Supporting Information for *Org. Lett.*:

Pd-catalyzed Asymmetric Hydrogenation of α-Fluorinated Iminoesters in Fluorinated Alcohol: A New and Catalytic Enantioselective Synthesis of Fluoro α-Amino Acid Derivatives

Hajime Abe,[†] Hideki Amii,*[,‡] and Kenji Uneyama*[,‡]

Venture Business Laboratory, Graduate School of Natural Science and Technology,[†] *and Department of Applied Chemistry, Faculty of Engineering,*[‡] *Okayama University*

3-1-1 Tsushimanaka, Okayama 700-8530, Japan

General. ^{1}H and ^{19}F NMR spectra were recorded at 200 and 188 MHz respectively, using $CDCl_3$ as a solvent. The chemical shifts are reported in δ (ppm) values relative to TMS (δ 0 ppm for ^{1}H NMR) and C_6F_6 (δ 0 ppm for ^{19}F NMR). Coupling constants are reported in hertz (Hz). Enantiomeric excess was determined by HPLC attached a Chiralcel OJ column (Daicel Chemical Industries, ltd.). 2,2,2-Trifluoroethanol (TFE) and 1,1,1,3,3,3-hexafluoro-2-propanol (HFIP) were distilled under argon. All other commercially available reagents were used as received. E. Merck silica gel (Kieselgel 60, 230-400 mesh) was employed for column chromatography.

The preparation of α-iminoesters **1a**,**c**[10b] and **1b**,**d**[10c] were described in our previous reports, and **1e**,**f** were obtained in a similar way[10b] from

the corresponding imidoyl iodides.

Benzyl 2-(4-Methoxyphenylimino)-3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-pentadecafluorononanoate (1e). Yellow oil. ^{1}H NMR δ 3.79 (s, 3 H), 5.19 (s, 2 H), 6.72 (d, J = 9.0, 2 H), 6.90 (d, J = 9.0, 2 H), 7.11-7.17 (m, 2 H), 7.26-7.34 (m, 3 H); ^{19}F NMR δ 35.6 (m, 2 F), 39.1 (m, 2 F), 39.8 (m, 2 F), 40.6-40.9 (m, 4 F), 49.3 (t, J = 13.8, 2 F), 81.0 (t, J = 10.4, 3 F); IR (neat) 3044, 1744, 1602, 1506 cm^{-1}; MS (EI) m/z 637 (M^+, 13), 502 (73), 91 (100). Anal. Calcd for $C_{23}H_{14}F_{15}NO_3$: C 43.34; H 2.21; N 2.20. Found: C 43.44; H 2.40; N 2.22.

Benzyl 3,3-Difluoro-2-(4-methoxyphenylimino)propanoate (1f). Yellow oil; mixture of *E*/*Z* isomers (7:1, the geometry has not been confirmed). ^{1}H NMR of major isomer: δ 3.79 (s, 3 H), 5.19 (s, 2 H), 6.30 (t, J = 55.7, 1 H), 6.73 (d, J = 9.1, 2 H), 6.86 (d, J = 9.1, 2 H), 7.11-7.17 (m, 2 H), 7.26-7.33 (m, 3 H); minor isomer: δ 3.83 (s, 3 H), 5.42 (s, 2 H), other peaks were not distinguished with major isomer's; ^{19}F NMR of major isomer: 41.5 (d, J = 55.7, 2 F); minor isomer: δ 44.3 (d, J = 55.7, 2 F); IR (neat) 3424, 2960, 1738, 1602, 1506 cm^{-1}; MS (EI) m/z 319 (M^+, 43), 184 (97), 91 (100). Anal. Calcd for $C_{17}H_{15}F_2NO_3$: C 63.95; H 4.74; N 4.39. Found: C 64.35; H 5.13; N 4.17.

1-Methoxy-4-(1-(4-methoxyphenylimino)-2,2,2-trifluoroethyl)benzene (1g). To a CH_2Cl_2 (25 mL) solution of *N*-(4-methoxyphenyl)trifluoroacetimidoyl chloride (1.19 g, 5 mmol) and

anisole (1.08 g, 10 mmol) added $AlCl_3$ (1.33 g, 10 mmol) and stirred for 4 h at room temperature. The resulted deep orange mixture was poured into ice-added saturated aqueous NaOAc, and extracted with ether (20 mL x 3). The combined organic phases were washed with water and brine subsequently, dried over Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane/AcOEt, 10:1) to afford **1g** as yellow oil (0.90 g, 58%) which slowly solidified, mp 47-49 °C. ^{1}H NMR δ 3.76 (s, 3 H), 3.80 (s, 3 H), 6.73-6.75 (m, 4 H), 6.82 (d, J = 9.1, 2 H), 7.19 (d, J = 9.1, 2 H); ^{19}F NMR δ 92.1 (s, 3 F); IR (neat) 2964, 1610, 1506 cm^{-1}; MS (EI) m/z 309 (M^+, 39), 240 (100). Anal. Calcd for $C_{16}H_{14}F_3NO_2$: C 62.13; H 4.56; N 4.53. Found: C 62.17; H 4.88; N 4.53.

Asymmetric Hydrogenation of Imines 1 to Amines 2. Typical procedure. A mixture of palladium(II) trifluoroacetate (3.3 mg, 0.01 mmol), (*R*)-BINAP (9.3 mg, 0.015 mmol), and acetone (1.0 mL) was stirred for 1 h under an argon atmosphere. The resulted yellow solution was evaporated in vacuo, and iminoester **1a** (69 mg, 0.25 mmol) was added with TFE (1.0 mL). A hydrogen pressure (100 atm) was subjected to the yellow solution and stirred for 24 h under ambient temperature. The resulted deep purple solution was partially condensed under reduced pressure, and chromatographed on a silica gel column (hexane/AcOEt, 30:1) to afford ethyl 2-(4-methoxyphenylamino)-3,3,3-

trifluoropropanoate (**2a**)[14] as a colorless oil (69 mg, 100%). The ee was determined (88% *R* excess) by HPLC analysis. ^{1}H NMR δ 1.31 (d, *J* = 7.1, 3 H), 3.75 (s, 3 H), 4.20-4.53 (m, 4 H), 6.70 (d, *J* = 9.1, 2 H), 6.81 (d, *J* = 9.1, 2 H); ^{19}F NMR δ 89.1 (d, *J* = 6.8, 3 F); $[\alpha]^{25}_D$ –17.1 (88% ee (*R* excess), *c* 1.24, $CHCl_3$), lit.[14] $[\alpha]^{23}_D$ –11.4 (32% ee (*R* excess), *c* 0.12, $CHCl_3$).

***t*-Butyl 2-(4-Methoxyphenylamino)-3,3,3-trifluoropropanoate (2b).** Colorless oil. ^{1}H NMR δ 1.45 (s, 9 H), 3.75 (s, 3 H), 6.34 (m, 2 H), 6.69 (d, *J* = 9.1, 2 H), 6.80 (d, *J* = 9.1, 2 H); ^{19}F NMR δ 89.2 (d, *J* = 5.8, 3 F); IR (neat) 3396, 2988, 1744, 1518 cm^{-1}; MS (EI) *m/z* 305 (M^+, 12), 249 (68), 204 (100); $[\alpha]^{25}_D$ –9.15 (85% ee (*R* excess), *c* 0.69, $CHCl_3$). Anal. Calcd for $C_{14}H_{18}F_3NO_3$: C 55.08; H 5.94; N 4.59. Found: C 55.48, H 6.21, N 4.46.

Benzyl 2-(4-Methoxyphenylamino)-3,3,3-trifluoropropanoate (2c).[14] Colorless oil. ^{1}H NMR δ 3.75 (s, 3 H), 4.31 (br d, *J* = 8.5, 1 H), 4.49-4.55 (m, 1 H), 5.24 (d, *J* = 12.3, 1 H), 5.27 (d, *J* = 12.3, 1 H), 6.84 (d, *J* = 8.8, 2 H), 6.79 (d, *J* = 8.8, 2 H), 7.30-7.38 (m, 5 H); ^{19}F NMR δ 89.2 (s, 3 F); $[\alpha]^{26}_D$ +0.35 (84% ee (*R* excess), *c* 5.22, $CHCl_3$), lit.[14] $[\alpha]^{23}_D$ –6.41 (62% ee (*R* excess), *c* 0.30, $CHCl_3$).

***t*-Butyl 3-Chloro-3,3-difluoro-2-(4-methoxyphenylamino)propanoate (2d).** Colorless oil. ^{1}H NMR δ 1.49 (s, 9 H), 3.75 (s, 3 H), 4.43 (br t, *J* = 6.2, 1 H), 6.71 (d, *J* = 9.2, 2

H), 6.81 (d, J = 9.2, 2 H); ^{19}F NMR δ 104.3 (dd, J = 16.6, 6.2, 2 F); IR (neat) 3392, 2984, 1738, 1516 cm^{-1}; MS (EI) m/z 321 (M$^+$, 25), 265 (94), 220 (100); $[\alpha]^{25}_D$ +7.96 (81% ee (*R* excess), *c* 0.57, $CHCl_3$). Anal. Calcd for $C_{14}H_{18}ClF_2NO_3$: C 52.26; H 5.64; N 4.35. Found: C 52.40; H 5.94; N 4.29.

Benzyl 2-(4-Methoxyphenylamino)-3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-pentadecafluorononanoate (2e). Colorless oil. ^{1}H NMR δ 3.75 (s, 3 H), 4.15 (br, 1 H), 4.7 (br 1 H), 5.21 (s, 2 H), 6.68 (d, J = 9.1, 2 H), 6.78 (d, J = 9.1, 2 H), 7.25-7.38 (m, 5 H); ^{19}F NMR δ 35.6 (m, 2 F), 39.0 (m, 2 F), 39.6-40.0 (m, 4 F), 40.8 (m, 2 F), 41.7-43.4 (m, 1 F), 45.9-47.4 (m, 1 F), 81.0 (t, J = 10.6, 3 F); IR (neat) 3400, 2930, 1752, 1518 cm^{-1}; MS (EI) m/z 639 (M$^+$, 6), 504 (37), 91 (100); $[\alpha]^{25}_D$ –5.23 (30% ee (*R* excess), *c* 1.45, $CHCl_3$). Anal. Calcd for $C_{23}H_{16}F_{15}NO_3$: C 43.21; H 2.52; N 2.19. Found: C 43.48; H 2.76; N 2.29.

Benzyl 3,3-Difluoro-2-(4-methoxyphenylamino)propanoate (2f). Colorless oil. ^{1}H NMR δ 2.65-2.93 (m, 1 H), 3.75 (s, 3 H), 4.2-4.4 (br m, 1 H), 5.23 (s, 2 H), 6.09 (dt, J = 2.2, 56.7, 1 H), 6.64 (d, J = 9.2, 2 H), 6.78 (d, J = 9.2, 2 H), 7.26-7.39 (m, 5 H) ; ^{19}F NMR δ 36.2 (dd, J = 56.7, 13.6, 2 F); IR (neat) 3412, 2928, 1744, 1516 cm^{-1}; MS (EI) m/z 321 (M$^+$, 42), 186 (100); $[\alpha]^{26}_D$ +2.21 (30% ee (*R* excess), *c* 1.60, $CHCl_3$). Anal. Calcd for $C_{17}H_{15}F_2NO_3$: C 63.54; H 5.33; N 4.36. Found: C 63.32; H

5.73; N 4.34.