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Asymmetric reduction using (*R*)-MeCBS and determination of absolute configuration of *para*-substituted 2-fluoroarylethanols

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ABSTRACT

The asymmetric reduction of eight α-fluoroacetophenones has been investigated using (*R*)-MeCBS as a catalyst in various media. Based on a solvent screen, 1,2-dimethoxyethane, diethyl ether and dichloromethane were used in reductions of the α-fluoroacetophenones. The enantiomeric excess of the products depended on the solvent and the electronic character of the aromatic substituents. Higher enantioselectivity and less solvent dependency were observed in the reduction of substrates bearing electron donating substituents, whereas the opposite was the case for reduction of the substrates with electron withdrawing substituents. The (*R*)-2-fluoro-1-arylethanols were obtained with enantiomeric excesses in the range of 91–99% using 1,2-dimethoxyethane as a solvent. Six of the alcohols produced are new chemical entities. The absolute configurations of the (*R*)-2-fluoro-1-arylethanols were determined by circular dichroism using the exciton chirality method of the (*S*)-benzoate esters of the alcohols. The (*S*)-benzoate esters were obtained by lipase-catalysed resolution using Novozym 435.

1. Introduction

The importance of fluorinated compounds has been well documented and there is a fast growing demand of optically active fluorinated building blocks, for example, in medicinal chemistry, biochemistry and material science.[1–4] Approximately 20% of drugs on the market contain fluorine, a number expected to grow.[5] The 1-arylethanol-skeleton is a frequently encountered structural element in bioactive molecules.[6–9] However, applications of 1-aryl-2-fluoroethanols are not numerous.

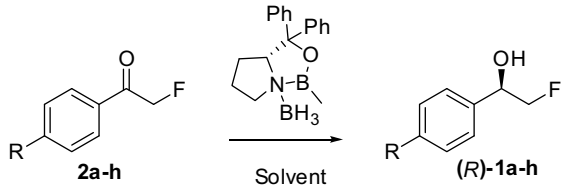
Enantioenriched (*R*)- and (*S*)-2-fluoro-1-phenylethanol are well known and have been prepared by microbial reductions,[10–13] reduction using DIP-Chlorine and Alpine-borane,[14] asymmetric epoxide opening[15,16] and hydrolase catalysed resolutions.[17–19] Also, (*R*)-1-(4-bromophenyl)-2-fluoroethanol has been prepared by Baker's yeast reduction.[10]

Chiral oxazaborolidine-catalysed borane reduction of prochiral ketones to chiral secondary alcohols is one of the most important methods in asymmetric synthesis. The present work deals with the asymmetric reduction and solvent selection for a series α-fluoroacetophenones using (*R*)-MeCBS.[20] The MeCBS catalyst had previously been used for the reduction of structurally related acetophenones, giving the corresponding alcohols in high enantiomeric excess (ee).[21,22] Mathre et al.,[21] compared the effect of three solvents on ee in reductions of a series of *para*-substituted acetophenones. Solvent effects have also been investigated experimentally by Gilmore et al.,[23] Xu et al.[24] and Corey et al.[25] whilst Xu et al.,[26] have investigated substrate electronic effects on the enantioselectivity in oxazaborolidine-catalysed reductions. Several theoretical studies of the catalyst have also been performed.[27–30]

2. Result and discussion

2.1. Asymmetric reduction

In order to find suitable conditions for the asymmetric reduction of a series of α-fluoroacetophenones, **2a**–**h** (Scheme 1), a solvent screen was performed. The investigation was carried out using nine different solvents, **2a** as the model substrate and



R = OMe (**a**), OBn (**b**), H (**c**), F (**d**), Br (**e**), CF_3 (**f**), CN (**g**), NO_2 (**h**)

Scheme 1. Asymmetric reduction of **2a**–**h** using (*R*)-MeCBS in various solvents.

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(*R*)-MeCBS as the catalyst (Table 1). The catalyst was prepared from (*R*)-α,α-diphenyl-2-pyrrolidinemethanol,[21] and was used as the borane complex in equimolar amounts.

Table 1
Effect of solvent on ee (%) in reduction of **2a** at 25 °C

Solvent	ee (%)	Absolute configuration
Diethyl ether	98.0	(*R*)
t-BuOMe	97.0	(*R*)
DME	97.0	(*R*)
THF	96.0	(*R*)
CH_2Cl_2	94.5	(*R*)
Toluene	86.5	(*R*)
i-Pr ether	86.0	(*R*)
Hexane	81.0	(*R*)
MeCN	74.5	(*R*)

The enantioselectivity of the reductions depended on the solvent. The product (*R*)-**1a** was obtained in high ee when the reaction was performed in diethyl ether, *tert*-butyl methyl ether (*t*-BuOMe) and 1,2-dimethoxyethane (DME). Acyclic ethers had previously been found to be suitable solvents for the asymmetric reduction of structurally related ketones.[31,32] The reductions of **2a** in dichloromethane and THF also gave acceptable ee-values, whereas the reductions in the other solvents resulted in moderate enantioselectivity. Surprisingly, reductions in diisopropyl ether gave low selectivity. The reason for this is not clear; however, both the catalyst and the substrate had a low solubility in the reaction medium.

To investigate the effect of solvents on the enantioselectivity further, the whole series of substrates, **2a–2h,** were reduced in diethyl ether, dichloromethane and DME. *t*-BuOMe was not included due to the low solubility of the catalyst in this medium. Dichloromethane was included to ensure a larger variability in solvent properties. The reductions of **2a–h** in the three solvents were performed using (*R*)-MeCBS at 25 °C. The results are summarised in Table 2.

Table 2
Effect of solvent on ee in reduction of **2a–h** at 25 °C

Product	ee (%)		
	Diethyl ether	CH_2Cl_2	DME
(*R*)-**1a**	98.0	94.5	97.0
(*R*)-**1b**	98.0	98.0	97.0
(*R*)-**1c**	91.5	78.0	96.5
(*R*)-**1d**	94.5	92.0	97.5
(*R*)-**1e**	90.0	81.5	93.5
(*R*)-**1f**	85.5	65.0	90.0
(*R*)-**1g**	[a]	74.0	89.0
(*R*)-**1h**	75.0	68.0	93.5

[a] Low solubility of substrate resulted in slow conversion.

The effect of the solvent on the enantioselectivity varied between the substrates. For the whole series, reductions in DME on average gave the highest ee-values, whilst reactions in dichloromethane gave the lowest enantioselectivity. Only minor effects of the solvent on the ee were observed in the reduction of **2a–b**, whereas for the reduction of **2c–2h** the choice of solvent was very important.

Solvent effects on enantioselectivity in similar reaction systems had previously been explained by changes in the equilibrium between the monomer and dimer species of the catalyst,[23] reduction caused by free borane,[21,24] and stabilisation of the reactive intermediates.[27,28] The solvent effect observed in this study is likely to be caused by a combination of all the above-mentioned mechanisms.

Clearly, the substrate structure has an effect on the outcome of the reaction. In all solvents, there was a decrease in ee going from **1a** to **1h**. Such effects have also been observed in similar systems.[25,26]

The enantioselectivity of (*R*)-MeCBS-catalysed asymmetric reductions has been observed to be dependant on the reaction temperature[24] and the addition time of the substrate. The effects of these two parameters were investigated in the reduction of **2a**. The reaction temperature was varied between –20 °C and +40 °C, and the substrate addition time was varied from 0 to 4 h. The results are given in Table 3.

Table 3
Effect of reaction temperature and addition time on ee in reduction of **2a**

Reaction temperature (°C)	Addition time (h)	ee (%)
40	0	92.5
40	4	93.5
10	2	98.0
10	2	98.5
−20	0	98.5
−20	4	98.5

The ee of the product, (*R*)-**1a**, depended on the reaction temperature. Lower enantioselectivity was experienced at 40 °C. The substrate addition time seemed to be less important, but a minor effect was observed at a higher reaction temperature.

Based on the above findings, all the substrates were reduced on a 1 mmol scale using (*R*)-MeCBS at −20 °C in DME. The addition of the substrates was carried out over 20 min; the results are given in Table 4.

Table 4
Asymmetric reduction of **2a–h** at −20 °C using (*R*)-MeCBS in DME

Product	Reaction time (min)	ee (%)	Isolated yield (%)
(R)-**1a**	30	99.5	88
(R)-**1b**	15	97.0	88
(R)-**1c**	20	96.5	84
(R)-**1d**	20	99.0	76
(R)-**1e**	20	98.5	82
(R)-**1f**	20	93.0	84
(R)-**1g**	20	91.5	74
(R)-**1h**	20	92.5	80

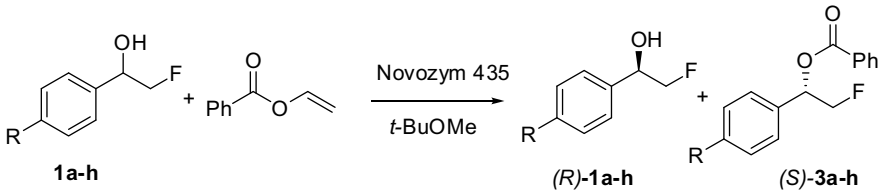
All the products were obtained in good to excellent ee, but a slight decrease in enantioselectivity was observed going from (*R*)-**1a** to (*R*)-**1h**. Comparing the reactions in DME performed at −20 °C with those at +25 °C, only minor changes in enantioselectivity were observed for most substrates. However, the enantioselectivity in the reduction of **2e** increased from 93.5% to 98.5%. This effect was not investigated, but might be due to either a temperature effect, addition time or a scale effect.

2.2. Determination of the absolute configuration

Optical rotation data had previously only been reported for (*R*)-**1c**,[10,18] and (*R*)-**1e**.[10] The absolute configuration of the remaining alcohols was determined by circular dichroism spectroscopy (CD) of the benzoates (*S*)-**3a–h**, (Scheme 2). The CD exciton chirality method,[33,34] had previously been used for assigning the absolute configuration of similar compounds.[35]

The stereopreference of lipase B from *Candida antarctica* is well documented.[36,37] Therefore, this lipase (Novozym 435) was used to obtain the benzoates, (*S*)-**3a–h**, from the racemic alcohols, *rac*-**1a–h**, by kinetic resolution via a 0.1 mmol scale. Vinyl benzoate was used as acyl donor and *t*-BuOMe as a solvent (Scheme 2).

The remaining substrate from the resolution had the same configuration as the alcohols, (*R*)-**1a–h**, obtained by the asymmetric reduction using (*R*)-MeCBS. Thus, the benzoates obtained, (*S*)-**3a–h**, had the opposite configuration.



Scheme 2. Kinetic resolution of racemic **1a**–**h** using Novozym 435 and vinyl benzoate as acyl donor.

The exciton chirality method depends on the conformation of the molecule. Therefore, an energy minimisation using Molecular Modelling Pro (MM2) was performed. The benzoates, (*S*)-**3a**–**h**, had similar preferred conformations, with the hydrogen atom at the stereogenic centre arranged in the same plane as the disubstituted aromatic ring, see Figure 1.

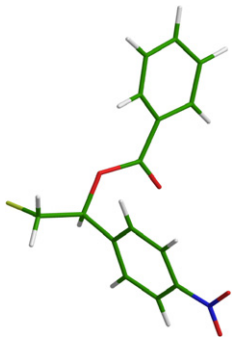


Figure 1. Favoured conformation of (*S*)-**3h**.

Table 5
Enantiomeric excess, $\Delta\varepsilon$ and λ for (*S*)-**3a**–**h**

Compound	R	ee (%)	$\Delta\varepsilon$	λ[a] (nm)
(*S*)-**3a**	OMe	73	−5.9	233
(*S*)-**3b**	OBn	99	−14.2	234
(*S*)-**3c**	H	88	−9.0	228
(*S*)-**3d**	F	79	−7.1	228
(*S*)-**3e**	Br	94	−22.3	232
(*S*)-**3f**	CF_3	96	−6.0	227
(*S*)-**3g**	CN	90	−19.6	237
(*S*)-**3h**	NO_2	94	−9.0	265

[a] Maximum of first Cotton effect.

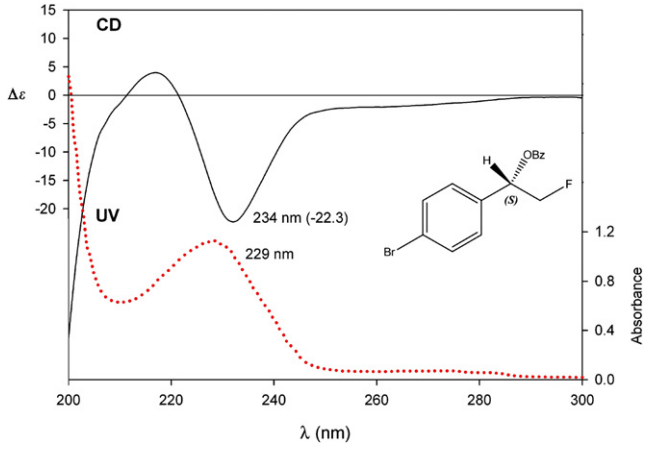


Figure 2. CD and UV spectra of (*S*)-**3e**.

The CD chirality exciton method predicts that upon looking through the centres of the two interacting dipoles, a negative sign is defined when an anticlockwise rotation brings the dipole in the front onto that in the back, and vice-versa.[38]

For the benzoates, (*S*)-**3a**–**h**, an anticlockwise rotation of the disubstituted phenyl ring brings it onto the benzoate dipole, thus a negative first Cotton effect was predicted. This was confirmed by CD measurements. The ee of the benzoates, (*S*)-**3a**–**h**, the molar extinction ($\Delta\varepsilon$) and UV absorption maximum (λ_{max}) are summarised in Table 5.

The second Cotton effect at lower wavelength was not observed because the CD spectrum is perturbed by other electronic transitions and effects caused by solvents, see Figure 2.

3. Conclusion

Eight α-fluoroacetophenones have been reduced with good to excellent enantioselectivity, using the (*R*)-MeCBS borane complex as catalyst. The enantiomeric excess of the products depended on the choice of solvent, DME being the preferred reaction medium. The enantioselectivity of the reactions was also affected by substrate structure. High enantioselectivity was obtained in the reduction of substrates having electron donating substituents, whereas a slight decrease in ee of the products were observed in reductions of substrates having electron withdrawing substituents.

Six of the prepared 2-fluoro-1-arylethanols had not previously been described. The absolute configuration of the alcohols, (*R*)-**1a**–**h**, was determined by CD spectroscopy using the exciton chirality method.

4. Experimental

4.1. General

The α-fluoroacetophenones were prepared as described previously.[39] The (*R*)-MeCBS borane complex was prepared according to Mathre et al.[21] starting with (*R*)-α,α-diphenyl-2-pyrolidinemethanol. Trimethylboroxine, borane dimethyl sulfide complex, vinyl benzoate and $NaBH_4$ were purchased from Aldrich. (*R*)-α,α-Diphenyl-2-pyrrolidinemethanol was a gift from Borregaard (Norway). Novozym 435 was from Novozymes A/S (Denmark). Column chromatography was performed using Silica Gel 60A from Fluka, pore size 40–63 μm. Preparative TLC plates were made by known procedures. Solvents were dried by standard procedures before use.

4.2. Analyses

NMR spectra were recorded with Bruker Avance DPX 400 operating at 400 MHz for ^1H, 375 MHz for ^{19}F and 100 MHz for ^{13}C. ^1H and ^{13}C NMR chemical shifts are in ppm relative to TMS, whilst for ^{19}F NMR, the shift values are relative to hexafluorobenzene. Coupling constants are in Hertz. Mass spectroscopy (EI): Finnigan MAT 95 XL Mass Spectrometer (EI/70 eV). Accurate mass determination (ESI) was performed on an Agilent 6520 QTOF MS instrument equipped with a dual electrospray ion source. Samples

were injected into the MS using an Agilent 1200 series HPLC, and analysis was performed as a flow injection analysis without any chromatographic steps. All melting points are uncorrected and measured by a Büchi melting point instrument. FTIR spectra were recorded on a Thermo Nicolet Avatar 330 infrared spectrophotometer. CD spectra were recorded on an OLIS DSM 1000 spectrophotometer in a 1 cm cuvette, using acetonitrile as a solvent. Optical rotations were measured using sodium D line at 589 nm on a Perkin–Elmer 243 B polarimeter. The ee of the alcohols was determined by HPLC using an Agilent 1100 series system equipped with a Bruker DAD detector and a Chiracel OD column (0.46 cm × 25 cm), mobile phase: hexane/2-propanol, 98:2, flow rate 1.0 mL/min. Retention times for the enantiomers: (*S*)-**1a** 24.7 min, (*R*)-**1a** 30.0 min, (*S*)-**1b** 46.7 min, (*R*)-**1b** 49.6 min, (*S*)-**1c** 16.2 min, (*R*)-**1c** 21.4 min, (*R*)-**1d** 15.2 min, (*S*)-**1d** 16.2 min, (*R*)-**1e** 17.8 min, (*S*)-**1e** 20.4 min, (*R*)-**1f** 16.3 min, (*S*)-**1f** 18.3 min, (*R*)-**1g** 47.3 min, (*S*)-**1g** 52.7 min, (*R*)-**1h** 42.5 min, (*S*)-**1h** 47.3 min.

4.3. Screening scale (*R*)-MeCBS reductions

Under anhydrous conditions, (*R*)-MeCBS (29 mg, 0.1 mmol) was dissolved in the given solvent (0.5 mL) and added to a solution of the α-fluoroacetophenone (0.1 mmol, 0.10 M) in the same solvent. The reaction mixture was then stirred at the given temperature until full conversion as monitored by HPLC.

4.4. Preparative scale (*R*)-MeCBS reductions

The α-fluoroacetophenone (1.5 mmol) was dissolved in DME (10 mL) and cooled to −20 °C. Through an addition funnel was added a solution of (*R*)-MeCBS (437 mg, 1.5 mmol) dissolved in DME (5 mL) over 20 min. The mixture was kept at −20 °C and stirred until complete consumption of the ketone as analysed by HPLC. The reaction mixture was then quenched with MeOH (5 mL) at −20 °C and acidified with HCl (1%) at 0 °C. Water (10 mL) was added before the reaction mixture was extracted with CH_2Cl_2 (3 × 15 mL). The organic phase was washed with water (2 × 20 mL) and dried over Na_2SO_4 before the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography (CH_2Cl_2/MeOH, 100:1).

4.5. Lipase-catalysed resolution

The racemic 2-fluoro-1-arylethanols, *rac*-**1a**–**h**, (0.1 mmol), obtained by $NaBH_4$ reduction of the α-fluoroacetophenones, **2a**–**h**, were dissolved in *t*-BuOMe (3 mL). Vinyl benzoate (74 mg, 0.5 mmol) and Novozym 435 (60 mg) were added. The reaction mixture was agitated at 45 °C and monitored by HPLC. The enzyme was filtered off, and the solvent was removed under reduced pressure. The benzoate esters, (*S*)-**3a**–**h**, and alcohols, (*R*)-**1a**–**h,** were separated by preparative TLC. Degree of conversions (*c*) was determined by ^{1}H NMR spectroscopy, whilst enantiomeric excess of the substrate alcohols (ee_s) was determined as described in Section 4.2. The ee of the benzoates (ee_p) was calculated by the formula $ee_p = (ee_s/c) - ee_s$.[40]

4.6. Analytical data for (*R*)-2-fluorophenylethanols

4.6.1. (*R*)-2-Fluoro-1-(4-methoxyphenyl)ethanol (*R*)-1a

Colourless oil (224 mg, 88%), ee = 99.5%, $[\alpha]_D^{25} = -38.5$ (*c* 0.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$) *δ*: 2.41 (br, 1H), 3.81 (s, 3H), 4.38 (ddd, *J* = 8.3, 9.5, 48.5, 1H), 4.49 (ddd, *J* = 3.4, 9.5, 46.8, 1H), 4.97 (ddd, *J* = 3.4, 8.3, 13.2, 1H), 6.89–6.93 (m, 2 H), 7.29–7.33 (m, 2H). ^{13}C NMR ($CDCl_3$) *δ*: 55.3, 72.5 (d, *J* = 19.8), 87.1 (d, *J* = 174.5), 114.0 (2 C), 127.6 (2 C), 130.2 (d, *J* = 8.1) and 159.7. ^{19}F NMR ($CDCl_3$, C_6F_6) *δ*: −220.8 (dt, *J* = 13.4, 47.4). IR (neat, cm^{-1}): 3420, 2955, 2839, 1612, 1514, 1250, 1177 and 1089. MS (EI, *m*/*z*, %): 170 (M^+, 14), 153 (29), 137 (100), 109 (27) and 77 (37). HRMS (EI): 170.0744 (calcd 170.0743).

4.6.2. (*R*)-1-(4-(Benzyloxy)phenyl)-2-fluoroethanol (*R*)-1b

White solid (216 mg, 88%), mp 71–73 °C, ee = 97.0%, $[\alpha]_D^{25} = -19.9$ (*c* 0.60, $CHCl_3$). ^{1}H NMR ($CDCl_3$) *δ*: 2.39 (dd, *J* = 1.1, 2.9, 1H), 4.40 (ddd, *J* = 8.4, 9.5, 48.5, 1H), 4.48 (ddd, *J* = 3.4, 9.5, 46.8, 1H), 4.97 (m, 1H), 5.07 (s, 2H), 6.95–7.01 (m, 2H), 7.28–7.45 (m, 7H). ^{13}C NMR ($CDCl_3$) *δ*: 70.3, 72.8 (d, *J* = 19.8), 87.4 (d, *J* = 175.2), 115.3 (2C), 127.7 (2C), 127.9 (2C), 128.2, 128.8 (2C), 130.7 (d, *J* = 8.4), 137.0 and 159.1 ^{19}F NMR ($CDCl_3$, C_6F_6) *δ*: −220.8 (dt, *J* = 13.4, 47.9). IR (KBr, cm^{-1}): 3427, 2948, 2860, 1612, 1512, 1248, 1170, 1078 and 1007. MS (EI, *m*/*z*, %): 246 (M^+, 3), 91 (100), 65 (11), 43 (12). HRMS (EI): 246.1056 (calcd 246.1056).

4.6.3. (*R*)-2-Fluoro-1-phenylethanol (*R*)-1c[10,18]

Colourless oil (174 mg, 84%), ee = 96.5%, $[\alpha]_D^{25} = -64.4$ (*c* 1.20, $CHCl_3$), Ref. $[\alpha]_D^{25} = -49.9$ (*c* 1.2, $CHCl_3$).[10] ^{1}H NMR ($CDCl_3$) *δ*: 2.51 (br, 1H), 4.41 (ddd, *J* = 8.3, 9.6, 48.5, 1H), 4.51 (ddd, *J* = 3.3, 9.6, 46.7, 1H), 5.01 (ddd, *J* = 3.3, 8.3, 14.0, 1H), 7.33–7.36 (m, 5H). ^{13}C NMR ($CDCl_3$) *δ*: 73.0 (d, *J* = 19.8), 87.2 (d, *J* = 174.1), 126.3 (d, *J* = 0.7, 2C), 128.5, 128.7 (2C) and 138.1 (d, *J* = 8.1). ^{19}F NMR ($CDCl_3$, C_6F_6) *δ*: −221.2 (dt, *J* = 13.9, 48.5). IR (neat, cm^{-1}): 3564, 3387, 2950, 1604, 1454, 1311, 1198, 1064 and 1009. MS (EI, *m*/*z*, %): 140 (M^+, 61), 123 (14), 107 (100), 105 (46), 91 (52), 79 (93) and 77 (88). HRMS (EI): 140.0639 (calcd 140.0637).

4.6.4. (*R*)-2-Fluoro-1-(4-fluorophenyl)ethanol (*R*)-1d

Colourless oil (180 mg, 76%), ee = 99.0%, $[\alpha]_D^{25} = -36.5$ (*c* 0.60, $CHCl_3$). ^{1}H NMR ($CDCl_3$) *δ*: 2.63 (br, 1H), 4.39 (ddd, *J* = 8.2, 9.6, 48.3, 1H), 4.48 (ddd, *J* = 3.3, 9.6, 46.7, 1H), 5.00 (ddd, *J* = 3.3, 8.3, 13.9, 1H), 7.00–7.08 (m, 2H), 7.32–7.36 (m, 2H). ^{13}C NMR ($CDCl_3$) *δ*: 72.3 (d, *J* = 19.6), 87.0 (d, *J* = 175.7), 115.5 (d, *J* = 21.6, 2C), 128.0 (d, *J* = 8.2, 2C), 134.7 (dd, *J* = 3.2, 11.3) and 162.7 (d, *J* = 245.3). ^{19}F NMR ($CDCl_3$, C_6F_6) *δ*: −114.2 (m), −221.4 (dt, *J* = 13.8, 48.2). IR (neat, cm^{-1}): 3588, 3385, 2952, 2892, 1606, 1510, 1223, 1197, 1088 and 1010. MS (EI, *m*/*z*, %): M^+ 158 (M^+, 5) 125 (72), 109 (10), 97 (52), 95 (23). HRMS (ESI): 157.0470, (calcd 157.0471 [M−H^+]).

4.6.5. (*R*)-1-(4-Bromophenyl)-2-fluoroethanol (*R*)-1e[10]

White solid (273 mg, 82%), mp 40–41 °C, ee = 98.5%. $[\alpha]_D^{25} = -32.3$ (*c* 0.90, $CHCl_3$), Ref. $[\alpha]_D^{25} = -25.9$ (*c* 0.9 $CHCl_3$).[10] ^{1}H NMR ($CDCl_3$) *δ*: 2.45 (dd, *J* = 1.1, 3.1, 1H), 4.38 (ddd, *J* = 8.2, 9.6, 48.3, 1H), 4.48 (ddd, *J* = 3.3, 9.6, 46.6, 1H), 4.97 (m, 1H), 7.27–7.30 (m, 2H), 7.45–7.53 (m, 2H). ^{13}C NMR ($CDCl_3$) *δ*: 72.3 (d, *J* = 20.2), 86.9 (d, *J* = 174.7), 122.4, 128.0 (2C), 131.8 (2C) and 137.1 (d, *J* = 8.3). ^{19}F NMR ($CDCl_3$, C_6F_6) *δ*: −221.9 (dt, *J* = 13.4, 47.4). IR (KBr, cm^{-1}): 3360, 2953, 2896, 1592, 1489, 1327, 1195, 1091 and 1008. MS (EI, *m*/*z*, %): 220/218 (M^+, 6) 187 (47), 185 (52), 78 (50), 77 (100). HRMS (EI): 217.9737 (calcd 217.9743).

4.6.6. (*R*)-2-Fluoro-1-(4-(trifluoromethyl)phenyl) ethanol (*R*)-1f

Colourless oil (265 mg, 84%), ee = 93.0%, $[\alpha]_D^{25} = -20.0$ (*c* 0.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$) *δ*: 2.54 (d, *J* = 3.1, 1H), 4.41 (ddd *J* = 8.1, 9.6, 48.0, 1H), 4.54 (ddd, *J* = 3.3, 9.6, 46.7, 1H), 5.10 (m, 1H), 7.51–7.53 (m, 2H), 7.63–7.69 (m, 2H). ^{13}C NMR ($CDCl_3$) *δ*: 72.4 (d, *J* = 20.5), 86.8 (d, *J* = 174.7), 124.0 (q, *J* = 272.3), 125.6 (q, *J* = 3.9, 2C), 126.7 (d, *J* = 0.7, 2C), 130.7 (q, *J* = 32.5) and 142.1 (dq, *J* = 1.4, 7.8). ^{19}F NMR ($CDCl_3$, C_6F_6) *δ*: −63.2 (s, 3F), −222.4 (dt, *J* = 13.8, 47.0). IR (neat, cm^{-1}): 3581, 3386, 2954, 2895, 1621, 1418, 1327, 1166, 1068 and 1016. MS (EI, *m*/*z*, %): M^+ 208 (M^+, 2), 189 (8), 175 (100), 145 (14), 127 (88), 95 (4). HRMS (EI): 208.0503 (calcd 208.0511).

4.6.7. 4-((*R*)-2-Fluoro-1-hydroxyethyl)benzonitrile (*R*)-1g

White solid (183 mg, 74%), mp 59–61 °C, ee = 91.5%. $[\alpha]_D^{25} = -27.1$ (*c* 0.70, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 2.63 (d, *J* = 3.1, 1H), 4.40 (ddd, *J* = 8.0, 9.5, 48.0, 1H), 4.54 (ddd, *J* = 3.4, 9.5, 46.7, 1H), 5.07 (m, 1H), 7.46–7.56 (m, 2H), 7.65–7.71 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 72.2 (d, *J* = 20.3), 86.5 (d, *J* = 173.3), 112.5, 118.5, 127.0 (2C), 132.4 (2C) and 143.3 (d, *J* = 7.6). ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −222.9 (dt, *J* = 13.8, 47.0). IR (KBr, cm^{-1}): 3456, 2947, 2239, 1609, 1454, 1323, 1202, 1096, and 1009. MS (EI, *m*/*z*, %): M^+ 165 (M^+, 5), 132 (100), 104 (50), 102 (14), 77 (29). HRMS (EI): 165.0589 (calcd 165.0590).

4.6.8. (*R*)-2-Fluoro-1-(4-nitrophenyl)ethanol (*R*)-1h

White solid (223 mg, 80%), mp 97–99 °C, ee = 92.5%, $[\alpha]_D^{25} = -17.7$ (*c* 0.70, $CHCl_3$). ^1H NMR ($CDCl_3$) δ: 2.65 (br, 1H), 4.43 (ddd *J* = 7.8, 9.6, 47.9, 1H), 4.57 (ddd, *J* = 3.4, 9.6, 46.5, 1H), 5.16 (ddd, *J* = 3.4, 7.8, 14.5, 1H), 7.57–7.63 (m, 2H), 8.22–8.27 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 72.1 (d, *J* = 20.5), 86.5 (d, *J* = 175.6), 123.8 (2C), 127.2 (2C), 145.2 (d, *J* = 7.4) and 147.9. ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −223.2 (dt, *J* = 14.4, 47.4). IR (KBr, cm^{-1}): 3482, 3116, 2943, 2889, 1604, 1560, 1521, 1349, 1197, 1092, and 1002. MS (EI, *m*/*z*, %): M^+ 185(M^+, 4), 152 (42), 102 (19), 83 (20). HRMS (EI): 185.0488 (calcd 185.0488).

4.7. Analytical data for the benzoates

4.7.1. (*S*)-2-Fluoro-1-(4-methoxyphenyl)ethyl benzoate (*S*)-3a

Colourless oil (11.5 mg, 43%), ee = 73%, $[\alpha]_D^{25} = -15.0$ (*c* 0.60, $CHCl_3$). CD (acetonitrile): $\Delta\varepsilon = -5.9$ (233 nm). ^1H NMR ($CDCl_3$) δ: 3.80 (s, 3H), 4.65 (ddd, *J* = 3.5, 10.1, 46.7, 1H), 4.75 (ddd, *J* = 7.6, 10.1, 47.8, 1H), 6.23 (ddd, *J* = 3.5, 7.6, 16.2, 1H), 6.89–6.93 (m, 2H), 7.37–7.48 (m, 4H), 7.55–7.59 (m, 1H), 8.09–8.13 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 55.3, 74.4 (d, *J* = 19.9), 84.2 (d, *J* = 179.3), 114.2 (2C), 127.6 (d, *J* = 6.8), 128.3 (2C), 128.4 (2C), 129.8 (2C), 130.0, 133.2, 160.0 and 165.7. ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −221.6 (dt, *J* = 16.1, 47.0). HRMS (ESI): 297.0895 (calcd 297.0897 [M+Na^+]).

4.7.2. (*S*)-1-(4-(Benzyloxy)phenyl)-2-fluoroethyl benzoate (*S*)-3b

White solid (13.5 mg, 39%), mp 91–92 °C, ee = 99%, $[\alpha]_D^{25} = -13.9$ (*c* 1.00, $CHCl_3$) CD (acetonitrile): $\Delta\varepsilon = -14.2$ (234 nm). ^1H NMR ($CDCl_3$) δ: 4.64 (ddd, *J* = 3.5, 10.1, 46.5, 1H), 4.74 (ddd, *J* = 7.6, 10.1, 48.0, 1H), 5.05 (s, 2H), 6.23 (ddd, *J* = 3.5, 7.6, 16.2, 1H), 6.97–6.99 (m, 2H), 7.25–7.47 (m, 9H), 7.55–7.59 (m, 1H), 8.09–8.11 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 70.1, 74.3 (d, *J* = 20.2), 84.2 (d, *J* = 179.3), 115.1 (2C), 127.4 (2C), 127.8 (d, *J* = 6.7), 128.1, 128.3 (2C), 128.4 (2C), 128.6 (2C), 129.8 (2C), 130.0, 133.2, 136.7, 159.2 and 165.7. ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −222.7 (dt, *J* = 16.1, 47.0). HRMS (ESI): 373.1207 (calcd 373.1210 [M+Na^+]).

4.7.3. (*S*)-2-Fluoro-1-phenylethyl benzoate (*S*)-3c

Colourless oil (12.0 mg, 50%), ee = 88%, $[\alpha]_D^{25} = -42.2$ (*c* 0.70, $CHCl_3$). CD (acetonitrile): $\Delta\varepsilon = -9.0$ (228 nm). ^1H NMR ($CDCl_3$) δ: 4.68 (ddd, *J* = 3.4, 10.1, 46.7, 1H), 4.76 (ddd, *J* = 7.3, 10.1, 47.7, 1H), 6.28 (ddd, *J* = 3.4, 7.3, 16.7, 1H), 7.33–7.48 (m, 7H), 7.56–7.60 (m, 1H), 8.11–8.13 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 74.7 (d, *J* = 19.8), 84.2 (d, *J* = 179.8), 126.8 (2C), 128.5 (2C), 128.8 (2C), 128.9, 129.8 (2C), 129.9, 133.3, 135.5 (d, *J* = 6.7) and 165.6. ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −223.0 (dt, *J* = 16.1, 47.0). HRMS (ESI): 267.0791 (calcd 267.0792 [M+Na^+]).

4.7.4. (*S*)-2-Fluoro-1-(4-fluorophenyl)ethyl benzoate (*S*)-3d

Colourless oil (9.0 mg, 37%), ee = 79%, $[\alpha]_D^{25} = -23.3$ (*c* 0.60, $CHCl_3$). CD (acetonitrile): $\Delta\varepsilon = -7.1$ (228 nm). ^1H NMR ($CDCl_3$) δ: 4.67 (ddd, *J* = 3.5, 10.1, 46.7, 1H), 4.74 (ddd, *J* = 7.1, 10.1, 47.5, 1H), 6.24 (ddd, *J* = 3.5, 7.1, 16.9, 1H), 7.06–7.10 (m, 2H), 7.43–7.48 (m, 4H), 7.57–7.61 (m, 1H), 8.10–8.12 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 74.0 (d, *J* = 20.1), 84.0 (dd, *J* = 1.1, 179.4), 115.8 (d, *J* = 21.6, 2C), 128.5 (2C), 128.8 (d, *J* = 8.5, 2C), 129.69, 129.81 (2C), 131.4 (dd, *J* = 2.8, 3.5), 133.4, 162.9 (d, *J* = 248.0) and 165.5. ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −113.3 (m), −223.8 (dt, *J* = 17.2, 47.0). HRMS (ESI): 285.0696 (calcd 285.0698 [M+Na^+]).

4.7.5. (*S*)-1-(4-Bromophenyl)-2-fluoroethyl benzoate (*S*)-3e

White solid (12.0 mg, 38%), mp 52–53 °C, ee = 94%, $[\alpha]_D^{25} = -49.5$ (*c* 0.90, $CHCl_3$). CD (acetonitrile): $\Delta\varepsilon = -22.3$ (232 nm). ^1H NMR ($CDCl_3$) δ: 4.67 (ddd, *J* = 3.5, 10.1, 46.7, 1H), 4.73 (ddd, *J* = 6.8, 10.1, 47.5, 1H), 6.20 (ddd, *J* = 3.5, 6.8, 17.4, 1H), 7.32–7.35 (m, 2H), 7.45–7.53 (m, 4H), 7.58–7.61 (m, 1H), 8.09–8.11 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 74.0 (d, *J* = 20.1), 83.9 (d, *J* = 179.8), 122.9, 128.5 (2C), 128.6 (2C), 129.6, 129.8 (2C), 132.0 (2C), 133.5, 134.6 (d, *J* = 6.7) and 165.5. ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −224.2 (dt, *J* = 17.2, 47.0). HRMS (ESI): 344.9901 (calcd 344.9897 [M+Na^+]).

4.7.6. (*S*)-2-Fluoro-1-(4-(trifluoromethyl)phenyl)ethyl benzoate (*S*)-3f

Colourless oil (13.5 mg, 40%), ee = 96%, $[\alpha]_D^{25} = -40.3$ (*c* 1.00, $CHCl_3$). CD (acetonitrile): $\Delta\varepsilon = -6.0$ (227 nm). ^1H NMR ($CDCl_3$) δ: 4.72 (ddd, *J* = 3.8, 10.1, 46.7, 1H), 4.76 (ddd, *J* = 6.3, 10.1, 47.2, 1H), 6.28 (ddd, *J* = 3.8, 6.3, 17.9, 1H), 7.46–7.50 (m, 2H), 7.55–7.67 (m, 5H), 8.11–8.13 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 74.0 (d, *J* = 20.1), 83.9 (d, *J* = 179.8), 123.9 (d, *J* = 272.7), 125.8 (q, *J* = 3.9), 127.2 (d, *J* = 0.7, 2C), 128.6 (2 C), 129.4, 129.9 (2C), 131.1 (q, *J* = 32.5), 133.6 (2C), 139.5–139.6 (m) and 165.5. ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −63.4 (s, 3F), −226.2 (dt, *J* = 17.2, 47.0). HRMS (ESI): 335.0662 (calcd 335.0666 [M+Na^+]).

4.7.7. (*S*)-1-(4-Cyanophenyl)-2-fluoroethyl benzoate (*S*)-3g

White solid (12.0 mg, 44%), mp 70–71 °C, ee = 90%, $[\alpha]_D^{25} = -49.5$ (*c* 0.90, $CHCl_3$). CD (acetonitrile): $\Delta\varepsilon = -19.6$ (237 nm). ^1H NMR ($CDCl_3$) δ: 4.72 (ddd, *J* = 3.8, 10.1, 46.7, 1H), 4.76 (ddd, *J* = 5.8, 10.1, 47.0, 1H), 6.25 (ddd, *J* = 3.8, 5.8, 18.7, 1H), 7.44–7.71 (m, 7H), 8.10–8.12 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 73.8 (d, *J* = 20.1), 83.6 (d, *J* = 179.8), 112.8, 118.3, 127.6 (d, *J* = 0.7, 2C), 128.62 (2C), 129.2, 129.9 (2C), 132.6 (2C), 133.7, 140.9 (d, *J* = 5.6) and 165.4. ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −226.0 (dt, *J* = 18.4, 47.0). HRMS (ESI): 292.0744 (M+Na^+), (calcd 292.0744 [M+Na^+]).

4.7.8. (*S*)-2-Fluoro-1-(4-nitrophenyl)ethyl benzoate (*S*)-3h

White solid (12.5 mg, 43%), mp 81–82 °C, ee = 94%, $[\alpha]_D^{25} = -33.4$ (*c* 0.70, $CHCl_3$). CD (acetonitrile): $\Delta\varepsilon = -9.0$ (265 nm). ^1H NMR ($CDCl_3$) δ: 4.75 (ddd, *J* = 4.3, 10.1, 47.0, 1H), 4.78 (ddd, *J* = 5.6, 10.1, 47.0, 1H), 6.30 (ddd, *J* = 4.3, 5.6, 19.0, 1H), 7.47–7.52 (m, 2H), 7.60–7.66 (m, 3H), 8.11–8.14 (m, 2H), 8.24–8.28 (m, 2H). ^{13}C NMR ($CDCl_3$) δ: 73.6 (d, *J* = 20.5), 83.6 (d, *J* = 180.1), 124.0 (2C), 127.8 (d, *J* = 0.7, 2C), 128.7 (2C), 129.1, 129.9 (2C), 133.8, 142.8 (d, *J* = 5.3), 148.2 and 165.4. ^{19}F NMR ($CDCl_3$, C_6F_6) δ: −226.2 (dt, *J* = 19.5, 47.0). HRMS (ESI): 312.0642 (calcd 312.0643 [M+Na^+]).

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