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A comparative study on the acylative kinetic resolution of racemic fluorinated and non-fluorinated 2-methyl-1,2,3,4-tetrahydroquinolines and 3,4-dihydro-3-methyl-2*H*-[1,4]benzoxazines

Dmitry A. Gruzdev, Evgeny N. Chulakov, Galina L. Levit *, Marina A. Ezhikova, Mikhail I. Kodess, Victor P. Krasnov

Postovsky Institute of Organic Synthesis of RAS (Ural Branch), 22/20 S. Kovalevskoy/Akademicheskaya St., Ekaterinburg 620990, Russia

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ABSTRACT

The acylative kinetic resolution of racemic 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline, 7,8-difluoro-3,4-dihydro-3-methyl-2*H*-[1,4]benzoxazine, and their non-fluorinated analogues with (*S*)-naproxen and *N*-phthaloyl-(*S*)-amino acyl chlorides has been carried out. It has been shown that the presence of fluorine atoms in the aromatic fragment of a heterocyclic amine results in the increasing stereoselectivity of acylation with (*S*)-naproxen acyl chloride and in a decrease in the efficiency of acylative kinetic resolution using *N*-phthaloyl-(*S*)-amino acyl chlorides. A method for the preparation of enantiopure (*S*)-6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (*ee* >99%) was developed.

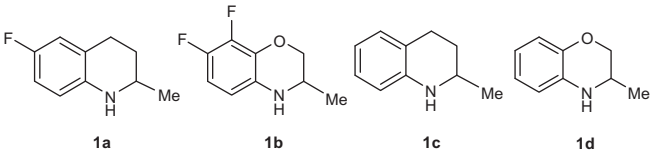
1. Introduction

The kinetic resolution (KR) of racemic organic substances is one of the most important methods for the preparation of enantiopure compounds. It is widely used in industry[1] and a great number of papers are concerned with its study. Non-enzymatic acylative KR is one of the main approaches to enantiopure amines and related compounds.[2] This method is based on the fact that under the action of a chiral acylating agent or in the presence of a chiral catalyst for acyl transfer, one of the enantiomers reacts faster than the other. As a result, the reaction product is enriched with a derivative of one of the enantiomers, while the other predominates in the unreacted substrate.

Recently, a number of examples showing the efficiency of this approach for the synthesis of enantiopure amines and their derivatives have been demonstrated by the research teams of Birman,[3] Karnik,[4] Seidel,[5] Miller,[6] Bode,[7] and others.[8] At the same time, despite occasional successful attempts to explain the mechanism of the process,[9] it is not always possible to put forward reasonable assumptions about the causes of the stereoselectivity. Therefore, studies aimed at clarifying the structural and electronic factors that determine the stereochemical outcome of KR are of considerable interest in terms of practical and theoretical points of view.

We have carried out a systematic study on the acylative KR of racemic heterocyclic amines with chiral acyl chlorides as resolving agents.[10] Previously we have shown that the electronic effects of substituents in the phenyl fragment of the acylating agent have a significant influence on the result of the KR of racemic amines with *N*-phthaloyl-3-aryl-(*S*)-alanyl chlorides.[10g]

Herein our aim was to study the KR of racemic heterocyclic amines **1a** and **1b**, which contain fluorine atom(s) in an aromatic fragment in comparison with their non-fluorinated analogues, **1c** and **1d** (Scheme 1), under the action of the acyl chlorides of (*S*)-naproxen **2** and *N*-phthaloyl-(*S*)-amino acids, such as phenylalanine **3a** and leucine **3b** (Scheme 2). Enantiomers of fluorine-containing heterocyclic amines are important key intermediates in the synthesis of antibacterials. In particular, (2*S*)-6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (*S*)-**1a** and (3*S*)-7,8-difluoro-3,4-dihydro-3-methyl-2*H*-[1,4]-benzoxazine (*S*)-**1b** are the precursors in the synthesis of (*S*)-flumequine[11] and levofloxacin,[12] respectively. Recently we have carried out the acylative KR of amines **1c** and **1d** with resolving agents **3a** and **3b**.[10e,j] Investigations of the KR of racemic amines **1b–d** with (*S*)-naproxen acyl chloride **2** were started earlier,[10a–c] and herein we give more detailed information about the peculiarities of the KR of these amines.



Scheme 1. Substrates for kinetic resolution.

* Corresponding author. Tel.: +7 343 3623057.
E-mail address: ca512@ios.uran.ru (G.L. Levit).

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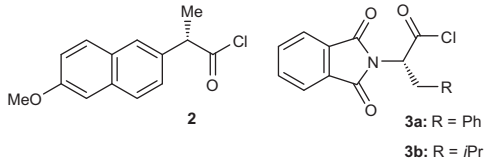


Scheme 2. Resolving agents.

It should be noted that in some published examples of the acylative KR of alcohols[13] as well as the desymmetrization of *meso*-epoxides with aryl amines,[14] the fluorine atoms in the reagent structure had no significant effect on the stereochemical results.

2. Results and discussion

2.1. Kinetic resolution of racemic amines 1a–d with acyl chlorides 2, 3a, and 3b

The acylative kinetic resolution of racemic amines **1a–d** with acyl chlorides **2**, **3a,** and **3b** was carried out with an amine–acyl chloride molar ratio of 2:1 in CH_2Cl_2 at +20 or −20 °C for 6 h (Scheme 3). After the acylation, amides **4–15** and unreacted amines **1a–d** were isolated from the reaction mixtures. The diastereoisomeric excess (*de*) of the amides was determined by HPLC on silica gel, and the enantiomeric excess (*ee*) of the unreacted amines, by chiral HPLC (Chiralcel OD-H). Based on the *de* and *ee* values, we calculated the conversion of the starting racemate $C = ee_{amine}/(ee_{amine} + de_{amide})$ and the selectivity factor that is the ratio of the rate constants of enantiomers: $s = k_{fast}/k_{slow} = \ln[(1 - C)\times(1 - ee_{amine})]/\ln[(1 - C) \times (1 + ee_{amine})]$.[15] The stereochemical results of the KR of amines **1a–d** are presented in Table 1.

It was found that in all cases, the (*S*,*S*)-diastereoisomers of amides **4–15** predominate in the products of the acylation of amines **1a–d** with acyl chlorides **2**, **3a**, and **3b**, and the unreacted amines are enriched with the (*R*)-enantiomer (Scheme 3). Major (*S*,*S*)-amides **4**, **8–11** were isolated from the mixtures of diastereoisomers by recrystallization or flash column chromatography on silica gel. For amides **8–11** we managed to isolate the minor (*R*,*S*)-amides by flash column chromatography. In order to assign the peaks in the HPLC chromatograms and signals in the NMR spectra of amide **4**, we obtained a mixture of diastereoisomeric amides **4** (*S*,*S*–*R*,*S* 53:47) starting from equimolar amounts of racemic amine **1a**, acyl chloride **2**, and *N*,*N*-diethylaniline as an HCl-acceptor.

The absolute configuration of amides (*S*,*S*)-**8**, (*R*,*S*)-**9,** and (*S*,*S*)-**10** was confirmed by X-ray diffraction from the known configuration of the acyl fragment (Figs. 1–3).

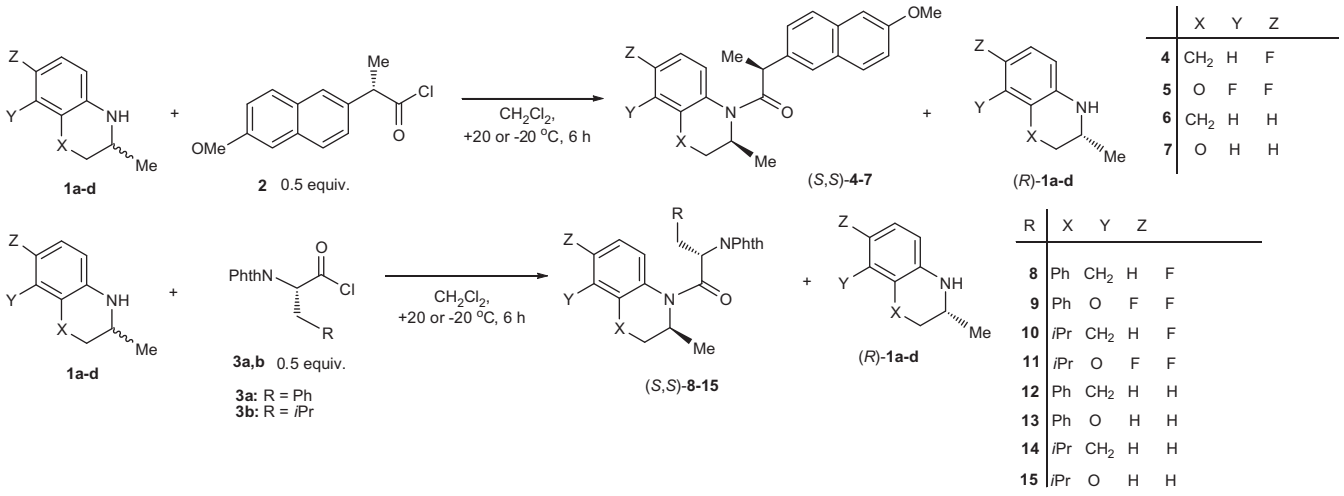
From the data presented in Table 1, it is clear that the presence of fluorine atoms in the aromatic moiety of heterocyclic amines has a significant impact on the stereochemical outcome of the KR. Thus, the stereoselectivity of the acylation of fluorinated amines **1a**, **b** with (*S*)-naproxen acyl chloride **2** at +20 °C was higher than that of their non-fluorinated analogues **1c**, **d** (Table 1, entries 1 and 3 vs 5 and 7). Acylation of fluorinated amines with *N*-phthaloyl-(*S*)-amino acyl chlorides **3a** and **3b** proceeded less selectively than the acylation of amines without the fluorine atoms. For example, the selectivity factor of the acylation of 6-fluoro amine **1a** with acyl chloride **3a** at +20 °C was 5.2, whereas in the KR of amine **1c**, it was 8.9 (Table 1, entries 9 and 13). In the case of the KR of 7,8-difluoro benzoxazine **1b** and its non-fluorinated analogue **1d**, the differences in stereoselectivity were even more pronounced (in acylation with acyl chloride **3a** at +20 °C, *s* was 1.7 and 6.2, respectively) (Table 1, entries 11 and 15).

Lowering the temperature in all cases (except in the KR of amine **1c** with chloride **2**) contributed to an increase in the stereoselectivity of the acylation with a small decrease in the racemate conversion.

Since the fluorine atoms in the structure of amines **1a** and **1b** are remote from the reaction center and do not create spatial hindrance, the cause of the observed differences in stereoselectivity of acylation may be associated with other types of molecular interactions. It is known that the introduction of fluorine atoms into an aromatic system leads to significant changes in the π–π aromatic and CH–π interactions.[16] In our case, the differences in stereoselectivity are likely due to the electronic factors determined primarily by the interactions of the aromatic fragments of the reactants in the transition states.

2.2. Preparation of enantiopure (*S*)-6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (*S*)-1a

In order to prepare the (*S*)-enantiomer of 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline **1a**, we carried out the KR of its racemate with (*S*)-naproxen acyl chloride **2** at −20 °C (Scheme 4). Amide (*S*,*S*)-**4** (*de* >99%) was isolated from the acylation product by a single recrystallization in 58% yield relative to the acylating agent. Acidic hydrolysis of amide (*S*,*S*)-**4** by heating in a mixture of acetic and hydrochloric acids gave (*S*)-amine **1a** in 84% yield without a loss of enantiomeric purity (*ee* >99%). The overall yield of (*S*)-**1a** was 24% relative to the starting racemate.



Scheme 3. Kinetic resolution of amines **1a–d** with acyl chlorides **2**, **3a,** and **3b**.

Table 1
Stereochemical results of the acylative KR of racemic amines **1a–d** with acyl chlorides **2**, **3a,** and **3b** in CH_2Cl_2[a]

Entry	Resolving agent	Racemic amine	T (°C)	(*S*,*S*)-Amide[b] (*de* %)	Unreacted (*R*)-amine[c] (*ee* %)	Conversion *C* (%)	Selectivity factor (*s*)
1	**2**	**1a**	+20	**4**, 87.2	74.4	46	32
2	**2**	**1a**	−20	**4**, 91.6	76.0	45	53
3	**2**	**1b**	+20	**5**, 80.7	72.5	47	20
4	**2**	**1b**	−20	**5**, 84.0	68.8	45	24
5	**2**	**1c**	+20	**6**, 77.0	66.0	46	15
6	**2**	**1c**	−20	**6**, 72.8	61.6	46	12
7	**2**	**1d**	+20	**7**, 74.2	71.1	49	14
8	**2**	**1d**	−20	**7**, 86.0	40.5	32	19
9	**3a**	**1a**	+20	**8**, 51.3	49.9	49	5.2
10	**3a**	**1a**	−20	**8**, 63.7	49.0	44	7.2
11	**3a**	**1b**	+20	**9**, 21.8	8.9	35	1.7
12	**3a**	**1b**	−20	**9**, 26.0	5.8	18	1.8
13	**3a**	**1c**	+20	**12**, 67.1	56.9	46	8.9[10e]
14	**3a**	**1c**	−20	**12**, 74.4	60.4	45	12[10e]
15	**3a**	**1d**	+20	**13**, 59.2	48.0	45	6.2[10e]
16	**3a**	**1d**	−20	**13**, 64.3	46.4	42	7.2[10e]
17	**3b**	**1a**	+20	**10**, 64.6	63.0	49	8.9
18	**3b**	**1a**	−20	**10**, 73.7	64.4	47	13
19	**3b**	**1b**	+20	**11**, 48.4	24.1	33	3.6
20	**3b**	**1b**	−20	**11**, 53.6	8.8	14	3.6
21	**3b**	**1c**	+20	**14**, 76.0	60.4	44	13[10j]
22	**3b**	**1c**	−20	**14**, 80.2	64.7	44	19[10j]
23	**3b**	**1d**	+20	**15**, 69.5	59.1	46	9.9[10j]
24	**3b**	**1d**	−20	**15**, 77.6	56.5	42	14[10j]

[a] Average values for 2–4 parallel runs are presented.
[b] Determined by HPLC (see Section 4).
[c] Determined by chiral HPLC (Chiralcel OD-H, see Section 4).

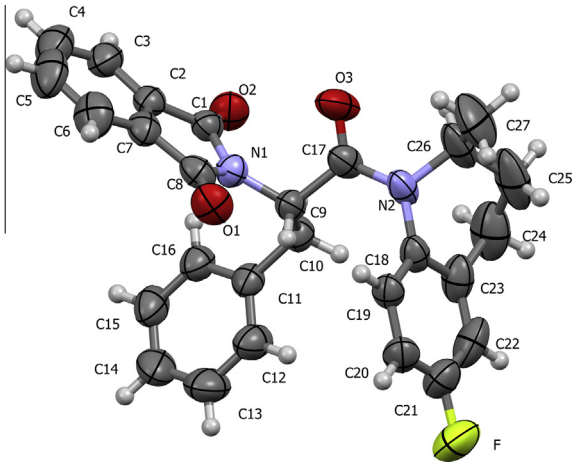


Figure 1. Structure of amide (*S*,*S*)-**8** (thermal ellipsoids of 50% probability).

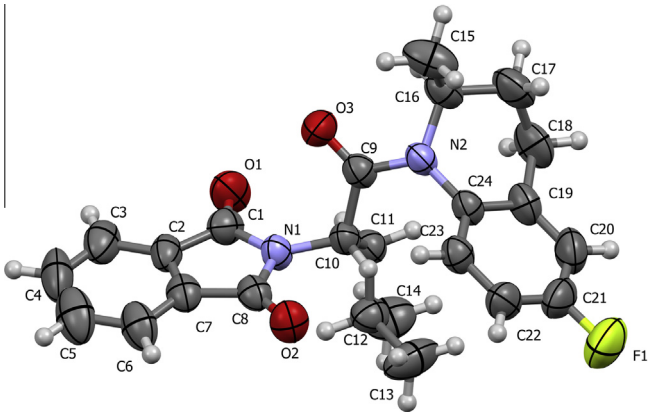


Figure 3. Structure of amide (*S*,*S*)-**10** (thermal ellipsoids of 50% probability).

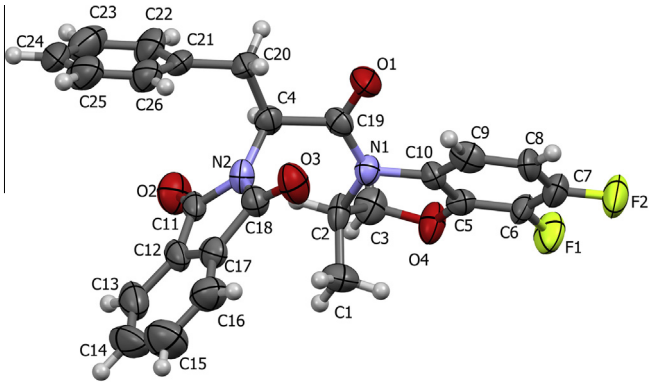
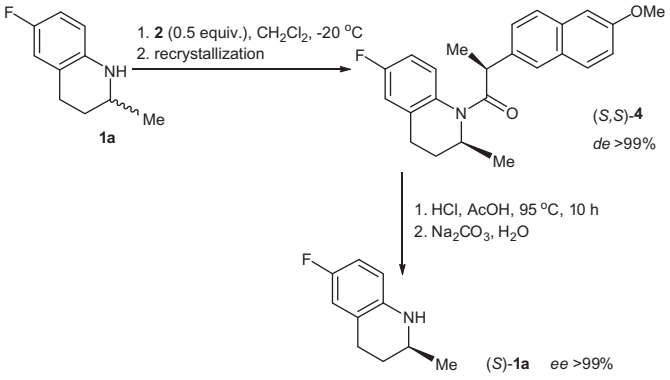


Figure 2. Structure of amide (*R*,*S*)-**9** (thermal ellipsoids of 50% probability).



Scheme 4. Preparation of enantiopure amine (*S*)-**1a** from the racemate via a KR protocol using acyl chloride **2**.

Although, the selectivity in the acylation of racemic amine **1a** with *N*-phthaloyl-(*S*)-amino acyl chlorides was lower than that with (*S*)-naproxen acyl chloride, this KR protocol can also be used for the preparation of enantiopure (*S*)-**1a** from the racemate. Thus, the acylation of racemic amine **1a** with 0.5 equiv of acyl chloride **3a** followed by recrystallization of the product led to diastereoisomerically pure amide (*S,S*)-**8** (*de* >99%) in 46% yield. Acidic hydrolysis of amide (*S,S*)-**8** resulted in enantiopure amine (*S*)-**1a** in 18% overall yield relative to the starting racemate.

It should be noted that two main approaches have recently been applied for the preparation of (*S*)-**1a**; the resolution of the racemate via diastereoisomeric salts[11,17] (the enantiomeric purity of the target compound was up to 99.2% *ee*[17b]) and the metal-catalyzed asymmetric hydrogenation of 6-fluoro-2-methylquinoline[18] (the enantiomeric purity of the target (*S*)-**1a** was up to 98% *ee*[18f]). Herein, based on the KR protocol, we prepared the (*S*)-enantiomer of amine **1a** with *ee* >99%.

3. Conclusion

In conclusion, we have studied the acylative kinetic resolution of racemic fluorinated heterocyclic amines, 6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline, and 7,8-difluoro-3,4-dihydro-3-methyl-2*H*-[1,4]benzoxazine, in comparison with their non-fluorinated analogues. It has been shown that the acylation of fluorinated amines with (*S*)-naproxen acyl chloride is more selective when compared with the non-fluorinated analogues, and in the case of *N*-phthaloyl-(*S*)-amino acyl chlorides the selectivity of acylation is lower than that of non-substituted analogues. The data obtained pointed to different mechanisms of stereoselectivity in the case of acylation with (*S*)-naproxen acyl chloride or *N*-phthaloyl-(*S*)-amino acyl chlorides. Based on the acylative kinetic resolution using (*S*)-naproxen or *N*-phthaloyl-(*S*)-phenylalanyl chlorides we have put forward a method for the preparation of enantiopure (*S*)-6-fluoro-2-methyl-1,2,3,4-tetrahydroquinoline from the racemate.

4. Experimental

4.1. General

(*RS*)-7,8-Difluoro-3,4-dihydro-3-methyl-2*H*-[1,4]benzoxazine **1b**,[19] (*RS*)-2-methyl-1,2,3,4-tetrahydroquinoline **1c**,[20] (*RS*)-3,4-dihydro-3-methyl-2*H*-[1,4]benzoxazine **1d**,[19] *N*-phthaloyl-(*S*)-phenylalanyl **3a**,[10e] and *N*-phthaloyl-(*S*)-leucyl chlorides **3b**[10j] were obtained as described earlier. (*RS*)-6-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoline **1a** was prepared in a similar way as described for amine **1c**.[20] (*S*)-Naproxen acyl chloride **2** was obtained by the treatment of (*S*)-naproxen with oxalyl chloride according to the literature.[10c] Other reagents were commercially available. Amides **5**–**7**[10a,b] and **12**–**15**[10e,i,j] have been described previously.

The solvents were dried according to standard methods[21] and used freshly prepared. Flash column chromatography was performed using Silica gel 60 (230–400 mesh) (Alfa Aesar). Melting points were obtained on an SMP3 apparatus (Barloworld Scientific) and are uncorrected. Optical rotations were measured on a Perkin Elmer M341 polarimeter. The ^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on Bruker DRX-400 (400, 100, and 376 MHz, respectively) or Bruker Avance 500 (500, 126, and 470 MHz, respectively) spectrometers with TMS and hexafluorobenzene as the internal standards. The NMR spectra of amides were recorded in DMSO-d_6 at 100 °C; the NMR spectra of amine **1a**, in $CDCl_3$ at ambient temperature. All of the signals in the ^{1}H and ^{13}C NMR spectra of the compounds obtained were assigned on the basis of 2D ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC, and HMBC experiments at 100 °C. Elemental analysis was performed using a Perkin Elmer 2400 II analyzer. The high-resolution mass spectra were obtained on a Bruker Daltonics series MicrOTOF-Q II mass spectrometer, electrospray ionization with direct sample inlet (flow rate 180 μL/h).

Analytical HPLC of amide **4** was performed on an Agilent 1100 instrument using a Phenomenex Luna C18(2) column (250 × 4.6 mm, 5 μm), detection at 230 nm, 0.8 mL/min flow rate, MeCN–H_2O 7:3 as eluting solvent. Analytical HPLC was also performed on a Knauer Smartline-1100 instrument using a ReproSil 100 Si column (250 × 4.6 mm, 5 μm) for amides **8**–**11**, detection at 220 nm, 1 mL/min flow rate, *n*-hexane–*i*-PrOH 80:1 mixture as eluting solvent; and a Chiralcel OD-H column (250 × 4.6 mm) for amines **1a**–**d**, detection at 200 nm, 1 mL/min flow rate, *n*-hexane–*i*-PrOH–MeOH 100:1:1 for **1a** ($\tau_{(R)\text{-}\mathbf{1a}}$ 5.8–6.0 min, $\tau_{(S)\text{-}\mathbf{1a}}$ 7.6–7.8 min); *n*-hexane–*i*-PrOH 40:1 for **1b** ($\tau_{(R)\text{-}\mathbf{1b}}$ 11.8–12.0 min, $\tau_{(S)\text{-}\mathbf{1b}}$ 14.7–14.9 min); *n*-hexane–*i*-PrOH–MeOH 140:0.7:0.3 for **1c** ($\tau_{(R)\text{-}\mathbf{1c}}$ 9.5–9.6 min, $\tau_{(S)\text{-}\mathbf{1c}}$ 10.5–10.7 min); *n*-hexane–*i*-PrOH–MeOH 100:1.5:1.5 for **1d** ($\tau_{(R)\text{-}\mathbf{1d}}$ 9.6–9.8 min, $\tau_{(S)\text{-}\mathbf{1d}}$ 10.5–10.6 min).

Crystallographic data for (*S,S*)-**8**, (*R,S*)-**9,** and (*S,S*)-**10** have been deposited with the Cambridge Crystallographic Data Centre (CCDC Nos. 926802–926804). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.2. (*RS*)-6-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoline 1a

Metallic sodium (3.5 g) was added portionwise to a stirred solution of 6-fluoro-2-methylquinoline (2.0 g, 12.4 mmol) in EtOH (40 mL) at 50 °C. The reaction mixture was stirred at 50 °C for 3 h and kept at ambient temperature overnight. Then, water (100 mL) and concentrated HCl (20 mL) were added, and the reaction mixture was concentrated to a volume of 110 mL, washed with benzene (2 × 20 mL), alkalized with NaOH to pH 9–10, and extracted with benzene (3 × 20 mL). Organic layer was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel using benzene as an eluent. Yield 1.4 g (68%). Colorless solid, mp 34–36 °C. ^{1}H NMR (500 MHz): δ 1.12 (3H, d, *J* 6.3 Hz, Me), 1.39 (1H, dddd, *J* 12.6, 11.3, 9.5, 5.2 Hz, H-3B), 1.82 (1H ddt, *J* 12.6, 5.8, 3.2 Hz, , H-3A), 2.61 (1H, ddd, *J* 16.7, 5.2, 3.7 Hz, H-4B), 2.72 (1H, ddd, *J* 16.7, 11.3, 5.8 Hz, H-4A), 3.24 (1H, dqd, *J* 9.5, 6.3, 3.1 Hz, H-2), 5.63 (1H, br s, NH), 6.43 (1H, m, H-8), 6.65–6.70 (2H, m, H-5, H-7). ^{13}C NMR (126 MHz): δ 21.88 (Me), 25.96 (C-4), 29.22 (C-3), 46.21 (C-2), 112.63 (d, $^{2}J_{CF}$ 22.0 Hz, C-7), 114.06 (d, $^{3}J_{CF}$ 7.4 Hz, C-8), 114.62 (d, $^{2}J_{CF}$ 21.2 Hz, C-5), 121.15 (d, $^{3}J_{CF}$ 6.8 Hz, C-4a), 141.60 (C-8a), 154.91 (d, $^{1}J_{CF}$ 230.8 Hz, C-6). ^{19}F NMR (376 MHz): δ 32.50 (td, *J* = 9.1, 5.2 Hz, F-6). Anal. Calcd for $C_{10}H_{12}FN$ (M 165.21): C 72.70, H 7.32, F 11.50, N 8.48. Found: C 72.63, H 7.15, F 11.16, N 8.58.

4.3. (2*RS*)-6-Fluoro-*N*-[(2*S*)-2-(6-methoxynaphth-2-yl)-propanoyl]-2-methyl-1,2,3,4-tetrahydroquinoline 4 (diastereomeric mixture)

A solution of acyl chloride **2** (64.7 mg, 0.26 mmol) in CH_2Cl_2 (2.0 mL) was added to a solution of amine **1a** (42.9 mg, 0.26 mmol) and *N,N*-diethylaniline (38.8 mg, 0.26 mmol) in CH_2Cl_2 (3.1 mL) with stirring at +20 °C. The reaction mixture was stirred at +20 °C for 24 h and washed successively with 4 N HCl (2 × 3 mL), saturated aqueous NaCl (4 × 4 mL), 5% aqueous $NaHCO_3$ (2 × 3 mL), and water (2 × 4 mL). The organic layer was separated, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was purified by flash column chromatography on silica gel using benzene–EtOAc as eluting solvent. Yield 58.9 mg, 60%. Colorless oil. (*S,S*-*R,S*) 53:47 (HPLC: Phenomenex Luna C18(2), MeCN–H_2O 7:3, $\tau_{(S,S)\text{-}\mathbf{4}}$ 17.8 min, $\tau_{(R,S)\text{-}\mathbf{4}}$ 22.5 min). ^{1}H NMR (500 MHz): δ 0.89

(1.59H, d, *J* 6.6 Hz, Me-2 (*S*,*S*)), 1.02 (1.41H, d, *J* 6.5 Hz, Me-2 (*R*,*S*)), 1.14 (0.53H, m, H-3B (*S*,*S*)), 1.27 (0.47H, ddt, *J* 13.2, 9.1, 5.9 Hz, H-3B (*R*,*S*)), 1.37 (1.41H, d, *J* 6.8 Hz, Me-2′ (*R*,*S*)), 1.44 (1.59H, d, *J* 6.9 Hz, Me-2′ (*S*,*S*)), 1.74 (0.53H, m, H-4B (*S*,*S*)), 2.03 (0.47H, m, H-4B (*R*,*S*)), 2.11 (0.53H, dddd, *J* 13.2, 7.6, 5.7, 5.2 Hz, H-3A (*S*,*S*)), 2.29 (0.53H, dt, *J* 15.0, 5.2, Hz, H-4A (*S*,*S*)), 2.43 (0.47H, m, H-3A (*R*,*S*)), 2.63 (0.47H, dt, *J* 15.5, 5.9 Hz, H-4A (*R*,*S*)), 3.84 (1.59H, s, OMe (*S*,*S*)), 3.86 (1.41H, s, OMe (*R*,*S*)), 4.12 (0.47H, q, *J* 6.8 Hz, H-2′ (*R*,*S*)), 4.36 (0.53H, q, *J* 6.9 Hz, H-2′ (*S*,*S*)), 4.67 (0.53H, dqw, *J* 7.6, 6.6 Hz, H-2 (*S*,*S*)), 4.75 (0.47H, m, H-2 (*R*,*S*)), 6.78 (0.53H, dd, *J* 9.0, 2.9 Hz, H-5 (*S*,*S*)), 6.93 (0.47H, td, *J* 9.0, 2.9 Hz, H-7 (*R*,*S*)), 6.98 (0.53H, m, H-3″ (*S*,*S*)), 7.02 (0.47H, dd, *J* 9.0, 2.9 Hz, H-7″ (*R*,*S*)), 7.05 (0.53H, td, *J* 9.0, 2.9 Hz, H-7 (*S*,*S*)), 7.08 (0.53H, dd, *J* 9.0, 2.6 Hz, H-7″ (*S*,*S*)), 7.12-7.15 (0.94H, m, H-5 and H-8 (*R*,*S*)), 7.17 (1.06H, m, H-5″ and H-1″ (*S*,*S*)), 7.27 (0.47H, d, *J* 2.9 Hz, H-5″ (*R*,*S*)), 7.41 (0.53H, dd, *J* 8.7, 5.2 Hz, H-8 (*S*,*S*)), 7.45 (0.47H, dd, *J* 8.5, 1.9 Hz, H-3″ (*R*,*S*)), 7.56–7.58 (1.06H, m, H-8″ and H-4″ (*S*,*S*)), 7.72 (0.47H, d, *J* 1.9 Hz, H-1″ (*R*,*S*)), 7.75–7.77 m (0.94H, m, H-4″ and H-8″ (*R*,*S*)). ^{19}F NMR (470 MHz): δ 45.44 (0.47F, m, F-6 (*R*,*S*)), 45.61 (0.53F, m, F-6 (*S*,*S*)). Anal. Calcd for $C_{24}H_{24}FNO_2$: C, 76.37; H, 6.41; N, 3.71; F, 5.03. Found: C, 76.33; H, 6.67; N, 3.51; F, 4.83.

4.4. Synthesis of diastereoisomeric amides 8–11. General procedure

A solution of the appropriate acyl chloride (1 mmol) in CH_2Cl_2 (10 mL) was added to a solution of amine **1a** or **1b** (2 mmol) in CH_2Cl_2 (10 mL) at +20 °C. The reaction mixture was kept in a thermostat at a given temperature for 6 h, then successively washed with 4 M HCl (2 × 5 mL), saturated aqueous NaCl (3 × 15 mL), 5% $NaHCO_3$ (10 mL), and water (2 × 15 mL). The organic layer was separated, dried over $MgSO_4$, and evaporated under reduced pressure. The diastereoisomers of amides **8**–**11** were isolated by recrystallization or flash column chromatography on silica gel.

4.4.1. (2*S*)-6-Fluoro-2-methyl-*N*-[*N*′-phthaloyl-(*S*)-phenylalanyl]-1,2,3,4-tetrahydroquinoline [(*S*,*S*)-8]

Yield 204 mg, 46% (recrystallization from hexane–ethyl acetate). Colorless solid, mp 189–190 °C. $[\alpha]_D^{20} = +346$ (*c* 1.0, $CHCl_3$). *De* >99.8% (HPLC: ReproSil 100 Si, hexane–*i*PrOH 80:1, τ 10.33 min). ^{1}H NMR (500 MHz): δ 1.02 (3H, d, *J* 6.5 Hz, Me-2), 1.30 (1H, dddd, *J* 13.1, 10.4, 6.9, 5.3 Hz, H-3B), 2.31 (1H, ddt, *J* 13.1, 7.4, 5.3 Hz, H-3A), 2.46 (1H, ddd, *J* 15.2, 10.4, 5.2 Hz, H-4B), 2.69 (1H, dt, *J* 15.2, 5.3 Hz, H-4A), 2.73 (1H, dd, *J* 14.2, 4.7 Hz, H-3′B), 3.71 (1H, dd, *J* 14.2, 11.2 Hz, H-3′A), 4.64 (1H, ddq, *J* 7.4, 6.9, 6.5 Hz, H-2), 5.69 (1H, dd, *J* 11.2, 4.7 Hz, H-2′), 6.78 (2H, m, H*o*), 7.03–7.11 (3H, m, H*p* and H*m*), 7.14 (1H, dd, *J* 8.9, 2.9 Hz, H-5), 7.19 (1H, td, *J* 8.8, 2.9 Hz, H-7), 7.56 (1H, dd, *J* 8.7, 5.1 Hz, H-8), 7.82 (4H, m, Phth). ^{13}C NMR (126 MHz): δ 19.20 (Me-2), 24.82 (C-4), 31.04 (C-3), 31.72 (C-3′), 48.72 (C-2), 54.38 (C-2′), 112.82 (d, $^2J_{CF}$ 23.0 Hz, C-7), 114.17 (d, $^2J_{CF}$ 22.7 Hz, C-5), 122.52 (C-4″, 7″), 125.98 (C*p*), 126.45 (d, $^3J_{CF}$ 8.7 Hz, C-8), 127.50 (C*o*), 127.71 (C*m*), 130.61 (C-3″a, 7″a), 132.20 (d, $^4J_{CF}$ 2.7 Hz, C-8a), 134.10 (C-5″, 6″), 136.49 (C*i*), 137.84 (d, $^3J_{CF}$ 8.1 Hz, C-4a), 159.67 (d, $^1J_{CF}$ 244.2 Hz, C-6), 166.84 (C-1′), 167.39 (C-1″, 3″). ^{19}F NMR (470 MHz, DMSO-d_6): δ 46.96 (m, F-6). Anal. Calcd for $C_{27}H_{23}FN_2O_3$: C, 73.29; H, 5.24; N, 6.22; F, 4.29. Found: C, 73.13; H, 5.12; N, 6.35; F, 4.04.

4.4.2. (2*R*)-6-Fluoro-2-methyl-*N*-[*N*′-phthaloyl-(*S*)-phenylalanyl]-1,2,3,4-tetrahydroquinoline (*R*,*S*)-8

Yield 48.7 mg, 11% (flash column chromatography of mother liquor after recrystallization, eluent hexane–ethyl acetate, fast eluting isomer). Amorphous solid. $[\alpha]_D^{20} = -311$ (*c* 0.5, $CHCl_3$). *De* 97% (HPLC: ReproSil 100 Si, hexane–*i*PrOH 80:1, τ 7.25 min). ^{1}H NMR (500 MHz): δ 0.97 (3H, d, *J* 6.5 Hz, Me-2), 1.13 (1H, m, H-3B), 2.18 (1H, ddd, *J* 14.6, 9.9, 5.2 Hz, H-4B), 2.25 (1H, ddt, *J* 12.8, 7.6, 5.2 Hz, H-3A), 2.34 (1H, ddd, *J* 14.6, 5.2 Hz, H-4A), 3.18 (1H, dd, *J* 14.1, 9.8 Hz, H-3′B), 3.53 (1H, dd, *J* 14.1, 5.3 Hz, H-3′A), 4.56 (1H, m, H-2), 5.46 (1H, dd, *J* 9.8, 5.3 Hz, H-2′), 6.52 (1H, dd, *J* 8.8, 2.9 Hz, H-5), 6.77 (1H, td, *J* 8.7, 2.9 Hz, H-7), 7.04–7.10 (5H, m, Ph), 7.26 (1H, dd, *J* 8.7, 5.2 Hz, H-8), 7.58 (2H, m, H-4″, 7″ Phth), 7.70 (2H, m, H-5″, 6″ Phth). ^{13}C NMR (126 MHz): δ 19.14 (Me-2), 24.24 (C-4), 30.78 (C-3), 34.99 (C-3′), 48.71 (C-2), 52.06 (C-2′), 112.86 and 112.90 (both d, $^2J_{CF}$ 22.7 Hz, C-5 and C-7), 122.02 (C-4″, 7″), 125.67 (C*p*), 125.92 (d, $^3J_{CF}$ 8.9 Hz, C-8), 127.36 (C*o*), 128.64 (C*m*), 130.04 (C-3″a, 7″a), 132.09 (d, $^4J_{CF}$ 2.7 Hz, C-8a), 133.82 (C-5″, 6″), 136.25 (d, $^3J_{CF}$ 8.2 Hz, C-4a), 137.03 (C*i*), .158.89 (d, $^1J_{CF}$ 243.1 Hz, C-6), 165.39 (C-1″, 3″), 166.70 (C-1′). ^{19}F NMR (470 MHz, DMSO-d_6): δ 45.37 (m, F-6). HRMS (ESI) *m*/*z*, Calcd for $C_{27}H_{24}FN_2O_3$ ([M+H]$^+$): 443.1771; found: 443.1765.

4.4.3. (3*S*)-7,8-Difluoro-3,4-dihydro-3-methyl-*N*-(*N*′-phthaloyl-(*S*)-phenylalanyl)-2*H*-[1,4]benzoxazine (*S*,*S*)-9

Yield 58.6 mg, 13% (flash column chromatography, eluent benzene–ethyl acetate, slow eluting isomer). Yellowish foam. $[\alpha]_D^{20} = +280$ (*c* 1.0, $CHCl_3$). *De* 99.8% (HPLC: ReproSil 100 Si, hexane–*i*PrOH 80:1, τ 11.65 min). ^{1}H NMR (500 MHz): δ 1.07 (3H, d, *J* 6.8 Hz, Me-3), 3.40 (1H, dd, *J* 14.1, 6.5 Hz, H-3′B), 3.71 (1H, dd, *J* 14.1, 9.3 Hz, H-3′A), 4.06 (1H, dd, *J* 11.1, 3.0 Hz, H-2B); 4.32 (1H, dd, *J* 11.1, 1.5 Hz, H-2A), 4.79 (1H, qdd, *J* 6.8, 3.0, 1.5 Hz, H-3), 5.69 (1H, dd, *J* 9.3, 6.4 Hz, H-2′), 6.95 (1H, td, *J* 9.8, 8.1 Hz, H-6), 7.04-7.18 (5H, m, Ph), 7.61 (1H, ddd, *J* 9.4, 5.3, 2.4 Hz, H-5), 7.82 (4H, s, Phth). ^{13}C NMR (126 MHz): δ 14.40 (Me-3), 33.58 (C-3′), 45.14 (C-3), 53.59 (C-2′), 69.77 (C-2), 106.63 (d, $^2J_{CF}$ 18.5 Hz, C-6), 118.95 (dd, $^3J_{CF}$ 8.1, $^4J_{CF}$ 4.2 Hz, C-5), 120.75 (dd, $^3J_{CF}$ 3.1, $^4J_{CF}$ 1.9 Hz, C-4a), 122.59 (C-4″, 7″), 126.11 (C*p*), 127.70 C*m*), 128.12 (C*o*), 130.56 (C-3″a, 7″a), 134.14 (C-5″, 6″), 136.14 (C*i*), 136.23 (dd, $^2J_{CF}$ 10.0, $^3J_{CF}$ 3.5 Hz, C-8a), 138.76 (dd, $^1J_{CF}$ 245.3, $^2J_{CF}$ 15.6 Hz, C-8), 147.02 (dd, $^1J_{CF}$ 243.1, $^2J_{CF}$ 10.0 Hz, C-7), 166.74 (C-1′), 167.10 (C-1″, 3″). ^{19}F NMR (470 MHz): δ 2.63 (1F, ddd, *J* 21.0, 8.1, 2.4 Hz, F-8), 21.71 (1F, ddd, *J* 21.0, 9.8, 5.3 Hz, F-7). Anal. Calcd for $C_{26}H_{20}F_2N_2O_4$: C, 67.53; H, 4.36; N, 6.06. Found: C, 67.70; H, 4.32; N, 5.97.

4.4.4. (3*R*)-7,8-Difluoro-3,4-dihydro-3-methyl-*N*-(*N*′-phthaloyl-(*S*)-phenylalanyl)-2*H*-[1,4]benzoxazine (*R*,*S*)-9

Yield 32.9 mg, 7.3% (flash column chromatography, eluent benzene–ethyl acetate, fast eluting isomer). Colorless powder, mp 185 °C. $[\alpha]_D^{20} = -391$ (*c* 1.0, $CHCl_3$). *De* 99.2% (HPLC: ReproSil 100 Si, hexane–*i*PrOH 80:1, τ 4.85 min). ^{1}H NMR (500 MHz): δ 0.86 (3H, d, *J* 6.9 Hz, Me-3), 3.28 (1H, dd, *J* 14.2, 9.7 Hz, H-3′B), 3.48 (1H, dd, *J* 14.2, 5.3 Hz, H-3′A), 4.17 (1H, dd, *J* 10.8, 3.0 Hz, H-2B), 4.27 (1H, dd, *J* 10.8, 1.6 Hz, H-2A), 4.54 (1H, m, H-3), 5.63 (1H, dd, *J* 9.7, 5.3 Hz, H-2′), 6.76 (1H, ddd, *J* 9.9, 9.3, 8.4 Hz, H-6), 7.07-7.15 (5H, m, Ph), 7.32 (1H, ddd, *J* 9.3, 5.4, 2.5 Hz, H-5), 7.72 (2H, m, Phth), 7.77 (2H, m, Phth). ^{13}C NMR (126 MHz): δ 14.09 (Me-3), 34.79 (C-3′), 44.92 (C-3), 51.93 (C-2′), 69.61 (C-2), 106.60 (d, $^2J_{CF}$ 18.5 Hz, C-6), 119.00 (dd, $^3J_{CF}$ 8.2, $^4J_{CF}$ 3.8 Hz, C-5), 120.52 (dd, $^3J_{CF}$ 2.7, $^4J_{CF}$ 1.9 Hz, C-4a), 122.49 (C4″, 7″), 125.88 (C*p*), 127.48 (C*m*), 128.69 (C*o*), 130.04 (C-3″a, 7″a), 134.24 (C-5″, 6″), 135.51 (dd, $^2J_{CF}$ 10.0, $^3J_{CF}$ 3.5 Hz, C-8a), 136.56 (C*i*), 138.35 (dd, $^1J_{CF}$ 245.1, $^2J_{CF}$ 15.5 Hz, C-8), 146.63 (dd, $^1J_{CF}$ 242.9, $^2J_{CF}$ 10.0 Hz, C-7), 165.90 (C-1″, 3″), 166.82 (C-1′). ^{19}F NMR (470 MHz, DMSO-d_6): δ 1.71 (1F, ddd, *J* 20.8, 8.4, 2.5 Hz, F-8), 21.04 (1F, m, F-7). Anal. Calcd for $C_{26}H_{20}F_2N_2O_4$: C, 67.53; H, 4.36; N, 6.06. Found: C, 67.36; H, 4.34; N, 6.19.

4.4.5. (2*S*)-6-Fluoro-2-methyl-*N*-[*N*′-phthaloyl-(*S*)-leucyl]-1,2,3,4-tetrahydroquinoline (*S*,*S*)-10

Yield 221 mg, 54% (flash column chromatography, eluent hexane–ethyl acetate, slow eluting isomer). Colorless crystals, mp 115–116 °C. $[\alpha]_D^{20} = +387$ (*c* 1.0, $CHCl_3$). *De* 99.8% (HPLC: ReproSil

100 Si, hexane–*i*PrOH 80:1, τ 9.75 min). ^{1}H NMR (500 MHz): δ 0.44 (3H, d, *J* 6.6 Hz, Me-4′), 0.67 (3H, d, *J* 6.6 Hz, Me-4′), 0.92 (1H, ddd, *J* 13.8, 9.8, 3.8 Hz, H-3′B), 1.01 (3H, d, *J* 6.6 Hz, Me-2), 1.27 (1H, dddd, *J* 13.2, 10.7, 7.2, 5.1 Hz, H-3B), 1.33 (1H, dseptd, *J* 9.8, 6.6, 3.9 Hz, H-4′), 2.34 (1H, dddd, *J* 13.2, 7.5, 5.4, 4.8 Hz, H-3A), 2.45 (1H, ddd, *J* 15.1, 10.7, 5.4 Hz, H-4B), 2.58 (1H, ddd, *J* 13.8, 12.0, 3.9 Hz, H-3′A), 2.71 (1H, dt, *J* 15.1, 4.9 Hz, H-4A), 4.59 (1H, tq, *J* 7.3, 6.6 Hz, H-2), 5.46 (1H, dd, *J* 12.0, 3.8 Hz, H-2′), 7.13–7.17 (2H, m, H-5 and H-7), 7.49 (1H, dd, *J* 8.9, 5.2 Hz, H-8), 7.86 (4H, m, Phth). ^{13}C NMR (126 MHz): δ 19.36 (Me-2), 19.61 (Me-4′), 21.90 (Me-4′), 24.26 (C-4′), 25.02 (C-4), 31.35 (C-3), 34.24 (C-3′), 48.63 (C-2), 51.73 (C-2′), 112.77 (d, $^2J_{CF}$ 23.0 Hz, C-7), 113.92 (d, $^2J_{CF}$ 22.8 Hz, C-5), 122.49 (C-4″, 7″), 126.44 (d, $^3J_{CF}$ 8.9 Hz, C-8), 130.91 (C-3″a, 7″a), 132.23 (d, $^4J_{CF}$ 2.8 Hz, C-8a), 134.01 (C-5″, 6″), 138.05 (d, $^3J_{CF}$ 8.5 Hz, C-4a), 159.71 (d, $^1J_{CF}$ 244.1 Hz, C-6), 167.72 (C-1″, 3″), 168.14 (C-1′). ^{19}F NMR (470 MHz): δ 46.82 (td, *J* 9.1, 5.2 Hz, F-6). Anal. Calcd for $C_{24}H_{25}FN_2O_3$: C, 70.57; H, 6.17; N, 6.86; F, 4.65. Found: C, 70.60; H, 6.05; N, 6.82; F, 4.63.

4.4.6. (2*R*)-6-Fluoro-2-methyl-*N*-[*N*′-phthaloyl-(*S*)-leucyl]-1,2,3,4-tetrahydroquinoline (*R*,*S*)-10

Yield 73.5 mg, 18% (flash column chromatography, eluent hexane–ethyl acetate, fast eluting isomer). Semi-solid. $[\alpha]_D^{20} = -176$ (*c* 1.0, $CHCl_3$). *De* 99% (HPLC: ReproSil 100 Si, hexane–*i*PrOH 80:1, τ 6.78 min). ^{1}H NMR (500 MHz): δ 0.86 (3H, d, *J* 6.6 Hz, Me-4′), 0.93 (3H, d, *J* 6.6 Hz, Me-4′), 0.97 (3H, d, *J* 6.5 Hz, Me-2), 1.13 (1H, m, H-3B), 1.48 (1H, dseptd, *J* 8.4, 6.6, 4.9 Hz, H-4′), 1.85 (1H, ddd, *J* 14.2, 9.3, 4.9 Hz, H-3′B), 2.06 (1H, ddd, *J* 14.2, 8.4, 5.1 Hz, H-3′A), 2.18 (1H, ddd, *J* 14.6, 9.9, 5.3 Hz, H-4B), 2.24 (1H, m, H-3A), 2.34 (1H, ddd, *J* 14.6, 5.0, 4.7 Hz, H-4A), 4.52 (1H, dqw, *J* 7.3, 6.6 Hz, H-2), 5.18 (1H, dd, *J* 9.3, 5.1 Hz, H-2′), 6.54 (1H, dd, *J* 8.8, 2.9 Hz, H-5), 6.83 (1H, td, *J* 8.8, 2.9 Hz, H-7), 7.28 (1H, dd, *J* 8.7, 5.1 Hz, H-8), 7.67 (2H, m, H-4″, 7″ Phth), 7.76 (2H, m, H-5″, 6″ Phth). ^{13}C NMR (126 MHz): δ 19.20 (Me-2), 21.26 (Me-4′), 22.40 (Me-4′), 23.82 (C-4′), 24.30 (C-4), 30.82 (C-3), 38.24 (C-3′), 48.62 (C-2), 49.25 (C-2′), 112.89 and 112.94 (both d, $^2J_{CF}$ 22.8 Hz, C-5 and C-7), 122.11 (C-4″, 7″), 125.94 (d, $^3J_{CF}$ 8.8 Hz, C-8), 130.29 (C-3″a, 7″a), 132.21 (d, $^4J_{CF}$ 2.6 Hz, C-8a), 133.87 (C-5″, 6″), 136.39 (d, $^3J_{CF}$ 7.7 Hz, C-4a), 159.93 (d, $^1J_{CF}$ 243.0 Hz, C-6), 165.87 (C-1″, 3″), 167.12 (C-1′). ^{19}F NMR (470 MHz): δ 45.39 (td, *J* 8.8, 5.1 Hz, F-6). HRMS (ESI) *m*/*z*, calcd for $C_{24}H_{26}FN_2O_3$ ($[M+H]^+$): 409.1928; found: 409.1922.

4.4.7. (3*S*)-7,8-Difluoro-3,4-dihydro-3-methyl-*N*-[*N*′-phthaloyl-(*S*)-leucyl]-2*H*-[1,4]benzoxazine (*S*,*S*)-11

Yield 137 mg, 32% (flash column chromatography, eluent benzene–ethyl acetate, slow eluting isomer). Colorless powder, mp 160–161 °C. $[\alpha]_D^{20} = +279$ (*c* 1.0, $CHCl_3$). *De* 98% (HPLC: ReproSil 100 Si, hexane–*i*PrOH 80:1, τ 9.33 min). ^{1}H NMR (500 MHz): δ 0.76 (3H, d, *J* 6.4 Hz, Me-4′), 0.83 (3H, d, *J* 6.4 Hz, Me-4′), 1.17 (3H, d, *J* 6.8 Hz, Me-3), 1.51 (1H, ddd, *J* 12.9, 9.1, 3.9 Hz, H-3′B), 1.56 (1H, m, H-4′), 2.60 (1H, ddd, *J* 12.9, 11.2, 3.4 Hz, H-3′A), 4.15 (1H, dd, *J* 11.1, 3.1 Hz, H-2B), 4.39 (1H, dd, *J* 11.1, 1.5 Hz, H-2A), 4.77 (1H, qdd, *J* 6.8, 3.1, 1.5 Hz, H-3), 5.47 (1H, dd, *J* 11.2, 3.9 Hz, H-2′), 6.97 (1H, td, *J* 9.8, 8.2 Hz, H-6), 7.48 (1H, ddd, *J* 9.4, 5.3, 2.5 Hz, H-5), 7.86 (4H, m, Phth). ^{13}C NMR (126 MHz): δ 14.44 (Me-3), 20.25 (Me-4′), 21.90 (Me-4′), 24.51 (C-4′), 35.47 (C-3′), 45.06 (C-3), 51.32 (C-2′), 70.04 (C-2), 106.84 (d, $^2J_{CF}$ 18.5 Hz, C-6), 119.04 (dd, $^3J_{CF}$ 8.5, $^4J_{CF}$ 4.6 Hz, C-5), 120.79 (m, C-4a), 122.61 (C-4″, 7″), 130.78 (C-3″a, 7″a), 134.12 (C-5″, 6″), 136.32 (dd, $^2J_{CF}$ 10.0, $^3J_{CF}$ 3.1 Hz, C-8a), 138.81 (dd, $^1J_{CF}$ 245.8, $^2J_{CF}$ 15.4 Hz, C-8), 147.13 (dd, $^1J_{CF}$ 243.5, $^2J_{CF}$ 10.0 Hz, C-7), 167.43 (C-1″, 3″), 167.85 (C-1′). ^{19}F NMR (470 MHz): δ 2.80 (1F, dd, *J* 21.2, 8.2 Hz, F-8), 22.02 (1F, m, F-7). Anal. Calcd for $C_{23}H_{22}F_2N_2O_4$: C, 64.48; H, 5.18; N, 6.54; F, 8.87. Found: C, 64.48; H, 5.08; N, 6.36; F, 8.61.

4.4.8. (3*R*)-7,8-Difluoro-3,4-dihydro-3-methyl-*N*-[*N*′-phthaloyl-(*S*)-leucyl]-2*H*-[1,4]benzoxazine (*R*,*S*)-11

Yield 64.3 mg, 15% (flash column chromatography, eluent benzene–ethyl acetate, fast eluting isomer). Colorless powder, mp 75–78 °C. $[\alpha]_D^{20} = -217$ (*c* 1.1, $CHCl_3$). *De* 99% (HPLC: ReproSil 100 Si, hexane–*i*PrOH 80:1, τ 4.93 min). ^{1}H NMR (500 MHz): δ 0.88 (3H, d, *J* 6.7 Hz, Me-3), 0.89 (3H, d, *J* 6.6 Hz, Me-4′), 0.95 (3H, d, *J* 6.6 Hz, Me-4′), 1.54 (1H, dseptd, *J* 8.5, 6.6, 5.0 Hz, H-4′), 1.95 (1H, ddd, *J* 14.1, 9.1, 5.0 Hz, H-3′B), 2.01 (1H, ddd, *J* 14.1, 8.5, 5.3 Hz, H-3′A), 4.19 (1H, dd, *J* 10.9, 3.2 Hz, H-2B), 4.27 (1H, dd, *J* 10.9, 1.4 Hz, H-2A), 4.56 (1H, m, H-3), 5.32 (1H, dd, *J* 9.1, 5.3 Hz, H-2′), 6.76 (1H, ddd, *J* 10.1, 9.3, 8.2 Hz, H-6), 7.31 (1H, ddd, *J* 9.3, 5.4, 2.5 Hz, H-5), 7.81 (4H, m, Phth). ^{13}C NMR (126 MHz): δ 14.16 (Me-3), 21.21 (Me-4′), 22.39 (Me-4′), 23.81 (C-4′), 37.99 (C-3′), 44.81 (C-3), 49.21 (C-2′), 69.94 (C-2), 106.59 (d, $^2J_{CF}$ 18.5 Hz, C-6), 118.97 (dd, $^3J_{CF}$ 8.1, $^4J_{CF}$ 3.8 Hz, C-5), 120.71 (t, J_{CF} 2.3 Hz, C-4a), 122.57 (C-4″, 7″), 130.29 (C-3″a, 7″a), 134.26 (C-5″, 6″), 135.53 (dd, $^2J_{CF}$ 10.0, $^3J_{CF}$ 3.5 Hz, C-8a), 138.35 (dd, $^1J_{CF}$ 244.9, $^2J_{CF}$ 15.2 Hz, C-8), 146.63 ($^1J_{CF}$ 242.5, $^2J_{CF}$ 10.2 Hz, C-7), 166.32 (C-1″, 3″), 167.32 (C-1′). ^{19}F NMR (470 MHz): δ 1.69 (1F, ddd, *J* 20.9, 8.2, 2.5 Hz, F-8), 20.97 (1F, m, F-7). HRMS (ESI) *m*/*z*, calcd for $C_{23}H_{23}F_2N_2O_4$ ($[M+H]^+$): 429.1626; found: 429.1620.

4.5. Kinetic resolution of racemic amines 1a and 1b. General procedure

A solution of the appropriate acyl chloride (0.15 mmol) in CH_2Cl_2 (1.5 mL) was added to a solution of amine (0.30 mmol) in CH_2Cl_2 (1.5 mL) at a specified temperature. The reaction mixture was kept at the appropriate temperature for 6 h, then washed with 4 M HCl (2 × 3 mL), saturated aqueous NaCl (3 × 3 mL), 5% $NaHCO_3$ (3 mL), and water (2 × 3 mL). The organic layer was separated, dried over $MgSO_4$, and evaporated under reduced pressure to give a mixture of diastereoisomeric amides, which was analyzed by HPLC. Acidic washing solutions were collected and alkalized with Na_2CO_3 up to pH 8–9, and extracted with $CHCl_3$ (2 × 3 mL). The organic layer was separated, dried over $MgSO_4$, and evaporated under reduced pressure to give an enantiomeric mixture of unreacted amine **1a** or **1b**, which was analyzed by chiral HPLC.

4.6. (2*S*)-6-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (*S*)-1a

A solution of acyl chloride **2** (550 mg, 2.21 mmol) in CH_2Cl_2 (22 mL) was added to a solution of amine **1a** (731 mg, 4.42 mmol) in CH_2Cl_2 (22 mL) with stirring at −20 °C. The reaction mixture was kept at −20 °C for 24 h and then washed successively with 4 M HCl (2 × 15 mL), saturated aqueous NaCl (4 × 20 mL), 5% aqueous $NaHCO_3$ (2 × 15 mL), and water (2 × 20 mL). The organic layer was separated, dried over $MgSO_4$, and evaporated under reduced pressure. The residue was recrystallized from a hexane–EtOAc mixture to afford amide (*S*,*S*)-**4** (474 mg, 58%). Colorless crystals, mp 90 °C. $[\alpha]_D^{20} = +58.0$ (*c* 1.0, $CHCl_3$). *De* >99% (HPLC: Phenomenex Luna C18(2), MeCN–H_2O 7:3, τ 17.8 min). ^{1}H NMR (500 MHz): δ 0.89 (3H, d, *J* 6.6 Hz, Me-2), 1.14 (1H, m, H-3B), 1.45 (3H, d, *J* 6.8 Hz, Me-2′), 1.74 (1H, m, H-4B), 2.11 (1H, dddd, *J* 13.2, 7.6, 5.6, 5.2 Hz, H-3A), 2.29 (1H, dt, *J* 15.0, 5.2 Hz, H-4A), 3.84 (3H, s, OMe), 4.36 (1H, q, *J* 6.8 Hz, H-2′), 4.67 (1H, dq, *J* 7.6, 6.6 Hz, H-2), 6.77 (1H, dd, *J* 9.0, 2.9 Hz, H-5), 6.98 (1H, dd, *J* 8.4, 1.5 Hz, H-3″ Naph), 7.05 (1H, td, *J* 8.7, 9.0 Hz, H-7), 7.08 (1H, dd, *J* 8.9, 2.5 Hz, H-7″ Naph), 7.17 (2H, m, H-5″ and H-1″ Naph), 7.41 (1H, dd, *J* 8.7, 5.2 Hz, H-8), 7.57 (2H, m, H-8″ and H-4″ Naph). ^{13}C NMR (126 MHz): δ 18.58 (Me-2′), 19.28 (Me-2), 24.27 (C-4), 31.00 (C-3), 41.73 (C-2′), 47.44 (C-2), 54.72 (OMe), 105.82 (C-5″), 112.18 (d, $^2J_{CF}$ 22.6 Hz, C-7), 113.10 (d, $^2J_{CF}$ 22.6 Hz, C-5), 117.76 (C-7″), 124.62 (C-1″), 125.13 (C-3″), 126.02 and 128.25 (C-4″ and C-8″), 127.39 (d, $^3J_{CF}$ 8.5 Hz, C-8), 127.92 (C-8″a), 132.52 (C-4″a), 133.00

(d, $^4J_{CF}$ 2.7 Hz, C-8a), 136.15 (C-2″), 137.41 (C-4a), 156.70 (C-6″), 159.23 (d, $^1J_{CF}$ 242.8 Hz, C-6), 172.24 (C-1′). ^{19}F NMR (376 MHz): δ 46.6 (m, F-6). Anal. Calcd for $C_{24}H_{24}FNO_2$: C, 76.37; H, 6.41; N, 3.71, F, 5.03. Found: C, 76.32; H, 6.47; N, 3.67; F, 5.05.

Concentrated HCl (10 mL) was added to a solution of amide (*S*,*S*)-**4** (474 mg, 1.27 mmol) in glacial AcOH (10 mL). The reaction mixture was heated at 95 °C for 10 h, then evaporated to a half volume and poured into water (150 mL). The precipitate was filtered off and the filtrate was alkalized with Na_2CO_3 to pH 8–9 and then extracted with benzene (4 × 30 mL). Combined organic layers were washed with water (2 × 15 mL), dried over $MgSO_4$, and evaporated under reduced pressure to afford amine (*S*)-**1a** (176 mg, 84%). Colorless solid, mp 40–41 °C (lit.[17b] mp 40–42 °C). $[\alpha]_D^{20} = -74.2$ (*c* 0.7, $CHCl_3$) {lit.[18i] $[\alpha]_D^{20} = -59.6$ (*c* 0.5, $CHCl_3$, 91% *ee*)}. *Ee* >99% (HPLC: Chiralcel OD-H, hexane–*i*PrOH–MeOH 100:1:1 τ 7.62 min). NMR spectra were identical to those of compound **1a**. Anal. Calcd for $C_{10}H_{12}FN$: C, 72.70; H, 7.32; N, 8.48; F, 11.50. Found: C, 72.70; H, 7.60; N, 8.50; F, 11.52.

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