

Supporting Information

Organocatalytic Asymmetric Michael Addition of 2,4-Pentandione to Nitroolefins

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General Information: Commercial reagents were used as received, unless otherwise stated. Merck 60 silica gel was used for chromatography, and Whatman silica gel plates with fluorescence F₂₅₄ indicator were used for thin-layer chromatography (TLC) analysis. ¹H and ¹³C NMR spectra were recorded on Bruker Advance 500, and tetramethylsilane (TMS) was used as a reference. Data for ¹H are reported as follows: chemical shift (ppm), and multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). High resolution mass spectra (HRMS) are obtained from Department of Chemistry, Ohio State University MS facility.

Procedures for preparation of binaphthyl-based thiourea catalyst VI.

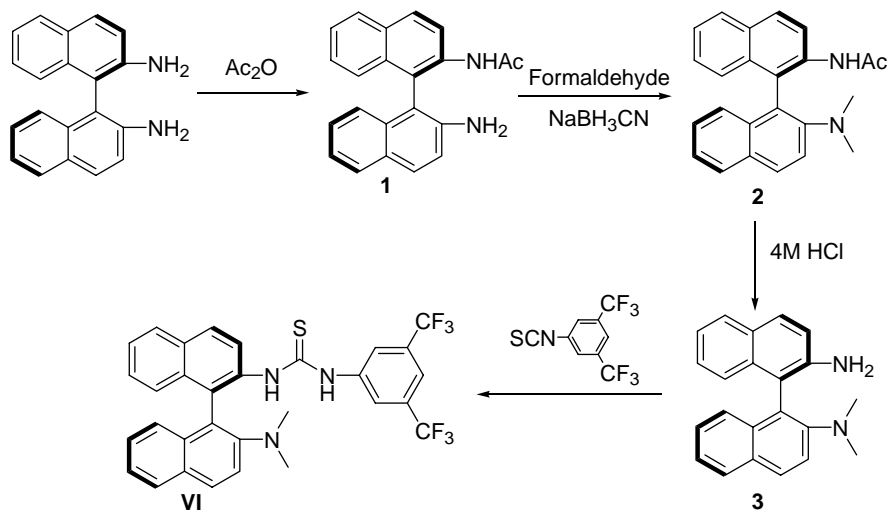
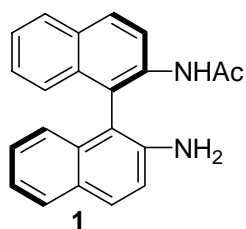
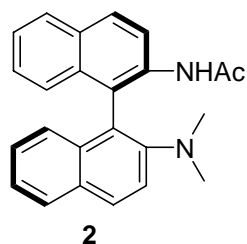


Figure. Synthesis of binaphthyl-based thiourea catalyst VI.

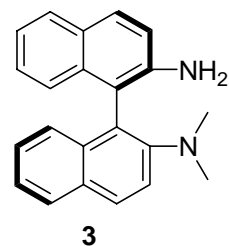


(R)-N-(1-(2-Aminonaphthalen-1-yl)naphthalen-2-yl)acetamide^[1] (1). To a solution of (R)-(+)-1,1'-Binaphthyl-2,2'-diamine (284.0 mg, 1.0 mmol) and AcOH (0.6 mL, 10 mmol) in 10 mL of dried CH₂Cl₂ was added acetic anhydride (104 μ L, 1.0 mmol) at 0 °C under N₂. The resulting solution was stirred for overnight at room temperature, then 2N NaOH aqueous solution was added to adjust the solution to pH \approx 7. The reaction mixture was extracted by CH₂Cl₂ (3 \times 50 mL) and the combined organic phases were washed with saturated brine and dried over MgSO₄. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (ethyl acetate/hexane = 2/1) to afford a colorless oil in 77% yield (0.25 g, 0.77 mmol). ¹H NMR (500 MHz, CDCl₃, TMS): δ = 8.63 (dd, ³J(H,H) = 8.0 Hz, ³J(H,H) = 4.5 Hz, 1H; Ar), 7.99 (d, ³J(H,H) = 9.0 Hz, 1H; Ar), 7.90 (d, ³J(H,H) = 8.0 Hz, 1H; Ar), 7.85 (d, ³J(H,H) = 9.0 Hz, 1H; Ar), 7.81 (d, ³J(H,H) = 8.0 Hz, 1H; Ar), 7.40 (t, ³J(H,H) = 9.0 Hz, 1H; Ar), 7.27-7.12 (m, 5H; CH), 7.04 (s, 1H; NH), 6.91 (d, ³J(H,H) = 8.0 Hz, 1H; Ar), 3.65 (s, 2H; NH₂), 1.84 (s, 3H; CH₃); ¹³C NMR (125 MHz, CDCl₃, TMS): δ = 168.7, 142.7, 135.0, 134.9, 133.5, 132.3, 131.2, 130.3, 129.2, 128.2, 128.1, 127.3, 126.8, 125.4, 125.1, 123.6, 122.7, 120.9, 120.8,

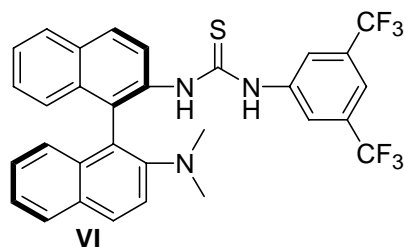
118.0, 110.3, 24.6.



(R)-N-(1-(2-(Dimethylamino)naphthalen-1-yl)naphthalen-2-yl)acetamide^[2] (2). A solution of *N*-(1-(2-aminonaphthalen-1-yl)naphthalen-2-yl)acetamide **1** (0.25 g, 0.77 mmol) and aqueous formaldehyde (37%, 0.75 mL, 9.0 mmol) in 10 mL of THF was stirred for 15 min. Then NaBH₃CN (200.0 mg, 5.3 mmol) was added and stirred for 15 min, following by addition of AcOH (1.0 mL). The resulting solution was stirred for 4 h at room temperature, then 1*N* NaOH aqueous solution was added to adjust the solution to pH \approx 7. The reaction mixture was extracted by CH₂Cl₂ (3 \times 50 mL) and the combined organic phases were washed with saturated brine and dried over MgSO₄. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (ethyl acetate/hexane = 1/5) to afford a brown powder in a quantitative yield (272 mg, 0.77 mmol). ¹H NMR (500 MHz, CDCl₃, TMS): δ = 8.48 (d, ³*J*(H,H) = 9.0 Hz, 1H; Ar), 7.96 (d, ³*J*(H,H) = 8.5 Hz, 2H; Ar), 7.88 (d, ³*J*(H,H) = 8.0 Hz, 1H; Ar), 7.83 (d, ³*J*(H,H) = 8.0 Hz, 1H; Ar), 7.53 (s, 1H; NH), 7.49 (d, ³*J*(H,H) = 9.0 Hz, 1H; Ar), 7.38 (t, ³*J*(H,H) = 8.0 Hz, 1H; Ar), 7.31 (t, ³*J*(H,H) = 7.0 Hz, 1H; Ar), 7.22 (t, ³*J*(H,H) = 7.0 Hz, 1H; Ar), 7.16-7.11 (m, 2H; Ar), 6.93 (d, ³*J*(H,H) = 8.5 Hz, 1H; Ar), 2.65 (s, 6H; CH₃), 1.86 (s, 3H; CH₃); ¹³C NMR (125 MHz, CDCl₃, TMS): δ = 169.2, 149.5, 133.6, 133.4, 131.2, 130.1, 129.7, 128.6, 128.2, 127.9, 126.8, 126.5, 126.4, 125.3, 125.0, 124.1, 121.8, 121.5, 118.6, 118.0, 48.6, 43.4, 24.4.

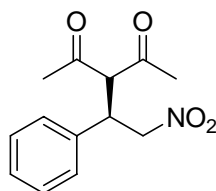


(R)-1-(2-(Dimethylamino)naphthalen-1-yl)naphthalen-2-amine^[2] (3). To a solution of *N*-(1-(2-(dimethylamino)naphthalen-1-yl)naphthalen-2-yl)acetamide **2** (0.18 g, 0.51 mmol) in 15 mL of EtOH was added 4*M* HCl (6 mL). The resulting solution was stirred for overnight at room temperature, then 1*N* NaOH aqueous solution was added to adjust the solution to pH \approx 7. The reaction mixture was extracted by CH₂Cl₂ (3 \times 50 mL) and the combined organic phases were washed with saturated brine and dried over MgSO₄. The solvent was removed under reduced pressure and the crude product was purified by flash chromatography (ethyl acetate/hexane = 1/10) to afford a colorless oil in 93% yield (148 mg, 0.47 mmol). ¹H NMR (500 MHz, CDCl₃, TMS): δ = 7.90 (d, ³*J*(H,H) = 9.0 Hz, 1H; Ar), 7.81 (d, ³*J*(H,H) = 8.0 Hz, 1H; Ar), 7.77 (d, ³*J*(H,H) = 8.0 Hz, 2H; Ar), 7.47 (d, ³*J*(H,H) = 9.0 Hz, 1H; Ar), 7.29-7.10 (m, 6H; Ar), 7.02 (d, ³*J*(H,H) = 8.5 Hz, 1H; Ar), 3.67 (s, 2H; NH₂), 2.59 (s, 6H; CH₃); ¹³C NMR (125 MHz, CDCl₃, TMS): δ = 150.4, 141.8, 134.2, 133.7, 129.7, 129.1, 128.8, 128.3, 127.9, 127.8, 126.5, 126.2, 124.9, 123.6, 122.1, 121.9, 119.5, 118.4, 116.8, 43.3.

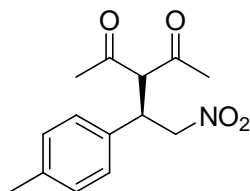


(R)-1-(3,5-Bis(trifluoromethyl)phenyl)-3-(1-(2-(dimethylamino)naphthalen-1-yl)naphthalen-2-yl)thiourea (VI). To a solution of 1-(2-(dimethylamino)naphthalen-1-yl)naphthalen-2-amine **3** (36.0 mg, 0.12 mmol) in 2 mL of dried CH₂Cl₂ was added 3,5-bis(trifluoromethyl)phenyl isothiocyanate (22.0 mg, 0.132 mmol) at 0 °C under N₂. The resulting solution was stirred for overnight at room temperature. The reaction mixture was concentrated *in vacuo* and then the crude product was purified by flash chromatography (ethyl acetate/hexane = 1/10) to afford a slight yellow solid in 91% yield (64 mg, 0.11 mmol). $[\alpha]_D^{25} = -8.3$ ($c = 0.5$ in CHCl₃); ¹H NMR (500 MHz, CDCl₃, TMS): $\delta = 8.37$ (s, 1H; NH), 8.06 (d, ³ J (H,H) = 8.5 Hz, 1H; Ar), 7.98 (d, ³ J (H,H) = 9.0 Hz, 2H; Ar), 7.82 (d, ³ J (H,H) = 8.0 Hz, 1H; Ar), 7.71 (d, ³ J (H,H) = 8.5 Hz, 1H; Ar), 7.56-7.50 (m, 5H; Ar), 7.41 (s, 1H; NH), 7.36 (s, 2H; Ar), 7.26 (m, 2H; Ar), 7.09 (t, ³ J (H,H) = 7.5 Hz, 1H; Ar), 6.90 (d, ³ J (H,H) = 7.5 Hz, 1H; Ar), 2.59 (s, 6H; CH₃); ¹³C NMR (125 MHz, CDCl₃, TMS): $\delta = 179.7, 149.9, 139.6, 134.0, 133.3, 133.2, 132.9, 132.0, 131.8, 131.6, 130.5, 130.0, 129.9, 128.5, 128.4, 127.5, 127.2, 126.8, 125.0, 124.6, 124.2, 123.9, 122.9, 121.8, 118.9, 44.0$. HRMS (EI) calcd for C₃₁H₂₃N₃SF₆ + Na⁺ 606.1409, obsd 606.1415.

Typical Procedure for Michael Addition Reaction: The catalyst amino-thiourea **VI** (1.0 mg, 0.0017 mmol) was added to a vial containing 2,4-pentanedione **1a** (38 μ L, 0.34 mmol) and *trans*- β -nitrostyrene **2a** (26.0 mg, 0.17 mmol) in Et₂O (1 mL) at room temperature. After 28 h of stirring, TLC analysis indicated completion of the reaction. The reaction mixture was concentrated *in vacuo*. The residue was purified by flash silica gel chromatography (ethyl acetate/hexane=1:10 to 1:3) to afford 37 mg (87%) of the adduct as a white solid.

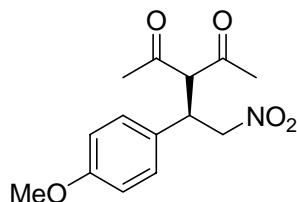


3-((R)-2-Nitro-1-phenylethyl)pentane-2,4-dione^[31] (Table 2, entry 1): The title compound (known compound) was prepared according the typical procedure, as described above in 87% yield. HPLC (Chiralpak AS-H, *i*-propanol/hexane = 15/85, flow rate 1.0 mL/min, $\lambda = 210$ nm): $t_{\text{minor}} = 14.5$ min, $t_{\text{major}} = 23.9$ min, ee = 95%; $[\alpha]_D^{25}$ (major) = -147.6 ($c = 3.0$ in CHCl₃).

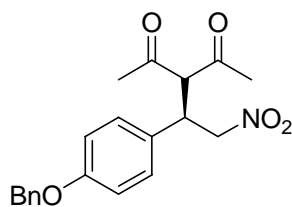


3-((R)-2-Nitro-1-*p*-tolylethyl)pentane-2,4-dione (Table 2, entry 2): The title compound was prepared according the typical procedure, as described above in 84% yield. ¹H NMR (500

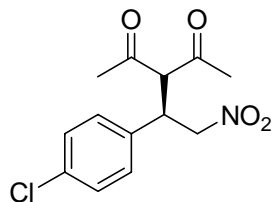
MHz, CDCl₃, TMS): δ = 7.12 (d, $^3J(\text{H,H})$ = 8.0 Hz, 2H; Ph), 7.06 (d, $^3J(\text{H,H})$ = 8.0 Hz, 2H; Ph), 4.65-4.57 (m, 2H; CH₂), 4.36 (d, $^3J(\text{H,H})$ = 11.0 Hz, 1H; CH), 4.24-4.17 (m, 1H; CH), 2.30 (s, 3H; CH₃), 2.29 (s, 3H; CH₃), 1.94 (s, 3H; CH₃); ¹³C NMR (125 MHz, CDCl₃, TMS): δ = 201.9, 201.1, 138.3, 132.7, 130.0, 127.7, 78.3, 70.8, 42.4, 30.4, 29.4, 21.0; HPLC (Chiralpak AS-H, *i*-propanol/hexane = 15/85, flow rate 1.0 mL/min, λ = 210 nm): t_{minor} = 11.8 min, t_{major} = 18.8 min, ee = 93%; $[\alpha]^{25}_{\text{D}}$ (major) = -71.9 (c = 3.0 in CHCl₃). HRMS (EI) calcd for C₁₄H₁₇NO₄ + Na⁺ 286.1050, obsd 286.1042



3-((R)-1-(4-Methoxyphenyl)-2-nitroethyl)pentane-2,4-dione (Table 2, entry 3): The title compound was prepared according the typical procedure, as described above in 92% yield. ¹H NMR (500 MHz, CDCl₃, TMS): δ = 7.10 (d, $^3J(\text{H,H})$ = 8.5 Hz, 2H; Ph), 6.84 (d, $^3J(\text{H,H})$ = 8.5 Hz, 2H; Ph), 4.61-4.57 (m, 2H; CH₂), 4.35 (d, $^3J(\text{H,H})$ = 11.0 Hz, 1H; CH), 4.24-4.18 (m, 1H; CH), 3.78 (s, 3H; OCH₃), 2.29 (s, 3H; CH₃), 1.95 (s, 3H; CH₃); ¹³C NMR (125 MHz, CDCl₃, TMS): δ = 201.8, 201.1, 159.4, 129.0, 127.5, 114.6, 78.4, 70.8, 55.1, 42.0, 30.3, 29.4; HPLC (Chiralpak AD, *i*-propanol/hexane = 20/80, flow rate 0.8 mL/min, λ = 210 nm): t_{minor} = 11.0 min, t_{major} = 15.2 min, ee = 97%; $[\alpha]^{25}_{\text{D}}$ (major) = -108.3 (c = 2.7 in CHCl₃). HRMS (EI) calcd for C₁₄H₁₇NO₅ + Na⁺ 302.0999, obsd 302.1005.

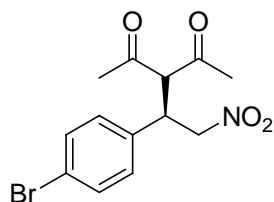


3-((R)-1-(4-(Benzyloxy)phenyl)-2-nitroethyl)pentane-2,4-dione (Table 2, entry 4): The title compound was prepared according the typical procedure, as described above in 90% yield. ¹H NMR (500 MHz, CDCl₃, TMS): δ = 7.42-7.33 (m, 5H; Ph), 7.10 (d, $^3J(\text{H,H})$ = 8.5 Hz, 2H; Ph), 6.91 (d, $^3J(\text{H,H})$ = 8.5 Hz, 2H; Ph), 5.00 (s, 2H; OCH₂), 4.62-4.56 (m, 2H; CH), 4.33 (d, $^3J(\text{H,H})$ = 10.5 Hz, 1H; CH), 4.23-4.16 (m, 1H; CH), 2.29 (s, 3H; CH₃), 1.95 (s, 3H; CH₃); ¹³C NMR (125 MHz, CDCl₃, TMS): δ = 201.8, 201.1, 158.7, 136.5, 129.1, 128.6, 128.1, 127.9, 127.5, 115.5, 78.4, 70.9, 70.0, 42.1, 30.4, 29.5; HPLC (Chiralpak AD, *i*-propanol/hexane = 30/70, flow rate 1.0 mL/min, λ = 210 nm): t_{minor} = 8.9 min, t_{major} = 11.6 min, ee = 94%; $[\alpha]^{25}_{\text{D}}$ (major) = -78.8 (c = 2.7 in CHCl₃). HRMS (EI) calcd for C₂₀H₂₁NO₅ + Na⁺ 378.1312, obsd 378.1313.

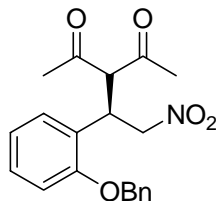


3-((R)-1-(4-Chlorophenyl)-2-nitroethyl)pentane-2,4-dione (Table 2, entry 5): The title compound was prepared according the typical procedure, as described above in 91% yield. ¹H

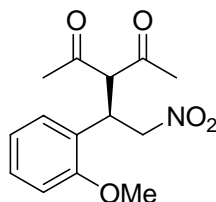
NMR (500 MHz, CDCl₃, TMS): δ = 7.32 (d, $^3J(\text{H,H})$ = 8.5 Hz, 2H; Ph), 7.14 (d, $^3J(\text{H,H})$ = 8.5 Hz, 2H; Ph), 4.65-4.60 (m, 2H; CH₂), 4.33 (d, $^3J(\text{H,H})$ = 11.0 Hz, 1H; CH), 4.27-4.20 (m, 1H; CH), 2.29 (s, 3H; CH₃), 1.98 (s, 3H; CH₃); ¹³C NMR (125 MHz, CDCl₃, TMS): δ = 201.4, 200.6, 134.5, 129.5, 129.3, 77.9, 70.4, 42.1, 30.4, 29.7; HPLC (Chiralpak AS-H, *i*-propanol/hexane = 15/85, flow rate 1.0 mL/min, λ = 210 nm): t_{minor} = 16.5 min, t_{major} = 34.7 min, ee = 97%; $[\alpha]_{\text{D}}^{25}$ (major) = -89.2 (c = 3.0 in CHCl₃). HRMS (EI) calcd for C₁₃H₁₄NO₄Cl + Na⁺ 306.0503, obsd 306.0508.



3-((R)-1-(4-Bromophenyl)-2-nitroethyl)pentane-2,4-dione (Table 2, entry 6): The title compound was prepared according the typical procedure, as described above in 89% yield. ¹H NMR (500 MHz, CDCl₃, TMS): δ = 7.47 (d, $^3J(\text{H,H})$ = 8.5 Hz, 2H; Ph), 7.08 (d, $^3J(\text{H,H})$ = 8.5 Hz, 2H; Ph), 4.65-4.58 (m, 2H; CH₂), 4.33 (d, $^3J(\text{H,H})$ = 10.5 Hz, 1H; CH), 4.26-4.19 (m, 1H; CH), 2.29 (s, 3H; CH₃), 1.98 (s, 3H; CH₃); ¹³C NMR (125 MHz, CDCl₃, TMS): δ = 201.3, 200.5, 135.0, 132.5, 129.6, 122.6, 77.8, 70.4, 42.1, 30.4, 29.7; HPLC (Chiralpak AS-H, *i*-propanol/hexane = 15/85, flow rate 1.0 mL/min, λ = 210 nm): t_{minor} = 17.1 min, t_{major} = 32.3 min, ee = 95%; $[\alpha]_{\text{D}}^{25}$ (major) = -37.2 (c = 1.2 in CHCl₃). HRMS (EI) calcd for C₁₃H₁₄NO₄Br + Na⁺ 349.9998, obsd 349.9987.

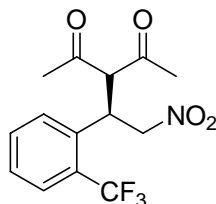


3-((R)-1-(2-(Benzyloxy)phenyl)-2-nitroethyl)pentane-2,4-dione (Table 2, entry 7): The title compound was prepared according the typical procedure, as described above in 80% yield. ¹H NMR (500 MHz, CDCl₃, TMS): δ = 7.52-7.35 (m, 5H; Ph), 7.28-7.22 (m, 1H; Ph), 7.10 (dd, $^3J(\text{H,H})$ = 7.5 Hz, $^3J(\text{H,H})$ = 1.0 Hz, 1H; Ph), 6.96 (d, $^3J(\text{H,H})$ = 8.0 Hz, 1H; Ph), 6.90 (t, $^3J(\text{H,H})$ = 7.5 Hz, 1H; Ph), 5.12 (s, 2H; OCH₂), 4.80 (dd, $^3J(\text{H,H})$ = 11.5 Hz, $^2J(\text{H,H})$ = 7.5 Hz, 1H; CH₂), 4.58-4.47 (m, 3H; CH, CH₂), 2.18 (s, 3H; CH₃), 1.91 (s, 3H; CH₃); ¹³C NMR (125 MHz, CDCl₃, TMS): δ = 202.2, 201.5, 156.2, 136.3, 130.4, 129.7, 128.8, 128.4, 127.8, 123.6, 121.4, 122.5, 76.3, 70.6, 68.8, 39.0, 30.5, 28.5; HPLC (Chiralpak AS-H, *i*-propanol/hexane = 15/85, flow rate 1.0 mL/min, λ = 210 nm): t_{minor} = 14.4 min, t_{major} = 15.9 min, ee = 89 %; $[\alpha]_{\text{D}}^{25}$ (major) = -44.5 (c = 1.0 in CHCl₃). HRMS (EI) calcd for C₂₀H₂₁NO₅ + Na⁺ 378.1312, obsd 378.1323.

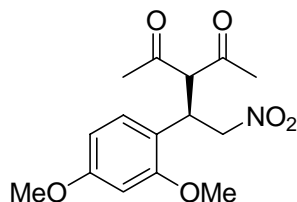


3-((R)-1-(2-Methoxyphenyl)-2-nitroethyl)pentane-2,4-dione (Table 2, entry 8): The title

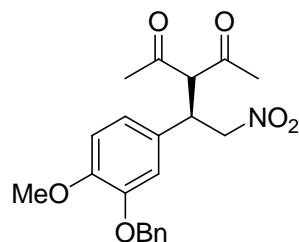
compound was prepared according the typical procedure, as described above in 92% yield. ^1H NMR (500 MHz, CDCl_3 , TMS): δ = 7.27 (dd, $^3J(\text{H,H})$ = 16.0 Hz, $^3J(\text{H,H})$ = 1.5 Hz, 1H; Ph), 7.08 (dd, $^3J(\text{H,H})$ = 8.0 Hz, $^3J(\text{H,H})$ = 1.5 Hz, 1H; Ph), 6.95-6.86 (m, 2H; Ph), 4.78 (dd, $^3J(\text{H,H})$ = 12.5 Hz, $^2J(\text{H,H})$ = 8.0 Hz, 1H; CH_2), 4.63-4.56 (m, 2H; CH, CH_2), 4.52-4.46 (m, 1H; CH), 3.88 (s, 3H; OCH_3), 2.28 (s, 3H; CH_3), 1.94 (s, 3H; CH_3); ^{13}C NMR (125 MHz, CDCl_3 , TMS): δ = 202.3, 201.6, 157.0, 130.2, 129.7, 123.4, 121.1, 111.2, 76.5, 68.9, 55.4, 38.9, 30.4, 28.7; HPLC (Chiralcel OD-H, *i*-propanol/hexane = 15/85, flow rate 0.5 mL/min, λ = 210 nm): t_{minor} = 37.9 min, t_{major} = 40.8 min, ee = 97 %; $[\alpha]_D^{25}$ (major) = -108.5 (c = 2.7 in CHCl_3). HRMS (EI) calcd for $\text{C}_{14}\text{H}_{17}\text{NO}_5 + \text{Na}^+$ 302.0999, obsd 302.0998.



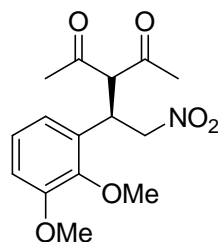
3-((*R*)-1-(2-(Trifluoromethyl)phenyl)-2-nitroethyl)pentane-2,4-dione (Table 2, entry 9): The title compound was prepared according the typical procedure, as described above in 86% yield. ^1H NMR (500 MHz, CDCl_3 , TMS): δ = 7.75 (d, $^3J(\text{H,H})$ = 7.5 Hz, 1H; Ph), 7.53 (t, $^3J(\text{H,H})$ = 7.5 Hz, 1H; Ph), 7.45 (t, $^3J(\text{H,H})$ = 7.5 Hz, 1H; Ph), 7.27 (d, $^3J(\text{H,H})$ = 7.5 Hz, 1H; Ph), 4.85 (dd, $^3J(\text{H,H})$ = 12.0 Hz, $^2J(\text{H,H})$ = 5.5 Hz, 1H; CH_2), 4.70-4.60 (m, 3H; CH, CH_2), 2.32 (s, 3H; CH_3), 2.01 (s, 3H; CH_3); ^{13}C NMR (125 MHz, CDCl_3 , TMS): δ = 201.9, 200.6, 134.8, 132.6, 128.6, 127.3, 127.2, 77.6, 69.7, 37.5, 31.2, 28.3; HPLC (Chiralcel OD-H, *i*-propanol/hexane = 10/90, flow rate 1.0 mL/min, λ = 210 nm): t_{minor} = 12.3 min, t_{major} = 13.1 min, ee = 93 %; $[\alpha]_D^{25}$ (major) = -77.7 (c = 2.8 in CHCl_3). HRMS (EI) calcd for $\text{C}_{14}\text{H}_{14}\text{NO}_4\text{F}_3 + \text{Na}^+$ 340.0767, obsd 340.0778.



3-((*R*)-1-(2,4-Dimethoxyphenyl)-2-nitroethyl)pentane-2,4-dione (Table 2, entry 10): The title compound was prepared according the typical procedure, as described above in 88% yield. ^1H NMR (500 MHz, CDCl_3 , TMS): δ = 6.97 (d, $^3J(\text{H,H})$ = 8.5 Hz, 1H; Ph), 6.44 (d, $^3J(\text{H,H})$ = 2.0 Hz, 1H; Ph), 6.40 (dd, $^3J(\text{H,H})$ = 8.0 Hz, $^3J(\text{H,H})$ = 2.5 Hz, 1H; Ph), 4.74 (dd, $^3J(\text{H,H})$ = 12.0 Hz, $^2J(\text{H,H})$ = 8.0 Hz, 1H; CH_2), 4.59-4.51 (m, 2H; CH, CH_2), 4.43 (ddd, $^3J(\text{H,H})$ = 12.0 Hz, $^2J(\text{H,H})$ = 8.0 Hz, $^3J(\text{H,H})$ = 4.0 Hz, 1H; CH), 3.86 (s, 3H; OCH_3), 3.77 (s, 3H; OCH_3), 2.28 (s, 3H; CH_3), 1.93 (s, 3H; CH_3); ^{13}C NMR (125 MHz, CDCl_3 , TMS): δ = 201.9, 200.6, 134.8, 132.6, 128.6, 127.3, 127.2, 77.6, 69.7, 37.5, 31.2, 28.3; HPLC (Chiralpak AS-H, *i*-propanol/hexane = 15/85, flow rate 1.0 mL/min, λ = 210 nm): t_{minor} = 20.4 min, t_{major} = 22.6 min, ee = 91 %; $[\alpha]_D^{25}$ (major) = -58.1 (c = 0.8 in CHCl_3). HRMS (EI) calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_6 + \text{Na}^+$ 332.1104, obsd 332.1111.

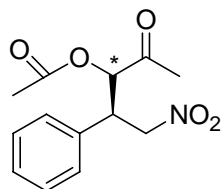


3-((R)-1-(3-(Benzyloxy)-4-methoxyphenyl)-2-nitroethyl)pentane-2,4-dione (Table 2, entry 11): The title compound was prepared according the typical procedure, as described above in 78% yield. ^1H NMR (500 MHz, CDCl_3 , TMS): δ = 7.45-7.28 (m, 5H; Ph), 6.81 (d, $^3J(\text{H,H})$ = 8.5 Hz, 1H; Ph), 6.71 (dd, $^3J(\text{H,H})$ = 8.0 Hz, $^3J(\text{H,H})$ = 1.5 Hz, 1H; Ph), 6.66 (d, $^3J(\text{H,H})$ = 1.5 Hz, 1H; Ph), 5.13 (dd, $^3J(\text{H,H})$ = 11.5 Hz, $^2J(\text{H,H})$ = 7.0 Hz, 2H; CH_2), 4.53 (d, $^3J(\text{H,H})$ = 6.0 Hz, 2H; OCH_2), 4.22 (d, $^3J(\text{H,H})$ = 11.0 Hz, 1H; CH), 4.12-4.06 (m, 1H; CH), 3.86 (s, 3H; CH_3), 2.24 (s, 3H; CH_3), 1.78 (s, 3H; CH_3); ^{13}C NMR (125 MHz, CDCl_3 , TMS): δ = 201.8, 201.1, 149.7, 148.1, 136.7, 128.6, 128.0, 127.9, 127.4, 120.8, 114.0, 112.0, 78.3, 71.0, 70.7, 55.9, 42.3, 30.3, 29.4; HPLC (Chiralpak AS-H, *i*-propanol/hexane = 15/85, flow rate 1.0 mL/min, λ = 210 nm): t_{minor} = 27.9 min, t_{major} = 49.4 min, ee = 88 %; $[\alpha]^{25}_{\text{D}}$ (major) = -43.8 (c = 1.5 in CHCl_3). HRMS (EI) calcd for $\text{C}_{21}\text{H}_{23}\text{NO}_6 + \text{Na}^+$ 408.1418, obsd 408.1435.



3-((R)-1-(2,3-Dimethoxyphenyl)-2-nitroethyl)pentane-2,4-dione (Table 2, entry 12): The title compound was prepared according the typical procedure, as described above in 87% yield. ^1H NMR (500 MHz, CDCl_3 , TMS): δ = 6.98 (t, $^3J(\text{H,H})$ = 8.0 Hz, 1H; Ph), 6.86 (d, $^3J(\text{H,H})$ = 8.0 Hz, 1H; Ph), 6.67 (d, $^3J(\text{H,H})$ = 8.0 Hz, 1H; Ph), 4.76 (dd, $^3J(\text{H,H})$ = 12.0 Hz, $^2J(\text{H,H})$ = 8.0 Hz, 1H; CH_2), 4.66 (dd, $^3J(\text{H,H})$ = 12.0 Hz, $^3J(\text{H,H})$ = 4.0 Hz, 1H; CH), 4.60-4.54 (m, 1H; CH), 4.47 (d, $^3J(\text{H,H})$ = 10.0 Hz, 1H; CH_2), 3.96 (s, 3H; CH_3), 3.86 (s, 3H; CH_3), 2.25 (s, 3H; CH_3), 2.04 (s, 3H; CH_3); ^{13}C NMR (125 MHz, CDCl_3 , TMS): δ = 202.4, 201.4, 152.8, 146.7, 129.1, 124.3, 120.2, 112.5, 76.9, 69.5, 60.8, 55.6, 37.4, 30.9, 29.0; HPLC (Chiralpak AS-H, *i*-propanol/hexane = 15/85, flow rate 1.0 mL/min, λ = 210 nm): t_{minor} = 13.6 min, t_{major} = 16.8 min, ee = 92 %; $[\alpha]^{25}_{\text{D}}$ (major) = -104.0 (c = 2.8 in CHCl_3). HRMS (EI) calcd for $\text{C}_{15}\text{H}_{19}\text{NO}_6 + \text{Na}^+$ 332.1104, obsd 332.1120.

Procedures for synthesis of (*R*) α -phenyl- β -alanine 4a (Scheme 1):



Diastereomer A: B = 1 : 0.8

Baeyer-Villiger oxidation of 3a: To a stirred suspension of **3a** (124.5 mg, 0.5 mmol), K_2CO_3 (691 mg, 5 mmol, 10 equiv.), and TBAI (37.0 mg, 0.1 mmol, 20 mol%) in CH_2Cl_2 , acetone, and

water (1/1/1, 15 mL) was added a solution of Oxone® (1.5 g, 2.5 mmol, 5 equiv.) in 15 mL of water over 30 min at 0 °C. When completed the addition, the resulting white suspension was diluted with water and extracted with CH₂Cl₂. Organic extract was dried over Na₂SO₄ and filtrated. After concentrated, the resulting clear oil α -acetoxy- γ -nitroketone was used for next reaction without further purification. Diastereomer **A**: ¹H NMR (500 MHz, CDCl₃, TMS): δ = 7.30-7.17 (m, 5H; Ph), 4.76-4.60 (m, 3H; CH, CH₂), 4.53 (d, J = 4.5 Hz, 1H; CH), 2.31 (s, 3H; OCH₃), 2.03 (s, 3H; CH₃). Diastereomer **B**: ¹H NMR (500 MHz, CDCl₃, TMS): δ = 7.30-7.17 (m, 5H; Ph), 4.76-4.60 (m, 3H; CH, CH₂), 4.51 (d, J = 4.5 Hz, 1H; CH), 2.55 (s, 3H; OCH₃), 1.95 (s, 3H; CH₃).

Synthesis of (*R*) α -phenyl- β -alanine 4a: To a solution of crude α -acetoxy- γ -nitroketone in 5 mL of toluene was added a 1 *M* solution of DIBAH in Et₂O (1.8 mL, 1.8 mmol) at -78 °C under N₂. Resulting solution was stirred for 2 h and quenched with 1 *M* aqueous solution of NaHSO₄. The mixture was extracted with CH₂Cl₂ and the organic phase was dried over MgSO₄. The crude residue was used for next reaction without further purification. The obtained crude diol was dissolved into 2 mL of 1,4-dioxane under N₂. To the solution was added H₂O (1 mL), Na₂CO₃ (27 mg, 0.26 mmol), NaIO₄ (434 mg, 2.0 mmol), and KMnO₄ (16 mg, 0.1 mmol) at room temperature and the resulting biphasic solution was stirred for 24 h. The reaction mixture was diluted with EtOAc and 1 *M* aqueous solution of NaHSO₄. After phase-separation, the organic phase was concentrated. The residue was dissolved into MeOH (10 mL) for hydrogenation with 10% Pd/C at 50 psi for overnight. The resulting solution was dissolved into saturated aqueous NaHCO₃ and extracted with Et₂O. The aqueous solution passed through a small pad of celite. Recrystallization from ethanol/water gave the title compound **4a** as a white solid in 38% yield (4 steps) ($[\alpha]_D^{25}$ = +88.2, c = 0.5, H₂O). ¹H NMR (500 MHz, D₂O, TMS): δ = 7.46-7.29 (m, 5H; Ph), 3.78 (dd, ³ J (H,H) = 7.5 Hz, ² J (H,H) = 7.5 Hz, 1H; CH₂), 3.45 (dd, ³ J (H,H) = 12.5 Hz, ² J (H,H) = 8.0 Hz, 1H; CH), 3.27 (dd, ³ J (H,H) = 12.5 Hz, ² J (H,H) = 7.5 Hz, 1H; CH₂); ¹³C NMR (125 MHz, D₂O+CD₃OD, TMS): δ = 179.1, 138.6, 130.3, 129.3, 129.0, 52.6, 43.6. The absolute stereochemistry was determined to be (*R*) configuration by comparison with optical rotation of literature value^[4] ($[\alpha]_D^{25}$ = +85, c = 0.2, H₂O) for the *R* configuration isomer.

Reference

- [1] S. Pieraccini, G. Gottarelli, R. Labruto, S. Masiero, O. Pandoli, G. P. Spada, *Chem. Eur. J.* **2004**, *10*, 5632.
- [2] C. -J. Wang, M. Shi, *J. Org. Chem.* **2003**, *68*, 6229.
- [3] T. Okino, Y. Hoashi, F. T. Furukawa, Y. Takemoto, *J. Am. Chem. Soc.* **2005**, *127*, 119.
- [4] H. M. L. Davies, P. Ren, *Tetrahedron Lett.* **2001**, *42*, 3149.