Supporting Information for:
Catalytic, Enantioselective [4+2]-Cycloadditions of Ketene Enolates and *o*-Quinones:
Efficient Entry to Chiral, α,α -Oxygenated Carboxylic Acid Derivatives

Tefsit Bekele, Meha H. Shah, Jamison Wolfer, Ciby J. Abraham, Anthony Weatherwax
and Thomas Lectka

Department of Chemistry, Johns Hopkins University, 3400 N. Charles St., Baltimore, MD 21218

General. Unless otherwise stated, all reactions were carried out under anhydrous, air-free conditions. All solvents were dried and distilled by standard procedures. The ^1H and ^{13}C NMR spectra were acquired on a Bruker Avance400 MHz spectrometer. The ^1H (400 MHz) and ^{13}C (101 MHz) chemical shifts are given in parts per million (δ) with respect to TMS standards and residual chloroform. FTIR spectra were recorded on a Bruker IFS-55 spectrometer and optical rotations were recorded on a Perkin Elmer 120 polarimeter at room temperature. Enantiomeric ratios were obtained using a Regis Technologies (*R,R*)-Whelk-01 Chiral HPLC column or Chiracel OD column. Benzoylquinidine (**3**) was formed from quinidine (Sigma) and benzoyl chloride according to the method of Pracejus.¹ All other chemicals were purchased from Aldrich Chemical Corporation and Acros Organics.

General procedure for the synthesis of *o*-chloranil cycloadducts from aromatic acid chlorides (4c,e,f**):**

Benzoylquinidine (0.055 mmol) was placed into a 25 mL round bottom flask equipped with a magnetic stir bar and was dissolved in 3 mL of THF. The reaction was cooled to -78°C and Hünig's base (0.55 mmol) was added followed by *o*-Chloranil (0.55 mmol) as a solution in 4 mL of THF. The acid chloride (0.55 mmol), as a solution in 3 mL of THF, was then added to the reaction over 5 h via syringe pump. The reaction was kept at -78°C during the entire addition and for 2 h thereafter. The reaction was monitored by TLC and stopped once all of the quinone was consumed. The reaction mixture was then filtered through a plug of silica, and the plug is then flushed thoroughly with hexanes. Concentration of the filtrate *in vacuo* yielded pure product.

General procedure for the synthesis of *o*-chloranil cycloadducts from aliphatic acid chlorides (4a,b,d**):**

Benzoylquinidine (0.055 mmol) was placed into a 25 mL round bottom flask equipped with a magnetic stir bar and was dissolved in 3 mL of THF. The flask was cooled to -78°C and Hünig's base (0.55 mmol) was added followed by *o*-Chloranil (0.55 mmol) as a solution in 4 mL of THF. The acid chloride (0.55 mmol), as a solution in 3 mL of THF, was then added to the reaction. The reaction was monitored by TLC and stopped once all of the quinone was consumed, about 5 h. The reaction mixture was then filtered through a plug of silica, and the plug is then flushed thoroughly with hexanes. Concentration of the filtrate *in vacuo* yielded pure product.

Procedure for the synthesis of *o*-bromanil cycloadduct (4g**):**

Benzoylquinidine (0.055 mmol) was placed into a 25 mL round bottom flask equipped with a magnetic stir bar and was dissolved in 8 mL of THF. The reaction was cooled to -78°C and Hünig's base (0.55 mmol) was added followed by butyryl chloride (0.55 mmol), as a solution in 2 mL of THF. *o*-Bromanil (0.55 mmol) as a solution in 3 mL of THF, was then added to the reaction over 5 h via syringe pump. The reaction mixture was then filtered through a plug of silica, and the plug is then flushed thoroughly with hexanes. Concentration of the filtrate *in vacuo* yielded pure product.

(1) Pracejus, H.; Maetje, H. *J. Prakt. Chem.* **1964**, 24, 195.

Procedure for the synthesis of phenanthrenequinone cycloadduct (4h):

Benzoylquinidine (0.055 mmol) was placed into a 25 mL round bottom flask equipped with a magnetic stir bar and was dissolved in 8 mL of THF. The reaction was cooled to -78°C and Hünig's base (0.55 mmol) was added followed by butyryl chloride (0.55 mmol), as a solution in 2 mL of THF. Phenanthrenequinone (0.55 mmol) as a solution in 3 mL of THF was then added to the reaction over 5 h via syringe pump. The reaction mixture was then filtered through a plug of silica, and the plug is then flushed thoroughly with hexanes. Concentration of the filtrate *in vacuo* yielded crude product, which was purified by column chromatography on silica gel (hexanes/EtOAc eluent).

General procedure for the synthesis of α -hydroxy esters (8):

The cyclized product **4(a-d)** (0.14 mmol) was placed into a 25 mL round bottom flask equipped with a magnetic stir bar and was dissolved in 3 mL of 5:1 (MeOH/ CH_2Cl_2). The reaction, as determined by TLC was completed in times varying from 30 min to 2 h at room temperature. Upon completion, the reaction mixture was concentrated down under reduced pressure. The residue was then dissolved in 2.6 mL of 4:1 ($\text{CH}_3\text{CN}/\text{H}_2\text{O}$) in a round bottom flask equipped with a magnetic stir bar. Cerium ammonium nitrate (0.14 mmol) was added to the reaction at 0°C and stirred overnight. Water was then added and the mixture was extracted 3X with EtOAc. The organic layer was dried over MgSO_4 and concentrated *in vacuo*. The crude product was then filtered through a plug of Florisil, and the plug is then flushed thoroughly with hexanes. Concentration of the filtrate *in vacuo* yielded pure product. The optical rotations for **8a-8d**² are known in literature and the results confirmed that the (R)-enantiomer is in excess.

Characterization Data:

5,6,7,8-Tetrachloro-3-phenyl-benzo[1,4]dioxin-2-one (4a). White crystalline solid: % yield = 90; % ee = 99; mp = $181\text{--}183^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25} = -21.5^{\circ}$ ($c = 0.010$, CHCl_3); ^1H NMR (CDCl_3) δ 7.41 (m, 5H), 6.00 (s, 1H) ppm; ^{13}C NMR (CDCl_3) δ 160.3, 138.2, 137.6, 131.0, 130.1, 129.4, 129.2, 127.5, 126.2, 121.7, 120.7, 76.6 ppm; IR (CH_2Cl_2) 1794 cm^{-1} . HPLC (Whelk-01, 1% *i*-PrOH/hexanes, 1.0 mL/min) (R) = 9.16, (S) = 10.64. Anal Calcd for $\text{C}_{14}\text{H}_6\text{Cl}_4\text{O}_3$ C, 46.2; H, 1.66. Found C, 46.4; H, 1.71.

5,6,7,8-Tetrachloro-3-isopropyl-benzo[1,4]dioxin-2-one (4b). White crystalline solid: % yield = 75, % ee = 93; mp = $102\text{--}105^{\circ}\text{C}$; $[\alpha]_{\text{D}}^{25} = -6.8^{\circ}$ ($c = 0.010$, CHCl_3); ^1H NMR (CDCl_3) δ 4.51 (d, 1H), 2.29 (m, 1H), 1.15 (d, 3H), 1.12 (d, 3H) ppm; ^{13}C NMR (CDCl_3) δ 161.1, 137.5, 128.8, 126.9, 125.8, 121.3, 120.4, 80.0, 29.8, 18.3, 17.4 ppm; IR (CH_2Cl_2) 1775 cm^{-1} . HPLC (Whelk-01, 1% *i*-PrOH/hexanes, 1.0 mL/min) (R) = 5.79, (S) = 6.72. Anal Calcd for $\text{C}_{11}\text{H}_8\text{Cl}_4\text{O}_3$ C, 40.0; H, 2.44. Found C, 39.8; H, 2.42.

(2) (a) Barrow, R. A.; Moore, R.; Li, L.-H.; Tius, M. A.; *Tetrahedron*, **2000**, 56, 3339-3352. (b) Moore, Wilner J.; Marel, Gijs A. Van der; Liskamp, Rob J.; *J. Org. Chem.* **1995**, 60, 5157-5169. (c) Caglioti, L. *Tetrahedron* **1969**, 25, 2193-2221. (c) Burk, M. J.; Kalberg, C. S.; Pizzano, A. *J. Am. Chem. Soc.* **1998**, 120, 4345-4353.

5,6,7,8-Tetrachloro-3-ethyl-benzo[1,4]dioxin-2-one (4c). White crystalline solid: % yield = 90; % ee = 90; mp = 120-122° C; $[\alpha]_D^{25} = +7.3^\circ$ (c = 0.005, CHCl₃); ¹H NMR (CDCl₃) δ 4.65 (m, 1H), 2.01 (m, 2H), 1.17 (m, 3H) ppm; ¹³C NMR (CDCl₃) δ 161.9, 138.7, 137.7, 129.0, 127.1, 121.5, 120.6, 60.3, 23.8, 9.18 ppm; IR (CH₂Cl₂) 1778 cm⁻¹. HPLC (Chiracel OD, 7% *i*-PrOH/hexanes, 1.0 mL/min) (S) = 6.95, (R) = 7.34. Anal Calcd for C₁₀H₆Cl₄O₃ C, 38.0; H, 1.91. Found C, 37.8; H, 1.92.

3-Benzyl-5,6,7,8-tetrachloro-benzo[1,4]dioxin-2-one (4d). White crystalline solid: % yield = 72, % ee = 99; mp = 154-156° C; $[\alpha]_D^{25} = +29.0^\circ$ (c = 0.010, CHCl₃); ¹H NMR (CDCl₃) δ 7.27 (m, 5H), 4.97 (m, 1H), 3.39 (m, 1H), 3.29 (m, 1H) ppm; ¹³C NMR (CDCl₃) δ 161.6, 138.6, 137.3, 133.9, 129.5, 129.0, 128.7, 127.7, 127.0, 121.3, 120.5, 75.9, 37.1 ppm; IR (CH₂Cl₂) 1789 cm⁻¹. HPLC (Whelk-01, 1% *i*-PrOH/hexanes, 1.0 mL/min) (R) = 8.84, (S) = 9.34. Anal Calcd for C₁₅H₈Cl₄O₃ C, 47.6; H, 2.12. Found C, 47.4; H, 2.11.

5,6,7,8-Tetrachloro-3-(4-methoxy-phenyl)-benzo[1,4]dioxin-2-one (4e). White crystalline solid: % yield = 58; % ee = 99; mp = 173-175° C; $[\alpha]_D^{25} = +1.6^\circ$ (c = 0.007, CHCl₃); ¹H NMR (CDCl₃) δ 7.30 (m, 2H), 6.92 (m, 2H), 5.94 (s, 1H), 3.80 (s, 3H) ppm; ¹³C NMR (CDCl₃) δ 161.2, 138.5, 138.0, 133.9, 129.4, 128.3, 123.2, 122.1, 120.8, 115.0, 114.3, 76.6, 55.6 ppm; IR (CH₂Cl₂) 1775 cm⁻¹. HPLC (Whelk-01, 1% *i*-PrOH/hexanes, 1.0 mL/min) (R) = 17.73, (S) = 19.38. Anal Calcd for C₁₅H₈Cl₄O₄ C, 45.7; H, 2.05. Found C, 45.4; H, 2.08.

5,6,7,8-Tetrachloro-3-p-tolyl-benzo[1,4]dioxin-2-one (4f). Clear viscous oil: % yield = 75, % ee = 93; $[\alpha]_D^{25} = +0.4^\circ$ (c = 0.003, CHCl₃); ¹H NMR (CDCl₃) δ 7.72 (m, 1H), 7.53 (m, 1H), 7.28 (m, 2H), 5.91 (s, 1H), 2.41 (s, 3H) ppm; ¹³C NMR (CDCl₃) δ 161.2, 137.7, 137.2, 131.9, 130.5, 129.1, 129.0, 128.5, 126.8, 121.2, 120.0, 76.1, 21.1 ppm; IR (CH₂Cl₂) 1781 cm⁻¹. HPLC (Whelk-01, 1% *i*-PrOH/hexanes, 1.0 mL/min) (R) = 9.15, (S) = 12.35. Anal Calcd for C₁₅H₈Cl₄O₃ C, 47.7; H, 2.13. Found C, 47.6; H, 2.14.

5,6,7,8-Tetrabromo-3-ethyl-benzo[1,4]dioxin-2-one (4g). Yellow crystalline solid: % yield = 90, % ee = 95; $[\alpha]_D^{25} = +1.4^\circ$ (c = 0.003, CHCl₃); ¹H NMR (CDCl₃) δ 4.62 (m, 1H), 2.02 (m, 2H), 1.05 (m, 3H) ppm; ¹³C NMR (CDCl₃) δ 161.0, 137.2, 137.1, 133.9, 131.5, 129.3, 129.1, 58.3, 23.1, 10.1 ppm; IR (CH₂Cl₂) 1771 cm⁻¹. HPLC (Whelk-01, 1% *i*-PrOH/hexanes, 1.0 mL/min) (R) = 9.15, (S) = 10.35. Anal Calcd for C₁₀H₆Br₄O₃ C, 24.3; H, 1.22. Found C, 24.5; H, 1.20.

3-Ethylphenanthro[9,10-b][1,4]dioxin-2-one (3H, 4aH, 12bH)-one (4h). Yellow wax: % yield = 60, % ee = 89; ¹H NMR (CDCl₃) δ 8.85 (d, 2H), 7.85 (t, 2H), 7.77 (t, 2H), 7.52 (t, 2H), 4.45 (t, 1H), 1.94 (m, 2H), 0.91 (t, 3H) ppm; ¹³C NMR (CDCl₃) δ 171.5, 149.7, 133.2, 129.7, 128.9, 128.7, 126.3, 126.1, 123.8, 123.4, 122.8, 122.1, 121.4, 120.8, 120.4, 90.3, 23.1, 8.1 ppm; IR (CH₂Cl₂) 1771 cm⁻¹. HPLC (1% *i*-PrOH/hexanes, 1.0 mL/min) (R) = 15.25, (S) = 16.76. Anal Calcd for C₁₈H₁₄O₃ C, 77.7; H, 5.07. Found C, 77.5; H, 5.10.