SUPPORTING INFORMATION FOR Enantioselective Hydrogenation of α -Aryloxy- α,β -Unsaturated Acids. Asymmetric Synthesis of α -Aryloxycarboxylic Acids

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Methyl 2-bromobut-2-enoate (2a): HPLC retention time = 2.30 min, HPLC conditions, assay F in Table S2.

Ethyl 2-bromooct-2-enoate (2b): HPLC retention time = 6.9 min, HPLC conditions, assay F in Table S2; ^1H NMR (400 MHz, CDCl_3) δ 7.28 (t, J = 7.2, 1 H), 4.27 (q, J = 7.1, 2 H), 2.33 (q, J = 7.4, 2 H), 1.52-1.31 (m, 5 H), 1.33 (t, J = 7.1, 3 H), 0.90 (m, 4 H); ^{13}C NMR (100 MHz, CDCl_3) δ 162.6, 146.3, 116.3, 62.4, 32.1, 31.5, 27.3, 22.4, 14.2, 13.9; FTIR (thin film) ν_{max} 2922, 1731, 1625, 1253, 1045 cm^{-1} .

Methyl 2-bromo-2-methylbut-2-enoate (2c): HPLC retention time = 2.63 min, HPLC conditions, assay F in Table S2.

General procedure for preparation of unsaturated aryloxy acids. A mixture of the phenol **1a-l** (20.0 mmol), 2-bromoenolate ester **2a-c** (22 mmol), K_2CO_3 (50 mmol) and MeCN (20 mL) was stirred at 80 °C for 16 h. The mixture was cooled to 35 °C and water (15 mL) was added. The upper organic phase was washed with 1M KOH (2 mL) and was then stirred with 45% aq KOH (3 mL) and water (10 mL) for 20 h at 22 °C to give a homogeneous mixture. The mixture was evaporated to half its volume at 30 °C and was diluted with water (20 mL) at 20 °C. The aqueous solution was assayed by quantitative HPLC for yield of **3a-m**. 5M HCl (8.0 mL) was added to the mixture (pH <2) was stirred at 10-15 °C for 2h. The mixture was filtered and the filter cake was washed with water (60 mL) and 3:1 water/MeCN (20 mL). The filter cake was dried to provide the unsaturated aryloxyacids **3a-k** and **3m** as white crystalline solids. Acid **3l** precipitated as an oil on acidification of the aqueous mixture with 5N HCl and was extracted with *t*-BuOMe. After addition of dicyclohexylamine to the *t*-BuOMe extract, the dicyclohexylamine salt of **3l** crystallized out of the mixture.

(2Z)-2-(2-Methylphenoxy)but-2-enoic acid (3b): mp = 122-124 °C; ^1H NMR (400 MHz, CDCl_3) δ 11.71 (br s, 1 H), 7.21 (d, J = 7.4, 1 H), 7.10 (m, 1 H), 6.95 (m, 1 H), 6.86 (q, J = 7.2, 1 H), 6.67 (d, J = 8.0, 1 H), 2.38 (s, 3 H), 1.83 (d, J = 7.2, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.5, 155.3, 141.8, 131.3, 129.8, 126.9, 126.7, 122.2, 112.3, 16.1, 11.7; FTIR (thin film) ν_{max} 1696, 1654, 1491, 1294, 1228 cm^{-1} ; ES HRMS m/z calcd for $\text{C}_{11}\text{H}_{11}\text{O}_3$ ($\text{M} - \text{H}^+$) 191.0708, found 191.0701; Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_3$: C, 68.74; H, 6.29. Found: C, 68.70; H, 6.30.

(2Z)-2-(4-Methylphenoxy)but-2-enoic acid (3c): mp = 123-124 °C; ^1H NMR (400 MHz, CDCl_3) δ 11.54 (br s, 1 H), 7.11 (m, 2 H), 6.84 (m, 3 H), 2.32 (s, 3 H), 1.82 (d, J =

7.2, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.5, 154.9, 141.3, 131.6, 130.2, 130.1, 114.6, 20.5, 11.7; FTIR (thin film) ν_{max} 1702, 1655, 1509, 1429, 1274 cm^{-1} ; ES HRMS m/z calcd for $\text{C}_{11}\text{H}_{11}\text{O}_3$ ($\text{M} - \text{H}^+$) 191.0708, found 191.0703; Anal. Calcd for $\text{C}_{11}\text{H}_{12}\text{O}_3$: C, 68.74; H, 6.29. Found: C, 68.61; H, 6.30.

(2Z)-2-(2-Methoxyphenoxy)but-2-enoic acid (3d):¹ mp = 89-90 °C; ^1H NMR (400 MHz, CDCl_3) δ 6.96 (m, 2 H), 6.82 (m, 2 H), 6.73 (dd, J = 8.0, 1.5, 1 H), 3.91 (s, 3 H), 1.81 (d, J = 7.2, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.5, 148.9, 146.4, 141.6, 129.7, 122.8, 120.9, 113.9, 112.9, 56.3, 11.8; FTIR (thin film) ν_{max} 1702, 1503, 1309, 1253, 1214 cm^{-1} ; ES HRMS m/z calcd for $\text{C}_{11}\text{H}_{11}\text{O}_4$ ($\text{M} - \text{H}^+$) 207.0657, found 207.0663.

(2Z)-2-(2-Fluorophenoxy)but-2-enoic acid (3e): mp = 101-103 °C; ^1H NMR (400 MHz, CDCl_3) δ 11.40 (br s, 1 H), 7.13 (m, 1 H), 6.99 (m, 2 H), 6.86 (m, 2 H), 1.85 (d, J = 7.2, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.9, 152.1 (d, J = 247), 144.8 (d, J = 11), 141.1, 130.5, 124.2 (d, J = 3.9), 122.8 (d, J = 6.7), 116.8 (d, J = 18), 115.6, 11.7; FTIR (thin film) ν_{max} 1698, 1657, 1503, 1295, 1201 cm^{-1} ; ES HRMS m/z calcd for $\text{C}_{10}\text{H}_8\text{FO}_3$ ($\text{M} - \text{H}^+$) 195.0457, found 195.0463.

(2Z)-2-(4-Fluorophenoxy)but-2-enoic acid (3f): mp = 145-146 °C; ^1H NMR (400 MHz, CDCl_3) δ 11.15 (br s, 1 H), 6.98 (m, 2 H), 6.86 (m, 3 H), 1.82 (d, J = 7.22, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 0 (q, J = 256); FTIR (thin film) ν_{max} 1699, 1652, 1503, 1272, 1202 cm^{-1} ; ES HRMS m/z calcd for $\text{C}_{10}\text{H}_8\text{FO}_3$ ($\text{M} - \text{H}^+$) 195.0457, found 195.0454; Anal. Calcd for $\text{C}_{10}\text{H}_9\text{FO}_3$: C, 61.22; H, 4.62. Found: C, 61.52; H, 4.59.

(2Z)-2-(2-Chlorophenoxy)but-2-enoic acid (3g): mp = 131-133 °C; ^1H NMR (400 MHz, CDCl_3) δ 11.74 (br s, 1 H), 7.41 (dd, J = 7.9, 1.5, 1 H), 7.15 (td, J = 7.9, 1.5, 1 H), 6.97 (td, J = 7.9, 1.1, 1 H), 6.90 (q, J = 7.2, 1 H), 6.76 (dd, J = 7.9, 1.1, 1 H), 1.83 (d, J = 7.2, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.9, 152.7, 141.2, 130.9, 130.8, 127.6, 123.1, 122.7, 114.2, 11.8; FTIR (thin film) ν_{max} 1696, 1654, 1478, 1445, 1298 cm^{-1} ; ES HRMS m/z calcd for $\text{C}_{10}\text{H}_8\text{ClO}_3$ ($\text{M} - \text{H}^+$) 211.0162, found 211.0161; Anal. Calcd for $\text{C}_{10}\text{H}_9\text{ClO}_3$: C, 56.49; H, 4.27. Found: C, 56.40; H, 4.33.

(2Z)-2-(3-Bromophenoxy)but-2-enoic acid (3h): mp = 148-150 °C; ^1H NMR (400 MHz, CDCl_3) δ 11.29 (br s, 1 H), 7.17 (m, 2 H), 7.08 (m, 1 H), 6.88 (m, 2 H), 1.81 (d, J = 7.2, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.9, 157.7, 140.8, 131.2, 130.8, 125.6, 123.0, 118.4, 113.8, 11.9; FTIR (thin film) ν_{max} 1697, 1656, 1581, 1469, 1352 cm^{-1} ; ES HRMS m/z calcd for $\text{C}_{10}\text{H}_8\text{BrO}_3$ ($\text{M} - \text{H}^+$) 254.9657, found 254.9660; Anal. Calcd for $\text{C}_{10}\text{H}_9\text{BrO}_3$: C, 46.72; H, 3.53. Found: C, 46.56; H, 3.47.

(2Z)-2-(2-Iodophenoxy)but-2-enoic acid (3i): mp = 139-141 °C; ^1H NMR (400 MHz, CDCl_3) δ 11.42 (br s, 1 H), 7.81 (dd, J = 7.7, 1.4, 1 H), 7.23 (td, J = 7.7, 1.4, 1 H), 6.90 (q, J = 7.2, 1 H), 6.77 (td, J = 7.7, 1.0, 1 H), 6.66 (dd, J = 8.1, 1.0, 1 H), 1.82 (d, J = 7.2, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 167.8, 156.0, 141.5, 140.0, 130.9, 129.4, 124.1, 113.0, 85.3, 12.00; FTIR (thin film) ν_{max} 1695, 1657, 1467, 1436, 1227 cm^{-1} ; ES HRMS m/z calcd for $\text{C}_{10}\text{H}_8\text{IO}_3$ ($\text{M} - \text{H}^+$) 302.9518, found 302.9520; Anal. Calcd for $\text{C}_{10}\text{H}_9\text{IO}_3$: C, 39.50; H, 2.98. Found: C, 39.48; H, 3.13.

(2Z)-2-(3-Iodophenoxy)but-2-enoic acid (3j): mp = 148-149 °C; ^1H NMR (400 MHz, CDCl_3) δ 11.48 (br s, 1 H), 7.37 (dt, J = 7.6, 1.1, 1 H), 7.27 (m, 1 H), 7.01 (t, J = 8.1, 1 H), 6.88 (m, 1 H), 1.81 (d, J = 7.2, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.0, 157.5, 140.8, 131.6, 131.1, 131.0, 124.2, 114.5, 94.4, 11.9; FTIR (thin film) ν_{max} 1695, 1653, 1575, 1464, 1299 cm^{-1} ; ES HRMS m/z calcd for $\text{C}_{10}\text{H}_8\text{IO}_3$ ($\text{M} - \text{H}^+$) 302.9518, found 302.9521; Anal. Calcd for $\text{C}_{10}\text{H}_9\text{IO}_3$: C, 39.50; H, 2.98. Found: C, 39.49; H, 3.01.

(2Z)-2-(4-Nitrophenoxy)but-2-enoic acid (3k): mp = 218-220 °C; ^1H NMR (400 MHz, CDCl_3) δ 13.13 (br s, 1 H), 8.18 (d, J = 9.2, 2 H), 7.07 (d, J = 9.2, 2 H), 6.74 (q, J = 7.1, 1 H), 1.67 (d, J = 7.1, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 163.3, 162.6, 142.5, 141.7, 128.5, 126.5, 115.9, 11.8; FTIR (thin film) ν_{max} 1699, 1657, 1611, 1510, 1354 cm^{-1} ; ES HRMS m/z calcd for $\text{C}_{10}\text{H}_8\text{NO}_5$ ($\text{M} - \text{H}^+$) 222.0403, found 222.0399.

(2Z)-2-(Phenoxy)oct-2-enoic acid (3l): mp (dicyclohexylamine salt) = 156-158 °C; ^1H NMR (free acid, 400 MHz, CDCl_3) δ 11.47 (br s, 1 H), 7.30 (m, 2 H), 7.03 (td, J = 7.4, 0.7, 1 H), 6.93 (dd, J = 7.8, 0.7, 2 H), 6.79 (t, J = 7.7, 1 H), 2.24 (q, J = 7.5, 2 H), 1.46 (m, 2 H), 1.30 (m, 4 H), 0.88 (m, 3 H); ^{13}C NMR (free acid, 100 MHz, CDCl_3) δ 168.5, 157.3, 140.3, 135.6, 129.6, 122.3, 115.0, 31.5, 27.9, 26.1, 22.4, 13.9; Anal. Calcd for $\text{C}_{26}\text{H}_{41}\text{NO}_3$ (dicyclohexylamine salt): C, 75.14; H, 9.94. Found: C, 74.88; H, 10.24.

2-(4-Methoxyphenoxy)-3-methylbut-2-enoic acid (3m): mp = 121-122 °C; ^1H NMR (400 MHz, CDCl_3) δ 10.95 (br s, 1 H), 6.83 (s, 4 H), 3.77 (s, 3 H), 2.25 (s, 3 H), 1.88 (s, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ 168.9, 154.7, 151.5, 143.8, 136.0, 115.5, 114.9, 55.8, 20.9, 20.4 FTIR (thin film) ν_{max} 1687, 1633, 1505, 1290, 1211 cm^{-1} ; ES HRMS m/z calcd for $\text{C}_{12}\text{H}_{13}\text{O}_4$ ($\text{M} - \text{H}^+$) 221.0814, found 221.0819; Anal. Calcd for $\text{C}_{12}\text{H}_{14}\text{O}_4$: C, 64.85; H, 6.35. Found: C, 64.57; H, 6.34.

General Procedure for the preparation of the Racemic 2-Aryloxy Acids 4a-m. A mixture of the phenol **1a-l** (20.0 mmol), methyl 2-bromocarboxylate **2a-c** (22 mmol), K_2CO_3 (50 mmol) and MeCN (20 mL) was stirred at 80 °C for 16 h. The mixture was cooled to 35 °C and water (15 mL) was added. The upper organic phase was washed with 1M KOH (2 mL) and was then stirred with 45% aq KOH (3 mL) and water (10 mL) for 20 h at 22 °C to give a homogeneous mixture. The mixture was evaporated to half its volume at 30 °C and was diluted with water (20 mL) at 20 °C. 5M HCl (8.0 mL) was added to the mixture (pH < 2) was stirred at 10-15 °C for 2h. The mixture was filtered and the filter cake was washed with water (60 mL) and 3:1 water/MeCN (20 mL). The filter cake was dried to provide the saturated aryloxyacids **4a-m** as white crystalline solids which were recrystallized to a constant melting point (*t*-BuOMe-hexane, 2-3 recrystallizations). These racemic materials were used to develop the various HPLC assays and to verify identities, purities and yields of the hydrogenation products by comparison of HPLC and NMR data.

General Procedure for Enantioselective Hydrogenation of Aryl Enol Ethers. Glass vials (8 mL, with pierced septum caps) were charged with aryl enol ethers **3a-m** (0.5 mmol) and (*S*)-BINAPRuCl₂ (1-20 mol%). MeOH (1 mL) and Et₃N (0.54 mmol) were

added, and the mixtures were hydrogenated in a glass pressure vessel at 25 °C under 90 psig hydrogen for 20 h. Assay yields were determined by quantitative HPLC. All reactions reached >99% conversion. The 2-aryloxyacids **4a-m** can be isolated by evaporation of the crude reaction mixtures followed by aqueous workup. The residue was partitioned between toluene and 0.1M NaOH. The aqueous phase was acidified and extracted with *t*-BuOMe. Evaporation afforded the saturated aryloxyacids **4a-m** which were shown to be >95% pure by HPLC analysis. All of the saturated acids **4a-m** showed a negative optical rotation² in *i*-PrOH corresponding to the (*S*) configuration.^{3, 13} Yields refer to material isolated after chromatography through a short column of silica eluting with *t*-BuOMe. Yields and optical rotations were obtained on material from hydrogenations using 20 mol% catalyst.

(2S)-2-Phenoxybutanoic acid (4a).³ 91% yield, $[\alpha]_{\text{D}}^{22}$ -48.3 (*c* 0.64, *i*-PrOH); $[\alpha]_{\text{D}}^{22}$ -60.9 (*c* 1.24, acetone).

(2S)-2-(2-Methylphenoxy)butanoic acid (4b).^{4, 5} 70% yield, $[\alpha]_{\text{D}}^{22}$ -36.6 (*c* 0.72, *i*-PrOH).

(2S)-2-(4-Methylphenoxy)butanoic acid (4c).⁴ 86% yield, $[\alpha]_{\text{D}}^{22}$ -50.8 (*c* 0.72, *i*-PrOH).

(2S)-2-(2-Methoxyphenoxy)butanoic acid (4d).⁶ 72% yield, $[\alpha]_{\text{D}}^{22}$ -59.9 (*c* 0.72, *i*-PrOH).

(2S)-2-(2-Fluorophenoxy)butanoic acid (4e).⁷ 67% yield, $[\alpha]_{\text{D}}^{22}$ -58.6 (*c* 0.66, *i*-PrOH).

(2S)-2-(4-Fluorophenoxy)butanoic acid (4f).⁸ 86% yield, $[\alpha]_{\text{D}}^{22}$ -46.4 (*c* 0.83, *i*-PrOH).

(2S)-2-(2-Chlorophenoxy)butanoic acid (4g).⁹ 76% yield, $[\alpha]_{\text{D}}^{22}$ -44.0 (*c* 0.77, *i*-PrOH).

(2S)-2-(3-Bromophenoxy)butanoic acid (4h). 75% yield, $[\alpha]_{\text{D}}^{22}$ -42.0 (*c* 0.95, *i*-PrOH); mp = 80-81 °C; ¹H NMR (400 MHz, CDCl₃) δ 10.90 (br s, 1 H), 7.27-7.13 (m, 2 H), 7.09 (m, 1 H), 6.84 (dt, *J* = 6.5, 2.5, 1 H), 6.61 (dd, *J* = 6.7, 5.1, 1 H), 2.06 (m, 2 H), 1.12 (t, *J* = 7.4, 3 H); ¹³C NMR (100 MHz, CDCl₃) δ 177.1, 158.5, 130.8, 125.1, 123.0, 118.9, 113.9, 77.3, 26.0, 9.6.

(2S)-2-(2-Iodophenoxy)butanoic acid (4i).¹⁰ 71% yield, $[\alpha]_{\text{D}}^{22}$ -39.1 (*c* 1.10, *i*-PrOH).

(2S)-2-(3-Iodophenoxy)butanoic acid (4j).^{10, 11} 81% yield, $[\alpha]_{\text{D}}^{22}$ -38.1 (*c* 1.19, *i*-PrOH).

(2S)-2-(4-Nitrophenoxy)butanoic acid (4k).¹² 62% yield, $[\alpha]_{\text{D}}^{22}$ -52.3 (*c* 0.67, *i*-PrOH).

(2S)-2-(Phenoxy)octanoic acid (4l).¹³ 57% yield, $[\alpha]_{\text{D}}^{22}$ -10.5 (*c* 1.48, *i*-PrOH).

(2S)-2-(4-Methoxyphenoxy)-3-methylbutanoic acid (4m).¹⁴ 80% yield, $[\alpha]_{\text{D}}^{22}$ -38.4 (*c* 0.58, *i*-PrOH).

Table S1. HPLC Assay Data for Hydrogenations

Substituents			Compounds			Assay Rxn			Assay F for Phenol 1		Chiral Assay		
						Name	Retention Times (min)		Retention Times (min)		Name	Retention Times (min) of Antipodes	
R ¹	R ²	R ³	1 ArOH	3 Enol ether	4 satd acid	LC assay	4	3	4	1	Chiral LC Assay	Major (-)- 4	Minor (+)- 4
H	Me	H	1a	3a	4a	A	43.7	47.2	1.80	1.57	G	2.73	3.46
2-Me	Me	H	1b	3b	4b	B	62.6	58.6	2.19	1.81	G	2.47	2.82
4-Me	Me	H	1c	3c	4c	B	47.2	51.1	2.06	1.73	H	5.33	7.62
2-OMe	Me	H	1d	3d	4d	A	34.5	33.5	1.67	1.62	G	3.57	4.70
2-F	Me	H	1e	3e	4e	D	24.5	25.9	1.83	1.61	H	5.20	6.67
4-F	Me	H	1f	3f	4f	A	61.7	67.5	1.84	1.59	H	4.72	5.59
2-Cl	Me	H	1g	3g	4g	C	22.4	21.0	2.13	1.80	H	5.49	7.44
3-Br	Me	H	1h	3h	4h	C	25.0	24.5	2.31	1.96	I	9.14	10.57
2-I	Me	H	1i	3i	4i	C	27.2	25.4	2.43	2.02	H	6.42	7.49
3-I	Me	H	1j	3j	4j	C	27.6	27.0	2.48	2.11	J	24.0	27.9
4-NO ₂	Me	H	1k	3k	4k	E	52.1	55.0	1.79	1.57	K	8.87	7.56
H	<i>n</i> Pent	H	1a	3l	4l	C	47.2	45.0	3.71	1.57	G	2.40	2.85
4-OMe	Me	Me	1l	3m	4m	C	20.0	18.5	1.98	1.48	H	6.57	9.16

Table S2. HPLC Conditions for Assays used in Hydrogenations

Assay	Column	Size (mm) ^b	Temp °C	Gradient ^a			Isocratic				Eluents		
				Flow ^c	%B	Time (min)	Flow ^c	%B	% mod	Time (min)	A	B	Mod ^d
A	Zorbax RX C18	4.6×150	35	-	-	-	1.4	10	0.1	80	H ₂ O	MeCN	H ₃ PO ₄ ^e
B	Zorbax RX C18	4.6×150	35	-	-	-	1.4	20	0.1	70	H ₂ O	MeCN	H ₃ PO ₄ ^e
C	Zorbax RX C18	4.6×150	35	1-1.5	20-40	30	1.5	40	0.1	30-47	H ₂ O	MeCN	H ₃ PO ₄ ^e
D	Zorbax SB Phenyl	4.6×250	35	-	-	-	1.4	20	0.1	35	H ₂ O	MeCN	H ₃ PO ₄ ^e
E	Zorbax SB Phenyl	4.6×250	35	-	-	-	1.4	10	0.1	70	H ₂ O	MeCN	H ₃ PO ₄ ^e
F	Zorbax RX C18	4.6×150	35	1-1.5	60-70	3.0	1.5	70	0.1	3.0-8.0	H ₂ O	MeCN	H ₃ PO ₄ ^e
G	Chiracel OD-H	4.6×250	30	-	-	-	1.5	15	0.15	8	hept	iPrOH	TFA
H	Chiracel OD-H	4.6×250	30	-	-	-	1.5	2.175	0.06	15	hept	iPrOH	TFA
I	Chiracel OD-H	4.6×250	30	-	-	-	1.5	1.035	0.05	15	hept	iPrOH	TFA
J	Chiracel OD-H	4.6×250	30	-	-	-	1.5	0.600	0.04	35	hept	iPrOH	TFA
K	Chiracel AD-H	4.6×250	40	1.5	4-40	40	-	-	-	-	CO ₂ ^f	MeOH	

^aGradient elution was performed first if indicated followed by isocratic elution, percentages indicated by volume. ^bDiameter × length. ^cmL/min. ^dModifier. ^e85% phosphoric acid reagent. ^fSupercritical phase LC (200 bar).

Figure S1. Structures and Commercial Sources of Ligands for Hydrogenation of **3a** to **4a**

Figure S2. ORTEP diagram of **3e**.

Figure S3. ORTEP diagram of (*S*)-**4h**.

Figure S4. Chiral HPLC traces of **4a-4m** racemic material and material from hydrogenations using 20 mol% catalyst isolated after chromatography through a short column of silica eluting with *t*-BuOMe.

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