Regioselective copper-catalyzed chlorination and bromination of arenes with O\textsubscript{2} as the oxidant

Lujuan Yang\textsuperscript{a,b}, Zhan Lu\textsuperscript{b} and Shannon S. Stahl\textsuperscript{*b}

\textsuperscript{a} State Key Laboratory of Physical Chemistry of Solid Surfaces and Department of Chemistry, College of Chemistry and Chemical Engineering, Xiamen University, Xiamen, 361005, China

\textsuperscript{b} Department of Chemistry, University of Wisconsin-Madison, 1101 University Avenue, Madison, WI 53706, USA.

E-mail: stahl@chem.wisc.edu

General Procedure for Catalytic Halogenation Reactions.

The amounts of CuCl\textsubscript{2} or CuBr\textsubscript{2} and LiCl or LiBr designated in Tables 1 and 2 were combined in disposable culture tubes, and the individual tubes were placed in a 48-well rack mounted on a Glas-Col pulsed shaker. The tubes were sealed, and the atmosphere within the tubes was purged with O\textsubscript{2} (1 atm). Solutions of each substrate (0.3 mmol) in AcOH (1 mL) were dispensed into the tubes, and the reaction mixtures were heated to the appropriate temperature while shaking for the times designated in Tables 1 and 2. When the reaction was complete, the reaction mixture was diluted with 10 mL water and 10 mL CH\textsubscript{2}Cl\textsubscript{2}. The organic layer was washed with saturated Na\textsubscript{2}CO\textsubscript{3} (15 mL) and brine solution (15 mL). The organic layer was dried over Na\textsubscript{2}SO\textsubscript{4} and concentrated under vacuum. The residue was purified by column chromatography (see conditions for each product below).

Product Characterization Data.

84% yield; oil (elution solvent – hexane:ether = 5:1). \textsuperscript{1}H NMR: (300 Hz, CDCl\textsubscript{3}): \(\delta\) 7.40 (d, \(J = 8.7\) Hz, 1H), 6.48 (d, \(J = 2.8\) Hz, 1H), 6.39 (dd, \(J = 8.9, 2.5\) Hz, 1H), 3.86 (s, 3H), 3.79 (s, 3H); \textsuperscript{13}C NMR (300 Hz, CDCl\textsubscript{3}): \(\delta\) 160.5, 156.8, 133.3, 106.1, 102.7, 100.2, 56.3, 55.8; HRMS (EI-EMM): Calcd for C\textsubscript{8}H\textsubscript{9}O\textsubscript{2}Br (\textsuperscript{79}Br) \(m/z = 215.9781\) found 215.9782.

100% yield; solid (purified without chromatography). \textsuperscript{1}H NMR: (300 Hz, CDCl\textsubscript{3}): \(\delta\) 7.65 (s, 1H), 6.48 (s, 1H), 3.90 (s, 6H); \textsuperscript{13}C NMR (300 Hz, CDCl\textsubscript{3}): \(\delta\) 156.4, 136.1, 102.6,
97.6, 56.7; melting point: 138-139°C; HRMS (EI-EMM): Calcd for C₈H₈O₂Br₂ (⁷⁹Br) m/z = 293.8886 found 293.8899.

82% yield, solid (elution solvent – gradient, hexane:ethyl acetate = 10:1 → 5:1) product obtained as inseparable mixture of 2b:2c (82:8%). \(^1\)H NMR: (300 Hz, CDCl₃): \(\delta\) 6.17 (s, 1H), 3.87 (s, 6H), 3.81 (s, 3H); \(^{13}\)C NMR (300 Hz, CDCl₃): \(\delta\) 160.7, 157.6, 92.2, 91.8, 56.5, 55.7; HRMS (EI-EMM): Calcd for C₉H₁₁O₂Br (⁷⁹Br) m/z = 245.9887 found 245.9892.

93% yield; solid (purified without chromatography). \(^1\)H NMR: (300 Hz, CDCl₃): \(\delta\) 6.35 (s, 1H), 3.91 (s, 6H), 3.87 (s, 3H); \(^{13}\)C NMR (300 Hz, CDCl₃): \(\delta\) 156.8, 155.9, 99.2, 93.4, 60.7, 56.8; melting point: 128-129°C; HRMS (EI-EMM): Calcd for C₉H₁₀O₃Br (⁷⁹Br) m/z = 323.8992 found 323.8996.

75% yield; solid (elution solvent – hexane:ethyl acetate =10:1). \(^1\)H NMR: (300 Hz, CDCl₃): \(\delta\) 7.25 (d, J = 0.7 Hz, 1H), 6.44 (s, 1H), 3.88 (s, 3H), 3.83 (s, 3H), 2.12 (s, 3H); \(^{13}\)C NMR (300 Hz, CDCl₃): \(\delta\) 158.0, 154.9, 134.2, 120.5, 101.4, 96.7, 56.7, 55.8, 15.3; melting point: 89-90°C; HRMS (EI-EMM): Calcd for C₉H₁₁O₂Br (⁷⁹Br) m/z = 229.9937 found 229.9932.

80% yield, oil (elution solvent – hexane:ethyl acetate = 100:1). \(^1\)H NMR: (300 Hz, CDCl₃): \(\delta\) 8.27 (d, J = 8.4 Hz, 1H), 8.16 (d, J = 7.9 Hz, 1H), 7.9 (d, J = 8.8 Hz, 1H), 7.62-7.57 (m, 1H), 7.57-7.45 (m, 1H), 6.66 (d, J = 8.1 Hz, 1H), 3.97 (s, 3H); \(^{13}\)C NMR (300 Hz, CDCl₃): \(\delta\) 155.5, 132.6, 129.7, 127.9, 127.0, 126.2, 122.6, 133.5, 104.7, 55.9; HRMS (EI-EMM): Calcd for C₁₁H₉BrO (⁷⁹Br) m/z = 235.9832, found 235.9824.
96% yield; oil (purified without chromatography). $^1$H NMR: (300 Hz, CDCl$_3$): $\delta$ 7.25 (s, 1H), 6.67 (s, 1H), 3.79 (s, 3H), 2.35 (s, 3H), 2.15 (s, 3H); $^{13}$C NMR (300 Hz, CDCl$_3$): $\delta$ 157.1, 135.9, 133.9, 126.3, 114.8, 112.7, 55.7, 23.1, 15.7; HRMS (EI-EMM): Calcd for C$_9$H$_{11}$BrO ($^{79}$Br) m/z = 213.9988, found 213.9981.

93% yield, solid (Additional purification conditions: The reaction mixture was diluted with 10 mL water and 10 mL CH$_2$Cl$_2$, and the phases were separated. Saturated Na$_2$CO$_3$ (20 mL) was added to the aqueous layer, which was then extracted with CH$_2$Cl$_2$. The organic layer was washed with 15 mL of saturated Na$_2$CO$_3$, followed by brine solution. column elution solvent – gradient, hexane:ethyl acetate =1:1 → 1:2). $^1$H NMR: (300 Hz, CDCl$_3$): $\delta$ 7.69 (s, 1H), 7.32 (s, 1H), 6.97 (s, 1H), 3.87 (s, 3H), 2.21 (s, 3H), 2.18 (s, 3H); $^{13}$C NMR (500 Hz, CDCl$_3$): $\delta$ 168.5, 154.6, 136.1, 134.3, 121.0, 106.7, 56.6, 24.9, 16.7; melting point: 194-195$^\circ$C. HRMS (EI-EMM): Calcd for C$_{10}$H$_{12}$BrNO$_2$ ($^{79}$Br) m/z = 257.0046 found 257.0040.

78% yield, oil (elution solvent – hexane: dichloromethane = 5:1). $^1$H NMR: (300 Hz, CDCl$_3$): $\delta$ 7.40-7.34 (m, 2H), 6.80-6.74 (m, 2H), 3.78 (s, 3H); $^{13}$C NMR (500 Hz, CDCl$_3$): $\delta$ 158.9, 132.4, 115.9, 113.0, 55.6; HRMS (EI-EMM): Calcd for C$_7$H$_7$BrO ($^{79}$Br) m/z = 185.9675 found 185.9681.

89% yield, oil (elution solvent – hexane:ethyl acetate = 20:1). $^1$H NMR: (300 Hz, CDCl$_3$): $\delta$ 7.03 (dd, J = 8.6, 2.4 Hz, 1H), 6.98 (d, J = 2.4 Hz, 1H), 6.73 (d, J = 8.6 Hz, 1H), 3.87 (s, 3H), 3.86 (s, 3H); $^{13}$C NMR (500 Hz, CDCl$_3$): $\delta$ 149.7, 148.3, 123.4, 114.8, 112.7, 112.5, 56.1, 56.0; HRMS (EI-EMM): Calcd for C$_8$H$_6$BrO$_2$ ($^{79}$Br) m/z = 215.7980 found 215.7980.
77% yield, oil (elution solvent – pentane). $^1$H NMR: (300 Hz, CDCl$_3$): $\delta$ 7.87-7.75 (m, 2H), 7.50-7.33 (m, 3H); $^{13}$C NMR (300 Hz, CDCl$_3$): $\delta$ 138.8, 137.7, 125.5, 125.2, 123.7, 123.4, 122.9, 111.1, 107.9; HRMS (EI-EMM): Calcd for C$_8$H$_5$SBr ($^{79}$Br) m/z = 211.9290 found 211.9291.

$\text{10b}$

63% yield, solid (elution solvent – hexane). $^1$H NMR: (300 Hz, CDCl$_3$): $\delta$ 7.73-7.67 (m, 2H), 7.39 (td, $J$ = 7.6, 1.0 Hz, 1H), 7.31 (td, $J$ = 7.6, 1.2 Hz, 1H), 2.54 (s, 3H); $^{13}$C NMR (300 Hz, CDCl$_3$): $\delta$ 138.6, 137.4, 135.4, 125.1, 124.9, 122.8, 122.3, 106.8, 15.7; melting point: 40-42°C; HRMS (EI-EMM): Calcd for C$_9$H$_7$SBr ($^{79}$Br) m/z = 225.9447 found 225.9444.

$\text{11b}$

66% yield, solid (elution solvent – hexane:ethyl acetate = 20:1). $^1$H NMR: (300 Hz, CDCl$_3$): $\delta$ 7.99 (d, $J$ = 8.1 Hz, 1H), 7.76 (d, $J$ = 8.1 Hz, 2H), 7.62 (s, 1H), 7.50-7.42 (m, 1H), 7.41-7.23 (m, 2H), 7.20 (d, $J$ = 8.7 Hz, 2H), 2.31 (s, 3H); $^{13}$C NMR (300 Hz, CDCl$_3$): $\delta$ 145.6, 135.1, 134.5, 130.2, 127.1, 126.0, 125.0, 124.1, 120.3, 113.8, 99.2, 21.8; melting point: 122-123°C; HRMS (EI-EMM): Calcd for C$_{13}$H$_{12}$NBrO$_2$S ($^{79}$Br) m/z = 348.9767 found 348.9782.

$\text{12b}$

48% yield, oil (elution solvent – hexane:ethyl acetate = 200:1). $^1$H NMR: (300 Hz, CDCl$_3$): $\delta$ 7.46-7.31 (m, 2H), 7.30-7.17 (m, 2H), 2.47 (s, 3H); $^{13}$C NMR (300 Hz, CDCl$_3$): $\delta$ 153.7, 152.3, 128.6, 124.6, 123.3, 119.2, 111.2, 94.7, 12.6; HRMS (EI-EMM): Calcd for C$_9$H$_7$OBr ($^{79}$Br) m/z = 209.9679 found 209.9675.

$\text{1d}$

77% yield, oil (condition: hexane:ether = 2:1). $^1$H NMR (300 Hz, CDCl$_3$): $\delta$ 7.24 (d, $J$ = 8.7 Hz, 1H), 6.50 (d, $J$ = 2.9 Hz, 1H), 6.43 (dd, $J$ = 8.9, 2.7 Hz, 1H), 3.87 (s, 3H), 3.79 (s, 3H); $^{13}$C NMR (300 Hz, CDCl$_3$): $\delta$ 159.6, 155.8, 130.2, 114.2, 105.3, 100.1, 56.1, 55.7; HRMS (EI-EMM): Calcd for C$_8$H$_8$ClO$_2$ ($^{35}$Cl) m/z = 172.0286 found 172.0287.
88% yield, solid (elution solvent – hexane:ether = 1:1). \textsuperscript{1}H NMR: (300 Hz, CDCl\textsubscript{3}), δ 7.34 (s, 1H), 6.524 (s, 1H), 3.91 (s, 6H); \textsuperscript{13}C NMR (300 Hz, CDCl\textsubscript{3}): δ 154.8, 130.8, 114.3, 98.0, 56.8; melting point: 119-121°C; HRMS (EI-EMM): Calcd for C\textsubscript{8}H\textsubscript{8}Cl\textsubscript{2}O (\textsuperscript{35}Cl) m/z = 205.9896 found 205.9897.

76% yield, solid (elution solvent – hexane:ethyl acetate = 4:1) product obtained as inseparable mixture of 2d:2e (76:12%). \textsuperscript{1}H NMR: (300 Hz, CDCl\textsubscript{3}), δ 6.18 (s, 2H), 3.88 (s, 6H), 3.81 (s, 3H); \textsuperscript{13}C NMR (300 Hz, CDCl\textsubscript{3}): δ 159.6, 156.8, 91.8, 56.5, 55.7; HRMS (EI-EMM): Calcd for C\textsubscript{9}H\textsubscript{11}ClO\textsubscript{3} (\textsuperscript{35}Cl) m/z = 202.0392 found 202.0385.

90% yield, solid (elution solvent – hexane:ethyl acetate = 20:1). \textsuperscript{1}H NMR: (300 Hz, CDCl\textsubscript{3}): δ 6.37 (s, 1H), 3.91 (s, 6H), 3.89 (s, 3H); \textsuperscript{13}C NMR (300 Hz, CDCl\textsubscript{3}): δ 155.0, 154.1, 109.9, 93.5, 60.8, 56.7; melting point: 126-127°C; HRMS (EI-EMM): Calcd for C\textsubscript{9}H\textsubscript{10}Cl\textsubscript{2}O\textsubscript{3} (\textsuperscript{35}Cl) m/z = 236.0002 found 235.9995.

75% yield, oil (elution solvent – hexane:ethyl acetate = 20:1). \textsuperscript{1}H NMR: (300 Hz, CDCl\textsubscript{3}): δ 7.04 (m, 1H), 7.48 (d, J = 8.2 Hz, 1H), 6.69 (d, J = 7.9 Hz, 1H), 3.97 (s, 3H); \textsuperscript{13}C NMR (300 Hz, CDCl\textsubscript{3}): δ 154.7, 131.4, 124.4, 123.4, 123.4, 123.4, 123.4, 123.4.
122.6, 104.0, 55.9; HRMS (EI-EMM): Calcd for C_{11}H_{9}ClO (^{35}\text{Cl}) m/z = 192.0337 found 192.0336.

76% yield, oil (elution solvent – hexane: ethyl acetate =3:1), get oil. \(^1\)H NMR: (300 Hz, CDCl\(_3\)): \(\delta\) 7.08 (s, 1H), 6.66 (s, 1H), 3.79 (s, 3H), 2.33 (s, 3H), 2.15 (s, 3H); \(^{13}\)C NMR (300 Hz, CDCl\(_3\)): \(\delta\) 156.4, 133.9, 130.8, 125.9, 124.9, 112.7, 55.7, 20.2, 15.8; HRMS (EI-EMM): Calcd for C_{9}H_{11}ClO (^{35}\text{Cl}) m/z = 170.0493, found 170.0494.

73% yield, solid (Additional purification conditions: The reaction mixture was diluted with 10 mL water and 10 mL CH\(_2\)Cl\(_2\), and the phases were separated. Saturated Na\(_2\)CO\(_3\) (20 mL) was added to the aqueous layer, which was then extracted with CH\(_2\)Cl\(_2\). The organic layer was washed with 15 mL of saturated Na\(_2\)CO\(_3\), followed by brine solution. column elution solvent – gradient, hexane:ethyl acetate =1:1 \(\rightarrow\) 1:2) \(^1\)H NMR: (300 Hz, CDCl\(_3\)): \(\delta\) 7.66 (s, 1H), 7.15 (s, 1H), 7.02 (s, 1H), 3.87 (s, 3H), 2.21 (s, 3H), 2.16 (s, 3H); \(^{13}\)C NMR (300 Hz, CDCl\(_3\)): \(\delta\) 168.8, 153.7, 135.3, 131.4, 121.1, 118.0, 107.2, 56.5, 24.7, 16.8; HRMS (EI-EMM): Calcd for C_{10}H_{12}ClNO_{2} (^{35}\text{Cl}) m/z = 213.0552 found 213.0558.

63% yield, oil (elution solvent – hexane). \(^1\)H NMR: (300 Hz, CDCl\(_3\)): \(\delta\) 7.72 (d, J = 8.5 Hz, 2H), 7.40 (td, J = 7.6, 1.0 Hz, 1H), 7.32 (td, J = 7.6, 1.2 Hz, 1H), 2.54 (s, 3H); \(^{13}\)C NMR (300 Hz, CDCl\(_3\)): \(\delta\) 137.2, 136.6, 133.5, 124.9, 124.9, 122.4, 121.4, 111.0, 14.0; HRMS (EI-EMM): Calcd for C_{9}H_{7}SCl (^{35}\text{Cl}) m/z = 181.9952 found 181.9951.

Isolated as a 7/45/15% mixture of 11a, 11c, and 11d (elution solvent – hexane:ethyl acetate = 20:1). 11c: HRMS (EI-EMM): Calcd for C_{15}H_{12}ClNO_{2}S (^{35}\text{Cl}) m/z = 305.0272 found 305.0276.
9b Br

Supplementary Material (ESI) for Chemical Communications
This journal is (c) The Royal Society of Chemistry 2009
Supplementary Material (ESI) for Chemical Communications
This journal is (c) The Royal Society of Chemistry 2009