Asymmetric Synthesis of 3-Substituted Hexahydro-3*H*-isochromenes via an Organocatalytic Triple Cascade/Yb-Catalyzed Hetero-Diels–Alder Sequence

Nico Erdmann, Iuliana Atodiresei, Dieter Enders*

Institute of Organic Chemisty, RWTH Aachen University, Landoltweg 1, 52074 Aachen, Germany
Fax +49(241)8092127; E-mail: enders@rwth-aachen.de

Received: 25.04.2012; Accepted: 25.04.2012

Abstract: An efficient two-step asymmetric synthesis of highly substituted 3-alkoxy-hexahydro-3*H*-isochromenes and 3-sulfenylated hexahydro-3*H*-isochromenes is described. The procedure involves an organocatalytic triple cascade reaction, followed by an intermolecular [Yb(fod)$_3$]-catalyzed inverse-electron-demand hetero-Diels–Alder reaction. Using this strategy, a total of six stereogenic centers are obtained with excellent diastereoselectivities and virtually complete enantioselectivities (>95:5 dr, >99% ee).

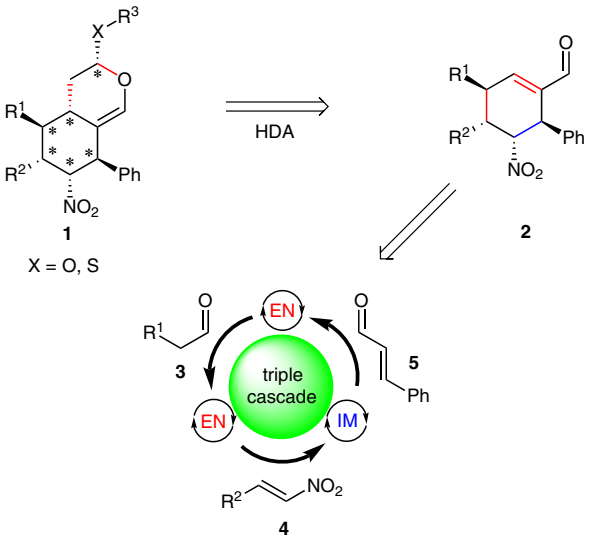
Key words: asymmetric synthesis, organocatalysis, Diels–Alder reaction, domino reaction, isochromenes

The inverse-electron-demand hetero-Diels–Alder reaction (HDA)[1,2] of α,β-unsaturated carbonyl compounds with electron-rich alkenes is a powerful tool in the synthesis of sugars and their derivatives.[3] Furthermore, it is frequently used in the synthesis of other natural products.[4] Generally, inverse-electron-demand HDA reactions have been catalyzed either by Lewis acids[5] or by organocatalysts.[6]

In this communication we would like to report on a two-step asymmetric approach to the synthesis of the hexahydro-3*H*-isochromene core. This structural element is present in several natural products that are known for their widespread biological activities, such as angiogenesis inhibitors,[7] herbicides,[8] compounds with cytotoxic activity in selected tumor lines,[9] and HeLa cells.[10] Other derivatives were tested as therapeutics for postmenopausal osteoporosis, lipid metabolic disorder, menopausal syndrome, and hypogonadism.[11]

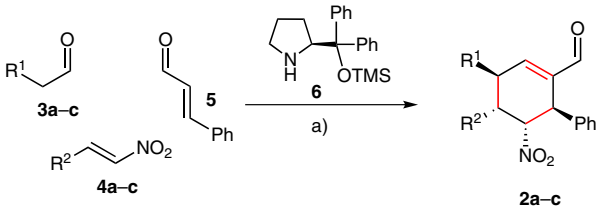
From a retrosynthetic perspective, we planned to build up the second dihydropyran ring of the isochromene title compounds **1** by an inverse-electron-demand HDA reaction between a chiral cyclohexene carbaldehyde and an electron-rich double bond present in vinylethers and vinylthioether (Scheme 1). The cyclohexene ring of **2** is constructed by an organocatalytic triple cascade reaction[12–14] based on a methodology developed in our group.[15,16]

The triple cascade reaction was performed in chloroform starting from aldehydes **3**, nitroalkenes **4**, and enals **5** catalyzed by 20 mol% TMS-diphenyl prolinol **6** (Scheme 2, Table 1) affording cyclohexene carbaldehydes **2** with 41–52% yield, good diastereoselectivities (dr >95:5) and virtually complete enantioselectivities (ee >99%).

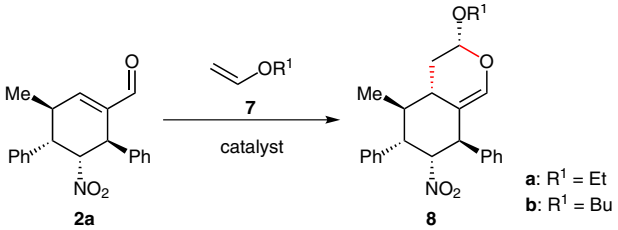


Scheme 1 Retrosynthetic analysis of the asymmetric synthesis of 3-substituted hexahydro-3*H*-isochromenes via a triple cascade/hetero-Diels–Alder (HDA) sequence

With the cyclohexene carbaldehydes in hand, several catalysts and conditions for the HDA reaction were screened using cyclohexene carbaldehyde **2a** and vinylethers **7a** and **7b** (Scheme 3).



Scheme 2 Organocatalytic triple cascade reaction: *Reagents and conditions*: (a) **6** (20 mol%), $CHCl_3$, 12 h at 0 °C then 48 h at r.t.



Scheme 3 Hetero-Diels–Alder reaction

SYNTHESIS 2012, 44, 2107–2113
Advanced online publication: 04.06.2012
DOI: 10.1055/s-0031-1290374; Art ID: SS-2012-Z0390-OP

Table 1 Variations of the Triple Cascade

2	R^1	R^2	Yield (%)	dr[a]	ee (%)[b]
a	Me	Ph	41	>95:5	>99
b	Me	4-ClC_6H_4	43	>95:5	>99
c	4-phenylbut-3-ynyl	Ph	52	>95:5	>99

[a] Determined by NMR spectroscopic analysis.
[b] Determined by chiral stationary phase HPLC.

For the first part of the screening, ethyl vinyl ether was used as an electron-rich dienophile. Whereas with 10 mol% catalyst loading of [Yb(fod)$_3$] and two hours microwave irradiation in a sealed flask no conversion could be detected (Table 2, entries 1 and 2), with 10 mol% [Yb(fod)$_3$] and an increased time as well as an increased amount of ethyl vinyl ether (20 equiv) the yield went up to 60% (Table 2, entries 3 and 4). To confirm the effect of microwave irradiation for the inverse-electron-demand HDA cycloaddition, the reaction was performed by heating in a sealed flask (Table 2, entry 5). Other commonly used catalysts for inverse-electron-demand HDA reactions on α,β-unsaturated aldehydes with vinylethers proved to be inferior to those obtained with [Yb(fod)$_3$] (Table 2, entries 6–8). Increasing the reaction time for the HDA reaction under microwave irradiation to 15 hours led to full conversion and 85% yield of the isolated 3-ethoxyhexahydro-3*H*-isocromene **8a** (Table 2, entry 9).

Encouraged by these results, this methodology was then applied to butyl vinyl ether. To our delight, the reaction was already finished after five hours (Table 2, entry 10). Based on this higher reactivity, the catalyst loading could be lowered to 6 mol% (Table 2, entry 12). Unfortunately, attempts to reduce the reaction time by increasing the temperature led to a decrease in diastereoselectivity (Table 2, entry 13). As above, conducting the HDA reaction with butyl vinyl ether in an oil bath resulted in a lower conversion and extended reaction time.

To determine the scope of the triple cascade/HDA sequence, other vinyl ethers were tested (Scheme 4, Table 3; **1c** and **1d**). Fortunately, even vinyl thioethers could be employed in the HDA reaction, and 3-sulfenylated hexahydro-3*H*-isochromenes **1g** and **1h** were obtained in good yields and excellent stereoselectivities. To further demonstrate the scope of the reaction, R^2 and R^3 were also varied (Table 3; **1e** and **1f**). Whereas an intramolecular HDA reaction of **2c** with the triple bond (Table 3, entry f) could be feasible, the cycloaddition product **1f** of the intermolecular HDA reaction was observed exclusively.

The relative and absolute configuration of the 3-alkoxy- or 3-sulfenylated hexahydro-3*H*-isochromenes was determined by ^{1}H NMR spectroscopic analysis (coupling constants) and by X-ray crystallography in the case of **1c** (Figure 1).[17]

In summary, we have developed an organocatalytic triple cascade/[Yb(fod)$_3$]-catalyzed inverse-electron-demand

Table 2 Optimization of the Hetero-Diels–Alder Reaction

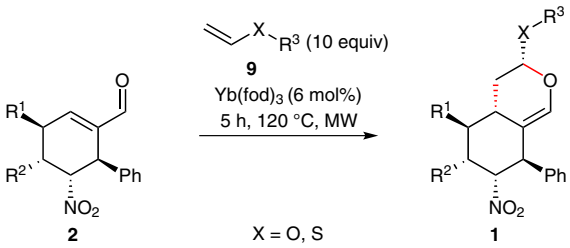
Entry	R^1	Catalyst[a]	mol%	**7** (equiv)	T (°C)	Time (h)	Conv. (%)[b]	dr[b]
1	Et	Yb(fod)$_3$	5	10	120	2	<5	n.d.
2	Et	Yb(fod)$_3$	8	10	120	2	<5	n.d.
3	Et	Yb(fod)$_3$	10	20	120	5	56	87:13
4	Et	Yb(fod)$_3$	10	20	120	10	64	88:12
5[c]	Et	Yb(fod)$_3$	10	20	120	24	40	89:11
6	Et	Eu(fod)$_3$	10	20	120	10	54	70:30
7	Et	Zn(OTf)$_3$	10	20	120	10	<5	n.d.
8	Et	Byp$_2$Cu(OTf)$_2$	10	20	120	10	<5	n.d.
9	Et	Yb(fod)$_3$	10	20	120	15	>95 (85)[c]	>95:5[d]
10	Bu	Yb(fod)$_3$	10	15	120	5	>95	82:18
11	Bu	Yb(fod)$_3$	3	10	120	10	69	85:15
12	Bu	Yb(fod)$_3$	6	10	120	5	>95 (85)[c]	86:14 (>95:5)[d]
13	Bu	Yb(fod)$_3$	6	10	140	2,5	>95	74:26
14[e]	Bu	Yb(fod)$_3$	6	15	120	20	87	81:19

[a] fod: 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionate, Byp: 2,2′-bipyridine.
[b] Determined by GC analysis.
[c] Yield of isolated hexahydro-3*H*-isochromene **8** given in parentheses.
[d] dr of isolated **8**.
[e] Heated in a sealed tube within an oil bath.

Table 3 Scope of the Triple Cascade/HDA Sequence

1	R^1	R^2	XR^3	Yield (%)	dr[a]
1a[b]	Me	Ph	OEt	85	>95:5
1b	Me	Ph	OBu	85	>95:5
1c	Me	Ph	OCH_2CH_2Cl	63	>95:5
1d	Me	Ph	O(*i*-Bu)	61	95:5
1e	Me	4-ClC_6H_4	OBu	81	>95:5
1f	4-phenylbut-3-ynyl	Ph	OBu	63	>95:5
1g	Me	Ph	SEt	78	>95:5
1h[c]	Me	Ph	SPh	49	>95:5

[a] Determined by NMR spectroscopic analysis.
[b] $[Yb(fod)_3]$ (10 mol%), **9** (20 equiv), 15 h.
[c] After 10 h at 120 °C.



Scheme 4 Scope of the hetero-Diels–Alder reaction

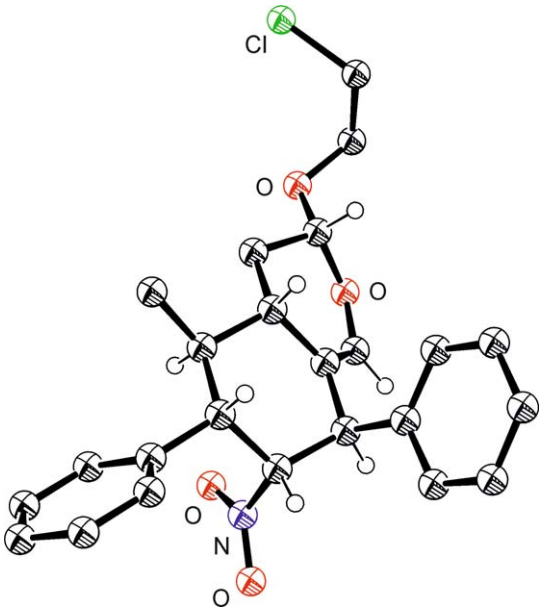


Figure 1 Determination of the absolute configuration of **1c** by X-ray analysis

hetero-Diels–Alder sequence to afford highly functionalized 3-substituted hexahydro-3*H*-isochromenes bearing six stereogenic centers in virtually enantiopure form with excellent diastereomeric ratios and in moderate to good yields.

Unless otherwise noted, all commercially available compounds were used without further purification. $CHCl_3$ was freshly distilled under argon from $CaCl_2$. The catalyst was prepared according to the previously described procedure.[18] Literature protocols were used to prepare **2a** and **2b**.[13] All microwave reactions were performed with a CEM Discover system. For preparative column chromatography, SIL G-25 UV254 (Macherey-Nagel, particle size 0.040–0.063 mm, 230–240 mesh, flash) was used. Visualization of the developed TLC plates was performed with ultraviolet irradiation (254 nm). Optical rotation values were measured with a Perkin–Elmer 241 polarimeter. Mass spectra were measured with a Finnigan SSQ7000 (EI 70 eV) spectrometer and a high-resolution mass spectra with a Thermo Fisher Scientific Orbitrap XL. IR spectra were recorded with a Perkin–Elmer FT-IR Spectrum 100 using an ATR-Unit. ^1H and ^{13}C NMR spectra were recorded at ambient temperature with Varian Mercury 300 or Inova 400 spectrometers with tetramethylsilane as an internal standard. Analytical HPLC was performed with a Hewlett–Packard 1100 Series instrument using chiral stationary phases (Chiralcel OD, Chiralcel OJ, Chiralpak AD, Chiralpak AS, Chiralcel IA).

General Procedure 1 (GP 1)

TMS-prolinol **6** (0.2 equiv) and nitroalkene **4** (1 equiv) were dissolved in $CHCl_3$ (2 mL per 1 mmol of **4**) at 0 °C. Aldehyde **3** (1.4 equiv) was slowly added, followed by slow addition of the α,β-unsaturated aldehyde **5** (1.4 equiv). The reaction was kept at 0 °C for 12 h and then allowed to warm to r.t. Stirring was continued for 48 h. The product was purified by flash chromatography.

General Procedure 2 (GP 2)

Cyclohexene carbaldehyde (0.31 mmol), $[Yb(fod)_3]$ (6 mol%) and vinyl ether (10 equiv) were mixed in a 5 mL microwave flask. The reaction mixture was heated for 5 h to 120 °C (300 W with 'cooling off' setting). The crude product was directly loaded onto a flash column and purified.

6-(4-Phenylbut-3-yn-1-yl)cyclohexene-carbaldehyde 2c

The synthesis followed GP 1 to give the main diastereomer.

Yield: 455 mg (52%); colorless crystals; mp 74 °C; ee >99%; R_f = 0.27 (pentane–Et_2O, 2:1); $[\alpha]_D^{24}$ –7.59 (*c* 1, $CHCl_3$).

IR ($CDCl_3$): 1686, 1491, 1366, 1160, 757, 695 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 1.77 (m, 1 H), 1.98 (m, 1 H), 2.60 (t, *J* = 6.6 Hz, 2 H), 3.13 (dd, *J* = 2.3, 10.4 Hz, 1 H), 3.66 (m, 1 H), 4.48 (s, 1 H), 4.90 (s, 1 H), 7.05 (m, 2 H), 7.34 (m, 14 H), 9.59 (s, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 16.8, 31.2, 36.2, 43.1, 82.5, 88.6, 92.6, 123.3, 127.0 (2C), 128.0 (3C), 128.1 (2C), 128.2, 128.4 (2C), 129.2 (2C), 129.4 (2C), 131.5 (2C), 136.9, 137.5, 138.8, 153.7, 192.0.

MS (EI): *m*/*z* = 388 $[M - HNO_2]^+$.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{29}H_{25}NO_3$: 436.1907; found: 436.1899.

Anal. Calcd for $C_{29}H_{25}NO_3$: C, 79.98; H, 5.79; N, 3.22. Found: C, 79.48; H, 5.57; N, 2.99.

3-Ethoxy-hexahydro-3*H*-isochromene (1a)
The synthesis followed GP 2 to give the main diastereomer.

Yield: 105 mg (85%); colorless solid; mp 55 °C; ee >99%; R_f = 0.18 (pentane–Et_2O, 20:1); $[\alpha]_D^{24}$ –60.5 (*c* 1, $CHCl_3$).

IR ($CDCl_3$): 2969, 2926, 2868, 1661, 1548, 1493, 1451, 1367, 1240, 1125, 1061, 1000, 948, 874, 761, 701 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.77 (d, *J* = 6.0 Hz, 3 H), 1.31 (t, *J* = 7.1 Hz, 3 H), 1.90 (ddd, *J* = 8.6, 12.9, 17.3 Hz, 1 H), 2.28 (m, 1 H), 2.37 (ddd, *J* = 2.0, 6.9, 12.9 Hz, 1 H), 2.70 (dd, *J* = 3.3, 12.0 Hz, 1 H), 2.77 (m, 1 H), 3.65 (m, 1 H), 3.94 (s, 1 H), 4.00 (m, 1 H), 5.07 (dd, *J* = 1.9, 8.5 Hz, 1 H), 5.32 (dd, *J* = 1.9, 3.3 Hz, 1 H), 6.32 (d, *J* = 1.6 Hz, 1 H), 7.06 (m, 2 H), 7.27 (m, 4 H), 7.44 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5, 18.1, 34.3, 35.0, 36.8, 47.2, 48.3, 64.7, 93.4, 99.8, 110.0, 127.5 (2C), 127.6, 127.8, 128.5 (2C), 129.1 (2C), 129.4 (2C), 139.0, 139.6, 141.0.

MS (EI): *m*/*z* = 393 $[M]^+$.

HRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{27}NO_4$: 416.1832; found: 416.1832.

3-Butoxy-hexahydro-3*H*-isochromene (1b)
The synthesis followed GP 2 to give the main diastereomer.

Yield: 110 mg (85%); colorless solid; mp 78 °C; R_f = 0.33 (pentane–Et_2O, 20:1); $[\alpha]_D^{24}$ –15.4 (*c* 6.1, $CHCl_3$).

IR ($CHCl_3$): 1649, 1544, 1372, 1235, 1133, 1071, 987, 946, 762, 703 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (d, *J* = 6.0 Hz, 3 H), 0.95 (t, *J* = 7.4 Hz, 3 H), 1.43 (m, 2 H), 1.65 (m, 2 H), 1.88 (ddd, *J* = 8.5, 12.9, 17.0 Hz, 1 H), 2.26 (m, 1 H), 2.35 (ddd, *J* = 2.0, 6.9, 12.9 Hz, 1 H), 2.73 (m, 2 H), 3.56 (td, *J* = 6.7, 9.4 Hz, 1 H), 3.93 (m, 2 H), 5.04 (dd, *J* = 2.0, 8.5 Hz, 1 H), 5.30 (dd, *J* = 1.9, 3.3 Hz, 1 H), 6.31 (d, *J* = 1.6 Hz, 1 H), 7.05 (m, 2 H), 7.28 (m, 4 H), 7.42 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 17.8, 19.3, 31.8, 33.9, 34.8, 36.6, 47.0, 48.2, 68.9, 93.1, 99.8, 109.8, 127.2 (2C), 127.3, 127.5, 128.3 (2C), 128.8 (2C), 129.1 (2C), 138.8, 139.5, 140.7.

MS (EI): *m*/*z* = 421 $[M]^+$.

HRMS (ESI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{31}NO_4$: 444.2145; found: 444.21456.

Anal. Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C, 74.11; H, 7.42; N, 3.24.

3-(2-Chloroethoxy)hexahydro-3*H*-isochromene (1c)
The synthesis followed GP 2 to give the main diastereomer.

Yield: 85 mg (63%); colorless crystals; mp 193 °C; R_f = 0.24 (pentane–Et_2O, 15:1); $[\alpha]_D^{24}$ –15.7 (*c* 1.2, $CHCl_3$).

IR ($CDCl_3$): 1654, 1542, 1450, 1366, 138, 1122, 1065, 945, 881, 767, 704, 659 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.77 (d, *J* = 6.4 Hz, 3 H), 1.98 (ddd, *J* = 7.7, 13.5, 15.4 Hz, 1 H), 2.26 (m, 1 H), 2.37 (ddd, *J* = 1.9, 6.9, 13.5 Hz, 1 H), 2.71 (dd, *J* = 3.3, 12.0 Hz, 1 H), 2.85 (m, 1 H), 3.75 (m, 2 H), 3.86 (s, 1 H), 3.95 (s, 1 H), 4.16 (td, *J* = 5.3, 10.7 Hz, 1 H), 5.14 (dd, *J* = 1.9, 7.7 Hz, 1 H), 5.34 (dd, *J* = 1.6, 3.3 Hz, 1 H), 6.32 (d, *J* = 1.3 Hz, 1 H), 7.08 (d, *J* = 7.3 Hz, 2 H), 7.28 (m, 4 H), 7.44 (m, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 17.7, 32.8, 34.5, 36.0, 42.9, 47.0, 48.3, 68.8, 93.1, 99.5, 110.5, 127.1 (2C), 127.3, 127.5, 128.3 (2C), 128.8 (2C), 129.1 (2C), 138.7, 139.1, 140.0.

MS (EI): *m*/*z* = 427 $[M]^+$.

HRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{26}NO_4Cl$: 450.1443; found: 450.1442.

Anal. Calcd for $C_{24}H_{26}NO_4Cl$: C, 67.36; H, 6.12; N, 3.27. Found: C, 67.40; H, 5.93; N, 3.20.

3-Isobutoxy-hexahydro-3*H*-isochromene (1d)
The synthesis followed GP 2 to give the main diastereomer.

Yield: 80 mg (61%); colorless solid; mp 30 °C; R_f = 0.26 (pentane–Et_2O, 40:1); $[\alpha]_D^{24}$ –19.0 (*c* 2, $CHCl_3$).

IR ($CDCl_3$): 2963, 2927, 2870, 1661, 1550, 1453, 1366, 1129, 1055, 759, 703 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.78 (d, *J* = 6.4 Hz, 3 H), 0.98 (m, 6 H), 1.94 (m, 2 H), 2.26 (m, 1 H), 2.36 (ddd, *J* = 1.8, 6.8, 13.2 Hz, 1 H), 2.70 (dd, *J* = 3.2, 12.0 Hz, 1 H), 2.79 (m, 1 H), 3.32 (dd, *J* = 6.9, 9.2 Hz, 1 H), 3.74 (dd, *J* = 6.6, 9.1 Hz, 1 H), 3.94 (s, 1 H), 5.05 (dd, *J* = 1.8, 8.1 Hz, 1 H), 5.32 (dd, *J* = 1.6, 3.2 Hz, 1 H), 6.33 (s, 1 H), 7.07 (d, *J* = 7.4 Hz, 2 H), 7.28 (m, 5 H), 7.43 (m, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 17.8, 19.3, 19.4, 28.6, 33.6, 34.7, 36.5, 47.0, 48.3, 75.9, 93.1, 99.9, 109.8, 127.2 (2C), 127.2, 127.5, 128.3 (2C), 128.8 (2C), 129.1 (2C), 138.8, 139.4, 140.7.

MS (EI): *m*/*z* = 421 $[M]^+$.

HRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{31}NO_4$: 444.2145; found: 444.2137.

Anal. Calcd for $C_{26}H_{31}NO_4$: C, 74.08; H, 7.41; N, 3.32. Found: C, 73.89; H, 7.61; N, 3.18.

3-Butoxy-6-(4-chlorophenyl)hexahydro-3*H*-isochromene (1e)
The synthesis followed GP 2 to give the main diastereomer.

Yield: 115 mg (81%); colorless solid; mp 29 °C; ee >99%; R_f = 0.27 (pentane–Et_2O, 20:1); $[\alpha]_D^{24}$ –56.3 (*c* 0.4, $CHCl_3$).

IR ($CDCl_3$): 2961, 2932, 2871, 1662, 1550, 1492, 1457, 1366, 1239, 1130, 1094, 911, 730 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.76 (d, *J* = 5.9 Hz, 3 H), 0.97 (t, *J* = 7.4 Hz, 3 H), 1.45 (m, 2 H), 1.67 (m, 2 H), 1.89 (ddd, *J* = 8.3, 12.9, 16.8 Hz, 1 H), 2.26 (m, 1 H), 2.35 (ddd, *J* = 2.0, 6.9, 12.9 Hz, 1 H), 2.72 (m, 2 H), 3.57 (td, *J* = 6.7, 9.5 Hz, 1 H), 3.94 (m, 2 H), 5.05 (dd, *J* = 2.0, 8.3 Hz, 1 H), 5.27 (dd, *J* = 1.9, 3.1 Hz, 1 H), 6.32 (d, *J* = 1.6 Hz, 1 H), 7.01 (m, 2 H), 7.25 (m, 2 H), 7.33 (m, 1 H), 7.42 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9, 17.7, 19.3, 31.8, 33.7, 34.7, 36.4, 47.0, 47.6, 68.8, 92.8, 99.7, 109.4, 127.1 (2C), 127.3, 129.0 (2C), 129.1 (2C), 129.7 (2C), 133.3, 137.3, 139.2, 140.8.

MS (EI): *m*/*z* = 455 $[M]^+$.

HRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{26}H_{30}NO_4Cl$: 478.1757; found: 478.0867.

3-Butoxy-5-(4-phenylbut-3-yn-1-yl)hexahydro-3*H*-isochromene (1f)
The synthesis followed GP 2 to give the main diastereomer.

Yield: 105 mg (63%); colorless crystals; mp 53 °C; R_f = 0.40 (pentane–Et_2O, 20:1); $[\alpha]_D^{24}$ –10.0 (*c* 2.5, $CHCl_3$).

IR ($CDCl_3$): 2925, 2866, 1548, 1491, 1452, 1366, 1126, 1079, 971, 872, 756, 698 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.96 (t, *J* = 7.4 Hz, 3 H), 1.44 (m, 2 H), 1.65 (m, 4 H), 1.99 (ddd, *J* = 8.4, 13.2, 16.7 Hz, 1 H), 2.13 (m, 2 H), 2.44 (ddd, *J* = 1.4, 6.5, 13.2 Hz, 1 H), 2.71 (m, 1 H), 2.96 (m,

1 H), 3.05 (dd, *J* = 3.3, 12.0 Hz, 1 H), 3.55 (td, *J* = 6.7, 9.3 Hz, 1 H), 3.94 (m, 2 H), 5.05 (dd, *J* = 1.4, 8.4 Hz, 1 H), 5.31 (dd, *J* = 2.1, 3.3 Hz, 1 H), 6.34 (s, 1 H), 7.10 (m, 2 H), 7.28 (m, 9 H), 7.40 (m, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 13.9, 15.3, 19.3, 28.8, 31.8, 33.1, 33.6, 38.3, 45.5, 46.8, 68.9, 80.9, 89.6, 93.3, 99.5, 109.9, 123.6, 127.2 (2C), 127.3, 127.6, 127.8, 128.2 (2C), 128.4 (2C), 129.0 (2C), 129.1 (2C), 131.4 (2xC), 138.3, 139.5, 140.9.

MS (EI): *m*/*z* = 488 $[M - HNO_2]^+$.

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{35}H_{37}NO_4$: 536.2795; found: 536.2799.

3-(Ethylthio)hexahydro-3*H*-isochromene (1g)
The synthesis followed GP 2 to give the main diastereomer.

Yield: 100 mg (78%); colorless crystals; mp 144 °C; ee >99%; R_f = 0.28 (pentane–Et_2O, 20:1); $[\alpha]_D^{24}$ –21.4 (*c* 0.8, $CHCl_3$).

IR ($CDCl_3$): 3020, 2970, 2906, 2873, 1660, 1548, 1450, 1369, 1221, 1128, 758, 707, 544 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.72 (d, *J* = 6.3 Hz, 3 H), 1.29 (t, *J* = 7.4 Hz, 3 H), 1.91 (m, 1 H), 2.31 (m, 1 H), 2.47 (ddd, *J* = 1.7, 6.7, 13.3 Hz, 1 H), 2.56 (m, 1 H), 2.65 (dd, *J* = 3.5, 12.1 Hz, 1 H), 2.75 (m, 2 H), 3.87 (s, 1 H), 5.09 (dd, *J* = 1.7, 11.2 Hz, 1 H), 5.21 (dd, *J* = 1.8, 3.5 Hz, 1 H), 6.36 (d, *J* = 1.5 Hz, 1 H), 6.97 (m, 2 H), 7.18 (m, 3 H), 7.26 (m, 1 H), 7.37 (m, 4 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 15.2, 18.0, 24.4, 34.9, 35.2, 37.9, 46.8, 47.8, 80.6, 93.0, 109.6, 127.2 (2C), 127.3, 127.6, 128.1 (2C), 128.9 (2C), 129.1 (2C), 138.5, 139.5, 143.1.

MS (EI): *m*/*z* = 409 $[M]^+$.

HRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{24}H_{27}NO_3S$: 432.1604; found: 432.1600.

3-(Phenylthio)hexahydro-3*H*-isochromene (1h)
The synthesis followed GP 2 to give the main diastereomer.

Yield: 70 mg (49%); colorless solid; mp 69 °C; ee >99%; R_f = 0.22 (pentane–Et_2O, 20:1); $[\alpha]_D^{24}$ –10.4 (*c* 2.2, $CHCl_3$).

IR ($CDCl_3$): 3555, 3363, 2923, 2861, 1660, 1552, 1461, 1125, 735, 487 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 0.72 (d, *J* = 6.3 Hz, 3 H), 1.93 (ddd, *J* = 11.2, 13.3, 21.2 Hz, 1 H), 2.33 (m, 1 H), 2.56 (m, 2 H), 2.64 (dd, *J* = 3.4z, 12.1 Hz, 1 H), 3.87 (s, 1 H), 5.20 (dd, *J* = 1.7, 3.4 Hz, 1 H), 5.29 (dd, *J* = 1.8, 11.2 Hz, 1 H), 6.36 (d, *J* = 1.5 Hz, 1 H), 6.97 (m, 2 H), 7.22 (m, 8 H), 7.34 (m, 3 H), 7.53 (m, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 18.0, 34.9, 35.0, 37.8, 46.8, 47.8, 83.3, 93.0, 109.7, 127.2 (2C), 127.3, 127.6, 127.9, 128.1 (2C), 128.9 (2C), 129.0 (2C), 129.1 (2C), 132.4 (2C), 133.1, 138.5, 139.3, 142.9.

MS (EI): *m*/*z* = 410 $[M - HNO_2]^+$.

HRMS (EI): *m*/*z* $[M + Na]^+$ calcd for $C_{28}H_{27}NO_3S$: 480.1604; found: 480.1603.

Acknowledgment

This work was supported by the Deutsche Forschungsgemeinschaft (Priority Program Organocatalysis) and the Fonds der Chemischen Industrie (Kekulé stipend to N.E.). We thank the former Degussa AG and BASF SE for the donation of chemicals, as well as Peter Becker for his experimental help.

References

(1) For recent reviews of HDA reactions of carbonyl compounds, see: (a) Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2000**, *39*, 3558; *Angew. Chem.* **2000**, *112*, 3702. (b) Pellissier, H. *Tetrahedron* **2009**, *65*, 2839.

(2) For leading references of inverse-electron-demand HDA reactions, see: (a) Desimoni, G.; Tacconi, G. *Chem. Rev.* **1975**, *75*, 651. (b) Boger, D. L.; Weinreb, S. M. *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, **1987**. (c) Waldmann, H. *Synthesis* **1994**, 535. (d) Tietze, L. F.; Kettschau, G. *Top. Curr. Chem.* **1997**, *189*, 1. (e) Tietze, L. F.; Kettschau, G. *Stereoselective Heterocyclic Synthesis I*; Vol. 189; Metz, P., Ed.; Springer: Berlin, **1997**, 1–120. (f) Ager, D. J.; East, M. B. *Tetrahedron* **1993**, *49*, 5683.

(3) For selected examples, see: (a) Schmidt, R. R. *Acc. Chem. Res.* **1986**, *19*, 250. (b) De Gaudenzi, L.; Apparao, S.; Schmidt, R. R. *Tetrahedron* **1990**, *46*, 277. (c) Tietze, L. F.; Montenbruck, A.; Schneider, C. *Synlett* **1994**, 509. (d) Streith, J.; Defoin, A. *Synlett* **1996**, 189. (e) Dujardin, G.; Rossignol, S.; Brown, E. *Synthesis* **1998**, 763. (f) Audrain, H.; Thorhauge, J.; Hazell, R. G.; Jørgensen, K. A. *J. Org. Chem.* **2000**, *65*, 4487. (g) Zhuang, W.; Thorhauge, J.; Jørgensen, K. A. *Chem. Commun.* **2000**, *6*, 459. (h) Liu, H.-M.; Zou, D.-P.; Zhang, F.; Zhu, W.-G.; Peng, T. *Eur. J. Org. Chem.* **2004**, 2103. (i) Yadav, J. S.; Reddy, B. V. S.; Narsimhaswamy, D.; Lakshmi, P. N.; Narsimulu, K.; Srinivasulu, G.; Kunwar, A. C. *Tetrahedron Lett.* **2004**, *45*, 3493. (j) Tietze, L. F.; Böhnke, N.; Dietz, S. *Org. Lett.* **2009**, *11*, 2948. (k) D'Alonzo, D.; Guaragna, A.; Palumbo, G. *Curr. Org. Chem.* **2009**, *13*, 71.

(4) For selected examples, see: (a) Tietze, L. F. *J. Heterocycl. Chem.* **1990**, *27*, 47. (b) Tietze, L. F.; Kettschau, G.; Gewert, J. A.; Schuffenhauer, A. *Curr. Org. Chem.* **1998**, *2*, 19. (c) Tietze, L. F.; Schneider, G.; Wölfling, J.; Fecher, A.; Nöbel, T.; Petersen, S.; Schuberth, I.; Wulff, C. *Chem.–Eur. J.* **2000**, *6*, 3755. (d) Chavez, D. E.; Jacobsen, E. N. *Org. Lett.* **2003**, *5*, 2563. (e) Messer, R.; Schmitz, A.; Moesch, L.; Häner, R. *J. Org. Chem.* **2004**, *69*, 8558. (f) Tietze, L. F.; Rackelmann, N. *Pure Appl. Chem.* **2004**, *76*, 1967. (g) Rodriguez, R.; Moses, J. E.; Adlington, R. M.; Baldwin, J. E. *Org. Biomol. Chem.* **2005**, *3*, 3488. (h) Carreaux, F.; Favre, A.; Carboni, B.; Rouaud, I.; Boustie, J. *Tetrahedron Lett.* **2006**, *47*, 4545. (i) El Sous, M.; Ganame, D.; Tregloan, P.; Rizzacasa, M. A. *Synthesis* **2010**, 3954.

(5) For selected examples of Lewis acid catalyzed HDA reactions of carbonyl compounds, see: (a) Boger, D. L.; Robarge, K. D. *J. Org. Chem.* **1988**, *53*, 3373. (b) Tietze, L. F.; Schneider, C. *Synlett* **1992**, 755. (c) Tietze, L. F.; Schneider, C.; Montenbruck, A. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 980; *Angew. Chem.* **1994**, *106*, 1031. (d) Wada, E.; Pei, W.; Yasuoka, H.; Chin, U.; Kanemasa, S. *Tetrahedron* **1996**, *52*, 1205. (e) Dujardin, G.; Rossignol, S.; Brown, E. *Tetrahedron Lett.* **1996**, *37*, 4007. (f) Tietze, L. F.; Schneider, C.; Grote, A. *Chem.–Eur. J.* **1996**, *2*, 139. (g) Johnson, S. C.; Crasto, C.; Hecht, S. M. *Chem. Commun.* **1998**, 1019. (h) Evans, D. A.; Johnson, J. S. *J. Am. Chem. Soc.* **1998**, *120*, 4895. (i) Thorhauge, J.; Johannsen, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **1998**, *37*, 2404; *Angew. Chem.* **1998**, *110*, 2543. (j) Evans, D. A.; Johnson, J. S.; Burgey, C. S.; Campos, K. R. *Tetrahedron Lett.* **1999**, *40*, 2879. (k) Evans, D. A.; Johnson, J. S.; Olhava, E. J. *J. Am. Chem. Soc.* **2000**, *122*, 1635. (l) Audrain, H.; Jørgensen, K. A. *J. Am. Chem. Soc.* **2000**, *122*, 11543. (m) Gademann, K.; Chavez, D. E.; Jacobsen, E. N. *Angew.*

Chem. Int. Ed. **2002**, *41*, 3059; *Angew. Chem.* **2002**, *114*, 3185. (n) Gao, X.; Hall, D. G. *J. Am. Chem. Soc.* **2003**, *125*, 9308. (o) Desimoni, G.; Faita, G.; Toscanini, M.; Boiocchi, M. *Chem.–Eur. J.* **2007**, *13*, 9478. (p) Shin, Y. J.; Yeom, C.-E.; Kim, M. J.; Kim, B. M. *Synlett* **2008**, 89. (q) Barroso, S.; Blay, G.; MuCoz, M. C.; Pedro, J. R. *Adv. Synth. Catal.* **2009**, *351*, 107. (r) Zhu, Y.; Xie, M.; Dong, S.; Zhao, X.; Lin, L.; Liu, X.; Feng, X. *Chem.–Eur. J.* **2011**, *17*, 8202. (s) Xu, Z.; Wang, H. *Synlett* **2011**, 2907.

(6) For selected examples of organocatalytic inverse-electron-demand HDA reactions with carbonyl compounds, see: (a) Juhl, K.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2003**, *42*, 1498; *Angew. Chem.* **2003**, *115*, 1536. (b) Samanta, S.; Krause, J.; Mandal, T.; Zhao, C.-G. *Org. Lett.* **2007**, *9*, 2745. (c) Zhao, Y.; Wang, X.-J.; Liu, J.-T. *Synlett* **2008**, 1017.

(7) (a) Kakeya, H.; Onose, R.; Koshino, H.; Yoshida, A.; Kobayashi, K.; Kageyama, S.-I.; Osada, H. *J. Am. Chem. Soc.* **2002**, *124*, 3496. (b) Kakeya, H.; Onose, R.; Yoshida, A.; Koshino, H.; Osada, H. *J. Antibiot.* **2002**, *55*, 829.

(8) Sassa, T.; Kinoshita, H.; Nukina, M.; Sugiyama, T. *J. Antibiot.* **1998**, *51*, 967.

(9) (a) Lee, J. C.; Strobel, G. A.; Lobkovsky, E.; Clardy, J. *J. Org. Chem.* **1996**, *61*, 3232. (b) Liang, M.-C.; Bardhan, S.; Li, C.; Pace, E. A.; Porco, J. A. Jr.; Gilmore, T. D. *Mol. Pharmacol.* **2003**, *64*, 123.

(10) Ding, G.; Zhang, F.; Chen, H.; Guo, L.; Zou, Z.; Che, Y. *J. Nat. Prod.* **2011**, *74*, 286.

(11) Ishikawa, T.; Sekine, K. Jpn. Kokai Tokkyo Koho JP 2001122871 A 20010508, **2001**; *Chem. Abstr.* **2001**, *134*, 344563.

(12) For selected general 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) De Figuiredo, R. M.; Christmann, M. *Eur. J. Org. Chem.* **2007**, 9267. (d) Vicario, J. L.; Badia, D.; Carillo, L. *Synthesis* **2007**, 2065. (e) Tsogoeva, S. B. *Eur. J. Org. Chem.* **2007**, 1701. (f) Dondoni, A.; Massi, A. *Angew. Chem. Int. Ed.* **2008**, *47*, 4638; *Angew. Chem.* **2008**, *120*, 4716. (g) MacMillan, D. W. C. *Nature* **2008**, *455*, 304. (h) Barbas, C. F. III *Angew. Chem. Int. Ed.* **2008**, *47*, 42; *Angew. Chem.* **2008**, *120*, 44. (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) Enders, D.; Wang, C.; Liebich, J. X. *Chem. Eur. J.* **2009**, *15*, 11058. (l) Jørgensen, K. A.; Bertelsen, S. *Chem. Soc. Rev.* **2009**, *38*, 2178. (m) Bella, M.; Gasperi, T. *Synthesis* **2009**, 1583. (n) Roca-Lopez, D.; Sadaba, D.; Delso, I.; Herrera, R. P.; Tejero, T.; Merino, P. *Tetrahedron: Asymmetry* **2010**, *21*, 2561. (o) Merino, P.; Marquéz-Lopéz, E.; Tejero, T.; Herrera, R. P. *Synthesis* **2010**, 1. (p) Marcelli, T.; Hiemstra, H. *Synthesis* **2010**, 1229. (q) Nielsen, M.; Worgull, D.; Zweifel, T.; Gschwend, B.; Bertelsen, S.; Jørgensen, K. A. *Chem. Commun.* **2011**, *47*, 632. (r) Ramachary, D. B.; Jain, S. *Org. Biomol. Chem.* **2011**, *9*, 1277. (s) Majano, A.; Rios, R. *Chem. Rev.* **2011**, *111*, 4703. (t) Loh, C. C. J.; Enders, D. *Chem.–Eur. J.* **2012**, in press; DOI: 10.1002/chem.201200287.

(13) For selected 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. (c) Grondal, C.; Jeanty, M.; Enders, D. *Nat. Chem.* **2010**, *2*, 167. (d) Grossmann, A.; Enders, D. *Angew. Chem. Int. Ed.* **2012**, *51*, 314; *Angew. Chem.* **2012**, *124*, 320. (e) Pellissier, H. *Adv. Synth. Catal.* **2012**, *354*, 237.

(14) For recent examples of (organocatalytic) domino reactions in the synthesis of chiral cyclohexanes and derivatives, see: (a) Huang, Y.; Walji, A. M.; Larsen, C. H.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2005**, *127*, 15051. (b) Wang, W.; Li, H.; Wang, J.; Zu, L. *J. Am. Chem. Soc.* **2006**, *128*, 10354. (c) Carlone, A.; Cabrera, S.; Marigo, M.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 1101; *Angew. Chem.* **2007**, *119*, 1119. (d) Hayashi, Y.; Okano, T.; Aratke, S.; Hazelard, D. *Angew. Chem. Int. Ed.* **2007**, *46*, 4922; *Angew. Chem.* **2007**, *119*, 5010. (e) Zhou, J.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 7498. (f) Enders, D.; Narine, A. A.; Benninghaus, T. R.; Raabe, G. *Synlett* **2007**, 1667. (g) Reyes, E.; Jiang, H.; Milelli, A.; Elsner, P.; Hazell, R. G.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2007**, *46*, 9202; *Angew. Chem.* **2007**, *119*, 9362. (h) Mukherjee, S.; List, B. *J. Am. Chem. Soc.* **2007**, *129*, 11336. (i) Enders, D.; Hüttl, M. R. M.; Runsink, J.; Raabe, G.; Wendt, B. *Angew. Chem. Int. Ed.* **2007**, *46*, 467; *Angew. Chem.* **2007**, *119*, 471. (j) Enders, D.; Hüttl, M. R. M.; Raabe, G.; Bats, J. W. *Adv. Synth. Catal.* **2008**, *350*, 267. (k) Cabrera, S.; Alemán, J.; Bolze, P.; Bertelsen, S.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2008**, *47*, 121; *Angew. Chem.* **2008**, *120*, 127. (l) Tan, B.; Chua, P. J.; Li, Y.; Zhong, G. *Org. Lett.* **2008**, *12*, 2437. (m) Hu, W.; Xu, X.; Zhou, J.; Liu, W.-J.; Huang, H.; Hu, J.; Yang, L.; Gong, L.-Z. *J. Am. Chem. Soc.* **2008**, *130*, 7782. (n) Yang, T.; Ferrali, A.; Campell, L.; Dixon, D. J. *Chem. Commun.* **2008**, 2923. (o) Chercheja, S.; Rothenbücher, T.; Eilbracht, P. *Adv. Synth. Catal.* **2009**, *251*, 339. (p) Wang, Y.; Han, R.-G.; Zhao, Y.-L.; Yang, S.; Xu, P.-F.; Dixon, D. J. *Angew. Chem. Int. Ed.* **2009**, *48*, 9834; *Angew. Chem.* **2009**, *121*, 10018. (q) Nodes, W. J.; Nutt, D. R.; Chippindale, A. M.; Cobb, A. J. A. *J. Am. Chem. Soc.* **2009**, *131*, 16016. (r) Hong, B.-C.; Jan, R.-H.; Tsai, C.-W.; Nimje, R. Y.; Liao, J.-H.; Lee, G.-H. *Org. Lett.* **2009**, *11*, 5246. (s) Garciá Ruano, J. L.; Marcos, V.; Suanzes, J. A.; Marzano, L.; Alemán, J. *Chem.–Eur. J.* **2009**, *15*, 6576. (t) Enders, D.; Wang, C.; Mukanova, M.; Greb, A. *Chem. Commun.* **2010**, *46*, 2447. (u) Enders, D.; Krüll, R.; Bettray, W. *Synthesis* **2010**, 567. (v) Bastlé, O.; Raimondi, W.; del Mar Sanchez, M.; Dugue, M. M. S.; Bonne, D.; Constantieux, T.; Rodriguez, J. *Org. Lett.* **2010**, *12*, 5246. (w) Resende, D. I. S. P.; Oliva, C. G.; Silva, A. M. S.; Almeida Paz, F. A.; Cavaleiro, J. A. S. *Synlett* **2010**, 115. (x) Nodes, W. J.; Shankland, K.; Rajkumar, S.; Cobb, A. J. A. *Synlett* **2010**, 3011. (y) Anwar, S.; Chang, H.-J.; Chen, K. *Org. Lett.* **2011**, *13*, 2200. (z) Hong, B.-C.; Sadani, A. A.; Nimje, R. Y.; Dange, N. S.; Lee, G.-H. *Synthesis* **2011**, 1887. (aa) Aoki, Y.; Mochizuki, Y.; Yoshinari, T.; Ohmori, K.; Suzuki, K. *Chem. Lett.* **2011**, *40*, 1192. (ab) McGarraugh, P. G.; Jones, J. H.; Brenner-Moyer, S. E. *J. Org. Chem.* **2011**, *76*, 6309. (ac) Chintala, P.; Ghosh, S. K.; Long, E.; Headley, A. D.; Ni, B. *Adv. Synth. Catal.* **2011**, *353*, 2905. (ad) Jia, Y.; Mao, Z.; Wang, R. *Tetrahedron: Asymmetry* **2011**, *22*, 2018. (ae) Yu, D.-F.; Wang, Y.; Xu, P.-F. *Adv. Synth. Catal.* **2011**, *353*, 2960. (af) Varga, S.; Jakab, G.; Drahos, L.; Holcbauer, T.; Czugler, M.; Soos, T. *Org. Lett.* **2011**, *13*, 5416. (ag) Wong, C. T. *Tetrahedron* **2012**, *68*, 481. (ah) Hong, B.-C.; Dange, N. S.; Ding, C.-F.; Liao, J.-H. *Org. Lett.* **2012**, *14*, 448. (ai) Shi, D.; Xie, Y.; Zhou, H.; Xia, C.; Huang, H. *Angew. Chem. Int. Ed.* **2012**, *51*, 1248; *Angew. Chem.* **2012**, *124*, 1274.

(15) Enders, D.; Hüttl, M. R. M.; Grondal, C.; Raabe, G. *Nature* **2006**, *441*, 861.

(16) For further examples of sequential approaches with the cyclohexene carbaldehydes, see: (a) Ref. 13a. (b) Enders, D.; Schmid, B.; Erdmann, N.; Raabe, G. *Synthesis* **2010**, 2271.

(17) Crystallographic data for **1c** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC 876519. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif or on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk].

(18) Marigo, M.; Wabnitz, T.; Fielenbach, D.; Jørgensen, K. A. *Angew. Chem. Int. Ed.* **2005**, *44*, 794; *Angew. Chem.* **2005**, *117*, 804.