Enantioselective Syn-Selective Scandium-Catalyzed Ene Reactions

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Supporting Information

General Information. All reactions were carried out under an atmosphere of argon or nitrogen in oven-dried glassware with magnetic stirring. THF, toluene, ether, and CH_2Cl_2 were purified by passage through a bed of activated alumina.¹ Solvents and reagents were purified prior to use following the guidelines of Perrin and Armarego.² Purification of reaction products was carried out by flash chromatography using EM Reagent silica gel 60 (230-400 mesh). Analytical thin layer chromatography was performed on EM Reagent 0.25 mm silica gel 60-F plates. Visualization was accomplished with UV light and ceric ammonium nitrate stain followed by heating. Optical rotations were measured on a Jasco DIP-0181 digital polarimeter with a sodium lamp and are reported as follows: $[\alpha]_D^{T^\circ\text{C}}$ (c g/100 mL, solvent). Infrared spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer. ^1H NMR spectra were recorded on a Varian Inova-500 (500 MHz) or Varian Mercury-400 (400 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl_3 at 7.26 ppm). Data reported as (s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, brs=broad; integration; coupling constant(s) in Hz). Proton-decoupled ^{13}C NMR spectra were recorded on Varian Inova-500 (125 MHz) or Varian Mercury-400 (100 MHz) spectrometer and are reported in ppm using solvent as an internal standard (CDCl_3 at 77.0 ppm). High resolution mass spectra were obtained on Jeol AX-505 or SX-102 spectrometers at the Harvard University Mass Spectrometry Laboratory. Analytical high performance liquid chromatography (HPLC) was performed on a Hewlett-Packard 1100 Series HPLC with a diode array detector using the indicated chiral column.

Preparation of *N*-Phenyl Glyoxamide³

3-Methyl-N-phenylbut-2-enamide: A previously dried round-bottom flask was charged with aniline (12.0 mL, 132 mmol), pyridine (19.4 mL, 239 mmol) and Et₂O (400 mL). The solution was cooled to 0 °C and 3,3-dimethylacryloyl chloride (14.4

mL, 129 mmol) was added dropwise (cannula transfer), forming a white paste. The ice bath was removed and the mixture was stirred at rt for 75 min. Then the mixture was diluted with Et₂O and washed 3 times with HCl 10% (v/v), saturated aqueous NaHCO₃, and brine. The organic phase was dried over MgSO₄, filtered and concentrated under reduced pressure. The unpurified solid (>95% pure as indicated by ¹H NMR spectroscopy) was used without any further purification. *R*_f 0.24 (20% EtOAc in hexanes); IR (neat) 3301, 3132, 3068, 2973, 1663, 1641, 1599, 1538, 1439, 1310, 1251, 1164, 753, 693 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.54 (d, 2H, *J* = 7 Hz), 7.35 (brs, 1H), 7.29 (t, 2H, *J* = 7 Hz), 7.07 (t, 1H, *J* = 7 Hz), 5.72 (s, 1H), 2.21 (d, 3H, *J* = 1 Hz), 1.88 (d, 3H, *J* = 1 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 165.1, 153.2, 138.2, 128.9, 123.9, 119.7, 118.7, 27.3, 19.9; HRMS (ES): Exact mass calcd for

C₁₁H₁₃NO [M+H]⁺, requires *m/z*: 176.1075, found *m/z*: 176.1073.

N-Phenyl Glyoxamide (2b): A 500-mL round-bottom flask equipped with a stirbar, 3-methyl-N-phenylbut-2-enamide (14.0 g, 79.9 mmol) was solubilized using ACS reagent grade CH₂Cl₂ (100 mL) and MeOH (100 mL). The flask was fitted with a septum, flushed using a N₂ stream and then cooled to -78 °C (a white precipitate forms upon cooling). Once at this temperature (internal monitoring), ozone/oxygen was introduced into the reaction using a fritted glass inlet at an approx. rate of 5 L per minute. The reaction was monitored by TLC and was found at all times to be complete upon appearance of the blue coloration of the saturated ozone solution. Oxygen was bubbled through for 15 min, yielding a clear colorless solution. Methyl sulfide (29.3 mL, 399 mmol) was then added and the dry ice/acetone bath was removed. Stirring was continued until all ozonide [*R*_f 0.18 (20% EtOAc in hexanes)] was consumed (2.5 – 3 hrs). The solution was then concentrated at 50 Torr and the resulting crude oil was transferred to a separatory funnel using Et₂O and diluted to a total volume of approx. 3.5 L. The solution was washed 4 times with water (150 mL) and concentrated under reduced pressure. Then, MeOH was azeotroped by adding Et₂O (~100 mL) and H₂O (~15 mL) and concentrated in vacuo at ~10 Torr (repeated once). At this stage a white solid forms, determined to be the hydrate of the title compound. Recrystallization from 1,2-dichloroethane (310 mL, avoid heating above 50 °C, allowed to stand at room temperature overnight) affords, after filtration and wash with cold CH₂Cl₂, 8.1 g (61%) of the title compound as colorless needles. mp = 110-113 °C; ¹H NMR (400 MHz, DMSO-*d*₆) δ 9.73 (s,

1H), 7.69-7.65 (m, 2H), 7.31-7.26 (m, 2H), 7.06-7.03 (m, 1H), 6.59 (d, 2H, $J = 7$ Hz), 5.06 (t, 1H, $J = 7$ Hz). A portion of this solid was then dehydrated by vacuum sublimation as follows: *N*-phenyl glyoxamide hydrate (4.0 g, 23.9 mmol) was charged in a vacuum sublimation apparatus. The vessel was immersed in an oil bath (65 °C), covered with aluminum foil, and after 5 min the flask was carefully opened to vacuum (55 mTorr). After 5 min, water was allowed to flow to the condenser. Then the temperature was slowly increased to 105 °C (~30 °C/hr). Sublimation occurred overnight, forming a slightly yellow solid and a dark orange tar at the bottom of the vessel. The next morning, the apparatus was cooled to room temperature, filled with argon and the pale yellow solid was isolated under inert atmosphere to afford 2.62 g (73%) of the title that was homogeneous as judged by ¹H NMR spectroscopy. IR (neat) 3332, 3118, 3056, 2868, 1737, 1682, 1600, 1551, 1493, 1444, 761, 716, 693 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.38 (s, 1H), 8.37 (brs, 1H), 7.66 (dd, 2H, $J = 1, 8$ Hz), 7.21 (tt, 1H, $J = 1, 7$ Hz); ¹³C NMR (100 MHz, CDCl₃) δ 188.8, 157.6, 136.0, 129.6, 125.9, 120.1.

General Procedure A: Scandium-Catalyzed Carbonyl Ene Reaction: To an oven-dried, 4-mL vial containing a magnetic stirring bar was added (*S,S,S,S*)-bis(indan-oxazoliny)pyridine⁴ (2.2 mg, 0.0055 mmol), Sc(OTf)₃ (2.4 mg, 0.005 mmol), and 4Å MS (10.0 mg, 100 mg/mmol) in an inert atmosphere (N₂) glove box. For Table 1, entries 5 - 9, (*S,S*)-bis(phenyloxazoliny)pyridine (2.0 mg, 0.0055 mmol) was used instead. To a separate vial was added **2b** (14.9 mg, 0.1 mmol). Both vials were fitted with serum caps and removed from the inert atmosphere box. The vial containing the metal/ligand was charged with CH₂Cl₂ (0.6 mL). The resulting suspension was stirred at room temperature for 1.5 h. To this solution was added the appropriate olefin (6 equiv) followed by **2b** (14.9 mg, 0.1 mmol) as a solution in CH₂Cl₂ (0.4 mL) via syringe. The vial that had contained **2b** was rinsed with CH₂Cl₂ (0.2 mL) and the solution was transferred to the reaction vial via syringe. For Table 1, entries 5 – 9, 12 equiv of olefin were used. The solution was stirred at ambient temperature overnight at which point all reactions were deemed complete by TLC. The reaction mixture was then loaded directly onto a silica gel flash column and eluted with the indicated solvent to provide the title compounds.

Preparation of (*S*)-2-hydroxy-*N*,4-diphenylpent-4-enamide (1b**):** The indicated compound was prepared according to General Procedure A and isolated by flash chromatography (15% EtOAc/hexanes) as a white solid that was homogeneous as judged by ¹H NMR spectroscopy (78% yield): mp 113-116 °C; [α]_D -12.8 ° ($c = 0.74$, CHCl₃); IR (film) 3366, 3056, 2928, 1666, 1599, 1532, 1496, 1445, 1316, 1078, 754, 693 cm⁻¹.

¹; ¹H NMR (400 MHz, CDCl₃) δ 8.43 (brs, 1H), 7.51 (dd, 2H, *J* = 7.8, 18.1 Hz), 7.34-7.29 (m, 2H), 7.12 (t, 1H, *J* = 7.3 Hz), 5.53 (s, 1H), 5.26 (s, 1H), 4.25-4.23 (m, 1H), 3.45 (dd, 1H, *J* = 2.0, 14.6 Hz), 2.73 (dd, 1H, *J* = 9.8, 14.6 Hz), 2.64 (d, 1H, *J* = 2.9 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 170.8, 144.4, 139.1, 137.4, 129.3, 129.0, 128.5, 126.6, 124.7, 120.0, 116.8, 70.5, 41.2; HRMS (ESI): Exact mass calcd for C₁₇H₁₇NO₂ [M+H]⁺, requires *m/z*: 268.1337, found *m/z*: 268.1335; Enantiomeric excess determined by HPLC with Chiracel ODH column, 10% *i*-PrOH/hexanes, 0.8 mL/min, 254 nm; *t*_r (major) = 16.2, *t*_r (minor) = 23.8, 94% ee.

Preparation of (S)-2-hydroxy-4-methyl-N-phenylpent-4-enamide (6b):

The indicated compound was prepared according to General Procedure A and isolated by flash chromatography (20% EtOAc/hexanes) as a white solid that was homogeneous as judged by ¹H NMR spectroscopy (73% yield): mp 68-69 °C; [α]_D -105.3 ° (*c* = 0.61, CHCl₃); IR (film) 3308, 2901, 1660, 1598, 1536, 1445, 1315, 1096, 757, 693 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.55 (brs, 1H), 7.57 (d, 2H, *J* = 8.1 Hz), 7.34 (t, 2H, *J* = 8.1 Hz), 7.13 (t, 1H, *J* = 7.5 Hz), 5.01 (s, 1H), 4.90 (s, 1H), 4.29 (td, 1H, *J* = 3.3, 9.9 Hz), 2.79 (dd, 1H, *J* = 2.9, 13.9 Hz), 2.68 (d, 1H, *J* = 3.3 Hz), 2.39 (dd, 1H, *J* = 9.5, 13.9 Hz), 1.82 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 171.0, 141.8, 137.5, 129.3, 124.7, 120.0, 115.7, 69.5, 43.4, 22.0; HRMS (ESI): Exact mass calcd for C₁₂H₁₅NO₂ [M+H]⁺, requires *m/z*: 206.1181, found *m/z*: 206.1178; Enantiomeric excess determined by HPLC with Chiracel ODH column, 10% *i*-PrOH/hexanes, 0.8 mL/min, 254 nm; *t*_r (major) = 12.3, *t*_r (minor) = 19.5, 92% ee.

Preparation of (S)-3-cyclopentenyl-2-hydroxy-N-phenylpropanamide (7b):

The indicated compound was prepared according to General Procedure A and isolated by flash chromatography (20% EtOAc/hexanes) as a white solid that was homogeneous as judged by ¹H NMR spectroscopy (99% yield): mp 79-81 °C; [α]_D -121.4 ° (*c* = 1.14, CHCl₃); IR (film) 3319, 2903, 2848, 1652, 1600, 1541, 1444, 1328, 1097, 1020 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.53 (brs, 1H), 7.56 (d, 2H, *J* = 8.1 Hz), 7.33 (t, 2H, *J* = 7.7 Hz), 7.12 (t, 1H, *J* = 7.7 Hz), 5.63 (s, 1H), 4.31-4.27 (m, 1H), 2.82 (d, 1H, *J* = 14.3 Hz), 2.73 (d, 1H, *J* = 3.7 Hz), 2.56 (dd, 1H, *J* = 9.1, 14.3 Hz), 2.36-2.24 (m, 4H), 1.94-1.87 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 171.3, 140.0, 137.5, 129.9, 129.3, 124.7, 120.0, 70.0, 36.7, 34.8, 32.8, 23.7; HRMS (ESI): Exact mass calcd for C₁₄H₁₇NO₂ [M+H]⁺, requires *m/z*: 232.1337, found *m/z*: 232.1341; Enantiomeric excess determined by HPLC with Chiracel ODH column, 10% *i*-PrOH/hexanes, 0.8 mL/min, 254 nm; *t*_r (major) = 12.5, *t*_r (minor) = 24.2, 94% ee.

Preparation of (S)-3-cyclohexenyl-2-hydroxy-N-phenylpropanamide (8b):

The indicated compound was prepared according to General Procedure A and isolated by flash chromatography (15% EtOAc/hexanes) as a white solid that was homogeneous as judged by ^1H NMR spectroscopy (89% yield): mp 110-112 °C; $[\alpha]_{\text{D}} -134.5^\circ$ ($c = 0.88$, CHCl_3); IR (film) 3321, 2931, 2845, 1659, 1603, 1538, 1500, 1445, 1324, 1088, 1066, 754 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.54 (brs, 1H), 7.57 (d, 2H, $J = 7.7$ Hz), 7.33 (t, 2H, $J = 7.7$ Hz), 7.12 (t, 2H, $J = 7.7$ Hz), 5.63 (s, 1H), 4.22 (td, 1H, $J = 3.3, 9.5$ Hz), 2.73-2.69 (m, 1H), 2.67 (d, 1H, $J = 2.9$ Hz), 2.28 (dd, 1H, $J = 9.9, 13.9$ Hz), 2.07-2.04 (m, 3H), 1.97-1.93 (m, 1H), 1.68-1.55 (m, 4H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.4, 137.6, 133.8, 129.3, 127.5, 124.6, 120.0, 69.5, 43.7, 27.9, 25.6, 22.9, 22.4; HRMS (ESI): Exact mass calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 246.1494, found m/z : 246.1489; Enantiomeric excess determined by HPLC with Chiracel ODH column, 10% *i*-PrOH/hexanes, 0.8 mL/min, 254 nm; t_{r} (major) = 12.7, t_{r} (minor) = 23.3, 94% ee.

Preparation of (2S,3R)-2-hydroxy-3,4-dimethyl-N-phenylpent-4-enamide (12b):

The indicated compound was prepared according to General Procedure A as a 13:1 syn:anti mixture of diastereomers. Flash chromatography (10% EtOAc/hexanes) yielded a single diastereomer (syn) as a white solid that was homogeneous as judged by ^1H NMR spectroscopy (78% yield): mp 103-106 °C; $[\alpha]_{\text{D}} -31.6^\circ$ ($c = 0.77$, CHCl_3); IR (film) 3354, 3254, 2966, 2905, 1666, 1596, 1532, 1442, 1298, 1238, 1203, 1123, 1073, 994, 889, 756, 707 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.49 (brs, 1H), 7.59 (d, 2H, $J = 8.8$ Hz), 7.34 (t, 2H, $J = 8.4$ Hz), 7.13 (t, 1H, $J = 7.7$ Hz), 5.07 (t, 1H, $J = 1.5$ Hz), 4.92 (s, 1H), 4.30 (t, 1H, $J = 1.5$ Hz), 2.91-2.89 (m, 1H), 2.29 (d, 1H, $J = 2.2$ Hz), 1.87 (s, 3H), 1.02 (d, 3H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 170.4, 147.1, 137.5, 129.3, 124.7, 120.0, 113.0, 72.2, 43.4, 22.6, 11.5; HRMS (ESI): Exact mass calcd for $\text{C}_{13}\text{H}_{17}\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 220.1337, found m/z : 220.1344; Enantiomeric excess determined by HPLC with Chiracel ODH column, 7.5% *i*-PrOH/hexanes, 0.8 mL/min, 254 nm; t_{r} (syn major) = 19.0, t_{r} (syn minor) = 17.3, 94% ee, t_{r} (anti major) = 13.9, t_{r} (anti minor) 20.4, 36% ee.

Preparation of (2S,3R,E)-4-ethyl-2-hydroxy-3-methyl-N-phenylhex-4-enamide (13b):

The indicated compound was prepared according to General Procedure A as a 24:1 syn:anti mixture of diastereomers. Flash chromatography (8% EtOAc/hexanes) yielded a single diastereomer (syn) as a

white solid that was homogeneous as judged by ^1H NMR spectroscopy (76% yield): mp 66-69 °C; $[\alpha]_{\text{D}} -110.7^\circ$ ($c = 0.92$, CHCl_3); IR (film) 3365, 2966, 2891, 1666, 1601, 1532, 1445, 1314, 1236, 1177, 1109, 997, 753, 692 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.47 (brs, 1H), 7.59 (d, 2H, $J = 7.7$ Hz), 7.34 (t, 2H, $J = 7.7$ Hz), 7.12 (t, 1H, $J = 7.7$ Hz), 5.39 (q, 1H, $J = 6.6$ Hz), 4.19 (d, 1H, $J = 2.6$ Hz), 2.97-2.95 (m, 1H), 2.34-2.28 (m, 2H), 1.98-1.93 (m, 1H), 1.70 (d, 3H, $J = 6.6$ Hz), 1.03 (t, 3H, $J = 7.3$ Hz), 0.98 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 170.6, 143.6, 137.6, 129.3, 124.6, 121.0, 120.0, 72.2, 41.9, 23.6, 13.4, 13.2, 11.8; HRMS (ESI): Exact mass calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 248.1650, found m/z : 248.1654; Enantiomeric excess determined by HPLC with Chiracel ODH column, 5% *i*-PrOH/hexanes, 0.8 mL/min, 254 nm; t_{r} (syn major) = 30.3, t_{r} (syn minor) = 22.1, 99% ee, t_{r} (anti major) = 18.1, t_{r} (anti minor) 38.8, 75% ee.

Preparation of (2*S*,3*R*)-3-cyclopentenyl-2-hydroxy-*N*-phenylbutanamide

(14b): The indicated compound was prepared according to General Procedure A as a 9.3:1 mixture of diastereomers. Flash chromatography (7% EtOAc/hexanes) yielded a single diastereomer (syn) as a white solid that was homogeneous as judged by ^1H NMR spectroscopy (82% yield): mp 134-137 °C; $[\alpha]_{\text{D}} -136.3^\circ$ ($c = 0.86$, CHCl_3); IR (film) 3360, 3246, 2925, 2844, 1660, 1602, 1531, 1444, 1297, 1120, 1035, 754, 701 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.50 (brs, 1H), 7.59 (d, 2H, $J = 7.7$ Hz), 7.34 (t, 2H, $J = 7.7$ Hz), 7.13 (t, 1H, $J = 7.7$ Hz), 5.63 (t, 1H, $J = 1.5$ Hz), 4.34 (t, 1H, $J = 2.2$ Hz), 3.02-3.00 (m, 1H), 2.45-2.29 (m, 4H), 2.27 (d, 1H, $J = 1.8$ Hz), 1.98-1.86 (m, 2H), 1.05 (d, 3H, $J = 7.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 170.5, 146.0, 137.5, 129.3, 127.6, 124.7, 120.0, 72.6, 38.9, 34.4, 32.8, 23.5, 11.8; HRMS (ESI): Exact mass calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 246.1494, found m/z : 246.1489; Enantiomeric excess determined by HPLC with Chiracel ADH column, 10% *i*-PrOH/hexanes, 0.8 mL/min, 254 nm; t_{r} (syn major) = 14.4, t_{r} (syn minor) = 13.3, 98% ee. Because the peaks of the major syn isomer and one of the anti diastereomers overlaps, flash column chromatography must be performed in order to measure the ee.

Preparation of (2*S*,3*R*)-3-cyclohexenyl-2-hydroxy-*N*-phenylbutanamide

(15b): The indicated compound was prepared according to General Procedure A as a 9.3:1 mixture of diastereomers. Flash chromatography (8% EtOAc/hexanes) yielded a single diastereomer (syn) as a white solid that was homogeneous as judged by ^1H NMR spectroscopy (78% yield): mp 132-135 °C; $[\alpha]_{\text{D}} -142.4^\circ$ ($c = 0.98$, CHCl_3); IR (film) 3350, 2936, 1657, 1602, 1531,

1444, 1310, 1290, 1022, 985, 757 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.47 (brs, 1H), 7.59 (d, 2H, $J = 8.0$ Hz), 7.34 (t, 2H, $J = 7.7$ Hz), 7.12 (t, 1H, $J = 7.3$ Hz), 5.64 (d, 1H, $J = 1.1$ Hz), 4.25 (t, 1H, $J = 2.5$ Hz), 2.78-2.76 (m, 1H), 2.30 (d, 1H, $J = 1.8$ Hz), 2.15-1.96 (m, 4H), 1.68-1.55 (m, 4H), 0.99 (d, 3H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 170.7, 139.0, 137.5, 129.3, 124.6, 124.2, 120.0, 72.4, 43.5, 28.5, 25.6, 23.1, 22.7, 11.3; HRMS (ESI): Exact mass calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 260.1650, found m/z : 260.1659; Enantiomeric excess determined by HPLC with Chiracel ODH column, 10% *i*-PrOH/hexanes, 0.8 mL/min, 254 nm; t_r (syn major) = 13.1, t_r (syn minor) = 16.3, 98% ee, t_r (anti major) = 11.2, t_r (anti minor) 23.0, 76% ee.

Preparation of (2*S*,3*R*)-3-ethyl-2-hydroxy-4-methyl-*N*-phenylpent-4-enamide (16b):

The indicated compound was prepared according to General Procedure A as a 9:1 syn:anti mixture of diastereomers. Flash chromatography (8% EtOAc/hexanes) yielded a single diastereomer (syn) as a white solid that was homogeneous as judged by ^1H NMR spectroscopy (58% yield): mp 86-89 $^{\circ}\text{C}$; $[\alpha]_D -90.6^{\circ}$ ($c = 0.61$, CHCl_3); IR (film) 3350, 3292, 2964, 2876, 1660, 1601, 1535, 1445, 1310, 1110, 1083, 896, 756 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.46 (brs, 1H), 7.58 (d, 2H, $J = 7.7$ Hz), 7.34 (t, 2H, $J = 7.7$ Hz), 7.13 (t, 1H, $J = 7.3$ Hz), 5.11 (t, 1H, $J = 1.5$ Hz), 4.90 (s, 1H), 4.18 (d, 1H, $J = 3.3$ Hz), 2.62 (td, 1H, $J = 3.7, 11.0$ Hz), 2.53 (brs, 1H), 1.85 (s, 3H), 1.63-1.47 (m, 2H), 0.86 (t, 3H, $J = 7.3$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 170.5, 145.3, 137.5, 129.3, 124.7, 120.0, 113.2, 73.0, 51.7, 23.1, 19.5, 12.1; HRMS (ESI): Exact mass calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 234.1494, found m/z : 234.1494; Enantiomeric excess determined by HPLC with Chiracel ADH column, 7.5% *i*-PrOH/hexanes, 0.8 mL/min, 254 nm; t_r (syn major) = 17.5, t_r (syn minor) = 12.2, 96% ee, t_r (anti major) = 22.6, t_r (anti minor) 13.8, 31% ee.

Preparation of (*S*)-2-hydroxy-6-methyl-4-methylene-*N*-phenylheptanamide (9a):

The indicated compound was prepared according to General Procedure A as a 4:1 inseparable mixture of regioisomers. Flash chromatography (15% EtOAc/hexanes) yielded a colorless oil as a mixture of regioisomers in the same ratio as the unpurified material as judged by ^1H NMR spectroscopy (78% yield): $[\alpha]_D -94.2^{\circ}$ ($c = 0.97$, CHCl_3); IR (film) 3365, 2955, 1666, 1601, 1538, 1446, 1315, 1080, 900, 751, 692 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) (major regioisomer) δ 8.54 (brs, 1H), 7.57 (d, 2H, $J = 8.0$ Hz), 7.33 (t, 2H, $J = 7.7$ Hz), 7.12 (t, 1H, $J = 7.7$ Hz), 4.98 (s, 1H), 4.96 (s, 1H), 4.26 (td, 1H, $J = 3.3, 10.2$ Hz), 2.80 (dd, 1H, $J = 3.3, 14.3$ Hz), 2.74 (d, 1H, $J = 2.9$ Hz), 2.32 (dd, 1H, $J = 10.2, 14.3$ Hz), 2.02

(dd, 1H, $J = 5.5, 13.2$ Hz), 1.98-1.78 (m, 2H), 0.92 (d, 3H, $J = 6.2$ Hz), 0.87 (d, 3H, $J = 6.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) (major regioisomer) δ 171.1, 144.8, 137.5, 129.3, 124.7, 120.0, 115.6, 69.7, 45.1, 41.4, 26.3, 23.0, 22.3; HRMS (ESI): Exact mass calcd for $\text{C}_{15}\text{H}_{21}\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 248.1650, found m/z : 248.1658; Enantiomeric excess of major regioisomer was determined by HPLC with Chiracel ODH column, 5% *i*-PrOH/hexanes, 0.8 mL/min, 254 nm; t_r (major) = 21.1, t_r (minor) = 34.0, 94% ee.

Preparation of (S)-2-hydroxy-5-methyl-4-methylene-N-phenylhexanamide (10a): The indicated compound was prepared according to General Procedure A as a 5.3:1 inseparable mixture of

regioisomers. Flash chromatography (25% EtOAc/hexanes) yielded a colorless oil as a mixture of regioisomers in the same ratio as the unpurified material as judged by ^1H NMR spectroscopy (60% yield): $[\alpha]_D -95.6^\circ$ ($c = 0.69$, CHCl_3); IR (film) 3364, 2943, 1665, 1600, 1536, 1445, 1314, 1079, 898, 754, 692 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) (major regioisomer) δ 8.52 (brs, 1H), 7.58 (d, 2H, $J = 8.0$ Hz), 7.34 (t, 2H, $J = 8.0$ Hz), 7.12 (t, 1H, $J = 7.3$ Hz), 5.05 (s, 1H), 4.91 (s, 1H), 4.28 (td, 1H, $J = 2.9, 10.2$ Hz), 2.92 (dd, 1H, $J = 2.9, 14.6$ Hz), 2.70 (d, 1H, $J = 2.9$ Hz), 2.36-2.27 (m, 2H), 1.09 (t, 6H, $J = 6.2$ Hz); ^{13}C NMR (100 MHz, CDCl_3) (major regioisomer) δ 171.1, 152.2, 137.5, 129.3, 124.7, 120.0, 111.5, 70.0, 40.7, 33.2, 22.3, 21.8; HRMS (ESI): Exact mass calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 234.1494, found m/z : 234.1488; Enantiomeric excess of major regioisomer was determined by HPLC with Chiracel ODH column, 5% *i*-PrOH/hexanes, 0.8 mL/min, 254 nm; t_r (major) = 22.3, t_r (minor) = 43.2, 96% ee.

Preparation of (S)-2-hydroxy-6,6-dimethyl-4-methylene-N-phenylheptanamide (11a): The indicated compound was prepared according to General Procedure A as a single regioisomer and isolated by

flash chromatography (20% EtOAc/hexanes) as a colorless oil that was homogeneous as judged by ^1H NMR spectroscopy (81% yield): $[\alpha]_D -69.9^\circ$ ($c = 1.07$, CHCl_3); IR (film) 3363, 2952, 1664, 1600, 1535, 1445, 1314, 1236, 1087, 753 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.52 (brs, 1H), 7.58 (d, 2H, $J = 7.7$ Hz), 7.33 (t, 2H, $J = 7.7$ Hz), 7.12 (t, 1H, $J = 7.7$ Hz), 5.06 (s, 1H), 4.98 (s, 1H), 4.24 (td, 1H, $J = 2.9, 9.9$ Hz), 2.89 (dd, 1H, $J = 2.6, 13.9$ Hz), 2.75 (d, 1H, $J = 2.9$ Hz), 2.34 (dd, 1H, $J = 10.2, 14.3$ Hz), 1.98 (dd, 2H, $J = 13.2, 19.0$ Hz), 0.95 (s, 9H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.0, 144.2, 137.5, 129.3, 124.7, 120.0, 117.7, 69.8, 48.5, 43.7, 32.0, 30.0; HRMS (ESI): Exact mass calcd for $\text{C}_{16}\text{H}_{23}\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 262.1807, found m/z : 262.1815; Enantiomeric excess was determined by HPLC with

Chiracel ODH column, 5% *i*-PrOH/hexanes, 0.8 mL/min, 254 nm; t_r (major) = 26.6, t_r (minor) = 35.8, 94% ee.

Preparation of (2*S*,3*R*)-2-hydroxy-3-methyl-4-methylene-*N*-phenylhexanamide

(17b): The indicated compound was prepared according to General Procedure A as

a 10:1 syn:anti mixture of diastereomers. Flash chromatography (10%

EtOAc/hexanes) yielded a single diastereomer (syn) as a white solid that was

homogeneous as judged by ^1H NMR spectroscopy (83% yield): mp 115-118 °C;

$[\alpha]_D -101.5^\circ$ ($c = 0.93$, CHCl_3); IR (film) 3354, 3266, 2972, 2887, 1660, 1599, 1533, 1445, 1301, 1204, 1118, 1070, 992, 896, 762, 710 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.50 (brs, 1H), 7.60 (d, 2H, $J = 7.8$ Hz), 7.34 (t, 2H, $J = 7.8$ Hz), 7.13 (t, 1H, $J = 7.3$ Hz), 5.07 (s, 1H), 4.96 (s, 1H), 4.24 (t, 1H, $J = 2.4$ Hz), 2.96-2.94 (m, 1H), 2.37 (d, 1H, $J = 2.0$ Hz), 2.23-2.18 (m, 1H), 2.14-2.09 (m, 1H), 1.10 (t, 3H, $J = 7.3$ Hz), 1.03 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 170.4, 153.1, 137.5, 129.3, 124.7, 120.0, 110.6, 72.3, 42.1, 28.7, 12.7, 11.8; HRMS (ESI): Exact mass calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 234.1494, found m/z : 234.1498; Enantiomeric excess determined by HPLC with Chiracel ODH column, 10% *i*-PrOH/hexanes, 0.8 mL/min, 254 nm; t_r (syn major) = 15.8, t_r (syn minor) = 11.9, 95% ee.

Preparation of (2*S*,3*R*,*E*)-2-hydroxy-3,4-dimethyl-*N*-phenylhex-4-enamide

(18b): The indicated compound was prepared according to General Procedure A

as a 20:1 syn:anti mixture of diastereomers. Flash chromatography (10%

EtOAc/hexanes) yielded a single diastereomer (syn) as a white solid that was

homogeneous as judged by ^1H NMR spectroscopy (75% yield): mp 97-100 °C;

$[\alpha]_D -139.2^\circ$ ($c = 0.83$, CHCl_3); IR (film) 3361, 2970, 2918, 1661, 1600, 1538,

1445, 1315, 754, 692 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.48 (brs, 1H), 7.59 (d, 2H, $J = 7.8$ Hz), 7.34 (t, 2H, $J = 7.8$ Hz), 7.13 (t, 1H, $J = 7.3$ Hz), 5.44 (q, 1H, $J = 6.9$ Hz), 4.26 (d, 1H, $J = 2.9$ Hz), 2.87-2.85 (m, 1H), 2.32 (s, 1H), 1.75 (s, 3H), 1.68 (d, 3H, $J = 6.8$ Hz), 1.00 (d, 3H, $J = 6.8$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ 170.7, 137.5, 137.2, 129.3, 124.6, 121.5, 120.0, 72.3, 44.7, 16.3, 13.8, 11.5; HRMS (ESI): Exact mass calcd for $\text{C}_{14}\text{H}_{19}\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 234.1494, found m/z : 234.1492; Enantiomeric excess determined by HPLC with Chiracel ODH column, 10% *i*-PrOH/hexanes, 0.8 mL/min, 254 nm; t_r (syn major) = 14.4, t_r (syn minor) = 13.1, 99% ee.

Mosher Ester Analysis of 1b: ^1H NMR (500 MHz, CDCl_3) δ 7.530-7.244 (m,

14H), 7.145-7.114 (m, 1H), 5.499 (dd, 1H, $J = 4.39, 8.3$ Hz), 5.330 (s, 1H),

5.126 (s, 1H), 3.475 (s, 3H), 3.411 (dd, 1H, $J = 3.42, 15.4$ Hz), 3.087 (dd, 1H, $J = 8.30, 15.14$ Hz).

Mosher Ester Analysis of 1b: ^1H NMR (500 MHz, CDCl_3) δ 7.531 (d, 1H, $J = 7.32$ Hz), 7.453-7.246 (m, 12H), 7.174 (d, 1H, $J = 7.81$ Hz), 7.105 (t, 1H, $J = 7.32$ Hz), 5.622 (dd, 1H, $J = 3.42, 8.80$ Hz), 5.397 (s, 1H), 5.191 (s, 1H), 3.549 (s, 3H), 3.475 (dd, 1H, $J = 1.47, 15.63$ Hz), 3.056 (dd, 1H, $J = 9.28, 15.63$ Hz).

Mosher Ester Analysis of 12b: ^1H NMR (500 MHz, CDCl_3) δ 7.645 (s, 1H), 7.551 (d, 1H, $J = 7.33$ Hz), 7.458-7.415 (m, 3H), 7.396 (d, 2H, $J = 7.81$ Hz), 7.324 (t, 2H, $J = 7.81$ Hz), 7.145 (t, 1H, $J = 7.32$ Hz), 5.697 (d, 1H, $J = 3.42$ Hz), 4.916 (s, 1H), 4.781 (s, 1H), 3.495 (s, 3H), 2.967-2.945 (m, 1H), 1.881 (s,

3H), 1.083 (d, 3H, $J = 6.84$ Hz).

Mosher Ester Analysis of 12b: ^1H NMR (500 MHz, CDCl_3) δ 7.562 (d, 2H, $J = 7.32$ Hz), 7.458-7.395 (m, 4H), 7.299-7.227 (m, 3H), 7.131-7.103 (m, 1H), 5.797 (d, 1H, $J = 2.93$ Hz), 4.965 (s, 1H), 4.807 (s, 1H), 3.589 (s, 3H), 2.991-2.045 (m, 1H), 1.918 (s, 3H), 1.107 (d, 1H, $J = 6.84$).

¹ Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. *Organometallics* **1996**, *15*, 1518-1520.

² Perrin, D. D. and Armarego, W. L. F. *Purification of Laboratory Chemicals*; 3rd ed., Pergamon Press, Oxford, 1988.

³ We thank Dr. André Beauchemin for providing an efficient synthesis of compound **2b**. Literature routes to compound **2b**: Kröhnke, F. *Chem. Ber.* **1939**, *72*, 527. Svetkin, Y. V.; Akmanova, N. A.; Murza, M. M. *Zh. Obshh. Khim.* **1969**, *41*, 183.

⁴ During the course of this study, all pybox ligands were prepared as described in Davies, I. W.; Gerena, L.; Nu, L.; Larsen, R. D.; Reider, P. J. *J. Org. Chem.* **1996**, *61*, 9629-9630.