(A) Hydrogenation of Benzophenone

Benzophenone (200.0 g, 0.684 mol),[1] 2-propanol (200 mL),[2] and *t*-C_4H_9OK (493 mg, 4.39 mmol) were placed in a 1-L stainless steel autoclave[3] equipped with a mechanically stirring blade, a pressure gauge, and a gas inlet tube attached to a hydrogen source. The mixture was degassed by bubbling of nitrogen[4] for 5 min. Solid *trans*-$RuCl_2[P(C_6H_4\text{-}4\text{-}CH_3)_3]_2(NH_2CH_2CH_2NH_2)$ (**3**) (46.2 mg, 0.055 mmol)[5] was added with a gentle flow of nitrogen. Air present in the gas inlet tube was removed by flushing with a stream of hydrogen.[6] Hydrogen was initially introduced into the autoclave at a pressure of 8 atm, before being reduced to 1 atm by carefully releasing the stop valve. After this procedure was repeated three times, the vessel was pressurized to 8 atm. The reaction mixture was vigorously stirred (700 rpm) at 35 °C for 48 h. The yield determined by GC analysis was 99.5%. GC (column, DB-1701 (86:14 poly(dimethylsiloxane)–poly(3-cyanopropylphenylsiloxane)), df = 1.00 μm, 0.53 mm i.d. x 30 m, J&W SCIENTIFIC); carrier gas, helium (9.0 mL/min); column temp, 175 °C; injection temp, 250 °C; split ratio, 100:1; retention time (t_R) of benzhydrol, 15.8 min (99.6%); t_R of benzophenone, 14.1 min (0.4%)). After carefully venting the hydrogen gas, the solvent was removed under reduced pressure. Subsequently, the residue was purified by filtration through silica gel (200 g), eluted with ether. The eluate was evaporated in vacuo to give benzhydrol (203 g, 100% yield). No ketone was detected by GC analysis in the isolated product. ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.23 (d, 1, J = 3.6 Hz, OH), 5.84 (d, 1, J = 3.6 Hz, C*H*OH), 7.1–7.5 (m, 10, aromatics). The product was identified by comparison of the GC, IR, MS, and NMR behaviors with those of with reference sample prepared by $NaBH_4$ reduction of benzophenone.

Notes

(1) Acidic impurities should be carefully removed from the substrate and solvent prior to use. Otherwise catalytic activity is substantially lowered.

(2) Guarantee-grade 2-propanol was freshly distilled over CaH_2 before use.

(3) For details, see: Kitamura, M.; Tokunaga, M.; Ohkuma, T.; Noyori, R. *Org. Synth.* **1993**, *71*, 1–13; Takaya, H.; Ohta, T.; Inoue, S.; Tokunaga, M.; Kitamura, M.; Noyori, R. *Org. Synth.* **1994**, *72*, 74–85.

(4) Nitrogen gas prepared by vaporization of liquid nitrogen was used.

(5) Preparation procedure, see: Doucet, H.; Ohkuma, T.; Murata, K.; Yokozawa, T.; Kozawa, M.; Katayama, E.; England, A. F.; Ikariya, T.; Noyori, R. *Angew. Chem., Int. Ed.* **1998**, *37*, 1703–1707.

(6) Hydrogen of 99.99% purity (Nippon Sanso) was used.

(B) Reaction Conditions and Analytical Data of Products

***o*-Methylbenzhydrol**. Conditions [**3** (1.75 mg, 0.0021 mmol), *o*-methylbenzophenone (1.23 g, 6.25 mmol), *t*-C_4H_9OK (2.8 mg, 0.025 mmol), 2-propanol (3 mL), 8 atm H_2, 35 °C, 18 h]. *o*-Methylbenzhydrol (1.25 g, 101% yield). GC (column, TC-WAX (polyethylene glycol, df = 0.25 μm, 0.25 mm i.d. x 30 m, GL Sciences Inc.); 100 kPa, column temp, 230 °C); t_R of alcohol, 12.8 min (99.5%); t_R of ketone, 6.7 min (0.5%). ***o*-Chlorobenzhydrol**. Conditions [**3** (1.0 mg, 0.0012 mmol), *o*-chlorobenzophenone (541 mg, 2.50 mmol), 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (10 μL, 0.010 mmol), 2-propanol (2.5 mL), 8 atm H_2, 28 °C, 12 h]. *o*-Chlorobenzhydrol (517 mg, 95% yield). GC (column, HP-INNOWax (polyethylene glycol, df = 0.25 μm, 0.25 mm i.d. x 30 m, Hewlett Packard); 100 kPa, column temp, 230 °C); t_R of alcohol, 15.2 min (97.4%); t_R of ketone, 9.0 min (2.6%). ***m*-Chlorobenzhydrol**. Conditions [**3** (1.0 mg, 0.0012 mmol), *m*-chlorobenzophenone (542 mg, 2.50 mmol), 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (10 μL, 0.010 mmol), 2-propanol (5 mL), 8 atm H_2, 28 °C, 12 h]. *m*-Chlorobenzhydrol (544 mg, 99.5% yield). GC (column, HP-INNOWax; 100 kPa, column temp, 230 °C); t_R of alcohol, 19.3 min (98.4%); t_R of ketone, 8.9 min (1.6%). ***p*-Phenylbenzhydrol**. Conditions [**3** (1.0 mg, 0.0012 mmol), *p*-phenylbenzophenone (646 mg, 2.50 mmol), 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (10

μL, 0.010 mmol), 2-propanol (5 mL), 8 atm H_2, 28 °C, 12 h]. *p*-Phenylbenzhydrol (646 mg, 99% yield). The purity of the alcohol was confirmed by ^{1}H- and ^{13}C-NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.35 (br s, 1, OH), 5.87 (s, 1, C*H*OH), 7.1–7.6 (m, 14, aromatics). ^{13}C NMR (125 MHz, $CDCl_3$) δ 76.0, 126.5, 127.0, 127.1, 127.2, 127.3, 127.6, 128.5, 128.7, 140.5, 140.8, 142.8, 143.7. ***p*-Methoxybenzhydrol**. Conditions [**3** (1.75 mg, 0.0021 mmol), *p*-methoxybenzophenone (1.33 g, 6.27 mmol), *t*-C_4H_9OK (2.8 mg, 0.025 mmol), 2-propanol (3 mL), 8 atm H_2, 35 °C, 18 h]. *p*-Methoxybenzhydrol (1.32 g, 98% yield). GC (column, TC-WAX; 68 kPa, column temp, 230 °C); t_R of alcohol, 28.7 min (99.7%); t_R of ketone, 19.6 min (0.3%). ***p*-Fluorobenzhydrol**. Conditions [**3** (1.0 mg, 0.0012 mmol), *p*-fluorobenzophenone (500 mg, 2.50 mmol), 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (10 μL, 0.010 mmol), 2-propanol (5 mL), 8 atm H_2, 28 °C, 12 h]. *p*-Fluorobenzhydrol (503 mg, 99.5% yield). GC (column, HP-INNOWax; 100 kPa, column temp, 200 °C); t_R of alcohol, 23.6 min (98.6%); t_R of ketone, 10.3 min (1.4%). ***p,p'*-Difluorobenzhydrol**. Conditions [**3** (1.75 mg, 0.0021 mmol), *p,p'*-difluorobenzophenone (1.36 g, 6.23 mmol), *t*-C_4H_9OK (2.8 mg, 0.025 mmol), 2-propanol (3 mL), 8 atm H_2, 35 °C, 18 h]. *p,p'*-Difluorobenzhydrol (1.31 g, 95% yield). GC (column, TC-WAX; 68 kPa, column temp, 230 °C); t_R of alcohol, 12.7 min (99.8%); t_R of ketone, 6.0 min (0.2%). ***p*-Chlorobenzhydrol**. Conditions [**3** (3.5 mg, 0.0042 mmol), *p*-chlorobenzophenone (2.71 g, 12.5 mmol), *t*-C_4H_9OK (5.6 mg, 0.050 mmol), 2-propanol (7 mL), 8 atm H_2, 35 °C, 8 h]. *p*-Chlorobenzhydrol (2.73 g, 99.8% yield). GC (column, TC-WAX; carrier gas, helium (68 kPa), column temp, 230 °C); t_R of alcohol, 23.5 min (100%); t_R of ketone, 11.0 min (0%). ***p*-Trifluoromethylbenzhydrol.** Conditions [**3** (1.0 mg, 0.0012 mmol), *p*-trifluoromethylbenzophenone (626 mg, 2.50 mmol), 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (10 μL, 0.010 mmol), 2-propanol (5 mL), 8 atm H_2, 28 °C, 1 h]. *p*-Trifluoromethylbenzhydrol (621 mg, 98% yield). GC (column, HP-INNOWax; 80 kPa, column temp, 200 °C); t_R of alcohol, 22.9 min (99.3%); t_R of ketone, 9.3 min (0.7%).

(C) Kinetic Study of Hydrogenation of *para*-Substitured Acetophenones and Benzophenones Catalyzed by *trans*-$RuCl_2[P(C_6H_4\text{-}4\text{-}CH_3)_3]_2(NH_2CH_2CH_2NH_2)$

Hydrogenation of *p*-methoxy- and *p*-trifluoromethylbenzophenone. Solid **3** (1.0 mg, 0.0012 mmol) was placed in a 100-mL glass autoclave equipped with a Teflon-coated magnetic stirring bar, a pressure gauge, a gas inlet tube attached to a hydrogen source, and a sampling needle with a stop cock. Air present in the autoclave was replaced by argon. *p*-Methoxybenzophenone (0.5 mmol) was placed in the autoclave under a stream of argon. And then, 2-propanol (4.6 mL) and a 1.0 M *t*-C_4H_9OK solution in *tert*-butyl alcohol (5 μL, 0.005 mmol) which had been degassed by bubbling argon were added under a stream of argon. The mixture was degassed by eight vacuum–filling with argon cycles. Air present in the gas inlet tube was removed by flushing with a stream of hydrogen. Hydrogen was initially introduced into the autoclave at a pressure of 5 atm, before being reduced to 1 atm by carefully releasing the stop valve. After this procedure was repeated three times, the vessel was pressurized to 5 atm. The reaction mixture was vigorously stirred at 28 °C, and small portions of the mixture were sampled after appropriate periods. Conversions were determined by GC analysis using an HP-INNOWax column. The initial rates of reaction were calculated from 3 experiment sets and were first-order-plotted. Hydrogenation of *p*-trifluoromethylbenzophenone was conducted in the same manner. The rate of hydrogenation of *p*-methoxy- and *p*-trifluoromethylbenzophenone was 3.7 and 41 mol/mol of Ru•min, respectively. The relative reactivity of these substrates was 1:11.

Competition experiments. A series of kinetic experiments was conducted at 28 °C using an equimolar mixture of acetophenone or benzophenone and the *para*-substituted substrate (Figure 1). **Hydrogenation of *para*-substituted acetophenones.** Solid **3** (1.0 mg, 0.0012 mmol) was placed in a 100-mL glass autoclave equipped with a Teflon-coated magnetic stirring bar, a pressure gauge, a gas inlet tube attached to a hydrogen source, and a sampling needle with a stop cock. Air present in the autoclave was replaced by argon. 2-Propanol (3.4 mL), acetophenone (120 mg, 1.0 mmol), a

para-substituted substrate (1.0 mmol), and a 1.0 M *t*-C_4H_9OK solution in *tert*-butyl alcohol (10 μL, 0.010 mmol) which had been degassed by bubbling argon were added to the autoclave under a stream of argon. The mixture was degassed by eight vacuum–filling with argon cycles. Air present in the gas inlet tube was removed by flushing with a stream of hydrogen. Hydrogen was initially introduced into the autoclave at a pressure of 4 atm, before being reduced to 1 atm by carefully releasing the stop valve. After this procedure was repeated three times, the vessel was pressurized to 4 atm. The reaction mixture was vigorously stirred at 28 °C, and small portions of the mixture were sampled after appropriate periods. Conversions were determined by GC analysis using an HP-INNOWax column. The initial rates of reaction of the substituted acetophenone (v_X) and the parent ketone (v_H) were calculated from 3 or 4 experiment sets and were first-order-plotted. Correlations between a substrate, $\log(v_X/v_H)$, and σ_p value of substituent are as follows: *p*-methoxyacetophenone, –0.36, –0.27; *p*-methylacetophenone, –0.14, –0.17; acetophenone, 0, 0; *p*-bromoacetophenone, 0.30, 0.23; *p*-trifluoromethylacetophenone, 0.46, 0.54. The ρ value of Hammett plot was determined to be +0.99.

Hydrogenation of *para*-substituted benzophenones. The reaction was conducted in a 0.1 M solution in 2-propanol because of the low solubility of the ketones. Hydrogenation was conducted using **3** (1.0 mg, 0.0012 mmol), benzophenone (45.6 mg, 0.25 mmol), a *para*-substituted substrate (0.25 mmol), 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (5 μL, 0.005 mmol), 2-propanol (4.6 mL) at 4 atm H_2 and 28 °C. Conversions were determined by GC analysis. Initial rates of hydrogenation of the substituted benzophenone (v_X) and benzophenone (v_H) were calculated from 3 or 4 experiment sets and were first-order-plotted. Correlations between a substrate, $\log(v_X/v_H)$, and σ_p value of substituent are as follows: *p*-methoxybenzophenone, –0.63, –0.27; *p*-methylbenzophenone, –0.21, –0.17; benzophenone, 0, 0; *p*-bromobenzophenone, 0.43, 0.23; *p*-trifluoromethylbenzophenone, 0.89, 0.54. The ρ value of Hammett plot was determined as +1.78.

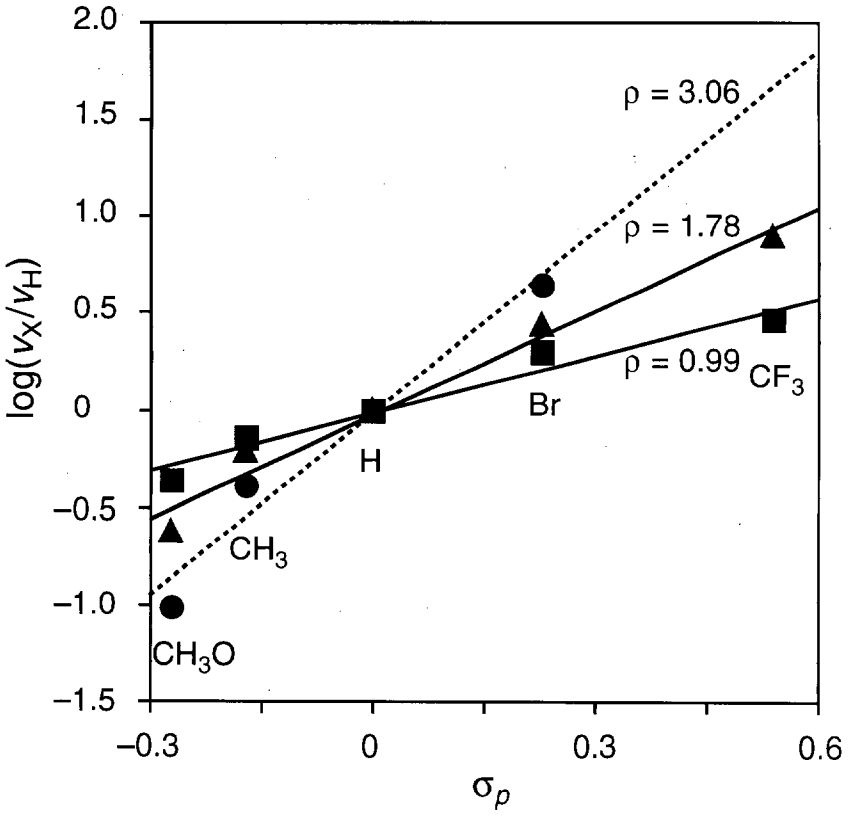

Figure 1. Hammett plots for hydrogenation of *p*-substituted acetophenones (■) and benzophenones (▲) with *trans*-$RuCl_2[P(C_6H_4\text{-}4\text{-}CH_3)_3]_2(NH_2CH_2CH_2NH_2)$ (4 atm, 28 °C). Reduction of *p*-substituted acetophenones with $NaBH_4$ is shown by ● [Bruce, G. T.; Cooksey, A. R.; Morgan, K.J. *J. Chem. Soc., Perkin Trans. 2* **1975**, 551–553].

(D) Asymmetric Hydrogenation of *o*-Chlorobenzophenone[1]

Solid (*S*,*S*)-**4a** (28.7 mg, 0.0235 mmol),[2] and *o*-chlorobenzophenone (**1d**) (101.8 g, 0.47 mol) were placed in a 1.5-L stainless steel autoclave equipped with a mechanical stirring blade, a pressure gauge, and a gas inlet tube attached to a hydrogen source. Air present in the autoclave was replaced by argon. 2-Propanol (150 mL) and a 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (4.7 mL, 4.7 mmol) were added to the autoclave under a stream of argon. The mixture was degassed by three vacuum–filling with argon cycles. Air present in the gas inlet tube was removed by flushing with a stream of hydrogen. The vessel was pressurized to 8 atm, and then the reaction mixture was

vigorously stirred for 55 h at 30 °C. The yield and enantiomeric excess (ee) of (*S*)-*o*-chlorobenzhydrol [(*S*)-**2d**] determined by GC and chiral HPLC analysis were 99 and 97%, respectively. GC (column, HP-INNOWax; 100 kPa, column temp, 230 °C); t_R of **2d**, 16.6 min (98.7%); t_R of **1d**, 9.9 min (1.3%). HPLC (column, CHIRALCEL OD (4.6 mm i.d. x 250 mm, Daicel Chemical Industries); eluent, 10:90 2-propanol–hexane; temp, 30 °C; flow rate, 0.5 mL/min; detection, 270-nm light; t_R of (*R*)-**2d**, 16.5 min (1.7%); t_R of *S* isomer, 20.7 min (98.3%)). After carefully venting the hydrogen gas, the solvent was removed under reduced pressure. Distillation of the residue gave (*S*)-**2d** (97.5 g, 95% yield). Bp 138–139 °C/0.3 mmHg, $[\alpha]^{20}_D$ –21.51° (*c* 1.136, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$) δ 2.34 (d, 1, *J* = 4.1 Hz, OH), 6.19 (d, 1, *J* = 4.1 Hz, C*H*OH), 7.1–7.6 (m, 9, aromatics). ^{13}C NMR (100 MHz, $CDCl_3$) δ 72.6, 126.9, 127.1, 127.7, 128.0, 128.4, 128.7, 129.5, 132.5, 140.9, 142.2. The determination of absolute configuration is given in Part G.

Notes

(1) See also Notes of Part A.

(2) Preparation procedure, see: Ohkuma, T.; Koizumi, M.; Doucet, H.; Pham, T.; Kozawa, M.; Murata, K.; Katayama, E.; Yokozawa, T.; Ikariya, T.; Noyori, R. *J. Am. Chem. Soc.* **1998**, *120*, 13529–13530.

(E) General Procedure for Asymmetric Hydrogenation

A small- or medium-scale reaction was normally conducted in a 100- or 500-mL glass autoclave. An example is given by hydrogenation of **1d**.

Solid (*S,S*)-**4a** (3.0 mg, 0.0025 mmol) and **1d** (10.83 g, 50.0 mmol) were placed in a 500-mL glass autoclave equipped with a Teflon-coated magnetic stirring bar, a pressure gauge, and a gas inlet tube attached to a hydrogen source. Air present in the autoclave was replaced by argon. 2-Propanol (25 mL) and a 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (200 μL, 0.20 mmol) which had been degassed by bubbling argon were

added to the autoclave under a stream of argon. The mixture was degassed by eight vacuum–filling with argon cycles. Air present in the gas inlet tube was removed by flushing with a stream of hydrogen. Hydrogen was initially introduced into the autoclave at a pressure of 4 atm, before being reduced to 1 atm by carefully releasing the stop valve. After this procedure was repeated three times, the vessel was pressurized to 8 atm. The reaction mixture was vigorously stirred at 35 °C. After stirring for 47 h, the hydrogen gas was carefully vented, and the solvent was removed under reduced pressure. The yield and ee of (*S*)-**2d** determined by GC and chiral HPLC analysis were 99.3 and 97%, respectively. After the solvent was removed under reduced pressure, the residue was distilled to give (*S*)-**2d** (10.30 g, 94% yield).

(F) Reaction Conditions of Asymmetric Hydrogenation and Analytical Data of Products

Hydrogenation of *o*-methylbenzophenone (1a). Conditions [(*S*,*S*)-**4a** (1.5 mg, 0.00125 mmol), **1a** (491 mg, 2.50 mmol), 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (10 μL, 0.010 mmol), 2-propanol (2.5 mL), 8 atm H_2, 28 °C, 11 h]. (*S*)-*o*-methylbenzhydrol [(*S*)-**2a**] (486 mg, 98% yield). GC (column, HP-INNOWax; 80 kPa, column temp, 200 °C); t_R of **2a**, 35.5 min (99.4%); t_R of **1a** 14.9 min (0.6%). The ee determined by chiral HPLC analysis was 93%: column, CHIRALCEL OB-H (4.6 mm i.d. x 250 mm, Daicel Chemical Industries); eluent, 10:90 2-propanol–hexane; temp, 30 °C; flow rate, 0.5 mL/min; detection, 270-nm light; t_R of (*S*)-**2a**, 22.5 min (96.5%); t_R of *R* isomer, 19.8 min (3.5%). $[\alpha]^{22}_D$ +6.38° (*c* 0.906, $CHCl_3$), lit. $[\alpha]^{23}_D$ –7.64° (*c* 1.51, $CHCl_3$), (*R*), Watanabe, M.; Kuwahara, S.; Harada, N.; Koizumi, M.; Ohkuma, T. *Tetrahedron: Asymmetry* **1999**, *10*, 2075–2078. **Hydrogenation of *o*-methoxybenzophenone (1b).** Conditions [(*S*,*S*)-**4a** (1.5 mg, 0.00125 mmol), **1b** (531 mg, 2.50 mmol), 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (10 μL, 0.010 mmol), 2-propanol (2.5 mL), 8 atm H_2, 28 °C, 15 h]. (*S*)-*o*-methoxybenzhydrol [(*S*)-**2b**] (527

mg, 98% yield). GC (column, HP-5 (95:5 poly(dimethylsiloxane)–poly(diphenylsiloxane)), df = 0.25 μm, 0.25 mm i.d. x 30 m, Hewlett Packard); 100 kPa, column temp, 150 °C); t_R of **2b**, 17.2 min (99.1%); t_R of **1b**, 10.1 min (0%). The ee determined by chiral HPLC analysis was 99.4%: column, CHIRALCEL OB-H; eluent, 10:90 2-propanol–hexane; temp, 30 °C; flow rate, 0.5 mL/min; detection, 270-nm light; t_R of (*R*)-**2b**, 33.7 min (0.3%); t_R of *S* isomer, 29.7 min (99.7%). $[\alpha]^{26}_D$ –40.4° (*c* 0.78, $CHCl_3$), lit. $[\alpha]^{25}_D$ –38.9° (*c* 0.745, $CHCl_3$), (*S*), Kuwahara, S.; Watanabe, M.; Harada, N.; Koizumi, M.; Ohkuma, T. *Enantiomer* in press. **Hydrogenation of *o*-fluorobenzophenone (1c).** Conditions [(*S*,*S*)-**4a** (1.5 mg, 0.00125 mmol), **1c** (500 mg, 2.50 mmol), 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (10 μL, 0.010 mmol), 2-propanol (2.5 mL), 8 atm H_2, 28 °C, 14 h]. (*S*)-*o*-fluorobenzhydrol [(*S*)-**2c**] (502 mg, 99% yield). GC (column, HP-INNOWax; 100 kPa, column temp, 210 °C); t_R of **2c**, 16.6 min (99.6%); t_R of **1c**, 9.3 min (0.4%). The ee determined by chiral HPLC analysis was 97%: column, CHIRALCEL OB-H; eluent, 5:95 2-propanol–hexane; temp, 30 °C; flow rate, 0.5 mL/min; detection, 270-nm light; t_R of (*R*)-**2c**, 38.2 min (1.5%); t_R of *S* isomer, 41.1 min (98.5%). $[\alpha]^{23}_D$ +5.49° (*c* 0.906, $CHCl_3$). The absolute configuration was determined as indicated in Part G. **Hydrogenation of *o*-chlorobenzophenone (1d).** See Part D and E. **Hydrogenation of *o*-bromobenzophenone (1e).** Conditions [(*S*,*S*)-**4a** (1.5 mg, 0.00125 mmol), **1e** (653 mg, 2.50 mmol), 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (10 μL, 0.010 mmol), 2-propanol (2.5 mL), 8 atm H_2, 23 °C, 13 h]. (*S*)-*o*-bromobenzhydrol [(*S*)-**2e**] (654 mg, 99.4% yield). GC (column, HP-INNOWax; 100 kPa, column temp, 230 °C); t_R of **2e**, 21.2 min (99.1%); t_R of **1e**, 12.2 min (0.9%). The ee determined by chiral HPLC analysis was 96%: column, CHIRALCEL OD; eluent, 10:90 2-propanol–hexane; temp, 30 °C; flow rate, 0.5 mL/min; detection, 270-nm light; t_R of (*R*)-**2e**, 18.8 min (1.9%); t_R of *S* isomer, 26.1 min (98.1%). $[\alpha]^{22}_D$ –41.9° (*c* 1.19, $CHCl_3$). The absolute configuration was determination as indicated in Part G. **Hydrogenation of *o*-bromo-*p'*-methylbenzophenone (1f).** Conditions [(*S*,*S*)-**4a** (1.5 mg, 0.00125 mmol), **1f** (688 mg, 2.50 mmol), 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (10 μL, 0.010 mmol), 2-propanol

(2.5 mL), 8 atm H_2, 28 °C, 15 h]. (*S*)-*o*-bromo-*p'*-methylbenzhydrol [(*S*)-**9**] (681 mg, 98% yield). GC (column, HP-INNOWax; 120 kPa, column temp, 230 °C); t_R of **9**, 23.4 min (99.5%); t_R of **1f**, 14.5 min (0.5%). The ee determined by chiral HPLC analysis was 98%: column, CHIRALPAC AD (4.6 mm i.d. x 250 mm, Daicel Chemical Industries); eluent, 2:98 2-propanol–hexane; temp, 30 °C; flow rate, 0.5 mL/min; detection, 270-nm light; t_R of (*R*)-**9**, 22.6 min (0.6%); t_R of *S* isomer, 46.9 min (99.4%). $[\alpha]^{26}_D$ –40.0° (*c* 0.94, $CHCl_3$). The absolute configuration was determination as indicated in Part G. **Hydrogenation of *m*-methylbenzophenone (1g)**. Conditions [(*S,S*)-**4a** (1.5 mg, 0.00125 mmol), **1g** (491 mg, 2.50 mmol), 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (10 μL, 0.010 mmol), 2-propanol (2.5 mL), 8 atm H_2, 28 °C, 13 h]. (*R*)- or (*S*)-*m*-methylbenzhydrol [(*R*)- or (*S*)-**2g**] (98% yield by GC). GC (column, HP-INNOWax; 100 kPa, column temp, 210 °C); t_R of **2g**, 20.5 min (98.3%); t_R of **1g**, 11.7 min (1.7%). The ee determined by chiral HPLC analysis was 33%: column, CHIRALCEL OB-H; eluent, 10:90 2-propanol–hexane; temp, 30 °C; flow rate, 0.8 mL/min; detection, 270-nm light; t_R of enantiomers of **2g**, 16.7 min (66.7%) and 23.7 min (33.3%). The absolute configuration was not determined. **Hydrogenation of *p*-methylbenzophenone (1h)**. Conditions [(*S,S*)-**4a** (1.5 mg, 0.00125 mmol), **1h** (491 mg, 2.50 mmol), 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (10 μL, 0.010 mmol), 2-propanol (2.5 mL), 8 atm H_2, 28 °C, 13 h]. (*R*)-*p*-methylbenzhydrol [(*R*)-**2h**] (98% yield by GC). GC (column, HP-INNOWax; 55 kPa, column temp, 210 °C); t_R of **2h**, 21.7 min (98.4%); t_R of **1h** 13.0 min (1.6%). The ee determined by chiral HPLC analysis was 8%: column, CHIRALCEL OB-H; eluent, 10:90 2-propanol–hexane; temp, 30 °C; flow rate, 0.5 mL/min; detection, 270-nm light; t_R of (*R*)-**2h**, 20.5 min (54.1%); t_R of *S* isomer, 23.7 min (45.9%). The absolute configuration was determined by comparison of its HPLC behavior with that of reference sample derived from (*S*)-**2e** (see Part G). **Hydrogenation of *p*-methoxybenzophenone (1i)**. Conditions [(*S,S*)-**4a** (1.5 mg, 0.00125 mmol), **1i** (531 mg, 2.50 mmol), 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (10 μL, 0.010 mmol), 2-propanol (5 mL), 8 atm H_2, 28 °C, 13 h]. (*R*)-*p*-methoxybenzhydrol [(*R*)-**2i**] (95% yield by GC). GC (column, HP-INNOWax; 100

kPa, column temp, 230 °C); t_R of **2i**, 21.5 min (95.0%); t_R of **1i**, 13.0 min (5.0%). The ee determined by chiral HPLC analysis was 35%: column, CHIRALCEL OB-H; eluent, 10:90 2-propanol–hexane; temp, 30 °C; flow rate, 0.5 mL/min; detection, 270-nm light; t_R of (*R*)-**2i** 50.6 min (67.5%); t_R of *S* isomer, 55.4 min (32.5%). $[\alpha]^{19}_D$ +7.66° (*c* 2.33, C_6H_6), lit. $[\alpha]^{25}_D$ –18.6° (*c* 2.69, $CHCl_3$), (*S*), Harada, N.; Fujita, K.; Watanabe, M. *Enantiomer* **1994**, *2*, 359–366. **Hydrogenation of *p*-chlorobenzophenone (1j)**. Conditions [(*S*,*S*)-**4a** (1.5 mg, 0.00125 mmol), **1j** (542 mg, 2.50 mmol), 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (10 μL, 0.010 mmol), 2-propanol (5 mL), 8 atm H_2, 28 °C, 12 h]. (*S*)-*p*-chlorobenzhydrol [(*S*)-**2j**] (97% yield by GC). GC (column, HP-INNOWax; 100 kPa, column temp, 230 °C); t_R of **2j**, 21.1 min (97.0%); t_R of **1j**, 10.0 min (3.0%). The ee determined by chiral HPLC analysis was 9%: column, CHIRALCEL OB-H; eluent, 10:90 2-propanol–hexane; temp, 30 °C; flow rate, 0.8 mL/min; detection, 270-nm light; t_R of (*R*)-**2j** 17.3 min (45.5%); t_R of *S* isomer, 25.5 min (54.5%). $[\alpha]^{20}_D$ +2.77° (*c* 0.932, $CHCl_3$), lit. $[\alpha]^{20}_D$ +22.0° (*c* 0.9, $CHCl_3$), (*S*), Wu, B.; Mosher, H. S. *J. Org. Chem.* **1986**, *51*, 1904–1906. **Hydrogenation of *p*-trifluoromethylbenzophenone (1k)**. Conditions [(*S*,*S*)-**4a** (1.5 mg, 0.00125 mmol), **1k** (626 mg, 2.50 mmol), 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (10 μL, 0.010 mmol), 2-propanol (2.5 mL), 8 atm H_2, 28 °C, 12 h]. (*S*)-*p*-trifluoromethylbenzhydrol [(*S*)-**2k**] (99% yield by GC). GC (column, HP-INNOWax; 80 kPa, column temp, 200 °C); t_R of **2k**, 22.0 min (99.3%); t_R of **1k**, 8.0 min (0.7%). The ee determined by chiral HPLC analysis was 47%: column, CHIRALCEL OB-H; eluent, 10:90 2-propanol–hexane; temp, 30 °C; flow rate, 0.8 mL/min; detection, 254-nm light; t_R of (*R*)-**2k** 9.3 min (26.2%); t_R of *S* isomer, 12.5 min (73.8%). $[\alpha]^{24}_D$ +19.0° (*c* 1.11, C_6H_6), lit. $[\alpha]^{22}_D$ +40.4° (*c* 5.0, C_6H_6), (*S*), Capillon, J-P; Guetté. *Tetrahedron* **1979**, *35*, 1801–1805. **Hydrogenation of benzoylferrocene (5)**. Conditions [(*S*,*S*)-**4b** (1.5 mg, 0.00125 mmol), **5** (725 mg, 2.50 mmol), 1.0 M *t*-C_4H_9OK in *tert*-butyl alcohol (10 μL, 0.010 mmol), 2-propanol (4 mL), toluene (1 mL), 8 atm H_2, 28 °C, 13 h]. (*S*)-ferrocenylphenylcarbinol [(*S*)-**6**] (716 mg, 98% yield). The purity of (*S*)-**6** was confirmed by ^{1}H- and ^{13}C-NMR analysis. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.45 (br d, 1,

J = 3.0 Hz, OH), 4.15–4.25 (m, 4, $C_5H_5FeC_5H_4$), 4.20 (s, 5, $C_5H_5FeC_5H_4$), 5.45 (d, 1, *J* = 3.0 Hz, C*H*OH), 7.24 (d, 1, *J* = 7.4 Hz, *p*-H in C_6H_5), 7.31 (dd, 2, *J* = 7.4 Hz, *m*-H in C_6H_5), 7.37 (d, 1, *J* = 7.4 Hz, *o*-H in C_6H_5). ^{13}C NMR (126 MHz, $CDCl_3$) δ 66.0, 67.4, 68.07, 68.13, 68.5, 71.9, 72.0, 94.2, 126.2, 127.4, 128.2, 143.2. The ee determined by chiral HPLC analysis was 95%: column, CHIRALCEL OD; eluent, 10:90 2-propanol–hexane; temp, 30 °C; flow rate, 1 mL/min; detection, 270-nm light; t_R of (*R*)-**6**, 11.1 min (2.5%); t_R of *S* isomer, 16.3 min (97.5%). $[\alpha]^{22}_D$ +92.14° (*c* 0.96, $CHCl_3$). The absolute configuration was determination as indicated in Part G.

(G) Determination of Absolute Configuration of Products

Absolute configuration of (*S*)-2c. A mixture of (*S*)-**2c** (404 mg, 2.0 mmol), (*R*)-1-naphthylethyl isocyanate (560 mg, 5.0 mmol), and 4-(dimethylamino)pyridine (305 mg, 2.5 mmol) in toluene (5.0 mL) was heated at 90 °C for 14 h. Usual aqueous workup followed by recrystallization from a 20:1 mixture of hexane and $CH_3COOC_2H_5$ gave the (*R*)-*N*-[1'-(1-naphthyl)ethyl]carbamate (639 mg, 1.6 mmol) in 80% yield, mp 115.0–115.8 °C. The stereochemistry was determined by single-crystal X-ray analysis (Figure 2). **Absolute configuration of (*S*)-2d.** The configuration was determined by comparison of its chiral HPLC behavior (see Part F) with that of a reference sample derived from (*S*)-**2e** as follows. Lithiation of the THP ether of (*S*)-**2e** (vide supra) (1.3 equiv of *n*-C_4H_9Li, THF, –78 °C, 1.5 h) followed by chlorination (5 equiv of *N*-chlorosuccinimide, THF, 28 °C, 4 h) afforded the THP ether of (*S*)-**2d** in 37% yield. Removal of THP group (0.1 equiv of *p*-toluenesulfonic acid, CH_3OH, 28 °C, 2 h) gave (*S*)-**2d** in 71% yield. **Absolute configuration of (*S*)-2e.** The structure was determined by transforming to (*S*)-**2a**. Protection of the hydroxy group of (*S*)-**2e** (1.3 equiv of 3,4-dihydro-2*H*-pyran, 0.1 equiv of pyridinium *p*-toluenesulfonate, CH_2Cl_2, 28 °C, 3 h) gave the THP ether in 94% yield. The THP ether was treated with 1.3 equiv of *n*-C_4H_9Li (THF, –78 °C, 2 h), and then with 5 equiv of CH_3I (THF, 28 °C,

3 h) followed by removal of THP group (0.1 equiv of *p*-toluenesulfonic acid, CH_3OH, 28 °C, 2 h) gave (*S*)-**2a** in 77% yield. HPLC (column, CHIRALCEL OB-H; eluent, 10:90 2-propanol–hexane; temp, 30 °C; flow rate, 0.5 mL/min; detection, 270-nm light); t_R of (*R*)-**2a**, 22.1 min (1.3%); t_R of *S* isomer, 25.0 min (98.7%). $[\alpha]^{21}_D$ +5.85° (*c* 0.77, $CHCl_3$). **Absolute configuration of (*S*)-9.** The absolute configuration was determined by the sign of rotation after converting to (*R*)-**10** (3 equiv of *n*-C_4H_9Li, THF, –78 °C, 10 min; workup with dil. HCl). HPLC (column, CHIRALCEL OB-H; eluent, 10:90 2-propanol–hexane; temp, 30 °C; flow rate, 0.5 mL/min; detection, 270-nm light); t_R of (*R*)-**10**, 21.2 min (98.9%); t_R of *S* isomer, 24.6 min (1.1%). $[\alpha]^{25}_D$ +7.73° (*c* 0.752, $CHCl_3$), lit. $[\alpha]^{25}_D$ –9.0° (*c* 0.7, $CHCl_3$), 100% ee, (*S*), Harada, N.; Fujita, K.; Watanabe, M. *Enantiomer* **1997**, *2*, 359–366. Recrystallization from a 1:20 mixture of $CH_3CO_2C_2H_5$ and hexane gave the (*R*)-**10** (96% recovery) in 99.7% ee, mp 59.5–60.7 °C, $[\alpha]_D^{25}$ +8.65° (*c* 0.780, $CHCl_3$). **Absolute configuration of (*S*)-6.** The stereochemistry was determined by single-crystal X-ray analysis after converting to the (2*R*,3*R*)-3-phenyl-2,3-epoxypropyl ether (Figure 3) according to the literature [(*S*)-**6** (146 mg, 0.50 mmol), (2*R*,3*R*)-3-phenylglycidyl tosylate (168 mg, 0.55 mmol), NaH (60% in mineral oil, 33 mg, 0.55 mmol), DMF (3.0 mL), 28 °C, 19 h, 97 mg (47% yield); recrystallized from a 20:1 mixture of hexane and $CH_3CO_2C_2H_5$; mp 80.1–80.3 °C; see Klunder, J. M.; Ko, S. Y.; Sharpless, K. B. *J. Org. Chem.* **1986**, *51*, 3710–3712].

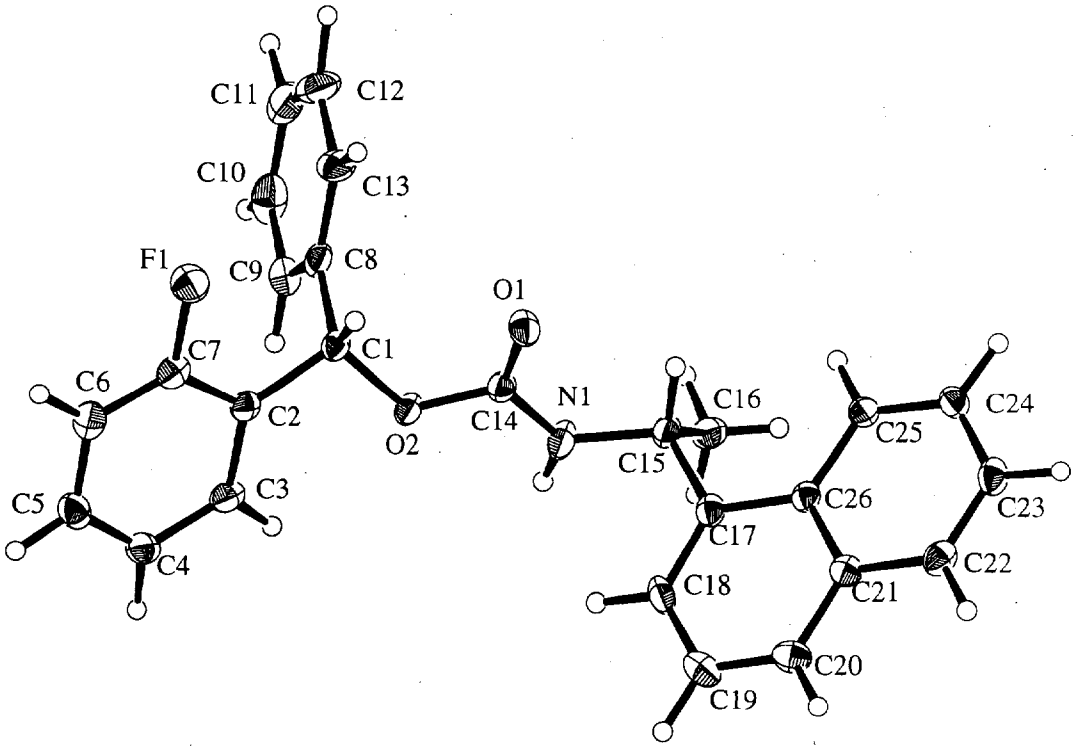

Figure 2. ORTEP plot of the molecular structure of (*S*)-2-fluorophenyl(phenyl)methyl (*R*)-*N*-[1'-(1-naphthyl)ethyl]carbamate. Crystallographic data: $C_{26}H_{22}FNO_2$, M_r = 399.46, colorless prisum, 0.2 x 0.3 x 0.4 mm, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 9.513(3), b = 31.096(3), c = 6.897(2) Å, V = 2040.3(9) Å^3, Z = 4, ρ_{calcd} = 1.300 g cm^{-3}, $\mu(MoK_\alpha)$ = 0.88 cm^{-1}, T = 150 K.

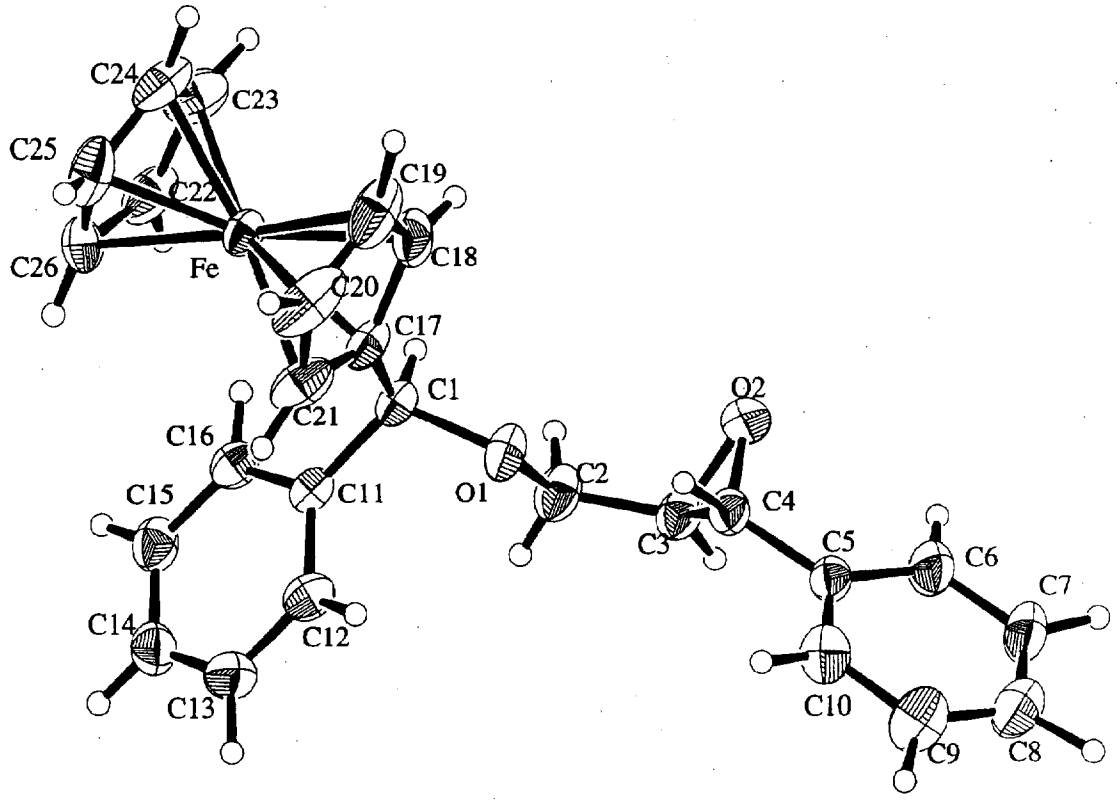

Figure 3. ORTEP plot of the molecular structure of (*S*)-ferrocenyl(phenyl)methyl (2*R*,3*R*)-3-phenyl-2,3-epoxypropyl ether. Crystallographic data: $C_{26}H_{25}FeO_2$, M_r = 425.33, pale orange prisum, 0.4 x 0.3 x 0.4 mm, orthorhombic, space group $P2_12_12_1$ (No. 19), a = 7.481(1), b = 10.2572(4), c = 27.3733(8) Å, V = 2100.5(3) Å^3, Z = 4, ρ_{calcd} = 1.345 g cm^{-3}, $\mu(MoK_\alpha)$ = 7.36 cm^{-1}, T = 295 K.

(H) Synthesis of (*S*)-Orphenadrine Hydrochloride

(*S*)-Orphenadrine [(*S*)-**7**] hydrochloride was synthesized according to the literature (van der Stelt, C.; Heus, W. J.; Nauta, W. T. *Arzneim.-Forsch.* **1969**, *19*, 2010–2012). Sodium hydride (60% in mineral oil, 255 mg, 2.1 mmol) was added to a mixture of (*S*)-**2a** (93% ee, 397 mg, 2.0 mmol) and 2-chloro-*N*,*N*-dimethylacetamide (126 mg, 2.1 mmol) in THF (5.0 mL) at 0 °C and then the reaction mixture was stirred at 25 °C for 4 h. It was poured into ice water and extracted with ether. The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. The crude compound was purified with silica-gel column (27 g), eluted with a 1:1 $CH_3CO_2C_2H_5$–hexane mixture. The eluate was evaporated under in vacuo to give dimethyaminocarbonylmethyl ether of (*S*)-**2a** (502 mg, 89% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.22 (s, 3, $C_6H_4CH_3$), 2.93 (s, 3, $N(CH_3)CH_3$), 2.96 (s, 3, $N(CH_3)CH_3$), 4.11 (d, 1, J = 13.7 Hz, $COCHH$), 4.19 (d, 1, J = 13.7 Hz, $COCHH$), 5.72 (s, 1, C_6H_5CHO), 7.1–7.5 (m, 9, aromatics). ^{13}C NMR (126 MHz, $CDCl_3$) δ 19.4, 35.4, 36.6, 67.9, 80.9, 126.0, 127.0, 127.6, 127.8, 128.3, 130.6, 136.1, 138.9, 140.4, 169.2. To a THF solution (5.0 mL) of the obtained ether (502 mg, 1.77 mmol) was added $LiAlH_4$ fractionally at 25 °C, and then the mixture was refluxed for 8 h. It was poured into ice water and was extracted with ether. The organic layer was dried with $MgSO_4$ and concentrated under reduced pressure. Addition of a 1.0 M ether solution of HCl (1.4 mL) to an ether solution (3.0 mL) of the crude (*S*)-**7** produced white precipitation. The collected powder was washed twice with $CH_3CO_2C_2H_5$ and dried under reduced pressure to give (*S*)-**7** as hydrochloride (272 mg, 50% yield). ^{1}H NMR (500 MHz, CD_3OD) δ 2.24 (s, 3, $C_6H_4CH_3$), 2.89 (s, 6, $N(CH_3)_2$), 3.35–3.45 (m, 2, NCH_2CH_2), 3.78 (t, 2, J = 4.9 Hz, NCH_2CH_2), 5.71 (s, 1, C_6H_5CHO), 7.1–7.5 (m, 9, aromatics). ^{13}C NMR (126 MHz, CD_3OD) δ 19.5, 43.9, 58.4, 63.8, 82.9, 127.1, 127.7, 128.86, 128.93, 129.0, 129.5, 131.7, 137.0, 140.1, 141.6. $[\alpha]^{25}_D$ +12.5° (*c* 0.54, CH_3OH), lit. $[\alpha]_D$ +15.2° (CH_3OH).