Supporting information

Enantioselective Mono-Reduction of 2-Alkyl-1,3-diketones Mediated by a Chiral Ruthenium Catalyst. Dynamic Kinetic Resolution

Florence Eustache, Peter I. Dalko, Janine Cossy*

Laboratoire de Chimie Organique associé au CNRS, ESPCI,

10 rue Vauquelin, 75231 - Paris Cedex 05- France.

General procedure for the reduction of 1,3-diketones

To a mixture of triethylamine (2 equiv.) and formic acid (5 equiv.) at 0 °C was added the diketone (1 equiv.). The mixture was degassed under vacuum by using the Schlenk method. A solution of (*R,R*)- or (*S,S*)-DPEN-RuCl-*p*-cymene (0.03M in CH₂Cl₂, 0.05 eq) was added to the mixture at rt and the reaction temperature was raised to 50 °C. The progress of the reaction was monitored by TLC. When the conversion of the starting material to β-hydroxyketone was complete, the mixture was washed with H₂O (3 times) and the combined aqueous phases were extracted with CH₂Cl₂ (3 times). The combined organic phases were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude product was purified by flash chromatography on silica gel.

4-(Benzyloxy)-3-hydroxy-2-methyl-1-phenylbutan-1-one (**2**) and (**2'**)

The reduction of diketone **1** (5.0 g, 17.73 mmol) by using a solution of (*R,R*)-DPEN-RuCl-*p*-cymene (0.03M in CH₂Cl₂, 5.91 mL, 0.177 mmol) afforded, after 1 night, 4.48 g (89%) of product as a mixture of *syn/anti* isomers (dr = 68:32). The isomers were separated by flash chromatography on silica gel (CH₂Cl₂/AcOEt: 95/5).

HPLC : Daicel Chiracel OD-H column; eluent: hexane/*i*-propanol: 98/2.

(2*R*,3*R*)-4-(Benzyloxy)-3-hydroxy-2-methyl-1-phenylbutan-1-one (2**)**: colorless oil, $[\alpha]_D^{20} -30^\circ$ (*c* 1.1, CH₂Cl₂) (93% ee); IR (neat) 3420, 1670, 1595, 1575, 1445, 1360, 1210 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.00-7.93 (m, 2H), 7.60-7.55 (m, 1H), 7.52-7.44 (m, 2H), 7.35-7.24 (m, 5H), 4.51 (s, 2H), 4.23 (m, 1H), 3.74 (qd, *J* = 7.2, 5.5 Hz, 1H), 3.57 (dd, *J* = 9.6, 5.1 Hz, 1H), 3.50 (dd, *J* = 9.6, 5.9 Hz, 1H), 2.91 (d, *J* = 4.4 Hz, 1H), 1.29 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 204.4, 137.8, 136.2, 133.3, 128.7 (2 C), 128.5 (2 C), 128.4 (2 C), 128.2, 127.7 (2 C), 73.4, 71.6, 71.1, 42.6, 12.8.

(2*R*,3*S*)-4-(Benzyloxy)-3-hydroxy-2-methyl-1-phenylbutan-1-one (2'**)**: colorless oil; $[\alpha]_D^{20} -36^\circ$ (*c* 1.0, CH₂Cl₂) IR (neat) 3420, 1670, 1595, 1575, 1445, 1360, 1210 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.00-7.94 (m, 2H), 7.63-7.56 (m, 1H), 7.52-7.44 (m, 2H), 7.36-7.22 (m, 5H), 4.54 (d, *J* = 11.9 Hz, 1H), 4.49 (d, *J* = 11.9 Hz, 1H), 4.10 (m, 1H), 3.83 (qd, *J* = 7.3 Hz, *J* = 6.1 Hz, 1H), 3.62 (dd, *J* = 9.7 Hz, *J* = 5.5 Hz, 1H), 3.57 (dd, *J* = 9.7 Hz, *J* = 4.9 Hz, 1H), 3.27 (d, *J* = 6.6 Hz, 1H), 1.25 (d, *J* = 7.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 205.1, 137.8, 136.7, 133.3 (2 C), 128.6 (2 C), 128.5 (2 C), 128.4 (2 C), 127.7 (2 C), 73.5, 73.0, 72.1, 42.1, 14.9.

2 and **2'** (mixture of diastereomers) MS (EI, 70 eV) *m/z* 285 (MH⁺, 33), 267 (20), 177 (70), 168 (22), 163 (25), 159 (23), 136 (37), 135 (100), 105 (48); HRMS Calculated for C₁₈H₂₁O₃ (MH⁺) 285.1491, Found: 285.1487.

3-Hydroxy-4-methoxy-2-methyl-1-phenylbutan-1-one (5) and (6)

The reduction of diketone **4** (0.1 g, 0.485 mmol), by using a solution of (*S,S*)-DPEN-RuCl-*p*-cymene afforded, after 45 min, an inseparable mixture of **5** and **6** [95.8 mg (96%) dr = 72:28]. Flash chromatography on silica gel (petroleum ether/AcOEt: 2/1).

HPLC: Daicel Chiracel OD-H column; eluent: hexane/*i*-propanol: 98/2.

(2*S*,3*S*)-3-Hydroxy-4-methoxy-2-methyl-1-phenylbutan-1-one (5): colorless oil, (92% ee); IR (neat) 3440, 1670, 1595, 1587, 1445, 1365 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.02-7.95 (m, 2H), 7.63-7.55 (m, 1H), 7.53-7.45 (m, 2H), 4.21-4.14 (m, 1H), 3.69 (qd, *J* = 7.2, 5.1 Hz, 1H), 3.47-3.38 (m, 2H), 3.35 (s, 3H), 2.84 (br s, 1H), 1.30 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 204.4, 136.2, 133.3, 128.7 (2 C), 128.4 (2 C), 74.0, 70.9, 59.0, 42.5, 12.6.

(2*S*,3*R*)-3-Hydroxy-4-methoxy-2-methyl-1-phenylbutan-1-one (6): colorless oil, (48% ee); IR (neat) 3440, 1670, 1595, 1587, 1445, 1365 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.02-7.95 (m, 2H), 7.63-7.55 (m, 1H), 7.53-7.45 (m, 2H), 4.12-4.03 (m, 1H), 3.79 (m, 1H), 3.53-3.48 (m, 2H), 3.36 (s, 3H), 1.62 (br s, 1H), 1.26 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 204.9, 136.7, 133.3, 128.6 (2 C), 128.5 (2 C), 74.6, 72.8, 59.1, 42.3, 14.7.

5 and **6** (mixture of diastereomers) MS (EI, 70 eV) *m/z* 209 (MH⁺, 64), 191 (16), 177 (100), 135 (68); HRMS Calculated for C₁₂H₁₇O₃ (MH⁺) 209.1178, Found: 209.1181.

3-Hydroxy-2-methyl-1-phenylbutan-1-one (8a) and (9a)

The reduction of diketone **7a** (0.2 g, 1.136 mmol), by using a solution of (*S,S*)-DPEN-RuCl-*p*-cymene afforded after 1 h, 169.3 mg (84%) of product as an inseparable mixture of *syn/anti* isomers (dr = 92:8). Flash chromatography on silica gel (petroleum ether/AcOEt: 4/1).

HPLC: Daicel Chiracel OD-H column; eluent: cyclohexane/*i*-propanol: 99/1.

(2*S*,3*R*)-3-Hydroxy-2-methyl-1-phenylbutan-1-one (8a): colorless oil, (96% ee); IR (neat) 3420, 1680 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.99-7.92 (m, 2H), 7.65-7.55 (m, 1H), 7.54-7.44 (m, 2H), 4.32-4.19 (m, 1H), 3.44 (qd, *J* = 6.7, 3.3 Hz, 1H), 3.16 (br s, 1H), 1.28 (d, *J* =

7.3 Hz, 3H), 1.24 (d, $J = 6.7$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 205.8, 135.9, 133.4, 128.7 (2 C), 128.4 (2 C), 67.4, 45.8, 20.3, 11.2.

(2S,3S)-3-hydroxy-2-methyl-1-phenylbutan-1-one (9a): colorless oil; IR (neat) 3420, 1680 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 7.99-7.92 (m, 2H), 7.65-7.55 (m, 1H), 7.54-7.44 (m, 2H), 4.17-4.06 (m, 1H), 3.56-3.40 (m, 1H), 3.16 (br s, 1H), 1.28 (d, $J = 6.6$ Hz, 3H), 1.22 (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 205.2, 136.4, 133.2, 128.6 (2 C), 127.4 (2 C), 69.8, 47.6, 20.7, 15.1.

8a and **9a** (mixture of diastereomers) MS (EI, 70 eV) m/z 179 (MH^+ , 100), 161 (12), 135 (52), 117 (11), 105 (57); HRMS Calculated for $\text{C}_{11}\text{H}_{15}\text{O}_2$ (MH^+): 179.1072; Found: 179.1071.

(2S,3R)-3-Hydroxy-2-methyl-1-phenylhept-6-en-1-one (8b)

The reduction of diketone **7b** (0.2 g, 0.926 mmol), by using a solution of (*S,S*)-DPEN-RuCl-*p*-cymene afforded, after 1 h, 175.6 mg (87%) of product as an inseparable mixture of *syn/anti* isomers **8b** and **9b** (dr = 91:9). Flash chromatography on silica gel (petroleum ether/AcOEt: 9/1).

HPLC : Daicel Chiracel OD-H column; eluent: cyclohexane/*i*-propanol: 95/5.

8b: colorless oil; (98% ee); IR (neat) 3415, 1675 cm^{-1} ; ^1H NMR (300 MHz, CDCl_3) δ 8.00-7.89 (m, 2H), 7.63-7.54 (m, 1H), 7.54-7.43 (m, 2H), 5.92-5.77 (m, 1H), 5.11-4.93 (m, 2H), 4.10-4.00 (m, 1H), 3.48 (qd, $J = 7.1, 3.1$, 1H), 3.20 (br s, 1H), 2.40-2.07 (m, 2H), 1.80-1.60 (m, 1H), 1.58-1.42 (m, 1H), 1.26 (d, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 205.6, 138.2, 133.4, 128.7 (2 C), 128.4 (2 C), 114.9, 70.8, 44.6, 33.5, 30.3, 11.2; MS (EI, 70 eV) m/z 219 (MH^+ , 100), 201 (15), 135 (6), 105 (10); HRMS Calculated for $\text{C}_{14}\text{H}_{19}\text{O}_2$ (MH^+): 219.1385; Found: 219.1382.

(2*S*,3*S*)-4-[[*(*Benzyloxy*)*carbonyl]amino]-3-hydroxy-2-methyl-1-phenylbutan-1-one
(8c)

The reduction of diketone **7c** (0.2 g, 0.308 mmol), by using a solution of (*S,S*)-DPEN-RuCl-*p*-cymene afforded, after 1 h, an inseparable mixture of *syn/anti* isomers **8c** and **9c** (dr = 83:17). The crude product was purified by silica gel column chromatography (petroleum ether/AcOEt: 2/1) to give 81.5 mg (81%) of product.

HPLC: Daicel Chiracel OJ-H column; eluent: hexane/*i*-propanol: 95/5.

8c: slightly brown colored oil; (89% ee); IR (neat) 3490, 1790 (2 C=O), 1530, 1450, 1205 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.98-7.90 (m, 2H), 7.64-7.54 (m, 1H), 7.52-7.43 (m, 2H), 7.41-7.30 (m, 5H), 5.27 (br s, 1H), 5.10 (s, 2H), 4.19-4.10 (m, 1H), 3.60-3.51 (m, 3H), 3.30-3.15 (m, 1H), 1.29 (d, *J* = 7.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 204.8, 157.0, 136.4, 135.5, 133.6 (2 C), 128.8 (2 C), 128.7 (2 C), 128.0, 128.2, 128.1, 128.0, 71.2, 66.88, 44.7, 43.0, 12.0; MS (EI, 70 eV) *m/z* 328 (MH⁺, 100), 310 (30), 284 (73), 194 (19), 135 (99); HRMS Calculated for C₁₉H₂₂O₄N (MH⁺): 328.1549; Found: 328.1550.

(2*S*,3*R*)-5-[(*tert*-Butoxycarbonyl)amino]-3-hydroxy-2-methyl-1-phenylpentan-1-one
(8d)

The reduction of diketone **7d** (0.1 g, 0.328 mmol), by using a solution of (*S,S*)-DPEN-RuCl-*p*-cymene afforded, after 1 h, an inseparable mixture of *syn/anti* isomers **8d** and **9d** [88.6 mg (88%), dr = 97:3]. Purification by silica gel column chromatography by using petroleum ether/AcOEt: 2/1.

HPLC: Daicel Chiracel OJ-H column; eluent: hexane/*i*-propanol: 95/5.

8d: slightly brown colored oil, (97% ee); IR (neat) 3380, 1680 (2 C=O), 1520, 1450, 1360, 1280, 1250, 1170 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.98-7.90 (m, 2H), 7.62-7.54 (m, 1H), 7.52-7.43 (m, 2H), 4.96 (br s, 1H), 4.05 (m, 1H), 3.74 (br s, 1H), 3.59-3.33 (m, 2H), 3.25-3.06 (m, 1H), 1.67-1.56 (m, 2H), 1.42 (s, 9H), 1.28 (d, *J* = 7.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 205.3, 154.6, 143.2, 136.0, 133.4, 128.7 (2 C), 128.4 (2 C), 125.5, 79.3, 69.7, 45.1, 37.7, 34.7, 28.3, 12.3. MS (EI, 70 eV) *m/z* 308 (MH⁺, 100), 252 (36), 135 (42), 127 (41), 118 (16); HRMS Calculated for C₁₇H₂₆O₄N (MH⁺): 308.1862; Found: 308.1860.

3-Hydroxy-2-methyl-1,3-diphenylpropan-1-one (11a) and (12a)

The reduction of diketone **10a** (0.2 g, 0.84 mmol), by using a solution of (*S,S*)-DPEN-RuCl-*p*-cymene afforded after 24 h an inseparable mixture of *syn/anti* isomers [76.6 mg (38%), dr = 67:33]. Purification by flash chromatography on silica gel by using pentane/AcOEt: 9/1.

HPLC: Daicel Chiracel OD-H column; eluent: hexane/*i*-propanol: 95/5.

(2*S*,3*S*)-3-Hydroxy-2-methyl-1,3-diphenylpropan-1-one (11a): (25% ee); IR (neat) 3450, 1780 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.05-7.90 (m, 2H), 7.70-7.20 (m, 8H), 5.25 (m, 1H), 3.72 (qd, *J* = 7.1, 3.1 Hz, 1H), 3.60 (br s, 1H), 1.21 (d, *J* = 7.1 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 205.6, 141.8, 133.6, 128.7 (2 C), 128.5 (3 C), 128.4 (2 C), 127.3, 126.0 (2 C), 73.1, 47.0, 11.6.

(2*S*,3*R*)-3-Hydroxy-2-methyl-1,3-diphenylpropan-1-one (12a): (25% ee); IR (neat) 3450, 1780 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 8.05-7.90 (m, 2H), 7.70-7.20 (m, 8H), 5.00 (d, *J* = 7.3 Hz, 1H), 3.86 (qd, *J* = 7.3, 7.3 Hz, 1H), 3.00 (br s, 1H), 1.08 (d, *J* = 7.3 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 204.9, 142.1, 136.7 (2 C), 133.3, 128.8 (2 C), 128.8 (3 C), 127.9, 126.7 (2 C), 76.7, 47.9, 15.6.

11a and 12a (mixture of diastereomers): MS (EI, 70 eV) *m/z* 241 (MH⁺, 40), 239 (30), 135 (100), 127 (39), 125 (22), 113 (23), 111 (36), 107 (86), 105 (70); HRMS Calculated for C₁₆H₁₇O₂ (MH⁺): 241.1229; Found: 241.1228.

1-Hydroxy-2, 4-dimethyl-1-phenylpentan-3-one (11b) and (12b)

The reduction of diketone **10b** (0.2 g, 0.98 mmol), by using a solution of (*S,S*)-DPEN-RuCl-*p*-cymene afforded, after 3 days, an inseparable mixture of *syn/anti* isomers **11b** and **12b** [72.7 mg (36%), dr = 66:34] as a colorless oil. Purification by flash chromatography on silica gel by using petroleum ether/AcOEt: 4/1.

HPLC: Daicel Chiracel OJ-H column; eluent: hexane/*i*-propanol: 98/2.

(2*S*,3*S*)-1-Hydroxy-2, 4-dimethyl-1-phenylpentan-3-one (11b): (91% ee); IR (neat) 3440, 1705 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.22 (m, 5H), 4.97 (d, *J* = 4.4 Hz, 1H), 3.15 (br s, 1H), 3.01 (qd, *J* = 6.8, 4.4 Hz, 1H), 2.56 (sept, *J* = 7.2 Hz, 1H), 1.10 (d, *J* = 7.2 Hz, 3H), 1.03 (d, *J* = 7.0 Hz, 3H), 0.96 (d, *J* = 6.8 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 219.3, 141.9, 128.2 (2 C), 127.4, 126.0 (2 C), 73.6, 50.8, 40.5, 17.9, 17.7, 11.2.

(2*S*,3*R*)-1-Hydroxy-2, 4-dimethyl-1-phenylpentan-3-one (12b): (18% ee); IR (neat) 3440, 1705 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.38-7.22 (m, 5H), 4.75 (m, 1H), 3.08 (qd, *J* = 7.2, 7.2 Hz, 1H), 2.65 (sept, *J* = 7.2 Hz, 1H), 1.60 (br s, 1H), 1.07 (d, *J* = 7.2 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 7.2 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 219.4, 142.4, 128.3 (2 C), 127.6, 126.4 (2 C), 76.8, 51.0, 41.3, 17.7, 17.6, 14.9.

11b and 12b (mixture of diastereomers): MS (EI, 70 eV) *m/z* 207 (MH⁺, 100), 205 (40), 189 (86), 171 (20), 119 (36), 107 (77); HRMS Calculated for C₁₃H₁₉O₂ (MH⁺): 207.1385; Found: 207.1380.

6-(Benzyloxy)-5-hydroxy-2,4-dimethylhexan-3-one (14) and (15)

The reduction of diketone **13** (0.15 g, 0.605 mmol), by using a solution of (*S,S*)-DPEN-RuCl-*p*-cymene afforded, after 16 h, at rt, 139.1 mg (92%) of product as a mixture of **14** and **15** (dr = 72:28). The diastereoisomers were separated by flash chromatography on silica gel (petroleum ether/ether: 1/1) to give **14** (100.2 mg) and **15** (39.0 mg) as colorless oils.

HPLC: Daicel Chiracel OJ-H column; eluent: hexane/*i*-propanol: 98/2.

(2*S*,3*S*)-6-(Benzyloxy)-5-hydroxy-2,4-dimethylhexan-3-one (14): colorless oil, [α]_D²⁰ +15° (*c* 2.3, CH₂Cl₂) (94% ee); IR (neat) 3440, 1705 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 7.40-7.25 (m, 5H), 4.53 (s, 2H), 4.08-4.00 (m, 1H), 3.48 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.42 (dd, *J* = 9.6, 6.2 Hz, 1H), 2.97 (qd, *J* = 7.0, 5.6 Hz, 1H), 2.76 (sept, *J* = 6.7 Hz, 1H), 2.74 (br s, 1H), 1.15 (d, *J* = 7.0 Hz, 3H), 1.09 (d, *J* = 6.7 Hz, 3H), 1.07 (d, *J* = 6.7 Hz, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 218.4, 137.8, 128.4 (2 C), 127.8 (3 C), 73.4, 71.6, 70.8, 46.0, 40.3, 18.1, 17.9, 12.0.

(2*S*,3*R*)-6-(Benzyloxy)-5-hydroxy-2,4-dimethylhexan-3-one (15): colorless oil; [α]_D²⁰ +20° (*c* 1.0, CH₂Cl₂) (85% ee); IR (neat) 3440, 1705 cm⁻¹; ¹H NMR (300 MHz, CDCl₃)

δ 7.40-7.27 (m, 5H), 4.57 (d, J = 11.8 Hz, 1H), 4.52 (d, J = 11.8 Hz, 1H), 3.89 (m, 1H), 3.51 (d, J = 5.1 Hz, 2H), 3.08 (br s, 1H), 3.02 (qd, J = 7.0, 7.0 Hz, 1H), 2.74 (sept, J = 7.2 Hz, 1H), 1.10 (d, J = 7.2 Hz, 6H), 1.07 (d, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 219.1, 137.8, 128.4 (2 C), 127.8, 127.4 (2 C), 73.5, 72.9, 72.2, 45.8, 41.0, 17.8 (2 C), 14.1.

14 and **15** (mixture of diastereomers) MS (EI, 70 eV) m/z 251 (MH^+ , 86), 233 (44), 143 (100), 125 (19), 119 (24), 101 (50); HRMS Calculated for $\text{C}_{15}\text{H}_{23}\text{O}_3$ (MH^+): 251.1647; Found: 251.1643.