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Highly Enantioselective Direct Organocatalytic Asymmetric α-Chlorination of Ketones

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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. 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. Commercially available substrates and organocatalysts were used without further purification. All solvents were of p.a. quality and used without further purification. Commercially available NCS was recrystallized from AcOH before use.

Preparation of catalyst 3i. Catalyst **3i** was prepared by condensation of (1*R*,2*R*)-diphenylethylenediamine (1.0 eq.) with paraformaldehyde (1.0 eq.) as a 0.1 M solution in CH_2Cl_2 overnight at ambient temperature. The catalyst was used directly as a solution, or isolated as the corresponding salt by addition of acid and removal of the solvent.

General procedure for the organocatalytic α-chlorination of ketones. To a cooled (-24°C) solution of the catalyst (0.05 mmol, 10 mol%) and the ketone (0.5 mmol) in CH_2Cl_2 (1.0 mL) NCS (1.0-2.0 eq.) was added and the reaction mixture was stirred at 24°C. The yield was determined by ^{1}H NMR using an internal standard and confirmed by GC. Pure products were isolated as described for the repective compounds (see below).

(*R*)-α-Chlorocyclohexanone 2a. 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 then isotherm for 5 min. R_t (min): 8.0 ((*S*)-**2a**); 8.2 ((*R*)-**2a**).

(*R*,*R*)-2,6-Dichlorocyclohexanone 2aa. NCS (67 mg, 0.5 mmol) was added to a solution of the catalyst (0.05 mmol) and (*rac*)-α-chlorocyclohexanone (66.3 mg, 0.5 mmol) in CH_2Cl_2 at ambient temperature. The mixture was stirred overnight and analysed by CSP-GC. Temperature program: From 70°C to 125°C at a rate of 10°C/min then isotherm for 3 min then to 200°C at a rate of 10°C/min. R_t (min): 8.0 ((*S*)-**2a**); 8.2 ((*R*)-**2a**); 12.5 (*S*,*S*)-**2aa**; 12.6 (*R*,*R*)-**2aa**.

α-Chlorotetrahydropyran-4-one 2b. ^{1}H NMR δ 4.43 (ddd, 1H, *J* = 1.2, 6.0 and 9.2 Hz, C*H*-Cl), 4.33 (ddd, 1H, *J* = 1.6, 6.0 and 11.6, OCH_2CHCl), 4.18 (m, 1H, OCH_2), 3.82 (ddd, 1H, *J* = 3.6, 11.2 and 14.8 Hz, OCH_2), 3.70 (dd, 1H, *J* = 9.2 and 11.6 Hz, OCH_2CHCl), 2.79 (dt, 1H, *J* = 3.6 and 10.8 Hz, C(O)CH_2), 2.71 (m, 1H, C(O)CH_2); ^{13}C NMR δ 198.5, 73.3, 68.2, 59.9, 41.8. The ee 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°C/min and then isotherm for 5 min. R_t (min): 9.5 (enantiomer-1); 9.7 (enantiomer-2).

α-Chloro-1,4-cyclohexanedionemonoethyleneketal 2c. The title compound was isolated as a racemate after FC over neutral alumina with CH_2Cl_2/Et_2O (9:1) as eluent. ^1H NMR δ 4.69 (dd, 1H, *J* = 6.4 and 13.2 Hz, C(*H*)-Cl), 3.99 (m, 4H, OCH_2CH_2O), 2.58 (m, 1H), 2.52 (m, 2H), 2.00 (m, 2H); ^{13}C NMR δ 201.2, 106.7, 64.9, 64.7, 60.2, 45.2, 34.3, 29.1; HRMS (TOF ES^+) calcd for $C_8H_{11}ClO_3$ $[M+Na+MeOH]^+$ 245.0557, found 245.0497. 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): 11.8 (enantiomer-1); 12.0 (enantiomer-2).

α-Chloro-1-Boc-4-piperidone 2d. The title compound was isolated as a racemate after FC over neutral alumina with CH_2Cl_2/Et_2O (9:1) as eluent. ^1H NMR (60°C) δ 4.25 (m, 2H), 3.87 (m, 1H,), 3.77 (t, 1H, *J* = 6.4 Hz), 3.62 (br m, 1H), 2.83 (m, 1H), 2.45 (m, 1H), 1.51 (s, 9H, $(CH_3)_3$); ^{13}C NMR δ 200.0, 154.4, 81.2, 59.7, 51.1, 43.3, 40.0, 28.2; HRMS (TOF ES^+) calcd for $C_{10}H_{16}ClNO_3$ $[M+Na+MeOH]^+$ 288.0979, found 288.0973. 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): 12.0 (enantiomer-1); 12.1 (enantiomer-2).

α-Chloro-pentane-3-one 2e. ^1H NMR δ 4.35 (dd, 1H, *J* = 6.8 and 13.6 Hz, C(*H*)-Cl), 2.75 (dd, 1H, *J* = 7.2 and 14.0 Hz, $C(O)CH_2$), 2.65 (dd, 1H, *J* = 7.2 and 14.4 Hz, $C(O)CH_2$), 1.60 (d, 3H, *J* = 6.8 Hz, CH_3), 1.09 (t, 3H, *J* = 7.2 Hz, CH_3); ^{13}C NMR δ 206.1, 58.3, 31.6, 20.2, 7.7. The ee was determined by GC on a Chrompak CP-Chirasil Dex CB-column. Temperature program: 70°C isotherm for 5 min then to 200°C at a rate of 10 °C/min. R_t (min): 6.4 (enantiomer-1); 6.7 (enantiomer-2). The title compound was isolated after conversion

to the corresponding thiophenylketone 2-phenylsulfanyl-pentan-3-one by the following procedure.[1] The reaction mixture from the α-chlorination reaction was filtered through a silica plug using CH_2Cl_2 to remove the catalyst, acid additive and succinimide. After evaporation of the CH_2Cl_2, the crude product was added to a mixture of NaOH (3.0 equiv.) and thiophenol (3.0 equiv.) in EtOH and the mixture was stirred for 3h at ambient temperature. After removal of the solvent the reaction mixture was diluted with water and extracted with CH_2Cl_2 and the non-volatile 2-phenylsulfanyl-pentan-3-one was isolated as a pale oil after FC on silica using CH_2Cl_2 as the eluent. ^{1}H NMR δ 7.27-7.38 (m, 5H, ArH), 3.78 (q, 3H, *J* = 7.2 Hz, C*H), 2.74 (dq, 1H, *J* = 17.6 and 7.6 Hz, CH*H*CO), 2.55 (dq, 1H, *J* = 17.6 and 7.6 Hz, C*H*HCO), 1.41 (d, 3H, *J* = 7.2 Hz, CHC*H*$_3$), 1.05 (t, 3H, *J* = 7.2 Hz, CH_2C*H*$_3$); ^{13}C NMR δ 208.3, 132.7, 129.0, 127.9, 51.1, 32.3, 16.2, 8.0; HRMS (TOF ES$^+$) calcd for $C_{11}H_{14}SONa$ $[M+Na]^+$ 217.0663, found 217.0666. The enantiomeric excess of the 2-phenylsulfanyl-pentan-3-one was found to be 75% ee as determined by HPLC using an Daicel Chiralcel OJ column using hexane/2-propanol 99/1 as the eluent.

α-Chloro-heptane-4-one 2f. ^{1}H NMR δ 4.13 (dd, 1H, *J* = 5.6 and 8.4 Hz, C(*H*)-Cl), 2.62 (dd, 2H, *J* = 6.7 and 6.8 Hz, C(O)C*H*$_2$), 1.97 (m, 1H, CHCl-C*H*$_2$), 1.86 (m, 1H, CHCl-C*H*$_2$), 1.63 (m, 2H, C*H*$_2$), 1.00 (t, 3H, *J* = 7.2 Hz, C*H*$_3$), 0.92 (t, 3H, *J* = 7.2 Hz, C*H*$_3$); ^{13}C NMR δ 205.5, 65.2, 40.5, 27.2, 17.0, 13.6, 10.6. The ee was determined by GC on a Chrompak CP-Chirasil Dex CB-column. Temperature program: 70°C isotherm for 5 min then to 200°C at a rate of 10 °C/min. R_t (min): 9.4 (enantiomer-1); 9.5 (enantiomer-2). The title compound was isolated after conversion to the corresponding thiophenylketone 3-phenylsulfanyl-heptan-4-one by the procedure described for compound **2e**. ^{1}H NMR δ 7.26-7.37 (m, 5H, ArH), 3.55 (t, 1H, *J* = 7.6 Hz, C*H), 2.55 (t, 2H, *J* = 7.4 Hz, $COCH_2$), 1.85 (m,

1H, CH*H*CH_3), 1.74 (m, 1H, C*H*HCH_3), 1.58 (sixtet, 2H, *J* = 7.4 Hz, C*H*$_2$$CH_3$), 1.01 (t, 3H, *J* = 7.4 Hz, CH_3), 0.89 (t, 3H, *J* = 7.4 Hz, CH_3); ^{13}C NMR δ 207.4, 133.2, 132.4, 129.0, 127.7, 58.6, 41.3, 23.7, 17.3, 13.7, 11.9; HRMS (TOF ES$^+$) calcd for $C_{13}H_{18}SONa$ [M+Na]$^+$ 245.0976, found 245.0974. The enantiomeric excess of the 3-phenylsulfanyl-heptan-4-one was found to be 86% ee as determined by HPLC using an Daicel Chiralcel OJ column using hexane/2-propanol 99/1 as the eluent.

(*R*,*R*)-2-Cyclohexyl-4,5-diphenylimidazolidine 3h. (1*R*,2*R*)-Diphenyl-ethylenediamine (10.6 mg, 0.05 mmol) and cyclohexanone (5 μL, 0.05 mmol) were mixed in $CDCl_3$ (0.7 mL) and the mixture was stirred for 2 h and analysed by NMR spectroscopy. ^{1}H NMR δ 7.22-7.11 (m, 10H, arom.), 4.12 (s, 2H, Ph-C*H*-C*H*-Ph), 2.27 (t, 1H, *J* = 6.8 Hz, C*H*$_2$), 2.00 (br s, 2H, N*H*), 1.83-1.37 (m, 9H, C*H*$_2$); ^{13}C NMR δ 140.7, 128.4, 127.3, 127.1, 69.7, 42.0, 39.8, 25.5, 23.9.

α-Chloro-ε-lactone 4. A chlorination reaction, as described above, between cyclohexanone and NCS was purified by filtration through a pad of silica with CH_2Cl_2, yielding the crude (*R*)-α-chlorocyclohexanone **2a** after evaporation most of the solvent. The mixture was diluted with CH_2Cl_2 (20 mL) and urea hydrogen peroxide (UHP) was added (2.15 g, 22.9 mmol, 40 equiv.) followed by dropwise addition of trifluoroacetic anhydride (10 equiv.). The reaction was stirred at ambient temperature until analysis by TLC indicated consumption of starting material (~30 min), at which point the reaction was quenched by slow addition of $NaHCO_3$ (sat. aq.). Extraction with CH_2Cl_2, and removal of solvent under reduced pressure yielded a crude mixture which was purified by FC on silica using Et_2O/pentaneto give pure **4** as a colourless oil in 54% yield (2 steps) and 97% ee. ^{1}H NMR δ 4.75 (dd, 1H, *J* = 2.8 and 8.4 Hz, C*H*-Cl), 4.56–4.51 (m, 1H, OC*H*$_2$), 4.21–4.16 (m, 1H, OC*H*$_2$), 2.13–

1.97 (m, 3H, CH_2), 1.85–1.73 (m, 3H, CH_2) ^{13}C NMR δ 170.3, 69.6, 58.6, 32.7, 28.9, 25.2. 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 then isotherm for 10 min and then 180°C at a rate of 10°C/min. R_t (min): 20.2 (enantiomer-1); 20.6 (enantiomer-2).

***cis*-2-Chloro-cyclohexan-1-ol 5**. To the α-chlorocyclohexanone **2a** (936 mg, 7.1 mmol) stirred in MeOH (35 mL) at 0°C was added dropwise a MeOH solution of $NaBH_4$ (322 mg, 8.5 mmol, 1.2 eq.). The reaction was stirred for 20 min and then quenched by addition of H_2O (50 mL). The mixture was extracted with EtOAc (3 x 50 mL) and combined organic phases were dried over $MgSO_4$ and filtered. Solvent was removed under reduced pressure and the compound was purified by filtration through silica in 1:1 Et_2O:pentane to give **5** as a colourless oil (0.732 g, 5.4 mmol, 76%) with a diastereomeric ratio >10:1 as determined by ^{1}H NMR spectroscopy.

***trans*-(*S*,*S*)-2-Azidocyclohexan-1-ol 6**. The *cis*-chloro alcohol **5** was dissolved in DMF (10 mL) and NaN_3 (10 eq.) was added. The reaction mixture was heated at 95°C for 40h, 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 **6** was isolated by FC (CH_2Cl_2/Et_2O 25:1). The absolute configuration was determined by optical rotation and was in accordance to literature values.[2a] The ee was determined on the corresponding TMS protected alcohol **7** (CH_2Cl_2, 1.1 eq. TMSOTf and 1.1 eq. NEt_3 for 1h) by GC on a Chrompak CP-Chirasil Dex CB-column. Temperature program: From 70°C to 160°C at a rate of 10 °C/min. R_t (min): 7.8 ((*R*,*R*)-**7**); 8.0 ((*S*,*S*)-**7**). Alternatively, the absolute configuration can be confirmed by optical rotation of **7**.[2b]

3-Chloro-tetrahydro-pyran-4-ol 9. The reduction was carried out as described for compound **5** (see above). ^{1}H NMR (major diastereoisomer) δ 4.19 (m, 1H), 4.05 (m, 1H), 3.87 (m, 1H), 3.59 (m, 1H), 2.15 (m, 1H, O*H*), 2.02-1.85 (m, 2H); ^{13}C NMR δ 70.6, 67.9, 63.4, 60.8, 31.8.

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