DOI: 10.1002/adsc.201200120

Control of Six Contiguous Stereocenters in an Asymmetric Organocatalytic One-Pot Michael/Michael/Aldol Addition Sequence

Dieter Enders,[a,*] Gregor Urbanietz,[a] Elisa Cassens-Sasse,[a] Sebastian Keeß,[a] and Gerhard Raabe[a]

[a] Institute of Organic Chemistry, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany
Fax: (+49)-241-809-2127; e-mail: enders@rwth-aachen.de

Received: February 14, 2012; Revised: April 3, 2012; Published online: ■■ ■■, 0000

Dedicated to Professor Hans-Joachim Gais on the occasion of his 70th birthday

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/adsc.201200120.

Abstract: The asymmetric organocatalytic one-pot synthesis of polyfunctionalized cyclohexanes is described. Starting from β-keto esters, nitroalkenes and α,β-unstaturated aldehydes and employing a bifunctional norephedrine-based thiourea catalyst, six contiguous stereocenters including one quarternary center are generated. The one-pot protocol follows a Michael/Michael/aldol addition sequence and affords the highly substituted cyclohexanes in moderate to very good yields (22–70%), diastereomeric ratios of $dr > 95:5$ and excellent enantioselectivities of 91–99% *ee*.

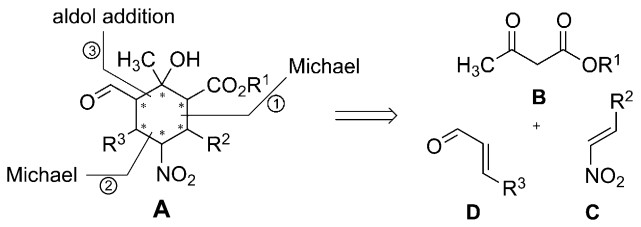
Keywords: asymmetric synthesis; cyclohexanes; one-pot reaction; organocatalysis; thioureas

Introduction

The rapid development of organocatalysis has opened new, efficient and elegant routes for the asymmetric synthesis of chiral building blocks, natural products and biologically active compounds in general.[1] When it comes to the construction of complex organic molecules bearing multiple stereocenters, the subfield of organocatalytic domino/cascade reactions seems to be ideal for this purpose and has been intensively investigated in recent years.[2] Besides the often used enamine/iminium activation modes *via* Lewis base catalysis, hydrogen-bonding catalysis employing various enantiopure thiourea catalysts is another elegant option.[3] In this context, the application of organocatalytic domino reactions in the asymmetric synthesis of polysubstituted carbocycles, such as cyclohexanes, has attracted a great deal of attention.[4]

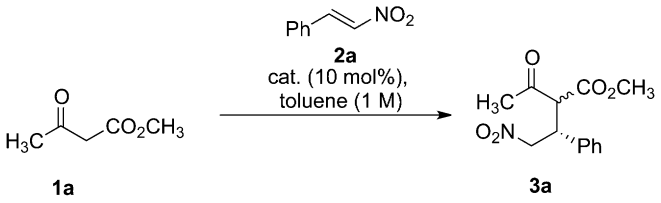
Results and Discussion

Herein we report on the asymmetric organocatalytic one-pot synthesis of polyfunctionalized cyclohexanes of type **A** bearing six contiguous stereocenters and four different synthetically important aldehyde, alcohol, ester and nitro groups. As is depicted in Scheme 1 the retrosynthetic analysis leads to three simple substrates, namely the β-keto esters **B**, the nitroalkenes **C** and the α,β-unsaturated aldehydes **D**. Mechanistically the new protocol consists of a first thiourea-catalyzed Michael addition of the β-keto esters to the nitroalkenes. The resulting intermediate γ-nitro keto esters then serve as the donor in a regioselective nitro-Michael addition to the α,β-unsaturated aldehydes. Subsequent cyclization *via* an intramolecular aldol addition of the aldehyde to the methyl ketone function forms the desired cyclohexanecarbal-

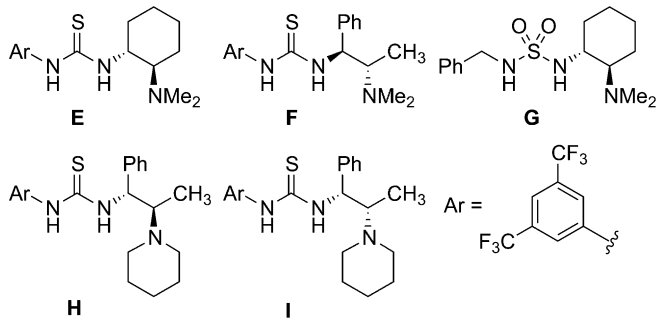


Scheme 1. One-pot asymmetric synthesis of polysubstituted cyclohexanes *via* an organocatalytic Michael/Michael/aldol addition sequence – retrosynthetic analysis.

Table 1. Catalyst screening for the Michael addition of methyl 3-oxobutanoate **1a** to nitrostyrene **2a** to yield **3a**.



cat.:



Entry[a]	Catalyst	Time [h]	Yield [%][b]	*ee* [%][c]
1	**E**	0.5	91	89[d]
2	**F**	16	96	91[d]
3	**G**	24	35	0
4	**H**	72	69	80[d]
5	**I**	24	65	97

[a] The reactions were performed on a 0.4–1.0 mmol scale at room temperature.
[b] Yield of isolated product **3a** as a *ca.* 1:1 mixture of epimers.
[c] Determined by HPLC analysis on a chiral stationary phase.
[d] The opposite enantiomer *ent*-**3a** was obtained.

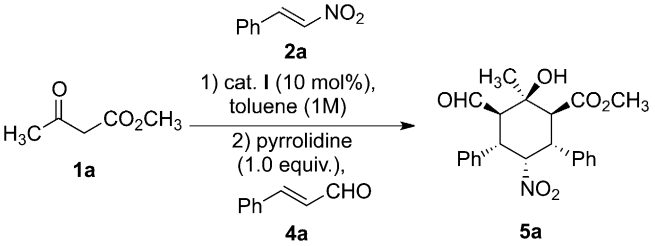
dehydes in a tandem manner through a substrate-controlled second cycle with pyrrolidine as the catalyst in order to prevent mismatched pairs and to generate four of the six stereogenic centers in the final operation. The challenge of designing such an efficient strategy mainly depends on the nucleophilicity and selectivity of the γ-nitro keto ester intermediate to react with the α,β-unsaturated aldehydes in a regioselective and stereoselective manner.

To guarantee that the first Michael addition proceeds with high diastereo- and enantioselectivity, we started our studies of the Michael/Michael/aldol reaction sequence by screening the organocatalysts **E–I** for the first Michael reaction of nitrostyrene (**2a**) with 1 equivalent of methyl 3-oxobutanoate (**1a**) (Table 1). The intermediate γ-nitro keto ester **3a** was obtained in moderate to excellent yields (35–96%) and good to excellent enantioselectivities (80–97% *ee*). It turned out that only thiourea-based catalysts (Table 1, **E**, **F**, **H**, **I**) are suitable to perform the conjugate addition of ß-keto esters and nitroalkenes.[5] The sulfuric acid diamide-derived catalyst **G** gave only a low yield of 35% and no enantiomeric excess could be detected (Table 1, entry 3). Readily accessible norpseudoephedrine (Table 1, entry 2) and norephedrine (Table 1, entry 5) derived catalysts **H** and **I**, which were developed recently in our group,[6b] have been identified as efficient bifunctional organocatalysts in asymmetric Michael reactions of **1a** and **2a**. With these thiourea organocatalysts the best enantioselectivities could be achieved, with the additional option to synthesize both enantiomers of **5** at will.

With a suitable catalyst in hand, we then tested if the γ-nitro keto ester **3a** can act as an intermediate to react with cinnamaldehyde (**4a**) in a regioselective and stereoselective tandem manner to form the cyclohexane **5a** with six contiguous stereocenters (Table 2). To find the best reaction conditions for the domino Michael/aldol addition reaction sequence we screened solvents, the temperature and the catalyst loading. As the base we used 1 equivalent of pyrrolidine for the iminium/enamine/activation of **4a** to circumvent the formation of mismatched pairs which could arise when chiral amines are employed.

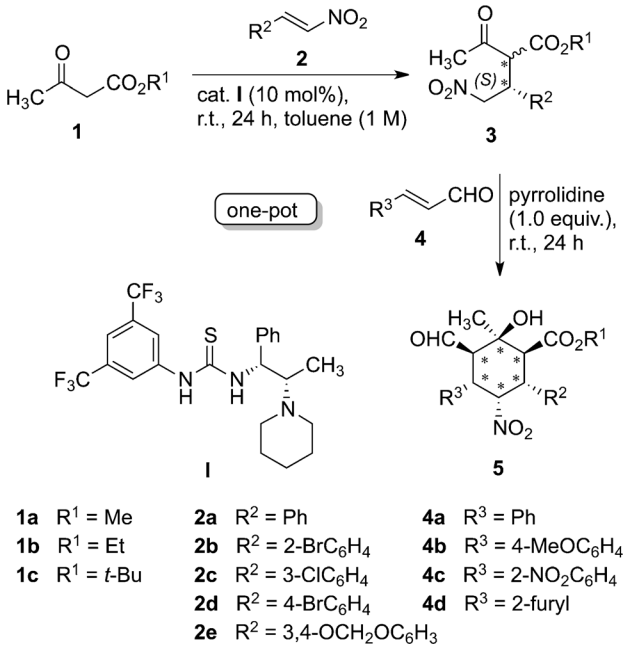
Based on the excellent enantioselectivity obtained with the norephedrine-based bifunctional thiourea

Table 2. Screening of solvent, temperature and loading of catalyst **I** in the one-pot tandem sequence of **1a**, **2a** and **4a** to form cyclohexane **5a**.



Entry[a]	Solvent	*T* [°C]	**I** mol%	Yield [%][b]	*ee* [%][c]
1	CH_2Cl_2	r.t.	10	37	95
2	$CHCl_3$	r.t.	10	36	96
3	THF	r.t.	10	31	98
4	CH_3CN	r.t.	10	–	–
5	toluene	0	10	33[d]	98
6	toluene	−26	10	49[d]	96
7	toluene	r.t.	20	47[d]	96
8	toluene	r.t.	10	70	96
9	toluene	r.t.	5	33	97
10	toluene	r.t.	1	30	98
11	toluene	r.t.	0	15	–

[a] The reactions were carried out on a 1.0 mmol scale for 48 h.
[b] Yield of isolated product **5a** after chromatography and crystallization (*dr* > 95:5).
[c] Determined by HPLC analysis on a chiral stationary phase.
[d] One week reaction time.



Scheme 2. Organocatalytic asymmetric one-pot reaction to form the highly functionalized cyclohexanes **5**.

catalyst **I** for the first Michael-addition step to form **3a** (Table 1, entry 5), the sequential one-pot procedure was carried out in toluene with 10 mol% of the chiral catalyst **I**. After 24 h at room temperature 1 equivalent of pyrrolidine was added[7] together with the α,β-unsaturated aldehyde **4a**. To our delight, the enantiomeric excess was conserved in the second cycle consisting of a diastereoselective domino Michael/aldol addition to yield the highly substituted cyclohexane **5a** with excellent stereoselectivity (*dr* > 95:5, *ee* = 96%, Table 2, entry 8). It turned out that several other solvents were quite suitable in terms of enantioselectivity, but the obtained yields of **5a** were quite low (Table 2, entries 1–4). Among the solvents used, the aprotic, non-polar solvent toluene was the most suitable one, in which an excellent 70% yield of **5a** was obtained with an enantiomeric excess of up to 98% after one recrystallization (Table 2, entry 8). Temperature as well as catalyst loading had an impact only on the yields but showed no influence on the diastereo- and enantioselectivities which stayed constantly excellent (> 96% *ee*) (Table 2, entries 5–7, 9, 10). It is interesting to note that the domino product **5a** was formed in a low yield of 15% using 1 equivalent of pyrrolidine (Table 2, entry 11) and without the presence of the bifunctional thiourea catalyst **I**, of course as a racemate.

Finally we investigated the scope of the new one-pot sequential protocol. Different acyclic β-keto esters (**1a–c**), nitroalkenes (**2a–e**) as well as α,β-unsaturated aldehydes (**4a–d**) were tested in the one-pot procedure (Scheme 2; Table 3). These modifications of the substrates were well tolerated and gave the respective polyfunctionalized cyclohexanes **5a–j** with excellent diastereo- and enantioselectivities after chromatography. All products **5** crystallized, except for **5f** which was isolated as yellow oil and gave the lowest yield. One recrystallization allowed a further enhancement of the enantiomeric excess to 96–99%. When the steric demand of the β-keto esters **1** was increased from R^1 = methyl to ethyl and *tert*-butyl, a slight decrease of the enantioselectivity was observed (Table 3, **5a–c**). The variation of R^3 in the aromatic α,β-unsaturated aldehydes **4** to electron-donating ($R^3 = p\text{-MeOC}_6H_4$) and electron-withdrawing groups ($R^3 = p\text{-NO}_2C_6H_4$) as well as to heterocycles (R^3 = 2-furyl) led to moderate yields of 42–46% while still keeping the excellent *ee* values (Table 3, **5h–j**). It is interesting to note that four of the six stereocenters of the cyclohexanes **5** are established in the second reaction cycle and each substituent occupies the thermodynamically preferred equatorial position, except for the nitro and the hydroxy groups. The relative

Table 3. Scope of the asymmetric one-pot Michael/Michael/aldol addition to polyfunctionalized cyclohexanes **5a–g**.

5[a]	R^1	R^2	R^3	Yield [%][b]	*ee* [%][c]
a	Me	Ph	Ph	70	96 (98)
b	Et	Ph	Ph	40	92 (98)
c	*t*-Bu	Ph	Ph	68	91 (96)
d	Me	2-BrC_6H_4	Ph	63	99
e	Me	3-ClC_6H_4	Ph	66	94
f	Me	4-BrC_6H_4	Ph	22	96
g	Me	3,4-$OCH_2OC_6H_3$	Ph	53	92
h	Me	Ph	4-$MeOC_6H_4$	42	95 (97)
i	Me	Ph	2-$NO_2C_6H_4$	44	94 (99)
j	Me	Ph	2-furyl	46	93

[a] All reactions were performed on a 0.3–1.0 mmol scale at room temperature with catalyst **I** with an overall reaction time of 2 days.
[b] Yield of isolated product **5a–g** after chromatography (*dr* > 95:5).
[c] Determined by HPLC analysis on a chiral stationary phase, values in brackets after recrystallization.

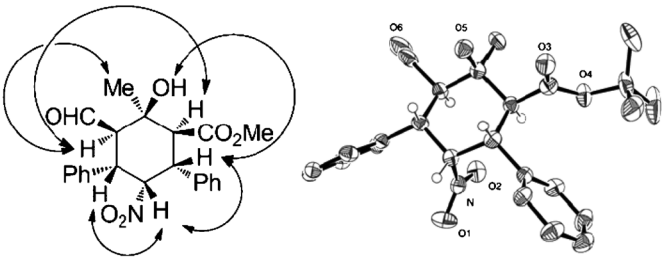


Figure 1. Determination of the relative and absolute configuration by NOE (**5a**) and X-ray crystal structure analysis (**5c**).

configuration of the cyclohexanes **5** was determined by NOE measurements on **5a** and the absolute configuration is based on a X-ray single crystal structure analysis of **5c** (Figure 1)[8] as well as by comparison with closely related literature data.[6]

Conclusions

In summary, we have developed a flexible and simple to perform asymmetric organocatalytic one-pot sequence for the assembly of highly substituted cyclohexanecarbaldehydes **5** bearing hydroxy, ester and nitro functional groups. Starting from simple β-keto esters, nitroalkenes and α,β-unsaturated aldehydes the products were formed in moderate to good yields (22–70%) with perfect atom economy and high levels of chemo-, regio- and stereoselectivities ($dr > 95:5$, 91–98% *ee*). The one-pot procedure is initiated by a bifunctional thiourea-amine-catalyzed asymmetric Michael addition, followed by an amine catalyzed Michael/aldol addition sequence through iminium/enamine activation modes. Three new C–C bonds, six adjacent stereogenic centers including one quaternary stereocenter are formed by combining bifunctional weak Brønsted acid/base and amine catalysis. Further work is aimed to expand this concept to the asymmetric synthesis of natural products and even more complex molecular structures.

Experimental Section

Flash column chromatography: SIL G-25 UV_{254} (size 0.040–0.063 mm) Machery&Nagel. TLC: silica gel 60 F254 plates, Merck, Darmstadt. Visualization of the developed TLC plates was performed with UV radiation (254 nm) or by staining with a potassium permanganate solution. Elemental analyses were carried out with a Vario EL element analyzer. Melting points were determined with a Büchi Melting Point B-540 apparatus. Optical rotation values were taken on a Perkin–Elmer P241 polarimeter. The ee-values were determined by analytical HPLC with a Hewlett–Packard 1100 Series instrument using chiral stationary phases. IR spectra were recorded on a Perkin–Elmer FT-IR Spectrum 100 Spectrometer. ^{1}H and ^{13}C NMR spectra were measured at ambient temperature with Varian Gemini 300, Varian Mercury 300 or Varian Innova 600 spectrometers using TMS as internal standard. Mass spectra were recorded on a Finnigan SSQ7000 (EI 70 eV) spectrometer, high resolution mass spectra on a Finnigan MAT 95 and high resolution ESI spectra on a ThermoFisher Scientific LTQ-Orbitrap XL.

General Procedure for the Asymmetric Synthesis of Cyclohexane Derivatives 5a–j

In a glass vial equipped with a magnetic stirring bar the nitroalkene **2** (1.0 equiv., 0.3–1.0 mmol) and catalyst **I** (10 mol%) were dissolved in toluene (1 mL mmol^{-1} nitroalkene) and stirred 10 min at room temperature followed by slow addition of the β-keto ester **1** (2.0 equiv., 0.6–2.0 mmol). After stirring at room temperature for 1 day the α,β-unsaturated aldehyde **4** (1.1 equiv., 0.33–1.1 mmol) and pyrrolidine (1.0 equiv., 0.3–1.0 mmol) were added and stirred for another day at room tempertaure. The crude product was directly purified by successive flash column chromatographies (first *n*-pentane/Et_2O = 6:1, then *n*-pentane/ethyl acetate = 3:1) to afford the polysubstituted cyclohexanes **5a–j**.

3-Formyl-2-hydroxy-2-methyl-5-nitro-4,6-diphenylcyclohexanecarboxylic acid methyl ester (5a): Synthesized according to the general procedure using methyl 3-oxobutanoate (**1a**) (0.22 mL, 2.0 mmol), (*E*)-(2-nitrovinyl)benzene (**2a**) (149 mg, 1.0 mmol) and cinnamaldehyde (**4a**) (0.14 mL, 1.1 mmol); yellow solid; yield: 278 mg (70%); $[\alpha]_D^{20}$: +4.8 (*c* 0.96, $CHCl_3$); 98% *ee*; R_f = 0.46 (*n*-pentane/ethyl acetate = 2:1); mp 165 °C. IR (film): ν = 3499, 2829, 1726, 1551, 1496, 1452, 1366, 1253, 1194, 1158, 751, 700 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$): δ = 1.47 (s, 3H, CH_3), 3.45 (s, 3H, CO_2CH_3), 3.53 (dd, J = 4, 13 Hz, 1H, C*H*CHO), 3.66 (s, 1H, O*H*), 3.89 (d, J = 13 Hz, 1H, $CHCO_2CH_3$), 4.03 (dd, J = 5, 13 Hz, 1H, C*H*Ph), 4.30 (dd, J = 5, 13 Hz, 1H, C*H*Ph), 5.05 (t, J = 5 Hz, 1H, $CHNO_2$), 7.15–7.29 (m, 10H, CH_{arom}), 9.51 (d, J = 5 Hz, 1H, C*H*O); ^{13}C NMR (150 MHz, $CDCl_3$): δ = 27.3 (CH_3), 41.7 (*C*HPh), 44.1 (*C*HPh), 49.8 ($CHCO_2CH_3$), 52.1 (CO_2CH_3), 54.7 (*C*HCHO), 72.1 (CCH_3OH), 93.2 ($CHNO_2$), 127.1–129.4 (CH_{arom}), 135.2 (C_{arom}), 135.5 (C_{arom}), 174.5 (CO_2CH_3), 202.9 (*C*HO); MS (EI, 70 eV): *m/z* (%) = 397 [M$^+$] (3), 368 (4), 351 (5), 336 (3), 321 (6), 305 (100), 273 (5), 245 (41), 229 (3), 205 (6), 167 (5), 133 (5), 131 (16), 115 (15), 103 (11), 101 (11), 91 (36), 77 (8), 59 (4); anal. calcd. for $C_{22}H_{23}NO_6$: C 66.49, H 5.83, N 3.52; found: C 66.30, H 5.65, N 3.43.

3-Formyl-2-hydroxy-2-methyl-5-nitro-4,6-diphenylcyclohexanecarboxylic acid ethyl ester (5b): Synthesized according to the general procedure using ethyl 3-oxobutanoate (**1b**) (0.26 mL, 2.0 mmol), (*E*)-(2-nitrovinyl)benzene (**2a**) (149 mg, 1.0 mmol) and cinnamaldehyde (**4a**) (0.14 mL, 1.1 mmol); yellow solid; yield: 163 mg (40%); $[\alpha]_D^{20}$: +6.8 (*c* 1.10, $CHCl_3$); 92% *ee*; R_f = 0.47 (*n*-pentane/ethyl acetate = 2:1); mp 120 °C. IR (film): ν = 3515, 2984, 1718, 1549, 1452, 1370, 1257, 1182, 1158, 1027, 750, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, J = 7 Hz, 3H, $CO_2CH_2CH_3$), 1.49 (s, 3H, CH_3), 3.53 (dd, J = 4, 14 Hz, 1H, C*H*CHO), 3.84 (d, J = 13 Hz, 1H, $CHCO_2CH_2CH_3$), 3.85 (s, 1H, O*H*), 3.94 (q, J = 7 Hz, 2H, $CO_2CH_2CH_3$), 4.02 (dd, J = 4, 13 Hz, 1H, C*H*Ph), 4.31 (dd, J = 5, 12 Hz, 1H, C*H*Ph), 5.06 (t, J = 4 Hz,

1H, C*H*NO_2), 7.15–7.29 (m, 10H, CH_{arom}), 9.52 (d, $J=4$ Hz, 1H, C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=13.6$ ($CO_2CH_2CH_3$), 27.2 (CH_3), 41.7 (*C*HPh), 44.3 (*C*HPh), 49.7 ($CHCO_2CH_2CH_3$), 54.7 (*C*HCHO), 61.3 ($CO_2CH_2CH_3$), 72.0 (CCH_3OH), 93.2 ($CHNO_2$), 127.3–129.3 (CH_{arom}), 135.3 (C_{arom}), 135.5 (C_{arom}), 174.1 (CO_2Me), 202.9 (*C*HO); MS (EI, 70 eV): *m/z* (%) = 412 $[M+H]^+$ (2), 394 (2), 373 (4), 365 (5), 348 (3), 331 (7), 320 (26), 319 (100), 284 (16), 273 (5), 246 (9), 245 (43), 205 (5), 177 (4), 131 (12), 115 (10), 103 (8), 91 (15), 77 (5); anal. calcd. for $C_{23}H_{25}NO_6$: C 67.14, H 6.12, N 3.40; found: C 66.58, H 6.04, N 3.84.

3-Formyl-2-hydroxy-2-methyl-5-nitro-4,6-diphenylcyclohexanecarboxylic acid *tert*-butyl ester (5c): Synthesized according to the general procedure using *tert*-butyl 3-oxobutanoate (**1c**) (0.32 mL, 2.0 mmol), (*E*)-(2-nitrovinyl)benzene (**2a**) (149 mg, 1.0 mmol) and cinnamaldehyde (**4a**) (0.14 mL, 1.1 mmol); colorless solid; yield: 300 mg (68%); $[\alpha]_D^{20}$: + 2.7 (*c* 1.01, $CHCl_3$); 91% *ee*; $R_f=0.68$ (*n*-pentane/ethyl acetate = 2:1); mp 207 °C. IR (film): $\nu=3461$, 2979, 1726, 1550, 1454, 1368, 1349, 1250, 1148, 1071, 836, 747, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=1.10$ [s, 9H, C(CH_3)$_3$], 1.50 (s, 3H, CH_3), 3.50 (dd, $J=3$, 12 Hz, 1H, C*H*CHO), 3.69 (d, $J=13$ Hz, 1H, C*H*CO_2CH_3), 3.95 (dd, $J=4$, 13 Hz, 1H, C*H*Ph), 4.15 (s, 1H, O*H*), 4.30 (dd, $J=5$, 13 Hz, 1H, C*H*Ph), 5.04 (t, $J=4$ Hz, 1H, C*H*NO_2), 7.15–7.30 (m, 10H, CH_{arom}), 9.51 (d, $J=5$ Hz, 1H, C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=27.1$ (CH_3), 27.4 [$CO_2C(CH_3)_3$], 41.6 (*C*HPh), 44.6 (*C*HPh), 49.8 ($CHCO_2CH_3$), 54.8 (*C*HCHO), 72.1 (CCH_3OH), 82.9 ($CO_2C(CH_3)_3$), 93.1 ($CHNO_2$), 127.4–129.3 (CH_{arom}), 135. (2C_{arom}), 173.8 (CO_2CH_3), 203.1 (*C*HO); MS (EI, 70 eV): *m/z* (%) = 440 $[(M+H]^+$ (3), 421 (7), 403 (6), 348 (3), 366 (8), 347 (11), 337 (4), 320 (5), 291 (72), 290 (74), 273 (6), 245 (34), 233 (7), 205 (7), 171 (5), 147 (5), 131 (10), 115 (12), 105 (12), 103 (10), 91 (25), 77 (5), 57 (100); anal. calcd. for $C_{25}H_{29}NO_6$: C 68.32, H 6.65, N 3.19; found: C 68.30, H 6.86, N 2.83.

6-*ortho*-Bromophenyl-3-formyl-2-hydroxy-2-methyl-5-nitro-4-phenylcyclohexanecarboxylic acid methyl ester (5d): Synthesized according to the general procedure using methyl 3-oxobutanoate (**1a**) (0.22 mL, 2.0 mmol), *(E)*-1-bromo-2-(2-nitrovinyl)benzene (**2b**) (228 mg, 1.0 mmol) and cinnamaldehyde (**4a**) (0.13 mL, 1.1 mmol); colorless solid; yield: 301 mg (63%); $[\alpha]_D^{20}$: −41.1 (*c* 1.00, $CHCl_3$); 99% *ee*; $R_f=0.29$ (*n*-pentane/ethyl acetate = 3:1); mp 224 °C. IR (film): $\nu=3455$, 2956, 1711, 1547, 1442, 1345, 1270, 1172, 1099, 1070, 1025, 994, 935, 905, 863, 824, 797, 742, 703 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.50$ (s, 3H, CH_3), 3.54 (s, 3H, CO_2CH_3), 3.57 (s, 1H, O*H*), 3.57 (d, $J=12$ Hz, 1H, C*H*CO_2CH_3), 3.91 (d, $J=13$ Hz, 1H, C*H*CHO), 4.36 (dd, $J=4$, 13 Hz, 1H, C*H*Ph), 4.69 (dd, $J=4$, 13 Hz, 1H, C*H*Ar), 5.20 (t, $J=4$ Hz, 1H, C*H*NO_2), 7.10–7.38 (m, 8H, CH_{arom}), 7.61 (m, 1H, CH_{arom}), 9.52 (d, $J=4$ Hz, 1H, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=27.2$ (CH_3), 41.5 (*C*HPh), 42.5 (*C*HAr), 49.7 ($CHCO_2CH_3$), 52.2 (CO_2CH_3), 54.7 (*C*HCHO), 72.1 (CCH_3OH), 90.7 ($CHNO_2$), 125.2 (C_{arom}), 127.8 (CH_{arom}), 128.0 (2CH_{arom}), 128.1 (CH_{arom}), 128.6 (CH_{arom}), 129.3 (2CH_{arom}), 130.0 (C_{arom}), 133.5 (CH_{arom}), 135.0 (C_{arom}), 134.3 (C_{arom}), 173.9 (CO_2CH_3), 202.7 (*C*HO); MS (EI, 70 eV): *m/z* (%) = 431 $[M^+-HNO_3]$ (6), 429 $[M^+-HNO_3]$ (6), 385 (100), 383 (100), 325 (54), 323 (54), 244 (83), 229 (18), 204 (24), 171 (25), 145 (15), 128 (24),115 (45), 91 (59), 77 (24), 59 (31); anal. calcd. for $C_{22}H_{22}BrNO_6$: C 55.47, H 4.66, N 2.94; found: C 55.56, H 4.75, N 2.78.

6-*meta*-Chlorophenyl-3-formyl-2-hydroxy-2-methyl-5-nitro-4-phenylcyclohexanecarboxylic acid methyl ester (5e): Synthesized according to the general procedure using methyl 3-oxobutanoate (**1a**) (0.22 mL, 2.0 mmol), *(E)*-1-chloro-3-(2-nitrovinyl)benzene (**2c**) (184 mg, 1.0 mmol) and cinnamaldehyde (**4a**) (0.13 mL, 1.1 mmol); colorless solid; yield: 283 mg (66%); $[\alpha]_D^{20}$: −28.1 (*c* 1.00, $CHCl_3$); 94% *ee*; $R_f=0.27$ (*n*-pentane/ethyl acetate = 3:1); mp 139 °C; IR (film): $\nu=3325$, 2931, 1722, 1549, 1437, 1359, 1261, 1153, 1060, 897, 785, 815, 744, 697 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): $\delta=1.49$ (s, 3H, CH_3), 3.47–3.57 (m, 4H, CO_2CH_3, $CHCO_2CH_3$), 3.59 (s, 1H, O*H*), 3.87 (d, $J=13$ Hz, 1H, C*H*CHO), 4.03 (dd, $J=4$, 13 Hz, 1H, C*H*Ph), 4.30 (dd, $J=4$, 13 Hz, 1H, C*H*Ar), 5.05 (t, $J=4$ Hz, 1H, C*H*NO_2), 7.06–7.13 (m, 1H, CH_{arom}), 7.14–7.20 (m, 2H, CH_{arom}), 7.22–7.36 (m, 6H, CH_{arom}), 9.52 (d, $J=5$ Hz, 1H, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta=27.2$ (CH_3), 41.6 (*C*HPh), 43.7 (*C*HAr), 49.6 ($CHCO_2CH_3$), 52.2 (CO_2CH_3), 54.5 (*C*HCHO), 72.0 (CCH_3OH), 92.9 ($CHNO_2$), 125.6 (C_{arom}), 128.0 (CH_{arom}), 128.4 (2CH_{arom}), 128.6 (CH_{arom}), 128.8 (CH_{arom}), 129.3 (2CH_{arom}), 130.3 (C_{arom}), 134.8 (CH_{arom}), 135.0 (C_{arom}), 137.5 (C_{arom}), 174.1 (CO_2CH_3), 202.6 (*C*HO); MS (EI, 70 eV): *m/z* (%) = 385 $[M^+-HNO_3]$ (2), 341 (34), 339 (100), 281 (22), 279 (62), 165 (15), 125 (10), 115 (17), 105 (10), 91 (22), 77 (8), 59 (11); anal. calcd. for $C_{22}H_{22}ClNO_6$: C 61.18, H 5.13, N 3.24; found: C 61.00, H 5.18, N 2.99.

6-*para*-Bromophenyl-3-formyl-2-hydroxy-2-methyl-5-nitro-4-phenylcyclohexanecarboxylic acid methyl ester (5f): Synthesized according to the general procedure using methyl 3-oxobutanoate (**1a**) (0.06 mL, 0.52 mmol), (*E*)-1-bromo-4-(2-nitrovinyl)benzene (**2d**) (60 mg, 0.26 mmol) and cinnamaldehyde (**4a**) (0.04 mL, 0.29 mmol); yellow soluid: yield: 27 mg (22%); $[\alpha]_D^{20}$: +3.1 (*c* 1.11, $CHCl_3$); 96% *ee*; $R_f=0.44$ (*n*-pentane/ethyl acetate = 2:1). IR (film): $\nu=3507$, 2927, 1715, 1549, 1491, 1439, 1354, 1258, 1162, 1075, 1008, 909, 815, 731, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=$ 1.47 (s, 3H, CH_3), 1.58 (s, 1H, O*H*), 3.51 (s, 3H, CO_2CH_3), 3.54 (dd, $J=2$, 12 Hz, 1H, C*H*CHO), 3.84 (d, $J=13$ Hz, 1H, C*H*CO_2Me), 4.00 (dd, $J=4$, 13 Hz, 1H, C*H*Ph), 4.28 (dd, $J=5$, 13 Hz, 1H, C*H*Ph), 5.00 (t, $J=4$ Hz, 1H, C*H*NO_2), 7.07–7.09 (m, 2H, CH_{arom}), 7.13–7.17 (m, 2H, CH_{arom}), 7.26–7.30 (m, 3H, CH_{arom}), 7.42–7.44 (m, 2H, CH_{arom}), 9.50 (d, $J=$ 4 Hz, 1H, C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=27.2$ (CH_3), 41.6 (*C*HPh), 43.6 (*C*HPh), 49.7 ($CHCO_2CH_3$), 52.2 (CO_2CH_3), 54.5 (*C*HCHO), 72.0 (CCH_3OH), 92.9 ($CHNO_2$), 122.7 (C_{arom}), 127.3–13.2 (CH_{arom}), 134.6 (C_{arom}), 140.0 (C_{arom}), 174.2 (CO_2CH_3), 202.6 (*C*HO); MS (EI, 70 eV): *m/z* (%) = 475 $[M+H]^+$ (5), 460 (1), 429 (26), 399 (18), 385 (100), 383 (90), 369 (18), 353 (11), 337 (12), 325 (29), 319 (10), 295 (5), 271 (5), 258 (5), 244 (21), 229 (8), 204 (9), 192 (7), 171 (14), 145 (6), 131 (10), 128 (14), 115 (23), 105 (18), 91 (37), 77 (13), 65 (4), 59 (12); HR-MS (ESI): *m/z* = 498.0523, calcd. for $C_{22}H_{22}NO_6BrNa$: 498.0528.

6-(Benzo[*d*][1,3]dioxol-5-yl)-3-formyl-2-hydroxy-2-methyl-5-nitro-4-phenylcyclohexanecarboxylic acid methyl ester (5g): Synthesized according to the general procedure using methyl 3-oxobutanoate (**1a**) (0.22 mL, 2.0 mmol), *(E)*-5-(2-nitrovinyl)benzo[*d*][1,3]dioxole (**2e**) (193 mg, 1.0 mmol) and cinnamaldehyde (**4a**) (0.13 mL, 1.1 mmol); colorless

solid; yield: 234 mg (53%); $[\alpha]_D^{20}$: −81.8 (*c* 1.00, $CHCl_3$); 72% *ee*; R_f = 0.24 (*n*-pentane/ethyl acetate = 3:1); mp 98 °C. IR (film): ν = 3497, 2922, 1717, 1549, 1493, 1444, 1359, 1241, 1104, 1034, 928, 865, 805, 754, 700 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.45 (s, 3H, CH_3), 3.50 (dd, *J* = 2, 13 Hz, 1H, $CHCO_2CH_3$), 3.54 (s, 3H, CO_2CH_3), 3.59 (d, *J* = 2 Hz, 1H, O*H*), 3.79 (d, *J* = 13 Hz, 1H, C*H*CHO), 3.94 (dd, *J* = 4, 13 Hz, 1H, C*H*Ph), 4.26 (dd, *J* = 5, 13 Hz, 1H, C*H*Ar), 5.00 (t, *J* = 4 Hz, 1H, $CHNO_2$), 5.91 (d, *J* = 2 Hz, 1H, CH_2), 5.92 (d, *J* = 2 Hz, 1H, CH_2), 6.61–6.76 (m, 3H, CH_{arom}), 7.14 (dd, *J* = 2, 8 Hz, 1H, CH_{arom}), 7.22–7.33 (m, 4H, CH_{arom}), 9.49 (d, *J* = 5 Hz, 1H, C*H*O); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 27.3 (CH_3), 41.7 (*C*HPh), 43.8 (*C*HAr), 50.0 ($CHCO_2CH_3$), 52.2 (CO_2CH_3), 54.6 (*C*HCHO), 72.1 (CCH_3OH), 93.4 ($CHNO_2$), 101.3 (OCH_2O), 108.1 (CH_{arom}), 108.7 (CH_{arom}), 121.3 (CH_{arom}), 125.2 (C_{arom}), 127.8 (CH_{arom}), 128.1 ($2CH_{arom}$), 128.6 (C_{arom}), 129.2 ($2CH_{arom}$), 129.3 (C_{arom}), 135.2 (C_{arom}), 174.5 (CO_2CH_3), 202.8 (*C*HO); MS (EI, 70 eV): *m/z* (%) = 441 [M^+] (100), 317 (15), 291 (31), 260 (48), 229 (57), 215 (20), 197 (19), 175 (29), 152 (50), 135 (39), 115 (52), 91 (96), 77(33), 59 (17); anal. calcd. for $C_{23}H_{23}NO_8$: C 62.85, H 5.25, N 3.17; found: C 62.68, H 5.16, N 3.08.

3-Formyl-2-hydroxy-4-*para*-methoxyphenyl-2-methyl-5-nitro-6-phenylcyclohexanecarboxylic acid methyl ester (5h): Synthesized according to the general procedure using methyl 3-oxobutanoate (**1a**) (0.22 mL, 2.0 mmol), (*E*)-(2-nitrovinyl)benzene (**2a**) (149 mg, 1.0 mmol) and (*E*)-3-(4-methoxyphenyl)acrylaldehyde (**4b**) (180 mg, 1.1 mmol); colorless solid; yield: 179 mg (42%); $[\alpha]_D^{20}$: +3.8 (*c* 0.48, $CHCl_3$); 95% *ee*; R_f = 0.49 (*n*-pentane/ethyl acetate = 2:1); mp 215 °C. IR (film): ν = 3519, 2957, 1720, 1612, 1552, 1512, 1437, 1354, 1308, 1256, 1156, 1098, 1030, 937, 913, 815, 745 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 3H, CH_3), 3.47 (s, 1H, O*H*), 3.47 (s, 3H, CO_2CH_3), 3.48 (dd, *J* = 2, 13 Hz, 1H, C*H*CHO), 3.74 (s, 3H, OCH_3), 3.87 (d, *J* = 13 Hz, 1H, $CHCO_2CH_3$), 4.00 (dd, *J* = 4, 13 Hz, 1H, C*H*Ph), 4.25 (dd, *J* = 5, 12 Hz, 1H, C*H*Ph), 5.01 (t, *J* = 4 Hz, 1H, $CHNO_2$), 6.79–6.83 (m, 2H, CH_{arom}), 7.05–7.10 (m, 2H, CH_{arom}), 7.17–7.21 (m, 2H, CH_{arom}), 7.25–7.31 (m, 3H, CH_{arom}), 9.49 (d, *J* = 5 Hz, 1H, C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3 (CH_3), 40.9 (*C*HPh), 44.2 (*C*HPh), 49.8 ($CHCO_2CH_3$), 52.1 (CO_2CH_3), 54.9 (*C*HCHO), 55.2 (OCH_3), 72.1 (CCH_3OH), 93.4 ($CHNO_2$), 114.7 (CH_{arom}), 127.0 (C_{arom}), 127.8–129.3 (CH_{arom}), 135.3 (C_{arom}), 159.5 (C_{arom}), 174.6 (CO_2CH_3), 203.0 (*C*HO); MS (EI, 70 eV): *m/z* (%) = 427 [M^+] (100), 396 (3), 363 (4), 335 (67), 321 (5), 303 (6), 275 (25), 265 (12), 243 (4), 201 (12), 163 (10), 145 (8), 131 (13), 121 (22), 108 (15), 91 (21), 77(9), 59 (7); anal. calcd. for $C_{23}H_{25}NO_7$: C 64.63, H 5.90, N 3.28; found: C 64.93, H 5.97, N 2.82.

3-Formyl-2-hydroxy-2-methyl-5-nitro-4-*ortho*-nitrophenyl-6-phenylcyclohexanecarboxylic acid methyl ester (5i): Synthesized according to the general procedure using methyl 3-oxobutanoate (**1a**) (0.22 mL, 2.0 mmol), (*E*)-(2-nitrovinyl)-benzene (**2b**) (149 mg, 1.0 mmol) and (*E*)-3-(2-nitrophenyl) acrylaldehyde (**4c**) (195 mg, 1.1 mmol); red solid; yield: 193 mg (44%); $[\alpha]_D^{20}$: −51.4 (*c* 1.36, $CHCl_3$); 94% *ee*; R_f = 0.42 (*n*-pentane/ethyl acetate = 2:1); mp 200 °C. IR (film): ν = 3663, 3506, 3063, 2850, 1959, 1734, 1608, 1550, 1441, 1379, 1073, 1032, 1006, 940, 857, 828, 791, 737, 704 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.51 (s, 3H, CH_3), 3.46 (s, 3H, CO_2CH_3), 3.60 (dd, *J* = 4, 12 Hz, 1H, C*H*CHO), 3.74 (s, 1H, O*H*), 3.98 (d, *J* = 13 Hz, 1H, $CHCO_2CH_3$), 4.08 (dd, *J* = 4, 13 Hz, 1H, C*H*Ph), 4.93 (dd, *J* = 4, 12 Hz, 1H, C*H*Ph), 5.45 (t, *J* = 4 Hz, 1H, $CHNO_2$), 7.17–7.19 (m, 1H, CH_{arom}), 7.24–7.30(m, 5H, CH_{arom}), 7.36–7.42(m, 1H, CH_{arom}), 7.46–7.49 (m, 1H, CH_{arom}), 7.91–7.94 (m, 1H, CH_{arom}), 9.51 (d, *J* = 4 Hz, 1H, C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.3 (CH_3), 36.2 (*C*HPh), 42.3 (*C*HPh), 49.8 ($CHCO_2CH_3$), 52.2 (CO_2CH_3), 55.5 (*C*HCHO), 71.9 (CCH_3OH), 91.8 ($CHNO_2$), 125.6 (CH_{arom}), 127.9–129.4 (CH_{arom}), 130.4 (C_{arom}), 133.9 (CH_{arom}), 135.3 (C_{arom}), 149.8 (C_{arom}), 174.1 (CO_2CH_3), 201.7 (*C*HO); MS (EI, 70 eV): *m/z* (%) = 443 $[M+H]^+$ (4), 427 (12), 396 (13), 378 (8), 350 (44), 332 (66), 317 (14), 300 (33), 290 (23), 272 (100), 256 (70), 244 (25), 230 (23), 216 (19), 204 (23), 178 (11), 175 (41), 159 (21), 145 (37), 131 (61), 115 (51), 103 (38), 91 (50), 77 (31), 59 (30); anal. calcd. for $C_{22}H_{22}N_2O_8$: C 59.73, H 5.01, N 6.33; found: C 59.44, H 5.35, N 6.17.

3-Formyl-4-furyl-2-hydroxy-2-methyl-5-nitro-6-phenylcyclohexanecarboxylic acid methyl ester (5j): Synthesized according to the general procedure using methyl 3-oxobutanoate (**1a**) (0.22 mL, 2.0 mmol), (*E*)-(2-nitrovinyl)benzene (**2b**) (149 mg, 1.0 mmol) and (*E*)-3-(furan-2-yl)acrylaldehyde (**4d**) (135 mg, 1.1 mmol); yellow solid; yield: 178 mg (46%); $[\alpha]_D^{20}$: +18.6 (*c* 1.14, $CHCl_3$); 93% *ee*; R_f = 0.49 (*n*-pentane/ethyl acetate = 2:1); mp 147 °C. IR (film): ν = 3509, 2958, 1715, 1554, 1498, 1437, 1346, 1262, 1197, 1153, 1120, 1069, 1011, 940, 817, 742, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.46 (s, 3H, CH_3), 3.30 (ddd, *J* = 2, 4, 13 Hz, 1H, C*H*CHO), 3.45 (s, 3H, CO_2CH_3), 3.66 (s, 1H, O*H*), 3.85 (d, *J* = 13 Hz, 1H, $CHCO_2CH_3$), 3.99 (dd, *J* = 4, 13 Hz, 1H, C*H*Ph), 4.43 (dd, *J* = 5, 13 Hz, 1H, C*H*Ph), 5.26 (t, *J* = 4 Hz, 1H, $CHNO_2$), 6.07–6.09 (m, 1H, CH_{furyl}), 6.23–6.25 (m, 1H, CH_{furyl}), 7.17–7.22 (m, 2H, CH_{arom}), 7.26–7.31 (m, 3H, CH_{arom}, 1H, CH_{furyl}), 9.59 (d, *J* = 4 Hz, 1H, C*H*O); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 26.5 (CH_3), 35.9 (*C*HPh), 43.4 (*C*HPh), 49.6 ($CHCO_2CH_3$), 52.1 (CO_2CH_3), 54.2 (*C*HCHO), 71.8 (CCH_3OH), 90.5 ($CHNO_2$), 109.2 (CH_{furyl}), 110.6 (CH_{furyl}), 126.7–129.1 (CH_{arom}), 135.4 (C_{arom}), 143.0 (CH_{furyl}), 149.4 (C_{furyl}), 174.3 (CO_2CH_3), 202.3 (*C*HO); MS (EI, 70 eV): *m/z* (%) = 387 [M^+] (24), 356 (2), 341 (10), 323 (5), 295 (100), 280 (11), 263 (8), 235 (74), 225 25), 219 (25), 192 (14), 165 (22), 161 (30), 152 (12), 141 (17), 131 (25), 115 (30), 103 (19), 91 (55), 77 (24), 65 (15), 55 (23); anal. calcd. for $C_{20}H_{21}NO_7$: C 62.01, H 5.46, N 3.62; found: C 62.18, H 5.23, N 3.21.

Acknowledgements

This work was supported by the Fonds der Chemischen Industrie. We thank BASF SE for the donation of chemicals and Dr. I. Atodiresei (X-ray data) and Dr. J. Runsink (NOE measurements) for their help.

References

[1] For selected general reviews on organocatalysis, see: a) A. Berkessel, H. Gröger, *Asymmetric Organocatalysis*, Wiley-VCH, Weinheim, **2005**; b) P. I. Dalko, *Enantioselective Organocatalysis*, Wiley-VCH, Weinheim, **2007**; c) special issue (Ed.: B. List): *Chem. Rev.* **2007**, *107*, 5413–5883; d) R. M. De Figuiredo, M. Christmann, *Eur.*

J. Org. Chem. **2007**, *63*, 9267–9331; e) J. L. Vicario, D. Badia, L. Carillo, *Synthesis* **2007**, 2065–2092; f) S. B. Tsogoeva, *Eur. J. Org. Chem.* **2007**, 1701–1716; g) A. Dondoni, A. Massi, *Angew. Chem*. **2008**, *120*, 4716–4739; *Angew. Chem. Int. Ed.* **2008**, *47*, 4638–4660; h) D. W. C. MacMillan, *Nature* **2008**, *455*, 304–308; i) C. F. Barbas III, *Angew. Chem.* **2008**, *120*, 44–50; *Angew. Chem. Int. Ed*. **2008**, *47*, 42–47; j) D. Enders, A. A. Narine, *J. Org. Chem*. **2008**, *73*, 7857–7870; k) P. Melchiorre, M. Marigo, A. Carlone, G. Bartoli, *Angew. Chem*. **2008**, *120*, 6232–6265; *Angew. Chem. Int. Ed*. **2008**, *47*, 6138–6171; l) D. Enders, C. Wang, J. X. Liebich, *Chem. Eur. J*. **2009**, *15*, 11058–11076; m) K. A. Jørgensen, S. Bertelsen, *Chem. Soc. Rev.* **2009**, *38*, 2178–2189; n) M. Bella, T. Gasperi, *Synthesis* **2009**, 1583–1614; o) D. Roca-Lopez, D. Sadaba, I. Delso, R. P. Herrera, T. Tejero, P. Merino, *Tetrahedron: Asymmetry* **2010**, *21*, 2561–2601; p) P. Merino, E. Marqués-Lopéz, T. Tejero, R. P. Herrera, *Synthesis* **2010**, 1–26; q) T. Marcelli, H. Hiemstra *Synthesis* **2010**, 1229–1279; r) M. Nielsen, D. Worgull, T. Zweifel, B. Gschwend, S. Bertelsen, K. A. Jørgensen, *Chem. Commun*. **2011**, *47*, 632–649; s) D. B. Ramachary, S. Jain, *Org. Biomol. Chem*. **2011**, *9*, 1277–1300; t) A. Moyano, R. Rios *Chem. Rev*. **2011**, *111*, 4703–4832.

[2] For selected reviews on organocatalytic domino reactions, see: a) D. Enders, C. Grondal, M. R. M. Hüttl, *Angew. Chem.* **2007**, *119*, 1590–1601; *Angew. Chem. Int. Ed.* **2007**, *46*, 1570–1581; b) X. Yu, W. Wang, *Org. Biomol. Chem.* **2008**, *6*, 2037–2046; c) C. Grondal, M. Jeanty, D. Enders, *Nature Chemistry* **2010**, *2*, 167–178; d) A. Grossmann, D. Enders, *Angew. Chem.* **2012**, *124*, 320–332; *Angew. Chem. Int. Ed.* **2012**, *51*, 314–325; e) H. Pellissier, *Adv. Synth. Catal.* **2012**, 354, 237–294.

[3] For selected reviews in hydrogen-bonding catalysis, see: a) P. R. Schreiner, *Chem. Soc. Rev.* **2003**, *32*, 289–296; b) M. S. Taylor, E. N. Jacobsen, *Angew. Chem.* **2006**, *118*, 1550–1573; *Angew. Chem. Int. Ed.* **2006**, *45*, 1520–1543; c) S. J. Connon, *Chem. Eur. J.* **2006**, *12*, 5418–5427; d) A. G. Doyle, E. N. Jacobsen, *Chem. Rev.* **2007**, *107*, 5713–5743; e) X. Yu, W. Wang, *Chem. Asian. J.* **2008**, *3*, 516–532; f) Z. Zhang, P. R. Schreiner, *Chem. Soc. Rev.* **2009**, *38*, 1187–1198; g) K. Etzenbach-Effers, A. Berkessel *Top. Curr. Chem.* **2009**, *291*, 1–27; h) M. Kotke, P. R. Schreiner, in: *Hydrogen Bonding in Organic Synthesis*, (Ed.: P. M. Pihko), Wiley-VCH, Weinheim, **2009**, pp 141–352; i) Y. Takemoto, *Chem. Pharm. Bull.* **2010**, *58*, 593–601; j) R. R. Knowles, E. N. Jacobsen, *Proc. Natl. Acad. Sci. USA* **2010**, *107*, 20678–20685; k) J. Alemán, A. Parra, H. Jiang, K. A. Jørgensen, *Chem. Eur. J.* **2011**, *17*, 6890–6899.

[4] For selected examples of asymmetric organocatalytic domino reactions in the synthesis of cyclohexane derivatives, see: a) D. Enders, M. R. M. Hüttl, C. Grondal, G. Raabe, *Nature* **2006**, *441*, 861–863; b) D. Enders, M. R. M. Hüttl, J. Runsink, G. Raabe, B. Wendt, *Angew. Chem.* **2007**, *119*, 471–473; *Angew. Chem. Int. Ed.* **2007**, *46*, 467–469; c) D. Enders, A. A. Narine, T. R. Benninghaus, G. Raabe, *Synlett* **2007**, 1667–1670; d) E. Reyes, H. Jiang, A. Milelli, P. Elsner, R. G. Hazell, K. A. Jørgensen, *Angew. Chem.* **2007**, *119*, 9362–9365; *Angew. Chem. Int. Ed.* **2007**, *46*, 9202–9205; e) J. Zhou, B. List, *J. Am. Chem. Soc.* **2007**, *129*, 7498–7499; f) D. Enders, M. R. M. Hüttl. G. Raabe, J. W. Bats, *Adv. Synth. Catal.* **2008**, *350*, 267–279; g) S. Cabrera, J. Alemán, P. Bolze, S. Bertelsen, K. A. Jørgensen, *Angew Chem.* **2008**, *120*, 127–131; *Angew. Chem. Int. Ed.* **2008**, *47*, 121–125; h) B. Tan, P. J. Chua, Y. li, G. Zhong, *Org. Lett.* **2008**, *12*, 2437–2440; i) L.-Y. Wu, G. Bencivenni, M. Mancinelli, A. Mazzanti, G. Bartoli, P. Melchiorre, *Angew. Chem.* **2009**, *121*, 7332–7335; *Angew. Chem. Int. Ed.* **2009**, *48*, 7196–7199; j) W. J. Nodes, D. R. Nutt, A. M. Chippindale, A. J. A. Cobb, *J. Am. Chem. Soc.* **2009**, *131*, 16016–16017; k) B.-C. Hong, R.-H. Jan, C.-W. Tsai, R. Y. Nimje, J.-H. Liao, G.-H. Lee, *Org. Lett.* **2009**, *11*, 5246–5249; l) J. L. Garciá Ruano, V. Marcos, J. A. Suanzes, L. Marzano, J. Alemán, *Chem. Eur. J.* **2009**, *15*, 6576–6580; m) D. Enders, C. Wang, M. Mukanova, A. Greb, *Chem. Commun.* **2010**, *46*, 2447–2449; n) D. Enders, R. Krüll, W. Bettray, *Synthesis* **2010**, 567–572; o) D. Enders, B. Schmid, N. Erdmann, *Synthesis* **2010**, 2271–2277; p) O. Baslé, W. Raimondi, M. del Mar Sanchez Duque, D. Bonne, T. Constantieux, J. Rodriguez, *Org. Lett.* **2010**, *12*, 5246–5249; q) S. Anwar, H.-J. Chang, K. Chen, *Org. Lett.* **2011**, *13*, 2200–2203; r) B.-C. Hong, A. A. Sadani, R. Y. Roshan, N. S. Dange, G.-H. Lee, *Synthesis* **2011**, 1887–1895; s) P. G. McGarraugh, J. H. Jones, S. E. Brenner-Moyer, *J. Org. Chem.* **2011**, *76*, 6309–6319; t) P. Chintala, S. K. Ghosh, E. Long, A. D. Headley, B. Ni, *Adv. Synth. Catal.* **2011**, *353*, 2905–2909; u) Y. Jia, Z. Mao, R. Wang, *Tetrahedron: Asymmetry* **2011**, *22*, 2018–2023; v) D.-F. Yu, Y. Wang, P.-F. Xu, *Adv. Synth. Catal.* **2011**, *353*, 2960–2965; w) S. Varga, G. Jakab, L. Drahos, T. Holczbauer, M. Czugler, T. Soós, *Org. Lett.* **2011**, *13*, 5416–5419; x) C. T. Wong, *Tetrahedron* **2012**, *68*, 481–487; y) B.-C. Hong, N. S. Dange, C.-F. Ding, J.-H. Liao, *Org. Lett.* **2012**, *14*, 448–451; z) S. Rajkumar, K. Shankland, G. D. Brown, A. J. A. Cobb, *Chem. Sci.* **2012**, *3*, 584–588.

[5] For selected examples of organocatalytic asymmetric Michael additions of 1,3-dicarbonyl compounds to nitroalkenes, see a) T. Okino, Y. Hoashi, Y. Takemoto, *J. Am. Chem. Soc.* **2003**, *125*, 12672–12673; b) M. Watanabe, A. Ikagawa, H. Wang, K. Murata, T. Ikariya, *J. Am. Chem. Soc.* **2004**, *126*, 11148–11149; c) S. H. McCooney, S. J. Connon, *Angew. Chem.* **2005**, *117*, 6525–6528; *Angew. Chem. Int. Ed.* **2005**, *44*, 6367–6370; d) J. P. Malerich, K. Haghihara, V. H. Rawal, *J. Am. Chem. Soc.* **2008**, *130*, 14416–11441; e) P. Gao, C. Wang, Y. Wu, Z. Zhou, C. Tang, *Eur. J. Org. Chem.* **2008**, 4563–4566; f) Z.-H. Zhang, X.-Q. Dong, D. Chen, C.-J. Wang, *Eur. J. Org. Chem.* **2008**, 8780–8783; g) Z. Yu, X. Liu, L. Zhou, L. Lin, X. Feng, *Angew. Chem.* **2009**, *121*, 5297–5300; *Angew. Chem. Int. Ed.* **2009**, *48*, 5195–5198; h) D. Almaşi, D. A. Alonso, E. Gómez-Bengoa, C. Nájera, *J. Org. Chem.* **2009**, *74*, 6163–6168; i) X. Jiang, Y. Zhang, X. Liu, G. Zhang, L. Lai, L. Wu, J. Zhang, R. Wang, *J. Org. Chem.* **2009**, *74*, 5562–5567; j) Y. Oh, S. M. Kim, D. Y. Kim, *Tetrahedron Lett.* **2009**, *50*, 4674–4676; k) X.-W. Pu, F.-Z. Peng, H.-B. Zhang, Z.-H. Shao, *Eur. J. Org. Chem.* **2009**, 4622–4626; l) Y. Wang, R.-G. Han, Y.-L. Zhao, S. Yang, P.-F. Xu, D. J. Dixon, *Angew. Chem.* **2009**, *121*, 10018–10022; *Angew. Chem. Int. Ed.* **2009**, *48*, 9834–9838; m) C. Min, X. Han, Z. Liao, X. Wu, H.-B. Zhou, C. Dong, *Adv. Synth. Catal.* **2011**, *353*, 2715–2720;

n) D. Enders, G. Urbanietz, R. Hahn, G. Raabe *Synthesis* **2012**, *44*, 773–783.
[6] a) A. M. Flock, A. Krebs, C. Bolm, *Synlett* **2010**, 1219–1222; b) D. Enders, G. Urbanietz, G. Raabe, *Synthesis* **2011**, 1905–1911.
[7] Product **5a** was obtained in 59% yield, when a catalytic amount (20 mol%) of pyrrolidine was used.
[8] CCDC 850476 (**5c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* www.ccdc.cam.ac.uk/data_request/cif.

Control of Six Contiguous Stereocenters in an Asymmetric Organocatalytic One-Pot Michael/Michael/Aldol Addition Sequence

Adv. Synth. Catal. **2012**, *354*, 1 – 9

Dieter Enders,* Gregor Urbanietz, Elisa Cassens-Sasse, Sebastian Keeß, Gerhard Raabe

9