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 F254 plates. Visualization on TLC was achieved by the use of UV light (254 nm) and treatment with basic aqueous solution of KMnO4 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•cm\(^{-1}\)g\(^{-1}\)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).

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 \(\alpha\)-nitrocyclohexanone (1) to 2-furyl-substituted nitroalkene 2a.\(^7\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ratio</th>
<th>Time (min)</th>
<th>Milling speed (rpm)</th>
<th>Additive</th>
<th>Yield (%)</th>
<th>dr (anti/sym)</th>
<th>er(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 : 1</td>
<td>30 300</td>
<td>-</td>
<td>-</td>
<td>83</td>
<td>95.5</td>
<td>92.8</td>
</tr>
<tr>
<td>2</td>
<td>1 : 1</td>
<td>30 300</td>
<td>-</td>
<td>-</td>
<td>60</td>
<td>93.7</td>
<td>89:11</td>
</tr>
<tr>
<td>3</td>
<td>1 : 1.5</td>
<td>30 300</td>
<td>-</td>
<td>-</td>
<td>40</td>
<td>95.5</td>
<td>89:11</td>
</tr>
<tr>
<td>4</td>
<td>1.5 : 1</td>
<td>30 300</td>
<td>-</td>
<td>-</td>
<td>56</td>
<td>91.9</td>
<td>88:12</td>
</tr>
<tr>
<td>5</td>
<td>1.5 : 1</td>
<td>45 300</td>
<td>-</td>
<td>-</td>
<td>76</td>
<td>93.7</td>
<td>89:11</td>
</tr>
<tr>
<td>6</td>
<td>1.5 : 1</td>
<td>60 300</td>
<td>-</td>
<td>-</td>
<td>74</td>
<td>95.5</td>
<td>89:11</td>
</tr>
<tr>
<td>7</td>
<td>1.5 : 1</td>
<td>30 150</td>
<td>-</td>
<td>-</td>
<td>63</td>
<td>92.8</td>
<td>89:11</td>
</tr>
<tr>
<td>8</td>
<td>1.5 : 1</td>
<td>30 500</td>
<td>-</td>
<td>-</td>
<td>83</td>
<td>95.5</td>
<td>91:9</td>
</tr>
<tr>
<td>9</td>
<td>1.5 : 1</td>
<td>30' 300</td>
<td>-</td>
<td>-</td>
<td>66</td>
<td>92.2</td>
<td>90:10</td>
</tr>
<tr>
<td>10</td>
<td>1.5 : 1</td>
<td>30 300</td>
<td>quartz sand(^6)</td>
<td>-</td>
<td>63</td>
<td>91.9</td>
<td>87:13</td>
</tr>
<tr>
<td>11</td>
<td>1.5 : 1</td>
<td>30 300</td>
<td>acidic silica(^7)</td>
<td>-</td>
<td>69</td>
<td>91.9</td>
<td>83:17</td>
</tr>
<tr>
<td>12</td>
<td>1.5 : 1</td>
<td>30 300</td>
<td>basic Al(_2)O(_3)</td>
<td>-</td>
<td>63</td>
<td>92.8</td>
<td>91:9</td>
</tr>
<tr>
<td>13</td>
<td>1.5 : 1</td>
<td>30 300</td>
<td>DCM (1 eq)</td>
<td>-</td>
<td>75</td>
<td>93.7</td>
<td>91:9</td>
</tr>
<tr>
<td>14</td>
<td>1.5 : 1</td>
<td>30 300</td>
<td>DCM (3 eq)</td>
<td>-</td>
<td>69</td>
<td>95.5</td>
<td>92:8</td>
</tr>
</tbody>
</table>

\(^a\) 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 \(\alpha\)-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 (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 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 mL of DCM or EtOAc. The resulting solution was concentrated in vacuo, and the product was purified by flash chromatography (gradient: heptane : 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)furan (2a) according to general procedure; white solid after column chromatography. HPLC-analysis: Chiralpak AD-H, n-heptane:i-PrOH = 95:5, 0.8 mL/min, t<sub>ret</sub>: 23.1 (anti, major), 26.6, 62.9, 68.3 (anti, major) min.

1H NMR (300 MHz, CDCl<sub>3</sub>) 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).

1H NMR (300 MHz, CDCl<sub>3</sub>) 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, 1.3 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).

13C NMR (75 MHz, CDCl<sub>3</sub>) 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.

13C NMR (75 MHz, CDCl<sub>3</sub>) 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<sub>2</sub>O. Mp.: 93-94 °C.

HPLC-analysis: Chiralpak OD-H, n-heptane:i-PrOH = 90:10, 0.8 mL/min, t<sub>ret</sub>: 31.3 (anti, major), 39.4, 45.8, 64.9 (anti, minor) min.

1H NMR (400 MHz, CDCl<sub>3</sub>) 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).

1H NMR (400 MHz, CDCl<sub>3</sub>) 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).

13C NMR (75 MHz, CDCl<sub>3</sub>) 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

13C NMR (75 MHz, CDCl<sub>3</sub>) 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 (3e)

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 Et₂O. Mp.: 127 °C.

HPLC-analysis: Chiralpak OD-H, n-heptane:i-PrOH = 95:5, 0.8 mL/min, t<sub>ret</sub>: 16.9 (anti, major), 19.5, 23.3, 33.1 (anti, minor) min.

1H NMR (300 MHz, CDCl₃) anti: δ = 7.39 – 7.30 (m, 1H), 7.18 – 6.69 (m, 2H), 4.86 (dd, J = 11.5, 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).

1H NMR (300 MHz, CDCl₃) syn: δ = 7.45 – 7.24 (m, 2H), 7.18 – 6.97 (m, 2H), 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).

13C NMR (75 MHz, CDCl₃) anti: δ = 112.1. O. Mp.: 127 °C.

13C NMR (75 MHz, CDCl₃) syn: δ = 129.2 (d, J = 14.0, 10.8 Hz, 2H), 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, 1H).

19F NMR (376 MHz, CDCl₃) anti: δ = -114.9, i δ = -113.7.

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

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<sub>ret</sub>: 20.4, 22.2, 23.8 (anti, minor), 30.2 (anti, major) min.

1H NMR (300 MHz, CDCl₃) anti: δ = 8.12 – 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, 1H).

1H NMR (300 MHz, CDCl₃) syn: δ = 7.32 – 7.24 (m, 2H), 7.07 – 6.98 (m, 2H), 5.24 (dd, J = 14.0, 10.8 Hz, 2H), 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).

13C NMR (75 MHz, CDCl₃) 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.

13C NMR (75 MHz, CDCl₃) 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.

19F NMR (282 MHz, CDCl₃): δ = 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), 43, 31.

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

Prepared from α-nitrocyclohexanone and 2-chloro-β-nitrostyrene according to general procedure; yellowish-white solid after column chromatography, white crystals after recrystallization from Et₂O. Mp.: 152 °C.

HPLC-analysis: Chiralpak AS-H, n-heptane:i-PrOH = 98:2, 0.8 mL/min, t<sub>ret</sub>: 29.9 (anti, minor), 40.1 (anti, major), 44.5, 52.5 min.
\( ^1 \text{H} \) NMR (400 MHz, CDCl\(_3\)) \textit{anti}: \( \delta = 7.39 - 7.33 \) (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 (dd, \( J = 15.3, 6.2, 3.0 \) 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).

\( ^1 \text{H} \) NMR (400 MHz, CDCl\(_3\)) \textit{syn}: \( \delta = 7.50 - 7.44 \) (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\(_3\)): \( \delta = \text{anti} \): 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\(_3\)): \( \delta = \text{syn} \): 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)

Prepared from \( \alpha \)-nitrocyclohexanone and 4-chloro-\( \beta \)-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, \( t_{\text{ret}} \): 32.4, 38.7 (\textit{anti}, minor), 44.4, 83.6 (\textit{anti}, major) min.

\( ^1 \text{H} \) NMR (600 MHz, CDCl\(_3\)) \textit{anti}: \( \delta = 7.25 \) (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).

\( ^1 \text{H} \) NMR (600 MHz, CDCl\(_3\)) \textit{syn}: \( \delta = 7.25 \) (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\(_3\)) \textit{anti}: \( \delta = 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\(_3\)) \textit{syn}: \( \delta = 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)

Prepared from \( \alpha \)-nitrocyclohexanone and 4-bromo-\( \beta \)-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, \( t_{\text{ret}} \): 33.8, 39.9 (\textit{anti}, minor), 49.0, 90.9 (\textit{anti}, major) min.

\( ^1 \text{H} \) NMR (400 MHz, CDCl\(_3\)) \textit{anti}: \( \delta = 7.47 \) (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).

\( ^1 \text{H} \) NMR (400 MHz, CDCl\(_3\)) \textit{syn}: \( \delta = 7.49 - 7.45 \) (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\(_3\)) \textit{anti}: \( \delta = 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\(_3\)) \textit{syn}: \( \delta = 199.8, 132.49, 132.46, 131.4, 123.6, 98.3, 75.8, 49.1, 40.3, 35.5, 25.7, 21.0.\)
(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, \( t_{\text{ret}} \): 18.5 (anti, major), 22.4, 25.6, 41.1 (anti, minor) min.

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \alpha \) anti: \( \delta = 7.03 - 6.98 \) (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 (dd, \( J = 14.6, 6.0, 3.2 \) Hz, 1H), 2.09 – 1.93 (m, 1H), 1.83 – 1.47 (m, 4H).

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \beta \) syn: \( \delta = 7.22 - 7.15 \) (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).

\(^1\)C NMR (100 MHz, CDCl\(_3\)) \( \alpha \) anti: \( \delta = 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.

\(^1\)C NMR (100 MHz, CDCl\(_3\)) \( \beta \) syn: \( \delta = 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-[(S)-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\(_3\)N (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 \emph{in vacuo} and the residue was dissolved in CH\(_2\)Cl\(_2\). The mixture was washed with Na\(_2\)CO\(_3\), the aqueous layer was extracted with CH\(_2\)Cl\(_2\) (2 x 4 mL) and the combined organic phases were dried over MgSO\(_4\), filtered, and concentrated \emph{in vacuo}. The product was purified by flash chromatography (first pentane : ethyl acetate 7:3, then ethyl acetate : MeOH : Et\(_3\)N = 100 : 4 : 4) and obtained as a white solid in quantitative yield. Mp.: 195-196 °C.
\[ \mathcal{I} = -17.9 \text{ (c= 1.00, EtOH).} \]

$^1$H NMR (600 MHz, CD$_3$OD): $\delta = 7.31-7.34$ (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$_3$OD): $\delta = 157.5, 140.9, 129.8, 123.4, 120.1, 62.0, 56.4, 47.3, 46.5, 30.9, 24.3$.

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): $\nu = 3300, 2932, 2779, 2469, 2433, 2061, 1631, 1567, 1442, 1305, 1232, 1148, 1061, 1017, 855, 762, 726, 670$.

CHN-Analysis for C$_{13}$H$_{19}$N$_3$O, 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$_3$O [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.

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

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 $\Delta \varepsilon_{\text{max}}$ 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).

<table>
<thead>
<tr>
<th>$\lambda$ / nm</th>
<th>$R / 10^{-40}$ erg cm Gauss$^{-1}$</th>
<th>MOs</th>
<th>Transition</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>186.1</td>
<td>-29.117</td>
<td>HOMO - 8 $\rightarrow$ LUMO</td>
<td>$\pi^{#}$NO2A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HOMO - 3 $\rightarrow$ LUMO + 3</td>
<td>$\pi^{#}$Ph</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HOMO - 1 $\rightarrow$ LUMO + 3</td>
<td>$\pi^{#}$Ph</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HOMO $\rightarrow$ LUMO + 4</td>
<td>$\pi^{#}$Ph</td>
<td></td>
</tr>
<tr>
<td>202.4</td>
<td>3.076</td>
<td>HOMO - 12 $\rightarrow$ LUMO</td>
<td>$\alpha_{\text{Cy-CH-Ph}}$ $\rightarrow$ $\pi^{#}$NO2A</td>
<td></td>
</tr>
<tr>
<td>277.2</td>
<td>-12.950</td>
<td>HOMO - 7 $\rightarrow$ LUMO</td>
<td>$\alpha_{\text{Cy-CH-CH}<em>2} + \alpha</em>{\text{NO2A}}$ $\rightarrow$ $\pi^{#}$NO2A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HOMO - 2 $\rightarrow$ LUMO</td>
<td>$\sigma_{\text{Cy}} + \sigma_{\text{O(C=O)}}$ $\rightarrow$ $\pi^{#}$NO2A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HOMO - 6 $\rightarrow$ LUMO</td>
<td>$\sigma_{\text{NO2A}}$ $\rightarrow$ $\pi^{#}$NO2A</td>
<td></td>
</tr>
<tr>
<td>323.1</td>
<td>6.492</td>
<td>HOMO - 2 $\rightarrow$ LUMO</td>
<td>$\sigma_{\text{Cy}} + \sigma_{\text{O(C=O)}}$ $\rightarrow$ $\pi^{#}$NO2A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HOMO - 1 $\rightarrow$ LUMO</td>
<td>$\alpha_{\text{Ph}}$ $\rightarrow$ $\pi^{#}$NO2A</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>HOMO $\rightarrow$ LUMO</td>
<td>$\alpha_{\text{Ph}}$ $\rightarrow$ $\pi^{#}$NO2A</td>
<td></td>
</tr>
</tbody>
</table>

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.](image)

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 correlated 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 CDCl₃.
6. Notes and References


[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.


[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 BaF₂ windows and a Teflon spacer of 50 nm layer thickness and a 0.86 mol/L solution of 3b in CDCl₃ were used. The base line was corrected by vertical shift.
(S)-1-(1-methylpiperidine-3-yl)-3-phenylurea (Cb)
HPLC analysis of 3a

**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

**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

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

HPLC analysis of 3d

HPLC-analysis: Chiralpak AD-H, n-heptane:i-PrOH = 90:10, 0.8 mL/min, t\textsubscript{ret}: 20.4, 22.2, 23.8 (anti, minor), 30.2 (anti, major) min.
HPLC analysis of 3e

![HPLC graph for 3e]

### Chiralpak AS-H, n-heptane:i-PrOH = 98:2, 0.8 mL/min, t\text{ret}: 29.9 (anti, minor), 40.1 (anti, major), 44.5, 52.5 min.

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

HPLC analysis of 3f

![HPLC graph for 3f]

### Chiralpak AD-H, n-heptane:i-PrOH = 95:5, 0.8 mL/min, t\text{ret}: 32.4, 38.7 (anti, minor), 44.4, 83.6 (anti, major) min.

HPLC-analysis: Chiralpak AD-H, n-heptane:i-PrOH = 95:5, 0.8 mL/min, t\text{ret}: 32.4, 38.7 (anti, minor), 44.4, 83.6 (anti, major) min.
HPLC analysis of 3g

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

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

HPLC-analysis: Chiralpak AD-H, n-heptane:i-PrOH = 98:2, 0.8 mL/min, t<sub>ret</sub>: 29.0, 32.9 (anti, minor), 36.7, 57.1 (anti, major) min.