Electronic Supporting Information

Ortho-Substituted Iodobenzenes as Novel Organocatalysts for Bromination of Alkenes

D. Christopher Braddock,*[a] Gemma Cansell[a] and Stephen A. Hermitage[b]

[a] *Department of Chemistry, Imperial College London, London SW7 2AZ, UK*

[b] *GlaxoSmithKline Ltd*, *Medicines Research Centre, Gunnels Wood Road, Stevenage SG1 2NY, UK.*

ESI Available: Preparation and full characterising details of catalysts **7g** and **7i**, and substrates **10-14**.

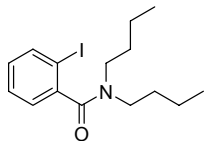
General Methods: Melting points were recorded on a Reichart-Thermovar melting point apparatus and are uncorrected. Fourier transform infra-red (IR) spectra were recorded through Diffuse Reference Infra-red Fourier Transform Spectroscopy (DRIFTS) or as thin films on NaCl plates using a Mattson 500 FT IR spectrometer. ^{1}H NMR were recorded at 270 MHz on a Jeol GSX-270 spectrometer or at 300 MHz on a 300 MHz Bruker DRX spectrometer. ^{13}C NMR were recorded at 68 MHz and 75 MHz on a Jeol GSX-270 spectrometer or a 300 MHz Bruker DRX spectrometer respectively. NMR samples were run in the indicated solvents and were referenced internally. All chemical shift values are quoted in ppm and coupling constants quoted in Hz. The following abbreviations are used for the multiplicity of NMR signals: br = broad, s = singlet, d = doublet, t = triplet, quint. = quintet, sext. = sextet, m = multiplet. Low Resolution Mass Spectra (MS) [EI, CI] and High Resolution Mass Spectra (HRMS) were recorded by the Imperial College Department of Chemistry Mass Spectroscopy Service and GSK Stevenage, UK. Elemental analyses were carried out by the University of North London Analytical Service.

Experimental procedures: Concentrated refers to removal of solvent under reduced pressure on a rotary evaporator. Analytical thin-layer chromatography (TLC) was carried out on silica gel $F_{254/366}$ 60 Å plates with visualisation using UV light (254 nm) or potassium permanganate as appropriate. Chromatography was performed using BDH 33-70 μm grade silica gel.

Reagents: Et_2O and THF were distilled from sodium and potassium respectively in the presence of benzophenone. CH_2Cl_2 was distilled from CaH_2. DMF was distilled from $MgSO_4$. All other reagents were used as received.

Catalyst Preparation

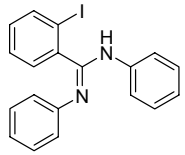
N,N-Di-*n*-butyl-2-iodobenzamide (**7g**)



Benzamide **7e** (1.0 g, 4.0 mmol) and 1-bromobutane (1.0 mL, 9.7 mmol) were added to a heated suspension of finely powdered NaOH (800 mg), K_2CO_3 (800 mg) and tetrabutylammonium hydrogen sulphate (140 mg, 0.4 mmol) in toluene (5.0 mL). The reaction mixture was heated to reflux for 3.5 h, cooled to room temperature and following aqueous work-up and purification by chromatography (1 : 1, petroleum ether : Et_2O) yielded di-*n*-butylamide **7g** (982 mg, 68%) as a colourless oil; R*f* 0.19 (CH_2Cl_2); FT IR (NaCl) ν_{max} 2957, 2931, 2781, 1638, 1585, 1458, 1425 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.0 Hz, 1H, Ar*H*), 7.32 (t, *J* = 7.4 Hz, 1H, Ar*H*), 7.14 (dd, *J* = 7.6, 1.9 Hz, 1H, Ar*H*), 6.99 (dt, *J* = 7.9, 1.9 Hz, 1H, Ar*H*), 3.78-3.68 (m, 1H, NCH*H*), 3.21-3.10 (m, 1H, NCH*H*), 3.00 (q, *J* = 7.4 Hz, 2H, CH_2), 1.74-1.58 (m, 2H, CH_2), 1.52-1.34 (m, 4H, CH_2), 1.16-1.00 (m, 2H, CH_2), 0.93 (t, *J* = 7.3 Hz, 3H, CH_3), 0.71 (t, *J* = 7.3 Hz, 3H,

C*H*$_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 170.4, 143.0, 139.1, 129.9, 128.2, 127.3, 92.9, 48.3, 44.5, 30.6, 29.2, 20.6, 19.9, 14.0, 13.7; MS (EI) 359 ($M^{+\cdot}$); HRMS calcd for (M) $C_{15}H_{22}INO$ 359.0746, found 359.0740; Anal. calcd for $C_{15}H_{22}INO$: C, 50.15; H, 6.17; N, 3.90. found: C, 49.99; H, 6.03; N, 3.90.

2-Iodo-*N*,*N'*-diphenylbenzamidine (**7i**)



Phosphorous pentachloride (1.20 g, 5.6 mmol) was dissolved in toluene (20 mL) over 30 min at room temperature. The solution was cooled to 0 °C and 2-iodo-*N*-phenylbenzamide (2.0 g, 6.2 mmol) was added portionwise. The reaction mixture was allowed to warm to room temperature and heated to reflux for 1.5 h. Aniline (570 μL, 6.2 mmol) in toluene (4 mL) was added dropwise to the refluxing mixture and the heating continued for a further 1 h. The reaction mixture was concentrated to dryness and dissolved in cold absolute ethanol (25 mL). The solution was cooled to 0 °C and cold 10% aqueous NaOH solution added until > pH 12. Further water (10 mL) was added to facilitate precipitation. The precipitate was filtered, washed with water and dried at 40 °C to yield amidine **7i** (1.60 g, 65%) as a fine white powder: m.p. 124-126 °C; R*f* 0.11 (CH_2Cl_2); FT IR (NaCl/$CDCl_3$) ν_{max} 3372, 3058, 3023, 1629, 1587, 1531, 1486, 1436, 1332 cm^{-1}; ^{1}H NMR (270 MHz, $CDCl_3$) δ 7.78 (d, *J* = 7.8 Hz, 1H, Ar*H*), 7.41-6.97 (m, 13H, Ar*H*), 6.32 (br s, 1H, N*H*); ^{13}C NMR (68 MHz, $CDCl_3$) δ 154.7, 149.8, 139.5, 130.6, 130.4, 128.7, 128.0, 122.7, 121.5-120.9 (br s) 96.0; MS (EI) 398 ($M^{+\cdot}$); HRMS calcd for (M) $C_{19}H_{15}IN_2$ 398.0280, found 398.0267; Anal. calcd for $C_{19}H_{15}IN_2$: C, 57.30; H, 3.80; N, 7.03; found: C, 57.23; H, 3.83; N, 6.89;

Preparation of substrates for bromination

General procedure for preparation of γ-unsaturated acids via Johnson-Claisen rearrangement and subsequent hydrolysis: A solution of appropriately substituted prop-2-en-1-ol (1 eq.), triethylorthoacetate (10 eq.) and cyclohexanoic acid (0.1 eq.) was heated at reflux for 3 h. The reaction mixture was allowed to cool and the organic layer extracted with Et_2O. The organic layer was washed with aqueous HCl solution (10%), saturated aqueous $NaHCO_3$ solution, water and brine, dried over $MgSO_4$, concentrated and purified by chromatography to give pure ethyl ester. To the ester in ethanol (0.16 M) was added 10% aqueous NaOH solution (4 × volume) and the reaction mixture heated to reflux for 2 h. On cooling Et_2O was added and the aqueous layer acidified to pH 4. The Et_2O layer was washed with water, brine, dried over $MgSO_4$ and concentrated to give pure acid.

Ethyl 4-methylpent-4-enoate and 4-methylpent-4-enoic acid (**11**)

11

Following the general procedure starting from 2-methyl-prop-2-en-1-ol gave first the desired ester as a colourless oil (56%): R*f* 0.36 (3 : 2, petroleum ether:CH_2Cl_2); FT IR (NaCl) ν_{max} 1737 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 4.68 (s, 1H, CH*H*=), 4.63 (s, 1H, C*H*H=), 4.07 (q, *J* = 7.2 Hz, 2H, OCH_2), 2.45-2.27 (m, 4H, CH_2CH_2), 1.71 (s, 3H, =CCH_3), 1.21 (t, *J* = 7.2 Hz, 3H, OCH_2CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.3, 144.1, 110.3, 60.3, 32.7, 32.6, 22.5, 14.2. Subsequent hydrolysis according to the general procedure gave acid **11** as a colourless oil (96%): R*f* 0.20 (CH_2Cl_2); FT IR (NaCl) ν_{max} 3508-2729, 1711 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 10.30 (br s, 1H, O*H*), 4.76 (s, 1H, *H*HC=), 4.70 (s, 1H, H*H*C=), 2.54-2.48 (m, 4H, CH_2), 1.74 (s, 3H, CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 179.8, 143.8, 110.6, 32.5, 32.3, 22.6; MS (CI^+) 132 ($M+NH_4^+$); HRMS calcd for $C_6H_{14}NO_2$ 132.1025, found 132.1028;

Ethyl 5-methylhex-4-enoate and 5-methylhex-4-enoic acid (**12**)

12

Following the general procedure starting from 1,1-dimethyl-prop-3-en-1-ol gave first the desired ester as a colourless oil (67%): R*f* 0.44 (2 : 3 CH_2Cl_2 : petroleum ether); FT IR (NaCl) ν_{max} 1738 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.07 (m, 1H, C=C*H*), 4.09 (q, *J* = 8.1 Hz, 2H, OCH_2), 2.30-2.27 (m, 4H, CH_2), 1.65 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.21 (t, *J* = 8.1 Hz, 3H, CH_2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.5, 133.0, 122.5, 60.2, 34.6, 25.7, 23.7, 17.7, 14.3; MS (CI^+) 157 ($M+H^+$); HRMS calcd for (M) $C_9H_{17}O_2$ 157.1229, found 157.1224. Subsequent hydrolysis according to the general procedure gave acid **12** as a colourless oil (83%): R*f* 0.12 (CH_2Cl_2); FT IR (NaCl) ν_{max} 3471-2345, 1709 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 11.20 (br s, 1H, O*H*), 5.09-5.07 (m, 1H, C=C*H*), 2.38-2.21 (m, 4H, CH_2), 1.64 (s, 3H, =C(CH_3)$_2$), 1.59 (s, 3H, =C(CH_3)$_2$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 179.8, 133.4, 122.2, 34.3, 23.7, 23.4, 17.7; MS (CI^+) 146 ($M+NH_4^+$); HRMS calcd for ($M+NH_4$) $C_7H_{16}NO_2$ 146.1181, found 146.1178;

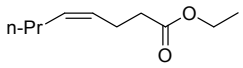
(*E*)-Ethyl oct-4-enoate and (*E*)-oct-4-enoic acid (**13**)

13

Following the general procedure starting from hex-1-en-3-ol gave first the desired ester as a colourless oil (94%): R*f* 0.45 (1 : 1, petroleum ether:CH_2Cl_2); FT IR (NaCl) ν_{max} 1737 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.46-5.30 (m, 2H, *H*C=C*H*), 4.07 (q, *J* = 7.0 Hz, 2H, OCH_2), 2.29-2.26 (m, 4H, CH_2), 1.93-1.86 (m, 2H, CH_2), 1.32 (m, 2H, $CH_2CH_2CH_3$), 1.19 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 0.82 (t, *J* = 7.2 Hz, 3H, $CH_2CH_2CH_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.2, 131.6, 128.2, 60.2, 34.6, 34.5, 28.0, 22.6, 14.3, 13.6. Subsequent hydrolysis according to the general procedure gave acid **13** as a pale yellow

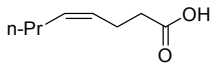
oil (61%): R*f* 0.18 (CH_2Cl_2); FT IR (NaCl) ν_{max} 3646-3031, 1710 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 11.0 (br s, 1H, O*H*), 5.44-5.39 (m, 2H, *H*C=C*H*), 2.44-2.28 (m, 4H, CH_2), 1.95 (q, *J* = 7.2 Hz, 2H, =CHCH_2), 1.32 (sext, *J* = 7.2 Hz, CH_2CH$_3$), 0.86 (t, *J* = 7.2 Hz, 3H, CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 180.0, 132.0, 127.8, 34.6, 34.3, 27.7, 22.6, 13.6; MS (CI^+) 160 ($M+NH_4^+$); HRMS calcd for ($M+NH_4$) $C_8H_{18}NO_2$ 160.1338, found 160.1334;

(*Z*)-Oct-4-enoic acid ethyl ester



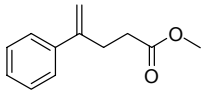
4-Bromobutyricacid ethyl ester (5.0 g, 25.6 mmol) and triphenylphosphine (9.5 g, 36 mmol) were heated to 120 °C for 15 min and allowed to cool. The crude solid was washed with Et_2O, and dried under vacuum to yield phosphonium salt (8.5 g, 70%) as a white solid: m.p. 171-173 °C. The salt (2.5 g, 5.5 mmol) was suspended in THF (17 mL) at -5 °C, Na(HMDS) (1 M in THF, 6 mL, 6 mmol) was added, and after 10 min the ylide was lowered to -78 °C. Butyraldehyde (0.54 mL, 6 mmol) was added and the reaction mixture stirred at room temperature for 18 h. The reaction was quenched with saturated aqueous NH_4Cl solution (10 mL) and extracted with EtOAc (2 × 30 mL). The combined extracts were washed with water (2 × 30 mL), brine (40 mL), dried over $MgSO_4$ and concentrated to give an orange oil. The oil was purified by chromatography (1 : 1, petroleum ether : CH_2Cl_2) to give the ester (430 mg, 46%) as a colourless oil: R*f* 0.28 (1 : 1, petroleum ether : CH_2Cl_2); FT IR (NaCl) ν_{max} 1728 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.41-5.29 (m, 2H, *H*C=C*H*), 4.10 (q, *J* = 7.0 Hz, 2H, OCH_2), 2.34-2.26 (m, 4H, CH_2), 2.00 (q, *J* = 7.3 Hz, 2H, =CHCH_2), 1.34 (sext, *J* = 7.3 Hz, $CH_2CH_2CH_3$), 1.22 (t, *J* = 7.0 Hz, 3H, OCH_2CH_3), 0.82 (t, *J* = 7.3 Hz, 3H, $CH_2CH_2CH_3$); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.2, 131.2, 127.6, 60.3, 34.5, 29.3, 22.9, 22.8, 14.2, 13.8.

(*Z*)-Oct-4-enoic acid (**14**)



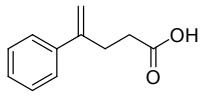
Following the general procedure for hydrolysis on the above *Z*-alkene ester gave acid **14** as a colourless oil (78%): R*f* 0.55 (4 : 6 petroleum ether : Et_2O); FT IR (NaCl) ν_{max} 3481-3083, 1711 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 5.50-5.29 (m, 2H, *H*C=C*H*), 2.41-2.32 (m, 4H, CH_2), 2.01 (q, *J* = 7.1 Hz, 2H, C$H_2CH_2CH_3$), 1.35 (sext, *J* = 7.1 Hz, 2H, CH_2CH_3), 0.85 (t, *J* = 7.1 Hz, 2H, CH_3); ^{13}C NMR (68 MHz, $CDCl_3$) δ 179.9, 131.7, 127.2, 34.2, 29.3, 22.8, 22.6, 13.8; MS (CI^+) 160 ($M+NH_4^+$); HRMS calcd for ($M+NH_4$) $C_8H_{18}NO_2$ 160.1338, found 160.1333;

4-Phenylpent-4-enoic acid methyl ester



Methyl triphenylphosphonium bromide (980 mg, 2.8 mmol) was suspended in toluene (15 mL) at -5 °C, Na(HMDS) (1 M in THF, 2.7 mL, 2.7 mmol) was added, and after 30 min the ylide sokution was lowered to -78 °C. 4-Oxo-4-phenylbutyric acid methyl ester (500 mg, 2.6 mmol) was added and the reaction mixture allowed to warm to room temperature and heated to reflux for 40 h. The reaction was quenched with saturated aqueous NH_4Cl solution (20 mL) and extracted with EtOAc (2 × 50 mL). The combined extracts were washed with water (2 × 60 mL), brine (80 mL), dried over $MgSO_4$ and concentrated to give a light brown oil oil. The oil was purified by chromatography (8 : 2, petroleum ether : CH_2Cl_2) to give the desired olefin (460 mg, 93%) as a pale yellow oil: R*f* 0.49(1 : 1, petroleum ether : CH_2Cl_2); FT IR (NaCl) ν_{max} 1732 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 7.44-7.23 (m, 5H, Ar*H*), 5.30 (br s, 1H, *H*HC=), 5.10 (br s, 1H, H*H*C=), 3.67 (s, 3H, OCH_3), 2.84 (dd, *J* = 9.0, 6.5 Hz, 2H, CH_2), 2.48 (dd, *J* = 9.0, 6.5 Hz, 2H, CH_2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 173.6, 146.9, 140.6, 128.5, 127.7, 126.2, 112.9, 51.7, 33.1, 30.5;

4-Phenylpent-4-enoic acid (**10**)



To a stirred solution of the above ester (528 mg, 2.8 mmol) in THF (20 mL) at 0 °C was added lithium hydroxide monohydrate (584 mg, 13.9 mmol) in water (20 mL). The reaction mixture was allowed to warm to room temperature and stirred for a further 18 h. The solution was acidified to <pH4 with aqueous HCl solution (1 M) and extracted with Et_2O (2 × 20 mL). The organic layers were combined, washed with water (30 mL), brine (30 mL), dried over $MgSO_4$ and concentrated to give acid **10** (450 mg, 92%) as off white crystals: m.p. 92-93 °C; R*f* 0.12 (CH_2Cl_2); FT IR (NaCl/$CDCl_3$) ν_{max} 3330-2581, 1694 cm^{-1}; ^1H NMR (270 MHz, $CDCl_3$) δ 10.85 (br s, 1, O*H*), 7.43-7.25 (m, 5H, Ar*H*), 5.33 (br s, 1H, *H*HC=), 5.12 (br s, 1H, H*H*C=), 2.86 (dd, *J* = 8.5, 7.0 Hz, 2H, CH_2), 2.54 (dd, *J* = 8.5, 7.0 Hz, 2H, CH_2); ^{13}C NMR (68 MHz, $CDCl_3$) δ 179.7, 146.6, 140.5, 128.5, 127.8, 126.2, 113.1, 33.1, 30.2; MS (CI^+) 194 ($M+NH_4^+$), 177 ($M+H^+$); HRMS calcd for ($M+NH_4$) $C_{11}H_{16}NO_2$ 194.1181, found 194.1182;