Enantioselective Synthesis of Cyclopenta[b]benzofurans via an Organocatalytic Intramolecular Double Cyclization
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1. General methods

NMR spectra were acquired on a Bruker AVANCE III HD spectrometer running at 400 MHz for $^1$H, 100 MHz for $^{13}$C and 162 MHz for $^{31}$P. Chemical shifts (δ) are reported in ppm relative to residual solvent signals (CHCl$_3$, 7.26 ppm for $^1$H NMR, CDCl$_3$, 77.16 ppm for $^{13}$C NMR). The following abbreviations are used to indicate the multiplicity in NMR spectra: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; bs, broad signal; dd, double doublet; ddd, double double doublet. $^{13}$C spectra were acquired in broad band decoupled mode. For characterization of isomeric mixtures * denotes minor isomer, # denotes overlap of signals of both isomers, whereas no sign denotes signal of major isomer. The number of protons given in parentheses is the sum over both isomers. Mass spectra were recorded on a Bruker Maxis Impact mass spectrometer using electrospray (ES$^+$) ionization (referenced to the mass of the charged species). Dry solvents were obtained from a MBraun MB SPS-800 solvent purification system. Analytical thin layer chromatography (TLC) was performed using pre-coated aluminium-backed plates (Merck Kieselgel 60 F254) and visualized by UV radiation, KMnO$_4$ or p-anisaldehyde stains. For flash chromatography (FC) silica gel (Silica gel 60, 230- 400 mesh, Sigma-Aldrich) or Iatrobeads 6RS - 8060 were used. Optical rotations were measured on a PerkinElmer 241 polarimeter, $[\alpha]_D$ values are given in deg·cm$^3$·g$^{-1}$·dm$^{-1}$; concentration c in g (100 mL)$^{-1}$. The diastereomeric ratio (dr) of products was evaluated by $^1$H NMR analysis of the crude mixture. The enantiomeric excess (ee) of products was determined by Ultraperformance Convergence Chromatography (Waters ACQUITY UPC$^2$) using Daicel Chiralpak IA, IB, IC, ID columns as chiral stationary phases. Racemates for UPC$^2$ analysis were made by mixing 3 and ent-3, formed from quinine 3a or quinidine 3b as catalysts. For the reactions in which the dr was poor and the diastereoisomers could not be well separated by FC, the diastereoisomeric mixture was characterized by means of chiral stationary phase UPC$^2$, in which all four peaks of both diastereoisomers were present; the correct correspondence of the peaks was confirmed by the juxtaposition of the UV spectra, recorded by the PDA detector of the UPC$^2$ system. Unless otherwise noted, analytical grade solvents and commercially available reagents were used without further purification.
2. Synthesis of aldehydes 1a-t

In a flame dried flask, the stabilized ylide S2 (1.1 eq, 5.5 mmol, 1.67 g) was dissolved in dry MeCN (20 mL). Afterwards, the respective 2-hydroxybenzaldehyde S1 (1.0 eq, 5 mmol) was added in one portion and the reaction mixture was heated to 40 °C for 16-24 h. After full conversion, the respective α-bromo-ketone S4 (1.2 eq, 6 mmol) was added and the reaction mixture was cooled to -20 °C. After stirring for 5 min, oven dried K2CO3 (1.2 eq, 6 mmol, 829 mg) was added in one portion. The reaction mixture was then stirred at -20 °C until full conversion, filtered over cotton, concentrated in vacuo and purified by FC over silica gel.

Following the general procedure, the second step was over in 4 d. The aldehyde 1a was purified by FC on silica (10:40:50 to 20:40:40 EtOAc/PhMe/pentane). The product was then recrystallized from CH2Cl2/pentane. The aldehyde 1a was isolated in 51% yield (679 mg) as a white solid.

1H NMR (400 MHz, CDCl3): δ 9.70 (d, J = 7.8 Hz, 1H), 8.03 – 7.93 (m, 2H), 7.69 – 7.58 (m, 2H), 7.53 (t, J = 7.8 Hz, 2H), 7.37 (ddd, J = 8.8, 7.5, 1.7 Hz, 2H), 7.05 (t, J = 7.5 Hz, 1H), 6.87 – 6.78 (m, 2H), 5.42 (s, 2H).

13C NMR (100 MHz, CDCl3): δ 194.7, 193.7, 156.7, 147.9, 134.4, 134.3, 132.7, 129.5, 129.1, 129.0, 128.2 (2C), 123.8, 122.0, 112.6, 71.0.

HRMS (ESI+) calculated for: [C17H14O3]+Na+ 289.0835; found: 289.0840.

IR, ν (cm-1): C=O 1618, 1596.

Following the general procedure, the second step was over in 1 d. The aldehyde 1b was purified by FC on silica (10:40:50 to 20:40:40 EtOAc/PhMe/pentane). The product was then recrystallized from CH2Cl2/pentane. The aldehyde 1b was isolated in 57% yield (810 mg) as a white solid.

1H NMR (400 MHz, CDCl3): δ 9.71 (dd, J = 7.7, 1.2 Hz, 1H), 8.01 – 7.96 (m, 2H), 7.93 (d, J = 16.1, 1H), 7.66 (t, J = 7.4 Hz, 2H), 7.53 (t, J = 7.7 Hz, 2H), 7.29 (ddd, J = 8.9, 3.2, 1.3 Hz, 1H), 7.10 – 7.03 (m, 1H), 6.82 – 6.72 (m, 2H), 5.41 (s, 2H).

13C NMR (100 MHz, CDCl3): δ 194.2, 193.5, 157.5 (d, J = 241.2 Hz), 153.0 (d, J = 2.1 Hz), 146.3 (d, J = 2.3 Hz), 134.4, 134.3, 130.2, 129.2 (2C), 128.1 (2C), 125.1 (d, J = 7.5 Hz), 118.9 (d, J = 23.7 Hz), 114.7 (d, J = 23.5Hz), 114.1 (d, J = 8.1Hz), 71.58.

19F NMR (376 MHz, CDCl3): δ -121.41


IR, ν (cm-1): C=O 1704, 1670.
Following the general procedure, the second step was over in 3 d. The aldehyde 1c was purified by FC on silica (10:40:50 to 15:40:45 EtOAc/PhMe/pentane). The product was then recrystallized from CH₂Cl₂/pentane. The aldehyde 1c was isolated in 52% yield (782 mg) as a white solid.

$^1$H NMR (400 MHz, CDCl₃): δ 9.71 (d, J = 7.7 Hz, 1H), 8.00 – 7.94 (m, 2H), 7.69 – 7.62 (m, 1H), 7.58 – 7.49 (m, 3H), 7.30 (dd, J = 8.9, 2.6 Hz, 1H), 6.84 – 6.74 (m, 2H), 5.42 (s, 2H).

$^{13}$C NMR (100 MHz, CDCl₃): δ 194.2, 193.2, 155.2, 146.1, 134.5, 134.2, 132.0, 130.4, 129.2 (2C), 128.4, 128.1 (2C), 127.2, 125.2, 114.0, 71.1.

HRMS (ESI+) calculated for: [C₁₇H₁₃O₃Cl+Na]+ 323.0445; found: 323.0444.

IR, $\tilde{\nu}$ (cm⁻¹): C=O 1705, 1670.

Following the general procedure, the second step was over in 5 d. The aldehyde 1d was isolated in 58% yield (1.00 g) as a white solid.

$^1$H NMR (400 MHz, CDCl₃): δ 9.69 (d, J = 7.7 Hz, 1H), 7.97 (d, J = 7.4 Hz, 2H), 7.86 (d, J = 16.1 Hz, 1H), 7.69 (d, J = 2.4 Hz, 1H), 7.66 (t, J = 7.5 Hz, 1H), 7.53 (t, J = 7.7 Hz, 2H), 7.43 (dd, J = 8.8, 2.4 Hz, 1H), 6.79 (dd, J = 16.1, 7.7 Hz, 1H), 6.71 (d, J = 8.8 Hz, 1H), 5.42 (s, 2H).

$^{13}$C NMR (100 MHz, CDCl₃): δ 194.2, 193.2, 155.7, 146.0, 134.9, 134.5, 134.2, 131.4, 130.4, 129.2 (2C), 128.1 (2C), 125.7, 114.4, 114.3, 71.0.

HRMS (ESI+) calculated for: [C₁₇H₁₃BrO₃+Na]+ 366.9940; found: 366.9940.

IR, $\tilde{\nu}$ (cm⁻¹): C=O 1703, 1668.

Following the general procedure, the second step was over in 3 d. The aldehyde 1e was purified by FC on silica (10:40:50 to 40:30:30) and isolated in 32% yield (466 mg) as a white solid.

$^1$H NMR (400 MHz, CDCl₃): δ 9.73 (d, J = 7.6 Hz, 1H), 8.01 – 7.93 (m, 3H), 7.67 – 7.61 (m, 1H), 7.52 (t, J = 7.8 Hz, 2H), 7.11 (d, J = 3.0 Hz, 1H), 6.93 (dd, J = 9.0, 3.0 Hz, 1H), 6.83 – 6.73 (m, 2H), 5.36 (s, 2H), 3.80 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl₃): δ 193.9, 192.2, 159.4, 144.9, 135.8, 134.7, 133.9, 133.0, 131.3, 129.3, 128.0, 124.9, 118.2, 113.2, 105.8, 70.7.

HRMS (ESI+) calculated for: [C₁₈H₁₃NO₃+Na]+ 314.0788; found: 314.0793.

IR, $\tilde{\nu}$ (cm⁻¹): C≡N 2169; C=O 1697, 1665.

Following the general procedure, the second step was over in 40 h. The aldehyde 1f was purified by FC on silica (EtOAc/PhMe/pentane 10:40:50 to 40:30:30) and isolated in 73% yield (1.08 g) as a yellow solid.

$^1$H NMR (400 MHz, CDCl₃): δ 9.70 (d, J = 7.8 Hz, 1H), 8.01 – 7.93 (m, 2H), 7.89 – 7.81 (m, 2H), 7.72 – 7.65 (m, 1H), 7.62 (dd, J = 8.7, 2.1 Hz, 1H), 7.55 (t, J = 7.8 Hz, 2H), 6.90 – 6.81 (m, 2H), 5.54 (s, 2H).

$^{13}$C NMR (100 MHz, CDCl₃): δ 193.9, 192.2, 159.4, 144.9, 135.8, 134.7, 133.9, 133.0, 131.3, 129.3, 128.0, 124.9, 118.2, 113.2, 105.8, 70.7.

HRMS (ESI+) calculated for: [C₁₈H₁₃NO₃+Na]+ 314.0788; found: 314.0793.

IR, $\tilde{\nu}$ (cm⁻¹): C≡N 2229; C=O 1697, 1665.
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 194.5, 194.1, 154.4, 151.2, 147.5, 134.5, 134.3, 129.5, 129.1 (2C), 128.1 (2C), 124.5, 118.5, 114.3, 112.8, 71.9, 55.9.

HRMS (ESI+) calculated for: [C$_{18}$H$_{16}$O$_{4}$+Na]$^+$ 319.0941; found: 319.0943.

IR, $\tilde{\nu}$ (cm$^{-1}$): C=O 1687, 1678.

Following the general procedure, the second step was over in 4 d. The aldehyde 1g was purified by FC on silica (10:40:50 to 20:40:40 EtOAc/PhMe/pentane) and isolated in 49% yield (726 mg) as a yellow solid.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.64 (d, $J$ = 7.9 Hz, 1H), 8.02 – 7.96 (m, 2H), 7.86 (d, $J$ = 16.0 Hz, 1H), 7.68 – 7.61 (m, 1H), 7.58 – 7.48 (m, 3H), 6.75 (dd, $J$ = 16.0, 7.9 Hz, 1H), 6.59 (dd, $J$ = 8.7, 2.3Hz, 1H), 6.36 (d, $J$ = 2.3 Hz, 1H), 5.38 (s, 2H), 3.82 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 194.7, 193.5, 163.6, 158.2, 148.0, 134.4, 134.3, 130.5, 129.1 (2C), 128.2 (2C), 127.3, 116.9, 106.6, 99.9, 71.0, 55.8.

HRMS (ESI+) calculated for: [C$_{18}$H$_{16}$O$_{4}$+Na]$^+$ 319.0941; found: 319.0948.

IR, $\tilde{\nu}$ (cm$^{-1}$): C=O 1659, 1594.

Following the general procedure, the second step was over in 4 d. The aldehyde 1h was purified by FC on silica (10:40:50 to 15:40:45 EtOAc/PhMe/pentane) and isolated in 82% yield (1.21 g) as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.68 (d, $J$ = 7.8 Hz, 1H), 8.15 (d, $J$ = 16.2 Hz, 1H), 7.99 – 7.92 (m, 2H), 7.65 – 7.59 (m, 1H), 7.50 (dd, $J$ = 8.4, 7.1 Hz, 2H), 7.23 (dd, $J$ = 8.0, 1.4 Hz, 1H), 7.12 (t, $J$ = 8.0 Hz, 1H), 7.00 (dd, $J$ = 8.1, 1.5 Hz, 1H), 6.70 (dd, $J$ = 16.1, 7.8 Hz, 1H), 5.42 (s, 2H), 3.85 (s, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 194.7, 193.5, 163.6, 158.2, 148.0, 134.4, 134.3, 130.5, 129.1 (2C), 128.2 (2C), 127.3, 116.9, 106.6, 99.9, 71.0, 55.8.

HRMS (ESI+) calculated for: [C$_{18}$H$_{16}$O$_{4}$+Na]$^+$ 319.0941; found: 319.0945.

IR, $\tilde{\nu}$ (cm$^{-1}$): C=O 1670, 1706.

Following the general procedure, the second step was over in 4 d. The aldehyde 1i was purified by FC on silica (10:40:50 to 20:40:40 EtOAc/PhMe/pentane) and isolated in 67% yield (952 mg) as a white solid.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 9.71 (d, $J$ = 7.8 Hz, 1H), 8.08 – 7.99 (m, 2H), 7.95 (d, $J$ = 16.0 Hz, 1H), 7.61 (dd, $J$ = 7.8, 1.7 Hz, 1H), 7.37 (ddd, $J$ = 8.7, 7.5, 1.7 Hz, 1H), 7.23 – 7.15 (m, 2H), 7.06 (t, $J$ = 7.5 Hz, 1H), 6.88 – 6.79 (m, 2H), 5.37 (s, 2H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 194.6, 192.3, 166.4 (d, $J$ = 256.50 Hz), 156.6, 147.7, 132.7, 131.0 (d, $J$ = 9.56 Hz) (2C), 130.8 (d, $J$ = 3.29 Hz), 129.6, 129.1, 123.8, 122.1, 116.4 (d, $J$ = 22.02 Hz) (2C), 112.5, 70.9.

$^{19}$F NMR (376 MHz, CDCl$_3$): $\delta$ -102.64

HRMS (ESI+) calculated for: [C$_{18}$H$_{16}$O$_{4}$+Na]$^+$ 307.0741; found: 307.0740.

IR, $\tilde{\nu}$ (cm$^{-1}$): C=O 1678, 1594.
Following the general procedure, the second step was over in 3 d. The aldehyde 1j was purified by FC on silica (10:40:50 to 15:40:45 EtOAc/PhMe/pentane). The product was then recrystallized from CH₂Cl₂/pentane. The aldehyde 1f was isolated in 66% yield (992 mg) as a white solid.

**¹H NMR (400 MHz, CDCl₃):** δ 9.71 (d, J = 7.8 Hz, 1H), 7.98 – 7.90 (m, 3H), 7.61 (dd, J = 7.8, 1.7 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.37 (ddd, J = 8.7, 7.4, 1.7 Hz, 1H), 7.05 (t, J = 15.1 Hz, 1H) (m, 1H), 6.87 – 6.79 (m, 2H), 5.37 (s, 2H).

**¹³C NMR (100 MHz, CDCl₃):** δ 194.6, 192.7, 156.4, 147.7, 140.9, 132.7 (2C), 129.7, 129.6 (2C), 129.5 (2C), 129.1, 123.8, 122.2, 112.5, 71.0.

HRMS (ESI+) calculated for: [C₁₇H₁₇O₃Cl+Na]⁺ 323.0445; found: 323.0447.

IR, ν (cm⁻¹): C=O 1703, 1658.

Following the general procedure, the second step was over in 5 d. The aldehyde 1k was purified by FC on silica (10:40:50 EtOAc/PhMe/pentane). The product was then recrystallized from CH₂Cl₂/pentane. The aldehyde 1k was isolated in 50% yield (863 mg) as a white solid.

**¹H NMR (400 MHz, CDCl₃):** δ 9.70 (d, J = 7.7 Hz, 1H), 7.94 (d, J = 16.1 Hz, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.67 (d, J = 7.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.05 (t, J = 7.4 Hz, 1H), 6.88 – 6.79 (m, 2H), 5.36 (s, 2H).

**¹³C NMR (100 MHz, CDCl₃):** δ 194.6, 192.9, 156.6, 147.7, 133.1, 132.7 (2C), 129.6 (2C), 129.6 (2C), 129.1, 123.8, 122.2, 112.5, 70.9.

HRMS (ESI+) calculated for: [C₁₇H₁₃O₃Cl+Na]⁺ 366.9940; found: 366.9940.

IR, ν (cm⁻¹): C=O 1703, 1664.

Following the general procedure, the second step was over in 3 d. The aldehyde 1l was purified by FC on silica (10:40:50 to 20:40:40 EtOAc/PhMe/pentane) and isolated in 76% (1.13 g) yield as a pale yellow solid.

**¹H NMR (400 MHz, CDCl₃):** δ 9.70 (d, J = 7.8 Hz, 1H), 8.02 – 7.94 (m, 3H), 7.60 (dd, J = 7.8, 1.7 Hz, 1H), 7.36 (ddd, J = 8.5, 7.4, 1.7 Hz, 1H), 7.04 (t, J = 7.6, 1H), 7.01 – 6.95 (m, 2H), 6.87 – 6.78 (m, 2H), 5.36 (s, 2H), 3.89 (s, 3H).

**¹³C NMR (100 MHz, CDCl₃):** δ 194.7, 192.2, 164.4, 156.9, 147.9, 132.7, 130.6 (2C), 129.6 (2C), 129.6 (2C), 129.1, 123.8, 122.2, 112.5, 70.9.

HRMS (ESI+) calculated for: [C₁₈H₁₆O₄+Na]⁺ 319.0941; found: 319.0945.

IR, ν (cm⁻¹): C=O 1670, 1595.

Following the general procedure, the second step was over in 6 h. The aldehyde 1m was purified by FC on silica (10:40:50 to 20:40:40 EtOAc/PhMe/pentane) and isolated in 76% (1.3 g) yield as a white solid.

**¹H NMR (400 MHz, CDCl₃):** δ 9.70 (d, J = 7.8 Hz, 1H), 8.02 – 7.94 (m, 3H), 7.60 (dd, J = 7.8, 1.7 Hz, 1H), 7.36 (ddd, J = 8.5, 7.4, 1.7 Hz, 1H), 7.04 (t, J = 7.6, 1H), 7.01 – 6.95 (m, 2H), 6.87 – 6.78 (m, 2H), 5.36 (s, 2H), 3.89 (s, 3H).

**¹³C NMR (100 MHz, CDCl₃):** δ 194.7, 193.5, 160.2, 156.7, 147.9, 135.6, 132.6, 130.1, 129.5, 129.0, 123.8, 122.0, 120.7, 120.5, 112.6, 112.5, 71.0, 55.7.

Following the general procedure, the second step was over in 6 h. The aldehyde 1m was purified by FC on silica (10:40:50 to 20:40:40 EtOAc/PhMe/pentane). The product was then recrystallized from CH₂Cl₂/pentane. The aldehyde 1m was isolated in 33% yield (489 mg) as a white solid.

**¹H NMR (400 MHz, CDCl₃):** δ 9.71 (d, J = 7.8 Hz, 1H), 7.98 (d, J = 16.1 Hz, 1H), 7.61 (dd, J = 7.7, 1.7 Hz, 1H), 7.58 – 7.50 (m, 2H), 7.43 (t, J = 7.9 Hz, 1H), 7.37 (ddd, J = 8.7, 7.5, 1.7 Hz, 1H), 7.19 (ddd, J = 8.3, 2.8, 1.0 Hz, 1H), 7.05 (t, J = 7.3 Hz, 1H), 6.88 – 6.80 (m, 2H), 5.41 (s, 2H), 3.87 (s, 3H).

**¹³C NMR (100 MHz, CDCl₃):** δ 194.7, 193.5, 160.2, 156.7, 147.9, 135.6, 132.6, 130.1, 129.5, 129.0, 123.8, 122.0, 120.7, 120.5, 112.6, 112.5, 71.0, 55.7.
HRMS (ESI+) calculated for: [C₁₈H₁₆O₄⁺Na]⁺ 319.0941; found: 319.0949.
IR, $\tilde{\nu}$ (cm⁻¹): C=O 1695, 1653.

Following the general procedure, the second step was over in 3 d. The aldehyde \( \text{1n} \) was purified by FC on silica (9:91 to 50:50 EtOAc/pentane). The product was then recrystallized from CH₂Cl₂/pentane. The aldehyde \( \text{1n} \) was isolated in 37% yield (548 mg) as a yellow solid.

\[ \begin{align*}
\text{1n} & \\
\end{align*} \]

\( ^1\text{H NMR (400 MHz, CDCl}_3 \): $\delta$ 9.68 (d, \( J = 7.8 \) Hz, 1H), 7.99 – 7.91 (m, 2H), 7.61 – 7.53 (m, 2H), 7.37 – 7.32 (m, 1H), 7.11 – 7.06 (m, 1H), 7.05 – 6.99 (m, 2H), 6.86 – 6.75 (m, 2H), 5.35 (s, 2H), 3.96 (s, 3H).

\( ^{13}\text{C NMR (100 MHz, CDCl}_3 \): $\delta$ 194.9, 194.8, 159.4, 157.2, 148.3, 135.1, 132.6, 131.2, 129.2, 128.8, 124.8, 123.5, 121.5, 112.4, 111.6, 74.6, 55.8.

HRMS (ESI+) calculated for: [C₁₈H₁₆O₄⁺Na]⁺ 319.0950.
IR, $\tilde{\nu}$ (cm⁻¹): C=O 1675, 1658.

Following the general procedure, the second step was over in 1 d. The aldehyde \( \text{1o} \) was purified by FC on silica (10:40:50 to 20:40:40 EtOAc/PhMe/pentane). The product was then recrystallized from CH₂Cl₂/pentane. The aldehyde \( \text{1o} \) was isolated in 34% yield (538 mg) as a yellow solid.

\[ \begin{align*}
\text{1o} & \\
\end{align*} \]

\( ^1\text{H NMR (400 MHz, CDCl}_3 \): $\delta$ 9.68 (d, \( J = 7.8 \) Hz, 1H), 8.54 (s, 1H), 8.07 – 7.88 (m, 5H), 7.68 – 7.56 (m, 3H), 7.38 (ddd, \( J = 8.7, 7.4, 1.7 \) Hz, 1H), 7.05 (t, \( J = 7.5 \) Hz, 1H), 6.93 – 6.80 (m, 2H), 5.54 (s, 2H).

\( ^{13}\text{C NMR (100 MHz, CDCl}_3 \): $\delta$ 194.6, 193.7, 156.8, 147.8, 136.1, 132.7, 131.7, 130.1, 129.7, 129.6, 129.2, 129.1, 129.0, 128.1, 127.4, 123.8, 123.6, 122.1, 112.7, 71.2.

IR, $\tilde{\nu}$ (cm⁻¹): C=O 1684, 1671.

Following the general procedure, the second step was over in 12 h. The aldehyde \( \text{1p} \) was purified by FC on silica (20:80 to 30:70 EtOAc/pentane). The product was then recrystallized from CH₂Cl₂/pentane. The aldehyde \( \text{1p} \) was isolated in 26% yield (354 mg) as a yellow solid.

\[ \begin{align*}
\text{1p} & \\
\end{align*} \]

\( ^1\text{H NMR (400 MHz, CDCl}_3 \): $\delta$ 9.72 (d, \( J = 7.8 \) Hz, 1H), 7.99 (d, \( J = 16.1 \) Hz, 1H), 7.90 (dd, \( J = 3.8, 1.1 \) Hz, 1H), 7.74 (dd, \( J = 4.9, 1.1 \) Hz, 1H), 7.61 (dd, \( J = 7.8, 1.7 \) Hz, 1H), 7.38 (ddd, \( J = 8.6, 7.5, 1.7 \) Hz, 1H), 7.19 (dd, \( J = 4.9, 3.8 \) Hz, 1H), 7.06 (t, \( J = 7.5 \) Hz, 1H), 6.90 – 6.78 (m, 2H), 5.25 (s, 2H).

\( ^{13}\text{C NMR (100 MHz, CDCl}_3 \): $\delta$ 194.6, 187.3, 156.6, 147.7, 140.4, 135.1, 132.9, 132.8, 129.6, 128.9, 128.6, 123.7, 122.2, 112.6, 71.4.

IR, $\tilde{\nu}$ (cm⁻¹): C=O 1677, 1661.
Following the general procedure, the second step was over in 5 d. The aldehyde 1q was purified by FC on silica (10:40:50 EtOAc/pentane). The product was then recrystallized from CH₂Cl₂/pentane. The aldehyde 1q was isolated in 55% yield (942 mg) as a white solid.

¹H NMR (400 MHz, CDCl₃): δ 9.61 (d, J = 7.8 Hz, 1H), 8.03 – 7.98 (m, 2H), 7.92 (d, J = 16.1 Hz, 1H), 7.58 (dd, J = 9.6, 7.7, 1.5 Hz, 4H), 7.47 – 7.34 (m, 5H), 7.30 (dd, J = 8.7, 7.4, 1.7 Hz, 1H), 7.02 (t, J = 7.5 Hz, 1H), 6.85 (dd, J = 8.4, 1.0 Hz, 1H), 6.74 (dd, J = 16.1, 7.8 Hz, 1H), 6.48 (s, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 195.0, 194.6, 156.2, 147.7, 134.8, 134.6, 133.9, 132.7, 129.4 (2C), 129.3, 129.2 (2C), 128.9 (2C), 128.7, 127.7 (2C), 124.1, 122.2, 113.9, 83.2.


IR, v (cm⁻¹): C=O 1668, 1595.

Following the general procedure, the second step was over in 22h. The aldehyde 1r was purified by FC on silica (1:15 to 1:5 EtOAc/ Pentane). The aldehyde 1r was isolated in 68% yield (742 mg) as a pale yellow solid.

¹H NMR (400 MHz, CDCl₃): δ 9.73 (d, J = 7.8 Hz, 1H), 7.93 (d, J = 16.1 Hz, 1H), 7.61 (dd, J = 7.8, 1.7 Hz, 1H), 7.39 (dd, J = 8.6, 7.4, 1.7 Hz, 1H), 7.06 (td, J = 7.6, 1.0 Hz, 1H), 6.82 (dd, J = 16.1, 7.8 Hz, 1H), 6.76 (dd, J = 8.4, 1.0 Hz, 1H), 4.69 (s, 2H), 2.63 (q, J = 7.3 Hz, 2H), 1.14 (t, J = 7.3 Hz, 3H).

¹³C NMR (100 MHz, CDCl₃): δ 207.1, 194.5, 156.4, 147.5, 132.8, 129.5, 129.0, 123.5, 122.1, 112.2, 72.8, 32.6, 7.2.


IR, v (cm⁻¹): C=O 1718, 1670.

Following the general procedure, the second step was over in 18h. The aldehyde 1s was purified by FC on silica (1:15 to 1:5 EtOAc/ Pentane). The aldehyde 1s was isolated in 42% yield (488 mg) as a yellow solid.

¹H NMR (400 MHz, CDCl₃): δ 9.72 (d, J = 7.8 Hz, 1H), 7.94 (d, J = 16.1 Hz, 1H), 7.60 (dd, J = 7.8, 1.7 Hz, 1H), 7.38 (dd, J = 8.4, 7.4, 1.7 Hz, 1H), 7.05 (td, J = 7.4, 0.9 Hz, 1H), 6.82 (dd, J = 16.1, 7.8 Hz, 1H), 6.75 (dd, J = 8.4, 1.0 Hz, 1H), 4.79 (s, 2H), 2.90 (hept, J = 6.9 Hz, 1H), 1.20 (d, J = 6.9 Hz, 6H).

¹³C NMR (100 MHz, CDCl₃): δ 209.5, 194.5, 156.5, 147.6, 132.7, 129.5, 129.0, 123.6, 122.0, 112.2, 71.6, 37.5, 18.1 (2C).

HRMS (ESI+) calculated for: [C₁₄H₁₆O₃+Na]⁺ 255.0992; found: 255.0997.

IR, v (cm⁻¹): C=O 1725, 1666.
Following the general procedure, the second step was over in 25h. The aldehyde 1t was purified by FC on silica (1:9 to 1:5 EtOAc/ Pentane). The aldehyde 1t was isolated in 75% yield (923 mg) as a yellow solid.

\( ^1H \) NMR (400 MHz, CDCl\(_3\)): \( \delta \) 9.72 (d, J = 7.8 Hz, 1H), 7.97 (d, J = 16.1 Hz, 1H), 7.59 (dd, J = 7.8, 1.7 Hz, 1H), 7.36 (ddd, J = 8.3, 7.4, 1.7 Hz, 1H), 7.06 – 7.00 (m, 1H), 6.84 (dd, J = 16.1, 7.8 Hz, 1H), 6.71 (dd, J = 8.4, 1.0 Hz, 1H), 5.01 (s, 2H), 1.27 (s, 9H).

\( ^{13}C \) NMR (100 MHz, CDCl\(_3\)): \( \delta \) 208.8, 194.8, 156.8, 147.9, 132.5, 129.4, 129.0, 123.8, 121.8, 112.3, 69.0, 43.3, 26.5 (3C).

HRMS (ESI+) calculated for: \([C_{15}H_{18}O_3]+Na]^+ \) 269.1148; found: 269.1154.

IR, \( \tilde{\nu} \) (cm\(^{-1}\)): C=O 1722, 1670.
3. The asymmetric synthesis of cyclopenta[b]benzofurans

3.1 Optimization

Table 1. Brønsted base catalyst screening.\(^a\)

![Chemical structures](attachment:image_url)

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>(t_1(^b)) (h)</th>
<th>(t_2(^b)) (h)</th>
<th>(d_{r1}(^c))</th>
<th>(d_{r2}(^c))</th>
<th>Yield (%)</th>
<th>ee(^d) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4a</td>
<td>24</td>
<td>24</td>
<td>10:1</td>
<td>20:1</td>
<td>54</td>
<td>92</td>
</tr>
<tr>
<td>4b</td>
<td>24</td>
<td>24</td>
<td>9:1</td>
<td>12:1</td>
<td>48</td>
<td>86</td>
</tr>
<tr>
<td>4c</td>
<td>24</td>
<td>24</td>
<td>10:1</td>
<td>19:1</td>
<td>54</td>
<td>-93</td>
</tr>
<tr>
<td>4d</td>
<td>24</td>
<td>24</td>
<td>7:1</td>
<td>16:1</td>
<td>53</td>
<td>-89</td>
</tr>
</tbody>
</table>

\(^a\) Reactions were performed on a 0.1 mmol scale. \(^b\) Determined by \(^1\)H NMR of the crude reaction mixture. \(^c\) Diastereomeric ratio was determined by \(^1\)H NMR analysis of the crude reaction mixture. \(^d\) Enantiomeric excess was determined by UPC\(^2\).
Table 2. Solvent screening:*

<table>
<thead>
<tr>
<th>Solvent</th>
<th>$t_1$(conversion)$^b$</th>
<th>$t_2$(conversion)$^b$</th>
<th>dr$^c$</th>
<th>dr$^c$</th>
<th>yield (%)</th>
<th>ee$^d$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhMe</td>
<td>48 h (100%)</td>
<td>&gt;8 d (61%)</td>
<td>10:1</td>
<td>12:1</td>
<td>28</td>
<td>93</td>
</tr>
<tr>
<td>PhCl</td>
<td>24 h (100%)</td>
<td>&gt;9 d (79%)</td>
<td>13:1</td>
<td>18:1</td>
<td>40</td>
<td>93</td>
</tr>
<tr>
<td>PhOMe</td>
<td>48 h (100%)</td>
<td>&gt;8 d (62%)</td>
<td>15:1</td>
<td>18:1</td>
<td>32</td>
<td>93</td>
</tr>
<tr>
<td>THF</td>
<td>&gt;24 h (13%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>MeCN</td>
<td>&gt;48 h (76%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CH$_2$Cl$_2$</td>
<td>48 h (100%)</td>
<td>1 d (100%)</td>
<td>12:1</td>
<td>&gt;20:1</td>
<td>56</td>
<td>91</td>
</tr>
<tr>
<td>ClCH$_2$CH$_2$Cl</td>
<td>48 h (100%)</td>
<td>1 d (100%)</td>
<td>7:1</td>
<td>&gt;20:1</td>
<td>61</td>
<td>91</td>
</tr>
</tbody>
</table>

*Reactions were performed on a 0.1 mmol scale. $^b$Determined by $^1$H NMR of the crude reaction mixture. $^c$Diastereomeric ratio was determined by $^1$H NMR analysis of the crude reaction mixture. $^d$Enantiomeric excess was determined by UPC$^2$.

Table 3. Concentration and temperature screening:*

<table>
<thead>
<tr>
<th>T [conc.]</th>
<th>$t_1$$^b$ (h)</th>
<th>$t_2$$^b$ (h)</th>
<th>dr$^c$</th>
<th>dr$^c$</th>
<th>yield (%)</th>
<th>ee$^d$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 °C 0.1M</td>
<td>96</td>
<td>24</td>
<td>12:1</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>0 °C 0.25M</td>
<td>72</td>
<td>&lt;12</td>
<td>11:1</td>
<td>15:1</td>
<td>60</td>
<td>93</td>
</tr>
<tr>
<td>0 °C 0.5M</td>
<td>36</td>
<td>&lt;12</td>
<td>10:1</td>
<td>16:1</td>
<td>51</td>
<td>91</td>
</tr>
<tr>
<td>rt 0.1M</td>
<td>&gt;48</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>rt 0.25M</td>
<td>32</td>
<td>&lt;12</td>
<td>13:1</td>
<td>19:1</td>
<td>62</td>
<td>93</td>
</tr>
<tr>
<td>rt 0.25M</td>
<td>32</td>
<td>&lt;12</td>
<td>10:1</td>
<td>19:1</td>
<td>55</td>
<td>-94$^e$</td>
</tr>
</tbody>
</table>

*Reactions were performed on a 0.25 mmol scale. $^b$Determined by $^1$H NMR of the crude reaction mixture. $^c$Diastereomeric ratio was determined by $^1$H NMR analysis of the crude reaction mixture. $^d$Enantiomeric excess was determined by UPC$^2$. $^e$Quinidide was used as a catalyst.
Table 4. Chiral NHC screening:

<table>
<thead>
<tr>
<th>NHC</th>
<th>t₁&lt;sup&gt;b&lt;/sup&gt; (h)</th>
<th>t₂&lt;sup&gt;b&lt;/sup&gt; (h)</th>
<th>dr&lt;sup&gt;c&lt;/sup&gt;</th>
<th>dr&lt;sup&gt;c&lt;/sup&gt;</th>
<th>yield (%)</th>
<th>ee&lt;sup&gt;c&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5b</td>
<td>20</td>
<td>16</td>
<td>7:1</td>
<td>5:1</td>
<td>44</td>
<td>95</td>
</tr>
<tr>
<td>5c</td>
<td>20</td>
<td>12</td>
<td>7:1</td>
<td>&gt;20:1</td>
<td>60</td>
<td>93</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were performed on a 0.25 mmol scale. <sup>b</sup> Determined by <sup>1</sup>H NMR of the crude reaction mixture. <sup>c</sup> Diastereomeric ratio was determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. <sup>d</sup> Enantiomeric excess was determined by UPC<sup>2</sup>.
3.2. General procedure for organocatalytic synthesis of 3a-p

The respective aldehyde 1 (1 eq, 0.25 mmol) and quinine 4a (0.1 eq, 0.025 mmol, 8.1 mg) were dissolved in dry CHCl₃ (1 mL). The reaction mixture was stirred at rt until full conversion. Afterwards, the NHC catalyst 5a (0.1 eq, 0.025 mol, 9.1 mg) was added in one portion and the reaction mixture was stirred at rt until full conversion. The crude reaction mixture was then loaded in silica gel and purified by FC.

3.3. Results and characterization

The product 3a was isolated by FC on silica (1:1:8 Et₂O/CH₂Cl₂/pentane) as a white solid, in 62% yield (41.3 mg), 19:1 dr and 93% ee; t₁: 28 h; t₂: 12 h.

^1H NMR (400 MHz, CDCl₃): δ 7.53 – 7.47 (m, 2H), 7.47 – 7.36 (m, 3H), 7.24 – 7.16 (m, 2H), 6.95 (t, J = 7.5, 1H), 6.90 (d, J = 8.0 Hz, 1H), 5.45 (d, d, J = 7.4 Hz, 1H), 4.15 (ddd, J = 11.1, 7.4, 3.6 Hz, 1H), 3.46 (s, 1H), 3.01 (dd, J = 18.7, 11.1 Hz, 1H), 2.26 (dd, J = 18.7, 3.6 Hz, 1H).

^13C NMR (100 MHz, CDCl₃): δ 213.4, 158.3, 158.7, 137.5, 130.9, 129.3 (3C), 129.2, 125.8 (2C), 124.7, 122.2, 110.4, 88.1, 82.2, 40.2, 38.6.

HRMS (ESI+) m/z calculated for: [C₁₇H₁₃O₃+Na]^+ 289.0835; found: 289.0839.

IR, ν (cm⁻¹): O-H 3471; C=O 1751.

The ee was determined by UPC² using a Chiralpak IB column [CO₂/iPrOH, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; t_major = 3.73 min, t_minor = 3.87 min (93% ee). [α]²⁰D = 53.6.2 (c = 0.25, CH₃Cl₂).

For ent-3a 55% yield (36.6 mg), 19:1 dr, t_major = 3.86 min, t_minor = 3.75 min (-94% ee).

The product 3b was isolated by FC on silica (1:1:8 Et₂O/CH₂Cl₂/pentane) as a white solid, in 58% yield (41.2 mg), 12:1 dr and 95% ee; t₁: 28 h; t₂: 16 h.

^1H NMR (400 MHz, CDCl₃): δ 7.50 – 7.36 (m, 5H), 6.94 – 6.84 (m, 2H), 6.80 (dd, J = 8.7, 4.2 Hz, 1H), 5.48 (d, J = 7.3 Hz, 1H), 4.10 (ddd, J = 11.2, 7.3, 3.7 Hz, 1H), 3.46 (s, 1H), 3.00 (dd, J = 18.8, 11.2 Hz, 1H), 2.24 (dd, J = 18.8, 3.7 Hz, 1H).

^13C NMR (100 MHz, CDCl₃): δ 212.9, 158.2 (d, J = 239.4 Hz), 154.7 (d, J = 1.7 Hz), 137.2, 132.2 (d, J = 8.6 Hz), 129.3 (3C), 125.76 (2C), 115.6 (d, J = 24.2 Hz), 111.7 (d, J = 25.0 Hz), 110.8 (d, J = 8.6 Hz), 88.8, 82.2, 39.9, 38.8 (d, J = 1.8 Hz).

^19F NMR (376 MHz, CDCl₃): δ -121.98.

HRMS (ESI+) m/z calculated for: [C₁₇H₁₃O₃F+Na]^+ 307.0741; found: 307.0739.

IR, ν (cm⁻¹): O-H 3471; C=O 1751.

The ee was determined by UPC² using a Chiralpak IC column [CO₂/iPrOH, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; t_major = 5.30 min, t_minor = 4.79 min (95% ee). [α]²⁰D = 54.0 (c = 0.2, CH₂Cl₂).

For ent-3b 65% yield (46.2 mg), 13:1 dr, t_major = 4.78 min, t_minor = 5.34 min (-95% ee).
The product 3c was isolated by FC on silica (1:1:8 Et2O/CH2Cl2/pentane) as a green oil, in 67% yield (50.4 mg), 14:1 dr and 95% ee; t1: 20 h; t2: 16 h.

1H NMR (400 MHz, CDCl3): δ 7.50 – 7.36 (m, 5H), 7.18 – 7.12 (m, 2H), 6.82 (d, J = 8.4 Hz, 1H), 5.48 (d, J = 7.3 Hz, 1H), 4.10 (ddd, J = 11.2, 7.3, 3.6 Hz, 1H), 3.42 (s, 1H), 3.01 (dd, J = 18.8, 11.2 Hz, 1H), 2.24 (dd, J = 18.8, 3.6 Hz, 1H).

The ee was determined by UPC IR, HRMS (ESI+) 1312.0, 88.7, 82.1, 39.9, 38.6.

For the other enantiomer: 52% yield, 89% ee.

IR, ν (cm⁻¹): O-H 3466; C=O 1750

The ee was determined by UPC IR, HRMS (ESI+) 111.5, 88.8, 82.1, 39.9, 38.6.

13C NMR (100 MHz, CDCl3): δ 212.7, 158.0, 137.2, 132.8, 129.4, 129.3 (2C), 129.2, 126.8, 125.8 (2C), 124.8, 111.5, 88.8, 82.1, 39.9, 38.6.

HRMS (ESI+) m/z calculated for: [C13H13O3Cl+Na]⁺ 323.0445; found: 323.0446.

The ee was determined by UPC² using a Chiralpak ID column [CO2/IPrOH, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; τmajor = 5.67 min, τminor = 5.49 min (95% ee). [α]²⁰ = 16.0 (c = 0.25, CH2Cl2).

For ent-3c 64% yield (48.1 mg), 12:1 dr, τmajor = 5.50 min, τminor = 6.64 min (-95% ee).

The product 3d was isolated by FC on silica (1:1:8 Et2O/CH2Cl2/pentane) as a white solid, in 66% yield (57.0 mg), 11:1 dr and 95% ee; t1: 20 h; t2: 22 h.

1H NMR (400 MHz, CDCl3): δ δ 7.42 – 7.30 (m, 5H), 7.26 – 7.18 (m, 2H), 6.70 (d, J = 8.4 Hz, 1H), 5.40 (d, J = 7.4 Hz, 1H), 4.03 (ddd, J = 11.1, 7.4, 3.6 Hz, 1H), 3.38 (s, 1H), 2.93 (dd, J = 18.8, 11.1 Hz, 1H), 2.17 (dd, J = 18.8, 3.6 Hz, 1H).

The ee was determined by UPC² using a Chiralpak ID column [CO2/IPrOH, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; τmajor = 7.59 min, τminor = 6.01 min (95% ee). [α]²⁰ = 54.2 (c = 0.25, CH2Cl2).

For ent-3d 53% yield (45.7 mg), 12:1 dr, τmajor = 5.99 min, τminor = 7.63 min (-96% ee).

The product 3e was isolated by FC on silica (EtOAc/pentane 1:10 to 1:4) as a white solid, in 45% yield (32.5 mg), 9:1 dr and 87% ee; t1: 7 h; t2: 20 h.

1H NMR (400 MHz, CDCl3): δ 7.54 – 7.39 (m, 7H), 6.95 (d, J = 8.3 Hz, 1H), 5.55 (d, J = 7.4 Hz, 1H), 4.17 (ddd, J = 11.1, 7.4, 3.6 Hz, 1H), 3.47 (s, 1H), 3.05 (dd, J = 18.8, 11.3 Hz, 1H), 2.22 (dd, J = 18.8, 3.6 Hz, 1H).

The ee was determined by UPC² using a Chiralpak IC-3 column [CO2/IPrOH, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; τmajor = 5.67 min, τminor = 6.31 min (87% ee). [α]²⁰ = -41.2 (c = 1.0, CH2Cl2).

For the other enantiomer: 52% yield, 89% ee.

For ent-3e 52% yield (37.9 mg), 8:1 dr, τmajor = 6.30 min, τminor = 5.67 min (-89% ee).
The product 3f was isolated by FC on silica (15:85 EtOAc/pentane) as a yellow oil, in 46% yield (34.1 mg), 12:1 dr and 95% ee. t1: 48 h; t2: 6 d.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.51 – 7.46 (m, 2H), 7.45 – 7.36 (m, 3H), 6.81 – 6.76 (m, 2H), 6.72 (dd, $\ J = 8.7, 2.7$ Hz, 1H), 5.43 (d, $\ J = 7.3$ Hz, 1H), 4.09 (ddd, $\ J = 11.2, 7.3, 3.6$ Hz, 1H), 3.76 (s, 3H), 3.49 (s, 1H), 2.99 (dd, $\ J = 18.8, 11.2$ Hz, 1H), 2.26 (ddd, $\ J = 18.8, 3.6$ Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 213.3, 155.2, 152.7, 137.5, 131.9, 129.2 (2C), 125.8 (2C), 114.0, 110.7, 110.4, 88.4, 82.2, 56.1, 40.0, 39.0.

HRMS (ESI+) m/z calculated for: [C$_{16}$H$_{14}$O$_4$+Na]$^+$ 319.0941; found: 319.0943.

IR, $\bar{\nu}$ (cm$^{-1}$): O-H 3447; C=O 1751.

The ee was determined by UPC$^2$ using a Chiralpak ID column [CO$_2$/iPrOH, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; $\tau_{\text{major}}$ = 7.49 min, $\tau_{\text{minor}}$ = 6.56 min (95% ee). $[\alpha]^{20}_D = 40.0$ (c = 0.2, CH$_2$Cl$_2$).

For ent-3f 40% yield (29.6 mg), 14:1 dr, $\tau_{\text{major}}$ = 6.42 min, $\tau_{\text{minor}}$ = 7.57 min (-96% ee).

The product 3g was isolated by FC on silica (15:85 EtOAc/pentane) as a yellow oil, in 53% yield (39.3 mg), 12:1 dr and 92% ee. t1: 48 h; t2: 24 h.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.51 – 7.46 (m, 4H), 7.46 – 7.31 (m, 6H), 7.08 (d, $\ J = 8.1$ Hz, 2H), 6.51 – 6.42 (m, 3H), 6.20 (dd, $\ J = 2.3$ Hz, 1H), 5.47 (d, $\ J = 7.4$ Hz, 1H), 5.14 (dd, $\ J = 8.0, 2.3$ Hz, 1H), 4.20 – 4.13 (m, 1H), 4.09 (ddd, $\ J = 10.9, 7.4, 3.4$ Hz, 1H), 3.77 (s, 3H), 3.70 (s, 3H), 3.47 (m, 2H), 3.32 (dd, $\ J = 19.2, 10.2$ Hz, 1H), 2.97 (dd, $\ J = 18.7, 10.9$ Hz, 1H), 2.50 (dd, $\ J = 19.2, 5.2$ Hz, 1H), 2.22 (dd, $\ J = 18.7, 3.4$ Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 213.5, 161.1, 160.0, 137.6, 129.3 (2C), 129.2, 125.7 (2C), 124.8, 122.8, 108.0, 96.8, 88.9, 82.07, 55.7, 40.4, 38.1.

HRMS (ESI+) m/z calculated for: [C$_{16}$H$_{14}$O$_4$+Na]$^+$ 319.0941; found: 319.0943.

IR, $\bar{\nu}$ (cm$^{-1}$): O-H 3475; C=O 1751.

The ee was determined by UPC$^2$ using a Chiralpak ID column [CO$_2$/iPrOH, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; $\tau_{\text{major}}$ = 6.70 min, $\tau_{\text{minor}}$ = 6.29 min (92% ee). $[\alpha]^{20}_D = 49.4$ (c = 0.3, CH$_2$Cl$_2$).

For ent-3g 49% yield (36.3 mg), 15:1 dr, $\tau_{\text{major}}$ = 6.25 min, $\tau_{\text{minor}}$ = 6.74 min (-94% ee).

The product 3h was isolated by FC on silica (15:85 EtOAc/pentane) as a yellow oil, in 57% yield (42.2 mg), 19:1 dr and 93% ee. t1: 48 h; t2: 24 h.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.52 – 7.47 (m, 4H), 7.46 – 7.34 (m, 6H), 6.91 (t, $\ J = 7.8$ Hz, 1H), 6.85 – 6.76 (m, 4H), 6.72 – 6.66 (m, 1H), 5.49 (d, $\ J = 7.5$ Hz, 1H), 5.20 (d, $\ J = 8.2$ Hz, 1H), 4.24 (ddd, $\ J = 10.3, 8.2, 4.8$ Hz, 1H), 4.16 (ddd, $\ J = 11.1, 7.5, 3.6$ Hz, 1H), 3.88 (s, 4H), 3.65 (s, 3H), 3.50 (s, 1H), 3.33 (dd, $\ J = 19.4, 10.3$ Hz, 1H), 2.99 (dd, $\ J = 18.7, 11.1$ Hz, 1H), 2.60 (ddd, $\ J = 19.4, 4.8$ Hz, 1H), 2.27 (dd, $\ J = 18.7, 3.6$ Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 213.3, 146.9, 144.9, 137.5, 132.1, 129.2 (2C), 129.1, 125.8 (2C), 123.1, 116.5, 112.1, 88.7, 82.1, 56.1, 40.1, 39.1.

HRMS (ESI+) m/z calculated for: [C$_{16}$H$_{14}$O$_4$+Na]$^+$ 319.0941; found: 319.0942.

IR, $\bar{\nu}$ (cm$^{-1}$): O-H 3484; C=O 1750.
The ee was determined by UPC² using a Chiralpak ID column [CO₂/iPrOH, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; t_major = 7.99 min, t_minor = 6.38 min (93% ee). [α]²⁰_D = 50.0 (c = 0.2, CH₂Cl₂).

For ent-3h 52% yield (38.5 mg), 9:1 dr, t_major = 6.36 min, t_minor = 8.11 min (-96% ee).

![3i](image)

The product 3i was isolated by FC on silica (1:1:8 Et₂O/CH₂Cl₂/pentane) as a white solid, in 48% yield (34.1 mg), 7:1 dr and 93% ee; t₁: 28 h; t₂: 16 h.

1H NMR (400 MHz, CDCl₃): δ 7.51 – 7.45 (m, 2H), 7.23 – 7.16 (m, 2H), 7.12 (t, J = 8.5 Hz, 2H), 6.95 (t, J = 7.4 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 5.41 (d, J = 7.4 Hz, 1H), 4.13 (ddd, J = 11.1, 7.4, 3.6 Hz, 1H), 3.53 – 3.43 (m, 1H), 2.98 (dd, J = 18.8, 11.1 Hz, 1H), 2.27 (dd, J = 18.8, 3.6 Hz, 1H).

13C NMR (100 MHz, CDCl₃): δ 213.0, 163.1 (d, J = 249.0 Hz), 158.6, 133.4 (d, J = 3.2 Hz), 130.8, 129.3, 127.8 (d, J = 8.4 Hz) (2C), 124.7, 122.3, 116.3 (d, J = 21.7 Hz) (2C), 110.4, 87.93, 81.6, 40.1, 38.5.

19F NMR (376 MHz, CDCl₃): δ -112.05

HRMS (ESI+) m/z calculated for: [C₁₇H₁₄O₃F+Na⁺] 307.0741; found: 307.0739.

IR, ν (cm⁻¹): O-H 3475; C=O 1751.

The ee was determined by UPC² using a Chiralpak ID column [CO₂/iPrOH, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; t_major = 5.14 min, t_minor = 4.63 min (93% ee). [α]²⁰_D = 52.0 (c = 0.2, CH₂Cl₂).

For ent-3i 42% yield (29.9 mg), 8:1 dr, t_major = 4.62 min, t_minor = 5.18 min (-98% ee).

![3j](image)

The product 3j was isolated by FC on silica (1:1:8 Et₂O/CH₂Cl₂/pentane) as a yellow oil, in 54% yield (40.6 mg), 12:1 dr and 93% ee; t₁: 18 h; t₂: 16 h.

1H NMR (400 MHz, CDCl₃): δ 7.46 – 7.38 (m, 4H), 7.24 – 7.16 (m, 2H), 6.96 (td, J = 7.5, 1.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 5.39 (d, J = 7.5 Hz, 1H), 4.15 (ddd, J = 11.1, 7.5, 3.6 Hz, 1H), 3.51 – 3.44 (m, 1H), 2.99 (dd, J = 18.8, 11.1 Hz, 1H), 2.29 (dd, J = 18.8, 3.6 Hz, 1H).

13C NMR (100 MHz, CDCl₃): δ 212.8, 158.6, 136.1, 135.3, 130.7, 129.4 (2C), 129.3, 127.2 (2C), 124.7, 122.3, 110.4, 87.8, 81.6, 40.1, 38.6.

HRMS (ESI+) m/z calculated for: [C₁₇H₁₃O₂Cl+Na⁺] 323.0445; found: 323.0445.

IR, ν (cm⁻¹): O-H 3491; C=O 1751.

The ee was determined by UPC² using a Chiralpak ID column [CO₂/iPrOH, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; t_major = 6.08 min, t_minor = 5.30 min (93% ee). [α]²⁰_D = 63.2 (c = 0.25, CH₂Cl₂).

For ent-3j 49% yield (36.8 mg), 8:1 dr, t_major = 6.15 min, t_minor = 5.30 min (-95% ee).

![3k](image)

The product 3k was isolated by FC on silica (1:1:8 Et₂O/CH₂Cl₂/pentane) as a white solid, in 48% yield (41.4 mg), 7:1 dr and 96% ee; t₁: 20 h; t₂: 22 h.

1H NMR (400 MHz, CDCl₃): δ 7.46 – 7.38 (m, 4H), 7.24 – 7.16 (m, 2H), 6.96 (td, J = 7.5, 1.0 Hz, 1H), 6.89 (d, J = 8.0 Hz, 1H), 5.39 (d, J = 7.5 Hz, 1H), 4.15 (ddd, J = 11.1, 7.5, 3.6 Hz, 1H), 3.51 – 3.44 (m, 1H), 2.99 (dd, J = 18.8, 11.1 Hz, 1H), 2.29 (dd, J = 18.8, 3.6 Hz, 1H).

13C NMR (100 MHz, CDCl₃): δ 212.8, 158.6, 136.1, 135.3, 130.7, 129.4 (2C), 129.3, 127.2 (2C), 124.7, 122.3, 110.4, 87.8, 81.6, 40.1, 38.6.

HRMS (ESI+) m/z calculated for: [C₁₇H₁₃O₃Br+Na⁺] 320.0445; found: 323.0445.

IR, ν (cm⁻¹): O-H 3502; C=O 1751.

The ee was determined by UPC² using a Chiralpak ID column [CO₂/iPrOH, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; t_major = 6.76 min, t_minor = 5.77 min (96% ee). [α]²⁰_D = 54.2 (c = 0.25, CH₂Cl₂).
For **ent-3k** 40% yield (34.5 mg), 7:1 dr, $\tau_{\text{major}} = 5.77$ min, $\tau_{\text{minor}} = 6.83$ min (-95% ee).

The product 3l was isolated by FC on silica (15:85 EtOAc/pentane) as a yellow oil, in 42% yield (31.1 mg), 11:1 dr and 94% ee; $t_1$: 72 h; $t_2$: 20 h.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.44 – 7.38 (m, 2H), 7.18 (ddd, $J = 9.0, 7.5, 1.7$ Hz, 2H), 6.91 (dd, $J = 25.3, 8.2$ Hz, 4H), 5.44 (d, $J = 7.3$ Hz, 1H), 4.08 (ddd, $J = 11.1, 7.3, 3.5$ Hz, 1H), 3.82 (s, 3H), 3.43 – 3.38 (m, 1H), 2.97 (ddd, $J = 18.7, 11.1$ Hz, 1H), 2.20 (dd, $J = 18.7, 3.5$ Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 213.5, 160.4, 158.7, 131.1, 129.3, 129.2, 127.3 (2C), 124.6, 122.1, 114.6 (2C), 110.4, 88.0, 81.9, 55.5, 40.0, 38.4.

HRMS (ESI+) m/z calculated for: [C$_{18}$H$_{16}$O$_4$+Na]$^+$ 319.0941; found: 319.0942.

IR, $\tilde{\nu}$ (cm$^{-1}$): O-H 3500; C=O 1750.

The ee was determined by UPC$^2$ using a Chiralpak ID column [CO$_2$/iPrOH, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; $\tau_{\text{major}} = 7.49$ min, $\tau_{\text{minor}} = 6.74$ min (94% ee). [a]$^{\text{D}}$ = 106.0 (c = 0.2, CH$_2$Cl$_2$).

For **ent-3l** 39% yield (28.9 mg), 15:1 dr, $\tau_{\text{major}} = 6.72$ min, $\tau_{\text{minor}} = 7.53$ min (-94% ee).

The product 3m was isolated by FC on silica (EtOAc/pentane 1:15 to 1:5) as a pale yellow oil, in 55% yield (40.7 mg), 15:1 dr and 95% ee; $t_1$: 48 h; $t_2$: 24 h.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.33 (t, $J = 8.0$ Hz, 1H), 7.23 – 7.15 (m, 2H), 7.09 (t, $J = 2.2$ Hz, 1H), 7.02 (ddd, $J = 7.8, 1.8, 0.9$ Hz, 1H), 6.97 – 6.85 (m, 3H), 5.41 (d, $J = 7.4$ Hz, 1H), 4.14 (ddd, $J = 11.1, 7.5, 3.6$ Hz, 1H), 3.82 (s, 3H), 3.53 (s, 1H), 3.02 (dd, $J = 18.7, 11.1$ Hz, 1H), 2.24 (dd, $J = 18.8, 3.5$ Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 213.2, 160.2, 158.6, 139.0, 130.9, 130.2, 129.2, 124.7, 122.1, 117.5, 114.6, 111.7, 110.3, 88.1, 82.0, 55.5, 40.1, 38.6.

HRMS (ESI+) m/z calculated for: [C$_{18}$H$_{16}$O$_4$+Na]$^+$ 319.0941; found: 319.0947.

IR, $\tilde{\nu}$ (cm$^{-1}$): O-H 3475; C=O 1750.

The ee was determined by UPC$^2$ using a Chiralpak IC column [CO$_2$/iPrOH, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; $\tau_{\text{major}} = 5.43$ min, $\tau_{\text{minor}} = 5.19$ min (95% ee). [a]$^{\text{D}}$ = +36.8 (c = 1.0, CH$_2$Cl$_2$).

For **ent-3m** 58% yield (43.0 mg), 15:1 dr, $\tau_{\text{major}} = 5.18$ min, $\tau_{\text{minor}} = 5.43$ min (-96% ee).

The product 3n was isolated by FC on silica (EtOAc/pentane 1:20 to 1:5) as a colorless oil, in 44% yield (32.2 mg), 8:1 dr and 94% ee; $t_1$: 7 d; $t_2$: 16 h.

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.69 (dd, $J = 7.6, 1.7$ Hz, 1H), 7.34 (td, $J = 7.8, 1.7$ Hz, 1H), 7.27 – 7.17 (m, 2H), 7.08 (td, $J = 7.5, 1.0$ Hz, 1H), 7.01 – 6.95 (m, 1H), 6.94 – 6.88 (m, 2H), 5.43 (d, $J = 9.3$ Hz, 1H), 4.27 (td, $J = 9.8, 5.8$ Hz, 1H), 3.81 (s, 3H), 3.56 (s, 1H), 3.11 (dd, $J = 19.1, 10.3$ Hz, 1H), 2.80 (dd, $J = 19.1, 5.8$ Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 213.0, 159.2, 154.8, 130.7, 130.2, 129.5, 129.0, 126.7, 124.9, 122.2, 121.4, 111.0, 110.1, 89.8, 77.6, 55.5, 42.3, 40.5.

HRMS (ESI+) m/z calculated for: [C$_{18}$H$_{16}$O$_4$+Na]$^+$ 319.0941; found: 319.0947.

IR, $\tilde{\nu}$ (cm$^{-1}$): O-H 3425; C=O 1731.

The ee was determined by UPC$^2$ using a Chiralpak ID-4 column [CO$_2$/iPrOH, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; $\tau_{\text{major}} = 5.57$ min, $\tau_{\text{minor}} = 6.44$ min (94% ee). [a]$^{\text{D}}$ = -46.8 (c = 1.0, CH$_2$Cl$_2$).

For **ent-3n** 40% yield (29.6 mg), 11:1 dr, $\tau_{\text{major}} = 6.40$ min, $\tau_{\text{minor}} = 5.59$ min (-95% ee).
The product 3o was isolated by FC on silica (EtOAc/pentane 1:20 to 1:5) as a yellow oil, in 51% yield (40.2 mg), 13:1 dr and 94% ee; \( t_1: 30 \text{ h}; t_2: 40 \text{ h} \).

\(^1\text{H NMR (400 MHz, CDCl}_3\): \( \delta \) 7.94 – 7.82 (m, 4H), 7.64 (dd, \( J = 8.6, 2.0 \text{ Hz}, 1\text{H} \)), 7.57 – 7.50 (m, 2H), 7.21 (ddd, \( J = 9.1, 7.5, 1.3 \text{ Hz}, 2\text{H} \)), 6.96 (td, \( J = 7.5, 1.0 \text{ Hz}, 1\text{H} \)), 6.91 (d, \( J = 8.0 \text{ Hz}, 1\text{H} \)), 5.57 (d, \( J = 7.4 \text{ Hz}, 1\text{H} \)), 4.19 (ddd, \( J = 11.1, 7.5, 3.6 \text{ Hz}, 1\text{H} \)), 3.64 (s, 1H), 3.04 (dd, \( J = 18.7, 11.1 \text{ Hz}, 1\text{H} \)), 2.29 (dd, \( J = 18.8, 3.6 \text{ Hz}, 1\text{H} \)).

The product 3p was isolated by FC on silica (1:1:8 EtOAc/pentane) as a yellow oil, in 53% yield (56.5 mg), 13:1 dr and 94% ee; \( t_1: 30 \text{ h}; t_2: 40 \text{ h} \).

\(^1\text{H NMR (400 MHz, CDCl}_3\): \( \delta \) 7.94 – 7.82 (m, 4H), 7.64 (dd, \( J = 8.6, 2.0 \text{ Hz}, 1\text{H} \)), 7.57 – 7.50 (m, 2H), 7.21 (ddd, \( J = 9.1, 7.5, 1.3 \text{ Hz}, 2\text{H} \)), 6.96 (td, \( J = 7.5, 1.0 \text{ Hz}, 1\text{H} \)), 6.91 (d, \( J = 8.0 \text{ Hz}, 1\text{H} \)), 5.57 (d, \( J = 7.4 \text{ Hz}, 1\text{H} \)), 4.19 (ddd, \( J = 11.1, 7.5, 3.6 \text{ Hz}, 1\text{H} \)), 3.64 (s, 1H), 3.04 (dd, \( J = 18.7, 11.1 \text{ Hz}, 1\text{H} \)), 2.29 (dd, \( J = 18.8, 3.6 \text{ Hz}, 1\text{H} \)).

\(^{13}\text{C NMR (100 MHz, CDCl}_3\): \( \delta \) 213.4, 158.7, 134.8, 133.4, 133.1, 130.9, 129.3, 129.2, 128.4, 127.8, 127.1, 126.8, 124.9, 124.7, 123.4, 122.2, 110.4, 88.0, 82.2, 40.2, 38.6.

HRMS (ESI+) m/z calculated for: \([\text{C}_2\text{H}_3\text{O}_3\text{Na}]^+\) 339.0992; found: 339.0996.

IR, \( \tilde{\nu} \) (cm\(^{-1}\)): O-H 3466; C=O 1749.

The ee was determined by UPC\(^2\) using a Chiralpak ID column [CO\(_2\)/iPrOH, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; \( \tau_{\text{major}} = 8.69 \text{ min, } \tau_{\text{minor}} = 7.27 \text{ min (94% ee)}. \)

For ent-3o 58% yield (45.9 mg), 14:1 dr, \( \tau_{\text{major}} = 7.26 \text{ min, } \tau_{\text{minor}} = 8.70 \text{ min (95% ee)}. \)

The product 3p was isolated by FC on silica (1:1:8 Et2O/CHCl\(_3\)/pentane) as a yellow oil, in 29% yield (19.7 mg), 6:1 dr and 89% ee; \( t_1: 18 \text{ h}; t_2: 14 \text{ h} \).

\(^{13}\text{C NMR (100 MHz, CDCl}_3\): \( \delta \) 211.7*, 211.2, 159.2*, 158.7, 140.6, 139.3*, 130.6*, 130.8, 129.3, 129.1*, 127.5, 127.3, 127.1*, 127.0*, 126.8*, 125.4, 124.6, 124.5*, 122.3, 121.7*, 110.4, 110.3*, 90.6*, 88.4, 80.4, 79.9*, 41.7*, 39.6, 39.0*, 38.4.

HRMS (ESI+) m/z calculated for: \([\text{C}_2\text{H}_3\text{O}_3\text{SNa}]^+\) 295.0399; found: 295.0399.

IR, \( \tilde{\nu} \) (cm\(^{-1}\)): O-H 3456; C=O 1749.

The ee was determined by UPC\(^2\) using a Chiralpak ID column [CO\(_2\)/iPrOH, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; \( \tau_{\text{major}} = 6.21 \text{ min, } \tau_{\text{minor}} = 6.04 \text{ min (89% ee)}. \)

For ent-3p 29% yield (19.7 mg), 6:1 dr, \( \tau_{\text{major}} = 6.02 \text{ min, } \tau_{\text{minor}} = 6.232 \text{ min (92% ee)}. \)

### 3.4 Procedure for the synthesis of 3a at 4.0 mmol scale

The respective aldehyde 1 (1 eq, 4 mmol, 1.06 g) and quinine 4a (0.1 eq, 0.4 mmol, 129.8 mg) were dissolved in dry CHCl\(_3\) (16 mL). The reaction mixture was stirred at rt for 28 h. Afterwards, the NHC catalyst 5a (0.1 eq, 0.4 mmol, 145.2 mg) was added in one portion and the reaction mixture was stirred at rt for 12 h. The crude reaction mixture was then loaded in silica gel and purified by FC. The product 3a was isolated as a white solid in 53% yield (565 mg), 11:1 dr and 93% ee.
4. Transformations

4.1 Reduction

Compound 3a (1.0 eq, 0.25 mmol, 66.6 mg) was dissolved in dry MeOH (2 mL), and the solution was cooled to -78 °C. NaBH₄ (2.5 eq, 0.625 mmol, 23.6 mg) was added and the reaction mixture was stirred at -78 °C for 40 min. The reaction was then quenched with NH₄Cl(aq), extracted with CH₂Cl₂, dried over Na₂SO₄, concentrated in vacuo and purified by FC over silica gel.

The product 6 was isolated by FC on silica (20:80 EtOAc/pentane) as a white foam, in 83% yield (55.4 mg), >20:1 dr and 94% ee.

¹H NMR (400 MHz, CDCl₃): δ 7.60 – 7.53 (m, 2H), 7.42 (dd, J = 8.5, 6.9 Hz, 2H), 7.37 – 7.29 (m, 1H), 7.24 – 7.12 (m, 2H), 6.94 (td, J = 7.4, 1.0 Hz, 1H), 6.86 (d, J = 8.0 Hz, 1H), 5.30 (d, J = 9.7 Hz, 1H), 4.27 (dd, J = 8.5, 6.2 Hz, 1H), 3.93 (td, J = 9.3, 7.3 Hz, 1H), 3.27 (s, 1H), 2.65 (ddd, J = 12.8, 9.0, 6.2 Hz, 1H), 2.29 (s, 1H), 2.03 (ddd, J = 12.8, 8.6, 7.3 Hz, 1H).

¹³C NMR (100 MHz, CDCl₃): δ 159.2, 142.5, 131.6, 128.7, 128.4, 127.8, 125.5, 124.5, 121.6, 109.7, 91.6, 81.2, 79.2, 42.1, 39.3.

HRMS (ESI+) m/z calculated for: [C₁₇H₁₆O₃+Na]+ 291.0992; found: 291.0996.

IR, ν (cm⁻¹): O–H 3470.

The ee was determined by UPC² using a Chiralpak ID-4 column [CO₂/iPrOH, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; τ_major = 5.26 min, τ_minor = 6.44 min (94% ee). [α]²⁰D = -88.2 (c = 1.0, CH₂Cl₂).

4.2 Allylation

Compound 3a (1.0 eq, 0.25 mmol, 66.6 mg) was dissolved in dry CH₂Cl₂ (2.5 mL), and allyltrimethylsilane (2.0 eq, 0.5 mmol, 79.5 µL) was added. The solution was cooled to -20 °C and BF₃·Et₂O (4 eq, 1.0 mmol, 123.4 µL) was added. The reaction mixture was stirred at -20 °C for 30 h. The reaction was then quenched with NaHCO₃(aq), extracted with CH₂Cl₂, concentrated in vacuo and purified by FC over silica gel.

The product 7 was isolated by FC on silica (5:95 to 17:83 Et₂O/pentane) as a yellow oil, in 54% yield (41.8 mg), >20:1 dr and 94% ee.

¹H NMR (400 MHz, CDCl₃): δ 7.57 – 7.50 (m, 2H), 7.46 – 7.39 (m, 2H), 7.38 – 7.32 (m, 1H), 7.22 (dt, J = 7.4, 1.2 Hz, 1H), 7.16 (td, J = 7.8, 1.4 Hz, 1H), 6.94 (td, J = 7.4, 1.0 Hz, 1H), 6.84 (d, J = 8.0 Hz, 1H), 5.79 (dddd, J = 16.8, 10.1, 8.0, 6.5 Hz, 1H), 5.42 (d, J = 9.2 Hz, 1H), 5.08 (ddt, J = 10.1, 2.0, 1.0 Hz, 1H), 4.99 (dq, J = 17.0, 1.5 Hz, 1H), 4.04 (td, J = 9.3, 4.0 Hz, 1H), 3.66 (s, 1H), 2.48 (dd, J = 13.7, 9.3 Hz, 1H), 2.38 (s, 1H), 2.11 (dd, J = 13.7, 4.0 Hz, 1H), 2.01 (ddt, J = 13.9, 6.5, 1.4 Hz, 1H), 1.65 (ddd, J = 14.0, 8.1, 1.1 Hz, 1H).
The ee was determined by UPC² using a Chiralpak ID column \([\text{CO}_2/\text{iPrOH, gradient, 120 bar, 40 °C}\]; flow rate 3.0 mL/min; τ_{major} = 4.26 min, τ_{minor} = 5.11 min (94% ee). \([\alpha]^{20}_{D} = +11.8 (c = 1.0, \text{CH}_2\text{Cl}_2)\).

4.3 Reductive amination

Compound 3a (1.0 eq, 0.25 mmol, 66.6 mg) was dissolved in CICH_2CH_2Cl (1.25 mL). p-Anisidine (1.2 eq, 0.3 mmol, 36.9 mg) and acetic acid (1.2 eq, 0.3 mmol, 17.2 µL) were added afterwards. The reaction was stirred at rt for 2 h. Afterwards, NaHB(OAc)_3 (2.0 eq, 0.5 mmol, 105 mg) was added and stirred at rt for 44 h. After full conversion, the reaction was quenched with NaHCO_3(aq), extracted with CH_2Cl_2, concentrated in vacuo and purified by FC over silica gel.

The product 8 was isolated by FC on silica (5:95 to 9:91 EtOAc/pentane) as a yellow oil, in 75% yield (70.0 mg), >20:1 dr and 95% ee.

1H NMR (400 MHz, CDCl_3): δ 7.55 – 7.44 (m, 4H), 7.44 – 7.38 (m, 1H), 7.28 – 7.21 (m, 2H), 7.01 (td, J = 7.4, 1.0 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 6.76 – 6.70 (m, 2H), 6.55 – 6.48 (m, 2H), 5.43 (d, J = 8.7 Hz, 1H), 4.13 (td, J = 8.8, 2.9 Hz, 1H), 3.91 (dd, J = 9.0, 6.0 Hz, 1H), 3.74 (s, 3H), 3.24 (s, 1H), 2.94 (s, 1H), 2.26 (ddd, J = 13.0, 6.0, 3.1 Hz, 1H), 2.07 (dt, J = 13.0, 9.0 Hz, 1H).

13C NMR (100 MHz, CDCl_3): δ 159.2, 152.3, 141.4, 139.4, 131.5, 128.6, 128.6, 128.2, 126.7, 126.4, 121.7, 115.3, 114.7, 109.6, 83.9, 62.4, 55.8, 42.7, 37.0.

HRMS (ESI+) m/z calculated for: [C_{24}H_{23}NO_3+Na]^+ 374.1751; found: 374.1767.

IR, v (cm⁻¹): O-H 3522.

The ee was determined by UPC² using a Chiralpak ID column \([\text{CO}_2/\text{iPrOH, gradient, 120 bar, 40 °C}\]; flow rate 3.0 mL/min; τ_{major} = 6.28 min, τ_{minor} = 6.89 min (95% ee). \([\alpha]^{20}_{D} = +31.1 (c = 2.0, \text{CH}_2\text{Cl}_2)\).

4.4 Barton’s vinyl iodide synthesis

Compound 3a (1.0 eq, 0.25 mmol, 66.6 mg) was dissolved in absolute EtOH (500 µL). Afterwards, hydrazine monohydrate (20 eq, 5 mmol, 243 µL) and Et₃N (15 eq, 3.75 mmol, 521 µL) were added. The reaction mixture was heated at 80 °C for 3 h. The crude reaction was then diluted with water (20 mL) and extracted with CH_2Cl_2 (3x10 mL), dried over with Na₂SO₄, filtered over cotton, concentrated in vacuo and used in the next step without further purification.
In a flame dried vial, the reaction crude was dissolved in dry THF (2 mL). Afterwards, Et₃N (3 eq, 0.75 mmol, 104 µL) was added in one portion. At rt, a solution of iodine (2.2 eq, 0.55 mmol, 140 mg) in dry THF (500 µL) was added dropwise. The reaction mixture was stirred at rt for 30 min. The reaction crude was diluted with Et₂O (30 mL), washed with 2x10 mL of Na₂SO₃(aq), 10 mL of NaHCO₃(aq), dried over MgSO₄, filtered over cotton, concentrated in vacuo and purified by FC over silica gel (2:98 to 5:95 Et₂O/pentane). The product 9 was obtained as a yellow oil, in 56% yield (52.7 mg) and 94% ee.

\[ \text{1H NMR (400 MHz, CDCl}_3\text{): } \delta 7.53 - 7.47 \text{ (m, 2H), 7.47} - 7.39 \text{ (m, 2H), 7.35} \text{ (td, } J = 7.1, 1.6 \text{ Hz, 1H), 7.29} - 7.18 \text{ (m, 2H), 6.96} \text{ (t, } J = 7.4 \text{ Hz, 1H), 6.90} \text{ (d, } J = 8.0 \text{ Hz, 1H), 6.37} \text{ (t, } J = 1.8 \text{ Hz, 1H), 5.02} \text{ (dd, } J = 7.0, 1.4 \text{ Hz, 1H), 4.41} \text{ (dd, } J = 6.9, 1.8 \text{ Hz, 1H), 3.61} \text{ (d, } J = 1.7 \text{ Hz, 1H).} \]

\[ \text{13C NMR (100 MHz, CDCl}_3\text{): } \delta 158.6, 141.4, 139.5, 129.2, 128.8 (2C), 128.1, 127.5, 125.3 (2C), 124.2, 122.0, 110.5, 108.8, 88.6, 88.5, 54.1. \]

HRMS (ESI+) m/z calculated for: [C₁₇H₁₃O₃I-6OH]⁺; 358.9927 found: 358.9928.

IR, \( \tilde{\nu} \text{ (cm}^{-1}\text{): O-H 3531; C-C 1595.} \)

The ee was determined by UPC² using a Chiralpak ID column [CO₂/iPrOH, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; \( \tau_{\text{major}} = 5.24 \text{ min, } \tau_{\text{minor}} = 4.42 \text{ min (94% ee).} \) [\( \alpha \)²⁰₀ = -153.6 (c = 0.25, CH₂Cl₂)].
5. Diastereodivergence

Aldehyde 1q (1 eq, 0.1 mol) and cinchonidine (0.1 eq, 0.01 mol, 2.9 mg) were dissolved in dry CHCl$_3$ (400 µL). The reaction mixture was stirred at rt until full conversion. Afterwards, the NHC catalyst 5b or 5c (0.1 eq, 0.01 mol, 4.7 mg) was added in one portion and the reaction mixture was stirred at rt until full conversion. The crude reaction mixture was then loaded in silica gel and purified by FC.

The product 3q was isolated by FC on silica (1:1:8 Et$_2$O/CH$_2$Cl$_2$/pentane) as a white solid, in 65% yield (55.6 mg), 6:1 dr and 92% ee. t$_1$: 16 h; t$_2$: 24 h. NHC catalyst 5c was used.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.38 – 7.33 (m, 2H), 7.29 – 7.26 (m, 2H), 7.22 – 7.08 (m, 8H), 6.92 (t, $J = 7.5$ Hz, 1H), 6.86 (d, $J = 7.9$ Hz, 1H), 4.50 (dd, $J = 11.4$, 4.2 Hz, 1H), 3.74 (s, 1H, 3.39 (dd, $J = 19.3$, 4.2 Hz, 1H), 3.41 (dd, $J = 19.3$, 4.2 Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 213.3, 157.0, 137.1, 136.6, 132.7, 129.2, 128.5, 128.4, 128.3 (2C), 128.1 (2C), 127.1 (2C), 126.5 (2C), 124.0, 122.2, 111.1, 97.9, 86.7, 42.5, 41.6.

HRMS (ESI+) m/z calculated for: [C$_{23}$H$_{18}$O$_3$+Na]$^+$ 365.1148; found: 365.1147.

IR, $\tilde{\nu}$ (cm$^{-1}$): O–H 3475; C=O 1745.

The ee was determined by UPC$^2$ using a Chiralpak ID column [CO$_2$/MecN, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; $\tau_{\text{major}} = 4.59$ min, $\tau_{\text{minor}} = 4.88$ min (92% ee). $[^{10}]\alpha_D = 77.0$ (c = 0.2, CH$_2$Cl$_2$).

The product epi-3q was isolated by FC on silica (1:1:8 Et$_2$O/CH$_2$Cl$_2$/pentane) as a white solid, in 63% yield (53.9 mg), 2:1 dr and 96% ee. t$_1$: 16 h; t$_2$: 48 h. NHC catalyst 5b was used.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.38 – 7.32 (m, 3H), 7.31 – 7.24 (m, 4H), 7.23 – 7.14 (m, 2H), 7.13 – 7.06 (m, 3H), 6.86 (t, $J = 7.5$, 1H), 6.78 (d, $J = 7.9$ Hz, 1H), 4.43 (dd, $J = 11.1$, 4.4 Hz, 1H), 3.63 (dd, $J = 19.1$, 11.1 Hz, 1H), 2.57 – 2.55 (m, 1H), 2.43 (dd, $J = 19.1$, 4.4 Hz, 1H).

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 211.4, 157.7, 136.5, 135.2, 132.2, 128.8, 128.7 (2C), 128.4 (2C), 127.9 (2C), 127.5 (2C), 127.4 (2C), 124.4, 121.9, 110.6, 98.4, 82.1, 45.0, 42.9.

HRMS (ESI+) m/z calculated for: [C$_{23}$H$_{18}$O$_3$+Na]$^+$ 365.1148; found: 365.1147.

IR, $\tilde{\nu}$ (cm$^{-1}$): O–H 3584; C=O 1751.

The ee was determined by UPC$^2$ using a Chiralpak ID column [CO$_2$/iPrOH, gradient, 120 bar, 40 °C]; flow rate 3.0 mL/min; $\tau_{\text{major}} = 4.05$ min, $\tau_{\text{minor}} = 3.92$ min (96% ee). $[^{10}]\alpha_D = -94.0$ (c = 0.2, CH$_2$Cl$_2$).
6. Attempts to react with alkyl substituted substrates

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<th>Solv.2</th>
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<td>CHCl₃</td>
<td>&gt;95%</td>
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<tr>
<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>10 (20)</td>
<td>-</td>
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<td>CHCl₃</td>
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<sup>a</sup>Reaction was performed at -20 °C. <sup>b</sup>Reaction was performed stepwise.
### Determination of the absolute configuration

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CCDC number 1545253.
8. NMR spectra
8. UPC² traces

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The image contains three chromatograms showing the retention times and areas for different compounds.

**rac-3d**

- Retention Time (min) | % Area
- 1: 5.967 | 50.35
- 2: 7.574 | 49.65

**3d**

- Retention Time (min) | % Area
- 1: 6.005 | 2.60
- 2: 7.585 | 97.40

**enf-3d**

- Retention Time (min) | % Area
- 1: 5.989 | 98.21
- 2: 7.627 | 1.79
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\[
\text{rac-7}
\]

\[
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2 & 5.104 & 47.31 \\
\hline
\end{array}
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\[
\text{7}
\]

\[
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\text{Retention Time (min)} & \% \text{ Area} \\
\hline
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2 & 5.106 & 2.85 \\
\hline
\end{array}
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10. IR Spectra

![IR Spectra of compound 1a](image1)

![IR Spectra of compound 1b](image2)