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A Facile Stereocontrolled Approach to CF_3-Substituted Triarylethenes: Synthesis of Panomifene

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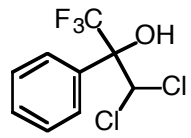
General information. ^{1}H, ^{13}C and ^{19}F NMR spectra were recorded on Varian Mercury 200 (^{1}H 200 MHz, ^{13}C 50 MHz, ^{19}F 188 MHz) and JEOL EX-270 (^{1}H 270 MHz, ^{13}C 67.5 MHz) spectrometers in $CDCl_3$ with chemical shifts referenced to internal standards Me_4Si (0 ppm, ^{1}H), $CDCl_3$(7.26 ppm ^{1}H, 77.0 ppm ^{13}C), $CFCl_3$ (0 ppm ^{19}F). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; brs, broad singlet for ^{1}H and ^{19}F NMR data. Mass spectra were performed on JEOL JMS-700 spectrometer. Elemental analyses were carried out by the Elemental Analysis Center of Kyoto University. TLC analyses were performed by means of Merck Kieselgel 60 F_{254} and column chromatography was carried out using Merck Kieselgel 60 (230-400 mesh). Anhydrous tetrahydrofuran was purchased from Kanto Chemicals. 3,3-Dichloro-1,1,1-trifluoropropan-2-one was generously provided by Central Glass Co. Ltd. Phenylmagnesium bromide (1.0 M in THF), 4-methoxyphenylmagnesium bromide (0.5 M in THF), 4-chlorophenylmagnesium bromide (1.0 M in Et_2O), and 4-fluorophenylmagnesium bromide (1.0 M in THF) were purchased from Aldrich and used as received. Phenyllithium in cyclohexane-Et_2O and *tert*-butyllithium in pentane were purchased from Kanto Chemicals, which were titrated prior to use. Bis(pinacolato)diboron was purchased from Frontier Science. Di(tri-*tert*-butyl)phosphine palladium was purchased from Strem Chemicals. All other reagents were obtained from commercial suppliers and used as received. All reactions involving air sensitive reagents were carried out under an argon atmosphere, using standard Schlenk technique.

Genneral procedure for preparation of Dichlorohydrin 3:

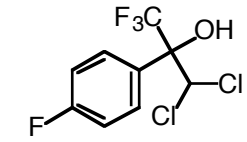
To a THF or Et_2O solution of arylmagnesium bromide (30 mmol) was added freshly distilled 3,3-dichloro-1,1,1-trifluoropropan-2-one (3.2 mL, 28 mmol) dropwise at room temperature with maintaining the reaction temperature below 40 ºC by use of water bath. The resulting mixture was stirred overnight quenching with saturated aqueous NH_4Cl solution. The aqueous layer was extracted with diethyl ether three times. The combined organic layer was washed with saturated NaCl aqueous solution, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was

purified by column chromatography on silica gel to give dichlorohydrin **3**.

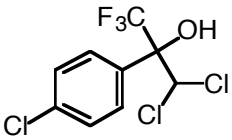
1,1-Dichloro-3,3,3-trifluoro-2-phenylpropan-2-ol (3a): The spectral data was reported in our previous publication. [M. Shimizu, T. Fujimoto, H. Minezaki, T. Hata, T. Hiyama, *J. Am. Chem. Soc.* **2001**, *123*, 6947]



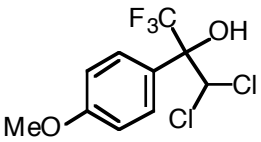
1,1-Dichloro-2-(4-fluorophenyl)-3,3,3-trifluoropropan-2-ol (3b): 54% yield, colorless oil. R_f 0.45 (hexane/ethyl acetate = 5 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 3.71 (s, 1H), 6.30 (s, 1H), 7.13 (m, 2H), 7.60 (m, 2H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 73.7, 79.8 (q, *J* = 28.1 Hz), 115.7 (d, *J* = 27.9 Hz), 121.5 (q, *J* = 286.2 Hz), 127.8 (d, *J* = 6.7 Hz), 129.8, 164.9 (d, *J* = 248.3 Hz). ^{19}F NMR (188 MHz, $CDCl_3$, □): -73.1 (s, 3F), -111.9 (m, 1F). EIMS (70 eV) *m*/*z*: 280 (0.1, M^++4), 278 (0.4, M^++2), 276 (0.7, M^+), 193 (100). Anal. Calcd for $C_9H_6Cl_2F_4O$: C, 39.02; H, 2.18. Found: C, 39.25; H, 2.23.



1,1-Dichloro-2-(4-chlorophenyl)-3,3,3-trifluoropropan-2-ol (3c): 46% yield, colorless viscous oil. R_f 0.4 (hexane/ethyl acetate = 5 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 3.61 (s, 1H), 6.30 (s, 1H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.53 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 73.5, 79.8 (q, *J* = 28.1 Hz), 125.6 (q, *J* = 286.2 Hz), 127.2, 128.7, 132.4, 135.6. ^{19}F NMR (188 MHz, $CDCl_3$, □): -73.1. EIMS (70 eV) *m*/*z*: 296 (0.6, M^++4), 294 (2, M^++2), 292 (2, M^+), 209 (100). Anal. Calcd for $C_9H_6Cl_3F_3O$: C, 36.83; H, 2.06. Found: C, 36.67; H, 2.25.



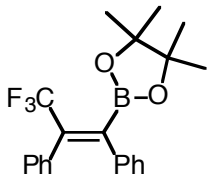
1,1-Dichloro-2-(4-methoxyphenyl)-3,3,3-trifluoropropan-2-ol (3d): 58% yield, white solid, m.p. 60.0–61.2 °C (dec). R_f 0.32 (hexane/ethyl acetate = 5 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 3.52 (s, 1H), 3.84 (s, 1H), 6.30 (s, 1H), 6.94 (d, *J* = 8.8 Hz, 2H), 7.53 (d, *J* = 8.8 Hz, 2H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 55.2, 73.9, 79.8 (q, *J* = 28.5 Hz), 113.8, 125.6 (q, *J* = 284.4 Hz), 125.9, 127.0, 160.1. ^{19}F NMR (188 MHz, $CDCl_3$, □): -73.2. EIMS (70 eV) *m*/*z*: 292 (0.5, M^++4), 290 (3, M^++2), 288 (4, M^+), 205 (100). Anal. Calcd for $C_{10}H_9Cl_2F_3O_2$: C, 41.55; H, 3.14. Found: C, 42.01; H, 3.18.



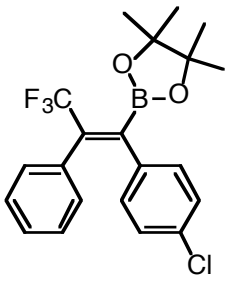
General procedure for the preparation of alkenylboronates 5:

To a solution of *p*-substituted bromobenzene (15.5 mmol) in THF (30 mL) was added a 1.00 M pentane solution of *tert*-butyllithium (31.0 mmol, 31.0 mL) at –78 ºC over a period of 0.5 h using a syringe pump. The resulting yellow-colored solution was stirred at –78 ºC for additional 1 h. Then, **3** (5.0 mmol) was added to a THF solution of the prepared aryllithium at –78 ºC. (In case of **3c** and **3d**, the compounds were added as a THF solution.) The reaction mixture was allowed to warm to room temperature over a period of 2 h, and quenched with saturated NH_4Cl aqueous solution. The aqueous layer was extracted with diethyl ether three times. The combined organic layer was washed by saturated NaCl aqueous solution, dried over $MgSO_4$, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography to afford **5**.

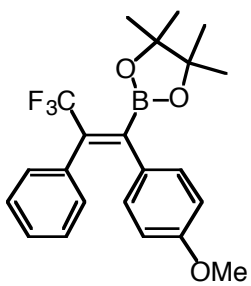
4,4,5,5-Tetramethyl-2-[(1,2-diphenyl-3,3,3-trifluoro)propenyl]-1,3,2-dioxaborolane (5a): 63% yield, a pale yellow solid, m.p. 110.4–111.5 °C (dec). R_f 0.41 (hexane/ethyl acetate = 10 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 1.26 (s, 12H), 7.01-7.15 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 24.6, 84.6, 125.9 (q, J = 272.1 Hz), 127.0, 127.8, 127.9 (2C), 128.4, 130.2, 133.3, 135.9 (q, J = 27.7 Hz), 142.0. ^{19}F NMR (188 MHz, $CDCl_3$, δ): -62.2. EIMS (70 eV) *m*/*z*: 376 (2, M^++2), 375 (16, M^++1), 374 (73, M^+), 189 (100). Anal. Calcd for $C_{21}H_{22}BF_3O_2$: C, 67.40; H, 5.93. Found: C, 67.35; H, 5.96.



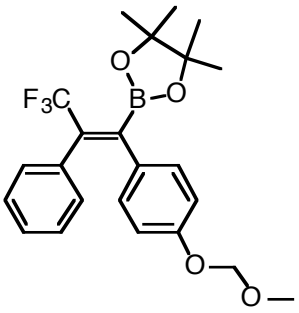
4,4,5,5-Tetramethyl-2-[1-(4-chlorophenyl)-3,3,3-trifluoro-2-phenylpropenyl]-1,3,2-dioxaborolane (5b): 73% yield, a white solid, m.p. 93.3–94.5 °C (dec). R_f 0.44 (hexane/ethyl acetate = 10 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 1.29 (s, 12H), 6.99 (m, 2H), 7.07 (m, 4H), 7.20 (m, 3H). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 24.5, 98.5, 121.6 (q, J = 272.3 Hz), 127.9 (2C), 128.1, 129.7, 129.9, 132.9, 135.5, 135.9, 136.7 (q, J = 27.7 Hz), 140.5. ^{19}F NMR (188 MHz, $CDCl_3$, δ): -62.3. EIMS (70 eV) *m*/*z*: 410 (32, M^++2), 409 (28, M^++1), 408 (95, M^+), 189 (100). Anal. Calcd for $C_{21}H_{21}BClF_3O_2$: C, 61.72; H, 5.18. Found: C, 61.78; H, 5.18.

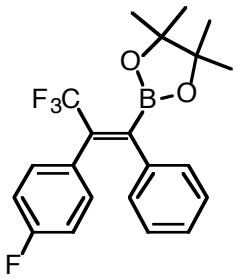


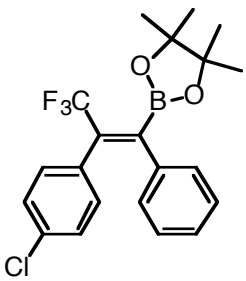
4,4,5,5-Tetramethyl-2-[3,3,3-trifluoro-1-(4-methoxyphenyl)-2-phenylpropenyl]-1,3,2-dioxaborolane (5c): 78% yield, a white solid, m.p. 106.0–107.0 °C (dec). R_f 041 (hexane/ethyl acetate = 5 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, δ): 1.31 (s, 12H), 3.69 (s, 3H), 6.63 (d, J = 9.0 Hz, 2H), 6.96 (d, J = 9.0 Hz, 2H), 7.16 (m, 5H). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 24.7, 55.0, 84.5, 113.4, 122.0 (q, J = 270.3 Hz), 127.7, 128.0, 129.2, 129.7, 130.2, 133.6, 135.2 (q, J = 27.4 Hz),



141.0, 158.5. ^{19}F NMR (188 MHz, $CDCl_3$, □): -61.8. EIMS (70 eV) *m*/*z*: 406 (3, M^++2), 405 (23, M^++1), 404 (100, M^+), 288 (48). Anal. Calcd for $C_{22}H_{24}BF_3O_3$: C, 65.37; H, 5.98. Found: C, 65.19; H, 5.96.

4,4,5,5-Tetramethyl-2-[3,3,3-trifluoro-1-(4-methoxymethoxyphenyl)-2-phenylpropenyl]-1,3,2-dioxaborolane (5d):  75% yield, a white solid, m.p. 89.3–90.3 °C. R_f 0.35 (hexane/ethyl acetate = 10 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 1.31 (s, 12H), 3.43 (s, 3H), 5.07 (s, 2H), 6.75 (d, *J* = 8.7 Hz, 2H), 6.94 (d, *J* = 8.7 Hz, 2H), 7.10 (m, 2H), 7.21 (m, 3H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 24.7, 56.1, 84.6, 94.3, 115.6, 122.2 (q, *J* = 272.0 Hz), 127.8, 127.9, 129.9, 130.0, 130.2, 133.6, 135.1 (q, *J* = 28.4 Hz), 141.1, 156.3. ^{19}F NMR (188 MHz, $CDCl_3$, □): -61.6. EIMS (70 eV) *m*/*z*: 436 (4, M^++2), 435 (25, M^++1), 434 (100, M^+), 404 (17, M^+-CH_2O). Anal. Calcd for $C_{23}H_{26}BF_3O_4$: C, 63.61; H, 6.03. Found: C, 63.40; H, 6.00.

4,4,5,5-Tetramethyl-2-[3,3,3-trifluoro-2-(4-fluorophenyl)-1-phenylpropenyl]-1,3,2-dioxaborolane (5e):  65% yield, a white solid, m.p. 143.2–144.0 °C. R_f 0.35 (hexane/ethyl acetate = 10 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 1.28 (s, 12H), 6.84 (t, *J* = 8.9 Hz, 2H), 7.00-7.12 (m, 7H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 24.6, 84.6, 114.9, 115.2, 121.8 (q, *J* = 272.5 Hz), 127.5 (d, *J* = 22.3 Hz), 128.3, 129.2, 131.9 (d, *J* = 7.8 Hz), 134.7 (q, *J* = 28.9 Hz), 137.0, 142.2, 160.3 (d, *J* = 246.6 Hz). ^{19}F NMR (188 MHz, $CDCl_3$, □): -62.4 (s, 3F), -113.6 (m, 1F). EIMS (70 eV) *m*/*z*: 394 (2, M^++2), 393 (16, M^++1), 392 (74, M^+), 207 (100). Anal. Calcd for $C_{21}H_{21}BF_4O_2$: C, 64.31; H, 5.40. Found: C, 64.30; H, 5.48.

4,4,5,5-Tetramethyl-2-[2-(4-chlorophenyl)-3,3,3-trifluoro-1-phenylpropenyl]-1,3,2-dioxaborolane (5f):  80% yield, a white solid, m.p. 148.4–149.5 °C (dec). R_f 0.39 (hexane/ethyl acetate = 10 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 1.28 (s, 12H), 7.00 (m, 4H), 7.16 (m, 5H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 24.5, 84.6, 125.6 (q, *J* = 272.3 Hz), 127.1, 127.9, 128.1, 128.2, 131.4, 131.7, 133.8, 134.9 (q, *J* = 28.1 Hz), 136.7, 142.7. ^{19}F NMR (188 MHz, $CDCl_3$, □): -62.5. EIMS (70 eV) *m*/*z*: 410 (33, M^++2), 409 (28, M^++1), 408 (94, M^+), 189 (100). Anal. Calcd for $C_{21}H_{21}BclF_3O_2$: C, 61.72; H, 5.18. Found: C, 61.44; H, 5.07.

4,4,5,5-Tetramethyl-2-[3,3,3-trifluoro-2-(4-methoxyphenyl)-1-phenylpropenyl]-1,3,2-dioxaborolane (5g): 63% yield, a white solid, m.p. 138.0–139.0 °C (dec). R_f 0.25 (hexane/ethyl acetate = 10 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 1.28 (s, 12H), 3.66 (s, 3H), 6.67 (d, *J* = 8.8 Hz, 2H), 7.10 (m, 7H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 24.5, 56.9, 83.6, 113.3, 125.4 (q, *J* = 272.4 Hz), 126.8, 127.9, 128.4, 131.3, 134.5, 135.3 (q, *J* = 28.4 Hz), 137.4, 142.2, 158.9. ^{19}F NMR (188 MHz, $CDCl_3$, □): -62.2. EIMS (70 eV) *m*/*z*: 406 (3, M^++2), 405 (24, M^++1), 404 (100, M^+), 288 (44). Anal. Calcd for $C_{22}H_{24}BF_3O_3$: C, 65.37; H, 5.98. Found: C, 65.53; H, 6.02.

General Procedure for cross coupling reaction of alkenylboronate 5 with aryl iodide:

A flame-dried Schlenk tube (20 mL) was charged with alkenylboronate **5** (0.20 mmol), Pd(*t*-$Bu_3P)_2$ (5.1 mg, 0.010 mmol), aryl iodide (0.22 mmol), dioxane (0.4 mL), and 5 M Cs_2CO_3 aqueous solution (120 □L, 0.60 mmol) in this order with the gentle flow of argon gas. The tube was then capped with a glass stopper and heated at 50 ºC overnight with monitoring the reaction by TLC analysis. The reaction mixture was allowed to cool to room temperature and diluted with Et_2O (5 mL). The organic layer was washed with saturated NH_4Cl aqueous solution (2 mL) and saturated NaCl aqueous solution (2 mL), and dried over $MgSO_4$. Evaporation of the organic solvent *in vacuo* afforded the crude product which was purified by short silica gel column chlomatography to give **6**.

3,3,3-Trifluoro-1,1,2-triphenylpropene (6a): 94% yield, a white solid, m.p. 83.8–84.6 °C. R_f 0.51 (hexane/ethyl acetate = 10 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 6.88-6.94 (m, 2H), 6.98-7.03 (m, 2H), 7.16-7.25 (m, 5H), 7.28-7.36 (m, 5H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 121.5 (q, *J* = 273.2 Hz), 127.2, 127.6, 127.7, 127.8 (2C), 127.9, 128.1 (q, *J* = 32.3 Hz), 128.4 (q, *J* = 2.2 Hz), 129.5, 131.3, 134.9, 140.3, 140.8, 150.2. ^{19}F NMR (188 MHz, $CDCl_3$, □): -56.2. EIMS (70 eV) *m*/*z*: 326 (3, M^++2), 325 (24, M^++1), 324 (100, M^+), 255 (M^+-CF_3, 53). HRMS-EI (*m*/*z*): M^+ calcd for $C_{21}H_{15}F_3$, 324.1126; found, 324.1124.

(*Z*)-1-(4-Ethoxycarbonylphenyl)-3,3,3-trifluoro-1,2-diphenylpropene (6b): 92% yield, a pale yellow solid, m.p. 95.0 –96.0 °C. R_f 0.35 (hexane/ethyl acetate = 5 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 1.39 (t, *J* = 7.2 Hz, 3H), 4.40 (q, *J* = 7.2 Hz, 2H), 6.87-6.92 (m, 2H), 7.02-7.06 (m, 3H), 7.21-7.25 (m, 5H), 7.38 (d, *J* = 8.2 Hz, 2H), 8.04 (d, *J* = 8.2 Hz, 2H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 14.4, 61.1, 121.3 (q, *J* = 273.2 Hz), 127.5, 127.7, 127.9(0), 127.9(3), 128.3 (q, *J* = 2.2 Hz), 129.2, 129.4, 129.8,

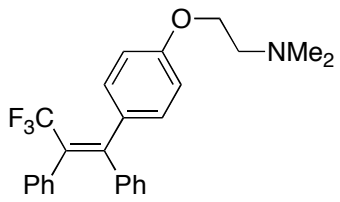
130.2 (q, *J* = 30.2 Hz), 131.1, 134.3, 140.0, 144.9, 149.0, 166.1. ^{19}F NMR (188 MHz, $CDCl_3$, □): -56.3. EIMS (70 eV) *m*/*z*: 398 (4, M^++2), 397 (26, M^++1), 396 (100, M^+), 351 (M^+-C_2H_5O, 36). HRMS-EI (*m*/*z*): M^+ calcd for $C_{24}H_{19}F_3O_2$, 396.1337; found, 396.1340.

(*Z*)-3,3,3-Trifluoro-1-(4-fluorophenyl)-1,2-diphenylpropene (6c): 91% yield, a white solid, m.p. 79.5–80.6 °C. R_f 0.43 (hexane/ethyl acetate = 10 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 6.87-6.92 (m, 2H), 7.01-7.10 (m, 5H), 7.17-7.32 (m, 7H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 114.8 (d, *J* = 21.1 Hz), 121.4 (q, *J* = 273.2 Hz), 127.4, 127.6, 127.8(1), 127.8(4), 129.6, 129.9 (q, *J* = 28.9 Hz), 130.3 (dq, *J* = 10.0, 2.2 Hz), 131.3, 134.7, 136.2 (d, *J* = 3.4 Hz), 140.6, 149.1, 160.5 (d, *J* = 245.4 Hz). ^{19}F NMR (188 MHz, $CDCl_3$, □): -56.1 (s, 3F), -114.2 (m, 1F). EIMS (70 eV) *m*/*z*: 344 (3, M^++2), 343 (23, M^++1), 342 (100, M^+), 273 (M^+-CF_3, 38). HRMS-EI (*m*/*z*): M^+ calcd for $C_{21}H_{14}F_4$, 342.1032; found, 342.1047.

(*Z*)-1-(4-Chlorophenyl)-3,3,3-trifluoro-1,2-diphenylpropene (6d): 96% yield, a white solid, m.p. 103.1–104.3 °C. R_f 0.50 (hexane/ethyl acetate = 10 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 6.86-6.91 (m, 2H), 7.02-7.07 (m, 2H), 7.21-7.22 (m, 5H), 7.27 (d, *J* = 8.6 Hz, 2H), 7.37 (d, *J* = 8.6 Hz, 2H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 121.2 (q, *J* = 273.3 Hz), 127.4, 127.6 (2C), 127.7, 128.1, 129.4, 129.7 (q, *J* = 2.2 Hz), 129.9 (q, *J* = 28.9 Hz), 131.1, 133.7, 134.4, 138.6, 140.2, 148.7. ^{19}F NMR (188 MHz, $CDCl_3$, □): -56.2. EIMS (70 eV) *m*/*z*: 360 (35, M^++2), 359 (24, M^++1), 358 (100, M^+), 254 (M^+-CF_3-Cl, 56). HRMS-EI (*m*/*z*): M^+ calcd for $C_{21}H_{14}F_3Cl$, 358.0736; found, 358.0733.

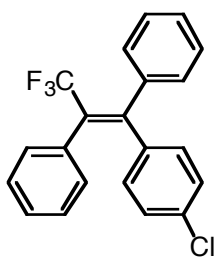
(*Z*)-3,3,3-Trifluoro-1-(4-methoxyphenyl)-1,2-diphenylpropene (6e): 95% yield, a white solid, m.p. 69.2–70.2 °C. R_f 0.29 (hexane/ethyl acetate = 10 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 3.81 (s, 3H), 6.86-6.94 (m, 4H), 6.99-7.04 (m, 3H), 7.16-7.30 (m, 7H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 55.1, 113.1, 121.5 (q, *J* = 272.1 Hz), 127.1, 127.4, 127.5, 127.6, 128.4 (q, *J* = 32.3 Hz), 128.4 (q, *J* = 2.2 Hz), 129.5, 131.3, 134.9, 140.3, 140.8, 150.2. ^{19}F NMR (188 MHz, $CDCl_3$, □): -56.1. EIMS (70 eV) *m*/*z*: 356 (6, M^++2), 355 (46, M^++1), 354 (100, M^+). HRMS-EI (*m*/*z*): M^+ calcd for $C_{22}H_{17}F_3O$, 354.1231; found, 354.1244.

(*Z*)-1-[4-(2-Dimethylamino)ethoxyphenyl]-3,3,3-trifluoro-1,2-diphenylpropene (6f): 95% yield, a white solid, m.p. 65.0–66.5 °C. R_f 0.20 (hexane/ethyl acetate / Et_3N = 10 : 10 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 2.34, 2.73 (t, *J* = 5.7 Hz, 2H), 4.07 (t, *J* = 5.7 Hz, 2H), 6.88-6.91 (m, 4H),

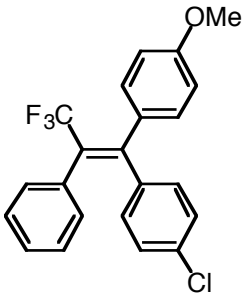


7.00-7.03 (m, 3H), 7.16-7.25 (m, 7H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 45.8, 58.2, 65.8, 113.7, 121.2 (q, *J* = 273.2 Hz), 127.0, 127.3, 127.5, 127.6, 128.3 (q, *J* = 27.8 Hz), 129.6, 129.8, 131.3, 132.6, 135.0, 141.1, 149.9, 158.3. ^{19}F NMR (188 MHz, $CDCl_3$, □): -56.1. EIMS (70 eV) *m*/*z*: 412 (1, M^++1), 411 (4, M^+), 58 (CH_2NMe_2, 100). HRMS-EI (*m*/*z*): M^+ calcd for $C_{25}H_{23}F_3NO$, 411.1810; found, 411.1811.

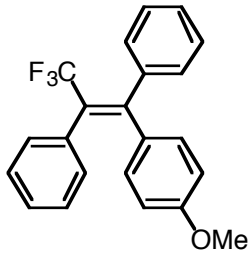
(*E*)-1-(4-Chlorophenyl)-3,3,3-trifluoro-1,2-diphenylpropene (6g): 92% yield, a white solid, m.p. 106.2–107.0 °C. R_f 0.58 (hexane/ethyl acetate = 10 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 6.82 (d, *J* = 8.6 Hz, 2H), 6.98 (d, *J* = 8.6 Hz, 2H), 7.23-7.38 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 121.3 (q, *J* = 273.3 Hz), 127.9 (2C), 128.0 (3C), 128.4 (q, *J* = 2.2 Hz),129.4 (q, *J* = 28.9 Hz), 131.0, 131.2, 133.3, 134.5, 139.2, 139.9, 148.9. ^{19}F NMR (188 MHz, $CDCl_3$, □): -56.3. EIMS (70 eV) *m*/*z*: 360 (36, M^++2), 359 (26, M^++1), 358 (100, M^+), 254 (56). HRMS-EI (*m*/*z*): M^+ calcd for $C_{21}H_{14}F_3Cl$, 358.0736; found, 358.0733.

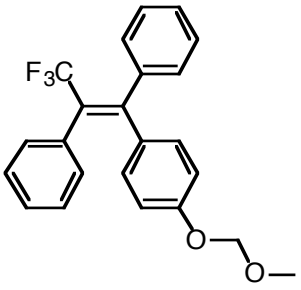


(*E*)-1-(4-Chlorophenyl)-3,3,3-trifluoro-1-(4-methoxyphenyl)-2-phenylpropene (6h): 89% yield, a white solid, m.p. 73.0-74.0 °C. R_f 0.39 (hexane/ethyl acetate = 10 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 3.82 (s, 3H), 6.82 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 6.99 (d, *J* = 8.4 Hz, 2H), 7.18 (d, *J* = 8.4 Hz, 2H), 7.22-7.23 (m, 5H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 55.2, 113.4, 121.4 (q, *J* = 273.1 Hz), 127.8, 127.9, 128.0, 129.0 (q, *J* = 28.9 Hz), 130.0 (q, *J* = 2.2 Hz), 131.1, 131.4, 132.3, 133.2, 134.8, 139.7, 148.8, 159.3. ^{19}F NMR (188 MHz, $CDCl_3$, □): -56.3. EIMS (70 eV) *m*/*z*: 390 (36, M^++2), 389 (26, M^++1), 388 (100, M^+), 284 (M^+-CF_3-Cl, 24). HRMS-EI (*m*/*z*): M^+ calcd for $C_{22}H_{16}F_3ClO$, 388.0842; found, 388.0834.

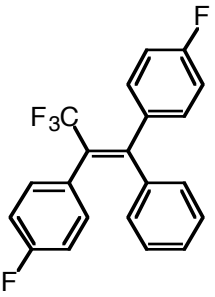


(*E*)-3,3,3-Trifluoro-1-(4-methoxyphenyl)-1,2-diphenylpropene (6i): 90% yield, a pale yellow solid, m.p. 72.5–73.0 °C. R_f 0.36 (hexane/ethyl acetate = 10 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 3.66 (s, 3H), 6.53 (d, *J* = 9.0 Hz, 2H), 6.79 (d, *J* = 9.0 Hz, 2H), 7.24-7.38 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 55.0, 112.9, 121.6 (q, *J* = 273.1 Hz), 127.6, 127.7, 127.8, 127.9, 128.5 (q, *J* = 2.2 Hz), 128.9 (q, *J* = 38.9 Hz), 131.3, 131.4, 133.1, 135.3, 140.7, 149.7, 158.5. ^{19}F NMR (188 MHz, $CDCl_3$, □): -55.8. EIMS (70 eV) *m*/*z*: 356 (5, M^++2), 355 (43, M^++1), 354 (100, M^+). HRMS-EI (*m*/*z*): M^+ calcd for $C_{22}H_{17}F_3O$, 354.1231; found, 354.1219.

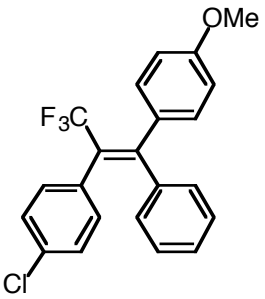


(*E*)-3,3,3-Trifluoro-1-(4-methoxymethoxyphenyl)-1,2-diphenylpropene (6j): 92% yield, R_f 0.41 (hexane/ethyl acetate = 5 : 1). 

^{1}H NMR (200 MHz, $CDCl_3$, □): 3.36 (s, 3H), 5.01 (s, 2H), 6.66 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 7.20-7.33 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 56.0, 94.2, 115.1, 121.8 (q, *J* = 273.2 Hz), 127.7, 127.8 (2C), 127.9, 128.2 (q, *J* = 36.5 Hz), 128.5 (q, *J* = 2.2 Hz), 131.2, 131.4, 134.2, 135.1, 140.6, 149.5, 156.3. ^{19}F NMR (188 MHz, $CDCl_3$, □): -55.6. EIMS (70 eV) *m*/*z*: 386 (3, M^++2), 385 (25, M^++1), 384 (100, M^+), 354 (25, M^+-CH_2O). HRMS-EI (*m*/*z*): M^+ calcd for $C_{23}H_{19}F_3O_2$, 384.1337; found, 388.1346.

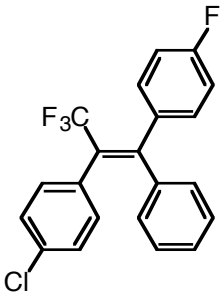
(*Z*)-1,2-Bis(4-fluorophenyl)-3,3,3-trifluoro-1-phenylpropene (6k): 91% yield, a white solid, m.p. 110.0–111.0 °C. R_f 0.46 (hexane/ethyl acetate = 10 : 1). 

^{1}H NMR (200 MHz, $CDCl_3$, □): 6.85-6.94 (m, 4H), 7.01-7.10 (m, 5H), 7.16-7.30 (m, 4H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 114.8 (d, *J* = 23.4 Hz) (2C), 121.3 (q, *J* = 273.2 Hz), 127.6, 127.8, 129.2 (q, *J* = 27.7 Hz), 129.5, 130.3 (dq, *J* = 7.1, 2.2 Hz), 130.6 (d, *J* = 3.3 Hz), 133.0 (d, *J* = 8.9 Hz), 136.0 (d, *J* = 4.3 Hz), 140.5, 149.7, 160.3 (d, *J* = 245.4 Hz), 160.5 (d, *J* = 245.2 Hz). ^{19}F NMR (188 MHz, $CDCl_3$, □): -56.3 (s, 3F), -113.7 (m, 1F), -114.0 (m, 1F). EIMS (70 eV) *m*/*z*: 362 (3, M^++2), 361 (24, M^++1), 360 (100, M^+), 291 (M^+-CF_3, 23). HRMS-EI (*m*/*z*): M^+ calcd for $C_{21}H_{13}F_5$, 360.0937; found, 360.0945.

(*Z*)-2-(4-chlorophenyl)-3,3,3-trifluoro-1-(4-methoxyphenyl)-1-phenylpropene (6l): 91% yield, a white solid, m.p. 139.0–140.0 °C. R_f 0.38 (hexane/ethyl acetate = 10 : 1). 

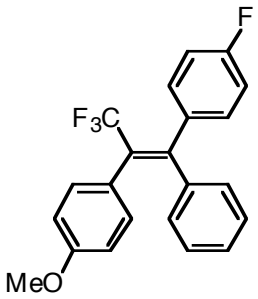
^{1}H NMR (200 MHz, $CDCl_3$, □): 3.79 (s, 3H), 6.86-6.89 (m, 4H), 7.04-7.05 (m, 3H), 7.15-7.22 (m, 6H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 55.2, 113.3, 121.4 (q, *J* = 273.3 Hz), 127.2 (q, *J* = 29.4 Hz), 127.5, 127.7, 128.1, 129.6, 129.9 (q, *J* = 2.2 Hz), 132.4, 132.8, 133.7, 140.9, 150.9, 159.3. ^{19}F NMR (188 MHz, $CDCl_3$, □): -56.1. EIMS (70 eV) *m*/*z*: 390 (36, M^++2), 389 (25, M^++1), 388 (100, M^+), 284 (M^+-CF_3-Cl, 11). HRMS-EI (*m*/*z*): M^+ calcd for $C_{22}H_{16}F_3ClO$, 388.0842; found, 388.0844.

(*Z*)-2-(4-Chlorophenyl)-1-(4-fluorophenyl)-3,3,3-trifluoro-1-phenylpropene (6m): 90% yield, a pale yellow solid, m.p. 141.0–142.0 °C. R_f 0.53 (hexane/ethyl acetate = 10 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 6.86-6.91 (m, 2H), 7.01-7.10 (m, 5H), 7.16-7.18 (m, 4H), 7.22-7.30 (m, 2H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 115.1 (d, *J* = 21.1 Hz), 121.1 (q, *J* = 273.1 Hz), 127.6, 127.7, 128.1, 129.4 (q, *J* = 25.6 Hz), 129.4, 130.1 (dq, *J* = 7.8, 2.2 Hz), 133.1, 133.8, 135.8 (d, *J* = 3.4 Hz), 140.2,



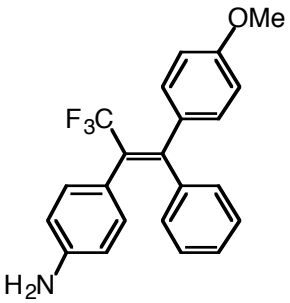
149.8, 160.4 (d, J = 245.2 Hz). ^{19}F NMR (188 MHz, $CDCl_3$, □): -56.2 (s, 3F), -113.9 (m, 1F). EIMS (70 eV) m/z: 378 (35, M^++2), 377 (23, M^++1), 376 (100, M^+), 272 (M^+-CF_3-Cl, 55). HRMS-EI (m/z): M^+ calcd for $C_{21}H_{13}F_4Cl$, 376.0642; found, 376.0641.

(*Z*)-3,3,3-Trifluoro-1-(4-fluorophenyl)-2-(4-methoxyphenyl)-1-phenylpropene (6n): 94% yield, a white solid, m.p. 131.2–131.8 °C. R_f 0.37 (hexane/ethyl acetate = 10 : 1).



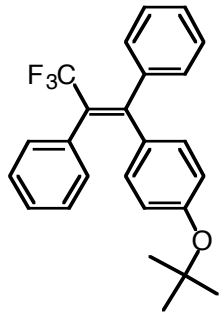
^{1}H NMR (200 MHz, $CDCl_3$, □): 6.71 (d, J = 8.8 Hz 2H), 6.87-7.00 (m, 2H), 7.04-7.18 (m, 7H), 7.23-7.30 (m, 2H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 55.1, 113.4, 114.8 (d, J = 21.1 Hz), 121.5 (q, J = 273.2 Hz), 126.9, 127.3, 127.7, 129.0 (q, J = 28.9 Hz), 129.9, 130.3 (dq, J = 7.8, 2.2 Hz), 132.5, 136.4 (d, J = 3.4 Hz), 140.9, 148.8, 159.0, 160.4 (d, J = 244.3 Hz). ^{19}F NMR (188 MHz, $CDCl_3$, □): -56.3 (s, 3F), -114.4 (m, 1F). EIMS (70 eV) m/z: 374 (3, M^++2), 373 (24, M^++1), 372 (100, M^+), 303 (M^+-CF_3, 12). HRMS-EI (m/z): M^+ calcd for $C_{22}H_{16}F_3ClO$, 372.1137; found, 372.1133.

(*Z*)-2-(4-Aminophenyl)-3,3,3-trifluoro-1-(4-methoxyphenyl)-1-phenylpropene (8): A flame-



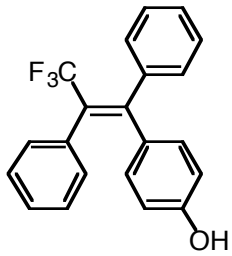
dried Schlenk tube (20 mL) under the gentle flow of argon gas was charged with **6l** (39 mg, 0.10 mmol), $Pd_2(dba)_3$ (2.3 mg, 0.0025 mmol), P(*t*-Bu)$_3$ (1.1 mg, 0.0050 mmol), toluene (1 mL), and LiN(TMP)$_2$ (0.11 mL, 1 M solution in THF) in this order. The tube was capped with a glass stopper and heated at 100 ºC for 12 h. To the reaction mixture was added diethyl ether (5 mL) and a few drops of 1 M HCl. The organic layer was washed with 1 M NaOH aqueous solution (5 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The residue was subjected to silica gel column chromatography to afford **8** (31 mg, 83% yield) as a pale yellow solid (m.p. 116.8–117.7 °C). R_f 0.42 (hexane/ethyl acetate = 2 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 3.61 (brs, 2H), 3.81 (s, 3H), 6.50 (d, J = 8.6 Hz, 2H), 6.85-6.97 (m, 4H), 7.01-7.06 (m, 5H), 7.22 (d, J = 8.6 Hz, 2H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 55.2, 113.2, 114.3, 121.8 (q, J = 273.1 Hz), 125.1, 126.9, 127.4, 128.4 (q, J = 28.2 Hz), 129.8, 130.0 (q, J = 2.2 Hz), 132.5, 133.2, 141.8, 145.7, 149.2, 159.0. ^{19}F NMR (188 MHz, $CDCl_3$, □): -56.3. EIMS (70 eV) m/z: 371 (3, M^++2), 370 (20, M^++1), 369 (100, M^+), 300 (M^+-CF_3, 11). HRMS-EI (m/z): M^+ calcd for $C_{22}H_{18}F_3NO$, 369.1340; found, 369.1338.

(*E*)-1-(4-*tert*-Butoxyphenyl)-3,3,3-trifluoro-1,2-diphenylpropene (9): To a flame-dried



Schlenk tube (20 mL) under the gentle flow of argon gas was added **6g** (36 mg, 0.1 mmol), NaO^{t}Bu (14 mg, 0.15 mmol), $Pd_2(dba)_3$ (4.6 mg, 0.0050 mmol), 2-Cy_2P-2'-Me_2N-biphenyl (4.7 mg, 0.012 mmol), and toluene (1 mL) in this order. The tube was capped with a glass stopper and heated at 100 ºC for 18 h. The reaction mixture was diluted with diethyl ether (5 mL), and then filtrated through a pad of Celite with rinsing by additional diethyl ether (5 mL x 2). Concentration of the filtrate *in vacuo* gave the crude product which was purified by silica gel column chromatography to afford **9** (21 mg, 52% yield) as a white solid [m.p. 70.6–71.6 (dec)]. R_f 0.48 (hexane/ethyl acetate = 2 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 1.22 (s, 9H), 6.61 (d, *J* = 8.8 Hz, 2H), 6.76 (d, *J* = 8.8 Hz, 2H), 7.15-7.24 (m, 5H), 7.31-7.37 (m, 5H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 28.8, 78.6, 121.5 (q, *J* = 272.3 Hz), 122.9, 127.6, 127.7, 127.7(8), 127.8(3), 128.5 (q, *J* = 2.2 Hz), 128.9 (q, *J* = 37.8 Hz), 130.4, 131.3, 135.1, 135.6, 140.4, 149.9, 154.5. ^{19}F NMR (188 MHz, $CDCl_3$, □): -56.0. EIMS (70 eV) *m*/*z*: 397 (0.6, M^++1), 396 (2, M^+), 381 (M^+-CH_3, 3), 340 (M^+-C_4H_8, 100). HRMS-EI (*m*/*z*): M^+ calcd for $C_{25}H_{23}F_3O$, 396.1701; found, 396.1702.

(*E*)-3,3,3-Trifluoro-1-(4-hydroxyphenyl)-1,2-diphenylpropene (10): To a flamed dried Schlenk



tube (20 mL) under the gentle flow of argon gas was added **6i** (71 mg, 0.20 mmol), NaSEt (27 mg, 0.30 mmol), and DMF (1 mL). The tube was sealed with a glass stopper and heated at 150 ºC for 10 h. To the reaction mixture was added water (3 mL) and the aqueous layer was extracted with diethyl ether (3 mL) four times. The combined organic layer was then washed with water and saturated NaCl aqueous solution, dried over anhydrous $MgSO_4$, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography to give **10** (53 mg, 78% yield). R_f 0.53 (hexane/ethyl acetate = 2 : 1). ^{1}H NMR (200 MHz, $CDCl_3$, □): 4.68 (s, 1H), 6.44 (d, *J* = 8.6 Hz, 2H), 6.74 (d, *J* = 8.6 Hz, 2H), 7.15-7.35 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$, □): 114.5, 121.8 (q, *J* = 273.2 Hz), 127.2, 127.8, 127.9, 128.4 (q, *J* = 34.2 Hz), 128.5 (q, *J* = 2.2 Hz), 129.7, 131.4, 133.2, 135.2, 140.6, 149.6, 154.7. ^{19}F NMR (188 MHz, $CDCl_3$, □): -55.5. EIMS (70 eV) *m*/*z*: 342 (5, M^++2), 341 (41, M^++1), 340 (100, M^+), 271 (31, M^+-Ph). HRMS-EI (*m*/*z*): M^+ calcd for $C_{21}H_{15}F_3O$, 340.1075; found, 340.1078.

Panomifene (2): To an oven-dried small round botton flask was charged with **10** (34 mg, 0.10 mmol), 2-chloroethyl *p*-toluenesulfonate (35 mg, 0.15 mmol), potassium carbonate (27.6 mg, 0.2 mmol), and MeCN (2 mL). The mixture was refluxed at 100 ºC overnight. The reaction mixture was filtered through a pad of Celite and the filtrate was concentrated *in vacuo*. The residue and 2-ethanolamine (60 μL, 1.0 mmol) were dissolved in 2-methoxyethanol (1 mL) and refluxed for 2 h. The organic solvent was removed under reduced pressure give the residue that was purified by column chromatography on silica gel to afford **2** (28 mg, 66% yield). The spectral data were identical with those reported in the literature. ^{1}H NMR (200 MHz, $CDCl_3$, δ): 2.41 (brs, 2H), 2.72 (t, *J* = 5.2 Hz, 2H), 2.86 (t, *J* = 5.2 Hz, 2H), 3.60 (t, *J* = 5.2 Hz, 2H), 3.86 (t, *J* = 5.2 Hz, 2H), 6.55 (d, *J* = 9.0 Hz, 2H), 6.80 (d, *J* = 9.0 Hz, 2H), 7.13-7.35 (m, 10H). ^{13}C NMR (67.5 MHz, $CDCl_3$, δ): 47.9, 51.1, 60.6, 67.0, 113.4, 123.7 (q, *J* = 273.2 Hz), 127.7 (2C), 127.8, 127.9, 128.4 (q, *J* = 28.9 Hz), 128.5 (q, *J* = 2.2 Hz), 131.2, 131.4, 133.2, 135.3, 140.7, 149.6, 157.8. ^{19}F NMR (188 MHz, $CDCl_3$, δ): -55.5.