An Effective and Useful Synthesis of Enantiomerically Enriched Arylglycinols

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A two-step synthesis of racemic arylglycinols, together with a simple and straightforward methodology for their resolution, is described. This method constitutes a practical means of preparing racemic and optically pure electron-rich or electron-poor substituted arylglycinols, useful building blocks for the synthesis of biologically active molecules and chiral ligands. All of the chiral β-amino alcohols **5**–**8** were isolated in good chemical yields and with excellent enantiomeric excesses: up to 99% in the cases of the arylglycinols **7** and **8**. Chiral fluoroaromatic vicinal amino alcohols can also be obtained with good enantiopurity using such a procedure. The key step of the strategy presented is an easy chromatographic separation of the diastereoisomeric amides prepared from acetyl mandeloyl chloride. The absolute configuration of the perfluorinated amino alcohols **5** was determined by X-ray analysis of the corresponding amide **14a**.

Introduction

The synthesis of β-amino alcohols continues to receive increasing attention in the organic chemistry community.[1] β-Amino alcohols can be converted into natural or unnatural subunits[2] of a variety of biologically active compounds. Enantiomerically pure 1,2-aminols have also found important application in the synthesis of chiral auxiliaries such as oxazolidinones[3] and oxazolines,[4] and they are also directly used as ligands in catalytic asymmetric processes mediated by organometallic complexes.[5] Because of their vicinal amino alcohol moiety, the chiral arylglycinols are important intermediates for the synthesis of arylglycines,[6] used for the preparation of biologically active compounds.[7] Unlike with other amino acids, which can be effectively prepared in enantiomerically pure form by asymmetric hydrogenation reactions,[8] a simple synthetic strategy for obtaining optically active arylglycines is still lacking. Although a variety of different approaches have been reported in the last decade,[9] such methods suffer from the large number of steps employed and from the lack of general applicability. A powerful catalytic methodology for the synthesis of optically active β-arylglycinols was recently reported by Sharpless.[10] The cinchona alkaloid approach shows general promise for catalysing the asymmetric aminohydroxylation reaction (AA) and offers a straightforward access to substituted chiral aromatic arylglycinols. However, regiocontrol is significantly affected by the presence of electron-withdrawing groups in the aromatic ring. A different, elegant approach towards the synthesis of arylglycinols was recently published by Petasis.[11] This stereocontrolled one-step synthesis involves organoboronic acids, amines and α-hydroxy aldehydes.

Due to the increasing demand for chiral compounds in both enantiomeric forms, synthetic methodologies should be as flexible as possible. This report provides a simple and general two-step approach for the preparation of racemic arylglycinols, using inexpensive and commercially available styrenes. Moreover, a general method for their resolution is also discussed. Such a protocol has been successfully employed in the preparation of variously substituted vicinal amino alcohols **5**−**8**. It is noteworthy that the high regioselectivities and stereoselectivities achieved are independent of the electronic characteristics of the aromatic rings of the starting styrene. In addition, it is worth pointing out that, starting from 2,3,4,5,6-pentafluorostyrene, our procedure enabled optically active (pentafluoroaryl)glycinols − useful starting material for the preparation of chiral ligands − to be prepared.

Results and Discussion

A general schematic of the discussed synthetic strategy is showed in Figure 1. The protocol consists of five steps and uses commercially available styrenes as starting materials.

Firstly, using an achiral modification of the AD reaction,[12] a variety of styrenes were converted into the corresponding diols (**1**−**4**). Each diol can easily be purified by crystallization (Scheme 1).

Although a variant of the AD Sharpless reaction was employed in the preparation of the racemic compounds **1**−**4**, other methods can also be considered. For instance, a new, ultrasound-accelerated process for the oxidation of substituted styrenes, making use of the inexpensive potassium permanganate, has recently been described.[13]

The preparation of the corresponding racemic arylglycinols **5**−**8** from **1**−**4**, respectively, was accomplished by ad-

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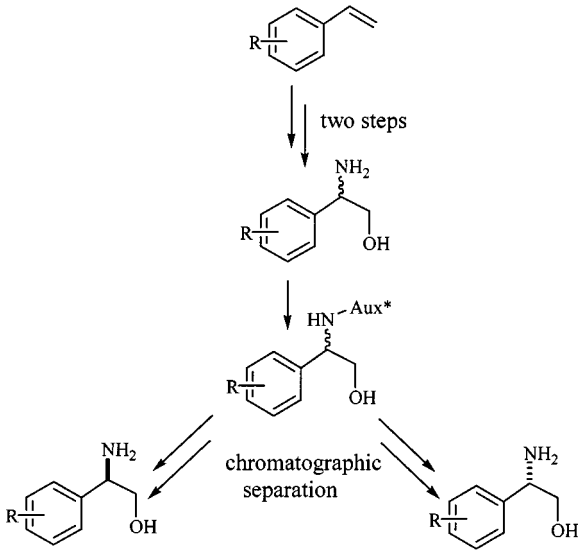
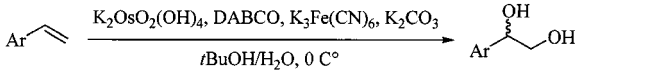
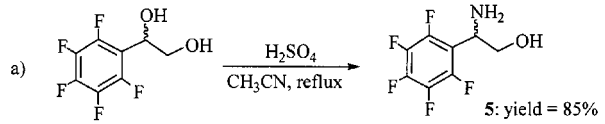


Figure 1. Schematic route to the synthesis of chiral 2-aryl-2-aminoethanols



1: Ar = C_6F_5, yield = 87%
2: Ar = Mesityl, yield = 84%
3: Ar = 4Br-C_6H_4, yield = 68%
4: Ar = β-Naphthyl, yield = 82%

Scheme 1. Synthesis of achiral 1,2-diols using a variant of the AD reaction



6: Ar = Mesityl, yield = 59%
7: Ar = 4Br-C_6H_4, yield = 83%
8: Ar = β-Naphthyl, yield = 65%

Scheme 2. The Ritter rearrangement in the synthesis of racemic 1,2-aminols

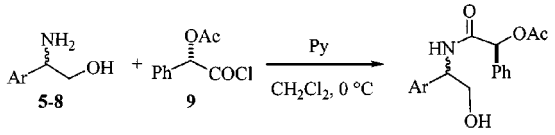
aptation of the Ritter rearrangement reaction described by a Merck group (Scheme 2, b).[14]

In this context, Senanayake and co-workers discovered that the Ritter reaction can be utilised in the preparation of the *cis*-1-amino-2-indanol from indene oxide.[14] Furthermore, starting from optically active indene oxide the rearrangement affords the aminoindanol with high enantioselectivity. Unfortunately, when such a procedure was adopted with the optically active diols **2** and **3**,[15] only racemic amino alcohols were isolated. A probable C-1 carbenium ion can be invoked to account for the complete lack of stereoinformation retention.

Optimal amination conditions for the perfluoro compound **5** involved the refluxing of **1** in anhydrous CH_3CN in the presence of an excess of H_2SO_4 (98%) instead of TfOH (trifluoromethanesulfonic acid) (Scheme 2, a).

Usually, all the amino alcohols were obtained sufficiently pure to be directly utilised in the successive transformations. However, further purification by acid-base treatment or by recrystallization can be performed if desired (see exp. section). At this stage, it is important to note the excellent regioselectivity observed. In fact, the regioisomeric 1-aryl-2-aminoethanol was never detected in the crude mixture by NMR analysis of the reaction.

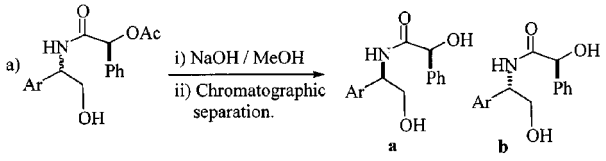
Our increasing interest in developing new enantioselective reactions catalysed by bis(oxazoline)−metal complexes[16] provided the stimulus to research a new simple strategy for the preparation of optically active arylglycinols. After a number of trials, we discovered a general method for the diastereoisomeric separation of arylglycinols derivatives by flash chromatography. The amino alcohols **5−8** were treated with (+)-(*S*)-*O*-acetylmandeloyl chloride (**9**)[17] in CH_2Cl_2 at 0 °C in the presence of pyridine, as shown in Scheme 3.



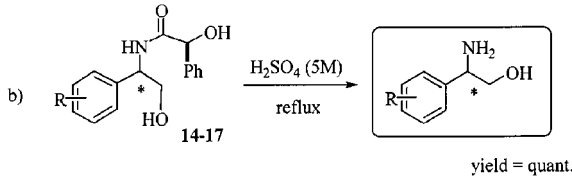
10: Ar = C_6F_5, yield = 38%
11: Ar = Mesityl, yield = 71%
12: Ar = 4Br-C_6H_4, yield = 61%
13: Ar = β-Naphthyl, yield = 66%

Scheme 3. Synthesis of the diastereoisomeric mixture **10−13** starting from **5−8** and (*S*)-(+)-*O*-acetylmandeloyl chloride

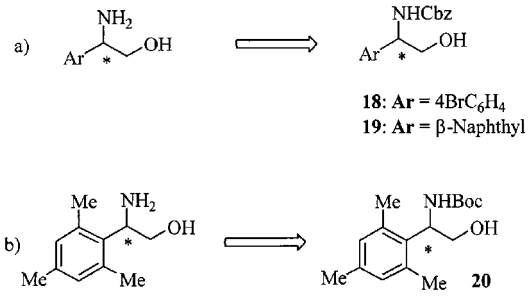
The desired amides (**10−13**) were isolated in fair to good yields (38−71%) as mixtures of two diastereoisomers.[18] The separation of the two diastereoisomeric amides was successfully accomplished by chromatography after the hydrolysis of the acetyl group, performed with diluted NaOH (0.5 M) in CH_3OH (Schema 4a), showing the considerable generality in scope of our procedure. Finally, the optically active amino alcohols **5−8** were isolated after acidic hydrolysis (HCl, 1 N) of the corresponding enantiomerically pure amides **14−17** (Scheme 4, b).[19]



14: Ar = C_6F_5, yield = 76%
15: Ar = Mesityl, yield = 70%
16: Ar = 4Br-C_6H_4, yield = 86%
17: Ar = β-Naphthyl, yield = 71%



Scheme 4. a) Procedure for the separation of the diastereoisomers **14−17(a,b)** by saponification and flash chromatography (see exp. section for more details); b) synthesis of the chiral vicinal amino alcohols by hydrolysis of the corresponding diastereoisomerically pure amides



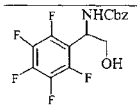
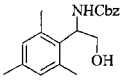
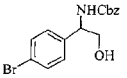
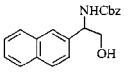
Scheme 5

The assignment of the absolute configuration of the chiral compounds (*R*)-**7**, (*S*)-**7**, (*R*)-**8** and (*S*)-**8**, obtained from diastereoisomers **16a, 16b, 17a** and **17b**, was based on the preparation of the *N*-Cbz derivatives **18** and **19**[20] followed by comparison of the optical rotation with the known values (Scheme 5, a).[21] The absolute configuration of product (*S*)-**6**, obtained from the acidic hydrolysis of the less polar diastereoisomer **15b**, was assigned by comparison of the optical rotation of the corresponding *N*-Boc derivative **20**, recently synthesised in moderate enantiomeric excess (*ee* = 56%, $[\alpha]_D = -15.2$, *c* = 1.00, EtOH) and low chemical yield (21%) by using the AA Sharpless methodology (Scheme 5, b).[12b]

The route described above also proved to be an effective way to synthesise perfluorinated aromatic amino alcohols. Perfluoroaromatic aminols are beginning to attract considerable interest in asymmetric catalysis. As a function of the reversal in electronic demand that the fluorine atoms can exert on the aromatic rings,[22] chiral fluorinated ligands can show intriguing behaviour in catalytic asymmetric processes. In fact, the substitution of aromatic rings with fluoroaryl groups might lead to chiral binding pockets of similar shape but with entirely different electronic properties. To date, effective routes for the synthesis of optically active perfluoro amino alcohols are still relatively unexplored.[23] Our synthesis permits the preparation of optically active **5** in good enantiomeric excess (88%). The absolute configuration of (*R*)-(−)-2-amino-2-pentafluorophenylethan-1-ol (**5**), was determined by X-ray crystallography performed on the less polar diastereoisomer **14a** (Figure 2).[24]

The values of enantiomeric excesses of the arylglycinols **5**−**8** were determined by chiral HPLC analysis on the *N*-Cbz derivatives. All the analytical details relating to the ascertaining of enantiopurity of the vicinal amino alcohols are summarised in Table 1.

Table 1. Methods used for the determination of the enantiopurity of the *N*-Cbz-arylglycinols

Amino alcohol	Condition for *ee* assay	Elution order and retention time [min]	*ee* (%)	$[\alpha]_D$ conc. Solv.
	HPLC. Chiralcel OF: 0.5 mL min^{-1} 90:10 Hex:IPA	*S* (23,2)	---[b]	---
		R (20,8)	88[a]	−5.2 0.24, $CHCl_3$
	HPLC. Chiralcel OD: 0.5 mL min^{-1} 90:10 Hex:IPA	*S* (19,5)	92	−25.3 0.81, EtOH[c]
		R (17,6)	---[b]	---
	HPLC. Chiralcel OD: 0.5 mL min^{-1} 80:20 Hex:IPA	*S* (16,5)	>99	+39.6 0.48, $CHCl_3$
		R (15,4)	>99	−37.7 0.32, $CHCl_3$
	HPLC. Chiralcel OD: 0.5 mL min^{-1} 70:30 Hex:IPA	*S* (8.9)	>99	+48.1 0.30, EtOH
		R (10.1)	>99	−49.0 0.32, EtOH

[a] After recrystallization from hexane. − [b] See ref.[19]. − [c] The optical rotation value is related to the *N*-Boc derivative.

The procedure affords high enantioselectivities for aryl (*p*Br-phenyl = 99% *ee*, 2-naphthyl = 99% *ee*, 2,4,6-trimethylphenyl = 92% *ee*, pentafluorophenyl = 88% *ee*) styrenes Table 1.

Conclusion

In summary, we have developed a shortcut for the preparation of chiral substituted arylglycinols and a simple methodology for their resolution. The arylaminols obtained are useful intermediates for the preparation of chiral auxiliaries. Particularly noteworthy is the simple preparation of chiral 2-amino-2-(perfluoroaryl)ethan-1-ol, which cannot be synthesised using the one-step AA reaction. Studies focusing on the preparation of perfluoro-bis(oxazoline) ligands from arylglycinols and their application in asymmetric catalysis will be the subjects of active investigations in our laboratories.

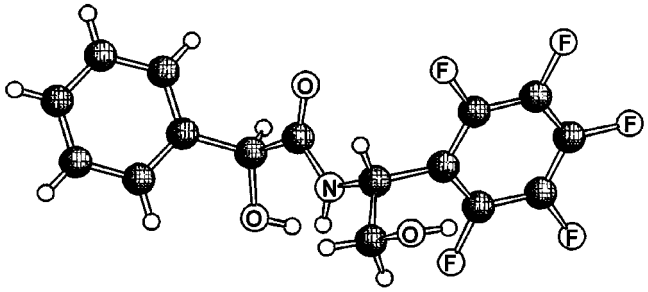


Figure 2. Molecular structure of **14a**; bond lengths [Å] in the peptidic region: C=O 1.22, C−N 1.33, N−C 1.45

Experimental Section

General Remarks: ^{1}H NMR spectra were recorded by means of Varian Gemini-200 (200 MHz) or Varian Gemini-300 (300 MHz) spectrometers. Chemical shifts are given in δ ppm from TMS with the undeuterated solvent as the internal standard (deuteriochloroform: δ = 7.26, deuteriodimethyl sulfoxide: δ = 2.50), and coupling constants *J* are measured in Hz. Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quadruplet, br = broad, m = multiplet). − ^{13}C NMR spectra were recorded on a Varian Gemini-200 (50 MHz) or Varian Gem-

ini-300 (75 MHz) spectrometers with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent as the internal standard (deuteriochloroform: δ = 77.0, deuteriodimethyl sulfoxide: δ = 39.0). − ^{19}F NMR spectra were recorded on a Varian Gemini-300 (282 MHz) spectrometer. Chemical shifts are reported in ppm with $C_6H_5CF_3$ as the external standard (δ = −67.7) and coupling constants *J* are measured in Hz. − GC-MS spectra were measured by EI ionization at 70 eV on a Hewlett−Packard 5971 with GC injection. They are reported as: *m*/*z* (rel. intense). − Column flash chromatography was performed over 270−400 mesh silica gel. − All the organic phases were dried over sodium sulfate. Anhydrous CH_3CN was purchased from the Fluka Co., CH_2Cl_2 was distilled from P_2O_5 and stored under nitrogen on activated molecular sieves. All the other chemicals were commercially available and used as received. − Elemental analyses were carried out by using a EACE 1110 CHNOS analyzer. − X-ray analysis was performed on a Bruker SMART2000 diffractometer equipped with CCD detector and graphite monochromated Mo-K_α radiation (λ = 0.71073 Å). The data handling was performed using the SMART software package. − Analytical high performance liquid chromatograph (HPLC) was performed on a HP 1090 liquid chromatograph equipped with a variable wavelength UV detector (deuterium lamp 190−600 nm), using a Daicel Chiralcel™ OD or OF column (0.46 cm I.D. × 25 cm) (Daicel Inc.). HPLC grade 2-propanol and hexane were used as the eluting solvents. − Optical rotations were determined in a 1 mL cell with a path length of 10 mm using a Perkin−Elmer 343 polarimeter (Na_D line). The experimental data for diols **2**,[25a] **3**,[25b] **4**[25c] and for amino alcohol **8**[25d] were in agreement with that previously reported.

General Procedure for the Preparation of 1-Arylethane-1,2-diols 1−4: *t*BuOH/H_2O (1:1, 100 mL), $K_3Fe(CN)_6$ (30 mmol), K_2CO_3 (30 mmol), DABCO (5 mol-%, 0.5 mmol) and $K_2OsO_2(OH)_4$ (1 mol-%, 0.1 mmol) were put into a 500 mL round-bottomed flask equipped with a mechanical stirrer. The orange solution was cooled to 0 °C and then the desired styrene (10 mmol) was added. The reaction mixture was vigorously stirred until disappearance of the starting material (checked by TLC). The solution was diluted with 25 mL of AcOEt, quenched with 10 g of Na_2SO_3 and left stirring for 10 minutes. The phases were separated and the aqueous layer was extracted with ethyl acetate (3 × 10 mL). The combined organic layers were washed with an aqueous solution of 10% HCl (40 mL) then with a saturated solution of $NaHCO_3$ (40 mL), and dried over Na_2SO_4. Evaporation of the solvent under reduced pressure afforded the pale yellow crude diol, which was purified by re-crystallization.

(±)-1-(Pentafluorophenyl)ethane-1,2-diol (1): Purification by recrystallization (CH_2Cl_2) gave 1.98 g (87%), as a white solid. − M.p. 91−93 °C. − ^{1}H NMR ($CDCl_3$): δ = 5.18 (q, 1 H, *J* = 3.96 Hz), 3.94−4.04 (m, 1 H), 3.81 (dd, 1 H, *J* = 4.12 Hz, *J* = 11.24 Hz), 2.75 (br, 1 H), 1.25 (d, 1 H, *J* = 4.12 Hz). − ^{13}C NMR ($CDCl_3$): δ = 65.2, 67.1, 113.6 (m), 135.1 (m), 142.5 (m), 143.7 (m), 148.8 (m). − ^{19}F NMR ($CDCl_3$, 282 MHz): δ = −166.5 (dt, 2 F, *J* = 7.33 Hz, *J* = 21.71 Hz), −159.1 (t, 1 F, *J* = 20.87 Hz), −147.7 (dd, 2 F, *J* = 7.05 Hz, *J* = 22.00 Hz). − Ms *m*/*z* (relative intensity): 228 (3), 197 (100), 181 (10), 169 (14), 149 (18), 119 (23), 99 (35), 75 (10). − IR (nujol): $\tilde{\nu}$ = 3421, 3336, 1658, 1523 cm^{-1}. − $C_8H_5F_5O_2$ (228.02): calcd. C 42.12, H 2.21, O 14.03; found C 42.08, H 2.15, O 14.02.

General Procedure for the Preparation of (±)-2-Amino-2-(pentafluorophenyl)ethanol (5): The diol **1** (2 mmol) and anhydrous CH_3CN (3.2 mL) were put into a dried 50 mL two-necked flask under nitrogen atmosphere. H_2SO_4 (98%, 20 mmol) was added dropwise at room temperature to the stirred reaction mixture, and the clear yellow solution was refluxed for 3 h. The mixture was then cooled to room temperature and H_2O (5 mL) was added. The solvent was removed by distillation at atmospheric pressure and the aqueous residue was refluxed for 2 h. After cooling, CH_2Cl_2 (5 mL) was added and the mixture was stirred for 5 min. The two phases were separated, the aqueous layer was treated with NaOH (50%) until pH = 13 and finally extracted with AcOEt (3 × 5 mL). The organic phases were collected, washed with brine (10 mL), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by recrystallization (cHex/AcOEt) gave 192 mg (85%) of the title compound, as a white solid. − M.p. 71−73 °C. − ^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.37 (dd, 1 H, *J* = 6.06 Hz, *J* = 8.34 Hz), 3.71−3.84 (m, 2 H), 2.09 (br). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 49.5, 65.1, 115.9 (t, *J* = 15.75 Hz), 135.00 (m), 137.7 (m), 140.0 (m), 142.6 (m), 147.3 (m). − ^{19}F NMR ($CDCl_3$, 282 MHz): δ = −166.6 (dt, 2 F, *J* = 7.61 Hz, *J* = 22.00 Hz), −160.4 (t, 1 F, *J* = 20.30 Hz), −148.7 (dd, 2 F, *J* = 6.77 Hz, *J* = 21.71 Hz). − IR (nujol): $\tilde{\nu}$ = 3330, 3288, 1528, 1498 cm^{-1}. − $C_8H_6F_5NO$ (227.13): calcd. C 42.30, H 2.66, O 7.04; found C 42.35, H 2.89, O 7.06.

General Procedure for the Synthesis of the *O*-Acetylamides (10−13): Pyridine (1.2 mmol) was added to a solution of **5−8** (1.0 mmol) in anhydrous CH_2Cl_2 (8 mL) and the mixture was cooled to 0 °C. A solution of freshly prepared (*S*)-(+)-mandeloyl chloride **9** (1.2 mmol) in 5 mL of CH_2Cl_2 was then added dropwise over 30 min. The reaction mixture was stirred at 0 °C for 18 h, and then quenched with aqueous HCl (1 N, 2 mL). The aqueous layer was washed with brine (3 × 4 mL), dried over Na_2SO_4 and evaporated under reduced pressure. Each crude product was purified using the conditions described below.

***O*-Acetyl-*N*-[2-hydroxy-1-(pentafluorophenyl)ethyl]mandelamide (10a+10b):** Purification by chromatography on silica gel (cHex/AcOEt, 1:1) gave 153 mg (38%), as a white solid. − R_f = 0.3. − ^{1}H NMR ($CDCl_3$, 300 MHz): δ = 7.41−7.35 (m, 5 H, Ar), 7.04 (t, 1 H, *J* = 9.00 Hz), 6.07 (d, 1 H, *J* = 9.90 Hz), 5.60−5.51 (m, 1 H), 3.87 (br, 2 H), 2.21 (s, 3 H); *less polar diastereoisomer* (diagnostic signals): 2.20 (s, 3 H). − ^{13}C NMR ($CDCl_3$, 50 MHz): δ = 30.9, 47.0, 63.7, 75.4, 112.7 (t, *J* = 15.75 Hz), 128.7, 129.0, 129.2, 134.8 (m), 138.1 (m), 140.0 (m), 142.5 (m), 147.5 (m), 168.6, 169.4; *more polar diastereoisomer* (diagnostic signals): 46.9, 127.1, 135.6, 169.2. − ^{19}F NMR ($CDCl_3$, 282 MHz): δ = −166.2 (dt, 2 F, *J* = 5.92 Hz, *J* = 20.87 Hz), −159.1 (t, 1 F, *J* = 20.87 Hz), −148.5 (dd, 1 F, *J* = 5.92 Hz, *J* = 15.51 Hz), −148.0 (dd, 1 F, *J* = 5.92 Hz, *J* = 15.51 Hz). − IR (nujol): $\tilde{\nu}$ = 3354, 3194, 3049, 1746, 1663, 1522, 1501, cm^{-1}. − $C_{18}H_{14}F_5NO_4$ (403.08): calcd. C 53.61, H 3.50, O 15.87; found C 53.50, H 3.47, O 15.86.

General Procedure for the Synthesis of the Enantiomerically Pure Mandelamides (14−17): A solution of amide (1 mmol, **10−13**) in MeOH was treated with NaOH (5 N, 5 mmol) and the resulting mixture was stirred at room temperature until disappearance of the starting material, checked by TLC. The reaction was diluted with AcOEt (5 mL) and quenched with an aqueous solution of 1 N HCl. The two phases were separated and the aqueous layer was extract with AcOEt (3 × 5 mL). Finally, the combined organic phases were collected, washed with brine (3 × 5 mL), dried over Na_2SO_4 and evaporated under reduced pressure. The two crude diastereoisomers were purified and separated by flash-chromatography.

***N*-[2-Hydroxy-1-(pentafluorophenyl)ethyl]mandelamide (14):** Purification by chromatography on silica gel (cHex/AcOEt, 1:1) gave 274 mg (76%), as a white solid. (*R*,*S*)-**14**: white solid. − ^{1}H NMR (DMSO, 300 MHz): δ = 8.38 (d, 1 H, *J* = 7.80 Hz), 7.40−7.25 (m,

5 H, Ar), 6.29 (d, 1 H, J = 5.10 Hz), 5.28 (t, 1 H, J = 6.30 Hz), 5.12 (q, 1 H, J = 7.20 Hz), 4.95 (br, 1 H), 3.73 (br,1 H), 3.01 (br, 1 H). – ^{13}C NMR (DMSO, 75 MHz): δ = 46.6, 61.3, 72.8, 113.9 (t, J = 19.88 Hz), 126.0, 127.0, 127.4, 134.6 (m), 137.9 (m), 140.3, 140.9 (m), 142.6 (m), 145.9 (m), 171.6. – ^{19}F NMR ($CDCl_3$, 282 MHz): δ = −168.0 (dd, 2 F, J = 14.06 Hz, J = 20.45 Hz), −161.1 (t, 1 F, J = 20.45 Hz), −147.8 (m, 2 F). – $C_{16}H_{12}F_5NO_3$ (361.26): calcd. C 53.19, H 3.35, O 13.29; found C 53.02, H 3.31, O 13.26. – **X-ray Analysis:** the crystallographic parameters found are: monoclinic space group $P2_1$ (No 4), a = 8.2368(7) Å, b = 11.3270(9) Å, c = 8.7791(7) Å, β = 102.843 (3), Z = 2, V = 293 (2) Å^3, $d_{calcd.}$ = 1.502 Mg m^{-3}, μ = 0.142 mm^{-1}. The final R factors obtained are: R_1 = 0.036, wR_2 = 0.144. – **(*S,S*)-14:** white solid – ^{1}H NMR (DMSO, 200 MHz): δ = 8.48 (d, 1 H, J = 7.82 Hz), 7.46–7.18 (m, 5 H, Ar), 6.32 (br, 1 H), 5.28 (br, 1 H), 5.12 (q, 1 H, J = 4.40 Hz), 4.97 (br, 1 H), 3.32 (br, 1 H). – ^{13}C NMR (DMSO, 50 MHz): δ = 46.3, 61.2, 72.6, 113.7 (t, J = 16.60 Hz), 126.0, 126.9, 127.4, 133.7 (m), 136.4 (m), 138.5 (m), 140.2, 141.4 (m), 146.6 (m), 171.4. – ^{19}F NMR ($CDCl_3$, 282 MHz): δ = −167.5 (dd, 2 F, J = 7.05 Hz, J = 14.10 Hz). −160.8 (t, 1 F, J = 20.59), −148.3 (dd, 2 F, J = 7.05 Hz, J = 14.95 Hz), – $C_{16}H_{12}F_5NO_3$ (361.26): calcd. C 53.19, H 3.35, O 13.29; found C 53.09, H 3.31, O 13.27. – $[\alpha]_D$ = +54.4 (c = 0.485, $CHCl_3$).

General Procedure for the Preparation of the Chiral Amino Alcohols 5–8: Amide **14–17a/17b** (0.5 mmol) were suspended in water (4 mL) and H_2SO_4 (98%, 2.5 mmol) was then added. The suspension was refluxed for 1–3 h until the starting amide disappeared. The clear solution was then treated with NaOH (50%) until the pH of the mixture was 13 and the aqueous layer was extracted with AcOEt (3 × 4 mL). The combined organic phases were collected, dried and evaporated under vacuum. Finally, the crude product was purified by recrystallization.

(*R*)-2-Amino-2-(pentafluorophenyl)ethanol (5): $[\alpha]_D$ = −12.0 (c = 0.206, $CHCl_3$).

(*S*)-2-Amino-2-(2,4,6-trimethylphenyl)ethanol (6): $[\alpha]_D$ = +27.4 (c = 0.404, $CHCl_3$).

(*R*)-2-Amino-2-(4-bromophenyl)ethanol (7): $[\alpha]_D$ = −37.7 (c = 0.32, $CHCl_3$).

(*S*)-7: $[\alpha]_D$ = +47.5 (c = 0.80, $CHCl_3$).

(*S*)-2-Amino-2-(2-naphthyl)ethanol (8): $[\alpha]_D$ = +30.6 (c =0.71, $CHCl_3$).

(*R*)-8: $[\alpha]_D$ = −32.6 (c = 0.82, $CHCl_3$).

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