Supporting information for:

Enantioselective Hydrogenation of 3-Alkylidenelactams: High-Throughput Screening Provides a Surprising Solution.

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Materials and Methods. Lactam and aldehyde starting materials were purchased from Aldrich Chemical Co. (*S,S*)-BDPP was purchased from Strem Chemical Company, Newburyport, MA and was used as received or from Digital Specialty Chemicals, Ltd., Mississauga, Ontario, Canada in which case it was recrystallized from isopropanol prior to use. Bis(cyclooctadiene)iridium(I) tetrafluoroborate was purchased from Strem Chemical Company, Newburyport, MA or from Colonial Metals, Inc., Elkton, MD and was used as received. Chiral HPLC analytical methods were developed using racemic samples prepared by hydrogenation of the corresponding substrates over a 5% palladium on carbon catalyst. The Chiralpak AD, Chiralpak AS, and Chiralpak OD columns used to determine enantiomeric purity of the products were purchased from Chiral Technologies, Inc., Exton, PA. NMR spectra were obtained at 25 °C in CDCl₃ except as indicated and field strengths for the various nuclei were as follows: ¹H (400.1 MHz), ¹³C (100.6 MHz), ¹⁹F (376.5 MHz), ³¹P (162.0 MHz). Coupling constants (*J*) are given in Hertz. Flash chromatography was performed on 220–400 mesh silica (E. Merck) following the standard procedure [Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923].

Synthesis of 3-(Alkylidene)lactam Substrates.

General Procedure: 3-(4-Fluorobenzylidene)valerolactam. Valerolactam (20.0g, 202 mmol) was dissolved in toluene (80 ml). To this solution, trifluoroacetic anhydride (TFAA) (46.7g, 222 mmol) was charged slowly at 5 °C. Upon complete addition, the solution was held at 25 °C for 30 min. Toluene was removed under vacuum using a rotary evaporator. Toluene (50 ml) was added to the concentrate and again removed under vacuum, and this process was repeated twice. The resulting liquid (TFA-protected lactam) was mixed with 4-fluorobenzaldehyde (22.6 g, 182 mmol) and the mixture was slowly charged to a 1M solution of potassium *t*-butoxide in THF (240 ml, 240 mmol) at 5 °C. Upon complete addition, the mixture was heated to 55 °C and held for 1 h. The reaction mixture was concentrated to a thick slurry under vacuum using a rotary evaporator. To the concentrate, water (300 ml) was added to precipitate the crude product. The slurry was cooled to 5 °C and held for 1 h. Solid was filtered, washed with water, and dried in vacuum oven overnight. The crude product was purified by re-slurry in 20% isopropyl acetate in heptane

(100 ml) at 65 °C for 1h. The slurry was cooled to 25 °C and held for 2 h. Solid was filtered, washed with 20% isopropyl acetate in heptane (3 x 30 ml). Purified product was dried in vacuum oven. Yield of dried product was 24.8 g (66%). ¹H NMR δ 1.88 (m, 2H), 2.80 (m, 2H), 3.45 (m, 2H), 7.08 (m, 3H), 7.40 (m, 2H), 7.77 (s, 1H). ¹³C NMR δ 23.16, 26.37, 42.17, 115.58 (d, *J* = 21.4, C-3'), 129.47 (C-3), 131.82 (d, *J* = 8.2, C-2'), 132.08 (d, *J* = 3.6, C-1'), 134.65 (olefinic), 162.53 (d, *J* = 249, C-4'), 166.99 (C-2). ¹⁹F NMR: δ -113.15.

3-(4-Trifluoromethylbenzylidene)valerolactam. ¹H NMR (DMSO-d₆) δ 1.71 (m, 2H), 2.72 (m, 2H), 3.27 (m, 2H), 7.62 (m, 3H), 7.78 (m, 2H), 7.93 (s, 1H). ¹⁹F NMR (DMSO-d₆): δ -61.53.

3-(4-Methoxybenzylidene)valerolactam. ¹H NMR δ 1.89 (m, 2H), 2.82 (m, 2H), 3.43 (m, 2H), 3.83 (s, 3H), 6.82 (br, 1H), 6.92 (d, *J* = 9.0, 2H), 7.38 (d, *J* = 9.0, 2H), 7.78 (s, 1H). ¹³C NMR δ 23.25, 26.53, 42.17, 55.50, 113.98 (C-3'), 127.60, 128.61, 131.74 (C-2'), 135.50 (olefin), 159.69 (C-4'), 167.36 (C-2).

3-(2-Furanylmethylidene)valerolactam. ¹H NMR δ 1.93 (m, 2H), 2.96 (m, 2H), 3.42 (m, 2H), 6.50 (s, 1H), 6.58 (2, 1H), 6.88 (br, 1H), 7.54 (m, 2H).

3-(3-Furanylmethylidene)valerolactam. ¹H NMR: δ 1.91 (m, 2H), 2.82 (m, 2H), 3.37 (m, 2H), 6.58 (s, 1H), 7.40 (br, 1H), 7.48 (s, 1H). ¹³C NMR: δ 22.71, 26.51, 41.80, 111.15, 122.01, 126.73, 127.49, 143.56, 144.14, 167.20.

3-(Butylidene)valerolactam. ¹H NMR: δ 0.93 (m, 3H), 1.48 (m, 2H), 1.82 (m, 2H), 2.10 (m, 2H), 2.48 (m, 2H), 3.35 (m, 2H), 6.84 (m, 1H).

3-(Isobutylidene)valerolactam. ¹H NMR: δ 1.02 (d, *J* = 8.0, 6H), 1.83 (m, 2H), 2.49 (m, 2H), 2.60 (m, 1H), 3.35 (m, 2H), 6.68 (d, *J* = 12.8, 1H), 7.05 (br, 1H). ¹³C NMR: δ 22.18, 23.00, 24.47, 27.17, 42.12, 126.53, 145.65, 167.42.

3-(4-Fluorobenzylidene)-2-pyrrolidinone. ¹H NMR (DMSO-d₆): δ 3.00 (br m, 2 H), 3.38 (m, 2 H), 7.09 (s, 1 H), 7.28 (m, 2H), 7.60 (m, 2 H), 8.18 (br s, 1H). ¹³C NMR (DMSO-d₆): δ 25.96, 39.04, 116.02 (d, *J* = 21), 126.94, 131.76, 132.60, 162.08 (d, *J* = 246), 170.81. ¹⁹F NMR (DMSO-d₆): δ -113.09.

3-(Butylidene)-2-pyrrolidinone. ¹H NMR: δ 0.90 (t, *J* = 7), 1.48 (m, 2H), 2.10 (m, 2H), 2.71 (m, 2 H), 3.44 (m, 2H), 6.41 (m, 1H), 7.87 (br s, 1H). ¹³C NMR: δ 14.01, 21.95, 23.98, 31.59, 39.71, 131.33, 133.17, 172.59.

3-(4-Fluorobenzylidene)caprolactam. ¹H NMR: δ 1.81 (m, 2H), 1.92 (m, 2H), 2.60 (m, 2H), 3.21 (m, 2H), 6.50 (br, 1H), 7.08 (m, 2H), 7.14 (s, 1H), 7.38 (m, 2H). ¹³C NMR: δ 27.46, 27.50, 28.79, 42.28, 115.61 (d, *J* = 21.4, C-3'), 131.09, (d, *J* = 8.1, C-2'), 132.13 (d, *J* = 3.4, C-1'), 133.52 (olefin), 137.97 (C-3), 162.39, (d, *J* = 248.3, C-4'), 176.17 (C-2). ¹⁹F NMR: δ -113.82.

1-Methyl-3-(4-fluorobenzylidene)valerolactam. ¹H NMR: δ 1.89 (m, 2H), 2.77 (m, 2H), 3.10 (s, 3H), 3.42 (m, 2H), 7.08 (m, 2H), 7.32 (m, 2H), 7.78 (s, 1H). ¹³C NMR: δ 23.05, 26.48, 36.01, 49.93, 115.47 (d, *J* = 21.5, C-3'), 130.04 (C-3), 131.60 (d, *J* = 8.1, C-2'), 132.51 (d, *J* = 3.2, C-1'), 133.85 (olefinic), 162.37 (d, *J* = 245.4, C-4'), 165.25 (C-2).

Hydrogenation Studies

Preparation of [(*S,S*)-(BDPP)Ir(COD)]BF₄. In a nitrogen-filled glove box, (*S,S*)-2,4-bis(diphenylphosphino)pentane (4.40 g, 100 mmol) and bis(1,5-cyclooctadiene)iridium(I) tetrafluoroborate (4.90 g, ca. 91% purity, 91 mmol) were dissolved in dichloromethane (50 mL). Diethyl ether (100 mL) was added dropwise to the stirred solution. The resultant precipitate was collected by filtration to afford [(*S,S*)-(BDPP)Ir(COD)]BF₄ (6.15 g, 82%) as a red-violet microcrystalline solid. The ³¹P NMR spectrum was particularly helpful in ascertaining catalyst purity; the purified complex exhibited a singlet at δ 16.7 ppm and was free of unreacted BDPP as indicated by the absence of a resonance at δ 0.5 ppm. ¹H NMR: δ 1.02 (t, *J* = 7, 3H), 1.04 (t, *J* = 7, 3H), 1.52-1.95 (m, 6H), 2.48 (m, 4H), 2.91 (m, 2H), 3.52 (m, 2H, vinyl), 4.33 (m, 2H, vinyl), 7.25 (m, 4H), 7.40-7.57 (m, 6H), 7.74 (m, 6H), 8.13 (m, 4H).

General Procedure: (*S*)-3-*p*-fluorobenzyl-2-piperidone. In a nitrogen-filled glove box, a Fisher-Porter tube was charged with [(*S,S*)-(BDPP)Ir(COD)]BF₄ (20 mg, 0.024 mmol) and 3-(*p*-fluorobenzylidene)-2-piperidone (1.00 g, 4.9 mmol). Methanol (5 mL) and dichloromethane (5 mL) were added and the system was flushed 4 times with hydrogen and pressured to 65 psi H₂. After 24 h the reaction mixture was filtered through a short pad of silica. The solvent was removed at reduced pressure to afford (*S*)-3-*p*-fluorobenzyl-2-piperidone (0.97 g, 97%) as a white crystalline solid. Chiral HPLC analysis (Chiralpak AS, 60% heptane, 39.2% isopropanol, 0.4% trifluoroacetic acid, 0.4% *n*-hexylamine, 40 °C) indicated that conversion was 100% and the enantiomeric excess was 91%. ¹⁹F NMR: δ -117.63; ¹³C NMR: δ 20.18, 24.33, 35.56, 41.27, 41.76, 114.06 (d, *J* = 21 Hz), 129.61, 134.44, 160.42 (d, *J* = 241 Hz), 173.49; ¹H NMR: δ 1.43 (m, 1H), 1.57-1.89 (m, 3H), 2.50 (m, 1H), 2.71 (app dd, 1H), 3.29 (m, 3H), 6.01 (br s, 1H), 6.98 (m, 2H), 7.16 (m, H).

3-*p*-Trifluoromethylbenzyl-2-piperidone. White crystalline solid (96%). Chiral HPLC analysis (Chiralpak AS, 60% heptane, 39.2% isopropanol, 0.4% trifluoroacetic acid, 0.4% *n*-hexylamine, 40 °C) indicated that conversion was 100% and the enantiomeric excess was 87%. ¹⁹F NMR: δ -62.78; ¹³C NMR: δ 21.50, 25.70, 37.40, 42.50, 42.79, 124.26 (q, *J* = 224), 125.46, 128.67 (q, *J* = 32), 144.32, 174.25; ¹H NMR: δ 1.42 (m, 1H), 1.60-1.89 (m, 3H), 2.58 (m, 1H), 2.79 (app dd, 1H), 3.31 (m, 2H), 3.43 (app dd, 1H), 7.10 (br s, 1H), 7.34 (d, *J* = 8, 2H), 7.53 (d, *J* = 8, 2H).

3-*p*-Methoxybenzyl-2-piperidone. White crystalline solid (92%). Chiral HPLC analysis (Chiralpak AS, 60% heptane, 39.2% isopropanol, 0.4% trifluoroacetic acid, 0.4% *n*-hexylamine, 40 °C) indicated that conversion was 100% and the enantiomeric excess was 90%. ¹³C NMR: δ 21.32, 25.49, 36.72, 42.56, 43.11, 55.40, 113.93, 130.37, 131.99, 158.18, 174.93; ¹H NMR: δ 1.44 (m, 1H), 1.62 (m, 1H), 1.68-1.75 (m, 2H), 2.50 (m, 1H), 2.64 (app dd, 1H), 3.20-3.37 (m, 3H), 3.79 (s, 3H), 6.82 (d, *J* = 9, 2H), 7.09 (br s, 1H), 7.12 (d, *J* = 9, 2H).

3-(2-Furanylmethyl)-2-piperidone. White crystalline solid (100%). Chiral HPLC analysis (Chiralpak AD, 85% heptane, 15% ethanol, 30 °C) indicated that conversion was 100% and the

enantiomeric excess was 95%. ^{13}C NMR: δ 21.55, 26.12, 29.99, 40.91, 42.57, 106.80, 110.39, 141.38, 153.99, 174.20; ^1H NMR: δ 1.49 (m, 1 H), 1.68 (m, 1 H), 1.75-1.91 (m, 2 H), 2.62 (m, 1 H), 2.82 (m, 1 H), 3.29 (m, 3 H), 6.06 (m, 1 H), 6.29 (m, 1 H), 7.29 (m, 1 H), 7.34 (br s, 1 H).

3-(3-Furanylmethyl)-2-piperidone. White crystalline solid (98%). Chiral HPLC analysis (Chiralpak AS, 60% heptane, 39.2% isopropanol, 0.4% trifluoroacetic acid, 0.4% n-hexylamine, 40 °C) indicated that conversion was 100% and the enantiomeric excess was 95%. ^1H NMR: δ 1.49 (m, 1H), 1.69 (m, 1H), 1.86 (m, 2H), 2.47 (m, 1H), 2.71 (m, 1H), 2.99 (m, 1H), 3.28 (m, 2H), 6.29 (s, 1H), 7.04 (br s, 1H), 7.24 (s, 1H), 7.32 (s, 1H). ^{13}C NMR: δ 21.49, 25.66, 26.58, 41.68, 42.52, 111.60, 122.34, 140.28, 142.98, 174.80.

3-Butyl-2-piperidone. White crystalline solid (93%). Chiral gas chromatographic analysis (Restek GammaDex-SA column, 130 °C for 5 min, then programmed to 200 °C at 10 °/min) indicated that conversion was 95% and the enantiomeric excess was 90%. ^{13}C NMR: δ 14.24, 21.27, 22.85, 26.04, 29.25, 31.36, 40.96, 42.38, 176.02; ^1H NMR: δ 0.91 (t, J = 7, 3H), 1.22-1.58 (m, 6H), 1.70 (m, 1H), 1.79-2.00 (m, 3H), 2.24 (m, 1H), 3.29 (m, 2H), 7.25 (br s, 1H).

3-Isobutyl-2-piperidone. White crystalline solid (100%). Chiral HPLC analysis (Chiralpak AS, 60% heptane, 39.2% isopropanol, 0.4% trifluoroacetic acid, 0.4% n-hexylamine, 40 °C) indicated that conversion was 100% and the enantiomeric excess was 81%. ^1H NMR: δ 0.88 (d, 3 H), 0.95 (d, 3H), 1.35 (m, 1H), 1.49 (m, 1H), 1.71 (m, 2H), 1.82 (m, 2H), 1.96 (m, 1H), 3.31 (m, 2H), 6.80 (br s, 1H). ^{13}C NMR: δ 21.16, 21.29, 23.82, 25.13, 6.24, 39.01, 40.72, 42.48, 176.12.

3-p-Fluorobenzyl-2-pyrrolidinone. White crystalline solid (100%). Chiral HPLC analysis (Chiralpak OD, 95% heptane, 4.9% isopropanol, 0.05% trifluoroacetic acid, 0.05% n-hexylamine, 40 °C) indicated that conversion was 100% and the enantiomeric excess was 89%. ^{19}F NMR δ -117.39; ^{13}C NMR δ 26.92, 35.90, 40.44, 42.88, 115.44 (d, J = 21), 130.58, 135.21, 161.77 (d, J = 241), 179.72; ^1H NMR: δ 1.83 (m, 1H), 2.15 (m, 1H), 2.66 (m, 2H), 3.11-3.32 (m, 3H), 6.47 (br s, 1H), 7.00 (m, 2H), 7.15 (m, 2H).

3-Butyl-2-pyrrolidinone. White crystalline solid (98%). Chiral HPLC analysis (Chiralcel AS-RH, solvent A = 0.05% trifluoroacetic acid in 20:80 MeOH/water, solvent B = 0.05% trifluoroacetic acid in 20:80 MeOH/acetonitrile) indicated 82% ee. ^1H NMR: δ 0.91 (t, J = 6.8, 3H), 1.36 (m, 5H), 1.75 (ddd, J = 3.6, 8.5, 11.8, 1H), 1.82-1.91 (m, 1H), 2.21-2.39 (m, 2H), 3.23-3.39 (m, 2H), 7.32 (s, 1H). ^{13}C NMR: δ 14.16, 22.82, 27.64, 29.68, 30.73, 40.73, 41.26, 181.44.

3-(p-Fluorobenzyl)caprolactam. White crystalline solid (92%). Chiral HPLC analysis (Chiralpak AS, 60% heptane, 39.2% isopropanol, 0.4% trifluoroacetic acid, 0.4% n-hexylamine, 40 °C) indicated that conversion was 100% and the enantiomeric excess was 75%. ^{19}F NMR: δ -117.99; ^{13}C NMR: δ 28.93, 29.47, 29.94, 36.73, 42.28, 45.65, 115.18 (d, J = 21), 130.81, 136.47, 161.49 (d, J = 241), 179.79; ^1H NMR: δ 1.43 (m, 3H), 1.70 (m, 1H), 1.76 (m, 1H), 1.91 (m, 1H), 2.54 (app dd, 1H), 2.67 (m, 1H), 3.12-3.31 (m, 3H), 6.78 (br s, 1H), 6.96 (m, 2H), 7.14 (m, 2H).

1-Methyl-3-(p-fluorobenzyl)-2-piperidone. White crystalline solid (97%).. HPLC analysis (Chiralpak AD, 95% heptane, 5% ethanol, 20 °C) indicated that conversion was 100% and the enantiomeric excess was 67%. ¹H NMR: δ 1.43 (m, 1H), 1.70 (br m, 2H), 1.82 (br m, 1H), 2.50 (br m, 1H), 2.67 (app t, 1H), 2.93 (s, 3H), 3.25 (br m, 2H), 3.36 (app d, 1H), 6.92 (m, H), 7.15 (m, 2H). ¹³C NMR: δ 21.54, 25.81, 34.98, 37.03, 43.40, 50.16, 115.08 (d, *J* = 21), 130.72, 135.92, 161.45 (d, *J* = 242), 171.76.

Operation at Multi-Kilogram Scale

Substrate Synthesis. A 30 gallon (120 L) glass-lined reactor was charged with valerolactam (18.0 kg) and toluene (42.0 kg). Trifluoroacetic anhydride (42.0 kg) was added over 30 min and the mixture was stirred for an additional 60 min. Volatiles were distilled off at 60-70 °C at 140 torr. Toluene (50.0 kg) was added and the mixture was further distilled until approximately 27 L remained in the pot and this process was repeated twice. To the residue was added *tert*-butanol (18.8 kg) and 4-fluorobenzaldehyde (20.3 kg). The resultant solution was slowly transferred to 100 gallon (400 L) glass-lined reactor containing potassium *tert*-butoxide in tetrahydrofuran (122 kg of a 20% solution). The mixture was warmed to 60 °C for 1 h. Volatiles were distilled at 40-50 °C at 250 torr to a volume of approximately 100 L. Water (180 L) was added to the slurry at 40 °C and the mixture was cooled to 5 °C for 2 h and collected by filtration. The wet cake was washed and reslurried with water (3 x 200 L) and dried in a tray dryer (50 °C, 50 torr) to afford crude 3-p-fluorobenzylidene-2-piperidone (32.6 kg) whose purity by HPLC was 70.3 wt % (95.4 area %).

Purification of Substrate. The crude product was charged to a 100 gallon (400 L) glass-lined reactor with isopropyl acetate (80 kg). Residual water was removed by distillation at atmospheric pressure to a volume of 70 L. Heptane (56 kg) was added at 80 °C and the slurry was cooled to 5 °C. Filtration, washing with a mixture of isopropyl acetate (8 kg) and heptane (62 kg) at 5 °C, and drying (50 °C, 50 torr) afforded purified 3-p-fluorobenzylidene-2-piperidone (20.0 kg, 54%) which by HPLC analysis was 99.1 wt % (99.6 area %). In order to ensure the material was free from catalyst poisons, a portion of the product (19.7 kg) was further crystallized by dissolution in isopropanol (80 L) and water (20 L) at 75 °C. The mixture was seeded at 70 °C and cooled to 30 °C whereupon water (140 L) was added. After standing overnight, the mixture was cooled to 2 °C and the product was collected by filtration, washed with 10% isopropanol in water (88 L), and dried (65 °C, 50 torr). This afforded crystalline 3-p-fluorobenzylidene-2-piperidone (19.5 kg) containing 0.2% residual isopropanol which was 99.7 area % by HPLC. ¹⁹F NMR: δ -112.99; ¹H NMR: δ 1.88 (m, 2H), 2.80 (m, 2H), 3.45 (m, 2H), 7.08 (m, 3H), 7.40 (m, 2H), 7.77 (s, 1H); ¹³C NMR: δ 23.16, 26.37, 42.17, 115.58 (d, *J* = 21.4, C-3'), 129.47(C-3), 131.82 (d, *J* = 8.2, C-2'), 132.08 (d, *J* = 3.6, C-1'), 134.65 (olefinic), 162.53 (d, *J* = 249, C-4'), 166.99 (C-2).

Large Scale Hydrogenation. A 100 gallon (400 L) glass-lined reactor was charged with recrystallized 3-p-fluorobenzylidene-2-piperidone (19.5 kg), methanol (75 kg, 5 volumes), and dichloromethane (126 kg, 5 volumes). (2*S*,4*S*)-(-)-2,4-bis(diphenylphosphino)pentane (97 g, 0.25 mol %)

and bis(1,5-cyclooctadiene)iridium(I) tetrafluoroborate (109 g, 0.25 mol %) was added to the stirred solution under nitrogen. The reactor was pressured to 55 psi (0.46 MPa) hydrogen and stirred for 13 h at which time no starting material remained. The solvent was replaced with toluene by successive vacuum distillation and toluene charges and the resultant solution was filtered through a bed of charcoal (Darco G-60) and silica gel 60. The resultant solution contained (*S*)-3-*p*-fluorobenzyl-2-piperidone (19.1 kg, 97%); NMR and chiral HPLC analysis as above indicated the enantiomeric excess was 91%.

Large scale LAH reduction. A solution of (*S*)-3-*p*-fluorobenzyl-2-piperidone (6.4 kg, 30.8 moles) in 120 L of toluene was cooled to 10 °C. A solution of LAH-bis THF in toluene (1.0M, 27.8 kg) was added at a temperature below 15 °C. The batch was heated to 40 °C and stirred for 3 h. The batch was quenched by slow addition to a Rochelle salt solution (16.4 kg in 90 L of water) and stirred for 15 min. The organic phase was washed with 10% brine followed by water. The toluene solution was concentrated by vacuum distillation to a volume of about 60 L. The resultant solution contained (*S*)-3-*p*-fluorobenzyl-piperidine (5.0 kg, 25.9 moles, 84%). Chiral HPLC analysis indicated enantiomeric excess was 90%.

Large scale mandelic acid salt formation. A solution of (*S*)-3-(*p*-fluorobenzyl)piperidine (12.2 kg, 63.1 moles at 90% e.e.) in 120 L of toluene was heated to 70 °C. To this hot solution was added a hot solution (at 70 °C) of *R*-(-)-mandelic acid (10.1 kg, 66.4 moles) in acetonitrile (50 L). The resulting mixture was stirred for 1 h at 70 °C, cooled to 25 °C over 2 h, and then held for 2 h. The slurry was filtered, washed with acetonitrile, and dried in vacuum dryer. Yield was 21.1 kg (96.7%). Chiral HPLC analysis indicated enantiomeric excess was 99%.

Details of Screening Protocol.

The metal precursors utilized in the initial screen were $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$, $[\text{Ir}(\text{COD})_2]\text{BF}_4$, $[\text{Ir}(\text{COD})\text{Cl}]_2$, $[\text{Rh}(\text{COD})_2]\text{BF}_4$, $[\text{Rh}(\text{COD})_2]\text{OTf}$, $[\text{Rh}(\text{COD})\text{Cl}]_2$, $(\text{COD})\text{Ru}(\text{methallyl})_2 + 2\text{HBr}$, and $(\text{COD})\text{Ru}(\text{methallyl})_2 + \text{BF}_3 + \text{HBF}_4$. The last two precursors have been described by Genet and coworkers in refs 6 and 7 of the text and are expected to provide LRuBr_2 and $[\text{LRuH}(\text{COT})]\text{BF}_4$ respectively. Structures for the 32 phosphine ligands are shown on the last page of this Supporting Information. BICP, (*S,R*)-Indan-Ambox, and the PennPhos ligands were obtained from Chiral Quest, Inc. (State College, PA). Josiphos type ligands were obtained from Solvias, Inc. All of the remaining ligands were purchased from the Strem Chemical Company.

Screening reactions were conveniently carried out in 1 mL vials contained in 96 well plates. The vials were charged in a Vacuum Atmospheres drybox using Gilson liquid handlers under an atmosphere of dry nitrogen. Each vial was charged with aliquots of three stock solutions as follows: (1) Chiral phosphines were added in the form of stock solutions (toluene): 30 μL of a 10 $\mu\text{mol/mL}$ solution per vial; e.g., 168 μg of BINAP per well. (2) Metal precursors were added in the form of stock solutions (ethanol or THF): 30 μL of a 9 $\mu\text{mol/mL}$ solution per well. (3) The substrate was added in the form of 300 μL of a 90 $\mu\text{mol/mL}$ solution (ethanol) per well, i.e. 6 mg of substrate per well. The plate was sealed with an air-tight

cover and removed from the drybox. The system was flushed with hydrogen and then maintained under 65 psi H_2 for 12 h at either room temperature (Rh and Ir precursors) or 40 °C (Ru precursors). Stirring was maintained using a locally modified commercial vortexing unit. At the conclusion of the run the plate was transferred to an autosampler and the yield and conversion were determined by chiral hplc analysis (Chiralpak AS, 60% heptane, 39.2% isopropanol, 0.4% trifluoroacetic acid, 0.4% n-hexylamine, 40 °C).

Diphosphine and Related Ligands Used in this Study.