Enantioselective Organocatalytic Allylic Amination

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Supporting Information

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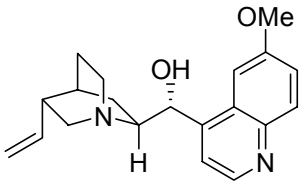
Catalyst Structures



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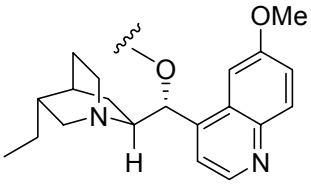
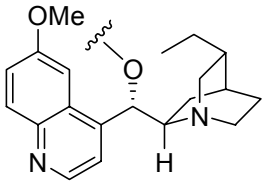
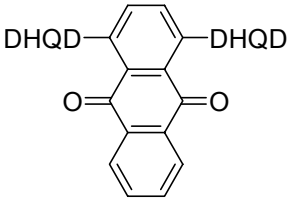


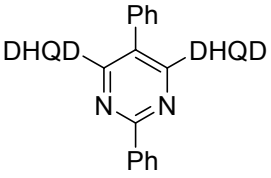
DHQ



DHQD



$(DHQD)_2AQN$



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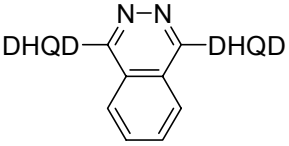


$(DHQD)_2PHAL$

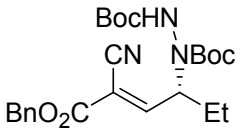
General Methods. NMR spectra were acquired on a Varian AS 400 spectrometer, running at 400 and 100 MHz for ^{1}H and ^{13}C, respectively. Chemical shifts (δ) are reported in ppm relative to residual solvent signals. All spectra were recorded at elevated temperatures (60 °C) in order to minimize the effect of rotameric isomers. ^{13}C NMR spectra were acquired on a broad band decoupled mode. Mass spectra were recorded on a micromass LCT spectrometer using electrospray (ES^{+}) ionization techniques. Flash column chromatography (FC) was carried out using the FlashMaster II from Jones Chromatography with columns containing silica gel. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by ultraviolet irradiation or $KMnO_4$ dip. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. The enantiomeric excess (ee) of the products was determined by chiral stationary phase HPLC (Daicel Chiralpak AS/AD or Daicel Chiralcel OD columns).

Materials. Analytical grade solvents were used as received. For flash chromatography (FC) silica gel was purchased from Iatron Laboratories Inc. (Iatrobeads 6RS-8060) or from Fluka (Silica gel 60, 230-400 mesh). Dialkyl azodicarboxylates and catalysts (**2**) are all commercially available and were used as received. Substrates **1a-k**,**o** were prepared by Knoevenagel condensation of the appropriate α-cyanoacetate and aldehyde following a literature procedure.[1] Substrate **1l** was synthesized by condensing malonitrile with butyraldehyde.[2] Substrates **1m**,**n** were prepared from malononitrile and the corresponding ketones.[3]

General Procedure for allylic amination of alkylidene cyanoacetates: To a test tube equipped with a magnetic stirring bar were added dichloromethane (1.0 mL), di-*tert*-butyl azodicarboxylate (0.24 mmol, 55.4 mg), and the alkylidene cyanoacetate (0.2 mmol). The test tube was fitted with a rubber septum, stirred at ambient temperature to dissolve the solids, and then cooled to -78 ^{o}C. $(DHQ)_2PYR$ (10 mol%, 0.02 mmol, 17.6 mg) was added as a solid to the cooled mixture, which was then placed at -24 ^{o}C for 41-47 h. The mixture was then cooled to -78 ^{o}C and loaded directly onto a chromatographic column

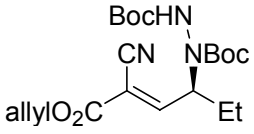
containing Iatrobeads. The pure product was isolated by FC. The enantiomeric excess of the products was determined by HPLC using a chiral stationary phase.

(*R*)-(*E*)-4-[*N*,*N*'-Bis(*tert*-butoxycarbonyl)-hydrazino]-2-cyanohex-2-enoic acid benzyl ester (2a):



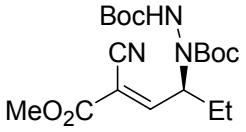
The title compound was obtained according to the general procedure, but using $(DHQD)_2PYR$ as the catalyst**,** after FC in Et_2O/*n*-hexane as a viscous colorless oil (83% yield). ^1H NMR ($CDCl_3$, 60 ^oC) δ 7.67 (d, *J* 9.1 Hz, 1H), 7.43-7.31 (m, 5H), 6.11 (br s, 1H), 5.30 (s, 2H), 4.94 (q, *J* 6.5 Hz, 1H), 1.88 (m, 1H), 1.66 (m, 1H), 1.48 (s, 9H), 1.46 (s, 9H), 0.99 (t, *J* 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 60 ^oC) δ 160.9, 160.3, 155.9, 154.3, 134.9, 128.6 (2C), 128.5 (2C), 128.2, 113.0, 109.3, 82.5, 81.9, 68.0, 60.3, 28.2 (3C), 28.0 (3C), 24.8, 10.4. HRMS calc.: $C_{24}H_{33}N_3NaO_6$ 482.2267; found: 482.2270. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (75:25)]; flow rate 1.0 mL/min; τ_{major} = 18.2 min, τ_{minor} = 11.8 min (94% ee).

(*S*)-(*E*)-4-[*N*,*N*'-Bis(*tert*-butoxycarbonyl)-hydrazino]-2-cyanohex-2-enoic acid allyl ester (2b):



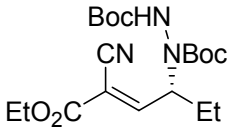
The title compound was obtained according to the general procedure after FC in Et_2O/*n*-hexane as a viscous colorless oil (90% yield). ^1H NMR ($CDCl_3$, 60 ^oC) δ 7.66 (d, *J* 9.1 Hz, 1H), 6.12 (br s, 1H), 5.96 (ddt, *J* 16.2, 10.8, 5.8 Hz, 1H), 5.40 (dd, *J* 17.2, 1.4 Hz, 1H), 5.30 (dd, *J* 10.6, 1.1 Hz, 1H), 4.95 (q, *J* 8.2 Hz, 1H), 4.75 (d, *J* 5.7 Hz, 2H), 1.88 (m, 1H), 1.67 (m, 1H), 1.49 (s, 9H), 1.49 (s, 9H), 1.00 (t, *J* 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 60 ^oC) δ 160.7, 160.2, 156.0, 154.3, 131.0, 119.2, 113.0, 109.2, 82.5, 81.9, 66.8, 60.3, 28.2 (3C), 28.1 (3C), 24.8, 10.4. HRMS calc.: $C_{20}H_{31}N_3NaO_6$ 432.2111; found: 432.2104. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (75:25)]; flow rate 1.0 mL/min; τ_{major} = 7.0 min, τ_{minor} = 11.4 min (97% ee).

(*S*)-(*E*)-4-[*N*,*N*'-Bis(*tert*-butoxycarbonyl)-hydrazino]-2-cyanohex-2-enoic acid methyl ester (2c):



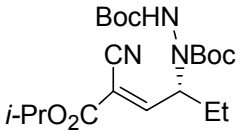
The title compound was obtained according to the general procedure after FC in Et_2O/*n*-hexane as a viscous colorless oil (84% yield). ^{1}H NMR ($CDCl_3$, 60 ^{o}C) δ 7.65 (d, *J* 9.2 Hz, 1H), 6.12 (br s, 1H), 4.93 (q, *J* 8.1 Hz, 1H), 3.87 (s, 3H), 1.87 (m, 1H), 1.66 (m, 1H), 1.49 (s, 18H), 0.99 (t, *J* 9.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 60 ^{o}C)[5] δ 161.5, 160.2, 156.0, 154.3, 113.1, 109.1, 82.5, 82.0, 60.3, 53.1, 53.0, 28.2 (3C), 28.1 (3C), 24.8, 10.4. HRMS calc.: $C_{18}H_{29}N_3NaO_6$ 406.1954; Found: 406.1942. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (75:25)]; flow rate 1.0 mL/min; τ_{major} = 6.4 min, τ_{minor} = 14.3 min (98% ee).

(*R*)-(*E*)-4-[*N*,*N*'-Bis(*tert*-butoxycarbonyl)-hydrazino]-2-cyanohex-2-enoic acid ethyl ester (2d):



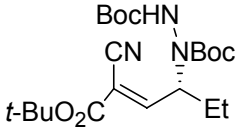
The title compound was obtained according to the general procedure, but using $(DHQD)_2PYR$ as the catalyst, after FC in Et_2O/*n*-hexane as a viscous colorless oil (71% yield). ^{1}H NMR ($CDCl_3$, 60 ^{o}C) δ 7.63 (d, *J* 9.2 Hz, 1H), 6.11 (br, s, 1H), 4.94 (q, *J* 8.1 Hz, 1H), 4.33 (q, *J* 7.1 Hz, 2H), 1.88 (m, 1H), 1.66 (m, 1H), 1.49 (s, 9H), 1.49 (s, 9H), 1.37 (t, *J* 7.1 Hz, 3H), 0.99 (t, *J* 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 60 ^{o}C) δ 161.0, 159.7, 156.0, 154.3, 113.1, 109.5, 82.5, 81.9, 62.5, 60.3, 28.2 (3C), 28.1 (3C), 24.8, 14.0, 10.4. HRMS calc.: $C_{19}H_{31}N_3NaO_6$ 420.2111; found: 420.2127. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (75:25)]; flow rate 1.0 mL/min; τ_{major} = 12.2 min, τ_{minor} = 6.3 min (90% ee).

(*R*)-(*E*)-4-[*N*,*N*'-Bis(*tert*-butoxycarbonyl)-hydrazino]-2-cyanohex-2-enoic acid *i*-propyl ester (2e):



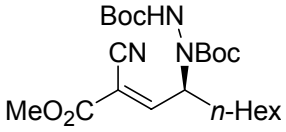
The title compound was obtained according to the general procedure, but using $(DHQD)_2PYR$ as the catalyst**,** after FC in Et_2O/*n*-hexane as a viscous colorless oil (62% yield). ^1H NMR ($CDCl_3$, 60 ^oC) δ 7.60 (d, *J* 9.1 Hz, 1H), 6.11 (br s, 1H), 5.14 (septet, *J* 6.2 Hz, 1H), 4.95 (q, *J* 8.3 Hz, 1H), 1.88 (m, 1H), 1.66 (m, 1H), 1.49 (s, 9H), 1.49 (s, 9H), 1.34 (d, *J* 6.3 Hz, 6H), 0.99 (t, *J* 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 60 ^oC)[5] δ 160.5, 159.4, 156.0, 154.3, 113.2, 110.0, 82.5, 81.9, 70.8, 70.7, 60.3, 28.2 (3C), 28.1 (3C), 24.9, 21.6 (2C), 10.4. HRMS calc.: $C_{20}H_{33}N_3NaO_6$ 434.2267; found: 420.2250. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (75:25)]; flow rate 1.0 mL/min; τ_{major} = 9.6 min, τ_{minor} = 5.8 min (93 % ee).

(*R*)-(*E*)-4-[*N*,*N*'-Bis(*tert*-butoxycarbonyl)-hydrazino]-2-cyanohex-2-enoic acid *t*-butyl ester (2f):



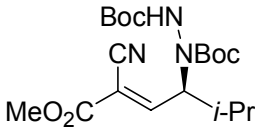
The title compound was obtained according to the general procedure, but using $(DHQD)_2PYR$ as the catalyst, after FC in Et_2O/*n*-hexane as a viscous colorless oil (21% yield). ^1H NMR ($CDCl_3$, 60 ^oC) δ 7.53 (d, *J* 9.1 Hz, 1H), 6.12 (br s, 1H), 4.93 (q, *J* 7.8 Hz, 1H), 1.86 (m, 1H), 1.64 (m, 1H), 1.54 (s, 9H), 1.49 (s, 9H), 1.48 (s, 9H), 0.99 (t, *J* 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 60 ^oC) δ 159.9, 158.6, 156.0, 154.4, 113.5, 111.1, 83.8, 82.5, 82.0, 60.2, 28.2 (3C), 28.1 (3C), 28.0 (3C), 24.9, 10.6. HRMS calc.: $C_{21}H_{35}N_3NaO_6$ 448.2424; found: 448.2427. The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (75:25)]; flow rate 1.0 mL/min; τ_{major} = 8.2 min, τ_{minor} = 5.5 min (91% ee).

(*S*)-(*E*)-4-[*N*,*N*'-Bis(*tert*-butoxycarbonyl)-hydrazino]-2-cyanodec-2-enoic acid methyl ester (2g):



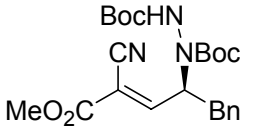
The title compound was obtained according to the general procedure after FC in Et_2O/*n*-hexane as a viscous colorless oil (90% yield). ^{1}H NMR ($CDCl_3$, 60 ^{o}C) δ 7.65 (d, *J* 9.2 Hz, 1H), 6.10 (br s, 1H), 5.02 (q, *J* 8.2 Hz, 1H), 3.87 (s, 3H), 1.84 (m, 1H), 1.58 (m, 1H), 1.49 (s, 18H), 1.41-1.25 (m, 8H), 0.90 (t, *J* 6.7 Hz, 3H). ^{13}C NMR ($CDCl_3$, 60 ^{o}C)[5] δ 161.5, 160.4, 156.0, 154.2, 113.0, 108.8, 82.5, 82.0, 58.7, 53.1, 53.0, 31.5, 31.4, 28.8, 28.2 (3C), 28.1 (3C), 25.7, 22.4, 13.8. HRMS calc.: $C_{22}H_{37}N_3NaO_6$ 462.2580; found: 462.2590. $[\alpha]_D^{20}$ +70 (*c* = 1.0, $CHCl_3$, 99% ee). The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (75:25)]; flow rate 1.0 mL/min; τ_{major} = 5.2 min, τ_{minor} = 9.9 min (99% ee).

(*S*)-(*E*)-4-[*N*,*N*'-Bis(*tert*-butoxycarbonyl)-hydrazino]-2-cyano-5-methylhex-2-enoic acid methyl ester (2h):



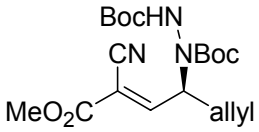
The title compound was obtained according to the general procedure, but at a temperature of 4 ^{o}C, after FC in Et_2O/*n*-hexane as a viscous colorless oil (87% yield). ^{1}H NMR ($CDCl_3$, 60 ^{o}C) δ 7.57 (d, *J* 10.4, 1H), 6.01 (br s, 1H), 4.71 (t, *J* 10.3 Hz, 1H), 3.88 (s, 3H), 2.08 (m, 1H), 1.50 (s, 9H), 1.48 (s, 9H), 1.05 (d, *J* 6.6 Hz, 3H), 0.93 (d, *J* 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, 60 ^{o}C)[5] δ 161.5, 158.6, 156.0, 154.3, 113.3, 110.2, 82.6, 82.0, 64.7, 53.1, 53.0, 30.0, 28.2 (3C), 28.0 (3C), 19.7, 18.7. HRMS calc.: $C_{19}H_{31}N_3NaO_6$ 420.2111; found: 420.2110. $[\alpha]_D^{20}$ +103 (*c* = 1.0, $CHCl_3$, 96% 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} = 7.8 min, τ_{minor} = 18.7 min (90% ee).

(*S*)-(*E*)-4-[*N*,*N*'-Bis(*tert*-butoxycarbonyl)-hydrazino]-2-cyano-5-phenylpent-2-enoic acid methyl ester (2i):



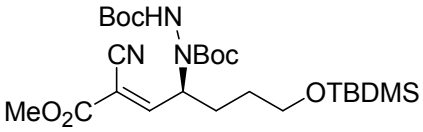
The title compound was obtained according to the general procedure after FC in Et_2O/*n*-hexane as a viscous colorless oil (89% yield). ^{1}H NMR ($CDCl_3$, 60 ^{o}C) δ 7.75 (d, *J* 8.9 Hz, 1H), 7.32 (m, 2H), 7.23 (m, 3H), 6.03 (br s, 1H), 5.34 (m, 1H), 3.86 (s, 3H), 3.16 (m, 1H), 2.96 (m, 1H), 1.49 (s, 9H), 1.41 (s, 9H). ^{13}C NMR ($CDCl_3$, 60 ^{o}C)[5] δ 161.3, 159.4, 156.0, 153.9, 135.9, 129.1 (2C), 128.8 (2C), 127.2, 112.9, 109.3, 82.6, 82.2, 60.5, 53.1, 53.0, 37.8, 28.1 (6C). HRMS calc.: $C_{23}H_{31}N_3NaO_6$ 468.2111; found: 468.2103. $[\alpha]_D^{20}$ +101 (*c* = 1.0, CH_2Cl_2, 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} = 8.3 min, τ_{minor} = 21.1 min (98% ee).

(*S*)-(*E*)-4-[*N*,*N*'-Bis(*tert*-butoxycarbonyl)-hydrazino]-2-cyanoocta-2,7-dienoic acid methyl ester (2j):



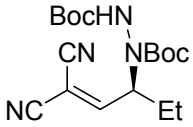
The title compound was obtained according to the general procedure after FC in Et_2O/*n*-hexane as a viscous colorless oil (85% yield). ^{1}H NMR ($CDCl_3$, 60 ^{o}C) δ 7.67 (d, *J* 8.9 Hz, 1H), 6.12 (br s, 1H), 5.77 (ddt, *J* 17.1, 10.1, 7.0 Hz, 1H), 5.21-5.06 (m, 3H), 3.87 (s, 3H), 2.63 (m, 1H), 2.42 (m, 1H), 1.49 (s, 9H), 1.49 (s, 9H).^{13}C NMR ($CDCl_3$, 60 ^{o}C)[5] δ 161.4, 159.6, 155.9, 154.0, 132.6, 119.0, 113.0, 109.2, 82.6, 82.0, 58.5, 53.1, 53.0, 35.8, 28.1 (3C), 28.1 (3C). HRMS calc.: $C_{19}H_{29}N_3NaO_6$ 418.1954; found: 418.1958. $[\alpha]_D^{20}$ +69 (*c* = 1.0, $CHCl_3$, 96% 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} = 7.6 min, τ_{minor} = 19.4 min (96% ee).

(*S*)-(*E*)-4-[*N*,*N*'-Bis(*tert*-butoxycarbonyl)-hydrazino]-7-(*tert*-butyldimethyl-silanyloxy)-2-cyanohept-2-enoic acid methyl ester (2k):



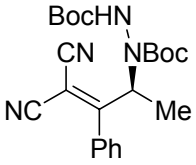
The title compound was obtained according to the general procedure after FC in Et_2O/CH_2Cl_2 as a viscous colorless oil (80% yield). ^{1}H NMR ($CDCl_3$, 60 ^{o}C) δ 7.66 (d, *J* 9.1 Hz, 1H), 6.24 (br s, 1H) 5.04 (br m, 1H), 3.87 (s, 3H), 3.66 (t, *J* 6.4 Hz, 2H), 1.94 (m, 1H), 1.70-1.55 (m, 3H), 1.49 (br s, 18H), 0.91 (s, 9H), 0.07 (s, 6H). ^{13}C NMR ($CDCl_3$, 60 ^{o}C)[5] δ 161.5, 160.3, 155.9, 154.2, 113.0, 108.9, 82.5, 81.9, 62.3, 58.6, 53.1, 53.0, 29.2, 28.2 (3C), 28.1 (3C), 27.8, 26.0 (3C), 18.3, -5.3, -5.4. HRMS calc.: $C_{25}H_{45}N_3NaO_7Si$ 550.2924; found: 550.2928. $[\alpha]_D^{20}$ +60 (*c* = 0.33, $CHCl_3$, 97% ee). The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 7.7 min, τ_{minor} = 13.2 min (97% ee).

(*S*)-4-[*N*,*N*'-Bis(*tert*-butoxycarbonyl)-hydrazino]-2-cyanohex-2-en nitrile (2l):



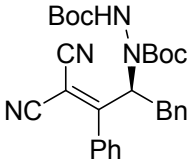
The title compound was obtained according to the general procedure after FC in Et_2O/*n*-hexane as a viscous colorless oil (65% yield). ^{1}H NMR ($CDCl_3$, 60^{o}C) δ 7.44 (br d, *J* 9.5 Hz, 1H), 6.16 (br s, 1H), 4.84 (q, *J* 8.0 Hz, 1H), 1.89 (m, 1H), 1.67 (m, 1H), 1.50 (s, 9H), 1.50 (s, 9H), 1.00 (t, *J* 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 60^{o}C) δ 166.5, 156.2, 154.1, 111.9, 110.3, 88.6, 83.2, 82.4, 60.9, 28.2, 28.1, 24.5, 10.3. HRMS calc.: $C_{17}H_{26}N_4O_4$ 373.1852; found: 373.1841. $[\alpha]_D^{20}$ +90 (*c* = 1.0, $CHCl_3$, 91% ee). The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (75:25)]; flow rate 1.0 mL/min; τ_{major} = 4.0 min, τ_{minor} = 6.3 min (91% ee).

(*S*)-4-[*N*,*N*'-Bis(*tert*-butoxycarbonyl-hydrazino]-2-cyano-3-phenylpent-2-en nitrile (2m):

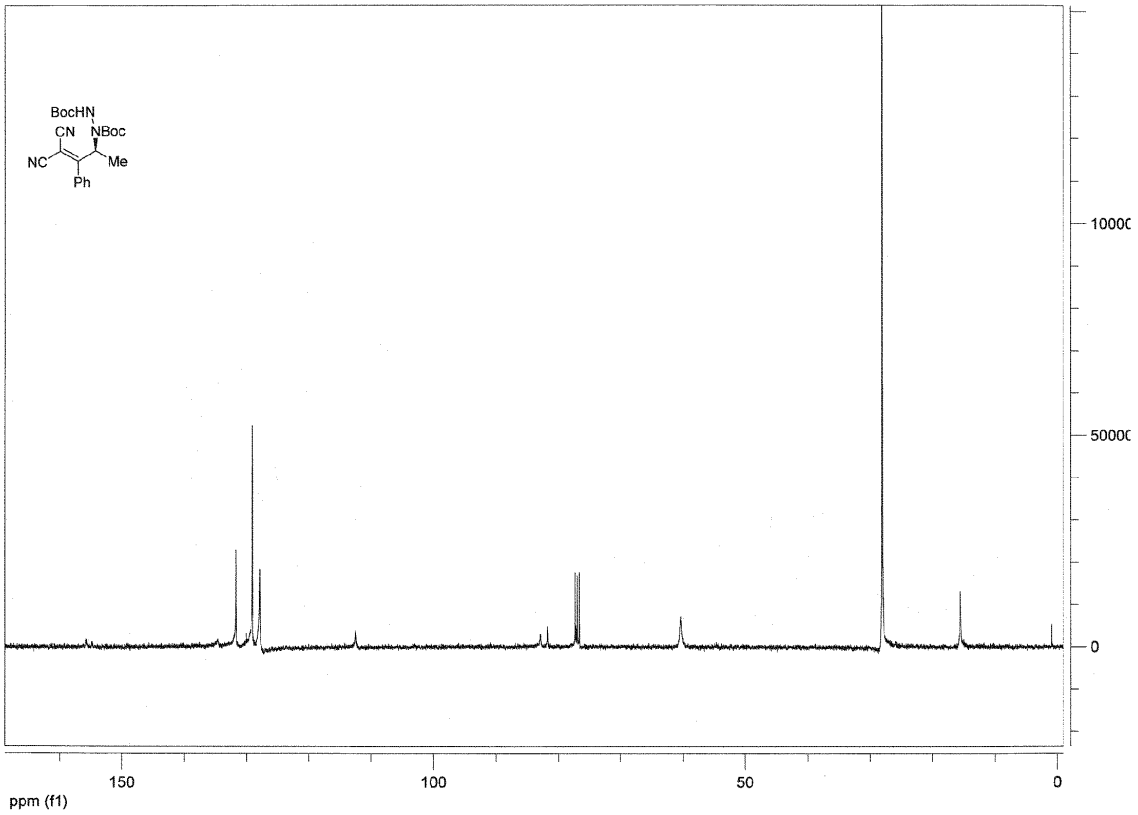


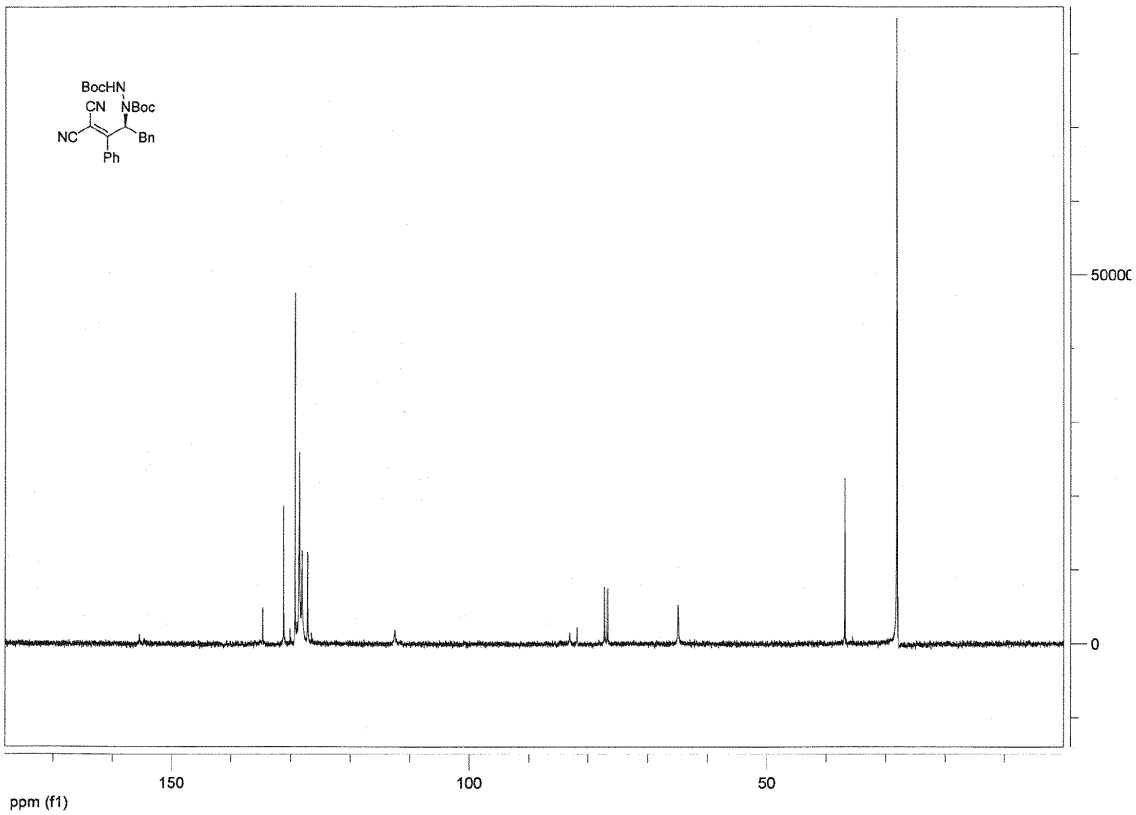
The title compound was obtained according to the general procedure after FC in Et_2O/CH_2Cl_2 as a viscous colorless oil (85% yield). ^{1}H NMR ($CDCl_3$, 60 ^{o}C) δ 7.69-7.47 (m, 5H), 6.41 (br s, 1H), 5.19 (m, 1H), 1.51 (s, 9H), 1.50 (s, 9H), 1.35 (br d, *J* 6.2 Hz, 3H). ^{13}C NMR Due to severe rotameric broadening of many of the signals, the spectrum is attached below. HRMS calc.: $C_{22}H_{28}N_4NaO_4$ 435.2008; found: 435.2010. $[\alpha]_D^{20}$ + 250 (*c* = 0.50, $CHCl_3$, 86% ee). The ee was determined by HPLC using two Chiralpak AS columns coupled in series [hexane/*i*PrOH (98:2)]; flow rate 1.0 mL/min; τ_{major} = 12.5 min, τ_{minor} = 10.8 min (86% ee).

(*S*)-4-(*N*,*N*'-Bis(*tert*-butoxycarbonyl-hydrazino)-2-cyano-3,5-diphenylpent-2-en nitrile (2n):

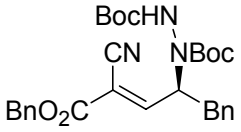


The title compound was obtained according to the general procedure after FC in Et_2O/CH_2Cl_2 as a colorless solid (mp = 48-50 ^{o}C, 84% yield). ^{1}H NMR ($CDCl_3$, 60 ^{o}C) δ 7.53-7.25 (m, 5H), 7.23-6.97 (m, 5H), 6.43 (br s, 1H), 5.56 (br t, *J* 7.3 Hz, 1H), 3.36 (dd, *J* 13.8, 6.7 Hz, 1H), 3.03 (dd, *J* 13.8, 9.4 Hz, 1H), 1.52 (s, 9H), 1.50 (s, 9H).^{13}C NMR Due to severe rotameric broadening of many of the signals, the spectrum is attached below. HRMS calc.: $C_{28}H_{32}N_4NaO_4$ 511.2321; found: 511.2320. $[\alpha]_D^{20}$ + 346 (c = 0.49, $CHCl_3$, 88% ee). The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 9.1 min, τ_{minor} = 13.3 min (88% ee).


BocHN
CN
NBoc
NC
Me
Ph
10000
50000
0
150
100
50
0
ppm (f1)


BocHN
CN
NBoc
NC
Bn
Ph
50000
0
150
100
50
ppm (f1)

(*S*)-(*E*)-4-[*N*,*N*'-Bis(*tert*-butoxycarbonyl)-hydrazino]-2-cyano-5-phenylpent-2-enoic acid benzyl ester (2o):

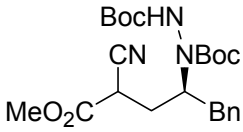


The title compound was obtained according to the general procedure after FC in Et_2O/*n*-hexane as a viscous colorless oil (85% yield). ^{1}H NMR ($CDCl_3$, 60 ^{o}C) δ 7.7 (d, *J* 8.9 Hz, 1H), 7.42-7.20 (m, 10H), 6.11 (br s, 1H), 5.36 (m, 1H), 5.28 (s, 2H), 3.15 (m, 1H), 2.94 (dd, *J* 13.4, 6.2 Hz, 1H), 1.46 (s, 9H), 1.40 (s, 9H) . ^{13}C NMR ($CDCl_3$, 60 ^{o}C) δ 160.7, 159.5, 156.0, 153.9, 135.9, 134.9, 129.1 (2C), 128.8 (2C), 128.6 (2C), 128.5 (2C), 128.2, 127.2, 112.8, 109.5, 82.5, 82.1, 68.0, 60.5, 37.7, 28.0 (6C). HRMS calc.: $C_{29}H_{35}N_3NaO_6$ 524.2424; found: 524.2410. $[\alpha]_D^{20}$ +95 (*c* = 0.49, CH_2Cl_2, 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} = 13.7 min, τ_{minor} = 26.7 min (98% ee).

Procedure for reduction of 2i to 3.

To an oven-dried flask equipped with a magnetic stirring bar were added **2i** (215 mg, 0.480 mmol, 98% ee), 10% Pd/C (50 mg), and EtOH (5 mL). The resulting mixture was cooled to 0 ^{o}C and stirred for 45 min under H_2 (1 atm). The mixture was filtered and the solvent was removed *in vacuo*. The pure product (193 mg, 0.432 mmol, 90%, 1:1.5 mixture of diastereomers) was obtained after FC on SiO_2 eluting with EtOAc/*n*-hexane (20:80).

(2*S*,4*S*) and (2*R*,4*S*)-4-[*N*,*N*'-Bis(*tert*-butoxycarbonyl)-hydrazino]-2-cyano-5-phenylpentanoic acid methyl ester (3i):

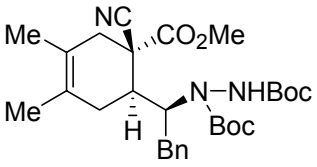


^{1}H NMR (benzene-d_6, 60 ^{o}C) δ 7.08-6.82 (m, 10H), 5.79 (br s, 2H), 4.75 (m, 2H), 3.24 (s, 3H), 3.22 (s, 3H), 2.78-2.22 (m, 6H), 2.02 (m, 2H), 1.75 (m, 2H), 1.39 (s, 9H), 1.36 (s, 9H), 1.33 (s, 9H), 1.28 (s, 9H). ^{13}C NMR (benzene-d_6, 60 ^{o}C) δ 166.9 (2C), 156.7 (2C), 154.9 (2C), 138.1 (2C), 129.1 (4C), 128.9 (2C), 128.8 (2C), 126.9, 126.8, 117.1, 116.9, 81.6 (2C), 81.4 (2C), 57.8, 56.3, 52.7, 52.7, 39.1 (2C), 35.0, 33.9, 32.4 (2C), 28.2 (3C), 28.1 (3C), 28.0 (6C). HRMS calc.: $C_{23}H_{33}N_3NaO_6$ 470.2267; Found: 470.2269. The ee was determined by HPLC using a Chiralcel OD column

[hexane/*i*PrOH (99:1)]; flow rate 1.0 mL/min; τ_{major} = 17.3 min, τ_{minor} = 19.9 min (98% ee). The stereocenter at C2 equilibrates so rapidly during the HPLC analysis that only one set of peaks is observed.

Procedure for Diels-Alder reaction of 2i with 2,3-dimethyl-1,3-butadiene. To a screw capped vial equipped with a magnetic stirrer bar were added **2i** (106 mg, 0.237 mmol, 98% ee) and 2,3-dimethyl-1,3-butadiene (288 μL, 2.5 mmol) and 3.5 mL of toluene. The mixture was stirred at 80 ^{o}C for 23 h and was then cooled to room temperature, concentrated *in vacuo* and subjected to FC on SiO_2 eluting with Et_2O in *n*-hexane (10:90 to 20:80) to afford the Diels-Alder cycloadduct **4** as a white solid (108 mg, 0.204 mmol, 86%). The compound was obtained as a >15:1 ratio of diastereomers favoring the isomer shown below (the diastereomers can be separated under the chromatographic conditions mentioned above).

(1*S*,6*S*)-6-{(*S*)-1-[*N*,*N*'-Bis(*tert*-butoxycarbonyl)-hydrazino]-2-phenylethyl}-1-cyano-3,4-dimethylcyclohex-3-ene carboxylic acid methyl ester (4):



^{1}H NMR ($CDCl_3$, 60 ^{o}C) δ 7.34-7.17 (m, 5H), 6.24 (br s, 1H), 5.07 (m, 1H), 3.84 (s, 3H), 3.25 (m, 1H), 2.86 (m, 1H), 2.61-2.31 (m, 3H), 2.30-2.14 (m, 2H), 1.68 (s, 3H), 1.57 (s, 3H), 1.50 (s, 9H), 1.48 (s, 9H). ^{13}C NMR ($CHCl_3$, 60 ^{o}C)[5] δ 169.2, 156.0, 155.1, 137.9, 128.9 (2C), 128.6 (2C), 126.4, 126.3, 120.3, 119.2, 81.5, 81.1, 54.4, 53.4, 53.3, 46.8, 42.4, 40.7, 35.2, 29.1, 28.2 (3C), 28.1 (3C), 18.9, 18.1. HRMS calc.: $C_{29}H_{41}N_3NaO_6$ 550.2893; Found: 550.2892. $[\alpha]_D^{20}$ +17 (*c* = 0.55, $CHCl_3$, 98% ee). The ee was determined by HPLC using a Chiralpak AD column [hexane/*i*PrOH (97:3)]; flow rate 1.0 mL/min; τ_{minor} = 6.2 min, τ_{major} = 6.9 min (98% ee).

The relative configuration of the Diels-Alder cycloadduct was determined by X-ray crystallography (Figure 1).

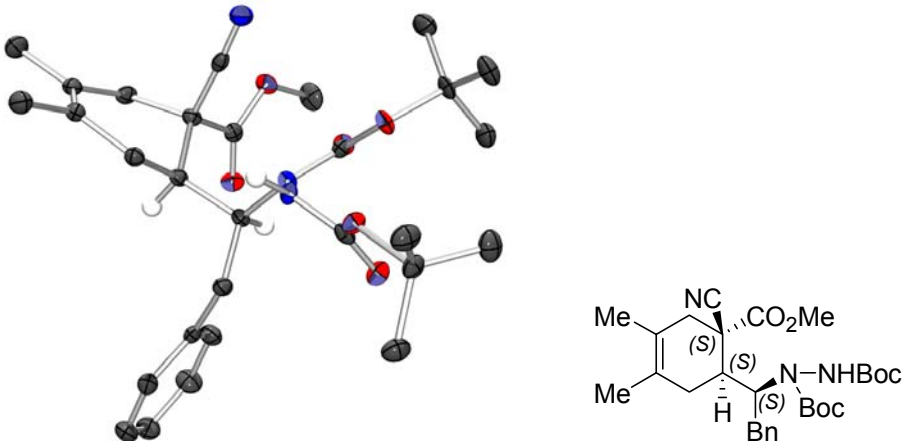
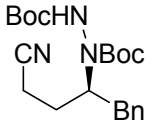


Figure 1. X-ray crystal structure of Diels-Alder cycloadduct (**4**). Most hydrogens have been omitted for clarity.

Procedure for reduction and decarboxylation of 2o.

A flask equipped with a magnetic stirring bar was loaded with **2o** (418 mg, 0.801 mmol, 98% ee). Then EtOH (10 mL) and 10% Pd/C (80 mg) were added. The resulting mixture was stirred at ambient temperature under H_2 (1 atm). After 2 h the mixture was filtered and the solvent was removed *in vacuo*. Then DMF (4 mL) was added and the solution was placed in an oil bath (preheated to 150 ^oC). After stirring at 150 ^oC for 2 h the solution was cooled to room temperature and H_2O (10 mL) was added. The mixture was extracted with Et_2O (4 x 25 mL) and the combined organic extracts were washed with brine (10 mL) and dried over $MgSO_4$. After removal of the drying agent, the solvent was evaporated and the pure product **5** (237 mg, 0.609 mmol, 76% yield) was isolated by FC on SiO_2 eluting with Et_2O in CH_2Cl_2 (0:100 to 15:85) as a colorless viscous oil.

(*R*)-4-(*N*,*N*'-Bis(*tert*-butoxycarbonyl-hydrazino)-5-phenylpentannitrile



^{1}H NMR ($CDCl_3$, 60 ^{o}C) δ 7.34-7.14 (m, 5H), 5.78 (br s, 1H), 4.52 (m, 1H), 2.95-2.60 (m, 4H), 1.93 (m, 1H), 1.78 (m, 1H), 1.50 (s, 9H), 1.39 (s, 9H). ^{13}C NMR ($CDCl_3$, 60 ^{o}C) δ 155.0, 154.3, 137.8, 128.7 (4C), 126.7, 119.9, 81.7 (2C), 58.6, 38.9, 28.4, 28.2 (3C), 28.1 (3C), 14.6. HRMS calc.: $C_{21}H_{31}N_3NaO_4$ 412.2212; found: 412.2224. $[\alpha]_D^{20}$ +14 (c = 1.0, $CHCl_3$, 98% ee). The ee was determined by HPLC using a Chiralcel AD column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 8.6 min, τ_{minor} = 11.7 min (98% ee).

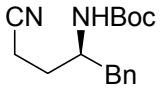
Procedure for N-N bond cleavage of 5.

Compound **5** (237 mg, 0.609 mmol) was placed in an oven-dried flask equipped with a magnetic stirring bar. Ac_2O (980 μL, 10.4 mmol), pyridine (510 μL, 6.1 mmol), and DMAP (10 mol%, 0.061 mmol, 9 mg) were added and the mixture was stirred under an argon atmosphere at 50 ^{o}C for 49 h. The mixture was then cooled to room temperature and diluted with Et_2O (ca. 7 mL). To the diluted mixture was added 1M $NaHCO_3$ (aq.) (10 mL) and stirring was continued at ambient temperature for 30 min. The layers were then separated and the aqueous layer was extracted with Et_2O (2 x 15 mL) and EtOAc (1 x 15 mL). The combined organic extracts were washed successively with 1M $NaHCO_3$ (aq.) (10 mL), 1M HCl (aq.) (10 mL), and brine (10 mL). The solution was dried over Na_2SO_4 and the solvent was evaporated. FC on SiO_2 eluting with Et_2O in CH_2Cl_2 (0:100 to 5:95) afforded the *N*-acetylated product (192 mg, 0.445 mmol, 73%) and recovered starting material (47 mg, 0.122 mmol, 20%).

The acetylated product (71.2 mg, 0.165 mmol) was dissolved in dry and deoxygenated THF (2 mL) under an Ar-atmosphere. Deoxygenated HMPA (0.3 mL) was added, followed by addition of 8 mL of SmI_2-solution (0.1M in THF) dropwise at room temperature. The resulting purple solution was stirred for 30 min at room temperature and was then quenced by addition of 5 mL 1M $NaHCO_3$ (aq). The solution was diluted with EtOAc and placed in a separating funnel. The layers were separated and the aqueous phase was extracted with EtOAc (2 x 20 mL). The combined organic extracts were washed with brine and dried ($MgSO_4$) and concentrated *in vacuo*. The pure product (42.3

mg, 0.154 mol, 93%) was obtained as an off-white solid (mp = 93-95 °C) by FC on SiO_2 eluting with Et_2O in CH_2Cl_2 (0:100 to 10:90).

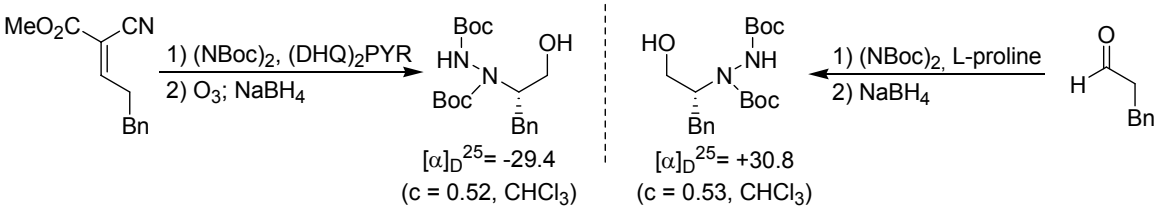
(*R*)-(1-Benzyl-3-cyano-propyl)-carbamic acid tert-butyl ester



^{1}H NMR ($CDCl_3$) δ 7.31 (m, 2H), 7.25 (m, 1H), 7.16 (m, 2H), 4.37 (br d, *J* 9.2 Hz, 1H), 3.85 (m, 1H), 2.87 (dd, *J*, 6.0, 13.7 Hz, 1H), 2.76 (dd, *J* 6.9, 13.4 Hz, 1H), 2.47-2.31 (m , 2H), 1.92 (m 1H), 1.70 (m, 1H), 1.41 (s, 9H). ^{13}C NMR ($CDCl_3$) δ 155.4, 137.0, 129.3 (2C), 128.6 (2C), 126.8, 119.6, 79.9, 51.2, 41.3, 30.4, 28.3 (3C), 14.4. HRMS calc.: $C_{16}H_{22}N_2NaO_2$ 297.1579; found: 297.1578. $[\alpha]_D^{20}$ +13 (c = 1.0, $CHCl_3$, 98% ee). The ee was determined by HPLC using a Chiralcel OJ column [hexane/*i*PrOH (90:10)]; flow rate 1.0 mL/min; τ_{major} = 14.2 min, τ_{minor} = 11.9 min (98% ee)

Determination of the Absolute Configuration of the Allylic Amination Products:

The absolute configuration was established by correlation with α-hydrazino aldehydes obtained by L-proline catalyzed α-amination.[4] When using $(DHQ)_2PYR$ as the catalyst the configuration of the products was found to be (*S*).



References

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5. Due to the presence of distinct rotameric isomers, the ^{13}C NMR spectrum contain extra peaks.