Enantioselective Scandium-catalyzed Vinylsilane Additions. A New Approach to the Synthesis of Enantiopure β,γ -Unsaturated α -Hydroxy Acid Derivatives

David A. Evans* and Yimon Aye

Department of Chemistry & Chemical Biology, Harvard University, Cambridge, Massachusetts 02138

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, h=heptet, m=multiplet, brs=broad singlet; integration; coupling constant(s) in Hz). Proton-decoupled ^{13}C NMR spectra were recorded on Varian Inova-600 (150 MHz), Varian Inova-500 (125 MHz) and Varian Mercury-400 (100 MHz) spectrometers 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) of the crude reaction products was performed on a Hewlett-Packard 1100 Series HPLC with a diode array detector using the indicated chiral column.

Scandium-Catalyzed Vinylsilane Additions.

General Procedure A: To an oven-dried, 4-mL vial containing a magnetic stirring bar was added (4*R*, 5*S*)-bis(norephedrine-oxazolinyl)pyridine³ (0.9 mg, 0.003 mmol), Sc(OTf)₃ (1.2 mg, 0.0025 mmol), and 4Å MS (15.0 mg, 150 mg/mmol) in an inert atmosphere (N₂) glove box. [For Table 2, entries 6 and 7 and for eq's 4 and 7, 4.4 mg, 0.011 mmol of (4*R*, 5*S*)-bis(norephedrine-oxazolinyl)pyridine and 4.9 mg, 0.010 mmol of Sc(OTf)₃ were used instead]. To a separate vial was added *N*-phenylglyoxamide **2** (14.9 mg, 0.1 mmol).ⁱ Both vials were fitted with serum caps and removed from the inert atmosphere box. The vial containing the metal/ligand was charged with CH₂Cl₂ (0.7 mL). The resulting suspension was stirred at room temperature for 1.5 h. (For Table 2, entries 6 and 7 and for eq 4, the suspension was stirred at room temperature for 1 h and the solvent was subsequently let to run dry under positive N₂ pressure over 1/2 h period while keeping the suspension stirred). To this vial was added via syringe the appropriate vinylsilane (4 equiv) followed by **3** (14.9 mg, 0.1 mmol) as a solution in CH₂Cl₂ (0.3 mL). (For Table 1, entries 6 and 7 and for eq 4, 8 equiv of vinylsilane was used instead. For Table 3, entries 1 and 2, 2 equiv of vinylsilane was used instead). The vial that had contained **2** was rinsed with CH₂Cl₂ (0.2 mL) and the solution was transferred to the reaction vial via syringe. The solution was stirred at room temperature over indicated times at which point all reactions were deemed complete by TLC. The reaction mixture was filtered over a silica gel plug followed by washing with Et₂O. The filtrate was concentrated in vacuo and redissolved in MeOH (1 mL) and treated with 1 drop of conc. H₂SO₄. The solution was swirled over a two-minute period and diluted with CH₂Cl₂ (15 mL). The solution was then transferred to a separatory funnel and washed with a saturated aqueous NaHCO₃ solution (15 mL). The aqueous solution was then back extracted with CH₂Cl₂ (2x 15 mL). Combined organic extracts were dried over MgSO₄ and concentrated in vacuo. The crude product was then loaded onto a silica gel flash column and eluted with the indicated solvent to provide the title compounds. The excess silanes were recovered and reused without loss of selectivity.

General Procedure B: To an oven-dried, 4-mL vial containing a magnetic stirring bar was added (4*R*, 5*S*)-bis(norephedrine-oxazolinyl)pyridine (2.2 mg, 0.0055 mmol), Sc(OTf)₃ (2.5 mg, 0.005 mmol), and 4Å MS (15.0 mg, 150 mg/mmol) in an inert atmosphere (N₂) glove box. To a separate vial was added **2**

(i) For the synthesis of *N*-phenylglyoxamide, see Evans, D. A.; Aye, Y.; Wu, J. *Org. Lett.* **2006**, 8, 2071.

(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 CH_2Cl_2 (0.7 mL). The resulting suspension was stirred at room temperature for 1.5 h. To this solution was added **2** (14.9 mg, 0.1 mmol) as a solution in CH_2Cl_2 (0.3 mL) via syringe. The vial that had contained **2** was rinsed with CH_2Cl_2 (0.2 mL) and the solution was transferred to the reaction vial via syringe. This was followed by addition of 2,6-di-*tert*-butylpyridine (35 μL of 0.1 M solution in CH_2Cl_2 , 0.0035 mmol) via syringe. The appropriate vinylsilane (2 equiv) was then added via syringe. The reaction was stirred at room temperature until it was judged complete by TLC analysis. The reaction mixture was then filtered over a silica gel plug and washed with Et_2O . The filtrate was concentrated in vacuo and redissolved in THF (1 mL). The solution was treated with tetrabutyl ammonium fluoride trihydrate (32 mg, 0.1 mmol) and was stirred over 1 min at rt. The yellow solution was concentrated in vacuo. The residue was loaded directly onto a silica gel flash column and eluted with the indicated solvent to provide the title compounds. The excess silanes were recovered and reused without loss of selectivity.

Preparation of (R,E)-2-hydroxy-N,4-diphenylbut-3-enamide.ⁱⁱⁱ 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 (92% yield): mp 90-91 ° C; $[\alpha]_D$ -6.70° ($c = 1.80$, CHCl_3); IR (film) 3356, 3058, 1663, 1599, 1532, 1497, 1445, 1315, 966, 753, 691 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.11 (brs, 1H), 7.56 (d, 2H, $J = 7.7$ Hz), 7.43 (d, 1H, $J = 7.0$ Hz), 7.36-7.28 (m, 6H), 7.14 (t, 1H, $J = 7.3$ Hz), 6.85 (d, 1H, $J = 16.5$ Hz), 6.39 (dd, 1H, $J = 6.9, 16.5$), 4.91-4.88 (m, 1H), 3.06 (d, 1H, $J = 3.7$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 169.8, 137.3, 135.9, 134.1, 129.5, 129.3, 128.9, 128.6, 127.1, 127.0, 126.4, 125.0, 120.0, 73.7; HRMS (ESI): Exact mass calcd for $\text{C}_{16}\text{H}_{16}\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 254.1181, found m/z : 254.1192; Enantiomeric excess determined by

(i) The known (*E*) 2-aryl-substituted vinylsilanes (**3a-e**) were prepared via a Heck arylation according to the procedure described in Jeffery, T. *Tetrahedron Lett.* **1999**, 40, 1673. We thank Mr. Vijay Yanamadala for the syntheses of vinylsilanes **3c** and **3d**.

HPLC with Chiracel ADH column, 10% *i*-PrOH/hexanes, 1.0 mL/min, 254 nm; t_r (major) = 13.6, t_r (minor) = 24.8, 99% ee.

Preparation of (R,E)-2-hydroxy-N-phenyl-4-p-tolylbut-3-enamide: 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 112-113 ° C; $[\alpha]_D +6.97^\circ$ ($c = 2.26$, CHCl_3); IR (film) 3355, 3034, 2917, 2857, 1665, 1595, 1543, 1444, 1313, 1255, 1116, 1047, 966, 898, 854, 812, 752, 691 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.23 (brs, 1H), 7.54 (d, 2H, $J = 7.7$ Hz), 7.34-7.26 (m, 4H), 7.15-7.11 (m, 3H), 6.78 (d, 1H, $J = 15.8$ Hz), 6.31 (dd, 1H, $J = 6.8, 15.8$), 4.86-4.83 (m, 1H), 3.41 (d, 1H, $J = 3.7$ Hz), 2.34 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 169.9, 138.6, 137.3, 134.3, 133.1, 129.6, 129.3, 127.0, 125.3, 125.0, 120.0, 73.8, 21.5; HRMS (ESI): Exact mass calcd for $\text{C}_{17}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 268.1337, found m/z : 268.1326; Enantiomeric excess determined by HPLC with Chiracel ADH column, 10% *i*-PrOH/hexanes, 1.0 mL/min, 254 nm; t_r (major) = 13.5, t_r (minor) = 19.7, 98% ee.

Preparation of (R,E)-2-hydroxy-4-(4-methoxyphenyl)-N-phenylbut-3-enamide: The indicated compound was prepared according to General Procedure A and isolated by flash chromatography (20% EtOAc/hexanes) as a yellow solid that was homogeneous as judged by ^1H NMR spectroscopy (87% yield): mp 138-139 ° C; $[\alpha]_D +4.51^\circ$ ($c = 2.33$, CHCl_3); IR (film) 3337, 1658, 1603, 1540, 1512, 1444, 1253, 1177, 1026, 964, 897, 825, 758, 691, 671 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.22 (brs, 1H), 7.55

(d, 2H, $J = 8.2$ Hz), 7.34-7.30 (m, 4H), 7.12 (t, 1H, $J = 7.3$ Hz), 6.84 (d, 2H, $J = 8.8$ Hz), 6.76 (d, 1H, $J = 15.9$ Hz), 6.21 (dd, 1H, $J = 7.0$, 15.9), 4.85-4.82 (m, 1H), 3.80 (s, 3H), 3.36 (d, 1H, $J = 3.7$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 170.2, 160.0, 137.3, 133.8, 129.3, 128.7, 128.3, 125.0, 124.1, 120.0, 114.3, 73.8, 55.5; HRMS (ESI): Exact mass calcd for $\text{C}_{17}\text{H}_{18}\text{NO}_3$ $[\text{M}+\text{H}]^+$, requires m/z : 284.1286, found m/z : 284.1299; Enantiomeric excess determined by HPLC with Chiracel ADH column, 10% *i*-PrOH/hexanes, 1.0 mL/min, 254 nm; t_r (major) = 22.0, t_r (minor) = 30.8, 97% ee.

Preparation of (R,E)-4-(4-fluorophenyl)-2-hydroxy-N-phenylbut-3-enamide: 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 (83% yield): mp 144-145 °C; $[\alpha]_D +14.9^\circ$ ($c = 1.69$, CHCl_3); IR (film) 3345, 1662, 1600, 1541, 1509, 1446, 1230, 1049, 965, 828, 750, 693 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.21 (brs, 1H), 7.56 (d, 2H, $J = 7.7$ Hz), 7.38-7.31 (m, 4H), 7.14 (t, 1H, $J = 7.3$ Hz), 7.01 (t, 2H, $J = 8.6$ Hz), 6.79 (d, 1H, $J = 15.7$ Hz), 6.30 (dd, 1H, $J = 6.7$, 16.1), 4.89-4.86 (m, 1H), 3.21 (d, 1H, $J = 4.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 169.8, 137.2, 132.7, 132.1, 129.3, 128.6, 126.2, 125.0, 120.0, 116.0, 115.8, 73.5; HRMS (ESI): Exact mass calcd for $\text{C}_{16}\text{H}_{15}\text{FNO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 272.1087, found m/z : 272.1099; Enantiomeric excess determined by HPLC with Chiracel ADH column, 10% *i*-PrOH/hexanes, 1.0 mL/min, 254 nm; t_r (major) = 13.7, t_r (minor) = 26.0, 99% ee.

Preparation of (R,E)-2-hydroxy-N-phenyl-4-(4-(trifluoromethyl)phenyl)but-3-enamide: The indicated compound was prepared according to General Procedure A and isolated by flash

chromatography (50% EtOAc/hexanes) as a yellow solid that was homogeneous as judged by ^1H NMR spectroscopy (86% yield): mp 163-164 ° C; $[\alpha]_{\text{D}} -5.94^\circ$ ($c = 0.70$, CHCl_3); IR (film) 3276, 1658, 1599, 1546, 1445, 1414, 1330, 1164, 1116, 1069, 966, 828, 752, 693 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.27 (brs, 1H), 7.58-7.48 (m, 6H), 7.34 (t, 2H, $J = 7.9$ Hz), 7.14 (t, 1H, $J = 7.3$ Hz), 6.86 (d, 1H, $J = 16.1$ Hz), 6.49 (dd, 1H, $J = 6.0, 15.9$), 4.95-4.92 (m, 1H), 3.22 (d, 1H, $J = 4.0$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 169.3, 137.1, 131.9, 129.3, 129.2, 127.1, 125.9, 125.8, 125.1, 120.0, 73.3; HRMS (ESI): Exact mass calcd for $\text{C}_{17}\text{H}_{15}\text{F}_3\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 322.1055, found m/z : 322.1047; Enantiomeric excess determined by HPLC with Chiracel ADH column, 10% *i*-PrOH/hexanes, 1.0 mL/min, 254 nm; t_{r} (major) = 11.8, t_{r} (minor) = 19.8, 98% ee.

Preparation of (R,E)-2-hydroxy-N-phenyloct-3-enamide:ⁱⁱⁱ The indicated compound was prepared according to General Procedure A and isolated by flash chromatography (10% EtOAc/hexanes) as a white solid that was homogeneous as judged by ^1H NMR spectroscopy (63% yield): mp 84-85 ° C; $[\alpha]_{\text{D}} -32.4^\circ$ ($c = 0.15$, CHCl_3); IR (film) 3324, 2858, 1660, 1599, 1532, 1445, 1315, 1248, 1108, 1043, 968, 753, 691 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.05 (brs, 1H), 7.55 (d, 2H, $J = 7.3$ Hz), 7.34 (t, 2H, $J = 8.1$ Hz), 7.13 (t, 1H, $J = 7.5$ Hz), 6.00-5.93 (m, 1H), 5.65 (dd, 1H, $J = 7.3, 15.4$), 4.64 (dd, 1H, $J = 3.3, 7.3$), 2.98 (d, 1H, $J = 3.3$ Hz), 2.12 (q, 2H, $J = 6.2$ Hz), 1.45-1.25 (m, 4H), 0.90 (t, 3H, $J = 7.1$ Hz); ^{13}C NMR (100 MHz, CDCl_3) δ 170.3, 137.2, 129.3, 127.4, 124.9, 119.9, 73.8, 32.1, 31.1, 22.5, 14.1; HRMS (ESI): Exact mass calcd for $\text{C}_{14}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 234.1494, found m/z : 234.1492; Enantiomeric excess determined by HPLC with Chiracel ADH column, 5% *i*-PrOH/hexanes, 1.0 mL/min, 254 nm; t_{r} (major) = 12.3, t_{r} (minor) = 24.3, 98% ee.

(ii) The known (*E*) aliphatic vinylsilanes (**3f** and **3g**) were prepared according to the procedures described in Westmijze, H.; Kleijn, H.; Vermeer, P. *J. Organomet. Chem.* **1984**, 276, 317.

Preparation of (R,E)-2-hydroxy-5-methyl-N-phenylhex-3-enamide: The indicated compound was prepared according to General Procedure A and isolated by flash chromatography (10% EtOAc/hexanes) as a white solid that was homogeneous as judged by ¹H NMR spectroscopy (55% yield): mp 64-65 ° C; [α]_D -16.5 ° (*c* = 0.13, CHCl₃); IR (film) 3458, 3284, 2924, 1666, 1599, 1537, 1445, 1069, 753 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.06 (brs, 1H), 7.55 (d, 2H, *J* = 8.4 Hz), 7.34 (t, 2H, *J* = 8.1 Hz), 7.13 (t, 1H, *J* = 7.5 Hz), 5.94 (dd, 1H, *J* = 6.6, 15.2), 5.61 (dd, 1H, *J* = 7.9, 15.2), 4.64 (dd, 1H, *J* = 3.4, 6.6), 2.97 (d, 1H, *J* = 3.4 Hz), 2.38 (h, 1H, *J* = 7.0 Hz), 1.04 (d, 6H, *J* = 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 170.4, 143.7, 137.4, 129.3, 124.8, 119.9, 73.7, 31.0, 22.2, 22.1; HRMS (ESI): Exact mass calcd for C₁₃H₁₈NO₂ [M+H]⁺, requires *m/z*: 220.1337, found *m/z*: 220.1332; Enantiomeric excess determined by HPLC with Chiracel ADH column, 5% *i*-PrOH/hexanes, 1.0 mL/min, 254 nm; *t_r* (major) = 16.4, *t_r* (minor) = 26.4, 99% ee.

Preparation of (R,Z)-2-hydroxy-N-phenylhept-3-enamide (5**):^{iv}** The indicated compound was prepared according to General Procedure A and isolated by flash chromatography (5% EtOAc/hexanes) as a colorless oil that was homogeneous as judged by ¹H NMR spectroscopy (49% yield): [α]_D -46.7 ° (*c* = 0.93, CHCl₃); IR (film) 3330, 2860, 1654, 1583, 1542, 1345, 1298, 1005, 1036, 955, 689 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.01 (brs, 1H), 7.53 (d, 2H, *J* = 8.8 Hz), 7.32 (t, 2H, *J* = 7.8 Hz), 7.13 (t, 1H,

(iii) The known (*Z*) vinylsilanes were prepared using Schwartz's reagent (see Hart, D. W.; Blackburn, T. F.; Schwartz, J. *J. Am. Chem. Soc.* **1975**, 97, 679) from the corresponding TMSalkynes by treatment with Cp₂Zr(H)Cl (1.1 equiv) in THF (0.25 M) and stirring from 0°C to room temperature overnight under N₂ and quenching with H₂O. Resulting crude reaction mixture after extractive workup yielded the known vinylsilanes cleanly and exclusively in (*Z*) geometry.

$J = 7.3$ Hz), 5.53-5.51 (m, 2H), 4.96 (d, 1H, $J = 9.3$ Hz), 2.38-2.26 (m, 2H), 2.16 (d, 1H, $J = 1.0$ Hz), 1.42-1.24 (m, 4H), 0.92, 0.86 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 170.6, 158.3, 151.5, 137.0, 129.3, 128.1, 124.8, 123.2, 119.8, 69.7, 32.0, 28.8, 23.0, 14.1; HRMS (ESI): Exact mass calcd for $\text{C}_{14}\text{H}_{20}\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 234.1494, found m/z : 234.1493; Enantiomeric excess determined by HPLC with Chiracel ADH column, 2.5% *i*-PrOH/hexanes, 0.7 mL/min, 254 nm; t_r (major) = 11.5, t_r (minor) = 20.9, 97% ee.

Preparation of (R,E)-2-hydroxy-N,4-diphenylpent-3-enamide:^v 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 (92% yield): mp 105-106 °C; $[\alpha]_D -12.8^\circ$ ($c = 2.08$, CHCl_3); IR (film) 3350, 3056, 1664, 1599, 1534, 1493, 1440, 1315, 1074, 1040, 870, 755, 693 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.21 (brs, 1H), 7.56 (d, 2H, $J = 8.1$ Hz), 7.45-7.42 (m, 2H), 7.36-7.28 (m, 5H), 7.14 (t, 1H, $J = 7.3$ Hz), 5.89 (d, 1H, $J = 8.8$ Hz), 5.11 (dd, 1H, $J = 2.5$, 8.8), 2.96 (d, 1H, $J = 2.5$ Hz), 2.29 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 170.5, 143.0, 142.2, 137.4, 129.3, 128.6, 128.2, 126.2, 125.0, 124.7, 120.0, 70.1, 17.1; HRMS (ESI): Exact mass calcd for $\text{C}_{17}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 268.1337, found m/z : 268.1326; Enantiomeric excess determined by HPLC with Chiracel ADH column, 10% *i*-PrOH/hexanes, 1.0 mL/min, 254 nm; t_r (major) = 24.5, t_r (minor) = 11.4, 98% ee.

(v) The known 2,2-disubstituted vinylsilanes (**6a-e**) were synthesized according to the procedures described in Koerwitz, F. L.; Hammond, G. B.; Wiemer, D. F. *J. Org. Chem.* **1989**, *54*, 743.

Preparation of (R,E)-2-hydroxy-N,4-diphenyloct-3-enamide: 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 (99% yield): mp 93-94 ° C; [α]_D -19.6 ° (*c* = 1.82, CHCl₃); IR (film) 3357, 2956, 1668, 1600, 1532, 1445, 1315, 1047, 755, 695 cm⁻¹; ¹H NMR (600 MHz, CDCl₃) δ 8.22 (brs, 1H), 7.60 (d, 2H, *J* = 7.9 Hz), 7.43-7.33 (m, 7H), 7.17 (t, 1H, *J* = 7.6 Hz), 5.77 (d, 1H, *J* = 9.1 Hz), 5.13 (d, 1H, *J* = 9.1 Hz), 2.95 (brs, 1H), 2.75 (t, 2H, *J* = 8.5 Hz), 1.49-1.38 (m, 4H), 0.92 (t, 3H, *J* = 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 170.5, 148.6, 141.6, 137.3, 129.3, 128.6, 128.1, 126.8, 124.9, 124.8, 119.9, 69.8, 31.4, 30.5, 23.0, 14.1; HRMS (ESI): Exact mass calcd for C₂₀H₂₄NO₂ [M+H]⁺, requires *m/z*: 310.1807, found *m/z*: 310.1810; Enantiomeric excess determined by HPLC with Chiracel ADH column, 5% *i*-PrOH/hexanes, 1.0 mL/min, 254 nm; *t*_r (major) = 14.2, *t*_r (minor) = 24.9, 99% ee.

Preparation of (R,E)-2-hydroxy-4-methyl-N-phenylpent-3-enamide: The indicated compound was prepared according to General Procedure B and isolated by flash chromatography (15% EtOAc/hexanes) as a white solid that was homogeneous as judged by ¹H NMR spectroscopy (64% yield): mp 79-80 ° C; [α]_D -114 ° (*c* = 0.27, CHCl₃); IR (film) 3456, 3354, 3256, 2898, 1670, 1600, 1531, 1444, 1314, 1054, 852 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.10 (brs, 1H), 7.56 (d, 2H, *J* = 7.7 Hz), 7.34 (t, 2H, *J* = 7.3 Hz), 7.13 (t, 1H, *J* = 7.7 Hz), 5.36-5.33 (m, 1H), 4.92 (dd, 1H, *J* = 3.1, 9.0 Hz), 2.68 (d, 1H, *J* = 3.1 Hz), 1.87 (d, 3H, *J* = 1.1 Hz), 1.83 (d, 3H, *J* = 1.1 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 170.1, 129.3, 124.8, 122.5, 119.9, 69.7, 26.2, 18.8; HRMS (ESI): Exact mass calcd for C₁₂H₁₆NO₂ [M+H]⁺, requires *m/z*: 206.1181, found *m/z*: 206.1182; Enantiomeric excess determined by HPLC with Chiracel ADH column, 10% *i*-PrOH/hexanes, 0.8 mL/min, 254 nm; *t*_r (major) = 12.0, *t*_r (minor) = 18.4, 98% ee.

Preparation of (*R,E*)-5-ethyl-2-hydroxy-4-methyl-*N*-phenylhept-3-enamide (8): The indicated compound was prepared according to General Procedure B and isolated by flash chromatography (15% EtOAc/hexanes) as a white solid that was homogeneous as judged by ¹H NMR spectroscopy (59% yield): mp 91-92 ° C; [α]_D -98.5 ° (*c* = 0.42, CHCl₃); IR (film) 3257, 2960, 1682, 1652, 1599, 1540, 1446, 1250, 1077, 751, 690 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.02 (brs, 1H), 7.53 (d, 2H, *J* = 7.7 Hz), 7.33 (t, 2H, *J* = 7.9 Hz), 7.12 (t, 2H, *J* = 7.3 Hz), 5.34 (d, 1H, *J* = 8.7 Hz), 4.97 (dd, 1H, *J* = 3.2, 9.0 Hz), 2.87 (d, 1H, *J* = 3.2 Hz), 1.90-1.83 (m, 1H), 1.73 (d, 3H, *J* = 1.1 Hz), 1.58-1.32 (m, 4H), 0.84 (q, 6H, *J* = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 171.1, 146.6, 137.5, 129.3, 124.7, 124.0, 119.8, 69.5, 52.8, 26.2, 26.0, 12.8, 12.6, 12.4; HRMS (ESI): Exact mass calcd for C₁₆H₂₄NO₂ [M+H]⁺, requires *m/z*: 262.1807, found *m/z*: 262.1803; Enantiomeric excess determined by HPLC with Chiracel ADH column, 10% *i*-PrOH/hexanes, 0.8 mL/min, 254 nm; *t*_r (major) = 7.8, *t*_r (minor) = 15.2, 98% ee.

Using General Procedure A, 1:0.9 mixture of 7 and 8 was observed (in the crude after aqueous workup) which proved to be only partially separable. Flash chromatography (15% EtOAc/hexanes) yielded (*R*)-5-ethyl-2-hydroxy-4-methylene-*N*-phenylheptanamide (7) as a white solid that was homogeneous as judged by ¹H NMR spectroscopy (40% yield): mp 59-60 ° C; [α]_D +96.0 ° (*c* = 0.41, CHCl₃); IR (film) 3360, 2958, 2874, 1664, 1600, 1545, 1445, 1314, 1079, 900, 752, 691 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.53 (brs, 1H), 7.59 (d, 2H, *J* = 8.1 Hz), 7.34 (t, 2H, *J* = 7.7 Hz), 7.13 (t, 1H, *J* = 7.7 Hz), 5.01 (d, 1H, *J* = 3.3 Hz), 4.30 (dt, 1H, *J* = 2.9, 10.6 Hz), 2.81 (dd, 1H, *J* = 2.6, 14.8 Hz), 2.65 (d, 1H, *J* = 2.2 Hz), 2.26 (dd, 1H, *J* = 10.6, 14.6 Hz), 1.93-1.88 (m, 1H), 1.54-1.37 (m, 4H), 0.87-0.83 (m, 6H); ¹³C NMR (100 MHz, CDCl₃) δ 171.0, 148.7, 137.5, 129.3, 124.7, 119.9, 113.3, 69.8, 48.9, 40.2, 26.9, 25.8, 12.2, 11.8; HRMS (ESI): Exact mass calcd for C₁₆H₂₄NO₂ [M+H]⁺, requires *m/z*: 262.1807, found *m/z*: 262.1806; Enantiomeric excess determined by HPLC with Chiracel ADH column, 10% *i*-PrOH/hexanes,

0.8 mL/min, 254 nm; t_r (major) = 7.9, t_r (minor) = 10.6, 98% ee. Further elution yielded **8** (*vide supra*) as a white solid that was homogeneous as judged by ^1H NMR spectroscopy (28% yield, 98% ee).

Preparation of (R,E)-2-hydroxy-4,5,5-trimethyl-N-phenylhex-3-enamide: The indicated compound was prepared according to General Procedure B and isolated by flash chromatography (15% EtOAc/hexanes) as a white solid that was homogeneous as judged by ^1H NMR spectroscopy (55% yield): mp 114-115 ° C; $[\alpha]_D -50.5^\circ$ ($c = 0.53$, CHCl_3); IR (film) 3308, 2964, 1667, 1601, 1532, 1444, 1315, 1036, 868, 754 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.09 (brs, 1H), 7.55 (d, 2H, $J = 7.7$ Hz), 7.34 (t, 2H, $J = 7.7$ Hz), 7.13 (t, 1H, $J = 7.0$ Hz), 5.42 (d, 1H, $J = 8.7$ Hz), 4.94 (dd, 1H, $J = 3.2, 8.7$ Hz), 2.69 (d, 1H, $J = 3.2$ Hz), 1.89 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.2, 153.7, 138.3, 130.0, 125.4, 120.4, 70.2, 36.8, 28.9, 13.6; HRMS (ESI): Exact mass calcd for $\text{C}_{15}\text{H}_{22}\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 248.1650, found m/z : 248.1651; Enantiomeric excess determined by HPLC with Chiracel ADH column, 10% *i*-PrOH/hexanes, 0.8 mL/min, 254 nm; t_r (major) = 8.7, t_r (minor) = 18.5, 98% ee.

Preparation of (R,E)-2-hydroxy-3,4-dimethyl-N-phenylpent-3-enamide (10):^{vi} 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 (45% yield): mp 81-82 ° C; $[\alpha]_D -29.4^\circ$ ($c = 0.37$, CHCl_3); IR (film) 3230, 2964, 2689, 1659, 1599, 1443, 1260, 1063, 889, 798, 754 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.10 (brs, 1H), 7.54 (d, 2H, $J = 8.3$ Hz), 7.35 (t, 2H, $J = 7.8$ Hz), 7.14 (t, 1H, $J = 7.3$ Hz), 5.17 (d, 1H, $J = 2.9$ Hz), 3.06 (d, 1H, $J = 2.9$ Hz), 1.93

(vi) The known vinylsilane **9** was prepared from the vinylbromide (commercially available) via a lithium-halogen exchange using 2.5 equiv of *t*-BuLi followed by addition of 1.1 equiv of chloromethyltrimethylsilane at -78°C in Et_2O (0.25M with respect to vinylbromide).

(s, 3H), 1.79 (s, 3H), 1.65 (s, 3H); ^{13}C NMR (100 MHz, CDCl_3) δ 171.1, 137.4, 133.6, 129.3, 126.1, 124.9, 120.0, 71.8, 21.5, 20.6, 12.9; HRMS (ESI): Exact mass calcd for $\text{C}_{13}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 220.1337, found m/z : 220.1334; Enantiomeric excess determined by HPLC with Chiracel ADH column, 7.5% *i*-PrOH/hexanes, 1.0 mL/min, 254 nm; t_r (major) = 12.0, t_r (minor) = 21.9, 99% ee.

Preparation of (*S*)-2-hydroxy-*N*,4-diphenylbut-3-enamide (12**):**^{vii} The indicated compound was prepared according to General Procedure A using catalyst **1e**. Flash chromatography (15% EtOAc/hexanes) yielded a yellow solid that was homogeneous as judged by ^1H NMR spectroscopy (60% yield): mp 91-92 ° C; $[\alpha]_D$ -69.8 ° (c = 1.12, CHCl_3); IR (film) 3337, 3060, 1670, 1560, 1538, 1490, 1446, 1318, 1260, 1072, 903, 754 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.23 (brs, 1H), 7.58 (d, 2H, J = 8.0 Hz), 7.47 (d, 2H, J = 7.8 Hz), 7.38-7.30 (m, 5H), 7.17 (t, 1H, J = 7.8 Hz), 5.19 (brs, 1H), 3.49 (brs, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 166.8, 137.1, 132.3, 129.4, 128.6, 125.3, 121.7, 120.1; HRMS (ESI): Exact mass calcd for $\text{C}_{16}\text{H}_{14}\text{NO}_2$ $[\text{M}+\text{H}]^+$, requires m/z : 252.1024, found m/z : 252.1036; Enantiomeric excess determined by HPLC with Chiracel ADH column, 7.5% *i*-PrOH/hexanes, 1.0 mL/min, 254 nm; t_r (minor) = 13.4, t_r (major) = 18.4, -89% ee.

Mosher's ester analysis of (*R,E*)-2-hydroxy-*N*,4-diphenylbut-3-enamide,

^1H NMR (600 MHz, CDCl_3) δ 7.637-7.321 (m, 15H), 7.179-7.151 (m, 1H), 6.936 (d, 1H, J = 15.96 Hz), 6.364 (dd, 1H, J = 7.32, 15.80 Hz), 6.170 (d, 1H, J = 7.32 Hz), 3.653 (s, 3H).

^1H NMR (500 MHz, CDCl_3) δ 7.730 (brs, 1H), 7.601-7.264 (m, 14H), 7.152 (t, 1H, J = 7.32 Hz), 6.805 (d, 1H, J = 16.11 Hz), 6.300 (dd, 1H, J = 6.84, 15.99 Hz), 6.073 (d, 1H, J = 6.84 Hz), 3.607 (s, 3H).

(vii) **12** was prepared using 10 mol % of catalyst **1e** in General Procedure A. Using catalyst **1f**, a lower ee (68%) was observed.

¹H NMR SPECTRA

YA-II-087-1H-Characterised

```

exp1 stdlh
SAMPLE
date Dec 7 2005
solvent CDCl3
file CDC13
ACQUISITION
sfrq 400.004
dn 400.004
dpr 40
dof 0
nnn
tn 2.731
dm 7500
at 32748
np 5995.2
temp 22.0
sw not used
fb 8
lb PROCESSING 0.10
bs 2
vtfile
proc not used
fn
tpwr 60
ps 25.0
dl 2.000
werr
tof 0
wexp
nt 32
wbs
ctt 17
wnt
atlock not used
gain
flags
ll n
ln n
dp n
y
Sp -200.2
Wp 3993.9
Vs 151
Sc 0
Wc 250
hzmm 16.00
ls 289.57
rf1 1003.6
rfp 0
th 0
ins 4
nm ph 1.000

```

YA-II-089-1H-characterised

```

exp2 stdih
SAMPLE
date Apr 26 2006 DEC. & VT
solvent CDCl3 dfrq 400.021
file ACQUISITION exp dpr 40
sfrq 400.021 dm nm
at 2.731 dmf 7500 C
np 32748 temp 22.0
sv 5895.2 PROCESSING
fb 3400 lb 0.10
bs 8 wfile
ss 2 proc ft
tpr 60 fn not used
dpr 100
dl 0.120 werr
nt 10 wexp svf(n1)
ct 14 wnt
clock not used
gain n
il n
in n
dp y
DISPLAY
sp -200.1
wp 3939.3
vs S1
sc 0
wc 250
hzmm 16.00
ls 283.57
rfi 1042.6
rfp 0
th 0
ins 6
nm 1.000 ph

```

(Table 2, entry 4)

YA-II-226-¹H-characterised

```

exp2 std1h
SAMPLE
date Apr 23 2006 DEC. & VT
solvent CDCl3 dn 400.021
file exp dpwr 40
ACQUISITION exp dof 0
sfrq 400.021 dm nnn
tn 2.731 dmf C
at 32748 temp 7500
np 5995.2 temp PROCESSING 22.0
sv 3400 lb 0.10
fb 8 wfile
bs 2 proc ft
ss 60 fn not used
tpwr 10.0
p1 0.120 werr
tof 0 wexp svf(n1)
nt 16 wbs
ct 16 wmt
a1ock n
gain not used
FLAGS
il n
in n
dp y
DISPLAY
sp -200.1
wp 3999.5
vs 42
sc 0
wc 250
l2mm 15.00
ls 289.57
rf1 1042.6
rfp 0
th 9
lms 1.000
nm ph

```

(Table 2, entry 5)

YA-II-231-col-811-C3
Pulse Sequence: s2pu1
Solvent: CDCl3
Temp: 23.0 C / 286.1 K
INOVA-500 -Inova500m

Relax. delay 2.000 sec
Pulse 79.4 degrees
Acq. time 2.045 sec
Width 8000.0 Hz
32 repetitions
OBSERVE H1, 499.6156790 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 32768
Total time 2 min, 17 sec

```

YA-II-018-1H-characterised
Data Collected on:
Acquisition: 1600
Archive directory:
Sample directory:
/export/home/1600/vnarsys/data
Sample directory:

File: PROTON

Pulse Sequence: s2pul
Solvent: CDCl3
Temp. 20.0 C / 293.1 K

Relax. delay 2.000 sec
Pulse 45.0 degrees
Acq. time 2.040 sec
Width 9596.9 Hz
20 repetitions
OSERVE H1 599.7764064 MHz
DATA PROCESSING
Line broadening 0.1 Hz
FT size 65536
Total time 2 min

```

YA-II-285-1H-characterised

exp1 std1h

SAMPLE DEC. & VT
 date May 25 2006 dfrq 400.021
 solvent CDCl3 dn 40
 file ACQUISITION exp 40
 sfrq 400.021 dm nnn
 tn 2.731 dm c
 at 32748 def 7500
 np 5995.2 temp 22.0
 fb 3400 lb PROCESSING 0.10
 bs 2 wfile
 ss 2 proc ft
 tpr 16.0 fn not used
 pw 2.000 werr
 dt 0 wexp
 nt 32 wds
 ct 32 wnt
 alock n
 gain not used
 FLAGS
 il n
 in n
 dp y
 DISPLAY
 sp -200.1
 wp 3899.9
 vs 98
 sc 0
 wc 250
 hzmm 16.00
 fs 289.57
 rfl 1042.8
 rfp 0
 th 4
 ins 1.000
 nm ph

Data Collected on:
narsun-inova600
Archive directory:
/export/home/1690/vnarsys/data
Sample directory:

File: PROTON

Pulse Sequence: zgpg30

Solvent: CDCl₃

Temp. 22.0 C / 295.1 K

Relax. delay 1.000 sec

Pulse 45.0 degrees

Acq. time 3.414 sec

Width 9596.9 Hz

repetitions 8

OBSERVE H1, 599.7764064 MHz

DATA PROCESSING

Line broadening 0.1 Hz

FT size 65536

Total time 0 min

(Table 3, entry 5)

YA-II-136-Agcol-frac6

```

exp6 s2pul
SAMPLE
date Feb 7 2006 dfrq 500.211
solvent CDCl3 dn H1
file C013 exp 32
ACQUISITION
sfrq 500.211 dm nmh
tn 2.048 dmf 8770
at 32768 dseq
sw 8000.0 dres 1.0
fb 4000 homo 22.0
bs 8 temp
cs 2 PROCESSING
tpwr 58 lb wfile 0.10
pw 5.0 wfile
di 0 proc ft
tof 0 fn not used
nt 16 math f
ct 16
alock n werr
gain not used wexp
flags wbs
il n wnt
in n
dp n
hs nn
DISPLAY
sp -250.3
wp 4752.0
vs 180
sc 0
wc 250
hzm 18.01
ls 758.76
rf1 1488.8
rfl 0
th 0
ins 1.000
nm ph

```

¹³C NMR SPECTRA

YA-II-231-13C-characterised

Pulse Sequence: s2pul

Solvent: CDCl₃

Temp. 25.0 C / 298.1 K

User: 1-14-87

INNOVA-500 "1NOVA500c"

Pulse 35.2 degrees

Acq. time 1.692 sec

Width 28945.3 Hz

34784 repetitions

OBSERVE CH1 125.6931345 MHz

DECOUPLE CH1 499.8754943 MHz

Power 44 dB

Continuously on

WALTZ-16 modulated

DATA PROCESSING

Line broadening 1.0 Hz

FT size 55336

Total time 305 hr, 55 min, 3 sec

YA-II-082-13C-characterised

Pulse Sequence: s2pul

Solvent: DCD₃

Temp: 25.0 C / 298.1 K

User: 1-14-87

INOVA-500 "Inova500c"

Pulse 35.2 degrees

Acq. time 1.092 sec

Width 25996.3 Hz

975 repetitions

OBSERVE C13, 125.8931345 MHz

DECOUPLE H1, 499.8753343 MHz

Power 44 dB

Continuously on

VAT2-processed

DATA PROCESSING

Line broadening 1.0 Hz

FT size 65536

Total time 3059 hr, 11 min, 23 sec

ANALYTICAL HPLC TRACES

(Table 2, entry 2)

(Table 2, entry 3)

(Table 2, entry 4)

(Table 2, entry 5)

(Table 2, entry 6)

(Table 2, entry 7)

(Table 3, entry 1)

(Table 3, entry 4)

(Table 3, entry 5)

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 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.