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Supporting Information

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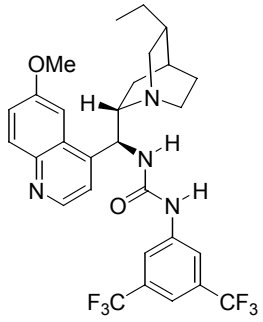
~~Novel Urea-s~~ubstituted Cinchona Alkaloid Derivatives as Highly Active and Selective Asymmetric Bifunctional Organocatalysts: Inversion of configuration at C-9 Dramatically Improves Catalyst Performance[**]

Séamus H. McCooey and Stephen J. Connon[*]
Centre for Synthesis and Chemical Biology, Department of Chemistry, University of Dublin, Trinity College, Dublin 2, Ireland. E-mail: connons@tcd.ie. Fax: 00353-1-6712826

General
Proton Nuclear Magnetic Resonance spectra were recorded on a 400 MHz spectrometer in $CDCl_3$ referenced relative to residual $CHCl_3$ (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 $60F_{254}$ slides, and visualised by either UV irradiation or $KMnO_4$ staining. Specific rotation measurements were made on a Rudolph research analytical Autopol IV instrument, and are quoted in units of $10^{-1}degcm^2g^{-1}$. Unless otherwise stated, all chemicals were purchased from Aldrich and used as received. Hydrazoic acid solution (4% w/v) was prepared according to the protocol of Wolff.[1] (*E*)-β-Nitrosytrenes **9**-**13** were prepared according to the literature procedure.[2] Toluene was dried by distillation over CaH_2, anhydrous THF was distilled over sodium-benzophenone ketyl radical before use. All reactions were carried out under a protective nitrogen atmosphere unless otherwise stated.

9-Epi-DHQU

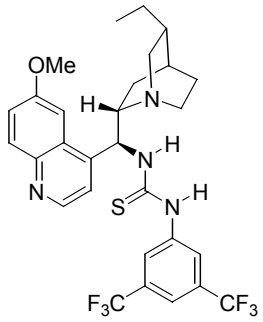


A solution of hydrazoic acid in benzene (4% w/v, 2.5 mL, 2.33 mmol) was added to a stirred solution of **DHQ** (0.500 g, 1.53 mmol) and triphenylphosphane (0.483 g, 1.84 mmol) in THF (15 mL) at 10 °C via syringe under a nitrogen atmosphere. After 5 min, the resulting solution was cooled to 0 °C, and diisopropyl azodicarboxylate (0.360 mL, 1.84 mmol) in THF (2 mL) was added

dropwise *via* syringe. The solution was stirred for 4 h at room temperature, after which triphenylphosphane (0.401 g, 1.53 mmol) in THF (2 mL) was added in one portion. The mixture was heated at 45 °C until gas evolution ceased (approx. 4 h). Water (1 mL) was added and the solution was stirred for a further 4 h. The reaction was concentrated *in vacuo* and the residue was partitioned between CH_2Cl_2 and 2 N HCl (1:1, 20 mL). After the mixture was vigorously shaken, the aqueous phase was separated and washed with CH_2Cl_2 (2 x 10 mL). The aqueous layer was concentrated under reduced pressure and the residue partitioned between 0.5M NaOH and CH_2Cl_2 (1:1, 100 mL). The organic layer was separated and the aqueous layer re-extracted with CH_2Cl_2 (2 x 10 mL). The combined organic extracts were concentrated to *ca*. 5mL *in vacuo* and passed through a short pad of silica (gradient system; 100% EtOAc to 85:5:10 EtOAc:Et_3N:MeOH) to give crude **9-amino-9-deoxydihydroquinine** as a colourless oil (0.375 g) after concentration which was >90% pure (^{1}H NMR, >98% *de*) and used without further purification.

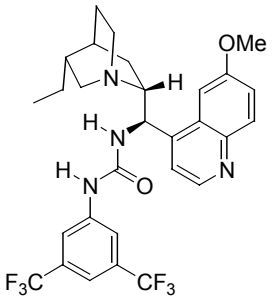
The crude amine was dissolved in CH_2Cl_2 (10.0 mL). 5.0 mL Of this solution was removed via syringe (for the synthesis of **9-epi-DHQT**) and the remainder cooled to 0°C under N_2. After 10 min at this temperature 3,5-bistrifluoromethylphenyl isocyanate (159 μL, 0.92 mmol) was added *via* syringe. The resulting solution was allowed to warm to room temperature and stirred for 12 h. The solvent was removed *in vacuo* and the residue purified by column chromatography (gradient system: 100% EtOAc to 90:5:5 EtOAc:Et_3N:MeOH, R_f 0.4) gave a crude hygroscopic solid. The crude solid was dissolved in a minimal amount of CH_2Cl_2 and slowly precipitated from solution by the addition of hexane at 0 ^{o}C. Filtration gave **9-epi-DHQU** (0.129 g, 29%) as an amorphous white solid: M.p. 136-140 °C. $[\alpha]_{589}^{21}$ -18.9 (*c* = 0.36 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.83 (d, ^3J (H,H) = 4.5, 1H), 8.08 (d, ^3J (H,H) = 9.0, 1H), 7.73-7.76 (m, 3H), 7.45 (dd, ^{3}J (H,H) = 9.0, 2.5, 1H), 7.39-7.41 (m, 2H), 6.25 (bs, 1H), 5.56 (bs, 1H), 4.04 (s, 3H), 3.42-3.49 (m, 1H), 3.28-3.33 (m, 1H), 3.10-3.12 (m, 1H), 2.01 (m, 2H), 1.49-1.60 (m, 4H), 1.20-1.25 (m, 4H), 0.97-1.02 (m, 1H), 0.79 ppm (t, ^3J (H,H) = 7.6, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.1, 154.1, 146.8, 144.6, 143.0, 139.9, 131.5, 131.4, 131.3 (q, ^2J (C,F) = 26.3), 122.6 (q, ^1J (C,F) = 273.7), 121.9, 117.8, 117.75, 115.5 (br signal, ^3J (C,F) = 2.9), 101.8, 76.8, 59.3, 56.8, 55.4, 41.1, 36.1, 27.5, 27.1, 26.5, 24.4, 11.4 ppm. IR (KBr): ύ 3415, 1688, 1623, 1572, 1512, 1475, 1388, 1277, 1178, 1130, 682 cm^{-1}. HRMS (ES): calcd. for $[C_{29}H_{30}F_6N_4O_2 + H]^+$ requires 581.2351; found 581.2338.

9-Epi-DHQT



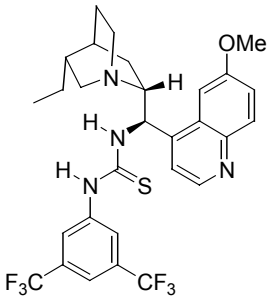
The solution of crude **9-amino-9-deoxydihydroquinine** (0.188 g) in CH_2Cl_2 (5.0 mL) (*vide supra*) was cooled to 0°C under N_2. After 10 min at this temperature 3,5-bistrifluoromethylphenyl isothiocyanate (168 μL, 0.92 mmol) was added *via* syringe with stirring. The resulting solution was allowed to warm to room temperature and stirred for 12 h. The solvent was removed *in vacuo* and the residue purified by column chromatography (gradient system: 100% EtOAc to 90:5:5 EtOAc:Et_3N:MeOH R_f 0.32) gave a crude hygroscopic solid. The crude solid was dissolved in a minimal amount of CH_2Cl_2 and slowly precipitated from solution by the addition of hexane at 0 °C. Filtration gave **9-epi-DHQT** (0.141 g, 31%) as an amorphous white solid: M.p. 150-154 °C. $[\alpha]_{589}^{21}$ -110.7 (*c* = 0.57 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.73 (d, ^3J (H,H) = 4.5, 1H), 8.09 (d, ^3J (H,H) = 9.0, 1H), 7.89 (bs, 2H), 7.70 (s, 1H), 7.45 (dd, ^{3}J (H,H) = 9.0, 2.0, 1H), 7.30-7.44 (m, 2H), 5.71 (bs, 1H), 3.99 (s, 3H), 3.21-3.33 (m, 3H), 2.81-2.87 (m, 1H), 2.59 (bs, 1H), 1.53-1.64 (m, 4H), 1.28-1.41 (m, 4H), 0.88-0.96 (m, 1H), 0.85 ppm (t, ^3J (H,H) = 7.0, 3H). Note: the N-H(aryl) resonance is not observable in $CDCl_3$.^{13}C NMR (100 MHz, $CDCl_3$): δ = 180.5, 157.7, 147.0, 144.3, 144.0, 139.5, 131.9 (q, ^2J (C,F) = 35.2), 131.4, 127.6, 123.1, 123.1, 122.8 (q, ^1J (C,F) = 272.7), 121.1, 118.3 (br signal, ^3J (C,F) = 1.9), 101.7, 76.8, 60.8, 56.1, 53.3, 40.9, 36.4, 27.4, 26.9, 24.9, 24.3, 11.5 ppm. IR (KBr): ύ 3416, 1623, 1510, 1475, 1385, 1278, 1181, 1135, 681 cm^{-1}. HRMS (ES): calcd. for $[C_{29}H_{30}F_6N_4O_2 + H]^+$ requires 597.2133; found 597.2123.

9-epi-DHQDU



Crude (>90% purity, >98% *de*) **9-amino-9-deoxydihydroquinidine** (0.364 g) was synthesised from **DHQD** (0.500 g, 1.53 mmol) using an identical procedure to that used to prepare **9-epi-DHQU** (*vide supra*). The crude amine was dissolved in CH_2Cl_2 (30.0 mL). 5.0 mL Of this solution was removed *via* syringe (for the synthesis of **9-epi-DHQDT)** and the remainder cooled to 0°C under N_2. After 10 min at this temperature 3,5-bistrifluoromethylphenyl isocyanate (159 μL, 0.92 mmol) was added *via* syringe. The resulting solution was allowed to warm to room temperature and stirred for 12 h. The solvent was removed *in vacuo* and the residue purified by column chromatography (gradient system: 100% EtOAc to 90:5:5 EtOAc:Et_3N:MeOH, R_f 0.25) gave a crude hygroscopic solid. The crude solid was dissolved in a minimal amount of ether and slowly precipitated from solution by the addition of hexane at 0 °C. Filtration gave **9-epi-DHQDU** (0.140 g, 32%) as an amorphous white solid: M.p. 139-144 °C. $[\alpha]_{589}^{21}$ +90.3 (*c* = 0.36 in $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.80 (d, ^3J (H,H) = 4.5, 1H), 8.08 (d, ^3J (H,H) = 9.0, 1H), 7.82 (m, 2H), 7.63 (d, ^{3}J (H,H) = 2.5, 1H), 7.43-7.46 (m, 3H), 6.29 (bs, 1H), 5.32 (bs, 1H), 4.02 (s, 3H), 3.08-3.18 (m, 1H), 3.01 (dd, ^3J (H,H) = 10.5, 4.0, 1H), 2.90-2.95 (m, 2H), 2.68-2.74 (m, 1H), 1.63 (bs, 1H), 1.52-1.58 (m, 3H), 1.44 (dq, ^3J (H,H) = 15.1, 7.6, 2H), 1.27-1.31 (m, 1H), 1.02-1.09 (m, 1H), 0.91 ppm (t, ^3J (H,H) = 7.5, 3H). Note: the N-H(aryl) resonance is not observable in $CDCl_3$.^{13}C NMR (100 MHz, $CDCl_3$): δ = 157.7, 154.5, 147.1, 144.4, 142.8, 140.3, 131.5, 131.4 (q, ^2J (C,F) = 33.0), 130.4,121.7, 122.7 (q, ^1J (C,F) = 273.1), 117.8, 117.7, 115.1 (q, ^3J (C,F) = 3.9), 97.2, 76.8, 65.4, 55.1, 48.7, 48.6, 36.6, 26.4, 25.4, 25.0, 24.6,11.4 ppm. IR (KBr): ύ 3358, 1716, 1623, 1590, 1509, 1477, 1394, 1278, 1172, 1129, 680 cm^{-1}, HRMS (ES): calcd. for $[C_{29}H_{30}F_6N_4O_2 + H]^+$ requires 581.2351; found 581.2353.

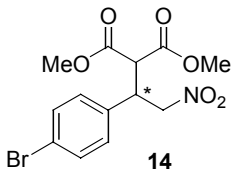
9-Epi-DHQDT



The solution of crude **9-amino-9-deoxydihydroquinine** (0.182 g) in CH_2Cl_2 (5 mL) (*vide supra*) was cooled to 0°C under N_2. After 10 min at this temperature 3,5-bistrifluoromethylphenyl isothiocyanate (168 μL, 0.92 mmol) was added *via* syringe with stirring. The resulting solution was allowed to warm to room temperature and stirred for 12 h. The solvent was removed *in vacuo* and the residue purified by column chromatography (gradient system: 100% EtOAc to 90:5:5 EtOAc:Et_3N:MeOH, R_f 0.22) gave a crude hygroscopic solid. The crude solid was dissolved in a minimal amount of ether and slowly precipitated from solution by the addition of hexane at 0 °C. Filtration gave **9-epi-DHQDT** (0.045 g, 10%) as an amorphous white solid: M.p. 116-120 °C, $[\alpha]_{589}^{21}$ +126.6 (*c* = 0.08 in $CHCl_3$) ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.83 (d, ^3J (H,H) = 4.5, 1H), 8.09 (d, ^3J (H,H) = 9.0, 1H), 8.04 (s, 2H), 7.64 (s, 1H), 7.45-7.49 (m, 3H), 4.02 (s, 3H), 3.64-3.75 (m, 1H), 3.29-3.38 (m, 1H), 3.11-3.24 (m, 2H), 2.01 (bs, 2H), 1.73-1.81 (m, 4H), 1.46-1.64 (m, 2H), 1.04-1.16 (m, 2H), 0.96 (t, ^3J (H,H) = 7.0, 3H) Note: the thiourea N-H resonances are not observable in $CDCl_3$. IR (KBr): ύ 3416, 1623, 1511, 1475, 1384, 1278, 1181, 1133, 680 cm^{-1}. HRMS (ES): calcd. for [$C_{29}H_{30}F_6N_4O_2$ + H^+] requires 597.2146; found 597.2123.

Catalytic asymmetric addition of dimethyl malonate to (*E*)-β-nitrostyrenes

(+)-14



14

Procedure A: A 1 mL reaction vial containing a stirring bar was charged with **6** (0.023 g, 0.100 mmol), and **DHQT** (0.0012 g, 0.002 mmol). The vial was fitted with a septum and placed under an Ar atmosphere (balloon). 0.400 mL Toluene was added *via* syringe and the resulting solution cooled to –20 °C, followed by the addition of dimethyl malonate (0.023 mL, 0.20 mmol) *via* syringe. When TLC analysis indicated complete consumption of **6** (40 h), the reaction solution

was concentrated *in vacuo* and the crude purified by column chromatography to give **14** (0.034 g, 94%) as a white solid: M.p. 93-94 °C, $[\alpha]_{589}^{21}$ +4.6 (*c* = 0.07 in $CHCl_3$).

Enantiomeric excess (93%) was determined by CSP-HPLC (Chiralpak OD-H 250 x 46 mm column), solvent: 70:30 Hexane:IPA, flow-rate: 0.8 mL/min, λ = 220 nm, retention times: 16.2 min (major), 18.1 min (minor).

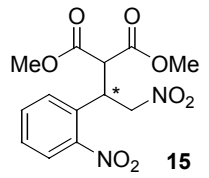
(-)-14

Prepared as per procedure A using **DHQDT** (0.0012 g, 0.002 mmol) to give **14** (0.029 g, 80%). $[\alpha]_{589}^{18}$ -10.0 (*c* = 0.15 in $CHCl_3$).

Enantiomeric excess (93%) was determined by CSP-HPLC (Chiralpak OD 250 x 46 mm column), solvent: 65:35 Hexane:IPA, flow-rate: 1.0 mL/min, λ = 220 nm, retention times: 10.7 min (minor), 12.1 min (major).

Note: NMR spectra data for all Michael adducts were identical to that reported in the literature.[3]

(+)-15

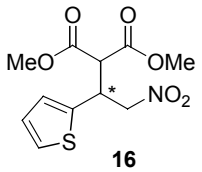


15

Prepared as per procedure A using **7** (0.019 g, 0.100 mmol), **DHQT** (0.0012 g, 0.002 mmol) to give **15** (0.030 g, 91%). $[\alpha]_{589}^{21}$ +17.1 (*c* = 0.03 in $CHCl_3$).

Enantiomeric excess (90%) was determined by CSP-HPLC (Chiralpak OD-H 250 x 46 mm column), solvent: 65:35 Hexane:IPA, flow-rate: 0.9 mL/min, λ = 220 nm, retention times: 11.2 min (major), 19.4 min (minor).

(-)-16

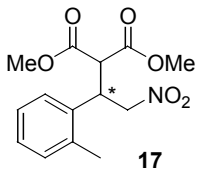


16

Prepared as per procedure A using **8** (0.016 g, 0.100 mmol), **DHQT** (0.0012 g, 0.002 mmol) to give **16** (0.027 g, 94%). $[\alpha]_{589}^{21}$ -8.4 (*c* = 0.3 in $CHCl_3$).

Enantiomeric excess (95%) was determined by CSP-HPLC (Chiralpak AD-H 250 x 46 mm column), solvent: 80:20 Hexane:IPA, flow-rate: 1.0 mL/min, λ = 220 nm, retention times: 9.2 min (minor), 11.5 min (major).

(-)-17

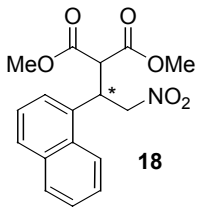


17

Prepared as per procedure A at 0 °C using **9** (0.016 g, 0.100 mmol), **DHQT** (0.0012 g, 0.002 mmol) to give **17** (0.027 g, 95%). $[\alpha]_{589}^{21}$ -4.85 (*c* = 0.1 in $CHCl_3$).

Enantiomeric excess (94%) was determined by CSP-HPLC (Chiralpak OD-H 250 x 46 mm column), solvent: 70:30 Hexane:IPA, flow-rate: 0.8 mL/min, λ = 220 nm, retention times: 12.4 min (minor), 13.4 min (major).

(-)-18

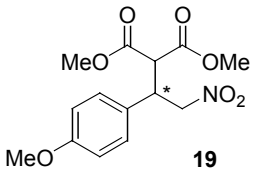


18

Prepared as per procedure A at 0 °C using **10** (0.020 g, 0.100 mmol), **DHQT** (0.0012 g, 0.002 mmol) to give **18** (0.031 g, 94%). $[\alpha]_{589}^{21}$ -13.9 (*c* = 0.06 in $CHCl_3$).

Enantiomeric excess (93%) was determined by CSP-HPLC (Chiralpak AD-H 250 x 46 mm column), solvent: 80:20 Hexane:IPA, flow-rate: 1.0 mL/min, λ = 220 nm, retention times: 10.2 min (minor), 14.7 min (major).

(+)-19



19

Prepared as per procedure A at 0 °C using **11** (0.018 g, 0.100 mmol), **DHQT** (0.0012 g, 0.002 mmol) to give **19** (0.029 g, 92%). $[\alpha]_{589}^{21}$ +21.5 (*c* = 0.02 in $CHCl_3$).

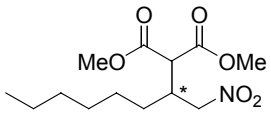
Enantiomeric excess (99%) was determined by CSP-HPLC (Chiralpak OD-H 250 x 46 mm column), solvent: 60:40 Hexane:IPA, flow-rate: 0.9 mL/min, λ = 220 nm, retention times: 11.1 min (minor), 12.1 min (major).

(-)-19

Prepared as per procedure A at 0 °C using **11** (0.018 g, 0.100 mmol), **DHQDT** (0.0012 g, 0.002 mmol) to give **19** (0.028 g, 90%). $[\alpha]_{589}^{19}$ -9.4 (*c* = 0.3 in $CHCl_3$).

Enantiomeric excess (91%) was determined by CSP-HPLC (Chiralpak AD-H 250 x 46 mm column), solvent: 60:40 Hexane:IPA, flow-rate: 0.9 mL/min, λ = 220 nm, retention times: 9.3 min (major), 15.7 min (minor).

(+)-20

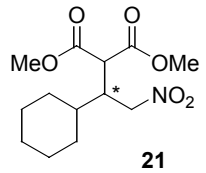


20

Prepared as per procedure A at -20 °C using **12** (0.016 g, 0.100 mmol), **DHQT** (0.0012 g, 0.002 mmol) to give **20** (0.026 g, 88%). $[\alpha]_{589}^{21}$ +14.2 (*c* = 0.03 in $CHCl_3$).

Enantiomeric excess (86%) was determined by CSP-HPLC (Chiralpak OD-H 250 x 46 mm column), solvent: 90:10 Hexane:IPA, flow-rate: 0.9 mL/min, λ = 220 nm, retention times: 6.3 min (major), 8.3 min (minor).

(+)-21



21

Prepared as per procedure A at 20 °C using **13** (0.016 g, 0.100 mmol), **DHQT** (0.0012 g, 0.002 mmol) to give **21** (0.018 g, 63%). $[\alpha]_{589}^{21}$ +36.7 (*c* = 0.025 in $CHCl_3$).

Enantiomeric excess (75%) was determined by CSP-HPLC (Chiralpak OD-H 250 x 46 mm column), solvent: 90:10 Hexane:IPA, flow-rate: 0.9 mL/min, λ = 220 nm, retention times: 8.9 min (major), 11.7 min (minor).

[1] H. Wolff, *Org. React.* **1946**, III, 327.

[2] a) Y. Kawai, Y. Inaba, N. Tokitoh, *Tetrahedron Asymm.* **2001**, *12*, 309; b) S. E. Denmark, L. R. Marcin, *J. Org. Chem.* **1993**, *58*, 3850.

[3] H. Li, Y. Wang, L. Tiang, L. Deng, *J. Amer. Chem. Soc.* **2004**, *126*, 9906.