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Enantioenriched 1-aryl-2-fluoroethylamines. Efficient lipase-catalysed resolution and limitations to the Mitsunobu inversion protocol

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ABSTRACT

Both enantiomers of eight 1-aryl-2-fluoroethylamines have been synthesised starting with 1-aryl-2-fluoroethanones. Kinetic resolution of the amines using lipase B from *Candida antarctica* with ethyl methoxyacetate as the acyl donor gave the (*R*)-amines in 96–99% ee and the (*S*)-methoxyacetamides in >99.5% ee. The resolution was robust with respect to variation in reaction temperature, acyl donor concentration, water activity and substrate structure. Nine other lipase preparations failed to catalyse the reaction or gave a low enantioselectivity. Secondly, a Mitsunobu inversion protocol starting with enantioenriched 1-aryl-2-fluoroethanols using phthalimide as nucleophile was employed in the synthesis of the (*S*)-1-aryl-2-fluoroethylamines. Both the inversion efficiency and yield depended on the aromatic substituents. For six of the substrates, clean inversion of the stereochemistry was observed. However, racemisation and low yields were the result when electron-donating substituents were present at the aromatic ring. When substituted with a cyano or a nitro group, an unexpected fluorine elimination occurred, limiting the yield for these transformations. The absolute configuration of the 1-aryl-2-fluoroethylamines was determined using circular dichroism.

1. Introduction

1-Arylethylamines are useful building blocks for the preparation of biological active compounds.[1–4] Introduction of fluorine atoms in the α-position of amines enables tuning of the basicity of the compounds in question.[5] This can be used to modify the binding properties, increase bioavailability, reduce toxicity or to increase metabolic stability of a drug candidate. Recently, 1-arylethylamines containing fluoroalkyl groups have emerged as a new class of building blocks for medicinal use.[6–8]

Although a vast amount of research have been devoted to the preparation of enantioenriched 1-arylethylamines, only a few routes to the monofluorinated derivatives are known. One method is based on the reductive amination of α-fluoroketones with enantiopure amines.[9] A stereoselective fluoromethylation of enantioenriched *N*-(*tert*-butanesulfinyl)imines[10] and cinchona-catalysed monofluorination of *N*-Boc α-amido sulfones have also been reported.[11]

Enzyme-catalysed resolution is a well-known method for synthesising enantiopure amines.[12–14] Hydrolases are able to catalyse the amidation of primary amines using activated esters as acyl donors. A number of 1-arylethylamines have been resolved, often with a high enantiomeric ratio (*E*-value).[15,16] In the case of fluorinated analogues, a few 2,2-difluoro- and 2,2,2-trifluoro-1-arylethylamines have been resolved by hydrolysis of the corresponding chloroacetamides using the *Pseudomonas fluorescens* lipase.[17,18] The use of hydrolases to resolve compounds containing a 1,2-fluoroamine moiety has not been documented.

Another common route to enantioenriched amines is by converting enantioenriched alcohols using the Mitsunobu inversion with phthalimide or azide as nucleophiles.[19] Although various types of fluorinated reactants have been used in the Mitsunobu coupling,[20–23] the conversion of 1,2-fluorohydrins to 1,2-fluoroamines has not been investigated.

With the aim of preparing enantiopure 1-aryl-2-fluoroethylamines, we have studied the lipase-catalysed resolution of 1-aryl-2-fluoroethylamines and the Mitsunobu inversion of 1-aryl-2-fluoroethanols.

2. Results and discussion

2.1. Lipase catalysed resolution

2.1.1. Preparation of racemic starting materials. The racemic amines **2a**–**h** were prepared from the corresponding α-fluoroacetophenones **1a**–**h**. The fluoroketones **1a**–**b** were synthesised by fluorination of the corresponding trimethylsilyl enol ethers using Selectfluor,[24]

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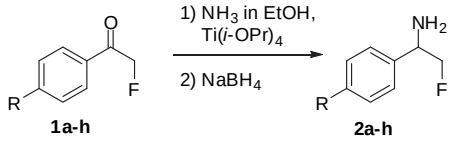
while **1c**–**h** were more conveniently prepared by a MW assisted fluorination of acetophenones.[25]

A reductive amination using ammonium acetate and $NaBH_3CN$, chosen for its simplicity, gave only mediocre conversion (33–44%). However, the use of ammonia in EtOH in the presence of titanium isopropoxide followed by sodium borohydride reduction,[26] was more successful and gave 68–92% yield (Scheme 1).



Scheme 1. Synthesis of **2a**–**h** from **1a**–**h**, R=OMe (**a**), OBn (**b**), H (**c**), F (**d**), Br (**e**), CF_3 (**f**), CN (**g**), NO_2 (**h**).

2.1.2. Lipase and solvent selection. Compared to their non-fluorinated counterparts, the amines **2a**–**h** have lower basicity and were expected to have altered reactivity. With the aim of identifying catalysts displaying a high activity and enantioselectivity towards these substrates, the use of 10 different lipase preparations was investigated. Being intermediate in both electronic character and size, 1-(4-bromophenyl)-2-fluoroethylamine (**2e**) was used as model substrate, and the reactions were performed in four different solvents. Ethyl methoxyacetate was used as acyl donor and the reactions were monitored for 72 h. Table 1 summarises the degree of conversion after 6 h.

Table 1
The conversion of **2e** to **3e** after kinetic resolution (6 h) catalysed by different enzymes in different solvents

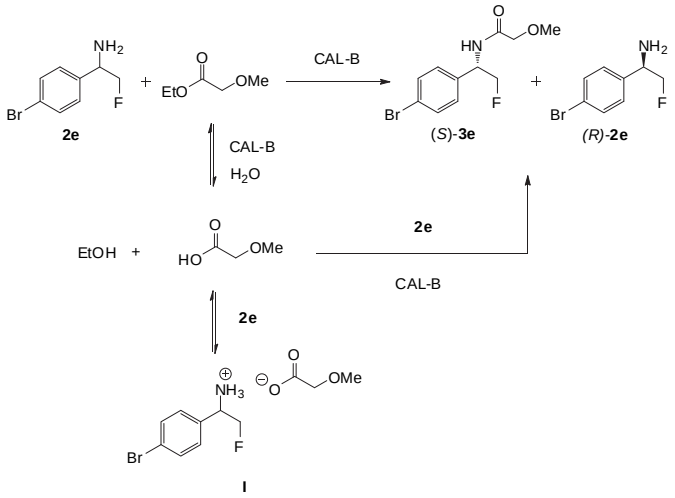
Enzyme	Conversion[b] (%)			
	THF	Toluene	Hexane	Dodecane
Seven lipase preparations[a]	0	0	0	0
Pseudomonas cepacia	2	0	0	0
Candida antarctica lipase A (Novozym 735)	0	8	14	16
Candida antarctica lipase B (Novozym 435)	23	39	50	50

[a] *Aspergillus niger*, *Aspergillus oryzae*, *Candida rugosa*, *Candida rugosa IM*, *Pseudomonas fluorescens*, *Rhizomucor miehei*, *Thermomyces lanuginosa*.
[b] The conversion was calculated by the formula conv.=ees/(eep+ees),[27] where ees and eep are the ee of the substrate and product, respectively.

Of the catalysts tested, only the two lipases from *Candida antarctica*, showed noticeable conversion within 72 h. The use of lipase B from *C. antarctica* (CAL-B) gave 50% conversion after 6 h in both hexane and dodecane, whereas 24 h were needed in THF and toluene. A high enantioselectivity ($E>200$) was experienced in all solvents. Using lipase A from *C. antarctica* as catalyst, a lower rate of reaction and a lower enantiomeric ratio ($E=4–5$) was observed. CAL-B was by far the best catalyst, and hexane was selected as solvent for further studies.

2.1.3. Reaction temperature, water activity and amount of acyl donor. The hydrolysis of ethyl methoxyacetate to produce methoxyacetic acid and ethanol was a side-reaction in the resolution. It was noticed that methoxyacetic acid and the amine **2e** formed the salt pair **I**, a process expected to reduce the reaction rate (see Scheme 2).

The reaction temperature, the concentration of acyl donor and the water activity were pinpointed as important parameters in the salt pair formation. Therefore, a two-level factorial design was performed with these three parameters as variables. The reaction temperature was varied from 20 to 60 °C, the amount of acyl donor from 1 to 3 equiv and the water activity (a_w) from ~0 to 0.33. The degree of conversion and enantioselectivity of the experiments are shown in Table 2.



Scheme 2. The enzymatic kinetic resolution and the equilibrium involving the acyl donor and water.

Table 2
Conversion and *E*-value after resolution of **2e** varying the reaction temperature, water activity and equivalents of acyl donor

Temp (°C)	a_w[a]	Equiv acyl donor	Conversion[b] (%)			*E*-value[c]
			1 h	2 h	6 h	
20	0.33	1	11	16	34	>200
20	0.33	3	13	21	42	>200
20	~0	1	14	22	37	>200
20	~0	3	19	27	42	>200
40	0.12	2	32	43	50	>200
40	0.12	2	34	45	50	>200
60	0.33	1	45	49	50	>200
60	0.33	3	43	43	49	>200
60	~0	1	44	49	50	>200
60	~0	3	41	47	49	>200

[a] Water activity (a_w) was fixed by equilibration in the presence of aqueous saturated salt solutions: $MgCl_2 \cdot 7H_2O$ (a_w=0.33), LiCl (a_w=0.12), dried over molecular sieves 4 Å (a_w=~0).
[b] The conversion was calculated by the formula conv.=ees/(eep+ees), where ees and eep are the ee of the substrate and product, respectively.[27]
[c] *E*-values were calculated by the method of Rakels et al. for irreversible reactions.[27]

Within the experimental constrains, the only statistically significant variable was found to be the reaction temperature (see Pareto chart in Fig. 1). A reaction temperature of 60 °C gave the highest rate, reaching 50% conversion in 2 h using 1 equiv of acyl donor. However, a temperature of 40 °C also offered acceptable

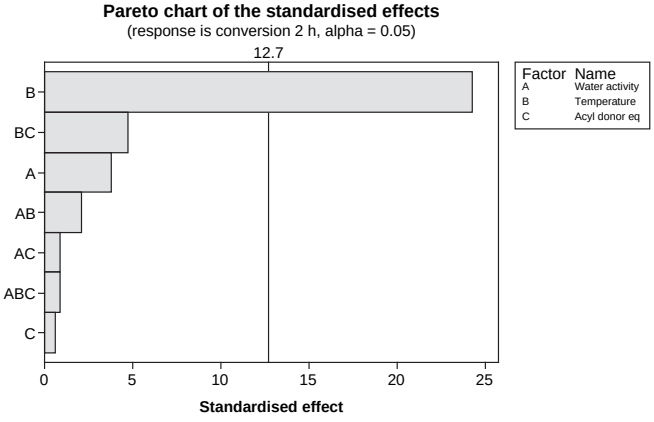


Figure 1. Pareto chart of the factorial design varying the amount of acyl donor, water activity and temperature.

reaction times at a_w=0.11 and 2 equiv of acyl donor. The enantiomeric ratio of the reactions was excellent under all conditions.

The amount of acyl donor was not a significant variable. However, at 20 °C the conversion increased when applying higher levels of acyl donor, whereas at 60 °C the highest conversion was obtained using 1 equiv of acyl donor. This observation could be accounted for by the rather complex equilibrium shown in Scheme 2. The reaction temperature is expected to have different effects on the relative rates for the amidation reaction, the non-productive hydrolysis of the acyl donor and the equilibrium between the free amine and the salt pair **I**.

The effect of changing the water activity was not significant. However, keeping a constant water activity was still considered to be important for the reproducibility of the resolutions.

It was further investigated if methoxyacetic acid could be used as acyl donor in the resolution of **2e**. Performing the resolution at 60 °C using 1 equiv of methoxyacetic acid, a 49% conversion was obtained after 6 h. This showed that the formation of **I** is reversible and that the resolution also can be performed under such conditions. Attempts to reduce the amount of acyl donor to 0.6 equiv led to an incomplete conversion after 6 h.

2.1.4. Effect of substrate structure on conversion and selectivity. Seven other 1-aryl-2-fluoroethylamines, **2a**–**d** and **2f**–**h** were then submitted to lipase-catalysed resolution using CAL-B and ethyl methoxyacetate (1 equiv) in hexane at 60 °C. The small-scale reactions of **2b**–**g** proceeded with rate comparable to that of the resolution of **1e** and with excellent enantioselectivity. A lower rate of reaction was observed for the resolution of **2a**, and the reaction stopped at 30% conversion. However, by adding fresh enzyme or diluting the reaction mixture the resolution could be driven to completion. Probably, some kind of reversible product or substrate inhibition occurs. The nitro-derivative **2h** had limited solubility in hexane and therefore reacted slowly. An increase in rate was observed when toluene was used as solvent.

Preparative kinetic resolutions were then performed on a 2.5 mmol scale. Based on results for the resolution of **2e**, a 16-fold more concentrated reaction mixture was used in the preparative resolutions. The ee of the product and substrate, conversions, enantiomeric ratio after 6 h and by completion are compiled in Table 3.

Table 3
CAL-B catalysed kinetic resolution of **2a**–**h** (2.5 mmol scale) at 60 °C using ethyl methoxyacetate (1 equiv) as acyl donor in hexane

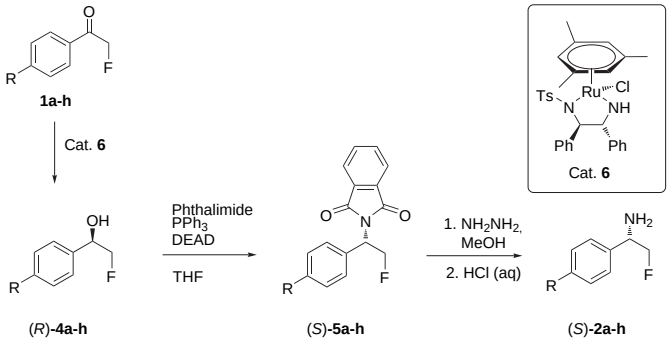
R	6 h			24 h		
	Conversion[c] (%)	**2** of ee (%)	**3** of ee (%)	Conversion[c] (%)	**2** of ee (%)	**3** of ee (%)
OMe (**a**)[a]	49.5	97.0	>99.5	49.5	97.0	>99.5
OBn (**b**)	48.0	92.5	>99.5	49.0	96.0	>99.5
H (**c**)	49.5	98.5	>99.5	50.0	>99.5	>99.5
F (**d**)	50.0	>99.5	>99.5	—	—	—
Br (**e**)	50.0	>99.5	>99.5	—	—	—
CF_3 (**f**)	50.0	>99.5	>99.5	—	—	—
CN (**g**)	47.0	87.0	>99.5	50.0	99.0	>99.5
NO_2 (**h**)[b]	—	—	—	50.0	>99.5	>99.5

[a] Hexane: 24 mL, CAL-B: 2 equiv wt.
[b] Toluene: 12 mL, CAL-B: 1 equiv wt , 48 h reaction time.
[c] The conversion was calculated by the formula conv.=ees/(eep+ees),[27] where ees and eep are the enantiomeric excess of the substrate and product, respectively.

The enantiomeric ratio was excellent in all cases (E>200) and the product (*S*)-amides **3a**–**h** could all be obtained in enantiomerically pure form. The kinetic resolution of **2d**–**f** gave full conversion and >99% ee of the amines within 6 h reaction time. The other substrates reacted slightly slower, thus, the amines **2a** and **2b** were after 24 h obtained in 97 and 96% ee, respectively. If the lower conversion is due to inhibition, low solubility of the amines or a displacement of the equilibrium towards the amine salt **I**, has not been further investigated. However, solvent tuning as demonstrated in the small-scale reaction of **2a** and **2h** is likely to bring conversion from 49 to 50% and thereby increasing the ee of the remaining substrate.

2.2. The Mitsunobu approach

The (*S*)-enantiomers of the fluoroamines **2a**–**h** were obtained from the ketones **1a**–**h** by asymmetric reduction followed by a Mitsunobu inversion protocol as depicted in Scheme 3.



Scheme 3. Synthesis of (*S*)-**2a**–**h** from **1a**–**h** using asymmetric transfer hydrogenation and Mitsunobu inversion.

2.2.1. Preparation of enantioenriched fluoroalcohols. Based on our previous findings,[28] the fluoroalcohols (*R*)-**4a**–**h** were synthesised from the corresponding α-fluoroacetophenones **1a**–**h** by asymmetric transfer hydrogenation catalysed by $[RuCl_2(mesitylene)]_2$ complexed with (1*S*,2*S*)-*N*-*p*-tosyl-1,2-diphenylethylenediamine ((*S*,*S*)-TsDPEN). The alcohols (*R*)-**4a**–**e** and (*R*)-**4g**–**h** were synthesised in a formic acid/triethylamine (5/2 mol ratio) medium, while (*R*)-**4f** was prepared using water with sodium formate as hydrogen donor. The yields and ee are summarised in Table 4. The reactions performed in formic acid/triethylamine gave the product alcohols in 61–91% yield and with good to excellent ee. However, in the reaction performed in water, the alcohol (*R*)-**3f** was isolated in a moderate 52% yield. The reason for this is somewhat unclear. ^{1}H NMR spectroscopy analysis of the distillation residue gave a spectrum with complex splitting pattern in the range of 4.2–5.3 ppm, indicating the presence of several structures containing alkyl fluoride fragments.

Table 4
Isolated yields and ee of the alcohols (*R*)-**4a**–**h**, *N*-substituted phthalimides (*S*)-**5a**–**h**, and fluoroamines (*S*)-**2a**–**h**

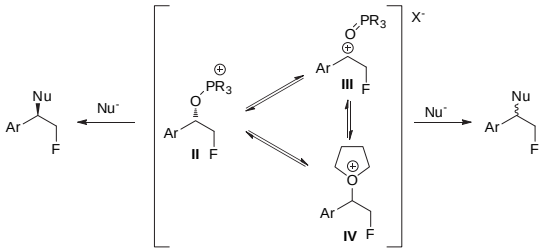
R	(*R*)-**4**		(*S*)-**5**		(*S*)-**2**	
	ee (%)	Yield (%)	ee (%)	Yield (%)	ee (%)	Yield (%)
OMe (**a**)	96.0	76	53.0	32	53.5	73
OBn (**b**)	99.5	61	60.0	37	60.0	72
H (**c**)	98.0	86	99.0	77	98.5	66
F (**d**)	93.0	79	92.5[a]	77	92.5	75
Br (**e**)	91.0	79	90.0	83	90.5	66
CF_3 (**f**)	92.5	52	92.0	78	91.5	71
CN (**g**)	87.0	85	87.5	66	87.5	75
NO_2 (**h**)	85.0	91	84.0	34	84.0	80

[a] Analysed as **2d**.

2.2.2. Mitsunobu inversion. The alcohols (*R*)-**4a**–**h** were then reacted with phthalimide in the presence of diethyl azodicarboxylate (DEAD) and triphenylphosphine to yield the corresponding *N*-substituted phthalimides (*S*)-**5a**–**h**. The isolated yields and the ee of the products are shown in Table 4.

The *N*-substituted phthalimides (*S*)-**5c**–**f** were isolated in 77–83% yield and with clean inversion of the stereochemistry. Somewhat disappointingly, the reactions leading to (*S*)-**5a**–**b**, were

plagued by racemisation and poor yields. Other alcohols have been shown to partly racemise under similar conditions.[29–33] The reactions have been found to proceed via the intermediate $ROPPh_3^+$ (**II**), which is attacked by a nucleophile in an S_N2 type mechanism (Scheme 4). However, when the substrate enables stabilisation of a developing positive charge, **II** can convert to **III** and **IV**.

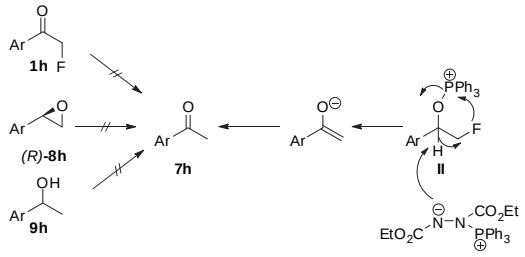


Scheme 4. Mechanistic rationale for the observed racemisation.[29]

These intermediates might react with nucleophiles via an S_N1 type mechanism to form a racemic product.[29,34] The low yields experienced indicated that other side products also might be formed via these pathways.

The alcohols (*R*)-**4g**–**h** reacted to (*S*)-**5g** and (*S*)-**5h** without racemisation, but in moderate and poor yields, respectively. The major by-product was the corresponding acetophenones **7g**–**h**. Further experiments performed on (*R*)-**4h** and racemic **4h** showed that **7h** was formed also in the absence of phthalimide. DEAD is able to oxidise alcohols to ketones,[35,36] but in this case a reaction using only DEAD failed to give **7h**. Thus, both DEAD and triphenylphosphine were required for the transformation. In an attempt to identify reaction intermediates, the reaction was run in THF-d_8 and continuously monitored by ^{1}H NMR spectroscopy. The reaction took place, but within the time scale of NMR no distinct intermediates could be detected. Having no indication of the possible mechanism, 2-fluoro-1-(4-nitrophenyl)ethanone (**1h**), (*R*)-2-(4-nitrophenyl)oxirane ((*R*)-**8h**) and 1-(4-nitrophenyl)ethanol (**9h**) were reacted with DEAD and triphenylphosphine to investigate if these compounds could be reaction intermediates. Compound **7h** was not observed in any of these experiments, excluding these possibilities.

Alcohols have been reported to undergo dehydrations, eliminations and rearrangement reactions under Mitsunobu conditions.[37–41] Phosphorus is known to have affinity for fluoride anions, and triphenylphosphine has been used as a defluorinating agent.[42,43] Based on this, and since no intermediates could be traced, we propose a concerted mechanism to **7g**–**h** via the known Mitsunobu intermediate **II** (Scheme 5). The nitro and the cyano group increase the acidity of the benzylic proton, possibly explaining why only **4g**–**h** reacted by this pathway in the presence of phthalimide.



Scheme 5. Possible explanation for the formation of the acetophenones **7g**–**h** in the Mitsunobu reaction.

To produce the target amines (*S*)-**2a**–**h**, (*S*)-**5a**–**h** were dissolved in methanol and reacted with hydrazine and hydrochloric acid. These hydrazinolysis reactions proceeded smoothly, giving the amines (*S*)-**2a**–**h** in good to moderate yields without altering the ee (Table 4).

2.3. Determination of the absolute configuration

Optical rotation data have previously only been reported for the hydrochloride salts of (*S*)-**2a** and (*S*)-**2c**.[10,11] These data were in agreement with our measurements.

The configuration of the previously unknown fluoroamines was strongly indicated by the stereoselectivity of the lipase-catalysed resolution and the Mitsunobu inversion. However, to unambiguously confirm this, the absolute configuration of the amines was determined by circular dichroism spectroscopy (CD) of the *N*-substituted phthalimides (*S*)-**5a**–**h** using the exciton chirality method.[44–46] The most stable conformation of the *N*-substituted phthalimides was predicted using semiempirical AM1 calculations. All the compounds showed the same preferred conformation, with the hydrogen attached to the stereogenic centre arranged in the same plane as the disubstituted phenyl ring (see Fig. 2A).

For (*S*)-**5a**–**h** an anticlockwise rotation of the disubstituted phenyl ring brings it onto the phthalimide dipole, thus a negative first Cotton effect was predicted. This was confirmed by CD measurements, exemplified by the CD spectrum of (*S*)-**5f** in Figure 2B. All the CD measurements are summarised in Table 5.

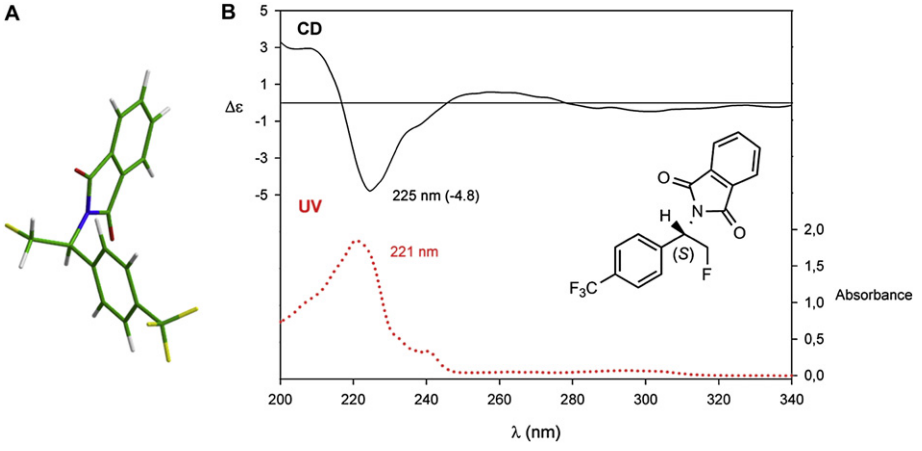


Figure 2. Favoured conformation (A) and CD and UV spectrum of (*S*)-**5f** (B).

Table 5
Enantiomeric excess, molar extinction (Δe) and absorption maximum for the first Cotton effect (λ) for (*S*)-**5a**–**h**

Compound	R	ee (%)	Δe	λ (nm)
(*S*)-**5a**	OMe	53.0	−1.3	232
(*S*)-**5b**	OBn	60.0	−3.8	234
(*S*)-**5c**	H	99.0	−3.5	223
(*S*)-**5d**	F	92.5[a]	−1.6	223
(*S*)-**5e**	Br	90.0	−3.9	230
(*S*)-**5f**	CF_3	92.0	−4.8	225
(*S*)-**5g**	CN	87.5	−2.7	237
(*S*)-**5h**	NO_2	84.0	−1.4	228

[a] Analysed as **2d**.

3. Conclusions

Starting with α-fluoroacetophenones, a lipase-catalysed resolution and a Mitsonobu inversion have been investigated for the preparation of enantioenriched 1-aryl-2-fluoroethylamines.

Using CAL-B as catalyst and ethyl methoxyacetate as acyl donor, the resolutions proceeded with high enantioselectivity and provided the product (*R*)-amines and (*S*)-amides in 96–99% and >99.5% ee, respectively. The method proved to be fairly robust with respect to the amount of acyl donor, water activity and the reaction temperature. One of the substrates (**2h**) had to be resolved in toluene due to limited solubility in hexane.

The Mitsunobu protocol gave clean inversion of the stereochemistry of the alcohols (*R*)-**4c**–**f**. The amines (*S*)-**2c**–**f** could be isolated in 90.5–98.5% ee. In the case of substrates containing electron-donating substituents, racemisation occurred. The yield decreased when both electron donating and strongly electron withdrawing substituents were present. For the latter substrates, a fluorine elimination was identified as the major side reaction.

The drawback of a kinetic resolution is the limitation of a maximum 50% yield. Therefore, despite the fact that the enzymatic resolution approach is one step shorter, the overall yields of the two routes were comparable in the case of **2c**–**g**. However, the resolution method appears more attractive since it gives the products in higher ee and involves only two simple steps from the ketone without the use of hazardous chemicals.

4. Experimental

4.1. Chemicals and equipment

The α-fluoroacetophenones, **1a**–**h**,[24,25] and $[RuCl_2(mesitylene)]_2$,[47,48] were prepared as described previously. (*R*)-2-(4-Nitrophenyl)oxirane, (*S*,*S*)-TsDPEN and phthalimide were from Aldrich. 1-(4-Nitrophenyl)ethanone, 4-acetylbenzonitrile, DEAD (40% solution in toluene) and Silica 60 were from Fluka. Triphenylphosphine was from Sigma–Aldrich.

C. antarctica lipase B (Novozym 435), *C. antarctica* lipase A (Novozym 735) and *Rhizomucor miehei* lipase (Lipozyme RM-IM) were kind gifts from Novozymes. *Pseudomonas cepacia*, *Aspergillus niger*, *Aspergillus oryzae*, *Candida rugosa*, *C. rugosa IM*, *Thermomyces lanuginosa*, *P. fluorescens* were from Aldrich. The enzymatic resolutions were performed in an Infors-HT Minitron type AY70 incubator.

4.2. Analyses

^1H and ^{13}C NMR spectra were recorded with Bruker Avance 400 spectrometer operating at 400 MHz and 100 MHz, respectively. ^{19}F NMR was performed on a Bruker Avance 500 operating at 470 MHz. For ^1H and ^{13}C NMR chemical shifts are in parts per million rel to TMS, while for ^{19}F NMR the shift values are relative to hexafluorobenzene. Coupling constants are in hertz. HPLC was performed using an Agilent 1100 series system with a DAD detector. GC was performed using a Varian 3380. Accurate mass determination (ESI) was performed on an Agilent G1969 TOF MS instrument equipped with a dual electrospray ion source. Samples were injected into the MS using an Agilent 1100 series HPLC and analysis was performed as a direct injection analysis without any chromatography. FTIR spectra were recorded on a Thermo Nicolet Avatar 330 infrared spectrophotometer. All melting points are uncorrected and measured by a Büchi melting point instrument. CD spectra were recorded on an OLIS DSM 1000 spectrophotometer in a 1 cm cell, at concentration 0.01 mg/mL in MeCN.

The ee of the amines **2a**–**h** was determined as follows: compounds **2b** and **2h** were analysed as their trifluoroacetamides by HPLC using a Daicel Chiralcel OD-H column with detection at 230 nm. Compound **2b** (trifluoroacetamide): hexane/2-propanol (85/15), flow rate 1.0 mL/min, (*S*)-**2b**: 9.2 min, (*R*)-**2a**: 13.0 min. Compound **2h** (trifluoroacetamide): hexane/2-propanol (90/10), flow rate 1.0 mL/min, (*S*)-**2h**: 12.4 min, (*R*)-**2a**: 16.8 min. Compounds **2a** and **2c**–**g** were analysed derivatised as their acetamides on GC using a CP-Chirasil-Dex CB column at 10 psi. Isothermal programs were used in each case. Compounds **2a** and **2g**: 160 °C, (*R*)-**2a**: 21.1 min, (*S*)-**2a**: 21.8 min, (*R*)-**2g**: 41.0 min, (*S*)-**2g**: 42.1 min, **2c**: 125 °C, (*R*)-**2c**: 26.5 min, (*S*)-**2c**: 28.9 min, **2d**: 135 °C, (*R*)-**2d**: 19.6 min, (*S*)-**2d**: 21.3 min, **2e**: 150 °C, (*R*)-**2e**: 38.5 min, (*S*)-**2e**: 40.9 min, **2f**: 140 °C, (*R*)-**2f**: 16.5 min, (*S*)-**2f**: 18.2 min.

The ee of the methoxyacetamides **3a**–**h** was determined as follows: compounds **3a** and **3c**–**f** were analysed on GC using a CP-Chirasil-Dex CB column at 10 psi. Isothermal programs were used in each case. Compound **3a**: 160 °C, (*R*)-**3a**: 24.8 min, (*S*)-**3a**: 25.8 min, **3c**: 125 °C, (*R*)-**3c**: 38.0 min, (*S*)-**3c**: 40.0 min, **3d**: 135 °C, (*R*)-**3d**: 26.0 min, (*S*)-**3d**: 27.1 min, **3e**: 150 °C, (*R*)-**3e**: 49.0 min, (*S*)-**3e**: 51.5 min, **3f**: 140 °C, (*R*)-**3f**: 19.5 min, (*S*)-**3f**: 20.9 min. Compound **3b** was analysed by HPLC using a Daicel Chiralcel OD-H column, eluting with hexane/2-propanol (90/10), flow rate 1.0 mL/min, detection at 230 nm: (*S*)-**3b**: 31.7 min, (*R*)-**3b**: 38.5 min. Compounds **3g**–**h**: analysed by an Astec Chirobiotic V2 column, 5 μm, 4.6×250 mm (Supelco, Pennsylvania, USA) for **3g** eluting with hexane/EtOH (concn 0.5% TFA), 91/9, flow rate: 1.0 mL/min, detection at 230 nm, (*S*)-**3g**: 47.7 min, (*R*)-**3g**: 49.2 min and for **3h** eluting with hexane/EtOH (concn 0.5% TFA), 98/2, flow rate: 3.0 mL/min, detection at 230 nm, (*R*)-**3g**: 50.1 min and (*S*)-**3h**: 53.8 min.

The ee of the alcohols (*S*)-**4a**–**h** was determined by HPLC analysis using a Daicel Chiralcel OD column (0.46 cm×25 cm) with mobile phase: hexane/2-propanol (98/2) at a flow rate of 1.0 mL/min.[49]

The ee of **5a**–**c** and **5e**–**h** was determined by HPLC using a Daicel Chiralcel OD-H column with detection at 270 nm. Compounds **5a**, **5e** and **5f**: eluent: hexane/2-propanol (90/10), flow rate 1.0 mL/min, (*S*)-**5a**: 11.2 min, (*R*)-**5a**: 12.6 min, (*R*)-**5e**: 8.9 min, (*S*)-**5e**: 10.1 min, (*R*)-**5f**: 7.5 min, (*S*)-**5f**: 8.1 min. Compound **5b**: eluent: hexane/2-propanol (99/1), flow rate: 1.0 mL/min, (*S*)-**5b**: 33.5 min, (*R*)-**5b**: 36.2 min. Compound **5c**: eluent: hexane/2-propanol (98/2), flow rate 1.0 mL/min, (*R*)-**5c**: 11.3 min, (*S*)-**5c**: 14.0 min. Compound **5g**: eluent: hexane/2-propanol (90/10), flow rate 1.2 mL/min, (*R*)-**5g**: 22.7 min, (*S*)-**5g**: 26.5 min. Compound **5h**: eluent: hexane/isopropanol (95/5), flow rate 1.0 mL/min, (*R*)-**5h**: 26.9 min, (*S*)-**5h**: 29.8 min.

4.3. General procedures

*4.3.1. Preparation of **2a**–**h**.* The following procedure is representative:

1-(4-Bromophenyl)-2-fluoroethanone (**1e**) (4.36 g, 20.1 mmol) and titanium isopropoxide (12.0 mL, ~40.0 mmol) were dissolved in an ethanol/ammonia solution (2 M, 50 mL) and stirred under argon atmosphere at room temperature for 24 h. Upon full conversion as detected by ^1H NMR spectroscopy, $NaBH_4$ (1.13 g, 30.30 mmol) was

added, and the reaction mixture was stirred under argon atmosphere at room temperature for 24 h. The reaction mixture was made acidic (pH=2) using HCl (6 M), and washed with *tert*-butyl methyl ether (TBME) (3×20 mL). The mixture was made alkaline with NaOH pellets (pH=10), saturated with sodium chloride and extracted with TBME (5×30 mL). The organic phase was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure. Purification using silica-gel column chromatography (EtOAc/MeOH, 4/1, R_f 0.45), gave 3.11 g (14.3 mmol, 71%) of a colourless oil.

4.3.2. Small-scale enzymatic resolution. The racemic 1-aryl-2-fluoroethylamines, **2a**–**h**, (0.04 mmol), ethyl methoxyacetate (1–4 mol equiv) and Novozym 435 (1 equiv wt) were mixed in the specified solvent (3 mL) and agitated in an incubator at 300 rpm at the specified temperature. Samples (150 μL) were withdrawn after 1, 2 and 6 h. The samples were analysed for ee of the product and remaining substrate. The water content of hexane was varied by equilibrating on the presence of saturated salt solutions: $MgCl_2 \cdot 7H_2O$ (a_w=0.33), LiCl (a_w=0.12) and dried over molecular sieves 4 Å (a_w= ~0).[50]

4.3.3. Preparative scale enzymatic resolution. The racemic amines **2b**–**g** (2.5 mmol), ethyl methoxyacetate (295 mg, 2.5 mmol) and Novozym 435 (1 equiv wt) were diluted with dry hexane (12 mL) and stirred in an incubator at 300 rpm at 60 °C. When 50% conversion was reached, the reaction mixture was diluted with TBME (20 mL) and extracted with water containing acetic acid (1 M, 5×15 mL). The combined water phases were washed with TBME (2×15 mL). The organic phase was dried over Na_2SO_4, and the solvent evaporated under reduced pressure, yielding the methoxyacetamides (*S*)-**3b**–**g**, which were purified by silica-gel column chromatography (EtOAc/MeOH, 4/1). The water phase was made alkaline with NaOH (pellets), saturated with sodium chloride and extracted with TBME (5×15 mL). The organic phase was dried over Na_2SO_4, and the solvent was evaporated under reduced pressure, yielding the amines (*R*)-**2b**–**g**, which were purified by silica-gel column chromatography (EtOAc/MeOH, 4/1).

*4.3.4. Asymmetric transfer hydrogenation[28] of **1a**–**e** and **1g**–**h**.* A suspension of the $[RuCl_2(mesitylene)]_2$ (23 mg, 0.04 mmol) and (*S*,*S*)-TsDPEN (44 mg, 0.12 mmol) in CH_2Cl_2 (8 mL) were stirred at 20 °C for 30 min. After removal of CH_2Cl_2, the α-fluoroacetophenone (4.0 mmol) in a mixture of HCO_2H/Et_3N (5/2 mol ratio, 10 mL) was added. The reaction mixture was stirred vigorously at 40 °C for the specified number of hours before it was quenched with water (10 mL) and extracted with CH_2Cl_2 (3×15 mL). The organic phase was then washed with brine (20 mL) and dried over Na_2SO_4 before the solvent was removed under reduced pressure. Purification is described for each individual compound.

*4.3.5. Mitsunobu inversion (S)-**5a**–**h** from (R)-**4a**–**h**.* Under an N_2-atmosphere PPh_3 (859 mg, 3.3 mmol) and phthalimide (487 mg, 3.3 mmol) were dissolved in THF (20 mL). To this mixture was added the 1-aryl-2-fluoroethanol, (*R*)-**4a**–**h**, (3.0 mmol) dissolved in THF (5 mL), followed by the DEAD solution (40% in toluene, 1.36 mL, 3.6 mmol). The mixture was stirred overnight at room temperature, before the solvent was removed under reduced pressure. The reaction mixture was then re-dissolved in CH_2Cl_2 (2 mL), K_2CO_3 (0.02 M, 10 mL) added and the mixture stirred for 1 h. The mixture was extracted with CH_2Cl_2 (3×15 mL) and the organic phase washed with brine (20 mL) and dried over $MgSO_4$. The solvent was removed under reduced pressure and the crude product was purified by silica-gel column chromatography.

*4.3.6. Hydrazinolysis of (S)-**5a**–**h**.* The *N*-substituted phthalimides **5a**–**h** (2.5 mmol) were dissolved in MeOH (40 mL) and N_2H_4 (1.0 M in THF, 25 mmol) was added. The mixture was stirred at room temperature until all the starting material had been consumed (TLC) (2–10 h.). Then HCl (2 M, 10 mL) was added and the reaction was stirred at room temperature overnight. Water (40 mL) was added and the mixture extracted with Et_2O (50 mL). The water phase was made alkaline with NaOH (2 M, 30 mL) and extracted with Et_2O (3×50 mL). The combined organic phases were washed with brine (30 mL), dried over $MgSO_4$ and evaporated under reduced pressure. The products, (*S*)-**1a**–**h** were purified by silica-gel column chromatography (EtOAc/MeOH, 9/1).

4.4. Racemic 1-aryl-2-fluoroethylamines (2a–h)

*4.4.1. 2-Fluoro-1-(4-methoxyphenyl)ethylamine (**2a**).* The synthesis was performed as described for **2e** (Section 4.3.1) starting with 2-fluoro-1-(4-methoxyphenyl)ethanone (**1a**) (2.18 g 12.94 mmol). This gave 1.96 g (11.58 mmol, 89%) of a colourless oil. R_f (EtOAc/MeOH, 4/1) 0.47. ^{1}H NMR ($CDCl_3$) δ: 1.70 (s, 2H, $-NH_2$), 3.80 (s, 3H, $-OCH_3$), 4.22–4.53 (m, 3H, $-CHCH_2F$), 6.89 (m, 2H, $-C_6H_4-$), 7.30 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 55.0 (d, *J*=19.4), 55.6, 88.3 (d, *J*=174.5), 114.1 (2C), 128.0 (2C), 132.2 (d, *J*=8.5), 159.2. ^{19}F NMR ($CDCl_3$) δ: −219.15 (m). IR (neat, cm^{-1}): 3381, 3315, 2954, 2904, 2838, 1611, 1513, 1463, 1249, 1179, 1032, 995, 833. HRMS (ESI): 169.0907 (calcd 169.0903, [M+]).

*4.4.2. 1-(4-(Benzyloxy)phenyl)-2-fluoroethylamine (**2b**).* The synthesis was performed as described for **2e** (Section 4.3.1) starting with 1-(4-benzyloxyphenyl)-2-fluoroethanone (**1b**) (0.76 g, 3.10 mmol). This gave 0.64 g (2.61 mmol, 84%) of a white solid, mp 42–43 °C, R_f (EtOAc/MeOH, 4/1) 0.45. ^{1}H NMR ($CDCl_3$) δ: 1.68 (s, 2H, $-NH_2$), 4.22–4.54 (m, 3H, $-CHCH_2F$), 5.07 (s, 2H, CH_2Ph), 6.97 (m, 2H, $-C_6H_4-$), 7.29 (m, 2H, $-C_6H_4-$), 7.30–7.34 (m, 5H, $-C_6H_5$). ^{13}C NMR ($CDCl_3$) δ: 55.0 (d, *J*=19.0), 70.0, 88.3 (d, *J*=174.5), 115.0 (2C), 127.0, 127.4 (2C), 128.0 (2C), 128.5 (2C), 132.5 (d, *J*=8.5), 136.9, 158.5. ^{19}F NMR ($CDCl_3$) δ: −219.20 (m). IR (KBr, cm^{-1}): 3381, 3279, 3033, 2947, 2872, 1611, 1513, 1242, 1174, 1014, 839, 745, 697. HRMS (ESI): 245.1215 (calcd 245.1216, [M^+]).

*4.4.3. 2-Fluoro-1-phenylethylamine (**2c**).* The synthesis was performed as described for **2e** (Section 4.3.1) starting with 2-fluoro-1-phenylethanone (**1c**) (0.49 g, 3.55 mmol). This gave 0.46 g (3.28 mmol, 92%) of a colourless oil, R_f (EtOAc/MeOH, 4/1) 0.46. ^{1}H NMR ($CDCl_3$) δ: 1.72 (s, 2H, $-NH_2$), 4.28–4.57 (m, 3H, $-CHCH_2F$), 7.23 (m, 2H, Ph), 7.37 (m, 2H, Ph), 7.36 (m, 1H, Ph). ^{13}C NMR ($CDCl_3$) δ: 55.6 (d, *J*=19.4), 88.2 (d, *J*=174.1), 126.9 (2C), 127.9, 128.6 (2C), 140.2 (d, *J*=8.1). ^{19}F NMR ($CDCl_3$) δ: −219.85 (m). IR (neat, cm^{-1}): 3384, 3314, 3063, 3030, 2950, 2890, 1604, 1493, 1454, 997, 861, 760, 701. HRMS (ESI): 139.0799 (calcd 139.0797, [M^+]).

*4.4.4. 2-Fluoro-1-(4-fluorophenyl)ethylamine (**2d**).* The synthesis was performed as described for **2e** (Section 4.3.1) starting with 2-fluoro-1-(4-fluorophenyl)ethanone (**1d**) (0.41 g, 2.61 mmol). This gave 0.39 g (2.48 mmol, 95%) of a colourless oil. R_f (EtOAc/MeOH, 4/1) 0.46. ^{1}H NMR ($CDCl_3$) δ: 1.68 (s, 2H, $-NH_2$), 4.25–4.50 (m, 3H, $-CHCH_2F$), 7.04 (m, 2H, $-C_6H_4-$), 7.35 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 55.0 (d, *J*=19.4), 88.0 (dd, *J*=174.5, 1.4), 115.4 (d, *J*=21.2, 2C), 128.5 (dd, *J*=8.1, 0.7, 2C), 135.9 (dd, *J*=8.1, 2.8), 162.3 (d, *J*=246.2). ^{19}F NMR ($CDCl_3$) δ: −115.14 (m), −219.87 (m.). IR (neat, cm^{-1}): 3388, 3321, 3044, 2952, 2891, 1734, 1605, 1510, 1229, 1158, 1093, 1003, 846. HRMS (ESI): 157.0706 (calcd 157.0703, [M^+]).

*4.4.5. 1-(4-Bromophenyl)-2-fluoroethylamine (**2e**).* The synthesis is described in Section 4.3.1. ^{1}H NMR ($CDCl_3$) δ: 1.68 (s, 2H, $-NH_2$), 4.22–4.52 (m, 3H, −CHCH2F), 7.27 (m, 2H, $-C_6H_4-$), 7.47 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 55.1 (d, *J*=19.8), 87.8 (d, *J*=174.5), 121.7, 128.6 (d, *J*=0.7, 2C), 131.7 (2C), 139.3 (d, *J*=7.8). ^{19}F NMR

($CDCl_3$) δ: −220.34 (m). IR (neat, cm^{-1}): 3383, 3330, 2950, 2890, 1590, 1488, 1406, 1073, 1004, 830. HRMS (ESI): 216.9904 (calcd 216.9902, [(^{79}Br)M^+]).

*4.4.6. 2-Fluoro-1-(4-(trifluoromethyl)phenyl)ethylamine (**2f**).* The synthesis was performed as described for **2e** (Section 4.3.1) starting with 2-fluoro-1-(4-(trifluoromethyl)phenyl)ethanone (**1f**) (0.91 g, 4.40 mmol). This gave 0.62 g (2.99 mmol, 68%) of a colourless oil, R_f (EtOAc/MeOH, 4/1) 0.49. ^{1}H NMR ($CDCl_3$) δ: 1.71 (s, 2H, −NH_2), 4.27–4.56 (m, 3H, −CHCH_2F), 7.52 (m, 2H, −C$_6H_4$−), 7.57 (m, 2H, −C$_6H_4$−). ^{13}C NMR ($CDCl_3$) δ: 55.4 (d, J=19.8), 87.7 (d, J=175.2), 124.0 (q, J=272.0), 125.5 (q, J=3.8, 2C), 127.3 (d, J=0.7, 2C), 130.1 (q, J=32.5), 144.4 (dq, J=7.6, 1.3). ^{19}F NMR ($CDCl_3$) δ: −63.18 (s, 3F), −221.06 (m). IR (neat, cm^{-1}): 3392, 3330, 2954, 2895, 1621, 1420, 1326, 1160, 1120, 1068, 1017, 842, 606. HRMS (ESI): 207.0668 (calcd 207.0671, [M^+]).

*4.4.7. 4-(1-Amino-2-fluoroethyl)benzonitrile (**2g**).* The synthesis was performed as described for **2e** (Section 4.3.1) starting with 1-(4-cyanophenyl)-2-fluoroethanone (**1g**) (1.03 g, 6.34 mmol). This gave 0.84 g (5.13 mmol, 81%) of a white solid, mp 48–49 °C, R_f (EtOAc/MeOH, 4/1) 0.42. ^{1}H NMR ($CDCl_3$) δ: 1.70 (s, 2H, −NH_2), 4.27–4.55 (m, 3H, −CHCH_2F), 7.53 (m, 2H, −C$_6H_4$−), 7.65 (m, 2H, −C$_6H_4$−). ^{13}C NMR ($CDCl_3$) δ: 55.4 (d, J=19.8), 87.3 (d, J=175.6), 111.8, 118.6, 127.8 (d, J=0.7, 2C), 132.4 (2C), 145.8 (d, J=7.0). ^{19}F NMR ($CDCl_3$) δ: −221.61 (m). IR (KBr, cm^{-1}): 3381, 3317, 2954, 2863, 2227, 1609, 1502, 1412, 1359, 1099, 1050, 992, 832, 564. HRMS (ESI): 164.0750 (calcd 164.0750, [M^+]).

*4.4.8. 2-Fluoro-1-(4-nitrophenyl)ethylamine (**2h**).* The synthesis was performed as described for **2e** (Section 4.3.1) starting with 2-fluoro-1-(4-nitrophenyl)ethanone (**1h**) (1.15 g, 6.26 mmol). This gave 0.91 g (4.95 mmol, 79%) of a white solid, mp 52–53 °C, R_f (EtOAc/MeOH, 4/1) 0.40. ^{1}H NMR ($CDCl_3$) δ: 1.72 (br s, 2H, −NH_2), 4.28–4.60 (m, 3H, CHCH_2F), 7.58–7.62 (m, 2H, −C$_6H_4$−), 8.21–8.24 (m, 2H, −C$_6H_4$−). ^{13}C NMR ($CDCl_3$) δ: 55.3 (d, J=20.1), 87.3 (d, J=175.6), 123.8 (2C), 128.0 (d, J=0.7, 2C), 147.7, 147.8, (d, J=7.1). ^{19}F NMR ($CDCl_3$) δ: −221.78 (m). IR (neat, cm^{-1}): 3379, 3113, 2952, 2852, 1599, 1510, 1346, 995, 855. HRMS (ESI): 185.0726 (calcd 185.0726, [M+H^+]).

4.5. (*R*)-1-Aryl-2-fluoroethylamines ((*R*)-2a–g)

Compounds (*R*)-**2a**–**h** were obtained by lipase-catalysed resolution as described in Section 4.3.3. The NMR spectroscopic properties corresponded with that reported for the corresponding racemates.

*4.5.1. (R)-2-Fluoro-1-(4-methoxyphenyl)ethylamine ((R)-**2a**).* The resolution was performed as described in Section 4.3.3, starting with **2a** (423 mg, 2.50 mmol), but with hexane (24 mL) and Novozym 435 (846 mg). Reaction time was 24 h. This gave after silica-gel column chromatography 180 mg (1.06 mmol, 43%) of (*R*)-**2a** as a colourless oil, ee=97.0%, $[\alpha]_D^{20}$ −37.4 (*c* 0.55, $CHCl_3$).

*4.5.2. (R)-1-(4-(Benzyloxy)phenyl)-2-fluoroethylamine ((S)-**2b**).* The resolution was performed as described in Section 4.3.3, starting with **2b** (613 mg, 2.50 mmol). Reaction time was 24 h. This gave after silica-gel column chromatography 211 mg (0.86 mmol, 34%) of (*R*)-**2b** as a white solid, mp 41.5–42 °C, ee=96.0%, $[\alpha]_D^{20}$ −29.1 (*c* 0.50, $CHCl_3$).

*4.5.3. (R)-2-Fluoro-1-phenylethylamine ((R)-**2c**)*[7]. The resolution was performed as described in Section 4.3.3, starting with **2c** (348 mg, 2.50 mmol). Reaction time was 24 h. This gave after silica-gel column chromatography 126 mg (0.91 mmol, 36%) of (*R*)-**2c** as colourless oil, ee >99.5%, $[\alpha]_D^{20}$ −40.5 (*c* 0.60, $CHCl_3$).

*4.5.4. (R)-Fluoro-1-(4-fluorophenyl)ethylamine ((R)-**2d**).* The resolution was performed as described in Section 4.3.3, starting with **2d** (393 mg, 2.49 mmol). Reaction time was 6 h. This gave after silica-gel column chromatography 169 mg (1.08 mmol, 43%) of (*R*)-**2d** as a colourless oil, ee >99.5%, $[\alpha]_D^{20}$ −39.7 (*c* 0.71, $CHCl_3$).

*4.5.5. (R)-1-(4-Bromophenyl)-2-fluoroethylamine ((R)-**2e**).* The resolution was performed as described in Section 4.3.3, starting with **2e** (545 mg, 2.50 mmol). Reaction time was 6 h. This gave after silica-gel column chromatography 213 mg (0.98 mmol, 39%) of (*R*)-**2e** as a colourless oil, ee >99.5%, $[\alpha]_D^{20}$ −28.5 (*c* 0.68, $CHCl_3$).

*4.5.6. (R)-2-Fluoro-1-(4-(trifluoromethyl)phenyl)ethylamine ((R)-**2f**).* The resolution was performed as described in Section 4.3.3, starting with **2f** (518 mg, 2.50 mmol). Reaction time was 6 h. This gave after silica-gel column chromatography 195 mg (0.94 mmol, 38%) of (*R*)-**2f** as a colourless oil, ee >99.5%, $[\alpha]_D^{20}$ −27.4 (*c* 0.61, $CHCl_3$).

*4.5.7. (R)-4-(1-Amino-2-fluoroethyl)benzonitrile ((R)-**2g**).* The resolution was performed as described in Section 4.3.3, starting with **2g** (411 mg, 2.50 mmol). Reaction time was 24 h. This gave after silica-gel column chromatography 150 mg (0.91 mmol, 37%) of (*R*)-**2g** as a white solid, mp 46.5–47.0 °C, ee=99.0%, $[\alpha]_D^{20}$ −32.0 (*c* 0.56, $CHCl_3$).

*4.5.8. (R)-2-Fluoro-1-(4-nitrophenyl)ethylamine ((R)-**2h**).* The resolution was performed as described in Section 4.3.3, starting with **2h** (460 mg, 2.50 mmol), but with toluene (12 mL) as solvent. Reaction time was 48 h. This gave after silica-gel column chromatography 200 mg (1.09 mmol, 43%) of (*R*)-**2h** as a pale yellow solid, mp 53.0–53.5 °C, ee >99.5%, $[\alpha]_D^{20}$ −20.1 (*c* 0.71, $CHCl_3$).

4.6. (*S*)-1-Aryl-2-fluoroethylamines ((*S*)-2a–h)

Compounds (*S*)-**2a**–**h** were obtained from the alcohols (*R*)-**4a**–**h** by the Mitsunobu inversion described in Sections 4.3.4–4.3.6. The NMR spectroscopic properties corresponded with that reported for the corresponding racemate.

*4.6.1. (S)-2-Fluoro-1-(4-methoxyphenyl)ethylamine ((S)-**2a**)*[10]. The hydrazinolysis was performed as described in Section 4.3.6 starting with (*S*)-**5a** (200 mg, 0.67 mmol). This gave 83 mg (0.49 mmol, 73%) of (*S*)-**2a** as a pale yellow oil, ee=53.5%, $[\alpha]_D^{20}$ +20.9 (*c* 0.54, $CHCl_3$), R_f (EtOAc/MeOH, 9/1) 0.37.

The hydrochloride salt of (*S*)-**2a** was obtained by treatment with HCl saturated ether (5 mL) under stirring for 20 min. The solvent was then evaporated under reduced pressure and the product isolated as a white powder, which decomposed on melting. The ^{1}H NMR data corresponded with that reported.[10] ^{1}H NMR (CD_3OD) δ: 3.82 (s, 3H, −OCH_3), 4.59–4.69 (m, 2H, −CH_2F), 4.81–8.83 (m, 1H, −CHCH$_2$F), 7.00–7.05 (m, 2H, −C$_6H_4$−), 7.38–7.43 (m, 2H, −C$_6H_4$−). $[\alpha]_D^{20}$ +17.7 (*c* 0.66, MeOH), lit.[10] +31.5 (*c* 0.66, MeOH).

*4.6.2. (S)-1-(4-(Benzyloxy)phenyl)-2-fluoroethylamine ((S)-**2b**).* The hydrazinolysis was performed as described in Section 4.3.6 starting with (*S*)-**5b** (205 mg, 0.55 mmol). This gave 97 mg (0.40 mmol, 72%) of (*S*)-**2b** as a white solid, mp 42–43 °C, ee=60.0%, $[\alpha]_D^{20}$ +16.0 (*c* 0.52, $CHCl_3$), R_f (EtOAc/MeOH, 9/1) 0.40.

*4.6.3. (S)-2-Fluoro-1-phenylethylamine ((S)-**2c**)*[9–11]. The hydrazinolysis was performed as described in Section 4.3.6 starting with (*S*)-**5c** (672 mg, 2.50 mmol). This gave 228 mg (1.64 mmol, 66%) of

(*S*)-**2c** as a colourless oil, ee=98.5%, $[\alpha]_D^{20}$ +44.0 (*c* 0.60, $CHCl_3$), R_f (EtOAc/MeOH, 9/1) 0.40.

The hydrochloride salt of (*S*)-**2c** was obtained by treatment with HCl saturated ether (5 mL) under stirring for 20 min. The solvent was then evaporated under reduced pressure and the product isolated as a white powder, which decomposed on melting. The ^1H NMR data corresponded with that reported.[10] ^1H NMR (CD_3OD) δ: 4,67–4.76 (m, 2H, $-CH_2F$), 4.84 (m, 1H, $-CHCH_2F$), 7.48–7.51 (m, 5H, Ph). $[\alpha]_D^{20}$ +29.4 (*c* 0.53, MeOH), lit.[10] +29.1 (*c* 0.57, MeOH).

*4.6.4. (S)-2-Fluoro-1-(4-fluorophenyl)ethylamine ((S)-**2d**).* The hydrazinolysis was performed as described in Section 4.3.6 starting with (*S*)-**5d** (760 mg, 2.65 mmol). This gave 311 mg (1.98 mmol, 75%) of (*S*)-**2c** as a pale yellow oil, ee=92.5%, $[\alpha]_D^{20}$ +36.4 (*c* 0.67, $CHCl_3$), R_f (EtOAc/MeOH, 9/1) 0.43.

*4.6.5. (S)-1-(4-Bromophenyl)-2-fluoroethylamine ((S)-**2e**).* The hydrazinolysis was performed as described in Section 4.3.6 starting with (*S*)-**5e** (836 mg, 2.40 mmol). This gave 436 mg (2.00 mmol, 83%) of (*S*)-**2e** as a pale yellow oil, which solidified at 0 °C, ee=90.5%, $[\alpha]_D^{20}$ +27.4 (*c* 0.66, $CHCl_3$), R_f (EtOAc/MeOH, 9/1) 0.40.

*4.6.6. (S)-2-Fluoro-1-(4-(trifluoromethyl)phenyl)ethylamine ((S)-**2f**).* The hydrazinolysis was performed as described in Section 4.3.6 starting with (*S*)-**5f** (840 mg, 2.49 mmol). This gave 366 mg (1.77 mmol, 71%) of (*S*)-**2f** as a colourless oil, ee=91.5%, $[\alpha]_D^{20}$ +25.7 (*c* 0.61, $CHCl_3$), R_f (EtOAc/MeOH, 9/1) 0.45.

*4.6.7. (S)-4-(1-Amino-2-fluoroethyl)benzonitrile ((S)-**2g**).* The hydrazinolysis was performed as described in Section 4.3.6 starting with (*S*)-**5g** (609 mg, 2.07 mmol). This gave 256 mg (1.56 mmol, 75%) of (*S*)-**2g** as a solid, mp 47–49 °C, ee=87.5%, $[\alpha]_D^{20}$ +28.5 (*c* 0.54, $CHCl_3$), R_f (EtOAc/MeOH, 9/1) 0.40.

*4.6.8. (S)-2-Fluoro-1-(4-nitrophenyl)ethylamine ((S)-**2h**).* The hydrazinolysis was performed as described in Section 4.3.6 starting with (*S*)-**5h** (310 mg, 0.99 mmol). This gave 145 mg (0.79 mmol, 80%) of (*S*)-**2h** as a white solid, mp 52–53 °C, ee=84.0%, $[\alpha]_D^{20}$ +15.9 (*c* 0.69 $CHCl_3$), R_f (EtOAc/MeOH, 9/1) 0.34.

4.7. (*S*)-*N*-(2-Fluoro-1-arylethyl)-2-methoxyacetamides ((*S*)-3a–h)

*4.7.1. (S)-N-(2-Fluoro-1-(4-methoxyphenyl)ethyl)-2-methoxyacetamide ((S)-**3a**).* The compound was prepared as described in Section 4.3.3. This gave 210 mg (0.87 mmol, 35%) of a white solid, mp 94–95 °C, ee >99.5%, $[\alpha]_D^{20}$ +77.1 (*c* 0.58, $CHCl_3$), R_f (EtOAc/MeOH, 4/1) 0.63. ^1H NMR ($CDCl_3$) δ: 3.43 (s, 3H, $-CH_2OCH_3$), 3.80 (s, 3H, $-OCH_3$), 3.92 (d, *J*=15.1, 1H, $-CH_2O-$), 3.95 (d, *J*=15.1, 1H, $-CH_2O-$), 4.63 (ddd, *J*=47.5, 9.5, 4.3, $-CH_2F$), 4.67 (ddd, *J*=47.5, 9.5, 4.8, $-CH_2F$), 5.27 (m, 1H, $-CHCH_2F$), 6.88–6.92 (m, 2H, $-C_6H_4-$), 7.04 (d, *J*=7.7, 1H, $-NH-$), 7.25–7.30 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 51.8 (d, *J*=19.4), 55.3, 59.1, 71.9, 84.7 (d, *J*=175.7), 114.2 (2C), 128.2 (d, *J*=1.2, 2C), 129.6 (d, *J*=3.4), 159.4, 169.1. ^{19}F NMR ($CDCl_3$) δ: −229.56 (td, *J*=47.2, 23.8). IR (neat, cm^{-1}): 3319, 1655, 1518, 1367, 1207, 1111, 1005, 833, 586. HRMS (ESI): 241.1122 (calcd 241.1114, $[M^+]$).

*4.7.2. (S)-N-(1-(4-(Benzyloxy)phenyl)-2-fluoroethyl)-2-methoxyacetamide ((S)-**3b**).* The compound was prepared as described in Section 4.3.3. This gave 246 mg (0.77 mmol, 31%) of a white solid, mp 109–110 °C, ee >99.5%, $[\alpha]_D^{20}$ +66.5 (*c* 0.53, $CHCl_3$), R_f (EtOAc/MeOH, 4/1) 0.66. ^1H NMR ($CDCl_3$) δ: 3.43 (s, 3H, $-CH_2OCH_3$), 3.92 (d, *J*=15.1, 1H, $-CH_2O-$), 3.94 (d, *J*=15.1, 1H, $-CH_2O-$), 4.63 (ddd, *J*=47.5, 9.5, 4.8, 1H, $-CH_2F$), 4.67 (ddd, *J*=47.5, 9.5, 4.3, 1H, $-CH_2F$), 5.01 (s, 2H, $-OCH_2Ph$), 5.26 (m, 1H, $-CHCH_2F$), 6.95–6.99 (m, 2H, $-C_6H_4$), 7.00 (d, *J*=7.9, 1H, $-NH$), 7.25–7.29 (m, 2H, $-C_6H_4$), 7.30–7.44 (m, 5H, $-CH_2-C_6H_5$). ^{13}C NMR ($CDCl_3$) δ: 51.8 (d, *J*=19.3), 59.1, 70.0, 71.9, 84.7 (d, *J*=175.8), 115.1 (2C), 127.4 (2C), 128.0, 128.2 (d, *J*=1.1, 2C), 128.6 (2C), 129.9 (d, *J*=3.4), 136.8, 158.6, 169.1. ^{19}F NMR ($CDCl_3$) δ: −229.60 (td, *J*=47.3, 24.0). IR (neat, cm^{-1}): 3294, 1650, 1532, 1116, 1003, 829, 542. HRMS (ESI): 317.1430 (calcd 317.1427, $[M^+]$).

*4.7.3. (S)-N-(2-Fluoro-1-phenylethyl)-2-methoxyacetamide ((S)-**3c**).* The compound was prepared as described in Section 4.3.3. This gave 170 mg (0.80 mmol, 32%) of a white solid, mp 111–112 °C, ee >99.5%, $[\alpha]_D^{20}$ +58.4 (*c* 0.46, $CHCl_3$), R_f (EtOAc/MeOH, 4/1) 0.62. ^1H NMR ($CDCl_3$) δ: 3.44 (s, 3H, $-CH_2OCH_3$), 3.94 (d, *J*=15.1, 1H, $-CH_2O-$), 3.96 (d, *J*=15.1, 1H, $-CH_2O-$), 4.66 (ddd, *J*=47.5, 9.5, 4.7, 1H, $-CH_2F$), 4.70 (ddd, *J*=47.5, 9.5, 4.3, 1H, $-CH_2F$), 5.32 (m, 1H, $-CHCH_2F$), 7.12 (d, *J*=5.1, 1H, $-NH-$), 7.29–7.41 (m, 5H, $-C_6H_5$). ^{13}C NMR ($CDCl_3$) δ: 52.3 (d, *J*=19.2), 59.2, 71.9, 84.7 (d, *J*=175.9), 126.9 (d, *J*=1.1, 2C), 128.1, 128.8 (2C), 137.5 (d, *J*=3.4), 169.2. ^{19}F NMR ($CDCl_3$) δ: −229.87 (td, *J*=47.7, 24.3). IR (neat, cm^{-1}): 3301, 1650, 1532, 1371, 1217, 1117, 1005, 847, 588. HRMS (ESI): 211.1015 (calcd 211.1009, $[M^+]$).

*4.7.4. (S)-N-(2-Fluoro-1-(4-fluorophenyl)ethyl)-2-methoxyacetamide ((S)-**3d**).* The compound was prepared as described in Section 4.3.3. Purification gave 228 mg (0.99 mmol, 40%) of a white solid, mp 79–80 °C, ee >99.5%, $[\alpha]_D^{20}$ +61.1 (*c* 0.5, $CHCl_3$), R_f (EtOAc/MeOH, 4/1) 0.65. ^1H NMR ($CDCl_3$) δ: 3.44 (s, 3H, $-CH_2OCH_3$), 3.93 (d, *J*=15.1, 1H, $-CH_2O-$), 3.95 (d, *J*=15.1, 1H, $-CH_2O-$), 4.64 (ddd, *J*=47.5, 9.5, 4.6, 1H, $-CH_2F$), 4.69 (ddd, *J*=47.5, 9.5, 4.1, 1H $-CH_2F$), 5.29 (m, , 1H, $-CHCH_2F$), 7.03–7.09 (m, 2H, $-C_6H_4-$), 7.10 (d, *J*=7.1, 1H, $-NH-$), 7.31–7.36 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 51.7 (d, *J*=19.3), 59.2, 71.8, 84.6 (d, *J*=175.9), 115.7 (d, *J*=21.6, 2C), 128.7 (dd, *J*=1.2, 8.2, 2C), 133.4 (d, *J*=3.2), 162.4 (d, *J*=246.5), 169.1. ^{19}F NMR ($CDCl_3$) δ: −230.38 (td, *J*=47.6, 25.4), −117.17 (s). IR (neat, cm^{-1}): 3308, 1656, 1511, 1217, 1112, 984, 834, 604. HRMS (ESI): 229.0917 (calcd 229.0914, $[M^+]$).

*4.7.5. (S)-N-(1-(4-Bromophenyl)-2-fluoroethyl)-2-methoxyacetamide ((S)-**3e**).* The compound was prepared as described in Section 4.4.3. Purification gave 305 mg (1.05 mmol, 42%) of a white solid, mp 111–112 °C, ee >99.5%, $[\alpha]_D^{20}$ +63.9 (*c* 0.57, $CHCl_3$). R_f (EtOAc/MeOH, 4/1) 0.66. ^1H NMR ($CDCl_3$) δ: 3.44 (s, 3H, $-CH_2OCH_3$), 3.93 (d, *J*=15.2, 1H, $-CH_2O-$), 3.96 (d, *J*=15.2, 1H, $-CH_2O-$), 4.64 (ddd, *J*=47.5, 9.5, 4.5, 1H, $-CH_2F$), 4.68 (ddd, *J*=47.5, 9.5, 4.3, 1H, $-CH_2F$), 5.26 (m, 1H, $-CHCH_2F$), 7.12 (d, *J*=7.5, 1H, $-NH-$), 7.21–7.25 (m, 2H, $-C_6H_4-$), 7.48–7.52 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 52.0 (d, *J*=19.1), 59.2, 71.8, 84.5 (d, *J*=176.3), 122.1, 128.7 (d, *J*=1.1, 2C), 132.0 (2C), 136.7 (d, *J*=3.2), 169.2. ^{19}F NMR ($CDCl_3$) δ: −230.60 (td, *J*=47.2, 25.8). IR (neat, cm^{-1}): 3290, 1653, 1527, 1368, 1228, 1112, 1008, 821, 594. HRMS (ESI): 289.0111 (calcd 289.0114, $[M^+]$).

*4.7.6. (S)-N-(2-Fluoro-1-(4-(trifluoromethyl)phenyl)ethyl)-2-methoxyacetamide ((S)-**3f**).* The compound was prepared as described in Section 4.4.3. Purification gave 245 mg (0.87 mmol, 35%) of a white solid, mp 108–109 °C, ee >99.5%, $[\alpha]_D^{20}$ +47.5 (*c* 0.58, $CHCl_3$), R_f (EtOAc/MeOH, 4/1) 0.66. ^1H NMR ($CDCl_3$) δ: 3.46 (s, 3H, $-CH_2OCH_3$), 3.94 (d, *J*=15.2, 1H, $-CH_2O-$), 3.97 (d, *J*=15.2, 1H, $-CH_2O-$), 4.68 (ddd, *J*=47.5, 9.6, 4.3, 1H, $-CH_2F$), 4.73 (ddd, *J*=47.5, 9.6, 4.0, 1H, $-CH_2F$), 5.35 (m, 1H, $-CHCH_2F$), 7.21 (d, *J*=7.2, 1H, $-NH-$), 7.43–7.50 (m, 2H, $-C_6H_4-$), 7.60–7.66 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 52.1 (d, *J*=19.0), 59.2, 71.8, 84.5 (d, *J*=176.2), 123.9 (q, *J*=272.1), 125.8 (q, *J*=3.8, 2C), 127.4 (d, *J*=1.2, 2C), 130.4 (q, *J*=32.6), 141.6 (m), 169.3. ^{19}F NMR ($CDCl_3$) δ: −230.98 (td, *J*=46.4, 28.3), −65.86 (s, 3F). IR (neat, cm^{-1}): 3292, 1658, 1532, 1375, 1228, 1116, 1011, 838, 606. HRMS (ESI): 279.0895 (calcd 279.0882, $[M^+]$).

*4.7.7. (S)-N-(1-(4-Cyanophenyl)-2-fluoroethyl)-2-methoxyacetamide ((S)-**3g**).* The compound was prepared as described in Section 4.4.3. Purification gave 249 mg (1.05 mmol, 42%) of a white solid, mp 76.5–77.0 °C, ee >99.5%, $[\alpha]_D^{20}$ +82.8 (*c* 0.53, $CHCl_3$), R_f

(EtOAc/MeOH, 4/1) 0.63. ^{1}H NMR ($CDCl_3$) δ: 3.46 (s, 3H, $-CH_2OCH_3$), 3.94 (d, J=15.3, 1H, $-CH_2O-$), 3.98 (d, J=15.3, 1H, $-CH_2O-$), 4.68 (ddd, J=47.4, 9.7, 4.1, 1H, $-CH_2F$), 4.72 (ddd, J=47.4, 9.7, 3.8, 1H, $-CH_2F$), 5.34 (m, 1H, $-CHCH_2F$), 7.24 (d, J=7.7, 1H, $-NH-$), 7.46–7.50 (m, 2H, $-C_6H_4-$), 7.65–7.69 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 59.2, 71.7, 84.4 (d, J=176.4), 112.1, 118.4, 127.8 (d, J=1.1, 2C), 132.6 (2C), 143.0 (d, J=3.0), 169.3. ^{19}F NMR ($CDCl_3$) δ: −231.46 (td, J=46.4, 27.9). IR (neat, cm^{-1}): 3310, 2232, 1655, 1532, 1372, 1226, 1117, 1014, 841, 563. HRMS (ESI): 236.0963 (calcd 236.0961, $[M^+]$).

*4.7.8. (S)-N-(2-Fluoro-1-(4-nitrophenyl)ethyl)-2-methoxyacetamide ((S)-**3h**).* The compound was prepared as described in Section 4.4.3. Purification by silica-gel column chromatography (EtOAc/MeOH, 4/1) gave 217 mg (0.90 mmol, 36%) of a white solid, mp 95.0–95.5 °C, ee >99.5%, $[\alpha]_D^{20}$ +70.8 (c=0.69, $CHCl_3$), R_f (EtOAc/MeOH, 4/1) 0.62. ^{1}H NMR ($CDCl_3$) δ: 3.47 (s, 3H, $-CH_2OCH_3$), 3.95 (d, J=15.3, 1H, $-CH_2O-$), 3.98 (d, J=15.3, 1H, $-CH_2O-$), 4.71 (ddd, J=47.4, 9.7, 4.0, 1H, $-CH_2F$), 4.75 (ddd, J=47.4, 9.7, 4.0, 1H, $-CH_2F$), 5.39 (m, 1H, $-CHCH_2F$), 7.28 (d, J=7.2, 1H, $-NH-$), 7.52–7.56 (m, 2H, $-C_6H_4-$), 8.21–8.26 (m, 2H, $-C_6H_4-$). ^{13}C NMR ($CDCl_3$) δ: 52.1 (d, J=19.1), 59.3, 71.8, 84.4 (d, J=176.6), 124.0 (2C), 128.0 (d, J=1.0, 2C), 145.0 (d, J=2.8), 147.7, 169.4. ^{19}F NMR ($CDCl_3$) δ: −231.62 (td, J=46.4, 28.3). IR (neat, cm^{-1}): 3273, 2970, 1650, 1516, 1348, 1110, 1012, 851, 697. HRMS (ESI): 256.0860 (calcd 256.0859, $[M^+]$).

4.8. (*R*)-1-Aryl-2-fluoroethanols ((*R*)-4a–h)

In the course of this work, calculation errors in the optical rotations data for (*R*)-**4a**–**h** in our previous study were discovered.[49] Corrected values for these data are therefore included.

*4.8.1. (R)-2-Fluoro-1-(4-methoxyphenyl)ethanol ((R)-**4a**)[49].* The reaction was performed as described in Section 4.3.4 starting with 2-fluoro-1-(4-methoxyphenyl)ethanone (**1a**) (673 mg, 4.00 mmol). Purification by silica-gel column chromatography (CH_2Cl_2/MeOH, 99/1, R_f 0.47) gave 515 mg (3.03 mmol, 76%) of a colourless oil, ee=96.0%, $[\alpha]_D^{20}$ −47.1 (c 0.69, $CHCl_3$), corr. ref. ee=99.5%, $[\alpha]_D^{20}$ −55.0 (c 0.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 2.41 (br, 1H, $-OH$), 3.81 (s, 3H, $-OCH_3$), 4.38 (ddd, J=48.5, 9.5, 8.3, 1H, $-CH_2F$), 4.49 (ddd, J=46.8, 9.5, 3.3, 1H, $-CH_2F$), 4.97 (ddd, J=13.2, 8.3, 3.3, 1H, $-CHCH_2F$), 6.87–6.91 (m, 2H, $-C_6H_4-$), 7.29–7.33 (m, 2H, $-C_6H_4-$).

*4.8.2. (R)-1-(4-(Benzyloxy)phenyl)-2-fluoroethanol ((R)-**4b**)[49].* The reaction was performed as described in Section 4.3.4 starting with 1-(4-benzyloxyphenyl)-2-fluoroethanone (**1b**) (733 mg, 3.00 mmol). Purification by silica-gel chromatography (CH_2Cl_2/MeOH, 99/1, R_f 0.26) gave 450 mg (1.83 mmol, 61%) of a white solid, mp 70–71 °C, ee=99.5%, $[\alpha]_D^{20}$ −38.3 (c 0.59, $CHCl_3$), corr. ref. ee=97.0%, $[\alpha]_D^{20}$ −33.2 (c 0.60, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 2.39 (dd, J=2.9, 1.1, 1H, $-OH$), 4.40 (ddd, J=48.5, 9.5, 8.3, 1H, $-CH_2F$), 4.48 (ddd, J=46.8, 9.5, 3.4, 1H, $-CH_2F$), 4.97 (m, 1H, $-CHCH_2F$), 5.09 (s, 2H, $-OCH_2Ph$), 6.95–7.01 (m, 2H, $-C_6H_4-$), 7.30–7.47 (m, 7H, Ar).

*4.8.3. (R)-2-Fluoro-1-phenylethanol ((R)-**4c**)[49].* The reaction was performed as described in Section 4.3.4 starting with 2-fluoro-1-phenylethanone (**1c**) (553 mg, 4.00 mmol). Purification by bulb-to-bulb distillation (35–40 °C at 5.0×10^{-3} mbar) gave 480 mg (3.42 mmol, 86%) of a colourless oil, ee=98.0%, $[\alpha]_D^{20}$ −56.8 (c 1.20, $CHCl_3$), corr. ref. ee=96.5%, $[\alpha]_D^{20}$ −53.7 (c 1.20, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 2.51 (br, 1H, $-OH$), 4.40 (ddd, J=48.5, 9.5, 8.3, 1H, $-CH_2F$), 4.51 (ddd, J=46.8, 9.5, 3.3, 1H, $-CH_2F$), 5.04 (ddd, J=14.0, 8.3, 3.3, 1H, $-CHCH_2F$), 7.33–7.36 (m, 5H, $-C_6H_5$).

*4.8.4. (R)-2-Fluoro-1-(4-fluorophenyl)ethanol ((R)-**4d**)[49].* The reaction was performed as described in Section 4.3.4 starting with 2-fluoro-1-(4-fluorophenyl)ethanone (**1d**) (752 mg, 4.82 mmol). Purification by bulb-to-bulb distillation (35–40 °C at 3.0×10^{-3} mbar) gave 603 mg (3.81 mmol, 79%) of a colourless oil, ee=93.0%, $[\alpha]_D^{20}$ −51.9 (c 0.59, $CHCl_3$), corr. ref. ee=99.0%, $[\alpha]_D^{20}$ −60.8 (c 0.60, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 2.63 (br, 1H, $-OH$), 4.37 (ddd, J=48.4, 9.6, 8.2, 1H, $-CH_2F$), 4.48 (ddd, J=46.7, 9.6, 3.3, 1H, $-CH_2F$), 5.03 (ddd, J=13.9, 8.2, 3.3, 1H, $-CHCH_2F$), 7.01–7.08 (m, 2H, $-C_6H_4-$), 7.32–7.36 (m, 2H, $-C_6H_4-$).

*4.8.5. (R)-1-(4-Bromophenyl)-2-fluoroethanol ((R)-**4e**)[49].* The reaction was performed as described in Section 4.3.4 starting with 1-(4-bromophenyl)-2-fluoroethanol (**1e**) (868 mg, 4.00 mmol). Purification by bulb-to-bulb distillation (60–65 °C at 1.1×10^{-2} mbar) gave 688 mg (3.14 mmol, 79%) of a white solid, mp 41–42 °C, ee=91.0%, $[\alpha]_D^{20}$ −33.4 (c 0.90, $CHCl_3$), corr. ref. ee=98.5%, $[\alpha]_D^{20}$ −35.9 (c 0.90, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 2.43 (dd, J=1.1, 3.1, 1H, $-OH$), 4.36 (ddd, J=48.1, 9.6, 8.2, 1H, $-CH_2F$), 4.49 (ddd, J=46.6, 9.6, 3.3, 1H, $-CH_2F$), 4.97 (m, 1H, $-CHCH_2F$), 7.28–7.30 (m, 2H, $-C_6H_4-$), 7.45–7.53 (m, 2H, $-C_6H_4-$).

*4.8.6. (R)-2-Fluoro-1-(4-(trifluoromethyl)phenyl) ethanol ((R)-**4f**)[49].* A suspension of $[RuCl_2(mesitylene)]_2$ (23 mg, 0.04 mmol) and the (*S*,*S*)-TsDPEN (44 mg, 0.12 mmol) in H_2O (20 mL) were stirred at 40 °C for 1 h. Sodium formate (1.36 g, 20.0 mmol) and 2-fluoro-1-(4-trifluoromethylphenyl)ethanone (**1f**) (825 mg, 4.0 mmol) were added and the mixture was stirred vigorously at 40 °C for 10 h before it was cooled to room temperature and extracted with CH_2Cl_2 (3×20 mL). The organic phase was then washed with brine (20 mL), filtered through a plug of silica gel and dried over Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by bulb-to-bulb distillation (40–45 °C at 1.0×10^{-2} mbar). This gave 429 mg (2.06 mmol, 52%) of a colourless oil, ee=92.5%, $[\alpha]_D^{20}$ −27.4 (c 0.69, $CHCl_3$), corr. ref. ee=93.0, $[\alpha]_D^{20}$ −28.6 (c 0.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 2.55 (d, J=3.1, 1H, $-OH$), 4.42 (ddd J=48.0, 9.6, 8.1, 1H, $-CH_2F$), 4.55 (ddd, J=46.7, 9.6, 3.4, 1H, $-CH_2F$), 5.11 (m, 1H, $-CHCH_2F$), 7.50–7.53 (m, 2H, $-C_6H_4-$), 7.63–7.69 (m, 2H, $-C_6H_4-$).

*4.8.7. 4-((R)-2-Fluoro-1-hydroxyethyl)benzonitrile ((R)-**4g**)[49].* The reaction was performed as described in Section 4.3.4 starting with 1-(4-cyanophenyl)-2-fluoroethanone (**1g**) (653 mg, 4.00 mmol). Purification by silica-gel column chromatography (CH_2Cl_2/MeOH, 99.5/0.5, R_f 0.43) gave 563 mg (3.41 mmol, 85%) of a white solid, mp 59–60 °C, ee=87.0%, $[\alpha]_D^{20}$ −35.6 (c 0.70, $CHCl_3$), corr. ref. ee=91.5%, $[\alpha]_D^{20}$ −38.7 (c 0.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 2.62 (d, J=3.3, 1H, $-OH$), 4.40 (ddd, J=48.0, 9.5, 8.0, 1H, $-CH_2F$), 4.55 (ddd, J=46.7, 9.5, 3.4, 1H, $-CH_2F$), 5.09 (m, 1H, $-CHCH_2F$), 7.46–7.56 (m, 2H, $-C_6H_4-$), 7.65–7.71 (m, 2H, $-C_6H_4-$).

*4.8.8. (R)-2-Fluoro-1-(4-nitrophenyl)ethanol ((R)-**4h**)[49].* The reaction was performed as described in Section 4.3.4 starting with 2-fluoro-1-(4-nitrophenyl)ethanone (**1h**) (733 mg, 4.00 mmol). Purification by silica-gel chromatography (CH_2Cl_2/MeOH, 95/5, R_f 0.52) gave 673 mg (3.63 mmol, 91%) of a white solid, mp 98–99 °C, ee=85.0%, $[\alpha]_D^{20}$ −24.7 (c 0.70, $CHCl_3$), corr. ref. ee=92.5%, $[\alpha]_D^{20}$ −25.3 (c 0.70, $CHCl_3$). ^{1}H NMR ($CDCl_3$) δ: 2.65 (br, 1H, $-OH$), 4.42 (ddd J=47.9, 9.6, 7.8, 1H, $-CH_2F$), 4.56 (ddd, J=46.5, 9.6, 3.4, 1H, $-CH_2F$), 5.16 (ddd, J=3.4, 7.8, 14.5, 1H, $-CHCH_2F$), 7.59–7.65 (m, 2H, $-C_6H_4-$), 8.22–8.28 (m, 2H, $-C_6H_4-$).

4.9. *N*-Substituted phthalimides (*S*)-5a–h

*4.9.1. (S)-2-(2-Fluoro-1-(4-methoxyphenyl)ethyl)isoindoline-1,3-dione ((S)-**5a**).* The synthesis was performed as described in Section 4.3.5 starting with (*R*)-**4a** (420 mg, 2.47 mmol), and reacting for 10 h prior to addition of HCl. Purification by silica-gel column chromatography eluting with CH_2Cl_2/MeOH (99.5/0.5, R_f 0.54)

followed by *i*-Pr_2O/pentane (7/3, R_f 0.28), gave 235 mg (0.79 mmol, 32%) of white solid, mp 75–76 °C, ee=53.0%, $[\alpha]_D^{20}$ −15.8 (*c* 0.50, EtOAc), CD (MeCN): Δε=−1.3 (232 nm). ^{1}H NMR ($CDCl_3$) δ: 3.78 (s, 3H, −O*CH*$_3$), 4.90 (ddd, *J*=45.7, 9.6, 5.3, 1H, −*CH*$_2$F), 5.52 (app. dt. *J*=47.0, 9.6, 1H, −*CH*$_2$F), 5.63 (ddd, *J*=12.1, 9.6, 5.3, 1H, −*CH*CH$_2$F), 6.86–6.89 (m, 2H, −C_6H_4OMe), 7.43–7.47 (m, 2H, −C_6H_4OMe), 7.68–7.73 (m, 2H, phthal.), 7.81–7.86 (m, 2H, phthal.). ^{13}C NMR ($CDCl_3$) δ: 54.3 (d, *J*=21.2), 55.3, 80.8 (d, *J*=175.2), 114.2 (2C), 123.4 (2C), 127.2 (d, *J*=7.8), 129.6 (2C), 131.9 (2C), 134.1 (2C), 159.8, 168.3 (2C). ^{19}F NMR ($CDCl_3$) δ: −220.30 (td, *J*=46.9, 12.1). IR (neat, cm^{-1}): 1773, 1706, 1610, 1514, 1363, 1238, 1087, 1001. HRMS (ESI): 322.0836 (calcd 322.0850 [M+Na$^+$]).

*4.9.2. (S)-2-(1-(4-(Benzyloxy)phenyl)-2-fluoroethyl)isoindoline-1,3-dione ((S)-**5b**).* The synthesis was performed as described in Section 4.3.5 starting with (*R*)-**4b** (452 mg, 1.84 mmol), and reacting for 8 h prior to addition of HCl. Purification by silica-gel column chromatography (CH_2Cl_2, R_f 0.55) gave 255 mg (0.68 mmol, 37%) of a white solid, mp 82–83 °C, ee=60.0%, $[\alpha]_D^{20}$ −11.1 (*c* 0.47, EtOAc), CD (MeCN): Δε=−3.8 (234 nm). ^{1}H NMR ($CDCl_3$) δ: 4.89 (ddd, *J*=45.7, 9.6, 5.3, 1H, −*CH*$_2$F), 5.04 (s, 2H, −O*CH*$_2$Ph), 5.52 (app. dt. *J*=47.0, 9.6, 1H, −*CH*$_2$F), 5.62 (ddd, *J*=12.1, 9.6, 5.3, 1H, −*CH*CH$_2$F), 6.92–6.96 (m, 2H, −C_6H_4OBn), 7.29–7.41 (m, 5H, −$CH_2C_6H_5$), 7.42–7.46 (m, 2H, −C_6H_4OBn), 7.68–7.73 (m, 2H, phthal.), 7.81–7.85 (m, 2H, phthal.). ^{13}C NMR ($CDCl_3$) δ: 54.3 (d, *J*=21.5), 70.0, 80.8 (d, *J*=175.2), 115.2 (2C), 123.4 (2C), 127.4 (2C), 127.5 (d, *J*=7.8), 128.0, 128.6 (2C), 129.7 (2C), 131.8 (2C), 134.1 (2C), 136.7, 159.0, 168.2 (2C). ^{19}F NMR ($CDCl_3$) δ: −220.29 (td, *J*=46.2, 11.9). IR (neat, cm^{-1}): 1771, 1708, 1608, 1508, 1359, 1242, 1083, 997. HRMS (ESI): 398.1148 (calcd 398.1163, [M+Na$^+$]).

*4.9.3. (S)-2-(2-Fluoro-1-phenylethyl)isoindoline-1,3-dione ((S)-**5c**).* The synthesis was performed as described in Section 4.3.5 starting with (*R*)-**4c** (460 mg, 3.28 mmol), and reacting for 2 h prior to addition of HCl. Purification by silica-gel chromatography (CH_2Cl_2/MeOH, 99/1, R_f 0.73) gave 681 mg (2.53 mmol, 77%) of a white solid, mp 69–70 °C, ee=99.0%, $[\alpha]_D^{20}$ −49.0 (*c* 0.61, EtOAc), CD (MeCN): Δε=−3.5 (223 nm). ^{1}H NMR ($CDCl_3$) δ: 4.95 (ddd, *J*=45.7, 9.1, 5.6, 1H, −*CH*$_2$F), 5.55 (app. dt. *J*=47.2, 9.1, 1H, −CH_2F), 5.69 (ddd, *J*=12.4, 9.1, 5.3, 1H, −*CH*CH$_2$F), 7.29–7.38 (m, 3H, −C_6H_5), 7.48–7.51 (m, 2H, −C_6H_5), 7.69–7.74 (m, 2H, phthal.), 7.82–7.87 (m, 2H, phthal.). ^{13}C NMR ($CDCl_3$) δ: 54.8 (d, *J*=21.6), 80.8 (d, *J*=174.8), 123.4 (2C), 128.2 (2C), 128.7, 128.9 (2C), 131.8 (2C), 134.2 (2C), 135.1 (d, *J*=7.4), 168.2 (2C). ^{19}F NMR ($CDCl_3$) δ: −219.83 (td, *J*=46.2, 11.9). IR (neat, cm^{-1}): 1770, 1704, 1611, 1493, 1385, 1357, 1086, 1000. HRMS (ESI): 292.0735 (calcd 292.0744, [M+Na$^+$]).

*4.9.4. (S)-2-(2-Fluoro-1-(4-fluorophenyl)ethyl)isoindoline-1,3-dione ((S)-**5d**).* The synthesis was performed as described in Section 4.3.5 starting with (*R*)-**4d** (583 mg, 3.69 mmol), and reacting for 4 h prior to addition of HCl. Purification by silica-gel column chromatography (CH_2Cl_2/MeOH, 99/1, R_f 0.62) gave 815 mg (2.84 mmol, 77%) of a white solid, mp 58–59 °C, ee=92.5% (analysed as **2d**), $[\alpha]_D^{20}$ −36.8 (*c* 0.73, EtOAc), CD (MeCN): Δε=−1.6 (223 nm). ^{1}H NMR ($CDCl_3$) δ: 4.93 (ddd, *J*=45.5, 9.4, 5.8, 1H, −*CH*$_2$F), 5.49 (app. dt, *J*=47.0, 9.4, 1H, −*CH*$_2$F), 5.66 (ddd, *J*=12.1, 9.4, 5.8, 1H, −*CH*CH$_2$F), 7.01–7.07 (m, 2H, −C_6H_4F), 7.48–7.53 (m, 2H, −C_6H_4F), 7.70–7.75 (m, 2H, phthal.), 7.82–7.87 (m, 2H, phthal.). ^{13}C NMR ($CDCl_3$) δ: 54.0 (d, *J*=22.3), 80.6 (d, *J*=175.6), 115.9 (d, *J*=21.6), 123.5, 130.2 (d, *J*=4.1), 131.1 (dd, *J*=4.1, 3.5), 131.7, 134.3, 162.8 (d, *J*=248.3), 168.1 (2C). ^{19}F NMR ($CDCl_3$) δ: −113.33 (s), −219.63 (td, *J*=46.2, 11.8). IR (neat, cm^{-1}): 1774, 1707, 1605, 1511, 1389, 1223, 1100, 1000. HRMS (ESI): 288.0838 (calcd 288.0831, [M+H$^+$]).

*4.9.5. (S)-2-(1-(4-bromophenyl)-2-fluoroethyl)isoindoline-1,3-dione ((S)-**5e**).* The synthesis was performed as described in Section 4.3.5 starting with (*R*)-**4e** (657 mg, 3.00 mmol), and reacting for 2 h prior to addition of HCl. Purification by silica-gel column chromatography (CH_2Cl_2/MeOH, 99/1, R_f 0.65) gave 871 mg (2.50 mmol, 83%) of a white solid, mp 66–67 °C, ee=90.0%, $[\alpha]_D^{20}$ −19.8 (*c* 0.60, EtOAc), CD (MeCN): Δε=−3.9 (230 nm). ^{1}H NMR ($CDCl_3$) δ: 4.95 (ddd, *J*=45.8, 9.4, 5.8, 1H, −*CH*$_2$F), 5.46 (app. dt, *J*=47.0, 9.4, 1H, −*CH*$_2$F), 5.64 (ddd, *J*=12.1, 9.4, 5.8, 1H, −*CH*CH$_2$F), 7.37–7.40 (m, 2H, C_6H_4Br), 7.47–7.50 (m, 2H, C_6H_4Br), 7.71–7.75 (m, 2H, phthal.), 7.82–7.87 (m, 2H, phthal.). ^{13}C NMR ($CDCl_3$) δ: 54.1 (d, *J*=22.6), 80.5 (d, *J*=175.6), 122.9, 123.5 (2C), 129.9 (2C), 131.7 (2C), 132.1 (2C), 134.2 (d, *J*=6.7), 134.3 (2C), 168.1 (2C). ^{19}F NMR ($CDCl_3$) δ: −220.87 (td, *J*=46.3, 11.9). IR (neat, cm^{-1}): 1770, 1708, 1591, 1491, 1385, 1355, 1077, 999. HRMS (ESI): 369.9853 (calcd 369.9849, [M+Na$^+$]).

*4.9.6. (S)-2-(2-Fluoro-1-(4-(trifluoromethyl)phenyl)ethyl)isoindoline-1,3-dione ((S)-**4f**).* The synthesis was performed as described in Section 4.3.5 starting with (*R*)-**3f** (717 mg, 3.45 mmol), and reacting for 4 h prior to addition of HCl. Purification by silica-gel column chromatography (CH_2Cl_2, R_f 0.63) gave 905 mg (2.68 mmol, 78%) of a colourless oil (solidified at 0 °C), ee=92.0%, $[\alpha]_D^{20}$ −32.4 (*c* 0.54, EtOAc), CD (MeCN): Δε=−4.8 (225 nm). ^{1}H NMR ($CDCl_3$) δ: 5.02 (ddd, *J*=45.8, 9.4, 6.1, 1H, −*CH*$_2$F), 5.48 (app. dt, *J*=46.7, 9.4, 1H, −*CH*$_2$F), 5.74 (ddd, *J*=12.1, 9.4, 6.1, 1H, −*CH*CH$_2$F), 7.59–7.65 (m, 4H, −$C_6H_4CF_3$), 7.72–7.77 (m, 2H, phthal.), 7.84–7.88 (m, 2H, phthal.). ^{13}C NMR ($CDCl_3$) δ: 54.1 (d, *J*=23.0), 80.5 (d, *J*=175.6), 123.7, 123.8 (q, *J*=272.3), 125.9 (q, *J*=3.9), 128.6, 130.9 (d, *J*=32.9), 131.7, 134.4, 139.1 (dq, *J*=6.7, 1.4), 168.0 (2C). ^{19}F NMR ($CDCl_3$) δ: −63.40 (s, 3F), −220.22 (td, *J*=46.1, 11.8). IR (neat, cm^{-1}): 1777, 1710, 1620, 1469, 1385, 1322, 1067, 1013. HRMS (ESI): 360.0617 (calcd 360.0618, [M+Na$^+$]).

*4.9.7. (S)-4-(1-(1,3-Dioxoisoindolin-2-yl)-2-fluoroethyl)benzonitrile ((S)-**5g**).* The synthesis was performed as described in Section 4.3.5 starting with (*R*)-**4g** (547 mg, 3.31 mmol), and reacting for 3 h prior to addition of HCl. Purification by silica-gel column chromatography (pentane/acetone, 8/2, R_f 0.52) gave 647 mg (2.20 mmol, 66%) of a white solid, mp 89–91 °C, ee=87.5%, $[\alpha]_D^{20}$ −24.4 (*c* 0.52, EtOAc), CD (MeCN): Δε=−2.7 (238 nm). ^{1}H NMR ($CDCl_3$) δ: 5.04 (ddd, *J*=45.7, 9.4, 6.3, 1H, −*CH*$_2$F), 5.40 (app. dt, *J*=46.7, 9.4, 1H, −*CH*$_2$F), 5.72 (ddd, *J*=12.4, 9.1, 6.3, 1H, −*CH*CH$_2$F), 7.61–7.68 (m, 4H, −C_6H_4CN), 7.73–7.78 (m, 2H, phthal.), 7.85–7.89 (m, 2H, phthal.). ^{13}C NMR ($CDCl_3$) δ: 54.0 (d, *J*=23.3), 80.3 (d, *J*=175.9), 112.7, 118.2, 123.7 (2C), 128.9 (2C), 131.5 (2C), 132.7 (2C), 134.5 (2C), 140.3 (d, *J*=6.0), 167.9 (2C). ^{19}F NMR ($CDCl_3$) δ: −220.36 (td, *J*=46.1, 12.2). IR (neat, cm^{-1}): 2227, 1777, 1706, 1610, 1465, 1361, 1334, 1088, 999. HRMS (ESI): 317.0694 (calcd 317.0697, [M+Na$^+$]).

*4.9.8. (S)-2-(2-Fluoro-1-(4-nitrophenyl)ethyl)isoindoline-1,3-dione ((S)-**5h**).* The synthesis was performed as described in Section 4.3.5 starting with (*R*)-**4h** (648 mg, 3.50 mmol), and reacting for 3 h prior to addition of HCl. Purification by silica-gel column chromatography using CH_2Cl_2/MeOH (99.5/0.5, R_f 0.49) followed by pentane/acetone (8/2, R_f 0.50) gave 374 mg (1.19 mmol, 34%) of a white solid, mp 92–94 °C, ee=84.0%, $[\alpha]_D^{20}$ −6.5 (*c* 1.05, $CHCl_3$), CD (MeCN): Δε=−1.4 (228 nm). ^{1}H NMR ($CDCl_3$) δ: 5.08 (ddd, *J*=45.5, 9.3, 6.3, 1H, −*CH*$_2$F), 5.43 (app. dt, *J*=46.5, 9.1, 1H, −*CH*$_2$F), 5.78 (ddd, *J*=12.4, 9.1, 6.3, 1H, −*CH*CH$_2$F), 7.67–7.70 (m, 2H, −$C_6H_4NO_2$), 7.74–7.79 (m, 2H, phthal.), 7.85–7.90 (m, 2H, phthal.), 8.21–8.24 (m, 2H, −$C_6H_4NO_2$). ^{13}C NMR ($CDCl_3$) δ: 53.7 (d, *J*=23.3), 80.4 (d, *J*=176.3), 123.7 (2C), 124.1 (2C), 129.2 (2C), 131.5 (2C), 134.6 (2C), 142.2 (d, *J*=6.0), 148.0, 167.9 (2C). ^{19}F NMR ($CDCl_3$) δ: −221.22 (td,=12.1, 46.0). IR (neat, cm^{-1}): 1776, 1712, 1606, 1521, 1386, 1347, 1087, 999. HRMS (ESI): 337.0605 (calcd 337.0595, [M+Na$^+$]).

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References and notes

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