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Acylative kinetic resolution of racemic amines using *N*-phthaloyl-(*S*)-amino acyl chlorides

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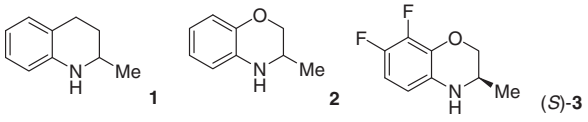
ABSTRACT

A comparative study of the kinetic resolution of racemic 2-methyl-1,2,3,4-tetrahydroquinoline and 2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine using *N*-phthaloyl-(*S*)-amino acyl chlorides as chiral acylating agents is described. Temperature and solvent effects on the stereochemical features have been examined. It has been found that *N*-phthaloyl-(*S*)-phenylalanyl and *N*-phthaloyl-(*S*)-2-phenylglycyl chlorides bearing aromatic substituents close to the stereogenic centre are more stereoselective acylating agents than *N*-phthaloyl-(*S*)-alanyl chloride. For the preparative kinetic resolution of racemic amines *N*-phthaloyl-(*S*)-phenylalanyl chloride proved to be the most appropriate chiral acylating agent.

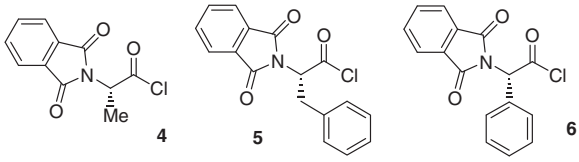
1. Introduction

Preparation of chiral substances in enantiomerically pure form is one of the main tasks of modern organic synthesis. Kinetic resolution is one of the oldest and most widely used approaches to obtain the individual stereoisomers.[1–3] In particular, acylative kinetic resolution has been applied for the synthesis of enantiopure amines. This type of kinetic resolution includes both enzymatic[4–7] and nonenzymatic processes in the presence of synthetic catalysts.[8–10] Recently the methods of kinetic resolution using enantiopure chiral acylating agents have attracted considerable attention,[11–15] most if not all of the agents being chiral acyl-transfer agents. Our efforts have been focused on the study of kinetic resolution processes of racemic amines using low-molecular weight acylating agents, that is, chiral acyl chlorides,[16–20] which make it possible to obtain individual enantiomers of heterocyclic amines in good-to-high yields. It should be noted that the use of chiral acyl derivatives resulting in the formation of diastereoisomers provides an opportunity to enhance the stereochemical purity of the acylation products by traditional (non-stereospecific) methods. Derivatives of natural amino acids are of considerable interest as chiral resolving agents since they are easily accessible and inexpensive enantiomerically pure compounds.

Previously we reported the efficient kinetic resolution of racemic 2-methyl-1,2,3,4-tetrahydroquinoline **1** and 2,3-dihydro-3-methyl-4*H*-1,4-benzoxazine **2** (Scheme 1) using *N*-phthaloyl-(*S*)-alanyl chloride **4** (Scheme 2) as a chiral acylating agent.[20] Enantiomers of 2-methyl-1,2,3,4-tetrahydroquinoline are of interest as structural fragments of a number of biologically active compounds.[21–24] Moreover, amines **1** and **2** are close structural analogues of 7,8-difluoro-2,3-dihydro-(3*S*)-methyl-4*H*-1,4-benzoxazine (*S*)-**3**, the key intermediate in the synthesis of antibacterial Levofloxacin.



Scheme 1. Racemic amines.



Scheme 2. Chiral acylating agents.

To elucidate the effects of the structure of resolving agents and the reaction conditions on the kinetic resolution efficiency we studied the acylation of racemic amines **1** and **2** with *N*-phthaloyl amino acyl chlorides **5** and **6** in comparison to acyl chloride **4**.

2. Results and discussion

Acyl chlorides **4–6** of >97% purity (according to ^{1}H NMR spectra) were prepared by the reaction of oxalyl chloride with the appropri-

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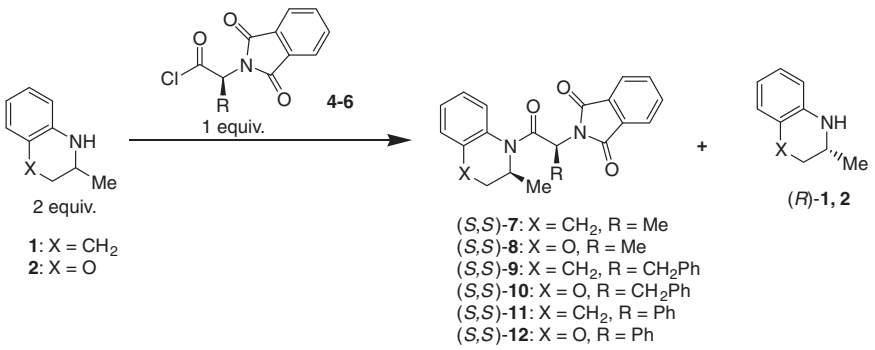


Scheme 3. Kinetic resolution of racemic amines **1** and **2** with chiral acylating agents **4–6**.

ate *N*-phthaloyl amino acid in a hexanes/benzene solution in the presence of catalytic amounts of DMF in 85–93% yields.[20] Freshly prepared acyl chlorides were used for further synthesis without additional purification.

Acylation of 2 equiv of racemic amines **1** and **2** was carried out with 1 equiv of acyl chlorides **4–6** in a variety of solvents at various temperatures over 6 h (Scheme 3). The initial concentration of racemic amine was 0.1 M. Diastereoisomeric amides **7–12** and unreacted amines **1** and **2** were isolated from the reaction mixtures and analyzed separately using HPLC to determine the de for amides **7–12** and the ee for amines **1–2** on a chiral stationary phase (Chiralcel OD-H).

The ratio of diastereoisomers in amides **7–12** can be also determined using ^{1}H NMR spectroscopy data. The most indicative signals which allow distinguishing the diastereoisomers are those of the groups near the stereogenic centres both in the amine and in the acyl moieties. The results obtained by ^{1}H NMR spectroscopy agreed with HPLC data. It should be noted that at ambient temperature the signals of almost all the protons broadened considerably both in DMSO-d_6 and in $CDCl_3$ solutions, whereas on heating the sample solution in DMSO-d_6 to 100 °C the signals became sharp. The same phenomena were observed previously for other amides containing the fragments of amines **1–3**.[16–18,20] The broadening of the resonance signals is likely to be caused by the restricted rotation about a partial double amide bond and by ring inversion.

Similar to the acylation of amines **1–2** with acyl chloride **4**,[20] kinetic resolution using compounds **5** and **6** resulted in the predominant formation of (*S,S*)-amides **9–12**, while unreacted amines were enriched with the (*R*)-enantiomers (Scheme 3).

The major (*S,S*)-diastereoisomers of amides **9–12** were isolated in enantiomerically pure form (de ⩾97%) after kinetic resolution of racemic amines **1** and **2** with acyl chlorides **5** and **6** in CH_2Cl_2 (or CH_3CN) at room temperature followed by crystallization of the acylation products. Single crystal X-ray structure determinations were performed for (*S,S*)-**9–11** and unambiguously confirmed the absolute configuration of the amine fragment taking into account the known absolute configuration of *N*-phthaloyl amino acyl moiety (Figs. 1–3).

We managed to isolate the minor (*R,S*)-diastereoisomer from the amide mixture by flash chromatography on silica gel only in the case of amides **10**. (*R,S*)-**9** and (*R,S*)-**11** were specially prepared starting from (*R*)-**1**[18] in moderate yields (Scheme 4). Although some data concerning the tendency of *N*-phthaloyl amino acids towards racemization are available in the literature,[25,26] we did not observe that on using NEt_3 as the base in the acylation of (*R*)-**1** with acyl chloride **5** and an excess of (*R*)-**1** as a base in the case of acylation with compound **6** (Scheme 4).

We carried out 2–4 parallel experiments on the kinetic resolution of racemic amines **1** and **2** (Scheme 3) to determine the average values of de for the reaction products **7–12** and ee for

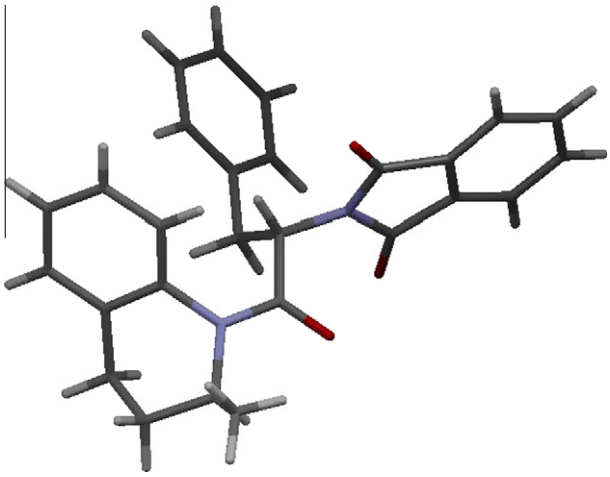


Figure 1. X-ray structure of (*S,S*)-**9**.

unreacted substrates **1** and **2**. Based on the data obtained we were able to calculate the conversion (*C*, %) of the starting racemate according to the equation: $C = [ee_{amine}/(ee_{amine} + de_{amide})] \times 100\%$ and the selectivity factor $s = \ln[(1 - C) \times (1 - ee_{amine})]/\ln[(1 - C) \times (1 + ee_{amine})]$.[1] The results for the kinetic resolution of racemic amines **1** and **2** acylated with acyl chlorides **4–6** at +20 °C in different solvents are presented in Table 1.

The highest stereoselectivity in acylation of the racemic amine **1** with acyl chlorides **4** and **5** and the highest conversion of racemic amine **1** were observed in CH_2Cl_2 and MeCN, selectivity factor

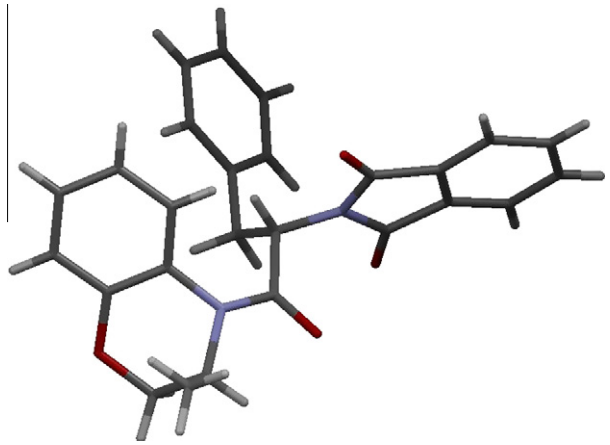


Figure 2. X-ray structure of (*S,S*)-**10**.

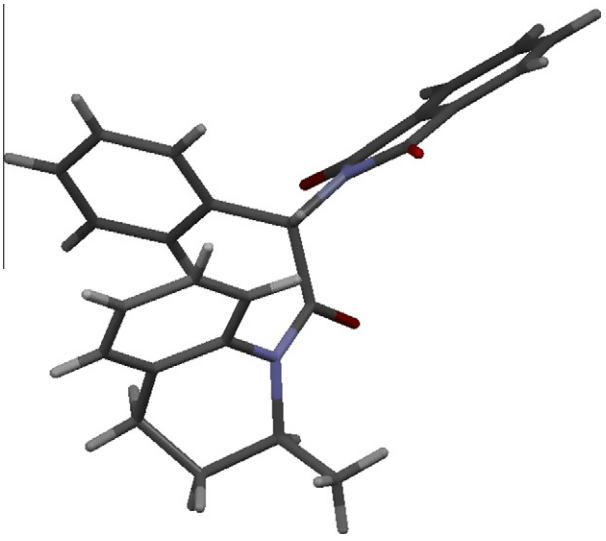
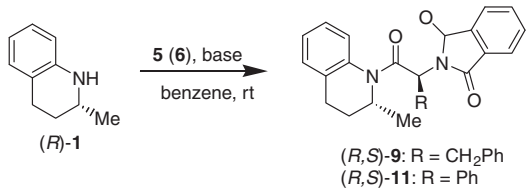


Figure 3. X-ray structure of (*S,S*)-**11**.



Scheme 4. Synthesis of (*R,S*)-amides **9** and **11**.

being 4.6, 8.0 and 8.9 (Table 1, entries 5, 8 and 9, respectively). In benzene, toluene, *p*-xylene and Et_2O, especially (entries 1–4, 6 and 7), the efficiency of the kinetic resolution was lower. Acylation of racemic amine **2** with acyl chlorides **4** and **5** showed the same tendencies (entries 14–18).

Unlike the kinetic resolution using acyl chlorides **4** and **5**, the highest selectivity in acylation of racemic amines **1** and **2** with acyl chloride **6** was observed in less polar solvents, such as benzene and toluene (Table 1, entries 10, 11 and 19), as compared with CH_2Cl_2 and MeCN (entries 12, 13 and 20).

The temperature effect on the stereochemical outcome of the kinetic resolution with acyl chlorides **4–6** can be exemplified by the acylation of racemic **1** in toluene and CH_2Cl_2 (Table 2).

It has been found that lowering the reaction temperature results in a marked increase in the selectivity of acylation of amine **1** with acyl chlorides **4** and **5**. Thus, for example, in the case of acyl chloride **5** in CH_2Cl_2 at +20 and −20 °C the selectivity factor *s* was 8.9 and 12, respectively (Table 2, entries 10 and 11). Conversion of the starting racemate **1** tended to decrease with decrease in reaction temperature only in toluene. In the case of kinetic resolution with acyl chloride **6** the values of de and *s* almost did not vary with temperature decrease in toluene (entries 12 and 13), but in CH_2Cl_2 we observed some increase in selectivity factor and de of (*S,S*)-amide with decrease in reaction temperature (entries 14 and 15).

The results obtained point to the fact that acyl chlorides **5** and **6** bearing aromatic substituents close to the stereogenic centre are more enantioselective in the acylation reactions than acyl chloride **4**. Thus, acylation of racemic **1** with acyl chloride **5** in benzene at +20 °C resulted in the formation of (*S,S*)-**9** of de 61.9% at conversion of the starting racemate *C* 42%, while acylation of amine **1** with acyl chloride **4** under the same conditions resulted in (*S,S*)-**7** of lower diastereoisomeric excess ($de_{(S,S)\text{-}7}$ 47.1%) at *C* 40% (Table 1, entries 6 and 1, respectively). Acyl chloride **6** showed the highest selectivity among the studied resolving agents: selectivity factor *s* has attained 22 when racemic amine **1** was acylated in toluene at +20 °C ($de_{(S,S)\text{-}11}$ 89.1%) (Table 1, entry 11). However, in that case conversion of the starting racemate *C* 18% was significantly lower than that using acyl chlorides **4** and **5**. Steric hindrances caused by phenyl and phthalimide substituents located close to the stereogenic centre in acyl chloride **6** are likely to complicate the acylation of heterocyclic amines **1** and **2** and at the same time they are responsible for the highest stereoselectivity among the studied acyl chlorides. Probably, not only steric factors effect the enantiodiscrimination, but also the aromatic interactions contribute to the process. Thus, in the acylation of racemic amines **1** and **2** with acyl chlorides **5** and **6** bearing aromatic fragments, values of the selectivity factor *s* were higher as compared with acyl chloride **4**.

Table 1
Results for the kinetic resolution of racemic amines **1** and **2** using acyl chlorides **4–6** (+20 °C, 6 h)

Entry	Racemic amine	Resolving agent	Solvent	Diastereoisomeric excess, de % [a][(*S,S*)-amide]	Enantiomeric excess, ee %[b] [(*R*)-amine]	Conversion, *C* %	Selectivity factor, *s*
1	**1**	**4** (R = Me)	Benzene	47.1	30.9	40	3.7
2	**1**	**4** (R = Me)	Toluene	38.3	22.0	36	2.8
3	**1**	**4** (R = Me)	*p*-Xylene	36.1	15.6	30	2.5
4	**1**	**4** (R = Me)	Et_2O	6.9	3.9	36	1.2
5	**1**	**4** (R = Me)	CH_2Cl_2	53.1	37.2	41	4.6
6	**1**	**5** (R = Bn)	Benzene	61.9	44.9	42	6.5
7	**1**	**5** (R = Bn)	Toluene	48.8	33.3	40	4.1
8	**1**	**5** (R = Bn)	CH_2Cl_2	67.1	56.9	46	8.9
9	**1**	**5** (R = Bn)	MeCN	64.8	56.1	47	8.0
10	**1**	**6** (R = Ph)	Benzene	89.5	15.8	15	21
11	**1**	**6** (R = Ph)	Toluene	89.1	20.3	18	22
12	**1**	**6** (R = Ph)	CH_2Cl_2	80.0	25.6	24	12
13	**1**	**6** (R = Ph)	MeCN	80.5	6.7	8	9.8
14	**2**	**4** (R = Me)	Toluene	42.6	20.3	32	3.0
15	**2**	**4** (R = Me)	MeCN	49.3	33.1	40	4.0
16	**2**	**5** (R = Bn)	Toluene	50.6	37.5	43	4.3
17	**2**	**5** (R = Bn)	CH_2Cl_2	59.2	48.0	45	6.2
18	**2**	**5** (R = Bn)	MeCN	59.8	48.7	45	6.3
19	**2**	**6** (R = Ph)	Toluene	83.7	26.3	24	15
20	**2**	**6** (R = Ph)	CH_2Cl_2	81.5	20.6	20	12

[a] Determined by HPLC (see Section 4).
[b] Determined by chiral HPLC (see Section 4).

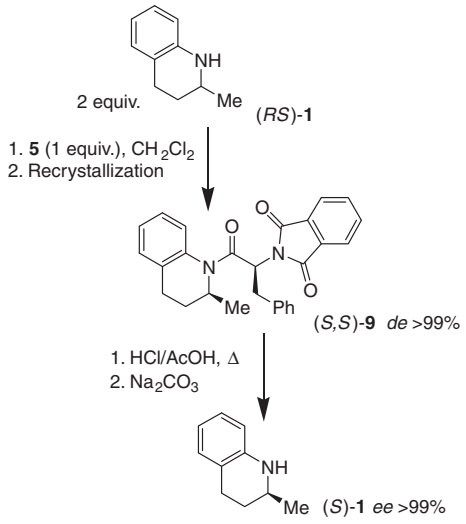
Table 2
Temperature effect on the kinetic resolution of (2*RS*)-methyl-1,2,3,4-tetrahydroquinoline **1** using acyl chlorides **4–6**

Entry	Resolving agent	Solvent	Temperature (°C)	Diastereoisomeric excess, de %[a] [(*S*,*S*)-amide]	Enantiomeric excess, ee %[b] [(*R*)-amine]	Conversion, *C* %	Selectivity factor, *s*
1	**4** (R = Me)	Toluene	+20	38.3	22.0	36	2.8
2	**4** (R = Me)	Toluene	0	49.0	23.7	33	3.7
3	**4** (R = Me)	Toluene	−20	51.3	17.8	26	3.7
4	**4** (R = Me)	Toluene	−40	68.4	7.2	10	5.8
5	**4** (R = Me)	CH_2Cl_2	+20	53.1	37.2	41	4.6
6	**4** (R = Me)	CH_2Cl_2	−20	63.3	41.5	40	6.6
7	**5** (R = Bn)	Toluene	+20	48.8	33.3	40	4.1
8	**5** (R = Bn)	Toluene	0	58.4	36.7	39	5.4
9	**5** (R = Bn)	Toluene	−20	68.9	33.3	32	7.6
10	**5** (R = Bn)	CH_2Cl_2	+20	67.1	56.9	46	8.9
11	**5** (R = Bn)	CH_2Cl_2	−20	74.4	60.4	45	12
12	**6** (R = Ph)	Toluene	+20	89.1	20.3	18	22
13	**6** (R = Ph)	Toluene	−20	91.9	12.5	12	21
14	**6** (R = Ph)	CH_2Cl_2	+20	80.0	25.6	24	12
15	**6** (R = Ph)	CH_2Cl_2	−20	89.6	16.2	15	22

[a] Determined by HPLC (see Section 4).
[b] Determined by chiral HPLC (see Section 4).

From these experiments one can conclude that *N*-phthaloyl-(*S*)-phenylalanyl chloride **5** is a better resolving agent for preparative kinetic resolution than acyl chlorides **4** and **6** and the kinetic resolution process should be carried out in CH_2Cl_2.

Acidic hydrolysis of individual (*S*,*S*)-amides **9–12** made it possible to obtain the (*S*)-enantiomers of amines **1** and **2** of high enantiomeric excess in good yields, as described previously for (*S*,*S*)-**7** and (*S*,*S*)-**8**.[20] Thus, refluxing (*S*,*S*)-**9** (de >99%) in a mixture of glacial AcOH and concentrated HCl for 12 h resulted in enantiomerically pure (*S*)-**1** (ee >99%) in 90% yield (Scheme 5). The overall yield of (*S*)-**1** from racemate was 23%.



Scheme 5. Preparation of (*S*)-**1** via kinetic resolution of racemate.

The preparation of (*S*)-**1** in enantiomerically pure form (ee >99% according to chiral HPLC) as a result of kinetic resolution of its racemate followed by acidic hydrolysis of (*S*,*S*)-**9** showed no racemization of the resolving acylating agent and/or amine during the chemical transformations.

3. Conclusion

In conclusion, the comparative study of the efficiency of kinetic resolution of racemic amines **1** and **2** with *N*-phthaloyl-(*S*)-amino acyl chlorides **4–6** as chiral acylating agents has been carried out. It has been found that *N*-phthaloyl-(*S*)-phenylalanyl **5** and *N*-phthaloyl-(*S*)-2-phenylglycyl **6** chlorides bearing aromatic substituents close to the chiral centre are more stereoselective acylating agents as compared with *N*-phthaloyl-(*S*)-alanyl chloride **4**. For the preparative kinetic resolution of racemic **1** and **2** acyl chloride **5** proved to be the most appropriate chiral acylating agent.

4. Experimental

4.1. General

N-Phthaloyl-(*S*)-alanine, *N*-phthaloyl-(*S*)-phenylalanine and *N*-phthaloyl-(*S*)-2-phenylglycine were obtained according to the known procedure.[27] (2*RS*)-2-Methyl-1,2,3,4-tetrahydroquinoline **1**,[28] (*R*)-**1**[18] and *N*-phthaloyl-(*S*)-alanyl chloride **4**[20] were synthesized as described previously. (3*RS*)-2,3-Dihydro-3-methyl-4*H*-1,4-benzoxazine **2** was prepared by analogy with the procedure.[29] The solvents were purified by standard methods. Melting points were obtained using a SMP3 apparatus (Barloworld Scientific, UK) and are uncorrected. Optical rotations were measured at a sodium D line with Perkin Elmer M 341 polarimeter. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 (400 and 100 MHz, respectively) spectrometer with TMS as the internal reference. ^{1}H and ^{13}C NMR spectra of amides **7–12** were recorded in DMSO-d_6 at 100 °C, ^{1}H NMR spectra of amines **1** and **2** and acid chlorides **4–6** were recorded in $CDCl_3$ at ambient temperature. All the signals in the ^{1}H and ^{13}C NMR spectra of (*S*,*S*)-**9** and (*R*,*S*)-**9** were assigned on the basis of 2D ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC and HMBC experiments at 100 °C. Elemental analyses were performed on a Perkin Elmer 2400 II instrument.

HPLC analyses of amides **7–10** and **12** were performed on Merck-Hitachi chromatograph with L-4000A Intelligent Pump, L-4000A UV Detector and D-2500A Chromato-Integrator using ReproSil 100 Si column (250 × 4.6 mm) for amides **8**, **9**, **12** and Finepak Sil column (250 × 4.6 mm) for amides **7** and **10**; detection at 220 nm, flow rate of 1 mL/min and hexanes/isopropanol as an eluting solvent. HPLC analyses of amide **11** were performed on Agilent 1100 chromatograph using Phenomenex Luna C18(2) column (250 × 4.6 mm), detection at 230 nm, flow rate of 0.8 mL/min and MeCN/water as an eluting solvent. HPLC analyses of amines **1** and **2** were performed on Knauer Smartline-1100 chromatograph using Chiralcel OD-H column (250 × 4.6 mm), detection at 220 nm, flow rate of 1 mL/min and hexanes/isopropanol 140:1 for **1** ($\tau_{(R)\text{-}\mathbf{1}}$ 11.2 and $\tau_{(S)\text{-}\mathbf{1}}$ 11.9 min) and 40:1 for **2** ($\tau_{(R)\text{-}\mathbf{1}}$ 15.1 and $\tau_{(S)\text{-}\mathbf{2}}$ 15.7 min) as eluting solvents.

Crystallographic data for (*S*,*S*)-amides **9–11** have been deposited with the Cambridge Crystallographic Data Centre (CCDC Nos. 770449–770451). 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 acid chlorides 4–6. General procedure[20]

Oxalyl chloride (3.5 mL, 40 mmol) was added dropwise to a stirred solution of *N*-phthaloyl-(*S*)-amino acid (20 mmol) and DMF (0.01 mL) in a benzene/hexanes 1:1 mixture (100 mL) at room temperature. The reaction mixture was stirred at room temperature for 8 h, evaporated to dryness under reduced pressure. The residue was treated with dry hexanes (20 mL) and the formed precipitate (in case of **4** and **5**) was filtered off and dried in vacuo.

4.2.1. *N*-Phthaloyl-(*S*)-alanyl chloride 4[20]

Colourless crystals (4.4 g, 93%): mp 55 °C. ^{1}H NMR ($CDCl_3$): δ 1.79 (d, J = 7.3 Hz, 3H, CH_3), 5.17 (q, J = 7.3 Hz, 1H, C^{2}H), 7.79 m and 7.92 m (4H, Phth). Anal. Calcd for $C_{11}H_8ClNO_3$: C, 56.00; H, 3.39; N, 5.89. Found: C, 55.70; H, 3.29; N, 5.94.

4.2.2. *N*-Phthaloyl-(*S*)-phenylalanyl chloride 5

Colourless crystals (5.46 g, 87%): mp 86 °C (lit.[30] mp 83–84 °C). ^{1}H NMR ($CDCl_3$): δ 3.55 (dd, J = 14.3 and 10.9 Hz, 1H, C^{3}H$_B$), 3.65 (dd, J = 14.3 and 5.2, 1H, C^{3}H$_A$), 5.33 (dd, J = 10.9 and 5.2 Hz, 1H, C^{2}H), 7.13–7.23 (m, 5H, Ph), 7.74 m and 7.83 m (4H, Phth). Anal. Calcd for $C_{17}H_{12}ClNO_3$: C, 65.08; H, 3.86; N, 4.46. Found: C, 65.10; H, 3.61; N, 4.42.

4.2.3. *N*-Phthaloyl-(*S*)-2-phenylglycyl chloride 6

Yellow oil (5.10 g, 85%). ^{1}H NMR ($CDCl_3$): δ 6.19 (s, 1H, C^{2}H), 7.38–7.43 (m, 3H, Ph), 7.57 (m, 2H, Ph), 7.77 m and 7.90 m (4H, Phth). Anal. Calcd for $C_{16}H_{10}ClNO_3$: C, 64.12; H, 3.36; N, 4.67. Found: C, 64.43; H, 3.30; N, 4.66.

4.3. General procedure for kinetic resolution of racemic amines 1 and 2 with *N*-phthaloyl-(*S*)-alanyl chloride 4 was described previously[20]

4.3.1. (2*S*)-2-Methyl-*N*-[*N*′-phthaloyl-(2′*S*)-alanyl]-1,2,3,4-tetrahydroquinoline (*S*,*S*)-7[20]

Colourless crystals: mp 230–231 °C. $[\alpha]_D^{20} = +461$ (c 1.45, benzene). De = >99.9% (HPLC: FinepakSil, hexanes/isopropanol 80:1; τ 21.3 min). Elemental analysis and ^{1}H NMR (DMSO-d_6, 100 °C) data are in good agreement with those published.[20] ^{13}C NMR (DMSO-d_6, 100 °C): δ 12.78, 19.32, 24.63, 31.43, 48.57, 48.66, 122.35, 124.49, 125.56, 126.13, 127.22, 131.07, 133.86, 134.97, 136.07, 168.76, 169.61.

4.3.2. (3*S*)-2,3-Dihydro-3-methyl-*N*-[*N*′-phthaloyl-(2′*S*)-alanyl]-4*H*-1,4-benzoxazine (*S*,*S*)-8[20]

Colourless crystals: mp 204–206 °C. $[\alpha]_D^{20} = +331$ (c 1.3, benzene). De = 100% (HPLC: ReproSil 100 Si, hexanes/isopropanol 80:1; τ 13.9 min). Elemental analysis and ^{1}H NMR (DMSO-d_6, 100 °C) data are in good agreement with those published.[20] ^{13}C NMR (DMSO-d_6, 100 °C): δ 13.91, 14.64, 45.31, 48.41, 69.36, 116.02, 119.78, 122.44, 122.92, 124.18, 125.46, 130.98, 133.93, 145.84, 167.20, 167.92.

4.4. General procedure for kinetic resolution of racemic amines 1 and 2 with *N*-phthaloyl-(*S*)-phenylalanyl chloride 5

A solution of **5** (0.32 g, 1 mmol) in CH_2Cl_2 (10 mL) was added to a stirred solution of racemic amine **1** or **2** (2 mmol) in CH_2Cl_2 (10 mL) at room temperature. After 6 h under stirring at room temperature the reaction mixture was washed with 1 N HCl (5 mL), water (3 × 5 mL), 5% $NaHCO_3$ (5 mL) and water (2 × 5 mL). Organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallized from a ethyl acetate/hexanes mixture to give (*S*,*S*)-amides **9** and **10**.

4.4.1. (2*S*)-2-Methyl-*N*-[*N*′-phthaloyl-(2′*S*)-phenylalanyl]-1,2,3,4-tetrahydroquinoline (*S*,*S*)-9

Colourless crystals (0.225 g, 53%): mp 186 °C. $[\alpha]_D^{20} = +364$ (c 1.0, $CHCl_3$). De = >99.9% (HPLC: ReproSil 100 Si, hexanes/isopropanol 80:1; τ 11.5 min). ^{1}H NMR (DMSO-d_6, 100 °C): δ 1.04 (d, J = 6.5 Hz, 3H, CH_3), 1.30 (dddd, J = 13.2, 10.6, 7.0 and 5.1 Hz, 1H, C^{3}H$_B$-quin.), 2.36 (dddd, J = 13.2, 7.8, 5.4 and 4.9 Hz, 1H, C^{3}H$_A$-quin.), 2.49 (ddd, J = 15.1, 10.6 and 5.4 Hz, 1H, C^{4}H$_B$-quin.), 2.64 (dd, J = 14.2 and 4.2 Hz, 1H, C^{3}H$_B$-Phe), 2.68 (dt, J = 15.1 and 5.0 Hz, 1H, C^{4}H$_A$-quin.), 3.71 (dd, J = 14.2 and 11.6 Hz, 1H, C^{3}H$_A$-Phe), 4.66 (ddq, J = 7.8, 7.0 and 6.5 Hz, 1H, C^{2}H-quin.), 5.77 (dd, J = 11.6 and 4.2 Hz, 1H, C^{2}H-Phe), 6.70 (dd, J = 7.8 and 1.8 Hz, 2H, H*o*), 7.08–6.99 (m, 3H, H*m* + H*p*), 7.28 (ddd, J = 7.5, 7.0 and 1.9 Hz, 1H, C^{6}H-quin.), 7.32 (dd, J = 7.5 and 2.0 Hz, 1H, C^{5}H-quin.), 7.40 (ddd, J = 7.8, 7.0 and 2.0 Hz, 1H, C^{7}H-quin.), 7.54 (dd, J = 7.8 and 1.0 Hz, 1H, C^{8}H-quin.), 7.81 (m, 4H, Phth). ^{13}C NMR (DMSO-d_6, 100 °C): δ 19.39 (CH_3-quin.), 24.82 (C^4-quin.), 31.35 (C^3-Phe), 31.56 (C^3-quin.), 48.80 (C^2-quin.), 54.64 (C^2-Phe), 122.44 (C$^{3\prime}$, C$^{6\prime}$), 124.68 (C^8-quin.), 125.84 (C^p), 125.86 (C^6-quin.), 126.22 (C^7-quin.), 127.42 (C^o), 127.45 (C^5-quin.), 127.61 (C^m), 130.63 (C$^{2a\prime}$, C$^{6a\prime}$), 134.00 (C$^{4\prime}$, C$^{5\prime}$), 135.48 (C^{4a}-quin.), 136.02 (C^{8a}-quin.), 136.56 (C^i), 166.87 (CONH), 167.42 (C$^{2\prime}$, C$^{7\prime}$). Anal. Calcd for $C_{27}H_{24}N_2O_3$: C, 76.39; H, 5.70; N, 6.60. Found: C, 76.20; H, 5.77; N, 6.66.

4.4.2. (3*S*)-2,3-Dihydro-3-methyl-*N*-[*N*′-phthaloyl-(2′*S*)-phenylalanyl]-4*H*-1,4-benzoxazine (*S*,*S*)-10

Colourless crystals (0.111 g, 26%): mp 168 °C. $[\alpha]_D^{20} = +341$ (c 1.0, $CHCl_3$). De = 99.4% (HPLC: FinepakSil, hexanes/isopropanol 80:1; τ 11.9 min). ^{1}H NMR (DMSO-d_6, 100 °C): δ 1.07 (d, J = 6.8 Hz, 3H, CH_3), 3.23 (dd, J = 14.0 and 5.6 Hz, 1H, C^{3}H$_B$-Phe), 3.73 (dd, J = 14.0 and 10.4 Hz, 1H, C^{3}H$_A$-Phe), 4.06 (dd, J = 11.0 and 3.2 Hz, 1H, C^{2}H$_B$-benz.), 4.18 (dd, J = 11.0 and 1.8 Hz, 1H, C^{2}H$_A$-benz.), 4.76 (qdd, J = 6.8, 3.2 and 1.8 Hz, 1H, C^{3}H-benz.), 5.76 (dd, J = 10.4 and 5.6 Hz, 1H, C^{2}H-Phe), 6.90 (dd, J = 8.1 and 1.5 Hz, 1H, C^{8}H-benz.), 6.97 (ddd, J = 8.1, 7.3 and 1.5, 1H, C^{6}H-benz.), 7.03 (d, J = 7.8 Hz, 2H, H*o*), 7.03–7.16 (m, 4H, H*m*, H*p*, C^{7}H-benz.), 7.72 (dd, J = 8.1 and 1.5 Hz, 1H, C^{5}H-benz.), 7.82 (s, 4H, Phth). ^{13}C NMR (DMSO-d_6, 100 °C): δ 14.52, 32.85, 45.27, 53.95, 69.41, 116.19, 119.79, 122.54, 122.86, 124.21, 125.75, 126.05, 127.70, 127.92, 130.56, 134.09, 136.31, 146.02, 166.52, 167.18. Anal. Calcd for $C_{26}H_{22}N_2O_4$: C, 73.23; H, 5.20; N, 6.57. Found: C, 72.84; H, 5.23; N, 6.50.

4.5. General procedure for kinetic resolution of racemic amines 1 and 2 with *N*-phthaloyl-(*S*)-2-phenylglycyl chloride 6

A solution of **6** (0.30 g, 1 mmol) in toluene (10 mL) was added to a stirred solution of racemic amine **1** or **2** (2 mmol) in toluene (10 mL) at room temperature. After 6 h under stirring at room temperature the reaction mixture was washed with 1 N HCl (5 mL), water (3 × 5 mL), 5% $NaHCO_3$ (5 mL) and water (2 × 5 mL). Organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was recrystallized from a ethyl acetate/hexanes mixture to give (*S*,*S*)-amides **11** and **12**.

4.5.1. (2*S*)-2-Methyl-*N*-[*N*′-phthaloyl-(2′*S*)-2-phenylglycyl]-1,2,3,4-tetrahydroquinoline (*S*,*S*)-11

Colourless crystals (0.123 g, 30%): mp 194–195 °C. $[\alpha]_D^{20} = +562$ (c 1.0, $CHCl_3$). De = 100% (HPLC: Phenomenex Luna C 18(2), MeCN/

H_2O 70:30; τ 13.6 min). ^{1}H NMR (DMSO-d_6, 100 °C): δ 0.94 (d, J = 6.4 Hz, 3H, CH_3), 1.26 (dddd, J = 13.0, 9.8, 6.7 and 5.5 Hz, 1H, C^3H_B-quin.), 2.16 (ddd, J = 15.0, 9.8 and 5.5 Hz, 1H, C^4H_B-quin.), 2.30 (ddt, J = 13.0, 7.4 and 5.5 Hz, 1H, C^3H_A-quin.), 2.42 (dt, J = 15.0 and 5.5 Hz, 1H, C^4H_A-quin.), 4.64 (m, 1H, C^2H-quin.), 6.60 (s, 1H, C^2H-Phg), 6.94 (d, J = 7.5 Hz, 1H, C^5H-quin.), 7.02 (ddd, J = 7.5, 7.3 and 1.2 Hz, 1H, C^6H-quin.), 7.11–7.22 (m, 6H, Ph, C^7H-quin.), 7.49 (d, J = 7.9 Hz, 1H, C^8H-quin.), 7.82 (m, 4H, Phth). ^{13}C NMR (DMSO-d_6): δ 19.98, 24.24, 31.19, 48.93, 56.53, 122.45, 124.77, 125.26, 125.68, 126.83, 126.93, 127.32, 129.25, 130.85, 131.87, 133.96, 134.68, 135.49, 166.04, 166.62. Anal. Calcd for $C_{26}H_{22}N_2O_3$: C, 76.08; H, 5.40; N, 6.82. Found: C, 75.76; H, 5.30; N, 6.73.

4.5.2. (3*S*)-2,3-Dihydro-3-methyl-*N*-[*N*′-phthaloyl-(2′*S*)-2-phenylglycyl]-4*H*-1,4-benzoxazine (*S*,*S*)-12

Colourless crystals (0.177 g, 43%): mp 178 °C. $[\alpha]_D^{20} = +228$ (c 1.0, $CHCl_3$). De = 97% (HPLC: ReproSil 100 Si, hexanes/isopropanol 80:1; τ 11.5 min). ^{1}H NMR (DMSO-d_6, 100 °C): δ 0.72 (d, J = 6.7 Hz, 3H, CH_3), 4.13 and 4.14 (ABX system, J_{AB} = 11.1 Hz, J_{BX} = 2.3 Hz, J_{AX} = 1.8 Hz, 2H, C^2H_2-benz.), 4.60 (qm, J = 6.7 Hz, 1H, C^3H-benz.), 6.60 (s, 1H, C^2H-Phg), 6.77 (dd, J = 8.1 and 1.5 Hz, 1H, C^8H-benz.), 6.87 (ddd, J = 8.2, 7.2 and 1.5 Hz, 1H, C^6H-benz.), 7.00 (ddd, J = 8.1, 7.2 and 1.5, 1H, C^7H-benz.), 7.27–7.31 (m, 3H, H*m* and H*p*), 7.48 (dd, J = 7.7 and 1.8 Hz, 2H, H*o*), 7.71 (dd, J = 8.2 and 1.5 Hz, 1H, C^5H-benz.), 7.83 (m, 4H, Phth). ^{13}C NMR (DMSO-d_6): δ 13.76, 45.85, 56.32, 69.29, 115.76, 119.49, 122.47, 122.53, 124.54, 125.29, 127.46, 127.78, 129.72, 130.80, 132.31, 134.05, 145.72, 165.33, 166.50. Anal. Calcd for $C_{25}H_{20}N_2O_4$: C, 72.80; H, 4.89; N, 6.79. Found: C, 72.75; H, 5.02; N, 6.51.

4.6. (*R*,*S*)-Amides 9–11

4.6.1. (2*R*)-2-Methyl-*N*-[*N*′-phthaloyl-(2′*S*)-phenylalanyl]-1,2,3,4-tetrahydroquinoline (*R*,*S*)-9

A solution of **5** (244 mg, 0.78 mmol) in CH_2Cl_2 (3 mL) was added to a solution of (*R*)-**1** (ee 98%; 115 mg, 0.78 mmol) and NEt_3 (109 μL, 0.78 mmol) in CH_2Cl_2 (4.8 mL). The reaction mixture was kept at +20 °C for 6 h, then washed with 1 N HCl (3 mL), brine (3 × 3 mL), 5% $NaHCO_3$ (3 mL) and water (2 × 3 mL). Organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by flash silica gel chromatography (eluent: hexanes/ethyl acetate) to give (*R*,*S*)-**9** (125 mg, 38%) as an amorphous solid. $[\alpha]_D^{20} = -360$ (c 0.8, $CHCl_3$). De = 96% (HPLC: ReproSil 100 Si, hexanes/isopropanol 80:1; τ 8.4 min). ^{1}H NMR (DMSO-d_6, 100 °C): δ 0.99 (d, J = 6.4 Hz, 3H, CH_3), 1.13 (m, 1H, C^3H_B-quin.), 2.16–2.35 (m, 3H, C^4H_2- and C^3H_A-quin.), 3.18 (dd, J = 13.9 and 9.7 Hz, 1H, C^3H_B-Phe), 3.55 (dd, J = 13.9 and 5.4 Hz, 1H, C^3H_A-Phe), 4.58 (m, 1H, C^2H-quin.), 5.49 (dd, J = 9.7 and 5.4 Hz, 1H, C^2H-Phe), 6.68 (d, J = 7.4 Hz, 1H, C^5H-quin.), 6.77 (dd, J = 7.4 and 7.5 Hz, 1.0, 1H, C^6H-quin.), 6.99 (dd, J = 7.5 and 7.6 Hz, 1H, C^7H-quin.), 7.03–7.10 (m, 5H, Ph-Phe), 7.19 (d, J = 7.6 Hz, 1H, C^8H-quin.), 7.54 (m, 2H, Phth), 7.67 (m, 2H, Phth), ^{13}C NMR (DMSO-d_6, 100 °C): δ 19.30 (CH_3-quin.), 24.15 (C^4-quin.), 31.19 (C^3-quin.), 35.07 (C^3-Phe), 48.79 (C^2-quin.), 52.18 (C^2-Phe), 121.93 ($C^{3\prime}$, $C^{6\prime}$), 124.13 (C^8-quin.), 124.52 (C^6-quin.), 125.62 (C^p), 126.22 (C^5-quin.), 126.36 (C^7-quin), 127.37 (C^m), 128.62 (C^o), 130.10 ($C^{2a\prime}$, $C^{6a\prime}$), 133.62 ($C^{4\prime}$, $C^{5\prime}$), 133.68 (C^{4a}-quin.), 135.82 (C^{8a}-quin.), 137.12 (C^i), 165.32 ($C^{2\prime}$, $C^{7\prime}$), 166.72 (CONH). Anal. Calcd for $C_{27}H_{24}N_2O_3$: C, 76.39; H, 5.70; N, 6.60. Found: C, 75.95; H, 5.47; N, 6.50.

4.6.2. (3*R*)-2,3-Dihydro-3-methyl-*N*-[*N*′-phthaloyl-(2′*S*)-phenylalanyl]-4*H*-1,4-benzoxazine (*R*,*S*)-10

This diastereoisomer was obtained by flash silica gel chromatography (eluent: benzene/ethyl acetate) of a diastereoisomeric mixture (*S*,*S*)-**9**/(*R*,*S*)-**9** 74:26 (195 mg) as a fast-eluting diastereoisomer. Colourless crystals (8 mg, 16%): mp 80–83 °C. $[\alpha]_D^{20} = -337$ (c 0.22, $CHCl_3$). De = 95% (HPLC: FinepakSil, hexanes/isopropanol 80:1; τ 9.2 min). ^{1}H NMR (DMSO-d_6, 100 °C): δ 0.88 (d, J = 6.8 Hz, 3H, CH_3), 3.29 (dd, J = 14.1 and 9.3 Hz, 1H, C^3H_B-Phe), 3.52 (dd, J = 14.1 and 5.6 Hz, 1H, C^3H_A-Phe), 4.08 (dd, J = 10.9 and 2.1 Hz, 1H, C^2H_B-benz.), 4.11 (dd, J = 10.9 and 3.1 Hz, 1H, C^2H_A-benz.), 4.54 (qdd, J = 6.8, 3.1 and 2.1 Hz, 1H, C^3H-benz.), 5.60 (dd, J = 9.3 and 5.6 Hz, 1H, C^2H-Phe), 6.60 (dd, J = 8.1 and 1.5 Hz, 1H, C^8H-benz.), 6.72 (ddd, J = 8.0, 7.4 and 1.5 Hz, 1H, C^6H-benz.), 6.83 (ddd, J = 8.1, 7.4 and 1.6, 1H, C^7H-benz.), 7.08–7.16 (m, 5H, Ph), 7.43 (dd, J = 8.0 and 1.6 Hz, 1H, C^5H-benz.), 7.66 (m, 2H, Phth), 7.73 (m, 2H, Phth). Anal. Calcd for $C_{26}H_{22}N_2O_4$: C, 73.23; H, 5.20; N, 6.57. Found: C, 73.18; H, 5.28; N, 6.37.

4.6.3. (2*R*)-2-Methyl-*N*-[*N*′-phthaloyl-(2′*S*)-2-phenylglycyl]-1,2,3,4-tetrahydroquinoline (*R*,*S*)-11

A solution of **6** (136 mg, 0.45 mmol) in CH_2Cl_2 (4.5 mL) was added to a solution of (*R*)-**1**, ee 91% (134 mg, 0.9 mmol) in CH_2Cl_2 (4.5 mL). The reaction mixture was kept at +20 °C for 6 h, then washed with 1 N HCl (3 mL), brine (3 × 3 mL), 5% $NaHCO_3$ (3 mL) and water (2 × 3 mL). Organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure. The residue was crystallized from hexanes/ethyl acetate to give (*R*,*S*)-**11** (110 mg, 59%). Colourless crystals: mp 235–237 °C (decomp.). $[\alpha]_D^{20} = -22.8$ (c 0.19, $CHCl_3$). De = 98% (HPLC: Phenomenex Luna C 18(2), MeCN/H_2O 70:30; τ 10.7 min). ^{1}H NMR (DMSO-d_6, 100 °C): δ 1.05 (d, J = 6.5 Hz, 3H, CH_3), 1.26 (m, 1H, C^3H_B-quin.), 2.16 (m, 2H, C^4H_B-quin), 2.30 (m, 1H, C^3H_A-quin.), 2.42 (m, 1H, C^4H_A-quin.), 4.64 (m, 1H, C^2H-quin.), 6.31 (s, 1H, C^2H-Phg), 6.84 (m, 1H, C^5H-quin.), 7.02 (m, 1H, C^6H-quin.), 7.29–7.42 (m, 6H, Ph and C^7H-quin.), 7.49 (m, 1H, C^8H-quin.), 7.73 (m, 2H, Phth), 7.79 (m, 2H, Phth). Anal. Calcd for $C_{26}H_{22}N_2O_3$: C, 76.08; H, 5.40; N, 6.82. Found: C, 75.68; H, 5.53; N, 6.88.

4.7. General procedure for studying the kinetic resolution

To a solution of amine **1** or **2** (0.3 mmol) in an appropriate solvent (1.5 mL) was added a solution of acyl chloride **4** (**5** or **6**) (0.15 mmol) in the same solvent (1.5 mL) at specified temperature. The reaction mixture was kept at the appropriate temperature for 6 h, then washed with 1 N HCl (3 mL), brine (3 × 3 mL), 5% $NaHCO_3$ (3 mL) and water (2 × 3 mL). In case of MeCN, 1 N HCl (3 mL) was added to the reaction mixture, then amides were extracted with benzene (3 × 3 mL). Organic layer was separated, dried over $MgSO_4$ and evaporated under reduced pressure to give a mixture of diastereoisomeric amides **7–12** which was analyzed by HPLC. Acidic washing solutions were collected and then alkalized with Na_2CO_3 up to pH 8–9, extracted with $CHCl_3$ (3 × 2 mL). Organic layers were separated, dried over $MgSO_4$ and evaporated under reduced pressure to give unreacted amines **1–2** which were analyzed by chiral HPLC.

4.8. (2*S*)-2-Methyl-1,2,3,4-tetrahydroquinoline (*S*)-1

To a solution of (*S*,*S*)-**9** (4.00 g, 9.42 mmol) in AcOH (40 mL) was added concentrated HCl (40 mL). The reaction mixture was heated at 110–115 °C for 12 h, then evaporated under reduced pressure. Water (250 mL) was added to the residue, the precipitate formed was filtered off. The filtrate was alkalized with Na_2CO_3 up to pH 8–9, extracted with benzene (3 × 50 mL). Organic layers were separated, dried over $MgSO_4$ and evaporated under reduced pressure to give (*S*)-**1** (1.25 g, 90%) as a yellowish oil. $[\alpha]_D^{20} = -85$ (c 1.5, benzene). {Lit.[31]: (*R*)-**1** $[\alpha]_D$ = +85 (c 2, benzene)}. Ee >99.0%. (HPLC: Chiralcel OD-H, hexanes/isopropanol 100:1; τ 11.64 min). Elemental analysis and ^{1}H NMR ($CDCl_3$) data are in good agreement with those published.[20]

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