

An Asymmetric Organocatalytic Quadruple Domino Reaction Employing a Vinylogous Friedel–Crafts/Michael/Michael/Aldol Condensation Sequence

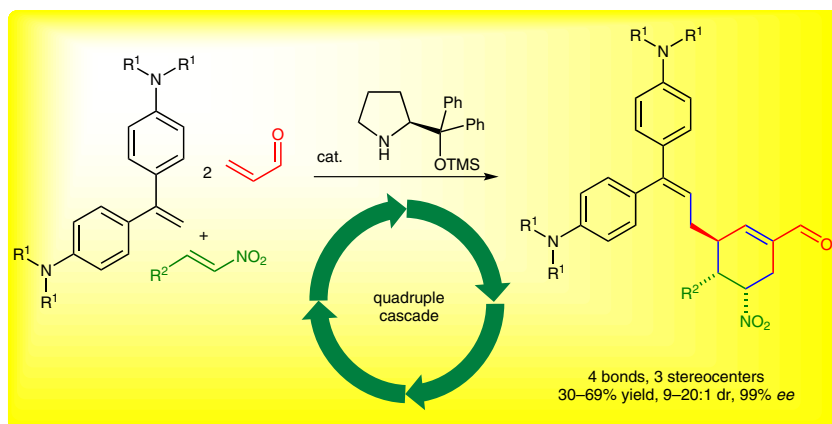
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Abstract An organocatalytic quadruple cascade initiated by a Friedel–Crafts-type reaction is described. The (*S*)-diphenylprolinol trimethylsilyl ether catalyzed reaction yields highly functionalized cyclohexenecarbaldehydes bearing a 1,1-bis[4-(dialkylamino)phenyl]ethene moiety and three contiguous stereogenic centers. The reaction tolerates various functional groups and all products are obtained with very good diastereoselectivity and with virtually complete enantiomeric excess.

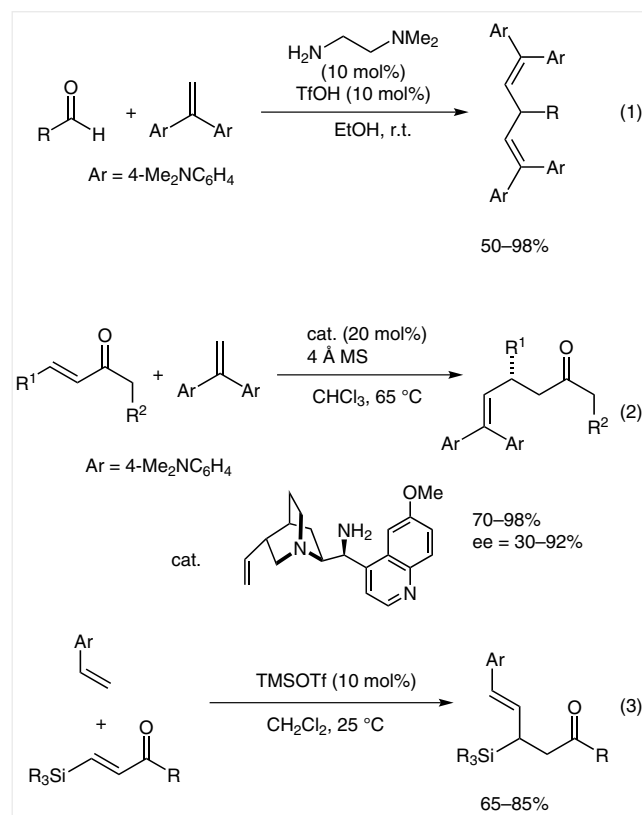
Key words organocatalysis, domino reaction, quadruple cascade, asymmetric catalysis, alkenylation

In contemporary organic chemistry, organocatalyzed domino reactions are widely regarded as powerful synthetic tools that are increasingly used in the synthesis of biologically active compounds, such as pharmaceuticals and agrochemicals.¹ They are of particular interest due to their ability to form complex molecules in a highly stereoselective manner in one-pot procedures.^{2,3} Secondary amines, such as proline and its derivatives or imidazolidinones, are well-suited catalysts for this type of reaction due to their iminium and enamine activation modes.⁴ Several simple,⁵ triple,⁶ and quadruple⁷ cascades have been reported so far.

One appealing and synthetically useful organic framework is the cyclohexene building block, which can be prepared by asymmetric amine-catalyzed domino reactions. Its enantioselective synthesis is well explored due to its inherent synthetic and biological importance.⁸

1,1-Bis(aryl)alkenes have been shown to be effective nucleophiles for addition to aldehydes⁹ affording bisallylic adducts through Knoevenagel-type 1,2-additions and con-

jugate additions to enones [Scheme 1 (1) and (2)].¹⁰ Similar to the well-studied typical enamine reactivity, the nucleophilicity of these electron-rich alkenes originates from an electron-donating phenylogous dialkylamino functionality.



Scheme 1 Examples of organocatalytic alkenylation reactions

This amino styrene motif has been successfully applied in the field of organic electronics¹¹ and serves as an important building block for a number of leuco dyes.¹²

In addition to these aniline-derived nucleophiles, there is precedence for electron-rich styrene derivatives to undergo conjugate addition to β -silyl enones [Scheme 1 (3)].¹³

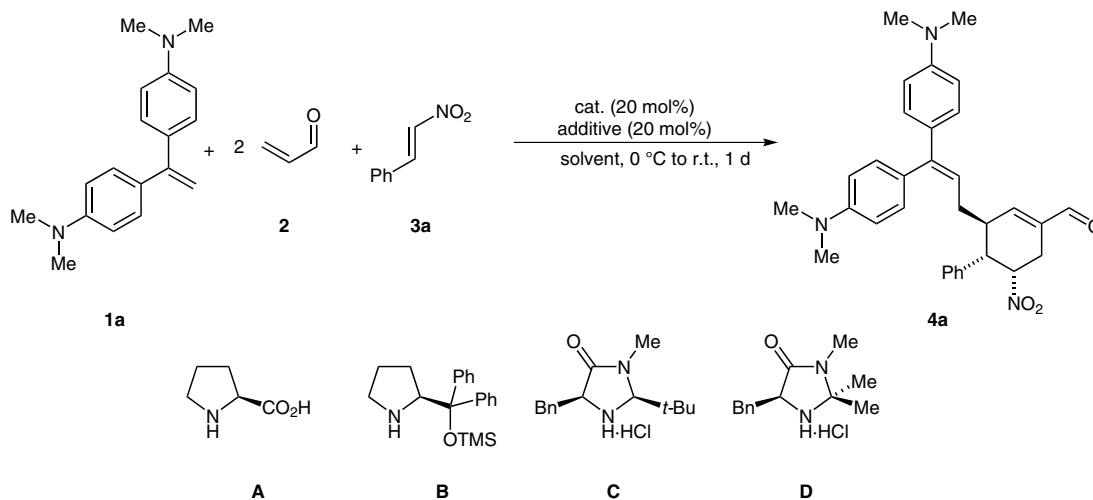
There have also been reports of oxa-Michael, aza-Michael, Michael, and Friedel–Crafts-type reactions for the initiation of quadruple cascades. To the best of our knowledge there are no reports of a quadruple cascade initiated by a vinylogous Friedel–Crafts-type reaction.⁷

Herein we report an organocatalytic quadruple cascade reaction initiated by a vinylogous Friedel–Crafts-type reaction of electron-rich arenes. The thus-formed aniline deriv-

atives feature three contiguous stereocenters and can be obtained in high yields and stereoselectivities in a single one-pot operation.

As can be seen from the retrosynthetic analysis in Scheme 2, after addition of the donor alkene **1** to the iminium-activated acrolein (**2**), the enamine intermediate will attack the nitroalkene **3** as a second Michael acceptor. The repetition of the catalytic activation of another molecule of acrolein (**2**) via iminium and enamine intermediates leads to the highly substituted cyclohexenecarbaldehyde **4** through a Michael/aldol condensation sequence.

Table 1 Optimization of the Reaction Conditions



Entry ^a	Catalyst	Additive	Solvent	Yield ^b (%)	ee ^c (%)	dr ^d
1	A	–	CHCl ₃	–	–	–
2	B	–	CHCl ₃	40	>99	20:1
3	C	–	CHCl ₃	5	–	–
4	D	–	CHCl ₃	–	–	–
5	B	PhCO ₂ H	CHCl ₃	50	>99	10:1
6	B	4-MeC ₆ H ₄ CO ₂ H	CHCl ₃	38	>99	20:1
7	B	4-O ₂ NC ₆ H ₄ CO ₂ H	CHCl ₃	49	>99	8:1
8	B	PhCO ₂ H	THF	traces	–	–
9	B	PhCO ₂ H	toluene	–	–	–
10	B	PhCO ₂ H	CH ₂ Cl ₂	34	>99	20:1
11 ^e	B	PhCO ₂ H	CHCl ₃	69	99	10:1
12 ^f	B	PhCO ₂ H	CHCl ₃	63	99	14:1

^a Reaction conditions: 1-mmol scale using **1a** (1 equiv), **2** (5 equiv), **3a** (1.1 equiv), additive (20 mol%), catalyst (20 mol%), solvent (3 mL).

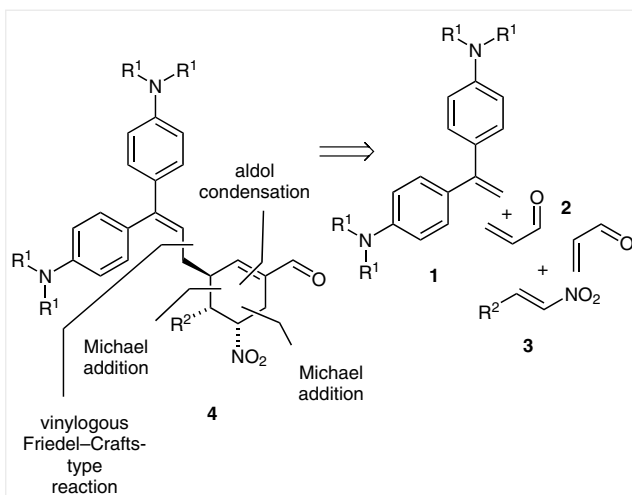
^b Yield of the isolated product **4a** after flash column chromatography.

^c Determined by HPLC on a chiral stationary phase.

^d Determined by ¹H NMR.

^e A ratio of 1.5:1.0 of **1a**/**3a** was used.

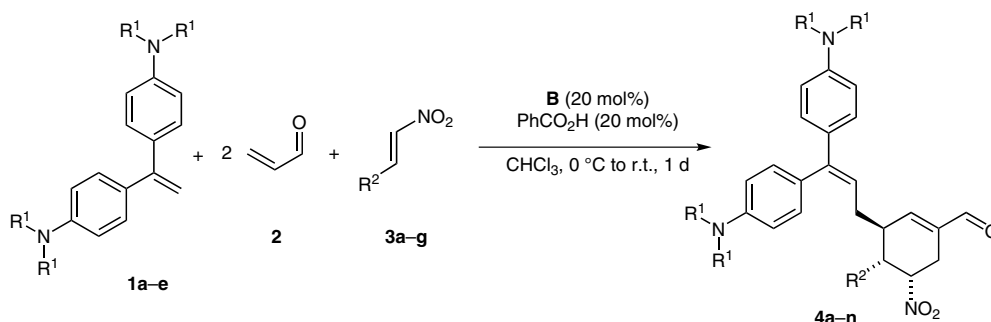
^f A ratio of 2.0:1.0 of **3a**/**1a** was used.



Scheme 2 Organocatalytic quadruple cascade initiated by a vinylogous Friedel–Crafts-type reaction; retrosynthetic analysis

1,1-Bis[4-(dimethylamino)phenyl]ethene (**1a**), acrolein (**2**), and β -nitrostyrene (**3a**) were chosen as test substrates. Initially, the reaction was performed with the electron-rich alkene **1a** (1 equiv), β -nitrostyrene (**3a**, 1.1 equiv), and catalyst **B** (20 mol%) in chloroform (0.33 M) with the addition of acrolein (**2**, 5 equiv) on a 1-mmol scale at 0 °C. Under these conditions the desired domino product **4a** was obtained in 40% yield with an enantioselectivity of 99% ee (Table 1, entry 2). In order to find the most suitable catalyst for this reaction, we tested several secondary amines known to act as efficient catalysts for iminium activation. It turned out that only the proline-derived trimethylsilyl ether **B** afforded the domino product in acceptable amounts, whereas the other catalysts failed to promote the reaction (entries 1, 3, and 4). After that, several acidic additives were screened in order to test them for a possible positive influence on the reactivity. While the use of *p*-toluic acid gave a very similar result, the yield increased when benzoic acid or 4-nitrobenzoic acid were utilized. In contrast to 4-nitrobenzoic acid,

Table 2 Scope of the Reaction



Product ^a	R ¹	R ²	Yield ^b (%)	ee ^c (%)	dr ^d
4a	Me	Ph	69	99	10:1
4b	Me	4-MeC ₆ H ₄	47	>99	12:1
4c	Me	4-MeOC ₆ H ₄	53	>99	14:1
4d	Me	2-ClC ₆ H ₄	50	>99	14:1
4e	Me	5-methyl-2-furyl	45	99	20:1
4f	Me	2-naphthyl	41	>99	9:1
4g	Me	2-thienyl	55	>99	20:1
4h	Et	Ph	35	>99	20:1
4i	Et	4-MeC ₆ H ₄	41	>99	20:1
4j	Et	4-MeOC ₆ H ₄	43	>99	20:1
4k	Et	2-ClC ₆ H ₄	45	>99	9:1
4l	(CH ₂) ₄	Ph	49	>99	20:1
4m	(CH ₂) ₅	Ph	30	>99	10:1
4n	(CH ₂) ₂ O(CH ₂) ₂	Ph	–	–	–

^a Reaction conditions: 1-mmol scale using **1** (1.5 equiv), **2** (5 equiv), **3** (1.0 equiv), PhCO₂H (20 mol%), **B** (20 mol%), CHCl₃ (3 mL).

^b Yield of isolated product.

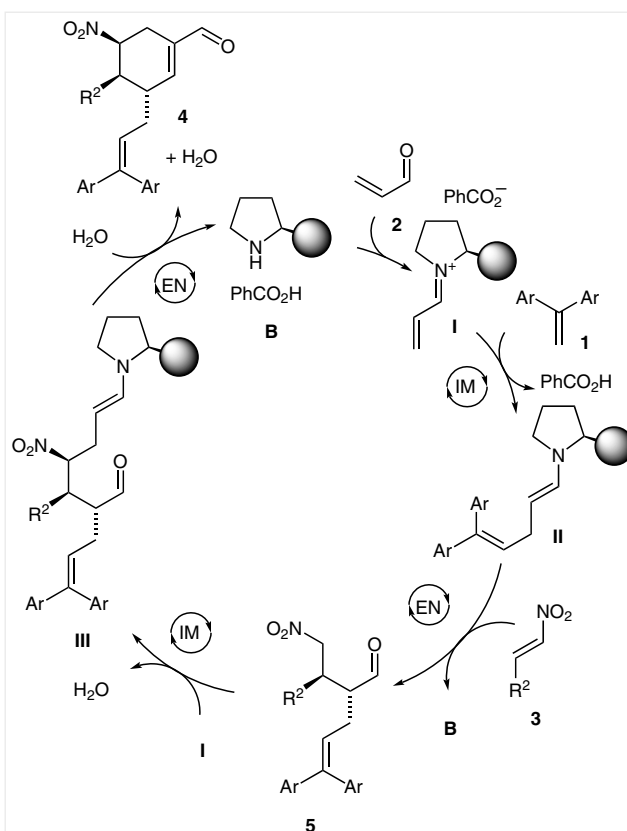
^c Determined by HPLC on a chiral stationary phase.

^d Determined by ¹H NMR.

benzoic acid gave a better diastereoselectivity, while the yields were on a comparable level with 49% and 50%, respectively (entries 5–7). After having evaluated an efficient catalyst system, the influence of the solvent on the outcome of the reaction was investigated. No reaction occurred in toluene, while for tetrahydrofuran only trace amounts of the desired product were obtained. With dichloromethane the yield decreased to 34%, albeit with a better diastereoselectivity of >20:1 (entries 8–10). Subsequently the ratios of the electron-rich alkene **1a** and the nitrostyrene **3a** were varied and it was found that an excess of nucleophile **1a** enhanced the yield to 69% (entries 11 and 12).

With the optimized conditions in hand, the reaction was then performed with different nitroalkenes **3** and alkenes **1** (Table 2). The reaction tolerates various substitutions of the nitrostyrene component. Electron-donating groups as well as electron-withdrawing functionalities could be embedded in the *ortho* or *para* position with good results. The yields for these substrates range from 47 to 53%, with superb enantioselectivities of $\geq 99\%$ ee and diastereoselectivities between 12:1 and 14:1. Additionally, it was possible to perform the reaction with two different heteroaromatic nitroalkenes as well as with the bulkier naphthalene functionality. For the heteroaromatic substrates yields of 45% and 55% were obtained, while the naphthalene substrate gave the lowest yield with the tested nitroalkenes with 41%. The enantioselectivity for all these different nitroalkenes was excellent (99– $\geq 99\%$). To enhance the scope of the transformation, the reaction was performed with a variety of electron-rich arenes. Changing the *N,N*-dimethylamine moiety to *N,N*-diethylamine, pyrrolidine, or piperidine did not have a pivotal effect on the general outcome of the reaction. However, with a morpholine group the electron density in the aromatic system seems to have decreased as no reaction occurred. For sterically hindered α,β -unsaturated aldehydes, such as crotonaldehyde or cinnamaldehyde, the domino product was not obtained and no reaction was observed.

The proposed mechanism is given in Scheme 3. First, the condensation of catalyst **B** with one equivalent of acrolein generates the highly electrophilic iminium ion **I**, which is attacked by alkene **1** to form the nucleophilic enamine intermediate **II**. This intermediate attacks the nitroalkene **3** and after hydrolysis the catalyst **B** is set free and the aldehyde **5** is formed. With another equivalent of the activated acrolein the Michael addition of the intermediate **5** occurs. In the last step the ring is closed in an aldol condensation reaction and under water consumption the cyclohexenecarbaldehyde **4** is released with the concurrent regeneration of the catalyst **B**. The relative and absolute configurations given for all products **4** are based on comparison of the spectroscopic data with our previously published cascade reactions.^{6a,7d,h,8b}



Scheme 3 Proposed mechanism of the quadruple cascade

In conclusion, we have developed a novel and flexible organocatalytic three-component, quadruple domino reaction initiated by a vinylogous Friedel–Crafts-type reaction of electron-rich arenes. We showed that not only several alkenes, but also different nitroalkenes can be utilized. The resulting cyclohexenecarbaldehydes, bearing three contiguous stereogenic centers and a 1,1-bis[4-(dialkylamino)phenyl]ethene moiety, constitute important scaffolds for biologically active compounds as well as in electronics and dyes. All products were obtained in good domino yields, good to very good diastereoselectivities (9:1 to >20:1), and virtually complete enantioselectivities ($\geq 99\%$).

Unless otherwise noted, all commercially available compounds were used without further purification. Preparative column chromatography was carried out with SIL G-25 UV254 from Macherey & Nagel, particle size 0.040–0.063 mm (230–240 mesh, flash). Visualization of the developed TLC plates was performed with UV irradiation (254 nm) and with vanillin stain. Optical rotations were measured on a Perkin-Elmer 241 polarimeter. Mass spectra were recorded on a Finnigan SSQ7000 (EI 70 eV) spectrometer and HRMS on a Thermo Fisher Scientific Orbitrap XL spectrometer. IR spectra were recorded on a Perkin-Elmer FT-IR Spectrum 100 using an ATR unit. ^1H and ^{13}C NMR spectra were recorded at r.t. on Varian Mercury 600 or Inova 400 instruments with TMS as an internal standard. Analytical HPLC was

performed on a Hewlett-Packard 1100 Series instrument using chiral stationary phases (Daicel AD, Daicel AS, Daicel IA, Daicel OD, Daicel OJ, or Chiralpak IC). Acrolein was purified by distillation and the vinylnilines **1a–e** were prepared as described previously.¹⁴ The catalyst was synthesized according to the described procedure.¹⁵

Quadruple Domino Reaction; General Procedure

Under an atmosphere of argon, nitroalkene **3** (1 mmol), catalyst **B** (20 mol%), benzoic acid (20 mol%), and 1,1-bis[4-(dialkylamino)phenyl]ethene **1** (1.5 mmol) were dissolved in CHCl₃ (2 mL) at 0 °C and then treated with a solution of acrolein (**2**, 5 mmol) in CHCl₃ (1 mL). After 1 d the mixture was concentrated under reduced pressure and the crude product was purified by flash chromatography to afford **4** as a yellowish oil or solid.

(1S,2S,6S)-6-{3,3-Bis[4-(dimethylamino)phenyl]allyl}-2-nitro-1,2,3,6-tetrahydrobiphenyl-4-carbaldehyde (**4a**)

Flash chromatography (*n*-pentane–Et₂O, 1:1) gave **4a** as a yellow oil; yield: 352 mg (69%); 99% ee [HPLC: (S,S)-Whelk O1]; *R*_f = 0.28 (*n*-pentane–Et₂O, 1:1); [α]_D²⁰ +115.1 (c 0.98, CHCl₃).

IR (ATR): 2890, 2812, 2251, 2093, 1888, 1681, 1607, 1526, 1452, 1352, 1164, 1063, 908, 725 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 9.55 (s, 1 H, CHO), 7.31–7.27 (m, 3 H, CH_{Ar}), 7.12 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 7.02 (dd, *J* = 12.6, 6.1 Hz, 5 H, CH_{Ar}), 6.66 (dd, *J* = 20.8, 8.8 Hz, 4 H, CH_{Ar}), 5.87 (t, *J* = 7.4 Hz, 1 H, =CH), 4.80–4.74 (m, 1 H, CHNO₂), 3.44–3.39 (m, 1 H, CHPh), 3.20 (s, 1 H, CH), 2.98 (s, 6 H, NCH₃), 2.94 (s, 6 H, NCH₃), 2.79–2.73 (m, 2 H, CH₂), 2.49–2.32 (m, 2 H, CH₂).

¹³C NMR (101 MHz, CDCl₃): δ = 192.4, 152.8, 149.9, 149.4, 145.3, 137.6, 136.4, 130.8, 130.6, 129.0, 128.0, 128.0, 127.8, 127.7, 120.0, 112.0, 83.3, 46.7, 40.9, 40.5, 33.6, 23.8.

MS (EI, 70 eV): *m/z* (%) = 509.3 (4), 279.2 (100), 264.3 (7), 235.2 (15), 191.2 (2), 165.1 (3), 134.1 (24), 77.2 (4).

HRMS: *m/z* [M + H]⁺ calcd for C₃₂H₃₆N₃O₃: 510.2757; found: 510.2744.

(1S,2S,6S)-6-{3,3-Bis[4-(dimethylamino)phenyl]allyl}-4'-methyl-2-nitro-1,2,3,6-tetrahydrobiphenyl-4-carbaldehyde (**4b**)

Flash chromatography (*n*-pentane–Et₂O, 1:1) gave **4b** as a yellow oil; yield: 246 mg (47%); ≥99% ee [HPLC: (S,S)-Whelk O1]; *R*_f = 0.32 (*n*-pentane–Et₂O, 1:1); [α]_D²⁰ +192.4 (c 0.96, CHCl₃).

IR (ATR): 3650, 3347, 2890, 2808, 2250, 2081, 1891, 1725, 1683, 1606, 1519, 1445, 1353, 1266, 1163, 1060, 945, 908, 815, 728 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 9.55 (s, 1 H, CHO), 7.16–7.07 (m, 4 H, CH_{Ar}), 7.04–6.98 (m, 3 H, CH_{Ar}), 6.92 (d, *J* = 8.1 Hz, 2 H, CH_{Ar}), 6.73–6.61 (m, 4 H, CH_{Ar}), 5.90–5.83 (m, 1 H, =CH), 4.75 (dd, *J* = 10.3, 5.8 Hz, 1 H, CHNO₂), 3.44–3.37 (m, 1 H, CHPh), 3.17 (s, 1 H, CH), 2.98 (s, 6 H, NCH₃), 2.95 (s, 6 H, NCH₃), 2.84–2.69 (m, 2 H, CH₂), 2.48–2.33 (m, 2 H, CH₂), 2.33 (s, 3 H, PhCH₃).

¹³C NMR (151 MHz, CDCl₃): δ = 192.4, 153.0, 149.9, 149.4, 145.2, 137.7, 136.4, 134.5, 130.9, 130.6, 129.7, 129.7, 128.2, 128.1, 127.7, 127.7, 120.1, 112.0, 83.4, 46.4, 41.0, 40.5, 33.7, 23.8, 21.1.

MS (EI, 70 eV): *m/z* (%) = 523.5 (8), 360.3 (1), 279.2 (100), 264.2 (4), 235.2 (11), 191.1 (1), 134.3 (3).

HRMS: *m/z* [M + H]⁺ calcd for C₃₃H₃₈N₃O₃: 524.2913; found: 524.2907.

(1S,2S,6S)-6-{3,3-Bis[4-(dimethylamino)phenyl]allyl}-4'-methoxy-2-nitro-1,2,3,6-tetrahydrobiphenyl-4-carbaldehyde (**4c**)

Flash chromatography (*n*-pentane–Et₂O, 1:1) gave **4c** as a yellow oil; yield: 288 mg (53%); ≥99% ee [HPLC: (S,S)-Whelk O1]; *R*_f = 0.23 (*n*-pentane–Et₂O, 1:1); [α]_D²⁰ +100.8 (c 0.97, CHCl₃).

IR (ATR): 2894, 2842, 2251, 2182, 2072, 1980, 1890, 1722, 1683, 1606, 1546, 1516, 1446, 1353, 1250, 1168, 1127, 1032, 945, 908, 816, 729, 665 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 9.54 (s, 1 H, CHO), 7.12 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 7.01 (d, *J* = 8.8 Hz, 3 H, CH_{Ar}), 6.94 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 6.80 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 6.69 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 6.64 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 5.86 (t, *J* = 7.4 Hz, 1 H, =CH), 4.75–4.69 (m, 1 H, CHNO₂), 3.78 (s, 3 H, OCH₃), 3.41–3.35 (m, 1 H, CHPh), 3.14 (s, 1 H, CH), 2.98 (s, 6 H, NCH₃), 2.94 (s, 6 H, NCH₃), 2.80–2.69 (m, 2 H, CH₂), 2.44 (dt, *J* = 14.5, 7.2 Hz, 1 H, CH₂), 2.36 (dt, *J* = 14.5, 7.2 Hz, 1 H, CH₂).

¹³C NMR (151 MHz, CDCl₃): δ = 192.4, 159.2, 152.9, 149.9, 149.4, 145.2, 136.4, 130.9, 130.6, 129.5, 128.8, 128.0, 128.1, 127.7, 120.1, 114.3, 112.0, 112.0, 83.4, 55.2, 46.0, 41.2, 40.5, 40.5, 33.7, 23.7.

MS (EI, 70 eV): *m/z* (%) = 539.3 (4), 434.3 (1), 417.3 (2), 360.2 (7), 279.2 (100), 235.1 (15), 165.1 (4), 134.1 (19), 77.2 (14).

HRMS: *m/z* [M + H]⁺ calcd for C₃₃H₃₈N₃O₄: 540.2862; found: 540.2839.

(1S,2S,6S)-6-{3,3-Bis[4-(dimethylamino)phenyl]allyl}-2'-chloro-2-nitro-1,2,3,6-tetrahydrobiphenyl-4-carbaldehyde (**4d**)

Flash chromatography (*n*-pentane–Et₂O, 1:1) gave **4d** as a yellow oil; yield: 272 mg (50%); ≥99% ee [HPLC: (S,S)-Whelk O1]; *R*_f = 0.37 (*n*-pentane–Et₂O, 1:1); [α]_D²⁰ +183.4 (c 1.02, CHCl₃).

IR (ATR): 3347, 1890, 2807, 2251, 2173, 2079, 1976, 1888, 1723, 1682, 1606, 1520, 1477, 1440, 1352, 1219, 1164, 1048, 945, 909, 816, 732 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 9.54 (s, 1 H, CHO), 7.42 (dd, *J* = 7.8, 1.5 Hz, 1 H, CH_{Ar}), 7.26–7.17 (m, 2 H, CH_{Ar}), 7.10 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 7.07–7.03 (m, 1 H, CH_{Ar}), 7.00 (s, 1 H, CH_{Ar}), 6.91 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 6.65–6.61 (m, 4 H, CH_{Ar}), 5.82 (dd, *J* = 8.8, 6.3 Hz, 1 H, =CH), 5.10–5.06 (m, 1 H, CHNO₂), 3.69–3.64 (m, 1 H, CHPh), 3.29 (s, 1 H, CH), 2.97 (s, 6 H, NCH₃), 2.94 (s, 6 H, NCH₃), 2.80–2.70 (m, 2 H, CH₂), 2.49–2.40 (m, 1 H, CH₂), 2.24–2.14 (m, 1 H, CH₂).

¹³C NMR (151 MHz, CDCl₃): δ = 192.7, 152.8, 149.9, 149.4, 145.4, 135.9, 134.5, 134.5, 130.9, 130.5, 130.1, 129.0, 128.1, 127.8, 127.7, 127.5, 119.5, 112.0, 83.1, 42.7, 40.5, 40.5, 37.1, 31.9, 26.4.

MS (EI, 70 eV): *m/z* (%) = 543.3 (1), 279.2 (100), 266.2 (86), 235.2 (30), 165.1 (12), 134.1 (61), 77.2 (18).

HRMS: *m/z* [M + H]⁺ calcd for C₃₂H₃₅ClN₃O₃: 544.2367; found: 544.2363.

(3S,4R,5S)-3-{3,3-Bis[4-(dimethylamino)phenyl]allyl}-4-(5-methylfuran-2-yl)-5-nitrocyclohex-1-ene-1-carbaldehyde (**4e**)

Flash chromatography (*n*-pentane–Et₂O, 1:1) gave **4e** as a yellow oil; yield: 231 mg (45%); 99% ee [HPLC: (S,S)-Whelk O1]; *R*_f = 0.35 (*n*-pentane–Et₂O, 1:1); [α]_D²⁰ +101.9 (c 0.99, CHCl₃).

IR (ATR): 3350, 2891, 1808, 2328, 2248, 2087, 1890, 1729, 1684, 1606, 1547, 1520, 1479, 1442, 1353, 1271, 1218, 1162, 1061, 1023, 908, 815, 730 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 9.50 (s, 1 H, CHO), 7.15 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 7.04 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 6.90–6.85 (m, 1 H, CH_{Ar}), 6.71 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 6.65 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 5.91–5.86 (m, 2 H, CH_{Ar}), 5.86–5.82 (m, 1 H, =CH), 4.73–4.67 (m, 1 H, CHNO₂), 3.63 (t,

$J = 4.4$ Hz, 1 H, CH-furyl), 3.12 (s, 1 H, CH), 2.98 (s, 6 H, NCH₃), 2.95 (s, 6 H, NCH₃), 2.79–2.73 (m, 2 H, CH₂), 2.48–2.41 (m, 2 H, CH₂), 2.21 (s, 3 H, furyl-CH₃).

¹³C NMR (101 MHz, CDCl₃): $\delta = 192.4, 152.0, 151.8, 149.9, 149.5, 149.3, 145.3, 136.2, 130.8, 130.6, 128.1, 127.7, 119.9, 112.0, 108.5, 106.3, 81.2, 40.5, 40.5, 40.4, 40.2, 33.6, 23.6, 13.5$.

MS (EI, 70 eV): m/z (%) = 513.3 (4), 279.2 (100), 264.1 (3), 235.1 (9), 134.0 (11).

HRMS: m/z [M + H]⁺ calcd for C₃₁H₃₆N₃O₄: 514.2706; found: 514.2688.

(3S,4S,5S)-3-{3,3-Bis[4-(dimethylamino)phenyl]allyl}-4-(naphthalen-2-yl)-5-nitrocyclohex-1-ene-1-carbaldehyde (4f)

Flash chromatography (*n*-pentane–Et₂O, 1:1) gave **4f** as a yellow oil; yield: 229 mg (41%); $\geq 99\%$ ee [HPLC: (S,S)-Whelk O1]; $R_f = 0.24$ (*n*-pentane–Et₂O, 1:1); $[\alpha]_D^{20} +42.3$ (c 0.93, CHCl₃).

IR (ATR): 2890, 2808, 2326, 2247, 2086, 1891, 1723, 1682, 1605, 1519, 1442, 1354, 1268, 1219, 1163, 1061, 1017, 945, 907, 815, 713 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): $\delta = 9.59$ (s, 1 H, CHO), 7.83–7.79 (m, 1 H, CH_{Ar}), 7.79–7.73 (m, 2 H, CH_{Ar}), 7.51 (s, 1 H, CH_{Ar}), 7.50–7.43 (m, 2 H, CH_{Ar}), 7.16–7.07 (m, 4 H, CH_{Ar}), 6.96 (d, $J = 8.8$ Hz, 2 H, CH_{Ar}), 6.60 (dd, $J = 13.2, 8.8$ Hz, 4 H, CH_{Ar}), 5.87 (t, $J = 7.4$ Hz, 1 H, =CH), 4.88 (dd, $J = 9.8, 5.8$ Hz, 1 H, CHNO₂), 3.56–3.52 (m, 1 H, CH-naphthyl), 3.34 (s, 1 H, CH), 2.94 (s, 6 H, NCH₃), 2.92 (s, 6 H, NCH₃), 2.83 (d, $J = 6.4$ Hz, 2 H, CH₂), 2.52–2.47 (m, 1 H, CH₂), 2.44–2.37 (m, 1 H, CH₂).

¹³C NMR (101 MHz, CDCl₃): $\delta = 192.4, 152.9, 149.9, 149.4, 145.3, 136.4, 135.0, 133.3, 132.9, 130.9, 130.5, 128.8, 128.1, 128.0, 127.6, 127.6, 127.0, 126.3, 126.2, 125.5, 119.9, 112.0, 111.9, 83.6, 46.9, 40.6, 40.5, 40.4, 33.5, 24.3$.

MS (EI, 70 eV): m/z (%) = 559.4 (2), 416.2 (7), 279.1 (100), 266.1 (10), 235.1 (9), 134.0 (10), 77.2 (2).

HRMS: m/z [M + H]⁺ calcd for C₃₆H₃₈N₃O₃: 560.2913; found: 560.2905.

(3S,4R,5S)-3-{3,3-Bis[4-(dimethylamino)phenyl]allyl}-5-nitro-4-(thiophen-2-yl)cyclohex-1-ene-1-carbaldehyde (4g)

Flash chromatography (*n*-pentane–Et₂O, 1:1) gave **4g** as a yellow oil; yield: 284 mg (55%); $\geq 99\%$ ee [HPLC: (S,S)-Whelk O1]; $R_f = 0.28$ (*n*-pentane–Et₂O, 1:1); $[\alpha]_D^{20} +113.0$ (c 0.94, CHCl₃).

IR (ATR): 2808, 2324, 2078, 1891, 1682, 1605, 1523, 1445, 1351, 1161, 1061, 944, 816, 703 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): $\delta = 9.53$ (s, 1 H, CHO), 7.18 (dd, $J = 5.1, 1.0$ Hz, 1 H, CH_{Ar}), 7.14 (d, $J = 8.8$ Hz, 2 H, CH_{Ar}), 7.04 (d, $J = 8.8$ Hz, 2 H, CH_{Ar}), 6.93–6.90 (m, 2 H, CH_{Ar}), 6.77 (d, $J = 3.4$ Hz, 1 H, CH_{Ar}), 6.70 (d, $J = 8.4$ Hz, 2 H, CH_{Ar}), 6.64 (d, $J = 8.4$ Hz, 2 H, CH_{Ar}), 5.88 (t, $J = 7.4$ Hz, 1 H, =CH), 4.66–4.60 (m, 1 H, CHNO₂), 3.95 (t, $J = 4.0$ Hz, 1 H, CH-thienyl), 3.17 (s, 1 H, CH), 2.97 (s, 6 H, NCH₃), 2.94 (s, 6 H, NCH₃), 2.87–2.74 (m, 2 H, CH₂), 2.45 (t, $J = 7.4$ Hz, 2 H, CH₂).

¹³C NMR (151 MHz, CDCl₃): $\delta = 192.2, 151.5, 150.0, 149.5, 145.5, 139.6, 136.5, 130.7, 130.6, 128.4, 128.1, 127.7, 127.0, 126.5, 125.1, 119.8, 112.1, 82.1, 43.7, 41.8, 40.6, 40.3, 34.1, 23.1$.

MS (EI, 70 eV): m/z (%) = 515.5 (4), 279.2 (100), 235.2 (11), 134.1 (12).

HRMS: m/z [M + H]⁺ calcd for C₃₀H₃₄N₃O₃S: 516.2315; found: 516.2305.

(1S,2S,6S)-6-{3,3-Bis[4-(diethylamino)phenyl]allyl}-2-nitro-1,2,3,6-tetrahydrobiphenyl-4-carbaldehyde (4h)

Flash chromatography (*n*-pentane–Et₂O, 1:1) gave **4h** as a yellow oil; yield: 198 mg (35%); $\geq 99\%$ ee [HPLC: (S,S)-Whelk O1]; $R_f = 0.58$ (*n*-pentane–Et₂O, 1:1); $[\alpha]_D^{20} +104.0$ (c 0.98, CHCl₃).

IR (ATR): 2969, 1889, 1683, 1605, 1520, 1457, 1359, 1263, 1191, 1078, 112, 907, 811, 725 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): $\delta = 9.45$ (s, 1 H, CHO), 7.20–7.16 (m, 3 H, CH_{Ar}), 7.02 (d, $J = 8.8$ Hz, 2 H, CH_{Ar}), 6.97–6.91 (m, 3 H, CH_{Ar}), 6.88 (d, $J = 8.8$ Hz, 2 H, CH_{Ar}), 6.53 (d, $J = 8.8$ Hz, 2 H, CH_{Ar}), 6.49 (d, $J = 8.8$ Hz, 2 H, CH_{Ar}), 5.74 (t, $J = 7.4$ Hz, 1 H, =CH), 4.69 (dd, $J = 10.2, 5.9$ Hz, 1 H, CHNO₂), 3.36–3.31 (m, 1 H, CHPh), 3.30–3.21 (m, 8 H, NCH₂), 3.10 (s, 1 H, CH), 2.76–2.59 (m, 2 H, CH₂), 2.33 (ddt, $J = 29.6, 14.6, 7.2$ Hz, 2 H, CH₂), 1.09 (t, $J = 7.0$ Hz, 6 H, CH₃), 1.06 (t, $J = 7.0$ Hz, 6 H, CH₃).

¹³C NMR (101 MHz, CDCl₃): $\delta = 192.4, 153.0, 147.1, 146.8, 145.4, 137.6, 136.4, 130.8, 129.7, 128.9, 128.3, 128.0, 127.8, 126.6, 119.2, 111.2, 111.1, 83.4, 46.7, 44.3, 44.2, 41.0, 33.6, 23.9, 12.7, 12.6$.

MS (EI, 70 eV): m/z (%) = 565.7 (3), 335.4 (100), 291.4 (12), 248.1 (9).

HRMS: m/z [M + H]⁺ calcd for C₃₆H₄₄N₃O₃: 566.3377; found: 566.3371.

(1S,2S,6S)-6-{3,3-Bis[4-(diethylamino)phenyl]allyl}-4'-methyl-2-nitro-1,2,3,6-tetrahydrobiphenyl-4-carbaldehyde (4i)

Flash chromatography (*n*-pentane–Et₂O, 1:1) gave **4i** as a yellow oil; yield: 238 mg (41%); $\geq 99\%$ ee [HPLC: (S,S)-Whelk O1]; $R_f = 0.56$ (*n*-pentane–Et₂O, 1:1); $[\alpha]_D^{20} +127.0$ (c 1.01, CHCl₃).

IR (ATR): 2970, 2252, 1894, 1683, 1606, 1518, 1457, 1359, 1263, 1193, 1153, 1078, 1012, 907, 810, 728 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): $\delta = 9.56$ (s, 1 H, CHO), 7.15–7.08 (m, 4 H, CH_{Ar}), 7.04–7.01 (m, 1 H, CH_{Ar}), 6.99 (d, $J = 8.8$ Hz, 2 H, CH_{Ar}), 6.94 (d, $J = 8.0$ Hz, 2 H, CH_{Ar}), 6.64 (d, $J = 8.8$ Hz, 2 H, CH_{Ar}), 6.59 (d, $J = 8.8$ Hz, 2 H, CH_{Ar}), 5.84 (t, $J = 7.4$ Hz, 1 H, =CH), 4.78 (dd, $J = 10.1, 5.9$ Hz, 1 H, CHNO₂), 3.47–3.29 (m, 9 H, NCH₂, CH), 3.19 (s, 1 H, CHPh), 2.84–2.70 (m, 2 H, CH₂), 2.53–2.34 (m, 2 H, CH₂), 2.33 (s, 3 H, PhCH₃), 1.21 (t, $J = 7.1$ Hz, 6 H, CH₃), 1.17 (t, $J = 7.1$ Hz, 6 H, CH₃).

¹³C NMR (101 MHz, CDCl₃): $\delta = 192.5, 153.2, 147.1, 146.8, 145.3, 137.6, 136.4, 134.6, 130.8, 129.8, 129.6, 128.3, 127.7, 126.6, 119.3, 111.2, 111.1, 83.5, 46.4, 44.3, 44.2, 41.0, 33.6, 23.9, 21.1, 12.7, 12.6$.

MS (EI, 70 eV): m/z (%) = 579.3 (4), 378.1 (26), 335.1 (100), 309.0 (41), 220.0 (12).

HRMS: m/z [M + H]⁺ calcd for C₃₇H₄₆N₃O₃: 580.3534; found: 580.3507.

(1S,2S,6S)-6-{3,3-Bis[4-(diethylamino)phenyl]allyl}-4'-methoxy-2-nitro-1,2,3,6-tetrahydrobiphenyl-4-carbaldehyde (4j)

Flash chromatography (*n*-pentane–Et₂O, 1:1) gave **4j** as a yellow oil; yield: 256 mg (43%); $\geq 99\%$ ee [HPLC: (S,S)-Whelk O1]; $R_f = 0.50$ (*n*-pentane–Et₂O, 1:1); $[\alpha]_D^{20} +98.6$ (c 1.00, CHCl₃).

IR (ATR): 2968, 1887, 1683, 1606, 1515, 1458, 1359, 1257, 1189, 1077, 1022, 813, 665 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): $\delta = 9.56$ (s, 1 H, CHO), 7.14 (d, $J = 8.8$ Hz, 2 H, CH_{Ar}), 7.03–7.02 (m, 1 H, CH_{Ar}), 6.99 (dd, $J = 18.1, 8.8$ Hz, 4 H, CH_{Ar}), 6.83 (d, $J = 8.8$ Hz, 2 H, CH_{Ar}), 6.65 (d, $J = 8.8$ Hz, 2 H, CH_{Ar}), 6.60 (d, $J = 8.8$ Hz, 2 H, CH_{Ar}), 5.85 (t, $J = 7.4$ Hz, 1 H, =CH), 4.77 (dd, $J = 10.3, 5.9$ Hz, 1 H, CHNO₂), 3.79 (s, 3 H, OCH₃), 3.43–3.41 (m, 1 H, CHPh), 3.40–3.35 (m, 8 H, NCH₂), 3.17 (s, 1 H, CH), 2.84–2.72 (m, 2 H, CH₂), 2.45 (ddt, $J = 29.6, 14.7, 7.1$ Hz, 2 H, CH₂), 1.21 (t, $J = 7.1$ Hz, 6 H, CH₃), 1.18 (t, $J = 7.1$ Hz, 6 H, CH₃).

¹³C NMR (151 MHz, CDCl₃): $\delta = 192.5, 159.2, 153.1, 147.1, 146.8, 145.3, 136.4, 130.9, 129.8, 129.6, 128.9, 128.3, 126.6, 119.3, 114.3, 111.2, 111.2, 83.5, 55.2, 46.0, 44.4, 44.3, 41.3, 33.7, 23.8, 12.7, 12.7$.

MS (EI, 70 eV): m/z (%) = 595.5 (3), 557.4 (6), 343.4 (10), 335.2 (100), 309.2 (16), 227.1 (14).

HRMS: m/z [M + H]⁺ calcd for C₃₇H₄₆N₃O₄: 596.3483; found: 596.3465.

(1S,2S,6S)-6-{3,3-Bis[4-(diethylamino)phenyl]allyl}-2'-chloro-2-nitro-1,2,3,6-tetrahydrobiphenyl-4-carbaldehyde (4k)

Flash chromatography (*n*-pentane–Et₂O, 1:1) gave **4k** as a yellow oil; yield: 270 mg (45%); ≥99% ee [HPLC: (S,S)-Whelk O1]; *R*_f = 0.52 (*n*-pentane–Et₂O, 1:1); [α]_D²⁰ +122.3 (*c* 1.13, CHCl₃).

IR (ATR): 2970, 2890, 1723, 1683, 1605, 1548, 1516, 1468, 1357, 1263, 1194, 1151, 1076, 1010, 812, 751 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 9.55 (s, 1 H, CHO), 7.42 (d, *J* = 7.6 Hz, 1 H, CH_{Ar}), 7.21 (ddd, *J* = 16.2, 14.3, 7.6 Hz, 2 H, CH_{Ar}), 7.11 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 7.06–7.01 (m, 2 H, CH_{Ar}), 6.88 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 6.60–6.56 (m, 4 H, CH_{Ar}), 5.79 (t, *J* = 7.6 Hz, 1 H, =CH), 5.12–5.08 (m, 1 H, CHNO₂), 3.68 (d, *J* = 10.6 Hz, 1 H, CHPh), 3.38–3.33 (m, 8 H, NCH₂), 3.29 (s, 1 H, CH), 3.04 (d, *J* = 19.1 Hz, 1 H, CH₂), 2.80–2.73 (m, 1 H, CH₂), 2.50–2.43 (m, 1 H, CH₂), 2.20 (dt, *J* = 14.9, 8.6 Hz, 1 H, CH₂), 1.19 (t, *J* = 8.1 Hz, 6 H, CH₃), 1.16 (t, *J* = 8.1 Hz, 6 H, CH₃).

¹³C NMR (151 MHz, CDCl₃): δ = 192.8, 153.0, 147.1, 146.7, 145.5, 135.8, 134.5, 134.5, 130.7, 130.1, 129.8, 129.0, 128.3, 127.8, 127.4, 126.5, 118.6, 111.1, 111.0, 83.1, 44.3, 44.2, 42.7, 37.1, 31.8, 26.4, 12.7, 12.6.

MS (EI, 70 eV): *m/z* (%) = 599.5 (1), 416.3 (35), 378.3 (76), 335.3 (100), 322.3 (66), 307.2 (27).

HRMS: *m/z* [M + H]⁺ calcd for C₃₆H₄₃ClN₃O₃: 600.2988; found: 600.2971.

(1S,2S,6S)-6-{3,3-Bis[4-(pyrrolidin-1-yl)phenyl]allyl}-2-nitro-1,2,3,6-tetrahydrobiphenyl-4-carbaldehyde (4l)

Flash chromatography (*n*-pentane–Et₂O, 1:1) gave **4l** as a yellow solid; yield: 275 mg (49%); mp 146–148 °C; ≥99% ee [HPLC: (S,S)-Whelk O1]; *R*_f = 0.52 (*n*-pentane–Et₂O, 1:1); [α]_D²⁰ +156.4 (*c* 0.92, CHCl₃).

IR (ATR): 2955, 2838, 2251, 1681, 1607, 1524, 1367, 1173, 965, 907, 814, 724 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 9.54 (s, 1 H, CHO), 7.29–7.27 (m, 3 H, CH_{Ar}), 7.11 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 7.05–6.98 (m, 5 H, CH_{Ar}), 6.50 (dd, *J* = 23.3, 8.2 Hz, 4 H, CH_{Ar}), 5.82 (t, *J* = 7.4 Hz, 1 H, =CH), 4.76 (dt, *J* = 10.0, 5.1 Hz, 1 H, CHNO₂), 3.46–3.41 (m, 1 H, CHPh), 3.33–3.28 (m, 8 H, NCH₂), 3.19 (s, 1 H, CH), 2.82–2.70 (m, 2 H, CH₂), 2.47–2.38 (m, 2 H, CH₂), 2.04–1.98 (m, 8 H, CH₂).

¹³C NMR (101 MHz, CDCl₃): δ = 192.4, 153.0, 147.3, 146.8, 145.7, 137.6, 136.4, 130.7, 129.9, 128.9, 128.2, 128.0, 127.8, 126.7, 119.2, 111.1, 83.3, 53.4, 47.6, 47.5, 46.7, 41.1, 33.7, 25.5, 25.4, 23.7.

MS (EI, 70 eV): *m/z* (%) = 561.2 (2), 331.1 (31), 197.0 (32), 82.8 (100), 57.1 (33).

HRMS: *m/z* [M + H]⁺ calcd for C₃₆H₄₀N₃O₃: 562.3064; found: 562.3064.

(1S,2S,6S)-6-{3,3-Bis[4-(piperidin-1-yl)phenyl]allyl}-2-nitro-1,2,3,6-tetrahydrobiphenyl-4-carbaldehyde (4m)

Flash chromatography (*n*-pentane–Et₂O, 1:1) gave **4m** as a yellow oil; yield: 177 mg (30%); ≥99% ee [HPLC: (S,S)-Whelk O1]; *R*_f = 0.48 (*n*-pentane–Et₂O, 1:1); [α]_D²⁰ +143.2 (*c* 1.01, CHCl₃).

IR (ATR): 2931, 2811, 2319, 2231, 2076, 1898, 1684, 1604, 1509, 1540, 1373, 1231, 1125, 1024, 911, 825, 726 cm⁻¹.

¹H NMR (600 MHz, CDCl₃): δ = 9.54 (s, 1 H, CHO), 7.32–7.27 (m, 3 H, CH_{Ar}), 7.12 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 7.05–6.97 (m, 5 H, CH_{Ar}), 6.89 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 6.82 (d, *J* = 8.8 Hz, 2 H, CH_{Ar}), 5.91 (t, *J* = 7.4 Hz, 1 H, =CH), 4.78–4.73 (m, 1 H, CHNO₂), 3.43–3.39 (m, 1 H, CHPh), 3.21–3.14 (m, 9 H, NCH₂, CH), 2.77 (qd, *J* = 18.4, 6.0 Hz, 2 H, CH₂), 2.39 (ddt, *J* = 29.7, 14.7, 7.2 Hz, 2 H, CH₂), 1.76–1.67 (m, 8 H, CH₂), 1.63–1.56 (m, 4 H, CH₂).

¹³C NMR (151 MHz, CDCl₃): δ = 192.4, 152.7, 151.4, 151.0, 145.0, 137.5, 136.5, 132.8, 130.5, 130.0, 129.0, 128.1, 127.9, 127.8, 121.0, 115.7, 115.6, 83.3, 50.2, 46.7, 40.8, 33.6, 25.9, 25.7, 24.3, 24.3, 23.8.

MS (EI, 70 eV): *m/z* (%) = 589.1 (3), 359.1 (100), 346.0 (26), 275.0 (5), 179.1 (11).

HRMS: *m/z* [M + H]⁺ calcd for C₃₈H₄₄N₃O₃: 590.3377; found: 590.3387.

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Supporting Information

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