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

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Abstract

A catalytically asymmetric synthesis of α -(hydroxyalkyl)-tri-*n*-butylstannanes **1** in good-excellent yields and enantioselectivities (up to 98% e.e.) via addition of ethyl(tri-*n*-butylstannyl)zinc to aldehydes was achieved. In practice, **1** was isolated after protection as its more stable ester or thiocarbamate (PG). The reagent was prepared from equimolar amounts of tri-*n*-butylstannyl hydride and Et₂Zn in DME so as to avoid contamination by lithium and magnesium ions which suppress enantioselectivity.

Keywords

aldehydes; asymmetric synthesis; organometallic compounds; tin; zinc

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-couplings,^[2] generation of configurationally stable anions,^[3] Wittig rearrangements,^[4] S_E'-additions to carbonyls,^[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 C₂-symmetric stannyl acetals,^[11] (v) electrophilic stannylation,^[12] and (vi) nucleophilic stannylation,^[13] however, the goal of a widely applicable, economic and operationally simple synthesis from readily available starting materials remains elusive. Herein, we report the catalytically asymmetric synthesis of α -(hydroxyalkyl)-tri-*n*-butylstannanes **1** in good-excellent yields and enantioselectivities via addition of ethyl(tri-*n*-butylstannyl)zinc to aldehydes (eq 1). In practice, **1** was isolated after protection as its more stable ester or thiocarbamate (PG).

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(eq 1)

Bolstered by the precedent of catalytic, asymmetric organozinc additions to carbonyls^[14] and the equally well documented preparation of racemic α -(hydroxyalkyl)triorganostannanes from aldehydes and ketones 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 using tri-*n*-butylstannyl lithium or Grignard^[16] in combination with various ratios with zinc halides and chiral ligands, **1** (PG = Ac) was generated with little, if any, useful enantioselectivity, albeit in good yield. Reasoning the Li or Mg-ions might have detrimental effects, alternative approaches to stannylzinc generation were systematically investigated. Finally, we were gratified to discover that addition of ethyl(tri-*n*-butylstannyl)zinc,^[17] generated *in situ* via 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 DME afforded adduct **4** in poor yield, but undeniably good stereoselectivity (i.e., 95% ee), following *in situ* acetylation (Table 1, entry 1).^[19] In the absence of catalyst **3**, the uncomplexed organozinc reagent was lifeless under the same conditions (entry 2); aldehyde addition did not proceed at an appreciable rate until 4°C (entry 3). Higher temperatures (entry 4) improved the yield modestly, but eventually started a downward trend in the % ee (entry 5). The most significant improvement was achieved with a 4-fold excess of ethyl(tri-*n*-butylstannyl)zinc (entry 6) which when combined with a doubling of the catalyst loading to 20 mol%, boosted the yield still further (entry 7), although further increases in the mol% catalyst had no effect (entry 8). THF (entry 9) and Et₂O (entry 10) were less effective as solvents compared with DME; toluene, CH₂Cl₂, acetonitrile and hexane were not suitable.

Evaluation of a series of commercial, chiral diphosphine, diamine, and amino-alcohol catalysts under the reaction conditions described in Table 1, entry 7, revealed the latter were the most efficacious (see 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**, Fig. 1), but the alcohol should be unsubstituted for maximum asymmetric induction (e.g., **3** vs. **6**).

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 the adduct **9** (entry 1) was established by comparisons (optical rotation, chiral HPLC) with a standard of known stereochemistry.^[11b,21] Dihydrocinnamaldehyde (**10**) was likewise well behaved and gave rise to acetate **11** (entry 2) and thiocarbamate **12** (entry 3) with equal ease, although catalyst **7** furnished a somewhat better enantioselectivity than **3**. As expected, the antipode of **12**, i.e., **13** (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 superior enantioselectivity with **7** and slightly better yields with **3** continued with cyclohexanecarboxaldehyde (**14**, entry 5), but was not as evident for the related aromatic, benzaldehyde (**2**, entry 6). The *ortho*-substituent of 2-tolualdehyde (**16**,

entry 7) did not significantly influence the reaction, but the presence of an electron-donating *para*-methoxy (entry 8) and even a *para*-bromo (entry 9) were well tolerated. On the other hand, moderately strong electron-withdrawing substituents, viz., methoxycarbonyl (entry 10), cyano (entry 11), and trifluoromethyl (entry 12), seemed to lower the enantioselectivity. It was gratifying to find that, despite the reputation of 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 and high % ee (entry 13).

In summary, this report describes a convenient, widely applicable, and highly enantioselective preparation of protected α -hydroxyalkylstannanes and, thus, 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, e.g., imines (eq 2).

(eq 2)

Experimental Section

General procedure: *n*-Bu₃SnH (1.06 mL, 4 mmol) was added dropwise to a stirring, -78°C solution of Et₂Zn (4 mL, 1M in hexane) in anhydrous DME (10 mL) under an argon atmosphere. 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 re-cooled -78°C and 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 the level indicated in the table and maintained using a cryogenic cooler. After complete reaction, typically 3-6 h, AcCl (0.2 mL) was added and the reaction mixture was warmed to rt over 0.5 h. After another 2 h, the reaction mixture was subjected to extractive isolation using CH₂Cl₂ and the crude product was purified by SiO₂ column chromatography.

For the thiocarbamate, the reaction mixture was quenched with saturated aq. NH₄Cl, extracted with CH₂Cl₂ (3 $\times$ 50 mL), and the combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The crude α -hydroxyalkylstannane was re-dissolved in CH₂Cl₂ (10 mL) to which was added Im₂C(S) (2 mmol) and DMAP (10 mol%) at rt. After ~ 2 h, the reaction mixture was filtered through a short pad of silica gel. The silica gel pad was rinsed with hexane (40 mL) first to remove the non-polar tin byproduct, then with hexane/EtOAc (1:1, 100 mL). The combined filtrates were concentrated in vacuo. The residue was immediately dissolved in neat, anhydrous pyrrolidine (2 mL) at rt. Evaporation of the pyrrolidine after 1 h and purification of the residue by SiO₂ column chromatography affords α -thiocarbamoyl protected stannane.

For the 4-nitrobenzoate (**29**), the reaction mixture was quenched with saturated aq. NH₄Cl, extracted with CH₂Cl₂ (3 $\times$ 15 mL). The combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The crude α -hydroxyalkylstannane was protected directly by stirred with 4-nitrobenzoyl chloride (0.5 mmol), Py (0.2 mL) in CH₂Cl₂ (10 mL) at rt. After ~ 4 h, the reaction was quenched with water, extracted with CH₂Cl₂. The combined organic extracts were washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The crude product was purified by SiO₂ column chromatography.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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

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

- [18]. At odds with our experience, at least one laboratory has reported transmetalation of trialkylstannyl hydrides with dialkylzinc leads to decomposed products: Des Tombe FJA, Van Der Kerk GJM. *J. Organomet. Chem.* 1972:247–252.
- [19]. It's 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 0% ee. Presumably, Lewis acids such as Li⁺ (and likely Mg²⁺) are capable of catalyzing the addition of uncomplexed stannylzinc to aldehydes. This would explain why reagents generated from stannyl lithium and - magnesium halide were not useful for asymmetric additions.
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Figure 1.
Preparation of 4 using select chiral catalysts.

Table 1

Reaction parameters.^[a]

Entry	<i>n</i> Bu ₃ SnH [equiv]	Et ₂ Zn [equiv]	3 [mol%]	Temp [°C]	Yield [%]	<i>ee</i> ^[b] [%]
1	1.5	1.5	10	-40	15	95
2	1.5	1.5	0	-40	0	na ^[c]
3	1.5	1.5	0	4	20	na
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]	34	94

^[a]Conducted on a 0.3 mmol scale in DME unless otherwise indicated.^[b]Measured by chiral HPLC.^[c]na = not applicable.^[d]THF as solvent.^[e]Et₂O as solvent.

Table 2

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

Entry	RCHO	Ligand	Temp [°C]	Adduct	Yield [%]	ee ^[b] [%]
1		3	-25		58	97
2		3	-30		66 ^[c]	96
3		3 7	-30		71 69	93 98
4		(R)-3	-30		68	93
5		3 7	-15 -25		73 70	90 98
6		3 7	-50 -40		60 58	96 95

Entry	RCHO	Ligand	Temp [°C]	Adduct	Yield [%]	ee ^[b] [%]
7		7	-40		54	95
8		3 7	-30 -40		72 83	92 97
9		7	-40		60	96
10		7	-50		40 ^[d]	90
11		7	-40		86	83
12		7	-40		72	86
13		3	-30		56 ^[c]	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. Derivatizations are described in the General Procedure.

^[b] Measured by chiral HPLC.

^[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 at higher temperatures, but the % ee dropped.

$p\text{K}_{\text{a}}^{\text{PNB}} = p\text{-nitrobenzoate}$.

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