A General Organocatalytic Enantioselective Nitrocyclopropanation Reaction

Veit Wascholowski, Henriette M. Hansen, Deborah A. Longbottom, Steven V. Ley*
Department of Chemistry, University of Cambridge, Lensfield Road, Cambridge, CB2 1EW, UK
Fax +44(1223)336442; E-mail: svl1000@cam.ac.uk
Received 21 December 2007

Abstract: A general organocatalytic enantioselective synthesis of nitrocyclopropanes from bromonitromethane and a variety of cyclic and acyclic enones is described.

Key words: asymmetric catalysis, carbocycles, cyclisation, organocatalysis, nitrocyclopropane, tetrazole

Since their first synthesis in 1884 by William Henry Perkin,1 structures containing the cyclopropane motif have been of great interest within the organic chemistry community. They are widely distributed in a range of naturally occurring compounds2 and enzymes,3 inhibitors,4 and therapeutic agents.5 In addition, due to their small, rigid structure and strain-driven reactivity, they serve as versatile synthetic intermediates in a variety of reactions.6 As a result, their stereoselective preparation is a valuable goal and to date, many methods have been developed for this purpose.7

The presence of substituents on the cyclopropane ring affects the properties, both physical and chemical.1,8 Moreover, they enable further transformations such as functional group interconversions or couplings with other molecules.9

More specifically, nitro-substituted cyclopropanes, which are also present in natural products, like the peptidolactone hormaomycin10 or intermediates in natural product synthesis, such as the broad-spectrum antibiotic Trovafoxacin11 are of potential utility. Furthermore, nitro-substituted cyclopropanes may be converted into a wide range of functionalities,12 and are prepared by a variety of methods.13 However, these methods often have drawbacks such as tedious procedures, the need for many steps, and the separate and time-consuming preparation of the starting material. Furthermore, the yields and enantioselectivities are mostly moderate.14

Since the introduction of the pyrrolidinyl tetrazole derivative 1 in enantioselective organocatalysed reactions by Arvidsson,15 Yamamoto,16 and ourselves17 its use is now widely accepted.18 In recent studies in this area, after an extensive screening of different organocatalysts, we described an enantioselective nitrocyclopropanation process between cyclohex-2-enone (2) and bromonitromethane (3) in the presence of morpholine (4) and the tetrazole catalyst 1. This new reaction sets up three new stereogenic centres in a single operation yielding the product 5 in 80% yield and 77% enantioselectivity after 24 hours in dichloromethane (Scheme 1).19

However, when the five- and seven-membered-ring congeners were assessed in this reaction, while yields of the products were high (73% and 93%, respectively), the enantioselectivities were only moderate (35% and 40%). Furthermore, with the acyclic example, non-3-en-2-one (6) (Table 1), the yield was only moderate (45%), and diastereoselectivities (3 isomers, 4.6:1.3:1) and enantioselectivities (14% to 42%) were disappointing (Table 1, entry 1). Here, we report the evolution of these studies and the resulting development of a more general and practical enantioselective organocatalytic nitrocyclopropanation reaction.

Table 1 Results of Nitrocyclopropanation on the Non-3-en-2-one (6)a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Yield (%)</th>
<th>Time (h)</th>
<th>dr (a:b:c)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>45d</td>
<td>24</td>
<td>4.6:1:3:1</td>
<td>42, 14, 42</td>
</tr>
<tr>
<td>2</td>
<td>78</td>
<td>16</td>
<td>5.6:1:3:1</td>
<td>54, 34, 53</td>
</tr>
<tr>
<td>3</td>
<td>87</td>
<td>48</td>
<td>4.4:1:4:1</td>
<td>34, 16, 39</td>
</tr>
<tr>
<td>4</td>
<td>81e</td>
<td>16</td>
<td>5.4:1:2:1</td>
<td>63, 33, 57</td>
</tr>
<tr>
<td>5</td>
<td>47f</td>
<td>16</td>
<td>6.4:1:8:1</td>
<td>65, 31, 55</td>
</tr>
<tr>
<td>6</td>
<td>84g</td>
<td>12</td>
<td>5.0:1:4:1</td>
<td>70, 37, 61</td>
</tr>
</tbody>
</table>

a Conditions: 6 (0.5 mmol), 3 (1.0 mmol), 4 (1.5 mmol), I (15 mol%), CH2Cl2 (2 mL), r.t.
b Isolated yield.
c Determined by chiral GC.
d Conditions: 6 (0.5 mmol), 3 (0.5 mmol), 4 (0.5 mmol), I (15 mol%), CH2Cl2 (2 mL), r.t.
e Solvent: CHCl3 (2 mL).
f Conditions: 6 (0.5 mmol), 3 (1.0 mmol), 4 (1.5 mmol), I (15 mol%), Bu4NI (1.5 mol%), CHCl3 (2 mL), r.t.
g Conditions: 6 (0.5 mmol), 3 (1.0 mmol), 4 (1.5 mmol), I (15 mol%), NaI (1.5 mol%), CHCl3 (2 mL), r.t.

SYNTHESIS 2008, No. 8, pp 1269–1275
Advanced online publication: 18.03.2008
DOI: 10.1055/s-2008-1042944; Art ID: P14907SS
© Georg Thieme Verlag Stuttgart · New York
The tetrazole catalyst was investigated (Table 2). First, the cyclic examples optimised reaction conditions to alternative substrates. From this, the following conclusions could be drawn at the 12 hour time point. The reaction had stopped and, while 50% of the starting material remained, all the bromonitromethane was consumed. Moreover, the reaction mixture had also become acidic (pH ≤ 4).

Control experiments then revealed that, although there was no side-reaction between bromonitromethane (1), there was one between bromonitromethane (3) and the tetrazole catalyst 1, there was one between bromonitromethane (3) and morpholine (4). We speculated that this side-reaction was potentially the source of the problems, and therefore the equivalents of each compound were systematically increased. Consequently with two equivalents of bromonitromethane (3) and three of morpholine (4), a marked improvement was seen: the yield of 7 was close to double and both diastereomer and enantioselectivity had undergone significant improvement with a reaction time of only 16 hours (Table 1, entry 2). Increase of the reaction time to 48 hours led to only a slight improvement of yield, but interestingly, both the diastereomer- and enantioselectivity decreased (Table 1, entry 3). Closer examination of the reaction solvent revealed that chloroform proved to be the optimal solvent in terms of both yield and enantioselection (Table 1, entry 4). To enhance the reaction rate, Finkelstein-type activation of the bromonitromethane with iodide sources was examined. As expected, the reaction took place when tetrabutyrammonium iodide was added, but the yield dramatically decreased, while the enantioselectivity was retained (Table 1, entry 5). Furthermore, purification by column chromatography became more difficult, due to the formation of many by-products. Pleasingly, however the use of sodium iodide achieved a further improvement in yield and enantioselectivity. Indeed, the best result was obtained with only 1.5 mol% of added sodium iodide (Table 1, entry 6).

In order to determine the stereochemical outcome of this reaction, NOE experiments were re-examined so as to obtain a comparison with the previous conditions. It was most encouraging to see that they did indeed react with generally high enantioselectivities and complete diastereoselection. Indeed, the reaction with cyclohex-2-enone (2) now gave the product 5 in 87% yield and impressive 90% ee in just two hours compared to 77% ee in 24 hours with the previous conditions (Table 2, entry 1). Furthermore, the seven-membered congener (Table 2, entry 2) was formed in a similarly high yield (91%), but with notably higher enantioselectivity (70%) to the previously reported result. In fact, only the five-membered cyclopent-2-enone (Table 2, entry 3) gave a moderate enantioselectivity (48%), but retained the high yield (87%). Steric and electronic effects were next examined, using the six-membered-ring system as the benchmark. Pleasingly, even the sterically hindered substrates 3-methylcyclohex-2-enone (Table 2, entry 4) and also the 4,4-diphenylcyclohex-2-enone (Table 2, entry 5), were obtained with both good yields (74% and ~100%, respectively) and enantioselectivities (76% and 77%). However, a methoxy substituent in the 3-position of cyclohex-2-enone (Table 2, entry 6) gave no reaction after 48 hours and only starting material was recovered. It is postulated that this is due to electronic rather than steric reasons, as the methyl substituted example 10 works well. In this case the donation of electrons from the oxygen into the α,β-unsaturated system is probably deactivating enough to prohibit the initial 1,4-addition of bromonitromethane (3), and thus the final nitrocyclopropanation product formation. However, the optimised reaction conditions also have limitations: for example, methyl substitution in the 2- or 3-position on the cyclopent-2-enone dramatically decreased the speed of reaction and, as a result, also the enantioselectivity and yield (Table 2, entries 7 and 8). Interestingly, in the case of methyl substitution in the 3-position on the cyclopent-2-enone two diastereomers were isolated (Table 2, entry 8), whereas all other cyclic exam-
ples showed complete diastereoselection. Further trials to optimise these reactions with cyclopent-2-enone have so far been unsuccessful.

The nitrocyclopropanation reaction was then applied to acyclic systems (Table 3). It was pleasing to find that

Table 2: Results of Nitrocyclopropanation on the Cyclic Enones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
<th>Time (h)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>87 (80)</td>
<td>2</td>
<td>90 (77)</td>
</tr>
<tr>
<td>2</td>
<td>8</td>
<td>91 (93)</td>
<td>16</td>
<td>70 (40)</td>
</tr>
<tr>
<td>3</td>
<td>9</td>
<td>87 (73)</td>
<td>2</td>
<td>48 (35)</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>56 (74)</td>
<td>24</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>~100</td>
<td>8</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>12</td>
<td>no reaction in 48 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>13</td>
<td>11</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>8</td>
<td>14</td>
<td>16</td>
<td>24</td>
<td>34</td>
</tr>
</tbody>
</table>

Conditions: substrate (0.5 mmol), 3 (1.0 mmol), 4 (1.5 mmol), 1 (15 mol%), NaI (1.5 mol%), CHCl₃ (2 mL), r.t.

Isolated yield.

Determined by chiral GC.

Results from the previous publication.

A syringe pump was used to add bromonitromethane over the indicated time.

Total isolated yield.

Yield based on recovered starting material.

Two diastereomers: 14a and 14b were isolated in a dr of 2:1.

Table 3: Results of Nitrocyclopropanation on the Acyclic Enones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield (%)</th>
<th>dr (a:b:c)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>84 (5)</td>
<td>5:1.4:1</td>
<td>70, 37, 61</td>
</tr>
<tr>
<td>2</td>
<td>15</td>
<td>72 (4.6)</td>
<td>4.6:1:1</td>
<td>75, 41, 68</td>
</tr>
<tr>
<td>3</td>
<td>16</td>
<td>63 (5.9)</td>
<td>5.9:1.3:1</td>
<td>76, 31, 60</td>
</tr>
<tr>
<td>4</td>
<td>17</td>
<td>no reaction in 48 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>18</td>
<td>69 (6.9)</td>
<td>6.9:1.3:1</td>
<td>63, 41, 51</td>
</tr>
<tr>
<td>6</td>
<td>19</td>
<td>no reaction in 48 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>20</td>
<td>47 (1.6)</td>
<td>1.6:1</td>
<td>42, 29</td>
</tr>
</tbody>
</table>

Conditions: substrate (0.5 mmol), 3 (1.0 mmol), 4 (1.5 mmol), 1 (15 mol%), NaI (1.5 mol%), CHCl₃ (2 mL), 16 h, r.t.

Isolated yield.

Determined by chiral GC.

Reaction time was 10 h.

apart from the optimised example, non-3-en-2-one (6, Table 3, entry 1), the hept-3-en-2-one (Table 3, entry 2) and pent-3-en-2-one (Table 3, entry 3) also worked well and were obtained in good yields, retaining the good diastereo- and enantioselectivity.

However, in contrast to the cyclic enone with a β-methyl substituent, the linear 4-methylpent-3-en-2-one (Table 3, entry 4) gave no reaction in 48 hours and only starting material was recovered. If the branching is not directly at the double bond, good yields and enantioselectivities were
obtained (Table 3, entry 5). Similar to the cyclic example 12, methoxy substitution directly at the double bond (Table 3, entry 6) gave no reaction, again probably due to the electron-donating substituent, which deactivates the system to nucleophilic attack.

In addition, replacing the α-methyl with alternative groups was also studied. Interestingly, with more bulky groups only two diastereomers were isolated. It is thought that the third diastereomer is not formed because in these cases a unfavoured interaction with the nitro group takes place. However, in both cases (ethyl, and phenyl, Table 3, entries 7 and 8) a greater amount of side-reactions and by-product formation was observed, unfortunately leading to decreased yields and enantioselectivities.

In summary, a general enantioselective organocatalytic nitrocyclopropanation reaction process has been developed. The reaction is efficiently catalysed by the simple pyrrolidinyl tetrazole catalyst 1. Results with cyclic substrates are good to excellent and with linear examples, yields are high with slightly reduced enantio- and diastereoselectivities. Mechanistic studies and synthetic applications of this transformation are ongoing in our laboratory.

All reactions were carried out under argon. Petroleum ether (PE) refers to the 40–60 °C boiling point fraction of petroleum. Anhydrous CHCl3 was bought from Sigma-Aldrich. All other reagents and solvents to the 40–60 °C boiling point fraction of petroleum. Anhydrous CHCl3 was used as an internal standard. 13C NMR spectra were recorded on a Bruker DRX-400 or Bruker DRX-600 spectrometer. The residual protic solvent CHCl3 (0.2% v/v) was used as a reference signal. 13C NMR spectra were recorded on a Bruker DRX-400 or Bruker DRX-600 spectrometer. The residual protic solvent CHCl3 (0.2% v/v) was used as a reference signal.

Nitrocyclopropanation of Enones; General Procedure
To a stirred suspension of the enone starting material (0.5 mmol) and the pyrrolidinyl tetrazole catalyst (15 mol%) in CHCl3 (2 mL) were added 1 H NMR (400 MHz, CDCl3): δ = 1.46–1.58 (m, 1 H, CH2), 1.80–1.88 (m, 1 H, CH2), 1.93–2.02 (m, 1 H, CH2), 2.09–2.18 (m, 2 H, CH2), 2.28–2.35 (m, 1 H, CH2), 2.62–2.67 (m, 1 H, CH), 2.80 (dd, J = 9.6, 2.6 Hz, 1 H, CH), 4.66 (t, J = 3.1 Hz, 1 H, CH3NO2).

13C NMR (100 MHz, CDCl3): δ = 18.70 (CH3), 20.09 (CH2), 27.28 (CH), 35.66 (CH), 37.71 (CH2), 61.02 (CH3NO2), 201.57 (C=O).

HRMS-ESI: m/z calcd for C10H17NO3 + Na [M + Na]+: 222.1101; found: 222.1101.
1,1,3,5,5-Pentamethyldi-2-nitrocyclopropanetetrazole (8b)
Yield: 0.067 g (87%); colourless oil; mp 178 °C.

1H NMR (400 MHz, CDCl3): δ = 9.80–9.87 (m, 2 H, CH2), 8.67–8.69 (m, 2 H, CH2), 8.20–8.28 (m, 2 H, CH2), 7.90–7.92 (m, 2 H, CH2), 7.50–7.52 (m, 2 H, CH2).

13C NMR (100 MHz, CDCl3): δ = 138.61 (CH2), 137.20 (CH2), 136.48 (CH2), 135.20 (CH2), 133.39 (CH2), 129.92 (CH), 129.19 (CH2), 125.56 (CH2), 124.91 (CH).


1,1,3,5,5-Pentamethyldi-2-nitrocyclopropanetetrazole (8a)
Yield: 0.067 g (87%); colourless oil; mp 178 °C. The reaction is efficiently catalysed by the simple pyrrolidinyl tetrazole catalyst 1. Results with cyclic substrates are good to excellent and with linear examples, yields are high with slightly reduced enantio- and diastereoselectivities. Mechanistic studies and synthetic applications of this transformation are ongoing in our laboratory.

All reactions were carried out under argon. Petroleum ether (PE) refers to the 40–60 °C boiling point fraction of petroleum. Anhydrous CHCl3 was bought from Sigma-Aldrich. All other reagents and solvents were used as supplied. Flash column chromatography was carried out using Merck Kieselgel (230–400 mesh). 1H NMR spectra were recorded on a Bruker DRX-400 or Bruker DRX-600 spectrometer. The residual protic solvent CHCl3 (0.2% v/v) was used as an internal standard. 13C NMR spectra were recorded on the same spectrometers at 100 and 150 MHz, using central resonance of CDCl3 (δc = 77.0). Accurate mass data were obtained on Micromass Q-TOF by electrospray ionisation (ESI). Optical rotations were measured on a PerkinElmer 343 polarimeter at 25 °C; concentrations (c) are reported in g/100 mL. Melting points were measured on a Reichert hot stage apparatus, and are uncorrected. The enaniotopic excess (ee) of the products was determined by chiral stationary phase GC (Chiralpak G-TA column).

Nitrocyclopropanation of Enones; General Procedure
To a stirred suspension of the enone starting material (0.5 mmol) and the pyrrolidinyl tetrazole 1 (15 mol%) in CHCl3 (2 mL) were added NaI (1.5 mol%), morpholine (4:15 mol%) and bromonitromethane (3:10 mmol) at rt during the indicated time. The mixture was diluted with CH2Cl2 (10 mL) and washed with H2O (10 mL). The aqueous phase was extracted with CH2Cl2 (3 × 10 mL). The combined organic phases were dried (MgSO4), concentrated in vacuo, and the residue was purified by flash chromatography (Tables 2 and 3).

1R,6S,7R)-7-Nitroisobicyclo[4.1.0]heptan-2-one (5)
Yield: 0.067 g (87%); white solid; mp 70–71 °C; Rf = 0.48 (CH2Cl2); [α]D25 +53.5 (c = 0.4, CHCl3).

1H NMR (400 MHz, CDCl3): δ = 1.46–1.58 (m, 1 H, CH2), 1.80–1.88 (m, 1 H, CH2), 1.93–2.02 (m, 1 H, CH2), 2.09–2.18 (m, 2 H, CH2), 2.28–2.35 (m, 1 H, CH2), 2.62–2.67 (m, 1 H, CH), 2.80 (dd, J = 9.6, 2.6 Hz, 1 H, CH), 4.66 (t, J = 3.1 Hz, 1 H, CH3NO2).

13C NMR (100 MHz, CDCl3): δ = 18.70 (CH3), 20.09 (CH2), 27.28 (CH), 35.66 (CH), 37.71 (CH2), 61.02 (CH3NO2), 201.57 (C=O).

1H NMR (400 MHz, CDCl3): δ = 1.14–1.16 (m, 1 H, CH), 1.86–1.90 (m, 2 H, CH2), 2.02–2.11 (m, 1 H, CH2), 2.17–2.23 (m, 1 H, CH), 2.32–2.38 (m, 1 H, CH2), 2.88 (d, J = 3.2 Hz, 1 H, CH), 4.78 (d, J = 3.3 Hz, 1 H, CHNO2).

HRMS-ESI: m/z calcd for C6H9NO3 + Na [M + Na]+: 166.0474; found: 166.0482.

1-(2-Nitro-3-propylcyclopropyl)ethanone (15) (Mixture of 15a and 15b)

Yield: 0.052 g (61%); colourless oil; Rf = 0.76 (CH2Cl2)

1H NMR (400 MHz, CDCl3): δ is (inseparable mixture of isomers, minor isomer 15b starred): 0.88–0.94 (m, 3 H, CH3), 1.49–1.61 (m, 4 H, 2 × CH2), 1.92–2.00 (m, 1 H, CH*), 2.24–2.31 (m, 2 H, CH2CO), 2.49–2.54 (m, 1 H, CH), 3.01 (dd, J = 7.4, 3.5 Hz, 1 H, CH*), 3.17 (dd, J = 11.0, 3.5 Hz, 1 H, CH), 4.02 (dd, d, J = 8.3, 3.5 Hz, 1 H, CHNO2).


1-(2-Methyl-3-nitrocyclopropyl)ethanone (16) (Mixture of 16a and 16b)

Yield: 0.039 g (55%); yellow oil; Rf = 0.61 (CH2Cl2).

1H NMR (400 MHz, CDCl3): δ is (inseparable mixture of isomers, minor isomer 16b starred): 1.19 (m, J = 6.2 Hz, 3 H, CH3), 1.36–1.52 (m, 4 H, 2 × CH2), 2.57–2.64 (m, 1 H, CH), 2.69 (m, 3 H, CH2CO), 2.76–2.81 (m, 1 H, CH), 3.00 (dd, J = 8.3, 3.5 Hz, 1 H, CHNO2).

HRMS-ESI: m/z calcd for C6H12NO + Na [M + Na]+: 146.0437; found: 146.0438.
1-(2-Isopropyl-3-nitrocyclopropyl)ethanone (18c)
d (inseparable mixture of isomers, mixture 21a and 21b)
Yield: 0.037 g (47%); colourless oil;
HRMS-ESI: m/z calcd for C₈H₁₀NO₃: 194.0787; found: 194.0797.

1-(2-M ethyl-3-nitrocyclopropyl)propan-1-one (20) (Mixture of 20a and 20b)
Yield: 0.037 g (47%); colourless oil; Rₖ = 0.78 (CH₂Cl₂).
1H NMR (400 MHz, CDCl₃): δ (inseparable mixture of isomers, minor isomer 20b starred) = 1.05–1.25 (m, 3 H, CH₃), 1.17 (d, J = 6.7 Hz, 3 H, CH₃), 1.35 (d, J = 6.5 Hz, 3 H, CH₃),
1.99–2.04 (m, 1 H, CH*), 2.41–2.79 (m, 2 H, CH₃), 2.90–2.96 (m, 1 H, CH₃), 3.15 (dd, J = 10.9, 3.2 Hz, 1 H, CH, 4.60 (dd, J = 4.4, 3.3 Hz, 1 H, CHNO₂), 4.64 (dd, J = 8.7, 3.3 Hz, 1 H, CH₂NO₂).
13C NMR (100 MHz, CDCl₃): δ (inseparable mixture of isomers, minor isomer 20b starred) = 31.75 (CH₃), 33.44 (CH), 34.78 (CH), 42.08 (CH*), 42.89 (CH₃), 203.79 (C=O), 205.41 (C=O*).

HRMS-ESI: m/z calcd for C₈H₁₀NO₃ + Na [M + Na]+: 194.0877; found: 194.0797.

1-2-Methyl-3-nitrocyclopropyl)-l'-phenylmethane (21) (Mixture of 21a and 21b)
Yield: 0.043 g (42%); colourless oil; Rₖ = 0.73 (CH₂Cl₂).
1H NMR (400 MHz, CDCl₃): δ (inseparable mixture of isomers, minor isomer 21b starred) = 1.20 (d, J = 6.7 Hz, 3 H, CH₃), 1.46 (d, J = 6.6 Hz, 3 H, CH₃*), 2.18–2.27 (m, 1 H, CH*), 2.64–2.75 (m, 1 H, CH), 3.70 (dd, J = 6.9, 3.3 Hz, 1 H, CH*), 3.82 (dd, J = 11.3, 3.6 Hz, 1 H, CH), 4.82–4.86 (m, 1 H, CHNO₂ and 1 H, CH₂NO₂), 7.49–7.54 (m, 2 H Harm and 2 H* Harm), 7.61–7.65 (m, 1 H Harm and 1 H* Harm), 8.00–8.03 (m, 2 Harm and 2 H* Harm).
13C NMR (100 MHz, CDCl₃): δ = 9.06 (CH₃), 10.27 (CH*), 27.73 (CH*), 28.78 (CH), 33.44 (CH*), 34.78 (CH), 64.69 (CHNO₂), 66.56 (CHNO₂*), 128.32, 128.38, 128.89, 133.94, 134.00 (5 × CH Harm and 5 × CH* Harm*), 136.18 (Cq*), 136.74 (Cq), 192.52 (C=O), 194.2 (C=O*).

HRMS-ESI: m/z calcd for C₂₉H₂₇NO₂ + Na [M + Na]+: 228.0631; found: 228.0641.

Acknowledgment
We thank the Deutsche Forschungsgemeinschaft (V.W.), the Danish University of Pharmaceutical Sciences and the Danish Medical Research Council (H.M.H.), the EPSRC and Trinity College (D.A.L.), and Novartis (through a Research Fellowship to S.V.L.) for financial support. In addition, we thank V. Aureggi and Dr. G. Sedelmeier at Novartis Pharma AG, Werk Klybeck, Postfach, CH-4002 Basel, Switzerland, for a generous gift of (R)-5-pyrrolidin-2-yl-1H-tetrazole (1).

References
(1) de Meijere, A. Chem. Rev. 2003, 103, 931.

Synthesis 2008, No. 8, 1269–1275 © Thieme Stuttgart · New York
Enantioselective Nitrocyclopropanation Reaction

(20) The reaction between bromonitromethane (3) and morpholine (4) may lead to the formation of the product 22 (Figure 2), which is confirmed by 1H and 13C NMR spectroscopy. MS analysis was unsuccessful.

Figure 2 Product formed from the reaction of bromonitromethane (3) and morpholine (4).

(21) One recrystallisation gives material of ≥99% ee.