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A new synthetic route to chiral 3-aryl-5-ethyl-1,4,2-oxazaphosphorines

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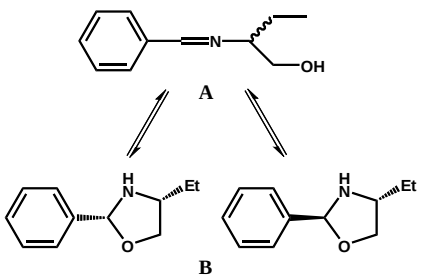
General remarks

^{1}H NMR spectra were recorded on a Bruker AVANCE-400 and AVANCE-600 instruments with the working frequency of 400.13 and 600.13 MHz correspondingly relative to the signals of residual protons of deuterated solvent ($CDCl_3$, DMSO-d_6, D_2O), ^{31}P NMR spectra were obtained on a Bruker AVANCE-400 and AVANCE-600 instruments with the working frequency of 161.97 and 242.93 MHz correspondingly relative to the external standard (85% H_3PO_4). All oxazaphosphorines samples were prepared with addition of K_2CO_3 in molar ratio equal 1:3. IR spectra were recorded on Bruker Tensor 27 Fourier spectrometer from KBr pellets. ESI measurements were performed using an AmazonX mass spectrometer. The ESI source conditions were as follows: capillary voltage -4500 V for positive ions and +4500 V for negative ions, the dry gas (N_2) temperature 220°C. The solution samples in H_2O (with K_2CO_3) at a concentration of 10^{-3} M were used. Optical rotations were measured on a Perkin Elmer (Model 341) polarimeter at 20°C. All oxazaphosphorines samples were prepared with addition of K_2CO_3 in molar ratio equal 1:3. Melting points were measured on a Boetius melting point microscope.

Experimental details

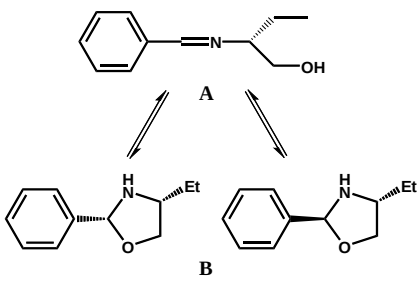
Synthesis of 2-(arylidenamino)butan-1-ols. A solution of benzaldehyde (4.24 g, 40 mmol) in benzene (10 ml) [or salicylaldehyde (4.88 g, 40 mmol) or 3-hydroxybenzaldehyde (4.88 g, 40 mmol, 20 ml benzene)] was added dropwise to a stirred solution of (±)- or (*R*)-(-)-2-amino-1-butanol (3.56 g, 40 mmol) in benzene (10 ml in the case of benzaldehyde or salicylaldehyde and 20 ml in the case of 3-hydroxybenzaldehyde). The resulted mixture was heated under reflux for 3 hours using Dean–Stark trap.



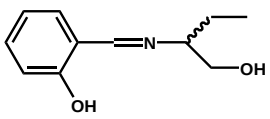
For tautomers **B** only one member from each pair of enantiomers is shown

(±)-2-(Benzylideneamino)butan-1-ol (±)-1a: The solvent was evaporated and the oily crude product was analyzed. Compound **(±)-1a** was a mixture of imine (**A**) and *cis*-, *trans*-oxazolidine (**B**) tautomers in 85:15 ratio in the $CDCl_3$ solution.

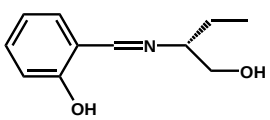
^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85 (t, $^3J_{H,H}$ 7.5 Hz, 2.55H, **A**; C<u>H</u>$_3$CH$_2$), 0.96, 0.99 (2t, $^3J_{H,H}$ 7.4 Hz for one tautomer and $^3J_{H,H}$ 7.5 Hz for another tautomer, 0.45H, **B**; C<u>H</u>$_3$CH$_2$), 1.42-1.69 (m, 2H, **A**+**B**; CH$_3$C<u>H</u>$_2$), 3.14-3.20 (m, 0.85H, **A**; NCH), 3.22-3.43 (m, 0.3H, **B**; HNC<u>H</u> and CH$_2$O (H_A)), 3.69 (dd, $^2J_{H,H}$ 11.1 Hz, $^3J_{H,H}$ 4.0 Hz, 0.85H, **A**; C<u>H</u>$_2$OH (H_A)), 3.75 (dd, $^2J_{H,H}$ 11.1 Hz, $^3J_{H,H}$ 7.6 Hz, 0.85H, **A**; C<u>H</u>$_2$OH (H_B)), 4.02, 4.06 (2dd, $^3J_{H,H}$ 6.8 Hz, $^2J_{H,H}$ 6.8 Hz for one tautomer and $^3J_{H,H}$ 7.7 Hz, $^2J_{H,H}$ 6.8 Hz for another tautomer, 0.15H, **B**; CH$_2$O (H_B)), 5.43, 5.49 (2s, 0.15H, **B**; PhC<u>H</u>NH), 7.32-7.70 (m, 5H, **A**+**B**; H_{arom}), 8.22 (s, 0.85H, **A**; PhCHN) ppm. IR (KBr): ν = 2961, 2927, 2874, 1644, 1580, 1455, 1386, 1375, 1055, 763 cm^{-1}. Found (%): C, 74.67, H, 8.47, N, 7.72. Calcd. for $C_{11}H_{15}NO$ (%): C, 74.54, H, 8.53, N, 7.90.



(*R*)-(+)-2-(Benzylideneamino)butan-1-ol (*R*)-1a: The solvent was evaporated and the crude product was recrystallized from hexane to give **(*R*)-1a** (4.8 g, 68%); mp 55-56°C {lit. [S1] mp 54-55 ºC}; $[\alpha]_D^{20}$ +28.0 (*c* = 13.2, MeOH) {lit. [S1] $[\alpha]_D^{20}$ +28.0 (*c* = 13.2, MeOH)}. Compound **(*R*)-1a** is a mixture of imine (**A**) and *cis*-, *trans*-oxazolidine (**B**) tautomers in 85:15 ratio in $CDCl_3$ solution. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, $^3J_{H,H}$ 7.5 Hz, 2.55H, **A**; C<u>H</u>$_3$CH$_2$), 1.01, 1.05 (2t, $^3J_{H,H}$ 7.4 Hz for both tautomers, 0.45H, **B**; C<u>H</u>$_3$CH$_2$), 1.48-1.74 (m, 2H, **A**+**B**; CH$_3$C<u>H</u>$_2$), 3.20-3.26 (m, 0.85H, **A**; NCH), 3.29-3.49 (m, 0.3H, **B**; HNC<u>H</u> and CH$_2$O (H_A)), 3.75 (dd, $^2J_{H,H}$ 11.1 Hz, $^3J_{H,H}$ 4.0 Hz, 0.85H, **A**; C<u>H</u>$_2$OH (H_A)), 3.80 (dd, $^2J_{H,H}$ 11.1 Hz, $^3J_{H,H}$ 7.5 Hz, 0.85H, **A**; C<u>H</u>$_2$OH (H_B)), 4.07, 4.11 (2dd, $^3J_{H,H}$ 6.8 Hz, $^2J_{H,H}$ 6.8 Hz for one tautomer and $^3J_{H,H}$ 7.8 Hz, $^2J_{H,H}$ 6.8 Hz for another tautomer, 0.15H, **B**; CH$_2$O (H_B)), 5.47, 5.53 (2s, 0.15H, **B**; PhC<u>H</u>NH), 7.36-7.77 (m, 5H, **A**+**B**; H_{arom}), 8.27 (s, 0.85H, **A**; PhCHN) ppm. IR (KBr): ν = 2964, 2927, 2873, 1644, 1580, 1456, 1388, 1374, 1055, 762 cm^{-1}. Found (%): C, 74.69, H, 8.43, N, 7.74. Calcd. for $C_{11}H_{15}NO$ (%): C, 74.54, H, 8.53, N, 7.90.

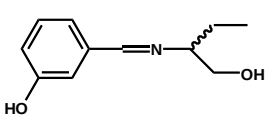


(±)-2-(2-Hydroxybenzylideneamino)butan-1-ol (±)-1b: The solvent was evaporated and the oily crude product was analyzed. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.93 (t, $^3J_{H,H}$ 7.4 Hz, 3H; C<u>H</u>$_3$CH$_2$), 1.56-1.75 (m, 2H; CH$_3$C<u>H</u>$_2$), 3.19-3.25 (m, 1H; NCH), 3.71 (dd, $^2J_{H,H}$ 11.2 Hz, $^3J_{H,H}$ 8.0 Hz, 1H; C<u>H</u>$_2$OH (H_A)), 3.78 (dd, $^2J_{H,H}$ 11.2 Hz, $^3J_{H,H}$ 4.0 Hz, 1H; C<u>H</u>$_2$OH (H_B)), 6.88-6.98 (m, 2H; H_{arom}), 7.28-7.36 (m, 2H; H_{arom}), 8.40 (s, 1H; ArCHN) ppm. IR (KBr): ν = 2965, 2922, 2873, 1631, 1582, 1498, 1462, 1413, 1278, 1057, 759 cm^{-1}. Found (%): C, 68.56, H, 7.71, N, 7.13. Calcd. for $C_{11}H_{15}NO_2$ (%): C, 68.37, H, 7.82, N, 7.25.

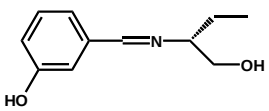


(*R*)-(+)-2-(2-Hydroxybenzylideneamino)butan-1-ol (*R*)-1b: The solvent was evaporated and obtained crude product was recrystallized from hexane/ethyl acetate mixture (5:1) to give **(*R*)-1b** (5.7 g, 74%); mp 52-53 ºC {lit. [S2] mp 50-51 ºC}; $[\alpha]_D^{20}$ +15.5 (*c* = 1.57, acetone) {lit. [S2] $[\alpha]_D$ +15.4 (c = 1.57 in acetone)}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, $^3J_{H,H}$ 7.4 Hz, 3H; C<u>H</u>$_3$CH$_2$), 1.56-1.75 (m, 2H; CH$_3$C<u>H</u>$_2$), 3.20-3.26 (m, 1H; NCH), 3.73 (dd, $^2J_{H,H}$ 11.2 Hz, $^3J_{H,H}$ 8.1 Hz, 1H; C<u>H</u>$_2$OH

(H_A)), 3.79 (dd, $^2J_{H,H}$ 11.2 Hz, $^3J_{H,H}$ 4.0 Hz, 1H; C<u>H</u>$_2$OH (H_B)), 6.89-6.99 (m, 2H; H_{arom}), 7.28-7.36 (m, 2H; H_{arom}), 8.40 (s, 1H; ArCHN) ppm. IR (KBr): ν = 2962, 2921, 2875, 1632, 1581, 1498, 1463, 1417, 1390, 1277, 1060, 761 cm^{-1}. Found (%): C, 68.52, H, 7.68, N, 7.09. Calcd. for $C_{11}H_{15}NO_2$ (%): C, 68.37, H, 7.82, N, 7.25.

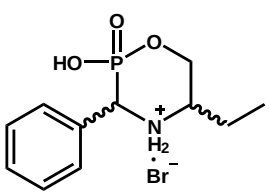


(±)-2-(3-Hydroxybenzylideneamino)butan-1-ol (±)-1c: The precipitate was filtered off, washed with benzene and dried *in vacuo* to give **(±)-1c** (6.5 g, 84%); mp 118-119 ºC. ^{1}H NMR (600 MHz, DMSO-d$_6$): δ = 0.78 (t, $^3J_{H,H}$ 7.5 Hz, 3H; C<u>H</u>$_3$CH$_2$), 1.39-1.47 (m, 1H; CH$_3$C<u>H</u>$_2$ (H_A)), 1.59-1.65 (m, 1H; CH$_3$C<u>H</u>$_2$ (H_B)), 3.05-3.09 (m, 1H; NCH), 3.38-3.42 (m, 1H; C<u>H</u>$_2$OH (H_A)), 3.50-3.54 (m, 1H; C<u>H</u>$_2$OH (H_B)), 4.50 (dd, $^3J_{H,H}$ 5.6 Hz, $^3J_{H,H}$ 5.1 Hz, 1H; CH$_2$O<u>H</u>), 6.83-6.85 (m, 1H; H_{arom}), 7.12-7.24 (m, 3H; H_{arom}), 8.18 (s, 1H; ArCHN), 9.48 (br.s, 1H; ArOH) ppm. IR (KBr): ν = 2960, 2929, 2878, 2849, 1644, 1599, 1450, 1398, 1314, 1278, 1225, 1039, 759 cm^{-1}. Found (%): C, 68.38, H, 7.78, N, 7.09. Calcd. for $C_{11}H_{15}NO_2$ (%): C, 68.37, H, 7.82, N, 7.25.



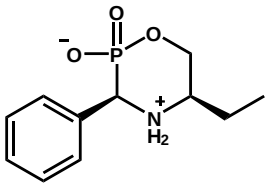
(*R*)-(+)-2-(3-Hydroxybenzylideneamino)butan-1-ol (*R*)-1c: The precipitate was filtered off, washed with benzene and dried *in vacuo* to give **(*R*)-1c** (6.1 g, 79%); mp 139-140°C; $[\alpha]_D^{20}$ +28.7 (*c* = 1.0, DMSO). ^{1}H NMR (600 MHz, DMSO-d$_6$): δ = 0.78 (t, $^3J_{H,H}$ 7.5 Hz, 3H; C<u>H</u>$_3$CH$_2$), 1.39-1.47 (m, 1H; CH$_3$C<u>H</u>$_2$ (H_A)), 1.59-1.66 (m, 1H; CH$_3$C<u>H</u>$_2$ (H_B)), 3.05-3.09 (m, 1H; NCH), 3.38-3.42 (m, 1H; C<u>H</u>$_2$OH (H_A)), 3.50-3.54 (m, 1H; C<u>H</u>$_2$OH (H_B)), 4.50 (m, 1H; CH$_2$O<u>H</u>), 6.82-6.84 (m, 1H; H_{arom}), 7.12-7.24 (m, 3H; H_{arom}), 8.18 (s, 1H; ArCHN), 9.48 (br.s, 1H; ArOH) ppm. IR (KBr): ν = 2960, 2929, 2877, 2849, 1644, 1599, 1449, 1397, 1314, 1278, 1225, 1039, 759 cm^{-1}. Found (%): C, 68.49, H, 7.84, N, 7.22. Calcd. for $C_{11}H_{15}NO_2$ (%): C, 68.37, H, 7.82, N, 7.25.

Synthesis of 1,4,2-oxazaphosphorines. Method A. A solution of triethyl phosphite (2 g, 12 mmol) in dichloromethane (5 ml) was added to the solution of **1a** ((±)- or (*R*)-) (1.77 g, 10 mmol), or **1b** ((±)- or (*R*)-) (1.93 g, 10 mmol) in dichloromethane (10 ml). The mixture was stirred for 10 min and cooled in an ice bath. A solution of trifluoroacetic acid (2.5 g, 22 mmol) in dichloromethane (5 ml) was added dropwise for 30 min. After the addition was complete, the mixture was stirred for 1 h at cooling and for 24 h at room temperature. The mixture was the cooled in an ice bath, and a solution of bromotrimethylsilane (4.59 g, 30 mmol in case of **1a**, or 6.12 g, 40 mmol in case of **1b**) in dichloromethane (10 ml) was added dropwise for 30 min. After the addition was complete, the reaction mixture is stirred for 24 hours at room temperature. The volatiles were fully evaporated. Further processing is given for each compound separately.

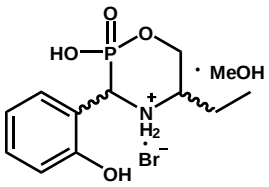


(*R*,*R*/*S*,*S*)-5-Ethyl-2-hydroxy-3-phenyl-1,4,2-oxazaphosphinane 2-oxide hydrobromide (*R*,*R*/*S*,*S*)-2a: Methanol (15 ml) was added to the residue, and the suspension was refluxed for 30 min, and the resulting suspension was kept at room temperature for 24 hours. The precipitate was filtered off, washed by cold methanol (5 ml) and dried *in vacuo* to give **(*R*,*R*/*S*,*S*)-2a** (2.25 g, 70%); mp 307-308 ºC {lit. [S3] mp 298-300°C}. ^{1}H NMR (600 MHz,

D_2O with K_2CO_3): δ = 0.93 (t, $^3J_{H,H}$ 7.6 Hz, 3H; C<u>H</u>$_3$CH$_2$), 1.40-1.51 (m, 2H; CH$_3$C<u>H</u>$_2$), 3.02 (ddt, $^3J_{H,H}$ 11.1 Hz, $^3J_{H,H}$ 7.2 Hz, $^3J_{H,H}$ 3.3 Hz, 1H; CH$_3$CH$_2$C<u>H</u>), 4.05 (d, $^2J_{P,H}$ 13.8 Hz, 1H; PCH), 4.08 (ddd, $^2J_{H,H}$ 11.6 Hz, $^3J_{H,H}$ 11.1 Hz, $^3J_{P,H}$ 2.4 Hz, 1H; CHC<u>H</u>$_2$O (H_A)), 4.22 (ddd, $^3J_{P,H}$ 17.6 Hz, $^2J_{H,H}$ 11.6 Hz, $^3J_{H,H}$ 3.3 Hz, 1H; CHC<u>H</u>$_2$O (H_B)), 7.33-7.41 (m, 5H; H_{arom}) ppm. ^{31}P NMR (600 MHz, D_2O with K_2CO_3): δ = 13.87 ppm. IR (KBr): ν = 2970, 1610, 1492, 1457, 1227, 1083, 1047, 844, 778, 698 cm^{-1}. MS (ESI+): *m*/*z* = 280 [M+K]$^+$, 242 [M+H]$^+$. MS (ESI-): *m*/*z* = 240 [M-H]$^-$. Found (%): C, 40.85, H, 5.15, Br, 24.85, N, 4.19, P, 9.81. Calcd. for $C_{11}H_{16}NO_3P\cdot HBr$ (%): C, 41.01, H, 5.32, Br, 24.80, N, 4.35, P, 9.62.

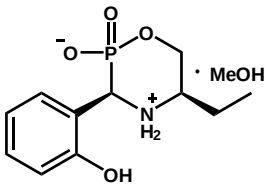


(*R*,*R*)-5-Ethyl-2-hydroxy-3-phenyl-1,4,2-oxazaphosphinane 2-oxide (*R*,*R*)-3a: The residue was dissolved in methanol (10 ml), and the solution was stirred for 4 h. Methanol was evaporated, and ethanol (15 ml) was added to the solid. The resulting suspension was stirred for 2 hours and kept at room temperature for 24 h. The precipitate was filtered off, washed with cold ethanol (5 ml) and dried *in vacuo* to give **(*R*,*R*)-3a** (1.65 g, 68%); mp 288-290 °C; $[\alpha]_D^{20}$ +82 (*c* = 0.5, H_2O with K_2CO_3). ^{1}H NMR (600 MHz, D_2O with K_2CO_3): δ = 0.93 (t, $^3J_{H,H}$ 7.6 Hz, 3H; C<u>H</u>$_3$CH$_2$), 1.40-1.51 (m, 2H; CH$_3$C<u>H</u>$_2$), 3.03 (ddt, $^3J_{H,H}$ 11.0 Hz, $^3J_{H,H}$ 7.2 Hz, $^3J_{H,H}$ 3.2 Hz, 1H; CH$_3$CH$_2$C<u>H</u>), 4.05 (d, $^2J_{P,H}$ 13.7 Hz, 1H; PCH), 4.07 (ddd, $^2J_{H,H}$ 11.5 Hz, $^3J_{H,H}$ 11.0 Hz, $^3J_{P,H}$ 2.3 Hz, 1H; CHC<u>H</u>$_2$O (H_A)), 4.22 (ddd, $^3J_{P,H}$ 17.6 Hz, $^2J_{H,H}$ 11.5 Hz, $^3J_{H,H}$ 3.2 Hz, 1H; CHC<u>H</u>$_2$O (H_B)), 7.33-7.42 (m, 5H; H_{arom}) ppm. ^{31}P NMR (600 MHz, D_2O with K_2CO_3): δ = 13.81 ppm. IR (KBr): ν = 2972, 1599, 1458, 1244, 1093, 1043, 842, 780, 698 cm^{-1}. MS (ESI+): *m*/*z* = 280 [M+K]$^+$, 242 [M+H]$^+$. MS (ESI-): *m*/*z* = 240 [M-H]$^-$. Found (%): C, 54.58, H, 6.54, N, 5.63, P, 12.92. Calcd. for $C_{11}H_{16}NO_3P$ (%): C, 54.77, H, 6.69, N, 5.81, P, 12.84.



(*R*,*R*/*S*,*S*)-5-Ethyl-2-hydroxy-3-(2-hydroxyphenyl)-1,4,2-oxazaphosphinane 2-oxide hydrobromide (*R*,*R*/*S*,*S*)-2b: The residue was dissolved in methanol (10 ml), and the solution was stirred until precipitate was formed, and this was kept at room temperature for 24 h. The precipitate was filtered off, washed by cold methanol (5 ml) and dried *in vacuo* to give **(*R*,*R*/*S*,*S*)-2b** (2.3 g, 62%) as solvate with methanol; mp 208-210 °C. ^{1}H NMR (600 MHz, D_2O with K_2CO_3): δ = 0.94 (t, $^3J_{H,H}$ 7.6 Hz, 3H; C<u>H</u>$_3$CH$_2$), 1.42-1.47 (m, 2H; CH$_3$C<u>H</u>$_2$), 3.05 (ddt, $^3J_{H,H}$ 11.1 Hz, $^3J_{H,H}$ 7.0 Hz, $^3J_{H,H}$ 3.3 Hz, 1H; CH$_3$CH$_2$C<u>H</u>), 3.34 (s, 3H; C<u>H</u>$_3$OH), 4.11 (ddd, $^2J_{H,H}$ 11.6 Hz, $^3J_{H,H}$ 11.1 Hz, $^3J_{P,H}$ 2.9 Hz, 1H; CHC<u>H</u>$_2$O (H_A)), 4.19 (ddd, $^3J_{P,H}$ 18.1 Hz, $^2J_{H,H}$ 11.6 Hz, $^3J_{H,H}$ 3.3 Hz, 1H; CHC<u>H</u>$_2$O (H_B)), 4.30 (d, $^2J_{P,H}$ 13.8 Hz, 1H; PCH), 6.87-6.94 (m, 2H; H_{arom}), 7.22-7.32 (m, 2H; H_{arom}) ppm. ^{31}P NMR (600 MHz, D_2O with K_2CO_3): δ = 13.54 ppm. IR (KBr): ν = 2985, 1608, 1507, 1457, 1258, 1095, 1035, 822, 763 cm^{-1}. MS (ESI+): *m*/*z* = 334 [M+2K-H]$^+$, 296 [M+K]$^+$, 258 [M+H]$^+$. MS (ESI-): *m*/*z* = 256 [M-H]$^-$. Found (%): C, 38.92, H, 5.57, Br, 21.30, N, 3.70, P, 8.17. Calcd. for $C_{11}H_{16}NO_4P\cdot HBr\cdot CH_4O$ (%): C, 38.94, H, 5.72, Br, 21.59, N, 3.78, P, 8.37.

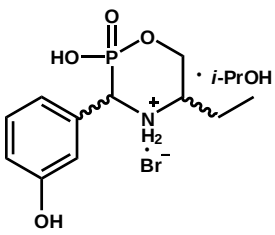
Single crystals, suitable for X-ray diffraction study, were obtained by slow evaporation of mother liquor after filtering off the precipitate.



(*R*,*R*)-5-Ethyl-2-hydroxy-3-(2-hydroxyphenyl)-1,4,2-oxazaphosphinane 2-oxide (*R*,*R*)-3b: The residue was dissolved in methanol (10 ml), and the solution was stirred until precipitate was formed. Then 2-propanol (10 ml) was added, and the mixture was kept at room temperature for 24 hours. The precipitate was filtered off, washed with cold 2-propanol (5 ml) and dried *in vacuo* to give **(*R*,*R*)-3b** (1.6 g, 55%) as solvate with methanol; mp 266-268 ºC; $[\alpha]_D^{20}$ +32 (*c* = 0.5, H_2O with K_2CO_3). ^{1}H NMR (600 MHz, D_2O with K_2CO_3): δ = 0.92 (t, $^3J_{H,H}$ 7.6 Hz, 3H; C<u>H</u>$_3$CH$_2$), 1.40-1.45 (m, 2H; CH$_3$C<u>H</u>$_2$), 3.04 (ddt, $^3J_{H,H}$ 11.1 Hz, $^3J_{H,H}$ 7.1 Hz, $^3J_{H,H}$ 3.2 Hz, 1H; CH$_3$CH$_2$C<u>H</u>), 3.33 (s, 3H; C<u>H</u>$_3$OH), 4.09 (ddd, $^2J_{H,H}$ 11.7 Hz, $^3J_{H,H}$ 11.1 Hz, $^3J_{P,H}$ 2.8 Hz, 1H; CHC<u>H</u>$_2$O (H_A)), 4.18 (ddd, $^3J_{P,H}$ 18.0 Hz, $^2J_{H,H}$ 11.7 Hz, $^3J_{H,H}$ 3.2 Hz, 1H; CHC<u>H</u>$_2$O (H_B)), 4.31 (d, $^2J_{P,H}$ 13.8 Hz, 1H; PCH), 6.84-6.90 (m, 2H; H_{arom}), 7.20-7.32 (m, 2H; H_{arom}) ppm. ^{31}P NMR (600 MHz, D_2O with K_2CO_3): δ = 13.73 ppm. IR (KBr): ν = 2967, 1610, 1512, 1459, 1237, 1089, 1033, 813, 771 cm^{-1}. MS (ESI+): *m*/*z* = 334 [M+2K-H]$^+$, 296 [M+K]$^+$, 258 [M+H]$^+$. MS (ESI-): *m*/*z* = 256 [M-H]$^-$. Found (%): C, 49.67, H, 6.80, N, 4.77, P, 10.81. Calcd. for $C_{11}H_{16}NO_4P \cdot CH_4O$ (%): C, 49.83, H, 6.97, N, 4.84, P, 10.71.

Single crystals, suitable for X-ray diffraction study, were obtained by slow evaporation of mother liquor after filtering off the precipitate.

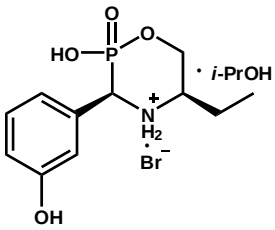
Method B. A solution of triethyl phosphite (1.5 g, 9 mmol) in ethyl acetate (5 ml) was added to a solution of **(±)-1c** or **(*R*)-1c** (1.45 g, 7.5 mmol) in ethyl acetate (10 ml). The resulting mixture was stirred for 10 min, cooled in an ice bath. A solution of trifluoroacetic acid (1.88 g, 16.5 mmol) in ethyl acetate (10 ml) was then added dropwise for 30 min. After the addition was complete, the mixture was stirred for 1 h at cooling and for 24 h at room temperature. The resulting precipitate was filtered off and dried *in vacuo*. To this solid dichloromethane (20 ml) was added, the resulting suspension was cooled in an ice bath. A solution of bromotrimethylsilane (4.6 g, 30 mmol) in dichloromethane (10 ml) was added dropwise for 30 min. After the addition was complete, the mixture was stirred at room temperature for 48 h. The volatiles were fully evaporated. Further processing is given for each compound separately.



(*R*,*R*/*S*,*S*)-5-Ethyl-2-hydroxy-3-(3-hydroxyphenyl)-1,4,2-oxazaphosphinane 2-oxide hydrobromide (*R*,*R*/*S*,*S*)-2c: The residue was dissolved in methanol (10 ml), and the solution was stirred at room temperature for 4 h. The solvent was evaporated, and the solid residue was dissolved in 2-propanol (15 ml) on heating. The mixture was kept at room temperature for 24 h, and the resulting precipitate was filtered off and dried *in vacuo* to

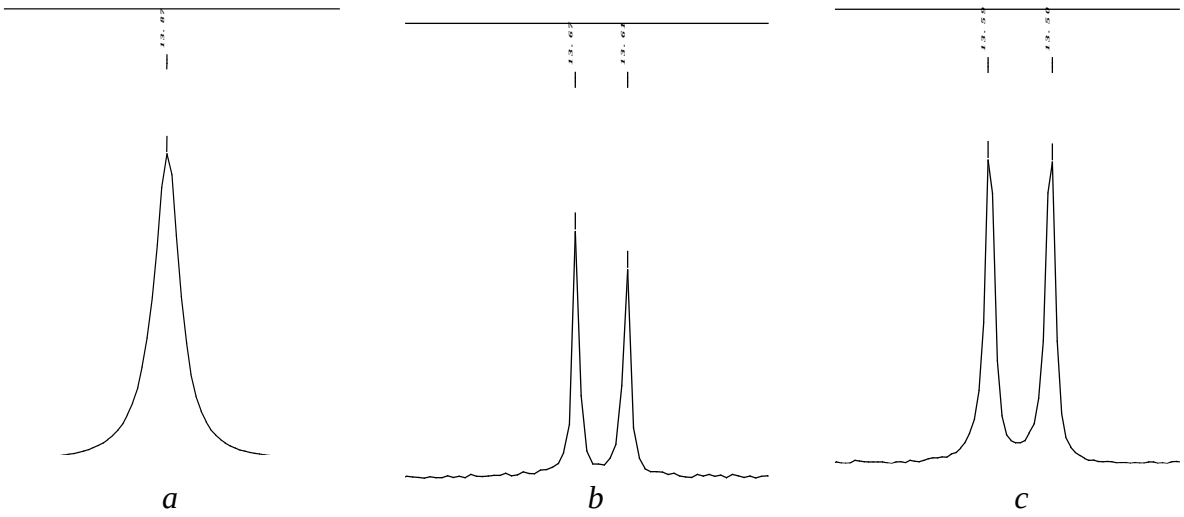
afford **(*R*,*R*/*S*,*S*)-2c** (1.95 g, 65%) as solvate with 2-propanol; mp 265-266 ºC. ^{1}H NMR (400 MHz, D_2O with K_2CO_3): δ = 0.91 (t, $^{3}J_{H,H}$ 7.5 Hz, 3H; C<u>H</u>$_3$CH$_2$), 1.14 (d, $^{3}J_{H,H}$ 6.2 Hz, 6H; (C<u>H</u>$_3$)$_2$CHOH), 1.36-1.49 (m, 2H; CH$_3$C<u>H</u>$_2$), 2.98 (ddt, $^{3}J_{H,H}$ 10.8 Hz, $^{3}J_{H,H}$ 6.8 Hz, $^{3}J_{H,H}$ 3.2 Hz, 1H; CH$_3$CH$_2$C<u>H</u>), 3.88 (d, $^{2}J_{P,H}$ 13.5 Hz, 1H; PCH), 3.98 (sep, $^{3}J_{H,H}$ 6.2 Hz, 1H; (CH$_3$)$_2$C<u>H</u>OH), 4.03 (ddd, $^{2}J_{H,H}$ 11.5 Hz, $^{3}J_{H,H}$ 10.8 Hz, $^{3}J_{P,H}$ 2.7 Hz, 1H; CHC<u>H</u>$_2$O (H$_A$)), 4.18 (ddd, $^{3}J_{P,H}$ 17.4 Hz, $^{2}J_{H,H}$ 11.5 Hz, $^{3}J_{H,H}$ 3.2 Hz, 1H; CHC<u>H</u>$_2$O (H$_B$)), 6.51-6.58 (m, 3H; H$_{arom}$), 7.07-7.11 (m, 1H; H$_{arom}$) ppm. ^{31}P NMR (400 MHz, D_2O with K_2CO_3): δ = 13.67 ppm. IR (KBr): ν = 2974, 1612, 1495, 1454, 1247, 1223, 1052, 1015, 826, 778 cm^{-1}. MS (ESI+): *m*/*z* = 334 [M+2K-H]$^{+}$, 296 [M+K]$^{+}$, 258 [M+H]$^{+}$. MS (ESI-): *m*/*z* = 256 [M-H]$^{-}$. Found (%): C, 42.36, H, 6.15, Br, 19.88, N, 3.61, P, 7.91. Calcd. for $C_{11}H_{16}NO_4P{\cdot}HBr{\cdot}C_3H_8O$ (%): C, 42.22, H, 6.33, Br, 20.06, N, 3.52, P, 7.78.

Compound **(*R*,*R*/*S*,*S*)-2c** was crystallized from dry 2-propanol resulting in conglomerate crystals. From this conglomerate, a single crystal was picked up, which according to X-ray diffraction study turned to be hydrobromide salt with solvate 2-propanol molecule **(*S*,*S*)-2''c**. Crystallization of **(*R*,*R*/*S*,*S*)-2c** from 1:1 mixture of water and 2-propanol gives sample **(*R*,*R*/*S*,*S*)-3c**, a racemic crystal of internal salt containing no solvate molecules.



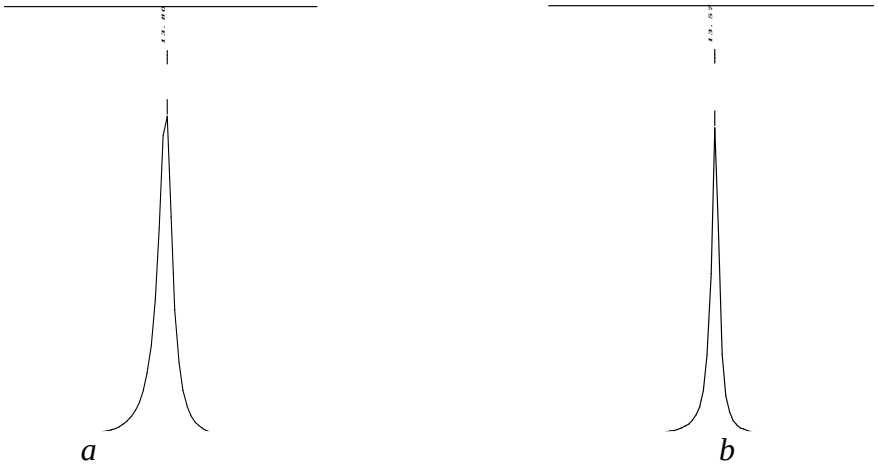
(*R*,*R*)-5-Ethyl-2-hydroxy-3-(3-hydroxyphenyl)-1,4,2-oxazaphosphinane 2-oxide hydrobromide (*R*,*R*)-2'c: the isolation procedure was the same as for **(*R*,*R*/*S*,*S*)-2c**. Compound **2'c** was obtained as solvate with 2-propanol (2.1 g, 70%); mp 250-252 ºC; $[\alpha]_D^{20}$ +45 (*c* = 0.5, H_2O with K_2CO_3). ^{1}H NMR (400 MHz, D_2O with K_2CO_3): δ = 0.91 (t, ^{3}J(H,H) = 7.5 Hz, 3H; C<u>H</u>$_3$CH$_2$), 1.13 (d, ^{3}J(H,H) = 6.2 Hz, 6H; (C<u>H</u>$_3$)$_2$CHOH), 1.34-1.51 (m, 2H; CH$_3$C<u>H</u>$_2$), 2.97 (ddt, $^{3}J_{H,H}$ 10.7 Hz, $^{3}J_{H,H}$ 6.8 Hz, $^{3}J_{H,H}$ 3.2 Hz, 1H; CH$_3$CH$_2$C<u>H</u>), 3.88 (d, ^{2}J(P,H) = 13.3 Hz, 1H; PCH), 3.98 (sep, $^{3}J_{H,H}$ 6.2 Hz, 1H; (CH$_3$)$_2$C<u>H</u>OH), 4.03 (ddd, $^{2}J_{H,H}$ 11.5 Hz, $^{3}J_{H,H}$ 10.7 Hz, $^{3}J_{P,H}$ 2.7 Hz, 1H; CHC<u>H</u>$_2$O (H$_A$)), 4.19 (ddd, $^{3}J_{P,H}$ 17.4 Hz, $^{2}J_{H,H}$ 11.5 Hz, $^{3}J_{H,H}$ 3.2 Hz, 1H; CHC<u>H</u>$_2$O (H$_B$)), 6.50-6.57 (m, 3H; H$_{arom}$), 7.07-7.11 (m, 1H; H$_{arom}$) ppm. ^{31}P NMR (400 MHz, D_2O with K_2CO_3): δ = 14.22 ppm. IR (KBr): ν = 2974, 1612, 1495, 1454, 1247, 1224, 1052, 1015, 826, 778 cm^{-1}. MS (ESI+): *m*/*z* = 334 [M+2K-H]$^{+}$, 296 [M+K]$^{+}$, 258 [M+H]$^{+}$. MS (ESI-): *m*/*z* = 256 [M-H]$^{-}$. Found (%): C, 42.04, H, 6.13, Br, 19.93, N, 3.33, P, 7.67. Calcd. for $C_{11}H_{16}NO_4P{\cdot}HBr{\cdot}C_3H_8O$ (%): C, 42.22, H, 6.33, Br, 20.06, N, 3.52, P, 7.78.

NMR experiments with chiral shift reagent. For NMR experiments, mixtures of oxazaphosphorines **2a** and **2b** (0.024 mmol) and K_2CO_3 (0.072 mmol) were dissolved in D_2O. α-Cyclodextrin (0.024 or 0.048 mmol) was dissolved on heating of the resulting solutions.



a *b* *c*

Figure S1. ^{31}P NMR spectra (600 MHz, D_2O with K_2CO_3) of **(*R*,*R*/*S*,*S*)-2a** in the absence of the shift reagent (a) and in the presence of equimolar amount (b) and two-fold molar excess of the shift reagent (c).



a *b*

Figure S2. ^{31}P NMR spectra (600 MHz, D_2O with K_2CO_3) of **(*R*,*R*)-3a** in the absence of the shift reagent (a) and in the presence two-fold molar excess of the shift reagent (b).

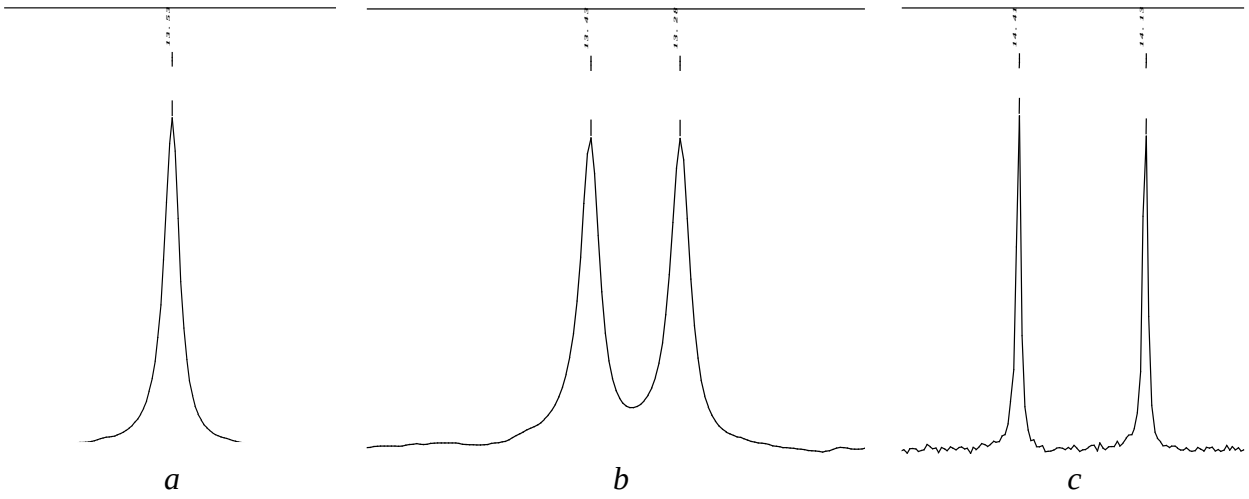


Figure S3. ^{31}P NMR spectra (600 MHz, D_2O with K_2CO_3) of **(*R*,*R*/*S*,*S*)-2b** in the absence of the shift reagent (a) and in the presence of equimolar amount (b) and two-fold molar excess of the shift reagent (c).

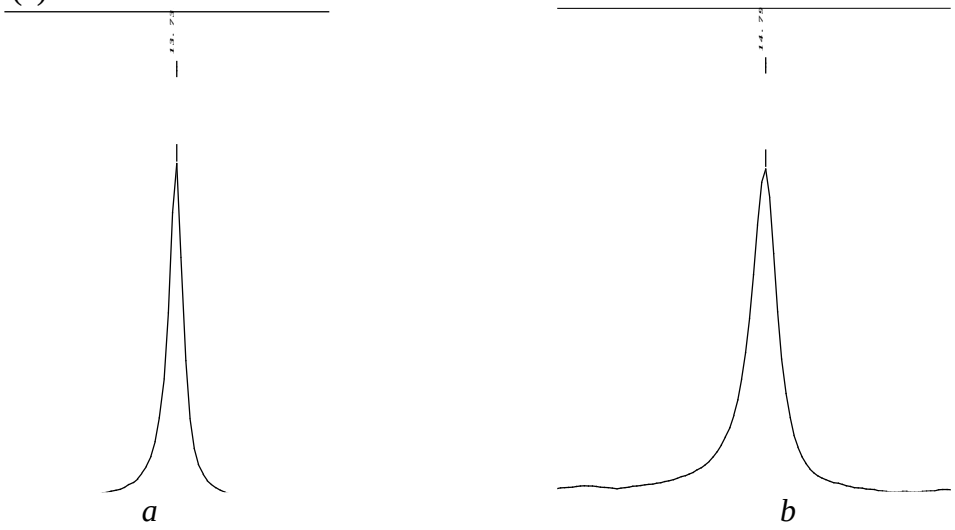


Figure S4. ^{31}P NMR spectra (600 MHz, D_2O with K_2CO_3) of **(*R*,*R*)-3b** in the absence of the shift reagent (a) and in the presence two-fold molar excess of the shift reagent (b).

X-ray crystallography. Data sets for single crystals **(*R*,*R*)-3b**, **(*R*,*R*/*S*,*S*)-2b**, **(*S*,*S*)-2''c, (*R*,*R*/*S*,*S*)-3c** were collected on a Bruker AXS Kappa APEX Duo diffractometer with graphite-monochromated Mo Kα radiation (λ = 0.71073 Å). The structures were solved by direct methods using APEX3 [S4] for data collection, SAINT [S5] for data reduction, SHELXS [S6] for structure solution, SHELXL [S6] for structure refinement by full-matrix least-squares against F^2, and SADABS [S7] for multi-scan absorption correction. Hydrogen atoms at carbon atoms were placed into calculated positions and refined as riding atoms. Hydrogen atoms of the hydroxyl groups were revealed from difference Fourier map and refined isotropically with geometry constraints. The data collection and refinement parameters are given in Table S1. CCDC 1843105-1843107, 1843768 contains the supplementary crystallographic data for this paper.

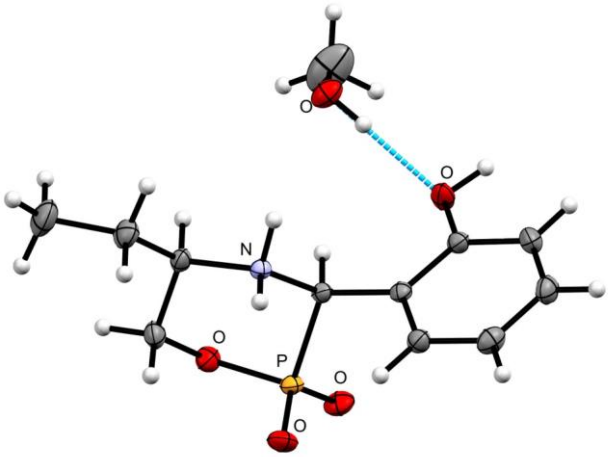


Figure S5. Molecular structure and hydrogen bonding of the compound **(*R*,*R*)-3b** (ORTEP drawing).

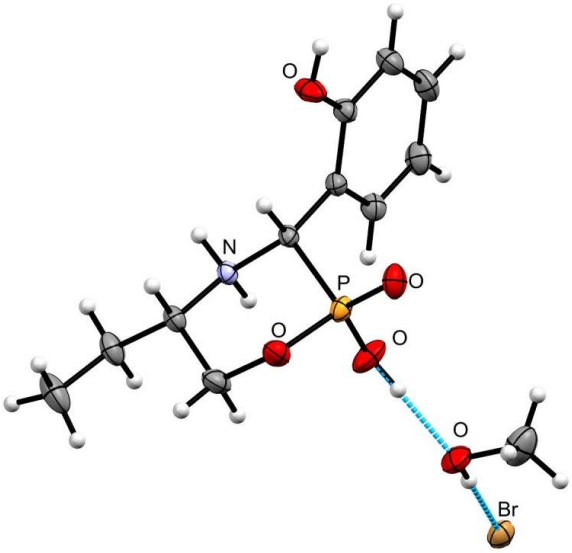


Figure S6. Molecular structure and hydrogen bonding of the compound **(*R*,*R*/*S*,*S*)-2b** (ORTEP drawing).

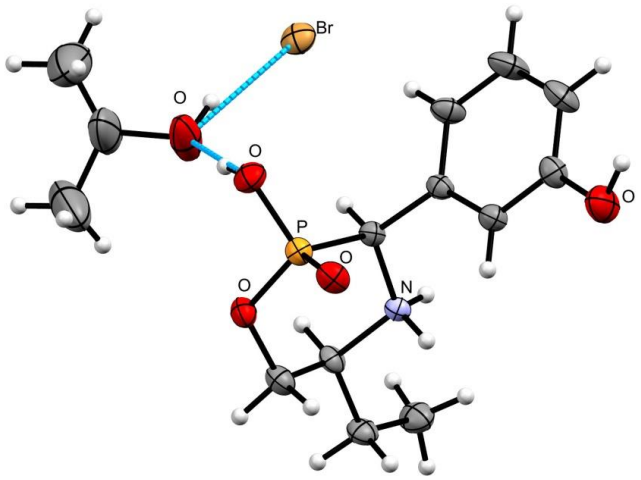


Figure S7. Molecular structure and hydrogen bonding of the compound **(*S*,*S*)-2''c** (ORTEP drawing).

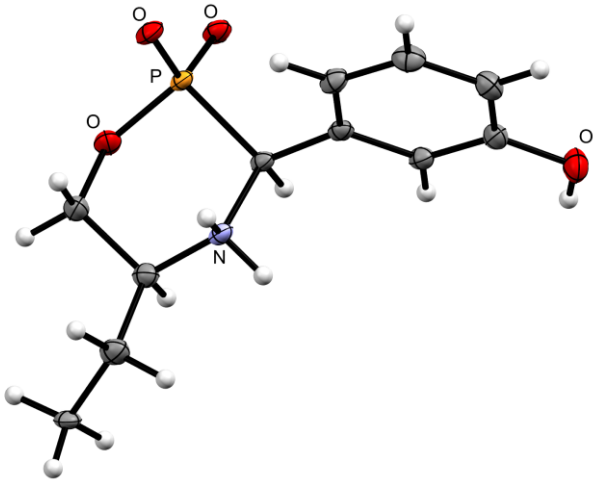


Figure S8. Molecular structure of the compound **(*R*,*R*/*S*,*S*)-3c** (ORTEP drawing).

Table S1. The data collection and refinement parameters.

Parameters	**(*R*,*R*)-3b**	**(*R*,*R*/*S*,*S*)-2b**	**(*S*,*S*)-2''c**	**(*R*,*R*/*S*,*S*)-3c**
Empirical formula	$C_{12}H_{20}NO_5P$	$C_{12}H_{21}BrNO_5P$	$C_{14}H_{25}BrNO_5P$	$C_{11}H_{16}NO_4P$
Formula weight	289.26	370.18	398.23	257.22
Temperature (K)	150 K	198 K	198 K	100 K
Wavelength (Mo K_α)	0.71073 Å	0.71073 Å	0.71073 Å	0.71073 Å
Crystal system	orthorhombic	monoclinic	orthorhombic	monoclinic
Space group	$P2_12_12_1$	$P2_1/n$	$P2_12_12_1$	$P2_1/c$
Unit cell dimensions	*a* = 7.8945(5) Å	*a* = 12.0242(7) Å	*a* = 10.6341(2) Å	*a* = 9.6572(6) Å
	b = 10.5491(6) Å	*b* = 9.9598(6) Å	*b* = 10.7346(2) Å	*b* = 10.8384(6) Å
	c = 16.9841(10) Å	*c* = 13.6024(9) Å	*c* = 15.4343(3) Å	*c* = 11.2655(7) Å
		β = 106.171(2)°		β = 97.302(3)°
Volume, $Å^3$	1414.43(15)	1564.55(17)	1761.87(6)	1169.58(12)
Z, Density (calculated)	4, 1.358 g·cm^{-3}	4, 1.572 g·cm^{-3}	4, 1.501 g·cm^{-3}	4, 1.461 g·cm^{-3}
Absorption coefficient, mm^{-1}	0.210	2.747	2.445	0.238
F(000)	616	760	824	544

Parameters	**(*R*,*R*)-3b**	**(*R*,*R*/*S*,*S*)-2b**	**(*S*,*S*)-2''c**	**(*R*,*R*/*S*,*S*)-3c**
Crystal size, mm	0.427 x 0.342 x 0.338	0.495 x 0.384 x 0.330	0.670 x 0.344 x 0.283	0.735 x 0.258 x 0.240
θ range for data collection	2.27° to 26.00°	2.00° to 28.00°	2.31° to 28.37°	3.52° to 30.62°
Limiting indices	*-9 ≤ h ≤ 9, -13 ≤ k ≤ 13, -20 ≤ l ≤ 20*	*-15 ≤ h ≤ 15, -13 ≤ k ≤ 13, -17 ≤ l ≤ 17*	*-14 ≤ h ≤ 14, -14 ≤ k ≤ 14, -20 ≤ l ≤ 20*	*-13 ≤ h ≤ 13, -15 ≤ k ≤ 15, -16 ≤ l ≤ 16*
Reflection collected	43276	58542	23326	23776
Independent reflection	2776 [R_{int} = 0.0212]	3766 [R_{int} = 0.0151]	4391 [R_{int} = 0.0236]	3587 [R_{int} = 0.0446]
Completeness to θ (%)	100	99.7	100	99.8
Data/restraints/parameters	2776/0/187	3766/7/209	4391/4/226	3587/209/178
Goodness-of-fit on F^2	1.241	0.812	1.057	1.048
Final R indices [I>2σ(I)]	R_1=0.0252, wR_2=0.0764	R_1=0.0192, wR_2=0.0832	R_1=0.0252, wR_2=0.0685	R_1=0.0393, wR_2=0.0934
R indices (all data)	R_1=0.0256, wR_2=0.0769	R_1=0.0202, wR_2=0.0851	R_1=0.0278, wR_2=0.0694	R_1=0.0568, wR_2=0.1011
Flack parameter	0.035(15)	–	0.002(3)	–
Max. residual electron density, e $Å^{-3}$	0.325 (-0.224)	0.364 (-0.337)	0.691 (-0.424)	0.431 (-0.393)

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