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The Dutch Resolution Variant of the Classical Resolution of Racemates by Formation of Diastereomeric Salts: Family Behaviour in Nucleation Inhibition

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Abstract: The resolution of racemates through their diastereomeric salts can be positively affected by the addition of small amounts of suitable nucleation inhibitors. This discovery is a logical extension of "Dutch Resolution", in which equimolar amounts of resolving agents that are members of the same family (i.e., structurally related) are used. We conducted a systematic search for nucleation inhibitors of the resolving agent 1-phenylethylamine. A wide range of amines that bear possible family resemblances to 1-phenylethylamine was investigated. It was found that (*R*)-1-phenylbutylamine is a good inhibitor of (*R*)-1-phenylethylamine. Results of turbidity measurements showed that, for the model case of mandelic acid resolution, the chief effect of this inhibitor was to widen the metastable zone for the more soluble diastereomer. This observation is in accordance with previous experience. Further scouting for possible family members revealed a wide variation in the effectiveness of inhibitors, dependent on their structure. By far the most effective inhibitors are bifunctional 1-phenylethylamine and/or 1-phenylbutylamine analogues. The effect of racemic inhibitors was found to approach that of enantiomerically pure inhibitors of the same absolute configuration of the 1-phenylethylamine used for resolution. The most effective inhibitors were tested for the resolution of a structural variety of racemates, and were shown to be broadly applicable.

Keywords: chiral resolution · chirality · crystal growth · diastereoselectivity · enantioselectivity

Introduction

"Dutch Resolution" is the use of families of resolving agents in the otherwise classical Pasteur separation of racemates through their diastereomeric salts.[1,2] As first described an equimolar mixture of, in general, three resolving agents of the same family (i.e., with close structural analogy, common absolute stereochemistry) was used. Non-stoichiometric incorporation of resolving agents and often improved diastereomeric excesses of the first salts were observed.

Further investigations revealed that certain family members of resolving agents failed to be, or were only slightly, incorporated into the salts, although they had a positive effect on the resolution.[3] An example is the *ortho*/*para*-nitro mixture (*R*)-**2b** and the classical resolving agent 1-phenylethylamine (*R*)-**2a**, as illustrated for the case of the resolution of mandelic acid (**1**) in Scheme 1. On the basis of turbidity measurements, it was shown that **2b** is an effective nucleation inhibitor. It is not detectably incorporated into the less soluble salt, which is obtained in significantly higher diastereomeric excess in the presence of **2b** (55% *de* compared to 14% *de* without inhibitor under the experimental conditions used). Inhibitor **2b** acts by widening the width of the metastable zone of supersaturation (the temperature zone between dissolution and the lower temperature at

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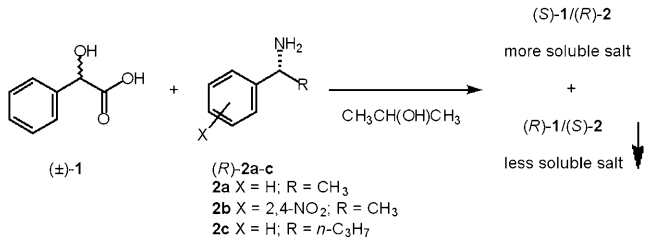


Scheme 1. Resolution of mandelic acid (**1**) with (*R*)-1-phenylethylamine **2a**: additives are (*R*)-**2b** and (*R*)-**2c**.

which precipitation begins) to a greater extent for the more soluble diastereomer than for the less soluble diastereomer. This results in, with correct temperature control, more opportunities for selective precipitation of the less soluble diastereomeric salt.[4a–c]

The use of a single resolving agent with a small amount of additive (nucleation inhibitor) instead of a mixture is technologically simpler, but how can nucleation inhibitors in the context of Dutch Resolution be identified? Here, we describe some guidelines derived from the study of amines, and indicate how these can be applied.

Results and Discussion

The model system that was used for scanning is that shown in Scheme 1, and the primary goal was to search as quickly as possible for nucleation inhibitors among other potential "family members" related to the parent resolving agent **2a**. We first looked at analogues of resolving agent **2a**, in which the side-chain rather than the aryl ring is modified structurally. In orientational experiments, it was observed that readily available[5] (in both enantiomeric forms) 1-phenylbutylamine (*R*)-**2c** induced significant improvements if used as an additive with (*R*)-**2a**. Notably, no (*R*)-**2c** can be detected in the precipitated salt. Yields and *de* values are shown in Table 1.[6] Diastereomerically pure salts cannot be obtained in more than 50% yield. We prefer the use of Fogassy S-factors ($2 \times \text{yield} \times de$) to express the overall efficiencies.[7] Scanning of **2a**/**2c** ratios revealed that the optimal concentration for nucleation inhibition was 6 mol% of **2c** (see Supporting Information).

Rather unexpectedly, it was observed that racemic **2c** is also nearly as effective as (*R*)-**2c** (Table 1, entry 3) and that the "wrong" enantiomer, (*S*)-**2c**, also has some positive effect (entry 4). Notably, (*R*)-**2c** alone is *not* a resolving agent for **1** (entry 5). The yield, *de* and S-factor of the reaction corresponding to entry 2, performed on a 10 g (65.8 mmol) scale, were within 1% of the results obtained on the 2 mmol scale reported in Table 1.

Table 1. Resolution of (±)-**1**[a] with (*R*)-**2a** in the absence and presence of 6 mol% **2c**.

Entry	Resolving agent	Additive	Yield [%]	*de* [%]	S-factor
1	(*R*)-**2a**	–	68	14	0.19
2	(*R*)-**2a**	(*R*)-**2c**	60	42	0.50
3	(*R*)-**2a**	(±)-**2c**	62	35	0.43
4	(*R*)-**2a**	(*S*)-**2c**	61	30	0.37
5	(*R*)-**2c**	–	no salts precipitate		

[a] Concentration = 0.40 mmol mL^{-1} in $CH_3CH(OH)CH_3$.

Turbidity measurements (see Supporting Information) revealed that, for (*R*)-**2c**, analogously to **2b**, the metastable zone width for the more soluble (*S*)-**1**/(*R*)-**2a** diastereomeric salt is increased from 7.3°C without inhibitor to 28.5°C (zone width 25.3°C for racemic **2c** and 13.0°C for (*S*)-**2c**), whereas for the less soluble (*R*)-**1**/(*R*)-**2a** diastereomeric salt, the zone width increases from 3.9°C without inhibitor to only 7.0°C (5.9°C for racemic **2c** and 7.0°C for (*S*)-**2c**). The conclusion is clear: **2c**, of the same relative configuration as resolving agent **2a**, is an effective nucleation inhibitor that affects chiefly the more soluble diastereomeric salt by increasing the metastable temperature zone width; the more soluble diastereomer remains in solution for a longer period of time.[4c] An analogous effect is observed in slightly diminished form for racemic **2c**, and relatively weakly for the "wrong" (*S*) enantiomer of **2c**.

Although **2c** is clearly an inhibitor, it seems unlikely that every small change in the structure of a resolving agent will result in a nucleation inhibitor. Are there predictable structural considerations and, if so, what are they? To examine further the effects of substitution in the aryl ring, the compounds **3**–**25** (all enantiomerically pure (*R*)) shown in Figure 1 were investigated as inhibitors for the resolution of mandelic acid (**1**) by 1-phenylethylamine (**2a**), as depicted in Scheme 1.[8] All experiments were performed in triplicate and the values of the S-factors are reproducible to within (±) 5%. If a "hit" is arbitrarily defined as $S \geq 0.35$, relative to $S = 0.24$ without additive (see farthest right bar in Figure 1, in which the concentration of resolving agent **2a** is identical to that in the inhibition experiment), then **2c** itself, the 3-nitro (**26**), 2-hydroxy (**23**), 1-naphthyl (**24**), 2-fluoro (**22**), 2-methoxy (**21**) and 2-naphthyl (**20**) derivatives are active inhibitors (7 out of a library of 24). Note that the halo-substituted derivatives **3**–**7** as additives lead to significantly lower S-values. The other compounds have only modest effects.

By contrast, the effects of structural modification of the side-chain are more profound (Figure 2). In this case, not only compounds with the (*R*) absolute configuration analogous to (*R*)-**2a** were examined, but also racemates and "wrong" (*S*)-enantiomers. By using the same arbitrary definition of a "hit", 17 of the 21 compounds examined show significant effects. The achiral additives **26**, **28**, **32** and **36** have virtually no effect. Cyclization of the side-chain (**33**–**35**) produces no dramatic improvements. Branching of the side-chain can, however, be quite effective, as exemplified by **41**.[9]

However, by far the most potent inhibitors are the diamine derivatives (**42**–**45**).[10] We included these compounds in the screen because molecules with repeating functionality in their structure often have a greater tendency to aggregate,

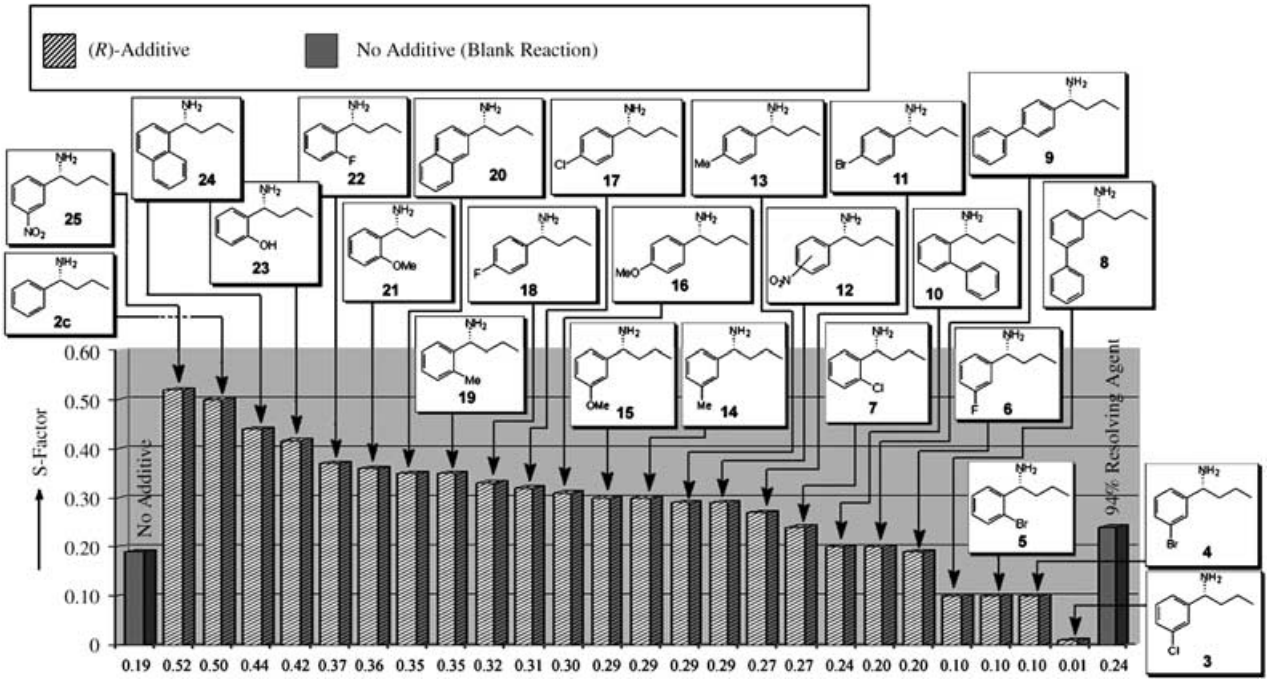


Figure 1. S-Factors of (*R*)-aryl substituted analogues of (*R*)-**2c** as possible nucleation inhibitors.

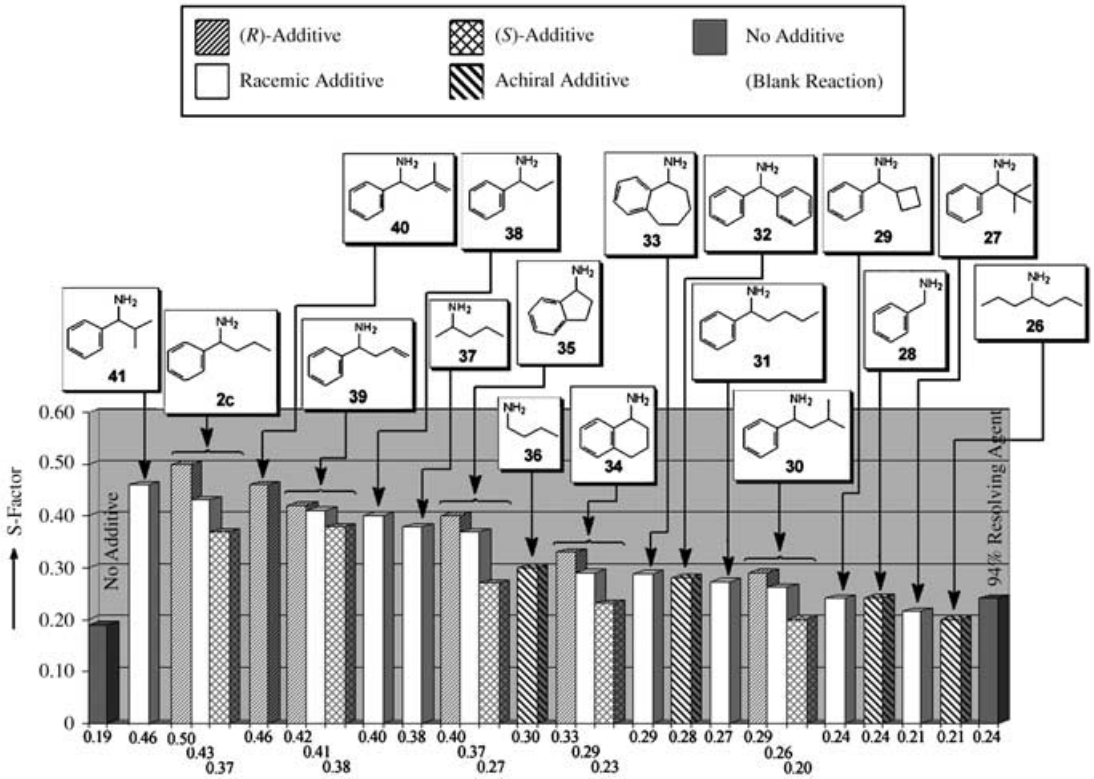


Figure 2. S-Factors of (*R*)-side-chain-substituted analogues of (*R*)-**2a** as possible nucleation inhibitors.

and might influence nucleation in a different manner (gemini effect).[11]

The proof of the pudding is in the tasting. Do the better nucleation inhibitors identified by screening also work in the resolution of other compounds? Those shown in Figure 3 are clearly the most potent. Selected results for the resolution of α-methylphenylacetic acid (**46**),[12] α-methoxyphenylacetic acid (**47**)[13] and *N*-acetylleucine (**48**)[14] with (*R*)-**2a** are summarised in Table 2.[15]

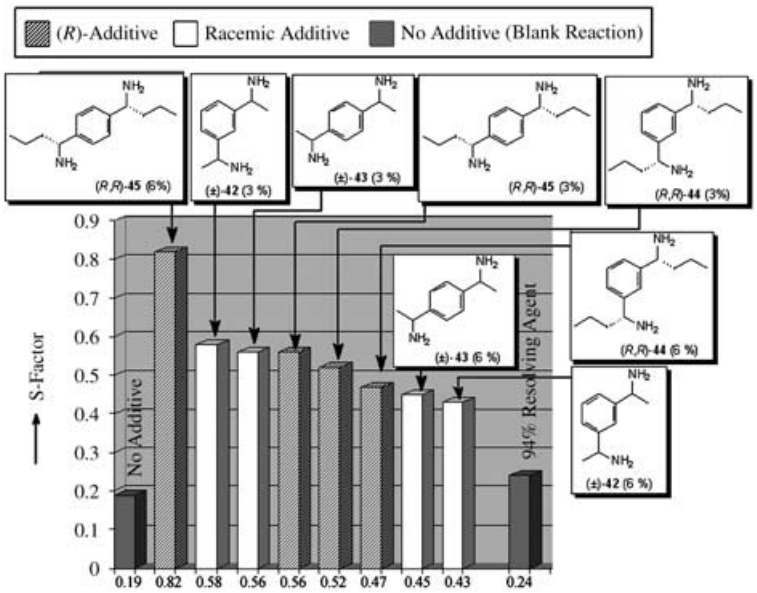
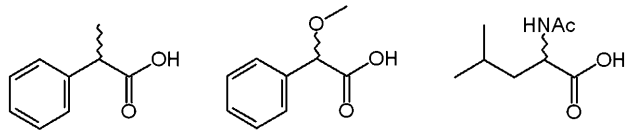


Figure 3. S-Factors of (*R*)- and racemic diamine inhibitors as possible nucleation inhibitors.

Table 2. Selected results for the resolution of racemates **46**–**48** with (*R*)-**2a**, obtained by using the most effective nucleation inhibitors shown in Figure 3.



46 **47** **48**

Entry	Racemate	Additive (mol %)	Yield [%]	*de* [%]	S-factor
1	**46**	–	60	7	0.08
2	**46**	(±)-**42** (3 %)	36	59	0.43
3	**46**	(±)-**43** (3 %)	54	52	0.56
4	**46**	(*R*,*R*)-**44** (6 %)	18	97	0.35
5	**47**	–	65	1	0.02
6	**47**	(±)-**42** (6 %)	16[a]	96	0.30
7	**48**	–	58	13	0.15
8	**48**	(±)-**43** (3 %)	35	75	0.53
9	**48**	(*R*,*R*)-**44** (3 %)	44	48	0.43
10	**48**	(*R*,*R*)-**45** (6 %)	56	32	0.36

[a] Salt isolated after 6 days.

In all cases, the *de* values of the first-isolated salts increase to very acceptable values, as the yields decrease. In our experience, this often, but not always, happens. We also emphasise that the experiments described here may not be optimal with regard to the concentration of inhibitor and temperature. Nevertheless, we consider these non-optimised results to be extremely promising.

Summary

We conclude that:

1) Nucleation inhibition is often involved in Dutch Resolution.
2) The effect of nucleation inhibition is greatest on the more soluble diastereomeric salt.[4c,16]
3) A search for inhibitors is best carried out among "family members" of the resolving agent.
4) There are, at least at this stage, no hard and fast rules for the identification with regard to structure, and all of the suspects must be subjected to screening.
5) Absolute stereochemistry is not an absolute prerequisite, and racemates may be used for screening purposes.
6) Although we are now able to identify inhibitors by using screening methods, our understanding of the inhibition phenomenon itself and of the stereochemical aspects in particular remains insufficient.

In future work, we intend to develop automated protocols for the screening of inhibitors, to develop specific inhibitors for the most commonly used resolving agents for which families exist, to find methodologies based on the discoveries described in this paper that permit application to large scale resolutions and to understand better the mechanism of action of nucleation inhibitors.

Experimental Section

General procedure for the small-scale nucleation inhibition experiments described in Table 1: In a Kimble reactor tube (dimensions ∅ 25 × 150 mm), provided with a cylindrical, PTFE-coated magnetic stirring bar (10 × 6 mm), 0.12 mmol (0.06 mol equiv) of additive **2c** and 1.88 mmol (0.94 mol equiv) of (*R*)-1-phenylethylamine (**2a**) were mixed in 3.33 mL of $CH_3CH(OH)CH_3$. Subsequently, 2.0 mmol racemic mandelic acid (**1**) (1.0 mol equiv) in 1.67 mL $CH_3CH(OH)CH_3$ was added. The mixture was heated until a clear solution was obtained. After the reactor tube was sealed with a rubber stopper, it was placed in the Varian thermostatted bath and mechanically stirred at 78 °C for 30 min. The tubes were gradually cooled to 20 °C at a ramp rate of −10 °C h^{-1} and stirred at that temperature for 12 h. The precipitated salts were collected by filtration by using a VacMaster®-20, then each was washed with 1.5 mL of $CH_3CH(OH)CH_3$ and dried. HPLC analysis was used to determine the diastereomeric excesses of the salts. To ensure accurate *de* determination, the racemic substrate was measured first in each case. The composition of the salt was determined by conducting mass spectrometry, and ^1H and ^{13}C NMR spectroscopy. The resolution experiments described in Tables S4, S5 and S6 of the Supporting Information were performed analogously to this general procedure, with either 0.03 or 0.06 mol equivalent of additive (and, respectively, 0.97 or 0.94 mol equiv of parent resolving agent **2a**) with respect to the 1.0 mol equivalent of racemic substrate. The solvent(s) and concentrations used are listed at the bottom of each table. The conditions used in the HPLC analysis for each substrate are given in

Table S7. All experiments were performed in triplicate and the error margin was ±5%.

The additives used in the screening for possible nucleation inhibitors, as described in Tables S5 and S6 of the Supporting Information, were either commercially available (additives **28** and **34–36**) or were synthesised by using a simple one-pot Leuckart synthesis (additives **2c**, **26**, **27**, **29**, **31–33**, **37**, **38** and **40–43**). The syntheses of enantiopure **2c**, **30**, **39** and **40** were as previously reported.[5]

General procedure for the Leuckart synthesis of additives 2c, 26, 27, 29, 31–33, 37, 38 and 40–43: A mixture of the corresponding aldehyde or ketone (10 mmol), formamide (20 mL) and formic acid (10 mL) was heated to reflux and then refluxed for 1 h. After cooling to ambient temperature, 30 mL of water was added and the mixture was extracted with diethyl ether (3×10 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to furnish the intermediate formamide. Aqueous HCl (20 mL, 30%) was added and the reaction mixture was refluxed for 1 h. After cooling to ambient temperature, 20 mL of water was added. The reaction mixture was carefully adjusted to pH 10 with aqueous NaOH (33%) and extracted with diethyl ether (3×20 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated to furnish the corresponding primary amines.

1-Propylbutylamine (26): Colourless liquid, 55% yield after Kugelrohr distillation; ^{1}H NMR (400 MHz, $CDCl_3$): δ=0.75–0.80 (m, 6H), 1.17–1.36 (m, 8H), 2.78 (t, J=5.32 Hz, 1H), 5.02 ppm (brs, 2H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.76 (q), 18.50 (t), 37.50 (t), 51.71 ppm (d); MS (CI): m/z: 116 $[M+H]^+$.

(±)-2,2-Dimethyl-1-phenyl-1-propanamine (27): Pale yellow oil, 95% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.86 (s, 9H), 1.40 (brs, 2H), 3.65 (s, 1H), 7.17–7.25 ppm (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=26.43 (q), 34.91 (s), 65.22 (d), 126.62 (d), 127.38 (d), 128.14 (d), 143.68 ppm (s); MS (EI): m/z: 163 $[M]^+$.

(±)-Cyclobutyl(phenyl)-methanamine (29): Orange oil, 61% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.39 (brs, 2H), 1.60–1.85 (m, 5H), 2.07–2.14 (m, 1H), 2.41–2.49 (m, 1H), 3.73 (d, J=9.15 Hz, 1H), 7.15–7.28 ppm (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=17.41 (t), 25.33 (t), 26.04 (t), 43.21 (d), 61.64 (d), 126.51 (d), 126.77 (d), 128.17 (d), 144.70 ppm (s); MS (CI): m/z: 162 $[M+H]^+$.

(±)-1-Phenyl-1-pentanamine (31): Yellow oil, 87% yield; ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.82 (t, J=6.78 Hz, 3H), 1.06–1.27 (m, 4H), 1.41 (brs, 2H), 1.57–1.63 (m, 2H), 3.80 (t, J=6.78 Hz, 1H), 7.13–7.31 ppm (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.79 (q), 22.46 (t), 28.55 (t), 39.21 (t), 56.08 (d), 126.07 (d), 126.54 (d), 128.14 (d), 146.69 ppm (s); MS (EI): m/z: 163 $[M]^+$.

(±)-6,7,8,9-Tetrahydro-5*H*-benzo[*a*]cyclohepten-5-amine (33): Colourless liquid, 53% yield after Kugelrohr distillation; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.52–2.02 (m, brs, 8H), 2.82–2.87 (m, 2H), 4.21–4.25 (m, 1H), 7.10–7.26 (m, 4H), 7.42–7.45 ppm (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=27.42 (t), 28.69 (t), 35.67 (t), 37.11 (t), 54.60 (d), 124.00 (d), 126.00 (d), 126.19 (d), 129.28 (d), 141.25 (s), 145.57 ppm (s); MS (EI): m/z: 161 $[M]^+$.

(±)-1-Methylbutylamine (37): Colourless oil, 65% yield after Kugelrohr distillation; ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.81–0.88 (m, 3H), 0.98 (d, J=6.34 Hz, 3H), 1.10–1.39 (m, 4H), 1.63 (brs, 2H), 2.77–2.86 ppm (m, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=13.86 (q), 19.29 (t), 23.63 (q), 42.18 (t), 46.37 ppm (d); MS (EI): m/z: 88 $[M]^+$.

(±)-2-Methyl-1-phenyl-1-propanamine (41): Yellow oil, 83% yield; ^{1}H NMR (200 MHz, $CDCl_3$): δ=0.72 (d, J=6.59 Hz, 3H), 0.92 (d, J=6.59 Hz, 3H), 1.41 (brs, 2H), 1.74–1.85 (m, 1H), 3.54 (d, J=7.32 Hz, 1H), 7.17–7.28 ppm (m, 5H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=18.81 (q), 19.70 (q), 35.36 (d), 62.37 (d), 128.03 (d), 126.91 (d), 128.03 (d), 150.91 ppm (s); MS (CI): m/z: 150 $[M+H]^+$.

Note that in the cases of **42** and **43**, two stereocenters are present and a *meso* compound is possible. After the Leuckart reductive amination of the corresponding bis-aldehydes, the reaction mixture contained a *rac*:*meso* ratio of 85:15 and 80:20, respectively, according to ^{1}H NMR analysis. After bulb-to-bulb distillation, the only products isolated were racemic **42** and **43** (*rac*:*meso* > 99:1).

(±)-1-[3-(1-Aminoethyl)phenyl]-1-ethanamine (42): After workup, the reaction mixture contained a *rac*:*meso* ratio of 85:15, according to ^{1}H NMR analysis. After Kugelrohr distillation, the only product isolated was racemic **42** (*rac*:*meso* > 99:1) as a colourless oil, 53% yield after bulb-to-bulb distillation; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.28 (d, J=6.59 Hz, 6H), 2.63 (brs, 4H), 3.98 (q, J=6.59 Hz, 2H), 7.07–7.17 ppm (m, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=25.07 (q), 49.64 (d), 122.85 (d), 124.10 (d), 128.60 (d), 147.29 ppm (s); MS (CI): m/z: 165 $[M+H]^+$.

(±)-1-[4-(1-Aminoethyl)phenyl]-1-ethanamine (43): After workup, the reaction mixture contained a {(*R*,*R*)+(*S*,*S*)}:*meso* ratio of 80:20, according to ^{1}H NMR analysis. After Kugelrohr distillation, the only product isolated was racemic **43** ({(*R*,*R*)+(*S*,*S*)}:*meso* > 99:1) as a colourless oil, 47% yield after Kugelrohr distillation; ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.33 (d, J=6.59 Hz, 6H), 1.51 (brs, 4H), 4.05 (q, J=6.59 Hz, 2H), 7.26 ppm (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=25.50 (q), 50.82 (d), 125.60 (d), 146.16 ppm (s); MS (CI): m/z: 165 $[M+H]^+$.

Bifunctional additives (*R*,*R*)-**44** and (*R*,*R*)-**45** were synthesised as enantiopure compounds by using a three-step procedure reported previously.[5]

Procedure for the synthesis of (*R*)-phenylglycine amide (PGA)-diimines: The disubstituted benzaldehyde (100 mmol) was added to a suspension of (*R*)-phenylglycine amide (200 mmol, 30.0 g) in CH_2Cl_2 (200 mL) at ambient temperature. The reaction mixture was stirred overnight at room temperature. After removal of the CH_2Cl_2, the residual solid was recrystallised once from acetone/hexane (1:20).

(2*R*)-2-({(*E*)-[3-({[(1*R*)-2-Amino-2-oxo-1-phenylethyl]imino}methyl)phenyl]methylidene}amino)-2-phenylethanamide (49): White solid, 96% yield. M.p. 143.8–144.5 °C; ^{1}H NMR (300 MHz, $CDCl_3$/[D$_6$]DMSO): δ=4.55 (s, 2H), 6.60 (brs, 2H), 6.63 (brs, 2H), 6.82–6.91 (m, 7H), 7.02–7.09 (m, 4H), 7.49 (d, J=7.99 Hz, 2H), 7.79 (s, 1H), 7.94 ppm (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$/[D$_6$]DMSO): δ=76.24 (d), 126.42 (d), 126.85 (d), 127.64 (d), 128.15 (d), 130.16 (d), 135.03 (s), 138.59 (s), 161.37 (d), 172.60 ppm (s); elemental analysis calcd (%) for $C_{24}H_{22}N_4O_2$: C 72.34, H 5.57, N 14.06; found: C 72.21, H 5.66, N 14.03; MS (CI): m/z: 399 $[M+H]^+$.

(2*R*)-2-({(*E*)-[4-({[(1*R*)-2-Amino-2-oxo-1-phenylethyl]imino}methyl)phenyl]ethylidene}amino)-2-phenylethanamide (50): White solid, 98% yield. M.p. 168.2 °C; ^{1}H NMR (300 MHz, $CDCl_3$/[D$_6$]DMSO): δ=4.53 (s, 2H), 6.58 (brs, 4H), 6.82–6.93 (m, 6H), 7.04 (dd, J=8.42, J=1.46 Hz, 4H), 7.45 (s, 4H), 7.93 ppm (s, 2H); ^{13}C NMR (50 MHz, $CDCl_3$/[D$_6$]DMSO): δ=76.39 (d), 126.42 (d), 126.88 (d), 127.67 (d), 127.83 (d), 137.01 (s), 138.61 (s), 161.32 (d), 172.483 ppm (s); elemental analysis calcd (%) for $C_{24}H_{22}N_4O_2$: C 72.34, H 5.57, N 14.06; found: C 71.95, H 5.58, N 13.87; MS (CI): m/z: 399 $[M+H]^+$.

Procedure for the allylation of (*R*)-PGA diimines 49 and 50: A solution of allylzinc bromide (3.0 equiv) was prepared by adding allyl bromide (25.7 mL, 292 mmol) to finely cut zinc wool (19.1 g, 292 mmol) in THF (150 mL). The solution of allylzinc bromide was cooled to room temperature and 97.3 mmol of the imine in THF (50 mL) was added at 0 °C. The reaction mixture was warmed to room temperature and then poured into water (100 mL). Ethyl acetate (70 mL) was added and the mixture was stirred vigorously. After filtration through Celite, the organic phase was separated and the water layer was extracted with ethyl acetate (2× 100 mL). The combined organic phase was dried over sodium sulfate and the ethyl acetate was evaporated to furnish the PGA allylamines **51** or **52**, which in both cases crystallised on standing.

(2*R*)-2-({(1*R*)-1-[3-((1*R*)-1-{[(1*R*)-2-Amino-2-oxo-1-phenylethyl]amino}-3-butenyl)phenyl]-3-butenyl}amino)-2-phenylethanamide (51): Yellow needles, 99% yield, >99:1 *dr*. M.p. 126.6–127.9 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.22 (brs, 2H), 2.36 (t, J=6.59 Hz, 4H), 3.67 (t, J=6.59 Hz, 2H), 3.94 (s, 2H), 4.97–5.03 (m, 4H), 5.59–5.72 (m, 2H), 6.58 (brs, 2H), 7.01–7.25 ppm (m, 16H); ^{13}C NMR (50 MHz, $CDCl_3$): δ=42.11 (t), 61.32 (d), 63.88 (d), 117.69 (t), 124.97 (d), 126.41 (d), 127.04 (d), 127.88 (d), 128.60 (d), 134.45 (d), 138.79 (s), 142.64 (s), 150.70 (d), 175.84 ppm (s); elemental analysis calcd (%) for $C_{30}H_{34}N_4O_2$: C 74.66, H

7.10, N 11.61; found: C 74.66, H 7.43, N 11.53; MS (CI): *m*/*z*: 483 $[M+H]^+$.

(2*R*)-2-({(1*R*)-1-[4-((1*R*)-1-{[(1*R*)-2-Amino-2-oxo-1-phenylethyl]amino}-3-butenyl)phenyl]-3-butenyl}amino)-2-phenylethanamide (52): Pale yellow brittle solid, 99% yield, >99% *dr*. M.p. 96.5–98.9°C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 2.16$–2.44 (m, brs, 5H), 3.70 (dt, $J = 6.2$ Hz, 2H), 4.05 (s, 2H), 4.95–5.10 (m, 4H), 5.61–5.69 (m, 2H), 6.26 (brs, 2H), 7.31–7.09 ppm (m, 16H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 42.01$ (d), 61.46 (d), 64.08 (d), 118.11 (t), 127.36 (d), 127.49 (d), 128.38 (d), 128.96 (d), 134.46 (d), 138.43 (s), 141.23 (s), 175.90 ppm (s); elemental analysis cald (%) for $C_{30}H_{34}N_4O_2$: C 74.66, H 7.10, N 11.61; found: C 74.70, H 7.06, N 11.62; MS (CI): *m*/*z*: 483 $[M+H]^+$.

Procedure for the synthesis of diamino additives (*R*,*R*)-44 and (*R*,*R*)-45 by catalytic hydrogenation of PGA allylamines 51 and 52: The PGA allylamine (5.0 mmol) was dissolved in $CH_3CH(OH)CH_3$ (50 mL). Water (50 mL), acetic acid (50 mL) and Pd-C (10%) (0.4 g, cat) were added successively. After application of two vacuum/H_2 cycles to remove air from the reaction flask, the stirred mixture of the substrate was hydrogenated at an ambient pressure of H_2 and room temperature for 5 d. After filtration, the $CH_3CH(OH)CH_3$ was evaporated under reduced pressure. The residue was diluted with water (50 mL) and the acidic reaction mixture was washed once with diethyl ether to remove any byproducts. The aqueous phase was adjusted to pH 10 with 10% NaOH and then extracted with CH_2Cl_2 (3×40 mL). The combined organic phase was washed with brine, dried over sodium sulfate and filtered. After evaporation of the CH_2Cl_2, pentane was added to the residue. After filtration through a glass funnel, the pentane was removed under reduced pressure. Bulb-to-bulb distillation yielded primary amines (*R*,*R*)-**44** and (*R*,*R*)-**45**.

1-{3-[(1*R*)-1-Aminobutyl]phenyl}-1-butylamine (44): Colourless oil, 80% yield; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.84$ (t, $J = 7.33$ Hz, 6H), 1.11–1.34 (m, 4H), 1.52–1.61 (m, brs, 8H), 3.82 (t, $J = 6.96$ Hz, 2H), 7.11 (d, $J = 7.69$ Hz, 2H), 7.18 (s, 1H), 7.21 ppm (t, $J = 6.96$ Hz, 1H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 13.96$ (q), 19.70 (t), 41.84 (t), 55.97 (d), 124.22 (d), 124.69 (d), 128.38 (d), 155.35 ppm (s); MS (CI): *m*/*z*: 441 $[2M+H]^+$.

1-{4-[(1*R*)-1-Aminobutyl]phenyl}-1-butylamine (45): Pale yellow oil, 74% yield; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 0.75$ (t, $J = 7.33$ Hz, 6H), 1.04–1.25 (m, 4H), 1.46–1.51 (m, brs, 8H), 3.70 (t, $J = 6.78$ Hz, 2H), 7.09 ppm (s, 4H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta = 13.64$ (q), 19.34 (t), 41.47 (t), 55.83 (d), 125.91 (d), 144.89 ppm (s); MS (CI): *m*/*z*: 441 $[2M+H]^+$.

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[9] A 1:1:1 mixture of enantiopure **2a**, **37** and **42**, the latter two of which appear to be nucleation inhibitors (Table 2) has been used in the past (ref. [1]) as a family of resolving agents ("PE-III mix").

[10] The preparation of these materials by means of a Leuckart reaction and subsequent easy isolation is described in the Supporting Information.

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[12] Conc. = 0.30 mmol mL^{-1} in $CH_3CH(OH)CH_3$:H_2O (20:1). On addition of additive, the crystallised material contained the (*R*)-**2a**/(*S*)-**46** in excess.

[13] Conc. = 0.25 mmol mL^{-1} in $CH_3CH(OH)CH_3$:H_2O (20:1). On addition of additive, the crystallised material contained the (*R*)-**2a**/(*R*)-**47** in excess.

[14] Conc. = 0.75 mmol mL^{-1} in $CH_3CH(OH)CH_3$:H_2O (5:2). On addition of additive, the crystallised material contained the (*R*)-**2a**/(*R*)-D-**48** in excess.

[15] The "habit modifier" (*R*,*R*)-bis(α-methylbenzyl)amine [K. Sakai, Y. Maekawa, K. Saigo, M. Sukegawa, H. Murakami, H. Nohira, *Bull. Chem. Soc. Jpn.* **1992**, *65*, 1747–1750], the secondary amine analog of 1-phenylethylamine **2a**, was only modestly effective and raised the S-factor for the resolution of **1** to 0.26 and that of **46** to 0.41; these results were not sufficient to encourage further investigation.

[16] From turbidity measurements performed to date, we have observed that "Dutch Resolution inhibitors" have the greatest effect on the more soluble diastereomeric salt. However, not every inhibitor has been subjected to turbidity measurements.

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