Synthesis of Atropisomeric 1-Phenylpyrrole-Derived Amino Alcohols: New Chiral Ligands

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ABSTRACT An efficient synthetic method has been developed for the preparation of a new family of atropisomeric amino alcohols with 1-phenylpyrrole backbone. The synthesis is based on the different reactivities of the two carboxylic groups in optically active 1-[2-carboxy-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxylic acid (**1**). The chemical structures of the key intermediates were confirmed by spectroscopic methods and single crystal X-ray diffraction measurements. The very first application of a new optically active amino alcohol as catalyst for the enantioselective addition of diethylzinc to benzaldehyde demonstrated the practical usefulness of atropisomeric compounds in which there are six-atom chains between the two functional groups. *Chirality 00:000–000, 2012.* © 2012 Wiley Periodicals, Inc.

KEY WORDS: site selective reaction; metalation; enantioselective reaction; chiral amino alcohol; organocatalyst

INTRODUCTION

Bifunctionalized atropisomeric biaryls are widely used in different enantioselective reactions as chiral ligands, auxiliaries, or optically active organocatalysts.[1] 2,2′-Disubstituted 1,1′-binaphtalenes and 1,1′-biphenyls, both with C_2 symmetry, are classical representatives of these compounds.[2,3] Most frequently, they have two hydroxyl, amino, or phosphino groups in the C2 and C2′ positions.[1] Simultaneous or separate modifications of the chemically identical groups of these biaryls are simple, applying the reactants in suitable molar ratios. Similarly, the simultaneous transformation of both functional groups of a bifunctionalized chiral compound of C_1 symmetry is relatively easy. For example, the dimethyl ester, two tetrasubstituted diol derivatives, and two pyrrolobenzoxazepine derivatives of optically active 1-[2-carboxy-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxylic acid (**1**) were prepared in our laboratory, using the reagents in excess.[4] The selective modification of one functional group of the two identical ones in atropisomeric compounds with C_1 symmetry, such as dicarboxylic acid **1**, requires a different strategy. With a careful selection of the reagents and conditions, however, the reactivity differences between the two carboxylic acid functions can be exploited.

In the present study, which was a part of our ongoing project on the chemistry of atropisomeric 1-phenylpyrrole derivatives, our aim is to develop a synthesis for new chiral amino alcohols, starting from dicarboxylic acid **1**. Optically active amino alcohols are among the most frequently applied compounds in enantioselective reactions. Recently, several papers have been published on the synthesis and application of β-amino alcohols,[5,6] and promising results have been published about the application of 1,4-amino alcohols[7] as chiral additives in enantioselective reactions.

In the designed new amino alcohols, the amino and the hydroxyl groups are separated by a six-atom chain, yet, they must be close in space, because they are both attached to the rotationally restricted 1-phenylpyrrole backbone. Therefore, these amino alcohols were expected to serve as new ligands in enantioselective reactions.

For an efficient synthesis for the target molecules to be found, detailed experimental studies were carried out in our laboratory.

EXPERIMENTAL

General

All commercial starting materials were purchased from Sigma Aldrich Kft. (Budapest, Hungary) and Merck Kft. (Budapest, Hungary) and were used without further purification. Tetrahydrofuran was obtained anhydrous by distillation from sodium wire, after the characteristic blue color of the *in situ* generated sodium diphenylketyl had been found to persist. The organometallic reactions and the reductions were carried out in Schlenk flasks under a dry nitrogen atmosphere. Thin-layer chromatography (TLC) was carried out on Kieselgel 60 F254 (Merck) sheets (visualization of the products was made by exposing the plate to UV radiation or by staining it with the aqueous solution of $(NH_4)_6Mo_7O_{24}$, $Ce(SO_4)_2$, and sulphuric acid. Routine ^1H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$, acetone-d_6 and DMSO-d_6 solution on a Bruker AV 300 or DRX 500 spectrometer (Bruker BioSpin GmbH, Rheinstetten, Germany). Proton chemical shifts are reported in ppm relative to the internal standard ($\delta_{TMS} = 0$ ppm) or solvents ($\delta_{Acetone} = 2.05$, $\delta_{DMSO} = 2.50$ ppm), and carbon chemical shifts are reported in ppm relative to the solvents ($\delta_{Chloroform} = 77.00$). The enantiomeric ratios of the optically active samples of **12a** were determined from the ^1H spectra recorded at

Contract grant sponsor: National Development Agency, New Hungary Development Plan. Project title: "Development of quality-oriented and harmonized R+D+I strategy and functional model at BME".; Contract grant number: TÁMOP-4.2.1/B-09/1/KMR-2010-0002.
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Received for publication 1 December 2011; Accepted 11 March 2012
DOI: 10.1002/chir.22049
Published online in Wiley Online Library (wileyonlinelibrary.com).

25 °C on a Varian Inova$_{400}$ spectrometer in the presence of (*R*)-**1**. The enantiomeric ratios of the optically active samples of **2** and **13a–c** were determined by high-performance liquid chromatography (HPLC) measurements carried out on Phenomonex (Torrance, USA) Lux Cellulose-2 or Amylose-2 columns (5 μm, 250 × 4.6 mm) (eluent hexane/ethanol). Infrared (IR) spectra were recorded on an appliance type PerkinElmer (Waltham, USA) 1600 with a Fourier Transformer. Data are given in cm^{-1}. Specific rotation of the optically active samples was determined on a PerkinElmer 245 MC polarimeter using sodium lamp (589 nm). Melting points were determined in capillary tubes, using a Gallenkamp (Loughborough, UK) melting point apparatus. Computations were performed at the AM1 semiempirical level implemented in the MOPAC (Stewart Computational Chemistry, Colorado Springs, USA) package of InsightII® commercial software. High-resolution mass spectra (HRMS) were recorded on Waters (Waters Kft., Budapest, Hungary) LCT Premier XE spectrometer in electrospray ionization (ESI, 2.5 kV) mode, using water (0.035% trifluoroacetic acid)/acetonitrile (0.035% trifluoroacetic acid) as eluent in gradient elution (5–95% acetonitrile); samples were made up in acetonitrile.

Synthesis

(*S*)-1-[2-Methoxycarbonyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxylic acid ((*S*)-2). (*S*)-1-[2-Carboxy-6-(trifluoromethyl) phenyl]-pyrrole-2-carboxylic acid (**1**, 16.7 mmol, 5.00 g, *ee* 99.8%) was dissolved in methanol (75 ml), and the solution was cooled down to 0 °C. Then thionyl chloride (116.9 mmol, 8.53 ml) was added dropwise into it, and the reaction mixture was stirred at room temperature for 48 h. The reaction was monitored by TLC (ethyl acetate/methanol = 3/1) until **1** was consumed. The solvent was evaporated *in vacuo*, and hexane (40 ml) was poured to the residue. The mixture was refluxed for an hour, and the solid was filtered off, washed with hexane to yield monoester (*S*)-**2** as white crystalline material (4.19 g, 80%, *ee* 99.8%). mp 159–160 °C (from hexane). IR (KBr, cm^{-1}): 3434, 1735, 1664, 1540, 1484. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.16 (1H, d, J = 8.5 Hz), 7.92 (1H, d, J = 8.5 Hz), 7.64 (1H, t, J = 8.5 Hz), 7.14 (1H, dd, J = 3.9, 1.8 Hz), 6.85 (1H, br s), 6.34 (1H, dd, J = 3.9, 3.0 Hz), 3.64 (3H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 164.64, 164.60, 134.09, 131.51, 131.25, 130.02 (q, J = 5 Hz), 129.17 (q, J = 31 Hz), 128.96, 128.83, 125.10, 122.65 (q, J = 272 Hz), 119.42, 109.68, 52.68. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −60.47. Anal. Calcd for $C_{14}H_{10}F_3NO_4$ (313.23): C, 53.68; H, 3.22; N, 4.47. Found: C, 54.01; H, 3.78; N 4.60. $[\alpha]_D^{25} = -55.5$ (*c* 1.2; EtOH). *Ee* was determined after the quantitative conversion into their dimethyl esters[4] (**3**) by HPLC analysis using a chiral stationary phase, Phenomonex Lux Cellulose-2 column (5 μm, 250 × 4.6 mm), eluent hexane/ethanol = 97/3, 0.8 ml/min, UV detector 256 nm, 20 °C, retention time for (*S*)-**3**: 12.2 min., for (*R*)-**3**: 13.6 min.

General Procedure for the Synthesis of Amides 6a–f

(*S*)-1-[2-Methoxycarbonyl-6-(trifluoromethyl) phenyl]-1*H*-pyrrole-2-carboxylic acid ((*S*)-**2**, 3.2 mmol, 1.00 g, *ee* 99.8%) was dissolved in dry toluene (10 ml) and thionyl chloride (3.84 mmol, 0.28 ml), and one drop dry dimethylformamide was added dropwise. The reaction mixture was stirred at 80 °C for 2 h. The solvent was evaporated *in vacuo*. The residue was dissolved in dry toluene (10 ml). A solution of the respected amine (8.0 mmol) in dry toluene (5 ml) was added dropwise at 0 °C, and the mixture was stirred for 15 min. 1-M solution of hydrogen chloride (10 ml) was added, the phases were separated, and the organic solution was washed with water (5 ml), then brine (5 ml) before drying over sodium sulfate and concentrated *in vacuo*.

***N,N*-Diethyl-(*S*)-1-[2-methoxycarbonyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxamide ((*S*)-6a).** The reaction was monitored by TLC (hexane/ethyl acetate = 1/1, R_f = 0.45). Pure (*S*)-**6a** is a white solid (1.16 g, 99%). Mp: 57–58 °C (from toluene). IR (KBr, cm^{-1}): 3099, 2977, 2952, 1738, 1616, 1544, 1479, 1330, 1289. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.13 (1H, dd, J = 7.8, 1.5 Hz), 7.87 (1H, dd, J = 7.5, 1.5 Hz), 7.57 (1H, t, J = 8.1 Hz), 6.78 (1H, br s), 6.55 (1H, dd, J = 3.6, 1.5 Hz), 6.30 (1H, dd, J = 3.6, 3.0 Hz), 3.67 (3H, s), 3.52 (2H, m), 3.39 (2H, m), 1.12 (6H, t, J = 5.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 164.84, 162.02, 139.06 (d, J = 1.6 Hz), 133.86, 132.22, 129.69 (q, J = 5.2 Hz), 128.64 (q, J = 31 Hz), 128.18, 127.56, 122.93 (q, J = 273 Hz), 111.59, 107.68, 52.49, 41.00, 40.43, 13,27. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −60.02. HRMS (EI) *m/z* calcd. for $C_{18}H_{19}F_3N_2O_3$ $(M)^+$: 368.1366, found 366.1348. $[\alpha]_D^{25} = -88.9$ (*c* 1.0; EtOH).

***N,N*-Diisopropyl-(*S*)-1-[2-methoxycarbonyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxamide ((*S*)-6b).** After the addition of diisopropyl amine, the reaction mixture was stirred for 24 h at 25 °C and was monitored by TLC (hexane/ethyl acetate = 3/1, R_f = 0.40). After general work-up, pure (*S*)-**6b** was yielded as white solid (1.24 g, 98%). Mp: 76–78 °C (from toluene). IR (KBr, cm^{-1}): 3099, 3009, 2973, 2933, 1748, 1614, 1540, 1438, 1246, 1211. ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 8.14 (1H, d, J = 8.0 Hz), 7.87 (1H, d, J = 8.0 Hz), 7.56 (1H, t, J = 8.0 Hz), 6.73 (1H, s), 6.45 (1H, dd, J = 3.5, 1.5 Hz), 6.27 (1H, t, J = 3.3 Hz), 5.80–2.40 (2H, br s), 3.67 (3H, s), 1.27 (6H, d, J = 6.5 Hz), 1.21 (6H, d, J = 6.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 165.05, 161.91, 139.27 (d, J = 1.4 Hz), 134.27, 132.38, 129.94 (q, J = 5.1 Hz), 128.76 (q, J = 30.3 Hz), 128.31, 127.11, 123.19 (q, J = 274.2 Hz), 110.81, 107.59, 52.63, 21.08, 20.99. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −59.64. $[\alpha]_D^{25} = -83.9$ (*c* 1.0; EtOH).

***N*-Isopropyl-(*S*)-1-[2-methoxycarbonyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxamide ((*S*)-6c).** The reaction was monitored by TLC (hexane/ethyl acetate = 1/1, R_f = 0.45). Pure (*S*)-**6c** is a white solid (1.11 g, 98%). Mp: 133–134 °C (from toluene). IR (KBr, cm^{-1}): 3323, 3275, 2974, 1733, 1628, 1551, 1484. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.15 (1H, d, J = 7.8 Hz), 7.91 (1H, d, J = 7.8 Hz), 7.60 (1H, t, J = 8.0 Hz), 6.75 (1H, br s), 6.63 (1H, dd, J = 3.75, 1.5 Hz), 6.30 (1H, t, J = 3.0 Hz), 5.60 (1H, d, J = 7.8 Hz), 4.03 (1H, octet, J = 6.9 Hz) 3.67 (3H, s), 1.13 (3H, d, J = 1.5 Hz), 1.11 (3H, d, J = 1.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 164.64, 159.80, 139.40, 133.94, 131.38, 129.94 (q, J = 5.1 Hz), 129.32, 128.79 (q, J = 30.4 Hz), 128.34, 122.85 (q, J = 274.0 Hz), 110.45, 108.55, 96.12, 52.50, 40.90, 22.92, 22.90. ^{13}C DEPT ($CDCl_3$, 75 MHz) δ_C 133.94, 129.94 (q, J = 5.1 Hz), 128.34, 110.45, 108.55, 52.50, 40.90, 22.92, 22.90. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −60.33. HRMS (EI) *m/z* calcd. for $C_{17}H_{17}F_3N_2O_2$ $(M)^+$: 354.1201, found 354.1191. $[\alpha]_D^{25} = -69.6$ (*c* 0.78; EtOH).

***N*-Benzyl-(*S*)-1-[2-methoxycarbonyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxamide ((*S*)-6d).** The reaction was monitored by TLC (hexane/ethyl acetate = 1/1, R_f = 0.50). Pure (*S*)-**6 d** is a white solid (1.31 g, 98%). Mp: 123–125 °C (from toluene). IR (KBr, cm^{-1}): 3352, 3288, 1735, 1637, 1558, 1482. ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 8.17 (1H, d, J = 8.0 Hz), 7.93 (1H, d, J = 7.5 Hz), 7.61 (1H, t, J = 8.0 Hz), 7.31–7.16 (5H, m) 6.78 (1H, br s), 6.67 (1H, dd, J = 3.5, 1.5 Hz), 6.31 (1H, dd, J = 4.0, 3.0 Hz), 6.09 (1H, br s), 4.42 (2H, d, J = 5.5 Hz), 3.66 (3H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 164.62, 160.39, 139.30, 138.46, 134.03, 131.32, 130.02 (q, J = 5.0 Hz), 128.88 (q, J = 31 Hz), 128.74, 128.59, 128.46, 127.60, 127.35, 122.85 (q, J = 274 Hz), 111.07, 108.74, 52.54, 43.02. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −60.24. HRMS (EI) *m/z* calcd. for $C_{21}H_{17}F_3N_2O_3$ $(M)^+$: 402.1187, found 402.1191. $[\alpha]_D^{25} = -45.5$ (*c* 0.7; EtOH).

***N*-[(*R*)-1-phenylethyl]-(*S*)-1-[2-methoxycarbonyl-6-(trifluoromethyl) phenyl]-1*H*-pyrrole-2-carboxamide ((*S*)-6e).** The reaction was monitored by TLC (hexane/ethyl acetate = 1/1, R_f = 0.75). Pure (*S*)-**6e** is a white solid (1.31 g, 99%). Mp: 132–134 °C (from toluene). IR (KBr, cm^{-1}): 3316, 1735, 1722, 1627, 1482, 1147. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.12

(1H, d, J = 7.8 Hz), 7.91 (1H, d, J = 7.2 Hz), 7.58 (1H, t, J = 7.8 Hz), 7.32–7.21 (5H, m), 6.76 (1H, br s), 6.76 (1H, dd, J = 3.9, 1.5 Hz), 6.29 (1H, t, J = 3.3 Hz), 6.03 (1H, d, J = 8.4 Hz), 5.09 (1H, quint, J = 7.4 Hz), 3.58 (3H, s), 1.45 (3H, d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 164.84, 159.92, 143.54, 139.42 (d, J = 1.5), 134.21, 131.63, 130.16 (q, J = 5.1 Hz), 129.23, 128.95 (q, J = 30.5 Hz), 128.82, 128.72, 128.63, 127.34, 126.29, 123.28 (q, J = 274.1 Hz), 111.19, 108.87, 52.67, 48.19, 21.96. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −60.23. $[\alpha]_D^{25}$ = +27.2 (c 0.85; EtOH).

(*S*)-1-[2-Methoxycarbonyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxamide ((*S*)-6f). To the solution of the acid chloride in dry toluene (10 ml) aqueous ammonia (15 M, 8.0 mmol, 1.88 ml) was added at 0 °C, then the mixture was stirred for 15 min. The reaction was monitored by TLC (pure ethyl acetate, R_f = 0.42). 1-M solutions of hydrogen chloride (10 ml) and toluene (40 ml) were added, the phases were separated, and the organic solution was washed with water (10 ml), then brine (10 ml) before drying over sodium sulfate and concentrated *in vacuo* to yield pure (*S*)-**6f** as white solid (0.97 g, 98%). Mp: 104–105 °C (from toluene). IR (KBr, cm^{-1}): 3497, 3428, 3355, 2952, 1741, 1729, 1635, 1608, 1483, 1448. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 8.15 (1H, d, J = 7.4 Hz), 7.92 (1H, d, J = 7.8 Hz), 7.60 (1H, t, J = 8.0 Hz), 6.79 (1H, s), 6.74 (1H, dd, J = 3.9, 1.5 Hz), 6.32 (1H, t, J = 3.3 Hz), 5.38 (1H, br s), 3.67 (3H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 164.88, 162.24, 139.39 (d, J = 1.7 Hz), 134.23, 131.57, 130.23 (q, J = 5.1 Hz), 129.52, 129.10 (q, J = 30.6 Hz), 128.70, 128.09, 123.05 (q, J = 274.2 Hz), 112.92, 109.11, 52.80. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −60.32. HRMS (ESI) m/z calcd. for $C_{14}H_{12}F_3N_2O_3$ $(M+H)^+$: 313.2513, found 313.2504. $[\alpha]_D^{25}$ = −60.0 (c 0.5; EtOH).

General Procedure for the Synthesis of Primary Alcohols 7a–f

Compound (*S*)-**6a–f** (3.0 mmol) was dissolved in dry tetrahydrofuran (9 ml) under nitrogen atmosphere, and well-powdered sodium tetrahydridoborate (4.50 mmol, 0.17 g) and ethanol (1 ml) were added. The reaction mixture was stirred at room temperature for 48–72 h. The reaction was monitored by TLC (hexane/ethyl acetate) until **6a–f** was consumed. The solvent was evaporated *in vacuo*. The residue was dissolved in diethyl ether (20 ml), and 1-M solution of hydrogen chloride (10 ml) was added at 0 °C. The phases were separated, and the organic solution was washed with water (5 ml), then brine (5 ml) before drying over sodium sulfate and concentrated *in vacuo*.

***N,N*-Diethyl-(*S*)-1-[2-hydroxymethyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxamide ((*S*)-7a).** The reaction was monitored by TLC (hexane/ethyl acetate = 1/1, R_f = 0.35). Pure (*S*)-**7a** is a white solid (0.97 g, 95%). Mp: 121–123 °C (from diethyl ether). IR (KBr, cm^{-1}): 3332, 1600, 1542, 1482, 1320. ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 7.79 (1H, dd, J = 7.2, 0.5 Hz), 7.65 (1H, dd, J = 7.5, 1.0 Hz), 7.55 (1H, t, J = 7.5 Hz), 6.69 (1H, br s), 6.54 (1H, dd, J = 3.75, 1.5 Hz), 6.31 (1H, dd, J = 3.75, 3.0 Hz), 5.37 (1H, br s), 4.27 (2H, s), 3.90–3.26 (4H, m), 1.28–1.03 (6H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 163.46, 142.18, 136.97, 134.63, 129.40, 128.24, 127.70, 127.44 (q, J = 32 Hz), 125.83 (q, J = 6.0 Hz), 123.21 (q, J = 273 Hz), 111.69, 108.26, 60.74, 43.24, 39.41, 14.10, 12.15. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −60.62. HRMS (EI) m/z calcd. for $C_{17}H_{19}F_3N_2O$ $(M)^+$: 340.1418, found 340.1399. $[\alpha]_D^{25}$ = −173.3 (c 0.86; EtOH).

A selected single crystal (0.4 × 0.3 × 0.2 mm) of (*R*)-**7a** was mounted on a Rigaku (Rigaku Europe SE, Berlin, Germany) R-AXIS RAPID diffractometer (graphite monochromator Cu Kα radiation, λ = 1.54187 Å). CCDC 846790 contains the supplementary crystallographic data for this article. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre website at www.ccdc.cam.ac.uk/data_request/cif.

***N,N*-Diisopropyl-(*S*)-1-[2-hydroxymethyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxamide ((*S*)-7b).** The reaction was monitored by TLC (hexane/ethyl acetate = 3/1, R_f = 0.25). Pure (*S*)-**7b** is a white solid (1.06 g, 96%). Mp: 143–146 °C (from diethyl ether). IR (KBr, cm^{-1}): 3304, 3001, 2970, 2936, 2879, 1590, 1466, 1323, 1164, 1126. ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 7.78 (1H, d, J = 7.5 Hz), 7.65 (1H, d, J = 8.0 Hz), 7.54 (1H, t, J = 7.5 Hz), 6.65 (1H, s), 6.46 (1H, dd, J = 2.5 Hz), 6.29 (1H, t, J = 3.0 Hz), 5.77 (1H, d, J = 7.5, 3.0 Hz), 4.68 (1H, br s), 4.27–4.20 (2H, m), 3.42 (1H, br s), 1.32 (6H, d, J = 6.5 Hz), 1.18 (6H, s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 163.11, 142.31, 137.02 (d, J = 1.5 Hz), 134.64, 129.69, 129.23, 127.40, 127,27 (q, J = 30.1 Hz), 125.69 (q, J = 5.2 Hz), 119.63 (q, J = 273.7 Hz), 110.98, 107.91, 60.62, 50.50, 46.47, 20.75, 19.95. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −60.30. $[\alpha]_D^{25}$ = −163.4 (c 0.5; EtOH).

***N*-Isopropyl-(*S*)-1-[2-hydroxymethyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxamide ((*S*)-7c).** The reaction was monitored by TLC (hexane/ethyl acetate = 1/1, R_f = 0.32). Pure (*S*)-**7c** is a white, amorphous material (0.93 g, 95%). IR (KBr, cm^{-1}): 3323, 2976, 2935, 2878, 1635, 1552, 1481, 1322, 1165, 1133. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.79 (1H, d, J = 7.2 Hz), 7.67 (1H, d, J = 7.5 Hz), 7.55 (1H, t, J = 7.8 Hz), 6.69 (1H, br s), 6.63 (1H, dd, J = 3.6, 1.5 Hz), 6.29 (1H, t, J = 3.0 Hz), 5.97 (1H, br s), 4.39 (1H, br s), 4.26 (2H, m), 4.01 (1H, octet, J = 7.1 Hz), 1.14 (3H, d, J = 6.6 Hz), 1.09 (3H, d, J = 6.6 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 161.50, 141.50, 136.83 (d, J = 1.7 Hz), 133.75, 129.31, 129.22, 128.66, 127.28 (q, J = 30.3 Hz), 125.86 (q, J = 5.2 Hz), 123.09 (q, J = 273.7 Hz), 111.50, 108.74, 60.35, 41.34, 22.57, 22.47. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −60.74. HRMS (EI) m/z calcd. for $C_{16}H_{17}F_3N_2O_2$ $(M)^+$: 326.1260, found 326.1242. $[\alpha]_D^{25}$ = −71.6 (c 0.86; EtOH).

***N*-Benzyl-(*S*)-1-[2-hydroxymethyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxamide ((*S*)-7d).** The reaction was monitored by TLC (hexane/ethyl acetate = 1/1, R_f = 0.36). Pure (*S*)-**7d** is a white, amorphous material (1.03 g, 92%). IR (KBr, cm^{-1}): 3422, 2925, 1639, 1552, 1480, 1321, 1130. ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 7.82 (1H, d, J = 7.5 Hz), 7.70 (1H, d, J = 8.0 Hz), 7.58 (1H, t, J = 7.5 Hz), 7.33–7.21 (5H, m), 6.74 (1H, br s), 6.69 (1H, d, J = 3.75 Hz), 6.31 (1H, t, J = 3.0 Hz), 6.27 (1H, br s), 4.44 (2H, sym m), 4.29 (2H, s), 4.04 (1H, br s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 162.39, 143.31, 141.81, 137.97, 137.04, 134.23, 129.67, 129.53, 129.05, 128.98, 127.86, 127.74 (q, J = 29.4 Hz), 126.34 (q, J = 5.0 Hz), 123.39 (q, J = 273.9 Hz), 112.28, 109.25, 60.80, 43.67. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −60.69. HRMS (EI) m/z calcd. for $C_{20}H_{17}F_3N_2O_2$ $(M)^+$: 374.1233, found 374.1242. $[\alpha]_D^{25}$ = −63.2 (c 1.0; EtOH).

***N*-[(*R*)-1-phenylethyl]-(*S*)-1-[2-hydroxymethyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxamide ((*S*)-7e).** The reaction was monitored by TLC (hexane/ethyl acetate = 2/1, R_f = 0.22). Pure (*S*)-**7e** is a colorless oil (1.11 g, 99%). IR (KBr, cm^{-1}): 3315, 3063, 2976, 2930, 1633, 1548, 1481, 1416, 1321, 1154. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.81 (1H, dd, J = 7.6, 0.5 Hz), 7.70 (1H, d, J = 7.8 Hz), 7.58 (1H, t, J = 7.8 Hz), 7.39–7.27 (5H, m), 6.72 (1H, s), 6.67 (1H, dd, J = 3.9, 1.5 Hz), 6.30 (1H, dd, J = 3.7, 2.9 Hz), 6.17 (1H, d, J = 8.0 Hz), 5.16–5.03 (1H, quintet, J = 7.5 Hz), 4.25 (2H, s), 3.98 (1H, br s), 1.45 (3H, d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 161.74, 142.96, 141.85, 137.01 (d, J = 1.8), 134.25, 129.66, 129.35, 129.33, 128.98, 127.71, 127.69 (q, J = 30.4 Hz), 126.32 (q, J = 5.2 Hz), 126.31, 123.41 (q, J = 273.7 Hz), 112.03, 109.19, 60.78, 48.82, 21.92. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −60.78. $[\alpha]_D^{25}$ = −56.8 (c 0.4; $CHCl_3$).

(*S*)-1-[2-Hydroxymethyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxamide ((*S*)-7f). The reaction was monitored by TLC (pure ethyl acetate, R_f = 0.35). Pure (*S*)-**7f** is a white solid (0.81 g, 95%). Mp: 160–161 °C (from diethyl ether). IR (KBr, cm^{-1}): 3516, 3375, 3172, 3115, 1668, 1623, 1484, 1435, 1320, 1134. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.83 (1H, d, J = 6.9 Hz), 7.68 (1H, d, J = 6.3 Hz), 7.62 (1H, t, J = 7.7 Hz), 7.49 (1H, br s), 6.99 (1H, dd, J = 3.9, 1.5 Hz), 6.82 (1H, s), 6.74 (1H, br s), 6.27

(1H, t, J = 3.3 Hz), 5.25 (1H, t, J = 5.4 Hz), 4.10 (1H, dd, J = 14.9, 5.4 Hz), 3.93 (1H, dd, J = 14.9, 5.4 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 164.33, 144.74, 137.78 (q, J = 1.7 Hz), 132.28, 129.26, 129.12, 129.06, 127.37 (q, J = 29.9 Hz), 125.51 (q, J = 5.3 Hz), 124.42 (q, J = 273.1 Hz), 114.62, 110.48, 60.92. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −58.85. HRMS (ESI) *m/z* calcd. for $C_{13}H_{12}F_3N_2O_2$ $(M+H)^+$: 285.2412, found 285.2419. $[\alpha]_D^{25}$ = −94.0 (*c* 0.65; acetone).

General Procedure for the Synthesis of Tertiary Alcohols 8a–c

A solution of bromobenzene (9.5 mmol, 1.5 g) in dry tetrahydrofuran (15 ml) was cooled down to −75 °C, and a hexane solution of butyllithium (9.5 mmol, 14.2 ml, 1.5 mol/L solution) was added into the stirred solution under nitrogen atmosphere. Compound (*S*)-**6a–c** (3.0 mmol) was added to the stirred reaction mixture for 15 min, and the stirring was continued for an additional 30 min at −75 °C. At room temperature, saturated aqueous ammonium chloride solution (15 ml) and diethyl ether (30 ml) were added into it. The phases were separated, the aqueous phase was washed with diethyl ether (2 × 25 ml), the collected organic solutions were washed with brine (25 ml), dried over sodium sulfate, concentrated *in vacuo*, and the residue was purified by column chromatography (Kieselgel, eluent hexane/ethyl acetate).

***N,N*-Diethyl-(*S*)-1-[2-diphenylhydroxymethyl-6-(trifluoromethyl) phenyl]-1*H*-pyrrole-2-carboxamide ((*S*)-8a).** The reaction was monitored by TLC, and the residue was purified by column chromatography (hexane/ethyl acetate = 4/1, R_f = 0.6). Pure (*S*)-**8a** is a white, amorphous material (1.42 g, 96%). IR (KBr, cm^{-1}): 3196, 2984, 1593, 1542, 1466, 1316, 1285, 1166, 1133, 1110. ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 8.14 (1H, s), 7.63 (1H, d, J = 7.5 Hz), 7.32 (1H, t, J = 7.5 Hz), 7.30–7.20 (8H, m), 7.16 (2H, m), 7.12 (1H, d, J = 8.0 Hz), 6.47 (1H, d, J = 2.5 Hz), 5.79 (1H, t, J = 3.3 Hz), 5.55 (1H, s), 3.97 (1H, br s), 3.52 (1H, br s), 3.32 (2H, sextet, J = 7.0 Hz), 1.28 (3H, br s), 1.07 (3H, br s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 164.46, 148.94, 147.63, 146.33, 137.50 (d, J = 1.4 Hz), 134.98, 129.31, 129.22 (q, J = 29.3 Hz), 128.40, 127.79, 127.60, 127.44, 127.30, 127.04, 126.86, 126.75, 126.01 (q, J = 5.5 Hz), 123.22 (q, J = 272.6 Hz), 112.18, 106.27, 81.19, 43.07, 39.28, 14.09, 12.21. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −60.48. HRMS (ESI) *m/z* calcd. for $C_{29}H_{28}F_3N_2O_2$ $(M+H)^+$: 493.2103, found 493.2089. $[\alpha]_D^{25}$ = −130.8 (*c* 6.0; $CHCl_3$).

***N,N*-Diisopropyl-(*S*)-1-[2-diphenylhydroxymethyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxamide ((*S*)-8b).** The reaction was monitored by TLC, and the residue was purified by column chromatography (hexane/ethyl acetate = 4/1, R_f = 0.65). Pure (*S*)-**8b** is a white solid (1.47 g, 94%). Mp: 148–149 °C (from ethyl acetate). IR (KBr, cm^{-1}): 3190, 2973, 2937, 2872, 2792, 1587, 1538, 1465, 1317, 1165. ^{1}H NMR ($CDCl_3$, 500 MHz) δ_H 8.50 (1H, s), 7.64 (1H, d, J = 8.0 Hz), 7.33 (1H, t, J = 8.0 Hz), 7.30–7.21 (8H, m), 7.16–7.12 (3H, m), 6.41 (1H, dd, J = 3.5, 1.5 Hz), 5.81 (1H, t, J = 6.5 Hz), 5.55 (1H, s), 4.77 (1H, br s), 3.46 (1H, br s), 1.42–1.12 (12H, m). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 164.54, 149.87, 148.01, 146.58, 137.78 (d, J = 1.3 Hz), 135.32, 129.38 (q, J = 29.0 Hz), 129.19, 128.74, 128.60, 128.43, 128.04, 127.66, 127.03, 126.96, 126.00 (q, J = 5.5 Hz), 123.56 (q, J = 274.3 Hz), 50.54, 46.66, 21.63, 21.39, 20.86, 20.05. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −60.08. $[\alpha]_D^{25}$ = −124.3 (*c* 1.0; EtOH).

***N*-Isopropyl-(*S*)-1-[2-diphenylhydroxymethyl-6-(trifluoromethyl) phenyl]-1*H*-pyrrole-2-carboxamide ((*S*)-8c).** The reaction was monitored by TLC, and the residue was purified by column chromatography (hexane/ethyl acetate = 4/1, R_f = 0.58). Pure (*S*)-**8c** is a white solid (1.33 g, 93%). Mp: 127–129 °C (from ethyl acetate). IR (KBr, cm^{-1}): 3313, 3130, 3066, 3026, 2975, 2768, 1602, 1550, 1464, 1315. ^{1}H NMR (acetone-d_6, 300 MHz) δ_H 7.77 (1H, d, J = 7.8 Hz), 7.57 (1H, s), 7.53 (2H, t, J = 7.2 Hz), 7.35–7.17 (11H, m), 6.60 (1H, s), 5.65 (1H, s), 5.60 (1H, s), 4.10 (1H, octet, J = 6.8 Hz), 1.22 (3H, d, J = 6.6 Hz), 1.11 (3H, d, J = 6.6 Hz). ^{13}C NMR (acetone-d_6, 75 MHz) δ_C 164.03, 150.65, 149.48, 148.32, 140.07, 136.64, 131.62, 131.11 (q, J = 29.5 Hz), 130.16, 129.90, 129.56, 129.24, 128.87, 128.76, 128.49, 128.29, 128.17 (q, J = 5.6 Hz), 125.28 (q, J = 273.9 Hz), 113.37, 108.33, 82.68, 43.08, 23.76, 23.46. ^{19}F NMR (acetone-d_6, 282 MHz) δ_F −60.93. HRMS (ESI) *m/z* calcd. for $C_{28}H_{26}F_3N_2O_2$ $(M+H)^+$: 479.1946, found 479.1944. $[\alpha]_D^{25}$ = −86.0 (*c* 0.4; EtOH).

Reaction of Primary Amide (S)-6f with Grignard's Reagent

Phenylmagnesium bromide (4.8 mmol, 0.87 g) was prepared in dry diethyl ether (10 ml) by the addition of bromobenzene to magnesium turnings. A solution of (*S*)-1-[2-methoxycarbonyl-6-(trifluoromethyl) phenyl]-1*H*-pyrrole-2-carboxamide ((*S*)-**6f**, 1.6 mmol, 0.5 g, *ee* 99.8%) in dry tetrahydrofuran (5 ml) was added into the stirred solution at 0 °C under nitrogen atmosphere. The reaction mixture was stirred for 30 min at 0 °C. When the mixture warmed to room temperature, saturated aqueous ammonium chloride solution (15 ml) and diethyl ether (30 ml) were added, the phases were separated, the aqueous phase was washed with diethyl ether (15 ml), the collected organic solutions were washed with brine (25 ml), dried over sodium sulfate, concentrated *in vacuo*, and the residue was purified by column chromatography (Kieselgel, eluent hexane/ethyl acetate = 1/1) to yield (*S*)-**10** and (*R*,*S*)-**11**.

(*S*)-1-[2-Benzoyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxamide ((*S*)-10). White solid (0.26 g, 45%, R_f = 0.3). Mp: 181–183 °C (from ethyl acetate). IR (KBr, cm^{-1}): 3466, 3300, 3189, 1661, 1610, 1475, 1444, 1333, 1286, 1116. ^{1}H NMR (DMSO, 500 MHz) δ_H 7.99 (1H, dd, J = 8.0, 1.0 Hz), 7.73 (1H, t, J = 7.8 Hz), 7.70–7.66 (3H, m), 7.60 (1H, t, J = 7.5 Hz), 7.42 (2H, t, J = 7.8 Hz), 7.32 (1H, br s), 6.87 (1H, s), 6.78 (1H, dd, J = 3.5, 1.5 Hz), 6.66 (1H, br s), 6.04 (1H, t, J = 3.2 Hz). ^{13}C NMR (DMSO, 75 MHz) δ_C 193.27, 161.32, 139.79, 137.17 (q, J = 1.8 Hz), 135.70, 133.52, 131.82 129.76 129.70, 128.57, 128.16, 128.00 (q, J = 5.1 Hz), 127.08 (q, J = 30.1 Hz), 122.97 (q, J = 274.1 Hz), 112.96, 107.84. ^{19}F NMR (DMSO, 282 MHz) δ_F −54.22. $[\alpha]_D^{25}$ = −17.4 (*c* 0.9; EtOH, *ee* 24%). *Ee* was determined by HPLC analysis using a chiral stationary phase (Phenomonex Lux Cellulose-2 column (5 μm, 250 × 4.6 mm), eluent hexane/ethanol = 85/15, 1.0 ml/min, UV detector 256 nm, 20 °C, retention time for (*S*)-**10**: 19.2 min, for (*R*)-**10**: 29.5 min.

(±)-1-[2-Aminocarbonyl-6-(trifluoromethyl)phenyl]-2-benzoyl-1*H*-pyrrole ((*R,S*)-11). White solid (0.17 g, 30%, *ee* 0%, R_f = 0.2). Mp: 195–197 °C (from ethyl acetate). IR (KBr, cm^{-1}): 3405, 3163, 3127, 1689, 1622, 1314, 1156, 1129, 726. ^{1}H NMR (DMSO, 500 MHz) δ_H 7.93 (1H, d, J = 7.5 Hz), 7.80 (1H, d, J = 7.0 Hz), 7.74 (1H, t, J = 7.8 Hz), 7.70 (2H, d, J = 7.5 Hz), 7.60 (1H, t, J = 7.5 Hz), 7.50 (2H, t, J = 7.5 Hz), 7.42 (1H, s), 7.33 (1H, s), 7.26 (1H, s), 6.79 (1H, dd, J = 4.0, 1.5 Hz), 6.37 (1H, t, J = 3.3 Hz). ^{13}C NMR (DMSO, 75 MHz) δ_C 183.97, 166.89, 138.33, 138.27, 135.47 (q, J = 1.7 Hz), 133.05, 132.89, 131.77, 131.74, 129.01, 128.81, 128.14, 127.23 (q, J = 5.1 Hz), 126.39 (q, J = 30.0 Hz), 123.01 (q, J = 273.9 Hz), 121.36, 109.28. ^{19}F NMR (DMSO, 282 MHz) δ_F −54.28. $[\alpha]_D^{25}$ = 0 (*c* 1.0; EtOH).

10-Trifluoromethyl-4*H*-pyrrolo[1,2-*a*][1,4]benzodiazepine-4,6-dione (9). To a solution of KO^{t}Bu (1.1 mmol, 0.12 g) in dry tetrahydrofuran (3 ml), (*S*)-1-[2-methoxycarbonyl-6-(trifluoromethyl) phenyl]-1*H*-pyrrole-2-carboxamide ((*S*)-**6f**, 1.0 mmol, 0.31 g) was added at 0 °C. After stirring for 10 min, 1-M solution of hydrogen chloride (5 ml) and ethyl acetate (15 ml) were added, the phases were separated, and the organic solution was washed with water (5 ml), then brine (5 ml) before drying over sodium sulfate and concentrated in vacuo to yield pure **9** as white solid (0.25 g, 90%, R_f = 0.9 in pure ethyl acetate). Mp: 207–208 °C (from tehtrahydrofuran). IR (KBr, cm^{-1}): 3463, 3417, 3363, 3159, 2991, 1735, 1643, 1610, 1480, 1387. ^{1}H NMR (acetone-d_6, 300 MHz) δ_H 10.24 (1H, s), 8.29 (1H, dd, J = 7.8, 1.2 Hz), 8.19 (1H, dd, J = 8.1, 1.5 Hz), 7.80 (1H, t, J = 7.8 Hz), 7.38 (1H, quint, J = 1.5 Hz), 7.13 (1H, dd, J = 3.8, 1.8 Hz), 6.54 (1H, t, J = 3.3 Hz). ^{13}C NMR (acetone-d_6,

75 MHz) δ_C 166.86, 160.03, 137.81, 136.68 (d, J = 1.4 Hz), 134.79 (q, J = 5.3 Hz), 132.99, 132.61 (q, J = 4.5 Hz), 130.50, 129.76, 126.42 (q, J = 31.4 Hz), 125.28 (q, J = 273.1 Hz), 122.67, 113.13. ^{19}F NMR (acetone-d_6, 282 MHz) δ_F −56.54.

General Procedure for the Synthesis of Amino Alcohols 12a–f and 13a–c

Compound (*S*)-**7a–f** or (*S*)-**8a–c** (1.5 mmol) was dissolved in dry toluene (4 ml), and borane dimethysulfide complex (3.0 mmol, 0.285 ml) was added dropwise. The reaction mixture was stirred at 80 °C for 72 h in case of primary alcohols or for 2 h in case of tertiary alcohols. Methanol (2 ml) was added slowly dropwise at 0 °C; the solvent was evaporated *in vacuo*. The residue was dissolved in methylene chloride (1 ml), and 5-M solution of hydrogen chloride (2 ml) was added. The mixture was stirred for 30 min. Then methylene chloride (5 ml) and aqueous sodium hydroxide (5-M, 5 ml) were added, the phases were separated, and the aqueous phase was washed with methylene chloride (5 ml), whereas the collected organic phases were dried over sodium sulfate and concentrated *in vacuo*. The crude residue was purified by column cromatography.

(*S*)-*N*,*N*-Diethyl-2-aminomethyl-1-[2-hydroxymethyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole ((*S*)-12a). The reaction was monitored by TLC, and the residue was purified by column chromatography (hexane/ethyl acetate = 1/1, R_f = 0.10–0.45). Pure (*S*)-**12a** is a white solid (0.37 g, 75%, *ee* 99.8%). Mp: 62–63 °C (from ethyl acetate). IR (KBr, cm^{-1}): 3362, 1486, 1321. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.81 (1H, d, J = 7.5 Hz), 7.73 (1H, d, J = 7.5 Hz), 7.58 (1H, t, J = 7.5 Hz), 6.64 (1H, br s), 6.24 (2H, d, J = 9.6 Hz), 4.13 (1H, d, J = 11.4 Hz), 3.93 (1H, d, J = 11.4 Hz), 3.21 (1H, d, J = 14.1 Hz), 3.07 (1H, d, J = 14.1 Hz), 2.71 (2H, m), 2.20 (2H, m), 0.76 (6H, t, J = 7.2 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 144.34, 135.59, 135.36, 131.09, 129.46, 128.60 (q, J = 30 Hz), 125.89 (q, J = 5 Hz), 124.59, 123.01 (q, J = 274 Hz), 111.10, 108.10, 59.24, 53.39, 49.97, 45.89, 9.82. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −63.27. HRMS (EI) m/z calcd. for $C_{17}H_{21}F_3N_2O$ $(M)^+$: 326.1611, found 326.1606. $[\alpha]_D^{25}$ = −75.6 (*c* 0.8; EtOH).

(*S*)-*N*,*N*-Diethyl-2-aminomethyl-1-[2-hydroxymethyl-6-(difluoromethyl)phenyl]-1*H*-pyrrole ((*S*)-12a′). ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.81 (1H, d, J = 7.5 Hz), 7.73 (1H, d, J = 7.5 Hz), 7.58 (1H, t, J = 7.5 Hz), 6.64 (1H, br s), 6.24 (2H, d, J = 9.6 Hz), 5.76 (1H, t, J = 54.5 Hz, –C*H*F$_2$), 4.13 (1H, d, J = 11.4 Hz), 3.93 (1H, d, J = 11.4 Hz), 3.21 (1H, d, J = 14.1 Hz), 3.07 (1H, d, J = 14.1 Hz), 2.71 (2H, m), 2.20 (2H, m), 0.76 (6H, t, J = 7.2 Hz). ^{19}F NMR ($CDCl_3$, 376 MHz) δ_F −110.47 (1F, dd, $^2J_{FF}$ = 309.1 Hz, $^2J_{HF}$ = 55.1 Hz), −114.82 (1F, dd, $^2J_{FF}$ = 309.1 Hz, $^2J_{HF}$ = 55.1 Hz).

(*S*)-*N*,*N*-Diisopropyl-2-aminomethyl-1-[2-hydroxymethyl-6-(difluoromethyl)phenyl]-1*H*-pyrrole ((*S*)-12b). The reaction was monitored by TLC, and the residue was purified by column chromatography (hexane/ethyl acetate = 1/1, R_f = 0.05–0.2). Pure (*S*)-**12b** is a white solid (0.36 g, 68%, *ee* 99.8%). Mp: 78–80 °C (from ethyl acetate). IR (KBr, cm^{-1}): 3374, 3110, 2970, 2938, 2889, 1597, 1487, 1321, 1182, 1163. ^{1}H NMR (acetone-d_6, 500 MHz) δ_H 7.94 (1H, d, J = 7.5 Hz), 7.80 (1H, d, J = 7.5 Hz), 7.71 (1H, t, J = 7.8 Hz), 6.64 (1H, s), 6.17 (2H, s), 4.87 (1H, br s), 4.22 (1H, d, J = 13.5 Hz), 4.16 (1H, d, J = 13.5 Hz), 3.41 (1H, d, J = 14.5 Hz), 3.22 (1H, d, J = 14.5 Hz), 3.09 (2H, sextet, J = 6.6 Hz), 0.90 (6H, d, J = 6.5 Hz), 0.72 (6H, d, J = 6.5 Hz). ^{13}C NMR (acetone-d_6, 75 MHz) δ_C 146.52, 137.21 (q, J = 1.8 Hz), 134.78, 134.20, 131.15, 129.72 (q, J = 29.9 Hz), 127.17 (q, J = 5.3 Hz), 125.43 (q, J = 273.3 Hz), 125.02, 111.99, 109.79, 60.74, 48.07, 41.03, 22.25, 19.78. ^{19}F NMR (acetone-d_6, 282 MHz) δ_F −60.52. HRMS (ESI) m/z calcd. for $C_{19}H_{26}F_3N_2O$ $(M+H)^+$: 355.1997, found 355.1991. $[\alpha]_D^{25}$ = +34.2 (*c* 0.5; EtOH).

(*S*)-*N*-Isopropyl-2-aminomethyl-1-[2-hydroxymethyl-6-(difluoromethyl)phenyl]-1*H*-pyrrole ((*S*)-12c). The reaction was monitored by TLC, and the residue was purified by column chromatography (hexane/ethyl acetate = 1/1, R_f = 0.05–0.2). Pure (*S*)-**12c** is a colorless oil (0.38 g, 82%, *ee* 99.8%). IR (KBr, cm^{-1}): 3261, 3106, 2968, 2871, 1596, 1486, 1321. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.82 (1H, d, J = 7.5 Hz), 7.72 (1H, d, J = 7.5 Hz), 7.58 (1H, t, J = 7.5 Hz), 6.61 (1H, br s), 6.26 (1H, t, J = 3.3 Hz), 6.22 (1H, m), 4.14 (1H, d, J = 12.0 Hz), 3.89 (1H, d, J = 12.0 Hz), 3.66 (1H, d, J = 12.9 Hz), 3.02 (1H, d, J = 12.9 Hz), 2.72 (1H, sextet, J = 6.3 Hz), 1.02 (3H, d, J = 6.3 Hz), 0.78 (3H, d, J = 6.3 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 144.52, 135.35 (q, J = 1.7 Hz), 135.25, 133.42, 129.47, 128.59 (q, J = 30 Hz), 125.81 (q, J = 5.1 Hz), 124.34, 123.03 (q, J = 273.7 Hz), 108.52, 108.39, 58.64, 48.40, 41.13, 22.88, 20.90. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −60.87. HRMS (ESI) m/z calcd. for $C_{16}H_{20}F_3N_2O$ $(M+H)^+$: 313.3375, found 313.3366. $[\alpha]_D^{25}$ = +52.9 (*c* 1.07; EtOH).

***N*-benzyl-(*S*)-2-aminomethyl-1-[2-hydroxymethyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole ((*S*)-12d).** The reaction was monitored by TLC, and the residue was purified by column chromatography (hexane/ethyl acetate = 1/1, R_f = 0.1–0.25). Pure (*S*)-**12d** is a colorless oil (0.35 g, 64%, *ee* 99.8%). IR (KBr, cm^{-1}): 3294, 3064, 2927, 2849, 1597, 1486, 1321, 1163, 1132. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.83 (1H, d, J = 7.5 Hz), 7.70 (1H, d, J = 7.5 Hz), 7.59 (1H, t, J = 8.0 Hz), 7.29–7.17 (5H, m), 6.60 (1H, br s), 6.26 (1H, t, J = 3.0 Hz), 6.23 (1H, dd, J = 2.1, 1.5 Hz), 4.17 (1H, d, J = 12.0 Hz), 3.91 (1H, d, J = 12.0 Hz), 3.71 (1H, d, J = 13.0 Hz), 3.69 (1H, d, J = 13.5 Hz), 3.63 (1H, d, J = 13.0 Hz), 3.10 (1H, d, J = 13.5 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 144.34, 137.99, 135.34 (d, J = 1.5 Hz), 135.16, 132.73, 129.56, 128.63 (q, J = 30.2 Hz), 128.57, 128.33, 127.38, 125.91 (q, J = 5.2 Hz), 124.55, 122.98 (q, J = 273.9 Hz), 109.19, 108.53, 58.85, 53.12, 43.11. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −60.90. HRMS (EI) m/z calcd. for $C_{20}H_{19}F_3N_2O$ $(M)^+$: 360.1442, found 360.1449. $[\alpha]_D^{25}$ = +52.7 (*c* 0.73; EtOH).

***N*-[(*R*)-1-phenylethyl]-(*S*)-2-aminomethyl-1-[2-hydroxymethyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole ((*S*)-12e).** The reaction was monitored by TLC, and the residue was purified by column chromatography (hexane/ethyl acetate = 2/1, R_f = 0.05–0.3). Pure (*S*)-**12e** is a white solid (0.49 g, 87%, *ee* 99.8%). Mp: 98–103 °C (from ethyl acetate). IR (KBr, cm^{-1}): 3312, 2960, 2852, 1594, 1487, 1321, 1157, 1129. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.89 (1H, t, J = 4.7 Hz), 7.60–7.58 (2H, m), 7.12–7.09 (3H, m), 6.98–6.95 (2H, m), 6.59 (1H, s), 6.25 (1H, t, J = 3.3 Hz), 6.22 (1H, dd, J = 3.5, 1.6 Hz), 4.21 (1H, d, J = 11.7 Hz), 3.96 (1H, d, J = 11.7 Hz), 3.81 (1H, q, J = 6.6 Hz), 3.45 (1H, d, J = 13.2 Hz), 2.87 (1H, d, J = 13.2 Hz), 1.28 (3H, d, J = 6.9 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 144.05, 142.73, 135.13, 133.15, 129.39, 128.56 (q, J = 30.1 Hz), 128.37, 126.98, 126.50, 125.87 (q, J = 5.3 Hz), 124.55, 122.82 (q, J = 273.7 Hz), 109.30, 108.45, 59.10, 58.07, 41.68, 24.15. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −59.68. HRMS (ESI) m/z calcd. for $C_{21}H_{22}F_3N_2O$ $(M+H)^+$: 375.4068, found 375.4060. $[\alpha]_D^{25}$ = +74.7 (*c* 0.7; EtOH).

(*S*)-2-Aminomethyl-1-[2-hydroxymethyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole ((*S*)-12f). The reaction was monitored by TLC, and the residue was purified by column chromatography (pure ethyl acetate, R_f = 0.05–0.25). Pure (*S*)-**12f** is a white solid (0.29 g, 71%, *ee* 99.8%). Mp: 97–98 °C (from ethyl acetate). IR (KBr, cm^{-1}): 3360, 3188, 3111, 2924, 2850, 1596, 1570, 1486, 1320, 1134. ^{1}H NMR ($CDCl_3$, 300 MHz) δ_H 7.83 (1H, d, J = 7.5 Hz), 7.72 (1H, d, J = 7.8 Hz), 7.59 (1H, t, J = 7.7 Hz), 6.61 (1H, s), 6.28–6.24 (2H, m), 4.18 (1H, d, J = 12.0 Hz), 3.95 (1H, d, J = 13.5 Hz), 3.29 (1H, d, J = 12.0 Hz), 3.14 (1H, d, J = 13.5 Hz), 2.99 (3H, br s). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 144.38, 135.35 (d, J = 1.5 Hz), 135.14, 134.60, 129.58, 128.69 (q, J = 30.0 Hz), 125.92 (q, J = 5.3 Hz), 124.56, 123.01 (q, J = 273.9 Hz), 108.56, 108.42, 58.65, 35.91. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −60.89. HRMS (ESI) m/z calcd.

for $C_{13}H_{14}F_3N_2O$ $(M+H)^+$: 271.2577, found 271.2588. $[\alpha]_D^{25}$ = +22.6 (*c* 1.0; EtOH).

***N,N*-Diethyl-(*S*)-2-aminomethyl-1-[2-diphenylhydroxymethyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole ((*S*)-13a).** The reaction was monitored by TLC, and the residue was purified by column chromatography (hexane/ethyl acetate = (8/1, R_f = 0.05–0.25). Pure (*S*)-**13a** is a white solid (0.53 g, 74%, *ee* 99.8%). Mp: 113–114 °C (from ethyl acetate). IR (KBr, cm^{-1}): 3100, 3086, 2978, 2881, 2825, 1589, 1481, 1449, 1315, 1165. ^1H NMR ($CDCl_3$, 500 MHz) δ_H 8.32 (1H, br s), 7.74 (1H, d, *J* = 7.5 Hz), 7.36 (1H, t, *J* = 8.0 Hz), 7.28 (2H, t, *J* = 7.3 Hz), 7.24–7.19 (6H, m), 7.14 (1H, d, *J* = 8.0 Hz), 7.05 (2H, m), 6.08 (1H, s), 5.77 (1H, t, *J* = 3.0 Hz), 5.41 (1H, s), 3.27 (1H, d, *J* = 14.5 Hz), 3.05 (1H, d, *J* = 14.5 Hz), 2.81 (2H, hextet, *J* = 7.0 Hz), 2.29 (2H, sextet, *J* = 7.0 Hz), 0.83 (3H, t, *J* = 7.0 Hz). ^{13}C NMR ($CDCl_3$, 75 MHz) δ_C 148.98, 148.93, 147.13, 137.19 (d, *J* = 1.4 Hz), 135.12, 131.13 (q, *J* = 29.2 Hz), 130.40, 128.22, 127.80, 127.68, 127.45, 127.23, 126.80, 126.69, 126.49 (q, *J* = 5.5 Hz), 125.43, 129.99 (q, *J* = 274.5 Hz), 109.80, 105.77, 80.73, 48.33, 45.95, 10.13. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −60.75. HRMS (ESI) *m/z* calcd. for $C_{29}H_{30}F_3N_2O$ $(M+H)^+$: 479.2310, found 479.2301. $[\alpha]_D^{25}$ = +81.3 (*c* 0.5; $CHCl_3$). *Ee* was determined by HPLC analysis using a chiral stationary phase, Phenomonex Lux Amylose-2 column (5 μm, 250 × 4.6 mm), eluent hexane/ethanol = 98.5/1.5, 0.5 ml/min, UV detector 222 nm, 15 °C, retention time for (*R*)-**13a**: 9.5 min, for (*S*)-**13a**: 12.0 min.

***N,N*-Diisopropyl-(*S*)-2-aminomethyl-1-[2-diphenylhydroxymethyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole ((*S*)-13b).** The reaction was monitored by TLC, and the residue was purified by column chromatography (hexane/ethyl acetate = 5/1, R_f = 0.15–0.35). Pure (*S*)-**13b** is a white solid (0.67 g, 88%, *ee* 99.8%). Mp: 113–114 °C (from ethyl acetate). IR (KBr, cm^{-1}): 3089, 3057, 2965, 2879, 2750, 1590, 1480, 1458, 1312, 1162. ^1H NMR (acetone-d_6, 500 MHz) δ_H 7.91 (1H, d, *J* = 8.0 Hz), 7.58 (1H, t, *J* = 8.0 Hz), 7.39–7.33 (4H, m), 7.29–7.21 (5H, m), 7.06–7.05 (2H, m), 6.91 (1H, s), 6.02 (1H, s), 5.63 (1H, t, *J* = 6.0 Hz), 5.35 (1H, s), 3.47 (1H, d, *J* = 14.5 Hz), 3.35 (2H, sextet, *J* = 6.5 Hz), 3.23 (1H, d, *J* = 14.5 Hz), 1.01 (6H, d, *J* = 6.5 Hz), 0.87 (6H, d, *J* = 6.5 Hz). ^{13}C NMR (acetone-d_6, 75 MHz) δ_C 150.50, 150.01, 149.63, 138.93 (d, *J* = 1.2 Hz), 137.04, 133.10, 132.81 (q, *J* = 29.1 Hz), 130.24, 129.62, 129.29, 128.87, 128.86 (q, *J* = 5.5 Hz), 128.61, 126.46, 125.19 (q, *J* = 274,1 Hz), 111.93, 107.89, 82.63, 48.05, 40.78, 22.82, 19.11. ^{19}F NMR (acetone-d_6, 282 MHz) δ_F −60.90. HRMS (ESI) *m/z* calcd. for $C_{31}H_{34}F_3N_2O$ $(M+H)^+$: 507.2623, found 507.2634. $[\alpha]_D^{25}$ = +73.4 (*c* 0.5; EtOH). *Ee* was determined by HPLC analysis using a chiral stationary phase, Phenomonex Lux Amylose-2 column (5 μm, 250 × 4.6 mm), eluent hexane/ethanol = 98.5/1.5, 0.5 ml/min, UV detector 222 nm, 15 °C, retention time for (*R*)-**13b**: 7.6 min, for (*S*)-**13b**: 7.9 min.

***N*-Isopropyl-(*S*)-2-aminomethyl-1-[2-diphenylhydroxymethyl-6-(trifluoromethyl)phenyl]-1*H*-pyrrole ((*S*)-13c).** The reaction was monitored by TLC, and the residue was purified by column chromatography (hexane/ethyl acetate = 3/1, R_f = 0.05–0.25). Pure (*S*)-**13c** is a white solid (0.55 g, 79%, *ee* 99.8%). Mp: 117–119 °C (from ethyl acetate). IR (KBr, cm^{-1}): 3422, 3298, 3086, 2965, 2751, 1587, 1481, 1447, 1315, 1137. ^1H NMR ($CDCl_3$, 300 MHz) δ_H 7.74 (1H, dd, *J* = 7.9, 1.3 Hz), 7.38 (1H, t, *J* = 7.9 Hz), 7.33–7.13 (9H, m), 7.05 (2H, dd, *J* = 6.7, 3.0 Hz), 6.10 (1H, dd, *J* = 3.3, 1.5 Hz), 5.82 (1H, t, *J* = 3.2 Hz), 5.48 (1H, s), 3.77 (2H, br s), 3.68 (1H, d, *J* = 13.7 Hz), 3.18 (1H, d, *J* = 13.7 Hz), 2.77 (sextet, *J* = 6.3 Hz), 1.09 (3H, d, *J* = 6.3 Hz), 0.82 (3H, d, *J* = 6.2 Hz). ^{13}C NMR ($CDCl_3$,75 MHz,) δ_C 210.99, 148.65, 147.00, 137.21 (d, *J* = 1.3 Hz), 135.42, 132.97, 131.25 (q, *J* = 29.4 Hz), 128.53, 128.00, 127.83, 127.77, 127.43, 127.17, 127.10, 126.65 (q, *J* = 5.5 Hz), 125.21, 123.23 (q, *J* = 274.5 Hz), 108.10, 106.65, 81.55, 48.24, 41.82, 23.24, 21.62. ^{19}F NMR ($CDCl_3$, 282 MHz) δ_F −60.67. HRMS (ESI) *m/z* calcd. for $C_{28}H_{28}F_3N_2O$ $(M+H)^+$: 465,5299, found 465,5292. $[\alpha]_D^{25}$ = +51.7 (*c* 0.9; $CHCl_3$). *Ee* was determined by HPLC analysis using a chiral stationary phase, Phenomonex Lux Amylose-2 column (5 μm, 250 × 4.6 mm), eluent hexane/ethanol = 98.5/1.5, 0.5 ml/min, UV detector 222 nm, 15 °C, retention time for (*R*)-**13c**: 13.6 min, for (*S*)-**13c**: 16.2 min.

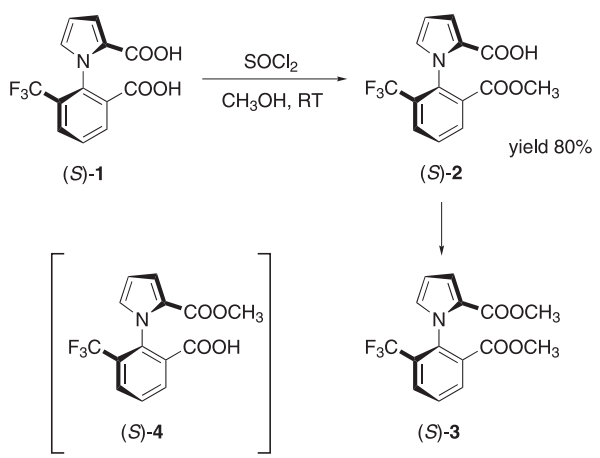
General Procedure for the Enantioselective Addition of Diethyl Zinc to Benzaldehyde using Chiral Amino Alcohol (S)-13c

Optically active amino alcohol (*S*)-**13c** (0.01 mmol, 5 mg, *ee* 99.8%) was dissolved in dry toluene (1 ml), a solution of diethyl zinc in hexane (1 mol/L, 0.4 mmol, 0.4 ml) was added, and the mixture was stirred for an hour at room temperature. After the addition of benzaldehyde (0.2 mmol, 20 μl), the mixture was stirred overnight. Saturated aqueous ammonium chloride solution (5 ml) and toluene (10 ml) were added, and the phases were separated. The aqueous phase was washed with toluene (5 ml), and the collected organic phases were dried over sodium sulfate and concentrated *in vacuo*. The crude residue was purified by column chromatography (hexane/ethyl acetate = 5/1) to yield (*S*)-1-phenylpropanol (**15**, 21.6 mg, 80%) with 86% enantiomeric excess. The *ee* was determined by gas chromatography analysis on an Agilent (Santa Clara, USA) 4890 D instrument equipped with a BETA-DEXP^{TMP} 120 fused silica capillary column (0.25 nm/0.25 μm, 30 m, Supelco, Sigma-Aldrich, 70 to 140 °C, 10 °C/min, retention time for (*R*)-**15**: 17.4 min, for (*S*)-**15**: 17.7 min). The absolute configuration of **15** was determined by the specific rotation of the product (*ee* 86%, $[\alpha]_D^{25}$ = −40.9 (*c* 1.25; $CHCl_3$),[11]: $[\alpha]_D^{25}$ = −47.5 (*c* 1; $CHCl_3$) for the pure *S* enantiomer).

RESULTS AND DISCUSSION

Synthesis of the Key Compound Monoester (2) by Selective Esterification of (S)-1

The synthesis of the desired atropisomeric amino alcohols was performed using (*S*)-**1** as starting material, via **2**, the monomethyl ester of the dicarboxylic acid **1**. The key compound **2** was obtained in high selectivity by the esterification of the carboxylic group connected to the phenyl ring in dicarboxylic acid **1**. This monoesterification was carried out with thionyl chloride in methanol (Scheme 1). The formation of the monoester and the diester (compounds **2** and **3**[4]) are consecutive reactions, for which the optimal conditions had to be determined. Varying the reaction conditions systematically, we found that the optimal amount of the thionyl chloride is 7 eq. The usage lower amounts of thionyl chloride resulted in lower monoester/diester product ratios and increased the reaction time as well. Higher temperatures favored the



Scheme 1. Selective monoesterification of (*S*)-**1**.

formation of the dimethyl ester. After 48 h, a 85:15 mixture of monomethyl and dimethyl esters was obtained using optimal conditions. The formation of the other possible monoester **4**—by the esterification of the carboxylic group connected to the pyrrole ring—was not detected in the crude product because of the big difference between the electron densities on the carbonyl carbon atoms connected to the phenyl and the pyrrole rings (Fig. 1). That difference is caused by two effects: the electron withdrawing CF_3 group connected to the phenyl ring and the electron excessive heterocyclic pyrrole ring, which decreases the electron deficiency on the carbonyl carbon atom connected to the α carbon atom of the ring. Pure (−)-(*S*)-**2** was obtained after recrystallization of the crude product from hexane in 80% yield.

The positions of the methoxycarbonyl and the carboxylic groups in (*S*)-**2** were proved by single crystal X-ray diffraction studies based on the structure of its mirror image derivative (+)-(*R*)-**7a** (Fig. 3). The latter compound was synthesized from (+)-(*R*)-**2**. The positions of the amide and the hydroxymethyl functions in (*R*)-**7a** have certified the structure of (*R*)-**2** and, consequently, confirmed the constitution of (*S*)-**2**.

The free carboxylic group of compound (*S*)-**2** was converted into an acid chloride (*S*)-**5** followed by acid amide formation ((*S*)-**6**, Scheme 2).

Preparation of Optically Active Amino Alcohol Derivatives of (S)-1

The method could be applied for a wide range of amines. We prepared primary, secondary, and tertiary amides as well with excellent yields in all cases (>95%). The formation of the alcoholic function from the ester groups was implemented in two ways. First, primary alcohols (*S*)-**7a–f** were synthesized by the reduction of the benzoic acid ester moiety by using sodium tetrahydridoborate (Scheme 3).

It was found that the mixture of tetrahydrofuran and ethanol is the most suitable solvent for the reduction. When 10% ethanol was used, the reaction was complete after 72 h and the usage of 1.5 Eq reducing agent was found enough. In pure alcoholic solvents, the reduction was never complete, even when sodium tetrahydridoborate was applied in large excess,

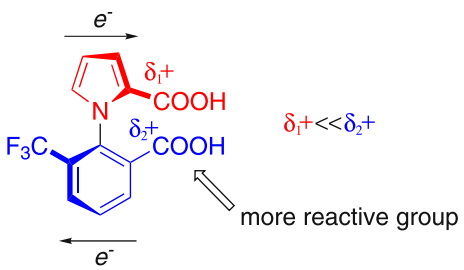


Fig. 1. Relative electron deficiencies on the carbonyl carbon atoms connected to the rings of (*S*)-**1**.

because the decomposition of the reducing agent was faster than the formation of the target compounds.

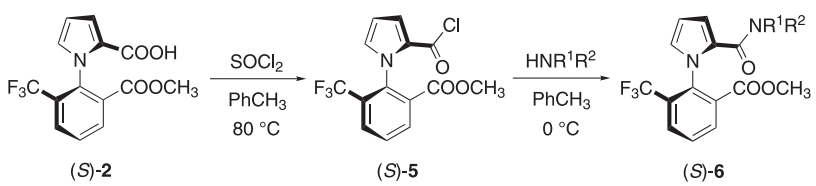
Tertiary alcohols (*S*)-**8a–c** were prepared by the addition of Grignard's reagents or phenyl lithium to the benzoic acid ester derivatives (*S*)-**6a–c** (Scheme 4) in excellent yields. The reactions were carried out at low temperature, and *in situ* formed organolithium reagents were used.

In one case, when (*S*)-**6f** was used as starting material, the aforementioned tertiary alcohol formation reaction failed. With the use of 3 Eq of Grignard's reagent, two main products **10** and **11** were obtained (in 1.5/1.0 ratio).

The anticipated product **10** was obtained in only 24% *ee*, whereas the unexpected compound **11** in racemic form, despite the enantiopure starting material. The supposed routes of formation of the two ketones can be seen in Scheme 5.

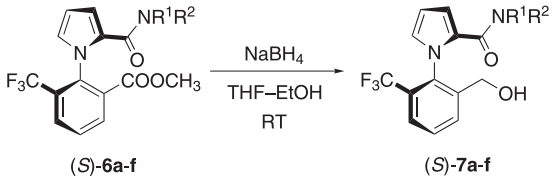
Our hypothesis was that compound **11** could be formed through an imide derivative (**9**). Compound **9** should be the product of the ring closure reaction of the functions in (*S*)-**6f**′, and this latter compound could serve as an intermediate for **10** as well. To confirm the formation of **9**, a separate reaction was carried out in which the starting material (*S*)-**6f** was treated with potassium *tert*-butoxide. Compound **9** was isolated after an acidic work-up procedure in excellent (95%) yield, but in racemic form. This phenomenon explains the observed low optical activities of products **10** and **11**. The rotational energy barrier around the C–N bond has to be much smaller in **9** than in **10** and **11**, hence the stereochemically labile intermediate is the reason for the formation of racemic products.

It has to mentioned that the observed side reaction, namely formation of compound **11** from **6f**, represents an interesting, unexpected amino group migration from the pyrrole-bonded carboxamide group into the methoxycarbonyl substituent of the benzene ring in the presence of phenylmagnesium bromide. The structure of **11** was confirmed by 2D NMR spectroscopic measurements. The results can be seen in Figure 2a and b. First, the ^{1}H–^{1}H COSY (correlation spectroscopy) experiment was performed (Fig. 3), and the proton signals were separated into four spin systems: namely, (a) the pyrrole ring protons between 6.37 and 7.26 ppm, (b) the proton signals of the trisubstituted phenyl ring between 7.71 and 7.93 ppm, and (c) the signals of the phenyl ring between 7.50 and 7.70 ppm. The two amide hydrogen signals appear separately at 7.42 and 7.33 ppm, and although these broad signals do not show any splitting, on the basis of the COSY spectrum, they form the fourth (AB) spin system. After the full assignment of the ^{1}H NMR spectrum, the structure can be postulated via the HMBC experiment. We have two carbonyl signals in the ^{13}C spectrum, one at 183.97 ppm, the other at 166.89 ppm. The former should belong to an unsaturated ketone, and the latter is in the range of amide carbonyl signals. In the HMBC spectrum, the signal at 189.97 ppm

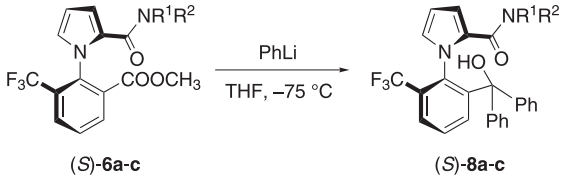


6	R^1	R^2
a	Et	Et
b	*i*-Pr	*i*-Pr
c	H	*i*-Pr
d	H	Bn
e	H	(*R*)-1-Phenylethyl
f	H	H

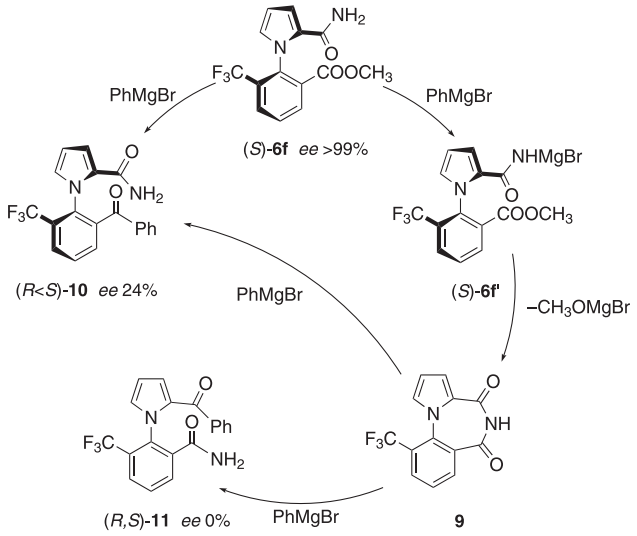
Scheme 2. Preparation of amides (*S*)-**6a–f**.



Scheme 3. Chemoselective reduction of the benzoic acid ester moiety of (*S*)-**7a–f**.



Scheme 4. Transformation of the benzoic acid ester functions of (*S*)-**6a–c** into tertiary alcohols ((*S*)-**8a–c**).



Scheme 5. Unexpected side reactions during the transformation of the benzoic acid ester moiety of (*S*)-**6f**.

shows correlations with the pyrrole 3-*H* (6.79 ppm) and the 2,6-*H* (*ortho*) signal (7.70 ppm) of the monosubstituted phenyl ring, whereas the signal at 166.89 ppm correlates with the two amide protons and the 3-*H* (7.80 ppm) signal of the trisubstituted phenyl ring. These correlations give unambiguous proof for the structure of compound **11**.

The synthesis of amino alcohols was completed by the reduction of the amide groups of (*S*)-**7a–f** and (*S*)-**8a–c**.

When lithium tetrahydridoaluminate was chosen as reducing agent, a defluorination side reaction was observed (Scheme 6). The usual purification attempts to produce pure **12a** have failed; therefore, the structure of compound **12a′** was determined from the ^{1}H and ^{19}F NMR spectra of the mixture of **12a** and **12a′**. Brabander and co-workers observed a similar phenomenon, using lithium tetrahydridoaluminate for the reduction of CF_3 group containing compounds.[8] The formation of the undesired side product could be avoided by using borane complexes.

The reduction rates of the amides containing primary alcohol function, using borane dimethysulfide complex, was moderate. After a 2-day reaction time, the optically active bifunctional atropisomeric derivatives ((*S*)-**12a–f**) were obtained as precipitates, in excellent (up to 90%) yields (Scheme 7).

The similar reduction of amides (**8a–c**) containing tertiary alcoholic functions proved to be much easier: the starting materials consumed within 2 h (Scheme 8).

Single-Crystal X-Ray Diffraction Studies

On the basis of previous X-ray studies of (+)-**1**·(*R*)-1-phenylethylamine salt, it is known that the absolute configuration of (+)-**1** is *R*.

We could also prepare single crystals from (+)-**7a** for X-ray studies by crystallization from diethyl ether. The structure of (+)-(*R*)-**7a** is shown in Figure 3. The structure is in agreement with the configuration of its starting material (+)-(*R*)-**1**. There is a well-defined intramolecular hydrogen bond between the oxygen atom of the amide group and the hydrogen of the hydroxyl group (Fig. 3). This sterically favorable intramolecular hydrogen bridge may be among the reasons for the unusual low reactivity of the primary hydroxyl group containing amides (**7a–f**) during the reduction with borane complexes.

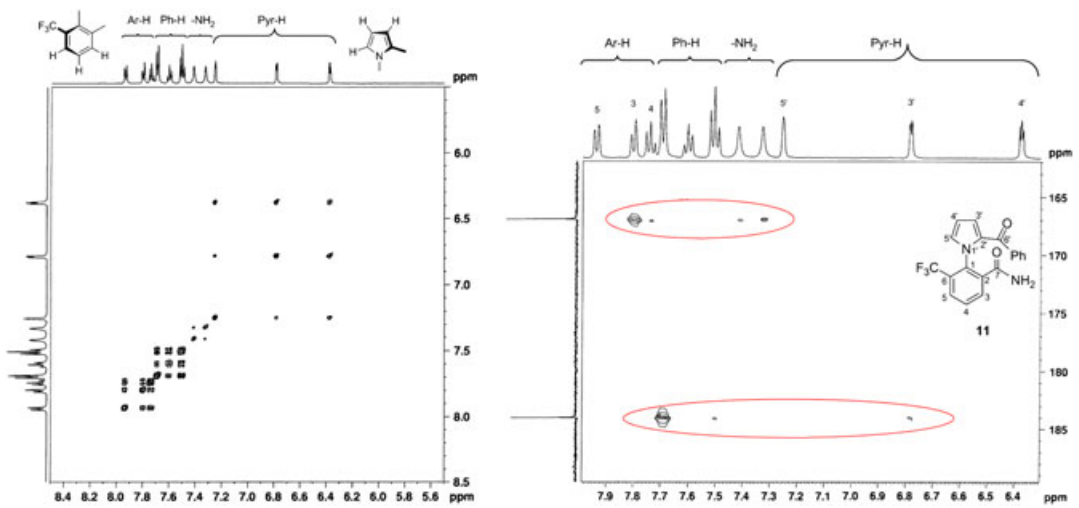
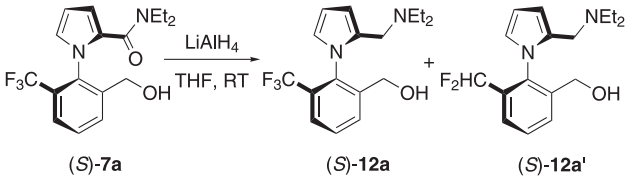
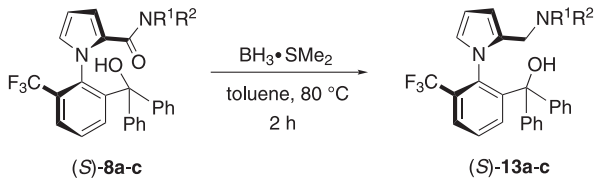


Fig. 2. 2D NMR spectra of **11**. ^{1}H-^{1}H COSY spectrum and the main part of the HMBC spectrum.



Scheme 6. Reduction of amide (*S*)-**7a** with $LiAlH_4$.

Scheme 7. Preparation of amino alcohols (*S*)-**12a–f**.



Scheme 8. Preparation of amino group containing tertiary alcohols (*S*)-**13a–c**.

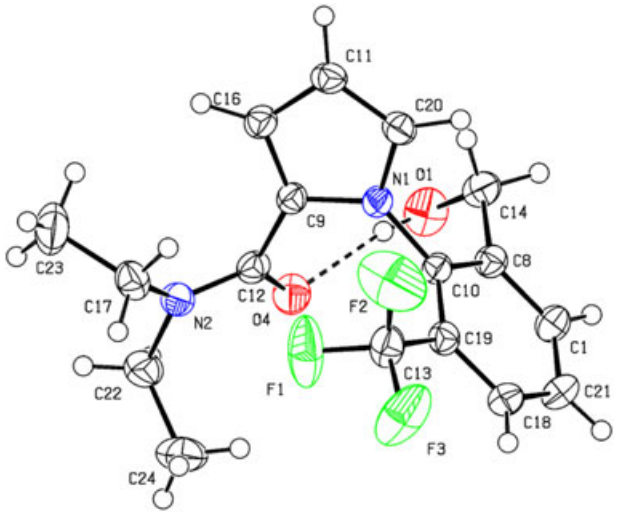


Fig. 3. X-ray crystal structure and solid-state conformation of (+)-(*R*)-**7a**.

Determination of the Ee Values and the Rotational Energy Barriers

A solution ^{1}H NMR spectroscopic method has been developed to assess the enantiomeric composition of **12a**. The enantiomeric purity was determined with the help of a well-established methodology[9]: by adding an optically active chiral solvating agent to the solution of **12a** in apolar aprotic solvents. The application of chiral solvating agents in NMR is often a method of choice when other chiral selectors (e.g., lanthanide shift reagents or cyclodextrins) fail to work properly. For the determination of the optical purity of amino alcohol **12a**, we employed its parent compound, dicarboxylic acid **1**. In a previous study, the effective application of 1-[2-carboxy-6-(trifluoromethly)phenyl]-2-carboxylic acid (*R*)-**1** was described as a chiral shift reagent for the determination of the enantiomeric ratio of oxetanes and *cis*-but-2-ene-1,4-diol derivatives, too.[10] Figure 4 shows the enantiomeric splitting of Pyr–CH_2–N (in **12a**) in the presence of (*R*)-**1**. Other resonances did not show enantiomeric splitting, but the signals of Pyr–CH_2–N (both enantiomer at ~3.65 ppm) were found to be adequate for the determination of *ee*. The signal ratio of the racemic form is 1:3, which means 1 and 1 + 2 protons (for the two enantiomers). From the ratio of the signals, the enantiomeric purity can be calculated.

Further measurements were carried out from the enantiomerically pure amino alcohol **12a** and from the enantiomeric mixture made by the addition of a small amount of the racemic form to the enantiopure compound (Fig. 5). The results have confirmed that the synthesis of the amino alcohol **12a** occurred without any racemization.

Recently, we have described the determination of the activation energy of rotation around the C–N bonds for compound **1**.[4] Molecular modeling calculations were carried out, with a parallel experimental determination of $\Delta G^{\#}$. We found that $\Delta G^{\#} = +31.6$ kcal/mol for compound **1**. The theoretically and the experimentally determined $\Delta G^{\#}$ values were in good agreement. To obtain more information about the optical stability of the target compounds, further computational studies were performed. The activation energy values were estimated using AM1 semiempirical quantum chemical method. The geometries of the transition states of **6a** and **12a** model compounds are visualized in Figure 6, whereas the calculated and experimentally determined activation energy values are collected in Table 1.

By viewing the growing order of the activation energies **1** < **6a** < **12a**, one can generally state that the increased size of the transformed carboxylic acid functions causes higher steric resistance. By reduction of the carboxylic acid derivative, the relative space filling of the formed groups will be greater because of their increased freedom of movement.

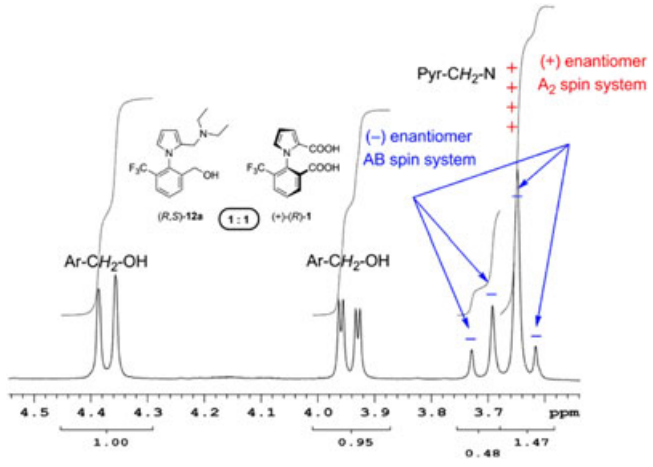


Fig. 4. ^{1}H NMR signals of methylene protons of amino alcohol **12a** in the presence of a molar equivalent chiral dicarboxylic acid (+)-(*R*)-**1**.

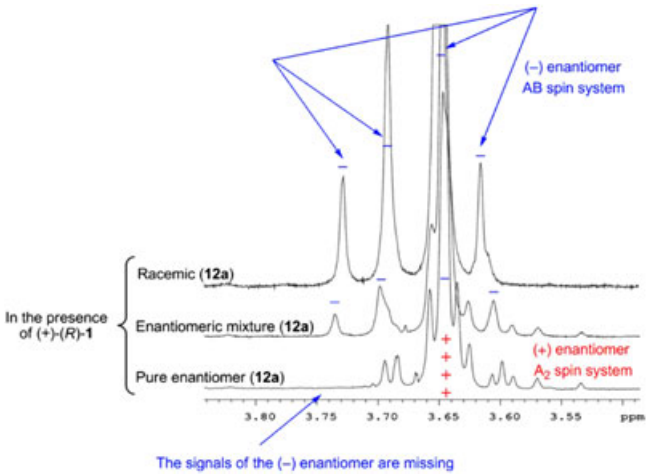


Fig. 5. Determination of the *ee* values for compound **12a** by ^{1}H NMR analysis. Spectra were recorded in the presence of (*R*)-**1**. The racemate was added to the solution in one case (middle spectrum) to check the validity of the NMR method and to confirm the chemical shift and the enantiomeric purity.

Fig. 6. Transition state geometries of **6a** and **12a** calculated by AM1 method (red: oxygen, blue: nitrogen, green: fluoro atom).

The optical stability of amino alcohol **12a** is twice as high as that of compound **1**.

Application of Optically Active Amino Alcohol Derivative (S)-13c as Catalyst

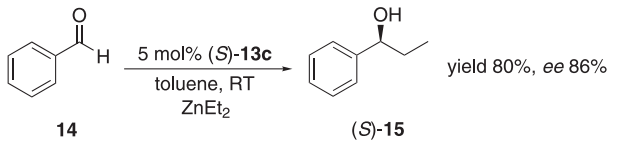
The addition of diethylzinc to benzaldehyde was chosen to test the utility of the prepared new chiral amino alcohols as enantioselective organocatalysts. Herein, we report the first successful example for the application of (*S*)-**13c** as an efficient catalyst of the aforementioned addition reaction. The (*S*) enantiomer of 1-phenylpropanol was obtained in a good (80%) yield and with 86% enantiomeric excess by using 5 mol% amino alcohol (*S*)-**13b** (Scheme 9).

CONCLUSION

The significant reactivity difference between the two carboxylic groups of dicarboxylic acid **1** could be utilized for the selective transformation of these groups into amino and hydroxyl functions, respectively. The selective monoesterification of dicarboxylic acid **1** served as the key step of the synthesis. The same phenomena—namely the increased electrophylicity of the carbonyl function connected to the substituted phenyl group and the decreased electrophylicity of the carbonyl function connected to the pyrrole ring—could be used for the further selective transformations of the functions. Thus, highly selective hydride reduction of the methylester group in compounds **4a–f** into **7a–f** could be achieved while the amide functions remained intact, independently of the substituents of the amide nitrogen atom. Furthermore, the deprotonated primary amide nitrogen of **6f** could easily attack the carbonyl carbon atom of the ester group to form compound **9**.

TABLE 1. Calculated and experimentally determined activation energies for isomerisation of compounds 1, 6a, and 12a

Compound	$\Delta G^{\#}_{calculated}$ (kcal/mol)	$\Delta G^{\#}_{measured}$ (kcal/mol)
1	32.9	31.6
6a	42.4	–
12a	64.5	–



Scheme 9. Enantioselective addition of diethyl zinc to benzaldehyde using chiral amino alcohol (*S*)-**13c**.

A smaller difference between the reactivities of the two carbonyl groups was observed during the reaction of **9** with phenylmagnesium bromide, where ketones **10** and **11** were formed in the same order of magnitude. Finally, a highly selective addition of phenyllithium to the aforementioned ester group could also be achieved in the cases of **6a-c** to yield the new optically active compounds **8a–c**.

The relative stereochemical stabilities of the prepared compounds were in accordance with the relative values of rotational energy barriers, calculated for the starting material (**1**) and two new products (**6a** and **12a**). The height of the rotational energy barrier for **1** was also determined by NMR spectroscopic experiments, which produced a value close to the calculated one.

The enantioselective addition of diethylzinc to benzaldehyde in the presence of a catalytic amount of (*S*)-**13c** demonstrated on the first occasion that the prepared new atropisomeric amino alcohols ((*S*)-**12a–f** and (*S*)-**13a–c**) can be used as efficient catalysts in such reactions.

Until now, chiral β-aminoalcohols has been known from the literature as good ligands; therefore, it is important to mention that the synthesized new atropisomeric amino alcohols represent the first examples of such chiral aminoalcohols in which the two functions are connected to each other across a six-atom long chain.

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