SUPPORTING INFORMATION

Catalytic Asymmetric Synthesis of α,α,α -Trifluoromethyl Amines by the Copper Catalyzed Nucleophilic Addition of Diorganozinc Reagents to Imines

Caroline Lauzon and André B. Charette*

Département de Chimie, Université de Montréal, P.O. Box 6128, Station Downtown, Montreal, Québec, Canada, H3C 3J7

E-mail: andre.charette@umontreal.ca

Experimental procedures. Characterization data for new compounds. ^1H and ^{13}C NMR spectra. GC/SFC/HPLC traces for 1:1 mixture and enantioenriched compounds.

General. Unless otherwise stated, reactions were run under argon atmosphere with rigid exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds.¹ Anhydrous *N,N*-dimethylformamide, dichloromethane, diethyl ether, tetrahydrofuran and benzene were obtained by filtration through drying columns using a GlassContour system (Irvine, CA). Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Merck 60 F₂₅₄). Visualization of the developed chromatogram was performed by UV and aqueous potassium permanganate. Flash column chromatographies were performed using 230-400 mesh silica.² Melting points are uncorrected. Optical rotations were determined at 589 or 546 nm. Data are reported as follows: $[\alpha]_D^{temp}$, concentration (*c* in g/100 mL), and solvent. Chemical shifts for ¹H NMR spectra are recorded in parts per million from tetramethylsilane using the chloroform (7.27 ppm) as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet and br = broad), coupling constant in Hz, integration. Chemical shifts for ¹³C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of the deuteriochloroform (77.00 ppm) as the internal standard. Chemical shift for ¹⁹F NMR spectra are recorded in parts per million from trifluorotoluene (-63.9 ppm) as the internal standard. All ¹³C NMR spectra were obtained with complete proton decoupling. High performance liquid chromatography data are reported as follows: column type, eluent, flow rate, and retention time (*t*_r).

Reagents: Unless otherwise stated, commercial reagents were used without purification. Me₂Zn and Cu(OTf)₂ were purchased from Strem Chemicals, Et₂Zn was purchased from Akzo Nobel Chemicals, and Ti(OEt)₄ was purchased from Aldrich. *P,P*-Diphenylphosphinic amide was prepared according to the procedure developed by Stec.³ Racemic samples for HPLC or SFC analysis were prepared by addition of EtMgBr or MeMgBr to the hemiaminals **10a-10f** in THF.

General procedure for the synthesis of hemiaminals 10: To a solution of *P,P*-diphenylphosphinic amide (**8**) (167 mg, 0.770 mmol, 1.10 equiv) in CH₂Cl₂ (7 mL) was added the corresponding trifluoromethyl ketone (2.10 mmol, 3.00 equiv) and titanium ethoxide (294 μL, 1.40 mmol, 2.00 equiv). After stirring at rt for 96 h, the reaction was quenched with a mixture of sand (5 g) and Na₂SO₄·10H₂O (2 g). CH₂Cl₂ (250 mL) was added and the reaction was stirred at rt for 30 min. The suspension was then filtered and washed with CH₂Cl₂ (3 x 100 mL). The combined organic layers were dried over Na₂SO₄. Concentration and purification by flash chromatography (50% EtOAc:hexanes) gave the corresponding hemiaminal as a colorless solid.

General procedure for diethylzinc addition to hemiaminals 10: Anhydrous toluene (2 mL) was added to a mixture of (*R,R*)-MeDuPHOS monoxide (**3**) (6.1 mg, 0.019 mmol, 0.05 equiv) and Cu(OTf)₂ (14 mg, 0.038 mmol, 0.10 equiv). The resulting heterogeneous dark green solution was stirred for 1 h at rt. Neat diethylzinc (117 μL, 1.14 mmol, 3.00 equiv) was then added at rt and the resulting red-brown suspension was stirred for an additional 20 min before cooling to 0 °C. After 10 min of stirring, a cooled solution (0 °C) of the hemiaminal (0.38 mmol, 1.0 equiv) in toluene (1 mL + 1 mL for washing) was cannulated (using a teflon cannula) into the catalyst suspension. After stirring 16 h at 0 °C, the reaction was quenched with saturated aqueous NH₄Cl (7 mL) and the aqueous phase was washed with CH₂Cl₂ (3 x 15 mL). The combined organic layers were dried over anhydrous Na₂SO₄. Concentration and purification by flash chromatography (50% EtOAc:hexanes) gave the corresponding addition product as a colorless solid.

General procedure for dimethylzinc addition to hemiaminals 10: Anhydrous toluene (3 mL) was added to (*R,R*)-MeDuPHOS monoxide (**3**) (10.0 mg, 0.030 mmol, 0.05 equiv) and [Cu(OTf)₂]₂·PhMe (16 mg, 0.030 mmol, 0.05 equiv). The resulting heterogeneous yellow solution was stirred for 1 h at rt. Neat dimethylzinc (165 μL, 2.38 mmol, 4.00 equiv) was added at rt and the resulting yellow suspension was stirred for an additional 20 min before cooling to 0 °C. After 10 min, a cooled

(¹) Shriver, D. F.; Drezdson, M. A. *The manipulation of air-sensitive compounds*; 2nd Edition; Ed. Wiley: New York, 1986.

(²) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(³) Stec, W. J.; Krzyzanowska, B. *Synthesis*, **1978**, 521-524.

solution (0 °C) of the hemiaminal (0.60 mmol, 1.00 equiv) in toluene (2 mL + 1 mL for washing) was cannulated (using a teflon cannula) into the catalyst suspension. After stirring for 48 h at 0 °C, the reaction was quenched with saturated NH_4Cl (7 mL) and the aqueous phase was washed with CH_2Cl_2 (3 x 15 mL). The combined organic layers were dried over Na_2SO_4 . Concentration and purification by flash chromatography gave the corresponding addition product as a colorless solid.

Typical procedure for the cleavage of the *P,P*-diphenylphosphinoyl group: Protected amine **9** (0.446 mmol, 1.00 equiv) was dissolved in concentrated aqueous HCl (3 mL). The mixture was heated to 90 °C for 9 h. The reaction was cooled to rt and neutralized with aqueous NaOH (1 M). The resulting mixture was extracted with CH_2Cl_2 (3 x 7 mL) and the combined organic layers were dried over anhydrous Na_2SO_4 . The solvent was then evaporated. The amine was precipitated as its hydrochloride salt from CH_2Cl_2 using a solution of HCl in Et_2O (1 M) (4.46 mmol, 10.0 equiv) to give a colorless solid.

***N*-(1-Ethoxy-2,2,2-trifluoro-1-phenylethyl)-*P,P*-diphenylphosphinic amide (10a):** The general procedure described above was followed. Yield: 47%; mp 91-92 °C; R_f 0.68 (50% EtOAc/hexane); ^1H NMR (CDCl_3 , 300 MHz) δ 7.95-7.89 (m, 2H), 7.77-7.71 (m, 2H), 7.61 (d, J = 7.1 Hz, 2H), 7.55-7.42 (m, 4H), 7.37-7.24 (m, 5H), 4.06 (d, J = 4.7 Hz, 1H), 3.82 (qdd, J = 15.1, 7.1, 6.9 Hz, 1H), 3.73 (qdd, J = 15.4, 7.1, 6.9 Hz, 1H), 1.25 (t, J = 6.9 Hz, 3H); ^{13}C NMR (CDCl_3 , 75 MHz) δ 134.0, 133.9, 133.5, 132.3, 132.2, 131.8, 131.7, 131.7, 131.7, 131.6, 131.4, 131.2, 129.4, 128.3, 128.3, 128.2, 128.1, 128.0, 121.4, 89.0, 60.1, 14.7; ^{19}F NMR (CDCl_3 , 282 MHz) δ -77.5; ^{31}P NMR (CDCl_3 , 120 MHz) δ 19.3; FTIR (neat) 3108, 2530, 1265, 1178, 1123, 909, 736, 705, 633 cm^{-1} ; LRMS (APCI+) calcd for $\text{C}_{22}\text{H}_{21}\text{F}_3\text{NO}_2\text{P}$ [M-OEt] $^+$: 374.1 m/z , Found: 374.0 m/z ; Anal. Calcd for $\text{C}_{22}\text{H}_{21}\text{F}_3\text{NO}_2\text{P}$: C, 63.01; H, 5.05; N, 3.34. Found: C, 62.69; H, 5.40; N, 3.21.

***N*-[1-(4-Bromophenyl)-1-ethoxy-2,2,2-trifluoroethyl]-*P,P*-diphenylphosphinic amide (10b):** The general procedure described above was followed. Yield: 56%; mp 112-116 °C; R_f 0.52 (50% EtOAc/hexane); ^1H NMR (CDCl_3 , 400 MHz) δ 7.89-7.84 (m, 2H), 7.70-7.65 (m, 2H), 7.56-7.41 (m, 1H), 7.48-7.41 (m, 5H), 7.35 (d, J = 3.3 Hz, 1H), 7.33 (d, J = 3.3 Hz, 1H), 7.32-7.25 (m, 2H), 4.11 (d, J = 4.1 Hz, 1H), 3.86 (qdd, J = 15.1, 7.1, 6.9 Hz, 1H), 3.76 (qdd, J = 15.1, 7.1, 6.9 Hz, 1H), 1.26 (t, J = 6.9 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 132.9, 132.8, 132.5, 132.4, 131.7, 131.7, 131.5, 131.4, 131.4, 131.3, 131.3, 131.2, 130.6, 129.9, 128.2, 128.0, 127.9, 123.7, 122.9, 88.1, 60.1, 14.6; ^{19}F NMR (CDCl_3 , 282 MHz) δ -77.6; ^{31}P NMR (CDCl_3 , 120 MHz) δ 19.5; FTIR (neat) 3080, 2901, 1590, 1479, 1291, 1195, 1067, 980, 824, 695 cm^{-1} ; LRMS (APCI+) Calcd for $\text{C}_{22}\text{H}_{20}\text{BrF}_3\text{NO}_2\text{P}$ [M-OEt] $^+$: 452.0. Found: 452.0. Anal. Calcd for $\text{C}_{22}\text{H}_{20}\text{BrF}_3\text{NO}_2\text{P}$: C, 53.03; H, 4.05; N, 2.81. Found: C, 53.02; H, 3.76; N, 2.77.

***N*-[1-Ethoxy-2,2,2-trifluoro-1-(3-methylphenyl)ethyl]-*P,P*-diphenylphosphinic amide (10c):** The general procedure described above was followed. Yield: 53%; mp 104 °C; R_f 0.44 (50% EtOAc/hexane); ^1H NMR (CDCl_3 , 300 MHz) δ 7.95-7.88 (m, 2H), 7.78-7.71 (m, 2H), 7.52-7.29 (m, 8H), 7.16 (t, J = 7.7 Hz, 1H), 7.09 (d, J = 7.3 Hz, 1H), 4.10 (d, J = 4.7 Hz, 1H), 3.93-3.81 (m, 1H), 3.80-3.70 (m, 1H), 2.21 (br s, 3H), 1.27 (t, J = 7.3 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 137.5, 134.1, 133.7, 133.6, 132.4, 131.9, 131.8, 131.6, 131.6, 131.3, 130.2, 128.8, 128.6, 128.4, 128.3, 128.1, 127.9, 125.2, 123.2, 89.1, 60.0, 21.3, 14.8; ^{19}F NMR (C_6D_6 , 282 MHz) δ -77.6; ^{31}P NMR (C_6D_6 , 120 MHz) δ 18.1; FTIR (neat) 3058, 2979, 2901, 1591, 1484, 1438, 1268, 1155, 1120, 1068, 893, 722, 692 cm^{-1} ; LRMS (APCI+) Calcd for $\text{C}_{23}\text{H}_{23}\text{F}_3\text{NO}_2\text{P}$ [M-OEt] $^+$: 388.1. Found: 388.1. Anal. Calcd for $\text{C}_{23}\text{H}_{23}\text{F}_3\text{NO}_2\text{P}$: C, 63.74; H, 5.35; N, 3.23. Found: C, 63.70; H, 5.28; N, 3.17.

***N*-[1-Ethoxy-2,2,2-trifluoro-1-(4-methylphenyl)ethyl]-*P,P*-diphenylphosphinic amide (10d):** The general procedure described above was followed. Yield: 46%; mp 107-108 °C; R_f 0.32 (50% EtOAc/hexane); ^1H NMR (CDCl_3 , 400 MHz) δ 7.95-7.88 (m, 2H), 7.78-7.71 (m, 2H), 7.49 (d, J = 8.0 Hz, 2H), 7.46-7.33 (m, 4H), 7.31-7.24 (m, 2H), 7.02 (d, J = 8.2 Hz, 2H), 4.15 (d, J = 5.2 Hz, 1H), 3.82 (qdd, J = 15.4, 8.0, 7.1 Hz, 1H), 3.68 (qdd, J = 15.4, 7.1, 7.1 Hz, 1H), 2.24 (br s, 3H), 1.22 (t, J = 7.1 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 139.2, 133.8, 133.1, 132.5, 131.8, 131.6, 131.5, 131.5, 131.3, 131.1, 131.0, 130.7, 128.5, 128.1, 128.0, 127.9, 127.9, 127.8, 123.0, 88.9, 59.8, 20.7, 14.5; ^{19}F NMR (CDCl_3 , 282 MHz) δ -77.6; ^{31}P NMR (CDCl_3 , 160 MHz) δ 19.2; FTIR (neat)

3059, 2979, 1438, 1265, 1172, 1070, 813, 719, 692 cm^{-1} ; LRMS (APCI+) Calcd for $\text{C}_{23}\text{H}_{23}\text{F}_3\text{NO}_2\text{P}$ [M-OEt] $^+$: 388.1. Found: 388.1.

***M*-[1-Ethoxy-2,2,2-trifluoro-1-(2-naphthyl)ethyl]-*P,P*-diphenylphosphinic amide (10e):** The general procedure described above was followed. Yield: 51%; mp 134-136 °C; R_f 0.21 (30% EtOAc/hexane); ^1H NMR (CDCl_3 , 400 MHz) δ 8.03 (s, 1H), 7.96-7.90 (m, 2H), 7.79-7.67 (m, 6H), 7.53-7.42 (m, 5H), 7.31 (dd, J = 7.1, 1.4 Hz, 1H), 7.27-7.23 (m, 2H), 4.20 (d, J = 4.4 Hz, 1H), 3.86 (m, 2H), 1.31 (t, J = 6.9 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 133.3, 132.2, 131.8, 131.8, 131.7, 131.6, 131.5, 131.5, 131.4, 131.3, 131.1, 131.1, 128.6, 128.3, 128.2, 128.1, 128.0, 127.7, 127.2, 126.9, 126.0, 125.0, 123.4, 89.2, 60.4, 14.8; ^{19}F NMR (CDCl_3 , 282 MHz) δ -77.2; ^{31}P NMR (CDCl_3 , 120 MHz) δ 19.3; FTIR (neat) 2919, 2254, 2131, 1455, 1393, 1201, 1180, 1010, 904, 725, 649 cm^{-1} ; LRMS (APCI+) Calcd for $\text{C}_{26}\text{H}_{23}\text{F}_3\text{NO}_2\text{P}$ [M-OEt] $^+$: 424.1. Found: 424.1.

***M*-[1-(4-Chlorophenyl)-1-ethoxy-2,2,2-trifluoroethyl]-*P,P*-diphenylphosphinic amide (10f):** The general procedure described above was followed. Yield: 63%; mp 117-120 °C; R_f 0.42 (50% EtOAc/hexane); ^1H NMR (CDCl_3 , 400 MHz) δ 7.87-7.83 (m, 2H), 7.70-7.65 (m, 2H), 7.55-7.36 (m, 6H), 7.33-7.26 (m, 2H), 7.12 (d, J = 8.9 Hz, 2H), 4.29 (d, J = 4.4 Hz, 1H), 3.87 (qdd, J = 15.4, 7.3, 7.0 Hz, 1H), 3.77 (qdd, J = 15.4, 7.3, 7.0 Hz, 1H), 1.26 (t, J = 7.0 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 135.2, 132.9, 132.8, 132.0, 132.0, 131.7, 131.6, 131.5, 131.4, 131.4, 131.3, 131.3, 131.2, 129.7, 128.1, 128.0, 127.9, 127.6, 122.9, 88.1, 60.0, 14.6; ^{19}F NMR (CDCl_3 , 282 MHz) δ -77.6; ^{31}P NMR (CDCl_3 , 160 MHz) δ 20.0; FTIR (neat) 3079, 2899, 1477, 1290, 1195, 1111, 1068, 827, 725, 695 cm^{-1} ; LRMS (APCI+) Calcd for $\text{C}_{22}\text{H}_{20}\text{ClF}_3\text{NO}_2\text{P}$ [M-OEt] $^+$: 408.1. Found: 408.0. Anal. Calcd for $\text{C}_{22}\text{H}_{20}\text{ClF}_3\text{NO}_2\text{P}$: C, 58.22; H, 4.44; N, 3.09. Found: C, 58.04; H, 4.24; N, 3.10.

***P,P*-Diphenyl-*N*[(1*R*)-1-phenyl-1-(trifluoromethyl)propyl]phosphinic amide (11):** The general procedure described above was followed. Yield: 83%, enantiomeric excess (91%) was determined by HPLC analysis (Chiralpak AD-H, 90:10 hexane: *i*-PrOH, 1 mL/min: (*S*) t_r = 13.4 min, (*R*) t_r = 14.5 min); R_f 0.41 (50% EtOAc/hexane); $[\alpha]_D^{20}$ = -27.0 (c 0.77, CHCl_3); ^1H NMR (CDCl_3 , 300 MHz) δ 8.03 (dd, J = 12.4, 6.9 Hz, 2H), 7.87-7.82 (m, 2H), 7.75 (d, J = 7.9 Hz, 2H), 7.55-7.31 (m, 9H), 3.55 (d, J = 6.0, 1H), 2.72-2.63 (m, 1H), 2.15 (dq, J = 14.7, 7.4, 6.4 Hz, 1H), 0.73 (t, J = 7.4 Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 138.2, 135.5, 134.7, 133.8, 133.0, 132.9, 132.7, 132.4, 132.3, 131.7, 131.5, 129.5, 129.2, 129.0, 128.9, 128.8, 128.7, 127.8, 127.8, 68.3, 27.5, 9.3; ^{19}F NMR (CDCl_3 , 282 MHz) δ -72.4; ^{31}P NMR (CDCl_3 , 160 MHz) δ 20.0; FTIR (neat) 3067, 2253, 1439, 1254, 1122, 905, 727, 651 cm^{-1} ; LRMS (APCI+) Calcd for $\text{C}_{22}\text{H}_{21}\text{F}_3\text{NOP}$ [M+H] $^+$: 404.1. Found: 404.1. Anal. Calcd for $\text{C}_{22}\text{H}_{21}\text{F}_3\text{NOP}$: C, 65.51; H, 5.25; N, 3.47. Found: C, 65.46; H, 5.42; N, 3.44.

Peak #	RT [min]	Area %
1	14.458	49.848
2	15.911	50.1521

Peak #	RT [min]	Area %
1	13.429	4.319
2	14.510	95.681

***P,P*-Diphenyl-*N*[(1*R*)-2,2,2-trifluoro-1-methyl-1-phenylethyl]phosphinic amide (12):** The general procedure described above was followed. Yield: 85%, enantiomeric excess (99%) was determined by HPLC analysis (Chiralpak AD-H, 90:10 hexane: *i*-PrOH, 1 mL/min: (*S*) t_r = 23.1 min, (*R*) t_r = 25.6 min); mp 97-99 °C; R_f 0.27 (50% EtOAc/hexane); $[\alpha]_D^{20}$ = -51.5 (c 0.81, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 8.00 (m, 2H), 7.81 (m, 1H), 7.64 (d, J = 7.9 Hz, 2H), 7.56-7.44 (m, 4H), 7.41-7.31 (m, 5H), 3.79 (d, J = 6.7 Hz, 1H), 1.82 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 139.4, 134.3, 134.1, 133.0, 132.8, 132.0, 131.9, 131.9, 131.8, 131.8, 131.3, 131.2, 128.6, 128.5, 128.4, 128.4, 128.2, 127.5, 126.4, 62.6, 20.3; ¹⁹F NMR (CDCl₃, 282 MHz) δ -78.6; ³¹P NMR (CDCl₃, 120 MHz) δ 20.3; FTIR (neat) 3169, 3058, 2882, 1438, 1271, 1147, 977, 846, 721, 692 cm⁻¹; LRMS (APCI+) Calcd for C₂₁H₁₉F₃NOP [M+H]⁺: 390.1. Found: 390.2.

Peak #	RT [min]	Area %
1	22.795	49.122
2	25.378	50.878

Peak #	RT [min]	Area %
1	23.128	0.707
2	25.579	99.293

***N*[(1*R*)-1-(4-Bromophenyl)-1-(trifluoromethyl)propyl]-*P,P*-diphenylphosphinic amide (13):** The general procedure described above was followed. Yield: 71%, enantiomeric excess (95%) was determined by HPLC analysis (Chiralpak AD-H, 90:10 hexane: *i*-PrOH, 1 mL/min: (*S*) t_r = 14.0 min, (*R*) t_r = 20.0 min); mp 135-137 °C; R_f 0.55 (60% EtOAc/hexane); $[\alpha]_D^{20}$ = -6.64 (c 0.71, CHCl₃); ¹H NMR (CDCl₃, 300 MHz) δ 8.02-7.95 (m, 2H), 7.81-7.74 (m, 2H), 7.65 (d, J = 8.6 Hz, 2H), 7.62-7.37 (m, 8H), 3.48 (d, J = 5.6 Hz, 1H), 2.69-2.51 (m, 1H), 2.13-1.98 (m, 1H), 0.69 (t, J = 7.3 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 136.4, 136.3, 134.1, 133.5, 132.8, 132.2, 132.0, 131.9, 131.6, 131.6, 131.2, 130.8, 130.7, 129.0, 128.4, 128.2, 128.1, 126.0, 122.2, 67.3, 26.9, 8.50; ¹⁹F NMR (CDCl₃, 282 MHz) δ -72.4; ³¹P NMR (CDCl₃, 160 MHz) δ 20.9; FTIR (neat) 3177, 1438, 1249, 1156, 1121, 1010, 906, 818, 726, 697 cm⁻¹; LRMS (APCI+) Calcd for C₂₂H₂₀BrF₃NOP [M+H]⁺: 482.0. Found: 482.0. Anal. Calcd for C₂₂H₂₀BrF₃NOP: C, 54.79; H, 4.18; N, 2.90. Found: C, 54.95; H, 4.14; N, 2.82.

Peak #	RT [min]	Area %
1	14.369	48.427
2	20.769	51.573

Peak #	RT [min]	Area %
1	14.026	2.752
2	20.023	97.248

***N*[(1*R*)-1-(4-Bromophenyl)-2,2,2-trifluoro-1-methylethyl]-*P,P*-diphenylphosphinic amide (14):**

The general procedure described above was followed. Yield: 89%, enantiomeric excess (97%) was determined by HPLC analysis (Chiralpak AD-H, 90:10 hexane: *i*-PrOH, 1 mL/min: (*S*) t_r = 19.7 min, (*R*) t_r = 31.1 min); mp 116-120 °C; R_f 0.38 (50% EtOAc/hexane); $[\alpha]_D^{20}$ = -31.7 (c 0.70, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 8.01-7.96 (m, 2H), 7.80-7.74 (m, 2H), 7.57-7.47 (m, 8H), 7.43-7.39 (m, 2H), 3.70 (d, J = 6.6 Hz, 1H), 1.79 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 138.4, 134.0, 133.8, 132.7, 132.6, 132.0, 131.9, 131.9, 131.9, 131.4, 131.1, 131.0, 128.6, 128.5, 128.5, 128.4, 128.3, 126.0, 122.6, 62.6, 20.4; ¹⁹F NMR (CDCl₃, 282 MHz) δ -78.6; ³¹P NMR (CDCl₃, 160 MHz) δ 20.3; FTIR (neat) 3057, 2867, 1438, 1149, 977, 851, 724, 693 cm⁻¹; LRMS (APCI+) Calcd for C₂₁H₁₈BrF₃NOP [M+H]⁺: 468.0. Found: 468.0. Anal. Calcd for C₂₁H₁₈BrF₃NOP: C, 53.87; H, 3.87; N, 2.99. Found: C, 53.60; H, 3.67; N, 3.00.

Peak #	RT [min]	Area %
1	19.729	49.652
2	32.752	50.348

Peak #	RT [min]	Area %
1	19.666	1.529
2	31.141	98.471

***N*[(1*R*)-1-(3-Methylphenyl)-1-(trifluoromethyl)propyl]-*P,P*-diphenylphosphinic amide (15):**

The general procedure described above was followed. Yield: 78%, enantiomeric excess (95%) was determined by SFC analysis (Chiralpak OD, 3% MeOH, 2 mL/min: (*R*) t_r = 9.0 min, (*S*) t_r = 9.9 min); R_f 0.35 (50% EtOAc/hexane); $[\alpha]_D^{20}$ = -18.2 (c 1.5, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 8.01-7.97 (m, 2H), 7.84-7.79 (m, 2H), 7.56-7.45 (m, 6H), 7.44-7.36 (m, 2H), 7.29-7.25 (m, 1H), 7.13 (d, J = 7.7 Hz, 1H), 3.49 (d, J = 6.3 Hz, 1H), 2.63 (dq, J = 14.5, 7.4, 7.1 Hz, 1H), 2.36 (s, 3H), 2.16 (dq, J = 14.6, 7.4, 7.1 Hz, 1H), 0.73 (t, J = 7.4 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 137.9, 137.4, 134.7, 134.0, 133.5, 132.7, 132.2, 132.1, 131.7, 131.1, 131.0, 128.8, 128.5, 128.4, 128.3, 128.3, 127.9, 126.4, 124.3, 67.6, 26.9, 21.6, 8.7; ¹⁹F NMR (CDCl₃, 282 MHz) δ -72.4; ³¹P NMR (CDCl₃, 160 MHz) δ 20.0; FTIR (neat) 2919, 2253, 1439, 1312, 1152, 814, 727 cm⁻¹; LRMS (APCI+) Calcd for C₂₃H₂₃F₃NOP [M+H]⁺: 418.2. Found: 418.1.

Peak #	Start [min]	Time [min]	End [min]	Area %
1	8.24	8.76	9.15	50.24
2	9.15	9.65	10.13	49.76

Peak #	Start [min]	Time [min]	End [min]	Area %
1	8.24	8.76	9.15	50.24
2	9.15	9.65	10.13	49.76

***P,P*-Diphenyl-*N*[(1*R*)-2,2,2-trifluoro-1-methyl-1-(3-methylphenyl)ethyl]phosphinic amide (16):** The general procedure described above was followed. Yield: 84%, enantiomeric excess (99%) was determined by HPLC analysis (Chiralpak AD-H, 90:10 hexane: *i*-PrOH, 1 mL/min: (*R*) t_r = 11.5 min, (*S*) t_r = 17.0 min); R_f 0.45 (EtOAc/hexane, 50:50); $[\alpha]_D^{20}$ = -39.7 (*c* 0.94, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 8.05-7.97 (m, 2H), 7.86-7.78 (m, 2H), 7.60-7.38 (m, 8H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.18 (d, *J* = 7.3 Hz, 1H), 3.76 (d, *J* = 6.6 Hz, 1H), 2.39 (s, 3H), 1.85 (s, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 139.2, 137.9, 134.3, 134.1, 133.1, 132.8, 131.9, 131.9, 131.8, 131.3, 129.0, 128.5, 128.5, 128.4, 128.4, 128.2, 127.1, 126.1, 123.4, 62.4, 21.5, 20.2; ¹⁹F NMR (CDCl₃, 282 MHz) δ -78.5; ³¹P NMR (CDCl₃, 160 MHz) δ 20.2; FTIR (neat) 3059, 2228, 1439, 1271, 907, 728 cm⁻¹; LRMS (APCI+) Calcd for C₂₂H₂₁F₃NOP [M+H]⁺: 404.4. Found: 404.4.

Peak #	RT [min]	Area %
1	11.512	50.069
2	17.008	49.931

Peak #	RT [min]	Area %
1	11.452	99.404
2	16.965	0.596

***N*[(1*R*)-1-(4-Methylphenyl)-1-(trifluoromethyl)propyl]-*P,P*-diphenylphosphinic amide (17):** The general procedure described above was followed. Yield: 77%, enantiomeric excess (97%) was determined by HPLC analysis (Chiralpak AD-H, 90:10 hexane: *i*-PrOH, 1 mL/min: (*S*) t_r = 16.5 min, (*R*) t_r = 18.9 min); R_f 0.45 (50% EtOAc/hexane); $[\alpha]_D^{20}$ = -10.4 (*c* 0.48, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 8.04-7.99 (m, 2H), 7.89-7.80 (m, 2H), 7.61 (d, *J* = 8.1 Hz, 2H), 7.57-7.47 (m, 4H), 7.44-7.39

(m, 2H), 7.19 (d, $J = 8.1$ Hz, 2H), 3.50 (d, $J = 5.9$ Hz, 1H), 2.71-2.51 (m, 1H), 2.36 (s, 3H), 2.19-2.10 (m, 1H), 0.75 (t, $J = 7.3$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 137.7, 134.5, 134.3, 134.3, 133.7, 133.2, 132.4, 132.0, 131.5, 131.5, 131.5, 130.8, 128.8, 128.3, 128.2, 128.1, 128.0, 127.0, 126.2, 67.3, 26.6, 20.6, 8.5; ^{19}F NMR (CDCl_3 , 282 MHz) δ -72.6; ^{31}P NMR (CDCl_3 , 120 MHz) δ 20.2; FTIR (neat) 3057, 1438, 1253, 1121, 1107, 870, 725, 696 cm^{-1} ; LRMS; (APCI+) Calcd for $\text{C}_{23}\text{H}_{23}\text{F}_3\text{NOP}$ $[\text{M}+\text{H}]^+$: 418.2. Found: 418.1.

Peak #	RT [min]	Area %
1	14.743	49.223
2	16.788	50.777

Peak #	RT [min]	Area %
1	16.510	1.540
2	18.868	98.460

***N*[(1*R*)-1-(2-Naphthyl)-1-(trifluoromethyl)propyl]-*P,P*-diphenylphosphinic amide (18):** The general procedure described above was followed. Yield: 73%, the enantiomeric excess (94%) was determined after hydrogenation of the naphthyl to give the tetrahydronaphthyl using Adam's Catalyst (PtO_2)³ by HPLC analysis (Chiralpak AD-H, 90:10 hexane: *i*-PrOH, 1 mL/min: (*S*) t_r = 12.8 min, (*R*) t_r = 15.9 min); mp 166-168 °C; R_f 0.56 (50% EtOAc/hexane); $[\alpha]_D^{20}$ = -13.2 (*c* 0.85, CHCl_3); ^1H NMR (CHCl_3 , 400 MHz) δ 8.11-8.07 (m, 1H), 8.05-7.99 (m, 3H), 7.91 (s, 1H) 7.89-7.79 (m, 4H), 7.58-7.48 (m, 5H), 7.46-7.34 (m, 3H), 3.62 (d, $J = 6.3$ Hz, 1H), 2.79 (dq, $J = 14.6, 7.4, 7.1$ Hz, 1H), 2.22 (dq, $J = 14.6, 7.4, 7.1$ Hz, 1H), 0.74 (t, $J = 7.4$ Hz, 3H); ^{13}C NMR (CDCl_3 , 100 MHz) δ 134.8, 134.6, 133.9, 133.3, 132.6, 132.6, 132.5, 132.3, 131.8, 131.8, 131.7, 131.0, 128.5, 128.4, 128.4, 128.2, 127.1, 126.7, 126.6, 126.4, 126.2, 125.0, 67.9, 26.9, 8.81; ^{19}F NMR (CDCl_3 , 282 MHz) δ -71.9; ^{31}P NMR (CDCl_3 , 120 MHz) δ 20.3; FTIR (neat) 3374, 3168, 3059, 2225, 1438, 1250, 1154, 1122, 1036, 908, 726, 698 cm^{-1} ; LRMS (APCI+) Calcd for $\text{C}_{26}\text{H}_{23}\text{F}_3\text{NOP}$ $[\text{M}+\text{H}]^+$: 454.2. Found: 454.1. Anal. Calcd for $\text{C}_{26}\text{H}_{23}\text{F}_3\text{NOP}$: C, 68.87; H, 5.11; N, 3.09. Found: C, 68.51; H, 4.73; N, 3.05.

(³) Cram, D. J.; Helgeson, R. C.; Peacock, S. C.; Kaplan, L. J.; Domeier, L. A.; Moreau, P.; Koja, K.; Mayer, J. M.; Chao, Y.; Siegel, M. G.; Hoffman, D. H.; Sogah, G. D. Y. *J. Org. Chem.* **1978**, *43*, 1930-1946.

Peak #	RT [min]	Area %
1	12.929	48.044
2	16.209	51.956

Peak #	RT [min]	Area %
1	12.779	2.926
2	15.938	97.074

***N*[(1*R*)-1-(4-Chlorophenyl)-1-(trifluoromethyl)propyl]-*P,P*-diphenylphosphinic amide (19):**

The general procedure described above was followed. Yield: 71%, enantiomeric excess (93%) was determined by HPLC analysis (Chiralpak AD-H, 90:10 hexane: *i*-PrOH, 1 mL/min: (*S*) t_r = 13.2 min, (*R*) t_r = 19.2 min); R_f 0.50 (50% EtOAc/hexane); $[\alpha]_D^{20}$ = -10.8 (*c* 0.78, CHCl₃); ¹H NMR (CDCl₃, 400 MHz) δ 8.00-7.95 (m, 2H), 7.80-7.75 (m, 2H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.55-7.34 (m, 6H), 7.30 (d, *J* = 9.1 Hz, 2H), 3.53 (d, *J* = 5.8 Hz, 1H), 2.69-2.51 (m, 1H), 2.17-2.00 (m, 1H), 0.69 (t, *J* = 7.1 Hz, 3H); ¹³C NMR (CDCl₃, 100 MHz) δ 136.0, 134.4, 134.2, 133.8, 133.1, 132.4, 132.2, 132.1, 131.9, 131.8, 131.8, 131.0, 130.9, 128.9, 128.5, 128.5, 128.4, 128.3, 126.3, 67.4, 27.2, 8.64; ¹⁹F NMR (CDCl₃, 282 MHz) δ -72.4; ³¹P NMR (CDCl₃, 160 MHz) δ 20.9; FTIR (neat) 3180, 2980, 1438, 1246, 1154, 1102, 1013, 907, 822, 726, 630 cm⁻¹; LRMS (APCI+) Calcd for C₂₂H₂₀ClF₃NOP [M+H]⁺: 438.1. Found: 438.1.

Peak #	RT [min]	Area %
1	13.452	47.597
2	19.565	52.403

Peak #	RT [min]	Area %
1	13.173	3.721
2	19.198	96.279

1-Bromo-4-[(1*S*)-1-methyl-1-(trifluoromethyl)propyl]benzene (20): The general procedure described above was followed. Yield: 84%; mp 196-198 °C; R_f 0.22 (MeOH/DCM, 20:80); $[\alpha]_D^{20}$ = +15.4 (*c* 1.08, H₂O); ¹H NMR (D₂O, 400 MHz) δ 7.63 (d, *J* = 8.6 Hz, 2H), 7.30 (d, *J* = 8.6 Hz, 2H), 4.70 (s, 3H), 2.60-2.42 (m, 1H), 2.27-2.11 (m, 1H), 0.78 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (D₂O, 100 MHz) δ 132.0, 132.0, 128.1, 123.7, 123.5, 64.3, 23.9, 5.37; ¹⁹F NMR (CDCl₃, 282 MHz) δ -76.6; FTIR (neat) 2806, 1607, 1520, 1273, 1165, 1109, 610 cm⁻¹; LRMS (APCI+) Calcd for C₁₀H₁₂BrClF₃N [M-HCl]⁺: 281.0. Found: 281.2. Anal. Calcd for C₁₀H₁₂BrClF₃N: C, 58.22; H, 4.44; N, 3.09. Found: C, 58.04; H, 4.24; N, 3.10.

^1H and ^{13}C spectra of selected compounds

10e

¹³C NMR (CDCl₃, 100 MHz)

10e

¹³C NMR (CDCl₃, 100MHz)

17

19

¹³C NMR (CDCl₃, 100MHz)

19

¹³C NMR (CDCl₃, 100MHz)

12