Supporting Information

for

One-Pot Synthesis of Enantiomerically Enriched 2,3-Disubstituted Cyclopentanones via Copper-Catalyzed 1,4-Reduction and Alkylation

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Experimental procedures and characterization data of all products (5 pages).

Experimental Section

General Methods Toluene and CH_2Cl_2 were purchased from J. T. Baker and purified by the solvent dispensing system designed by J. C. Meyer. THF was distilled under argon from sodium/benzophenone ketyl. CuCl (99.995%) and NaOt-Bu were purchased from Aldrich and stored in a nitrogen-filled glovebox. (S)-p-tol-BINAP was purchased from Strem. TBAT was purchased from Aldrich and treated as the following: Anhydrous benzene (25 mL) was added to 3g of TBAT, stirred for 30 min under argon, and removed in vacuo. The solid was dried in vacuo for hours before use. All other reagents were available from commercial sources and were used without further purification. Flash chromatography was performed on silica gel from Silicycle Inc. (230–400 mesh). Yields refer to isolated yields of compounds of greater than 95% purity as estimated by capillary GC and ^1H NMR. Yields reported in this section refer to a single experiment, while those reported in the tables are an average of two or more runs, so the numbers may differ slightly. All the reported spectra below are those of the major product. All ^1H NMR spectra are reported parts per million (ppm) downfield from tetramethylsilane. ^{13}C NMR spectra are reported in ppm referenced to deuteriochloroform (77.23 ppm). Infrared spectra (IR) were obtained on Perkin-Elmer 1600 series FT-IR and are recorded in cm^{-1}. Optical rotations were recorded on a Perkin-Elmer 241 polarimeter.

General procedure for one-pot synthesis of chiral 2,3-disubstituted cyclopentanones (Table 2):

2-Benzyl-3-phenethyl-cyclopentanone (Table 1; entry 7 and Table 2; entry 1)

Asymmetric conjugate reduction of β-substituted cyclopentenones:

(S)-p-tol-BINAP (10.2 mg, 0.015 mmol) was placed into a flame-dried Schlenk tube and toluene (0.7 mL) was added. The Schlenk tube was transferred into a nitrogen-filled glovebox. In the glovebox, NaOt-Bu (1.4 mg, 0.015 mmol) and CuCl (1.5 mg, 0.015 mmol) were weighed into a vial. The toluene solution of the chiral bis-phosphine was added via pipet to the vial to dissolve the solids and the resulting solution was then transferred back into the Schlenk tube. After the Schlenk tube was removed from the glovebox, the solution was stirred 5–10 min and Ph_2SiH_2 (30 μL, 0.16 mmol) was added by syringe to the solution under argon. The resulting solution turned a reddish orange color. The solution was then cooled to 0 °C. 3-Phenethylcyclopentenone was dissolved in toluene (0.5 mL) and added to the cooled reaction solution via canula, washed with toluene (0.3 mL), and again transferred. The resulting solution was stirred until no enone was detected by TLC. **Alkylation:** To the reaction mixture from the conjugate reduction was added BnBr (71 μL, 0.6 mmol) by syringe at room temperature. TBAT was weighed into a flame-dried flask, dissolved in CH_2Cl_2 (1.0 mL) and then added to the reaction solution via canula. The flask was washed with another CH_2Cl_2 (0.5 mL) and transferred. The reaction Schlenk tube was sealed and stirred for 24 h at room temperature. The solvent was evaporated and the resulting residue was purified by silica gel column chromatography. Purification by flash chromatography afforded the desired product as a colorless oil which contains a small amount of coeluted Ph_3SiF. This impurity was eliminated by chromatography to yield the product (56.3 mg, 67.5% yield). **Equilibration:** A mixture of diastereomers was dissolved in MeOH and a catalytic amount (~20%) of NaOMe was added. The reaction mixture was stirred at room temperature for 24 h. A 97:3 diastereomeric ratio was measured by GC analysis : ^1H NMR (300 MHz, $CDCl_3$) 7.29–7.14 (m, 6H), 7.09–7.04 (m, 4H), 2.93 (dd, J = 5.4, 13.9 Hz, 1H), 2.87 (dd, J = 5.6, 13.9 Hz,

1H), 2.67 (ddd, J = 5.1, 9.3, 13.6 Hz, 1H), 2.50 (ddd, J = 7.1, 9.3, 13.8 Hz, 1H), 2.35 (tdd, J = 1.6, 8.3, 18.6 Hz, 1H), 2.21–1.78 (m, 5H), 1.56–1.36 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 220.1, 142.0, 139.4, 129.5, 128.6, 128.5, 128.4, 126.3, 126.0, 56.5, 40.3, 38.3, 36.5, 34.2, 33.4, 27.2; IR (neat) 3025, 2919, 2849, 1731 cm^{-1}; Anal. Calcd for $C_{20}H_{22}O_1$: C, 86.29; H, 7.96. Found: C, 86.18; H, 7.91; $[\alpha]_D$ -55.6° (c 0.95, $CHCl_3$) for 95% ee and 94% de.

2-Allyl-3-phenethyl-cyclopentanone (entry 2): Using the general procedure the title compound was prepared as a colorless oil in 64% yield. After equilibration, a 95:5 diastereomeric ratio was measured by GC: ^1H NMR (300 MHz, $CDCl_3$) 7.32–7.24 (m, 2H), 7.22–7.17 (m, 3H), 5.68 (tdd, J = 7.1, 10.2, 17.0 Hz, 1H), 5.04–4.96 (m, 2H) 2.78 (ddd, J = 5.1, 10.2, 13.6 Hz, 1H), 2.61 (ddd, J = 6.7, 9.8, 13.7 Hz, 1H), 2.42–2.33 (m, 3H), 2.28–2.18 (m, 1H), 2.13–2.00 (m, 2H), 1.95–1.84 (m, 2H), 1.64–1.39 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) 220.1, 142.1, 135.5, 128.5, 128.4, 126.0, 117.2, 54.8, 40.8, 38.2, 36.5, 33.6, 32.5, 27.3; IR (neat) 3013, 2919, 2861, 1737 cm^{-1}; Anal. Calcd for $C_{16}H_{20}O_1$: C, 84.16; H, 8.83. Found: C, 83.87; H, 8.76; $[\alpha]_D$ -65.5° (c 0.70, $CHCl_3$) for 95% ee and 90% de.

2-Methyl-3-phenethyl-cyclopentanone (entry 4): Using the general procedure the title compound was prepared as a colorless oil in 66% yield. After equilibration, a 94:6 diastereomeric ratio was measured by GC: ^1H NMR (300 MHz, $CDCl_3$) 7.34–7.27 (m, 2H), 7.25–7.19 (m, 3H), 2.87–2.78 (m, 1H), 2.70–2.60 (m, 1H), 2.45–2.36 (m, 1H), 2.30–2.02 (m, 3H), 1.81–1.51 (m, 3H), 1.50–1.42 (m, 1H), 1.07 (d, J = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 221.1, 142.2, 128.6, 128.4, 126.0, 50.7, 44.6, 37.6, 36.6, 33.7, 27.5, 12.9; IR (neat) 3012, 2948, 2916, 2863, 1740 cm^{-1}; Anal. Calcd for $C_{14}H_{18}O_1$: C, 83.12; H, 8.97. Found: C, 83.20; H, 8.96; $[\alpha]_D$ -61.5° (c 2.60, $CHCl_3$) for 95% ee and 88% de.

2-Benzyl-3-methyl-cyclopentanone (entry 5): Using the general procedure the title compound was prepared as a colorless oil in 62% yield. After equilibration, a 93:7 diastereomeric ratio was measured by GC: ^{1}H NMR (300 MHz, $CDCl_3$) 7.30–7.16 (m, 5H), 3.00 (dd, J = 5.2, 14.0 Hz, 1H), 2.90 (dd, J = 5.6, 14.0 Hz, 1H), 2.39–2.20 (m, 1H), 2.09–1.94 (m, 3H), 1.89–1.80 (m, 1H), 1.45–1.38 (m, 1H), 1.02 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 220.4, 139.7, 129.5, 128.6, 128.4, 126.3, 58.3, 38.5, 36.4, 33.9, 29.8, 19.8; IR (neat) 3025, 2943, 2872, 1738 cm^{-1}; HRMS (EI) m/z calcd for $C_{13}H_{16}O_1$ 188.1201, Found 188.1204; $[\alpha]_D$ -140° (c 0.60, $CHCl_3$) for 93% ee and 86% de.

Ethyl (trans-5-methyl-2-oxocyclopentyl)acetate (entry 6): Using the general procedure the title compound was prepared as a colorless oil in 54% yield after kugelrohr-distillation. After equilibration in the presence of cat. NaOEt in EtOH, a 92:8 diastereomeric ratio was measured by GC. The major diastereomer of this reaction was deteremined to be trans by comparing published ^{1}H NMR and ^{13}C NMR data[14]: ^{1}H NMR (300 MHz, $CDCl_3$) 4.13 (q, J = 7.14 Hz, 2H), 2.62 (dd, J = 4.7, 16.8 Hz, 1H), 2.53 (dd, J = 5.2, 16.8 Hz, 1H), 2.39 (ddd, J = 0.8, 8.8, 18.4 Hz, 1H), 2.30–2.10 (m, 2H), 2.06–1.90 (m, 2H), 1.49–1.37 (m, 1H), 1.26 (t, J = 7.1 Hz, 3H) 1.14 (d, J = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 218.9, 172.2, 60.9, 53.4, 37.9, 37.2, 32.5, 30.0, 19.4, 14.5; IR (neat) 2955, 2872, 1737 cm^{-1}; Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.60; H, 8.52; $[\alpha]_D$ -82.8° (c 1.74, $CHCl_3$) for 93% ee and 88% de.

3-Methyl-2-(3-methyl-but-2-enyl)-cyclopentanone (entry 7): Using the general procedure the title compound was prepared as a colorless oil in 54% yield. After equilibration, a 93:7 diastereomeric ratio was measured by GC: ^{1}H NMR (300 MHz, $CDCl_3$) 5.05 (tsept, J = 1.4, 7.4Hz, 1H), 2.39–2.21 (m, 3H), 2.18–2.03 (m, 2H), 1.99–1.80 (m, 1H), 1.77–1.65 (m, 1H), 1.67 (d, J = 1.4 Hz, 3H), 1.62 (br s, 3H), 1.44–1.29 (m, 1H), 1.13 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75

MHz, $CDCl_3$) 221.1, 133.3, 121.3, 57.0, 38.6, 36.6, 29.9, 26.3, 26.1, 20.0, 18.1; IR (neat) 2956, 2926, 2871, 1741 cm^{-1}; Anal. Calcd for $C_{11}H_{18}O_1$: C, 79.46; H, 10.91. Found: C, 79.71; H, 11.06; $[\alpha]_D$ -112° (c 0.63, $CHCl_3$) for 93% ee and 86% de (4% regioisomer).

2-n-Butyl-3-phenethyl-cyclopentanone (entry 8): Using the general procedure the title compound was prepared as a colorless oil in 43% yield. After equilibration, a 93:7 diastereomeric ratio was measured by GC: ^1H NMR (300 MHz, $CDCl_3$) 7.32–7.23 (m, 2H), 7.22–7.16 (m, 3H), 2.79 (ddd, J = 5.2, 10.2, 13.6 Hz, 1H), 2.61 (ddd, J = 6.5, 10.0, 13.6 Hz, 1H), 2.35 (ddt, J = 1.6, 8.5, 18.4 Hz, 1H), 2.27–2.17 (m, 1H), 2.15–1.95 (m, 2H), 1.91–1.82 (m, 1H), 1.75 (dtd, J = 1.4, 5.4, 10.3 Hz, 1H), 1.65–1.38 (m, 4H), 1.36–1.13 (m, 4H), 0.87 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 221.1, 142.2, 128.6, 128.4, 126.0, 55.2, 41.5, 38.2, 36.9, 33.7, 29.3, 28.0, 27.4, 23.3, 14.3; IR (neat) 3025, 2919, 2861, 1737 cm^{-1}; Anal. Calcd for $C_{17}H_{24}O_1$: C, 83.55; H, 9.90. Found: C, 83.47; H, 9.94; $[\alpha]_D$ -38.3° (c 0.85, $CHCl_3$) for 95% ee and 86% de (10% regioisomer).