Highly Enantioselective Conjugate Addition of Nitromethane to Chalcones Using Bifunctional Cinchona Organocatalysts

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General. Nuclear Magnetic Resonance spectra (NMR) were acquired on a Bruker DRX-500 (500 MHz) instrument using TMS or NH₃ as internal standard. ¹⁵N-NMR chemical shifts of the potential cinchona catalysts were obtained by ¹H-¹⁵N-HMBC experiments. All assignments are confirmed by 2D-COSY, 2D-HSC, 2D-HMBC and DNOE measurements. IR spectra were recorded on a Nicolet Avatar 320 FT-IR spectrophotometer and are reported in wavenumbers (cm⁻¹). Exact mass (HR-MS) spectra were recorded on a VG ZAB2-SEQ tandem mass spectrometer. Elemental analyses were performed with a Fisons EA 1108 instrument. For column chromatography, Merck Silica gel 60 and for flash chromatography Merck Silica gel 60H were employed. Enantiomer ratios were determined by chiral HPLC analysis using a Waters 600 and Waters 996 Photodiode Array Detector with a Chiralpak AD column (0.46 cm × 25 cm).

Materials. Hydroquinine, quinine, quinidine, and diisopropyl azodicarboxylate were purchased from Fluka. Diphenylphosphoryl azide and trans-chalcone were purchased from Aldrich Inc. Substituted chalcones^{1a-d} and amine substituted epiquinine², epiquinidine³ and quinine⁴ were prepared as described in literature. THF was distilled from sodium/benzophenone prior to use.

9-amino(9-deoxy)epihydroquinine (S1). Hydroquinine (3.26 g, 10.0 mmol) and triphenylphosphine (3.15 g, 12.0 mmol) were dissolved in 50 mL of dry THF and the solution was

cooled to 0 °C. Diisopropyl azodicarboxylate (2.43 g, 12.0 mmol) was added all at once. Then solution of diphenyl phosphoryl azide (3.30 g, 12.0 mmol) in 20 mL of dry THF was added dropwise at 0 °C. The mixture was allowed to warm to room temperature. After being stirred for 12 h, the solution was heated to 50 °C for 2 h. Then triphenylphosphine (3.41 g, 13.0 mmol) was added and heating was maintained until the gas evolution has ceased (2 h). The solution was cooled to room temperature, and 1 mL of water was added and the solution was stirred for 3 h. Solvents were removed *in vacuo* and the residue was dissolved in CH₂Cl₂ and 10% hydrochloric acid (1:1, 100 mL). The aqueous phase was washed with CH₂Cl₂ (4 × 50 mL). Then the aqueous phase was made alkaline with excess cc. aqueous ammonia and was washed with CH₂Cl₂ (4 × 50 mL). The combined organic phases were dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel (EtOAc/MeOH/cc. aq. NH₄OH = 50/50/1 as eluant) affording the title compound as a yellowish viscous oil. (2.30 g, 71%): $[\alpha]_D^{23} +71.8$ (*c* 0.97, CHCl₃);

¹H-NMR (500 MHz, CD₃OD, T = 310 K, $\delta_{TMS} = 0$ ppm) δ 8.69 (d, *J* = 4.7 Hz, 1H, H-2'), 7.97 (d, *J* = 9.3 Hz, 1H, H-8'), 7.69 (br s, 1H, H-5'), 7.61 (d, *J* = 4.7 Hz, 1H, H-3'), 7.45 (dd, *J* = 9.3, 2.6 Hz, 1H, H-7'), 4.72 (d, *J* = 11.0 Hz, 1H, H-9), 4.00 (s, 3H, OCH₃), 3.32 (dddd, *J* = 15.6, 10.5, 7.8, 2.3 Hz, 1H, H-6 α), 3.28 (dd, *J* = 13.6, 9.9 Hz, 1H, H-2-*exo*), 3.16 (pseudo q, *J* = 10.7 Hz, 1H, H-8), 2.79 (ddd, *J* = 15.6, 13.8, 4.9 Hz, 1H, H-6 β), 2.56 (ddd, *J* = 13.6, 4.7, 2.3 Hz, 1H, H-2-*endo*), 1.60 (unresolved partly overlapping signal, 1H, H-5 α), 1.60 (dd, *J* = 13.3, 10.4 Hz, 1H, H-7 α), 1.56 (br m, 1H, H-4), 1.53 (unresolved partly overlapping signal, 1H, H-5 β), 1.53 (ddd, *J* = 13.3, 10.4, 2.7 Hz, 1H, H-7 β), 1.47 (br m, 1H, H-3), 1.35 (m, 2H, CH₂CH₃), 0.85 (t, *J* = 7.3 Hz, 3H, CH₂CH₃) ppm; ¹³C-NMR (125 MHz, CD₃OD, T = 310 K, $\delta_{TMS} = 0$ ppm) δ 158.8 (C-6'), 148.3 (C-4'), 147.5 (C-2'), 144.2 (C-8a'), 130.6 (C-8'), 129.4 (C-4a'), 122.3 (C-7'), 120.2 (C-3'), 102.1 (C-5'), 62.2 (C-8), 57.8 (C-2), 55.2 (OCH₃), 51.9 (C-9), 40.8 (C-6), 37.8 (C-3), 28.6 (C-5), 27.6 (CH₂CH₃), 25.8 (C-7), 25.7 (C-4), 11.4 (CH₂CH₃) ppm; ¹⁵N-NMR (50 MHz, CD₃OD, T = 310 K, $\delta_{NH_3} = 0$ ppm) δ 25 (quinuclidine-N), 293 (quinoline-N), NH₂ could not be detected under the applied conditions. IR (CH₂Cl₂) ν 1622, 1507, 1473, 1433, 1265, 1032, 915, 737, 635 cm⁻¹; HRMS (EI) Exact mass calculated for C₂₀H₂₇N₃O [M]⁺ 325.2154;

Found: 325.2160. *Anal.* Calcd. for C₂₀H₂₇N₃O: C, 73.81; H, 8.36; N, 12.91; O, 4.92. Found: C, 73.75; H, 8.33; N, 12.75.

General Procedure for Preparing Thiourea Catalysts. Reaction of 9-amino(9-deoxy)epihydroquinine (S1) is typical.

To a solution of 9-amino(9-deoxy)epihydroquinine (**S1**, 2.20 g, 6.8 mmol) in dry THF (20 mL) was slowly added a solution of 3,5-bis(trifluoromethyl)phenyl isothiocyanate (1.84 g, 6.8 mmol) in 10 mL of dry THF at ambient temperature. The mixture was stirred overnight, and the solvent was removed *in vacuo*. The residue was purified by column chromatography on silica gel (EtOAc/MeOH/cc. aq. NH₄OH = 300/5/1 as eluant) affording thiourea **5b** (3.30 g, 81%) as an off-white amorphous solid.

5a. Amorphous solid. Yield: 88%. $[\alpha]_D^{25}$ -127.9 (c 0.50, CHCl₃); ¹H-NMR (500 MHz, CD₃OD, T = 310 K, δ_{TMS} = 0 ppm) δ 8.68 (d, J = 4.7 Hz, 1H, H-2'), 8.11 (br s, 2H, H-2''), 8.07 (br d, J = 2.6 Hz, 1H, H-5'), 7.95 (d, J = 9.3 Hz, 1H, H-8'), 7.59 (br s, 1H, H-4''), 7.55 (d, J = 4.7 Hz, 1H, H-3'), 7.44 (dd, J = 9.3, 2.6 Hz, 1H, H-7'), 6.32 (d, J = 11.0 Hz, 1H, H-9), 5.84 (ddd, J = 17.2, 10.5, 6.2 Hz, 1H, CH=CH₂), 5.02 (dt, J = 10.5,

1.5 Hz, 1H, CH=CH₂), 4.98 (dt, J = 17.2, 1.5 Hz, 1H, CH=CH₂), 4.03 (s, 3H, OCH₃), 3.56 (dddd, J = 15.6, 10.5, 7.8, 2.3 Hz, 1H, H-6 α), 3.39 (br pseudo q, J = 10.7 Hz, 1H, H-8), 3.29 (dd, J = 13.6, 9.9 Hz, 1H, H-2-*exo*), 2.82 (ddd, J = 15.6, 13.8, 4.9 Hz, 1H, H-6 β), 2.79 (ddd, J = 13.6, 4.7, 2.3 Hz, 1H, H-2-*endo*), 2.36 (br m, 1H, H-3), 1.70 (overlapping br m, 2H, H-5 α and H-5 β), 1.63 (br m, 1H, H-4), 1.45 (ddd, J = 13.3, 10.4, 2.7 Hz, 1H, H-7 β), 0.89 (dd, J = 13.3, 10.4 Hz, 1H, H-7 α) ppm; ¹³C-NMR (125 MHz, CD₃OD, T = 310 K, δ_{TMS} = 0 ppm) δ 181.6 (C=S), 158.7 (C-6'), 147.3 (C-2'), 146.6 (C-4'), 144.2 (C-8a'), 142.0 (C-1''), 141.5 (CH=CH₂), 131.8 (q, ² J_{CF} = 33.0 Hz, C-3''), 130.3 (C-8'), 129.2 (C-4a'), 123.6 (q, ¹ J_{CF} = 272.2 Hz, CF₃), 122.7 (C-7'), 122.6 (C-2''), 120.2 (C-3'), 116.9 (sept, ³ J_{CF} = 3.7 Hz, C-4''), 114.0 (CH=CH₂), 103.3 (C-5'), 60.7 (C-8), 55.8 (C-2), 55.5 (OCH₃), 55.4 (C-9), 41.8 (C-6), 39.7 (C-3), 27.8 (C-4), 27.7 (C-5), 25.9 (C-7) ppm; ¹⁵N-NMR (50

MHz, CD₃OD, T = 310 K, $\delta_{\text{NH}_3} = 0$ ppm) δ 25 (quinuclidine-N), 294 (quinoline-N), 131 (N_A), 125 (N_B) ppm; IR (KBr) ν 1623, 1510, 1474, 1384, 1278, 1179, 1133, 850, 683 cm⁻¹; HRMS (EI) Exact mass calculated for C₂₉H₂₈F₆N₄OS [M]⁺ 594.1888; Found: 594.1878.

5b Amorphous solid. Yield: 81%. $[\alpha]_{\text{D}}^{25} -124.6$ (c 0.50, CHCl₃); ¹H-NMR (500 MHz, CD₃OD, T = 310 K, $\delta_{\text{TMS}} = 0$ ppm) δ 8.69 (d, $J = 4.7$ Hz, 1H, H-2'), 8.11 (br s, 2H, H-2''), 8.08 (br d, $J = 2.6$ Hz, 1H, H-5'), 7.96 (d, $J = 9.3$ Hz, 1H, H-8'), 7.59 (br s, 1H, H-4''), 7.57 (d, $J = 4.7$ Hz, 1H, H-3'), 7.44 (dd, $J = 9.3$,

2.6 Hz, 1H, H-7'), 6.33 (d, $J = 11.0$ Hz, 1H, H-9), 4.03 (s, 3H, OCH₃), 3.57 (dddd, $J = 15.6, 10.5, 7.8, 2.3$ Hz, 1H, H-6 α), 3.37 (pseudo q, $J = 10.7$ Hz, 1H, H-8), 3.29 (dd, $J = 13.6, 9.9$ Hz, 1H, H-2-exo), 2.82 (ddd, $J = 15.6, 13.8, 4.9$ Hz, 1H, H-6 β), 2.53 (ddd, $J = 13.6, 4.7, 2.3$ Hz, 1H, H-2-endo), 1.70 (overlapping br m, 2H, H-5 α and H-5 β), 1.53 (br m, 1H, H-3), 1.40 (br m, 1H, H-4), 1.38 (ddd, $J = 13.3, 10.4, 2.7$ Hz, 1H, H-7 β), 1.32 (m, 2H, CH₂CH₃), 0.86 (t, $J = 7.3$ Hz, 3H, CH₂CH₃), 0.70 (dd, $J = 13.3, 10.4$ Hz, 1H, H-7 α), ppm; ¹³C-NMR (125 MHz, CD₃OD, T = 310 K, $\delta_{\text{TMS}} = 0$ ppm) δ 181.6 (C=S), 158.7 (C-6'), 147.3 (C-2'), 146.7 (C-4'), 144.2 (C-8a'), 142.1 (C-1''), 131.8 (q, $^2J_{\text{CF}} = 33.0$ Hz, C-3''), 130.3 (C-8'), 129.2 (C-4a'), 123.6 (q, $^1J_{\text{CF}} = 272.2$ Hz, CF₃), 122.7 (coalesced lines, C-2'' and C-7'), 120.2 (C-3'), 116.9 (br signal, $^3J_{\text{CF}} = 3.7$ Hz, C-4''), 103.3 (C-5'), 60.6 (C-8), 57.5 (C-2), 55.5 (OCH₃), 55.3 (C-9), 41.9 (C-6), 37.4 (C-3), 28.3 (C-5), 27.4 (CH₂CH₃), 25.7 (C-7), 25.5 (C-4), 11.5 (CH₂CH₃) ppm; ¹⁵N-NMR (50 MHz, CD₃OD, T = 310 K, $\delta_{\text{NH}_3} = 0$ ppm) δ 25 (quinuclidine-N), 294 (quinoline-N), 131 (N_A), 125 (N_B) ppm; IR (KBr) ν 1623, 1510, 1474, 1385, 1278, 1181, 1135, 681 cm⁻¹; HRMS (EI) Exact mass calculated for C₂₉H₃₀F₆N₄OS [M]⁺ 596.2045; Found: 596.2038.

6. Amorphous solid. Yield: 67%. $[\alpha]_D^{25} +28.6$ (c 0.50, CHCl_3); ^1H -NMR (500 MHz, CD_3OD , $T = 310$ K, $\delta_{\text{TMS}} = 0$ ppm) δ 8.70 (d, $J = 4.7$ Hz, 1H, H-2'), 8.16 (br d, $J = 2.6$ Hz, 1H, H-5'), 8.00 (br s, 2H, 2H-2''), 7.95 (d, $J = 9.3$ Hz, 1H, H-8'), 7.61 (br s, 1H, H-4''), 7.58 (d, $J = 4.7$ Hz, 1H, H-3'), 7.42 (dd, $J = 9.3, 2.6$ Hz, 1H, H-7'), 6.83 (d, $J = 11.0$ Hz, 1H, H-9), 6.04 (ddd, $J = 17.2, 10.5, 6.2$ Hz, 1H, $\text{CH}=\text{CH}_2$), 5.12 (dt, $J = 10.5, 1.5$ Hz, 1H, $\text{CH}=\text{CH}_2$), 5.09 (dt, $J = 17.2, 1.5$ Hz, 1H, $\text{CH}=\text{CH}_2$), 4.02 (s, 3H, OCH_3), 3.69 (br pseudo q, $J = 10.7$ Hz, 1H, H-8), 3.13 (dddd, $J = 15.6, 10.5, 7.8, 2.3$ Hz, 1H, H-6 α), 3.02 (dd, $J = 13.6, 9.9$ Hz, 1H, H-2-*exo*), 2.71 (ddd, $J = 13.6, 4.7, 2.3$ Hz, 1H, H-2-*endo*), 2.57 (ddd, $J = 15.6, 13.8, 4.9$ Hz, 1H, H-6 β), 2.35 (br m, 1H, H-3), 2.09 (closely coupled m, 1H, H-7 β), 2.05 (closely coupled m, 1H, H-7 α), 1.96 (unresolved partly overlapping signal, 1H, H-5 α), 1.88 (pseudo sext, $J = 3.3$ Hz, 1H, H-4), 1.60 (unresolved partly overlapping signal, 1H, H-5 β) ppm; ^{13}C -NMR (125 MHz, CD_3OD , $T = 310$ K, $\delta_{\text{TMS}} = 0$ ppm) δ 182.6 (C=S), 158.9 (C-6'), 147.4 (C-2'), 146.4 (C-4'), 144.5 (C-8a'), 141.9 ($\text{CH}=\text{CH}_2$), 141.5 (C-1''), 131.9 (q, $^2J_{\text{CF}} = 33.0$ Hz, C-3''), 130.3 (C-8'), 129.1 (C-4a'), 123.6 (q, $^1J_{\text{CF}} = 272.2$ Hz, CF_3), 123.0 (C-2''), 122.9 (C-7'), 119.7 (C-3'), 117.2 (br signal, $^3J_{\text{CF}} = 3.7$ Hz, C-4''), 114.0 ($\text{CH}=\text{CH}_2$), 103.2 (C-5'), 59.1 (C-8), 56.0 (OCH_3), 55.7 (C-2), 54.2 (C-9), 41.8 (C-6), 39.8 (C-3), 28.0 (C-4), 27.3 (C-5), 24.4 (C-7) ppm; ^{15}N -NMR (50 MHz, CD_3OD , $T = 310$ K, $\delta_{\text{NH}_3} = 0$ ppm) δ 27 (quinuclidine-N), 293 (quinoline-N), 128 (N_A), 124 (N_B) ppm; IR (KBr) ν 1623, 1542, 1513, 1474, 1385, 1278, 1178, 1134, 955, 847, 681 cm^{-1} ; MS (FAB) Mass calculated for $\text{C}_{29}\text{H}_{28}\text{F}_6\text{N}_4\text{OS}$ $[\text{M}+\text{H}]^+$ 595; Found: 595; HRMS (EI) Exact mass calculated for $\text{C}_{29}\text{H}_{28}\text{F}_5\text{N}_4\text{OS}$ $[\text{M}-\text{F}]^+$ 575.1904; Found: 575.1892.

7. Amorphous solid. Yield: 69%. $[\alpha]_D^{25} +225.3$ (c 0.50, CHCl_3); ^1H -NMR (500 MHz, CD_3OD , $T = 310$ K, $\delta_{\text{TMS}} = 0$ ppm) δ 8.67 (d, $J = 4.7$ Hz, 1H, H-2'), 8.11 (br s, 2H, 2H-2''), 8.03 (br d, $J = 2.6$ Hz, 1H, H-5'), 7.94 (d, $J = 9.3$ Hz, 1H, H-8'), 7.59 (br s, 1H, H-4''), 7.56 (d, $J = 4.7$ Hz, 1H, H-3'), 7.43 (dd, $J = 9.3, 2.6$ Hz, 1H, H-7'), 6.35

(d, $J = 11.0$ Hz, 1H, H-9), 5.96 (ddd, $J = 17.2, 10.5, 6.2$ Hz, 1H, $\text{CH}=\text{CH}_2$), 5.22 (dt, $J = 10.5, 1.5$ Hz, 1H, $\text{CH}=\text{CH}_2$), 5.15 (dt, $J = 17.2, 1.5$ Hz, 1H, $\text{CH}=\text{CH}_2$), 4.03 (s, 3H, OCH_3), 3.04 (dd, $J = 13.6, 9.9$ Hz, 1H, H-2-*exo*), 3.34 (ddd, $J = 13.6, 4.7, 2.3$ Hz, 1H, H-2-*endo*), 3.33 (pseudo q, $J = 10.7$ Hz, 1H, H-8), 3.01 (m, 2H, H-6 α and H-6 β), 2.37 (br m, 1H, H-3), 1.63 (br m, 1H, H-4), 1.60 (overlapping br m, 2H, H-5 α and H-5 β), 1.23 (ddd, $J = 13.3, 10.4, 2.7$ Hz, 1H, H-7 β), 1.03 (dd, $J = 13.3, 10.4$ Hz, 1H, H-7 α) ppm; ^{13}C -NMR (125 MHz, CD_3OD , $T = 310$ K, $\delta_{\text{TMS}} = 0$ ppm) δ 181.7 (C=S), 158.6 (C-6'), 147.3 (C-2'), 146.9 (C-4'), 144.2 (C-8a'), 142.1 (C-1''), 140.8 ($\text{CH}=\text{CH}_2$), 131.8 (q, $^2J_{\text{CF}} = 33.0$ Hz, C-3''), 130.2 (C-8'), 129.2 (C-4a'), 123.7 (q, $^1J_{\text{CF}} = 272.2$ Hz, CF_3), 122.9 (C-2''), 122.7 (coalesced lines, C-3' and C-7'), 116.9 (br signal, $^3J_{\text{CF}} = 3.7$ Hz, C-4''), 114.3 ($\text{CH}=\text{CH}_2$), 103.8 (C-5'), 60.7 (C-8), 55.5 (OCH_3), 54.6 (C-9), 49.2 (C-6), 47.6 (C-2), 39.2 (C-3), 27.7 (C-4), 26.4 (C-5), 25.5 (C-7) ppm; ^{15}N -NMR (50 MHz, CD_3OD , $T = 310$ K, $\delta_{\text{NH}_3} = 0$ ppm) δ 25 (quinuclidine-N), 294 (quinoline-N), 131 (N_A), 124 (N_B) ppm; IR (KBr) ν 1622, 1511, 1475, 1384, 1278, 1172, 1131, 1033, 886, 682 cm^{-1} ; HRMS (EI) Exact mass calculated for $\text{C}_{29}\text{H}_{28}\text{F}_6\text{N}_4\text{OS}$ $[\text{M}]^+$ 594.1888; Found: 594.1878.

Representative procedure for enantioselective Michael addition of nitromethane to chalcones.

Reaction of p-fluorochalcone **2c** is typical.

Toluene (3.0 mL), p-fluorochalcone **2c** (1.13 g, 5.0 mmol) and nitromethane (**1**) (5.0 eq, 1.53 g) were loaded in capped vial. Then thiourea catalyst **5b** (298 mg, 0.50 mmol) was added to the mixture and stirring was maintained for 122 h at room temperature. The volatiles were removed *in vacuo* and the residue was purified by column chromatography on silica gel (hexane/EtOAc = 3/1 as eluant) affording Michael adduct **3c** as a white solid.

3a.⁵ (Only 3.0 eq of nitromethane was added.) $[\alpha]_{\text{D}}^{25} +26.7$ (c 1.00, CHCl_3 , 96% ee); ^1H -NMR (500 MHz, CDCl_3 , $T = 300$ K, $\delta_{\text{TMS}} = 0$ ppm) δ 7.93 (d, $J = 7.9$ Hz, 2H, H-2' and H-6'), 7.59 (t, $J = 7.2$ Hz, 1H, H-4'), 7.47 (t, $J = 7.2$ Hz, 2H, H-3' and H-5'), 7.35 (t, $J = 7.2$ Hz, 2H, H-3 and H-5), 7.31 (d, $J = 7.2$ Hz, 2H, H-2 and H-6), 7.28 (t, $J = 7.2$ Hz, 1H, H-4), 4.85 (ABX, $J_{\text{AB}} = 12.6$ Hz, $J_{\text{AX}} = 6.6$ Hz, $J_{\text{BX}} = 8.1$ Hz, 1H, CH_2NO_2), 4.71 (ABX, $J_{\text{AB}} = 12.6$ Hz, $J_{\text{AX}} = 6.6$ Hz, $J_{\text{BX}} = 8.1$

Hz, 1H, CH₂NO₂), 4.25 (br pseudo quintet, $J = 7.1$ Hz, 1H, CH), 3.49 (ABX, $J_{AB} = 17.4$ Hz, $J_{AX} = 6.5$ Hz, $J_{BX} = 8.0$ Hz, 1H, CH₂CO), 3.45 (ABX, $J_{AB} = 17.4$ Hz, $J_{AX} = 6.5$ Hz, $J_{BX} = 8.0$ Hz, 1H, CH₂CO) ppm; ¹³C-NMR (125 MHz, CDCl₃, T = 300 K, $\delta_{TMS} = 0$ ppm) δ 196.8 (C=O), 139.1 (C-1), 136.4 (C-1'), 133.5 (C-4'), 129.0 (C-3,5), 128.7 (C-3',5'), 128.0 (C-2',6'), 127.8 (C-4), 127.4 (C-2,6), 79.5 (CH₂NO₂), 41.5 (CH₂CO), 39.3 (CH) ppm; ¹⁵N-NMR (50 MHz, CDCl₃, T = 300 K, $\delta_{NH_3} = 0$ ppm) δ 383 (NO₂) ppm; 96% ee Enantioselectivity was determined by HPLC analysis with a Chiralpak AD column, 10% isopropyl alcohol in hexane, 1.0 mL/min, $\lambda = 254$ nm, retention times minor 14.9 min, major 19.8 min.

3b.⁶ The crude product was purified by flash chromatography on silica gel (hexane/ EtOAc = 3/1 as eluant). ¹H-NMR (500 MHz, CDCl₃, T = 300 K, $\delta_{TMS} = 0$ ppm) δ 7.92 (d, $J = 7.9$ Hz, 2H, H-2' and H-6'), 7.59 (t, $J = 7.2$ Hz, 1H, H-4'), 7.47 (t, $J = 7.2$ Hz, 2H, H-3' and H-5'), 7.31 (t, $J = 8.0$ Hz, 2H, H-3 and H-5), 7.24 (d, $J = 8.0$ Hz, 2H, H-2 and H-6), 4.82 (ABX, $J_{AB} = 12.6$ Hz, $J_{AX} = 6.6$ Hz, $J_{BX} = 8.1$ Hz, 1H, CH₂NO₂), 4.67 (ABX, $J_{AB} = 12.6$ Hz, $J_{AX} = 6.6$ Hz, $J_{BX} = 8.1$ Hz, 1H, CH₂NO₂), 4.23 (br pseudo quintet, $J = 7.1$ Hz, 1H, CH), 3.46 (ABX, $J_{AB} = 17.4$ Hz, $J_{AX} = 6.5$ Hz, $J_{BX} = 8.0$ Hz, 1H, CH₂CO), 3.43 (ABX, $J_{AB} = 17.4$ Hz, $J_{AX} = 6.5$ Hz, $J_{BX} = 8.0$ Hz, 1H, CH₂CO) ppm; ¹³C-NMR (125 MHz, CDCl₃, T = 300 K, $\delta_{TMS} = 0$ ppm) δ 196.5 (C=O), 137.6 (C-1), 136.2 (C-1'), 133.7 (C-4'), 132.2 (C-4), 129.2 (C-3,5), 128.9 (C-2,6), 128.7 (C-3',5'), 128.0 (C-2',6'), 79.3 (CH₂NO₂), 41.3 (CH₂CO), 38.7 (CH) ppm; ¹⁵N-NMR (50 MHz, CDCl₃, T = 300 K, $\delta_{NH_3} = 0$ ppm) δ 383 (NO₂) ppm; 95% ee Enantioselectivity was determined by HPLC analysis with a Chiralpak AD column, 10% isopropyl alcohol in hexane, 1.0 mL/min, $\lambda = 254$ nm, retention times minor 17.9 min, major 25.5 min.

3c. Slightly yellow oil. $[\alpha]_D^{25} +26.7$ (c 1.00, CHCl₃, 98% ee); mp 42-43 °C; ¹H-NMR (500 MHz, CDCl₃, T = 300 K, $\delta_{TMS} = 0$ ppm) δ 7.93 (d, $J = 7.9$ Hz, 2H, H-2' and H-6'), 7.59 (t, $J = 7.2$ Hz, 1H, H-4'), 7.47 (t, $J = 7.2$ Hz, 2H, H-3' and H-5'), 7.28 (dd, $J = 8.7, 5.3$ Hz, 2H, H-2 and H-6), 7.03 (t, $J = 8.7$ Hz, 2H, H-3 and H-5), 4.83 (ABX, $J_{AB} = 12.6$ Hz, $J_{AX} = 6.6$ Hz,

$J_{\text{BX}} = 8.1$ Hz, 1H, CH_2NO_2), 4.67 (ABX, $J_{\text{AB}} = 12.6$ Hz, $J_{\text{AX}} = 6.6$ Hz, $J_{\text{BX}} = 8.1$ Hz, 1H, CH_2NO_2), 4.24 (br pseudo quintet, $J = 7.1$ Hz, 1H, CH), 3.46 (ABX, $J_{\text{AB}} = 17.4$ Hz, $J_{\text{AX}} = 6.5$ Hz, $J_{\text{BX}} = 8.0$ Hz, 1H, CH_2CO), 3.43 (ABX, $J_{\text{AB}} = 17.4$ Hz, $J_{\text{AX}} = 6.5$ Hz, $J_{\text{BX}} = 8.0$ Hz, 1H, CH_2CO) ppm; ^{13}C -NMR (125 MHz, CDCl_3 , T = 300 K, $\delta_{\text{TMS}} = 0$ ppm) δ 196.6 (C=O), 162.2 (d, $^1J_{\text{CF}} = 246.5$ Hz, C-4), 136.3 (C-1'), 134.9 (d, $^4J_{\text{CF}} = 3.7$ Hz, C-1), 133.6 (C-4'), 129.1 (d, $^3J_{\text{CF}} = 8.2$ Hz, C-2,6), 128.8 (C-3',5'), 128.0 (C-2',6'), 116.0 (d, $^2J_{\text{CF}} = 21.1$ Hz, C-3,5), 79.6 (CH_2NO_2), 41.5 (CH_2CO), 38.6 (CH) ppm; ^{15}N -NMR (50 MHz, CDCl_3 , T = 300 K, $\delta_{\text{NH}_3} = 0$ ppm) δ 382 (NO_2) ppm; IR (KBr) ν 1685, 1545, 1512, 1364, 1230, 1162, 840, 685, 557 cm^{-1} ; *Anal.* Calcd. for $\text{C}_{16}\text{H}_{14}\text{FNO}_3$: C, 66.89; H, 4.91; F, 6.61; N, 4.88; O, 16.71. Found: C, 67.01; H, 5.18; N, 4.79. Enantioselectivity was determined by HPLC analysis with a Chiralpak AD column, 10% isopropyl alcohol in hexane, 1.0 mL/min, $\lambda = 254$ nm, retention times minor 16.8 min, major 23.1 min.

3d. Slightly yellow oil. $[\alpha]_{\text{D}}^{25} +40.1$ (c 1.00, CHCl_3 , 89% ee); ^1H -NMR (500 MHz, CDCl_3 , T = 300 K, $\delta_{\text{TMS}} = 0$ ppm) δ 7.93 (d, $J = 7.9$ Hz, 2H, H-2' and H-6'), 7.59 (t, $J = 7.2$ Hz, 1H, H-4'), 7.47 (t, $J = 7.2$ Hz, 2H, H-3' and H-5'), 7.14-7.23 (m, 4H, H-2-5), 4.80 (ABX, $J_{\text{AB}} = 12.6$ Hz, $J_{\text{AX}} = 6.6$ Hz, $J_{\text{BX}} = 8.1$ Hz, 1H, CH_2NO_2), 4.68 (ABX, $J_{\text{AB}} = 12.6$ Hz, $J_{\text{AX}} = 6.6$ Hz, $J_{\text{BX}} = 8.1$ Hz, CH_2NO_2), 4.55 (br pseudo quintet, $J = 7.1$ Hz, 1H, CH), 3.49 (ABX, $J_{\text{AB}} = 17.4$ Hz, $J_{\text{AX}} = 6.5$ Hz, $J_{\text{BX}} = 8.0$ Hz, 1H, CH_2CO), 3.41 (ABX, $J_{\text{AB}} = 17.4$ Hz, $J_{\text{AX}} = 6.5$ Hz, $J_{\text{BX}} = 8.0$ Hz, 1H, CH_2CO), 2.49 (s, 3H, CH_3) ppm; ^{13}C -NMR (125 MHz, CDCl_3 , T = 300 K, $\delta_{\text{TMS}} = 0$ ppm) δ 196.9 (C=O), 137.4 (C-1), 136.5 (C-2,6), 133.5 (C-4'), 131.2 (C-3,5), 128.7 (C-3',5'), 128.0 (C-2',6'), 127.5 (C-3,5), 126.6 (C-4), 125.4 (C-2,6), 79.0 (CH_2NO_2), 41.6 (CH_2CO), 34.4 (CH), 19.6 (CH_3) ppm; ^{15}N -NMR (50 MHz, CDCl_3 , T = 300 K, $\delta_{\text{NH}_3} = 0$ ppm) δ 384 (NO_2) ppm; IR (CH_2Cl_2) ν 1688, 1555, 1449, 1422, 1378, 1265, 896 cm^{-1} ; HRMS (EI) Exact mass calculated for $\text{C}_{17}\text{H}_{17}\text{NO}_3$ $[\text{M}]^+$ 283.1208; Found: 287.1208; *Anal.* Calcd. for $\text{C}_{17}\text{H}_{17}\text{NO}_3$: C, 72.07; H, 6.05; F, 6.61; N, 4.94; O, 16.94. Found: C, 71.75; H, 6.03; N, 4.87. Enantioselectivity was determined by HPLC analysis with a Chiralpak AD column, 10% isopropyl alcohol in hexane, 1.0 mL/min, $\lambda = 254$ nm, retention times minor 10.7 min, major 13.3 min.

3e.⁷ $[\alpha]_D^{25} +40.0$ (*c* 1.00, CHCl₃, 96% ee); ¹H-NMR (500 MHz, CDCl₃, T = 300 K, $\delta_{TMS} = 0$ ppm) δ 7.91 (d, *J* = 9.0 Hz, 2H, H-2' and H-6'), 7.35 (t, *J* = 7.2 Hz, 2H, H-3 and H-5), 7.31 (d, *J* = 7.2 Hz, 2H, H-2 and H-6), 7.28 (t, *J* = 7.2 Hz, 1H, H-4), 6.91 (d, *J* = 9.0

Hz, 2H, H-3' and H-5'), 4.85 (ABX, *J*_{AB} = 12.6 Hz, *J*_{AX} = 6.6 Hz, *J*_{BX} = 8.1 Hz, 1H, CH₂NO₂), 4.69 (ABX, *J*_{AB} = 12.6 Hz, *J*_{AX} = 6.6 Hz, *J*_{BX} = 8.1 Hz, 1H, CH₂NO₂), 4.22 (br pseudo quintet, *J* = 7.1 Hz, 1H, CH), 3.87 (s, 3H, OCH₃), 3.42 (ABX, *J*_{AB} = 17.4 Hz, *J*_{AX} = 6.5 Hz, *J*_{BX} = 8.0 Hz, 1H, CH₂CO), 3.38 (ABX, *J*_{AB} = 17.4 Hz, *J*_{AX} = 6.5 Hz, *J*_{BX} = 8.0 Hz, 1H, CH₂CO) ppm; ¹³C-NMR (125 MHz, CDCl₃, T = 300 K, $\delta_{TMS} = 0$ ppm) δ 195.3 (C=O), 163.8 (C-4'), 139.3 (C-1), 130.3 (C-2',6'), 129.5 (C-1'), 129.0 (C-3,5), 127.7 (C-4), 127.4 (C-2,6), 113.8 (C-3',5'), 79.6 (CH₂NO₂), 55.5 (OCH₃), 41.1 (CH₂CO), 39.4 (CH) ppm; ¹⁵N-NMR (50 MHz, CDCl₃, T = 300 K, $\delta_{NH_3} = 0$ ppm) δ 382 (NO₂) ppm; Enantioselectivity was determined by HPLC analysis with a Chiralpak AD column, 10% isopropyl alcohol in hexane, 1.0 mL/min, λ = 254 nm, retention times minor 30.8 min, major 47.2 min.

References:

- ¹ (a) Dannhardt, G.; Kiefer, W.; Kraemer, G.; Maehrlein, S.; Nowe, U.; Fiebich, B. *Eur. J. Med. Chem. Chim. Ther.* **1991**, *34*, 2804. (b) Frank, R. L.; Seven, R. P. *J. Am. Chem. Soc.* **1949**, *71*, 2629. (c) Hine, J.; Skoglund, M. J. *J. Org. Chem.* **1982**, *47*, 4758. (d) Kellogg, R. M.; Nieuwenhuijzen, J. W.; Pouwer, K.; Vries, T. R.; Broxterman, Q. B.; Grimbergen, R. F. P.; Kaptein, B.; Crois, R. M. La; Wever, E. de; Zwaagstra, K.; Laan, A. C. van der *Synthesis* **2003**, 1626.
- ² Brunner, H.; Bügler, J.; Nuber, B. *Tetrahedron: Asymmetry* **1995**, *6*, 1699.
- ³ Brunner, H.; Schmidt, P. *Eur. J. Org. Chem.* **2000**, 2119.
- ⁴ Brunner, H.; Bügler, J. *Bull. Soc. Chim. Belg.* **1997**, *106*, 77.
- ⁵ Botteghi, C.; Paganelli, S.; Schionato, A.; Boga, C.; Fava, A. *J. Mol. Catal.* **1991**, *66*, 7.
- ⁶ Corey, E. J.; Zhang, F.-Y., *Org. Lett.* **2000**, *2*, 4257.
- ⁷ Worrall, D. E.; Bradway, C. J., *J. Am. Chem. Soc.* **1936**, *58*, 1607.

Figure 1. ^1H NMR spectra of 5a

Figure 2. ^1H NMR spectra of 5b

Figure 3. ^1H NMR spectra of 6

Figure 4. ^1H NMR spectra of 7