Enantioselective PCCP Brønsted Acid Catalyzed Aminalization of Aldehydes

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Supporting information
# Table of content

Table of content.................................................................................................................. 2  
General ................................................................................................................................. 3  
Starting materials.................................................................................................................. 4  
Preparation of PCCP catalysts............................................................................................... 4  
Preparation of anthranilamide derivatives............................................................................ 6  
General procedure for aminalization of aldehydes............................................................... 7  
Literature ............................................................................................................................... 13  
NMR spectra .......................................................................................................................... 14  
HPLC chromatograms.......................................................................................................... 40  
X-Ray section ....................................................................................................................... 56
General

Chemicals and solvents were either purchased puriss *p.a.* from commercial suppliers or purified by standard techniques. For thin-layer chromatography (TLC), silica gel plates Merck 60 F254 were used and compounds were visualized by irradiation with UV light and/or by treatment with a solution of phosphomolybdic acid (AMC) or vanillic acid followed by heating. The solution of AMC was prepared from phosphomolybdic acid (25 g), Ce(SO$_4$)$_2$·H$_2$O (10 g), conc. H$_2$SO$_4$ (60 ml) and H$_2$O (940 ml). The solution of vanillin was prepared from vanillin (15 g) in ethanol (250 ml) and conc. sulfuric acid (2.5 ml). Column chromatography was performed using silica gel Fluka (40-63 µm). $^1$H, $^{19}$F and $^{13}$C NMR spectra were recorded with Bruker AVANCE III 400. Chemical shifts for protons are given in δ and are referenced to residual protium in the NMR solvent (Chloroform-$d$: δ = 7.26 ppm, DMSO-$d_6$: δ = 2.50 ppm, Acetonitrile-$d_3$ = 1.94 ppm). Chemical shifts for carbon are referenced to the carbon in NMR solvent (Chloroform-$d$: δ = 77.0 ppm, DMSO-$d_6$: δ = 39.5 ppm, Acetonitrile-$d_3$ = 118.2 ppm). The coupling constants $J$ are given in Hz. Chiral HPLC was carried out using a LC20AD Shimadzu liquid chromatograph with SPD-M20A diode array detector with columns Daicel Chiralpak® IA, Daicel Chiralpak® IB, Daicel Chiralpak® AD, Daicel Chiralpak® ODH, Daicel Chiralpak® IG. Optical rotations were measured on AU-Tomatica polarimeter, Autopol III. Specific optical rotations are given in concentrations *c [g/100 ml]*. IR DRIFT spectras were recorded with Nicolet AVATAR 370 FT-IR in cm$^{-1}$. High-resolution mass spectras were recorded with a LCQ Fleet spectrometer.
Starting materials

Preparation of PCCP catalysts

Tetramethyl 5-(hydroxy(methoxy)methylene)cyclopenta-1,3-diene-1,2,3,4-tetracarboxylate (I):

Compound I was prepared according to literature\(^1\): \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta_H = 20.09\) (s, 1H), 4.04 (s, 6H), 3.90 (s, 6H), 3.76 (s, 3H) ppm; \(^{13}\)C-NMR (101 MHz, CDCl\(_3\)): \(\delta_C = 172.4\) (2C), 167.8 (2C), 163.3, 133.7 (2C), 117.0, 106.4 (2C), 55.7 (2C), 52.7 (2C), 52.0 ppm; MS (ESI+) \(m/z\): calc. for C\(_{15}\)H\(_{15}\)O\(_{10}\) [M-H]: 355.1, found: 355.0.

Tetrakis((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl) 5-(hydroxy(((1R,2S,5R)-2-isopropyl-5-methylcyclohexyl)oxy)methylene)cyclopenta-1,3-diene-1,2,3,4-tetracarboxylate (II):

Compound II was prepared according to the published procedure\(^1\): \(^1\)H-NMR (400 MHz, CDCl\(_3\)): \(\delta_H = 20.30\) (s, 1H), 5.11 – 4.63 (m, 5H), 2.72 – 0.40 (m, 90H) ppm; \(^{13}\)C-NMR \(\delta_C = 172.1\) (2C) 167.1 (2C), 162.7, 134.3 (2C), 118.8, 106.5 (2C), 81.2 (2C), 76.6 (2C), 75.7, 47.5 (2C), 46.2 (3C), 41.6 (2C), 40.8, 40.3 (2C), 34.4-34.0 (5C), 32.0-31.7 (5C), 25.6-25.4 (5C), 23.3-21.0 (15C), 16.6-15.7 (5C) ppm; HRMS (ESI+) \(m/z\): calc. for C\(_{60}\)H\(_{96}\)O\(_{10}\)Na [M+Na\(^+\)]: 999.7, found: 999.9.

Trimethyl (E)-5-(hydroxy(((S)-1,2,3,4-tetrahydronaphthalen-1-yl)amino)methylene)-4-(((S)-1,2,3,4-tetrahydronaphthalen-1-yl)carbamoyl)cyclopenta-1,3-diene-1,2,3-tricarboxylate (III):

Red-brown syrup, 42 % yield (206 mg); \(R_f = 0.89\) (CH\(_2\)Cl\(_2\)/MeOH = 7:1, detected in vanilline). \(^1\)H-NMR (600 MHz, CDCl\(_3\)): \(\delta_H = 19.94\) (s, 1H), 11.43 (s, 2H), 7.25 – 7.08 (m, 8H), 5.36 (d, \(J = 6.7\) Hz, 2H), 3.79 (s, 3H), 3.69 (s, 6H), 2.91 (dt, \(J = 17.0, 6.2\) Hz, 2H), 2.80 (dt, \(J = 16.9, 6.3\) Hz, 2H), 2.15 (td, \(J = 7.5, 6.4, 3.5\) Hz, 2H), 1.99 (dt, \(J = 12.8, 7.0\) Hz, 4H), 1.94 – 1.85 (m, 2H) ppm; \(^{13}\)C-NMR (151 MHz, CDCl\(_3\)): \(\delta_C = 168.9, 168.6\) (2C), 167.5 (2C), 137.5 (2C), 135.4 (2C), 131.7, 129.4 (2C), 128.8 (2C), 127.7 (2C), 126.3 (2C), 117.8, 115.3 (2C), 52.8 (2C), 52.1 (2C), 49.7 (2C), 29.8 (2C), 29.2 (2C), 20.2 (2C) ppm; IR (KBr): \(\nu = 3431, 2950, 2863, 1739, 1631, 1607, 1440, 1350, 1299, 1222, 1162, 1099, 1072, 1024, 1003\) cm\(^{-1}\); [\(\alpha\)]\(_D\)^20 = –14.2 (\(c = 0.53\); MeOH); HRMS (ESI-) \(m/z\): calc. for C\(_{33}\)H\(_{34}\)N\(_2\)O\(_8\) [M-H]: 585.2242, for: 585.2251.
Tetramethyl 5-(((1R,2R)-2-(3-(3,5-bis(trifluoromethyl)phenyl)thiourea)cyclohexyl)amino)(hydroxy)methylene)cyclopenta-1,3-diene-1,2,3,4-tetracarboxylate (IV):

In dry flask PCCP I (200 mg, 0.561 mmol, 1.0 equiv.) and 1-((1R,2R)-2-aminocyclohexyl)-3-(3,5-bis(trifluoromethyl)phenyl)thiourea (216 mg, 0.561 mmol, 1.0 equiv.) were dissolved in dry toluene (7 mL). Then the reaction mixture was refluxed for 60 min. After cooling to room temperature, solvents were evaporated on rotavap. The crude product was purified by column chromatography (CH$_2$Cl$_2$/MeOH 20:1). Then combined organic phases were washed by 1M HCl (3×25 mL), dried over anhydrous MgSO$_4$, and solvents were evaporated in vacuo to give desired product IV as brown solid in 82% yield (330 mg).

Brown solid, yield 82% (330 mg), m.p. 67-68 °C; R$_f$ = 0.89 (CH$_2$Cl$_2$/MeOH = 7:1, detected in vanilline).

$^1$H-NMR (400 MHz, MeOD) δH 8.25 (s, 2H), 7.67 (s, 1H), 4.60 (bs, 1H), 3.73 (s, 12H), 2.91 (dd, J = 11.8, 10.6, 4.2 Hz, 1H), 2.20 – 2.00 (m, 2H), 1.83 (d, J = 10.2 Hz, 2H), 1.53 (q, J = 12.3, 11.8 Hz, 1H), 1.48 – 1.27 (m, 3H) ppm;

$^{13}$C-NMR (101 MHz, MeOD): δC = δ 183.6, 169.9, 169.86 (3C), 142.96 (2C), 132.63 (q, J = 33.4 Hz, 2C), 124.7 (q, J = 273 Hz, 2C); 124.4 (3C), 118.4 (2C), 118.3 (q, J = 4 Hz, 2C), 64.1, 56.5, 56.3, 52.0 (4C), 32.1, 31.1, 25.5, 24.7 ppm; $^{19}$F NMR (376 MHz, MeOD) δF -64.5; IR (KBr) ν = 3550, 3311, 3049, 3005, 2951, 2868, 2787, 1699, 1601, 1545, 1469, 1385, 1360, 1329, 1279, 1219, 1178, 1134, 1109, 1074 cm$^{-1}$; [$\alpha$]$^D_{D}$ = −40.8 (c = 2.04; DMSO); HRMS (ESI-) m/z: calc. for C$_{29}$H$_{28}$F$_6$N$_3$O$_9$S [M-H]$^-$: 708.1529, for: 708.1531.
Preparation of anthranilamide derivatives

2-Amino-4-bromobenzamide (1g) and 2-amino-5-methylbenzamide (1m) and were prepared according to the literature\(^2\), 2-amino-6-bromobenzamide (1i) was prepared according to the published procedure\(^3\), 2-(2-aminophenyl)acetamide (1p) was prepared according to the published procedure\(^4\) and 2-(benzylamino)benzamide (1q) was prepared according to the published procedure\(^5\).

2-Amino-4-bromobenzamide (1g)

Characterization according to the literature\(^6\). \(^1\)H-NMR (400 MHz, DMSO-\(d_6\)) \(\delta_H = 7.78\) (s, 1H), 7.46 (d, \(J = 8.5\) Hz, 1H), 7.15 (s, 1H), 6.99 – 6.86 (m, 1H), 6.80 (s, 2H), 6.71 – 6.57 (m, 1H) ppm; \(^13\)C-NMR (101 MHz, DMSO-\(d_6\)) \(\delta_C = 170.5, 151.6, 130.7, 125.3, 118.1, 116.8, 112.7\) ppm; MS (ESI+) \(m/z\): calc. for C\(_7\)H\(_6\)BrN\(_2\)ONa [M-H+Na]\(^+\): 236.0, found: 236.2.

2-Amino-6-bromobenzamide (1i)

Characterization according to the literature\(^2\). \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta_H = 6.98\) (t, \(J = 8.0\) Hz, 1H), 6.91 (dd, \(J = 7.9\) Hz, \(J' = 1.0\) Hz, 1H), 6.63 (dd, \(J = 8.0\) Hz, \(J' = 1.0\) Hz, 1H), 6.03 (s, 2H), 4.59 (s, 2H) ppm; \(^13\)C-NMR (101 MHz, CDCl\(_3\)) \(\delta_C = 169.5, 147.5, 131.7, 122.4, 121.2, 119.9, 115.5\) ppm; MS (ESI+) \(m/z\): calc. for C\(_7\)H\(_8\)BrN\(_2\)O [M-H]\(^+\): 215.0, found: 215.0.

2-Amino-5-methylbenzamide (1m)

Characterization according to the literature\(^2\). \(^1\)H-NMR (400 MHz, DMSO-\(d_6\)) \(\delta_H = 7.67\) (d, \(J = 15.3\) Hz, 1H), 7.41 – 7.30 (m, 2H), 6.98 (s, 1H), 6.95 (dd, \(J = 8.3\) Hz, \(J' = 1.8\) Hz, 1H), 6.59 (d, \(J = 8.3\) Hz, 1H), 6.31 (s, 2H), 2.14 (s, 3H) ppm; \(^13\)C-NMR (101 MHz, DMSO-\(d_6\)) \(\delta_C = 171.3, 147.9, 132.7, 128.7, 122.7, 116.5, 113.8, 20.0\) ppm; MS (ESI+) \(m/z\): calc. for C\(_8\)H\(_{10}\)N\(_2\)O [M+Na]\(^+\): 173.1, found: 173.1.

2-(2-aminophenyl)acetamide (1p)

Brown solid, yield 50 % (110 mg), m.p. 140-141 °C; \(^1\)H-NMR (400 MHz, CDCl\(_3\)) \(\delta_H = 7.11\) (td, \(J = 7.7\) Hz, \(J' = 1.5\) Hz, 1H), 7.07 – 7.01 (m, 1H), 6.78 – 6.67 (m, 2H), 5.75 (bs, 2H), 4.05 (bs, 1H), 3.47 (s, 2H) ppm; \(^13\)C-NMR (101 MHz, CDCl\(_3\)) \(\delta_C = 173.9, 145.5, 131.0, 128.9, 120.2, 119.2, 116.6, 40.5\) ppm; IR (KBr): \(\nu = 3348, 3400, 3195, 1658, 1622, 1281\) cm\(^{-1}\); HRMS (ESI+) \(m/z\): calc. for C\(_8\)H\(_{11}\)N\(_2\)O [M+H]\(^+\): 151.0866, found: 151.0865.

2-(benzylamino)benzamide (1q)

Characterization according to the literature\(^7\). \(^1\)H-NMR (400 MHz, DMSO) \(\delta_H = 8.59\) (s, 1H), 7.86 (s, 1H), 7.62 (d, \(J = 7.2\) Hz, 1H), 7.33 (d, \(J = 3.7\) Hz, 3H), 7.28 – 7.16 (m, 4H), 6.61 (d, \(J = 8.2\) Hz, 1H), 6.53 (t, \(J = 7.1\) Hz, 1H), 4.38 (d, \(J = 5.3\) Hz, 2H) ppm; \(^13\)C-NMR (101 MHz, DMSO) \(\delta_C = 171.6, 149.6, 139.7, 132.5, 129.1, 128.5\) (2C), 128.2, 127.1 (2C), 126.8, 114.2, 111.5, 46.0 ppm; MS (ESI+) \(m/z\): calc. for C\(_{14}\)H\(_{15}\)N\(_2\)O [M+H]\(^+\): 227.1, found: 227.1.
General procedure for aminalization of aldehydes

General procedure:
To the amide 1 (0.1 mmol, 1.0 equiv.) in dry flask, catalyst II (10 mg, 0.01 mmol, 0.1 equiv.) and molecular sieves (5 Å, 30 mg) were added. The reaction mixture was degassed and filled with argon. Solids were dissolved in dry toluene or THF (1 mL), and a resulted solution was cooled to −45 °C followed by dropwise addition of corresponding aldehyde 2 (0.1 mmol, 1.0 equiv.) dissolved in dry toluene or THF (1 mL). Then the reaction mixture was allowed to stir at the indicated temperature until complete consumption of starting material was observed. The reaction mixture was then directly loaded on silica and purified by column chromatography (n-Hexane/EtOAc) to give desired aminals 3a-p.
(R)-2-Isobutyl-2,3-dihydroquinazolin-4(1H)-one (3a):
The title compound 3a was prepared according to the general procedure (reaction time: 20 hours, solvent: toluene, mobile phase (n-hexane/EtOAc 3:1 to 2:1), affording the title compound as white solid in yield 96 % (19.5 mg), m.p. 144-145 °C, 81 % (93% after recrystallization) ee; Rf = 0.39 (n-hexane/EtOAc = 1:1). 1H-NMR (400 MHz, (CDCl3): δH = 7.87 (dd, J = 7.8 Hz, J’ = 1.5 Hz, 1H), 7.28 (ddd, J = 8.4 Hz, J’ = 7.5, 1.7 Hz, 1H), 6.89 (s, 1H), 6.88 – 6.79 (m, 1H), 6.71 – 6.64 (m, 1H), 4.91 (tt, J = 6.5 Hz, J’ = 1.6 Hz, 1H), 4.35 (s, 1H), 1.80 (dp, J = 13.2 Hz, J’ = 6.6 Hz, 1H), 1.73 – 1.60 (m, 2H), 0.97 (d, J = 1.3 Hz, 3H), 0.95 (d, J = 1.3 Hz, 3H) ppm; 13C-NMR (101 MHz, CDCl3) δc = 165.7, 147.6, 133.8, 128.6, 119.4, 116.4, 115.0, 63.7, 44.5, 23.9, 22.8, 22.7 ppm; [α]D20 = −107.7 (c = 0.39, THF); Enantiomeric excess (84 % e.e.) was determined by HPLC using chiral OD-H column (mobile phase: n-heptane/propan-2-ol = 80:20, λ = 210 nm, V = 1 mL/min, T = 25 °C), tR = 8.1 min (minor. enantiomer), tR = 10.1 min (major. enantiomer); MS (ESI+) m/z: calc. for C13H16N2O [M+Na]+: 227, found: 227.

(R)-2-Cyclohexyl-2,3-dihydroquinazolin-4(1H)-one (3b):
The title compound 3b was prepared according to the general procedure (reaction time: 40 hours, solvent: toluene, mobile phase (n-Hexane/EtOAc 1:1), affording the title compound as white solid in yield 96 % (22 mg), 74 % ee.; Rf = 0.25 (n-Hexane/EtOAc = 1:1). 1H-NMR (400 MHz, (CDCl3): δH = 7.86 (d, J = 7.8 Hz, 1H), 7.31 – 7.25 (m, 1H), 6.85 – 6.76 (m, 1H), 6.65 (d, J = 8.1 Hz, 1H), 6.33 (bs, 1H), 4.63 (d, J = 5.0 Hz, 1H), 4.31 (bs, 1H), 1.94 – 1.56 (m, 6H), 1.44 – 0.99 (m, 5H) ppm; 13C-NMR (101 MHz, CDCl3) δc = 165.4, 147.5, 133.9, 128.6, 119.1, 115.8, 114.6, 69.7, 42.8, 27.6, 26.3, 25.9 ppm; [α]D20 = –68.2 (c = 0.33, THF); Enantiomeric excess (74 % e.e.) was determined by HPLC using chiral IA column (mobile phase: n-Heptane/propan-2-ol = 80:20, λ = 190 nm, V = 1 mL/min, T = 25 °C), tR = 7.9 min (minor enantiomer), tR = 9.7 min (major enantiomer); MS (ESI+) m/z: calc. for C14H18N2Oa [M+Na]+: 253.1, found: 253.2.

(R)-2-tert-Butyl-2,3-dihydroquinazolin-4(1H)-one (3c):
The title compound 3c was prepared according to the general procedure (reaction time: 72 hours, solvent: toluene, mobile phase (n-Hexane/EtOAc = 1:1), affording the title compound as white solid in yield 95 % (19.0 mg), b.p. 156-159 °C, 10% ee.; Rf = 0.30 (n-Hexane/EtOAc = 1:1). 1H-NMR (400 MHz, (CDCl3): δH = 7.85 (dd, J = 7.8 Hz, J’ = 1.3 Hz, 1H), 7.27 (ddd, J = 8.7 Hz, J’ = 7.6 Hz, J’’ = 1.5 Hz, 1H), 6.83 – 6.75 (m, 1H), 6.65 (d, J = 8.0 Hz, 1H), 6.24 (s, 1H), 4.57 (s, 1H), 4.32 (s, 1H), 1.01 (s, 6H) ppm; 13C-NMR (101 MHz, CDCl3) δc = 165.5, 147.7, 134.0, 128.6, 119.0, 115.1, 114.4, 73.6, 35.5, 24.7 ppm; [α]D20 = –4.0 (c = 0.25, THF); Enantiomeric excess (10 % e.e.) was determined by HPLC using chiral IH column (mobile phase: n-Heptane/propan-2-ol = 80:20, λ = 190 nm, V = 1 mL/min, T = 25 °C), tR = 12.1 min (minor enantiomer), tR = 13.9 min (major enantiomer); HRMS (ESI+) m/z: calc. for C12H17N2O [M+H]+: 205.1335, found: 205.1336.

(R)-2-Butyl-2,3-dihydroquinazolin-4(1H)-one (3d):
The title compound 3d was prepared according to the general procedure (reaction time: 21 hours, solvent: toluene, mobile phase (n-Hexane/EtOAc 3:1 to 2:1), affording the title compound as white solid in yield 97 % (19.7 mg) and 76 % ee. Rf = 0.39 (n-Hexane/EtOAc = 1:1, detected in vanilline). 1H-NMR (400 MHz, CDCl3): δH = 7.87 (d, J = 7.7 Hz, 1H), 7.32 – 7.27 (m, 1H), 6.89 – 6.80 (m, 1H), 6.13 (s, 1H), 4.87 (t, J = 5.8 Hz, 1H), 4.20 (s, 1H), 1.90 – 1.71 (m, 2H), 1.40 (dq, J =
7.0 Hz, J′ = 3.6 Hz, 4H), 0.94 (t, J = 7.0 Hz, 3H) ppm; 13C-NMR (101 MHz, CDCl3) δc = 165.3, 147.5, 133.9, 128.8, 119.6, 116.1, 114.9, 65.5, 35.5, 26.3, 22.6, 14.1 ppm; [α]D20 = −97.8 (c = 0.23, THF); Enantiomeric excess (76 % e.e.) was determined by HPLC using chiral IG column (mobile phase: n-heptane/propan-2-ol = 80:20, λ = 200 nm, V = 1 mL/min, T = 25 °C), tR = 9.3 min (minor enantiomer), tR = 10.1 min (major enantiomer); MS (ESI+) m/z: calc. for C12H16N2O [M + Na]+: 227, found: 227.

(R)-2-Phenyl-2,3-dihydroquinazolin-4(1H)-one (3e):

The title compound 3e was prepared according to the general procedure (reaction time: 96 hours, solvent: toluene, mobile phase (n-Hexane/EtOAc 3:1), affording the title compound as white solid in the yield 77 % (17.3 mg), 68 % ee. Rf = 0.48 (n-Hexane/EtOAc = 1:1). 1H-NMR (400 MHz, (CD3)2SO): δH = 8.28 (t, J = 2.0 Hz, 1H), 7.61 (dd, J = 7.8, 1.6 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.45 – 7.31 (m, 3H), 7.24 (ddd, J = 8.6, 7.2, 1.6 Hz, 1H), 7.11 (s, 1H), 6.75 (dd, J = 8.1, 1.0 Hz, 1H), 6.67 (td, J = 7.4, 1.1 Hz, 1H) ppm; [α]D20 = −135.3 (c = 0.26; THF); Enantiomeric excess (68 % e.e.) was determined by HPLC using chiral AD-H column (mobile phase: n-heptane/propan-2-ol = 80:20, λ = 228 nm, V = 1 mL/min, T = 25 °C), tR = 11.7 min (minor enantiomer), tR = 13.7 min (major enantiomer); MS (ESI+) m/z: calc. for C14H12N2O [M + Na]+: 247, found: 246.

(R)-2-Tolyl-2,3-dihydroquinazolin-4(1H)-one (3f):

The title compound 3f was prepared according to the general procedure (reaction time: 112 hours, solvent: toluene, mobile phase (n-Hexane/EtOAc 2:1), affording the title compound as white solid in the yield 83 % (20 mg), b.p. 222 °C, 70% (97% after recrystallization) e.e. Rf = 0.25 (n-Hexane/EtOAc = 1:1). 1H-NMR (400 MHz, CDCl3): δH = 7.95 (d, J = 6.6 Hz, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.37 – 7.30 (m, 1H), 7.25 (d, J = 8.2 Hz, 2H), 6.90 (t, J = 7.5 Hz, 1H), 6.66 (d, J = 8.0 Hz, 1H), 5.87 (s, 1H), 5.77 (s, 1H), 4.35 (s, 1H), 2.40 (s, 3H) ppm; 13C-NMR (101 MHz, CDCl3) δc = 165.0, 147.5, 140.4, 135.8, 134.1, 129.9, 128. 9, 127.5, 119.8, 114.7, 69.1, 21.4 ppm; [α]D20 = −52.5 (c = 0.20; THF); Enantiomeric excess (70 % e.e.) was determined by HPLC using chiral IA column (mobile phase: n-Heptane/propan-2-ol = 90:10, λ = 190 nm, V = 1 mL/min, T = 25 °C), tR = 25. 9 min (minor enantiomer), tR = 29.8 min (major enantiomer); HRMS (ESI+) m/z: calc. for C13H15N2O [M+H]+: 239.1179, found: 239.1181.

(R)-8-Bromo-2-isobutyl-2,3-dihydroquinazolin-4(1H)-one (3g):

The title compound 3g was prepared according to the general procedure (reaction time: 96 hours, mobile phase (n-Hexane/EtOAc 2:1 to 1:1), affording the title compound as white solid in yield 71 % (20 mg), b.p. 142-143 °C, 30 % ee. Rf = 0.5 (n-Hexane/EtOAc = 1:1). 1H-NMR (400 MHz, CDCl3): δH = 7.89 – 7.82 (m, 1H), 7.53 (dd, J = 7.9 Hz, J′ = 1.4 Hz, 1H), 6.73 (t, J = 7.8 Hz, 1H), 6.53 (s, 1H), 4.98 (tt, J = 6.4 Hz, J′ = 1.5 Hz, 1H), 4.77 (s, 1H), 1.82 (dq, J = 12.9 Hz, J′ = 6.5 Hz, 1H), 1.75 – 1.68 (m, 1H), 1.02 (s, 3H), 1.00 (s, 3H) ppm; 13C-NMR NMR (101 MHz, CDCl3) δc = 164.5, 144.9, 136.7, 128.1, 119.7, 117.3, 108.9, 63.6, 44.6, 24.1, 22.7 ppm; IR (KBr): ν = 3402, 3305, 2964, 1684, 1383, 748 cm−1; [α]D20 = −8.6 (c = 0.29; THF); enantiomeric excess (30 % e.e.) was determined by HPLC using chiral IA column (mobil phase: n-Heptane/propan-2-ol = 80:20, λ = 190 nm, V = 1 mL/min, T = 25 °C), tR = 5.0 min (minor enantiomer), tR = 5.9 min (major enantiomer); HRMS (ESI+) m/z: calc. for C12H13BrN2NaO [M+Na] +: 305.0260, found: 305.0266.
(R)-7-Bromo-2-isobutyl-2,3-dihydroquinazolin-4(1H)-one (3h):

The title compound 3h was prepared according to the general procedure (reaction time: 96 hours, mobile phase (n-Hexane/EtOAc 2:1)), affording the title compound as white solid in yield 89 % (25 mg), b.p. 166 °C, 70% ee. Rf = 0.33 (n-Hexane/EtOAc = 1:1). 1H-NMR (400 MHz, (CDCl3): δH = 7.72 (d, J = 8.3 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.85 (d, J = 1.6 Hz, 1H), 6.61 (bs, 1H), 4.92 (t, J = 6.2 Hz, 1H), 4.34 (s, 1H), 1.78 (tq, J = 15.2 Hz, J′ = 8.6 Hz, J′′ = 7.7 Hz, 1H), 1.71 – 1.61 (m, 2H), 0.98 (s, 3H), 0.96 (s, 3H) ppm; 13C-NMR NMR (101 MHz, CDCl3) δ = 164.8, 148.3, 130.2, 128.4, 122.7, 117.6, 115.1, 63.8, 44.6, 24.0, 22.7, 22.7 ppm; IR (KBr): ν = 3305, 3197, 2870, 1651, 1375, 1265 cm⁻¹; [α]D²⁰ = –63.6 (c = 0.30; THF); enantiomeric excess (70 % e.e.) was determined by HPLC using chiral IA column (mobil phase: n-Heptane/propan-2-ol = 80:20, λ = 190 nm, V = 1 mL/min, T = 25 °C), tR = 7.3 min (minor enantiomer), tR = 8.2 min (major enantiomer); HRMS (ESI+) m/z: calc. for C12H16BrN2O [M+H]+: 283.0441, found: 283.0441.

(R)-6-Bromo-2-isobutyl-2,3-dihydroquinazolin-4(1H)-one (3i):

The title compound 3i was prepared according to the general procedure (reaction time: 96 hours, solvent: toluene, mobile phase (n-Hexane/EtOAc 3:1 to 2:1), affording the title compound as light-yellow solid in yield 78 % (22 mg) and 80 % ee. Rf = 0.51 (n-Hexane/EtOAc = 1:1). 1H-NMR (400 MHz, CDCl3): δH = 7.99 (d, J = 2.3 Hz, 1H), 7.37 (dd, J = 8.6 Hz, J′ = 2.4 Hz, 1H), 6.57 (d, J = 8.6 Hz, 1H), 6.32 (s, 1H), 4.91 (t, J = 6.3 Hz, 1H), 4.23 (s, 1H), 1.78 (dp, J = 13.0 Hz, J′ = 6.6 Hz, 1H), 1.66 (td, J = 7.7 Hz, J′ = 7.1 Hz, J′′ = 1.9 Hz, 2H), 0.99 (d, J = 1.3 Hz, 3H), 0.98 (d, J = 1.3 Hz, 3H) ppm; 13C-NMR (101 MHz, CDCl3) δc = 164.2, 146.3, 136.6, 131.3, 117.9, 116.8, 111.6, 63.7, 44.5, 24.0, 22.7 (2C) ppm; [α]D²⁰ = –90.3 (c = 0.31; THF); Enantiomeric excess (80 % e.e.) was determined by HPLC using chiral OD-H (mobile phase: n-heptane/propan-2-ol = 80:20, λ = 190 nm, V = 1 mL/min, T = 25 °C), tR = 9.7 min (minor enantiomer), tR = 14.2 min (major enantiomer); MS (ESI+) m/z: calc. for C12H15BrN2O [M+H]+: 283.0, found: 282.93.

(R)-5-Bromo-2-isobutyl-2,3-dihydroquinazolin-4(1H)-one (3j):

The title compound 3j was prepared according to the general procedure (reaction time: 112 hours in a toluene, mobile phase (n-Hexane/EtOAc 2:1), affording the title compound as white solid in yield 83 % (23 mg), m.p. 173 °C, 66 % ee. Rf = 0.15 (n-Hexane/EtOAc = 2:1). 1H-NMR (400 MHz, (CDCl3): δH = 7.11 – 7.00 (m, 2H), 6.92 (s, 1H), 6.65 (dd, J = 7.9 Hz, J′ = 1.1 Hz, 1H), 4.79 (t, J = 6.2 Hz, 1H), 4.40 (s, 1H), 1.84 (dp, J = 13.2 Hz, J′ = 6.6 Hz, 1H), 1.71 (dt, J = 13.6 Hz, J′ = 6.8 Hz, 1H), 1.59 (ddd, J = 13.7 Hz, J′ = 7.7 Hz, J′′ = 5.9 Hz, 1H), 0.97 (d, J = 4.0 Hz, 3H), 0.96 (d, J = 4.0 Hz, 3H) ppm; 13C-NMR (101 MHz, CDCl3) δc = 163.3, 150.3, 133.3, 126.4, 123.7, 115.3, 114.9, 62.8, 43.8, 24.0, 22.9, 22.6 ppm; IR (KBr): ν = 3317, 2954, 1639, 1599, 1381, 1334 cm⁻¹; [α]D²⁰ = –93.9 (c = 0.33; THF); Enantiomeric excess (66 % e.e.) was determined by HPLC using chiral IA (mobile phase: n-Heptane/propan-2-ol = 80:20, λ = 190 nm, V = 1 mL/min, T = 25 °C), tR = 6.0 min (minor enantiomer), tR = 6.7 min (major enantiomer); HRMS (ESI+) m/z: calc. for C12H16BrN2O [M+H]+: 283.0441, found: 283.0438.

(R)-6-Chloro-2-isobutyl-2,3-dihydroquinazolin-4(1H)-one (3k):

The title compound 3k was prepared according to the general procedure (reaction time: 72 hours, solvent: toluene, mobile phase (n-Hexane/EtOAc 2:1), affording the title compound as white solid in yield 83 % (20 mg), m.p.
154-155 °C, 76 % ee. Rf = 0.39 (n-Hexane/EtOAc = 1:1, detected in vanilline). ^1H-NMR (400 MHz, CDCl3) δH = 7.88 – 7.78 (m, 1H), 7.23 (dd, J = 8.6 Hz, J′ = 2.5 Hz, 1H), 6.88 (s, 1H), 6.62 (d, J = 8.6 Hz, 1H), 4.90 (t, J = 6.3 Hz, 1H), 4.31 (s, 1H), 1.79 (dq, J = 13.2 Hz, J′ = 6.6 Hz, 1H), 1.66 (td, J = 6.8 Hz, J′ = 4.8 Hz, 2H), 0.98 (s, 3H), 0.97 (s, 3H) ppm; ^13C-NMR (101 MHz, CDCl3) δc = 164.5, 146.0, 133.7, 128.2, 124.5, 117.5, 116.5, 63.8, 44.4, 24.0, 22.8, 22.7 ppm; [α]D20 = −116.1 (c = 0.28; THF); Enantiomeric excess (76 % e.e.) was determined by HPLC using chiral OD-H column (mobile phase: n-Heptane/propan-2-ol = 90:10, λ = 190 nm, V = 1 mL/min, T = 25 °C), tR = 9.2 min (minor enantiomer), tR = 13.0 min (major enantiomer); MS (ESI+) m/z: calc. for C12H15ClN2O [M + Na]+: 261, found: 261.

(R)-2-Isobutyl-7-nitro-2,3-dihydroquinazolin-4(1H)-one (3l):

The title compound 3l was prepared according to the general procedure (reaction time: 40 hours, solvent: THF at -65 °C, mobile phase (n-Hexane/EtOAc 2:1), affording the title compound as orange solid in yield 96 % (24 mg), b.p. 184 °C, 42 % ee. Rf = 0.37 (n-Hexane/EtOAc = 1:1, detected in vanilline). ^1H-NMR (400 MHz, CDCl3) δH 8.03 (d, J = 8.5 Hz, 1H), 7.63 (dd, J = 8.5 Hz, J′ = 2.1 Hz, 1H), 7.53 (d, J = 2.1 Hz, 1H), 6.63 (s, 1H), 5.01 (t, J = 6.3 Hz, 1H), 4.61 (s, 1H), 1.83 (dt, J = 13.3 Hz, J′ = 6.6 Hz, 1H), 1.71 (td, J = 7.6 Hz, J′ = 7.0 Hz, J″ = 2.3 Hz, 2H), 1.02 (s, 3H), 1.00 (s, 2H) ppm; ^13C-NMR (101 MHz, CDCl3) δc = 163.5, 151.5, 147.8, 130.3, 120.5, 113.6, 109.8, 63.9, 44.7, 24.0, 22.7 (2C) ppm; [α]D20 = −55.9 (c = 0.34; THF); IR (KBr): ν = 3512, 3067, 2944, 1745, 1329, 1269, 1159 cm⁻¹; Enantiomeric excess (36 % e.e.) was determined by HPLC using chiral IG column (mobile phase: n-Heptane/propan-2-ol = 80:20, λ = 254 nm, V = 1 mL/min, T = 25 °C), tR = 7.06 min (major enantiomer), tR = 8.08 min (minor enantiomer); HRMS (ESI+) m/z: calc. for C12H15N3O3 [M+Na]+: 272.1006 found: 272.1007.

(R)-2-Isobutyl-7-methyl-2,3-dihydroquinazolin-4(1H)-one (3m):

The title compound 3m was prepared according to the general procedure (reaction time: 84 hours, solvent: toluene, mobile phase (n-Hexane/EtOAc 3:1 to 2:1), affording the title compound as yellow solid in yield 80 % (18 mg), 69 % ee. Rf = 0.2 (n-Hexane/EtOAc = 1:1). ^1H-NMR (400 MHz, CDCl3) δH = 7.76 (d, J = 7.8 Hz, 1H), 6.67 (d, J = 7.9 Hz, 1H), 6.48 (s, 1H), 6.85 (t, J = 6.2 Hz, 1H), 4.13 (s, 1H), 2.29 (s, 3H), 1.76 (dq, J = 13.2 Hz, J′ = 6.6 Hz, 1H), 1.64 (t, J = 6.7 Hz, 3H), 0.96 (s, 3H), 0.98 (s, 3H) ppm; ^13C-NMR (101 MHz, CDCl3) δc = 165.5, 147.6, 144.8, 128.8, 121.0, 115.3, 113.9, 63.8, 44.5, 24.1, 22.8, 22.7, 21.9 ppm; [α]D20 = −89.2 (c = 0.19; THF); Enantiomeric excess (69 % e.e.) was determined by HPLC using chiral IG column (mobile phase: n-Heptane/propan-2-ol = 80:20, λ = 223 nm, V = 1 mL/min, T = 25 °C), tR = 17.0 min (minor enantiomer), tR = 18.5 min (major enantiomer); MS (ESI+) m/z: calc. for C13H18N2O [M + Na]+: 241, found: 241.

(R)-2-Isobutyl-6-methyl-2,3-dihydroquinazolin-4(1H)-one (3n):

The title compound 3n was prepared according to the general procedure (reaction time: 16 hours, solvent: toluene, mobile phase (n-hexane/EtOAc 3:1 to 2:1), affording the title compound as white solid in yield 96 % (20 mg) and 73 % ee. Rf = 0.18 (n-Hexane/EtOAc = 1:1, detected in vanilline). ^1H-NMR (400 MHz, CDCl3) δH = 7.69 (s, 1H), 7.12 (dd, J = 8.1 Hz, J′ = 1.9 Hz, 1H), 6.60 (d, J = 8.1 Hz, 1H), 6.12 (s, 1H), 4.87 (t, J = 6.2 Hz, 1H), 4.07 (s, 1H), 2.27 (s, 3H), 1.77 (dq, J = 13.3 Hz, J′ = 6.7 Hz, 1H), 1.65 (t, J = 6.7 Hz, 2H), 0.98 (d, J = 1.1 Hz, 3H), 0.97 (d, J = 1.1 Hz, 3H) ppm.; ^13C-NMR (101 MHz, CDCl3) δc = 165.6, 145.3, 134.8, 129.2, 128.6, 116.5,
Enantiomeric excess (73 % e.e.) was determined by HPLC using chiral OD-H column (mobile phase: n-Heptane/propan-2-ol = 80:20, λ = 220 nm, V = 1 mL/min, T = 25 °C), t_R = 7.2 min (minor enantiomer), t_R = 9.3 min (major enantiomer); MS (ESI+) m/z: calc. for C_{13}H_{18}N_2O [M + Na]^+: 241, found: 241.

(R)-2-Isobutyl-6-methoxy-2,3-dihydroquinazolin-4(1H)-one (3o):

The title compound 3o was prepared according to the general procedure (reaction time: 24 hours, solvent: toluene, mobile phase (n-Hexane/EtOAc 2:1 to 1:1), affording the title compound as white solid in yield 74 % (17 mg), b.p. 127 °C, 64 % ee. R_f = 0.52 (n-Hexane/EtOAc = 1:3, detected in vanilene): ^1H-NMR (400 MHz, CDCl_3): δ_H = 7.40 (d, J = 3.0 Hz, 1H), 6.93 (dd, J = 8.7 Hz, J’ = 3.0 Hz, 1H), 6.67 (d, J = 8.7 Hz, 1H), 6.62 (s, 1H), 4.84 (t, J = 6.2 Hz, 1H), 4.00 (s, 1H), 3.78 (s, 3H), 1.80 (dp, J = 13.2 Hz, J’ = 6.6 Hz, 1H), 1.65 (t, J = 6.7 Hz, 2H), 0.97 (d, J = 1.3 Hz, 3H), 0.95 (d, J = 1.3 Hz, 3H) ppm; ^13C-NMR (101 MHz, CDCl_3) δ_C = 165.6, 153.6, 141.6, 122.4, 117.7, 117.4, 110.6, 64.0, 55.9, 44.2, 24.0, 22.8, 22.7 ppm; [α]_D^20 = −72.7 (c = 0.55; THF); Enantiomeric excess (64 % e.e.) was determined by HPLC using chiral IG column (mobile phase: n-Heptane/propan-2-ol = 80:20, λ = 190 nm, V = 1 mL/min, T = 25 °C), t_R = 11.6 min (minor enantiomer), t_R = 13.0 min (major enantiomer); MS (ESI+) m/z: calc. for C_{13}H_{18}N_2O [M + Na]^+: 257, found: 257.

(R)-2-Isobutyl-1,2,3,5-tetrahydro-4H-benzo[d][1,3]diazepin-4-one (3p):

The title compound 3p was prepared according to the general procedure (reaction time: 24 hours, solvent: toluene, mobile phase (n-Hexane/EtOAc 1:1), affording the title compound as white solid in yield 55 % (12 mg), b.p. 170-172 °C, 35 % ee. ^1H-NMR (400 MHz, CDCl_3): δ_H = 7.05 (t, J = 7.6 Hz, 1H), 6.97 (d, J = 7.6 Hz, 1H), 6.72 (td, J = 7.5 Hz, J’ = 1.1 Hz, 1H), 6.53 (dd, J = 8.0 Hz, J’ = 1.0 Hz, 1H), 6.13 (d, J = 7.2 Hz, 1H), 5.21 (p, J = 6.9 Hz, 1H), 4.56 (d, J = 15.1 Hz, 1H), 3.99 (d, J = 6.9 Hz, 1H), 3.29 (dd, J = 15.1 Hz, J’ = 1.7 Hz, 1H), 1.80 (dp, J = 13.4 Hz, J’ = 6.7 Hz, 1H), 1.56 (t, J = 7.0 Hz, 2H), 0.99 (s, 3H), 0.97 (s, 3H) ppm; ^13C-NMR (101 MHz, CDCl_3) δ_C = 172.8, 144.0, 132.3, 128.4, 119.7, 117.7, 116.1, 61.1, 43.8, 42.4, 24.7, 22.6, 22.5 ppm; [α]_D^20 = −26.0 (c = 0.25; THF); IR (KBr): ν = 3305, 3192, 2960, 1654, 1495 cm⁻¹; Enantiomeric excess (35 % e.e.) was determined by HPLC using chiral IA column (mobile phase: n-Heptane/propan-2-ol = 80:20, λ = 190 nm, V = 1 mL/min, T = 25 °C), t_R = 7.0 min (major enantiomer), t_R = 10.7 min (minor enantiomer); HRMS (ESI+) m/z: calc. for C_{13}H_{19}N_2O [M+Na]^+: 219.1491 found: 219.1488.
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NMR spectra

$^1$H NMR (400 MHz, DMSO) of 1g.

$^{13}$C$[^1]$H NMR (101 MHz, DMSO) of 1g.
$^1$H NMR (400 MHz, DMSO) of II.

$^{13}$C$[^1]$H NMR (101 MHz, DMSO) of II.
$^1$H NMR (400 MHz, DMSO) of 1m.

$^{13}$C$[^1]$H NMR (101 MHz, DMSO) of 1m.
$^1$H NMR (400 MHz, DMSO) of \textbf{1p}.

$^{13}$C\textsuperscript{1}H NMR (101 MHz, DMSO) of \textbf{1p}.
$^1$H NMR (400 MHz, DMSO) of 1q.

$^{13}$C$[^1]$H NMR (101 MHz, DMSO) of 1q.
$^1$H NMR (400 MHz, DMSO) of I.

$^{13}$C$[^1]$H NMR (101 MHz, DMSO) of I.
$^1$H NMR (400 MHz, DMSO) of II.

$^{13}$C($^1$H) NMR (101 MHz, DMSO) of II.
$^1$H NMR (400 MHz, DMSO) of III.

$^{13}$C\{$^1$H} NMR (101 MHz, DMSO) of III.
H NMR (400 MHz, MeOD) of IV.

$^{13}$C$^{1}H$ NMR (101 MHz, MeOD) of IV.
$^{19}$F NMR (376 MHz, MeOD) of IV.
$^1$H NMR (400 MHz, CDCl$_3$) of 3a.

$^{13}$C$[^1]$H NMR (101 MHz, CDCl$_3$) of 3a.
$^1$H NMR (400 MHz, CDCl$_3$) of 3b.

$^{13}$C($^1$H) NMR (101 MHz, CDCl$_3$) of 3b.
\[ ^1H \text{NMR (400 MHz, CDCl}_3\text{)} \text{ of 3c.} \]

\[ ^{13}C\left[^1H\right] \text{NMR (101 MHz, CDCl}_3\text{)} \text{ of 3c.} \]
$^1$H NMR (400 MHz, CDCl$_3$) of 3d.

$^{13}$C $^1$H NMR (101 MHz, CDCl$_3$) of 3d.
$^1$H NMR (400 MHz, CDCl$_3$) of 3e.

$^{13}$C [$^1$H] NMR (101 MHz, CDCl$_3$) of 3e.
$^1$H NMR (400 MHz, CDCl$_3$) of 3f.

$^{13}$C-$^1$H NMR (101 MHz, CDCl$_3$) of 3f.
$^1$H NMR (400 MHz, CDCl$_3$) of 3g.

$^{13}$C[$^1$H] NMR (101 MHz, CDCl$_3$) of 3g.
$^1$H NMR (400 MHz, CDCl$_3$) of 3h.

$^{13}$C\(^{1}$H\) NMR (101 MHz, CDCl$_3$) of 3h.
$^1$H NMR (400 MHz, CDCl$_3$) of 3i.

$^{13}$C\{$^1$H} NMR (101 MHz, CDCl$_3$) of 3i.
$^1$H NMR (400 MHz, CDCl$_3$) of 3j.

$^{13}$C$^1$H NMR (101 MHz, CDCl$_3$) of 3j.
$^1$H NMR (400 MHz, CDCl$_3$) of 3k.

$^{13}$C$[^1]$H NMR (101 MHz, CDCl$_3$) of 3k.
$^1$H NMR (400 MHz, CDCl$_3$) of 3l.

$^{13}$C$[^1]$H NMR (101 MHz, CDCl$_3$) of 3l.
$^1$H NMR (400 MHz, CDCl$_3$) of $3m$.

$^{13}$C$[^1]$H NMR (101 MHz, CDCl$_3$) of $3m$. 
$^1$H NMR (400 MHz, CDCl$_3$) of 3n.

$^{13}$C$[^1]$H NMR (101 MHz, CDCl$_3$) of 3n.
$^1$H NMR (400 MHz, CDCl$_3$) of 3o.

$^{13}$C[$^1$H] NMR (101 MHz, CDCl$_3$) of 3o.
$^1$H NMR (400 MHz, CDCl$_3$) of 3p.

$^{13}$C$^{1}$H NMR (101 MHz, CDCl$_3$) of 3p.
HPLC chromatograms

**Conditions:** OD-H column, mobile phase: *n*-Heptane / *i*-PrOH – 80:20, λ = 191 nm, V = 1.0 ml/min, t = 25 °C,  
$t_R$ = 8.1 min (minor), $t_R$ = 10.1 min (major), ee 81% (93% after recrystalization).

After recrystalillation of 6a.
Conditions: 1A column, mobile phase: \( n \)-Heptane / \( i \)-PrOH – 80:20, \( \lambda \) = 190 nm, \( V \) = 1.0 ml/min, \( r \) = 25 °C, \( t_R \) = 8.0 min (minor), \( t_R \) = 9.7 min (major), \( ee \) 74%. 

![Chemical structure](image)

| Compound | Group | Area   | Height | Similarity Index | Mark | Peak Start | Peak End | Area % |
|----------|-------|--------|--------|------------------|------|------------|----------|--------|
| 7.945    | 50.25 | 364182 | 213906 | 0.0000000        | M    | 7.563      | 8.501   | 50.25  |
| 5.173    | 49.75 | 360170 | 179010 | 0.0000000        | M    | 5.184      | 10.368  | 49.75  |

| Compound | Group | Area   | Height | Similarity Index | Mark | Peak Start | Peak End | Area % |
|----------|-------|--------|--------|------------------|------|------------|----------|--------|
| 7.505    | 57.05 | 259752 | 155965 | 0.0000000        | M    | 7.616      | 8.665   | 12.32  |
| 5.795    | 37.05 | 175044 | 390756 | 0.0000000        | M    | 5.184      | 10.638  | 67.06  |

![Graph](image)
Conditions: IH column, mobile phase: n-Heptane / i-PrOH – 80:20, λ= 190 nm, V= 1.0 ml/min, r= 25 °C, tR= 12.1 min (minor), tR= 13.9 min (major), ee [0][1]%.
**Conditions:** AD-H column, mobile phase: $n$-Heptane / $i$-PrOH – 80:20, $\lambda = 220$ nm, $V = 1.0$ ml/min, $r = 25 \ ^\circ C$, $t_R = 11.73$ min (minor), $t_R = 13.79$ min (major), ee 68%.

![HPLC chromatogram with retention times and peak areas for two compounds.](image)

| Ret. Time | Conc. | Area      | Height | Similarity Index | Mark  | Peak Start | Peak End | Area % |
|-----------|-------|-----------|--------|------------------|-------|------------|----------|-------|
| 11.72     | 13.814| 2299970   | 61871  | 0.000000         | M     | 11.715     | 12.723   | 15.814 |
| 13.793    | 84.186| 12774759  | 36849  | 0.000000         | M     | 13.065     | 16.326   | 84.186 |

![Another HPLC chromatogram with retention times and peak areas for two compounds.](image)
Conditions: IA column, mobile phase: \( n \)-Heptane / i-PrOH – 90:10, \( \lambda = 190 \) nm, \( V = 1.0 \) ml/min, \( t = 25 \) °C, \( t_R = 25.9 \) min (minor), \( t_R = 29.8 \) min (major), \( ee = 70\% \) (after recrystallization 97%).

After crystallization of 3f.
Conditions: IG column, mobile phase: n-Heptane / i-PrOH – 80:20, λ= 199 nm, V= 1.0 ml/min, r= 25 °C, t_R= 9.4 min (minor), t_R= 10.1 min (major), ee 76%.
**Conditions:** OD-H column, mobile phase: \( n \)-Heptane / \( i \)-PrOH – 90:10
\( \lambda = 190 \text{ nm}, V = 1.0 \text{ ml/min}, t = 25 ^\circ \text{C}, t_R = 5.0 \text{ min (minor), } t_R = 5.9 \text{ min (major), ee } 30\%. \)
Conditions: OD-H column, mobile phase: $n$-Heptane / $i$-PrOH – 90:10
\( \lambda = 190 \text{ nm}, \) \( V = 1.0 \text{ ml/min}, \) \( t = 25 \, ^\circ\text{C}, \) \( t_R = 9.7 \text{ min (minor)}, \) \( t_R = 14.0 \text{ min (major)}, \) ee 80\%.
Conditions: 1A column, mobile phase: n-Heptane/i-PrOH – 80:20, 1.0 mL/min, $\lambda = 190$ nm, $T = 25^\circ$C, $t_R = 7.3$ min (minor), $t_R = 8.2$ min (major), ee 70% (80% after recrystallization).

After crystallization of 3h.
Conditions: 1A column, mobile phase: $n$-Heptane/$i$-PrOH – 80:10, 1.0 ml/min, $i$ = 190 nm, $t$ = 25 °C, $t_R$= 6.0 min (minor), $t_R$= 6.7 min (major), $ee$ 66%.
Conditions: OD-H column, mobile phase: \( n \)-heptane / \( i \)-PrOH – 90:10, \( \lambda = 223 \) nm, \( V = 1.0 \) ml/min, \( t = 25 \) °C, \( t_R = 9.2 \) min (minor), \( t_R = 13.0 \) min (major), \( ee 76\% \).
Conditions: IG column, mobile phase: n-Heptane / i-PrOH – 80:20, \( \lambda = 190 \) nm, \( V = 1.0 \) ml/min, \( r = 25 \) °C, \( t_R = 7.0 \) min (major), \( t_R = 8.0 \) min (minor) ee 36%.
Conditions: IG column, mobile phase: n-heptane / i-PrOH – 80:20, \( \lambda = 190 \) nm, \( V = 1.0 \) ml/min, \( t = 25 ^\circ C \); \( t_R = 11.6 \) min (minor), \( t_R = 13.0 \) min (major), \( ee = 64\% \).
Conditions: OD-H column, mobile phase: $n$-Heptane / i-PrOH – 80:20, $\lambda$ = 220 nm, $V$ = 1.0 ml/min, $t$ = 25 °C, $t_R$ = 7.18 min (minor), $t_R$ = 9.47 min (major), $ee$ 72%.
**Conditions:** 1G column, mobile phase: *n*-Heptane / *i*-PrOH – 80:20, λ = 223 nm, V = 1.0 ml/min, r = 25 °C, t_R = 16.76 min (minor), t_R = 18.28 min (major), ee 69%.
Conditions: IA column, mobile phase: \( n \)-Heptane / \( i \)-PrOH – 80:20, \( \lambda \) = 190 nm, \( V \) = 1.0 ml/min, \( t \) = 25 °C, \( t_R \) = 7.0 min (major), \( t_R \) = 10.7 min (minor), ee 35%.
X-Ray section

The diffraction experiment for crystal structure determination was performed on Bruker D8 VENTURE Kappa Duo with PHOTONIII detector by IμS micro-focus sealed tube with MoKα (0.71073) radiation at a temperature 120(2) K. The structure was solved by direct methods (XT\textsuperscript{1a}) and refined by full matrix least squares based on $F^2$ (SHELXL\textsuperscript{1b}). The hydrogen atoms on carbon were fixed into idealized positions (riding model) and assigned temperature factors either $H_{iso}(H) = 1.2 \text{ U}_{eq}(\text{pivot atom})$ or $H_{iso}(H) = 1.5 \text{ U}_{eq}(\text{pivot atom})$ for methyl moiety, the hydrogen atoms in –N-H moieties were found on difference Fourier maps and refined under rigid body assumption with assigned temperature factors $H_{iso}(H) = 1.2 \text{ U}_{eq}(\text{pivot atom})$.

Crystal data for 3\textit{h}: $\text{C}_{12}\text{H}_{15}\text{BrN}_{2}\text{O}; Mr = 283.17$; Monoclinic, $P2_1$ (No 4), $a = 11.0816$ (3) Å, $b = 9.0888$ (3) Å, $c = 12.4473$ (4) Å, $\beta = 95.745$ (1)$^\circ$, $V = 1247.38$ (7) Å$^3$, $Z = 4$, $D_x = 1.508$ Mg m$^{-3}$. Prism, colourless of dimensions 0.19 × 0.12 × 0.12 mm, multi-scan absorption correction ($\mu = 3.28$ mm$^{-1}$) $T_{\text{min}} = 0.63$, $T_{\text{max}} = 0.70$; a total of 38831 measured reflections ($\theta_{\text{max}} = 30^\circ$), from which 7225 were unique ($R_{\text{int}} = 0.028$) and 6671 observed according to the $I > 2\sigma(I)$ criterion. The refinement converged ($\Delta/\sigma_{\text{max}} = 0.002$) to $R = 0.022$ for observed reflections and $wR(F^2) = 0.059$, $GOF = 1.14$ for 293 parameters and all 7225 reflections. The final difference map displayed no peaks of chemical significance ($\Delta\rho_{\text{max}} = 0.53$, $\Delta\rho_{\text{min}} = -0.31$ e.Å$^{-3}$).

The two symmetrically independent molecules fit each other well, with maximal deviation 0.7 Å between isopropyl moieties. The determination of absolute structure was based on anomalous scattering of bromine atom. Absolute structure parameter: -0.011 (2).\textsuperscript{2}

X-ray crystallographic data have been deposited with the Cambridge Crystallographic Data Centre (CCDC) under deposition number 2081064 for 3\textit{h} and can be obtained free of charge from the Centre via its website (www.ccdc.cam.ac.uk/getstructures).

\textsuperscript{1a} SHELXT: Sheldrick, G.M. (2015). Acta Cryst. A71, 3-8.
\textsuperscript{1b} SHELXL: Sheldrick, G.M. (2015). Acta Cryst. C71, 3-8.
\textsuperscript{2} Parsons, S., Flack, H.D. and Wagner, T. (2013) Acta Cryst. B69, 249-259.
Fig. 1. View on the one of two symmetrically independent molecules of 3h. Displacement ellipsoid are drawn on 30% probability level. Two independent molecules fit one on other almost perfectly with maximal difference of corresponding atoms 0.275 Å.