Stereoinversion in the diastereoselective acylation of benzoxazine derivatives with 2-aryloxypropionyl chlorides*

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A comparative study of the kinetic resolution of racemic derivatives of 3,4-dihydro-3-methyl-2*H*-[1,4]benzoxazine using racemic 2-aryloxypropionyl chlorides was performed. It was found that the acylation of racemic amines with racemic 2-(1-naphthyloxy)propionyl chloride leads to amides enriched with (3*R**,2′*R**)-diastereomers, while the acylation with 2-phenoxypropionyl chloride gives predominantly (3*R**,2′*S**)-amides. Quantum chemical modeling of the process of kinetic resolution at the COSMO-CH_2Cl_2-B3LYP-D3-gCP/def2-TZVP//B3LYP-D3-gCP/def2-SVP level of theory was performed. The computational results are in a good agreement with the experimental data.

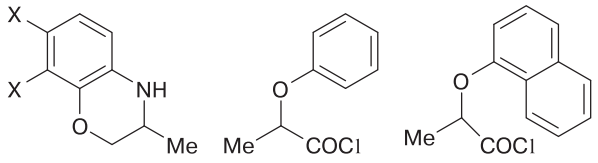
Key words: acylation, heterocyclic amines, acyl chlorides, 2-alkyloxy acids, stereoselectivity, stereoinversion, density functional theory (DFT).

Kinetic resolution of racemates is one of the methods for obtaining individual enantiomers of various classes of compounds,[1] including practically valuable heterocyclic amines. This method is based on the difference in the rates of the reactions of stereoisomers of a racemic substrate with a chiral or achiral agent in the presence of a chiral catalyst. It is relatively rare to observe a situation when during kinetic resolution two structurally close chiral resolving agents of the same stereoconfiguration preferably react with different enantiomers of the racemic substrate. To refer to such a phenomenon, the term inversion of stereoselectivity, or stereoinversion, is commonly used.[2]

The synthetic precursors of many chiral catalysts, chiral synthesis agents, and chiral derivatizing agents are natural compounds such as carboxylic acids, alcohols, and amines. These compounds are often available from natural sources only as a single stereoisomer; therefore, such agents can be used to obtain enantiomerically pure amines of one configuration, while the synthesis of its optical antipode can be significantly more complex. Reactions in which the inversion of stereoselectivity is observed are under intense studies, since stereoinversion opens the way to the synthesis of both stereoisomers of the racemic substrate using the agents obtained from one chiral precursor.[3]

We have systematically studied the stereoselective reactions of racemic heterocyclic amines with 2-hydroxy acyl chlorides.[4—8] The COSMO-CH_2Cl_2-B3LYP-D3-gCP/def2-TZVP calculation method was demonstrated to be applicable for establishing the reaction mechanism and explanation of the reasons for the differences in the kinetic resolution.[7]

The purpose of the present work was to study the mutual kinetic resolution of racemic 3-methylbenzoxazines **1a** and **1b** with racemic 2-(1-naphthyloxy)propionyl chloride (**2b**) structurally close to 2-phenoxypropionyl chloride (**2a**), as well as to analyze the stereochemical results using quantum chemical simulation of the diastereomeric transition states (TSs) at the COSMO-CH_2Cl_2-B3LYP-D3-gCP/def2-TZVP//B3LYP-D3-gCP/def2-SVP level. The density functional theory (DFT) method, being not time consuming and allowing one to accurately enough evaluate noncovalent interactions, provided not only qualitative but also quantitative agreement of the calculated and the



1a,b **2a** **2b**

1: X = H (**a**), F (**b**)

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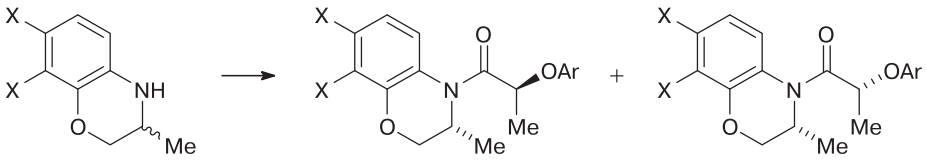
Scheme 1



(*RS*)-**1a,b** (3*R**,2′*S**)-**3a,b, 4a,b** (3*R**,2′*R**)-**3a,b, 4a,b**

2: Ar = Ph (**a**), 1-naphthyl (**b**)

Compound	X	Ar	Compound	X	Ar
3a	H	Ph	**4a**	F	Ph
3b	H	1-naphthyl	**4b**	F	1-naphthyl

Reagents and conditions: 2a,b (0.5 equiv.), CH_2Cl_2, 6 h, −20 °C.

experimental results of the acylation of heterocyclic amines with 2-aryloxy acyl chlorides.[7] Chiral heterocycles **1a**,**b** were used by us earlier as model substrates for studying the kinetic resolution of racemic amines by carboxylic acid derivatives, that is why we used them in the present work, too.

The selectivity factor *s* is the most important characteristic of kinetic resolution, which is the ratio of reaction rates of rapidly and slowly reacting enantiomers. To determine the *s* value of the acylation of heterocycles **1a**,**b**, we used an approach based o n the reaction of racemic reagents, *i.e.*, the limiting version of mutual kinetic resolution.[1] In this case, the *s* value can be determined quite accurately.[9]

The acylation of racemic amines **1a** and **1b** with acyl chloride **2a** was described in the work.[7] The acylation of amines (*RS*)-**1a** and (*RS*)-**1b** with its analog **2b** was carried out under the same conditions, namely, in dichloromethane at −20 °C for 6 h at a 2 : 1 molar ratio of amine : acyl chloride (Scheme 1).

The reaction led to a mixture of (3*R*,2′*R*)/(3*S*,2′*S*)- and (3*R*,2′*S*)/(3*S*,2′*R*)-amides **3a,b** and **4a**,**b** (or (3*R**,2′*R**)- and (3*R**,2′*S**)-amides, respectively). The ratio of diastereomers (*dr*) of amides in the reaction mixtures equal to the parameter *s* was determined by GLC (Table 1).

To unambiguously assign the peaks of diastereomers in the GLC chromatograms, we synthesized mixtures of (3*S*,2′*R*)- and (3*S*,2′*S*)-diastereomers of amides **3b** and **4b** (the ratio of diastereomers ~1 : 1) starting from the equimolar amounts of (*S*)-amines **1a** and **1b** and racemic acyl chloride **2b** in the presence of *N*,*N*-diethylaniline (as an HCl acceptor), which were isolated from the reaction mixture by column flash chromatography and characterized by a combination of physicochemical methods of analysis.

Table 1. Stereochemical results of acylation of amines **1a** and **1b** with acyl chlorides **2a** and **2b**

Amine	Acyl chloride	*Dr* of amides (R^*,S^*)/(R^*,R^*)[a]	Selectivity factor *s*
1a	**2a**	96.2 : 3.8	25[b]
	2b	11.4 : 88.6	7.8
1b	**2a**	98.4 : 1.6	62[b]
	2b	5.5 : 94.5	17

[a] An average value of the results of two experiments according to GLC.

[b] The results are taken from the work.[7]

To assign the configuration of the predominant amides **3b** and **4b**, we acylated enantiopure (*S*)-amines **1a** and **1b** with racemic acyl chloride **2b** in the presence of *N*,*N*-diethylaniline (as an HCl acceptor) at a ratio of (*S*)-amine : acyl chloride : *N*,*N*-diethylaniline equal to 1 : 2 : 1. In this case, a kinetic resolution of the racemic acylating agent took place. The reaction gave diastereomerically enriched amides **3b** and **4b** and unreacted enantiomerically enriched acyl chloride **2b**, which was hydrolyzed with subsequent isolation of the corresponding acid. A comparison of the sign of optical rotation of the acid obtained with the literature data[10] showed that the unreacted acyl chloride belongs to the (*R*)-series and, therefore, its optical antipode reacted with (*S*)-3-methylbenzoxazines faster, with (3*R**,2′*R**)-diastereomers predominating among the amides obtained by the reaction of racemic reagents. Earlier, we showed that the reaction of racemic amines **1a** and **1b** with racemic acyl chloride **2a** predominantly gave (3*S**,2′*R**)-amides.[7] This result means that a stereoinversion occurred on going from agent **2a** (Ar = Ph) to acyl chloride **2b** (Ar = 1-naphthyl), with the selectivity factor in the case of acylation of amines **1a** and **1b** with acyl chloride **2b** being significantly lower (*s* 7.8 and 17, respectively) than in the case of agent **2a** (*s* 25 and 62, respectively) (see Table 1). At the same time, difluoro-containing 3-methylbenzoxazine **1b** reacted with acyl chloride **2b** much more selectively than its non-fluorinated analog **1a** (*s* 17 and 7.8, respectively).

Recently,[7] we showed for the first time that the COSMO-CH_2Cl_2-B3LYP-D3-gCP/def2-TZVP//B3LYP-D3-gCP/def2-SVP method is applicable for the study of kinetic resolution in diastereoselective acylation. It was

found that the acylation of chiral benzoxazines with 2-hydroxycarboxylic acyl chlorides follows the S_N2-like mechanism through the transition state corresponding to the energy maximum in the reaction pathway. According to the proposed model, the addition of the nucleophile to the carbonyl carbon atom of the acylating agent occurs with the simultaneous elimination of the chloride ion.[7]

To explain the observed stereoinversion, as well as the differences in the stereoselectivity of acylation of benzoxazines **1a** and **1b** with acyl chloride **2b**, we performed DFT calculations of the parameters of the reaction of (*R*)-amines **1a** and **1b** with (*RS*)-2-(1-naphthyloxy)propionyl chloride (**2b**) at the COSMO-CH_2Cl_2-B3LYP-D3-gCP/def2-TZVP or def2-SVP)//B3LYP-D3-gCP/def2-SVP level and compared the results with the computational data[7] for the reaction of (*R*)-amines **1a** and **1b** and acyl chloride **2a**.

Before the quantum chemical modeling of the acylation of amines **1a** and **1b** with acyl chloride **2b**, we carried out a conformational search and selected the most favorable conformations of the aliphatic ring of amines, in which the methyl group occupies an axial position.

The selectivity factor can be calculated from the difference in the Gibbs free energies of activation of the reactions of enantiomers of a racemic substrate with a chiral agent or a catalyst.[11] In a qualitative evaluation of stereoselectivity, one often compare not the activation energies, but the Gibbs free energies (*G*) of diastereomeric TSs.[11—13] This simplified approach is based on the assumption that the Gibbs free energies of pre-reaction complexes (PCs) do not differ or the differences in them are negligibly small.[12] Its application is justified in the situations when the PC is unstable (the equilibrium is shifted towards the reagents), as well as in the cases when the structure of the reagent complexes is unclear[13] or it is necessary to single out the predominant mechanism from the many possible pathways of the reaction of one PC.[14]

Using the BLYP/TZVP methods, we showed the formation of stable diastereomeric PCs during the acylation of heterocyclic amines **1a,b** with acyl chloride **2a**.[7] The DFT calculation of the Gibbs free energy of activation of two competing reactions as the difference between the Gibbs free energies of TS and the corresponding PC (see Ref. 15) or stable intermediates[16] allows one to achieve a good agreement between the calculated and the experimental values.

Earlier, we similarly calculated the Gibbs free energies of activation for the reactions of (*R*)-amines **1a**,**b** with acyl chloride **2a** (Table 2).[7]

It was found that the Gibbs free energies of activation of the reactions leading to (3*R*,2′*S*)-amides **3a** and **4a** are lower than the activation energies of the reactions with the formation of (3*R*,2′*R*)-amides, which is consistent with the experimental data. The simulation of the acylation of amines **1a,b** with acyl chloride **2b** showed that the activation energies of the reactions leading to (3*R*,2′*S*)-amides **3a** and **4a**, on the contrary, are higher than the activation energies of the competing reactions giving (3*R*,2′*R*)-diastereomers as the products (Fig. 1, see Table 2). The quantum chemical computational results are consistent with the observed stereoinversion of the acylation of amines **1a**,**b** on going from 2-phenoxy-substituted acyl chloride **2a** to 2-(1-naphthyloxy)-substituted agent **2b**. For example, the difference in the Gibbs activation energies for the pairs of reagents (*S*)-**2b**/(*R*)-**1a** and (*R*)-**2b**/(*R*)-**1a** is 3.17 kJ mol^{-1}, with the experimental value being 4.31 kJ mol^{-1}.

Analysis of the TS geometries showed that in the case of the reactions of amines **1a** and **1b** with both acyl chloride **2a** and acyl chloride **2b**, there is a "sandwich" π-stacking of the aromatic fragments of reagents in both (3*R*,2′*S*)-TS, which is not observed in the case of (3*R*,2′*R*)-TS (Fig. 2). At the same time, the Gibbs absolute free energies of formation for (3*R*,2′*S*)-TS **1a**/**2a** and **1b**/**2a** are lower than for (3*R*,2′*S*)-TS **1a**/**2b** and **1b**/**2b**. It can be assumed that the π-stacking of aryl fragments of reagents in the case of acylation of amines with reagent **2a**, stabilizing (3*R*,2′*S*)-TS, is more favorable than the aromatic interactions in

Table 2. Calculated values of the Gibbs free activation energies ($\Delta G^{\#}$, kJ mol^{-1}) at −20 °C in CH_2Cl_2 for the reaction of (*R*)-amines **1a** and **1b** with (*R*)- and (*S*)-acyl chlorides **2a**,**b** at the COSMO-CH_2Cl_2-B3LYP-D3-gCP/def2-TZVP//B3LYP-D3-gCP/def2-SVP level

Reagents	$\Delta G^{\#}$	$\Delta\Delta G^{\#}$	
		Calculation	Experiment[a]
(*S*)-**2a**/(*R*)-**1a**, (*R*)-**2a**/(*R*)-**1a**	28.19, 34.82	6.63	6.77[b]
(*S*)-**2a**/(*R*)-**1b**, (*R*)-**2a**/(*R*)-**1b**[c]	38.66, 45.45	6.79	8.68[b]
(*S*)-**2b**/(*R*)-**1a**, (*R*)-**2b**/(*R*)-**1a**	43.21, 40.04	3.17	4.31
(*S*)-**2b**/(*R*)-**1b**, (*R*)-**2b**/(*R*)-**1b**[c]	45.74, 41.04	4.70	5.94

[a] The experimental $\Delta\Delta G^{\#}$ values are calculated by the formula $\Delta\Delta G^{\#} = -RT\ln s$.
[b] The results are taken from the work.[7]
[c] Geometric optimization of the complex of reagents was carried out from the model structure of TS.

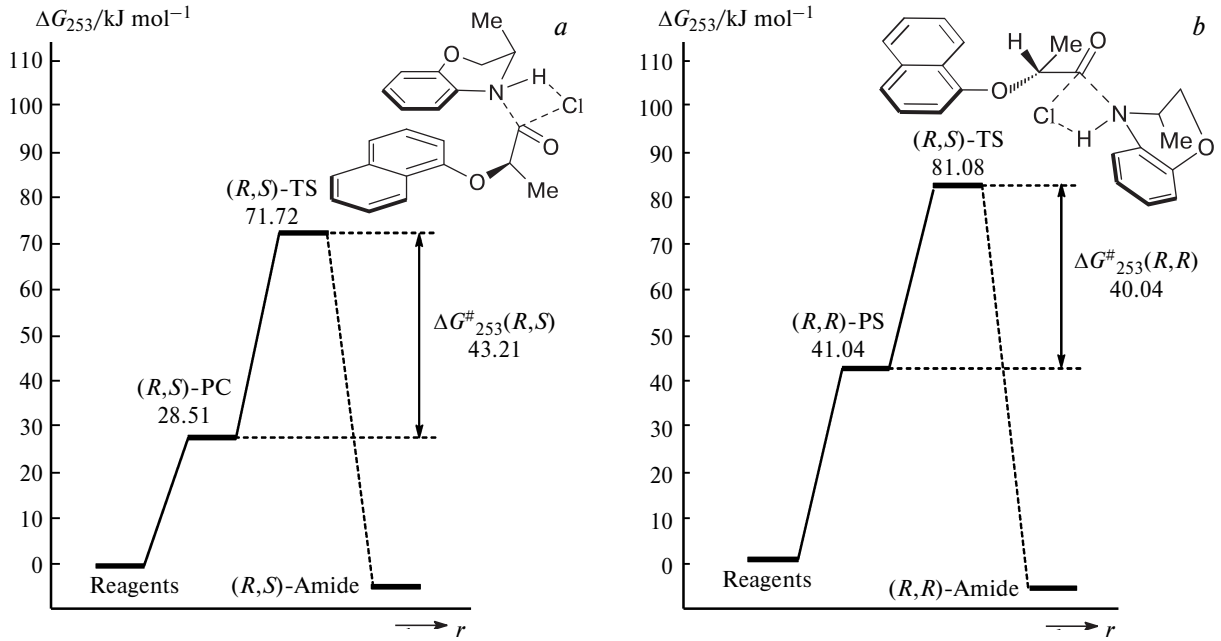


Fig. 1. The calculated coordinate of the reaction (*r*) of amine **1a** and acyl chloride **2b** leading to (*R*,*S*)- (*a*) and (*R*,*R*)-amides (*b*) in dichloromethane at −20 °C (COSMO-CH_2Cl_2-B3LYP-D3-gCP/def2-TZVP//B3LYP-D3-gCP /def2-SVP).

(3*R*,2′*S*)-TS **1a**/**2b** and **1b**/**2b**. According to the quantum chemical calculations, the benzene ring of amines **1a** and **1b** in (3*R*,2′*S*)-TS **1a**/**2b** and **1b**/**2b** is located above the central double bond of the naphthyl fragment of acyl chloride **2b**. According to the literature data,[17] such an arrangement is characteristic of the benzene—naphthalene "sandwich" dimeric π—π-complexes. The calculated values of the bonding energy of benzene molecules in the "sandwich" dimer[18] and the formation energy of the benzene—naphthalene complex[17] are known. The formation energy of the π—π-complex calculated by the standard method of coupled clusters with a complete CCSD(T)/CBS basis set is 2.76 times higher in the second case than in the first.

According to the DFT calculation, amine **1b** is less nucleophilic than its analogue **1a**. This leads to the fact that the nitrogen atom of the amino group of benzoxazine **1b** reacts with the carbonyl carbon atom of acyl chlorides **2a** and **2b** at a shorter distance compared with the reactions of the same acyl chlorides and amine **1a**. The shortening of the N—C bond in TS probably increases the steric requirements to the molecules of reagents in the process of stereodifferentiation, and, as a consequence, the selectivity factor also increases.

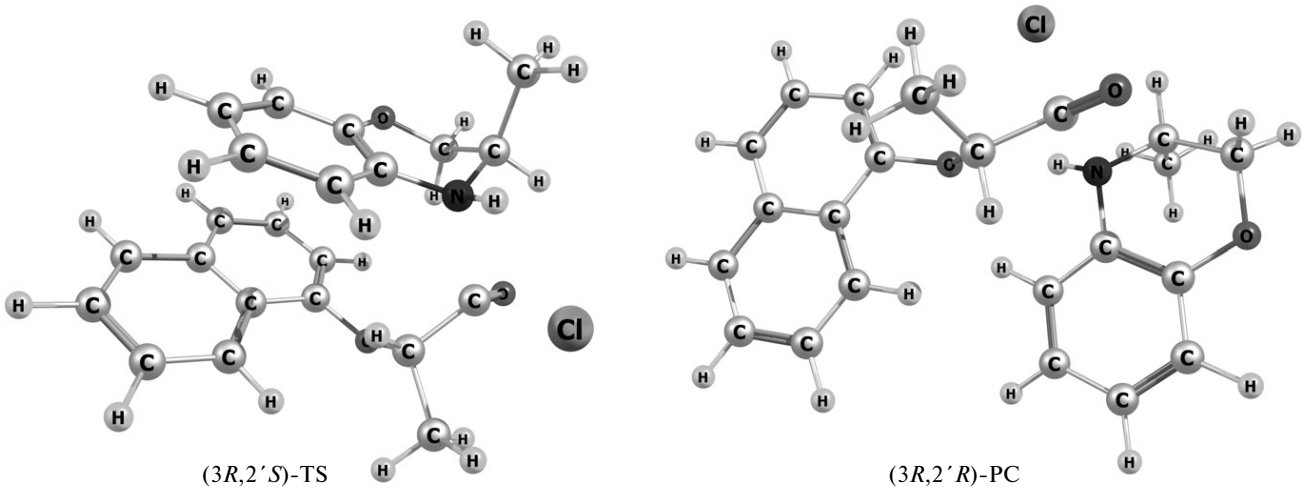


Fig. 2. The geometry of diastereomeric transition states of the reaction of **1a** with **2b** calculated at the COSMO-CH_2Cl_2-B3LYP-D3-gCP/def2-TZVP//B3LYP-D3-gCP/def2-SVP level.

In conclusion, we carried out a comparative study of the mutual kinetic resolution of heterocyclic amines and racemic 2-aryloxypropionyl chlorides. It was established that the acylation of racemic 3,4-dihydro-3-methyl-2*H*-[1,4]benzoxazines by racemic 2-(1-naphthyloxy)-propionyl chloride leads to amides with a predominance of (3*R**,2′*R**)-diastereomers, in contrast to the reaction of these amines with 2-phenoxypropionyl chloride, in which (3*R**,2′*S**)-amides are predominantly formed. Quantum chemical modeling of diastereoselective acylation was performed. It was established that the calculated Gibbs free energies of activation of the reactions of (*R*)-amines and racemic 2-(1-naphthyloxy)propionyl chloride agree with the data obtained experimentally. It was shown that the chosen calculation method is sensitive to a slight change in the structure of the agents, since it leads to the results reflecting the observed in experiments inversion of stereoselectivity in the acylation of 3,4-dihydro-3-methyl-2*H*-[1,4]benzoxazines when a phenoxy group in the structure of the acylating agent is replaced with the (1-naphthyloxy) group.

Experimental

(*RS*)-3,4-Dihydro-3-methyl-2*H*-[1,4]benzoxazine (**1a**),[19] (*RS*)-3,4-dihydro-3-methyl-7,8-difluoro-2*H*-[1,4]benzoxazine (**1b**),[19] (3*S*)-3,4-dihydro-3-methyl-2*H*-[1,4]benzoxazine [(*S*)-**1a**],[20] and (3*S*)-3,4-dihydro-3-methyl-7,8-difluoro-2*H*-[1,4]-benzoxazine [(*S*)-**1b**][21] were synthesized by known procedures. Acyl chloride **2a**, amides (3*R**,2′*S**)-**3a**, (3*R**,2′*S**)-**4a**, as well as mixtures of diastereomeric (3*R*,2′*S*)- and (3*S*,2′*S*)-amides **3a** and **4a** were described earlier.[4] Other reagents were commercially available. Solvents were purified using standard procedures.

^{1}H, ^{13}C, and ^{19}F NMR spectra were recorded on a Bruker Avance 500 spectrometer (500, 126, and 470 MHz, respectively), using tetramethylsilane as an internal standard. ^{1}H NMR spectrum of acyl chloride **2b** was recorded on a Bruker Avance 400 spectrometer (400 MHz). ^{1}H NMR spectra of amides **3a** and **3b** were recorded in DMSO-d_6 at 100 °C, spectra of other compound, in $CDCl_3$ at ~20 °C. Melting points were determined on a Stuart SMP3 apparatus (Barloworld Scientific, UK). Elemental analysis was performed on a Perkin—Elmer 2400 II automatic CHNS-O analyzer. Analytical TLC was performed on Sorbfil plates (Imid Ltd., Russia), silica gel (230—400 mesh) (Alfa Aesar, UK) was used for flash chromatography. Optical rotation of scalemic 2-(1-naphthyloxy)propionic acid were measured on a Perkin—Elmer M341 polarimeter (Perkin—Elmer Instruments, USA). Specific rotation is expressed in deg mL g^{-1} dm^{-1}, concentration of solutions, in g (100 mL)$^{-1}$. HPLC analysis of 2-(1-naphthyloxy)propionic acid was performed on a Shimadzu LC-20 Prominence instrument: a Chiralcel OD-H column (250×4.6 mm, Daicel Corp., Japan), detection at 220 nm, the eluent flow rate was 1 mL min^{-1}, the mobile phase hexane—Pr^{i}OH—CF_3COOH (60 : 0.8 : 0.2). GLC analysis of amides **3b** and **4b** was carried out using a Shimadzu GC 2010 gas chromatograph with a flame ionization detector, a ZB-5 quartz capillary column (length 30 m, diameter 0.25 mm, film thickness 0.25 μm); the initial column temperature was 40 °C (3 min plateau), programming at 10 °C min^{-1} to 280 °C (30 min plateau). The injector and detector temperatures were 250 and 300 °C, respectively, nitrogen was a carrier gas, the flow separation was 1 : 30, the flow through the column was 1.0 mL min^{-1} with the injection of 1.0 μL of amide solution in MeCN with a concentration of 1—3 mg mL^{-1}.

(*RS*)-2-(1-Naphthyloxy)propionic acid. A solution of α-naphthol (3.98 g, 27.6 mmol) in THF (30 mL) was added dropwise to a cooled to 0 °C suspension of NaH (1.04 g, 43.3 mmol) in THF (30 mL) with vigorous stirring. The resulting mixture was stirred for another 15 min at the same temperature, followed by the addition of a solution of methyl 2-bromopropionate (9.79 g, 58.6 mmol) in THF (30 mL). Then, the mixture was stirred for 5 h at 20 °C, concentrated *in vacuo* to 20 mL, poured into water (60 mL), and extracted with chloroform (4×15 mL). The organic layer was washed with water (3×20 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The residue was dissolved in EtOH (100 mL), the resulting solution was cooled to 0 °C, and 2 *M* NaOH (27.6 mL) was added dropwise with stirring. The reaction was stirred for 24 h at 20 °C and concentrated *in vacuo*, the residue was acidified with concentrated HCl and extracted with chloroform (4×25 ml). The organic layer was washed with brine (3×20 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The residue, a brown oil crystallizing on standing, was recrystallized from a mixture of hexane—EtOAc (12 : 1) to obtain (*RS*)-2-(1-naphthyloxy)propionic acid. The yield was 3.82 g (64%), a colorless crystalline powder, m.p. 154—156 °C (hexane—EtOAc) (*cf.* Ref. 9: m.p. 154—155 °C). Found (%): C, 72.50; H, 5.39. $C_{13}H_{12}O_3$. Calculated (%): C, 72.21; H, 5.59. HPLC: $\tau_{(R)}$ 20.2 min; $\tau_{(S)}$ 39.7 min. The ^{1}H and ^{13}C NMR spectra are identical to those published earlier.[10]

(*RS*)-2-(1-Naphthyloxy)propionyl chloride (2b). Oxalyl chloride (1.13 mL, 12.9 mmol) and DMF (5 μL) were added to a solution of (*RS*)-2-(1-naphthyloxy)propionic acid (1.00 g, 4.62 mmol) in anhydrous dichloromethane (50 mL). The reaction mixture was stirred for 6 h at ~20 °C and concentrated *in vacuo*. The yield was 1.08 g (quantitative). ^{1}H NMR, δ: 1.86 (d, 3 H, Me, J = 6.8 Hz); 5.12 (q, 1 H, 2-CH, J = 6.8 Hz); 6.68—6.70 (m, 1 H, Ar); 7.29—7.37 (m, 1 H, Ar); 7.47—7.54 (m, 3 H, Ar); 7.77—7.84 (m, 1 H, Ar); 8.28—8.34 (m, 1 H, Ar).

Stereoselective acylation of racemic amines 1a,b with acyl chlorides 2a,b (general procedure). A solution of the corresponding acyl chloride (0.5 mmol) in dichloromethane (5 mL) was added to a solution of amine **1a** or **1b** (1.0 mmol) in the same solvent (5 mL) at −20 °C and the mixture was thermostated for 6 h at −20 °C. Then, the reaction mixture was sequentially washed with 4 *M* HCl (2×4 mL), brine (4×5 mL), 5% aqueous $NaHCO_3$ (2×5 mL), and H_2O (2×5 mL), dried with Na_2SO_4, and concentrated. The residue was analyzed by GLC. The diastereomers of amides were isolated by recrystallization.

(3*R,2′*R**)-3,4-Dihydro-3-methyl-*N*-[2′-(1″-naphthyloxy)-propionyl]-2*H*-[1,4]benzoxazine [(3*R**,2′*R**)-3b].** The yield was 76.4 mg (44%) after recrystallization from a mixture of hexane—EtOAc (1 : 1), a white amorphous powder. Found (%): C, 76.33; H, 6.20; N, 4.19. $C_{22}H_{21}NO_3$. Calculated (%): C, 76.06; H, 6.09; N, 4.03. GLC: $\tau_{(R^*,S^*)\text{-}\mathbf{3b}}$ 33.9 min; $\tau_{(R^*,R^*)\text{-}\mathbf{3b}}$ 32.9 min; (*R**,*S**)—(*R**,*R**) (10.3 : 89.7). ^{1}H NMR, δ: 1.10 (d, 3 H, Me of benzoxazine, J = 6.8 Hz); 1.69 (d, 3 H, MeCH, J = 6.3 Hz); 3.97 (dd, 1 H, 2-CH_B of benzoxazine, J_1 = 11.0 Hz, J_2 = 2.8 Hz); 4.14 (dd, 1 H, 2-CH_A of benzoxazine, J_1 = 11.0 Hz, J_2 = 1.6 Hz); 4.73 (qdd, 1 H, 3-CH of benzoxazine, J_1 = 6.8 Hz, J_2 = 2.8 Hz,

J_3 = 1.6 Hz); 5.61 (q, 1 H, 2-CH, J = 6.3 Hz); 6.70—6.77 (m, 1 H, Ar); 6.82—6.89 (m, 2 H, Ar); 7.00—7.07 (m, 1 H, Ar); 7.26—7.32 (m, 1 H, Ar); 7.42—7.53 (m, 3 H, Ar); 7.62—7.68 (m, 1 H, Ar); 7.78—7.85 (m, 1 H, Ar); 8.14—8.20 (m, 1 H, Ar). ^{13}C NMR, δ: 15.14, 17.22, 45.62, 69.25, 70.79, 105.60, 116.45, 119.94, 120.60, 121.64, 122.85, 124.80, 125.06, 125.34, 125.71 (2 C), 126.51, 127.35, 134.15, 145.69, 152.21, 168.54.

(3*R,2′*R**)-7,8-Difluoro-3,4-dihydro-3-methyl-*N*-[2′-(1″-naphthyloxy)propionyl]-2*H*-[1,4]benzoxazine [(3*R**,2′*R**)-4b].** The yield was 95.8 mg (50%) after recrystallization from a mixture of hexane—EtOAc (1.7 : 1), a white crystalline powder. M.p. 144—147 °C (hexane—EtOAc). Found (%): C, 69.02; H, 5.08; F, 9.68; N, 3.49. $C_{22}H_{19}F_2NO_3$. Calculated (%): C, 68.92; H, 5.00; F, 9.71; N, 3.65. GLC: $\tau_{(R^*,S^*)\text{-}\mathbf{4b}}$ 33.9 min; $\tau_{(R^*,R^*)\text{-}\mathbf{4b}}$ 32.8 min; (*R**,*S**)—(*R**,*R**) (2.6 : 97.4). ^{1}H NMR, δ: 1.11 (d, 3 H, Me of benzoxazine, J = 6.8 Hz); 1.66 (d, 3 H, CH<u>Me</u>, J = 6.3 Hz); 4.06 (dd, 1 H, 2-CH_B of benzoxazine, J_1 = 11.1 Hz, J_2 = 2.7 Hz); 4.31 (dd, 1 H, 2-CH_A of benzoxazine, J_1 = 11.1 Hz, J_2 = 1.4 Hz); 4.77 (qdd, 1 H, 3-CH of benzoxazine, J_1 = 6.8 Hz, J_2 = 2.8 Hz, J_3 = 1.5 Hz); 5.65 (q, 1 H, 2-C<u>H</u>Me, J = 6.3 Hz); 6.74—6.87 (m, 2 H, Ar of acid, H(6) of benzoxazine); 7.30—7.36 (m, 1 H, Ar of acid); 7.43—7.57 (m, 4 H, Ar of acid, H(5) of benzoxazine); 7.80—7.85 (m, 1 H, Ar Acyl); 8.10—8.17 (m, 1 H, Ar Acyl). ^{13}C NMR, δ: 15.27, 16.84, 45.59, 69.81, 72.11, 105.72, 106.91 (d, J = 18.0 Hz); 119.42 (dd, J_1 = 7.8 Hz, J_2 = 3.9 Hz); 120.66, 120.88, 121.51, 125.04, 125.32, 125.77, 126.50, 127.36, 134.13, 136.09 (dd, J_1 = 9.9 Hz, J_2 = 3.0 Hz); 138.85 (dd, J_1 = 243.8 Hz, J_2 = 15.4 Hz); 146.85 (m); 152.10, 168.73. ^{19}F NMR, δ: 2.12—2.29 (m, 1 F, C(8)F); 21.07—21.26 (m, 1 F, C(7)F).

Synthesis of mixtures of diastereomeric amides 3b and 4b (general procedure). A solution of (*RS*)-2-(1-naphthyloxy)propionyl chloride (117 mg, 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. The mixture was thermostated for 24 h at 20 °C and then sequentially washed with 4 *M* HCl (2×5 mL), brine (3×15 mL), 5% aq. $NaHCO_3$ (10 mL), and water (2×15 mL). The organic layer was separated, dried with Na_2SO_4, and concentrated. The residue was purified by flash chromatography (eluent hexane—EtOAc).

3,4-Dihydro-3-methyl-*N*-[2′-(1″-naphthyloxy)propionyl]-2*H*-[1,4]benzoxazine [3b (mixture of diastereomers)]. The yield was 158 mg (91%) after flash chromatography (eluent hexane—EtOAc (95 : 5)), a white amorphous powder. Found (%): C, 76.04; H, 6.27; N, 4.33. $C_{22}H_{21}NO_3$. Calculated (%): C, 76.06; H, 6.09; N, 4.03. GLC: $\tau_{(R,S)\text{-}\mathbf{3b}}$ 34.0 min; $\tau_{(S,S)\text{-}\mathbf{3b}}$ 33.0 min; (*R*,*S*)—(*S*,*S*) (45.0 : 55.0). ^{1}H NMR, δ: 1.05 (d, 1.5 H, Me of benzoxazine (*R*,*S*), J = 6.8 Hz); 1.10 (d, 3 H, Me of benzoxazine (*S*,*S*), J = 6.8 Hz); 1.63 (d, 1.5 H, <u>Me</u>CH (*R*,*S*), J = 6.5 Hz); 1.69 (d, 3 H, <u>Me</u>CH (*S*,*S*), J = 6.3 Hz); 3.97 (dd, 0.5 H, 2-CH_B of benzoxazine (*S*,*S*), J_1 = 11.0 Hz, J_2 = 2.8 Hz); 4.12—4.17 (m, 1 H, 2-CH_B of benzoxazine (*R*,*S*) and 2-CH_A of benzoxazine (*S*,*S*)); 4.20 (dd, 0.5 H, 2-CH_A of benzoxazine (*R*,*S*), J_1 = 11.0 Hz, J_2 = 1.6 Hz); 4.73 (qdd, 0.5 H, 3-CH of benzoxazine (*S*,*S*), J_1 = 6.8 Hz, J_2 = 2.8 Hz, J_3 = 1.6 Hz); 4.85 (qdd, 0.5 H, 3-CH of benzoxazine (*R*,*S*), J_1 = 6.8 Hz, J_2 = 2.8 Hz, J_3 = 1.7 Hz); 5.58 (q, 1 H, 2-C<u>H</u>Me (*R*,*S*), J = 6.5 Hz); 5.61 (q, 1 H, 2-C<u>H</u>Me (*S*,*S*), J = 6.3 Hz); 6.70—6.77 (m, 0.5 H, Ar (*S*,*S*)); 6.80—6.88 (m, 2 H, Ar); 6.92—6.96 (m, 0.5 H, Ar (*R*,*S*)); 7.00—7.07 (m, 1 H, Ar); 7.26—7.32 (m, 0.5 H, Ar (*S*,*S*)); 7.37—7.42 (m, 0.5 H, Ar (*R*,*S*)); 7.42—7.53 (m, 3 H, Ar); 7.62—7.69 (m, 1 H, Ar), 7.78—7.87 (m, 1 H, Ar); 8.14—8.20 (m, 0.5 H, Ar); 8.20—8.25 (m, 0.5 H, Ar).

7,8-Difluoro-3,4-dihydro-3-methyl-*N*-[2′-(1″-naphthyloxy)-propionyl]-2*H*-[1,4]benzoxazine [4b (mixture of diastereomers)]. The yield was 153 mg (80%) after flash chromatography (eluent hexane—EtOAc (95 : 5), a white amorphous powder. Found (%): C, 68.98; H, 5.09; F, 9.81; N, 3.63. $C_{22}H_{19}F_2NO_3$. Calculated (%): C, 68.92; H, 5.00; F, 9.71; N, 3.65. GLC: $\tau_{(R,S)\text{-}\mathbf{4b}}$ 33.9 min; $\tau_{(S,S)\text{-}\mathbf{4b}}$ 32.8 min; (*R*,*S*)—(*S*,*S*) (54.4 : 45.6). ^{1}H NMR, δ: 1.06 (d, 1.8 H, Me of benzoxazine (*R*,*S*), J = 6.5 Hz); 1.11 (d, 1.2 H, Me of benzoxazine (*S*,*S*), J = 6.8 Hz); 1.657 (d, 1.8 H, CH<u>Me</u> (*R*,*S*), J = 6.3 Hz); 1.662 (d, 1.2 H, C<u>H</u>Me (*S*,*S*), J = 6.3 Hz); 4.06 (dd, 0.4 H, 2-CH_B of benzoxazine (*S*,*S*), J_1 = 11.1 Hz, J_2 = 2.7 Hz); 4.20 (dd, 0.6 H, 2-CH_B of benzoxazine (*R*,*S*), J_1 = 11.2 Hz, J_2 = 2.6 Hz); 4.31 (dd, 0.4 H, 2-CH_A of benzoxazine (*S*,*S*), J_1 = 11.1 Hz, J_2 = 1.4 Hz); 4.35 (dd, 0.6 H, 2-CH_A of benzoxazine (*R*,*S*), J_1 = 11.0 Hz, J_2 = 1.5 Hz); 4.77 (qdd, 0.4 H, 3-CH of benzoxazine (*S*,*S*), J_1 = 6.8 Hz, J_2 = 2.8 Hz, J_3 = 1.5 Hz); 4.91 (qdd, 0.6 H, 3-CH of benzoxazine (*R*,*S*), J_1 = 6.8 Hz, J_2 = 2.9 Hz, J_3 = 1.5 Hz); 5.57 (q, 0.6 H, 2-C<u>H</u>Me (*R*,*S*), J = 6.6 Hz); 5.65 (q, 0.4 H, 2-C<u>H</u>Me (*S*,*S*), J = 6.3 Hz); 6.74—6.95 (m, 2 H, Ar); 7.30—7.36 (m, 0.4 H, Ar of acid (*S*,*S*)); 7.37—7.41 (m, 0.6 H, Ar (*R*,*S*)); 7.43—7.57 (m, 4 H, Ar); 7.80—7.85 (m, 1 H, Ar of acid); 8.10—8.17 (m, 0.4 H, Ar of acid (*S*,*S*)); 8.18—8.23 (m, 0.6 H, Ar of acid (*R*,*S*)). ^{19}F NMR, δ: 2.08 (ddd, 0.6 F, C(8)F (*R*,*S*), J_1 = 21.0 Hz, J_2 = 8.1 Hz, J_3 = 2.1 Hz); 2.20 (ddd, 0.4 F, C(8)F (*S*,*S*), J_1 = 21.0 Hz, J_2 = 7.8 Hz, J_3 = 2.0 Hz); 21.07—21.27 (m, 1 F, C(7)F).

Kinetic resolution of acyl chloride 2b by (*S*)-amines 1a and 1b (general procedure). A solution of acyl chloride **2b** (141 mg, 0.6 mmol) in toluene (2 mL) was added to a solution of (*S*)-amine **1a** or **1b** (0.3 mmol) and $PhNEt_2$ (44.8 mg, 0.3 mmol) in toluene (4 mL) at 20 °C. The mixture was thermostated for 24 h at 20 °C and then concentrated to dryness *in vacuo*. The residue was dissolved in MeCN (10 mL) and a saturated solution of Na_2CO_3 (10 mL) was added. The reaction mixture was vigorously stirred for 1 h, MeCN was evaporated *in vacuo*. The aqueous solution was extracted with $CHCl_3$ (2×5 mL). The organic layer was sequentially washed with water (2×5 mL), 4 *M* HCl (2×4 mL), brine (4×5 mL), and water (2×5 mL). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. The residue was analyzed by GLC.

The alkaline aqueous solutions (after extraction with $CHCl_3$) were combined, acidified with 4 *M* HCl to pH 1—2, and extracted with $CHCl_3$ (2×5 mL). The organic layer was washed with brine (2×5 mL), dried with Na_2SO_4, and concentrated *in vacuo*. The residue was purified by flash chromatography (eluent hexane—EtOAc) and analyzed by HPLC on a chiral stationary phase.

(*R*)-2-(1-Naphthyloxy)propionic acid was obtained by kinetic resolution of (*RS*)-**2b** with (*S*)-amine **1b**. The yield was 46.7 mg (72%), a white crystalline powder. M.p. 124—125 °C (hexane—EtOAc), $[\alpha]_D^{20}$ +31.4 (*c* 0.54, $CHCl_3$) (*cf.* Ref. 10: $[\alpha]_D^{20}$ +58.9 (*c* 1.08, $CHCl_3$)). Found (%): C, 72.02; H, 5.79. $C_{13}H_{12}O_3$. Calculated (%): C, 72.21; H, 5.59. *Ee* 60%, HPLC: $\tau_{(R)}$ 20.2 min; $\tau_{(S)}$ 39.7 min. The ^{1}H and ^{13}C NMR spectra are identical to those published earlier.[10]

Quantum chemical calculations. Graphic modeling and primary optimization of transition state geometries was carried out using molecular mechanics and molecular dynamics methods (Ammp software package) and the VEGA ZZ program.[22,23] As

a result, model structures of all diastereomers of transition states were obtained.

DFT calculations based on the model structures were performed using the ORCA 3.0.3.[24,25] In each EFSP calculation, geometrical optimization was performed using D3 type dispersion corrections.[26,27] The solvent (CH_2Cl_2) was taken into account using the conductor-like screening model (COSMO).[28] The geometry and energy of the starting compounds, transition states, and then pre-reaction complexes (at a fixed CO—Cl bond length of 1.82 Å) were determined using the Beke—Lee—Yang—Parr hybrid meta-GGA functional (B3LYP)[29,30] and Ahlrichs´s basic sets def2-SVP and def2-TZVP.[31]

The search for transition states at the first stage and the initial calculation of the Hessian in the gas phase were carried out at the B3LYP-D3/def2-SVP level, changing the length of the key N—CO bond. Each iteration during geometry optimization was accompanied by determining the energy of single-point calculations as a sum of the total energy and the D3 dispersion correction together with the geometric counterpoise correction gCP for the basis superposition error.[32] The calculations were speeded up using a RIJCOSX approximation.[25,33] The total thermal energies were calculated as a sum of the total electron energy, zero-point vibration energy, and thermal corrections (vibrational, rotational, translation). In calculation of the Gibbs free energy, the entropy component value was chosen to correspond to the symmetry number $n = 1$ (since all the reagents are chiral compounds).[34]

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