Asymmetric Synthesis of 5-Arylcyclohexenones by Rhodium(I)-Catalyzed Conjugate Arylation of Racemic 5-(Trimethylsilyl)cyclohexenone with Arylboronic Acid

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General. All melting points are not corrected. ^1H and ^{13}C NMR spectra were taken at 500 and 125 MHz, respectively, in CDCl_3 . Chemical shift values are expressed in ppm relative to internal tetramethylsilane. Abbreviations are as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. IR spectra were expressed in cm^{-1} .

Preparation of racemic 5-(trimethylsilyl)cyclohex-2-enone (1). Racemic **1** (CAS 56917-71-6; Asaoka, M.; Shima, K.; Takei, H. *Tetrahedron Lett.* **1987**, 28, 5669–5672.) was prepared according to the reported procedures.

Catalytic asymmetric conjugate phenylation of 5-(trimethylsilyl)cyclohex-2-enone (1) using $[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2$ (Table 1, entry 1): a flask charged with $[\text{RhCl}(\text{C}_2\text{H}_4)_2]_2$ (5.8 mg, 0.015 mmol), ligand **5** (11.6 mg, 0.033 mmol), and phenylboronic acid (610 mg, 5.0 mmol) was flushed with argon. 1,4-Dioxane (2.5 mL) and 0.25 mL of 4 M aq. KOH (1.0 mmol) were successively added. The mixture was stirred at rt for 1 h and then 5-trimethylsilylcyclohex-2-enone (**1**) (168 mg, 1.0 mmol) was added. The resulting mixture was stirred at 60 °C for 3 h. After dilution with AcOEt (40 mL), the mixture was washed with 10% NaOH (10 mL) and brine (20 mL), and then dried over Na_2SO_4 . Concentration and silica gel column chromatography (hexane/AcOEt = 30/1) gave a 59:41 mixture of *trans*-**2a** and *cis-ent*-**3a** (224 mg, 91%) as a colorless oil.

and *cis-ent*-**3a**): **2a:ent-3a** = 59:41 (determined by the integration area of ^1H NMR signals at 3.52–3.56 ppm of the *trans*-**2a** and 3.01–3.07 ppm of the *cis*-**3a**). 76% ee for **2a** and 98% ee for *ent*-**3a** (Daicel Chiralcel OD-H, hexane/2-propanol = 50/1, 254 nm, 0.5 mL/min, *trans*-**2a**: 14.7 and 15.7 min for major and minor; *cis-ent*-**3a**: 17.0 and 21.1 min for major and minor).

With (*S*)-BINAP **6** and $\text{Rh}(\text{acac})(\text{C}_2\text{H}_4)_2$ the asymmetric reaction was carried out as shown in text.

silica gel chromatography (hexane/ Et_2O = 25/1). **2b:ent-3b** = 61:39 (determined by the integration area of ^1H NMR signals at 3.48–3.53 ppm of the *trans*-**2b** and 3.00–3.04 ppm of the *cis-ent*-**3b**). 83% ee for **2b** and 99% ee for *ent*-**3b** (Daicel Chiralpak AD-H, hexane/2-propanol = 100/1, 254 nm, 0.5 mL/min, *trans*-**2b**: 19.5 and 22.4 min for major and minor; *cis-ent*-**3b**: 24.9 and 24.1 min for major and minor).

silica gel chromatography (hexane/acetone = 50/1). **2c:ent-3c** = 63:37 (determined by the integration area of ^1H NMR signals at 3.48–3.52 ppm of the *trans*-**2c** and 2.98–3.04 ppm of the *cis-ent*-**3c**). Ee %

was not determined because of poor separation by HPLC (Daicel Chiralpak AD-H, hexane/2-propanol = 50/1, 254 nm, 0.5 mL/min). Directly used in the next elimination to **4c** with 90% ee.

trimethylsilylcyclohexanone (*trans*-**2d** and *cis-ent*-**3d**) (Table 1, entry 8): a colorless oil purified by silica gel chromatography (hexane/acetone = 50/1). **2d:ent-3d** = 63:37 (determined by the integration area of ¹H NMR signals at 3.60–3.64 ppm of the *trans*-**2d** and 3.07–3.13 ppm of the *cis-ent*-**3d**). 88% ee for **2d** and 99% ee for *ent*-**3d** (Daicel Chiralpak AD-H, hexane/2-propanol = 100/1, 254 nm, 0.5 mL/min, *trans*-**2d**: 25.9 and 31.5 min for major and minor; *cis-ent*-**3d**: 35.2 and 28.7 min for major and minor).

trimethylsilylcyclohexanone (*trans*-**2e** and *cis-ent*-**3e**) (Table 1, entry 10): a white solid purified by silica gel chromatography (C₆H₆/AcOEt = 50:1). **2e:ent-3e** = 51:49 (determined by the integration area of ¹H NMR signals at 3.61–3.65 ppm of the *trans*-**2e** and 3.08–3.13 ppm of the *cis-ent*-**3e**). 83% ee for **2e** and 99% ee for *ent*-**3e** (Daicel Chiralcel OD-H, hexane/2-propanol = 50/1, 254 nm, 0.5 mL/min, *trans*-**2e**: 19.1 and 23.1 min for major and minor; *cis-ent*-**3e**: 27.2 and 38.7 min for major and minor).

Oxidative dehydrosilylation. (*S*)-5-Phenylcyclohex-2-en-1-one (*S*)-**4a** (Table 2, entry 1): a mixture of **2a** and *ent*-**3a** (123 mg, 0.50 mmol) and anhydrous CuCl₂ (201 mg, 1.5 mmol) in DMF (2 mL) was stirred at 60 °C for 3 h. The mixture was diluted with water (10 mL) and filtered through short pad of celite. The filtrate was extracted with ether and the extract was dried over Na₂SO₄. Concentration and silica gel column chromatography (hexane/AcOEt = 15/1) gave (*S*)-5-phenylcyclohex-2-en-1-one (*S*)-**4a** (63 mg, 73%) with 83% ee as a colorless oil of [α]_D²⁰ +31.4 (*c* 1.2, CHCl₃) ([α]_D²³ –46.4 (*c* 5.0, CHCl₃) for (*R*)-**4a**: Asaok, M.; Shima, K.; Fujii, N.; Takei, H. *Tetrahedron* **1988**, *44*, 4757–4766). 83% ee (Daicel Chiralcel OJ-H, hexane/2-propanol = 7/1, 254 nm, 0.5 mL/min, 32.9 and 28.6 min for major and minor).

(S)-5-(3-Methoxyphenyl)cyclohex-2-enone (4b) (Table 1, entry 4): a colorless oil purified by silica gel chromatography (hexane/acetone = 10/1). $[\alpha]_D^{20} +24.1$ (*c* 1.12, CHCl₃). 93% ee (Daicel Chiralcel OD-H, hexane/2-propanol = 5/1, 254 nm, 0.5 mL/min, 36.0 and 38.9 min for major and minor). ¹H NMR: 2.54–2.57 (m, 1H), 2.61–2.73 (m, 3H), 3.30–3.36 (m, 1H), 3.81 (s, 3H), 6.12 (d, *J* = 10 Hz, 1H), 6.79–6.85 (m, 3H), 7.04–7.07 (m, 1H), 7.26–7.29 (m, 1H). ¹³C NMR: 33.6, 40.9, 44.8, 55.2, 111.9, 112.9, 119.0, 129.8, 144.9, 149.5, 159.9, 199.2. IR (neat): 1678. EIMS *m/z*: 202 (M⁺). HRMS–EI: [M]⁺ Calcd for C₁₃H₁₄O₂, 202.0994; found, 202.0987.

(S)-5-(3-Chlorophenyl)cyclohex-2-enone (S)-4c (Table 1, entry 6): a colorless oil purified by silica gel chromatography (hexane/acetone=40/1). $[\alpha]_D^{20} +32.2$ (*c* 1.23, CHCl₃). 90% ee (Daicel Chiralpak AS-H, hexane/2-propanol = 5/1, 254 nm, 0.5 mL/min, 27.3 and 30.0 min for major and minor). ¹H NMR: 2.49–2.56 (m, 1H), 2.59–2.72 (m, 3H), 3.30–3.37 (m, 1H), 6.14 (d, *J* = 9.8 Hz, 1H), 7.03–7.06 (m, 1H), 7.13 (d, *J* = 7.4 Hz, 1H), 7.24–7.30 (m, 3H). ¹³C NMR: 33.3, 40.5, 44.5, 124.9, 127.0, 127.2, 129.9, 130.1, 134.6, 145.2, 149.1, 198.6. IR (neat): 1678. EIMS *m/z*: 206 (M⁺). HRMS–EI: [M]⁺ Calcd for C₁₂H₁₁ClO, 206.0498; found, 206.0503.

(S)-5-(4-(Trifluoromethyl)phenyl)cyclohex-2-enone (S)-4d (Table 1, entry 8): a colorless oil purified by silica gel chromatography (hexane/Et₂O = 10/1). $[\alpha]_D^{20} +34.5$ (*c* 1.02, CHCl₃). 93% ee (Daicel Chiralpak AD, hexane/2-propanol = 50/1, 254 nm, 0.5 mL/min, 29.2 and 27.4 min for major and minor). ¹H NMR: 2.55–2.59 (m, 1H), 2.64–2.75 (m, 3H), 3.40–3.47 (m, 1H), 6.15 (d, *J* = 10 Hz, 1H), 7.04–7.08 (m, 1H), 7.37 (d, *J* = 8.2 Hz, 2H), 7.62 (d, *J* = 8.2 Hz, 2H). ¹³C NMR: 33.2, 40.6, 44.3, 124.1 (q, *J* = 270.7 Hz), 125.8, 127.1, 129.3 (q, *J* = 32.9 Hz), 129.9, 147.1, 148.9, 198.3. IR(neat): 1682. EIMS *m/z*: 240 (M⁺). HRMS–EI: [M]⁺ Calcd for C₁₃H₁₁F₃O, 240.0762; found, 240.0759.

(S)-5-(Naphth-2-yl)cyclohex-2-enone (S)-4e (Table 1, entry 10): a white solid of mp 95–98 °C. $[\alpha]_D^{25} +41$ (*c* 1.02, CHCl₃). 90% ee (Daicel Chiralcel OD-H, hexane/2-propanol = 2/1, 254 nm, 0.5 mL/min, 20.5 and 25.3 min for major and minor). ¹H NMR: 2.60–2.82 (m, 4H), 3.46–3.55 (m,

1H), 6.16 (d, $J = 10$ Hz, 1H), 7.05–7.08 (m, 1H), 7.37 (d, $J = 8.6$ Hz, 1H), 7.45–7.50 (m, 2H), 7.66 (s, 1H), 7.80–7.84 (m, 3H). ^{13}C NMR: 33.5, 41.0, 44.8, 125.0, 125.2, 125.8, 126.3, 127.7, 127.8, 128.5, 129.8, 132.5, 133.5, 140.6, 149.4, 199.1. IR (nujol): 1662. EIMS m/z : 222 (M^+). Anal. Calcd for $\text{C}_{16}\text{H}_{14}\text{O}$: C, 86.45; H, 6.35. Found: C, 86.25; H, 6.49.

Correlation of the absolute configuration of 5-arylcylohexenones **4 with that reported by hydrogenation to 5-arylcylohexanones.** (*S*)-3-(Naphth-2-yl)cyclohexanone: A mixture of (*S*)-**4e** with 94 % ee (50 mg, 0.23 mmol, not listed in Table) and 10% Pd/C (60 mg, 0.056 mmol) in AcOEt (8 mL) was stirred under H_2 atmosphere for 1.5 h. Filtration, concentration and silica gel column chromatography (hexane/acetone = 10/1) gave (*S*)-3-(naphth-2-yl)cyclohexanone (50 mg, 99%) as a white solid of mp 110–112 °C. $[\alpha]_{\text{D}}^{20} -7.8$ (c 1.04, CHCl_3) ($[\alpha]_{\text{D}}^{20} -8.3$ (c 0.89, CHCl_3) for (*S*)-compound with 99% ee: Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1999**, *40*, 6957–6961). 94% ee (Daicel Chiralcel OD-H, hexane/2-propanol = 50/1, 254 nm, 0.5 mL/min, 44.4 and 51.6 min for major and minor).

(*S*)-3-(3-Chlorophenyl)cyclohexanone: Hydrogenation of **4c** with 78% ee (Table 1, entry 5) and silica gel column chromatography (hexane/acetone = 15/1) gave (*S*)-3-(3-chlorophenyl)cyclohexanone as a colorless oil in 98% yield. $[\alpha]_{\text{D}}^{20} -11.1$ (c 1.04, CHCl_3) ($[\alpha]_{\text{D}}^{20} -9.5$ (c 1.13, CHCl_3) for (*S*)-compound with 96% ee: Takaya, Y.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **1998**, *120*, 5579–5580). 80% ee (Daicel Chiralpak AD, hexane/2-propanol = 50/1, 254 nm, 0.5 mL/min, 18.1 and 21.0 min for major and minor).

(*S*)-3-(3-Methoxyphenyl)cyclohexanone: Hydrogenation of **4b** with 84% ee (Table 1, entry 3) and silica gel column chromatography (hexane/acetone = 20/1) gave (*S*)-3-(3-methoxyphenyl)cyclohexanone as a colorless oil. $[\alpha]_{\text{D}}^{20} -12.4$ (c 0.99, CHCl_3) ($[\alpha]_{\text{D}}^{20} -13.0$ (c 0.91, CHCl_3) for (*S*)-compound with 96% ee: Takaya, Y.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **1998**, *120*, 5579–5580). 84% ee (Daicel Chiralcel OD-H, hexane/2-propanol = 50/1, 254 nm, 1 mL/min, 27.3 and 31.0 min for major and minor).

Supporting Information

(S)-3-(4-(Trifluoromethyl)phenyl)cyclohexanone: Hydrogenation of **4d** with 80% ee

(Table 1, entry 7) and silica gel column chromatography (hexane/acetone = 15/1) gave a white solid of mp 75–77 °C. $[\alpha]_D^{20}$ –8.0 (*c* 0.99, CHCl₃) ($[\alpha]_D^{20}$ –11.0 (*c* 0.97, CHCl₃) for (*S*)-compound with 99% ee: Takaya, Y.; Ogasawara, M.; Hayashi, T. *J. Am. Chem. Soc.* **1998**, *120*, 5579–5580). 80% ee (Daicel Chiralcel OD-H, hexane/2-propanol = 50/1, 254 nm, 0.5 mL/min, 25.3 and 23.7 min for major and minor).

General: Daicel Chiralpak AD or AS-H, or Chiralcel OJ-H or OD-H were used with detection at 254 nm.

trans-**2a**: 76% ee; *cis-ent*-**3a**: 98% ee (OD-H, hexane/2-propanol = 50/1, 0.5 mL/min, *trans*: 14.7 and 15.7 min for major and minor; *cis*: 17.0 and 21.1 min for major and minor).

trans-**2b**: 83% ee; *cis-ent*-**3b**: 99.9% ee (AD-H, hexane/2-propanol = 100/1, 0.5 mL/min, *trans*: 19.5 and 22.4 min for major and minor; *cis*: 24.9 and 24.1 min for major and minor).

Supporting Information

trans-**2c**: 70% ee; *cis*-ent-**3c**: 97% ee (AD-H, hexane/2-propanol = 50/1, 0.5 mL/min, *trans*: 22.8 and 27.9 min for major and minor; *cis*: 26.4 and 24.7 min for major and minor).

trans-**2d**: 88% ee; *cis*-ent-**3d**: 99% ee (AD-H, hexane/2-propanol = 100/1, 0.5 mL/min, *trans*: 25.9 and 31.5 min for major and minor; *cis*: 35.2 and 28.7 min for major and minor).

trans-**2e**: 90% ee; *cis*-ent-**3e**: 99% ee (OD-H, hexane/2-propanol = 50/1, 0.5 mL/min, *trans*: 21.8 and 26.4 min for major and minor; *cis*: 31.1 and 43.5 min for major and minor).

Supporting Information

(R)-4a: 96% ee (OJ-H, hexane/2-propanol = 7/1, 0.5 mL/min, 19.4 and 23.0 min for major and minor).

4c: 90% ee (AS-H, hexane/2-propanol = 5/1, 0.5 mL/min, 27.3 and 30.0 min for major and minor).

4b: 93% ee (OD-H, hexane/2-propanol = 5/1, 0.5 mL/min, 36.0 and 38.9 min for major and minor).

Supporting Information

4d: 93% ee (AD, hexane/2-propanol = 50/1, 0.5 mL/min, 29.2 and 27.4 min for major and minor).

4e: 90% ee (OD-H, hexane/2-propanol = 3/1, 254 nm, 0.5 mL/min, 21.7 and 27.4 min for major and minor).

84% ee (OD-H, hexane/2-propanol = 50/1, 1 mL/min, 27.3 and 31.0 min for major and minor).

Supporting Information

80% ee (AD, hexane/2-propanol = 50/1, 0.5 mL/min, 18.1 and 21.0 min for major and minor).

80% ee (OD-H, hexane/2-propanol = 50/1, 0.5 mL/min, 25.3 and 23.7 min for major and minor).

94% ee (OD-H, hexane/2-propanol = 50/1, 0.5 mL/min, 44.4 and 51.6 min for major and minor).