

Supporting Information

Catalytic, Asymmetric α -Halogenation

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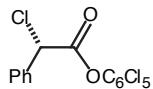
General Supporting Information: Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions. All reagents used are commercially available from Aldrich, Fluka, and Acros Chemicals. The jacketed addition funnels were purchased from ChemGlass. All solvents were dried and distilled by standard procedures. The chlorinating agent **5a** was purchased or else very easily prepared¹ and proved to be bench stable for weeks. The commercially available brominating reagent **5b** (Acros) was found to contain up to 33% 2,4,6-tribromophenol. The impurity was removed by washing with dry diethyl ether and filtering off the insoluble brominating reagent (99% purity). BEMP was purchased from Aldrich and specified as 100-200 mesh, 1% crosslinked with a typical loading of 2.0-2.5 mmol/g. All acid halides were purified by standard procedures, usually distillation. Merck Silica Gel 60 (0.040-0.063) was used for standard chromatography. The ¹H and ¹³C NMR spectra were acquired on a Varian Unity Plus 400 MHz instrument in CDCl₃. The ¹H (400 MHz) and ¹³C (101 MHz) chemical shifts are given in parts per million with respect to internal TMS standard or residual solvent peaks. HPLC analysis was performed with a Waters Millipore Model 510 head unit, a Chiracel AD analytical column, a Waters Millipore Lambda-Max Model 481LC spectrophotometer and a Hewlett Packard integrator. Racemates for **6a**, **6b** and **6h** were prepared by derivatizing commercially available α -halogenated acids. For all other substrates equimolar mixtures of the "pseudoenantiomers" **2a** and **2b** were used as catalyst to prepare the racemic mixture. Although this method for the synthesis of racemic mixtures is unconventional, it was found to work quite well. Solution phase IR data were recorded on a Bruker IFS-55 FTIR spectrometer.

General procedure for proton sponge reaction. A solution of phenylacetyl chloride **1a** (0.150 mmol) in 1 mL of toluene was added dropwise into a 25 mL round bottom flask (-78 °C) containing 10 mL of toluene, BQ **2a** (0.015 mmol) and proton sponge **3** (0.165 mmol). The resulting light yellow solution was stirred for 5 min, and then the halogenating agent **5a** (0.150 mmol in 1 mL toluene) was added via syringe into the bottom flask to form a dark red solution. The reaction was kept at -78 °C for 2 h and then quenched with a saturated NaHCO₃ solution. The aqueous solution was extracted three times with 5 mL of Et₂O and the combined organic extracts were dried with Na₂SO₄. Absorption onto silica gel followed by column chromatography with hexanes as eluent afforded **6a** in 40% yield and 95% ee, with **8a** as a byproduct.

General procedure for BEMP reaction. The jacketed addition funnel (2 cm wide) was plugged with a minimal amount of glass wool above the stopcock, and loaded under nitrogen with the BEMP resin **9** (75 mg, 0.150 mmol) and an appropriately sized magnetic stir bar. It was then connected to a 10 mL three-neck round bottom flask that contained (0.015 mmol) catalyst **2a**. Into the addition funnel 2 mL of THF was added and catalyst **2a** was in turn dissolved in 1 mL of THF. The funnel and flask were cooled to -78 °C with a dry ice/acetone mixture. An overhead stirrer attached to a magnet was then positioned close to the jacketed funnel so that *vigorous agitation* of the heterogeneous BEMP/acid chloride solution was ensured. A solution of phenylacetyl chloride **1a** (0.150 mmol) in THF (1 mL) was added dropwise into the funnel and *vigorously* stirred for 4 min. The stopcock was then opened to allow the ketene solution to drip by *gravity* into the bottom flask. The halogenating agent **5a** (0.150 mmol in 1 mL THF) was then added via syringe into the bottom flask. The reaction was kept at -78 °C for 3 h and then allowed to warm to

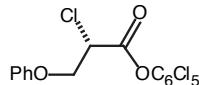
¹ Hedayatullah, M.; Lion, C.; Tourki, A. *Bull. Soc. Chim. Belg.* **1993**, 102, 281-291.

room temperature. Absorption onto silica gel followed by column chromatography with hexanes as eluent afforded **6a** in 80% yield and 99% ee.



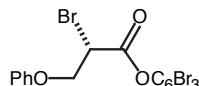
(S)-2-Chloro-2-phenyl-acetic acid pentachlorophenyl ester (6a). White crystalline solid, analytical sample was recrystallized from hexanes: mp = 98 °C; $[\alpha]_{25} = +36$ (c = 0.01, CHCl₃) HPLC (99.5% hexanes/0.5% i-PrOH, 1.0 mL/min) (S) = 8.1, (R) = 16.0 min. ¹H NMR 7.60 (m, 2H), 7.41 (m, 3H), 5.68 (s, 1H) ppm; ¹³C NMR 164.2, 143.2, 133.9, 131.9, 129.8, 128.9, 128.2, 127.4, 58.1 ppm; IR (CHCl₃): 1791, 1420, 1263 cm⁻¹. Anal Calcd for C₁₄H₆O₂Cl₆: C, 40.4; H, 1.45; Cl, 50.45. Found C, 40.93; H, 1.61; Cl, 49.82. Proof of absolute configuration was obtained for the ethyl ester of **(S)-6a**.²

(R)-2-Chloro-2-phenylacetic acid pentachlorophenyl ester (6a). $[\alpha]_{25} = -35.5$ (c = 0.01, CHCl₃). All other data are consistent with **(S)-6a**.

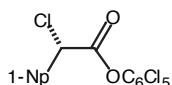


(S)-2-Chloro-3-phenoxypropionic acid pentachlorophenyl ester (6b). White crystalline solid; analytical sample was recrystallized from hexanes: mp = 84-85 °C; $[\alpha]_{25} = +19.5$ (c = 0.01, CHCl₃) HPLC (99.7% hexanes/0.3% i-PrOH, 1.0 mL/min) (S) = 20.2, (R) = 22.4 min. ¹H NMR 7.27-7.31 (m, 2H), 6.89-6.99 (m, 3H), 4.87-4.91 (q, 1H), 4.55-4.59 (m, 1H), 4.45-4.47 (m, 1H) ppm; ¹³C NMR 163.9, 157.7, 143.4, 132.5, 132.4, 129.9, 127.7, 122.3, 114.9, 68.7, 53.2 ppm; IR (CHCl₃): 1793, 1466 cm⁻¹. Anal Calcd for C₁₅H₈O₃Cl₆: C, 40.13; H, 1.8; Cl, 47.06. Found C, 40.17; H, 1.96; Cl, 46.84.

(R)-2-Chloro-3-phenoxypropionic acid pentachlorophenyl ester (6b). $[\alpha]_{25} = -20$ (c = 0.01, CHCl₃). All other data are consistent with **(S)-6b**.



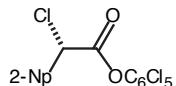
(S)-2-Bromo-3-phenoxypropionic acid (2,4,6-tribromophenyl) ester (6c). Off white paste; $[\alpha]_{25} = +22$ (c = 0.01, CHCl₃) HPLC (99% hexanes/1% i-PrOH, 1.0 mL/min) (S) = 12.8, (R) = 14.9 min. ¹H NMR 7.72 (s, 2H), 7.26-7.33 (m, 2H), 6.92-7.03 (m, 3H), 4.79-4.82 (m, 1H), 4.64-4.69 (m, 1H), 4.44-4.46 (m, 1H) ppm; ¹³C NMR 164.2, 157.5, 143.5, 135.0, 129.7, 121.9, 120.5, 118.2, 114.8, 68.4, 39.8 ppm; IR (CHCl₃): 1777, 1599, 1496 cm⁻¹. Anal Calcd for C₁₅H₁₀O₃Br₄: C, 35.59; H, 1.99; Br, 62.42. Found C, 35.63; H, 1.95; Br, 62.74.



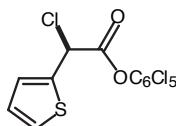
(S)-2-Chloro-2-(1-naphthyl)acetic acid pentachlorophenyl ester (6d). White crystalline solid; analytical sample was recrystallized from hexanes: mp = 116-117 °C; $[\alpha]_{25} = +24$ (c = 0.007, CHCl₃)

² Puy, C. H.; Breitbeil, F. W.; DeBruin, K. R. *J. Am. Chem. Soc.* **1966**, 88, 3347-3354.

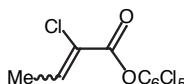
HPLC (99.5% hexanes/0.5% i-PrOH, 1.0 mL/min) (*S*) = 13.7, (*R*) = 29.3 min. ¹H NMR 8.2 (d, 1H), 7.84-7.93 (m, 3H), 7.49-7.63 (m, 3H), 6.4 (s, 1H) ppm; ¹³C NMR 164.6, 143.4, 133.9, 132.1, 130.9, 130.8, 130.3, 129.8, 129.2, 128.8, 127.7, 127.2, 126.4, 125.3, 123.1, 56.4 ppm; IR (CHCl₃): 1792, 1642 cm⁻¹. Anal Calcd for C₁₈H₈O₂Cl₆: C, 46.37; H, 1.73; Cl, 45.04. Found C, 46.28; H, 1.69; Cl, 45.24. Proof of absolute configuration was obtained for the ethyl ester of (**S**)-**6d**.³



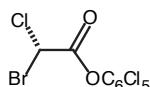
(S)-2-Chloro-2-(2-naphthyl)acetic acid pentachlorophenyl ester (6e). White crystalline solid; analytical sample was recrystallized from hexanes: mp = 124-125 °C; [α]₂₅ = +42 (c = 0.007, CHCl₃) HPLC (99% hexanes/1% i-PrOH, 1.0 mL/min) (*S*) = 16.5, (*R*) = 30.9 min. ¹H NMR 8.07 (s, 1H), 7.88-7.94 (m, 3H), 7.71-7.74 (dd, 1H), 7.55-7.57 (m, 2H), 5.87 (s, 1H) ppm; ¹³C NMR 164.3, 143.3, 133.7, 132.9, 132.1, 131.3, 129.1, 128.3, 128.2, 128.1, 127.8, 127.5, 127.3, 126.9, 124.9, 58.6 ppm; IR (CHCl₃): 1790, 1672 cm⁻¹. Anal Calcd for C₁₈H₈O₂Cl₆: C, 46.37; H, 1.73; Cl, 45.04. Found C, 46.41; H, 1.72; Cl, 45.15.



(S)-2-Chloro-2-thienylacetic acid pentachlorophenyl ester (6f). White crystalline solid; analytical sample was recrystallized from hexanes: mp = 85 °C; [α]₂₅ = -5 (c = 0.003, CHCl₃) HPLC (99.75% hexanes/0.25% i-PrOH, 1.0 mL/min) (*S*) = 12.4, (*R*) = 18.7 min. ¹H NMR 7.45 (dd, 1H), 7.36 (dd, 1H), 7.04 (q, 1H), 5.97 (s, 1H) ppm; ¹³C NMR 163.4, 143.2, 135.9, 132.3, 132.2, 129.1, 128.6, 127.5, 127.0, 53.3 ppm; IR (CHCl₃): 1789, 1579, 1463 cm⁻¹. Anal Calcd for C₁₂H₄O₂SCl₆: C, 34.14; H, 0.96; Cl, 49.74. Found C, 34.23; H, 1.02; Cl, 49.86.



2-Chlorocrotonic acetic acid pentachlorophenyl ester (6g). White paste; analytical sample was recrystallized from hexanes. Stereochemistry was not assigned. ¹H NMR 7.53 (q, 1H), 2.1 (d, 3H) ppm; ¹³C NMR 158.6, 142.6, 132.4, 132.2, 127.9, 123.8, 119.9, 15.9 ppm; IR (CHCl₃): 1766, 1630 cm⁻¹. Anal Calcd for C₁₀H₄O₂Cl₆: C, 32.56; H, 1.09; Cl, 57.67. Found C, 32.78; H, 1.13; Cl, 57.26.

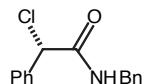


(S)-2-Bromo-2-chloroacetic acid pentachlorophenyl ester (6h). A solution of **2** (71 mg, 1.650 mmol) in 3 mL of THF was cooled to -78 °C. To this a solution of 2-bromoacetyl bromide **1g** (30 mg, 0.150 mmol) in 1 mL THF was added and stirred for 5 min. The chlorinating agent **5a** (50 mg, 0.165 mmol) in 1 mL of THF was then added and the reaction was allowed to warm to room temperature overnight. Absorption onto silica gel followed by column chromatography with hexanes as eluent afforded **6h** in 51% yield and 97% ee. White crystalline solid; analytical sample was recrystallized from hexanes: mp

³ Mc Kenzie, A.; Gow, E. R. L. *J. Chem. Soc.* **1933**, 705-714.

$\lambda = 71\text{-}73\text{ }^{\circ}\text{C}$; $[\alpha]_{25} = +21$ ($c = 0.01$, CHCl_3) HPLC (100% hexanes, 1.0 mL/min) ($S = 18.0$, $(R) = 20.2$ min). ^1H NMR 6.24 (s, 1H) ppm; ^{13}C NMR 160.5, 142.6, 132.5, 132.3, 127.4, 46.8 ppm; IR (CHCl_3): 1782, 1419 cm^{-1} . Anal Calcd for $\text{C}_8\text{HO}_2\text{BrCl}_6$: C, 22.78; H, 0.24; Cl, 58.84. Found C, 22.79; H, 0.24; Cl, 59.04.

N-Chloroquinine (2c). 1.00 g of polymer supported quinine (2.00 mmol/g, 1.00 mmol),⁴ through which a solution of compound **5a** and phenylketene **1a** had been passed on a column, was suspended in 25 mL of EtOH (reagent grade). The suspension was cooled to 0 $^{\circ}\text{C}$ and NaBH_4 (151 mg, 4.00 mmol) was added portionwise over 15 min. The reaction was then allowed to warm to room temperature and subsequently heated to reflux overnight. At the end of this period the reaction was cooled and filtered through Celite. The solvent was removed *in vacuo* and the residual crude solid purified by column chromatography to give a white crystalline solid. ^1H NMR 8.51 (d, 1H), 7.84 (d, 1H), 7.43 (d, 1H), 7.25(dd, 1H), 7.19 (d, 1H), 5.54 (m, 1H), 5.49 (d, 1H), 4.58 (m, 2H), 4.7 (bs, 1H), 3.65 (s, 3H), 3.40 (m, 1H), 3.05 (m, 2H), 2.52 (m, 2H), 2.43 (m, 1H), 1.53-1.56 (m, 3H), 1.40-1.51 (m, 2H); m/z 359.2 (35.15).



(S)-N-benzyl-2-chloro-2-phenylacetamide (10a). (S)-2-Chloro-2-phenyl-acetic acid pentachlorophenyl ester (**6a**) (0.100 mmol) was dissolved in 1 mL of THF and benzylamine (0.100 mmol) was added to the solution. After 2 h at room temperature the reaction was quenched with a saturated NaHCO_3 solution. The aqueous solution was extracted three times with 5 mL of Et_2O and the combined organic extracts were dried with Na_2SO_4 . Absorption onto silica gel followed by column chromatography with hexanes as eluent afforded **10a** in 99% yield and 99% ee. $[\alpha]_{25} = +19$ ($c = 0.01$, CHCl_3) HPLC (99% hexanes/1% i-PrOH, 1.0 mL/min) ($S = 13.0$, $(R) = 19.5$ min. All other data are consistent with literature precedent.⁵

⁴ Hafez, A. M.; Taggi, A. E.; Wack, H.; Drury, W. J., III; Lectka, T. *Org. Lett.* in press.
⁵ Choi, D.; Stables, J. P.; Kohn, H. *Bioorg. Med. Chem.* **1996**, *12*, 2105-2114.