Supporting Information

Preparation of Substituted Enol Derivatives from Terminal Alkynes and Their Synthetic Utility

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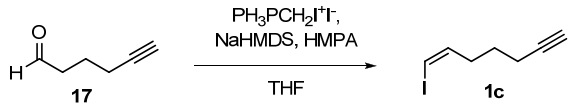
Method and Materials

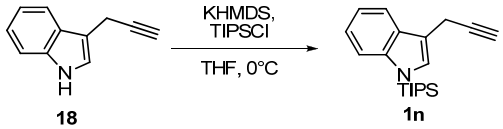
General. Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly purified solvents. Solvents were purified using solvent purification columns purchased from Glass Contour, Laguna Beach, CA. All reactions were monitored by thin-layer chromatography with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). Gas chromatography (GC) was performed on an HP 6890N autosampling GC with an HP-5 capillary column and equipped with a FID detector. Flash chromatography was performed with indicated solvents using silica gel (particle size 0.032-0.063 μm) purchased from Sorbent Technologies.^{1}H and ^{13}C NMR spectra were recorded on Varian Inova-400 or Mercury-300 spectrometer. Chemical shifts are reported relative to internal chloroform ($CDCl_3$: ^{1}H, δ = 7.27, ^{13}C, δ = 77.26). Coupling constants are in Hz and are reported as d (doublet), t (triplet), q (quartet), p (pentet) sep (septet), and app for apparent. For signals having multiple coupling patterns, the coupling constant are listed in the same order as the pattern (e.g. dt, J = 2.0, 4.0; 2.0 is the coupling constant for the doublet and 4.0 is for the coupling constant for the triplet). Infrared spectra were recorded on a Perkin- Elmer 1000 series FTIR. Low-resolution mass spectra were acquired on a Shimadzu QP5000 GC/MS using the indicated ionization method. HPLC analyses were carried out on a Shimadzu LC-2010A system. Optical rotations were measured on a Rudolph Research Analytical Autopol® IV Polarimeter.

Materials. Cp_2ZrCl_2 was purchased from Strem Chemicals Inc. Me_3Al (2.0M in toluene), Me_2Zn (2.0M in toluene), and AD-mix α and β were purchased from Aldrich. Anhydrous ^{t}BuOOH in toluene was prepared from the known Sharpless procedure.[1] Unless otherwise noted, all terminal alkyne starting materials were purchased from Aldrich. 1-Hepten-6-yne (**1i**, Table 1)[2] and 1-octen-7-yne (**1j**, Table 1)[3] were prepared following the known literature procedures.

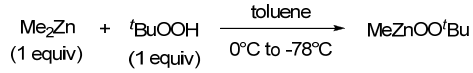
Preparation of alkyne starting materials (Table 1, entries 3 and 12)**:**



1c: Vinyl iodide **1c** was prepared from the reaction of aldehyde **17**[4] with $PH_3PCH_2I[I]$[5] following a similar olefination procedure.[6] The crude vinyl iodide was purified by flash chromatography (100% pentane) and the fractions were analyzed by GC. The desired compound was obtained as pink solution in pentane (0.734 g, 45%, Z/E ratio 25/1). ^{1}H NMR ($CDCl_3$) δ = 1.68 (app p, J = 7.4, 2H), 1.98 (t, J = 2.4, 1H), 2.22-2.29 (m, 4H), 6.18 (q, J = 6.8, 1H), 6.25 (d, J = 7.4, 1H). ^{13}C NMR ($CDCl_3$) δ = 18.21, 27.09, 33.99, 69.02, 83.53, 84.08, 140.35. EI-MS (m/z): 220 $[M]^+$.

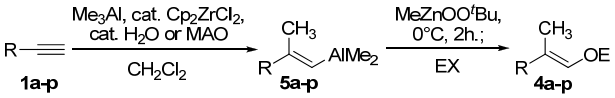


1n: To a stirred solution of indole **18**[7] (7.1 mmol) in 15 mL of THF at 0˚C was added KHMDS (in 15 mL THF, 1.56 g, 7.46 mmol, 1.05 equiv). The reaction was stirred for 30 minutes at this temperature, at which time TIPSCl (1.84 mL, 7.81 mmol, 1.1 equiv) was added. The reaction was stirred overnight, quenched with water, and extracted 3 times with EtOAc. The combined organic extracts were concentrated and the crude indole was purified by flash chromatography (5% EtOAc in hexanes) to give the desired product as a white solid (1.5 g, 68% yield). ^{1}H NMR ($CDCl_3$) δ = 1.34 (d, J = 7.2, 18H), 1.63-1.75 (m, 3H), 2.14 (t, J = 2.4, 1H), 3.69 (dd, J = 2.4, J = 1.2, 2H), 7.11-7.18 (m, 2H), 7.18 (s, 1H), 7.48 (dd, J = 7.2, J = 2, 1H), 7.61 (dd, J = 6.4, J = 2, 1H). ^{13}C NMR ($CDCl_3$) δ = 13.06, 15.64, 18.39, 69.21, 82.66, 112.83, 114.26, 118.65, 119.72, 121.85, 129.04, 130.33, 141.71. EI-MS (m/z): 311 $[M]^+$.



Procedure for preparing MeZnOO^{t}Bu: To a stirred solution of Me_2Zn (1.0 equiv) in dry toluene at -78˚C was added dropwise anhydrous ^{t}BuOOH (3.9M in toluene, 1.0 equiv).[1] After adding the solution of ^{t}BuOOH, the concentration of peroxide should be 0.3M in toluene. The resulting mixture was stirred for 15 minutes at -78˚C, at which time the flask was quickly transferred to an ice-water bath to warm the solution to 0˚C. The reaction was complete after stirring for an additional 15 minutes at 0˚C. At this time a solution of vinyl alane was immediately transferred to the zinc peroxide at 0˚C.

Preparation of Enol Benzoates from Terminal Alkynes:



Methylalumination-oxygenation:

Method A (Table 1, entries 1-4, 9-11): To a stirred solution of Cp_2ZrCl_2 (0.59 g, 0.2 mmol, 0.1 equiv.) and Me_3Al (2.0M in Toluene, 1.5 mL, 3.0 mmol, 1.5 equiv.) in 6.5 mL CH_2Cl_2 at 0˚C was slowly added H_2O (0.9 µL, 0.05 mmol, 2.5 mol%) (reaction is exothermic and produces smoke). The reaction was allowed to warm to room temperature, and after 10 minutes the terminal alkyne (2.0 mmol, 1.0 equiv.) was added. When the methylalumination appeared complete by TLC, the reaction solution was quickly transferred via canula into a stirred solution of $MeZnOO^tBu$ (0.3M in toluene, 14 mL, 4.0 mmol, 2.0 equiv) at 0˚C. The oxygenation was complete after stirring for 2 hours at 0˚C. Electrophilic was trapping performed as described below.

Method B [Table 1, entries 5, 14 (for free alcohols)**]:** To a stirred solution of Me_3Al and MAO in 3.0mL CH_2Cl_2 at 0˚C was added terminal alkyne in 3.0mL CH_2Cl_2. The resulting solution was allowed to stir for 1 hour at room temperature before Cp_2ZrCl_2 in 1.0 mL CH_2Cl_2 was added. When the methylalumination appeared complete by TLC, the reaction solution was quickly transferred via canula into a stirred solution of $MeZnOO^tBu$ (0.3M in toluene) at 0˚C. The oxygenation was complete after stirring for 2 hours at 0˚C. Electrophilic trapping was performed as described below. In entry 5, after benzoylation of the enolate, BzCl (2 equiv) was added at 0°C to benzoylate the primary alcohol.

Method C (Table 1, entries 6, 7, 12-13): To a stirred solution of Cp_2ZrCl_2 and Me_3Al in 6.5 mL CH_2Cl_2 at room temperature was added MAO and terminal alkyne. When the methylalumination appeared complete by TLC, the reaction solution was quickly transferred via canula into a stirred solution of $MeZnOO^tBu$ (0.3M in toluene) at 0˚C. The oxygenation was complete after stirring for 2 hours at 0˚C. Electrophilic trapping was performed as described below.

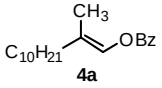
Electrophilic trapping:

Benzoylation: After methylalumination-oxygenation was complete, $^nBu_3P$ (0.4 mmol, 0.2 equiv) and Bz_2O (16 mmol, 8 equiv) in 10-15 mL CH_2Cl_2 (pre-mixed at 0˚C for 10 minutes) were transferred to the methylalumination-oxygenation reaction mixture via canula at 0˚C. The reaction was allowed to warm to room temperature and the benzoylation was complete after 15 hours. The reaction was quenched by transferring the contents of the flask into 100 mL of a stirred 10% aqueous solution of citric acid (CA) at 0˚C. The reaction flask was washed with 10 mL CH_2Cl_2 (2 X 5) and this was transferred to the 10% CA solution as well. The resulting slurry was stirred for 3 hours or until the two phases were homogenous, at which time it was extracted 3 times with CH_2Cl_2. The combined organic extracts were washed once with saturated $NaHCO_3$, dried over $MgSO_4$, and concentrated. Before purification by flash chromatography (silica gel, EtOAc/hexanes), 2-3 mm of Et_3N was added to the top of the SiO_2 surface of the column. The crude enol benzoate was loaded onto the column when the Et_3N had receded to ½ mm above the SiO_2 surface. Pretreating the column with Et_sN in this fashion helps separate the desired product from a streaky yellow impurity. Reaction times, purification conditions and characterization data are provided below for all entries in Table 1.

Acylation: After methylalumination-oxygenation was complete (2 hours at 0˚C), Ac_2O (1.1 mL, 12 mmol, 6.0 equiv.) was added to the reaction at 0˚C. The reaction was allowed to warmed r.t. and then heated to 35˚C. Acylation was complete in 4 hours at this temperature. The reaction was then cooled to 0˚C and 1.0 mL H_2O was added slowly with vigorous stirring. When H_2O addition was complete, the mixture was stirred for 15 minutes at room temperature, after which time 1.0 g $MgSO_4$ was added. The mixture was filtered through a plug of silica gel and the solvent was removed to give the crude enol acetate.

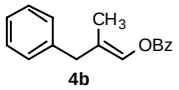
Silylation: After methylalumination-oxygenation was complete (2 hours at 0˚C), a solution of TESOTf (3.2 mL, 14 mmol, 7.0 equiv) in 6.0 mL CH_2Cl_2 and 6.0 mL pyridine was transferred to the reaction at 0˚C. The solution was allowed to stir overnight at 4˚C. At this time, 1.5 mL H_2O was added slowly to the vigorous stirring reaction solution at 0˚C. After 15 min at r.t., 3.0g $MgSO_4$ was added and the resulting mixture was filtered through a plug of silica gel. The solvent was removed to give the crude TES enol ether.

Characterization data for enol benzoate compounds and reaction details (Table 1)**:**



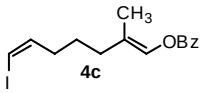
4a

4a (Table 1, entry 1, Method A): Methylalumination was complete in 5 hours. Chromatography (0.5-1.0% EtOAc in hexane) provided 0.47g (78% yield) of a white solid. ^1H NMR ($CDCl_3$) δ = 0.88 (t, *J* = 6.5, 3H), 1.28 (m, 14H), 1.45 (t, *J* = 7.0, 2H), 1.81 (d, *J* = 1.3, 3H), 2.04 (t, *J* = 7.3, 2H), 7.15 (d, *J* = 1.3, 1H), 7.47 (t, *J* = 7.9, 2H), 7.59 (tt, *J* = 7.4, *J* = 1.2, 1H), 8.11 (dd, *J* = 8.4, *J* = 1.4, 2H). ^{13}C NMR ($CDCl_3$) δ = 14.1, 14.4, 22.9, 27.8, 29.5, 29.6, 29.7, 29.9, 29.9, 32.2, 34.3, 122.8, 128.6, 130.0, 130.4, 133.4, 163.8. FTIR (thin film) 2923, 1689, 1288 cm^{-1}. EI-MS (m/z): 302 $[M]^+$.



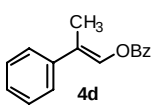
4b

4b (Table 1, entry 2, Method A): Methylalumination was complete in 4.5 hours. Chromatography (1.0% EtOAc in hexane) provided 0.45g (89% yield) of a white solid. ^1H NMR ($CDCl_3$) δ = 1.74 (d, *J* = 1.2, 3H), 3.36 (s, 2H), 7.21-7.27 (m, 2H), 7.29-7.33 (m, 3H), 7.47 (t, *J* = 8.0, 2H), 7.60 (t, *J* = 7.6, 1H), 8.11 (d, *J* = 7.6, 2H). ^{13}C NMR ($CDCl_3$) δ = 14.1, 40.7, 122.1, 126.7, 128.7, 128.8, 129.1, 129.8, 130.1, 131.7, 133.6, 139.2, 163.9. FTIR (thin film) 2918, 1726, 1261 cm^{-1}. EI-MS (m/z): 252 $[M]^+$



4c

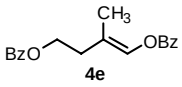
4c (Table 1, entry 3, Method A): Methylalumination was complete in 3.5 hours. Chromatography (1.0% EtOAc in hexane) provided 0.58g (82% yield) of a brown oil. ^1H NMR ($CDCl_3$) δ = 1.62 (app p, *J* = 7.8, 2H), 1.83 (d, *J* = 1.3, 3H), 2.10 (t, *J* = 7.6, 2H), 2.17 (dt, *J* = 6.2, *J* = 7.4, 2H), 6.17-6.24 (m, 2H), 7.18 (d, *J* = 1.2, 1H), 7.47 (t, *J* = 8, 2H), 7.59 (t, 7.6, 1H), 8.11 (d, *J* = 8, 2H). ^{13}C NMR ($CDCl_3$) δ = 14.1, 26.2, 33.7, 34.5, 83.2, 122.0, 128.7, 129.8, 130.0, 130.8, 133.5, 141.0, 163.8. FTIR (thin film) 2933, 1778, 1271 cm^{-1}. EI-MS (m/z): 229 $[M-I]^+$.



4d

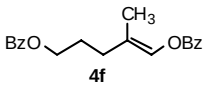
4d (Table 1, entry 4, Method A): Methylalumination was complete in 4 hours. Chromatography (1.0% EtOAc in hexane) provided 0.38g (80% yield) of a white solid. ^1H NMR ($CDCl_3$) δ = 2.25 (d, *J* = 1.2, 3H), 7.25-7.31 (m, 1H), 7.37 (t, *J* = 7.2, 2H), 7.45 (d, *J*

= 7.2, 2H), 7.51 (t, *J* = 8, 2H), 7.63 (t, *J* = 7.6, 1H), 7.78 (s, 1H), 8.17 (d, *J* = 8, 2H). ^{13}C NMR ($CDCl_3$) δ = 14.1, 122.5, 126.1, 127.6, 128.7, 128.8, 129.6, 130.1, 132.9, 133.8, 139.3, 163.8. FTIR (thin film) 2362, 1721, 127 cm^{-1}. EI-MS (m/z): 238 $[M]^+$.



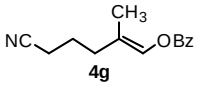
4e

4e (Table 1, entry 5, Method B): Reagent amounts: Alkyne (2.0 mmol, 1.0 equiv), Me_3Al (8.0 mmol, 4.0 equiv), Cp_2ZrCl_2 (0.4 mmol, 0.2 equiv), MAO (0.1 mmol, 5 mol%), MeZnOO^{t}Bu (0.3M in tol, 32 mL, 9.6 mmol, 4.8 equiv), Bz_2O (24 mmol, 12 equiv), ^{n}Bu$_3$P (0.82mmol, 0.3 equiv). Methylalumination was complete in 8 hours. Chromatography (5.0% EtOAc in hexanes) provided 0.37g (59% yield) of a white solid. ^{1}H NMR ($CDCl_3$) δ = 1.91 (d, *J* = 1.4, 3H), 2.52 (t, *J* = 6.6, 2H), 4.45 (t, *J* = 6.6, 2H), 7.28 (d, *J* = 1.3, 1H), 7.28-7.48 (m, 4H), 7.52-7.61 (m, 2H), 8.04 (dd, *J* = 8.5, *J* = 1.1, 2H), 8.10 (dd, *J* = 8.5, *J* = 1.1, 2H). ^{13}C NMR ($CDCl_3$) δ = 14.3, 33. 7, 63.1, 118.7, 128.6, 128.7, 129.7, 129.8, 130.4, 133.3, 133.2, 133.2, 133.62 163.7, 166.8. FTIR (thin film) 2913, 1723, 1283 cm^{-1}. EI-MS (m/z): 205 $[M\text{-}PhCHO]^+$.



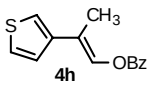
4f

4e (Table 1, entry 5, Method B): Reagent amounts: Alkyne (2.0 mmol, 1.0 equiv), Me_3Al (6.0 mmol, 3.0 equiv), Cp_2ZrCl_2 (0.4 mmol, 0.2 equiv), MAO (0.1 mmol, 5 mol%), MeZnOO^{t}Bu (0.3M in tol, 23 mL, 7.0 mmol, 3.5 equiv), Bz_2O (18 mmol, 9 equiv), ^{n}Bu$_3$P (0.4 mmol, 0.2 equiv). Methylalumination was complete in 22 hours. Chromatography (2.0-5.0% EtOAc in hexanes) provided 0.5g (79% yield) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ = 1.86 (d, *J* = 1.2, 3H), 1.93-2.00 (m, 2H), 2.24 (t, *J* = 7.2, 2H), 4.36 (t, *J* = 6.8, 2H), 7.22 (d, *J* = 1.2, 1H), 7.42-7.49 (m, 4H), 7.54-7.61 (m, 2H), 8.06 (dd, *J* = 8.4, *J* = 1.4, 2H), 8.11 (dd, *J* = 8.2, *J* = 1.5, 2H). ^{13}C NMR ($CDCl_3$) δ = 14.1, 27.0, 30.9, 64.6, 94.6, 121.5, 128.6, 128.7, 129.8, 130.0, 130.5, 131.0, 133.1, 133.6, 163.8, 166.8. FTIR (thin film) 2952, 1723, 1273 cm^{-1}. EI-MS (m/z): 324 $[M]^+$.



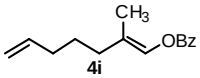
4g

4g (Table 1, entry 6, Method C): Reagent amounts: Alkyne (2.0 mmol, 1.0 equiv), Me_3Al (6.0 mmol, 3.0 equiv), Cp_2ZrCl_2 (0.6 mmol, 0.3 equiv), MAO (0.4 mmol, 0.2 equiv), MeZnOO^{t}Bu (0.3M in tol, 27 mL, 8.0 mmol, 4.0 equiv), Bz_2O (18 mmol, 9 equiv), ^{n}Bu$_3$P (0.4 mmol, 0.2 equiv). Methylalumination was complete in 3 days. Chromatography (10% EtOAc in hexanes) provided 0.32g (71% yield) of a yellow oil. ^{1}H NMR ($CDCl_3$) δ = 1.82-1.91 (m, 2H), 1.84 (d, *J* = 1.5, 3H), 2.23 (t, *J* = 7.5, 2H), 2.37 (t, *J* = 7.2, 2H), 7.19-7.22 (m, 1H), 7.48 (tt, *J* = 7.7, *J* = 1.5, 2H), 7.60 (tt, *J* = 7.4, *J* = 1.4, 1H), 8.09-8.13 (m, 2H). ^{13}C NMR ($CDCl_3$) δ = 13.7, 16.5, 23.4, 32.9, 119.7, 120.2, 128.7, 129.5, 129.9, 131.5, 133.6, 163.6. FTIR (thin film) 2928, 1728, 1268 cm^{-1}. EI-MS (m/z): 229 $[M]^+$.



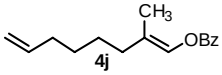
4h

4h (Table 1, entry 7, Method C): Reagent amounts: Alkyne (2.0 mmol, 1.0 equiv), Me_3Al (6.0 mmol, 3.0 equiv), Cp_2ZrCl_2 (0.6 mmol, 0.2 equiv), MAO (0.4 mmol, 0.2 equiv), MeZnOO^{t}Bu (0.3M in tol, 27 mL, 8.0 mmol, 4.0 equiv), Bz_2O (18 mmol, 9 equiv), ^{n}Bu$_3$P (0.4 mmol, 0.2 equiv). Methylalumination was complete in 48 hours. Chromatography (1.5% EtOAc in hexanes) provided 0.4g (83% yield) of a yellow solid. ^{1}H NMR ($CDCl_3$) δ = 2.21 (d, *J* = 1.2, 3H), 7.20-7.22 (m, 1H), 7.28 (dd, *J* = 5.1, *J* = 1.5, 1H), 7.32 (app q, *J* = 3.0, 1H), 7.50 (t, *J* = 7.6, 2H), 7.62 (tt, *J* = 7.5, *J* = 1.3, 1H), 7.90 (d, *J* = 1.3, 1H), 8.15 (dd, *J* = 8.3, *J* = 1.3, 2H). ^{13}C NMR ($CDCl_3$) δ = 13.9, 118.0, 120.4, 124.8, 126.3, 128.9, 129.5, 130.2, 132.9, 133.8, 140.3, 163.6. FTIR (thin film) 3101, 1720, 1268 cm^{-1}. EI-MS (m/z): 244 $[M]^+$.



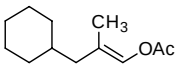
4i

4i (Table 1, entry 8, Method D): Methylalumination was complete in 6.5 hours at 0˚C. Chromatography (1.0% EtOAc in hexanes) provided 0.37g (76% yield) of a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ = 1.53-1.61 (m, 2H), 1.81 (d, *J* = 1.4, 3H), 2.05-2.11 (m, 4H), 4.96-5.07 (m, 2H), 5.77-5.88 (m, 1H), 7.16 (d, *J* = 1.4, 1H), 7.47 (t, *J* = 7.4, 2H), 7.59 (tt, *J* = 7.4, *J* = 1.3, 1H), 8.11 (dt, *J* = 8.1, *J* = 1.4, 2H). ^{13}C NMR ($CDCl_3$) δ = 14.0, 27.0, 33.4, 33.6, 115.0, 133.3, 128.7, 129.91, 123.0, 130.7, 133.4, 138.6, 163.8. FTIR (thin film) 2933, 1728, 1266 cm^{-1}. EI-MS (m/z): 230 $[M]^+$.



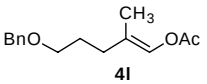
4j

4i (Table 1, entry 8, Method D): Methylalumination was complete in 6.5 hours at 0˚C. Chromatography (1.0% EtOAc in hexanes) provided 0.35g (75% yield) of a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ = 1.37-1.52 (m, 4H), 1.81 (d, *J* = 1.2, 3H), 2.04-2.11 (m, 4H), 4.94-5.04 (m, 2H), 5.76-5.87 (m, 1H), 7.15 (d, *J* = 1.3, 1H), 7.47 (t, *J* = 7.6, 2H), 7.59 (tt, *J* = 7.4, *J* = 1.2, 1H), 8.10 (dd, *J* = 8.0, *J* = 1.2, 2H). ^{13}C NMR ($CDCl_3$) δ = 14.0, 27.2, 28.6, 33.8, 34.0, 114.7, 122.6, 128.76, 129.9, 130.0, 130.5, 133.4, 139.0, 163.8. FTIR (thin film) 2933, 1728, 1266 cm^{-1}. EI-MS (m/z): 244 $[M]^+$.



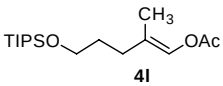
4k

4k (Table 1, entry 9, Method A): Reagent amounts: Cp_2ZrCl_2 (0.59 g, 0.2 mmol, 0.1 equiv.), Me_3Al (2M in Toluene, 1.5 mL, 3.0 mmol, 1.5 equiv.), MeZnOO^{t}Bu (0.3M in toluene, 13.3 mL, 4 mmol, 2.0 equiv). Enol acetate **4k** (0.36 g, 91%) was obtained as a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ = 0.78-0.87 (m, 2H), 1.14-1.25 (m, 4H), 1.34-1.45 (m, 1H), 1.59-1.72 (m, 4H), 1.64 (d, *J* = 1.4, 3H), 1.82 (d, *J* = 7.2, 2H), 2.13 (s, 3H), 6.84 (d, *J* = 1.3, 1H). ^{13}C NMR ($CDCl_3$) δ = 13.9, 21.0, 26.5, 26.8, 33.4, 35.3, 42.0, 120.5, 130.9, 168.6. FTIR (thin film) 2928, 1750, 1213 cm^{-1}. EI-MS (m/z): 196 $[M]^+$.



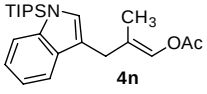
4l

4l (Table 1, entry 10, Method A): Reagent amounts: Cp_2ZrCl_2 (0.117 g, 0.4 mmol, 0.2 equiv), Me_3Al (3.0 mL, 6.0 mmol, 3.0 equiv), 0.3M MeZnOO^{t}Bu in toluene (25 mL, 7.6 mmol, 3.8 equiv). Methylalumination was complete in 24 hours. Enol acetate **4l** was obtained as a yellow oil (0.48 g, 96%). ^{1}H NMR ($CDCl_3$) δ = 1.65 (d, *J* = 1.2, 3H), 1.73 (m, 2H), 2.06 (t, *J* = 7.0, 2H), 2.12 (s, 3H), 3.45 (t, *J* = 6.4, 2H), 4.49 (s, 2H), 6.89 (d, *J* = 1.1, 1H), 7.25-7.36 (m, 5H). ^{13}C NMR ($CDCl_3$) δ = 18.6, 25.7, 32.7, 35.5, 74.5, 77.7, 125.7, 132.5, 132.6, 133.3, 135.4, 143.8, 172.8. FTIR (thin film) 2864, 1745, 1222 cm^{-1}. EI-MS (m/z): 205 $[M\text{-}CH_3CHO]^+$.



4l

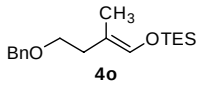
4m (Table 1, entry 11, Method A): Reagent amounts: Cp_2ZrCl_2 (0.117 g, 0.4 mmol, 0.2 equiv), Me_3Al (3.0 mL, 6.0 mmol, 3.0 equiv), 0.3M MeZnOO^{t}Bu in toluene (25 mL, 7.6 mmol, 3.8 equiv). Enol acetate **4m** was obtained as a pale yellow oil (0.43g, 92%). ^{1}H NMR ($CDCl_3$) δ = 1.04-1.07 (m, 18H), 1.62-1.68 (m, 3H), 1.68 (d, *J* = 1.2, 3H), 2.05 (t, *J* = 7.2, 2H), 2.13 (s, 3H), 3.67 (t, *J* = 6.4, 2H), 6.90 (d, *J* = 1.2, 1H). ^{13}C NMR ($CDCl_3$) δ = 12.2, 13.9, 18.2, 21.0, 30.5, 31.2, 63.0, 94.6, 121.8, 130.4. FTIR (thin film) 2928, 1750, 1219 cm^{-1}. EI-MS (m/z): 271 $[M\text{-}CH_2CH_3]^+$.



4n

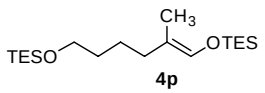
4n (Table 1, entry 12, Method C): Reagent amounts: Cp_2ZrCl_2 (0.175 g, 0.6 mmol, 0.3 equiv), Me_3Al (2.0M in toluene, 3.0 mL, 6.0 mmol, 3.0 equiv), MAO (10% solution, 0.133 mL, 0.2 mmol, 0.1 equiv) 0.3M MeZnOO^{t}Bu (25 mL, 7.6 mmol, 3.8 equiv). Enol acetate **4n** (0.71 g, 92%) was isolated as a yellow syrup. ^{1}H NMR ($CDCl_3$) δ = 1.14 (d, *J* = 7.6, 18H), 1.64 (d, *J*

= 1.2, 3H), 1.65-1.73 (m, 3H), 2.13 (s, 3H), 3.43 (s, 2H), 7.02 (s, 1H), 7.08-7.15 (m,3H), 7.46 (d, J = 8, 1H), 7.58 (d, J = 8, 1H). ^{13}C NMR ($CDCl_3$) δ = 13.1, 14.0, 18.5, 21.1, 30.4, 114.2, 115.1, 119.2, 119.7, 121.4, 121.7, 129.6, 131.2, 131.3, 141.8, 168.5. FTIR (thin film) 2948, 2866, 1753, 1451, 1229 cm^{-1}. EI-MS (m/z): 385 $[M]^+$.



4o

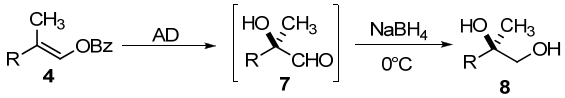
4o (Table 1, entry 13, Method C): Reagent amounts: Cp_2ZrCl_2 (0.175 g, 0.6 mmol, 0.3 equiv), Me_3Al (2.0M in toluene, 3.0 mL, 6.0 mmol, 3.0 equiv), MAO (10% wt. solution, 0.265 mL, 0.4 mL, 0.2 equiv.) 0.3M MeZnOO^{t}Bu (25 mL, 7.6 mmol, 3.8 equiv). TES enol ether **4o** was isolated as a bright yellow oil (0.48 g, 79%). ^{1}H NMR ($CDCl_3$) δ = 0.65 (q, J = 8, 6H), 0.97 (t, J = 8, 9H), 1.62 (d, J = 1.4, 3H), 2.20 (t, J = 7.2, 2H), 3.50 (t, J = 7.2, 2H), 4.50 (s, 2H), 6.15 (d, J = 1.4, 1H), 7.25-7.31 (m, 2H), 7.33 (d, J = 4.5, 3H). ^{13}C NMR ($CDCl_3$) δ = 4.8, 6.9, 13.2, 34.5, 69.8, 73.1, 114.3, 127.7, 127.8, 128.6, 135.5, 138.9. FTIR (thin film) 2908, 1673, 1456, 1164 cm^{-1}. EI-MS (m/z): 277 $[M\text{-}CH_2CH_3]^+$.



4p

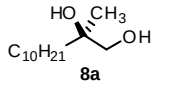
4p (Table 1, entry 14, Method B): Reagent amounts: Alkyne (2.0 mmol, 1.0 equiv), Me_3Al (6.0 mmol, 3.0 equiv), Cp_2ZrCl_2 (0.4 mmol, 0.2 equiv), MAO (0.1 mmol, 5 mol%), MeZnOO^{t}Bu (0.3M in tol, 23 mL, 7.0 mmol, 3.5 equiv). TES enol ether **4p** was isolated as a colorless oil (0.54 g, 83%). ^{1}H NMR ($CDCl_3$) δ = 0.61-0.63 (m, 12H), 0.96 (t, J = 7.9, 9H), 0.97 (t, J = 7.9, 9H), 1.36-1.1.40 (m, 2H), 1.42-1.50 (m, 2H), 1.57 (d, J = 1.3, 3H), 1.86 (t, J = 7.1, 2H), 3.59 (t, J = 6.4, 2H), 6.06 (d, J = 1.3, 1H). ^{13}C NMR ($CDCl_3$) δ = 4.6, 4.7, 6.7, 6.9, 12.5, 24.5, 32.6, 33.7, 62.9, 117.3, 133.9. FTIR (thin film) 2918, 1671, 1457, 1160 cm^{-1}. EI-MS (m/z): 358 $[M]^+$.

Preparation of 1,2-diols from enol benzoates (Table 2)**:**



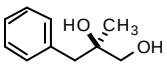
General procedure for the preparation of 1,2-diols (8) from enol benzoates (4) (Table 2): All AD reactions performed followed Sharpless' general procedure.[8] Thus, a 1:1 mixture of ^{t}BuOH/H_2O (0.1M based on olefin) was added to flask containing AD-mix β (1.4 g per 1 mmol of olefin) and the mixture was stirred to produce two clear phases. The resulting solution was then stirred at 0˚C until the dissolved salts precipitated. The olefin (1.0 equiv) in ^{t}BuOH was added and the slurry was stirred vigorously at 0˚C until the reaction was complete (12-24 hours). Once complete, $NaBH_4$ (6 equiv to olefin) was added to the mixture at 0˚C and the reaction was kept at this temperature until reduction was complete (about 2 hours). Saturated NH_4Cl was added and the reaction was extracted 3 times with EtOAc. The combined organic extracts were dried with $MgSO_4$ and concentrated to give crude diol product. The diols were further purified by flash chromatography. The ee's of the diols were determined from their monobenzoylated analogues (BzCl, Et_3N, cat. DMAP, CH_2Cl_2). Specific HPLC conditions and chromatograms are located in the section of the supporting information containing NMR spectra. Absolute stereochemistry was assigned by comparison of the optical rotation to reported values the reported value for **8d**. For **8a**, **8d** and **8q**, we further confirmed that the major enantiomer was the same as obtained from dihydroxylation of the 1,1-disubstituted olefin. Other diols are assigned by analogy.

Characterization data for 1,2-diol compounds (Table 2)**:**



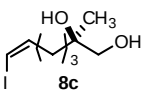
8a

8a (Table 2, entry 1): Chromatography (35% EtOAc in hexanes) provided 66 mg (78% yield) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ = 0.88 (t, J = 6.7, 3H), 1.16 (s, 3H), 1.19-1.41 (m, 16H), 1.45-1.51 (m, 2H), 1.9 (br s, 2H), 3.41 (d, J = 10.9, 1H), 3.47 (d, J = 10.9, 1H). ^{13}C NMR ($CDCl_3$) δ = 14.3, 14.4, 21.3, 23.5, 24.0, 29.6, 29.8, 30.5, 32.1, 39.0, 70.0, 73.2. EI-MS (m/z): 216 $[M\text{-}CH_3]^+$. HPLC analysis of the monobenzoate (Chiralcel AS-H, 1 mL/min, 3% iPrOH/Hexanes; $t_{r(minor)}$ = 7.1 min, $t_{r(major)}$ = 8.2 min) indicated 96% ee. $[\alpha]^{20}_D$ = -2.4 (c = 0.51, $CHCl_3$).



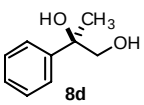
8b

8b (Table 2, entry 2): Chromatography (50% EtOAc in hexanes) provided 56 mg (84% yield) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ = 1.15 (s, 3H), 1.81 (br s, 1H), 1.84 (br t, J = 5, 1H), 2.79 (d, 13.3, 1H), 2.86 (d, J = 13.3, 1H), 3.45 (dd, J = 10.9, 5.6, 2H), 3.51 (dd, J = 10.9, 5.6), 7.25 (m, 3H), 7.32 (t, J = 6.9, 2H). ^{13}C NMR ($CDCl_3$) δ = 23.9, 44.9, 69.5, 73.2, 126.9, 128.6, 130.7, 137.2. EI-MS (m/z): 166 $[M]^+$. HPLC analysis of the monobenzoate (Chiralcel AS-H, 1 mL/min, 3% iPrOH/Hexanes; $t_{r(minor)}$ = 18.5 min, $t_{r(major)}$ = 19.5 min) indicated 95% ee. $[\alpha]^{20}_D$ = -2.2 (c = 0.63, $CHCl_3$).



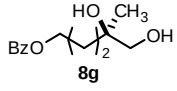
8c

8c (Table 2, entry 3): Chromatography (50% EtOAc in hexanes) provided 48 mg (59% yield) of a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ = 1.18 (s, 3H), 1.52-1.53 (m, 4H), 2.15-2.19 (m, 2H), 2.27 (br s, 2H), 3.42 (d, J = 10.9, 1H), 3.48 (d, J = 10.9, 1H), 6.16-6.23 (m, 2H). ^{13}C NMR ($CDCl_3$) δ = 22.4, 23.5, 35.3, 38.2, 70.0, 73.1, 83.1, 141.1. EI-MS (m/z): 255 $[M\text{-}CH_3]^+$. HPLC analysis of the monobenzoate (Chiralcel AS-H, 1 mL/min, 4% iPrOH/Hexanes; $t_{r(minor)}$ = 15.0 min, $t_{r(major)}$ = 18.1 min) indicated 96% ee. $[\alpha]^{20}_D$ = -3.1 (c = 0.61, $CHCl_3$).



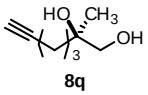
8d

8d (Table 2, entry 4): Chromatography (50% EtOAc in hexanes) provided 11 mg (75% yield) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ = 1.54 (s, 3H), 2.55 (br s, 2H), 3.64 (d, J = 11.2, 1H), 3.81 (d, J = 11.2, 1H), 7.29 (t, J = 8.5, 1H), 7.38 (t, J = 7.9, 2H), 7.46 (d, J = 7.9, 2H). ^{13}C NMR ($CDCl_3$) δ = 26.3, 71.3, 75.1, 125.3, 127.4, 128.7, 145.2. EI-MS (m/z): 152 $[M]^+$. HPLC analysis of the monobenzoate (Chiralcel AD-H, 1 mL/min, 3% EtOH/Hexanes; $t_{r(minor)}$ = 36.3 min, $t_{r(major)}$ = 39.9 min) indicated 95% ee. $[\alpha]^{20}_D$ = -5.8 (c = 0.55, EtOH); lit.[9] $[\alpha]^{23}_D$ = -5.8 (c = 0.17, EtOH).



8g

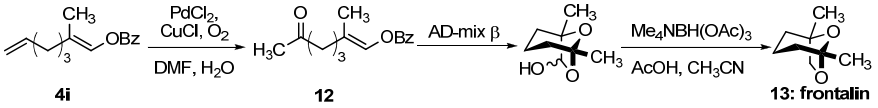
8g (Table 2, entry 5): Chromatography (75% EtOAc in hexanes) provided 18 mg (87% yield) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ = 1.23 (s, 1H), 1.57-1.72 (m, 2H), 1.82-1.93 (m, 3H), 3.50 (dd, J = 22.6, J = 10.8, 2H), 4.37 (t, J = 6.6, 2H), 7.45 (t, J = 7.8, 2H), 7.57 (t, J = 7.4, 1H), 8.04 (t, J = 8.4, 2H). ^{13}C NMR ($CDCl_3$) δ = 23.5, 23.5, 35.1, 65.5, 70.1, 72.8, 128.6, 129.8, 130.5, 133.7, 166.9. EI-MS (m/z): 131 $[M\text{-}PhCHO]^+$. HPLC analysis of the monobenzoate (Chiralcel AS-H, 1 mL/min, 6% iPrOH/Hexanes; $t_{r(minor)}$ = 25.5 min, $t_{r(major)}$ = 21.9 min) indicated 96% ee. $[\alpha]^{20}_D$ = -12.0 (c = 0.15, $CHCl_3$).



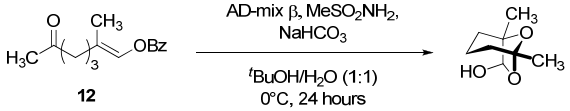
8q

8q (Table 2, entry 6): Chromatography (40% EtOAc in hexanes) provided 14.5mg (75% yield) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ = 1.17 (s, 3H), 1.57-1.62 (m, 4H), 1.73-2.26 (br s, 2H), 1.96 (t, *J* = 2.6, 1H), 2.19-2.23 (m, 2H), 3.42 (d, *J* = 10.9, 1H), 3.48 (d, *J* = 10.9, 1H). ^{13}C NMR ($CDCl_3$) δ = 19.1, 23.0, 23.4, 37.8, 68.9, 70.0, 73.0, 84.5. EI-MS (m/z): 142 $[M]^+$. HPLC analysis of the monobenzoate (Chiralcel OJ-H, 1 mL/min, 6% iPrOH/Hexanes; $t_{r(minor)}$ = 17.7 min, $t_{r(major)}$ = 15.7 min) indicated 95% ee. $[\alpha]^{20}_D$ = -3.0 (c = 0.67, $CHCl_3$).

Total synthesis of Frontalin (Scheme 2, **13**)**:**



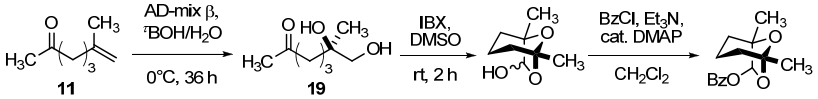
Preparation of methyl ketone 12 from 4i (Scheme 2)**:** A flask was charged with $PdCl_2$ (36 mg, 0.2 mmol, 0.1 equiv) and CuCl (0.2 g, 2.0 mmol, 1.0 equiv) and flushed with N_2. A 3.0 mL mixture of DMF/H_2O (7:1) was added and O_2 was bubbled through the suspension as it stirred vigorously for 1 hour. Olefin **4i** (0.46 g, 2.0 mmol, 1.0 equiv) was added to the reaction at room temperature and O_2 was bubbled through the mixture for an additional 30 minutes. At this time, the flask was sealed and the reaction was stirred overnight. When complete, the mixture was diluted with EtOAc and washed twice with a premixed solution of saturated aqueous NH_4Cl and 10% aqueous NH_4OH (1:1) (this dissolves copper and turns brilliant blue). The organic portion was dried with $MgSO_4$ and solvent was removed to give the pure product (**12**) as a yellow oil (0.49 g, 100%). ^{1}H NMR ($CDCl_3$) δ = 1.76 (m, 2H), 1.80 (d, *J* = 1.1, 3H), 2.06 (t, *J* = 7.2, 2H), 2.15 (s, 3H), 2.45 (t, *J* = 7.2, 2H), 7.14 (s, 1H), 7.47 (t, *J* = 7.7, 2H), 7.60 (t, *J* = 7.5, 1H), 8.11 (d, *J* = 7.2, 2H). ^{13}C NMR ($CDCl_3$) δ = 13.8, 21.5, 30.2, 33.4, 42.7, 121.8, 128.7, 129.7, 129.9, 130.8, 133.5, 163.7, 208.7. EI-MS (m/z): 228 $[M\text{-}H_2O]^+$.



Preparation of 7-hydroxy-frontalin (Scheme 2)**:** A 1:1 mixture of ^{t}BuOH/H_2O (7 mL) was added to flask containing AD-mix β (1.04 g, 1.5 g per mmol of olefin) and $NaHCO_3$ (0.174 g, 2.1 mmol, 3.0 equiv) at rt. The two clear phases were stirred at 0˚C until salts precipitated. The olefin (in 0.5 mL ^{t}BuOH, 0.17 g, 0.69 mmol, 1.0 equiv) was then added and the slurry was stirred for 24 hours at 0˚C. The reaction was quenched with Na_2SO_3 (1.1 g) at 0˚C and stirred at room temperature for 1 hour. The mixture was diluted with CH_2Cl_2, washed with brine, and extracted 3 times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$ and the solvent was removed. The crude product was purified by flash chromatography (15-20% EtOAc in hexanes) to give a 7-hydroxy-frontalin as a 4:1 (endo:exo) mixture of diastereomers (93 mg, 86% yield, 93% ee). The ee of this compound (93%) was determined from its benzoate (BzCl, Et_3N, cat. DMAP, CH_2Cl_2) by HPLC (Chiralcel OD-H, 1 ml/min, 1% iPrOH/Hexanes, $t_{r(minor)}$ = 7.4 min, $t_{r(major)}$ = 6.0 min). Endo-7-hydroxy-frontalin: ^{1}H NMR ($CDCl_3$) δ = 1.27 (s, 3H), 1.49 (s, 3H), 1.44-1.85 (m, 6H), 2.34 (d, *J* = 9.6, 1H), 5.07 (d, *J* = 9.6, 1H). ^{13}C NMR ($CDCl_3$) δ = 17.6, 20.7, 25.6, 31.9, 33.1, 83.2, 98.3, 108.6. EI-MS (m/z): 141 $[M\text{-}OH]^+$. $[\alpha]^{20}_D$ = +28.3 (c = 0.72, $CHCl_3$). Exo-7-hydroxy-frontalin: ^{1}H NMR ($CDCl_3$) δ = 1.25 (s, 3H), 1.42 (s, 3H), 1.44-1.85 (m, 6H), 3.08 (d, *J* = 5.2, 1H), 5.10 (d, *J* = 5.2, 1H). ^{13}C NMR ($CDCl_3$) δ = 17.8, 22.4, 25.6, 29.5, 33.5, 80.9, 101.8, 107.6. EI-MS (m/z): 141 $[M\text{-}OH]^+$. $[\alpha]^{20}_D$ = +28.3 (c = 0.72, $CHCl_3$).

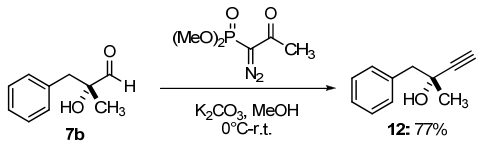
Preparation of frontalin (13) from 7-hydroxy-frontalin (Scheme 2)**:** 7-hydroxy-frontalin (93 mg, 0.59 mmol, 1.0 equiv) was dissolved in 3.0 mL AcOH and 3.0 mL CH_3CN and cooled to 0˚C. $[Me_4N]BH(OAc)_3$ (0.33 g, 1.18 mmol, 2.0 equiv) was added at 0˚C and the reaction was allowed to stir overnight at room temperature. A solution of 10% citric acid was added and the reaction was stirred for an additional 30 minutes. The acid was slowly neutralized with aqueous $NaHCO_3$ and extracted 3 times with pentane. The combined organic extracts were dried with $MgSO_4$ and the solvent was evaporated to give (+)-frontalin (84% wt in pentane, 75 mg, 76% yield). ^{1}H NMR ($CDCl_3$) δ = 1.31 (s, 3H), 1.42 (s, 3H), 1.47-1.67 (m, 6H), 3.44 (dd, *J* = 6.8, *J* = 1.7, 1H), 3.90 (dd, *J* = 6.7, 1H). ^{13}C NMR ($CDCl_3$) δ = 18.26, 23.32, 24.96, 34.16, 34.77, 74.44, 80.29, 108.32. EI-MS (m/z): 142 $[M]^+$. $[\alpha]^{20}_D$ = +53.6 (c = 1.43, Et_2O); lit.[10] $[\alpha]^{23}_D$ = +54.4 (c = 1.33, Et_2O).

Asymmetric dihydroxylation of terminal olefin 11 (Scheme 2):

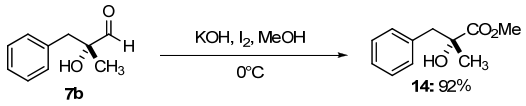


To compare the AD of **11** and **12**, we subjected terminal olefin **11** to the transformations outlined in the scheme above. **11** was dihydroxylated under the standard conditions (see general procedure for AD of enol benzoates), using AD-mix β in ^{t}BOH/H_2O (1:1) at 0˚C. The crude dihydroxylated product was oxidized with IBX (1.2 equiv to diol) in DMSO at rt for 2 hours. The ee was determined from benzoylated 7-hydroxy-frontalin.

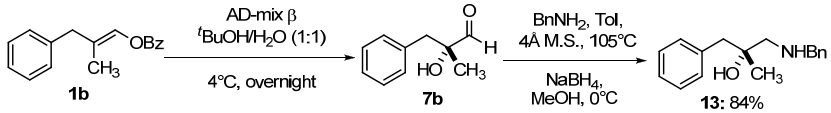
Transformations of α-hydroxy aldehydes (Scheme 3)**:**



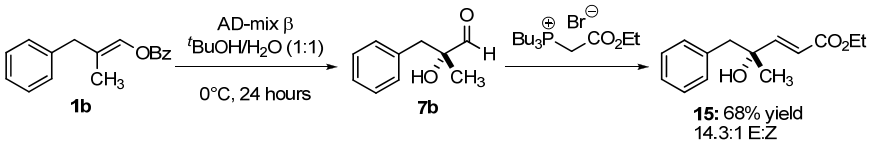
Preparation of propargylic alcohol 12 from 7b (Scheme 3)**:** α-Hydroxy aldehyde **7b** (0.52 mmol) was prepared as described in the general procedure from enol benzoate **4b** (0.52 mmol) except $NaHCO_3$ (3 equiv) was included during the dihydroxylation. After the asymmetric dihydroxylation reaction was quenched with Na_2SO_3, the reaction mixture was diluted with CH_2Cl_2, washed with brine, and extracted 3 times with CH_2Cl_2. The combined organic extracts were dried with Na_2SO_4 and concentrated to no less than 4 mL. The solvent was exchanged by adding 10 mL of dry MeOH and concentrating the volume to 4 mL. This was repeated 2 times and dry MeOH was again added to bring the final reaction concentration to ca 0.05 M (about 10 mL MeOH). This solution was cooled to 0˚C and K_2CO_3 (0.18 g, 1.3 mmol, 2.5 equiv) and $(MeO)_2POCN_2COMe$[11] (0.15 g, 0.78 mmol, 1.5 equiv, in 1.0 mL MeOH) were added sequentially. The reaction was stirred for 1 hour at 0˚C and 4 hours at room temperature, after which time it was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$, and extracted 3 times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$, concentrated, and purified by flash chromatography (10% EtOAc/Hexanes) to give pure alkyne (64 mg, 77% yield). ^{1}H NMR ($CDCl_3$) δ = 1.56 (s, 3H), 2.02 (s, 1H), 2.47 (s, 1H), 2.93 (d, *J* = 13.3, 1H), 3.01 (d, *J* = 13.2, 1H), 7.31-7.34 (m, 5H). ^{13}C NMR ($CDCl_3$) δ = 29.7, 49.5, 68.1, 72.9, 87.4, 127.3, 128.4, 131.0, 136.2. EI-MS (m/z): 160 $[M-1]^+$. $[\alpha]^{20}_D$ = +5.4 (c = 0.71, $CHCl_3$).



Preparation of methyl ester 14 from 7b (Scheme 3)**:** α-Hydroxy aldehyde **7b** (0.52 mmol) was prepared as described in the general procedure from enol benzoate **1b** (0.52 mmol) except $NaHCO_3$ (3 equiv) was included during the dihydroxylation. After the asymmetric dihydroxylation reaction was quenched with Na_2SO_3, the reaction mixture was diluted with CH_2Cl_2, washed with brine, and extracted 3 times with CH_2Cl_2. The combined organic extracts were dried with Na_2SO_4 and concentrated to no less than 4 mL. The solvent was exchanged by adding 10 mL of dry MeOH and concentrating the volume to 4 mL. Dry MeOH was again added to bring the final reaction concentration to 0.05M in MeOH (about 10 mL). This solution was brought to 0˚C and KOH (dissolved in 1.0 mL MeOH, 0.76 g, 1.3 5mmol, 2.6 equiv) and I_2 (dissolved in 1.0 mL MeOH, 0.86 g, 0.68 mmol, 1.3 equiv) were added sequentially. After 1.5 hours at 0˚C, starting material was still present, so KOH (0.76 g in MeOH) and I_2 (0.86 g in MeOH) were added again. After stirring an additional 1.5 hours at 0˚C, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The reaction was filtered, washed with aqueous $NaHCO_3$, and extracted 3 times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$ and concentrated to give (*R*)-**11** (92% yield). ^{1}H NMR ($CDCl_3$) δ = 1.50 (s, 3H), 2.90 (d, *J* = 13.5, 1H), 3.01 (s, 1H), 3.07 (d, 13.5, 1H), 3.73 (s, 3H), 7.16 (m, 2H), 7.25 (m, 3H). ^{13}C NMR ($CDCl_3$) δ = 26.0, 46.7, 52.8, 75.5, 127.2, 128.4, 130.2, 136.2, 176.8. EI-MS (m/z): 194 $[M-1]^+$. $[\alpha]^{20}$ = +5.3 (c = 2.05, $CHCl_3$); lit. for (*S*)-**11** $[\alpha]^{20}$ = -113 (c = 1.0, $CHCl_3$).[12,13]



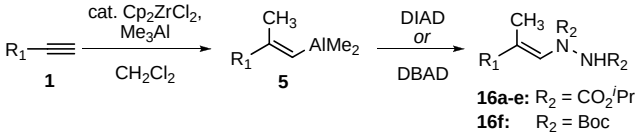
Preparation of amino alcohol 13 from 1b (Scheme 3)**:** α-Hydroxy aldehyde **7b** (0.52 mmol) was prepared as described in the general procedure from enol benzoate **1b** (0.52 mmol). After the asymmetric dihydroxylation reaction was complete the reaction was extracted three times with Et_2O and dried over Na_2SO_4. Without evaporating to dryness, the solvent was exchanged to approximately 10 mL toluene under reduced pressure. Benzylamine (0.3 mmol, 1.5 equiv) and 4Å molecular sieves were added before bringing the temperature to 105°C. Imine formation was monitored by GC/MS. Upon completion, the molecular sieves were removed and the toluene evaporated under reduced pressure. The residue was diluted in 10 mL methanol and cooled to 0°C. After 1 hour, the reaction was quenched with saturated $NaHCO_3$ and extracted with Et_2O three times. After concentrating the combined organic layers, the residue was dissolved in hexanes was extracted with 1M HCl. The aqueous layer was washed with hexanes and then brought to pH 13 with 1M NaOH. After extracting the basic aqueous layer three times with EtOAc, the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to provide 42.5 mg (84% yield) of the desired compound. No additional purification was necessary. ^{1}H NMR ($CDCl_3$) δ = 1.14 (s, 3H), 2.10 (br s, 1H), 2.55 (d, *J* = 11.98, 1H), 2.66 (d, *J* = 11.98, 1H), 2.75 (d, *J* = 13.3, 1H), 2.82 (d, *J* = 13.3, 1H), 3.81 (d, *J* = 7.4, 2H), 3.83 (s, 1H), 7.21-7.37 (m, 10H). ^{13}C NMR ($CDCl_3$) δ = 25.9, 46.8, 54.7, 58.2, 71.8, 126.6, 127.3, 128.3, 128.4, 128.7, 130.6, 138.0, 140.5. $[\alpha]^{20}_D$ = -3.1 (c = 0.975, $CHCl_3$).



Preparation of α, β-unsaturated ester 15 from 1b (Scheme 3)**:** α-Hydroxy aldehyde **7b** (0.52 mmol) was prepared as described in the general procedure from enol benzoate **1b** (0.52 mmol). After the asymmetric dihydroxylation reaction was complete the reaction mixture was extracted three times with Et_2O and diluted with 4mL toluene. Ether was removed under reduced pressure. Separately, 0.3 mmol (1.5 equiv) phosphonium bromide was dissolved in 2 mL CH_2Cl_2 and washed twice with 1M NaOH. Methylene chloride was removed under reduced pressure after diluting with 4 mL toluene. To the aldehyde in toluene was added the prepared ylide, and the solution was heated to 90°C for 3 hours at which point a second 0.3 mmol of prepared ylide in 4 mL toluene was added. After 90 minutes, the reaction was cooled to room temperature, dried over anhydrous Na_2SO_4, filtered, and concentrated. The product was purified by flash silica gel chromatography (2:3 Et_2O:hexanes) to give 32.0 mg (68.3% isolated yield) of the desired compound. ^{1}H NMR ($CDCl_3$) δ = 1.28 (t, *J* = 7.1, 3H), 1.33 (s, 3H), 2.03 (s, 1H), 2.82 (d, *J* = 13.4, 1H), 2.92 (d, *J* = 13.4, 1H), 4.19 (dq, *J* = 7.1, *J* = 0.9, 2H), 5.92 (d, *J* = 15.6, 1H), 7.04 (d, *J* = 15.6, 1H), 7.16 (dd, *J* = 8.2, *J* = 1.7, 2H), 7.23-7.32 (m, 3H). ^{13}C NMR ($CDCl_3$) δ = 14.0, 27.0,

48.0, 60.2, 72.7, 118.9, 126.8, 128.2, 130.3, 135.6, 153.5, 166.4. FTIR (thin film) 3474, 2978, 1716, 1306 cm^{-1}. EI-MS (m/z): 189 $[M\text{-}OCH_2CH_3]^+$. $[\alpha]^{20}_D = +53.3$ (c = 1.11, $CHCl_3$).

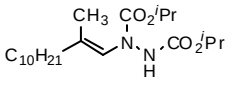
Preparation of Ene-hydrazines from Terminal Alkynes (Table 3)**:**



General Procedure for preparation of ene-hydrazines:

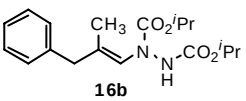
To a stirred solution of Cp_2ZrCl_2 and Me_3Al in CH_2Cl_2 (0.3M to alkyne) at room temperature was added terminal alkyne. Methylaluminoxane (MAO) was then added at room temperature and the yellow solution was stirred until the methylalumination was complete. Once complete, the reaction was brought to -25˚C and diisopropyl azodicarboxylate (DIAD, for **16a-e**) or Di-*tert*-butyl azodicarboxylate (DBAD, for **16f**) was added dropwise to the freshly prepared vinylalane. This solution was stirred for an additional 3 hours at -25˚C, after which time the reaction was quenched by slow addition of AcOH (1 mL) at this temperature. The mixture was allowed to warm to room temperature and an aqueous solution of 10% citric acid was added slowly until gas evolution ceased. The resulting slurry was stirred for 15-30 minutes or until the two phases were homogenous, at which time it was extracted 3 times with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$, concentrated, and purified by flash chromatography (silica gel, EtOAc/hexanes). Reaction times, reagent amounts, purification conditions and characterization data are provided below for all entries in Table 3.

Characterization data for ene-hydrazine compounds and reaction details:



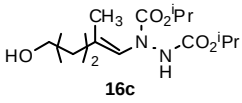
16a

16a (Table 3, entry 1): Reagent amounts: 1-dodecyne (40 µL, 0.187 mmol, 1.0 equiv), Cp_2ZrCl_2 (11 mg, 0.0374 mmol, 0.2 equiv), Me_3Al (2.0M in Toluene, 1.61 mL, 3.22 mmol, 2.0 equiv), DIAD (43 µL, 0.206 mmol, 1.1 equiv). Methylalumination was complete in 4 hours (addition of MAO was not necessary). Chromatography (10% EtOAc in hexanes) provided 59 mg (79% yield) of a colorless syrup. ^1H NMR ($CDCl_3$) δ = 0.875 (t, *J* = 6.6, 3H), 1.18-1.33 (m, 28 H), 1.41 (m, 2H), 1.64 (d, *J* = 0.9, 3H), 2.00 (t, *J* = 7.3, 2H), 4.91-4.99 (m, 2H), 5.96 (br s, 1H), 6.51 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ = 14.3, 16.2, 22.2, 22.3, 22.9, 27.7, 29.6, 29.7, 29.8, 29.9, 32.1, 36.5, 36.6, 70.0, 70.6, 70.7, 122.7, 156.0. FTIR (thin film) 3294, 2919, 2359, 1718, 1373, 1108 cm^{-1}. EI-MS (m/z): 385 $[M]^+$.



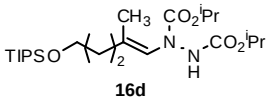
16b

16b (Table 3, entry 2): Reagent amounts: phenyl-3-propyne (0.2 mL, 1.61 mmol, 1.0 equiv), Cp_2ZrCl_2 (94 mg, 0.322 mmol, 0.2 equiv), Me_3Al (2.0M in Toluene, 3.22 mL, 0.374 mmol, 2.0 equiv), DIAD (0.51 mL, 2.42 mmol, 1.5 equiv). Methylalumination was complete in 5.5 hours (addition of MAO was not necessary). Chromatography (11% EtOAc in hexanes) provided 0.48 g (89% yield) of a colorless syrup. ^1H NMR ($CDCl_3$) δ = 1.26 (d, *J* = 6.24, 14H), 1.59 (s, 3H), 3.33 (s, 2H), 4.98 (m, 2H), 5.90-6.40 (br s, 1H), 6.40-6.80 (br s, 1H), 7.18-7.21 (m, 3H), 7.29 (t, *J* = 1.6, 2H). ^{13}C NMR ($CDCl_3$) δ = 16.4, 22.1, 22.3, 42.95, 70.2, 70.9, 124.4, 124.5, 126.6, 128.5, 130.0, 139.3.[14] FTIR (thin film) 3294, 2986, 1718, 1373, 1105 cm^{-1}. EI-MS (m/z): 334 $[M]^+$.



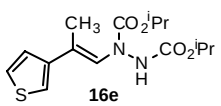
16c

16c (Table 3, entry 3): Reagent amounts: 4-Pentyne-1-ol (0.185 mL, 2.0 mmol, 1.0 equiv), Cp_2ZrCl_2 (0.117 g, 0.4 mmol, 0.2 equiv), Me_3Al (2.0M in Toluene, 3.0 mL, 6.0 mmol, 3.0 equiv), MAO (66 µL, 0.1 mmol, 5 mol %), DIAD (1.27 mL, 6.0 mmol, 3.0 equiv). Methylalumination was complete after allowing reaction to stir overnight. Chromatography (50% EtOAc in hexanes) provided 0.521 g (86% yield) of a colorless syrup. ^1H NMR ($CDCl_3$) δ = 1.26 (d, J = 6.3, 12H), 1.69 (s, 3H), 1.72 (m, 2H), 2.13 (t, J = 7.0, 2H), 2.25 (br s, 1H), 3.65 (t, J = 6.1, 2H), 4.96 (m, 2H), 5.99 (br s, 1H), 6.64 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ = 16.0, 22.1, 22.2, 30.4, 30.5, 33.2, 62.1, 69.9, 70.6, 122.9.[14] FTIR (thin film) 3457, 3289, 2975, 1712, 1376, 1111 cm^{-1}. EI-MS (m/z): 243 $[M\text{-}O^iPr]^+$.



16d

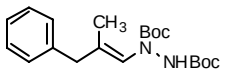
16d (Table 3, entry 4): Reagent amounts: 4-(triisopropylsilyloxy)-1-pentyne (0.509 g, 2.0 mmol, 1.0 equiv), Cp_2ZrCl_2 (0.117 g, 0.4 mmol, 0.2 equiv), Me_3Al (2.0M in Toluene, 3.0 mL, 6.0 mmol, 3.0 equiv), MAO (66 µL, 0.1 mmol, 5 mol %), DIAD (1.27 mL, 6.0 mmol, 3.0 equiv). Methylalumination was complete after allowing reaction to stir overnight. Chromatography (10% EtOAc in hexanes) provided 0.781 g (83% yield) of a colorless syrup. ^1H NMR ($CDCl_3$) δ = 1.07 (m, 18H), 1.25 (d, J = 6.2, 12H), 1.51(m, 2H), 1.65 (s, 3H), 2.04 (t, J = 5.9, 2H), 3.67 (t, J = 5.7, 2H), 4.97 (m, 2H), 5.98 (br s, 1H), 6.59 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ = 16.0, 18.2, 18.3, 22.2, 22.3, 24.1, 32.4, 36.4, 63.3, 70.0, 70.7, 122.8.[14] FTIR (thin film) 3294, 2936, 2863, 1718, 1373, 1113 cm^{-1}. EI-MS (m/z): 458 $[M]^+$.



16e

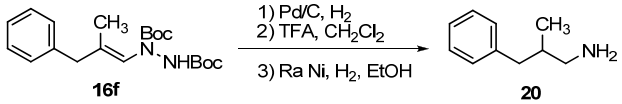
16e (Table 3, entry 5): Reagent amounts: 2-ethynyl thiophene (0.197 mL, 2.0 mmol, 1.0 equiv), Cp_2ZrCl_2 (0.117 g, 0.4 mmol, 0.2 equiv), Me_3Al (2.0M in Toluene, 3.0 mL, 6.0 mmol, 3.0 equiv), MAO (66 µL, 0.1 mmol, 5 mol %), DIAD (1.27 mL, 6.0 mmol, 3.0 equiv). Methylalumination was complete in 3 days. Chromatography (12% EtOAc in hexanes) provided

0.502 g (77% yield) of a colorless syrup. ^{1}H NMR ($CDCl_3$) δ = 1.28 (m, 12H), 2.06 (s, 3H), 5.0 (m, 2H), 6.67 (br s, 1H), 6.71 (br s, 1H), 7.20 (s, 1H), 7.22 (d, J=4.9, 1H), 7.27 (d, J = 2.8, 1H). ^{13}C NMR ($CDCl_3$) δ = 16.1, 22.3, 22.3, 70.3, 71.4, 120.7, 120.8, 124.6, 124.7, 125.3, 126.0, 142.0, 155.7. FTIR (thin film) 3294, 2986, 1715, 1373, 1236, 775 cm^{-1}. EI-MS (m/z): 326 $[M]^+$.



16f

17 (Table 3, entry 6): Reagent amounts: phenyl-3-propyne (0.249 mL, 2.0 mmol, 1.0 equiv), Cp_2ZrCl_2 (0.117 g, 0.4 mmol, 0.2 equiv), Me_3Al (2.0M in Toluene, 2.0 mL, 4.0 mmol, 2.0 equiv), MAO (66 μL, 0.1 mmol, 5 mol %), DBAD (in 5 mL CH_2Cl_2, 0.94 g, 4.0 mmol, 2.0 equiv). Methylalumination was complete after stirring overnight. Chromatography (10% EtOAc in hexanes) provided 0.609 g (84% yield) of a colorless syrup. Chromatography (11% EtOAc in hexanes) provided 0.48 g (89% yield) of a colorless syrup. ^{1}H NMR ($CDCl_3$) δ = 1.47 (s, 18H), 1.57 (s, 3H), 3.30 (s, 2H), 6.19 (br s, 1H), 6.49 (br s, 1H), 7.20 (d, J = 6.3, 2H), 7.27 (m, 3H). ^{13}C NMR ($CDCl_3$) δ = 16.2, 28.4, 28.44, 38.9, 43.0, 68.3, 81.9, 124.9, 126.4, 128.5, 129.0, 131.2, 139.5, 155.9. FTIR (thin film) cm^{-1}. EI-MS (m/z): 385 $[M+Na]^+$.



16f **20**

Procedure for preparating of primary amine 20:

Nitrogen was bubbled through a solution of ene-hydrazine **16f** (0.185 g, 0.5 mmol, 1.0 equiv) in 4 mL EtOAc for 15 minutes. Once complete, Pd/C (53 mg, 0.05 mmol, 0.1 equiv) was added to the flask and H_2 was bubbled through the mixture for 30 minutes. The reaction was allowed to stir overnight at room temperature under an H_2 atmosphere, after which N_2 was once again bubbled through the mixture for 15 minutes. The mixture was filtered through celite, washed with EtOAc, and concentrated. The crude Boc-protected hydrazine was dissolved in 4 mL CH_2Cl_2 and brought to 0˚C, at which time 4 mL trifluoroacetic acid was added. After stirring for 45 minutes at 0˚C, the reaction was brought to room temperature and the solvent was removed *in vacuo*. The crude 2-methyl-3-phenylpropylhydrazine was dissolved in 5 mL EtOH and approximately 1.3 g of Raney-Nickel (activated catalyst, 50% slurry in H_2O; Acros Chemical) was added to the solution at room temperature. H_2 was bubbled through the slurry for 30 minutes and the reaction was stirred under an H_2 atmosphere for 39 hours. The Raney-Nickel residue was separated by filtration and the EtOH was removed *in vacuo*. The crude amine was diluted with CH_2Cl_2, washed with 1 M NaOH, and extracted 3 times with CH_2Cl_2. The combined organic extracts were dried with Na_2SO_4 and concentrated to give **20** (68 mg, 91%) as a yellow oil. ^{1}H NMR ($CDCl_3$) δ = 0.90 (d, J = 6.7, 3H), 1.39 (br s, 2H), 1.79 (m, 1H), 2.39 (dd, J = 13.4, J = 8.2, 1H), 2.54 (dd, J = 12.6, J = 6.9, 1H), 2.68 (dd, J = 12.2, J = 5.5, 1H), 2.71 (m, 3H), 7.18 (m, 3H), 7.29 (t, J = 7.9, 2H). ^{13}C NMR ($CDCl_3$) δ = 17.6, 36.2, 41.21, 48.0, 126.1, 128.5, 129.4, 141.0. EI-MS (m/z): 150 $[M+H]^+$.

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