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Highly efficient resolutions with isopropylidene glycerol 3-carboxy-2-naphthoate

Marco Pallavicini,* Cristiano Bolchi, Laura Fumagalli, Ermanno Valoti and Luigi Villa

Istituto di Chimica Farmaceutica e Tossicologica, Università di Milano, viale Abruzzi 42, I-20131 Milano, Italy

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Abstract—A number of chiral 1-arylethylamines and 1-alkylethylamines were resolved with the 3-carboxy-2-naphthoate of isopropylidene glycerol **2**, previously reported to be an even more efficient resolving agent for 1-phenylethylamine than the corresponding hemiphthalate **1**. The results obtained for the 1-arylethylamines confirm such a trend, revealing impressive resolution ability, in particular, for 1-(4-bromophenyl)-, 1-(4-nitrophenyl)- and 1-(2-naphthyl)ethylamine, whose enantiomers were almost quantitatively separated with (*S*)-**2** by a single precipitation of the less soluble (*S*,*S*) diastereomeric salt. Additionally, the success of the resolutions of 1-alkylethylamines (1-phenyl-2-propylamine, 1-cyclohexylethylamine and 2-butylamine), which could not be resolved with **1**, indicates that the novel carboxy ester **2** has a wider range of application than **1**.

1. Introduction

It was recently shown that isopropylidene glycerol 3-carboxy-2-naphthoate **2** resolves 1-phenylethylamine even more efficiently than the corresponding hydrogen phthalate **1**. Additionally it was found that **2** has more suitable properties for use as a resolving agent than **1**.[1] On the basis of these results, it seemed worthwhile to test its ability to resolve other racemic amines. Firstly, we selected 1-arylethylamines **3**–**6** (Fig. 1), which had previously been resolved with high efficiencies using **1**,[2] with the aim of confirming the further improvement of resolution ability. Secondly, we considered 1-alkylethylamines **7**–**9**, whose resolution with **1** was unsuccessful,[3] in order to verify the greater versatility of the new acid, in particular with respect to substrates harder to resolve than 1-arylethylamines.

2. Results

The results from the resolutions of **3**–**9** with (*S*)-**2** are summarized in Table 1, where the yields and the e.e.s are reported.

As with our preceding resolution of 1-phenylethylamine,[1] we decided to utilise the *S* enantiomer of **2** and to combine the latter with stoichiometric quantities of the racemic amines in methanol. In the case of 2-butylamine, the 2-propanol solvent was replaced with methanol and, for the recrystallization of the precipitate, ethanol was used due to the high solubility of the diastereomeric salts of this amine with (*S*)-**2** in methanol.

As shown in Table 1 (entry 1), treatment of **3** with equimolar (*S*)-**2** resulted in the near-quantitative precipitation of the (*S*,*S*) salt, which contained (*S*)-**3** with >99.5% e.e. and was so insoluble that its recrystallization was unfeasible, even when using large volumes of boiling methanol. Such an excellent resolution efficiency allowed the isolation of (*R*)-**3** with 94% e.e. from the (*S*,*R*) salt quantitatively recovered by simple concentration of the mother liquors (Table 1, entry 2). The enantiomeric excesses were accurately determined by reversed-phase chiral HPLC according to the procedure described previously for the resolution of the same amine with (*S*)-**1**.[2]

The resolution of 1-(4-nitrophenyl)ethylamine with (*S*)-**2** was also very efficient (Table 1, entries 3 and 4): precipitation of the (*S*,*S*) salt was immediate, quantitative and highly diastereoselective, allowing both the *S* and *R* enantiomers of the amine to be isolated, from the precipitate and the mother liquors respectively, with 93.1% and 97.2% e.e. In order to maximise their recovery from the respective salts with the resolving agent, we decided to isolate them as the neutral sulphate salts

* Corresponding author. E-mail: marco.pallavicini@unimi.it

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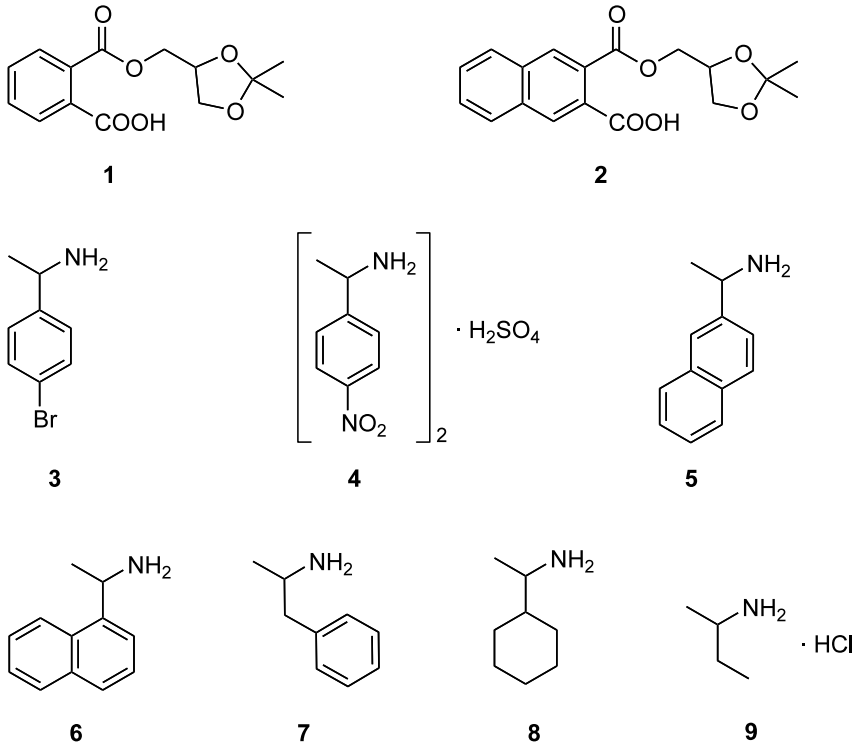

Figure 1.

Table 1. Resolutions of amines **3**–**9** by selective crystallization of the salts with (*S*)-**2** from methanol[a]

Entry	Compd.	Yield (%)[b]			E.e. (%)[c]		*E* (%)[d]
		Crude salt with (*S*)-**2**[e]	Recrystallized salt with (*S*)-**2**	Recovered substrate	Crude salt with (*S*)-**2**	Recrystallized salt with (S)-2	
1	(*S*)-**3**	90	–	80.5	>99.5	–	90
2	(*R*)-**3**	102.7	–	95.9	94.0	–	97
3	(*S*)-**4**	101.1	–	85.9	93.1[f]	–	94
4	(*R*)-**4**	96.7	–	86.9	97.2[g]	–	94
5	(*S*)-**5**	98.1	80.5	78.9	91.6	97.6	90
6	(*R*)-**5**	97.1	–	88.6	94.4	–	92
7	(*R*)-**6**	46.9	–	44.2	97.0	–	45
8	(*S*)-**7**	77.1	–	70.2	78.0	–	60
9	(*S*)-**8**	61.7	–	61.0	94.1	–	58
10	(*S*)-**9**	88.4	27.3	26.2	43.5	77.9	38

[a] The crude salt of (*S*)-2-butylamine with (*S*)-**2** (entry 10) was precipitated from 2-propanol and recrystallized from ethanol.
[b] Relative to the theoretical amount, i.e. half of the starting racemate.
[c] Enantiomeric excess (determined by HPLC) of the amine liberated from the salt.
[d] Experimental resolution efficiency calculated from the yield of the crude diastereomeric salt and the enantiomeric excess of the amine liberated from the salt.
[e] Precipitated from the solution containing equivalent amounts of racemic amine and (*S*)-**2** or, in the case of (*R*)-**3**, (*R*)-**4** and (*R*)-**5** (entries 2, 4 and 6), recovered by concentration of the methanolic solution remaining from the isolation of the crude salt of (*S*)-**2** with the respective *S* amine.
[f] 97.3% after conversion into the neutral sulphate salt.
[g] 98.9% after conversion into the neutral sulphate salt.

by extraction with equivalent amounts of dilute aqueous sulphuric acid. The concentration of the aqueous extracts gave crude (*S*)-**4** and (*R*)-**4**. Successive treatment with boiling ethanol further enhanced their enantiomeric excesses to 97.3 and 98.9%, respectively, with minimal reduction of yield. Analytical determinations of the enantiomeric compositions were successfully accomplished by HPLC on Crownpack chiral stationary phase achieving a sensibly higher accuracy than by the previously reported NMR method in the presence of $Eu(hfc)_3$.[2]

The resolution of **5** (Table 1, entries 5 and 6) resembled those of **3** and 1-(4-nitrophenyl)ethylamine leading to

the quantitative precipitation of the (*S*,*S*) salt with >91% e.e. Consequently, the (*S*,*R*) salt was obtained from the mother liquor in analogous chemical yield and diastereomeric purity. Again, recrystallization of the highly insoluble crude (*S*,*S*) diastereomeric salt was unfeasible. Nevertheless, the enantiomeric excess of the *S* amine could be further improved by prolonged trituration with boiling methanol.

The opposite stereochemical outcome was observed for the resolution of amine **6**, which was successful, but not as efficient as those of substrates **3**–**5** (Table 1, entry 7). In fact, (*R*)-**6** was recovered with very high enantiomeric excess (97%) from the crude (*S*)-**2**·(*R*)-**6** precipitate, which, however, separated in a moderate 47% yield. The use of smaller volumes of methanol led to lower resolution efficiency, indicating that the initially adopted solvent/salt ratio (4.9 ml/g) could be considered nearly optimal. On the other hand, alternative crystallizations effected in ethanol or 2-propanol showed a modest diastereoselectivity.

Amines **7** and **8** were resolved by (*S*)-**2** with 60 and 58% efficiency, respectively (Table 1, entries 8 and 9). The enantiomeric excesses of the *S* isomers liberated from the precipitates were determined by chiral HPLC after conversion into the benzamide derivatives.

Finally, crystallization of the diastereomeric salts of 2-butylamine with (*S*)-**2** were performed in 2-propanol and ethanol, due to their high solubility in methanol (Table 1, entry 10). After the recrystallization, the *S* amine was isolated from the salt with (*S*)-**2** as the hydrochloride salt (*S*)-**9** with 77.9% e.e. (as determined by chiral HPLC analysis of the benzamide) and in 26% yield.

Some of these experiments were performed using recycled resolving agents recovered in nearly quantitative yield and with unaltered chemical and enantiomeric purity from the precipitates and the mother liquors of previous resolutions.

3. Discussion and conclusion

As previously described, replacement of the phenyl group of **1** with a naphthyl moiety led to the new acid, carboxy naphthoate **2**, which resolved 1-phenylethylamines with very high efficiency. Such a trend is confirmed by the results from the resolutions of 1-arylethylamines **3**–**6** with (*S*)-**2** reported herein. In particular, amines **3**–**5** were all resolved with efficiencies higher than 90%, while, in the corresponding resolutions with **1**, the efficiencies were ca.70% for **3** and **4**, and 50% for **5**.[4] The same comparison is in favour of **2** for the resolution of **6** (45% versus 23%),[5] which is significantly less efficient with both resolving agents. Moreover, in contrast to the hemiphthalate **1**, the carboxynaphthoate **2** was able to resolve the structurally heterogeneous 1-alkylethylamines **7**–**9**. The efficiencies of the resolutions of **7** and **8**, 60 and 58%, respectively, with **2** can be appreciated considering that other acids, like the dipeptide (*R*)-phenylglycyl-(*R*)-phenylglycine[6] or 2-naphthylglycolic acid,[7] resolve the same amines with much lower efficiency than 1-arylethylamines. This indicates that 1-alkylethylamines are a more severe challenge for such resolving agents than 1-arylethylamines, which is probably due to the absence or different position of the aromatic residue. In particular, the resolution of 2-butylamine **9** further substantiates the greater versatility of **2**, because the enantiomers of **9** are particularly difficult to separate via diastereomeric salt formation, as demonstrated by the limited number of reported procedures.

In summary, we have shown that **2** resolves (a) some 1-arylethylamines with extraordinary efficiency, effecting quantitative separation of the two enantiomers by a single precipitation of the less soluble diastereomeric salt, and (b) some 1-alkylethylamines with lower, but always workable efficiency. On the basis of these results, superior resolving power and improved range of application can be attributed to the novel acid **2**, compared with the parent hemiphthalate **1**.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on a Varian Gemini 300 (300 MHz) instrument. Melting points were recorded on a Büchi Melting Point B-450 apparatus and are uncorrected. Optical rotations were measured in a 1-dm cell of 1 ml capacity using a Perkin Elmer 241 polarimeter. HPLC analyses were performed on Chiralcel and Crownpack columns from Daicel using a Waters 510 pump, a Hitachi L-7400 UV detector and a Hitachi D-7000 HPLC System Manager software.

Starting materials: The resolving agent (*S*)-**2** was prepared from (*R*)-isopropylidene glycerol and 2,3-naphthalic anhydride, as previously reported.[1] (*RS*)-**6** and (*RS*)-2-butylamine were obtained from commercial suppliers. (*RS*)-**7** was synthesized from racemic 1-phenyl-2-propanol by tosylation, conversion to the azide and reduction. (*RS*)-**3**, (*RS*)-**5** and (*RS*)-**8** were synthesized by the Leuckart reaction from the corresponding ketones according to the experimental procedure described for 1-phenylethylamine.[8] (*RS*)-1-(4-Nitrophenyl)ethylamine was prepared from acetophenone by the method previously reported.[9]

4.2. (*S*)-1-(4-Bromophenyl)ethylamine, (*S*)-3

The acid (*S*)-**2** (14.36 g, 43.5 mmol) and (*RS*)-**3** (8.7 g, 43.5 mmol) were combined in methanol (230 ml). A white precipitate immediately separated. The suspension was heated to boiling temperature for 10 min and then cooled to 25°C and filtered. The isolated solid was rinsed with methanol twice and dried to give (*S*)-**2**·(*S*)-**3** salt (10.38 g, 90%): mp 171.5–172.5°C; e.e. of (*S*)-**3** >99.5% (determined by HPLC of the amine liberated from a sample of the salt on a Chiralcel OD-R column; 85/15 1 M $NaClO_4$/CH_3CN, 0.8 ml/min); ^{1}H NMR

(DMSO-d_6) δ 1.28 (s, 3H), 1.33 (s, 3H), 1.37 (d, 3H), 3.82 (dd, 1H), 4.06 (pseudo t, 1H), 4.19 (q, 1H), 4.24 (d, 2H), 4.36 (m, 1H), 7.39 (d, 2H), 7.52 (d, 2H), 7.58–7.62 (m, 2H), 7.98–8.05 (m, 3H), 8.28 (s, 1H). The salt was decomposed by treatment with 2N H_2SO_4 and ethyl acetate. The aqueous phase was separated, made alkaline with NaOH and extracted with dichloromethane. Removal of the solvent from the extract, previously dried over Na_2SO_4, gave a colourless oil, which was distilled under vacuum yielding (*S*)-**3** (3.50 g, 81%) as a pale yellow oil: $[\alpha]_D^{20} = -21.0$ (*c* 2.8, methanol); the e.e. was identical to that previously determined for the amine liberated from a sample of the salt with (*S*)-**2**; ^{1}H NMR ($CDCl_3$) δ 1.35 (d, 3H), 1.47 (bs, 2H), 4.09 (q, 1H), 7.22 (d, 2H), 7.44 (d, 2H).

4.3. (*R*)-1-(4-Bromophenyl)ethylamine, (*R*)-3

The methanolic filtrate resulting from the isolation of (*S*)-**2**·(*S*)-**3** was concentrated to afford (*S*)-**2**·(*R*)-**3** (11.84 g, 103%). The salt was decomposed in the same way as reported for (*S*)-**2**·(*S*)-**3** and the resultant crude amine distilled under vacuum yielding (*R*)-**3** (4.17 g, 96%): $[\alpha]_D^{20} = +18.2$ (*c* 2.5, methanol); e.e.: 94.0% (determined by HPLC under the same conditions as described for (*S*)-**3**); ^{1}H NMR identical to (*S*)-**3**.

4.4. (*S*)-1-(4-Nitrophenyl)ethylamine sulphate, (*S*)-4

The acid (*S*)-**2** (15.27 g, 46.2 mmol) and (*RS*)-1-(4-nitrophenyl)ethylamine (7.68 g, 46.2 mmol) were combined in methanol (280 ml). A white precipitate immediately separated. The suspension was heated to boiling temperature for 10 min and then cooled to 28°C and filtered. The isolated solid was rinsed with methanol twice and dried to give the salt of (*S*)-1-(4-nitrophenyl)ethylamine with (*S*)-**2** (11.6 g, 101%): mp 173–174°C; the e.e. of the amine liberated from a sample of the salt was 93.1% (by HPLC on a Crownpack CR(+) column; pH 1.5 $HClO_4$ aq., 0.6 ml/min); ^{1}H NMR (CD_3OD+D_2O) δ 1.34 (s, 3H), 1.40 (s, 3H), 1.62 (d, 3H), 3.94 (dd, 1H), 4.17 (q, 1H), 4.25–4.40 (m, 2H), 4.46 (m, 1H), 4.55 (q, 1H), 7.58 (m, 2H), 7.68 (d, 2H), 7.93 (m, 2H), 8.06 (s, 1H), 8.23 (s, 1H), 8.29 (d, 2H). The salt was decomposed by treatment with 1N H_2SO_4 (23.3 ml), water (30 ml) and ethyl acetate (50 ml). The aqueous phase was separated, washed with ethyl acetate twice and concentrated. The resultant solid residue was dried, refluxed with ethanol (60 ml), cooled to 5°C, and filtered to give (*S*)-**4** (4.25 g, 86%) as a white solid: mp 198°C; $[\alpha]_D^{20} = -6.9$ (*c* 1.07, 0.05 M NaOH); e.e.: 97.3% (determined by HPLC as described for the amine liberated from a sample of the salt with (*S*)-**2**); ^{1}H NMR (D_2O) δ 1.50 (d, 3H), 4.50 (q, 1H), 7.50 (d, 2H), 8.10 (d, 2H).

4.5. (*R*)-1-(4-Nitrophenyl)ethylamine sulphate, (*R*)-4

The methanolic solution remaining from the isolation of the salt of (*S*)-**2** with (*S*)-1-(4-nitrophenyl)ethylamine was concentrated to afford the salt of (*R*)-1-(4-nitrophenyl)ethylamine with (*S*)-**2** (11.1 g, 97%): e.e. of the *R* amine: 97.2% (by HPLC on a Crownpack CR(+) column; pH 1.5 $HClO_4$ aq., 0.6 ml/min). The salt was decomposed by treatment with 1N H_2SO_4 (22.4 ml), water (30 ml) and ethyl acetate (50 ml). The aqueous phase was separated, washed with ethyl acetate twice and concentrated. The resultant solid residue was dried, refluxed with ethanol (60 ml), cooled to 5°C, and filtered to give (*R*)-**4** (4.3 g; 87%) as a white solid: mp 198°C; $[\alpha]_D^{20} = +6.6$ (*c* 1.07, 0.05 M NaOH); e.e.: 98.9% (determined by HPLC as described for the amine liberated from a sample of the salt with (*S*)-**2**); ^{1}H NMR identical to (*S*)-**4**.

4.6. (*S*)-1-(2-Naphthyl)ethylamine, (*S*)-5

The acid (*S*)-**2** (27 g, 81.7 mmol) and (*RS*)-**5** (14 g, 81.7 mmol) were combined in methanol (270 ml). The white precipitate (20.11 g) was collected by filtration, rinsed with methanol, dried, and refluxed with methanol (200 ml) for 5 h. After cooling to 35°C, (*S*)-**2**·(*S*)-**5** salt (16.5 g, 81%) was isolated by filtration and rinsed with methanol: mp 150.5–151.5°C; e.e. of (*S*)-**5**: 97.6% (92% before the treatment with boiling methanol) (determined by HPLC of the amine liberated from the salts on a Chiralcel OD-R column; 60/40 0.1 M $NaClO_4$/CH_3CN, 0.5 ml/min); ^{1}H NMR (DMSO-d_6) δ 1.25 (s, 3H), 1.32 (s, 3H), 1.55 (d, 3H), 3.80 (dd, 1H), 4.02 (pseudo t, 1H), 4.21 (d, 2H), 4.33 (m, 1H), 4.46 (q, 1H), 7.45–7.70 (m, 5H), 7.85–8.05 (m, 7H), 8.27 (s, 1H). The salt was decomposed by treatment with 2N H_2SO_4 and ethyl acetate. The aqueous phase was separated, made alkaline with NaOH, and extracted with ethyl acetate. Removal of the solvent from the extract, previously dried over Na_2SO_4 gave (*S*)-**5** (5.52 g; 79%): $[\alpha]_D^{25} = -20.5$ (*c* 2.5, ethanol); the e.e. was identical to that previously determined for the amine liberated from a sample of the salt with (*S*)-**2**; ^{1}H NMR ($CDCl_3$) δ 1.48 (d. 3H), 1.58 (bs, 2H), 4.28 (q, 1H), 7.48 (m, 3H), 7.80 (m, 4H).

4.7. (*R*)-1-(2-Naphthyl)ethylamine, (*R*)-5

The methanolic filtrate resulting from the isolation of the first precipitate of (*S*)-**2**·(*S*)-**5** (20.11 g) was concentrated to afford the salt of (*R*)-**5** with (*S*)-**2** (19.91 g, 97%): e.e. of (*R*)-**5**: 94.4% (determined by HPLC of the amine liberated from a sample of the salt under the analytical conditions described for (*S*)-**5**). The salt was decomposed in the same way as reported above for (*S*)-**2**·(*S*)-**5** salt yielding (*R*)-**5** (6.2 g, 88.6%): $[\alpha]_D^{25} = +19.9$ (*c* 2.5, ethanol); the e.e. was identical to that previously determined for the amine liberated from a sample of the salt with (*S*)-**2**; ^{1}H NMR identical to (*S*)-**5**.

4.8. (*R*)-1-(1-Naphthyl)ethylamine, (*R*)-6

The acid (*S*)-**2** (14.9 g, 45 mmol) and (*RS*)-**6** (7.7 g, 45 mmol) were combined in methanol (110 ml) at room temperature. The white precipitate of (*S*)-**2**·(*R*)-**6** salt (5.3 g, 47%) was collected by filtration and rinsed with cold methanol: mp 135–136°C; e.e. of (*R*)-**6**: 97.0% (determined by HPLC of the amine liberated from a sample of the salt on a Chiralcel OD-R column; 60/40

0.1 M $NaClO_4/CH_3CN$, 0.5 ml/min); ^1H NMR (DMSO-d_6) δ 1.22 (s, 3H), 1.30 (s, 3H), 1.60 (d, 3H), 3.82 (dd, 1H), 4.02 (pseudo t, 1H), 4.20 (d, 2H), 4.33 (m, 1H), 5.20 (q, 1H), 7.44 (m, 5H), 7.82 (d, 1H), 7.88 (d, 1H), 7.97 (m, 4H), 8.13 (d, 1H), 8.28 (s, 1H). The salt was decomposed by treatment with 2N H_2SO_4 and ethyl acetate. The aqueous phase was separated, made alkaline with NaOH and extracted with ethyl acetate. Removal of the solvent from the extract, previously dried over Na_2SO_4, gave an oil, which was distilled under vacuum yielding (*R*)-**6** (1.70 g, 44%): $[\alpha]_D^{20}=+53.5$ (*c* 2, ethanol); the e.e. was identical to that previously determined for the amine liberated from a sample of the salt with (*S*)-**2**; ^1H NMR ($CDCl_3$) δ 1.58 (d, 3H), 1.72 (bs, 2H), 4.97 (q, 1H), 7.50 (m, 3H), 7.67 (d, 1H), 7.76 (d, 1H), 7.89 (d, 1H), 8.13 (d, 1H).

4.9. (*S*)-1-Phenyl-2-propylamine, (*S*)-7

The acid (*S*)-**2** (5.01 g, 15.2 mmol) and (*RS*)-**7** (2.05 g, 15.2 mmol) were combined in methanol (20 ml) at room temperature. After cooling to 5°C, the white precipitate of (*S*)-**2**·(*S*)-**7** salt (2.72 g, 77%) was collected by filtration and rinsed with cold methanol: mp 141–142°C; e.e. of (*S*)-**7**: 78.0% (determined by HPLC of the corresponding benzamide on a Chiralcel-OB column, hexane/2-propanol 9/1, 2 ml/min); ^1H NMR (DMSO-d_6) δ 1.08 (d, 3H), 1.24 (s, 3H), 1.30 (s, 3H), 2.62 (dd, 1H), 3.08 (dd, 1H), 3.37 (m, 1H), 3.80 (dd, 1H), 4.02 (pseudo t, 1H), 4.20 (d, 2H), 4.33 (m, 1H), 7.15–7.35 (m, 5H), 7.55 (m, 2H), 7.90–8.02 (m, 3H), 8.25 (s, 1H). The salt was decomposed by treatment with 2N H_2SO_4 and ethyl acetate. The aqueous phase was separated, made alkaline with NaOH, and extracted with dichloromethane. Removal of the solvent from the extract, previously dried over Na_2SO_4, gave a colourless oil, which was distilled under vacuum yielding (*S*)-**7** (0.72 g, 70%): $[\alpha]_D^{21}=+25.4$ (*c* 2.85, methanol); $[\alpha]_D^{20}=+30.5$ (*c* 1.8, benzene); the e.e. was identical to that previously determined for the amine liberated from a sample of the salt with (*S*)-**2** and benzoylated; ^1H NMR ($CDCl_3$) δ 1.11 (d, 3H), 1.25 (bs, 2H), 2.50 (dd, 1H), 2.72 (dd, 1H), 3.16 (m, 1H), 7.15–7.33 (m, 5H).

4.10. (*S*)-1-Cyclohexylethylamine, (*S*)-8

The acid (*S*)-**2** (19.33 g, 58.5 mmol) and (*RS*)-**8** (7.44 g, 58.5 mmol) were combined in methanol (70 ml) at room temperature. After cooling to 5°C, the white precipitate of (*S*)-**2**·(*S*)-**8** salt (8.26 g, 62%) was collected by filtration and rinsed with cold methanol: mp 146–147°C; e.e. of (*S*)-**8**: 94.1% (determined by HPLC of the corresponding benzamide on a Chiralcel-OD column; hexane/2-propanol 9/1, 0.7 ml/min); ^1H NMR (DMSO-d_6) δ 0.85–1.80 (m, 11H), 1.10 (d, 3H), 1.28 (s, 3H), 1.33 (s, 3H), 2.94 (m, 1H), 3.82 (pseudo t, 1H), 4.04 (pseudo t, 1H), 4.20 (d, 2H), 4.37 (m, 1H), 7.52 (m, 2H), 7.85–8.0 (m, 3H), 8.22 (s, 1H). The salt was decomposed by treatment with 10% HCl and ethyl acetate. The aqueous phase was separated, made alkaline with NaOH, and extracted with dichloromethane. Removal of the solvent from the extract, previously dried over Na_2SO_4, gave a colourless oil, which was distilled under vacuum yielding (*S*)-**8** (2.27 g, 61.0%): $[\alpha]_D^{20}=+3.8$ (neat); the e.e. was identical to that previously determined for the amine liberated from a sample of the salt with (*S*)-**2** and benzoylated; ^1H NMR ($CDCl_3$) δ 0.80–1.25 (m, 8 H), 0.98 (d, 3H), 1.55–1.78 (m, 5H), 2.60 (m, 1H). The filtrate from the crystallization of (*S*)-**2**·(*S*)-**8** was concentrated and the residual salt decomposed in the same way as described for (*S*)-**2**·(*S*)-**8** to afford the *R*-enriched amine (5.0 g): $[\alpha]_D^{20}=-1.4$ (neat); e.e.: 42.0% (determined by HPLC of the corresponding benzamide).

4.11. (*S*)-2-Butylamine hydrochloride, (*S*)-9

The acid (*S*)-**2** (13.8 g, 41.8 mmol) and (*RS*)-2-butylamine (3.06 g, 41.8 mmol) were combined in 2-propanol (50 ml) at room temperature. The white precipitate (7.28 g) was collected by filtration, rinsed with cold 2-propanol, dried, and recrystallized from ethanol (7 ml) at 0°C yielding the salt of (*S*)-2-butylamine with (*S*)-**2** (2.3 g, 27%): mp 106–107°C; e.e. of (*S*)-2-butylamine: 77.9% (43.5% before the recrystallization) (determined by HPLC of the corresponding benzamides on a Chiralcel OB column; hexane/2-propanol 95/5, 1.2 ml/min); ^1H NMR (DMSO-d_6) δ 0.88 (t, 3H), 1.17 (d, 3H), 1.28 (s, 3H), 1.33 (s, 3H), 1.45 (m, 1H), 1.64 (m, 1H), 3.05 (m, 1H), 3.82 (pseudo t, 1H), 4.04 (pseudo t, 1H), 4.19 (d, 2H), 4.36 (m, 1H), 7.52 (m, 2H), 7.85–8.0 (m, 3H), 8.21 (s, 1H). The salt was decomposed by treatment with 10% HCl and ethyl acetate. The aqueous phase was separated, washed with ethyl acetate, and concentrated to give (*S*)-**9** (0.60 g, 26%) as a white solid: mp 145–147°C; $[\alpha]_D^{37}=-2.6$ (*c* 1, ethanol); the e.e. was identical to that previously determined for the benzamide of the amine liberated from a sample of the recrystallized salt with (*S*)-**2**; ^1H NMR (DMSO-d_6) δ 0.86 (t, 3H), 1.15 (d, 3H), 1.45 (m, 1H), 1.62 (m, 1H), 3.01 (m, 1H), 8.12 (bs, 3H).

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4. The experimental efficiencies of the resolutions with (*S*)-**1** are calculated from the chemical yields and the enantiomeric excesses reported in Ref. 2 for the same substrates. In the case of **5**, the comparison is made with the resolution with (*S*)-**1** in 2-propanol, because no precipitation occurred in methanol.
5. The 23% value is calculated from the chemical yield and the enantiomeric excess reported in Ref. 2 for the resolution with (*S*)-**1** in methanol. In the same reference, the resolution of **6** with (*S*)-**1** in 2-propanol is described and its efficiency is about 67%.

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