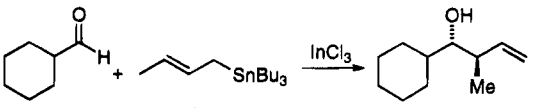
(2)

In recent years, we have developed methodology for the synthesis of nonracemic γ-alkoxy and silyloxy allylic stannanes.[1d] Though less reactive and more labile than their crotyl counterparts, these stannanes afford monoprotected *syn* 1,2-diols in high yield with excellent diastereoselectivity upon reaction with various aldehydes in the presence of BF_3·OEt_2.[4] Unfortunately, their lability precludes transmetalation with $TiCl_4$ or $SnCl_4$: admixture of these Lewis acids and the oxygenated stannanes at −78 °C causes total destruction of the reagents.

We have now found that $InCl_3$ in various donor solvents undergoes transmetalation with allylic stannanes and the resulting intermediates afford *anti* adducts with aldehydes.[5] These findings allow direct access to monoprotected *anti* 1,2-diols for the first time and considerably expand the scope of this reaction.

Our initial studies were conducted with the more reactive and less labile crotylstannane **2** and cyclohexanecarboxaldehyde (**1c**) to establish feasibility and optimize conditions (Table 1). Best results were obtained in acetone or acetonitrile at low temperature.

Table 1. Effect of Solvent and Temperature on $InCl_3$-Promoted Additions of Crotyl Tri-*n*-butylstannane to Cyclohexanecarboxaldehyde



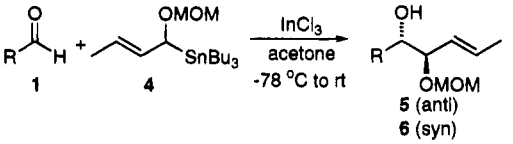
1c 2 3

solvent	*T*, °C	*t*, h	yield, %	anti:syn
aq/EtOH	rt	24	67	81:19
THF	rt	24	78	86:14
DMF	rt	24	33	84:16
MeCN	rt	0.5	88	87:13
MeCN	−40	18	90	94:6
acetone	rt	0.25	96	87:13
acetone	−78 to rt	5	90	98:2

In all reactions the crotylstannane was added to a solution of the aldehyde and $InCl_3$. Premixing the stannane and $InCl_3$ produced an immediate precipitate (polymer?), and subsequent addition of aldehyde resulted in slow formation of product, which was isolated in low yield after prolonged reaction times.

The next series of experiments was performed with the racemic α-(methoxymethoxy) allylic stannane **4** in acetone (Table 2). Premixing of the aldehyde and $InCl_3$ at rt and then cooling to −78 °C followed by addition of stannane **4** led to the *anti* and *syn* monoprotected diols **5** and **6**, with the former being strongly favored. Negligible decomposition of the stannane occurred under these conditions. It is noteworthy that reactions of the crotylstannane **2** proceed with net allylic inversion whereas stannane **4** reacts with allylic retention.

Table 2. Addition of α-OMOM Crotylstannane (R,S)-4 to Aldehydes



1 4

series	R	yield, %	anti:syn
a	C_6H_{13}	83[a]	91:9
b	i-Pr	77[a]	98:2
c	c-C_6H_{11}	90[b]	98:2
d	(*E*)-BuCH=CH	74[a]	84:16
e	C_6H_{13}–≡	78[a]	84:16
c	c-C_6H_{11}	76[c,d]	97:3

[a] Ca. 10% of acetone adduct was also formed. [b] Ca. 5% of acetone adduct was also formed. [c] Reaction in MeCN at rt. [d] Ca. 10% of the γ adduct was also formed.

During the course of these studies, we detected a small amount of a persistent byproduct which appeared to be the S_E2' adduct of stannane **4** and acetone. This byproduct was easily separated from the alcohol products. As an alternative, the addition could be conducted in acetonitrile at rt with comparable efficiency. In this case, a small amount of the γ adduct (allylic inversion) was also formed.

A third series of studies was conducted with the nonracemic stannane (*R*)-**4** of >95% ee in order to evaluate the stereospecificity of the process.[6] Addition of the stannane to cyclohexanecarboxaldehyde (**1c**) and $InCl_3$ in acetone afforded a 98:2 mixture of *anti*-**5c** and

(1) Recent reviews: (a) Yamamoto, Y.; Shida, N. *Advances in Detailed Reaction Mechanisms*; JAI Press Inc.: Greenwich, 1994; Vol. 3, pp 1–44. (b) Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207. (c) Nishigaichi, Y.; Takuwa, A.; Naruto, Y.; Maruyama, K. *Tetrahedron* **1993**, *49*, 7395. (d) Marshall, J. A. *Chemtracts–Org. Chem.* **1992**, 75.

(2) Keck, G. E.; Abbott, D. E.; Boden, E. P.; Enholm, E. J. *Tetrahedron Lett.* **1984**, *25*, 3927.

(3) A similar process has recently been uncovered for allenylstannanes and $SnCl_4$: Marshall, J. A.; Perkins, J. *J. Org. Chem.* **1994**, *59*, 3509. See also: Boaretto, A.; Marton, D.; Tagliavini, G. *J. Organomet. Chem.* **1985**, *297*, 149.

(4) *Cf.* (a) Marshall, J. A.; Jablonowski, J. A.; Luke, G. P. *J. Org. Chem.* **1994**, *59*, 7825. (b) Marshall, J. A.; Beaudoin, S. *J. Org. Chem.* **1994**, *59*, 7833.

(5) For previous uses of allylindium reagents, see: (a) Kim, E.; Gordon, D. M.; Schmid, W.; Whitesides, G. M. *J. Org. Chem.* **1993**, *58*, 5500. (b) Araki, S.; Shimizu, T.; Johar, P. S.; Jin, S.- J. ; Butsugan, Y. *J. Org. Chem.* **1991**, *56*, 2538 and references cited therein.

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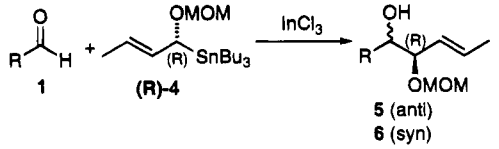
Table 3. Addition of Stannane (*R*)-4 to Achiral Aldehydes

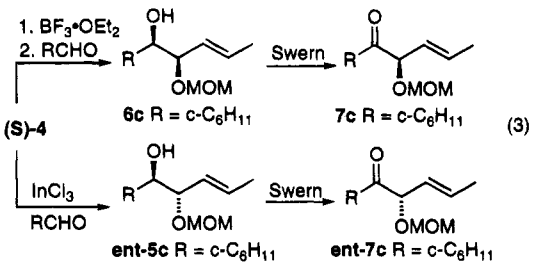


series	R	yield, %	anti:syn	ee,[d] %
c	c-C_6H_{11}	88[a]	98:2	>95%[d]
d	(*E*)-BuCH=CH	76[b]	84:16	*e*
c	c-C_6H_{11}—≡	88[c]	96:4	*e*
d	(E)-BuCH=CH	87[c]	83:17	>95%[d]

[a] Acetone at −78 °C to rt; ca. 5% of the acetone adduct was also formed. [b] Acetone at −78 °C to rt; ca. 10% of the acetone adduct was also formed. [c] MeCN at rt; ca. 5% of the γ adduct was also formed. [d] Anti adduct. [e] Not determined.

the known *syn* product **6c**[6] in 88% yield, along with 5% of the acetone adduct (Table 3).

The absolute configuration and ee of the *anti* adduct **5c** was surmised from ^{1}H NMR analysis of the (*R*)- and (*S*)-*O*-methyl mandelates.[6] Heptenal **1d** showed somewhat lower diastereoselectivity in the $InCl_3$-promoted reaction with stannane (*R*)-**4** but the ee of the *anti* product **5d** was comparable to that of the starting stannane. The *anti* adduct *ent*-**5c** derived from stannane (*S*)-**4** was correlated with the known *syn* adduct **6c**[6] through oxidation to ketones *ent*-**7c** and **7c** (eq 3). The



two ketones were of opposite but nearly equal rotations, as expected.

A simplified pathway for these additions is depicted in Figure 1.[7] Accordingly, the α-alkoxy stannane effects *anti* S_E2' attack on the $InCl_3$ to afford mainly (*E*,*S*)-**11** or a solvate thereof.[8] Subsequent addition to the aldehyde can take place through a chairlike arrangement, affording the *anti* and *syn* products after aqueous quench.

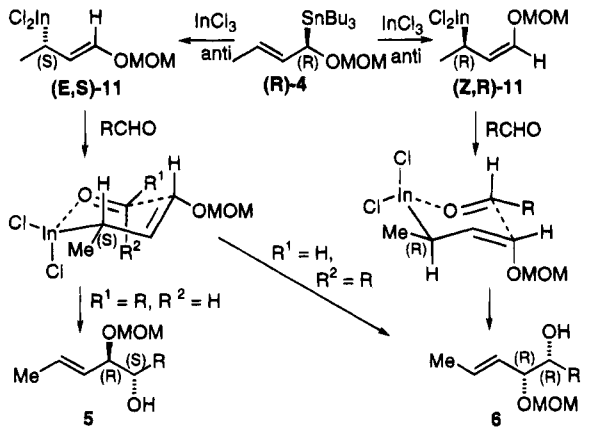
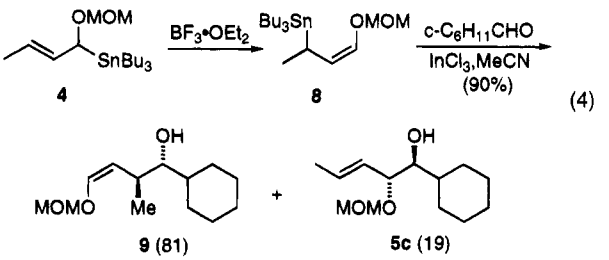


Figure 1. Possible pathways for $InCl_3$-promoted additions of α-alkoxy allylic stannanes to aldehydes.

The minor *syn* product **6** could also arise in part from allylindium (*Z*,*R*)-**11** along similar lines.

Alternative pathways involving 1,3-isomerization of the tri-*n*-butylstannane (*R*)-**4** to the thermodynamically favored isomer (*R*)-**8** followed by *anti* S_E2' addition to an aldehyde−$InCl_3$ complex are excluded by stereochemistry.[6] In that case, the OMOM center would have the (*S*) configuration. Additional evidence for a transmetalation pathway was secured from the γ-OMOM stannane **8** which reacted with aldehyde **1c** and 1 equiv of $InCl_3$ to afford an 81:19 mixture of the *anti* adducts **9** and **5c** (eq 4). With BF_3 as the Lewis acid, stannane **8** afforded predominantly (85:15) the *syn* diastereomer of adduct **5c**.[6]



The ability to access *syn* or *anti* monoprotected nonracemic 1,2-diols of high ee from a common precursor alkoxystannane by simply changing the Lewis acid promoter from BF_3•OEt_2 to $InCl_3$ significantly extends the synthetic potential of these additions. Additional applications as illustrated in eq 4 are also of intrinsic synthetic interest.

Acknowledgment. Support for this work was provided by a grant from the National Science Foundation (CHE-9220166).

Supplementary Material Available: ^{1}H NMR spectra and experimental procedures for all new compounds (28 pages).

JO950152Q

(6) Marshall, J. A.; Welmaker, G. S.; Gung, B. W. *J. Am. Chem. Soc.* **1991**, *113*, 647.

(7) Most likely, the In species incorporate solvent and possibly additional aldehyde in their coordination spheres. These issues have not yet been addressed. We have recently found that the reactions proceed, albeit more slowly, with as little as 0.5 equiv of $InCl_3$.

(8) For an analogous process with $TiCl_4$ and γ-Bu_3Sn allylic carbamates, see: Zschage, O.; Schwark, J.-R.; Kramer, T.; Hoppe, D. *Tetrahedron* **1992**, *48*, 8377.