Readily Accessible 9-*epi*-amino Cinchona Alkaloid Derivatives promote Efficient,
Highly Enantioselective Additions of Aldehydes and Ketones to Nitroolefins

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1.0 General

Proton Nuclear Magnetic Resonance spectra were recorded on a 400 MHz spectrometer in CDCl₃ (unless otherwise stated) referenced relative to residual CHCl₃ (δ = 7.26 ppm). Chemical shifts are reported in ppm and coupling constants in Hertz. Carbon NMR spectra were recorded on the same instrument (100 MHz) with total proton decoupling. All melting points are uncorrected. Flash chromatography was carried out using silica gel, particle size 0.04-0.063 mm. TLC analysis was performed on precoated 60F₂₅₄ slides, and visualised by UV irradiation, KMnO₄ or anisaldehyde staining. Optical rotation measurements are quoted in units of 10⁻¹ deg cm² g⁻¹. Unless otherwise stated all standard reagents were obtained from commercial sources and used as received. Nitroolefins were sourced commercially or prepared as per the literature procedure.¹ Toluene was distilled from calcium hydride. Analytical CSP-HPLC was performed on a Daicel CHIRALPAK AD-H, OD-H and AS columns (4.6 mm x 25 cm).

2.0 Catalyst Synthesis

9-Amino-9-deoxydihydroquinine 3HCl Salt (DHQA-3HCl).

Diisopropyl azodicarboxylate (1.46 g, 7.21 mmol) was added to a stirred solution of **9-epi-DHQ**² (1.57 g, 4.81 mmol) and triphenylphosphane (1.51 g, 5.77 mmol) in THF (0.18 M, 30 mL) at 0 °C *via* syringe under an argon atmosphere. After 5 min, diphenylphosphoryl azide (DPPA) (1.99 g, 7.21 mmol) was added dropwise by syringe. The solution was stirred for 4 h at room temperature, after which the mixture was heated at 45 °C for 2 h. Triphenylphosphane (1.51 g, 5.77 mmol) was added in one portion, and the solution was heated until gas evolution ceased (*ca.* 2 h). Water (2 mL) was added and the solution was stirred for 4 h. The reaction was concentrated *in vacuo* and the residue was partitioned between CH₂Cl₂ and 2 N HCl (1:1, 80 mL). After the mixture was vigorously shaken, the aqueous phase was separated and washed with CH₂Cl₂ (2 x 10 mL). The aqueous layer was concentrated under reduced pressure. The resulting solid was recrystallised from EtOAc and MeOH to give **DHQA-3HCl** (1.19 g, 57 %) as a yellow solid. M.p. 132-133 °C. $[\alpha]_D^{23} = -57.7$ (c 0.3, MeOH). ¹H NMR (CDCl₃) δ 0.81 (t, 3H, J = 7.5 Hz), 1.44 (app. dt, 2H, J = 2.2, 7.6 Hz), 1.79-1.86 (m, 1H), 1.91-1.98 (m, 2H), 2.05-2.11 (m, 1H), 2.24 (d, 1H, J = 2.4 Hz), 2.47-2.54 (m, 1H), 2.86 (dq, 1H, J = 2.8, 13.4 Hz), 2.93 (dt, 1H, J = 4.9, 12.4 Hz), 3.18-3.25 (m, 1H), 3.28 (dd, 1H, J = 10.5, 13.0 Hz), 3.95 (s, 3H), 4.21 (q, 1H, J = 9.0 Hz), 5.68 (d, 1H, J = 10.5 Hz), 7.61 (d, 1H, J = 2.4 Hz), 7.70 (dd, 1H, J = 2.4, 9.3 Hz), 7.98 (d, 1H, J = 5.52 Hz), 8.12 (d, 1H, J = 9.6 Hz), 8.89 (d, 1H, J = 5.0 Hz). ¹³C NMR (CDCl₃) δ 10.3, 22.6, 22.9, 23.1, 25.5, 33.7, 42.2, 48.9, 55.8, 56.1, 59.0, 100.8, 120.7, 124.4, 127.6, 129.0 (q), 135.5 (q), 141.5, 144.6 (q), 161.0 (q). IR (solid) 3370, 2567, 1619, 1606, 1381, 1243, 1019, 850. HRMS (*m/z* -ES) (free base) calcd for C₂₀H₂₈N₃O (M+H)⁺ 326.2232, found 326.2225.

9-epi-9-Amino-9-deoxydihydroquinine 3HCl Salt (9-epi-DHQA-3HCl).

Diisopropyl azodicarboxylate (1.49 g, 7.35 mmol) was added to a stirred solution of **DHQ** (2.00 g, 6.13 mmol) and triphenylphosphane (1.93 g, 7.35 mmol) in THF (0.18 M, 35 mL) at 0 °C *via* syringe under an argon atmosphere. After 5 min, diphenylphosphoryl azide (DPPA) (2.02 g, 7.35 mmol) was added dropwise by syringe. The solution was stirred for 4 h at room temperature, after which the mixture was heated at 45 °C for 2 h. Triphenylphosphane (1.93 g, 7.35 mmol) was added in one portion, and the solution was heated until gas evolution ceased (approx. 2 h). Water (2 mL) was added and the solution was stirred for 4 h. The reaction was concentrated *in vacuo* and the residue was partitioned between CH₂Cl₂ and 2 N HCl (1:1, 80 mL). After the mixture was vigorously shaken, the aqueous phase was separated and washed with CH₂Cl₂ (2 x 20 mL). The aqueous layer was concentrated under reduced pressure. The resulting solid was recrystallised from EtOAc and MeOH to give **9-epi-DHQA-3HCl** (2.67 g, 86 %) as a yellow solid. M.p. 214-215 °C (dec). $[\alpha]_D^{23} = +12.6$ (c 0.4, MeOH). ¹H NMR (CDCl₃) δ 0.73 (t, 3H, J = 7.5 Hz), 1.03 (ddd, 1H, J = 2.0, 5.5, 14.0 Hz), 1.24-1.39 (m, 2H), 1.73-1.80 (m, 1H), 1.86-1.97 (m, 4H), 2.97 (ddd, 1H, J = 3.0, 6.1, 13.0 Hz), 3.26-3.31 (m, 1H), 3.66 (dd, 1H, J = 10.5, 13.0 Hz), 3.76-3.83 (m, 1H), 3.97 (s, 3H), 4.04 (ddd, 1H, J = 3.5, 7.0, 18.1 Hz), 5.22 (d, 1H, J = 11.0 Hz), 7.67 (d, 1H, J = 2.0 Hz), 7.76 (dd, 1H, J = 2.5, 9.5 Hz), 7.96 (d, 1H, J = 6.0 Hz), 8.12 (d, 1H, J = 9.5 Hz), 8.85 (d, 1H, J = 6.0 Hz). ¹³C NMR (CDCl₃) δ 10.1, 22.6, 22.8, 23.4, 25.3, 33.7, 41.1, 48.3, 55.3, 55.8, 59.9, 102.1, 119.4, 123.5, 126.7, 128.7 (q), 134.6 (q), 140.9, 146.34 (q), 160.1 (q). IR (solid) 3372, 2560, 1619, 1606, 1498, 1378, 1245, 1017, 853 cm⁻¹. HRMS (*m/z* –ES) (free base) calcd for C₂₀H₂₈N₃O (M+H)⁺ 326.2232, found 326.2231.

9-epi-9-Amino-9-Deoxy-Dihydroquinidine 3HCl Salt (9-epi-DHQDA-3HCl)

Diisopropyl azodicarboxylate (3.13 g, 15.5 mmol) was added to a stirred solution of **DHQD** (4.20 g, 12.9 mmol) and triphenylphosphane (3.13 g, 15.5 mmol) in THF (0.20 M, 63 mL) at 0 °C *via* syringe under an argon atmosphere. After 5 min, diphenylphosphoryl azide (DPPA) (4.26 g, 15.5 mmol) was added dropwise by syringe. The solution was stirred for 4 h at room temperature, after which the mixture was heated at 45 °C for 2 h. Triphenylphosphane (4.07 g, 15.5 mmol) was added in one portion, and the solution was heated until gas evolution ceased (approx. 2 h). Water (3 mL) was added and the solution was stirred for 4 h. The reaction was concentrated *in vacuo* and the residue was partitioned between CH₂Cl₂ and 2 N HCl (1:1, 170 mL). After the mixture was vigorously shaken, the aqueous phase was separated and washed with CH₂Cl₂ (2 x 30 mL). The aqueous layer was concentrated

under reduced pressure. The resulting solid was recrystallised from EtOAc and MeOH to give **9-epi-DHQDA-3HCl** (3.09 g, 55 %) as a fine white solid. M.p. 224-226 °C (dec). $[\alpha]_D^{20} = +36.7$ (c 0.7, MeOH). ^1H NMR (CDCl_3) δ 0.77 (t, 3H, $J = 7.3$ Hz), 1.21-1.41 (m, 4H), 1.79-1.84 (bs, 3H), 1.94 (t, 1H, $J = 8.5$ Hz), 3.22 (ddd, 1H, $J = 1.4, 8.0, 11.7$ Hz), 3.38 (ddd, 1H, $J = 3.7, 12.4, 22.0$ Hz), 3.45-3.50 (m, 1H), 3.55 (dd, 1H, $J = 10.2, 11.7$ Hz), 3.64 (s, 3H), 4.04-4.10 (m, 1H), 5.56 (d, 1H, $J = 10.0$ Hz), 7.69 (d, 1H, $J = 2.0$ Hz), 7.79 (dd, 1H, $J = 2.0, 9.0$ Hz), 8.08 (d, 1H, $J = 5.5$ Hz), 8.16 (d, 1H, $J = 9.5$ Hz), 8.93 (d, 1H, $J = 4.0$ Hz). ^{13}C NMR (CDCl_3) δ 10.0, 22.0, 22.2, 23.2, 24.0, 33.6, 47.7, 48.4, 48.8, 56.0, 59.7, 101.4, 120.2, 123.4, 127.8, 129.0 (q), 134.4 (q), 140.6, 147.5 (q), 161.7 (q). IR (solid) 3377, 2557, 1619, 1606, 1429, 1381, 1243, 1020, 850 cm^{-1} . HRMS (m/z –ES) (free base) calcd for $\text{C}_{20}\text{H}_{28}\text{N}_3\text{O}$ ($\text{M}+\text{H}$) $^+$ 326.2232, found 326.2232.

***N*-Benzyl-9-epi-9-amino-9-deoxy-dihydroquinine 3HCl Salt (9-epi-9-amino-DHQBA-3HCl).**

To a suspension of **9-epi-DHQA-3HCl** (0.800 g, 1.84 mmol), molecular sieves (4Å) and MeOH (0.8 M, 2.4 mL) was added triethylamine (0.745 g, 7.36 mmol) under an atmosphere of argon. The solution was cooled to 0 °C, whereupon benzaldehyde (0.390 g, 3.68 mmol) was added dropwise *via* syringe. The reaction was allowed to warm to room temperature and left to stir for 3.5 h. The solution was re-cooled to 0 °C and sodium borohydride (0.139 g, 3.68 mmol) was introduced in small portions over 30 min. The reaction was diluted with EtOAc (30 mL) and washed with water (5 x 50 mL). The organic layer was acidified with 2M HCl (20 mL). The aqueous layer was concentrated *in vacuo*. The resulting solid was recrystallised from EtOAc and MeOH to give **9-epi-DHQBA-3HCl** (0.657 g, 68 %) as an off-white solid. M.p. 209-210 °C (dec). $[\alpha]_D^{20} = -59.4$ (c 0.3, MeOH). ^1H NMR (CDCl_3) δ 0.70 (t, 3H, $J = 7.5$ Hz), 0.95 (dd, 1H, $J = 7.0, 13.5$ Hz), 1.20-1.33 (m, 2H), 1.56 (dt, 1H, $J = 1.5, 11.5$ Hz), 1.81-1.85 (m, 3H), 1.89-1.96 (m, 1H), 2.90 (dd, 1H, $J = 3.5, 12.0$ Hz), 3.16-3.24 (m, 1H), 3.45-3.51 (m, 1H), 3.53-3.61 (m, 1H), 3.56 (d, 1H, $J = 13.5$ Hz), 3.66 (d, 1H, $J = 13.5$ Hz), 3.70-3.77 (m, 1H), 3.89 (s, 3H, OMe), 4.59 (d, 1H, $J = 11.0$ Hz), 6.93 (bs, 5H), 7.32 (d, 1H, $J = 1.5$ Hz), 7.73 (dd, 1H, $J = 1.0, 9.3$ Hz), 7.98 (d, 1H, $J = 6.0$ Hz), 8.02 (d, 1H, $J = 9.3$ Hz), 8.75 (d, 1H, $J = 6.0$ Hz). ^{13}C NMR (CDCl_3) δ 10.2, 22.1, 22.9, 23.5, 25.3, 33.8, 41.1, 49.8, 54.8, 54.9, 55.9, 60.0, 102.2, 120.1, 122.5, 127.3, 127.4, 127.7, 128.5, 129.7 (q), 132.8 (q), 136.2 (q), 139.7, 153.7 (q), 160.0 (q). IR (solid) 3371, 2553, 1619, 1606, 1381, 1243, 1019, 850 cm^{-1} . HRMS (m/z –ES (free base) calcd for $\text{C}_{27}\text{H}_{34}\text{N}_3\text{O}$ ($\text{M}+\text{H}$) $^+$ 416.2712, found 416.2702.

3.0 Procedure for the synthesis of ketone adducts (2-7).

Procedure A: A 1 mL reaction vial containing a stirring bar was charged with (*E*)- β -nitrostyrene (60 mg, 0.400 mmol), and benzoic acid (5 mg, 0.040 mmol). The amine catalyst (13 mg, 0.040 mmol) in a solution of the appropriate ketone (2.000 mmol) was added *via* syringe. The vial was fitted with a lid and stirred for the time indicated in Tables 1 and 2. When conversion was adjudged to be complete (TLC) the solution was diluted with 1:5 EtOAc-Hexane and purified by column chromatography.

4.0 Procedure for the synthesis of ketone adducts (8-18).

Procedure B: A 1 mL reaction vial containing a stirring bar was charged with the appropriate nitroolefin (0.400 mmol), and benzoic acid (5 mg, 0.040 mmol). The reaction vessel was fitted with a septum and flushed with argon gas. **9-*epi*-DHQDA** (13 mg, 0.040 mmol), in a solution of the appropriate aldehyde (2.000 mmol) was added *via* syringe. The vial was fitted with a lid and stirred for the time indicated in Tables 3 and 4. When conversion was adjudged to be complete (TLC) the solution was diluted with 1:5 EtOAc-Hexane and purified by column chromatography.

5.0 Procedure for lower temperature reactions (2, 5, and 11).

Procedure C: A reaction vial containing a stirring bar was charged with (*E*)- β -nitrostyrene (60 mg, 0.400 mmol), and benzoic acid (7 mg, 0.060 mmol) was fitted with a septum, flushed with argon gas and then cooled to the required temperature. **9-*epi*-DHQDA** (20 mg, 0.060 mmol) in a solution of the appropriate carbonyl compound (2.000 mmol) was cooled to the desired temperature and added *via* syringe. The vial was fitted with a lid and stirred for the time indicated. When conversion was adjudged to be complete (TLC) the solution was diluted with 1:5 EtOAc-Hexane and purified by column chromatography.

6.0 Characterisation data

(-)-(R)-5-Nitro-4-phenyl-pentan-2-one (**2**, entry 15).³

Prepared as per procedure C using **9-epi-DHQDA** (0.080 mmol, 26 mg) and benzoic acid (0.080 mmol, 10 mg). Flash chromatography (1:10 EtOAc-Hexane) gave **2** (60 mg, 73%) as a white solid. M.p. 101-102 °C (lit.,⁴ 101-102 °C).

71% *ee*. $[\alpha]_D^{22} = -13.3$ (c 0.1, CHCl₃). Chiralpak AS (4.6 mm x 25 cm), hexane/IPA, 65/35, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 9.6 min (minor enantiomer) and 11.4 min (major enantiomer).

¹H NMR (DMSO-d₆) δ 2.04 (s, 3H), 2.92 (d, 2H, J = 7.0 Hz), 3.79-3.87 (m, 1H), 4.77 (dd, 1H, J = 9.5, 13.0 Hz), 4.87 (dd, 1H, J = 6.0, 13.0 Hz), 7.21 – 7.26 (m, 1H), 7.31 (m, 4H, J = 4.0 Hz).

(-)-(3S,4R)-3-Methyl-5-nitro-4-phenyl-pentan-2-one (**3**).⁵

Prepared as per procedure A using **9-epi-DHQDA** (0.080 mmol, 26 mg) and benzoic acid (0.080 mmol, 10 mg). Flash chromatography (1:10 EtOAc-Hexane) gave **3** (62 mg, 71%) as a waxy white solid (4.8:1 mixture of diastereomers). M.p. 81-82 °C.

96% *ee*. $[\alpha]_D^{22} = -22.2$ (c 0.1, CHCl₃). Chiralpak AS (4.6 mm x 25 cm), hexane/IPA, 90/10, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 10.5 min (minor enantiomer, major diastereomer) and 12.1 min (major enantiomer, major diastereomer). 15.6 min (minor enantiomer, minor diastereomer) and 16.3 min (major enantiomer, minor diastereomer).

¹H NMR (CDCl₃) δ 1.00 (d, 3H, J = 7.0 Hz), 2.27 (s, 3H), 2.97-3.06 (m, 1H), 3.70 (app dt, 1H, J = 5.0, 9.6 Hz), 4.63-4.72 (m, 2H), 7.15 – 7.20 (m, 2H), 7.29 – 7.43 (m, 3H).

(+)-(4*S*,5*R*)-4-Methyl-6-nitro-5-phenyl-hexan-3-one (4).

Prepared as per procedure A using **9-*epi*-DHQDA** (0.080 mmol, 26 mg) and benzoic acid (0.080 mmol, 10 mg). Flash chromatography (1:10 EtOAc-Hexane) gave **4** (82 mg, 87%) as a pale yellow oil (10:1 mixture of diastereomers).

99% *ee*. $[\alpha]_D^{22} = +8.9$ (c 0.2, CHCl₃). Chiralpak OD-H (4.6 mm x 25 cm), hexane/IPA, 97/3, 0.5 mL min⁻¹, RT, UV detection at 220 nm, retention times: 37.5 min (minor enantiomer, major diastereomer) and 29.1 min (major enantiomer, major diastereomer). 39.5 min (minor enantiomer, minor diastereomer) and 54.7 min (major enantiomer, minor diastereomer).

¹H NMR (CDCl₃) δ 1.00 (d, 3H, J = 7.0 Hz), 1.09 (app. t, 3H, J = 7.5 Hz), 2.43 (dq, 1H, J = 7.5, 18.0 Hz), 2.64 (dq, 1H, J = 7.0, 18.0 Hz), 2.98-3.06 (m, 1H), 3.72 (app dt, 1H, J = 4.5, 9.0 Hz), 4.62 (dd, 1H, J = 4.5, 12.0 Hz), 4.70 (dd, 1H, J = 6.5, 12.0 Hz), 7.18–7.21 (m, 2H), 7.30–7.37 (m, 3H).

(-)-(S)-3-[(R)-2-Nitro-1-phenyl-ethyl]-tetrahydro-pyran-4-one (5, entry 4).

Prepared as per procedure C. Flash chromatography (1:10 EtOAc-Hexane) gave **5** (91 mg, 91%) as a white solid. M.p. 119-120 °C (10:1 mixture of diastereomers).

78% *ee*. $[\alpha]_D^{23} = -19.5$ (c 0.2, CHCl₃). Chiralpak OD-H (4.6 mm x 25 cm), hexane/IPA, 90/10, 0.5 mL min⁻¹, RT, UV detection at 220 nm, retention times: 59.3 min (minor enantiomer, major diastereomer) and 66.2 min (major enantiomer, major diastereomer). 79.5 min (minor and minor enantiomer, minor diastereomer).

¹H NMR (CDCl₃) δ 2.59 (dt, 1H, J = 4.0, 17.6 Hz), 2.66-2.74 (m, 1H), 2.88-2.94 (m, 1H), 3.30 (dd, 1H, J = 9.0, 11.5 Hz), 3.70-3.74 (m, 1H), 3.77-3.89 (m, 2H), 4.15-4.20 (m, 1H), 7.21 (d, 2H, J = 7.0 Hz), 7.26–7.39 (m, 3H).

(-)-(S)-3-[(R)-2-Nitro-1-phenyl-ethyl]-tetrahydro-thiopyran-4-one (6).

A 1mL reaction vial containing a stirring bar was charged with (*E*)- β -nitrostyrene (60 mg, 0.400 mmol), tetrahydro-thiopyran-4-one (2.000 mmol), and benzoic acid (5 mg, 0.040 mmol). **9-*epi*-DHQDA** (13 mg, 0.040 mmol) in a solution of toluene (100 μ L) was added via syringe. The lid was put in place and wrapped in parafilmTM. When conversion was adjudged to be complete (TLC) the solution was diluted with 1:5 EtOAc-Hexane. The crude solution was loaded onto flash silica and purified by column chromatography (1:15 EtOAc-Hexane) to give **6** (88 mg, 88%) as a white solid. M.p. 144-145 °C (11:1 mixture of diastereomers).

69% *ee*. $[\alpha]_D^{22} = -21.9$ (c 0.2, CHCl₃). Chiralpak AS (4.6 mm x 25 cm), hexane/IPA, 90/10, 0.5 mL min⁻¹, RT, UV detection at 220 nm, retention times: 47.2 min (minor enantiomer, major diastereomer) and 55.6 min (major enantiomer major diastereomer). 62.5 min (minor enantiomer, minor diastereomer) and 79.5 min (major enantiomer, minor diastereomer).

¹H NMR (CDCl₃) δ 2.48 (dd, 1H, J = 9.0, 14.0 Hz), 2.64 (ddd, 1H, J = 1.5, 4.0, 14.0 Hz) 2.73-3.03 (m, 5H), 4.00 (app dt, 1H, J = 4.5, 10.5 Hz), 4.66 (dd, 1H, J = 9.6, 12.6 Hz), 4.76 (dd, 1H, J = 4.5, 12.6), 7.22 (d, 2H, J = 7.0 Hz), 7.29 – 7.38 (m, 3H).

(-)-(S)-2-[(R)-2-Nitro-1-phenyl-ethyl]-cyclohexanone (7).⁶

Prepared as per procedure A using **9-*epi*-DHQDA**. Flash chromatography (1:10 EtOAc-Hexane) gave **7** (90 mg, 91%) as an off-white solid (7.1:1 mixture of diastereomers). M.p. 103-104 °C (lit.,⁷ 106 °C).

84% *ee*. $[\alpha]_D^{22} = -9.1$ (c 0.1, CHCl₃). Chiralpak OD-H (4.6 mm x 25 cm), hexane/IPA, 90/10, 0.2 mL min⁻¹, RT, UV detection at 220 nm, retention times: 80.7 min (minor enantiomer, major diastereomer) and 84.1 min (major enantiomer, major diastereomer). 110.2 min (minor enantiomer, minor diastereomer) and 88.9 min (major enantiomer, minor diastereomer).

^1H NMR (CDCl_3) δ 1.21-1.30 (m, 1H), 1.63-1.84 (m, 4H), 2.07-2.13 (m, 1H), 2.43 (dd, 1H, $J = 5.5, 12.0$ Hz), 2.48-2.53 (m, 1H), 2.68-2.75 (m, 1H), 3.78 (app dt, 1H, $J = 4.5, 10.0$ Hz), 4.66 (dd, 1H, $J = 10.4, 12.5$ Hz), 4.96 (dd, 1H, $J = 4.5, 12.5$ Hz), 7.19 (d, 2H, $J = 7.0$ Hz), 7.26 – 7.37 (m, 3H).

(-)-(R)-1-(2-Nitro-1-phenyl-ethyl)-cyclopentanecarbaldehyde (8).⁸

Prepared as per procedure B. Flash chromatography (1:20 EtOAc-Hexane) gave **8** (96 mg, 97%) as a colourless oil.

91% *ee*. $[\alpha]_{\text{D}}^{22} = -13.2$ (c 0.2, CHCl_3). Chiralpak OD-H (4.6 mm x 25 cm), hexane/IPA, 90/10, 0.7 mL min^{-1} , RT, UV detection at 220 nm, retention times: 32.1 min (minor enantiomer) and 22.3 min (major enantiomer).

^1H NMR (CDCl_3) δ 1.54-1.69 (m, 6H), 1.88-1.93 (m, 1H), 2.05-2.09 (m, 1H), 3.72 (dd, 1H, $J = 4.0, 11.5$ Hz), 4.72 (dd, 1H, $J = 3.5, 13.3$ Hz), 4.99 (dd, 1H, $J = 11.5, 13.3$ Hz), 7.22 (dd, 2H, $J = 1.5, 8.0$ Hz), 7.26 – 7.36 (m, 3H), 9.52 (s, 1H)

(+)-(R)-2,2-Dimethyl-4-nitro-3-phenyl-butyraldehyde (9, entry 2).⁹

Prepared as per procedure B. Flash chromatography (1:20 EtOAc-Hexane) gave **9** (80 mg, 93%) as a colourless oil.

88% *ee*. $[\alpha]_{\text{D}}^{21} = +10.0$ (c 0.3, CHCl_3). Chiralpak AS (4.6 mm x 25 cm), hexane/IPA, 90/10, 0.7 mL min^{-1} , RT, UV detection at 220 nm, retention times: 15.2 min (minor enantiomer) and 16.5 min (major enantiomer).

^1H NMR (CDCl_3) δ 1.04 (s, 3H), 1.16 (s, 3H), 3.81 (dd, 1H, $J = 4.1, 11.4$ Hz), 4.71 (dd, 1H, $J = 4.1, 12.8$), 4.88 (dd, 1H, $J = 11.4, 12.8$ Hz), 7.22 (d, 2H, $J = 6.4$ Hz), 7.30–7.38 (m, 3H), 9.56 (s, 1H).

(+)-(2*R*,3*S*)-2-Ethyl-2-methyl-4-nitro-3-phenyl-butyraldehyde (10).

Prepared as per procedure B. Flash chromatography (1:20 EtOAc-Hexane) gave **10** (89 mg, 95%) as a colourless oil (2:1 mixture of diastereomers).

92% *ee*. $[\alpha]_D^{22} = +16.7$ (c 0.2, CHCl₃). Chiralpak OD-H (4.6 mm x 25 cm), hexane/IPA, 95/5, 1.0 mL min⁻¹, RT, UV detection at 220 nm, retention times: 41.5 min (minor enantiomer, major diastereomer) and 23.8 min (major enantiomer major diastereomer). 27.3 min (minor enantiomer, minor diastereomer) and 20.3 min (major enantiomer, minor diastereomer).

¹H NMR (Both diastereomers, CDCl₃) δ 0.84 (t, 3H, J = 7.5 Hz), 0.91 (t, 2H, J = 7.5 Hz), 1.13 (s, 5H), 1.28-1.37 (m, 2H), 1.53-1.68 (m, 1H), 1.71-1.81 (m, 0.6H), 3.78-3.84 (m, 2H), 4.64 (dd, 1H, J = 4.0, 13.0 Hz), 4.78 (dd, 0.6H, J = 4.5, 13.0 Hz), 4.83-4.91 (m, 2H), 7.18-7.24 (m, 3H), 7.30-7.38 (m, 5H), 9.54 (s, 0.5H), 9.56 (s, 1H).

(+)-(2*R*,3*S*)-2-Methyl-4-nitro-2,3-diphenyl-butyraldehyde (11).

Prepared as per procedure B/C. Flash chromatography (1:20 EtOAc-Hexane) gave **11** (105 mg, 93%) as a waxy white solid. M.p. 79-80 °C (lit.,¹⁰ 101-103 °C, mixture of diastereomers).

66% *ee*. $[\alpha]_D^{23} = +84.6$ (c 0.4, CHCl₃). Chiralpak AS (4.6 mm x 25 cm), hexane/IPA, 97/3, 0.7 mL min⁻¹, RT, UV detection at 220 nm, retention times: 25.5 min (minor enantiomer) and 27.5 min (major enantiomer).

¹H NMR (CDCl₃) δ 1.55 (s, 3H), 4.22 (dd, 1H, J = 4.0, 11.6 Hz), 4.88 (dd, 1H, J = 3.5, 13.0 Hz), 5.05 (dd, 1H, J = 11.6, 13.0 Hz), 6.95-6.97 (m, 2H), 7.08 (d, 2H, J = 7.0 Hz), 7.17-7.14 (m, 3H), 7.29-7.36 (m, 3H), 9.59 (s, 1H).

(+)-(2R)-Isopropyl-(3S)-phenyl-4-nitro-butyaldehyde (12).¹¹

Prepared as per procedure B using **9-epi-DHQDA** (20 mg, 0.060 mmol) and benzoic acid (7 mg, 0.060 mmol). Flash chromatography (1:20 EtOAc-Hexane) gave **12** (71 mg, 76%) as a colourless oil (6.7:1 mixture of diastereomers).

95% *ee*. $[\alpha]_D^{21} = +51.4$ (c 0.1, CHCl₃). Chiralpak OD-H (4.6 mm x 25 cm), hexane/IPA, 97/3, 0.7 mL min⁻¹, RT, UV detection at 220 nm, retention times: 41.2 min (minor enantiomer, major diastereomer) and 37.9 min (major enantiomer, major diastereomer). 31.6 min (minor enantiomer, minor diastereomer) and 30.6 min (major enantiomer, minor diastereomer).

¹H NMR (CDCl₃) δ 0.91 (d, 3H, 7.0 Hz), 1.12 (d, 3H, J = 7.0 Hz), 1.70-1.78 (m, 1H), 2.80 (ddd, 1H, J = 2.5, 4.5, 10.5 Hz), 3.89-3.96 (m, 1H), 4.60 (dd, 1H, J = 10.5, 12.6 Hz), 4.71 (dd, 1H, J = 4.5, 12.6 Hz), 7.21 (dd, 2H, J = 1.5, 8.5 Hz), 7.30 – 7.39 (m, 3H), 9.95 (d, 1H, 2.5 Hz)

(-)-(2R)-2-[(S)-2-Nitro-1-phenyl-ethyl]-hexanal (13).⁸

Prepared as per procedure B. Flash chromatography (1:20 EtOAc-Hexane) gave **13** (91 mg, 91%) as a colourless oil (12.5:1 mixture of diastereomers).

83% *ee*. $[\alpha]_D^{21} = +7.6$ (c 0.8, CHCl₃). Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA, 90/10, 0.5 mL min⁻¹, RT, UV detection at 220 nm, retention times: 14.4 min (minor enantiomer, major diastereomer) and 13.1 min (major enantiomer, major diastereomer). 15.8 (minor enantiomer, minor diastereomer) and 13.8 (major enantiomer, minor diastereomer).

¹H NMR (CDCl₃) δ 0.81 (t, 3H, J = 6.6 Hz), 1.14-1.54 (m, 6H), 2.29-2.75 (m, 1H), 3.80 (app dt, 1H, J = 5.5, 10.0 Hz), 4.67 (dd, 1H, J = 9.5, 12.5 Hz), 4.73 (dd, 1H, J = 5.0, 12.5 Hz), 7.19 (d, 2H, J = 7.0 Hz), 7.30 – 7.39 (m, 3H), 9.73 (d, 1H, J = 2.5 Hz).

(+)-(3*R*)-2,2-Dimethyl-4-nitro-3-(*o*)-tolyl-butylaldehyde (14**).**

Prepared as per procedure B. Flash chromatography (1:20 EtOAc-Hexane) gave **14** (86 mg, 91%) as a colourless oil.

94% *ee*. $[\alpha]_D^{22} = +7.2$ (c 0.3, CHCl₃). Chiralpak AS (4.6 mm x 25 cm), hexane/IPA, 97/3, 0.7 mL min⁻¹, RT, UV detection at 220 nm, retention times: 14.7 min (minor enantiomer) and 18.5 min (major enantiomer).

¹H NMR (CDCl₃) δ 1.05 (s, 3H), 1.20 (s, 3H), 2.43 (s, 3H), 4.22 (dd, 1H, J = 4.3, 11.0 Hz), 4.71 (dd, 1H, J = 4.3, 13.3 Hz), 4.84 (dd, 1H, J = 11.0, 13.3 Hz), 7.18 – 7.23 (m, 4H), 9.56 (s, 1H). ¹³C (CDCl₃) δ 18.5, 20.0, 20.7, 41.6, 48.4 (q), 76.4, 125.9, 126.3, 127.4, 130.9, 133.8 (q), 137.4 (q), 204.1 (q). IR (film) 2970, 2877, 2720, 1725, 1555, 1467, 1378 cm⁻¹

(-)-(3*R*)-3-Furan-2-yl-2,2-dimethyl-4-nitro-butylaldehyde (15**).**

Prepared as per procedure B. Flash chromatography (1:20 EtOAc-Hexane) gave **15** (80 mg, 95%) as a pale yellow oil.

91% *ee*. $[\alpha]_D^{22} = -27.3$ (c 0.2, CHCl₃). Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA, 99/1, 0.7 mL min⁻¹, RT, UV detection at 220 nm, retention times: 42.0 min (minor enantiomer) and 30.6 min (major enantiomer).

¹H NMR (CDCl₃) δ 1.07 (s, 3H), 1.21 (s, 3H), 3.94 (dd, 1H, J = 4.0, 11.0 Hz), 4.61 (dd, 1H, J = 4.0, 13.0 Hz), 4.78 (dd, 1H, J = 11.0, 13.0 Hz), 6.24 (dd, 1H, J = 1.0, 3.5 Hz), 6.34 (dd, 1H, J = 2.0, 3.5 Hz), 7.40 (dd, 1H, J = 1.0, 2.0 Hz), 9.55 (s, 1H). ¹³C NMR (CDCl₃) δ 18.7, 20.7, 41.8, 47.7 (q), 74.3, 109.3, 110.0, 142.3, 149.3 (q), 203.0 (q). IR (film) 2973, 2934, 2721, 1726, 1556, 1468, 1434, 1377, 742 cm⁻¹

(+)-(3*R*)-2,2-Dimethyl-4-nitro-3-thiophen-2-yl-butyraldehyde (16).⁸

Prepared as per procedure B. Flash chromatography (1:20 EtOAc-Hexane) gave **16** (87 mg, 96%) as a colourless oil.

82% *ee*. $[\alpha]_D^{21} = +16.0$ (c 0.3, CHCl₃). Chiralpak AD-H (4.6 mm x 25 cm), hexane/IPA, 99/1, 0.7 mL min⁻¹, RT, UV detection at 220 nm, retention times: 44.2 min (minor enantiomer) and 37.9 min (major enantiomer).

¹H NMR (CDCl₃) δ 1.11 (s, 3H), 1.24 (s, 3H), 4.16 (dd, 1H, J = 4.0, 10.5 Hz), 4.68 (dd, 1H, J = 4.0, 12.5 Hz), 4.75 (dd, 1H, J = 10.5, 12.5 Hz), 6.95 (dd, 1H, J = 1.0, 3.5 Hz), 6.99 (dd, 1H, J = 3.5, 5.0 Hz), 7.27 (bs, 1H), 9.56 (s, 1H).

(+)-(3*R*)-(4-Bromo-phenyl)-2,2-dimethyl-4-nitro-butyraldehyde (17).¹²

Prepared as per procedure B. Flash chromatography (1:20 EtOAc-Hexane) gave **17** (114 mg, 95%) as a white solid. M.p. 85-86 °C.

85% *ee*. $[\alpha]_D^{22} = +4.2$ (c 0.3, CHCl₃). Chiralpak AS (4.6 mm x 25 cm), hexane/IPA, 90/10, 0.7 mL min⁻¹, RT, UV detection at 220 nm, retention times: 24.8 min (minor enantiomer) and 30.3 min (major enantiomer).

¹H NMR (CDCl₃) δ 1.04 (s, 3H), 1.15 (s, 3H), 3.78 (dd, 1H, J = 4.3, 11.5 Hz), 4.71 (dd, 1H, J = 4.3, 13.3 Hz), 4.84 (dd, 1H, J = 11.5, 13.3 Hz), 7.11 (d, 2H, J = 8.3 Hz), 7.49 (d, 2H, J = 8.3 Hz), 9.52 (s, 1H). IR (solid) 2924, 2857, 1727, 1555, 1457, 1377, 1009 cm⁻¹.

(+)-(3*R*)-2,2,5-Trimethyl-3-nitromethyl-hexanal (18**).¹²**

Prepared as per procedure B. Flash chromatography (1:20 EtOAc-Hexane) gave **18** (45 mg, 56%) as an oil.

94% *ee*. $[\alpha]_{\text{D}}^{22} = +19.7$ (c 0.4, CHCl₃). Chiralpak OD-H (4.6 mm x 25 cm), hexane/IPA, 90/10, 0.7 mL min⁻¹, RT, UV detection at 220 nm, retention times: 10.6 min (minor enantiomer) and 8.4 min (major enantiomer).

¹H NMR (CDCl₃) δ 0.93 (d, 3H, J = 6.0 Hz), 0.95 (d, 3H, J = 6.0 Hz), 1.09 (s, 3H), 1.10 (s, 3H), 1.13-1.19 (m, 1H), 1.25-1.34 (m, 1H), 2.67-2.73 (m, 1H), 4.26 (dd, 1H, J = 5.5, 13.0 Hz), 4.47 (dd, 1H, J = 5.5, 13.0 Hz), 9.48 (s, 1H). ¹³C (CDCl₃) δ 17.9, 19.3, 21.0, 23.1, 25.5, 38.2, 39.0, 48.3 (q), 74.3, 203.7 (q). IR (film) 2961, 2874, 1723, 1641, 1554, 1467, 1378 cm⁻¹.

7.0 NMR Spectra

DHQA-HCl

9-*epi*-DHQA-HCl

9-*epi*-DHQDA-HCl

9-*epi*-DHQBA-HCl

Compound 2

Compound 3

Compound 4

Compound 5

Compound 6

Compound 7

Compound 8

Compound 9

Compound 10

Compound 11

Compound 12

Compound 13

Compound 14

Compound 15

Compound 16

Compound 17

Compound 18

8.0 References

1. Denmark, S. E.; Marcin, L. R. *J. Org. Chem.* **1993**, 58, 3850.
2. McCooey S. H.; Connon, S. J. *Angew. Chem. Int. Ed.*, **2005**, 44, 6763.
3. Absolute configuration determined by comparison with literature HPLC retention times, see: Cao, C.-L.; Ye, M. -C.; Sun X.-L.; Tang, Y. *Org. Lett.* **2006**, 8, 2901.
4. Irie, K.; Miyazu K.; Wantanabe, K. *Chem. Lett.* **1980**, 353.
5. Absolute configuration determined by comparison with literature specific rotation data, see ref. 3.
6. Absolute configuration determined by comparison with literature HPLC retention times (see ref. 3) and specific rotation data, see: Wang, W.; Wang J.; Li, H. *Angew. Chem. Int. Ed.* **2005**, 44, 1369.
7. Brook, M. A.; Seebach, D. *Can. J. Chem.* **1987**, 654, 836.
8. Absolute configuration determined by comparison with literature specific rotation from: Wang, W.; Wang J.; Li, H. *Angew. Chem. Int. Ed.* **2005**, 44, 1369.
9. Absolute configuration determined by comparison with literature specific rotation and HPLC retention times, see: Cao, C.-L.; Ye, M.-C.; Sun X.-L.; Tang, Y. *Org. Lett.* **2006**, 8, 2901.
10. Felluga, F.; Nitti, P.; Pitacco G.; Valentin, E. *J. Chem. Soc. Perkin Trans. I* **1992**, 2331.
11. Absolute configuration determined by comparison with specific rotation data from Mossé, S.; Laars, M.; Kriis, K.; Kanger, T.; Alexakis, A. *Org. Lett.* **2006**, 8, 2559.
12. Zhu, M.-K.; Cun, L.-F.; Mi, A.-Q.; Jiang, Y.-Z.; Gong, L.-Z. *Tetrahedron: Asymmetry* **2006**, 17, 491.