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Supporting Information

69451 Weinheim, Germany

Structural Aspects of Nucleation Inhibitors for Diastereomeric Resolutions and the Relationship to Dutch Resolution.

M.S. Leeman, G. Brasile, E. Gelens, T.R. Vries, B. Kaptein, R.M. Kellogg

Methods

Materials

All chemicals were obtained form commercial sources and used without further purification.

HPLC analysis of enantiomeric excess (*de*) and additives

Chiral HPLC analysis of 3-methoxyphenylethylamine (3MeOPEA) salts were separated on a Crownpak CR(-) column with an aqueous solution of $HClO_4$ (pH 2) as eluent at 20°C and 0.6 mL/min. UV-VIS detection at 192 nm. The salts were dissolved in eluent and injected as such. (*R*)-3MeOPEA R_f: 39.59 min, (*S*)-3MeOPEA R_f: 42.98 min.
When 1,3-bis(2-amino-2-propyl)benzene (1,3-BAPB) was used as additive, its percentage (against total area under the 3MeOPEA peaks) in the precipitated salts and mother liquors was measured with the same HPLC conditions, using (S)-mandelic acid (MA) as an internal standard. 1,3-BAPB R_f: 9.17 min, (*S*)-MA R_f: 19.86 min

RP-HPLC analysis of other additives was performed by comparing a solution of the precipitated salts with a solution of the additive. The separation was performed on a Zorbax Extend C18 (4.6 x 50 mm, 3.5 µm) column, mobile phase: Solution A: Solution B = 95:5 (3 min)→(5 min)→ 0:100 (4 min). Solution A: 9,65 g NH_4Ac; 2250 ml H_2O; 150 ml MeOH; 100 ml Acetonitrile, Solution B: 9,65 g NH_4Ac; 250 ml H_2O; 1350 ml MeOH; 900 ml Acetonitrile, at 1.0 mL/min and 22°C. Massdet: API-ES. Amounts were determined relative to the area under the 3MeOPEA or MA peak without internal standard.

NMR spectra

^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Mercury 300MHz machine.

Mass

Samples were dissolved in MeOH and injected as such. Mobile phase: Acetonitrile : 0.1% formic acid in water 50 : 50 (1 min.), flow: 0.2 ml/min, injection volume: 5 εl.

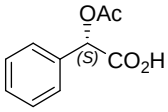
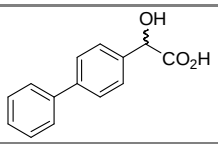
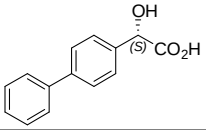
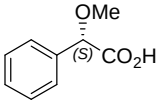
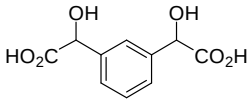
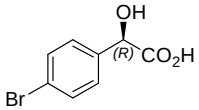
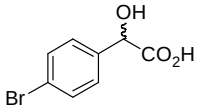
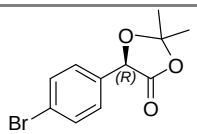
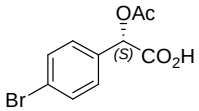
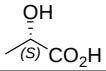
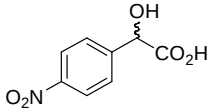
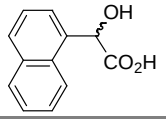
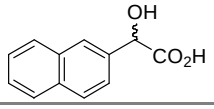
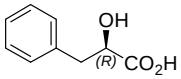
Resolutions with additives

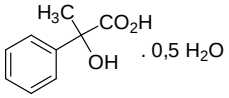
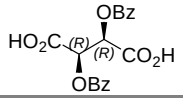
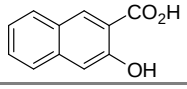
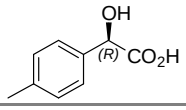
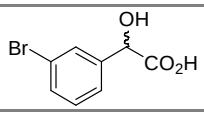
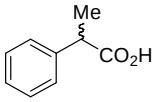
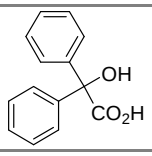
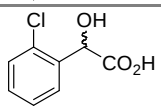
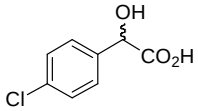
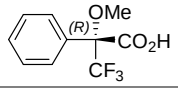
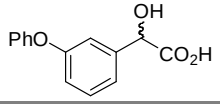
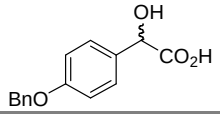
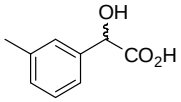
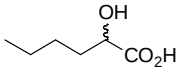
A typical resolution experiment was performed by charging a Kimble reactor tube (Ø 25 x 150 mm) with a PTFE coated cylindrical magnetic stirring bar (19 mm x 10 mm) and 2.5 mL 0.13 M (±)-3MeOPEA in 2-butanone (MEK) and 2.5 mL 0.13M (S)- or (R)-mandelic acid (MA) in MEK. This mixture was stirred and after a while crystals started to form. When additives were used, an equimolar amount of (±)-3MeOPEA or MA was replaced by a solution of the additive so the whole system remains neutral and of equal volume.
The suspension was heated to dissolution and placed in a Reactiv8 computer controlled reactor station and stirred magnetically at 600rpm and 70°C for 30 min. Then the tubes were cooled to 20°C with 0.1°/min and kept at 20°C for an additional 8 hours. The formed crystals were collected on pre-weighted disposable filters and washed with 1.0 mL MEK. The solids were subsequently dried and weighted and the *de* was determined of the salts.
The eutectic composition lies at 71 mol% of the more soluble (*R*),(*S*)-diastereomer in methylethyl ketone (MEK). The solubility of the less soluble (*S*),(*S*)-diastereomer is 4.2 mmol l^{-1} and that of the (*R*),(*S*)-diastereomer 8.4 mmol l^{-1}. The phase diagram shows that this system could deliver pure (*S*)-3MeOPEA-(*S*)-MA in 30% yield (S=0.60) when optimized without nucleation inhibitor..

Results of resolutions with additives

Additives resembling the resolving agent

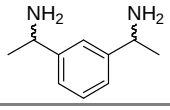
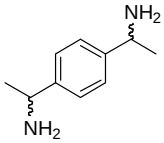
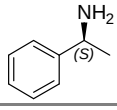
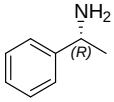
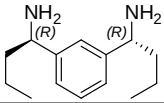
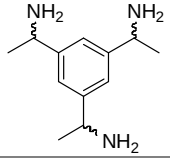
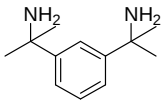
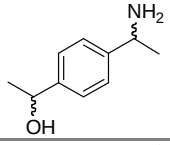
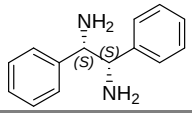
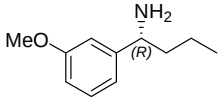
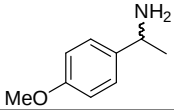
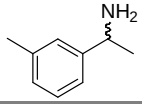
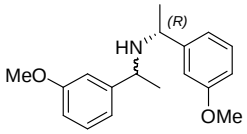
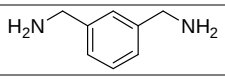
Entry	Nucleation Inhibitor	R/S-MA	$\%_{MA}$	$\%_{NI}$	Yield (%)	*de*(%)	S-factor[i]	% additive in salt
1	None	R/S	100	-	72	10	0.14	-

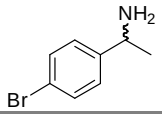
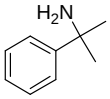
2a[ii]		S	94		42	97	0.81	<0.1%
2b[ii]	ñ	R	94		70	12	0.17	n.d.
3a[iii]		S	94	6	36	95	0.68	1%
3b[iii]		S	94	6	42	95	0.80	<0.1%
3c[iii]	ñ	R	94	6	68	15	0.20	n.d.
4a[ii]		S	94	6	40	96	0.77	<0.1%
4b[ii]	ñ	R	94	6	63	11	0.15	n.d.
5[iv]	 mix: *meso,S,S & R,R*	R	94	3	16	93	0.30	<0.1%
6a[ii]		R	94	6	40	93	0.73	4%
6b[ii]		R	94	6	46	32	0.30	3%
7[iv]		R	100	6	67	12	0.15	n.d.
8[iv]		S	94	6	31	99	0.61	<0.1%
9[ii]		S	94	6	69	13	0.18	n.d.
10[iv]		S	94	6	60	26	0.31	2%
11[iv]		S	94	6	66	13	0.17	n.d.
12[iv]		S	94	6	26	94	0.48	<0.1%
13[ii]		R	94	6	67	15	0.20	n.d.

14[ii]		S	94	6	48	18	0.16	<0.1%
15[ii]		R	94	3	63	22	0.27	n.d.
16[ii]		R	94	6	63	16	0.20	n.d.
17[v]		R	94	6	64	15	0.19	<0.1%
18[ii]		R	94	6	63	19	0.23	<0.1%
19[ii]		R	94	6	62	14	0.17	n.d.
20[ii]		S	94	6	56	20	0.22	n.d.
21[ii]		S	94	6	52	15	0.15	n.d.
22[ii]		R	94	6	33	95	0.62	6%
23[ii]		R	94	6	46	32	0.29	n.d.
24[iv]		R	94	6	61	26	0.32	n.d.
25[ii]		R	94	6	35	95	0.67	3%
26[ii]		R	94	6	66	12	0.16	n.d.
27[ii]	Oxalic acid	R	94	3	68	10	0.14	n.d.
28[ii]	Citric acid	R	94	2	67	25	0.30	n.d.
29[ii]	Glycolic acid	R	94	6	65	14	0.19	n.d.
30[ii]		R	94	6	66	19	0.25	n.d.

Additives resembling the racemate

Entry	Nucleation Inhibitor	R/S-MA	$\%_{3MeOPEA}$	$\%_{NI}$	Yield (%)	*de*(%)	S-factor	NI in salt?
1	None	R/S	100	-	72	10	0.14	-

2[vi]			94	3	32	96	0.61	<0.1%
3[vi]		S	94	3	35	89	0.63	<0.1%
4[ii]		S	94	6	43	23	0.20	<0.1%
5[ii]		S	94	6	46	14	0.13	<0.1%
6a[vi]		S	94	3	32	97	0.62	<0.1%
6b[vi]	ñ	R	94	3	31	96	0.60	<0.1%
7[iv]		S	94	2	27	95	0.51	4%
8[iv]		S	94	3	42	97	0.82	5%
9[iv]		S	94	6	75	12	0.18	n.d.
10[ii]		R	94	3	73	11	0.17	n.d.
11a[vi]		R	94	6	69	12	0.17	n.d.
11b[vi]	ñ	S	94	6	69	13	0.17	n.d
12[iii]		R	94	6	67	11	0.16	n.d.
13[iii]		R	94	6	69	19	0.27	n.d.
14[iv]		S	94	6	64	10	0.12	<0.1%
15[ii]		S	94	3	69	13	0.15	1%

16[ii]		S	94	6	61	15	0.17	2%
17[ii]		R	94	6	69	14	0.20	n.d.

Experimental section

(±)-2-{3-[carboxy(hydroxy)methyl]phenyl}-2-hydroxyacetic acid. A mixture of isophtaldehyde (1.14 g, 8.5 mmol, 1.0 eq), ZnI_2 (54 mg, 0.17 mmol, 0.02 eq) and I_2 (43 mg, 0.17 mmol, 0.02 eq) were stirred in CH_2Cl_2 (20mL). To this mixture was added trimethylsilyl cyanide (2.72 mL, 20.4 mmol, 2.4 eq) dropwise upon which the reaction mixture started boiling. The reaction mixture was kept at 40°C overnight. The mixture was subsequently allowed to cool to roomtemperature and was carefully treated with sat. $NaHCO_3$ (20 mL) under expulsion of HCN gas. By bubbling N_2 though the mixture for 15 minutes, all HCN was removed. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated to dryness. This delivered 2.76 g (65%) (±)-2-(3-{cyano[(trimethylsilyl)oxy]methyl}phenyl)-2-[(trimethylsilyl)oxy]acetonitrile as a brown oil which was used without further purification. ^{1}H-NMR (300MHz, $CDCl_3$): δ= 0.24 (s, 18H), 5.52 (s, 2H), 7.48-7.49 (m, 3H), 7.49 (s, 1H) ppm. ^{13}C-NMR(75MHz, $CDCl_3$): δ= 0.0, 63.5, 119.1, 124.3, 127.4, 129.9, 137.5 ppm. MS (EI): *m/z*=350 [M+NH_4^+]

A solution of the cyanohydrin (1.92 g, 5.77 mmol, 1.0 eq) in dioxane (10 mL) was treated with 10% HCl (10 mL) and subsequently heated to 60°C for 6 hours after which the dioxane was removed by distillation. The residue was brought to pH 12 with conc. NaOH and washed with TBME (2 x 20 mL). The aqueous layer was filtered, brought to pH 1 with conc. HCl and washed with TBME (2 x 20 mL). The aqueous layer was concentrated to dryness and the residue stirred in acetone and filtered. The filtrate was concentrated to dryness to furnish 1.01 g (78%) of the title compound as a brown solid. ^{1}H-NMR (300MHz, DMSO-d6): δ= 5.03 (s, 2H), 6.90 (bs, 4H), 7.30-7.34 (m, 3H), 7.48 (s, 1H) ppm. ^{13}C-NMR (75MHz, DMSO-d6): δ= 72.99, 125.54, 126.83, 126.86, 128.68, 140.77, 140.78, 174.71 ppm. MS (EI): *m/z*=225 [M-H^+], 451 [2M-H^+].

(*R*)-5-(4-bromophenyl)-2,2-dimethyl-1,3-dioxolan-4-one. To an ice-cooled solution of (*R*)-4-bromomandelic acid[v] (25 g, 108 mmol, 1.0 eq) in acetone (50 mL) was added concentrated H_2SO_4 (6.34 mL, 119 mmol, 1.1 eq) dropwise in 5 minutes thereby keeping the temperature below 22°C. After addition, Na_2SO_4 (3.5 g) was added to the mixture and stirring was continued for another 4.5 hours after which the reaction mixture was carefully poured out in a mixture of sat. $NaHCO_3$ (350 mL) and ice (250 g). The resulting mixture was extracted with CH_2Cl_2 (1 x 100 mL & 2 x 50 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4) and concentrated to yield 15.4 g (53%) of the title compound as a yellow oil. ^{1}H-NMR (300MHz, $CDCl_3$): δ= 1.67 (s, 3H), 1.71 (s, 3H), 5.34 (s, 1H), 7.35 (d, *J*=8.7 Hz, 2H), 7.54 (d, *J*=8.4 Hz, 2H) ppm.

(*S*)-2-(4-bromophenyl)-2-(acetyloxy)acetic acid. (*S*)-4-bromomandelic acid[v] (500 mg, 2.16 mmol, 1.0 eq) was suspended in CH_2Cl_2 (10 mL). Acetyl chloride (0.19 mL, 2.60 mmol, 1.2 eq) and Et_3N (0.33 mL, 2.38 mmol, 1.1 eq) were added dropwise and the resulting mixture was stirred for another hour after which the reaction mixture was poured out in ice water (10 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The combined organic layers were washed with 1M HCl (10 mL) and brine (10 mL) and subsequently dried (Na_2SO_4) and concentrated to dryness. This yielded 530 mg (90%) of the title compound as a white solid. ^{1}H-NMR (300MHz, DMSO-d6): δ= 2.11 (s, 3H), 5.80 (s, 1H), 7.41 (d, *J*=8.4Hz, 2H), 7.61 (d, *J*=8.4 Hz, 2H), 12.90 (bs, 1H) ppm.

(±)-4-nitromandelic acid. A mixture of 4-nitrobenzaldehyde (2.57 g, 17 mmol, 1.0 eq), ZnI_2 (54 mg, 0.17 mmol, 0.01 eq) and I_2 (43 mg, 0.17 mmol, 0.01 eq) were stirred in CH_2Cl_2 (20mL). To this mixture was added trimethylsilyl cyanide (2.72 mL, 20.4 mmol, 1.2 eq) dropwise upon which the reaction mixture started boiling. The reaction mixture was kept at 40°C overnight. The mixture was subsequently allowed to cool to roomtemperature and was carefully treated with sat. $NaHCO_3$ (20 mL) under expulsion of HCN gas. By bubbling N_2 though the mixture for 15 minutes, all HCN was removed. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated to dryness. This delivered 2.76 g (65%) (±)-2-(4-nitrophenyl)-2-[(trimethylsilyl)oxy]acetonitrile as a brown oil which was used without further purification. ^{1}H-NMR (300MHz, $CDCl_3$): δ= 0.27 (s, 9H), 5.58 (s, 1H), 7.66 (d, *J*=9.0 , 2H), 8.27 (d, *J*=9.0 , 2H) ppm. ^{13}C-NMR(75MHz, $CDCl_3$): δ= -0.1, 62.9, 118.4, 124.4, 127.4, 143.1, 148.7 ppm. MS (EI): *m/z*=177 [M+H^+]

A solution of the cyanohydrin (2.76 g, 11.0 mmol, 1.0 eq) in dioxane (10 mL) was treated with 10% HCl (10 mL) and subsequently heated to 60°C for 6 hours after which the dioxane was removed by distillation. The residue was brought to pH 12 with conc. NaOH and washed with TBME (2 x 20 mL). The aqueous layer was filtered, brought to pH 1 with conc. HCl and extracted with TBME (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated to dryness to furnish 1.29 g (57%) of the title compound as an orange solid. ^{1}H-NMR (300MHz, DMSO-d6): δ= 3.90 (bs, 1H), 5.23 (s, 1H), 6.10 (bs, 1H), 7.69 (d, *J*=9.0, 2H), 8.20 (d, *J*=8.7, 2H) ppm. ^{13}C-NMR (75MHz, DMSO-d6): δ= 72.4, 124.0, 128.4, 147.6, 148.3, 173.8 ppm. MS (EI): *m/z*=196 [M-H^+], 393 [2M-H^+].

(±)-2-hydroxy-2-(naphthalen-1-yl)acetic acid. A mixture of 1-naphthaldehyde (2.31 mL, 17 mmol, 1.0 eq), ZnI_2 (54 mg, 0.17 mmol, 0.01 eq) and I_2 (43 mg, 0.17 mmol, 0.01 eq) were stirred in CH_2Cl_2 (20mL). To this mixture was added

trimethylsilyl cyanide (2.72 mL, 20.4 mmol, 1.2 eq) dropwise upon which the reaction mixture started boiling. The reaction mixture was kept at 40°C overnight. The mixture was subsequently allowed to cool to roomtemperature and was carefully treated with sat. $NaHCO_3$ (20 mL) under expulsion of HCN gas. By bubbling N_2 though the mixture for 15 minutes, all HCN was removed. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated to dryness. This delivered 3.63 g (83%) (±)-2-(naphthalen-1-yl)-2-[(trimethylsilyl)oxy]acetonitrile as a brown oil which was used without further purification. ^{1}H-NMR (300MHz, $CDCl_3$): δ= 0.19 (s, 9H), 6.04 (s, 1H), 7.47 (t, *J*=7.8, 1H), 7.51-7.63 (m, 2H), 7.69 (d, *J*=7.2, 1H), 7.89 (d, *J*=8.1Hz, 1H), 8.16 (d, *J*=8.7Hz, 1H) ppm. ^{13}C-NMR (75MHz, $CDCl_3$): δ= 0.1, 63.0, 119.4, 123.4, 125.3, 125.7, 126.6, 127.3, 129.2, 130.2, 130.7, 131.6, 134.2 ppm. MS (EI): *m/z*= 229 [M-HCN+H$^+$]

A solution of the cyanohydrin (3.63 g, 14.2 mmol, 1.0 eq) in dioxane (10 mL) was treated with 10% HCl (10 mL) and subsequently heated to 60°C for 6 hours after which the dioxane was removed by distillation. The residue was brought to pH 12 with conc. NaOH and washed with TBME (2 x 20 mL). The aqueous layer was filtered, brought to pH 1 with conc. HCl and extracted with TBME (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated to dryness to furnish 1.88 g (65%) of the title compound as a yellow solid. ^{1}H-NMR (300MHz, DMSO-d6): δ= 5.65 (s, 1H), 6.10 (bs, 1H), 7.45-7.59 (m, 4H), 7.84-7.94 (m, 2H), 8.25-8.28 (m, 1H) ppm. ^{13}C-NMR (75MHz, DMSO-d6): δ= 71.7, 125.3, 126.0, 126.3, 126.4, 126.7, 128.9, 129.1, 131.3, 134.1, 137.0, 175.0 ppm. MS (EI): *m/z*=201 [M-H$^+$].

(±)-2-hydroxy-2-(naphthalen-2-yl)acetic acid. A mixture of 2-naphthaldehyde (2.66 g, 17 mmol, 1.0 eq), ZnI_2 (54 mg, 0.17 mmol, 0.01 eq) and I_2 (43 mg, 0.17 mmol, 0.01 eq) were stirred in CH_2Cl_2 (20mL). To this mixture was added trimethylsilyl cyanide (2.72 mL, 20.4 mmol, 1.2 eq) dropwise upon which the reaction mixture started boiling. The reaction mixture was kept at 40°C overnight. The mixture was subsequently allowed to cool to roomtemperature and was carefully treated with sat. $NaHCO_3$ (20 mL) under expulsion of HCN gas. By bubbling N_2 though the mixture for 15 minutes, all HCN was removed. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated to dryness. This delivered 3.41 g (78%) (±)-2-(naphthalen-2-yl)-2-[(trimethylsilyl)oxy]acetonitrile as a brown oil which was used without further purification. ^{1}H-NMR (300MHz, $CDCl_3$): δ= 0.25 (s, 9H), 5.64 (s, 1H), 7.50-7.56 (m, 3H), 7.83-7.92 (m, 4H) ppm. ^{13}C-NMR (75MHz, $CDCl_3$): δ= 0.07, 64.15, 119.43, 123.91, 125.98, 127.00, 127.19, 128.05, 128.50, 129.36, 133.24, 133.82, 133.84 ppm. MS (EI): *m/z*= 229 [M-HCN+H$^+$]

A solution of the cyanohydrin (3.41 g, 13.4 mmol, 1.0 eq) in dioxane (10 mL) was treated with 10% HCl (10 mL) and subsequently heated to 60°C for 6 hours after which the dioxane was removed by distillation. The residue was brought to pH 12 with conc. NaOH and washed with TBME (2 x 20 mL). The aqueous layer was filtered, brought to pH 1 with conc. HCl and extracted with TBME (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated to dryness to furnish 1.07g (40%) of the title compound as a yellow solid. ^{1}H-NMR (300MHz, DMSO-d6): δ= 5.28 (s, 1H), 6.10 (bs, 1H), 7.52-7.65 (m, 3H), 7.91-8.01 (m, 4H) ppm. ^{13}C-NMR (75MHz, DMSO-d6): δ= 71.7, 125.3, 126.0, 126.3, 126.4, 126.7, 128.9, 129.1, 131.3, 134.1, 137.0, 175.0 ppm. MS (EI): *m/z*=201 [M-H$^+$].

(±)-3-phenoxyphenylmandelic acid. A mixture of 3-phenoxybenzaldehyde (3.37 g, 17 mmol, 1.0 eq), ZnI_2 (54 mg, 0.17 mmol, 0.01 eq) and I_2 (43 mg, 0.17 mmol, 0.01 eq) were stirred in CH_2Cl_2 (20mL). To this mixture was added trimethylsilyl cyanide (2.72 mL, 20.4 mmol, 1.2 eq) dropwise upon which the reaction mixture started boiling. The reaction mixture was kept at 40°C overnight. The mixture was subsequently allowed to cool to roomtemperature and was carefully treated with sat. $NaHCO_3$ (20 mL) under expulsion of HCN gas. By bubbling N_2 though the mixture for 15 minutes, all HCN was removed. The aqueous layer was extracted with CH_2Cl_2 (2 x 20 mL) and the combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated to dryness. This delivered 4.65 g (92%) (±)-2-(3-phenoxyphenyl)-2-[(trimethylsilyl)oxy]acetonitrile as a brown oil which was used without further purification. ^{1}H-NMR (300MHz, $CDCl_3$): δ= 0.20 (s, 9H), 5.44 (s, 1H), 6.98-7.03 (m, 3H), 7.08-7.19 (m, 3H), 7.31-7.37 (m, 3H) ppm. ^{13}C-NMR (75MHz, $CDCl_3$): δ= -0.1, 63.4, 116.6, 119.1, 119.5, 120.9, 124.0, 130.0, 130.5, 138.3, 156.7, 158.2 ppm. MS (EI): *m/z*= 315 [M+NH_4^+].

A solution of the cyanohydrin (4.48 g, 15.1 mmol, 1.0 eq) in dioxane (10 mL) was treated with 10% HCl (10 mL) and subsequently heated to 60°C for 6 hours after which the dioxane was removed by distillation. The residue was brought to pH 12 with conc. NaOH and washed with TBME (2 x 20 mL). The aqueous layer was filtered, brought to pH 1 with conc. HCl and extracted with TBME (2 x 20 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated to dryness to furnish 3.10g (84%) of the title compound as a brown solid. ^{1}H-NMR (300MHz, DMSO-d6): δ= 5.02 (s, 1H), 5.90 (bs, 1H), 6.88-6.93 (m, 1H), 6.97-7.02 (m, 2H), 7.04-7.06 (m, 1H), 7.09-7.19 (m, 2H), 7.30-7.40 (m, 3H) ppm. ^{13}C-NMR (75MHz, DMSO-d6): δ= 72.0, 116.5, 117.7, 118.8, 121.7, 123.6, 129.8, 130.1, 142.4, 156.5, 156.7, 173.8 ppm. MS (EI): *m/z*=243 [M-H$^+$].

(±)-1-[3,5-bis(1-aminoethyl)phenyl]ethan-1-amine. A solution of 1,3,5-triacetylbenzene (5.00 g, 24.5 mmol, 1.0 eq) in pyridine (90 mL). Added hydroxylamine hydrochloride (17.0 g, 245 mmol, 10 eq) portionwise and the temperature rises to 34°C. The reaction mixture was heated to 75°C. After 30 minutes, the reaction mixture was allowed to cool to roomtemperature. The mixture was parted between water (3 x 50 mL) and EtOAc (400 mL). The organic layer was washed with brine (50 mL), dried (Na_2SO_4), concentrated and the last traces of pyridine were removed by co-distillation with toluene (3x). This furnished 6.0 g (98%) *N*-(1-{3,5-bis[1-(hydroxyimino)ethyl]phenyl}ethylidene)hydroxylamine. ^{1}H-NMR (300MHz, DMSO-d6): δ= 2.17 (s, 9H), 7.88 (s, 3H), 11.27 (s, 3H) ppm. ^{13}C-NMR (75MHz, DMSO-d6): δ= 11.6, 122.8, 137.2, 152.6 ppm.

The trisoxime (1.0 g, 4.01 mmol, 1.0 eq) was suspended in MeOH (50 mL) and Pd/C (10% Pd, 60 mg) was added carefully. The mixture was hydrogenated at ambient pressure. After 2 days, ^{1}H-NMR showed complete conversion and the suspension

was filtered over a path of Celite. The filtrate was concentrated to yield 0.70 g (85%) of the title compound as a colorless oil. ^{1}H-NMR (300MHz, $CDCl_3$): δ= 1.39 (d, *J*=6.6Hz, 9H), 1.52 (bs, 6H), 4.12 (q, J=6.6Hz, 3H), 7.20 (s, 3H) ppm. ^{13}C-NMR (75MHz, $CDCl_3$): δ= 25.8, 51.4, 121.6, 148.3 ppm. MS (EI): *m/z*= 208 [$M+H^+$], 191 [$M-NH_3+H^+$].

1,3-bis(2-amino-2-propyl)benzene (1,3-BAPB). At 200°C and 0.02mbar $CeCl_3$·7H2O was dried for 2 hours to a white powder. Dry $CeCl_3$ (11.5 g, 46.8 mmol, 6 eq) was suspended in fresh THF (250 mL) and heated to reflux for 1 hour. The suspension was cooled to -60°C and a solution of MeLi (~1.6M in Et_2O, 29 mL, 46.8 mmol, 6 eq) was added over 5 minutes which resulted in a yellow suspension. After 20 minutes, a solution of the trinitrile (1.0 g, 7.80 mmol, 1.0 eq) in fresh THF (20 mL) was added over 1 minute. The now orange suspension was allowed to warm to roomtemperature and after 3 hours, the reaction mixture was poured out in water and the resulting mixture was brought to pH 10 with conc NaOH and was subsequently parted with EtOAc (3 x 200 mL) and solids were removed during the first extraction and discarded. The combined organic layers were washed with brine (100 mL), dried (Na_2SO_4) and concentrated to yield a brown oil which was purified by column chromatography over silica with a gradient of 1M NH_3 in MeOH and CH_2Cl_2. This yielded the pure title compound in 0.78 g (52%). ^{1}H-NMR (300MHz, $CDCl_3$): δ= 1.51 (s, 12H), 1.66 (bs, 4H), 7.25-7.37 (m, 3H), 7.67-7.69 (m, 1H) ppm. ^{13}C-NMR (75MHz, $CDCl_3$): δ= 33.1, 52.7, 121.0, 122.7, 128.1, 150.3 ppm. MS (EI): *m/z*= 159 [$M-2NH_3+H^+$], 176 [$M-NH_3+H^+$].

(±)-1-[4-(1-aminoethyl)phenyl]ethan-1-ol. A solution of (±)-1-(4-bromophenyl)ethan-1-amine (2.0 mL, 14.0 mmol, 1.0 eq) in CH_2Cl_2 (20 mL) was treated with Boc_2O (3.66 g, 16.8 mmol, 1.2 eq) and the temperature rose from 18°C to 27°C with gas evolution. After 10 minutes a suspension formes. After 90 minutes the reaction mixture was concentrated and the residue was stirred in Et_2O (10 mL). The solids were collected by filtration and dried on air. This yielded 3.52 g (84%) of (±)-*tert*-butyl *N*-[1-(4-bromophenyl)ethyl]carbamate as a white solid. ^{1}H-NMR (300MHz, $CDCl_3$): δ= 1.36-1.43 (m, 12H), 4.71 (bs, 1H), 4.75-4.83 (m, 1H), 7.16 (d, *J*=8.7Hz, 2H), 7.43 (d, *J*=8.4Hz, 2H) ppm. ^{13}C-NMR (75MHz, $CDCl_3$): δ= 22.7, 28.5, 49.8, 49.7, 120.9, 127.7, 131.7, 143.4, 155.1 ppm. MS (EI): *m/z*= 183 [$M-NH_2Boc+H^+$], 322 [$M+Na^+$].

The bromide (3.5 g, 11.7 mmol, 1.0 eq) was dissolved in THF (25 mL) and cooled to -78°C. A solution of n-BuLi (2.5M in hexane, 10.3 mL, 25.6 mmol, 2.2 eq) was added dropwise so the temperature was kept below -65°C. On addition, a very thick suspension was formed and extra THF (5 mL) was added to keep the reaction mixture stirable. Next, acetaldehyde (1.65 mL, 29.3 mmol, 2.5 eq) was added to the suspension in one portion and the internal temperature rose to -44°C and a clear solution was formed. The reaction mixture was allowed to warm to room temperature and was subsequently parted between water (20 mL) and EtOAc (2 x 50 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated to a colorless oil which was stirred in CH_2Cl_2 (20 mL) and the resulting solids were removed by filtration and the filtrate was concentrated. The resulting oil was purified by column chromatography over silica with 25:75 EtOAc:heptanes as eluent. The compound with R_f 0.22 proved to be (±)-*tert*-butyl *N*-{1-[4-(1-hydroxyethyl)phenyl]ethyl} carbamate. This compound was isolated as a colorless oil (2.85 g, 92%). ^{1}H-NMR (300MHz, $CDCl_3$): δ= 1.40-1.50 (m, 12H), 4.78 (bs, 1H), 4.86-4.92 (m, 1H), 7.27 (d, *J*=9.0Hz, 2H) ppm. ^{13}C-NMR (75MHz, $CDCl_3$): δ= 22.7, 25.2, 28.5, 49.9, 70.0, 79.5, 125.7, 126.0, 143.3, 144.9, 155.2 ppm. MS (EI): *m/z*= 288 [$M+Na^+$].

The Boc protected amine (500 mg, 1.89 mmol, 1.0 eq) was suspended in CH_2Cl_2 (20 mL) and trifluoroacetic acid (0.84 mL, 11.3 mmol, 6 eq) was added after which the reaction mixture became a clear solution and was heated to reflux for 2 days. ^{1}H-NMR showed complete deprotected but also dehydrated product. The reaction mixture was concentrated and stirred in a mixture of THF (3 mL) and 1M NaOH (6 mL) and stirred for 2 days. Then the THF was removed by distillation and the aqueous mixture was extracted with EtOAc (2 x 20 mL). The combined organic layers were washed with brine (10 mL) and concentrated to yield 250 mg (80%) of the title compound as a white solid. ^{1}H-NMR (300MHz, $CDCl_3$): δ= 1.37 (d, *J*=6.6Hz, 3H), 1.49 (d, *J*=6.3Hz, 3H), 1.80 (bs, 3H), 4.10 (q, *J*=6.6Hz, 1H), 4.88 (q, *J*=6.3Hz, 1H), 7.29-7.36 (m, 4H) ppm. ^{13}C-NMR (75MHz, $CDCl_3$): δ= 25.3, 25.4, 51.0, 69.7, 125.7, 125.8, 126.5, 145.0 ppm. MS (EI): *m/z*= 131 [$M-NH_3-H_2O+H^+$], 149 [$M-NH_3+H^+$].

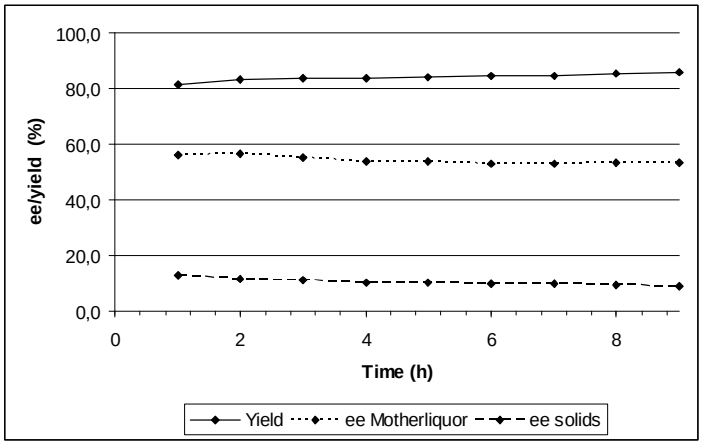
[(*1R*)-1-(3-methoxyphenyl)ethyl][(±)-1-(3-methoxyphenyl)ethyl]amine. A mixture of (R)- 1-(3-methoxyphenyl)ethan-1-amine (0.895 g, 5.92 mmol, 1.0 eq), 3-methoxyacetophenone (0.816 mL, 5.92 mmol, 1.0 eq), $Ti(O^iPr)_4$ (5.3 mL, 17.8 mmol, 3.0 eq) was stirred for 20 minutes and became warm to the touch. Pd/C (10% Pd, 120 mg) was added and a hydrogen atmosphere was applied by a balloon overnight. The reaction mixture was basified with 1M NaOH (25 mL) and EtOAc (20 mL) was added and the resulting mixture was filtered over a path of Celite. The aqueous layer was extracted with more EtOAc (2 x 10 mL). The combined organic layers were washed with brine (20 mL), dried (Na_2SO_4) and concentrated to dryness. The title compound was isolated as a colorless oil (1.43 g, 85%). RP-HPLC analysis of the material revealed an 1:10 mixture of diastereomers. ^{1}H-NMR (300MHz, $CDCl_3$): δ= 1.28 (d, *J*=6.6Hz, 6H), 3.51 (q, *J*=6.6Hz, 1H), 3.82 (s, 6H), 6.75-6.83 (m, 6H), 7.22-7.28 (m, 2H) ppm. ^{13}C-NMR (75MHz, $CDCl_3$): δ= 25.01, 55.27, 55.30, 112.21, 112.30, 112.36, 112.39, 119.21, 129.48, 147.66, 159.90 ppm. MS (EI): *m/z*= 286 [$M+H^+$].

Large scale resolutions with and without 1,3-BAPB

A mixture of (±)-3MeOPEA (19.66 g, 130 mmol, 1.0 eq), (*S*)-MA (19.78 g, 130 mmol, 1.0 eq) and MEK (2.00 L) was mechanically stirred in a thermostated double jacketed 2L flask at 20°C and allowing the mixture to crystallize. At this point, 0.5%n/n or 1.0%n/n of 1,3-BAPB·2(*S*)-MA could be added: 323mg or 646mg respectively. The mixture was heated to 70°C as fast as possible and then stirred at this temperature for 30 minutes resulting in complete dissolution of the salts. Then the mixture was cooled with 0.1°C/min to 20°C. When the mixture reached 20°C hourly samples of ~0.6 ml were taken and the solids were collected and sucked dry. The evaporated mother liquor and filter cake were analyzed by chiral HPLC for *de* and

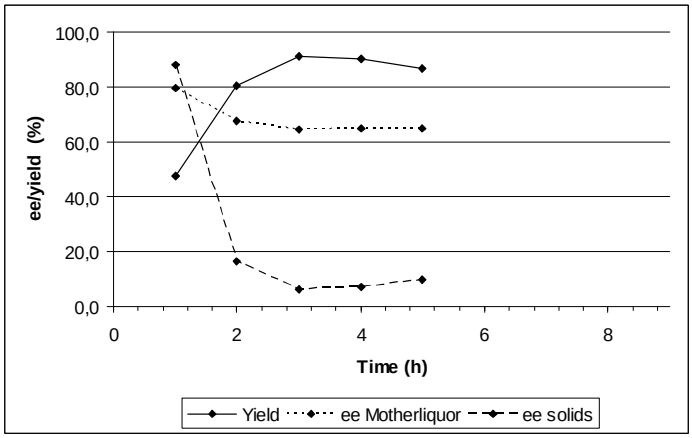
amount of additive. From both *de*ôs, the yield can be calculated. Please note that small amounts of mother liquor are still present in the solids and hereby lowering and fluctuating the *de* of the later. Proper washing of the filtercake of the salts obtained after 5 days from the resolution with 1.0% additive furnished 17.1g (41%) of salts with 96% *de* and contained 1.4% 1,3-BAPB compared to 3MeOPEA. The results are depicted in the schemes below

Scheme 1



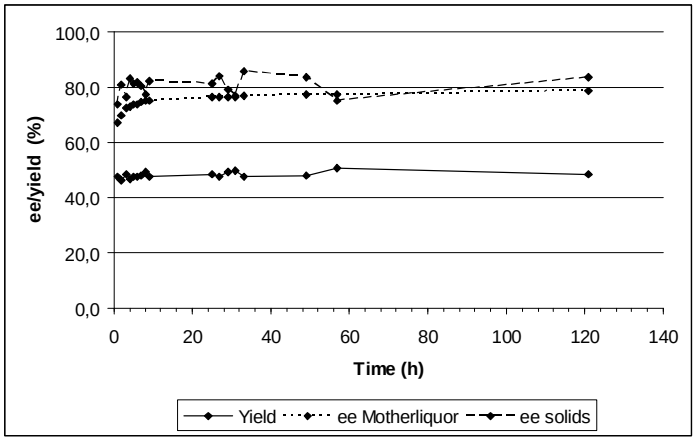
Blanc resolution

Scheme 2



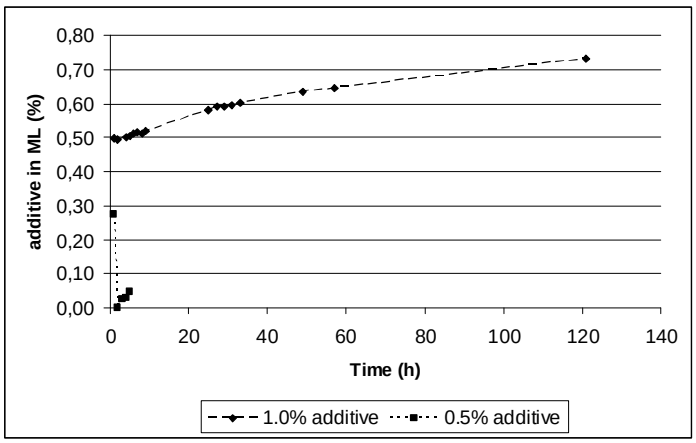
Resolution with 0.5% additive

Scheme 3



Resolution with 1.0% additive

Scheme 4

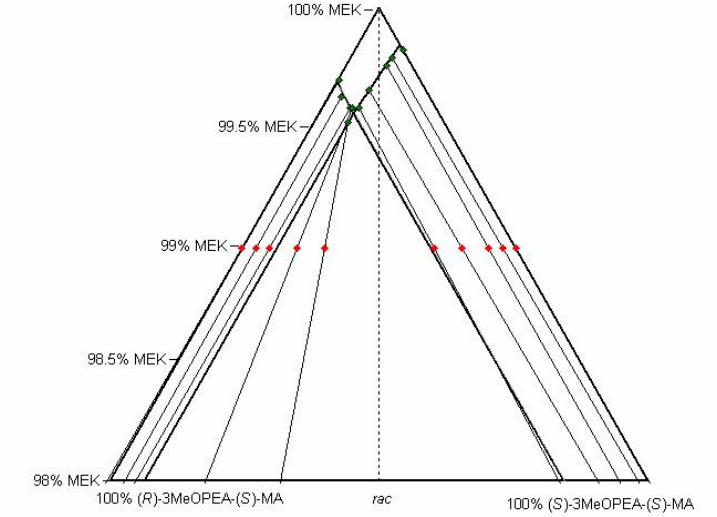


Percentage additive in the mother liquors

Phase diagrams

Ternary phase diagram after 2 days

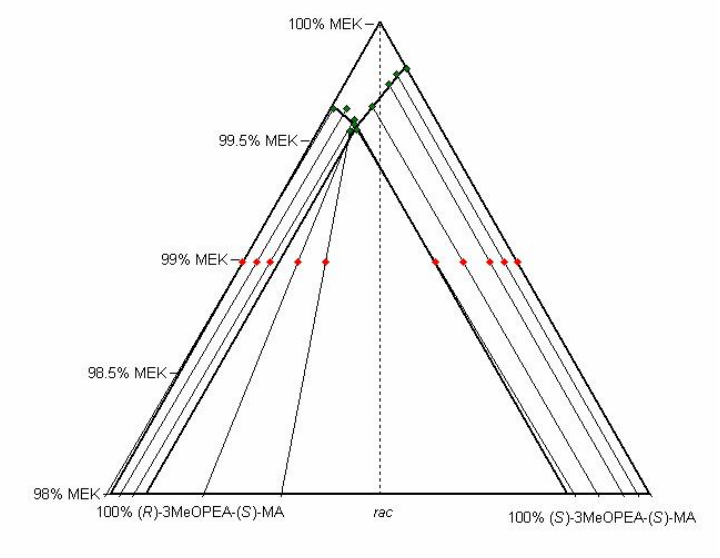
To determine the thermodynamic ternary phase diagram, suspensions were made in varying in composition between (*R*) and (*S*)-3MeOPEA and treated like a typical resolution experiments as described above. However, the mixtures were stirred at 20°C for an additional days to ensure that thermodynamic equilibrium as been reached. The composition of the mother liquors was determined and with the method of algebraic extrapolation the compositions of the solids were determined[vii]. The results are depicted in the Schemes below which are a representation of the top 2% of the full phase diagram.



Thermodynamic phase diagram of 3-MeOPEA-(*S*)-MA. The points in the diagrams represent the start composition and the mother liquor compositions.

Ternary phase diagram after a normal resolution experiment

A ternary phase diagram was made using the same method as for the phase diagram above, but now the motherliquor composition was determined after 8 hours at 20°C similar to a normal resolution experiment. The results are depicted in the Scheme below which are a representation of the top 2% of the full phase diagram.

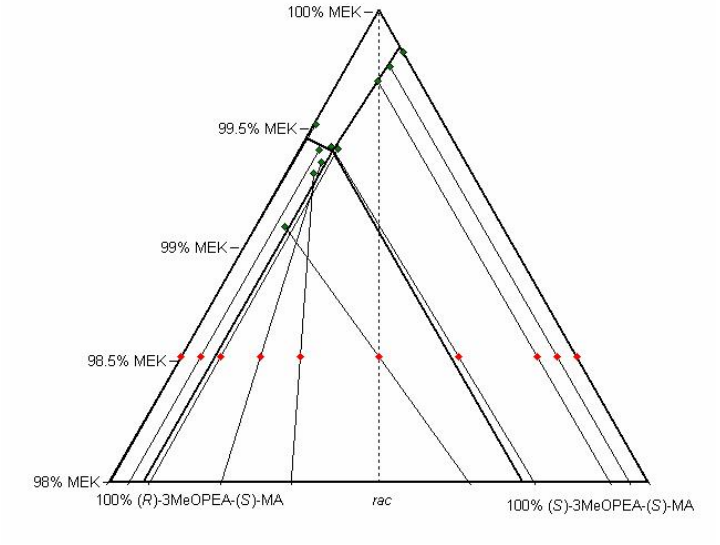


Thermodynamic phase diagram of 3-MeOPEA-(S)-MA. The points in the diagrams represent the start composition and the mother liquor compositions.

When both phase diagrams in this and the previous experiment were superimposed, no significant differences were found. We conclude that after a normal resolution experiment as described above, the thermodynamically equilibrium has been reached.

Ternary phase diagram after a normal resolution experiment with 1% additive

When 1% (S)-MA in the previous phase diagram was replaced by (*S*)-*O*-acetylmandelic acid a phase diagram was constructed: The results are depicted in the Scheme below which are a representation of the top 2% of the full phase diagram.

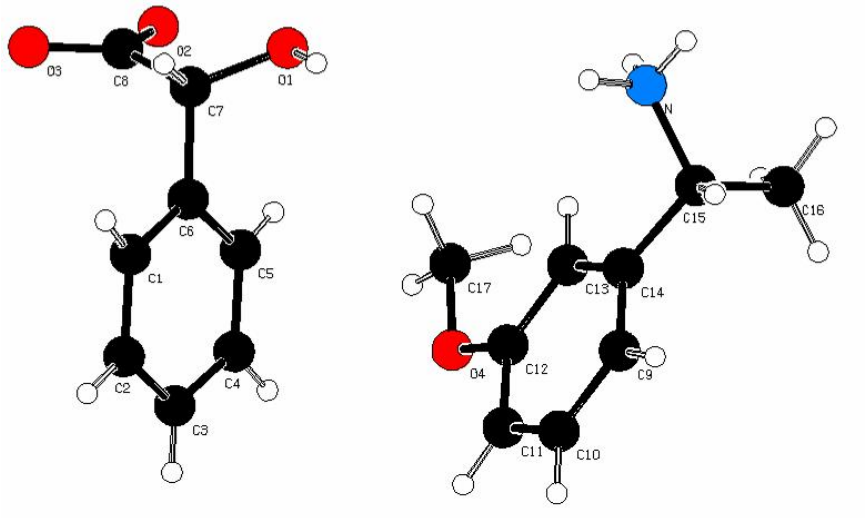


Kinetic phase diagram of 3-MeOPEA-(S)-MA with 1% (*S*)-*O*-acetylmandelic acid. The points in the diagrams represent the start composition and the mother liquor compositions.

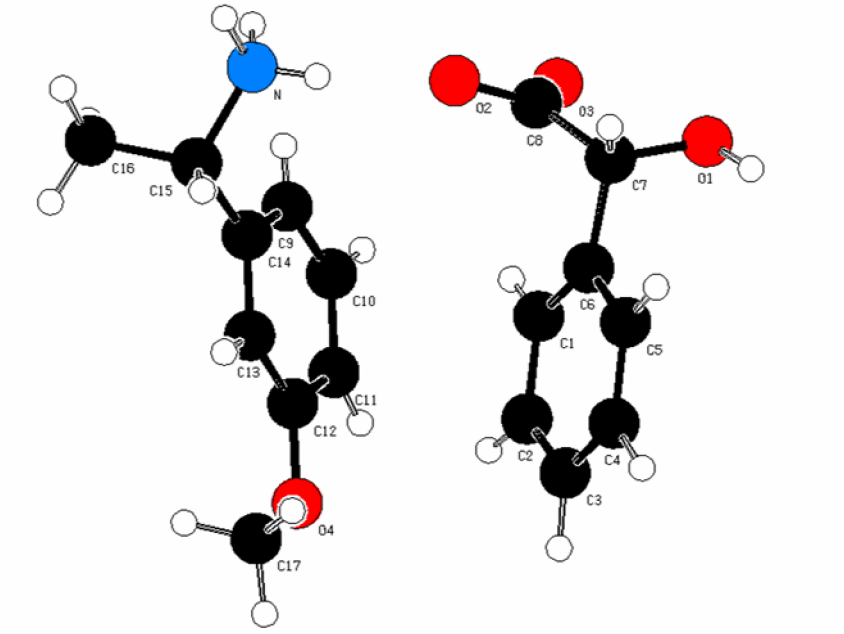
In this phase diagram it is clearly shown how an additive affects the resolution.

Crystal studies of 3MeOPEA-MA salts

Proper crystals were obtained by slow evaporation of concentrated solutions.
Less soluble (*R*)-3MeOPEA-(*R*)-MA (CCDC 657163):



More soluble (*S*)-3MeOPEA-(*R*)-MA salt (CCDC 657164):



References

[i] Resolution efficiency: S-factor = Yield x de x 2: E. Fogassy, A. Lopata, F. Faigl, F. Darvas, M. Ács, L. Toke, *Tetrahedron Lett.*, **1980**, *21*, 647.

[ii] Commercially available.

[iii] Synthesized according to: J.W. Nieuwenhuijzen, R.F.P. Grimbergen, C. Koopman, R.M. Kellogg, T.R. Vries, K. Pouwer, E. van Echten, B. Kaptein, L.A. Hulshof, Q.B. Broxterman, *Angew. Chem. Int. Ed.*, **2002**, *41*, 4281.

[iv] See experimental for preparation.

[v] Synthesized according to: T. Vries, H. Wynberg, E. van Echten, J. Koek, W. ten Hoeve, R.M. Kellogg, Q.B. Broxterman, A. Minnaard, B. Kaptein, S. van der Sluis, L. Hulshof, J. Kooistra, *Angew. Chem. Int. Ed.*, **1998**, *37*, 2349.

[vi] J. Dalmolen, T.D. Tiemersma-Wegman, J.W. Nieuwenhuijzen, M. van der Sluis, E. van Echten, T.R. Vries, B. Kaptein, Q.B. Broxtrrman, R.M. Kellogg, *Chem. Eur. J.*, **2005**, *11*, 5619.

[vii] J. Jacques, A. Collet, S.H. Wilen, ***ñ****Enantiomers, Racemates and Resolutions****ò***, Krieger Publ. Co., Malabar, Florida, **1994**, chapter 3.1.6.