Supporting Information

Organocatalytic Enantioselective Nucleophilic Vinylic Substitution by α -Substituted- α -Cyanoacetates under Phase-Transfer Conditions

Mark Bell, Thomas B. Poulsen and Karl Anker Jørgensen*

Danish National Research Foundation: Center for Catalysis, Department of Chemistry, Aarhus University, DK 8000 Aarhus C, Denmark. Fax: (45) 8619 6199; Tel: (45) 8942 3910

E-mail: kaj@chem.au.dk

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General Methods

NMR spectra were acquired running at 400 and 100 MHz for ^1H and ^{13}C , respectively. Chemical shifts (δ) are reported in ppm relative to CDCl_3 ($\delta = 7.26$) for ^1H NMR and relative to the central resonance of CDCl_3 ($\delta = 77.0$) for ^{13}C NMR. ^{13}C NMR spectra were acquired on a broad band decoupled mode. All coupling constants are measured in Hz. Mass spectra were recorded using electrospray (ES^+) ionization techniques. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates and visualized by ultraviolet irradiation or KMnO_4 dip unless otherwise stated. Optical rotations were measured on a Perkin-Elmer polarimeter and $[\alpha]_{\text{D}}^{20}$ values are given in $10^{-1} \text{ deg cm}^2 \text{ g}^{-1}$. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AD or Daicel Chiralcel OD columns).

Materials

Analytical grade solvents were used as received. For flash chromatography (FC) silica gel 60, 230-400 mesh was used. Catalysts **4a** and **b** used in the screening are commercially available and were used as received unless otherwise stated. Catalysts **4c** and **d** were prepared using a known method.¹ α -Substituted- α -cyanoacetates **1a-h**² and (Z)- β -chloro-alkenones **2a-f**³ were prepared using literature procedures.

General method for the vinylic substitution reaction

Method A: *tert*-Butyl α -substituted- α -cyanoacetates **1a-h** (0.2 mmol) was added to a stirring bar equipped test tube and dissolved in CHCl_3 (0.4 mL). (Z)- β -Chloro-alkene **2a-f** (0.24 mmol) and catalyst **4a-d** (3 mol%) were added, and the resulting mixture cooled to -30°C (unless otherwise stated), before 0.4 mL of pre-cooled 66% Cs_2CO_3 (aq.) was added. The reaction was stirred at this temperature for the stated time before the organic phase was passed through a plug of silica and the reaction mixture eluted with Et_2O . The pure product **3a-m** was obtained by FC using petroleum ether: Et_2O 20:1 to remove the electrophile followed by a 4:1 mixture of the same solvents to give **3a-m**.

Method B: The same procedure as Method A, but (Z)- β -chloro-alkene **2a-f** (0.4 mmol) and catalyst **4d** (6 mol%) were used.

Analytical and Spectroscopic Data

(*R,Z*)-2-Cyano-5-oxo-2,5-diphenyl-pent-3-enoic acid tert-butyl ester (**3a**)

Method A was used (19 h, 66 mg, 95%, 93% ee, *Z/E* 99/1). ^1H NMR (CDCl_3) δ 7.98 (2H, dd, *J* 3.8, 5.7), 7.66 (2H, m), 7.59 (1H, m), 7.48 (2H, t, *J* 7.6), 7.41 (3H, m), 7.26 (1H, d, *J* 11.4), 6.52 (1H, d, *J* 11.4), 1.38 (9H, s). ^{13}C NMR (CDCl_3) δ 189.7, 164.7, 141.1, 137.3, 136.7, 133.8, 129.3, 129.0, 128.9, 128.8, 128.3, 126.6, 116.8, 84.8, 54.4, 27.7. HRMS: $\text{C}_{22}\text{H}_{21}\text{NO}_3$ $[\text{M}+\text{Na}]^+$ calc.: 370.1419, found: 370.1414. $[\alpha]_{\text{D}}^{20}$ -130.3 (*c* = 1.0, CH_2Cl_2 , 93% ee). The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 19.4 min, τ_{minor} = 24.3 min (93% ee).

(*R,Z*)-2-Cyano-5-oxo-2-phenyl-5-(4-trifluoromethyl-phenyl)-pent-3-enoic acid tert-butyl ester (**3b**)

Method A was used (20 h, 82 mg, 99%, 75% ee, *Z/E* 97/3). ^1H NMR (CDCl_3) δ 8.08 (2H, d, *J* 8.1), 7.75 (2H, d, *J* 8.2), 7.64 (2H, dd, *J* 8.2, 1.3), 7.43 (3H, m), 7.25 (1H, d, *J* 11.4), 6.61 (1H, d, *J* 11.4), 1.39 (9H, s). ^{13}C NMR (CDCl_3) δ 189.0, 164.6, 142.3, 139.9, 136.4, 134.8 (q, *J* 32.7), 129.4, 129.3, 129.1, 127.8, 126.5, 126.0 (q, *J* 3.7), 123.7 (q, *J* 272.5), 116.6, 85.1, 54.3, 27.8. (HRMS: $\text{C}_{23}\text{H}_{20}\text{F}_3\text{NO}_3$ $[\text{M}+\text{Na}]^+$ calc.: 438.1293, found: 438.1293. $[\alpha]_{\text{D}}^{20}$ -81.9 (*c* = 1.0, CH_2Cl_2 , 75% ee). The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 22.7 min, τ_{minor} = 41.7 min (75% ee).

(*R,Z*)-2-Cyano-5-(4-methoxy-phenyl)-5-oxo-2-phenyl-pent-3-enoic acid tert-butyl ester (3c)

Method A was used (22 h, 69 mg, 92%, 95% ee, *Z/E* 97/3). ¹H NMR (CDCl₃) δ 7.97 (2H, d, *J* 8.9), 7.65 (2H, dd, *J* 8.2, 1.3), 7.40 (3H, m), 7.22 (1H, d, *J* 11.3), 6.94 (2H, d, *J* 8.9), 6.45 (1H, d, *J* 11.3), 3.88 (3H, s), 1.36 (9H, s). ¹³C NMR (CDCl₃) δ 188.2, 164.7, 164.1, 140.2, 136.8, 131.2, 130.5, 129.3, 129.0, 128.4, 126.6, 116.9, 114.2, 84.6, 55.8, 54.5, 27.7. HRMS: C₂₃H₂₃NO₄ [M+Na]⁺ calc.: 400.1525, found: 400.1528. [α]_D²⁰ -134.3 (c = 1.0, CH₂Cl₂, 95% ee). The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 34.2 min, τ_{minor} = 46.0 min (95% ee).

(*R,Z*)-2-Cyano-5-oxo-2-phenyl-5-thiophen-2-yl-pent-3-enoic acid tert-butyl ester (3d)

Method A was used (18 h, 62 mg, 95%, 97% ee, *Z/E* 97/3). ¹H NMR (CDCl₃) δ 7.79 (1H, dd, *J* 3.9, 1.1), 7.70 (1H, dd, *J* 4.9, 1.1), 7.65 (2H, dd, *J* 8.3, 1.4), 7.42 (3H, m), 7.15 (1H, dd, *J* 4.9, 3.8), 7.14 (1H, d, *J* 11.3), 6.49 (1H, d, *J* 11.3), 1.38 (9H, s). ¹³C NMR (CDCl₃) δ 181.5, 164.6, 144.9, 141.2, 136.7, 135.4, 132.9, 129.3, 129.1, 128.6, 128.0, 126.6, 116.7, 84.8, 54.3, 27.7. HRMS: C₂₀H₁₉SNO₃ [M+Na]⁺ calc.: 376.0983, found: 376.0982. [α]_D²⁰ -152.3 (c = 1.0, CH₂Cl₂, 97% ee). The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 28.0 min, τ_{minor} = 33.4 min (97% ee).

The absolute configuration was determined by X-ray crystallography (Figure 1):

Figure 1. X-ray crystal structure of **3d**. Hydrogens have been omitted for clarity.

(*R,Z*)-2-Cyano-5-naphthalen-1-yl-5-oxo-2-phenyl-pent-3-enoic acid tert-butyl ester (3e)

 Method B was used (22 h, 73 mg, 93%, 43% ee, *Z/E* 88/12). ¹H NMR (CDCl₃) δ 8.66 (1H, d, *J* 8.6), 7.92 (1H, dd, *J* 7.2, 1.2), 7.88 (1H, d, *J* 8.6), 7.71 (2H, m), 7.65-7.34 (7H, m), 7.14 (1H, d, *J* 11.3), 6.53 (1H, d, *J* 11.3), 1.40 (9H, s). ¹³C NMR (CDCl₃) δ 192.9, 164.8, 140.5, 136.7, 135.6, 134.0, 133.6, 131.8, 130.5, 129.4, 129.2, 129.1, 128.6, 128.3, 126.9, 126.6, 126.1, 124.7, 116.9, 84.8, 54.4, 27.7. MS: C₂₆H₂₃NO₃ [M+Na]⁺ 420.1. [α]_D²⁰ -43.8 (c = 1.0, CH₂Cl₂, 43% ee). The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 19.3 min, τ_{minor} = 30.9 min (43% ee).

(*R,Z*)-2-Cyano-5-oxo-2-phenyl-hex-3-enoic acid tert-butyl ester (3f)

Method B was used (24 h, 57 mg, 99%, 38% ee, *Z/E* 95/5). ¹H NMR (CDCl₃) δ 7.59 (2H, d, *J* 6.8), 7.40 (3H, m), 6.53 (1H, d, *J* 11.1), 6.25 (1H, d, *J* 11.1), 2.29 (3H, s), 1.38 (9H, s). ¹³C NMR (CDCl₃) δ 197.2, 164.7, 139.7, 136.7, 131.0, 129.3, 129.0, 126.4, 116.6, 84.7, 53.9, 31.4, 27.8. MS: C₁₇H₁₉NO₃ [M+Na]⁺ 308.1. [α]_D²⁰ -52.0 (c = 1.0, CH₂Cl₂, 38% ee). The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 15.0 min, τ_{minor} = 23.9 min (38% ee).

(*R,Z*)-2-Cyano-2-(2-fluoro-phenyl)-5-oxo-5-phenyl-pent-3-enoic acid tert-butyl ester (3g)

Method A was used (20 h, 58 mg, 80%, 84% ee, *Z/E* >95/5). ¹H NMR (CDCl₃) δ 7.91 (2H, d, *J* 8.5), 7.75 (1H, dt, *J* 7.9, 1.6), 7.56 (1H, m), 7.45 (2H, t, *J* 7.5), 7.33 (1H, ddd, *J* 9.6, 7.4, 1.6), 7.21 (1H, dt, *J* 7.7, 1.1), 7.14 (1H, d, *J* 11.7), 7.04 (1H, ddd, *J* 11.2, 8.2, 1.0), 6.74 (1H, dd, *J* 11.7, 3.9), 1.45 (9H, s). ¹³C NMR (CDCl₃) δ 190.1, 164.1, 156.0 (d, *J* 249.6), 138.0 (d, *J* 2.0), 137.1, 133.7, 130.9 (d, *J* 8.5), 130.1 (d, *J* 2.5), 129.0 (d, *J* 5.1), 128.9, 128.8, 128.3, 124.6 (d, *J* 3.4), 116.4 (d, *J* 21.2), 115.7, 85.4, 51.5, 27.7. HRMS: C₂₂H₂₀FNO₃ [M+Na]⁺ calc.: 388.1325, found: 388.1324. [α]_D²⁰ -50.3 (c = 1.0, CH₂Cl₂, 84% ee). The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 16.3 min, τ_{minor} = 20.8 min (84% ee).

(*R,Z*)-2-Cyano-5-oxo-5-phenyl-2-*m*-tolyl-3-pentenoic acid tert-butyl ester (3h)

Method A was used (21 h, 70 mg, 97%, 92% ee, *Z/E* 99/1). ¹H NMR (CDCl₃) δ 7.99 (2H, d, *J* 7.0), 7.59 (1H, m), 7.50-7.43 (4H, m), 7.30 (1H, t, *J* 7.7), 7.24 (1H, d, *J* 11.4), 7.18 (1H, d, *J* 7.6), 6.49 (1H, d, *J* 11.4), 2.38 (3H, s), 1.45 (9H, s). ¹³C NMR (CDCl₃) δ 189.8, 164.7, 141.2, 139.2, 137.3, 136.5, 133.7, 129.8, 129.2, 128.9, 128.8, 128.1, 127.2, 123.6, 116.9, 84.7, 54.4, 27.7, 21.7. HRMS: C₂₃H₂₃NO₃

$[M+Na]^+$ calc.: 384.1576, found: 384.1579. $[\alpha]_D^{20}$ -113.8 ($c = 1.0$, CH_2Cl_2 , 92% ee). The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; $\tau_{major} = 14.6$ min, $\tau_{minor} = 17.8$ min (92% ee).

(*R,Z*)-2-(4-Chloro-phenyl)-2-cyano-5-oxo-5-phenyl-pent-3-enoic acid tert-butyl ester (3i)

Method A was used (21 h, 56 mg, 92%, 90% ee, *Z/E* 99/1). 1H NMR ($CDCl_3$) δ 7.97 (2H, dd, J 8.3, 1.2), 7.60 (3H, m), 7.48 (2H, t, J 7.6), 7.39 (2H, d, J 8.8), 7.27 (1H, d, J 11.4), 6.50 (1H, d, J 11.4), 1.38 (9H, s). ^{13}C NMR ($CDCl_3$) δ 188.8, 163.7, 139.6, 136.5, 134.5, 134.4, 133.2, 128.8, 128.3, 128.1, 127.8, 127.4, 115.8, 84.5, 53.2, 27.0. HRMS: $C_{22}H_{20}ClNO_3$ $[M+Na]^+$ calc.: 404.1029, found: 404.1024. $[\alpha]_D^{20}$ -109.9 ($c = 1.0$, CH_2Cl_2 , 90% ee). The ee was determined by HPLC using a Chiralcel OD column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; $\tau_{major} = 14.9$ min, $\tau_{minor} = 12.0$ min (90% ee).

(*R,Z*)-2-Cyano-2-naphthalen-2-yl-5-oxo-5-phenyl-pent-3-enoic acid tert-butyl ester (3j)

Method A was used (18 h, 80 mg, 99%, 94% ee, *Z/E* 98/2). 1H NMR ($CDCl_3$) δ 8.21 (1H, d, J 2.0), 7.97 (2H, d, J 7.1), 7.71 (2H, dd, J 8.7, 2.1), 7.85 (1H, m), 7.71 (1H, dd, J 8.7, 2.1), 7.51-7.62 (3H, m), 7.48 (2H, t, J 7.6), 7.30 (1H, d, J 11.3), 6.60 (1H, d, J 11.3), 1.39 (9H, s). ^{13}C NMR ($CDCl_3$) δ 189.8, 164.7, 141.0, 137.3, 133.8, 133.7, 133.2, 133.1, 129.5, 129.0, 128.8, 128.7, 128.3, 127.7, 127.3, 127.1, 126.4, 123.6, 116.9, 84.9, 54.6, 27.8. HRMS: $C_{26}H_{23}NO_3$ $[M+Na]^+$ calc.: 420.1576, found: 420.1577. $[\alpha]_D^{20}$ -129.9 ($c = 1.0$, CH_2Cl_2 , 94% ee). The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; $\tau_{major} = 31.2$ min, $\tau_{minor} = 41.8$ min (94% ee).

(*R,Z*)-2-Cyano-2-(1-methyl-1H-indol-3-yl)-5-oxo-5-phenyl-pent-3-enoic acid tert-butyl ester (3k)

Method A was used (18 h, 69 mg, 86%, 98% ee, *Z/E* >95/5). ¹H NMR (CDCl₃) δ 8.01 (2H, dd, *J* 8.2, 1.2), 7.80 (1H, d, *J* 8.2), 7.59 (1H, t, *J* 7.5), 7.48 (2H, t, *J* 7.5), 7.38 (1H, s), 7.33 (1H, d, *J* 8.2), 7.27 (1H, m), 7.25 (1H, d, *J* 11.2), 7.15 (1H, m), 6.68 (1H, d, *J* 11.2), 3.78 (3H, s), 1.38 (9H, s). ¹³C NMR (CDCl₃) δ 190.0, 164.4, 141.6, 138.0, 137.3, 133.7, 129.0, 128.9, 128.8, 128.7, 127.8, 124.4, 122.6, 120.4, 120.1, 117.3, 110.1, 84.5, 49.2, 33.2, 27.8. HRMS: C₂₅H₂₄N₂O₃ [M+Na]⁺ calc.: 423.1685, found: 423.1680. [α]_D²⁰ -71.0 (c = 1.0, CH₂Cl₂, 98% ee). The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (80:20)]; flow rate 1.0 mL/min; τ_{major} = 18.6 min, τ_{minor} = 14.8 min (98% ee).

(*S,Z*)-2-Cyano-2-methyl-5-oxo-5-phenyl-pent-3-enoic acid tert-butyl ester (3l)

Method B was used (22 h, 54 mg, 95%, 92% ee, *Z/E* 99/1). ¹H NMR (CDCl₃) δ 7.96 (2H, d, *J* 7.1), 7.58 (1H, t, *J* 7.4), 7.48 (2H, m), 7.11 (1H, d, *J* 11.4), 6.19 (1H, d, *J* 11.4), 1.88 (3H, s), 1.48 (9H, s). ¹³C NMR (CDCl₃) δ 189.9, 166.7, 140.6, 137.2, 133.8, 128.9, 128.6, 127.7, 118.7, 84.3, 44.5, 27.9, 26.3. HRMS: C₁₇H₁₉NO₃ [M+Na]⁺ calc.: 308.1263, found: 308.1267. [α]_D²⁰ -44.1 (c = 1.0, CH₂Cl₂, 92% ee). The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; τ_{major} = 11.2 min, τ_{minor} = 14.7 min (92% ee).

(*S,Z*)-2-Cyano-2-(3-oxo-3-phenyl-propenyl)-hexanoic acid tert-butyl ester (3m)

Method B was used (22 h, 49 mg, 75%, 76% ee, *Z/E* >95/5). ¹H NMR (CDCl₃) δ 7.97 (2H, d, *J* 7.2), 7.58 (1H, t, *J* 7.4), 7.48 (2H, t, *J* 7.6), 7.11 (1H, d, *J* 11.5), 6.14 (1H, d, *J* 11.5), 2.12 (2H, td, *J* 10.6, 5.9), 1.65 (2H, m), 1.50 (9H, s), 1.40 (2H, dd, *J* 14.5, 7.3), 0.94 (3H, t, *J* 7.3). ¹³C NMR (CDCl₃) δ 190.0, 166.3, 139.8, 137.2, 133.7, 128.9, 128.8, 128.2, 117.7, 84.4, 49.3, 39.7, 27.9, 27.3, 22.6, 14.0. HRMS: C₂₀H₂₅NO₃ [M+Na]⁺ calc.: 350.1732, found: 350.1734. [α]_D²⁰ -63.2 (c = 1.0, CH₂Cl₂, 76% ee). The ee was determined by

HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 13.6$ min, $\tau_{\text{minor}} = 22.3$ min (76% ee).

(*R,E*)-2-Cyano-5-oxo-2,5-diphenyl-pent-3-enoic acid tert-butyl ester (3a)

Compound (*Z*)-**3a** (34.7mg, 0.1 mmol, 90% ee) was dissolved in CHCl_3 (0.5 mL) and iodine (5.0 mg, 0.02 mmol) added. The mixture was stirred at 45 °C for 14 h, cooled to room temperature and extracted with CH_2Cl_2 (3 x 10 mL) and $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL). The pure product (*E*)-**3a** was obtained by FC using petroleum ether: Et_2O 20:1. (30.1 mg, 87%, 90% ee, *Z/E* <1:99). ^1H NMR (CDCl_3) δ 7.98 (2H, dd, *J* 1.1, 8.3), 7.66 (1H, t, *J* 7.4), 7.57-7.38 (9H, m), 1.48 (9H, s). ^{13}C NMR (CDCl_3) δ 189.1, 164.5, 140.5, 137.1, 134.3, 133.8, 129.7, 129.5, 129.0, 128.9, 127.4, 126.4, 116.8, 86.0, 57.1, 27.8. HRMS: $\text{C}_{22}\text{H}_{21}\text{NO}_3$ [$\text{M}+\text{Na}$] $^+$ calc.: 370.1419, found: 370.1416. $[\alpha]_{\text{D}}^{20}$ -1.4 (*c* = 1.0, CH_2Cl_2 , 90% ee). The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (95:5)]; flow rate 1.0 mL/min; $\tau_{\text{major}} = 15.0$ min, $\tau_{\text{minor}} = 23.9$ min (90% ee).

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Spectra