Supporting Information
for

Organocatalytic solvent-free hydrogen bonding-mediated asymmetric Michael additions under ball milling conditions

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1. General:

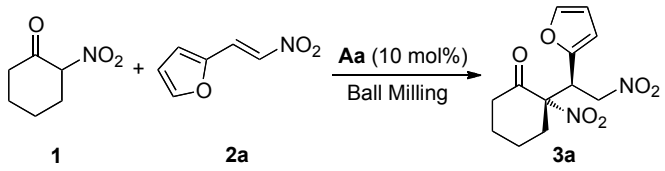
Unless otherwise stated, all commercial reagents and solvents were used without additional purification. Reactions in solvents were performed under argon atmosphere in dried glassware if not mentioned otherwise. All solvents were dried and distilled according to standard procedures. Analytical thin layer chromatography (TLC) was performed on Merck pre-coated silica gel 60 F_{254} plates. Visualization on TLC was achieved by the use of UV light (254 nm) and treatment with basic aqueous solution of $KMnO_4$ or acidic ninhydrine-solution in aceton followed by heating. Flash column chromatography was undertaken on silica gel (Acros, 35-70 μm, 60 Å). Melting points were measured with a Büchi Melting Point B-540 apparatus. HPLC analysis was performed with an Agilent 1200- or an Agilent 1100-series system and chiral stationary phases from Chiral Technologies Inc. Optical rotations were determined on a Perkin Elmer PE-241 instrument at room temperature and are given in $deg \bullet cm^3 \bullet g^{-1} \bullet dm^{-1}$. The measurements were carried out using a light wavelength of 589 nm in a cuvette (d = 1 dm, concentration c is given in g/100 mL). ^{1}H NMR, ^{13}C NMR and ^{19}F NMR spectra were recorded on a Varian Mercury 300, a Varian Inova 400 or a Bruker AVANCE 600 spectrometer. Chemical shifts are quoted in parts per million (ppm) referenced to the appropriate solvent peak or 0.00 ppm for tetramethylsilane. The following abbreviations were used to describe peak splitting patterns when appropriate: br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants, *J*, are reported in Hertz (Hz). Infrared (IR) spectra were recorded on a Perkin Elmer Spectrum 100 FT-IR spectrometer or on a Bruker TENSOR 27 FT-IR spectrophotometer. Wave numbers are given in reciprocal centimeters (cm^{-1}). Mass spectra were acquired on a Finnigan SSQ 7000 spectrometer and HRMS were recorded on a Thermo Scientific LTQ Orbitrap XL spectrometer. Elemental analyses were performed on an Elemantar Vario EL instrument.

All organocatalytic transformations were carried out in air, performed in a FRITSCH Planetary micro mill model "Pulverisette 7 classic line". It consists of a main disk, which can rotate at a speed of 100-800 rpm and accommodates two grinding vessels with a volume of 12 mL each. Typical grinding balls have a diameter of 4 mm and both, vessels and balls, are made of ZrO_2.

Thioureas **Aa-f**, **B**, **Ca** and **Cc** were prepared following the literature procedure.[1]

2. Initial screening of reaction conditions

Table 1 Screening of reaction and milling conditions for the Michael addition of α-nitrocyclohexanone (**1**) to 2-furyl-substituted nitroalkene **2a**.[a]



1 **2a** **3a**

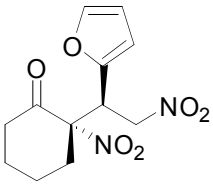
Entry	Ratio **1** : **2a**	Time (min)[b]	Milling speed (rpm)	Additive	Yield (%)[c]	dr (*anti*:*syn*)[d]	er[d]
1	1.5 : 1	30	300	-	83	95:5	92:8
2	1 : 1	30	300	-	60	93:7	89:11
3	1 : 1.5	30	300	-	40	95:5	89:11
4	1.5 : 1	15	300	-	56	91:9	88:12
5	1.5 : 1	45	300	-	76	93:7	89:11
6	1.5 : 1	60	300	-	74	95:5	89:11
7	1.5 : 1	30	150	-	63	92:8	89:11
8	1.5 : 1	30	500	-	83	95:5	91:9
9	1.5 : 1	30[e]	300	-	66	92:2	90:10
10	1.5 : 1	30	300	quartz sand[f]	63	91:9	87:13
11	1.5 : 1	30	300	acidic silica[f]	69	91:9	83:17
12	1.5 : 1	30	300	basic Al_2O_3[f]	63	92:8	91:9
14	1.5 : 1	30	300	DCM (1 eq)	75	93:7	91:9
15	1.5 : 1	30	300	DCM (3 eq)	69	95:5	92:8

[a] Reactions were carried out on a 0.2 mmol scale; ball milling conditions: 15 min at 300 rpm and 15 min pause. [b] Total milling time. [c] After aqueous workup and column chromatography. Because a small amount (1-5%) of α-nitrocyclohexanone (**1**) remained in the product, the "yield" reported here was "corrected" after analysis by ^{1}H-NMR spectroscopy. [d] Determined by HPLC of the crude product using a chiral stationary phase. [e] Milling without pause. [f] 15.4 mg of the additive were added (20 w%).

3. General procedure for the catalytic transformation

Thiourea **Af**[2] (0.01 mmol, 0.025 equiv), α-nitrocyclohexanone (**1**, 0.4 mmol) and nitroalkene **2** (0.6 mmol, 1.5 equiv) were transferred to a clean, dry ball milling vessel loaded with 7.8 g[3] of grinding balls. The vessel was placed in the micro mill and milling was started (milling cycle: 15 min of milling followed by a 15 minutes pause). The mixture was obtained by washing the vessel and the balls with 3 x 3-5 mL of DCM or EtOAc.[4] The resulting solution was concentrated *in vacuo*, and the product was purified by flash chromatography (gradient: pentane : ethyl acetate = 9 : 1 to 8 : 2, the diastereomers could be separated under these conditions but were combined to determine the yield).

(*S*)-2-[(*S*)-1-(Furan-2-yl)-2-nitroethyl]-2-nitrocyclohexanone (3a)[1]



Prepared from α-nitrocyclohexanone (**1**) and 2-(2-nitrovinyl)furane (**2a**) according to general procedure; brown oil after column chromatography.

HPLC-analysis: Chiralpak AD-H, *n*-heptane:*i*-PrOH = 95:5, 0.8 mL/min, t_{ret}: 23.1 (*anti*, minor), 26.6, 62.9, 68.3 (*anti*, major) min.

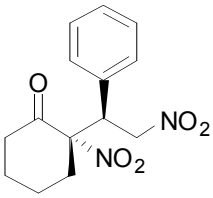
^{1}H NMR (300 MHz, $CDCl_3$) *anti*: δ = 7.38 (dd, *J* = 1.9, 0.7 Hz, 1H), 6.35 – 6.32 (m, 1H), 6.28 – 6.26 (m, 1H), 4.98 (dd, *J* = 13.6, 2.8 Hz, 1H), 4.64 (dd, *J* = 13.6, 10.8 Hz, 1H), 4.50 (dd, *J* = 10.9, 2.8 Hz, 1H), 2.69 – 2.39 (m, 3H), 2.11 – 1.98 (m, 1H), 1.89 – 1.52 (m, 4H).

^{1}H NMR (300 MHz, $CDCl_3$) *syn*: δ = 7.37 – 7.36 (m, 1H), 6.32 – 6.30 (m, 2H), 5.10 (dd, *J* = 13.7, 10.4 Hz, 1H), 4.61 (dd, *J* = 13.6, 3.1 Hz, 1H), 4.57 (dd, *J* = 10.2, 3.1 Hz, 1H), 2.94 – 2.81 (m, 1H), 2.67 – 2.52 (m, 2H), 2.11 – 1.97 (m, 1H), 1.89 – 1.51 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) *anti*: δ = 199.8, 146.7, 143.75, 111.0, 110.9, 97.1, 74.5, 40.9, 39.7, 36.5, 27.3, 21.3.

^{13}C NMR (75 MHz, $CDCl_3$) *syn*: δ = 199.0, 146.7, 143.69, 111.4, 111.1, 97.6, 74.3, 42.7, 40.0, 34.7, 25.8, 21.0.

(*S*)-2-Nitro-2-[(*S*)-2-nitro-1-phenylethyl]cyclohexanone (3b)[1]



Prepared from α-nitrocyclohexanone (**1**) and β-nitrostyrene (**2b**) according to general procedure; white solid after column chromatography, white crystals after recrystallisation from Et_2O. Mp.: 93-94 °C.

HPLC-analysis: Chiralpak OD-H, *n*-heptane:*i*-PrOH = 90:10, 0.8 mL/min, t_{ret}: 31.3 (*anti*, major), 39.4, 45.8, 64.9 (*anti*, minor) min.

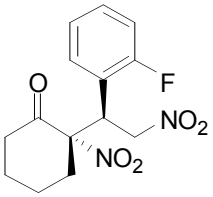
^{1}H NMR (400 MHz, $CDCl_3$) *anti*: δ = 7.34 – 7.29 (m, 3H), 7.10 – 7.04 (m, 2H), 5.12 (dd, *J* = 13.7, 3.2 Hz, 1H), 4.69 (dd, *J* = 13.7, 11.0 Hz, 1H), 4.28 (dd, *J* = 11.0, 3.1 Hz, 1H), 2.68 – 2.49 (m, 2H), 2.28 (ddd, *J* = 14.7, 6.2, 3.3 Hz, 1H), 2.08 – 1.97 (m, 1H), 1.80 – 1.48 (m, 4H).

^{1}H NMR (400 MHz, $CDCl_3$) *syn*: δ = 7.34 – 7.29 (m, 3H), 7.28 – 7.23 (m, 2H), 5.26 (dd, *J* = 14.0, 10.7 Hz, 1H), 4.69 (dd, *J* = 14.0, 3.0 Hz, 1H), 4.25 (dd, *J* = 10.7, 3.1 Hz, 1H), 2.80 – 2.69 (m, 1H), 2.67 – 2.50 (m, 2H), 2.08 – 1.97 (m, 1H), 1.80 – 1.48 (m, 4H).

^{13}C NMR (75 MHz, $CDCl_3$) *anti*: δ = 200.3, 132.6, 129.34, 129.22, 129.1, 97.6, 76.3, 46.9, 39.9, 37.4, 27.6, 21.3

^{13}C NMR (75 MHz, $CDCl_3$) *syn*: δ = 199.9, 133.4, 129.7, 129.30, 129.20, 98.5, 76.1, 49.6, 40.4, 35.3, 25.7, 21.0.

(*S*)-2-[(*S*)-1-(2-Fluorophenyl)-2-nitroethyl]-2-nitrocyclohexanone (3c)[1]



Prepared from α-nitrocyclohexanone (**1**) and 2-fluoro-β-nitrostyrene (**2c**) according to general procedure; yellowish-white solid after column chromatography, white crystals after recrystallisation from Et_2O. Mp.: 127 °C.

HPLC-analysis: Chiralpak OD-H, *n*-heptane:*i*-PrOH = 95:5, 0.8 mL/min, t_{ret}: 16.9 (*anti*, major), 19.5, 23.3, 33.1 (*anti*, minor) min.

^{1}H NMR (300 MHz, $CDCl_3$) *anti*: δ = 7.39 – 7.30 (m, 1H), 7.18 – 6.97 (m, 3H), 5.22 (dd, *J* = 13.5, 2.8 Hz, 1H), 4.78 (dd, *J* = 11.2, 2.3 Hz, 1H), 4.66 (dd, *J* = 13.5, 11.1 Hz, 1H), 2.71 – 2.46 (m, 2H), 2.39 - 2.27 (m, 1H), 2.13 – 1.98 (m, 1H), 1.87 – 1.65 (m, 3H), 1.65 – 1.45 (m, 1H).

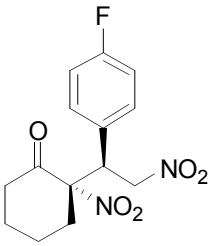
^{1}H NMR (300 MHz, $CDCl_3$) *syn*: δ = 7.45 – 7.24 (m, 2H), 7.18 – 6.97 (m, 2H), 5.36 (dd, *J* = 15.5, 11.3 Hz, 1H), 4.82 – 4.60 (m, 2H), 2.98 – 2.86 (m, 1H), 2.70 – 2.47 (m, 2H), 2.13 – 1.98 (m, 1H), 1.87 – 1.65 (m, 1H), 1.65 – 1.45 (m, 3H).

^{13}C NMR (75 MHz, $CDCl_3$) *anti*: δ = 200.0, 161.3 (d, *J* = 247.6 Hz), 131.0 (d, *J* = 8.7 Hz), 129.0, 124.9 (d, *J* = 3.7 Hz), 120.2 (d, *J* = 13.9 Hz), 116.1 (d, *J* = 22.9 Hz), 97.1, 74.9 (d, *J* = 1.7 Hz), 39.9, 39.2, 36.4, 27.5, 21.2

^{13}C NMR (75 MHz, $CDCl_3$) *syn*: δ = 199.8, 161.5 (d, *J* = 247.9 Hz), 130.9 (d, *J* = 8.8 Hz), 130.6, 125.2 (d, *J* = 3.6 Hz), 120.9 (d, *J* = 13.2 Hz), 116.2 (d, *J* = 23.1 Hz), 98.6, 75.1 (d, *J* = 1.6 Hz), 40.3, 39.2, 34.8, 25.6, 21.0.

^{19}F NMR (376 MHz, $CDCl_3$) *anti*: δ = –114.9, i δ = –113.7.

(*S*)-2-[(*S*)-1-(4-Fluorophenyl)-2-nitroethyl]-2-nitrocyclohexanone (3d)[1]



Prepared from α-nitrocyclohexanone and 4-fluoro-β-nitrostyrene according to general procedure; yellow-white solid after column chromatography. Mp.: 86 °C.

HPLC-analysis: Chiralpak AD-H, *n*-heptane:*i*-PrOH = 90:10, 0.8 mL/min, t_{ret}: 20.4, 22.2, 23.8 (*anti*, minor), 30.2 (*anti*, major) min.

^{1}H NMR (300 MHz, $CDCl_3$) *anti*: δ = 7.12 – 6.97 (m, 4H), 5.11 (dd, *J* = 13.7, 3.2 Hz, 1H), 4.65 (dd, *J* = 13.7, 11.1 Hz, 1H), 4.28 (dd, *J* = 11.1, 3.2 Hz, 1H), 2.71 – 2.47 (m, 2H), 2.38 – 2.22 (m, 1H), 2.13 – 1.96 (m, 1H), 1.85 – 1.44 (m, 4H),

^{1}H NMR (300 MHz, $CDCl_3$) *syn*: δ = 7.32 – 7.24 (m, 2H), 7.07 – 6.98 (m, 2H), 5.24 (dd, *J* = 14.0, 10.8 Hz, 1H), 4.68 (dd, *J* = 14.0, 3.1 Hz, 1H), 4.25 (dd, *J* = 10.8, 3.1 Hz, 1H), 2.75 (dt, *J* = 11.6, 2.8 Hz, 1H), 2.65 – 2.55 (m, 2H), 2.07 – 1.93 (m, 1H), 1.87 – 1.75 (m, 1H), 1.64 – 1.46 (m, 3H).

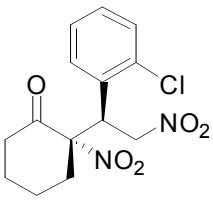
^{13}C NMR (75 MHz, $CDCl_3$) *anti*: δ = 200.2, 163.2 (d, *J* = 249.0 Hz), 131.0 (d, *J* =8.3 Hz), 128.5 (d, *J* = 2.7 Hz), 116.3 (d, *J* = 21.7 Hz), 97.5, 76.3, 46.4, 40.0, 37.4, 27.5, 21.3.

^{13}C NMR (75 MHz, $CDCl_3$) *syn*: δ = 199.9, 163.1 (d, *J* = 249.3 Hz), 131.6 (d, *J* =8.2 Hz), 129.2 (d, *J* = 3.1 Hz), 116.4 (d, *J* = 21.6 Hz), 98.5, 76.1, 48.9, 40.4, 35.5, 25.8, 21.1.

^{19}F NMR (282 MHz, $CDCl_3$): δ = *anti*: 111.9, *syn*: δ = 112.1.

MS (EI): *m/z* (%) = 310 ([M]$^+$, 17), 217 (69), 147 (42), 146 (32), 133 (33), 122 (100), 109 (90), 84 (17), 67 (23),

(*S*)-2-[(*S*)-1-(2-Chlorophenyl)-2-nitroethyl]-2-nitrocyclohexanone (3e)[1]



Prepared from α-nitrocyclohexanone and 2-chloro-β-nitrostyrene according to general procedure; yellowish-white solid after column chromatography, white crystals after recrystallization from Et_2O. Mp.: 152 °C.

HPLC-analysis: Chiralpak AS-H, *n*-heptane:*i*-PrOH = 98:2, 0.8 mL/min, t_{ret}: 29.9 (*anti*, minor), 40.1 (*anti*, major), 44.5, 52.5 min.

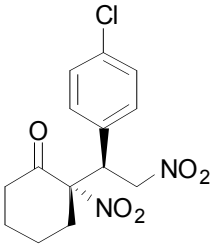
^{1}H NMR (400 MHz, $CDCl_3$) *anti*: δ = 7.39 – 7.33 (m, 1H), 7.20 (dt, *J* = 5.5, 2.9 Hz, 2H), 6.92 – 6.87 (m, 1H), 5.17 (dd, *J* = 13.8, 3.4 Hz, 1H), 5.11 (dd, *J* = 11.0, 3.4 Hz, 1H), 4.47 (dd, *J* = 13.7, 11.0 Hz, 1H), 2.62 – 2.54 (m, 1H), 2.48 (td, *J* = 13.4, 5.9 Hz, 1H), 2.18 (ddd, *J* = 15.3, 6.2, 3.0 Hz, 1H), 2.04 – 1.94 (m, 1H), 1.92 – 1.81 (m, 1H), 1.73 – 1.58 (m, 2H), 1.50 – 1.35 (m, 1H).

^{1}H NMR (400 MHz, $CDCl_3$) *syn*: δ = 7.50 – 7.44 (m, 1H), 7.37 – 7.30 (m, 1H), 7.23 – 7.13 (m, 2H), 5.38 (dd, *J* = 14.5, 10.6 Hz, 1H), 4.95 (dd, *J* = 10.6, 2.6 Hz, 1H), 4.59 (dd, *J* = 14.5, 2.7 Hz, 1H), 2.99 – 2.84 (m, 1H), 2.63 – 2.42 (m, 2H), 1.95 – 1.78 (m, 1H), 1.73 – 1.58 (m, 1H), 1.52 – 1.28 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = *anti*: 199.8, 136.1, 131.2, 130.4, 130.3, 128.1, 127.7, 97.5, 75.7, 41.0, 39.8, 35.7, 27.5, 21.1.

^{13}C NMR (100 MHz, $CDCl_3$): *syn*: δ = 200.5, 136.6, 130.6, 130.1, 129.8, 128.0, 127.6, 99.2, 76.4, 44.8, 40.5, 35.1, 25.5, 20.9.

(*S*)-2-[(*S*)-1-(4-Chlorophenyl)-2-nitroethyl]-2-nitrocyclohexanone (3f)[1]



Prepared from α-nitrocyclohexanone and 4-chloro-β-nitrostyrene according to general procedure; yellow oil after column chromatography.

HPLC-analysis: Chiralpak AD-H, *n*-heptane:*i*-PrOH = 95:5, 0.8 mL/min, t_{ret}: 32.4, 38.7 (*anti*, minor), 44.4, 83.6 (*anti*, major) min.

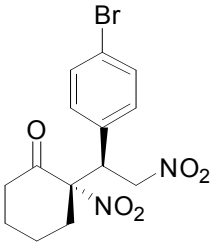
^{1}H NMR (600 MHz, $CDCl_3$) *anti*: δ = 7.25 (d, *J* = 8.3 Hz, 2H), 6.97 (d, *J* = 8.4 Hz, 2H), 5.05 (dd, *J* = 13.9, 3.1 Hz, 1H), 4.58 (dd, *J* = 13.8, 11.2 Hz, 1H), 4.21 (dd, *J* = 11.1, 3.0 Hz, 1H), 2.62 – 2.55 (m, 1H), 2.55 – 2.47 (m, 1H), 2.25 (dd, *J* = 15.0, 2.7 Hz, 1H), 2.03-1.95 (m, 1H), 1.79 – 1.55 (m, 3H), 1.55 – 1.41 (m, 1H).

^{1}H NMR (600 MHz, $CDCl_3$) *syn*: δ = 7.25 (d, *J* = 8.3 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 5.17 (dd, *J* = 14.0, 10.9 Hz, 1H), 4.62 (dd, *J* = 14.1, 3.0 Hz, 1H), 4.17 (dd, *J* = 11.0, 2.7 Hz, 1H), 2.71 – 2.65 (m, 1H), 2.61 – 2.55 (m, 2H), 1.95 – 1.90 (m, 1H), 1.77-1.67 (m, 1H), 1.55 – 1.41 (m, 3H).

^{13}C NMR (150 MHz, $CDCl_3$) *anti*: δ = 200.1, 135.5, 131.2, 130.6, 129.4, 97.2, 76.0, 46.5, 39.9, 37.4, 27.5, 21.3

^{13}C NMR (150 MHz, $CDCl_3$) *syn*: δ = 199.8, 135.4, 131.9, 131.1, 129.5, 98.2, 75.9, 49.0, 40.3, 35.5, 25.8, 21.0.

(*S*)-2-[(*S*)-1-(4-Bromophenyl)-2-nitroethyl]-2-nitrocyclohexanone (3g)[1]



Prepared from α-nitrocyclohexanone and 4-bromo-β-nitrostyrene according to general procedure; yellow-white solid after column chromatography. Mp.: 112-113 °C.

HPLC-analysis: Chiralpak AD-H, *n*-heptane:*i*-PrOH = 95:5, 0.8 mL/min, t_{ret}: 33.8, 39.9 (*anti*, minor), 49.0, 90.9 (*anti*, major) min.

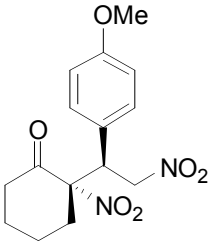
^{1}H NMR (400 MHz, $CDCl_3$) *anti*: δ = 7.47 (dt, *J* = 4.7, 2.6 Hz, 2H), 7.02 – 6.95 (m, 2H), 5.11 (dd, *J* = 13.8, 3.2 Hz, 1H), 4.64 (dd, *J* = 13.8, 11.1 Hz, 1H), 4.26 (dd, *J* = 11.1, 3.2 Hz, 1H), 2.69 – 2.50 (m, 2H), 2.36 – 2.26 (m, 1H), 2.10 – 1.96 (m, 1H), 1.84 – 1.48 (m, 4H).

^{1}H NMR (400 MHz, $CDCl_3$) *syn*: δ = 7.49 – 7.45 (m, 2H), 7.19 – 7.14 (m, 2H), 5.23 (dd, *J* = 14.0, 10.8 Hz, 1H), 4.68 (dd, *J* = 14.1, 3.1 Hz, 1H), 4.22 (dd, *J* = 10.8, 3.0 Hz, 1H), 2.79 – 2.70 (m, 1H), 2.69 – 2.50 (m, 2H), 2.36 – 2.26 (m, 1H), 2.10 – 1.96 (m, 1H), 1.84 – 1.47 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) *anti*: δ = 200.0, 132.3, 131.8, 130.9, 123.7, 97.3, 76.0, 46.5, 39.9, 37.4, 27.5, 21.3.

^{13}C NMR (100 MHz, $CDCl_3$) *syn*: δ =199.8, 132.49, 132.46, 131.4, 123.6, 98.3, 75.8, 49.1, 40.3, 35.5, 25.7, 21.0.

(*S*)-2-[(*S*)-1-(4-Methoxyphenyl)-2-nitroethyl]-2-nitrocyclohexanone (3h)[1]



Prepared from α-nitrocyclohexanone and 4-methoxy-β-nitrostyrene according to general procedure; yellow oil after column chromatography.

HPLC-analysis: Chiralpak OT+, *n*-heptane:*i*-PrOH = 97:3, 0.8 mL/min, t_{ret}: 18.5 (*anti*, major), 22.4, 25.6, 41.1 (*anti*, minor) min.

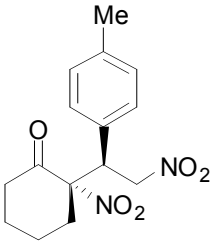
^{1}H NMR (400 MHz, $CDCl_3$) *anti*: δ = 7.03 – 6.98 (dm, *J* = 8.8 Hz 2H), 6.87 – 6.82 (dm, *J* = 8.8 Hz, 2H), 5.09 (dd, *J* = 13.6, 3.2 Hz, 1H), 4.66 (dd, *J* = 13.6, 11.1 Hz, 1H), 4.24 (dd, *J* = 11.1, 3.2 Hz, 1H), 3.78 (s, 3H), 2.69 – 2.50 (m, 2H), 2.33 (ddd, *J* = 14.6, 6.0, 3.2 Hz, 1H), 2.09 – 1.93 (m, 1H), 1.83 – 1.47 (m, 4H).

^{1}H NMR (400 MHz, $CDCl_3$) *syn*: δ = 7.22 – 7.15 (dm, *J* = 8.8 Hz, 2H), 6.87 – 6.82 (dm, *J* = 8.8 Hz 2H), 5.23 (dd, *J* = 13.8, 10.9 Hz, 1H), 4.66 (dd, *J* = 14.0, 2.8 Hz, 1H), 4.20 (dd, *J* = 10.9, 3.0 Hz, 1H), 3.77 (s, 3H), 2.78 – 2.71 (m, 1H), 2.64 – 2.52 (m, 2H), 2.09 – 1.93 (m, 1H), 1.83 – 1.47 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) *anti*: δ = 200.4, 160.2, 130.3, 124.3, 114.5, 97.9, 76.4, 55.4, 46.4, 39.9, 37.3, 27.6, 21.3.

^{13}C NMR (100 MHz, $CDCl_3$) *syn*: δ = 200.0, 160.1, 130.9, 125.0, 114.6, 98.6, 76.3, 55.4, 49.1, 40.4, 35.4, 25.7, 21.0.

(*S*)-2-Nitro-2-[(*S*)-2-nitro-1-*p*-tolylethyl]cyclohexanone (3i)[1]



Prepared from α-nitrocyclohexanone and 4-methyl-β-nitrostyrene according to general procedure; yellow oil after column chromatography.

HPLC-analysis: Chiralpak AD-H, *n*-heptane:*i*-PrOH = 98:2, 0.8 mL/min, t_{ret}: 29.0, 32.9 (*anti*, minor), 36.7, 57.1 (*anti*, major) min.

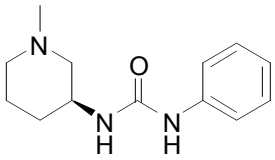
^{1}H NMR (400 MHz, $CDCl_3$) *anti*: δ = 7.13 (d, *J* = 7.7 Hz, 2H), 6.97 (d, *J* = 8.1 Hz, 2H), 5.11 (dd, *J* = 13.6, 3.1 Hz, 1H), 4.68 (dd, *J* = 13.6, 11.1 Hz, 1H), 4.26 (dd, *J* = 11.1, 3.1 Hz, 1H), 2.69 – 2.52 (m, 2H), 2.32 (s, 3H), 2.36 – 2.26 (m, 1H), 2.10 – 1.97 (m, 1H), 1.82 – 1.47 (m, 4H).

^{1}H NMR (400 MHz, $CDCl_3$) *syn*: δ = 7.17 – 7.09 (m, 4H), 5.25 (dd, *J* = 13.8, 10.8 Hz, 1H), 4.69 (dd, *J* = 13.9, 3.3 Hz, 1H), 4.23 (dd, *J* = 10.9, 3.1 Hz, 1H), 2.79 – 2.73 (m, 1H), 2.69 – 2.52 (m, 2H), 2.31 (s, 3H), 2.10 – 1.97 (m, 1H), 1.82 – 1.45 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) *anti*: δ = 200.4, 139.3, 129.8, 129.5, 129.1, 97.7, 76.4, 46.7, 39.9, 37.3, 27.6, 21.3, 21.2.

^{13}C NMR (100 MHz, $CDCl_3$) *syn*: δ = 200.0, 139.1, 130.0, 129.6, 129.5, 98.6, 76.2, 49.4, 40.4, 35.3, 25.7, 21.2, 21.0.

4. Synthesis of (*S*)-1-(1-methylpiperidine-3-yl)-3-phenylurea (Cb)



A flame-dried flask with a magnetic stirrer bar was charged with 1 mmol of the deprotected HCl-salt of (*S*)-*tert*-butyl 1-methylpiperidin-3-ylcarbamate, which was prepared following the literature procedure.[1] It was dissolved in dry THF (4 mL). Et_3N (2.5 mmol, 2.5 equiv) and phenyl isocyanate (1 mmol, 1.0 equiv) were added consecutively at 0 °C. The mixture was allowed to warm to room temperature and stirred for 16 h. The solvent was removed *in vacuo* and the residue was dissolved in CH_2Cl_2. The mixture was washed with Na_2CO_3, the aqueous layer was extracted with CH_2Cl_2 (2 x 4 mL) and the combined organic phases were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The product was purified by flash chromatography (first pentane : ethyl acetate 7:3, then ethyl acetate : MeOH : Et_3N = 100 : 4 : 4) and obtained as a white solid in quantitative yield. Mp.: 195-196 °C.

$|\alpha|_D^{22}$ = –17.9 (c= 1.00, EtOH).

^{1}H NMR (600 MHz, CD_3OD): δ = 7.31-7.34 (m, 2H), 7.23 (t, J = 8.0 Hz, 2H), 6.96 (t, J = 7.3 Hz, 1H), 3.86 – 3.79 (m, 1H), 2.83 (br s, 1H), 2.58 (br s, 1H), 2.27 (s, 3H), 2.16 (br s, 1H), 2.01 (br s, 1H), 1.84 (br s, 1H), 1.80 – 1.71 (m, 1H), 1.69 – 1.58 (m, 1H), 1.28 (br s, 1H).

^{13}C NMR (151 MHz, CD_3OD): δ = 157.5, 140.9, 129.8, 123.4, 120.1, 62.0, 56.4, 47.3, 46.5, 30.9, 24.3.

MS (EI): *m/z* (%) = 234 ([M+H]$^+$, 1), 141 (2), 119 (1), 98 (6), 97 (100), 96 (8), 82 (10), 77 (2), 70 (7), 58 (5).

IR (ATR): υ = 3300, 2932, 2779, 2469, 2433, 2061, 1631, 1567, 1442, 1305, 1232, 1148, 1101, 1061, 1017, 855, 762, 726, 670.

CHN-Analysis for $C_{13}H_{19}N_3O$, calc.: C: 66.92, H: 8.21, N: 18.01; found: C: 66.50, H: 8.07, N: 18.06.

HRMS (ESI) *m/z* calculated for $C_{13}H_{20}N_3O$ [M+H]$^+$: 234.1601, found 234.1596.

5. Determination of absolute configuration of 3b by ECD and VCD spectroscopy

By a Monte-Carlo-type conformational search for (*R*,*R*)-**3b** with Spartan '08[7] applying the MMFF force field, six different conformers in an energy range of 21 kJ/mol were found. Subsequently, these structures were optimized using Gaussian 09[8] on the B3LYP/6-311++G(d,p)-level. Normal coordinate analyses were done on the same level to prove all conformers to be local minima. In Table 2, the energies obtained from the optimizations, the zero point energies (*ZPE*) resulting from the normal coordinate analyses, the energies relative to the lowest conformer (1), and the Boltzmann factors obtained by the given formula are listed.

$$f_i = \frac{e^{-\frac{E_{rel,i}}{kT}}}{\sum_i e^{-\frac{E_{rel,i}}{kT}}}$$

$E_{rel,i}$ ≙ relative energy of conformer i
k ≙ Boltzmann constant
T ≙ room temperature

Table 2 Energies of the conformers of (*R*,*R*)-**3b** resulted from the calculations on B3LYP/6-311++G(d,p)-level.

Conformer #	*E* / a.u.	*ZPE* / a.u.	*E+ZPE* / a.u.	*E+ZPE* / kJ/mol	E_{rel} / kJ/mol	*f*
1	–1028.848560	0.293258	–1028.555302	–2700472	0	0.862
2	–1028.845966	0.293188	–1028.552778	–2700465	7	0.059
3	–1028.842275	0.292813	–1028.549462	–2700456	15	0.002
4	–1028.845286	0.293351	–1028.551935	–2700463	9	0.024
5	–1028.844247	0.293265	–1028.550982	–2700460	11	0.009
6	–1028.845924	0.293431	–1028.552493	–2700464	7	0.044

Applying the same functional and basis set, TD-DFT calculations were carried out taking into account 40 excited singlet states. The rotational strength associated with the excited states gave the ECD spectra of the single conformers. These were weighted with the corresponding Boltzmann factors (cf. Table 2) to obtain the total ECD spectrum (Figure 1). It has a strong negative Cotton effect at 186.0 nm and a weak positive signal at 205.7 nm. Two more intense signals can be seen, a negative one at 276.9 nm and a positive one at 322.7 nm. The spectrum of the main conformer (1) including the rotational strengths for the electronic transitions is shown in Figure 2. The most important rotational strengths for the band shape are listed in Table 3.

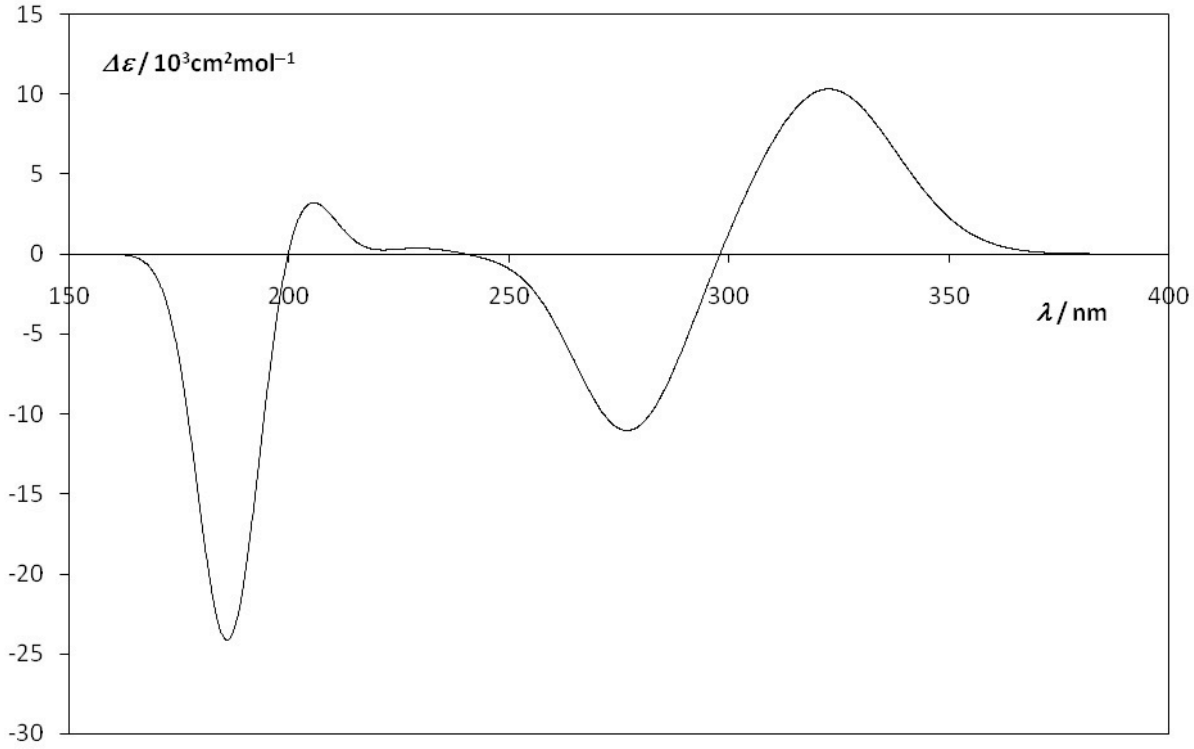


Figure 1 Calculated Boltzmann-weighted ECD spectrum of (*R*,*R*)-**3b**.

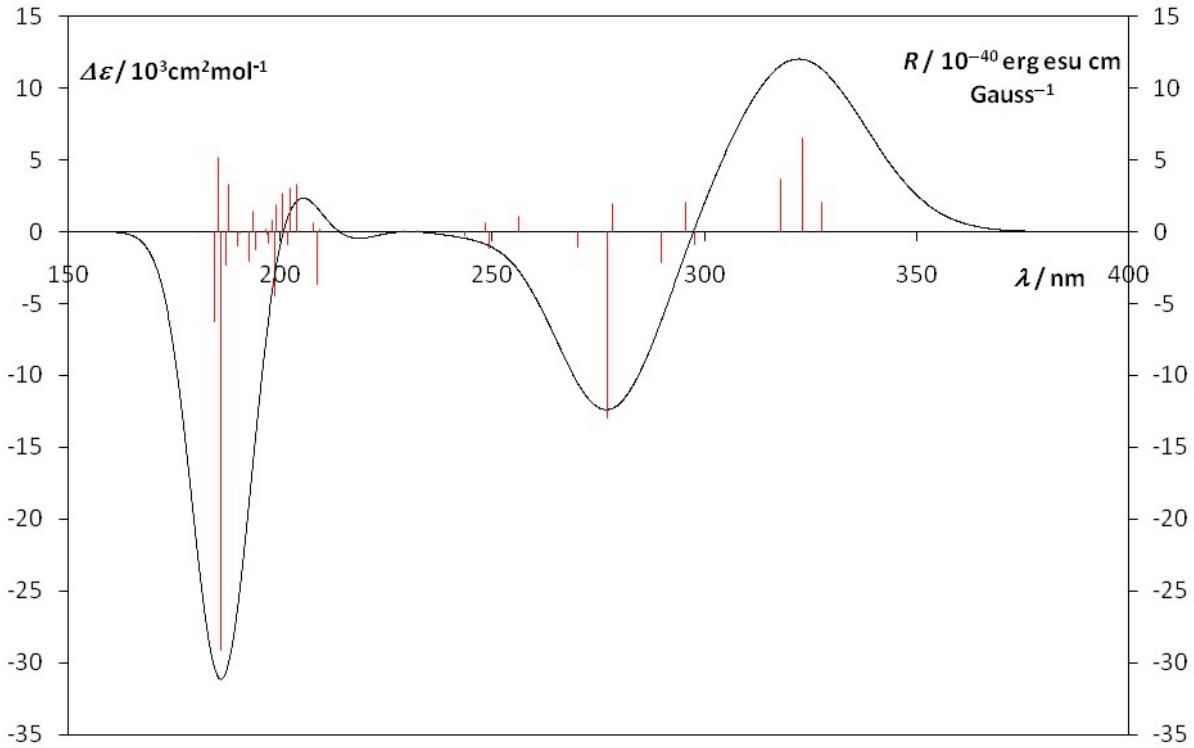


Figure 2 Calculated ECD spectrum of the main conformer (1) of (*R*,*R*)-**3b** and the rotational strengths of the electronic excitations. The bars are the $\Delta\varepsilon_{max}$ of the single Gaussians and are proportional to the corresponding rotational strengths.

Table 3 Rotational strengths *R* and the corresponding electronic transitions of the main conformer (1) of (*R*,*R*)-**3b** (Cy = cyclohexanone, NO2A means the nitro group on the cyclohexanone ring, NO2B the substituent on the benzylic carbon atom).

λ / nm	R / 10^{-40} erg esu cm Gauss^{-1}	Transition	
		MOs	Type
186.1	−29.117	HOMO − 8 → LUMO	$\pi_{NO2A} \rightarrow \pi^*_{NO2A}$
		HOMO − 3 → LUMO + 3	$n_{O(NO2B)} \rightarrow \pi^*_{Ph}$
		HOMO − 1 → LUMO + 3	$\pi_{Ph} \rightarrow \pi^*_{Ph}$
		HOMO → LUMO + 4	$\pi_{Ph} \rightarrow \pi^*_{Ph}$
202.4	3.076	HOMO − 12 → LUMO HOMO − 11 → LUMO HOMO − 10 → LUMO	$\sigma_{Cy\text{-}CH\text{-}Ph} \rightarrow \pi^*_{NO2A}$
277.2	−12.950	HOMO − 7 → LUMO	$\sigma_{Cy\text{-}CH\text{-}CH2} + \pi_{NO2A} \rightarrow \pi^*_{NO2A}$
		HOMO − 2 → LUMO	$\sigma_{Cy} + n_{O(C=O)} \rightarrow \pi^*_{NO2A}$
323.1	6.492	HOMO − 6 → LUMO	$n_{O(NO2A)} \rightarrow \pi^*_{NO2A}$
		HOMO − 2 → LUMO	$\sigma_{Cy} + n_{O(C=O)} \rightarrow \pi^*_{NO2A}$
		HOMO − 1 → LUMO	$\pi_{Ph} \rightarrow \pi^*_{NO2A}$
		HOMO → LUMO	$\pi_{Ph} \rightarrow \pi^*_{NO2A}$

The experimental ECD spectrum of **3b** could be measured down to about 190 nm and is depicted in Figure 3.[9] Two positive Cotton effects at 212.8 nm and 249.4 nm can be correlated with the negative signals calculated for (*R*,*R*)-**3b** at 186.0 nm and 276.9 nm. The region in between is heavily clinched and the positive signal at a calculated wavelength of 205.7 nm has no counterpart in the measured curve. The maximum calculated at 322.7 nm is experimentally found as a minimum at 289.4 nm. In summary, the measured curve corresponds to the mirror image of the calculated spectrum, leading to the conclusion that the product of the synthesis is (*S*,*S*)-**3b**.

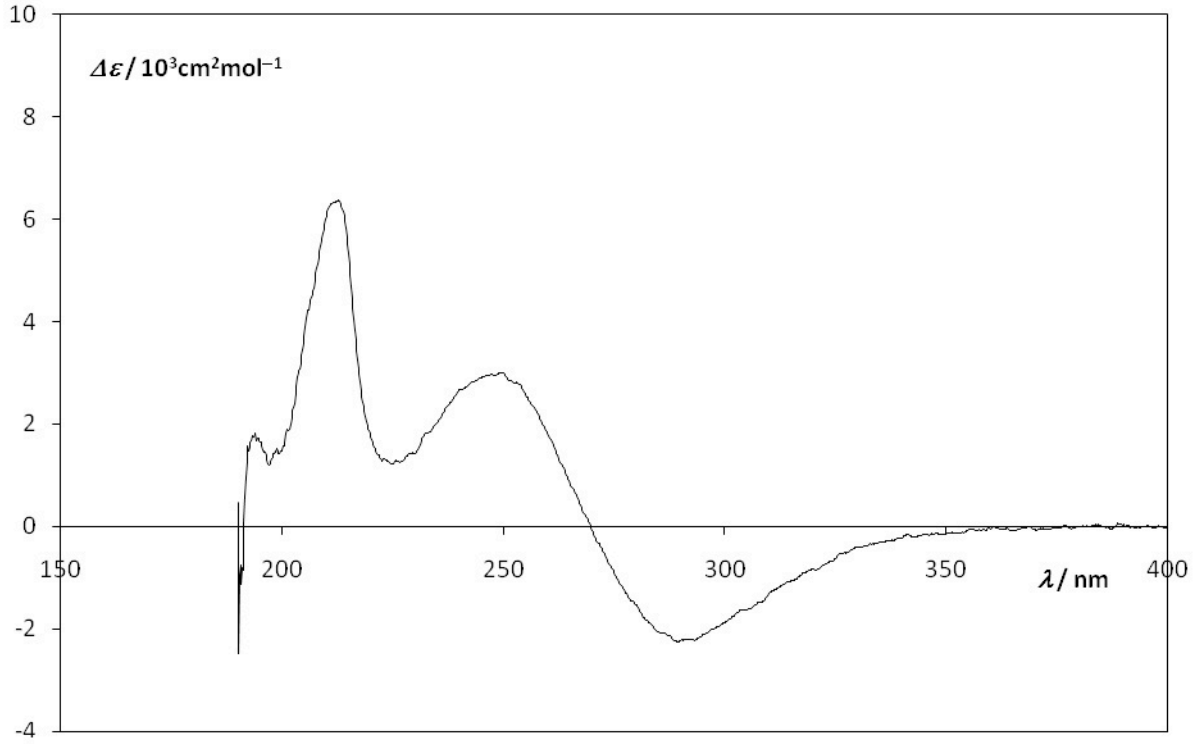


Figure 3 Experimental ECD spectrum of **3b** in acetonitrile.

The calculated VCD spectrum of (*R*,*R*)-**3b** was obtained by weighting the single VCD curves of the six conformers with the Boltzmann factors (Figure 4). The calculated and the measured VCD spectrum[10] of **3b** (Figure 5) could be corrrelated between 1500 cm^{-1} to 1200 cm^{-1} as it is indicated by the peak labels in Figures 4 and 5. In agreement with the ECD results, the experimental VCD curve is the mirror image of the calculated one.

Both, ECD and VCD investigations, are in good agreement and show that (*S*,*S*)-**3b** is formed during the synthesis.

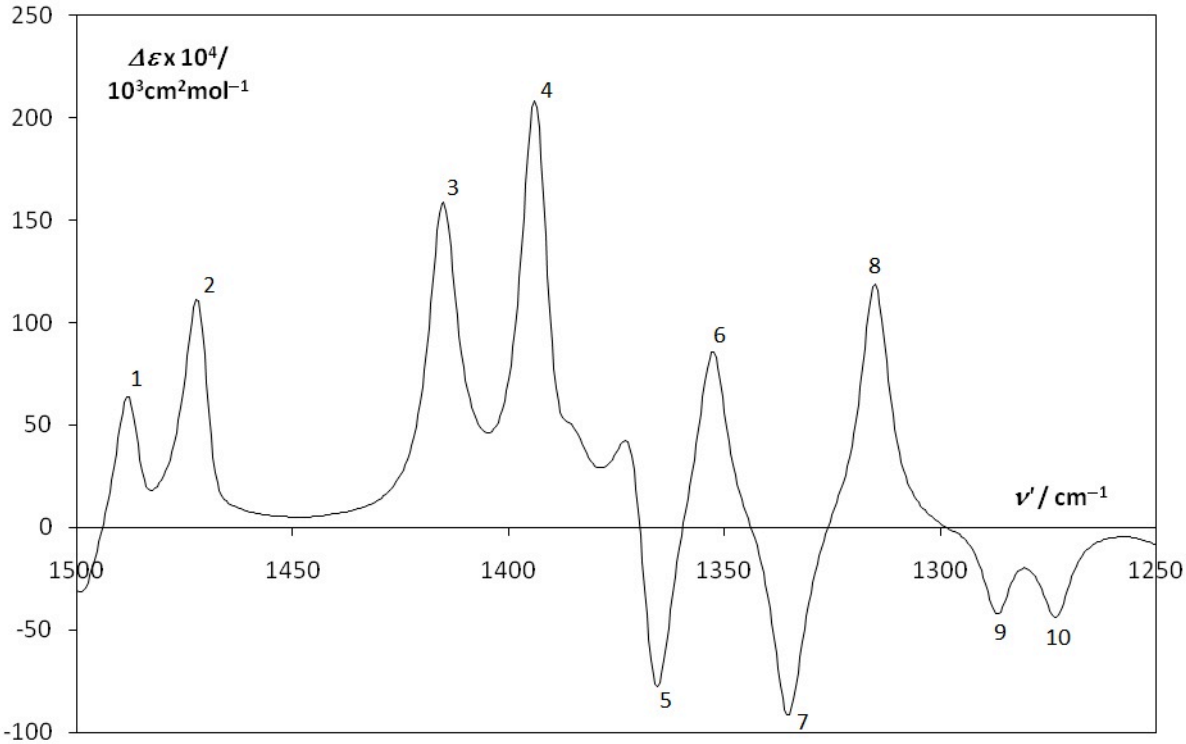


Figure 4 Calculated Boltzmann-weighted VCD spectrum of (*R*,*R*)-**3b**.

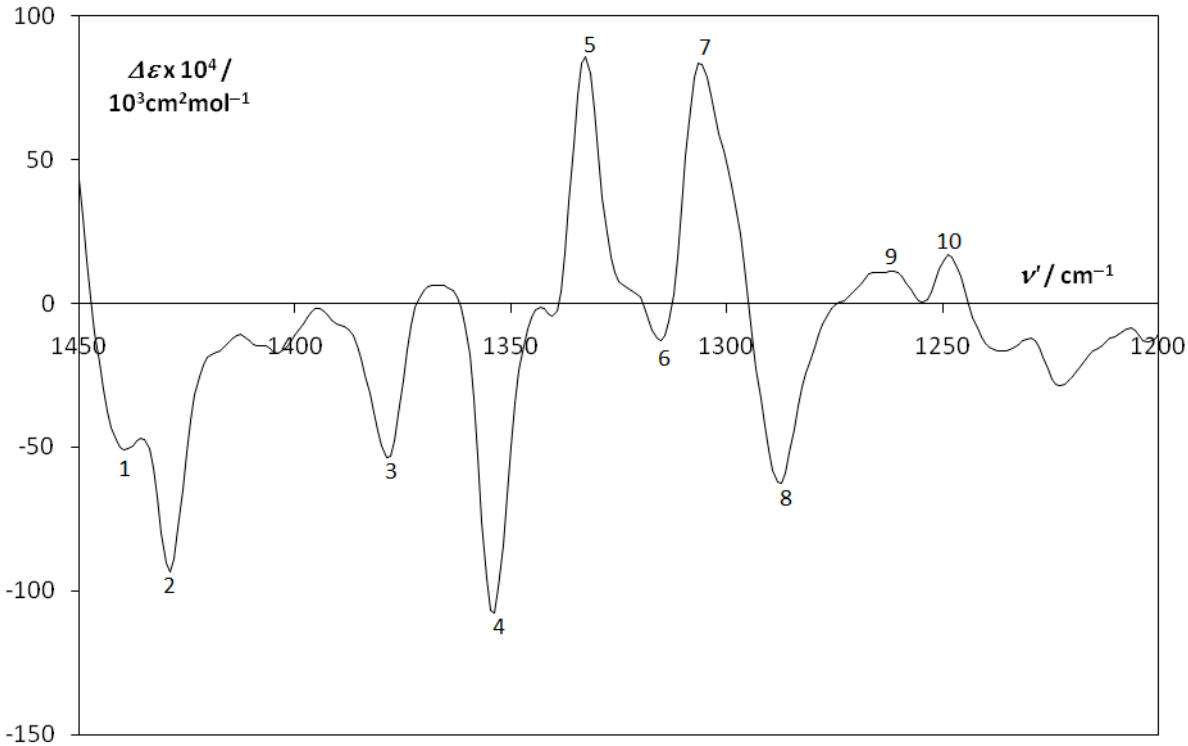


Figure 5 Experimental VCD spectrum of **3b** in $CDCl_3$.

6. Notes and References

[1] M. Jörres, I. Schiffers and C. Bolm, *Org. Lett.*, 2012, **14**, 4518.

[2] Before weighting in catalyst **Af** (which was obtained as an orange glue) it was frozen with liquid nitrogen in a flask under argon atmosphere for easier transfer.

[3] Only 1.2 g of grinding balls with a diameter of 0.1 cm were used.

[4] Typically, the vessels were washed with DCM. For products **3c** and **3e** washing with EtOAc as a 'greener' solvent was successfully tested.

[6] S.-H. Moon and S. Lee, *Synth. Comm.*, 1998, **28**, 3919.

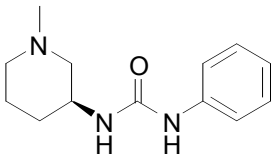
[7] Spartan'08, Wavefunction Inc., Irvine, CA.

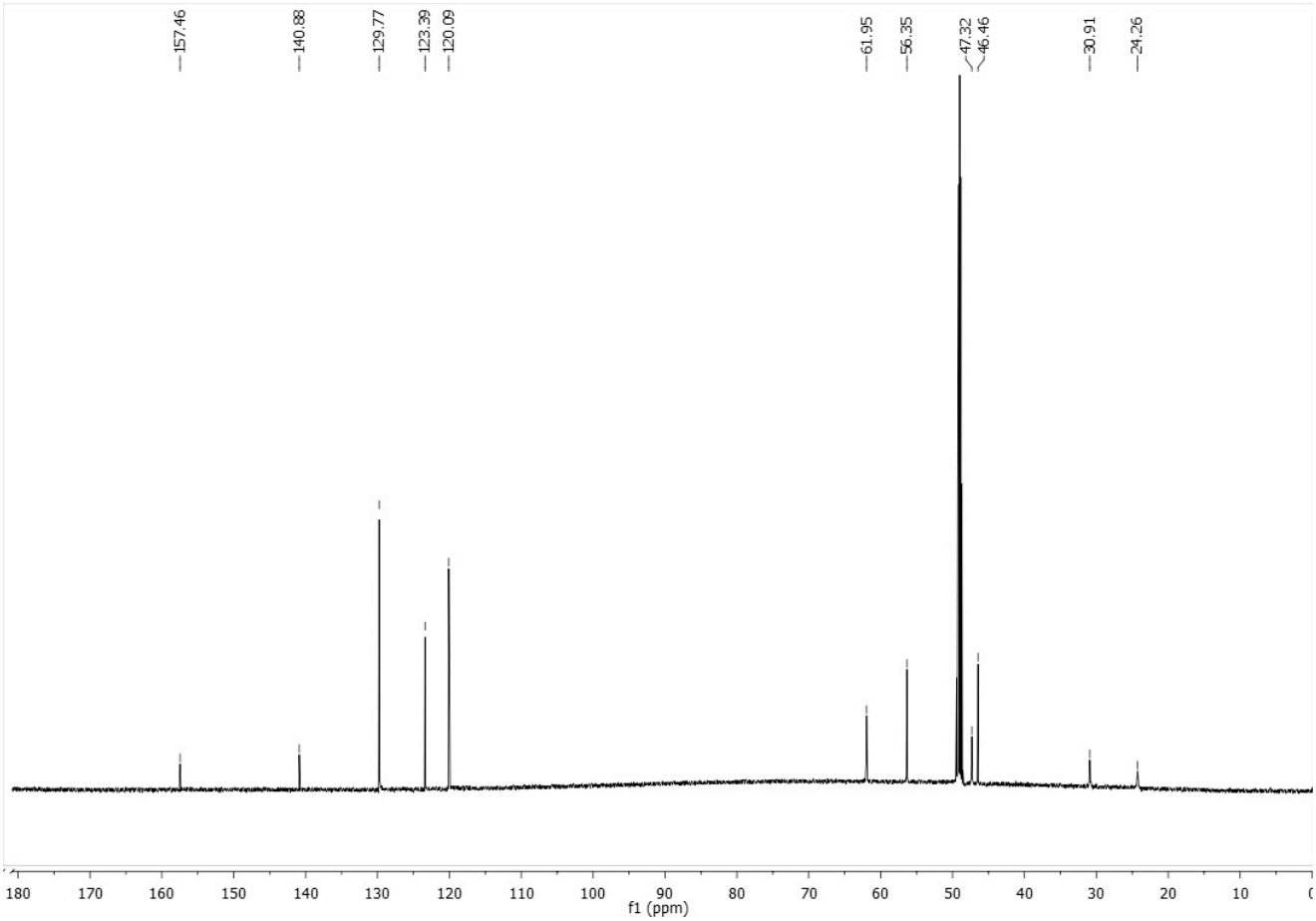
[8] Gaussian 09, Revision A.02, Gaussian, Inc., Wallingford CT, 2009.

[9] The experimental ECD spectrum was recorded at room temperature using a 50 mmol/L solution of **3b** in acetonitrile on a JASCO J-815 circular dichroism spectrometer. A path length of 1 cm, a band width of 2.0 nm, and a step size of 0.2 nm were used. The pure solvent was measured under the same conditions and the background was subtracted from the sample curve.

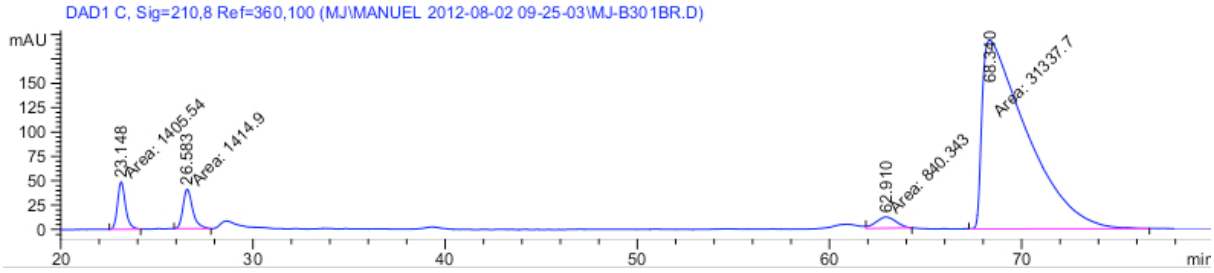
[10] The experimental VCD spectrum was recorded at room temperature with a combined IR- and VCD-spectrometer of Bruker Optik GmbH (VERTEX 70/PMA 50, LIA: 1 mV, PEM: 1500 cm^{-1}). A liquid cell with BaF_2 windows and a Teflon spacer of 50 mm layer thickness and a 0.86 mol/L solution of **3b** in $CDCl_3$ were used. The base line was corrected by vertical shift.

(*S*)-1-(1-methylpiperidine-3-yl)-3-phenylurea (Cb)





HPLC analysis of 3a

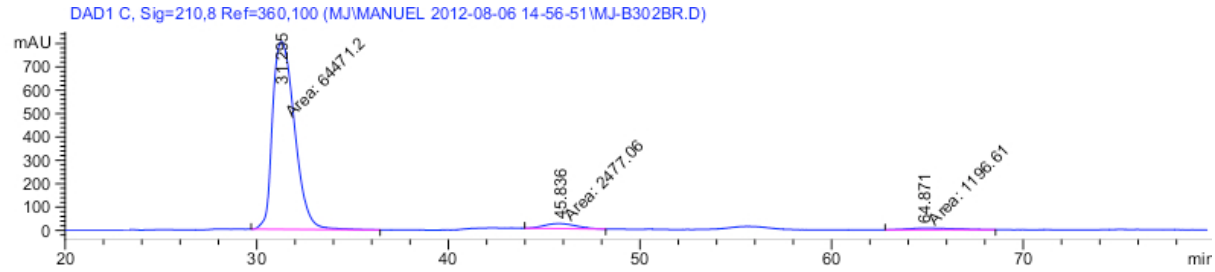


Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	23.148	MM	0.4823	1405.53503	48.57065	4.0160
2	26.583	MM	0.5821	1414.90332	40.51065	4.0428
3	62.910	FM	1.2275	840.34277	11.40991	2.4011
4	68.340	MM	2.6987	3.13377e4	193.53546	89.5402
Totals :				3.49985e4	294.02667	

HPLC-analysis: Chiralpak AD-H, *n*-heptane:*i*-PrOH = 95:5, 0.8 mL/min, t_{ret}: 23.1 (*anti*, minor), 26.6, 62.9, 68.3 (*anti*, major) min.

HPLC analysis of 3b

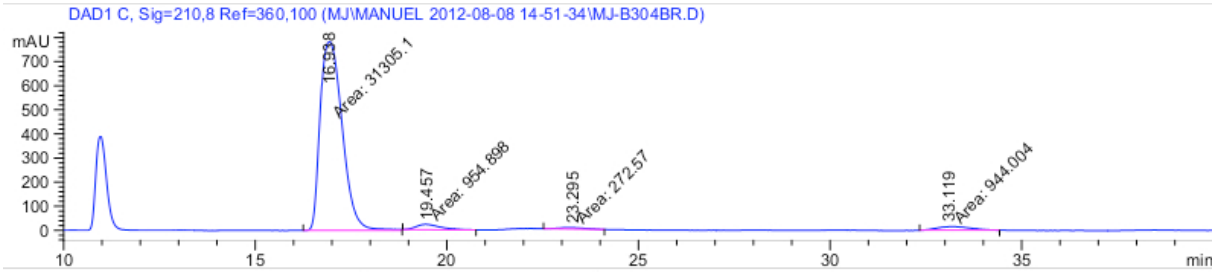


Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	31.295	MM	1.3383	6.44712e4	802.89886	94.6090
2	45.836	MM	1.9208	2477.06055	21.49308	3.6350
3	64.871	MM	2.6848	1196.61475	7.42839	1.7560
Totals :				6.81449e4	831.82034	

HPLC-analysis: Chiralpak OD-H, *n*-heptane:*i*-PrOH = 90:10, 0.8 mL/min, t_{ret}: 31.3 (*anti*, major), 39.4, 45.8, 64.9 (*anti*, minor) min.

HPLC analysis of 3c

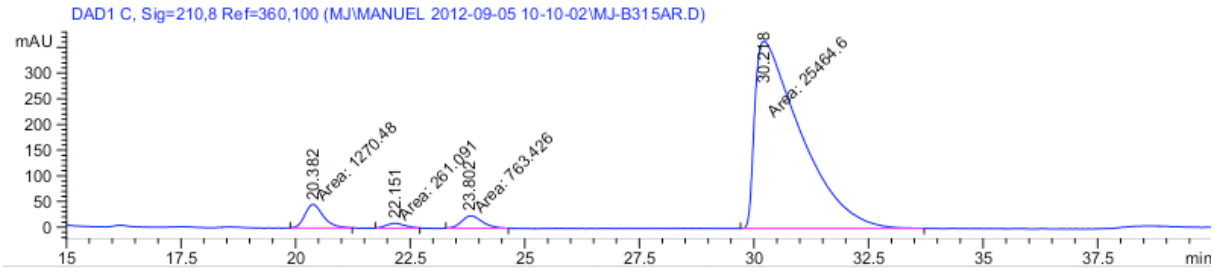


Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	16.938	MF	0.6660	3.13051e4	783.46118	93.5135
2	19.457	MM	0.7261	954.89764	21.91969	2.8524
3	23.295	MM	0.7345	272.57043	6.18454	0.8142
4	33.119	MM	1.0372	944.00415	15.16871	2.8199
Totals :				3.34766e4	826.73412	

HPLC-analysis: Chiralpak OD-H, *n*-heptane:*i*-PrOH = 95:5, 0.8 mL/min, t_{ret}: 16.9 (*anti*, major), 19.5, 23.3, 33.1 (*anti*, minor) min.

HPLC analysis of 3d

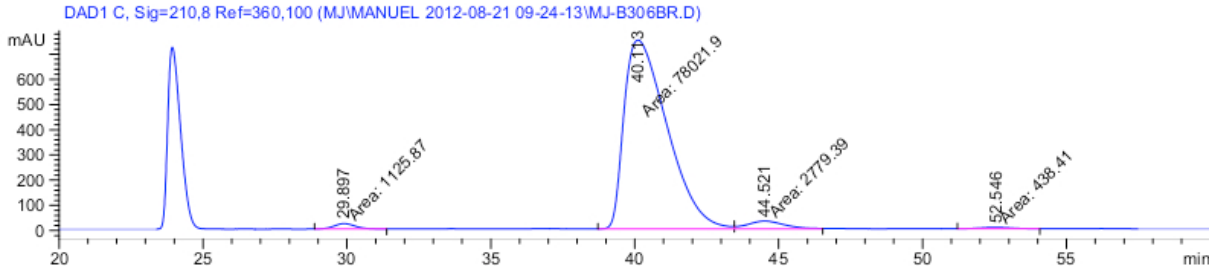


Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	20.382	MM	0.4637	1270.48193	45.65995	4.5767
2	22.151	MM	0.4669	261.09116	9.31966	0.9405
3	23.802	MM	0.5292	763.42645	24.04458	2.7501
4	30.218	MM	1.1649	2.54646e4	364.32523	91.7326
Totals :				2.77596e4	443.34942	

HPLC-analysis: Chiralpak AD-H, *n*-heptane:*i*-PrOH = 90:10, 0.8 mL/min, t_{ret}: 20.4, 22.2, 23.8 (*anti*, minor), 30.2 (*anti*, major) min.

HPLC analysis of 3e

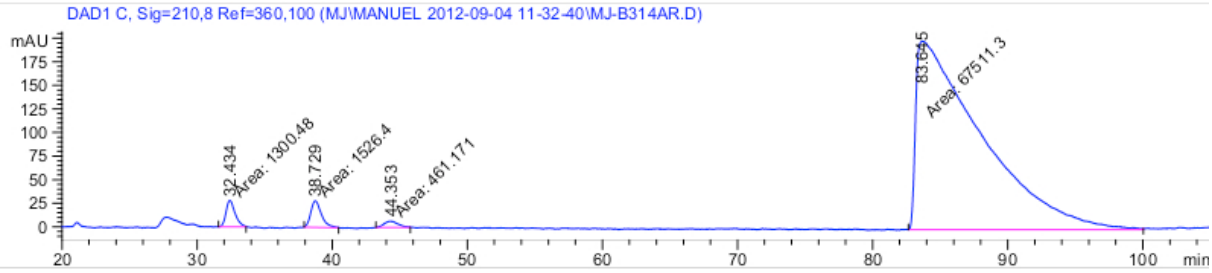


Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	29.897	MM	0.8617	1125.87097	21.77620	1.3669
2	40.113	MF	1.7362	7.80219e4	748.95679	94.7263
3	44.521	MF	1.4950	2779.38965	30.98530	3.3745
4	52.546	MM	1.3132	438.41013	5.56418	0.5323
Totals :				8.23655e4	807.28247	

HPLC-analysis: Chiralpak AS-H, *n*-heptane:*i*-PrOH = 98:2, 0.8 mL/min, t_{ret}: 29.9 (*anti*, minor), 40.1 (*anti*, major), 44.5, 52.5 min.

HPLC analysis of 3f

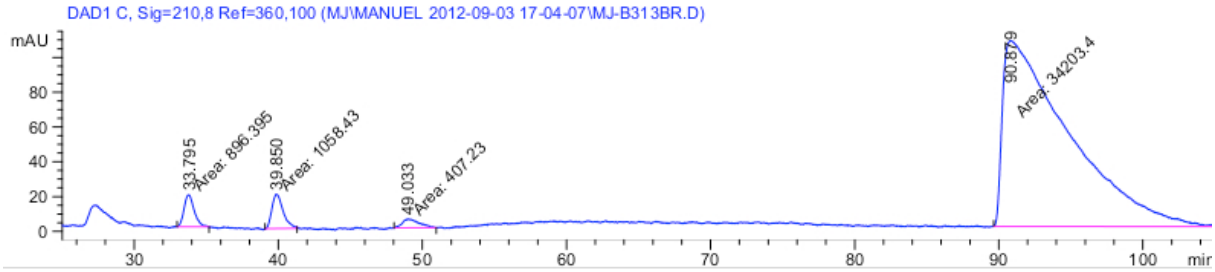


Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	32.434	MM	0.7829	1300.47876	27.68552	1.8369
2	38.729	MM	0.9078	1526.39941	28.02236	2.1560
3	44.353	MM	1.1727	461.17059	6.55440	0.6514
4	83.645	MM	5.6279	6.75113e4	199.92920	95.3558
Totals :				7.07993e4	262.19148	

HPLC-analysis: Chiralpak AD-H, *n*-heptane:*i*-PrOH = 95:5, 0.8 mL/min, t_{ret}: 32.4, 38.7 (*anti*, minor), 44.4, 83.6 (*anti*, major) min.

HPLC analysis of 3g

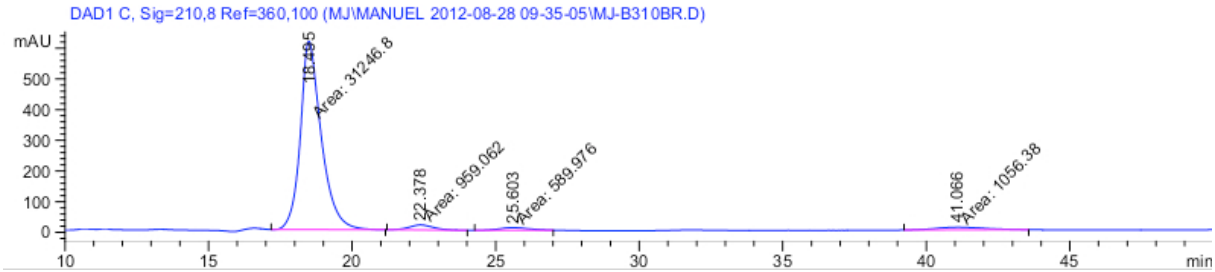


Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	33.795	MM	0.8125	896.39453	18.38783	2.4515
2	39.850	MM	0.8954	1058.43054	19.70020	2.8946
3	49.033	MM	1.3405	407.22983	5.06306	1.1137
4	90.879	MM	5.3409	3.42034e4	106.73367	93.5402
Totals :				3.65655e4	149.88476	

HPLC-analysis: Chiralpak AD-H, *n*-heptane:*i*-PrOH = 95:5, 0.8 mL/min, t_{ret}: 33.8, 39.9 (*anti*, minor), 49.0, 90.9 (*anti*, major) min.

HPLC analysis of 3h

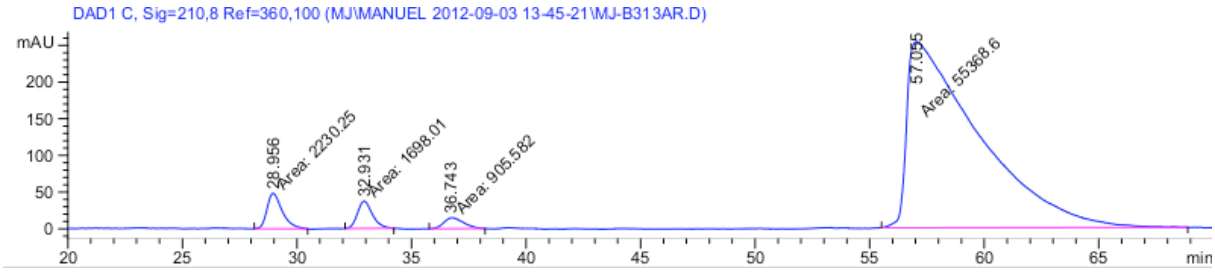


Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	18.495	MM	0.8481	3.12468e4	614.05371	92.3035
2	22.378	MM	0.9734	959.06201	16.42105	2.8331
3	25.603	MM	1.1782	589.97595	8.34553	1.7428
4	41.066	MM	2.0159	1056.38379	8.73358	3.1206
Totals :				3.38522e4	647.55387	

HPLC-analysis: Chiralpak OT+, *n*-heptane:*i*-PrOH = 97:3, 0.8 mL/min, t_{ret}: 18.5 (*anti*, major), 22.4, 25.6, 41.1 (*anti*, minor) min.

HPLC analysis of 3i



Signal 2: DAD1 C, Sig=210,8 Ref=360,100

Peak #	RetTime [min]	Type	Width [min]	Area [mAU*s]	Height [mAU]	Area %
1	28.956	MM	0.7682	2230.24780	48.38781	3.7046
2	32.931	MM	0.7554	1698.01074	37.46339	2.8205
3	36.743	MM	1.0090	905.58221	14.95876	1.5042
4	57.055	MM	3.6350	5.53686e4	253.86624	91.9707
Totals :				6.02024e4	354.67620	

HPLC-analysis: Chiralpak AD-H, *n*-heptane:*i*-PrOH = 98:2, 0.8 mL/min, t_{ret}: 29.0, 32.9 (*anti*, minor), 36.7, 57.1 (*anti*, major) min.