Organocatalytic Asymmetric $\alpha$-Bromination of Aldehydes and Ketones

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Supporting Information - Experimental for Bromination

**General Methods.** The $^1$H NMR and $^{13}$C NMR spectra were recorded at 400 MHz and 100 MHz, respectively. The chemical shifts are reported in ppm relative to CHCl$_3$ ($\delta = 7.26$) for $^1$H NMR and relative to the central CDC$_3$ resonance ($\delta = 77.0$) for $^{13}$C NMR. $J$ values are given in Hz. Flash chromatography (FC) was carried out using Merck silica gel 60 (230-400 mesh) unless otherwise stated. Optical rotation was measured on a Perkin-Elmer 241 polarimeter. NMR data of known compounds is in agreement with literature values.

**Materials.** Commercially available substrates and organocatalysts were used without further purification. All solvents were of p.a. quality and used without further purification. Commercially available NBS was recrystallised from H$_2$O before use.

**General procedure for the organocatalytic $\alpha$-bromination of aldehydes.** To a cooled (-40 °C) solution of the catalyst (0.10 mmol, 20 mol%), benzoic acid (0.10 mmol), water (1.0 mmol) and aldehyde (1.0 mmol) in CH$_2$Cl$_2$-pentane 1:1 (2.0 mL) the bromine source (0.50 mmol) was added and the reaction mixture was stirred at -40 °C. After 90 min. the reaction was diluted with 4 mL MeOH and NaBH$_4$ (2.0 mmol) was added and the reaction mixture was allowed to warm to room temperature. The reaction was quenched with NH$_4$Cl after 20 min. The mixture was extracted twice with Et$_2$O and the combined organic phases washed successively with H$_2$O, sat. NaHCO$_3$ and 1 M HCl. The organic phase was dried (MgSO$_4$), filtered and concentrated under reduced pressure. **OBS: The alcohols are fairly volatile and attention should be paid to avoid excessive evaporation.** Purification by FC (20 % Et$_2$O in Pentane) gave the pure products.

**2-Bromo 3-methyl propionaldehyde 4a.** The ee was determined by GC on a Chrompak CPChirasil Dex CB-column. Temperature program: 70 °C isotherm. $R_t$ (min): 11.9 ((R)-4a); 12.4 ((S)-4a). Enantiomers assigned by analogy to 5f. Isolated as 2-Bromo-3-methyl-butan-1-ol (5a) after reduction with NaBH$_4$. $^1$H
NMR δ 1.01 (3H, d, J 6.6), 1.04 (3H, d, J 6.7), 1.96-2.07 (1H, m), 2.09 (1H, br s), 3.82 (2H, d, J 6.1) and 4.10 (1H, dt, J 6.3, 10.8). 13C NMR δ 19.0, 20.8, 31.4, 65.7, 68.2.

2-Bromo 3,3-dimethyl propionaldehyde 4b. The ee was determined by GC on a Chrompak CPChirasil Dex CB-column. Temperature program: From 70 °C to 90 °C at 10 °C/min and then isotherm. R	extsubscript{t} (min): 8.0 ((R)-4b); 8.4 ((S)-4b). Enantiomers assigned by analogy to 5f. Isolated as 2-Bromo-3,3-dimethyl-butan-1-ol (5b) after reduction with NaBH	extsubscript{4}. 1H NMR δ 1.09 (9H, s), 2.04 (1H, br s) 3.75 (1H, dd, J 9.5, 12.4), 3.92 (1H, d, J 12.3) and 4.07-4.10 (1H, m). 13C NMR δ 27.8 (3C), 34.8, 64.4, 74.7.

2-Bromo butanal 4c. The ee was determined by GC on a Chrompak CPChirasil Dex CB-column. Temperature program: 55 °C isotherm for 11 min, then to 150 °C at a rate of 10 °C/min. R	extsubscript{t} (min): 13.2 ((R)-4c); 13.5 ((S)-4c). Enantiomers assigned by analogy to 5f. Isolated as 2-Bromo-butan-1-ol (5c) after reduction with NaBH	extsubscript{4}. 1H NMR δ 1.05 (3H, t, J 7.3), 1.77-1.97 (2H, m), 2.30 (1H, br s), 3.72-3.83 (2H, m) and 4.04-4.10 (1H, m). 13C NMR δ 12.0, 28.0, 61.6, 68.9.

2-Bromo Pentanal 4d. The ee was determined by GC on a Chrompak CPChirasil Dex CB-column. Temperature program: 70 °C isotherm. R	extsubscript{t} (min): 12.0 ((R)-4d); 12.7 ((S)-4d). Enantiomers assigned by analogy to 5f. Isolated as 2-Bromo-pentan-1-ol (5d) after reduction with NaBH	extsubscript{4}. 1H NMR δ 0.92 (3H, t, J 7.4), 1.36-1.63 (2H, m), 1.77-1.83 (2H, m), 2.45 (1H, br s), 3.70-3.82 (2H, m) and 4.09-4.16 (1H, m). 13C NMR δ 13.4, 20.6, 36.7, 59.5, 67.2.

2-Bromo octanal 4e. The ee was determined by GC on a Chrompak CPChirasil Dex CB-column. Temperature program: 70 °C to 100 °C at a rate of 10 °C/min then isotherm. R	extsubscript{t} (min): 19.0 ((R)-4e); 19.5 ((S)-4e). Enantiomers assigned by analogy to 5f. Isolated as 2-Bromo-octan-1-ol (5e) after reduction with NaBH	extsubscript{4}. Spectroscopic data are in agreement with literature data.1

Bromo-cyclohexyl-acetaldehyde 4f. The ee was determined by GC on a Chrompak CPChirasil Dex CB-column. Temperature program: 70 °C to 105 °C at a rate of 10 °C/min then isotherm. R	extsubscript{t} (min): 26.9 ((R)-4f); 27.4 ((S)-4f). Isolated as 2-Bromo-2-cyclohexyl-ethanol (5f) after reduction with NaBH	extsubscript{4}. 13C NMR δ 25.8, 25.9, 26.0, 30.0, 30.8, 41.1, 65.1, 67.0. [α]^{20}D -20.1 (c 0.80, CH	extsubscript{2}Cl	extsubscript{2}). (Litt: [α]^{20}D -22.9 (c 0.75, CH	extsubscript{2}Cl	extsubscript{2})). 1H-NMR spectroscopic data are in agreement with literature data. Absolute configuration determined by comparison with optical rotation.2

2-Bromo-pent-4-enal 4g. The ee was determined by GC on a Chrompak CPChirasil Dex CB-column. Temperature program: 65 °C isotherm. R	extsubscript{t} (min): 18.8 ((R)-4g); 19.9 ((S)-4g). Enantiomers assigned by
analogy to 5f. Isolated as 2-Bromo-pent-4-en-1-ol (5g) after reduction with NaBH₄. ¹H NMR δ 2.40 (1H, br s), 2.57-2.71 (2H, m), 3.73-3.83 (2H, m), 4.09-4.15 (2H, m), 5.13-5.17 (2H, m) and 5.76-5.87 (1H, m). ¹³C NMR δ 39.1, 57.1, 66.5, 118.3, 134.0.

**General procedure for the preparation of catalyst 3d.** Catalyst 3d was prepared by condensation of (1R,2R)-diphenylethylenediamine (1.0 eq.) with paraformaldehyde (1.0 eq.) as a 0.10 M solution in CH₂Cl₂ for 24 h at ambient temperature. The catalyst was used directly as a solution, or isolated as the corresponding salt by addition of benzoic acid and removal of the solvent at ambient temperature.

**General procedure for the organocatalytic α-bromination of ketones.** To a cooled (-30 °C) solution of the catalyst 3d (0.10 mmol, 20 mol%) and the ketone (0.75 mmol) in THF (1.0 mL) 4,4-dibromo-2,6-di-tert-butyl-cyclohexa-2,5-dienone (0.50 mmol) was added and the reaction mixture was stirred at -30 °C. After the time indicated in Table 3, the cold reaction mixture was filtered through a short pad of Iatrobeads 6RS-8060 using 10% Et₂O in CH₂Cl₂ to remove the catalyst. After evaporation of the solvent (several of the α-bromoketones are volatile) the α-bromoketones were purified by FC on Iatrobeads 6RS-8060 using CH₂Cl₂/Et₂O.

**α-Bromo-cyclohexanone 4h.** Isolated as the syn-2-bromocyclohexanol 5h after NaBH₄ reduction of the α-bromo-cyclohexanone 4h in 70% yield (2 steps) by the following procedure. The reaction mixture from the α-bromination reaction was diluted with 5 mL of cold MeOH (-30 °C) and 150 mg of NaBH₄ was added. After 5 min at -30 °C the reaction was allowed to go to 0 °C and stirred at that temperature for another 20 min after which it was quenched by the addition of 1 mL 1M HCl. The mixture was extracted twice with EtOAc and the organic phases dried over Na₂SO₄. After evaporation of the solvent the syn-2-bromocyclohexanol was obtained as a single diastereomer after FC on silica gel using CH₂Cl₂/Et₂O as the eluent. syn-2-Bromocyclohexanol 5h. ¹H NMR δ 1.32-1.48 (2H, m), 1.63-1.77 (3H, m), 1.79-1.87 (1H, m), 1.88-1.97 (1H, m), 2.04 (1H, d, J 6.4), 2.15-2.24 (1H, m), 3.69 (1H, br m) and 4.50 (1H, m); ¹³C NMR δ 21.5, 23.1, 31.2, 32.4, 62.2, 70.4; HRMS (TOF ES⁺) m/z 200.9907 (M+Na) calcd. for C₆H₁₁OBrNa⁺ 200.9891.

Alternatively, the α-Bromo-cyclohexanone 4h could be purified directly by FC on iatrobeads as described in the general procedure using CH₂Cl₂ as the eluent, but a decrease of 10-15% in optical purity was usually observed. The ee was determined by GC on a Astec G-TA column. Temperature program: From 70 °C to 125 °C at a rate of 10 °C/min and then isotherm. Rₜ (min): 9.3 and 9.6 min.

**α-Bromotetrahydropyran-4-one 4i.** Isolated as described in the general procedure above. ¹H NMR δ 2.60-2.68 (1H, m), 2.98 (1H, dt, J 4.8, 14.8), 3.86-3.96 (2H, m), 4.06-4.12 (1H, m), 4.29 (1H, dd, J 5.6, 12.8) and
4.47 (1H, dd, J 4.8, 5.6); $^{13}$C NMR δ 41.2, 51.0, 68.3, 73.7, 198.1; HRMS (TOF ES$^+$) m/z 200.9514 (M+Na) calcd. for C$_5$H$_7$O$_2$BrNa$^+$ 200.9527. The ee was determined by GC on a Chrompak CP-Chirasil Dex CB-column. Temperature program: From 70 °C to 130 °C at a rate of 10 °C/min and then isotherm. R, (min): 10.0 and 10.2 min.

α-Bromo-1,4-cyclohexanedionemonoethyleneketal 4j. Isolated as described in the general procedure above. $^1$H NMR δ 2.02-2.07 (2H, m), 2.39 (1H, dd, J 12.8, 13.2), 2.61 (1H, dd, J 6.4, 13.2), 2.67-2.71 (2H, m), 4.01-4.08 (4H, m) and 4.82 (1H, dd, J 6.4, 12.8); $^{13}$C NMR δ 34.3, 35.9, 45.8, 51.2, 64.7, 65.0, 106.9, 200.6; HRMS (TOF ES$^+$) m/z 256.9785 (M+Na) calcd. for C$_5$H$_7$O$_2$BrNa$^+$ 256.9789. The ee was determined by GC on a Chrompak CP-Chirasil Dex CB-column. Temperature program: From 70 °C to 180 °C at a rate of 10 °C/min and then isotherm. R, (min): 13.1 and 13.4 min.

X-Ray work:
Crystals of 3-bromotetrahydropyran-4-one, C$_5$H$_7$BrO$_2$, are orthorhombic, P2$_1$2$_1$2$_1$, with unit cell: a = 4.3135(4)Å, b = 11.327(1)Å, c = 12.558(1)Å, V = 613.57(9)Å$^3$, Z = 4. Data were collected at 100K on an APEX diffractometer with CCD detector. The structure solved by direct methods and refined by least squares methods to final R = 0.031, Rw = 0.033, GOF = 0.870 using 2585 reflections with I > 0, 103 parameters refined. Least squares refinement included a parameter according to Rogers$^4$ refined against all positive reflections including 1063 Bijvoet pairs.

3. The quality of 1,2-diphenylethylenediamine obtained from commercial sources was found to vary from batch to batch and therefore the 1,2-diphenylethylenediamine was recrystallized from tBuOMe before use.