Supplementary Information

The Direct Catalytic Asymmetric Aldol Reaction of α-Substituted Nitroacetates with Aqueous Formaldehyde under Base-Free Neutral Phase-Transfer Conditions

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General Information

¹H, ¹³C NMR spectra were measured on a JEOL JNM-FX 400 NMR instrument (400 MHz for ¹H NMR, 100 MHz for ¹³C NMR). Tetramethylsilane (TMS) served as the internal standard (0 ppm) for ¹H NMR, and CDCl₃ served as the internal standard (77.0 ppm) for ¹³C NMR. The following abbreviations were used to express the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. High performance liquid chromatography (HPLC) was performed on Shimadzu 10A instruments using a Daicel Chiralpak IA, 4.6 mm × 25 mm column. High-resolution mass spectra (HRMS) were performed on BRUKER microTOF focus–KR. Optical rotations were measured on a JASCO DIP-1000 digital polarimeter. All reactions were monitored by thin-layer chromatography carried out on Merck precoated TLC plates (silica gel 60GF-254, 0.25 mm), visualization by using UV (254 nm), or dyes such as KMnO₄. The products were purified by flash column chromatography on silica gel 60N [Kanto Chemical Co., Inc. (spherical, neutral)].

Experimental Section

General procedure for the direct aldol reaction of α -substituted nitroacetates with aqueous formaldehyde.

To a solution of α -substituted nitroacetate (0.050 mmol) in mesitylene (0.80 mL) was added a stock solution of (*S*)-1 (0.20 mL, 2.5 × 10⁻⁴ M in mesitylene, 0.1 mol %). To this mixture was added water (1.0 mL) and 37% aqueous formaldehyde solution (0.25 mmol) at 0 °C. The resulting mixture was stirred vigorously at 0 °C for 60 h, and then diluted with water (5.0 mL). The organic phase was separated, and the aqueous phase was extracted with CH₂Cl₂. The combined extracts were dried over Na₂SO₄ and concentrated. The residue was purified by column chromatography on silica gel (hexane/ethyl acetate as eluent) to afford the product as colorless oil. The enantiomeric excess of the product was determined by chiral HPLC analysis.

O₂N CO₂CHPh₂ Me OH

2d: $[\alpha]_{D}^{27} = +13.9$ (*c* = 1.5, CHCl₃), HPLC analysis (91% ee): Daicel Chiralpak IA, hexane/2-propanol = 40:1, flow rate = 1.0 mL/min, 210 nm; retention time: 32.8 min (major) and 38.1 min (minor). ¹H NMR (400 MHz, CDCl₃) δ 7.26–7.39 (m, 10H), 6.93 (s, 1H), 4.21 (dd, J = 7.6, 12.4 Hz, 1H), 4.08 (dd, J = 7.0, 12.6 Hz, 1H), 2.54 (t, J = 7.4 Hz, 1H), 1.85 (s, 3H); ¹³C

NMR (100 MHz, CDCl₃) δ 165.4, 138.6, 138.5, 128.69, 128.66, 128.45, 128.43, 126.94, 126.92, 93.1, 79.7, 66.0, 18.9; IR (neat) 3564, 3065, 3032, 2943, 2891, 1748, 1553, 1454, 1256, 1138, 1057, 756, 745, 696 cm⁻¹; HRMS (ESI-TOF) calcd for C₁₇H₁₇NO₅Na⁺: 338.0999 ([M+Na]⁺), found 338.1004.

2c: $[\alpha]^{27}{}_{D}$ = +10.7 (*c* = 0.75, CHCl₃), HPLC analysis (87% ee): Daicel Chiralpak IA, hexane/2-propanol = 40:1, flow rate = 1.0 mL/min, 210 nm; retention time: 24.7 min (major) and 38.0 min (minor). ¹H NMR (400 MHz, CDCl₃) δ 7.30–7.41 (m, 5H), 5.27 (s, 2H), 4.19 (dd, *J* = 7.6, 12.8 Hz, 1H), 4.08 (dd, *J* = 7.4, 12.6 Hz, 1H), 2.59 (t, *J* = 7.4 Hz, 1H), 1.83 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 166.2, 134.2, 128.8, 128.7, 128.1, 93.4, 68.5, 66.0, 18.9; IR (neat) 3537, 2951, 2918, 1746, 1553, 1456, 1267, 1138, 1057, 741, 696 cm⁻¹; HRMS (ESI-TOF) calcd for C₁₁H₁₃NO₅Na⁺: 262.0686 ([M+Na]⁺), found 262.0676.

3a: $[\alpha]^{28}{}_{D}$ = +6.2 (*c* = 0.70, CHCl₃), HPLC analysis (83% ee): Daicel Chiralpak IA, hexane/2-propanol = 40:1, flow rate = 1.0 mL/min, 210 nm; retention time: 28.4 min (major) and 36.4 min (minor). ¹H NMR (400 MHz, CDCl₃) δ 7.28–7.38 (m, 10H), 6.95 (s, 1H), 4.20–4.23 (m, 2H), 2.26–2.40 (m, 3H), 0.91 (t, *J* = 7.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.0, 138.64, 138.56, 128.64, 128.63, 128.44, 128.37, 127.1, 127.0, 96.8, 79.6, 63.9, 26.0, 8.1; IR (neat) 3551, 3065, 3032, 2978, 2945, 1746, 1551, 1454, 1234, 1061, 758, 745, 696 cm⁻¹; HRMS (ESI-TOF) calcd for C₁₈H₁₉NO₅Na⁺: 352.1155 ([M+Na]⁺), found 352.1141.

O₂N CO₂CHPh₂

3b: $[\alpha]^{28}{}_{D}$ = +14.0 (*c* = 0.90, CHCl₃), HPLC analysis (81% ee): Daicel Chiralpak IA, hexane/2-propanol = 40:1, flow rate = 1.0 mL/min, 205 nm; retention time: 26.5 min (major) and 30.9 min (minor). ¹H NMR (400 MHz, CDCl₃) δ 7.26–7.38 (m, 10H), 6.95 (s, 1H), 4.22 (dd, *J* = 7.4, 12.6 Hz, 1H), 4.18 (dd, *J* = 7.0, 13.0 Hz, 1H), 2.40 (t, *J* = 7.2 Hz, 1H), 2.16–2.32 (m, 2H), 1.18–1.28 (m, 2H), 0.89 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.1, 138.6, 138.5, 128.63, 128.61, 128.5, 128.4, 127.1, 127.0, 96.4, 79.6, 64.3, 34.6, 17.1, 13.9; IR (neat)

3566, 2965, 2932, 2876, 1744, 1553, 1454, 1223, 1146, 1065, 1003, 745, 696 cm⁻¹; HRMS (ESI-TOF) calcd for $C_{19}H_{21}NO_5Na^+$: 366.1312 ([M+Na]⁺), found 366.1304.

3c: $[\alpha]^{28}{}_{\rm D}$ = +14.6 (*c* = 0.60, CHCl₃), HPLC analysis (81% ee): Daicel Chiralpak IA, hexane/2-propanol = 40:1, flow rate = 1.0 mL/min, 210 nm; retention time: 23.6 min (major) and 27.6 min (minor). ¹H NMR (400 MHz, CDCl₃) δ 7.26–7.39 (m, 10H), 6.96 (s, 1H), 4.24 (dd, *J* = 7.6, 12.8 Hz, 1H), 4.18 (dd, *J* = 7.0, 12.6 Hz, 1H), 2.39 (t, *J* = 7.2 Hz, 1H), 2.18–2.33 (m, 2H), 1.21–1.31 (m, 2H), 1.10–1.20 (m, 2H), 0.81 (t, *J* = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.1, 138.7, 138.5, 128.64, 128.62, 128.5, 128.4, 127.3, 127.0, 96.5, 79.6, 64.3, 32.4, 25.7, 22.7, 13.5; IR (neat) 3559, 2959, 2930, 2872, 1748, 1551, 1454, 1211, 1067, 1015, 758, 743, 696 cm⁻¹; HRMS (ESI-TOF) calcd for C₂₀H₂₃NO₅Na⁺: 380.1468 ([M+Na]⁺), found 380.1468.



3d: $[\alpha]^{29}{}_{D} = \pm 11.3$ (*c* = 0.50, CHCl₃), HPLC analysis (82% ee): Daicel Chiralpak IA, hexane/2-propanol = 40:1, flow rate = 1.0 mL/min, 210 nm; retention time: 22.8 min (major) and 30.8 min (minor). ¹H NMR (400 MHz, CDCl₃) δ 7.26–7.38 (m, 10H), 6.97 (s, 1H), 4.24 (dd, J = 7.6, 12.8 Hz, 1H), 4.16 (dd, J = 7.2, 12.8 Hz, 1H), 2.38 (t, J = 7.2 Hz, 1H), 2.18–2.33 (m, 2H), 1.41–1.51 (m, 1H), 0.98–1.08 (m, 2H), 0.82 (d, J = 6.8 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 165.1, 138.6, 138.5, 128.64, 128.60, 128.5, 128.3, 127.3, 126.9, 96.5, 79.5, 64.3, 32.2, 30.7, 28.1, 22.08, 22.06; IR (neat) 3545, 2957, 2932, 2872, 1746, 1553, 1454, 1213, 1022, 758, 745, 696 cm⁻¹; HRMS (ESI-TOF) calcd for C₂₁H₂₅NO₅Na⁺: 394.1625 ([M+Na]⁺), found 394.1617.

O₂N CO₂CHPh₂

3e: $[\alpha]_{D}^{29} = +16.9$ (*c* = 1.0, CHCl₃), HPLC analysis (76% ee): Daicel Chiralpak IA, hexane/2-propanol = 40:1, flow rate = 1.0 mL/min, 210 nm; retention time: 27.3 min (major) and 34.1 min (minor). ¹H NMR (400 MHz, CDCl₃) δ 7.28–7.39 (m, 10H), 6.96 (s, 1H),

5.62–7.72 (m, 1H), 4.94–4.99 (m, 2H), 4.25 (dd, J = 7.8, 12.6 Hz, 1H), 4.19 (dd, J = 7.2, 12.8 Hz, 1H), 2.29–2.44 (m, 3H), 1.96–2.04 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 164.8, 138.5, 138.4, 135.7, 128.64, 128.60, 128.5, 128.3, 127.2, 126.9, 116.2, 96.0, 79.6, 64.1, 31.6, 27.7; IR (neat) 3560, 3065, 3032, 2978, 2943, 1746, 1553, 1450, 1211, 1030, 914, 758, 745, 696 cm⁻¹; HRMS (ESI-TOF) calcd for C₂₀H₂₁NO₅Na⁺: 378.1312 ([M+Na]⁺), found 378.1310.



3f: $[\alpha]^{25}_{D} = +11.3$ (*c* = 1.1, CHCl₃), HPLC analysis (74% ee): Daicel Chiralpak IA, hexane/2-propanol = 40:1, flow rate = 1.0 mL/min, 210 nm; retention time: 44.1 min (major) and 50.4 min (minor). ¹H NMR (400 MHz, CDCl₃) δ 7.25–7.40 (m, 10H), 6.94 (s, 1H), 4.23 (dd, J = 8.0, 12.8 Hz, 1H), 4.14 (dd, J = 7.2, 12.8 Hz, 1H), 3.60 (t, J = 7.2 Hz, 2H), 2.49 (t, J = 7.2 Hz, 1H), 2.16–2.33 (m, 2H), 1.63 (s, 9H), 1.30–1.37 (m, 2H), 1.05–1.13 (m, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 164.7, 152.2, 138.5, 138.4, 128.72, 128.65, 128.6, 128.4, 127.2, 126.9, 95.9, 85.7, 79.7, 63.9, 39.6, 31.6, 28.0, 26.7, 20.8; IR (neat) 3512, 2980, 2941, 1744, 1555, 1369, 1134, 993, 760, 737, 698 cm⁻¹; HRMS (ESI-TOF) calcd for C₂₅H₃₂N₂O₇Na⁺: 495.2102 ([M+Na]⁺), found 495.2124.

Reduction of the nitro group on product 2d.¹

To a solution of the product **2d** (0.040 mmol, 91% ee) in 2-propanol (0.15 mL) was added zinc dust (55 mg) and acetic acid (75 μ L) at room temperature. The resulting mixture was stirred for 6 h and then quenched with saturated aqueous NaHCO₃. The solution was filtrated over celite to remove zinc dust. The filtrate was extracted with CH₂Cl₂, and the extracts were washed with brine and dried over Na₂SO₄. After evaporation of solvents, the residue was purified by column chromatography on silica gel (CH₂Cl₂/MeOH = 10:1 as eluent) to afford the product **4** in 85% yield. The enantiomeric excess of **4** was confirmed by chiral HPLC analysis after derivatization to *N*-Boc protected compound.

H₂N CO₂CHPh₂ Me OH

4: $[\alpha]_{D}^{28} = +4.6 \ (c = 0.80, \text{ CHCl}_3)$. ¹H NMR (400 MHz, CDCl₃) δ 7.28–7.38 (m, 10H), 6.88 (s, 1H), 3.82 (d, J = 10.4 Hz, 1H), 3.51 (d, J = 10.4 Hz, 1H), 1.63 (br, 3H), 1.34 (s, 3H); ¹³C NMR

 $(100 \text{ MHz}, \text{CDCl}_3) \delta 175.4, 139.8, 128.6, 128.08, 128.05, 127.0, 126.9, 77.8, 68.6, 59.1, 22.8;$ IR (neat) 3358, 3300, 3063, 3032, 2928, 1732, 1454, 1215, 1126, 1061, 756, 743, 696 cm⁻¹; HRMS (ESI-TOF) calcd for C₁₇H₁₉NO₃Na⁺: 308.1257 ([M+Na]⁺), found 308.1256.

BocHN CO₂CHPh₂ Me OH

 $[\alpha]^{28}_{D} = -8.3$ (*c* = 0.70, CHCl₃), HPLC analysis (91% ee): Daicel Chiralpak IA, hexane/2-propanol = 10:1, flow rate = 0.5 mL/min, 210 nm; retention time: 29.9 min (minor) and 49.9 min (major). ¹H NMR (400 MHz, CDCl₃) δ 7.26–7.34 (m, 10H), 6.90 (s, 1H), 5.31 (br, 1H), 4.01–4.06 (m, 1H), 3.82–3.86 (m, 1H), 1.50 (s, 3H), 1.39 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 172.4, 155.3, 139.6, 128.5, 128.1, 128.0, 127.2, 127.0, 80.3, 78.3, 67.1, 61.1, 28.2, 20.7; IR (neat) 3412, 2978, 2932, 1715, 1497, 1368, 1250, 1167, 1125, 1055, 758, 743, 698 cm⁻¹; HRMS (ESI-TOF) calcd for C₂₂H₂₇NO₅Na⁺: 408.1781 ([M+Na]⁺), found 408.1776.

Determination of absolute configuration.

The absolute configuration of the products was assigned to be *R* by comparison of the optical rotation with the literature value for compound 5^{2} , which was prepared from product 2c (87% ee).

H₂N Me OH

5:² $[\alpha]^{29}{}_{D}$ = +7.5 (*c* = 1.1, CHCl₃), {lit. $[\alpha]^{29}{}_{D}$ = -9.0 (*c* = 0.66, CHCl₃) for (*S*)}.^{2b 1}H NMR (400 MHz, CDCl₃) δ 7.32–7.39 (m, 5H), 5.18 (s, 2H), 3.78 (d, *J* = 10.8 Hz, 1H), 3.48 (d, *J* = 10.4 Hz, 1H), 1.95 (br, 3H), 1.31 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 176.0, 135.6, 128.6, 128.3, 127.9, 68.5, 67.0, 59.1, 22.7; IR (neat) 3347, 3223, 3063, 3032, 2930, 2872, 1734, 1454, 1211, 1069, 1047, 1022, 735, 696 cm⁻¹; HRMS (ESI-TOF) calcd for C₁₁H₁₅NO₃Na⁺: 232.0944 ([M+Na]⁺), found 232.0950.

References

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