Supporting Information

**General.** Infrared (IR) spectra are recorded on a Perkin Elmer 781 spectro-photometer, \( \nu_{\text{max}} \) in cm\(^{-1}\). Bands are characterized as broad (br), strong (s), medium (m), and weak (w). \(^1\)H NMR spectra are recorded on a Varian Unity INOVA 400 (400 MHz) or Varian Gemini 2000 (400 MHz). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl\(_3\): \( \delta \) 7.26). Data are reported as follows: chemical shift, multiplicity \((s = \text{singlet}, d = \text{doublet}, t = \text{triplet}, q = \text{quartet}, \text{br} = \text{broad}, m = \text{multiplet})\), coupling constants (Hz), and integration. \(^{13}\)C NMR spectra are recorded on a Varian Unity INOVA 400 (100 MHz) or Varian Gemini 2000 (100 MHz) with complete proton decoupling. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard (CDCl\(_3\): \( \delta \) 77.7). Enantiomer ratios were determined by chiral GLC analysis (Alltech Associates Chiraldex GTA column (30 m x 0.25 mm) or chiral HPLC analysis (Chiral Technologies Chiracel OJ (25 cm x 0.46 cm) in comparison with authentic materials. Elemental analyses are performed by Robertson Microlit Laboratories (Madison, New Jersey). High-resolution mass
spectrometry is performed by the University of Illinois Mass Spectrometry Laboratories (Urbana, Illinois). Absolute stereochemistry is determined by optical rotation on a Rudolph Research Analytical Autopol IV polarimeter.

All reactions are conducted in oven- (135 °C) and flame-dried glassware under an inert atmosphere of dry nitrogen. Solvents are purified under a positive pressure of dry argon by a modified Advanced Chem Tech purification system: toluene is purified through Cu and alumina columns. Al(OiPr)₃ and TMSCN are purchased from Aldrich and distilled. Aromatic and aliphatic ketones were purchased from Aldrich and stored over calcium chloride and distilled prior to use or readily synthesized from commercially available starting materials. Molecular sieves are activated by heating at 180 °C for 3h under high vacuum. EDC, HOBt, piperidine, Fmoc-Gly-Wang resin, Fmoc-protected amino acids are purchased from commercial sources and used without further purification.

**Preparation of Schiff-base tripeptides on the solid phase.** Reactions were performed in polypropylene Bio-spin chromatography tubes from Bio-Rad Laboratories with a fritted bottom and a cap on either end. Fmoc-Gly-Wang resin (100 mg, 0.04 mmol) was placed in the polypropylene reaction vessel and washed with DMF (3x1.5 mL). The resin was swelled by rotation in DMF (1.5 mL) for 12 h, washed with additional DMF (3x1.5 mL). The resin was subsequently deprotected by washing with 20 % piperidine/DMF (1.5 mL), rotation for 1.5 h in 20% piperidine/DMF (1.5 mL), and then washing with DMF (10x1.5 mL). The Fmoc protected amino acid AA2 (0.17 mmol) was activated as a symmetrical anhydride by treatment with an excess of DIC (49 µL, 0.25 mmol) in DMF (1.5 mL, 20 min). The resulting solution was added to H₂N-Gly-Wang, rotated for 1.5 h and then washed with DMF (10x1.5 mL). Fmoc-AA2-Gly-Wang was deprotected by washing with 20 % piperidine/DMF (1x1.5 mL), rotation for 1.5 h in 20 % piperidine/DMF (1.5 mL), and then washing with DMF (10x1.5 mL). The second amino acid coupling and deprotection was performed in the same manner as before. Following coupling and deprotection, H₂N-AA1-AA2-Gly-Wang was treated with 4.0 equiv (0.17 mmol) of an ortho-hydroxy
aldehyde in 1.5 mL DMF for 3 h and then washed with DMF (10x1.5 mL). The ligand can be used either on or off the solid support. On the support: The SB-AA1-AA2-Gly-Wang resin was washed with toluene (3x1.5 mL) then dried under reduced pressure for 12 h. The resin was transferred to 96-well plates and stored in a dessicator until needed. Cleavage from the resin: The ligand was cleaved from the resin by rotation with 2.0 mL of triethylamine/DMF/MeOH (1:1:9) for 72h. The solution was filtered and resin was washed thoroughly with distilled THF (3x2 mL). Solvent was removed in vacuo and the resulting yellow solid was taken up in EtOAc (1.0 mL) and loaded onto a pipet packed with a cotton plug and silica gel. The ligand was eluted with EtOAc (~10 mL). The product was dissolved in toluene (5 mL) and concentrated on a rotary evaporator to azeotrope off water and DMF. The product was dried in vacuo to give a pale to bright yellow solid. When the ligands were prepared on a large scale (~5 g) the product was purified by recrystallization (methanol/water) or silica gel chromatography. Typical yields for the seven steps were 70-90%.

2-Hydroxy-5-methoxy-salicyl-Val-Gln(Trt)-Gly(OMe) (1): IR (neat): 3393 (w), 3298 (s), 3060 (w), 2953 (m), 2930 (w), 2870 (w), 2260 (w), 1747 (m), 1652 (s), 1586 (w), 1491 (s), 1450 (m), 1271 (s), 1164 (m), 1033 (w), 701 (w) cm⁻¹; ¹H NMR (400 MHz): δ 12.05 (s, 1H), 8.21 (s, 1H), 7.31-7.13 (m, 16H), 7.07-7.04 (m, 2H), 6.93 (dd, J = 9.2, 2.8 Hz, 1H), 6.89 (d, J = 9.2 Hz, 1H), 4.32 (q, J = 6.8 Hz, 1H), 4.00 (dd, J = 18, 6.4 Hz, 1H), 3.76 (s, 3H), 3.69 (d, J = 5.2 Hz, 1H), 3.65 (s, 3H), 3.61 (d, J = 4.4 Hz, 1H), 2.42 (dt, J = 7.2, 2.8 Hz, 2H), 2.46-2.40 (m, 2H), 2.04 (dt,J = 6.8, 6.4 Hz, 2H), 0.92 (d, J = 6.8 Hz, 2H), 0.89 (d, J = 6.8 Hz, 2H); ¹³C NMR (100 MHz): δ 172.4, 171.4, 171.1, 170.2, 167.7, 155.3, 152.4, 144.6, 128.9, 128.2, 127.3, 120.6, 118.3, 118.2, 115.4, 79.6, 71.0, 56.2, 52.4, 51.9, 41.2, 33.7, 32.2, 29.9, 19.8, 17.6; HRMS Calcd. for C₄₀H₄₄N₄O₇+H: 693.3288, Found: 693.3287; Anal. Calcd. for C₄₀H₄₄N₄O₇: C, 69.35; H, 6.40; N, 8.09. Found: C, 69.12; H, 6.51; N, 8.01. [α]₂⁰° +9.6° (c = 1.40, CHCl₃)
2-Trimethylsilyloxy-2-phenylpropanenitrile (3): IR (neat): 3062 (w), 3024 (w), 2993 (w), 2967 (m), 2904 (w), 1495 (w), 1451 (m), 1369 (w), 1256 (s), 1230 (s), 1155 (s), 1123 (s), 1073 (m), 991 (s), 847 (s), 752 (s), 702 (s) cm⁻¹; ¹H NMR (400 MHz): δ 7.56-7.53 (m, 2H), 7.41-7.34 (m, 3H), 1.85 (s, 3H), 0.17 (s, 9H); ¹³C NMR (100 MHz): δ 142.2, 128.9, 121.9, 71.8, 33.8, 1.3; HRMS Calcd. for C₁₂H₁₇NOSi: 219.1079, Found: 219.1082; Anal. Calcd for C₁₂H₁₇NOSi: C, 65.71; H, 7.81; N, 6.39; Found: C, 65.78; H, 7.84; N, 6.59; [α]₂₀°D +18.5° (c = 1.25, CHCl₃, 88% ee) [lit. [α]₂₄°D +21.9 (c = 1.18, CHCl₃, 93% ee)]¹; GC (CDGTA: column temperature = 80 °C (isothermal), injector and detector temperature = 250 °C, inlet pressure = 15 psi): tᵣ (major) = 46.2 min, tᵣ (minor) = 51.1 min. The chromatograms are illustrated below.

2-Trimethylsilyloxy-2-(4'-methoxyphenyl)propanenitrile (5): IR (neat): 2993 (w), 2961 (m), 2904 (w), 2836 (w), 2880 (w), 1608 (s), 1583 (w), 1514 (s), 1463 (w), 1306 (m), 1255 (s), 1230 (s), 1180 (s), 1155 (m), 1111 (s), 1036 (m), 997 (s), 840 (br, s), 752 (m) cm⁻¹; ¹H NMR (400 MHz): δ 7.44 (d, J = 8.8 Hz, 2H), 6.88 (d, J = 8.8 Hz, 2H), 3.80 (s, 3H), 1.83 (s, 3H), 0.15 (s, 9H); ¹³C NMR (100 MHz): δ 160.0, 134.2, 126.3, 122.0, 114.2, 71.5, 55.5, 33.6, 1.3; HRMS Calcd. for C₁₃H₁₉NO₂Si: 249.1185, Found: 249.1184; Anal. Calcd. for C₁₃H₁₉NO₂Si: C, 62.61; H, 7.68; N, 5.62; Found: C, 62.88; H, 7.49; N, 5.82; [α]₂₀°D +22.6° (c = 1.09, CHCl₃, 91% ee); GC (CDGTA: column temperature = 95 °C (isothermal), injector and detector temperature = 250 °C, inlet pressure = 15 psi): tᵣ (major) = 127.4 min, tᵣ (minor) = 135.5 min.

2-Trimethylsilyloxy-2-(4′-nitrophenyl)propanenitrile (7):
IR (film on NaCl): 3112 (w), 3074 (w), 2993 (w), 2961 (s), 2904 (w), 2855 (w), 2360 (w), 1935 (w), 1608 (s), 1526 (s), 1488 (m), 1451 (m), 1406 (m), 1350 (s), 1255 (s), 1225 (s), 1161 (s), 1123 (s), 1073 (m), 998 (s), 853 (s), 752 (m), 702 (m) cm⁻¹; 
¹H NMR (400 MHz): δ 8.26 (dd, J = 7.1, 2.0 Hz, 2H), 7.72 (dd, J = 7.1, 2.0 Hz, 2H), 1.86 (s, 3H), 0.22 (s, 9H); 
¹³C NMR (100 MHz): δ 149.2, 148.5, 125.9, 124.2, 120.9, 71.1, 33.7, 1.3; 
HRMS Calcd. for C₁₂H₁₃N₂O₃Si⁺H: 265.1008, Found: 265.1007; 
Anal. Calcd. for C₁₂H₁₃N₂O₃Si: C, 54.52; H, 6.10; N, 10.60; Found: C, 54.80; H, 5.79; N, 10.30; [α]₂⁰° +16.2° (c = 1.67, CHCl₃, 88% ee); 
GC (CDGTA: column temperature = 130 °C (isothermal), injector and detector temperature = 250 °C, inlet pressure = 15 psi): tᵣ (major) = 74.1 min, tᵣ (minor) = 83.4 min.

2-Trimethylsilyloxy-2-(2′-chlorophenyl)propanenitrile (9):
IR (neat): 3068 (br, w), 2993 (w), 2955 (m), 2898 (w), 1590 (w), 1530 (w), 1469 (m), 1432 (m), 1369 (w), 1265 (m), 1255 (s), 1218 (m), 1161 (s), 1117 (s), 1092 (m), 1036 (m), 998 (s), 853 (s), 758 (s), 726 (w), 701 (w) cm⁻¹; 
¹H NMR (400 MHz): δ 7.71-7.69 (m, 1H), 7.41–7.38 (m, 1H), 7.32–7.27 (m, 2H), 1.99 (s, 3H), 0.28 (s, 9H); 
¹³C NMR (100 MHz): δ 138.3, 131.7, 131.4, 127.3, 127.2, 120.6, 70.5, 30.0, 1.4; 
HRMS Calcd. for C₁₂H₁₃ClNOSi: 253.0690, Found: 253.0695; 
Anal. Calcd. for C₁₂H₁₃ClNOSi: C, 56.79; H, 6.35; N, 5.52; Found: C, 56.85; H, 6.24; N, 5.68; [α]₂⁰° +2.3° (c = 1.69, CHCl₃, 85% ee); 
GC (CDGTA: column temperature = 90 °C (isothermal), injector and detector temperature = 250 °C, inlet pressure = 15 psi): tᵣ (major) = 105.5 min, tᵣ (minor) = 115.5 min.

2-Trimethylsilyloxy-2-(2′-naphthyl)propanenitrile (11):
IR (film on NaCl): 3056 (w), 2987 (w), 2961 (m), 2898 (w), 1602 (w), 1507 (w), 1451 (w), 1406 (w), 1369 (w), 1356 (w), 1256 (s), 1218 (m), 1186 (m), 1149 (m), 1120 (s), 1102 (s), 1067 (w), 997 (s), 953 (w), 847 (s), 815 (m), 752 (m) cm⁻¹; 
¹H NMR (400 MHz): δ 8.04 (d, J = 1.6 Hz, 1H), 7.90–7.84 (m, 3H), 7.60 (dd, J = 8.4, 1.6 Hz, 1H), 7.50 (m, 2H), 1.94 (s, 3H), 0.19 (s, 9H); 
¹³C NMR (100 MHz): δ 139.4, 133.4, 133.0,
129.0, 128.6, 127.9, 127.0, 123.9, 122.6, 121.9, 72.1, 33.7, 1.4; HRMS Calcd. for C_{16}H_{19}NOSi: 269.1236, Found: 269.1236; Anal. Calcd. for C_{16}H_{19}NOSi: C, 71.33; H, 7.11; N, 5.20; Found: C, 71.46; H, 7.14; N, 5.47; [α]_{20}^{D} +12.6° (c = 1.99, CHCl_{3}, 94% ee); HPLC (CHIRALCEL OJ, iPrOH/hexane=1/99, flow=0.5 ml/min): t_{r} (major) = 12.1 min, t_{r} (minor) = 15.4 min. The chromatograms are illustrated below.

2-Trimethylsilyloxy-2-phenyl-butanenitrile (13): IR (neat): 3062 (w), 3030 (w), 2967 (br, m), 2886 (w), 1488 (w), 1451 (m), 1256 (s), 1205 (w), 1148 (w), 1117 (m), 1104 (m), 1079 (w), 1029 (m), 928 (w), 865 (s), 840 (s), 758 (m), 695 (m) cm^{-1}; ^{1}H NMR (400 MHz): δ 7.52-7.50 (m, 2H), 7.40-7.33 (m, 3H), 2.08-2.03 (m, 1H), 1.96-1.91 (m, 1H), 0.98 (t, J = 7.6 Hz, 3H), 0.13 (s, 3H); ^{13}C NMR (100 MHz): δ 141.1, 128.8, 128.7, 125.4, 121.0, 76.5, 39.4, 8.9, 1.4; HRMS Calcd. for C_{13}H_{19}NOSi: 233.1236, Found: 233.1237; Anal. Calcd. for C_{13}H_{19}NOSi: C, 66.90; H, 8.21; N, 6.00; Found: C, 66.49; H, 8.21; N, 6.11; [α]_{20}^{D} +19.4° (c = 1.39, CHCl_{3}, 88% ee); GC (CDGTA: column temperature = 80 °C (isothermal), injector and detector temperature = 250 °C, inlet pressure = 15 psi): t_{r} (major) = 62.7 min, t_{r} (minor) = 66.3 min.

1-Chloro-2-phenyl-2-trimethylsilyloxypropanenitrile (15): IR (neat): 3069 (w), 3031 (w), 2961 (w), 2899 (w), 1488 (w), 1451 (m), 1419 (w), 1255 (s), 1199 (m), 1123 (s), 1098 (m), 1060 (m), 1004 (w), 970 (m), 922 (m), 853 (s), 758 (m), 733 (m), 695 (m) cm^{-1}; ^{1}H NMR (400 MHz): δ 7.58-7.55 (m, 2H), 7.44-7.41 (m, 3H), 3.74 (d, J = 11.6 Hz, 1H), 3.65
(d, J = 11.6 Hz, 1H), 0.18 (s, 9H); 13C NMR (100 MHz): δ 138.1, 129.9, 129.1, 125.8, 119.0, 76.1, 52.9, 1.1; HRMS Calcd. for C12H13ClNOSi: 253.0690, Found: 253.0695; Anal. Calcd. for C12H13ClNOSi: C, 56.79; H, 6.35; N, 5.52; Found: C, 56.72; H, 6.44; N, 5.63; [α]20D +17.7 ° (c = 1.70, CHCl3, 80% ee); GC (CDGTA: column temperature = 90 °C (isothermal), injector and detector temperature = 250 °C, inlet pressure = 15 psi): tR(minor) = 120.9 min, tR(major) = 124.2 min.

1-Trimethylsilyloxy-1-indanecarbonitrile (17): IR (neat): 3075 (w), 3030 (w), 2955 (m), 2924 (w), 2225 (w), 1602 (w), 1476 (w), 1460 (w), 1449 (w), 1300 (w), 1255 (s), 1180 (m), 1130 (m), 1080 (s), 997 (m), 878 (s), 846 (s), 765 (s) cm-1; 1H NMR (400 MHz): δ 7.53 (d, J = 7.0 Hz, 1H), 7.26 (m, 3H), 3.07 (ddd, J = 15.7, 7.7, 5.4 Hz, 1H), 2.98 (ddd, J = 15.7, 7.7, 5.7 Hz, 1H), 2.67 (ddd, J = 13.2, 7.7, 5.7 Hz, 1H), 2.41 (ddd, J = 13.2, 7.7, 5.4 Hz, 1H), 0.19 (s, 9H); 13C NMR (100 MHz): δ 142.8, 142.4, 130.2, 127.6, 125.4, 124.3, 121.3, 76.7, 43.0, 29.6, 1.4; HRMS Calcd. for C13H17NOSi: 231.1079, Found: 231.1080; Anal. Calcd. for C13H17NOSi: C, 67.49; H, 7.41; N, 6.05; Found: C, 67.49; H, 7.46; N, 6.22; [α]20D +31.6° (c = 1.52, CHCl3, 88% ee); GC (CDGTA: column temperature = 105 °C (isothermal), injector and detector temperature = 250 °C, inlet pressure = 15 psi): tR(major) = 92.0 min, tR(minor) = 96.5 min.

4-Trimethylsilyloxy-4-chromanecarbonitrile (19): IR (neat): 3068 (w), 3037 (w), 2961 (m), 2886 (w), 1608 (m), 1583 (m), 1488 (s), 1451 (s), 1313 (m), 1290 (m), 1262 (s), 1230 (s), 1118 (s), 1095 (m), 1048 (s), 1016 (m), 895 (m), 846 (s), 758 (s) cm-1; 1H NMR (400 MHz): δ 7.57 (dd, J = 7.8, 1.7 Hz, 1H), 7.27 (ddd, J = 8.3, 7.3, 1.7 Hz, 1H), 6.97 (ddd, J = 7.8, 7.3, 0.8 Hz, 1H), 6.82 (dd, J = 8.3, 0.8 Hz, 1H), 4.33 (m, 2H), 2.48-2.33 (m, 2H), 0.17 (s, 9H); 13C NMR (100 MHz): δ 153.8, 131.6, 128.9, 121.2, 121.0, 117.8, 65.8, 61.5, 36.5, 1.4; HRMS Calcd. for C13H17NO2Si: 247.1029, Found: 247.1027; Anal. Calcd. for C13H17NO2Si: C, 63.12; H, 6.93; N, 5.66; Found: C, 63.40; H, 6.78; N, 5.85; [α]20D +60.7° (c = 1.79, CHCl3, 88% ee); GC (CDGTA: column temperature = 90 °C (isothermal), injector and detector temperature = 250 °C, inlet pressure = 15 psi): tR(major) = 169.6 min, tR(minor) = 175.3 min.

2-Methyl-4-phenyl-2-trimethylsilyloxybutanenitrile (21). IR (neat): 3087 (w), 3062 (w), 3030 (w), 2993 (w), 2955 (w), 2867 (w), 1608 (w), 1501 (w), 1457 (w), 1375 (w), 1255 (s), 1180 (m), 1117 (m), 1073 (m), 1041 (w), 985 (m),
846 (s), 758 (m), 702 (m) cm\(^{-1}\); \(^1\)H NMR (400 MHz): \(\delta\) 7.34-7.30 (m, 2H), 7.24-7.21 (m, 3H), 2.92-2.81 (m, 2H), 2.08-1.66 (m, 2H), 1.65 (s, 3H), 0.30 (s, 9H); \(^{13}\)C NMR (100 MHz): \(\delta\) 141.0, 128.8, 128.6, 126.4, 122.1, 69.6, 45.5, 31.0, 29.3, 1.6; HRMS Calcd for C\(_{14}\)H\(_{21}\)NOSi: 247.1392, Found: 247.1390; Anal. Calcd. for C\(_{14}\)H\(_{21}\)NOSi: C, 67.96; H, 8.56; N, 5.66; Found: C, 67.82; H, 8.42; N, 5.94; \([\alpha]_{D}^{20}\) +9.7° (c = 1.78, CHCl\(_3\), 80% ee); GC (CDGTA: column temperature = 85 °C (isothermal), injector and detector temperature = 250 °C, inlet pressure = 15 psi): \(t_r\) (major) = 228.1 min, \(t_r\) (minor) = 240.2 min.

2-Methyl-4-phenyl-2-trimethylsilyloxybut-3-enenitrile (23). IR (neat): 3062 (w), 3030 (w), 2993 (w), 2904 (w), 1495 (w), 1451 (w), 1255 (s), 1193 (m), 1130 (m), 1087 (s), 1004 (m), 966 (m), 847 (s), 752 (m), 690 (m) cm\(^{-1}\); \(^1\)H NMR (400 MHz): \(\delta\) 7.44-7.42 (m, 2H), 7.39-7.37 (m, 2H), 7.36-7.31 (m, 1H), 6.89 (dd, \(J = 16, 2.0\) Hz, 1H), 6.13 (dd, \(J = 16, 1.6\) Hz, 1H), 1.76 (s, 3H), 0.27 (s, 9H); \(^{13}\)C NMR (100 MHz): \(\delta\) 135.4, 131.2, 129.8, 129.1, 128.9, 127.2, 120.9, 70.2, 31.1, 1.7; HRMS Calcd. for C\(_{14}\)H\(_{19}\)NOSi: 245.1236, Found: 245.1236; Anal. Calcd. for C\(_{14}\)H\(_{19}\)NOSi: C, 68.52; H, 7.80; N, 5.71; Found: C, 68.54; H, 7.58; N, 5.95; \([\alpha]_{D}^{20}\) +62.3° (c = 1.76, CHCl\(_3\), 95% ee); GC (CDGTA: column temperature = 105 °C (isothermal), injector and detector temperature = 250 °C, inlet pressure = 25 psi): \(t_r\) (major) = 77.6 min, \(t_r\) (minor) = 81.3 min.

2-Methyl-2-trimethylsilyloxy-nonanenitrile (25). IR (neat): 2955 (w), 2923 (w), 2854 (w), 1463 (w), 1375 (w), 1255 (w), 1186 (w), 1142 (w), 1104 (w), 1079 (w), 1035 (w), 985 (m), 754 (w) cm\(^{-1}\); \(^1\)H NMR (400 MHz): \(\delta\) 1.70-1.65 (m, 2H), 1.53 (s, 3H), 1.52-1.38 (m, 1H), 1.29-1.26 (m, 6H), 0.86 (t, \(J = 7.2\) Hz, 3H), 0.21 (s, 9H); \(^{13}\)C NMR (100 MHz): \(\delta\) 122.4, 69.9, 43.6, 31.9, 29.5, 29.3, 29.1, 24.5, 22.8, 14.2, 1.5; HRMS Calcd. for C\(_{13}\)H\(_{27}\)NOSi: 241.1862, Found: 241.1863; Anal. Calcd. for C\(_{13}\)H\(_{27}\)NOSi: C, 64.67; H, 11.27; N, 5.80; Found: C, 64.52; H, 11.48; N, 6.11; \([\alpha]_{D}^{20}\) +9.3° (c = 1.25, CHCl\(_3\), 86% ee) GC (CDGTA: column temperature = 90 °C (isothermal), injector and detector temperature = 250 °C, inlet pressure = 15 psi): \(t_r\) (major) = 41.5 min, \(t_r\) (minor) = 44.1 min.

2-Methyl-2-trimethylsilyloxy-non-3-enenitrile (27). IR (neat): 2990 (w), 2958 (m), 2929 (s), 2873 (m), 2858 (m), 1666 (w), 1467 (w), 1460 (w), 1372 (w), 1254 (s), 1208 (w), 1188 (w), 1149 (m), 1112 (s), 1003 (m), 972 (m), 846 (s),
757 (m) cm⁻¹; \(^1\)H NMR (400 MHz): \(\delta 5.96\) (dt, \(J = 15.4, 6.8\) Hz, 1H), 5.41 (dt, \(J = 15.4, 1.5\) Hz, 1H), 2.09-2.03 (m, 2H), 1.61 (s, 3H), 1.42-1.36 (m, 2H), 1.32-1.24 (m, 4H), 0.88 (t, \(J = 6.9\) Hz, 3H), 0.19 (s, 9H); \(^{13}\)C NMR (100 MHz): \(\delta 133.1, 130.9, 121.3, 70.1, 31.9, 31.6, 31.3, 28.5, 22.7, 14.2, 1.6\); HRMS Calcd. for \(\text{C}_{13}\text{H}_{25}\text{NOSi}\): 239.1705, Found: 239.1705; Anal. Calcd. for \(\text{C}_{14}\text{H}_{19}\text{NOSi}\): C, 65.21; H, 10.52; N, 5.85; Found: C, 65.48; H, 10.42; N, 5.98; \([\alpha]^{20}_{D} -3.6^\circ\) (c = 1.12, CHCl₃, 95% ee); GC (CDGTA: column temperature = 80 °C (isothermal), injector and detector temperature = 250 °C, inlet pressure = 15 psi): \(t_r\) (major) = 64.6 min, \(t_r\) (minor) = 66.5 min.

2-Methyl-2-trimethylsilyloxy-dec-3-ynenitrile (29). IR (neat): 2999 (w), 2961(s), 2930 (s), 2854 (m), 2231 (w), 1734 (w), 1677 (w), 1463 (w), 1369 (w), 1250 (m), 1211 (m), 1142 (m), 1111 (s), 985 (m), 846 (s), 758 (m) cm⁻¹; \(^1\)H NMR (400 MHz): \(\delta 2.20\) (t, 2H), 1.80 (s, 3H), 1.55-1.48 (m, 2H), 1.40-1.25 (m, 6H), 0.87 (t, \(J = 7.2\) Hz, 3H), 0.26 (s, 9H); \(^{13}\)C NMR (100 MHz): \(\delta 120.2, 88.0, 78.0, 60.6, 33.0, 31.4, 28.7, 28.1, 22.7, 18.7, 14.2, 1.2\); HRMS Calcd. for \(\text{C}_{14}\text{H}_{25}\text{NOSi}\): 250.1627, Found: 250.1625; Anal. Calcd. for \(\text{C}_{14}\text{H}_{25}\text{NOSi}\): C, 66.87; H, 10.02; N, 5.57; Found: C, 67.02; H, 10.14; N, 5.67; \([\alpha]^{20}_{D} -4.5^\circ\) (c = 1.48, CHCl₃, 90% ee); GC (CDGTA: column temperature = 100 °C (isothermal), injector and detector temperature = 250 °C, inlet pressure = 15 psi): \(t_r\) (minor) = 43.5 min, \(t_r\) (major) = 45.6 min. The chromatograms are illustrated below.

Catalyst Screening

Phase 1. Metal screening: Using the randomly chosen ligand 3 for the metal screening. The results showed Al(OiPr)₃ the optimal metal salt (Figure 1).
Figure 1: Metal Screening. Acetophenone (Acph., blue and yellow) and 2-nonanone (Nona., plum and turquoise) were reacted in toluene (PhMe, front rows) and 1,2-dichloroethane (DCE, back rows); The bars indicate conversion in the presence of chiral ligand A plus transition metal relative to conversion in the presence of the transition metal only; the furthest right lane reflects acceleration of the reaction by the ligand.

Phase 2. Schiff base screening: By just modification of Schiff base in ligand A, 31 variations of ligands were screened in 1,2-dichloroethane. Although Schiff base 6 gave best ee, the result was not reproducible. Therefore, Schiff base 14, 5-methoxy salicyl, was chosen for the rest ligand screening (Figure 2).

Phase 3. AA1 screening: 25 different amino acid residues at AA1 position were screened in 1,2-dichloroethane and L-Val was the optimal (Figure 3).

Phase 4. AA2 Screening: 25 variations at AA2 were screened in 1, 2-dichloroethane at –30 °C and L-Gln(Trt) was the optimal (Figure 4).
Figure 2: Schiff base library. Ligands in descending order of ee are derived from: 6 (4-hydroxysalicylaldehyde), 14 and 19 (5- and 4-methoxysalicylaldehyde, respectively.), 17 (o-vanillin), 23 (2-hydroxy-1-naphthaldehyde, average of two runs), 11 (5-hydroxysalicylaldehyde) and 21 (3-fluorosalicylaldehyde).
Figure 3: AA1-library. Results of 5-MeO-Sal.C=AA1-Phe-Gly-Wang-PS (ligands 33–57, and 14) screened with acetophenone, Al(iPrO)₃, in DCE at −30°C.

Figure 4: AA2-library. Results of 5-MeO-Sal.C=Val-AA2-Gly-Wang-PS (ligands 58–83, and 14) screened with acetophenone, Al(iPrO)₃, in DCE at −30°C.

Phase 5. Transfering solid phase ligand to solution phase. Variation of the protection group on AA2 amino group from n-Bu to glycine methyl ester increased ee by 15%.
**Phase 6.** Additives Screening: additions of 3 Å MS with MeOH increased both conversion of the reaction and the ee of the product (Figure 5).

**Figure 5:** Additives screen. Reactions performed with 20 mol% 5-MeO-Sal.C=Val-Gln(Trt)-Gly(OMe), Al(iPrO),, in PhMe at −78°C for 48h with various additives compared to ee and conversion in the absence of any additive (86% ee, 64% Conv., left, light turquoise). Best result (highlighted in gold/red) was obtained with 0.2 equiv. MeOH in presence of 3Å MS (88% ee, 98% Conv.) 3Å, 4Å: powdered molecular sieves, 3 equiv. weight; 3Å Pyridine: powdered molecular sieves with 0.2 equiv. pyridine; NMO: anhydrous NMO; NMO·H₂O: NMO monohydrate; NMO 3Å: anhydrous NMO plus 3 equiv. weight powdered 3Å MS; (O)PPh₃: triphenylphosphine oxide; (O)PBu₃: tributylphosphine oxide; MeOH 0.2 equiv: 20 mol% anhydrous MeOH; MeOH: 1 equiv. anhydrous MeOH; MeOH 3Å: 20 mol% anhydrous MeOH plus 3 equiv. weight powdered 3Å MS.