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Mutual kinetic resolution of 3-methyl-3,4-dihydro-2*H*-1,4-benzoxazines and 2-alkoxyacyl chlorides

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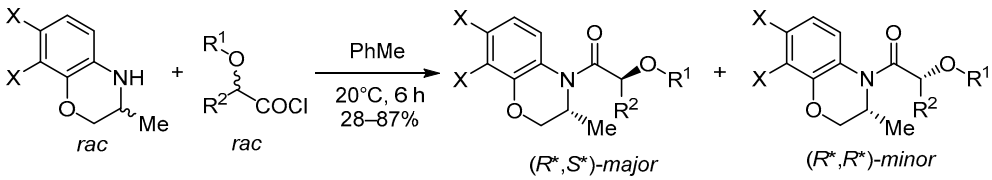


X = H, F; R^1 = Me, Bn; R^2 = Me, *i*-Pr, Ph, Bn (*R**,*S**)/(*R**,*R**) up to 97:3 (*s* 32)

Stereoselective acylation of racemic 3-methyl-3,4-dihydro-2*H*-1,4-benzoxazine and its 7,8-difluoro-substituted analog with racemic 2-alkoxyacyl chlorides was stidied. The reactions of 3-methyl-3,4-dihydro-2*H*-1,4-benzoxazines with 2-methoxyisopentanoyl chloride were found to be more selective (selectivity factor *s* 31–32) compared to the acylation with other studied propanoyl chlorides (*s* 18–21). This fact was probably caused by the significant steric hindrance due to the isopropyl substituent in acyl chloride compared to the methyl group in reagents derived from propanoic acid.

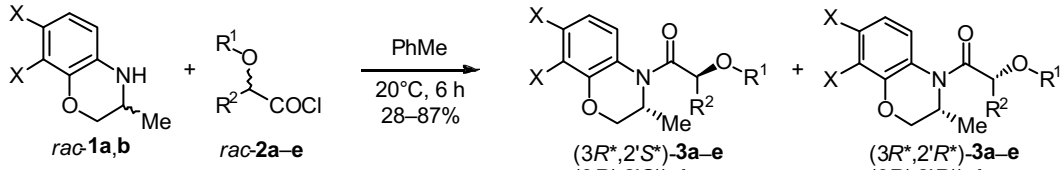
Keywords: acyl chlorides, 2-alkoxycarboxylic acids, heterocyclic amines, acylation, kinetic resolution, stereoselectivity.

Kinetic resolution (KR) of racemates is a common method for preparation of individual enantiomers of organic compounds belonging to various classes. The KR is based on reaction rate differences between the two enantiomers of racemic starting material and a chiral resolving reagent.[1,2] This approach allows obtaining of a stereoisomerically enriched product and the unreacted substrate, thus eventually providing access to both enantiomers of the target compound. One frequently used method for the preparation of enantiopure amines, including practically valuable products, involves their stereoselective acylation with chiral agents derived from carboxylic acids.[3,4] Correspondingly, enantiopure amines can be used as chiral reagents for the resolution of racemic acids and preparation of their optical isomers. Studying the reactions between racemic amines and racemic acylating reagents may be useful for the purpose of developing effective methods for the synthesis of stereoisomers of both amines and acids. Besides that, the investigation of stereoselective reactions between chiral amines and acylating agents is useful for establishing the reasons for stereoselectivity and recognizing the structural criteria for substrates and reagents that may be suitable for KR.

The individual enantiomers of heterocyclic aromatic amines, as well as of 2-substituted carboxylic acids are of significant interest as precursors and structural building blocks for natural and synthetic biologically active compounds (drugs, herbicides, and other products).[5,6] We have previously studied diastereoselective reactions between racemic heterocyclic amines and acyl chlorides derived from chiral 2-arylpropanoic acids,[7–10] *N*-protected amino acids,[9–17] and 2-phenoxycarboxylic acids.[18,19] The highest stereoselectivity with respect to 3-methylbenzoxazine derivatives **1a**,**b** (Scheme 1) was observed in the case of reagents containing the 2-phenoxy group, therefore we were interested in studying stereoselective acylation of these amines with 2-alkoxyacyl chlorides.

The purpose of the current work was to study the electronic and steric factors affecting the stereoselectivity of reaction between 3-methylbenzoxazines **1a**,**b** and chiral 2-alkoxyacyl chlorides **2a**–**e** (Scheme 1).

Scheme 1



1a, **3a–e** X = H, **1b, 4a–e** X = F

a R^1 = Me, R^2 = Me; **b** R^1 = Me, R^2 = *i*-Pr; **c** R^1 = Me, R^2 = Ph; **d** R^1 = Me, R^2 = Bn; **e** R^1 = Bn, R^2 = Me

When studying the determining factors for the stereoselectivity in acylation reactions of racemic amines **1a**,**b** with chiral acyl chlorides, we used an approach based on the reactions of racemic reagents, in other words, the limiting case of mutual KR.[2] In this case, the ratio of the diastereomeric amides formed was equal to the selectivity factor *s* representing a ratio of the reaction rates for the fast and slow reacting enantiomers of the substrate. Furthermore, the ratio of the starting reagents, their concentration, and the reaction duration does not affect the stereochemical outcome, and therefore the value of selectivity factor *s* can be determined quite accurately.[20]

The acylation of racemic amines **1a**,**b** with acyl chlorides **2a–e** was performed at 20°C for 6 h at amine-acyl chloride molar ratio 2:1 and 0.1 M initial concentration of the amine (Scheme 1). We have previously established that the acylation of amines **1a**,**b** with acyl chlorides derived from 2-phenoxycarboxylic acids proceeds most selectively in toluene,[18] therefore we selected toluene as the solvent in this study as well. The reaction resulted in the formation of a mixture consisting of 4 stereoisomers: (3*R*,2'*R*)/(3*S*,2'*S*)- and (3*R*,2'*S*)/(3*S*,2'*R*)-amides **3** and **4 a–e** (further denoted as (3*R**,2'*S**)- and (3*R**,2'*R**)-amides). The diastereomeric ratio (*dr*) of amides **3** and **4 a–e**, which is equal to the selectivity factor *s*, was determined by GC and HPLC.

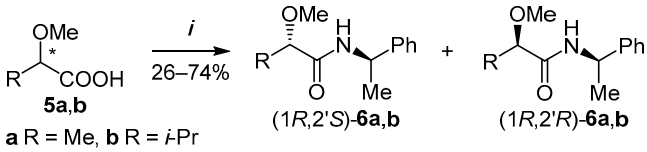
The predominant diastereomers (3*R**,2'*S**)-**3a**,**e** and (3*R**,2'*S**)-**4a**,**e** were obtained in diastereomerically pure form by recrystallization of the acylation products. Compounds (3*R**,2'*S**)-**3b–d** and (3*R**,2'*S**)-**4b–d** were isolated from the reaction mixtures by flash chromatography on silica gel.

The reactions using equimolar amounts of (*S*)-amines **1a**,**b** and racemic acyl chlorides **2a–e** in the presence of *N*,*N*-diethylaniline (as an HCl acceptor) allowed us to synthesize mixtures of (3*R*,2'*S*)- and (3*R*,2'*R*)-diastereomers of amides **3** and **4 a–e** (1:1 ratio of diastereomers), which were isolated from the reaction mixtures by flash chromatography and characterized by the physicochemical data sets. The analysis of the obtained mixtures of amides **3**, **4 a–e** allowed us to unequivocally assign the chromatographic peaks of (3*S*,2'*R*)- and (3*S*,2'*S*)-isomers of the mutual KR products.

In order to establish the configurations of the obtained amides **3**, **4 a–e**, acylation of enantiopure (*S*)-amines **1a**,**b** was performed using racemic acyl chlorides **2a–e** in the presence of *N*,*N*-diethylaniline (as an HCl acceptor) in 1:2:1 ratio of 3-methylbenzoxazine–acyl chloride–*N*,*N*-diethylaniline (Scheme 2).

In this case, the maximum possible conversion of the starting acyl chloride is 50% and KR of the racemic acylating agent occurs. As a result of the reaction, we obtained diastereomerically enriched amides **3**, **4 a–e** and unreacted enantiomerically enriched acyl chlorides **2a–e**, which were converted to the corresponding carboxylic acids **5a–e** by alkaline hydrolysis (Scheme 2). In order to determine the enantiomeric excess (*ee*, %) of carboxylic acids obtained in this way, we performed the condensation of acids **5a**,**b** and (*R*)-1-phenylethylamine using a carbodiimide coupling reagent (EDC·HCl) in the presence of 1-hydroxybenzotriazole (HOBt) and *N*-methylmorpholine additives (Scheme 3). The obtained mixtures of (*R*,*S*)- and (*R*,*R*)-diastereomers of amides **6a**,**b** were analyzed by HPLC. Based on the literature data on the order of elution of diastereomeric amides **6a**, we established that the scalemic carboxylic acid obtained from the unreacted acyl chloride was enriched in (*S*)-enantiomer.[21]

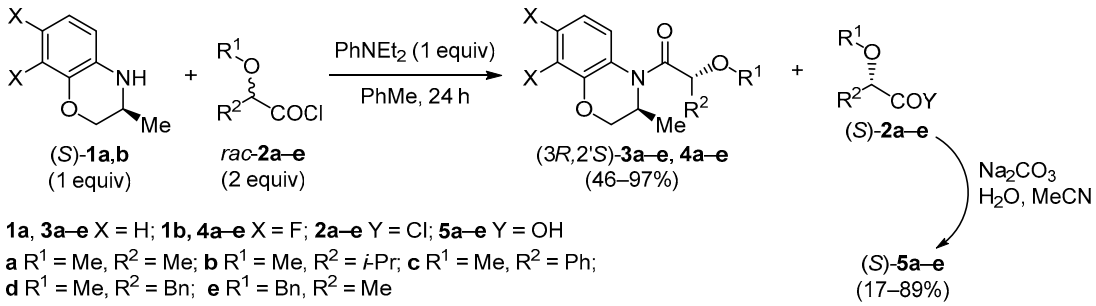
Scheme 3



a R = Me, **b** R = *i*-Pr

i: (*R*)-1-phenylethylamine (1 equiv), EDC·HCl (1.5 equiv), NMM (1.5 equiv), HOBt (1.5 equiv), DMF, rt, 48 h

Scheme 2



1a, **3a–e** X = H; **1b, 4a–e** X = F; **2a–e** Y = Cl; **5a–e** Y = OH

a R^1 = Me, R^2 = Me; **b** R^1 = Me, R^2 = *i*-Pr; **c** R^1 = Me, R^2 = Ph; **d** R^1 = Me, R^2 = Bn; **e** R^1 = Bn, R^2 = Me

The stereoconfiguration of (1*R*,2'*S*)-diastereomer of amide **6b** was established on the basis of X-ray structural analysis (Fig. 1), which allowed us to assign the HPLC peaks of individual diastereomers.

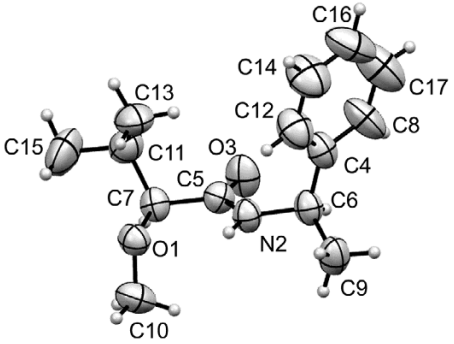


Figure 1. The molecular structure of amide (1*R*,2'*S*)-**6b** with atoms represented by thermal ellipsoids of 50% probability.

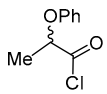
It was established that (1*R*,2'*S*)-amide dominated in the products of scalemic acid **5b** derivatization, therefore the carboxylic acid used in reaction with (*R*)-phenylethylamine was enriched in the (*S*)-enantiomer. The configuration of scalemic acids **5c–e** obtained by KR using 3-methylbenzoxazines **1a**,**b** was assigned by comparing the sign of optical rotation of the obtained samples with published data.[22–24] It can be concluded from the obtained results that the carboxylic acids obtained from unreacted acyl chlorides always contained the (*S*)-enantiomers as the major components, therefore, (*S*)-amines **1a**,**b** reacted with (*R*)-isomers of acyl chlorides **2a**–**e** at a greater rate and the predominant products were (3*S*,2'*R*)-diastereomers of amides **3**, **4 a**–**e**. Hence, the products of reactions between racemic amines and racemic acyl chlorides were enriched in (3*R**,2'*S**)-amides **3**, **4a**–**e**.

The stereochemical outcomes from acylation of amines **1a**,**b** with acyl chlorides **2a**–**e** are presented in Table 1. According to these results, the best stereoselectivity (*s* 31–32) was achieved in acylation of 3-methylbenzoxazines with 2-methoxyisopentanoyl chloride (**2b**) (entries 5 and 6). However, the selectivity factor *s* was lower than for the acylation of amines **1a**,**b** with acyl chlorides containing the aryloxy group, such as 2-phenoxypropanoyl chloride (*s* 35 and 56, entries 1 and 2). The replacement of isopropyl group (acyl chloride **2b**) at the chiral center of the acyl chloride derived from 2-methoxycarboxylic acid with the methyl group (acyl chloride **2a**) resulted in lower stereoselectivity of the reactions. The reactions of 3-methylbenzoxazines **1a**,**b** and derivatives of lactic (**2a**), mandelic (**2c**), and 3-phenyllactic acids (**2d**) proceeded with equal selectivity (*s* about 20, entries 3, 4, 7–9). 2-(Benzyloxy)propanoyl chloride (**2e**) reacted with amines **1a**,**b** with the same stereoselectivity as 2-methoxypropanoyl chloride (**2a**) (entries 3, 4 and 11, 12).

It is interesting to note that, in contrast to the reagents derived from 2-phenoxycarboxylic acids,[18] 2-methoxycarbonyl chlorides **2a**–**e** reacted with 3-methylbenzoxazine **1a** nearly as selectively as with its 7,8-difluoro analog **1b**. This observation could be apparently explained by the fact that the acylation of amines with acyl chlorides derived from 2-aryloxycarboxylic acids was affected by intermolecular interactions between the aromatic rings of the acylating agent and the nucleophilic reagent and were therefore influenced by the electronic effects of aromatic ring substituents in the amine molecule. In the case when 3-methylbenzoxazines **1a**,**b** were acylated with acyl chlorides derived from 2-methoxycarboxylic acids, the stereoselectivity was likely determined exclusively by the steric hindrance occurring during the intermolecular interaction of amine and the acylating agent.

Thus, we investigated the influence of electronic and steric factors on the stereochemical outcome of the acylation of racemic 3-methylbenzoxazines with acyl chlorides derived from 2-alkoxycarboxylic acids. It has been established that the reaction of 3-methyl-3,4-dihydrobenzoxazines with 2-methoxyisopentanoyl chloride proceeds more stereoselectively than the reactions of these amines with acyl chlorides derived from substituted propanoic acids. Such a result was probably associated with the significant steric hindrance created by the isopropyl substituent of acyl chloride. It has been found earlier that the selectivity factors for the acylation of 3-methylbenzoxazines with 2-phenoxypropanoyl chloride were 35 and 56, respectively, that is, 2-phenoxypropanoyl chloride showed better stereoselectivity compared to the structurally related 2-methoxy-2-phenylacetyl chloride, 2-methoxy-3-phenylpropanoyl chloride, and 2-benzyloxypropanoyl chloride. This comparative analysis of results of the acylation experiments using 3-methylbenzoxazines and acyl chlorides derived from 2-phenoxycarboxylic acids and 2-alkoxycarboxylic acids has made it possible to conclude that high stereoselectivity in such

Table 1. The stereochemical results of the acylation of racemic amines **1a**,**b** with racemic acyl chlorides **2a**–**e** in toluene at 20°C (average values for two parallel runs are presented).

Entry	Amine	Acyl chloride	Amide, *dr* ((*R**,*S**):(*R**,*R**))	Selectivity factor *s*
1	**1a**		97.2:2.8[18]	35
2	**1b**		98.2:1.8[18]	56
3	**1a**	**2a**	**3a**, 94.9:5.1*	19
4	**1b**	**2a**	**4a**, 94.6:5.4*	18
5	**1a**	**2b**	**3b**, 96.9:3.1**	31
6	**1b**	**2b**	**4b**, 97.0:3.0*	32
7	**1a**	**2c**	**3c**, 95.4:4.6*	21
8	**1b**	**2c**	**4c**, 95.3:4.7*	20
9	**1a**	**2d**	**3d**, 95.2:4.8*	20
10	**1b**	**2d**	**4d**, 95.2:4.8*	20
11	**1a**	**2e**	**3e**, 95.4:4.6***	21
12	**1b**	**2e**	**4e**, 95.2:4.8***	20

* Determined by HPLC (ReproSil 100 Si column).
** Determined by HPLC (Phenomenex Luna C18 column).
*** Determined by GC.

reactions requires the presence of the phenyl group directly linked to the oxygen atom at position 2 of acyl chloride.

Experimental

^{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) instruments using TMS and hexafluorobenzene as internal standards. ^{1}H NMR spectra of amides **3** and **4 a**–**e**, as well as ^{13}C NMR spectra of amides **3** and **4 a**–**c**,**e** were recorded at 100°C, while the spectra for the rest of the compounds were recorded at room temperature. High-resolution mass spectra of amides (3*R**,2'*S**)-**3b**, (3*R**,2'*S**)-**4b**, (3*R**,2'*S**)-**4c**, as well as carboxylic acids (*S*)-**5c**–**e** were obtained on a Bruker maXis Impact HD mass spectrometer (electrospray ionization) in positive ion mode (compounds **3b**, **4b**,**c**) or negative ion mode (compounds **5c**–**e**), flow rate of carrier gas (N_2) 4 l/min, 0.4 bar, spray voltage 4.5 kV. Melting points were determined on an SMP3 apparatus (Barloworld Scientific, UK). Elemental analysis was performed on PerkinElmer 2400 Series II or EuroVector EA3000 elemental analyzers. The fluorine content in the synthesized compounds was determined by a procedure based on mineralization according to Schöniger, followed by spectrophotometric analysis of the obtained samples (with comparison to reference samples). Analytical TLC was performed on Sorbfil plates (Imid Ltd., Russia). Flash chromatography was performed on 230–400 mesh silica gel (Alfa Aesar, UK).

HPLC analysis of 2-methoxycarboxylic acids **5a**,**b** was performed on a Knauer Smartline-1100 chromatograph after preliminary derivatization with (*R*)-1-phenylethylamine using ReproSil 100 Si column; detection at 220 nm, eluent flow rate 1 ml/min. HPLC analysis of carboxylic acids **5c**–**e** was performed on Knauer Smartline-1100 (compounds **5c**,**e**) and Shimadzu LC-20 Prominence (compound **5d**) chromatographs using Chiralpak AD (250 × 4.6 mm, Daicel Corp., Japan) (compound **5c**), Chiralcel OD-H (250 × 4.6 mm, Daicel Corp., Japan) (compound **5d**), and S,S-Whelk O1 (250 × 4.6 mm, Regis Technologies Inc.) (compound **5e**) columns; detection at 220 and 230 nm, eluent flow rate 1 ml/min. Eluent hexane–*i*-PrOH–CF_3COOH, 40:1:0.02 (compounds **5c**,**d**); 20:1:0.02 (compound **5e**): $\tau_{(R)\text{-}\mathbf{5c}}$ 20.8 min; $\tau_{(S)\text{-}\mathbf{5c}}$ 18.8 min; $\tau_{(R)\text{-}\mathbf{5d}}$ 14.0 min; $\tau_{(S)\text{-}\mathbf{5d}}$ 20.4 min; $\tau_{(S)\text{-}\mathbf{5e}}$ 7.1 min; $\tau_{(R)\text{-}\mathbf{5e}}$ 7.8 min. The specific rotations were determined on a PerkinElmer 341 polarimeter. HPLC analysis of amides **3a**,**c** and **4a**–**c** was performed on a Knauer Smartline-1100 chromatograph using ReproSil 100 Si column; detection at 220 nm, eluent flow rate 1 ml/min. HPLC analyses of amides **3d** and **4d** were performed on a Shimadzu LC-20 Prominence chromatograph, using a ReproSil 100 Si column; detection at 220 nm, eluent flow rate 1 ml/min. HPLC analysis of amide **3b** was performed on an Agilent 1100 chromatograph, using a Phenomenex Luna C18(2) column (250 × 4.6 mm), eluent flow rate 0.8 ml/min, detection at 220 nm.

GC analysis of amides **3e** and **4e** was performed using a Shimadzu GC 2010 gas chromatograph with flame ionization detector, ZB-5 quartz capillary column (30 m × 0.25 mm × 0.25 μm); the initial column temperature was 40°C (maintained for 3 min), followed by programmed temperature increase at 10 K/min rate to 280°C (maintained for 30 min). The evaporator temperature was 250°C, detector temperature 300°C. The carrier gas was nitrogen, split ratio 1:30, flow through the column 1.0 ml/min, 1.0 μl injection volume of amide solution in acetonitrile at the concentration of 1–3 mg/ml. The chromatographic peaks of diastereomers were assigned on the basis of GC-MS data.

(*RS*)-3-Methyl-3,4-dihydro-2*H*-1,4-benzoxazine (**1a**),[25] (*RS*)-7,8-difluoro-3-methyl-3,4-dihydro-2*H*-1,4-benzoxazine (**1b**),[25] (3*S*)-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazine ((*S*)-**1a**),[11] (3*S*)-7,8-difluoro-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazine ((*S*)-**1b**),[26] (*RS*)-2-methoxypropanoic acid (**5a**),[27] (*RS*)-2-methoxyisopentanoic acid (**5b**),[28] (*RS*)-2-methoxy-2-phenylacetic acid (**5c**),[29] (*RS*)-2-methoxy-3-phenylpropanoic acid (**5d**),[30,31] and (*RS*)-2-benzyloxypropanoic acid (**5e**)[32] were obtained according to published procedures. The other reagents were commercially available. The solvents were purified according to the standard procedures.

Preparation of acyl chlorides 2a–e (General method). A solution of the appropriate carboxylic acid (5 mmol) in 20 ml of CH_2Cl_2 (carboxylic acids **2a**–**c**,**e**) or benzene (carboxylic acid **2d**) was treated by the addition of oxalyl chloride (0.87 ml, 10 mmol) in the case of carboxylic acid **5a**, (1.31 ml, 15 mmol) in the case of carboxylic acids **5b**,**d**,**e**, (4.38 ml, 50 mmol) in the case of carboxylic acid **5c**, along with DMF (5 μl). The reaction mixture was stirred at ambient temperature for 6 h, then evaporated at reduced pressure. The residue was dried at reduced pressure over P_2O_5. Acyl chloride **2a** was used immediately after evaporation of the solvent. Acylating reagents **2a**–**e** were unstable during storage and were therefore used in freshly prepared form (purity not less than 97% according to ^{1}H NMR spectroscopy data).

(*RS*)-2-Methoxypropanoyl chloride (2a). Yield 610 mg (99%), yellow oil. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 1.53 (3H, d, *J* = 6.9, CH_3); 3.45 (3H, s, OCH_3); 4.01 (1H, q, *J* = 7.1, CH).

(*RS*)-2-Methoxy-3-methylbutanoyl chloride (2b). Yield 750 mg (99%), yellow oil. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 0.97 (3H, d, *J* = 6.9, $CH(C\underline{H}_3)_2$); 1.03 (3H, d, *J* = 6.9, $CH(C\underline{H}_3)_2$); 2.27–2.57 (1H, sept d, *J* = 6.9; *J* = 4.9, $C\underline{H}(CH_3)_2$); 3.44 (1H, s, OCH_3); 3.72 (1H, d, *J* = 4.9, CH).

(*RS*)-2-Methoxy-2-phenylacetyl chloride (2c). Yield 940 mg (98%), yellow oil. ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 3.51 (3H, s, OCH_3); 4.99 (1H, s, CH); 7.39–7.48 (5H, m, H Ph).

(*RS*)-2-Methoxy-3-phenylpropanoyl chloride (2d). Yield 980 mg (99%), colorless oil. ^{1}H NMR spectrum (500 MHz, $CDCl_3$), δ, ppm (*J*, Hz): 3.07 (1H, dd, *J* = 14.2, *J* = 8.0, CH_2); 3.20 (1H, dd, *J* = 14.2, *J* = 4.3, CH_2); 3.40 (3H, s, OCH_3); 4.18 (1H, dd, *J* = 8.0, *J* = 4.4, CH); 7.24–7.34 (5H, m, H Ph).

(*RS*)-(2-Benzyloxy)propanoyl chloride (2e). Yield 980 mg (99%), yellow oil. ^{1}H NMR spectrum (400 MHz,

$CDCl_3$), δ, ppm (*J*, Hz): 1.57 (3H, d, *J* = 6.8, CH_3); 4.28 (1H, q, *J* = 6.8, CH); 4.46 (1H, d, *J* = 11.4, CH_2); 4.75 (1H, d, *J* = 11.4, CH_2); 7.29–7.39 (5H, m, H Ph).

Stereoselective acylation of racemic amines 1a,b with acyl chlorides 2a–e (General method). A solution of amine **1a** or **1b** (1.0 mmol) in the appropriate solvent (5 ml) was treated with a solution of the appropriate acyl chloride (0.5 mmol) in the same solvent (5 ml) at 20°C. The reaction mixture was kept at 20°C for 6 h. The reaction mixture was successively washed with 4 N HCl (2×4 ml), saturated aqueous NaCl solution (4×5 ml), aqueous 5% $NaHCO_3$ solution (2×5 ml), and H_2O (2×5 ml), then dried over Na_2SO_4, and evaporated at reduced pressure. The diastereomers of amides were isolated by recrystallization or by flash chromatography on silica gel.

(2*S)-2-Methoxy-1-((3*R**)-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)propan-1-one ((2*S**,3*R**)-3a)**. Yield 54 mg (46%) after recrystallization from hexane, colorless powder, mp 86–87°C (hexane). HPLC analysis (ReproSil 100 Si column; hexane–*i*-PrOH, 20:1): $\tau_{(3R^*,2'S^*)\text{-}\mathbf{3a}}$ 8.5 min, $\tau_{(3R^*,2'R^*)\text{-}\mathbf{3a}}$ 6.5 min; (3*R**,2'*S**)/(3*R**,2'*R**) = 99.5:0.5. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.15 (3H, d, *J* = 6.8, 3-CH_3); 1.33 (3H, d, *J* = 6.4, CHC<u>H</u>$_3$); 3.20 (3H, s, OCH_3); 4.12 (1H, dd, *J* = 11.0, *J* = 2.7, CH_2); 4.21 (1H, dd, *J* = 11.0, *J* = 1.6, CH_2); 4.43 (1H, q, *J* = 6.4, C<u>H</u>CH_3); 4.64–4.68 (1H, m, 3-CH); 6.83–6.90 (2H, m, H-6,8); 7.03 (1H, ddd, *J* = 8.2, *J* = 7.2, *J* = 1.2, H-7); 7.70–7.71 (1H, m, H-5). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm: 14.8; 15.9; 45.0; 54.9; 69.2; 73.9; 115.8; 119.4; 123.2; 124.2; 124.7; 145.5; 169.2. Found, %: C 66.37; H 7.27; N 5.96. $C_{13}H_{17}NO_3$. Calculated, %: C 66.36; H 7.28; N 5.95.

(2*S)-((3*R**)-7,8-Difluoro-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)-2-methoxypropan-1-one ((2*S**,3*R**)-4a)**. Yield 80 mg (59%) after recrystallization from a mixture of hexane–EtOAc, colorless powder, mp 78–80°C (hexane–EtOAc). HPLC analysis (Reprosil 100 Si column; hexane–*i*-PrOH, 40:1): $\tau_{(3R^*,2'S^*)\text{-}\mathbf{4a}}$ 17.9 min, $\tau_{(3R^*,2'R^*)\text{-}\mathbf{4a}}$ 12.8 min; (3*R**,2'*S**)/(3*R**,2'*R**) = 99.9:0.1. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.18 (3H, d, *J* = 6.8, 3-CH_3); 1.32 (3H, d, *J* = 6.4, CHC<u>H</u>$_3$); 3.23 (3H, s, OCH_3); 4.19 (1H, dd, *J* = 11.0, *J* = 2.6, CH_2); 4.37 (1H, dd, *J* = 11.0, *J* = 1.4, CH_2); 4.43 (1H, q, *J* = 6.4, C<u>H</u>CH_3); 4.69 (1H, qdd, *J* = 6.7, *J* = 2.6, *J* = 1.5, 3-CH); 6.86 (1H, ddd, *J* = 9.8, *J* = 9.8, *J* = 8.4, H-6); 7.62 (1H, ddd, *J* = 9.4, *J* = 5.5, *J* = 2.6, H-5). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 14.7; 15.6; 45.0; 54.9; 69.7; 74.0; 106.2 (d, *J* = 18.2); 118.8 (dd, *J* = 7.9, *J* = 4.2); 121.2; 135.8 (dd, *J* = 10.1, *J* = 3.2); 138.6 (dd, *J* = 243.9, 15.5); 146.4 (dd, *J* = 242.2, *J* = 10.4); 169.4. ^{19}F NMR spectrum (470 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.0 (ddd, *J* = 20.6, *J* = 8.6, *J* = 2.4, F-8); 20.5 (ddd, *J* = 21.0, *J* = 10.1, *J* = 5.4, F-7). Found, %: C 57.71; H 5.71; F 14.07; N 5.23. $C_{13}H_{15}F_2NO_3$. Calculated, %: C 57.56; H 5.57; F 14.01; N 5.16.

(2*S)-2-Methoxy-3-methyl-1-((3*R**)-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)butan-1-one ((2*S**,3*R**)-3b)**. Yield 112 mg (85%) after flash chromatography (eluent hexane–EtOAc, 95:5), colorless oil. HPLC analysis (Phenomenex Luna C 18(2) column; 50% MeCN): $\tau_{(3R^*,2'S^*)\text{-}\mathbf{3b}}$ 17.5 min, $\tau_{(3R^*,2'R^*)\text{-}\mathbf{3b}}$ 16.7 min; (*R**,*S**)/(*R**,*R**) = 99.0:1.0. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.95 (3H, d, *J* = 6.8, CH(C<u>H</u>$_3$)$_2$); 0.99 (3H, d, *J* = 6.6, CH(C<u>H</u>$_3$)$_2$); 1.15 (3H, d, *J* = 6.8, CHC<u>H</u>$_3$); 2.01–2.12 (1H, m, C<u>H</u>(CH$_3$)$_2$); 3.23 (3H, s, OCH_3); 3.92 (1H, d, *J* = 7.8, C<u>H</u> *i*-Pr); 4.09 (1H, dd, *J* = 11.0, *J* = 2.9, CH_2); 4.24 (1H, dd, *J* = 11.0, *J* = 1.7, CH_2); 4.83 (1H, qdd, *J* = 6.8, *J* = 2.9, *J* = 1.7, C<u>H</u>CH_3); 6.86–6.89 (2H, m, H-6,8); 7.02–7.06 (1H, m, H-7); 7.80 (1H, dd, *J* = 8.5, *J* = 1.1, H-5). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 14.9; 17.5; 18.0; 29.4; 44.7; 56.4; 69.3; 84.8; 115.9; 119.4; 123.2; 124.5; 124.9; 145.6; 168.5. Found, *m*/*z*: 264.1598 $[M+H]^+$. $C_{15}H_{22}NO_3$. Calculated, *m*/*z*: 264.1594.

(2*S)-1-((3*R**)-7,8-Difluoro-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)-2-methoxy-3-methylbutan-1-one ((2*S**,3*R**)-4b)**. Yield 153 mg (85%) after flash chromatography (eluent hexane–EtOAc, 95:5), colorless oil. HPLC analysis (ReproSil 100 Si column; hexane–*i*-PrOH, 40:1): $\tau_{(3R^*,2'S^*)\text{-}\mathbf{4b}}$ 4.2 min, $\tau_{(3R^*,2'R^*)\text{-}\mathbf{4b}}$ 4.7 min; (3*R**,2'*S**)/(3*R**,2'*R**) = 99.5:0.5. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.94 (3H, d, *J* = 6.8, CH(C<u>H</u>$_3$)$_2$); 0.99 (3H, d, *J* = 6.6, CH(C<u>H</u>$_3$)$_2$); 1.17 (3H, d, *J* = 6.8, CHC<u>H</u>$_3$); 2.01–2.10 (1H, m, C<u>H</u>(CH$_3$)$_2$); 3.26 (3H, s, OCH_3); 3.90 (1H, d, *J* = 7.8, C<u>H</u> *i*-Pr); 4.16 (1H, dd, *J* = 11.0, *J* = 2.7, CH_2); 4.40 (1H, dd, *J* = 11.0, *J* = 1.5, CH_2); 4.87 (1H, qdd, *J* = 6.8, *J* = 2.8, *J* = 1.6, C<u>H</u>CH_3); 6.87 (1H, td, *J* = 9.9, *J* = 8.2, H-6); 7.62 (1H, ddd, *J* = 9.4, *J* = 5.5, *J* = 2.6, H-5). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 14.8; 17.5; 17.9; 29.4; 44.7; 56.5; 69.8; 85.1; 106.2 (d, *J* = 18.1); 119.0 (dd, *J* = 7.9, *J* = 4.2); 121.0; 136.0 (dd, *J* = 9.9, *J* = 3.3); 138.6 (dd, *J* = 244.0, *J* = 15.5); 146.5 (dd, *J* = 242.7, *J* = 9.9); 168.7. ^{19}F NMR spectrum (470 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.0 (ddd, *J* = 21.0, *J* = 8.2, *J* = 2.4, F-8); 20.8 (ddd, *J* = 20.8, *J* = 10.1, *J* = 5.5, F-7). Found, *m*/*z*: 300.1405 $[M+H]^+$. $C_{15}H_{20}F_2NO_3$. Calculated, *m*/*z*: 300.1406.

(2*S)-2-Methoxy-1-((3*R**)-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)-2-phenylethanone ((2*S**,3*R**)-3c)**. Yield 110 mg (74%) after flash chromatography (eluent hexane–EtOAc, 95:5), colorless oil. HPLC analysis (ReproSil 100 Si column; hexane–*i*-PrOH, 100:1): $\tau_{(3R^*,2'S^*)\text{-}\mathbf{3c}}$ 6.1 min, $\tau_{(3R^*,2'R^*)\text{-}\mathbf{3c}}$ 7.0 min; (3*R**,2'*S**)/(3*R**,2'*R**) = 98.1:1.9. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.98 (3H, d, *J* = 6.8, CHC<u>H</u>$_3$); 3.35 (3H, s, OCH_3); 3.86 (1H, dd, *J* = 10.9, *J* = 2.8, CH_2); 4.12 (1H, dd, *J* = 10.9, *J* = 1.7, CH_2); 4.66 (1H, qdd, *J* = 6.8, *J* = 2.7, *J* = 1.7, C<u>H</u>CH_3); 5.29 (1H, s, CHPh); 6.81–6.90 (2H, m, H-6,8); 7.03 (1H, td, *J* = 7.7, *J* = 1.5, H-7); 7.32–7.45 (5H, m, H Ph); 7.82–7.83 (1H, m, H-5). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 14.6; 45.1; 56.4; 68.9; 81.8; 115.8; 119.4; 123.1; 124.2; 124.9; 126.7; 127.6; 127.8; 136.0; 145.4; 167.1. Found, %: C 72.73; H 6.71; N 4.65. $C_{18}H_{19}NO_3$. Calculated, %: C 72.71; H 6.44; N 4.71.

(2*S)-1-((3*R**)-7,8-Difluoro-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)-2-methoxy-2-phenylethanone ((2*S**,3*R**)-4c)**. Yield 145 mg (87%) after flash chromatography (eluent hexane–EtOAc, 95:5), colorless oil. HPLC analysis (ReproSil 100 Si column; hexane–*i*-PrOH, 100:1): $\tau_{(3R^*,2'S^*)\text{-}\mathbf{4c}}$ 7.1 min, $\tau_{(3R^*,2'R^*)\text{-}\mathbf{4c}}$ 8.3 min; (3*R**,2'*S**)/(3*R**,2'*R**) = 96.8:3.2.

^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.99 (3H, d, *J* = 6.8, CHC<u>H</u>$_3$); 3.37 (1H, s, OCH$_3$); 3.92 (1H, dd, *J* = 10.9, *J* = 2.6, CH$_2$); 4.29 (1H, dd, *J* = 11.0, *J* = 1.5, CH$_2$); 4.70 (1H, qdd, *J* = 6.8, *J* = 2.7, *J* = 1.6, C<u>H</u>CH$_3$); 5.30 (1H, s, CHPh); 6.87 (1H, td, *J* = 9.9, *J* = 8.2, H-6); 7.32–7.43 (5H, m, H Ph); 7.71 (1H, ddd, *J* =9.5, *J* = 5.5, *J* = 2.6, H-5). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 14.4; 45.1; 56.5; 69.4; 81.9; 106.3 (d, *J* = 18.1); 118.9 (dd, *J* = 7.8, *J* = 4.3); 121.0; 126.6; 127.7; 127.9; 135.7; 135.9 (dd, *J* = 12.8, *J* = 9.7); 138.6 (dd, *J* = 244.0, *J* = 15.3); 146.5 (dd, *J* = 242.7, *J* = 9.9); 167.4. ^{19}F NMR spectrum (470 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.0 (ddd, *J* = 21.0, *J* = 8.2, *J* = 2.5, F-8); 20.8 (ddd, *J* = 21.0, *J* = 10.3, *J* = 5.5, F-7). Found, *m*/*z*: 356.1071 [M+Na]$^+$. $C_{18}H_{17}F_2NNaO_3$. Calculated, *m*/*z*: 356.1069.

(2*S)-2-Methoxy-1-((3*R**)-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)-3-phenylpropan-1-one ((2*S**,3*R**)-3d)**. Yield 65 mg (42%) after recrystallization from hexane–EtOAc mixture, yellowish crystalline powder, mp 76–78°C (hexane–EtOAc). HPLC analysis (ReproSil 100 Si column; hexane–*i*-PrOH, 60:1): $\tau_{(3R^*,2'S^*)\text{-}\mathbf{3d}}$ 6.8 min, $\tau_{(3R^*,2'R^*)\text{-}\mathbf{3d}}$ 6.1 min; (3*R**,2'*S**)/(3*R**,2'*R**) = 99.5:0.5. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.12 (3H, d, *J* = 6.8, CHC<u>H</u>$_3$); 3.02 (1H, d, *J* = 14.0, *J* = 7.2, CH$_2$Ph); 3.09 (1H, d, *J* = 14.0, *J* = 6.4, CH$_2$Ph); 3.19 (3H, s, OCH$_3$); 3.81 (1H, dd, *J* = 11.0, *J* = 2.7, CH$_2$); 4.10 (1H, dd, *J* = 11.0, *J* = 1.3, CH$_2$); 4.55–4.65 (2H, m, C<u>H</u>CH$_3$, C<u>H</u>Bn); 6.80–6.87 (2H, m, H-6,8); 7.02 (1H, td, *J* = 7.7, *J* = 1.2, H-7); 7.17–7.30 (5H, m, H Ph); 7.56–7.61 (1H, m, H-5). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 15.4; 37.2; 46.0; 55.8; 69.0; 78.7; 116.5; 120.0; 122.9; 124.8; 125.4; 126.5; 128.3; 129.5; 137.1; 145.5; 168.9. Found, %: C 73.09; H 6.98; N 4.31. $C_{19}H_{21}NO_3$. Calculated, %: C 73.29; H 6.80; N 4.50.

(2*S)-1-((3*R**)-7,8-Difluoro-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)-2-methoxy-3-phenylpropan-1-one ((2*S**,3*R**)-4d)**. Yield 111 mg (64%) after recrystallization from hexane–EtOAc mixture, colorless crystalline powder, mp 72–74°C (hexane–EtOAc). HPLC analysis (ReproSil 100 Si column; hexane–*i*-PrOH, 60:1): $\tau_{(3R^*,2'S^*)\text{-}\mathbf{4d}}$ 8.3 min, $\tau_{(3R^*,2'R^*)\text{-}\mathbf{4d}}$ 7.5 min; (3*R**,2'*S**)/(3*R**,2'*R**) = 98.9:1.1. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.15 (3H, d, *J* = 6.8, CHC<u>H</u>$_3$); 3.03 (1H, dd, *J* = 14.0, *J* = 7.2, CH$_2$Ph); 3.08 (1H, dd, *J* = 14.0, *J* = 6.4, CH$_2$Ph); 3.22 (3H, s, OCH$_3$); 3.85 (1H, dd, *J* = 11.0, *J* = 2.7, CH$_2$); 4.27 (1H, dd, *J* = 11.0, *J* = 1.4, CH$_2$); 4.59 (1H, t, *J* = 6.8, CHBn); 4.61–4.68 (1H, m, C<u>H</u>CH$_3$); 6.85 (1H, td, *J* = 9.8, *J* = 2.3, H-6); 7.18–7.30 (5H, m, H Ph); 7.50–7.58 (1H, m, H-5). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 15.3; 36.9; 45.8; 55.7; 69.7; 78.6, 106.9 (d, *J* = 17.9); 119.4 (dd, *J* = 7.5, *J* = 3.9); 120.9; 126.4; 128.2; 129.4; 136.0 (dd, *J* = 9.8, *J* = 2.1); 137.0, 138.9 (dd, *J* = 243.5, *J* = 15.4); 145.6–147.9 (m); 169.15. ^{19}F NMR spectrum (470 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.1 (ddd, *J* = 21.0, *J* = 8.0, *J* = 1.7, F-8); 20.8–21.0 (м, F-7). Found, %: C 65.91; H 5.77; F 10.92; N 3.86. $C_{19}H_{19}F_2NO_3$. Calculated, %: C 65.70; H 5.51; F 10.94; N 4.03.

(2*S)-2-(Benzyloxy)-1-((3*R**)-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl])propan-1-one ((2*S**,3*R**)-3e)**. Yield 86 mg (55%) after recrystallization from hexane–EtOAc mixture, colorless crystalline powder, mp 77–80°C (hexane–EtOAc). GC: $\tau_{(3R^*,2'S^*)\text{-}\mathbf{3e}}$ 28.0 min, $\tau_{(3R^*,2'R^*)\text{-}\mathbf{3e}}$ 28.3 min; (3*R**,2'*S**)/(3*R**,2'*R**) = 97.4:2.6. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.09 (3H, d, *J* = 6.8, CHC<u>H</u>$_3$); 1.40 (3H, d, *J* = 6.4, CHOC<u>H</u>$_3$); 4.09 (1H, dd, *J* = 11.0, *J* = 2.6, CH$_2$); 4.18 (1H, dd, *J* = 11.0, *J* = 1.6, CH$_2$); 4.40 (1H, d, *J* = 11.7, CH$_2$Ph); 4.44 (1H, d, *J* = 11.7, CH$_2$Ph); 4.64 (1H, q, *J* = 6.4, C<u>H</u>OCH$_3$); 4.70 (1H, qdd, *J* = 6.7, *J* = 2.8, *J* = 1.7, C<u>H</u>CH$_3$); 6.84–6.87 (2H, m, H-6,8); 7.03 (1H, ddd, *J* = 8.3, *J* = 7.1, *J* = 1.4, H-7); 7.18–7.30 (5H, m, H Ph); 7.67 (1H, d, *J* = 8.2, H-5). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 14.8; 16.6; 44.7; 69.2; 69.7; 72.2; 115.8; 119.4; 123.2; 124.3; 124.9; 126.9; 127.1; 127.5; 137.4; 145.6; 169.2. Found, %: C 73.45; H 6.80; N 4.61. $C_{19}H_{21}NO_3$. Calculated, %: C 73.29; H 6.80; N 4.50.

(2*S)-2-Benzyloxy-1-((3*R**)-7,8-difluoro-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)propan-1-one ((2*S**,3*R**)-4e)**. Yield 49 mg (28%) after recrystallization from hexane–EtOAc mixture, colorless crystalline powder, mp 90–92°C (hexane–EtOAc). GC: $\tau_{(3S,2'R)\text{-}\mathbf{4e}}$ 28.1 min, $\tau_{(R,S)\text{-}\mathbf{4e}}$ 28.5 min; (3*R**,2'*S**)/(3*R**,2'*R**) = 98.5:1.5. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.10 (3H, d, *J* = 6.8, CHC<u>H</u>$_3$); 1.40 (3H, d, *J* = 6.4, CHOC<u>H</u>$_3$); 4.16 (1H, dd, *J* = 11.0, *J* = 2.8, CH$_2$); 4.33 (1H, dd, *J* = 11.0, *J* = 1.3, CH$_2$); 4.44 (1H, d, *J* = 11.8, CH$_2$Ph); 4.47 (1H, d, *J* = 11.8, CH$_2$Ph); 4.62 (1H, q, *J* = 6.4, C<u>H</u>OCH$_3$); 4.74 (1H, qdd, *J* = 6.8, *J* = 2.8, *J* = 1.5, C<u>H</u>CH$_3$); 6.81–6.87 (1H, m, H-6); 7.23–7.31 (5H, m, H Ph); 7.56 (1H, ddd, *J* = 9.0, *J* = 5.8, *J* = 2.8, H-5). ^{13}C NMR spectrum (126 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 14.7; 16.3; 44.7; 69.7 (2C); 72.2; 106.2 (d, *J* = 18.2); 118.8 (dd, *J* = 8.0, *J* = 4.2); 121.1; 126.9; 127.1; 127.5; 135.9 (dd, *J* = 10.2, *J* = 3.3); 137.3; 138.6 (dd, *J* = 244.1, *J* = 15.5); 146.5 (dd, *J* = 242.5, *J* = 10.0); 169.4. ^{19}F NMR spectrum (470 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.0 (ddd, *J* = 20.9, *J* = 8.1, *J* = 2.2, F-8); 20.7 (ddd, *J* = 20.7, *J* = 9.8, *J* = 5.3, F-7). Found, %: C 65.68; H 5.61; F 11.05; N 4.07. $C_{19}H_{19}F_2NO_3$. Calculated, %: C 65.70; H 5.51; F 10.94; N 4.03.

Preparation of mixtures of (3*S*,2'*R*)- and (3*S*,2'*S*)-diastereomers 3, 4 a–e (General method). A solution of the appropriate acyl chloride (0.5 mmol) in CH_2Cl_2 (5 ml) was added to a solution of (*S*)-amine **1a** or **1b** (0.5 mmol) and $PhNEt_2$ (75 mg, 0.5 mmol) in CH_2Cl_2 (10 ml) at 20°C, then kept at 20°C for 24 h. The reaction mixture was then washed with aqueous 4 N solution of HCl (2×5 ml), saturated aqueous NaCl solution (3×15 ml), 5% $NaHCO_3$ solution (10 ml), and H_2O (2×15 ml). The organic layer was dried over Na_2SO_4, and the solvent was removed by evaporation under reduced pressure. The residue was purified by flash chromatography on silica gel (eluent hexane–EtOAc, 95:5).

2-Methoxy-1-(3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)propan-1-one (3a) (mixture of diastereomers). Yield 95 mg (81%), colorless oil. HPLC analysis (ReproSil 100 Si column; hexane–*i*-PrOH, 20:1): $\tau_{(3S,2'R)\text{-}\mathbf{3a}}$ 8.5 min, $\tau_{(3S,2'S)\text{-}\mathbf{3a}}$ 6.5 min; (3*S*,2'*R*)/(3*S*,2'*S*) = 50.5:49.5. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.13 (1.5H, d, *J* = 6.8, CHC<u>H</u>$_3$ (*S*,*S*)); 1.15 (1.5H, d, *J* = 6.8, CHC<u>H</u>$_3$

(*S*,*R*)); 1.26 (1.5H, d, *J* = 6.4, CHOC$\underline{H}_3$ (*S*,*S*)); 1.33 (1.5H, d, *J* = 6.4, CHOC$\underline{H}_3$ (*S*,*R*)); 3.20 (1.5H, s, OCH$_3$ (*S*,*R*)); 3.31 (1.5H, s, OCH$_3$ (*S*,*S*)); 4.08–4.13 (1H, m, CH$_2$ (*S*,*R*) and (*S*,*S*)); 4.20–4.22 (1H, m, CH$_2$ (*S*,*R*) and (*S*,*S*)); 4.41 (1H, m, C$\underline{H}$OCH$_3$ (*S*,*R*) and (*S*,*S*)); 4.63–4.68 (1H, m, C$\underline{H}$CH$_3$ (*S*,*R*)); 4.77 (0.5H, qdd, *J* = 6.8, *J* = 2.9, *J* = 1.7, C$\underline{H}$CH$_3$ (*S*,*S*)); 6.84–6.89 (2H, m, H-6,8 (*S*,*R*) and (*S*,*S*)); 7.01–7.05 (1H, m, H-7 (*S*,*R*) and (*S*,*S*)); 7.70–7.71 (1H, m, H-5 (*S*,*R*) and (*S*,*S*)). Found, %: C 66.38; H 7.11; N 5.90. $C_{13}H_{17}NO_3$. Calculated, %: C 66.36; H 7.28; N 5.95.

1-(7,8-Difluoro-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)-2-methoxypropan-1-one (4a) (mixture of diastereomers). Yield 103 mg (76%), yellowish oil. HPLC analysis (ReproSil 100 Si column; hexane–*i*-PrOH, 40:1): $\tau_{(3S,2'R)\text{-}\mathbf{4a}}$ 17.9 min, $\tau_{(3S,2'S)\text{-}\mathbf{4a}}$ 12.8 min; (3*S*,2'*R*)/(3*S*,2'*S*) = 52.3:47.7. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.16 (1.5H, dd, *J* = 6.9, *J* = 0.5, CHC$\underline{H}_3$ (*S*,*S*)); 1.18 (1.5H, dd, *J* = 6.8, *J* = 0.5, CHC$\underline{H}_3$ (*S*,*R*)); 1.29 (1.5H, d, *J* = 6.5, CHC$\underline{H}_3$ (*S*,*S*)); 1.29 (1.5H, d, *J* = 6.5, CHC$\underline{H}_3$ (*S*,*R*)); 3.23 (1.5H, s, OCH$_3$ (*S*,*R*)); 3.30 (1.5H, s, OCH$_3$ (*S*,*S*)); 4.16 (0.5H, ddd, *J* = 10.0, *J* = 2.8, *J* = 0.6, CH$_2$ (*S*,*S*)); 4.19 (0.5H, ddd, *J* = 11.2, *J* = 2.9, *J* = 0.5, CH$_2$ (*S*,*R*)); 4.35–4.44 (2H, m, CH$_2$ (*S*,*R*) and (*S*,*S*)); 4.69 (0.5H, qdd, *J* = 6.8, *J* = 2.8, *J* = 1.6, C$\underline{H}$OCH$_3$ (*S*,*R*)); 4.82 (0.5H, qdd, *J* = 6.8, *J* = 2.9, *J* = 1.6, C$\underline{H}$OCH$_3$ (*S*,*S*)); 6.85 (0.5H, ddd, *J* = 10.2, *J* = 8.2, *J* = 6.5, H-6 (*S*,*R*)); 6.88 (0.5H, ddd, *J* = 10.2, *J* = 8.2, *J* = 6.5, H-6 (*S*,*S*)); 7.56 (0.5H, ddd, *J* = 9.5, *J* = 5.5, *J* = 2.6, H-5 (*S*,*S*)); 7.62 (0.5H, ddd, *J* = 9.5, *J* = 5.5, *J* = 2.6, H-5 (*S*,*R*)). ^{19}F NMR spectrum (470 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.9 (0.5F, ddd, *J* = 21.0, *J* = 8.2, *J* = 2.5, F-8 (*S*,*S*)); 2.0 (0.5F, ddd, *J* = 21.0, *J* = 8.1, *J* = 2.4, F-8 (*S*,*R*)); 20.5 (0.5F, ddd, *J* = 20.8, *J* = 10.2, *J* = 5.4, F-7 (*S*,*R*)); 20.7–21.0 (0.5F, m, F-7 (*S*,*S*)). Found, %: C 57.67; H 5.80; F 13.88; N 5.22. $C_{13}H_{15}F_2NO_3$. Calculated, %: C 57.56; H 5.57; F 14.01; N 5.16.

2-Methoxy-3-methyl-1-(3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)butan-1-one (3b) (mixture of diastereomers). Yield 84 mg (64%), yellowish oil. HPLC analysis (Phenomenex Luna C 18(2) column; 50% MeCN): $\tau_{(3S,2'R)\text{-}\mathbf{3b}}$ 17.5 min, $\tau_{(3S,2'S)\text{-}\mathbf{3b}}$ 16.7 min; (3*S*,2'*R*)/(3*S*,2'*S*) = 53.5:46.5. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.83 (1.38H, d, *J* = 6.8, CH(C$\underline{H}_3$)$_2$ (*S*,*S*)); 0.91 (1.38H, d, *J* = 6.7, CH(C$\underline{H}_3$)$_2$ (*S*,*S*)); 0.95 (1.62H, d, *J* = 6.8 CH(C$\underline{H}_3$)$_2$ (*S*,*R*)); 0.99 (1.62H, d, *J* = 6.6, CH(C$\underline{H}_3$)$_2$ (*S*,*R*)); 1.13 (1.38H, d, *J* = 6.8, CHC$\underline{H}_3$ (*S*,*S*)); 1.15 (1.62H, d, *J* = 6.8, CHC$\underline{H}_3$ (*S*,*R*)); 1.96–2.11 (1H, m, C$\underline{H}$(CH$_3$)$_2$); 3.23 (1.5H, s, OCH$_3$, (*S*,*R*)); 3.34 (1.38H, s, OCH$_3$, (*S*,*S*)); 3.92 (0.54H, d, *J* = 7.8, C$\underline{H}$CH(CH$_3$)$_2$ (*S*,*R*)); 4.03 (0.46H, d, *J* = 7.4, C$\underline{H}$CH(CH$_3$)$_2$ (*S*,*S*)); 4.06 (0.46H, dd, *J* = 11.2, *J* = 3.2, CH$_2$ (*S*,*S*)); 4.09 (0.54H, dd, *J* = 11.0; *J* = 2.9, CH$_2$ (*S*,*R*)); 4.22 (0.46H, dd, *J* = 11.0, *J* = 1.7, CH$_2$ (*S*,*S*)); 4.24 (0.54H, dd, *J* = 11.0, *J* = 1.7, CH$_2$ (*S*,*R*)); 4.80–4.84 (1H, m, C$\underline{H}$CH$_3$); 6.86–6.89 (2H, m, H-6,8); 7.02–7.06 (1H, m, H-7); 7.61–7.62 (0.46H, m, H-5 (*S*,*S*)) 7.79–7.81 (0.54H, m, H-5 (*S*,*R*)). Found, %: C 68.43; H 8.10; N 5.26. $C_{15}H_{21}NO_3$. Calculated, %: C 68.42; H 8.04; N 5.32.

1-(7,8-Difluoro-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)-2-methoxy-3-methylbutan-1-one (4b) (mixture of diastereomers). Yield 105 mg (70%), yellowish oil. HPLC analysis (ReproSil 100 Si column; hexane–*i*-PrOH, 40:1): $\tau_{(3S,2'R)\text{-}\mathbf{4b}}$ 4.2 min, $\tau_{(3S,2'S)\text{-}\mathbf{4b}}$ 4.7 min; (3*S*,2'*R*)/(3*S*,2'*S*) = 58.7:41.3. ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.85 (1.23H, d, *J* = 6.7, CH(C$\underline{H}_3$)$_2$ (*S*,*S*)); 0.93 (1.23H, d, *J* = 6.7, CH(C$\underline{H}_3$)$_2$ (*S*,*S*)); 0.94 (1.77H, d, *J* = 6.8, CH(C$\underline{H}_3$)$_2$ (*S*,*R*)); 0.99 (1.77H, d, *J* = 6.7, CH(C$\underline{H}_3$)$_2$ (*S*,*R*)); 1.15–1.18 (3H, m, CHC$\underline{H}_3$ (*S*,*R*) and (*S*,*S*)); 1.97–2.11 (1H, m, CH*i*-Pr (*S*,*R*) and (*S*,*S*)); 2.61 (1.77H, s, OCH$_3$ (*S*,*R*)); 2.66 (1.23H, s, OCH$_3$ (*S*,*S*)); 3.90 (0.59H, d, *J* = 7.8, C$\underline{H}$(CH$_3$)$_2$ (*S*,*R*)); 3.99 (0.41H, d, *J* = 7.4, C$\underline{H}$(CH$_3$)$_2$ (*S*,*S*)); 4.10–4.18 (2H, m, CH$_2$ (*S*,*R*) and (*S*,*S*)); 4.39 (0.41H, dd, *J* = 11.0, *J* = 1.5, CH$_2$ (*S*,*S*)); 4.40 (0.59H, dd, *J* = 11.1, *J* = 1.4, CH$_2$ (*S*,*R*)); 4.84–4.92 (1H, m, C$\underline{H}$CH$_3$ (*S*,*R*) and (*S*,*S*)); 6.84–6.91 (1H, m, H-6 (*S*,*R*) and (*S*,*S*)); 7.50 (0.41H, ddd, *J* = 9.3, *J* = 5.5, *J* = 2.6, H-5 (*S*,*S*)); 7.71 (0.59H, ddd, *J* = 9.5, *J* = 5.5, *J* = 2.6, H-5 (*S*,*R*)). ^{19}F NMR spectrum (376 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.03 (0.59F, ddd, *J* = 21.0, *J* = 8.7, *J* = 2.2, F-8 (*S*,*R*)); 2.05–2.15 (0.41F, m, F-8 (*S*,*S*)); 20.8 (0.59F, ddd, *J* = 20.9, *J* = 10.1, *J* = 5.4, F-7 (*S*,*R*)); 20.9–21.0 (0.41F, m, F-7 (*S*,*S*)). Found, %: C 60.14; H 6.63; F 12.95; N 4.64. $C_{15}H_{19}F_2NO_3$. Calculated, %: C 60.19; H 6.40; F 12.69; N 4.68.

2-Methoxy-1-(3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)-2-phenylethanone (3c) (mixture of diastereomers). Yield 123 mg (83%), colorless oil. HPLC analysis (ReproSil 100 Si column; hexane–*i*-PrOH, 100:1): $\tau_{(3S,2'R)\text{-}\mathbf{3c}}$ 6.1 min, $\tau_{(3S,2'S)\text{-}\mathbf{3c}}$ 7.0 min; (3*S*,2'*R*)/(3*S*,2'*S*) = 50.2:49.8. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.93 (1.5H, d, *J* = 6.8, CHC$\underline{H}_3$ (*S*,*S*)); 0.98 (1.5H, d, *J* = 6.8, CHC$\underline{H}_3$ (*S*,*R*)); 3.35 (1.5H, s, OCH$_3$ (*S*,*R*)); 3.41 (1.5H, s, OCH$_3$ (*S*,*S*)); 3.75 (0.5H, dd, *J* = 10.9, *J* = 2.9, CH$_2$ (*S*,*S*)); 3.86 (0.5H, dd, *J* = 11.0, *J* = 2.5, CH$_2$ (*S*,*R*)); 4.03 (0.5H, dd, *J* = 10.9, *J* = 1.6, CH$_2$ (*S*,*S*)); 4.12 (0.5H, dd, *J* = 10.9, *J* = 1.6, CH$_2$ (*S*,*R*)); 4.62–4.68 (1H, m, C$\underline{H}$CH$_3$ (*S*,*R*) and (*S*,*S*)); 5.29 (0.5H, s, C$\underline{H}$Ph (*S*,*R*)); 5.39 (0.5H, s, C$\underline{H}$Ph (*S*,*S*)); 6.80–6.90 (2H, m, H Ph); 7.01–7.05 (1H, m, H Ph); 7.28–7.35 (5H, m, H Ph); 7.37–7.41 (1H, m, H Ph); 7.69 (0.5H, dd, *J* = 8.1, *J* = 1.4, H-5 (*S*,*S*)); 7.81–7.83 (0.5H, m, H-5 (*S*,*R*)). Found, %: C 72.53; H 6.69; N 4.71. $C_{18}H_{19}NO_3$. Calculated, %: C 72.71; H 6.44; N 4.71.

1-(7,8-Difluoro-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)-2-methoxy-2-phenylethanone (4c) (mixture of diastereomers). Yield 162 mg (97%), colorless oil. HPLC analysis (ReproSil 100 Si column; hexane–*i*-PrOH, 100:1): $\tau_{(3S,2'R)\text{-}\mathbf{4c}}$ 7.1 min, $\tau_{(3S,2'S)\text{-}\mathbf{4c}}$ 8.3 min; (3*S*,2'*R*)/(3*S*,2'*S*) = 50.1:49.9. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.91 (1.5H, d, *J* = 6.8, CHC$\underline{H}_3$ (*S*,*S*)); 0.99 (1.5H, d, *J* = 6.9, CHC$\underline{H}_3$ (*S*,*R*)); 3.37 (1.5H, s, OCH$_3$ (*S*,*R*)); 3.40 (1.5H, s, OCH$_3$ (*S*,*S*)); 3.85 (0.5H, dd, *J* = 11.0, *J* = 2.7, CH$_2$ (*S*,*S*)); 3.92 (0.5H, dd, *J* = 11.0, *J* = 2.8, CH$_2$ (*S*,*R*)); 4.21 (0.5H, dd, *J* = 11.0, *J* = 1.4, CH$_2$ (*S*,*S*)); 4.29 (0.5H, dd, *J* = 11.0; *J* = 1.5, CH$_2$ (*S*,*R*)); 4.67–4.72 (1H, m, CHC$\underline{H}_3$ (*S*,*R*) and (*S*,*S*)); 5.30 (0.5H, s, CHPh (*S*,*R*)); 5.37 (0.5H, m, CHPh (*S*,*S*)); 6.84–6.91 (1H, m, H-6 (*S*,*R*) and (*S*,*S*)); 7.30–7.43 (5H, m, H Ph); 7.56 (0.5H, ddd, *J* = 9.4, *J* = 5.5, *J* = 2.5, H-5 (*S*,*S*)); 7.71 (0.5H, ddd, *J* = 9.5, *J* = 5.5, *J* = 2.6, H-5 (*S*,*R*)). ^{19}F NMR spectrum (470 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.9–2.0 (1F, m, F-8); 20.8 (0.5F, ddd, *J* = 21.2, *J* = 10.0, *J* = 5.4, F-7 (*S*,*R*)); 21.0–

21.1 (0.5F, m, F-7 (*S*,*S*)). Found, %: C 64.58; H 5.18; F 11.25; N 4.19. $C_{18}H_{17}F_2NO_3$. Calculated, %: C 64.86; H 5.14; F 11.40; N 4.20.

2-Methoxy-1-(3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)-3-phenylpropan-1-one (3d) (mixture of diastereomers). Yield 112 mg (72%), colorless oil. HPLC analysis (ReproSil 100 Si column; hexane–*i*-PrOH, 60:1): $\tau_{(3S,2'R)\text{-}\mathbf{3d}}$ 6.7 min, $\tau_{(3S,2'S)\text{-}\mathbf{3d}}$ 5.9 min; (3*S*,2'*R*)/(3*S*,2'*S*) = 49.3:50.7. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.00 (1.5H, d, *J* = 6.8, CHC<u>H</u>$_3$ (*S*,*S*)); 1.12 (1.5H, d, *J* = 6.8, CHC<u>H</u>$_3$ (*S*,*R*)); 2.97 (0.5H, dd, *J* = 13.6, *J* = 6.8, CH_2Ph (*S*,*S*), overlapped with the signal of CH_2Ph (*S*,*S*)); 3.00 (0.5H, dd, *J* = 13.6, *J* = 6.6, CH_2Ph (*S*,*R*), overlapped with the signals of CH_2Ph (*S*,*S*) and CH_2Ph (*S*,*R*)); 3.02 (0.5H, dd, *J* = 14.0, *J* = 7.2, CH_2Ph (*S*,*R*)); 3.09 (0.5H, dd, *J* = 14.0, *J* = 6.4, CH_2Ph (*S*,*R*)); 3.19 (1.5H, s, OCH_3 (*S*,*R*)); 3.35 (1.5H, s, OCH_3 (*S*,*S*)); 3.71–3.78 (0.5H, m, CH_2 (*S*,*S*)); 3.81 (0.5H, dd, *J* = 11.0, *J* = 2.9, CH_2 (*S*,*R*)); 4.09 (0.5H, dd, *J* = 10.9, *J* = 1.6, CH_2 (*S*,*S*)); 4.10 (0.5H, dd, *J* = 11.0, *J* = 1.7, CH_2 (*R*,*S*)); 4.56–4.64 (1.5H, m, CHBn (*S*,*R*) and (*S*,*S*); C<u>H</u>CH$_3$ (*S*,*R*)); 4.72 (0.5H, qdd, *J* = 6.8, *J* = 3.0, *J* = 1.6, CHBn (*S*,*S*)); 6.80–6.90 (2H, m, H Ph); 6.99–7.30 (5H, m, H Ph); 7.50–7.62 (1H, m, H-5 (*S*,*R*) and (*S*,*S*)). Found, %: C 73.30; H 6.98; N 4.63. $C_{19}H_{21}NO_3$. Calculated, %: C 73.29; H 6.80; N 4.50.

1-(7,8-Difluoro-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)-2-methoxy-3-phenylpropan-1-one (4d) (mixture of diastereomers). Yield 111 mg (64%), colorless oil. HPLC analysis (ReproSil 100 Si column; hexane–*i*-PrOH, 60:1): $\tau_{(3S,2'R)\text{-}\mathbf{4d}}$ 8.1 min, $\tau_{(3S,2'S)\text{-}\mathbf{4d}}$ 7.3 min; (3*S*,2'*R*)/(3*S*,2'*S*) = 51.3:48.7. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.02 (1.44H, d, *J* = 6.9, CHC<u>H</u>$_3$ (*S*,*S*)); 1.15 (1.56H, d, *J* = 6.8, CHC<u>H</u>$_3$ (*S*,*R*)); 2.95–3.11 (2H, m, CH_2Ph (*S*,*R*) and (*S*,*S*)); 3.26 (1.56H, s, OCH_3 (*S*,*R*)); 3.34 (1.44H, s, OCH_3 (*S*,*S*)); 3.81–3.89 (1H, m, CH_2 (*S*,*R*) and (*S*,*S*)); 4.27 (1H, dd, *J* = 11.0, *J* = 1.3, CH_2 (*S*,*R*) and (*S*,*S*)); 4.59 (0.52H, t, *J* = 6.7, CHBn (*S*,*R*), overlapped with the signal of CHBn (*S*,*S*)); 4.60 (0.48H, t, *J* = 6.6, CHBn (*S*,*R*), overlapped with the signals of CHBn (*S*,*S*) and C<u>H</u>CH$_3$ (*S*,*R*)); 4.61–4.68 (0.52H, m, C<u>H</u>CH$_3$ (*S*,*R*)); 4.78 (0.48H, qdd, *J* = 6.7, *J* = 2.9, *J* = 1.4, CHBn (*S*,*S*)); 6.81–6.91 (1H, m, 6-H); 7.12–7.31 (5H, m, H Ph); 7.38–7.44 (0.48H, m, H-5 (*S*,*S*)) 7.50–7.58 (0.52H, m, H-5 (*S*,*R*)). ^{19}F NMR spectrum (470 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 2.0–2.1 (0.52F, m, F-8 (*S*,*R*)); 2.1–2.2 (0.48F, m, F-8 (*S*,*S*)); 20.8–21.0 (0.52F, m, F-7 (*S*,*R*)); 21.0–21.2 (0.48F, m, F-7 (*S*,*S*)). Found, %: C 65.48; H 5.72; F 10.99; N 4.23. $C_{19}H_{19}F_2NO_3$. Calculated, %: C 65.70; H 5.51; F 10.94; N 4.03.

2-Benzyloxy-1-(3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)propan-1-one (3e) (mixture of diastereomers). Yield 72 mg (46%), yellow amorphous powder. GC data: $\tau_{(3S,2'R)\text{-}\mathbf{3e}}$ 28.0 min, $\tau_{(3S,2'S)\text{-}\mathbf{3e}}$ 28.3 min; (3*S*,2'*R*)/(3*S*,2'*S*) = 79.2:20.8. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.09 (2.25H, d, *J* = 6.6, CHC<u>H</u>$_3$ (*S*,*R*)); 1.10 (0.75H, d, *J* = 6.6, CHC<u>H</u>$_3$ (*S*,*S*)); 1.34 (0.75H, d, *J* = 6.5, CHOC<u>H</u>$_3$ (*S*,*S*)); 1.40 (2.25H, d, *J* = 6.4, CHOC<u>H</u>$_3$ (*S*,*R*)); 4.06 (0.25H, dd, *J* = 10.9, *J* = 2.9, CH_2 (*S*,*S*)); 4.09 (0.75H, dd, *J* = 11.0, *J* = 2.9, CH_2 (*S*,*R*)); 4.17 (0.25H, dd, *J* = 10.9; *J* = 1.6, CH_2 (*S*,*S*), overlapped with the signal of CH_2 (*S*,*R*)); 4.18 (0.75H, dd, *J* = 11.0, *J* = 1.6, CH_2 (*S*,*R*)); 4.39 (0.75H, d, *J* = 11.7, CH_2Ph (*S*,*R*)); 4.44 (0.75H, d, *J* = 11.7, CH_2Ph (*S*,*R*)); 4.54 (0.25H, d, *J* = 11.7, CH_2Ph (*S*,*S*)); 4.58 (0.25H, d, *J* = 11.7, CH_2Ph (*S*,*S*)); 4.63 (0.75H, q, *J* = 6.4, C<u>H</u>OCH$_3$ (*S*,*R*), overlapped with the signal of C<u>H</u>OCH$_3$ (*S*,*S*)); 4.66 (0.25H, q, *J* = 6.5, C<u>H</u>OCH$_3$ (*S*,*S*)); 4.69 (0.75H, qdd, *J* = 6.7, *J* = 2.5, *J* = 1.7, C<u>H</u>CH$_3$ (*S*,*R*), overlapped with the signal of C<u>H</u>CH$_3$ (*S*,*S*)); 4.74 (0.25H, qdd, *J* = 6.7, *J* = 2.7, *J* = 1.7, C<u>H</u>CH$_3$ (*S*,*S*)); 6.81–6.87 (2H, m, H-6,8); 7.01–7.05 (1H, m, H-7); 7.23–7.35 (5H, m, H Ph); 7.63 (0.25H, d, *J* = 8.4, H-5 (*S*,*S*)); 7.67 (0.75H, d, *J* = 8.1, H-5 (*S*,*R*)). Found, %: C 73.44; H 7.08; N 4.31. $C_{19}H_{21}NO_3$. Calculated, %: C 73.29; H 6.80; N 4.50.

2-Benzyloxy-1-(7,8-difluoro-3-methyl-2,3-dihydro-4*H*-1,4-benzoxazin-4-yl)propan-1-one (4e) (mixture of diastereomers). Yield 135 mg (78%), yellow amorphous powder. GC: $\tau_{(3S,2'R)\text{-}\mathbf{4e}}$ 28.1 min, $\tau_{(3S,2'S)\text{-}\mathbf{4e}}$ 28.5 min; (3*S*,2'*R*)/(3*S*,2'*S*) = 58.3:41.7. ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.10 (1.56H, d, *J* = 6.8, CHC<u>H</u>$_3$ (*S*,*R*)); 1.12 (1.44H, d, *J* = 6.8, CHC<u>H</u>$_3$ (*S*,*S*)); 1.37 (1.44H, d, *J* = 6.5, CHOC<u>H</u>$_3$ (*S*,*S*)); 1.40 (1.56H, d, *J* = 6.4, C<u>H</u>OCH$_3$ (*S*,*R*)); 4.12 (0.48H, dd, *J* = 11.0, *J* = 2.9, CH_2 (*S*,*S*)); 4.16 (0.52H, dd, *J* = 11.0, *J* = 2.9, CH_2 (*S*,*R*)); 4.327 (0.52H, dd, *J* = 11.0, *J* = 1.6, CH_2 (*S*,*R*), overlapped with the signal of CH_2 (*S*,*S*)); 4.330 (0.48H, dd, *J* = 11.0, *J* = 2.0, CH_2 (*S*,*S*)); 4.44 (1H, d, *J* = 11.8, CH_2Ph (*S*,*R*) and (*S*,*S*)); 4.47 (1H, d, *J* = 11.8, CH_2Ph (*S*,*R*) and (*S*,*S*)); 4.62 (1H, q, *J* = 6.4, C<u>H</u>OCH$_3$ (*S*,*R*) and (*S*,*S*)); 4.73 (0.52H, qdd, *J* = 6.8, *J* = 2.8, *J* = 1.5, C<u>H</u>CH$_3$ (*S*,*R*)); 4.79 (0.48H, qdd, *J* = 6.8, *J* = 2.8, *J* = 1.5, C<u>H</u>CH$_3$ (*S*,*S*)); 6.81–6.87 (1H, m, H-6); 7.23–7.35 (5H, m, H Ph); 7.53 (0.48H, ddd, *J* = 9.3, *J* = 5.4, *J* = 2.5, H-5 (*S*,*S*)); 7.56 (0.52H, ddd, *J* = 9.0, *J* = 5.3, *J* = 2.6, H-5 (*S*,*R*)). ^{19}F NMR spectrum (470 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 1.9 (0.52F, ddd, *J* = 21.0, *J* = 8.3, *J* = 2.3, F-8 (*S*,*R*)); 2.0 (0.48F, ddd, *J* = 21.7, *J* = 8.6, *J* = 1.7, F-8 (*S*,*S*)); 20.7 (0.52F, ddd, *J* = 20.8, *J* = 10.1, *J* = 5.4, F-7 (*S*,*R*)); 20.8 (0.48F, ddd, *J* = 20.6, *J* = 10.0, *J* = 5.5, F-7 (*S*,*S*)). Found, %: C 65.74; H 5.64; F 10.98; N 4.06. $C_{19}H_{19}F_2NO_3$. Calculated, %: C 65.70; H 5.51; F 10.94; N 4.03.

Derivatization of racemic carboxylic acids 5a,b (General method). *N*-Methylmorpholine (0.17 ml, 1.5 mmol), (*R*)-1-phenylethylamine (0.13 ml, 1 mmol), HOBt (200 mg, 1.5 mmol), and EDC·HCl (290 mg, 1.5 mmol) were added to a solution of racemic 2-methoxycarboxylic acid **5a** or **5b** (1 mmol) in DMF (3 ml) under stirring. The reaction mixture was stirred until dissolution of the reagents and then kept at ambient temperature for 48 h. The reaction mixture was diluted with EtOAc (20 ml), washed with 1 N HCl (3×15 ml), saturated aqueous NaCl solution (3×20 ml), aqueous 1 N NaOH solution (2×15ml), saturated aqueous NaCl solution (3×20 ml), then dried over Na_2SO_4, and evaporated. The diastereomeric excess of the synthesized amides was determined by HPLC on silica gel. The diastereomeric amides were isolated by flash chromatography on silica gel.

(2*S*)-2-Methoxy-*N*-((1*R*)-1-phenylethyl)propanamide (6a) (mixture of diastereomers).[21] Yield 153 mg (74%) after flash chromatography (eluent hexane–EtOAc, gradient from 4:1 to 3:2), white amorphous powder. HPLC analysis

(ReproSil 100 Si column; hexane–*i*-PrOH, 40:1): $\tau_{(1R,2'S)\text{-}\mathbf{6a}}$ 8.8 min, $\tau_{(1R,2'R)\text{-}\mathbf{6a}}$ 7.5 min; (1*R*,2'*S*)/(1*R*,2'*R*) = 46.7:53.3.

(2*R*)-2-Methoxy-3-methyl-*N*-((1*R*)-1-phenylethyl)butanamide ((1*R*,2'*R*)-6b). Yield 61 mg (26%) after flash chromatography (eluent hexane–EtOAc, 98:2), colorless crystalline powder, mp 73–76°C. HPLC analysis (ReproSil 100 Si column; hexane–*i*-PrOH, 40:1): $\tau_{(1R,2'S)\text{-}\mathbf{6b}}$ 4.2 min, $\tau_{(1R,2'R)\text{-}\mathbf{6b}}$ 4.7 min; (1*R*,2'*S*)/(1*R*,2'*R*) = 1.4:98.6. $[\alpha]_D^{20}$ +125 (*c* 0.9, $CHCl_3$). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.92 (3H, d, *J* = 6.9, CH(C<u>H</u>$_3$)$_2$); 1.01 (3H, d, *J* = 6.9, CH(C<u>H</u>$_3$)$_2$); 1.51 (3H, d, *J* = 6.9, NHCHC<u>H</u>$_3$); 2.07–2.16 (1H, m, C<u>H</u>(CH$_3$)$_2$); 3.34 (3H, s, OCH$_3$); 3.41 (1H, d, *J* = 4.0, C<u>H</u>OCH$_3$); 5.18 (1H, dq, *J* = 7.1, *J* = 6.9, NHC<u>H</u>CH$_3$); 6.73 (1H, d, *J* = 7.1, N<u>H</u>CHCH$_3$); 7.26–7.29 (1H, m, H Ph); 7.32–7.37 (4H, m, H Ph). Found, %: C 71.20; H 9.14; N 5.82. $C_{14}H_{21}NO_2$. Calculated, %: C 71.46; H 8.99; N 5.95.

((2*S*)-2-Methoxy-3-methyl-*N*-((1*R*)-1-phenylethyl)butanamide ((1*R*,2'*S*)-6b). Yield 73 mg (31%) after flash chromatography (eluent hexane–EtOAc, 98:2), colorless crystalline powder, mp 90–91°C. HPLC analysis (ReproSil 100 Si column; hexane–*i*-PrOH, 40:1): $\tau_{(1R,2'S)\text{-}\mathbf{6b}}$ 4.2 min, $\tau_{(1R,2'R)\text{-}\mathbf{6b}}$ 4.7 min; (1*R*,2'*S*)/(1*R*,2'*R*) = 99.7:0.3. $[\alpha]_D^{20}$ +18.2 (*c* 1.3, $CHCl_3$). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm (*J*, Hz): 0.81 (3H, d, *J* = 6.9, CH(C<u>H</u>$_3$)$_2$); 0.95 (3H, d, *J* = 6.9, CH(C<u>H</u>$_3$)$_2$); 1.52 (3H, d, *J* = 6.9, NHCHC<u>H</u>$_3$); 2.01–2.10 (1H, m, C<u>H</u>(CH$_3$)$_2$); 3.41–3.43 (4H, m, OCH$_3$ and C<u>H</u>OCH$_3$); 5.14–5.20 (1H, m, NHC<u>H</u>CH$_3$); 6.72 (1H, d, *J* = 6.6, N<u>H</u>CHCH$_3$); 7.24–7.27 (1H, m, H Ph); 7.30–7.35 (4H, m, H Ph). Found, %: C 71.44; H 8.92; N 5.91. $C_{14}H_{21}NO_2$. Calculated, %: C 71.46; H 8.99; N 5.95.

Kinetic resolution of acyl chlorides 2a–e by (*S*)-amines 1a,b (General method). A solution of the appropriate acyl chloride (0.6 mmol) in PhMe (2 ml) was added at 20°C to a solution of amine **1a** or **1b** (0.3 mmol) and *N*,*N*-diethylaniline (44.8 mg, 0.3 mmol) in PhMe (4 ml). The reaction mixture was kept at 20°C for 24 h. In order to perform KR of acyl chlorides **2a**,**b**, the reaction mixture was treated by the addition of saturated Na_2CO_3 solution and vigorously stirred for 1 h. In the rest of the cases, the reaction mixture was evaporated, the residue was dissolved in MeCN (10 ml) and added to a saturated solution of Na_2CO_3 (10 ml). The mixture was vigorously stirred for 1 h, then concentrated by evaporation at reduced pressure, and extracted with $CHCl_3$ (2×5 ml). The organic layer was washed with aqueous 4 N HCl solution (2×4 ml), saturated NaCl solution (4×5 ml), and H_2O (2×5 ml), dried over Na_2SO_4, and evaporated. The ratio of diastereomeric amides in the mixture was determined by GC.

The alkaline aqueous solutions were acidified with 4 N HCl solution to pH 1–2 and extracted with $CHCl_3$ (2×5 ml). The organic layer was washed with saturated aqueous NaCl solution (2×5 ml), dried over Na_2SO_4, and evaporated. The obtained carboxylic acids **5a**–**e** were purified by flash chromatography on silica gel and analyzed by HPLC. Carboxylic acids **5a**,**b** were derivatized with (*R*)-1-phenylethylamine prior to the analysis, the obtained diastereomeric amides were analyzed by HPLC on silica gel.

(2*S*)-2-Methoxypropanoic acid ((*S*)-5a). Yield 15 mg (49%), yellowish oil. The obtained carboxylic acid was derivatized with (*R*)-1-phenylethylamine according to the general method for carboxylic acids **5a**,**b**. The chromatographic peaks of the diastereomeric amides **6a** were assigned on the basis of literature data.[21] The *de* of (1*R*,2'*S*)-amide **6a** was 63%, HPLC analysis (ReproSil 100 Si column; hexane–*i*-PrOH, 40:1): $\tau_{(1R,2'S)\text{-}\mathbf{6a}}$ 8.8 min, $\tau_{(1R,2'R)\text{-}\mathbf{6a}}$ 7.5 min.

(2*S*)-2-Methoxy-3-methylbutanoic acid ((*S*)-5b). Yield 7 mg (17%), yellowish oil. The obtained carboxylic acid was derivatized with (*R*)-1-phenylethylamine according to the general method for carboxylic acids **5a**,**b**. The *de* of (1*R*,2'*S*)-amide **6b** 74%, HPLC analysis (ReproSil 100 Si column; hexane–*i*-PrOH, 40:1): $\tau_{(1R,2'S)\text{-}\mathbf{6b}}$ 4.2 min, $\tau_{(1R,2'R)\text{-}\mathbf{6b}}$ 4.7 min.

(2*S*)-2-Methoxy-2-phenylacetic acid ((*S*)-5c). Yield 44 mg (89%), yellow amorphous powder. The *ee* was 65%, HPLC analysis (hexane–*i*-PrOH–CF_3COOH mobile phase, 40:1:0.02): $\tau_{(S)\text{-}\mathbf{5c}}$ 20.8 min, $\tau_{(R)\text{-}\mathbf{5c}}$ 18.8 min. $[\alpha]_D^{20}$ +104 (*c* 1.0, EtOH) ($[\alpha]_D^{20}$ +146.0 (*c* 1.04, EtOH)[22]). ^{1}H NMR spectrum was identical to the published one.[33] Found, *m*/*z*: 165.0555 $[M–H]^-$. $C_9H_9O_3$. Calculated, *m*/*z*: 165.0557.

(2*S*)-2-Methoxy-3-phenylpropanoic acid ((*S*)-5d). Yield 36 mg (67%), colorless oil. The *ee* was 67%, HPLC analysis (hexane–*i*-PrOH–CF_3COOH mobile phase, 40:1:0.02): $\tau_{(S)\text{-}\mathbf{5d}}$ 20.4 min, $\tau_{(R)\text{-}\mathbf{5d}}$ 14.0 min. $[\alpha]_D^{20}$ –21.4 (*c* 0.5, Me_2CO) ($[\alpha]_D^{20}$ –36.7 (*c* 0.6, Me_2CO) (*ee* 99.3%)[31]). ^{1}H NMR spectrum was identical to the published one.[31] Found, *m*/*z*: 179.0715 $[M–H]^-$. $C_{10}H_{11}O_3$. Calculated, *m*/*z*: 179.0714.

(2*S*)-(2-Benzyloxy)propanoic acid ((*S*)-5e). Yield 20 mg (37%) after flash chromatography (eluent PhH–EtOAc, 9:1), yellow oil, *ee* 63%, HPLC analysis (hexane–*i*-PrOH–CF_3COOH mobile phase, 20:1:0.02): $\tau_{(S)\text{-}\mathbf{5c}}$ 7.1 min, $\tau_{(R)\text{-}\mathbf{5c}}$ 7.8 min. $[\alpha]_D^{20}$ –42.9 (*c* 2.4, PhH) ($[\alpha]_D^{20}$ –74.2 (*c* 4.6, PhH)[24]). ^{1}H NMR spectrum was identical to the published one.[24] Found, *m*/*z*: 179.0713 $[M–H]^-$. $C_{10}H_{11}O_3$. Calculated, *m*/*z*: 179.0714.

X-ray structural analysis of (*R*,*S*)-amide 6b was performed on an Xcalibur-3 (Oxford Diffraction) diffractometer equipped with a CCD-detector, using the standard procedure (λ(MoKa) 0.07107 nm, graphite monochromator, ω-scanning). Crystals suitable for the analysis were obtained by evaporation of amide solution in MeOH at room temperature. The data were acquired and processed with the CrysAlis software package.[34] The structures of compounds were solved by direct method using the SHELXS-97 program and refined with the SHELXL-97 program[35] in anisotropic approximation (isotropically for hydrogen atoms). The hydrogen atom positions were partially solved and refined independently, and partially included in the refinement according to the "rider" model with dependent temperature parameters. The crystallographic data: crystal size 0.25 × 0.12 × 0.03 mm; colorless needles; monoclinic syngony; space group $P2_1$; *a* 9.325(3), *b* 5.2567(7), *c* 14.973(4) Å; α 90, β 104.20(3), γ 90°; *V* 711.5(3) Å^3; *Z* 2; d_{calc} 1.0983 g/cm^3; μ 0.073 mm^{-1}; 2.2770 < θ < 20.5630. The completeness for θ ≤ 28.22°

was 99.9%. A total of 3867 reflections were collected (2741 independent, R_{int} 0.0616), including 899 reflections with $I \geq 2\sigma(I)$. The value of S by F^2 was 0.958786. The final probability factors were R_1 ($I > 2\sigma(I)$) 0.053388, R_1 0.213027 (all data), wR_2 0.150363 (all data). The X-ray structural dataset was deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1434293).

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