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Stannyl-oriented Regioselective Allylation and Its Application to the Synthesis of Silyl Misoprostol

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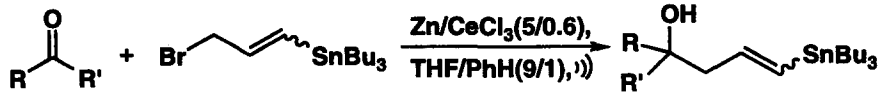
Abstract: A mixture of Zn, $CeCl_3$, 3-bromo-1-tributylstannylpropene and aldehyde or ketone in THF/PhH (v/v=9/1) was sonicated in a commercial cleaning bath. δ-Tributylstannylhomoallyl alcohol was produced as the sole regioselective product and (E)-stereoisomer was formed as major adduct. Silyl Misoprostol was synthesized by the coupling reaction of cyclopentenone and stannylhomoallyl alcohol.

Introduction

The reaction of allylic organometallics with carbonyl compounds has received much more attention and applications in organic synthesis.[1-3] Studies on the reactions of substituted allylmetals with unhindered aldehydes and ketones were carried out which foused on the regioselectivity of the allylic unit (S_E2 or S_E2'). The allylation of carbonyl compound with 3-substituted allylic organometallic reagents such as M= Li[4], Mg[5], Zn[6-8], Cd[9], B[10-15], Al[16,17], In[18,19], Si[20-25], Sn[26-33], Ce[34,35], Cr[36], generally results γ-adduct (S_E2') in which the allylic group is attached at more highly substituted position. The extraordinary α-selectivity (S_E2) of the carbonyl addition of allylmetal provide an unprecedented route to homoallylic alcohols. This type of reaction is becoming increasingly important as a basic synthetic strategy for stereoregulated synthesis of acyclic systems. Most allylmetal reagent reacted with aldehyde to afford γ-adduct as major product via an S_E2' pathway. Prof. H. Yamamoto's group reported that using allylbarium as allylating agent produce the homoallyl alcohol with remarkbly high α-selectivity.[37] Prof. Y. Yamamoto's laboratory found that allylation of crotylmagnesium chloride with aldehyde in the presence of $AlCl_3$ at -78 °C gave predominantly α-adduct.[38] Herewith, We wish to report a regioselective allylation reaction of 3-bromo-1-tributylstannylpropene with aldehyde or ketone which produced α-adduct as sole regioisomer under ultrasonic reaction condition (Scheme 1).

Scheme 1



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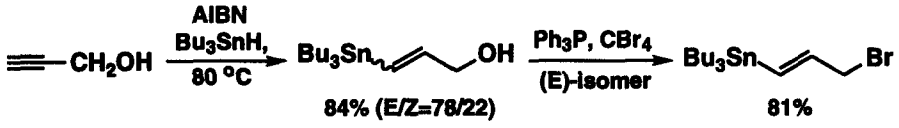
PII: S0040-4020(99)00743-7

Results and Discussion

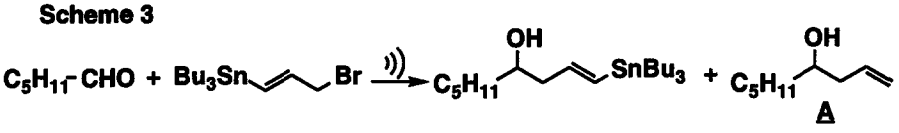
Previous studies showed that 3-substituted allylmetal having substituents such as alkyl, aryl, alkoxy, alkylthio and trialkylsilyl[39] which reacted with carbonyl compounds were extensively investigated and afforded γ-adduct as major product. Interestingly, trialkylstannyl group as substituent at 3-position is not investigated. Therefore, we are interesting in studying the regioselectivity for allylation reaction of carbonyl compound with 3-bromo-1-tributylstannylpropene. 3-Bromo-1-tributylstannylpropene was prepared by the hydrostannylation of propargyl alcohol with AIBN, Bu_3SnH at 80 °C for 2 hours and (E)- and (Z)-1-tributylstannylpropen-3-ol (E/Z=78/22) were produced in 84% yield.[40] (E)-1-Tributylstannylpropen-3-ol was separated by chromatography and then converted to its corresponding (E)-3-bromo-1-tributylstannylpropene by treatment of CBr_4, PPh_3 mixture[41] (Scheme 2).

Scheme 2



We first investigated the Barbier-type allylation reaction of (E)-3-bromo-1-tributylstannylpropene with aldehyde using different metals such as Li, Mg, Bi, Zn and In. Interestingly, only zinc metal can pursue this allylation reaction under different energy sources such as thermal and ultrasound. The reaction rate is faster and the yield is higher under ultrasonic reaction condition. Therefore, we decided to investigate the allylation reaction using ultrasound as energy source. It should be noted that only α-adduct (S_E2) was generated and γ-adduct (S_E2') could not be observed . We also found that the yield of δ-tributylstannylhomoallyl alcohol was increased in the presence of Lewis acid (Scheme 3). Unfortunately, destannyl product A was generated in the absence or presence of Lewis acid.

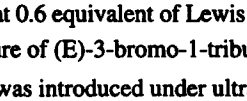
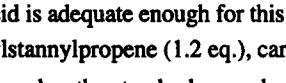
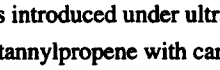
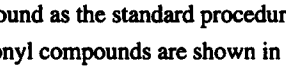
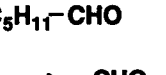
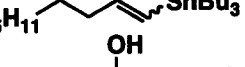
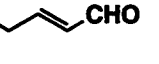
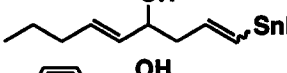
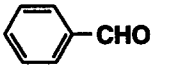
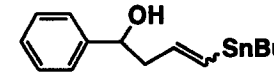
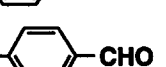
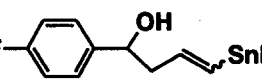
Scheme 3



* 5 Zn, THF, reflux, 5h	31% + A (22%)
* 5 Zn, THF, 2h	41% + A (17%)
* 5 Zn, THF / PhH (9/1), 2h	52% + A (14%)
* 5 Zn / 1 $ZnCl_2$, THF / PhH (9/1), 1h	68% + A (4%)
* 5 Zn / 1 $ZnBr_2$, THF / PhH (9/1), 2h	50% + A (14%)
* 5 Zn / 1 $MgBr_2$, THF / PhH (9/1), 4h	24% + A (14%)
* 5 Zn / 1 $HgCl_2$, THF / PhH (9/1), 4h	26% + A (13%)
* 5 Zn / 1 $CuCl_2$, THF / PhH (9/1), 4h	31% + A (10%)
* 5 Zn / 1 $CoCl_2$, THF / PhH (9/1), 4h	25% + A (14%)
* 5 Zn / 1 $CeCl_3$, THF / PhH (9/1), 2h	63% + A (9%)

The $CeCl_3$ and $ZnCl_2$ are the best Lewis acids for the sonochemical Barbier-type allylation and the reaction is much cleaner when $CeCl_3$ is introduced. The investigation was proceeded in equal molar ratio of aldehyde and (E)-3-bromo-1-tributylstannylpropene. The yield of δ-tributylstannylhomoallyl alcohol was increased when (E)-3-Bromo-1-tributylstannylpropene was introduced in 1.2 equivalent to carbonyl compound. It also was investigated that 0.6 equivalent of Lewis acid is adequate enough for this allylation reaction. Based on these results, a mixture of (E)-3-bromo-1-tributylstannylpropene (1.2 eq.), carbonyl compound (1.0 eq.) and Zn/$CeCl_3$ (5 eq./0.6 eq.) was introduced under ultrasound as the standard procedure. The results of allylations of (E)-3-bromo-1-tributylstannylpropene with carbonyl compounds are shown in the Table 1.

Table 1. Allylation of (E)-3-Bromo-1-tributylstannylpropene to Aldehydes and ketones

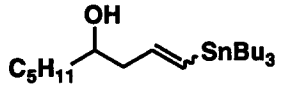
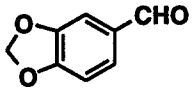
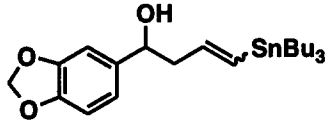
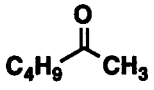
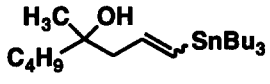
Entry	Substrate	Product	Yield[a](E/Z)[b]	Yield[c]
1			73%(77/23)	7%
2			53%(72/28)	9%
3			62%(66/34)	16%
4			63%(67/33)	10%
5			67%(68/32)	11%
6			66%(66/34)	12%
7			55%(75/25)	17%
8			51%(74/26)	22%
9			55%(81/19)	11%
10			54%(82/18)	15%

a. The yields were determined after chromatographic purification.
b. The ratio of *E*- and *Z*-vinylstannane (HPLC).
c. The yield of destannyl homoallyl alcohol. 

The results showed that a mixture of stereoisomers, (E)- and (Z)-δ-tributylstannylhomoallyl alcohols, was produced via S_E2 process under the reaction conditions. The γ-adduct via S_E2' process can not be obtained and observed by crude ^{1}H-NMR spectrum. The destannylhomoallyl alcohols were also generated due to the instability of vinyltins in the absence or presence of Lewis acid.

We further investigated the allylation of (Z)-3-bromo-1-tributylstannylpropene with carbonyl compounds and the results are shown in the Table 2. A mixture of stereoisomers, (E)- and (Z)-δ-tributylstannyl homoallylalcohols, was also produced when (Z)-3-bromo-1-tributylstannylpropene was used as allylating agent. It should be noted that either pure (E)- or (Z)-3-bromo-1-tributylstannylpropene reacted with aldehyde or ketone generated a mixture of (E)- and (Z)-stereoisomers and coincident E/Z ratios. The *cis-trans* isomerization of double bond may caused by the thermodynamically equlibrium of *in situ* generated stannylallylzinc agent.

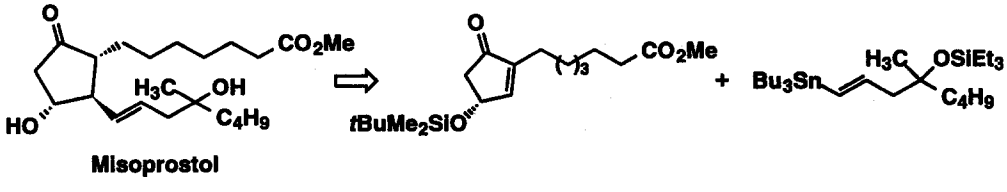
Table 2. Allylation of (Z)-3-Bromo-1-tributylstannylpropene to Aldehydes and Ketones

Entry	Substrate	Product	Yield[a](E/Z)[b]	Yield[c]
1	C_5H_{11}–CHO		74%(82/18)	9%
2			71%(67/33)	11%
3			68%(85/15)	12%

a. The yields were determined after chromatographic purification.
b. The ratio of E/Z was determined by HPLC.
c. The yield of destannyl homoallyl alcohol. 

The Prostaglandins (PGs), a group of natural products occurring in animal tissues, have attracted widespread attention over the past thirty years because of their diverse pharmacological properties and potential clinical applications in a number of therapeutic areas.[42] The E-type PGs have been used widely for peptic ulcer and cardiovascular diseases. A Searle market drug, Misoprostol[43, 44], can be synthesized by the coupling reaction of commercially available (R)-4-*tert*-butyldimethylsilyloxy-2-(6-carbomethoxyhexyl)-cyclopent-2-enone with (E)-4-methyl-4-triethylsilyloxy-1-tributylstannyl-1-octene[45,46] (Scheme 4).

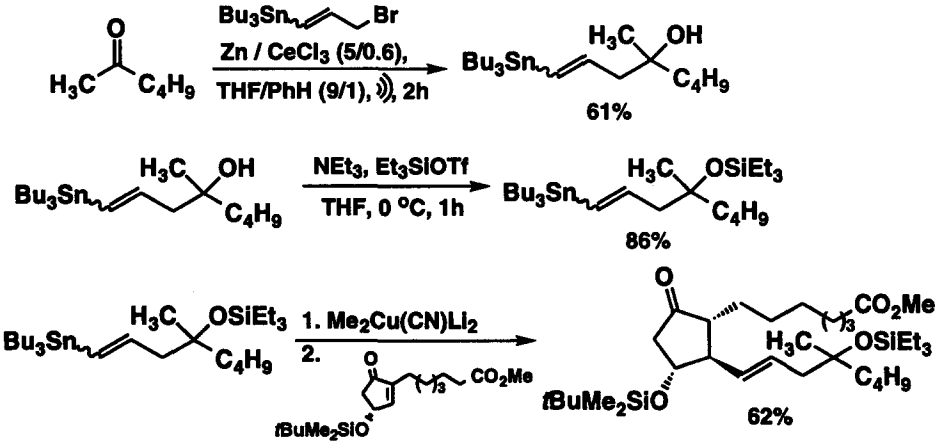
Scheme 4



Misoprostol

A mixture of Zn, $CeCl_3$ and 3-bromo-1-tributylstannylpropene (E/Z=78/22) was reacted with 2-hexanone by the standard allylation method and δ-tributylstannylhomoallyl alcohol (E/Z=84/16) was produced in 61% yield after chromatography. The silyl Misoprostol was synthesized by the known coupling procedure[47-50] of chiral cyclopentenone with silyl-δ-tributylstannylhomoallyl alcohol (Scheme 5).

Scheme 5



Experimental Section

General

The ^{1}H-NMR (proton nuclear magnetic resonance) spectra were recorded at 300 MHz (Bruker-AC300P) with deuteriochloroform ($CDCl_3$, Aldrich 99.8 atom% D) as the solvent and the internal standard. The ^{13}C-NMR (carbon nuclear magnetic resonance) spectra were recorded at 75.5 MHz (Bruker-AC300P) with $CDCl_3$ as the solvent and the internal standard. Chemical shifts are reported in parts per million and resonance patterns are reported with the notations of either s (singlet), d (doublet), t (triplet), q (quartet), or m (multiplet). Coupling constants (J) are reported in hertz (Hz). Mass spectra (MS) were recorded on a JEOL SX-102A and VG 70-250S spectrophotometers and are reported in *m/e* units for the most abundant peaks. All experiments were carried out under a nitrogen atmosphere which was dried primarily by passing through a column of potassium hydroxide (KOH) layered with calcium sulfate ($CaSO_4$). Tetrahydrofuran (THF) was distilled from sodium benzophenone ketyl and recirculated prior to use. Hexane and ethyl acetate were distilled from calcium hydride, and benzene was distilled from sodium and recirculated prior to use. Thin-layer chromatography (TLC) analysis was performed on a plastic plate (or aluminum sheet) precoated with silica gel (Merck, 5554 Silica gel $60F_{254}$). Visualization was accomplished by UV light or developed by spraying with a 10% phosphomolybdic acid ethanol solution. Column chromatography was performed using silica gel (Merck 230-400 mesh) and ethyl acetate/hexane mixtures as the eluent. Spectral grade purification by high performance liquid chromatography (HPLC) was carried out using a Rheodyne 7000 sample injector, Jasco PU-980 intelligent pumps, Jasco RI-930 Refractive Index Detector and Phenomenex columns (Spherex 10 Silica).

All aldehydes and ketones (Table 1 and 2) were purchased from Aldrich, Merck and Riedel-deHaen and all were used directly without further purification. Allylations were investigated under the typical procedure shown below and the yields are the isolated yields after chromatography.

Preparation of 1-Tributylstannylpropen-3-ol

A mixture of propargyl alcohol (5.0 mmol), Bu_3SnH (7.5 mmol) and AIBN (0.1 mmol) was refluxed at 80 °C for two hours and the reaction mixture was introduced directly to a silical gel column. The separation of (E)- and (Z)-1-tributylstannylpropen-3-ols was achieved on a flash chromatograph with ethyl acetate/hexane as eluant (E/Z=78/22).

Preparation of 3-Bromo-1-tributylstannylpropene

A solution of PPh_3 (3.3 mmol) in 5 mL CH_2Cl_2 was added slowly to a mixture of CBr_4 (4.5 mmol) and 1-tributylstannylpropen-3-ol (3.0 mmol) in 5 mL CH_2Cl_2 and the reaction mixture was stirred at room temperature for four hours. Hexane was added to generate white solid and then the solid was filtered. An aqueous 5% $NaHCO_3$ (50 mL) was added to the filtrate and the solution was extracted with hexane (30 mLx2). The organic layers were collected, washed with brine (50 mL), dried with $MgSO_4$ and the organic solvent was removed under reduced pressure. Further purification was achieved on a flash chromatograph with silica gel and ethyl acetate/hexane.

(E)-3-Bromo-1-tributylstannylpropene

^{1}H-NMR: δ 0.81-1.08 (15H, m), 1.21-1.37 (6H, m), 1.38-1.69 (6H, m), 3.95 (2H, d, J=5.9), 6.15 (1H, dt, J=18.9, 5.9), 6.27 (1H, d, J=18.9). ^{13}C-NMR: δ 10.3 (J_{Sn-C}=354), 13.5, 27.5 (J_{Sn-C}=54), 29.1, 35.9, 135.5, 143.1.

(Z)-3-Bromo-1-tributylstannylpropene

^{1}H-NMR: δ 0.87-1.01 (15H, m), 1.25-1.37 (6H, m), 1.38-1.66 (6H, m), 3.88 (2H, d, J=7.7), 6.10 (1H, d, J=12.4), 6.71 (1H, dt, J=12.4, 7.7). ^{13}C-NMR: δ 10.3 (J_{Sn-C}=346), 13.7, 27.2 (J_{Sn-C}=56), 29.1, 34.9, 135.5, 143.3.

Typical Procedure for The Synthesis of δ-Tributylstannylhomoallyl Alcohol (Table 1, 2)

A mixture of aldehyde or ketone (1.0 mmol), Zn (5.0 mmol), $CeCl_3$ (0.6 mmol) and 3-bromo-1-tributylstannylpropene (1.2 mmol) in 5 mL THF/PhH (v/v=9/1) is sonicated in a commercial ultrasonic cleaning bath[51] (Crest 575-D, 39 kHz) for two hours at around 43 °C. After the sonication, the solution was passed through a short silica gel column. The eluate was washed with 5% NH_4Cl (15 mLx2), brine (25 mL), dried with $MgSO_4$, filtered, and the organic solvent was removed under reduced pressure. Further purification was achieved on a flash chromatograph with silica gel and ethyl acetate/hexane. The stereoisomers, (E)- and (Z)-δ-tributylstannylhomoallyl alcohols, were separated by HPLC chromatography.

(E)-1-Tributylstannylnonen-4-ol (Table 1, Entry 1)

^{1}H-NMR: δ 0.75-0.99 (18H, m), 1.24-1.36 (12H, m), 1.37-1.54 (8H, m), 1.58 (1H, d, J=3.8), 2.00 (1H, m), 2.41 (1H, m), 3.65 (1H, m), 5.95 (1H, dt, J=18.9, 6.8), 6.05 (1H, d, J=18.9). ^{13}C-NMR: δ 9.5, 13.7, 14.0, 22.6, 25.3, 27.2, 29.1, 31.9, 36.7, 46.2, 70.5, 132.6, 145.2. HRMS: 375.1708 (calcd. for $C_{17}H_{35}OSn$, M-C_4H_9=375.1709). MS: *m/z* 377 (15), 376 (18), 375 (M-C_4H_9, base), 374 (37), 373 (74), 372 (30), 371 (42), 319 (23), 318 (18), 317 (17), 316 (6), 315 (10), 177 (15), 175 (12), 83 (20), 57 (8), 55 (28), 41 (24).

(Z)-1-Tributylstannylnonen-4-ol

^{1}H-NMR: δ 0.78-1.01 (18H, m), 1.24-1.36 (12H, m), 1.37-1.58 (9H, m), 2.18 (1H, m), 2.25 (1H, m), 3.65 (1H, m), 6.02 (1H, d, J=12.4), 6.54 (1H, m). ^{13}C-NMR: δ 10.4, 13.7, 14.0, 22.6, 25.8, 27.2, 29.1, 32.1, 36.7, 47.2, 72.1, 132.9, 145.8.

(E)-1-Tributylstannyl-1,5-nonadien-4-ol (Table 1, Entry 2)

^{1}H-NMR: δ 0.75-0.99 (18H, m), 1.21-1.55 (14H, m), 1.63 (1H, d, J=3.7), 2.01 (2H, dd, J=13.8, 7.2), 2.37 (2H, m), 4.12 (1H, m), 5.48 (1H, dd, J=15.6, 6.5), 5.65 (1H, dt, J=15.6, 6.2), 5.92 (1H, dt, J=18.8, 6.4), 6.05 (1H, d, J=18.9). ^{13}C-NMR: δ 9.5, 13.6, 22.3, 27.2, 28.9, 29.1, 34.3, 46.2, 71.7, 131.8, 132.3, 132.6, 144.6. HRMS: 373.1552 (calcd. for $C_{17}H_{33}OSn$, M-C_4H_9=373.1553). MS: *m/z* 375 (15), 374 (18), 373 (M-C_4H_9, base), 372 (38), 371 (75), 370 (30), 369 (42), 355 (36), 354 (14), 353 (26), 352 (10), 351 (15), 251 (68), 250 (21), 249 (51), 248 (18), 247 (30), 177 (45), 175 (45), 57 (35), 41 (15).

(Z)-1-Tributylstannyl-1,5-nonadien-4-ol

^{1}H-NMR: δ 0.86-1.08 (18H, m), 1.27-1.55 (15H, m), 2.02 (2H, dd, J=14.6, 6.9), 2.27 (2H, m), 4.12 (1H, m), 5.48 (1H, dd, J=15.4, 6.7), 5.65 (1H, dt, J=15.4, 6.4), 5.99 (1H, d, J=12.6), 6.52 (1H, dt, J=12.6, 1.5). ^{13}C-NMR: δ 10.3, 13.6, 22.3, 27.3, 28.9, 29.2, 34.3, 44.8, 72.4, 132.0, 132.3, 132.4, 144.3.

(E)-1-Tributylstannyl-4-phenylbuten-4-ol (Table 1, Entry 3)

^{1}H-NMR: δ 0.78-0.98 (15H, m), 1.24-1.36 (6H, m), 1.37-1.56 (6H, m), 2.06 (1H, d, J=3.2), 2.47 (2H, m), 4.74 (1H, m), 5.93 (1H, dt, J=18.9, 6.2), 6.09 (1H, d, J=18.9), 7.26-7.35 (5H, m). ^{13}C-NMR: δ 9.5, 13.7, 27.2, 29.2, 48.1, 73.1, 125.8, 127.4, 128.3, 133.4, 143.9, 144.5. HRMS: 381.1237 (calcd. for $C_{18}H_{29}OSn$, M-C_4H_9=381.1240). MS: *m/z* 383 (16), 382 (20), 381 (M-C_4H_9, base), 380 (39), 379 (75), 378 (30), 377 (43), 363 (9), 291 (12), 275 (18), 274 (8), 273 (14), 272 (6), 271 (8), 251 (25), 250 (9), 249 (20), 248 (7), 247 (11), 107 (10), 41 (3).

(Z)-1-Tributylstannyl-4-phenylbuten-4-ol

^{1}H-NMR: δ 0.86-1.06 (15H, m), 1.21-1.36 (6H, m), 1.37-1.54 (6H, m), 2.01 (1H, d, J=2.9), 2.47 (2H, m), 4.74 (1H, m), 6.04 (1H, dt J=12.6), 6.54 (1H, ddd, J=12.6, 7.8, 1.5), 7.26-7.36 (5H, m). ^{13}C-NMR: δ 10.3, 13.7, 27.3, 29.2, 46.7, 73.7, 125.8, 127.5, 128.3, 133.1, 140.1, 144.2.

4-Phenylbuten-4-ol (Destannylhomoallyl alcohol, Table 1, Entry 3)

^{1}H-NMR: δ 2.40 (1H, s), 2.47-2.57 (2H, m), 4.74 (1H, m), 5.12-5.20 (2H, m), 5.82 (1H, m), 7.25-7.38 (5H, m). ^{13}C-NMR: δ 43.0, 73.0, 118.4, 125.8, 127.5, 128.4, 134.4, 143.9.

(E)-1-Tributylstannyl-4-(4'-fluorophenyl)buten-4-ol (Table 1, Entry 4)

^{1}H-NMR: δ 0.75-0.98 (15H, m), 1.24-1.36 (6H, m), 1.37-1.54 (6H, m), 2.06 (1H, d, J=3.1), 2.57 (2H, m), 4.73 (1H, m), 5.90 (1H, ddd, J=18.9, 7.1, 1.1), 6.08 (1H, d, J=18.9), 7.02 (2H, m), 7.33 (2H, m). ^{13}C-NMR: δ 9.5, 13.7, 27.6, 29.2, 48.2, 72.4, 114.9, 115.2, 127.5, 133.8, 139.7, 143.9. HRMS: 399.1147 (calcd. for $C_{18}H_{28}FOSn$, M-C_4H_9=399.1146). MS: *m/z* 401 (12), 400 (14), 399 (M-C_4H_9, 74), 398 (28), 397 (54), 396 (21), 395 (30), 381 (6), 251 (25), 250 (8), 249 (18), 248 (8), 247 (18), 179 (9), 177 (17), 175 (14), 125 (base), 121 (13), 97 (45), 57 (6), 41 (13), 29 (14).

(Z)-1-Tributylstannyl-4-(4'-fluorophenyl)buten-4-ol

^{1}H-NMR: δ 0.84-1.01 (15H, m), 1.24-1.36 (6H, m), 1.36-1.54 (6H, m), 2.01 (1H, d, J=2.8), 2.40 (2H, m), 4.73 (1H, m), 6.05 (1H, d, J=12.6), 6.50 (1H, m), 7.02 (2H, m), 7.33 (2H, m). ^{13}C-NMR: δ 10.4, 13.7,

27.6, 29.2, 46.8, 72.9, 115.1, 115.4, 127.5, 133.5, 139.7, 143.9.

(E)-1-Tributylstannyl-4-(4'-methoxyphenyl)buten-4-ol (Table 1, Entry 5)

^{1}H-NMR: δ 0.75-0.94 (15H, m), 1.23-1.36 (6H, m), 1.36-1.54 (6H, m), 2.00 (1H, d, J=3.1), 2.58 (2H, m), 3.80 (3H, s), 4.69 (1H, m), 5.95 (1H, dd, J=18.9, 6.8), 6.08 (1H, d, J=18.9), 6.87 (2H, m), 7.28 (2H, m). ^{13}C-NMR: δ 9.5, 13.6, 27.2, 29.1, 48.1, 55.3, 72.8, 113.8, 127.1, 133.1, 139.2, 144.7, 159.0. HRMS: 411.1348 (calcd. for $C_{19}H_{31}O_2Sn$, M-C_4H_9=411.1346). MS: *m/z* 413 (12), 412 (16), 411 (M-C_4H_9, 78), 410 (30), 409 (57), 408 (23), 407 (31), 393 (41), 392 (16), 391 (30), 390 (12), 389 (16), 269 (19), 251 (base), 250 (32), 249 (41), 248 (26), 247 (41), 179 (16), 177 (17), 175 (13), 139 (81), 109 (18), 77 (11), 57 (5), 41 (7), 29 (7).

(Z)-1-Tributylstannyl-4-(4'-methoxyphenyl)buten-4-ol

^{1}H-NMR: δ 0.76-1.03 (15H, m), 1.20-1.36 (6H, m), 1.36-1.54 (6H, m), 1.92 (1H, d, J=2.8), 2.46 (2H, m), 3.80 (3H, s), 4.69 (1H, m), 6.02 (1H, d, J=12.7), 6.50 (1H, ddd, J=12.7, 7.6, 1.3), 6.87 (2H, d, J=8.7), 7.28 (2H, d, J=8.7). ^{13}C-NMR: δ 10.4, 13.6, 27.2, 29.1, 46.6, 55.3, 73.4, 113.8, 127.1, 133.1, 139.2, 144.7, 159.2.

(E)-1-Tributylstannyl-4-piperonyl-buten-4-ol (Table 1, Entry 6)

^{1}H-NMR: δ 0.78-0.98 (15H, m), 1.24-1.36 (6H, m), 1.37-1.54 (6H, m), 2.01 (1H, d, J=2.9), 2.55 (2H, m), 4.66 (1H, m), 5.85-5.96 (3H, m), 6.08 (1H, d, J=18.9), 6.77 (2H, m), 6.87 (1H, s). ^{13}C-NMR: δ 9.5, 13.7, 27.6, 29.2, 48.1, 72.9, 100.9, 106.4, 107.9, 119.2, 133.5, 138.1, 144.5, 147.2, 148.5. HRMS: 425.1135 (calcd. for $C_{19}H_{28}O_3Sn$, M-C_4H_9=425.1057). MS: *m/z* 427 (14), 426 (18), 425 (M-C_4H_9, 84), 424 (34), 423 (65), 422 (26), 421 (36), 407 (15), 275 (34), 274 (14), 273 (25), 272 (11), 271 (14), 251 (88), 250 (22), 249 (64), 248 (23), 247 (37), 179 (31), 178 (38), 177 (51), 176 (17), 175 (38), 151 (baser), 149 (75), 119 (21), 93 (48), 57 (16), 41 (29).

(Z)-1-Tributylstannyl-4-piperonyl-buten-4-ol

^{1}H-NMR: δ 0.81-1.07 (15H, m), 1.24-1.39 (6H, m), 1.40-1.54 (6H, m), 1.95 (1H, d, J=2.9), 2.55 (2H, m), 4.66 (1H, m), 5.95 (2H, s), 6.03 (1H, d, J=12.4), 6.49 (1H, m), 6.78 (2H, m), 6.88 (1H, s). ^{13}C-NMR: δ 10.5, 13.7, 27.6, 29.3, 46.9, 72.6, 101.9, 107.4, 107.9, 120.1, 133.5, 138.2, 144.5, 147.2, 149.3.

(E)-1-Tributylstannyl-4-furanylbuten-4-ol (Table 1, Entry 7)

^{1}H-NMR: δ 0.75-0.99 (15H, m), 1.20-1.39 (6H, m), 1.40-1.54 (6H, m), 2.03 (1H, d, J=4.9), 2.71 (2H, m), 4.67 (1H, td, J=12.5, 4.9), 5.92 (1H, dt, J=18.9, 6.4), 6.11 (1H, d, J=18.9), 6.24 (1H, m), 6.32 (1H, dd, J=3.3, 1.8), 7.38 (1H, m). ^{13}C-NMR: δ 9.5, 13.6, 27.2, 29.1, 46.1, 67.9, 105.9, 110.1, 133.5, 141.8, 143.6, 156.2. HRMS: 371.1035 (calcd. for $C_{16}H_{27}O_2Sn$, M-C_4H_9=371.1033). MS: *m/z* 371 (M-C_4H_9, 38), 370 (15), 369 (29), 368 (11), 367 (17), 353 (9), 251 (49), 250 (17), 249 (37), 248 (14), 247 (22), 177 (17), 175 (14), 137 (11), 121 (14), 119 (12), 97 (base), 91 (12), 57 (10), 41 (17).

(Z)-1-Tributylstannyl-4-furanylbuten-4-ol

^{1}H-NMR: δ 0.80-1.05 (15H, m), 1.25-1.36 (6H, m), 1.37-1.54 (6H, m), 1.93 (1H, d, J=5.3), 2.62 (2H, m), 4.74 (1H, dt, J=12.7, 5.3), 6.06 (1H, d, J=12.6), 6.24 (1H, d, J=3.2), 6.33 (1H, dd, J=3.2, 1.4), 6.51 (1H, dt, J=12.6, 7.1), 7.37 (1H, m). ^{13}C-NMR: δ 10.3, 13.6, 27.2, 29.1, 44.2, 66.8, 105.9, 110.1, 133.5, 141.9, 143.6, 155.2.

(E)-1-Tributylstannyl-4-thiophenylbuten-4-ol (Table 1, Entry 8)

^{1}H-NMR: δ 0.75-1.05 (15H, m), 1.24-1.39 (6H, m), 1.40-1.54 (6H, m), 2.18 (1H, d, J=3.8), 2.69 (2H, m), 4.99 (1H, m), 5.96 (1H, dt, J=18.9, 6.2), 6.13 (1H, d, J=18.9), 6.97 (2H, m), 7.23 (1H, dd, J=4.2, 2.1). ^{13}C-NMR: δ 9.5, 13.7, 27.6, 29.2, 47.9, 69.3, 123.5, 124.5, 126.6, 133.8, 143.8, 147.9. HRMS: 387.0795 (calcd. for $C_{16}H_{27}OSSn$, M-C_4H_9=387.0805). MS: *m/z* 389 (25), 388 (26), 387 (M-C_4H_9, 99), 386 (51), 385 (97), 384 939), 383 (55), 369 (32), 368 (12), 367 (24), 366 (8), 365 (12), 255 (22), 251 (base), 250 (39), 249 (92), 248 (32), 247 (53), 113 (65), 85 (19), 57 (5), 41 (7).

(Z)-1-Tributylstannyl-4-thiophenylbuten-4-ol

^{1}H-NMR: δ 0.83-1.05 (15H, m), 1.24-1.39 (6H, m), 1.40-1.54 (6H, m), 2.12 (1H, d, J=3.8), 2.58 (2H, m), 4.99 (1H, m), 6.07 (1H, d, J=12.6), 6.56 (1H, m), 6.97 (2H, m), 7.24 (1H, m). ^{13}C-NMR: δ 10.4, 13.7, 27.3, 29.2, 46.7, 69.8, 123.6, 124.5, 126.6, 133.7, 143.6, 148.6.

4-Thiophenylbuten-4-ol (Destannylhomoallyl alcohol, Table 1, Entry 8)

^{1}H-NMR: δ 2.33 (1H, s), 2.63 (2H, m), 4.98 (1H, m), 5.14 (2H, m), 5.83 (1H, m), 6.95-6.98 (2H, m), 7.24 (1H, m). ^{13}C-NMR: δ 43.7, 69.3, 118.7, 123.6, 124.5, 126.6, 133.8, 147.8.

(E)-4-Methyl-1-tributylstannyl-1-octen-4-ol (Table 1, Entry 9)

^{1}H-NMR: δ 0.85-0.98 (18H, m), 1.16 (3H, s), 1.26-1.36 (10H, m), 1.42-1.56 (9H, m), 2.30 (2H, m), 6.10 (2H, m). ^{13}C-NMR: δ 9.5, 13.6, 14.1, 23.3, 26.1, 26.9, 27.3, 29.2, 41.6, 50.4, 72.1, 133.2, 144.6. HRMS: 375.1701 (calcd. for $C_{17}H_{35}OSn$, M-C_4H_9=375.1709). MS: *m/z* 377 (16), 376 (18), 375 (M-C_4H_9, base), 374 (38), 373 (75), 372 (29), 371 (42), 357 (21), 356 (9), 355 (16), 354 (7), 353 (10), 301 (23), 300 (9), 299 (18), 298 (7), 289 (10), 251 (10), 177 (11), 101 (57), 57 (21), 41 (14).

(Z)-4-Methyl-1-tributylstannyl-1-octen-4-ol

^{1}H-NMR: δ 0.86-1.08 (18H, m), 1.17 (3H, s), 1.27-1.38 (12H, m), 1.39-1.54 (7H, m), 2.23 (2H, m), 6.01 (1H, d, J=12.5), 6.59 (1H, dt, J=12.5, 7.1). ^{13}C-NMR: δ 10.4, 13.7, 14.1, 23.3, 26.1, 26.9, 27.3, 29.2, 42.1, 48.7, 72.2, 132.7, 143.9.

(E)-1-Tributylstannyl-4-phenylpenten-4-ol (Table 1, Entry 10)

^{1}H-NMR: δ 0.71-0.97 (15H, m), 1.20-1.36 (6H, m), 1.37-1.58 (9H, m), 2.12 (1H, s), 2.55 (1H, ddd, J=13.4, 7.7, 0.4), 2.77 (1H, ddd, J=13.4, 6.1, 1.3), 5.73 (1H, ddd, J=18.9, 7.7, 1.6), 6.06 (1H, dt, J=18.9, 2.2), 7.23 (1H, m), 7.33 (2H, m), 7.42 (2H, m). ^{13}C-NMR: δ 9.5, 13.6, 27.2, 29.2, 29.7, 52.8, 73.4, 124.7, 126.6, 127.9, 134.4, 144.1, 147.8. HRMS: 395.1400 (calcd. for $C_{19}H_{31}OSn$, M-C_4H_9=395.1397). MS: *m/z* 397 (12), 396 (15), 395 (M-C_4H_9, 75), 394 (30), 393 (56), 392 (23), 391 (31), 377 (56), 376 (22), 375 (41), 374 (16), 373 (24), 251 (19), 179 (11), 177 (21), 176 (7), 175 (17), 174 (6), 161 (18), 121 (base), 105 (20), 57 (16), 43 (34), 41 (27).

(Z)-1-Tributylstannyl-4-phenylpenten-4-ol

^{1}H-NMR: δ 0.86-1.05 (15H, m), 1.27-1.36 (6H, m), 1.37-1.54 (6H, m), 1.55 (3H, s), 2.03 (1H, s), 2.46 (1H, ddd, J=13.8, 8.3, 0.8), 2.71 (1H, ddd, J=13.8, 6.1, 2.1), 6.03 (1H, d, J=12.7), 6.34 (1H, ddd, J=12.7, 6.1, 2.1), 7.24 (1H, m), 7.34 (2H, m), 7.46 (2H, m). ^{13}C-NMR: δ 10.4, 13.6, 27.2, 29.2, 30.1, 50.9, 73.6, 124.7, 126.5, 128.0, 134.4, 143.4, 147.9.

1-Tributylstannyl-4-triethylsilyloxy-4-methyl-1-octenene (Scheme 5)

A solution of 4-methyl-1-tributylstannyl-1-octen-4-ol (1.0 mmol, E/Z=84/16) and Et_3N (1.1 mmol) in 5 mL THF was added Et_3SiOTf (1.2 mmol) at 0 °C. The reaction mixture was stirred at 0 °C for one hour and then H_2O (5 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (3x10 mL). The collected organic extracts were washed with brine (10 mL), dried with $MgSO_4$, fitered and the organic solvent was removed under reduced pressure. The crude was purified on a flash chromatograph with silica gel and ethyl acetate/hexane (3%) and a 86% yield was obtained. The ^{1}H-NMR spectrum of major isomer (E)-tributylstannyl-4-triethylsilyloxy-4-methyl-1-octenene is shown below.
^{1}H-NMR: δ 0.56 (6H, q, J=8.0), 0.82-1.01 (27H, m), 1.16 (3H, s), 1.26-1.34 (10H, m), 1.35-1.54 (8H, m), 2.29 (2H, m), 5.91-5.93 (2H, m).

(R)-4-*tert*-Butyldimethylsilyloxy-2-(6-carbomethoxyhexyl)-cyclopene-2-enone
^{1}H-NMR: δ 0.12 (3H, s), 0.13 (3H, s), 0.91 (9H, s), 1.30-1.70 (8H, m), 2.16 (2H, t, J=7.8), 2.26 (1H, dd, J=16.2, 2.1), 2.30 (2H, t, J=7.2), 2.73 (1H, dd, J=18.2, 6.0), 3.66 (3H, s), 4.88 (1H, m), 7.03 (1H, m).
^{13}C-NMR: δ -5.1, 17.6, 23.9, 24.3, 25.4, 26.8, 28.4, 28.5, 33.5, 45.0, 50.8, 68.6, 146.5, 156.1, 173.4, 205.3.

(8R,11R,12R)-11-(*tert*-Butyldimethylsilyloxy)-16-methyl-16-triethylsilyloxy-9-oxo-prost-13-en-1-oic acid, methyl ester (Silyl Misoprostol)[45, 46]

A solution of MeLi (2.0 mmol) and CuCN (1.0 mmol) in 2 mL THF at 0 °C was added 1-tributylstannyl-4-triethylsilyloxyl-4-methyl-1-octenene (1.0 mmol). The reaction mixture was warmed to room temperature and stirred at room temperature for 2.5 hours. The reaction mixture was cooled to -78 °C and then (R)-4-*tert*-butyldimethylsilyloxy-2-(6-carbomethoxyhexyl)-cyclopene-2-enone (0.7 mmol) was added. After stirring at -78 °C for 2 minutes, the mixture was warmed to -30 °C and stirred at -30 °C for 10 minutes and then saturated NH_4Cl solution (2 mL) was added. The mixture was warmed to room temperature and Et_2O (10 mL) and saturated NH_4Cl (10 mL) was added. The organic layer was separated and the aqueous layer was extracted with Et_2O (3x10 mL). The collected organic extracts were washed with brine (15 mL), dried with $MgSO_4$, filtered and the organic solvent was removed under reduced pressure. Further purification was achieved on a flash chromatograph with silica gel and ethyl acetate/hexane (10%) and a 62% yield was obtained.
^{1}H-NMR: δ 0.03 (6H, s), 0.58 (6H, q, J=7.8), 0.80-1.01 (21H, m), 1.14 (3H, s), 1.15-1.67 (18H, m), 1.93 (1H, m), 2.16 (1H, dd, J=17.9, 8.5), 2.27 (2H, t, J=7.5), 2.41 (1H, dt, J=10.9, 7.9), 2.60 (1H, dd, J=18.2, 6.1), 3.65 (3H, s), 3.99 (1H, m), 5.30(1H, m), 5.59 (1H, m). ^{13}C-NMR: δ -4.7, -4.8, 6.9, 7.2, 14.2, 18.0, 23.3, 24.9, 25.7, 26.2, 26.4, 26.7, 27.9, 28.9, 29.5, 34.1, 41.9, 42.3, 45.7, 47.5, 51.4, 53.9, 54.3, 73.3, 75.3, 130.1, 130.3, 132.3, 174.2, 216.2.

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References and Notes

1. Yamamoto, Y.; Asao, N. *Chem. Rev.* **1993**, *93*, 2207-2293.
2. Santelli, M.; Pons, J.-M. *Lewis Acids and Selectivity in Organic Synthesis*, CRC Press: New York, 1996, p91-184.
3. Schlosser, M. *Pure Appl. Chem.* **1988**, *60*, 1627.
4. Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152.
5. Burns, T. P.; Rieke, R. D. *J. Org. Chem.* **1987**, *52*, 3674.
6. Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Org. Chem.* **1989**, *54*, 5198.
7. Shono, T.; Ishifune, M.; Kashimura, S. *Chem. Lett.* **1990**, 449.
8. Wilson, S. R.; Guazzaroni, M. E. *J. Org. Chem.* **1989**, *54*, 3087.
9. Araki, S.; Itoh, H.; Butsugan, Y. *J. Organomet. Chem.* **1988**, *347*, 5.
10. Andemichael, Y. W.; Wang, K. K. *J. Org. Chem.* **1992**, *57*, 796.
11. Yamamoto, Y.; Maruyama, K.; Komatsu, T.; Ito, W. *J Org. Chem.* **1986**, *51*, 886.
12. Hoffmann, R. W.; Kemper, B. *Tetrahedron*, **1984**, *40*, 2219.
13. Yamaguchi, M.; Mukaiyama, T. *Chem. Lett.* **1980**, 993.
14. Wang, Z.; Meng, X. J.; Kabalka, G. W. *Tetrahedron Lett.* **1991**, *32*, 5677; **1991**, *32*, 4619.
15. Tsai, D. J. S.; Matteson, D. S. *Tetrahedron Lett.* **1981**, *22*, 2751.
16. Hoppe, D.; Lichtenberg, F. *Angew. Chem., Int. Ed. Engl.* **1984**, *23*, 239.
17. Courtois, G.; Harama, M.; Miginiac, P. *J. Organomet. Chem.* **1981**, *218*, 1.
18. Araki, S.; Imai, A.; Shimizu, K.; Butsugan, Y. *Tetrahedron Lett.* **1992**, *33*, 2581.
19. Araki, S.; Shimizu, K.; Johar, P. S.; Jin, S. J.; Butsugan, Y. *J. Org. Chem.* **1991**, *56*, 2538.
20. Sato, K.; Kira, M.; Sakura, H. *J. Am. Chem. Soc.* **1989**, *111*, 6429.
21. Davis, A. P.; Jaspars, M. *J. Chem. Soc. Chem. Commun.* **1990**, 1176.
22. Fleming, I.; Kindon, N. D.; Sakar, A. K. *Tetrahedron Lett.* **1987**, *28*, 5921.
23. Hayashi, T.; Konishi, M.; Kumada, M. *J. Am. Chem. Soc.* **1982**, *104*, 4963.
24. Kira, M.; Hino, T.; Sakurai, H. *Chem. Lett.* **1991**, 277.
25. Tokoroyama, Y.; Pan, L. R. *Tetrahedron Lett.* **1989**, *30*, 197.
26. Marshall, J. A.; Luke, J. P. *J. Org. Chem.* **1991**, *56*, 483.
27. Yamamoto, Y.; Hatsuya, S.; Yamada, J. *J. Chem. Soc. Chem. Commun.* **1987**, 561.
28. Keck, G. E.; Abbott, D. E.; Wiley, M. R. *Tetrahedron Lett.* **1987**, *28*, 139.
29. Korreda, M.; Tanaka, Y. *Tetrahedron Lett.* **1987**, *28*, 143.
30. Nishigaichi, Y.; Ishida, N.; Nishida, M.; Takuwa, A. *Tetrahedron Lett.* **1996**, *37*, 3701.
31. Miyake, H.; Yamamura, K. *Chem. Lett.* **1992**, 1369.
32. Mikami, K.; Kawamoto, K.; Loh, T.-P.; Nakai, T. *J. Chem. Soc. Chem. Commun.* **1990**, 1161.
33. Yamamoto, Y.; Maeda, N.; Maruyama, K. *J. Chem. Soc. Chem. Commun.* **1983**, 742.
34. Guo, B. S.; Doubleday, W.; Cohen, T. *J. Am. Chem. Soc.* **1987**, *109*, 4710.
35. Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904.
36. Cintas, P. *Synthesis*, **1992**, 248.
37. Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 8955.

38. Yamamoto, Y.; Murayama, K. *J. Org. Chem.* **1983**, *48*, 1564.
39. Yamamoto, Y.; Saito, Y.; Maruyama, K. *J. Organomet. Chem.* **1985**, *292*, 311.
40. Cochran, J. E.; Williams, L. E.; Bronk, B. S.; Calhoun, J. A.; Fassberg, J.; Clark, K. G. *Orgamometallics*, **1989**, *8*, 804.
41. Nicolaou, K. C.; Veale, C. A.; Webber, S. E.; Katerinopoulos, H. *J. Am. Chem. Soc.* **1985**, *107*, 7515.
42. Collins, P. W.; Djuric, S. W. *Chem. Rev.* **1993**, *93*, 1533.
43. Collins, P. W.; Dajani, E. Z.; Driskill, D. R.; Bruhn, M. S.; Jung, C. J.; Pappo, R. *J. Med. Chem.* **1977**, *20*, 1152.
44. Chen, S.-M. L.; Schaub, R. E.; Grudzinskas, C. V. *J. Org. Chem.* **1978**, *43*, 3450.
45. Taylor, R. J. K. *Synthesis*, **1985**, 364.
46. Caton, M. P. L. *Tetrahedron*, **1979**, *35*, 2705.
47. Gooding, O. W. *J. Org. Chem.* **1990**, *55*, 4209.
48. Noyori, R.; Suzuki, M. *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 847.
49. Behling, J. R.; Babiak, K. A.; Ng, J. S.; Campbell, A. L.; Moretti, R.; Koerner, M.; Lipshutz, B. H. *J. Am. Chem. Soc.* **1988**, *110*, 2641.
50. Wipf, P. *Synthesis*, **1993**, 537.
51. The bath should be filled with water containing 5% detergent. In our laboratory, we used Decon 90 which permits much more even cavitation in bath water.