Supporting Information

Copper Hydride-Catalyzed Enantioselective Synthesis of Axially Chiral 1,3-Disubstituted Allenes

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I. Materials and Methods

General procedural information. All reactions were carried out under an atmosphere of nitrogen in oven-dried glassware with magnetic stirring unless otherwise stated. Anhydrous tetrahydrofuran (THF), toluene and dichloromethane (CH_2Cl_2) were purchased from Sigma-Aldrich, stored in CYCLE-TAINER® solvent delivery kegs and dried by passage under argon pressure through two packed columns of neutral alumina and copper(II) oxide. Anhydrous 1,2-dimethoxyethane (DME, anhydrous, 99.5%, inhibitor free) was purchased from Sigma Aldrich and stored in a nitrogen-filled glovebox over activated 4Å molecular sieves. Liquids and solutions were transferred via syringe. Copper(II) acetate was purchased from Strem Chemicals Inc. and used as received. 1,2-Bis((2*S*,5*S*)2,5-diphenylphospholano)ethane, 1,2-Bis((2*R*,5*R*)2,5-diphenylphospholano)ethane (Ph-BPE) ligands were purchased from Namena Corp. and stored in a nitrogen-filled glove box. 2,4,6,8-Tetramethylcyclotetrasiloxane (TMCTS, moisture sensitive, CAS 2370-88-9) was purchased from Oakwood Chemical and used as received. Deionized water was obtained directly from the in-house DI water line and used as is. All other commercially obtained materials were used as received. Flash chromatography purifications were conducted with the assistance of a Biotage Isolera Chromatography System unless otherwise indicated. Reusable SNAP cartridges (10–100g) were refilled with silica gel purchased from Silicycle (SilicaFlash® F60, 40–63 μm). Organic solutions were concentrated with the aid of a Buchi rotary evaporator. Isolated yields and enantiomeric ratios (er) reported in tables 2 and 3 of the manuscript reflect an average of two independent runs unless specified otherwise.

General analytical information. All reactions were monitored by thin-layer chromatography using Silicycle Siliaplate pre-coated plates (0.25 mm) and visualized with UV light and/or iodine stain. All nuclear magnetic resonance (NMR) spectra were recorded on a Bruker 400, 500 or 600 MHz instrument. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ (unless otherwise noted) and chemical shifts are reported in δ units, parts per million (ppm), relative to residual chloroform in the deuterated solvent (7.26 ppm for ^{1}H NMR and 77.16 ppm for ^{13}C NMR), multiplicity, coupling constant (Hz) and integration. Infrared (IR) spectra were recorded on a Thermo Scientific Nicolet iS5 spectrometer (iD5 ATR, diamond) and reported in terms of frequency of absorption (cm^{-1}). Melting points were obtained by use of a Mel-Temp capillary melting point apparatus. Elemental analysis (EA) was acquired by Atlantic Microlabs Inc., Norcross, GA. High resolution mass spectrometry (HRMS) analysis was performed on a JEOL AccuTOF LC-Plus 46 DART system or an Agilent Technologies 6545 Q-TOF LC/MS system. Low resolution mass spectrometry (LRMS) data were measured using an Agilent Technologies 6850 series gas chromatography (GC) system equipped with a 5975 series inert mass selective detector. Optical rotations were measured on a Jasco Model 1010 polarimeter ([α]D values are reported in degrees and concentration in g/100 mL). GC analyses were performed on an Agilent Technologies 6850 series gas chromatograph with FID detector and high pressure liquid chromatography (HPLC) analyses were conducted on an Agilent Technologies 1200 series system. Enantiomeric ratios (er) of the allene products were determined by GC, HPLC, or Waters Acquity UPC2 SFC chiral stationary phase analysis as detailed for each product.

II. General Procedures for the Asymmetric Semi-Reduction of 1,3-Enynes

General procedure A: Synthesis of enantioenriched allenes from terminal 1,3-enynes

In a nitrogen-filled glovebox, a stock solution of catalyst was prepared as follows: an oven-dried screw-cap 1 dram vial (VWR cat.66010-243) equipped with a magnetic stir bar was charged with copper(II) acetate (5.5 mg, 30 μM, 3 mol%) and ((+)-1,2-Bis((2S,5S)-2,5-diphenylphospholano)ethane ((S,S)-Ph-BPE, 16.7 mg, 33μM, 3.3 mol%). The solids were dissolved in 1,2-dimethoxyethane (DME, 300 μL), the vial was capped and the mixture was stirred for 30-40 min to yield a homogenous blue solution. At this point, the resulting catalyst solution should be used within 30 min.

Meanwhile, in a nitrogen-filled glovebox an oven-dried screw-cap reaction tube (16mm × 125mm, Fisherbrand, part # 1495935A) with magnetic stir bar was charged with 1,3-enyne substrate (1.00 mmol, 1 equiv) and DME (1.9 mL). Then the $Cu(OAc)_2$•(S,S)-Ph-BPE catalyst solution (100 μL, 1 mol%) was added to the substrate and the reaction tube was capped with a Teflon-lined silicone septum screw cap (National, part # B7995-15; Kimble Chase, part # 73804-15425) and removed from the glovebox. Water (9.4 μL, 0.52 mmol, 0.52 equiv) was added to the reaction solution using a Hamilton gastight glass microsyringe, and the reaction tube was placed in cooling bath equipped with a Julabo FT902 immersion cooler set to –10 ºC with stirring. 2,4,6,8-Tetramethylcyclotetrasiloxane (TMCTS, 121.5 μL, 0.5 equiv, 0.5 mmol) was added slowly down the wall of the reaction tube. The reaction was stirred for 15 – 20 h as indicated below for each substrate. Subsequently, the reaction tube was removed from the cooling bath, uncapped and 2 mL of solvent (as indicated for each substrate) was added to the reaction solution. The solution was quickly passed through a plug of silica gel (ca. 0.5 g) before the reaction mixture could warm to rt (in order to avoid further unselective CuH-mediated reaction), the silica was further rinsed with solvent to ensure the product was fully eluted. The resulting crude reaction mixture was concentrated *in vacuo* with the aid of a rotary evaporator and purified by column chromatography (see details for each substrate below) to afford the desired product. For reactions where traces of starting material remain or trace over-reduction of the allene product is observed, careful column chromatography followed by GC analysis of product-containing fractions was required to ensure high purity. Enantiopurity of the allene products was determined by GC, HPLC, or Waters Acquity UPC2 SFC chiral stationary phase analysis as described below for each substrate. The absolute stereochemistry was assigned by analogy to that of **S2**.

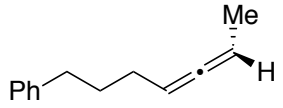
General procedure B: Synthesis of enantioenriched allenes from internal 1,3-enynes

In a nitrogen-filled glovebox, a stock solution of catalyst was prepared according to general procedure **A** using 150 μL DME instead to yield a solution containing 1 mol% catalyst loading per 50 μL DME.

Meanwhile, in a nitrogen-filled glovebox, an oven-dried screw-cap reaction tube (16mm × 125mm, Fisherbrand, part # 1495935A) with magnetic stir bar was charged with 1,3-enyne substrate (0.50 mmol, 1 equiv) and DME (0.4 mL). Then, the catalyst $Cu(OAc)_2$•(S,S)-Ph-BPE solution (100 μL, 2 mol%) was added to the substrate and the reaction tube was capped with a

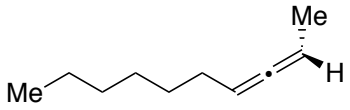
Teflon-lined silicone septum screw cap (National, part # B7995-15; Kimble Chase, part # 73804-15425). A separate 1 dram vial was charged with DME (1.5 mL), capped with a Teflon-lined silicone septum screw cap and removed from the glovebox along with the reaction tube. The reaction tube was placed in a cooling bath equipped with a Julabo FT902 immersion cooler set to –10 ºC with stirring. Water (amount indicated for each substrate) was added to the 1 dram vial containing DME using a Hamilton gastight glass microsyringe to yield a stock solution of water with three reaction portions. Silane (amount indicated for each substrate) was added slowly down the wall of the reaction tube. Slow addition of one-third of the water/DME stock solution (taken into a 1 mL syringe with a needle, amount indicated for each substrate) was immediately initiated with the aid of a Harvard Apparatus PHD Ultra syringe pump at a rate of 0.5 µL/min. After stirring for a total of 17 – 22 h at –10 ºC, the reactions were worked up and purified according to general procedure **A**. The absolute stereochemistry was assigned by analogy to (R)-laballenic acid (**4s**).

III. Characterization Data for 1,3-Disubstituted Allenes



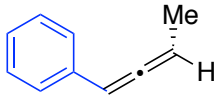
(***R*)-hepta-4,5-dien-1-ylbenzene (4a):** Following general procedure **A**, hept-6-en-4-yn-1-ylbenzene (170 mg, 1.00 mmol, 1 equiv) was used. After 16.5 h, the reaction was diluted with hexanes (2.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt (in order to avoid further unselective CuH-mediated reaction), the silica gel was washed with hexanes. The crude mixture was concentrated with the aid of a rotary evaporator and purified with the aid of a Biotage Isolera (25 g SNAP cartridge, 100% hexanes eluting at 60 mL/min and collecting 4 mL fractions in order to avoid significant contamination from adjacent impurities) to afford the title compound as a volatile colorless oil. (Run 1: 1.00 mmol scale, 158 mg, 92% yield, >99:1 er; Run 2: 1.00 mmol scale, 152 mg, 88% yield, >99:1 er).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.28 – 7.30 (m, 2H), 7.18 – 7.21 (m, 3H), 5.06 – 5.11 (m, 2H), 2.67 (dd, *J* = 7.7 Hz, 2H), 2.01 – 2.05 (m, 2H), 1.75 (p, *J* = 7.5 Hz, 2H), 1.68 (dd, *J* = 4.9 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 205.0, 142.7, 128.6, 128.4, 125.8, 90.1, 85.9, 35.4, 31.0, 28.4, 14.8.
IR (neat): 2925, 1963, 1496, 871, 743, 697 cm^{-1}
HRMS (DART) Calcd. m/z for $C_{13}H_{17}$ $[M+H]^+$:173.1330. Found: 173.1326
Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20ß GC Column (30 m, 0.25 mm, 0.25 µm, 7 inch cage), 8 psi: 70 ºC, hold for 50 min, 1 ºC/min to 100 ºC, hold for 20 min, 2 ºC/min to 150 ºC; t_r = 121.3 min (major) and 121.6 min (minor).
Specific rotation $[\alpha]_D^{23}$: -51.09 (c =1.0, $CHCl_3$)



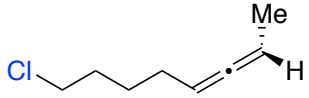
(R)-deca-2,3-diene (4b): Following general procedure **A**, dec-1-en-3-yne (136 mg, 1.00 mmol, 1 equiv) was used. After 16 h, the crude reaction mixture was directly purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 100% pentane eluting at 60 mL/min) to afford the title compound as a volatile colorless oil. (Run 1: 1.00 mmol scale, 104 mg, 75% yield, >99:1 er; Run 2: 1.00 mmol scale, 100 mg, 72% yield, >99:1 er). The spectral data match those previously reported in the literature.[1]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.10 – 4.97 (m, 2H), 2.04 – 1.92 (m, 2H), 1.65 (dd, *J* = 5.8, 4.4 Hz, 3H), 1.46 – 1.19 (m, 8H), 0.89 (t, *J* = 6.9 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 204.9, 90.5, 85.5, 31.9, 29.3, 29.1, 28.9, 22.8, 14.8, 14.2.
Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20ß GC Column (30 m, 0.25 mm, 0.25 µm, 7 inch cage), 8 psi: 70 ºC isocratic; t_r = 24.1 min (major) and 24.9 min (minor).
Specific rotation $[\alpha]_D^{23}$: -44.92 (c =1.0, $CHCl_3$).



(R)-buta-1,2-dien-1-ylbenzene (4c): Following general procedure **A**, but-3-en-1-yn-1-ylbenzene (128 mg, 1.00 mmol, 1 equiv) was used. After 17 h, the reaction was diluted with pentane (5.0 mL) and quickly passed through a short plug of silica gel atop a plug of basic alumina (ca. 0.5 g each) before the reaction solution could warm to rt (in order to avoid further unselective CuH-mediated reaction), and the silica gel/basic alumina were washed with pentane. Due to the volatility of the desired product, the crude mixture was carefully concentrated with the aid of a rotary evaporator to approx. 0.5 mL, diluted with $CDCl_3$ and mesitylene (0.10 mmol) was added as an internal standard. This product is unstable when stored at rt on the bench and should therefore be stored diluted under argon at low temperature. (Run 1: 1.00 mmol scale, 86% ^{1}H-NMR yield, 98.5:1.5 er; Run 2: 1.00 mmol scale, 86% ^{1}H-NMR yield, 99:1 er). The spectral data match those previously reported in the literature.[2]

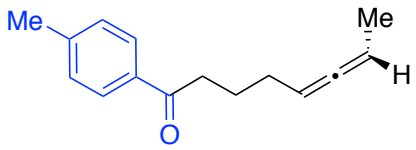
Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20ß GC Column (30 m, 0.25 mm, 0.25 µm, 7 inch cage), 8 psi: 70 ºC for 50 min, then 1 ºC/min to 150 ºC; t_r = 70.4 min (major) and 71.1 min (minor).



(R)-8-chloroocta-2,3-diene (4d): Following general procedure **A**, 8-chlorooct-1-en-3-yne (143 mg, 1.00 mmol, 1 equiv) was used. After 16.5 h, the reaction was diluted with pentane (2.0 mL)

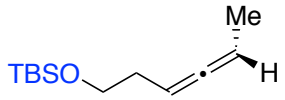
and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt (in order to avoid further unselective CuH-mediated reaction), the silica gel was washed with pentane. The crude mixture was concentrated with the aid of a rotary evaporator and purified with the aid of a Biotage Isolera (25 g SNAP cartridge, 100% pentane eluting at 60 mL/min and collecting 4 mL fractions in order to avoid significant contamination from adjacent impurities) to afford the title compound as a volatile colorless oil. (Run 1: 1.00 mmol scale, 118 mg, 82% yield, 99:1 er; Run 2: 1.00 mmol scale, 120 mg, 82% yield, 99:1 er). Due to product volatility and limitations of available HRMS equipment, LRMS data is reported for this compound.

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 – 4.97 (m, 2H), 3.54 (t, *J* = 6.7 Hz, 2H), 2.01 (ddd, *J* = 13.7, 7.2, 3.2 Hz, 2H), 1.88 – 1.76 (m, 2H), 1.65 (dd, *J* = 6.8, 3.4 Hz, 3H), 1.55 (tt, *J* = 9.7, 6.4 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 205.0, 89.8, 86.0, 45.1, 32.1, 28.2, 26.4, 14.7.
IR (neat): 2938, 1963, 1441, 1282, 871, 700 cm^{-1}
LRMS (GC-MS) Calcd. for $C_8H_{13}Cl$ [M+]: 144.07. Found: 144.10.
Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20ß GC Column (30 m, 0.25 mm, 0.25 µm, 7 inch cage), 8 psi: 70 ºC isocratic; t_r = 63.7 min (major) and 65.6 min (minor).
Specific rotation $[\alpha]_D^{23}$: -39.99 (*c* =10, $CHCl_3$).



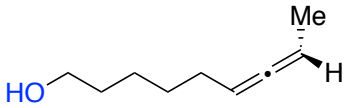
(R)-1-(p-tolyl)octa-5,6-dien-1-one (4e): Following general procedure **A**, 1-(*p*-tolyl)oct-7-en-5-yn-1-one (106 mg, 0.50 mmol, 1 equiv) was used. After 16.5 h, the reaction was diluted with CH_2Cl_2 (1.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt (in order to avoid further unselective CuH-mediated reaction), the silica gel was washed with CH_2Cl_2. The crude mixture was concentrated with the aid of a rotary evaporator and purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 0-7% EtOAc/hexanes) to afford the title compound as a colorless oil. (Run 1: 0.50 mmol scale, 69.8 mg, 65% yield, 99:1 er; Run 2: 1.00 mmol scale, 165 mg, 77% yield, 99:1 er).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.6 Hz, 2H), 5.06 (h, *J* = 5.1 Hz, 2H), 3.02 – 2.94 (m, 2H), 2.41 (s, 3H), 2.08 (tt, *J* = 7.1, 4.8 Hz, 2H), 1.86 (p, *J* = 7.3 Hz, 2H), 1.67 – 1.61 (m, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 205.1, 200.1, 143.8, 134.8, 129.4, 128.3, 89.8, 86.1, 37.8, 28.5, 23.9, 21.8, 14.7.
IR (neat,): 2857, 1965, 1680, 1606, 1229, 806 cm^{-1}
HRMS (DART) Calcd. *m/z* for $C_{15}H_{19}O$ $[M+H]^+$: 215.1430. Found: 215.1437.
Determination of enantiomeric ratio by SFC analysis: OJ-H column, 2.5 mL/min: 99:1 scCO2/MeOH isocratic; t_r = 5.32 min (major) and 5.53 min (minor).
Specific rotation $[\alpha]_D^{23}$: -38.60 (c =1.0, $CHCl_3$)



(R)-tert-butyl(hexa-3,4-dien-1-yloxy)dimethylsilane (4f): Following general procedure **A**, tert-butyl(hex-5-en-3-yn-1-yloxy)dimethylsilane (145 mg, 0.69 mmol, 1 equiv) was used. After 17 h, the reaction was diluted with pentane (1.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt (in order to avoid further unselective CuH-mediated reaction), the silica gel was washed with pentane. The crude mixture was concentrated with the aid of a rotary evaporator and purified on silica gel eluting with 100% pentane to afford the title compound as a volatile colorless oil. (Run 1: 0.69 mmol scale, 126 mg, 86% yield, >99:1 er; Run 2: 1.00 mmol scale, 202 mg, 89% yield, >99:1 er).

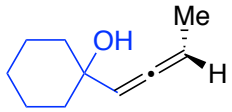
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.00 – 5.08 (m, 2H), 3.66 (t, *J* = 6.8 Hz, 2H), 2.17 – 2.23 (m, 2H), 1.64 (dd, *J* = 5.4, 4.7 Hz, 3H), 0.90 (s, 9H), 0.06 (s, 6H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 205.5, 87.0, 85.5, 63.2, 32.8, 26.1, 18.5, 14.6, -5.1.
IR (neat): 2954, 1966, 1254, 1100, 833, 774 cm^{-1}
HRMS (APCI) Calcd. m/z for $C_{12}H_{25}OSi$ $[M+H]^+$: 213.1675. Found: 213.1669
Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20ß GC Column (30 m, 0.25 mm, 0.25 µm, 7 inch cage), 8 psi: 70 ºC hold for 50 min, 0.1 ºC/min to 75 ºC; t_r = 96.6 min (major) and 97.8 min (minor).
Specific rotation $[\alpha]_D^{23}$: -27.45 (*c* =1.0, $CHCl_3$)



(R)-nona-6,7-dien-1-ol (4g): Following general procedure **A**, non-8-en-6-yn-1-ol (138 mg, 1.00 mmol, 1 equiv) and water (4.51 µL, 0.25 mmol, 0.25 equiv) was used. After 16.5 h, the reaction was directly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt (in order to avoid further unselective CuH-mediated reaction), the silica gel was washed with EtOAc (8 mL). The crude mixture was concentrated on a rotary evaporator. Subsequently, 1.25M HCl in MeOH (5 mL) was added to the resulting pale-yellow oil along with a small magnetic stir bar. The solution was stirred vigorously for 30 min at rt during which time a white precipitate formed. The solution was concentrated to yield a white residue which was suspended in EtOAc (ca. 10 mL), sonicated for 5 min and filtered through a plug of silica gel and the silica gel was washed with EtOAc. The filtrate was concentrated and purified with the aid of a Biotage Isolera (25 g SNAP cartridge, 5-20% EtOAc/hexanes) to afford the title compound as a colorless oil. (Run 1: 1.00 mmol scale, 125 mg, 89% yield, 97.5:2.5 er; Run 2: 1.00 mmol scale, 119 mg, 85% yield, 99:1 er).

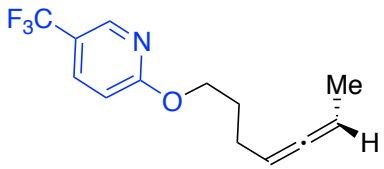
^{1}H NMR (400 MHz, $CDCl_3$) δ 5.06 – 4.95 (m, 2H), 3.59 (t, *J* = 6.7 Hz, 2H), 2.03 (s, 1H), 2.01 – 1.90 (m, 2H), 1.61 (dd, *J* = 5.9, 4.3 Hz, 3H), 1.54 (p, *J* = 6.8 Hz, 2H), 1.44 – 1.31 (m, 4H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 204.8, 90.2, 85.6, 62.9, 32.6, 29.0, 28.9, 25.2, 14.7.
IR (neat): 3324 (br), 2930, 2857, 1962, 1051, 871 cm^{-1}
HRMS (ESI) Calcd. m/z for $C_9H_{17}O$ $[M+H]^+$: 141.1272. Found: 141.1272.

Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20ß GC Column (30 m, 0.25 mm, 0.25 µm, 7 inch cage), 8 psi: 70 ºC hold for 50 min, 1 ºC/min to 100 ºC, hold for 20 min, 2 ºC/min to 150 ºC; t_r = 109.9 min (major) and 110.4 min (minor).
Specific rotation $[\alpha]_D^{23}$: -40.10 (c =1.0, CHCl3)



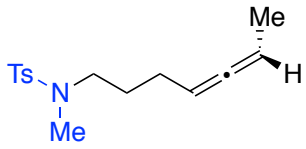
(R)-1-(buta-1,2-dien-1-yl)cyclohexan-1-ol (4h): Following general procedure **A**, 1-(but-3-en-1-yn-1-yl)cyclohexan-1-ol (150 mg, 1.00 mmol, 1 equiv) was used. After 17.5 h, the crude reaction mixture was directly purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 0-45% EtOAc/Hexanes) to afford the title compound as a fragrant colorless oil. (Run 1: 1.00 mmol scale, 127 mg, 83% yield, >99:1 er; Run 2: 1.00 mmol scale, 145 mg, 92% yield, >99:1 er).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.27 (p, *J* = 7.0 Hz, 1H), 5.21 – 5.24 (m, 1H), 1.69 (dd, *J* = 7.0, 3.3 Hz, 3H), 1.67 – 1.51 (m, 6H), 1.52 – 1.41 (m, 3H), 1.39 – 1.30 (m, 1H)
^{13}C NMR (126 MHz, $CDCl_3$) δ 202.5, 99.8, 89.4, 70.9, 38.6, 38.5, 25.7, 22.8, 22.7, 14.6.
IR (neat): 3357 (br), 3928, 1965, 1445, 956, 869 cm^{-1}
HRMS (ESI) Calcd. m/z for $C_{10}H_{17}O$ $[M+H]^+$: 153.1274. Found: 153.1276.
Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20ß GC Column (30 m, 0.25 mm, 0.25 µm, 7 inch cage), 8 psi: 70 ºC hold for 50 min, 1 ºC/min to 100 ºC, hold for 20 min, 2 ºC/min to 150 ºC; t_r = 108.4 min (major) and 110.3 min (minor).
Specific rotation $[\alpha]_D^{23}$: -30.50 (c =1.0, $CHCl_3$)



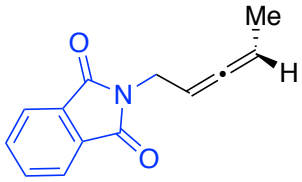
(R)-2-(hepta-4,5-dien-1-yloxy)-5-(trifluoromethyl)pyridine (4i): Following general procedure **A**, 2-(hept-6-en-4-yn-1-yloxy)-5-(trifluoromethyl)pyridine (255 mg, 1.00 mmol, 1 equiv) was used. After 18 h, the reaction was diluted with hexanes (2.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt (in order to avoid further unselective CuH-mediated reaction), the silica gel was washed with 1:9 CH_2Cl_2/hexanes. The crude mixture was concentrated with the aid of a rotary evaporator and purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 2-7% EtOAc/hexanes) to afford the title compound as a colorless oil. (Run 1: 1.00 mmol scale, 235 mg, 92% yield, >99:1 er; Run 2: 1.00 mmol scale, 229 mg, 89% yield, >99:1 er).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.42 (s, 1H), 7.74 (dd, *J* = 8.8, 2.6 Hz, 1H), 6.79 (d, *J* = 8.7 Hz, 1H), 5.13 – 5.02 (m, 2H), 4.39 (t, *J* = 6.6 Hz, 2H), 2.17 – 2.09 (m, 2H), 1.90 (p, *J* = 6.9 Hz, 2H), 1.63 (dd, *J* = 6.7, 3.5 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 205.0, 166.2, 145.1 (q, $J_{C–F}$ = 4.6 Hz), 135.6 (q, $J_{C–F}$ = 3.2 Hz), 124.2 (q, $J_{C–F}$ = 271.0 Hz), 119.9 (q, $J_{C–F}$ = 33.2 Hz), 111.3, 89.5, 86.3, 66.2, 28.4, 25.3, 14.6.
^{19}F NMR (565 MHz, $CDCl_3$) δ -61.6.
IR (neat): 1962, 1613, 1501, 1313, 1120, 834 cm^{-1}
HRMS (ESI) Calcd. m/z for $C_{13}H_{15}F_3NO$ $[M+H]^+$: 258.1100. Found: 258.1102.
Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20ß GC Column (30 m, 0.25 mm, 0.25 µm, 7 inch cage), 8 psi: 70 ºC hold for 50 min, 1 ºC/min to 100 ºC, hold for 20 min, 0.5 ºC/min to 150 ºC; t_r = 156.4 min (major) and 157.0 min (minor).
Specific rotation $[\alpha]_D^{23}$: -32.25 (c =1.0, $CHCl_3$)



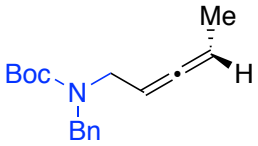
(R)-N-(hepta-4,5-dien-1-yl)-N,4-dimethylbenzenesulfonamide (4j): Following general procedure **A**, N-(hept-6-en-4-yn-1-yl)-N,4-dimethylbenzenesulfonamide (277 mg, 1.00 mmol, 1 equiv) was used. After 16.5 h, the reaction was diluted with EtOAc (2.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt (in order to avoid further unselective CuH-mediated reaction), the silica gel was washed with EtOAc. The crude mixture was concentrated with the aid of a rotary evaporator and purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 5-20% EtOAc/hexanes) to afford the title compound as a colorless oil. (Run 1: 1.00 mmol scale, 269 mg, 96% yield, 99:1 er; Run 2: 1.00 mmol scale, 278 mg, 99% yield, 99:1 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (d, *J* = 7.8 Hz, 2H), 7.29 (d, *J* = 7.4 Hz, 2H), 5.00 – 5.08 (m, 2H), 2.99 (t, *J* = 7.1 Hz, 2H), 2.69 (s, 3H), 2.40 (s, 3H), 2.05 – 1.94 (m, 2H), 1.68 – 1.56 (m, 5H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 204.8, 143.3, 134.6, 129.7, 127.4, 89.3, 86.3, 49.7, 34.8, 27.0, 25.7, 21.5, 14.6.
IR (neat): 2930, 2853, 1962,1338, 1158, 715 cm^{-1}
Elemental Analysis Calcd. for $C_{15}H_{21}NO_2S$: C, 64.48; H, 7.58. Found: C, 64.78; H, 7.60
Determination of enantiomeric ratio by HPLC analysis: OJ-H column, 1 mL/min: 100% hexanes for 80 min then gradient to 97:3 hexanes/iPrOH over 20 min, hold for 10 min, gradient to 100% hexanes over 5 min; t_r = 105.2 min (major) and 110.9 min (minor) λ = 230 nm.
Specific rotation $[\alpha]_D^{23}$: -30.50 (c =1.0, $CHCl_3$)



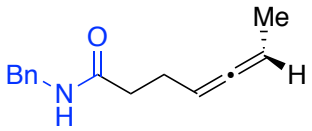
(R)-2-(penta-2,3-dien-1-yl)isoindoline-1,3-dione (4k): Following general procedure **A**, 2-(pent-4-en-2-yn-1-yl)isoindoline-1,3-dione (106 mg, 0.50 mmol, 1 equiv) was used. After 16 h, the crude reaction mixture was directly purified with the aid of a Biotage Isolera (25 g SNAP cartridge, 0-30% EtOAc/Hexanes) to afford the title compound as a white solid. (Run 1: 0.50 mmol scale, 93.3 mg, 88% yield, 97:3 er; Run 2: 0.50 mmol scale, 96.0 mg, 90% yield, 97:3 er). The spectral data match those previously reported in the literature.[3]

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.71 (dd, *J* = 5.4, 3.1 Hz, 2H), 5.20 – 5.11 (m, 2H), 4.27 (dd, *J* = 4.9, 3.6 Hz, 2H), 1.56 (dd, *J* = 5.7, 4.5 Hz, 4H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 204.9, 168.0, 134.0, 123.4, 123.4, 89.2, 86.2, 36.9, 14.0.
Determination of enantiomeric ratio by SFC analysis: OD-H column, 2.5 mL/min: 95:5 to 80:20 scCO2/MeOH over 7 min; t_r = 3.7 min (minor) and 3.9 min (major). **Specific rotation** $[\alpha]_D^{23}$: -39.01 (c =1.0, $CHCl_3$). [lit.[3] (S)-isomer: $[\alpha]_D^{19}$: +38.9 (c = 0.98 in CHCl3)]
MP: 50 – 51 ºC



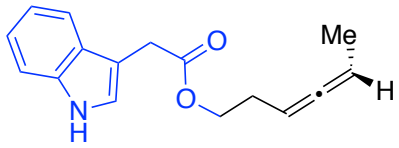
***Tert*-butyl (R)-benzyl(penta-2,3-dien-1-yl)carbamate (4l):** Following general procedure **A**, tert-butyl benzyl(pent-4-en-2-yn-1-yl)carbamate (271 mg, 1.00 mmol, 1 equiv) was used. After 15.5 h, the reaction was diluted with CH_2Cl_2 (2.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt (in order to avoid further unselective CuH-mediated reaction), and the silica gel was washed with CH_2Cl_2. The crude mixture was concentrated with the aid of a rotary evaporator and purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 0-12% EtOAc/hexanes) to afford a mixture of two rotamers of the title compound as a viscous colorless oil (Run 1: 1.00 mmol scale, 252 mg, 92% yield, Run 2: 0.50 mmol scale, 123 mg, 90% yield). The enantiomeric ratio was determined to be 99:1 for both runs after deprotecting **4l** to yield **S3** (see experimental procedure for **S3**).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.28 (m, 2H), 7.28 – 7.20 (m, 3H), 5.21 – 4.94 (m, 2H), 4.44 (bs, 2H), 3.96 – 3.63 (m, 2H), 1.66 (dd, *J* = 7.0, 3.2 Hz, 3H), 1.47 (bs, 9H).
^{13}C NMR (151 MHz, $CDCl_3$) δ (205.7 and 205.3), (155.8 and 155.5), (138.5 and 138.3), 128.5, 128.1, 127.5, 127.2, (87.1 and 86.9), (79.8 and 79.8), (49.6 and 49.2), 45.4, 28.5, 14.4.
IR (neat): 2973, 1962, 1691, 1234, 1162, 872 cm^{-1}
Elemental Analysis Calcd. for $C_{17}H_{23}O_2$: C, 74.69; H, 8.48. Found: C, 74.67; H, 8.63
Specific rotation $[\alpha]_D^{23}$: -28.42 (c =1.0, $CHCl_3$)



(R)-N-benzylhepta-4,5-dienamide (4m): Following general procedure **A**, N-benzylhept-6-en-4-ynamide (107 mg, 0.50 mmol, 1 equiv) was used. After 18 h, the reaction was quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt (in order to avoid further unselective CuH-mediated reaction), the silica gel was washed with EtOAc. The crude mixture was concentrated on a rotary evaporator and purified with the aid of a Biotage Isolera (25 g SNAP cartridge, 10-40% EtOAc/Hexanes) to afford the title compound as a white solid. (Run 1: 0.50 mmol scale, 99.1 mg, 92% yield, 80:20 er; Run 2: 0.50 mmol scale, 98.8 mg, 92% yield, 88:12 er).

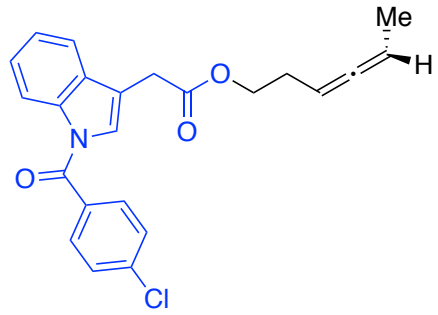
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34 – 7.31 (m, 2H), 7.28 – 7.26 (m, 3H), 6.25 (bs, 1H), 5.13 – 5.04 (m, 2H), 4.41 (dq, *J* = 14.7, 5.8 Hz, 2H), 2.32 (m, 4H), 1.61 (dd, *J* = 7.0, 3.3 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 204.6, 172.4, 138.5, 128.7, 127.8, 127.4, 89.3, 87.0, 43.6, 35.6, 24.6, 14.5.
IR ($CHCl_3$): 3284, 1962, 1642, 1543, 872, 696 cm^{-1}
HRMS (ESI) Calcd. m/z for $C_{14}H_{18}NO$ $[M+H]^+$: 216,1383. Found: 216.1384.
Determination of enantiomeric ratio by SFC analysis: AD-H column, 2.5 mL/min: 97:3 to 90:10 scCO2/MeOH over 25 min; t_r = 21.3 min (major) and 22.6 min (minor).
Specific rotation $[\alpha]_D^{23}$: -36.70 (c =1.0, CHCl3)
MP: 38 – 39 ºC



(R)-hexa-3,4-dien-1-yl 2-(1H-indol-3-yl)acetate (4n): Following general procedure **A**, hex-5-en-3-yn-1-yl 2-(1H-indol-3-yl)acetate (127 mg, 0.50 mmol, 1 equiv) was used. After 16.5 h, the reaction was diluted with EtOAc (1.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt (in order to avoid further unselective CuH-mediated reaction), the silica gel was washed with EtOAc. The crude mixture was concentrated with the aid of a rotary evaporator and purified with the aid of a Biotage Isolera (25 g SNAP cartridge, 2-20% EtOAc/hexanes) to afford the title compound as a colorless oil. (Run 1: 0.50 mmol scale, 115 mg, 90% yield, 87:13 er; Run 2: 0.75 mmol scale, 174 mg, 91% yield, 88.5:11.5 er).

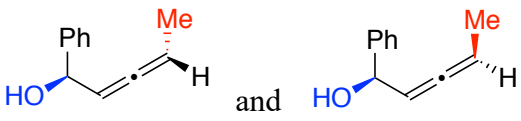
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08 (bs, 1H), 7.63 (d, *J* = 7.9 Hz, 1H), 7.36 (d, *J* = 8.0 Hz, 1H), 7.24 – 7.11 (m, 3H), 5.14 – 4.96 (m, 2H), 4.17 (t, *J* = 6.8 Hz, 2H), 3.79 (s, 2H), 2.31 (qd, *J* = 6.7, 3.0 Hz, 2H), 1.63 (dd, *J* = 6.9, 3.3 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 205.5, 172.4, 136.2, 127.2, 123.3, 122.1, 119.6, 118.8, 111.3, 108.2, 86.5, 86.1, 64.2, 31.4, 28.3, 14.4.
IR (neat): 3404, 1962, 1723, 1451, 1157, 740 cm^{-1}

HRMS (ESI) calcd. m/z for $C_{16}H_{18}NO_2$ [M+H]+: 256.1332. Found: 256.1333.
Determination of enantiomeric ratio by HPLC analysis: AD-H column, 0.7 mL/min: 99:1 hexanes/iPrOH for 30 min, gradient to 97:3 hexanes/iPrOH over 30 min, hold at 97:3 hexanes/iPrOH; t_r = 113.0 min (minor) and 115.5 min (major), λ = 210 nm.
Specific rotation $[\alpha]_D^{23}$: -21.90 (c =1.0, $CHCl_3$)



(R)-hexa-3,4-dien-1-yl 2-(1-(4-chlorobenzoyl)-1H-indol-3-yl)acetate (4o): Following general procedure **A**, hex-5-en-3-yn-1-yl 2-(1-(4-chlorobenzoyl)-1H-indol-3-yl)acetate (196 mg, 0.50 mmol, 1 equiv) was used. After 16.5 h, the reaction was diluted with EtOAc (1.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt (in order to avoid further unselective CuH-mediated reaction), and the silica gel was washed with EtOAc. The crude mixture was concentrated on a rotary evaporator and purified with the aid of a Biotage Isolera (100 g SNAP cartridge, 0-8% EtOAc/hexanes) to afford the title compound as a viscous colorless oil. (Run 1: 0.50 mmol scale, 174 mg, 88% yield, 99:1 er; Run 2: 0.50 mmol scale, 170 mg, 86% yield, 98:2 er).

^{1}H NMR (600 MHz, $CDCl_3$) δ 8.38 (d, *J* = 8.2 Hz, 1H), 7.69 (d, *J* = 8.5 Hz, 2H), 7.59 (d, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 8.4 Hz, 2H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.29 (s, 1H), 5.10 – 5.04 (m, 1H), 5.03 – 4.97 (m, 1H), 4.18 (t, *J* = 6.8 Hz, 2H), 3.71 (d, *J* = 1.2 Hz, 2H), 2.30 (qd, *J* = 6.7, 2.9 Hz, 2H), 1.62 (dd, *J* = 7.0, 3.2 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 205.5, 170.7, 167.4, 138.4, 136.2, 133.0, 130.7, 130.6, 129.1, 125.7, 125.5, 124.2, 119.2, 116.6, 115.1, 86.6, 85.9, 64.5, 31.0, 28.3, 14.5.
IR (neat): 2853, 1965, 1734, 1682, 1451, 1358 cm^{-1}
HRMS (ESI) Calcd. for $C_{23}H_{21}ClNO_3$ [M+Na]+: 416.1024. Found: 416.1027.
Determination of enantiomeric ratio by SFC analysis: Cel-1 column, 2.5 mL/min: 95:5 to 80:20 scCO2/MeOH over 6 min; t_r = 2.6 min (minor) and 2.7 min (major).
Specific Rotation $[\alpha]_D^{23}$: -17.33 (c =1.0, $CHCl_3$)

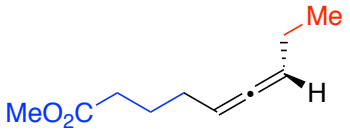


(1R,3R)- and (1R,3S)-1-phenylpenta-2,3-dien-1-ol (4p): Following general procedure **A**, (S)-1-phenylpent-4-en-2-yn-1-ol (79.1 mg, 0.50 mmol, 1 equiv) and either (S,S)-Ph-BPE (to yield **(1R,3R)-4p**) or (R,R)-Ph-BPE (to yield **(1R,3S)-4p**) was used. After 17 h, the reaction was

diluted with EtOAc (2.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt (in order to avoid further unselective CuH-mediated reaction), the silica gel was washed with EtOAc. The crude mixture was concentrated with the aid of a rotary evaporator and subsequently diluted with THF (3.0 mL) and taken into a rubber septum sealed oven-dried 10 mL round-bottom flask equipped with a magnetic stir bar under an atmosphere of nitrogen. After the solution was cooled to 0 ºC, tetrabutylammonium fluoride (1.0 mL, 1M THF, 2 equiv) was added dropwise to the stirring solution. After stirring for 1 h, the reaction was complete as indicated by TLC analysis and quenched by adding brine (25 mL). The resulting solution was extracted with CH_2Cl_2 (3 x 20 mL) and the combined extracts were dried over sodium sulfate, filtered and concentrated *in vacuo* with the aid of a rotary evaporator. The crude material was purified with the aid of a Biotage Isolera (25 g SNAP cartridge, 0-15% EtOAc/hexanes) to afford the title compound as a pale-yellow oil. (With (S,S)-Ph-BPE: 0.50 mmol scale, 70.0 mg, 87% yield, >15:1 dr; With (R,R)-Ph-BPE: 0.50 mmol scale, 68.4 mg, 85% yield, 1:>15 dr).

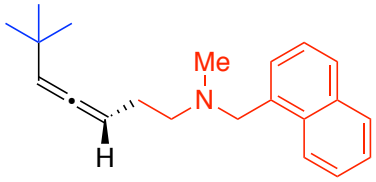
(1R,3R)-1-phenylpenta-2,3-dien-1-ol
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 – 7.38 (m, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 5.42 – 5.30 (m, 2H), 5.26 – 5.20 (m, 1H), 2.13 (bs, 1H), 1.73 (dd, J = 7.0, 3.2 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 203.1, 143.2, 128.6, 127.8, 126.3, 95.7, 89.9, 72.3, 14.5.
IR (neat): 3348 (br), 1966, 1270, 1118, 870, 697 cm^{-1}
HRMS (ESI) Calcd. for $C_{11}H_{13}O$ [M+H]+: 161.0961. Found: 161.0962.

(1R,3S)-1-phenylpenta-2,3-dien-1-ol
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.40 (d, J = 7.2 Hz, 2H), 7.36 (t, J = 7.6 Hz, 2H), 7.29 (t, J = 7.2 Hz, 1H), 5.42 – 5.32 (m, 2H), 5.27 – 5.22 (m, 1H), 2.17 (s, 1H), 1.71 (dd, J = 7.0, 3.2 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 203.2, 143.3, 128.6, 127.8, 126.2, 95.7, 89.8, 72.4, 14.4.



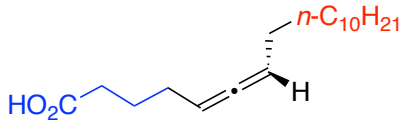
Methyl (R)-nona-5,6-dienoate (4q): Following general procedure **B**, methyl (E)-non-7-en-5-ynoate (166 mg, 1.0 mmol, 1 equiv), and TMCTS (121.5 µL, 0.5 equiv, 0.5 mmol) was used. The stock solution of water was prepared using 28.11 µL (1.56 mmol, 1.56 equiv) and 0.509 µL of this water/DME solution was used in the slow addition step. After 17 h, the reaction was diluted with CH_2Cl_2 (1.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt (in order to avoid further unselective CuH-mediated reaction), and the silica gel was washed with CH_2Cl_2. The crude mixture was concentrated with the aid of a rotary evaporator and purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 0-9% EtOAc/hexanes) to afford the title compound as a volatile colorless oil. (Run 1: 0.50 mmol scale, 83.6 mg, 50% yield, >99:1 er; Run 2: 0.50 mmol scale, 75.8 mg, 45% yield, >99:1 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.15 (qt, J = 6.1, 3.0 Hz, 1H), 5.08 (qt, J = 6.5, 3.3 Hz, 1H), 3.66 (s, 3H), 2.35 (t, J = 7.6 Hz, 2H), 2.08 – 1.93 (m, 4H), 1.74 (p, J = 7.7 Hz, 2H), 0.99 (t, J = 7.4 Hz, 3H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 203.8, 174.3, 93.3, 90.7, 51.6, 33.5, 28.5, 24.5, 22.1, 13.6.
IR (neat): 2965, 1959, 1737 (s), 1436, 1153, 878 cm^{-1}
HRMS (ESI) Calcd. for $C_{10}H_{17}O_2$ [M+H]+: 169.1223. Found: 169.1222
Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20ß GC Column (30 m, 0.25 mm, 0.25 µm, 7 inch cage), 8 psi: 70 ºC hold for 50 min, 1 ºC/min to 100 ºC, hold for 20 min, 2 ºC/min to 150 ºC; t_r = 96.2 min (major) and 97.9 min (minor).
Specific rotation $[\alpha]_D^{23}$: -54.56 (c =1.0, $CHCl_3$)



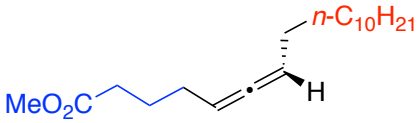
(R)-N,6,6-trimethyl-N-(naphthalen-1-ylmethyl)hepta-3,4-dien-1-amine (4r): Following general procedure B, terbinafine (146 mg, 0.50 mmol, 1 equiv), and TMCTS (182 µL, 1.5 equiv, 0.75 mmol) was used. The stock solution of water was prepared using 33.9 µL (1.88 mmol, 3.75 equiv) and 0.511 µL of this water/DME solution was used in the slow addition step. After 20 h, the reaction was diluted with CH_2Cl_2 (1.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt (in order to avoid further unselective CuH-mediated reaction), and the silica gel was washed with CH_2Cl_2. The crude mixture was concentrated on a rotary evaporator and purified with the aid of a Biotage Isolera (100 g SNAP cartridge, 0-5% EtOAc/hexanes) to afford the title compound as a viscous colorless oil. (Run 1: 0.50 mmol scale, 98.5 mg, 67% yield, 99:1 er; Run 2: 0.50 mmol scale, 99.3 mg, 68% yield, 99:1 er).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.2 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.59 – 7.37 (m, 4H), 5.22 (q, *J* = 6.5 Hz, 1H), 5.17 – 5.09 (m, 1H), 4.02 – 3.85 (m, 2H), 2.63 (t, *J* = 7.6 Hz, 2H), 2.37 – 2.21 (m, 5H), 1.06 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 201.4, 135.2, 134.0, 132.7, 128.5, 128.0, 127.5, 125.9, 125.7, 125.3, 124.9, 103.3, 90.8, 60.8, 57.9, 42.4, 31.8, 30.4, 27.3.
IR (neat): 2957, 2787, 1959, 1360, 790, 773 cm^{-1}
Elemental Analysis Calcd. for $C_{21}H_{27}N$: C, 85.96; H, 9.27. Found: C, 84.06; H, 9.40.
Determination of enantiomeric ratio by HPLC analysis: IC column, 0.4 mL/min: 100% hexanes with 0.15% DEA; t_r = 12.5 min (minor) and 12.8 min (major), λ = 254 nm.
Specific rotation $[\alpha]_D^{23}$: -40.08 (c =1.0, $CHCl_3$)



(R)-Laballenic Acid (4s): General procedure **B** was modified as follows: After adding catalyst solution to (E)-octadec-7-en-5-ynoic acid (139 mg, 0.50 mmol, 1 equiv) in DME (0.4 mL), in the glovebox, dimethoxy(methyl)silane (DMMS) (309 µL, 5 equiv, 2.5 mmol) was added to the uncapped reaction tube. The solution was left to stir vigorously for 20 min until gas evolution subsided and the solution became a strong yellow color, at which point the reaction tube was capped and removed from the glovebox to continue stirring at rt for an additional 1 h. H_2O (33.9 µL, 1.88 mmol, 3.75 equiv) was added to the 1 dram vial containing DME (1.5 mL) using a Hamilton gastight glass microsyringe to yield a stock solution of water. After cooling the reaction solution to -10 ºC, 0.511 µL of the water/DME mixture was taken into a 1 mL syringe with needle and inserted into the reaction tube. Slow addition of the water solution was initiated with the aid of a Harvard Apparatus PHD Ultra syringe pump at a rate of 0.5 µL/min. After 21 h, the reaction was diluted with EtOAc (1.0 mL) and quickly passed through a short plug of silica gel (ca. 0.5 g) before the reaction solution could warm to rt (in order to avoid further unselective CuH-mediated reaction), the silica gel was washed with EtOAc.
1N aqueous HCl (15 mL) was added to the yellow solution which immediately became colorless. The mixture was stirred vigorously for 3 h to ensure complete deprotection of the carboxylic acid followed by extraction of the aqueous with EtOAc (3x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated on a rotary evaporator. The crude reaction material was purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 0-10-40% EtOAc/hexanes) to afford the title compound as a pale-yellow oil. The enantiomeric ratio was determined after conversion of the free acid to the methyl ester (**S1**) using Ma's previously reported conditions.[4] (Run 1: 0.50 mmol scale, 74.5 mg, 53% yield, 93:7 er; Run 2: 0.250 mmol scale, 32.3 mg, 46% yield, 93.5:6.5 er). The spectral data match those previously reported in the literature.[4]

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.10 (ddt, J = 6.4, 3.0, 3.0 Hz, 1H), 5.05 (ddt, J = 6.3, 3.0, 3.0 Hz, 1H), 2.40 (t, J = 7.5 Hz, 2H), 2.04 (qd, J = 7.2, 2.9 Hz, 2H), 1.97 (qd, J = 7.0, 3.0 Hz, 2H), 1.76 (p, J = 7.4 Hz, 2H), 1.43 – 1.18 (m, 18H), 0.88 (t, J = 6.9 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 204.2, 179.5, 91.8, 89.8, 33.4, 32.1, 29.8, 29.8, 29.6, 29.5, 29.4, 29.4, 29.3, 29.1, 28.4, 24.2, 22.8, 14.3.
IR (neat): 2923, 2853, 1959, 1709, 1455, 1078 cm^{-1}
Specific rotation $[\alpha]_D^{23}$: -38.07 (c =0.96, $CHCl_3$). [lit.[4] $[\alpha]_D^{29}$: -42.7 (c = 0.96 in $CHCl_3$)]



S1

Alternative workup to yield methyl ester S1 directly: After following the procedure detailed for the synthesis of **4s** (0.5 mmol scale), a methanolic HCl solution (8 mL, 1.25 N, 20 equiv) was

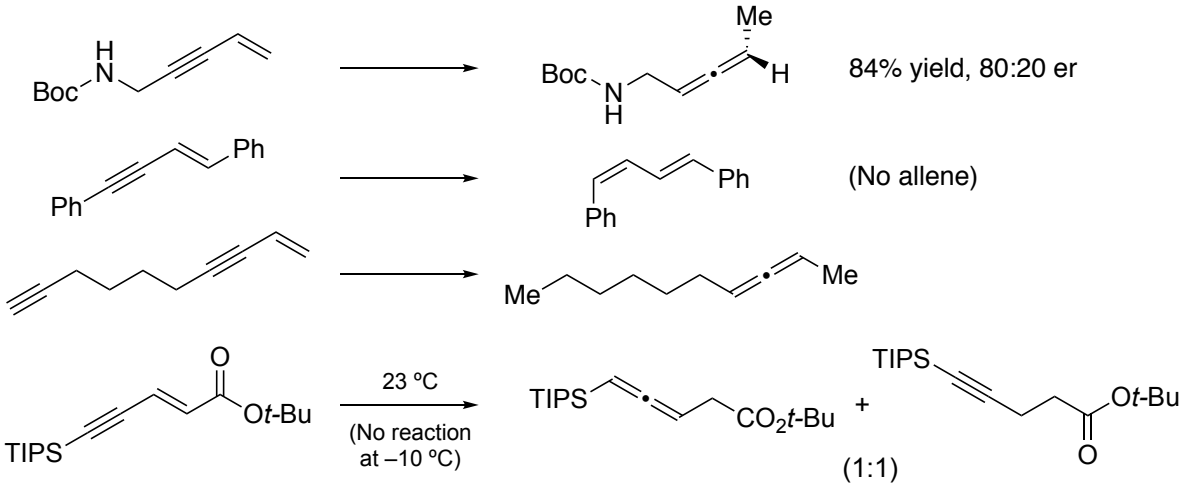
used in place of the aforementioned aqueous HCl solution. After stirring for 1 h at rt, the solution was transferred into a separatory funnel with saturated ammonium chloride (20 mL) and extracted with CH_2Cl_2 (3x 20 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated with the aid of a rotary evaporator. The crude reaction mixture was purified with the aid of a Biotage Isolera (25g SNAP cartridge, 0-8% EtOAc/Hexanes) to yield the methyl ester derivative **S1** (68.2 mg, 46% yield, 98:2 er). The spectral data match those previously reported in the literature.[4]

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12–5.01 (m, 2H), 3.67 (s, 3H), 2.35 (t, J = 7.6 Hz, 2H), 1.98 (dtd, J = 19.8, 7.0, 3.1 Hz, 4H), 1.74 (p, J = 7.5 Hz, 2H), 1.45 – 1.17 (m, 18H), 0.88 (t, J = 6.7 Hz, 3H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 204.2, 174.2, 91.7, 89.9, 51.6, 33.5, 32.1, 29.8, 29.8, 29.6, 29.5, 29.4, 29.3, 29.1, 28.5, 24.5, 22.8, 14.3.

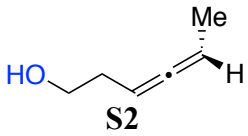
Determination of enantiomeric ratio by HPLC analysis: Chiralcel OD-H column, 0.5 ml/min: 100% hexanes; t_R = 20.4 min (minor) and 21.5 min (major) [Lit.[4]: t_R = 21.7 min (minor) and 22.8 min (major), λ = 214 nm]

IV. Additional Substrates Surveyed

Following General Procedure A (unless otherwise noted), we observed the following:



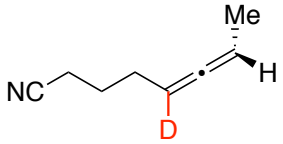
V. Further Confirmation of Absolute Configuration



S2

(R)-hexa-3,4-dien-1-ol (S2): To an oven-dried 10 mL round-bottom flask equipped with a magnetic stir bar and sealed with a rubber septum under an atmosphere of nitrogen were added THF (1.57 mL) and allene **4f** (100 mg, 0.47 mmol, 1 equiv) sequentially. Tetrabutylammonium fluoride (1.04 mL, 1M THF, 2.2 equiv) was added dropwise to the stirring solution. After stirring for 4 h, the reaction was complete as indicated by TLC analysis and quenched by adding deionized water (3 mL). The resulting solution was extracted with Et_2O (3 x 5 mL) and the combined extracts were dried over magnesium sulfate, filtered and concentrated *in vacuo* with the aid of a rotary evaporator. The crude material was purified on silica gel (0–50% pentane/Et_2O) to afford the title compound as a colorless oil (19.2 mg, 41% yield). The spectral data match those previously reported in the literature.[3]
Specific rotation $[\alpha]_D^{23}$: -62.4 (*c* =0.9, $CHCl_3$) [lit.[3] $[\alpha]_D^{20}$: -33.6 (*c* =0.66, $CHCl_3$)]

VI. Deuterium Labeling Experiments

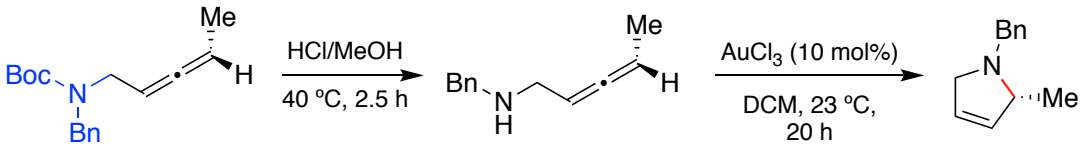


(R)-octa-5,6-dienenitrile-5-d (5): Following general procedure **A**, oct-7-en-5-ynenitrile (477 mg, 4.0 mmol, 1 equiv) and D_2O (0.52 equiv, 20.0 mg, 37.5 µL) was used. After 17.5 h, the reaction was diluted with CH_2Cl_2 (4.0 mL) and quickly passed through a short plug of silica gel (ca. 2 g) before the reaction solution could warm to rt (in order to avoid further unselective CuH-mediated reaction), the silica gel was washed with CH_2Cl_2. The crude mixture was concentrated with the aid of a rotary evaporator and purified with the aid of a Biotage Isolera (100 g SNAP cartridge, 0-15% EtOAc/hexanes) to afford the title compound as a volatile colorless oil. Percent deuterium incorporation was determined by ^{2}H NMR analysis with methanol-d4 as an internal standard in additional to comparison of the ^{1}H NMR spectra with those of the non-deutero isomer obtained from the use of H_2O instead (Run 1: 4.0 mmol scale, 390 mg, 80% yield, 99:1 er, 98:2 D/H incorporation; Run 2: 1.8 mmol scale, 160 mg, 73% yield, 99:1 er, 98:2 D/H incorporation).

^{1}H NMR (400 MHz, $CDCl_3$) δ 5.12 (qt, J = 6.8, 3.6 Hz, 1H), 2.38 (t, J = 7.2 Hz, 2H), 2.12 (td, J = 7.1, 2.8 Hz, 2H), 1.77 (p, J = 7.2 Hz, 2H), 1.65 (d, J = 7.0 Hz, 3H).
^{2}H NMR (77 MHz, CH_2Cl_2) δ 5.06

^{13}C NMR (126 MHz, $CDCl_3$) δ 205.2, 119.8, 88.0 (t, J = 25 Hz), 86.9, 27.4, 24.7, 16.4, 14.5.
IR (neat): 2939, 2247, 1959, 1441, 798, 553 cm^{-1}
HRMS (ESI) Calcd. for $C_8H_{11}DN$ [M+H]+: 123.1027. Found: 123.1036.
Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20ß GC Column (30 m, 0.25 mm, 0.25 µm, 7 inch cage), 8 psi: 70 ºC for 50 min, then 1 ºC/min to 100 ºC, hold for 5 min; t_R = 79.6 min (major) and 80.4 min (minor)
Specific Rotation $[\alpha]_D^{23}$: -62.84 (c =1.0, $CHCl_3$)

VII. Cycloisomerization of Alleneamine 4l



4l **S3** **6**

(R)-N-benzylpenta-2,3-dien-1-amine (S3): Allene **4l** (137 mg, 0.5 mmol, 1 equiv) was taken into an oven-dried screw-cap reaction tube (16mm × 125mm, Fisherbrand, part # 1495935A) with magnetic stir bar and diluted in methanolic HCl (2.0 mL, 1.25 N, 2.5 mmol, 5 equiv). The reaction tube was capped with a Teflon-lined silicone septum screw cap (National, part # B7995-15; Kimble Chase, part # 73804-15425) and transferred to an oil bath pre-heated to 40 ºC. The reaction solution was stirred vigorously at 40 ºC until complete conversion was indicated by TLC analysis (ca. 2.5 h). Concentration of the crude reaction solution with the aid of a rotary evaporator furnished a white salt which was dissolved in saturated aqueous $NaHCO_3$ (80 mL) and taken into a separatory funnel. CH_2Cl_2 (30 mL) was added and the solution was shaken vigorously. The organics were collected and the aqueous was re-extracted with CH_2Cl_2 (2x 30 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated with the aid of a rotary evaporator. The crude oil was purified with the aid of a Biotage Isolera (10 g SNAP cartridge, 0-50% EtOAc/hexanes) to afford **S3** as a pale-yellow oil (85.0 mg, 88% yield, 99:1 er). The spectral data match those previously reported.[5]

Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20ß GC Column (30 m, 0.25 mm, 0.25 µm, 7 inch cage), 8 psi: 100 ºC for 60 min, then 0.25 ºC/min to 150 ºC; t_r = 148.0 min (major) and 149.1 min (minor).

(R)-1-benzyl-2-methyl-2,5-dihydro-1H-pyrrole (6): To an oven-dried 1 dram vial containing a magnetic stir bar and gold(III) chloride under nitrogen atmosphere was added a solution of **S3** (30.0 mg, 0.17 mmol, 1 equiv) in anhydrous CH_2Cl_2 (0.5 mL). After the reaction mixture was stirred vigorously at rt for 20 h, the vial was uncapped and the solution was filtered through a plug of celite atop a plug of silica gel (ca. 0.3 g each), and the silica gel and celite were washed with Et_2O. The crude reaction solution was concentrated with the aid of a rotary evaporator and

purified with the aid of a Biotage Isolera (10g SNAP cartridge, 0-80% EtOAc/Hexanes) to afford the title compound as a pale-yellow oil (18.5 mg, 62% yield, 99:1 er).

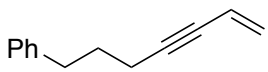
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 2H), 7.31 (t, J = 7.5 Hz, 2H), 7.24 (td, J = 7.2, 3.5 Hz, 1H), 5.76 – 5.70 (m, 1H), 5.70 – 5.64 (m, 1H), 4.03 (d, J = 13.1 Hz, 1H), 3.69 – 3.60 (m, 2H), 3.56 (d, J = 13.1 Hz, 1H), 3.26 – 3.17 (m, 1H), 1.18 (d, J = 6.2 Hz, 3H).
^{13}C NMR (126 MHz, $CDCl_3$) δ 133.5, 128.9, 128.6, 128.4, 127.0, 126.6, 65.5, 60.1, 58.4, 20.5.
IR (neat): 3059, 2916, 2870, 2782, 1491, 695 cm^{-1}
HRMS (ESI) Calcd. for $C_{12}H_{16}N$ [M+H]+: 174.1277. Found: 174.1283.
Determination of enantiomeric ratio by GC analysis: Hydrodex β-3P column (25 m, 0.25 mm), 7.5 PSI: 110 ºC for 20 min, then 10 ºC/min to 220 ºC, hold for 5 min; t_R = 27.0 min (minor) and 27.1 min (major).
Specific Rotation $[\alpha]_D^{23}$: -138.0 (c =0.8, $CHCl_3$)

VIII. Preparation of 1,3-Enyne Substrates

The following substrates were prepared according to literature reports: **1b**,[6] **1c**,[7] **1d**,[8] **1f**,[9] **1g**,[8] **1h**,[10] **1j**,[8] **1m**,[8] and **1t**.[11] Terbinafine was purchased as the HCl salt from Combi Blocks Inc.

General procedure C: Sonogashira coupling for the synthesis of 1,3-enynes

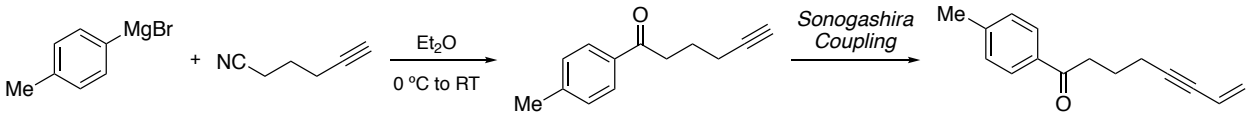
In a nitrogen-filled glovebox, an oven-dried 50 mL three-neck flask containing a magnetic stir-bar was charged with bis(triphenylphosphine)palladium(II) chloride (281 mg, 0.40 mmol, 3 mol%) and copper(I) iodide (114 mg, 0.60 mmol, 4 mol%). The reaction flask was sealed with a rubber septum and removed from the glovebox. Under an atmosphere of nitrogen, triethylamine (11.2 mL, 80.0 mmol, 4.0 equiv) was added *via* syringe and the suspension was cooled to 0 ºC in an ice/water bath. Alkyne starting material (20.0 mmol, 1 equiv) was added slowly at 0 ºC and the solution was allowed to stir for approximately 10-20 min. Vinyl halide starting material (40.0 mmol, 2.0 equiv) was slowly added to the reaction mixture at 0 ºC. After stirring for 10 min, the reaction solution was allowed to warm to rt. After vigorously stirring for an additional 16 h at rt, or upon the complete consumption of alkyne starting material as indicated by GC analysis, the flask was uncapped and the crude reaction mixture was quenched by adding deionized water (400 mL). The resulting mixture was extracted with EtOAc (3 x 200 mL) and the combined extracts were dried over sodium sulfate, filtered and concentrated on a rotary evaporator. All crude reaction mixtures were purified on silica gel to afford the desired 1,3-enyne products.



Hept-6-en-4-yn-1-ylbenzene (1a): Following general procedure **C**, copper(I) iodide (114 mg, 0.60 mmol, 3 mol%), bis(triphenylphosphine)palladium(II) chloride (281 mg, 0.40 mmol, 2 mol%), triethylamine (13.3 mL, 96.0 mmol, 4.8 equiv), pent-4-yn-1-ylbenzene (3.04 mL, 20.0

mmol, 1 equiv) and bromoethene (34.0 mL, 1M in THF, 34.0 mmol, 1.7 equiv) was used. After stirring for 16.5 h at rt, the crude reaction solution was diluted with hexanes (30 mL) and filtered through a plug of silica gel and concentrated on a rotary evaporator. The crude reaction mixture was purified with the aid of a Biotage Isolera (100 g SNAP cartridge, 100% hexanes) to afford the title compound as a colorless oil (2.64 g, 78% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (t, *J* = 7.6 Hz, 2H), 7.26 – 7.21 (m, 3H), 5.85 (ddt, *J* = 17.6, 11.1, 2.2 Hz, 1H), 5.62 (dd, *J* = 17.5, 2.2 Hz, 1H), 5.43 (dd, *J* = 11.1, 2.2 Hz, 1H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.36 (td, *J* = 7.1, 2.1 Hz, 2H), 1.90 (p, *J* = 7.3 Hz, 2H).
^{13}C NMR (126 MHz, CDCl3) δ 141.6, 128.6, 128.4, 126.0, 125.7, 117.7, 90.7, 79.9, 34.7, 30.3, 18.8.
IR (neat): 2942, 2225, 1206, 1496, 973, 698 cm^{-1}
HRMS (ESI) Calcd. m/z for $C_{13}H_{15}$ $[M+H]^+$: 171.1174. Found: 171.1168.



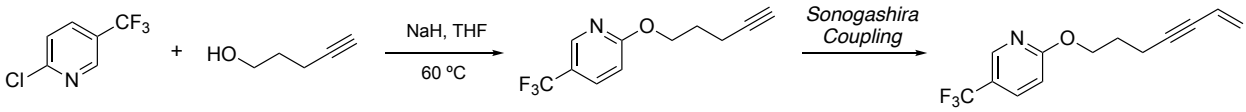
S4

1-(p-tolyl)hex-5-yn-1-one (S4): An oven-dried 500 mL round bottom flask was equipped with a magnetic stir bar and sealed with a rubber septum. The flask was evacuated and backfilled with nitrogen (this process was repeated a total of three times). Anhydrous diethyl ether (45 mL) was added via syringe followed by p-tolylmagnesium bromide (0.5 M in Et_2O, 66 mL, 33 mmol, 2.2 equiv). The solution was cooled to ca. 0 ºC using an ice-water bath. Hex-5-ynenitrile (1.4 g, 15 mmol, 1 equiv) was added to the Grignard solution dropwise over a period of 10 min with vigorous stirring, eventually yielding an opaque white suspension. The reaction mixture was left to slowly warm to rt while stirring. After 15.5 h, the reaction mixture was cooled to 0 ºC using an ice-water bath and carefully quenched by addition of water (20 mL) over 2 h with the aid of a Harvard Apparatus PHD Ultra syringe pump. After further dilution with water (40 mL), the crude mixture was poured into a separatory funnel and extracted with EtOAc (3x 50 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated on a rotary evaporator to yield a yellow oil. Subsequent purification with the aid of a Biotage Isolera (100 g SNAP cartridge, 025% EtOAc/Hexanes) provided the title compound as a yellow oil (2.38 g, 85% yield). The spectral data match those previously reported in the literature.[12]

1-(p-tolyl)oct-7-en-5-yn-1-one (1e): Following general procedure **C**, 1-(p-tolyl)hex-5-yn-1-one (**S4**) (3.04 mL, 20.0 mmol, 1 equiv) was used. After stirring for 16 h at rt, the crude reaction solution was diluted with hexanes (20 mL) and filtered through a plug of silica gel and concentrated with the aid of a rotary evaporator. The crude reaction mixture was purified with the aid of a Biotage Isolera (100 g SNAP cartridge, 0-7% EtOAc/hexanes) to afford the title compound as a yellow oil (2.01 g, 82% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.2 Hz, 2H), 7.26 (d, *J* = 8.1 Hz, 2H), 5.78 (ddt, *J* = 17.6, 11.0, 2.2 Hz, 1H), 5.55 (dd, *J* = 17.5, 2.3 Hz, 1H), 5.39 (dd, *J* = 11.0, 2.3 Hz, 1H), 3.09 (t, *J* = 7.2 Hz, 2H), 2.48 – 2.38 (m, 5H), 1.98 (p, *J* = 7.0 Hz, 2H).

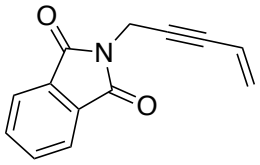
^{13}C NMR (101 MHz, $CDCl_3$) δ 199.5, 143.9, 134.6, 129.4, 128.3, 125.9, 117.6, 90.3, 80.3, 37.3, 23.3, 21.8, 19.0.
IR (neat): 2936, 2224, 1679 (s), 1606, 1232, 806 cm^{-1}
HRMS (DART) Calcd. for $C_{15}H_{17}O$ [M+H]+: 213.1274. Found: 213.1281.



2-(hept-6-en-4-yn-1-yloxy)-5-(trifluoromethyl)pyridine (1i): In a nitrogen-filled glovebox, an oven-dried round bottom flask with magnetic stir bar was charged with sodium hydride (432 mg, 18.0 mmol, 1.2 equiv) and the flask was sealed with a rubber septum and removed from the glovebox. Under an atmosphere of nitrogen, anhydrous THF (20 mL) was added followed by careful addition of 2-chloro-5-(trifluoromethyl)pyridine (2.72 g, 15.0 mmol, 1 equiv) in THF (4 mL) while stirring (caution: gas evolution was observed). After stirring for 20 min at rt, the reaction solution was heated to 60 ºC and stirred for 17.5 h. The reaction mixture was allowed to cool to rt and quenched by addition of water (5 mL). The orange-red solution was poured into a separatory funnel containing 15 mL water and extracted with CH_2Cl_2 (3x 25 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated with the aid of a rotary evaporator. Purification with the aid of a Biotage Isolera (50g SNAP cartridge, 2-20% EtOAc/Hexanes) afforded the desired alkyne intermediate, 2-(pent-4-yn-1-yloxy)-5-(trifluoromethyl)pyridine. The isolated material was taken directly on to the Sonogashira coupling.

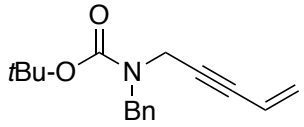
Compound **4i** was prepared following general procedure **C**, with 2-(pent-4-yn-1-yloxy)-5-(trifluoromethyl)pyridine (1.60 g, 7.0 mmol, 1 equiv), bis(triphenylphosphine)palladium(II) chloride (195 mg, 0.28 mmol, 4 mol%), and copper(I) iodide (63.5 mg, 0.33 mmol, 5 mol%). The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 2-10% EtOAc/hexanes) to afford the title compound as colorless oil (1.0 g, 58% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.75 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.80 (d, *J* = 8.7 Hz, 1H), 5.76 (ddt, *J* = 17.5, 11.0, 2.1 Hz, 1H), 5.55 (dd, *J* = 17.5, 2.2 Hz, 1H), 5.38 (dd, *J* = 11.0, 2.2 Hz, 1H), 4.45 (t, *J* = 6.2 Hz, 2H), 2.50 (dt, *J* = 7.1, 2.2 Hz, 2H), 2.02 (p, *J* = 6.6 Hz, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 166.0, 145.0 (q, *J* = 4.5 Hz), 135.6 (q, *J* = 3.2 Hz), 125.8, 124.2 (q, *J* = 271.1 Hz), 120.0 (q, *J* = 33.0 Hz), 117.6, 111.3, 89.7, 80.1, 65.4, 28.1, 16.2.
^{19}F NMR (565 MHz, $CDCl_3$) δ -61.7.
IR (neat): 2957, 2229, 1613, 1120, 1290, 659 cm^{-1}
HRMS (ESI) Calcd. for $C_{13}H_{13}F_3NO$ [M+H]+: 256.0944. Found: 256.0948.



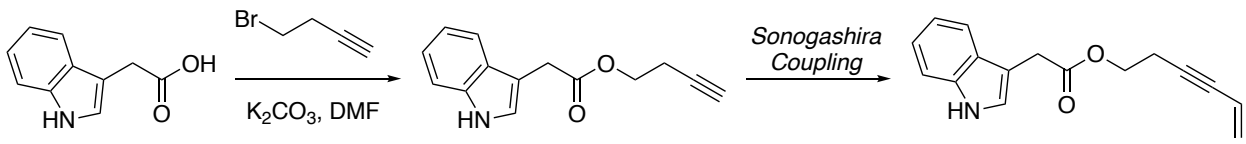
2-(pent-4-en-2-yn-1-yl)isoindoline-1,3-dione (1k): Following general procedure **C**, 2-(prop-2-yn-1-yl)isoindoline-1,3-dione (1.10 g, 5.9 mmol, 1 equiv) was used, and the reaction was stirred for 20 h at rt. The crude reaction mixture was purified with the aid of a Biotage Isolera (100 g SNAP cartridge, 10-100% EtOAc/hexanes) to afford the title compound as an off-white solid (512 mg, 41% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.74 (ddt, *J* = 17.6, 11.0, 2.0 Hz, 1H), 5.63 (dd, *J* = 17.6, 2.2 Hz, 1H), 5.47 (dd, *J* = 11.1, 2.2 Hz, 1H), 4.57 (s, 2H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 167.2, 134.3, 132.2, 128.2, 123.7, 116.6, 83.4, 81.8, 27.9.
IR (neat): 1766, 1704, 1389, 1317, 1109, 721 cm^{-1}
HRMS (ESI) Calcd. for $C_{13}H_{10}NO_2$ [M+H]+: 212.0706. Found: 212.0710.
MP: 114–115 ºC



Tert-butyl benzyl(pent-4-en-2-yn-1-yl)carbamate (1l): Following general procedure **C**, tert-butyl benzyl(prop-2-yn-1-yl)carbamate (prepared according to literature report,[13] 4.66 g, 19.0 mmol, 1 equiv) was used. The crude reaction mixture was purified with the aid of a Biotage Isolera (100 g SNAP cartridge, 0-20% EtOAc/hexanes) to afford the title compound as a yellow oil consisting of a rotameric mixture (3.45 g, 67% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.28 (m, 5H), 5.80 (ddt, *J* = 17.6, 11.0, 2.0 Hz, 1H), 5.62 (dd, *J* = 17.6, 2.2 Hz, 1H), 5.48 (dd, *J* = 11.0, 2.2 Hz, 1H), 4.57 (s, 2H), 4.29 – 3.95 (m, 2H), 1.50 (s, 9H).
^{13}C NMR (151 MHz, $CDCl_3$) δ 155.3, 137.8, (128.6 and 128.2), 127.7, 127.4, 127.3, 117.0, 85.6, (82.5 and 82.2), 80.6, (49.5 and 49.2), (36.3 and 36.0), 28.5.
IR (neat): 2976, 2926, 1694 (s), 1406, 1159, 698 cm^{-1}
HRMS (ESI) Calcd. for $C_{17}H_{22}NO_2$: 272.1645. Found: 272.1646.

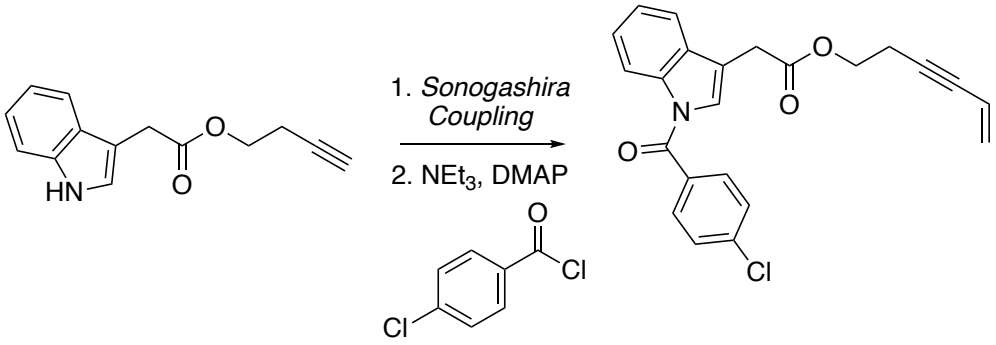


Hex-5-en-3-yn-1-yl 2-(1H-indol-3-yl)acetate (1n): An oven-dried 50 mL round bottom flask with magnetic stir bar was charged with potassium carbonate (3.87 g, 28.0 mmol, 2 equiv) and 2-(1H-indol-3-yl)acetic acid (2.45 g, 14.0 mmol, 1 equiv) and the vessel was subsequently sealed

with a rubber septum. The flask was evacuated and backfilled with nitrogen (this process was repeated a total of three times). DMF (28 mL) was added to the solids via syringe and the suspension was heated to 50 ºC with vigorous stirring for 15 min prior to the addition of 4-bromobut-1-yne (3.72 g, 28.0 mmol, 2 equiv) via syringe. After stirring for 4.5 h, the reaction solution was allowed to cool to rt and then filtered through a plug of celite. The filtrate was concentrated with the aid of a rotary evaporator and the crude reaction material was purified with the aid of a Biotage Isolera (100g SNAP cartridge, 20-80% EtOAc/Hexanes) to afford but-3-yn-1-yl 2-(1H-indol-3-yl)acetate as a yellow oil (1.15 g, 36% yield). The isolated material was taken directly on to the Sonogashira coupling.

Compound **1n** was prepared following general procedure **C**, with but-3-yn-1-yl 2-(1H-indol-3-yl)acetate (1.14 g, 5.0 mmol, 1 equiv). The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 5-20% EtOAc/hexanes) to afford the title compound as a yellow oil (540 mg, 43% yield).

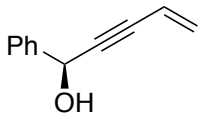
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.66 (d, *J* = 7.7 Hz, 1H), 7.31 (d, *J* = 7.9 Hz, 1H), 7.25 – 7.13 (m, 2H), 7.09 (d, *J* = 2.5 Hz, 1H), 5.79 (ddt, *J* = 17.5, 11.0, 2.0 Hz, 1H), 5.61 (dd, *J* = 17.6, 2.3 Hz, 1H), 5.46 (dd, *J* = 11.0, 2.3 Hz, 1H), 4.26 (t, *J* = 6.9 Hz, 2H), 3.83 (s, 2H), 2.68 (td, *J* = 6.8, 2.1 Hz, 2H).
^{13}C NMR (101 MHz, $CDCl_3$) δ 172.1, 136.2, 127.2, 126.6, 123.3, 122.2, 119.7, 118.9, 117.2, 111.3, 108.1, 86.4, 80.9, 62.7, 31.3, 19.9.
IR (neat): 3404, 1727, 1458, 1156, 911, 740 cm^{-1}
HRMS (ESI) Calcd. for $C_{16}H_{16}NO_2$ [M+H]+: 254.1176. Found: 254.1180.



Hex-5-en-3-yn-1-yl 2-(1-(4-chlorobenzoyl)-1H-indol-3-yl)acetate (1o): Compound **1o** was prepared following the Sonogashira protocol (10.8 mmol scale) outlined for **1n**, followed by benzoylation of the indole as follows: the crude reaction mixture was taken into an oven-dried 100 mL round bottom flask with magnetic stir bar and DMAP (132 mg, 1.08 mmol, 10 mol%) was added. The flask was sealed with a rubber septum and evacuated and backfilled with nitrogen. Anhydrous CH_2Cl_2 (33 mL) was syringed in to the flask and the solution cooled to 0 ºC in an ice-water bath followed by addition of triethylamine (4.5 mL, 32.3 mmol, 3 equiv). After stirring for 30 min, 4-chlorobenzoyl chloride (2.08 mL, 16.2 mmol, 1.5 equiv) was added by syringe and the solution was allowed to warm to rt. After stirring for 23 h, the reaction mixture was poured onto saturated aqueous ammonium chloride (60 mL) and extracted with CH_2Cl_2 (2x 40 mL). The combined organic extracts were dried over sodium sulfate, filtered and concentrated

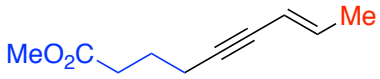
with the aid of a rotary evaporator. Purification with the aid of a Biotage Isolera (100g SNAP cartridge, 0-20% EtOAc/Hexanes) afforded the title compound as an off-white solid (1.30 g, 32% 2-step yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 8.1 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 2H), 7.60 (d, *J* = 7.7 Hz, 1H), 7.51 (d, *J* = 8.2 Hz, 2H), 7.41 (t, *J* = 7.6 Hz, 1H), 7.35 (t, *J* = 7.4 Hz, 1H), 7.29 (s, 1H), 5.72 (dd, *J* = 17.5, 11.0 Hz, 1H), 5.55 (d, *J* = 16.0 Hz, 1H), 5.42 (d, *J* = 11.0 Hz, 1H), 4.23 (t, *J* = 6.7 Hz, 2H), 3.74 (s, 2H), 2.64 (t, *J* = 6.3 Hz, 2H).
^{13} CNMR (101 MHz, $CDCl_3$) δ 170.5, 167.4, 138.4, 136.3, 133.0, 130.7, 130.5, 129.1, 126.8, 125.8, 125.6, 124.2, 119.2, 117.2, 116.6, 114.9, 86.1, 80.9, 63.0, 31.0, 19.9.
IR (neat): 3072, 2956, 1736, 1674, 1451, 749 cm^{-1}
HRMS (ESI) Calcd. for $C_{23}H_{19}ClNO_3$ [M+H]+: 392.1048. Found: 392.1056.
MP: 71–72 ºC



(S)-1-phenylpent-4-en-2-yn-1-ol (1p): Following general procedure **C**, (R)-1-phenylprop-2-yn-1-ol (1.98 g, 15.0 mmol, 1 equiv) was used, and the solution was stirred for 49 h at rt. The crude reaction mixture was purified with the aid of a Biotage Isolera (100 g SNAP cartridge, 0–15% EtOAc/hexanes) to afford the title compound as an off-white solid (1.10 g, 46% yield,). The spectral data match those previously reported in the literature.[14]

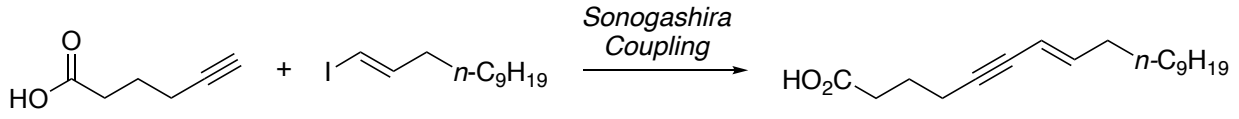
Determination of enantiomeric ratio by GC analysis: Agilent Technologies 19091G-B233 J&W HP-Chiral 20ß GC Column (30 m, 0.25 mm, 0.25 µm, 7 inch cage), 8 psi: 90 ºC for 50 min then 0.5 ºC/min to 150 ºC; t_r = 158.0 min (major) and 160.6 min (minor).



Methyl (E)-non-7-en-5-ynoate (1q): Following general procedure **C**, methyl hex-5-ynoate (2.60 g, 20.0 mmol, 1 equiv) and 1-bromoprop-1-ene (4.84 g, 40.0 mmol, 2 equiv, mixture of E/Z isomers) was used. After stirring for 20 h at rt, the reaction solution was diluted with hexanes (20 mL) and filtered through a plug of silica gel and concentrated on a rotary evaporator. The crude reaction mixture was carefully purified with the aid of a Biotage Isolera (100 g SNAP cartridge, 0–7% EtOAc/hexanes, 70 mL/min). The product was collected in two fractions in order to separate some of the E-isomer from the Z-isomer. The title compound was isolated as a colorless oil (920 mg of >20:1 E/Z and 1.88 g of a 4:1 E/Z mixture, 70% total yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.05 (dq, J = 15.7, 6.7 Hz, 1H), 5.45 (dq, J = 15.7, 1.9 Hz, 1H), 3.67 (s, 3H), 2.44 (t, J = 7.5 Hz, 2H), 2.35 (td, J = 6.9, 2.1 Hz, 2H), 1.83 (p, J = 7.1 Hz, 2H), 1.74 (dd, J = 6.7, 1.8 Hz, 3H).
^{13}C NMR (151 MHz, CDCl3) δ 173.8, 138.6, 111.0, 87.0, 80.2, 51.7, 33.0, 24.1, 18.9, 18.6.
IR (neat): 2953, 1736 (s), 1436, 1212, 1155, 953 cm^{-1}

HRMS (ESI) Calcd. for $C_{10}H_{15}O_2$ [M+H]+: 167.0167. Found: 167.1068.



(E)-octadec-7-en-5-ynoic acid (1s): Following general procedure **C**, hex-5-ynoic acid (1.02 g, 9.1 mmol, 1 equiv) and (E)-1-iodododec-1-ene (4.00 g, 3.6 mmol, 1.5 equiv, prepared according to literature report[15]) was used. After stirring for 12 h at rt, the crude reaction solution was taken into 1N aqueous HCl (50 mL) and extracted with CH_2Cl_2 (3x 40 mL). The combined organic extracts were washed with brine (1x 30 mL), dried over magnesium sulfate, filtered and concentrated. The crude reaction mixture was purified with the aid of a Biotage Isolera (50 g SNAP cartridge, 0–25% EtOAc/hexanes). The title compound was isolated as an off-white solid (854 mg, 34% yield). The spectral data match those previously reported in the literature.[16]

IX. References

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