Organocatalytic Asymmetric α-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 $CHCl_3$ (δ = 7.26) for ^{1}H NMR and relative to the central $CDCl_3$ resonance (δ = 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_2O before use.

General procedure for the organocatalytic α-bromination of aldehydes. To a cooled (-40 ^{o}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_2Cl_2-pentane 1:1 (2.0 mL) the bromine source (0.50 mmol) was added and the reaction mixture was stirred at -40 ^{o}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_4Cl after 20 min. The mixture was extracted twice with Et_2O and the combined organic phases washed successively with H_2O, 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_2O 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 ^{o}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). ^{13}C 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 ^{o}C to 90 ^{o}C at 10 ^{o}C/min and then isotherm. R_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 $NaBH_4$. ^{1}H 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). ^{13}C 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_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 $NaBH_4$. ^{1}H 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). ^{13}C 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 ^{o}C isotherm. R_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 $NaBH_4$. ^{1}H 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). ^{13}C 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_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 $NaBH_4$. 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 ^{o}C to 105 ^{o}C at a rate of 10 ^{o}C/min then isotherm. R_t (min): 26.9 ((R)-**4f**); 27.4 ((S)-**4f**). Isolated as 2-Bromo-2-cyclohexyl-ethanol (**5f**) after reduction with $NaBH_4$. ^{13}C NMR δ 25.8, 25.9, 26.0, 30.0, 30.8, 41.1, 65.1, 67.0. $[\alpha]^{20}_D$ -20.1 (*c* 0.80, CH_2Cl_2). (Litt: $[\alpha]^{20}_D$ -22.9 (*c* 0.75, CH_2Cl_2)). ^{1}H-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_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 $NaBH_4$. ^{1}H 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). ^{13}C 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 (1*R*,2*R*)-diphenylethylenediamine (1.0 eq.) with paraformaldehyde (1.0 eq.) as a 0.10 M solution in CH_2Cl_2 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 ^{o}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 **2b** (0.50 mmol) was added and the reaction mixture was stirred at -30 ^{o}C. After the time indicated in Table 3, the cold reaction mixture was filtered through a short pad of Iatrobeads 6RS-8060 using 10% Et_2O in CH_2Cl_2 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 CH_2Cl_2/Et_2O.

α-Bromo-cyclohexanone 4h. Isolated as the syn-2-bromocyclohexanol **5h** after $NaBH_4$ 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 ^{o}C) and 150 mg of $NaBH_4$ was added. After 5 min at -30 ^{o}C the reaction was allowed to go to 0 ^{o}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 Na_2SO_4. After evaporation of the solvent the syn-2-bromocyclohexanol was obtained as a single diastereomer after FC on silica gel using CH_2Cl_2/Et_2O as the eluent. syn-2-Bromocyclohexanol **5h**. ^{1}H 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); ^{13}C 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 $C_6H_{11}OBrNa^+$ 200.9891.

Alternatively, the α-Bromo-cyclohexanone **4h** could be purified directly by FC on iatrobeads as described in the general procedure using CH_2Cl_2 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. R_t (min): 9.3 and 9.6 min.

α-Bromotetrahydropyran-4-one 4i. Isolated as described in the general procedure above. ^{1}H 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 $C_5H_7O_2BrNa^+$ 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_t (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 $C_5H_7O_2BrNa^+$ 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_t (min): 13.1 and 13.4 min.

X-Ray work:

Crystals of 3-bromotetrahydropyran-4-one , $C_5H_7BrO_2$, are orthorhombic, $P2_12_12_1$, 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.

[1] H. Masuda, K. Takase, M. Nishio, A. Hasegawa, Y. Nishiyama and Y. Ishii; *J. Org. Chem.* **1994**, *59*, 5550.

[2] P. L. Bailey, A. D. Briggs, R. F. W. Jackson and J. Pietruszka; *J. Chem. Soc., Perkin Trans. 1,* **1998**, 3359.

[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.

[4] D. Rogers, *Acta Cryst.* **1981**, *A37*, 734.