A General Organocatalytic Enantioselective Nitrocyclopropanation Reaction

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Received 21 December 2007

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

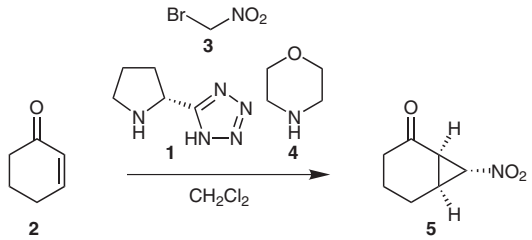
Key words: asymmetric catalysis, carbocycles, cyclisation, organocatalysis, nitrocyclopropane, tetrazole

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 compounds[2] and biologically active agents, for example, peptidomimetics,[3] enzyme 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 hormaomycin[10] or intermediates in natural product synthesis, such as the broad-spectrum antibiotic Trovafloxacin[11] 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 ourselves[17] 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]



Scheme 1 Enantioselective nitrocyclopropanation

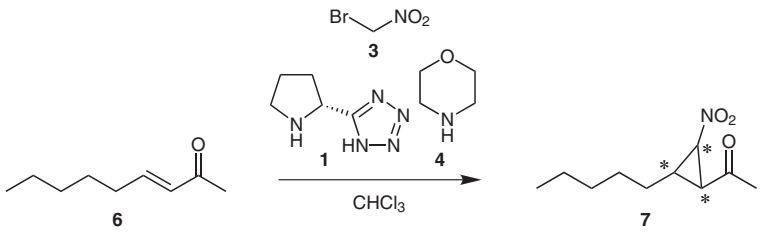
However, when the five- and seven-membered-ring congeners were assessed in this reaction, while yields of the products were high (73% and 93%, respectively), the enantioselectivities were only moderate (35% and 40%). Furthermore, with the acyclic example, non-3-en-2-one (**6**) (Table 1), the yield was 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]

Entry	Yield (%)[b]	Time (h)	dr (a:b:c)	ee (%)[c]
1	45[d]	24	4.6:1.3:1	42, 14, 42
2	78	16	5.6:1.3:1	54, 34, 53
3	87	48	4.4:1.4:1	34, 16, 39
4	81[e]	16	5.4:1.2:1	63, 33, 57
5	47[f]	16	6.4:1.8:1	65, 31, 55
6	84[g]	12	5.0:1.4:1	70, 37, 61

[a] Conditions: **6** (0.5 mmol), **3** (1.0 mmol), **4** (1.5 mmol), **1** (15 mol%), CH_2Cl_2 (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), **1** (15 mol%), CH_2Cl_2 (2 mL), r.t.
[e] Solvent: $CHCl_3$ (2 mL).
[f] Conditions: **6** (0.5 mmol), **3** (1.0 mmol), **4** (1.5 mmol), **1** (15 mol%), Bu_4NI (1.5 mol%), $CHCl_3$ (2 mL), r.t.
[g] Conditions: **6** (0.5 mmol), **3** (1.0 mmol), **4** (1.5 mmol), **1** (15 mol%), NaI (1.5 mol%), $CHCl_3$ (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



Scheme 2 Nitrocyclopropanation of non-3-en-2-one (**6**)

Firstly, in the search for a general nitrocyclopropanation procedure, the reaction of non-3-en-2-one (**6**) was carefully monitored (Scheme 2). 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 (**3**) and the tetrazole catalyst **1**, there was one between bromonitromethane (**3**) and morpholine (**4**).[20]

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 diastereo- and enantioselection 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 diastereo- 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 tetrabutylammonium 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 conducted on each single diastereomer of **7** (Figure 1), and it was interesting to see that the major diastereomer **7a** has the same relative stereochemistry as the cyclic example, cyclohex-2-enone.[19]

With such a dramatic improvement in the results for the acyclic non-3-en-2-one (**6**) example, application of these optimised reaction conditions to alternative substrates was investigated (Table 2). First, the cyclic examples

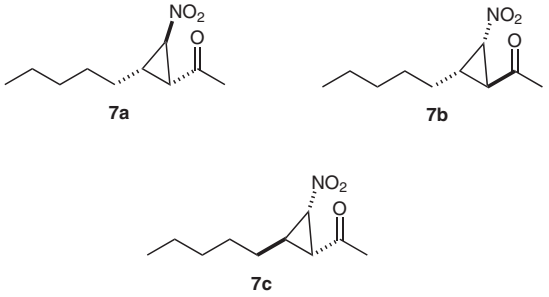
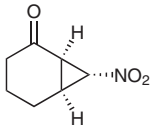
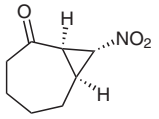
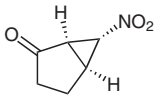
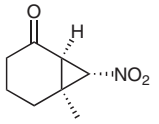
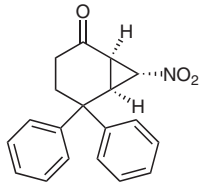
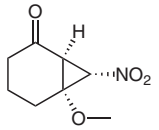
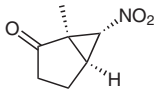
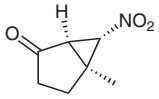


Figure 1 Stereochemical assignment by NOE experiments

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).[21] 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-

Table 2 Results of Nitrocyclopropanation on the Cyclic Enones[a]

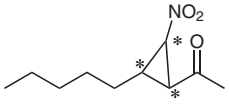
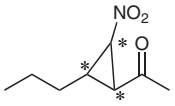
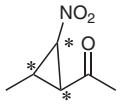
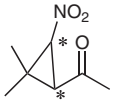
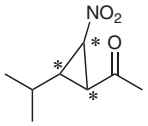
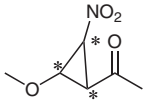
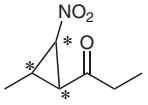
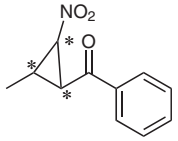
Entry	Product	Yield (%)[b]	Time (h)	ee (%)[c]
1	 **5**	87 (80)[d]	2	90 (77)[d]
2	 **8**	91[e] (93)[d]	16	70 (40)[d]
3	 **9**	87 (73)[d]	2	48 (35)[d]
4	 **10**	56[f] 74[g]	24	76
5	 **11**	~100	8	77
6	 **12**	no reaction in 48 h		
7	 **13**	11	24	14
8	 **14**	16[h] 8[h]	24 24	34 28

[a] Conditions: substrate (0.5 mmol), **3** (1.0 mmol), **4** (1.5 mmol), **1** (15 mol%), NaI (1.5 mol%), $CHCl_3$ (2 mL), r.t.
[b] Isolated yield.
[c] Determined by chiral GC.
[d] Results from the previous publication.[19]
[e] A syringe pump was used to add bromonitromethane over the indicated time.
[f] Total isolated yield.
[g] Yield based on recovered starting material.
[h] Two diastereomers: **14a** and **14b** were isolated in a dr of 2:1.

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 3 Results of Nitrocyclopropanation on the Acyclic Enones[a]

Entry	Product	Yield (%)[b]	dr (a:b:c)	ee (%)[c]
1	 **7**	84[d]	5:1.4:1	70, 37, 61
2	 **15**	72[d]	4.6:1:1	75, 41, 68
3	 **16**	63[d]	5.9:1.3:1	76, 31, 60
4	 **17**	no reaction in 48 h		
5	 **18**	69	6.9:1.3:1	63, 41, 51
6	 **19**	no reaction in 48 h		
7	 **20**	47	4.6:1	63, 37
8	 **21**	42	1.6:1	42, 29

[a] Conditions: substrate (0.5 mmol), **3** (1.0 mmol), **4** (1.5 mmol), **1** (15 mol%), NaI (1.5 mol%), $CHCl_3$ (2 mL), 16 h, r.t.
[b] Isolated yield.
[c] Determined by chiral GC.
[d] 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 diastereoselectivites. 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 $CHCl_3$ 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). ^{1}H NMR spectra were recorded on a Bruker DRX-400 or Bruker DRX-600 spectrometer. The residual protic solvent $CHCl_3$ (δ_H = 7.26) in $CDCl_3$ was used as an internal standard. ^{13}C NMR spectra were recorded on the same spectrometers at 100 and 150 MHz, using central resonance of $CDCl_3$ (δ_C = 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 enantiomeric excess (ee) of the products was determined by chiral stationary phase GC (Chiraldex G-TA column).

Nitrocyclopropanation of Enones; General Procedure

To a stirred suspension of the enone starting material (0.5 mmol) and pyrrolidinyl tetrazole **1** (15 mol%) in $CHCl_3$ (2 mL) were added NaI (1.5 mol%), morpholine (**4**; 1.5 mmol) and bromonitromethane (**3**; 1.0 mmol) at r.t. during the indicated time. The mixture was diluted with CH_2Cl_2 (10 mL) and washed with H_2O (10 mL). The aqueous phase was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic phases were dried ($MgSO_4$), concentrated in vacuo, and the residue was purified by flash chromatography (Tables 2 and 3).

(1*R*,6*S*,7*R*)-7-Nitrobicyclo[4.1.0]heptan-2-one (5)

Yield: 0.067 g (87%); white solid; mp 70–71 °C; R_f = 0.48 (CH_2Cl_2); $[\alpha]_D^{25}$ –53.5 (*c* = 0.4, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.46–1.58 (m, 1 H, CH_{2a}), 1.80–1.88 (m, 1 H, CH_{2b}), 1.93–2.02 (m, 1 H, CH_{2c}), 2.09–2.18 (m, 2 H, $CH_{2d,}$ CH_{2e}), 2.28–2.35 (m, 1 H, CH_{2f}), 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, $CHNO_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 18.70 (CH_2), 20.09 (CH_2), 27.28 (CH), 35.66 (CH), 37.71 (CH_2), 61.02 ($CHNO_2$), 201.57 (C=O).

HRMS-ESI: *m*/*z* calcd for $C_7H_9NO_3$ + Na $[M + Na]^+$: 178.0474; found: 178.0479.

1-[(1*S*,2*S*,3*R*)-2-Nitro-3-pentylcyclopropyl]ethanone (7a) (Major Diastereomer)

Yield: 0.056 g (57%); colourless oil; R_f = 0.68 (CH_2Cl_2); $[\alpha]_D^{25}$ +42.3 (*c* = 1, $CHCl_3$).

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.85–0.87 (m, 3 H, CH_3), 1.21–1.44 (m, 7 H, 3 × CH_2, CH_{2a}), 1.53–1.58 (m, 1 H, CH_{2b}), 2.33 (s, 3 H, CH_3CO), 2.40–2.45 (m, 1 H, CH), 3.16 (dd, *J* = 11.0, 3.5 Hz, 1 H, CH), 4.60 (t, *J* = 3.9 Hz, 1 H, $CHNO_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.83 (CH_3), 22.31 (CH_2), 23.71 (CH_2), 28.48 (CH_2), 31.07 (CH_2), 31.61 (CH_3), 34.29 (CH), 36.97 (CH), 64.37 ($CHNO_2$), 200.90 (C=O).

HRMS-ESI: *m*/*z* calcd for $C_{10}H_{17}NO_3$ + Na $[M + Na]^+$: 222.1100; found: 222.1101.

1-[(1*S*,2*S*,3*S*)-2-Nitro-3-pentylcyclopropyl]ethanone (7b) (1st Minor Diastereomer)

Yield: 0.016 g (16%); colourless oil; R_f = 0.64 (CH_2Cl_2); $[\alpha]_D^{25}$ –25.0 (*c* = 0.15, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.86–0.89 (m, 3 H, CH_3), 1.27–1.47 (m, 6 H, 3 × CH_2), 1.54–1.74 (m, 2 H, CH_2), 1.91–1.99 (m, 1 H, CH), 2.53 (s, 3 H, CH_3CO), 3.01 (dd, *J* = 7.0, 3.3 Hz, 1 H, CH), 4.66 (dd, *J* = 8.5, 3.5 Hz, 1 H, $CHNO_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.86 (CH_3), 22.34 (CH_2), 23.72 (CH_2), 24.95 (CH_2), 28.28 (CH_2), 31.10 (CH_3), 33.24 (CH), 36.10 (CH), 64.37 ($CHNO_2$), 200.90 (C=O).

HRMS-ESI: *m*/*z* calcd for $C_{10}H_{17}NO_3$ + Na $[M + Na]^+$: 222.1100; found: 222.1108.

1-[(1*R*,2*S*,3*R*)-2-Nitro-3-pentylcyclopropyl]ethanone (7c) (2nd Minor Diastereomer)

Yield: 0.011 g (11%); colourless oil; R_f = 0.61 (CH_2Cl_2); $[\alpha]_D^{25}$ –10.0 (*c* = 0.2, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.90 (t, *J* = 7.1 Hz, 3 H, CH_3), 1.23–1.33 (m, 4 H, 2 × CH_2), 1.38–1.47 (m, 4 H, 2 × CH_2), 2.25–2.30 (m, 1 H, CH), 2.29 (s, 3 H, CH_3CO), 2.48–2.50 (m, 1 H, CH), 4.24 (q, *J* = 4.2 Hz, 1 H, $CHNO_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.88 (CH_3), 22.41 (CH_2), 27.74 (CH_2), 28.47 (CH_3), 30.06 (CH_2), 30.64 (CH), 31.08 (CH_2), 37.91 (CH), 65.51 ($CHNO_2$), 199.12 (C=O).

HRMS-ESI: *m*/*z* calcd for $C_{10}H_{17}NO_3$ + Na $[M + Na]^+$: 222.1100; found: 222.1109.

(1*R*,7*S*,8*R*)-8-Nitrobicyclo[5.1.0]octan-2-one (8)

Yield: 0.077 g (91%); colourless oil; R_f = 0.62 (CH_2Cl_2); $[\alpha]_D^{25}$ –16.0 (*c* = 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.29–1.75 (m, 5 H, 2 CH_2, CH_{2a}), 2.15–2.23 (m, 1 H, CH_{2b}), 2.37–2.48 (m, 2 H, CH, CH_{2c}), 2.56–2.68 (m, 1 H, CH_{2d}), 3.11 (dd, *J* = 12.1, 3.7 Hz, 1 H, CH), 4.62 (t, *J* = 3.9 Hz, 1 H, $CHNO_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.42 (CH_2), 25.57 (CH_2), 26.96 (CH_2), 27.29 (CH), 39.86 (CH), 43.12 (CH_2), 62.91 ($CHNO_2$), 203.24 (C=O).

HRMS-ESI: *m*/*z* calcd for $C_8H_{11}NO_3$ + Na $[M + Na]^+$: 192.0631; found: 192.0640.

(1*R*,5*S*,6*R*)-6-Nitrobicyclo[3.1.0]hexan-2-one (9)

Yield: 0.062 g (87%); light yellow solid; mp 62 °C; R_f = 0.50 (CH_2Cl_2); $[\alpha]_D^{25}$ +6.4 (*c* = 0.5, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.91–2.01 (m, 1 H, CH_{2a}), 2.16–2.36 (m, 3 H, CH_{2b}, CH_2), 2.77 (d, *J* = 6.7 Hz, 1 H, CH), 2.94–2.97 (m, 1 H, CH), 4.40 (t, *J* = 1.9 Hz, 1 H, $CHNO_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.48 (CH_2), 31.29 (CH), 32.93 (CH_2), 38.01 (CH), 62.34 ($CHNO_2$), 207.99 (C=O).

HRMS-ESI: *m*/*z* calcd for $C_6H_7NO_3$ + Na $[M + Na]^+$: 164.0318; found: 164.0323.

(1*R*,6*S*,7*R*)-6-Methyl-7-nitrobicyclo[4.1.0]heptan-2-one (10)
Yield: 0.048 g (56%); yield based on recovered starting material: 0.062 g (74%); colourless solid; mp 39 °C; R_f = 0.39 (CH_2Cl_2); $[\alpha]_D^{25}$ +43.5 (*c* = 0.7, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.41 (s, 3 H, CH_3), 1.49–1.61 (m, 1 H, CH_{2a}), 1.78–1.90 (m, 2 H, CH_{2b}, CH_{2c}), 2.02–2.11 (m, 1 H, CH_{2d}), 2.17–2.23 (m, 1 H, CH_{2e}), 2.32–2.38 (m, 1 H, CH_{2f}), 2.88 (d, *J* = 3.2 Hz, 1 H, CH), 4.78 (d, *J* = 3.3 Hz, 1 H, $CHNO_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.86 (CH_2), 17.91 (CH_3), 28.76 (CH_2), 32.95 (Cq), 36.75 (CH_2), 40.79 (CH), 65.79 ($CHNO_2$), 202.36 (C=O).

HRMS-ESI: *m*/*z* calcd for $C_8H_{11}NO_3$ + Na $[M + Na]^+$: 192.0631; found: 192.0626.

(1*R*,6*S*,7*R*)-7-Nitro-5,5-diphenylbicyclo[4.1.0]heptan-2-one (11)
Yield: 0.153 g (quant); white solid; mp 65–71 °C; R_f = 0.50 (CH_2Cl_2); $[\alpha]_D^{25}$ –223.6 (*c* = 0.7, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.90–2.01 (m, 1 H, CH_{2a}), 2.29–2.36 (m, 3 H, CH_{2b}, CH_2), 3.22 (dd, *J* = 9.4, 2.9 Hz, 1 H, CH), 3.29 (dd, *J* = 9.4, 3.2 Hz, 1 H, CH), 4.81 (t, *J* = 3.1 Hz, 1 H, $CHNO_2$), 7.24–7.29 (m, 6 H_{arom}), 7.31–7.37 (m, 4 H_{arom}).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.04 (CH_2), 33.96 (CH_2), 36.03 (CH), 37.64 (CH), 43.56 (Cq), 60.29 ($CHNO_2$), 126.48, 127.33, 128.88, 128.92 (10 × CH_{arom}), 144.42 (Cq_{arom}), 145.76 (Cq_{arom}), 200.28 (C=O).

HRMS-ESI: *m*/*z* calcd for $C_{19}H_{17}NO$ + Na $[M + Na]^+$: 330.1100; found: 330.1085.

(1*R*,5*S*,6*R*)-1-Methyl-6-nitrobicyclo[3.1.0]hexan-2-one (13)
Yield: 0.009 g (11%); yellow oil; R_f = 0.64 (CH_2Cl_2); $[\alpha]_D^{25}$ –6.1 (*c* = 0.6, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (s, 3 H, CH_3), 1.99–2.10 (m, 1 H, CH_{2a}), 2.13–2.31 (m, 3 H, CH_{2b}, CH_2), 3.00–3.01 (m, 1 H, CH), 4.32 (d, *J* = 2.2 Hz, 1 H, $CHNO_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 7.55 (CH_3), 20.92 (CH_2), 31.93 (CH_2), 33.88 (CH), 41.62 (Cq), 65.99 ($CHNO_2$), 209.65 (C=O).

HRMS-ESI: *m*/*z* calcd for $C_7H_9NO_3$ + Na $[M + Na]^+$: 178.0474; found: 178.0482.

5-Methyl-6-nitrobicyclo[3.1.0]hexan-2-one (14a) (Major Diastereomer)
Yield: 0.012 g (16%); light yellow oil; R_f = 0.42 (CH_2Cl_2); $[\alpha]_D^{25}$ –1.6 (*c* = 0.4, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.52 (s, 3 H, CH_3), 1.98–2.39 (m, 4 H, 2 × CH_2), 2.88 (br, 1 H, CH), 4.44 (d, *J* = 1.6 Hz, 1 H, $CHNO_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.15 (CH_3), 30.23 (CH_2), 33.58 (CH_2), 37.56 (Cq), 41.80 (CH), 67.05 ($CHNO_2$), 207.53 (C=O).

HRMS-ESI: *m*/*z* calcd for $C_7H_9NO_3$ + Na $[M + Na]^+$: 178.0474; found: 178.0477.

5-Methyl-6-nitrobicyclo[3.1.0]hexan-2-one (14b) (Minor Diastereomer)
Yield: 0.006 g (8%); light yellow oil; R_f = 0.35 (CH_2Cl_2); $[\alpha]_D^{25}$ –93.0 (*c* = 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.50 (s, 3 H, CH_3), 2.21–2.25 (m, 2 H, CH_2), 2.37–2.53 (m, 3 H, CH, CH_2), 4.55 (d, *J* = 8.4 Hz, 1 H, $CHNO_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.76 (CH_3), 26.29 (CH_2), 38.44 (CH_2), 42.02 (Cq), 43.30 (CH), 72.74 ($CHNO_2$), 208.22 (C=O).

HRMS-ESI: *m*/*z* calcd for $C_7H_9NO_3$ + Na $[M + Na]^+$: 178.0474; found: 178.0474.

1-(2-Nitro-3-propylcyclopropyl)ethanone (15) (Mixture of 15a and 15b)
Yield: 0.052 g (61%); colourless oil; R_f = 0.76 (CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$): δ (inseparable mixture of isomers, minor isomer **15b** starred) = 0.88–0.94 (m, 3 H, CH_3 and 3 H, CH_3*), 1.24–1.58 (m, 4 H, 2 × CH_2 and 4 H, 2 × CH_2*), 1.92–2.00 (m, 1 H, CH*), 2.34 (s, 3 H, CH_3CO), 2.35 (s, 3 H, CH_3*CO), 2.40–2.50 (m, 1 H, CH), 3.01 (dd, *J* = 7.1, 3.5 Hz, 1 H, CH*), 3.16 (dd, *J* = 11.0, 3.4 Hz, 1 H, CH), 4.61 (dd, *J* = 4.8, 3.3 Hz, 1 H, $CHNO_2$), 4.66 (dd, *J* = 8.6, 3.4 Hz, 1 H, CH*NO_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ (inseparable mixture of isomers, minor isomer **15b** starred) = 13.41 (CH_3), 13.44 (CH_3*), 21.33 (CH_2*), 22.03 (CH_2), 25.69 (CH_2), 26.92 (CH_2*), 30.97 (CH_3*), 31.62 (CH_3), 32.98 (CH*), 34.03 (CH), 36.03 (CH*), 36.89 (CH), 64.38 ($CHNO_2$), 65.80 (CH*NO_2), 200.93 (C=O), 202.55 (C=O*).

HRMS-ESI: *m*/*z* calcd for $C_8H_{13}NO_3$ + Na $[M + Na]^+$: 194.0787; found: 194.0793.

1-(2-Nitro-3-propylcyclopropyl)ethanone (15c)
Yield: 0.010 g (11%); colourless oil; R_f = 0.66 (CH_2Cl_2); $[\alpha]_D^{25}$ –8.0 (*c* = 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 (t, *J* = 7.2 Hz, 3 H, CH_3), 1.36–1.52 (m, 4 H, 2 × CH_2), 2.23–2.29 (m, 1 H, CH), 2.29 (s, 3 H, CH_3CO), 2.54–2.61 (m, 1 H, CH), 4.20 (dd, *J* = 8.4, 4.8 Hz, 1 H, $CHNO_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.42 (CH_3), 21.34 (CH_2), 28.22 (CH), 30.64 (CH_3), 32.04 (CH_2), 37.84 (CH), 65.50 ($CHNO_2$), 199.14 (C=O).

HRMS-ESI: *m*/*z* calcd for $C_8H_{13}NO_3$ $[M + Na]^+$ + Na: 194.0787; found: 194.0791.

1-(2-Methyl-3-nitrocyclopropyl)ethanone (16) (Mixture of 16a and 16b)
Yield: 0.039 g (55%); colourless oil; R_f = 0.61 (CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ (inseparable mixture of isomers, minor isomer **16b** starred) = 1.19 (d, *J* = 6.2 Hz, 3 H, CH_3), 1.36 (d, *J* = 6.6 Hz, 3 H, CH_3*), 1.98–2.05 (m, 1 H, CH*), 2.34 (s, 3 H, CH_3CO), 2.36 (s, 3 H, CH_3*CO), 2.47–2.54 (m, 1 H, CH), 2.99 (dd, *J* = 7.8, 3.3 Hz, 1 H, CH*), 3.17 (dd, *J* = 11.0, 3.6 Hz, 1 H, CH), 4.58 (dd, *J* = 4.3, 3.8 Hz, 1 H, $CHNO_2$), 4.64 (dd, *J* = 8.8, 3.3 Hz, 1 H, CH*NO_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ (inseparable mixture of isomers, minor isomer **16b** starred) = 9.18 (CH_3), 10.08 (CH_3*), 27.34 (CH*), 28.29 (CH), 31.19 (CH_3*), 31.67 (CH_3), 36.81 (CH*), 37.03 (CH), 64.92 ($CHNO_2$), 66.25 (CH*NO_2), 200.85 (C=O), 202.50 (C=O*).

HRMS-ESI: *m*/*z* calcd for $C_6H_9NO_3$ + Na $[M + Na]^+$: 166.0474; found: 166.0483.

1-(2-Methyl-3-nitrocyclopropyl)ethanone (16c)
Yield: 0.006 g (8%); colourless oil; R_f = 0.46 (CH_2Cl_2); $[\alpha]_D^{25}$ –31.0 (*c* = 0.15, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (d, *J* = 6.3 Hz, 3 H, CH_3), 2.24–2.31 (m, 1 H, CH), 2.29 (s, 3 H, CH_3CO), 2.56–2.64 (m, 1 H, CH), 4.23 (dd, *J* = 8.4, 4.3 Hz, 1 H, $CHNO_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.18 (CH_3), 22.93 (CH), 30.86 (CH_3), 38.92 (CH), 66.30 ($CHNO_2$), 199.08 (C=O).

HRMS-ESI: *m*/*z* calcd for $C_6H_9NO_3$ + Na $[M + Na]^+$: 166.0474; found: 166.0479.

1-(2-Isopropyl-3-nitrocyclopropyl)ethanone (18) (Mixture of 18a and 18b)
Yield: 0.050 g (59%); colourless oil; R_f = 0.68 (CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ (inseparable mixture of isomers, minor isomer **18b** starred) = 0.88 (d, *J* = 6.5 Hz, 3 H, CH_3), 0.94 (d, *J* = 6.1 Hz, 3 H, CH_3*), 1.06 (d, *J* = 6.5 Hz, 3 H, CH_3), 1.11 (d, *J* = 6.6 Hz, 3 H, CH_3*), 1.58–1.88 [m, 1 H, CH* and 1 H, $CH(CH_3)_2$ and 1 H, CH*$(CH_3)_2$], 2.19–2.26 (m, 1 H, CH), 2.35 (s, 3 H, CH_3*CO), 2.37 (s, 3 H, CH_3CO), 3.03 (dd, *J* = 6.8, 3.2 Hz, 1 H, CH*), 3.18 (dd, *J* = 11.0, 3.3 Hz, 1 H, CH), 4.65 (dd, *J* = 4.8, 3.3 Hz, 1 H, $CHNO_2$), 4.70 (dd, *J* = 8.5, 3.3 Hz, 1 H, CH*NO_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ (inseparable mixture of isomers, minor isomer **18b** starred) = 21.29 (CH_3*), 21.71 (CH_3), 21.86 (CH_3), 22.40 (CH_3*), 23.99 [*C*H$(CH_3)_2$], 25.67 [*C*H*$(CH_3)_2$], 30.92 (CH_3), 31.75 (CH_3), 35.86 (CH*), 37.35 (CH), 40.73 (CH*), 42.08 (CH), 64.19 ($CHNO_2$), 65.99 (CH*NO_2), 200.95 (C=O), 202.44 (C=O*).

HRMS-ESI: *m*/*z* calcd for $C_8H_{10}NO_3$ + Na [M + Na]$^+$: 194.0787; found: 194.0794.

1-(2-Isopropyl-3-nitrocyclopropyl)ethanone (18c)
Yield: 0.009 g (10%); colourless oil; R_f = 0.53 (CH_2Cl_2); $[\alpha]_D^{25}$ –31.0 (*c* = 0.1, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.01 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.05 (d, *J* = 7.1 Hz, 3 H, CH_3), 1.30–1.41 [m, 1 H, $CH(CH_3)_2$], 2.28–2.33 (m, 1 H, CH), 2.30 (s, 3 H, CH_3CO), 2.41–2.47 (m, 1 H, CH), 4.28 (dd, *J* = 8.4, 4.9 Hz, 1 H, $CHNO_2$).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.06 (CH_3), 21.27 (CH_3), 29.85 [*C*H$(CH_3)_2$], 30.99 (CH_3), 36.02 (CH), 37.25 (CH), 65.01 ($CHNO_2$), 199.58 (C=O).

HRMS-ESI: *m*/*z* calcd for $C_8H_{10}NO_3$ + Na [M + Na]$^+$: 194.0787; found: 194.0797.

1-(2-Me thyl-3-nitrocyclopropyl)propan-1-one (20) (Mixture of 20a and 20b)
Yield: 0.037 g (47%); colourless oil; R_f = 0.78 (CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ (inseparable mixture of isomers, minor isomer **20b** starred) = 1.05–1.25 (m, 3 H, CH_3 and 3 H, CH_3*), 1.17 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.35 (d, *J* = 6.5 Hz, 3 H, CH_3*), 1.99–2.04 (m, 1 H, CH*), 2.41–2.79 (m, 2 H, CH_2 and 2 H, CH_2* and 1 H, CH), 2.90–2.96 (m, 1 H, CH*), 3.15 (dd, *J* = 10.9, 3.2 Hz, 1 H, CH), 4.60 (dd, *J* = 4.4, 3.3 Hz, 1 H, $CHNO_2$), 4.64 (dd, *J* = 8.7, 3.3 Hz, 1 H, CH*NO_2).

^{13}C NMR (100 MHz, $CDCl_3$): δ (inseparable mixture of isomers, minor isomer **20b** starred) = 9.32 (CH_3), 10.11 (CH_3*), 27.23 (CH_3*), 28.28 (CH_3), 36.10 (CH*), 36.41 (CH), 36.46 (CH*), 36.66 (CH), 37.57 (CH_2*), 37.86 (CH_2), 64.84 ($CHNO_2$), 66.17 (CH*NO_2), 203.79 (C=O), 205.41 (C=O*).

HRMS-ESI: *m*/*z* calcd for $C_7H_{11}NO_3$ + Na [M + Na]$^+$: 180.0631; found: 180.0631.

1-(2-Methyl-3-nitrocyclopropyl)-1′phenylmethanone (21) (Mixture of 21a and 21b)
Yield: 0.043 g (42%); colourless oil; R_f = 0.73 (CH_2Cl_2).

^{1}H NMR (400 MHz, $CDCl_3$): δ (inseparable mixture of isomers, minor isomer **21b** starred) = 1.20 (d, *J* = 6.7 Hz, 3 H, CH_3), 1.46 (d, *J* = 6.6 Hz, 3 H, CH_3*), 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, $CHNO_2$ and 1 H, CH*NO_2), 7.49–7.54 (m, 2 H_{arom} and 2 H_{arom}*), 7.61–7.65 (m, 1 H_{arom} and 1 H_{arom}*), 8.00–8.03 (m, 2 H_{arom} and 2 H_{arom}*).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 9.06 (CH_3), 10.27 (CH_3*), 27.73 (CH*), 28.78 (CH), 33.44 (CH*), 34.78 (CH), 64.69 ($CHNO_2$), 66.56 ($CHNO_2$*), 128.32, 128.38, 128.89, 133.94, 134.00 (5 × CH_{arom} and 5 × CH_{arom}*), 136.18 (Cq*), 136.74 (Cq), 192.52 (C=O), 194.2 (C=O*).

HRMS-ESI: *m*/*z* calcd for $C_{11}H_{11}NO_3$ + 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-1*H*-tetrazole (**1**).

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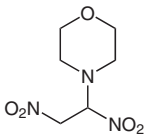
(20) The reaction between bromonitromethane (**3**) and morpholine (**4**) may lead to the formation of the product **22** (Figure 2), which is confirmed by ^{1}H and ^{13}C NMR spectroscopy. MS analysis was unsuccessful.



22

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

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