SUPPORTING INFORMATION

Highly Enantioselective Rhodium-Catalyzed Hydrogenation of β -Dehydroamino Acid Derivatives using Monodentate Phosphoramidites

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General Procedures.

All reactions were performed in a dry nitrogen or argon atmosphere using standard Schlenk techniques. Solvents were reagent grade, dried and distilled before use following standard procedures. ¹H-NMR, ¹³C-NMR and ³¹P-NMR spectra were recorded at room temperature in CDCl₃ on a Varian Gemini 200 (200 MHz) or a Varian VXR300 (300 MHz) spectrometers. Chemical shifts were determined relative to the residual solvent peaks (CHCl₃, δ = 7.26 ppm for proton atoms, δ = 77 ppm for carbon atoms; H₃PO₄, δ = 0 ppm for phosphorus atoms). Enantiomeric excesses were determined by capillary GC analysis with a CP-Chirasil-L-Val column (25.0 m x 250 μ m x 0.25 μ m) for **7** and with a CP-Chirasil-Dex-CB column (25.0 m x 250 μ m x 0.25 μ m) for **5a-f**.

Synthesis of Phosphoramidite (S)-2.

A solution of (S)-MonoPhos¹ (359 mg, 1 mmol), 1*H*-tetrazole (70 mg, 1 mmol) and benzylmethylamine (336 μ L, 2.6 mmol) in toluene (6 mL) was heated under reflux and a slight stream of nitrogen during 5 hours. After filtration over a small plug of silica and concentration of the solvent, the residue was subjected to column chromatography (SiO₂; 1:9 CH₂Cl₂/hexane) to afford (S)-**2** as a white foam (325 mg, 75%). [α]_D = +301.0 (c 0.37, CHCl₃); ¹H-NMR (300 MHz, CDCl₃) δ 8.03-7.85 (m, 4H), 7.63 (d, *J* = 9.0 Hz, 1H), 7.47-7.24 (m, 12H), 4.41 (dd, *J* = 15.0, 9.6 Hz, 1H), 4.00 (t, *J* = 14.3 Hz, 1H), 2.32 (d, *J* = 6.0 Hz, 3H) ppm; ¹³C-NMR (75.5 MHz, CDCl₃) δ 149.6 (d, *J* = 37.8 Hz, C), 138.2 (d, *J* = 3.7 Hz, C), 132.6 (d, *J* = 19.1 Hz, C), 131.0 (d, *J* = 52.5 Hz, C), 130.1 (d, *J* = 18.3 Hz, CH), 128.4 (s, CH), 128.3 (d, *J* = 7.3 Hz, CH), 128.1 (s, CH), 127.3 (s, CH), 126.9 (d, *J* = 7.3 Hz, CH), 126.0 (s, CH), 124.6 (d, *J* = 15.9 Hz, CH), 123.3 (d, *J* = 92.8 Hz, C), 121.9 (d, *J* = 14.6 Hz, CH), 53.2 (d, *J* = 34.2 Hz, CH₂), 32.1 (d, *J* = 8.5 Hz, CH₃) ppm; ³¹P-NMR (81 MHz, CDCl₃) δ 147.2 ppm; MS, *m/z* (%): 435 (87); HRMS for C₂₈H₂₂NO₂P, calcd: 435.1388, found: 435.1399.

Synthesis of Phosphoramidite (S,R)-3.

A solution of (S)-MonoPhos¹ (718 mg, 2 mmol), 1*H*-tetrazole (140 mg, 2 mmol) and (*R*)- α -methylbenzylamine (645 μ L, 5 mmol) in toluene (12 mL) was heated under reflux and a slightly stream of nitrogen during 6 hours. The mixture was filtered over a small plug of silica and concentrated to afford (*S,R*)-**3** as a white foam (836 mg, 96%). Further purification is possible by crystallization from toluene. [α]_D = +155.5 (c 0.33, CHCl₃); ¹H-NMR (300 MHz, CDCl₃) δ 7.99-7.87 (m, 3H), 7.78 (d, *J* = 13.2 Hz, 1H), 7.53 (d, *J* = 13.2 Hz, 1H), 7.45-7.20 (m, 11H), 6.78 (d, *J* = 13.2 Hz, 1H), 4.55 (m, 1H), 3.42 (d, *J* = 15.3 Hz, 1H), 1.53 (d, *J* = 10.2 Hz, 3H) ppm; ³¹P-NMR (81 MHz, CDCl₃) δ 151.5 ppm; MS, *m/z* (%): 435 (85); HRMS for C₂₈H₂₂NO₂P, calcd: 435.1388, found: 435.1397.

General Procedure for the Hydrogenation of Methyl 2-Acetamido Cinnamate (**6**).²

To a Schlenk tube equipped with septum and stirring bar, methyl 2-acetamido cinnamate (**6**, 43.9 mg, 0.2 mmol), Rh(COD)₂BF₄ (4.1 mg, 0.01 mmol) and the ligand (**1**, 7.85 mg, 0.022 mmol; **2-3**, 9.57 mg, 0.022 mmol) were added. After two vacuum/nitrogen and two vacuum/hydrogen cycles, CH₂Cl₂ (5 mL) was added through the septum and the reaction was left stirring at room temperature under ambient H₂ pressure during 4 hours (**1-2**) or 5 minutes (**3**). The mixture was filtered over a short silica column and subjected to conversion determination (¹H-NMR; full conversion) and ee determination (capillary GC, Chrompack Chirasil-L-Val [25.0 m x 250 μm x 0.25 μm], 160 °C; 93% [**1**], 95% [**2**], 90% [**3**] ee). Absolute configuration was determined by comparison with reference compound.

General Procedure for the Synthesis of (*E*)- and (*Z*)-β-(Acylamino)acrylates (**4a-f**).³

A solution of β-keto alkanoate (**8a-f**, 1.29 mL, 12 mmol) and NH₄OAc (4.62 g, 60 mmol) in MeOH (15 mL) was stirred at room temperature during 60 h. The solvent was evaporated under reduced pressure and CHCl₃ (30 mL) was added. The resulting solid was filtered off and washed with CHCl₃ (2 x 25 mL). The combined filtrate was washed with water (25 mL) and brine (25 mL), and dried over Na₂SO₄. Evaporation of the solvent gave the 3-amino-2-alkenoate (**9a-f**). A solution of **9a-f**, pyridine (2 mL, 24.8 mmol) and acetic anhydride (6 mL, 63.6 mmol) in THF (15 mL) was heated under reflux for 15 h. After partial evaporation of the solvent, the residue was dissolved in EtOAc (20 mL) and the solution was washed with water (10 mL), HCl (1M, 10 mL), NaHCO₃ (1M, 10 mL) and brine (10 mL). Then the solution was dried over Na₂SO₄, the solvent was evaporated under reduced pressure and the residue was subjected to column chromatography (SiO₂; 1:9 EtOAc/hexane) to afford (*E*) and/or (*Z*)-β-(acylamino)acrylates. Both isomers can be separated by silica gel column chromatography.

Methyl 3-Acetamido-2-butenolate.^{3c,d} 52% yield, Z/E = 1:1.3. (*Z*)-**4a**: ¹H-NMR (300 MHz, CDCl₃) δ 11.09 (br, 1H), 4.90 (s, 1H), 3.69 (s, 3H), 2.38 (s, 3H), 2.14 (s, 3H) ppm. (*E*)-**4a**: ¹H-NMR (300 MHz, CDCl₃) δ 7.45 (br, 1H), 6.76 (s, 1H), 3.67 (s, 3H), 2.35 (s, 3H), 2.11 (s, 3H) ppm.

Methyl 3-Acetamido-2-pentenoate.^{3c} 68% yield, Z/E = 1.2:1. (*Z*)-**4b**: ¹H-NMR (300 MHz, CDCl₃) δ 11.10 (br, 1H), 4.97 (s, 1H), 3.71 (s, 3H), 2.81 (q, *J* = 7.3 Hz, 2H), 2.15 (s, 3H), 1.13 (t, *J* = 7.3 Hz, 3H) ppm. (*E*)-**4b**: ¹H-NMR (300 MHz, CDCl₃) δ 6.79 (s, 1H), 6.63 (br, 1H), 3.68 (s, 3H), 2.75 (q, *J* = 7.5 Hz, 2H), 2.13 (s, 3H), 1.18 (t, *J* = 7.5 Hz, 3H) ppm.

Ethyl 3-Acetamido-2-butenolate.^{3a,c} 68% yield, Z/E = 2.6:1. (*Z*)-**4c**: ¹H-NMR (300 MHz, CDCl₃) δ 11.13 (br, 1H), 4.89 (s, 1H), 4.15 (q, *J* = 7.3 Hz, 2H), 2.38 (s, 3H), 2.14 (s, 3H), 1.28 (t, *J* = 7.3 Hz, 3H) ppm. (*E*)-**4c**: ¹H-NMR (300 MHz, CDCl₃) δ 6.85 (br, 1H), 6.74 (s, 1H), 4.12 (q, *J* = 7.2 Hz, 2H), 2.34 (s, 3H), 2.11 (s, 3H), 1.26 (t, *J* = 7.2 Hz, 3H) ppm.

Ethyl 4-Methyl-3-acetamido-2-pentenoate.^{3a,c} 65% yield, Z/E = 3:1. (*Z*)-**4d**: ¹H-NMR (300 MHz, CDCl₃) δ 11.20 (br, 1H), 5.06 (s, 1H), 4.16 (q, *J* = 7.0 Hz, 2H), 3.87 (m, 1H), 2.15 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H), 1.13 (d, *J* = 6.6 Hz, 6H) ppm. (*E*)-**4d**: ¹H-NMR (300 MHz, CDCl₃) δ 6.85 (s, 1H), 6.69 (br, 1H), 4.29 (m, 1H), 4.12 (q, *J* = 7.0 Hz, 2H), 2.14 (s, 3H), 1.26 (t, *J* = 7.1 Hz, 3H), 1.11 (d, *J* = 7.0 Hz, 6H) ppm.

Ethyl 3-Acetamido-3-phenyl-2-propenoate.^{3a,b} 55% yield. (*Z*)-**4e**: ¹H-NMR (300 MHz, CDCl₃) δ 10.65 (br, 1H), 7.37 (m, 5H), 5.28 (s, 1H), 4.22 (q, *J* = 7.2 Hz, 2H), 2.16 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H) ppm.

Methyl 3-Acetamido-3-(4-fluorophenyl)-2-propenoate.^{3b} 48% yield. (*Z*)-**4f**: ¹H-NMR (300 MHz, CDCl₃) δ 10.63 (br, 1H), 7.36 (m, 2H), 7.05 (t, *J* = 8.5 Hz, 2H), 5.25 (s, 1H), 3.77 (s, 3H), 2.18 (s, 3H) ppm.

General Procedure for the Hydrogenation of (*Z*)- β -(Acylamino)acrylates (**4a-f**).

In a Schlenk tube equipped with septum and stirring bar, a mixture of Rh(COD)₂BF₄ (5.1 mg, 12.5 μ mol) and ligand (*S,R*)-**3** (10.9 mg, 25 μ mol) was dissolved in CH₂Cl₂ (1.25 mL). In a glass tube, an aliquot of this solution (1 mL) was added over a mixture of (*Z*)-**4a-f** (0.5 mmol) in *i*-PrOH (4 mL). This small glass tube was placed in an autoclave with eight reactors (Endeavor™) and it was purged twice with nitrogen and once with hydrogen. Then, the autoclave was pressurized with H₂ to 10 bar and the reaction was stirred at room temperature. The resulting mixture was filtered over a short silica column and subjected to conversion (¹H-NMR) and ee determination (capillary GC). The configuration of products were *R* (**5a-d**) and *S* (**5e-f**), determined by comparing the sign of optical rotations with that of the reported ones.^{3b,c} Racemic products **5a-f** were prepared by hydrogenation of **4a-f** using 10% Pd/C (10%) in MeOH under 1 atm of H₂ for 16 hours.

General Procedure for the Hydrogenation of (*E*)- β -(Acylamino)acrylates (**4a-d**).

In a Schlenk tube equipped with septum and stirring bar, a mixture of Rh(COD)₂BF₄ (5.1 mg, 12.5 μ mol) and ligand (*S*)-**2** (10.9 mg, 25 μ mol) was dissolved in CH₂Cl₂ (1.25 mL). In a glass tube, an aliquot of this solution (1 mL) was added over a mixture of (*E*)-**4a-d** (0.5 mmol) in CH₂Cl₂ (4 mL). This small glass tube was placed in an autoclave with eight reactors (Endeavor™) and it was purged twice with nitrogen and once with hydrogen. Then, the autoclave was pressurized with H₂ to 10 bar and the reaction was stirred at room temperature. The resulting mixture was filtered over a short silica column and subjected to conversion (¹H-NMR) and ee determination (capillary GC). The configuration of products were *R* (**5a-d**), determined by comparing the sign of optical rotations with that of the reported ones.^{3c} Racemic products **5a-d** were prepared by hydrogenation of **4a-d** using 10% Pd/C (10%) in MeOH under 1 atm of H₂ for 16 hours.

Methyl 3-Acetamidobutanoate (5a).^{3c,d} ¹H-NMR (300 MHz, CDCl₃) δ 6.14 (br, 1H), 4.33 (m, 1H), 3.67 (s, 3H), 2.51 (d, *J* = 5.1 Hz, 2H), 1.94 (s, 3H), 1.20 (d, *J* = 7.0 Hz, 3H) ppm. GC (CP-Chirasil-Dex-CB column, 160 °C): (*S*) *t*_r = 11.08 min; (*R*) *t*_r = 11.27 min.

Methyl 3-Acetamidopentanoate (5b).^{3c} ¹H-NMR (300 MHz, CDCl₃) δ 6.06 (br, 1H), 4.15 (m, 1H), 3.67 (s, 3H), 2.52 (m, 2H), 1.96 (s, 3H), 1.55 (m, 2H), 0.90 (t, *J* = 7.3 Hz, 3H) ppm. GC (CP-Chirasil-Dex-CB column, 160 °C): (*S*) *t*_r = 11.78 min; (*R*) *t*_r = 11.88 min.

Ethyl 3-Acetamidobutanoate (5c).^{3a,c} ¹H-NMR (300 MHz, CDCl₃) δ 6.17 (br, 1H), 4.32 (m, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 2.48 (d, *J* = 5.1 Hz, 2H), 1.93 (s, 3H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.19 (d, *J* = 7.0 Hz, 3H) ppm. GC (CP-Chirasil-Dex-CB column, 160 °C): (*S*) *t*_r = 11.79 min; (*R*) *t*_r = 11.97 min.

Ethyl 4-Methyl-3-acetamidopentanoate (5d).^{3a,c} ¹H-NMR (300 MHz, CDCl₃) δ 6.05 (br, 1H), 4.12 (q, *J* = 7.1 Hz, 2H), 4.03 (m, 1H), 2.50 (d, *J* = 5.5 Hz, 2H), 1.97 (s, 3H), 1.80 (m, 1H), 1.25 (t, *J* = 7.1 Hz, 3H), 0.91 (d, *J* = 5.6 Hz, 6H) ppm. GC (CP-Chirasil-Dex-CB column, 160 °C): (*S*) *t*_r = 12.93 min; (*R*) *t*_r = 13.01 min.

Ethyl 3-Acetamido-3-phenyl-2-propanoate (5e).^{3a,b} ¹H-NMR (300 MHz, CDCl₃) δ 7.30-7.18 (m, 5H), 6.54 (d, *J* = 7.0 Hz, 1H), 5.38 (m, 1H), 4.01 (q, *J* = 7.0 Hz, 2H), 2.81 (m, 2H), 1.97 (s, 3H), 1.11 (t, *J* = 7.1 Hz, 3H) ppm. GC (CP-Chirasil-Dex-CB column, 160 °C): (*S*) *t*_r = 37.50 min; (*R*) *t*_r = 38.10 min.

Methyl 3-Acetamido-3-(4-fluorophenyl)-2-propanoate (5f).^{3b} ¹H-NMR (300 MHz, CDCl₃) δ 7.20 (m, 2H), 6.94 (t, *J* = 9.4 Hz, 2H), 6.63 (br, 1H), 5.33 (m, 1H), 3.56 (s, 3H), 2.80 (m, 2H), 1.95 (s, 3H) ppm. GC (CP-Chirasil-Dex-CB column, 160 °C): (*S*) *t*_r = 33.63 min; (*R*) *t*_r = 34.08 min.

References.

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Pulse Sequence: s2pul