Synthetic Methods

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Synthesis of Enantioenriched α-(Hydroxyalkyl)-tri-*n*-butylstannanes**

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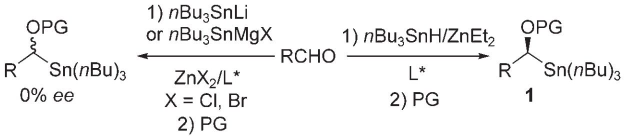
Dedicated to Professor E. J. Corey on the occasion of his 80th birthday

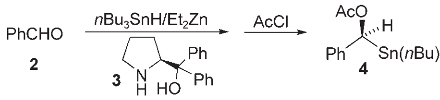
α-(Hydroxyalkyl)triorganostannanes are versatile synthetic intermediates that have found wide applicability in natural products total synthesis.[1] Most notably, they offer a higher level of structural and stereochemical complexity compared with their tetraorganotin congeners, yet still participate in a variety of stereospecific transformations including transition-metal-catalyzed cross-coupling reactions,[2] generation of configurationally stable anions,[3] Wittig rearrangements,[4] S_E' additions to carbonyl groups,[5] nucleophilic displacements,[6] and other reactions.[7] Numerous synthetic strategies to enantioenriched α-(hydroxyalkyl)triorganostannanes have been devised, inter alia, i) asymmetric reduction of acyl stannanes,[8] ii) classical resolution,[9] iii) enzymatic resolution,[10] iv) cleavage of C_2-symmetric stannyl acetals,[11] v) electrophilic stannylation,[12] and vi) nucleophilic stannylation,[13] however, the goal of a widely applicable, economical, and operationally simple synthesis from readily available starting materials remains elusive. Herein, we report the catalytic, asymmetric synthesis of α-(hydroxyalkyl)-tri-*n*-butylstannanes (**1**) in good to excellent yields and enantioselectivities by the addition of ethyl(tri-*n*-butylstannyl)zinc to various aldehydes [Eq. (1)]. In practice, the adduct was isolated after protection as its more stable ester or thiocarbamate (**1**; PG = protecting group).



(1)

Bolstered by the precedent of catalytic, asymmetric organozinc additions to carbonyl groups[14] and the equally well documented preparation of racemic α-(hydroxyalkyl)-triorganostannanes from aldehydes and ketones by using triorganostannyl nucleophiles,[15] we were attracted to the possibility of comparable asymmetric additions of tri-*n*-butylstannylzinc reagents to aldehydes. Yet, this proved not to be straightforward. Despite extensive attempts to use tri-*n*-butylstannyllithium or Grignard reagents[16] in combination with various ratios of zinc halides and chiral ligands, **1** (PG = Ac) was generated with little, if any, useful enantioselectivity, albeit in good yield. Reasoning that the Li or Mg ions might have detrimental effects, alternative approaches to stannylzinc generation were systematically investigated. Finally, we were gratified to discover that the addition of ethyl(tri-*n*-butylstannyl)zinc,[17] generated in situ by transmetalation of tri-*n*-butyltin hydride with diethylzinc,[18] to benzaldehyde (**2**) in the presence of (*S*)-α,α-diphenyl-2-pyrrolidinemethanol (**3**, 10 mol%) at −40 °C in dimethoxyethane (DME) afforded adduct **4** in poor yield, but undeniably good stereoselectivity (i.e. 95% *ee*), after in situ acetylation (Table 1, entry 1).[19] In the absence of catalyst **3**, the uncomplexed organozinc reagent was lifeless under the same conditions (Table 1, entry 2); aldehyde addition did not proceed at an appreciable rate until 4 °C was attained (Table 1, entry 3). Higher temperatures (Table 1, entry 4) improved the yield modestly, but eventually started a downward trend in the *ee* values (Table 1, entry 5). The most significant improvement was achieved with a four-fold excess of ethyl(tri-*n*-butylstannyl)zinc (Table 1, entry 6) which, when combined with a doubling of the catalyst loading to 20 mol%, additionally increased the yield (Table 1, entry 7); additional increases in the mol% of the catalyst had no effect (Table 1, entry 8). Solvents such as THF (Table 1, entry 9) and Et_2O (Table 1, entry 10) were less effective compared with DME; toluene, CH_2Cl_2, acetonitrile, and hexane were also not suitable.

Table 1: Reaction parameters.[a]



Entry	nBu_3SnH (equiv)	Et_2Zn (equiv)	**3** [mol%]	*T* [°C]	Yield [%]	*ee*[b] [%]
1	1.5	1.5	10	−40	15	95
2	1.5	1.5	0	−40	0	n.a.[c]
3	1.5	1.5	0	4	20	n.a.[c]
4	1.5	1.5	10	−20	23	95
5	1.5	1.5	10	4	29	90
6	4	4	10	−20	58	95
7	4	4	20	−20	65	96
8	4	4	50	−20	67	96
9	4	4	20	−20[d]	57	96
10	4	4	20	−20[e]	54	94

[a] Conducted on a 0.3 mmol scale in DME unless otherwise indicated. [b] Measured by chiral HPLC analysis. [c] n.a. = not applicable. [d] THF used as the solvent. [e] Et_2O used as the solvent.

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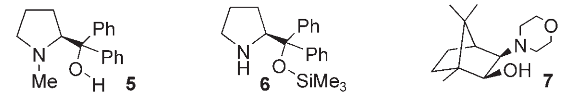
Evaluation of a series of commercial, chiral diphosphine, diamine, and amino alcohol catalysts under the reaction conditions described in Table 1, entry 7, revealed that the latter were the most efficacious (see the Supporting Information). In concert with the proposed structure for other chiral zinc intermediates,[20] the amine can be either secondary (e.g. **3**) or tertiary (e.g. **5** and **7** in Figure 1), but the alcohol should be unsubstituted for maximum asymmetric induction (e.g. **3** versus **6**).

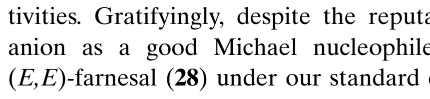


57% yield, 93% *ee* 30% yield, 24% *ee* 58% yield, 95% *ee*

Figure 1. Select chiral catalysts used in the preparation of **4**. The yields and *ee* values of **4** are given.

To help define the scope of the reaction, a panel of representative aldehydes was subjected to asymmetric stannylation (Table 2). In the case of propionaldehyde (**8**), the absolute configuration of adduct **9** (Table 2, entry 1) was established by comparisons (optical rotation and chiral HPLC analysis) with a standard compound of known stereochemistry.[11b,21] Dihydrocinnamaldehyde (**10**) was also well-behaved and gave rise to acetate **11** (Table 2, entry 2) and thiocarbamate **12** (Table 2, entry 3) with equal ease, although catalyst **7** furnished a somewhat better enantioselectivity than **3**. As expected, the antipode of **12**, that is, **13** (Table 2, entry 4), was formed in virtually the same yield and optical purity when **3** was replaced by (*R*)-α,α-diphenyl-2-pyrrolidinemethanol ((*R*)-**3**). The trend of obtaining superior enantioselectivity with **7,** and slightly better yields with **3** was also observed with cyclohexanecarboxaldehyde (**14**; Table 2, entry 5), but less evident for the related benzaldehyde (**2**; Table 2, entry 6). The *ortho* substituent of 2-tolualdehyde (**16**; Table 2, entry 7) did not significantly influence the reaction, but the presence of an electron-donating *para*-methoxy group (Table 2, entry 8) and even a *para*-bromo group (Table 2, entry 9) were well tolerated. In contrast, moderately strong electron-withdrawing substituents, such as methoxycarbonyl (Table 2, entry 10), cyano (Table 2, entry 11), and trifluoromethyl (Table 2, entry 12) groups, seemed to lower the enantioselectivities. Gratifyingly, despite the reputation of the stannyl anion as a good Michael nucleophile,[22] its addition to (*E*,*E*)-farnesal (**28**) under our standard conditions produced allylic adduct **29** in useful yield with a high *ee* value (Table 2, entry 13).

In summary, this report describes a convenient, widely applicable, and highly enantioselective preparation of protected α-hydroxyalkylstannanes, which should expedite applications of this intriguing, but comparatively inaccessible class of tin reagents. We hope, in the future, to extend these studies to other electrophiles such as imines [Eq. (2)].



(2)

Experimental Section

General procedure: $n\mathrm{Bu_3SnH}$ (1.06 mL, 4 mmol) was added dropwise to a stirred solution of $\mathrm{Et_2Zn}$ (4 mL, 1 M in hexanes) in anhydrous DME (10 mL) under an argon atmosphere at −78 °C . After 5 min, the reaction mixture was warmed to 4 °C and kept at this temperature for 1 day. Upon dilution with more DME (27 mL), the reaction mixture was recooled to −78 °C and then the catalyst (0.2 mmol) in DME (2 mL) and aldehyde (1 mmol) in DME (1 mL) were added sequentially. After 5 min, the temperature was raised to that indicated in the table and maintained by using a cryogenic cooler. After complete reaction, typically 3–6 h, AcCl (0.2 mL) was added and the reaction mixture was then warmed to RT over 0.5 h. After an additional 2 h, the reaction mixture was subjected to extractive isolation by using $\mathrm{CH_2Cl_2}$ and the crude product was purified by $\mathrm{SiO_2}$ column chromatography.

Thiocarbamate product: The reaction mixture was quenched with saturated aq. $\mathrm{NH_4Cl}$, extracted with $\mathrm{CH_2Cl_2}$ (3 × 50 mL), and the combined organic extracts were then washed with brine, dried over $\mathrm{Na_2SO_4}$, and concentrated in vacuo. The crude α-hydroxyalkylstannane was redissolved in $\mathrm{CH_2Cl_2}$ (10 mL), to which was added $\mathrm{Im_2C(S)}$ (2 mmol) and DMAP (10 mol %) at RT. After ca. 2 h, the reaction mixture was filtered through a short pad of silica gel. The silica gel pad was rinsed with hexanes (40 mL) first to remove the nonpolar tin byproduct, then with hexanes/EtOAc (1:1, 100 mL). The combined hexanes/EtOAc filtrates were concentrated in vacuo. The residue was immediately dissolved in neat, anhydrous pyrrolidine (2 mL) at RT and after 1 h the pyrrolidine was removed and the residue was purified by $\mathrm{SiO_2}$ column chromatography to afford α-thiocarbamoyl protected stannane.

The 4-nitrobenzoate (**29**): The reaction mixture was quenched with saturated aq. $\mathrm{NH_4Cl}$ and then extracted with $\mathrm{CH_2Cl_2}$ (3 × 15 mL). The combined organic extracts were washed with brine, dried over $\mathrm{Na_2SO_4}$, and concentrated in vacuo. The crude α-hydroxyalkylstannane was protected by directly adding 4-nitrobenzoyl chloride (0.5 mmol) and pyridine (0.2 mL) in $\mathrm{CH_2Cl_2}$ (10 mL) at RT. After stirring for ca. 4 h, the reaction was quenched with water and then extracted with $\mathrm{CH_2Cl_2}$. The combined organic extracts were washed with brine, dried over $\mathrm{Na_2SO_4}$, and concentrated in vacuo. The crude mixture was purified by $\mathrm{SiO_2}$ column chromatography.

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[1] Representative examples: a) J. R. Falck, D. K. Barma, S. Mohapatra, A. Bandyopadhyay, K. M. Reddy, J. Qi, W. B. Campbell, *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4987–4990; b) J. Ye, R. K. Bhatt, J. R. Falck, *Tetrahedron Lett.* **1993**, *34*, 8007–8010; c) J. A. Marshall, D. V. Yashunsky, *J. Org. Chem.* **1991**, *56*, 5493–5495; d) J. M. Chong, E. K. Mar, *Tetrahedron* **1989**, *45*, 7709–7716; e) E. Fouquet, A. Herve in *Handbook of Functionalized Organometallics*, *Vol. 1* (Ed.: P. Knochel), Wiley-VCH, Weiheim, **2005**, pp. 203–249.

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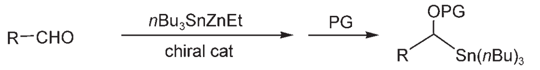
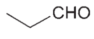
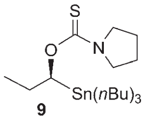
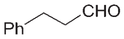
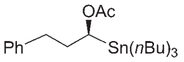
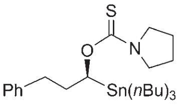
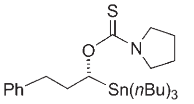
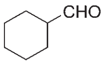
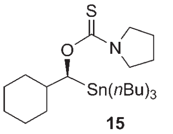
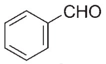
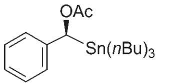
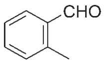
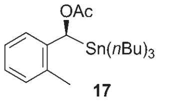
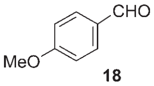
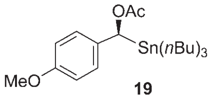
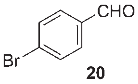
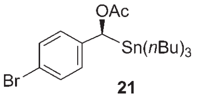
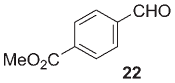
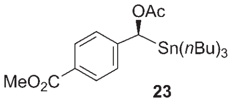
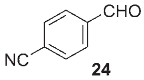
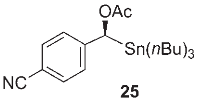
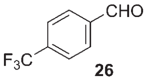
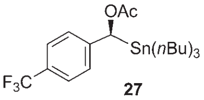
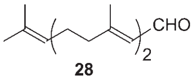
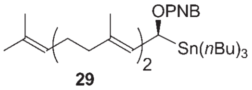
Table 2: Asymmetric synthesis of protected α-(hydroxyalkyl)-tri-*n*-butylstannanes.[a]



Entry	RCHO	Ligand	T [°C]	Adduct	Yield [%]	ee[b] [%]
1	 **8**	**3**	−25	 **9**	58	97
2	 **10**	**3**	−30	 **11**	66[c]	96
3	**10**	**3** **7**	−30 −30	 **12**	71 69	93 98
4	**10**	(*R*)-**3**	−30	 **13**	68	93
5	 **14**	**3** **7**	−15 −25	 **15**	73 70	90 98
6	 **2**	**3** **7**	−50 −40	 **4**	60 58	96 95
7	 **16**	**7**	−40	 **17**	54	95
8	 **18**	**3** **7**	−30 −40	 **19**	72 83	92 97
9	 **20**	**7**	−40	 **21**	60	96
10	 **22**	**7**	−50	 **23**	40[d]	90
11	 **24**	**7**	−40	 **25**	86	83
12	 **26**	**7**	−40	 **27**	72	86
13	 **28**	**3**	−30	 **29**	56[e]	95

[a] Reaction conditions: ethyl(tri-*n*-butylstannyl)zinc (4 equiv) and catalyst (20 mol%) in DME. Entries 1–6 and 8 were performed on a 1 mmol scale and all others on a 0.3 mmol scale. The reaction temperature was varied to give the optimum *ee* values. Derivatizations are described in the General Procedure. [b] Measured by chiral HPLC analysis. [c] 3-Phenylpropan-1-ol was the main product in THF and **11** was obtained in only 20% yield. [d] 40% recovered starting material. The yield of **23** improved when reaction was run at higher temperatures, but the *ee* values decreased. [e] PNB = *p*-nitrobenzoate.

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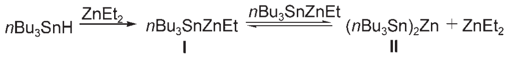
[14] Reviews: a) V. Dimitrov, K. Kostova, *Lett. Org. Chem.* **2006**, *3*, 176–182; b) L. Pu, H.-B. Yu, *Chem. Rev.* **2001**, *101*, 757–824.

[15] a) R. J. Linderman in *Encyclopedia of Reagents for Organic Syn-*

thesis, *Vol. 7* (Ed.: L. A. Paquette), Wiley, Chichester, **1995**, pp. 5026–5029; b) T. Sato, *Synthesis* **1990**, 259–270.

[16] J. Podlech, *Sci. Synth.***2003**, *5*, 285–297.

[17] Whereas ethyl(tri-*n*-butylstannyl)zinc (**I**) is generated by using equimolar amounts of reagents, other species, such as **II,** may be present.



$$n\mathrm{Bu_3SnH}\xrightarrow{\mathrm{ZnEt_2}}\underset{\mathbf{I}}{n\mathrm{Bu_3SnZnEt}}\xrightleftharpoons{n\mathrm{Bu_3SnZnEt}}\underset{\mathbf{II}}{(n\mathrm{Bu_3Sn})_2\mathrm{Zn}}+\mathrm{ZnEt_2}$$

[18] In contrast with our experience, at least one laboratory has reported transmetalation of trialkylstannyl hydrides with dialkylzinc leads to decomposed products: F. J. A. Des Tombe, G. J. M. Van Der Kerk, *J. Organomet. Chem.* **1972**, *34*, 247–252.

[19] It is instructive that similar additions [**2**, ethyl(tri-*n*-butylstannyl)zinc (4 equiv), **3** (20 mol %) in DME] when conducted in the presence of LiBr (2 equiv) at −78 °C and −20 °C furnished **4** in 53 % and 76 % yields, respectively, but with 0 % *ee*. Presumably, Lewis acids such as $\mathrm{Li^+}$ (and likely $\mathrm{Mg^{2+}}$) are capable of catalyzing the addition of uncomplexed stannylzinc to aldehydes. This assertion would explain why reagents generated from stannyllithium and stannylmagnesium halides were not useful for asymmetric additions.

[20] E. Erdik, *Organozinc Reagents in Organic Synthesis*, CRC, Boca Raton, FL, **1996**, chap. 4, pp. 108–206.

[21] The absolute configurations of all other adducts were assigned in analogy. Catalysts **3** and **7** furnished the same major stereoisomer in Table 2, entries 3, 5, 6, and 8.

[22] For example, see: A. Kirschning, J. Harders, *Synlett* **1996**, 772–774.