Organocatalytic C–H Hydroxylation with Oxone® Enabled by an Aqueous Fluoroalcohol Solvent System

Supplementary Material

(16 pages)

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**General.** All reagents were obtained commercially unless otherwise noted. Reactions were performed using oven-dried glassware under an atmosphere of dry nitrogen. Air- and moisture-sensitive solutions were transferred via syringe. Solvent removal was effected by concentration of organic solutions under reduced pressure (ca. 20 Torr) by rotary evaporation. Tetrahydrofuran (THF) and dichloromethane (CH₂Cl₂) were passed through two columns of activated alumina prior to use. tert-Butyl alcohol was purified by distillation over CaH₂ and stored over activated 3Å molecular sieves. 1,1,3,3,6-Hexafluorisopropanol (HFIP, Oakwood HO242) and 2,2,2-trifluoroethanol (TFE) were used without further purification. Chromatographic purification of products was accomplished using forced flow chromatography on Silicycle silica gel 60 (40-63 μm). Thin layer chromatography was performed on EM science silica gel 60 F254 plates (250 μm). Visualization of the developed chromatogram was accomplished by fluorescence quenching and by staining with ethanolic anisaldehyde, aqueous potassium permanganate, or aqueous ceric ammonium molybdate (CAM) solution.

Nuclear magnetic resonance (NMR) spectra were acquired on a Varian Mercury 400 operating at 400, 100, and 376 MHz for ¹H, ¹³C, and ¹⁹F, respectively. ¹H and ¹³C spectra are referenced internally according to residual solvent signals (CDCl₃, δ = 7.26 ppm, ¹³CDCl₃, δ = 77.23 ppm). ¹⁹F NMR spectra are referenced internally using α,α,α-trifluorotoluene as a standard (δ = -63.72 ppm). Data for ¹H NMR are recorded as follows: chemical shift (δ, ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), integration, and coupling constant (Hz). Data for ¹³C NMR and ¹⁹F NMR are reported in terms of chemical shift (δ, ppm). Infrared (IR) spectra were recorded as either thin films using NaCl plates on a Thermo-Nicolet 300 FT-IR spectrometer and are reported in frequency of absorption. High resolution mass spectra were obtained from the Vincent Coates Foundation Mass Spectrometry Laboratory at Stanford University.

Oxaziridine 1 and benzoxathiazinanone 2 were prepared as described by Brodsky and Du Bois.¹ Characterization data for compounds appearing in entries 2, 3, and 6a (Table 2) has been previously reported.¹²

**Oxaziridine Stability Measurements**

To a 0.5 dram vial was added oxaziridine 1 (20 mg, 66 μmol), 1.3 mL of solvent, and a stir bar. After stirring for the given amount of time at 50 °C, the solution was cooled to room temperature and transferred to a 20 mL scintillation vial using 0.25 mL of CH₂Cl₂. This mixture was concentrated in vacuo (40 °C) to an oily residue. The percentage of 1 was determined by integration of the ¹H NMR spectrum using pyrazine as an internal standard and by ¹⁹F NMR.

**General Procedure for C–H Hydroxylation**

To a 10 mL round bottom flask containing substrate (1.0 mmol), catalyst (58 mg, 0.20 mmol, 0.2 equiv), and Oxone (768 mg, 2.5 mmol, 2.5 equiv) was added 4.0 mL of a 9:1 H₂O/HFIP solution. The flask was fitted with a Teflon cap, sealed, and placed in an oil bath pre-heated to 70 °C. The reaction mixture was stirred vigorously at this temperature for 12-24 h, then cooled to ambient temperature and transferred to a separatory funnel containing 7 mL of H₂O and 10 mL EtOAc. The organic layer was collected and the aqueous layer was extracted with 10 mL of EtOAc. The combined organic extracts were dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification of the isolated material by chromatography on silica gel (conditions given below) furnished the desired product.

**7-Hydroxy-3,7-dimethyloctanoic acid (Entry 1, Table 2).** Purified by chromatography on silica gel using 30% acetone/hexanes (colorless oil, 85%). TLC Rᵣ = 0.22 (3:1 hexanes:acetone); ¹H NMR (CDCl₃, 400 MHz) δ 2.36 (dd, 1H, J = 14.8, 6.0 Hz), 2.18 (dd, 1H, J = 15.2, 8.0 Hz), 2.04-1.95 (m, 1H), 1.50-1.30 (m, 6H), 1.31-1.25 (m, 6H), 1.26-1.19 (m, 1H), 0.94 (d, 3H, J = 6.6 Hz) ppm; ¹³C NMR (CDCl₃, 100 MHz) δ 179.4, 72.1, 44.3, 42.2, 37.7, 30.7, 29.8, 29.7, 21.2, 20.4 ppm; IR (thin film) ν 3745, 2968, 2341, 1707, 1458, 1380, 907 cm⁻¹; HRMS (ES⁺) calcd for C₁₀H₂₀O₃Na⁺ 211.1130 found 211.23 [MNa⁺].
1,1,1-Trifluoro-N-(3-hydroxy-3-methylbutyl)methanesulfonamide (Entry 2c, Table 2). Purified by chromatography on silica gel using 25% EtOAc/hexanes (pale yellow oil, 40%). TLC Rf = 0.12 (7:1 hexanes/EtOAc); 1H NMR (CDCl3, 400 MHz) δ 6.51 (br s, 1H), 3.48 (m, 2H), 1.79-1.76 (m, 2H), 1.67 (s, 1H), 1.31 (s, 6H) ppm; 13C NMR (CDCl3, 100 MHz) δ 120.3, 72.8, 41.5, 41.9, 30.2 ppm; IR (thin film) v 3548, 3315, 3125, 2976, 2934, 1425, 1370, 1298, 1077 cm⁻¹; HRMS (ES⁺) calcd for C18H23F4NO3S 343.1170 found 343.1169 [M⁺].

3α-Hydroxyoctahydronapentalen-1-yl benzoate (Entry 4a, Table 2). Purified by chromatography on silica gel using 10% EtOAc/hexanes (colorless oil, 38%). TLC Rf = 0.13 (4:1 hexanes/EtOAc); 1H NMR (500 MHz, CDCl3) δ 8.05-8.01 (m, 2H), 7.56 (tt, 1H, J = 7.4, 1.5 Hz), 7.47-7.43 (m, 2H), 5.49 (dt, 1H, J = 7.6, 5.8 Hz), 2.59-2.55 (m, 1H), 2.26-2.20 (m, 1H), 1.99-1.69 (m, 9H), 1.65-1.59 (m, 1H) ppm; 13C NMR (100 MHz, CDCl3) δ 166.2, 133.0, 130.5, 129.6, 128.7, 128.5, 90.5, 76.9, 55.2, 42.5, 42.4, 37.9, 31.9, 26.9, 26.8 ppm; IR (thin film) v 3409, 2955, 2870, 1718, 1451, 1315, 1276, 1116, 984 cm⁻¹; HRMS (ES⁺) calcd for C15H18O3Na⁺ 269.1154 found 269.1143 [MNa⁺].

6α-Hydroxyoctahydronapentalen-1-yl benzoate (Entry 4b, Table 2). Purified by chromatography on silica gel using 10% EtOAc/hexanes (colorless oil, 7%). TLC Rf = 0.21 (4:1 hexanes/EtOAc); 1H NMR (500 MHz, CDCl3) δ 8.09 (dd, 2H, 8.2, 1.0 Hz), 7.63-7.59 (m, 1H), 7.48 (dt, 2H, J = 12.0, 5.7 Hz), 5.06 (dd, 1H, J = 10.3, 6.6 Hz), 2.40-2.36 (m, 1H), 2.17-2.10 (m, 2H), 2.03-1.90 (m, 2H), 1.77-1.66 (m, 3H), 1.63-1.51 (m, 1H), 1.51-1.41 (m, 1H, 1.32-1.26 (m, 1H), 1.25-1.14 (m, 1H) ppm; 13C NMR (CDCl3, 100 MHz) δ 168.6, 133.6, 130.4, 130.0 128.8, 91.0, 87.1, 50.9, 37.8, 35.2, 30.2, 26.6, 26.1 ppm; IR (thin film) v 3447, 2953, 2870, 1781, 1451, 1378, 1274, 1070, 1011 cm⁻¹; HRMS (ES⁺) calcd for C15H18O3Na⁺ 269.1154 found 269.11 [MNa⁺].

4-Cyclopropyl-4-oxobutyl benzoate (Entry 5a, Table 2). Purified by chromatography on silica gel using 10% EtOAc/hexanes (white solid, 29%). TLC Rf = 0.49 (4:1 hexanes/EtOAc); 1H NMR (CDCl3, 400 MHz) δ 8.07-8.05 (m, 2H), 7.58-7.54 (m, 1H), 7.47-7.43 (m, 2H), 4.34 (t, 2H, J = 6.7 Hz), 2.73 (t, 2H, J = 7.2 Hz), 2.11-2.05 (m, 2H), 2.05-1.90 (m, 1H), 1.02 (m, 2H), 0.88-0.85 (m, 2H) ppm; 13C NMR (CDCl3, 100 MHz) δ 210.0, 166.7, 133.1, 130.3, 129.7, 128.5, 64.4, 39.8, 23.1, 20.7, 10.9 ppm; IR (thin film) v 3379, 1716, 1601, 1451, 1387, 1273, 1777, 1111, 1068 cm⁻¹; HRMS (ES⁺) calcd for C14H18O3 233.1177 found 233.1170 [MH⁺].

4-Cyclopropyl-4-hydroxybutyl benzoate (Entry 5b, Table 2). Purified by chromatography on silica gel using 10% EtOAc/hexanes (colorless oil, 11%). TLC Rf = 0.17 (4:1 hexanes/EtOAc); 1H NMR (CDCl3, 400 MHz) δ 8.07-8.04 (m, 2H), 7.59-7.55 (m, 1H), 7.47-7.43 (m, 2H), 4.38 (t, 2H, J = 6.6 Hz), 2.94 (ddd, 1H, J = 8.5, 7.3, 5.2 Hz), 2.07-1.83 (m, 2H), 1.86-1.74 (m, 2H), 0.99-0.89 (m, 2H), 0.62-0.50 (m, 2H), 0.33-0.23 (m, 2H) ppm; 13C NMR (CDCl3, 100 MHz) δ 166.9, 133.0, 130.5, 129.7, 115.2, 76.7, 65.2, 33.6, 25.3, 18.1, 3.0, 2.7 ppm; IR (thin film) v 3443, 3078, 3003, 2926, 2360, 1717, 1277, 1179, 1117 cm⁻¹; HRMS (ES⁺) calcd for C14H18O3Na⁺ 257.1154 found 257.1148 [MH⁺].
4-(2-Hydroxypropan-2-yl)phenyl methanesulfonate (Entry 6b, Table 2). Purified by chromatography on silica gel using 25% EtOAc/hexanes (white solid, 55%). TLC Rf = 0.18 (4:1 hexanes/EtOAc); 1H NMR (CDCl3, 400 MHz) δ 7.53 (d, 2H, J = 4.6 Hz), 7.23 (d, 2H, J = 4.6 Hz), 3.12 (s, 3H), 1.57 (s, 6H) ppm; 13C NMR (CDCl3, 100 MHz) δ 148.6, 147.9, 126.4, 121.7, 73.4, 37.4, 31.9 ppm; IR (thin film) ν 3278, 3038, 3028, 3973, 2940, 2360, 1502, 1375, 1170, 1152, 871 cm⁻¹; HRMS (ES⁺) calcd for C10H13O3Na⁺ 253.0511 found 253.0505 [MNa⁺].

5-(2-Hydroxypropan-2-yl)-2-methylphenyl methanesulfonate (Entry 7, Table 2). Purified by chromatography on silica gel using 25% EtOAc/hexanes (colorless oil, 30%). TLC Rf = 0.17 (4:1 hexanes/EtOAc); 1H NMR (CDCl3, 400 MHz) δ 7.41 (d, 1H, J = 1.8 Hz), 7.29 (dd, 1H, J = 8.0, 1.8 Hz), 7.22 (d, 1H, J = 8.0 Hz), 3.19 (s, 3H), 2.34 (s, 3H), 1.50 (s, 6H) ppm; 13C NMR (CDCl3, 100 MHz) δ 149.2, 147.8, 131.7, 129.5, 123.5, 118.5, 72.3, 38.3, 31.8, 16.4 ppm; IR (thin film) ν 3530, 2976, 2935, 1506, 1400, 1353, 1186, 1165, 1120, 969, 932, 852, 811 cm⁻¹; HRMS (ES⁺) calcd for C11H14O3Na⁺ 267.0667 found 267.18 [MNa⁺].

4-Acetylphenyl benzenesulfonate (Entry 8, Table 2). Purified by chromatography on silica gel using 15% acetone/hexanes (yellow oil, 53%). TLC Rf = 0.42 (4:1 hexanes/EtOAc); 1H NMR (CDCl3, 400 MHz) δ 7.90-7.87 (m, 2H), 7.83-7.81 (m, 2H), 7.69-7.65 (m, 1H), 7.55-7.51 (m, 2H), 7.08-7.05 (m, 2H), 2.55 (s, 3H) ppm; 13C NMR (CDCl3, 100 MHz) δ 196.8, 152.9, 135.8, 135.1, 134.7, 130.2, 129.4, 128.5, 122.5, 26.7 ppm; IR (thin film) ν 3069, 3006, 1687, 1596, 1377, 1202, 1155, 1092, 865 cm⁻¹.

(8S,9S,13S,14S)-13-methyl-11,17-dioxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl methanesulfonate (Figure 2). Purified by chromatography on silica gel using 5% acetone/hexanes (white foam, 30%). TLC Rf = 0.28 (2:1 hexanes/acetone); 1H NMR (CDCl3, 400 MHz) δ 7.07 (s, 1H), 6.99 (d, 2H, J = 1.6 Hz), 3.70 (d, 1H, J = 5.4 Hz), 3.12 (s, 3H), 2.55-2.39 (m, 3H), 2.25-2.02 (m, 6H), 1.86-1.76 (m, 3H), 0.92 (s, 3H) ppm; 13C NMR (CDCl3, 100 MHz) δ 217.2, 210.5, 148.0, 138.1, 130.3, 129.5, 123.5, 120.3, 54.2, 50.6, 46.7, 41.8, 37.7, 36.2, 32.8, 24.8, 22.9, 21.6, 15.0 ppm; IR (thin film) ν 2934, 1739, 1701, 1492, 1473, 1179, 1167, 1139, 1026, 857, 731 cm⁻¹; HRMS (ES⁺) calcd for C20H21O3SNa⁺ 385.1086 found 385.15 [MNa⁺].

7-Hydroxy-3,7-dimethyloctanoic acid

[Chemical structure image]

Electronic Supplementary Material (ESI) for Chemical Science
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1,1,1-Trifluoro-N-(3-hydroxy-3-methylbutyl) methanesulfonamide
3α-Hydroxyoctahydropentalen-1-yl benzoate
6α-Hydroxyoctahydropentalen-1-yl benzoate
4-Cyclopropyl-4-oxobutyl benzoate
4-Cyclopropyl-4-hydroxybutyl benzoate
4-(2-Hydroxypropan-2-yl)phenyl methanesulfonate
5-(2-Hydroxypropan-2-yl)-2-methylphenyl methanesulfonate
4-Acetylphenyl benzenesulfonate

Electronic Supplementary Material (ESI) for Chemical Science
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(8S,9S,13S,14S)-13-Methyl-11,17-dioxo-7,8,9,11,12,13,14,15,16,17-decahydro-6H-cyclopenta[a]phenanthren-3-yl methanesulfonate.
2D NMR Spectra for product appearing in Figure 2:

HSQC

HMBC