Highly Enantioselective Synthesis of Fluorinated γ -Amino Alcohols Through Proline-Catalyzed Cross-Mannich Reaction

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General procedure for the preparation of amino alcohols 2a-g: A mixture of the imine **1** (0.172 mmol) and proline (4 mg, 20 mol %) in NMP (1M) was stirred at room temperature for 1 hour. The reaction mixture was cooled to -20 °C and the corresponding aldehyde (0.344 mmol) was added. The mixture was kept at -20 °C for 24 h, then at -10 °C for 24 h, and finally allowed to reach 0 °C and stirred at that temperature for another 24 h. The standard workup with saturated aqueous NH_4Cl solution, followed by extraction with ethyl acetate, afforded a crude mixture which was taken up in methanol (3 mL), cooled to 0 °C, and to which sodium borohydride (19.6 mg, 0.516 mmol) was added in small portions. After 3 hours at 0 °C, the reaction was quenched with saturated ammonium chloride solution and extracted with dichloromethane. The organic layer was washed with brine and dried over sodium sulfate. The corresponding fluorinated γ -amino alcohol **2** was isolated after silica gel column purification with hexane-ethyl acetate (3:1) as eluent.

(2S, 3S)-3-(4-Methoxyphenylamino)-4,4,4-trifluoro-2-methylbutan-1-ol (2a):^{S1} Prepared with the procedure described above to afford amino alcohol **2a** as a white solid in 41% overall yield; mp: 113-115 °C; $[\alpha]_D^{20} = -28.3$ ($c = 1.28$ in CHCl_3); $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 0.97 (d, 3H, $J = 7.0$), 1.70 (s, 1H), 2.25 (m, 1H), 3.54 (m, 3H), 3.73 (s, 3H), 4.25 (m, 1H), 6.70 (d, $J = 9.2$; 2H), 6.77 (d, $J = 9.2$; 2H); $^{13}\text{C-NMR}$ (CDCl_3 , 75.5 MHz) δ 10.2 (q), 35.1 (d), 55.7 (q), 56.3 (q, $^2J_{\text{C,F}} = 27.4$), 64.6 (t), 114.9 (d), 115.4 (d), 126.6 (q, $^1J_{\text{C,F}} = 283.3$), 140.9 (s), 153.0 (s); $^{19}\text{F-NMR}$ (CDCl_3 , 282.4 MHz) δ -96.70 (d, $J_{\text{F,H}} = 7.7$, 3F); HRMS Calcd. for $\text{C}_{12}\text{H}_{16}\text{F}_3\text{NO}_2$ ($\text{M} + \text{H}$)⁺ 263.1133; found 263.1182.

[S1] Fustero, S.; Pina, B.; Salavert, E.; Navarro, A.; Arellano, C. R.; Simón, A. *J. Org. Chem.* **2002**, *67*, 4667-4679.

(2S, 3S)-3-(4-Methoxyphenylamino)-4,4,5,5,5-pentafluoro-2-methylpentan-1-ol (2b):¹ Prepared with the procedure described in the Experimental Section to afford amino alcohol **2b** as a white solid in 32% overall yield; mp: 132-133 °C; $[\alpha]_D^{20}=+11.8$ ($c=0.71$ in CHCl_3); $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 0.95 (d, 3H, $J=7.0$), 2.32 (m, 1H), 3.43 (t, 1H, $J=10.3$), 3.53 (dd, $J_1=10.3$, $J_2=4.7$, 1H), 3.72 (s, 3H), 4.45 (m, 1H), 6.67 (d, $J=9.2$, 2H), 6.76 (d, $J=9.2$, 2H); $^{13}\text{C-NMR}$ (CDCl_3 , 75.5 MHz) δ 10.3 (q), 35.3 (d), 53.1 (dd, $^2J_{\text{C,F}}=24.0$, $^2J_{\text{C,F}}=20.0$), 55.7 (q), 64.3 (t), 114.7 (d), 115.0 (d), 140.8 (s), 152.8 (s); $^{19}\text{F-NMR}$ (CDCl_3 , 282.4 MHz) δ -82.7 (s, 3F), -119.7 (dd, $J_{\text{F,F}}=272.9$, $J_{\text{F,H}}=7.7$, 1F), -123.7 (dd, $J_{\text{F,F}}=272.9$, $J_{\text{F,H}}=21.5$); HRMS Calcd. for $\text{C}_{13}\text{H}_{16}\text{F}_5\text{NO}_2$ ($\text{M}+\text{H}$)⁺ 313.1101; found 313.1011.

(2S, 3S)-3-(4-Methoxyphenylamino)-4-chloro-4,4-difluoro-2-methylbutan-1-ol (2c): Prepared with the procedure described in the Experimental Section to afford amino alcohol **2c** as a white solid in 35% overall yield; mp: 122-125 °C; $[\alpha]_D^{20}=-23.0$ ($c=1.11$ in CHCl_3); $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 0.96 (d, $J=7.0$, 3H), 1.70 (s, 1H), 2.25 (m, 1H), 3.53 (m, 3H), 3.73 (s, 3H), 4.26 (m, 1H), 6.70 (d, $J=9.2$, 2H), 6.77 (d, $J=9.2$, 2H); $^{13}\text{C-NMR}$ (CDCl_3 , 75.5 MHz) δ 10.2 (t, $^4J_{\text{C,F}}=1.7$), 35.9 (d), 55.7 (q), 61.6 (t, $^2J_{\text{C,F}}=21.9$), 64.9 (t), 114.9 (d), 115.3 (d), 131.0 (t, $^1J_{\text{C,F}}=297.6$), 141.0 (s), 153.0 (s); $^{19}\text{F-NMR}$ (CDCl_3 , 282.4 MHz) δ -59.09 (dd, $J_{\text{F,F}}=162.7$, $J_{\text{F,H}}=10.3$, 1F), -60.3 (dd, $J_{\text{F,F}}=162.7$, $J_{\text{F,H}}=10.3$, 1F); HRMS Calcd. for $\text{C}_{12}\text{H}_{16}\text{ClF}_2\text{NO}_2$ ($\text{M}+\text{H}$)⁺ 279.0838; found 279.0896.

(2S, 3S)-3-(4-Methoxyphenylamino)-4,4-difluoro-2-methyl-4-phenylbutan-1-ol (2d): Prepared with the procedure described in the Experimental Section to afford amino alcohol **2d** as a white solid in 40% overall yield; mp: 105-106 °C; $[\alpha]_D^{20}=+11.5$ ($c=3.29$ in CHCl_3); $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 0.92 (d, $J=7.0$, 3H), 1.68 (s, 1H), 1.99 (m, 1H), 3.46 (m, 2H), 3.62 (m, 1H), 3.70 (s, 3H), 4.25 (m, 1H), 6.60 (d, $J=9.0$, 2H), 6.69 (d, $J=9.0$, 2H), 7.36 (m, 3H), 7.47 (m, 2H); $^{13}\text{C-NMR}$ (CDCl_3 , 75.5 MHz) δ 10.5 (q), 35.4 (d), 55.7 (q), 59.9 (t, $^2J_{\text{C,F}}=26.2$), 65.6 (t), 114.8 (d), 115.1 (d), 123.6 (t, $^1J_{\text{C,F}}=246.0$), 125.3 (d), 128.3 (d), 128.8 (d), 129.8 (d), 136.0 (t, $^2J_{\text{C,F}}=25.9$), 142.3 (s), 152.5 (s); $^{19}\text{F-NMR}$ (CDCl_3 , 282.4 MHz) δ -98.8 (dd, $J_{\text{F,F}}=246.2$, $J_{\text{F,H}}=13.8$, 1F), -106.7 (dd, $J_{\text{F,F}}=246.2$, $J_{\text{F,H}}=15.5$, 1F); HRMS Calcd. for $\text{C}_{18}\text{H}_{21}\text{F}_2\text{NO}_2$ ($\text{M}+\text{H}$)⁺ 321.1540; found 321.1532.

(2S, 3S)-3-(4-Methoxyphenylamino)-2-ethyl-4,4,4-trifluorobutan-1-ol (2e): Prepared with the procedure described in the Experimental Section to afford amino alcohol **2e** as a white solid in 31% overall yield; mp: 109-111 °C; $[\alpha]_D^{20} = -41.9$ ($c = 0.96$ in CHCl_3); $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 0.98 (t, $J = 7.3$, 3H), 1.28 (m, 1H), 1.62 (m, 1H), 1.77 (m, 1H), 1.95 (m, 1H), 3.59 (m, 2H), 3.73 (s, 3H), 3.80 (m, 1H), 4.24 (m, 1H), 6.69 (d, $J = 9.0$, 2H), 6.76 (d, $J = 9.0$, 2H); $^{13}\text{C-NMR}$ (CDCl_3 , 75.5 MHz) δ 11.9 (q), 17.9 (t), 42.1 (d), 55.5 (q), 57.0 (q, $^2J_{\text{C,F}} = 27.7$), 61.8 (t), 114.7 (d), 115.3 (d), 126.4 (q, $^1J_{\text{C,F}} = 283.5$), 140.6 (s), 152.7 (s); $^{19}\text{F-NMR}$ (CDCl_3 , 282.4 MHz) δ -74.2 (d, $J_{\text{F,H}} = 8.6$, 3F); HRMS Calcd. for $\text{C}_{13}\text{H}_{18}\text{F}_3\text{NO}_2$ ($\text{M} + \text{H}$) $^+$ 277.1290; found 277. 1224.

(2S, 3S)-3-(4-Methoxyphenylamino)-2-benzyl-4,4,4-trifluorobutan-1-ol (2f): Prepared with the procedure described in the Experimental Section to afford amino alcohol **2f** as a white solid in 35% overall yield; mp: 156-159 °C; $[\alpha]_D^{20} = -28.3$ ($c = 1.25$ in CHCl_3); $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 1.65 (s, 1H), 2.34 (m, 1H), 2.50 (dd, $J_1 = 13.4$, $J_2 = 10.7$, 1H), 2.96 (dd, $J_1 = 13.4$, $J_2 = 3.8$, 1H), 3.64 (m, 3H), 3.73 (s, 3H), 4.31 (m, 1H), 6.66 (d, $J = 9.1$, 2H), 6.77 (d, $J = 9.1$, 2H), 7.16-7.32 (m, 5H); $^{13}\text{C-NMR}$ (CDCl_3 , 75.5 MHz) δ 32.4 (t), 43.1 (d), 56.1 (q), 57.4 (q, $^2J_{\text{C,F}} = 27.4$), 62.1 (t), 115.3 (d), 116.0 (d), 126.9 (d), 129.0 (d), 129.5 (d), 139.5 (s), 141.0 (s), 153.6 (s); $^{19}\text{F-NMR}$ (CDCl_3 , 282.4 MHz) δ -71.8 (d, $J_{\text{F,H}} = 8.6$, 3F); HRMS Calcd. for $\text{C}_{18}\text{H}_{20}\text{F}_3\text{NO}_2$ ($\text{M} + \text{H}$) $^+$ 339.1446; found 339.1439.

(S)-2-[(S)-1-(4-Methoxyphenylamino)-2,2,2-trifluoroethyl]pent-4-en-1-ol (2g): Prepared with the procedure described in the Experimental Section to afford amino alcohol **2g** as a white solid in 40% overall yield; mp: 126-127 °C; $[\alpha]_D^{20} = -1.8$ ($c = 1.01$ in CHCl_3); $^1\text{H-NMR}$ (CDCl_3 , 300 MHz) δ 1.68 (s, 1H), 2.11 (m, 2H), 2.37 (m, 1H), 3.61 (m, 2H), 3.73 (s, 3H), 3.77 (m, 1H), 4.26 (m, 1H), 5.09 (m, 2H), 4.72-5.85 (m, 1H), 6.68 (d, $J = 9.1$, 2H), 6.77 (d, $J = 9.1$, 2H); $^{13}\text{C-NMR}$ (CDCl_3 , 75.5 MHz) δ 30.4 (t), 40.3 (d), 55.7 (q), 56.7 (q, $^2J_{\text{C,F}} = 26.8$), 62.1 (t), 114.9 (d), 115.3 (d), 117.5 (t), 126.4 (q, $^1J_{\text{C,F}} = 283.0$), 135.5 (d), 140.7 (s), 153.1 (s); $^{19}\text{F-NMR}$ (CDCl_3 , 282.4 MHz) δ -72.1 (d, $J_{\text{F,H}} = 8.6$, 3F); HRMS Calcd. for $\text{C}_{14}\text{H}_{18}\text{F}_3\text{NO}_2$ ($\text{M} + \text{H}$) $^+$ 289.1290; found 289.1273.

Scheme S1: HPLC-MS analysis of the products formed in the cross-Mannich condensation of imine **1a** and 3-butenal catalyzed by 20 mol % L-proline.

In order to determine which secondary products limit the yields in these reactions, we decided to use HPLC-MS methods to analyze the crude reaction mixture resulting from the condensation between aldimine **1a** and 3-butenal in a reaction carried out in the same conditions as described in the main text (20 mol % L-proline in NMP, entry 4, Table 2). We were thus able to identify the major components of the crude mixture as follows: 42% of γ-amino alcohol **2g**, 14% of amine **5** from reduction of the unreacted starting imine, 9% of diamine **6**, 7% of the diol **7** derived from aldehyde self-aldol condensation, and 4% of aminodiol **8**, generated by aldol condensation of 3-butenal with the β-amino aldehyde arising from the cross-Mannich reaction of **1a** and butenal. Twenty-four percent of the crude product corresponded to other minor components that were individually present in proportions lower than 3% (see Scheme S1 above).

(2*S*, 3*S*)-Methyl 3-(4-methoxyphenylamino)-4,4,4-trifluoro-2-methylbutanoate (*syn-4*):^{S1} A mixture of the imine **1a** (127 mg, 0.625 mmol) and proline (14 mg, 20 mol %) in NMP (0.65 mL) was stirred at room temperature for 1 hour. The reaction mixture was cooled at -20 °C and then propanal (94 μL, 1.25 mmol) was added. The mixture was kept at -20 °C for 24 h, then at -10 °C for 24 h, and finally allowed to reach 0 °C and stirred at that temperature for further 24 h. The usual workup with saturated aqueous NH₄Cl solution, followed by extraction with ethyl acetate afforded a crude mixture which was taken up in *t*-BuOH-H₂O 5:1 (6.5 mL). To this solution, NaClO₂ (240 mg, 2.13 mmol), NaH₂PO₄ (127 mg, 1.06 mmol) and 2-methyl-2-butene (480 μL, 4.31 mmol) were added and the suspension was stirred at room temperature. After completion of the reaction as monitored by TLC (2h) the volatile components were removed under vacuum. The crude material was extracted with ethyl acetate and washed with brine and water. The resulting crude acid was dissolved in 14 mL MeOH and treated with 0.63 mL of 2M solution of (trimethylsilyl)diazomethane in ether (1.25 mmol) and stirred for 10 minutes. Solvent removal under vacuum followed by silica gel column chromatography (Hexane-EtOAc 6:1) provided the corresponding pure ester *syn-4* as a colorless oil (85 mg, 47% yield); [α]_D²⁰ = +2.37 (c=0.60 in CHCl₃); ¹H-NMR (CDCl₃, 300 MHz) δ 1.23 (d, 3H, *J*=7.1), 3.45 (d, 1H, *J*=8.3), 3.58 (s, 3H), 3.68 (s, 3H), 4.35 (m, 1H), 6.62 (d, *J*=6.8, 2H), 6.76 (d, *J*=6.8, 2H); ¹³C-NMR (CDCl₃, 75.5 MHz) δ 10.5 (q), 38.6 (d), 51.3 (q), 54.7 (q), 57.5 (CHCF₃, quadruplet ²*J*_{C,F}=213.5), 113.8 (d), 114.8 (d), 124.7 (CF₃, quadruplet ²*J*_{C,F}=21.2), 139.0 (s), 152.4 (s), 172.3 (s); ¹⁹F-NMR (CDCl₃, 282.4 MHz) δ -73.7 (s, 3F); HRMS Calcd. for C₁₃H₁₆F₃NO₃ 291.1082; found 291.1093.

(2*S*,3*S*)

2a

2f

(2S,3S)

2g