Asymmetric preparation of polysubstitued cyclopentanes by synergistic Pd(0)/amine catalyzed formal [3+2] cycloadditions of vinyl cyclopropanes with enals

Maxime Laugeois, a Sudipta Ponra, a Virginie Ratovelomanana-Vidal, * a Véronique Michelet, * a and Maxime R. Vitale * a

a PSL Research University, Chimie ParisTech – CNRS, Institut de Recherche de Chimie Paris, Paris 75005, France

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General considerations

All reactions were run under argon atmosphere unless specified. Reaction vessels were oven-dried, cooled under vacuum and flushed with argon before use. Cyclohexane and ethyl acetate were distilled under reduced pressure. Acetonitrile, 1,2-dichloroethane and α,α,α-trifluorotoluene were distilled over calcium hydride. THF, Et₂O, CH₂Cl₂, DMF and toluene were dried over alumina columns in an Innovative Technologies apparatus. Reagent grade tert-butyl methyl ether, hexane and methanol were purchased and used without further purification. Every reagent was either purified following the methods described in the literature or used without further purification.

Acros Silica Gel 60 (0.0040-0.0063 mm) was employed for flash column chromatography. Analytical thin layer chromatography (TLC) was carried out using commercial silica-gel plates (Merck 60 F254), spots were detected with UV light (254 nm) and revealed with a KMnO₄ or para-anisaldehyde stain.

Proton nuclear magnetic resonance (¹H NMR) spectra were recorded using a Bruker AVANCE 300 (300 MHz) or a Bruker AVANCE 400 (400 MHz). Chemical shifts are reported in delta (δ) units part per million (ppm) relative to the signal of the solvent. Coupling constants are reported in Hertz (Hz). The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Carbon-13 nuclear magnetic resonance (¹³C NMR) spectra were recorded using a Bruker AVANCE 300 (75 MHz) or a Bruker AVANCE 400 (100 MHz). Chemical shifts are reported in delta (δ) units part per million (ppm) relative to the center line of the triplet at 77.16 ppm for deuterochloroform. ¹³C NMR experiments were routinely run with broadband decoupling. Fluorine-19 nuclear magnetic resonance (¹⁹F NMR) spectra were recorded using a Bruker AVANCE 300 (282 MHz).

SFC analyses were performed on a Berger apparatus equipped with Daicel ChiralPak columns coupled with a dual wavelength (215/254 nm) Waters 2489 UV detector. Optical rotations were measured on a Perkin-Elmer 241 Polarimeter (λ = 589 nm, Na lamp, 1 dm cell). HPLC analyses were performed on a Waters alliance e2695 system equipped with Daicel ChiralPak columns and UV detector at 215 nm.

Mass spectra (Chemical ionization, NH₃) were recorded at ENSCP Chimie ParisTech. HRMS analyses were performed at the Université Pierre et Marie Curie.

Vinylcyclopropanes¹,² and enals³ were prepared according to the procedures described in the literature. Spectral data were in accordance with the literature values. Pd₂(db₃)₃.CHCl₃ was prepared from PdCl₂ following the procedure of Ananikov.⁴ Catalyst O₁ was prepared following the procedures of Periasamy⁵ and Jørgensen.⁶ Catalysts O₂ and O₃ were prepared following the procedures of MacMillan.⁷,⁸

CCDC 1456321, CCDC 1456333 and CCDC 1456334 contain the supplementary crystallographic data for this paper. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.
I – [3+2] cycloaddition of vinylcyclopropanes and enals

1 – Preparation of 3-formyl-2-phenyl-4-vinylcyclopentane-1,1-dicarbonitrile 3 and alcohol 3’

Preparation of 3-formyl-2-phenyl-4-vinylcyclopentane-1,1-dicarbonitrile 3 (A)

\[
\begin{align*}
\text{NC} & \quad \text{CN} \\
\text{Ph} & \quad \text{O}
\end{align*}
\]

\(1\)

\[
\begin{align*}
\text{Ph} & \quad \text{O} \\
\text{OTMS} & \quad \text{Pd} \text{[dba]_3.CHCl}_3 (5 \text{ mol\%})
\end{align*}
\]

\(2\)

\[
\begin{align*}
\text{PhCF}_3 \quad \text{rt}
\end{align*}
\]

\(3a\)

\(3b\)

\(3c\)

In a screw cap vial under argon atmosphere, 2-vinylcyclopropane-1,1-carbodinitrile \(1\) (59 mg, 0.5 mmol), diphenylprolinol trimethylsilyl ether \(O1\) (32.5 mg, 0.1 mmol), benzotrifluoride (1.0 mL) and cinnamaldehyde \(2\) (95 μL, 0.75 mmol) were successively added. The mixture was stirred for 5 minutes at room temperature and \(para\)-nitrobenzoic acid (16.7 mg, 0.1 mmol) was added. The resulting mixture was stirred for another 5 minutes at room temperature before a solution of \(Pd_2(dba)_3.CHCl_3\) (26 mg, 0.025 mmol) and dppe (20 mg, 0.05 mmol) in benzotrifluoride (1.0 mL), previously stirred at room temperature for 30 minutes, was transferred into the vial containing the vinylcyclopropane via cannula. The cannula was washed with additional benzotrifluoride (0.5 mL, total volume = 2.5 mL) and the mixture was stirred at room temperature for 1h. The mixture was then diluted with 5 mL \(tert\)-butyl methyl ether, loaded on a small Florisil© plug (d = 1 cm, h = 2 cm), eluted with \(tert\)-butyl methyl ether (50 mL) and concentrated under reduced pressure. The diastereomeric ratio of the reaction was monitored by \(^1\text{H}\) NMR of the crude reaction mixture, which was then purified by using flash column chromatography (cyclohexane/ethyl acetate 9/1) to afford the compound as a pale yellow solid (mixture of diastereoisomers \(3a/3b/3c\), 104 mg, \(dr\) 87/8/5, \(er\) > 99.5/0.5, 83 % overall yield).

Protocol for the reduction of (\(2S,3S,4R\))-3-(formyl)-2-phenyl-4-vinylcyclopentane-1,1-dicarbonitrile 3’ (B)

\[
\begin{align*}
\text{OH} & \quad \text{Ph} \\
\text{NC} & \quad \text{CN}
\end{align*}
\]

\( \text{Et}_3\text{SiH} (1.5 \text{ equiv}) \quad \text{BF}_3.\text{OEt}_2 (10 \text{ equiv}) \quad \text{CH}_2\text{Cl}_2, 0^\circ\text{C, 30 min} \)

To a stirred solution of (\(2S,3S,4R\))-3-formyl-2-phenyl-4-vinylcyclopentane-1,1-dicarbonitrile (50 mg, 0.20 mmol, mixture of diastereomers \(3a\) and \(3c\), initial \(dr\) = 95/5) in dichloromethane (2.0 mL) at 0°C were successively added triethylsilane (48 μL, 0.30 mmol) and \(BF_3.\text{OEt}_2\) (247 μL, 2.0 mmol). The mixture was stirred at 0°C for 30 minutes, then an aqueous saturated solution of sodium carbonate (5 mL) was added. The mixture was vigorously stirred at 0°C for 20 minutes. The aqueous phase was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts were washed with an aqueous saturated solution of sodium chloride (1
x 10 mL), dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The resulting crude material was purified using flash column chromatography (cyclohexane / ethyl acetate 4/1) to afford the desired compound as a white solid (45 mg, 90% yield, isolated $dr = 95/5$).

(2S,3S,4R)-3-formyl-2-phenyl-4-vinylcyclopentane-1,1-dicarbonitrile (3)

Obtained following the general procedure after flash column chromatography (cyclohexane / ethyl acetate 9/1) as a pale yellow solid (104 mg, 87/7.5/5.5 $dr$, 83% overall yield). A fraction containing isomers a and c of 3 was obtained after a second flash column chromatography (cyclohexane / tert-butyl methyl ether 10/1) as pale yellow solid (50 mg).

Analytical data for 3a

$^1$H NMR (500 MHz, CDCl$_3$) δ 9.72 (d, $J = 1.2$ Hz, 1H), 7.53 – 7.37 (m, 5H), 5.76 (ddd, $J = 16.9$, 10.1, 8.5 Hz, 1H), 5.36 (dd, $J = 35.0$, 13.5 Hz, 2H), 4.28 (dd, $J = 9.7$, 5.3 Hz, 1H), 3.87 – 3.67 (m, 2H), 2.86 (dd, $J = 13.3$, 6.5 Hz, 1H), 2.40 (dd, $J = 13.3$, 10.3 Hz, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 199.0, 133.9, 133.3, 129.6, 129.4, 128.3, 120.0, 114.8, 114.2, 55.9, 53.7, 43.7, 41.8 ppm.

HRMS (ESI$^+$) [M+Na$^+$] calculated for C$_{16}$H$_{14}$N$_2$NaO+: 273.0998, found: 273.0998

$[\alpha]_D = -14.8$ (c 1.0, CHCl$_3$).

Analytical data for 3b

$^1$H NMR (300 MHz, CDCl$_3$) δ 9.66 (d, $J = 1.8$ Hz, 1H), 7.44 (m, 5H), 5.97 (ddd, $J = 17.0$, 10.2, 7.9 Hz, 1H), 5.41 – 5.15 (m, 3H), 3.93 (d, $J = 11.6$ Hz, 1H), 3.56 – 3.39 (m, 1H), 3.35 – 3.17 (m, 1H), 2.90 (dd, $J = 14.2$, 9.7 Hz, 1H), 2.63 (dd, $J = 14.2$, 6.8 Hz, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 197.7, 136.1, 132.4, 129.7, 129.4, 128.2, 118.4, 115.2, 114.2, 59.2, 55.9, 43.1, 42.6, 41.0 ppm.

Mass spectrometry (CI) found m/z = 251, calculated for C$_{16}$H$_{15}$N$_2$O$^+$ (M+H$^+$) = 251.

$[\alpha]_D = -10.3$ (c 1.0, CHCl$_3$).
3-(hydroxymethyl)-2-phenyl-4-vinylcyclopentane-1,1-dicarbonitrile (3')

Compound 3 (50 mg, mixture of diastereomers a and c) was subjected to reducing conditions following procedure B to yield alcohol 3' after flash column chromatography (cyclohexane / ethyl acetate 4/1) as a white solid (45 mg, 90% yield).

Analytical data for 3a'

\( ^1H \text{ NMR} \) (300 MHz, CDCl\(_3\)) \( \delta \) 7.50 – 7.39 (m, 5H), 6.11 – 5.96 (m, 1H), 5.32 – 5.19 (m, 2H), 3.69 (dd, \( J = 10.5, 8.1 \text{ Hz} \), 2H), 3.58 – 3.46 (m, 1H), 3.41 – 3.25 (m, 1H), 2.90 – 2.75 (m, 2H) ppm.

\( ^{13}C \text{ NMR} \) (75 MHz, CDCl\(_3\)) \( \delta \) 136.2, 133.9, 129.3, 129.2, 128.6, 118.4, 115.6, 114.7, 60.2, 56.2, 46.5, 43.8, 43.1, 41.8 ppm.

Mass spectrometry (Cl) found m/z = 253, calculated for C\(_{16}\)H\(_{17}\)N\(_2\)O\(_2\) (M+H\(^{+}\)) = 253.

Enantiomeric ratio (er) determined by chiral phase SFC analysis in comparison with authentic racemic material after reduction to the alcohol (AD-H column, 150 bar, 3.0 mL/min, 10% MeOH): \( t \) (major enantiomer) = 8.81 min, \( t \) (minor enantiomer) = 2.45 min, > 99.5/0.5 er.

Analytical data for 3c'

\( ^1H \text{ NMR} \) (400 MHz, CDCl\(_3\)) \( \delta \) 7.47 – 7.31 (m, 1H), 5.92 – 5.78 (m, 1H), 5.23 – 5.10 (m, 1H), 4.00 (d, \( J = 8.4 \text{ Hz} \), 1H), 3.62 (dd, \( J = 11.1, 5.2 \text{ Hz} \), 1H), 3.42 (dd, \( J = 11.0, 8.4 \text{ Hz} \), 1H), 3.01 – 2.87 (m, 1H), 2.72 – 2.60 (m, 1H), 2.58 – 2.47 (m, 1H) ppm.

\( ^{13}C \text{ NMR} \) (100 MHz, CDCl\(_3\)) \( \delta \) 138.5, 133.5, 129.3, 129.2, 129.0, 117.4, 116.8, 115.0, 61.6, 57.9, 50.7, 44.8, 44.0, 39.0 ppm.

HRMS (ESI+) [M+H\(^{+}\)] calculated for C\(_{16}\)H\(_{17}\)N\(_2\)O\(_2\): 253.1335, found: 253.1337
Determination of the configuration of cycloadducts 3a, 3b and 3c

A – Isomers 3a and 3b

A fraction containing only a mixture of diastereomers 3a and 3c could be obtained by subjecting the isolated cycloadducts 3a/3b/3c to a second column chromatography using a 40/1 cyclohexane / tert-butyl methyl ether mixture as the eluent. Crystalline samples of this fraction were obtained in a hexane / toluene mixture. NOESY NMR experiments confirmed the postulated relative configuration of isomer 3a. The crystalline sample also contained a small amount of 3c (> 5% by 1H NMR), but the good Flack parameter obtained for the X-ray diffraction analysis enabled us to ascertain the absolute configuration of isomer 3a as described below.

Under otherwise optimized reaction conditions, the use of 20 mol% P(o-Tol)₃ as a ligand (see Table 1, entry 14) led to the formation of cycloadducts 3a/3b/3c with very poor stereocontrol (dr 55/42/3). This however enabled us to isolate isomer 3b from the diastereomeric mixture by flash column chromatography using a 40/1 cyclohexane / tert-butyl methyl ether mixture as the eluent. Subsequent NOESY NMR experiments and X-ray diffraction analysis of crystalline samples of 3b obtained in a hexane / toluene mixture enabled us to determine the relative and absolute configuration of 3b as described below.

X-ray structure of 3a (CCDC 1456321)

\[
\begin{align*}
a &= 6.4272(1) \\
b &= 11.7684(2) \\
c &= 18.3674(4)
\end{align*}
\]

X-ray structure of 3b (CCDC 1456333)

\[
\begin{align*}
a &= 9.0535(2) \\
b &= 7.4148(2) \\
c &= 10.4203(3)
\end{align*}
\]
B – Isomer 3c

The reaction of 1 and 2 proceeded successfully under the optimized conditions on a 10 mmol scale (80% yield, 83/10/7 dr, 99.5/0.5 er). Following the isolation of 3a and 3c and their reduction to the alcohol form, separation by semi-preparative reversed-phase HPLC employing a C18-Stability column eluting in gradient mode from 60/40 to 20/80 H2O + 0.1% TFA / MeCN + 0.1% TFA was carried out in order to obtain a fraction containing only the reduced form of isomer 3c. Attempts to crystallise this compound were however unsuccessful.

Esterification of 3c' with 4-chloro-3-nitrobenzoyl chloride led to benzoate 3c'-Bz in 89% yield. This compound could not be crystallized either. Subsequent saponification of 3c'-Bz failed to recover alcohol 3c'; instead, the rearranged product 3c'' was obtained in 51% yield. This compound was fully characterized and its absolute configuration was confirmed by X-ray diffraction studies. Neither the reduction, the esterification nor the saponification step described above allow epimerization of product 3c or its derivatives; therefore we can conclude that the absolute configuration of 3c reflects that of 3c''.

Preparation of ((1R,2S,5R)-3,3-dicyano-2-phenyl-5-vinylcyclopentyl)methyl 4-chloro-3-nitrobenzoate (3c'-Bz)

To a solution of 3c (37 mg, 0.146 mmol) in DCE (2.5 mL) were added trimethylamine (122 μL, 0.876 mmol) and DMAP (18 mg, 0.146 mmol), and 4-chloro-3-nitrobenzoyl chloride (161 mg, 0.73 mmol). The reaction mixture was stirred at room temperature for 1 h, then quenched by addition of 5 mL of an aqueous saturated NaHCO3 solution. The mixture was vigorously stirred at room temperature for 20 minutes. The aqueous phase was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts were washed with an aqueous saturated solution of sodium chloride (1 x 10 mL), dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The resulting crude material was purified using flash column
chromatography (cyclohexane / ethyl acetate 100/0 to 4/1) to afford the desired compound as an orange oil (57 mg, 89% yield).

Analytical data for 3c'-Bz

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.18 (d, $J = 2.0$ Hz, 1H), 7.96 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.61 (d, $J = 8.4$ Hz, 1H), 7.51 – 7.29 (m, 5H), 5.87 (ddd, $J = 17.3$, 10.0, 7.8 Hz, 1H), 5.38 – 5.11 (m, 2H), 4.36 (dd, $J = 11.5$, 6.0 Hz, 1H), 4.18 (dd, $J = 11.5$, 8.1 Hz, 1H), 3.99 (t, $J = 7.7$ Hz, 1H), 3.21 – 2.78 (m, 3H), 2.55 (dt, $J = 12.6$, 6.2 Hz, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 163.1, 147.9, 137.5, 133.4, 132.9, 132.2, 131.9, 129.4, 129.2, 128.9, 126.4, 118.0, 116.1, 114.7, 64.6, 57.7, 46.8, 45.5, 44.0, 39.1 ppm.

Preparation of (1S,5R,6R,8S)-2-imino-8-phenyl-6-vinyl-3-oxabicyclo[3.2.1]octane-1-carbonitrile (3c’’)

To a stirred solution of 3c'-Bz (47 mg, 0.108 mmol) in methanol (1 mL) at 0°C was added potassium carbonate (45 mg, 0.324 mmol). The reaction mixture was warmed to room temperature and stirred for 60 h. Solvent was evaporated under reduced pressure, ethyl acetate (5 mL) and water (5 mL) were added. The aqueous phase was extracted with ethyl acetate (3 x 5 mL), and the combined organic extracts were washed with an aqueous saturated sodium chloride solution (1 x 5 mL), dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The resulting crude material was purified using flash column chromatography (cyclohexane / ethyl acetate 15/1 to 10/1) to afford compound 3c’’ as a white solid (14 mg, 51% yield). Crystalline samples of 3c’’ were obtained in a hexane / diethyl ether (20/1) mixture.

Analytical data for 3c’’

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.58 – 7.32 (m, 5H), 6.18 – 5.91 (m, 1H), 5.29 – 5.08 (m, 2H), 3.94 (s, 1H), 3.78 (d, $J = 5.1$ Hz, 12H), 2.98 (dd, $J = 14.2$, 7.6 Hz, 1H), 2.78 (dd, $J = 13.7$, 9.0 Hz, 1H), 2.65 – 2.31 (m, 2H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 163.4, 140.0, 134.5, 129.1, 127.8, 127.7, 118.9, 115.3, 71.3, 50.0, 45.8, 43.7, 42.6 ppm.

mp (°C) 153-157

Mass spectrometry (CI) found m/z = 253, calculated for C$_{16}$H$_{17}$N$_2$O$^+$ (M+H$^+$) = 253.
X-ray structure of 3e'' (CCDC 1456334)

a=6.9841(7)  b=12.5978(13)  c=15.7350(16)
3 – Spectral description of cycloadducts 15-24 and 30-34

The absolute and/or relative stereochemistry of all cycloadducts is established proceeding by analogy with compounds 3a/3b/3c. Due to the very small amounts of minor diastereomers formed in the cycloaddition reactions, only the major diastereomer will be described for compounds 15-24 and 30-34 in this section.

(2S,3S,4R)-3-formyl-2-(p-tolyl)-4-vinylcyclopentane-1,1-dicarbonitrile (15)

Obtained following the general procedure after flash column chromatography (cyclohexane / ethyl acetate 12/1) as an orange oil (203 mg, 87/8/5 dr, 77% overall yield). A fraction containing isomers a and c of 15 was obtained after a second flash column chromatography (cyclohexane / tert-butyl methyl ether 10/1) as an orange oil (56 mg).

Analytical data for 15a

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.57 (d, $J = 1.2$ Hz, 1H), 7.25 (d, $J = 8.2$ Hz, 2H), 7.13 (d, $J = 7.9$ Hz, 3H), 5.63 (ddd, $J = 17.0$, 10.0, 8.3 Hz, 1H), 5.21 (dd, $J = 19.7$, 13.5 Hz, 2H), 4.13 (d, $J = 9.5$ Hz, 1H), 3.73 – 3.51 (m, 2H), 2.72 (dd, $J = 13.3$, 6.6 Hz, 1H), 2.32 – 2.20 (m, 5H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 199.0, 139.4, 133.9, 130.2, 129.9, 128.0, 119.6, 114.9, 114.2, 55.7, 53.4, 43.4 (2 C), 41.8, 21.1 ppm.

HRMS (ESI+) [M+H$^+$] calculated for C$_{17}$H$_{17}$N$_2$O$^+$: 287.1155, found: 287.1155.

(2S,3S,4R)-3-formyl-2-(m-tolyl)-4-vinylcyclopentane-1,1-dicarbonitrile (16)

Obtained following the general procedure after flash column chromatography (cyclohexane / ethyl acetate 9/1) as a yellow solid (91 mg, 86/9/5 dr, 68% overall yield). A fraction containing isomers a and c of 16 was obtained after a second flash column chromatography (cyclohexane / tert-butyl methyl ether 10/1) as a yellow solid (70 mg).

Analytical data for 16a

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.68 (d, $J = 1.2$ Hz, 1H), 7.35 – 7.17 (m, 5H), 5.73 (ddd, $J = 17.0$, 10.0, 8.3 Hz, 1H), 5.42 – 5.24 (m, 2H), 4.22 (d, $J = 9.4$ Hz, 1H), 3.85 – 3.63 (m, 2H), 2.83 (dd, $J = 13.3$, 6.6 Hz, 1H), 2.42 – 2.34 (m, 5H) ppm.
^{13}C\ NMR\ (75\ MHz, CDCl_3)\ \delta\ 198.9,\ 139.0,\ 133.8,\ 133.1,\ 130.2,\ 129.1,\ 129.0,\ 125.1,\ 119.7,\ 114.8,\ 114.1,\ 55.7,\ 53.6,\ 43.6,\ 41.7,\ 21.4\ ppm.

\textbf{mp} (°C) 88-92

\textbf{HRMS} (ESI+) [M+Na^+] calculated for C_{17}H_{16}N_{2}NaO: 287.1155, found: 287.1159.

(2S,3S,4R)-3-formyl-2-(o-tolyl)-4-vinylcyclopentane-1,1-dicarbonitrile (17)

\begin{center}
\includegraphics[width=1in]{17.png}
\end{center}

Obtained following the general procedure after flash column chromatography (cyclohexane / ethyl acetate 15/1 to 10/1) as a white solid (191 mg, 88/9.5/2.5 \textit{dr}, 72\%\ overall\ yield). A fraction containing isomers \textit{a} and \textit{c} of 17 was obtained after a second flash column chromatography (cyclohexane / \textit{tert}-butyl methyl ether 15/1) as a white solid (71 mg).

Analytical data for 17

\textbf{1H NMR} (300 MHz, CDCl_3) \delta\ 9.66\ (d, \ J = 0.8\ Hz, 1H), 7.44\ (dd, \ J = 6.5, 2.0\ Hz, 1H), 7.33 – 7.19\ (m, 4H), 5.74\ (ddd, \ J = 17.0, 10.0, 8.3\ Hz, 1H), 5.53 – 5.22\ (m, 3H), 4.75\ (d, \ J = 8.8\ Hz, 1H), 3.90 – 3.60\ (m, 2H), 2.83\ (dd, \ J = 13.2, 6.5\ Hz, 1H), 2.61\ (s, 3H), 2.52\ (d, \ J = 13.8\ Hz, 1H), 2.39\ (dd, \ J = 13.2, 10.6\ Hz, 1H) ppm.

\textbf{13C NMR} (75 MHz, CDCl_3) \delta\ 199.2,\ 137.9,\ 133.7,\ 132.2,\ 131.3,\ 128.9,\ 126.9,\ 126.6,\ 119.7,\ 115.1,\ 114.4,\ 58.3,\ 47.9,\ 44.1,\ 43.9,\ 40.6,\ 19.9\ ppm.

\textbf{mp} (°C) 144-148

\textbf{HRMS} (ESI+) [M+Na^+] calculated for C_{17}H_{16}N_{2}NaO: 287.1155, found: 287.1155.

(2S,3S,4R)-2-(4-(\textit{tert}-butyl)phenyl)-3-formyl-4-vinylcyclopentane-1,1-dicarbonitrile (18)

\begin{center}
\includegraphics[width=1in]{18.png}
\end{center}

Obtained following the general procedure after flash column chromatography (cyclohexane / \textit{tert}-butyl methyl ether 40/1 to 10/1) as a pale yellow solid (270 mg, 90/8/2 \textit{dr}, 88\%\ overall\ yield). A fraction containing isomers \textit{a} and \textit{c} of 18 was obtained after a second flash column chromatography (cyclohexane / \textit{tert}-butyl methyl ether 15/1) as a white solid (154 mg).

Analytical data for 18a
**1H NMR** (300 MHz, CDCl$_3$) $\delta$ 9.67 (d, $J = 1.3$ Hz, 1H), 7.49 – 7.30 (m, 4H), 5.72 (ddd, $J = 16.9$, 10.0, 8.3 Hz, 1H), 5.45 – 5.23 (m, 2H), 4.24 (d, $J = 9.5$ Hz, 1H), 3.82 – 3.62 (m, 2H), 2.82 (dd, $J = 13.3$, 6.6 Hz, 1H), 2.36 (dd, $J = 13.3$, 10.2 Hz, 1H), 1.32 (s, 9H) ppm.

**13C NMR** (75 MHz, CDCl$_3$) $\delta$ 199.0, 152.5, 133.9, 130.0, 127.8, 126.2, 119.6, 114.8, 114.2, 55.8, 53.4, 43.6, 43.5, 41.7, 34.7, 31.2 ppm.

**mp** (°C) 140-144

**HRMS (ESI+)** [M+Na$^+$] calculated for C$_{20}$H$_{22}$N$_2$O: 329.1624, found: 329.1626.

Obtained following the general procedure after flash column chromatography (cyclohexane / ethyl acetate 10/1) as a pale yellow solid (223 mg, 88/8/4 dr, 83% overall yield). A fraction containing isomers a and c of 19 was obtained after a second flash column chromatography (cyclohexane / tert-butyl methyl ether 15/1) as a white solid (50 mg).

**Analytical data for 19a**

**1H NMR** (300 MHz, CDCl$_3$) $\delta$ 9.68 (s, 1H), 7.43 (ddd, $J = 8.0$, 5.0, 2.4 Hz, 2H), 7.19 – 7.07 (m, 2H), 5.71 (ddd, $J = 16.9$, 10.0, 8.5 Hz, 1H), 5.43 – 5.26 (m, 2H), 4.31 – 4.17 (m, 1H), 3.84 – 3.63 (m, 2H), 2.89 – 2.77 (m, 1H), 2.40 – 2.27 (m, 1H) ppm.

**13C NMR** (75 MHz, CDCl$_3$) $\delta$ 198.6, 163.3 (d, $J = 249.2$ Hz), 161.6, 133.6, 130.0 (d, $J = 8.4$ Hz), 128.9 (d, $J = 2.8$ Hz), 120.0, 116.3 (d, $J = 21.8$ Hz), 114.5, 113.9, 55.8, 52.9, 43.4, 41.6 ppm.

**19F NMR** (282 MHz, CDCl$_3$) $\delta$ -112.8 ppm.

**mp** (°C) 108-112


Obtained following the general procedure after flash column chromatography (cyclohexane / ethyl acetate 10/1) as a clear oil (172 mg, 89.5/8/2.5 dr, 54% overall yield). A fraction containing isomers a and c of
20 was obtained after a second flash column chromatography (cyclohexane / tert-butyl methyl ether 15/1) as a yellow oil (17 mg).

Analytical data for 20a

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.61 (s, 1H), 7.63 (d, \(J = 8.3\) Hz, 2H), 7.51 (d, \(J = 8.3\) Hz, 2H), 5.64 (ddd, \(J = 17.0, 9.9, 8.4\) Hz, 1H), 5.27 (dd, \(J = 20.8, 13.5\) Hz, 3H), 4.22 (d, \(J = 9.5\) Hz, 1H), 3.81 – 3.60 (m, 3H), 2.88 – 2.73 (m, 1H), 2.35 – 2.23 (m, 1H) ppm.

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 198.4, 137.2, 133.5, 131.7 (q, \(J = 33\) Hz), 128.8, 126.3 (q, \(J = 3\) Hz), 126.8 (q, \(J = 272\) Hz), 120.2, 114.3, 113.8, 55.6, 53.1, 43.5, 43.4, 41.3 ppm.

\(^{19}\)F NMR (282 MHz, CDCl\(_3\)) \(\delta\) -63.9 ppm.

mp (°C) 144-148

HRMS (ESI+) [M+H\(^+\)] calculated for C\(_{17}\)H\(_{14}\)F\(_3\)N\(_2\)O: 319.1053, found: 319.1053.

(2S,3S,4R)-2-(4-chlorophenyl)-3-formyl-4-vinylcyclopentane-1,1-dicarbonitrile (21)

Obtained following the general procedure after flash column chromatography (cyclohexane / ethyl acetate 15/1) as an orange oil (197 mg, 86/10/4 dr, 69% overall yield). A fraction containing isomers a and e of 21 was obtained after a second flash column chromatography (cyclohexane / tert-butyl methyl ether 12/1) as an orange oil (70 mg).

Analytical data for 21a

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.65 (s, 1H), 7.39 (d, \(J = 8.7\) Hz, 4H), 5.70 (ddd, \(J = 18.0, 9.9, 8.3\) Hz, 1H), 5.45 – 5.14 (m, 2H), 4.31 – 4.09 (m, 1H), 3.80 – 3.57 (m, 2H), 3.03 – 2.71 (m, 1H), 2.52 – 2.24 (m, 1H) ppm.

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 198.6, 135.5, 133.6, 131.8, 129.6, 129.5, 119.9, 114.6, 113.9, 55.6, 52.9, 43.3, 41.5 ppm.


(2S,3S,4R)-3-formyl-2-(3-methoxyphenyl)-4-vinylcyclopentane-1,1-dicarbonitrile (22)

Obtained following the general procedure after flash column chromatography (cyclohexane / ethyl acetate 8/1) as a yellow oil (219 mg, 86/8.5/5.5 dr, 68% overall yield). A fraction containing isomers a and e of
22 was obtained after a second flash column chromatography (cyclohexane / tert-butyl methyl ether 15/1) as a yellow oil (35 mg).

Analytical data for 22a

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.60 (d, \(J = 1.2\) Hz, 1H), 7.25 (t, \(J = 7.9\) Hz, 1H), 6.97 – 6.82 (m, 3H), 5.64 (ddd, \(J = 17.0, 10.0, 8.3\) Hz, 1H), 5.24 (dd, \(J = 19.6, 13.5\) Hz, 2H), 4.15 (d, \(J = 9.5\) Hz, 1H), 3.75 (s, 3H), 3.70 – 3.55 (m, 2H), 2.75 (dd, \(J = 13.3, 6.6\) Hz, 1H), 2.28 (dd, \(J = 13.3, 10.1\) Hz, 1H) ppm.

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 198.8, 160.1, 134.6, 133.8, 130.3, 120.2, 119.7, 114.8, 114.1, 55.7, 55.3, 53.6, 43.6, 43.5, 41.6 ppm.

HRMS (ESI+) [M+Na\(^+\)] calculated for C\(_{17}\)H\(_{16}\)N\(_2\)O\(_2\)+: 303.1104, found: 303.1104.

Methyl 3-((1S,4R,5S)-2,2-dicyano-5-formyl-4-vinylcyclopentyl)benzoate (23)

![Methyl 3-((1S,4R,5S)-2,2-dicyano-5-formyl-4-vinylcyclopentyl)benzoate (23)](image)

Obtained following the general procedure after flash column chromatography (cyclohexane / ethyl acetate 9/1) as a clear oil (121 mg, 86/9.5/4.5 \(dr\), 79% overall yield). A fraction containing isomers a and c of 23 was obtained after a second flash column chromatography (cyclohexane / tert-butyl methyl ether 10/1) as a clear oil (50 mg).

Analytical data for 23a

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 9.68 (d, \(J = 1.0\) Hz, 1H), 8.18 – 8.01 (m, 2H), 7.71 – 7.61 (m, 1H), 7.51 (t, \(J = 7.7\) Hz, 1H), 5.72 (ddd, \(J = 16.9, 10.0, 8.4\) Hz, 1H), 5.42 – 5.26 (m, 2H), 4.31 (d, \(J = 9.6\) Hz, 1H), 3.92 (s, 3H), 3.89 – 3.63 (m, 2H), 2.85 (dd, \(J = 13.3, 6.5\) Hz, 1H), 2.37 (dd, \(J = 13.4, 10.3\) Hz, 1H)

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 198.4, 166.2, 133.7, 133.6, 132.8, 131.3, 130.6, 129.4, 129.0, 120.0, 114.5, 113.8, 76.6, 55.7, 53.2, 52.3, 43.5, 43.5, 42.6, 41.4

HRMS (ESI+) [M+H\(^+\)] calculated for C\(_{18}\)H\(_{17}\)N\(_2\)O\(_3\)+: 309.1234, found: 309.1237.

(2S,3S,4R)-3-formyl-2-(naphthalen-2-yl)-4-vinylcyclopentane-1,1-dicarbonitrile (24)

![Methyl 3-((1S,4R,5S)-2,2-dicyano-5-formyl-4-vinylcyclopentyl)benzoate (23)](image)

Obtained following the general procedure after flash column chromatography (cyclohexane / ethyl acetate 15/1) as a yellow solid (101 mg, 90/8/2 \(dr\), 67% overall yield). A fraction containing isomers a and c of
24 was obtained after a second flash column chromatography (cyclohexane / tert-butyl methyl ether 15/1) as an off-white solid (30 mg).

Analytical data for 24 (major diastereomer)

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.73 (d, $J = 1.3$ Hz, 1H), 8.06 – 7.76 (m, 4H), 7.65 – 7.47 (m, 3H), 5.77 (ddd, $J = 16.9$, 10.1, 8.7 Hz, 1H), 5.36 (dd, $J = 23.3$, 13.5 Hz, 2H), 4.44 (d, $J = 9.8$ Hz, 1H), 3.92 (dd, $J = 15.9$, 6.2 Hz, 1H), 3.87 – 3.73 (m, 1H), 2.88 (dd, $J = 13.3$, 6.6 Hz, 1H), 2.42 (dd, $J = 13.3$, 10.5 Hz, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 198.9, 133.8, 133.6, 133.2, 130.6, 129.2, 128.0, 127.8, 127.0, 126.8, 125.2, 119.7, 114.9, 114.2, 55.8, 53.7, 43.6, 41.7 ppm.

mp (°C) 148-152

HRMS (ESI+) [M+H$^+$] calculated for C$_{20}$H$_{17}$N$_2$O$: 301.1341$, found: 301.1335.

(2S,3S,4R)-1',3'-dioxo-2-phenyl-4-vinyl-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-3-carbaldehyde (30)

Obtained following the general procedure after flash column chromatography (cyclohexane / ethyl acetate 20/1) as a white solid (310 mg, 86/10/4 dr, 94% overall yield). A fraction containing isomers a and c of 30 was obtained after a second flash column chromatography (cyclohexane / tert-butyl methyl ether 40/1) as a white solid (50 mg).

Analytical data for 30a

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.68 (d, $J = 2.5$ Hz, 1H), 7.89 – 7.81 (m, 1H), 7.72 – 7.58 (m, 3H), 7.05 – 6.92 (m, 5H), 5.97 (dt, $J = 16.9$, 9.7 Hz, 1H), 5.32 – 5.12 (m, 2H), 4.25 (d, $J = 11.6$ Hz, 1H), 4.12 – 4.02 (m, 1H), 3.92 – 3.74 (m, 1H), 2.31 (dd, $J = 13.5$, 7.7 Hz, 1H), 2.16 (dd, $J = 13.6$, 7.4 Hz, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 202.9, 202.1, 201.8, 142.0, 141.7, 137.5, 135.7, 135.5, 135.4, 128.3, 127.9, 127.5, 123.0, 122.9, 117.3, 64.8, 57.8, 53.0, 44.0, 39.1 ppm.

mp (°C) 111-115

HRMS (ESI+) [M+Na$^+$] calculated for C$_{22}$H$_{18}$NaO$_3$: 353.1148, found: 353.1144.

(2S,3S,4R)-2-(4-fluorophenyl)-1',3'-dioxo-4-vinyl-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-3-carbaldehyde (31)
Obtained following the general procedure after flash column chromatography (cyclohexane / ethyl acetate 20/1) as a white solid (310 mg, 91/4.5/4.5 \text{dr}, 98\% overall yield). A fraction containing isomers a and c of 31 was obtained after a second flash column chromatography (cyclohexane / tert-butyl methyl ether 40/1) as a white solid (50 mg).

Analytical data for 31a

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.66 (d, $J = 2.3$ Hz, 1H), 7.93 – 7.79 (m, 1H), 7.79 – 7.60 (m, 3H), 7.09 – 6.87 (m, 2H), 6.80 – 6.61 (m, 2H), 5.92 (dt, $J = 16.9, 9.8$ Hz, 1H), 5.36 – 5.10 (m, 2H), 4.22 (d, $J = 11.6$ Hz, 1H), 4.13 – 3.95 (m, 1H), 3.95 – 3.70 (m, 1H), 2.29 (dd, $J = 13.5, 7.7$ Hz, 1H), 2.12 (dd, $J = 13.6, 7.4$ Hz, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 202.8, 201.9, 201.5, 161.8 (d, $J = 246$ Hz), 141.9, 141.6, 137.4, 135.9, 135.7, 131.4 (d, $J = 3$ Hz), 129.5 (d, $J = 8$ Hz), 122.9, 122.9, 117.3, 115.1 (d, $J = 21$ Hz), 64.6, 58.0, 52.0, 43.7, 39.1 ppm.

$^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -115.63.

mp (°C) 123-127

HRMS (ESI+) [M+Na$^+$] calculated for C$_{22}$H$_{17}$FNaO$_3$: 371.1054, found: 371.1053.

(2S,3S,4R)-2-(naphthalen-2-yl)-1',3'-dioxo-4-vinyl-1',3'-dihydrospiro[cyclopentane-1,2'-indene]-3-carbaldehyde (32)

Obtained following the general procedure after flash column chromatography (cyclohexane / ethyl acetate 20/1) as a white solid (352 mg, 89/6/5 \text{dr}, 92\% overall yield). A fraction containing isomers a and c of 32 was obtained after a second flash column chromatography (cyclohexane / tert-butyl methyl ether 40/1) as a white solid (130 mg).

Analytical data for 32a

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 9.68 (d, $J = 2.5$ Hz, 1H), 7.89 – 7.81 (m, 1H), 7.72 – 7.58 (m, 3H), 7.05 – 6.92 (m, 7H), 5.97 (dt, $J = 16.9, 9.7$ Hz, 1H), 5.32 – 5.12 (m, 2H), 4.25 (d, $J = 11.6$ Hz, 1H), 4.12 – 4.02 (m, 1H), 3.92 – 3.74 (m, 1H), 2.31 (dd, $J = 13.5, 7.7$ Hz, 1H), 2.16 (dd, $J = 13.6, 7.4$ Hz, 1H) ppm.
\(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \(\delta\) 202.9, 202.1, 201.8, 142.0, 141.7, 137.5, 135.7, 135.5, 135.4, 128.3, 127.9, 127.5, 123.0, 122.9, 117.3, 64.8, 57.8, 53.0, 44.0, 39.1 ppm.

**mp** 132-136 °C

**HRMS (ESI+)** [M+Na\(^+\)] calculated for C\(_{26}\)H\(_{20}\)NaO\(_3\): 403.1305, found: 403.1306.

(1S,2S,3R)-7,9-dimethyl-6,8,10-trioxo-1-phenyl-3-vinyl-7,9-diaza[4.5]decane-2-carbaldehyde (33)

Obtained following the general procedure after flash column chromatography (cyclohexane / ethyl acetate 12/1) as an orange oil (228 mg, 81/19 dr, 67% overall yield).

**Analytical data for 33a**

\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) 9.60 (d, \(J = 1.9\) Hz, 1H), 7.29 – 7.19 (m, 4H), 5.96 (dt, \(J = 16.9, 9.8\) Hz, 1H), 5.35 – 5.11 (m, 2H), 4.13 (d, \(J = 11.9\) Hz, 1H), 4.01 – 3.87 (m, 1H), 3.78 (dt, \(J = 15.3, 6.4\) Hz, 1H), 3.23 (s, 3H), 2.83 (s, 3H), 2.67 (dd, \(J = 13.8, 8.2\) Hz, 1H), 2.52 (dd, \(J = 13.8, 5.8\) Hz, 1H) ppm.

\(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \(\delta\) 200.7, 171.2, 170.6, 150.3, 137.8, 134.4, 128.7, 127.3, 127.0, 117.3, 62.6, 58.4, 57.4, 44.2, 39.5, 28.8, 28.1 ppm.

**HRMS (ESI+)** [M+Na\(^+\)] calculated for C\(_{19}\)H\(_{20}\)N\(_2\)NaO\(_4\): 363.1315, found: 363.1320.

(1S,2S,3R)-8,8-dimethyl-6,10-dioxo-1-phenyl-3-vinyl-7,9-dioxaspiro[4.5]decane-2-carbaldehyde (34)

Obtained following the general procedure after flash column chromatography (cyclohexane / ethyl acetate 12/1) as a yellow oil (95 mg, 62/38 dr, 29% overall yield).

**Analytical data for 34a**

\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) 9.65 (d, \(J = 2.0\) Hz, 1H), 7.32 – 7.18 (m, 5H), 5.87 (dt, \(J = 16.9, 9.9\) Hz, 1H), 5.31 – 5.14 (m, 2H), 4.53 (d, \(J = 12.0\) Hz, 1H), 4.22 – 4.08 (m, 1H), 3.94 – 3.75 (m, 2H), 2.60 (dd, \(J = 13.6, 8.0\) Hz, 1H), 2.43 (dd, \(J = 13.6, 7.8\) Hz, 1H), 1.59 (s, 3H), 0.97 (s, 3H) ppm.

\(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \(\delta\) 200.9, 170.1, 168.4, 137.1, 134.9, 129.0, 128.6, 128.4, 128.3, 117.9, 105.5, 57.6, 55.9, 44.3, 44.1, 29.5, 28.0 ppm.

**HRMS (ESI+)** [M+Na\(^+\)] calculated for C\(_{19}\)H\(_{20}\)NaO\(_5\): 351.1203, found: 351.1204.
Determination of the enantiomeric excesses for the major diastereomers of 3, 15-24 and 30-34

Standard HPLC analysis on the mixture of 3a, 3b and 3c obtained after purification proved ineffective for determining the enantiomeric excess of 3a. Indeed, under no practical conditions were we able to observe cleanly defined peaks corresponding to the three diastereomers of 3 and their respective enantiomers.

Attempts to separate isomer 3b from the diastereomeric mixture were carried out by running a second flash column chromatography, using a cyclohexane / tert-butyl methyl ether mixture as the eluent. Following this method, a fraction of cycloadduct 3 containing only isomers 3a and 3c could be obtained. It should be noted that, due to the extremely similar polarity of the three diastereomers, this method usually did not lead to complete separation of 3b from 3a and 3c; the total amount of 3a and 3c contained in the mixture after the isolation of the cycloadduct was therefore not fully recovered.

The mixture containing isomers 3a and 3c was then reduced to the alcohol form. Usual methods employing sodium borohydride or derivatives thereof lead in our case to low yields and/or apparent epimerisation of the stereocenter located in the α position relative to the aldehyde moiety. Satisfying results were obtained using a boron trifluoride-mediated reduction with triethylsilane (protocol B).

The enantiomeric excess of major isomer 3a was determined by supercritical fluid chromatography (SFC) or liquid HPLC with chiral stationary phases. Analytical data were compared to those of the authentic racemic material prepared using the same methods as described previously, with racemic Hayashi-Jørgensen catalyst as the organocatalyst.

(2S,3S,4R)-3-(hydroxymethyl)-2-(p-tolyl)-4-vinylcyclopentane-1,1-dicarbonitile (15*)

Compound 15 (52 mg, mixture of diastereomers a and c) was subjected to reducing conditions following procedure B to yield alcohol 15* after flash column chromatography (cyclohexane / ethyl acetate 9/1) as a clear oil (51 mg, 97% yield).

Analytical data for 15a*
^1H NMR (300 MHz, CDCl₃) δ 7.28 (d, J = 8.1 Hz, 2H), 7.23 – 7.10 (m, 2H), 6.06 – 5.88 (m, 1H), 5.28 – 5.13 (m, 2H), 3.69 – 3.54 (m, 1H), 3.47 (dd, J = 11.2, 5.5 Hz, 1H), 3.34 – 3.16 (m, 1H), 2.79 – 2.68 (m, 1H), 2.43 – 2.32 (m, 1H), 2.30 (s, 3H), 1.40 (s, 1H) ppm.
$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 139.2, 136.3, 130.7, 129.9, 128.4, 118.3, 115.6, 114.7, 60.3, 55.9, 46.4, 43.7, 42.9, 41.8, 21.2 ppm.

**Mass spectrometry** (CI) found m/z = 267, calculated for C$_{17}$H$_{19}$N$_2$O$^+$ (M+H$^+$) = 267.

**Enantiomeric ratio** ($er$) determined by chiral phase SFC analysis in comparison with authentic racemic material after reduction to the alcohol (AD-H column, 150 bar, 3.0 mL/min, 10% MeOH) : $t$ (major enantiomer) = 7.58 min, $t$ (minor enantiomer) = 2.56 min, 99.6/0.4 $er$.

(2S,3S,4R)-3-(hydroxymethyl)-2-(m-tolyl)-4-vinylcyclopentane-1,1-dicarbonitrile (16')

Compound 16 (70 mg, mixture of diastereomers a and c) was subjected to reducing conditions following procedure B to yield alcohol 16' after flash column chromatography (cyclohexane / ethyl acetate 9/1) as a clear oil (58 mg, 83% yield).

Analytical data for 16a'

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.48 – 7.09 (m, 4H), 6.18 – 5.93 (m, 1H), 5.43 – 5.13 (m, 2H), 3.77 – 3.61 (m, 2H), 3.43 – 3.26 (m, 1H), 2.90 – 2.76 (m, 2H), 2.49 – 2.41 (m, 1H), 2.39 (s, 3H), 1.46 (s, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 138.9, 136.2, 133.6, 130.1, 129.3, 129.0, 125.4, 118.3, 115.6, 114.7, 60.3, 56.1, 46.4, 43.9, 43.0, 41.7, 21.5 ppm.

**Mass spectrometry** (CI) found m/z = 267, calculated for C$_{17}$H$_{19}$N$_2$O$^+$ (M+H$^+$) = 267.

**Enantiomeric ratio** ($er$) determined by chiral phase SFC analysis in comparison with authentic racemic material after reduction to the alcohol (AD-H column, 150 bar, 3 mL/min, 3% MeOH) : $t$ (major isomer) = 10.02 min, $t$ (minor isomer) = 6.15 min, 99.7/0.3 $er$.

(2S,3S,4R)-3-(hydroxymethyl)-2-(o-tolyl)-4-vinylcyclopentane-1,1-dicarbonitrile (17')

Compound 17 (54 mg, mixture of diastereomers a and c) was subjected to reducing conditions following procedure B to yield alcohol 17' after flash column chromatography (cyclohexane / ethyl acetate 9/1) as a clear oil (43 mg, 80% yield).
Analytical data for 17a′

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.69 – 7.45 (m, 1H), 7.45 – 7.16 (m, 3H), 6.18 – 5.97 (m, 1H), 5.36 – 5.14 (m, 2H), 4.23 (d, \(J = 10.8\) Hz, 1H), 3.67 (d, \(J = 11.0\) Hz, 1H), 3.47 (d, \(J = 11.2\) Hz, 1H), 3.43 – 3.26 (m, 1H), 2.83 (dt, \(J = 9.1, 4.6\) Hz, 1H), 2.79 – 2.66 (m, 1H), 2.58 – 2.43 (m, 4H) ppm.

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 138.0, 136.2, 132.6, 131.1, 128.7, 127.1, 126.7, 118.3, 115.9, 115.0, 60.2, 50.3, 48.6, 44.5, 43.2, 40.4, 20.0 ppm.

Mass spectrometry (CI) found m/z = 267, calculated for \(\text{C}_{17}\text{H}_{19}\text{N}_{2}\text{O}^{+}\) (M+H\(^+\)) = 267.

Enantiomeric ratio (er) determined by chiral phase HPLC analysis in comparison with authentic racemic material after reduction to the alcohol (ID column, hexane/iPrOH 90/10, 0.8 mL/min): \(t\) (major isomer) = 11.38 min, \(t\) (minor isomer) = 13.77 min, 99.1/0.9 er.

(2S,3S,4R)-2-(4-(tert-butyl)phenyl)-3-(hydroxymethyl)-4-vinylcyclopentane-1,1-dicarbonitrile (18′)

Compound 18 (54 mg, mixture of diastereomers a and c) was subjected to reducing conditions following procedure B to yield alcohol 18′ after flash column chromatography (cyclohexane / ethyl acetate 9/1) as a pale yellow solid (43 mg, 80% yield).

Analytical data for 18a′

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.40 – 7.27 (m, 1H), 6.05 – 5.89 (m, 1H), 5.20 (dd, \(J = 11.5, 5.8\) Hz, 1H), 3.70 – 3.55 (m, 1H), 3.47 (dd, \(J = 11.2, 5.4\) Hz, 1H), 3.35 – 3.18 (m, 1H), 2.84 – 2.65 (m, 1H), 2.35 (dd, \(J = 13.2, 9.9\) Hz, 1H), 1.41 (s, 1H), 1.26 (s, 2H) ppm.

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 152.3, 136.4, 130.5, 128.2, 126.1, 118.2, 115.6, 114.7, 60.3, 55.8, 46.4, 43.8, 42.9, 41.7, 34.7, 31.3 ppm.

Mass spectrometry (CI) found m/z = 309, calculated for \(\text{C}_{20}\text{H}_{25}\text{N}_{2}\text{O}^{+}\) (M+H\(^+\)) = 309.

Enantiomeric ratio (er) determined by chiral phase SFC analysis in comparison with authentic racemic material after reduction to the alcohol (OD-H column, 150 bar, 2 mL/min, 2% MeOH): \(t\) (major isomer) = 15.36 min, \(t\) (minor isomer) = 17.73 min, 99.8/0.2 er.

(2S,3S,4R)-2-(4-fluorophenyl)-3-(hydroxymethyl)-4-vinylcyclopentane-1,1-dicarbonitrile (19′)
Compound 19 (50 mg, mixture of diastereomers a and c) was subjected to reducing conditions following procedure B to yield alcohol 19' after flash column chromatography (cyclohexane / ethyl acetate 8/2) as a clear oil (38 mg, 76% yield).

Analytical data for 19a’

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.51 – 7.42 (m, 1H), 7.14 (ddd, $J$ = 8.7, 5.9, 2.6 Hz, 1H), 6.04 (ddd, $J$ = 17.4, 9.9, 8.5 Hz, 1H), 5.34 – 5.20 (m, 1H), 3.72 (d, $J$ = 11.1 Hz, 1H), 3.55 (dd, $J$ = 10.5, 5.2 Hz, 1H), 3.43 – 3.24 (m, 1H), 2.81 (dd, $J$ = 13.3, 7.1 Hz, 1H), 2.43 (dd, $J$ = 13.3, 10.0 Hz, 1H), 1.42 (s, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 164.9, 161.6, 136.1, 130.3, 130.2, 129.5, 118.5, 116.4, 116.1, 115.4, 114.5, 60.1, 55.4, 46.6, 43.6, 42.9, 41.7 ppm.

$^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -113.2 ppm.

Mass spectrometry (Cl) found m/z = 271, calculated for C$_{16}$H$_{16}$F$_2$N$_2$O$^+$ (M+H$^+$) = 271.

Enantiomeric ratio (er) determined by chiral phase SFC analysis in comparison with authentic racemic material after reduction to the alcohol (AD-H column, 150 bar, 3 mL/min, 10% MeOH) : $t$ (major isomer) = 18.04 min, $t$ (minor isomer) = 2.21 min, 99.5/0.5 er.

(2S,3S,4R)-3-(hydroxymethyl)-2-(4-(trifluoromethyl)phenyl)-4-vinylcyclopentane-1,1-dicarbonitrile (20’)

Compound 20 (17 mg, mixture of diastereomers a and c) was subjected to reducing conditions following procedure B to yield alcohol 20' after flash column chromatography (cyclohexane / ethyl acetate 4/1) as a clear oil (13 mg, 77% yield).

Analytical data for 20a’

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.64 (d, $J$ = 8.2 Hz, 2H), 7.54 (d, $J$ = 8.3 Hz, 2H), 5.98 (ddd, $J$ = 17.4, 9.9, 8.5 Hz, 1H), 5.27 – 5.15 (m, 2H), 3.75 (d, $J$ = 10.9 Hz, 1H), 3.66 (d, $J$ = 10.5 Hz, 1H), 3.47 (dd, $J$ = 10.8, 4.5 Hz, 1H), 3.38 – 3.22 (m, 2H), 2.77 (dd, $J$ = 13.2, 7.1 Hz, 1H), 2.40 (dd, $J$ = 13.2, 10.2 Hz, 1H), 1.36 (s, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 137.9, 135.9, 129.1, 126.2, 118.7, 115.1, 114.3, 60.0, 55.7, 46.4, 43.9, 43.1, 41.4 ppm.

$^{19}$F NMR (282 MHz, CDCl$_3$) $\delta$ -63.8 ppm.

Mass spectrometry (Cl) found m/z = 321, calculated for C$_{17}$H$_{16}$F$_3$N$_2$O$^+$ (M+H$^+$) = 321.
Enantiomeric ratio \((er)\) determined by chiral phase HPLC analysis in comparison with authentic racemic material after reduction to the alcohol (ID column, 0.8 mL/min, hexane/i-PrOH 90/10) : \(t\) (major isomer) = 12.45 min, \(t\) (minor isomer) = 7.63 min, 99.6/0.4 \(er\).

\[(2S,3S,4R)-2-(4-chlorophenyl)-3-(hydroxymethyl)-4-vinylcyclopentane-1,1-dicarbonitrile (21')\]

Compound 21 (70 mg, mixture of diastereomers a and c) was subjected to reducing conditions following procedure B to yield alcohol 21' after flash column chromatography (cyclohexane / ethyl acetate 4/1) as a clear oil (63 mg, 90% yield).

Analytical data for 21a'

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.34 (s, 1H), 5.96 (ddd, \(J = 17.4, 9.9, 8.5\) Hz, 1H), 5.32 – 5.11 (m, 1H), 3.63 (dd, \(J = 11.1, 4.6\) Hz, 1H), 3.51 – 3.35 (m, 1H), 3.24 (dt, \(J = 12.1, 5.5\) Hz, 1H), 2.84 – 2.57 (m, 1H), 2.36 (dd, \(J = 13.3, 10.1\) Hz, 1H), 1.45 (s, 1H) ppm.

\(^{13}\)C NMR (75 MHz, CDCl\(_3\)) \(\delta\) 134.0, 135.4, 132.3, 129.9, 129.4, 118.5, 115.3, 114.5, 60.0, 55.5, 46.4, 43.7, 43.0, 41.6 ppm.

Mass spectrometry (Cl) found m/z = 287, calculated for C\(_{17}\)H\(_{16}\)ClN\(_2\)O\(^+\) (M+H\(^+\)) = 287.

Enantiomeric ratio \((er)\) determined by chiral phase SFC analysis in comparison with authentic racemic material after reduction to the alcohol (ID column, 150 bar, 3 mL/min, 6% MeOH) : \(t\) (major isomer) = 5.46 min, \(t\) (minor isomer) = 2.97 min, 99.7/0.3 \(er\).

(2S,3S,4R)-3-(hydroxymethyl)-2-(3-methoxyphenyl)-4-vinylcyclopentane-1,1-dicarbonitrile (22')

Compound 22 (35 mg, mixture of diastereomers a and c) was subjected to reducing conditions following procedure B to yield alcohol 22 after flash column chromatography (cyclohexane / ethyl acetate 4/1) as a clear oil (30 mg, 85% yield).

Analytical data for 22a'

\(^1\)H NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.28 (t, \(J = 7.9\) Hz, 1H), 7.06 – 6.78 (m, 3H), 5.98 (ddd, \(J = 17.5, 9.9, 8.5\) Hz, 1H), 5.21 (dd, \(J = 10.2, 5.9\) Hz, 2H), 3.76 (s, 3H), 3.63 (dd, \(J = 18.6, 6.9\) Hz, 2H), 3.49 (dd, \(J = 11.2, 5.4\) Hz, 1H), 3.38 – 3.18 (m, 1H), 2.74 (dd, \(J = 13.2, 7.2\) Hz, 2H), 2.36 (dd, \(J = 13.2, 9.9\) Hz, 1H), 1.38 (s, 1H) ppm.
$^{13}$C NMR (75 MHz, CDCl$_3$) δ 160.1, 136.2, 135.2, 130.2, 120.7, 118.3, 115.5, 114.7, 114.7, 114.3, 60.3, 56.1, 55.3, 46.4, 43.9, 42.9, 41.6 ppm.

**Mass spectrometry** (CI) found m/z = 283, calculated for C$_{17}$H$_{19}$N$_2$O$_2$ + (M+H$^+$) = 283.

**Enantiomeric ratio** (er) determined by chiral phase SFC analysis in comparison with authentic racemic material after reduction to the alcohol (AD-H column, 150 bar, 3 mL/min, 10% MeOH) : $t$ (major diastereomer) = 4.06 min, $t$ (minor diastereomer) = 2.28 min, 99.6/0.4 er.

Methyl 3-((1S,4R,5S)-2,2-dicyano-5-(hydroxymethyl)-4-vinylcyclopentyl)benzoate (23$^\prime$)

![Chemical Structure](image)

Compound 23 (51 mg, mixture of diastereomers a and c) was subjected to reducing conditions following procedure B to yield alcohol 23$^\prime$ after flash column chromatography (cyclohexane / ethyl acetate 4/1) as a clear oil (38 mg, 75% yield).

Analytical data for 23a$^\prime$

$^1$H NMR (300 MHz, CDCl$_3$) δ 8.17 – 8.03 (m, 2H), 7.69 (d, $J$ = 7.8 Hz, 1H), 7.52 (dd, $J$ = 9.6, 5.9 Hz, 1H), 6.14 – 5.96 (m, 1H), 5.34 – 5.22 (m, 2H), 3.92 (s, 3H), 3.81 (d, $J$ = 10.9 Hz, 1H), 3.71 (dd, $J$ = 11.2, 3.2 Hz, 1H), 3.53 (dd, $J$ = 11.2, 5.1 Hz, 1H), 3.35 (dd, $J$ = 17.1, 9.0 Hz, 1H), 2.94 – 2.75 (m, 2H), 2.47 (dd, $J$ = 13.2, 10.2 Hz, 1H), 1.62 (s, 1H)

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 166.4, 134.0, 134.5, 133.0, 131.2, 130.5, 129.7, 129.4, 118.5, 118.5, 115.3, 114.4, 60.1, 55.8, 52.3, 46.5, 43.9, 43.1, 41.5

**Mass spectrometry** (CI) found m/z = 311, calculated for C$_{18}$H$_{19}$N$_2$O$_3$ + (M+H$^+$) = 311.

**Enantiomeric ratio** (er) determined by chiral phase SFC analysis in comparison with authentic racemic material after reduction to the alcohol (AD-H column, 150 bar, 4.0 mL/min, 10% MeOH) : $t$ (major enantiomer) = 2.27 min, $t$ (minor enantiomer) = 1.71 min, 99.6/0.4 er.

(2S,3S,4R)-3-(hydroxymethyl)-2-(naphthalen-2-yl)-4-vinylcyclopentane-1,1-dicarbonitrile (24$^\prime$)

![Chemical Structure](image)

Compound 24 (30 mg, mixture of diastereomers a and c) was subjected to reducing conditions following procedure B to yield alcohol 24$^\prime$ after flash column chromatography (cyclohexane / ethyl acetate 4/1) as a clear oil (26 mg, 86% yield).
Analytical data for 24' (major diastereomer)

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.91 – 7.75 (m, 1H), 7.56 – 7.40 (m, 1H), 6.01 (ddd, $J = 17.0, 10.3, 8.5$ Hz, 1H), 5.30 – 5.13 (m, 1H), 3.81 (d, $J = 11.1$ Hz, 1H), 3.67 (dd, $J = 11.2, 2.6$ Hz, 1H), 3.51 (dd, $J = 11.1, 5.2$ Hz, 1H), 3.43 – 3.19 (m, 1H), 3.03 – 2.84 (m, 1H), 2.78 (dd, $J = 13.2, 7.1$ Hz, 1H), 2.42 (dd, $J = 13.2, 9.9$ Hz, 1H), 1.40 (s, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 136.2, 133.6, 133.3, 131.2, 129.1, 128.3, 128.2, 127.7, 126.8, 126.6, 125.5, 118.4, 115.6, 114.7, 60.3, 56.3, 46.6, 43.9, 43.1, 41.7 ppm.

Mass spectrometry (CI) found m/z = 303, calculated for C$_{20}$H$_{19}$N$_2$O (M+H$^+$) = 303.

Enantiomeric ratio (er) determined by chiral phase SFC analysis in comparison with authentic starting material after reduction to the alcohol (OD-H column, 150 bar, 3 mL/min, 2% MeOH) : t (major isomer) = 77.21 min, t (minor isomer) = 109.48 min, 99.7/0.3 er.

(2S,3S,4R)-3-(hydroxymethyl)-2-phenyl-4-vinylspiro[cyclopentane-1,2'-indene]-1',3'-dione (30')

Compound 30 (50 mg, mixture of diastereomers a and c) was subjected to reducing conditions following procedure B to yield alcohol 30' after flash column chromatography (cyclohexane / ethyl acetate 4/1) as a clear oil (36 mg, 72% yield).

Analytical data for 30a'

$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.80 – 7.72 (m, 1H), 7.63 – 7.51 (m, 3H), 6.17 (dt, $J = 17.1, 9.8$ Hz, 1H), 5.30 – 5.08 (m, 2H), 3.52 (dd, $J = 8.0, 4.1$ Hz, 3H), 3.46 – 3.33 (m, 1H), 3.32 – 3.17 (m, 1H), 2.25 (dd, $J = 13.6, 7.9$ Hz, 1H), 2.02 (dd, $J = 13.6, 6.0$ Hz, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 203.3, 142.0, 139.5, 136.2, 135.5, 135.2, 128.3, 127.3, 122.8, 122.7, 116.4, 65.4, 62.1, 55.9, 48.5, 43.9, 38.2 ppm.

Mass spectrometry (CI) found m/z = 333, calculated for C$_{22}$H$_{21}$O$_3$ (M+H$^+$) = 333.

Enantiomeric ratio (er) determined by chiral phase SFC analysis in comparison with authentic racemic material after reduction to the alcohol (AD-H column, 150 bar, 3 mL/min, 6% MeOH) : t (major enantiomer) = 19.10 min, t (minor enantiomer) = 22.43 min, 99.5/0.5 er.

(2S,3S,4R)-2-(4-fluorophenyl)-3-(hydroxymethyl)-4-vinylspiro[cyclopentane-1,2'-indene]-1',3'-dione (31')
Compound 31 (50 mg, mixture of diastereomers a and c) was subjected to reducing conditions following procedure B to yield alcohol 31' after flash column chromatography (cyclohexane / ethyl acetate 4/1) as a clear oil (36 mg, 72% yield).

Analytical data for 31a’

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.85 – 7.77 (m, 1H), 7.71 – 7.48 (m, 7H), 7.37 – 7.30 (m, 2H), 7.18 (dd, $J$ = 8.5, 1.8 Hz, 1H), 6.36 – 6.18 (m, 1H), 5.39 – 5.18 (m, 2H), 3.79 (d, $J$ = 11.7 Hz, 1H), 3.69 – 3.58 (m, 2H), 3.58 – 3.38 (m, 2H), 2.34 (dd, $J$ = 13.6, 7.7 Hz, 1H), 2.14 (dd, $J$ = 13.6, 6.1 Hz, 1H), 1.69 (s, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 203.3, 141.9, 139.5, 135.6, 135.3, 135.1, 132.6, 128.0, 127.8, 127.6, 127.4, 126.2, 125.9, 125.7, 122.9, 122.8, 116.5, 65.4, 62.1, 55.7, 48.8, 44.0, 38.8 ppm.

Mass spectrometry (CI) found m/z = 351, calculated for C$_{22}$H$_{20}$F$_3$O$_3$+ (M+H$^+$) = 351.

Enantiomeric ratio (er) determined by chiral phase SFC analysis in comparison with authentic racemic material after reduction to the alcohol (AD-H column, 150 bar, 3 mL/min, 6% MeOH) : $t$ (major enantiomer) = 19.10 min, $t$ (minor enantiomer) = 22.43 min, er > 99.5/0.5.

(2S,3S,4R)-3-(hydroxymethyl)-2-(naphthalen-2-yl)-4-vinylspiro[cyclopentane-1,2'-indene]-1',3'-dione (32')

Compound 32 (131 mg, mixture of diastereomers a and c) was subjected to reducing conditions following procedure B to yield alcohol 32' after flash column chromatography (cyclohexane / ethyl acetate 4/1) as a clear oil (107 mg, 82% yield).

Analytical data for 32a’

$^1$H NMR (300 MHz, CDCl$_3$) δ 7.80 – 7.72 (m, 1H), 7.63 – 7.51 (m, 3H), 6.17 (dt, $J$ = 17.1, 9.8 Hz, 1H), 5.30 – 5.08 (m, 2H), 3.52 (dd, $J$ = 8.0, 4.1 Hz, 3H), 3.46 – 3.33 (m, 1H), 3.32 – 3.17 (m, 1H), 2.25 (dd, $J$ = 13.6, 7.9 Hz, 1H), 2.02 (dd, $J$ = 13.6, 6.0 Hz, 1H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) δ 203.3, 142.0, 139.5, 136.2, 135.5, 135.2, 128.3, 127.3, 122.8, 122.7, 116.4, 65.4, 62.1, 55.9, 48.5, 43.9, 38.2 ppm.

Mass spectrometry (CI) found m/z = 383, calculated for C$_{26}$H$_{23}$O$_3$+ (M+H$^+$) = 383.
Enantiomeric ratio \((er)\) determined by chiral phase SFC analysis in comparison with authentic racemic material after reduction to the alcohol (IA column, 150 bar, 3 mL/min, 10% MeOH) : \(t\) (major enantiomer) = 15.56 min, \(t\) (minor enantiomer) = 20.36 min, 99.2/0.8 \(er\).

\[(1S,2S,3R)-2-(\text{hydroxymethyl})-7,9\text{-dimethyl-1-phenyl-3-vinyl}-7,9\text{-diazaspiro[4.5]decane-6,10-trione (33')}\]

Compound 33 (40 mg, mixture of diastereomers a and b) was subjected to reducing conditions following procedure B to yield alcohol 33' after flash column chromatography (cyclohexane / ethyl acetate 4/1) as a clear oil (35 mg, 87% yield).

Analytical data for 33a’

\(^1\text{H NMR}\) (300 MHz, CDCl\(_3\)) \(\delta\) 7.35 – 7.03 (m, 3H), 7.03 – 6.81 (m, 2H), 6.18 (dt, \(J = 17.0, 10.0\) Hz, 1H), 5.29 – 5.03 (m, 2H), 3.54 – 3.40 (m, 2H), 3.16 (s, 3H), 2.74 (s, 3H), 2.65 – 2.54 (m, 1H), 2.40 (dd, \(J = 13.8, 4.6\) Hz, 1H), 1.41 (s, 1H) ppm.

\(^{13}\text{C NMR}\) (75 MHz, CDCl\(_3\)) \(\delta\) 172.12, 170.7, 150.5, 140.4, 139.7, 135.0, 128.8, 127.8, 127.4, 116.4, 63.4, 61.5, 61.2, 47.7, 44.4, 38.4, 28.8, 28.2 ppm.

Mass spectrometry (CI) found \(m/z = 343\), calculated for \(C_{19}H_{23}N_2O_4^+\) (M+H') = 343.

Enantiomeric ratio \((er)\) determined by chiral phase SFC analysis in comparison with authentic racemic material after reduction to the alcohol (AD-H column, 150 bar, 3 mL/min, 5% MeOH) : \(t\) (major enantiomer) = 20.86 min, \(t\) (minor enantiomer) = 26.03 min, 99.5/0.5 \(er\).

\[(1S,2S,3R)-2-(\text{hydroxymethyl})-8,8\text{-dimethyl-1-phenyl-3-vinyl}-7,9\text{-dioxaspiro[4.5]decane-6,10-dione (34')}\]

Compound 34 (50 mg, mixture of diastereomers a and b) was subjected to reducing conditions following procedure B to yield alcohol 34' after flash column chromatography (cyclohexane / ethyl acetate 4/1) as a clear oil (45 mg, 90% yield).

Analytical data for 34’
$^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 7.32 – 7.10 (m, 5H), 6.13 (dt, $J = 17.0$, 9.8 Hz, 1H), 5.32 – 5.09 (m, 2H), 3.84 (d, $J = 12.2$ Hz, 1H), 3.50 (t, $J = 4.3$ Hz, 1H), 3.46 – 3.32 (m, 1H), 2.55 – 2.43 (m, 1H), 2.32 (dd, $J = 13.6$, 6.6 Hz, 1H), 1.51 (s, 3H), 1.04 (s, 1H), 0.91 (s, 3H) ppm.

$^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 171.1, 168.6, 139.1, 135.5, 129.0, 128.6, 116.9, 105.1, 61.6, 58.8, 48.1, 44.2, 43.3, 29.7, 27.9 ppm.

Mass spectrometry (CI) found m/z = 331, calculated for C$_{19}$H$_{23}$O$_5$ (M+H$^+$) = 331.

Enantiomeric ratio (er) determined by chiral phase HPLC analysis in comparison with authentic racemic material after reduction to the alcohol (IE column, 0.8 mL/min, hexane/i-PrOH 90/10): $t$ (major isomer) = 32.22 min, $t$ (minor isomer) = 43.40 min, 99.2/0.8 er.
**II – Additional experiments**

In order to determine if the conjugate addition of the zwitterionic π-allyl complex was the enantiodetermining step of this process, we had to determine whether this step was, or not, reversible and whether it led to sufficient enantiofacial discrimination.

We postulated that the use of a simplified analogue of this π-allylic complex in similar reaction conditions would shed light onto this process. 2-allyl malononitrile 36 was thus chosen as a suitable analogue that does not possess an electrophilic moiety. In the event that its conjugate addition onto cinnamaldehyde 1 did occur, no cyclisation would happen; we would be able to isolate the corresponding Michael adduct and determine its enantiomeric excess as a testimony for the stereofacial discrimination occurring in this process.

![Reaction Scheme]

Product 37 was isolated in 17% yield after sodium borohydride reduction, and its enantiopurity was assessed. We found that the enantiomeric excess of 37 was virtually null \((er = 51/49)\). Barring any possible epimerisation of 37 during workup or purification, this result could be viewed as proof that the Hayashi-Jørgensen catalyst O1 does not promote the addition of 36 onto cinnamaldehyde in an enantioselective fashion.

By analogy, we could surmise that in our catalytic cycle, the addition of π-allyl complex A onto iminium B is not stereoselective, and is not the only enantiodetermining step of the process.
2-allyl-2-(3-hydroxy-1-phenylpropyl)malononitrile (37)

2-allylmalononitrile 36 (106 mg, 1 mmol in 2 mL benzotrifluoride) was added to a solution of cinnamaldehyde (190 μL, 1.5 mmol), organocatalyst O1 (65 mg, 0.2 mmol) and pNBA (33.4 mg, 0.2 mmol) in benzotrifluoride (3 mL). The reaction mixture was stirred at room temperature for 20 h. After completion of the reaction, the mixture was cooled to -10°C, and methanol (1 mL) and NaBH₄ (76 mg, 2 mmol) were added. The mixture was stirred for 1 h at 0°C, then quenched by addition of an aqueous saturated solution of ammonium chloride (5 mL). The aqueous phase was extracted with dichloromethane (3 x 10 mL) and the combined organic extracts were washed with an aqueous saturated solution of sodium chloride (1 x 10 mL), dried over anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. Purification of the crude material was carried out by preparative TLC (cyclohexane/CH₂Cl₂/EtOAc 20/20/3) to afford compound 37 (42 mg, 17 % yield).

Analytical data for 37

¹H NMR (300 MHz, CDCl₃) δ 7.51 – 7.29 (m, 5H), 5.89 (ddt, J = 17.1, 10.2, 7.2 Hz, 1H), 5.59 – 5.13 (m, 2H), 3.81 – 3.61 (m, 1H), 3.36 (dd, J = 11.9, 3.4 Hz, 2H), 2.65 – 2.18 (m, 4H) ppm.

¹³C NMR (75 MHz, CDCl₃) δ 135.0, 129.3, 129.1, 129.0, 128.7, 123.1, 115.4, 114.6, 59.2, 47.6, 43.4, 40.5, 34.6 ppm.

Enantiomeric ratio (er) determined by chiral phase HPLC analysis in comparison with authentic racemic material after reduction to the alcohol (IC column, 1.0 mL/min, hexane/i-PrOH 80/20) : t (major isomer) = 6.93 min, t (minor isomer) = 8.71 min, 51/49 er.
III – References


IV – Copies of analytical data

$^1$H NMR of 3 (mixture of 3 diastereomers, $dr = 87/8/5$)

$^1$C NMR of 3a
$^1$H NMR of 3 (mixture of diastereomers a and c, dr = 95/5)

$^1$H NMR of 3b
$^{13}$C NMR of 3b

$^1$H NMR of 3c'
$^{13}$C NMR of 3c'

$^1$H NMR of 3a'/3c' ($dr = 95/5$)
SFC chromatogram of 3a’/3c’ (racemic mixture – AD-H, 150 bar, 3 mL/min, 10% MeOH)

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SFC chromatogram of 3a’/3c’ (enantioenriched – AD-H, 150 bar, 3 mL/min, 10% MeOH)

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35
COSY NMR of 3c’ (in C₆D₆)

NOESY NMR of 3c’ (in C₆D₆)
$^1$H NMR of 3c’-Bz

$^{13}$C NMR of 3c’-Bz
$^1$H NMR of 3c''

$^{13}$C NMR of 3c''
COSY NMR of 3c''
$^1$H NMR of 15 (mixture of 3 diastereomers, $dr = 87/8/5$)

$^{13}$C NMR of 15 (mixture of 3 diastereomers)
$^1$H NMR of 15 (mixture of diastereomers a and c)

$^1$H NMR of 15a*/15c* ($dr = 97/3$)
$^{13}$C NMR of $15a'/15c'$

SFC chromatogram of $15a'/15c'$ (racemic material, $dr = 97/3$ – AD-H, 150 bar, 3 mL/min, 10% MeOH)
SFC chromatogram of 15a'/15c' (enantioenriched, $dr$ 97/3 – AD-H, 150 bar, 3 mL/min, 10% MeOH)
$^1$H NMR of 16 (mixture of 3 diastereomers, $dr = 86/9/5$)

$^{13}$C NMR of 16 (mixture of 3 diastereomers)
$^1$H NMR of 16 (mixture of diastereomers a and c)

![NMR Spectrum of 16a and 16c](image)

$^1$H NMR of 16a*/16c* ($dr = 94/6$)

![NMR Spectrum of 16a*/16c*](image)
$^{13}$C NMR of 16a'/16c'

SFC chromatogram of 16a'/16c' (racemic material, $d_r = 94/6$ – AD-H, 150 bar, 3 mL/min, 3% MeOH)

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SFC chromatogram of 16a’/16c’ (enantioenriched, $dr = 94/6$ – AD-H, 150 bar, 3 mL/min, 3% MeOH)
^1H NMR of 17 (mixture of 3 diastereomers, \( dr = 88/9.5/2.5 \))

\[ \text{Diagram of } 17 \]

^13C NMR of 17 (mixture of 3 diastereomers)

\[ \text{Diagram of } 17 \]
$^1$H NMR of 17 (mixture of diastereomers a and c)

$^1$H NMR of 17a'/17c' ($dr = 97/3$)
$^{13}$C NMR of 17a'/17c'

HPLC chromatogram of 17a'/17c' (racemic material, $dr = 97/3$ - ID, 90/10 hexane/iPrOH, 0.8 mL/min)
HPLC chromatogram of 17a'/17c' (enantioenriched, $dr = 97/3$ - ID, 90/10 hexane/iPrOH, 0,8 mL/min)
$^1$H NMR of 18 (mixture of 3 diastereomers, $dr = 90/8/2$)

$^{13}$C NMR of 18 (mixture of 3 diastereomers)
$^1$H NMR of 18 (mixture of diastereomers a and c)

$^1$H NMR of 18a'/18c' ($dr = 92/8$)
$^{13}$C NMR of 18a'/18c'

SFC chromatogram of 18a'/18c' (racemic material, dr = 92/8 – OD-H, 150 bar, 2 mL/min, 2% MeOH)
SFC chromatogram of 18a’/18c’ (enantioenriched, $dr = 92/8$ – OD-H, 150 bar, 2 mL/min, 2% MeOH)
$^1$H NMR of 19 (mixture of 3 diastereomers, $dr = 88/8/4$)

$^{13}$C NMR of 19 (mixture of 3 diastereomers)
$^{19}$F NMR of 19 (mixture of 3 diastereomers)

$^1$H NMR of 19 (mixture of diastereomers a and c)
$^1$H NMR of 19a'/19c' ($dr = 95/5$)

$^{13}$C NMR of 19a'/19c'}
$^{19}$F NMR of $19a'/19c'$

SFC chromatogram of $19a'/19c'$ (racemic material, $dr = 95/5$ – AD-H, 150 bar, 3 mL/min, 10% MeOH)

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SFC chromatogram of 19a'/19c' (enantioenriched, $dr = 95/5$ – AD-H, 150 bar, 3 mL/min, 10% MeOH)
$^1$H NMR of 20 (mixture of 3 diastereomers, $dr = 90/8/2$)

$^{13}$C NMR of 20 (mixture of 3 diastereomers)
$^{19}$F NMR of 20 (mixture of 3 diastereomers)

$^1$H NMR of 20 (mixture of diastereomers a and c)
$^1$H NMR of 20a'/20c' (dr = 98/2)

$^{13}$C NMR of 20a'/20c'
$^{19}$F NMR of 20a'/20c'

HPLC chromatogram of 20a'/20c' (racemic material, $dr = 98/2$ – ID, 90/10 hexane / iPrOH, 0.8 mL/min)

HPLC chromatogram of 20a'/20c' (enantioenriched, $dr = 98/2$ – ID, 90/10 hexane / iPrOH, 0.8 mL/min)
$^1$H NMR of 21 (mixture of 3 diastereomers, $dr = 86/10/4$)

$^{13}$C NMR of 21 (mixture of 3 diastereomers)
$^1\text{H} \text{NMR of} \ 21 \ (\text{mixture of diastereomers a and c})$

$^1\text{H} \text{NMR of} \ 21\text{a}'/21\text{c}' \ (dr = 96/4)$

$^1\text{H} \text{NMR of} \ 21\text{a}'/21\text{c}' \ (dr = 96/4)$
$^{13}$C NMR of 21a'/21c'

SFC chromatogram of 21a'/21c' (racemic material, $dr = 96/4$ – ID, 150 bar, 3 mL/min, 6% MeOH)
SFC chromatogram of 21a’/21c’ (enantioenriched, \(dr = 96/4\) – ID, 150 bar, 3 mL/min, 6% MeOH)

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SFC chromatogram of 21a’/21c’ (mixture of racemic and enantioenriched material – ID, 150 bar, 3 mL/min, 6% MeOH)

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<th>Time</th>
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68
$^1$H NMR of 22 (mixture of 3 diastereomers, $dr = 86/8.5/5.5$)

$^{13}$C NMR of 22 (mixture of 3 diastereomers)
\(^1\)H NMR of 22 (mixture of diastereomers a and c)

\(^1\)H NMR of 22a/22c\(^\star\star\) (\(dr = 95/5\))
$^{13}$C NMR of $22a'/22c'$

SFC chromatogram of $22a'/22c'$ (racemic material, $dr = 95/5$ – AD-H, 150 bar, 3 mL/min, 10% MeOH)
SFC chromatogram of 22a’/22c’ (enantioenriched, $d_r = 95/5$ – AD-H, 150 bar, 3 mL/min, 10% MeOH)
$^1$H NMR of 23 (mixture of 3 diasteromers, $dr = 86/9.5/4.5$)

$^{13}$C NMR of 23 (mixture of 3 diastereomers)
\(^1\)H NMR of 23 (mixture of diastereomers a and c)

\(^1\)H NMR of 23a'/23c' (\(dr = 96/4\))
$^{13}$C NMR of 23a’/23c’

SFC chromatogram of 23a’/23c’ (racemic material, $dr = 96/4$ – AD-H, 150 bar, 4 mL/min, 10% MeOH)
SFC chromatogram of 23α'/'23c' (enantioenriched, $d_r = 96/4$ – AD-H, 150 bar, 4 mL/min, 10% MeOH)
$^1$H NMR of 24 (mixture of 3 diastereomers, $dr = 90/8/2$)

$^{13}$C NMR of 24 (mixture of 3 diastereomers)
$^1$H NMR of 24 (mixture of diastereomers a and c)

$^1$H NMR of 24a$^\prime$/24c$^\prime$ ($dr = 95/5$)
$^{13}$C NMR of 24a’/24c’

SFC chromatogram of 24a’/24c’ (racemic material, $dr = 95/5$ – OD-H, 150 bar, 3 mL/min, 2% MeOH)
SFC chromatogram of 24a’/24c’ (racemic material, $dr = 95/5$ – OD-H, 150 bar, 3 mL/min, 2% MeOH)
$^1$H NMR of 30 (mixture of 3 diastereomers, $dr = 86/10/4$)

$^{13}$C NMR of 30 (mixture of 3 diastereomers)
$^1$H NMR of 30 (mixture of diastereomers a and c)

$^1$H NMR of 30a'/30c' ($dr = 95/5$)
$^1$C NMR of 30a'/$30c'$

SFC chromatogram of 30a'/$30c'$ (racemic material, $dr = 95/5$ – AD-H, 150 bar, 3 mL/min, 6% MeOH)
SFC chromatogram of 30a'/30e' (enantioenriched, $dr = 95/5$ – AD-H, 150 bar, 3 mL/min, 6% MeOH)

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$^1$H NMR of 31 (mixture of 3 diastereomers, $dr = 91/4.5/4.5$)

$^{13}$C NMR of 31 (mixture of 3 diastereomers)
$^1$H NMR of 31 (mixture of diastereomers a and c)

$^{19}$F NMR of 31 (mixture of diastereomers a and c)
\(^1\)H NMR of 31a'/31c' (dr = 94/6)

\(^{13}\)C NMR of 31a'/31c'
$^{19}$F NMR of $31\text{a}'/31\text{c}'$

SFC chromatogram of $31\text{a}'/31\text{c}'$ (racemic material, $dr = 94/6$ – AD-H, 150 bar, 3 mL/min, 5% MeOH)
SFC chromatogram of 31a’/31c’ (enantioenriched, $dr = 94/6$ – AD-H – 150 bar, 3 mL/min, 5% MeOH)

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$^1$H NMR of 32 (mixture of 3 diastereomers, $dr = 89/6/5$)

$^{13}$C NMR of 32 (mixture of 3 diastereomers)
$^1$H NMR of 32 (mixture of diastereomers a and c)

$^1$H NMR of 32a'/32c' ($dr = 95/5$)
$^{13}$C NMR of 32a’/32c’

SFC chromatogram of 32a’/32c’ (racemic material, $dr = 95/5$ – IA, 150 bar, 3 mL/min, 10% MeOH)

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SFC chromatogram of 32a'\textbackslash 32c' (enantioenriched, $dr = 95/5$ – 1A – 150 bar, 3 mL/min, 10% MeOH)
$^1$H NMR of 33 (mixture of 2 diastereomers, $dr = 81/19$)

$^{13}$C NMR of 33
$^1$H NMR of 33a’/33b’ ($dr = 79/21$)

$^{13}$C NMR of 33a’/33b’
SFC chromatogram of $33a'/33b'$ (racemic material, $dr = 79/21$ – AD-H, 150 bar, 3 mL/min, 5% MeOH)

SFC chromatogram of $33a'/33b'$ (enantiomeric, $dr = 79/21$ – AD-H, 150 bar, 3 mL/min, 5% MeOH)
$^1$H NMR of 34 (mixture of 2 diastereomers, $dr = 62/38$)

$^{13}$C NMR of 34 (mixture of 2 diastereomers)
$^1$H NMR of $34a'/34b'$ ($dr = 62/38$)

$^{13}$C NMR of $34a'/34b'$
HPLC chromatogram of $34a'$/34b' (racemic material, $dr = 62/38$ – IE, 90/10 hexane / iPrOH, 0.8 mL/min)

HPLC chromatogram of $34a'$/34b' (enantioenriched, $dr = 62/38$ – IE, 90/10 hexane / iPrOH, 0.8 mL/min)
$^1$H NMR of 35 (crude reaction mixture, reaction run a 0.5 mmol scale with 0.17 mmol 1,3,5-trimethoxybenzene as an internal standard, $dr = 62/25/13$, NMR yield = 32%)
**$^1$H NMR of 37**

![H NMR spectrum of 37](image)

**$^{13}$C NMR of 37**

![C NMR spectrum of 37](image)
HPLC chromatogram of 37 (racemic material - IC, 80/20 hexane / iPrOH, 1.0 mL/min)

HPLC chromatogram of 37 (enantioenriched - IC, 80/20 hexane / iPrOH, 1.0 mL/min)