Direct Organocatalytic Asymmetric α -Chlorination of Aldehydes

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Supporting Information

General. The ^1H 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 ^1H NMR and relative to the central CDCl_3 resonance ($\delta = 77.0$) for ^{13}C NMR. Flash chromatography (FC) was carried out using Merck silica gel 60 (230-400 mesh). Optical rotation was measured on a Perkin-Elmer 241 polarimeter. NMR data of known compounds is in agreement with literature values.

Materials. The commercially available aldehydes and organocatalysts were used without further purifications. Substrate **1h**¹ and the catalysts **3d**,² **3h**,³ **3i**⁴ and **3j**⁵ were synthesized according to literature procedures. All solvents were of p. a. quality and used without further purification. The commercially available NCS was recrystallized from AcOH before use.

General procedure for the organocatalytic α -chlorination of aldehydes. The catalyst (0.05 mmol, 10 mol%) was added to a stirred ice-cooled (0 °C) solution of the aldehyde (0.5 mmol) in CH_2Cl_2 (1.0 mL) followed by the addition of NCS (87 mg, 0.65 mmol, 1.3 eq.). The reaction mixture was after 1 h allowed to warm to ambient temperature and stirred until the aldehyde was completely consumed as determined by ^1H NMR spectroscopy of the reaction mixture and confirmed by GC analysis. Pentane was added to the reaction mixture and the precipitated NCS, succinimide and the catalyst were filtered off. After removal of the solvents the pure products could be extracted into pentane and isolated.

2-chloro-3-methyl butanal 2a: The ee was determined by GC on a Chrompak CP-Chirasil Dex CB-column. Temperature program: 70 °C isotherm for 9 min. R_t (min): 6.7 ((*R*)-enantiomer); 7.0 ((*S*)-enantiomer). The absolute configuration was determined by optical rotation and compared with literature values.⁶

2-chloro propanal 2b: The title compound was isolated as the corresponding methyl ester by the following procedure: The reaction mixture was diluted with 3.0 mL *t*-BuOH and 3.0 mL 1M NaH₂PO₄ (aq.) and 3.0 mL 1M KMnO₄ (aq.) were added successively. After 1 min of vigorous stirring 3.0 mL sat. NaHSO₃ (aq.) was added and the pH was adjusted to approximately 3 with 1M HCl at 0 °C. The resulting mixture was extracted with EtOAc, washed with water and brine, and dried over Na₂SO₄. The organic layer was concentrated and the residual acid was dissolved in toluene (2.0 mL) and MeOH (5.0 mL), and TMSCHN₂ (2.0 M in hexane) was added drop-wise until the yellow color persisted. The solution was stirred for an additional 5 min and quenched with a drop of AcOH. The solvents were removed and the crude product was purified by FC using pentane/Et₂O (9:1) to afford the pure product. The ee was determined by GC on a Chrompak CP-Chirasil Dex CB-column. Temperature program: 70 °C isotherm for 9 min. R_t (min): 3.7 ((*R*)-enantiomer); 4.0 ((*S*)-enantiomer). The title compound **2b** was reduced to the corresponding alcohol by the analogous procedure described for **2d** (see below). The absolute configuration of the chloro alcohol was determined by optical rotation and compared with literature values.⁶

2-chloro butanal 2c: The ee was determined by GC on a Chrompak CP-Chirasil Dex CB-column. Temperature program: 55 °C isotherm for 9 min. R_t (min): 6.7 ((*R*)-enantiomer); 6.9 ((*S*)-enantiomer).

2-chloro-3,3-dimethyl butanal 2d: The ee was determined by GC on a Chrompak CP-Chirasil Dex CB-column. Temperature program: 65 °C isotherm for 10 min. R_t (min): 4.9 ((*R*)-enantiomer); 5.1 ((*S*)-enantiomer). The absolute configuration was determined by an X-ray structure of a single crystal of **4b**,⁷ which was obtained by the following procedure: The reaction mixture was diluted with MeOH (2.0 mL) and NaBH₄ (100 mg, 2.6 mmol) was added in several portions.

Figure S1. X-ray structure of compound **4b**

The mixture was then stirred for 10 min, quenched with H₂O and extracted with EtOAc. The organic layer was separated, dried over Na₂SO₄ and the solvent was removed. The crude product was purified by FC over silica with CH₂Cl₂/Et₂O (9:1).

2-chloro octanal 2e: The title compound was isolated as the corresponding methyl ester **7c** by the same procedure as described for compound **2b**. The ee was determined by GC on a Chrompak CP-Chirasil Dex CB-column. Temperature program: From 70 °C to 200 °C at a rate of 10 °C/min. R_t (min): 8.1 (enantiomer-1); 8.2 (enantiomer-2). Alternatively the title compound can be isolated as the corresponding epoxide **5** by the following procedure:⁶ The reaction mixture was diluted with MeOH (2.0 mL) and NaBH₄ (100 mg, 2.6 mmol) was added in several portions. The mixture was then stirred for 10 min, quenched with H₂O and extracted with EtOAc. The organic layer was separated, dried over Na₂SO₄ and the solvent was removed. The crude product was purified by FC over silica with CH₂Cl₂/Et₂O (9:1). The 2-chloro octanol **4c** was then distilled over KOH (2 eq.) in order to isolate the pure 1,2-epoxy octane **5**. The ee of the epoxide was determined by GC on a Chrompak CP-Chirasil Dex CB-column. Temperature program: 75 °C isotherm for 16 min. R_t (min): 15.4 ((*S*)-enantiomer); 15.7 ((*R*)-enantiomer). The absolute configuration was determined by measurement of the optical rotation of the epoxide **5** and comparison with literature values.⁸

2-chloro pentenal 2f: ¹H NMR δ 9.51 (d, 1H, *J* = 2.4 Hz, C(H)O), 5.82 (*m*, 1H, CH₂CH-), 5.19 (*m*, 2H, -CH₂), 4.22 (ddd, 1H, *J* = 2.4, 6.0 and 8.0 Hz, CH-Cl), 2.77 (*m*, 1H, CH₂CHCH₂), 2.59 (*m*, 1H, CH₂CHCH₂) ¹³C NMR δ 195.0, 131.8, 119.8, 62.8, 36.6. The ee was determined by GC on a Chrompak CP-Chirasil Dex CB-column. Temperature program: 65 °C isotherm for 10 min. R_t (min): 9.0 (enantiomer-1); 9.2 (enantiomer-2).

2-chloro-3-phenyl propanal 2g: The title compound was isolated as the corresponding alcohol **4a** as described for **2d**. The ee was determined by HPLC on a Daicel Chiralpak AS column with hexane/*i*-PrOH (97:3) as the eluent. R_t (min): 7.9 (enantiomer-1); 9.3 (enantiomer-2).

2-chloro-4-(tert-butyldimethylsilyloxy)-butanal 2h: The title compound was isolated as the corresponding methyl ester **7d** by the same procedure as described for compound **2b**. ^1H NMR δ 4.49 (dd, 1H, $J = 4.8$ and 8.8 Hz, C(H)-Cl), 3.75 (s, 3H, OCH_3), 3.73 (m, 2H, OCH_2), 2.22 (m, 1H, CH_2), 2.00 (m, 1H, CH_2), 0.85 (s, 9H, $(\text{CH}_3)_3$), 0.02 (d, 6H, $J = 6.6$ Hz, $\text{Si}(\text{CH}_3)_2$). ^{13}C NMR δ 170.4, 58.7, 54.1, 52.9, 37.5, 25.8, -5.5. The ee of **7d** was determined by GC on a Chrompak CP-Chirasil Dex CB-column. Temperature program: From 70°C to 120°C at a rate of $10^\circ\text{C}/\text{min}$, then isotherm for 20 min at 120°C . R_t (min): 20.6 (enantiomer-1); 21.3 (enantiomer-2).

2-amino butyric acid methyl ester 9: Compound **9** was prepared according to Scheme 1. The chloro ester **7a** was synthesized in analogy to the procedure described for **2b** (see above). The ee of **7a** was determined by GC on a Chrompak CP-Chirasil Dex CB-column. Temperature program: From 70°C to 90°C at a rate of $10^\circ\text{C}/\text{min}$, then isotherm for 10 min at 90°C . R_t (min): 7.7 ((*R*)-enantiomer); 7.9 ((*S*)-enantiomer). The chloro ester **7a** (100 mg, 0.73 mmol) was dissolved in DMF (10 mL) and NaN_3 (300 mg, 4.6 mmol, 6.3 eq.) was added. The reaction mixture was heated at 60°C overnight, cooled to ambient temperature, quenched with H_2O and extracted with Et_2O . The organic layer was washed with H_2O (3 x 40 mL) and dried over Na_2SO_4 . After removal of the solvent compound **8** was isolated. ^1H NMR δ 3.72 (s, 4H, CH-N_3 and OCH_3), 1.82 (m, 1H, CH_2), 1.75 (m, 1H, CH_2), 0.95 (t, 3H, $J = 7.2$ Hz, CH_3). ^{13}C NMR: δ 171.0, 63.3, 52.6, 24.9, 10.2. The ee of **8** was determined by GC on a Chrompak CP-Chirasil Dex CB-column. Temperature program: From 70°C to 85°C at a rate of $10^\circ\text{C}/\text{min}$, then isotherm for 10 min at 85°C . R_t (min): 8.7 ((*S*)-enantiomer); 9.4 ((*R*)-enantiomer). Compound **9** was obtained by reduction of **8** with Pd/C in MeOH with H_2 (1 atm) overnight in a 40% yield from butanal **1c**.

2-amino butanol 11: The title compound was synthesized in analogy to compound **9** starting from 2-chloro butanol **4d**. The substitution reaction from **4d** to **10** was conducted at 90°C for 24 h. ^1H NMR: δ 3.71 (dd, 1H, $J = 3.6$ and 11.2 Hz, CH_2), 3.56 (dd, 1H, $J = 7.6$ and 11.2 Hz, CH_2), 3.41 (m, 1H, CH-N_3), 1.77 (br s, 1H, OH), 1.57 (m, 2H, CH_2), 1.02 (t, 3H, $J = 7.6$ Hz, CH_3). ^{13}C NMR: δ 65.9, 64.9, 23.7, 10.5. The ee was maintained during this transformation as confirmed by GC analysis. The ee of the **10** was determined by GC on a

Chrompak CP-Chirasil Dex CB-column. Temperature program: From 70 °C to 90° C at a rate of 10° C/min, then isotherm at 90° C. R_t (min): 21.2 ((*R*)-enantiomer); 21.4 ((*S*)-enantiomer). The title compound was obtained by reduction of **10** with Pd/C in MeOH with H₂ (1 atm) for 5 h. The absolute configuration was determined by comparison with a commercially available sample of the title compound.

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7. X-Ray work: Crystals of **4b**, C₆H₁₃ClO, are hexagonal, P3₂, with unit cell: $a = 17.826(2)\text{\AA}$, $c = 6.193(2)\text{\AA}$, $V = 1704.3(6)\text{\AA}^3$, $Z = 4$. Data were collected at 100K on a SMART diffractometer with CCD detector. The structure solved by direct methods and refined by least squares methods to final $R = 0.103$, $R_w = 0.128$, GOF = 1.99 using 3737 reflections with $I > 3\sigma(I)$, 214 parameters refined. The crystals are of low quality as their melting point is close to room temperature. Some disorder of the t-Bu groups is obviously frozen in at 100K as is seen from large residual density between the carbon atoms of these groups, and from the unreasonable displacement parameters. Least squares refinement included a parameter according to Rogers (1981) refined against all 37737 significant reflections including 1595 Bijvoet pairs. The indication from this – although weak – supports the chirality found in other ways.
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