New C-substituted (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane derivatives. Preparation utilizing the directed metalation strategy. Application in enantioselective catalysis

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Abstract

New C-substituted derivatives of (1*S*,4*S*)-2-methyl-2,5-diazabicyclo[2.2.1]heptane were synthesized utilizing the directed metalation strategy. The absolute configuration of the 3-substituted derivative rests on the comparison of the NMR spectra with a product of proven configurational assignment by X-ray crystallographic analysis.

Keywords: Enantioselective catalysis, directed lithiation, borolidine reduction

Introduction

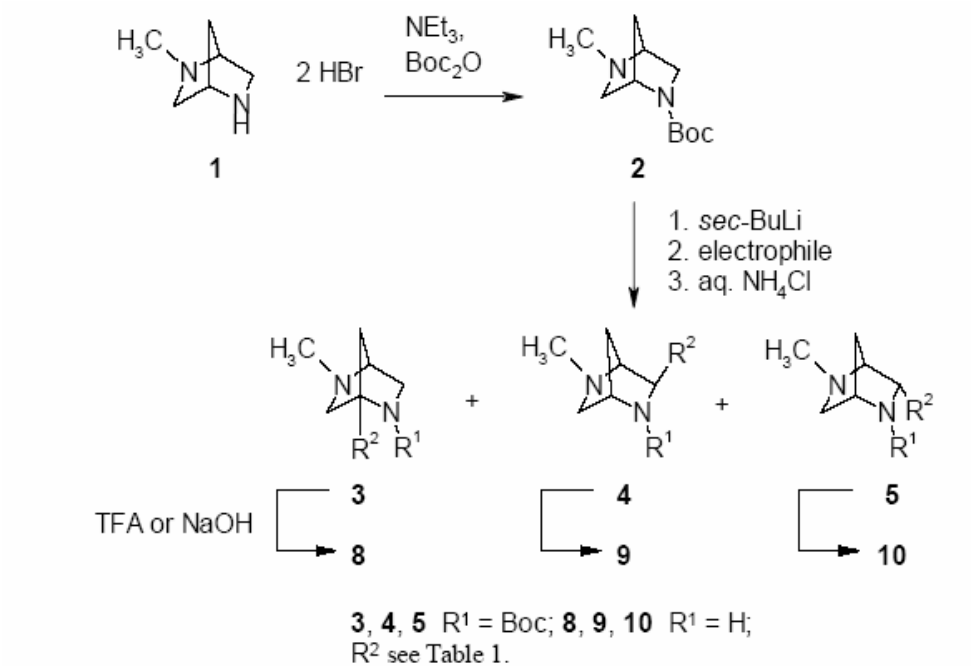
Various N-substituted derivatives of (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane are known in the literature.[1] C-Substituted derivatives are rather scarce and include methyl derivatives,[2] lactams (3-oxo-substituted),[3] and a 7-hydroxy-7-phenyl-substituted species.[4] Compounds containing the (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane moiety have proven to be useful building blocks in organic synthesis, and particularly, in medicinal chemistry.[1d,le,1h,1i,1j,1l] Contrary to the conformationally flexible piperazine, the 2,5-diazabicyclo[2.2.1]heptane scaffold is rigid and chiral. The parent compound is synthesized from the naturally occurring amino acid *trans*-4-hydroxy-L-proline.[5] *Beak* and *Hoppe* pioneered the directed lithiation of N-protected amines,[6] a procedure, which allows asymmetric induction in this step when the generally applicable *sec*-butyllithium/(−)-sparteine system is employed for deprotonation.[7,8]

In a recent communication we published the synthesis of novel C-substituted derivatives of (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane (**1**) (Scheme 1). This has been achieved by lithiation of the Boc-protected derivative **2** followed by the reaction with suitable electrophiles.[9] After deprotection the resulting -functionalized amines have been tested as ligands catalyzing the asymmetric addition of diethylzinc to benzaldehyde.[10]

In this paper we provide full experimental details of the synthesis and characterization of the products. Furthermore, three of the products were tested as chiral auxiliaries in the borolidine-induced reduction of propiophenone.[11]

Results and Discussion

The synthesis of **1** started from commercially available *trans*-4-hydroxy-L-proline, which was N-tosylated and subsequently reduced to (2*S*,4*S*)-4-hydroxyprolinol. Upon tosylation of both hydroxy groups the reaction with methylamine under pressure formed the additional ring of **1**. Finally, the *N*-tosyl group was removed by cleavage with hydrobromic acid.



Scheme 1

In the course of this work this procedure was slightly altered by replacing the two O-tosyl leaving groups with O-mesyl thus slightly improving the yield of the cyclization reaction (92% vs 86% in the original procedure). The cyclization was carried out in toluene solution instead of methanol. N-Detosylation was performed in 33% hydrobromic acid (30% HBr/AcOH in the literature) improving the yield of 1·2 HBr.

After N-Boc protection of **1** with Boc-anhydride/triethylamine the deprotonation of **2** was performed with 1.5 equivalents of *sec*-butyllithium/*N*,*N*,*N'*,*N'*-tetramethyl-ethylenediamine (TMEDA) followed by the addition of a suitable electrophilic reactant and furnished the C-substituted products **3**, **4**, and/or **5** (Scheme 1). The reactivity of some electrophiles with monocyclic aromatic groups (benzophenone, diphenyldisulfide) appears to depend on the choice of solvent; thus dry diethyl ether instead of tetrahydrofuran (THF) enhanced the regioselectivity

but dramatically decreased the conversion rate and yield (as evidenced from TLC monitoring of the reactions). For most electrophiles, substitution at position 1 of **2** affording **3** is favored over substitution at position 3 furnishing **4** and/or **5**. Most 3-substituents R_2 have been found to adopt the axial orientation as in products **4** (vide infra). As an exception, the group R_2 = 1,1-bis[(3-trifluoromethyl)phenyl]-1-hydroxymethyl has been introduced both as axial and equatorial substituent in **4b** and **5b**, respectively (Table 1). The lithiated species derived from **2** seem to exist in an equilibrium of 1- and 3-deprotonated species before the reaction with the electrophilic reactant furnished either of the three C-substituted products **3**, **4**, and/or **5.**

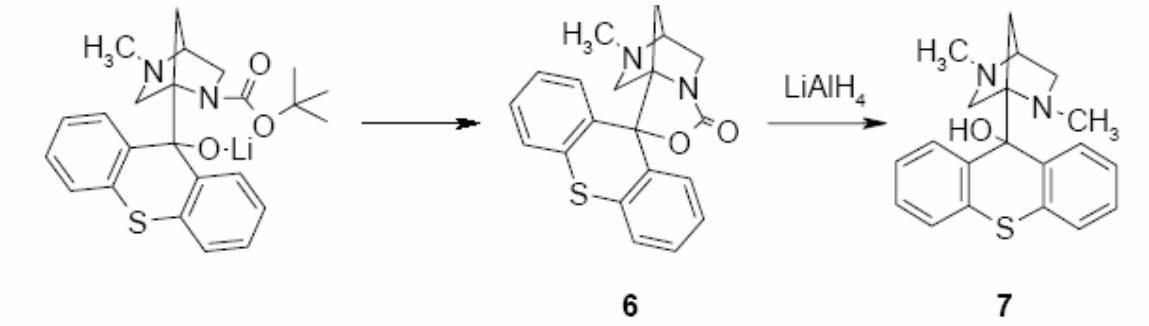
Table 1. Yields of **3**, **4**, **5** obtained from the reaction of **2** with electrophiles

Entry	R^2	Yield **3**[%]	Yield **4**[%]	Yield **5** [%]
a		27	–	16
b		12	12	4
c		26	–	14
d		33	–	34
e		25	–	3
f		–	–	13
g		(4)[a]	–	–

[a] See text.

The coupling patterns of three versus two methylene groups permitted the distinction between 1- and 3-substituted products **3** and **4** and/or **5**, respectively. X-Ray diffraction determined the stereochemistry of compound **4b**[9] and established the equatorial orientation of the 3- substituent. Conventional NMR techniques were not applicable because the coupling constants required for the configurational assignment were within the linewidths of the NMR signals. Comparison of the ^{1}H NMR spectrum of **4b** with those of other 3-substituted products allowed the unequivocal configurational assignment of these compounds **5a-f**. The electrophiles with polycyclic armatic groups (**c**, **e**) resulted in predominant substitution at the bridgehead (Table 1), in contrast to the electrophiles with monocycloc aromatic groups (**a**, **d**) resulting in low regioselectivity. Surprisingly, with 3,3'-bis(trifluormethyl)benzophenone as electrophile the resulting substituent assumes the equatorial position at C-3.

In the case of 9*H*-thioxanth-9-one as electrophile two different products were obtained depending on the amount of *sec*-BuLi utilized for deprotonation. With 1.2 equivalents of *sec*-BuLi the expected 1-substituted product **3g** (Table 1) was isolated in only 4% yield. Using 1.5 equivalents of *sec*-BuLi resulted in the formation of the spiro compound **6** (24% yield). This is explained by the intramolecular nucleophilic attack of the O-lithiated intermediate (i.e. the lithium salt of **3g**) on the carbamate functionality, a mechanism not uncommon in the literature.[12] The structure **6** was further proven by the formation of **7** upon $LiAlH_4$ (LAH) reduction (Scheme 2).



Scheme 2

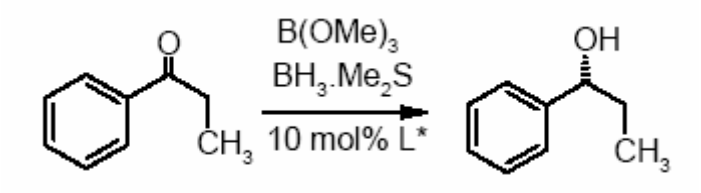
Table 2. Yields of the deprotection reactions

Product	Reagent	Yield [%]
8a	NaOH	46
10a	NaOH	47
8b	TFA	81
9b	NaOH	71
8c	TFA	82
8d	LAH	18
8e	TFA	20

Generally, cleavage of the Boc-group in **3**, **4**, and **5** was achieved either by treatment with trifluoro acetic acid (TFA), aqueous sodium hydroxide or LAH (Table 2). In some cases the yields were disappointingly low. Boc-cleavage of **3d** (featuring a thioether functionality) could not be achieved with sodium hydroxide. Utilization of TFA resulted in partial cleavage of the thioether group and decreased the yield of **8d** to almost zero. A viable solution was the utilization of LAH although the yield of **8d** remained very low.

Application of (1*S*,4*S*)-2-methyl-2,5-diazabicyclo[2.2.1]heptane derivatives in asymmetric catalysis

Three selected compounds **8a-c** were also tested as chiral auxiliaries in the asymmetric reduction of propiophenone by a chiral borolidine species formed in situ prior to addition of the ketone. Borolidine reduced propiophenone to 1-phenyl-1-propanol (Scheme 4), and the resulting enantiomers were analyzed by chiral HPLC. Only with **8a** very modest enantiomeric excess was achieved. (Table 3).



Scheme 3

Table 3. Borolidine reductions

Ligand L*	ee	Configuration
8a	27	*S*
8b	rac.	–
8c	rac.	–

In conclusion, we describe a new class of -amino alcohols prepared by directed metalation of Boc-protected (1*S*,4*S*)-2,5-diazabicyclo[2.2.1]heptane and subsequent addition to aromatic ketones followed by deprotection.

Experimental Section

General Procedures. All employed reagents were commercial compounds. (*S,trans*)-4-hydroxyproline was purchased from SIGMA. Dry THF, diethyl ether, and toluene were freshly distilled from sodium/benzophenone ketyl radical. *sec*-BuLi was purchased from Fluka Corp. and was titrated before use against 2-butanol (in dry toluene, indicated by phenanthroline hydrochloride). Thin-layer chromatography (TLC) was performed using Merck silica gel (60 F-254) plates (0.25 mm). For the monitoring of compounds not detectable under UV light a ninhydrin spray reagent was used. Column chromatography was performed using J. T. Baker silica gel 60 (40–63 m). Melting points (mp) were determined using a Kofler hot stage microscope. Proton (^{1}H) and carbon (^{13}C) magnetic resonance spectra (NMR) were recorded on a Bruker 200 FS (200 MHz for ^{1}H, 50 MHz for ^{13}C) Fourier transform spectrometer, and chemical shifts were expressed in parts per million () relative to tetramethylsilane using solvent signals as an internal reference: DMSO-d_6, 2.50 (^{1}H) and 39.5 (^{13}C) or $CHCl_3$, 7.24 (^{1}H) and 77.0 (^{13}C); multiplicities: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet). Reaction temperatures were measured using a digital thermometer inside the reaction vessel. Enantiomeric excess (ee) was determined by chiral HPLC using a Chiralcel OD-H column (4.6 mm x 250 mm, Daicel Chem. Ind. Ltd), detection at 254 nm, pump and detector from Waters. Optical rotations were determined with a Perkin-Elmer polarimeter.

(1*S*,4*S*)-2-Methyl-2,5-diazabicyclo[2.2.1]heptane dihydrobromide (1). (2*S*,4*S*)-*O*,*O*-Dimesyl-1-tosyl-4-hydroxy-2-hydroxymethylpyrrolidine (200.0 g, 0.468 mol) were suspended in toluene (2000 mL) in a 5 L steel autoclave precooled to –20°C. Liquid methylamine was prepared by treating solid sodium hydroxide (50.0 g) with an aqueous methylamine solution (40%, 300 mL) and condensing the developing methylamine gas in a cool trap at –20°C. Liquid methylamine (58.0 g, 1.872 mol) was added, the autoclave was closed and heated to 100°C internal temperature. The reaction was finished after 16 hours the pressure decreasing to almost zero indicating the end of the conversion. The reaction mixture (clear solution with some precipitate) was filtered and extracted twice with aqueous sodium hydroxide (10%, 500 mL each). The

aqueous phases were extracted with toluene (2 x 200 mL), the combined organic phases were washed with saturated brine (200 mL), dried over sodium sulfate and evaporated affording a yellow oil which was either crystallized by digesting with petroleum ether yielding (1*S*,4*S*)-2-methyl-5-tosyl-2,5-diazabicyclo[2.2.1]heptane (114.0 g, 91.5%) or used directly for the detosylation by heating to reflux in hydrobromic acid (33%, 300 mL) for 2 h followed by evaporation to dryness. The crude product was triturated using diethyl ether/methanol (2:1, v/v, 300 mL), filtered and washed with diethyl ether (100 mL) to give **1**·2 HBr as pale yellow crystals; mp 256–258 °C; α_D^{20} = +11.8° (c = 1, MeOH); spectral data were consistent with those published.[5]

1,1-Dimethylethyl (1*S*,4*S*)-5-methyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (2). A solution of **1** (20.0 g, 73 mmol) in dry dichloromethane (200 mL) was cooled to 5 °C and treated drop-wise with dry triethylamine (30.0 g, 0.29 mol, 4 equiv.). Boc anhydride (20.0 g, 88 mmol, 1.25 equiv.) was added, and the mixture was stirred for 6 h. The solvent was removed, the residue was dissolved in water (100 mL) and extracted continuously with ethyl acetate for 24 h. The organic layer was dried (sodium sulfate) and evaporated. The oily residue was Kugelrohr distilled (60 °C, 0.05 mbar) to yield a colorless oil **2** (12.0 g, 77%); R_f 0.40 (methanol); ^{1}H NMR (200 MHz, $CDCl_3$): 1.39 (s, 9H), 1.65 (d, *J* = 9.5 Hz, 1H), 1.78 (d, *J* = 9.5 Hz, 1H), 2.34 (s, 3H,), 2.47 (d, *J* = 9.4 Hz, 1H), 2.63 (d, *J* = 9.4 Hz, 1H), 2.73 (d, *J* = 9.4 Hz, 1H), 2.87 (d, *J* = 9.4 Hz, 1H), 3.10 (d, *J* = 10.8 Hz, 1H), 3.26–3.33 (m, 1H), 3.40 (d, *J* = 10.8 Hz, 1H), 3.50 (d, *J* = 10.8 Hz, 1H), 4.10–4.17 (m, 1H), 4.22–4.31 (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): 28.4, 34.9, 36.1, 40.3, 41.2, 48.2, 49.7, 57.2, 58.2, 61.3, 62.3, 62.9, 79.1, 154.2. HRMS Calcd. for $C_{11}H_{20}N_2O_2$: 212.1525. Found: 212.1531.

Lithiation of 2 followed by reaction with an electrophile. General procedure A

To a solution of TMEDA (778 mg, 7.10 mmol, 1.5 equiv.) in dry THF (15 mL) was added 1.3 M *sec*-BuLi in hexanes (5.4 mL, 7.10 mmol; 1.5 equiv.) at –78 °C. The mixture was stirred for 30 min. A solution of **2** (1.0 g, 4.70 mmol) in dry THF (10 mL) was added drop-wise. The solution was stirred for at –78 °C for 2 h. The appropriate electrophile (14.1 mmol; 3 equiv.) dissolved in dry THF (20 mL) was added through a syringe, and the mixture was warmed up to room temperature in the course of 2 h. The reaction was quenched with a saturated aqueous ammonium chloride solution (40 mL) and stirred for 30 min. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The organic layers were collected, dried (sodium sulfate) and evaporated to dryness. The residue was purified by flash chromatography, and the product(s) thus obtained were recrystallized.

Lithiation of 2 followed by reaction with an electrophile. General procedure B

To a solution of TMEDA (778 mg, 7.10 mmol; 1.5 equiv.) in dry diethyl ether (15 mL) was added 1.3 M *sec*-BuLi in hexanes (5.4 mL, 7.10 mmol; 1.5 equiv.) at –78 °C, and the mixture was stirred for 30 min. A solution of **2** (1.0 g, 4.70 mmol) in dry diethyl ether (10 mL) was added drop-wise. After the solution was stirred at –78 °C for 2 h, the temperature was allowed to rise

to –40 °C and was kept for 30 min. The mixture was cooled again to –78 °C, and the appropriate electrophile (14.10 mmol, 3 equiv.) dissolved in dry diethyl ether (20 mL) was added. The mixture was warmed up to room temperature in the course of 2 h. The reaction was quenched with saturated aqueous ammonium chloride solution (40 mL) and stirred for 30 min. The layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 50 mL). The organic layers were combined, dried (sodium sulfate) and evaporated. The residue was purified by flash chromatography and the product(s) thus obtained were recrystallized.

1,1-Dimethylethyl (1*S*,4*S*)-1-[hydroxy(diphenyl)methyl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (3a) and 1,1-dimethylethyl (1*S*,3*R*,4*S*)-3-[hydroxy(diphenyl)methyl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (5a). The procedure of lit.[9] was followed, however, different product mp's were determined: **3a** mp 204–206 °C (diisopropyl ether); **5a** mp (decomp.) 260 °C (diisopropyl ether).

1,1-Dimethylethyl (1*S*,4*S*)-1-[hydroxy[bis[3-(trifluoromethyl)phenyl]]methyl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (3b), 1,1-dimethylethyl (1*S*,3*S*,4*S*)-3-[hydroxy[bis[(3-trifluoromethyl)phenyl]]methyl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (4b) and **1,1-dimethylethyl (1*S*,3*R*,4*S*)-3-[hydroxy[bis[(3-trifluoromethyl)phenyl]]methyl]-5-methyl-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (5b).** Application of Procedure A to bis(3,3'-trifluoromethyl)benzophenone furnished a mixture of **3b**, **4b** and **5b**, which was separated by flash chromatography using toluene/diethyl ether (1:1). **3b**: Colorless crystals (302 mg, 12%); mp 190–192 °C (cyclohexane);. R_f 0.25 (toluene/diethyl ether 1:1); $[]_{D20}$ –219.38 (c = 0.26, $CHCl_3$). ^{1}H NMR (200 MHz, $CDCl_3$): δ 1.22 (s, 9H), 1.34 (d, *J* = 10.2 Hz, 1H), 2.34 (s, 3H), 2.38 (d, *J* = 10.2 Hz, 1H), 3.08 (d, *J* = 9.5 Hz, 1H), 3.11 (d, *J* = 9.5 Hz, 1H); 3.27–3.33 (m, 1H, H-4), 3.51 (d, *J* = 12.1 Hz, 1H, H-6), 3.90 (d, *J* = 12.1 Hz, 1H, H-6), 7.28–7.92 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$): 26.8, 27.8, 40.9, 42.2, 54.0, 60.7, 61.4, 77.2, 81.1, 122.6, 123.6, 123.9, 124.0, 124.1, 127.8, 128.2, 129.6, 129.8, 130.2, 130.5, 131.1, 144.9, 1456.9, 155.5. Anal. Calcd. for $C_{26}H_{28}F_6N_2O_3$: C, 58.87; H, 5.32; N, 5.28. Found: C, 58.90; H, 5.35; N, 5.17. **4b**: Colorless crystals (297 mg, 12%); mp 138–140 °C (cyclohexane); R_f 0.13 (toluene/diethyl ether 1:1). ^{1}H NMR (200 MHz, $CDCl_3$): 1.26 (d, *J* = 10.2 Hz, 1H), 1.38–1.57 (m, 10H), 2.51 (s, 3H), 2.64–2.76 (m, 2H), 3.32–3.40 (m, 1H), 3.98–4.08 (m, 1H), 4.69–4.80 (m, 1H), 7.32–7.82 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$): 28.0, 31.6, 41.0, 58.8, 61.0, 66.4, 67.7, 78.1, 82.1, 121.2, 123.3, 135.1, 124.2, 124.6, 126.7, 128.0, 128.7, 129.8, 130.5, 131.0, 131.3, 144.5, 147.5, 158.2. Anal. Calcd. for $C_{26}H_{28}F_{66}N_2O_3$: C, 58.87; H, 5.32; N, 5.28. Found: C, 58.94; H, 5.05; N, 5.01. **5b**: Colorless oil (104 mg, 4.0%); R_f 0.70 (toluene/diethyl ether 1:1). ^{1}H NMR (200 MHz, $CDCl_3$): 1.13 (s, 9H), 1.48 (d, *J* = 9.5 Hz, 1H), 1.72 (d, *J* = 9.5 Hz, 1H), 2.18 (s, 3H), 2.38 (dd, *J* = 11.4, 1.9 Hz, 1H), 3.30–3.37 (m, 1H), 3.60 (d, *J* = 11.4 Hz, 1H), 4.40 (d, *J* = 1.8 Hz, 1H), 4.60–4.70 (m, 1H), 7.20–8.00 (m, 8H). ^{13}C NMR (50 MHz, $CDCl_3$): 27.7, 33.8, 42.9, 60.0, 63.0, 66.4, 68.0, 78.5, 80.2, 123.2, 123.4, 123.8, 123.9, 124.0, 127.5, 128.6, 129.3, 130.3, 130.4, 130.9, 145.8, 147.6, 157.2. Anal. Calcd. for $C_{26}H_{28}F_6N_2O_3$: C, 58.87; H, 5.32; N, 5.28. Found: C, 58.94; H, 5.05; N, 5.01. δ

1,1-Dimethylethyl (1*S*,4*S*)-1-(9-hydroxy-9*H*-fluoren-9-yl)-5-methyl-2,5-diaza-bicyclo[2.2.1]heptane-2-carboxylate (3c) and **1,1-dimethylethyl (1*S*,3*R*,4*S*)-3-(9-hydroxy-9*H*-fluoren-9-yl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane2-carboxylate (5c).** Applying Procedure A to fluorenone gave a mixture of **3c** and **5c**, which was separated by flash chromatography using toluene/diethyl ether (1:1). **3c**: Colorless crystals (480 mg, 26%); mp 191–193 °C (cyclohexane); R_f 0.23 (toluene/diethyl ether 1:1); ^{1}H NMR (200 MHz, $CDCl_3$): 0.98 (d, *J* = 10.2 Hz, 1H), 1.11 (d, *J* = 10.2 Hz, 1H), 1.62 (s, 9H), 2.38 (s, 3H), 2.86–2.94 (m, 1H), 3.08 (d, *J* = 8.9 Hz, 1H), 3.20 (d, *J* = 10.8 Hz, 1H), 3.67 (d, *J* = 8.9 Hz, 1H), 3.82 (d, *J* = 10.8 Hz, 1H), 7.14–7.65 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): 28.3, 39.9, 41.0, 55.1, 59.2, 60.2, 77.4, 81.2, 82.8, 119.3, 119.7, 124.0, 124.9, 127.2, 127.3, 128.3, 128.7, 139.7, 140.0, 147.9, 148.1, 158.0. Anal. Calcd. for $C_{24}H_{28}N_2O_3$: C, 73.44; H, 7.19; N, 7.14. Found: C, 73.66; H, 7.24; N, 7.33. **5c**: Colorless crystals (250 mg, 14%); mp (decomp.) 230 °C (cyclohexane); R_f 0.28 (toluene/diethyl ether 1:1); ^{1}H NMR (200 MHz, $CDCl_3$): 0.54 (d, *J* = 9.5 Hz, 1H), 1.02 (d, *J* = 9.7 Hz, 1H), 1.58 (s, 9H), 2.20 (s, 3H), 2.32–2.37 (m, 1H), 2.44 (d, *J* = 9.4 Hz, 1H), 2.66 (d, *J* = 9.4 Hz, 1H), 4.00–4.06 (m, 1H), 4.48–4.52 (m, 1H), 7.10–7.65 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 28.3, 30.8, 33.1, 39.8, 59.7, 60.1, 64.9, 68.1, 81.5, 82.5, 119.8, 119.9, 125.2, 127.4, 128.1, 128.5, 128.8, 128.9, 139.4, 139.7, 147.6, 147.7, 158.3. Anal. Calcd. for $C_{24}H_{28}N_2O_3$.0.33 H_2O: C, 72.35; H, 7.25; N, 7.03. Found: C, 72.45; H, 7.32; N, 7.11.

1,1-Dimethylethyl (1*S*,4*S*)-5-Methyl-1-(phenylsulfanyl)-2,5-diazabicyclo-[2.2.1]-heptane-2-carboxylate (3d) and 1,1-dimethylethyl (1*S*,2*R*,4*S*)-5-methyl-3-(phenylsulfanyl)-2,5-diazabicyclo[2.2.1]heptane-2-carboxylate (5d). Following Procedure B diphenyldisulfide gave a mixture of **3d** and **5d**, which was separated by flash chromatography using petroleum ether/ethyl acetate (3:1). **3d**: Yellow crystals (503 mg, 33%); mp 86–88 °C (diisobutyl ether); R_f 0.40 (petroleum ether/ethyl acetate 0.40). $[\alpha]_D^{20}$ +147.8 (c = 0.18, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): 1.50 (s, 9H), 1.68 (d, *J* = 11.4 Hz, 1H), 1.81 (d, *J* = 11.4 Hz, 1H), 2.36 (s, 3H), 3.08 (s, 2H), 3.13–3.20 (m, 1H), 3.32 (d, *J* = 11.0 Hz, 1H), 3.81 (d, *J* = 11.0 Hz, 1H), 7.23–7.38 (m, 3H), 7.53–7.61 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 28.4, 40.7, 44.2, 53.7, 59.7, 65.2, 75.2, 80.5, 128.7, 128.8, 132.3, 136.2, 155.1. HRMS Calcd. for $C_{17}H_{24}N_2O_2S$: 320.1558. Found: 320.1567. **5d**: Yellow crystals (510 mg, 34%); mp 88–90°C(diisobutyl ether); R_f 0.15 (petroleum ether/ethyl acetate 3:1); $[\alpha]_D^{20}$ –109.1 (c = 0.32, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): 1.20 (s, 9H), 2.33 (dd, *J* = 10.7, 1.6 Hz, 1H), 2.46 (s, 3H), 3.24 (d, *J* = 10.7 Hz, 1H), 3.35–3.42 (m, 1H), 4.44–4.55 (m, 1H), 5.03–5.12 (m, 1H), 7.10–7.60 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): 28.0, 33.1, 44.8, 60.2, 60.9, 69.3, 74.6, 76.4, 77.2, 80.2, 126.6, 127.5, 128.6, 129.0, 131.9, 154.1. HRMS Calcd. for $C_{17}H_{24}N_2O_2S$: 320.1558. Found: 320.1569.

1,1-Dimethylethyl (1*S*,4*S*)-1-(9-hydroxy-9*H*-xanthen-9-yl)-5-methyl-2,5-diazabi-cyclo[2.2.1]heptane-2-carboxylate (3e). Following Procedure A and employing 9-xanthone the resulting product was isolated and purified by flash chromatography using toluene/diethyl ether (1:1) yielding colorless crystals **3e** (470 mg, 25%); mp 167–168 °C (cyclohexane/petroleum ether 1:1); R_f 0.25 (toluene/diethyl ether 1:1); $[\alpha]_D^{20}$ +63.9 (c = 0.21, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): 1.33 (d, *J* = 10.2 Hz, 1H), 1.49–1.59 (m, 10H), 2.25 (s,

3H), 2.90–3.10 (m, 3H), 3.21 (d, *J* = 11.4 Hz, 1H), 3.72 (d, *J* = 10.2 Hz, 1H), 7.05–7.35 (m, 6H), 7.68–7.88 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 28.4, 40.2, 41.0, 55.8, 58.3, 59.2, 70.3, 80.0, 81.5, 115.8, 115.9, 122.8, 123.0, 126.4, 126.6, 126.8, 127.7, 128.4, 128.8, 150.6, 151.7, 158.4. Anal. Calcd. for $C_{24}H_{28}N_2O_4$: C, 70.57; H, 6.91; N, 6.86. Found: C, 70.50; H, 7.07; N, 6.92.

1,1-Dimethylethyl (1*S*,3*R*,4*S*)-5-methyl-3-phenylaminocarbonyl-2,5-diazabicyclo[2.2.1]heptane carboxylate (5f). The reaction was conducted following Procedure B except that the lithiated species after stirring for 2 h was transferred into a solution of phenylisocyanate in dry diethyl ether via a transfer needle. The product was purified by flash chromatography using toluene/diethyl ether/methanol (20:20:1) yielding **5f** (200 mg, 13%) as colorless crystals; mp 191–192 °C (2-propanol); R_f 0.25 (toluene/diethyl ether/methanol 20:20:1); ^{1}H NMR (200 MHz, $CDCl_3$): 1.40 (s, 9H), 1.62 (d, *J* = 9.5 Hz, 1H), 1.88 (d, *J* = 9.5 Hz, 1H), 2.32–2.50 (m, 4H), 3.20 (d, *J* = 10.2 Hz, 1H), 3.63–3.71 (m, 1H), 4.10–4.15 (m, 1H), 4.59–4.67 (m, 1H), 7.02–7.56 (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): 28.2, 33.6, 44.0, 59.9, 61.7, 66.9, 68.6, 81.1, 119.7, 124.0, 128.9, 137.8, 155.1, 168.6. Anal. Calcd. for $C_{18}H_{25}N_3O_3$.0.11 H_2O: C, 64.85; H, 7.62; N, 12.60. Found: C, 64.48; H, 7.25; N, 12.36.

(5*S*,7a*S*)-Spiro-[tetrahydro-1*H*-5,7a-methano-3*H*-furo[3,4-*a*]pyrazin-1,9'[9*H*]thio-xanthen]-3-one (6). Following Procedure A using 9*H*-thioxanthen-9-one (3.0 g, 14.1 mmol) the resulting product was purified by flash chromatography using toluene/diethyl ether (1:1) yielding a colorless, viscous oil **6** (403 mg, 24%); R_f 0.20 (toluene:diethyl ether 1:1); ^{1}H NMR (200 MHz, $CDCl_3$): 1.22 (d, *J* = 11.4 Hz, 1H), 1.47 (d, *J* = 11.4 Hz, 1H), 1.98 (d, *J* = 9.5 Hz, 1H), 2.25 (s, 3H), 3.04 (d, *J* = 9.5 Hz, 1H), 3.32–3.42 (m, 2H), 3.53 (d, *J* = 8.9 Hz, 1H), 7.13–7.82 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): 39.5, 39.9, 47.8, 61.9, 64.6, 80.2, 80.5, 125.2, 125.3, 126.7, 127.0, 128.2, 128.3, 129.0, 129.8, 133.4, 133.8, 157.4. Anal. Calcd. for $C_{20}H_{18}N_2O_2S$: C, 68.55; H, 5.18; N, 7.99. Found: C, 68.99; H, 5.69; N, 7.44.

(1*S*,4*S*)-1-(9-Hydroxy-9*H*-thioxanthen-9-yl)-2,5-dimethyl-2,5-diazabicyclo[2.2.1]heptane (7). A solution of **6** (300 mg, 0.86 mmol) in dry THF (10 mL) was cooled to 5 °C and treated with lithium aluminum hydride (195 mg, 5.10 mmol, 6 equiv.) in portions. The mixture was stirred at room temperature for 1 h and hydrolyzed with 2 N hydrochloric acid. The solution was made alkaline (pH 9) with 2 N aqueous potassium hydroxide and extracted with diethyl ether (3 x 30 mL). The combined organic layers were dried (sodium sulfate) and evaporated to dryness. The residue was recrystallized from diisopropyl ether to yield **7** (150 mg, 53%) as colorless crystals; mp 191–193 °C; R_f 0.10 (toluene/diethyl ether:methanol 1:1:1). $[\alpha]_D^{20}$ +147.7 (c = 0.17, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): 1.13 (d, *J* = 11.4 Hz, 1H), 1.78 (d, *J* = 11.4 Hz, 1H), 2.12, 2.18 (2 s, 6H), 2.49 (d, *J* = 8.9 Hz, 1H), 3.77–3.82 (m, 1H), 2.93 (d, *J* = 10.2 Hz, 1H), 3.04 (d, *J* = 8.9 Hz, 1H), 3.26 (d, *J* = 10.2 Hz, 1H), 7.14–7.41 (m, 6H), 7.92–8.08 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 39.2, 39.4, 42.3, 55.3, 61.4, 64.1, 72.9, 81.0, 125.9, 126.0, 126.1, 126.7, 127.1, 127.1, 127.3, 128.2, 130.9, 131.3, 137.2, 137.6. Anal. Calcd. for $C_{20}H_{22}N_2O_2S$: C, 70.97; H, 6.55; N, 8.28. Found: C, 70.71; H, 6.59; N, 8.05.

Boc-Deprotection of 3, 4, 5 with trifluoroacetic acid. **General procedure A**

A solution of the respective starting material **3**, **4**, **5** (10% w/v, 1 equiv.) in dry dichloromethane was cooled to 5 °C and treated drop-wise with 100 equiv. trifluoroacetic acid. The temperature was allowed to rise to room temperature, and the mixture was stirred for 6 h. The solvent and excess of trifluoroacetic acid was removed, and the residue was suspended in a 100-fold amount of 2 N aqueous potassium hydroxide. The resulting solid product was filtered off, washed with water until neutral and dried at 50°C/0.5 mbar.

Boc-deprotection of 3, 4, 5 with sodium hydroxide. General procedure B

A solution of the respective starting material **3**, **4**, **5** (10% w/v, 1 equiv.) in ethanol was refluxed with freshly powdered sodium hydroxide (6 equiv.) for 14 h. The solvent was removed and the residue was suspended in water (100-fold amount). The solid product was filtered off, washed with water to neutral pH, and dried at 50 °C/0.5 mbar.

(1*S*,4*S*)-(5-Methyl-2,5-diazabicyclo[2.2.1]hept-1-yl)diphenylmethanol (8a). Boc-de-protection (Procedure B) of **3a** (500 mg, 1.27 mmol) gave a crude product that was recrystallized from toluene to afford **8a** (170 mg, 46%) as colorless crystals; mp 125–126 °C; R_f 0.15 (chloroform/ethyl acetate/methanol 1:1:0.5); ^{1}H NMR (200 MHz, $CDCl_3$): 1.85 (d, *J* = 10.8 Hz, 1H), 1.93 (d, *J* = 10.8 Hz, 1H), 2.30–2.41 (m, 4H), 2.87 (d, *J* = 11.1 Hz, 1H), 3.19–3.32 (m, 3H), 3.57 (d, *J* = 11.1 Hz, 1H), 7.18–7.68 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): 37.8, 40.0, 62.3, 65.3, 75.5, 76.9, 126.8, 126.9, 127.0, 127.3, 127.7, 127.9, 143.8, 145.6. Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.52; H, 7.65; N, 9.51.

(1*S*,4*S*)-(5-Methyl-2,5-diazabicyclo[2.2.1]hept-1-yl)[bis[3-(trifluoromethyl)phenyl]]-methanol (8b). Boc-Deprotection (Procedure A) of **3b** (100 mg, 0.23 mmol) gave an oily crude product that was extracted with diethyl ether (3 x 10 mL). The organic layers were combined, dried (sodium sulfate) and evaporated to dryness to yield **8b** (65 mg, 81%) as a colorless oil; R_f 0.20 (toluene/diethyl ether/methanol 1:1:1); ^{1}H NMR (200 MHz, $CDCl_3$): 1.20 (d, *J* = 9.5 Hz, 1H), 1.88 (d, *J* = 9.5 Hz, 1H), 2.38 (s, 3H), 2.54 (d, *J* = 11.4 Hz, 1H), 2.91 (d, *J* = 11.1 Hz, 1H), 3.28–3.37 (m, 2H), 3.50 (d, *J* = 11.1 Hz, 1H), 7.33–8.00 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): 15.2, 29.7, 37.6, 39.7, 47.0, 62.4, 64.2, 65.8, 75.3, 76.6, 121.3, 123.8, 123.9, 124.0, 124.3, 124.4, 126.7, 128.4, 128.6, 130.1, 130.3, 130.5, 130.8, 131.0, 144.2, 145.4). HRMS Calcd. for $C_{21}H_{20}N_2OF_6$: 430.1480. Found: 430.1495.

(1*S*,4*S*)-1-(9-Hydroxy-9*H*-fluoren-9-yl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane (8c). Boc-deprotection (Procedure A) of **3c** (330 mg, 0.84 mmol) gave **8c** (198 mg, 82%) as colorless crystals; mp 258–261 °C; R_f 0.03 (toluene:diethyl ether, 1:1); $[\alpha]_D^{20}$ +24.5 (c=0.20, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): 1.73 (d, *J* = 9.8 Hz, 1H, H-7), 1.97 (d, *J* = 10.2 Hz, 1H, H-6), 2.08–2.18 (m, 4H, N-CH_3, H-7), 2.28 (d, *J* = 10.2 Hz, 1H, H-6), 3.00 (d, *J* = 10.8 Hz, 1H, H-3), 3.23–3.30 (m, 1H, H-1), 3.26 (d, *J* = 10.8 Hz, 1H, H-3), 7.22–7.66 (m, 8H, H_{arom}); ^{13}C NMR (50 MHz, $CDCl_3$): 29.7, 36.6, 48.3, 63.6, 63.7, 73.5, 77.0, 81.1, 119.8, 120.2, 124.0, 125.0, 127.4, 128.8, 129.2, 139.4, 140.5, 146.0, 148.3. Anal. Calcd. for $C_{19}H_{20}N_2O.0.33\ H_2O$: C, 76.45; H, 6.98; N, 9.38. Found: C, 76.53; H, 6.97; N, 9.26.

(1*S*,4*S*)-5-Methyl-1-(phenylsulfanyl)-2,5-diazabicyclo[2.2.1]heptane (8d). To a suspension of lithium aluminum hydride (142 mg, 3.7 mmol, 8 equiv.) in dry THF (5 mL) **3d** (150 mg, 0.47 mmol) was added in portions. The mixture was stirred at 50 °C for 12 h, hydrolyzed with 2 N hydrochloric acid and extracted with diethyl ether (20 mL). The aqueous layer was made alkaline (pH 8) with conc. ammonia and extracted with diethyl ether (3 x 20 mL). The combined organic layers were dried (sodium sulfate) and evaporated to dryness, yielding **8d** (20 mg, 18%) as colorless oil; R_f 0.50 (petroleum ether/ethyl acetate/methanol 1:1:1); ^{1}H NMR (200 MHz, $CDCl_3$): 1.82 (d, *J* = 7.6 Hz, 1H), 1.90 (d, *J* = 7.6 Hz, 1H), 2.50 (s, 3H), 2.54–2.68 (m, 2H), 3.00–3.18 (m, 3H), 7.23–7.40 (m, 3H), 7.5–7.63 (m, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): 35.0, 41.2, 41.7, 58.0, 58.2, 61.6, 78.9, 128.0, 128.5, 134.8. HRMS Calcd. for $C_{12}H_{16}N_2S$: 220.1034. Found: 220.1026.

(1*S*,4*S*)-1-(9-Hydroxy-9*H*-xanth-9-yl)-3-methyl-2,5-diazabicyclo[2.2.1]heptane (8e). The Boc-deprotection (Procedure A) of **3e** (340 mg, 1.10 mmol) yielded **8e** (50 mg, 20%) as colorless crystals; mp 178–179 °C; R_f 0.10 (toluene/diethyl ether/methanol 1:1:1); ^{1}H NMR (200 MHz, $CDCl_3$): 1.34 (d, *J* = 9.5 Hz, 1H), 1.63 (d, *J* = 9.8 Hz, 1H), 1.76 (d, *J* = 9.5 Hz, 1H), 2.12 (s, 3H), 2.70 (d, *J* = 9.8 Hz, 1H), 2.85 (d, *J* = 11.4 Hz, 1H), 3.00–3.10 (m, 1H), 3.18 (d, *J* = 11.4 Hz, 1H), 7.03–7.78 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): 35.9, 40.4, 48.2, 62.9, 63.4, 67.6, 76.6, 116.0, 116.2, 123.0, 123.1, 124.7, 126.1, 126.2, 127.1, 128.5, 128.7, 150.5, 151.3. HRMS Calcd. for $C_{19}H_{20}N_2O_2$: 308.1525. Found: 308.1518.

(1*S*,3*S*,4*S*)-(5-Methyl-2,5-diazabicyclo[2.2.1]hept-3-yl)[bis[3-(trifluoromethyl)phenyl]]-methanol (9b). Following Procedure B **4b** (70 mg, 0.13 mmol) gave **9b** (40 mg, 71%) as colorless crystals; mp 62–64 °C; R_f 0.25 (toluene/diethyl ether/methanol, 1:1:1); ^{1}H NMR (200 MHz, $CDCl_3$): 1.45 (d, *J* = 11.1 Hz, 1H, H-7), 1.87 (d, *J* = 11.1 Hz, 1H, H-7), 2.32 (s, 9H, N-CH_3), 2.59 (d, *J* = 9.5 Hz, 1H, H-6), 2.70 (d, *J* = 9.5 Hz, 1H, H-6), 2.78–2.83 (m, 1H, H-1), 3.58–3.64 (m, 1H, H-4), 4.15–4.25 (m, 1H, H-3), 7.32–7.88 (m, 8H, arom. H's); ^{13}C NMR (50 MHz, $CDCl_3$): 31.7, 41.3, 56.9, 63.4, 64.3, 64.7, 76.2, 121.4, 122.2, 122.3, 122.7, 123.8, 126.8, 128.8, 129.0, 129.5, 130.4, 131.0, 145.1, 148.4; HRMS Calcd. for $C_{21}H_{20}N_2OF_6$: 430.1480. Found: 430.1480.

(1*S*,3*S*,4*S*)-3-(9-Hydroxy-9*H*-fluoren-9-yl)-5-methyl-2,5-diazabicyclo[2.2.1]heptane (9c). Boc-deprotection (Procedure A) of **3c** (330 mg, 0.84 mmol) gave **9c** (198 mg, 82%) as colorless crystals; mp 258–261 °C; R_f 0.03 (toluene/diethyl ether 1:1); $[\alpha]_D^{20}$ +24.5 (c = 0.20, $CHCl_3$); ^{1}H NMR (200 MHz, $CDCl_3$): 1.73 (d, *J* = 9.8 Hz, 1H), 1.97 (d, *J* = 10.2 Hz, 1H), 2.08–2.18 (m, 4H), 2.28 (d, *J* = 10.2 Hz, 1H), 3.00 (d, *J* = 10.8 Hz, 1H), 3.23–3.30 (m, 1H), 3.26 (d, *J* = 10.8 Hz, 1H), 7.22–7.66 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): 29.7, 36.6, 48.3, 63.6, 63.7, 73.5, 77.0, 81.1, 119.8, 120.2, 124.0, 125.0, 127.4, 128.8, 129.2, 139.4, 140.5, 146.0, 148.3. Anal. Calcd. for $C_{19}H_{20}N_2O.0.33\ H_2O$: C, 76.45; H, 6.98; N, 9.38. Found: C, 76.53; H, 6.97; N, 9.26.

(1*S*,3*R*,4*S*)-(5-Methyl-2,5-diazabicyclo[2.2.1]hept-3-yl)diphenylmethanol (10a). Boc-deprotection (Procedure B) of **5a** (200 mg, 0.51 mmol) gave a crude product that was recrystallized from toluene yielding **10a** (120 mg, 80%) as colorless crystals; mp 135–136 °C. R_f 0.10 (chloroform/ethyl acetate/methanol 1:1:0.5); ^{1}H NMR (200 MHz, $CDCl_3$): 1.48 (d, *J* = 10.2 Hz,

1H), 1.90 (d, *J* = 10.2 Hz, 1H), 2.33 (s, 3H), 2.53 (d, *J* = 9.8 Hz, 1H), 2.74 (d, *J* = 9.8 Hz, 1H), 1.85–1.91 (m, 1H), 3.53–3.60 (m, 1H), 4.20–4.28 (m, 1H), 7.10–7.58 (m, 10H); ^{13}C NMR (50 MHz, $CDCl_3$): 29.7, 32.2, 41.0, 56.8, 63.5, 65.0, 76.7, 125.5, 126.0, 126.5, 127.9, 128.2, 144.7, 147.8. Anal. Calcd. for $C_{19}H_{22}N_2O$: C, 77.52; H, 7.53; N, 9.52. Found: C, 77.76; H, 7.72; N, 9.55.

(1*S*,3*R*,4*S*)-(5-Methyl-2,5-diazabicyclo[2.2.1]heptyl)[bis[3-(trifluoromethyl)phenyl]]-methanol (10b). Boc-deprotection (Procedure A) of **5b** (70 mg, 0.13 mmol) gave **10b** (40 mg, 71%) as colorless crystals; mp 62–64 °C; R_f 0.25 (toluene/diethyl ether/methanol 1:1:1); ^{1}H NMR (200 MHz, $CDCl_3$): 1.45 (d, *J* = 11.1 Hz, 1H), 1.87 (d, *J* = 11.1 Hz, 1H), 2.32 (s, 9H), 2.59 (d, *J* = 9.5 Hz, 1H), 2.70 (d, *J* = 9.5 Hz, 1H), 2.78–2.83 (m, 1H), 3.58–3.64 (m, 1H), 4.15–4.25 (m, 1H), 7.32–7.88 (m, 8H); ^{13}C NMR (50 MHz, $CDCl_3$): 31.7, 41.3, 56.9, 63.4, 64.3, 64.7, 76.2, 121.4, 122.2, 122.3, 122.7, 123.8, 126.8, 128.8, 129.0, 129.5, 130.4, 131.0, 145.1, 148.4. HRMS: Calcd. for $C_{21}H_{20}N_2OF_6$: 430.1480. Found: 430.1480.

Asymmetric reduction of propiophenone. General procedure

A solution (in some cases a suspension) of the ligands **8a**, **8b**, or **8c** (0.10 mmol) in dry THF (1 mL) was treated with trimethyl borate (14 L, 0.12 mmol) and was stirred for 1 h. To this mixture was added borane·dimethylsulfide (neat; 0.1 mL, 1.00 mmol), and the mixture was stirred for further 10 min. With a syringe propiophenone (133 L, 1.00 mmol) was added over a period of 30 min, and the mixture was stirred until completion (as monitored by TLC)of the reaction (usually 30 min after addition of propiophenone). After 2 N hydrochloric acid (5 mL) was added, the layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 5 mL). The organic combined organic layers were dried (sodium sulfate) and evaporated to dryness. The resulting colorless oil was separated by chiral HPLC. t_r (*R*)-1-phenylpropanol: 14 min; t_r (*S*)-1-phenylpropanol: 16 min; cf. Table 3.

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