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General synthetic method for preparation of optically active propargyl and allylstannanes

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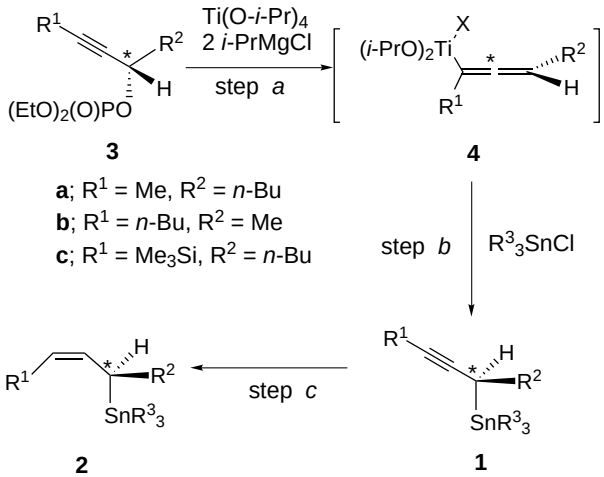
Abstract—The reaction of chiral allenyltitaniums, generated from optically active secondary propargyl phosphates and a Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl reagent, with trialkylstannyl chloride proceeded with a high chirality transfer of more than 93% to afford optically active secondary propargylstannanes in excellent yield, and which, in turn, were converted to optically active (*Z*)-allylstannanes by reaction with Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl and the following hydrolysis.

Allylic, allenylic, and propargylic stannanes have, respectively, been accepted as useful nucleophilic reagents for carbon–carbon bond forming reactions.[1] These optically active stannanes where the stannyl group is connected to the stereogenic center, therefore, might be useful as reagents in asymmetric synthesis. Non-racemic allenylstannanes that can be easily prepared by the S_N2'-type substitution reaction of optically active propargyl mesylates with stannyl anions have been effectively used for asymmetric synthesis.[1a,c] However, synthetic reactions using optically active allyl- and propargylstannanes have been largely limited due to the lack of a general method for preparation of these stannanes.[2] Thus, the optically active allylstannanes which are accessible are restricted to those having an alkoxy group at the α- or γ-position[3] or an ester group at the β′-position.[4] For non-racemic propargylstannanes, propargyl-trichloro- and -butyldichlorostannanes were synthesized and used for allenylation reaction of aldehydes; however, these stannanes must be generated in situ at low temperature of −40°C and used immediately because they have a tendency to isomerize readily to the corresponding allenyl form.[5] Herein we wish to report an efficient and general method to prepare optically active propargylstannanes (**1**) and (*Z*)-allylstannanes (**2**).

Previously, we reported that the reaction of propargyl alcohol derivatives such as acetates, carbonates and phosphates with a Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX (X = Cl or Br) reagent[6] proceeds via an oxidative addition pathway to afford the corresponding allenyltitaniums,[7] and the reaction of which with Bu_3SnCl provides the corresponding propargylstannanes exclusively.[7f] We also reported that the reaction of optically active secondary propargyl phosphates **3** with Ti(O-*i*-Pr)$_4$/2 *i*-PrMgX proceeds with excellent chirality transfer to provide optically active allenyltitaniums **4** (step *a* in Scheme 1).[7c–e] With these results in hand, we anticipated, as shown in Scheme 1, that optically active propargylstannanes **1** might be obtained from optically active **4** (via step *b*), and that **1** thus produced could be converted



Scheme 1.

Keywords: propargylstannane; allylstannane; optically active; titanium; chirality transfer.

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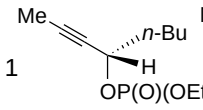
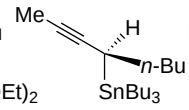
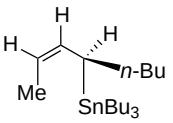
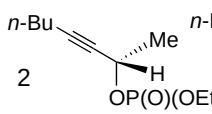
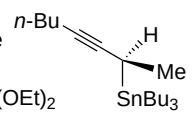
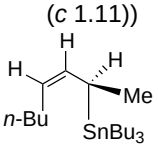
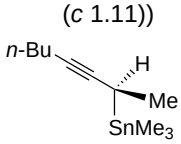
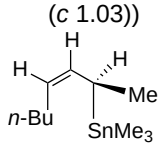
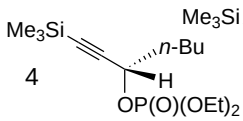
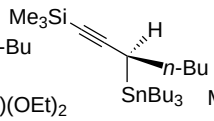
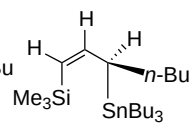
into allylstannanes **2** by reduction of the triple bond to a double bond (step *c*). Herein reported is the realization of our expectation.

Allenyltitanium **4a** (**4**: R^1 = Me, R^2 = *n*-Bu), prepared from diethyl (*S*)-2-octyn-4-yl phosphate (**3a**) with 94.1% enantiomeric excess (ee) and a Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl reagent, reacted with Bu_3SnCl to afford 78% yield of the corresponding propargylstannane **1a** (R^3 = *n*-Bu) having the structure shown in Scheme 1 and entry 1 in Table 1, the ee of which was determined to be 91.4% by GC analysis with use of a chiral column after derivatization (vide infra). Thus, the overall chirality transfer from **3a** to **1a** was 97%. The absolute configuration of **1a** thus obtained was verified to be *R* by comparison with the authentic **1a** having (*S*)-configuration (vide infra). As the reaction of the step *a* in Scheme 1 proceeds with 97% chirality transfer,[7c] the degree of chirality transfer for the reaction of the allenyltitanium with Bu_3SnCl (step *b*) was estimated to be almost 100%. It should be noted that the compound **1** thus prepared is the first example of an optically active propargylstannane which can be isolated.

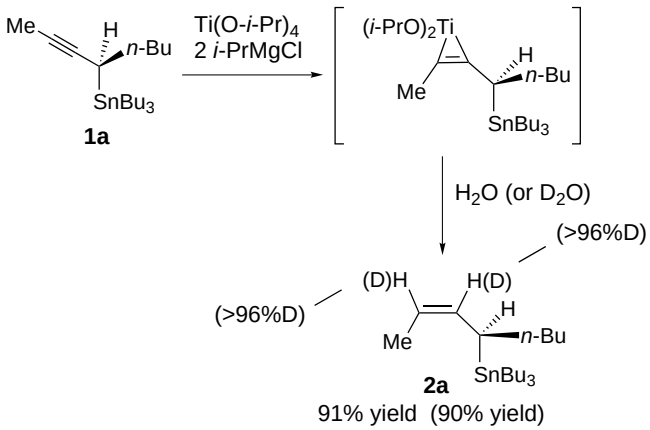
Table 1. Yield, ee and $[\alpha]_D$ value of propargyl and allylstannanes **1** and **2** obtained from **3**

Entry	**3**[a] (Ee)	**1** Yield[b] ($[\alpha]_D$)[c]	**2**[d] Yield[b] ($[\alpha]_D$)[c]	Ee of **2**[e] (Chirality Transfer)[f]
1	 **3a** (94%)	 **1a** 78% ($[\alpha]_D^{26}$+7.5 (*c* 1.05))	 **2a** 91% ($[\alpha]_D^{26}$+113 (*c* 1.11))	>91% (>97%)
2	 **3b** (94%)	 **1b** 79% ($[\alpha]_D^{24}$+7.5 (*c* 1.11))	 **2b** 91% ($[\alpha]_D^{24}$+117 (*c* 1.03))	>91% (>97%)
3	**3b** (94%)	 **1b'** 77% (n.d.)[g]	 **2b'** 88% (n.d.)[g]	>91% (>97%)
4	 **3c** (92%)	 **1c** 80% ($[\alpha]_D^{30}$+9.3 (*c* 1.33))	 **2c** 85% ($[\alpha]_D^{30}$+93.2 (*c* 1.16))	>86%[h] (>93%)

[a]Prepared from the corresponding propargyl alcohol. Ee indicated is of the parent alcohol. [b]Isolated yield. [c]Optical rotations were measured as a solution in $CHCl_3$. [d]Absolute configuration of **2** was determined for entry 1 (see text). For other entries, configuration was speculated in analogy with entry 1 and by the sign of optical rotation. [e]Unless otherwise stated, ee of **2** was determined by chiral GC analysis of the reaction products with benzaldehyde in the presence of BF_3-OEt_2 (see text). [f]The calculated values expected by simple extrapolation if **3** is of 100% ee are shown in parentheses. [g]Not determined. [h]Ee of **1c**; for determination, see footnote 13.

With optically active **1** in hand, our next concern was its conversion to **2** (step *c* in Scheme 1). However, this was not attained by routine procedure. Thus, hydrogenation of **1a** using a Lindlar or Pd/C catalyst under various reaction conditions did not proceed effectively and the reaction afforded a mixture of the corresponding allenylstannane (isomerization product) and the starting **1a**. Treatment of **1a** with *i*-Bu_2AlH gave an inseparable mixture of **2a**, the allenylstannane and other unidentified products. Isomerization to the allenylstannane was again the main reaction with $NaAlH_2(OCH_2CH_2OCH_3)_2$, and the reaction with Li in liquid NH_3 afforded a complex mixture. Finally, we found that the partial reduction of the triple bond of **1a** to **2a** with (*Z*)-olefin geometry can be cleanly carried out in essentially quantitative yield by the reaction with a Ti(O-*i*-Pr)$_4$/2 *i*-PrMgCl reagent and the following hydrolysis.[6,8] This protocol also allows the synthesis of **2a** having a bis-deuterated olefinic moiety by using D_2O instead of H_2O (Scheme 2).

The ee of **2a**, thus eventually that of **1a**, was determined by the GC analysis of its reaction product with benzaldehyde in the presence of BF_3–OEt_2.[9] The reaction provided a mixture of four homoallyl alcohols in a ratio of 65:13:11:11 in 65% combined yield, and the GC analysis using a chiral column (Chirasil-DEX CB, Chrompack) of the main product having the structure

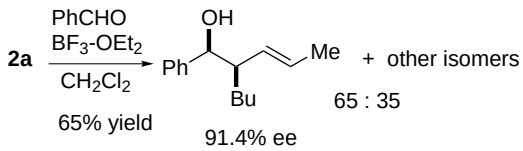


Scheme 2.

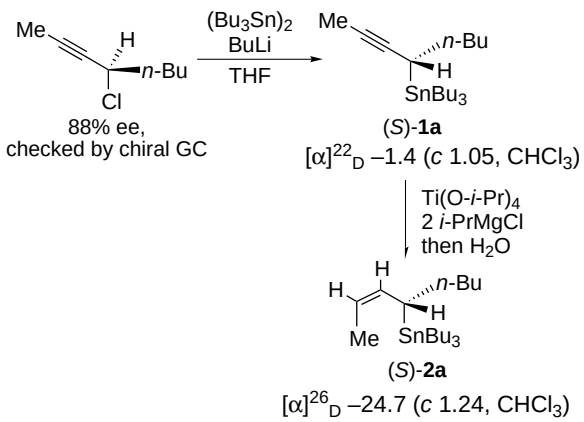
shown in Scheme 3 showed that its ee was 91.4%.[10] Thus, these results indicated that ee of **2a**, and thus **1a**, must be more than 91.4%.

Meanwhile, the absolute configuration of **1a** was confirmed to be *R* by comparing the sign of its optical rotation ($[\alpha]_D^{26}$ +7.5 (*c* 1.05, $CHCl_3$) with the authentic (*S*)-**1a** ($[\alpha]_D^{22}$ −1.4 (*c* 1.05, $CHCl_3$),[11] prepared by the nucleophilic substitution reaction of (*R*)-4-chloro-2-octyne with $LiSnBu_3$ (Scheme 4).[12] The absolute configuration of **2a** obtained by Scheme 2 was also confirmed to be *R* by comparing with (*S*)-**2a**[11] prepared from authentic (*S*)-**1a** and $Ti(O\text{-}i\text{-}Pr)_4/2$ *i*-PrMgCl (Scheme 4).

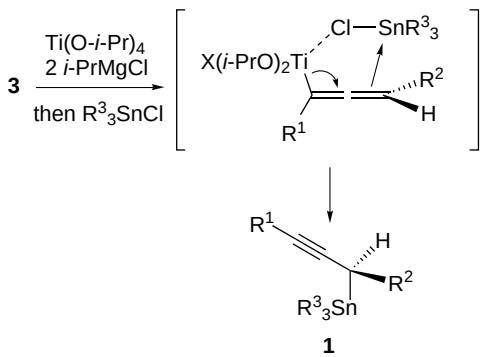
Similarly, optically active propargyltributylstannanes **1** where $R^1 = n$-Bu, R^2 = Me (**1b**) and $R^1 = SiMe_3$, $R^2 = n$-Bu (**1c**) could be prepared from the corresponding phosphate, and which, in turn, were converted to the corresponding **2** in excellent yield. The yield as well as ee and $[\alpha]_D$ value of **1** and **2** thus prepared are given in Table 1. As shown in entry 3, **1** and **2** having a



Scheme 3.



Scheme 4.



Scheme 5.

trimethylstannyl group can also be synthesized by the reaction of **4** with trimethylstannyl chloride instead of tributylstannyl chloride. As revealed from Table 1, excellent chirality transfer was attained in all cases.

The stereochemical outcome of the reaction of step *b* in Scheme 1 observed here might be explained by assuming that the transmetallation from the titanium to the tin proceeds by an S_E2'-*syn* type reaction pathway through the intermediate shown in Scheme 5 where the chlorine moiety of R_3SnCl coordinates to the titanium.

In conclusion, a general method for synthesizing optically active propargylstannanes **1** and (*Z*)-allylstannanes **2** has been developed, and their utilization for asymmetric synthesis is underway in our laboratories.[13]

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10. The major product has the *syn*- and *trans*-stereochemistry which was determined by its ^1H NMR coupling constants. The absolute configuration was not determined. Chiral GC analysis of the major product: Chirasil-DEX CB, 0.25 mm×25 m, Chrompack, 130°C, 0.5 kg/cm^2 H_2; $t=23.7$ min and $t'=26.3$ min.
11. The ee of authentic **1a** and **2a** was calculated to be 17 and 20%, respectively, based on their $[\alpha]_D$ values by comparison with those of **1a** and **2a** prepared by the present method.
12. Marshall, J. A.; Wang, X.-J. *J. Org. Chem*. **1990**, *55*, 6246–6248. The reaction afforded a 1:1 mixture of (*S*)-**1a** and the corresponding allenylstannane (S_N2' reaction product), from which (*S*)-**1a** was isolated in 32% yield.
13. Since the reaction of **2c** with benzaldehyde did not afford the corresponding adduct(s) in good yield, **1c** was converted to the corresponding allenylbromide **5** by the reaction with NBS (the scheme shown below), and the ee of which was determined by chiral GC analysis to be 86%. Chiral GC analysis of **5**: Chirasil-DEX CB, 0.25 mm×25 m, Chrompack, 110°C, 0.5 kg/cm^2 H_2); $t=5.28$ min and $t'=5.34$ min. For destannylhalogenation of propargylstannanes providing hologenated allenes, see: (a) Simo, M.; Sipeuhou, J. A.; Lequan, M. *J. Organomet. Chem*. **1972**, *35*, C23–C24; (b) Reich, H. J.; Yelm, K. E.; Reich, I. L. *J. Org. Chem*. **1984**, *49*, 3438–3440.