Supporting Information

Highly Enantioselective Synthesis of 3,4-Dihydropyran Derivatives via Michael Addition Reaction Catalysed by Chiral PYBOX-DIPH-Zn(II) Complex.

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General. All reactions were carried out under an atmosphere of nitrogen in oven dried glassware with magnetic stirring. $^1$H and $^{13}$C NMR spectra were recorded on Jeol (500 MHz) spectrometers in CDCl$_3$. Chemical shifts are reported in delta (δ) units, in parts per million (ppm). Tetramethylsilane and CDCl$_3$ were used as internal standard for $^1$H and $^{13}$C NMR respectively. Coupling constants were reported in Hz. Splitting patterns are designated as s for singlet; d for doublet; t for triplet; q for quartet; m for multiplet and bs for broad singlet. IR spectra were measured with Bruker FT/IR Vector 22 spectrometer. Mass spectrometric analysis was done on waters Q Tof Premier Micromass (ESI). Routine monitoring of reactions were performed using precoated silicagel TLC plates from E-Merck. All the chromatographic separations were carried out by using silica gel (Acme’s, 100–200 mesh). Enantiomeric excess was determined by HPLC analysis on Daicel chiral columns using iso-propanol and n-hexane as eluent at 25ºC.

Materials. Zinc (II) triflate was commercially available from Sigma-Aldrich and used without further purification. All cyclic 1,3- diketones (2a-2c) were commercially available. Ligands 1a – 1f were prepared according to our procedure.$^1$ 1g– 1i were commercially available. 1j was prepared according to procedures known in literature. 2-Enoylpyridine-N-oxides were prepared by earlier reported method.$^3$

General Procedure for enantioselective Michael reaction: A solution of a ligand 1a (7.3 mg, 0.012 mmol) and Zn(OTf)$_2$ (3.6 mg, 0.01 mmol) in dry dichloromethane (1 mL) was stirred at room temperature for 1 h under nitrogen atmosphere. Trans–2–enoylpyridine–N–oxide (0.20 mmol) was added and the whole mixture was stirred for additional 15 min at RT. The reaction mixture was cooled to -20 ºC and stirred for 10 min before the cyclic 1,3- diketone (0.24 mmol) was added and the reaction mixture was stirred at -20 ºC until the completion of the reaction (monitored by TLC). The mixture was concentrated in vacuo and purified over silica gel by column chromatography (methanol/ethyl acetate 1:20) to afford the product.

The Michael addition product was found to exist in rapid equilibrium with a pseudo–diastereomeric hemiketal form in solution. The equilibrium is very rapid and therefore no
Pseudo-diastereomers were observed during HPLC analysis using the mixture of hexane/2-propanol containing 0.1% TFA as the eluent. As the Michael addition product was found to exist in rapid equilibrium with a pseudo-diastereomeric hemiketal form in solution, it gave highly complicated and concentration dependant NMR spectra.

Characterization data for Michael products 4:

The compound 4aa was isolated as solid in 96% yield; mp 169-171 °C and 92% ee; [α]D25 = -11.3 (c 1.2, CHCl3). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralpack AD-H column, n-hexane/2-propanol (70:30) as eluent, flow rate = 1.0 mL/min. tR (major) = 10.70 min, tR (minor) = 18.97 min. 1H NMR (500 MHz; CDCl3): δ 1.09 (s, 3.0H), 1.16 (s, 2.5H), 1.21 (s, 0.5H), 2.15 - 2.27 (m, 3H), 2.36 – 2.50 (m, 2H), 2.64 – 2.68 (m, 0.8H), 2.81 – 2.84 (m, 0.2H), 4.05 – 4.09 (m, 1H), 7.12 – 7.25 (m, 5H), 7.29 – 7.32 (m, 1H), 7.31 – 7.40 (m, 0.8H), 7.43 (dd, J = 1.2, 7.6 Hz, 0.2H), 7.48 (dd, J = 1.9, 8.0 Hz, 0.8H), 7.51 (dd, J = 1.9, 8.0Hz, 0.2H), 8.20 (d, J = 6.4 Hz, 0.2H), 8.23 (d, J = 6.4 Hz, 0.8H), 8.73 (bs, 0.2H), 9.83 (bs, 0.8H). 13C NMR (125 MHz, CDCl3): δ 27.5, 28.1, 31.6, 32.2, 32.5, 34.2, 37.2, 40.7, 42.6, 42.7, 50.9, 51.0, 97.6, 98.1, 112.3, 114.3, 123.1, 123.6, 125.9, 126.0, 126.1, 126.2, 127.0, 127.6, 128.0, 128.3, 128.5, 128.6, 140.6, 140.7, 143.3, 144.5, 147.5, 147.8, 167.1, 167.5, 196.2, 197.0. IR (thin film): v = 3.84, 3.27, 2958, 2927, 2247, 1656, 1624, 1491, 1468, 1452, 1302 cm-1. HRMS (ES+): Exact mass calc for C22H24NO4 [M + H]+: 366.1705. Found: 366.1709.

The compound 4ba was isolated as semisolid in 95% yield and 97% ee; [α]D25 = + 19.5 (c 1.5, CHCl3). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OD-H column, n-hexane/2-propanol (70:30) (2-propanol contains 0.1 % TFA) as eluent, flow rate: 1.0 mL/min. tR (major) = 20.56 min, tR (minor) = 29.02 min. 1H NMR (500 MHz; CDCl3): δ 1.09 (s, 3.0H), 1.16 (s, 2.5H), 1.21 (s, 0.5H), 2.15 - 2.27 (m, 3H), 2.36 – 2.50 (m, 2H), 2.64 – 2.68 (m, 0.8H), 2.81 – 2.84 (m, 0.2H), 4.05 – 4.09 (m, 1H), 7.12 – 7.25 (m, 5H), 7.29 – 7.32 (m, 1H), 7.31 – 7.40 (m, 0.8H), 7.43 (dd, J = 1.2, 7.6 Hz, 0.2H), 7.48 (dd, J = 1.9, 8.0 Hz, 0.8H), 7.51 (dd, J = 1.9, 8.0Hz, 0.2H), 8.20 (d, J = 6.4 Hz, 0.2H), 8.23 (d, J = 6.4 Hz, 0.8H), 8.73 (bs, 0.2H), 9.83 (bs, 0.8H). 13C NMR (125 MHz, CDCl3): δ 27.5, 28.1, 31.6, 32.2, 32.5, 34.2, 37.2, 40.7, 42.6, 42.7, 50.9, 51.0, 97.6, 98.1, 112.3, 114.3, 123.1, 123.6, 125.9, 126.0, 126.1, 126.2, 127.0, 127.6, 128.0, 128.3, 128.5, 128.6, 140.6, 140.7, 143.3, 144.5, 147.5, 147.8, 167.1, 167.5, 196.2, 197.0. IR (thin film): v = 3.84, 3.27, 2958, 2927, 2247, 1656, 1624, 1491, 1468, 1452, 1302 cm-1. HRMS (ES+): Exact mass calc for C22H24NO4 [M + H]+: 366.1705. Found: 366.1709.
MHz; CDCl$_3$): $\delta$ 1.98 – 2.05 (m, 2H), 2.14 – 2.56 (m, 5H), 2.67 (dd, $J = 6.7$, 13.2 Hz, 0.8H), 2.82 – 2.85 (m, 0.2H), 4.08 – 4.12 (m, 1H), 7.13 – 7.25 (m, 5H), 7.30 – 7.34 (m, 1H), 7.40 (td, $J = 1$, 7.5 Hz, 0.8H), 7.44 (dd, $J = 1.5$ Hz, 8.0Hz, 0.2H), 7.49 (dd, $J = 2.0$, 8.0 Hz, 0.8H), 7.53 (dd, $J = 2.0$, 8.0 Hz, 0.2H), 8.22 (d, $J = 5.5$ Hz, 0.2H), 8.25 (d, $J = 6.5$ Hz, 0.8H), 8.76 (bs, 0.2H), 9.85 (bs, 0.8H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 20.3, 29.0, 29.2, 29.6, 34.1, 37.1, 40.7, 115.6, 123.7, 126.1, 126.9, 128.5, 129.1, 140.7, 144.3, 147.7. IR (thin film): $\nu$ = 3061, 2925, 1712, 1654, 1620, 1491, 1453, 1425, 1367, 1331 cm$^{-1}$. HRMS (ES+): Exact mass calc for C$_{20}$H$_{20}$NO$_4$ [M + H]$^+$: 338.1392. Found: 338.1397.

The compound 4ca was isolated as semi solid in 85% yield and 96% ee; $[\alpha]_D^{25} = +21.4$ (c 1.5, CHCl$_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OD-H column, n-hexane/2-propanol (70:30) (2-propanol contains 0.1 % TFA) as eluant, flow rate: 1.0 mL/min. $t_R$ (major) = 25.77 min, $t_R$ (minor) = 12.50 min. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 2.52 (s, 4H), 2.92 (m, 2H), 4.14 (m, 1H), 7.17 – 7.53 (m, 8H), 8.30 (d, $J = 6.3$Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 29.4, 33.7, 41.4, 114.1, 117.4, 117.4, 124.4, 126.7, 127.7, 128.6, 129.1, 140.7, 142.2, 147.0. IR (thin film): $\nu$ = 3058, 2924, 2853, 2633, 1693, 1602, 1491, 1430, 1386, 1292 cm$^{-1}$. HRMS (ES+): Exact mass calc for C$_{19}$H$_{18}$NO$_4$ [M + H]$^+$: 324.1236. Found: 324.1232.

The compound 4ab was isolated as solid in 93% yield; mp 147 - 149 °C and 77% ee; $[\alpha]_D^{25} = +13.4$ (c 1.1, CHCl$_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralpack AD-H column, n-hexane/2-propanol (80:20) (2-propanol contains 0.1 % TFA) as eluant, Flow rate: 1.0 mL/min. $t_R$ (major) = 13.16 min, $t_R$ (minor) = 18.59. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 1.10 (s, 3H), 1.17 (s, 2.46H), 1.21 (s, 0.54H), 2.18 – 2.61 (m, 5H), 2.67 (dd, $J = 6.4$, 13.1 Hz, 0.82H), 2.84 (dd, $J =$
3.1, 13.5Hz, 0.18H), 4.07 – 4.10 (m, 1H), 7.14 – 7.24 (m, 4H), 7.30 – 7.44 (m, 2H), 7.49 (dd, J = 1.5, 7.9 Hz, 0.82H), 7.52 (dd, J = 1.5, 7.6 Hz, 0.18H), 8.21 (d, J = 6.5 Hz, 0.18H), 8.24 (d, J = 6.5Hz, 0.82H), 8.77 (bs, 0.18H), 9.80 (bs, 0.82H). ^{13}C NMR (125 MHz, CDCl\textsubscript{3}): δ 27.5, 28.1, 31.6, 32.2, 32.5, 34.2, 37.2, 40.7, 42.6, 42.7, 50.9, 51.0, 97.6, 98.1, 112.2, 114.3, 123.6, 125.9, 126.0, 126.1, 127.0, 127.6, 128.0, 128.2, 128.4, 128.5, 140.6, 144.5, 147.5, 147.8, 167.1, 167.5, 196.2, 197.0. IR (thin film): v = 30.60, 2959, 1655, 1625, 1491, 1468, 1422, 1375, 1290 cm\textsuperscript{-1}. HRMS (ES+): Exact mass calc for C\textsubscript{22}H\textsubscript{23}ClNO\textsubscript{4} [M + H]\textsuperscript{+}: 400.1316. Found: 400.1315.

The compound \textit{4ac} was isolated as solid in 97% yield; mp 148-150 °C and 95% ee; [α]\textsubscript{D}\textsuperscript{25} = -31.0 (c 0.6, CHCl\textsubscript{3}). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralpak AD-H column, n-hexane/2-propanol (80:20) (2-propanol contains 0.1 % TFA) as eluent, flow rate: 1.0 mL/min. \textit{t}\textsubscript{R} (major) = 20.90 min, \textit{t}\textsubscript{R} (minor) = 32.06 min. ^{1}H NMR (500 MHz; CDCl\textsubscript{3}): δ 1.12 (s, 3H), 1.17 (s, 2.46H), 1.22(s, 0.54H), 2.14 -2.63 (m, 5H), 2.67 (dd, J = 6.5, 13.0 Hz, 0.82H), 2.82 (dd, J = 2.5, 13.8 Hz, 0.18 H), 4.04 – 4.11 (m, 1H), 7.08 – 7.51 (m, 7H), 8.23 (d, J = 5.8Hz, 0.18H), 8.26 (dd, J = 1.0, 6.5 Hz, 0.82H), 8.95 (bs, 0.18H), 9.77 (bs, 0.82H). ^{13}C NMR (125 MHz, CDCl\textsubscript{3}): δ 27.6, 28.0, 31.7, 32.0, 32.4, 34.0, 37.0, 40.4, 42.6, 50.8, 50.9, 97.5, 98.0, 112.7, 113.7, 123.1, 123.5, 125.5, 126.0, 126.1, 126.3, 127.0, 128.1, 128.5, 129.1, 129.8, 134.1, 140.6, 140.8, 145.4, 146.7, 147.4, 167.4, 196.2. IR (thin film): v = 3062, 2959, 2926, 1655, 1625, 1491, 1468, 1422, 1375, 1293 cm\textsuperscript{-1}. HRMS (ES+): Exact mass calc for C\textsubscript{22}H\textsubscript{23}ClNO\textsubscript{4} [M + H]\textsuperscript{+}: 400.1316. Found: 400.1318.

The compound \textit{4ad} was isolated as solid in 93% yield; mp 172-175 °C and 92% ee; [α]\textsubscript{D}\textsuperscript{25} = -27.7 (c 1.4, CHCl\textsubscript{3}). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralpak AD-H column, n-hexane/2-propanol (70:30) (2-
propanol contains 0.1 % TFA) as eluent, flow rate: 1.0 mL/min. \( t_R \) (major) = 9.64 min, \( t_R \) (minor) = 18.82 min. \(^1\)H NMR (500 MHz; CDCl\(_3\)): \( \delta \) 1.10 (s, 3H), 1.15 (s, 2.28 H), 1.21 (s, 0.72H), 2.11 – 2.67 (m, 5.76H), 2.81 (dd, \( J = 2.4, 13.4 \) Hz, 0.24H), 4.04 – 4.07 (m, 1H), 7.10 – 7.53 (m, 7H), 8.25 (d, \( J = 1.0 \)Hz, 0.24H), 8.26 (d, \( J = 1.0 \)Hz, 0.76H), 8.92 (bs, 0.24H), 9.79 (bs, 0.76H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 27.5, 28.0, 31.6, 32.0, 32.2, 33.7, 37.0, 40.6, 42.4, 42.7, 50.8, 51.0, 97.6, 98.0, 114.0, 123.3, 125.5, 125.9, 126.0, 128.1, 128.3, 128.4, 128.6, 129.2, 131.6, 140.7, 143.1, 147.4, 167.3, 167.6, 196.2, 196.9. IR (thin film): \( \nu = 3063, 2958, 1655, 1624, 1490, 1269, 1410, 1374, 1292 \) cm\(^{-1}\). HRMS (ES+): Exact mass calc for C\(_{22}\)H\(_{23}\)ClNO\(_4\) [M + H]\(^+\): 400.1316. Found: 400.1313.

The compound 4ae was isolated as solid in 90% yield; mp 156-159 °C and 95% ee; \([\alpha]_D^{25} = -48.7 (c 1.4, \text{CHCl}_3)\). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OD-H column, \( n \)-hexane/2-propanol (70:30) (2-propanol contains 0.1 % TFA) as eluent, Flow rate 1.0 mL/min. \( t_R \) (major) = 13.46 min, \( t_R \) (minor) = 18.53 min. \(^1\)H NMR (500 MHz; CDCl\(_3\)): \( \delta \) 1.11 (s, 3H), 1.18 (s, 2.25H), 1.25 (s, 0.75 H), 2.12 – 2.87 (m, 6H), 4.17 – 4.22 (m, 1H), 7.35 – 8.11 (m, 7H), 8.23 (d, \( J = 6.5\)Hz, 0.25 H), 8.27 (d, \( J = 6.5\)Hz, 0.75H), 9.19 (bs, 0.25H), 9.84 (bs, 0.75H). \(^{13}\)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 27.5, 28.0, 31.6, 32.2, 32.3, 34.2, 36.7, 40.3, 42.7, 50.8, 50.9, 97.5, 98.0, 111.1, 113.3, 121.1, 121.3, 121.5, 126.1, 126.2, 128.5, 128.6, 128.7, 129.3, 134.2, 134.3, 140.7, 146.9, 147.2, 148.5, 168.0, 168.5, 196.2. IR (thin film): \( \nu = 3085, 2958, 2926, 2854, 2248, 1712, 1654, 1625, 1527, 1468, 1423, 1376 \) cm\(^{-1}\). HRMS (ES+): Exact mass calc for C\(_{22}\)H\(_{23}\)N\(_2\)O\(_6\) [M + H]\(^+\): 411.1556. Found: 411.1559.

The compound 4af was isolated as solid in 92% yield; mp 152-154 °C and 94% ee; \([\alpha]_D^{25} = -94.2 (c 1.0, \text{CHCl}_3)\). The enantiomeric ratio was determined by chiral
HPLC using Daicel Chiralpak AD-H column, \( n \)-hexane/2-propanol (70:30) (2-propanol contains 0.1 % TFA) as eluent, flow rate: 1.0 mL/min, \( t_R \) (major) = 18.87 min, \( t_R \) (minor) = 46.31 min. \( ^1 \)H NMR (500 MHz; CDCl\(_3\)): \( \delta \) 1.11 (s, 3H), 1.16 (s, 2.22H), 1.23 (s, 0.78H), 2.11 – 2.88 (m, 6H), 4.15 – 4.21 (m, 1H), 7.30 – 7.55 (m, 5H), 8.11 – 8.13 (m, 2H), 8.23 (dd, \( J = 1.0, 6.5 \text{Hz}, 0.26 \)H), 8.27 (dd, \( J = 1.0, 6.5 \text{Hz}, 0.74 \)H), 9.13 (bs, 0.26H), 9.90 (bs, 0.74H). \( ^{13} \)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 27.5, 27.9, 31.7, 32.3, 34.5, 36.7, 40.2, 42.6, 42.7, 50.7, 50.9, 97.5, 97.9, 111.2, 113.4, 123.1, 123.3, 123.5, 123.9, 126.1, 126.2, 127.9, 128.5, 128.6, 128.7, 140.8, 146.3, 147.1, 151.5, 152.8, 168.0, 168.3, 196.1, 196.9. IR (thin film): \( \nu = 3077, 2927, 2959, 2870, 2247, 1654, 1625, 1515, 1489, 1468, 1420, 1303 \text{cm}^{-1} \). HRMS (ES+): Exact mass calc for C\(_{22}\)H\(_{23}\)N\(_2\)O\(_6\) [M + H]\(^+\): 411.1556. Found: 411.1556.

The compound 4ag was isolated as solid in 89% yield; mp 139-142 °C and 92% ee; \([\alpha]_D^{25} = + 2.9 \,(c \, 1.2, \text{ CHCl}_3)\). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralpak AD-H column, \( n \)-hexane/2-propanol (70:30) (2-propanol contains 0.1 % TFA) as eluent, flow rate: 1.0 mL/min. \( t_R \) (major) = 13.87 min, \( t_R \) (minor) = 23.15 min. \( ^1 \)H NMR (500 MHz; CDCl\(_3\)): \( \delta \) 1.09 (s, 3H), 1.15 (s, 2.46H), 1.20 (s, 0.54H), 2.20-2.60 (m, 5H), 2.64 (dd, \( J = 6.4, 13.1 \text{Hz}, 0.82 \)H), 2.78 (dd, \( J = 2.8, 13.5 \text{Hz}, 0.18 \)H), 3.74 (s, 3H), 4.04-4.08 (m, 1H), 6.77-6.80 (m, 3H), 7.20 – 7.36 (m, 2H), 7.39 (td, \( J = 1.0, 8.0 \text{Hz}, 0.82 \) H), 7.43 (dd, \( J = 1 \text{Hz}, 7.5 \text{Hz}, 0.18 \)H), 7.49 (dd, \( J = 2.0, 8.0 \text{Hz}, 0.82 \)H), 7.52 (dd, \( J = 2.0, 8.0 \text{Hz}, 0.18 \)H), 8.22 (d, \( J = 6.8 \text{Hz}, 0.18 \) H), 8.24 (dd, \( J = 0.6 \text{Hz}, 6.5 \text{Hz}, 0.82 \)H), 8.78 (bs, 0.18H), 9.78 (bs, 0.82H). \( ^{13} \)C NMR (125 MHz, CDCl\(_3\)): \( \delta \) 27.5, 28.1, 31.6, 31.8, 32.2, 33.3, 37.3, 40.7, 42.6, 42.7, 50.9, 51.0, 55.1, 55.2, 97.7, 98.1, 112.6, 113.5, 114.0, 114.5, 123.1, 123.6, 125.8, 125.9, 127.9, 128.2, 128.4, 128.6, 135.4, 136.4, 140.6, 140.8, 147.6, 157.6, 166.8, 167.3, 196.3, 197.0. IR (thin film): \( \nu = 2957, 2928, 1709, 1656, 1624, 1511, 1465, 1421, 1375 \text{cm}^{-1} \). HRMS (ES+): Exact mass calc for C\(_{23}\)H\(_{26}\)NO\(_5\) [M + H]\(^+\): 396.1811. Found: 396.1812.

The compound 4ah was isolated as solid in 95% yield; mp 164-166 °C and >99% ee; \([\alpha]_D^{25} = - 34.6 \,(c \, 1.5, \text{ CHCl}_3)\). The
The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OD-H column, n-hexane/2-propanol (70:30) (2-propanol contains 0.1 % TFA) as eluent, flow rate: 1.0 mL/min. $t_R$ (major) = 14.45 min, $t_R$ (minor) = 23.42 min. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 1.13 (s, 6H), 2.10 – 2.66 (m, 6H), 4.02 - 4.11 (m, 1H), 7.05 (d, $J$ = 7.9Hz, 2H), 7.33 – 7.53 (m, 6H), 8.24 (d, $J$ = 4.0Hz, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 31.7, 33.7, 40.4, 42.4, 50.8, 119.7, 124.1, 126.3, 129.0, 129.1, 134.4, 140.8, 142.2, 147.5. IR (thin film): $\nu$ = 2957, 2925, 1655, 1623, 1487, 1468, 1405, 1374 cm$^{-1}$. HRMS (ES+): Exact mass calc for C$_{22}$H$_{23}$BrNO$_4$ [M + H]$^+$: 444.0810. Found: 444.0816.

The compound 4ai was isolated as solid in 85% yield; mp 156-158 °C and 87% ee; $[\alpha]_D^{25}$ = + 80.0 (c 1.5, CHCl$_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OD-H column, n-hexane/2-propanol (70:30) (2-propanol contains 0.1 % TFA) as eluent, flow rate: 1.0 mL/min. $t_R$ (major) = 24.68 min. $t_R$ (minor) = 45.37 min. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 1.12 (s, 3H), 1.14 (s, 0.54H), 1.23 (s, 2.26H), 2.03-2.93 (m, 6H), 4.83-5.00 (m, 1H), 7.20-7.53 (m, 7H), 7.66 (d, $J$ = 7.9 Hz, 1H), 7.82 (d, $J$ = 7.9 Hz, 1H), 8.05 (d, $J$ = 8.6 Hz, 0.18H), 8.11 (d, $J$ = 6.4 Hz, 0.18H), 8.21 (d, $J$ = 6.1 Hz, 0.82H), 8.24 (d, $J$ = 8.3 Hz, 0.82 H), 8.74 (bs, 0.18H), 10.08 (bs, 0.82H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 27.9, 28.0, 28.3, 28.5, 31.7, 32.2, 36.2, 39.7, 42.8, 42.9, 50.9, 51.2, 97.8, 98.0, 112.4, 114.8, 122.9, 123.1, 123.2, 123.5, 124.9, 125.1, 125.4, 125.6, 125.8, 125.9, 126.0, 126.7, 126.9, 128.2, 128.5, 129.0, 129.4, 130.8, 131.3, 134.1, 134.3, 138.0, 140.6, 147.3, 148.0, 167.4, 167.8, 196.0, 196.8. IR (thin film): $\nu$ =3061, 3082, 3026, 2925, 2854, 2245, 1654, 1621, 1491, 1453, 1423, 1376, 1300 cm$^{-1}$. HRMS (ES+): Exact mass calc for C$_{26}$H$_{16}$NO$_4$ [M + H]$^+$:416.1862. Found: 416.1861.

The compound 4aj was isolated as semisolid in 92% yield and 98% ee; $[\alpha]_D^{25}$ = − 3.7 (c 1.3, CHCl$_3$). The enantiomeric ratio was determined by chiral HPLC
using Daicel Chiralcel OD-H column, \textit{n}-hexane/2 propanol (85:15) (2-propanol contains 0.1 \% TFA) as eluent, flow rate: 1.0 mL/min. $t_R$ (major) = 34.74 min, $t_R$ (minor) = 53.53. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 1.07 (s, 1.2H), 1.09 (s, 1.8H), 1.14 (s, 1.8H), 1.16 (s, 1.2H), 2.26–2.55 (m, 5H), 2.64 (dd, $J = 9.5$, 13.2 Hz, 0.6H), 3.11 (dd, $J = 1.9$, 13.5 Hz, 0.4H), 4.17-4.20 (m, 1H), 5.88 (d, $J = 3.4$ Hz, 0.4 H), 5.96 (d, $J = 3.1$ Hz, 0.6H), 6.17 (dd, $J = 2.0$Hz, 3.5Hz, 0.6H), 6.25 (dd, $J = 2.0$, 3.5 Hz, 0.4H), 7.10 (m, 0.6H), 7.26 - 7.56 (m, 3.4H), 8.24 (d, $J = 6.1$Hz, 0.6H), 8.26 (d, $J = 6.4$Hz, 0.4H), 8.99 (bs, 0.4H) 9.65 (bs, 0.6H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 26.1, 27.5, 28.1, 28.9, 31.8, 32.2, 32.9, 36.3, 42.6, 42.7, 50.8, 50.9, 97.6, 105.0, 105.3, 110.4, 110.5, 110.6, 112.1, 123.2, 123.6, 125.9, 126.0, 128.4, 128.5, 140.2, 140.5, 140.6, 140.8, 147.5, 147.6, 155.4, 155.7, 166.9, 167.4, 196.4, 197.0. IR (thin film): $\nu$ = 3116, 2958, 2926, 2854, 1691, 1627, 1467, 1429, 1374 cm$^{-1}$. HRMS (ES+): Exact mass calc for C$_{20}$H$_{20}$NO$_5$ [M + H]$^+$: 356.1498. Found: 356.1498

The compound \textbf{4ak} was isolated as semisolid in 90\% yield and 94\% ee; $[\alpha]_D^{25} = -109.9$ (c 0.8, CHCl$_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralpack AD-H column, \textit{n}-hexane/2-propanol (80:20) (2-propanol contains 0.1 \% TFA) as eluent, flow rate: 1.0 mL/min. $t_R$ (major) = 17.30 min, $t_R$ (minor) = 38.04 min. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 1.05 (s, 1.5H), 1.09 (s, 1.5H), 1.11 (s, 1.5H), 1.13 (s, 1.5H), 2.20 – 2.56 (m, 5.5H), 2.69 (dd, $J = 1.5$, 13.4Hz, 0.5H), 3.65 – 3.72 (m, 1H), 6.14 (dd, $J = 7.0$, 15.9 Hz, 0.5H), 6.35 (dd, $J = 1.1$, 16.0 Hz, 0.5H), 6.51 – 6.62 (m, 1H), 7.11 – 7.46 (m, 7H0), 7.49 (dd, $J = 1.9$, 8.3 Hz, 0.5H), 7.54 (dd, $J = 1.9$, 8.3 Hz, 0.5H), 8.24 (dd, $J = 0.6$, 6.5 Hz, 0.5H), 8.27 (dd, $J = 0.6$, 6.5Hz, 0.5H), 9.43,(bs, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 27.7, 27.8, 29.1, 29.2, 30.3, 30.7, 31.8, 32.2, 35.3, 36.9, 42.5, 51.1, 97.5, 97.9, 112.5, 113.8, 123.3, 123.7, 125.9, 126.0, 126.1, 126.4, 126.8, 127.0, 127.5, 128.3, 128.5, 128.6, 128.9, 129.4, 129.6, 130.3, 131.6, 132.2, 137.5, 137.8, 140.6, 140.8, 142.8, 144.7, 147.9, 148.2, 165.8, 166.4, 196.9, 197.2. IR (thin film): $\nu$ = 2957, 2924, 2851, 1619, 1428, 1378, 1259, 1231 cm$^{-1}$. HRMS (ES+): Exact mass calc for C$_{24}$H$_{26}$NO$_4$ [M + H]$^+$: 392.1862. Found: 392.1863.
The compound 4al was isolated as semisolid in 80% yield; $[\alpha]_D^{25} = + 21.4$ (c 1.6, CHCl$_3$). The enantiomeric excess was not determined as the compound was not completely separable by chiral columns available in our laboratory (Diacel chiralpak AD-H, AS-H, AD, IA-3, IB-3, IC-3; Chiralcel OD-H, OD, OJ-H, OA, OF). $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 1.05 (s, 1H), 1.08 (s, 1H), 1.12 (s, 1H), 1.13 (s, 1H), 1.23 – 2.26 (m, 3H), 2.15 – 2.48 (m, 5H), 2.72 (dd, $J = 6.0, 12.6$ Hz, 0.53H), 3.09 (d, $J = 13.5$ Hz, 0.47 H), 3.67 – 3.71 (m, 1H), 4.11 – 4.17 (m, 2H), 7.30 – 7.58 (m, 3H), 8.29 (t, $J = 5.2$Hz, 1H), 9.73 (bs, 0.47H), 9.79 (bs, 0.53H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 14.1, 14.2, 27.2, 28.6, 29.0, 29.4, 29.6, 31.7, 32.1, 32.4, 33.6, 33.9, 34.2, 42.2, 50.2, 50.5, 61.2, 97.1, 97.3, 109.3, 110.7, 114.1, 123.4, 123.6, 126.2, 126.3, 128.5, 128.7, 140.7, 140.8, 172.2, 174.5, 196.6, 197.0. IR (thin film): $\nu$ = 3084, 2959, 2927, 2871, 1729, 1632, 1466, 1430 cm$^{-1}$. HRMS (ES+): Exact mass calc for C$_{19}$H$_{24}$NO$_6$ [M + H]$^+$: 362.1604. Found: 362.1602.

The synthesis of hexahydroquinoline derivative:

To a solution of 4 (0.2 mmol) in MeOH (1 mL) was added ammonium acetate (10 mmol). The resulting mixture was refluxed for 2 h. Then, the mixture was concentrated in vacuo and purified over silica gel by column chromatography (methanol/ethyl acetate 1:20) to afford the product 5 $[\alpha]_D^{25} = + 162.5$ (c 1.0, CHCl$_3$). The enantiomeric ratio was determined by chiral HPLC using Daicel Chiralcel OD-H column, n-hexane/2 propanol (80:20) as eluent, flow rate: 1.0 mL/min. $t_R$ (major) = 32.45 min, $t_R$ (minor) = 18.87 min. $^1$H NMR (500 MHz; CDCl$_3$): $\delta$ 0.99 (s, 3H), 1.07 (s, 3H), 2.13 – 2.24 (m, 2H), 2.30 – 2.41 (m, 2H), 4.77 (d, $J = 5.5$Hz, 1H), 5.55 (d, $J = 5.8$Hz, 92% ee, 70% yield, 92% ee.
1H), 7.11 – 7.53 (m, 7H), 7.52 (dd, J = 1.9, 8.3 Hz, 1H), 8.18 (d, J = 6.5 Hz, 1H), 9.47 (s, 1H).

$^{13}$C NMR (125 MHz, CDCl$_3$): δ 27.4, 29.4, 32.5, 37.9, 41.8, 50.8, 107.0, 113.5, 125.1, 125.8, 126.4, 128.0, 128.2, 128.5, 130.4, 140.8, 143.3, 146.9, 151.0, 195.6. HRMS (ES+): Exact mass calc for C$_{22}$H$_{23}$N$_2$O$_2$ [M + H]$^+$: 347.1760. Found: 347.1768.

References:


X-ray crystal structure of 4ac and 4ah
Table 1. Crystallographic Data and Pertinent Refinement Parameters for 4e and 4j

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<tr>
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<th>4ac</th>
<th>4ah</th>
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<tr>
<td>Formula</td>
<td>C_{22}H_{22}ClNO_{4}</td>
<td>C_{22}H_{22}BrNO_{4}</td>
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<tr>
<td>MW /g.mol^{-1}</td>
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<td>Crystal system</td>
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<td>Space group</td>
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<td>P2\textsubscript{1}</td>
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<td>Unit cell dimensions (Å ,deg)</td>
<td>\begin{align*} a &amp;= 10.6173(7) \ b &amp;= 9.2220(6) \ c &amp;= 10.9711(7) \ \alpha &amp;= 90 \ \beta &amp;= 115.165(2) \ \gamma &amp;= 90 \end{align*}</td>
<td>\begin{align*} a &amp;= 10.1531(9) \ b &amp;= 9.1685(7) \ c &amp;= 11.3968(7) \ \alpha &amp;= 90 \ \beta &amp;= 110.669(2) \ \gamma &amp;= 90 \end{align*}</td>
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<td>\mu /mm\textsuperscript{-1}</td>
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<td>F(000)</td>
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<td>Crystal size (mm\textsuperscript{3})</td>
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<td>2.14 to 26.49</td>
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<td>\begin{align*} -12 \leq h \leq 12 \ -11 \leq k \leq 11 \ -13 \leq l \leq 14 \end{align*}</td>
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<td>Refinement method</td>
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<td>Full-matrix least-squares on F\textsuperscript{2}</td>
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<td>Data/restraints/params.</td>
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<td>4091 / 1 / 256</td>
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<td>Goodness-of-fit on F\textsuperscript{2}</td>
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<td>Final R indices [I &gt; 2s(I)]</td>
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<td>\begin{align*} R_1 &amp;= 0.0521 \ wR_2 &amp;= 0.0676 \end{align*}</td>
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<td>0.707 and -0.502</td>
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500 MHz $^1$H NMR spectra of compound 4aa in CDCl$_3$

125 MHz $^{13}$C NMR spectra of compound 4aa in CDCl$_3$
HPLC chromatogram of compound 4aa (racemic)

HPLC chromatogram of compound 4aa (Chiral)
500 MHz $^1$H NMR spectra of compound 4ba in CDCl$_3$

125 MHz $^{13}$C NMR spectra of compound 4ba in CDCl$_3$
HPLC chromatogram of compound 4ba (racemic)

HPLC chromatogram of compound 4ba (chiral)
500 MHz $^1$H NMR spectra of compound 4ca in CDCl$_3$

125 MHz $^{13}$C NMR spectra of compound 4ca in CDCl$_3$
HPLC chromatogram of compound 4ca (racemic)

HPLC chromatogram of compound 4ca (Chiral)
500 MHz $^1$H NMR spectra of compound 4ab in CDCl$_3$

125 MHz $^{13}$C NMR spectra of compound 4ab in CDCl$_3$
HPLC chromatogram of compound 4ab (racemic)

HPLC chromatogram of compound 4ab (chiral)
500 MHz $^1$H NMR spectra of compound 4ac in CDCl$_3$

125 MHz $^{13}$C NMR spectra of compound 4ac in CDCl$_3$
HPLC chromatogram of compound 4ac (racemic)

HPLC chromatogram of compound 4ac (chiral)
500 MHz $^1$H NMR spectra of compound 4ad in CDCl$_3$

125 MHz $^{13}$C NMR spectra of compound 4ad in CDCl$_3$
HPLC chromatogram of compound 4ad (racemic)

HPLC chromatogram of compound 4ad (chiral)
500 MHz $^1$H NMR spectra of compound 4ae in CDCl$_3$

125 MHz $^{13}$C NMR spectra of compound 4ae in CDCl$_3$
HPLC chromatogram of compound 4ae (racemic)

HPLC chromatogram of compound 4ae (chiral)
500 MHz $^1$H NMR spectra of compound 4af in CDCl$_3$

125 MHz $^{13}$C NMR spectra of compound 4af in CDCl$_3$
HPLC chromatogram of compound 4af (racemic)

HPLC chromatogram of compound 4af (chiral)
500 MHz $^1$H NMR spectra of compound 4ag in CDCl$_3$

125 MHz $^{13}$C NMR spectra of compound 4ag in CDCl$_3$
HPLC chromatogram of compound 4ag (racemic)

HPLC chromatogram of compound 4ag (chiral)
500 MHz $^1$H NMR spectra of compound 4ah in CDCl$_3$

125 MHz $^{13}$C NMR spectra of compound 4ah in CDCl$_3$
HPLC chromatogram of compound **4ah** (racemic)

HPLC chromatogram of compound **4ah** (chiral)
500 MHz $^1$H NMR spectra of compound 4ai in CDCl$_3$

125 MHz $^{13}$C NMR spectra of compound 4ai in CDCl$_3$
HPLC chromatogram of compound 4ai (racemic)

HPLC chromatogram of compound 4ai (chiral)
500 MHz $^1$H NMR spectra of compound 4aj in CDCl$_3$

125 MHz $^{13}$C NMR spectra of compound 4aj in CDCl$_3$
HPLC chromatogram of compound 4aj (racemic)

HPLC chromatogram of compound 4aj (chiral)
500 MHz $^1$H NMR spectra of compound 4ak in CDCl$_3$

125 MHz $^{13}$C NMR spectra of compound 4ak in CDCl$_3$
HPLC chromatogram of compound 4ak (racemic)

HPLC chromatogram of compound 4ak (chiral)

S39
500 MHz $^1$H NMR spectra of compound 4al in CDCl$_3$

125 MHz $^{13}$C NMR spectra of compound 4al in CDCl$_3$
500 MHz $^1$H NMR spectra of compound 5a in CDCl$_3$

125 MHz $^{13}$C NMR spectra of compound 5a in CDCl$_3$
HPLC chromatogram of compound 5a (racemic)

HPLC chromatogram of compound 5a (chiral)
Mass spectrum of compound 4aa

Mass spectrum of compound 4ba
Mass spectrum of compound 4ca

Mass spectrum of compound 4ab
Mass spectrum of compound 4ac

Mass spectrum of compound 4ad

S45
Mass spectrum of compound 4ae
Mass spectrum of compound 4af

Mass spectrum of compound 4ag

Mass spectrum of compound 4ah
Mass spectrum of compound 4ai
Mass spectrum of compound 4aj

Mass spectrum of compound 4ak

Mass spectrum of compound 4al
Mass spectrum of compound 5a