CHEMISTRY
A EUROPEAN JOURNAL

Supporting Information

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Highly Enantioselective Hydrogenation of Enol Ester Phosphonates: A Versatile Procedure for the Preparation of Chiral β-Hydroxy Phosphonates

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Supporting Information

General Procedures. All reactions and manipulations were performed under nitrogen or argon, either in a Braun Labmaster 100 glovebox or using standard Schlenk-type techniques. All solvents were distilled under nitrogen using the following dessicants: Sodium-benzophenone-ketyl for diethylether (Et_2O) and tetrahydrofuran (THF); sodium for *n*-hexane and toluene; CaH_2 for dichloromethane (CH_2Cl_2) and NaOMe for methanol (MeOH). Rh catalyst precursors were prepared as described previously,[1] while β-ketophosphonates used in preparation of **1** were either commercially available (β-Me and β-Ph derivatives) or prepared from dimethylmethylphosphonate and an appropriate ester.[2] NMR spectra were obtained on Bruker DPX-300, DRX-400 or DRX-500 spectrometers. $^{31}P\{^1H\}$ NMR shifts were referenced to external 85 % H_3PO_4, while $^{13}C\{^1H\}$ and ^1H shifts were referenced to the residual signals of deuterated solvents. All data are reported in ppm downfield from Me_4Si. HPLC analyses were performed by using Waters 2690. HRMS data was obtained at the Instrumental Services of Universidad de Sevilla (CITIUS) using a Jeol JMS-SX 102A mass spectrometer. Optical rotations were measured on a Perkin-Elmer Model 341 polarimeter.

***Z*-2-benzoyloxy-1-dimethylphosphonyl-1-propene (1a).** To a solution of dimethyl-2-oxopropylphosphonate (4.62 g, 27.8 mmol) in THF (30 mL) was added NaH (1.11 g, 60 % w/w dispersion in mineral oil) in small portions. The mixture was stirred for 30 min afterwhich benzoyl chloride (3.2 mL, 27.8 mmol) was added slowly. The resulting mixture was stirred for 16 h and to the obtained suspension CH_2Cl_2 (50 mL) was added and then HCl (3 mL, 1M solution). Phases were separated and the aqueous one treated with CH_2Cl_2 (2 × 10 mL). Organic fractions were collected, dried over $MgSO_4$ and the solvent evaporated. The resulting residue was purified by column chromatography on silica (AcOEt/MeOH, 9:1), yielding **1a** as a colorless oil (3.21 g, 42 %). ^{1}H NMR ($CDCl_3$): δ 2.16 (s, 3H, Me), 3.57 (d, J_{HP} = 11.5 Hz, 6H, 2 OMe), 5.35 (d, J_{HP} = 11.0 Hz, 1H, =CH), 7.41 (t, J_{HH} = 7.5 Hz, 2H, 2 H arom), 7.54 (t, J_{HH} = 7.5 Hz, 1H, H arom), 8.04 (d, J_{HH} = 7.5 Hz, 2H, H arom). ^{31}P{^{1}H} NMR ($CDCl_3$): δ 15.4. ^{13}C{^{1}H} NMR ($CDCl_3$): δ 22.0 (d, J_{CP} = 15 Hz, Me), 52.3 (d, J_{CP} = 5 Hz, 2 OMe), 103.3 (d, J_{CP} = 191 Hz, =CH), 128.5 (2 CH arom), 129.0 (C_q arom), 130.3 (2 CH arom), 133.6 (CH arom), 163.9 (=CO), 164.0 (CO). Elem. Anal. Calcd for $C_{12}H_{15}O_5P$: C, 53.3; H, 5.6. Found: C, 53.0; H, 5.6.

General procedure for Enantioselective Hydrogenation

Olefins **1** were hydrogenated as detailed below for **1a**. In a glove box, a Fischer-Porter reactor (80 mL) was charged with **1a** (0.060 g, 0.22 mmol) and catalyst precursor [Rh(COD)(**4b**)]BF_4 (0.002 g, 0.002 mmol) in CH_2Cl_2 (5 mL). The vessel was brought outside the glove box, submitted to vacuum-hydrogen cycles and finally pressurized to 4 atm. The reaction mixture was kept on stirring for 24 h, then the reactor was depressurized, the mixture evaporated to dryness and conversion determined by ^{1}H NMR analysis of the resulting residue. Purification of the latter by column chromatography using EtOAc as eluent yielded **2a** as a colorless oil (0.054 g, 88 %). $[\alpha]_D^{20}$ = -3.7 (c 1.0, THF). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.48 (d, $^3J_{HH}$ = 6.3 Hz, 3H, CH_3), 2.15 (ddd, $^2J_{HP}$ = 18.6 Hz, $^2J_{HH}$ = 15.3 Hz, $^3J_{HH}$ = 6.9 Hz, 1H, PC*H*H), 2.37 (ddd, $^2J_{HP}$ = 19.2 Hz, $^2J_{HH}$ = 15.3 Hz, $^3J_{HH}$ = 6.0 Hz, 1H, PCH*H*), 3.70 (d, $^3J_{HP}$ = 6.6 Hz, 3H, OMe), 3.74 (d, $^3J_{HP}$ = 6.3 Hz, 3H, OMe), 5.39 (m, 1H, OCH), 7.39 (m, 2H, 2 H arom), 7.52 (m, 1H, H arom), 8.03 (m, 2H, 2 H arom). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121.5 MHz): δ 28.5. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 21.4 (d, J_{CP} = 8 Hz, CH_3), 32.2 (d, J_{CP} = 140 Hz, PCH_2), 52.7 (d, J_{CP} = 6 Hz, 2 OMe), 67.0 (OCH), 128.6 (2 CH arom), 129.8 (2 CH arom), 130.5 (C_q arom), 133.3 (CH arom), 165.9 (CO). Elem. Anal. Calcd for $C_{12}H_{17}O_5P$: C, 53.0; H, 6.3. Found: C, 52.5; H, 6.3. Enantiomeric excess was determined by chiral HPLC as detailed below.

2-benzoyloxy-1-dimethylphosphonylpropane (Chiralcel OJ, 30 °C, 1.0 mL/min, *n*-hexane/isopropanol: 90/10) *(S)* t_1 = 10.3 min, *(R)* t_2 = 12.3 min.

2-benzoyloxy-1-dimethylphosphonyl-3-methylbutane (Chiralpack AD, 30 °C, 1.0 mL/min, *n*-hexane/isopropanol: 95/5) *(S)* t_1 = 13.3 min, *(R)* t_2 = 14.3 min.

2-benzoyloxy-1-dimethylphosphonylhexane (Chiralpack AD, 30 °C, 1.0 mL/min, *n*-hexane/isopropanol: 95/5) *(S)* t_1 = 12.9 min, *(R)* t_2 = 13.9 min.

2-benzoyloxy-1-diethylphosphonyl-2-phenylethane (Chiralcel OJ, 30 °C, 1.0 mL/min, *n*-hexane/isopropanol: 97/3) *(S)* t_1 = 27.8 min, *(R)* t_2 = 35.5 min.

2-benzoyloxy-1-dimethylphosphonyl-2-(4-methoxyphenyl)ethane (Chiralcel OJ, 30 °C, 1.0 mL/min, *n*-hexane/isopropanol: 90/10) *(S)* t_1 = 30.6 min, *(R)* t_2 = 34.9 min.

2-benzoyloxy-1-dimethylphosphonyl-2-(β-naphthyl)ethane (Chiralcel OJ, 30 °C, 1.0 mL/min, *n*-hexane/isopropanol: 90/10) *(S)* t_1 = 30.0 min, *(R)* t_2 = 53.9 min.

2-benzoyloxy-3-(N-terc-butoxycarbonylamino)dimethylphosphonylpropane (Chiralpack AD, 30 °C, 1.0 mL/min, *n*-hexane/isopropanol: 90/10) *(R)* t_1 = 14.8 min, *(S)* t_2 = 17.3 min.

Phosphonates **2e** and **2g** were analyzed by chiral HPLC analysis of the corresponding alcohols **3** (see below).

General procedure for debenzoylation of 2.

Below is detailed procedure is exemplified below for **2g**. Na_2CO_3 (0.147 g, 1.4 mmol) is added to a solution of **2g** (0.141 g, 0.34 mmol) in MeOH (5 mL). The reaction mixture is stirred for 16 h and solvent evaporated. To the resulting mixture is added EtOAc (10 mL), and the mixture washed with saturated solutions of $NaHCO_3$ (10 mL) and NaCl (10 mL). Organic phase was then dried over $MgSO_4$, filtered and solvent evaporated. Residue was then purified by column chromatography (silica, AcOEt/MeOH 9:1) yielding **3g** as a colorless oil (0.055 g, 67 %, 99 % ee). $[\alpha]_D^{20}$ = -11.8 (c 1.2, THF). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 2.18 (m, 2H, PCH_2), 3.47 (brm, 1H, OH), 3.70 (d, $^3J_{HP}$ = 9.0 Hz, 3H, OMe), 3.74 (d, $^3J_{HP}$ = 9.0 Hz, 3H, OMe), 5.06 (ddd, $^3J_{HP}$ = 10.2 Hz, $^3J_{HH}$ = 10.2 Hz, $^3J_{HH}$ = 3.6 Hz, 1H, OCH), 7.24 (d, $^3J_{HH}$ = 8.1 Hz, 2H, 2 H arom), 7.44 (d, $^3J_{HH}$ = 8.4 Hz, 2H, 2 H arom). $^{31}P\{^1H\}$ NMR ($CDCl_3$, 121.5 MHz): δ 30.6. $^{13}C\{^1H\}$ NMR ($CDCl_3$, 75.5 MHz): δ 35.2 (d, J_{CP} = 137 Hz, PCH_2), 52.7 (d, J_{CP} = 7 Hz, OCH_3), 53.0 (d, J_{CP} = 6 Hz, OCH_3), 68.3 (d, J_{CP} = 4 Hz, OCH), 121.8 (C_q arom), 127.3 (2 CH arom), 131.6 (2 CH arom), 142.8 (d, J_{CP} = 16 Hz, C_q arom). HRMS (CI):

m/z 309.9787, $[M]^+$ (exact mass calcd for $C_{10}H_{14}BrO_4P$: 309.9792). Enantiomeric excess was determined by chiral HPLC as detailed below.

2-hydroxy-1-dimethylphosphonyl-2-(4-methylphenyl)ethane (Chiralcel OB, 30 °C, 1.0 mL/min, *n*-hexane/isopropanol: 97/3) *(S)* t_1 = 17.8 min, *(R)* t_2 = 20.3 min.

2-hydroxy-1-dimethylphosphonyl-2-(4-bromophenyl)ethane (Chiralcel OB, 30 °C, 1.0 mL/min, *n*-hexane/isopropanol: 97/3) *(S)* t_1 = 28.4 min, *(R)* t_2 = 36.4 min.

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