Enantioselective Nazarov Reactions Through Catalytic Asymmetric Proton Transfer

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Supporting Information

General. Unless otherwise noted, infrared spectra (IR) were obtained on NaCl plates with an ATI Mattson Gemini FTIR spectrometer. Proton NMR spectra (^1H NMR) and carbon NMR spectra (^{13}C NMR) were recorded in CDCl_3 on either a Bruker AV-400 or a Bruker DRX-500 spectrometer. High-resolution mass spectra (HRMS) were obtained on a VG ProSpec Mass Spectrometer using electron impact (EI) at 70 eV unless otherwise noted. Preparative HPLC was performed on a Varian preparative HPLC instrument with a dynamax Microsorb Si column (ID: 21.4 mm, particle size 8 μm , length: 25 cm, pore size: 60 Å) with a linear gradient of 8% EtOAc in hexanes to 25% EtOAc in hexanes over a course of 30 min with a flow rate of 21.6 mL/min.

All reaction mixtures were magnetically stirred in oven-dried glassware under a blanket of nitrogen. The reaction was performed at room temperature unless otherwise noted. External bath temperatures were used to record all reaction mixture temperatures. Analytical thin layer chromatography (TLC) was carried out on Merck silica gel 60 F₂₅₄ TLC plates. TLC visualization was accomplished using 254 nm UV light or charring solutions of KMnO_4 . Flash column chromatography was performed on ICN siliTech 32-63 D 60 Å silica gel according to the procedure of Still.¹

Tetrahydrofuran (THF) and dichloromethane (CH_2Cl_2) were dried according to the procedure described by Bergman.² Acetonitrile (MeCN) was distilled from CaH_2 immediately prior to use. Extracts were dried over anhydrous Na_2SO_4 and solvents were removed with a rotary evaporator at aspirator pressure.

Preparation of substrates **14**, **17a**, **17b**, **17e** and **17j** and the corresponding cyclization products **15a**, **15b**, **18a**, **18b**, **18e** and **18j** were reported in our previous paper.³ Preparation of substrates **17c**, **17d**, **17f**, **17g**, **17h** and **17k** followed the same strategy and general procedures described in the previous paper.

A general procedure for the catalytic asymmetric Nazarov cyclization: MeCN (4 mL) was added into a mixture of $\text{Sc}(\text{OTf})_3$ (18.0 mg, 0.0366 mmol), **16** (25.0 mg, 0.0636 mmol) and 3 Å molecular sieves (210.0 mg). The reaction mixture was stirred for 80 min at which time the substrate (0.366 mmol) in MeCN (1 mL) was added. When the reaction was complete, the mixture was filtered through Celite and washed with EtOAc (15 mL). The mixture was concentrated *in vacuo* and the crude mixture was purified by flash column chromatography. Enantioselectivities were measured on chiral analytical HPLC with either CHIRALPAK[®] AD[™] column (250 X 4.6 mm) or CHIRALPAK[®] AS column

(250 X 4.6 mm) with a flow rate of 1.0 mL/min. Integration was done manually and the estimated error of e.e. is $\pm 1\%$.

15a

15b

Asymmetric cyclization of **14** (61.0 mg, 0.367 mmol) catalyzed by **16** produced (1 h) **15a** and **15b** as a diastereomeric mixture. The two diastereomers were separated by preparative HPLC affording enantioenriched **15a** (37.8 mg, 62.0 %) and **15b** (11.0 mg, 18.0 %).

Cis-5,6-Dimethyl-3,4,5,6-tetrahydro-2H-cyclopenta[b]pyran-7-one (15a) The enantiomeric excess was determined by chiral HPLC [AS column, 22% *i*-PrOH in hexanes; t_R (minor enantiomer) = 7.99 min, t_R (major enantiomer) = 9.75 min] to be 40%.

Trans-5,6-Dimethyl-3,4,5,6-tetrahydro-2H-cyclopenta[b]pyran-7-one (15b) The enantiomeric excess was determined by chiral HPLC [AS column, 22% *i*-PrOH in hexanes; t_R (minor enantiomer) = 7.79 min, t_R (major enantiomer) = 9.40 min] to be 79%.

18a

6-Methyl-3,4,5,6-tetrahydro-2H-cyclopenta[b]pyran-7-one (18a) Asymmetric cyclization of **17a** (56.0 mg, 0.366 mmol) catalyzed by **16** produced (3 h) enantioenriched **18a**. Purification by flash column chromatography (EtOAc: hexanes = 1:4) afforded **18a** (36.0 mg, 65%) as a colorless oil. The enantiomeric excess was determined by chiral HPLC [AS column, 22% *i*-PrOH in hexanes; t_R (minor enantiomer) = 8.60 min, t_R (major enantiomer) = 11.35 min] to be 85%. $[\alpha]_D = -28.6$ ($c = 1.9$, CHCl_3).

18b

6-Ethyl-3,4,5,6-tetrahydro-2H-cyclopenta[b]pyran-7-one (18b) Asymmetric cyclization of **17b** (61.0 mg, 0.366 mmol) catalyzed by **16** produced (1.5 h) enantioenriched **18b**. Purification by flash column chromatography (EtOAc: hexanes = 1:4) afforded **18b** (46.0 mg, 75%) as a colorless oil. The enantiomeric excess was determined by chiral HPLC [AS column, 22% *i*-PrOH in hexanes; t_R (minor enantiomer) = 8.59 min, t_R (major enantiomer) = 12.04 min] to be 92%. $[\alpha]_D = -68.8$ ($c = 1.9$, CHCl_3).

1-(5,6-Dihydro-4H-pyran-2-yl)-2-propyl-prop-2-en-1-ol

Yield: 91%; Clear oil; R_f 0.23 (EtOAc: hexanes = 1:6); IR 3434(br), 2957, 2930, 2871, 2849, 1675, 1649 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ_{H} 5.08 (s, 1 H), 4.86 (s, 1 H), 4.74 (t, 1 H, J = 3.7 Hz), 4.27 (d, 1 H, J = 6.0 Hz), 3.95 (m, 1 H), 3.87 (m, 1 H), 2.51 (d, 1 H, J = 6.2 Hz), 2.01-1.86 (m, 4 H), 1.76-1.68 (m, 2 H), 1.45-1.36 (m, 2 H), 0.83 (t, 3 H, J = 7.3 Hz); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} 153.17, 148.58, 109.95, 97.88, 75.21, 66.31, 34.25, 22.23, 20.94, 19.90, 13.83; HRMS calcd for $\text{C}_{11}\text{H}_{18}\text{O}_2$ (M) $^+$ 182.1307, found: 182.1304.

1-(5,6-Dihydro-4H-pyran-2-yl)-2-propyl-propenone (17c)

Dess-Martin oxidation. Yield: 80%; Clear oil; R_f 0.29 (EtOAc: hexanes = 1:9); IR 2958, 2932, 2871, 1660, 1623 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ_{H} 5.80 (t, 1 H, J = 4.2 Hz), 5.52 (s, 1 H), 5.48 (d, 1 H, J = 1.1 Hz), 4.05 (t, 2 H, J = 5.1 Hz), 2.25 (t, 2 H, J = 7.5 Hz), 2.16 (m, 2 H), 1.81 (m, 2 H), 1.36 (m, 2 H), 0.84 (t, 3 H, J = 7.3 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 192.95, 151.26, 147.35, 122.08, 114.63, 66.32, 34.70, 21.41, 21.12, 20.90, 13.68; HRMS calcd for $\text{C}_{11}\text{H}_{16}\text{O}_2$ (M) $^+$ 180.1150, found: 180.1146.

6-Propyl-3,4,5,6-tetrahydro-2H-cyclopenta[b]pyran-7-one (18c)

Asymmetric cyclization of **17c** (66.0 mg, 0.366 mmol) catalyzed by **16** produced (1.5 h) enantioenriched **18c**. Purification by flash column chromatography (EtOAc: hexanes = 1:5) afforded **18c** (46.0 mg, 70%) as a colorless oil. The enantiomeric excess was determined by chiral HPLC [AS column, 22% *i*-PrOH in hexanes; t_{R} (minor enantiomer) = 8.08 min, t_{R} (major enantiomer) = 10.71 min] to be 93%. $[\alpha]_{\text{D}} = -57.7$ (c = 2.1, CHCl_3). R_f 0.21 (EtOAc: hexanes = 1:4); IR 2956, 2929, 2872, 1708, 1650 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ_{H} 4.08-3.99 (m, 2 H), 2.56 (dd, 1 H, J = 17.4, 6.3 Hz), 2.28 (m, 3 H), 2.07 (dd, 1 H, J = 17.4, 1.6 Hz), 1.88 (m, 2 H), 1.79-1.69 (m, 1 H), 1.42-1.18 (m, 3 H), 0.86 (t, 3 H, J = 7.2 Hz); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 203.03, 150.54, 144.19, 66.75, 43.31, 33.60, 32.79, 24.03, 21.61, 20.27, 14.00; HRMS calcd for $\text{C}_{11}\text{H}_{16}\text{O}_2$ (M) $^+$ 180.1150, found: 180.1148.

2-Butyl-1-(5,6-dihydro-4H-pyran-2-yl)-prop-2-en-1-ol

Yield: 82%; Clear oil; R_f 0.21 (EtOAc: hexanes = 1:6); IR 3442(br), 2954, 2929, 2870, 1675, 1649 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ_{H} 5.14 (s, 1 H), 4.94 (s, 1 H), 4.81 (t, 1 H, $J = 3.7$ Hz), 4.36 (d, 1 H, $J = 6.2$ Hz), 4.03 (m, 1 H), 3.96 (m, 1 H), 2.15 (d, 1 H, $J = 6.4$ Hz), 2.06-1.98 (m, 4 H), 1.79 (m, 2 H), 1.43 (m, 2 H), 1.30 (m, 2 H), 0.88 (t, 3 H, $J = 7.3$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} 153.04, 148.90, 109.88, 98.18, 75.43, 66.46, 31.93, 30.09, 22.48, 22.27, 19.95, 13.94; HRMS calcd for $\text{C}_{12}\text{H}_{20}\text{O}_2$ (M) $^+$ 196.1463, found: 196.1465.

17d

2-Butyl-1-(5,6-dihydro-4H-pyran-2-yl)-propenone (17d)

Dess-Martin oxidation. Yield: 75%; Clear oil; R_f 0.27 (EtOAc: hexanes = 1:9); IR 2955, 2931, 2872, 1660, 1625 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ_{H} 5.83 (t, 1 H, $J = 4.1$ Hz), 5.54 (s, 1 H), 5.51 (s, 1 H), 4.08 (t, 2 H, $J = 5.1$ Hz), 2.30 (t, 2 H, $J = 7.5$ Hz), 2.19 (dd, 2 H, $J = 10.7, 6.1$ Hz), 1.84 (m, 2 H), 1.35 (m, 2 H), 1.27 (m, 2 H), 0.85 (t, 3 H, $J = 7.2$ Hz); ^{13}C NMR (125 MHz, CDCl_3) δ_{C} 192.98, 151.24, 147.56, 121.84, 114.63, 66.29, 32.34, 30.04, 22.28, 21.37, 20.88, 13.80; HRMS calcd for $\text{C}_{12}\text{H}_{18}\text{O}_2$ (M) $^+$ 194.1307, found: 194.1305.

18d

6-Butyl-3,4,5,6-tetrahydro-2H-cyclopenta[b]pyran-7-one (18d)

Asymmetric cyclization of **17d** (71.0 mg, 0.366 mmol) catalyzed by **16** produced (1.5 h) enantioenriched **18d**. Purification by flash column chromatography (EtOAc: hexanes = 1:5) afforded **18d** (50.0 mg, 70%) as a colorless oil. The enantiomeric excess was determined by chiral HPLC [AS column, 22% *i*-PrOH in hexanes; t_{R} (minor enantiomer) = 7.81 min, t_{R} (major enantiomer) = 10.55 min] to be 94%. $[\alpha]_{\text{D}} = -56.6$ ($c = 2.45$, CHCl_3). R_f 0.21 (EtOAc: hexanes = 1:4); IR 2955, 2927, 2871, 2857, 1710, 1650 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ_{H} 4.04 (m, 2 H), 2.60-2.54 (m, 1 H), 2.29 (t, 3 H, $J = 6.2$ Hz), 2.07 (dd, 1 H, $J = 17.4, 1.7$ Hz), 1.91 (m, 2 H), 1.79 (m, 1 H), 1.32-1.21 (m, 5 H), 0.87-0.80 (m, 3 H); ^{13}C NMR (100 MHz, CDCl_3) δ_{C} 203.03, 150.56, 144.21, 66.75, 43.49, 32.79, 31.15, 29.20, 24.04, 22.65, 21.62, 13.94; HRMS calcd for $\text{C}_{12}\text{H}_{18}\text{O}_2$ (M) $^+$ 194.1307, found: 194.1304.

(S)-6-Isopropyl-3,4,5,6-tetrahydro-2H-cyclopenta[b]pyran-7-one (18e) Asymmetric cyclization of **17e** (66.0 mg, 0.366 mmol) catalyzed by **16** at 0 °C produced (3 h) enantioenriched **18e**. Purification by flash column chromatography (EtOAc: hexanes = 1:5) afforded **18e** (58.0 mg, 88%) as a colorless oil. The enantiomeric excess was determined by chiral HPLC [AS column, 22% *i*-PrOH in hexanes; t_R (minor enantiomer) = 7.59 min, t_R (major enantiomer) = 10.02 min] to be 95%. $[\alpha]_D = -92.2$ ($c = 2.2$, CHCl_3).

2-tert-Butyl-1-(5,6-dihydro-4H-pyran-2-yl)-prop-2-en-1-ol

Yield: 92%; Clear oil; R_f 0.14 (EtOAc: hexanes = 1:9); IR 3413(br), 2963, 2932, 2907, 2870, 2849, 1677cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ_H 5.26 (s, 1 H), 5.11 (s, 1 H), 4.88 (t, 1 H, $J = 3.7$ Hz), 4.58 (d, 1 H, $J = 5.6$ Hz), 4.04-3.93 (m, 2 H), 2.09-2.02 (m, 2 H), 1.91 (d, 1 H, $J = 5.7$ Hz), 1.80 (m, 2 H), 1.11 (s, 9 H); ^{13}C NMR (125 MHz, CDCl_3) δ_C 157.87, 154.87, 109.43, 97.38, 70.88, 66.35, 35.49, 29.44, 22.29, 19.98; HRMS calcd for $\text{C}_{12}\text{H}_{20}\text{O}_2$ (M) $^+$ 196.1463, found: 196.1458.

2-tert-Butyl-1-(5,6-dihydro-4H-pyran-2-yl)-propenone (17f)

Dess-Martin oxidation. Yield: 82%; Clear oil; R_f 0.16 (EtOAc: hexanes = 1:9); IR 2957, 2910, 2871, 1666, 1625cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ_H 5.91 (t, 1 H, $J = 4.2$ Hz), 5.41 (s, 1 H), 5.12 (s, 1 H), 4.09 (t, 2 H, $J = 5.1$ Hz), 2.25-2.18 (m, 2 H), 1.87-1.80 (m, 2 H), 1.14 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3) δ_C 194.77, 155.80, 152.02, 116.89, 115.69, 66.42, 35.42, 29.63, 21.36, 21.14; HRMS calcd for $\text{C}_{12}\text{H}_{18}\text{O}_2$ (M) $^+$ 194.1307, found: 194.1311.

6-tert-Butyl-3,4,5,6-tetrahydro-2H-cyclopenta[b]pyran-7-one (18f)

Asymmetric cyclization of **17f** (71.0 mg, 0.366 mmol) catalyzed by **16** produced (30 min) enantioenriched **18f**. Purification by flash column chromatography (EtOAc: hexanes = 1:6) afforded **18f** (67.0 mg, 94%) as a colorless oil. The enantiomeric excess was

determined by chiral HPLC [AS column, 22% *i*-PrOH in hexanes; t_R (minor enantiomer) = 5.52 min, t_R (major enantiomer) = 7.52 min] to be 97%; $[\alpha]_D = -40.5$ ($c = 3.2$, CHCl_3); R_f 0.26 (EtOAc: hexanes = 1:4); IR 2954, 2916, 2870, 1705, 1655 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ_H 4.05 (m, 2 H), 2.41 (dd, 1 H, $J = 17.5, 6.4$ Hz), 2.35-2.25 (m, 2 H), 2.21 (dd, 1 H, $J = 17.5, 1.5$ Hz), 2.11 (d, 1 H, $J = 5.7$ Hz), 1.90 (m, 2 H), 0.96 (s, 9 H); ^{13}C NMR (100 MHz, CDCl_3) δ_C 201.75, 151.32, 143.10, 66.74, 52.76, 33.43, 29.68, 27.31, 23.87, 21.69; HRMS calcd for $\text{C}_{12}\text{H}_{18}\text{O}_2$ (M) $^+$ 194.1307, found: 194.1305.

2-Cyclohexyl-1-(5,6-dihydro-4H-pyran-2-yl)-prop-2-en-1-ol

Yield: 75%; Clear oil; R_f 0.20 (EtOAc: hexanes = 1:9); IR 3445(br), 2925, 2850, 1675, 1646 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ_H 5.14 (s, 1 H), 4.93 (s, 1 H), 4.80 (t, 1 H, $J = 3.7$ Hz), 4.38 (d, 1 H, $J = 5.7$ Hz), 3.96 (m, 2 H), 2.19 (d, 1 H, $J = 6.2$ Hz), 2.09-1.94 (m, 2 H), 1.87 (t, 1 H, $J = 11.2$ Hz), 1.81-1.67 (m, 6 H), 1.63 (d, 1 H, $J = 11.6$ Hz), 1.29-1.02 (m, 5 H); ^{13}C NMR (100 MHz, CDCl_3) δ_C 154.51, 153.30, 108.48, 98.13, 74.81, 66.39, 40.43, 33.76, 32.88, 26.86, 26.77, 26.26, 22.28, 19.97; HRMS calcd for $\text{C}_{14}\text{H}_{22}\text{O}_2$ (M) $^+$ 222.1620, found: 222.1623.

17g

2-Cyclohexyl-1-(5,6-dihydro-4H-pyran-2-yl)-propenone (17g)

Dess-Martin oxidation. Yield: 85%; Clear oil; R_f 0.25 (EtOAc: hexanes = 1:9); IR 2926, 2851, 1661, 1625 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ_H 5.79 (t, 1 H, $J = 4.2$ Hz), 5.33 (s, 1 H), 5.31 (s, 1 H), 4.02 (t, 2 H, $J = 4.1$ Hz), 2.41 (t, 1 H, $J = 11.6$ Hz), 2.14 (dd, 2 H, $J = 10.7, 6.2$ Hz), 1.77 (m 2 H), 1.69-1.61 (m, 4 H), 1.61-1.52 (m, 1 H), 1.27-1.14 (m, 2 H), 1.11-1.95 (m, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ_C 193.84, 152.61, 151.60, 118.15, 115.63, 66.26, 39.59, 31.63, 26.24, 26.02, 21.29, 20.90; HRMS calcd for $\text{C}_{14}\text{H}_{20}\text{O}_2$ (M) $^+$ 220.1463, found: 220.1463.

18g

6-Cyclohexyl-3,4,5,6-tetrahydro-2H-cyclopenta[b]pyran-7-one (18g)

Asymmetric cyclization of **17g** (81.0 mg, 0.366 mmol) catalyzed by **16** produced (3 h) enantioenriched **18g**. Purification by flash column chromatography (EtOAc: hexanes = 1:5) afforded **18g** (61.0 mg, 76%) as a colorless oil. The enantiomeric excess was

determined by chiral HPLC [AD column, 10% *i*-PrOH in hexanes; t_R (minor enantiomer) = 8.56 min, t_R (major enantiomer) = 12.26 min] to be 76%; $[\alpha]_D = -56.2$ ($c = 2.7$, CHCl₃); R_f 0.21 (EtOAc: hexanes = 1:4); IR 2922, 2851, 1706, 1650 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ_H 4.04 (m, 2 H), 2.39 (dd, 1 H, $J = 17.4, 6.3$ Hz), 2.35-2.24 (m, 3 H), 2.21 (dd, 1 H, $J = 17.4, 1.3$ Hz), 1.94-1.81 (m, 3 H), 1.62-1.56 (m, 4 H), 1.38 (d, 1 H, $J = 12.7$ Hz), 1.20 (m, 2 H), 1.11-0.93 (m, 3 H); ¹³C NMR (125 MHz, CDCl₃) δ_C 202.63, 151.15, 144.61, 66.68, 48.81, 38.81, 30.65, 28.98, 27.34, 26.42, 26.22, 25.97, 23.96, 21.58; HRMS calcd for C₁₄H₂₀O₂ (M)⁺ 220.1463, found: 220.1464; mp: 62.0-64.0 °C (racemic)

1-(5,6-Dihydro-4H-pyran-2-yl)-2-phenyl-prop-2-en-1-ol

Yield: 70%; Clear oil; R_f 0.24 (EtOAc: hexanes = 1:6); IR 3441(br), 2929, 2875, 2847, 1675 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ_H 7.46-7.41 (m, 2 H), 7.36-7.27 (m, 3 H), 5.53 (s, 1 H), 5.49 (s, 1 H), 4.98 (d, 1 H, $J = 5.6$ Hz), 4.84 (t, 1 H, $J = 3.8$ Hz), 4.02 (m, 2 H), 2.34 (d, 1 H, $J = 5.9$ Hz), 2.09-1.93 (m, 2 H), 1.86-1.72 (m, 2 H); ¹³C NMR (100 MHz, CDCl₃) δ_C 153.00, 148.15, 139.73, 128.14, 127.51, 126.89, 114.21, 98.99, 74.12, 66.53, 22.25, 19.98; HRMS calcd for C₁₄H₁₆O₂ (M)⁺ 216.1150, found: 216.1149.

17h

1-(5,6-Dihydro-4H-pyran-2-yl)-2-phenyl-propenone (17h)

Dess-Martin oxidation. Yield: 65%; Clear oil; R_f 0.27 (EtOAc: hexanes = 1:6); IR 2934, 2875, 1666, 1623 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ_H 7.39-7.35 (m, 2 H), 7.35-7.27 (m, 3 H), 6.01 (t, 1 H, $J = 4.2$ Hz), 5.87 (s, 1 H), 5.55 (s, 1 H), 4.10 (t, 2 H, $J = 5.1$ Hz), 2.24-2.14 (m, 2 H), 1.85 (m, 2 H); ¹³C NMR (125 MHz, CDCl₃) δ_C 192.58, 151.46, 147.12, 136.83, 128.52, 128.31, 126.50, 119.08, 117.64, 66.41, 21.28, 21.09; HRMS calcd for C₁₄H₁₄O₂ (M)⁺ 214.0994, found: 214.0991.

18h

6-Phenyl-3,4,5,6-tetrahydro-2H-cyclopenta[b]pyran-7-one (18h)

Asymmetric cyclization of **17h** (78.0 mg, 0.366 mmol) catalyzed by **16** produced (1 h) enantioenriched **18h**. Purification by flash column chromatography (EtOAc: hexanes = 1:3) afforded **18h** (51.0 mg, 65%) as a white solid. The enantiomeric excess was determined by chiral HPLC [AS column, 35% *i*-PrOH in hexanes; t_R (minor enantiomer) = 12.38 min, t_R (major enantiomer) = 16.04 min] to be 87%; $[\alpha]_D = +71.0$ ($c = 2.1$, CHCl₃); R_f 0.15 (EtOAc: hexanes = 1:3); IR 2943, 2875, 1705, 1644 cm⁻¹; ¹H NMR (500

MHz, CDCl₃) δ_{H} 7.33-7.27 (m, 2 H), 7.25-7.20 (m, 1 H), 7.17-7.12 (m, 2 H), 4.16 (t, 2 H, $J = 5.2$ Hz), 3.56 (d, 1 H, $J = 6.0$ Hz), 2.99 (dd, 1 H, $J = 17.7, 6.8$ Hz), 2.53 (dd, 1 H, $J = 17.7, 1.7$ Hz), 2.42 (m, 2 H), 2.06-1.95 (m, 2 H); ^{13}C NMR (125 MHz, CDCl₃) δ_{C} 200.01, 150.33, 144.84, 139.56, 128.73, 127.65, 126.91, 66.90, 49.33, 35.91, 24.09, 21.54; HRMS calcd for C₁₄H₁₄O₂ (M)⁺ 214.0994, found: 214.0994. mp: 117.2-119.0 °C

6-Isopropyl-2,3,6,7-tetrahydro-cyclopenta[1,4]dioxin-5-one (18j)

Asymmetric cyclization of **17j** (67.0 mg, 0.366 mmol) catalyzed by **16** at 0 °C produced (3 h) enantioenriched **18j**. Purification by flash column chromatography (EtOAc: hexanes = 1:2) afforded **18j** (43.0 mg, 65%) as a colorless oil. The enantiomeric excess was determined by chiral HPLC [AS column, 35% *i*-PrOH in hexanes; t_{R} (minor enantiomer) = 8.83 min, t_{R} (major enantiomer) = 11.93 min] to be 72%; $[\alpha]_{\text{D}} = -60.2$ ($c = 2.0$, CHCl₃); R_{f} 0.22 (EtOAc: hexanes = 1:2); IR 2957, 2930, 2873, 1707, 1641 cm⁻¹; ^1H NMR δ_{H} 4.30 (m, 2 H), 4.12 (t, 2 H, $J = 4.0$ Hz), 2.48 (dd, 1 H, $J = 17.0, 6.6$ Hz), 2.40 (m, 1H), 2.28 (m, 2 H), 0.95 (d, 3 H, $J = 7.0$ Hz), 0.76 (d, 3 H, $J = 6.8$ Hz); ^{13}C NMR δ_{C} 196.92, 165.08, 134.31, 66.88, 63.84, 47.66, 28.06, 24.78, 20.40, 16.54; HRMS calcd for C₁₀H₁₄O₃ (M)⁺ 182.0943, found: 182.0944.

2-tert-Butyl-1-(5,6-dihydro-[1,4]dioxin-2-yl)-prop-2-en-1-ol

Yield: 70%; Clear oil; R_{f} 0.27 (EtOAc: hexanes = 1:3); IR 3420(br), 2965, 2936, 2908, 2874, 1680 cm⁻¹; ^1H NMR (400 MHz, CDCl₃) δ_{H} 6.12 (s, 1 H), 5.30 (s, 1 H), 5.15 (s, 1 H), 4.62 (d, 1 H, $J = 4.5$ Hz), 4.13-4.02 (m, 2 H), 4.02-3.95 (m, 2 H), 1.97 (d, 1 H, $J = 4.3$ Hz), 1.09 (s, 9 H); ^{13}C NMR (100 MHz, CDCl₃) δ_{C} 156.68, 138.25, 125.29, 110.08, 68.90, 64.55, 63.99, 35.44, 29.39; HRMS calcd for C₁₁H₁₈O₃ (M)⁺ 198.1256, found: 198.1253.

2-tert-Butyl-1-(5,6-dihydro-[1,4]dioxin-2-yl)-propenone (17k)

Dess-Martin oxidation. Yield: 30%; Clear oil; R_{f} 0.27 (EtOAc: hexanes = 1:3); IR 2959, 2906, 2875, 1654, 1611 cm⁻¹; ^1H NMR (400 MHz, CDCl₃) δ_{H} 7.11 (s, 1 H), 5.37 (s, 1 H), 5.10 (s, 1 H), 4.15 (s, 4 H), 1.14 (s, 9 H); ^{13}C NMR (100 MHz, CDCl₃) δ_{C} 192.34, 155.48, 143.07, 137.89, 115.39, 65.11, 63.47, 35.38, 29.64; HRMS calcd for C₁₁H₁₆O₃ (M)⁺ 196.1100, found: 196.1098.

18k

6-tert-Butyl-2,3,6,7-tetrahydro-cyclopenta[1,4]dioxin-5-one (18k)

Asymmetric cyclization of **17k** (72.0 mg, 0.366 mmol) catalyzed by **16** produced (30 min) enantioenriched **18k**. Purification by flash column chromatography (EtOAc: hexanes = 1:2) afforded **18k** (57.0 mg, 80%) as a colorless oil. The enantiomeric excess was determined by chiral HPLC [AS column, 35% *i*-PrOH in hexanes; t_R (minor enantiomer) = 5.54 min, t_R (major enantiomer) = 7.76 min] to be 91%; $[\alpha]_D = -35.6$ ($c = 1.6$, CHCl₃); R_f 0.12 (EtOAc: hexanes = 1:3); IR 2955, 2907, 2871, 1706, 1648 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ_H 4.29 (m, 2 H), 4.10 (t, 2 H, $J = 4.0$ Hz), 2.51 (dd, 1 H, $J = 17.3, 6.7$ Hz), 2.31 (dd, 1 H, $J = 17.3, 2.2$ Hz), 2.20 (dd, 1 H, $J = 6.7, 2.2$ Hz), 0.98 (s, 9 H); ¹³C NMR (100 MHz, CDCl₃) δ_C 196.25, 163.92, 134.28, 66.86, 63.90, 51.45, 33.24, 27.32, 26.45; HRMS calcd for C₁₁H₁₆O₃ (M)⁺ 196.1100, found: 196.1100.

ent-18e-1

(6R, 7S)-6-Isopropyl-2,3,4,5,6,7-hexahydro-cyclopenta[b]pyran-7-ol (ent-18e-1)

To 0.66 mL lithium tri-sec-butylborohydride solution (1M in THF) was added 5 mL THF and the solution was cooled to 0 °C. Then 0.10 g (0.55 mmol) of **ent-18e** (94% e.e.) in 5 mL THF, was added. The reaction mixture was stirred vigorously for 0.5 h at 0 °C and then allowed to warm to r.t. To the reaction mixture was added 0.5 mL of water, 1 mL of ethanol, 0.5 mL of 30% hydrogen peroxide and 0.5 mL of 6 M sodium hydroxide solution. The reaction mixture was diluted with 10 mL of brine and 20 mL of EtOAc. The two layers were separated and the aqueous layer was extracted with EtOAc (2 X 10 mL). The combined organic layers were washed with brine (30 mL), dried, filtered and concentrated *in vacuo*. The product was purified by flash column chromatography (EtOAc: hexanes = 1:6) to afford 0.095 g (95%) of **ent-18e-1** as a clear oil; R_f 0.15 (EtOAc: hexanes = 1:6); IR 3349(br), 2952, 2918, 2880, 2867, 2833, 1692 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ_H 4.34 (d, 1 H, $J = 5.8$ Hz), 3.99 (m, 2 H), 2.10 (m, 2 H), 1.97 (m, 2 H), 1.82 (m, 2 H), 1.76 (m, 1 H), 1.65 (m, 2 H), 0.99 (d, 3 H, $J = 6.4$ Hz), 0.88 (d, 3 H, $J = 6.6$ Hz); ¹³C NMR (125 MHz, CDCl₃) δ_C 152.92, 112.25, 74.22, 67.05, 48.33, 35.25, 27.47, 22.55, 21.97, 21.70, 20.83; HRMS calcd for C₁₁H₁₈O₂ (M)⁺ 182.1307, found: 182.1308; $[\alpha]_D = -75.2$ ($c = 3.7$, CHCl₃); mp: 60.8-62.0 °C (Racemic).

19

4,7,7-Trimethyl-3-oxo-2-oxa-bicyclo[2.2.1]heptane-1-carboxylic acid 6-isopropyl-2,3,4,5,6,7-hexahydro-cyclopenta[b]pyran-7-yl ester (19)

To a mixture of **ent-18e-1** (0.052 g, 0.285 mmol), (-)-camphanoyl chloride (0.074 g, 0.342 mmol) and DMAP (0.052 g, 0.428 mmol) was added CH₂Cl₂ (8 mL). The reaction mixture was stirred for 10 min before water (10 mL) was added. The reaction mixture was diluted with CH₂Cl₂ (20 mL) and the two layers were separated. The organic layer was washed with brine (10 mL) dried, filtered and concentrated *in vacuo*. The product was purified by flash column chromatography (EtOAc: hexanes = 1:6) to afford 0.078 g (75%) of **19** as a white solid; R_f 0.21 (EtOAc: hexanes = 1:6); IR 2965, 2927, 2870, 2847, 1787, 1743, 1690cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ_H 5.81 (d, 1 H, *J* = 6.1 Hz), 4.05-3.95 (m, 1 H), 3.94-3.85 (m, 1 H), 2.39 (m, 1 H), 2.27-2.11 (m, 2 H), 2.09-1.97 (m, 3 H), 1.97-1.61 (m, 6 H), 1.09 (s, 3 H), 1.03 (s, 3 H), 0.95 (s, 3 H), 0.90 (d, 3 H, *J* = 6.5 Hz), 0.86 (d, 3 H, *J* = 6.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ_C 178.35, 167.08, 149.55, 115.58, 91.35, 77.47, 67.04, 54.79, 54.18, 46.82, 35.54, 30.68, 29.18, 27.66, 22.45, 21.91, 21.84, 20.76, 16.89, 16.48, 9.71; HRMS calcd for C₂₁H₃₀O₅ (M)⁺ 362.2093, found: 362.2087; mp: 107-108 °C; [α]_D = -143.0 (*c* = 0.6, CHCl₃).

1 Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923-2925.

2 Alaimo, P. J.; Peters, D. W.; Arnold, J.; Bergman, R. G. *J. Chem. Ed.* **2001**, *78*, 64.

3 Liang, G.; Gradl, S. N.; Trauner, D. *Org. Lett.* **2003**, *5*, 4931-4934.

18k

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Injection Date   : 4/6/04 4:09:57 PM          Seq. Line :    1
Sample Name     : P-32-01                    Vial       :    1
Acq. Operator   : G(Trauner)                 Inj        :    1
Acq. Instrument : analytical HPLC             Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\1\METHODS\G-060-AS.M
Last changed    : 4/5/04 6:31:12 PM by G(Trauner)
Analysis Method : C:\HPCHEM\1\METHODS\BAHARI1.M
Last changed    : 10/31/03 6:08:20 PM by bahar
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Area Percent Report
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000

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18b

Signal 1: MWD1 A, Sig=250,100 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.590	MM	0.4629	325.10721	11.70442	4.4377
2	12.039	MM	0.8457	7000.98389	137.96927	95.5623

Totals : 7326.09109 149.67369

Results obtained with enhanced integrator!

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*** End of Report ***

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Injection Date   : 4/9/04 1:44:42 PM          Seq. Line :    2
Sample Name     : P38-02                     Vial       :    2
Acq. Operator   : G(Trauner)                  Inj        :    1
Acq. Instrument : analytical HPLC             Inj Volume  : 5 µl
Acq. Method     : C:\HPCHEM\1\METHODS\G-060-AS.M
Last changed    : 4/8/04 2:10:26 PM by G(Trauner)
Analysis Method : C:\HPCHEM\1\METHODS\BAHAR1.M
Last changed     : 10/31/03 6:08:20 PM by bahar
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                        Area Percent Report
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000

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Signal 1: MWD1 A, Sig=250,100 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	8.078	PB	0.4186	1332.46558	47.02840	3.5147
2	10.706	MM	0.9966	3.65788e4	611.70398	96.4853

Totals : 3.79112e4 658.73238

Results obtained with enhanced integrator!

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*** End of Report ***

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Injection Date : 4/10/04 11:52:28 AM Seq. Line : 2
Sample Name : P39-02 Vial : 32
Acq. Operator : G(Trauner) Inj : 1
Acq. Instrument : analytical HPLC Inj Volume : 5 µl
Acq. Method : C:\HPCHEM\1\METHODS\G-060-AS.M
Last changed : 4/8/04 2:10:26 PM by G(Trauner)
Analysis Method : C:\HPCHEM\1\METHODS\BAHAR1.M
Last changed : 10/31/03 6:08:20 PM by bahar
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Area Percent Report
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Sorted By : Signal
Multiplier : 1.0000
Dilution : 1.0000

Signal 1: MWD1 A, Sig=250,100 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.807	BB	0.4083	1075.75012	38.70185	3.1373
2	10.546	PB	0.8754	3.32129e4	549.31268	96.8627

Totals : 3.42887e4 588.01454

Results obtained with enhanced integrator!

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*** End of Report ***
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Injection Date   : 3/9/04 10:48:37 PM      Seq. Line :    1
Sample Name     : P9-1                    Vial      :    1
Acq. Operator   : G(Trauner)              Inj       :    1
Acq. Instrument : analytical HPLC          Inj Volume: 5 µl
Acq. Method     : C:\HPCHEM\1\METHODS\G-060-AS.M
Last changed    : 2/26/04 2:53:11 PM by Stuart Smith
Analysis Method : C:\HPCHEM\1\METHODS\BAHAR1.M
Last changed     : 10/31/03 6:08:20 PM by bahar
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                        Area Percent Report
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000

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Signal 1: MWD1 A, Sig=250,100 Ref=360,100

18e

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	7.588	MM	0.4515	856.50562	31.61518	2.5153
2	10.024	MM	0.8083	3.31948e4	684.48767	97.4847

Totals : 3.40513e4 716.10285

Results obtained with enhanced integrator!

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*** End of Report ***

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product from Rh cat. arylation of N-sulfinyl p-tolualdi
mine

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Injection Date   : 3/30/04 12:41:57 PM           Seq. Line :    1
Sample Name      : P-25-02                       Vial       :   51
Acq. Operator    : G(Trauner)                    Inj        :    1
Acq. Instrument  : analytical HPLC                Inj Volume : 5 µl
Acq. Method      : C:\HPCHEM\1\METHODS\G-060-AS.M
Last changed     : 2/26/04 2:53:11 PM by Stuart Smith
Analysis Method  : C:\HPCHEM\1\METHODS\BAHAR1.M
Last changed     : 10/31/03 6:08:20 PM by bahar
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Area Percent Report

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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000
  
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Signal 1: MWD1 A, Sig=250,100 Ref=360,100

18f

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.515	PP	0.2599	154.58113	8.75804	1.5782
2	7.522	BB	0.4333	9639.89453	329.50665	98.4218

Totals : 9794.47566 338.26469

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Injection Date   : 4/10/04 6:41:57 PM           Seq. Line :    2
Sample Name     : P40-04                       Vial       :   32
Acq. Operator   : G(Trauner)                   Inj        :    1
Acq. Instrument : analytical HPLC              Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\1\METHODS\G-099-AS.M
Last changed    : 4/10/04 5:58:20 PM by Ian Stewart
Analysis Method : C:\HPCHEM\1\METHODS\BAHAR1.M
Last changed    : 10/31/03 6:08:20 PM by bahar
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                        Area Percent Report
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Sorted By      :      Signal
Multiplier     :      1.0000
Dilution       :      1.0000

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18k

Signal 1: MWD1 A, Sig=250,100 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	5.543	BB	0.2982	1899.12390	93.01701	4.7419
2	7.760	MM	0.6264	3.81511e4	1015.16644	95.2581

Totals : 4.00502e4 1108.18345

Results obtained with enhanced integrator!

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*** End of Report ***
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