Supporting Information for: Palladium(II)-Catalyzed Aerobic Hydroalkoxylation of Styrenes Containing a Phenol

Keith M. Gligorich, Mitchell J. Schultz, and Matthew S. Sigman*

Contribution from: the Department of Chemistry, University of Utah, 315 South 1400 East, Salt Lake City, UT 84112-8500

E-mail: sigman@chem.utah.edu

Table of Contents

S1	General Considerations
S2	Preparation of Propenylphenol Derivatives
S2	Preparation of 2-(1,2-dimethoxypropyl)phenol (2)
S3	General Hydroalkoxylation Procedure
S3-S5	Characterization Data for Hydroalkoxylation Products
S5	Preparation of 1-(1,1-diethoxyethyl)-4-methylbenzene
S5	Deuterium Labeling Experiments
S6	Chiral Separations
S7	References
S8-S33	¹ H- and ¹³ C-NMR Spectra
S34-S39	Deuterium Labeling Experimental Data & Calculations

General Considerations: EtOH, 2-propanol, and ethylene glycol were dried by refluxing over calcium oxide for 12 hr followed by fractional distillation. MeOH used as solvent was distilled from magnesium methoxide. PhCH₃ used as solvent, was dried before use by passing through a column of activated alumina.¹ THF was dried by distilling from sodium benzophenone ketyl. The 3 Å molecular sieves were powdered and activated by putting under vacuum in a flask and heating with a Bunsen burner. ¹H-NMR spectra were obtained at 500 MHz or 300 MHz and referenced to the CHCl₃ singlet at 7.27 ppm and ¹³C-NMR spectra were obtained at 75 MHz and referenced to the center line of the CDCl₃ triplet at 77.2 ppm. Flash chromatography was performed using EM Reagent silica 60 (230-400 mesh). All melting points are uncorrected and were recorded on an electrothermal melting point apparatus. IR spectra were recorded using a Mattson Satellite FTIR instrument and GC/MS were obtained on an HP 5890 (EI) 50:1 split. Caution should be taken when heating flammable solvents in the presence of O₂.

Preparation of Propenylphenol Derivatives:² To a 250 mL flame dried round bottom flask equipped with a stir bar was placed 2.56 g of ethyltriphenylphosphonium bromide (6.9 mmol, 2.3 equiv.) and 42 mL of toluene under a nitrogen atmosphere. To this was added a solution of 785 mg KO^tBu (7 mmol, 2.33 equiv.) in 10 mL of THF dropwise via cannulation. The reaction mixture slowly turned a deep red color over 4 hrs. The mixture was cooled to -78 °C and 3 mmol of aldehyde (1 equiv.), dissolved in 8 mL of toluene, was added dropwise via cannulation. The mixture was allowed to slowly warm to ambient temperature and stirred 12 h then quenched with 20 mL of saturated NH₄Cl solution. The mixture was diluted with an additional 40 mL of H₂O and extracted 3 times with 20 mL each of diethyl ether. The organic extracts were combined, washed once with 15 mL brine, dried over MgSO₄, filtered, and the solvent removed *in vacuo*. The product was purified by bulb to bulb distillation.

4-chloro-2-(prop-1-enyl)phenol (1b): Yield: 91% (10:1 *Z:E*); *R*_f = 0.35 w/ 4:1 EtOAc/Hexanes; Clear oil; IR (neat) 3432, 3024, 2980, 2942, 2914, 1481, 1413, 1269, 1200, 1163, 1112, 815, 759; ¹H-NMR (500 MHz, CDCl₃) (*Z*-isomer) δ 1.72 (d, *J* = 5.8 Hz, 3H), 4.96 (s, 1H), 6.03-6.12 (m, 1H), 6.33 (d, *J* = 10.8 Hz, 1H), 6.85 (d, *J* = 8.5 Hz, 1H), 7.08-7.10 (m, 1H), 7.12-7.16 (m, 1H); ¹³C-NMR {¹H} (75 MHz, CDCl₃) δ 14.8, 116.6, 123.2, 125.1, 127.8, 128.6, 129.4, 132.7, 151.5; MS (E.I.) *m/z* (*M*)⁺ calcd. 168.03 obsd. 168.00.

For **1c**, **1d**, **1e**, **1f**, **7**, and **10**: 2.46 g of methyltriphenylphosphonium bromide (6.9 mmol, 2.3 equiv.) were used. For **1c**³, **1e**⁴, **1f**⁵, **7**⁶, and **10**⁶ spectra of the products were compared to previously reported spectra.

4-chloro-2-vinylphenol (1d): Yield: 80%; *R*_f = 0.45 w/ 2:5 Et₂O/Hexanes; White solid; mp: 51–53 °C; IR (KBr) 3264, 2722, 1867, 1828, 1628, 1598, 1491, 1413, 1232, 1178, 910, 661 cm⁻¹; ¹H-NMR (300 MHz CDCl₃) δ 4.94 (s, 1H), 5.42 (dd, *J* = 11.3, 1.1 Hz, 1H), 5.75 (dd, *J* = 17.8, 1.1 Hz, 1H), 6.74 (d, *J* = 8.8 Hz, 1H), 6.87 (dd, *J* = 17.8, 11.1 Hz, 1H), 7.10 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.36 (d, *J* = 2.6 Hz, 1H); ¹³C-NMR {¹H} (75 MHz, CDCl₃) δ 117.2, 117.3, 126.1, 126.6, 127.0, 128.6, 130.3, 151.2; MS (E.I.) *m/z* (*M*)⁺ calcd. 154.02 obsd. 154.05.

- For **1g**: 2.98 g of *iso*-propyltriphenylphosphonium iodide (6.9 mmol, 2.3 equiv.) were used and the spectra were compared to previously reported spectra.⁷

Preparation of 2-(1,2-dimethoxypropyl)phenol (2): To a flame dried 50 mL Schlenk flask equipped with a stir bar was added 20.6 mg of Pd[(-)sparteine]Cl₂ (0.05 mmol, 0.05 equiv.),⁸ 26.9 mg of CuCl₂ (0.2 mmol, 0.2 equiv.), 500 mg of freshly activated, crushed 3 Å molecular sieves, and 10 mL of MeOH. A three-way joint fitted with a balloon of O₂ was attached and the flask was evacuated via water aspiration and refilled with oxygen three times. The mixture was stirred **vigorously** for ca. 20 minutes at room temperature under O₂ followed by addition of 1 mmol of propenylphenol **1a** dropwise via a syringe over 5 min. The reaction mixture was stirred **vigorously** at room temperature under a balloon of O₂. After 13 h, the reaction mixture was passed through a short plug of silica eluting with 100 mL of 1:1 Et₂O/Hexanes. The solvent was removed *in vacuo* and the product was purified via silica-gel column chromatography (dry loaded) by eluting with 1 to 2% Et₂O/hexanes. Note; only the major (*syn*) diastereomer was characterized via ¹H and ¹³C-NMR.

(2): Yield: 70%; *R*_f = 0.30 w/ 4:1 EtOAc/Hexanes; Clear oil; IR (neat) 3349, 2981, 2932, 2832, 1586, 1486, 1460, 1375, 1245, 1088, 758; ¹H-NMR (500 MHz CDCl₃) δ 1.10 (d, *J* = 6.8, 3H), 3.39 (s, 3H), 3.42 (s, 3H), 3.68-3.78 (m, 1H), 4.27 (d, *J* = 4.9, 1H), 6.82-6.93 (m, 2H), 7.04-7.08 (m, 1H), 7.19-7.25 (m, 2H), 8.0 (s, 1H); ¹³C-NMR {¹H} (75 MHz CDCl₃) δ 15.4, 57.3, 57.9, 80.0, 87.1, 117.5, 119.9, 123.2, 129.5, 129.6, 155.7; MS (E.I.) *m/z* (*M*)⁺ calcd. 196.11 obsd. 196.05.

General Hydroalkoxylation Procedure: To a flame dried 100 mL Schlenk flask equipped with a stir bar was added 20.6 mg Pd[(-)sparteine]Cl₂ (0.05 mmol, 0.05 equiv.), 26.9 mg of CuCl₂ (0.2 mmol, 0.2 equiv.), 500 mg of freshly activated, crushed 3 Å molecular sieves, and 9.2 mL of ethanol. A condenser was placed on the flask and a three-way joint fitted with a balloon of O₂ was attached to the condenser. The flask was evacuated via water aspiration and refilled with oxygen three times and the mixture was stirred **vigorously** for ca. 20 minutes at room temperature under O₂. To the reaction mixture, was added 0.8 mL (1.0 mmol, 1 equiv.) of a 1.25M solution of propenylphenol in ethanol dropwise via a syringe over 5 min and the flask was placed into a 35 °C oil bath. The reaction mixture was stirred **vigorously** under a balloon of O₂. After 24 h, the reaction mixture was passed through a short plug of silica eluting with 100 mL of 1:1 Et₂O/Hexanes. The solvent was removed *in vacuo* and the product was purified via silica-gel column chromatography (dry loaded) by eluting with 0 to 1% Et₂O/hexanes.

- For product **3b** and **3g**: The reaction was carried out for 48 h.
- For products **3c**, **3d**, **3e**, and **8**: 10.3 mg of Pd[(-)sparteine]Cl₂ (0.025 mmol, 0.025 equiv.), and 10.1 mg CuCl₂ (0.075 mmol, 0.075 equiv.) were used and the reactions were carried out at room temperature. For product **3c**: the reaction was completed in 12 h and for products **3d**, **3e**, and **8**: the reactions were completed in 14 h. Product **8** was purified via silica-gel column chromatography (dry loaded) by eluting with 5 to 20% Et₂O/hexanes.
- For product **3f**: 10.3 mg of Pd[(-)sparteine]Cl₂ (0.025 mmol, 0.025 equiv.), 13.4 mg CuCl₂ (0.1 mmol, 0.1 equiv.) were used and the reaction was carried out at room temperature in 20 h.
- For product **3h**: Ethylene glycol was used as the solvent and to make a 1.25 M solution of **1a**, in which 0.8 mL was added to the reaction mixture. The reaction was carried out at room temperature for 48 h. After completion, the reaction mixture was transferred to a 50 mL flask and diluted with ca. 20 mL water. The aqueous mixture was extracted three times with 20 mL Et₂O and the organic extracts were combined. The extracts were subsequently washed with brine, dried with Na₂SO₄, and filtered. The product was purified via silica-gel column chromatography (dry loaded) by eluting with 10% to 20% EtOAc/hexanes.
- For product **3i**: 10.3 mg of Pd[(-)sparteine]Cl₂ (0.025 mmol, 0.025 equiv.), and 10.1 mg CuCl₂ (0.075 mmol, 0.075 equiv.) were used and the reaction was carried out at room temperature for 48 hours. Isopropanol was used as the solvent and to make a 1.25 M solution of **1i**, in which 0.8 mL was added to the reaction mixture.

Characterization Data: In order to obtain > 95% pure material for compounds **3c**, **3d**, **3e**, **3f**, and **3i**, the product was transferred to a 25 mL round bottom flask equipped with a stir bar under a nitrogen atmosphere. To the flask, ca. 15 mL of methanol was added followed by addition of 2.5 eq. of NaBH₄ portion-wise with stirring. After 20 min, 15 mL of sat. NH₄Cl was added and the mixture was transferred to a separatory funnel. The mixture was extracted three times with CH₂Cl₂ and the extracts were combined. The mixture was dried with Na₂SO₄, filtered and concentrated *in vacuo*. The products were purified via silica-gel column chromatography (dry loaded) by eluting with 0-1 % Et₂O/hexanes.

2-(1-ethoxypropyl)phenol (3a): Yield: 64%; R_f = 0.60 w/ 1:5 Et₂O/Hexanes; Clear oil; IR (neat) 3347, 3051, 2974, 2973, 2931, 2886, 1621, 1586, 1490, 1455, 1390, 1244, 1072, 750, 639 cm⁻¹; ¹H-NMR (500 MHz CDCl₃) δ 0.94 (t, *J* = 7.5 Hz, 3H), 1.26 (t, *J* = 7.3 Hz, 3H), 1.74-1.79 (m, 1H), 1.90-1.96 (m, 1H), 3.49-3.55 (m, 1H), 3.59-3.65 (m, 1H), 4.27 (t, *J* = 7.4 Hz, 1H), 6.81-6.87 (m, 2H), 6.91-6.94 (m, 1H), 7.16-7.20 (m, 1H), 8.22 (s, 1H); ¹³C-NMR {¹H} (75 MHz, CDCl₃) δ 10.6, 15.4, 29.4, 65.5, 85.8, 117.0, 119.7, 125.7, 128.6, 129.0, 155.8; MS (E.I.) *m/z* (M)⁺ calcd. 180.12 obsd. 180.10.

4-chloro-2-(1-ethoxypropyl)phenol (3b): Yield: 70%; $R_f = 0.40$ w/ 1:5 Et₂O/Hexanes; Clear oil; IR (neat) 3342, 2971, 2936, 2878, 1584, 1486, 1242, 1066, 827, 695 cm⁻¹; ¹H-NMR (300 MHz CDCl₃) δ 0.94 (t, $J = 7.4$ Hz, 3H), 1.26 (t, $J = 7.0$ Hz, 3H), 1.66-1.81 (m, 1H), 1.82-1.98 (m, 1H), 3.46-3.65 (m, 2H), 4.22 (t, $J = 6.9$ Hz, 1H), 6.79 (d, $J = 8.5$ Hz, 1H), 6.91 (d, $J = 2.7$ Hz, 1H), 7.13 (dd, $J = 8.7, 2.7$ Hz, 1H), 8.22 (s, 1H); ¹³C-NMR {¹H} (75 MHz, CDCl₃) δ 10.5, 15.3, 29.3, 65.8, 85.2, 118.4, 124.3, 127.2, 128.1, 128.8, 154.4; MS (E.I.) m/z (M)⁺ calcd. 214.08 obsd. 214.10.

2-(1-ethoxyethyl)phenol (3c): Yield: 72%; $R_f = 0.45$ w/ 1:5 Et₂O/Hexanes; Clear oil; IR (neat) 3367, 3054, 2976, 2922, 2351, 1589, 1496, 1267, 1081, 744 cm⁻¹; ¹H-NMR (300 MHz CDCl₃) δ 1.25 (t, $J = 6.9$ Hz, 3H), 1.52 (d, $J = 6.6$ Hz, 3H), 3.49-3.61 (m, 2H), 4.57 (q, $J = 6.7$ Hz, 1H), 6.79-6.89 (m, 2H), 6.94 (dd, $J = 7.6, 1.8$ Hz, 1H), 7.13-7.21 (m, 1H), 8.16 (s, 1H); ¹³C-NMR {¹H} (75 MHz, CDCl₃) δ 15.5, 22.4, 65.1, 80.0, 117.1, 119.9, 126.9, 127.8, 129.1, 155.6; MS (E.I.) m/z (M)⁺ calcd. 166.10 obsd. 166.05.

4-chloro-2-(1-ethoxyethyl)phenol (3d): Yield: 82%; $R_f = 0.40$ w/ 1:5 Et₂O/Hexanes; White solid; mp: 57–60 °C; IR (KBr) 3230, 2981, 2927, 2391, 1633, 1608, 1491, 1423, 1276, 1100, 812, 656 cm⁻¹; ¹H-NMR (300 MHz CDCl₃) δ 1.25 (t, $J = 7.0$ Hz, 3H), 1.50 (d, $J = 6.8$ Hz, 3H), 3.50-3.58 (m, 2H), 4.51 (q, $J = 6.5$ Hz, 1H), 6.79 (d, $J = 8.6$ Hz, 1H), 6.92 (d, $J = 2.8$ Hz, 1H), 7.16 (dd, $J = 8.5, 2.5$ Hz, 1H), 8.15 (s, 1H); ¹³C-NMR {¹H} (75 MHz, CDCl₃) δ 15.4, 22.2, 65.3, 79.3, 118.5, 124.6, 127.4, 128.5, 128.8, 154.2; MS (E.I.) m/z (M)⁺ calcd. 200.06 obsd. 200.00.

4-bromo-2-(1-ethoxyethyl)phenol (3e): Yield: 84%; $R_f = 0.40$ w/ 1:5 Et₂O/Hexanes; Clear oil; IR (neat) 3332, 2971, 2932, 2878, 1585, 1486, 1369, 1247, 1081, 832, 666, 617 cm⁻¹; ¹H-NMR (300 MHz CD₂Cl₂) δ 1.23 (t, $J = 7.0$ Hz, 3H), 1.48 (d, $J = 6.9$ Hz, 3H), 3.48-3.57 (m, 2H), 4.52 (q, $J = 6.7$ Hz, 1H), 6.72 (d, $J = 8.8$ Hz, 1H), 7.09 (d, $J = 2.5$ Hz, 1H), 7.25 (dd, $J = 8.5, 2.5$ Hz, 1H), 8.17 (s, 1H); ¹³C-NMR {¹H} (75 MHz, CD₂Cl₂) δ 15.6, 22.4, 65.7, 79.5, 111.9, 119.2, 129.7, 130.7, 131.9, 155.2; MS (E.I.) m/z (M)⁺ calcd. 244.01 obsd. 244.00.

2-(1-ethoxyethyl)-4-methylphenol (3f): Yield: 41%; $R_f = 0.70$ w/ 1:5 Et₂O/Hexanes; Clear oil; IR (neat) 3035, 2982, 2927, 2874, 1597, 1467, 1375, 1237, 1087, 773, 666 cm⁻¹; ¹H-NMR (300 MHz CDCl₃) δ 1.26 (t, $J = 7.1$ Hz, 3H), 1.53 (d, $J = 6.6$ Hz, 3H), 2.25 (s, 3H), 3.47-3.63 (m, 2H), 4.57 (q, $J = 6.8$ Hz, 1H), 6.75 (app. q., $J = 7.4$ Hz, 1H), 6.78-6.82 (m, 1H), 7.03-7.08 (m, 1H), 8.28 (s, 1H); ¹³C-NMR {¹H} (75 MHz, CDCl₃) δ 15.5, 16.0, 22.4, 65.1, 80.1, 119.4, 125.4, 125.9, 126.1, 130.3, 153.7; MS (E.I.) m/z (M)⁺ calcd. 180.12 obsd. 180.10.

2-(1-ethoxy-2-methylpropyl)phenol (3g): Yield: 48%; $R_f = 0.60$ w/ 1:5 Et₂O/Hexanes; Clear oil; IR (neat) 3347, 2971, 2869, 1623, 1589, 1486, 1242, 1076, 754 cm⁻¹; ¹H-NMR (300 MHz CDCl₃) δ 0.81 (d, $J = 6.6$ Hz, 3H), 1.05 (d, $J = 6.5$ Hz, 3H), 1.25 (t, $J = 6.9$ Hz, 3H), 1.97-2.15 (m, 1H), 3.42-3.54 (m, 1H), 3.57-3.69 (m, 1H), 4.00 (d, $J = 7.7$, 1H), 6.78-6.93 (m, 3H), 7.14-7.22 (m, 1H), 8.30 (s, 1H); ¹³C-NMR {¹H} (75 MHz, CDCl₃) δ 15.3, 19.1, 19.6, 33.9, 65.9, 90.1, 116.9, 119.3, 124.4, 128.9, 129.5, 155.9; MS (E.I.) m/z (M)⁺ calcd. 194.13 obsd. 194.15.

2-(1-(2-hydroxyethoxy)propyl)phenol (3h): Yield: 52%; $R_f = 0.45$ w/ 5:3 EtOAc/Hexanes; Clear oil; IR (neat) 3357, 3049, 2971, 2936, 2873, 1579, 1486, 1447, 1383, 1344, 1237, 1105, 1052, 739 cm⁻¹; ¹H-NMR (500 MHz CDCl₃) δ 0.95 (t, $J = 7.3$ Hz, 3H), 1.76-1.85 (m, 1H), 1.94-2.02 (m, 1H), 1.94-2.04 (bs, 1H), 3.56-3.60 (m, 1H), 3.63-3.69 (m, 1H), 3.79 (t, $J = 4.5$ Hz, 2H), 4.34 (t, $J = 7.4$ Hz, 1H), 6.83-6.89 (m, 2H), 6.92-6.95 (m, 1H), 7.18-7.21 (m, 1H), 7.80 (s, 1H); ¹³C-NMR {¹H} (75 MHz, CDCl₃) δ 10.6, 29.1, 62.0, 71.1, 86.1, 117.2, 120.0, 125.2, 128.7, 129.3, 155.3; MS (E.I.) m/z (M)⁺ calcd. 196.11 obsd. 196.05.

4-chloro-2-(1-isopropoxyethyl)phenol (3i): Yield: 57%; $R_f = 0.50$ w/ 1:5 Et₂O/Hexanes; Clear oil; IR (neat) 3332, 2976, 2932, 2883, 1584, 1491, 1369, 1247, 1071, 1013, 817, 680 cm⁻¹; ¹H-NMR (300 MHz CDCl₃) δ 1.19 (d, $J = 6.2$ Hz, 3H), 1.22 (d, $J = 6.1$ Hz, 3H), 1.49 (d, $J = 6.9$ Hz, 3H), 3.73 (app. heptet, $J = 6.18$ Hz, 1H), 4.61 (q, $J = 6.7$ Hz, 1H), 6.80 (d, $J = 8.5$ Hz, 1H), 6.92 (d, $J = 2.5$ Hz, 1H), 7.12 (dd, $J = 8.7, 2.6$ Hz, 1H), 8.31 (s, 1H); ¹³C-NMR {¹H} (75 MHz, CDCl₃) δ 21.6, 22.8, 23.0, 70.9, 76.6, 118.6, 124.4, 127.2, 128.7, 129.1, 154.5; MS (E.I.) m/z (M)⁺ calcd. 214.08 obsd. 214.10.

4-(1-ethoxyethyl)phenol (**8**): Yield: 54%; $R_f = 0.40$ w/ 2:5 Et₂O/Hexanes; White solid; mp: 80–83 °C; IR (KBr) 3220, 2976, 2917, 2888, 2350, 1618, 1510, 1457, 1233, 842 cm⁻¹; ¹H-NMR (300 MHz CDCl₃) δ 1.17 (t, $J = 6.9$ Hz, 3H), 1.42 (d, $J = 6.3$ Hz, 3H), 3.33 (q, $J = 6.9$ Hz, 2H), 4.35 (q, $J = 6.5$ Hz, 1H), 4.78–4.82 (bm, 1H), 6.77–6.83 (m, 2H), 7.16–7.22 (m, 2H), ¹³C-NMR {¹H} (75 MHz, DMSO-*d*₆) δ 16.0, 24.6, 63.3, 77.0, 115.6, 127.8, 134.8, 157.2; MS (E.I.) m/z (M)⁺ calcd. 166.10 obsd. 166.10.

- The ketone products **4c**, **4d**, and **4f** were isolated as a mixture with the hydroalkoxylation product and reported as a mixture measured by ¹H-NMR. The spectra for **4c**⁹, **4d**¹⁰, and **4f**¹¹ were compared to previously reported spectra.
- The ketone product **9**¹² was isolated in 33% yield and the spectra were compared to those previously reported.
- For product **11**, the general hydroalkoxylation procedure was used except: 10.3 mg of Pd[(-)-sparteine]Cl₂ (0.025 mmol, 0.025 equiv.), and 10.1 mg CuCl₂ (0.075 mmol, 0.075 equiv.) were used and the reaction was carried out at room temperature for 14 hours. There was very little conversion, therefore in an attempt to detect the presence of the hydroalkoxylation product, a ¹H-NMR spectrum of the reaction mixture was obtained after the mixture was passed through a plug of silica, eluting with 1:1 Et₂O/Hexanes, and the solvent was removed *in vacuo*. The ¹H-NMR indicated the presence of the starting material **10** and the ketone **11**. The spectra of **11**⁹ were compared to previously reported spectra.

Preparation of 1-(1,1-diethoxyethyl)-4-methylbenzene: To a flame dried 10 mL Schlenk flask equipped with a stir bar was added 16.5 mg of Pd[(-)-sparteine]Cl₂ (0.04 mmol, 0.04 equiv.), 6.7 mg of CuCl₂ (0.05 mmol, 0.05 equiv.), 200 mg of freshly activated, crushed 3 Å molecular sieves, and 3.3 mL of EtOH. A three-way joint fitted with a balloon of O₂ was attached and the flask was evacuated via water aspiration and refilled with oxygen three times. The mixture was stirred **vigorously** for ca. 20 minutes at room temperature under O₂ followed by addition of 0.132 mL of 4-methylstyrene (1.0 mmol, 1 equiv.) dropwise via a syringe over 5 min.. The reaction mixture was stirred **vigorously** at room temperature under a balloon of O₂. Upon completion, the reaction mixture was passed through a short plug of silica eluting with 100 mL of 1:1 Et₂O/Hexanes. The solvent was removed *in vacuo* and the product spectra were compared to previously reported spectra.¹³

Deuterium Labeling Experiments:

Preparation of 5: In a flame dried 5 mL round bottom flask, was added 300 mg (2.5 mmol) of 2-vinylphenol **1c** and ca. 2 mL of CD₃OD. The solvent was removed *in vacuo* and this was repeated two more times. The phenol proton was not detectable by ¹H-NMR.

Both the experiments performed in CH₃CH₂OD (99.5% deuterium incorporation) and CD₃CD₂OD (99.5% deuterium incorporation) were performed in the same manner as the general hydroalkoxylation except: a 10 mL Schlenk flask was used along with 2.6 mg of Pd[(-)-sparteine]Cl₂ (0.00625 mmol, 0.025 equiv.), 1.7 mg CuCl₂ (0.0125 mmol, 0.05 equiv.), 125 mg of freshly activated, crushed 3 Å molecular sieves, 30 mg of **5** (0.25 mmol, 1 equiv.), and 1.25 mL of deuterated ethanol and the substrate was added neat to the reaction mixture over 2 min via a syringe. The reaction was carried out at room temperature for 24 hours and was worked up in the same manner described in the general hydroalkoxylation procedure.

- For the reaction performed in CH₃CH₂OD: there was no deuterium incorporation detected by ¹H-NMR.
- For the reaction performed in CD₃CD₂OD: GC/MS was used to characterize the ratio of isotopomers **6a** and **6b**. The ¹H-NMR does not indicate the presence of **3c**.

GC Chiral Separations:

All chiral separations were performed on a permethylated β -cyclodextrin chiral column. For each substrate the ee was <5% and the retention times are reported below.

Table 1: Retention times and methods for chiral separation.

Entry	Substrate	Method	Retention Times (min)
1	2	80 °C Isothermal	104.1 and 105.8 113.8 and 117.0
2	3a	80 °C Isothermal	48.0 and 51.0
3	3d	80 °C for 70 min. ramp to 120 °C, 5 °C/min 120 °C for 10 min	83.1 and 84.0
4	3g	80 °C Isothermal	55.3 and 59.7
5	8	80 °C Isothermal	42.9 and 50.6

References:

- (1) Pnagborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. *Organometallics* **1996**, *15*, 1518-1520.
- (2) Adapted from: Johannes, C. W.; Visser, M. S.; Weatherhead, G. S.; Hoveyda, A. H. *J. Am. Chem. Soc.* **1998**, *120*, 8340-8347.
- (3) Yus, M.; Foubelo, F.; Ferrández, J. *Eur. J. Org. Chem.* **2001**, 2809-2813.
- (4) Serrano, L. P.; Blanco-Urgoiti, J.; Casarrubios, L.; Domínguez, G.; Pérez-Castells, J. *J. Org. Chem.* **2000**, *65*, 3513-3519.
- (5) Yamaguchi, M.; Arisawa, M.; Omata, K.; Kabuto, K.; Hiramata, M.; Uchimaru, T. *J. Org. Chem.* **1998**, *63*, 7298-7305.
- (6) Yoshizawa, Y.; Kawai, S.; Kanauchi, M.; Chida, M.; Mizutani, *Biosci. Biotechnol. Biochem.*, **1993**, *57*, 1572-1574.
- (7) Casnati, G.; Pochini, A.; Terenghi, M. G.; Ungaro, R. *J. Org. Chem.* **1983**, *48*, 3783-3787.
- (8) Mandal, S. K.; Sigman, M. S. *J. Org. Chem.* **2003**, *68*, 7535-7537.
- (9) Gogoi, P.; Sarmah, G. K.; Konwar, D. *J. Org. Chem.* **2004**, *69*, 5153-5154.
- (10) Wu, S.-Y.; Hirashima, A.; Kuwano, E.; Eto, M. *Agric. Biol. Chem.* **1987**, *51*, 537-547.
- (11) Seidel, J. L.; Epstein, W. W.; Davidson, D. W. *J. Chem. Ecol.* **1990**, *16*, 1791-1816.
- (12) Kobayashi, S.; Moriwaki, M.; Hachiya, I. *Bull. Chem. Soc. Jpn.* **1997**, *70*, 267-273.
- (13) Firouzabadi, H.; Iranpoor, N.; Karimi, B. *Syn. Lett.* **1999**, 321-323.

Pulse Sequence: s2pul

Pulse Sequence: s2pul

Experiment performed in CH₃CH₂OD.
No deuterium incorporation.

Experiment Performed in CD₃CD₂OD:

See GC/MS Data

GC/MS Data for Compound 3c:

m/z	abund.	m/z	abund.	m/z	abund.	m/z	abund.
12.95	47	29.05	11272	44.00	886	55.95	206
14.05	347	30.05	1078	45.00	6993	57.00	91
15.05	1859	31.00	3169	46.00	533	59.00	157
16.00	117	31.90	111	46.95	111	59.95	61
17.05	27	37.00	857	49.00	318	60.95	1151
17.95	39	38.00	3169	50.00	5782	62.00	4351
19.05	283	39.00	21725	51.00	17244	63.05	14480
25.00	60	40.00	3239	51.95	4998	64.05	6192
26.05	1439	41.00	3763	52.95	8528	65.05	44131
27.05	8265	42.00	1346	53.95	653	66.05	9943
28.05	1129	43.00	17085	54.95	5250	67.05	2855

m/z	abund.	m/z	abund.	m/z	abund.	m/z	abund.
68.00	947	78.00	10548	89.00	7584	99.85	21
69.00	320	79.00	4662	90.10	5615	101.00	1939
69.85	33	79.95	475	91.00	233472	102.00	8324
70.05	52	81.00	1855	92.05	80885	103.05	29080
71.05	90	82.00	199	92.95	16694	104.00	4810
72.05	69	83.90	17	93.95	7053	105.05	6768
73.00	951	84.95	195	94.95	30384	106.00	751
73.95	2527	86.00	518	95.95	1980	107.05	5729
75.00	4513	87.00	605	97.00	151	108.00	638
76.00	7562	87.90	94	98.00	169	109.05	3891
77.00	75211	88.10	97	98.90	40	110.00	390

m/z	abund.	m/z	abund.	m/z	abund.
110.95	39	128.00	17	153.05	213
115.00	72	130.95	49	162.60	17
115.85	71	133.05	81	164.10	31
116.80	75	134.90	82	166.05	121021
119.00	154304	135.95	994	167.10	13873
120.00	568128	137.05	1148	168.05	1161
121.00	138824	137.90	103	168.90	23
122.00	16585	148.95	41	169.10	19
123.00	61360	149.15	28		
124.00	4723	151.05	22669		
124.95	372	152.05	2051		

GC/MS Data for the Experiment Performed CD₃CD₂OD:

m/z	abund.	m/z	abund.	m/z	abund.	m/z	abund.
13.95	154	27.05	4709	38.00	7410	49.10	2524
15.05	586	28.05	5693	39.00	39208	50.00	11420
16.05	1311	29.05	3564	40.00	17080	51.00	28440
17.05	367	30.05	22376	41.00	6560	52.05	15736
18.05	2980	31.00	892	42.00	5805	52.95	15311
18.95	174	32.10	3803	43.00	9899	54.05	6782
20.05	288	33.00	6782	44.00	23056	55.05	7328
21.05	243	34.10	21480	45.00	1722	55.95	2921
22.15	62	35.10	482	46.10	5789	57.05	440
25.05	143	36.10	90	47.10	12468	57.95	136
26.05	1025	37.00	1926	48.00	717	59.05	281

m/z	abund.	m/z	abund.	m/z	abund.	m/z	abund.
61.05	2348	71.85	86	83.10	1909	94.05	23888
62.05	7576	72.90	722	84.00	424	95.05	8276
63.05	22936	74.00	4440	85.00	486	96.05	37952
64.05	15650	75.00	7089	86.00	892	97.05	17504
65.05	48072	76.00	13574	87.00	1139	98.05	1291
66.05	46664	77.00	70312	88.00	761	98.95	254
67.05	11867	78.00	64992	89.00	5646	99.85	92
68.05	4540	79.00	16528	90.00	11835	101.05	1876
69.05	1774	80.00	5821	91.10	69928	102.05	5903
69.95	504	81.00	2696	92.10	350848	103.05	20672
71.05	179	82.00	1926	93.05	145792	104.05	29872

m/z	abund.	m/z	abund.	m/z	abund.	m/z	abund.
105.05	10203	120.00	263936	133.10	90	157.10	14695
105.95	5430	121.00	1003456	133.85	68	158.00	1623
107.05	1904	122.00	189632	134.95	100	159.00	166
108.05	5491	123.00	19416	135.95	426	168.10	58
109.05	3330	124.00	77528	136.95	1638	168.80	65
110.05	3445	125.00	36432	137.95	855	171.10	13279
111.05	6188	126.00	3416	139.05	1360	172.10	211392
112.05	464	126.90	304	139.95	175	173.10	24552
113.05	62	128.10	172	143.15	235	174.10	2030
115.90	105	129.00	78	153.15	62	175.05	166
119.00	35848	131.10	62	156.00	30112		

Calculation of the ratio of 6a and 6b from GC/MS:

Calculated m/z:

GC/MS Data From S37 & S38:

From **3c**:

m/z **3c** = 166.05 abund. = 121021

m/z **X** = 151.05 abund. = 22669

m/z **X** + 1 = 152.05 abund. = 2051

From **6a** & **6b**:

m/z **6a** & **6b** = 172.10 abund. = 211392

m/z **Y** = 156.00 abund. = 30112

m/z **Z** = 157.10 abund. = 14695

Calculation of the ratio of 6a to 6b:

$$(\text{abund. } \mathbf{X} + 1) / (\text{abund. } \mathbf{X}) = 22669 / 2051 = 0.09$$

$$[(\text{abund. } \mathbf{X} + 1) / (\text{abund. } \mathbf{X})] \times (\text{abund. } \mathbf{Y}) = 0.09 \times 30112 = 2710$$

$$(\text{abund. } \mathbf{Z}) - \{[(\text{abund. } \mathbf{X} + 1) / (\text{abund. } \mathbf{X})] \times (\text{abund. } \mathbf{Y})\} = 14695 - 2710 = 11985$$

$$(\text{abund. } \mathbf{Y}) / [(\text{abund. } \mathbf{Z}) - \{[(\text{abund. } \mathbf{X} + 1) / (\text{abund. } \mathbf{X})] \times (\text{abund. } \mathbf{Y})\}] = 30112 / 11985 = 2.5$$

2.5 : 1