A New Method for the Synthesis of β,β-Bis(4'-methoxy)phenyl-α-phenylvinylstannane Reagents and Their Synthetic Utilities

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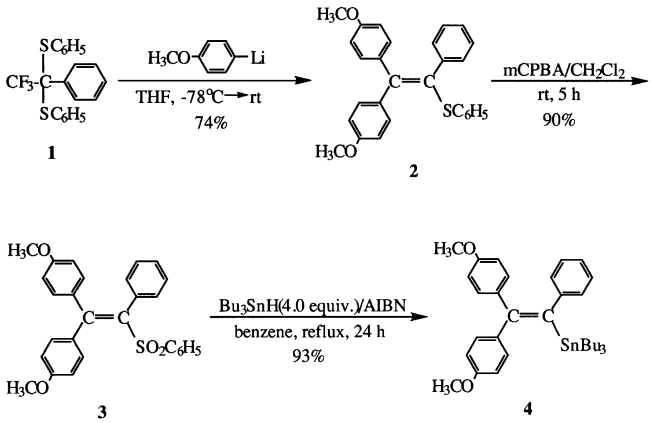
It has been well known that triphenylethylene derivatives such as tamoxifen, droloxifene, toremifene and panomifene are very useful selective estrogen receptor modulators to prevent bone loss and breast cancer.[1] The triphenylvinyl moiety is a very important framework in these types of analogs. Among the triphenylvinyl moieties, β,β-bis(4'-methoxy)phenyl-α-phenylvinyl moiety is of particular important because a metabolite of tamoxifen formed in patients is 1-(4'-hydroxy)phenyl-1-(4'-dimethylaminoethoxy)phenyl-2-phenyl-1-butene[2] which binds to estrogen receptor much more effectively than tamoxifen.[3] Therefore, a variety of easy transformations of functionality on vinyl carbon with keeping the β,β-bis(4'-methoxy)phenyl-α-phenylvinyl moiety is a quite important synthetic target for the synthesis of various relevant compounds. Generally, most of triphenylethylene derivatives have been synthesized *via* several methods. A classical method for the preparation of triphenylethylene derivatives involves addition of an aryl Grignard reagent to 1-alkyl-1-phenylacetophenone, followed by dehydration under acidic condition.[4-7] Another efficient synthetic strategy showed McMurry reductive cross-coupling reaction of substituted benzophenones with propiophenone in the presence of Ti metal.[8-10] Finally, triphenylvinyl bromide provided an ideal and versatile intermediate for the synthesis of tamoxifen derivatives.[11-12] However, these types of synthetic methods still have some drawbacks such as specific preparation of triphenylethylene derivatives, lack of transformations of functionality on vinyl carbon and low yield. Thus, we wish to describe a new and efficient method for the preparation of an ideal and promise intermediate, β,β-bis(4'-methoxy)phenyl-α-phenylvinylstannane reagent, for providing a variety of functionality on vinyl carbon and to show several transformations *via* tributylstannyl group in this paper.

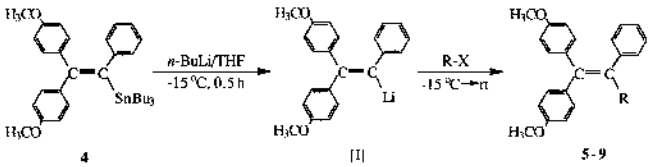
β,β-bis(4'-methoxy)phenyl-α-phenylvinylstannane reagent can be synthesized *via* 3 steps from the reaction of 2,2,2-trifluoro-1,1-bis(phenylthio)ethylbenzene (**1**).[13] The reaction of **1** with (4'-methoxy)-phenyllithium in THF at -78 °C, followed by warming to 0 °C, afforded β,β-bis(4'-methoxy)phenyl-α-phenylvinylsulfide 2 in 74% yield. (4'-Methoxy)phenyllithium reagent was prepared from the reaction of 4-methoxy-1-iodobenzene (8.0 mmol) with *n*-butyllithium (6.0 mmol) in ether at room temperature for 20 min. The reaction pathway seems likely that the initial reaction of



1 with (4'-methoxy)phenyllithium *via* attack of sulfur atom provided the carbanion bearing trifluoromethyl group which quickly underwent β-defluorination to give β,β-difluorovinyl sulfide. This sulfide is so reactive that it quickly underwent addition-elimination reaction with (4'-methoxy)-phenyllithium twice to provide **2**. Oxidation of **2** with mCPBA (2.5 equiv.) in methylene chloride at room temperature for 5 h resulted in the formation of β,β-bis(4'-methoxy)phenyl-α-phenylvinylsulfone **3** in 90% yield. When **3** was reacted with tributyltin hydride (6.0 equiv.) and catalytic amount of AIBN in benzene at reflux temperature for 24 h, finally, β,β-bis(4'-methoxy)phenyl-α-phenylvinylstannane **4** was obtained in 93% yield.

The synthetic transformations *via* stannyl group in **4** to provide a variety of functionalities on vinyl carbon have been well known procedures in organic synthesis. Therefore, the treatment of **4** with *n*-BuLi (1.5 equiv.) in THF at -15 °C for 0.5 h resulted in the formation of β,β-bis(4'-methoxy)-phenyl-α-phenylvinyllithium reagent [I] which was quite stable in THF at -15 °C for a long time and can be reacted with methyl iodide, ethyl bromide, benzyl chloride and trimethylsilyl chloride at -15 °C for 1 h, followed by warming to room temperature, to give the corresponding alkylated and silylated products **5**, **6**, **7** and **8** in 89%, 63%, 11% and 72% yields, respectively. The reaction of [I] with benzyl chloride or allyl chloride afforded self-dimerization product as the major product. The reaction of [I] with 2,2,2-trifluoroethyltriflate did not give any trifluoroethylated product at all. However, iodination of [I] under the same

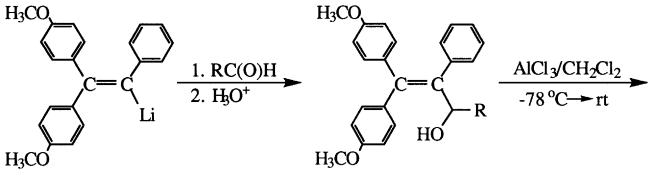
Table 1. Alkylation, silylation and iodination reactions of [I]



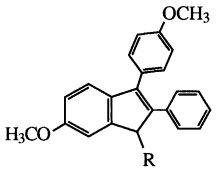
4 [I] 5-9

Compound No.	R-X	Yield (%)[a]
5	CH_3-I	89
6	CH_3CH_2-Br	63
7	$C_6H_5CH_2$-Cl	11
8	$(CH_3)_3$Si-Cl	72
9	I_2	73

[a]Isolated yield.

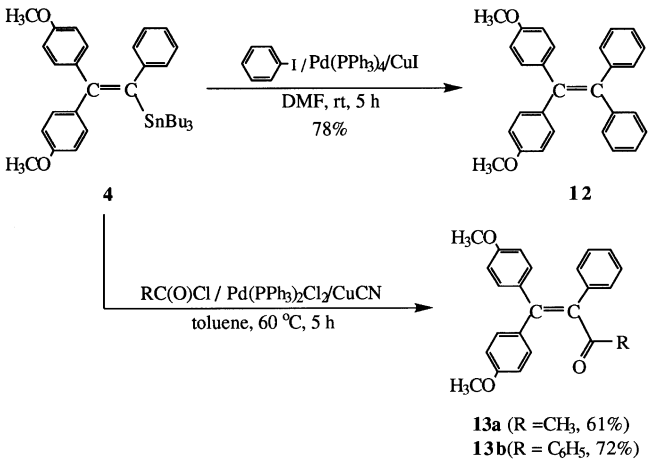


[I] **10a** (R = CH_3, 61%)
10b (R = C_6H_5, 80%)



11 (R = C_6H_5, 78%)

reaction condition also provid the corresponding vinyl iodide **9** in 73% yield. The results of the alkylation, silylation and iodination reactions of [I] are summarized in Table 1. When [I] was treated with acetaldehyde and benzaldehyde at -15 °C for 1 h, the corresponding allylic alcohols **10a** and **10b** were obtained in 61% and 80% yields, respectively. However, [I] did not react with ketones, such as acetone, acetophenone, cyclohexanone and 1,1,1-trifluoroacetone, except for trifluoroacetophenone. The product **10b** underwent the cyclization in the presence of $AlCl_3$ (1.0 equiv.) in CH_2Cl_2 at -78 °C, followed by slowly warming to room temperature to give the indene derivative **11** in 78% yield.



13a (R =CH_3, 61%)
13b(R = C_6H_5, 72%)

The cross-coupling reaction of **4** with iodobenzene in the presence of a mixture of 10 mol% $Pd(PPh_3)_4$ and 10 mol% CuI afforded the coupling product **12** in 78% yield. The acylation reaction of **4** with acetyl and benzoyl chloride in the presence of a mixture of 10 mol% $Pd(PPh_3)_2Cl_2$ and 10 mol% CuCN also provided the coupling products **13a** and **13b** in 61% and 72% yields, respectively.

In conclusion, we have developed a new and efficient synthetic route to β,β-bis(4'-methoxy)phenyl-α-phenylvinylstannane reagent and demonstrated the introduction of a variety of functionality on vinyl carbon *via* tributylstannyl group.

Experimental Section

General. ^{1}H NMR spectra were recorded on a 100 MHz Bruker AC-100F NMR Spectrometer with tetramethylsilane (TMS) as an internal standard. Infrared spectra were determined on a Mattson Genesis series FT High Resolution Spectrophotometer. Mass spectra were obtained using Hewlett-Packard 5890 GC/5970B MSD (EI, 70 eV).

Commercially available reagents were purchased from Aldrich, PCR and Tokyo Kasei. All solvents were dried by general purification methods.

Preparation of 1,1-bis[(4'-methoxy)phenyl]-2-phenyl-2-phenylthioethene (2). *n*-BuLi (2.5 M solution in hexane) (4.8 mL, 12.0 mmol) was added to a solution of *p*-iodoanisole (3.74 g, 16.0 mmol) dissolved in 10 mL of dry ether at room temperature and then the mixture was allowed to stir for 20 min. The mixture was cooled to -78 °C by using dry-ice/isopropanol slush and then a solution of 1,1-bis(phenylthio)-2,2,2-trifluoroethylbenzene[13] (0.76 g, 2.0 mmol) dissolved in 1 mL of THF was added into the mixture. After slowly warming to room temperature, followed by further stirring at room temperature for 3 h, the reaction mixture was quenched with 3% HCl (20 mL) solution, extracted with ether (20 mL × 3) and dried with anhydrous $MgSO_4$. Column chromatography (hexane) provided 0.62 g (74% yield) of **2**: mp 121-123 °C; ^{1}H NMR ($CDCl_3$) δ 7.45-6.50 (m, 18H), 3.80 (s, 3H), 3.70 (s, 3H); MS, m/z (relative intensity) 424 (M^+, 100), 315 (45), 239 (15); IR (KBr) 3050, 2950, 2800, 1600, 1571, 1523, 1497, 830, 743, 690 cm^{-1}. Anal. Calcd for $C_{28}H_{24}O_2S$: C, 79.22; H, 5.70. Found: C, 79.04; H, 5.64.

Preparation of 1,1-bis[(4'-methoxy)phenyl]-2-phenyl-2-phenylsulfonylethene (3). A solution of **2** (0.42 g, 1.0 mmol) dissolved in 10 mL of dry CH_2Cl_2 was cooled to 0 °C and then mCPBA (2.5 mmol) was added, followed by stirring at room temperature for 5 h. The mixture was washed with saturated $NaHCO_3$ and 10% $NaHSO_3$. After extraction with CH_2Cl_2 (20 mL × 2) and drying with anhydrous $MgSO_4$, column chromatography (hexane : ethyl acetate = 4 : 1) provided 0.41 g (90% yield) of **3**: mp 127-128 °C; ^{1}H NMR ($CDCl_3$) δ 7.51-6.46 (m, 18H), 3.84 (s, 3H), 3.65 (s, 3H); MS, m/z (relative intensity) 456 (M^+, 49), 315 (100), 239 (10), 77 (12); IR (KBr) 3060, 2956, 2837, 1604, 1509, 1445, 831, 750, 699 cm^{-1}. Anal. Calcd for

$C_{28}H_{24}O_4S$: C, 73.66; H, 5.30. Found: C, 73.85; H, 5.40.

Preparation of 1,1-bis[(4'-methoxy)phenyl]-2-tributylstannanyl-2-phenylethene (4). A mixture of **3** (0.40 g, 0.88 mmol), tributyltin hydride (1.03 g, 3.52 mmol), AIBN (10 mol%) and 10 mL dry benzene was heated to 80-90 °C for 24 h. After the reaction mixture was cooled to room temperature, benzene was removed. Column chromatography (hexane) provided 0.49 g (93% yield) of **4**: oil; ^{1}H NMR ($CDCl_3$) δ 7.26-6.49 (m, 13H), 3.83 (s, 3H), 3.66 (s, 3H), 1.41-0.46 (m, 27H); MS, m/z (relative intensity) 549 (M^+-56, 56), 315 (15), 227 (100), 177 (14), 121 (17); IR (neat) 3056, 2954, 2926, 2851, 1605, 1506, 1463, 831, 701 cm^{-1}. Anal. Calcd for $C_{34}H_{46}O_2Sn$: C, 67.43; H, 7.66. Found: C, 67.29; H, 7.59.

Preparation of 1,1-bis[(4'-methoxy)phenyl]-2-phenylpropene (5). A solution of **4** (0.12 g, 0.2 mmol) dissolved in 5 mL of dry THF was cooled to -15 °C and then *n*-BuLi (2.5 M solution in hexane) (0.12 mL, 0.3 mmol) was added. After stirring for 1 h, CH_3I (0.043 g, 0.3 mmol) was added and then a mixture was allowed to stir at -15 °C for 1 h, followed by warming to room temperature. After a mixture was washed with saturated NaCl solution, extracted with ether (20 mL × 2) and dried with anhydrous $MgSO_4$, column chromatography (hexane) provided 0.059 g (89% yield) of **5**: mp 90-91 °C; ^{1}H NMR ($CDCl_3$) δ 7.26-6.50 (m, 13H), 3.83 (s, 3H), 3.69 (s, 3H), 2.13 (s, 3H); MS, m/z (relative intensity) 330 (M^+, 100), 222 (12), 178 (17), 108 (9); IR (KBr) 3046, 2995, 2953, 2832, 1606, 1507, 1461, 838, 739, 689 cm^{-1}. Anal. Calcd for $C_{23}H_{22}O_2$: C, 83.59; H, 6.72. Found: C, 83.48; H, 6.67.

Preparation of 1,1-bis[(4'-methoxy)phenyl]-2-phenyl-1-butene (6). mp 118-119 °C; ^{1}H NMR ($CDCl_3$) δ 7.31-6.49 (m, 13H), 3.83 (s, 3H), 3.68 (s, 3H), 2.48 (q, J = 7.4 Hz, 2H), 0.93 (t, J = 7.4 Hz, 3H); MS, m/z (relative intensity) 344 (M^+, 100), 329 (26), 221 (22), 121 (10); IR (KBr) 3043, 2977, 2951, 2832, 1604, 1506, 1462, 834, 741, 704 cm^{-1}. Anal. Calcd for $C_{24}H_{24}O_2$: C, 83.68; H, 7.03. Found: C, 83.82; H, 7.09.

Preparation of 1,1-bis[(4'-methoxy)phenyl]-2,3-diphenylpropene (7). Oil; ^{1}H NMR ($CDCl_3$) δ 7.26-6.55 (m, 18H), 3.91 (s, 2H), 3.80 (s, 3H), 3.69 (s, 3H); MS, m/z (relative intensity) 406 (M^+, 100), 375 (10), 315 (16), 298 (13), 227 (53), 164 (15); IR (KBr) 3046, 2980, 2945, 1600, 1505, 1460, 834, 745, 701 cm^{-1}. Anal. Calcd for $C_{29}H_{26}O_2$: C, 85.67; H, 6.45. Found: C, 85.79; H, 6.36.

Preparation of 1,1-bis[(4'-methoxy)phenyl]-2-trimethylsilyl-2-phenylethene (8). mp 77-78 °C; ^{1}H NMR ($CDCl_3$) δ 7.25-6.46 (m, 13H), 3.82 (s, 3H), 3.64 (s, 3H), 0.20 (s, 9H); MS, m/z (relative intensity) 388 (M^+, 69), 373 (28), 165 (100); IR (KBr) 3071, 3009, 2961, 2899, 2838, 1605, 1506, 1465, 864, 755, 699 cm^{-1}. Anal. Calcd for $C_{25}H_{28}O_2Si$: C, 77.26; H, 7.27. Found: C, 77.09; H, 7.35.

Preparation of 1,1-bis[(4'-methoxy)phenyl]-2-iodo-2-phenylethene (9). Oil; ^{1}H NMR ($CDCl_3$) δ 7.31-6.51 (m, 13H), 3.84 (s, 3H), 3.69 (s, 3H); MS, m/z (relative intensity) 442 (M^+, 67), 315 (100), 239 (10); IR (neat) 3049, 2962, 2833, 1604, 1505, 1462, 803, 751, 704 cm^{-1}. Anal. Calcd for $C_{22}H_{19}O_2I$: C, 59.72; H, 4.33. Found: C, 59.91; H, 4.23.

Preparation of 4,4-bis[(4'-methoxy)phenyl]-3-phenylbut-3-en-2-ol (10a). mp 95-96 °C; ^{1}H NMR ($CDCl_3$) δ 7.28-6.48 (m, 13H), 4.89 (dq, J = 6.5 Hz, 6.3 Hz, 1H), 3.83 (s, 3H), 3.66 (s, 3H), 1.46 (d, J = 6.3 Hz, 1H), 1.20 (d, J = 6.5 Hz, 3H); MS, m/z (relative intensity) 342 (M^+-18, 100), 311 (26), 251 (35), 221 (27), 121 (16); IR (KBr) 3511, 2955, 2927, 2844, 1605, 1509, 1466, 839, 760, 706 cm^{-1}. Anal. Calcd for $C_{24}H_{24}O_3$: C, 79.96; H, 6.72. Found: C, 79.79; H, 6.61.

Preparation of 3,3-bis[(4'-methoxy)phenyl]-1,2-diphenylpropenol (10b). Oil; ^{1}H NMR ($CDCl_3$) δ 7.36-6.56 (m, 18H), 5.98 (d, J = 6.4 Hz, 1H), 3.82 (s, 3H), 3.67 (s, 3H), 1.91 (d, J = 6.4 Hz, 1H); MS, m/z (relative intensity) 404 (M^+-18, 100), 389 (5), 327 (6); IR (neat) 3396, 3059, 3028, 2932, 2835, 1605, 1508, 1452, 833, 758, 701 cm^{-1}. Anal. Calcd for $C_{29}H_{26}O_3$: C, 82.43; H, 6.21. Found: C, 82.61; H, 6.30.

Preparation of 5-methoxy-1-(4'-methoxy)phenyl-2,3-diphenylindene (11). To a methylene chloride (3 mL) solution of **10b** (0.08 g, 0.19 mmol) was added $AlCl_3$ (0.01 g, 0.28 mmol) at -78 °C, and the reaction mixture was allowed to warm to room temperature. After the reaction mixture was quenched with 10% HCl, solution was extracted with methylene chloride twice. The methylene chloride solution was dried with anhydrous K_2CO_3 and column chromatography (hexane : ethyl acetate = 20 : 1) provided 0.06 g (78% yield) of **11**: mp 144-145 °C; ^{1}H NMR ($CDCl_3$) δ 7.31-6.41 (m, 17H), 4.96 (s, 1H), 3.78 (s, 3H), 3.68 (s, 3H); MS, m/z (relative intensity) 404 (M^+, 100), 389 (7), 327 (9); IR (KBr) 3060, 2963, 2932, 2855, 1605, 1508, 1481, 803, 748, 699 cm^{-1}. Anal. Calcd for $C_{29}H_{24}O_2$: C, 86.10; H, 5.99. Found: C, 86.31; H, 5.92.

Preparation of 1,1-bis[(4'-methoxy)phenyl]-2,2-diphenylethene (12). To a DMF (5 mL) solution of iodobenzene (0.041 g, 0.20 mmol) and **4** (0.08 g, 0.13 mmol) was added $Pd(PPh_3)_4$ (10 mol%) and CuI (10 mol%), and the reaction mixture was stirred at room temperature for 5 h under argon atmosphere. After the reaction mixture was quenched with water and then washed with 5% KF solution and brine, solution was extracted with ether twice. The ether solution was dried and column chromatography (hexane : ethyl acetate = 50 : 1) provided 0.053 g (78% yield) of **12**: mp 132-133 °C; ^{1}H NMR ($CDCl_3$) δ 7.30-6.58 (m, 18H), 3.82 (s, 3H); MS, m/z (relative intensity) 392 (M^+, 100), 239 (10), 165 (8); IR (KBr) 3018, 2954, 2835, 1603, 1505, 1442, 833, 765, 699 cm^{-1}. Anal. Calcd for $C_{28}H_{24}O_2$: C, 85.67; H, 6.17. Found: C, 85.56; H, 6.23.

Preparation of 4,4-bis[(4'-methoxy)phenyl]-3-phenyl-3-buten-2-one (13a). To a toluene (5 mL) solution of acetyl chloride (0.016 g, 0.20 mmol) and **4** (0.08 g, 0.13 mmol) was added $PdCl_2(PPh_3)_2$ (10 mol%) and CuCN (10 mol%), and the reaction mixture was heated at 60 °C for 5 h under argon atmosphere. After the reaction mixture was quenched with water and then washed with 5% KF solution and brine, solution was extracted with ether twice. The ether solution was dried with anhydrous $MgSO_4$ and column chromatography (hexane : ethyl acetate = 8 : 1) provided 0.029 g (61% yield) of **13a**: mp 129-130 °C; ^{1}H NMR ($CDCl_3$) δ

7.22-6.59 (m, 13H), 3.83 (s, 3H), 3.74 (s, 3H), 2.05 (s, 3H); MS, m/z (relative intensity) 358 (M^+, 100), 315 (69), 269 (13), 239 (39), 226 (27), 165 (26), 135 (53), 113 (10), 77 (9); IR (KBr) 3005, 2961, 2837, 1679, 1604, 1509, 1463, 835, 757, 699 cm^{-1}. Anal. Calcd for $C_{24}H_{22}O_3$: C, 80.41; H, 6.19. Found: C, 80.59; H, 6.09.

Preparation of 3,3-bis[(4'-methoxy)phenyl]-1,2-diphenylpropenone (13b). mp 98-99 °C; ^1H NMR ($CDCl_3$) δ 7.88-7.79 (m, 2H), 7.27-6.49 (m, 16H), 3.69 (s, 3H), 3.62 (s, 3H); MS, m/z (relative intensity) 420 (M^+, 100), 315 (49), 269 (12), 228 (22), 165 (15), 135 (13), 105 (79); IR (KBr) 3012, 2959, 2837, 1660, 1602, 1504, 1444, 834, 765, 699 cm^{-1}. Anal. Calcd for $C_{29}H_{24}O_3$: C, 82.82; H, 5.76. Found: C, 82.59; H, 5.87.

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