SUPPORTING INFORMATION

Catalytic Asymmetric Hydrogenation of *N*-Iminopyridinium Ylides: Expedient Approach to Enantioenriched Substituted Piperidine Derivatives

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General: All non-aqueous reactions were run under an inert atmosphere (nitrogen or argon) with rigid exclusion of moisture from reagents and glassware using standard techniques for manipulating air-sensitive compounds.¹ All glassware was stored in the oven and/or was flame-dried prior to use under an inert atmosphere of gas. Anhydrous solvents were obtained either by filtration through drying columns (THF, ether, CH₂Cl₂, benzene, DMF, CH₃CN, toluene, hexane, methanol) on a GlassContour system (Irvine, CA), by distillation over calcium hydride (Et₃N, ClCH₂CH₂Cl, pyridine, diisopropylamine, isopropanol) or by distillation over sodium/benzophenone (DME). Analytical thin-layer chromatography (TLC) was performed on precoated, glass-backed silica gel (Merck 60 F₂₅₄). Visualization of the developed chromatogram was performed by UV absorbance, aqueous cerium molybdate, ethanolic phosphomolybdic acid, iodine, or aqueous potassium permanganate. Flash column chromatography was performed using 230-400 mesh silica (EM Science or Silicycle) of the indicated solvent system according to standard technique.² Melting points were obtained on a Buchi melting point apparatus and are uncorrected. Infrared spectra were taken on a Perkin Elmer Spectrum One FTIR and are reported in reciprocal centimeters (cm⁻¹). Nuclear magnetic resonance spectra (¹H, ¹³C, DEPT 135, COSY, HMQC, NOESY) were recorded either on a Bruker AV 300, AMX 300, AV 400, ARX 400, or DMX 600 spectrometer. Chemical shifts for ¹H NMR spectra are recorded in parts per million from tetramethylsilane with the solvent resonance as the internal standard (chloroform, δ 7.27 ppm). Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, sext = sextuplet, m = multiplet and br = broad), coupling constant in Hz, integration. Chemical shifts for ¹³C NMR spectra are recorded in parts per million from tetramethylsilane using the central peak of deuteriochloroform (77.23 ppm) as the internal standard. All spectra were obtained with complete proton decoupling. When ambiguous, proton and carbon assignments were established using COSY, NOESY, HMQC and DEPT experiments. High resolution mass spectra were performed by the Centre régional de spectroscopie de masse de l'Université de Montréal. Combustion analyses were performed by the Laboratoire d'analyse élémentaire de l'Université de Montréal.

Analytical High Performance Liquid Chromatography was performed either on an Agilent 1100 Series LC system equipped with a electrospray (ES) or APCI mass detector with simultaneous diode array UV detection. Data are reported as follows: (column type, eluent, flow rate: retention time (*t_r*)).

Figure S1. Ligand screening

Feringa's phosphoramidite was shown to be effective at 2:1 ligand:Ir ratio.

Table S1. Effect of counterion exchange.

Entry	X	Y (mol %)	Conv (%)	ee 2 (%)
1	-	0	>95	68
2	F ₃ CCO ₂	4.2	>95	55
3	F ₃ CCO ₂	8.4	>95	34
4	F ₃ CCO ₂	12.6	>95	6
5	F ₃ CSO ₃	4.2	>95	60
6	F ₃ CSO ₃	8.4	>95	77
7	F ₃ CSO ₃	12.6	Decomp.	-

Entry 6, which resulted in the formation of a grey precipitate, led us to believe, due to the enhanced enantioselectivity, that a cationic catalyst was generated and was more effective. We tested [Ir(COD)₂]BF₄ and found that it was rapidly deactivated, leading to inefficient hydrogenation. Based on the work of Pfaltz, we chose to use catalysts with the BARF counter ion.

Experimental Section

General amination/benzoylation procedure : 2-Methyl-N-benzoyliminopyridinium ylide (4a). 2-Picoline (0.100 mL, 1.24 mmol) and O-(2,4-dinitrophenyl)hydroxylamine (272 mg, 1.36 mmol) were added to 0.5 mL of a (1:1) mixture of H₂O and THF. The reaction flask was sealed and the resulting suspension was stirred at 40 °C for 12 h. During this period, the reaction mixture turned dark red. The reaction was poured into aqueous NaOH (2.5N, 6 mL) at room temperature and benzoyl chloride (0.215 mL, 1.84 mmol) was slowly added. After 4 h, the reaction was diluted with 5 mL of H₂O and extracted three times with 10 mL of CHCl₃. The combined organic phases were washed once with 5 mL of 2.5N NaOH. The organic phase was dried over Na₂SO₄, filtered and concentrated under reduced pressure affording **4a** as a beige solid (236 mg, 98% yield): mp 111 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.58 (d, *J* = 6.2 Hz, 1H), 8.19-8.15 (m, 2 H), 7.80 (dt, *J* = 7.7, 1.3 Hz, 1 H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.43-7.38 (m, 3H), 2.69 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.3, 154.3, 145.4, 137.8, 137.6, 130.5, 128.5, 128.4, 128.2, 128.1, 124.0, 19.9; IR (neat) 3054, 1593, 1553, 1491, 1330, 773, 707 cm⁻¹; Anal. calcd for C₁₃H₁₂N₂O: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.41; H, 6.09; N, 13.08.

2-Ethyl-N-benzoyliminopyridinium ylide (4b). The title compound was obtained as an orange oil (76%) according to the general procedure: ¹H NMR (300 MHz, CDCl₃) δ 8.60 (dd, *J* = 6.3, 1.2 Hz, 1H), 8.20-8.16 (m, 2H), 7.87 (dt, *J* = 7.7, 1.3 Hz, 1H), 7.59 (dd, *J* = 7.9, 0.9 Hz, 1H), 7.49 (ddd, *J* = 7.2, 6.2, 1.4 Hz, 1H), 7.44-7.38 (m, 3H), 3.11 (q, *J* = 7.5 Hz, 2H), 1.33 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 170.0, 158.2, 145.6, 137.7, 137.3, 130.2, 128.2, 128.0, 125.7, 123.4, 25.4, 11.3; IR (neat) 3066, 1594, 1555, 1337, 1179, 911, 715 cm⁻¹; LRMS (APCI, Pos) calcd for C₁₄H₁₄N₂O [M+H]⁺: 227.1 *m/z*, observed: 227.2 *m/z*.

2-n-Propyl-N-benzoyliminopyridinium ylide (4c). The title compound was obtained as a white solid (77%) according to the general procedure: mp 78 °C; ¹H NMR (400 MHz, CDCl₃) δ 8.63 (dd, *J* = 6.4, 1.0 Hz, 1H), 8.22-8.16 (m, 2H), 7.87 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.59 (dd, *J* = 8.0, 1.3 Hz, 1H), 7.51 (ddd, *J* = 7.7, 6.2, 1.6 Hz, 1H), 7.46-7.39 (m, 3H), 3.07 (t, *J* = 7.6 Hz, 2H), 1.81 (sext, *J* = 7.6 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.1, 157.1, 145.9, 137.4, 130.2, 128.2, 128.0, 126.6, 123.5, 34.1, 20.6, 14.1; IR (neat) 3089, 2960, 2877, 1596, 1547, 1334, 772, 714 cm⁻¹; LRMS (APCI, Pos) calcd for C₁₅H₁₆N₂O [M+H]⁺: 241.1 *m/z*, observed: 241.1 *m/z*.

2-Benzyl-N-benzoyliminopyridinium ylide (4d). The title compound was obtained as a yellow gum (91%) according to the general procedure: ^1H NMR (400 MHz, CDCl_3) δ 8.70 (dd, $J = 6.3, 0.9$ Hz, 1H), 8.24-8.20 (m, 2H), 7.80 (dt, $J = 7.3, 1.1$ Hz, 1H), 7.53 (t, $J = 7.9$ Hz, 1H), 7.46-7.40 (m, 3H), 7.40-7.29 (m, 2H), 7.29-7.24 (m, 3H), 4.47 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.1, 156.6, 145.4, 137.5, 137.2, 135.3, 130.4, 130.1, 129.3, 128.3, 127.7, 126.9, 123.6, 37.9; IR (neat) 3060, 1593, 1553, 1490, 1330, 1176, 714 cm^{-1} ; LRMS (APCI, Pos) calcd for $\text{C}_{19}\text{H}_{16}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 288.1 m/z , observed: 289.2 m/z .

2-(benzyloxymethyl)pyridine (9). In a flame dried round bottom flask under argon was added NaH (700 mg (60% w/w in oil), 17.5 mmol) then 50 mL of THF. To this stirring suspension at room temperature was slowly added 2-pyridinemethanol (1.50 mL, 15.5 mmol) over 5 minutes. The reaction was stirred for 5 minutes then cooled to 0 °C. Benzyl bromide (1.84 mL, 15.5 mmol) was slowly added dropwise and the reaction was stirred at 0 °C for 20 minutes. The reaction was warmed to room temperature and stirred for 26 h under argon. Silica gel (10 g) was added to the reaction flask and the solvent is evaporated under reduced pressure. The drypack was then flashed on silica gel (10 $\rightarrow$ 40% EtOAc/Hex) affording the desired pyridine **9** as a yellow oil (2.60 g, 84% yield): $R_f = 0.51$ (30% EtOAc/Hex); ^1H NMR (400 MHz, CDCl_3) δ 8.55 (dd, $J = 4.1, 0.8$ Hz, 1H), 7.66 (t, $J = 7.6$ Hz, 1H), 7.48 (d, $J = 7.8$ Hz, 1H), 7.41-7.32 (m, 4H), 7.31-7.28 (m, 1H), 7.17-7.13 (m, 1H), 4.70 (s, 2H), 4.65 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 158.6, 149.1, 138.0, 136.6, 128.5, 127.8, 122.4, 121.4, 73.2, 72.9; IR (neat) 3064, 3029, 2858, 1591, 1435, 1106, 1076, 698 cm^{-1} ; LRMS (APCI, Pos) calcd for $\text{C}_{13}\text{H}_{13}\text{NO}$ $[\text{M}+\text{H}]^+$: 200.1 m/z , observed: 200.0 m/z .

2-Benzyloxymethyl-N-benzoyliminopyridinium ylide (4e). The title compound was obtained as a yellow gum (87%) according to the general procedure: ^1H NMR (400 MHz, CDCl_3) δ 8.74 (d, $J = 6.3$ Hz, 1H), 8.18-8.15 (m, 2H), 7.99 (d, $J = 8.0$ Hz, 1H), 7.90 (t, $J = 7.7$ Hz, 1H), 7.52 (t, $J = 7.0$ Hz, 1H), 7.45-7.39 (m, 3H), 7.39-7.28 (m, 5H), 4.97 (s, 2H), 4.68 (s, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.9, 153.5, 144.7, 137.2(2), 130.3, 128.7, 128.2, 128.1, 127.9, 127.8, 124.3, 123.8, 73.7, 66.9; IR (neat) 3063, 2862, 1594, 1556, 1331, 909, 716 cm^{-1} ; LRMS (APCI, Pos) calcd for $\text{C}_{20}\text{H}_{18}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 319.1 m/z , observed: 319.1 m/z .

2-[3-(benzyloxy)propyl]pyridine (10). In a flame dried round bottom flask under argon was added NaH (700 mg (60% w/w in oil), 17.5 mmol) then 50 mL of THF. To this stirring suspension at room temperature was slowly added 2-pyridinepropanol (2.00 mL, 15.5 mmol) over 5 minutes. The reaction was stirred for 5 minutes then cooled to 0 °C. Benzyl bromide (1.84 mL, 15.5 mmol) was slowly added dropwise and the reaction was stirred at 0 °C for 20 minutes. The reaction was warmed to room temperature and stirred for 26 h under argon. Silica gel (10 g) was added to the reaction flask and the solvent was evaporated under reduced pressure. The drypack was then flashed on silica gel (10 $\rightarrow$ 40% EtOAc/Hex) affording the desired pyridine **10** as a yellow oil (2.87 g, 82% yield): $R_f = 0.53$ (30% EtOAc/Hex); ^1H NMR (400 MHz, CDCl_3) δ 8.50 (d, $J = 4.9$ Hz, 1H), 7.50 (t, $J = 5.8$ Hz, 1H), 7.34-7.28 (m, 4H), 7.28-7.22 (m, 1H), 7.10 (d, $J = 7.8$ Hz, 1H), 7.08-7.00 (m, 1H), 4.47 (s, 2H), 3.50 (t, $J = 6.3$ Hz, 2H), 2.88 (t, $J = 7.5$ Hz, 2H), 2.06 (qn, $J = 6.3$ Hz, 2H); ^{13}C NMR (100 MHz, CDCl_3) δ 161.6, 149.2, 138.6, 136.2, 128.3, 127.6, 127.4, 122.8, 120.9, 72.8, 69.5, 34.9, 29.6; IR (neat) 2857, 1591, 1569, 1475, 1435, 1101 737 cm^{-1} ; LRMS (APCI, Pos) calcd for $\text{C}_{15}\text{H}_{17}\text{NO}$ $[\text{M}+\text{H}]^+$: 228.1 m/z , observed: 228.1 m/z .

2-[3-(benzyloxy)propyl]-N-benzoyliminopyridinium ylide (4f). The title compound was obtained as a yellow oil (89%) according to the general procedure: ^1H NMR (400 MHz, CDCl_3) δ 8.58 (d, $J = 6.3$ Hz, 1H), 8.21-8.17 (m, 2H), 7.71 (t, $J = 7.9$ Hz, 1H), 7.46 (d, $J = 7.7$ Hz, 1H), 7.43-7.36 (m, 4H), 7.30-7.24 (m, 5H), 4.43 (s, 2H), 3.47 (t, $J = 5.8$ Hz, 2H), 3.18 (t, $J = 7.4$ Hz, 2H), 2.05 (qn, $J = 6.0$ Hz, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.9, 156.2, 145.6, 138.2, 137.4, 137.1, 130.0, 128.4, 128.0, 127.8, 127.7, 127.6, 126.9, 123.4, 72.8, 68.8, 29.3, 27.1; IR (neat) 3062, 2858, 1592, 1548, 1492, 1333, 1100, 911, 713 cm^{-1} ; LRMS (APCI, Pos) calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$: 347.2 m/z , observed: 347.2 m/z .

2,3-Dimethyl-N-benzoyliminopyridinium ylide (4g). The title compound was obtained as an orange oil (96%) according to the general procedure: ^1H NMR (300 MHz, CDCl_3) δ 8.16 (d, J = 6.2 Hz, 1H), 8.04-7.99 (m, 2H), 7.42 (d, J = 7.7 Hz, 1H), 7.24-7.18 (m, 3H), 7.12 (t, J = 6.7 Hz, 1H), 2.42 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.4, 152.4, 141.8, 138.2, 137.0, 135.9, 129.5, 127.5, 127.3, 122.2, 19.3, 15.1; IR (neat) 3063, 1592, 1548, 1335, 907, 713 cm^{-1} ; LRMS (APCI, Pos) calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 227.1 m/z , observed: 227.2 m/z .

2,5-Dimethyl-N-benzoyliminopyridinium ylide (4h). The title compound was obtained as an orange oil (98%) according to the general procedure: ^1H NMR (300 MHz, CDCl_3) δ 8.16 (s, 1H), 8.02-7.98 (m, 2H), 7.35 (d, J = 8.1 Hz, 1H), 7.22-7.16 (m, 4H), 2.38 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 169.2, 150.0, 143.6, 138.3, 137.0, 133.9, 129.4, 127.5, 127.3, 126.7, 18.3, 17.5; IR (neat) 2968, 1593, 1549, 1335, 909, 727, 712 cm^{-1} ; LRMS (APCI, Pos) calcd for $\text{C}_{14}\text{H}_{14}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 227.1 m/z , observed: 227.2 m/z .

Preparation of a stock solution of the catalyst. In a flame dried round bottom flask under argon was added complex **8e** (64 mg, 0.040 mmol) and toluene (15 mL) at room temperature. Iodine (15 mg, 0.061 mmol) in toluene (5 mL) was added to the flask and was stirred to 8 h in darkness under argon. The solvent and excess iodine was removed under reduced pressure and the catalyst dried under vacuum. The residue was redissolved in toluene (20 mL) under argon and used as a 2.0 mM catalyst stock solution.

General hydrogenation procedure : N-[(2S)-2-methylpiperidiny]benzamide (5a).³ In a flame dried 10 mL test tube under argon is added **4a** (42 mg, 0.20 mmol) and 2 mL of the catalyst stock solution (0.0040 mmol, 2 mol %). The reaction is stirred under argon until **4a** is dissolved. The test tube is inserted in a high pressure hydrogenation vessel and purged three times with 100 psi of hydrogen. A pressure of 400 psi of hydrogen is applied, the vessel is sealed and the reaction is stirred at room temperature for 6 h. The pressure is released and the reaction is poured directly on a pad of silica gel (6(h) x 1(w) cm), washed with 10 mL of dichloromethane and the product is recovered using 20 mL of 50% EtOAc/ CH_2Cl_2 . The solvent is removed under reduced pressure affording the crude mixture of **5a** and **7a** (89:11, 42 mg, 98% yield). The residue is dissolved in a round bottom flask with 2 mL of MeOH and 10% Pd/C (2 mg, 1 mol %) is added. The flask is purged three times by cycle of vacuum/hydrogen and the reaction is stirred under 1 atmosphere of hydrogen at room temperature for 1 h. The solvent is reduced under pressure, the residue dissolved in 50% EtOAc/ CH_2Cl_2 and filtered on a short silica gel pad (2(h) x 1(w) cm). The solvent is removed under reduced pressure affording the desired product **5a** as a white solid (42 mg, 98% yield, 90% ee): enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H+AS, 70:30 hexanes:*i*-PrOH, 0.7 mL/min: (*R*)-**5a** t_r = 13.3 min, (*S*)-**5a** t_r = 21.6 min); R_f = 0.29 (50% EtOAc/Hex); mp 158 $^\circ\text{C}$; $[\alpha]_D^{25}$ +34.0 (c 2.2, CH_2Cl_2); ^1H NMR (300 MHz, CDCl_3) * denotes minor conformers δ 7.83* (d, J = 7.1 Hz), 7.72 (d, J = 6.9 Hz, 2H), 7.47 (t, J = 7.4 Hz, 1H), 7.39 (t, J = 6.9 Hz, 2H), 6.63 (s(br), 1H), 6.23* (s(br)), 3.26-3.14 (m, 1H), 2.67-2.52 (m, 2H), 1.87-1.58 (m, 4H), 1.58-1.36 (m, 1H), 1.35-1.16 (m, 1H), 1.14 (d, J = 6.2 Hz, 3H), 0.94* (d, J = 6.2 Hz); ^{13}C NMR (75 MHz, CDCl_3) * denotes minor conformers δ 166.2, 134.3, 131.6, 130.8*, 129.4*, 128.7, 127.6*, 127.1, 60.8, 57.5, 33.7, 25.7, 24.1, 20.0; IR (neat) 3189, 3031, 2926, 1641, 1557, 1307, 692 cm^{-1} ; LRMS (APCI, Pos) calcd for $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}$ $[\text{M}+\text{H}]^+$: 219.1 m/z , observed: 219.1 m/z . Rapid recrystallization in boiling ethyl acetate afforded **5a** (84% yield, 97% ee).

N-[(2S)-2-ethylpiperidinyl]benzamide (5b). The title compound was obtained as a white solid (96% yield, 83% ee) according to the general hydrogenation procedure: enantiomeric excess was determined by HPLC analysis (Chiralcel OD, 97:3 hexanes:*i*-PrOH, 1.0 mL/min: (*R*)-**5b** t_r = 28.1 min, (*S*)-**5b** t_r = 51.2 min); R_f = 0.40 (50% EtOAc/CH₂Cl₂); mp 164 °C; $[\alpha]_D^{25} +38.0$ (c 2.3, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) * denotes minor conformers δ 7.80* (d, J = 7.0 Hz), 7.69 (d, J = 7.0 Hz, 2H), 7.42 (t, J = 7.0 Hz, 1H), 7.34 (t, J = 7.0 Hz, 2H), 6.88 (s(br), 1H), 6.25* (s(br)), 3.24-3.10 (m, 1H), 2.68-2.51 (m, 1H), 2.48-2.31 (m, 1H), 1.82-1.51 (m, 5H), 1.50-1.29 (m, 2H), 1.29-1.09 (m, 1H), 0.83 (t, J = 7.5 Hz, 3H), 0.63* (t, J = 7.5 Hz); ¹³C NMR (100 MHz, CDCl₃) * denotes minor conformers δ 166.0, 134.2, 131.5, 130.9*, 129.4*, 128.6, 127.6*, 127.1, 66.1, 57.7, 29.7, 25.9, 25.3, 24.0; IR (neat) 3234, 3064, 2934, 2856, 1646, 1552, 1310, 695 cm⁻¹; LRMS (APCI, Pos) calcd for C₁₄H₂₀N₂O $[M+H]^+$: 233.2 m/z , observed: 233.2 m/z . Rapid recrystallization in boiling ethyl acetate afforded **5b** (78% yield, 94% ee).

***N*-[*(2S)*-2-*n*-propylpiperidinyl]benzamide (**5c**).** The title compound was obtained as a white solid (98% yield, 84% ee) according to the general hydrogenation procedure: enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H, 80:20 hexanes:*i*-PrOH, 1.0 mL/min: (*R*)-**5c** t_r = 5.4 min, (*S*)-**5c** t_r = 7.7 min); R_f = 0.44 (50% EtOAc/CH₂Cl₂); mp 140 °C; $[\alpha]_D^{25} +45.0$ (c 2.4, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) * denotes minor conformers δ 7.84* (d, J = 7.0 Hz), 7.71 (d, J = 7.0 Hz, 2H), 7.47 (t, J = 7.3 Hz, 1H), 7.39 (t, J = 7.3 Hz, 2H), 6.72 (s(br), 1H), 6.19* (s(br)), 3.29-3.14 (m, 1H), 2.74-2.58 (m, 1H), 2.57-2.41 (m, 1H), 1.86-1.52 (m, 5H), 1.51-1.10 (m, 6H), 0.84 (t, J = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) * denotes minor conformers δ 166.1, 134.3, 131.7, 128.8, 127.7*, 127.2, 65.1, 57.9, 35.4, 30.4, 25.3, 24.1, 18.9, 14.7; IR (neat) 3236, 2933, 1645, 1551, 1304, 917, 694 cm⁻¹; LRMS (APCI, Pos) calcd for C₁₅H₂₂N₂O $[M+H]^+$: 247.2 m/z , observed: 247.2 m/z . Rapid recrystallization in boiling ethyl acetate afforded **5c** (75% yield, 95% ee).

***N*-[*(2R)*-2-benzylpiperidinyl]benzamide (**5d**).** The title compound was obtained as a white solid (97% yield, 58% ee) according to the general hydrogenation procedure: enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H, 80:20 hexanes:*i*-PrOH, 1.0 mL/min: (*S*)-**5d** t_r = 8.8 min, (*R*)-**5d** t_r = 10.9 min); R_f = 0.44 (50% EtOAc/CH₂Cl₂); mp 127 °C; $[\alpha]_D^{25} -1.0$ (c 2.9, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) * denotes minor conformers δ 7.94* (d, J = 7.2 Hz), 7.67 (d, J = 7.3 Hz, 2H), 7.51 (t, J = 7.3 Hz, 1H), 7.42 (t, J = 7.3 Hz, 2H), 7.28-7.22 (m, 2H), 7.21-7.15 (m, 3H), 7.07* (d, J = 7.1 Hz), 6.87 (s(br), 1H), 6.43* (s(br)), 3.36-3.27 (m, 1H), 3.21 (dd, J = 13.6, 4.4 Hz, 1H), 2.95-2.81 (m, 1H), 2.78-2.67 (m, 1H), 2.64 (dd, J = 13.6, 8.6 Hz, 1H), 1.91-1.76 (m, 1H), 1.76-1.62 (m, 3H), 1.54-1.39 (m, 1H), 1.30-1.13 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) * denotes minor conformers δ 166.2, 139.5, 134.1, 131.7, 129.5, 128.7, 128.5, 127.2, 126.2, 66.5, 57.9, 40.4, 30.9, 25.5, 23.9; IR (neat) 3217, 3054, 2920, 2846, 1640, 1299, 696, 664 cm⁻¹; LRMS (APCI, Pos) calcd for C₁₉H₂₂N₂O $[M+H]^+$: 295.2 m/z , observed: 295.2 m/z .

***N*-[(2*R*)-2-(benzyloxymethyl)piperidiny]benzamide (5e).** The title compound was obtained as a white solid (85% yield, 76% ee) according to the general hydrogenation procedure: enantiomeric excess was determined by HPLC analysis (Chiralpak AS, 80:20 hexanes:*i*-PrOH, 1.0 mL/min: (*S*)-**5e** t_r = 6.7 min, (*R*)-**5e** t_r = 11.2 min); R_f = 0.40 (50% EtOAc/CH₂Cl₂); mp 109 °C; $[\alpha]_D$ +2.0 (c 2.6, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) * denotes minor conformers δ 7.66 (d, J = 7.5 Hz, 2H), 7.52 (s(br), 1H), 7.45 (t, J = 7.4 Hz, 1H), 7.34-7.24 (m, 5H), 7.23-7.16 (m, 2H), 4.43 (s, 2H), 3.80 (dd, J = 9.9, 6.0 Hz, 1H), 3.50 (dd, J = 9.9, 3.2 Hz, 1H), 3.37-3.28 (m, 1H), 2.99-2.84 (m, 1H), 2.73-2.60 (m, 1H), 1.88-1.65 (m, 4H), 1.65-1.51 (m, 1H), 1.41-1.25 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) * denotes minor conformers δ 165.4, 137.8, 134.1, 131.4, 128.6, 128.5, 128.1, 127.8, 127.1, 73.9, 73.7, 64.2, 56.7, 29.2, 25.3, 23.4; IR (neat) 3255, 3067, 2921, 2844, 1634, 1553, 1305, 1103, 694, 661 cm⁻¹; LRMS (APCI, Pos) calcd for C₂₀H₂₄N₂O₂ [M+H]⁺: 325.2 m/z , observed: 325.2 m/z .

***N*-[(2*R*)-2-[(3-benzyloxy)propyl]piperidiny]benzamide (5f).** The title compound was obtained as a white solid (88% yield, 88% ee) according to the general hydrogenation procedure: enantiomeric excess was determined by HPLC analysis (Chiralpak AS, 80:20 hexanes:*i*-PrOH, 1.0 mL/min: (*S*)-**5f** t_r = 6.5 min, (*R*)-**5f** t_r = 10.7 min); R_f = 0.39 (50% EtOAc/CH₂Cl₂); mp 98 °C; $[\alpha]_D$ +26.0 (c 2.6, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) * denotes minor conformers δ 7.88* (d, J = 7.1 Hz), 7.73 (d, J = 7.4 Hz, 2H), 7.50 (t, J = 7.3 Hz, 1H), 7.40 (t, J = 7.4 Hz, 2H), 7.34-7.21 (m, 5H), 6.83 (s(br), 1H), 6.19* (s(br)), 4.51-4.41 (m, 2H), 3.54-3.40 (m, 1H), 3.34-3.21 (m, 1H), 2.77-2.51 (m, 2H), 1.91-1.40 (m, 9H), 1.39-1.19 (m, 1H); ¹³C NMR (75 MHz, CDCl₃) * denotes minor conformers δ 166.2, 138.6, 134.3, 131.6, 128.7, 128.5, 127.8, 127.6, 127.2, 72.9, 70.6, 64.6, 57.7, 30.3, 29.8, 25.6, 25.3, 24.0; IR (neat) 3246, 2942, 2855, 2804, 1643, 1538, 1304, 1289, 1102, 728, 693 cm⁻¹; LRMS (APCI, Pos) calcd for C₂₂H₂₈N₂O₂ [M+H]⁺: 353.2 m/z , observed: 353.2 m/z .

N-[(2S,3S)-2,3-dimethylpiperidinyllbenzamide (5g).⁴ The title compound was obtained as a white solid (91% yield, >95:5 diastereoselectivity, 54% ee) according to the general hydrogenation procedure: enantiomeric excess was determined by HPLC analysis (Chiralpak AD-H, 80:20 hexanes:*i*-PrOH, 1.0 mL/min: (2*R*,3*R*)-**5g** t_r = 6.2 min, (2*S*,3*S*)-**5g** t_r = 7.9 min); R_f = 0.46 (50%

EtOAc/CH₂Cl₂); mp 188 °C; $[\alpha]_D^{25} +18.0$ (c 2.2, CH₂Cl₂); ¹H NMR (400 MHz, CDCl₃) * denotes minor conformers δ 7.84* (d, J = 7.3 Hz), 7.75 (d, J = 7.3 Hz, 2H), 7.51 (t, J = 7.4 Hz, 1H), 7.43 (t, J = 7.6 Hz, 2H), 6.98 (s(br), 1H), 6.24* (s(br)), 3.18-2.99 (m, 2H), 2.91-2.77 (m, 1H), 2.55-2.34* (m), 2.07-1.95 (m, 1H), 1.93-1.80 (m, 1H), 1.80-1.75* (m), 1.71-1.60 (m, 1H), 1.58-1.37 (m, 2H), 1.21* (d, J = 6.2 Hz), 1.07 (d, J = 6.5 Hz, 3H), 1.01 (d, J = 7.0 Hz, 3H), 0.96* (d, J = 6.6 Hz), 0.93* (d, J = 6.4 Hz), 0.77* (d(br), J = 5.1 Hz); ¹³C NMR (100 MHz, CDCl₃) * denotes minor conformers δ 166.0, 134.4, 131.6, 130.9*, 129.4*, 128.8, 127.6*, 127.2, 61.7, 54.2, 34.3, 29.3, 22.6, 15.0, 12.6; IR (neat) 3235, 3074, 2926, 1646, 1552, 1306, 695, 664 cm⁻¹; LRMS (APCI, Pos) calcd for C₁₄H₂₀N₂O [M+H]⁺: 233.2 m/z , observed: 233.2 m/z .

N-[(2S,5R)-2,5-dimethylpiperidinyllbenzamide (5h).⁴ The title compound was obtained as a white solid (92% yield, 57:43 diastereoselectivity (5h:5h'), 84% ee and 86% ee respectively) according to the general hydrogenation procedure: enantiomeric excess was determined by HPLC

analysis (Chiralpak AS, 80:20 hexanes:*i*-PrOH, 1.0 mL/min: (2*R*,5*S*)-**5h** t_r = 11.0 min, (2*S*,5*R*)-**5h** t_r = 16.5 min); R_f = 0.58 (50% EtOAc/CH₂Cl₂); mp 129 °C; ¹H NMR (300 MHz, CDCl₃+5% TFA) δ 11.80 (s(br), 2H), 7.97 (d, J = 7.3 Hz, 2H), 7.63 (t, J = 7.4 Hz, 1H), 7.53 (t, J = 7.7 Hz, 2H), 4.53-4.30 (m, 2H), 3.47-3.34 (m, 1H), 2.49-2.34 (m, 1H), 2.07-1.85 (m, 2H), 1.74-1.61 (m, 1H), 1.42 (d, J = 6.5 Hz, 3H), 1.31 (d, J = 7.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃+5% TFA) δ 166.1, 133.8, 129.8, 129.3, 128.0, 62.7, 61.1, 28.6, 27.7, 27.4, 17.0, 16.5; IR (neat) 3257, 2928, 1650, 1550, 1303, 1289, 906, 693 cm⁻¹; LRMS (APCI, Pos) calcd for C₁₄H₂₀N₂O [M+H]⁺: 233.2 m/z , observed: 233.2 m/z . **N-[(2S,5S)-2,5-dimethylpiperidinyllbenzamide (5h').**⁴ enantiomeric excess was determined

by HPLC analysis (Chiralpak AS, 80:20 hexanes:*i*-PrOH, 1.0 mL/min: (2*R*,5*R*)-**5h'** t_r = 7.0 min, (2*S*,5*S*)-**5h'** t_r = 15.6 min); R_f = 0.50 (50% EtOAc/CH₂Cl₂); mp 153 °C; ¹H NMR (400 MHz, CDCl₃) * denotes minor conformers δ 7.88* (d, J = 7.7 Hz), 7.77 (d, J = 7.5 Hz, 2H), 7.52 (t, J = 7.3 Hz, 1H), 7.45 (t, J = 7.7 Hz, 2H), 6.81 (s(br), 1H), 6.22* (s(br)), 3.29-3.21 (m, 1H), 3.21-3.15* (m), 2.80-2.55 (m, 1H), 2.51-2.30 (m, 1H), 2.27-2.15* (m), 2.05-1.90 (m, 1H), 1.82-1.69 (m, 2H), 1.64-1.51 (m, 1H), 1.21 (d, J = 6.1 Hz, 3H), 1.09-0.96 (m, 1H), 0.91 (d, J = 6.6 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) * denotes minor conformers δ 166.2, 131.8, 131.0*, 129.6*, 128.8, 127.7*, 127.2, 64.8, 60.5, 33.4, 32.9, 31.3, 19.8, 19.4; IR (neat) 3203, 3045, 2953, 2817, 1640, 1560, 1306, 697, 668 cm⁻¹; LRMS (APCI, Pos) calcd for C₁₄H₂₀N₂O [M+H]⁺ : 233.2 m/z , observed: 233.2 m/z .

Iridium(I) complexes synthesis

(4*S*)-2-Bromophenyl-4-*t*-butyl-4,5-dihydrooxazole (11). Triethylamine (1.5 mL, 10.8 mmol) and *S*-*t*-leucinol (1.00 g, 8.53 mmol) were dissolved in CH₂Cl₂ at room temperature under argon. The reaction solution was cooled to 0 °C and 2-bromobenzoyl chloride (1.2 mL, 9.2 mmol) was added slowly dropwise over 5 minutes. The reaction was stirred at room temperature for 4 h, diluted with 30 mL of water and extracted twice with ethyl acetate (15 mL). The combined organic phases were washed with 10 mL of brine then dried with Na₂SO₄, filtered and the solvent was removed under reduced pressure to afford the crude chiral amide as a white solid (2.6 g), which was used without further purification. Thionyl chloride (9 mL) was stirred and cooled to -10 °C and then the crude amide was added portionwise over 10 minutes. The reaction was then stirred and let to warm to room temperature for 2 h. The thionyl chloride was removed under reduced pressure. The resulting residue was dissolved in 25 mL of CH₂Cl₂ and 25 mL of 10% NaOH were added and the biphasic mixture was stirred vigorously for 1 h. The aqueous phase was extracted three times with dichloromethane (10 mL), the combined organic phases were dried with Na₂SO₄, filtered and the

solvent was removed under reduced pressure. The crude was purified on silica gel (50% Et₂O/Hexanes) affording the desired product **11** (2.33 g, 95% yield over two steps) as a pale yellow oil: ¹H NMR (400 MHz, CDCl₃) δ 7.69-7.60 (m, 2H), 7.34 (dd, *J* = 7.5, 1.3 Hz, 1H), 7.27 (dd, *J* = 7.8, 2.0 Hz, 1H), 4.39 (dd, *J* = 10.2, 8.7 Hz, 1H), 4.27 (t, *J* = 8.3 Hz, 1H), 4.11 (dd, *J* = 10.2, 7.9 Hz, 1H), 1.00 (s, 9H). The product was spectroscopically comparable to literature values.⁵

Bis(4-methoxyphenyl)chlorophosphine (12d). The compound was synthesized according to the literature procedure: ³¹P NMR (121 MHz, CDCl₃) δ 85.4 (s). Spectroscopic data was consistent with that reported.⁶

Bis(4-fluorophenyl)chlorophosphine (12e). The compound was synthesized according to the literature procedure: ³¹P NMR (121 MHz, CDCl₃) δ 80.3 (t, *J* = 5.1 Hz). Spectroscopic data was consistent with that reported.⁶

Bis[4-(trifluoromethyl)phenyl]chlorophosphine (12f). The compound was synthesized according to the literature procedure: ³¹P NMR (162 MHz, CDCl₃) δ 76.0 (s). Spectroscopic data was consistent with that reported.⁶

Bis(pentafluorophenyl)chlorophosphine (12g). The compound was synthesized according to the literature procedure: ³¹P NMR (162 MHz, CDCl₃) δ 36.4 (quint, *J* = 38.0 Hz). Spectroscopic data was consistent with that reported.⁷

General procedure for iridium complex synthesis. Complex (8d). To a flame dried round bottom flask under argon was dissolved **11** (102 mg, 0.36 mmol) in diethyl ether (5 mL). The resulting solution was cooled to -78 °C and *n*-BuLi (1.6M/Hexanes, 0.250 mL, 0.40 mmol) was added by slow dropwise over a period of 5 minutes. The reaction was stirred at -78 °C for another 20 minutes then **12d** (112 mg, 0.40 mmol) was added and the flask was let to stir and slowly warm to room temperature and stirred for 12 h. The reaction

mixture was filtered through a pad of silica gel (degassed) under argon to remove metallic salts and the solvent was removed under reduced pressure affording the crude ligand as a pale yellow gum and was used without further purification. The crude ligand (120 mg, 0.268 mmol) was dissolved in dichloromethane (4 mL) in a flame dried round bottom flask under argon. [Ir(COD)Cl]₂ (90 mg, 0.134 mmol) was added to the solution and the reaction was stirred at 40 °C for 1 h. The reaction was cooled to room temperature and NaBArF (340 mg, 0.384 mmol) and water (4 mL) were added and the reaction mixture was stirred for 30 minutes. The reaction mixture was extracted twice with dichloromethane, the organic phases combined and the solvent removed under reduced pressure. The residue was purified on silica gel (100% CH₂Cl₂) affording the desired iridium complex **8d** (289 mg, 67% yield) as a bright red solid: mp 74 °C; [α]_D -179 (c 0.75, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 8.22-8.16 (m, 1H), 7.76-7.70 (m, 8H), 7.64-7.59 (m, 2H), 7.54 (s, 4H), 7.42-7.30 (m, 3H), 7.06-6.98 (m, 4H), 6.98-6.93 (m, 2H), 4.96-4.88 (m, 2H), 4.60 (dd, *J* = 9.8, 2.6 Hz, 1H), 4.34 (t, *J* = 9.4 Hz, 1H), 3.96 (dd, *J* = 9.1, 2.9 Hz, 1H), 3.85 (s, 3H), 3.84 (s, 3H), 3.52-3.46 (m, 1H), 3.11-3.02 (m, 1H), 2.63-2.36 (m, 4H), 2.08-1.95 (m, 2H), 1.70-1.58 (m, 1H), 1.51-1.38 (m, 1H), 0.70 (s, 9H); ³¹P NMR (121 MHz, CDCl₃) δ 14.9 (s); IR (neat) 2967, 1596, 1353, 1273, 1116 cm⁻¹; LRMS (APCI, Pos) calcd for C₃₅H₄₂IrNO₃P [M-BArF]⁺: 748(100), 746(57), 749(38), 747(23), 750(8) *m/z*, observed: 748(100), 746(61), 749(37), 747(19), 750(9) *m/z*.

Complex (8e). The complex was synthesized using the general procedure to afford **8e** as a bright red solid: mp 83 °C; [α]_D -175 (c 0.45, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 8.24-8.15 (m, 1H), 7.76-7.70 (m, 8H), 7.67-7.59 (m, 2H), 7.54 (s, 4H), 7.52-7.43 (m, 2H), 7.35-7.06 (m, 7H), 5.07-4.97 (m, 2H), 4.60 (dd, *J* = 9.9, 2.8 Hz, 1H), 4.35 (t, *J* = 9.2 Hz, 1H), 3.96 (dd, *J* = 8.9, 2.6 Hz, 1H), 3.48-3.39 (m, 1H), 3.02-2.90 (m, 1H), 2.61-2.39 (m, 4H), 2.14-1.93 (m, 2H), 1.76-1.60 (m, 1H), 1.55-1.38 (m, 1H), 0.68 (s, 9H); ³¹P NMR (121 MHz, CDCl₃) δ 16.2 (t, *J* = 2.4 Hz); ¹⁹F NMR (282 MHz, CDCl₃) δ -62.8 (s), -104.4 (m), -105.4 (m); IR (neat) 2967, 1594, 1353, 1272, 1116 cm⁻¹; LRMS (APCI, Pos) calcd for C₃₃H₃₆F₂IrNOP [M-BArF]⁺: 724(100), 722(57), 725(36), 723(21), 726(7) *m/z*, observed: 724(100), 722(55), 725(34), 723(20), 726(7) *m/z*.

Complex (8f). The complex was synthesized using the general procedure to afford **8f** as a bright red solid: mp 144 °C; [α]_D -166 (c 0.48, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 8.26-8.17 (m, 1H), 7.89-7.81 (m, 2H), 7.80-7.70 (m, 10H), 7.70-7.65 (m, 4H), 7.54 (s, 4H), 7.35-7.23 (4H), 5.17-5.02 (m, 2H), 4.60 (dd, *J* = 9.9, 2.5 Hz, 1H), 4.34 (t, *J* = 9.6 Hz, 1H), 3.97 (dd, *J* = 8.9, 2.5 Hz, 1H), 3.51-3.40 (m, 1H), 3.00-2.87 (m, 1H), 2.63-2.37 (m, 4H), 2.14-1.95 (m, 2H), 1.78-1.61 (m, 1H), 1.56-1.41 (m, 1H), 0.64 (s, 9H); ³¹P NMR (121 MHz, CDCl₃) δ 17.7 (s); ¹⁹F NMR (282 MHz, CDCl₃) δ -62.8 (s), -63.9 (s), -64.0 (s); IR (neat) 2968, 1354, 1324, 1273, 1115, 1061 cm⁻¹; LRMS (APCI, Pos) calcd for C₃₅H₃₆F₆IrNOP [M-BArF]⁺: 824(100), 822(57), 825(38), 823(22), 826(7) *m/z*, observed: 824(100), 822(54), 825(32), 823(20), 826(7) *m/z*.

Complex (8g). The complex was synthesized using the general procedure to afford **8g** as an orange solid: mp 79 °C; [α]_D -102 (c 0.38, CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 8.22-8.12 (m, 1H), 7.76-7.70 (m, 8H), 7.69-7.58 (m, 3H), 7.54 (s, 4H), 5.33-5.21 (m, 1H), 4.99 (quint, *J* = 7.6 Hz, 1H), 4.65 (dd, *J* = 10.1, 3.0 Hz, 1H), 4.39 (t, *J* = 9.6 Hz, 1H), 4.08 (dd, *J* = 9.6, 3.1 Hz, 1H), 4.02-3.93 (m, 1H), 2.80-2.66 (m, 1H), 2.65-2.49 (m, 2H), 2.46-2.24 (m, 2H), 2.18-1.96 (m, 2H), 1.83-1.66 (m, 1H), 1.66-1.48 (m, 1H), 0.82 (s, 9H); ³¹P NMR (121 MHz, CDCl₃) δ -10.9 (m); ¹⁹F NMR (282 MHz, CDCl₃) δ -62.9 (s), -140.8 (m), -141.5 (m); IR (neat) 2967, 1522, 1474, 1354, 1274, 1117, 1094, 983 cm⁻¹; LRMS (APCI, Pos) calcd for C₃₃H₂₈F₁₀IrNOP [M-BArF]⁺: 868(100), 866(57), 869(35), 867(21), 870(6) *m/z*, observed: 868(100), 866(54), 869(36), 867(23), 870(4) *m/z*.

1 Shriver, D. F.; Drezdson, M. A. *The manipulation of air-sensitive compounds*; 2nd Edition; Wiley: New York, 1986.

2 Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

3 Absolute configuration was determined by cleavage of a 70% ee hydrogenation product, benzoylation and comparison of optical rotation with a value of the literature. [α]_D (expt.) +28.9 (c 0.40, CHCl₃); [α]_D (lit)⁸ +32.9 (c 0.8, CHCl₃). Other hydrogenation products were assigned by analogy and based on the relative retention of their respective enantiomers.

4 Assignment of relative configuration of **5g** was done by comparison of ¹³C chemical shifts based on the conformational analysis of the corresponding N-methylpiperidine.⁹ Assignments of **5h** and **5h'** were done by coupling constant analysis and confirmed by the comparison of ¹³C chemical shifts.

5 Zhou, Q.-L.; Pfaltz, A. *Tetrahedron* **1994**, *50*, 4467-4478.

6 Casalnuovo, A. L.; RajanBabu, T. V.; Ayers, T. A.; Warren, T. H. *J. Am. Chem. Soc.* **1994**, *116*, 9869-9882.

7 RajanBabu, T. V.; Radetich, B.; You, K. K.; Ayers, T. A.; Casalnuovo, A. L.; Calabrese, J. C. *J. Org. Chem.* **1999**, *64*, 3429-3447.

8 Al-Sehemi, A. G.; Atkinson, R. S.; Fawcett, J. *J. Chem. Soc., Perkin Trans. 1* **2002**, 257-274.

9 Eliel, E. L.; Kandasamy, D.; Yen, C.-Y.; Hargrave, K. D. *J. Am. Chem. Soc.* **1980**, *102*, 3698-3707.

^1H and ^{13}C spectra of selected compounds