Electronic Supplementary Information

Flow trifluoromethylation of carbonyl compounds by Ruppert-Prakash reagent and its application for pharmaceuticals, Efavirenz, and HSD-016

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Experimental Section

General Methods:

All reactions were performed in oven-dried glassware. Solvents were transferred *via* syringe. A 7×146 mm Pasteur pipette (IWAKI) or 3×50 mm glass column (EYELA) were filled with base/Celite 503 (Kishida Chemical Co., Ltd.). A syringe pump (YMC) was used. All reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm Merck silica-gel (60-F254). The TLC plates were visualized with UV light and 7% phosphomolybdic acid or $KMnO_4$ in water/heat. Column chromatography was carried out on a column packed with silica-gel 60N spherical neutral size 63-210 μm. The ^{1}H-NMR (300 MHz), ^{19}F-NMR (282 MHz), ^{13}C-NMR (100.6 MHz or 125.8 MHz) spectra for solution in $CDCl_3$ were recorded on a Buruker Avance 600 and a Varian Mercury 300. Chemical shifts (δ) are expressed in ppm downfield from internal TMS, $CHCl_3$ or $CClF_3$. HPLC analyses were performed on a JASCO U-2080 Plus using 4.6 x 250 mm CHIRALPAK OD-3 column. Mass spectra were recorded on a SHIMADZU GCMS-QP5050A. Optical rotations were measured on a HORIBA SEPA-300. Mass spectra were recorded on a SHIMADZU GCMS-QP5050A or SHIMADZU LCMS-2010EV. Infrared spectra were recorded on a JASCO FT/ IR-200 spectrometer. Melting points were recorded on a BÜCHI Melting Point M-565. The ketone **1p** was prepared according to literature[1]. The ketone **1q** was prepared according to literature[2]. The catalyst A was prepared according to literature[3].

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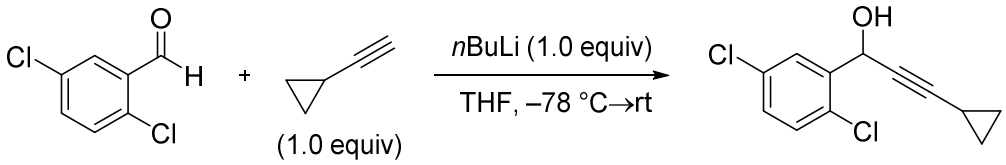
[1] H. Kawai, T. Kitayama, E. Tokunaga, N. Shibata, *Eur. J. Org. Chem.* **2011**, 5959.

[2] J. S. Xiang, E. Saiah, S. Y. Tam, J. C. Mckew, L. Chen, M. Ipek, K. Lee, H.-Q. Li, J. Li, W. Li, T. S. Mansour, V. Suri, R. Vargas, Y. Wu, Z.-K. Wan, J. Lee, E. Binnun, D. P. Wilson, WO2007092435, **2007**.

[3] T. Tozawa, H. Nagao, Y. Yamane, T. Mukaiyama, *Chem. Asian J.* **2007**, *2*, 123.

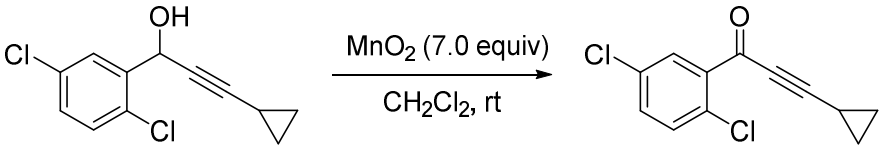
1-(2,5-Dichlorophenyl)-3-cyclopropylprop-2-yn-1-ol (S1)



To a solution of cyclopropylacetylene (1.02 mL, 12.0 mmol, 1.0 equiv) in THF (60 mL) was added *n*BuLi (1.35 M in *n*-hexane) (8.64 mL, 12.0 mmol, 1.0 equiv) dropwise at –78 ºC under nitrogen atmosphere. After the reaction mixture was stirred at –78 ºC for 1 h, 2,5-dichlorobenzaldehyde (2.10 g, 12.0 mmol, 1.0 equiv) in THF (10 mL) was added dropwise at -78 ºC. Upon stirring at same temperature for 1 h, the reaction mixture was stirred at ambient temperature for 1h. Then, it was concentrated under reduced pressure, extracted with ethyl acetate, washed with brine, dried over Na_2SO_4, filtered, concentrated, and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 90/10) to give **S1** (2.69 g, 93%) as a white solid.

^{1}H NMR ($CHCl_3$, 300 MHz) δ 0.74-0.82 (m, 4H), 1.31 (brs, 1H), 2.41 (s, 1H), 5.70 (s, 1H), 7.22-7.31 (m, 2H), 7.72 (s, 1H); ^{13}C NMR ($CHCl_3$, 100.6 MHz) δ -0.5, 8.4, 61.7, 73.3, 91.3, 128.3, 129.4, 130.7, 130.8, 133.1, 140.1; IR (KBr) 3275, 2233, 1888, 1587, 1566, 1462, 1396, 1358, 1289, 1252, 1186, 1156, 1132, 1098, 1052, 1011, 887, 861, 809, 708, 676, 557, 533 cm^{-1}; mp = 59.8-60.5 ºC ($CHCl_3$); MS (EI, *m/z*) 240 (M^+), HRMS (EI) calcd. for $C_{12}H_{10}Cl_2O$ (M^+): 240.0109 Found: 240.0080.

1-(2,5-Dichlorophenyl)-3-cyclopropylprop-2-yn-1-one (1q)



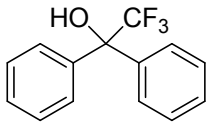
To a stirred solution of **S1** (2.69g, 11.2 mmol) in CH_2Cl_2 (83 mL) was added activated manganese dioxide (7.58 g, 78.4 mmol, 7.0 equiv) at room temperature under nitrogen atmosphere. After 24 h, the reaction mixture was filtered over Celite pad with CH_2Cl_2. The filtrate was concentrated and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 90/10) to give **1q** (2.68 g, 99%) as a white solid.

^{1}H NMR ($CHCl_3$, 300 MHz) δ 1.05-1.08 (m, 4H), 1.51-1.61 (m, 1H), 7.39 (m, 2H), 7.90 (s, 1H); ^{13}C NMR ($CHCl_3$, 100.6 MHz) δ 0.2, 10.1, 76.8, 103.5, 131.4, 131.9, 132.5, 132.7, 132.8, 137.2, 175.2; IR (KBr) 3749, 3089, 2690, 2510, 2205, 1931, 1813, 1615, 1456, 1384, 1262, 1184, 1036, 931, 837, 803, 749, 670, 638, 570 cm^{-1}; mp = 40.0-40.2 ºC ($CHCl_3$); MS (ESI, *m/z*) 239 $[M+H]^+$, HRMS (ESI) calcd. for $C_{12}H_9Cl_2O$ $(M)^+$: 239.0030 Found: 239.0022.

General procedure for the trifluoromethylation to carbonyl compounds by KOH/Celite 503.

KOH/Celite 503 (1/1, 100 mg) was packed into the Pasteur pipette (7 ϕ ×146 mm). Carbonyl compound **1a-q** (0.2 mmol) and Me_3SiCF_3 (0.4 mmol, 59.1 μL, 2.0 equiv) in DMF (2.0 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 4.0 mL of DMF and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, and purified by column chromatography on silica gel to give α-trifluoromethyl alcohol **2a-q**.

2,2,2-Trifluoro-1,1-diphenylethanol (2a)

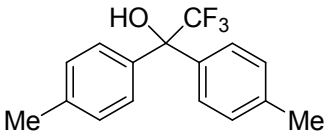


KOH/Celite 503 (1/1, 100 mg) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1a** (0.2 mmol, 36.4 mg) and Me_3SiCF_3 (0.4 mmol, 59.1 μL, 2.0 equiv) in DMF (2.0 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 4.0 mL of DMF and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 98/2) to give **2a** (39.9 mg, 79%) as a colorless oil.

This compound has been previously synthesized and characterized.[4]

^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.89 (s, 1H), 7.35-7.38 (m, 6H), 7.48-7.51 (m, 4H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -74.8 (s, 3F); MS (EI, *m/z*) 252 (M^+).

2,2,2-Trifluoro-1,1-bis(4-methylphenyl)ethanol (2b)



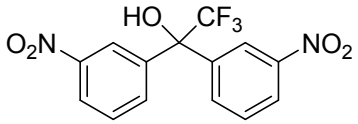
KOH/Celite 503 (1/1, 100 mg) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1b** (0.2 mmol, 42.1 mg) and Me_3SiCF_3 (0.4 mmol, 59.1 μL, 2.0 equiv) in DMF (2.0 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 4.0 mL of DMF and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 98/2) to give **2b** (37.6 mg, 67%) as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.35 (s, 6H), 2.79 (s, 1H), 7.16 (d, J = 8.4 Hz, 4H), 7.36 (d, J = 7.8

[4] G. K. S. Prakash, J. Hu , G. A. Olah, *Org. Lett.* **2003**, *5*, 3253.

Hz, 4H); ^{13}C NMR ($CHCl_3$, 100.6 MHz) δ 21.1, 79.2 (q, J = 28.5 Hz), 125.4 (q, J = 286 Hz), 127.3 (d, J = 2.0 Hz), 128.9, 136.6, 138.4; ^{19}F NMR ($CDCl_3$, 282 MHz) δ -75.0 (s, 3F); IR (KBr) 3545, 2926, 2359, 1917, 1734, 1718, 1700, 1684, 1653, 1635, 1617, 1559, 1507, 908, 816, 735, 668, 620, 593 cm^{-1}; mp = 60.0-61.0 ºC ($CHCl_3$); MS (EI, *m/z*) 280 (M^+), HRMS (EI) calcd. for $C_{16}H_{15}F_3O_2$ (M^+): 280.1075 Found: 280.1086.

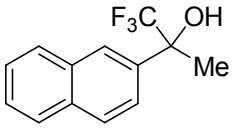
2,2,2-Trifluoro-1,1-bis(3-nitrophenyl)ethanol (2c)



KOH/Celite 503 (1/1, 100 mg) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1c** (0.2 mmol, 54.4 mg) and Me_3SiCF_3 (0.4 mmol, 59.1 μL, 2.0 equiv) in DMF (2.0 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 4.0 mL of DMF and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 70/30) to give **2c** (67.8 mg, 99%) as a pale yellow solid.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.63 (brs, 1H), 7.62 (t, J = 8.0 Hz, 2H), 7.84 (d, J = 7.2 Hz, 2H), 8.28 (d, J = 8.4 Hz, 2H), 8.42 (s, 2H); ^{13}C NMR ($CHCl_3$, 100.6 MHz) δ 78.6 (q, J = 29.3 Hz), 122.5 (d, J = 1.0 Hz), 124.3, 124.4 (q, J = 286 Hz), 129.9, 133.2 (d, J = 2.0 Hz), 140.1, 148.4; ^{19}F NMR ($CDCl_3$, 282 MHz) δ -75.0 (s, 3F); IR (KBr) 3853, 3744, 3675, 3650, 3629, 3421, 2360, 1734, 1718, 1700, 1684, 1653, 1635, 1539, 1457, 1340, 1177, 816, 741, 668 cm^{-1}; mp = 88.0-89.0 ºC ($CHCl_3$); MS (ESI, *m/z*) 341 $[M-H]^-$, HRMS (ESI) calcd. for $C_{14}H_8F_3N_2O_5$ $[M-H]^-$: 341.0385 Found: 341.0393.

1,1,1-Trifluoro-2-(naphthalen-2-yl)propan-2-ol (2d)

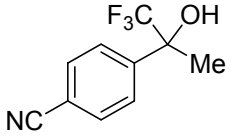


KOH/Celite 503 (1/1, 100 mg) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1d** (0.2 mmol, 34.0 mg) and Me_3SiCF_3 (0.4 mmol, 59.1 μL, 2.0 equiv) in DMF (2.0 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 4.0 mL of DMF and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 95/5) to give **2d** (38.0 mg, 79%) as a white solid.

This compound has been previously synthesized and characterized.[5]

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.88 (s, 3H), 2.55 (s, 1H), 7.50-7.53 (m, 2H), 7.67 (d, J = 8.4 Hz, 1H), 7.86-7.89 (m, 3H), 8.07 (s, 1H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -81.1 (s, 3F); MS (EI, *m/z*) 240 (M^+).

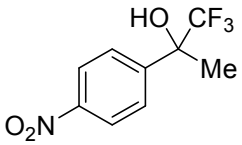
1,1,1-Trifluoro-2-(4-cyanophenyl)propan-2-ol (2e)



KOH/Celite 503 (1/1, 100 mg) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1e** (0.2 mmol, 29.0 mg) and Me_3SiCF_3 (0.4 mmol, 59.1 μL, 2.0 equiv) in DMF (2.0 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 4.0 mL of DMF and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 90/10) to give **2e** (38.3 mg, 89%) as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.81 (s, 3H), 2.60 (s, 1H), 7.72 (m, 4H); ^{13}C NMR ($CHCl_3$, 100.6 MHz) δ 23.9, 74.6 (q, J = 29.8 Hz), 112.6, 118.3, 125.1 (q, J = 285 Hz), 127.1, 132.1, 143.4; ^{19}F NMR ($CDCl_3$, 282 MHz) δ -81.4 (s, 3F); IR (KBr) 3853, 3744, 3675, 3629, 3420, 3360, 2241, 1734, 1700, 1684, 1653, 1635, 1610, 1559, 1540, 1507, 1467, 1419, 1157, 826, 668 cm^{-1}; mp = 119.6-120.6 ºC ($CHCl_3$); MS (EI, *m/z*) 215 (M^+), HRMS (EI) calcd. for $C_{10}H_8F_3NO_2$ (M^+): 215.0558 Found: 215.0544.

1,1,1-Trifluoro-2-(4-nitrophenyl)propan-2-ol (2f)



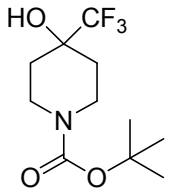
KOH/Celite 503 (1/1, 100 mg) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1f** (0.2 mmol, 33.0 mg) and Me_3SiCF_3 (0.4 mmol, 59.1 μL, 2.0 equiv) in DMF (2.0 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 4.0 mL of DMF and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 90/10) to give **2f** (29.0 mg, 88%) as a white solid.

[5] I. A. Sanhueza, K. J. Bonney, M. C. Nielsen, F. Schoenebeck, *J. Org. Chem.* **2013**, *78*, 7749.

This compound has been previously synthesized and characterized.[6]

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.85 (s, 3H), 2.72 (s, 1H), 7.80 (d, J = 9.3 Hz, 2H), 8.26 (d, J = 8.1 Hz, 2H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -81.3 (s, 3F); MS (EI, *m/z*) 235 (M^+).

***Tert*-butyl 4-hydroxy-4-(trifluoromethyl)-1-piperidinecarboxylate (2g)**

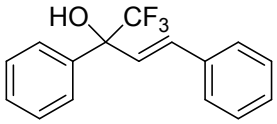


KOH/Celite 503 (1/1, 100 mg) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1g** (0.2 mmol, 39.9 mg) and Me_3SiCF_3 (0.4 mmol, 59.1 μL, 2.0 equiv) in DMF (2.0 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 4.0 mL of DMF and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 80/20) to give **2g** (49.0 mg, 91%) as a white solid.

This compound has been previously synthesized and characterized.[7]

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.47 (s, 9H), 1.69-1.83 (m, 4H), 2.87 (s, 1H), 3.07 (m, 2H), 4.04 (m, 2H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -85.4 (s, 3F); MS (EI, *m/z*) 269 (M^+).

(*E*)-1,1,1-Trifluoro-2,4-diphenylbut-3-en-2-ol (2h)



KOH/Celite 503 (1/1, 100 mg) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1h** (0.2 mmol, 41.7 mg) and Me_3SiCF_3 (0.4 mmol, 59.1 μL, 2.0 equiv) in DMF (2.0 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 4.0 mL of DMF and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 90/10) to give **2h** (41.2 mg, 74%) as a colorless oil.

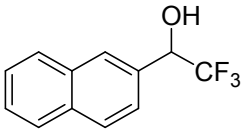
This compound has been previously synthesized and characterized.[8]

^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.74 (s, 1H), 6.73 (d, J = 16.2 Hz, 1H), 6.89 (d, J = 16.2 Hz, 1H),

[6] D. van der Born, J. D. M. Herscheid, R. V. A. Orru, D. J. Vugts, *Chem. Commun.* **2013**, *49*, 4018.
[7] D. S. Middleton, A. Stobie, WO 2003051868, **2003**.
[8] K. Aikawa, W. Toya, Y. Nakamura, K. Mikami, *Org. Lett.* **2015**, *17*, 4996.

7.30-7.44 (m, 8H), 7.65 (d, J = 6.6 Hz, 2H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -79.0 (s, 3F); MS (EI, *m/z*) 278 (M^+).

2,2,2-Trifluoro-1-(naphthalen-2-yl)ethanol (2i)

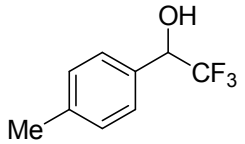


KOH/Celite 503 (1/1, 100 mg) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1i** (0.2 mmol, 31.2 mg) and Me_3SiCF_3 (0.4 mmol, 59.1 μL, 2.0 equiv) in DMF (2.0 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 4.0 mL of DMF and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 90/10) to give **2i** (35.3 mg, 78%) as a white solid.

This compound has been previously synthesized and characterized.[9]

^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.73 (m, 1H), 5.16-5.21 (m, 1H), 7.51-7.58 (m, 3H), 7.86-7.90 (m, 3H), 7.95 (s, 1H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -78.5 (d, J = 5.9 Hz, 3F); MS (EI, *m/z*) 226 (M^+).

2,2,2-Trifluoro-1-(4-methylphenyl)ethanol (2j)



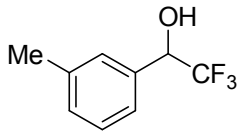
KOH/Celite 503 (1/1, 100 mg) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1j** (0.2 mmol, 30.2 mg) and Me_3SiCF_3 (0.4 mmol, 59.1 μL, 2.0 equiv) in DMF (0.5 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 5.5 mL of DMF and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 90/10) to give **2j** (33.2 mg, 75%) as a colorless oil.

This compound has been previously synthesized and characterized.[9]

^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.37 (s, 3H), 2.66 (m, 1H), 4.98 (m, 1H), 7.22 (d, J = 7.5 Hz, 2H), 7.36 (d, J = 7.2 Hz, 2H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -78.9 (d, J = 5.9 Hz, 3F); MS (EI, *m/z*) 190 (M^+).

[9] G. K. S. Prakash, Z. Zhang, F. Wang, S. Munoz, G. A. Olah, *J. Org. Chem.* **2013**, *78*, 3300.

2,2,2-Trifluoro-1-(3-methylphenyl)ethanol (2k)

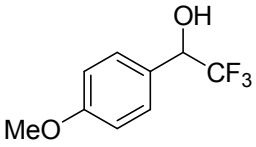


KOH/Celite 503 (1/1, 100 mg) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1k** (0.2 mmol, 30.2 mg) and Me_3SiCF_3 (0.4 mmol, 59.1 μL, 2.0 equiv) in DMF (0.5 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 5.5 mL of DMF and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 90/10) to give **2k** (33.2 mg, 75%) as a colorless oil.

This compound has been previously synthesized and characterized.[9]

^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.38 (s, 3H), 2.69 (m, 1H), 4.96-4.98 (m, 1H), 7.23-7.28 (m, 4H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -78.8 (d, J = 7.1 Hz, 3F); MS (EI, *m/z*) 190 (M^+).

2,2,2-Trifluoro-1-(4-methoxyphenyl)ethanol (2l)



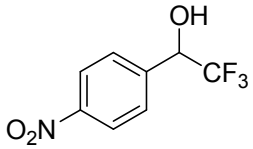
KOH/Celite 503 (1/1, 100 mg) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1l** (0.2 mmol, 27.2 mg) and Me_3SiCF_3 (0.4 mmol, 59.1 μL, 2.0 equiv) in DMF (0.5 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 5.5 mL of DMF and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 90/10) to give **2l** (38.8 mg, 94%) as a colorless oil.

This compound has been previously synthesized and characterized.[10]

^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.78 (m, 1H), 3.82 (s, 3H), 4.95-4.97 (m, 1H), 6.93 (d, J = 8.4 Hz, 2H), 7.40 (d, J = 7.5 Hz, 2H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -79.0 (d, J = 6.8 Hz, 3F); MS (EI, *m/z*) 206 (M^+).

[10] Q. Xu, H. Zhou, X. Geng, P. Chen, *Tetrahedron*, **2009**, 65, 2232.

2,2,2-Trifluoro-1-(4-nitrophenyl)ethanol (2m)

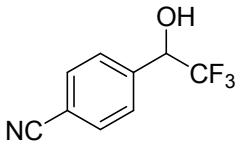


LiOAc/Celite 503 (1/1, 100 mg) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1m** (0.2 mmol, 30.2 mg) and Me_3SiCF_3 (0.4 mmol, 59.1 μL, 2.0 equiv) in DMF (2.0 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 4.0 mL of DMF and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers was washed with brine, dried over Na_2SO_4 The trimethylsilyl ether was treated with nBu$_4$NF (57.5 mg, 0.22 mmol, 1.1 equiv) in THF (2.0 mL) at ambient temperature for 1 h. The resulting mixture was concentrated under reduced pressure, and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 80/20) to give **2m** (26.5 mg, 60%) as a pale yellow solid.

This compound has been previously synthesized and characterized.[4]

^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.99 (brs, 1H), 5.19 (q, J = 6.2 Hz, 1H), 7.70 (d, J = 8.1 Hz, 2H), 8.28 (d, J = 7.2 Hz, 2H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -78.7 (d, J = 5.9 Hz, 3F); MS (EI, *m/z*) 221 (M^+).

2,2,2-Trifluoro-1-(4-cyanophenyl)ethanol (2n)

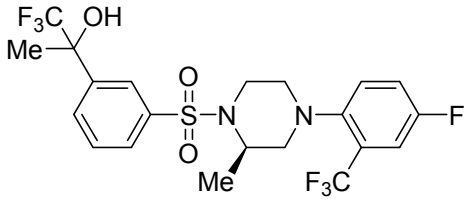


LiOAc/Celite 503 (1/1, 100 mg) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1n** (0.2 mmol, 26.2 mg) and Me_3SiCF_3 (0.4 mmol, 59.1 μL, 2.0 equiv) in DMF (2.0 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 4.0 mL of DMF and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers was washed with brine, dried over Na_2SO_4 The trimethylsilyl ether was treated with nBu$_4$NF (57.5 mg, 0.22 mmol, 1.1 equiv) in THF (2.0 mL) at ambient temperature for 1 h. The resulting mixture was concentrated under reduced pressure, and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 80/20) to give **2n** (34.2 mg, 85%) as a white solid.

This compound has been previously synthesized and characterized.[10]

^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.19 (m, 1H), 5.13-5.15 (m, 1H), 7.64 (d, J = 7.5 Hz, 2H), 7.72 (d, J = 9.6 Hz, 2H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -78.7 (d, J = 5.1 Hz, 3F); MS (EI, *m/z*) 201 (M^+).

1,1,1-Trifluoro-2-[3-({(2*R*)-4-[4-fluoro-2-(trifluoromethyl)-phenyl]-2-methylpiperazin-1-yl} sulfonyl)phenyl]propan-2-ol (2o)

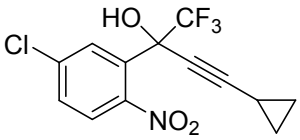


KOH/Celite 503 (1/1, 100 mg) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1o** (0.2 mmol, 88.9 mg) and Me_3SiCF_3 (0.4 mmol, 59.1 μL, 2.0 equiv) in DMF (2.0 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 4.0 mL of DMF and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, and purified by column chromatography on silica gel (benzene/ethyl acetate = 95/5) to give **2o** (82.3 mg, 80%) as a white solid.

This compound has been previously synthesized and characterized.[11]

^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.19 (d, *J* = 6.3 Hz, 3H), 1.84 (s, 3H), 2.67-2.70 (m, 2H), 2.85-2.88 (m, 2H), 3.12 (s, 1H), 3.36 (t, *J* = 11.0 Hz, 1H), 3.75 (d, *J* = 12.0 Hz, 1H), 4.23 (s, 1H), 7.21 (d, *J* = 5.1 Hz, 2H), 7.32 (d, *J* = 8.4 Hz, 1H), 7.57 (t, *J* = 7.8 Hz, 1H), 7.84-7.87 (m, 2H), 8.11 (s, 1H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -114.7 (d, *J* = 4.7 Hz, 1F), -81.5 (s, 3F), -61.4 (s, 3F); MS (ESI, *m/z*) 515 $[M+H]^+$.

2-(5-Chloro-2-nitrophenyl)-4-cyclopropyl-1,1,1-trifluorobut-3-yn-2-ol (2p)



KOH/Celite 503 (1/1, 100 mg) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1p** (0.2 mmol, 49.9 mg) and Me_3SiCF_3 (0.4 mmol, 59.1 μL, 2.0 equiv) in DMF (2.0 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 4.0 mL of DMF and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 95/5) to give **2p** (56.3 mg, 88%) as a colorless oil.

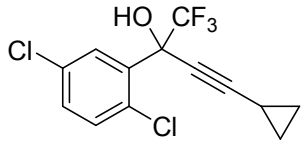
This compound has been previously synthesized and characterized.[1]

^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82-0.89 (m 4H), 1.25-1.32 (m, 1H), 3.65 (s, 1H), 7.44-7.48 (m, 2H),

[11] Z.-K. Wan, E. Chenail, H.-Q. Li, C. Kendall, Y. Wang, S. Gingras, J. Xiang, W. W. Massefski, T. S. Mansour, E. Saiah, *J. Org. Chem.* **2011**, *76*, 7048.

7.80 (s, 1H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -78.8 (s, 3F) ; MS (ESI, *m/z*) 318 $[M-H]^-$.

2-(2,5-Dichlorophenyl)-4-cyclopropyl-1,1,1-trifluorobut-3-yn-2-ol (2q)



KOH/Celite 503 (1/1, 100 mg) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1q** (0.2 mmol, 47.8 mg) and Me_3SiCF_3 (0.4 mmol, 59.1 μL, 2.0 equiv) in DMF (2.0 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 4.0 mL of DMF and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with Et_2O, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure, and purified by column chromatography on silica gel (*n*-hexane/ethyl acetate = 95/5) to give **2q** (53.2 mg, 86%) as a colorless oil.

This compound has been previously synthesized and characterized.[12]

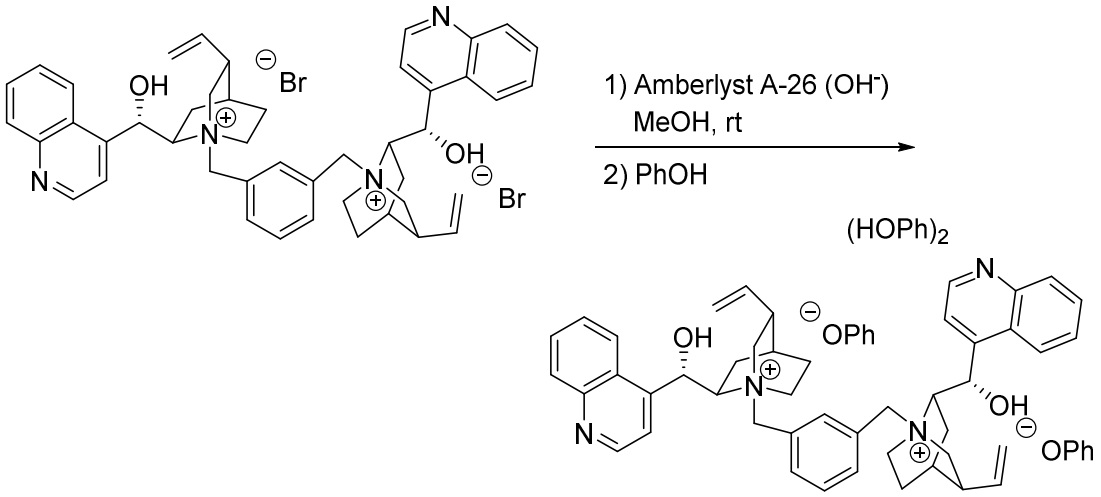
^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.82-0.88 (m, 4H), 1.34-1.39 (m, 1H), 3.41 (s, 1H), 7.26-7.38 (m, 2H), 7.88 (s, 1H); ^{19}F NMR ($CDCl_3$, 282 MHz) δ -79.1 (s, 3F); MS (ESI, *m/z*) 309 $[M+H]^+$.

General continuous-flow procedure for the trifluoromethylation to carbonyl compounds by KOH/Celite 503.

KOH/Celite 503 (1/1) was packed into the glass column (3 ϕ × 50 mm). **1p** (0.1 M in DMF) and Me_3SiCF_3 (2.0 equiv) was fed into the column using the syringe pump (3.0 mL/min). The product was quenched with sat. NH_4Cl aq. At this stage, ^{19}F NMR analysis was performed on a small sample, in the presence of $PhCF_3$ as internal standard.

[12] C. A. Correia, K. Gilmore, D. T. McQuade, P. H. Seeberger, *Angew. Chem. Int. Ed.* **2015**, *54*, 4945.

α,α'-Biscinchonium-*m*-xylene diphenoxide-phenol complex (catalyst A)



Ion-exchange resin Amberlyst A-26 (OH^-) (2.84 g) was added to a stirred solution of α,α'-biscinchonium-*m*-xylene dibromide (1.54 g, 1.81 mmol) in methanol (15 mL) at ambient temperature. The mixture was stirred for 10 h at the same temperature, filtered, and washed with methanol. Phenol (340 mg, 3.61 mmol, 2.0 equiv) was added to the filtrate, and the resulting mixture was co-evaporated three times with benzene. Crystallization of the residue from diethyl ether afforded, which was collected by filtration and dried under reduced pressure to form cinchonine-derived chiral quaternary ammonium salt **catalyst A** (770 mg, 48% yield) as a white solid.

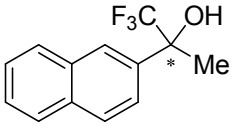
^{1}H NMR ($CHCl_3$, 300 MHz) δ 1.10 (m, 2H), 1.86 (m, 4H), 1.97 (m, 2H), 2.49-2.56 (m, 4H), 3.16-3.19 (m, 2H), 3.57 (t, *J* = 10.4 Hz, 2H), 3.82 (m, 2H), 3.95-4.07 (m, 2H), 6.03-6.15 (m, 2H), 6.54 (t, *J* = 7.1 Hz, 4H), 6.66 (d, *J* = 7.5 Hz, 8H), 7.02 (t, *J* = 7.7 Hz, 8H), 7.81 (m, 4H), 7.87-7.91 (m, 5H), 7.98-8.06 (m, 3H), 8.15 (d, *J* = 7.8 Hz, 2H), 8.27 (d, *J* = 7.5 Hz, 2H), 8.97 (d, *J* = 4.2 Hz, 2H); ^{13}C NMR ($CHCl_3$, 125.8 MHz) δ 22.2, 24.7, 28.5, 39.0, 56.0, 58.1, 64.0, 66.8, 69.5, 117.2, 118.0, 118.5, 121.4, 124.2, 126.2, 129.1, 130.1, 130.2, 130.3, 131.2, 131.3, 136.9, 137.6, 140.2, 147.6, 148.7, 151.1, 164.0; IR (KBr) 3857, 3741, 3363, 2360, 2063, 1925, 1647, 1577, 1469, 1392, 1261, 1161, 1119, 987, 926, 868, 818, 764, 690 cm^{-1}; mp = 110.1-111.6 ºC ($CHCl_3$); MS (ESI, *m/z*) 346 $[1/2(M-2(OPh)-2(HOPh))]^+$, HRMS (ESI) calcd. for $C_{23}H_{40}NO$ $[1/2(M-2(OPh)-2(HOPh))]^+$: 346.3110 Found: 346.3127; $[\alpha]_D^{25}$ = +63.9 (c = 0.38, $CHCl_3$).

General procedure for the asymmetric trifluoromethylation to carbonyl compounds by ammonium phenoxide/Celite 503.

Ammonium phenoxide/Celite 503 (1/1, 2.0 equiv) was packed into the Pasteur pipette (7 ϕ ×146 mm). Carbonyl compound (0.1 mmol) and Me_3SiCF_3 (0.2 mmol, 29.6 μL, 2.0 equiv) in toluene/CH_2Cl_2 (0.1 mL) was fed into the Pasteur pipette using the syringe. The product was run out

using 2.9 mL of toluene/CH_2Cl_2 and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The trimethylsilyl ether was treated with nBu$_4$NF (28.8 mg, 0.11 mmol, 1.1 equiv) in THF (1.0 mL) at ambient temperature for 1 h. The resulting mixture was concentrated under reduced pressure, and purified by column chromatography on silica gel to give α-trifluoromethyl alcohol .

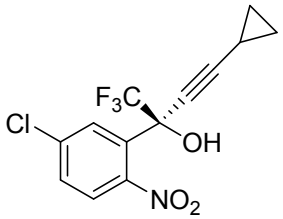
1,1,1-Trifluoro-2-(naphthalen-2-yl)propan-2-ol (2i)



Catalyst A/Celite 503 (1/1, 2.0 equiv) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1i** (17.0 mg, 0.1 mmol) and Me_3SiCF_3 (0.2 mmol, 29.6 μL, 2.0 equiv) in toluene/CH_2Cl_2 (0.1 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 2.9 mL of toluene/CH_2Cl_2 and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The trimethylsilyl ether was treated with nBu$_4$NF (28.8 mg, 0.11 mmol, 1.1 equiv) in THF (1.0 mL) at ambient temperature for 1 h. The resulting mixture was concentrated under reduced pressure, and purified by column chromatography on silica gel to give **2i** (12.5 mg, 52% yield, 36% ee) as a white solid.

The ee of the product was determined by HPLC using an OD-3 column (n-hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm, τ_{maj} = 8.9 min, τ_{min} = 17.1 min); $[\alpha]_D^{25}$ = +2.13 (c = 0.34, $CHCl_3$) , 36% ee.

(*S*)-2-(5-Chloro-2-nitrophenyl)-4-cyclopropyl-1,1,1-trifluorobut-3-yn-2-ol (2p)

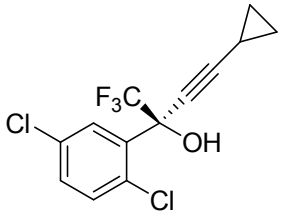


Catalyst B/Celite 503 (1/1, 2.0 equiv) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1p** (25.0 mg, 0.1 mmol) and Me_3SiCF_3 (0.2 mmol, 29.6 μL, 2.0 equiv) in toluene/CH_2Cl_2 (0.1 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 2.9 mL of toluene/CH_2Cl_2 and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The trimethylsilyl ether was treated with nBu$_4$NF (28.8 mg, 0.11 mmol, 1.1 equiv) in THF (1.0 mL)

at ambient temperature for 1 h. The resulting mixture was concentrated under reduced pressure, and purified by column chromatography on silica gel to give (*S*)-**2p** (14.7 mg, 46% yield, 36% ee) as a colorless oil.

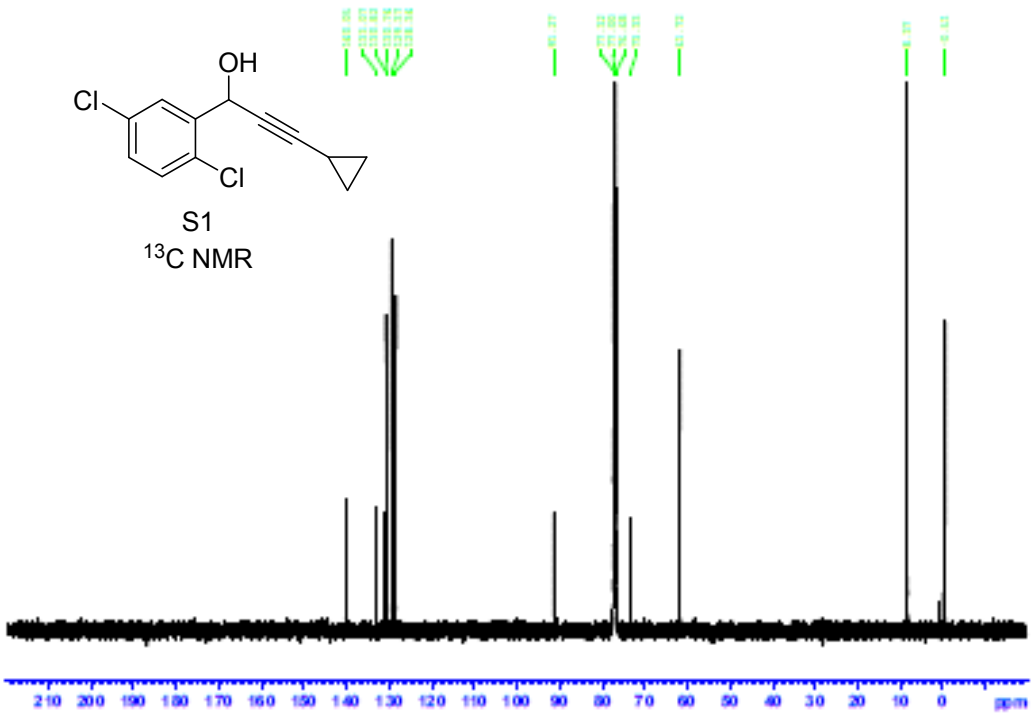
The ee of the product was determined by HPLC using an OD-3 column (*n*-hexane/*i*-PrOH = 95/5, flow rate 1.0 mL/min, λ = 254 nm, τ_{maj} = 13.0 min, τ_{min} = 10.6 min); $[\alpha]_D^{25}$ = -5.18 (c = 0.14, $CHCl_3$) , 36% ee.

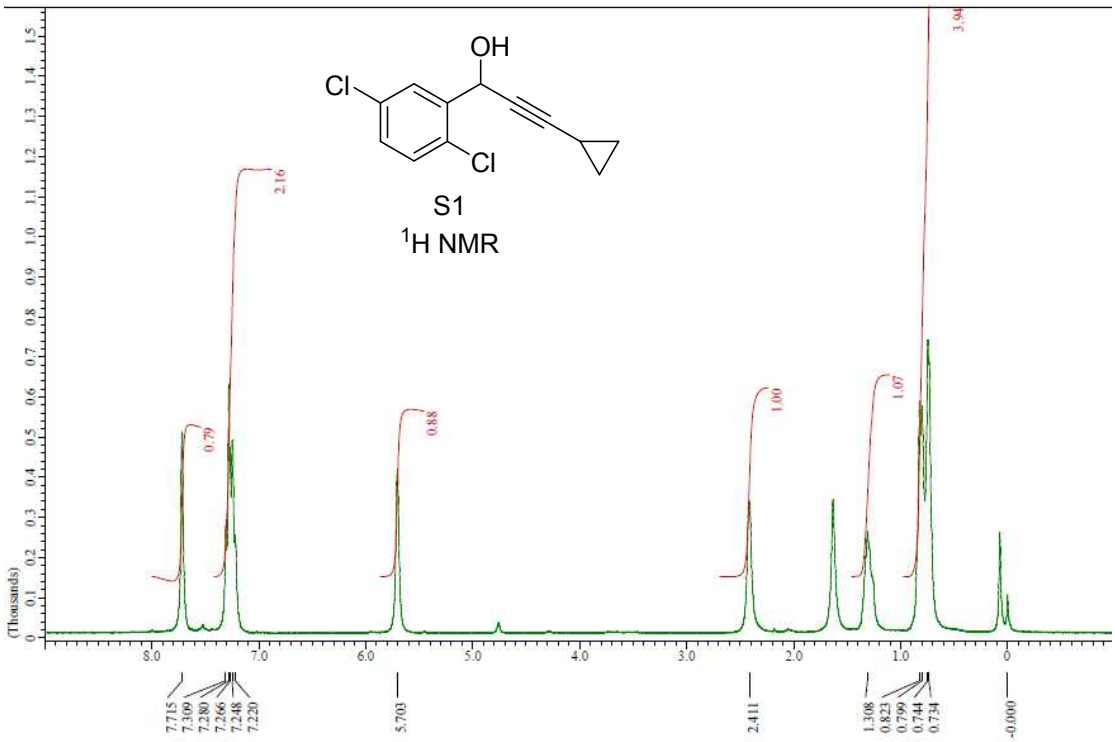
(*S*)-2-(2,5-Dichlorophenyl)-4-cyclopropyl-1,1,1-trifluorobut-3-yn-2-ol (2q)

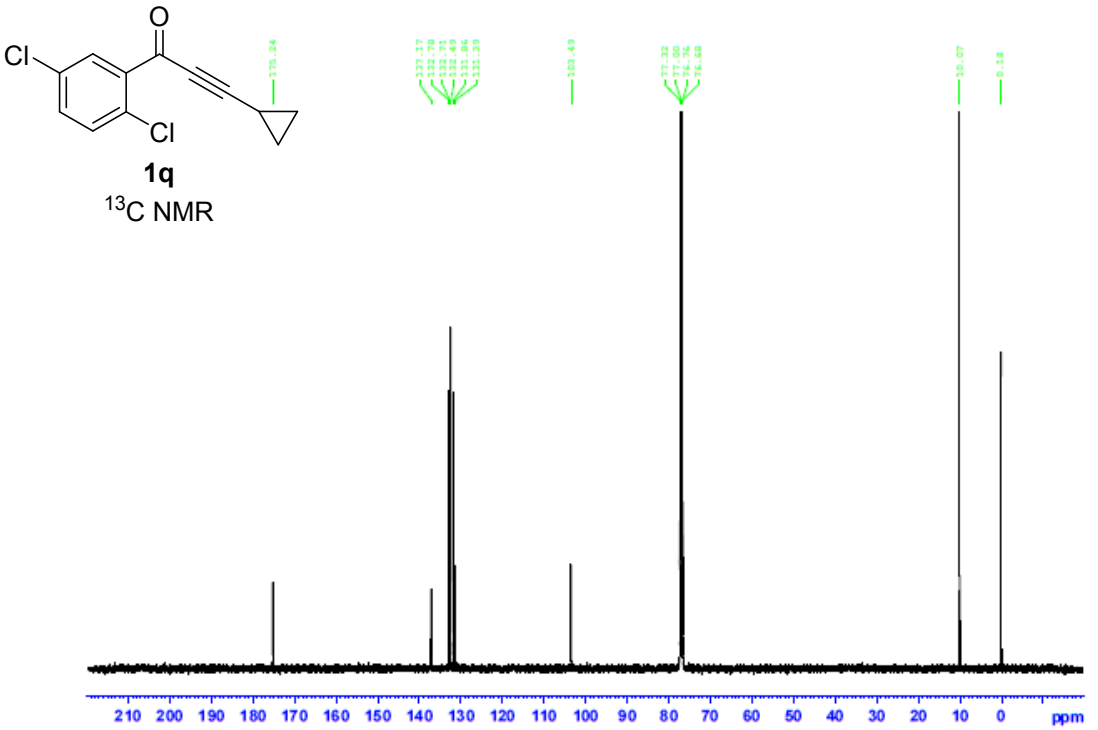


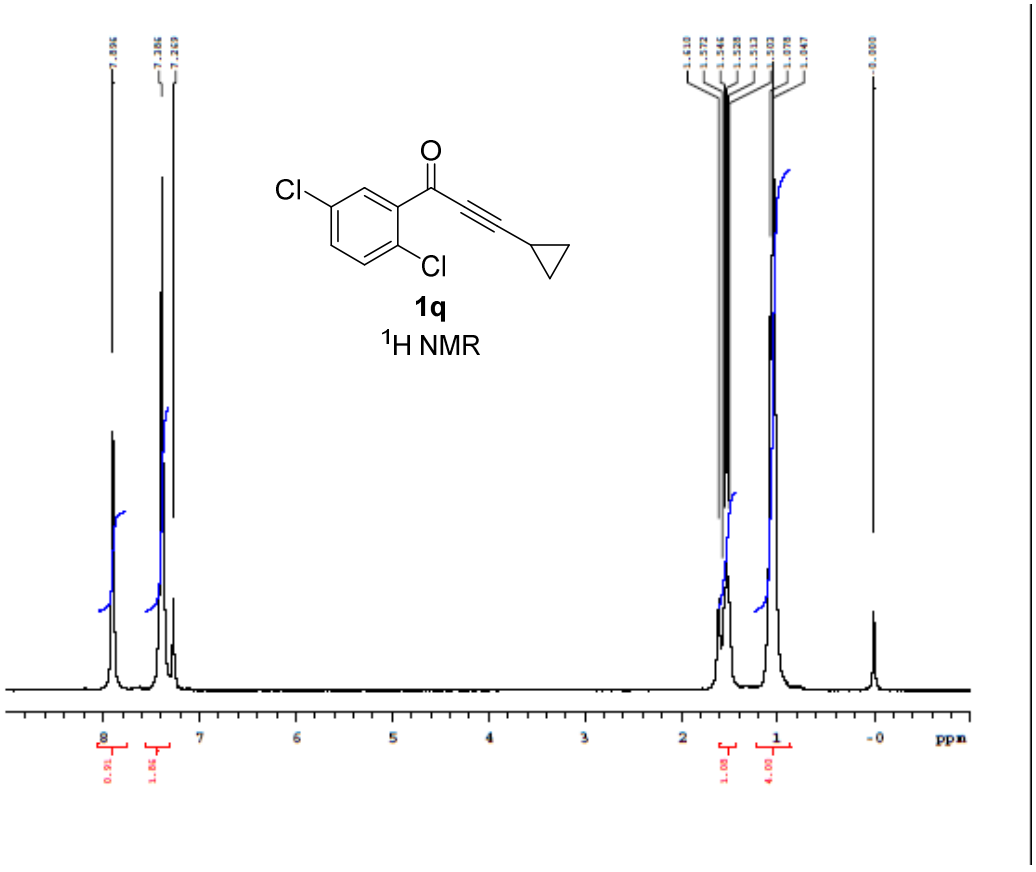
Catalyst B/Celite 503 (1/1, 2.0 equiv) was packed into the Pasteur pipette (7 ϕ ×146 mm). **1q** (23.9 mg, 0.1 mmol) and Me_3SiCF_3 (0.2 mmol, 29.6 μL, 2.0 equiv) in toluene/CH_2Cl_2 (0.1 mL) was fed into the Pasteur pipette using the syringe. The product was run out using 2.9 mL of toluene/CH_2Cl_2 and quenched with sat. NH_4Cl aq. The aqueous layer was extracted with CH_2Cl_2, and the combined organic layers was washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure. The trimethylsilyl ether was treated with nBu$_4$NF (28.8 mg, 0.11 mmol, 1.1 equiv) in THF (1.0 mL) at ambient temperature for 1 h. The resulting mixture was concentrated under reduced pressure, and purified by column chromatography on silica gel to give (*S*)-**2q** (14.5 mg, 47% yield, 30% ee) as a colorless oil.

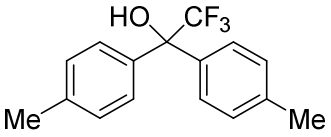
The ee of the product was determined by HPLC using an IA column (*n*-hexane/*i*-PrOH = 98/2, flow rate 0.2 mL/min, λ = 230 nm, τ_{maj} = 42.6 min, τ_{min} = 47.6 min); $[\alpha]_D^{25}$ = +5.52 (c = 0.51, $CHCl_3$) , 30% ee.


OH
Cl
Cl
S1
13C NMR
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


OH
Cl
Cl
S1
1H NMR
(Thousands)
2.16
0.79
0.88
1.00
1.07
3.94
8.0 7.0 6.0 5.0 4.0 3.0 2.0 1.0 0
7.715
7.309
7.280
7.266
7.248
7.220
5.703
2.411
1.308
0.823
0.799
0.744
0.734
-0.000

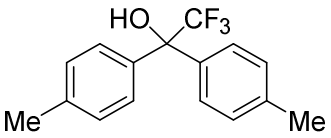

O
Cl
Cl
1q
13C NMR
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


O
Cl
Cl
1q
1H NMR
8 7 6 5 4 3 2 1 -0 ppm



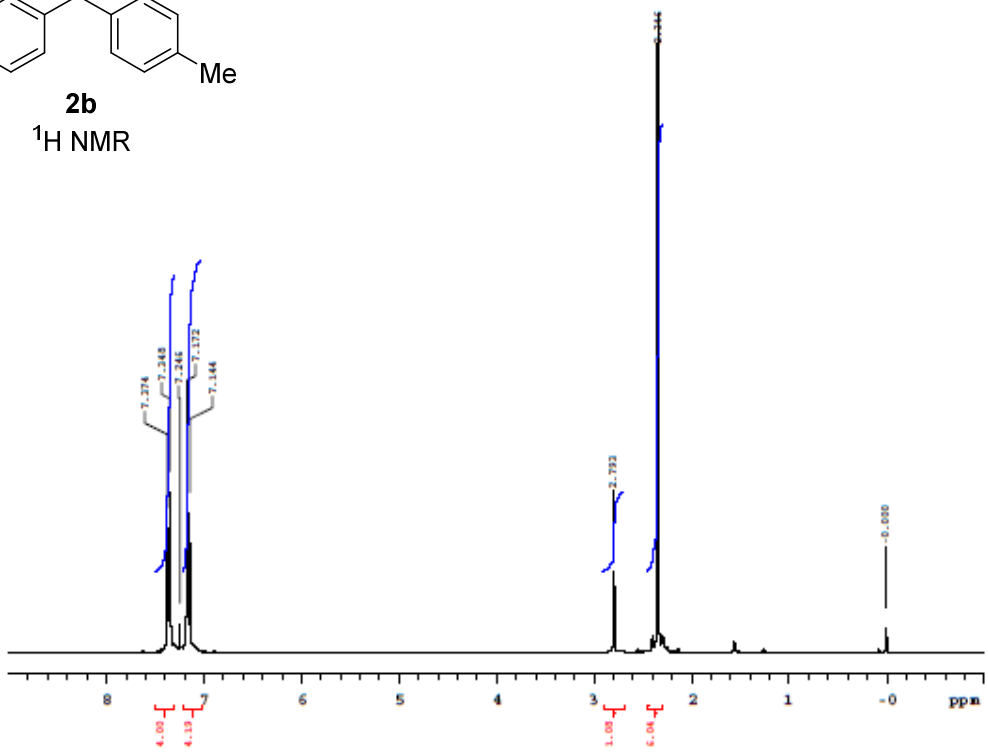
2b

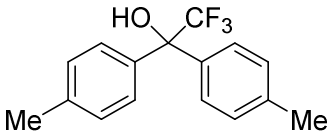
^{13}C NMR



2b

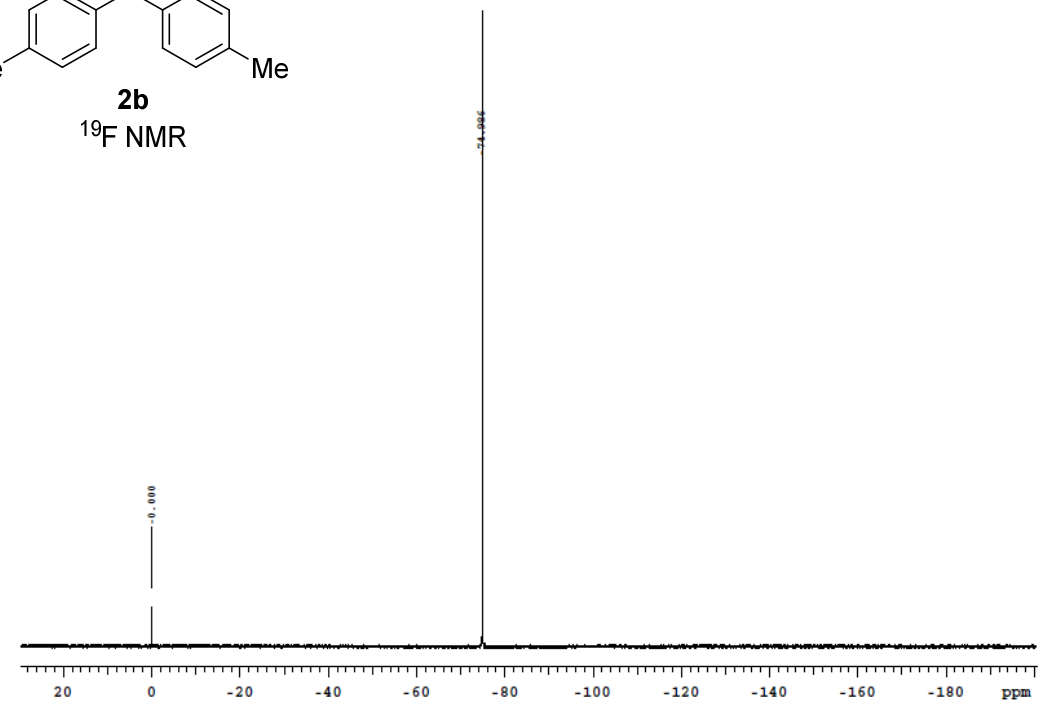
^{1}H NMR

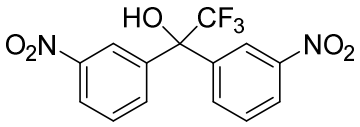




2b

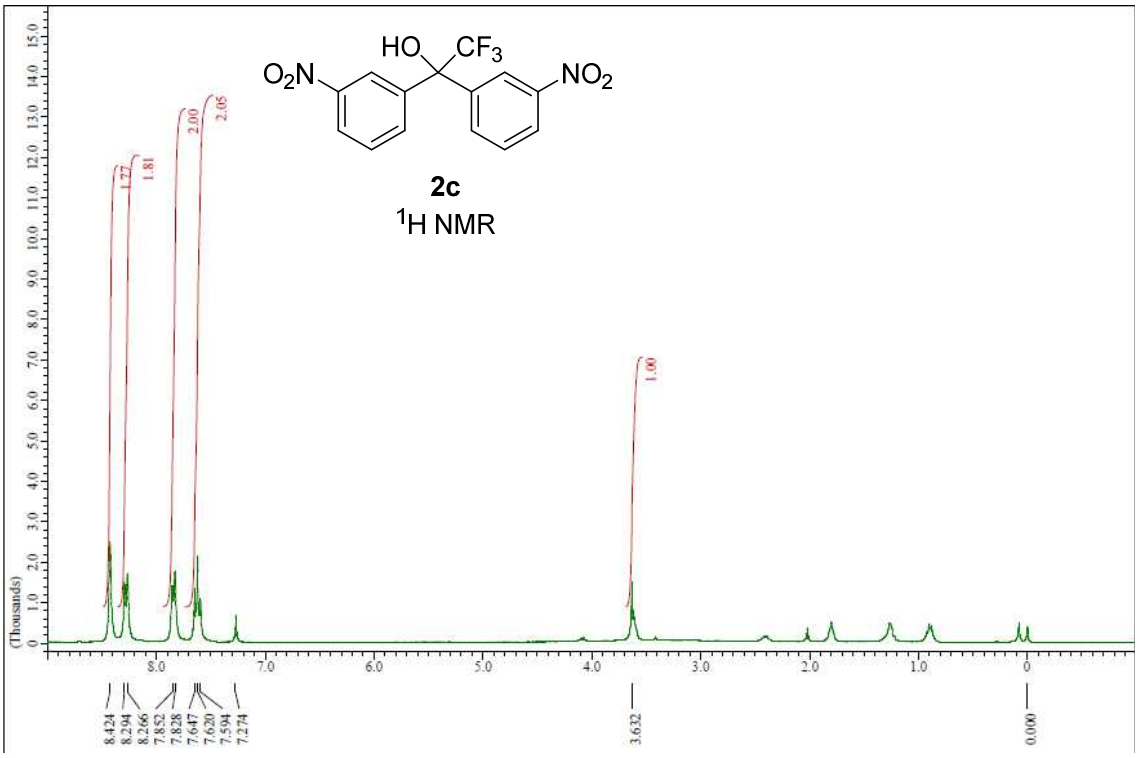
^{19}F NMR

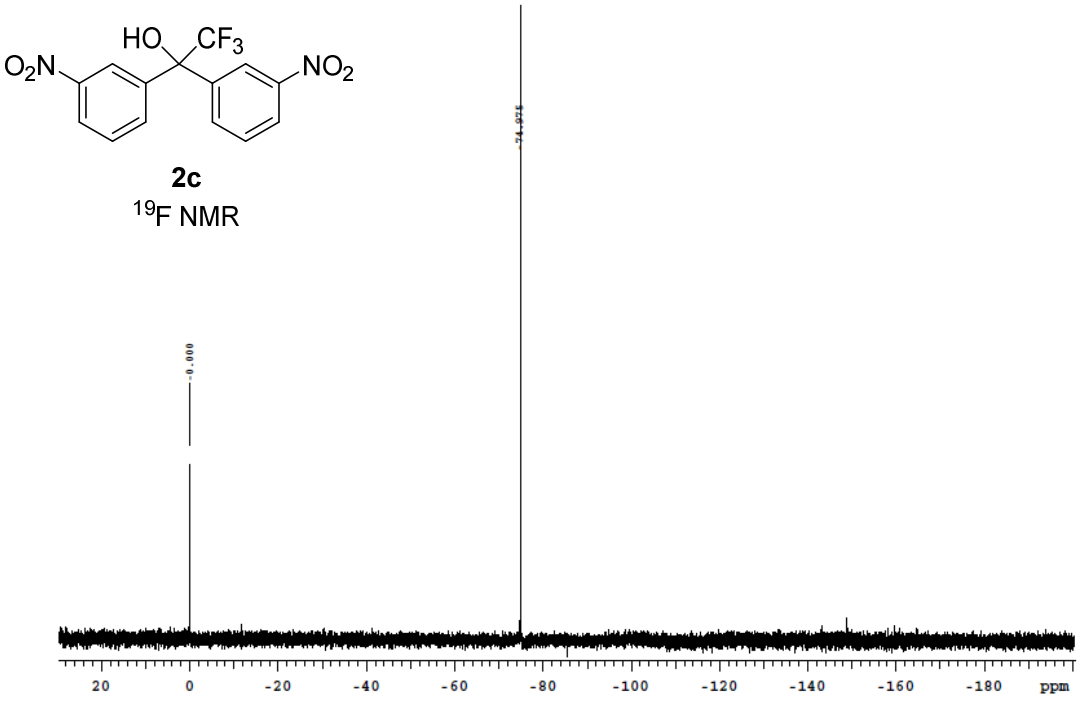


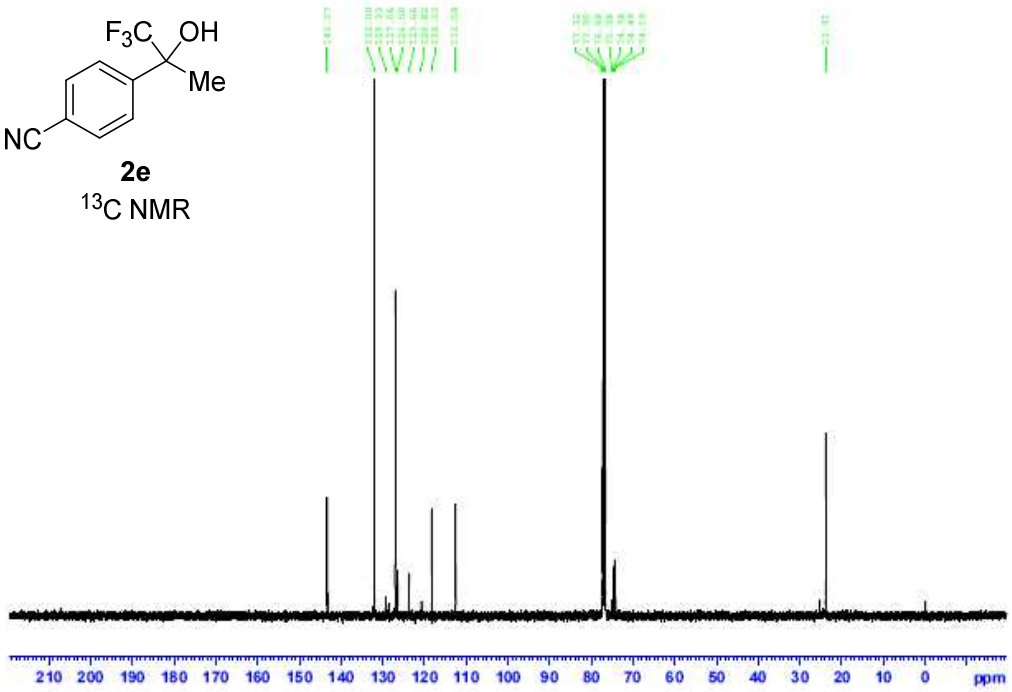


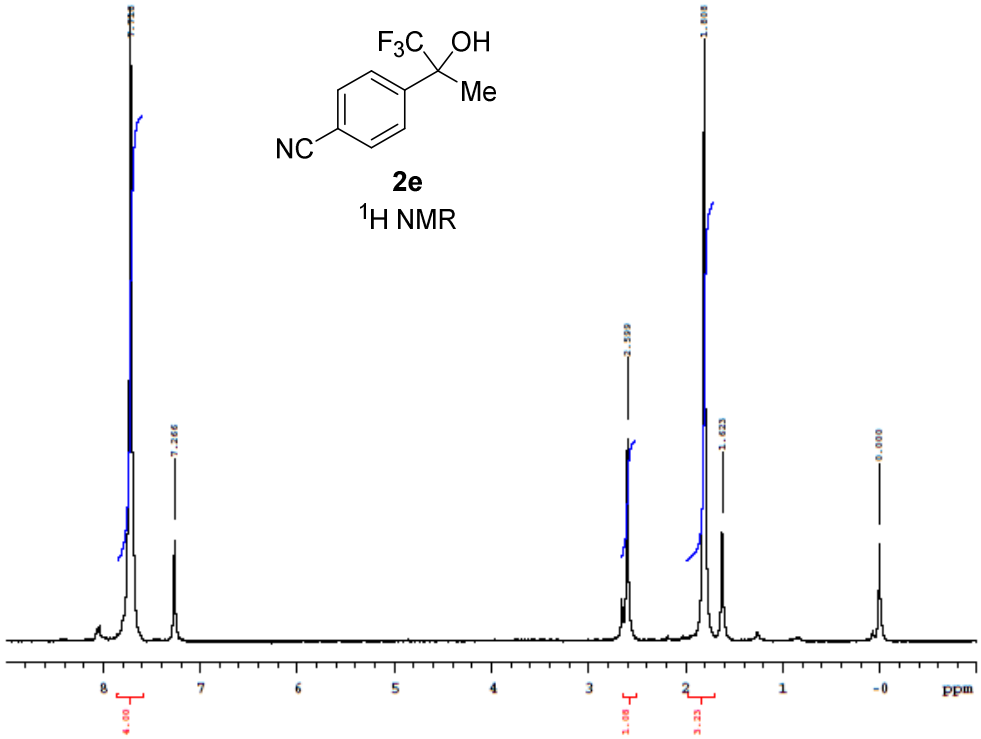
2c

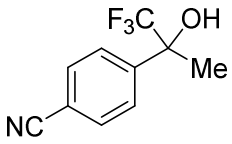
^{13}C NMR


HO
CF3
O2N
NO2
2c
1H NMR
(Thousands)
1.27
1.81
2.00
2.05
1.00
8.424
8.294
8.266
7.852
7.826
7.647
7.620
7.594
7.274
3.632
0.000


HO
CF3
O2N
NO2
2c
19F NMR
-74.975
-0.000
20
0
-20
-40
-60
-80
-100
-120
-140
-160
-180
ppm

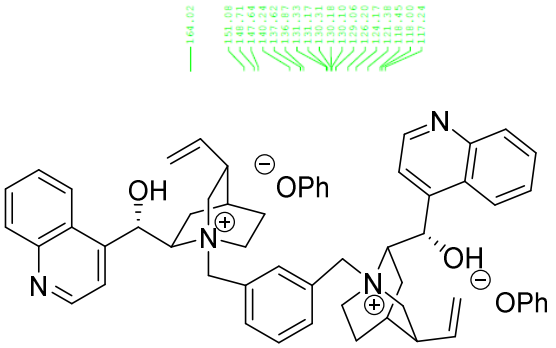

F3C
OH
Me
NC
2e
13C NMR
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


F3C
OH
Me
NC
2e
1H NMR
8 7 6 5 4 3 2 1 -0 ppm



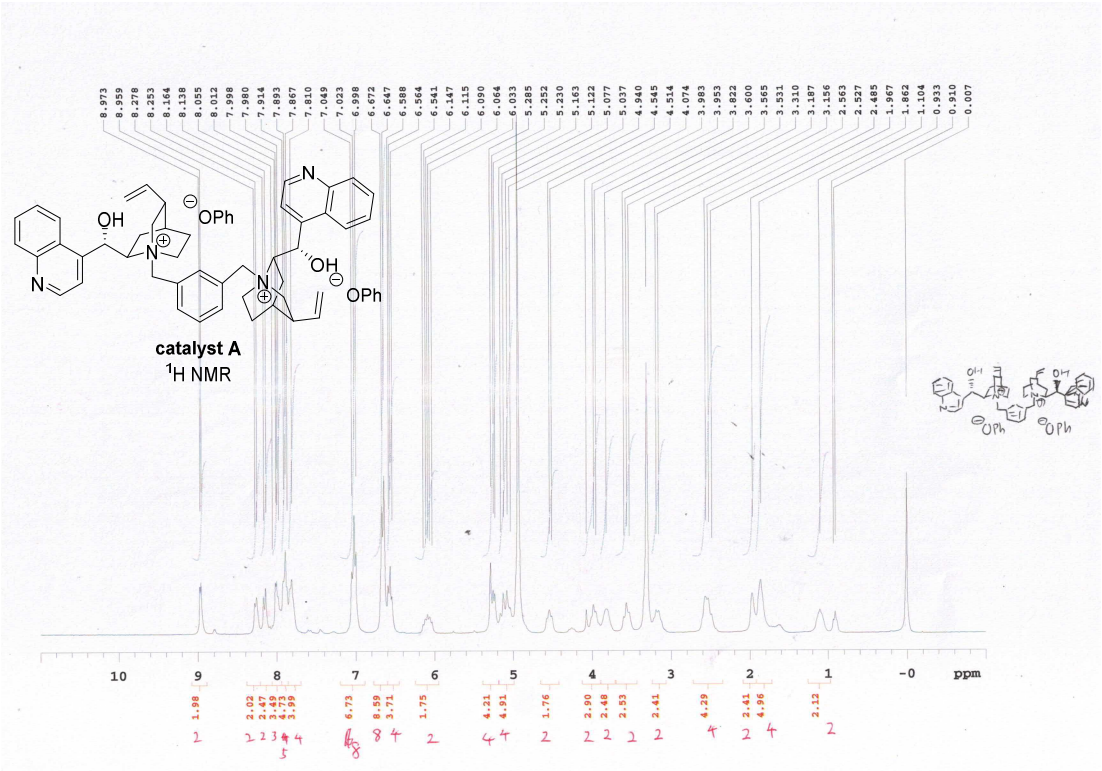
2e

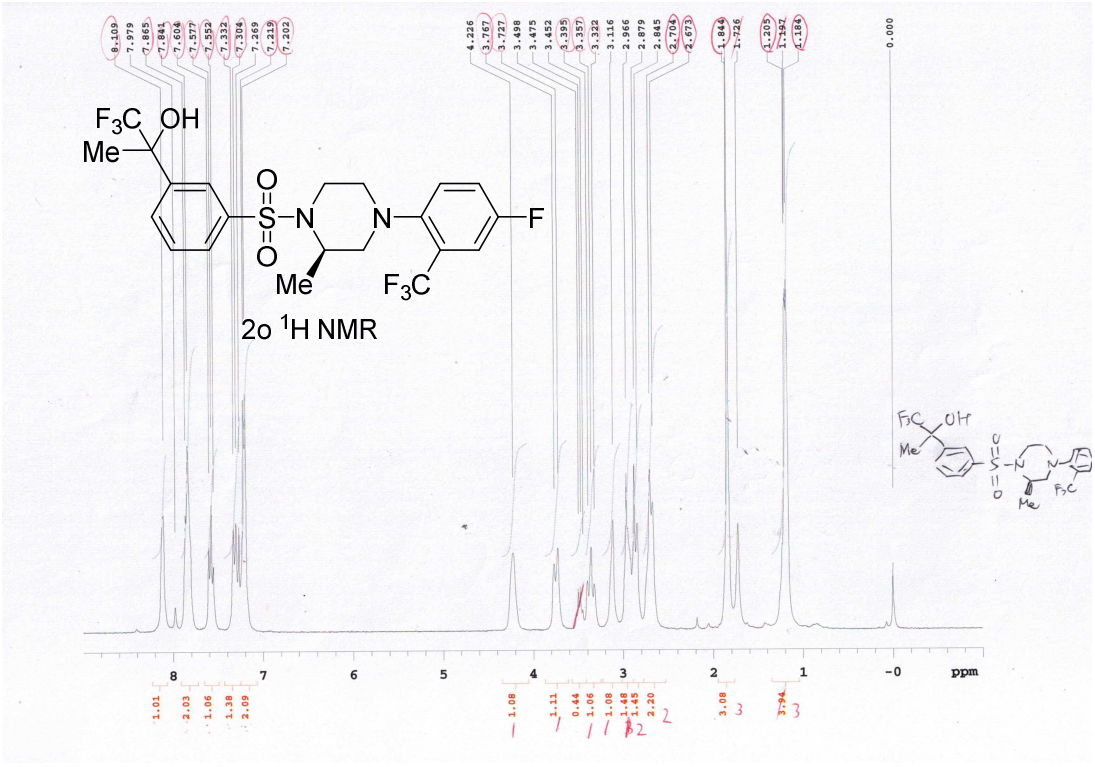
^{19}F NMR

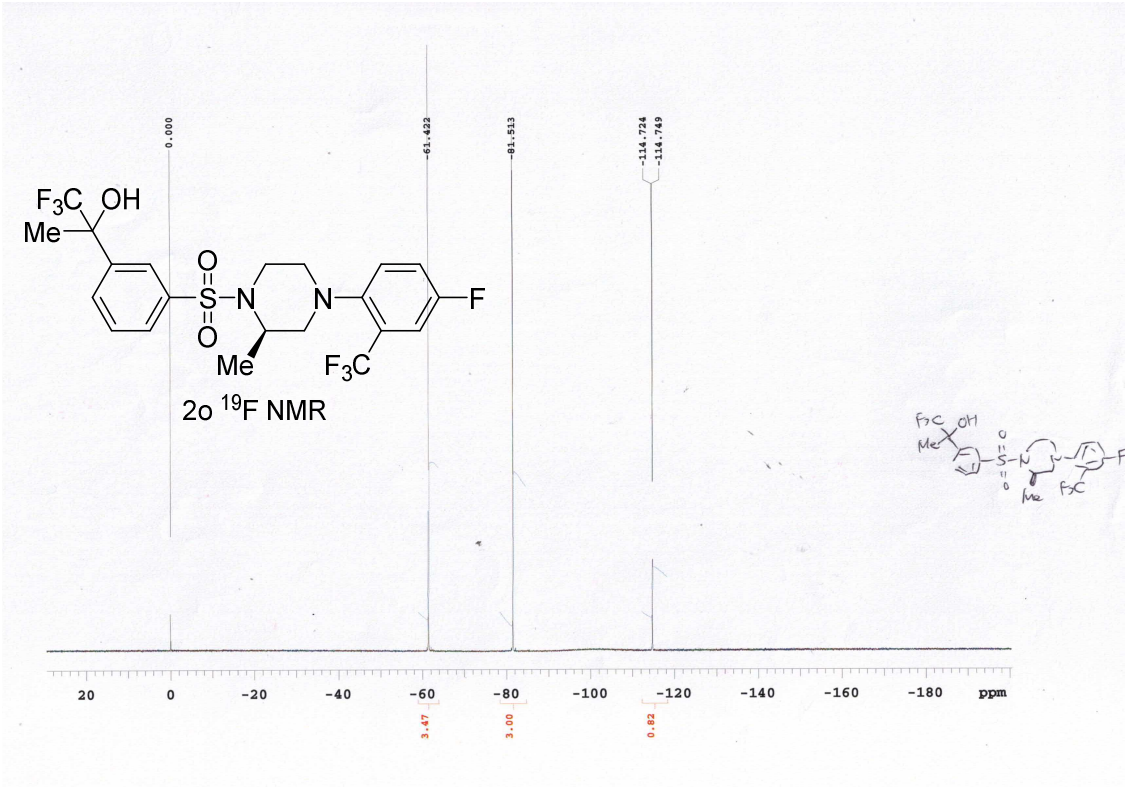


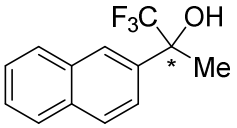
catalyst A

^{13}C NMR


OH
OPh
N
OH
OPh
catalyst A
1H NMR
10
9
8
7
6
5
4
3
2
1
-0
ppm


F3C
OH
Me
O
S
N
N
F
O
Me
F3C
2o 1H NMR
8
7
6
5
4
3
2
1
-0
ppm

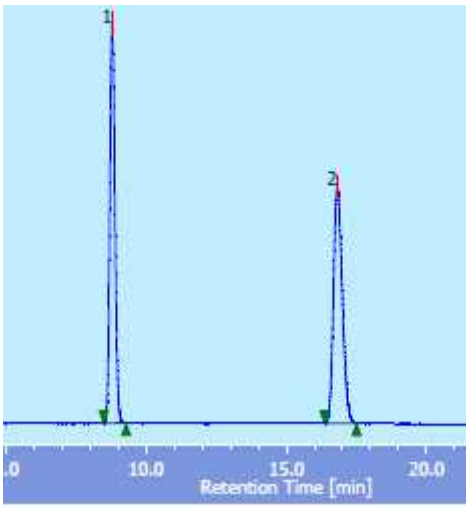


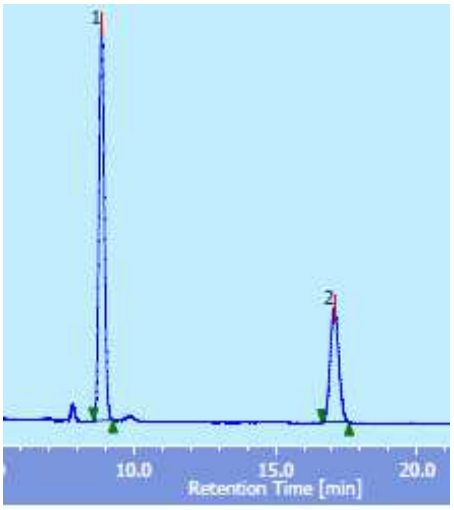


2i

HPLC using an OD-3 colum

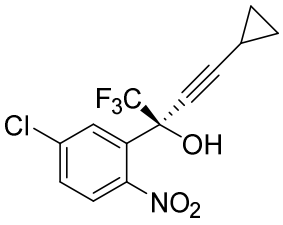
(n-Hexan/iPrOH=90/10, flow rate 1.0 mL/min, λ=254 nm)





No.	tR (min)	Area (%)	High (%)
1	8.792	49.858	62.927
2	17.067	50.142	37.073

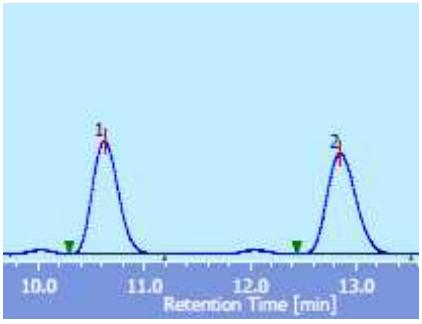
No.	tR (min)	Area (%)	High (%)
1	8.867	67.848	77.565
2	17.067	32.152	22.435

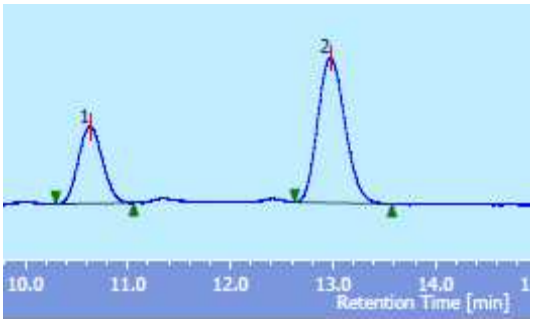


2p

HPLC using an OD-3 colum

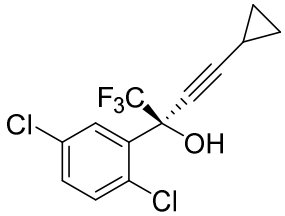
(n-Hexan/iPrOH=95/5, flow rate 1.0 mL/min, λ=254 nm)





No.	tR (min)	Area (%)	High (%)
1	10.625	49.807	52.787
2	12.850	50.193	47.213

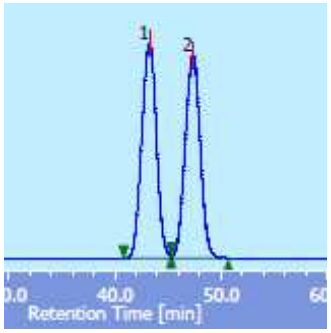
No.	tR (min)	Area (%)	High (%)
1	10.633	32.0087	34.610
2	12.975	67.913	65.390

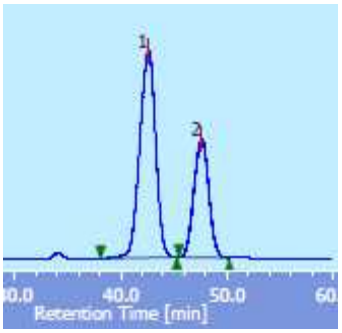


2q

HPLC using an IA colum

(n-Hexan/iPrOH=98/2, flow rate 0.2 mL/min, λ=230 nm)





No.	tR (min)	Area (%)	High (%)
1	43.242	50.719	51.460
2	47.333	49.281	48.540

No.	tR (min)	Area (%)	High (%)
1	42.583	65.164	63.569
2	47.592	34.836	36.431