

Reactive Ketenes through a Carbonate/Amine Shuttle Deprotonation Strategy: Catalytic, Enantioselective α -Bromination of Acid Halides

Ahmed M. Hafez, Andrew E. Taggi, Harald Wack,
Julie Esterbrook, and Thomas Lectka*

General. Unless otherwise stated, all reactions were carried out under strictly anhydrous, air-free conditions. All reagents used are commercially available from Aldrich and Acros Chemicals. The double-filtration flasks were purchased from ChemGlass. The brominating agent **4** may be purchased (Acros), but was very easily prepared. All solvents and reagents were dried and distilled by standard procedures. The ^1H and ^{13}C NMR spectra were acquired on a Varian Unity Plus 400 MHz instrument in CDCl_3 . The ^1H (400 MHz) and ^{13}C (101 MHz) chemical shifts are given in parts per million (δ) with respect to internal TMS standard or residual solvent peaks. HPLC analysis was performed with a Waters Millipore Model 510 head unit, a Chiracel OD analytical column (for **5a**, **5e**, **5f**) or a Chiracel AD analytical column (for **5b**, **5c**, **5d**) a Waters Millipore Lambda-Max Model 481L spectrophotometer and a Hewlett Packard integrator. Racemate of **5a** was prepared by derivatizing commercially available α -brominated phenylacetic acid. Racemate of **5e** was prepared by derivatizing commercially available α -brominated butyric acid. For all other substrates equimolar mixtures of the "pseudoenantiomers" benzoylquinine **3** and benzoylquinidine were used as catalysts to prepare the racemic mixture.¹ Solution phase IR data were recorded on a Bruker IFS-55 FTIR spectrometer. The absolute configuration of the products were consistent with literature precedent.²

General procedure for brominations. A dual reaction/filtration flask was equipped with two stir bars. One side of the flask was charged with excess K_2CO_3 (-325 mesh) (179 mg, 1.3 mmol, 10.0 eq) and 5 mol % benzoylquinine **3** (3 mg, 0.007 mmol). The other side of the vessel was loaded with 5 mol % of **3**. 3 mL of toluene were added to the side of the vessel charged with carbonate and 1 mL of toluene was added to the other side containing only **3**. The apparatus was cooled to -78°C so that the fritted disc was completely submerged in the dry ice/acetone bath. Phenylacetyl chloride (20 mg, 0.13 mmol, in 1 mL toluene) was added dropwise to the potassium carbonate mixture. The ketene was allowed to form for 12 hours at -78°C . After 12 hours, the apparatus was canted to allow the solution of ketene to flow through the fritted disc into the other side of the vessel while filtering off any solid byproducts. 2,4,4,6-Tetrabromo-2,5-cyclohexadien-1-one **4** (27 mg, 0.065 mmol, in 2 mL of toluene) was added to the ketene solution. The reaction was allowed to warm to room temperature for 12 hours. The toluene was removed *in vacuo* and the residue was dissolved in chloroform (10 mL). The chloroform solution was washed (3x, 5 mL) with a 0.1 M sodium carbonate solution. The organic layer was dried with MgSO_4 , filtered through Celite, and concentrated. The residue was taken up in chloroform again and absorbed onto silica before undergoing flash column chromatography (100% Hexanes) to give a white solid **5a** (76 % yield based on **4**, 91% ee).

Synthesis of 2,4,4,6-tetrabromo-2,5-cyclohexadien-1-one (4). A 9:1 glacial acetic acid / distilled water solution (635 mL) was added to 2,4,6-tribromophenol (10.0 g, 30 mmol, 1.0 eq). The solution was heated to dissolve the 2,4,6-tribromophenol, then cooled to 0°C in an ice bath. Bromine (5.3 g, 33 mmol, 1.1 eq) was added in five portions over 10 minutes. The reaction was stirred at 0°C for 30 minutes. Ice was added to the reaction causing the formation of a light yellow precipitate, which was collected on a coarse glass frit and washed with distilled water. The solid was dissolved in

¹ Although this method for the synthesis of racemic mixtures is unconventional, it was found to work quite well.

² See Supporting Information of Wack, H.; Taggi, A. E.; Hafez, A. M.; Drury, W. J., III; Lectka, T. *J. Am. Chem. Soc.* **2001**, *123*, 1531-1532.

CH₂Cl₂, dried with MgSO₄, filtered and concentrated. Additional drying was performed using five freeze/thaw cycles, with liquid nitrogen under high vacuum, yielding a light yellow crystalline solid **4** (11.0 g, 90% yield).

(S)-2-Bromo-2-phenylacetic acid (2,4,6-tribromophenyl) ester (5a). White crystalline solid; analytical sample was recrystallized from hexanes: mp = 75 °C; [α]₂₅ = +18 (c = 0.01, CHCl₃) HPLC (100% hexanes, 1.0 mL/min) (*S*) = 34.6, (*R*) = 37.2 min. ¹H NMR 7.67 (m, 4H), 7.39 (m, 3H), 5.65 (s, 1H) ppm; ¹³C NMR 164.2, 144.9, 134.9, 134.3, 129.7, 129.0, 128.8, 120.4, 118.2, 45.5 ppm; IR (CHCl₃): 1784, 1558, 1437 cm⁻¹. Anal. Calcd. for C₁₄H₈O₂Br₄: C, 31.86; H, 1.53; Br, 60.55 Found C, 31.85; H, 1.57; Br, 60.77.

(S)-2-Bromo-3-phenoxypropionic acid (2,4,6-tribromophenyl) ester (5b). Off white paste; [α]₂₅ = +22 (c = 0.01, CHCl₃) Identity and absolute configuration of compound is consistent with literature precedent.²

(S)-2-Bromo-2-(1-naphthyl)acetic acid (2,4,6-tribromophenyl) ester (5c). White crystalline solid; analytical sample was recrystallized from hexanes: mp = 106 °C; [α]₂₅ = +14 (c = 0.01, CHCl₃) HPLC (100% hexanes, 1.0 mL/min) (*S*) = 16.6, (*R*) = 20.4 min. ¹H NMR 8.24 (d, 2H), 8.01 (d, 1H), 7.91 (d, 2H), 7.62 (m, 2H), 7.55 (m, 2H), 6.48 (s, 1H) ppm; ¹³C NMR 164.6, 145.3, 135.3, 134.2, 130.8, 130.6, 130.1, 129.3, 128.6, 127.3, 126.6, 125.7, 123.5, 120.6, 118.4, 43.8 ppm; IR (CHCl₃): 1785, 1434 cm⁻¹. Anal. Calcd. for C₁₈H₁₀O₂Br₄: C, 37.41; H, 1.74; Br, 55.31. Found C, 37.88; H, 1.77; Br, 54.83.

(S)-2-Bromo-2-(2-naphthyl)acetic acid (2,4,6-tribromophenyl) ester (5d). White crystalline solid; analytical sample was recrystallized from hexanes: mp = 102 °C; [α]₂₅ = +21 (c = 0.01, CHCl₃) HPLC (99.5% hexanes/0.5% *i*-PrOH, 1.0 mL/min) (*S*) = 22.8, (*R*) = 24.6 min. ¹H NMR 8.09 (s, 1H), 7.86 (m, 4H), 7.69 (s, 2H), 7.53 (m, 2H), 5.84 (s, 1H) ppm; ¹³C NMR 164.9, 145.6, 135.6, 134.2, 133.5, 132.3, 129.6, 129.2, 128.9, 128.4, 127.9, 127.4, 126.7, 121.1, 118.8, 46.5 ppm; IR (CHCl₃): 1783, 1435 cm⁻¹. Anal. Calcd. for C₁₈H₁₀O₂Br₄: C, 37.41; H, 1.74; Br, 55.31. Found C, 37.33; H, 1.72; Br, 55.98.

(S)-2-Bromo-2-butyric acid (2,4,6-tribromophenyl) ester (5e). Clear oil; [α]₂₅ = -17 (c = 0.01, CHCl₃) HPLC (100% hexanes, 1.0 mL/min) (*S*) = 28.2, (*R*) = 31.9 min. ¹H NMR 7.69 (s, 2H), 4.56 (t, 1H), 2.30 (m, 1H), 2.16 (m, 1H), 1.15 (t, 3H) ppm; ¹³C NMR 166.0, 145.4, 135.4, 120.8, 118.7, 46.5, 28.8, 12.6 ppm; IR (CHCl₃): 1774, 1561, 1437 cm⁻¹. Anal. Calcd. for C₁₀H₈O₂Br₄: C, 25.03; H, 1.68; Br, 66.62. Found C, 25.59; H, 1.71; Br, 65.84.

(S)-2-Bromo-2-(*p*-methoxyphenyl)acetic acid (2,4,6-tribromophenyl) ester (5f). White crystalline solid; analytical sample was recrystallized from hexanes: mp = 82 °C; [α]₂₅ = -14 (c = 0.01, CHCl₃) HPLC (99.8% hexanes/0.2% *i*-PrOH, 1.0 mL/min) (*S*) = 25.4, (*R*) = 33.8 min. ¹H NMR 7.69 (s, 2H), 7.60 (d, 2H), 6.92 (d, 2H), 5.64 (s, 1H), 3.83 (s, 3H) ppm; ¹³C NMR 165.0, 161.2, 135.5, 131.1, 130.5, 126.9, 121.0, 118.8, 114.9, 56.0, 46.0 ppm; IR (CHCl₃): 1781, 1509, 1255 cm⁻¹. Anal. Calcd. for C₁₅H₁₀O₃Br₄: C, 32.30; H, 1.81; Br, 57.29. Found C, 32.27; H, 1.79; Br, 57.21.