

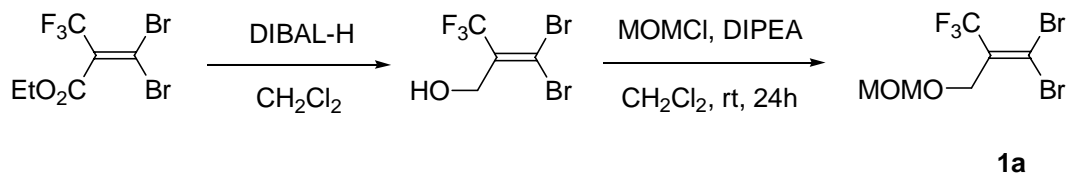
Supporting Information

High Stereo-Selective Preparation of O-Protected 2-Trifluoromethyl-3-Bromoallylic Alcohols from 1,1-Dibromo-1-Alkenes

Youhua Li, Long Lu*, Xiaoming Zhao

General: Infrared (IR) spectra were recorded on a JASCO FT/IR 410 Fourier transform infrared spectrophotometer. NMR spectra were recorded on a JEOL JNM-LA500 spectrometer, operating at 300 MHz for ^1H NMR, 75.5 MHz for ^{13}C NMR, and 282 MHz for ^{19}F NMR. Chemical shifts were reported downfield from TMS for ^1H NMR. For ^{13}C NMR, chemical shifts were reported in the scale relative to the solvent used as an internal reference. ^{19}F NMR was carried out with fluorotrichloromethane as an external standard. EI mass spectra were measured on JEOL JMS-BU20 GC mate. In general, reactions were carried out in flame-dried glassware under an argon atmosphere, unless noted otherwise. Dry solvents of tetrahydrofuran (THF), hexane and ether were distilled over sodium/benzophenone ketyl. Other reagents were purified by literature methods.

Preparation of lithiation precursor 1



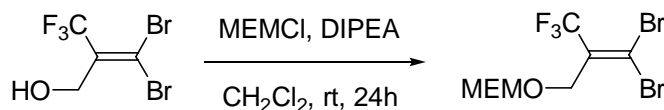
(a) 3,3-dibromo-2-(trifluoromethyl)prop-2-en-1-ol

Ethyl 3,3-dibromo-2-(trifluoromethyl)acrylate (11.52 g, 35 mmol) dissolved in CH_2Cl_2 (100 mL) and cooled to -78°C . DIBAL-H (80 mL, 1 mol/l in toluene, 80 mmol) was added dropwise to the solution. After stirred at -78°C for 1 h the reaction mixture was warmed to r. t. and stirred for another 2 h. The reaction mixture was poured into a mixture of HCl and ice. HCl (10%) was added until the precipitate was dissolved. The aqueous was extracted with ether (3×100 mL). The organic phase were combined and washed with water (3×100 mL) and brine (100 mL) and dried with anhydrous Na_2SO_4 . Removing the solvent and subsequent recrystallization from petroleum afforded 3,3-dibromo-2-(trifluoromethyl)prop-2-en-1-ol (9.6 g, 96%) as a white solid. ν_{max} (KBr) $/\text{cm}^{-1}$ 3179, 1594, 1299, 1181, 1135, 985, 822, 714; ^1H NMR (300 MHz, CDCl_3) δ 4.48 (s, 2H), 2.00 (s, 1H); ^{19}F NMR (282 MHz) δ 60.46 (t, $J = 1.1$ Hz, 3F); MS (EI) m/z 284 (M^+ , 6.0), 183 (100); HRMS Calcd for $\text{C}_4\text{H}_3\text{Br}_2\text{F}_3\text{O}$: 281.85037, Found: 281.85347.

(b) 1,1-dibromo-3,3,3-trifluoro-2-[(methoxymethoxy)methyl]prop-1-ene

To a stirred mixture of 3,3-dibromo-2-(trifluoromethyl)prop-2-en-1-ol (2.90 g, 10.2 mmol) and diisopropylethylamine (2.58 g, 20 mmol) in dichloromethane (50 mL) chloro(methoxy)methyl (1.70 g, 20 mmol) was added dropwise and the mixture was stirred overnight at room temperature. The reaction was quenched with water and extracted with ether (3×50 mL). The organic phase was washed with diluted HCl (2×50 mL), water (3×50 mL) and brine (2×50 mL) and then dried over anhydrous Na_2SO_4 . Removing the solvent and subsequent column chromatography (hexanes/AcOEt 20:1) afforded 1,1-dibromo-3,3,3-trifluoro-2-

[(methoxymethoxy)methyl]prop-1-ene (3.31 g, 99%) as a colorless liquid. ν_{\max} (neat) / cm^{-1} 2953, 1600, 1380, 1302, 1183, 1141, 1103, 1037, 945, 922, 642; ^1H NMR (300 MHz, CDCl_3) δ 4.66 (s, 2H), 4.36 (s, 2H), 3.40 (s, 3H); ^{19}F NMR (282 MHz) δ -56.09; MS (EI) m/z 267 (M^+ -61, 26.6), 45 (100); Anal Calcd for $\text{C}_6\text{H}_7\text{Br}_2\text{F}_3\text{O}_2$: C, 21.98; H, 2.15; Found: C, 21.94; H, 2.19.

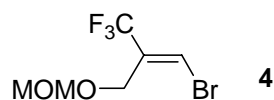


1b

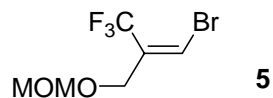
To a stirred mixture of 3,3-dibromo-2-(trifluoromethyl)prop-2-en-1-ol (2.92 g, 10.3 mmol) and diisopropylethylamine (2.58 g, 20 mmol) in dichloromethane (40 mL) 1-(chloromethoxy)-2-methoxyethane (2.49 g, 20 mmol) was added dropwise and the mixture was stirred overnight at room temperature. The reaction was quenched with water and extracted with ether (3×50 mL). The organic phase was washed with water (3×50 mL) and brine (2×50 mL) and then dried over anhydrous Na_2SO_4 . Removing the solvent and subsequent column chromatography (hexanes/ AcOEt 20:1) afforded 1,1-dibromo-3,3,3-trifluoro-2-[(2-methoxyethoxy)methoxy]methyl]prop-1-ene (3.48 g, 91%) as a colorless liquid. ν_{\max} (neat) / cm^{-1} 2935, 2891, 1600, 1456, 1303, 1180, 1139, 1044, 943, 838, 643; ^1H NMR (300 MHz, CDCl_3) δ 4.77 (s, 2H), 4.39 (s, 2H), 3.74 (t, J = 4.5 Hz, 2H), 3.57 (t, J = 4.5 Hz, 2H), 3.40 (s, 3H); ^{19}F NMR (282 MHz) δ -60.24; ^{13}C NMR (75.5 MHz) δ 133.20 (q, J = 30.8 Hz), 122.22 (q, J = 276.6 Hz), 105.26 (q, J = 3.8 Hz), 95.20, 71.61, 67.21, 66.73 (q, J = 1.9 Hz), 59.02; MS (EI) m/z 322 (M^+ -50, 1.6); Anal. Calcd for $\text{C}_8\text{H}_{11}\text{Br}_2\text{F}_3\text{O}_3$ (372): C, 25.83; H, 2.98; Found: C, 25.88; H, 2.97.

General procedure for mono-lithiation:

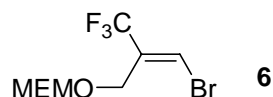
1,1-Dibromo-3,3,3-trifluoro-2-((methoxymethoxy)methyl)prop-1-ene (164 mg, 0.5 mmol) dissolved in THF (5 mL) and the mixture was cooled to -78°C . Butyl lithium (2 mol/L in cyclohexane, 0.25 mL, 0.5 mmol) was added slowly to the mixture. The reaction was quenched with methanol after stirred for 0.5 h at -78°C . The ratio of isomer was determined by ^{19}F NMR of the quenched mixture. The mixture was diluted with ether (50 mL), washed with water (3×50 mL) and dried over anhydrous Na_2SO_4 . Removing the solvent and subsequent column chromatography give 1-bromo-3,3,3-trifluoro-2-[(methoxymethoxy)methyl]prop-1-ene as a colorless oil.



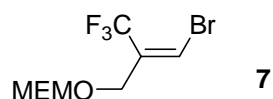
(*E*)-1-bromo-3,3,3-trifluoro-2-[(methoxymethoxy)methyl]prop-1-ene: colorless oil; ν_{\max} (neat) / cm^{-1} 2947, 1640, 1335, 1259, 1176, 1135, 1033, 969, 817; ^1H NMR (300 MHz, CDCl_3) δ 7.29 (q, J = 1.7 Hz, 1H), 4.84 (s, 2H), 4.68 (s, 2H), 3.42 (s, 3H); ^{19}F NMR (282 MHz) δ -66.02; MS (EI) m/z 247 (M^+ , 2.9), 45 (100).



(*Z*)-1-bromo-3,3,3-trifluoro-2-[(methoxymethoxy)methyl]prop-1-ene: colorless oil; ν_{\max} (neat) / cm^{-1} 2964, 2907, 1262, 1095, 1022, 865, 801, 701; ^1H NMR (300 MHz, CDCl_3) δ 6.94 (t, $J = 1.2$ Hz, 1H), 4.66 (s, 2H), 4.19 (d, $J = 1.2$ Hz, 2H), 3.39 (s, 3H); ^{19}F NMR (282 MHz) δ -62.99; MS (EI) m/z 211 (M^+ -36, 27.2), 132 (100).



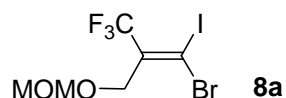
(*E*)-1-bromo-3,3,3-trifluoro-2-{[(2-methoxyethoxy)methoxy]methyl}prop-1-ene: colorless liquid; ^1H NMR (300 MHz, CDCl_3) δ 7.26 (q, $J = 1.2$ Hz, 1H), 4.77 (s, 2H), 4.39 (s, 2H), 3.76-3.73 (m, 2H), 3.60-3.58 (m, 2H), 3.41 (s, 3H); ^{19}F NMR (282 MHz) δ -65.97.



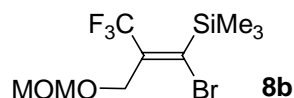
(*Z*)-1-bromo-3,3,3-trifluoro-2-{[(2-methoxyethoxy)methoxy]methyl}prop-1-ene: colorless liquid; ν_{\max} (neat) / cm^{-1} 2933, 2892, 1638, 1365, 1176, 1139, 1041, 848; ^1H NMR (300 MHz, CDCl_3) δ 6.94 (t, $J = 1.2$ Hz, 1H), 4.75 (s, 2H), 4.22 (d, $J = 1.2$ Hz, 2H), 3.73-3.70 (m, 2H), 3.57-3.54 (m, 2H), 3.40 (s, 3H); ^{19}F NMR (282 MHz) δ -62.52; ^{13}C NMR (75.5 MHz) δ 132.35 (q, $J = 30.3$ Hz), 122.28 (q, $J = 275.7$ Hz), 114.80 (q, $J = 4.2$ Hz), 94.54, 71.60, 67.19, 65.76 (q, $J = 2.9$ Hz), 58.96; MS (EI) m/z 242 (M^+ -50, 2.0), 59 (100).

General procedure for reaction of (*E*)-1-bromovinyl lithium reagent with electrophiles:

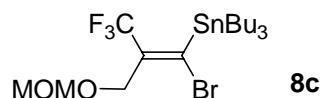
1,1-Dibromo-3,3,3-trifluoro-2-[(methoxymethoxy)methyl]prop-1-ene (164 mg, 0.5 mmol) dissolved in THF (5 mL) and the mixture was cooled to -78°C . Butyl lithium (2 mol/L in cyclohexane, 0.25 mL, 0.5 mmol) was added slowly to the mixture and stirred for 0.5 h. Iodine (254 mg, 1mmol) was added and stirred for another 1 h. The reaction mixture was quenched with water and extracted with ether (30 mL \times 3). The organic phase was washed with water (30 mL \times 3), dried over anhydrous Na_2SO_4 . Removing the solvent and subsequent column chromatography gave (*Z*)-1-bromo-3,3,3-trifluoro-1-iodo-2-[(methoxymethoxy)methyl]prop-1-ene (177 mg, 95%) as a colorless liquid.



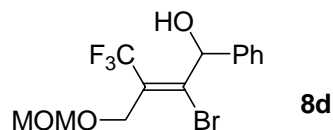
(*Z*)-1-bromo-3,3,3-trifluoro-1-iodo-2-[(methoxymethoxy)methyl]prop-1-ene, Colorless liquid, 95%; ν_{\max} (neat) / cm^{-1} 2953, 2891, 1599, 1379, 1296, 1181, 1138, 1101, 1039, 943, 921; ^1H NMR (300 MHz, CDCl_3) δ 4.65 (s, 2H), 4.32 (s, 2H), 3.39 (s, 3H); ^{19}F NMR (282 MHz) δ -60.59; ^{13}C NMR (75.5 MHz) δ 138.61 (q, $J = 30.6$ Hz), 122.37 (q, $J = 277.0$ Hz), 96.04, 65.97 (q, $J = 1.8$ Hz), 65.52 (q, $J = 3.7$ Hz), 55.63; MS (EI) m/z 343 (M^+ -31, 2.1), 313 (100); HRMS Calcd for $\text{C}_6\text{H}_7\text{F}_3\text{O}_2\text{BrI}$: 373.86286; Found: 373.86470.



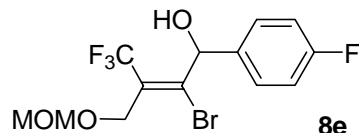
(*E*)-{1-bromo-3,3,3-trifluoro-2-[(methoxymethoxy)methyl]prop-1-enyl}trimethylsilane, colorless liquid, 91%; ν_{\max} (neat) /cm⁻¹ 2956, 2890, 1595, 1309, 1257, 1173, 1130, 1045, 869, 850; ¹H NMR (300 MHz, CDCl₃) δ 4.71 (s, 2H), 4.50 (s, 2H), 3.43 (s, 3H), 0.35 (s, 9H); ¹⁹F NMR (282 MHz) δ -58.20; ¹³C NMR (75.5 MHz) δ 148.49 (q, J = 4.8 Hz), 138.61 (q, J = 29.57 Hz), 122.88 (q, J = 276.22 Hz), 96.33, 66.82, 55.53, 0.56; MS (EI) m/z 275 (M^+ -45, 6.2), 45 (100); HRMS Calcd for C₇H₁₁BrF₃SiO: 274.97151, Found: 274.97397.



(*Z*)-{1-bromo-3,3,3-trifluoro-2-[(methoxymethoxy)methyl]prop-1-enyl}tributylstannane, colorless oil, 87%; ν_{\max} (neat) /cm⁻¹ 2959, 2927, 1598, 1465, 1310, 1262, 1166, 1125, 1098, 1045, 805; ¹H NMR (300 MHz, CDCl₃) δ 4.69 (s, 2H), 4.47 (s, 2H), 3.43 (s, 3H), 1.57-1.48 (m, 6H), 1.40-1.28 (m, 6H), 1.18-1.12 (m, 6H), 0.95-0.89 (m, 9H); ¹⁹F NMR (282 MHz) δ -61.00; ¹³C NMR (75.5 MHz) δ 149.56 (q, J = 8.1 Hz), 138.83 (q, J = 27.9 Hz), 123.44 (q, J = 275.6 Hz), 96.08, 65.18, 55.49, 28.51, 27.17, 13.58, 13.24 (q, J = 2.5 Hz);

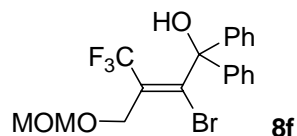


(*E*)-2-bromo-4,4,4-trifluoro-3-[(methoxymethoxy)methyl]-1-phenylbut-2-en-1-ol, pale yellow oil, 93%; ν_{\max} (neat) /cm⁻¹ 3420, 2953, 2893, 1631, 1452, 1309, 1174, 1129, 1033, 700; ¹H NMR (300 MHz, CDCl₃) δ 7.43-7.37 (m, 5H), 7.00 (d, J = 7.2 Hz, 1H), 4.70 (s, 2H), 4.51 (s, 2H), 3.42 (s, 3H), 3.00 (d, J = 7.2 Hz, 1H); ¹⁹F NMR (282 MHz) δ -55.86; ¹³C NMR (75.5 MHz) δ 147.28 (q, J = 3.5 Hz), 139.07, 128.85 (q, J = 29.7 Hz), 128.26, 128.12, 125.82, 122.83 (q, J = 277.6 Hz), 96.23, 71.95 (q, J = 2.9 Hz), 66.59 (q, J = 2.0 Hz), 55.60; MS (EI) m/z 292 (M^+ -62, 6.2), 45 (100); Anal Calcd for C₁₃H₁₄BrF₃O₃: C, 43.97; H, 3.97; Found: C, 44.35; H, 4.20.

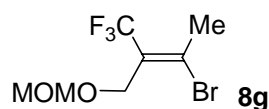


(*E*)-2-bromo-4,4,4-trifluoro-1-(4-fluorophenyl)-3-[(methoxymethoxy)methyl]but-2-en-1-ol, yield: 75%, white solid, m. p.: 52-53 °C; ν_{\max} (neat) /cm⁻¹ 3387, 2968, 2901, 1631, 1510, 1314, 1123, 1024, 997, 904, 838, 606; ¹H NMR (300 MHz, CDCl₃) δ 7.42-7.37 (m, 2H), 7.10-7.04 (m, 2H), 5.95 (d, J = 6.6 Hz, 1H), 4.69 (s, 2H), 4.49 (s, 2H), 3.41 (s, 3H), 2.71 (d, J = 6.6 Hz, 1H); ¹⁹F NMR (282 MHz) δ -55.88 (s, 3F), -114.30 (m, 1F); ¹³C NMR (75.5 MHz) δ 162.56 (d, J = 247.0 Hz), 164.81 (d, J = 2.5 Hz), 134.70 (d, J = 2.1 Hz), 129.16 (q, J = 29.6 Hz), 127.64 (d, J = 8.2 Hz), 122.73 (q, J = 277.6 Hz), 115.38 (d, J = 21.7 Hz), 96.31, 71.48 (d, J = 1.6 Hz), 66.53, 55.65;

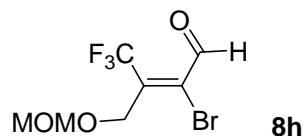
MS (EI) m/z 372 (M^+ , 1.1), 45 (100); Anal. Calcd for $C_{13}H_{13}BrF_4O_3$: C, 41.85; H, 3.51; Found: C, 41.90; H, 3.52.



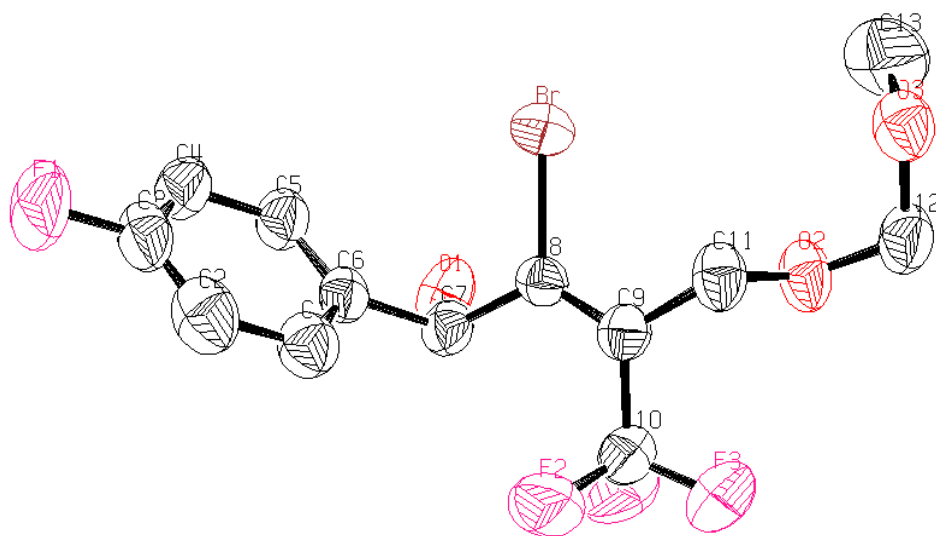
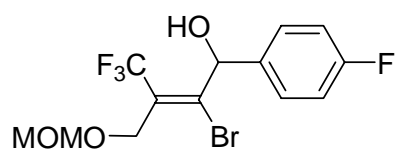
(*E*)-2-bromo-4,4,4-trifluoro-3-[(methoxymethoxy)methyl]-1,1-diphenylbut-2-en-1-ol, yellow oil, 63%; ν_{\max} (neat) $/\text{cm}^{-1}$ 3411, 2949, 2891, 1609, 1495, 1449, 1301, 1177, 1139, 1103, 1047, 754, 701; ^1H NMR (300 MHz, CDCl_3) δ 7.40-7.34 (m, 10H), 4.55 (s, 1H), 4.40 (s, 2H), 4.11 (s, 2H), 3.28 (s, 3H); ^{19}F NMR (282 MHz) δ -61.61; MS (EI) m/z 368 (M^+ -62, 2.4), 183 (100); HRMS Calcd for $C_{19}H_{18}BrF_3O_3$: 430.03918, Found: 430.04016.



(*E*)-3-bromo-1,1,1-trifluoro-2-[(methoxymethoxy)methyl]but-2-ene, colorless liquid and volatile liquid, 68%; ν_{\max} (neat) $/\text{cm}^{-1}$; ^1H NMR (300 MHz, CDCl_3) δ 4.67 (s, 2H), 4.39 (s, 2H), 3.41 (s, 3H), 2.62 (q, $J = 0.6$ Hz, 3H); ^{19}F NMR (282 MHz) δ -57.57; ^{13}C NMR (75.5 MHz) δ 138.94 (q, $J = 2.8$ Hz), 127.31 (q, $J = 29.4$ Hz), 122.92 (q, $J = 276.8$ Hz), 95.99, 66.50 (q, $J = 1.7$ Hz), 55.50, 27.37 (q, $J = 1.5$ Hz); MS (EI) m/z 230 (M^+ -32, 2), 45 (100);



(*E*)-2-bromo-4,4,4-trifluoro-3-[(methoxymethoxy)methyl]but-2-enal, colorless and volatile liquid, 33%; ν_{\max} (neat) $/\text{cm}^{-1}$ 2955, 2895, 1710, 1610, 1303, 1191, 1139, 1056, 1035, 944; ^1H NMR (300 MHz, CDCl_3) δ 9.74 (q, $J = 1.8$ Hz, 1H), 4.72 (s, 2H), 4.63 (s, 2H), 3.42 (s, 3H); ^{19}F NMR (282 MHz) δ -54.53; MS (EI) m/z 245 (M^+ -31, 2.0), 45 (100); HRMS Calcd for $C_7H_7BrF_3O_3$: 274.95311, Found: 274.97397.



ORTEP drawing of 4e with all H atoms omitted for clarity