Stereospecific Synthesis of Novel (*Z*)-β-Fluoro-β-trifluoromethyl-α-phenylvinylstannane and Its Cross-Coupling Reactions with Aryl Iodides

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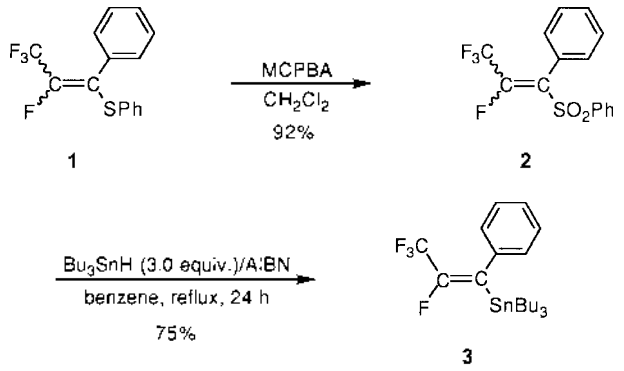
The considerable efforts have been paid to the development of trifluoromethylated building blocks because of their potential to give new synthetic routes to a variety of trifluoromethylated compounds, some of which exhibit unique biological properties in the areas of agrochemicals, pharmaceuticals and material science.[1] In the course of our synthetic studies on trifluoromethylated building blocks, we recently synthesized a new α-trifluoromethylated β,β-diphenylvinylstannane and utilized this compound to prepare trifluoromethylated triphenylethene derivatives.[2] However, we also need β-trifluoromethylated vinylstannane compounds to provide a diversity of synthesis of trifluoromethylated compounds. Of particular interests in this conjuction is (*Z*)-β-fluoro-β-trifluoromethyl-α-phenylvinylstannane which is a quite useful building block for stereospecific synthesis of β-fluoro-β-trifluoromethylated enones or olefins *via* the conversion of tributylstannyl group. Although several papers described about chemistry of β-trifluoromethylated vinylmetal reagents such as cadmium,[3] copper,[4] lithium,[5] mercury[6] and zinc,[7] methodology for the preparation of β-trifluoromethylated vinylstannane reagent has not been exploited. Knunyants prepared β,β-bis(trifluoromethyl)-vinylmercury reagent *via* transmetallation of β,β-bis(trifluoromethyl)vinyllithium reagent with mercury(II) chloride in low to moderate yield.[6] Burton synthesized several stable β-trifluoromethylated vinylmetal reagents.[3,7] β-Trifluoromethylated vinylcadmium reagents were prepared in high yields from the direct reaction of β-trifluoromethylated vinyl bromides or iodides with cadmium in DMF.[3] However, the synthetic utilities of this reagent were quite limited. Similarly, the stable β-trifluoromethylated vinylzinc reagents were also prepared in high yields from the direct reaction of β-trifluoromethylated vinyl iodides with zinc in tryglyme.[7] The coupling reactions of β-trifluoromethylated vinylzinc reagents with aryl iodides[7a,7b] and trifluorovinyl iodides[7c] in the presence of palladium catalyst have been quite successful. Transmatallation of β-trifluoromethylated vinylzinc reagents with copper bromide provided β-trifluoromethylated vinylcopper reagents in high yields.[4] These vinylcopper reagents participated in a variety of alkylation, coupling reaction with aryl and vinyl iodides, and acylation reactions. Recently, β-trifluoromethylated vinyllithium reagents was prepared *via* metal-hydrogen exchange reaction and utilized for the synthesis of CF_3 substituted allylic alcohols.[5] Since all of these β-trifluoromethylated vinylmetal reagents must to be prepared and utilized in solution and also are moisture sensitive, handling is not easy for those reagents. Therefore, we wish to describe a new and efficient method for the synthesis of novel (*Z*)-β-fluoro-β-trifluoromethyl-α-phenylvinylstannane reagent and cross coupling reactions with aryl iodides to give 1-fluoro-1-trifluoromethylalkene derivatives.

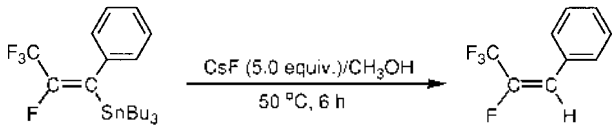
A novel starting material, (*Z*)-β-fluoro-β-trifluoromethyl-α-phenylvinylstannane **3**, was prepared *via* two steps from an *E* and *Z* isomeric mixture (84/16) of β-fluoro-β-trifluoromethyl-α-phenylvinylsulfide **1**.[8] Oxidation of **1** with MCPBA (2.5 equiv.) in CH_2Cl_2 at reflux temperature for 24 h afforded an *E* and *Z* isomeric mixture (84/16) of β-fluoro-β-trifluoromethyl-α-phenylvinylsulfone **2** in 92% yield.[2] Treatment of **2** with Bu_3SnH (3.0 equiv.)/AIBN (10 mol%) in benzene at reflux for 24 h resulted in the formation of **3** in 75% yield. Only one stereoisomer was observed in the GC-MS spectroscopy and the reducing product, (*E*)-2,3,3,3-tetrafluoro-1-phenylpropene, was not observed. The use of less than 3.0 equiv. of tributyltin hydride caused to recover some amount of **2**.



1 **2** **3**

The assignment of stereoisomer **3** was made by the comparison with ^1H and ^{19}F NMR of authentic sample[9] after the conversion to reducing product **4** which can be obtained from the reaction of **3** with CsF (5 equiv.) in methanol at 50 °C for 6 h. It was found that this reducing process from the vinylstannane reagents was stereospecific reaction and the reaction was proceeded with the retention of configuration.[10] ^{19}F NMR spectrum of **4** exhibited a characteristic doublet of quartet ($J_{F,H}$ = 20.4 Hz, J_{F,CF_3} = 9.9 Hz) at -125.62 ppm and ^1H NMR showed a doublet ($J_{H,F}$ = 21.0 Hz) at 6.77 ppm. It is

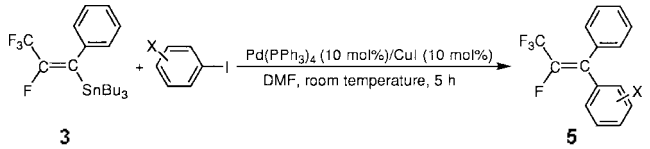
postulated that the appearance of doublet in ^1H and ^{19}F NMR is due to the cis H-F coupling.



3 4

The carbon-carbon bond formation *via* tributylstannyl group with electrophiles in the presence of palladium catalyst[11] is one of the most advanced process in organic synthesis. Thus, we introduced this process to the reaction of **3** with aryl iodides bearing a substituent on benzene ring in the presence of several palladium catalysts. No cross-coupling product was obtained by using Pd catalyst such as $Pd(PPh_3)_4$ or $Pd(PPh_3)_2Cl_2$ in THF, DMF, or toluene. When **3** was reacted with iodobenzene in the presence of a mixture of 10 mol% $Pd(PPh_3)_4$ and 10 mol% CuI in DMF at room temperature for 5 h, however, the cross-coupling product **5a** was obtained in 70% yield. The use of bromobenzene instead of iodobenzene in the same reaction provided a trace amount of **5a** along with several unidentified adducts. Aryl iodides bearing a bromo, chloro, fluoro, methoxy, methyl, nitro or trifluoromethyl group on *para* or *meta*-position of benzene ring underwent the cross-coupling reaction with **3** under the same reaction condition, and the corresponding coupling products were obtained in 61-82% yields. The reaction of **3** with 2-iodotoluene under the same reaction condition also afforded the coupling product **5m** in 71% yield, but the same reaction of **3** with 2-iodoanisole and 2-iodobenzotrifluoride provided the only trace amount of corresponding products. All of these coupling reactions proceeded with retention of configuration at the double bond except for the reaction with *para*-iodonitrobenzene in which an *E* and *Z* isomeric mixture (75/25) of coupling product was obtained. The experimental results are summarized in Table 1.

Table 1. The cross-coupling reactions of **3** with aryl iodides

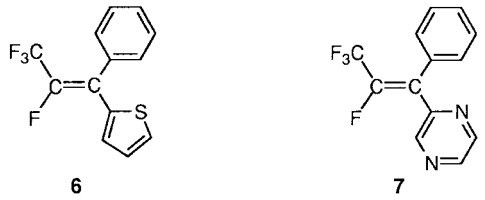


3 5

Compound	X	Yield (%)[a]
5a	H	70
5b	*p*-Br	68
5c	*p*-Cl	67
5d	*p*-F	61
5e	*p*-OCH_3	82
5f	*p*-CH_3	71
5g	*p*-NO_2	77[b]
5h	*p*-CF_3	75
5i	*m*-Br	71
5j	*m*-OCH_3	79
5k	*m*-CH_3	68
5l	*m*-CF_3	77
5m	*o*-CH_3	71
5n	*o*-OCH_3	–[c]
5o	*o*-CF_3	–[c]

[a]Isolated yields. [b]An isomeric mixture of products (75:25) was obtained. [c]A trace amount of product was obtained.

The reactions of **3** with iodo substituted heterocyclic compounds were also examined. Therefore, when **3** was reacted with 2-iodothiophene and 2-iodopyrazine under the same reaction condition, the corresponding coupling products **6** and **7** were obtained in 63% and 65% yields, respectively. Acylation and vinylation of **3** *via* cross-coupling reactions are now in progress.



6 7

Experimental Section

Genaral. ^1H NMR and ^{19}F NMR spectra were recorded on a 100 MHz Bruker AC-100F NMR spectrometer with tetramethylsilane (TMS) and $CFCl_3$ as an internal standard, respectively and the upfield as negative. All chemical shifts (δ) are expressed in parts per million and coupling constant (J) are given in Herz. Infrared spectra were determined on a Mattson Genesis series FT High Resolution Spectrophotometer. Mass spectra were obtained by using Hewlett-Packard 5890 GC/5970B MSD (EI, 70 eV). Melting points were determined in open capillary tubes and are uncorrected.

Commercially available reagents were purchased from Aldrich, Lancaster, Tokyo Kasei and Fluorochem. All solvent were dried by general purification method.

1-Tributylstannanyl-2,3,3,3-tetrafluoro-1-phenylpropene (3) To a dry benzene (50 mL) solution of **2** (2.64 g, 8 mmol) was added tributyltin hydride (24 mmol) and AIBN (catalytic amount) and the reaction mixture was heated at 80-90 °C for 24 h. After cooling, the reaction mixture was concentrated and then the residue was chromatographed on SiO_2 column. Elution with n-hexane provided **3** in 75% yield. **3**: oil; ^1H NMR ($CDCl_3$) δ 7.37-6.89 (m, 5H), 1.72-0.71 (m, 27H); ^{19}F NMR ($CDCl_3$) δ -62.40 (d, J = 10.2 Hz, 3F), -104.8 (q, J = 10.4 Hz, 1F); MS, *m/z* (relative intensity) 479 (M^+, 1), 423 (4), 310 (4), 291 (7), 253 (100), 251 (77), 195 (5), 177 (26), 151 (98), 121 (7), 41 (9), 29 (7); IR (CCl_4) 3078, 3061, 2924, 2958, 2925, 2872, 1671, 1596, 1554, 1490, 1378, 1310, 1196, 1143, 1093, 1001, 961, 893, 866, 698, 670 cm^{-1}. Anal. Calcd for $C_{21}H_{32}F_4Sn$: C, 52.64; H, 6.73. Found: C, 52.29; H, 6.65.

2,3,3,3-Tetrafluoro-1,1-diphenylpropene (5a) To a DMF (5 mL) solution of iodobenzne (0.306 g, 1.50 mmol) and **3** (0.479 g, 1.00 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 chromatographed on SiO_2 column. Elution with hexane provided 0.186 g of 2,3,3,3-tetrafluoro-1,1-diphenylpropene **5a** in 70% yield. **5a**: oil; ^{1}H NMR ($CDCl_3$) δ 7.42-7.26 (m, 10H); ^{19}F NMR ($CDCl_3$) δ -64.87 (d, J = 9.9 Hz, 3F), -129.29 (q, J = 9.8 Hz, 1F); MS, *m/z* (relative intensity) 266 (M^+, 100), 245 (15), 196 (85), 177 (17), 165 (29), 98 (15), 51 (14); IR (CCl_4) 3062, 1731, 1549, 1344, 1282, 1195, 1143, 1100, 1010, 699 cm^{-1}. Anal. Calcd for $C_{15}H_{10}F_4$: C, 67.67; H, 3.79. Found: C, 67.34; H, 3.75.

5b: oil; ^{1}H NMR ($CDCl_3$) δ 7.55-7.00 (m, 9H); ^{19}F NMR ($CDCl_3$) δ -64.95 (d, J = 9.8 Hz, 3F), -128.16 (q, J = 9.9 Hz, 1F); MS, *m/z* (relative intensity) 346 (M^-+2, 31), 344 (M^+, 32), 245 (20), 196 (100); IR (CCl_4) 3082, 3033, 1727, 1585, 1550, 1490, 1338, 1280, 1206, 1195, 1145, 1101, 1075, 1012, 700 cm^{-1}. Anal. Calcd for $C_{15}H_9BrF_4$: C, 52.20; H, 2.63. Found: C, 52.01; H, 2.59.

5c: oil; ^{1}H NMR ($CDCl_3$) δ 7.68-7.12 (m, 9H); ^{19}F NMR ($CDCl_3$) δ -64.92 (d, J = 9.9 Hz, 3F), -128.35 (q, J = 9.9 Hz, 1F); MS, *m/z* (relative intensity) 302 (M^-+2, 33), 300 (M^+, 100), 265 (17), 245 (13), 196 (79). Anal. Calcd for $C_{15}H_9ClF_4$: C, 59.92; H, 3.02. Found: C, 59.53; H, 3.05.

5d: oil; ^{1}H NMR ($CDCl_3$) δ 7.43-6.94 (m, 9H); ^{19}F NMR ($CDCl_3$) δ -64.83 (d, J = 10.0 Hz, 3F), -112.18 (s, 1F), -129.35 (q, J = 9.9 Hz, 1F); MS, *m/z* (relative intensity) 284 (M^-, 100), 214 (46), 183 (34), 107 (11). Anal. Calcd for $C_{15}H_9F_5$: C, 63.34; H, 3.19. Found: C, 63.03; H, 3.14.

5e: oil; ^{1}H NMR ($CDCl_3$) δ 7.42-6.81 (m, 9H), 3.80 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -64.60 (d, J = 10.1 Hz, 3F), -131.01 (q, J = 10.0 Hz, 1F); MS, *m/z* (relative intensity) 296 (M^+, 100), 277 (4), 226 (7), 212 (10), 195 (35), 183 (31), 152 (6); IR (CCl_4) 3061, 3004, 2957, 2930, 2855, 1659, 1606, 1564, 1512, 1463, 1342, 1287, 1254, 1194, 1140, 1098, 1038, 700 cm^{-1}. Anal. Calcd for $C_{16}H_{12}F_4O$: C, 64.86; H, 4.08. Found: C, 64.73; H, 4.02.

5f: oil; ^{1}H NMR ($CDCl_3$) δ 7.42-7.00 (m, 9H), 2.35 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -64.80 (d, J = 10.0 Hz, 3F), -130.01 (q, J = 9.9 Hz, 1F); MS, *m/z* (relative intensity) 280 (M^+, 100), 265 (24), 245 (12), 211 (26), 196 (86), 179 (27), 133 (5), 128 (6), 91 (11); IR (CCl_4) 3063, 3028, 2960, 2928, 2873, 2857, 1730, 1579, 1549, 1463, 1379, 1340, 1284, 1206, 1140, 1121, 1073, 1006, 977, 702 cm^{-1}. Anal. Calcd for $C_{16}H_{12}F_4$: C, 68.57; H, 4.32. Found: C, 68.70; H, 4.24.

5g: oil; ^{1}H NMR ($CDCl_3$) δ 8.31-7.26 (m, 9H); ^{19}F NMR ($CDCl_3$) δ -64.90 (d, J = 9.8 Hz, 3F, one isomer), -65.10 (q, J = 9.9 Hz, 3F, other isomer), -125.30 (q, J = 9.7 Hz, 1F, one isomer), -126.30 (q, J = 9.8 Hz, 1F, other isomer); MS, *m/z* (relative intensity) 311 (M^+, 100), 264 (18), 245 (6), 225 (5), 214 (5), 196 (33), 183 (7); IR (CCl_4) 3060, 3028,1728, 1665, 1603, 1527, 1494, 1447, 1341, 1284, 1261, 1196, 1149, 1103, 1101, 938, 701 cm^{-1}. Anal. Calcd for $C_{15}H_9F_4NO_2$: C, 57.89; H, 2.91. Found: C, 57.60; H, 2.97.

5h: oil; ^{1}H NMR ($CDCl_3$) δ 7.89-6.96 (m, 9H); ^{19}F NMR ($CDCl_3$) δ -63.46 (m, 6F), -127.12 (q, J = 9.3 Hz, 1F); MS, *m/z* (relative intensity) 344 (M^+, 100), 315 (18), 265 (31), 245 (27), 233 (10), 196 (58); IR (CCl_4) 3063, 3031, 1717, 1663, 1619, 1598, 1492, 1445, 1343, 1286, 1208, 1171, 1142, 1069, 1019, 936, 723, 701 cm^{-1}. Anal. Calcd for $C_{16}H_9F_7$: C, 57.50; H, 2.71. Found: C, 57.81; H, 2.75.

5i: oil; ^{1}H NMR ($CDCl_3$) δ 7.87-6.96 (m, 9H); ^{19}F NMR ($CDCl_3$) δ -65.00 (d, J = 9.9 Hz, 3F), -127.40 (q, J = 9.4 Hz, 1F); MS, *m/z* (relative intensity) 346 (M^++2, 70), 344 (M^-, 72), 265 (11), 245 (22), 196 (100), 170 (7), 122 (8); IR (CCl_4) 3084, 3063, 1727, 1592, 1560, 1474, 1336, 1280, 1195, 1143, 1104, 999, 908, 890, 866, 701 cm^{-1}. Anal. Calcd for $C_{15}H_9BrF_4$: C, 52.20; H, 2.63. Found: C, 52.07; H, 2.60.

5j: oil; ^{1}H NMR ($CDCl_3$) δ 7.42-6.80 (m, 9H), 3.77 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -64.92 (d, J = 9.6 Hz, 3F), -128.41 (q, J = 9.5 Hz, 1F); MS, *m/z* (relative intensity) 296 (M^-, 100), 277 (9), 265 (11), 245 (9), 227 (23), 212 (37), 196 (47), 183 (62), 165 (6), 152 (8); IR (CCl_4) 3086, 3064, 2957, 2854, 2837, 1580, 1551, 1488, 1464, 1447, 1431, 1394, 1339, 1289, 1201, 1196, 1143, 1101, 1054, 1008, 975, 698 cm^{-1}. Anal. Calcd for $C_{16}H_{12}F_4O$: C, 64.86; H, 4.08. Found: C, 64.58; H, 4.00.

5k: oil; ^{1}H NMR ($CDCl_3$) δ 7.38-7.10 (m, 9H), 2.32 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -64.90 (d, J = 10.0 Hz, 3F), -129.02 (q, J = 9.9 Hz, 1F); MS, *m/z* (relative intensity) 280 (M^-, 100), 265 (31), 245 (10), 196 (45), 179 (10); IR (CCl_4) 3061, 3028, 2958, 2925, 2856, 1729, 1583, 1549, 1493, 1445, 1338, 1310, 1288, 1201, 1143, 1103, 1002, 978, 880, 663 cm^{-1}. Anal. Calcd for $C_{16}H_{12}F_4$: C, 68.57; H, 4.32. Found: C, 68.76; H, 4.27.

5l: oil; ^{1}H NMR ($CDCl_3$) δ 7.95-6.96 (m, 9H); ^{19}F NMR ($CDCl_3$) δ -63.36 (m, 6F), -127.47 (q, J = 9.3 Hz, 1F); MS, *m/z* (relative intensity) 344 (M^+, 100), 315 (18), 265 (28), 245 (29), 233 (11), 224 (12), 196 (61); IR (CCl_4) 3036, 3030, 1717, 1685, 1575, 1492, 1445, 1323, 1272, 1208, 1170, 1139, 1078, 1032, 944, 890, 699 cm^{-1}. Anal. Calcd for $C_{16}H_9F_7$: C, 57.50; H, 2.71. Found: C, 57.76; H, 2.77.

5m: oil; ^{1}H NMR ($CDCl_3$) δ 7.37-7.03 (m, 9H), 2.28 (s, 3H); ^{19}F NMR ($CDCl_3$) δ -65.20 (d, J = 10.2 Hz, 3F), -123.70 (q, J = 10.2 Hz, 1F); MS, *m/z* (relative intensity) 280 (M^-, 52), 196 (413), 179 (100), 133 (7); IR (CCl_4) 3065, 3024, 2927, 2857, 1555, 1446, 1439, 1340, 1292, 1267, 1145, 1123, 1094, 695 cm^{-1}. Anal. Calcd for $C_{16}H_{12}F_4$: C, 68.57; H, 4.32. Found: C, 68.33; H, 4.21.

6: oil; ^{1}H NMR ($CDCl_3$) δ 7.51-6.86 (m, 8H); ^{19}F NMR ($CDCl_3$) δ -64.14 (d, J = 9.8 Hz, 3F), -124.44 (q, J = 9.7 Hz, 1F); MS, *m/z* (relative intensity) 272 (M^-, 100), 202 (43), 171 (25). Anal. Calcd for $C_{13}H_8F_4S$: C, 57.35; H, 2.96. Found: C, 57.11; H, 2.87.

7: oil; ^{1}H NMR ($CDCl_3$) δ 8.62-7.07 (m, 8H); ^{19}F NMR ($CDCl_3$) δ -65.42 (d, J = 9.1 Hz, 3F), -124.92 (q, J = 9.1 Hz, 1F); MS, *m/z* (relative intensity) 268 (M^-, 51), 267 (100), 217 (11), 199 (41). Anal. Calcd for $C_{13}H_8F_4N_2$: C, 58.21; H, 3.01. Found: C, 57.97; H, 3.07.

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