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Acylative kinetic resolution of racemic heterocyclic amines using *N*-phthaloyl-(*S*)-amino acyl chlorides with alkyl side chains

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ABSTRACT

A comparative study of the acylative kinetic resolution of racemic 2-methyl-1,2,3,4 tetrahydroquinoline and 3,4-dihydro-3-methyl-2*H*-[1,4]benzoxazine using *N*-phthaloyl-(*S*)-amino acyl chlorides with alkyl side chains has been carried out. The influence of steric factors on the stereoselectivity of the acylation was demonstrated. The (*S*)-enantiomers of the heterocyclic amines (*ee* >99%) were obtained in good yields via a kinetic resolution protocol using *N*-phthaloyl-(*S*)-leucyl chloride.

1. Introduction

Enantiomerically pure heterocyclic amines have attracted considerable attention as the structural fragments of biologically active compounds, including alkaloids,[1] antibacterials,[2] modulators of various types of receptors[3] and chiral ligands.[4]

To obtain enantiomerically pure amines, acylative kinetic resolution (KR) is frequently applied.[5] Different approaches to the kinetic resolution of racemic amines including the use of acylating enzymes,[6] synthetic chiral acyl-transfer catalysts[7] and chiral acylating agents[8] are under active investigation.

Over the last few years, we have studied the diastereoselective acylation of racemic heterocyclic amines with 2-arylpropionyl[9] and N-protected amino acyl chlorides.[10] In particular, we studied the KR of 2-methyl-1,2,3,4-tetrahydroquinoline **1a** and 3,4-dihydro-3-methyl-2*H*-[1,4]benzoxazine **1b** (Fig. 1) using *N*-phthaloyl-(*S*)-amino acyl chlorides.[10b–d] It has been established that the presence of aromatic substituents in the amino acid side chain contributes to an increase in stereoselectivity.[10c] We also used *N*-phthaloyl-(*S*)-phenylalanyl chloride and its structural analogues to demonstrate the influence of aromatic π–π interactions on the stereochemical results of the KR.[10d] *N*-Phthaloyl-(*S*)-leucyl chloride was applied as a chiral acylating agent in the stereo- and regio-directed synthesis of 6-substituted derivatives of 2-methyl-1,2,3,4-tetrahydroquinoline.[10e]

Herein we report the effect of the structure of the resolving agent on the stereochemical result of acylation of heterocyclic amines **1a** and **1b**.

2. Results and discussion

N-Phthaloyl amino acyl chlorides derived from natural and unnatural (*S*)-amino acids such as valine **2b**, *tert*-leucine **2c**, leucine **2d** and 3-cyclohexylalanine **2e** were studied as the resolving agents in comparison with the previously described *N*-phthaloyl-(*S*)-alanyl[10b] **2a** and *N*-phthaloyl-(*S*)-phenylalanyl **2f** chlorides[10c] (Scheme 1).

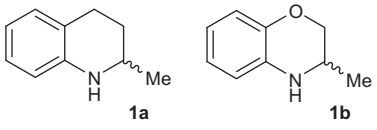
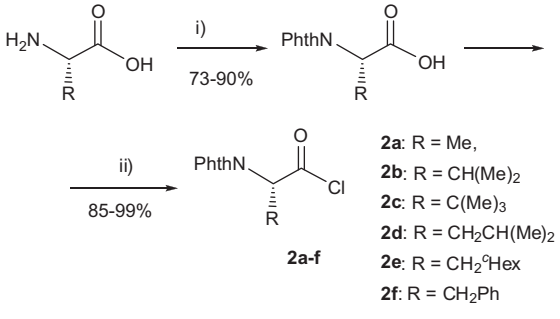


Figure 1. Substrates for kinetic resolution.



Reagents and conditions:
i) Phthalic anhydride (1 equiv.), NEt_3 (0.1 equiv.), toluene, Δ;
ii) $(COCl)_2$, DMF (cat.), C_6H_6/hexane, rt

Scheme 1. Synthesis of chiral resolving agents **2a**–**f**.

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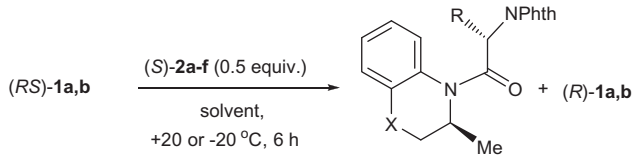


3: X = CH_2, R = Me
4: X = CH_2, R = *i*-Pr
5: X = CH_2, R = *t*-Bu
6: X = CH_2, R = CH_2*i*-Pr
7: X = CH_2, R = CH_2^{c}Hex
8: X = CH_2, R = CH_2Ph
9: X = O, R = Me
10: X = O, R = *i*-Pr
11: X = O, R = *t*-Bu
12: X = O, R = CH_2*i*-Pr
13: X = O, R = CH_2^{c}Hex
14: X = O, R = CH_2Ph

Scheme 2. KR of racemic amines **1a** and **1b** using acyl chlorides **2a–f**.

N-Phthaloyl-(*S*)-amino acids were obtained according to the literature[11] by heating amino acids with phthalic anhydride in toluene in the presence of NEt_3. Acyl chlorides **2a–f** were prepared by the reaction of the appropriate acids with oxalyl chloride in the presence of catalytic amounts of DMF (Scheme 1). Freshly prepared acyl chlorides of >98% purity (according to ^{1}H NMR spectra) were used without further purification.

Acylation of amines **1a** and **1b** using acyl chlorides **2b–e** with an amine-acyl chloride molar ratio of 2:1 was carried out in toluene, dichloromethane or acetonitrile at +20 or −20 °C for 6 h (Scheme 2). The initial concentration of the racemic amine was 0.1 M. Similar to the acylation of amines **1a**,**b** with *N*-phthaloyl-(*S*)-amino acyl chlorides **2a** and **2f**,[10b–d] the reaction with acyl chlorides **2b–e** under the same conditions resulted in the predominant formation of (*S*,*S*)-amides **4–7**, **10–13**; unreacted amines **1a** or **1b** were enriched with the (*R*)-enantiomers (according to chiral HPLC).

The major (*S*,*S*)-diastereoisomers of amides **4**, **6**, **7** and **12** were isolated from the diastereoisomeric mixtures by recrystallisation; (*S*,*S*)-amides **5**, **10**, **11** and **13** and the minor (*R*,*S*)-diastereoisomers of amides **4**, **5** and **10–13** were isolated by flash column chromatography on silica gel. In order to obtain the diastereoisomers of amides **5** and **11** we carried out the acylation of amines **1a** and **1b** with acyl chloride **2c** bearing the bulky *tert*-butyl substituent in toluene at +50 °C, since the reaction at +20 °C afforded amides in low yields.

The configurations of amides (*S*,*S*)-**4**, (*S*,*S*)-**7**, (*R*,*S*)-**10**, (*S*,*S*)-**11** and (*S*,*S*)-**12** were confirmed unambiguously by X-ray crystallography taking into account the absolute (*S*)-configuration of the *N*-phthaloyl amino acyl fragment. Figures 2 and 3 show the structures of amides (*S*,*S*)-**7** and (*S*,*S*)-**12**.

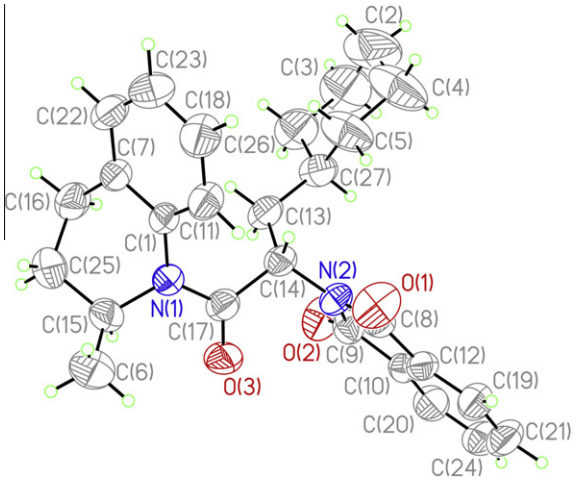


Figure 2. Structure of amide (*S*,*S*)-**7** (thermal ellipsoids of 50% probability).

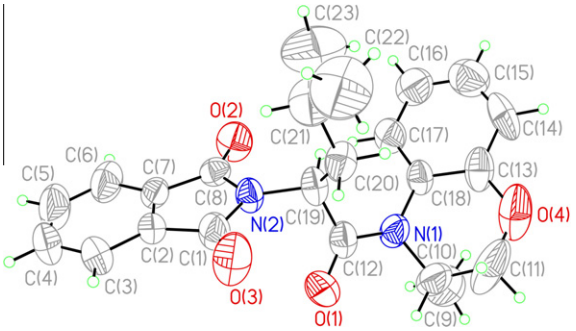


Figure 3. Structure of amide (*S*,*S*)-**12** (thermal ellipsoids of 50% probability).

After the acylative KR was completed, the reaction mixtures were treated appropriately to determine the diastereoisomeric excess (*de*, %) of the amides formed (using HPLC and ^{1}H NMR spectroscopy) and the enantiomeric excess (*ee*, %) of the unreacted amines (chiral HPLC). Based on the de and ee values, the conversion of the racemic substrate (*C*, %) and the selectivity factor (*s*) was calculated according to Kagan's equations:

$$C = [ee_{amine}/(ee_{amine} + de_{amide})] \times 100\%;$$

$$s = \ln[(1 - C) \times (1 - ee_{amine})]/\ln[(1 - C) \times (1 + ee_{amine})]$$ [5a]

The results of the KR of racemic amines **1a** and **1b** with acyl chlorides **2a–f** in different solvents at +20 °C are presented in Table 1. As can be seen from Table 1, acylation of racemic amines **1a** and **1b** with *N*-phthaloyl-(*S*)-amino acyl chlorides **2a–f** proceeded more stereoselectively in dichloromethane or acetonitrile than in toluene. *N*-Phthaloyl-(*S*)-leucyl chloride **2d** and *N*-phthaloyl-3-cyclohexyl-(*S*)-alanyl chloride **2e** (Table 1, entries 9–14, 25–30) were more selective reagents as compared to alanine **2a**, valine **2b** or *tert*-leucine **2c** derivatives. For example, in the acylation of racemic amines **1a** and **1b** with acyl chloride **2e** the selectivity factors *s* were 13 and 11, respectively.

The stereochemical results of the KR of racemic amines **1a** and **1b** in dichloromethane at −20 °C are presented in Table 2. As can be seen, lowering the reaction temperature led in all the cases to an increase in de of (*S*,*S*)-amides formed and selectivity factors, although conversions decreased slightly. Thus, for the KR of amine **1a** with acyl chloride **2e** in CH_2Cl_2, the *de* of amide (*S*,*S*)-**7** was 75.2% (*C* 45%, *s* 13) at +20 °C (Table 1, entry 13) and 83.7% (*C* 43%, *s* 21) at −20 °C (Table 2, entry 4).

A comparison of the results of the KR of racemic amines **1a** and **1b** with acyl chlorides **2a–e** indicated that the stereoselectivity was unaffected by the volume of the R substituent attached directly to the asymmetric carbon atom. Thus, the KR of amines **1a**,**b** with acyl chlorides **2a** (R = Me), **2b** (R = *i*-Pr) and **2c** (R = *t*-Bu) occurred with almost the same selectivity. For example, the selectivity factors *s* in the KR of racemic amine **1a** carried out in CH_2Cl_2 at +20 °C were 4.6, 5.1 and 5.7, respectively. At the same time, the conversion of amine **1a** when acylated with agent **2c** (*C* 17%) was significantly lower compared with the acylation with acyl chlorides **2a** (*C* 41%) or **2b** (*C* 46%). It should be noted that the KR of amines **1a**,**b** using *N*-phthaloyl-(*S*)-phenylglycyl chloride also proceeded with low conversion.[10c]

Increasing the volume of the substituent close to the reaction centre of acyl chlorides **2b** (R = *i*-Pr) and **2c** (R = *t*-Bu) seemed to cause steric hindrances in the interaction of the reacting molecules. In the case of acylating agents **2d** (R = CH_2*i*-Pr) and **2e** (R = CH_2*c*Hex), the branched alkyl chain separated from the

Table 1
Results of the kinetic resolution of racemic amines **1a** and **1b** via acylation with acyl chlorides **2a–f** at +20 °C[a]

Entry	Racemic amine	Resolving agent	Solvent	(*S*,*S*)-Amide, *de*[b] (%)	Unreacted (*R*)-amine, *ee*[c] (%)	Conversion, *C* (%)	Selectivity factor, *s*
1	**1a**	**2a** (R = Me)	Toluene	38.3	22.0	36	2.8[10c]
2	**1a**	**2a** (R = Me)	CH_2Cl_2	53.1	37.2	41	4.6[10c]
3	**1a**	**2b** (R = *i*-Pr)	Toluene	37.9	22.2	37	2.7
4	**1a**	**2b** (R = *i*-Pr)	CH_2Cl_2	52.8	46.0	46	5.1
5	**1a**	**2b** (R = *i*-Pr)	MeCN	55.8	53.1	49	5.9
6	**1a**	**2c** (R = *t*-Bu)	Toluene	55.9	4.0	7	3.7
7	**1a**	**2c** (R = *t*-Bu)	CH_2Cl_2	66.7	13.9	17	5.7
8	**1a**	**2c** (R = *t*-Bu)	MeCN	70.5	18.4	21	6.9
9	**1a**	**2d** (R = CH_2*i*-Pr)	Toluene	64.1	43.0	40	6.9
10	**1a**	**2d** (R = CH_2*i*-Pr)	CH_2Cl_2	76.0	60.4	44	13
11	**1a**	**2d** (R = CH_2*i*-Pr)	MeCN	76.0	59.6	44	13
12	**1a**	**2e** (R = CH_2*c*Hex)	Toluene	60.5	36.9	38	5.8
13	**1a**	**2e** (R = CH_2*c*Hex)	CH_2Cl_2	75.2	60.5	45	13
14	**1a**	**2e** (R = CH_2*c*Hex)	MeCN	67.9	59.4	47	9.4
15	**1a**	**2f** (R = CH_2Ph)	Toluene	48.8	33.3	40	4.1[10c]
16	**1a**	**2f** (R = CH_2Ph)	CH_2Cl_2	67.1	56.9	46	8.9[10c]
17	**1a**	**2f** (R = CH_2Ph)	MeCN	64.8	56.1	47	8.0[10c]
18	**1b**	**2a** (R = Me)	Toluene	42.6	20.3	32	3.0[10c]
19	**1b**	**2a** (R = Me)	CH_2Cl_2	49.3	33.1	40	4.0[10c]
20	**1b**	**2b** (R = *i*-Pr)	Toluene	49.1	16.0	25	3.4
21	**1b**	**2b** (R = *i*-Pr)	CH_2Cl_2	55.6	32.4	37	4.7
22	**1b**	**2b** (R = *i*-Pr)	MeCN	63.9	39.9	38	6.7
23	**1b**	**2c** (R = *t*-Bu)	CH_2Cl_2	56.6	6.6	10	3.8
24	**1b**	**2c** (R = *t*-Bu)	MeCN	72.3	9.1	11	6.8
25	**1b**	**2d** (R = CH_2*i*-Pr)	Toluene	63.6	45.6	42	6.9
26	**1b**	**2d** (R = CH_2*i*-Pr)	CH_2Cl_2	69.5	59.1	46	9.9
27	**1b**	**2d** (R = CH_2*i*-Pr)	MeCN	68.5	58.7	46	9.5
28	**1b**	**2e** (R = CH_2*c*Hex)	Toluene	56.3	40.6	42	5.3
29	**1b**	**2e** (R = CH_2*c*Hex)	CH_2Cl_2	71.1	59.3	46	11
30	**1b**	**2e** (R = CH_2*c*Hex)	MeCN	67.7	57.4	46	9.1
31	**1b**	**2f** (R = CH_2Ph)	Toluene	50.6	37.5	43	4.3[10c]
32	**1b**	**2f** (R = CH_2Ph)	CH_2Cl_2	59.2	48.0	45	6.2[10c]
33	**1b**	**2f** (R = CH_2Ph)	MeCN	59.8	48.7	45	6.3[10c]

[a] Average values for 2–4 parallel runs are presented.
[b] Determined by HPLC (Reprosil 100Si, see Section 4).
[c] Determined by chiral HPLC (Chiralcel OD-H, see Section 4).

Table 2
Results of the kinetic resolution of racemic amines **1a** and **1b** using acyl chlorides **2a**, **b**, **d–f** in CH_2Cl_2 at −20 °C[a]

Entry	Racemic amine	Resolving agent	(*S*,*S*)-Amide, de[b] (%)	Unreacted (*R*)-amine, ee[c] (%)	Conversion, *C* (%)	Selectivity factor, *s*
1	**1a**	**2a** (R = Me)	63.3	41.5	40	6.6[10c]
2	**1a**	**2b** (R = *i*-Pr)	72.1	27.2	27	8.0
3	**1a**	**2d** (R = CH_2*i*-Pr)	80.2	64.7	44	19[10e]
4	**1a**	**2e** (R = CH_2*c*Hex)	83.7	62.3	43	21
5	**1a**	**2f** (R = CH_2Ph)	74.4	60.4	45	12[10c]
6	**1b**	**2d** (R = CH_2*i*-Pr)	77.6	56.5	42	14
7	**1b**	**2e** (R = CH_2*c*Hex)	74.8	49.8	40	11

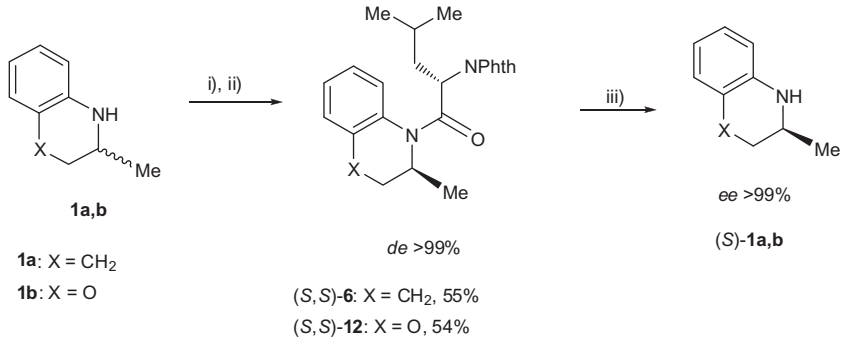
[a] Average values for 2–4 parallel runs are presented.
[b] Determined by HPLC (Reprosil 100Si, see Section 4).
[c] Determined by chiral HPLC (Chiralcel OD-H, see Section 4).

asymmetric carbon by an additional methylene group causes less steric hindrance for the reaction and at the same time enhances the stereochemical differentiation.

N-Phthaloyl-3-cyclohexyl-(*S*)-alanyl chloride **2e** (R = CH_2*c*Hex) turned out to be a more stereoselective acylating agent than *N*-phthaloyl-(*S*)-phenylalanyl chloride **2f** (R = CH_2Ph): for the KR of amine **1a** in CH_2Cl_2 at +20 °C, *s* values of 13 and 8.9, respectively (Table 1, entries 13 and 16). When the KR was carried out at −20 °C, the difference in selectivity was more significant (*s* 21 and 12, respectively) (Table 2, entries 4 and 5). In the acylation of amine **1b** the same regularities were observed (Table 2, entries 6 and 7). This is probably because the planar phenyl substituent in compound **2f** causes less steric hindrance than the bulkier, conformationally labile, cyclohexyl fragment of reagent **2e**.

Thus, we established that the KR of heterocyclic amines via acylation with *N*-phthaloyl-(*S*)-amino acyl chlorides bearing branched alkyl side chains can proceed with higher stereoselectivity than the KR using amino acyl chlorides with aromatic substituents in the backbone. This allowed us to conclude that both steric factors and aromatic interactions make an equally important contribution to the stereoselectivity of the acylation.

N-Phthaloyl-(*S*)-leucyl chloride **2d**, the most efficient of the resolving agents studied, was used to obtain enantiopure amines (*S*)-**1a** and (*S*)-**1b** from racemates (Scheme 3). KR in dichlorometh-



Scheme 3. Preparation of enantiopure amines (*S*)-**1a**,**b** from racemates via KR protocol using acyl chloride **2d**.

ane at −20 °C followed by recrystallisation of the acylation products led to the diastereoisomerically pure amides (*S*,*S*)-**6** and (*S*,*S*)-**12** (*de* >99%, according to HPLC) in 55% and 54% yields, respectively. Acidic hydrolysis of (*S*,*S*)-amides readily afforded enantiopure amines (*S*)-**1a** and (*S*)-**1b** (*ee* >99%, according to chiral HPLC) in 25% and 23% total yields relative to the starting racemates.

It should be noted that the problem of racemisation of the chiral acylating agent in the course of KR is very important. It is known that acyl chlorides and other derivatives of *N*-phthaloyl amino acids are prone to racemisation,[12] especially in the presence of various highly basic and highly nucleophilic tertiary amines, which take place through ketene formation.[13] Acyl ammonium salts of *N*-phthaloyl amino acids and DMAP are also prone to racemisation in the presence of DCC.[14]

In our case, we carried out the acylation of amines **1a** and **1b** with *N*-phthaloyl amino acyl chlorides without the use of auxiliary bases. Obtaining the enantiopure amines (*S*)-**1a** or (*S*)-**1b** as a result of the KR of racemates under the action of *N*-phthaloyl-(*S*)-leucyl chloride **2d** indicates the absence of racemization both at the acylation step and at the stage of subsequent acidic hydrolysis of amides. Previously we have shown that the loss of enantiomeric activity does not occur during the synthesis of amines (*S*)-**1a** or (*S*)-**1b** via KR with *N*-phthaloyl-(*S*)-alanyl chloride **2a**[10b] and *N*-phthaloyl-(*S*)-phenylalanyl chloride **2f**[10c] followed by acidic hydrolysis.

Herein we required additional experimental confirmation of the absence of epimerisation of the acyl moiety in the amides formed. To do this, we carried out the acylation of enantiopure amine (*S*)-**1b** (1 equiv, 97% *ee*) with *N*-phthaloyl-(*S*)-*tert*-leucine **2c** (0.5 equiv) in CH_2Cl_2 at +20 °C. Analysis of the reaction mixture by HPLC on silica gel showed the presence of only one of the amides, (*S*,*S*)-**11** which was isolated in diastereoisomerically pure form (97% *de*) in 75% yield relative to the starting acyl chloride.

3. Conclusion

We have shown that the diastereoselectivity of the acylation of racemic 2-methyl-1,2,3,4-tetrahydroquinoline and 3,4-dihydro-3-methyl-2*H*-[1,4]benzoxazine with *N*-phthaloyl-(*S*)-amino acyl chlorides significantly depends on steric factors and not just aromatic interactions. It has been found that the steric hindrance caused by the bulky substituents attached to the stereogenic centre of the acylating agent hinders the reaction without increasing the stereoselectivity. At the same time, *N*-phthaloyl-(*S*)-leucyl and *N*-phthaloyl-3-cyclohexyl-(*S*)-alanyl chlorides with branched alkyl side chains separated from stereogenic centre by a methylene group were found to be more selective acylating agents in the kinetic resolution of the racemic amines studied. Enantio pure (*S*)-2-methyl-1,2,3,4-tetrahydroquinoline and (*S*)-3,4-dihydro-3-methyl-2*H*-[1,4]benzoxazine were obtained in good yields via kinetic resolution of racemates using *N*-phthaloyl-(*S*)-leucyl chloride.

4. Experimental

4.1. General

(*RS*)-2-Methyl-1,2,3,4-tetrahydroquinoline **1a**,[15] (*RS*)-3,4-dihydro-3-methyl-2*H*-[1,4]benzoxazine **1b**,[16] *N*-phthaloyl-(*S*)-alanyl chloride **2a**,[10b] *N*-phthaloyl-(*S*)-leucyl chloride **2d**[10e] and *N*-phthaloyl-(*S*)-phenylalanyl chloride **2f**[10c] were synthesised according to the literature. Other reagents were commercially available. Amides **3**, **6**, **8**, **9** and **14** were obtained as previously described.[10b,10c,10e] The solvents were dried according to standard methods[17] and used freshly prepared. Flash column chromatography was performed using Silica gel 60 (230–400 mesh) (Alfa Aesar, UK). Melting points were obtained on a SMP3 apparatus (Barloworld Scientific, UK) and are uncorrected. Optical rotations were measured on a Perkin Elmer M341 polarimeter. The ^{1}H NMR spectra were recorded on a Bruker DRX-400 (400 MHz) spectrometer with TMS as an internal reference. The ^{1}H NMR spectra of amides were recorded in DMSO at 100 °C; the ^{1}H NMR spectra of all other compounds were recorded in $CDCl_3$ at ambient temperature. Elemental analysis was performed using Perkin Elmer 2400 II or EuroVector EA3000 analysers. Analytical HPLC was performed on a Knauer Smartline-1100 instrument using a ReproSil 100 Si column (250 × 4.6 mm, 5 μm) for amides **3**–**14**, detection at 220 nm, 1 mL/min flow rate, *n*-hexane–*i*-PrOH mixtures as eluting solvents; and a Chiralcel OD-H column (250 × 4.6 mm) for amines **1a** and **1b**, detection at 220 nm, 1 mL/min flow rate, *n*-hexane–*i*-PrOH–MeOH mixtures as eluting solvents. The HRMS spectra were registered on 1200 Infinity (Agilent Technologies) instrument using 6540 Accurate-Mass Q-TOF (Agilent Technologies) detector operating in positive ion mode with ESI probe installed at N_2 flow rate 10 L/min, nebulizer pressure 40 psi. The probe voltage was set to 3.5 kV.

Crystallographic data for (*S*,*S*)-**4**, (*S*,*S*)-**7**, (*R*,*S*)-**10**, (*S*,*S*)-**11** and (*S*,*S*)-**12** have been deposited with the Cambridge Crystallographic Data Centre (CCDC Nos. 894452–894456). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].

4.2. *N*-Phthaloyl-(*S*)-amino acyl chlorides 2b, c, e. General procedure

Oxalyl chloride (1.15 mL, 13.2 mmol) and DMF (5 μL) were added to a suspension of *N*-phthaloyl-(*S*)-amino acid (6 mmol) in a hexane–C_6H_6 1:1 mixture (30 mL). The reaction mixture was stirred at ambient temperature for 5–7 h and then evaporated under reduced pressure. The residue was treated with hexane (40 mL) and the precipitate formed was filtered off and dried in vacuo over P_2O_5.

4.2.1. *N*-Phthaloyl-(*S*)-valyl chloride 2b

Colourless solid (1.36 g, 85%): mp 122–123 °C (hexane) (lit. 120–121 °C[18a]; 121–122 °C[18b]). $[\alpha]_D^{25} = -100$ (*c* 1.0, C_6H_6) {lit.[18b] $[\alpha]_D = -101$ (*c* 1.5, C_6H_6)}. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92 (3H, d, *J* 6.8 Hz, Me-3B); 1.17 (3H, d, *J* 6.8 Hz, Me-3A); 2.76 (1H, dsept, *J* 8.4, 6.8 Hz, H-3); 4.75 (1H, d, *J* 8.4 Hz, H-2); 7.81 (2H, m, Phth); 7.94 (2H, m, Phth). Anal. calcd for $C_{13}H_{12}ClNO_3$ (265.70): C, 58.77; H, 4.55; N, 5.27; Cl, 13.34; found: C, 59.05; H, 4.38; N, 5.25; Cl, 13.06.

4.2.2. *N*-Phthaloyl-(*S*)-*tert*-leucyl chloride 2c

Colourless solid (1.66 g, 99%): mp 90.6 °C (hexane). $[\alpha]_D^{25} = -86.0$ (*c* 1.2, C_6H_6). ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.15 (9H, s, *t*-Bu); 4.78 (1H, s, H-2); 7.81 (2H, m, Phth); 7.95 (2H, m, Phth). Anal. calcd for $C_{14}H_{14}ClNO_3$ (279.72): C, 60.12; H, 5.04; N, 5.01; Cl, 12.67; found: C, 60.22; H, 5.01; N, 5.12; Cl, 12.72.

4.2.3. *N*-Phthaloyl-3-cyclohexyl-(*S*)-alanyl chloride 2e

Colourless solid (1.78 g, 93%): mp 84 °C (hexane). $[\alpha]_D^{20} = -73.9$ (*c* 1.2, C_6H_6). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.96 (2H, m, *c*Hex); 1.16 (4H, m, *c*Hex); 1.67 (4H, m, *c*Hex); 1.86 (1H, m, *c*Hex); 2.11 (1H, ddd, *J* 14.5, 9.8, 4.4 Hz, H-3B); 2.31 (1H, ddd, *J* 14.5, 10.9, 4.0 Hz, H-3A); 5.16 (1H, dd, *J* 10.9, 4.4 Hz, H-2); 7.80 (2H, m, Phth); 7.93 (2H, m, Phth). Anal. calcd for $C_{17}H_{18}ClNO_3$ (319.79): C, 63.85; H, 5.67; N, 4.38; Cl, 11.09; found: C, 63.96; H, 5.74; N, 4.38; Cl, 11.11.

4.3. Diastereoisomeric amides 4, 5, 7, 10–13. General procedure

A solution of the appropriate acyl chloride (1 mmol) in CH_2Cl_2 (10 mL) was added to a solution of amine **1a** or **1b** (2 mmol) in CH_2Cl_2 (10 mL) at +20 °C (in the case of acyl chloride **2c**, the reactions were carried out in toluene at +50 °C). The reaction mixture was kept in a thermostat at a given temperature for 6 h, then successively washed with 1 M HCl (2 × 5 mL), saturated aqueous NaCl (3 × 15 mL), 5% $NaHCO_3$ (10 mL) and water (2 × 15 mL). The organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure. The diastereoisomers of amides **4**, **5**, **7** and **10**–**13** were isolated by recrystallisation or flash column chromatography on silica gel (eluent benzene–ethyl acetate).

4.3.1. (2*S*)-2-Methyl-1-[*N*-phthaloyl-(*S*)-valyl]-1,2,3,4-tetrahydroquinoline (*S*,*S*)-4

Colourless crystals (118 mg, 31%): mp 185–186 °C (hexane–EtOAc). $[\alpha]_D^{20} = +406$ (*c* 1.0, $CHCl_3$). *De* >99.8% (ReproSil 100 Si, hexane–*i*-PrOH 80:1, τ 10.30 min). ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C): δ 0.79 (3H, d, *J* 7.4 Hz, Me-3′); 0.81 (3H, d, *J* 7.4 Hz, Me-3′); 1.02 (3H, d, *J* 6.3 Hz, Me-2); 1.35 (1H, dddd, *J* 13.2, 9.2, 6.1, 5.9 Hz, H-3B); 2.23 (1H, m, H-3A); 2.44–2.51 (1H, overlapped by DMSO, m, H-4B); 2.66 (1H, ddd, *J* = 15.4, 6.0, 5.9 Hz, H-4A); 2.82–2.95 (overlapped by water signal, 1H, m, H-3′); 4.69 (1H, m, H-2); 5.11 (1H, d, *J* 9.3 Hz, H-2′); 7.14–7.26 (3H, m, H-5, H-6 and H-7); 7.62 (1H, d, *J* 7.8 Hz, H-8); 7.83–7.89 (4H, m, Phth). Anal. calcd for $C_{23}H_{24}N_2O_3$ (376.46): C, 73.38; H, 6.43; N, 7.44; found: C, 73.35; H, 6.46; N, 7.15.

4.3.2. (2*R*)-2-Methyl-1-[*N*-phthaloyl-(*S*)-valyl]-1,2,3,4-tetrahydroquinoline (*R*,*S*)-4

Colourless crystals (80 mg, 21% after flash column chromatography of the mother liquor after recrystallization, fast eluting isomer): mp 99–101 °C. $[\alpha]_D^{20} = -241$ (*c* 0.7, $CHCl_3$). *De* >99.0% (ReproSil 100 Si, hexane–*i*-PrOH 80:1, τ 6.67 min). ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C): δ 0.77 (3H, d, *J* 6.9 Hz, Me); 0.98 (3H, d, *J* 6.5 Hz, Me); 1.06 (3H, d, *J* 6.7 Hz, Me); 1.08–1.16 (1H, m, H-3B); 2.11–2.30 (3H, m, C^4H_2 and H-3A); 2.70 (1H, m, H-3′); 4.56 (1H, dqd, *J* 6.8, 6.7, 6.5 Hz, H-2); 4.95 (1H, d, *J* 7.2 Hz, H-2′); 6.65 (1H, d, *J* 7.4 Hz, H-5); 6.79 (1H, ddd, *J* 7.5, 7.4, 0.9 Hz, H-6); 7.03 (1H, m, H-7); 7.19 (1H, d, *J* 8.0 Hz, H-8); 7.60–7.65 (2H, m, Phth); 7.70–7.75 (2H, m, Phth). Anal. calcd for $C_{23}H_{24}N_2O_3$ (376.46): C, 73.38; H, 6.43; N, 7.44; found: C, 73.20; H, 6.44; N, 7.56.

4.3.3. (2*S*)-2-Methyl-1-[*N*-phthaloyl-(*S*)-*tert*-leucyl]-1,2,3,4-tetrahydroquinoline (*S*,*S*)-5

Colourless powder (117 mg, 30% after flash column chromatography, slow eluting isomer): mp 59–60 °C. $[\alpha]_D^{20} = +252$ (*c* 0.9, $CHCl_3$). *De* 99.2% (ReproSil 100 Si, hexane–*i*-PrOH 80:1, τ 7.72 min). ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C): δ 0.99 (3H, d, *J* 6.5 Hz, Me-2); 1.00 (9H, s, *t*-Bu); 1.31 (1H, dddd, *J* 13.2, 9.1, 6.0, 5.8 Hz, H-3B); 2.10 (1H, m, H-3A); 2.39 (1H, ddd, *J* 15.3, 9.1, 6.2 Hz, H-4B); 2.62 (1H, ddd, *J* 15.3, 5.8, 5.8 Hz, H-4A); 4.51 (1H, dqd, *J* 6.6, 6.5, 6.2 Hz, H-2); 5.06 (1H, s, H-2′); 7.14 (3H, m, H-5, H-6 and H-7); 7.35 (1H, m, H-8); 7.88 (4H, m, Phth). HRMS for $C_{24}H_{27}N_2O_3$ (M+H$^+$), calcd 391.2016, found 391.2019.

4.3.4. (2*R*)-2-Methyl-1-[*N*-phthaloyl-(*S*)-*tert*-leucyl]-1,2,3,4-tetrahydroquinoline (*R*,*S*)-5

Colourless powder (78 mg, 20% after flash column chromatography, fast eluting isomer): mp 116–121 °C. $[\alpha]_D^{20} = -219$ (*c* 0.5, $CHCl_3$). *De* 98.8% (ReproSil 100 Si, hexane–*i*-PrOH 80:1, τ 4.95 min). ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C): δ 0.95 (3H, d, *J* 6.4 Hz, Me-2); 1.03 (1H, m, H-3B); 1.11 (9H, s, *t*-Bu); 2.08 (1H, m, H-3A); 2.21 (2H, m, C^4H_2); 4.51 (1H, m, H-2); 4.95 (1H, s, H-2′); 6.58 (1H, d, *J* 7.5 Hz, H-5); 6.79 (1H, ddd, *J* 7.6, 7.5, 0.9 Hz, H-6); 7.04 (1H, ddd, *J* 7.9, 7.6, 0.5 Hz, H-7); 7.18 (1H, d, *J* 7.9 Hz, H-8); 7.60–7.64 (2H, m, Phth); 7.71–7.75 (2H, m, Phth). HRMS for $C_{24}H_{27}N_2O_3$ (M+H$^+$), calcd 391.2016, found 391.2014.

4.3.5. (2*S*)-2-Methyl-1-[*N*-phthaloyl-3-cyclohexyl-(*S*)-alanyl]-1,2,3,4-tetrahydroquinoline (*S*,*S*)-7

Colourless crystals (162 mg, 38%): mp 184–184.5 °C (hexane–EtOAc). $[\alpha]_D^{20} = +416$ (*c* 1.0, $CHCl_3$). *De* 99.2% (ReproSil 100 Si, hexane–*i*-PrOH 160:1, τ 14.60 min). ^{1}H NMR (DMSO-d_6, 100 °C, 400 MHz): δ 0.18–0.25 (1H, m, *c*Hex); 0.62–0.70 (1H, m, *c*Hex); 0.87–0.96 (2H, m, *c*Hex); 0.96–1.05 (2H, m, *c*Hex); 1.01 (3H, d, *J* 6.5 Hz, Me-2); 1.21–1.45 (6H, m, 5H-*c*Hex and H-3B); 2.36 (1H, ddd, *J* 13.0, 8.1, 5.0, 4.9 Hz, H-3A); 2.42–2.51 (3H, overlapped by DMSO, m, $C^{3'}H_2$ and H-4B); 2.69 (1H, ddd, *J* 14.8, 4.7, 4.7 Hz, H-4A); 4.58 (1H, m, H-2); 5.56 (1H, dd, *J* 11.9, 3.4 Hz, H-2′); 7.25 (1H, ddd, *J* 7.5, 7.4, 0.8 Hz, H-6); 7.30–7.35 (2H, m, H-5, H-7); 7.47 (1H, d, *J* 7.8 Hz, H-8); 7.86 (4H, m, Phth). Anal. calcd for $C_{27}H_{30}N_2O_3$ (430.55): C, 75.32; H, 7.02; N, 6.51; found: C, 75.43; H, 7.16; N, 6.54.

4.3.6. (3*S*)-3,4-Dihydro-3-methyl-4-[*N*-phthaloyl-(*S*)-valyl]-2*H*-[1,4]benzoxazine (*S*,*S*)-10

Colourless powder (217 mg, 48% after flash column chromatography, slow eluting isomer): mp 161 °C. $[\alpha]_D^{20} = +163$ (*c* 1.0, $CHCl_3$). *De* 99.4% (ReproSil 100 Si, hexane–*i*-PrOH 80:1, τ 10.58 min). ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C): δ 0.90 (3H, d, *J* 6.6 Hz, Me); 0.96 (3H, d, *J* 6.7 Hz, Me); 1.17 (3H, d, *J* 6.7 Hz, Me-3); 3.11 (1H, dsept, *J* 10.0, 6.7 Hz, H-3′); 4.05 (1H, dd, *J* 11.0, 3.1 Hz, H-2B); 4.19 (1H, dd, *J* 11.0, 1.8 Hz, H-2A); 4.82 (1H, qdd, *J* 6.7, 3.1,

1.8 Hz, H-3); 5.03 (1H, d, *J* 10.1 Hz, H-2′); 6.87 (1H, dd, *J* 8.1, 1.4 Hz, H-8); 6.90 (1H, ddd, *J* 8.4, 7.4, 1.4 Hz, H-6); 7.06 (1H, ddd, *J* 8.0, 7.4, 1.8 Hz, H-7); 7.83–7.88 (5H, m, Phth and H-5). Anal. calcd for $C_{22}H_{22}N_2O_4$ (378.43): C, 69.83; H, 5.86; N, 7.40; found: C, 69.90; H, 5.84; N, 7.37.

4.3.7. (3*R*)-3,4-Dihydro-3-methyl-4-[*N*-phthaloyl-(*S*)-valyl]-2*H*-[1,4]benzoxazine (*R*,*S*)-10

Colourless powder (38 mg, 8.4% after flash column chromatography, fast eluting isomer): mp 182–183 °C. $[\alpha]_D^{20} = -256$ (*c* 1.0, $CHCl_3$). *De* 99.0% (ReproSil 100 Si, hexane–*i*-PrOH 80:1, τ 5.77 min). ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C): δ 0.84 (3H, d, *J* 6.8 Hz, Me); 0.85 (3H, d, *J* 6.7 Hz, Me); 1.07 (3H, d, *J* 6.7 Hz, Me-3); 2.74 (1H, dsept, *J* 7.4, 6.8 Hz, H-3′); 4.07 (1H, dd, *J* 10.9, 1.7 Hz, H-2B); 4.12 (1H, dd, *J* 10.9, 3.0 Hz, H-2A); 4.60 (1H, m, H-3); 5.07 (1H, d, *J* 7.4 Hz, H-2′); 6.55 (1H, dd, *J* 8.1, 0.9 Hz, H-8); 6.73 (1H, ddd, *J* 8.0, 7.7, 1.4 Hz, H-6); 6.81 (1H, ddd, *J* 8.1, 7.7, 1.5 Hz, H-7); 7.40 (1H, dd, *J* 8.0, 1.2 Hz, H-5); 7.74–7.80 (4H, m, Phth). Anal. calcd for $C_{22}H_{22}N_2O_4$ (378.43): C, 69.83; H, 5.86; N, 7.40; found: C, 70.06; H, 5.89; N, 7.41.

4.3.8. (3*S*)-3,4-Dihydro-3-methyl-4-[*N*-phthaloyl-(*S*)-*tert*-leucyl]-2*H*-[1,4]benzoxazine (*S*,*S*)-11

Colourless powder (59 mg, 15% after flash column chromatography, slow eluting isomer): mp 130.5 °C. $[\alpha]_D^{20} = +77.8$ (*c* 1.0, $CHCl_3$). *De* 99.6% (ReproSil 100 Si, hexane–*i*-PrOH 80:1, τ 7.32 min). ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C): δ 1.11 (9H, s, *t*-Bu); 1.15 (3H, d, *J* 6.7 Hz, Me-3); 3.80 (1H, dd, *J* 10.9, 2.8 Hz, H-2B); 4.10 (1H, dd, *J* 10.9, 1.5 Hz, H-2A); 4.37 (1H, m, H-3); 5.10 (1H, s, H-2′); 6.83 (1H, dd, *J* 8.1, 1.1 Hz, H-8); 6.89 (1H, m, H-6); 7.04 (1H, m, H-7); 7.84 (1H, dd, *J* 8.3, 0.9 Hz, H-5); 7.86–7.90 (4H, m, Phth). Anal. calcd for $C_{23}H_{24}N_2O_4$ (392.46): C, 70.39; H, 6.16; N, 7.14; found: C, 70.38; H, 6.37; N, 7.09.

4.3.9. (3*R*)-3,4-Dihydro-3-methyl-4-[*N*-phthaloyl-(*S*)-*tert*-leucyl]-2*H*-[1,4]benzoxazine (*R*,*S*)-11

Colourless powder (17 mg, 4.4% after flash column chromatography, fast eluting isomer): mp 149–151 °C. $[\alpha]_D^{20} = -266$ (*c* 1.0, $CHCl_3$). *De* >99.0% (ReproSil 100 Si, hexane–*i*-PrOH 80:1, τ 4.22 min). ^{1}H NMR (DMSO-d_6, 100 °C, 400 MHz): δ 0.77 (3H, d, *J* 6.8 Hz, Me-3); 1.13 (9H, s, *t*-Bu); 4.02 (1H, dd, *J* 10.8, 1.5 Hz, H-2B); 4.10 (1H, dd, *J* 10.8, 3.2 Hz, H-2A); 4.55 (1H, br s, H-3); 5.04 (1H, s, H-2′); 6.47 (1H, d, *J* 7.5 Hz, H-8); 6.73 (1H, ddd, *J* 7.6, 7.6, 1.4 Hz, H-6); 6.79 (1H, ddd, *J* 7.6, 7.6, 1.1 Hz, H-7); 7.35 (1H, d, *J* 7.6 Hz, H-5); 7.72-7.79 (4H, m, Phth). HRMS for $C_{23}H_{25}N_2O_4$ ($M+H^+$), calcd 393.1809, found 393.1805.

4.3.10. (3*S*)-3,4-Dihydro-3-methyl-4-[*N*-phthaloyl-(*S*)-leucyl]-2*H*-[1,4]benzoxazine (*S*,*S*)-12

Colourless crystals (211 mg, 54%): mp 183 °C (hexane–EtOAc). $[\alpha]_D^{20} = +370$ (*c* 1.0, $CHCl_3$). *De* 99.8% (ReproSil 100 Si, hexane–*i*-PrOH 80:1, τ 7.80 min). ^{1}H NMR (DMSO-d_6, 100 °C, 400 MHz): δ 0.66 (3H, d, *J* 6.4 Hz, Me); 0.77 (3H, d, *J* 6.5 Hz, Me); 1.13 (3H, d, *J* 6.8 Hz, Me-3); 1.40 (1H, ddd, *J* 13.5, 9.3, 4.0 Hz, H-3′B); 1.44–1.54 (1H, m, H-4′); 2.58 (1H, ddd, *J* 13.5, 11.4, 3.9 Hz, H-3′A); 4.10 (1H, dd, *J* 11.1, 3.4 Hz, H-2B); 4.20 (1H, dd, *J* 11.1, 1.8 Hz, H-2A); 4.75 (1H, qdd, *J* 6.8, 3.4, 1.8 Hz, H-3); 5.57 (1H, dd, *J* 11.4, 4.0 Hz, H-2′); 6.93 (1H, dd, *J* 8.0, 1.4 Hz, H-8); 6.96 (1H, ddd, *J* 8.0, 7.4, 1.4 Hz, H-6); 7.13 (1H, ddd, *J* = 8.0, 7.4, 1.5 Hz, H-7); 7.60 (1H, dd, *J* 8.0, 1.5 Hz, H-5); 7.83–7.89 (4H, m, Phth). Anal. calcd for $C_{23}H_{24}N_2O_4$ (392.46): C, 70.39; H, 6.16; N, 7.14; found: C, 70.19; H, 6.27; N, 7.11.

4.3.11. (3*R*)-3,4-Dihydro-3-methyl-4-[*N*-phthaloyl-(*S*)-leucyl]-2*H*-[1,4]benzoxazine (*R*,*S*)-12

Amorphous solid (16 mg, 4.0% after flash column chromatography of the mother liquor after recrystallisation, fast eluting isomer). $[\alpha]_D^{20} = -216$ (*c* 0.2, $CHCl_3$). *De* 95.0% (ReproSil 100 Si, hexane–*i*-PrOH 80:1, τ 4.93 min). ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C): δ 0.886 (3H, d, *J* 6.8 Hz, Me); 0.892 (3H, d, *J* 6.6 Hz, Me); 0.95 (3H, d, *J* 6.6 Hz, Me); 1.54 (1H, m, H-4′); 1.95 (1H, ddd, *J* 14.1, 9.0, 5.1 Hz, H-3′B); 2.04 (1H, ddd, *J* 14.1, 8.6, 5.2 Hz, H-3′A); 4.09 (1H, dd, *J* 11.0, 1.9 Hz, H-2B); 4.13 (1H, dd, *J* 11.0, 3.0 Hz, H-2A); 4.52 (1H, m, H-3); 5.32 (1H, dd, *J* 9.0, 5.2 Hz, H-2′); 6.60 (1H, dd, *J* 8.1, 1.4 Hz, H-8); 6.75 (1H, ddd, *J* 8.1, 7.3, 1.5 Hz, H-7); 6.84 (1H, ddd, *J* 8.0, 7.3, 1.4 Hz, H-6); 7.43 (1H, dd, *J* 8.0, 1.5 Hz, H-5); 7.74–7.80 (4H, m, Phth). Anal. calcd for $C_{23}H_{24}N_2O_4$ (392.46): C, 70.39; H, 6.16; N, 7.14; found: C, 69.97; H, 6.26; N, 6.80.

4.3.12. (3*S*)-3,4-Dihydro-3-methyl-1-[*N*-phthaloyl-3-cyclohexyl-(*S*)-alanyl]-2*H*-[1,4]benzoxazine (*S*,*S*)-13

Colourless crystals (61 mg, 14% after flash column chromatography, slow eluting isomer): mp 170–172 °C. $[\alpha]_D^{20} = +344$ (*c* 1.0, $CHCl_3$). *De* 99.7% (ReproSil 100 Si, hexane–*i*-PrOH 80:1, τ 7.60 min). ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C): δ 0.57–0.67 (1H, m, *c*Hex); 0.79–0.89 (1H, m, *c*Hex); 1.01–1.08 (3H, m, *c*Hex); 1.12 (3H, d, *J* 6.8 Hz, Me-3); 1.18–1.29 (1H, m, *c*Hex); 1.47–1.55 (6H, m, 6H-*c*Hex and H-3′B); 2.54 (1H, ddd, *J* 14.1, 11.3, 4.4 Hz, H-3′A); 4.10 (1H, dd, *J* 11.0, 3.2 Hz, H-2B); 4.21 (1H, dd, *J* 11.0, 1.7 Hz, H-2A); 4.75 (1H, qdd, *J* 6.8, 3.2, 1.7 Hz, H-3); 5.59 (1H, dd, *J* 11.3, 4.3 Hz, H-2′); 6.93 (1H, dd, *J* 7.9, 1.4 Hz, H-8); 6.96 (1H, ddd, *J* 8.0, 7.4, 1.4 Hz, H-6); 7.13 (1H, ddd, *J* 8.0, 7.5, 1.4 Hz, H-7); 7.60 (1H, dd, *J* 8.0, 1.4 Hz, H-5); 7.84–7.89 (4H, m, Phth). Anal. calcd for $C_{26}H_{28}N_2O_4$ (432.52): C, 72.20; H, 6.52; N, 6.48; found: C, 72.10; H, 6.55; N, 6.42.

4.3.13. (3*R*)-3,4-Dihydro-3-methyl-1-[*N*-phthaloyl-3-cyclohexyl-(*S*)-alanyl]-2*H*-[1,4]benzoxazine (*R*,*S*)-13

Colourless foam (27 mg, 6.2% after flash column chromatography, fast eluting isomer). $[\alpha]_D^{20} = -183$ (*c* 0.4, $CHCl_3$). *De* 96.0% (ReproSil 100 Si, hexane–*i*-PrOH 80:1, τ 4.70 min). ^{1}H NMR (400 MHz, DMSO-d_6, 100 °C): δ 0.89 (3H, d, *J* 6.8 Hz, Me-3); 0.93–1.04 (2H, m, *c*Hex); 1.11–1.18 (3H, m, *c*Hex); 1.20–1.31 (1H, m, *c*Hex); 1.52–1.68 (4H, m, *c*Hex); 1.89 (1H, m, *c*Hex); 1.92 (1H, ddd, *J* 14.2, 9.0, 5.2 Hz, H-3′B); 2.08 (1H, ddd, *J* 14.2, 8.4, 5.2 Hz, H-3′A); 4.09 (1H, dd, *J* 10.9, 1.8 Hz, H-2B); 4.13 (1H, dd, *J* 10.9, 2.7 Hz, H-2A); 4.52 (1H, qdd, *J* 6.8, 2.7, 1.8 Hz, H-3); 5.34 (1H, dd, *J* 9.0, 5.2 Hz, H-2′); 6.60 (1H, dd, *J* 8.1, 1.5 Hz, H-8); 6.74 (1H, ddd, *J* 8.1, 7.4, 1.5 Hz, H-6); 6.84 (1H, ddd, *J* 8.1, 7.4, 1.5 Hz, H-7); 7.43 (1H, dd, *J* 8.1, 1.5 Hz, H-5); 7.74–7.80 (4H, m, Phth). HRMS for $C_{26}H_{29}N_2O_4$ ($M+H^+$), calcd 433.2122, found 433.2117.

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

A solution of the appropriate acyl chloride (0.15 mmol) in the chosen solvent (1.5 mL) was added to a solution of amine (0.30 mmol) in the same solvent (1.5 mL) at a specified temperature. The reaction mixture was kept at the appropriate temperature for 6 h, then washed with 1 M HCl (2 × 3 mL), saturated aqueous NaCl (3 × 3 mL), 5% $NaHCO_3$ (3 mL) and water (2 × 3 mL) [in the case of acetonitrile solution, 1 M HCl (3 mL) was added to the reaction mixture and amides were extracted with benzene]. The organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure to give a mixture of diastereoisomeric amides **3**–**14**, which was analysed by HPLC and ^{1}H NMR spectroscopy. Acidic washing solutions were collected and alkalised with Na_2CO_3 up to pH 8–9, and extracted with $CHCl_3$ (2 × 3 mL). The organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure to give an enantiomeric mixture of unreacted amine **1a** or **1b**.

4.5. Enantiopure amines (*S*)-1a and (*S*)-1b. General procedure

A solution of acyl chloride **2d** (4.20 g, 15 mmol) was added to a solution of racemic amine **1a** or **1b** (30 mmol) in CH_2Cl_2 (150 mL) at −20 °C. The reaction mixture was kept at −20 °C for 6 h, then washed with 1 M HCl (2 × 100 mL), saturated aqueous NaCl (3 × 100 mL), 5% $NaHCO_3$ (2 × 100 mL) and water (2 × 100 mL). The organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallised from hexane–ethyl acetate to give amide (*S*,*S*)-**6** (de >99%, 3.22 g, 55% yield) or (*S*,*S*)-**12** (de >99%, 3.18 g, 54% yield). (*S*,*S*)-Amide **6** or **12** was dissolved in AcOH (30 mL) after which concentrated HCl (30 ml) was added to the solution, and the resulting mixture was heated at 90 °C for 15 h. The reaction mixture was evaporated under reduced pressure to half-volume, and then poured into water (200 mL). The aqueous solution was washed with $CHCl_3$ (2 × 25 mL), then alkalised with Na_2CO_3 up to pH 8–9 and extracted with $CHCl_3$ (3 × 40 mL). The organic layer was washed with water (2 × 30 mL), dried over $MgSO_4$ and evaporated under reduced pressure.

4.5.1. (2*S*)-2-Methyl-1,2,3,4-tetrahydroquinoline (*S*)-1a

Colourless oil (1.10 g, 25% relative to *rac*-**1a**). $[\alpha]_D^{20} = -85$ (*c* 1.5, C_6H_6) [lit.[19] (*R*)-**1a**: +85 (*c* 2, C_6H_6)]. *Ee* >99% (Chiralcel OD-H, *n*-hexane–*i*-PrOH–MeOH 100:0.8:0.2, *τ* 10.02 min). ^{1}H NMR ($CDCl_3$) data are in good agreement with the literature.[10c]

4.5.2. (3*S*)-3,4-Dihydro-3-methyl-2*H*-[1,4]benzoxazine (*S*)-1b

Yellowish oil (1.07 g, 23% relative to *rac*-**1b**). $[\alpha]_D^{20} = +23.0$ (*c* 1.0, $CHCl_3$) [lit.[10b] +19.8 (*c* 1, $CHCl_3$)]. *Ee* >99% (Chiralcel OD-H, *n*-hexane–*i*-PrOH–MeOH 100:1.5:1.5, *τ* 11.97 min). ^{1}H NMR ($CDCl_3$) data are in good agreement with the literature.[9a,10b]

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