Tetrahedron: *Asymmetry* 26 (2015) 593–599

Contents lists available at ScienceDirect

Tetrahedron: *Asymmetry*

journal homepage: www.elsevier.com/locate/tetasy

Steric and electronic tuning of atropisomeric amino alcohol type ligands with a 1-arylpyrrole backbone

Szilvia Deák [a], Béla Mátravölgyi [b], Gyula Feczku [a], Zsuzsa Erdélyi [a], Miklós Nyerges [c], Ferenc Faigl [a,b,*]

[a] *Department of Organic Chemistry and Technology, Budapest University of Technology and Economics, Budafoki út 8, H-1111 Budapest, Hungary*
[b] *MTA-BME Organic Chemical Technology Research Group, Hungarian Academy of Sciences, Budafoki út 8, H-1111 Budapest, Hungary*
[c] *Servier Research Institute of Medicinal Chemistry, Záhony u. 7, H-1031 Budapest, Hungary*

ARTICLE INFO

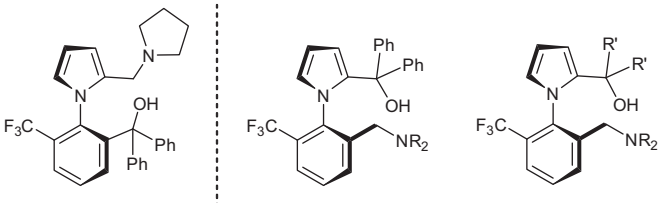
Article history:
Received 30 March 2015
Accepted 7 April 2015
Available online 23 April 2015

ABSTRACT

The synthesis of new, trifluoromethyl group containing atropisomeric amino alcohols and their application in enantioselective diethylzinc additions to aldehydes is described. A significant improvement of the enantioinductive effects of the new ligands by increasing the Brønsted acidity and bulkiness of the triarylcarbinol moiety is also reported. Tuning was achieved by the introduction of phenyl substituents containing two trifluoromethyl groups onto the α-carbon of the tertiary alcohol part of the ligand. The application of the new catalysts provided 1-(substituted phenyl)propanols with excellent enantiomeric purities.

1. Introduction

The enantioselective alkylation of aldehydes by dialkylzinc reagents was described for the first time in 1984 by Oguni and Omi, who employed (*S*)-leucinol as a chiral catalyst ligand.[1] Since then large amount of different chiral catalytic precursors have been developed, often leading to high levels of enantioinduction. A number of ligands developed for asymmetric organozinc additions are derived from 1,2-amino alcohols[2a] and 1,3-amino alcohols.[2b] In addition to these chiral amino alcohols, numerous other chiral ligands such as diamines (*N*,*N*-ligands), diols (*O*,*O*-ligands),[3–7] and axially chiral 3,3′-diphosphoryl-1,1′-binaphthalene-2,2′-diols as conjugate Lewis acid–Lewis base bifunctional catalyst ligands have also been developed.[8] Moreover, experimental and theoretical investigations have defined the mechanism with a good degree of certainty for determining the asymmetric induction.[9] Amino alcohols react with dialkylzincs to generate zinc-based chiral Lewis acid complexes, which can further coordinate with both the aldehyde substrates and the dialkylzinc reagents to conduct the catalytic addition. Thus, the in situ generated zinc complex is a multifunctional catalyst. It acts as a Lewis acid to activate the carbonyl substrate and also as a Lewis base to activate the organozinc reagent. The chiral environment [usually asymmetric carbon atom(s) situated close to the amino and/or hydroxyl groups] of the ligand controls the stereoselectivity.[2a] Much less is known, however, on the enantioinductive properties of such amino alcohol type ligands, in which four[10] or even more carbon atoms can be found between the two functions. This arrangement can be found in axially chiral biaryls, where the amino and the hydroxyl functions are connected to two different aryl rings, separately. Recently, the first representatives of this novel class of atropisomeric amino alcohol type ligands have been prepared and tested in our laboratory.[11,12] In these C_1 symmetric ligands (e.g., **1**, Scheme 1), the dialkylaminomethyl group was connected to an electron rich pyrrole ring and the diphenylmethylcarbinol moiety was attached to the trifluoromethyl group containing benzene ring of 1-phenylpyrrole skeleton. Compound **1** was an excellent chiral ligand for diethylzinc addition to arylaldehydes and the product 1-arylpropanols were obtained with 88–95% ee in the best cases.[12] We have synthesized several new regioisomeric derivatives of **1** in order to collect more experimental data on the effect of steric and



Scheme 1. Atropisomeric amino alcohol type ligands with 1-phenylpyrrole skeleton (NR_2 = NMe_2, 1-pyrrolidinyl, R′ = H, 3-CF_3-C_6H_4, 3,5-$(CF_3)_2$-C_6H_3).

* Corresponding author. Tel.: +36 1 463 5389; fax: +36 1 463 3648.
E-mail address: ffaigl@mail.bme.hu (F. Faigl).

http://dx.doi.org/10.1016/j.tetasy.2015.04.002
0957-4166/

electronic changings of molecular structure.[13] The new ligands **2** formed efficient catalysts with diethylzinc, and the addition reaction occurred, however each one performed significantly smaller asymmetric induction effects (46–85% ee) than compound **1**.

On the basis of these experimental results we concluded that exchange of the two functions makes significant differences in the electronic properties of the hydroxyl group. The acidity of the OH group in compounds **2** should be significantly smaller than in compound **1** and this fact may influence the stereochemical outcomes of the diethylzinc addition reactions. In compounds **2** there is a methylene group between the dialkylamino group and the phenyl ring, therefore the electron donating ability of the nitrogen atom remains more or less intact during the structural change from **1** to **2**. Steric arrangements of the active catalysts formed from **1** and **2** might also be different. Therefore we aimed to prepare several new ligands such as **3** (derivatives of type **2**) in which the bulkiness and the electron withdrawing ability of the R′ groups are different from the phenyl substituents in compounds **2**. Herein we report on the first synthesis of ligands **3** and their application on enantioselective catalytic additions of diethylzinc to aldehydes.

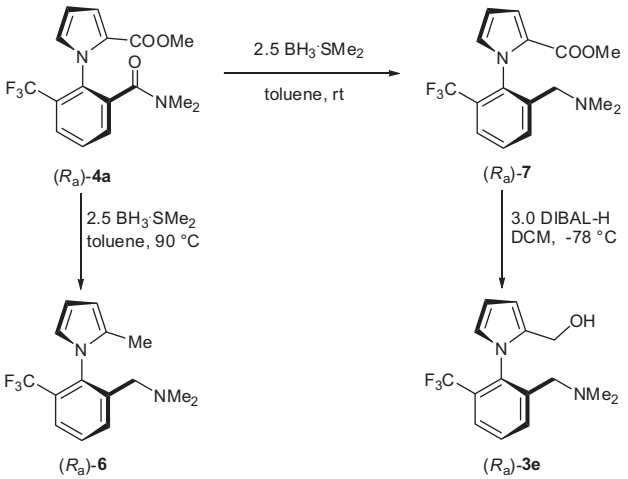
2. Results and discussion

2.1. Synthesis of new chiral ligands

Ligands (R_a)-**3** could be easily prepared from the optically active amido ester precursors (R_a)-**4** in two steps (Scheme 2). The starting materials (R_a)-**4a**,**b** were prepared from the corresponding optically active dicarboxylic acid[14] using the known synthetic pathway.[13] The addition of 2 equiv of arylmagnesium bromide to the ester moiety of (R_a)-**4a** and (R_a)-**4b**, respectively, provided the corresponding pure (R_a)-**5a**–**d** carbinols in good yields. The borane complex was then used for the reduction of the amide groups because this reducing agent did not attack the trifluoromethyl group in **5a**–**d** while lithium aluminium hydride could cause partial reductive defluorination.[11] Each new optically active amino alcohol **3a**–**d** was isolated in good yield after flash chromatography, and HPLC control of the ee values showed that no partial racemization occurred during the above mentioned multistep transformations.

In order to gain further insight into the steric effects of the aryl groups and the importance of Brønsted acidic nature of the hydroxyl moiety on the enantioinduction ability of the ligands, the primary hydroxyl group containing compound (R_a)-**3e** was also prepared (Scheme 3).

First we attempted the borane reduction of (R_a)-**4a** in toluene at 90 °C, however the reduction did not stop at the primary alcohol level but reductive dehydroxylation occurred and (R_a)-**6** was isolated as the only product. This reaction demonstrated the steric stability of our atropisomeric compound under the above mentioned conditions, however (R_a)-**6** contains only one tertiary amine function, which prohibits its application as a chiral ligand. In a second run the methoxycarbonyl and the dimethylamide groups were

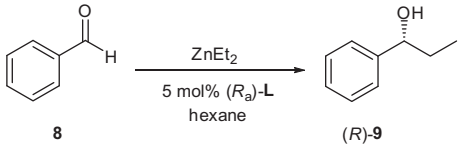


Scheme 3. Synthesis of (R_a)-**3e**.

transformed into the corresponding amino and primary alcoholic functions stepwise. Selective reduction of the dimethylamide group was accomplished with borane at ambient temperature, after which the ester was reduced with DIBAL-H at low temperature. This way pure (R_a)-**3e** was obtained with approximately 50% overall yield.

2.2. Investigation of the ligands (R_a)-3a–e in enantioselective addition reactions

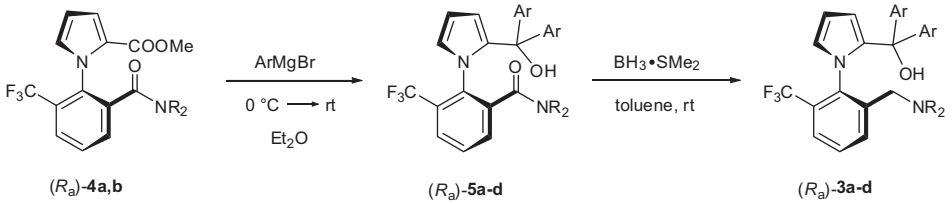
The new optically active amino alcohols were tested in the enantioselective addition of diethylzinc to benzaldehyde (Scheme 4). The experimental results are collected in Table 1.



Scheme 4. Diethylzinc addition to benzaldehyde in the presence of (R_a)-**L** ligands.

On the basis of the chemical yields, each new ligand formed active catalysts with diethylzinc; the reactions were complete within 5 h at ambient temperature. The asymmetric induction effect was almost the same or slightly smaller at 0 °C, but a much longer reaction time (20 h) was necessary for complete conversion. Comparison of the ee values obtained with different ligands confirmed a significant dependence of the enantioinduction effect on the steric and electronic properties of the R′ substituents in compounds (R_a)-**3a**–**e**.

The primary hydroxyl group containing ligand (R_a)-**3e** formed an active catalyst without significant asymmetric induction power (Table 1, entry 10). Compounds **3a**–**d** have a much higher influence



	NR_2	Ar
a	NMe_2	3-CF_3-C_6H_4
b	1-pyrrolidinyl	3-CF_3-C_6H_4
c	NMe_2	3,5-$(CF_3)_2$-C_6H_3
d	1-pyrrolidinyl	3,5-$(CF_3)_2$-C_6H_3

Scheme 2. Synthesis of ligands (R_a)-**3a**–**d**.

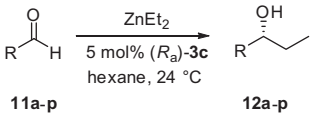
Table 1
Results of diethylzinc addition to benzaldehyde in the presence of 5 mol % (R_a)-**L**[a]

Entry	(R_a)-**L**	T (°C)	Yield of **9**[b] (%)	ee[c] (%)	Configuration[d]
1	(R_a)-**3a**	24	93	88	(*R*)
2	(R_a)-**3a**	0	88	90	(*R*)
3	(R_a)-**3b**	24	93	83	(*R*)
4	(R_a)-**3b**	0	89	86	(*R*)
5	(R_a)-**3c**	24	92	94	(*R*)
6[e]	(R_a)-**3c**	24	89	92	(*R*)
7	(R_a)-**3c**	0	90	91	(*R*)
8	(R_a)-**3d**	24	92	88	(*R*)
9	(R_a)-**3d**	0	91	91	(*R*)
10	(R_a)-**3e**	24	95	5	(*R*)

[a] The reactions were performed for 5 h at 24 °C and 20 h at 0 °C using 3 mol equivalents of $ZnEt_2$.
[b] Isolated yields.
[c] Determined by GC analysis using a Supelco β-DEX 120 chiral capillary column.
[d] Absolute configuration of the major enantiomer of **9** was assigned from the specific rotation of the product known from the literature.[15]
[e] The reaction was performed using 1 mol % of the ligand.

on the enantiomeric excess of product **9**. The dimethylamino group containing ligands **3a** and **3c** performed better selectivities than the 1-pyrrolidine group containing **3b** and **3d**. The most important difference was observed between the two and four electron withdrawing groups containing ligand pairs; **3a** versus **3c** and **3b** versus **3d**. The pK_a values of the OH groups in the new ligands are unknown, however the predicted pK_a values of the structurally similar triphenylmethanol (pK_a = 12.73 ± 0.29), 1,1-bis(3-trifluoromethylphenyl)benzyl alcohol (pK_a = 12.35 ± 0.29), 1,1-bis(3,5-ditrifluoromethylphenyl)benzyl alcohol (pK_a = 11.85 ± 0.29) and diphenylhydroxymethyl-1-phenylpyrrole (pK_a = 13.13 ± 0.29) could be collected from the literature.[16] These data show that the pyrrole containing triarylcarbinol is significantly less acidic (ΔpK_a = 0.40) while the two and four trifluoromethyl groups containing alcohols are more acidic (ΔpK_a = −0.38 and −0.68, respectively) than the unsubstituted triphenylmethanol. Thus the acidity of the OH group in **3a** should be approximately equal with the acidity of the OH group of triphenylmethanol, while the acidity of **3c** should be close to the one in (R_a)-**1** [predicted pK_a = 12.54 ± 0.29 for the corresponding diphenyl-(3-trifluorophenyl)methanol[16]]. In other words, the bis-(3,5-ditrifluoromethyl)phenyl groups containing ligands **3c** and **3d** form more stable ethylzinc alkoxide complexes in which the Lewis-acidic character of the zinc atom is significantly higher than it is in the ligands **3a** and **3b**. Furthermore, the disubstituted phenyl groups are much bulkier than the monosubstituted (or unsubstituted) ones and a dimethylamino group is probably a better electron donor than 1-pyrrolidinyl group. Consequently, the **3c** type catalyst can form a stronger, more rigid complex with a second molecule of diethylzinc and benzaldehyde, which results in higher differences between the diastereoisomeric transition states such as **10a** (favoured) and **10b** (Scheme 5) and higher ee values of

Table 2
Results of diethylzinc addition to different aldehydes in the presence of 5 mol % (R_a)-**3c**[a]

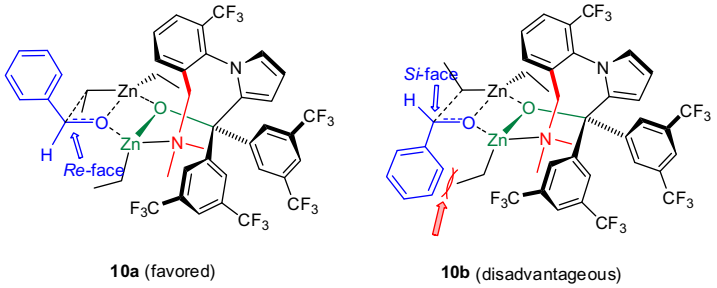


Entry	R	Yield[b] (%)	ee[c] (%)	Product[d]
1	2-Me-C_6H_4	91	83	(*R*)-**12a**
2	3-Me-C_6H_4	89	92	(*R*)-**12b**
3	4-Me-C_6H_4	93	94	(*R*)-**12c**
4	2-MeO-C_6H_4	93	77	(*R*)-**12d**
5	3-MeO-C_6H_4	90	93	(*R*)-**12e**
6	4-MeO-C_6H_4	94	91	(*R*)-**12f**
7	2-F-C_6H_4	92	94	(*R*)-**12g**
8	2-Cl-C_6H_4	90	93	(*R*)-**12h**
9	2-Br-C_6H_4	89	94	(*R*)-**12i**
10	3-F-C_6H_4	95	94	(*R*)-**12j**
11	4-F-C_6H_4	95	96	(*R*)-**12k**
12	4-Cl-C_6H_4	93	95	(*R*)-**12l**
13	1-Naph	92	93	(*R*)-**12m**
14	2-Naph	89	93	(*R*)-**12n**
15	Ph-CH=CH	87	58[e]	(*R*)-**12o**
16	3-BnO-4-MeO-C_6H_3	90	93	(*R*)-**12p**

[a] The reactions were performed for 5 h using 3 mol equiv of $ZnEt_2$.
[b] Isolated yields.
[c] Determined by GC analysis using a Supelco β-DEX 120 chiral capillary column.
[d] Absolute configurations of the major enantiomers of products were assigned from the specific rotations of the products known from the literature.[15,17–22]
[e] Determined by HPLC analysis using Phenomenex Lux Cellulose-1 chiral column.

product (*R*)-**9**. In the best case, the **3c** containing catalyst provided the product **9** in a 97:3 enantiomeric ratio (er). This is significantly better than the result obtained earlier under the same conditions with ligand (R_a)-**2** [(*R*)-**9** er 91:9][13] and practically equal to the results achieved with the regioisomeric ligand (R_a)-**1** at 0 °C [(*R*)-**9** er 97:3].[12]

Ligand **3c** was also tested in the reactions of numerous substituted benzaldehydes **11a–l** and several other aldehydes **11m–p**. The results are shown in Table 2. Diethylzinc addition was complete within 5 h in all cases and the product alcohols **12a–p** were obtained with excellent ee values (91–96% ee) in most cases. Cinnamaldehyde **11o** smoothly reacted with diethylzinc in the presence of **3c**, however the ee of **12o** (Table 2, entry 15) was 58%, only. The ee value was also below 80% in the case of **12d** (Table 2, entry 4), probably due to a complex forming interaction between the *ortho* methoxy group and diethylzinc. However this result is much better than the previously observed small ee (19% for **12d**) in the presence of ligand **2**.[13] The quality and position of the halogen substituents did not influence the enantiomeric purity (93–96% ee) of the products **12g–l** (Table 2, entries 7–12), and the same, excellent ee values were achieved during the preparation of 1-(1-naphthyl)-, 1-(2-naphthyl)propanol **12m–n** (Table 2, entries



10a (favored) **10b** (disadvantageous)

Scheme 5. Proposed transition state complexes of **3c** containing catalyst with diethylzinc and benzaldehyde.

13 and 15) and the disubstituted phenylpropanol **12p** (Table 2, entry 16).

3. Conclusion

An experimental investigation of the steric and electronic tuning of 1-phenylpyrrol based atropisomeric amino alcohols has been accomplished. Comparison of the enantioinductive abilities of the primary hydroxyl group containing ligand with the monotrifluoromethylated and ditrifluoromethylated phenyl groups containing tertiary amino alcohols allowed us to conclude that the presence of bulky phenyl substituents in the quasi benzylic position is crucial and the acidity of the triaryl carbinol moiety is also important for the formation of an active ethylzinc alkoxide type catalyst with high asymmetric induction capability. Even the electron rich pyrrole decreased the acidity of the OH group in the connected diphenylcarbinol moiety in compound (R_a)-**2**, it could be overcompensated with the exchange of the simple phenyl groups into 3,5-difluoromethylphenyl substituents in compound **3c**. The increased Lewis-acidity of the zinc atom in the active ethylzinc alkoxide type catalyst **3c**–ZnEt may cause the formation of a more stable complex with another molecule of diethylzinc and arylaldehyde. This fact together with the steric effects of the two disubstituted phenyl rings may cause higher energy differences between the diastereoisomeric transition states such as **10a** and **10b** resulting in the production of 1-arylpropanols with excellent ee values of up to 96%. Consequently, the steric and electronic tuning of 1-arylpyrrole based amino alcohols provided insight into the making of efficient catalysts and it expanded the libraries of the chiral, C_1-symmetric atropisomers with a new family of excellent ligands.

4. Experimental

4.1. General

All commercial starting materials were purchased from Sigma–Aldrich Kft. Hungary and Merck Kft. Hungary and were used without further purification. The organometallic reactions, the reductions and the asymmetric diethylzinc addition reactions were carried out in Schlenk-flasks under a dry nitrogen atmosphere. Solvents were typically freshly distilled or dried over molecular sieves. All reactions were monitored by thin-layer chromatography. TLC was carried out on Kieselgel 60 F254 (Merck) aluminium 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 sulfuric acid]. Flash column chromatography was performed using a CombiFlash® (Teledyne ISCO). Routine ^1H, ^{13}C and ^{19}F NMR spectra were obtained on a Bruker AV 300 or DRX 500 spectrometer. The chemical shifts (δ) are reported in parts per million (ppm) and the coupling constants (J) in Hz. Usually deuterated chloroform ($CDCl_3$) with tetramethylsilane (TMS) was used as the solvent, and signal positions were measured relative to the signal for TMS (δ_{TMS} = 0 ppm for ^1H NMR) and for $CDCl_3$ (δ_{CDCl_3} = 77.0 ppm for ^{13}C NMR). Infrared (IR) spectra were recorded on an appliance type Perkin Elmer 1600 with a Fourier Transformer. Data are given in cm^{-1}. Melting points were determined in capillary tubes, using a Gallenkamp melting point apparatus. The enantiomeric ratios of the optically active samples were determined by high-performance liquid chromatography (HPLC) measurement and by gas chromatography (GC) analysis. HPLC was performed on a Perkin Elmer Series 200 system using a Phenomenex Lux Amylose-2 column (5 μm, 250 × 4.6 mm). GC analysis was performed on an Agilent 4890 D instrument equipped with a Supelco β-DEX™ 120 fused silica capillary column (0.25 nm/0.25 μm, 30 m). Specific rotation of the optically active samples was determined on a Perkin Elmer 245 MC polarimeter using sodium lamp (589 nm). High-resolution mass spectra (HRMS) were recorded on Waters 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) except for two cases, compounds **3d** and **5b**, when the measurements were made in negative mode in the presence of ammonium bicarbonate; samples were made up in acetonitrile.

4.2. Typical procedure for the preparation of alcohols (R_a)-5a–d

Arylmagnesium bromide (4.8 mmol) was prepared in dry diethyl ether (10 mL) by the addition of bromobenzene derivative to the magnesium turnings. A solution of the corresponding (R_a)-methyl-1-[2-disubstitutedaminocarbamoyl-6-(trifluoromethyl)-phenyl]-1*H*-pyrrole-2-carboxylate (R_a)-**4a** or (R_a)-**4b** (1.6 mmol) in dry toluene (5 mL) was added into the stirred solution at 0 °C under dry nitrogen atmosphere. The reaction mixture was allowed to warm up and stirred for 1 h. Aqueous ammonium chloride solution (5 M, 15 mL) and toluene (15 mL) were then added. The phases were separated, the aqueous phase was washed with toluene (15 mL) and the collected organic solutions were washed with brine (25 mL), dried over sodium sulfate, and concentrated in vacuo. The residue was purified by flash column chromatography.

4.2.1. (R_a)-1-[2-(*N*,*N*-Dimethylcarbamoyl)-6-(trifluoromethyl) phenyl]-1*H*-pyrrole-2-yl-[bis(3-trifluoromethyl) phenyl]methanol (R_a)-5a

Flash column chromatography was performed in hexane/ethyl acetate = 2:1 eluent ($R_{f,\mathbf{5a}}$ = 0.32). Pure (R_a)-**5a** is a white solid, 0.67 g, 70% yield, $[\alpha]_D^{25} = -25.6$ (c 0.7, $CHCl_3$). Mp 124–125 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.80 (s, 1H), 7.62 (dd, J = 7.9, 1.2 Hz, 1H), 7.59 (s, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.51–7.42 (m, 5H), 7.38–7.30 (m, 3H), 6.49 (s, 1H), 6.17 (t, J = 3.3 Hz, 1H), 5.74 (dd, J = 3.6, 1.7 Hz, 1H), 2.99 (s, 3H), 2.79 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −59.32 (s, 3F), −62.52 (s, 3F), −62.57 (s, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 149.7, 144.3, 139.7, 137.4, 136.6 (d, J = 1.5 Hz), 131.4, 131.3, 130.2 (q, J = 31.7 Hz), 130.1 (q, J = 31.7 Hz), 129.7, 128.6 (q, J = 30.9 Hz), 129.5, 128.4 (q, J = 4.3 Hz), 128.2, 128.0, 124.6 (q, J = 272.4 Hz), 124.5 (q, J = 272.4 Hz), 125.5 (q, J = 4.0 Hz), 124.7, 124.2 (q, J = 3.8 Hz), 124.1–123.9 (m, 2C), 122.4 (q, J = 274.7 Hz), 113.2, 108.5, 78.5, 39.3, 34.9. IR (KBr, cm^{-1}) 3144, 2940, 2764, 1615, 1482, 1406, 1328, 1281, 1193, 1126. HRMS (ESI) calculated for $C_{29}H_{20}F_9N_2O$ [$(MH-H_2O)^+$]: 583.1432, found: 583.1415.

4.2.2. (R_a)-1-[2-(Pyrrolidine-1-carbonyl)-6-(trifluoromethyl) phenyl]-1*H*-pyrrole-2-yl-bis[(3-trifluoromethyl)phenyl]methanol (R_a)-5b

Flash column chromatography was performed in hexane/ethyl acetate = 2:1 eluent ($R_{f,\mathbf{5b}}$ = 0.33). Pure (R_a)-**5b** is a white solid, 0.90 g, 90% yield, $[\alpha]_D^{25} = -14.0$ (c 0.4, $CHCl_3$). Mp 67–69 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.72 (s, 1H), 7.62–7.58 (m, 2H), 7.57 (t, J = 7.7 Hz, 1H), 7.51–7.44 (m, 4H), 7.42 (d, J = 8.0 Hz, 1H), 7.36 (td, J = 7.7, 3.2 Hz, 2H), 6.48 (s, 1H), 6.16 (t, J = 3.3 Hz, 1H), 5.74 (dd, J = 3.6, 1.7 Hz, 1H), 3.55 (quin, J = 6.4 Hz, 1H), 3.41 (quin, J = 6.5 Hz, 1H), 3.23–3.16 (m, 1H), 3.09–3.02 (m, 1H), 1.95–1.84 (m, 3H), 1.84–1.75 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −59.31 (s, 3F), −62.50 (s, 3F), −62.58 (s, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 149.7, 144.2, 140.0, 138.4, 136.3, (d, J = 1.5 Hz), 131.6, 131.4, 130.1 (q, J = 31.7 Hz, 2C), 129.6, 129.5, 128.5 (q, J = 30.9 Hz), 128.4 (q, J = 4.3 Hz), 128.3, 128.0, 125.5 (q, J = 4.0 Hz), 124.6 (q, J = 272.4 Hz), 124.5 (q, J = 272.4 Hz), 124.3, 124.2 (q, J = 3.4 Hz), 124.1–123.8 (m, 2C), 122.4 (q, J = 274.7 Hz),

113.1, 108.6, 78.4, 49.3, 46.0, 25.9, 24.5. IR (KBr, cm^{-1}) 3198, 2982, 2887, 1616, 1475, 1449, 1329, 1165, 1122, 1077. HRMS (ESI) calculated for $C_{31}H_{21}F_9N_2O$ [$(MH-H_2O)^+$]: 609.1583, found: 609.1577.

4.2.3. (R_a)-1-[2-(*N*,*N*-Dimethylcarbamoyl)-6-(trifluoromethyl) phenyl]-1*H*-pyrrole-2-yl-[bis(3,5-bis(trifluoromethyl)phenyl] methanol (R_a)-5c

Flash column chromatography was performed in hexane/ethyl acetate = 2:1 eluent ($R_{f,\mathbf{5c}}$ = 0.29). Pure (R_a)-**5c** is a white solid, 0.97 g, 82% yield, $[\alpha]_D^{25} = -22.6$ (*c* 0.7, $CHCl_3$). Mp 136–137 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 7.95 (s, 1H), 7.83–7.78 (m, 4H), 7.77 (s, 2H), 7.66 (dd, *J* = 7.9, 1.6 Hz, 1H), 7.63 (t, *J* = 8.0 Hz, 1H), 7.49 (dd, *J* = 7.2, 1.3 Hz, 1H), 6.52 (s, 1H), 6.21 (t, *J* = 3.3 Hz, 1H), 5.73 (dd, *J* = 3.6, 1.5 Hz, 1H), 3.00 (s, 3H), 2.82 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −59.63 (s, 3F), −62.91 (s, 6F), −62.97 (s, 6F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 150.5, 145.3, 138.2, 137.2, 136.2 (d, *J* = 1.5 Hz), 131.3 (q, *J* = 33.2 Hz, 4C), 129.8 (4C), 128.6 (q, *J* = 31.0 Hz), 128.6 (q, *J* = 4.5 Hz), 128.5–128.3 (m, 2C), 128.0–127.8 (m, 2C), 125.4, 123.6 (q, *J* = 272.6 Hz), 123.5 (q, *J* = 272.7 Hz), 122.3 (q, *J* = 274.7 Hz), 122.0–121.7 (m), 121.6 (sep, *J* = 3.8 Hz), 113.5, 109.1, 78.1, 39.3, 34.9. IR (KBr, cm^{-1}) 3097, 2942, 1613, 1480, 1363, 1326, 1279, 1172, 1137. HRMS (ESI) calculated for $C_{31}H_{18}F_{15}N_2O$ [$(MH-H_2O)^+$]: 719.1180, found: 719.1169.

4.2.4. (R_a)-1-[2-(Pyrrolidine-1-carbonyl)-6-(trifluoromethyl) phenyl]-1*H*-pyrrole-2-yl-[bis(3,5-bis(trifluoromethyl)phenyl] methanol (R_a)-5d

Flash column chromatography was performed in hexane/ethyl acetate = 2:1 eluent ($R_{f,\mathbf{5d}}$ = 0.36). Pure (R_a)-**5d** is a white solid, 0.99 g, 81% yield, $[\alpha]_D^{25} = -17.1$ (*c* 0.4, $CHCl_3$). Mp 68–70 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.25 (s, 1H), 7.83 (s, 2H), 7.79 (s, 2H), 7.77 (s, 2H), 7.65–7.59 (m, 2H), 7.52 (dd, *J* = 6.7, 2.2 Hz, 1H), 6.51 (s, 1H), 6.20 (t, *J* = 3.3 Hz, 1H), 5.73 (dd, *J* = 3.6, 1.6 Hz, 1H), 3.57 (quin, *J* = 6.4 Hz, 1H), 3.39 (quin, *J* = 6.6 Hz, 1H), 3.26–3.19 (m, 1H), 3.10–3.03 (m, 1H), 1.96–1.87 (m, 3H), 1.86–1.77 (m, 1H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −59.62 (s, 3F), −62.89 (s, 6F), −62.98 (s, 6F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.5, 150.5, 145.3, 138.5, 138.2, 135.9, 131.3 (q, *J* = 33.3 Hz, 4C), 129.9 (2C), 129.8, 128.4 (q, *J* = 28.4 Hz), 128.6–128.3 (2C), 128.0–127.7 (2C), 127.0 (q, *J* = 247.5 Hz, 2C), 127.0 (q, *J* = 245.3 Hz, 2C), 125.1, 122.3 (q, *J* = 275.5 Hz), 121.9–121.7 (m), 121.6–121.4 (m), 113.4, 109.2, 78.0, 49.3, 46.1, 25.9, 24.5. IR (KBr, cm^{-1}) 3108, 2985, 2889, 1614, 1475, 1459, 1366, 1321, 1280, 1173, 1132. HRMS (ESI) calculated for $C_{33}H_{20}F_{15}N_2O_2$ [$(M-H)^+$]: 761.1363, found: 761.1322.

4.3. Typical procedure for the preparation of amino alcohols (R_a)-3a–d

To a stirred solution of compound (R_a)-**5a–d** (1.0 mmol) in dry toluene (5 mL), borane dimethylsulfide complex (2.0 mmol, 0.19 mL) was added dropwise, after which the reaction mixture was stirred at room temperature for 24 h. Methanol (2 mL) was added slowly, and after half an hour the solvent was evaporated in vacuo. The residue was dissolved in methanol (4 mL) and a 5 M solution of sodium hydroxide (1 mL) was added and the mixture was stirred at 45 °C. After decomposition of the borane–amine complex (followed by TLC), the solvent was evaporated. Methylene chloride (10 mL) and water (5 mL) were then added, the phases were separated, and the aqueous phase was washed with methylene chloride (5 mL). The collected organic phases were dried over sodium sulfate and concentrated in vacuo. The crude residue was purified by flash column chromatography. The enantiomeric ratios of amino alcohols **3a–d** were determined by chiral HPLC with a Phenomenex Lux Amylose-2 column. General method for the HPLC analysis: column temp: 15 °C, eluent hexane/ethanol = 98.5:1.5 in isocratic mode, flow: 0.5 mL/min, detection at 222 nm.

4.3.1. (R_a)-1-[2-(*N*,*N*-Dimethylamino)methyl-6-(trifluoromethyl) phenyl]-1*H*-pyrrole-2-yl-[bis(3-trifluoromethyl)phenyl]methanol (R_a)-3a

Flash column chromatography was performed in hexane/ethyl acetate = 3:1 eluent ($R_{f,\mathbf{3a}}$ = 0.25). Pure (R_a)-**3a** is a white solid, 0.42 g, 71% yield, $[\alpha]_D^{25} = -70.7$ (*c* 0.7, $CHCl_3$), 99% ee determined by HPLC analysis, general method. Retention times: (S_a)-enantiomer 9.2 min (minor); (R_a)-enantiomer 10.1 min (major). Mp 105–106 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.79 (s, 1H), 7.85 (s, 1H), 7.54–7.39 (m, 7H), 7.37–7.30 (m, 3H), 6.50 (s, 1H), 6.25 (t, *J* = 3.2 Hz, 1H), 5.98 (dd, *J* = 3.6, 1.7 Hz, 1H), 3.09 (d, *J* = 12.1 Hz, 1H), 2.80 (d, *J* = 12.2 Hz, 1H), 2.28 (s, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −58.74 (s, 3F), −62.32 (s, 3F), −62.56 (s, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.3, 144.9, 140.1 (d, *J* = 1.5 Hz), 139.2, 137.3, 135.0, 131.3, 131.2, 130.3 (q, *J* = 32.0 Hz), 130.1 (q, *J* = 32.0 Hz), 128.5, 128.3 (q, *J* = 30.9 Hz), 128.2, 128.1, 127.7 (q, *J* = 4.3 Hz), 125.8, 124.6 (q, *J* = 272.4 Hz), 124.6 (q, *J* = 272.4 Hz), 124.3 (q, *J* = 3.8 Hz), 124.0 (q, *J* = 3.8 Hz), 123.9 (q, *J* = 3.8 Hz), 123.7 (q, *J* = 3.8 Hz), 122.8 (q, *J* = 274.8 Hz), 112.6, 108.6, 77.5, 59.5, 45.3 (2C). IR (KBr, cm^{-1}) 2986, 2962, 2790, 1472, 1372, 1327, 1288, 1171, 1152, 1123. HRMS (ESI) calculated for $C_{29}H_{24}F_9N_2O$ [$(M+H)^+$]: 587.1667, found: 587.1728.

4.3.2. (R_a)-1-[2-(1-Pyrrolidino)methyl-6-(trifluoromethyl) phenyl]-1*H*-pyrrole-2-yl-[bis(3-(trifluoromethyl)phenyl] methanol (R_a)-3b

Flash column chromatography was performed in hexane/ethyl acetate = 4:1 eluent ($R_{f,\mathbf{3b}}$ = 0.30). Pure (R_a)-**3b** is a white solid, 0.47 g, 77% yield, $[\alpha]_D^{25} = -58.8$ (*c* 0.6, $CHCl_3$), 99% ee determined by HPLC analysis, general method. Retention times: (S_a)-enantiomer 8.8 min (minor); (R_a)-enantiomer 9.2 min (major). Mp 90–91 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.74 (s, 1H), 7.82 (s, 1H), 7.55–7.28 (m, 10H), 6.50 (s, 1H), 6.27 (t, *J* = 3.3 Hz, 1H), 6.05 (dd, *J* = 3.6, 1.7 Hz, 1H), 3.40 (d, *J* = 11.9 Hz, 1H), 2.92 (d, *J* = 11.9 Hz, 1H), 2.72–2.60 (m, 2H), 2.57–2.44 (m, 2H), 1.77–1.61 (m, 4H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −59.02 (s, 3F), −62.39 (s, 3F), −62.58 (s, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.8, 145.2, 139.5 (d, *J* = 1.5 Hz), 139.1, 138.1, 134.4, 131.5, 131.3, 130.2 (q, *J* = 31.9 Hz), 130.1 (q, *J* = 31.9 Hz) 128.5, 128.3, 128.0, 128.3 (q, *J* = 30.8 Hz), 127.4 (q, *J* = 4.4 Hz), 125.5, 124.6 (q, *J* = 272.5 Hz), 124.5 (q, *J* = 272.5 Hz), 124.3 (q, *J* = 3.8 Hz), 124.2 (q, *J* = 3.7 Hz), 123.8 (q, *J* = 3.7 Hz), 123.6 (q, *J* = 3.9 Hz), 122.8 (q, *J* = 275.0 Hz), 112.5, 108.6, 77.4, 55.7, 54.3 (2C), 23.2 (2C). IR (KBr, cm^{-1}) 3112, 2969, 2823, 2752, 1478, 1468, 1327, 1168, 1120, 1074. HRMS (ESI) calculated for $C_{31}H_{26}F_9N_2O$ [$(M+H)^+$]: 613.1823, found: 613.1688.

4.3.3. (R_a)-1-[2-(*N*,*N*-Dimethylamino)methyl-6-(trifluoromethyl) phenyl]-1*H*-pyrrole-2-yl-[bis(3,5-bis(trifluoromethyl)phenyl] methanol (R_a)-3c

Flash column chromatography was performed in hexane/ethyl acetate = 4:1 eluent ($R_{f,\mathbf{3c}}$ = 0.33). Pure (R_a)-**3c** is a white solid, 0.52 g, 72% yield, $[\alpha]_D^{25} = -74.8$ (*c* 0.5, $CHCl_3$), 99% ee determined by HPLC analysis, general method. Retention times: (S_a)-enantiomer 6.6 min (minor); (R_a)-enantiomer 7.3 min (major). Mp 134–135 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 9.59 (s, 1H), 7.80 (s, 3H), 7.76 (s, 1H), 7.70 (s, 2H), 7.54–7.45 (m, 3H), 6.55 (s, 1H), 6.29 (t, *J* = 3.3 Hz, 1H), 5.94 (dd, *J* = 3.5, 1.4 Hz, 1H), 3.10 (d, *J* = 12.2 Hz, 1H), 2.87 (d, *J* = 12.2 Hz, 1H), 2.31 (s, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −59.02 (s, 3F), −62.80 (s, 6F), −63.00 (s, 6F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.1, 145.7, 139.4 (q, *J* = 1.5 Hz), 137.6, 137.1, 135.3, 131.4 (q, *J* = 33.2 Hz, 2C), 131.3 (q, *J* = 33.2 Hz, 2C), 128.9 (2C), 128.2 (q, *J* = 30.2 Hz), 127.8–127.5 (m, 4C), 126.5, 123.6 (q, *J* = 272.7 Hz, 2C), 123.5 (q, *J* = 272.7 Hz, 2C), 122.6 (q, *J* = 274.7 Hz), 121.6 (sep, *J* = 4.2 Hz, 2C), 113.0, 109.2, 76.9, 59.5, 45.2 (2C). IR (KBr, cm^{-1}) 2997, 2877, 2842, 1622,

1369, 1326, 1275, 1173, 1132. HRMS (ESI) calculated for $C_{31}H_{22}F_{15}N_2O$ [(M+H)$^+$]: 723.1414, found: 723.1477.

4.3.4. (R_a)-1-[2-(1-Pyrrolidino)methyl-6-(trifluoromethyl) phenyl]-1*H*-pyrrole-2-yl-[bis(3,5-bis(trifluoromethyl)phenyl] methanol (R_a)-3d

Flash column chromatography was performed in hexane/ethyl acetate = 4:1 eluent ($R_{f,\mathbf{3d}}$ = 0.46). Pure (R_a)-**3d** is a white solid, 0.55 g, 73% yield, $[\alpha]_D^{25}$ = −59.5 (*c* 0.4, $CHCl_3$), 99% ee determined by HPLC analysis, general method. Retention times: (S_a)-enantiomer 6.8 min (minor); (R_a)-enantiomer 7.3 min (major). Mp 49–50 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.66 (s, 1H), 7.83 (s, 2H), 7.80 (s, 1H), 7.74 (s, 1H), 7.68 (s, 2H), 7.56–7.41 (m, 3H), 6.55 (s, 1H), 6.30 (t, *J* = 3.2 Hz, 1H), 6.02 (dd, *J* = 3.6, 1.5 Hz, 1H), 3.40 (d, *J* = 12.0 Hz, 1H), 2.97 (d, *J* = 12.0 Hz, 1H), 2.78–2.64 (m, 2H), 2.59–2.46 (m, 2H), 1.83–1.63 (m, 4H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −59.20 (s, 3F), −62.84 (s, 6F), −63.02 (s, 6F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.6, 146.1, 138.8 (d, *J* = 1.5 Hz), 138.0, 137.5, 134.7, 131.4 (q, *J* = 33.1 Hz, 2C), 131.3 (q, *J* = 33.2 Hz, 2C), 129.0 (2C), 128.1 (q, *J* = 30.9 Hz), 127.9–127.5 (m, 4C), 126.3, 123.6 (q, *J* = 272.7 Hz, 2C), 123.5 (q, *J* = 272.7 Hz, 2C), 122.6 (q, *J* = 274.7 Hz), 121.8–121.6 (m), 121.4 (sep, *J* = 3.8 Hz), 112.9, 109.1, 76.8, 55.6, 54.3 (2C), 23.2 (2C). IR (KBr, cm^{-1}) 2978, 2830, 1625, 1480, 1368, 1320, 1280, 1174, 1132. HRMS (ESI) calculated for $C_{33}H_{22}F_{15}N_2O$ [(M−H)$^+$]: 747.1571, found: 747.1577.

4.4. Study of the reduction of (R_a)-methyl-1-[2-(dimethylcarbamoyl)-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxylate (R_a)-4a

To a stirred solution of compound (R_a)-**4a** (2.0 mmol, 680 mg) in dry toluene (5 mL), borane dimethylsulfide complex (2.5 mmol, 0.48 mL) was added dropwise, after which the reaction mixture was stirred at room temperature or 90 °C for 24 h. Methanol (4 mL) was added slowly and after half an hour, the solvent was evaporated in vacuo. The residue was dissolved in methanol (8 mL) and a 5 M solution of sodium hydroxide (2 mL) was added, after which the mixture was stirred at 45 °C. After decomposition of the borane–amine complex (followed by TLC) the solvent was evaporated. Methylene chloride (20 mL) and water (10 mL) were added, the phases were separated, and the aqueous phase was washed with methylene chloride (10 mL). The collected organic phases were dried over sodium sulfate and concentrated in vacuo. The crude residue was purified by flash column chromatography.

4.4.1. (R_a)-1-[2-(*N*,*N*-Dimethylaminomethyl)-6-(trifluoromethyl) phenyl]-2-methyl-1*H*-pyrrole (R_a)-6

The reaction was performed at 90 °C. Flash column chromatography was performed in dichloromethane/ethyl acetate = 10:1 eluent ($R_{f,\mathbf{6}}$ = 0.21). Pure (R_a)-**6** is a colourless oil, 0.44 g, 77% yield, $[\alpha]_D^{25}$ = −15.3 (*c* 0.5, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 7.7 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.53 (t, *J* = 7.8 Hz, 1H), 6.52 (s, 1H), 6.21 (t, *J* = 3.0 Hz, 1H), 6.02 (s, *J* = 0.8 Hz, 1H), 2.98 (d, *J* = 14.6 Hz, 1H), 2.73 (d, *J* = 14.6 Hz, 1H), 2.14 (s, 6H), 1.89 (s, 3H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −60.36 (s, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 136.8 (d, *J* = 0.9 Hz), 128.8 (q, *J* = 30.0 Hz), 125.2 (q, *J* = 5.2 Hz), 123.2 (q, *J* = 273.7 Hz), 133.1, 130.7, 128.7, 122.1, 108.1, 106.9, 57.4, 45.6 (2C), 11.8. IR (neat, cm^{-1}) 2945, 2822, 2773, 1488, 1319, 1162, 1137, 1078. HRMS (ESI) calculated for $C_{15}H_{18}F_3N_2$ [(M+H)$^+$]: 283.1417, found: 283.1418.

4.4.2. (R_a)-Methyl-1-[2-(*N*,*N*-dimethylaminomethyl)-6-(trifluoromethyl)phenyl]-1*H*-pyrrole-2-carboxylate (R_a)-7

The reaction was performed at room temperature. Flash column chromatography was performed in dichloromethane/ethyl acetate = 5:1 eluent ($R_{f,\mathbf{7}}$ = 0.18). Pure (R_a)-**7** is a colourless oil, 0.46 g, 70% yield, $[\alpha]_D^{25}$ = +40.4 (*c* 0.6, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.6 Hz, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.53 (t, *J* = 7.7 Hz, 1H), 7.09 (d, *J* = 3.0 Hz, 1H), 6.79 (s, 1H), 6.34 (t, *J* = 3.1 Hz, 1H), 3.63 (s, 3H), 2.98 (d, *J* = 14.1 Hz, 1H), 2.76 (d, *J* = 14.1 Hz, 1H), 2.09 (s, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −60.50 (s, 3F). ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.6, 140.1, 137.3 (d, *J* = 1.5 Hz), 133.1, 129.8, 128.6, 127.7 (q, *J* = 30.2 Hz), 125.2, 125.1 (q, *J* = 5.3 Hz), 123.2 (q, *J* = 273.8 Hz), 117.5, 109.3, 57.9, 51.0, 45.5 (2C). IR (neat, cm^{-1}) 2949, 2822, 2773, 1717, 1483, 1440, 1321, 1271. HRMS (ESI) calculated for $C_{16}H_{18}F_3N_2O_2$ [(M+H)$^+$]: 327.1315, found: 327.1318.

4.5. Procedure for the synthesis of (R_a)-1-[2-(*N*,*N*-dimethylaminomethyl)-6-(trifluoromethyl)phenyl]-2-hydroxymethyl-1*H*-pyrrole (R_a)-3e

Compound (R_a)-**7** (1.0 mmol, 326 mg) was dissolved in dry dichloromethane (4 mL) under a nitrogen atmosphere, after which a 1 M solution of DIBAL-H in toluene (3.0 mmol) was added into the stirred solution at −78 °C. The reaction was monitored by TLC (hexane/ethyl acetate) until (R_a)-**7** was consumed. The solvent was evaporated in vacuo. The residue was dissolved in toluene (10 mL) and 1 M solution of hydrogen chloride (4 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. The crude residue was purified by flash column chromatography (hexane/ethyl acetate = 1:5 eluent, $R_{f,\mathbf{3e}}$ = 0.17). Pure (R_a)-**3e** is a white solid, 0.22 g, 74% yield, $[\alpha]_D^{25}$ = −58.1 (*c* 0.4, $CHCl_3$), 99% ee determined by HPLC analysis, modified general method (hexane/ethanol = 90.0:10.0 in isocratic mode, flow: 0.8 mL/min). Retention times: (S_a)-enantiomer 6.9 min (minor); (R_a)-enantiomer 7.4 min (major). Mp 53–54 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.2 Hz, 1H), 7.60–7.48 (m, 2H), 6.62 (br s, 1H) 6.54 (s, 1H), 6.37–6.33 (m, 1H), 6.31–6.27 (m, 1H), 4.40 (d, *J* = 13.0 Hz, 1H), 4.15 (d, *J* = 13.0 Hz, 1H), 3.28 (d, *J* = 12.2 Hz, 1H), 2.78 (d, *J* = 12.2 Hz, 1H), 2.12 (s, 6H). ^{19}F NMR (282 MHz, $CDCl_3$) δ −60.66 (s). ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 138.4, 136.5, 135.3, 129.7 (d, *J* = 30.2 Hz), 128.6, 126.6 (d, *J* = 5.2 Hz), 123.2, 122.9 (d, *J* = 273.9 Hz), 109.2, 109.1, 58.9, 55.3, 44.8 (2C). IR (KBr, cm^{-1}) 3126, 2991, 2871, 1485, 1321, 1162, 1134, 1025. HRMS (ESI) calculated for $C_{15}H_{18}F_3N_2O$ [(M+H)$^+$]: 299.1366, found: 299.1375.

4.6. General procedure for the enantioselective addition of diethylzinc to aldehydes using chiral amino alcohols (R_a)-3a–e

Ligand (R_a)-**3a**–**e** (0.01 mmol, 99% ee) was dissolved in a solution of diethylzinc (1 M in hexane, 0.6 mmol, 0.6 mL) under a nitrogen atmosphere. The mixture was stirred for an hour at room temperature after which freshly distilled aldehyde (0.2 mmol) was added to the mixture. The colour of the resulting mixture turned to a distinctive yellow. After stirring for 5 h, the mixture turned colourless indicating the completion of the reaction. The reaction was quenched by the addition of saturated aqueous ammonium chloride (5 mL). The mixture was extracted with toluene (3 × 5 mL). The combined organic layers were dried over anhydrous sodium sulfate, and evaporated under reduced pressure. Purification of the residue by column chromatography (ethyl acetate in hexane) afforded the corresponding alcohol. The ee was determined by GC analyses using a chiral column. General method for the GC analysis: Supelco β-DEX 120, T_{Inj}: 250 °C, T_{Det}: 250 °C (FID), N_2: 1 mL min^{-1}, split: 100:1, oven: 60 → 140 °C (10 °C min^{-1}).

Acknowledgements

The project was supported by the Hungarian Scientific Research Fund, Hungary (OTKA K 104528), by the Richter Gedeon Talentum

Foundation and it is connected to the New Széchenyi Development Plan (TÁMOP-4.2.1/B-09/1/KMR-2010-0002).

References

1. Oguni, N.; Omi, T. *Tetrahedron Lett.* **1984**, *25*, 2823–2824.
2. (a) Pu, L.; Yu, H.-B. *Chem. Rev.* **2001**, *101*, 757–824; (b) Lait, S. M.; Rankic, D. A.; Keay, B. A. *Chem. Rev.* **2007**, *107*, 767–796.
3. For reviews on catalytic enantioselective dialkylzinc additions to aldehydes and ketones, see: (a) Soai, K.; Niwa, S. *Chem. Rev.* **1992**, *92*, 833–856; (b) Bolm, C.; Hildebrand, J. P.; Muniz, K.; Hermanns, N. *Angew. Chem., Int. Ed.* **2001**, *40*, 3284–3308; (c) Pu, L. *Tetrahedron* **2003**, *59*, 9873–9886.
4. (a) Noyori, R.; Kitamura, M. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 40–69; (b) Noyori, R.; Suga, S.; Kawai, K.; Okada, S.; Kitamura, M.; Oguni, N.; Hayashi, M.; Kaneko, T.; Matsuda, Y. *J. Organomet. Chem.* **1990**, *382*, 19–37.
5. (a) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 99–101; (b) Schmidt, B.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1321–1323; (c) Seebach, D.; Pichota, A.; Beck, A. K.; Pinkerton, A. B.; Litz, T.; Karjalainen, J.; Gramlich, V. *Org. Lett.* **1999**, *1*, 55–58.
6. (a) Wu, Y.; Yun, H.; Wu, Y.; Ding, K.; Zhou, Y. *Tetrahedron: Asymmetry* **2000**, *11*, 3543–3552; (b) Du, H.; Ding, K. *Org. Lett.* **2003**, *5*, 1091–1093; (c) Du, H.; Zhang, X.; Wang, Z.; Ding, K. *Tetrahedron* **2005**, *61*, 9465–9477.
7. (a) Costa, A. M.; Jimeno, C.; Gavenonis, J.; Carroll, P. J.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 6929–6941; (b) Balsells, J.; Davis, T. J.; Carroll, P.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 10336–10348; (c) Walsh, P. J. *Acc. Chem. Res.* **2003**, *36*, 739–749; (d) Costa, A. M.; Garcia, C.; Carroll, P. J.; Walsh, P. J. *Tetrahedron* **2005**, *61*, 6442–6446; (e) Jeon, S.-J.; Li, H.; Walsh, P. J. *J. Am. Chem. Soc.* **2005**, *127*, 16416–16425.
8. Hatano, M.; Miyamoto, T.; Ishihara, K. *J. Org. Chem.* **2006**, *71*, 6474–6484.
9. (a) Yamakawa, M.; Noyori, R. *J. Am. Chem. Soc.* **1995**, *117*, 6327–6335; (b) Goldfuss, B.; Houk, K. N. *J. Org. Chem.* **1998**, *63*, 8998–9006; (c) Paleo, M. R.; Cabeza, I.; Sardina, F. J. *J. Org. Chem.* **2000**, *65*, 2108–2113; (d) Rasmussen, T.; Norrby, P. O. *J. Am. Chem. Soc.* **2001**, *123*, 2464–2465.
10. Kasashima, Y.; Hanyu, N.; Aoki, T.; Mino, T.; Sakamoto, M.; Fujita, T. *J. Oleo Sci.* **2005**, *9*, 495–504.
11. (a) Faigl, F.; Mátravölgyi, B.; Szöllősy, Á.; Czugler, M.; Tárkányi, G.; Vékely, K.; Kubinyi, M. *Chirality* **2012**, *24*, 532–542; (b) Mátravölgyi, B.; Kovács, E.; Hegedűs, L.; Jászay, Zs.; Thurner, A.; Deák, Sz.; Erdélyi, Zs.; Pham, T. S.; Gönczi, K.; Sólyom, Sz.; Tőke, L.; Faigl, F. *Period. Polytech. Chem. Eng.* **2015**, *59*, 38–50.
12. Faigl, F.; Erdélyi, Zs.; Deák, Sz.; Nyerges, M.; Mátravölgyi, B. *Tetrahedron Lett.* **2014**, *55*, 6891–6894.
13. Faigl, F.; Deák, Sz.; Erdélyi, Zs.; Holczbauer, T.; Czugler, M.; Nyerges, M.; Mátravölgyi, B. *Chirality* **2014**, *27*, 216–222.
14. Faigl, F.; Mátravölgyi, B.; Holczbauer, T.; Czugler, M. J. *Tetrahedron: Asymmetry* **2011**, *22*, 1879–1884.
15. Huang, J.; Ianni, J. C.; Antoline, J. E.; Hsung, R. P.; Kozlowski, M. C. *Org. Lett.* **2006**, *8*, 1565–1568.
16. The pK_a values were calculated using Advanced Chemistry Development (ACD/Labs) Software V11.02 (© 1994–2015 ACD/Labs) by SciFinder®. The corresponding triarylmethanols are described in the following articles. Triphenylmethanol: Law, H. D.; Perkin, F. M. *J. Chem. Soc.* **1908**, *93*, 1633–1638; Diphenyl-(3-trifluoromethylphenyl)methanol: Benkeser, R. A. *J. Am. Chem. Soc.* **1958**, *80*, 3314–3322; 1,1-Bis(3-trifluoromethylphenyl)benzyl alcohol: Teng, M.; Liu, Y.; Li, S.; Huang, G.; Jiang, J.; Wang, L. *RSC Adv.* **2013**, *3*, 9016–9022; 1,1-Bis(3,5-ditrifluoromethylphenyl)benzyl alcohol: Zhao, P.; Hartwig, J. F. *Organometallics* **2008**, *27*, 4749–4757; Diphenylhydroxymethyl-1-phenylpyrrole: Faigl, F.; Schlosser, M. *Tetrahedron* **1993**, *49*, 10271–10278.
17. Qi, G.; Judeh, Z. M. A. *Tetrahedron: Asymmetry* **2010**, *21*, 429–436.
18. Seebach, D.; Beck, A. K.; Schmidt, B.; Wang, Y. M. *Tetrahedron* **1994**, *50*, 4363–4384.
19. Zhong, J.; Guo, H.; Wang, M.; Yin, M.; Wang, M. *Tetrahedron: Asymmetry* **2007**, *18*, 734–741.
20. Dai, W.-M.; Zhu, H.-J.; Hao, X.-J. *Tetrahedron: Asymmetry* **2000**, *11*, 2315–2337.
21. Cakici, M.; Catir, M.; Karabuga, S.; Ulukanli, S. H. *Tetrahedron: Asymmetry* **2011**, *22*, 300–308.
22. Osorio-Planes, L.; Rodríguez-Escrich, C.; Pericás, M. A. *Org. Lett.* **2012**, *14*, 1816–1819.