Highly Enantioselective Amination of α -Substituted α -Cyanoacetates with Chiral Catalysts Accessible from Both Quinine and Quinidine

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Supporting Information

General Information. ^1H and ^{13}C NMR spectra were recorded on a Varian instrument (400 MHz and 100 MHz, respectively) and internally referenced to tetramethylsilane signal or the residual proton solvent signals. Infrared spectra were recorded on a Perkin Elmer FT-IR Spectrometer and are reported in frequency of absorption. High resolution mass spectra for all the new compounds were done by either a Micromass 70-VSE instrument (CI) or a Micromass Q-ToF instrument (ESI). Specific rotations were measured on a Jasco Digital Polarimeter.

High performance liquid chromatography (HPLC) analysis was performed on a Hewlett-Packard 1100 Series instrument equipped with a quaternary pump, using a Daicel Chiralcel OD Column (250 x 4.6 mm), Chiralpak AS Column (250 x 4.6 mm) or Chiralpak AD Column (250 x 4.6 mm). UV detection was monitored at 220 nm.

Ethyl α -methyl- α -cyanoacetate was purchased from TCI and was used as received. Ethyl α -phenyl- α -cyanoacetate and all dialkyl azodicarboxylate were purchased from Lancaster and were used as received. Other ethyl α -aryl- α -cyanoacetates were prepared according to literature procedures.^{1,2} All solvents were freshly distilled from sodium or CaH_2 before use.

Preparation of Q-Bn:

To a solution of quinine (4.0 g, 12.4 mmol) in DMF (40 mL) under nitrogen atmosphere, NaH (1.36 g, 57% suspension in mineral oil, 32.3 mmol) was added in small portions and the resulting mixture was stirred at room temperature for 2h. BnCl (1.56 mL, 13.6 mmol) was added dropwise via a syringe in 10 min. The mixture was stirred at room temperature overnight. After the starting material was completely consumed, brine (40 mL) was added carefully and the resulting mixture was extracted with ethyl acetate (200 mL). The organic phase was washed with H_2O (5×100 mL), brine (100 mL) and dried over Na_2SO_4 . The solvent was removed in *vacuo* to afford a light yellow oil (5.1 g, 99%). This crude product (Q-Bn) was used without further purification.

Preparation of Q-2c:

Under N₂ atmosphere, a suspension of Q-Bn (5.1 g, 12.3 mmol) and NaSEt (4.2 g, 50.0 mmol) in dry DMF (75 mL) was stirred at 110 °C for 9 hours. The reaction mixture was cooled to room temperature, and the reaction was quenched with sat. NH₄Cl (80 mL) and H₂O (60 mL). The solution was acidified to pH = 2 by conc. HCl. This aqueous solution was washed by ethyl acetate (2 × 100 mL) and its pH value was adjusted to 8 by conc. ammonium hydroxide. The resulting mixture was extracted with ethyl acetate (2 × 150 mL). The combined organic phase was dried over Na₂SO₄, and concentrated in *vacuo* to afford a yellowish solid. This solid was washed by CH₂Cl₂ (2 × 30 mL) and then dissolved in aqueous HCl (2 N, 150 mL). The resulting solution was washed by ethyl acetate (50 mL) and adjusted to pH = 7 by conc. ammonium hydroxide. The aqueous phase was extracted by ethyl acetate (300 mL). The organic phase was dried quickly with Na₂SO₄. After concentration, Q-2c was obtained as a white powder (3.764 g, 77%). $[\alpha]_D^{23} = -78.9$ (c 0.98, EtOH); ¹H NMR (400 MHz, DMSO-d₆) δ (ppm) 10.03 (br, 1H), 8.63 (d, J = 4.4 Hz, 1H), 7.89 (d, J = 9.2 Hz, 1H), 7.70-7.15 (m, 8H), 5.92-5.77 (m, 1H), 5.14-4.82 (m, 3H), 4.34 (d, J = 11.6 Hz, 1H), 4.27 (d, J = 11.6 Hz, 1H), 3.30-2.94 (m, 2H), 2.88-2.70 (m, 1H), 2.50-2.10 (m, 3H), 1.94-1.32 (m, 5H); ¹³C NMR (100 MHz, DMSO-d₆) δ (ppm) 155.4, 146.6, 144.3, 143.4, 142.3, 138.1, 131.3, 128.2, 127.7, 127.6, 127.5, 121.4, 114.2, 104.7, 70.5, 59.9, 56.0, 54.9, 41.7, 39.4, 27.4, 27.3, 24.6; IR (KBr) ν (cm⁻¹) 3395, 3063, 3033, 2953, 2908, 2863, 2753, 2686, 2613, 2539, 1906, 1638, 1613, 1591, 1509, 1499, 1463, 1401, 1355, 1331, 1280, 1241, 1215, 1132, 1100, 1030, 1014, 921, 853, 814, 751, 702; HRMS (ESI) m/z calcd for (C₂₆H₂₉N₂O₂+H⁺): 401.2229, found: 401.2228.

General Procedure for Enantioselective Amination of Ethyl α-Substituted α-Cyanoacetate with Dialkyl Azodicarboxylate

Reaction Catalyzed by QD-2c:

To a solution of ethyl α-substituted α-cyanoacetate (0.22 mmol, 1.1 eq) and QD-2c (4 mg or 8 mg, 5 mol% or 10 mol%) in toluene (2 mL) at -78 °C (or at RT) under stirring, a solution of di-*tert*-butyl azodicarboxylate or dibenzyl azodicarboxylate in toluene (0.4 mL, 0.5 M, 0.2 mmol, 1.0 eq) was added dropwise within 5-10 min. The reaction mixture was stirred until the color of the solution turned from yellow to colorless (1 min-8 h), after which it was allowed to warm to room temperature and the pure product was isolated by flash chromatography.

Reaction Catalyzed by Q-2c:

A suspension of Q-2c (4 mg or 8 mg, 5 mol% or 10 mol%) in toluene (2 mL) was subjected to ultrasound until no chunky solid was visible (*c.a.* 15 min). The resulting mixture was heated to 110 °C until a clear solution was formed (10-15 min). While it was still hot, the solution was allowed to pass a cotton plug to remove any trace amount of insoluble residue and then cooled to room temperature. Then ethyl α -substituted α -cyanoacetate (0.22 mmol, 1.1 eq) was added. This mixture was stirred and cooled to -78 °C (or at RT). A solution of di-*tert*-butyl azodicarboxylate or dibenzyl azodicarboxylate in toluene (0.4 mL, 0.5 M, 0.2 mmol, 1.0 eq) was added dropwise within 5-10 min and stirring was continued until the color of the solution turned from yellow to colorless (1 min-12 h). The reaction mixture was allowed to warm to room temperature and the pure product was isolated by flash chromatography.

(+)-5a. This reaction was catalyzed by Q-2c and the product was obtained as a white foam in 92% yield after purification by flash chromatography (hexanes/ether = 3/1) and 97% ee as determined by HPLC analysis [Chiralpak AD, Hexanes:IPA, 85:15, 1.0 mL/min, λ 220 nm, *t* (minor) = 10.7 min, *t* (major) = 32.3 min]. $[\alpha]_D^{23} = +64.0$ (c 0.175, CHCl₃); ¹H NMR (400 MHz, CD₃CN) see the attached spectrum; ¹³C NMR (100 MHz, CD₃CN) see the attached spectrum; IR (CHCl₃) ν (cm⁻¹) 3347, 2980, 1744, 1718, 1453, 1368, 1242, 1154, 1052; HRMS (CI) *m/z* calcd. for (M+ H)⁺: 420.2135, found 420.2132.

(-)-5a. This reaction was catalyzed by QD-2c and the product was obtained as a white foam in 92 % yield and 95% ee.

(+)-5b. This reaction was catalyzed by Q-2c and the product was obtained as a white foam in 95% yield after purification by flash chromatography (hexanes/ether = 3/1) and 96% ee as determined by HPLC analysis [Chiralpak AD, Hexanes:IPA, 85:15, 1.0 mL/min, λ 220 nm, *t* (minor) = 10.9 min, *t* (major) = 34.4 min]. $[\alpha]_D^{23} = +59.7$ (c 1.14, CHCl₃); ¹H NMR (400 MHz, CD₃CN) see the attached spectrum; ¹³C NMR (100 MHz, CD₃CN) see the attached spectrum; IR (CHCl₃) ν (cm⁻¹) 3348, 2980, 2929, 1745, 1719, 1607, 1510, 1476, 1369, 1241, 1157, 1054, 1016; HRMS (ESI) *m/z* calcd. for (M+ H)⁺: 438.2029, found 438.2024.

(-)-5b. This reaction was catalyzed by QD-2c and the product was obtained as a white foam in 97% yield and 94% ee.

(+)-5c. This reaction was catalyzed by Q-2c and the product was obtained as a white foam in 94% yield after purification by flash chromatography (hexanes/ether = 4/1) and 97% ee as determined by HPLC analysis [Chiralpak AD, Hexanes:IPA, 85:15, 1.0 mL/min, λ 220 nm, *t* (minor) = 11.6 min, *t* (major) = 36.6 min].

$[\alpha]_D^{23} = +61.6$ (c 1.635, CHCl_3); ^1H NMR (400 MHz, CDCl_3) see the attached spectrum; ^{13}C NMR (100 MHz, CDCl_3) see the attached spectrum; IR (CHCl_3) ν (cm^{-1}) 3335, 2982, 2935, 1747, 1721, 1494, 1478, 1370, 1244, 1154, 1097, 1016.

(-)-5c. This reaction was catalyzed by QD-2c and the product was obtained as a white foam in 96% yield and 93% ee.

(+)-5d. This reaction was catalyzed by Q-2c and the product was obtained as a white foam in 97% yield after purification by flash chromatography (hexanes/ether = 4/1) and 96% ee as determined by HPLC analysis [Chiralpak AD, Hexanes:IPA, 85:15, 1.0 mL/min, λ 220 nm, t (minor) = 12.4 min, t (major) = 35.3 min]. $[\alpha]_D^{23} = +54.4$ (c 0.54, CHCl_3); ^1H NMR (400 MHz, CD_3CN) see the attached spectrum; ^{13}C NMR (100 MHz, CD_3CN) see the attached spectrum; IR (CHCl_3) ν (cm^{-1}) 3422, 2980, 2932, 1745, 1718, 1644, 1488, 1369, 1243, 1154, 1012; HRMS (ESI) m/z calcd. for $(\text{M} + \text{H})^+$: 498.1240, found 498.1253.

(-)-5d. This reaction was catalyzed by QD-2c and the product was obtained as a white foam in 99% yield and 93% ee.

(+)-5e. This reaction was catalyzed by Q-2c and the product was obtained as a white foam in 98% yield after purification by flash chromatography (hexanes/ether = 3/1) and 99% ee as determined by HPLC analysis [Chiralpak AD, Hexanes:IPA, 60:40, 1.0 mL/min, λ 220 nm, t (minor) = 9.6 min, t (major) = 39.6 min]. $[\alpha]_D^{23} = +63.9$ (c 0.49, CHCl_3); ^1H NMR (400 MHz, CD_3CN) see the attached spectrum; ^{13}C NMR (100 MHz, CD_3CN) see the attached spectrum; IR (CHCl_3) ν (cm^{-1}) 3440, 2981, 1721, 1645, 1476, 1369, 1244, 1152, 1015; HRMS (CI) m/z calcd. for $(\text{M} + \text{H})^+$: 470.2291, found 470.2295.

(-)-5e. This reaction was catalyzed by QD-2c and the product was obtained as a white foam in 99% yield and 96% ee.

(+)-5f. This reaction was catalyzed by Q-2c and the product was obtained as a white foam in 96% yield after purification by flash chromatography (hexanes/ether = 3/1) and 96% ee as determined by HPLC analysis [Chiralpak AD, Hexanes:IPA, 85:15, 1.0 mL/min, λ 220 nm, t (minor) = 11.5 min, t (major) = 31.6 min]. $[\alpha]_D^{23} = +70.8$ (c 0.655, CHCl_3); ^1H NMR (400 MHz, CD_3CN) see the attached spectrum; ^{13}C NMR (100 MHz, CD_3CN) see the attached spectrum; IR (CHCl_3) ν (cm^{-1}) 3428, 2980, 2933, 1745, 1719, 1649, 1511, 1476, 1458, 1369, 1242, 1155, 1055, 1018; HRMS (CI) m/z calcd. for $(\text{M} + \text{H})^+$: 434.2291, found 434.2271.

(-)-5f. This reaction was catalyzed by QD-2c and the product was obtained as a white foam in 96% yield and 94% ee.

(+)-5g. This reaction was catalyzed by Q-2c and the product was obtained as a white foam in 96% yield after purification by flash chromatography (hexanes/ether = 3/1) and 97% ee as determined by HPLC analysis [Chiralpak OD, Hexanes:IPA, 97:3, 1.0 mL/min, λ 220 nm, t (minor) = 10.3 min, t (major) = 12.7 min]. $[\alpha]_D^{23} = +70.0$ (c 0.67, CHCl_3); ^1H NMR (400 MHz, CD_3CN) see the attached spectrum; ^{13}C NMR (100 MHz, CD_3CN) see the attached spectrum; IR (CHCl_3) ν (cm^{-1}) 3355, 2980, 2935, 1744, 1718, 1610, 1512, 1460, 1369, 1245, 1155, 1055, 1031; HRMS (ESI) m/z calcd. for $(\text{M} + \text{H})^+$: 450.2240, found 450.2250.

(-)-5g. This reaction was catalyzed by QD-2c and the product was obtained as a white foam in 96 % yield and 94% ee.

(+)-5h. This reaction was catalyzed by Q-2c and the product was obtained as a white foam in 83% yield after purification by flash chromatography (hexanes/ether = 3/1) and 92% ee as determined by HPLC analysis [Chiralpak AS, Hexanes:IPA, 75:25, 1.0 mL/min, λ 220 nm, t (minor) = 10.6 min, t (major) = 18.9 min]. $[\alpha]_D^{23} = +45.2$ (c 0.405, CHCl_3); ^1H NMR (400 MHz, CDCl_3) see the attached spectrum; ^{13}C NMR (100 MHz, CDCl_3) see the attached spectrum; IR (CHCl_3) ν (cm^{-1}) 3454, 3033, 2089, 1749, 1727, 1650, 1635, 1395, 1340, 1229, 1012; HRMS (ESI) m/z calcd. for $(\text{M} + \text{H})^+$: 566.0927, found 566.0916.

(-)-5h. This reaction was catalyzed by QD-2c and the product was obtained as a white foam in 86 % yield and 91% ee.

(+)-5i. This reaction was catalyzed by Q-2c and the product was obtained as a white foam in 72% yield after purification by flash chromatography (hexanes/ether = 2/1) and 87% ee as determined by HPLC analysis [Chiralpak OD, Hexanes:IPA, 90:10, 1.0 mL/min, λ 220 nm, t (minor) = 42.7 min, t (major) = 34.8 min]. $[\alpha]_D^{23} = +18.9$ (c 2.73, CHCl_3); ^1H NMR (400 MHz, CD_3CN) see the attached spectrum; ^{13}C NMR (100 MHz, CD_3CN) see the attached spectrum; IR (CHCl_3) ν (cm^{-1}) 3318, 2924, 1732, 1495, 1455, 1391, 1333, 1227, 1092, 1023; HRMS (ESI) m/z calcd. for $(\text{M} + \text{H})^+$: 502.1978, found 502.1983.

(-)-5i. This reaction was catalyzed by QD-2c and the product was obtained as a white foam in 71 % yield and 82% ee.

(-)-5j. This reaction was catalyzed by Q-2c and the product was obtained as a white foam in 74 % yield after purification by flash chromatography (hexanes/ether = 2/1) and 23% ee as determined by HPLC analysis [Chiralpak OD, Hexanes:IPA, 93:7, 1.0 mL/min, λ 220 nm, t (major) = 31.2 min, t (minor) = 36.9 min]. $[\alpha]_D^{23} = -0.9$ (c 3.045, CHCl_3); ^1H NMR (400 MHz, CDCl_3) see the attached spectrum; ^{13}C NMR (100 MHz, CDCl_3) see the attached spectrum; IR (CHCl_3) ν (cm^{-1}) 3439, 3033, 2354, 2066, 1746, 1720, 1635, 1499,

1454, 1395, 1347, 1288, 1233, 1174, 1123, 1049; HRMS (ESI) m/z calcd. for $(M+H)^+$: 426.1665, found 426.1653.

(+)-5j. This reaction was catalyzed by QD-2c and the product was obtained as a white foam in 75 % yield and 35% ee.

HPLC Conditions: Daicel Chirapak AD, hexanes:IPA 85:15, 1.0 ml/min.

(+)-5a
Product of **Q-2c**
catalyzed reaction

(-)-5a
Product of **QD-2c**
catalyzed reaction

HPLC Conditions: Daicel Chirapak AD, hexanes:IPA 85:15, 1.0 ml/min.

(+)-5b
Product of **Q-2c**
catalyzed reaction

(-)-5b
Product of **QD-2c**
catalyzed reaction

HPLC Conditions: Daicel Chirapak AD, hexanes:IPA 85:15, 1.0 ml/min.

(+)-5c
Product of **Q-2c**
catalyzed reaction

(-)-5c
Product of **QD-2c**
catalyzed reaction

HPLC Conditions: Daicel Chirapak AD, hexanes:IPA 85:15, 1.0 ml/min.

(+)-5d
Product of **Q-2c**
catalyzed reaction

(-)-5d
Product of **QD-2c**
catalyzed reaction

HPLC Conditions: Daicel Chirapak AD, hexanes:IPA 60:40, 1.0 ml/min.

Racemic **5e**

(+)-5e
Product of **Q-2c**
catalyzed reaction

(-)-5e
Product of **QD-2c**
catalyzed reaction

HPLC Conditions: Daicel Chirapak AD, hexanes:IPA 85:15, 1.0 ml/min.

(+)-5f
Product of **Q-2c**
catalyzed reaction

(-)-5f
Product of **QD-2c**
catalyzed reaction

HPLC Conditions: Daicel Chirapak OD, hexanes:IPA 97:3, 1.0 ml/min.

(+)-5g
Product of **Q-2c**
catalyzed reaction

(-)-5g
Product of **QD-2c**
catalyzed reaction

HPLC Conditions: Daicel Chirapak AS, hexanes:IPA 75:25, 1.0 ml/min.

(+)-5h
Product of **Q-2c**
catalyzed reaction

(-)-5h
Product of **QD-2c**
catalyzed reaction

HPLC Conditions: Daicel Chirapak OD, hexanes:IPA 90:10, 1.0 ml/min.

Racemic **5i**

(+)-**5i**

Product of **Q-2c**
catalyzed reaction

(-)-**5i**

Product of **QD-2c**
catalyzed reaction

HPLC Conditions: Daicel Chirapak OD, hexanes:IPA 93:7, 1.0 ml/min.

Racemic **5j**

(-)-5j

Product of **Q-2c**
catalyzed reaction

(+)-5j

Product of **QD-2c**
catalyzed reaction

X-Ray Structure Determination. Single crystal of (-)-**5c** (prepared using catalyst QD-**2c** as described in this supporting information) suitable for X-ray diffraction measurement was obtained by recrystallization from hexanes/diethyl ether.

Data were collected using a Bruker SMART CCD (charge coupled device) based diffractometer equipped with an Oxford Cryostream low-temperature apparatus operating at 193 K. A suitable crystal was chosen and mounted on a glass fiber using grease. Data were measured using omega scans of 0.3 ° per frame for 45 seconds, such that a hemisphere was collected. A total of 1271 frames were collected with a maximum resolution of 0.76 Å. The first 50 frames were recollected at the end of data collection to monitor for decay. Cell parameters were retrieved using SMART³ software and refined using SAINT on all observed reflections. Data reduction was performed using the SAINT software⁴ which corrects for Lp and decay. The structures are solved by the direct method using the SHELXS-97⁵ program and refined by least squares method on F², SHELXL-97,⁶ incorporated in SHELXTL-PC V 6.10.⁷

The structure was solved in the space group P2₁2₁2₁ (# 19) by analysis of systematic absences. All non-hydrogen atoms are refined anisotropically. Hydrogens were found by difference Fourier methods and refined isotropically. The crystal used for the diffraction study showed no decomposition during data collection. All drawing are done at 50% ellipsoids.

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¹ Kaiser, E. M.; Solter, L. E.; Schwarz, R. A.; Beard, R. D.; Hauser, C. R. *J. Am. Chem. Soc.* **1971**, *93*, 4237.

² Albarella, J. M. *J. Org. Chem.* **1977**, *42*, 2009.

³ SMART V 5.625 (NT) *Software for the CCD Detector System*; Bruker Analytical X-ray Systems, Madison, WI (2001).

⁴ SAINT V 6.22 (NT) *Software for the CCD Detector System* Bruker Analytical X-ray Systems, Madison, WI (2001).

⁵ Sheldrick, G. M. SHELXS-90, *Program for the Solution of Crystal Structure*, University of Göttingen, Germany, 1990.

⁶ Sheldrick, G. M. SHELXL-97, *Program for the Refinement of Crystal Structure*, University of Göttingen, Germany, 1997.

⁷ SHELXTL 6.1 (PC-Version), *Program library for Structure Solution and Molecular Graphics*; Bruker Analytical X-ray Systems, Madison, WI (2000).

^a Obtained with graphite monochromated Mo K α (λ = 0.71073 Å) radiation. ^b $R1 = \sum ||F_o| - |F_c|| / \sum |F_o|$. ^c $wR2 = \{ \sum [w(F_o^2 - F_c^2)^2] / \{ \sum [w(F_o^2)^2] \} \}^{1/2}$.

Figure 1. Molecular Structure of **5c** (prepared using catalyst QD-**2c** as described in this supporting information)