Enantioselective Synthesis of Propargylamines Through Zr- Catalyzed Addition of Mixed Alkynylzinc Reagents to Imines

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Supporting Information

General. Infrared (IR) spectra were recorded on a Perkin Elmer 781 spectrophotometer, ν_{max} in cm^{-1} . Bands are characterized as broad (br), strong (s), medium (m), or weak (w). ^1H NMR spectra were recorded on a Varian GN-400 (400 MHz). Chemical shifts are reported with the solvent resonance as the internal standard (CDCl_3 : δ 7.26; $\text{C}_5\text{D}_5\text{N}$: δ 8.74, 7.58, 7.22 ppm). Data are reported as follows: chemical shift (ppm), integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), and coupling constants (Hz). ^{13}C NMR spectra were recorded on a Varian GN-400 (100 MHz) with complete proton decoupling. Chemical shifts are reported as ppm with the solvent as the internal standard (CDCl_3 : δ 77.0 ppm; $\text{C}_5\text{D}_5\text{N}$: δ 150.34, 135.91, 123.87 ppm). Elemental analysis were performed by Robertson Microlit Laboratories, Madison, NJ. Enantiometric ratios were determined by chiral HPLC or GLC. Analytical liquid chromatography (HPLC) was performed on a Shimadzu chromatograph with a Chiracel OD (4.6 x 250 mm) chiral column by Chiral Technologies. Analytical gas liquid chromatography was performed on a Hewlett Packard HP 6890 with a Beta Dex 120 (30 m x 0.25 mm x 0.25 μm film thickness) column by Supelco. Optical rotations were measured on a Rudolph Research Analytical Autopol IV polarimeter. Melting points were measured on a Mel-Temp by Laboratory Devices Inc. and were uncorrected.

All reactions were conducted in oven (140 $^\circ\text{C}$) or flame dried glassware under an atmosphere of dry argon or nitrogen. Methanol (99.8%), acetonitrile (99.8%), *o*-anisidine, all aldehydes, all alkynes, $\text{Zr}(\text{OiPr})_4 \bullet \text{HOiPr}$ (99.9%), NaOH, iodobenzenediacetate, (trimethylsilylmethyl)magnesium chloride (1.0 M in diethyl ether) and diethylzinc (1.1 M in toluene) were purchased from Aldrich and used as received with the exception of the alkynes which were distilled before use. Anhydrous zinc chloride (99.99%) was purchased from Strem. Toluene, diethyl ether and dichloromethane were purchased from Fisher and were dried on alumina columns using a solvent dispensing system.¹ Imines were formed by condensing the aldehyde with *o*-anisidine in methylene chloride with anhydrous magnesium sulfate as the drying agent. Bis-[(trimethylsilyl)-methyl]-zinc **5**

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

was prepared according to literature procedure.² Bis-alkynylzinc reagents with the exception of bis(trimethylsilanyl-ethynyl)-zinc **4** were prepared as reported previously.³ Peptide ligand **1** was prepared as reported previously.⁴

Synthesis of Bis-(trimethyl-silanyl-ethynyl)-zinc (4). The glassware set up for the synthesis was as follows: All glassware was flame dried and kept under N₂. A 250 mL 2 necked round-bottom flask was fitted with a gas adapter and an air free fritted funnel. On the other end of the funnel, a two-necked 500 mL round bottom flask receiver, also with a gas adapter were fitted. *All joints were well greased and the apparatus was constantly kept air free, as diethylzinc is pyrophoric and explosions can occur if air is introduced.* To this setup was charged (trimethylsilyl)acetylene (10.0 mL, 70.8 mmol), toluene (100 mL), and diethylzinc (26.8 mL of a 1.1 M solution in toluene, 29.5 mmol). The reaction was heated to 60 °C for 64 hours, in which time a white fibrous solid formed. The solid was collected on the fritted funnel and washed with dry toluene (3 x 50 mL). Under an N₂ atmosphere, the solid was transferred to a fresh dry round bottom flask and dried to constant weight under reduced pressure to yield a white fibrous solid (3.2 g, 42% yield). ¹H NMR (C₅D₅N, 400 MHz): δ 0.35 (9 H, s); ¹³C (C₅D₅N, 100 MHz): δ 138.6, 115.0, 2.2.

General procedure for addition of Bis-(trimethylsilanyl-ethynyl)-zinc to imines.

Peptide ligand **1**, Zr(OiPr)₄•HOiPr, and imine were weighed into a oven dried round bottom flask or test tube inside a N₂ atmosphere glovebox. The contents were dissolved in toluene, followed by the addition of the bis-(trimethylsilanyl-ethynyl)-zinc **4** and bis-[(trimethylsilyl)-methyl]-zinc **5**, respectively. The reaction vessels were sealed with a rubber septum and Teflon tape and were allowed to stir (see individual examples for reaction time and temperature). The reactions were quenched with saturated ammonium chloride and extracted with diethyl ether (3 x). The combined organics were washed with brine (1 x) and dried over anhydrous Na₂SO₄. After filtration and removal of the solvent under reduced pressure, the products were further purified by silica gel chromatography and analyzed for enantioselectivity by chiral HPLC.

(R)-(2-Methoxy-phenyl)-(1-phenyl-3-trimethylsilanyl-prop-2-ynyl)-amine (3a) The general procedure was followed by dissolving peptide ligand **1** (91 mg, 0.20 mmol), Zr(OiPr)₄•HOiPr (86 mg, 0.22 mmol), and benzyldiene-(2-methoxy-phenyl)-amine **2a** (420 mg, 2.0 mmol) in toluene (9.0 mL, 0.2 M). Bis-(trimethylsilanyl-ethynyl)-zinc **4** (310 mg, 1.2 mmol) and bis-[(trimethylsilyl)-methyl]-zinc **5** (1.1 mL, 4.0 mmol) were then added. The reaction vessel was sealed with a septum and Teflon tape and was allowed to stir at 22 °C for 48 h. After workup, silica gel chromatography (49:1 hexanes:Et₂O) afforded the desired amine as a pale yellow oil (510 mg, 83% yield, 90% ee). HPLC conditions: Chiracel OD (4.6 x 250 mm), 96:4 hexanes:HOi-Pr, 1.0 mL/min,

² Westerhausen, M.; Rademacher, B.; Poll, W. *J. Organomet. Chem.* **1991**, 421, 175-188.

Caution: Keep air free! Bis-[(trimethylsilyl)-methyl]-zinc is pyrophoric.

³ De Koning, A.J.; Van Rijn, P.E.; Boersma, J.; Van Der Kerk, G.J.M. *J. Organomet. Chem.* **1979**, 174, 129-140. For an alternate synthesis of dialkynylzinc reagents see: Dabdoub, M.J.; Dabdoub, V.B.; Marino, J.P. *Tetrahedron Lett.* **2000**, 41, 437-440.

⁴ Porter, J.R.; Traverse, J.F.; Hoveyda, A.H.; Snapper, M.L. *J. Am. Chem. Soc.* **2001**, 123, 984-985.

$\lambda = 254$ nm. IR (neat, thin film): 3425 (br), 3064 (w), 2960 (m), 2899 (w), 2831 (w), 2164 (w), 1595 (m), 1510 (s), 1448 (m), 1338 (w), 1240 (s), 1222 (m), 1224 (m), 1032 (m), 837 (s), 757 (m), 696 (m) cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.60 (2 H, d, $J = 7.6$ Hz), 7.39 (2 H, t, $J = 7.2$ Hz), 7.33 (1H, d, $J = 7.2$ Hz), 6.69 (1 H, dt, $J = 7.6, 1.2$ Hz), 6.81 (1H, dd, $J = 7.6, 1.2$ Hz), 6.79 (1H, dd, $J = 7.6, 1.2$ Hz), 6.75 (1H, dt, $J = 7.6, 1.6$ Hz), 5.29 (1H, s), 4.72 (1H, br), 3.84 (3H, s), 0.16 (9H, s); ^{13}C (CDCl_3 , 100 MHz): δ 147.3, 139.8, 136.6, 128.8, 128.1, 127.5, 121.2, 117.9, 112.0, 109.8, 105.2, 89.8, 55.8, 50.9, 0.4; Anal. calcd. for $\text{C}_{19}\text{H}_{23}\text{NOSi}$: C, 73.73; H, 7.49; N, 4.53. Found: C, 74.02; H, 7.54; N, 4.57. Optical Rotation: $[\alpha]^{25}_{\text{D}} +76.5$ (c 1.0, CHCl_3).

(*R*)-[1-(4-Chloro-phenyl)-3-trimethylsilanyl-prop-2-ynyl]-(2-methoxy-phenyl)-amine (3b). The general procedure was followed by dissolving peptide ligand **1** (9.1 mg, 0.020 mmol), $\text{Zr}(\text{OiPr})_4 \bullet \text{HOiPr}$ (8.6 mg, 0.022 mmol), and (4-chloro-benzylidene)-(2-methoxyphenyl)-amine **2b** (49 mg, 0.20 mmol) in toluene (0.90 mL, 0.2 M). Bis-(trimethylsilanyl-ethynyl)-zinc **4** (31 mg, 0.12 mmol) and bis-[(trimethylsilyl)methyl]-zinc **5** (0.11 mL, 0.40 mmol) were then added. The reaction vessel was sealed with a septum and Teflon tape and was allowed to stir at 22 °C for 72 h. After workup, silica gel chromatography (49:1 hexanes: Et_2O) yielded the desired amine as a yellow oil (63 mg, 90% yield, 81% ee). HPLC conditions: Chiralcel OD (4.6 x 250 mm), 98:2 hexanes: HOi-Pr , 1.0 mL/min, $\lambda = 254$ nm. IR (neat, thin film): 3419 (br), 3064 (w), 2954 (m), 2892 (w), 2170 (m), 1545 (m), 1509 (s), 1485 (m), 1448 (m), 1344 (w), 1240 (s), 1222 (m), 1130 (m), 1087 (m), 1026 (w), 837 (s), 763 (w), 739 (m) cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.52 (2H, d, $J = 8.8$ Hz), 7.35 (2H, d, $J = 8.4$ Hz), 6.84 (1H, dt, $J = 8.0, 2.0$ Hz), 6.81 (1H, dd, $J = 8.0, 2.0$ Hz), 6.74 (1H, dt, $J = 7.6, 1.6$ Hz), 6.69 (1H, dd, $J = 7.6, 1.6$ Hz), 5.25 (1H, s), 4.67 (1H, br), 3.85 (3H, s), 0.16 (9H, s); ^{13}C (CDCl_3 , 100 MHz): δ 147.0, 138.2, 136.0, 133.5, 128.7, 128.5, 120.9, 117.8, 111.6, 109.5, 104.3, 89.9, 55.5, 50.0, 0.0; Anal. calcd. for $\text{C}_{19}\text{H}_{22}\text{ClNOSi}$: C, 66.35; H, 6.45; N, 4.07. Found: C, 66.51; H, 6.53; N, 4.10. Optical Rotation: $[\alpha]^{25}_{\text{D}} +50.8$ (c 1.0, CHCl_3).

(*R*)-(2-Methoxy-phenyl)-[1-(4-methoxy-phenyl)-3-trimethylsilanyl-prop-2-ynyl]-amine (3c). The general procedure was followed by dissolving peptide ligand **1** (9.1 mg, 0.020 mmol), $\text{Zr}(\text{OiPr})_4 \bullet \text{HOiPr}$ (8.6 mg, 0.022 mmol), and (4-methoxy-benzylidene)-(2-methoxy-phenyl)-amine **2c** (48 mg, 0.20 mmol) in toluene (0.90 mL, 0.2 M). Bis-(trimethylsilanyl-ethynyl)-zinc **4** (31 mg, 0.12 mmol) and bis[(trimethylsilyl)-methyl]-zinc **5** (0.11 mL, 0.40 mmol) were then added. The reaction vessel was sealed with a septum and Teflon tape and was allowed to stir at 22 °C for 72 h. After workup, silica gel chromatography (19:1 hexanes: Et_2O) yielded the desired amine as a white solid (47 mg, 69% yield, 86% ee). HPLC conditions: Chiralcel OD (4.6 x 250 mm), 98:2 hexanes: HOi-Pr , 1.0 mL/min, $\lambda = 254$ nm. MP = 99-100 °C. IR (neat, thin film): 3406 (br), 3069 (br), 3009 (w), 2966 (m), 2905 (w), 2831 (m), 2158 (m), 1601 (m), 1509 (s), 1455 (m), 1247 (s), 1173 (m), 1130 (m), 1032 (m), 843 (s), 757 (m), 733 (m) cm^{-1} ; ^1H NMR (CDCl_3 , 400 MHz): δ 7.51 (2H, d, $J = 8.4$ Hz), 6.91 (2H, d, $J = 8.8$ Hz), 6.87 (1H, dt, $J = 8.0, 1.6$ Hz), 6.81-6.78 (2H, m), 6.73 (1H, dt, $J = 7.2, 1.6$ Hz), 5.20 (1H, s), 4.60 (1H, br), 3.83 (3H, s), 0.18 (9H, s); ^{13}C (CDCl_3 , 100 MHz): δ 159.4, 147.3, 136.7, 132.0, 128.7, 121.2, 117.8, 114.2, 112.0, 109.7, 105.5, 89.5, 55.8, 55.7, 50.3, 0.4; Anal. calcd. for $\text{C}_{20}\text{H}_{25}\text{NO}_2\text{Si}$: C, 70.75; H, 7.42; N, 4.13. Found: C, 70.66; H, 7.52; N, 4.13. Optical Rotation: $[\alpha]_D^{25} +73.0$ (c 1.0, CHCl_3).

(R)-[1-(2-Bromo-phenyl)-3-trimethylsilanyl-prop-2-ynyl]-(2-methoxy-phenyl)-amine (3d). The general procedure was followed by dissolving peptide ligand **1** (9.1 mg, 0.020 mmol), Zr(OiPr)₄•HOiPr (8.6 mg, 0.022 mmol), and (2-bromo-benzylidene)-(2-methoxy-phenyl)-amine **2d** (58 mg, 0.20 mmol) in toluene (0.90 mL, 0.2 M). Bis-(trimethylsilanyl-ethynyl)-zinc **4** (31 mg, 0.12 mmol) and bis-[(trimethylsilyl)-methyl]-zinc **5** (0.11 mL, 0.40 mmol) were then added. The reaction vessel was sealed with a septum and Teflon tape and was allowed to stir at 22 °C for 48 h. After workup, silica gel chromatography (49:1 hexanes:Et₂O) yielded the desired amine as a yellow oil (65 mg, 84% yield, 69% ee). Enantiomeric excess was determined from desilylated product (*vide infra*). IR (neat, thin film): 3425 (br), 3070 (w), 2960 (m), 2831 (w), 2177 (w), 1608 (m), 1516 (s), 1455 (m), 1448 (m), 1240 (s), 1222 (s), 1124 (m), 1026 (m), 843 (s), 763 (s), 726 (s) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.73 (1H, dd, *J* = 7.6, 1.2 Hz), 7.59 (1H, dd, *J* = 8.0, 1.2 Hz), 7.33 (1H, dt, *J* = 8.4, 1.2 Hz), 7.18 (1H, dt, *J* = 7.6, 1.6 Hz), 6.83 (1H, t, *J* = 7.6 Hz), 6.80 (1H, d, *J* = 8.4 Hz), 6.72 (1H, t, *J* = 8.0 Hz), 6.63 (1H, d, *J* = 7.6 Hz), 5.56 (1H, d, *J* = 6.4 Hz), 4.74 (1H, d, *J* = 6.4 Hz), 3.86 (3H, s), 0.16 (9H, s); ¹³C (CDCl₃, 100 MHz): δ 146.9, 138.6, 136.0, 133.0, 129.3, 128.7, 127.7, 123.5, 121.0, 117.7, 111.5, 109.5, 103.8, 89.5, 55.6, 50.6, 0.1; Anal. calcd. for C₁₉H₂₂BrNOSi: C, 58.76; H, 5.71; N, 3.61. Found: C, 58.61; H, 5.66; N, 3.45. Optical Rotation: [α]_D²⁵ +58.0 (c 1.0, CHCl₃).

(R)-(2-Methoxy-phenyl)-(1-naphthalen-1-yl-3-trimethylsilanyl-prop-2-ynyl)-amine (3e) The general procedure was followed by dissolving peptide ligand **1** (9.1 mg, 0.020 mmol), Zr(OiPr)₄•HOiPr (8.6 mg, 0.022 mmol), and (2-methoxy-phenyl)-naphthalen-1-ylmethylene-amine **2e** (52 mg, 0.20 mmol) in toluene (0.90 mL, 0.2 M). Bis-(trimethylsilanyl-ethynyl)-zinc **4** (31 mg, 0.12 mmol) and bis-[(trimethylsilyl)-methyl]-zinc **5** (0.11 mL, 0.40 mmol) were then added. The reaction vessel was sealed with a septum and Teflon tape and was allowed to stir at 22 °C for 72 h. After workup, silica gel chromatography (24:1 hexanes:Et₂O) yielded the desired amine as a off-white solid (56 mg, 77% yield, 86% ee). Enantiomeric excess was determined from desilylated product (*vide infra*). MP = 137-138 °C. IR (neat, thin film): 3425 (br), 3052 (br), 2997 (w), 2960 (m), 2899 (w), 2825 (w), 2170 (m), 1601 (s), 1516 (s), 1461 (m), 1412 (w), 1247 (s), 1216 (s), 1118 (m), 1020 (m), 837 (s), 775 (s), 739 (s) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 8.13 (1H, dd, *J* = 6.4, 3.6 Hz), 7.94 (1H, d, *J* = 7.2 Hz), 7.90 (1H, dd, *J* = 5.6, 3.6 Hz), 7.86 (1H, d, *J* = 8.4 Hz), 7.53–7.48 (3H, m), 6.90 (1H, t, *J* = 8.0 Hz), 6.88 (1H, d, *J* = 7.2 Hz), 6.81 (1H, d, *J* = 7.6 Hz), 6.76 (1H, dt, *J* = 6.4, 2.0 Hz), 5.89 (1H, d, *J* = 6.0 Hz), 4.74 (1H, d, *J* = 6.0 Hz), 3.79 (3H, s), 0.16 (9H, s); ¹³C (CDCl₃, 100 MHz): δ 147.0, 136.4, 134.3, 133.9, 130.7, 128.8, 128.6, 126.2, 125.6, 125.3, 125.3, 123.6, 121.0, 117.5, 111.4, 109.4, 104.7, 90.0, 55.4, 48.3, 0.1; Anal. calcd. for C₂₃H₂₅NOSi: C, 76.83; H, 7.01; N, 3.90. Found: C, 76.62; H, 7.06; N, 3.77. Optical Rotation: [α]_D²⁵ +56.8 (c 1.0, CHCl₃).

(R)-(2-Methoxy-phenyl)-(1-naphthalen-2-yl-3-trimethylsilanyl-prop-2-ynyl)-amine (3f) The general procedure was followed by dissolving peptide ligand **1** (9.1 mg, 0.020 mmol), Zr(OiPr)₄•HOiPr (8.6 mg, 0.022 mmol), and (2-methoxy-phenyl)-naphthalen-2-ylmethylene-amine **2f** (52 mg, 0.20 mmol) in toluene (0.90 mL, 0.2 M). Bis-(trimethylsilanyl-ethynyl)-zinc **4** (31 mg, 0.12 mmol) and bis-[(trimethylsilyl)-methyl]-zinc **5** (0.11 mL, 0.40 mmol) were then added. The reaction vessel was sealed

with a septum and Teflon tape and was allowed to stir at 22 °C for 48 h. After workup, silica gel chromatography (24:1 hexanes:Et₂O) yielded the desired amine as a yellow solid (61 mg, 85% yield, 81% ee). HPLC conditions: Chiralcel OD (4.6 x 250 mm), 96:4 hexanes:HOi-Pr, 1.0 mL/min, λ = 254 nm. MP = 126 °C. IR (neat, thin film): 3419 (br), 3052 (w), 2954 (m), 2899 (w), 2825 (w), 2170 (w), 1601 (m), 1510 (s), 1454 (m), 1418 (m), 1247 (s), 1124 (m), 1026 (m), 843 (s), 739 (m) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 8.06 (1H, s), 7.88–7.84 (3H, m), 7.64 (1H, dd, J = 8.8, 2.0 Hz), 7.51–7.48 (2H, m), 6.85 (1H, dt, J = 8.0, 1.2 Hz), 6.81 (1H, dd, J = 9.2, 2.0 Hz), 6.79 (1H, dd, J = 8.0, 1.6 Hz), 6.74 (1H, dt, J = 8.0, 2.0 Hz), 5.43 (1H, d, J = 6.0 Hz), 4.78 (1H, d, J = 6.0 Hz), 3.85 (3H, s), 0.18 (9H, s); ¹³C (CDCl₃, 100 MHz): δ 147.0, 137.0, 136.3, 133.2, 132.9, 128.4, 128.0, 127.5, 126.0, 125.9, 125.2, 121.0, 117.6, 111.7, 109.4, 104.9, 89.8, 55.5, 50.8, 0.1; Anal. calcd. for C₂₃H₂₅NOSi: C, 76.83; H, 7.01; N, 3.90. Found: C, 76.66; H, 7.11; N, 3.77. Optical Rotation: $[\alpha]^{25}_{\text{D}}$ +47.0 (c 1.0, CHCl₃).

(*R*)-(1-Furan-2-yl-3-trimethylsilanyl-prop-2-ynyl)-(2-methoxy-phenyl)-amine (3g)

The general procedure was followed by dissolving peptide ligand **1** (9.1 mg, 0.020 mmol), Zr(OiPr)₄•HOiPr (8.6 mg, 0.022 mmol), and furan-2-ylmethylene-(2-methoxy-phenyl)-amine **2g** (40 mg, 0.20 mmol) in toluene (0.90 mL, 0.2 M). Bis-(trimethylsilanyl-ethynyl)-zinc **4** (31 mg, 0.12 mmol) and bis-[(trimethylsilyl)-methyl]-zinc **5** (0.11 mL, 0.40 mmol) were then added. The reaction vessel was sealed with a septum and Teflon tape and was allowed to stir at 22 °C for 24 h. After workup, silica gel chromatography (49:1 hexanes:Et₂O) yielded the desired amine as a yellow oil (43 mg, 72% yield, 82% ee). Enantiomeric excess was determined from desilylated product (*vide infra*). IR (neat, thin film): 3413 (br), 2960 (m), 2831 (w), 2366 (w), 2170 (w), 1608 (m), 1504 (s), 1454 (m), 1442 (m), 1247 (s), 1240 (m), 1124 (m), 1038 (m), 843 (s), 739 (s) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.41 (1H, t, J = 0.8 Hz), 6.89 (1H, dt, J = 8.0, 2.0 Hz), 6.84 (1H, dd, J = 8.0, 2.0 Hz), 6.81 (1H, dd, J = 7.6, 2.0 Hz), 6.76 (1H, dt, J = 6.8, 2.0 Hz), 6.45 (1H, d, J = 3.6 Hz), 6.36 (1H, dd, J = 3.2, 2.0 Hz), 5.37 (1H, s), 4.74 (1H, s), 3.85 (3H, s), 0.17 (9H, s); ¹³C (CDCl₃, 100 MHz): δ 151.8, 147.2, 142.4, 135.8, 120.8, 118.0, 111.9, 110.2, 109.6, 107.5, 102.3, 88.7, 55.5, 44.9, 0.0; Anal. calcd. for C₁₇H₂₁NO₂Si: C, 68.19; H, 7.07; N, 4.68. Found: C, 67.99; H, 6.90; N, 4.66. Optical Rotation: $[\alpha]^{25}_{\text{D}}$ +49.4 (c 1.0, CHCl₃).

(*R*)-(2-Methoxy-phenyl)-(1-phenyl-hept-2-ynyl)-amine (6). The general procedure was followed by dissolving peptide ligand **1** (9.1 mg, 0.020 mmol), $\text{Zr}(\text{OiPr})_4 \bullet \text{HOiPr}$ (8.6 mg, 0.022 mmol), and benzylidene-(2-methoxy-phenyl)-amine **2a** (42 mg, 0.20 mmol) in toluene (0.9 mL, 0.2 M). Bis-(1-hexynyl)-zinc (91 mg, 0.40 mmol) and bis-[(trimethylsilyl)-methyl]-zinc **5** (0.11 mL, 0.40 mmol) were then added. The reaction vessel was sealed with a septum and Teflon tape and was allowed to stir at 22 °C for 24 h. After workup, silica gel chromatography (49:1 hexanes:Et₂O) afforded the desired amine as a pale yellow oil (50 mg, 81% yield, 79% ee). HPLC conditions: Chiracel OD (4.6 x 250 mm), 97:3 hexanes:HOi-Pr, 1.0 mL/min, λ = 254 nm. IR (neat, thin film): 3419 (br), 3064 (w), 2960 (m), 2862 (m), 2837 (w), 1601 (s), 1504 (s), 1455 (s), 1424 (m), 1344 (w), 1240 (m), 1216 (m), 1112 (m), 1026 (m), 739 (s), 702 (s) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.60 (1H, d, J = 7.2, Hz), 7.39 (2H, t, J = 7.2 Hz), 7.32 (1H, t, J = 7.2 Hz), 6.86 (1H, dt, J = 8.0, 1.6 Hz), 6.80 (1H, dd, J = 8.0, 0.8 Hz), 6.78 (1H, dd, J = 8.0, 1.2 Hz), 6.73 (1H, dt, J = 7.2, 1.2 Hz), 5.23 (1H, d, J = 6.4 Hz), 4.67 (1H, d, J = 6.4 Hz), 3.84 (3H, s), 2.23 (2H, dt, J = 7.2, 2.0 Hz), 1.55–1.34 (4H, m), 0.89 (3H, t, J = 7.2 Hz); ¹³C (CDCl₃, 100 MHz): δ 146.6, 140.1, 136.2, 128.1, 127.3, 126.8, 120.6, 117.0, 111.2, 109.1, 85.0, 79.1, 55.1, 49.7, 30.6, 21.7, 18.3, 13.4; Anal. calcd. for C₂₀H₂₃NO: C, 81.87; H, 7.90; N, 4.77. Found: C, 81.68; H, 8.06; N, 4.85. Optical Rotation: $[\alpha]_D^{25} +57.0$ (c 1.0, CHCl₃).

(*R*)-(1,3-Diphenyl-prop-2-ynyl)-(2-methoxy-phenyl)-amine (7). The general procedure was followed by dissolving peptide ligand **1** (9.1 mg, 0.020 mmol), $\text{Zr}(\text{OiPr})_4 \bullet \text{HOiPr}$ (8.6 mg, 0.022 mmol), and benzylidene-(2-methoxy-phenyl)-amine **2a** (42 mg, 0.20 mmol) in toluene (0.9 mL, 0.2 M). Bis-(2-phenyl-ethynyl)-zinc (54 mg, 0.20 mmol) and bis-[(trimethylsilyl)-methyl]-zinc **5** (0.11 mL, 0.40 mmol) were then added. The reaction vessel was sealed with a septum and Teflon tape and was allowed to stir at 22 °C for 24 h. After workup, silica gel chromatography (49:1 hexanes:Et₂O) afforded the desired amine as a pale yellow oil (51 mg, 81% yield, 68% ee). HPLC conditions: Chiracel OD (4.6 x 250 mm), 96:4 hexanes:HOi-Pr, 1.0 mL/min, λ = 254 nm. IR (neat, thin film): 3417 (br), 3063 (m), 2933 (w), 2839 (w), 2361 (w), 1604 (m), 1505 (s), 1449 (m), 1424 (w), 1344 (w), 1250 (m), 1220 (m), 1121 (m), 1027 (m), 760 (m), 742 (m), 686 (m) cm⁻¹; ¹H

NMR (CDCl₃, 400 MHz): δ 7.68 (2H, dd, J = 6.8, 1.6 Hz), 7.44–7.40 (4H, m), 7.35 (1H, tt, J = 7.6, 1.6 Hz), 7.31–7.27 (3H, m), 6.92–6.85 (2H, m), 6.83 (1H, dd, J = 8.0, 1.2 Hz), 6.76 (1H, dt, J = 6.8, 2.4 Hz), 5.52 (1H, s), 4.83 (1H, br), 3.85 (3H, s); ¹³C (CDCl₃, 100 MHz): δ 147.0, 139.8, 136.3, 131.6, 128.6, 128.1, 128.0, 127.8, 127.2, 122.8, 121.0, 117.6, 111.6, 109.5, 88.6, 84.8, 55.5, 50.4; Anal. calcd. for C₂₂H₁₉NO: C, 84.31; H, 6.11; N, 4.47. Found: C, 84.40; H, 5.93; N, 4.33. Optical Rotation: $[\alpha]_D^{25}$ +52.2 (c = 1.0, CHCl₃).

General procedure for the desilylation of alkynes. The alkyne was dissolved in a minimal amount of acetonitrile. NaOH in methanol (0.1 M) was then added to yield a concentration of approximately 0.1 M in substrate. The reaction was stirred at 22 °C and monitored by thin layer chromatography (TLC) until deemed complete by consumption of starting material (typically 1 h). Water was then added to the reaction and the product was extracted with methylene chloride (3 x). The combined organics were washed with brine (1 x) and dried over anhydrous Na₂SO₄. The products were purified further by silica gel chromatography and analyzed for enantioselectivity by chiral HPLC.

(S)-(2-Methoxy-phenyl)-(1-phenyl-prop-2-ynyl)-amine (8). The general procedure was followed by dissolving (*R*)-(2-methoxy-phenyl)-(1-phenyl-3-trimethylsilyl-prop-2-ynyl)-amine **3a** (250 mg, 0.80 mmol, 90% ee) in acetonitrile (2.5 mL). NaOH in methanol (6.0 mL, 0.1 M) was added and the reaction was allowed to stir for 1 h, 22 °C. After workup, silica gel chromatography (49:1 hexanes:Et₂O) afforded the product as a yellow oil (170 mg, 87% yield, 90% ee). HPLC conditions: Chiralcel OD (4.6 x 250 mm), 97:3 hexanes:HO*i*-Pr, 1.0 mL/min, λ = 254 nm. IR (neat, thin film): 3419 (w), 3284 (m), 3058 (w), 2960 (w), 2941 (w), 2831 (w), 1595 (m), 1509 (s), 1454 (m), 1424 (w), 1344 (w), 1240 (s), 1222 (m), 1173 (w), 1118 (m), 1026 (m), 738 (s), 702 (m), 653 (m) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.63 (2H, dd, J = 7.2, 1.6 Hz), 7.43–7.33 (3H, m), 6.89 (1 H, dt, J = 7.2, 2.0 Hz), 6.83–6.74 (3H, m), 5.31 (1H, br), 4.69 (1H, br), 3.84 (3H, s), 2.47 (1H, d, J = 2.0 Hz); ¹³C (CDCl₃, 100 MHz): δ 147.0, 139.0, 136.0, 128.6, 128.0, 127.1, 120.9, 117.8, 111.5, 109.6, 83.1, 72.9, 55.5, 49.6; Anal. calcd. for

$C_{16}H_{15}NO$; C, 80.98; H, 6.37; N, 5.90. Found: C, 81.24; H, 6.32; N, 5.76. Optical Rotation: $[\alpha]_D^{25} +75.6$ (c 1.0, $CHCl_3$).

(S)-[1-(2-Bromo-phenyl)-prop-2-ynyl]-(2-methoxy-phenyl)-amine (Desilylated 3d).

The general procedure was followed by dissolving (*R*)-[1-(2-bromo-phenyl)-3-trimethyl-silanyl-prop-2-ynyl]-(2-methoxy-phenyl)-amine **3d** (210 mg, 0.53 mmol) in acetonitrile (2.0 mL). NaOH in methanol (5.0 mL, 0.1 M) was added and the reaction was allowed to stir for 1 h, 22 °C. After workup, silica gel chromatography (49:1 hexanes:Et₂O) afforded the product as a off white solid (160 mg, 93% yield, 69% ee). HPLC conditions: Chiralcel OD (4.6 x 250 mm), 98:2 hexanes:HO*i*-Pr, 1.0 mL/min, λ = 254 nm. MP = 71–72 °C. IR (neat, thin film): 3419 (br), 3296 (m), 3064 (w), 3003 (w), 2960 (w), 2935 (w), 2831 (w), 1601 (m), 1504 (s), 1455 (m), 1430 (m), 1344 (w), 1240 (s), 1210 (s), 1130 (m), 1026 (s), 733 (m), 647 (m) cm^{-1} ; 1H NMR ($CDCl_3$, 400 MHz): δ 7.77 (1H, dd, J = 7.6, 1.6 Hz), 7.71 (1H, d, J = 8.4 Hz), 7.35 (1H, t, J = 7.6 Hz), 7.21 (1H, dt, J = 7.6, 1.6 Hz), 6.87–6.73 (3H, m), 6.64 (1H, d, J = 8.0 Hz), 5.60 (1H, dd, J = 6.0, 2.0 Hz), 4.77 (1H, d, J = 6.4 Hz), 3.86 (3H, s), 2.48 (1H, d, J = 2.4 Hz); ^{13}C ($CDCl_3$, 100 MHz): δ 148.1, 139.1, 136.9, 134.2, 130.7, 129.7, 129.0, 124.5, 122.2, 119.1, 112.4, 110.7, 83.5, 74.0, 56.7, 50.8; Anal. calcd. $C_{16}H_{14}BrNO$: C, 60.78; H, 4.46; N, 4.43. Found: C, 60.53; H, 4.35; N, 4.38. Optical Rotation: $[\alpha]_D^{25} +63.8$ (c 1.0, $CHCl_3$).

(S)-(2-Methoxy-phenyl)-(1-naphthalen-1-yl-prop-2-ynyl)-amine (Desilylated 3e).

The general procedure was followed by dissolving (*R*)-(2-methoxy-phenyl)-(1-naphthalen-1-yl-3-trimethylsilanyl-prop-2-ynyl)-amine **3e** (190 mg, 0.53 mmol) in acetonitrile (2.0 mL). NaOH in methanol (5.0 mL, 0.1 M) was added and the reaction was allowed to stir for 75 min, 22 °C. After workup, silica gel chromatography (49:1 hexanes:Et₂O) afforded the product as an off white solid (130 mg, 85% yield, 86% ee). HPLC conditions: Chiralcel OD (4.6 x 250 mm), 99:1 hexanes:HO*i*-Pr, 1.0 mL/min, λ = 254 nm. MP = 136-137 °C. IR (neat, thin film): 3419 (br), 3290 (m), 3052 (w), 3014 (w), 2954 (w), 2929 (w), 2825 (w), 2366 (w), 2336 (w), 1608 (s), 1509 (s), 1455 (m), 1418 (m), 1240 (s), 1216 (m), 1179 (w), 1130 (m), 1032 (m), 775 (m), 739 (s), 653 (m) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 8.13 (1H, m), 7.99 (1H, d, *J* = 7.6 Hz), 7.92 (1H, m), 7.88 (1H, d, *J* = 8.4 Hz), 7.56–7.49 (3H, m), 6.93 (1H, dt, *J* = 7.6, 1.6 Hz), 6.90 (1H, dd, *J* = 8.0, 1.6 Hz), 6.83 (1H, dd, *J* = 8.0, 1.6 Hz), 6.78 (1H, dt, *J* = 6.4, 1.6 Hz), 5.94 (1H, dd, *J* = 6.8, 2.4 Hz), 4.78 (1H, d, *J* = 6.8 Hz), 3.79 (3H, s), 2.53 (1H, d, *J* = 2.4 Hz); ¹³C (CDCl₃, 100 MHz): δ 147.3, 136.5, 134.2, 134.1, 130.9, 129.3, 129.0, 126.7, 126.1, 125.6, 125.5, 123.7, 121.3, 118.0, 111.4, 109.9, 83.3, 73.7, 55.7, 47.5; Anal. calcd. C₂₀H₁₇NO: C, 83.59; H, 5.96; N, 4.87. Found: C, 83.28; H, 6.19; N, 4.69. Optical Rotation: $[\alpha]_D^{25}$ +68.4 (c 1.0, CHCl₃).

(S)-(1-Furan-2-yl-prop-2-ynyl)-(2-methoxy-phenyl)-amine (Desilylated 3g).

The general procedure was followed by dissolving (*R*)-(1-furan-2-yl-3-trimethylsilanyl-prop-2-ynyl)-(2-methoxy-phenyl)-amine **3g** (180 mg, 0.59 mmol) in acetonitrile (2.0 mL). NaOH in methanol (5.0 mL, 0.1 M) was added and the reaction was allowed to stir for 1 h, 22 °C. After workup, silica gel chromatography (24:1 hexanes:Et₂O) afforded the product as a yellow oil (86 mg, 64% yield, 82% ee). HPLC conditions: Chiralcel OD (4.6 x 250 mm), 90:10 hexanes:HO*i*-Pr, 1.0 mL/min, λ = 254 nm. IR (neat, thin film): 3413 (br), 3284 (m), 3119 (w), 3064 (w), 3045 (w), 3009 (w), 2972 (w), 2923 (w), 2837 (w), 1595 (m), 1516 (s), 1461 (m), 1430 (m), 1332 (w), 1308 (w), 1247 (s), 1222 (m), 1124 (m), 1026 (m), 733 (s), 653 (m), 604 (m) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.43 (1H, d, *J* = 1.2 Hz), 6.90 (1H, dt, *J* = 8.0, 1.6 Hz), 6.85–6.76 (3H, m), 6.49 (1H, d, *J* = 3.2 Hz), 6.38 (1H, dd, *J* = 3.2, 2.0 Hz), 5.40 (1H, d, *J* = 6.4 Hz), 4.76 (1H, d, *J* = 7.2 Hz), 3.85 (3H, s), 2.42 (1H, d, *J* = 2.0 Hz); ¹³C (CDCl₃, 100 MHz): δ 151.3, 147.3, 142.6, 135.5, 120.9, 118.3, 111.7, 110.3, 109.7, 107.6, 80.9, 71.9, 55.5, 43.9; Anal. calcd.

C₁₄H₁₃NO₂: C, 73.99; H, 5.77; N, 6.16. Found: C, 74.02; H, 5.75; N, 6.15. Optical Rotation: $[\alpha]_D^{25} +50.8$ (c 0.5, CHCl₃).

Oxidative deprotection procedure: Preparation of (*S*)-*N*-(1-Phenyl-prop-2-ynyl)-acetamide (9**) and stereochemistry proof.** Iodobenzenediacetate (530 mg, 1.6 mmol) was dissolved in methanol (5.0 mL). (*S*)-(2-Methoxy-phenyl)-(1-phenyl-prop-2-ynyl)-amine **8** (97 mg, 0.41 mmol) was separately dissolved in acetonitrile (0.9 mL). The substrate (**8**) was added to the oxidant over 30 minutes via syringe pump at 22 °C. After complete addition of substrate the reaction was allowed to stir for an additional 30 minutes (1 h total). HCl (aq) (10 mL, 1N) was then added and the reaction was allowed to stir for 1.5 h. The reaction was then washed with methylene chloride (3 x 15 mL). The combined organic layers were backwashed with 0.1 M HCl (1 x 10 mL). The aqueous backwash was then washed with methylene chloride (1 x 5 mL). The aqueous layers were pooled and were added to fresh methylene chloride (15 mL) with vigorous stirring. Acetic anhydride (190 μ L, 2.1 mmol) was added followed by solid Na₂CO₃ until a pH of 10–11 was reached. The biphasic system was allowed to stir vigorously for 2.5 h after which time the layers were separated. The aqueous layer was extracted with methylene chloride (2 x 15 mL). The combined organics were washed with brine (1 x 10 mL), and dried over anhydrous Na₂SO₄. Silica gel chromatography (99:1 CH₂Cl₂:CH₃OH) afforded a white solid (50 mg, 71% yield, 90% ee). GLC conditions: Supelco Beta Dex 120 (30 m x 0.25 mm x 0.25 μ m film thickness), 140 to 160 °C, 0.25 °C/min. 15 psi. MP = 117–118 °C. IR (neat, thin film): 3290 (br), 3039 (w), 2929 (w), 1650 (s), 1534 (s), 1455 (w), 1367 (m), 1295 (m), 1081 (w), 757 (w), 702 (m), 647 (m), 567 (m) cm⁻¹; ¹H NMR (CDCl₃, 400 MHz): δ 7.53 (2H, d, *J* = 6.8 Hz), 7.39 (2H, t, *J* = 6.8 Hz), 7.34 (1H, d, *J* = 6.8 Hz), 6.04 (1H, dd, *J* = 8.4, 2.0 Hz), 5.92 (1H, br), 2.51 (1H, d, *J* = 2.4 Hz), 2.01 (3H, s); ¹³C (CDCl₃, 100 MHz): δ 168.6, 138.1, 128.6, 128.1, 126.9, 81.7, 72.9, 44.5, 23.2; Anal. calcd. C₁₁H₁₁NO: C, 76.28; H, 6.40; N, 8.09. Found: C, 76.04; H, 6.47; N, 7.86. Optical Rotation: $[\alpha]_D^{25} -44.8$ (c 1.0, CHCl₃).⁵

⁵ Corresponds to (*S*) enantiomer: Messina, F.; Botta, M.; Corelli, F.; Schneider, M.P.; Fazio, F. *J. Org. Chem.* **1999**, *64*, 3767-3769.