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Asymmetric Hetero-Ene Reactions of Trimethylsilyl Enol Ethers Catalyzed by Tridentate Schiff Base Chromium(III) Complexes

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General methods.

Unless otherwise stated, compounds were purchased from Aldrich, Alfa Aesar or Strem. Solvents were purified and dried using standard methods: THF and Et_2O were distilled from sodium/benzophenone ketyl;. CH_2Cl_2 and DIPEA were distilled from CaH_2. 2-trimethylsilyloxypropene, 1-trimethylsilyloxycyclopentene, and 1-trimethylsilyloxycyclohexene were prepared by a slight modification of the method of Cazeau *et al.*,[1] distilled from CaH_2, and stored over 3Å molecular sieves under nitrogen. 1-Trimethylsilyloxycyclobutene was prepared by the method of Vidal and Huet[2] and purified and stored as above. 2-Bromobenzaldehyde was distilled from CaH_2 and stored under nitrogen; other liquid aldehydes were used as purchased; solid aldehydes were recrystallized from ethanol and dried under vacuum. Powdered 4Å molecular sieves were activated in a vacuum oven; 90% BaO was used as purchased from Acros. Flash chromatography was performed using silica gel 60 (230-400 mesh) from EM Science. All ^{1}H and ^{13}C NMR spectra were recorded using Bruker AM 500 or AM 400 FT spectrometers at ambient temperature. IR spectra were recorded on a Matteson FTIR 3000. Optical rotations were measured using a 2 mL cell with a 1 dm path length on a Jasco DIP 370 digital polarimeter. Chiral GC analysis was performed on a Hewlett-Packard 5890 gas chromatograph. Chiral HPLC analysis was performed on a Shimadzu VP-series instrument.

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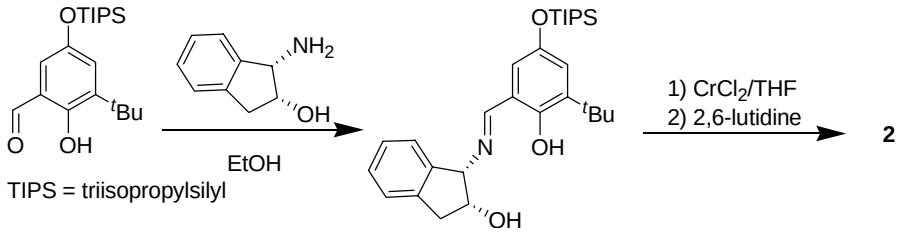
[1] In the final work-up step, the pentane-trimethylsilyl enol ether solution was washed three times with cold saturated $CuSO_4$ solution: Cazeau, P.; Duboudin, F.; Moulines, F.; Babot, O.; Dunogues, J. *Tetrahedron* **1987**, *43*, 2075-2088.

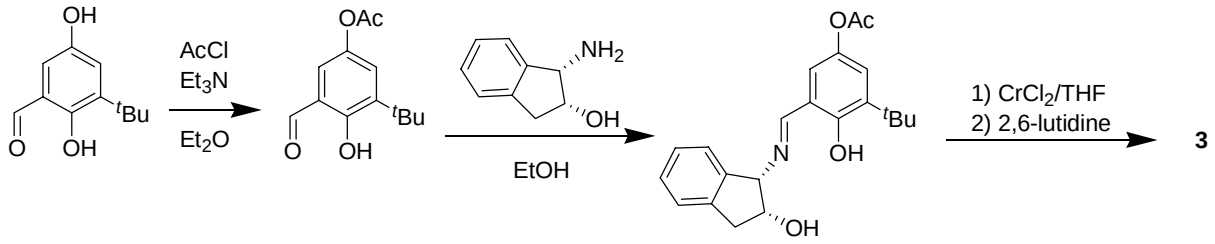
[2] Vidal, J.; Huet, F. *J. Org. Chem.* **1988**, *53*, 611-616.



Chromium(III) complex (1*S*,2*R*) 2. (1*S*, 2*R*) Aminoindanol (667 mg, 4.47 mmol) was added to a solution of 3-*tert*-butyl-2-hydroxy-5-triisopropylsilyloxybenzaldehyde[3] contaminated with triisopropylsilanol (1.31 g, theoretically, 4.06 mmol) in EtOH (60 mL). After one hour of stirring, ethanol was removed on the rotary evaporator. The remaining solid was chromatographed twice on silica gel to remove all traces of silanol (10% EtOAc/hexanes; R_f=0.35), eluting 1.27 g of the ligand, (1*S*,2*R*)-1-[(5-triispropylsilyloxy-2-hydroxy-3-*tert*-butyl-benzylidene)-amino]-indan-2-ol, as a bright yellow band. $[\alpha]^{26}_D$ –16.5^0 (c 1.01, CH_2Cl_2). IR (KBr disk) 3300, 2955, 2866, 1632, 1597, 1439, 1327, 1242, 1005, 853 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.11 (d, *J*=7.3 Hz, 18H), 1.21-1.29 (m, 3H), 1.39 (s, 9H), 2.18 (d, *J*=4.4 Hz, 1H), 3.15 (dd, *J*=5.4, 16.1 Hz, 1H), 3.24 (dd, *J*=5.9, 16.1 Hz, 1H), 4.70 (m, 1H), 4.81 (d, *J*=5.4 Hz, 1 H), 6.70 (d, *J*=2.9 Hz, 1H), 6.97 (d, *J*=2.9 Hz), 7.21-7.32 (m, 6H), 8.53 (s, 1H), 12.81 (s, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 12.9, 18.2, 29.5, 35.1, 39.9, 75.5, 76.1, 118.5, 119.4, 123.3, 125.2, 125.7, 127.3, 128.8, 138.8, 141.0, 141.1, 147.6, 154.8, 167.9.

Chromium(II) chloride (130 mg, 1.06 mmol) was added in one portion to a solution of the Schiff base ligand (400 mg, 0.882 mmol) in dry THF (13 mL) in the dry box. The mixture was allowed to stir 45 minutes, and 2,6-lutidine (335 µL, 2.88 mmol) was added. The mixture was stirred 30 additional minutes. The solution was then diluted with TBME (50 mL), washed with 1N HCl (2 x 30 mL) and sat. NaCl (1 x 30 mL). The organic solution was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The brown solid was azeotroped with hexanes and dried by high vacuum (494, 100%).

[3] Chang, S.; Heid, R.M.; Jacobsen, E.N. *Tetrahedron Lett.* **1994**, *35*, 669-672.



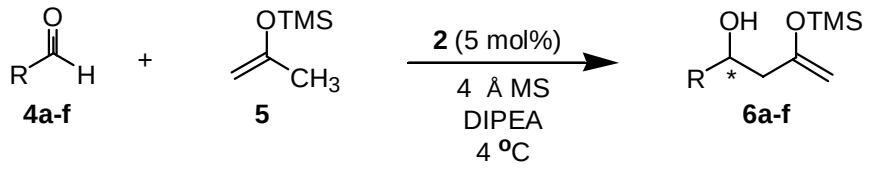
Chromium(III) complex (1*S*,2*R*) 3. 3-*tert*-Butyl-2,5-dihydroxybenzaldehyde[4] (971 mg, 5.00 mmol) was dissolved in Et_2O (100 mL) under N_2. Triethylamine (1.06 g, 1.46 mL, 10.5 mmol) was added followed by fast addition of acetyl chloride (412 mg, 373 µL, 5.25 mmol) to afford the best regioselectivity for acylation). The solution was stirred for 30 minutes (until the yellow color of the starting aldehyde disappeared). The ether layer was then washed with 1N HCl (1x 75 mL), saturated $NaHCO_3$ solution (2 x 75 mL), and brine (1 x 75 mL) and dried over $MgSO_4$. The organic extracts were filtered, and solvent was removed on the rotary evaporator. The residue was eluted through a small volume of silica gel with CH_2Cl_2 to provide acetic acid 3-*tert*-butyl 5-formyl-4-hydroxy-phenyl ester (1.09 g, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.31 (s, 3H), 7.17 (d, *J*=2.6 Hz, 1 H), 7.21 (d, *J*=2.9 Hz, 1H), 9.82 (s, 1H), 11.71 (s, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 21.4, 29.4, 35.3, 120.2 123.4, 128.3, 140.4, 142.6, 159.2, 170.0, 196.6.

(1*S*,2*R*)-Aminoindanol (417 mg, 2.79 mmol) was added to a solution of the salicylaldehyde (600 mg, 2.54 mmol) in EtOH (40 mL). After 30 minutes, the progress of the reaction was checked by TLC (30% EtOAc/hexanes). The higher R_f spot (0.75) corresponding to the starting salicylaldehyde remained, so additional aminoindanol (25 mg) was added to drive Schiff base formation to completion. After 30 more minutes of stirring, ethanol was removed on the rotary evaporator. The remaining solid was chromatographed on a small volume silica gel (30% EtOAc/hexanes; R_f=0.35), eluting 904 mg (97% yield) of the ligand, (1*S*,2*R*)-1-[(5-Acetoxy-2-hydroxy-3-*tert*-butyl-benzylidene)-amino]-indan-2-ol, as a bright yellow band. $[\alpha]^{26}_D$ –39.6^0 (c 1.00, CH_2Cl_2). IR (KBr disk) 3420, 2955, 1757, 1630, 1437, 1213 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.40 (s, 9H), 2.17 (d, *J*=4.4 Hz, 1H), 2.30 (s, 1H), 3.12 (dd, *J*=5.1, 16.1 Hz, 1H), 3.25 (dd, *J*=5.9, 16.1 Hz, 1H), 4.70 (m, 1H), 4.81 (d, *J*=5.5 Hz, 1 H), 6.97 (d, *J*=2.9 Hz, 1H), 7.05 (d, *J*=2.6 Hz), 7.18 (d, *J*=7.3 Hz, 1H), 7.24 (t, *J*=6.6 Hz, 1H), 7.29-7.33 (m, 2H), 8.53 (s, 1H), 13.38 (s, 1H). ^{13}C NMR

[4] Vachal, P.; Su, J.T.; Jacobsen, E.N. *Adv. Synth. & Catal* **2001**, *343*, 197-200.

(125.8 MHz, $CDCl_3$) δ 21.3, 29.4, 35.2, 39.9, 75.5, 75.7, 118.4, 122.1, 123.9, 125.2, 125.8, 127.4, 128.9, 139.4, 140.8, 141.0, 142.0, 158.4, 167.2, 170.

Chromium(II) chloride (118 mg, 0.960 mmol) was added in one portion to a solution of the Schiff base ligand (294 mg, 0.800 mmol) in dry THF (13 mL) in the dry box. The mixture was allowed to stir 45 minutes, and 2,6-lutidine (335 µL, 2.88 mmol) was added. The mixture was stirred 30 additional minutes. The solution was then diluted with TBME (50 mL), washed with 1N HCl (2 x 30 mL) and sat. NaCl (1 x 30 mL). The organic solution was dried (Na_2SO_4), filtered and concentrated *in vacuo*. The brown solid was azeotroped three times with toluene and dried by high vacuum (355 mg, 98%).



General procedure for ene reaction between aliphatic aldehydes and 2-trimethylsilyloxypropene. Complex **2** (28.4 mg, 0.05 mmol) and powdered 4Å molecular sieves (400 mg) were combined in a 2 dram vial equipped with stirbar. 2-Trimethylsilyloxypropene (480 µL, ~95% purity) and diisopropylethylamine (25 µL) were added sequentially, and the resulting suspension was stirred for one hour. The vial was cooled with stirring to 4 ^{0}C. After cooling, the aldehyde (1.0 mmol) was added in one portion. The suspension was stirred for a specified length of time, at which time the reaction mixture was filtered through a small amount of Celite with CH_2Cl_2 to remove the 4Å MS. CH_2Cl_2 was removed and the product dried under house or high vacuum. The masses of yields reported are in the presence of **2**. Yields were calculated by subtracting the mass of catalyst introduced into the reaction (28.4 mg) from the mass of the crude product, and dividing the difference by the theoretical yield. Characterization was performed after hydrolysis to the β-hydroxyketone.

(*R*)-2-Trimethylsilyloxy-hept-1-en-4-ol (6a). (1*S*,2*R*)-**2** was employed in this reaction. For this substrate, butyraldehyde was added over 22 h at a rate of 4 µL/hour. Total reaction time from beginning of aldehyde addition was 65 h. Isolated yield: 199 mg of **6a** in 89% ee by Chiral GC (γ-TA, 90 ^{o}C isothermal, t_R(minor) = 7.4 min; t_R(major) = 9.1 min). $[\alpha]^{26}_D$ –54.6^0 (c 0.58,

CH_2Cl_2). IR (thin film) 3431, 2957, 1709 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.88-0.95 (m, 3H), 1.30-1.53 (m, 4H), 2.18 (s, 3H), 2.50-2.63 (m, 2H), 4.05 (s, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 14.2, 18.9, 31.0, 38.7, 50.1, 67.6, 210.4.

(*S*)-2-Methyl-5-trimethylsilyloxy-hex-5-en-3-ol (6b). (1*S,2R*)-**2** was employed in this reaction. The mixture was stirred for 72 h. Isolated yield: 163 mg of **6b** in 90% ee by Chiral GC (γ-TA, 90 °C isothermal, t_R(minor) = 7.1 min; t_R(major) = 8.2 min). $[\alpha]^{24}_D$ -56.4^0 (c 1.00, CH_2Cl_2). IR (thin film) 3597, 2972, 1711 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.90 (d, *J*=6.8 Hz, 3H), 0.92 (d, *J*=6.8 Hz, 3H), 1.67 (septet, *J*=6.8 Hz, 1H), 2.19 (s, 3H), 2.51 (dd, *J*=6.8, 17.4 Hz, 1H), 2.60 (dd, *J*=2.9, 17.1 Hz, 1H), 2.92 (s, 1H) 3.79-3.82 (m, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 18.0, 18.6, 31.1, 33.2, 47.2, 72.4, 210.6.

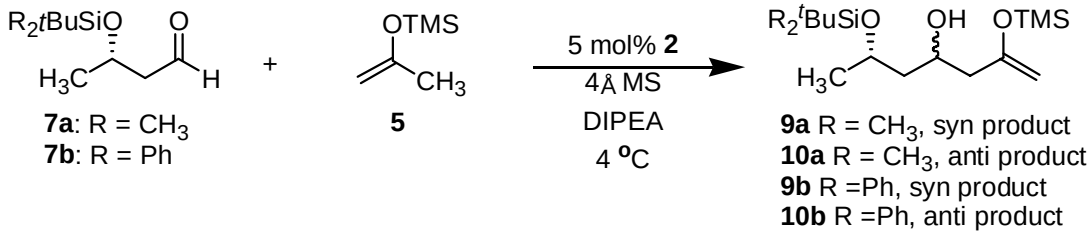
(*S*)-6-Methyl-2-trimethylsilyloxy-hept-1-en-4-ol (6c). (*R,S*)-**2** was employed in this reaction. The mixture was stirred for 72 h. Isolated yield: 163 mg of **6c** in 87% ee by Chiral GC (γ-TA, 60 °C isothermal, t_R(minor) = 55.6 min; t_R(major) = 58.0 min). $[\alpha]^{25}_D$ 27.0^0 (c 1.02, CH_2Cl_2). IR (thin film) 3416, 2955, 1709 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, *J*=6.8 Hz, 6H), 1.09-1.15 (m, 1H), 1.43-1.49 (m, 1H), 1.78 (septet, *J*=6.8 Hz, 1H), 2.17 (s, 3H), 2.51 (dd, *J*=8.8, 17.5 Hz, 1H), 2.60 (dd, *J*=2.9, 8.1 Hz, 1H), 2.95 (s, 1H) 4.09-4.14 (m, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 22.2, 23.5, 24.6, 31.0, 45.7, 50.7, 65.8, 210.4.

(*S*)-1-cyclopropyl-3-trimethylsilyloxy-but-3-en-1-ol (6d). (*S,R*)-**2** was employed in this reaction. The mixture was stirred for 72 h. Isolated yield: 94 mg of **6d** in 93% ee by Chiral GC (γ-TA, 95 °C isothermal, t_R(minor) = 12.3 min; t_R(major) = 15.1 min). $[\alpha]^{25}_D$ -27.9^0 (c 0.24, CH_2Cl_2). IR (thin film) 3430, 3005, 1709 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 0.17 (quintet, *J*=4.9 Hz, 1H), 0..38 (quintet, *J*=4.9 Hz, 1H), 0.46-0.52 (m, 1H), 0.52-0.59 (m, 1H), 0.86-0.96(m, 1H), 2.20 (s, 3H), 2.69-2.81 (m, 2H), 2.84 (s, 1H) 3.31 (td, *J*=3.4, 8.3 Hz, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 2.4, 3.5, 17.0, 31.0, 50.1, 72.6, 209.8.

(*S*)-1-(*tert*-Butyl-diphenyl-silyloxy)-5-trimethylsilyloxy-hex-5-en-3-ol (6e). (*R,S*)-**2** was employed in this reaction. The mixture was stirred for 20 h. Isolated yield: 430 mg of **6e** in 93% ee by Chiral HPLC ((*R,R*)-Whelk-01, 2.0% EtOH/hexanes, 1.0 mL/min, t_R(minor) = 14.9 min; t_R(major) = 16.4 min). $[\alpha]^{26}_D$ 7.7^0 (c 1.00, CH_2Cl_2). IR (thin film) 3493, 2938, 2864, 1711 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$) δ 1.06 (s, 9H), 1.63-1.70 (m, 1H), 1.72-1.79

(m, 1H), 2.18 (s, 3H), 2.58 (dd, *J*=4.40, 17.1 Hz, 1H), 2.64 (dd, *J*=8.3, 17.5 Hz, 1H), 3.49 (d, *J*=2.9 Hz, 1H), 3.80-3.89 (m, 2H), 4.34 (octet, *J*=3.9 Hz, 1H), 7.38-7.46 (m, 6H), 7.65-7.69 (m, 4H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 19.3, 27.1, 31.1, 38.5, 50.6, 62.3, 67.0, 128.0, 130.0, 133.4, 133.5, 135.78, 135.80, 209.2.

(R)-7-(*tert*-Butyl-diphenyl-silyloxy)-2-trimethylsilyloxy-hept-1-en-4-ol (6f). (*S,R*)-**2** was employed in this reaction. The mixture was stirred for 40 h. Isolated yield: 435 mg of **6f** in 90% ee (as the TMS-enol ether) by Chiral HPLC ((*S,S*)-Whelk-01, 2.0% EtOH/hexanes, 1.0 mL/min, t_R(minor) = 14.0 min; t_R(major) = 15.3 min). $[\alpha]^{24}_D$ –14.8^0 (c 1.00, CH_2Cl_2). IR (thin film) 3455, 2951, 2861, 1709 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9H), 1.51-1.75 (m, 6H), 2.18 (s, 3H), 2.53-2.63 (m, 2H), 3.21 (d, *J*=2.9 Hz, 1H), 3.65-3.73 (m, 2H) 4.02-4.09 (m, 1H), 7.36-7.45 (m, 6H), 7.66 (d, *J*=6.3 Hz, 4H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 19.4, 27.1, 28.8, 31.0, 33.4, 50.3, 64.0, 67.6, 127.9, 129.9, 133.98, 134.00, 135.80, 135.81, 210.0.



7a: R = CH_3
7b: R = Ph

5

9a R = CH_3, syn product
10a R = CH_3, anti product
9b R =Ph, syn product
10b R =Ph, anti product

General procedure for doubly diastereoselective 2-trimethylsilyloxypropene. Cr complex **2** (7.1 mg, 0.0125 mmol) and powdered 4Å molecular sieves (100 mg) were combined in a 1/2 dram vial equipped with stirbar. 2-Trimethylsilyloxypropene (120 µL, ~95% purity) and diisopropylethylamine (6 µL) were added sequentially, and the resulting suspension was stirred for one hour. The vial was cooled with stirring to 4 ^{0}C. After cooling, aldehyde **7a**[5] (50.6 mg, 0.25 mmol) or **7b**[6] (81.6 mg, 0.25 mmol) was added in one portion. The suspension was stirred for 40 h, at which time the reaction mixture was filtered through a small amount of Celite® with CH_2Cl_2 to remove the 4Å MS. Solvent was removed and the product dried under house or high vacuum. Yields were determined by subtracting the mass of catalyst introduced (7.1 mg) from the mass of crude product, and the difference was divided by the theoretical yield. Conversion was

[5] Ishiyama, H.; Ishibashi, M.; Ogawa, A.; Yoshida, S.; Kobayashi, J. *J. Org. Chem.* **1997**, *62*, 3831-3836.
[6] Kobayashi, Y.; Kishihara, K.; Watatani, K. *Tetrahedron Lett.* **1996**, *37*, 4385-4388.

determined by ^{1}H NMR. The diastereomeric ratio was determined by GC on an HP-5 column (100 ^{o}C for 4.00 min; ramp at 15 ^{o}C/min until 200 ^{o}C; ramp at 25 ^{o}C/min until 280 ^{o}C; hold at 280 ^{o}C for 1.13 min). Characterization was performed directly on the crude trimethylsilyl enol ether products contaminated with residual catalyst.

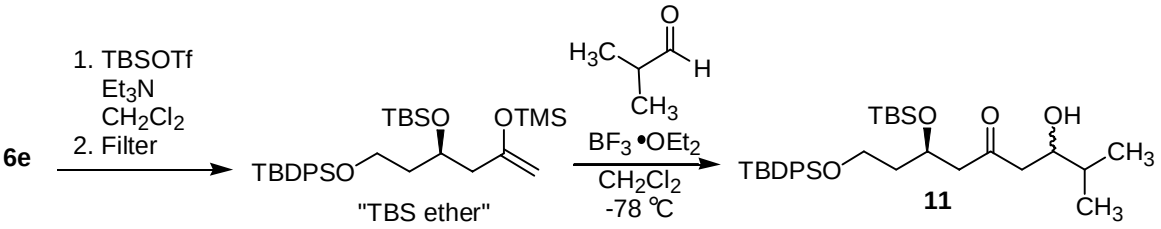
(4S,6S)-6-(*tert*-Butyl-dimethyl-silyloxy)-2-trimethylsilyloxy-hept-1-en-4-ol (9a). (1*R,*2*S*)-**2** was employed in this reaction. The mixture was stirred for 40 h. Isolated yield: 82 mg (88%, >90% purity) of **9a** in a >46:1 syn:anti ratio by GC (HP-5; t_R(minor) = 9.2 min; t_R(major) = 9.4 min). IR (thin film) 3524, 2959, 2863, 1628 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.10 (s, 3H), 0.11 (s, 3H) 0.22 (s, 9H), 0.90 (s, 9H), 1.18 (d, *J*=5.9 Hz, 3H), 1.60 (m, 2H), 2.14 (dd, *J*=5.4, 13.8 Hz, 1H), 2.20 (dd, *J*=7.3, 13.7 Hz, 1H), 3.30 (s, 1H), 3.94 (m, 1H), 4.05 (m, 1H), 4.13 (d, *J*=4.4 Hz, 2H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ -4.5, -3.8, 0.3, 18.2, 24.5, 26.1, 44.8, 45.7, 68.7, 69.2, 92.6, 156.8.

(4R,6S)-6-(*tert*-Butyl-dimethyl-silyloxy)-2-trimethylsilyloxy-hept-1-en-4-ol (10a). (1*S,*2*R*)-**2** was employed in this reaction. The mixture was stirred for 40 h. Isolated yield: 85 mg (91%, >90% purity) of **10a** in a 1:14.4 syn:anti ratio by GC (HP-5; t_R(major) = 9.2 min; t_R(minor) = 9.4 min). IR (thin film) 3461, 2957, 2861, 1628 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.08 (s, 3H), 0.09 (s, 3H) 0.22 (s, 9H), 0.89 (s, 9H), 1.17 (d, *J*=5.4 Hz, 3H), 1.54-1.56 (m, 2H), 2.13 (dd, *J*=4.9, 13.7 Hz, 1H), 2.20 (dd, *J*=7.8, 13.7 Hz, 1H), 3.05 (s, 1H), 4.12 (d, *J*=4.9 Hz, 2H), 4.13-4.19 (m, 2H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ -4.7, -4.3, 0.3, 18.2, 23.8, 26.1, 45.0, 45.1, 66.2, 66.9, 92.3, 156.8.

(4S,6S)-6-(*tert*-Butyl-diphenyl-silyloxy)-2-trimethylsilyloxy-hept-1-en-4-ol (9b). (1*R,*2*S*)-**2** was employed in this reaction. The mixture was stirred for 40 h. The yield was not determined and characterization not completed because the reaction only proceeded to 51% conversion. **9b** in a 3.8:1 syn:anti ratio by GC (HP-5; t_R(minor) = 14.46 min; t_R(major) = 14.52 min).

(4R,6S)-6-(*tert*-Butyl-diphenyl-silyloxy)-2-trimethylsilyloxy-hept-1-en-4-ol (10b). (1*S,*2*R*)-**2** was employed in this reaction. The mixture was stirred for 40 h. Isolated yield: 85 mg (90%, >85% purity) of **10b** in a 1:14.4 syn:anti ratio by GC (HP-5; t_R(major) = 9.2 min; t_R(minor) = 9.4 min). IR (thin film) 3513, 2959, 2863, 1628 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.21 (s, 9H), 1.1 (s, 9H), 1.18 (d, *J*=6.3 Hz, 3H), 1.57-1.64 (m, 2H), 2.10 (dd, *J*=5.4, 13.7 Hz, 1H), 2.18 (dd, *J*=7.3, 13.7 Hz, 1H), 2.98

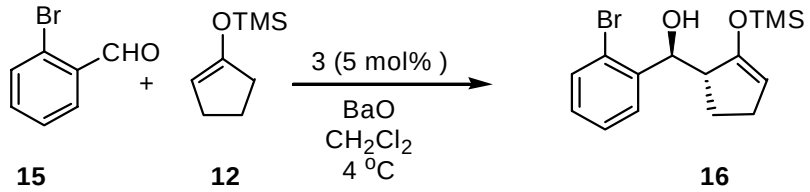
(s, 1H), 4.09 (d, *J*=8.8 Hz, 2H), 4.15-4.22 (m, 2H), 7.36-7.46 (m, 6H), 7.66-7.75 (m, 4H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 0.3, 19.5, 23.3, 27.2, 45.03, 45.08, 66.2, 68.4, 92.2, 127.7, 127.8, 129.8, 130.0, 133.8, 134.6, 136.14, 136.16, 156.8.



(3*R*,7*R*)- and (3*R*,7*S*)-3-(*tert*-Butyl-dimethyl-silyloxy)-1-(*tert*-butyl-diphenyl-silyloxy)-7-hydroxy-8-methyl-nonan-5-one (11). (1*S*,2*R*)-**2** was used to prepare (*R*)-**6e** on a 0.5 mmol scale. The crude reaction mixture was diluted with anhydrous CH_2Cl_2 (1.5 mL). Triethylamine (300 µL, 2.15 mmol) and *tert*-butyldimethylsilyl triflate (220 µL, 1.04 mmol) were added sequentially. Over 15 minutes of stirring, the solution turned red. After those 15 minutes, the reaction mixture was diluted with diethyl ether and filtered through a small pad of silica gel over a small pad of Celite. The solvent was evaporated and the remaining brown residue containing Cr catalyst and TBS ether were dried under high vacuum.

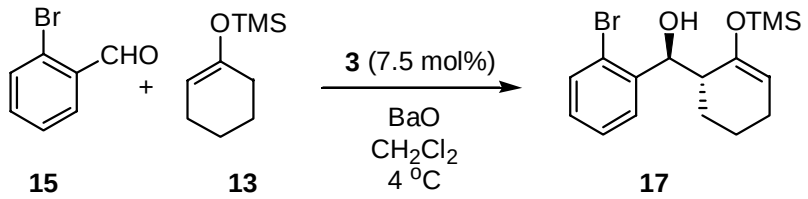
In a flame-dried flask equipped with a stirbar, isobutyraldehyde (91 µL, 1.0 mmol) was dissolved in CH_2Cl_2 under nitrogen and the flask cooled to -78 °C. $BF_3{\cdot}OEt_2$ (98 µL, 0.75 mmol) was added. The mixture of TBS ether and catalyst was dissolved up in anhydrous CH_2Cl_2 (3 mL) under nitrogen, and the flask was cooled to -78 °C. The solution was added by syringe to the flask containing isobutyraldehyde and $BF_3{\cdot}OEt_2$. The flask that had contained the solution of TBS ether was rinsed with anhydrous CH_2Cl_2 (2 x 2.0 mL) and the washes added as well. The reaction mixture was stirred for 30 minutes at -78 °C, at which point saturated NH_4Cl solution (5 mL) was added to quench the reaction. The solution was allowed to warm to room temperature and diluted with Et_2O (25 mL). The layers were separated and the organic layer washed with 1N HCl (2 x 10 mL) and brine (1 x 10 mL). The aqueous washes were extracted with Et_2O (1 x 10 mL), and the combined organic extracts dried over Na_2SO_4. The solution was filtered and the solvent removed by rotary evaporation. Chromatography on silica gel (10% EtOAc/hexanes) provided 230 mg (83% over 3 steps) of **11** as a clear oil. This yield represents a 59:41 ratio of syn:anti diastereomers as determined by ^{1}H NMR [δ(O*H*-syn) = 3.04; δ(O*H*-anti) = 3.07]. IR (thin film) 3420, 2953, 2863, 1709 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.03 (s, 3H),

0.05 (s, 3H), 0.85 (s, 9H), 0.91 (d, *J*=6.8 Hz, 3H), 0.94 (d, *J*=6.8 Hz, 3H), 1.07 (s, 3H), 1.62-1.82 (m, 2H), 2.32-2.69 (m, 3H), 3.04 (d, O*H*-syn, *J*=3.4 Hz), 3.07 (d, O*H*-anti, *J*=2.9 Hz), 3.66-3.77 (m, 2H), 3.80 (t, 1H, *J*=5.4 Hz), 4.38-4.45 (m, 1H), 7.35-7.47 (m, 6H), 7.65-7.75 (m, 4H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ -4.49, -4.44, -4.40, 18.0, 18.1, 18.2, 18.5, 18.6, 19.4, 26.1, 26.8, 27.1, 33.1, 33.2, 40.3, 40.4, 47.9, 48.2, 51.18, 51.23, 60.5, 60.6, 66.6, 66.8, 72.2, 72.4, 127.92, 127.95, 127.97, 129.88, 129.91, 130.0, 133.89, 133.92, 135.1, 135.5, 135.80, 135.83, 211.8.



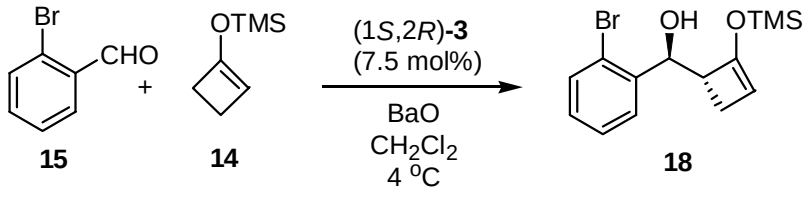
15 **12** **16**

2*R*,1'*S*)-(2-Bromo-phenyl)-[2-trimethylsilyloxy-cyclopent-2-enyl)-methanol (16). Cr complex **3** (22.6 mg, 0.05 mmol) and BaO (600 mg) were combined in a 2 dram vial equipped with stirbar. CH_2Cl_2 (600 μL) and 1-trimethylsilyloxycyclopentene (360 μL, ~2.0 mmol) were added sequentially, and the vial was cooled with stirring to 0 ^{0}C in an ice-water bath. After cooling, aldehyde **15** (116 μL, 1.0 mmol) was added in one portion. The suspension was stirred for 8 h, at which time the reaction mixture was filtered through a small amount of silica gel with CH_2Cl_2 to remove catalyst and BaO. CH_2Cl_2 was removed and the product dried under vacuum. Compound **16** was isolated as a clear oil (335 mg, 98%). Hydrolysis provided the hydroxyketone in 96% ee by chiral HPLC analysis (Chiralpak AD, 10% EtOH/hexanes, 1.0 mL/min) t_R(minor) = 12.64 min, t_R(major) = 15.15 min) and >100:1 dr by ^{1}H NMR; $[\alpha]^{28}_D$ -75.0^0 (c 1.03, CH_2Cl_2). IR (thin film) 3534, 3065, 2957, 2859, 1643, 1254, 853 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.26 (s, 9H), 1.51-1.58 (m, 1H), 1.62-1.69 (m, 1H), 2.13-2.19 (m, 1H), 2.23-2.29 (m, 1H), 2.89-2.95 (m, 1H), 3.89 (d, *J*=1.5 Hz, 1H), 4.77 (q, *J*=1.5 Hz, 1H), 5.14 (dd, *J*=1.5, 8.8 Hz, 1H), 7.12 (td, *J*=1.4, 7.8 Hz, 1H), 7.24 (t, *J*=7.8 Hz, 1H), 7.40 (td, *J*=1.5, 7.8 Hz, 2H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 6.6, 25.0, 27.0, 51.7, 77.0, 103.8, 123.7, 127.9, 129.1, 132.7, 142.0, 155.8.



15 **13** **17**

(2*R*,1'*S*)-(2-Bromo-phenyl)-[2-trimethylsilyloxy-cyclohex-2-enyl)-methanol (17). Chromium complex (1*R*,2*S*)-**3** (33.9 mg, 0.075 mmol) and BaO (900 mg) were combined in a 2 dram vial equipped with stirbar. CH_2Cl_2 (400 µL) and 1-trimethylsilyloxycyclohexene (800 µL, ~ 4.0 mmol) were added sequentially, and the vial was cooled with stirring to 0 ^{0}C in an ice-water bath. After cooling, the aldehyde **15** (116 µL, 1.0 mmol) was added in one portion. The suspension was stirred for 40 h, at which time the reaction mixture was filtered through a small pad of silica gel with CH_2Cl_2 to remove catalyst and BaO. CH_2Cl_2 was removed and the product dried under vacuum. Isolated yield: 276 mg (77% yield; 85% yield based on recovered starting material) of **17** as a clear oil (average of two runs). Hydrolysis provided the hydroxyketone in 95% ee by chiral HPLC analysis (Chiralpak AD, 10% EtOH/hexanes, 1.0 mL/min) t_R(minor) = 12.13 min, t_R(major) = 13.15 min) and >100:1 dr by ^{1}H NMR; $[\alpha]^{27}_D$ –63.7^0 (c 1.035, CH_2Cl_2). IR (thin film) 3508, 3052, 2937, 1667, 1439, 1181, 861 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.25 (s, 9H), 1.27-1.42 (m, 3H), 1.56-1.71 (m, 1H), 1.96-2.12 (m, 2H), 2.41-2.49 (m, 1H), 4.48 (d, *J*=1.5 Hz, 1H), 5.03 (m, 1H), 5.15 (d, *J*=8.4 Hz, 1H), 7.10 (td, *J*=1.5, 7.3 Hz, 1H), 7.33 (td, *J*=0.7, 7.7 Hz, 1H), 7.52 (m, 2H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ 0.5, 21.1, 24.3, 26.4, 46.1, 76.8, 106.6, 123.8, 128.0, 129.0, 129.1, 132.6, 142.5, 152.0.



15 **14** **18**

(2*R*,1'*S*)-(2-Bromo-phenyl)-[2-trimethylsilyloxy-cyclobut-2-enyl)-methanol (18). Cr complex **3** (33.9 mg, 0.075 mmol) and BaO (900 mg) were combined in a 2 dram vial equipped with stirbar. CH_2Cl_2 (600 µL) and 1-trimethylsilyloxycyclobutene (260 µL, ~ 2.0 mmol) were added sequentially, and the vial was cooled with stirring to 0 ^{0}C in an ice-water bath. After cooling, **15** (116 µL, 1.0 mmol) was added in one portion. The suspension was stirred for 10 h, at which time the reaction mixture was filtered through a

small amount of silica gel with CH_2Cl_2 to remove catalyst and BaO. CH_2Cl_2 was removed and the product dried under vacuum. Purification yielded 288 mg (88%) **18** as a clear oil. Hydrolysis provided the hydroxyketone in 75% ee by chiral HPLC analysis ((*R,R*)-Whelk-01, 2.5% EtOH/hexanes, 1.0 mL/min) t_R(minor) = 24.69 min, t_R(major) = 27.60 min) and 13.1:1 dr by ^{1}H NMR; $[\alpha]^{27}_D$ –62.5^0 (c 1.02, CH_2Cl_2). IR (thin film) 3457, 3067, 2957, 2861, 1626, 1258, 876 cm^{-1}. Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.23 (s, 9H), 1.93 (d, *J*=10.7 Hz, 1H), 2.03 (dd, *J*=4.4, 10.7 Hz, 1H), 2.57 (s, 1H), 3.28-3.33 (m, 1H), 4.67 (s, 1H), 5.18 (d, *J*=7.3 Hz, 1H), 7.12 (td, *J*=1.5, 7.8 Hz, 1H), 7.31 (t, *J*=7.8 Hz, 1H), 7.52 (dd, *J*=1.0, 7.8 Hz, 1H), 7.57 (dd, *J*=1.5, 7.8 Hz, 1H). ^{13}C NMR (125.8 MHz, $CDCl_3$) δ -0.1, 23.6, 52.4, 75.0, 102.8, 122.8, 127.7, 128.8, 129.1, 132.8, 141.9, 149.9.