Microwave-Assisted Organocatalytic Quadruple Domino Reactions of Acetaldehyde and Nitroalkenes

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Abstract: A microwave-assisted, organocatalytic domino Michael/Henry condensation/Michael/aldol condensation reaction has been developed. Employing acetaldehyde and nitroalkenes as substrates, this quadruple cascade allows an efficient asymmetric synthesis of trisubstituted cyclohexene carbaldehydes in moderate to good yields (25–45%) and high enantioselectivities (ee = 89 to >99%). ESI-MS measurements were carried out to support the proposed complex catalytic cycle.

Key words: organocatalysis, cascade reaction, Michael addition, aldol condensation, cyclohexene carbaldehydes

Over the last decade the area of organocatalysis has received much attention, evolving from a narrow field of research with fairly limited examples to one of the main branches in asymmetric catalysis.[1] Within this area, considerable attention has been paid to the development of highly stereoselective asymmetric domino reactions leading to complex molecular structures by convenient one-pot protocols via a reaction cascade.[2] A large number of organocatalytic domino reactions have been developed over the last few years.[3,4] Our group, for example, published a diphenylprolinol-TMS-ether catalyzed triple domino reaction[5–9] that forms tri- and tetrasubstituted cyclohexene carbaldehydes.[4c,e–n] As carbon–carbon bond forming reactions with acetaldehyde provide access to synthetically useful polyketides, many groups have tried to integrate acetaldehyde into aldol, Michael or Mannich reactions using enzymes,[10a,h] trimethyl siloxyethenes as a synthetic equivalent[10e–g] or organocatalysis.[10b–d] The first synthetically useful organocatalytic reactions with acetaldehyde were reported in 2008 by the groups of List and Hayashi; these approaches involved secondary amine catalysed Michael, (self-)aldol and Mannich reactions.[10i–o] Following these protocols, we envisaged a quadruple domino reaction of acetaldehyde with aromatic nitroalkenes, yielding trisubstituted cyclohexene carbaldehydes. To the best of our knowledge, only two amine-catalyzed quadruple domino reactions have been reported so far; these involved an oxa-Michael reaction followed by a Michael addition to a nitroalkene, a consecutive Michael addition of the resulting nitroalkane to an α,β-unsaturated aldehyde followed by an intramolecular aldol reaction.[11]

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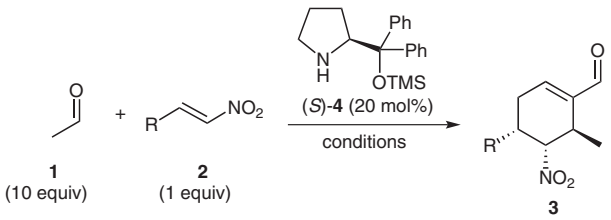
In addition, we planned to undertake mechanistic investigations to endorse the proposed mechanism.[12]

At first we performed the reaction between acetaldehyde (**1**) and nitrostyrene (**2a**) in dioxane at room temperature using (*S*)-diphenylprolinol TMS-ether [(*S*)-**4**, 20 mol%] as a catalyst. The reaction was completed in 14 days, affording the aldehyde **3a** with a moderate yield, high enantioselectivity and a good diastereomeric ratio (96% ee, 4:1 dr, Table 1, entry 1). In the course of the optimization we tested several other solvents (toluene, CH_2Cl_2, MeCN, Et_2O) or even neat acetaldehyde and additives (DABCO, benzoic acid, TFA, *p*-nitrobenzoic acid, chloroacetic acid). To our delight, the best result, with the most significant acceleration of the reaction at room temperature, occurred upon adding two equivalents of water (Table 1, entry 7). To further improve the reaction we tried to apply a modern technique and tested it in a microwave oven (Table 1, entries 4, 5 and 9–12).



Scheme 1 Asymmetric synthesis of cyclohexene carbaldehydes **3** from acetaldehyde (**1**) and nitroalkenes **2**

In the absence of water, formation of the aldehyde **3a** was not observed. However, in the presence of at least two equivalents of water, the reaction went to completion within five hours in high yield (45%), excellent enantioselectivity and with a diastereomeric ratio of 3.5:1 (Table 1, entry 9). Adding more than two equivalents of water (Table 1, entries 10 and 11) or performing the reaction at a higher temperature (Table 1, entry 12) did not lead to any further improvements.

Based on these results, we investigated the scope of the reaction by varying the substituents of the aromatic nitroalkene **2**. In all cases, the cyclohexene carbaldehydes **3** were synthesized at 60 °C in good yields (25–45%), excellent enantioselectivities (89 to >99%) but, unfortunately, low diastereomeric ratios (1.4:1 to 3.5:1, Table 2). The diastereomers were separated by flash chromatography (>96% de, Table 2). The electronic features and the position of the substituent on the aromatic ring had significant influ-

Table 1 Optimization of the Organocatalytic Quadruple Domino Reaction

Entry	Solvent	Temp (°C)	H_2O (equiv)	Time (h)	Yield (%)[a]	ee (%)[b]	dr[c]
1	dioxane	r.t.	0	14 d	29	96	4:1
2	dioxane	40	0	23 d	20	97	2.5:1
3	dioxane	r.t.	2	7 d	20	>99	2.5:1
4[d]	dioxane	70	0	8	0	–	–
5[d]	dioxane	60	2	4.5	30	>99	2.5:1
6	anhyd THF	r.t.	0	14 d	0	–	–
7	anhyd THF	r.t.	2	7 d	25	>99	3.5:1
8	anhyd THF	r.t.	4	7 d	20	>99	3.5:1
9 [d]	anhyd THF	60	2	5	45	>99	3.5:1
10[d]	anhyd THF	60	4	4.5	31	98	3.5:1
11[d]	anhyd THF	60	6	4.5	30	>99	3.5:1
12[d]	anhyd THF	100	2	0.8	0	–	1:1

[a] Yield of the two isolated diastereomers.
[b] Determined by HPLC analysis on a chiral stationary phase.
[c] Determined by GC.
[d] Carried out in a microwave oven at the temperature and the time given.

ence on the reaction time required (from 5 hours up to 12 hours) and the diastereoselectivity obtained (from 3.5:1 down to 1.4:1 dr) but had no influence on the enantioselectivity.

In the case of **3a**, the absolute configuration of the major diastereomer was determined to be 4*S*,5*S*,6*R* (Scheme 1) by NMR measurements and based on previous assignments, whereas the minor diastereomer was shown to be the epimer at the carbon atom bearing the nitro group with 4*S*,5*R*,6*R* configuration.

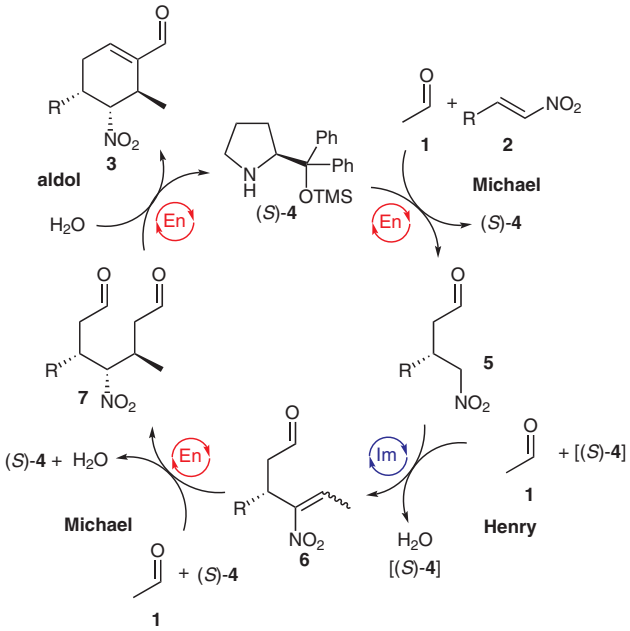
Table 2 Yield and Stereoselectivity of the Organocatalytic Domino Reaction[a]

3	R	Time (h)	Yield (%)[b]	dr[c]	ee (%)[d]	de (%)[e]
a	Ph	5	45	3.5:1	>99	>96
b	*o*-ClC_6H_4	8	33	1.7:1	89	>96
c	*p*-ClC_6H_4	8	40	1.4:1	97	>96
d	Naph	8	31	1.5:1	>99	>96
e	*p*-MeC_6H_4	12	25	1.5:1	>99	>96

[a] Reaction conditions: **1** (10 mmol), nitroalkene **2** (1 mmol), (*S*)-**4** (20 mol%, 0.2 equiv), THF (2 mL), H_2O (2 mmol, 2 equiv), MW (Ramp-time: 1 min, 60 W, 60 °C, PowerMax: Off).
[b] Yield of the two isolated diastereomers.
[c] Determined by GC.
[d] Determined by HPLC analysis on a chiral stationary phase.
[e] Major diastereomer obtained after flash chromatography, determined by NMR spectroscopy.

A plausible catalytic cycle is shown in Scheme 2. The reaction starts with enamine activation of acetaldehyde **1** by the amine catalyst (*S*)-**4** and Michael addition to the nitroalkene **2**. In the next step, the resulting nitroalkane **5** performs a Henry reaction with a second acetaldehyde followed by a condensation, which leads to the newly formed nitroalkene **6**. Enamine activation of a third acetaldehyde and Michael addition of this to the nitroalkene **6** affords the dialdehyde **7**. After an enamine activated intramolecular aldol condensation reaction followed by hydrolysis, the final product **3** is formed and (*S*)-**4** is regenerated for the next catalytic cycle. The result of the Henry condensation step can be explained either by a direct reaction of the iminium nitronate form of **5** with **1** or by the reaction of the nitronate anion of **5** with **1** under iminium activation of **1** and direct elimination of the catalyst.

To support the proposed mechanism and to show that all steps are catalyzed, we conducted additional experiments as well as performing ESI-MS measurements. Both List et al. and Hayashi et al. reported that the Michael addition of acetaldehyde to nitroalkenes proceeded with high enantioselectivities, and therefore this first step can be seen as being catalyzed by the diphenylprolinol (*S*)-**4**.[10i,k]



Scheme 2 Proposed catalytic cycle of the quadruple cascade reaction

For the second step – the Henry reaction of nitroalkane **5** with acetaldehyde – we isolated the 4-nitroaldehyde **5** and tried to apply it as a starting point for our domino reaction under the following conditions: (a) without any additive or catalyst; (b) with triethylamine as an additive and (c) with the diphenylprolinol TMS-ether catalyst. Only in case (c) was the formation of **3a** observed. In the case of the third step – the formation of dialdehyde **7** – we made

the observation that when the enantiopure catalyst (*S*)-**4** was used, only two diastereomers were formed as the major products; the other two diastereomers were formed in only trace amounts that were detectable only by GC-MS. Applying the racemic catalyst *rac*-**4**, all four diastereomers could be detected via GC-MS in the particular diastereomeric ratio given in Table 2. We concluded that this is caused by attack of one enamine-activated acetaldehyde bearing either the (*S*)- or the (*R*)-prolinol **4** on a nitroalkene formed by either (*S*)- or (*R*)-prolinol. This would lead to the formation of all four possible diastereomers and proves that the catalyst controls the stereochemical outcome of this step.

We then performed ESI-MS measurements of the reaction mixture to find evidence of the proposed intermediates. We were glad to see that all of the corresponding iminium ions of product **3b** and all the intermediates given in Scheme 2 could be observed (Figure 1). We also detected two further intermediates (**13** and **14**), which indicate side reactions of acetaldehyde with the other intermediates. The measured and calculated high resolution masses of the intermediates are given in Table 3. The results of the experiments and the ESI-MS measurements support the proposed mechanism.

In summary, we have developed a quadruple domino reaction based on a Michael addition – Henry condensation – Michael addition – aldol condensation sequence of acetaldehyde and aromatic nitroalkenes **2**. This process is efficiently catalyzed by (*S*)-diphenylprolinol TMS-ether to afford trisubstituted functionalised cyclohexene carbaldehydes with three stereogenic centres in moderate to good yields (25–45%; 70–85% per step) and excellent enantioselectivities (89 to >99% ee). The practically pure major diastereomer (de >96%) could be obtained after flash chromatography. The proposed mechanism of the catalytic cycle was supported by additional experiments and ESI-MS measurements.

Table 3 HRMS (ESI) Analysis of Detected Intermediates Leading to **3b**

Species	Mass (calcd)	Mass (measured)[a]	Formula	Error (ppm)
8	236.14338	236.14301	$C_{17}H_{18}N$	–0.4
[**4** + H]$^+$	326.19347	326.19305	$C_{20}H_{28}ONSi$	–0.4
9	535.21782	535.21753	$C_{30}H_{36}O_3N_2ClSi$	0.3
10	561.23347	561.23297	$C_{32}H_{38}O_3N_2ClSi$	0.5
11	605.259689	605.25928	$C_{34}H_{42}O_4N_2ClSi$	0.4
12	587.24913	587.24933	$C_{34}H_{40}O_3N_2ClSi$	0.3
13	649.28590	649.28583	$C_{36}H_{46}O_5N_2ClSi$	0.1
14	693.31212	693.31207	$C_{38}H_{50}O_6N_2ClSi$	–0.1

[a] Calibration using internal standard (MRFA).

All solvents were dried by conventional methods. THF was freshly distilled from Na/molecular sieve (Solvona pellets) under argon. Acetaldehyde was freshly distilled before use with a drop of concentrated sulfuric acid at 60 °C oil bath temperature. The nitroalkenes were prepared according to literature procedures. Preparative column chromatography used Merck silica gel 60, particle size 0.040–0.064 mm (230–240 mesh; flash). Silica gel 60, F254 plates from Merck, Darmstadt were used for analytical TLC. IR spectra

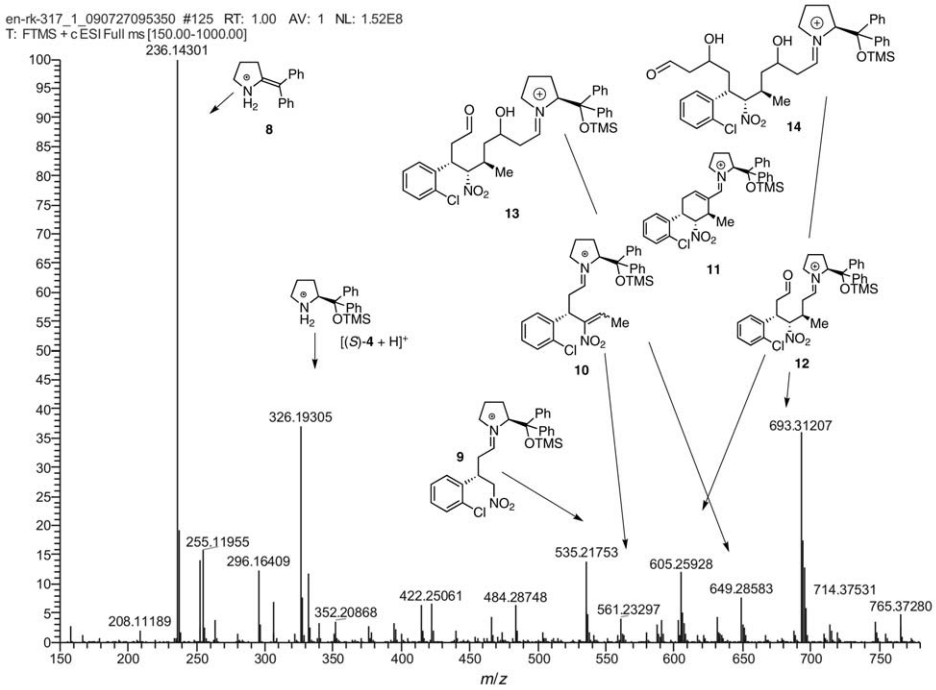


Figure 1 ESI-MS spectrum (positive mode) of the cascade reaction for the synthesis of cyclohexene carbaldehydes, five minutes after the start of the reaction

were taken on a Perkin–Elmer FT-IR 1760 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded on Varian Gemini 300, Mercury 300 or Inova 400 spectrometers and all measurements were performed with TMS as internal standard. HRMS (EI) were acquired on a Finnigan MAT 95 spectrometer. Microanalyses were obtained with a Vario EL elemental analyzer. ESI-MS measurements were made on a LTQ Orbitrap XL, Fa. ThermoFisher Scientific instrument equipped with an ESI source. The microwave oven used was a CEM Discover BenchMate.

Microwave-Assisted Organocatalytic Quadruple Domino Reaction; General Procedure

In a 10-mL microwave vial, diphenylprolinol TMS-ether (*S*)-**4** (65 mg, 0.2 mmol), the aromatic nitroalkene **2** (1 mmol) and distilled H_2O (36 mg, 2 mmol) were dissolved in anhydrous THF (2 mL). After addition of freshly distilled acetaldehyde (0.53 mL, 10 mmol), the vial was closed and heated under microwave irradiation for the time given in Table 2 (1 min Ramptime, 60 W, 60 °C, PowerMax: off). The reaction mixture was then concentrated and directly purified by flash column chromatography (*n*-pentane–Et_2O, 10:1→2:1).

Preparation of ESI-MS Samples

Samples were taken after 5 min of microwave irradiation. After evaporation of the solvent the residue was dissolved in MeCN (1 mL). For measurements with an internal standard the tetrapeptide Met-Arg-Phe-Ala (MRFA) was added.

(4*S*,5*S*,6*R*)-6-Methyl-5-nitro-4-phenylcyclohex-1-enecarbaldehyde (3a)

Yield: 110 mg (45%); pale-yellow oil; ee >99% (Daicel Chiralpak AD; heptane–*i*-PrOH, 9:1); dr = 3.5:1 (GC); $[\alpha]_D^{22}$ +177.1 (*c* 1.00, $CHCl_3$); R_f = 0.3 (pentane–Et_2O, 2:1).

IR (KBr): 2969, 2918, 2852, 1677, 1648, 1540, 1495, 1454, 1408, 1374, 1338, 1278, 1251, 1163, 1140, 1077, 1006, 903, 881, 835, 762, 698 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 7.1 Hz, 3 H, CH_3), 2.75 (ddd, *J* = 20.3, 4.9, 4.9 Hz, 1 H, CH*H*), 3.10–3.22 (m, 1 H, C*H*H), 3.33 (br q, *J* = 7.1 Hz, 1 H, C*H*CH_3), 3.43 (m, 1 H, CHPh), 4.81 (m, 1 H, $CHNO_2$), 7.01 (dd, *J* = 2.7, 4.7 Hz, 1 H, HC=C), 7.18–7.38 (m, 5 H, PhH), 9.51 (s, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 27.8, 31.3, 37.9, 90.7, 126.9 (2 × C), 127.9 (2 × C), 128.8, 137.9, 141.1, 148.9, 192.4.

MS (EI, 70 eV): *m*/*z* (%) = 51 (11), 65 (12), 77 (24), 91 (100), 105 (24), 115 (29), 127 (13), 128 (23), 192 (23), 141 (18), 152 (13), 153 (17), 154 (18), 155 (44), 165 (11), 169 (58), 170 (12), 171 (13), 181 (12), 183 (47), 197 (17), 198 (34), 199 (14), 245 (16) $[M]^+$.

Anal. Calcd for $C_{14}H_{15}NO_3$: C, 68.56; H, 6.16; N, 5.71. Found: C, 68.25; H, 6.22; N, 5.39.

(4*S*,5*S*,6*R*)-4-(2-Chlorophenyl)-6-methyl-5-nitrocyclohex-1-enecarbaldehyde (3b)

Yield: 92 mg (33%); pale-yellow oil; ee >89% (Daicel Chiralpak IA; heptane–*i*-PrOH, 8:2); dr = 1.7:1 (GC); $[\alpha]_D^{22}$ +225.4 (c 1.00, $CHCl_3$); R_f = 0.4 (pentane–EtOAc, 6:1).

IR (KBr): 2929, 2827, 1677, 1645, 1593, 1543, 1475, 1439, 1417, 1404, 1369, 1335, 1265, 1191, 1166, 1127, 1102, 1035, 1015, 906, 885, 844, 762, 700, 673 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (d, *J* = 7.9 Hz, 3 H, CH_3), 2.65 (ddd, *J* = 19.8, 5.5, 5.5 Hz, 1 H, C*H*H), 3.12–3.22 (m, 1 H, CH*H*), 3.43 (br q, *J* = 7.9 Hz, 1 H, C*H*CH_3), 4.03 (m, 1 H, CHAr), 4.94 (m, 1 H, $CHNO_2$), 7.15 (dd, *J* = 2.7, 4.9 Hz, 1 H, HC=C), 7.18–7.38 (m, 4 H, ArH), 9.53 (s, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.2, 29.7, 32.7, 34.3, 87.9, 127.3, 127.9, 129.1, 129.9, 141.4, 148.2, 192.3.

MS (EI, 70 eV): *m*/*z* (%) = 75 (11), 76 (11), 77 (18), 82 (12), 83 (15), 88 (11), 91 (13), 114 (16), 125 (100), 126 (25), 127 (29), 128 (12), 138 (26), 140 (20), 151 (28), 152 (32), 153 (11), 164 (19), 167 (19), 168 (13), 189 (18), 197 (13), 203 (53), 204 (11), 205 (23), 217 (32), 231 (20), 232 (13), 233 (10), 279 (7) $[M]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{14}NO_3Cl$: 279.0662; found: 279.0657.

(4*S*,5*S*,6*R*)-4-(4-Chlorophenyl)-6-methyl-5-nitrocyclohex-1-enecarbaldehyde (3c)

Yield: 105 mg (40%); pale-yellow oil; ee >97% (Daicel Chiralpak AD; heptane–*i*-PrOH, 9:1); dr = 1.4:1 (GC); $[\alpha]_D^{22}$ +65.1 (*c* 1.00, $CHCl_3$); R_f = 0.3 (pentane–Et_2O, 2:1).

IR (KBr): 3436, 3021, 2920, 2851, 1723, 1685, 1649, 1547, 1493, 1455, 1417, 1372, 1337, 1256, 1216, 1165, 1141, 1094, 1014, 883, 822, 757, 665, 525 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.55 (d, *J* = 7.2 Hz, 3 H, CH_3), 2.95 (dt, *J* = 5.7, 20.0 Hz, 1 H, C*H*H), 3.24–3.34 (m, 1 H, CH*H*), 3.51–3.61 (m, 2 H, C*H*CH_3, CHAr), 5.11 (dd, *J* = 2.7, 9.7 Hz, 1 H, $CHNO_2$), 7.17 (dd, *J* = 2.0, 4.7 Hz, 1 H, HC=C), 7.28–7.35 (m, 2 H, ArH), 7.45–7.56 (m, 2 H, ArH), 9.70 (s, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 27.8, 32.3, 37.5, 90.8, 128.7, 128.9, 128.9, 129.2, 133.9, 136.7, 141.3, 148.5, 192.5.

MS (EI, 70 eV): *m*/*z* (%) = 77 (12), 91 (13), 115 (15), 125 (73), 127 (36), 128 (22), 139 (20), 141 (18), 149 (10), 151 (11), 152 (31), 153 (35), 154 (17), 165 (23), 167 (11), 168 (11), 179 (11), 189 (30), 191 (14), 197 (13), 199 (18), 203 (21), 205 (10), 217 (55), 219 (19), 231 (12), 232 (100), 233 (65), 234 (42), 235 (22), 279 (20) $[M]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{14}NO_3Cl$: 279.0662; found: 279.0657.

(4*S*,5*S*,6*R*)-6-Methyl-4-(naphthalene-2-yl)-5-nitrocyclohex-1-enecarbaldehyde (3d)

Yield: 91 mg (31%); pale-yellow oil; ee >99% (Daicel Chiralpak AS; heptane–*i*-PrOH, 8:2); dr = 1.5:1 (GC); $[\alpha]_D^{23}$ +53.7 (*c* 1.00, $CHCl_3$); R_f = 0.2 (pentane–Et_2O, 2:1).

IR ($CHCl_3$): 3387, 3056, 3018, 2919, 2851, 1684, 1649, 1547, 1453, 1418, 1375, 1334, 1217, 1142, 963, 894, 860, 820, 754, 668, 478 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.59 (d, *J* = 7.2 Hz, 3 H, CH_3), 3.04 (ddd, *J* = 20.0, 5.4, 5.4 Hz, 1 H, C*H*H), 3.43–3.50 (m, 1 H, CH*H*), 3.52–3.60 (m, 1 H, C*H*CH_3), 3.73–3.83 (m, 1 H, CHNaph), 5.15 (dd, *J* = 3.2, 1.2 Hz, 1 H, $CHNO_2$), 7.24 (dd, *J* = 4.9, 2.5 Hz, 1 H, HC=C), 7.49–7.72 (m, 3 H, Naph), 7.92–8.07 (m, 3 H, Naph), 9.73 (s, 1 H, CHO).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.7, 27.9, 32.8, 38.1, 90.4, 125.2, 126.1, 126.2, 126.3, 126.5, 127.6, 127.9, 132.9, 133.4, 135.5, 141.4, 192.7.

MS (EI, 70 eV): *m*/*z* (%) = 77 (17), 91 (11), 93 (14), 101 (11), 115 (16), 127 (12), 128 (19), 141 (72), 152 (17), 155 (22), 165 (40), 166 (11), 178 (42), 179 (34), 189 (19), 190 (13), 191 (22), 192 (11), 202 (30), 203 (28), 204 (20), 205 (52), 206 (12), 215 (34), 216 (14), 219 (30), 220 (11), 231 (34), 232 (12), 233 (25), 247 (30), 248 (88), 249 (39), 295 (100) $[M]^+$, 296 (20) $[M + H]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{17}NO_3$: 295.1208; found: 295.1203.

(4*S*,5*S*,6*R*)-6-Methyl-5-nitro-4-*p*-tolylcyclohex-1-enecarbaldehyde (3e)

Yield: 65 mg (25%); pale-yellow oil; ee >99% (Daicel Chiralpak IA; heptane–*i*-PrOH, 8:2); dr = 1.7:1 (GC); $[\alpha]_D^{23}$ +55.4 (*c* 1.00, $CHCl_3$); R_f = 0.3 (pentane–Et_2O, 1:1).

IR (KBr): 2929, 2851, 1685, 1648, 1547, 1515, 1451, 1418, 1372, 1337, 1265, 1165, 1145, 1080, 1045, 884, 839, 814, 737, 704, 547 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (d, *J* = 7.1 Hz, 3 H, CH_3), 2.47 (s, 3 H, $ArCH_3$), 2.87 (ddd, *J* = 20.1, 5.5, 5.5 Hz, 1 H, C*H*H), 3.21–3.31 (m, 1 H, CH*H*), 3.43 (dq, *J* = 1.0, 7.1 Hz, 1 H, C*H*CH_3), 3.48–3.52 (m, 1 H, CHAr), 4.91 (dd, 1 H, *J* = 1.4, 3.0 Hz, $CHNO_2$), 7.11–7.14 (m, 1 H, HC=C), 7.20–7.30 (m, 4 H, ArH), 9.64 (s, 1 H, CHO).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.7, 21.2, 28.1, 32.8, 37.8, 90.7, 127.3, 127.8 (2 × C), 129.4, 129.7, 141.3, 149.1, 192.5.

MS (EI, 70 eV): *m/z* (%) = 77 (13), 91 (21), 93 (12), 105 (100), 115 (18), 119 (17), 138 (18), 129 (16), 141 (11), 143 (14), 145 (12), 153 (10), 169 (43), 183 (32), 184 (38), 185 (16), 195 (12), 197 (32), 212 (22), 213 (13), 259 (24) $[M]^+$.

HRMS (ESI): *m/z* $[M + H]^+$ calcd for $C_{15}H_{17}NO_3$: 259.1208; found: 259.1203.

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References

(1) For recent reviews on organocatalysis, see: (a) Berkessel, A.; Gröger, H. *Asymmetric Organocatalysis*; Wiley-VCH: Weinheim, **2005**. (b) Dalko, P. I. *Enantioselective Organocatalysis*; Wiley-VCH: Weinheim, **2007**. (c) Special issue on organocatalysis: *Chem. Rev.* **2007**, *107*, issue 12. (d) Pellisier, H. *Tetrahedron* **2007**, *63*, 9267. (e) de Figueiredo, R. M.; Christmann, M. *Eur. J. Org. Chem.* **2007**, 2575. (f) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; *Angew. Chem.* **2008**, *120*, 4716. (g) Kotsuki, H.; Ikishima, H.; Okuyama, A. *Heterocycles* **2008**, *75*, 493. (h) Kotsuki, H.; Ikishima, H.; Okuyama, A. *Heterocycles* **2008**, *75*, 757. (i) Enders, D.; Narine, A. A. *J. Org. Chem.* **2008**, *73*, 7857. (j) Melchiorre, P.; Marigo, M.; Carlone, A.; Bartoli, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 6138; *Angew. Chem.* **2008**, *120*, 6232. (k) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583. (l) Bertelsen, S.; Jørgensen, K. A. *Chem. Soc. Rev.* **2009**, *38*, 2178.

(2) For recent reviews on domino reactions, see: (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Tietze, L. F.; Brasche, G.; Gericke, K. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, **2006**. (c) Pellisier, H. *Tetrahedron* **2006**, *62*, 1619. (d) Pellisier, H. *Tetrahedron* **2006**, *62*, 2143. (e) Nicolaou, K. C.; Edmonds, D. J.; Bulger, P. G. *Angew. Chem. Int. Ed.* **2006**, *45*, 7134; *Angew. Chem.* **2006**, *118*, 7292. (f) Chapman, C. J.; Frost, C. G. *Synthesis* **2007**, 1. (g) Walji, A. M.; MacMillan, D. W. C. *Synlett* **2007**, 1477.

(3) For reviews on organocatalytic domino reactions, see: (a) Enders, D.; Grondal, C.; Hüttl, M. R. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 1570; *Angew. Chem.* **2007**, *119*, 1590. (b) Yu, X.; Wang, W. *Org. Biomol. Chem.* **2008**, *6*, 2037.

(4) For selected examples of organocatalytic domino reactions, see: (a) Yang, J. W.; Fonseca, M. T. H.; List, B. *J. Am. Chem. Soc.* **2005**, *127*, 15036. (b) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (c) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861. (d) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354. (e) Enders, D.; Hüttl, M. R. M.; Runsink, J.; Raabe, G.; Wendt, B. *Angew. Chem. Int. Ed.* **2007**, *46*, 467; *Angew. Chem.* **2007**, *119*, 471. (f) Enders, D.; Narine, A. A.; Benninghaus, T. R.; Raabe, G. *Synlett* **2007**, 1667. (g) Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 1101; *Angew. Chem.* **2007**, *119*, 1119. (h) Hayashi, Y.; Okano, T.; Aratake, S.; Hazelard, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 4922; *Angew. Chem.* **2007**, *119*, 5010. (i) Vicario, J. L.; Reboredo, L.; Badía, D.; Carillo, L. *Angew. Chem. Int. Ed.* **2007**, *46*, 5168; *Angew. Chem.* **2007**, *119*, 5260. (j) Rueping, M.; Sugiono, E.; Merino, E. *Angew. Chem. Int. Ed.* **2008**, *47*, 3046; *Angew. Chem.* **2008**, *120*, 3089. (k) Enders, D.; Wang, C.; Bats, J. W. *Angew. Chem. Int. Ed.* **2008**, *47*, 7539; *Angew, Chem.* **2008**, *120*, 7649. (l) Zhao, G.-L.; Rios, R.; Vesley, J.; Eriksson, L.; Córdova, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 8468; *Angew. Chem.* **2008**, *120*, 8596. (m) Lu, M.; Zhu, D.; Lu, Y.; Hou, Y.; Tan, B.; Zhong, G. *Angew. Chem. Int. Ed.* **2008**, *47*, 10187; *Angew. Chem.* **2008**, *120*, 10341. (n) Enders, D.; Hüttl, M. R. M.; Raabe, G.; Bats, J. W. *Adv. Synth. Catal.* **2008**, *350*, 267. (o) Kotame, P.; Hong, B.-C.; Liao, J.-H. *Tetrahedron Lett.* **2009**, *50*, 704. (p) Franzén, J.; Fisher, A. *Angew. Chem. Int. Ed.* **2009**, *48*, 787; *Angew. Chem.* **2009**, *121*, 801.

(5) For reviews on organocatalytic Michael additions, see: (a) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (b) Sulzer-Mossé, S.; Alexakis, A. *Chem. Commun.* **2007**, 3123. (c) Vicario, J. L.; Badía, D.; Carillo, L. *Synthesis* **2007**, 2065. (d) Almasi, D.; Alonso, D. A.; Nájera, C. *Tetrahedron: Asymmetry* **2007**, *18*, 299.

(6) For a review on organocatalytic aldol reactions, see: Guillena, G.; Nájera, C.; Ramón, D. J. *Tetrahedron: Asymmetry* **2007**, *18*, 2249.

(7) For selected examples of organocatalytic intramolecular aldol reactions, see: (a) Pidathala, C.; Hoang, L.; Vignola, N.; List, B. *Angew. Chem. Int. Ed.* **2003**, *42*, 2785; *Angew. Chem.* **2003**, *115*, 2891. (b) Kriis, K.; Kanger, T.; Laars, M.; Müürisepp, A.-M.; Pehk, T.; Lopp, M. *Synlett* **2006**, 1699. (c) Enders, D.; Niemeier, O.; Straver, L. *Synlett* **2006**, 3399. (d) Hayashi, Y.; Sekiziwa, H.; Yamaguchi, J.; Gotoh, H. *J. Org. Chem.* **2007**, *72*, 6493. (e) Yoshitomi, Y.; Makino, K.; Hamada, Y. *Org. Lett.* **2007**, *9*, 2457.

(8) For selected examples of organocatalytic domino reactions involving intramolecular aldol reactions, see refs 4c–g, 4n, 4o and: (a) Halland, N.; Abruel, P. S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2004**, *43*, 1272; *Angew. Chem.* **2004**, *116*, 1292. (b) Brandau, B.; Maerten, E.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2006**, *128*, 14986. (c) Govender, T.; Hojbri, L.; Moghaddam, F. M.; Arvidsson, P. I. *Tetrahedron: Asymmetry* **2006**, *17*, 1763. (d) Wang, J.; Li, H.; Xie, H.; Zu, L.; Shen, X.; Wang, W. *Angew. Chem. Int. Ed.* **2007**, *46*, 9050; *Angew. Chem.* **2007**, *119*, 9208. (e) Li, H.; Wang, J.; Xie, H.; Zu, L.; Liang, W.; Duesler, E. N.; Wang, W. *Org. Lett.* **2007**, *9*, 965. (f) Hong, B.-C.; Nimje, R. Y.; Sadani, A. A.; Liao, J.-H. *Org. Lett.* **2008**, *10*, 2345. (g) Penon, O.; Carlone, A.; Mazzanti, A.; Locatelli, M.; Sambri, L.; Bartoli, G.; Melchiorre, P. *Chem. Eur. J.* **2008**, *14*, 4788.

(9) For reviews on diphenylprolinol TMS-ether, see: (a) Palomo, C.; Mielgo, A. *Angew. Chem. Int. Ed.* **2006**, *45*, 7876; *Angew. Chem.* **2006**, *118*, 8042. (b) Mielgo, A.; Palomo, C. *Chem. Asian J.* **2008**, *3*, 922.
(10) For reactions with acetaldehyde, see: (a) Gijsen, H. J. M.; Wong, C.-H. *J. Am. Chem. Soc.* **1994**, *116*, 8422. (b) Bogevig, A.; Kumaragurubaran, N.; Jørgensen, K. A. *Chem. Commun.* **2002**, 620. (c) Cordova, A.; Notz, W.; Barbas, C. F. III *J. Org. Chem.* **2002**, *67*, 301. (d) Northrup, A. B.; MacMillan, D. W. C. *Science* **2004**, *305*, 1752. (e) Denmark, S. E.; Bui, T. *J. Org. Chem.* **2005**, *70*, 10190. (f) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2006**, *128*, 48. (g) Boxer, M. B.; Yamamoto, H. *J. Am. Chem. Soc.* **2007**, *129*, 2762. (h) Dean, S. M.; Greenberg, W. A.; Wong, C.-H. *Adv. Synth. Catal.* **2007**, *349*, 1308. (i) García-García, P.; Ladépêche, A.; Halder, R.; List, B. *Angew. Chem. Int. Ed.* **2008**, *47*, 4719; *Angew. Chem.* **2008**, *120*, 4797. (j) Hayashi, Y.; Itoh, T.; Aratake, S.; Ishikawa, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 2082; *Angew. Chem.* **2008**, *120*, 2112. (k) Hayashi, Y.; Itoh, T.; Ohkubo, M.; Ishikawa, H. *Angew. Chem. Int. Ed.* **2008**, *47*, 4722; *Angew. Chem.* **2008**, *120*, 4800. (l) Hayashi, Y.; Okano, T.; Itoh, T.; Urushima, T.; Ishikawa, H.; Uchimaru, T. *Angew. Chem. Int. Ed.* **2008**, *47*, 9053; *Angew. Chem.* **2008**, *120*, 9193. (m) Hayashi, Y.; Samanta, S.; Itoh, T.; Ishikawa, H. *Org. Lett.* **2008**, *10*, 5581. (n) Yang, J. W.; Chandler, C.; Stadler, M.; Kampen, D.; List, B. *Nature* **2008**, *452*, 453. (o) Chandler, C.; Galzerano, P.; Michrowska, A.; List, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 1978; *Angew. Chem.* **2009**, *121*, 2012. (p) Itoh, T.; Ishikawa, H.; Hayashi, Y. *Org. Lett.* **2009**, *11*, 3854.
(11) For organocatalytic quadruple domino reactions, see: (a) Kotame, P.; Hong, B.-C.; Liao, J.-H. *Tetrahedron Lett.* **2009**, *50*, 704. (b) Zhang, F.-L.; Xu, A.-W.; Gong, Y.-F.; Wei, M.-H.; Yang, X.-L. *Chem. Eur. J.* **2009**, *15*, 6815.
(12) For the elucidation of the mechanism of an organocatalytic reaction, see: Schrader, W.; Handayani, P. P.; Zhou, J.; List, B. *Angew. Chem. Int. Ed.* **2009**, *48*, 1463; *Angew. Chem.* **2009**, *121*, 1491.