Asymmetric Synthesis of Chiral β-Alkynyl Carbonyl and Sulfonyl Derivatives via Sequential Palladium and Copper Catalysis

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Supporting Information

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General Considerations: Unless otherwise noted, all alkyne-alkyne coupling reactions were performed in 2-dram vials equipped with Teflon coated stir bars. Importantly, care was not taken to exclude moisture or oxygen from the reaction mixture. Following the addition of solids and liquids to the reaction vessel, the vial was simply capped, and stirring was continued for the specified amount of time. Commercially available terminal alkynes were distilled prior to use in these reactions. Unless otherwise noted, all conjugate reduction reactions were performed in 5 mL conical microwave vials equipped with Teflon-coated stir bars under an atmosphere of argon (balloon). PhMe was freshly distilled over CaH₂, and THF was freshly distilled over Na/benzophenone. CH₂Cl₂ was obtained from a Seca solvent purification system by Glass Contour. Solvents and reagents were transferred via syringes using stainless steel needles that were dried in an oven and cooled in a desiccator.

Analytical thin-layer chromatography was performed on pre-coated 250 µm layer thickness silica gel 60 F₂₅₄ plates (EMD Chemicals Inc.). Visualization was performed by ultraviolet light and/or by staining with aqueous potassium permanganate or acidic, ethanolic para-anisaldehyde. Unless otherwise indicated, flash column chromatography was performed using 40-63 µm silica gel (Silicycle silica gel) using compressed air. The eluent employed for flash chromatography is reported using volume/volume ratios. Proton nuclear magnetic resonance (¹H NMR) spectra were acquired using a Varian Inova 500 MHz, Varian Inova 300 MHz, or Varian Mercury 400 MHz spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) and are calibrated to the residual solvent peak: proton (CDCl₃ 7.26 ppm, C₆D₆ 7.16 ppm). Coupling constants (J) are reported in Hz. Multiplicities are reported using the following abbreviations: s = singlet; d = doublet; t = triplet; q = quartet; sex = sextet; m = multiplet (range of multiplet is given). Carbon nuclear magnetic resonance (¹³C NMR) spectra were recorded using a Varian Inova spectrometer at 125 MHz, Varian Inova spectrometer at 75 MHz, or a Varian Mercury spectrometer at 100 MHz. Chemical shifts (δ) are reported in parts per million (ppm) and are calibrated to solvent peaks: carbon (CDCl₃ 77.16 ppm, C₆D₆ 128.06 ppm). Infrared spectroscopic data was recorded on a Thermo Scientific Nicolet IR100 FT-IR spectrometer, using thin films of the sample on NaCl plates. The absorbance frequencies are recorded in wavenumbers (cm⁻¹).
Chiral HPLC analysis was performed using an Agilent Technologies 1200 Series HPLC equipped with a Daicel Chemical Chiralpak® chiral stationary phase column (either IA [amylose tris(3,5-dimethylphenylcarbamate) immobilized on silica support], IB [cellulose tris(3,5-dimethylphenylcarbamate) immobilized on silica support], or IC [cellulose tris(3,5-dichlorophenylcarbamate) immobilized on silica support]). Optical rotations were measured using a JASCO P2000 polarimeter with 5 cm glass cells and a sodium 589 nm filter, and they are reported as $[\alpha]_D^T$, concentration (g/100 mL), and solvent. Melting points were determined on a Thomas Hoover Capillary Melting Point Apparatus and are uncorrected. High-resolution mass spectra were acquired by the Vincent Coates Foundation Mass Spectrometry Laboratory, Stanford University Mass Spectrometry (http://massspec.stanford.edu).

**Experimental Procedures**

A 2-dram screw-cap vial was charged with Pd(OAc)$_2$ (6.7 mg, 0.03 mmol, 3 mol %) and tris(2,6-dimethoxyphenyl)phosphine (13.3 mg, 0.03 mmol, 3 mol %). PhMe (1.0 mL) was added. The mixture was allowed to stir for 15 minutes, generating a homogeneous, orange-red solution. Methyl 2-nonynoate (184 µL, 1.0 mmol, 1.0 equivalent) was added followed immediately by 4-phenyl-1-butyn-1-yl)non-2-enoate (8aa):

A 2-dram screw-cap vial was charged with Pd(OAc)$_2$ (6.7 mg, 0.03 mmol, 3 mol %) and tris(2,6-dimethoxyphenyl)phosphine (13.3 mg, 0.03 mmol, 3 mol %). PhMe (1.0 mL) was added. The mixture was allowed to stir for 15 minutes, generating a homogeneous, orange-red solution. Methyl 2-nonynoate (184 µL, 1.0 mmol, 1.0 equivalent) was added followed immediately by 4-phenyl-1-butyn-1-yl)non-2-enoate (175 µL, 1.25 mmol, 1.25 equivalents). Upon addition of the donor alkyne, the reaction quickly changed in appearance to homogeneous and black. The reaction mixture was stirred for 18 h, at which point it was filtered through a pipette plug of Florisil® (3 cm), which was rinsed with Et$_2$O (10 mL). The solution was concentrated, and the residue was purified via column chromatography (20:1 hexanes:Et$_2$O) to afford the title compound as a brown oil (287.4 mg, 96%). $R_f = 0.38$ (10:1 hexanes:EtOAc) $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.33-7.29 (m, 2H), 7.25-7.22 (m, 3H), 5.96 (s, 1H), 3.70 (s, 3H), 2.87 (t, $J =$ 2.9 Hz, 2H), 2.12 (s, 3H), 1.20 (d, 6H), 0.87 (t, 3H), 0.82 (s, 3H).
7.4 Hz, 2H), 2.72-2.64 (m, 4H), 1.54-1.49 (m, 2H), 1.33-1.28 (m, 6H), 0.90 (t, J = 6.9 Hz, 3H) 13C NMR (100 MHz, CDCl3) δ 166.6, 144.5, 140.5, 128.7, 128.6, 126.6, 122.8, 95.5, 82.9, 51.3, 35.0, 32.8, 31.9, 29.2, 28.6, 22.9, 22.0, 14.4 IR (film): 3063, 3028, 2929, 2858, 2218, 1717, 1611, 1496, 1452, 1343, 1270, 1243, 1191, 1158, 1077, 1032, 871, 748, 698 cm⁻¹. HRMS: Calculated for C20H27O2 (M+H)⁺: 299.2006; Found 299.2004.

methyl (E)-3-(phenylethynyl)non-2-enoate (8ba)

Prepared using Representative Procedure A using Pd(OAc)2 (6.7 mg, 0.03 mmol, 3 mol %), tris(2,6-dimethoxyphenyl)phosphine (13.3 mg, 0.03 mmol, 3 mol %), methyl 2-nonynoate (184 µL, 1.0 mmol, 1.0 equivalent), and phenylacetylene (137 µL, 1.25 mmol) in PhMe (1.0 mL). After 3 h 30 min, additional phenylacetylene (55 µL, 0.50 mmol) was added, and stirring was continued for an additional 2 h, at which point the reaction was worked up as described in the representative procedure. Purification via column chromatography (25:1 hexanes:EtOAc) afforded the title compound as a brown oil (228 mg, 84% yield). Rf = 0.17 (25:1 hexanes:Et2O). 1H NMR (300 MHz, CDCl3) δ 7.49-7.46 (m, 2H), 7.36-7.34 (m, 3H), 6.15 (t, J = 0.9 Hz, 1H), 3.73 (s, 3H), 2.88 (td, J = 7.7 Hz, 0.9 Hz, 2H), 1.69-1.63 (m, 2H), 1.45-1.29 (m, 6H), 0.89 (m, 3H). 13C NMR (75 MHz, CDCl3) δ 166.4, 143.7, 132.0, 129.1, 128.5, 123.4, 122.5, 94.5, 90.4, 51.4, 32.4, 31.8, 29.1, 28.6, 22.7, 14.2. IR (film): 2953, 2929, 2858, 2202, 1718, 1609, 1490, 1433, 1353, 1314, 1272, 1199, 1140, 1027, 922, 870, 756, 690 cm⁻¹ HRMS: Calculated for C18H22O2Na (M+Na)⁺: 293.1517; Found 293.1513.
methyl (E)-3-((4-methoxyphenyl)ethynyl)non-2-enoate (8ca)

Prepared according to Representative Procedure A using Pd(OAc)$_2$ (3.3 mg, 0.015 mmol, 3 mol %) and tris(2,6-dimethoxyphenyl)phosphine (6.7 mg, 0.015 mmol, 3 mol %), methyl 2-nonynoate (92 µL, 0.50 mmol), and 4’-methoxyphenylacetylene (81 µL, 0.625 mmol) in PhMe (0.50 mL). The reaction duration was 1 h. Purification via column chromatography (10:1 hexanes:EtOAc) afforded the title compound (143.1 mg, 95%) as a clear, faintly yellow oil. Note: TLC analysis (6:1 hexanes:EtOAc) could be used to monitor for the consumption of acceptor alkyne; however, in this solvent system, the donor alkyne and enynoate product are co-polar. TLC analysis using 6:1 hexanes:Et$_2$O differentiates both the donor alkyne ($R_f$ = 0.56) and the acceptor ($R_f$ = 0.50) from the product enynoate ($R_f$ = 0.42). $R_f$ = 0.38 (10:1 hexanes:EtOAc). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.43-7.39 (m, 2H), 6.88-6.85 (m, 2H), 6.10 (s, 1H), 3.82 (s, 3H), 3.72 (s, 3H), 2.83 (t, $J$ = 7.7 Hz, 2H), 1.69-1.61 (m, 2H), 1.43-1.29 (m, 6H), 0.89 (t, $J$ = 7.1 Hz, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 166.5, 160.3, 144.1, 133.6, 122.6, 114.6, 114.2, 95.0, 89.5, 55.5, 51.3, 32.5, 31.8, 29.1, 28.7, 22.7, 14.3. IR (film): 2889, 2818, 2167, 1692, 1576, 1489, 1414, 1355, 1273, 1233, 1156, 1123, 1061, 1018, 911, 857, 821, 716 cm$^{-1}$ HRMS (ESI+): Calculated for C$_{19}$H$_{25}$O$_3$ (M+H)$^+$: 301.1798; Found 301.1792.

![Chemical structure](image)

methyl (E)-3-((4-bromophenyl)ethynyl)non-2-enoate (8da)

Prepared according to Representative Procedure A using Pd(OAc)$_2$ (3.3 mg, 0.015 mmol, 3 mol %), tris(2,6-dimethoxyphenyl)phosphine (6.7 mg, 0.015 mmol, 3 mol %), methyl 2-nonynoate (92 µL, 0.50 mmol), and 4-bromophenylacetylene (113.2 mg, 0.625 mmol) in PhMe (0.50 mL). After 5 h, additional 4-bromophenylacetylene (45.3 mg, 0.25 mmol) was added, and the reaction mixture was stirred for an additional 12 h. Purification via
column chromatography (20:1 hexanes:Et₂O) afforded the title compound (137.0 mg, 78%) as a clear, red-brown oil. \( R_f = 0.55 \) (10:1 hexanes:EtOAc). \(^1\)H NMR (300 MHz; CDCl₃): \( \delta \) 7.50-7.46 (m, 2H), 7.34-7.30 (m, 2H), 6.14 (t, \( J = 0.9 \) Hz, 1H), 3.73 (s, 3H), 2.85-2.80 (m, 2H), 1.68-1.58 (m, 2H), 1.43-1.27 (m, 6H), 0.89 (d, \( J = 14.1 \) Hz, 3H). \(^{13}\)C NMR (100 MHz; CDCl₃): 166.3, 143.3, 133.4, 131.9, 123.9, 123.5, 121.5, 93.2, 91.4, 51.4, 32.3, 31.8, 29.1, 28.6, 22.7, 14.2 IR (film): 2887, 2818, 1694, 1586, 1561, 1465, 1413, 1334, 1155, 1124, 1054, 997, 859, 812 cm⁻¹ HRMS (ESI+): Calculated for C₁₈H₂₂O₂Br (M+H)⁺: 349.0798; Found 349.0789.

methyl \((E)-3-((\text{benzylidimethylsilyl})\text{ethynyl})\text{non-2-enolate} \ (8\text{ea})\)

Prepared according to Representative Procedure A using Pd(OAc)_2 (6.7 mg, 0.03 mmol, 3 mol %), tris(2,6-dimethoxyphenyl)phosphine (13.3 mg, 0.03 mmol, 3 mol %), methyl 2-nonynoate (184 \( \mu \)L, 1.0 mmol, 1.0 equivalent), and benzylidimethysilylacetylene (218 mg, 1.25 mmol) in PhMe (1.0 mL). The reaction duration was 6 h 30 min. Purification via column chromatography (50:1 hexanes:Et₂O) afforded the title compound (313 mg, 92%) as a brown oil. \( R_f = 0.45 \) (10:1 hexanes:EtOAc). \(^1\)H NMR (400 MHz, CDCl₃) \( \delta \) 7.26-7.21 (m, 2H), 7.12-7.06 (m, 3H), 6.06 (t, \( J = 1.0 \) Hz, 1H), 3.71 (s, 3H), 2.71 (td, \( J = 7.7 \) Hz, 0.8 Hz, 2H), 2.23 (s, 2H), 1.58-1.54 (m, 2H), 1.31-1.29 (m, 6H), 0.89 (t, \( J = 7.0 \) Hz, 3H), 0.17, s, 6H. \(^{13}\)C NMR (125 MHz, CDCl₃) \( \delta \) 166.3, 143.1, 138.7, 128.5, 128.3, 124.6, 124.5, 106.9, 98.6, 51.4, 32.1, 31.8, 29.0, 28.5, 26.1, 22.7, 14.2, -2.1. IR (film): 3025, 2956, 2929, 2859, 2144, 1720, 1610, 1493, 1453, 1434, 1352, 1251, 1149, 1057, 1026, 926, 841, 762, 698. HRMS: Calculated for C₂₁H₃₁O₂Si (M+H)⁺: 343.2088; Found 343.2095.
methyl (E)-3-((trimethylsilyl)ethynyl)non-2-enoate (8fa)

Prepared according to Representative Procedure A using Pd(OAc)$_2$ (20.2 mg, 0.09 mmol, 3 mol %), tris(2,6-dimethoxyphenyl)phosphine (39.8 mg, 0.09 mmol, 3 mol %), methyl 2-nonynoate (550 µL, 3.0 mmol) and trimethylsilylacetylene (530 µL, 3.75 mmol, 1.25 equivalent) in PhMe (3 mL). The reaction duration was 2 h. Purification via column chromatography (30:1 to 20:1 hexanes:EtOAc) afforded the title compound (731.9 mg, 92%) as a clear, brown oil. $R_f$ = 0.57 (10:1 hexanes:EtOAc). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 6.06 (s, 1H), 3.69 (s, 3H), 2.71 (t, $J$ = 7.6 Hz, 2H), 1.60-1.52 (m, 2H), 1.36-1.27 (m, 6H), 0.88 (t, $J$ = 6.8 Hz, 3H), 0.20 (s, 9H). $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 166.4, 143.4, 124.3, 105.6, 100.3, 51.4, 32.1, 31.7, 29.0, 28.4, 22.7, 14.2, -0.1. IR (film): 2916, 2819, 2115, 1698, 1588, 1414, 1334, 1234, 1132, 1075, 1011, 914, 833, 750, 691, 693 cm$^{-1}$. HRMS (ESI+): Calculated for C$_{15}$H$_{26}$NaO$_2$Si (M+Na)$^+$: 289.1594; Found 289.1599.

methyl (E)-3-((tert-butyldimethylsilyl)oxy)-3,3-dimethylbut-1-yn-1-yl)non-2-enoate (8ga)

Prepared according to Representative Procedure A using Pd(OAc)$_2$ (3.4 mg, 0.015 mmol, 3 mol %), tris(2,6-dimethoxyphenyl)phosphine (TDMPP, 6.3 mg, 0.015 mmol, 3 mol %), methyl 2-nonynoate, (92 µL, 0.50 mmol, 1.0 equivalent) and known donor alkyne tert-butyl((2,2-dimethylbut-3-yn-1-yl)oxy)dimethylsilane$^2$ (133 mg, 0.625 mmol) in PhMe (0.50 mL). The reaction duration was 24 h. Purification via column chromatography (20:1 hexanes:EtOAc) afforded the title compound (180.4 mg, 95%) as a viscous, orange oil. $R_f$ = 0.58 (10:1 hexanes:EtOAc). $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 5.96 (t, $J$ = 1.0 Hz, 1H), 3.69 (s, 3H), 3.45 (s, 2H), 2.72-2.69 (m, 2H), 1.57-1.53 (m, 2H), 1.34-1.28 (m, 6H), 1.20 (s, 6H), 0.90-0.88 (m, 12H), 0.05 (s, 6H). $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 166.7, 144.6, 122.5, 102.3, 81.9, 71.1, 51.2, 34.5, 32.6, 31.8, 29.0, 28.4, 26.0, 25.4, 22.7, 18.4, 14.2, -5.3. IR (film):
2889, 2818, 1696, 1589, 1449, 1341, 1237, 1132, 1093, 827, 766 cm\(^{-1}\). **HRMS** (ESI\(^{+}\)):
Calculated for C\(_{22}\)H\(_{41}\)O\(_3\)Si (M+H\(^{+}\)):\ 381.2819; Found 381.2816.

![methyl (E)-3-(3-methylbut-3-en-1-yn-1-yl)non-2-enoate (8ha)]

Prepared according to Representative Procedure A using Pd(OAc)\(_2\) (3.4 mg, 0.015 mmol, 3 mol%), tris-2,6-dimethoxyphenylphosphine (TDMPP, 6.3 mg, 0.015 mmol, 3 mol%), methyl 2-nonynoate, (92 µL, 0.50 mmol, 1.0 equivalent) and 2-methyl-1-buten-3-yne (60 µL, 0.625 mmol) in PhMe (0.50 mL). In light of the volatility of this donor alkyne (b. p. = 32 °C), the vial threads were wrapped with PTFE tape, and the capped vial was sealed with Parafilm\textregistered. The reaction duration was 18 h. Purification via column chromatography (20:1 hexanes:EtOAc) afforded the title compound (94.4 mg, 81%) as a clear, brown oil. **R\(_f\)** = 0.53 (10:1 hexanes:EtOAc). **\(^1\)H NMR** (500 MHz; CDCl\(_3\)): \(\delta\) 6.04 (s, 1H), 5.37 (s, 1H), 5.32 (s, 1H), 3.70 (s, 3H), 2.75 (t, \(J = 7.6\) Hz, 2H), 1.92 (s, 3H), 1.60-1.54 (m, 2H), 1.36-1.30 (m, 6H), 0.88 (t, \(J = 6.1\) Hz, 3H). **\(^{13}\)C NMR** (100 MHz; CDCl\(_3\)): \(\delta\) 166.4, 143.7, 126.5, 123.7, 123.4, 95.7, 89.4, 51.3, 32.4, 31.8, 29.1, 28.6, 23.3, 22.7, 14.2. **IR** (film): 2888, 2819, 2166, 1696, 1591, 1414, 1333, 1300, 1134, 1015, 887, 859, 715 cm\(^{-1}\). **HRMS** (ESI\(^{+}\)):
Calculated for C\(_{15}\)H\(_{23}\)O\(_2\) (M+H\(^{+}\)):\ 235.1693; Found 235.1687.

![ethyl (E)-3-(4-phenylbut-1-yn-1-yl)non-2-enoate (8ab)]

S8
Prepared according to Representative Procedure A using Pd(OAc)$_2$ (3.4 mg, 0.015 mmol, 3 mol %), tris-2,6-dimethoxyphenylphosphine (TDMPP, 6.3 mg, 0.015 mmol, 3 mol %), 4-phenyl-1-butyn (88 µL, 0.625 mmol) and known acceptor ethyl 2-hexynoate$^3$ (91.1 mg, 0.50 mmol) in PhMe (0.50 mL). The reaction duration was 4 h. Purification via column chromatography (20:1 hexanes:Et$_2$O) afforded the title compound (145.9 mg, 93%) as an oil. \( R_f = 0.53 \) (10:1 hexanes:EtOAc). $^1$H NMR (400 MHz; CDCl$_3$): \( \delta \) 7.33-7.28 (m, 2H), 7.24-7.22 (m, 3H), 5.95 (s, 1H), 4.15 (q, \( J = 7.1 \) Hz, 2H), 2.86 (t, \( J = 7.4 \) Hz, 2H), 2.70-2.63 (m, 4H), 1.52-1.48 (m, 2H), 1.33-1.25 (m, 9H), 0.89 (t, \( J = 6.9 \) Hz, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): \( \delta \) 166.2, 144.0, 140.5, 128.6, 128.5, 126.5, 123.2, 95.2, 82.8, 60.0, 35.0, 32.7, 31.8, 29.1, 28.6, 22.8, 21.9, 14.4, 14.3. IR (film): 2914, 2888, 2818, 2188, 1690, 1588, 1475, 1434, 1349, 1324, 1282, 1251, 1138, 1080, 1027, 860, 737, 688 cm$^{-1}$. HRMS (ESI+): Calculated for C$_{21}$H$_{29}$O$_2$ (M+H)$^+$: 313.2162; Found 313.2158.

benzyl (E)-3-(4-phenylbut-1-yn-1-yl)non-2-enoate (8ac)

Prepared according to Representative Procedure A using Pd(OAc)$_2$ (3.4 mg, 0.015 mmol, 3 mol %), tris-2,6-dimethoxyphenylphosphine (TDMPP, 6.3 mg, 0.015 mmol, 3 mol %), 4-phenyl-1-butyn (88 µL, 0.625 mmol) and known acceptor benzyl 2-hexynoate$^4$ (122.2 mg, 0.50 mmol) in PhMe (0.50 mL). The reaction duration was 3 h. Purification via column chromatography (30:1 hexanes:Et$_2$O) afforded the title compound (176.8 mg, 94%) as a clear, light orange oil. \( R_f = 0.39 \) (20:1 hexanes:Et$_2$O). $^1$H NMR (400 MHz; CDCl$_3$): \( \delta \) 7.37-7.29 (m, 7H), 7.25-7.22 (m, 3H), 6.02 (s, 1H), 5.15 (s, 2H), 2.86 (t, \( J = 7.4 \) Hz, 2H), 2.70 (t, \( J = 7.7 \) Hz, 2H), 2.66 (t, \( J = 7.4 \) Hz, 2H), 1.56-1.47 (m, 2H), 1.33-1.22 (m, 6H), 0.89 (t, \( J = 6.8 \) Hz, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): 165.9, 144.8, 140.4, 136.3, 128.7, 128.6, 128.5, 128.2 (2C), 126.5, 122.8, 95.7, 82.8, 65.9, 34.9, 32.8, 31.8, 29.1, 28.6, 22.8, 21.9, 14.3. IR (film): 2887, 2818, 2186, 1690, 1586, 1476, 1357, 1249, 1130, 1013, 859, 735, 687 cm$^{-1}$. HRMS (ESI+): Calculated for C$_{26}$H$_{31}$O$_2$ (M+H)$^+$: 375.2319; Found 375.2313.
Prepared according to Representative Procedure A using Pd(OAc)$_2$ (3.4 mg, 0.015 mmol, 3 mol %), tris-2,6-dimethoxyphenylphosphine (TDMPP, 6.3 mg, 0.015 mmol, 3 mol %), 4-phenyl-1-butyn (88 µL, 0.625 mmol) and known acceptor methyl 3-cyclopropylpropiolate$^5$ (62.0 mg, 0.50 mmol) in PhMe (0.50 mL). The reaction duration was 14 h. Purification via column chromatography (10:1 hexanes:EtOAc) afforded the title compound (122.5 mg, 96%) as a clear, light brown oil. $R_f = 0.41$ (10:1 hexanes:EtOAc). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.33-7.29 (m, 2H), 7.25-7.19 (m, 3H), 5.99 (s, 1H), 3.71 (s, 3H), 3.17-3.10 (m, 1H), 2.83 (t, $J = 7.3$ Hz, 2H), 2.61 (t, $J = 7.4$ Hz, 2H), 0.85-0.79 (m, 4H). $^{13}$C NMR (100 MHz; CDCl$_3$): 167.3, 147.5, 140.2, 128.6, 128.5, 126.6, 121.5, 95.0, 78.1, 51.2, 34.8, 21.6, 12.7, 8.6. IR (film): 3043, 2985, 2907, 2192, 1688, 1574, 1475, 1434, 1413, 1369, 1250, 1175, 1144, 1016, 949, 909, 845 cm$^{-1}$. HRMS (ESI+): Calculated for C$_{17}$H$_{19}$O$_2$ (M+H)$^+$: 255.1380; Found 255.1372.

Prepared according to Representative Procedure A using Pd(OAc)$_2$ (3.4 mg, 0.015 mmol, 3 mol %), tris-2,6-dimethoxyphenylphosphine (TDMPP, 6.3 mg, 0.015 mmol, 3 mol %), 4-phenyl-1-butyn (88 µL, 0.625 mmol) and known acceptor methyl 3-cyclopropylpropiolate$^6$ (80.3 mg, 0.50 mmol) in PhMe (0.50 mL). The reaction duration was 1 h. Purification via column chromatography (20:1 to 10:1 hexanes:EtOAc) afforded the title compound (143.2
mg, 98%) as a clear, light yellow oil. \( R_f = 0.43 \) (10:1 hexanes:EtOAc). \(^1\)H NMR (400 MHz; CDCl\(_3\)): \( \delta \) 7.34-7.29 (m, 2H), 7.25-7.22 (m, 3H), 6.00 (s, 1H), 3.70 (s, 3H), 3.52 (t, \( J = 6.9 \) Hz, 2H), 2.89-2.81 (m, 4H), 2.69-2.65 (m, 2H), 2.01-1.94 (m, 2H). \(^{13}\)C NMR (100 MHz; CDCl\(_3\)): 166.3, 142.0, 142.3, 128.59, 128.57, 126.6, 123.7, 96.3, 82.2, 51.4, 44.4, 34.8, 31.4, 30.1, 21.8. IR (film): 2985, 2908, 2186, 1691, 1590, 1475, 1413, 1325, 1233, 1175, 1146, 1062, 1018, 860 cm\(^{-1}\). HRMS (ESI+): Calculated for C\(_{17}\)H\(_{20}\)ClO\(_2\) (M+H\(^{+}\)): 291.1146; Found 291.1143.

methyl (E)-3-methyl-5-phenylpent-2-en-4-ynoate (8bf)

Prepared according to Representative Procedure A using Pd(OAc)_2 (6.7 mg, 0.03 mmol, 3 mol %), tris(2,6-dimethoxyphenyl)phosphine (13.3 mg, 0.03 mmol, 3 mol %), methyl but-2-ynoate (98 mg, 1.0 mmol), and phenylacetylene (137 µL, 1.25 mmol) in PhMe (1.0 mL). After 3 h 30 min additional phenylacetylene (55 µL, 0.5 mmol) was added. The reaction mixture was stirred for an additional 2 h, at which point it was worked up as described. Purification via column chromatography (20:1 hexanes:EtoAc) afforded the title compound as a light brown oil (190 mg, 0.95 mmol, 95% yield). \( R_f = 0.25 \) (20:1 hexanes:EtoAc). \(^1\)H NMR (300 MHz, CDCl\(_3\)): \( \delta \) 7.49-7.44 (m, 2H), 7.37-7.30 (m, 3H), 6.17 (q, \( J = 1.5 \) Hz, 1H), 3.74 (s, 3H), 2.40 (d, \( J = 1.5 \) Hz, 3H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)): \( \delta \) 166.6, 138.3, 132.0, 129.2, 128.5, 123.7, 122.4, 93.9, 91.2, 51.3, 20.0. IR (film): 2949, 2204, 1716, 1614, 1489, 1434, 1375, 1344, 1304, 1273, 1198, 1137, 1070, 1030, 922, 869, 756, 689 cm\(^{-1}\). These \(^1\)H and \(^{13}\)C NMR data matched that previously reported for this compound.

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ethyl (E)-3-ethyl-5-phenylpent-2-en-4-ynoate (8bg)

Prepared according to Representative Procedure A using Pd(OAc)$_2$ (3.4 mg, 0.015 mmol, 3 mol %), tris-2,6-dimethoxyphenylphosphine (TDMPP, 6.3 mg, 0.015 mmol, 3 mol %), ethyl pent-2-ynoate (66 µL, 0.50 mmol), and phenylacetylene (69 µL, 0.625 mmol) in PhMe (0.50 mL). The reaction duration was 3 h. Purification via column chromatography (30:1 to 20:1 hexanes:EtOAc) afforded the title compound (96.8 mg, 85%) as a clear, brown oil. $R_f = 0.41$ (10:1 hexanes:EtOAc). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.49-7.46 (m, 2H), 7.36-7.33 (m, 3H), 6.13 (t, $J$ = 1.0 Hz, 1H), 4.19 (q, $J$ = 7.1 Hz, 2H), 2.85 (qd, $J$ = 7.5, 1.0 Hz, 2H), 1.30 (t, $J$ = 7.1 Hz, 3H), 1.23 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 166.0, 144.4, 132.0, 129.1, 128.6, 123.5, 122.6, 94.6, 90.2, 60.2, 25.9, 14.4, 13.1. IR (film): 2935, 2895, 2170, 1690, 1587, 1423, 1349, 1327, 1288, 1250, 1171, 1121, 1019, 860, 746, 680 cm$^{-1}$. HRMS (ESI$^+$): Calculated for C$_{15}$H$_{16}$NaO$_2$ (M+Na$^+$): 251.1043; Found 251.1053.

methyl (E)-3-(phenylethynyl)hex-2-enoate (8bh)

Prepared according to Representative Procedure A using Pd(OAc)$_2$ (3.4 mg, 0.015 mmol, 3 mol %), tris-2,6-dimethoxyphenylphosphine (TDMPP, 6.3 mg, 0.015 mmol, 3 mol %), methyl hex-2-ynoate (67 µL, 0.50 mmol), and phenylacetylene (69 µL, 0.625 mmol) in PhMe (0.50 mL). The reaction duration was 1 h. Purification via column chromatography (20:1 to 10:1 hexanes:EtOAc) afforded the title compound (103.9 mg, 91%) as a clear, brown oil. $R_f = 0.26$ (10:1 hexanes:EtOAc). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.49-7.46 (m, 2H), 7.36-7.33 (m, 3H), 6.17 (t, $J$ = 1.0 Hz, 1H), 3.73 (s, 3H), 2.84 (t, $J$ = 7.6 Hz, 2H), 1.75-1.66 (m, 2H), 1.01 (t, $J$ = 7.4 Hz, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 166.4, 143.4, 132.0, 129.1, 128.5, 123.6, 122.5, 94.5, 90.3, 51.4, 34.2, 22.0, 13.9. IR (film): 2985, 2908, 2186, 1691, 1590, 1475, 1413, 1325, 1233, 1175, 1146, 1062, 1018, 860 cm$^{-1}$. HRMS (ESI$^+$): Calculated for C$_{17}$H$_{20}$ClO$_2$ (M+H$^+$): 291.1146; Found 291.1143.
methyl (E)-6-((tert-butyldimethylsilyl)oxy)hex-4-en-2-ynoate (7i)

To a – 78 °C solution of known alkyne (E)-tert-butyldimethyl(pent-2-en-4-yn-1-yl)oxy)silane (589.1 mg, 3.0 mmol, 1.0 equivalent) in THF (12 mL) was added n-BuLi (1.6 M in hexanes, 2.06 mL, 3.3 mmol, 1.1 equivalents), yielding a homogeneous, deep pink mixture that soon progressed to homogeneous and red-brown. The reaction mixture was stirred for 30 min at – 78 °C, and then methyl chloroformate (0.29 mL, 3.75 mmol, 1.25 equivalents) was added. This resulted in a change in appearance to homogeneous and golden yellow. The reaction mixture was stirred for 5 min, and then the cooling bath was removed and the vessel allowed to warm to room temperature. After 30 min, the reaction mixture was quenched with saturated aqueous NH₄Cl (20 mL) and poured into Et₂O (20 mL). The phases were separated, and the aqueous phase was extracted with Et₂O (20 mL). The pooled organic phases were dried over MgSO₄, filtered, and concentrated. Purification via column chromatography (20:1 to 10:1 hexanes:EtOAc) afforded the title compound (608.3 mg, 80 %) as a clear, yellow oil. 

Rf = 0.34 (10:1 hexanes:EtOAc). ¹H NMR (400 MHz; CDCl₃): δ 6.56 (dt, J = 15.8, 3.6 Hz, 1H), 5.90 (dt, J = 15.7, 2.5 Hz, 1H), 4.28 (dd, J = 3.6, 2.4 Hz, 2H), 3.79 (s, 3H), 0.91 (s, 9H), 0.07 (s, 6H). ¹³C NMR (100 MHz; CDCl₃): δ 154.6, 149.8, 105.7, 85.6, 80.7, 62.7, 52.8, 25.9, 18.4, -5.3. IR (film): 2914, 2818, 2188, 1693, 1415, 1358, 1224, 1118, 1086, 995, 939, 826, 768, 739, 668 cm⁻¹. HRMS (ESI+): Calculated for C₁₃H₂₅O₃Si (M+H)⁺: 255.1411; Found 255.1406.
methyl \((E)-3-((E)-3-(((\text{tert-butyldimethylsilyl})oxy)prop-1-en-1-yl)-7-phenylhept-2-en-4-ynoate\) (8ai)

Prepared according to Representative Procedure A using Pd(OAc)\(_2\) (3.4 mg, 0.015 mmol, 3 mol %), tris-2,6-dimethoxyphenolphosphine (TDMPP, 6.3 mg, 0.015 mmol, 3 mol %), acceptor methyl \((E)-6-(((\text{tert-butyldimethylsilyl})oxy)hex-4-en-2-ynoate\) (127.2 mg, 0.50 mmol) and donor 4-phenyl-1-butyne (88 \(\mu\)L, 0.625 mmol) in PhMe (0.50 mL). The reaction duration was 16 h. Purification via column chromatography (20:1 to 10:1 hexanes:EtOAc) afforded the title compound (175.9 mg, 91%) as a clear, red-orange oil. \(R_f\) = 0.38 (10:1 hexanes:EtOAc). \(^1\)H NMR (400 MHz; CDCl\(_3\)): \(\delta\) 7.62 (dtd, \(J = 15.4, 1.9, 0.8\) Hz, 1H), 7.33-7.29 (m, 2H), 7.25-7.21 (m, 3H), 6.41 (dtd, \(J = 15.4, 4.6, 0.7\) Hz, 1H), 5.92 (s, 1H), 4.31 (ddd, \(J = 4.6, 1.9, 0.8\) Hz, 2H), 3.72 (s, 3H), 2.90 (t, \(J = 7.4\) Hz, 2H), 2.70 (t, \(J = 7.4\) Hz, 2H), 0.94 (s, 9H), 0.10 (s, 6H). \(^{13}\)C NMR (100 MHz; CDCl\(_3\)): \(\delta\) 166.3, 141.5, 140.4, 136.9, 128.63, 128.58, 126.6, 124.3, 121.1, 95.6, 79.3, 63.4, 51.4, 34.9, 26.1, 21.7, 18.6, -5.1. IR (film): 2910, 2816, 2195, 1690, 1616, 1558, 1413, 1339, 1228, 1216, 1143, 1061, 995, 958, 825, 767, 736, 688 cm\(^{-1}\). HRMS (ESI+): Calculated for C\(_{23}\)H\(_{33}\)O\(_3\)Si (M+H): 385.2193; Found 385.2187.

methyl \((Z)-3-(((\text{methoxycarbonyl})oxy)methyl)-7-phenylhept-2-en-4-ynoate\) (8aj)

Prepared according to Representative Procedure A using Pd(OAc)\(_2\) (6.7 mg, 0.03 mmol, 3 mol %), tris(2,6-dimethoxyphenolphosphine (13.3 mg, 0.03 mmol, 3 mol %), known acceptor methyl 4-(((\text{methoxycarbonyl})oxy)but-2-ynoate\(^9\) (172 mg, 1.0 mmol), and 4-phenyl-1-butyne (176 \(\mu\)L, 1.25 mmol) in PhMe (1.0 mL). The reaction duration was 18 h. Purification via column chromatography (6:1 hexanes:EtOAc) afforded the title compound as a dark yellow oil (233 mg, 0.77 mmol, 77% yield). \(R_f\) = 0.40 (6:1 hexanes:EtOAc). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.34-7.28 (m, 2H), 7.25-7.20 (m, 3H), 6.08 (t, \(J = 1.8\) Hz, 1H), 5.22 (d, \(J\)
= 1.8 Hz, 2H), 3.80 (s, 3H), 3.72 (s, 3H), 2.86 (t, \( J = 7.5 \) Hz, 2H), 2.65 (t, \( J = 7.6 \) Hz, 2H). \(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \( \delta \) 165.8, 155.6, 140.2, 137.9, 128.53, 128.46, 126.5, 124.2, 98.9, 78.5, 65.1, 55.1, 51.7, 34.6, 22.0. \( \text{IR (film)}: \) 3063, 3028, 2954, 2220, 1755, 1714, 1608, 1496, 1443, 1373, 1262, 1192, 1166, 1124, 1030, 986, 907, 872, 789, 750, 700 \( \text{cm}^{-1} \). \( \text{HRMS:} \) Calculated for C\(_{17}\)H\(_{19}\)O\(_5\) (M+H\(^{+}\)): 303.1227; Found 303.1229.

methyl \((Z)-3-(((\text{methoxycarbonyl})\text{oxy})\text{methyl})-5\)-phenylpent-2-en-4-ynoate (8bj)

Prepared according to Representative Procedure A using Pd(OAc)\(_2\) (6.7 mg, 0.03 mmol, 3 mol %), tris(2,6-dimethoxyphenyl)phosphine (13.3 mg, 0.03 mmol, 3 mol %), methyl 4-((methoxycarbonyl)oxy)but-2-ynoate (172 mg, 1.0 mmol), and phenylacetylene (137 \( \mu \)L, 1.25 mmol) in PhMe (1.0 mL). The reaction was stirred for 2 h at room temperature, at which point additional phenylacetylene (55 \( \mu \)L, 0.5 mmol) was added. The reaction mixture was stirred for an additional 2 h 30 min and then worked up as described. Purification via column chromatography (8:1 hexanes:EtOAc) afforded the title compound as a brown solid (210 mg, 0.77 mmol, 77% yield). \( R_f = 0.20 \) (8:1 hexanes:EtOAc). \( \text{MP} = 68 – 69 \text{ °C} \). \(^1\)H NMR (300 MHz, CDCl\(_3\)) \( \delta \) 7.50-7.45 (m, 2H), 7.39-7.31 (m, 3H), 6.26 (t, \( J = 2.0 \) Hz, 1H), 5.34 (d, \( J = 2.0 \) Hz, 2H), 3.82 (s, 3H), 3.76 (s, 3H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \( \delta \) 165.8, 155.8, 137.9, 132.2, 129.6, 128.6, 124.3, 122.0, 97.9, 86.2, 65.2, 55.2, 51.9. \( \text{IR (film):} \) 3021, 2949, 2207, 1760, 1705, 1610, 1593, 1488, 1448, 1435, 1348, 1313, 1260, 1208, 1120, 1071, 1026, 1012, 979, 926, 904, 872, 845, 786, 760, 693 \( \text{cm}^{-1} \). \( \text{HRMS:} \) Calculated for C\(_{15}\)H\(_{15}\)O\(_5\) (M+H\(^{+}\)): 275.0914; Found 275.0912.
Methyl (Z)-5-(benzyldimethylsilyl)-3-(((methoxycarbonyl)oxy)methyl)pent-2-en-4-ynoate (8ej)

Prepared according to Representative Procedure A using Pd(OAc)$_2$ (6.7 mg, 0.03 mmol, 3 mol %), tris(2,6-dimethoxyphenyl)phosphine (13.3 mg, 0.03 mmol, 3 mol %), methyl 4-((methoxycarbonyl)oxy)but-2-ynoate (172 mg, 1.0 mmol), and benzyldimethylsilylacetylene (218 mg, 1.25 mmol) in PhMe (1.0 mL). The reaction duration was 9 h. Purification via column chromatography (8:1 hexanes:EtOAc) afforded the title compound as a light brown oil (233 mg, 0.67 mmol, 67% yield). $R_f$ = 0.32 (8:1 hexanes:EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.24-7.21 (m, 2H), 7.13-7.06 (m, 3H), 6.18 (t, $J$ = 2.0 Hz, 1H), 5.22 (d, $J$ = 2.0 Hz, 2H), 3.79 (s, 3H), 3.74 (s, 3H), 2.23 (s, 2H), 0.16 (s, 6H). $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 165.8, 155.8, 138.6, 137.4, 128.6, 128.5, 125.9, 124.8, 102.8, 102.1, 64.9, 55.3, 52.1, 26.0, -2.3. IR (film): 3025, 2957, 1757, 1716, 1607, 1494, 1443, 1337, 1239, 1151, 1057, 988, 906, 842, 790, 764, 700 cm$^{-1}$. HRMS: Calculated for C$_{18}$H$_{23}$O$_5$Si (M+H)$^+$: 347.1309; Found 347.1312.

methyl (Z)-3-(((tert-butoxycarbonyl)amino)methyl)-7-phenylhept-2-en-4-ynoate (8ak)

Prepared according to Representative Procedure A using Pd(OAc)$_2$ (3.4 mg, 0.015 mmol, 1.5 mol %), tris-2,6-dimethoxyphenylphosphine (TDMPP, 6.3 mg, 0.015 mmol, 1.5 mol %), 4-phenyl-1-butyn (176 µL, 1.25 mmol), and known acceptor methyl 4-((tert-butoxycarbonyl)amino)but-2-ynoate$^{10}$ (213 mg, 1.0 mmol) in PhMe (1.0 mL). The reaction duration was 3 h. The crude product was purified by column chromatography (6:1 to 4:1 hexanes:EtOAc) to afford the title compound as a light yellow solid (311 mg, 0.91 mmol, 91% yield). $R_f$ = 0.30 (4:1 hexanes:EtOAc). MP = 84 – 85 °C. $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.34-7.30 (m, 2H), 7.25-7.22 (m, 3H), 6.03 (s, 1H), 4.96 (br s, 1H), 4.29 (d, $J$ = 5.8 Hz, 2H), 3.71 (s, 3H), 2.89-2.86 (t, $J$ = 7.4 Hz, 2H), 2.68-2.65 (t, $J$ = 7.5 Hz, 2H), 1.45 (s, 9H). $^{13}$C
**NMR** (125 MHz, CDCl$_3$) $\delta$ 166.2, 155.8, 141.0, 140.3, 128.64, 128.56, 126.6, 123.7, 98.2, 80.6, 79.5, 51.6, 41.3, 34.7, 28.5, 22.1. **IR** (film): 3419, 2978, 1717, 1605, 1498, 1455, 1368, 1253, 1160, 750, 700 cm$^{-1}$. **HRMS**: Calculated for C$_{20}$H$_{25}$NNaO$_4$ (M+Na)$^+$: 366.1676; Found 366.1682.

![Chemical Structure](image)

methyl (Z)-3-(((tert-butoxycarbonyl)amino)methyl)-5-phenylpent-2-en-4-ynoate (8bk)

Prepared according to Representative Procedure A using Pd(OAc)$_2$ (3.4 mg, 0.015 mmol, 1.5 mol %), tris-2,6-dimethoxyphenylphosphine (TDMPP, 6.3 mg, 0.015 mmol, 1.5 mol %), phenylacetylene (137 $\mu$L, 1.25 mmol), and methyl 4-((tert-butoxycarbonyl)amino)but-2-ynoate (213 mg, 1.0 mmol) in PhMe (1.0 mL). The reaction duration was 1 hour. The crude product was purified by column chromatography (5:1 hexanes:EtOAc) to afford the title compound as a white solid (295 mg, 0.94 mmol, 94% yield). **$^1$H NMR** (400 MHz, CDCl$_3$) $\delta$ 7.51-7.45 (m, 2H), 7.39-7.30 (m, 3H), 6.21 (t, $J$ = 1.6 Hz, 1H) 5.20-4.85 (N-H, br, 1H), 4.44-4.35 (br, d, $J$ = 6 Hz, 2H), 3.74 (s, 3H), 1.43 (s, 9H). These **$^1$H NMR data matched that previously reported for this compound.$^{10}$

![Chemical Structure](image)

methyl (Z)-5-(benzylimethylsilyl)-3-(((tert-butoxycarbonyl)amino)methyl)pent-2-en-4-ynoate (8ek)

Prepared according to Representative Procedure A using Pd(OAc)$_2$ (3.4 mg, 0.015 mmol, 1.5 mol %), tris-2,6-dimethoxyphenylphosphine (TDMPP, 6.3 mg, 0.015 mmol, 1.5 mol %), benzylimethylsilylacetylene (218 mg, 1.25 mmol), and known acceptor methyl 4-
Cu-catalyzed Asymmetric Conjugate Reduction of Ynenoates: Representative Procedure B, Synthesis of methyl (S)-3-(4-phenylbut-1-yn-1-yl)nonanoate (9aa):

An oven-dried round-bottom Biotage® microwave vial (0.50 – 2.0 mL size) was charged with Cu(OAc)$_2$$

\cdot$H$_2$O (3.0 mg, 0.015 mmol, 5 mol %) and WALPHOS ligand W001-1 (17, (R)-1-[(R)-2-(2′-diphenylphosphinophenyl)-ferrocenyl]-ethyl-di-bis(3,5-trifluoromethyl-phenyl)phosphine, 14.0 mg, 0.015 mmol, 5 mol %). The vial was sealed with a septum, purged with Ar, and kept under an Ar atmosphere (balloon). Distilled, degassed (N$_2$ sparged) PhMe (1.5 mL) was added, and the mixture was stirred for 30 min. A homogeneous blue-green solution resulted. Diethoxymethylsilane (96 µL, 0.60 mmol, 2 equivalents) was added, and over 30 min, the appearance changed to homogeneous and yellow-brown. The vial was cooled to 0 °C, and methyl (E)-3-(4-phenylbut-1-yn-1-yl)non-2-enoate (90.0 mg, 0.30 mmol, 1 equivalent) was added neat via microliter syringe, followed by tert-butanol (57 µL, 0.60 mmol, 2 equivalents). The vessel was moved to a cold room (4 °C) where it was stirred for 14 h. After this time, the reaction mixture was filtered through a pipette plug of Florisil® (3 cm), which was rinsed with 2:1 hexanes:EtOAc (3 x 3 mL). The solution was concentrated, and the residue was purified via column chromatography (20:1 hexanes:EtOAc) to afford the title compound (81.9 mg, 90%, 99% ee) as a light yellow oil. $R_f = 0.20$ (20:1 hexanes:EtOAc). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.35-7.30 (m, 2H), 7.24-7.22 (m, 3H), 3.72 (s, 3H), 2.84-2.80 (m, 3H), 2.53-2.40 (m, 4H), 1.49-1.25 (m, 10H), 0.93 (t, $J = 7.0$ Hz, 3H). $^{13}$C NMR (100 MHz,
$\text{CDCl}_3 \delta 172.5, 141.0, 128.6, 128.4, 82.6, 81.2, 51.7, 40.5, 35.6, 35.0, 31.9, 29.1, 28.4, 27.2, 22.8, 21.1, 14.2$. **IR** (film): 2953, 2928, 2857, 1742, 1455, 1436, 1163, 699 cm$^{-1}$.

**HRMS:** Calculated for $\text{C}_{20}\text{H}_{29}\text{O}_2$ (M+H)$^+$: 301.2162, Found 301.2163. **Chiral HPLC:** Chiralpak® IB column; heptane/isopropanol 999:1; flow rate = 0.4 mL/min; detection at 214 nm; $t_1 = 31.0$ min (major); $t_2 = 33.7$ min (minor). $\left[\alpha\right]_D^{25} = +4.95^\circ (c = 0.76, \text{CH}_2\text{Cl}_2, 99\% \text{ ee})$

Note 1: Filtration of the reaction mixture through Florisil® removes the catalyst and ligand, providing a solution containing the desired product and silane-containing byproducts. The pure product was typically isolated free of these byproducts after chromatography; however, on some occasions, the byproducts co-eluted. In these cases, the impure material was dissolved in THF and treated (at 23 °C) with TBAF (1 M in THF), which rapidly destroyed the silane-derived impurities. Chromatography on silica gel then provided analytically pure products.

Note 2: Very viscous substrates could alternatively be added to the catalyst solution as a solution in PhMe.

![methyl (S)-3-(phenylethynyl)nonanoate (9ba):](image)

Prepared according to Representative Procedure B using Cu(OAc)$_2$$\cdot$H$_2$O (3.0 mg, 0.015 mmol, 5 mol %), WALPHOS ligand 17 (14.0 mg, 0.015 mmol, 5 mol %), methyl (E)-3-(phenylethynyl)non-2-enoate (81.0 mg, 0.30 mmol), diethoxymethylsilane (96 µL, 0.60 mmol, 2 equivalents), and tert-butanol (57 µL, 0.60 mmol, 2 equivalents) in PhMe (1.5 mL). The reaction duration was 14 h. Purification via column chromatography (20:1 hexanes:EtOAc) afforded the title compound (73.7 mg, 90%, 99% ee) as a light yellow oil. $R_f = 0.20$ (20:1 hexanes:EtOAc). $^1\text{H NMR}$ (500 MHz, $\text{CDCl}_3$) $\delta$ 7.39-7.37 (m, 2H), 7.29-7.26 (m, 3H), 3.72 (s, 3H), 3.10-3.04 (m, 1H), 2.64-2.60 (dd, $J = 15.3$ Hz, 7.6 Hz, 1H), 2.55-2.50
S20

(dd, $J = 15.3$ Hz, 7.0 Hz, 1H), 1.58-1.43 (m, 4H), 1.31-1.29 (m, 6H), 0.89 (t, $J = 6.7$ Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 172.3, 131.8, 128.3, 127.8, 123.7, 91.6, 82.2, 51.9, 40.2, 34.8, 31.9, 29.14, 29.07, 27.3, 22.8, 14.2. IR (film): 2954, 2929, 2857, 1742, 1438, 1164, 756 cm$^{-1}$.

HRMS: Calculated for C$_{16}$H$_{25}$O$_2$ (M$^+$H)$^+$: 273.1849; Found 273.1847.

Chiral HPLC: Chiralpak® IB column; heptane/isopropanol 999:1; flow rate = 0.5 mL/min; detection at 214 nm; $t_1 = 18.4$ min (major); $t_2 = 35.2$ min (minor). $[\alpha]_D^{25} = +1.42^\circ$ ($c = 0.73$, CH$_2$Cl$_2$, 99% ee).

methyl (S)-3-((4-methoxyphenyl)ethynyl)nonanoate (9ca):

Prepared according to Representative Procedure B using Cu(OAc)$_2$•H$_2$O (2.0 mg, 0.01 mmol, 5 mol %), WALPHOS ligand 17 (9.3 mg, 0.01 mmol, 5 mol %), diethoxymethylsilane (64 µL, 0.40 mmol), tert-butanol (38 µL, 0.40 mmol), and methyl (E)-3-((4-methoxyphenyl)ethynyl)non-2-enoate (60.0 mg, 0.20 mmol) in PhMe (1.0 mL). The reaction duration was 16 h. Purification via column chromatography (10:1 to 8:1 hexanes:EtOAc) afforded the title compound (57.2 mg, 95%, ca. 90% purity as judged by $^1$H NMR, 99% ee) as a clear, faintly yellow oil. $R_f = 0.29$ (8:1 hexanes:EtOAc). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.33-7.29 (m, 2H), 6.81-6.79 (m, 2H), 3.79 (s, 3H), 3.71 (s, 3H), 3.08-3.01 (m, 1H), 2.61 (dd, $J = 15.2$, 7.6 Hz, 1H), 2.51 (dd, $J = 15.3$, 7.1 Hz, 1H), 1.58-1.27 (m, 10H), 0.89 (t, $J = 6.9$ Hz, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): 172.4, 159.3, 133.1, 115.9, 113.9, 90.0, 81.9, 55.4, 51.8, 40.3, 34.9, 31.9, 29.1, 29.0, 27.3, 22.8, 14.2. IR (film): 2888, 2817, 1716, 1585, 1489, 1418, 1271, 1230, 1154, 1091, 1019, 821 cm$^{-1}$. HRMS (ESI+): Calculated for C$_{19}$H$_{27}$O$_3$ (M$^+$H)$^+$: 303.1955; Found 303.1946. Chiral HPLC: CHIRALPAK® AD-H, 99:1 heptane:isopropanol, 0.5 mL/min, 254 nm, 21.51 min (major), 24.19 min (minor). $[\alpha]_D^{25} = -2.7^\circ$ ($c = 0.50$, CHCl$_3$).
methyl (S)-3-((4-bromophenyl)ethynyl)nonanoate (9da):

Prepared according to Representative Procedure B using Cu(OAc)$_2$$\cdot$H$_2$O (2.0 mg, 0.01 mmol, 5 mol %), WALPHOS ligand 17 (9.3 mg, 0.01 mmol, 5 mol %), diethoxymethylsilane (64 $\mu$L, 0.40 mmol), tert-butanol (38 $\mu$L, 0.40 mmol), and methyl (E)-3-((4-bromophenyl)ethynyl)non-2-enoate (69.9 mg, 0.20 mmol) in PhMe (1.0 mL). The reaction duration was 18 h. After this time, the reaction mixture was passed through a silica gel column (eluting with 20:1 hexanes:EtOAc) to afford the product contaminated with small amounts of silane and/or byproducts thereof. This material was treated with TBAF (1 M in THF, 0.30 mL, 0.30 mmol), and the mixture was stirred for 10 min. The mixture was then directly chromatographed on silica gel (20:1 hexanes:EtOAc) to afford the title compound (59.6 mg, 85%, 99% ee) as a viscous, clear, light yellow oil, free of the silicon byproducts. $R_f$ = 0.39 (8:1 hexanes:EtOAc). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.42-7.39 (m, 2H), 7.25-7.22 (m, 2H), 3.71 (s, 3H), 3.08-3.02 (m, 1H), 2.60 (dd, $J = 15.3$, 7.7 Hz, 1H), 2.51 (dd, $J = 15.4$, 7.0 Hz, 1H), 1.57-1.42 (m, 4H), 1.34-1.25 (m, 6H), 0.89 (t, $J = 6.8$ Hz, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): 172.2, 133.2, 131.5, 122.7, 122.0, 92.9, 81.2, 51.9, 40.0, 34.7, 31.9, 29.11, 29.10, 27.3, 22.8, 14.2. IR (film): 2887, 2816, 1717, 1465, 1416, 1342, 1148, 1056, 997, 812 cm$^{-1}$. HRMS (ESI+): Calculated for C$_{18}$H$_{24}$O$_2$Br (M+H)$^+$: 351.0954; Found 351.0948. Chiral HPLC: Agilent IB, 400:1 heptane:isopropanol, 0.8 mL/min, 254 nm, 8.13 min (major), 8.96 min (minor). $[\alpha]_D^{25} = -2.2^\circ$ ($c = 0.50$, CHCl$_3$)

methyl (S)-3-((benzyldimethylsilyl)ethynyl)nonanoate (9ea):
Prepared according to Representative Procedure B using \(\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}\) (3.0 mg, 0.015 mmol, 5 mol %), WALPHOS ligand 17 (14.0 mg, 0.015 mmol, 5 mol %), methyl \((E)-3-((\text{benzyldimehtylsilyl})\text{ethynyl})\text{non-2-enoate}\) (103.0 mg, 0.30 mmol), diethoxymethylsilane (96 \(\mu\text{L}, 0.60\ \text{mmol, 2 equivalents})\), and \textit{tert}-butanol (57 \(\mu\text{L}, 0.60\ \text{mmol, 2 equivalents})\) in PhMe (1.5 mL). The reaction duration was 14 h. The crude product was purified by column chromatography (20:1 hexanes:EtOAc) to afford the title compound as a light yellow oil (90.2 mg, 0.26 mmol, 87% yield, 99% ee). 

\[ R_f = 0.23 \] (20:1 hexanes:EtOAc).

\[ ^1\text{H NMR} \] (500 MHz, CDCl\(_3\)) \(\delta 7.23-7.20\) (m, 2H), 7.10-7.06 (m, 3H), 3.69 (s, 3H), 2.89-2.83 (m, 1H) 2.54-2.40 (dd, \(J = 15.3\ \text{Hz, 7.4 Hz, 1H})\), 2.44-2.40 (dd, \(J = 15.4\ \text{Hz, 7.3 Hz, 1H})\), 2.16 (s, 2H), 1.48-1.26 (m, 10H), 0.89 (t, \(J = 6.9\ \text{Hz, 3H})\), 0.10 (s, 6H).

\[ ^{13}\text{C NMR} \] (125 MHz, CDCl\(_3\)) \(\delta 172.1, 139.3, 128.5, 128.2, 124.4, 110.1, 84.4, 51.8, 40.0, 34.5, 31.8, 29.4, 29.1, 27.1, 26.6, 22.7, 14.2, -1.8.

\[ \text{IR} \] (film): 3025, 2956, 2929, 2858, 2710, 1250, 1208, 1160, 839, 698 cm\(^{-1}\).

\[ \text{HRMS} \] Calculated for \(\text{C}_{21}\text{H}_{33}\text{O}_2\text{Si} \ (\text{M}^+\text{H}^+)\): 345.2244; Found 345.2248.

\[ \left[\alpha\right]_0^{25} = +1.03^\circ \] (\(c = 1.18, \text{CH}_2\text{Cl}_2, 99\%\ \text{ee})\).

\[ \text{Chiral HPLC} \]: Chiralpak® IB column; heptane/isopropanol 999:1; flow rate = 0.5 mL/min; detection at 214 nm; \(t_1 = 14.2\) min (major); \(t_2 = 16.2\) min (minor).

methyl \((S)-3\)-ethynylnonanoate (9fa):

Prepared using a modification of Representative Procedure B. A flame-dried 50 mL flask equipped with a stir bar was charged with \(\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}\) (12.5 mg, 0.0625 mmol, 5 mol %) and WALPHOS ligand 17 (58.2 mg, 0.0625 mmol, 5 mol %). The flask was sealed with a septum and flushed with Ar (balloon). Freshly distilled, degassed (Ar sparge) PhMe (10.0 mL) was added, and the mixture was stirred for 20 min to afford a bright green, homogeneous solution. Diethoxymethylsilane (0.80 mL, 5 mmol, 2 equivalents) was added, and the mixture was stirred until a change in appearance to homogeneous and brown was observed (< 30 min). The flask was cooled to 0 ℃, and a solution of methyl \((E)-3-((\text{trimethylsilyl})\text{ethynyl})\text{non-2-enoate}\) (666.1 mg, 2.5 mmol, 1.0 equivalent) in PhMe (2 mL)
was added via cannula syringe, using additional PhMe (0.50 mL) to rinse the vial containing the substrate and the cannula. To the mixture was then added tert-butanol (0.48 mL, 5 mmol, 2 equivalents). The vessel was kept under an Ar balloon and transferred to a cold room (4 °C) where it was stirred for 18 h.

The reaction mixture was then warmed to room temperature and loaded directly onto a silica gel column that was eluted with 40:1 to 30:1 hexanes:EtOAc. The fractions containing the TMS-protected, 1,4-reduction product ($R_f = 0.53$, 10:1 hexanes:EtOAc) were concentrated, and this crude material was redissolved in THF (2.5 mL) and treated with TBAF (1 M in THF, 6.0 mL, 6.0 mmol, 2.4 equivalents). The resulting black solution was stirred for 30 minutes, at which point it was poured into a mixture of saturated NH$_4$Cl (10 mL) and Et$_2$O (25 mL). The phases were separated, and the aqueous phase was extracted with Et$_2$O (25 mL). The pooled organic phases were dried over MgSO$_4$, filtered, and concentrated. The crude material was purified by column chromatography (30:1 hexanes:EtOAc) to deliver the title compound (378.9 mg, 77%) as a light yellow, clear oil. $R_f = 0.47$ (10:1 hexanes:EtOAc).

$^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 3.69 (s, 3H), 2.84-2.81 (m, 1H), 2.53 (dd, $J = 15.5$, 7.8 Hz, 1H), 2.43 (dd, $J = 15.5$, 6.9 Hz, 1H), 2.06 (d, $J = 2.4$ Hz, 1H), 1.51-1.27 (m, 10H), 0.87 (t, $J = 6.3$ Hz, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): $\delta$ 172.1, 86.1, 69.8, 51.8, 39.9, 34.5, 31.8, 29.1, 28.1, 27.1, 22.7, 14.2. IR (film): 3263, 2889, 2818, 1718, 1418, 1342, 1233, 1149, 1094, 1006, 871, 626 cm$^{-1}$. HRMS (ESI+): Calculated for C$_{12}$H$_{20}$NaO$_2$ (M+H)$^+$: 219.1356; Found 219.1359. $[\alpha]_D^{25} = -6.6^\circ$ ($c = 0.5$, CHCl$_3$). Determination of the ee: a sample of the ester obtained was converted to a mixture of diastereomeric amides via hydrolysis (3 equiv KOH, 3:1:1 MeOH:THF:H$_2$O, 50 °C for 1 h) and subsequent amidation with (S)-α-methylbenzylamine (EDCI-HCl, 5 equiv of amine, 1.5 equiv DMAP, CH$_2$Cl$_2$, overnight). After extractive workup, drying of the organic phase, and concentration, the crude material was analyzed by $^1$H NMR, which indicated a single diastereomer (> 19:1 dr or > 90% ee). This was verified upon the independent synthesis of the corresponding 1:1 mixture of diastereomeric amides by the analogous amidation of racemic β-alkynyl ester. Well-resolved diagnostic peaks include those for the terminal alkyne C-H ($\delta$ 2.13, d, $J = 2.4$ Hz, minor and $\delta$ 2.07, d, $J = 2.4$ Hz, major).
methyl (S)-3-(4-((tert-butyldimethylsilyl)oxy)-3,3-dimethylbut-1-yn-1-yl)nonanoate (9ga):

Prepared according to Representative Procedure B using Cu(OAc)$_2$•H$_2$O (2.0 mg, 0.01 mmol, 5 mol %) WALPHOS ligand 17 (9.3 mg, 0.01 mmol, 5 mol %), diethoxymethylsilane (64 µL, 0.40 mmol), tert-butanol (38 µL, 0.40 mmol), and methyl (E)-3-(4-((tert-butyldimethylsilyl)oxy)-3,3-dimethylbut-1-yn-1-yl)non-2-enoate (76.1 mg, 0.20 mmol) in PhMe (1.0 mL). The reaction duration was 18 h. Purification via column chromatography (20:1 hexanes:EtOAc) afforded the title compound (72.8 mg, 95%) as a viscous, light yellow oil. $R_f$ = 0.48 (8:1 hexanes:EtOAc). $^1$H NMR (500 MHz; CDCl$_3$): δ 3.68 (s, 3H), 3.37 (s, 2H), 2.81-2.76 (m, 1H), 2.45 (dd, $J$ = 14.9, 7.5 Hz, 1H), 2.38 (dd, $J$ = 14.9, 7.3 Hz, 1H), 1.43-1.25 (m, 10H), 1.11 (s, 6H), 0.90-0.87 (m, 12H), 0.04 (s, 6H). $^{13}$C NMR (100 MHz; CDCl$_3$): 172.6, 88.2, 81.8, 71.6, 51.7, 40.8, 35.0, 33.5, 31.9, 29.1, 28.6, 27.2, 26.1, 25.89, 25.88, 22.8, 18.5, 14.3, -5.2. IR (film): 2915, 2889, 2818, 1721, 1449, 1417, 1341, 1235, 1146, 1090, 826, 765 cm$^{-1}$. HRMS (ESI+): Calculated for C$_{22}$H$_{43}$O$_3$Si(M+H)$^+$: 383.2976; Found 383.2975. $[\alpha]_D^{25}$ = −1.7° ($c = 0.50$, CHCl$_3$). Determination of the ee: analogously to the previous example, a sample of the material was hydrolyzed and amidated with (S)-α-methylbenzylamine. > 19:1 dr (corresponding to > 90% ee) was observed in the $^1$H NMR spectrum of the mixture of amides, which was verified by the independent synthesis of a 1:1 mixture of diastereomers from racemic material. Well-resolved diagnostic peaks include those for the methylene α to oxygen (6.28, d, $J$ = 7.8 Hz, major), 6.25 (d, $J$ = 8.2 Hz, minor).

methyl (S)-3-(3-methylbut-3-en-1-yn-1-yl)nonanoate (9ha):
Prepared according to Representative Procedure B using Cu(OAc)\(_2\)•H\(_2\)O (1.0 mg, 0.005 mmol, 5 mol %), WALPHOS ligand 17 (4.7 mg, 0.005 mmol, 5 mol %), diethoxymethylsilane (32 µL, 0.20 mmol), tert-butanol (19 µL, 0.20 mmol), and methyl (E)-3-(3-methylbut-3-en-1-yn-1-yl)non-2-enoate (23.4 mg, 0.10 mmol) in PhMe (0.5 mL). The reaction duration was 15 h. After this time, the reaction mixture was treated, at 4 °C, with TBAF (1 M in THF, 0.35 mL, 0.35 mmol) to consume silane byproducts previously found to be inseparable from the product via chromatography. Vigorous gas evolution occurred, and the dark red/brown solution was stirred for 10 min. The reaction mixture was then directly chromatographed on silica gel (20:1 hexanes:EtOAc) to afford the title compound (21.6 mg, 92%, 99% ee) as a viscous, clear, light yellow oil. 

**\( \text{R}_f = 0.42 \) (8:1 hexanes:EtOAc).**

**\( ^1 \text{H NMR} \) (400 MHz; CDCl\(_3\)):** \( \delta \) 5.20-5.18 (m, 1H), 5.15-5.13 (m, 1H), 3.69 (s, 3H), 2.98-2.91 (m, 1H), 2.53 (dd, \( J = 15.2, 7.5 \) Hz, 1H), 2.45 (dd, \( J = 15.2, 7.2 \) Hz, 1H), 1.85 (dd, \( J = 1.5, 1.0 \) Hz, 3H), 1.51-1.41 (m, 4H), 1.31-1.25 (m, 6H), 0.87 (d, \( J = 7.0 \) Hz, 3H). **\( ^{13} \text{C NMR} \) (100 MHz; CDCl\(_3\)):** 172.3, 127.2, 120.9, 90.6, 83.4, 51.8, 40.2, 34.8, 31.9, 29.1, 28.9, 27.2, 23.9, 22.7, 14.2. **\( ^{13} \text{C NMR} \) (film):** 2913, 2888, 2818, 1719, 1593, 1417, 1354, 1231, 1147, 997, 880 cm\(^{-1}\). **HRMS (ESI+):** Calculated for C\(_{15}\)H\(_{25}\)O\(_2\) (M+H): 237.1849; Found 237.1843.

**Chiral HPLC:** Agilent IB, 2000:1 heptane:isopropanol, 0.4 mL/min, 220 nm, 17.92 min (major), 19.28 min (minor).

**\( [\alpha]_D^{24} = -5.0^\circ \) (c = 0.50, CHCl\(_3\)).**

![ethyl (S)-3-(4-phenylbut-1-yn-1-yl)nonanoate (9ab):](image)

Prepared according to Representative Procedure B using Cu(OAc)\(_2\)•H\(_2\)O (2.0 mg, 0.01 mmol, 5 mol %), WALPHOS ligand 17 (9.3 mg, 0.01 mmol, 5 mol %), diethoxymethylsilane (64 µL, 0.40 mmol), tert-butanol (38 µL, 0.40 mmol), and ethyl (E)-3-(4-phenylbut-1-yn-1-yl)non-2-enoate (62.5 mg, 0.20 mmol) in PhMe (1.0 mL). The reaction duration was 16 h. Purification via column chromatography (20:1 hexanes:EtOAc) afforded the title compound...
(53.0 mg, 84%, 98% ee) as a clear, faintly yellow oil. $R_f = 0.43$ (8:1 hexanes:EtOAc). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.30-7.26 (m, 2H), 7.22-7.18 (m, 3H), 4.14 (q, $J = 7.1$ Hz, 2H), 2.78 (t, $J = 7.5$ Hz, 3H), 2.47-2.36 (m, 4H), 1.45-1.22 (m, 13H), 0.89 (t, $J = 6.9$ Hz, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): 172.0, 141.1, 128.6, 128.4, 126.3, 82.7, 81.1, 60.5, 40.8, 35.6, 35.0, 31.9, 29.2, 28.5, 27.2, 22.8, 21.1, 14.4, 14.3. IR (film): 3020, 2986, 2887, 2817, 1713, 1582, 1475, 1434, 1352, 1328, 1229, 1145, 1091, 1062, 1019 cm$^{-1}$. HRMS (ESI+): Calculated for C$_{21}$H$_{31}$O$_2$ (M+H)$^+$: 315.2319; Found 315.2313. Chiral HPLC: Agilent IB, 1000:1 heptane:isopropanol, 0.8 mL/min, 214 nm, 14.52 min (major), 16.73 min (minor). $[\alpha]_D^{25} = -4.2^\circ$ ($c = 0.50$, CHCl$_3$).

benzyl (S)-3-(4-phenylbut-1-yn-1-yl)nonanoate (9ac):

Prepared according to Representative Procedure B using Cu(OAc)$_2$$\cdot$H$_2$O (2.0 mg, 0.01 mmol, 5 mol %), WALPHOS ligand 17 (9.3 mg, 0.01 mmol, 5 mol %), diethoxymethylsilane (64 µL, 0.40 mmol), tert-butanol (38 µL, 0.40 mmol), and benzyl (E)-3-(4-phenylbut-1-yn-1-yl)non-2-enoate (74.9 mg, 0.20 mmol) in PhMe (1.0 mL). The reaction duration was 18 h. Purification via column chromatography (20:1 hexanes:EtOAc) afforded the title compound (64.0 mg, 85%, 99% ee) as a clear, light yellow oil. $R_f = 0.45$ (10:1 hexanes:EtOAc). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.37-7.27 (m, 7H), 7.22-7.18 (m, 3H), 5.14 (d, $J = 1.2$ Hz, 2H), 2.85-2.80 (m, 1H), 2.76 (t, $J = 7.5$ Hz, 2H), 2.54-2.39 (m, 4H), 1.44-1.24 (m, 10H), 0.89 (t, $J = 7.0$ Hz, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): 171.8, 141.0, 136.1, 128.7, 128.6, 128.4, 128.32, 128.31, 126.3, 82.6, 81.3, 66.4, 40.7, 35.6, 35.0, 31.9, 29.1, 28.6, 27.2, 22.8, 21.1, 14.2 IR (film): 2987, 2887, 1716, 1582, 1476, 1434, 1360, 1331, 1141, 1091, 986, 737, 688 cm$^{-1}$. HRMS (ESI+): Calculated for C$_{26}$H$_{33}$O$_2$ (M+H)$^+$: 377.2475; Found 377.2470. Chiral HPLC: Agilent IB, 99:1 heptane:isopropanol, 0.8 mL/min, 220 nm, 8.89 min (major), 10.52 min (minor). $[\alpha]_D^{25} = -3.8^\circ$ ($c = 0.50$, CHCl$_3$).
methyl (R)-3-cyclopropyl-7-phenylhept-4-ynoate (9ad):

Prepared according to Representative Procedure B using Cu(OAc)$_2$•H$_2$O (1.0 mg, 0.005 mmol, 5 mol %), WALPHOS ligand 17 (4.7 mg, 0.005 mmol, 5 mol %), diethoxymethylsilane (32 µL, 0.20 mmol), tert-butanol (19 µL, 0.20 mmol), and methyl (E)-3-cyclopropyl-7-phenylhept-2-en-4-ynoate (23.4 mg, 0.10 mmol) in PhMe (0.5 mL). The reaction duration was 24 h. After this time, the reaction mixture was warmed to room temperature, diluted with Et$_2$O (3 mL), and filtered through a short pipette plug of Florisil®. The solution was concentrated, and $^1$H NMR analysis of the crude material indicated 68% conversion and ca. 4:1 1,4:Σ1,6 regioselectivity. The residue was purified by preparative thin-layer chromatography (20:1 hexanes:EtOAc) to afford the title compound (13.9 mg, 54% yield, 99% ee) as a clear, light yellow oil. R$_f$ = 0.29 (10:1 hexanes:EtOAc). $^1$H NMR (600 MHz; CDCl$_3$): δ 7.30-7.27 (m, 2H), 7.21-7.16 (m, 3H), 3.68 (s, 3H), 2.79-2.67 (m, 2H), 2.62-2.58 (m, 1H), 2.55-2.52 (m, 2H), 2.44-2.41 (m, 2H), 0.88-0.82 (m, 1H), 0.44-0.38 (m, 2H), 0.30-0.25 (m, 2H). $^{13}$C NMR (100 MHz; CDCl$_3$): 172.4, 141.0, 128.6, 128.4, 126.3, 81.6, 80.4, 51.8, 40.9, 35.5, 32.2, 21.0, 14.8, 3.8, 2.5. IR (film): 3038, 2961, 2908, 1716, 1581, 1475, 1434, 1416, 1334, 1250, 1149, 1006, 814, 737, 689 cm$^{-1}$. HRMS (ESI+): Calculated for C$_{17}$H$_{21}$O$_2$ (M+H)$^+$: 257.1536; Found 257.1529. Chiral HPLC: Agilent IB, 400:1 heptane:isopropanol, 0.8 mL/min, 214 nm, 14.66 min (major), 17.34 min (minor). [α]$_D^{25} = -34.7^\circ$ (c = 0.50, CHCl$_3$).

methyl (S)-3-(3-chloropropyl)-7-phenylhept-4-ynoate (9ae):
Prepared according to Representative Procedure B using Cu(OAc)$_2$•H$_2$O (2.0 mg, 0.01 mmol, 5 mol %), WALKPHOS ligand 17 (9.3 mg, 0.01 mmol, 5 mol %), diethoxymethylsilane (64 µL, 0.40 mmol), tert-butanol (38 µL, 0.40 mmol), and methyl (E)-3-(3-chloropropyl)-7-phenylhept-2-en-4-ynoate (58.2 mg, 0.20 mmol) in PhMe (1.0 mL). The reaction duration was 16 h. Purification via column chromatography (8:1 hexanes:EtOAc) afforded the title compound (55.0 mg, 94%, 99% ee) as a clear, light yellow oil. $R_f = 0.27$ (8:1 hexanes:EtOAc).

$^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.31-7.27 (m, 2H), 7.23-7.19 (m, 3H), 3.69 (s, 3H), 3.52 (t, $J = 6.6$ Hz, 2H), 2.86-2.81 (m, 1H), 2.78 (t, $J = 7.5$ Hz, 2H), 2.52-2.36 (m, 4H), 1.95-1.74 (m, 2H), 1.67-1.57 (m, 1H), 1.50-1.40 (m, 1H). $^{13}$C NMR (100 MHz; CDCl$_3$): 172.1, 140.9, 128.6, 128.4, 126.3, 82.0, 81.8, 51.8, 44.9, 40.4, 35.4, 32.1, 30.3, 27.9, 20.9. IR (film): 2909, 2887, 1715, 1432, 1416, 1344, 1247, 1154, 1061, 737, 690 cm$^{-1}$. HRMS (ESI+): Calculated for C$_{17}$H$_{22}$ClO$_2$ (M+H)$^+$: 293.1303; Found 293.1307. Chiral HPLC: Agilent IB, 500:1 heptane/isopropanol, 0.5 mL/min, 220 nm, 43.90 min (major), 46.61 min (minor). $[\alpha]_D^{25} = -3.2^\circ$ (c = 0.50, CHCl$_3$)

![methyl (S)-3-methyl-5-phenylpent-4-ynoate (9bf)](image)

Prepared according to Representative Procedure B using Cu(OAc)$_2$•H$_2$O (1.0 mg, 0.005 mmol, 5 mol %), WALKPHOS ligand 17 (4.7 mg, 0.005 mmol, 5 mol %), diethoxymethylsilane (32 µL, 0.20 mmol), tert-butanol (19 µL, 0.20 mmol), and methyl (E)-3-methyl-5-phenylpent-2-en-4-ynoate (20.0 mg, 0.10 mmol) in PhMe (0.5 mL). The reaction duration was 14 h. After this time, the reaction mixture was warmed to room temperature, diluted with Et$_2$O (3 mL), and filtered through a short pipette plug of Florisil®. The solution was concentrated, and $^1$H NMR analysis of the crude material indicated ca. 2.3:1 1,4:$\Sigma$1,6 regioselectivity (determined by integration of the methyl ester signals). The crude product was purified by column chromatography (30:1 hexanes:EtOAc) to afford the analytically pure title compound as a clear oil (11.9 mg, 0.059 mmol, 59% yield, 99% ee). $R_f = 0.40$ (10:1 hexanes:EtOAc).
hexanes:EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.40-7.37 (m, 2H), 7.29-7.27 (m, 3H), 3.72 (s, 3H), 3.24-3.12 (sex, $J$ = 7.1 Hz, 1H), 2.70-2.62 (dd, $J$ = 15.4 Hz, 7.1 Hz, 1H), 2.53-2.45 (dd, $J$ = 15.4 Hz, 7.6 Hz, 1H), 1.33 (d, $J$ = 6.9 Hz, 3H). 13$^C$ NMR (75 MHz, CDCl$_3$) δ 172.1, 131.7, 128.3, 127.9, 123.6, 92.6, 81.2, 51.8, 41.5, 23.5, 20.9. IR (film): 2975, 2952, 1740, 1490, 1438, 1358, 1281, 1253, 1171, 757, 692 cm$^{-1}$. HRMS: Calculated for C$_{13}$H$_{14}$O$_2$Na (M+Na)$^+$: 225.0891; Found 225.0896. Chiral HPLC: Chiralpak® IB column; heptane/isopropanol 500:1; flow rate = 0.8 mL/min; detection at 214 nm; $t_1$ = 11.9 min (major); $t_2$ = 15.7 min (minor). [α]$_D^{25} = +34.56^\circ$ (c = 0.71, CH$_2$Cl$_2$, 99% ee).

![Ethyl (S)-3-ethyl-5-phenylpent-4-ynoate](image)

ethyl (S)-3-ethyl-5-phenylpent-4-ynoate (9bg):

Prepared according to Representative Procedure B using Cu(OAc)$_2$$\cdot$H$_2$O (2.0 mg, 0.01 mmol, 5 mol %), WALPHOS ligand 17 (9.3 mg, 0.01 mmol, 5 mol %), diethoxymethylsilane (64 µL, 0.40 mmol), tert-butanol (38 µL, 0.40 mmol), and ethyl (E)-3-ethyl-5-phenylpent-2-en-4-ynoate (45.6 mg, 0.20 mmol) in PhMe (1.0 mL). The reaction duration was 16 h. Purification via column chromatography (20:1 to 10:1 hexanes:EtOAc) afforded the title compound (50.0 mg, > 100%, 99% ee) as a clear, yellow oil and as an inseparable mixture of regioisomers (2.7:1 1,4:Σ1,6, determined by integration of the signals corresponding to the ethyl ester methylene groups). R$_f$ = 0.31 (10:1 hexanes:EtOAc). $^1$H NMR (600 MHz, CDCl$_3$, major isomer) δ 7.39-7.38 (m, 2H), 7.28-7.26 (m, 3H), 4.18 (q, $J$ = 7.1 Hz, 2H), 3.05-3.00 (m, 1H), 2.60 (dd, $J$ = 15.2, 7.7 Hz, 1H), 2.51 (dd, $J$ = 15.2, 7.0 Hz, 1H), 1.68-1.63 (m, 1H), 1.58-1.53 (m, 1H), 1.27 (t, $J$ = 7.1 Hz, 3H), 1.09 (t, $J$ = 7.4 Hz, 3H). 13$^C$ NMR (100 MHz, CDCl$_3$, major isomer) δ 171.8, 131.8, 128.3, 127.8, 123.8, 91.5, 82.3, 68.3, 60.7, 40.1, 30.7, 27.9, 14.4, 11.8. IR (film): 2924, 2890, 1712, 1576, 1469, 1441, 1352, 1256, 1157, 1019, 746, 683 cm$^{-1}$. HRMS: Calculated for C$_{15}$H$_{18}$NaO$_2$ (M+Na)$^+$: 253.1199; Found 253.1201. Chiral HPLC:
Chiralpak® IA column; heptane/isopropanol 500:1; flow rate = 0.8 mL/min; detection at 220 nm; \( t_1 = 10.0 \) min (major); \( t_2 = 14.3 \) min (minor). \( [\alpha]_D^{25} = + 13.5^\circ \ (c = 0.50, \text{CHCl}_3) \).

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\text{OMe} \\
\text{Ph} \\
\text{n-Pr}
\]

methyl (S)-3-(phenylethynyl)hexanoate (9bh):

Prepared according to Representative Procedure B using Cu(OAc)$_2$•H$_2$O (2.0 mg, 0.01 mmol, 5 mol %), WALPHOS ligand 17 (9.3 mg, 0.01 mmol, 5 mol %), diethoxymethylsilane (64 µL, 0.40 mmol), tert-butanol (38 µL, 0.40 mmol), and methyl (E)-3-(phenylethynyl)hex-2-enoate (45.6 mg, 0.20 mmol) in PhMe (1.0 mL). The reaction duration was 16 h. The reaction mixture was filtered through Florisil®, and the solution was concentrated. $^1$H NMR analysis of the crude material indicated ca. 12.5:1 1,4:Σ1,6 regioselectivity (determined by integration of the methyl ester signals). Purification via column chromatography (20:1 to 10:1 hexanes:EtOAc) afforded the title compound (42.3 mg, 86%, 99% ee) as a clear, yellow oil in ca. 92% purity with traces of regioisomeric byproducts. $R_f = 0.31$ (10:1 hexanes:EtOAc). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.40-7.36 (m, 2H), 7.29-7.26 (m, 3H), 3.72 (s, 3H), 3.12-3.05 (m, 1H), 2.63 (dd, $J = 15.3$, 7.6 Hz, 1H), 2.52 (dd, $J = 15.3$, 7.1 Hz, 1H), 1.65-1.47 (m, 4H), 0.96 (t, $J = 7.1$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 172.3, 131.8, 128.3, 127.8, 123.7, 91.5, 82.2, 51.9, 40.2, 36.9, 28.8, 20.6, 14.0. IR (film): 2916, 2832, 1717, 1576, 1470, 1418, 1343, 1192, 1151, 1084, 1055, 1005, 902, 747 cm$^{-1}$. HRMS: Calculated for C$_{15}$H$_{18}$NaO$_2$ (M+Na)$^+$: 253.1199; Found 253.1203. Chiral HPLC: Chiralpak® IB column; heptane/isopropanol 500:1; flow rate = 0.8 mL/min; detection at 220 nm; $t_1 = 9.6$ min (major); $t_2 = 13.6$ min (minor). $[\alpha]_D^{25} = + 14.9^\circ \ (c = 0.50, \text{CHCl}_3)$.
methyl \((Z)-3-((\text{tert-butyldimethylsilyl})\text{oxy})\text{propylidene})-7\text{-phenylhept-4-ynoate (20)}\)

Prepared according to Representative Procedure B using \(\text{Cu(OAc)}_2\cdot\text{H}_2\text{O}\) (2.0 mg, 0.01 mmol, 5 mol %), WALPHOS ligand 17 (9.3 mg, 0.01 mmol, 5 mol %), diethoxymethylsilane (64 \(\mu\)L, 0.40 mmol), \(\text{tert-butanol}\) (38 \(\mu\)L, 0.40 mmol), and methyl \((E)-3-((\text{tert-butyldimethylsilyl})\text{oxy})\text{prop-1-en-1-yl})-7\text{-phenylhept-2-en-4-ynoate (76.9 mg, 0.20 mmol)}\) in PhMe (1.0 mL). The reaction duration was 16 h. Purification \textit{via} column chromatography (20:1 to 10:1 hexanes:EtOAc) afforded the title compound (69.3 mg, 90%, exclusively as its \((Z)\) olefin isomer) as a clear oil. \(R_f = 0.28\) (10:1 hexanes:EtOAc). \(^1\text{H NMR}\) (400 MHz; CDCl\(_3\)): \(\delta 7.31-7.27\) (m, 2H), 7.24-7.19 (m, 3H), 5.79 (t, \(J = 7.3\) Hz, 1H), 3.69 (s, 3H), 3.63 (t, \(J = 6.7\) Hz, 2H), 3.10 (d, \(J = 0.9\) Hz, 2H), 2.85 (t, \(J = 7.5\) Hz, 2H), 2.63 (t, \(J = 7.5\) Hz, 2H), 2.45 (q, \(J = 7.0\) Hz, 2H), 0.90 (s, 9H), 0.06 (s, 6H). \(^{13}\text{C NMR}\) (100 MHz; CDCl\(_3\)): 171.5, 140.8, 136.9, 128.6, 128.5, 126.4, 117.4, 94.3, 78.8, 62.3, 52.1, 42.7, 35.3, 34.4, 26.1, 21.9, 18.5, -5.1. \(\text{IR (film):} 2986, 2911, 1721, 1415, 1238, 1143, 1084, 993, 924, 825, 766, 690\) cm\(^{-1}\). \(\text{HRMS (ESI+): Caluclated for C}_{23}\text{H}_{35}\text{O}_3\text{Si (M+H)}^+: 387.2350; Found 387.2346.\)

Determination of olefin geometry:

The product is assigned as its \((Z)\)-isomer on the basis of an observed nOe between the \(\alpha\)-methylene (\(\delta 3.10\)) and the vinyl hydrogen (\(\delta 5.79\)): irradiation of the methylene resulted in a + 5.3% enhancement at the vinylic hydrogen.
Prepared according to Representative Procedure B using Cu(OAc)$_2$•$\text{H}_2\text{O}$ (5.0 mg, 0.025 mmol, 5 mol %), WALPHOS ligand 17 (23.1 mg, 0.025 mmol, 5 mol %), diethoxymethylsilane (159 µL, 1.0 mmol), tert-butanol (95 µL, 1.0 mmol), and methyl (Z)-3-(((methoxycarbonyl)oxy)methyl)-7-phenylhept-2-en-4-ynoate (150.0 mg, 0.50 mmol) in PhMe (2.5 mL). The reaction duration was 20 h. The crude product was purified by column chromatography (6:1 hexanes:EtOAc) to afford the title compound as a light yellow oil (148 mg, 0.49 mmol, 98% yield, 99% ee). $R_f = 0.33$ (6:1 hexanes:EtOAc).

$\text{1H NMR}$ (400 MHz, CDCl$_3$) $\delta$ 7.31-7.27 (m, 2H), 7.22-7.18 (m, 3H), 4.24-4.20 (dd, $J = 10.5$ Hz, 5.5 Hz, 1H), 4.09-4.05 (dd, $J = 10.5$ Hz, 7.5 Hz, 1H), 3.79 (s, 3H), 3.69 (s, 3H), 3.23-3.17 (m, 1H), 2.77 (t, $J = 7.5$ Hz, 2H), 2.61-2.55 (dd, $J = 15.8$ Hz, 6.5 Hz, 1H), 2.52-2.46 (dd, $J = 7.9$ Hz, 1H), 2.45-2.40 (td, $J = 7.5$ Hz, 2.2 Hz, 2H).

$\text{13C NMR}$ (125 MHz, CDCl$_3$) $\delta$ 171.6, 155.5, 140.7, 128.6, 128.4, 126.3, 82.9, 78.3, 69.1, 55.0, 52.0, 36.8, 35.2, 28.3, 21.0. $\text{IR}$ (film): 3028, 2955, 2856, 1750, 1441, 1385, 1365, 1271, 1171, 971, 791, 700 cm$^{-1}$. $\text{HRMS}$: Calculated for C$_{17}$H$_{20}$O$_5$Na (M+Na)$^+$: 327.1208; Found 327.1213.

$\text{Chiral HPLC}$: Chiralpak® IB column; heptane/isopropanol 99:1; flow rate = 0.8 mL/min; detection at 214 nm; $t_1 = 16.8$ min (major); $t_2 = 19.3$ min (minor). $[\alpha]_D^{25} = +9.25^\circ$ (c = 1.3, CH$_2$Cl$_2$, 99% ee).

\[
\begin{array}{c}
\text{MeO}_2\text{CO} \\
\text{Ph} \\
\text{H} \\
\text{OMe}
\end{array}
\]

methyl (S)-3-(((methoxycarbonyl)oxy)methyl)-5-phenylpent-4-ynoate (9bj):

Prepared according to Representative Procedure B using Cu(OAc)$_2$•H$_2$O (1.4 mg, 0.007 mmol, 5 mol %), WALPHOS ligand 17 (6.6 mg, 0.007 mmol, 5 mol %), diethoxymethylsilane (45 µL, 0.28 mmol), tert-butanol (27 µL, 0.28 mmol), and methyl (Z)-3-(((methoxycarbonyl)oxy)methyl)-5-phenylpent-2-en-4-ynoate (39.0 mg, 0.14 mmol) in PhMe (0.70 mL). The reaction duration was 16 h. The crude product was purified by column chromatography (4:1 hexanes:EtOAc) to afford the title compound as a light yellow oil (36.3 mg, 0.13 mmol, 92% yield, 99% ee). $R_f = 0.40$ (4:1 hexanes:EtOAc). $\text{1H NMR}$ (500 MHz, CDCl$_3$) $\delta$ 7.39-7.38 (m, 2H), 7.31-7.27 (m, 3H), 4.39-4.35 (dd, $J = 10.6$ Hz, 5.5 Hz, 1H),

S32
4.25-4.22 (dd, J = 10.6 Hz, 7.4 Hz, 1H), 3.80 (s, 3H), 3.72 (s, 3H), 3.49-3.45 (m, 1H), 2.74-2.69 (dd, J = 15.9 Hz, 6.7 Hz, 1H), 2.69-2.64 (dd, J = 15.9 Hz, 7.5 Hz, 1H). 13C NMR (125 MHz, CDCl3) δ 171.5, 155.7, 132.0, 128.5, 123.0, 87.0, 83.6, 68.6, 55.2, 52.3, 52.0, 36.7, 29.2. IR (film): 2957, 1752, 1491, 1442, 1386, 1271, 1171, 969, 895, 790, 759, 693 cm⁻¹.

HRMS: Calculated for C₁₅H₁₆O₅Na (M+Na)⁺: 299.0895; Found 299.0902.

Chiral HPLC: Chiralpak® IB column; heptane/isopropanol 99:1; flow rate = 0.8 mL/min; detection at 214 nm; t₁ = 13.9 min (major); t₂ = 16.2 min (minor). [α]D²⁵ = +17.16° (c = 0.91, CH₂Cl₂, 99% ee).

methyl (S)-5-(benzylidimethylsilyl)-3-(((methoxycarbonyl)oxy)methyl)pent-4-ynoate (9ej):

Prepared according to Representative Procedure B using Cu(OAc)₂•H₂O (1.4 mg, 0.007 mmol, 5 mol %), WALPHOS ligand 17 (6.6 mg, 0.007 mmol, 5 mol %), diethoxymethylsilane (45 µL, 0.28 mmol), tert-butanol (27 µL, 0.28 mmol), and methyl (Z)-5-(benzylidimethylsilyl)-3-(((methoxycarbonyl)oxy)methyl)pent-2-en-4-ynoate (48.0 mg, 0.14 mmol) in PhMe (0.70 mL). The reaction duration was 16 h. The crude product was purified by column chromatography (6:1 hexanes:EtOAc) to afford the title compound as a brown oil (39.3 mg, 0.11 mmol, 81% yield, 99% ee). Rf = 0.33 (4:1 hexanes:EtOAc). ¹H NMR (500 MHz, CDCl₃) δ 7.23-7.20 (m, 2H), 7.10-7.04 (m, 3H), 4.28-4.25 (dd, J = 10.6 Hz, 5.4 Hz, 1H), 4.14-4.10 (dd, J = 10.6 Hz, 7.5 Hz, 1H), 3.80 (s, 3H), 3.70 (s, 3H), 3.29-3.24 (m, 1H), 2.64-2.59 (dd, J = 15.9 Hz, 6.8 Hz, 1H), 2.57-2.53 (dd, J = 15.9 Hz, 7.3 Hz, 1H), 2.16 (s, 2H), 0.10 (s, 6H). 13C NMR (125 MHz, CDCl₃) δ 171.3, 155.5, 139.0, 128.4, 128.2, 124.4, 104.9, 86.5, 68.5, 55.1, 52.0, 36.4, 29.2, 26.3, -2.0. IR (film): 3025, 2958, 2174, 1752, 1600, 1494, 1441, 1385, 1364, 1271, 1208, 1171, 1057, 972, 840, 794, 764, 700 cm⁻¹. HRMS: Calculated for C₁₈H₂₄O₅NaSi (M+Na⁺): 371.1285; Found 371.1291. Chiral HPLC: Chiralpak® IB column; heptane/isopropanol 99:1; flow rate = 0.8 mL/min; detection at 214 nm; t₁ = 9.7 min (major); t₂ = 11.7 min (minor). [α]D²⁵ = +11.86° (c = 1.17, CH₂Cl₂, 99% ee).
Cu-catalyzed Asymmetric Conjugate Reduction of Carbamates: Representative Procedure C, Synthesis of methyl \((R)-3-(((\text{tert-butoxycarbonyl})\text{amino})\text{methyl})-7\text{-phenylhept-4-ynoate (9ak):}\n
An oven-dried Biotage® microwave vial (0.50 – 2.0 mL size) equipped with a stir bar was charged with Cu(OAc)$_2$•H$_2$O (0.9 mg, 0.0045 mmol, 2 mol %) and JOSIPHOS ligand J002-1 \((13, (R)-1-[(S)-2-(\text{diphenylphosphino})\text{ferrocenyl}]\text{-ethyl-di-\text{tert}-butylphosphine, 2.5 mg, 0.0046 mmol, 2 mol %}),$ sealed with a septum, purged with argon, then kept under an argon atmosphere (balloon). Distilled, degassed (N$_2$ sparged) PhMe (0.92 mL) was added via syringe, and the mixture was stirred for 30 min. Diethoxymethylsilane (56 µL, 0.35 mmol, 1.5 equivalents) was added via syringe, and the mixture was stirred for 30 min. The vial was cooled to 0 °C, and then a solution of methyl \((Z)-3-(((\text{tert-butoxycarbonyl})\text{amino})\text{methyl})-7\text{-phenylhept-2-en-4-ynoate (79.0 mg, 0.23 mmol, 1.0 equivalent}) in THF (0.23 mL) was cannulated into the reaction mixture. tert-Butanol (33 µL, 0.35 mmol, 1.5 equivalents) was added, and the vial was placed in a cold room (4 °C) and stirred for 4 h. The crude reaction mixture was then warmed to room temperature, filtered through Florisil (3.5 cm, eluting with 2:1 hexanes:EtOAc, 3 x 3 mL), and the resulting solution was concentrated in vacuo. The crude product was purified by column chromatography (6:1 Hexanes:EtOAc) to afford the title compound as a viscous oil (71.5 mg, 90% yield, 94% ee). $R_F = 0.17$ (6:1 hexanes:EtOAc). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.32-7.29 (m, 2H), 7.23-7.20 (m, 3H), 4.67-4.45 (br s, 1H), 3.68 (s, 3H), 3.25-3.20 (m, 1H), 3.16-3.11 (m, 1H), 2.99-2.96 (m, 1H), 2.78 (t, $J = 7.3$ Hz, 2H), 2.47-2.43 (m, 4H), 1.44 (s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 171.9, 156.0, 140.8, 128.6, 128.5, 126.4, 82.5, 80.4, 79.5, 51.9, 44.2, 37.4, 35.2, 29.5, 28.5, 21.0. IR (film): 3374, 3027, 2977, 2931, 1740, 1716, 1512, 1454, 1437, 1392, 1368, 700 cm$^{-1}$. HRMS: Calculated for C$_{20}$H$_{27}$NO$_4$Na (M+Na)$^+$: 368.1838; Found 368.1844. Chiral HPLC: Chiralpak® IB column; heptane/isopropanol 99:1; flow rate = 0.8 mL/min; detection
at 214 nm; \( t_1 = 24.7 \text{ min (minor)} \); \( t_2 = 31.0 \text{ min (major)} \). \( [\alpha]_D^{25} = -2.29^\circ \) (\( c = 0.83, \text{CH}_2\text{Cl}_2 \), 94% ee).

One-pot synthesis:

An oven-dried Biotage® microwave vial (2.0 – 5.0 mL size) equipped with a stir bar was charged with Pd(OAc)_2 (1.7 mg, 0.0076 mmol, 1.5 mol %), tris(2,6-dimethoxyphenyl)phosphine (TDMPP) (3.3 mg, 0.0075 mmol, 1.5 mol %), and methyl (Z)-3-(((tert-butoxycarbonyl)amino)methyl)-7-phenylhept-2-en-4-ynoate (128.0 mg, 0.60 mmol, 1.2 equivalents). The vial was capped with a rubber septum. PhMe (0.5 mL) was added via syringe, and the mixture was stirred at room temperature for 20 min. 4-Phenyl-1-butyne (65.0 mg, 0.50 mmol, 1.0 equivalent) was then added via syringe, and the mixture was stirred at room temperature for 24 h. The reaction tube was then purged with N\(_2\) and cooled to 0 °C. A pre-formed solution of Cu(OAc)_2·H\(_2\)O/JOSIPHOS J002-1 ligand (13), prepared by mixing 5.0 mg of Cu(OAc)_2·H\(_2\)O (0.025 mmol, 5.0 mol %) and 13.6 mg of ligand (0.025 mmol, 5.0 mol %) in PhMe:THF (4:1, 1.0 mL) for 30 min, was then added via cannula. Diethoxymethylsilane (0.24 mL, 1.50 mmol, 3 equivalents) was added, followed by tert-butanol (95 µL, 1.0 mmol, 2 equivalents). The mixture was stirred under N\(_2\) at 0 °C until the reaction was complete by TLC (3-6 hrs). The crude reaction mixture was then warmed to room temperature, loaded directly onto a silica gel column, and purified by column chromatography (19:1 to 7:3 hexanes:EtOAc) to afford methyl (R)-3-(((tert-butoxycarbonyl)amino)methyl)-7-phenylhept-4-ynoate as a viscous oil (134 mg, 0.39 mmol, 78% yield, 92% ee). Spectral data matched that of the previously reported product (vide supra).

\[ \text{BocHN} \]
\[ \text{Ph} \]

methyl (R)-3-(((tert-butoxycarbonyl)amino)methyl)-5-phenylpent-4-ynoate (9bk):
Prepared according to Representative Procedure C using Cu(OAc)$_2$•H$_2$O (2.0 mg, 0.010 mmol, 2 mol %), JOSIPHOS ligand 13 (5.6 mg, 0.010 mmol, 2 mol %), diethoxymethylsilane (121 µL, 0.75 mmol), tert-butanol (72 µL, 0.75 mmol), methyl (Z)-3-(((tert-butoxycarbonyl)amino)methyl)-5-phenylpent-2-en-4-ynoate (158 mg, 0.50 mmol), PhMe (2.0 mL), and THF (0.5 mL). The reaction duration was 4 h. The crude product was purified by column chromatography (19:1 hexanes:EtOAc to 7:3 hexanes:EtOAc) to afford the title compound as a white solid (149 mg, 0.47 mmol, 94% yield, 92% ee). $R_f = 0.22$ (4:1 hexanes:EtOAc). M.P. = 69 – 70 °C. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.42-7.38 (m, 2H), 7.32-7.28 (m, 3H), 4.95-4.55 (N-H, br, 1H), 3.73 (s, 3H), 3.37 (m, 2H), 3.29 (m, 1H), 2.61, (d, $J = 7.1$ Hz, 2H), 1.46 (s, 9H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 171.8, 156.0, 131.9, 128.4, 128.3, 123.1, 89.0, 83.3, 79.8, 52.1, 44.1, 37.3, 30.2, 28.6. IR (film) = 3359, 2974, 2930, 1727, 1693, 1519, 1438, 1365, 1268, 1250, 1166 cm$^{-1}$. HRMS: Calculated for C$_{18}$H$_{23}$NO$_4$Na (M+Na)$^+$: 340.1525; Found 340.1523. Chiral HPLC: Chiralpak® IB column; heptane/isopropanol 99:1; flow rate = 0.8 mL/min; detection at 254 nm; $t_1 = 18.5$ min (minor); $t_2 = 21.9$ min (major). $[\alpha]_D^{24} = -3.95^\circ$ ($c = 0.36$, CH$_2$Cl$_2$, 92% ee).

methyl (R)-5-(benzyl dimethylsilyl)-3-(((tert-butoxycarbonyl)amino)methyl)pent-4-ynoate (9ek):

Prepared according to Representative Procedure C using Cu(OAc)$_2$•H$_2$O (0.8 mg, 0.004 mmol, 2 mol %), JOSIPHOS ligand 13 (2.2 mg, 0.004 mmol, 2 mol %), diethoxymethylsilane (48 µL, 0.30 mmol), tert-butanol (29 µL, 0.30 mmol), and methyl (Z)-5-(benzyl dimethylsilyl)-3-(((tert-butoxycarbonyl)amino)methyl)pent-2-en-4-ynoate (77.0 mg, 0.20 mmol), PhMe (0.8 mL), and THF (0.2 mL). The reaction duration was 4 h. The crude product was purified by column chromatography (4:1 hexanes:EtOAc) to afford the title compound as a light yellow oil (66.1 mg, 0.17 mmol, 85% yield, 97% ee). $R_f = 0.20$ (6:1 hexanes:EtOAc). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.25-7.21 (m, 2H), 7.09-7.05 (m, 3H), 4.76-
4.54 (br s, 1H), 3.69 (s, 3H), 3.29-3.18 (m, 2H), 3.08-3.02 (m, 1H), 2.49 (d, J = 7.2 Hz, 2H), 2.16 (s, 2H), 1.46 (s, 9H), 0.11 (s, 6H). 13C NMR (125 MHz, CDCl₃) δ 171.5, 155.9, 139.1, 128.4, 128.3, 124.4, 107.4, 85.9, 79.6, 51.9, 43.7, 37.0, 30.3, 28.5, 26.4, -1.9. IR (film): 3382, 3025, 2976, 2173, 1741, 1718, 1600, 1510, 1453, 1438, 1392, 1366, 1251, 1208, 1168, 1057, 1009, 971, 840, 797, 763, 700 cm⁻¹. HRMS: Calculated for C₂₁H₃₁NO₄NaSi (M+Na)⁺: 412.1920; Found 412.1917

Chiral HPLC: Chiralpak® IB column; heptane/isopropanol 99:1; flow rate = 0.8 mL/min; detection at 214 nm; t₁ = 12.4 min (minor); t₂ = 13.2 min (major). [α]D²⁴ = −1.28° (c = 1.41, CH₂Cl₂, 97% ee)

methyl (Z)-1-(2-(2-methoxy-2-oxoethylidene)-6-phenylhex-3-ynyl-1-yl)-1H-pyrrole-2-carboxylate (22a):

An oven-dried Biotage® microwave vial (2.0 – 5.0 mL size) equipped with a stir bar was charged with [(η³-C₃H₅)PdCl]₂ (1.8 mg, 0.005 mmol, 2.5 mol %), dpff (8.3 mg, 0.015 mmol, 7.5 mol %), methyl 2-pyrrolecarboxylate (75.1 mg, 0.60 mmol, 3.0 equivalents), and Cs₂CO₃ (71.7 mg, 0.22 mmol, 1.1 equivalents). The vial was sealed with a septum cap and flushed with N₂. Freshly distilled 1,2-dichloroethane (1.0 mL) was added, and the mixture was stirred for 15 minutes. To this heterogeneous, orange mixture was added methyl (Z)-3-(((methoxycarbonyl)oxy)methyl)-7-phenylhept-2-en-4-ynoate (60.5 mg, 0.20 mmol, 1.0 equivalent) as a solution in 1,2-dichloroethane (200 µL + 50 µL rinse), which was prepared in a flame-dried ½-dram vial. The reaction mixture was stirred vigorously for 6 h, during which time its appearance changed from heterogeneous and orange to heterogeneous and brown. After this time, the reaction mixture was poured into a mixture of saturated aqueous NaHCO₃ (10 mL) and Et₂O (10 mL). The phases were separated, and the aqueous phase was extracted with Et₂O (2 x 10 mL). The pooled organic phases were dried over MgSO₄, filtered, and concentrated. ¹H NMR analysis of the crude mixture indicated a 9:1 mixture of olefin
isomers. The major isomer was isolated by column chromatography (8:1 hexanes:EtOAc), which provided the title compound (47.6 mg, 68%) as a tan solid. \(R_f = 0.38\) (4:1 hexanes:EtOAc). \(\text{M. P.} = 65–67^\circ\text{C.}\) 

**\(^1\text{H NMR}\)** (400 MHz; CDCl\(_3\)): \(\delta\) 7.30-7.27 (m, 2H), 7.23-7.21 (m, 1H), 7.11-7.09 (m, 2H), 6.97 (dd, \(J = 3.9, 1.8\) Hz, 1H), 6.81 (t, \(J = 2.2\) Hz, 1H), 6.15 (dd, \(J = 3.9, 2.6\) Hz, 1H), 6.14 (dd, \(J = 3.9, 2.6\) Hz, 1H), 6.06 (t, \(J = 1.9\) Hz, 1H), 5.61 (d, \(J = 2.0\) Hz, 2H), 3.79 (s, 3H), 3.77 (s, 3H), 2.62 (t, \(J = 7.6\) Hz, 2H), 2.39 (t, \(J = 7.6\) Hz, 2H). 

**\(^{13}\text{C NMR}\)** (100 MHz; CDCl\(_3\)): 166.3, 161.7, 140.4, 140.3, 129.7, 128.5, 128.4, 126.5, 122.8, 122.5, 118.1, 108.3, 98.4, 78.6, 51.7, 51.2, 49.7, 34.4, 21.7. **IR** (film): 2908, 2188, 1685, 1586, 1512, 1417, 1392, 1310, 1231, 1148, 1093, 1064, 1016, 858, 732, 690 cm\(^{-1}\). **HRMS** (ESI+): Calculated for C\(_{21}\)H\(_{21}\)NNaO\(_4\) (M+Na\(^+\)): 374.1363; Found 374.1363.

**Determination of the olefin geometry:**

Irradiation of the vinylic hydrogen (\(\delta 6.06\)) of the major product isomer led to a very weak nOe enhancement (+ 0.4 %) at the indicated methylene (\(\delta 5.61\)):

In contrast, irradiation of the vinylic hydrogen (\(\delta 5.04\)) of the minor product isomer led to a stronger nOe enhancement (+ 3.6%) at the methylene group (\(\delta 5.47\)). These results suggest \((E)\)-geometry for the minor product and \((Z)\)-geometry for the major product.
methyl (S)-1-(2-(2-methoxy-2-oxoethyl)-6-phenylhex-3-yn-1-yl)-1H-pyrrole-2-carboxylate (23a):

An oven-dried Biotage® microwave vial (0.50 – 2.0 mL size) equipped with a stir bar was charged with Cu(OAc)₂•H₂O (2.0 mg, 0.010 mmol, 10 mol %) and WALPHOS ligand 17 (9.3 mg, 0.010 mmol, 10 mol %). The vial was sealed with a septum and flushed with Ar (balloon). Freshly distilled, degassed (Ar sparged) PhMe (300 µL) was added, and the mixture was stirred for 20 min to afford a bright green, homogeneous solution. Diethoxymethylsilane (32 µL, 0.20 mmol, 2.0 equivalents) was added, and the mixture was stirred until a change in appearance to homogeneous and brown was observed (ca. 15-30 min). The vial was cooled to 0 °C, and methyl (Z)-1-(2-(2-methoxy-2-oxoethylidene)-6-phenylhex-3-yn-1-yl)-1H-pyrrole-2-carboxylate (35.1 mg, 0.10 mmol, 1.0 equivalent) was added as a solution in PhMe (200 µL), which was prepared in a flame-dried ½-dram vial. To the mixture was then added tert-butanol (19 µL, 0.20 mmol, 2.0 equivalents). The vessel was kept under an Ar balloon and transferred to a cold room (4 °C) where it was stirred for 18 h. After this time, TBAF (1 M in THF, 300 µL, 0.30 mmol, 3.0 equivalents) was added, and the mixture was stirred for 10 minutes. The mixture was then applied to a silica gel column that was eluted with 6:1 to 4:1 hexanes:EtOAc to afford the title compound (29.7 mg, 84%, 99% ee) as a viscous light yellow oil. **R_f** = 0.30 (4:1 hexanes:EtOAc). **¹H NMR** (600 MHz; CDCl₃): δ 7.30-7.27 (m, 2H), 7.22-7.17 (m, 3H), 6.95 (dd, J = 3.9, 1.8 Hz, 1H), 6.79 (t, J = 2.1 Hz, 1H), 6.08 (dd, J = 3.9, 2.6 Hz, 1H), 4.45 (dd, J = 13.3, 6.7 Hz, 1H), 4.35 (dd, J = 13.3, 7.5 Hz, 1H), 3.80 (s, 3H), 3.66 (s, 3H), 3.32-3.30 (m, 1H), 2.78-2.73 (m, 2H), 2.45-2.37 (m, 4H). **¹³C NMR** (100 MHz; CDCl₃): 171.6, 161.7, 140.8, 130.0, 128.6, 128.4, 126.4, 121.6, 118.7, 108.1, 83.3, 79.6, 52.2, 51.9, 51.2, 37.2, 35.2, 30.7, 21.0. **IR** (film): 2909, 1716, 1861, 1418, 1391, 1351, 1233, 1093, 734, 690 cm⁻¹. **HRMS** (ESI+): Calculated for C₂₁H₂₃NNaO₄ (M+Na)⁺: 376.1519; Found
376.1515. **Chiral HPLC**: Agilent IB, 98:2 heptane:isopropanol, 0.8 mL/min, 254 nm, 13.40 min (major), 14.74 min (minor). \([\alpha]_D^{25} = -19.3^\circ (c = 0.5, \text{CHCl}_3)\).

methyl (Z)-3-(((4-methoxyphenoxy)methyl)-7-phenylhept-2-en-4-ynoate (22b):

An oven-dried Biotage® microwave vial (2.0 – 5.0 mL size) equipped with a stir bar was charged with \([\eta^3-\text{C}_3\text{H}_5]\text{PdCl}_2\) (1.8 mg, 0.005 mmol, 2.5 mol %), dppf (8.3 mg, 0.015 mmol, 7.5 mol %), 4-methoxyphenol (74.5 mg, 0.60 mmol, 3.0 equivalents), and \(\text{Cs}_2\text{CO}_3\) (71.7 mg, 0.22 mmol, 1.1 equivalents). The vial was sealed with a septum cap and flushed with \(\text{N}_2\). Freshly distilled 1,2-dichloroethane (1.0 mL) was added, and the mixture was stirred for 15 minutes. To this heterogeneous, orange mixture was added methyl (Z)-3-(((methoxycarbonyl)oxy)methyl)-7-phenylhept-2-en-4-ynoate (60.5 mg, 0.20 mmol, 1.0 equivalent) as a solution in 1,2-dichloroethane (200 µL + 50 µL rinse), which was prepared in a flame-dried ½-dram vial. The reaction mixture was stirred *vigorously* for 6 h. After this time, the reaction mixture was poured into a mixture of saturated aqueous \(\text{NaHCO}_3\) (10 mL) and \(\text{Et}_2\text{O}\) (10 mL). The phases were separated, and the aqueous phase was extracted with \(\text{Et}_2\text{O}\) (2 x 10 mL). The pooled organic phases were dried over \(\text{MgSO}_4\), filtered, and concentrated. \(^1\text{H NMR} \) analysis of the crude mixture indicated a single olefin isomer. Column chromatography (8:1 hexanes:EtOAc) delivered the title compound (48.2 mg, 69%) as a viscous, light yellow oil. The product was assigned as the (Z)-isomer by analogy to the preceding Pd-AA reaction; in support of this, no detectable nOe enhancement (< 0.1 %) was observed between the vinylic hydrogen (δ 6.12) and the allylic hydrogens (δ 5.11). \(R_f = 0.38\) (6:1 hexanes:EtOAc). \(^1\text{H NMR} \) (400 MHz; CDCl₃): δ 7.30-7.18 (m, 5H), 6.90-6.80 (m, 4H), 6.12 (t, \(J = 1.7\) Hz, 1H), 5.11 (d, \(J = 1.8\) Hz, 2H), 3.77 (s, 3H), 3.74 (s, 3H), 2.80 (t, \(J = 7.4\) Hz, 2H).
Hz, 2H), 2.63 (t, \( J = 7.4 \) Hz, 2H). \(^{13}\text{C NMR}\) (100 MHz; CDCl\(_3\)): 166.2, 154.1, 152.7, 140.5, 140.4, 128.6, 128.5, 126.5, 124.2, 116.1, 114.6, 98.8, 79.9, 66.5, 55.8, 51.7, 34.5, 22.1. \(\text{IR}\) (film): 2985, 2908, 2794, 2189, 1688, 1584, 1486, 1415, 1344, 1318, 1215, 1148, 1092, 1023, 861, 814 cm\(^{-1}\). \(\text{HRMS}\) (ESI+): Calculated for C\(_{22}\)H\(_{22}\)NaO\(_4\) (M+Na\(^{+}\)): 373.1410; Found 373.1409.

![Chemical Structure](image_url)

methyl (S)-3-((4-methoxyphenoxy)methyl)-7-phenylhept-4-ynoate (23b):

An oven-dried Biotage\(^{\circledR}\) microwave vial (0.50 – 2.0 mL size) equipped with a stir bar was charged with Cu(OAc)\(_2\)\(\cdot\)H\(_2\)O (1.0 mg, 0.005 mmol, 5 mol %) and WALPHOS ligand 17 (4.6 mg, 0.005 mmol, 5 mol %). The vial was sealed with a septum and flushed with Ar (balloon). Freshly distilled, degassed (Ar sparged) PhMe (300 \(\mu\)L) was added, and the mixture was stirred for 20 min to afford a bright green, homogeneous solution. Diethoxymethylsilane (32 \(\mu\)L, 0.20 mmol, 2.0 equivalents) was added, and the mixture was stirred until a change in appearance to homogeneous and brown was observed (ca. 15-30 min). The vial was cooled to 0 °C, and methyl (Z)-3-((4-methoxyphenoxy)methyl)-7-phenylhept-2-en-4-ynoate (35.0 mg, 0.10 mmol, 1.0 equivalent) was added as a solution in PhMe (200 \(\mu\)L), which was prepared in a flame-dried ½-dram vial. To the mixture was then added tert-butanol (19 \(\mu\)L, 0.20 mmol, 2.0 equivalents). The vessel was kept under an Ar balloon and transferred to a cold room (4 °C) where it was stirred for 24 h. After this time, TBAF (1 M in THF, 300 \(\mu\)L, 0.30 mmol, 3.0 equivalents) was added, and the mixture was stirred for 10 minutes. The mixture was then applied to a silica gel column which was eluted with 10:1 to 8:1 hexanes:EtOAc to afford the title compound (30.3 mg, 86%, 99% ee) as a viscous yellow oil. \(R_f\) = 0.30 (6:1 hexanes:EtOAc). \(^1\text{H NMR}\) (400 MHz; CDCl\(_3\)): \(\delta\) 7.30-7.26 (m, 2H), 7.22-7.20 (m, 3H), 6.83
(s, 4H), 4.01 (dd, \(J = 9.2, 5.0 \text{ Hz}, \text{ 1H}\)), 3.84 (dd, \(J = 9.1, 8.2 \text{ Hz}, \text{ 1H}\)), 3.77 (s, 3H), 3.70 (s, 3H), 3.32-3.24 (m, 1H), 2.81-2.72 (m, 3H), 2.53 (dd, \(J = 15.7, 8.0 \text{ Hz}, \text{ 1H}\)), 2.45 (td, \(J = 7.5, 2.2 \text{ Hz}, \text{ 2H}\)). \(\text{\textsuperscript{13}C NMR}\) (100 MHz; CDCl\(_3\)): \(\delta\) 172.1, 154.2, 152.7, 140.8, 128.6, 128.4, 126.3, 115.8, 114.7, 82.5, 79.4, 70.5, 55.9, 51.9, 37.1, 35.3, 28.9, 21.1. \(\text{IR}\) (film): 2985, 2908, 1715, 1487, 1418, 1344, 1214, 1153, 1092, 1028, 814, 739, 690 cm\(^{-1}\). \(\text{HRMS}\) (ESI+): Calculated for \(\text{C}_{22}\text{H}_{25}\text{O}_4\) (M+H): 353.1747; Found 353.1743. \textbf{Chiral HPLC}: Agilent IB, 95:5 heptane:isopropanol, 0.8 mL/min, 220 nm, 16.22 min (major), 22.24 min (minor). \([\alpha]_D^{25} = +6.9^\circ\) (c = 0.5, CHCl\(_3\)).

![Chemical Structure](image)

\((4'^-\text{(trifluoromethyl)}-[1,1'^-\text{biphenyl}]-3-\text{yl})\text{methanol}\)

A flame-dried 100 mL round-bottomed flask equipped with a stir bar was charged with \(\text{Pd(dppf)}\text{Cl}_2\cdot\text{CH}_2\text{Cl}_2\) (408.3 mg, 0.50 mmol, 5 mol %) and 3-(hydroxymethyl)phenylboronic acid (1.90 g, 12.5 mmol, 1.25 equivalents). The flask was sealed with a septum and flushed with Ar, and then degassed (Ar sparged) DMF (10 mL) and THF (freshly distilled, 10 mL) were added. \(\text{Cs}_2\text{CO}_3\) (6.52 g, 20.0 mmol, 2.0 equivalents) was added under Ar flow, and then 4-bromobenzotrifluoride (1.40 mL, 10.0 mmol, 1.0 equivalent) was added \textit{via} syringe. The vessel was heated to 90 °C, and then it was sealed with a yellow plastic cap. The reaction mixture was stirred for 18 h. The vessel was cooled to room temperature, and the reaction mixture was poured into Et\(_2\)O (200 mL). The organic phase was washed with H\(_2\)O (2 x 100 mL), 10% aqueous LiCl (50 mL), and brine (50 mL). The organic phase was dried over MgSO\(_4\), filtered, and concentrated. Purification of the residue by column chromatography (2:1 to 1:1 hexanes:EtOAc) afforded the title compound (2.32 g, 92%) as a viscous, brown oil that solidified on standing, yielding an off-white solid. \(R_f = 0.30\) (2:1 hexanes:EtOAc). \(\text{\textsuperscript{1}H NMR}\) (600 MHz; CDCl\(_3\)): \(\delta\) 7.72-7.69 (m, 4H), 7.62 (s, 1H), 7.54-7.52 (m, 1H), 7.47 (t, \(J = 7.6 \text{ Hz}, \text{ 1H}\)), 7.42-7.40 (m, 1H), 4.79 (d, \(J = 4.9 \text{ Hz}, \text{ 2H}\)), 1.74 (s, 1H).

These \(\text{\textsuperscript{1}H NMR data matched literature data.}\)\(^{11}\)
3-(bromomethyl)-4'-{(trifluoromethyl)}-1,1'-biphenyl (26):

A flame-dried 50 mL round-bottomed flask equipped with a stir bar was charged with alcohol \((4'-(\text{trifluoromethyl})-\text{-}[1,1'-\text{biphenyl}]-3-\text{-yl})\text{methanol (1.73 g, 6.87 mmol, 1.0 equivalent). The flask was sealed with a septum and flushed with N}_2, and then PhMe (13.7 mL) was added followed by Et\textsubscript{3}N (96 \mu L, 0.69 mmol, 10 mol %). The vessel was heated to 35 °C. Neat SOBr\textsubscript{2} (0.60 mL, 7.72 mmol, 1.125 equivalents) was added via syringe pump over 2 h. The reaction mixture was stirred for an additional 0.5 h, and then it was cooled to room temperature. H\textsubscript{2}O (15 mL) was added cautiously in portions, and then the mixture was poured into Et\textsubscript{2}O (50 mL). The phases were separated, and the organic phase was washed with saturated aqueous NaHCO\textsubscript{3} (2 x 50 mL). The organic phase was dried over MgSO\textsubscript{4}, filtered, and concentrated. The residue was purified by column chromatography (10:1 hexanes:EtOAc) to afford the title compound (1.98 g, 92%) as a clear, colorless oil that solidified upon standing in a refrigerator, yielding a white solid. \(R_f = 0.53\) (10:1 hexanes:EtOAc). M. P. = 50–52 °C (lit. M. P. = 60–62 °C\textsuperscript{12} \textbf{H NMR} (600 MHz; CDCl\textsubscript{3}): \(\delta\) 7.72-7.68 (m, 4H), 7.62 (d, \(J = 1.6\) Hz, 1H), 7.53 (dt, \(J = 7.1, 1.8\) Hz, 1H), 7.47-7.43 (m, 2H), 4.57 (s, 2H). \textit{These \textsuperscript{1}H NMR data matched literature data.}\textsuperscript{12}

ethyl 3-{(4-hydroxyphenyl)}propiolate (25):

A flame-dried 100 mL round-bottomed flask equipped with a large stir bar was charged with 4-iodophenol (2.20 g, 10.0 mmol, 1.0 equivalent) and Cu\textsubscript{2}O (2.146 g, 15.0 mmol, 1.5 equivalents). The flask was sealed with a septum and flushed with N\textsubscript{2}. Degassed
(N₂ sparged) DMF (20 mL) was added, followed by ethyl propiolate (2.03 mL, 20.0 mmol, 2.0 equivalents). The vessel was heated to 110 °C, and then it was sealed with a yellow plastic cap. The reaction mixture was stirred for 18 h. The vessel was then cooled to room temperature, and the reaction mixture was vacuum filtered through a Celite® pad, which was rinsed with Et₂O (150 mL). The filtrate was washed with H₂O (2 x 50 mL) then 10% aqueous LiCl (50 mL), and then these aqueous phases were pooled and back-extracted with Et₂O (50 mL). The pooled organic phases were washed with brine (50 mL), dried over MgSO₄, filtered, and concentrated. The residue was purified by column chromatography (6:1 to 2:1 hexanes:EtOAc) to afford the title compound (1.402 g, 74%) as an orange solid. Rᵢ = 0.33 (2:1 hexanes:EtOAc). M. P. = 83–84 °C. ¹H NMR (400 MHz; CDCl₃): δ 7.48-7.45 (m, 2H), 6.85-6.82 (m, 2H), 5.87 (br s, 1H), 4.30 (q, J = 7.1 Hz, 2H), 1.35 (t, J = 7.1 Hz, 3H). ¹³C NMR (100 MHz; CDCl₃): 158.2, 154.9, 135.3, 116.0, 111.5, 87.5, 80.1, 62.3, 14.2. IR (film): 3219 (br), 2178, 1647, 1582, 1492, 1421, 1355, 1298, 1266, 1192, 1149, 1007, 825, 740 cm⁻¹.

These ¹H and ¹³C NMR data matched literature data.¹³

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etyl 3-(4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)phenyl)propiolate (27):

A flame-dried 2-dram vial equipped with a large stir bar was charged with propiolate ethyl 3-(4-hydroxyphenyl)propiolate (285.0 mg, 1.50 mmol, 1.0 equivalent) and DMF (3.0 mL). 3-(Bromomethyl)-4'-(trifluoromethyl)-1',1'-biphenyl (543.0 mg, 1.72 mmol, 1.15 equivalents) was added, followed by K₂CO₃ (414.2 mg, 3.00 mmol, 2.0 equivalents). The heterogeneous reaction mixture was stirred vigorously for 1 h, at which point the reaction mixture was applied directly to a silica gel column that was eluted with 6:1 to 4:1 hexanes:EtOAc to afford the title compound (578.6 mg, 91%) as a white solid. Rᵢ = 0.46 (4:1 hexanes:EtOAc). M. P. = 98–100 °C. ¹H NMR (400 MHz; CDCl₃): δ 7.70 (s, 4H), 7.66-7.64 (m, 1H), 7.59-7.44 (m, 5H), 7.00-6.96 (m, 2H), 5.16 (s, 2H), 4.29 (q, J = 7.1 Hz, 2H), 1.35 (t,
$J = 7.1$ Hz, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): 160.6, 154.4, 144.3 (q, $J = 1.2$ Hz), 140.4, 137.1, 135.1, 129.7 (q, $J = 32.4$ Hz), 129.5, 127.6, 127.4, 127.3, 126.5, 125.9 (q, $J = 3.6$ Hz), 124.3 (q, $J = 270.5$ Hz), 115.2, 112.0, 86.8, 80.4, 70.0, 62.1, 14.3. $^{19}$F NMR (376 MHz; CDCl$_3$): –62.7. IR (film): 2173, 1678, 1584, 1491, 1316, 1239, 1151, 1105, 1058, 833 cm$^{-1}$. HRMS (ESI+): Calculated for C$_{25}$H$_{19}$F$_3$NaO$_3$ (M+Na)$^+$: 447.1179; Found 447.1172.

![Chemical structure](image)

ethyl (E)-3-((4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)phenyl)-5-(triisopropylsilyl)pent-2-en-4-ynoate (28b):

A 2-dram vial equipped with a stir bar was charged with Pd(OAc)$_2$ (15.0 mg, 0.067 mmol, 5 mol %) and tris(2,6-dimethoxyphenyl)phosphine (29.6 mg, 0.067 mmol, 5 mol %). THF (1.0 mL) was added, and the mixture was stirred for 15 minutes, generating a homogeneous, orange-red solution. To a separate 2-dram vial containing acceptor ethyl 3-(4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)phenyl)propiolate (568.4 mg, 1.34 mmol, 1.0 equivalent) was added a stir bar and THF (1.0 mL). The former solution was transferred to the latter by pipette, and then triisopropylsilylacetylene (900 µL, 4.02 mmol, 3.0 equivalents) was added. The homogeneous, black mixture was stirred for 24 h, at which point it was loaded directly onto a silica gel column that was eluted with 20:1 to 10:1 hexanes:EtOAc to afford the title compound (747.8 mg, 92%) as a viscous, red-orange oil. $R_f = 0.53$ (4:1 hexanes:EtOAc). $^1$H NMR (600 MHz; CDCl$_3$): $\delta$ 7.70 (s, 4H), 7.67-7.66 (m, 1H), 7.57 (dt, $J$
= 7.4, 1.7 Hz, 1H), 7.52-7.46 (m, 4H), 6.98-6.96 (m, 2H), 6.29 (s, 1H), 5.16 (s, 2H), 4.11 (q, J = 7.1 Hz, 2H), 1.19 (t, J = 7.1 Hz, 3H), 1.12-1.05 (m, 2H). 13C NMR (125 MHz; CDCl3): 165.6, 159.5, 144.4 (q, J = 1.1 Hz), 140.2, 137.74, 137.70, 130.8, 129.6 (q, J = 32.4 Hz), 129.4, 128.7, 127.6, 127.4, 127.1, 126.5, 125.8 (q, J = 3.6 Hz), 124.4 (q, J = 270.5 Hz), 123.8, 114.0, 107.6, 97.4, 69.9, 60.5, 18.7, 14.2, 11.3. 19F NMR (376 MHz; CDCl3): –62.8. IR (film): 2902, 2826, 1694, 1583, 1488, 1443, 1308, 1208, 1150, 1058, 1003, 824, 780, 662 cm⁻¹. HRMS (ESI+): Calculated for C₃₆H₄₂F₃O₃Si (M+H)+: 607.2850; Found 607.2841.

![Chemical structure](image-url)

ethyl (R)-3-((4-((4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)phenyl)pent-4-ynoate (30):

An oven-dried round-bottom Biotage® microwave vial (2.0 – 5.0 mL size) equipped with a stir bar was charged with Cu(OAc)₂·H₂O (7.5 mg, 0.0375 mmol, 5 mol %) and JOSIPHOS ligand 14 ((R)-1-[(S)-2-(diphenylphosphino)ferrocenyl]-ethyl-di-3,5-xylylphosphone, 24.0 mg, 0.0375 mmol, 5 mol %). The vial was sealed with a septum, flushed with Ar (balloon), and kept under an Ar atmosphere. Distilled, degassed (Ar sparged) PhMe (2.0 mL) was added, and the mixture was stirred for 30 min. Diethoxymethylsilane (0.60 mL, 3.75 mmol, 5 equivalents) was added. The mixture was stirred for 30 min, during which time the original blue-green, homogeneous appearance of the catalyst solution turned to golden yellow and homogeneous. The vessel was cooled to 0 °C. A separate oven-dried round-bottomed Biotage® microwave vial (2.0 – 5.0 mL size) was charged with ethyl (E)-3-((4'-(trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)phenyl)-5-(triisopropylsilyl)pent-2-en-4-ynoate (455.1 mg, 0.75 mmol, 1 equivalent), and the vessel was flushed with Ar (balloon). Distilled, degassed PhMe (1.25 mL) was added to dissolve the substrate, and the solution was cooled to 0 °C. The substrate solution was transferred to the catalyst/silane mixture via
cannula, using additional PhMe (0.50 mL) to rinse the vial and cannula. tert-Butanol (215 µL, 2.25 mmol, 3 equivalents) was added, and the vessel was transferred to a cold room (4 °C) where it was stirred for 24 h.

After this time, a 50 µL aliquot was removed. This sample was diluted with Et₂O and filtered through a small pipette plug of Florisil®. The solution was concentrated, and ¹H NMR analysis of this sample indicated the formation of the corresponding β-alkynyl ester with 96% reaction conversion and with 8:1 1,4:Σ1,6 regioselectivity.

The remainder of the reaction mixture was transferred to a pre-cooled (0 °C), flame-dried 50 mL round-bottom flask via cannula, using THF (3.75 mL) to rinse the vial and cannula. To this mixture was added TBAF (1 M in THF, 7.5 mL, 7.5 mmol, 10 equivalents). Gas evolution occurred. The reaction mixture was stirred at 0 °C for 4 h, at which point it was warmed to room temperature and filtered through a column of Florisil® (10 cm by 5 cm), eluting with Et₂O (150 mL). The solution was concentrated, and the residue was purified by column chromatography (10:1 to 6:1 hexanes:EtOAc) to yield the title compound as a single regioisomer and as a white gum (251.3 mg, 74%, 82% ee). R_f = 0.50 (4:1 hexanes:EtOAc).

¹H NMR (600 MHz; CDCl₃): δ 7.70 (s, 4H), 7.67 (s, 1H), 7.57-7.55 (m, 1H), 7.51-7.46 (m, 2H), 7.35-7.32 (m, 2H), 6.98-6.96 (m, 2H), 5.13 (s, 2H), 4.18-4.12 (m, 3H), 2.82 (dd, J = 15.4, 8.3 Hz, 1H), 2.71 (dd, J = 15.4, 7.0 Hz, 1H), 2.29 (d, J = 2.5 Hz, 1H), 1.24-1.22 (m, 3H). ¹³C NMR (125 MHz; CDCl₃): 170.8, 158.0, 144.4 (q, J = 1.4 Hz), 140.2, 137.9, 132.5, 129.5 (q, J = 32.4 Hz), 129.3, 128.6, 127.5, 127.3, 127.0, 126.4, 125.8 (q, J = 3.9 Hz), 124.4 (q, J = 270.5 Hz), 115.0, 84.5, 71.4, 69.9, 60.8, 43.2, 33.2, 14.2. ¹⁹F NMR (376 MHz; CDCl₃): – 62.8. IR (film): 3251, 2993, 2941, 2895, 1710, 1591, 1563, 1489, 1443, 1383, 1352, 1309, 1228, 1149, 1109, 1057, 1004, 832, 781, 731, 712, 690 cm⁻¹. HRMS (ESI+): Calculated for C_{27}H_{24}F_{3}O_{3} (M+H)^+: 453.1672; Found 453.1662. [α]_b^{23} = + 3.8 ° (c = 0.65, CHCl₃)

The ee was determined by converting a sample of the title compound to a mixture of diastereomeric amides via amidation with (S)-α-methylbenzylamine. To a solution of the title compound (22.6 mg, 0.05 mmol) in EtOH/THF (5:1, 0.60 mL) at 23 °C was added a solution of NaOH (10 mg, 0.25 mmol, 5 equiv) in H₂O (0.10 mL). The mixture was heated to 50 °C for 1 h, at which point it was cooled to room temperature, acidified with 1 N HCl, and
extracted with Et₂O. The extracts were dried over MgSO₄, filtered, and concentrated. Flash column chromatography (1:1 hexanes:EtOAc) delivered 9.2 mg of the corresponding acid, which was dissolved in 1,2-dichloroethane (0.25 mL). This solution was treated with triethylamine (15 µL, 0.10 mmol, 5 equivalents), EDCI-HCl (12.5 mg, 0.065 mmol, 3 equivalents), (S)-α-methylbenzylamine (28 µL, 0.22 mmol, 10 equivalents), and a single small crystal of DMAP. The reaction mixture was stirred for 5 h at 23 °C, at which point it was diluted with Et₂O and quenched with 1 N HCl. The phases were separated, the aqueous phase was extracted with Et₂O, and the pooled organic phases were dried over MgSO₄, filtered, and concentrated. The crude mixture was analyzed by 600 MHz ¹H NMR spectroscopy. The dr was determined to be 91:9, corresponding to an ee of 82%. Salient, well-resolved, diastereotopic NMR signals include the terminal alkyne C−H (2.33 ppm, d, J = 2.4 Hz, major; 2.25 ppm, d, J = 2.4, minor) and the methyl group of the amide (1.47 ppm, d, J = 7.2 Hz, major; 1.35 ppm, d, J = 6.6 Hz, minor).

The assignment of these signals was confirmed upon the independent synthesis of a 1:1 mixture of amide diastereomers from a sample of racemic β-aryl, β-alkynyl ester. The latter compound was prepared via a conjugate reduction performed using an equimolar mixture of enantiomeric JOSIPHOS ligands.

ethyl (S)-3-(4-((4′-(trifluoromethyl)-[1,1′-biphenyl]-3-yl)methoxy)phenyl)hex-4-ynoate (32):

An oven-dried round bottom Biotage® microwave vial (0.50 – 2.0 mL size) equipped with a stir bar was charged with [η³-C₃H₅]PdCl₂ (1.4 mg, 0.0038 mmol, 5 mol % Pd), Cul (2.1 mg, 0.0113 mmol, 7.5 mol %), 1,3-bis-(1-adamantyl)imidazolium chloride (2.8 mg, 0.0075 mmol, 5 mol %), and Cs₂CO₃ (68.5 mg, 0.21 mmol, 1.4 equivalents). The vial was
sealed with a septum and flushed with Ar (balloon). A separate oven-dried round bottom Biotage® microwave vial (0.50 – 2.0 mL size) was charged with ethyl (R)-3-(4-((4'- (trifluoromethyl)-[1,1'-biphenyl]-3-yl)methoxy)phenyl)pent-4-ynoate (67.9 mg, 0.15 mmol, 1 equivalent). This vial was sealed with a septum and flushed with Ar (balloon). The substrate was dissolved in degassed (N₂ sparged) Et₂O (0.50 mL), and the solution was transferred to the remaining vial via cannula. Degassed (N₂ sparged) DMF (0.25 mL) was added to vial previously containing the substrate and was transferred similarly. Iodomethane (47 µL, 0.75 mmol, 5 equivalents) was added to the reaction mixture. The vial was sealed with a septum-lined metal cap and then heated to 40 °C. The reaction mixture was stirred vigorously at this temperature for 24 h. The appearance was initially brown/black, but this yielded to a yellow color after a few hours. After the 24 h, the vessel was cooled to 23 °C, and the reaction mixture was diluted with Et₂O (3 mL). The mixture was filtered through a pipette plug of Florisil®, which was rinsed with additional Et₂O (10 mL). The clear yellow solution was concentrated, and purification of the residue by column chromatography (4:1 hexanes:EtOAc) delivered the title compound as a viscous yellow oil (41.9 mg, 60%). Rf = 0.50 (4:1 hexanes:EtOAc). ¹H NMR (400 MHz; CDCl₃): δ 7.70 (s, 4H), 7.66 (s, 1H), 7.57-7.55 (m, 1H), 7.51-7.45 (m, 2H), 7.33-7.29 (m, 2H), 6.97-6.93 (m, 2H), 5.12 (s, 2H), 4.16-4.04 (m, 3H), 2.74 (dd, J = 15.1, 8.4 Hz, 1H), 2.64 (dd, J = 15.1, 7.0 Hz, 1H), 1.83 (d, J = 2.4 Hz, 3H), 1.22 (t, J = 7.1 Hz, 3H). ¹³C NMR (125 MHz; CDCl₃): 171.2, 157.8, 144.5 (q, J = 1.4 Hz), 140.2, 138.0, 133.8, 129.6 (q, J = 32.4 Hz), 129.4, 128.6, 127.6, 127.4, 127.0, 126.4, 125.8 (q, J = 3.6 Hz), 124.4 (q, J = 270.4 Hz), 115.0, 79.7, 78.9, 70.0, 60.7, 43.7, 33.6, 14.3, 3.8. ¹⁹F NMR (376 MHz; CDCl₃): – 62.8. IR (film): 2880, 1711, 1590, 1489, 1382, 1352, 1226, 1148, 1108, 1056, 1003, 832, 780, 690 cm⁻¹. HRMS (ESI+): Calculated for C₂₈H₂₆F₃O₃ (M+H)⁺: 467.1829; Found 467.1827. [α]D²³ = + 4.9 ° (c = 1.0, CHCl₃)
(S)-3-((4′-(trifluoromethyl)-[1,1′-biphenyl]-3-yl)methoxy)phenyl)hex-4-ynoic acid (AMG 837, 24):

To a solution of ethyl (S)-3-((4′-(trifluoromethyl)-[1,1′-biphenyl]-3-yl)methoxy)phenyl)hex-4-ynoate (11.6 mg, 0.025 mmol, 1 equivalent) in EtOH (0.40 mL) in a 2-dram vial and at 23 °C was added a solution of NaOH (10 mg, 0.25 mmol, 10 equivalents) in H₂O (0.10 mL). The homogeneous, light yellow substrate solution immediately turned milky-white upon addition of the NaOH solution, but within 5 min the appearance returned to homogeneous and light yellow. After 90 min, the reaction mixture was poured into a separatory funnel containing EtOAc (5 mL) and 1 N H₂SO₄ (3 mL). The mixture was shaken, and the phases were separated. The aqueous phase was extracted with EtOAc (5 mL). The pooled organic phases were washed with H₂O (5 mL) and then with brine (5 mL), dried over Na₂SO₄, filtered, and concentrated. The residue was purified by preparative thin-layer chromatography (19:1 CH₂Cl₂:MeOH), which afforded the title compound as a clear film (9.0 mg, 83%). Rf = 0.20 (1:1 hexanes:EtOAc). ¹H NMR (600 MHz; CDCl₃): δ 7.70 (s, 4H), 7.66-7.64 (m, 1H), 7.57-7.55 (m, 1H), 7.50-7.45 (m, 2H), 7.33-7.31 (m, 2H), 6.98-6.94 (m, 2H), 5.12 (s, 2H), 4.08-4.04 (m, 1H), 2.81 (dd, J = 15.7, 8.4 Hz, 1H), 2.72 (dd, J = 15.7, 6.7 Hz, 1H), 1.83 (d, J = 2.4 Hz, 3H). ¹³C NMR (125 MHz; CDCl₃): 176.7, 157.9, 144.5 (q, J = 1.0 Hz), 140.3, 138.0, 133.5, 129.6 (q, J = 32.4 Hz), 129.5, 128.6, 127.6, 127.4, 127.0, 126.5, 125.9 (q, J = 3.8 Hz), 124.4 (q, J = 270.5 Hz), 115.1, 79.5, 79.3, 70.0, 43.3, 33.3, 3.8. ¹⁹F NMR (376 MHz; CDCl₃): −62.8. IR (film): 2881, 1687, 1590, 1489, 1384, 1308, 1225, 1150, 1109, 1056, 1003, 944, 831, 780, 748, 710, 690 cm⁻¹. HRMS (ESI+): Calculated for C₂₈H₂₁F₃O₃ (M+H)⁺: 439.1516; Found 439.1510. [α]D²⁵ = +4.4 ° (c = 0.9, CHCl₃); lit.: +7.2 ° (c = 0.5, CHCl₃);¹⁴ lit.: +10.9 ° (c = 0.44, CHCl₃).¹⁵
Pd-catalyzed Alkyne-Alkyne Coupling with Ketone Acceptors: Representative Procedure D, Synthesis of (E)-4-ethyl-8-phenyloct-3-en-5-yn-2-one (8al):

A 2-dram, screw-cap vial equipped with a stir bar was charged with Pd(OAc)$_2$ (11.2 mg, 0.05 mmol, 5 mol %) and tris(2,6-dimethoxyphenyl)phosphine (TDMPP, 22.1 mg, 0.05 mmol, 5 mol %). PhMe (1.0 mL) was added. The mixture was stirred for 15 minutes, generating a homogeneous, orange-red solution. To the solution was added 3-hexyn-2-one (GFS Chemicals, 164 µL, 1.5 mmol, 1.5 equivalents) followed by 4-phenyl-1-butyne (141 µL, 1.0 mmol, 1.0 equivalent). Upon addition of the donor alkyne, the reaction quickly changes in appearance to homogeneous and black. The reaction mixture was stirred for 14 h, at which point it was filtered through a pipette plug of Florisil® (3 cm), which was rinsed with Et$_2$O (10 mL). The solution was concentrated, and the residue was purified via column chromatography (10:1 hexanes:EtOAc) to afford the title compound (165.0 mg, 73%) as a clear, orange oil. $R_f = 0.35$ (10:1 hexanes:EtOAc). $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 7.33-7.29 (m, 2H), 7.24-7.22 (m, 3H), 6.31 (s, 1H), 2.88 (t, $J = 7.4$ Hz, 2H), 2.68-2.63 (m, 4H), 2.18 (s, 3H), 1.06 (t, $J = 7.5$ Hz, 3H). $^{13}$C NMR (125 MHz; CDCl$_3$): 197.9, 143.8, 140.4, 129.6, 128.6, 128.5, 126.5, 95.9, 83.0, 34.9, 32.0, 26.1, 21.9, 12.9. IR (film): 2986, 2928, 2893, 2182, 1656, 1562, 1434, 1337, 1154, 689 cm$^{-1}$. HRMS (ESI+): Calculated for C$_{16}$H$_{19}$O (M+H)$^+$: 227.1431; Found 227.1430.

Note: This acceptor alkyne is co-polar on silica gel with some of the ynenone products; however, the excess acceptor can be removed in vacuo (rotary evaporator or high vacuum, ca. 1 torr).
(E)-4-ethyl-6-phenylhex-3-en-5-yn-2-one (8bl):

Prepared according to Representative Procedure D using Pd(OAc)$_2$ (11.2 mg, 0.05 mmol, 5 mol %), tris(2,6-dimethoxyphenyl)phosphine (TDMPP, 22.1 mg, 0.05 mmol, 5 mol %), 3-hexyn-2-one (164 µL, 1.5 mmol), and freshly distilled phenylacetylene (110 µL, 1.0 mmol) in PhMe (1.0 mL). The reaction duration was 14 h. Purification via column chromatography (20:1 hexanes:EtOAc) afforded the title compound (126.0 mg, 64%) as a clear, orange oil. R$_f$ = 0.35 (10:1 hexanes:EtOAc). $^1$H NMR (500 MHz; CDCl$_3$): δ 7.49-7.47 (m, 2H), 7.37-7.33 (m, 3H), 6.50 (s, 1H), 2.81 (qd, $J$ = 7.5, 1.1 Hz, 2H), 2.24 (s, 3H), 1.21 (t, $J$ = 7.5 Hz, 3H). $^{13}$C NMR (125 MHz; CDCl$_3$): 197.8, 143.0, 132.1, 130.2, 129.2, 128.6, 122.5, 94.9, 90.7, 32.1, 26.0, 13.0. IR (film): 2929, 2162, 1658, 1556, 1469, 1422, 1336, 1169, 1128, 1055, 942, 840, 746 cm$^{-1}$. HRMS (ESI+): Calculated for C$_{14}$H$_{15}$O (M+H)$^+$: 199.1117; Found 199.1122.

\[ \text{PhMe}_2	ext{Si} \equiv \text{Et} \backslash \overset{\text{O}}{\text{Me}} \]

(E)-6-(dimethyl(phenyl)silyl)-4-ethylhex-3-en-5-yn-2-one (8ii):

Prepared according to Representative Procedure D using Pd(OAc)$_2$ (11.2 mg, 0.05 mmol, 5 mol %), tris(2,6-dimethoxyphenyl)phosphine (TDMPP, 22.1 mg, 0.05 mmol, 5 mol %), 3-hexyn-2-one (110 µL, 1.0 mmol, 1.0 equivalent), and (dimethylphenylsilyl)acetylene (353 µL, 2.0 mmol, 2.0 equivalents) in PhMe (1.0 mL). The reaction duration was 24 h. Purification via column chromatography (20:1 hexanes:EtOAc) afforded the title compound (183.4 mg, 72%) as a clear, red-brown oil. R$_f$ = 0.38 (10:1 hexanes:EtOAc). $^1$H NMR (400 MHz; CDCl$_3$): δ 7.65-7.62 (m, 2H), 7.42-7.38 (m, 3H), 6.48 (s, 1H), 2.72 (qd, $J$ = 7.5, 1.1 Hz, 2H), 2.21 (s, 3H), 1.16 (t, $J$ = 7.5 Hz, 3H), 0.47 (s, 6H). $^{13}$C NMR (125 MHz; CDCl$_3$): 197.9, 142.3, 136.4, 133.8, 131.2, 129.7, 128.1, 107.4, 98.4, 32.0, 25.7, 12.9, -0.9. IR (film): 3027, 2925, 2113, 1661, 1562, 1440, 1408, 1338, 1233, 1195, 1143, 1100, 1036, 1003, 943, 903,
827, 807, 771 cm$^{-1}$. **HRMS (ESI+):** Calculated for C$_{16}$H$_{21}$OSi (M+H)$^+$: 257.1356; Found 257.1348.

(E)-9-phenyl-5-propynon-4-en-6-yn-3-one (8am):

Prepared according to Representative Procedure D using known acceptor 4-octyn-3-one$^{16}$ (123.7 mg, 1.0 mmol, 2.0 equivalents), 4-phenyl-1-butyne (70 µL, 0.50 mmol, 1.0 equivalents), Pd(OAc)$_2$ (5.6 mg, 0.025 mmol, 5 mol %), and TDMPP (11.0 mg, 0.025 mmol, 5 mol %) in PhMe (0.50 mL). The reaction duration was 24 h. Purification via column chromatography (20:1 hexanes:EtOAc) afforded the title compound (81.2 mg, 64%) as a clear, red-orange oil. $R_f = 0.42$ (10:1 hexanes:EtOAc). $^1$H NMR (600 MHz; CDCl$_3$): $\delta$ 7.32-7.29 (m, 2H), 7.24-7.21 (m, 3H), 6.33 (s, 1H), 2.87 (t, $J = 7.4$ Hz, 2H), 2.67-2.62 (m, 4H), 2.45 (q, $J = 7.3$ Hz, 2H), 1.55-1.50 (m, 2H), 1.07 (t, $J = 7.3$ Hz, 3H), 0.91 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): 200.9, 142.0, 140.4, 129.9, 128.6, 128.5, 126.5, 91.2, 83.4, 37.7, 35.0, 34.7, 21.92, 21.90, 13.9, 8.1. **IR** (film): 2986, 2920, 2183, 1660, 1563, 1475, 1434, 1342, 1104, 1019, 852, 738, 689 cm$^{-1}$; **HRMS (ESI+):** Calculated for C$_{18}$H$_{23}$O (M+H)$^+$: 255.1743; Found 255.1737.

(E)-3-butyl-1-cyclohexyl-7-phenylhept-2-en-4-yn-1-one (8an):

Prepared according to Representative Procedure D using known acceptor 1-cyclohexylhept-2-yn-1-one$^{17}$ (96.2 mg, 0.50 mmol, 1.0 equivalents), 4-phenyl-1-butyne (141 µL, 1.0 mmol, 2.0 equivalents), Pd(OAc)$_2$ (5.6 mg, 0.025 mmol, 5 mol %), and TDMPP (11.1 mg, 0.025 mmol, 5 mol %) in PhMe (0.50 mL). The reaction duration was 24 h. Purification
via column chromatography (30:1 hexanes:Et₂O) afforded the title compound (114.8 mg, 71%) as a clear, red-orange oil. **Rf  = 0.49** (10:1 hexanes:EtOAc). **¹H NMR** (400 MHz; CDCl₃): δ 7.33-7.29 (m, 2H), 7.25-7.21 (m, 3H), 6.37 (s, 1H), 2.87 (t, J = 7.4 Hz, 2H), 2.68-2.61 (m, 4H), 2.33-2.27 (m, 1H), 1.84-1.77 (m, 4H), 1.68-1.65 (m, 1H), 1.48-1.43 (m, 2H), 1.36-1.19 (m, 7H), 0.90 (t, J = 7.3 Hz, 3H). **¹³C NMR** (100 MHz; CDCl₃): 203.6, 142.6, 140.4, 129.4, 128.6, 128.5, 126.5, 95.0, 83.6, 51.9, 35.0, 32.6, 30.8, 28.6, 26.0, 25.9, 22.6, 21.9, 14.1. **IR** (film): 2986, 2888, 2816, 2184, 1653, 1560, 1475, 1431, 1354, 1232, 1128, 1052, 1016, 849, 737, 689 cm⁻¹. **HRMS** (ESI+): Calculated for C₂₃H₃₁O (M+H)⁺: 323.2369; Found 323.2363.

Cu-catalyzed Asymmetric Conjugate Reduction of Ynenones: Representative Procedure E, Synthesis of (S)-4-ethyl-8-phenyloct-5-yn-2-one (9al):

An oven-dried Biotage® microwave vial (0.50 – 2.0 mL size) equipped with a stir bar was charged with Cu(OAc)₂•H₂O (2.0 mg, 0.01 mmol, 5 mol %) and WALPHOS W001-1 ligand (17, 9.3 mg, 0.01 mmol, 5 mol %). The vial was sealed with a septum and flushed with Ar (balloon). Freshly distilled, degassed (Ar sparged) PhMe (0.75 mL) was added, and the mixture was stirred for 20 min to afford a bright green, homogeneous solution. Diethoxymethylsilane (32 µL, 0.20 mmol, 2.0 equivalents) was added, and the mixture was stirred until a change in appearance to homogeneous and brown was observed (ca. 15-30 min). To this solution was added (E)-4-ethyl-8-phenyloct-3-en-5-yn-2-one (45.3 mg, 0.20 mmol, 1 equivalent) as a solution in PhMe (200 µL + 50 µL rinse, prepared in a flame-dried ½-dram vial). The reaction was monitored by TLC (10:1 hexanes:EтOAc) for consumption of substrate and formation of its higher-R₇ silyl enol ether. After 15 min, TBAF (1 M in THF, 0.70 mL, 0.70 mmol, 3.5 equivalents) was added, resulting in vigorous gas evolution. The deep red solution was stirred for 15 min, at which point TLC analysis (10:1 hexanes:EтOAc) indicated complete consumption of both the silyl enol ether and the starting material and the
formation of the conjugate reduction product. The reaction mixture was directly loaded onto a silica gel column that was eluted with 10:1 hexanes:EtOAc to afford the title compound (38.3 mg, 84%, 99% ee) as a clear, faintly yellow oil. \( R_f = 0.19 \) (10:1 hexanes:EtOAc). **\(^1\)H NMR** (400 MHz; CDCl\(_3\)): \( \delta \) 7.30-7.27 (m, 2H), 7.22-7.18 (m, 3H), 2.76-2.72 (m, 1H), 2.57 (dd, \( J = 16.0, 8.0 \) Hz, 1H), 2.47-2.42 (m, 3H), 2.13 (s, 3H), 1.53-1.30 (m, 2H), 0.95 (t, \( J = 7.4 \) Hz, 3H). **\(^{13}\)C NMR** (100 MHz; CDCl\(_3\)): 207.4, 141.0, 128.6, 128.4, 126.3, 82.9, 81.2, 49.1, 35.6, 30.6, 29.0, 28.2, 21.0, 11.7. **IR** (film): 2922, 2886, 2835, 1695, 1434, 1411, 1341, 1146, 1062, 739, 689 cm\(^{-1}\). **HRMS** (ESI+): Calculated for C\(_{16}\)H\(_{21}\)O (M+H): 229.1587; Found 229.1591. **Chiral HPLC**: Agilent IA, 500:1 heptane:isopropanol, 0.5 mL/min, 220 nm, 22.93 min (major), 24.51 min (minor). \([\alpha]_D^{25} = + 3.4^\circ \) (c = 0.50, CHCl\(_3\)).

![Chemical Structure](image)

**(S)-4-ethyl-6-phenylhex-5-yn-2-one (9bl):**

Prepared according to Representative Procedure E using Cu(OAc)\(_2\)•H\(_2\)O (2.0 mg, 0.01 mmol, 5 mol %), WALPHOS ligand 17 (9.3 mg, 0.01 mmol, 5 mol %), (E)-4-ethyl-6-phenylhex-3-en-5-yn-2-one (39.6 mg, 0.20 mmol), and diethoxymethylsilane (32 \( \mu \)L, 0.20 mmol, 2.0 equivalents) in PhMe (0.75 mL for the catalyst solution and 0.25 mL total to transfer the substrate, including the rinse). The reaction duration was 15 min. Purification via column chromatography (10:1 hexanes:EtOAc) afforded the title compound (30.5 mg, 76%, 99% ee) as a viscous yellow oil. \( R_f = 0.19 \) (10:1 hexanes:EtOAc). **\(^1\)H NMR** (400 MHz; CDCl\(_3\)): \( \delta \) 7.37-7.35 (m, 2H), 7.27-7.24 (m, 3H), 3.04-2.97 (m, 1H), 2.74 (dd, \( J = 16.3, 7.6 \) Hz, 1H), 2.58 (dd, \( J = 16.3, 6.5 \) Hz, 1H), 2.20 (s, 3H), 1.64-1.41 (m, 2H), 1.06 (t, \( J = 7.4 \) Hz, 3H). **\(^{13}\)C NMR** (100 MHz; CDCl\(_3\)): 207.0, 131.7, 128.3, 127.8, 123.7, 91.9, 82.2, 48.7, 30.7, 29.5, 28.1, 11.8. **IR** (film): 2924, 2888, 2835, 1694, 1575, 1469, 1422, 1341, 1226, 1146, 1055, 747, 683 cm\(^{-1}\). **HRMS** (ESI+): Calculated for C\(_{14}\)H\(_{17}\)O (M+H): 201.1274; Found 201.1276. **Chiral HPLC**: Agilent IA, 500:1 heptane:isopropanol, 0.8 mL/min, 214 nm, 12.58 min (major), 14.60 min (minor) \([\alpha]_D^{25} = + 10.3^\circ \) (c = 0.50, CHCl\(_3\)).
(S)-6-(dimethyl(phenyl)silyl)-4-ethylhex-5-yn-2-one (9ii):  

Prepared using a modification of Representative Procedure E. An oven-dried Biotage® microwave vial (0.50 – 2.0 mL size) equipped with a stir bar was charged with Cu(OAc)$_2$•H$_2$O (2.0 mg, 0.01 mmol, 5 mol %) and WALPHOS ligand 17 (9.3 mg, 0.01 mmol, 5 mol %). The vial was sealed with a septum and flushed with Ar (balloon). Freshly distilled, degassed (Ar sparged) PhMe (1.0 mL) was added, and the mixture was stirred for 20 min to afford a bright green, homogeneous solution. Diethoxymethylsilane (32 µL, 0.20 mmol, 2.0 equivalents) was added, and the mixture was stirred until a change in appearance to homogeneous and brown was observed (ca. 15-30 min). The vessel was then cooled to 0 °C, and substrate (E)-6-(dimethyl(phenyl)silyl)-4-ethylhex-3-en-5-yn-2-one (51.2 mg, 0.20 mmol) was added neat. The reaction mixture was stirred for 2 h, and then it was treated with 1% methanolic HCl (1.0 mL). After 10 min, the reaction mixture was loaded directly onto a silica gel column. Elution with 20:1 to 10:1 hexanes:EtOAc afforded the title compound (34.4 mg, 67%, 99% ee) as a viscous, clear, light yellow oil. $R_f = 0.22$ (10:1 hexanes:EtOAc). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.63-7.60 (m, 2H), 7.40-7.34 (m, 3H), 2.92-2.85 (m, 1H), 2.70 (dd, $J = 16.2, 7.3$ Hz, 1H), 2.54 (dd, $J = 16.2, 6.7$ Hz, 1H), 2.18 (s, 3H), 1.61-1.39 (m, 2H), 1.03 (t, $J = 7.4$ Hz, 3H), 0.38 (s, 6H). $^{13}$C NMR (100 MHz; CDCl$_3$): 206.9, 137.6, 133.8, 129.4, 127.9, 111.0, 83.9, 48.5, 30.8, 29.9, 27.8, 11.7, -0.5. IR (film): 3026, 2923, 2890, 2836, 2138, 1969, 1440, 1408, 1341, 1232, 1145, 1100, 824, 769 cm$^{-1}$. HRMS (ESI+): Calculated for C$_{16}$H$_{23}$O$_3$Si (M+H)$^+$: 259.1513; Found 259.1506. Chiral HPLC: Agilent IA, 1000:1 heptane:isopropanol, 0.8 mL/min, 220 nm, 12.04 min (major), 13.55 min (minor). $[\alpha]_D^{25} = +4.1^\circ$ (c = 0.50, CHCl$_3$).
(S)-9-phenyl-5-propynon-6-yn-3-one (9am):

Prepared according to Representative Procedure E using Cu(OAc)$_2$•H$_2$O (2.0 mg, 0.01 mmol, 5 mol %), WALPHOS ligand 17 (9.3 mg, 0.01 mmol, 5 mol %), (E)-9-phenyl-5-propynon-4-en-6-yn-3-one (50.8 mg, 0.20 mmol), and diethoxymethylsilane (32 µL, 0.20 mmol, 2.0 equivalents) in PhMe (0.75 mL for the catalyst solution and 0.25 mL total to transfer the substrate, including the rinse). The reaction duration was 2 h. Purification via column chromatography (20:1 hexanes:EtOAc) afforded the title compound (37.0 mg, 72%, 98% ee) as a clear, viscous, light yellow oil. $R_f = 0.31$ (10:1 hexanes:EtOAc). $^1$H NMR (400 MHz; CDCl$_3$): δ 7.30-7.26 (m, 2H), 7.22-7.19 (m, 3H), 2.86-2.80 (m, 1H), 2.77 (t, $J = 7.5$ Hz, 2H), 2.55 (dd, $J = 15.8$, 7.9 Hz, 1H), 2.45-2.38 (m, 5H), 1.49-1.29 (m, 4H), 1.04 (t, $J = 7.3$ Hz, 3H), 0.89 (t, $J = 6.9$ Hz, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): 210.0, 141.0, 128.6, 128.4, 126.3, 83.2, 80.9, 48.2, 37.4, 36.7, 35.6, 27.3, 21.0, 20.5, 14.0, 7.8. IR (film): 2985, 2916, 2890, 2832, 1692, 1475, 1434, 1391, 1342, 1101, 1061, 1016, 736 cm$^{-1}$. HRMS (ESI+): Calculated for C$_{18}$H$_{25}$O (M+H)$^+$: 257.1900; Found 257.1894. Chiral HPLC: CHIRALPAK® AD-H, 200:1 heptane:isopropanol, 0.8 mL/min, 214 nm, 15.23 min (major), 18.15 min (minor). $[\alpha]_D^{25} = +2.0^\circ$ ($c = 0.50$, CHCl$_3$).

(S)-3-butyl-1-cyclohexyl-7-phenylhept-4-yn-1-one (9an):

Prepared according to Representative Procedure E using Cu(OAc)$_2$•H$_2$O (2.0 mg, 0.01 mmol, 5 mol %), WALPHOS ligand 17 (9.3 mg, 0.01 mmol, 5 mol %), (E)-3-butyl-1-cyclohexyl-7-phenylhept-2-en-4-yn-1-one (64.5 mg, 0.20 mmol), and diethoxymethylsilane (32 µL, 0.20 mmol, 2.0 equivalents) in PhMe (0.75 mL for the catalyst solution and 0.25 mL total to transfer the substrate, including the rinse). The reaction duration was 1 h 30 min. Purification via column chromatography (10:1 to 6:1 hexanes:EtOAc) afforded impure product, which was repurified via column chromatography (20:1 hexanes:Et$_2$O) to deliver the
title compound (analytically pure, 32.7 mg, 50%, 99% ee) as a viscous yellow oil. \( R_f = 0.37 \) (10:1 hexanes:EtOAc). \(^1\)H NMR (300 MHz; CDCl\(_3\)): \( \delta \) 7.31-7.27 (m, 2H), 7.22-7.17 (m, 3H), 2.87-2.75 (m, 3H), 2.61 (dd, \( J = 16.4, 7.3 \) Hz, 1H), 2.46-2.39 (m, 3H), 2.36-2.28 (m, 1H), 1.84-1.75 (m, 4H), 1.68-1.64 (m, 1H), 1.40-1.20 (m, 11H), 0.89 (t, \( J = 7.1 \) Hz, 3H). \(^{13}\)C NMR (75 MHz; CDCl\(_3\)): 212.4, 141.1, 128.6, 128.4, 126.3, 83.6, 80.6, 51.2, 46.6, 35.6, 34.9, 29.6, 28.4, 28.3, 27.1, 26.0, 25.81, 25.79, 22.6, 21.1, 14.2. IR (film): 3019, 2985, 2888, 2815, 1686, 1581, 1475, 1355, 1128, 1062, 1016, 880, 737, 689 cm\(^{-1}\). HRMS (ESI+): Calculated for C\(_{23}\)H\(_{33}\)O (M+H): 325.2526; Found 325.2517. Chiral HPLC: Agilent IB, 400:1 heptane:isopropanol, 0.8 mL/min, 214 nm, 13.40 min (major), 15.85 min (minor). \([\alpha]D^{25} = -6.0^\circ \) (c = 0.50, CHCl\(_3\)).

\[\text{C}_6\text{H}_{13} \overset{\text{SO}_2\text{Ph}}{\longrightarrow}\]

(Oct-1-yn-1-ylsulfonyl)benzene (7o):

The procedure was adapted from the literature.\(^{18}\) To a –78 °C solution of 1-octyne (0.44 mL, 3 mmol, 1 equivalent) in THF (6 mL) was added \( n \)-BuLi (2.5 M in hexanes, 1.26 mL, 3.15 mmol, 1.05 equivalents). The reaction mixture was stirred for 30 min, and then a solution of diphenyl disulfide (688 mg, 3.15 mmol, 1.05 equivalents) in THF (6.3 mL) was added \textit{via} cannula. The cooling bath was removed, and the mixture was stirred at room temperature for 1 h, after which time it was again cooled to –78 °C and a solution of 2-nitrobenzyl bromide (713 mg, 3.3 mmol, 1.1 equivalents) in THF (6.6 mL) was added \textit{via} cannula to consume phenylthiolate. After 5 min, the cooling bath was removed, and the mixture was stirred at room temperature for 1 h 30 min. The now bright red solution was quenched with saturated NH\(_4\)Cl (20 mL), and the mixture was poured into Et\(_2\)O (20 mL). The phases were separated, and the aqueous phase was extracted with Et\(_2\)O (3 x 20 mL). The pooled organic phases were dried over MgSO\(_4\), filtered, and concentrated. Purification \textit{via} column chromatography (20:1 hexanes:EtOAc) afforded the intermediate alkynyl sulfide (585 mg, 89%, \textit{ca.} 90% purity judged by \(^1\)H NMR) as a clear, colorless oil. \(^1\)H NMR (400 MHz;
CDCl₃): δ 7.42-7.40 (m, 2H), 7.34-7.29 (m, 2H), 7.21-7.17 (m, 1H), 2.45 (t, J = 7.1 Hz, 2H), 1.64-1.28 (m, 8H), 0.90 (t, J = 7.0 Hz, 3H).

To a 0 °C solution of this intermediate (575 mg, 2.6 mmol, 1 equivalent) in CH₂Cl₂ (6.5 mL) was added, dropwise, a freshly prepared solution of m-CPBA (77% purity, 1.0 g, 5.8 mmol, 2.2 equivalents) in CH₂Cl₂ (14.5 mL). During the addition, the homogeneous, clear solution became milky white. After 5 min, the cooling bath was removed, and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was then poured into Et₂O (50 mL) and washed with saturated aqueous NaHCO₃ (3 x 50 mL). The organic phase was dried over MgSO₄, filtered, and concentrated. Purification via column chromatography (8:1 hexanes:EtOAc) afforded the title compound (496 mg, 75%) as a clear, colorless oil. Rf = 0.50 (2:1 hexanes:EtOAc). ¹H NMR (400 MHz; CDCl₃): δ 8.01-7.99 (m, 2H), 7.68-7.64 (m, 1H), 7.59-7.55 (m, 2H), 2.36 (t, J = 7.2 Hz, 2H), 1.58-1.51 (m, 2H), 1.36-1.20 (m, 6H), 0.86 (t, J = 6.9 Hz, 3H). ¹³C NMR (100 MHz; CDCl₃): 142.2, 134.0, 129.4, 127.3, 98.1, 78.3, 31.2, 28.5, 27.0, 22.5, 19.1, 14.1. IR (film): 2888, 2818, 2170, 1427, 1311, 1147, 1075, 747, 718, 677, 627, 567 cm⁻¹. HRMS (ESI+): Calculated for C₁₄H₁₉O₂S (M+H): 251.1100; Found 251.1096.

Pd-catalyzed Alkyne-Alkyne Coupling with Sulfone Acceptors: Representative Procedure F, Synthesis of (E)-((2-(phenylethynyl)oct-1-en-1-yl)sulfonyl)benzene (8bo):

A 2-dram, screw-cap vial equipped with a stir bar was charged with Pd(OAc)₂ (3.4 mg, 0.015 mmol, 3 mol %) and tris-2,6-dimethoxyphenylphosphine (6.3 mg, 0.015 mmol, 3 mol %). PhMe (0.50 mL) was added, and the mixture was stirred for 15 minutes, generating a homogeneous, orange-red solution. To the solution was added (oct-1-yn-1-ylsulfonyl)benzene (125.1 mg, 0.50 mmol, 1 equivalent) followed by freshly distilled phenylacetylene (69 µL, 0.625 mmol, 1.25 equivalents). The vial was capped, and the reaction mixture was stirred for
18 h. After this time, the reaction mixture was filtered through a pipette plug of Florisil® (3 cm), which was rinsed with Et₂O (10 mL). The solution was concentrated, and the residue was purified via column chromatography (8:1 to 4:1 hexanes:EtOAc) to afford the title compound (169.4 mg, 96%) as a viscous, brown oil. \( R_f = 0.50 \) (2:1 hexanes:EtOAc). \(^1\)H NMR (400 MHz; CDCl₃): \( \delta \) 7.96-7.94 (m, 2H), 7.66-7.62 (m, 1H), 7.58-7.55 (m, 2H), 7.44-7.42 (m, 2H), 7.37-7.32 (m, 3H), 6.62 (t, \( J = 0.9 \) Hz, 1H), 2.79-2.75 (m, 2H), 1.63-1.55 (m, 2H), 1.36-1.27 (m, 6H), 0.89 (t, \( J = 6.9 \) Hz, 3H). \(^{13}\)C NMR (100 MHz; CDCl₃): 142.0, 141.1, 133.6, 133.5, 132.1, 129.6, 129.4, 128.6, 127.5, 121.8, 96.7, 88.0, 31.8, 31.7, 29.0, 28.4, 22.7, 14.2. IR (film): 3364, 2914, 2887, 2817, 2164, 1575, 1550, 1468, 1437, 1425, 1300, 1134, 1070, 1055, 1011, 985, 803, 745 cm\(^{-1}\). HRMS (ESI+): Calculated for C\(_{22}\)H\(_{25}\)O\(_2\)S (M+H): 353.1570; Found 353.1564.

\((E)-((2-(4-phenylbut-1-yn-1-yl)oct-1-en-1-yl)sulfonyl)benzene (8ao):\)

Prepared according to Representative Procedure F using Pd(OAc)\(_2\) (3.4 mg, 0.015 mmol, 3 mol %), tris-2,6-dimethoxyphenylphosphine (6.3 mg, 0.015 mmol, 3 mol %), (oct-1-yn-1-yl)sulfonyl)benzene (125.1 mg, 0.50 mmol), and 4-phenyl-1-butyn (88 µL, 0.625 mmol) in PhMe (0.50 mL). The reaction duration was 17 h. Purification via column chromatography (8:1 to 4:1 hexanes:EtOAc) afforded the title compound (190.4 mg, > 99% yield) as a viscous oil. \( R_f = 0.50 \) (2:1 hexanes:EtOAc). \(^1\)H NMR (400 MHz; CDCl₃): \( \delta \) 7.91-7.89 (m, 2H), 7.63-7.59 (m, 1H), 7.56-7.52 (m, 2H), 7.31-7.17 (m, 5H), 6.42 (s, 1H), 2.83 (t, \( J = 7.3 \) Hz, 2H), 2.65-2.58 (m, 4H), 1.43-1.38 (m, 2H), 1.30-1.22 (m, 6H), 0.89 (t, \( J = 6.9 \) Hz, 3H). \(^{13}\)C NMR (100 MHz; CDCl₃): 142.1, 141.9, 140.0, 133.4, 133.0, 129.3, 128.6, 128.5, 127.4, 126.6, 97.9, 80.6, 34.6, 32.0, 31.7, 29.0, 28.2, 22.7, 21.8, 14.2. IR (film): 2888, 2818, 2186, 1555, 1426, 1289, 1131, 1070, 806, 740 cm\(^{-1}\). HRMS (ESI+): Calculated for C\(_{24}\)H\(_{29}\)O\(_2\)S (M+H): 381.1883; Found 381.1878.
(E)-dimethyl(phenyl)(3-((phenylsulfonyl)methylene)non-1-yn-1-yl)ilane (8io):

Prepared according to Representative Procedure F using Pd(OAc)$_2$ (3.4 mg, 0.015 mmol, 3 mol %), tris-2,6-dimethoxyphenylphosphine (6.3 mg, 0.015 mmol, 3 mol %), (oct-1-yn-1-ylsulfonyl)benzene (125.1 mg, 0.50 mmol), and (dimethylphenylsilyl)acetylene (111 µL, 0.625 mmol) in PhMe (0.50 mL). The reaction duration was 22 h. Purification via column chromatography (8:1 hexanes:EtOAc) afforded the title compound (180.2 mg, 88% yield) as a viscous, golden yellow oil. $R_f = 0.53$ (2:1 hexanes:EtOAc). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.93-7.90 (m, 2H), 7.65-7.61 (m, 1H), 7.59-7.53 (m, 4H), 7.40-7.35 (m, 3H), 6.58 (t, $J = 1.0$ Hz, 1H), 2.72-2.68 (m, 2H), 1.58-1.50 (m, 2H), 1.32-1.24 (m, 6H), 0.88 (t, $J = 6.9$ Hz, 3H), 0.43 (s, 6H). $^{13}$C NMR (100 MHz; CDCl$_3$): 141.7, 140.4, 135.9, 134.9, 133.7, 133.6, 129.9, 129.4, 128.2, 127.6, 104.3, 101.0, 31.7, 21.5, 28.9, 28.2, 22.6, 14.2, -1.1. IR (film): 3026, 2916, 2888, 2818, 2116, 1555, 1426, 1408, 1359, 1289, 1233, 1134, 1101, 1070, 1010, 985, 873, 826, 803 cm$^{-1}$. HRMS (ESI+): Calculated for C$_{24}$H$_{31}$O$_2$SSi (M+H)$^+$: 411.1809; Found 411.1802.

Cu-catalyzed Asymmetric Conjugate Reduction of Enynyl Sulfones: Representative Procedure G, Synthesis of (R)-((2-(phenylethynyl)octyl)sulfonyl)benzene (9bo):

An oven-dried Biotage® microwave vial (0.50 – 2.0 mL size) equipped with a stir bar was charged with Cu(OAc)$_2$•H$_2$O (1.0 mg, 0.005 mmol, 5 mol %) and WALPHOS W001-1 ligand (17, 4.6 mg, 0.005 mmol, 5 mol %). The vial was sealed with a septum and flushed with Ar (balloon). Freshly distilled, degassed (Ar sparged) PhMe (0.25 mL) was added, and the mixture was stirred for 20 min to afford a bright green, homogeneous solution.
Diethoxymethylsilane (32 µL, 0.20 mmol, 2.0 equivalents) was added, and the mixture was stirred until a change in appearance to homogeneous and brown was observed (ca. 15-30 min). Substrate (E)-((2-(phenylethynyl)oct-1-en-1-yl)sulfonyl)benzene (35.2 mg, 0.10 mmol, 1 equivalent) was added as a solution in PhMe (200 µL + 50 µL rinse, prepared in a ½-dram vial that was not dried). Water (9 µL, 0.50 mmol, 5 equivalents) was added, and the vessel was heated to 50 °C and stirred under an Ar balloon. After 4 h, the vessel was cooled to room temperature and the reaction mixture was directly loaded onto a silica gel column. Elution with 8:1 to 4:1 hexane:EtOAc afforded the title compound (28.9 mg, 82%, 98% ee) as a viscous, light yellow oil. \( R_f = 0.52 \) (2:1 hexanes:EtAc). \(^1H\) NMR (500 MHz; CDCl\(_3\)): \( \delta \) 7.98-7.96 (m, 2H), 7.59-7.50 (m, 3H), 7.25-7.16 (m, 5H), 3.45 (dd, \( J = 14.3, 8.0 \) Hz, 1H), 3.27 (dd, \( J = 14.3, 5.1 \) Hz, 1H), 3.21-3.15 (m, 1H), 1.74-1.69 (m, 1H), 1.64-1.56 (m, 1H), 1.53-1.42 (m, 2H), 1.34-1.23 (m, 6H), 0.88 (t, \( J = 7.0 \) Hz, 3H). \(^{13}C\) NMR (100 MHz; CDCl\(_3\)): 139.7, 133.8, 131.7, 129.3, 128.5, 128.2, 128.1, 123.0, 89.3, 83.6, 60.8, 35.1, 31.8, 28.9, 27.9, 26.9, 22.7, 14.2. IR (film): 3019, 2887, 2817, 1576, 1469, 1426, 1289, 1128, 1070, 1011, 846, 745 cm\(^{-1}\). HRMS (ESI+): Calculated for C\(_{22}\)H\(_{27}\)O\(_2\)S (M+H): 355.1726; Found 355.1721.

**Chiral HPLC:** Agilent IB, 98:2 heptane:isopropanol, 0.6 mL/min, 254 nm, 21.06 min (major), 23.37 min (minor). \([\alpha]D^{25} = +27.4^\circ \) (c = 0.50, CHCl\(_3\))

\((R)-((2-(4-phenylbut-1-yn-1-yl)octyl)sulfonyl)benzene (9ao):

Prepared according to Representative Procedure G using Cu(OAc)\(_2\)•H\(_2\)O (1.0 mg, 0.005 mmol, 5 mol %), WALPHOS ligand 17 (4.6 mg, 0.005 mmol, 5 mol %), (E)-((2-(4-phenylbut-1-yn-1-yl)oct-1-en-1-yl)sulfonyl)benzene (37.9 mg, 0.10 mmol), diethoxymethylsilane (32 µL, 0.20 mmol, 2.0 equivalents), and water (9 µL, 0.50 mmol, 5 equivalents) in PhMe (0.25 mL for the catalyst solution and 0.25 mL total to transfer the substrate, including the rinse). The reaction duration was 2 h 30 min. Purification via column chromatography (6:1 to 4:1 hexanes:Et\(_2\)O) afforded the title compound (28.3 mg, 74%, 99%)
ee) as a viscous, clear, light yellow oil. \( R_f = 0.55 \) (2:1 hexanes:EtOAc). \(^1\)H NMR (400 MHz; CDCl\(_3\)): \( \delta \) 7.92-7.90 (m, 2H), 7.65-7.61 (m, 1H), 7.56-7.50 (m, 2H), 7.29-7.25 (m, 2H), 7.21-7.17 (m, 1H), 7.15-7.12 (m, 2H), 3.28 (dd, \( J = 14.3, 8.0 \) Hz, 1H), 3.13 (dd, \( J = 14.3, 5.1 \) Hz, 1H), 2.93-2.83 (m, 1H), 2.62 (t, \( J = 7.5 \) Hz, 2H), 2.22-2.17 (m, 2H), 1.60-1.53 (m, 1H), 1.41-1.19 (m, 9H), 0.88 (t, \( J = 7.0 \) Hz, 3H). \(^{13}\)C NMR (100 MHz; CDCl\(_3\)): 140.8, 139.8, 133.7, 129.2, 128.54, 128.49, 128.40, 126.4, 82.9, 80.6, 61.0, 35.2, 35.1, 31.8, 28.9, 27.2, 26.7, 22.7, 20.9, 14.2. IR (film): 3020, 2985, 2886, 2817, 1475, 1427, 1302, 1289, 1132, 1070, 774, 737 cm\(^{-1}\). HRMS (ESI+): Calculated for C\(_{24}\)H\(_{31}\)O\(_2\)S (M+H): 383.2039; Found 383.2036. Chiral HPLC: Agilent IB, 98:2 heptane:isopropanol, 0.8 mL/min, 220 nm, 18.92 min (major), 21.28 min (minor). \([\alpha]_D^{25} = +19.6^\circ \) (c = 0.50, CHCl\(_3\)).

(R)-dimethyl(phenyl)(3-((phenylsulfonyl)methyl)non-1-yn-1-yl)silane (9io):

Prepared according to Representative Procedure G using Cu(OAc)$_2$•H$_2$O (1.0 mg, 0.005 mmol, 5 mol %), WALPHOS ligand 17 (4.6 mg, 0.005 mmol, 5 mol %), (E)-dimethyl(phenyl)(3-((phenylsulfonyl)methylene)non-1-yn-1-yl)silane (41.1 mg, 0.10 mmol), diethoxymethylsilane (32 µL, 0.20 mmol, 2.0 equivalents), and water (9 µL, 0.50 mmol, 5 equivalents) in PhMe (0.25 mL for the catalyst solution and 0.25 mL total to transfer the substrate, including the rinse). The reaction duration was 6 h. Purification via column chromatography (6:1 to 4:1 hexanes:Et\(_2\)O) afforded the title compound (37.6 mg, 91%, 99% ee) as a viscous, clear, light yellow oil. \( R_f = 0.58 \) (2:1 hexanes:EtOAc). \(^1\)H NMR (400 MHz; CDCl\(_3\)): \( \delta \) 7.93-7.91 (m, 2H), 7.62-7.57 (m, 1H), 7.53-7.47 (m, 4H), 7.40-7.33 (m, 3H), 3.40 (dd, \( J = 14.3, 7.1 \) Hz, 1H), 3.20 (dd, \( J = 14.3, 5.8 \) Hz, 1H), 3.07-3.00 (m, 1H), 1.69 (s, 1H), 1.59-1.45 (m, 2H), 1.41-1.23 (m, 7H), 0.88 (t, \( J = 6.9 \) Hz, 3H), 0.28 (s, 3H), 0.28 (s, 3H). \(^{13}\)C NMR (100 MHz; CDCl\(_3\)): 139.6, 137.1, 133.9, 133.8, 129.5, 129.3, 128.4, 127.9, 107.8, 85.7, 60.6, 34.9, 31.7, 28.8, 28.2, 26.7, 22.7, 14.2, -0.67, -0.70. IR (film): 2887, 2818, 2141, 1427, 1408, 1303, 1232, 1129, 1100, 1071, 824, 805, 770, 723, 691, 654 cm\(^{-1}\) HRMS (ESI+):
Calculated for C_{24}H_{33}O_{2}SSi \,(M+H)^{+}: 413.1965; Found 413.1959. **Chiral HPLC**: Agilent IB, 99:1 heptane:isopropanol, 0.8 mL/min, 220 nm, 15.27 min (major), 16.25 min (minor). $[\alpha]_{D}^{25} = + 25.0^\circ \,(c = 0.50, \text{CHCl}_3)$.

![Chemical Structure](image)

methyl (S)-3-(hydroxymethyl)-7-phenylhept-4-ynoate (33):

An oven-dried Biotage® microwave vial (0.5 – 2.0 mL size) was equipped with a stir bar, sealed with a septum, purged with nitrogen, and kept under a nitrogen atmosphere. A solution of methyl (S)-3-(((methoxycarbonyl)oxy)methyl)-7-phenylhept-4-ynoate (30.0 mg, 0.099 mmol, 1.0 equivalent) in freshly-distilled methanol (1.0 mL) was added *via* syringe. Anhydrous potassium carbonate (1.6 mg, 0.012 mmol, 0.12 equivalent) was added under nitrogen, and the reaction mixture was stirred for 3 h at room temperature. The reaction mixture was quenched with pH 7 phosphate buffer (1 mL), stirred for 10 min, and diluted with EtOAc (2 mL). The phases were separated, and the aqueous phase was extracted three times with EtOAc (3 x 2 mL). The organic phases were combined, washed with water, dried with sodium sulfate, and concentrated *in vacuo*. The crude product was purified *via* column chromatography (2:1 hexanes:EtOAc) to afford the title compound as a clear oil (15.7 mg, 65%). The corresponding lactone (*vide infra*) was also isolated (5.1 mg, 24%). $R_f = 0.17 \,(4:1$ hexanes:EtOAc). $^1H\text{ NMR}$ (400 MHz, CDCl$_3$) $\delta$ 7.32-7.28 (m, 2H), 7.24-7.20 (m, 3H), 3.69 (s, 3H), 3.61-3.50 (m, 2H), 3.04-2.98 (m, 1H), 2.79 (t, $J = 7.3$ Hz, 2H), 2.57-2.45 (m, 4H), 1.74 (br s, 1H). $^{13}C\text{ NMR}$ (125 MHz, CDCl$_3$) $\delta$ 172.3, 140.7, 128.6, 128.5, 126.5, 83.2, 79.8, 65.0, 52.0, 36.5, 35.2, 31.7, 21.0. $\text{IR}$ (film): 3446, 3027, 2950, 1737, 1454, 1437, 1361, 1259, 1211, 1165, 1059, 700 cm$^{-1}$. $\text{HRMS}$: Calculated for C$_{15}$H$_{18}$O$_3$Na \,(M+Na)$^{+}$: 269.1154; Found 269.1154. $[\alpha]_{D}^{25} = + 21.54^\circ \,(c = 0.52; \text{CH}_2\text{Cl}_2)$

S64
(S)-4-(4-phenylbut-1-yn-1-yl)dihydrofuran-2(3H)-one (34):

Methyl (S)-3-(((methoxycarbonyl)oxy)methyl)-7-phenylhept-4-ynoate (30.0 mg, 0.099 mmol, 1.0 equivalent) was hydrolyzed as described above. The crude material was transferred to a separate oven-dried Biotage® microwave vial (0.5 – 2.0 mL size) equipped with a stir bar, to which was added 1,1,3,3-tetrabutyl-1,3-diisothiocyanatodistannoxane (Otera’s catalyst$^{19}$) (11.8 mg, 0.0099 mmol, 0.10 equivalent). The vial was sealed with a septum and purged with nitrogen. PhMe (0.5 mL) was added via syringe, and the vial was sealed and heated to 85 °C for 2 h 30 min. The vial was cooled to room temperature, and the solvent was removed in vacuo. The crude product was purified via column chromatography (4:1 hexanes:EtOAc) to afford the title compound as a clear oil (16.5 mg, 0.077 mmol, 78% yield). $R_f = 0.41$ (2:1 hexanes:EtOAc). $^1H$ NMR (400 MHz, CDCl$_3$) δ 7.31-7.27 (m, 2H), 7.23-7.17 (m, 3H), 4.43-4.39 (dd, $J = 8.7$ Hz, 7.6 Hz, 1H), 4.10-4.06 (dd, $J = 8.7$ Hz, 7.5 Hz, 1H), 3.34-3.25 (m, 1H), 2.79 (t, $J = 7.5$ Hz, 2H), 2.74-2.68 (dd, $J = 17.3$ Hz, 8.5 Hz, 1H), 2.52-2.43 (m, 3H). $^{13}C$ NMR (125 MHz, CDCl$_3$): δ 175.6, 140.4, 128.6, 128.5, 126.5, 83.4, 78.3, 72.7, 35.4, 35.0, 27.5, 20.9. IR (film): 3062, 3027, 2917, 1786, 1170, 1026, 700 cm$^{-1}$. HRMS: Calculated for C$_{14}$H$_{14}$O$_2$Na (M+Na)$^+$: 237.0891; Found 237.0887. [α]$_D^{25}$ = + 26.56$^o$ (c = 0.845; CH$_2$Cl$_2$)

methyl 2-((3R)-5-ethoxy-5-phenyltetrahydrofuran-3-yl)acetate (35):

This procedure was adapted from the literature.$^{20}$ A flame-dried Biotage® microwave vial (0.5 – 2.0 mL size) equipped with a stir bar was charged with AuCl (2.2 mg, 9.5 µmol,
0.10 equivalent) and pyridinium \( p \)-toluenesulfonate (2.3 mg, 9.2 \( \mu \)mol, 0.10 equivalent). The reaction vessel was sealed with a rubber septum and evacuated and backfilled with argon (3 x cycle). To these solids was then added EtOH (200 \( \mu \)L) to afford a homogeneous, light yellow reaction mixture which was then cooled to 0 °C. To this solution was then added methyl (\( S \))-3-(hydroxymethyl)-7-phenylhept-4-ynoate (24.0 mg, 0.09 mmol, 1.0 equivalent, prepared as described above) as a solution in EtOH (500 \( \mu \)L, followed by a 200 \( \mu \)L rinse). The resulting mixture was then stirred at 0 °C for 30 min, diluted with EtOAc (5 mL), and then poured into a separatory funnel containing a saturated aqueous solution of NaHCO\(_3\) (3 mL). The phases were separated, and the organic phase was washed with additional NaHCO\(_3\) (3 x 5 mL) and brine (3 x 5 mL). The organic phase was dried over Na\(_2\)SO\(_4\), filtered, and concentrated in vacuo. The resulting residue was purified by chromatography over basic alumina (10:1 hexanes:EtOAc) to afford the title compound as a 1:1 mixture of diastereomers and as a colorless oil (14.2 mg, 0.05 mmol, 50% yield). \( \text{Rf} = 0.60 \) (2:1 hexanes:EtOAc). \( ^1\text{H NMR} \) (500 MHz, CDCl\(_3\)) \( \delta \) 7.19-7.07 (m, 5H), 4.09 (dd, \( J = 8.0, 8.0 \) Hz, 1H), 4.08 (dd, \( J = 8.0, 8.0 \) Hz, 1H), 3.57-3.44 (m, 4 H), 3.35-3.27 (m, 8H), 2.92-2.82 (m, 1H), 2.74-2.47 (m, 5H), 2.41-2.15 (m, 5H), 2.09-2.00 (m, 2H), 1.90-1.81 (m, 3H), 1.66 (dd, \( J = 5.0, 15.0 \) Hz, 1H), 1.22 (dd, \( J = 10.5, 12.5 \) Hz, 1H), 1.13-1.07 (m, 6H). \( ^{13}\text{C NMR} \) (125 MHz, C\(_6\)D\(_6\)): \( \delta \) 172.5, 172.1, 142.33, 142.31, 128.6, 128.5, 126.0, 109.4, 109.2, 72.3, 55.8, 55.6, 50.9, 50.9, 42.7, 42.3, 38.6, 38.3, 37.4, 37.1, 34.8, 34.6, 31.5, 31.4, 15.9, 15.9. \( \text{IR} \) (film): 2952, 1739, 1438, 1261, 1175, 1068 cm\(^{-1}\). \( \text{HRMS} \): Calculated for C\(_{17}\)H\(_{24}\)O\(_4\)Na (M+Na): 315.1572; Found 315.1583. \([\alpha]_D^{24} = -4.7^\circ \) (\( c = 1.00, \text{CH}_2\text{Cl}_2 \)).

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\begin{align*}
\text{tert-butyl (R)-2-oxo-4-(phenylethynyl)pyrrolidine-1-carboxylate (36):}
\end{align*}
\]

An oven-dried Biotage® microwave vial (0.5 – 2.0 mL size) equipped with a stir bar was charged with methyl (\( R \))-3-(((\text{tert-butoxycarbonyl})amino)methyl)-5-phenylpent-4-ynoate
(40 mg, 0.126 mmol), capped with a rubber septum, and purged with argon. PhMe (2.5 mL) was added via syringe, and the mixture was cooled to −20 °C. A solution of AlMe₃ (0.095 mL, 0.190 mmol, 2.0 M in PhMe) was then added dropwise slowly over 10 min. The reaction was stirred at −20 °C for 2 h, and then it was quenched with saturated aqueous Rochelle’s salt (3.0 mL). The mixture was warmed to room temperature and extracted with EtOAc (3 x 5 mL). The combined organic phases were dried over Na₂SO₄, filtered, concentrated in vacuo, and purified by column chromatography (9:1 to 7:3 hexanes:EtOAc) to afford the title compound as a colorless oil (29 mg, 0.102 mmol, 81% yield, 99% brsm). Rₚ = 0.30 (3:1 hexanes:EtOAc). ¹H NMR (500 MHz, CDCl₃) δ 7.42-7.38 (m, 2H), 7.33-7.29 (m, 3H), 4.08 (dd, J = 10.7, 8.1 Hz, 1H), 3.78 (dd, J = 10.7, 7.5 Hz, 1H), 3.37 (m, 1H), 2.86 (dd, J = 17.3, 8.5 Hz, 1H), 2.72 (dd, J = 17.1, 8.9 Hz, 1H), 1.55 (s, 9H). ¹³C NMR (125 MHz, CDCl₃) δ 172.1, 149.8, 131.8, 128.6, 128.5, 122.7, 88.0, 83.5, 82.9, 51.9, 39.9, 28.2, 23.5. IR (film) = 2978, 2927, 2358, 2337, 1788, 1752, 1714, 1367, 1342, 1314, 1255, 1150 cm⁻¹. HRMS: Calculated for C₁₇H₁₉NO₃Na (M+Na)⁺: 308.1263; Found 308.1267. [α]D²⁴ = + 46.05° (c = 0.35; CH₂Cl₂).

tert-butyl (R)-3-(2-methoxy-2-oxoethyl)-4-(3-oxopropyl)-5-phenyl-2,3-dihydro-1H-pyrrole-1-carboxylate (37):

This procedure was adapted from the literature. A flame-dried Biotage® microwave vial (0.5 – 2.0 mL size) equipped with a stir bar was charged with LiBr (43.8 mg, 0.50 mmol, 2 equivalents). The reaction vessel was then capped with a septum, placed under high vacuum, and flame-dried. Upon cooling to room temperature, the septum was removed and Pd(OAc)₂ (2.8 mg, 13.0 µmol, 0.05 equivalent) was added. The reaction vessel was then sealed, evacuated, and backfilled with N₂. In a separate vial, methyl (R)-3-((tert-
butoxycarbonyl)amino)methyl)-5-phenylpent-4-ynoate (80.0 mg, 0.25 mmol, 1.0 equivalent) was dissolved in THF (300 µL), and to the resulting homogeneous, colorless solution was added acrolein (168.0 µL, 141.0 mg, 10.0 equivalents). The resulting homogeneous mixture was transferred to the Pd(OAc)$_2$/LiBr mixture via cannula, using THF (200 µL) to rinse the vial containing the substrate. The resulting homogeneous, dark red mixture was stirred at 23 °C for 4 h, at which point additional Pd(OAc)$_2$ (1.4 mg, 6.5 µmol, 0.025 equivalent) and LiBr (21.9 mg, 0.25 mmol, 1 equivalent, not dried) were added. The resulting homogeneous, deep red mixture was stirred at 23 °C for an additional 10 h. The reaction mixture was diluted with EtOAc/CH$_2$Cl$_2$ (1:1, 1 mL) and filtered through a short pipette column of Florisil®, eluting with EtOAc/CH$_2$Cl$_2$ (1:1, 5 mL). The resulting yellow/green reaction mixture was then concentrated in vacuo, and the resulting residue was dissolved in hexanes:EtOAc (3:1, 2 mL) to afford a heterogeneous mixture that was once again filtered through Florisil®, eluting with hexanes:EtOAc (3:1, 5 mL). Concentration of the resulting solution in vacuo afforded a light yellow residue that was purified by column chromatography (3:1 hexanes:EtOAc) to afford the title compound as a colorless oil (60.0 mg, 0.16 mmol, 64% yield). $R_f$ = 0.25 (2:1 hexanes:EtOAc). $^1$H NMR (400 MHz, CDCl$_3$) δ 9.61 (s, 1H), 7.34-7.28 (m, 3H), 7.17-7.15 (m, 2H), 4.06 (dd, $J$ = 2.0, 9.6 Hz, 1H), 3.75-3.70 (m, 4H), 3.20 (tt, $J$ = 4.4, 9.3 Hz, 1H), 2.61 (dd, $J$ = 4.4, 16.0 Hz, 1H), 2.55-2.46 (m, 1H), 2.44-2.34 (m, 3H), 2.24-2.19 (m, 1H), 1.07 (s, 9H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 201.6, 172.6, 152.5, 138.8, 133.8, 128.9, 128.0, 127.8, 121.7, 80.0, 53.4, 52.0, 42.5, 38.3, 37.8, 27.9, 18.3. IR (film) = 2977, 1735, 1688, 1395, 1366, 1166 cm$^{-1}$. HRMS: Calculated for C$_{21}$H$_{28}$O$_5$ (M+H)$^+$: 374.1967, Found 374.1956. $[\alpha]_D^{25}$ = +42.7° (c = 0.50, CH$_2$Cl$_2$).

![Structure](image)

(S,Z)-4-hexyl-5-(4-methoxybenzyldiene)dihydropuran-2(3H)-one (39):
This procedure was adapted from the literature. A 2-dram vial equipped with a stir bar was charged with methyl (S)-3-((4-methoxyphenyl)ethyl)ynyl)nonanoate (30.2 mg, 0.10 mmol, 1 equivalent), and to the vial were added MeOH (0.45 mL) and H₂O (50 µL). LiOH•H₂O (12.6 mg, 0.30 mmol, 3 equivalents) was added, and the homogeneous light yellow solution was stirred at 23 °C for 18 h. The reaction mixture was acidified with 1 N H₂SO₄ (1 mL) and extracted with Et₂O (2 x 5 mL). The pooled organic phases were dried over MgSO₄, filtered, and concentrated into an oven-dried Biotage® microwave vial (0.50 mL – 2.0 mL size). A stir bar was added, and the vial was flushed with N₂ (balloon). Degassed (N₂ sparged) MeCN (0.20 mL) was added, followed by Et₃N (ca. 0.7 µL, 0.005 mmol, 5 mol %) and Pd(PhCN)₂Cl₂ (1.0 mg, 0.0025 mmol, 0.025 equivalents). The vial was sealed with a septum-lined cap and heated to 80 °C, yielding a homogeneous light yellow solution. After 2 h, the vessel was cooled to room temperature, and additional Pd(PhCN)₂Cl₂ (1.0 mg, 0.0025 mmol, 0.025 equivalents) was added. The vessel was sealed again and heated to 80 °C for an additional 3 h. The vessel was cooled to room temperature, and the reaction mixture was diluted with Et₂O (3 mL). The mixture was filtered through a pipette plug of Florisil®, rinsing with additional Et₂O (10 mL). The solution was concentrated, and the residue was purified via preparative thin-layer chromatography (6:1 hexanes:EtOAc) to afford the title compound (17.0 mg, 59%) as a viscous, light yellow oil and as an inseparable mixture of olefin isomers (8:1 as judged by ¹H NMR spectroscopy based on the methyl ester and vinylic hydrogen signals). The major isomer was characterized, and the assignment of the olefin geometry was made by analogy to the above literature precedent cited. Rf = 0.69 (4:1 hexanes:EtOAc). ¹H NMR (400 MHz, CDCl₃, major isomer) δ 7.52-7.48 (m, 2H), 6.88-6.85 (m, 2H), 5.47 (d, J = 1.1 Hz, 1H), 3.82 (s, 3H), 3.19-3.11 (m, 1H), 2.81 (dd, J = 17.9, 9.5 Hz, 1H), 2.37 (dd, J = 17.9, 5.6 Hz, 1H), 1.78-1.71 (m, 1H), 1.56-1.49 (m, 9H), 0.89 (t, J = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃, major isomer) δ 174.5, 158.5, 151.3, 129.8, 126.8, 114.0, 104.1, 55.4, 39.0, 34.5, 33.6, 31.8, 29.2, 26.8, 22.7, 14.2. IR (film) = 2888, 2816, 1781, 1661, 1586, 1490, 1443, 1399, 1279, 1233, 1163, 1109, 1085, 1019, 948, 837 cm⁻¹. HRMS: Calculated for C₁₈H₂₅O₃ (M+H)⁺: 289.1798, Found 289.1806. [α]D²⁵ = + 6.9° (c = 0.50, CH₂Cl₂).
methyl (S)-3-((R,E)-3-hydroxy-5-phenylpent-4-en-1-yn-1-yl)nonanoate (43):

This procedure was adapted from the literature. An oven-dried Biotage® microwave vial (0.50 – 2.0 mL size) equipped with a stir bar was charged with (S,S)-ProPhenol catalyst (6.4 mg, 0.010 mmol, 10 mol %) and triphenylphosphine oxide (5.6 mg, 0.020 mmol, 20 mol %). The vial was sealed with a septum and flushed with Ar, and then distilled, degassed (Ar sparge) PhMe (75 µL) was added. Methyl (S)-3-ethynlnonanoate (23.6 mg, 0.120 mmol, 1.2 equivalents) was added via tared µL syringe, and the vessel was cooled to 0 °C. ZnMe$_2$ (1.2 M in PhMe, 125 µL, 0.150 mmol, 1.5 equivalents) was added, and the cooling bath was removed. The reaction mixture was stirred for 45 min at room temperature, and then it was again cooled to 0 °C. Freshly distilled trans-cinnamaldehyde (12.6 µL, 0.10 mmol, 1.0 equivalent) was added, and the vessel was transferred to a cold room (4 °C) where it was stirred for 48 h under an Ar balloon. The vessel was then warmed to room temperature, and the reaction mixture was quenched by the addition of 1 N HCl (3 mL). The mixture was poured into Et$_2$O (10 mL), and the phases were separated. The aqueous phase was extracted with Et$_2$O (3 x 5 mL), and the pooled organic phases were dried over MgSO$_4$, filtered, and concentrated. Only a single diastereomer was observed by $^1$H NMR analysis of the crude material. The crude material was purified by column chromatography (4:1 to 2:1 hexanes:EtOAc) to afford the title compound (27.8 mg, 85%, > 19:1 dr) as a viscous, light yellow oil. Assignment of (R)-stereochemistry at the carbon bearing the alcohol was made by analogy to the literature precedent cited. $R_f = 0.41$ (2:1 hexanes:EtOAc). $^1$H NMR (400 MHz; CDCl$_3$): $\delta$ 7.42-7.39 (m, 2H), 7.35-7.31 (m, 2H), 7.28-7.24 (m, 1H), 6.76 (dd, $J = 15.8$, 1.0 Hz, 1H), 6.28 (dd, $J = 15.8$, 5.8 Hz, 1H), 5.04 (tt, $J = 6.0$, 1.6 Hz, 1H), 3.69 (s, 3H), 2.97-2.90 (m, 1H), 2.56 (dd, $J = 15.4$, 7.8 Hz, 1H), 2.48 (dd, $J = 15.4$, 6.9 Hz, 1H), 2.08 (d, $J = 6.0$ Hz, 1H), 1.54-1.27 (m, 10H), 0.87 (t, $J = 6.9$ Hz, 3H). $^{13}$C NMR (100 MHz; CDCl$_3$): 172.2, 136.3, 131.8, 128.7, 128.6, 128.1, 126.9, 88.9, 80.9, 63.1, 51.9, 40.0, 34.6, 31.9, 29.1, 28.5, 29.1, 28.5.
27.3, 22.8, 14.2. **IR** (film): 3375 (br), 2984, 2887, 2817, 1714, 1418, 1344, 1249, 1148, 1053, 1001, 953, 742, 684 cm⁻¹. **HRMS** (ESI+): Calculated for C₂₁H₂₈NaO₃ (M+Na)⁺: 351.1931; Found 351.1934. \[\alpha\]D²⁵ = +1.6° (c = 0.5, CHCl₃)

methyl (S)-3-(1-tosyl-1H-1,2,3-triazol-4-yl)nonanoate (41):

This procedure was adapted from the literature. An oven-dried Biotage® microwave vial (0.5 – 2.0 mL size) equipped with a stir bar was charged with methyl (S)-3-ethynylnonanoate (47.1 mg, 0.24 mmol, 1.2 equivalents). The vial was sealed with a septum and evacuated and backfilled with N₂ three times. Distilled, degassed (N₂ sparged) PhMe (1.0 mL) was added, followed by copper(I)thiophene-2-carboxylate (3.8 mg, 0.02 mmol, 10 mol %). To the homogeneous, light yellow solution was added tosyl azide (39.5 mg, 0.20 mmol, 1 equivalent) dropwise, using a tared microliter syringe. Within 20 min, the appearance changed to bright green and homogeneous. After 1 h, the reaction mixture was applied directly to a silica gel column that was eluted with 4:1 hexanes:EtOAc to deliver the title compound (78.0 mg, 99%) as a viscous, clear oil. Rf = 0.40 (2:1 hexanes:EtOAc). **¹H NMR** (300 MHz, CDCl₃) δ 7.98-7.94 (m, 2H), 7.89 (s, 1H), 7.38-7.35 (m, 2H), 3.57 (s, 3H), 3.35-3.25 (m, 1H), 2.71 (dd, J = 15.2, 7.0 Hz, 1H), 2.64 (dd, J = 15.2, 5.8 Hz, 1H), 2.43 (s, 3H), 1.74-1.59 (m, 2H), 1.25-1.11 (m, 8H), 0.83 (t, J = 6.8 Hz, 3H). **¹³C NMR** (75 MHz, CDCl₃) δ 172.4, 150.0, 147.2, 133.3, 130.5, 128.7, 120.8, 51.7, 39.1, 34.4, 33.1, 31.7, 29.1, 27.0, 22.6, 22.0, 14.2. **IR** (film) = 3103, 2887, 2817, 1713, 1573, 1529, 1417, 1375, 1277, 1178, 1162, 1077, 995, 959 cm⁻¹. **HRMS**: Calculated for C₁₉H₂₈N₃O₄S (M+H)⁺: 394.1795, Found 394.1799. \[\alpha\]D²³ = −0.33° (c = 0.67, CHCl₃).
(S)-(5-hexylhept-3-yne-1,7-diyl)dibenzene (44):

This procedure was adapted from the literature. To a homogeneous, light yellow solution of (R)-(2-(4-phenylbut-1-yn-1-yl)octyl)sulfonyl)benzene (45.9 mg, 0.12 mmol, 1 equivalent) in THF (0.48 mL) at – 78 °C was added n-butyllithium (2.3 M in hexanes, 55 µL, 0.126 mmol, 1.05 equivalents). The resulting homogeneous, red-brown mixture was stirred at – 78 °C for 15 min, and then a solution of benzyl bromide (17 µL, 0.144 mmol, 1.2 equivalents) in THF (0.48 mL) was added. The cooling bath was removed, and the resulting homogeneous, brown mixture was allowed to warm to room temperature. After 30 minutes, the reaction mixture was diluted with Et₂O (3 mL), and then it was quenched with 2 N HCl (3 mL). The phases were separated, and the aqueous phase was extracted with Et₂O (3 x 3 mL). The pooled organic phases were dried over MgSO₄ and filtered through a pipette plug of Florisil®. The filtrate was concentrated.

This crude material (R_f = 0.48, 4:1 hexanes:EtOAc) was dissolved in a mixture of freshly distilled MeOH (0.80 mL) and THF (0.40 mL). To the resulting solution was added, first, Na₂HPO₄ (68.1 mg, 0.48 mmol, 4 equivalents) and then sodium-mercury amalgam (55 mg, spherical pellets, 20% sodium by weight, Strem Chemicals, Inc.; corresponds to ca. 11 mg of sodium, 0.48 mmol, 4 equivalents). The resulting heterogeneous, orange mixture was stirred at room temperature for 2 h, at which point it was diluted with Et₂O (5 mL) and water (5 mL). The phases were separated, and the aqueous phase was extracted with Et₂O (3 x 5 mL). The pooled organic phases were dried over MgSO₄ and filtered through a pipette plug of Florisil®. The filtrate was concentrated, and the crude material was purified by column chromatography (10:1 hexanes:EtOAc) to afford the title compound (33.2 mg, 83%) as a viscous, clear yellow oil. R_f = 0.92 (4:1 hexanes:EtOAc); 0.80 (10:1 hexanes:EtOAc).

_H NMR (500 MHz, CDCl₃) δ 7.32-7.27 (m, 5H), 7.25-7.17 (m, 5H), 2.85 (t, J = 7.5 Hz, 2H), 2.84-2.77 (m, 1H), 2.67-2.61 (m, 1H), 2.53 (td, J = 7.5, 2.2 Hz, 2H), 2.31-2.25 (m, 1H), 1.71-1.67 (m, 2H), 1.43-1.38 (m, 2H), 1.31-1.25 (m, 8H), 0.90 (t, J = 7.0 Hz, 3H)._C NMR (125 MHz, CDCl₃) δ 142.6, 141.1, 128.7, 128.6, 128.41, 128.39, 126.7, 125.8, 84.3, 81.2, 37.4, 35.8, 35.6, 33.8, 32.0, 31.5, 29.4, 27.5, 22.8, 21.1, 14.3. IR (film) = 3042, 3020, 2886, 2816,
1581, 1475, 1434, 1358, 1324, 736, 688 cm$^{-1}$. **HRMS:** Calculated for C$_{25}$H$_{32}$Na (M+Na) 355.2396; Found 355.2394. [$\alpha$]$_D$$^2$$^4$ = + 20.44° (c = 0.85, CHCl$_3$).

methyl (R)-3-methyl-5-phenylpentanoate (45):

To a 5 mL conical vial equipped with a stir bar was added a solution of 9bf (31.0 mg, 0.153 mmol, 1 equivalent) in EtOAc (0.55 mL). Palladium on carbon (2.0 mg, 5 weight percent dry basis, wet, 6 weight percent) was added, and the vial was sealed with a septum and purged with hydrogen for 5 min (balloon). The reaction mixture was stirred at room temperature under a hydrogen atmosphere (balloon) for 24 h. The reaction mixture was then diluted with EtOAc (1 mL) and filtered through a small pipette plug of Florisil, eluting with EtOAc (10 mL). The resulting solution was concentrated to afford the title compound as a clear oil (30.2 mg, 0.146 mmol, 96% yield). R$_f$ = 0.45 (10/1 Hexanes/EtOAc). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.31–7.26 (m, 2H), δ 7.20–7.15 (m, 3H), 3.67 (s, 3H), 2.71–2.53 (tdt, $J = 13.9$ Hz, 10.2, 7.0 Hz, 2H), 2.40–2.33 (dd, $J = 14.7$ Hz, 6.1 Hz, 1H), 2.22–2.14 (dd, $J = 14.7$ Hz, 8.0 Hz, 1H), 2.10–1.94 (m, 1H), 1.73–1.45 (m, 2H), 1.02 (d, $J = 6.6$ Hz, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$) δ 173.7, 142.4, 128.5, 128.4, 125.9, 51.4, 41.7, 38.7, 33.4, 30.2, 19.8. IR (film) 3027, 2953, 2931, 2857, 1738, 1496, 1455, 1436, 1367, 1304, 1260, 1201, 1157, 1090, 1010, 748, 699 cm$^{-1}$. **HRMS:** Calculated for C$_{13}$H$_{19}$O$_2$ (M+H)$^+$: 207.1380; Found 207.1372. [$\alpha$]$_D$$^2$$^5$ = +18.50° (c = 0.88; CH$_2$Cl$_2$).

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\text{\text{Ph}} \quad \text{Si} \quad \text{C}_5\text{H}_{11} \quad \text{C} \quad \text{H}_5 \quad \text{H} \quad \text{O} \quad \text{Ome}
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S230
\[
\text{S232}
\]