Palladium-Catalyzed Asymmetric Alkylation in the Synthesis of Cyclopentanoid and Cycloheptanoid Core Structures Bearing All-Carbon Quaternary Stereocenters

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Supporting Information (Experimental Procedures)

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Materials and Methods. Unless otherwise stated, reactions were performed in flame-dried glassware under an argon or nitrogen atmosphere using dry, deoxygenated solvents. Reaction progress was monitored by thin-layer chromatography (TLC). THF was distilled over sodium/halogen or dried by passage through an activated alumina column under argon prior to use. p-Dioxane was distilled over sodium or dried by passage through an activated alumina column under argon prior to use. Methanol was distilled over Mg(OMe)$_2$ prior to use. Other solvents were dried by passage through an activated alumina column under argon. Diisopropylamine and triethylamine was distilled over CaH$_2$ prior to use. Iodomethane, iodoethane, acrylonitrile, methyl vinyl ketone, and acrolein were distilled prior to use. Purified water was obtained using a Barnstead NANOpure Infinity UV/UF system. Brine solutions are saturated aqueous solutions of sodium chloride. MePh$_2$PBr from Sigma-Aldrich was stored in a glove box prior to use. NaH (60% wt. dispersion in mineral oil) from Sigma-Aldrich was purified by trituration with hexanes under a N$_2$ atmosphere and removal of residual solvent under vacuum. LiOCH$_2$CF$_3$ was prepared according to the method of Shreeve.$^{[1]}$ Allyl cyanoformate was prepared according to the method of Mander or Rattigan.$^{[2]}$ Gramine methiodide was prepared according to the method of Armen.$^{[3]}$ The procedure of Maruyama and Naruta was used to prepare 1-chloro-2,4-pentadiene (92:8 E:Z).$^{[4]}$ Grignard and organolithium reagents were purchased from Sigma-Aldrich or prepared according to previously reported procedures.$^{[5]}$ Phosphinooxazoline (PHOX) ligands L1 ((S)-t-Bu-PHOX)$^{[6]}$ and L2 ((S)-p-(CF$_3$)$_3$t-Bu-PHOX)$^{[7]}$ were prepared by methods described in our previous work. Tris(4,4'-methoxydibenzylideneacetonitrile)dipalladium(0) (Pd$_2$(pmdba)$_3$) was prepared according to the method of Ibers$^{[8a]}$ or Fairlamb.$^{[8b]}$ Herrmann–Beller’s catalyst was prepared according to a literature procedure.$^{[9]}$ All other reagents were purchased from Sigma-Aldrich, Acros Organics, Strem, or Alfa Aesar and used as received unless otherwise stated. Reaction temperatures were controlled by an IKAmag temperature modulator. Microwave-assisted reactions were performed in a Biotage Initiator 2.5 microwave reactor. Glove box manipulations were performed under a N$_2$ atmosphere. TLC was performed using E. Merck silica gel 60 F254 precoated glass plates (0.25 mm) and visualized by UV fluorescence quenching, p-anisaldehyde, or KMnO$_4$ staining. SiliaFlash P60 Academic Silica gel (particle size 0.040–0.063 mm) or ICN silica gel (particle size 0.032–0.0653 mm) was used for flash column chromatography. Automated flash column chromatography was performed on a Teledyne Isco CombiFlash R$_f$ system. $^1$H NMR spectra were recorded on a Varian Mercury 300 MHz, a Varian 400 MR 400 MHz, or a Varian Inova 500 MHz spectrometer and are reported relative to residual CHCl$_3$ (δ 7.26 ppm). $^{13}$C NMR spectra were recorded on a Varian Mercury 300 MHz, a Varian 400 MR 400 MHz, or a Varian Inova 500 MHz spectrometer (at 75 MHz, 100 MHz, and 125 MHz respectively) and are reported relative to CDC$_3$ (δ 77.16 ppm). $^{19}$F spectra were recorded on a Varian Mercury 300 MHz or a Varian Inova 500 MHz spectrometer (at 282 MHz and 470 MHz respectively) and are reported without the use of a reference peak. Data for $^1$H NMR are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration. Multiplicities are reported as follows: s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, sept = septuplet, m = multiplet, br s = broad singlet, br d = broad doublet, app = apparent. Data for $^{13}$C and $^{19}$F NMR are reported in terms of chemical shifts (δ ppm). IR spectra were obtained using a Perkin Elmer Paragon 1000 or Perkin Elmer Spectrum BXII spectrometer using thin films deposited on NaCl plates and reported in frequency of absorption (cm$^{-1}$). Optical rotations were measured with a Jasco P-1010 or Jasco P-2000 polarimeter operating on the sodium D-line (589 nm) using a 100 mm path-length cell and are reported as: [α]$_b$$^D$ (concentration in g/100 mL, solvent, ee). Melting points were measured using a Thomas-Hoover capillary melting point apparatus and the reported
values are uncorrected. Analytical chiral HPLC was performed with an Agilent 1100 Series HPLC utilizing a Chiralcel AD or OD-H column (4.6 mm x 25 cm) obtained from Daicel Chemical Industries Ltd. with visualization at 254 nm. Analytical chiral SFC was performed with a Mettler Toledo SFC supercritical CO\textsubscript{2} analytical chromatography system with a Chiralcel AD-H column (4.6 mm x 25 cm) with visualization at 254 nm/210 nm. Analytical chiral GC was performed with an Agilent 6850 GC utilizing a G-TA (30 m x 0.25 mm) column (1.0 mL/min carrier gas flow). High-resolution mass spectra (HRMS) were obtained from the Caltech Mass Spectral Facility (El+ or FAB+) or on an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI+), atmospheric pressure chemical ionization (APCI+), or mixed ionization mode (MM: ESI-APCI+).

**List of Abbreviations.** The following abbreviations are used in experimental procedures:

- **CDI** = 1,1’-carbonyldiimidazole
- **DBU** = 1,8-diazabicyclo[5.4.0]undec-7-ene
- **DDQ** = 2,3-dichloro-5,6-dicyano-p-benzoquinone
- **DMA** = N,N’-dimethylacetamide
- **DMAD** = dimethyl acetylenedicarboxylate
- **DMAP** = 4-(dimethylamino)pyridine
- **DMF** = N,N’-dimethylformamide
- **DMSO** = dimethyl sulfoxide
- **DIBAL** = diisobutylaluminum hydride
- **HFIP** = 1,1,1,3,3,3-hexafluoro-2-propanol
- **i-Bu** = isobutyl
- **IPA** = isopropanol
- **LDA** = lithium diisopropylamide
- **MsCl** = methanesulfonyl chloride
- **Pd\textsubscript{2}(pmdba)\textsubscript{3}** = tris(4,4’-methoxydibenzylideneacetone)dipalladium(0)
- **PHOX** = phosphinooxazoline ligand
- **PPTS** = pyridinium p-toluenesulfonate
- **TBAA** = tetrabutylammonium acetate
- **TBAF** = tetrabutylammonium fluoride
- **TBAI** = tetrabutylammonium iodide
- **TBDDS** = tert-butyl diphenyl silyl
- **TBDSCl** = tert-butyl(chloro)diphenylsilane
- **TBSOTf** = tert-butyl(dimethyl)silyl trifluoromethanesulfonate
- **TBME** = tert-butyl methyl ether
- **TFE** = 2,2,2-trifluoroethanol
- **TMG** = 1,1,3,3-tetramethylguanidine.
- **TMS** = trimethylsilyl
- **TMSCl** = chlorotrimethylsilane
- **Selectfluor** = 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)
- **µwaves** = microwave irradiation
Procedures for the Preparation of $\beta$-Ketoesters 6

Vinylogous ester 5 and $\beta$-ketoesters 6a–k, 6m were prepared according to previously reported procedures.$^{[10,11]}$

$\beta$-Ketoester 6a. To a solution of diisopropylamine (6.46 mL, 46.1 mmol, 1.20 equiv) in THF (180 mL) in a 500 mL round-bottom flask at 0 °C was added n-BuLi (17.2 mL, 44.2 mmol, 2.57 M in hexanes, 1.15 equiv) dropwise over 15 min using a syringe pump. After 15 min of stirring at 0 °C, the mixture was cooled to −78 °C using an acetone/CO$_2$(s) bath. A solution of vinylogous ester 5 (7.01 g, 38.4 mmol, 1.00 equiv) in THF (20 mL) was added dropwise over 20 min using a syringe pump. After an additional 1 h of stirring at −78 °C, allyl cyanoformate (4.60 mL, 42.2 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at −78 °C for 2.5 h, quenched by addition of sat. aqueous NH$_4$Cl and H$_2$O (30 mL each), and allowed to warm to ambient temperature. The reaction was diluted with Et$_2$O (100 mL) and the phases were separated. The aqueous phase was extracted with Et$_2$O (2 x 100 mL). The combined organic phases were dried over MgSO$_4$, filtered, and concentrated under reduced pressure to afford a pale orange oil.

The crude oil was dissolved in CH$_3$CN (130 mL) in a 500 mL round-bottom flask and treated with MeI (7.2 mL, 115 mmol, 3.00 equiv) and Cs$_2$CO$_3$ (16.76 g, 49.9 mmol, 1.30 equiv). The flask was fitted with a condenser, immersed in an oil bath, and heated to 80 °C with vigorous stirring. After 12 h of stirring at 80 °C, the reaction was allowed to cool to ambient temperature, diluted with EtOAc (100 mL), dried over MgSO$_4$, filtered, and concentrated under reduced pressure to afford an orange oil. The crude product was purified by flash column chromatography (SiO$_2$, 5 x 15 cm, 19:1 → 9:1 Hexanes:EtOAc, dry-loaded using Celite) to afford $\beta$-ketoester 6a (8.51 g, 30.4 mmol, 79% yield over 2 steps) as a pale yellow oil; $R_f = 0.43$ (4:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, CDCl$_3$) δ 5.86 (ddd, $J = 17.1, 10.7, 5.6, 5.6$ Hz, 1H), 5.39 (s, 1H), 5.29 (app dq, $J = 17.1, 1.5$ Hz, 1H), 5.20 (app dq, $J = 10.5, 1.4$ Hz, 1H), 4.62 (dddd, $J = 13.3, 5.6, 1.2, 1.2$ Hz, 1H), 4.56 (dddd, $J = 13.4, 5.6, 1.2, 1.2$ Hz, 1H), 3.54–3.42 (m, 2H), 2.59 (ddd, $J = 17.8, 9.8, 3.9$ Hz, 1H), 2.45–2.38 (m, 2H), 2.02–1.94 (m, 2H), 1.84–1.75 (m, 1H), 1.70 (ddd, $J = 14.4, 7.3, 4.4$ Hz, 1H), 1.43 (s, 3H), 0.94 (d, $J = 6.6$ Hz, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 199.1, 174.0, 173.5, 132.0, 118.4, 105.2, 74.8, 65.8, 59.1, 34.3, 33.9, 27.9, 24.2, 21.4, 19.3; IR (Neat Film NaCl) 2959, 2936, 2875, 1734, 1650, 1613, 1456, 1384, 1233, 1170, 1115, 994 cm$^{-1}$; HRMS (EI+) $m/z$ calc’d for C$_{16}$H$_{24}$O$_4$ [M]$^+$: 280.1675; found 280.1686.
β-Ketoester 6l. To a solution of diisopropylamine (0.92 mL, 6.58 mmol, 1.20 equiv) in THF (27 mL) in a 100 mL round-bottomed flask at 0 °C in an ice/water bath was added n-BuLi (2.56 mL, 2.46 M in hexanes, 6.30 mmol, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to −78 °C using an acetone/CO₂(s) bath. A solution of vinylogous ester 5 (1.00 g, 5.48 mmol, 1.00 equiv) in THF (2 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at −78 °C, allyl cyanoformate (0.67 mL, 6.02 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at −78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH₄Cl (8 mL), and then allowed to warm to ambient temperature. The reaction mixture was diluted with Et₂O (25 mL) and the layers were separated. The aqueous phase was extracted with Et₂O (3 x 25 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford a pale orange oil.

The crude oil was dissolved in CH₂CN (55 mL) in a 100 mL round-bottomed flask under N₂ and TiCl₄ (53.7 µL, 0.49 mmol, 9.0 mol %) was added dropwise, giving a dark purple-brown mixture. After 10 min, Selectfluor (2.33 g, 6.58 mmol, 1.20 equiv) was added in one portion. After 3.5 h, the reaction mixture was an orange suspension. The reaction was concentrated under reduced pressure and the orange residue was partitioned between water (25 mL) and Et₂O (25 mL). The layers were separated and the aqueous layer was extracted with Et₂O (3 x 25 mL). The combined organic layers were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified by automated flash column chromatography using Teledyne Isco CombiFlash Rf (SiO₂, 25 g loading cartridge, 120 g column, 10% EtOAc in Hexanes) to afford β-ketoester 6l (639 mg, 2.25 mmol, 41% yield over 2 steps) as a pale yellow oil; Rf = 0.44 (4:1 Hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 5.86 (ddd, J = 17.1, 10.7, 5.6, 5.6 Hz, 1H), 5.39 (s, 1H), 5.29 (ddd, J = 19.0, 13.2, 5.6, 1.2 Hz, 2H), 3.50 (dd, J = 9.3, 6.8 Hz, 1H), 3.47 (dd, J = 9.3, 6.6 Hz, 1H), 2.59 (ddd, J = 17.8, 9.8, 3.9 Hz, 1H), 2.45–2.38 (m, 2H), 2.02–1.94 (m, 1H), 1.84–1.75 (m, 1H), 1.70 (ddd, J = 14.4, 7.3, 4.4 Hz, 1H), 1.43 (s, 3H), 0.94 (d, J = 6.6 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 192.1 (d, J_CF = 24.1 Hz), 178.0, 167.6 (d, J_CF = 25.4 Hz), 131.3, 119.0, 102.0 (d, J_CF = 1.1 Hz), 99.3 (d, J_CF = 193.5 Hz), 75.3, 66.6, 34.0 (d, J_CF = 2.1 Hz), 31.9 (d, J_CF = 22.5 Hz), 27.8, 20.7 (d, J_CF = 1.7 Hz), 19.1; ¹⁹F NMR (282 MHz, CDCl₃) δ −148.54 (dd, J = 35.4, 20.7 Hz); IR (Neat Film NaCl) 3086, 2960, 2938, 2876, 1752, 1654, 1649, 1603, 1471, 1453, 1422, 1403, 1385, 1369, 1282, 1249, 1229, 1204, 1176, 1137, 1095, 1045, 991, 953, 927, 874, 862, 843, 829, 795, 758 cm⁻¹; HRMS (EI+) m/z calc’d for C₁₅H₂₁O₄F [M⁺]: 284.1425; found 284.1424.
**β-Ketoester 6n.** To a solution of diisopropylamine (1.84 mL, 13.15 mmol, 1.20 equiv) in THF (54 mL) in a 250 mL round-bottomed flask at 0 °C in an ice/water bath was added n-BuLi (5.12 mL, 2.51 M in hexanes, 12.60 mmol, 1.15 equiv) dropwise over 10 min. After 15 min of stirring at 0 °C, the mixture was cooled to −78 °C using an acetone/CO$_2$(s) bath. A solution of vinylogous ester 5 (2.00 g, 10.96 mmol, 1.00 equiv) in THF (4 mL) was added dropwise using positive pressure cannulation. After an additional 1 h of stirring at −78 °C, allyl cyanoformate (1.34 mL, 12.06 mmol, 1.10 equiv) was added dropwise over 10 min. The mixture was stirred at −78 °C for 2.5 h, quenched by addition of 50% sat. aqueous NH$_4$Cl (16 mL), and then allowed to warm to ambient temperature. The reaction mixture was diluted with Et$_2$O (20 mL) and the layers were separated. The aqueous phase was extracted with Et$_2$O (3 x 10 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure to afford a pale orange oil (2.92 g).

Half of the crude oil (1.46 g) was dissolved in toluene (30 mL) in a 100 mL round-bottomed flask, cooled to 0 °C, and stirred vigorously as hexane-washed NaH (197 mg, 8.22 mmol, 1.50 equiv) was added in one portion. Evolution of gas was observed and the reaction mixture was stirred at 0 °C for 30 min. Benzoyl peroxide (1.99 g, 8.22 mmol, 1.50 equiv) was added slowly portionwise, giving a thick, pasty suspension. The reaction was warmed to ambient temperature and diluted with toluene (20 mL) to give a more freely stirring turbid yellow mixture. After 30 min, the reaction was diluted with toluene (50 mL) and washed with H$_2$O (2 x 5 mL) and brine (2 x 5 mL). The aqueous layers were combined and extracted with EtOAc (2 x 25 mL). The combined organic layers were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash column chromatography (SiO$_2$, 5 x 13 cm, 10:1 Hexanes:EtOAc) to afford β-ketoester 6n (1.85 g, 4.79 mmol, 87% yield over 2 steps) as a pale yellow oil; $R_f$ = 0.46 (4:1 Hexanes:EtOAc); $^1$H NMR (300 MHz, CDCl$_3$) δ 8.09–7.99 (m, 2H), 7.64–7.53 (m, 1H), 7.50–7.38 (m, 2H), 5.89 (dddd, $J$ = 17.2, 10.5, 5.7, 5.7 Hz, 1H), 5.42 (s, 1H), 5.31 (app dq, $J$ = 17.2, 1.5 Hz, 1H), 5.20 (app dq, $J$ = 10.4, 1.3 Hz, 1H), 4.80–4.62 (m, 2H), 3.57 (d, $J$ = 6.5 Hz, 2H), 2.87–2.46 (m, 4H), 2.12–1.85 (m, 3H), 0.96 (d, $J$ = 6.7 Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 192.1, 175.9, 168.0, 165.1, 133.6, 131.7, 130.0, 129.6, 128.6, 118.7, 102.2, 88.8, 75.2, 66.6, 33.8, 31.2, 27.9, 21.2, 19.2, 19.2; IR (Neat Film NaCl) 3070, 2960, 2937, 2875, 1753, 1727, 1661, 1605, 1471, 1452, 1423, 1384, 1369, 1315, 1280, 1222, 1206, 1175, 1107, 1097, 1070, 1044, 1026, 1002, 933, 849, 792 cm$^{-1}$; HRMS (EI+) m/z calc'd for C$_{22}$H$_{26}$O$_6$ [M]$^+$: 386.1733; found 386.1729.
Enantioselective Pd-Catalyzed Decarboxylative Alkylation Screening Protocol

Table SI-1. Solvent Screen for the Enantioselective Alkylation of 6a

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<td>9</td>
<td>L3</td>
<td>PhCH₃</td>
<td>77</td>
<td>72</td>
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*Conditions: β-ketoester 6a (1.0 equiv), Pd₂(pmdba)₃ (2.5 mol %), ligand (6.25 mol %) in solvent (0.1 M) at 30 °C; pmdba = 4,4'-methoxydibenzylideneacetone.

Enantioselective Alkylation Screen to Produce Vinylogous Ester 7a (0.20 mmol scale). To a 25 mL flask was added Pd₂(pmdba)₃ (5.00 µmol, 2.5 mol %) and ligand L (12.5 µmol, 6.25 mol %). The flask was evacuated/backfilled with N₂ (3 cycles, 5 min evacuation per cycle). Solvent (most of total volume, 0.1 M final concentration) was added and the black suspension was stirred for 30 min at 30 °C using an oil bath. A solution of β-ketoester 6a (0.20 mmol, 1.00 equiv) in solvent (remainder of total volume) was transferred to the catalyst solution using positive pressure cannulation. When judged complete by TLC analysis, the reaction was filtered through a small plug of SiO₂, eluted with Et₂O, and concentrated under reduced pressure. Purification by flash column chromatography (SiO₂, 1.5 x 15 cm, 9:1→6:1 Hexanes:EtOAc) or preparative TLC (SiO₂, 2:1 Hexanes:EtOAc) provided vinylogous ester 7a for analysis. HPLC conditions: 1% IPA in Hexanes, 1.0 mL/min, OD-H column, tᵣ (min): major = 6.30, minor = 7.26. (For characterization data, see p. 11).
Procedures for the Synthesis of Ligands L3 and L4

Ligands L1\(^6\) and L2\(^7\) were prepared according to previously reported procedures.

**Dihydroxazole SI-1.** (S)-**tert**-Leucinol (1.02 g, 8.66 mmol, 1.00 equiv) was placed in a 250-mL round-bottom flask and dissolved in CH\(_2\)Cl\(_2\) (14 mL). Na\(_2\)CO\(_3\) (2.75 g, 26.0 mmol, 3.00 equiv) in H\(_2\)O (27.0 mL) was added dropwise via syringe to the vigorously stirred biphasic system. To the biphasic mixture was added a solution of 1-bromonaphthalene-2-carbonyl chloride (2.68 g, 9.96 mmol, 1.15 equiv) in CH\(_2\)Cl\(_2\) (15 mL). The reaction was stirred vigorously at 23 °C for 9.5 h. The phases were separated and the aqueous phase was extracted with CH\(_2\)Cl\(_2\) (4 x 50 mL). The combined organics were stirred with KOH (10 mL, 10 mmol, 1.0 N in MeOH) for 30 min then transferred to a separatory funnel. H\(_2\)O (10 mL) was added and the mixture was neutralized with HCl (6.0 M in H\(_2\)O). The phases were separated and the aqueous phase was extracted with CH\(_2\)Cl\(_2\) (4 x 50 mL). The combined organics were dried over MgSO\(_4\) and concentrated under reduced pressure to afford the intermediate amide (3.03 g) as a pale yellow solid.

The intermediate amide (3.03 g) was dissolved in CH\(_2\)Cl\(_2\) (43.3 mL) in a 100-mL 3-neck round-bottom flask fitted with a reflux condenser. The solution was cooled to 0 °C by use of an ice/water bath and Et\(_3\)N (2.90 mL, 20.8 mmol, 2.40 equiv) was added. Methanesulfonyl chloride (0.77 mL, 9.96 mmol, 1.15 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and heated to 40 °C in a water bath. After 21 h of stirring, the mixture was allowed to cool to ambient temperature and saturated aqueous NaHCO\(_3\) was added. The biphasic system was stirred vigorously for 5 min and the layers were separated. The aqueous phase was extracted with CH\(_2\)Cl\(_2\) (2 x 50 mL). The combined organics were washed with brine (50 mL), dried over MgSO\(_4\), and concentrated under reduced pressure to afford a pale yellow oil. The crude oil was purified by flash chromatography (SiO\(_2\), 3 x 15 cm, 9:1 Hexanes:EtOAc) to afford SI-1 (2.36 g, 7.12 mmol, 82% yield over two steps) as a pale yellow oil that solidifies when placed in a –20 °C freezer; \(R_f = 0.73\) (9:1 CHCl\(_3\) : MeOH); \(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta = 8.41\) (dd, \(J = 7.7, 0.5\) Hz, 1H), 7.85–7.81 (m, 2H), 7.64 (d, \(J = 8.5\) Hz, 1H), 7.60 (app dt, \(J = 8.2, 1.3\) Hz, 1H), 7.56 (app dt, \(J = 6.9, 1.3\) Hz, 1H), 4.46 (dd, \(J = 10.4, 8.5\) Hz, 1H), 4.33 (dd, \(J = 8.5, 8.0\) Hz, 1H), 4.17 (dd, \(J = 10.4, 8.2\) Hz, 1H), 1.05 (s, 9H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta = 163.8, 134.9, 132.3, 128.8, 128.3, 128.3, 128.0, 127.8, 127.7, 126.9, 123.2, 76.9, 69.2, 34.1, 26.1; IR (Neat Film NaCl) 3065, 2956, 2899, 2863, 1667, 1620, 1594, 1556, 1499, 1476, 1463, 1393, 1372, 1362, 1359, 1321, 1300, 1238, 1264, 1210, 1161, 1104, 1024, 977, 956, 920, 817, 752 cm\(^{-1}\); HRMS (EI+) \(m/z\) calc’d for C\(_{17}\)H\(_{18}\)ONBr [M]+: 331.0572; found 331.0583; \([\alpha]_D^{20.0} = -64.0\) (c 0.92, CHCl\(_3\)); mp = 66–68 °C.
Phosphine Ligand L3. Prepared by the typical method as described for L4 below by employing SI-1 (830.6 mg, 2.50 mmol). After 24 h of stirring, the reaction mixture was filtered through a plug of Celite, eluted with CH₂Cl₂ (2 x 25 mL), and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO₂, 2.5 x 8 cm, Hexanes→9:1 CH₂Cl₂:Et₂O) to afford a bright yellow oil. The crude oil was purified by flash chromatography (SiO₂, 2.5 x 25 cm, 19:1 Hexanes:Acetone and then 2.5 x 21 cm, 9:1→6:1 Hexanes:EtOAc) to afford L3 (950.8 mg, 2.17 mmol, 90% yield) as a white solid.  

2-(2-Bromo-phenyl)-4,5-dihydrooxazole SI-2. To a solution of ethanolamine (1.32 mL, 21.9 mmol, 1.20 equiv) in CH₂Cl₂ (60 mL) in a 250-mL round-bottom flask was added a solution of Na₂CO₃ (5.80 g, 54.7 mmol, 3.00 equiv) in H₂O (45 mL). Neat 2-bromobenzoyl chloride (4.00 g, 2.38 mL, 18.2 mmol, 1.00 equiv) was added dropwise via syringe to the vigorously stirred biphasic system. The reaction flask was capped with a yellow plastic stopper and stirred for 7.5 h at 23 °C. The layers were separated and the aqueous phase was washed with CH₂Cl₂ (2 x 25 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated under reduced pressure to afford a white solid. The crude product was dissolved in CH₂Cl₂ (50 mL) and hexanes (10 mL) was added. The solution was concentrated to ~25 mL under reduced pressure resulting in precipitation of the intermediate amide (4.02 g, 16.4 mmol, 90% yield) as a white solid. The intermediate amide (2.0 g, 8.2 mmol, 1.00 equiv) was dissolved in CH₂Cl₂ (62 mL) in a 100-mL round-bottom flask equipped with a reflux condenser. Et₃N (3.43 mL, 24.5 mmol, 3.00 equiv) was added and the solution was cooled to 0 °C by use of an ice/water bath. Methanesulfonyl chloride (952 µL, 12.3 mmol, 1.50 equiv) was added dropwise. The reaction mixture was stirred at 0 °C for 30 min and heated to 40 °C in an oil bath. After 5 h of stirring, the resulting yellow solution was allowed to cool to ambient temperature, diluted with CH₂Cl₂ (25
2-(2-Diphenylphosphanyl-phenyl)-4,5-dihydrooxazole L4. A 250-mL Schlenk flask was charged with CuI (66.7 mg, 0.35 mmol, 2 mol %), Ph₂PH (3.85 mL, 22.1 mmol, 1.25 equiv), \(N,N\)'-dimethylethylene diamine (191 mL, 1.77 mmol, 10 mol %), and toluene (18 mL). The solution was stirred at 23 °C for 20 min. 2-(2-Bromo-phenyl)-4,5-dihydrooxazole SI-2 (4.0 g, 17.7 mmol, 1.00 equiv) was azeotroped with toluene (2 x 5 mL) under reduced pressure, dissolved in toluene (18 mL), and transferred quantitatively to the Schlenk flask by use of positive pressure cannula. \(Cs_2CO_3\) (8.65 g, 26.5 mmol, 1.50 equiv) was added in one portion and the flask was evacuated/backfilled with Ar (three cycles). The teflon was sealed and the yellow heterogeneous reaction mixture was stirred vigorously, immersed in an oil bath, and heated to 110 °C. After 20 h of stirring at 110 °C, the mixture was allowed to cool to ambient temperature and filtered through a pad of Celite using CHCl₃ (2 x 50 mL). The filtrate was concentrated under reduced pressure to afford a clear orange oil. The crude oil was flushed through a plug of silica gel (SiO₂, 5 x 10 cm, Hexanes:EtoAc:Toluene) to afford 2-(2-diphenylphosphanyl-phenyl)-4,5-dihydrooxazole L4 (5.03 g, 15.2 mmol, 86% yield) as a colorless viscous oil that crystallized upon standing; \(R_\gamma = 0.50\) (7:3 Hexanes:EtoAc); \(^1\)H NMR (500 MHz, CDCl₃) \(\delta = 7.85\) (dd, \(J = 7.6, 3.4\) Hz, 1H), 7.37–7.26 (comp. m, 12H), 6.89 (dd, \(J = 4.1, 7.6\) Hz, 1H), 4.08 (t, \(J = 9.5\) Hz, 2H), 3.78 (t, \(J = 9.5\) Hz, 2H); \(^13\)C NMR (125 MHz, CDCl₃) \(\delta = 164.5\) (d, \(J_{CP} = 2.8\) Hz), 139.1 (d, \(J_{CP} = 24.9\) Hz), 138.0 (d, \(J_{CP} = 11.5\) Hz), 134.1 (d, \(J_{CP} = 20.7\) Hz), 133.7 (d, \(J_{CP} = 1.8\) Hz), 131.9 (d, \(J_{CP} = 18.9\) Hz), 130.5, 129.9 (d, \(J_{CP} = 2.8\) Hz), 128.7, 128.5 (d, \(J_{CP} = 7.4\) Hz), 128.1, 67.2, 55.0; \(^31\)P NMR (121 MHz, CDCl₃) \(\delta = -3.99\) (s); IR (Neat Film NaCl) 3053, 3000, 2971, 2901, 2876, 1650, 1585, 1562, 1478, 1434, 1354, 1326, 1248, 1133, 1089, 1070, 1041, 974, 942, 898, 743 cm⁻¹; HRMS (FAB+) \(m/z\) calc’d for \(C_{31}H_{19}NOP\) [M+H]⁺: 332.1204; found 332.1218; mp = 99–101 °C.

Procedures for Synthesis of Enantioenriched Vinylogous Esters 7 using Enantioselective Decarboxylative Alkylation Reactions

Chiral vinylogous esters 7a–k, 7m, 7o–q were prepared according to previously reported procedures.¹⁰⁰ Racemic reactions were performed using Pd(PPh₃)₄ (5 mol %) or achiral PHOX
ligand \( \text{L4} \) (6.25 mol %) and Pd\( \text{pmdba}_3 \), (2.5 mol %) in toluene at 30 °C. For the synthesis of ligand \( \text{L4} \), see p. 10.

**General Method SI-A: Schlenk Manifold Method**

Vinyllogous Ester \( 7a \) (**Table 2, entry 1**). Pd\( \text{pmdba}_3 \) (5.0 mg, 4.5 \text{µmol}, 2.5 mol %) and (\( S \))-t-Bu-PHOX (4.4 mg, 11 \text{µmol}, 6.25 mol %) were placed in a 1 dram vial. The flask was evacuated/backfilled with \( \text{N}_2 \) (3 cycles, 10 min evacuation per cycle). Toluene (1.3 mL, sparged with \( \text{N}_2 \) for 1 h immediately before use) was added to the black suspension was immersed in an oil bath preheated to 30 °C. After 30 min of stirring, \( \beta \)-ketoester \( 6a \) (50.7 mg, 0.181 mmol, 1.00 equiv) was added as a solution in toluene (0.5 mL, sparged with \( \text{N}_2 \) immediately before use) using positive pressure cannulation. The dark orange catalyst solution turned olive green immediately upon addition of \( \beta \)-ketoester \( 6a \). The reaction was stirred at 30 °C for 21 h, allowed to cool to ambient temperature, filtered through a silica gel plug (2 x 2 cm, \( \text{Et}_2\text{O} \)), and concentrated under reduced pressure. The crude oil was purified by preparative TLC (\( \text{SiO}_2 \), 4:1 Hexanes:EtOAc) to afford vinylogous ester \( 7a \) (38.8 mg, 0.164 mmol, 91% yield, 88% ee) as a pale yellow oil; \( R_y = 0.31 \) (3:1 Hexanes:EtO); \(^1\text{H} \text{NMR} \) (500 MHz, CDCl\(_3 \)) \( \delta \) 5.72 (dddt, \( J = 16.6, 10.5, 7.3, 7.3 \text{ Hz}, 1\text{H} \)), 5.31 (s, 1\text{H}), 5.05–5.00 (m, 2\text{H}), 3.50 (dd, \( J = 9.3, 6.6 \text{ Hz}, 1\text{H} \)), 3.47 (dd, \( J = 9.3, 6.6 \text{ Hz}, 1\text{H} \)), 2.53–2.42 (m, 2\text{H}), 2.38 (dd, \( J = 13.7, 7.1 \text{ Hz}, 1\text{H} \)), 2.20 (dd, \( J = 13.7, 7.8 \text{ Hz}, 1\text{H} \)), 1.98 (app sept, \( J = 6.6 \text{ Hz}, 1\text{H} \)), 1.86–1.70 (m, 3\text{H}), 1.62–1.56 (m, 1\text{H}), 1.14 (s, 3\text{H}), 0.95 (d, \( J = 6.6 \text{ Hz}, 6\text{H} \)); \(^{13}\text{C} \text{NMR} \) (125 MHz, CDCl\(_3 \)) \( \delta \) 206.7, 171.3, 134.6, 117.9, 105.0, 74.5, 51.5, 45.4, 36.1, 35.2, 28.0, 25.2, 19.9, 19.3, 19.3; \( \text{IR} \) (Neat Film NaCl) 2960, 2933, 2873, 1614, 1470, 1387, 1192, 1171, 998, 912 cm\(^{-1} \); \( \text{HRMS} \) (EI+) \( m/z \) calc’d for \( \text{C}_{15}\text{H}_{22}\text{O}_2 \) [M]\(^+\): 236.1776; found 236.1767; \([\alpha]_D^{25.6} = -69.04 \) (c 1.08, CHCl\(_3 \), 88.0% ee); \( \text{HPLC} \) conditions: 1% IPA in Hexanes, 1.0 mL/min, OD-H column, \( t_R \) (min): major = 6.30, minor = 7.26.

**General Method SI-B: Glove Box Method**

Vinyllogous Ester \( 7j \) (**Table 2, entry 10**). A 20 mL scintillation vial was loaded with \( \beta \)-ketoester \( 6j \) (447 mg, 0.81 mmol, 1.00 equiv). A separate 20 mL scintillation vial was loaded with Pd\( \text{pmdba}_3 \) (19.7 mg, 0.051 mmol, 6.25 mol %), (\( S \))-t-Bu-PHOX (22.3 mg, 0.020 mmol, 2.5 mol %), and magnetic stir bar. The two vials and a teflon-lined hard cap were
evacuated/backfilled with N$_2$ in a glove box antechamber (3 cycles, 5 min evacuation per cycle) before being transferred into the glove box. Toluene (5 mL) was added to the vial containing Pd$_2$(pmdba)$_2$ and (S)-t-BuPHOX. The vial was capped and heated to 30 °C for 30 min. During this time, the mixture developed a dark orange color. β-Ketoester 6j was dissolved in toluene (3 mL) and added to the catalyst solution dropwise, causing the solution to turn olive green. The solution was stirred at 30 °C in a heating block. The capped vial was removed from the glove box after 29 h of stirring. The crude product was concentrated under reduced pressure and purified by flash column chromatography (SiO$_2$, 5 x 25 cm, 15:1→10:1→8:1→6:1 Hexanes:EtOAc) to afford vinylogous ester 7j (403 mg, 0.796 mmol, 98% yield, 82.9% ee) as a thick, white semi-solid. $R_f = 0.49$ (4:1 Hexanes:EtOAc); $^1$H NMR (300 MHz, CDCl$_3$) δ 7.96 (dm, $J = 8.4$ Hz, 1H), 7.70 (dm, $J = 8.4$ Hz, 2H), 7.48 (dm, $J = 7.9$ Hz, 1H), 7.31–7.13 (m, 5H), 5.86–5.68 (m, 1H), 5.32 (s, 1H), 5.13–5.00 (m, 2H), 2.73 (d, $J = 14.1$ Hz, 1H), 2.51 (dd, $J = 13.7$, 6.9, 1.3, 1.3 Hz, 1H), 2.44–2.15 (m, 6H), 1.92 (app sept, $J = 6.7$ Hz, 1H), 1.76–1.46 (m, 4H), 0.92 (d, $J = 6.7$ Hz, 6H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 205.2, 171.7, 144.8, 135.4, 135.0, 134.1, 132.4, 129.8, 126.9, 125.4, 124.5, 123.2, 120.1, 119.6, 118.6, 113.8, 106.4, 74.6, 55.9, 44.1, 36.3, 33.0, 31.9, 27.9, 21.7, 19.5, 19.3; IR (Neat Film NaCl) 3584, 3401, 2068, 2958, 2930, 2873, 1609, 1494, 1470, 1448, 1422, 1402, 1368, 1306, 1279, 1215, 1188, 1174, 1120, 1097, 1020, 975, 916, 876, 813, 782, 747 cm$^{-1}$; HRMS (FAB+) $m/z$ calc'd for C$_{30}$H$_{36}$O$_4$NS $[M+H]^+$: 506.2365; found 506.2358; $[\alpha]_D^{25.0} +9.10$ (c 1.00, CHCl$_3$, 82.9% ee); HPLC conditions: 5.0% EtOH in Hexanes, 1.0 mL/min, AD column, $t_R$ (min): major = 11.11, minor = 16.64.

Vinylogous Ester 7l (Table 2, entry 12). Prepared using General Method SI-A. 172.5 mg, 0.552 mmol, 98% yield. Flash column chromatography (SiO$_2$, 3 x 24 cm, 20:1→15:1→10:1 Hexanes:EtOAc); $R_f = 0.59$ (4:1 Hexanes:EtOAc); $^1$H NMR (300 MHz, CDCl$_3$) δ 5.89–5.72 (m, 1H), 5.28 (s, 1H), 5.18–5.08 (m, 2H), 3.53 (dd, $J = 10.6$, 6.5 Hz, 1H), 3.50 (dd, $J = 10.6$, 6.6 Hz, 1H), 2.80–2.46 (m, 3H), 2.46–2.33 (m, 1H), 2.22–1.67 (m, 5H), 0.97 (d, $J = 6.7$ Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 198.2 (d, $J_{CF} = 24.9$ Hz), 176.9 (d, $J_{CF} = 1.8$ Hz), 131.9 (d, $J_{CF} = 4.4$ Hz), 119.3, 101.7, 101.2 (d, $J_{CF} = 180.6$ Hz), 75.0, 42.1 (d, $J_{CF} = 23.2$ Hz), 34.4 (d, $J_{CF} = 23.2$ Hz), 34.1 (d, $J_{CF} = 2.4$ Hz), 27.9, 21.7 (d, $J_{CF} = 2.1$ Hz), 19.3, 19.2; $^{19}$F NMR (282 MHz, CDCl$_3$) δ –145.81 (m); IR (Neat Film NaCl) 3086, 2960, 2957, 1752, 1654, 1649, 1603, 1471, 1453, 1422, 1403, 1385, 1369, 1282, 1249, 1229, 1204, 1176, 1137, 1095, 1066, 145, 991, 927, 873, 843, 795, 758 cm$^{-1}$; HRMS (EI+) $m/z$ calc'd for C$_{14}$H$_{21}$O$_2$F $[M]^+$: 240.1526; found 240.1524; $[\alpha]_D^{25.0} +0.61$ (c 1.02, CHCl$_3$, 91.2% ee); HPLC conditions: 1.0% IPA in Hexanes, 1.0 mL/min, OD-H column, $t_R$ (min): minor = 8.05, major = 8.80.
Vinylogous Ester 7n (Table 2, entry 14). Prepared using General Method SI-A. 589.8 mg, 1.72 mmol, 75% yield. Flash column chromatography (SiO₂, 5 x 13 cm, 20:1→15:1→10:1→6:1 Hexanes:EtOAc); Rₜ = 0.57 (4:1 Hexanes:EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 8.03–7.96 (m, 2H), 7.55 (t, J = 7.4 Hz, 1H), 7.42 (t, J = 7.5 Hz, 2H), 5.96–5.78 (m, 1H), 5.27 (s, 1H), 5.19–5.08 (m, 2H), 3.42 (dd, J = 9.4, 6.6 Hz, 1H), 3.39 (dd, J = 9.4, 6.5 Hz, 1H), 3.06 (dddd, J = 14.8, 6.7, 1.4, 1.4 Hz, 1H), 2.83–2.67 (m, 2H), 2.55–2.34 (m, 2H), 2.10–1.74 (m, 4H), 0.80 (dd, J = 6.6, 4.7 Hz, 6H); ¹³C NMR (75 MHz, CDCl₃) δ 198.1, 174.3, 165.5, 133.1, 132.5, 130.6, 129.7, 128.5, 119.2, 102.1, 88.6, 74.9, 40.8, 34.0, 27.7, 21.9, 19.1, 19.0; IR (Neat Film NaCl) 3073, 2959, 2934, 2873, 1718, 1672, 1649, 1613, 1479, 1451, 1421, 1382, 1368, 1315, 1291, 1258, 1231, 1199, 1174, 1108, 1070, 1026, 1004, 919, 866, 820, 801, 762, 715 cm⁻¹; HRMS (EI⁺) m/z calc'd for C₂₁H₂₆O₄ [M⁺]: 342.1815; found 342.1831; [α]D₂⁵ = +79.72 (c 1.02, CHCl₃, 57.1% ee); HPLC conditions: 1.0% IPA in Hexanes, 1.0 mL/min, OD-H column, tᵣ (min): major = 18.28, minor = 22.01.

Synthetic Studies on Vinylogous Esters 8/7a and 12/5

Vinylogous esters 5 and 8 were prepared according to previously reported procedures.¹⁰¹

Cyclohexenone 9. A 50 mL round-bottom flask was charged with Et₂O (11.1 mL) and cooled to 0 °C in an ice/water bath. LiAlH₄ (13.6 mg, 0.36 mmol, 0.55 equiv) was added in one portion. After 10 min, a solution of vinylogous ester 8 (146 mg, 0.66 mmol, 1.00 equiv) in Et₂O (2.0 mL) was added dropwise using positive pressure cannulation. After 30 min of stirring at 0 °C, an additional portion of LiAlH₄ (2.5 mg, 0.066 mmol, 0.10 equiv) was added. After 60 min of stirring, the reaction was quenched by slow addition of aqueous HCl (1.0 mL, 10% w/w). The resulting biphasic system was allowed to warm to ambient temperature and stirred vigorously for 8.5 h. The phases were separated and the aqueous phase was extracted with Et₂O (3 x 15 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified using flash column chromatography (SiO₂, 2 x 25 cm, 10:1→4:1→1:1→1:2 Hexanes:Et₂O) to afford cyclohexenone 9 (90.5 mg, 0.60 mmol, 92% yield) as a yellow oil; Rₜ = 0.51 (4:1 Hexanes:EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 6.67 (d, J = 10.2 Hz, 1H), 5.88 (d, J = 10.2 Hz, 1H), 5.79 (dddd, J = 16.8, 10.3, 7.4, 7.4 Hz, 1H), 5.20–5.01 (m, 2H), 2.54–2.36 (m, 2H), 2.29–2.10 (m, 2H), 2.05–1.89 (m, 1H), 1.85–1.69 (m, 1H), 1.14 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 199.4, 158.4, 133.4, 127.6, 118.6, 45.2, 35.7, 34.1, 33.6, 24.7; IR (Neat Film NaCl) 3077, 3005, 2960, 2917, 2868, 2849, 1682, 1639, 1616, 1459, 1419,
1390, 1373, 1332, 1250, 1223, 1193, 1115, 996, 918, 871, 803, 757 cm\(^{-1}\); HRMS (EI+) \(m/z\) calc'd for C\(_{10}\)H\(_{14}\)O [M]*: 150.1045; found 150.1056; \([\alpha]\)\(_D\)\(^{25.0}\) +26.72 (c 1.02, CHCl\(_3\), 86.3% ee).

Cycloheptenone 3a and \(\beta\)-Hydroxyketone 10a. For procedure and characterization data, see General Method A, p. 18–19.

Acylcyclopentene 1a. For procedure and characterization data, see General Method E, p. 21.

Cyclohexenone 13. A 25 mL round-bottom flask with magnetic stir bar and LiAlH\(_4\) (22.8 mg, 0.60 mmol, 0.60 equiv) was charged with Et\(_2\)O (4 mL) and cooled to 0 °C in an ice/water bath. After 10 min, a solution of vinylogous ester 12 (168.23 mg, 1.00 mmol, 1.00 equiv) in Et\(_2\)O (1 mL) was added dropwise using positive pressure cannulation. After 30 min of stirring at 0 °C, the reaction was quenched by slow addition of aqueous HCl (2.60 mL, 10% w/w). The resulting biphasic system was allowed to warm to ambient temperature. The phases were separated and the aqueous phase was extracted with Et\(_2\)O (3 x 10 mL). The combined organic phases were dried over MgSO\(_4\), filtered, and concentrated carefully under reduced pressure in an ice-water bath. The crude product purified using flash column chromatography (SiO\(_2\), 2 x 25 cm, 5:1→4:1 Hexanes:EtOAc) to afford cyclohexenone 13 (39.4 mg, 0.41 mmol, 40% yield) as a volatile pale yellow oil. Spectra for the compound match data for commercially available material.
Cyloheptenone 14 and $\beta$-Hydroxyketone 15. A 50 mL round-bottom flask with magnetic stir bar and LiAlH₄ (806 mg, 21.2 mmol, 0.60 equiv) was charged with Et₂O (8 mL) and cooled to 0 °C in an ice/water bath. After 10 min, a solution of vinylogous ester 5 (328.2 mg, 1.80 mmol, 1.00 equiv) in Et₂O (2 mL) was added dropwise using positive pressure cannulation. After 30 min of stirring at 0 °C, the reaction was quenched by slow addition of aqueous HCl (4.73 mL, 10% w/w). The resulting biphasic system was allowed to warm to ambient temperature. The phases were separated and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated carefully under reduced pressure in an ice-water bath. The crude product purified using flash column chromatography (SiO₂, 2 x 25 cm, 6:1→4:1→2:1→1:1→1:2→1:4 Hexanes:EtOAc) to afford $\beta$-hydroxyketone 15 (107.1 mg, 0.84 mmol, 46% yield) as a pale yellow oil and cycloheptenone 14 (47.9 mg, 0.44 mmol, 24% yield) as a colorless oil.

Cycloheptenone 14. Spectra for the compound match data for commercially available material.

$\beta$-Hydroxyketone 15. $R_f = 0.26$ (1:1 Hexanes:EtOAc); $^1$H NMR (500 MHz, CDCl₃) $\delta$ 4.18–3.97 (m, 1H), 2.89–2.67 (m, 2H), 2.55–2.35 (m, 2H), 2.10 (br s, 1H), 1.95–1.69 (m, 5H), 1.65–1.49 (m, 1H); $^{13}$C NMR (125 MHz, CDCl₃) $\delta$ 212.6, 67.5, 51.8, 44.4, 38.8, 24.4, 23.8; IR (Neat Film NaCl) 3420, 2930, 2861, 1696, 1449, 1410, 1349, 1263, 1196, 1157, 1109, 1043, 1016, 929, 878, 829, 752, 710 cm⁻¹; HRMS (EI+) $m/z$ calc’d for C₇H₁₂O₂ [M]+: 128.0837; found 128.0828.

Acylcyclopentene 16. Alcohol 15 (101.3 mg, 0.79 mmol, 1.00 equiv) was dissolved in THF (7.9 mL) in a 20 mL scintillation vial with magnetic stir bar. The solution was treated with 2,2,2-trifluoroethanol (86.4 µL, 1.19 mmol, 1.50 equiv) and anhydrous LiOH (28.4 mg, 1.19 mmol, 1.50 equiv). The headspace of the vial was purged with N₂ and the vial was capped with a teflon-
lined hard cap and stirred at 60 °C in a heating block. After 16 h of stirring, the suspension was allowed to cool to ambient temperature, diluted with Et₂O (150 mL), dried over Na₂SO₄ (30 min of stirring), filtered, and concentrated carefully under reduced pressure in an ice-water bath. The crude product was purified using flash column chromatography (SiO₂, 2 x 20 cm, 15:1→10:1 Hexanes:Et₂O) to afford acylcyclopentene 16 (27 mg, 0.25 mmol, 31% yield) as a colorless fragrant oil. Spectra for the compound match data for commercially available material.

Ring Contraction Screening Protocol

Table SI-2. Ring Contraction Screen of β-Hydroxyketone 10a<sup>a</sup>

<table>
<thead>
<tr>
<th>Entry</th>
<th>Base</th>
<th>Additive</th>
<th>Solvent</th>
<th>Temp (°C)</th>
<th>Conversion (%)</th>
<th>Time (h)</th>
<th>Yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiOT-Bu</td>
<td>—</td>
<td>i-BuOH</td>
<td>40</td>
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<td>9</td>
<td>71</td>
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<tr>
<td>2</td>
<td>LiOT-Bu</td>
<td>—</td>
<td>THF</td>
<td>40</td>
<td>100</td>
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<td>60</td>
</tr>
<tr>
<td>3</td>
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<td>THF</td>
<td>40</td>
<td>100</td>
<td>5</td>
<td>81</td>
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<td>4</td>
<td>KOt-Bu</td>
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<td>THF</td>
<td>40</td>
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<td>85</td>
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<tr>
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<td>100</td>
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<td>—</td>
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<td>78</td>
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<td>19&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>HFiP&lt;sup&gt;c&lt;/sup&gt;</td>
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<td>—</td>
<td>CH₃CN</td>
<td>60</td>
<td>86</td>
<td>24</td>
<td>10</td>
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</table>

<sup>a</sup> Conditions: β-hydroxyketone 10a (1.0 equiv), additive (1.5 equiv), base (1.5 equiv), solvent (0.1 M) at indicated temperature for 9–24 h. <sup>b</sup> GC yield using an internal standard at ≥ 98% conversion unless otherwise stated. <sup>c</sup> HFiP = 1,1,1,3,3-hexafluoro-2-propanol; TFE = 2,2,2-trifluoroethanol. <sup>d</sup> Several reaction intermediates observed by TLC and GC analysis; proceeded to 78% conversion. <sup>e</sup> Isolated yield.

Ring Contraction Screen to Produce Acylcyclopentene 1a (0.10 mmol scale, Table 1, entries 1–4 and Table SI-2, entries 1–10). A benzene solution of β-hydroxyketone 10a was transferred to a dry 1 dram vial and concentrated under reduced pressure to obtain a starting mass. To this vial was added a magnetic stir bar and 1,4-diisopropylbenzene (internal standard). The contents were solvated in either i-BuOH or THF (0.1 M). After complete solvation, an appropriate additive (i-BuOH, TFE, or HFiP; 1.50 equiv) was added, followed by base (1.50 equiv). The head space of the vial was purged with N₂ and the vial was capped with a teflon-lined hard cap...
and stirred at the appropriate temperature (40 or 60 °C) in a heating block. Reaction progress was initially followed by TLC analysis and when necessary, aliquots were removed and flushed through a small SiO₂ plug with EtOAc for GC analysis. GC conditions: 90 °C isothermal for 5 min, then ramp 10 °C/min to 250 °C, DB-WAX column, tᵣ(min): 1,4-diisopropylbenzene = 5.3, acylcyclopentene 1a = 9.3, β-hydroxyketone 10a = 17.1 and 17.2 (two diastereomers). (For characterization data, see p. 19, 21).

**Additional Conditions.** Additional reaction conditions are listed in Table SI-2, entries 16–21.

**Unsuccessful Conditions.** No reaction was observed using the following bases, with or without TFE additive: DBU, TMG, Na₂CO₃, K₂CO₃, BaCO₃, CaH₂. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene, TMG = 1,1,3,3-tetramethylguanidine.

**Ring Contraction using LiOCH₂CF₃ (Table SI-2, entry 11).** β-Hydroxyketone 10a (30.0 mg, 0.16 mmol, 1.00 equiv) was measured into a 1 dram vial with magnetic stir bar with a septum-fitted screw cap. LiOCH₂CF₃ [1] (26.0 mg, 0.25 mmol, 1.50 equiv) was measured into a separate 1 dram vial, capped with a septum, evacuated/backfilled with N₂ (3 cycles, 5 min evacuation per cycle), and dissolved in THF (0.5 mL). The solution was cannulated into the vial containing β-hydroxyketone along with additional THF rinses (2 x 0.5 mL). The yellow solution was stirred at 60 °C in a heating block. After 10 h, the reaction was cooled to ambient temperature. The turbid brown solution was diluted with Et₂O and stirred with Na₂SO₄ for 30 min. The reaction was filtered and concentrated in vacuo at 0 °C in an ice/water bath. The residue was purified by flash column chromatography (SiO₂, 1 x 20 cm, 15:1 Hexanes:Et₂O) to afford acylcyclopentene 1a (24.4 mg, 0.149 mmol, 90% yield) as a clear, colorless oil. (For characterization data, see p. 21).
Procedures for the Synthesis of Acylcyclopentenes 1 by Ring Contraction

β-Hydroxyketones 10a–j, 10m, 10o–r, cycloheptenones 3a, 3r, and acylcyclopentenes 1a–j, 1m, 1o–r were prepared according to previously reported procedures. For β-hydroxyketone intermediate 10n, Rf, IR, and HRMS data are reported and 1H NMR and IR spectra are provided for reference. Representative procedures for General Methods A–E are described below.

General Method A: Lithium Aluminum Hydride Reduction / 10% Aq HCl Hydrolysis

Cycloheptenone 3a and β-Hydroxyketone 10a. A 500 mL round-bottom flask with magnetic stir bar was charged with Et₂O (150 mL) and cooled to 0 °C in an ice/water bath. LiAlH₄ (806 mg, 21.2 mmol, 0.55 equiv) was added in one portion. After 10 min, a solution of vinylogous ester 7a (9.13 g, 38.6 mmol, 1.00 equiv) in Et₂O (43 mL) was added dropwise using positive pressure cannulation. The grey suspension was stirred for 40 min and additional LiAlH₄ (148 mg, 3.9 mmol, 0.10 equiv) was added in one portion. After an additional 30 min of stirring at 0 °C, the reaction was quenched by slow addition of aqueous HCl (110 mL, 10% w/w). The resulting biphasic system was allowed to warm to ambient temperature and stirred vigorously for 8.5 h. The phases were separated and the aqueous phase was extracted with Et₂O (3 x 100 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was azeotroped with toluene (3 x 20 mL) and purified using flash column chromatography (SiO₂, 5 x 15 cm, 9:1 → 3:1 Hexanes:EtOAc, dry-loaded using Celite) to afford β-hydroxyketone 10a (6.09 g, 33.41 mmol, 87% yield, 1.3:1 dr) as a colorless semi-solid and cycloheptenone 3a (387 mg, 6% yield) as a colorless oil.

Cycloheptenone 3a. Rf = 0.54 (7:3 Hexanes:EtOAc); 1H NMR (500 MHz, CDCl₃) δ 6.04 (dd, J = 12.9, 0.7 Hz, 1H), 5.82 (d, J = 12.9 Hz, 1H), 5.75 (dddd, J = 17.1, 10.3, 7.8, 7.1 Hz, 1H), 5.10 (dddd, J = 10.3, 1.2, 1.2, 1.2 Hz, 1H), 5.08–5.03 (m, 1H), 2.65–2.52 (m, 2H), 2.19 (app dd, J = 13.7, 6.8 Hz, 1H), 2.11 (app dd, J = 13.7, 8.1 Hz, 1H), 1.84–1.76 (m, 3H), 1.68–1.63 (m, 1H), 1.10 (s, 3H); 13C NMR (75 MHz, CDCl₃) δ 204.7, 152.5, 133.8, 128.6, 118.6, 47.2, 45.1, 42.7, 38.2, 27.1, 18.4; IR (Neat Film NaCl) 3076, 3011, 2962, 2934, 2870, 1659, 1454, 1402, 1373, 1349, 1335, 1278, 1208, 1172, 997, 916, 874, 822, 772 cm⁻¹; HRMS (EI+) m/z calc’d for C₁₅H₂₆O[M]⁺: 210.1945; found 210.1944; [α]D²¹.0 = +9.55 (c 1.07, CHCl₃, 88.0% ee).
Supporting Information for Hong, Bennett, Krout, Jensen, Harned, and Stoltz

β-Hydroxyketone 10a (Table 4, entry 1). Rf = 0.23 (7:3 Hexanes:EtOAc); 1H NMR (500 MHz, CDCl3) δ major epimer: 5.88 (dddd, J = 15.1, 9.0, 7.6, 7.6 Hz, 1H), 5.12–5.08 (m, 2H), 3.70 (dd, J = 4.9, 3.9 Hz, 1H), 2.86 (dd, J = 15.6, 1.7 Hz, 1H), 2.65 (dd, J = 15.6, 7.3 Hz, 1H), 2.54–2.43 (m, 2H), 2.24 (dd, J = 13.7, 7.8 Hz, 1H), 2.07 (dd, J = 13.4, 7.3 Hz, 1H), 1.99 (dd, J = 15.9, 4.4 Hz, 1H), 1.82–1.69 (m, 2H), 1.45–1.41 (m, 1H), 0.96 (s, 3H); minor epimer: 5.83 (dddd, J = 14.9, 10.3, 7.6, 7.6 Hz, 1H), 5.12–5.06 (m, 2H), 3.68 (dd, J = 4.1, 2.4 Hz, 1H) 2.80 (dd, J = 15.4, 2.4 Hz, 1H), 2.74 (dd, J = 15.4, 8.1 Hz 1H), 2.46–2.38 (m, 2H), 2.18 (dd, J = 13.9, 7.3 Hz, 1H), 2.09 (dd, J = 12.9, 7.8 Hz, 1H), 1.82–1.65 (m, 3H) 1.50–1.47 (m, 1H), 1.02 (s, 3H); 13C NMR (75 MHz, CDCl3) δ major epimer: 213.2, 135.0, 118.1, 72.9, 46.7, 44.9, 44.2, 41.0, 36.3, 21.9, 18.9; minor epimer: 212.6, 134.2, 118.3, 73.3, 47.2, 42.8, 41.0, 35.9, 22.6, 18.7; IR (Neat Film NaCl) 3436, 3074, 2932, 1692, 1638, 1443, 1403, 1380, 1352, 1318, 1246, 1168, 1106, 1069, 999, 913, 840 cm–1; HRMS (EI+) m/z calc’d for C11H18O2 [M]+: 182.1313; found 182.1307; [α]D 22.8–57.10 (c 2.56, CHCl3, 88.0% ee).

General Method B: DIBAL Reduction / Oxalic Acid Hydrolysis

β-Hydroxyketone 10i. A 25 mL pear shaped flask was charged with vinylogous ester 7i (29.4 mg, 0.094 mmol, 1.00 equiv) and toluene (3.0 mL). The solution was cooled to –78 °C using an acetone/CO2(s) bath. A 1.0 M solution of DIBAL in toluene (112.6 µL, 0.113 mmol, 1.00 equiv) was added dropwise and the solution was stirred for 10 min. MeOH (180 µL), Na2SO4·10H2O (1.08 g), and Celite (360 mg) were added. The reaction was stirred vigorously and allowed to warm slowly to ambient temperature. The mixture was filtered through a Celite plug (3 x 3 cm, EtOAc), and concentrated in vacuo. Rf = 0.28, broad (1:2 Hexanes:EtOAc).

The crude hydroxy isobutyl enol ether was added to a 25 mL round-bottom flask and dissolved in MeOH (4.0 mL). Oxalic acid dihydrate (354.9 mg, 2.82 mmol, 30.0 equiv) was added in one portion. After 1 h of stirring, the reaction was neutralized to pH 7 with 1 M aqueous pH 7 NaH2PO4/Na2HPO4 buffer (6 mL). The biphasic mixture was stirred vigorously for 10 min and the phases were separated. The aqueous layer was extracted with Et2O (4 x 15 mL). The combined organic phases were dried over Na2SO4, filtered, and concentrated under reduced pressure. The crude product was purified using flash column chromatography (SiO2, 1.5 x 25 cm, 4:1→2:1→1:2 Hexanes:Acetone) to afford β-hydroxyketone 10i as a mixture of diastereomers (21.6 mg, 0.083 mmol, 89% yield over 2 steps, 2.8:1 dr) as a clear, colorless residue which solidified upon standing. Rf = 0.10 (2:1 Hexanes:Acetone); 1H NMR (300 MHz, CDCl3) mixture of two diastereomers, see Figure SI-43 in the Supporting Information of ref. 10; IR (Neat Film NaCl) 3391, 3201, 3073, 2929, 2865, 1699, 1636, 1603, 1557, 1497, 1456, 1418,
1352, 1332, 1297, 1258, 1222, 1187, 1161, 1113, 1069, 1005, 995, 972, 915, 886, 851, 802, 735 cm⁻¹; HRMS (FAB+) m/z calc'd for C₁₆H₂₂O₂N [M+H⁺]: 260.1650; found 260.1649.

**General Method C: Luche Reduction / 10% Aq HCl Hydrolysis**

**β-Hydroxyketone 10m.** A 100 mL round-bottom flask with magnetic stir bar was charged with vinylogous ester 7m (65.6 mg, 0.134 mmol, 1.00 equiv) and anhydrous MeOH (8.3 mL). The solution was cooled to 0 °C in an ice/water bath. CeCl₃·7H₂O (78.2 mg, 0.21 mmol, 1.56 equiv) was added in one portion and the mixture was stirred for 5 min. Addition of NaBH₄ (23.8 mg, 0.63 mmol, 4.70 equiv) led to the evolution of gas and a turbid solution that became clear after several minutes. The reaction was stirred at 0 °C. After 15 min, the reaction was diluted with CH₂Cl₂ (20 mL) until turbid, filtered through a Celite plug (3 x 3 cm, CH₂Cl₂), and concentrated in vacuo. The residue was taken up in CH₂Cl₂, filtered through a Celite plug (3 x 5 cm, CH₂Cl₂), and concentrated in vacuo a second time. Rₚ = 0.33 (10:1 Hexanes:EtOAc).

The crude hydroxy isobutyl enol ether was added to a 25 mL round-bottom flask with a magnetic stir bar and dissolved in Et₂O (3.8 mL). The vigorously stirred solution was cooled to 0 °C and aqueous HCl (384 µL, 10% w/w) was added dropwise via syringe. After 30 min, the reaction was allowed to warm to ambient temperature and extracted with Et₂O (3 x 5 mL). The combined organic phases were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified using flash column chromatography (SiO₂, 1.5 x 25 cm, 6:1 → 4:1 Hexanes:EtOAc) to afford β-hydroxyketone 10m as a mixture of diastereomers (55.6 mg, 0.13 mmol, 95% yield over 2 steps, 3.5:1 dr) as a colorless oil; Rₚ = 0.22, 0.28 (two diastereomers) (4:1 Hexanes:EtOAc); ¹H NMR (300 MHz, CDCl₃) mixture of two diastereomers, see Figure SI-45 in the Supporting Information of ref. 10; IR (Neat Film NaCl) 3468, 3072, 3050, 2999, 3013, 2931, 2895, 2858, 2248, 1960, 1891, 1823, 1772, 1698, 1638, 1590, 1472, 1462, 1446, 1428, 1391, 1361, 1337, 1260, 1222, 1186, 1172, 1158, 1113, 1088, 1030, 1006, 999, 976, 914, 841, 823, 810, 740 cm⁻¹; HRMS (FAB+) m/z calc'd for C₂₇H₃₇O₃Si [M+H⁺]: 437.2512; found 437.2517.

**General Method D: DIBAL Reduction / 10% Aq HCl Hydrolysis**

**β-Hydroxyketone 10n.** A 50 mL pear shaped flask was charged with vinylogous ester 7n (100 mg, 0.292 mmol, 1.00 equiv) and toluene (9.5 mL). The solution was cooled to –78 °C using an acetone/CO₂(s) bath. A 1.0 M solution of DIBAL in toluene (963 µL, 0.963 mmol, 1.00 equiv)
was added dropwise and the mixture was stirred for 15 min. MeOH (1.0 mL), Na₂SO₄·10 H₂O (6.0 g), and Celite (1.2 g) were added and the mixture was stirred vigorously and allowed to warm slowly to ambient temperature. The mixture was filtered through a Celite plug (3 x 3 cm, EtOAc), and concentrated in vacuo. Rₜ = 0.30 (2:1 Hexanes:EtOAc).

The crude hydroxy isobutyl enol ether was added to a 50 mL pear shaped flask, dissolved in Et₂O (10 mL), and cooled to 0 °C in an ice/water bath. Aqueous HCl (0.835 mL, 10% w/w) was added dropwise and the biphasic mixture was stirred vigorously at 0 °C. After 40 min of stirring, additional aqueous HCl (0.835 mL, 10% w/w) was added. After 1.5 h, the layers were separated and the aqueous layer was extracted with Et₂O (5 x 15 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude product was purified using flash column chromatography (SiO₂, 1.5 x 25 cm, 10:1 → 6:1 → 4:1 → 2:1 → 1:1 → 1:2 Hexanes:EtOAc) to afford hydroxyketone 10n as a mixture of diastereomers (20.3 mg, 0.110 mmol, 38% yield over 2 steps) as a clear, colorless oil; Rₜ = 0.19 (1:1 Hexanes:EtOAc); ¹H NMR (300 MHz, CDCl₃) mixture of two diastereomers, see Figure SI-10; IR (Neat Film NaCl) 3369, 3077, 3011, 2947, 2924, 1688, 1641, 1469, 1439, 1343, 1268, 1216, 1193, 1128, 1079, 1052, 1032, 999, 966, 909, 889, 808, 731 cm⁻¹; HRMS (MM: ESI-APCI+) m/z calc'd for C₁₀H₁₅O [M–OH]⁺: 167.1067; found 167.1066.

General Method E: β-Hydroxyketone Ring Contraction

Acylcyclopentene 1a. Alcohol 10a (6.09 g, 33.4 mmol, 1.00 equiv) was dissolved in THF (334 mL) in a 500 mL round-bottom flask. The solution was treated with 2,2,2-trifluoroethanol (3.67 mL, 50.1 mmol, 1.50 equiv) and anhydrous LiOH (1.20 g, 50.1 mmol, 1.50 equiv). The flask was fitted with a condenser, purged with N₂, and heated to 60 °C using an oil bath. After 18 h of stirring, the suspension was allowed to cool to ambient temperature, diluted with Et₂O (150 mL), dried over Na₂SO₄ (30 min of stirring), filtered, and concentrated carefully under reduced pressure, allowing for a film of ice to form on the outside of the flask. The crude product was purified using flash column chromatography (SiO₂, 5 x 15 cm, 15:1 Hexanes:EtOAc) to afford acylcyclopentene 1a (5.29 g, 32.2 mmol, 96% yield) as a colorless fragrant oil; Rₜ = 0.67 (8:2 Hexanes:EtOAc); ¹H NMR (500 MHz, CDCl₃) δ 6.45 (app t, J = 1.7 Hz, 1H), 5.76 (ddd, J = 16.4, 10.7, 7.3, 7.3 Hz, 1H), 5.07–5.03 (m, 2H), 2.59–2.48 (m, 2H), 2.30 (s, 3H), 2.21–2.14 (m, 2H), 1.85 (ddd, J = 12.9, 8.3, 6.3 Hz, 1H), 1.64 (ddd, J = 12.9, 8.5, 6.1 Hz, 1H), 1.11 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 197.5, 151.9, 143.8, 134.9, 117.8, 50.0, 45.3, 36.0, 29.7, 26.8, 25.6; IR (Neat Film NaCl) 3077, 2956, 2863, 1668, 1635, 1616, 1454, 1435, 1372, 1366, 1309, 1265, 1213, 1177, 993, 914, 862 cm⁻¹; HRMS (El+) m/z calc'd for C₁₀H₁₇O [M+H]⁺: 165.1279; found 165.1281; [α]D⁺21.4 +17.30 (c 0.955, CHCl₃, 88.0% ee); GC conditions: 80 °C isothermal, GTA column, tᵣ (min): major = 54.7, minor = 60.2.
Acylcyclopentene 1i (Table 4, entry 9). Prepared using General Method E. 15.7 mg, 0.065 mmol, 90% yield. Flash column chromatography (SiO₂, 1.5 x 16 cm, 2:1→1:1 Hexanes:Acetone); Rᵋ = 0.47 (2:1 Hexanes:Acetone); ¹H NMR (300 MHz, CDCl₃) δ 8.49 (br d, J = 3.8 Hz, 2H), 7.04 (d, J = 5.7 Hz, 2H), 6.40 (dd, J = 1.7, 1.7 Hz, 1H), 5.75 (dddd, J = 17.3, 10.3, 7.3, 7.3 Hz, 1H), 5.16–5.04 (m, 2H), 2.77 (d, J = 13.0 Hz, 1H), 2.71 (d, J = 13.0 Hz, 1H), 2.52–2.39 (m, 1H), 2.33–2.35 (m, 1H), 2.28 (s, 3H), 2.24–2.20 (m, 2H), 1.85–1.80 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) 196.8, 149.6, 148.6, 147.3, 145.4, 134.0, 125.7, 118.8, 54.2, 44.4, 43.3, 33.3, 30.0, 27.0; IR (Neat Film NaCl) 3401, 3071, 3025, 2922, 2856, 1668, 1640, 1618, 1557, 1495, 1441, 1415, 1373, 1318, 1277, 1265, 1220, 1194, 1071, 994, 917, 874, 844, 810, 763 cm⁻¹; HRMS (EI+) m/z calc’d for C₁₆H₁₉ON [M⁺]: 176.1467; found 176.1458; [α]D²⁵⁰ –8.58 (c 0.77, CHCl₃, 84.6% ee).

Acylcyclopentene 1m (Table 4, entry 11). Prepared using General Method E. 32.6 mg, 0.078 mmol, 96% yield. Flash column chromatography (SiO₂, 1 x 20 cm, 15:1 Hexanes:EtOAc); Rᵋ = 0.60 (4:1 Hexanes:EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 7.67–7.60 (m, 4H), 7.47–7.34 (m, 6H), 6.50 (dd, J = 1.8, 1.8 Hz, 1H), 5.71 (dddd, J = 17.0, 10.1, 7.8, 6.9 Hz, 1H), 5.12–5.08 (m, 1H), 5.06–5.02 (m, 1H), 3.57 (d, J = 9.8 Hz, 1H), 3.53 (d, J = 9.8 Hz, 1H), 2.54–2.48 (m, 2H), 2.38 (dd, J = 13.8, 6.9, 1.1 Hz, 1H), 2.31–2.25 (m, 1H), 2.29 (s, 3H), 1.81–1.72 (m, 2H), 1.07 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 197.2, 148.5, 145.7, 135.8, 134.5, 133.6, 133.6, 129.9, 129.9, 127.8, 118.0, 69.1, 56.5, 40.4, 30.7, 30.0, 27.0, 26.8, 19.5; IR (Neat Film NaCl) 3072, 3050, 2999, 2956, 2931, 2896, 2857, 1671, 1639, 1618, 1472, 1463, 1427, 1367, 1320, 1266, 1232, 1188, 1112, 998, 936, 915, 864, 824, 740 cm⁻¹; HRMS (EI+) m/z calc’d for C₂₇H₃₄O₂Si [M⁺]: 433.1712; found 433.1694; [α]D²⁵⁰ –17.58 (c 0.94, CHCl₃, 51.4% ee).

Acylcyclopentene 1n (Table 4, entry 15). Prepared using General Method E. 12.2 mg, 0.073 mmol, 67% yield. Flash column chromatography (SiO₂, 1.5 x 25 cm, 10:1→4:1→2:1→1:1 Hexanes:Acetone); Rᵋ = 0.50 (2:1 Hexanes:Acetone); ¹H NMR (300 MHz, CDCl₃) δ 8.49 (br d, J = 3.8 Hz, 2H), 7.04 (d, J = 5.7 Hz, 2H), 6.40 (dd, J = 1.7, 1.7 Hz, 1H), 5.75 (dddd, J = 17.3, 10.3, 7.3, 7.3 Hz, 1H), 5.16–5.04 (m, 2H), 2.77 (d, J = 13.0 Hz, 1H), 2.71 (d, J = 13.0 Hz, 1H), 2.52–2.39 (m, 1H), 2.33–2.35 (m, 1H), 2.28 (s, 3H), 2.24–2.20 (m, 2H), 1.85–1.80 (m, 2H); ¹³C NMR (75 MHz, CDCl₃) 196.8, 149.6, 148.6, 147.3, 145.4, 134.0, 125.7, 118.8, 54.2, 44.4, 43.3, 33.3, 30.0, 27.0; IR (Neat Film NaCl) 3401, 3071, 3025, 2922, 2856, 1668, 1640, 1618, 1600, 1557, 1495, 1441, 1415, 1373, 1318, 1277, 1265, 1220, 1194, 1071, 994, 917, 874, 844, 810, 763 cm⁻¹; HRMS (EI+) m/z calc’d for C₁₆H₁₉ON [M⁺]: 176.1467; found 176.1458; [α]D²⁵⁰ –8.58 (c 0.77, CHCl₃, 84.6% ee).
Hexanes:EtOAc); \( R_f = 0.44 \) (1:1 Hexanes:EtOAc); \( \text{\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3})} \delta \text{6.48 (app t, } J \text{ = 1.9 Hz, 1H), 5.91–5.77 (dddd, } J \text{ = 16.5, 10.7, 7.4, 7.4 Hz, 1H), 5.23–5.15 (m, 2H), 2.67 (dddd, } J \text{ = 17.0, 8.9, 4.1, 1.7 Hz, 1H), 2.50–2.40 (m, 3H), 2.33 (s, 3H), 2.14 (ddd, } J \text{ = 13.7, 8.5, 4.1 Hz, 1H), 2.03 (br s, 1H), 1.91 (ddd, } J \text{ = 13.7, 9.0, 5.8 Hz, 1H); \text{\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3})} \delta \text{197.5, 145.9, 145.5, 132.9, 119.8, 85.2, 44.9, 37.4, 29.1, 27.0; IR (Neat Film NaCl) 3400, 3077, 3004, 2961, 2929, 2856, 1841, 1668, 1622, 1428, 1372, 1295, 1267, 1205, 1173, 1070, 1057, 1016, 998, 966, 935, 862, 776 cm}\textsuperscript{–1}; \text{HRMS (MM: ESI-APCI+) } m/z \text{ calc'd for C}_{10}H_{13}O [M–OH]\textsuperscript{+}: 149.0961; found 149.0967; [\alpha]_D^{25.0} –22.45 (c 1.22, CHCl\textsubscript{3}, 57.1% ee).

**Cyclic Dione 17.** A 20 mL scintillation vial equipped with a stir bar was charged with vinylogous ester \( 7a \) (144.6 mg, 0.61 mmol, 1.00 equiv), THF (1 mL), and aqueous HCl (1 mL, 10% w/w, 2.87 mmol, 4.69 equiv). After 4.5 h of vigorous stirring, the solution was diluted with \( \text{H}_2\text{O} \) (5 mL) and transferred to a separatory funnel where the aqueous phase was extracted four times with Et\textsubscript{2}O. The combined organics (70 mL) were dried over MgSO\textsubscript{4}, filtered, and concentrated. The crude oil was purified by flash chromatography (SiO\textsubscript{2}, 27.5 x 2 cm, 100% Hexanes$\rightarrow$10% EtOAc in Hexanes) to afford cyclic dione \( 17 \) (99.4 mg, 0.55 mmol, 90% yield) as a pale yellow oil; \( R_f = 0.48 \) (30% EtOAc in Hexanes); \( \text{\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3})} \delta \text{5.69 (d, } J \text{ = 14.0 Hz, 1H), 5.12–5.04 (m, 2H), 3.72 (d, } J \text{ = 14.0 Hz, 1H), 3.53 (d, } J \text{ = 14.0 Hz, 1H), 2.48 (t, } J \text{ = 6.6 Hz, 2H), 2.40 (ddd, } J \text{ = 13.9, 7.1, 1.2, 1.2 Hz, 1H), 2.22 (ddd, } J \text{ = 13.9, 7.7, 1.1, 1.1 Hz, 1H), 2.02–1.75 (m, 4H), 1.15 (s, 3H); \text{\textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3})} \delta \text{208.4, 203.7, 133.1, 119.1, 57.6, 50.9, 43.5, 42.9, 36.7, 21.9, 19.8; IR (Neat Film NaCl) 3076, 2972, 2935, 2871, 1719, 1695, 1639, 1463, 1417, 1378, 1337, 1210, 1160, 1112, 1059, 1026, 921 cm}\textsuperscript{–1}; \text{HRMS (EI+) calc'd for C}_{11}H_{16}O_{2} [M]\textsuperscript{+}: 180.1150; found 180.1165; [\alpha]_D^{25.0} –19.38 (c 1.00, CHCl\textsubscript{3}, 88.0% ee).

**Cycloheptenone 3r and \( \beta \)-Hydroxyketone 10r.** CeCl\textsubscript{3}·7H\textsubscript{2}O (419 mg, 1.13 mmol, 2.55 equiv) in a 100 mL round-bottom flask was immersed in a preheated oil bath at 150 °C and placed under vacuum for 4 h while stirring. The flask was cooled to ambient temperature, backfilled with \( \text{N}_2 \), and charged with THF (4 mL). After 15 h of stirring, additional THF (4 mL) and \( n \)-butylmagnesium chloride solution (1.2 mL, 1.86 M in THF, 2.23 mmol, 5.02 equiv) were added to the flask. The resulting slurry was stirred for 4.25 h before vinylogous ester \( 7a \) (105 mg, 0.444 mmol, 1.00 equiv) dissolved in THF (1 mL) was added using positive pressure cannulation followed by two THF rinses (2 x 0.5 mL). After 45 min of stirring, the reaction was quenched by addition of aqueous HCl (10 mL). The phases were separated and the aqueous layer was
extracted with EtOAc (3 x 15 mL). The combined organic phases were washed with brine, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography using a Teledyne Isco CombiFlash Rf system (SiO₂, 25 g loading cartridge, 12 g column, multi-step gradient, hold 0% [1 min]→ramp to 10% [5 min]→hold 10% [31 min]→100% EtOAc in Hexanes [10 min]) to afford cycloheptenone 3r (28 mg, 0.13 mmol, 28% yield) and β-hydroxyketone 10r (69 mg, 0.29 mmol, 65% yield) as pale yellow oils.

**Cycloheptenone 3r.** \( R_f = 0.68 \) (30% EtOAc in Hexanes); \(^1\)H NMR (500 MHz, CDCl₃) \( \delta \) 5.89 (s, 1H), 5.63 (ddddd, \( J = 16.9, 10.3, 7.9, 6.7 \text{ Hz}, 1H \)), 5.10–4.98 (m, 2H), 2.61–2.54 (m, 2H), 2.37 (ddd, \( J = 14.1, 6.7, 1.3, 1.3 \text{ Hz}, 1H \)), 2.18–2.03 (m, 3H), 1.85–1.72 (m, 3H), 1.66–1.56 (m, 1H), 1.53–1.43 (m, 2H), 1.37 (app. septuplet, \( J = 7.3 \text{ Hz}, 2H \)), 1.15 (s, 3H), 0.92 (t, \( J = 7.3 \text{ Hz}, 3H \)); \(^{13}\)C NMR (125 MHz, CDCl₃) \( \delta \) 205.4, 163.0, 134.2, 128.7, 118.1, 45.7, 45.3, 44.4, 38.8, 34.0, 32.4, 25.7, 23.0, 17.6, 14.1; IR (Neat Film NaCl) 3076, 2957, 2933, 2872, 1652, 1611, 1467, 1414, 1379, 1342, 1263, 1218, 1109, 1072, 996, 962, 914, 841, 780, 713 cm\(^{-1}\); HRMS (MM: ESI–APCI+) calc’d for C₁₅H₂₅O [M+H]\(^+\): 221.1900; found 221.1905; \([\alpha]_D^{25.0} \) –33.17 (c 1.17, CHCl₃, 88.0% ee).

**β-Hydroxyketone 10r.** \( R_f = 0.48 \) (30% EtOAc in Hexanes); \(^1\)H NMR (500 MHz, CDCl₃) mixture of two diastereomers, see Figure SI-66 in the Supporting Information of ref. 10; IR (Neat Film NaCl) 3502, 3076, 2957, 2933, 2872, 1652, 1611, 1467, 1414, 1379, 1342, 1263, 1218, 1178, 1109, 1072, 996, 962, 914, 841, 780, 713 cm\(^{-1}\); HRMS (MM: ESI–APCI+) calc’d for C₁₅H₂₇O₂ [M+H]\(^+\): 239.2006; found 239.2013.

**Linear Dione 11r.** A 50 mL round-bottom flask equipped with a magnetic stir and fitted with a water condenser was charged with β-hydroxyketone 10r (56.9 mg, 0.24 mmol, 1.00 equiv), THF (3 mL), TFE (60 µL, 0.83 mmol, 3.50 equiv), and LiOH (17.3 mg, 0.72 mmol, 3.03 equiv). The flask was backfilled with argon and lowered into a preheated oil bath (60 °C). After 3 h, the reaction was removed from the bath, allowed to cool to room temperature, dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO₂, 3 x 21 cm, 10%→20%→30% EtOAc in Hexanes) to afford linear dione 11r (40.1 mg, 0.17 mmol, 71% yield) as a pale yellow oil; \( R_f = 0.57 \) (30% EtOAc in Hexanes);
$^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.68–5.57 (m, 1H), 5.06–4.98 (m, 2H), 2.43 (t, $J$ = 7.3 Hz, 2H), 2.39 (t, $J$ = 6.4 Hz, 2H), 2.31 (dddd, $J$ = 14.0, 7.3, 1.2, 1.2 Hz, 1H), 2.18 (dddd, $J$ = 14.0, 7.7, 1.2, 1.2 Hz, 1H), 2.11 (s, 3H), 1.63–1.34 (m, 6H), 1.33–1.24 (m, 2H), 1.10 (s, 3H), 0.89 (t, $J$ = 7.3 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 214.9, 208.6, 133.9, 118.1, 50.9, 44.0, 42.6, 37.4, 37.4, 30.1, 25.9, 22.6, 21.1, 18.7, 14.1; IR (Neat Film NaCl) 3076, 2958, 2933, 2873, 1718, 1701, 1639, 1465, 1409, 1378, 1174, 1142, 994, 916, 766, 728 cm$^{-1}$; HRMS (MM: ESI–APCI+) calc’d for C$_{15}$H$_{27}$O$_2$ [M+H]$^+$: 239.2006; found 239.2005; $[\alpha]_D^{25.0}$ 5.57 (c 1.17, CHCl$_3$, 88.0% ee).

**Acylcyclopentene 1r.** A 25 mL round-bottom flask equipped with a stir bar and fitted with a water condenser was charged with $\beta$-hydroxyketone 10r (91.5 mg, 0.38 mmol, 1.00 equiv), THF (4 mL), and KOt-Bu (66.5 mg, 0.59 mmol, 1.55 equiv). The flask was lowered into a preheated oil bath (60 °C) and stirred overnight. Additional THF (4 mL) was added after 19 h of heating. After an additional 3 h, the reaction was removed from the bath, allowed to cool to room temperature, dried over Na$_2$SO$_4$, filtered through a silica gel plug, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO$_2$, 3 x 27 cm, 100% pentane→2%→5%→10% Et$_2$O in pentane) to afford acylcyclopentene 1r (55.1 mg, 0.25 mmol, 65% yield) as a pale yellow oil; $R_f$ = 0.81 (30% EtOAc in Hexanes); $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 5.77–5.65 (m, 1H), 5.08–5.00 (m, 2H), 2.60–2.49 (m, 2H), 2.45–2.37 (m, 1H), 2.24–2.17 (m, 4H), 2.15–2.10 (m, 2H), 1.85 (ddd, $J$ = 12.8, 7.7, 6.2 Hz, 1H), 1.60–1.51 (m, 1H), 1.47–1.34 (m, 4H), 1.06 (s, 3H), 0.93 (t, $J$ = 7.1 Hz, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) $\delta$ 198.8, 164.2, 135.0, 134.7, 117.6, 52.6, 43.8, 35.0, 32.1, 31.5, 30.4, 27.6, 24.7, 23.8, 14.0; IR (Neat film NaCl) 3075, 3002, 2957, 2930, 2870, 2859, 1677, 1653, 1639, 1602, 1456, 1432, 1373, 1355, 1311, 1275, 1258, 1188, 1141, 1089, 995, 959, 913, 848, 801, 726 cm$^{-1}$; HRMS (MM: ESI–APCI+) calc’d for C$_{15}$H$_{25}$O$_2$ [M+H]$^+$: 221.1900; found 221.1900; $[\alpha]_D^{25.0}$ –1.44 (c 1.35, CHCl$_3$, 88.0% ee).

**Acylcyclopentene 1r.** KOt-Bu (32 mg, 0.283 mmol, 1.62 equiv), THF (1.75 mL), and $\beta$-hydroxyketone 10r (175 µL, 1.0 M in benzene, 0.175 mmol, 1.00 equiv) were added to a 0.5–2.0 mL microwave vial with a magnetic spin vane. The pale yellow solution was subjected to microwave irradiation in a Biotage Initiator microwave reactor (temperature: 85 °C, sensitivity: normal). After 5 min of irradiation, the crimp cap was removed and Na$_2$SO$_4$ was added to the vial. The contents were filtered through a silica gel plug with Et$_2$O, concentrated under reduced
pressure, and purified by flash column chromatography (5% Et₂O in Pentane) to yield acyclopentene 1r (31 mg, 0.14 mmol, 73% yield) as a pale yellow oil.

**Procedures for the Synthesis of Acyclopentene Derivatives 21–24, 28, 42**

Acyclopentene derivatives 18–20, 25–27, 29–32, 35–39, 41 were prepared according to previously reported procedures.[10]

**Oxime 21.** A 1 dram vial with magnetic stir bar was charged with acyclopentene 1a (40.0 mg, 0.24 mmol, 1.00 equiv), MeOH (0.24 mL), 50% wt aqueous hydroxylamine (47 µL, 0.76 mmol, 3.13 equiv), and 3 M aqueous NaOH (125 µL, 0.376 mmol, 0.51 equiv). After 9 d, the reaction was diluted with Et₂O (10 mL) and H₂O (2 mL) and stirred vigorously for several minutes. The layers were separated and the aqueous layer was extracted with Et₂O (5 x 10 mL). The combined organic layers were dried over MgSO₄, filtered, and concentrated under reduced pressure. The residue was taken up in CH₂Cl₂, filtered through a cotton plug, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, 1.5 x 20 cm, 20:1→15:1 Hexanes:EtOAc) to afford oxime 21 (39.3 mg, 0.21 mmol, 90% yield) as a clear oil; Rᵥ = 0.52 (4:1 Hexanes:EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 9.73 (br s, 1H), 5.90 (br t, J = 1.5 Hz, 1H), 5.85–5.66 (m, 1H), 5.02 (m, 2H), 2.70–2.45 (m, 2H), 2.14 (m, 2H), 2.05 (s, 3H), 1.85 (ddd, J = 12.9, 8.1, 6.6 Hz, 1H), 1.65 (ddd, J = 12.8, 8.3, 6.3 Hz, 1H), 1.08 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 154.0, 141.8, 139.1, 135.6, 117.2, 48.9, 45.9, 36.3, 30.6, 26.2, 11.3; IR (Neat Film NaCl) 3272, 3233, 3075, 3003, 2952, 2925, 2864, 1639, 1455, 1437, 1414, 1379, 1322, 1280, 1103, 1010, 995, 913, 850, 756, 715 cm⁻¹; HRMS (EI+) m/z calc’d for C₈H₁₂NO [M–C₃H₅]^+: 138.0919; found 138.0960; [α]D²⁵⁺ +21.34 (c 1.57, CHCl₃, 88.0% ee).

**Tosylhydrazone 22.** A 25 mL flask with magnetic stir bar was charged with acyclopentene 1a (40.0 mg, 0.24 mmol, 1.00 equiv), 1,2-dichloroethane (2.7 mL), cetyltrimethylammonium bromide (26.6 mg, 0.073 mmol, 0.30 equiv), KOH (136.7 mg, 2.44 mmol, 10.0 equiv), and TsHNNH₂ (271.9 mg, 1.46 mmol, 6.00 equiv), forming a thick white suspension. After 43 h, the reaction was quenched by the addition of sat. aqueous NH₄Cl (5 mL). The mixture was extracted with CH₂Cl₂ (5 x 10 mL) and the combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography
using a Teledyne Isco CombiFlash Rf system (SiO₂, 3 x 25 cm, 4:1→3:1 Hexanes:EtOAc) to afford tosylhydrazone 22 (196.7 mg, 0.94 mmol, 74% yield) as a clear oil; \( R_f = 0.41 \) (2:1 Hexanes:EtOAc); \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 7.86 (d, \( J = 8.3 \) Hz, 2H), 7.54 (br s, 1H), 7.31 (d, \( J = 8.0 \) Hz, 2H), 5.85 (app t, \( J = 1.6 \) Hz, 1H), 5.81–5.62 (m, 1H), 5.06–4.92 (m, 2H), 2.58–2.48 (m, 2H), 2.43 (s, 3H), 2.19–2.00 (m, 2H), 1.89 (s, 3H), 1.85–1.71 (m, 1H), 1.71–1.50 (m, 1H), 1.03 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 151.5, 144.1, 142.4, 141.6, 135.5, 135.4, 129.5, 128.3, 117.2, 49.3, 45.8, 36.2, 30.7, 26.1; IR (Neat Film NaCl) 3584, 3318, 2956, 2866, 1697, 1669, 1639, 1618, 1598, 1587, 1537, 1494, 1454, 1401, 1337, 1307, 1292, 1212, 1185, 1168, 1094, 1059, 1029, 914, 870, 850, 830, 813, 706 cm⁻¹; HRMS (EI+) \( m/z \) calc'd for C₁₅H₁₉O₂N₂S [M+C₃H₅]⁺: 291.1167; found 291.1181; [\( \alpha \)]D²⁵⁺ +34.25 (c 1.05, CHCl₃, 88.0% ee).

**Bis-enone SI-3.** To an oven-dried reaction tube with magnetic stir bar was added acyclocyclopentene 1a (50 mg, 0.304 mmol, 1.00 equiv). The headspace was purged with \( \text{N}_2 \) and dry degassed toluene (2.0 mL, sparged with \( \text{N}_2 \) for 1 h immediately before use) was added, followed by methyl vinyl ketone (124 \( \mu \)L, 1.53 mmol, 5.03 equiv). Grubbs–Hoveyda 2nd Generation catalyst (9.5 mg, 15.2 \( \mu \)mol, 5 mol %) was quickly added to the reaction, giving the solution an olive green color. A reflux condenser was attached and the reaction was inserted into a 50 °C heating block. The solution quickly developed a dark brown color. After 2 h, the reaction was cooled to ambient temperature. The solution was filtered through a short silica gel plug (2 x 4 cm, Et₂O). The filtrate was concentrated under reduced pressure and the brown residue was purified by flash column chromatography (SiO₂, 2 x 25 cm, 10:1→4:1→2:1→1:1 Hexanes:EtOAc) to afford bis-enone SI-3 (62.3 mg, 0.30 mmol, 99% yield) as a brown liquid; \( R_f = 0.31 \) (2:1 Hexanes:EtOAc); \(^1\)H NMR (300 MHz, CDCl₃) \( \delta \) 6.71 (ddd, \( J = 15.5, 7.6, 7.6 \) Hz, 1H), 6.42 (s, 1H), 6.10 (d, \( J = 15.8 \) Hz, 1H), 2.68–2.40 (m, 2H), 2.33 (dd, \( J = 7.6, 0.9 \) Hz, 2H), 2.28 (s, 3H), 2.22 (s, 3H), 1.84 (ddd, \( J = 14.7, 8.2, 6.6 \) Hz, 1H), 1.70 (ddd, \( J = 13.1, 8.4, 6.1 \) Hz, 1H), 1.14 (s, 3H); \(^{13}\)C NMR (75 MHz, CDCl₃) \( \delta \) 198.1, 197.1, 150.2, 144.3, 143.8, 133.8, 50.1, 43.7, 36.2, 29.8, 27.3, 26.8, 25.7; IR (Neat Film NaCl) 3584, 3318, 2956, 2866, 1697, 1669, 1626, 1454, 1429, 1365, 1308, 1254, 1182, 1098, 1021, 982, 937, 867 cm⁻¹; HRMS (EI+) \( m/z \) calc'd for C₁₃H₁₈O₂ [M⁺]: 206.1307; found 206.1303; [\( \alpha \)]D²⁵⁺ +47.61 (c 1.02, CHCl₃, 88.0% ee).

**Mono-enone 23.** An oven-dried 2-neck flask fitted with a magnetic stir bar, rubber septum, and glass T-joint with 14/20 adapter was charged with bis-enone SI-3 (50.0 mg, 0.24 mmol, 1.00 equiv) and evacuated/backfilled with \( \text{N}_2 \) in a glove box antechamber (3 cycles, 5 min evacuation per cycle) before being transferred into the glove box. CH₂Cl₂ (2.5 mL) and Rh(PPh₃)₂Cl (22.4
mg, 0.024 mmol, 10 mol %) were added to the flask, giving a red solution. The flask was sealed with a septum on one neck and T-joint (set to the closed position) on the other neck and carefully brought out of the glove box. A H₂ balloon was attached to the T-joint and the flask was gently evacuated/backfilled with H₂ (3 cycles, 2 min evacuation per cycle). After 10 h of stirring, the brown reaction mixture was filtered through a short silica gel plug (2 x 4 cm, Et₂O) and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, 2 x 25 cm, 10:1→4:1→2:1 Hexanes:EtOAc) to afford enone 23 (46.8 mg, 0.23 mmol, 93% yield) as an orange liquid; Rᵣ = 0.40 (2:1 Hexanes:EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 6.43 (app t, J = 1.7 Hz, 1H), 2.65–2.46 (m, 2H), 2.40 (t, J = 7.1 Hz, 2H), 2.27 (s, 3H), 1.88–1.72 (m, 1H), 1.71–1.46 (m, 3H), 1.46–1.29 (m, 2H), 1.08 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 208.8, 197.5, 152.0, 143.6, 50.0, 44.2, 40.4, 36.1, 30.1, 29.7, 26.8, 25.6, 19.4; IR (Neat Film NaCl) 2998, 2953, 2866, 1716, 1667, 1616, 1456, 1427, 1367, 1308, 1270, 1225, 1190, 1170, 1103, 1058, 1021, 841, 871, 726 cm⁻¹; HRMS (EI+) m/z calc’d for C₁₃H₂₀O₂ [M⁺]: 208.1463; found 208.1460; [α]D²⁵.⁰ +25.55 (c 1.46, CHCl₃, 88.0% ee).

**Bis-enone SI-4.** To a 2-neck round-bottomed flask with magnetic stir bar and attached reflux condenser was added acyclopentenone 24 (100 mg, 0.608 mmol, 1.00 equiv). The flask was evacuated/backfilled with N₂ (3 cycles, 30 s evacuation per cycle). Dry degassed benzene (8.0 mL, sparged with N₂ for 1 h immediately before use) was added, followed by crotonaldehyde (251 µL, 3.06 mmol, 5.03 equiv). Grubbs–Hoveyda 2nd Generation catalyst (19.0 mg, 30.4 µmol, 5 mol %) was quickly added to the reaction, giving the solution an olive green color. The flask was immersed in a 50 °C oil bath. The solution quickly developed a dark brown color. After 2 h, the reaction was cooled to ambient temperature. Several drops of ethyl vinyl ether were added and the reaction mixture was stirred for 5 min. The mixture was concentrated under reduced pressure and the brown residue was purified by flash column chromatography (SiO₂, 2 x 25 cm, 10:1→4:1→2:1 Hexanes:EtOAc) to afford bis-enone SI-4 (105.4 mg, 0.55 mmol, 90% yield) as a brown oil; Rᵣ = 0.38 (2:1 Hexanes:EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 9.50 (d, J = 7.8 Hz, 1H), 6.76 (app dt, J = 15.4, 7.6 Hz, 1H), 6.42 (app t, J = 1.8 Hz, 1H), 6.13 (app ddt, J = 15.5, 7.8, 1.3 Hz, 1H), 2.68–2.50 (m, 2H), 2.45 (dd, J = 7.6, 1.3 Hz, 2H), 2.28 (s, 3H), 1.85 (ddd, J = 13.1, 8.4, 6.5 Hz, 1H), 1.72 (ddd, J = 13.1, 8.5, 6.0 Hz, 1H), 1.16 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 197.0, 193.5, 154.0, 149.7, 144.5, 135.6, 50.1, 43.9, 36.1, 31.9, 29.8, 26.8, 25.8; IR (Neat Film NaCl) 3359, 3317, 3041, 2957, 2928, 2867, 2820, 2743, 2708, 1691, 1668, 1636, 1618, 1456, 1431, 1378, 1369, 1341, 1308, 1269, 1203, 1162, 1149, 1109, 1093, 1036, 1013, 978, 936, 893, 868 cm⁻¹; HRMS (FAB+) m/z calc’d for C₁₃H₂₁O₂ [M+H⁺]: 193.1229; found 193.1224; [α]D²⁵.⁰ +46.07 (c 1.13, CHCl₃, 88.0% ee).
Mono-enone 24. An oven-dried 2-neck flask fitted with a magnetic stir bar, rubber septum, and a glass T-joint with 14/20 adapter was charged with and bis-enone SI-4 (42.8 mg, 0.22 mmol, 1.00 equiv) and evacuated/backfilled with N₂ in a glove box antechamber (3 cycles, 5 min evacuation per cycle) before being transferred into the glove box. CH₂Cl₂ (2.5 mL) and Rh(PPh₃)₃Cl (10.3 mg, 0.011 mmol, 5 mol %) were added to the flask, giving a red solution. The flask was sealed with a septum on one neck and T-joint (set to the closed position) on the other neck and carefully brought out of the glove box. A H₂ balloon was attached to the T-joint and the flask was gently evacuated/backfilled with H₂ (five cycles, 2 min evacuation per cycle). After 20 h of stirring, an additional portion of Rh(PPh₃)₃Cl (10.3 mg, 0.011 mmol, 5 mol %) in CH₂Cl₂ (0.5 mL) was added to the reaction using positive pressure cannulation. After 1.5 h of stirring, the reaction was diluted with Et₂O, filtered through a short silica gel plug (2 x 4 cm, Et₂O), and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, 2 x 25 cm, 10:1→4:1 Hexanes:EtOAc) to afford enone 24 (39.2 mg, 0.20 mmol, 90% yield) as a pale colorless oil; Rᵢ = 0.48 (2:1 Hexanes:EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 202.3, 197.5, 151.7, 143.8, 50.0, 44.5, 40.4, 36.1, 29.8, 26.8, 25.6, 17.8; IR (Neat Film NaCl) 3427, 3314, 3042, 2951, 2865, 2721, 1723, 1665, 1564, 1457, 1411, 1378, 1367, 1340, 1308, 1269, 1193, 1156, 1105, 970, 942, 867, 801 cm⁻¹; HRMS (EI⁺) m/z calc’d for C₁₂H₁₈O₂ [M⁺]: 194.1307; found 194.1321; [α]D²⁵ +32.50 (c 0.69, CHCl₃, 88.0% ee).

Divinylketone 28. A 25 mL round-bottomed flask with magnetic stir bar was charged with amide 27¹⁰¹ (97.0 mg, 0.46 mmol, 1.00 equiv), evacuated/backfilled with N₂ (3 cycles, 5 min evacuation per cycle), dissolved in THF (3.0 mL), and cooled to −15 °C using an ethylene glycol/CO₂ (s) bath. The yellow solution became cloudy. Vinylimagnesium bromide solution (1.38 mL, 1.0 M in THF, 1.38 mmol, 3.00 equiv) was added dropwise. The solution was maintained at −15 °C for 20 min before the flask was allowed to warm to ambient temperature. The reaction was quenched by addition into sat. aqueous NH₄Cl (2.0 mL) using positive pressure cannulation. The mixture was extracted with Et₂O (3 x 10 mL), dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (SiO₂, 2 x 25 cm, 0%→1%→2%→3% Et₂O in Hexanes) to afford divinylketone 28 (36.2 mg, 0.21 mmol, 45% yield) as a pale yellow liquid; Rᵢ = 0.68 (4:1 Hexanes:EtOAc); ¹H NMR (300 MHz, CDCl₃) δ 6.88 (dd, J = 17.1, 10.5 Hz, 1H), 6.53 (app t, J = 1.7 Hz, 1H), 6.28 (dd, J = 17.1, 1.9 Hz, 1H), 5.85–5.65 (m, 1H), 5.69 (dd, J = 10.5, 1.9 Hz, 1H), 5.11–4.99 (m, 2H), 2.76–2.50 (m, 2H), 2.29–2.09 (m, 2H), 1.87 (ddd, J = 12.9, 8.2, 6.8 Hz, 1H), 1.67 (ddd, J = 12.9, 8.3, 6.3 Hz, 1H), 1.13 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 188.9, 152.1, 143.7, 134.8, 132.6, 127.7, 117.8, 50.3, 45.3, 35.8, 30.1, 25.5; IR (Neat Film NaCl) 3584, 3314, 3078, 2955, 2927, 2866, 2162, 1606, 1453, 1440, 1408, 1374, 1348, 1308, 1255, 1204, 1169, 1059, 981, 956, 915, 783
cm⁻¹; HRMS (EI+) m/z calc’d for C₉H₁₁O [M–C₃H₅]⁺: 135.0846; found 135.0810; [α]D²⁵⁺₀.₈₄ (c 0.81, CHCl₃, 88.0% ee).

Procedures for Carbonyl Transposition to γ-Quaternary Cycloheptenones 3

Grignard and organolithium reagents were purchased from Sigma-Aldrich or prepared according to previously reported procedures.[⁵] Cycloheptenones 3ₐ, 3ᵣ₋ₐᵇ were prepared according to previously reported procedures.[⁵,¹⁰] Representative procedures for General Methods F–H are described below.

Cycloheptenone 3ₐ. A round-bottom flask charged with vinylogous ester 7ₐ (367.0 mg, 1.55 mmol, 1.00 equiv) and THF (5 mL, 0.3 M) was cooled in a 0 °C bath (water/ice) and LiAlH₄ (34.0 mg, 0.90 mmol, 0.58 equiv) was added. After 25 min of stirring, the reaction was quenched at 0 °C with the addition of aqueous HCl (10 mL, 10% w/w) and transferred to a separatory funnel where the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. To the resulting crude oil was added Ac₂O (3.8 mL) and NaOAc•3H₂O (1.28 g, 9.43 mmol, 6.08 equiv) and the mixture was lowered into a preheated oil bath (110 °C). After 15 h of heating, the reaction was allowed to cool to ambient temperature and quenched with K₂CO₃ (5.59 g, 40.5 mmol) and water (10 mL). After an addition 30 min of stirring, the solution was transferred to a separatory funnel where the aqueous phase was extracted with EtOAc (4 x 10 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO₂, 2 x 16 cm, 20:1 Hexanes:EtOAc) to afford cycloheptenone 3ₐ (203.9 mg, 1.24 mmol, 80% yield) as a pale yellow oil. (For characterization data, see p. 18–19).

Cycloheptenone 3ₐ and β-Hydroxyketone 10ₐ. A 100 mL round-bottom flask with magnetic stir bar was charged with vinylogous ester 7ₐ (186.8 mg, 0.79 mmol, 1.00 equiv) and anhydrous MeOH (14 mL). The solution was cooled to 0 °C (water/ice bath). CeCl₃•7H₂O (294.5 mg, 0.79 mmol, 1.56 equiv) was added in one portion and the mixture was stirred for 5 min. Portionwise addition of NaBH₄ (89.7 mg, 2.37 mmol, 3.00 equiv) at 0 °C led to the evolution of gas and a turbid solution that became clearer after several minutes. TLC analysis indicated that no starting material remained after 2 min. Consequently, the reaction was quenched by dropwise addition of
aqueous HCl (2 mL, 10% w/w) at 0 °C. After an additional 10 min of stirring, the reaction was diluted with CH₂Cl₂ (60 mL) and H₂O (2 mL). The layers were separated. The aqueous layer was extracted with CH₂Cl₂ (6 x 5 mL). The combined organic layers were washed with sat. aqueous NaHCO₃ (2 x 5 mL) and brine (2 x 5 mL), dried over Na₂SO₄, filtered, and evaporated to give a pale yellow oil. The crude mixture was purified using flash chromatography (SiO₂, 2 x 25 cm, 20:1→15:1→3:1 Hexanes:EtOAc) to afford volatile enone 3a (106.9 mg, 0.645 mmol, 82% yield) as a pale yellow oil and β-hydroxyketone 10a as a mixture of diastereomers (1.4 mg, 0.0077 mmol, 1% yield, 3.5:1 dr) as a colorless oil. (For characterization data of 3a and 10a, see p. 18–19).

Cycloheptenone 3r and Cycloheptenone Isomer 42. An oven dried 15 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box. The flask was loaded with anhydrous cerium chloride (130.4 mg, 0.53 mmol, 2.49 equiv), fitted with a septum, removed from the glove box, and connected to an argon-filled Schlenk manifold. A portion of THF (5.5 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of n-butyrmagnesium chloride (340 µL, 1.89 M in THF, 0.64 mmol, 3.03 equiv) was added and the mixture turned pale yellow. After 45 min of stirring, neat vinylogous ester 7a (50.2 mg, 0.21 mmol, 1.00 equiv) was added to the flask. The slurry maintained the yellow color with the addition. TLC analysis indicated that no starting material remained after 5 min. After an additional 10 min of stirring, the reaction was quenched with aqueous HCl (1 mL, 10% w/w) and lowered into a preheated oil bath (60 °C). After 17 h, the yellow suspension was removed from the bath, cooled to ambient temperature, and transferred to a separatory funnel where the aqueous phase was extracted four times with Et₂O. The combined organics (75 mL) were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO₂, 1 x 27 cm, 100% Hexanes→2%→10% EtOAc in Hexanes) to afford moderately contaminated cycloheptenone 3r and pure alkene isomer 42 (35.4 mg, 0.16 mmol, 76% yield) as an orange oil. Additional purification by flash chromatography (SiO₂, 1 x 27 cm, 100% Hexanes→2%→5% EtOAc in Hexanes) furnished cycloheptenone 3r (1.7 mg at 95% purity, 0.0076 mmol, 4% yield) as a yellow oil. (For characterization data of 3r, see p. 24).
Cycloheptenone Isomer 10a. R_f = 0.76 (30% EtOAc in Hexanes); The relative alkene stereochemistry was assigned based on NOE interactions of H^a proton; ^1H NMR (500 MHz, CDCl_3) δ 5.66 (dddd, J = 16.9, 10.6, 7.9, 6.6 Hz, 1H), 5.43 (t, J = 7.1 Hz, 1H), 5.03–4.97 (m, 2H), 3.20 (d, J = 14.6 Hz, 1H), 3.13 (d, J = 14.6 Hz, 1H), 2.47–2.38 (m, 1H), 2.36–2.26 (m, 2H), 2.15–1.95 (m, 3H), 1.82–1.69 (m, 2H), 1.66–1.58 (m, 1H), 1.58–1.50 (m, 1H), 1.40–1.32 (m, 2H), 1.07 (s, 3H), 0.88 (t, J = 7.4 Hz, 3H); ^13C NMR (125 MHz, CDCl_3) δ 210.0, 136.2, 135.1, 130.0, 117.2, 44.8, 43.3, 43.3, 41.8, 41.1, 30.2, 25.0, 22.9, 19.6, 13.9; IR (Neat Film NaCl) 3074, 3042, 2959, 2929, 2871, 1706, 1638, 1457, 1436, 1378, 1351, 1302, 1262, 1231, 1163, 1098, 1069, 996, 953, 912, 805, 776, 729 cm^{-1}; HRMS (EI+) calc’d for C_{15}H_{24}O_2 [M]+: 220.1827; found 220.1780; [α]_D^{25.0} –10.92 (c 0.76, CHCl_3, 88.0% ee).

Cycloheptenone 3r. A 50 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box. The flask was loaded with anhydrous cerium chloride (260.8 mg, 1.06 mmol, 2.50 equiv), fitted with a septum, removed from the glove box, and connected to an argon-filled Schlenk manifold. A portion of THF (8.5 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of n-butylmagnesium bromide (680 µL, 1.87 M in THF, 1.27 mmol, 3.00 equiv) was added and the mixture turned grey. After 30 min of stirring, vinylogous ester 7a (100.0 mg, 0.42 mmol, 1.00 equiv) was added neat from a Hamilton syringe and the needle was rinsed with a small portion of THF (2 mL; total THF added = 10.5 mL, 0.04 M). The color of the slurry initially transitioned to yellow with the vinylogous ester addition before turning back to grey. TLC analysis indicated that no starting material remained after 15 min. After an additional 10 min of stirring, the reaction was quenched with pH 6.5 Na_3PO_4 buffer (8 mL). A thick grey emulsion formed. The mixture was transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (125 mL) were dried over MgSO_4, filtered, and concentrated under reduced pressure. The crude oil was transferred to a 20 mL scintillation vial and concentrated under reduced pressure. A stir bar, CH_3CN (1.0 mL), and 6 mM aqueous HCl (1.0 mL) were added to the vial. The resulting cloudy solution was stirred vigorously for 5 min before being transferred to a separatory funnel where the aqueous phase was extracted four times with Et_2O. The combined organics (100 mL) were dried over MgSO_4, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO_2, 3 x 30 cm, 100% Hexanes→2%→5% EtOAc in Hexanes) to afford cycloheptenone 3r (82.4 mg, 0.35 mmol, 84% yield) as a pale yellow oil. (For characterization data of 3r, see p. 24).
General Method F: Organometallic Addition / Na₃PO₄ Buffer Quench / Dilute HCl Workup

Cycloheptenone 3w. A 100 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box. The flask was loaded with anhydrous cerium chloride (616.2 mg, 2.50 mmol, 2.50 equiv), fitted with a septum, removed from the glove box, and connected to an argon-filled Schlenk manifold. A portion of THF (13 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of pent-4-enylmagnesium bromide (8.6 mL, 0.35 M in THF, 3.01 mmol, 3.01 equiv) was added and the mixture turned grey. After 30 min of stirring, vinylogous ester 7a (236.3 mg, 1.00 mmol, 1.00 equiv) was cannula-transferred to the slurry from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M). TLC analysis indicated that no starting material remained after 5 min. After an additional 10 min of stirring, the reaction was quenched with pH 6.5 Na₃PO₄ buffer (20 mL). A thick grey emulsion formed. The mixture was transferred to a separatory funnel where the aqueous phase was extracted four times with Et₂O. The combined organic (150 mL) were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude oil was transferred to a 20 mL scintillation vial and concentrated under reduced pressure. A stir bar, CH₃CN (2.0 mL), and aqueous HCl (2.0 mL, 6 mM) were added to the vial. The resulting cloudy solution was stirred vigorously for 30 min before being transferred to a separatory funnel where the aqueous phase was extracted four times with Et₂O. The combined organics (75 mL) were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO₂, 3 x 30 cm, 100% Hexanes→1%→2%→5% EtOAc in Hexanes) to afford cycloheptenone 3w (214.2 mg, 0.92 mmol, 92% yield) as a clear colorless oil; R_f = 0.65 (30% EtOAc in Hexanes); ¹H NMR (500 MHz, CDCl₃) δ 5.88 (s, 1H), 5.79 (dddd, J = 16.9, 10.2, 6.7, 6.7 Hz, 1H), 5.67–5.57 (m, 1H), 5.07–4.96 (m, 4H), 2.60–2.53 (m, 2H), 2.35 (dddd, J = 14.1, 6.7, 2.5, 1.2 Hz, 1H), 2.20–2.04 (m, 5H), 1.83–1.73 (m, 3H), 1.66–1.53 (m, 3H), 1.14 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 205.3, 162.6, 138.2, 134.1, 128.8, 118.2, 115.3, 45.7, 45.2, 44.3, 38.7, 33.8, 33.5, 29.3, 25.7, 17.6; IR (Neat Film NaCl) 3076, 2975, 2937, 2870, 1652, 1611, 1456, 1415, 1380, 1343, 1257, 1218, 1179, 1110, 1071, 994, 913 cm⁻¹; HRMS (MM: ESI–APCI+) calc’d for C₁₆H₂₅O [M+H]⁺: 233.1900; found 233.1900; [α]D²⁵.₀ –34.96 (c 1.46, CHCl₃, 88.0% ee).
**General Method G: Organometallic Addition / Aq HCl Quench**

**Cycloheptenone 3ab.** A 100 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box. The flask was loaded with anhydrous cerium chloride (616.2 mg, 2.50 mmol, 2.50 equiv), fitted with a septum, removed from the glove box, and connected to an argon-filled Schlenk manifold. A portion of THF (13 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of thiophen-2-ylmagnesium chloride (6.8 mL, 0.44 M in THF, 2.99 mmol, 2.99 equiv) was added and the mixture turned dark grey. After 30 min of stirring, vinylogous ester 7a (236.4 mg, 1.00 mmol, 1.00 equiv) was cannula-transferred to the slurry from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M). TLC analysis indicated that no starting material remained after 25 min. After an additional 5 min of stirring, the reaction was quenched with aqueous HCl (5 mL, 10% w/w) and lowered into a preheated oil bath (60 °C). After 20 h, additional aqueous HCl (5 mL, 10% w/w) was added. After 26 h, the yellow solution was removed from the bath, cooled to ambient temperature, treated with sat. aqueous NaHCO₃ solution (25 mL), and transferred to a separatory funnel where the aqueous phase was extracted four times with Et₂O. The combined organics (150 mL) were rinsed once with sat. aqueous NaHCO₃, dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO₂, 3 x 30 cm, 100% Hexanes→2%→5% EtOAc in Hexanes) to afford cycloheptenone 3ab (206.1 mg, 0.84 mmol, 84% yield) as a yellow/orange oil; Rᶠ = 0.70 (30% EtOAc in Hexanes); ¹H NMR (500 MHz, CDCl₃) δ 7.27 (dd, J = 5.0, 1.5 Hz, 1H), 7.00–6.95 (m, 2H), 6.17 (s, 1H), 5.69 (dddd, J = 16.7, 10.2, 8.1, 6.4 Hz, 1H), 5.06 (dddd, J = 10.2, 2.0, 1.0, 1.0 Hz, 1H), 5.01 (dddd, J = 16.9, 3.4, 1.5 Hz, 1H), 2.74–2.59 (m, 2H), 2.50 (dddd, J = 14.1, 6.4, 1.4, 1.4 Hz, 1H), 2.12 (dddd, J = 14.1, 8.1, 1.1, 1.1 Hz, 1H), 1.96–1.84 (m, 3H), 1.77–1.68 (m, 1H), 1.29 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 204.2, 154.6, 143.8, 134.0, 133.7, 127.0, 126.7, 125.5, 118.5, 45.6, 45.1, 44.2, 38.8, 26.4, 17.7; IR (Neat Film NaCl) 3103, 3075, 2964, 2938, 2871, 1671, 1655, 1590, 1519, 1454, 1438, 1415, 1378, 1341, 1251, 1234, 1218, 1178, 1134, 1107, 1077, 1045, 996, 917, 849, 836, 761, 708 cm⁻¹; HRMS (MM: ESI–APCI+) calc’d for C₁₅H₁₉OS [M+H⁺]: 247.1151; found 247.1152; [α]D₂⁵.₀ = −3.65 (c 1.31, CHCl₃, 88.0% ee).
General Method H: Organometallic Addition / Aq H$_2$SO$_4$ Quench

Cycloheptenone 3y. A 100 mL round-bottom flask equipped with a magnetic stir bar was cycled into a glove box. The flask was loaded with anhydrous cerium chloride (616.2 mg, 2.50 mmol, 2.50 equiv), fitted with a septum, removed from the glove box, and connected to an argon-filled Schlenk manifold. A portion of THF (13 mL) was added, rinsing the cerium chloride to the bottom of the flask. As the resulting thick white slurry was stirred, a solution of prop-1-ynylmagnesium bromide (12 mL, 0.25 M in THF, 3.00 mmol, 3.00 equiv) was added and the mixture turned yellow. After 30 min of stirring, vinylogous ester 7a (236.4 mg, 1.00 mmol, 1.00 equiv) was cannula-transferred to the slurry from a flame-dried 10 mL conical flask using several THF rinses (3 x 4 mL; total THF added = 25 mL, 0.04 M). The slurry maintained the yellow color with the addition. TLC analysis indicated that no starting material remained after 5 min. After an additional 10 min of stirring, the reaction was quenched with 2 M H$_2$SO$_4$ (5 mL) and lowered into a preheated oil bath (60 °C). A white precipitate formed within several minutes. After 12 h, the yellow suspension was removed from the bath, cooled to ambient temperature, treated with sat. aqueous NaHCO$_3$ solution (50 mL), and transferred to a separatory funnel where the aqueous phase was extracted four times with Et$_2$O. The combined organics (175 mL) were rinsed once with sat. aqueous NaHCO$_3$, dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude oil was purified by flash chromatography (SiO$_2$, 3 x 30 cm, 100% Hexanes→2%→5% EtOAc in Hexanes) to afford cycloheptenone 3y (195.4 mg, 0.97 mmol, 97% yield) as a yellow oil; R$_f$ = 0.65 (30% EtoAc in Hexanes); $^1$H NMR (500 MHz, CDCl$_3$) δ 6.20 (s, 1H), 5.70 (dddd, $J$ = 16.8, 10.5, 8.2, 6.6 Hz, 1H), 5.10–5.01 (m, 2H), 2.65–2.49 (m, 3H), 2.16 (ddddd, $J$ = 13.8, 8.2, 1.0, 1.0 Hz, 1H), 2.01 (s, 3H), 1.83–1.75 (m, 3H), 1.66–1.59 (m, 1H), 1.24 (s, 3H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 203.5, 145.6, 135.0, 134.3, 118.3, 92.9, 80.7, 46.5, 45.4, 44.6, 37.3, 27.0, 17.6, 4.7; IR (Neat Film NaCl) 3076, 2969, 2937, 2219, 1652, 1580, 1455, 1415, 1377, 1346, 1255, 1225, 1184, 1110, 998, 916, 893, 866, 813, 784, 716 cm$^{-1}$; HRMS (MM: ESI–APCI+) calc’d for C$_{14}$H$_{19}$O [M+H]$^+$: 203.1430; found 203.1428; $[\alpha]_D^{25.0} = -49.25$ (c 1.21, CHCl$_3$, 88.0% ee).
Procedures for Synthesis of Cycloheptenone Derivatives 43–47

Cycloheptenone derivatives 43–47 were prepared according to previously reported procedures.\(^{[5]}\) A representative procedure for General Method I is described below.

**General Method I: Ring Closing Metathesis**

**Enone 43w.** A 100 mL round-bottom flask equipped with a magnetic stir bar, fitted with a water condenser, and connected to a Schlenk manifold (through the condenser) was flame-dried three times, backfilling with argon after each drying cycle. Once cool, the flask was loaded with neat cycloheptenone 3w (50.0 mg, 0.22 mmol, 1.00 equiv) and backfilled with argon twice. Benzene (1 h argon sparge before use, 43 mL, 0.005 M) was added to the flask, followed by Grubbs–Hoveyda 2nd Generation catalyst (6.7 mg, 0.011 mmol, 5 mol %). The solution color turned pale green with addition of catalyst. The flask was lowered into a preheated oil bath (50 °C). The reaction was removed from the oil bath after 30 min, cooled to room temperature (23 °C), and quenched with ethyl vinyl ether (1 mL). The reaction was filtered through a short silica gel plug rinsing with Et\(_2\)O and concentrated under reduced pressure. The crude oil was purified twice by flash chromatography (SiO\(_2\), both columns 2 x 28 cm, 100% Hexanes→2%→5% EtOAc in Hexanes) to afford cycloheptenone 43w (43.5 mg, 0.21 mmol, 99% yield) as a yellow oil; \(R_f = 0.56\) (30% EtOAc in Hexanes); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 5.77–5.70\) (m, 1H), \(5.65\) (tdt, \(J = 10.4, 6.4, 1.3\) Hz, 1H), \(2.68–2.55\) (m, 2H), \(2.54–2.44\) (m, 1H), \(2.30–2.24\) (m, 2H), \(2.24–2.15\) (m, 1H), \(2.13–2.04\) (m, 1H), \(1.94–1.69\) (m, 7H), \(1.52–1.41\) (m, 1H), \(1.22\) (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 204.2, 165.6, 132.2, 131.9, 128.5, 49.0, 44.2, 39.8, 39.5, 35.5, 31.1, 27.0, 26.5, 17.8\); IR (Neat Film NaCl) 3018, 2928, 2859, 1645, 1608, 1468, 1448, 1411, 1380, 1343, 1327, 1279, 1253, 1214, 1178, 1131, 1102, 1088, 1051, 1015, 987, 965, 937, 920, 899, 880, 845, 796, 777, 747 cm\(^{-1}\); HRMS (MM: ESI–APCI+) calc’d for C\(_{14}\)H\(_{21}\)O [M+H]\(^+\): 205.1587; found 205.1587; \([\alpha]_D^{25.0} = -141.99\) (c 1.01, CHCl\(_3\), 88% ee).
Methods for Determination of Enantiomeric Excess

**Table SI-3.** Methods for the Determination of Enantiomeric Excess (Chiral HPLC and SFC).

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References


Ring Contraction Strategy for the Practical, Scalable, Catalytic
Asymmetric Synthesis of Versatile γ-Quaternary Acylcyclopentenes

Allen Y. Hong, Nathan B. Bennett, Michael R. Krout, Thomas Jensen,
Andrew M. Harned, Brian M. Stoltz*

Supporting Information (1H NMR, 13C NMR, IR, HPLC)

Warren and Katharine Schlinger Laboratory for Chemistry and Chemical Engineering,
Division of Chemistry and Chemical Engineering, California Institute of Technology,
Pasadena, California 91125, USA

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Supporting Information for Hong, Bennett, Krout, Jensen, Harned, and Stoltz

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Supporting Information for Hong, Bennett, Krout, Jensen, Harned, and Stoltz

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