Supporting Information

Hydroxy-Directed Enantioselective Hydroxyalkylation in the Carbocyclic Ring of Indoles

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General Experimental Methods

Starting materials synthesis, catalysts synthesis, racemic and enantioselective reactions were performed in overnight oven-dried (120 °C) round bottom flasks. THF, dioxane and Et₂O were freshly distilled from Na/benzophenone ketyl under nitrogen. iPr₂O and EtOAc were dried and stored over 4 Å molecular sieves. CH₂Cl₂ and toluene were distilled from CaH₂ under nitrogen. Reactions were monitored by analytical TLC using Merck Silica Gel 60 F-254 thin layer plates. Flash column chromatography was performed on Merck silica gel 60, 0.040-0.063 mm, and visualized using both a UV lamp (254 nm) and then a CAM solution (an aqueous solution of ceric ammonium molybdate). Melting points were measured in capillary tubes, although products decomposed upon heating. NMR spectra were run at 300 MHz for ¹H and at 75 for ¹³C, respectively, using residual nondeuterated solvent as internal standard (CHCl₃: δ 7.26 for ¹H and 77.0 ppm for ¹³C; MeOD- $d^4 \delta$ 3.31 for ¹H and 49.0 ppm for ¹³C) and at 282 MHz for ¹⁹F NMR using CFCl₃ as internal standard. Chemical shifts are given in ppm. The carbon type was determined by DEPT experiments. High resolution mass spectra (ESI) were recorded on a Q-TOF spectrometer equipped with an electrospray source with a capillary voltage of 3.3 kV(ESI). Specific optical rotations were measured using sodium light (D line 589 nm) at 20°C in a 10 cm cell. Concentrations are given in g/100mL. Chiral HPLC analyses were performed in a chromatograph equipped with a UV diode-array detector using chiral stationary columns from Daicel.

Catalysts I is commercially available.

Catalyts **II** and **IV** were prepared from quinine following the methodology reported by Deng.¹ Catalyt **III** was prepared from quinine following the methodology reported by Deng.² Catalyt **V** was prepared from quinine following the methodology reported by Soós.³ Catalyt **VI** was prepared from quinine following the methodology reported by Du. $_4$

7-Hydroxyindole **1d** (purchased from Fluorochem) was purified by column chromatography prior to be used (hexanes:EtOAc).

Synthesis and characterization of compounds 3, 5 and 7

General procedure for the enantioselective Friedel-Crafts of hydroxydinoles 1 and isatins 2, 4 or 6

To a test tube containing hydroxyindole 1 (0.1 mmol), isatin 2, 4 or 6 (0.1 mmol) and catalyst VI (3.5 mg, 0.005 mmol, 5% mol), Et_2O (1.5 mL) was added and the resulting mixture was stirred at room temperature until completion (TLC). Then, the reaction mixture was directly poured into a column for chromatography, using hexanes:EtOAc as eluent to afford product 3, 5 or 7, respectively

General procedure for the racemic Friedel-Crafts reaction with ketones

A test tube was charged with hydroxyindole 1 (0.1 mmol), isatin 2, 4 or 6 (0.1 mmol) and a 1:1 mixure of catalyst **VI** and its pseudoenatiomer synthesized from quinidine (3.5 mg in total, 0.005 mmol, 5% mol). Then, Et₂O (1.5 mL) was added and the mixture was stirred at room temperature. Monitoring of the reaction and purification of the products were carried out as described above.

This procedure does not afford purely racemic compounds in some cases, but ¹H NMR spectra demonstrated compounds are identical to those obtained with the enantioselective methodology. Other racemic or non-chiral catalyst afforded complex mixtures due to lack of regioselectivity.

Procedure for the enantioselective Friedel-Crafts of hydroxydinoles **1a** and isatins **2a** at <u>1 mmol scale</u>

To a 50 ml round bottom flask containing hydroxyindole **1a** (133.2 mg, 1 mmol) and isatin **2a** (237.3, 1 mmol) and catalyst **VI** (35,2 mg, 0.05 mmol, 5% mol), Et₂O (15 mL) was added and the resulting mixture was stirred at room temperature for 7 hours (TLC). Then, the reaction mixture was directly poured into a column for chromatography, using hexanes:EtOAc (8:2 to 6:4) as eluent to afford product **3aa** (348 mg, 94% yield, 88% ee), as a white solid.

Analytitcal data for the products obtained by F-C reaction

(+)-(*R*)-1-Benzyl-3-hydroxy-3-(4-hydroxy-1*H*-indol-5-yl)-5-methylindolin-2-one (3aa)



Enantiomeric excess (90%) was determined by chiral HPLC (Chiralpak AD-H), hexanes-^{*i*}PrOH 70:30, 1.0 mL/min, major enantiomer $t_r = 21.8$ min, minor enantiomer $t_r = 19.8$ min.

White solid (33.7 mg, 91% yield), mp decomp. ; $[\alpha]_D^{20}$ + 47.8 (*c* 1.11, MeOH) (90% *ee*). ¹H NMR (300 MHz, MeOD) δ 7.49 – 7.13 (m, 8H), 7.09 (d, *J* = 3.2 Hz, 1H), 7.00 (dd, *J* = 8.0, 4.4 Hz,

2H), 6.88 (d, J = 8.6 Hz, 1H), 6.80 (d, J = 7.7 Hz, 1H), 6.53 (d, J = 3.2 Hz, 1H), 5.02 (d, J = 15.9 Hz, 1H), 4.92 (d, J = 15.9 Hz, 1H) ppm. ¹³C NMR (75.5 MHz, MeOD) δ 180.7 (C), 149.7 (C), 144.2 (C), 139.5 (C), 137.5 (C), 134.2 (C), 130.2 (CH), 129.7 (CH), 128.5 (CH), 128.4 (CH), 125.7 (CH), 124.4 (CH), 124.15 (CH), 121.5 (CH), 120.2 (C), 114.6 (C), 110.6 (CH), 104.0 (CH), 99.65 (CH), 79.55 (C), 44.7 (CH₂) ppm. HRMS (ESI) *m/z*: 369.1236 [M - H]⁻, C₂₃H₁₇N₂O₃ requires 369.1239.

(+)-(*R*)-1-Benzyl-3-hydroxy-3-(4-hydroxy-1*H*-indol-5-yl)-5-methoxyindolin-2-one (3ab)



Enantiomeric excess (86%) was determined by chiral HPLC (Chiralpak AD-H), hexanes-^{*i*}PrOH 80:20, 1.5 mL/min, major enantiomer $t_r = 54.3$ min, minor enantiomer $t_r = 63.4$ min.

Brown solid (31.5 mg, 79% yield), mp decomp.; $[\alpha]_D^{20}$ +1.72 (*c* 1.305, MeOH) (86% *ee*). ¹H NMR (300 MHz, MeOD) δ 7.40 (d, J = 7.2 Hz, 2H), 7.37 – 7.12 (m, 3H), 7.09 (d, J = 3.2 Hz,

1H), 6.97 (d, J = 8.5 Hz, 1H), 6.88 (dd, J = 8.5, 0.8 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 6.79 – 6.52 (m, 3H), 4.98 (d, J = 15.9 Hz, 1H), 4.87 (d, J = 14.7 Hz, 1H, *overlapped with* H_2O signal), 3.64 (s, 3H) ppm. ¹³C NMR (75.5 MHz, MeOD) δ 180.5 (C), 158.0 (C), 149.8 (C), 139.5 (C), 137.46 (C), 137.43 (C) 135.4 (C), 129.7 (CH) 128.5 (CH), 128.4 (CH), 124.4 (CH), 121.5 (CH), 120.3 (C), 114.8 (CH), 112.7 (CH), 111.2 (CH), 104.0 (CH), 99.7 (CH), 80.0 (C), 56.1, (CH3), 44.8 (CH₂) ppm. HRMS (ESI) *m*/*z*: 399.1343 [M - H]⁻, C₂₄H₁₉N₂O₄ requires 399.1345.

(+)-(*R*)-1-Benzyl-5-chloro-3-hydroxy-3-(4-hydroxy-1*H*-indol-5-yl)indolin-2-one (3ac)



Enantiomeric excess (87%) was determined by chiral HPLC (Chiralpak AD-H), hexanes-^{*i*}PrOH 70:30, 1.0 mL/min, major enantiomer $t_r = 15.9$ min, minor enantiomer $t_r = 22.4$ min.

Brown solid (40.5 mg, 97% yield), mp decomp.; $[\alpha]_D^{20}$ +33.1 (*c* 0.95, MeOH) (87% *ee*). ¹H NMR (300 MHz, MeOD) δ 7.50 –

3ac 7.41 (m, 2H), 7.40 – 7.13 (m, 5H), 7.12 – 7.07 (m, 2H), 6.96 (dd, J = 8.5, 0.8 Hz, 1H), 6.75 (d, J = 8.3 Hz, 1H), 6.56 – 6.50 (m, 1H), 5.03 (d, J = 16.0 Hz, 1H), 4.93 (d, J = 15.9 Hz, 1H) ppm. ¹³C NMR (75.5 MHz, MeOD) δ 180.4 (C), 148.9 (C), 143.1 (C), 139.7(C), 137.2 (C), 136.4 (C), 129.8 (CH), 129.75 (CH), 129.3 (C), 128.6 (CH), 128.4 (CH), 125.7 (CH), 124.5 (CH), 121.2 (CH), 120.2 (C), 114.75 (C), 111.7 (CH), 104.1 (CH), 99.5 (CH), 78.7 (C), 44.8 (CH₂) ppm. HRMS (ESI) *m/z*: 403.0842 [M - H]⁻, C₂₃H₁₆ClN₂O₃ requires 493.0849.

(+)-(*R*)-3-Hydroxy-3-(4-hydroxy-1*H*-indol-5-yl)indolin-2-one (5aa)



Enantiomeric excess (85%) was determined by chiral HPLC (Chiralpak AD-H), hexanes-^{*i*}PrOH 80:20, 1.5 mL/min, major enantiomer $t_r = 17.0$ min, minor enantiomer $t_r = 22.1$ min.

Brown solid (20.7 mg, 70% yield), mp decomp.; $[\alpha]p^{20} + 16.5$ (*c* 0.685, MeOH) (85% *ee*). ¹H NMR (300 MHz, MeOD) 7.29 - 7.17 (m, 2H), 7.08 (d, J = 3.2 Hz, 1H), 7.01 (td, J = 7.5, 1.0 Hz, 1H),

6.93 (dd, J = 7.6, 0.7 Hz, 1H), 6.85 – 6.77 (m, 2H), 6.52 (d, J = 3.2 Hz, 1H) ppm. ¹³C **NMR (75.5 MHz, MeOD)** δ 182.65 (C), 150.4 (C), 143.2 (C), 139.4(C), 134.7 (C), 130.4 (CH), 126.2 (CH), 124.4 (CH), 123.7 (CH), 121.6 (CH), 120.4 (C), 114.1 (C), 111.1 (CH), 103.9 (CH), 99.7 (CH), 80.5 (C) ppm. **HRMS (ESI)** m/z: 279.0776 [M - H]⁻, C₁₆H₁₁N₂O₃ requires 279.0770.

(+)-(*R*)-5-Bromo-3-hydroxy-3-(4-hydroxy-1*H*-indol-5-yl)indolin-2-one (5ab)



Enantiomeric excess (84%) was determined by chiral HPLC (Chiralpak AD-H), hexanes-^{*i*}PrOH 80:20, 1.0 mL/min, major enantiomer $t_r = 29.6$ min, minor enantiomer $t_r = 21.7$ min.

Brown solid (25.8 mg, 69% yield), mp decomp.; $[a]_{D^{20}} + 2.3$ (*c* 1.025, MeOH) (84% *ee*). ¹H NMR (300 MHz, MeOD) δ 7.37 (dd,

J = 8.2, 2.0 Hz, 1H), 7.25 (d, J = 1.8 Hz, 1H), 7.09 (d, J = 3.2 Hz, 1H), 7.02 (d, J = 8.5 Hz, 1H), 6.90 (d, J = 8.5 Hz, 1H), 6.85 (d, J = 8.3 Hz, 1H), 6.52 (d, J = 3.2 Hz, 1H) ppm. ¹³C NMR (75.5 MHz, MeOD) δ 182.1 (C), 149.5 (C), 142.55 (C), 139.6 (C), 137.2 (C), 133.0 (CH), 128.9 (CH), 124.5 (CH), 121.3 (CH), 120.2 (C), 115.8 (C), 114.3 (C), 112.7 (CH), 104.1 (CH), 99.6 (CH), 79.6 (C) ppm. HRMS (ESI) m/z: 356.9885/358.9865 [M - H]⁻, C₁₆H₁₀BrN₂O₃ requires 356.9875/358.9854.

(+)-(*R*)-6-Chloro-3-hydroxy-3-(4-hydroxy-1*H*-indol-5-yl)indolin-2-one (5ac)



Enantiomeric excess (78%) was determined by chiral HPLC (Chiralcel OD-H), hexanes-^{*i*}PrOH 80:20, 1.0 mL/min, major enantiomer $t_r = 28.3$ min, minor enantiomer $t_r = 20.5$ min.

Brown solid (16.4 mg, 50% yield), mp decomp.; $[\alpha]_D^{20}$ +3.7 (*c* 0.218, MeOH) (78% *ee*). ¹H NMR (300 MHz, MeOD) δ 7.14 – 7.05 (m, 2H), 7.03 – 6.92 (m, 3H), 6.88 (dd, *J* = 8.6, 0.8 Hz, 1H),

6.50 (dd, J = 3.2, 0.8 Hz, 1H) ppm. ¹³C NMR (75.5 MHz, MeOD) δ 182.5 (C), 149.6 (C), 144.8 (C), 139.5 (C), 135.7 (C), 133.6 (C), 127.1 (CH), 124.4 (CH), 123.3 (CH), 121.3 (CH), 120.2 (C), 114.4 (C), 111.3 (CH), 104.0 (CH), 99.6 (CH), 79.3 (C). ppm. HRMS (ESI) m/z: 313.0377 [M - H]⁻, C₁₆H₁₀ClN₂O₃ requires 313.0380.

(+)-(R)-3-Hydroxy-3-(4-hydroxy-1*H*-indol-5-yl)-1-methylindolin-2-one (7aa)



Enantiomeric excess (80%) was determined by chiral HPLC (Chiralpak AD-H), hexanes-^{*i*}PrOH 80:20, 1.5 mL/min, major enantiomer $t_r = 17.5$ min, minor enantiomer $t_r = 21.3$ min.

Brown solid (23.8 mg, 77% yield), mp decomp.; $[\alpha]_D^{20}$ +35.9 (*c* 1.09, MeOH) (80% *ee*). ¹H NMR (300 MHz, MeOD) δ 7.32 (ddd, J = 7.7, 1.3, 0.6 Hz, 1H), 7.26 – 7.15 (m, 1H), 7.10 – 6.97

(m, 3H), 6.94 (d, J = 8.6 Hz, 1H), 6.85 (dd, J = 8.6, 0.8 Hz, 1H), 6.50 (dd, J = 3.2, 0.8 Hz, 1H), 3.24 (s, 3H) ppm. ¹³C NMR (75.5 MHz, MeOD) δ 180.7 (C), 149.7 (C), 145.1 (C), 139.4 (C), 134.1 (C), 130.45 (CH), 125.6 (CH), 124.4 (CH), 124.1 (CH), 121.4 (CH), 120.2 (C), 114.6 (C), 109.6 (CH), 103.9 (CH), 99.6 (CH), 79.6 (C), 26.6 (CH3) ppm. HRMS (ESI) m/z: 293.0932 [M - H]⁻, C₁₇H₁₃N₂O₃ requires 293.0926.

(+)-(*R*)-1-Benzyl-3-hydroxy-3-(5-hydroxy-1*H*-indol-4-yl)indolin-2-one (3ba)



Enantiomeric excess (96%) was determined by chiral HPLC (Chiralpak AD-H), hexanes-^{*i*}PrOH 70:30, 1.0 mL/min, major enantiomer $t_r = 25.3$ min, minor enantiomer $t_r = 36.2$ min.

Brown oil (19.3 mg, 52% yield), $[\alpha]\mathbf{p}^{20}$ +118.6 (*c* 0.835, MeOH) (96% *ee*). ¹H NMR (300 MHz, CDCl₃) δ 7.52 – 7.42 (m, 2H), 7.39 – 7.12 (m, 6H), 7.09 – 6.78 (m, 3H), 6.67 (d, *J* = 8.5 Hz, 1H), 5.03 (d, *J* = 15.8

Hz, 1H), 4.95 (d, J = 15.5 Hz, 1H) ppm. ¹³C NMR (75.5 MHz, CDCl₃) δ 179.9 (C), 144.3 (C), 137.4 (C), 133.8 (C), 133.1 (C), 130.5 (CH), 129.7 (CH), 128.7 (CH), 128.6 (CH), 125.7 (CH), 125.9 (CH), 124.2 (CH), 113.5 (C), 112.85 (CH), 110.7 (CH), 102.2 (C), 44.8 (CH₂) ppm. HRMS (ESI) *m*/*z*: 369.1268 [M - H]⁻, C₂₃H₁₇N₂O₃ requires 369.1239.

(-)-(*R*)-1-Benzyl-5-chloro-3-hydroxy-3-(5-hydroxy-1*H*-indol-4-yl)indolin-2-one (3bb)



Enantiomeric excess (94%) was determined by chiral HPLC (Chiralpak AD-H), hexanes-^{*i*}PrOH 70:30, 1.0 mL/min, major enantiomer $t_r = 15.2$ min, minor enantiomer $t_r = 29.4$ min.

Brown oil (35.6 mg, 88% yield), $[\alpha]_D^{20}$ –117.5 (*c* 0.86, MeOH) (94% *ee*). ¹H NMR (300 MHz, CDCl₃) δ 8.79 (s, 1H), 8.21 (s, 1H),

3bb 7.38 (d, J = 1.9 Hz, 1H), 7.34 – 7.20 (m, 5H), 7.16 (dd, J = 8.3, 2.1 Hz, 1H), 7.07 (d, J = 8.7 Hz, 1H), 6.91 (s, 1H), 6.75 (d, J = 7.7 Hz, 1H), 6.67 (d, J = 8.3 Hz, 1H), 5.84 (s, 1H), 4.94 (d, J = 15.7 Hz, 1H), 4.86 (d, J = 15.8 Hz, 1H) ppm. ¹³C NMR (75.5 MHz, CDCl₃) δ 177.9 (C), 141.0 (C), 134.6 (C), 132.6 (C), 131.5 (C), 129.85 (CH), 129.0 (C), 128.8 (CH), 127.8 (CH), 127.4 (CH), 126.1 (CH), 124.9 (CH), 114.3 (C), 112.6 (CH), 110.8 (CH), 101.2 (C), 79.4 (C), 44.25 (CH2) ppm. HRMS (ESI) *m/z*: 403.0853 [M - H]⁻, C₂₃H₁₆ClN₂O₃ requires 403.0849.

(-)-(*R*)-1-Benzyl-6-chloro-3-hydroxy-3-(5-hydroxy-1*H*-indol-4-yl)indolin-2-one (3bc)



Enantiomeric excess (89%) was determined by chiral HPLC (Chiralpak IC), hexanes-^{*i*}PrOH 80:20, 1.0 mL/min, major enantiomer $t_r = 20.6$ min, minor enantiomer $t_r = 73.7$ min.

Yellow oil (23.5 mg, 58% yield), $[\alpha]_D^{20}$ –160.3 (*c* 0.44, MeOH) (89% *ee*). ¹H NMR (300 MHz, CDCl₃) δ 7.47 (d, *J* = 7.3 Hz, 2H), 7.42 – 7.24 (m, 3H), 7.24 – 7.01 (m, 3H), 6.92 (d, *J* = 7.8 Hz, 1H), 6.81 (s, 1H), 5.05 (d, *J* = 15.9 Hz, 1H), 4.93 (d, *J* = 15.8 Hz, 1H)

ppm. ¹³C NMR (**75.5** MHz, CDCl₃) δ 180.1 (C), 145.8 (C), 137.0 (C), 135.9 (C), 133.3 (C), 132.5 (C), 129.8 (CH), 128.7 (CH), 128.6 (CH), 126.8 (CH), 125.8 (CH), 123.7 (CH), 113.1 (CH), 112.8 (CH), 111.0 (CH), 102.3 (CH), 44.9 (CH₂) ppm. HRMS (ESI) *m/z*: 403.0861 [M - H]⁻, C₂₃H₁₆ClN₂O₃ requires 403.0849.

(+)-(*R*)-1-Benzyl-7-fluoro-3-hydroxy-3-(5-hydroxy-1*H*-indol-4-yl)indolin-2-one (3bd)



Enantiomeric excess (85%) was determined by chiral HPLC (Chiralpak IC), hexanes-^{*i*}PrOH 80:20, 1.5 mL/min, major enantiomer $t_r = 14.3$ min, minor enantiomer $t_r = 56.8$ min.

Grey oil (31.8 mg, 82% yield), $[\alpha]p^{20}$ +437.5 (*c* 0.25, MeOH) (85% *ee*). ¹H NMR (300 MHz, MeOD) δ 7.40 (d, *J* = 7.3 Hz, 2H), 7.31 – 7.12 (m, 4H), 7.11 – 6.75 (m, 4H), 6.64 (d, *J* = 8.5 Hz, 1H), 5.13 – 5.00 (m, 2H) ppm. ¹³C NMR (75.5 MHz, MeOD) δ 179.85 (C), 148.7 (d, *J* = 243.5 Hz, CF), 138.4 (C), 136.77 (d, *J* = 2.0 Hz, C), 133.2 (C), 130.61

(d, J = 8.5 Hz, C), 129.5 (CH), 128.3 (CH), 125.9 (CH), 125.0 (CH), 121.85 (CH), 118.22 (d, J = 21 Hz, CH), 112.9 (CH), 102.5 (C), 80.1 (C), 46.4 (d, J = 4.5 Hz, CH₂). ¹⁹F NMR (282 MHz, MeOD) δ -136.8 ppm; HRMS (ESI) m/z: 387.1147 [M - H]⁻, C₂₃H₁₆FN₂O₃ requires 387.1145.

(-)-(*R*)-3-Hydroxy-3-(5-hydroxy-1*H*-indol-4-yl)indolin-2-one (5ba)



Enantiomeric excess (90%) was determined by chiral HPLC (Chiralpak AD-H), hexanes-^{*i*}PrOH 80:20, 1.5 mL/min, major enantiomer $t_r = 20.5$ min, minor enantiomer $t_r = 32.8$ min.

Brown oil (21.9 mg, 78% yield), $[\alpha]_D^{20}$ –174.6 (*c* 0.13, MeOH) (90% *ee*). ¹H NMR (300 MHz, MeOD) δ 8.90-8.40 (m, 7H), 8.24 (d, *J* = 8.7 Hz, 1H), ppm. ¹³C NMR (75.5 MHz, MeOD) δ 143.2 (C), 139.6 (C),134.5 (C), 132.9 (CH), 130.7 (CH), 126.2 (CH), 125.7 (CH), 123.8

(CH), 113.8 (CH), 112.9 (CH), 111.2 (CH), 101.5 (C) ppm. **HRMS (ESI)** *m/z*: 279.0788 [M - H]⁻, C₁₆H₁₁N₂O₃ requires 279.0770.

(-)-(*R*)-1-Benzyl-3-hydroxy-3-(6-hydroxy-1*H*-indol-7-yl)indolin-2-one (3ca)



Enantiomeric excess (91%) was determined by chiral HPLC (Chiralpak IC), hexanes-^{*i*}PrOH 80:20, 1.0 mL/min, major enantiomer $t_r = 14.3$ min, minor enantiomer $t_r = 16.6$ min.

Brown oil (12.9 mg, 35% yield), $[\alpha]_D^{20}$ -175.4 (*c* 0.35, MeOH) (91% *ee*). ¹H NMR (300 MHz, CDCl₃) δ 7.51 (d, *J* = 7.3 Hz, 1H), 7.40 – 7.23 (m, 5H), 7.18 – 7.07 (m, 3H), 6.89 (td, *J* = 7.5, 0.9 Hz, 1H), 6.72 (d, *J* = 7.6 Hz, 1H), 6.51 (d, *J* = 8.4 Hz, 1H), 6.37 (d, *J* = 3.2 Hz, 1H),

5.10 (d, J = 16.0 Hz, 1H), 4.88 (d, J = 18.5 Hz, 1H, overlapped with the H₂O signal) ppm. ¹³C NMR (75.5 MHz, CDCl₃) δ 180.5 (C), 150.1 (C), 144.45 (C), 137.65 (C), 137.4 (C), 134.2 (C), 130.1 (CH), 129.7 (CH), 128.5 (CH), 128.4 (CH), 124.9 (CH), 124.7 (C), 124.0 (CH), 123.9 (CH), 121.1 (CH), 110.51 (CH), 110.47 (CH), 110.1 (C), 101.7 (CH), 79.4 (C)., 45.0 (CH2) ppm. HRMS (ESI) m/z: 369.1251 [M - H]⁻, C₂₃H₁₇N₂O₃ requires 369.1239.

(-)-(*R*)-1-Benzyl-3-hydroxy-3-(7-hydroxy-1*H*-indol-6-yl)indolin-2-one (3da)



Enantiomeric excess (86%) was determined by chiral HPLC (Chiralpak IC), hexanes-^{*i*}PrOH 80:20, 1.5 mL/min, major enantiomer $t_r = 18.9$ min, minor enantiomer $t_r = 23.5$ min.

Black oil (22.6 mg, 61% yield), $[\alpha] p^{20} - 1.3$ (*c* 0.23, MeOH) (86% *ee*). ¹H NMR (300 MHz, CDCl₃) δ 8.64 (s, 1H), 7.53 (dd, *J* =

7.3, 1.4 Hz, 1H), 7.36 – 7.12 (m, 7H), 7.03 (dd, J = 8.3, 0.6 Hz, 1H), 6.77 (d, J = 7.4 Hz, 1H), 6.48 (d, J = 8.3 Hz, 1H), 6.47-6.45 (m, 1H), 4.93 (d, J = 15.7 Hz, 1H), 4.80 (d, J = 15.7 Hz, 1H) ppm. ¹³C NMR (75.5 MHz, CDCl₃) δ 179.9 (C), 143.3 (C), 142.35 (C), 134.8 (C), 130.6 (C), 130.2 (CH), 129.6 (C), 128.9 (CH), 128.3 (C), 127.8 (CH), 127.1 (CH), 126.5 (CH), 125.45 (CH), 123.8 (CH), 119.2 (CH), 115.85 (C), 112.6 (CH), 110.2 (CH), 102.7 (CH), 80.3 (C), 44.1 (CH₂) ppm. HRMS (ESI) m/z: 369.1268 [M - H]⁻, C₂₃H₁₇N₂O₃ requires 369.1239.

(+)-(*R*)-1-Benzyl-3-hydroxy-3-(4-hydroxy-9*H*-carbazol-3-yl)indolin-2-one (3ea)



Enantiomeric excess (74%) was determined by chiral HPLC (Chiralpak IC), hexanes-^{*i*}PrOH 80:20, 1.0 mL/min, major enantiomer $t_r = 28.2$ min, minor enantiomer $t_r = 73.05$ min.

Brown oil, (23.1 mg, 55% yield), $[\alpha]_D^{20}$ +144.9 (*c* 0.275, MeOH) (74% *ee*). ¹H NMR (300 MHz, CDCl₃) δ 8.37 – 8.28 (m, 1H), 7.46 – 7.19 (m, 9H), 7.13 (dtd, *J* = 16.1, 7.3, 1.1 Hz, 2H), 6.85 (d, *J* = 7.9 Hz, 1H), 6.77 (d, *J* = 8.5 Hz, 1H), 6.62

(d, J = 8.5 Hz, 1H), 4.95 (d, J = 15.7 Hz, 1H), 4.88 (d, J = 15.5 Hz, 1H) ppm. ¹³C NMR (75.5 MHz, CDCl₃) δ 180.2 (C), 155.25 (C), 143.75 (C), 143.3 (C), 141.2 (C), 137.1 (C), 133.55 (C), 130.8 (CH), 129.8 (CH), 128.7 (CH), 128.4 (CH), 126.4 (CH), 125.8 (CH), 125.7 (CH), 124.6 (CH), 124.01 (CH), 123.96 (C), 119.9 (CH), 114.4 (C), 114.1 (C), 111.1 (CH), 111.05 (CH), 102.9 (CH), 81.4 (C), 44.5 (CH₂) ppm. HRMS (ESI) *m/z*: 419.1394 [M - H]⁻, C₂₇H₁₉N₂O₃ requires 419.1396.

(+)-Ethyl 3,3,3-trifluoro-2-hydroxy-2-(4-hydroxy-9*H*-carbazol-3-yl)propanoate (9e)



Enantiomeric excess (98%) was determined by chiral HPLC (Chiralpak AD-H), hexanes-^{*i*}PrOH 90:10, 1.5 mL/min, major enantiomer $t_r = 26.05$ min, minor enantiomer $t_r = 21.3$ min.

9e White oil, (24.7 mg, 70% yield), $[α]_D^{20}$ +167.2 (*c* 1.2, CHCl₃) (98% *ee*). ¹H NMR (300 MHz, CDCl₃) δ 9.48 (s, 1H), 8.38 (dd, *J* = 7.7, 0.7 Hz, 1H), 8.06 (s, 1H), 7.52 (dd, *J* = 8.7, 1.1 Hz, 1H), 7.46 – 7.35 (m, 2H), 7.33 – 7.21 (m, 1H), 6.93 (d, *J* = 8.7 Hz, 1H), 5.21 (s, 1H), 4.61 – 4.47 (m, 2H), 1.45 (t, *J* = 7.1 Hz, 3H). ppm. ¹³C NMR (75.5 MHz, CDCl₃) δ 168.6 (C), 154.6 (C), 141.6 (C), 138.9 (C), 125.3 (CH), 125.22 (q, *J* = 1.8 Hz, CH), 123.4 (CH), 123.1 (q, *J* = 286.0 Hz, CF₃), 122.9 (C), 120.2 (CH), 113.3 (C), 110.0 (CH), 104.1 (C), 102.3 (CH), 80.7 (q, *J* = 31.1 Hz, C), 65.05 (CH₂), 13.9 (CH₃). ¹⁹F NMR (282 MHz, CHCl₃) δ -77.5 ppm; HRMS (ESI) *m/z*: 352.0787 [M - H]⁻, C₁₇H₁₃F₃NO₄ requires 352.0797.

Procedure and characterization data for compound 10aa (+)-(S)-1-Benzyl-3-hydroxy-3-(1*H*-indol-5-yl)indolin-2-one



Compound **3aa** (37 mg, 0.1 mmol) and 4-dimethylaminopyridine (36.7 mg, 0.3 mmol, 3 eq) were placed in a 10 mL round bottomed flask. Then, the flask was purged with N₂ and CH₂Cl₂ (2 mL) was added. After 5 minutes, *N*-phenylbis(trifluoromethanesulfonimide (71.4 mg, 0.2 mmol, 2 eq) was added and the mixture was stirred at room temperature. The

reaction was monitored by thin layer chromatography eluting with CH_2Cl_2 . When the starting material was consumed, H_2O was added (5 mL) and the mixture was extracted with EtOAc (3 x 20 mL). The combined organic layers were washed with brine (30 mL) and dried under anhydrous Na₂SO₄.

The organic solvents were removed in vacuo and the residue was transfered to a 25 mL round bottomed flask, which was purged with N₂. Then, MeOH (3 mL) was added, followed by 10% Pd/C (6 mg, 10 wt %) and Et₂NH (13 μ L, mmol, 1.2 eq). Then, the reaction vessel was repeatedly purged with H₂ using a balloon and a needle as a vent. Finally, the reaction was stirred at room temperature under H₂ (1 atm, balloon). The reaction was monitored by thin layer chromatography eluting with CH₂Cl₂. When the reaction was completed, the suspension was passed through a pad of Celite® and the organic solvents were removed under vacuum. The residue was purified by column chromatography eluting with CH₂Cl₂ affording product **10aa** as an oil (27.5 mg, 78% yield).

Enantiomeric excess (85%) was determined by chiral HPLC (Chiralpak AD-H), hexanes-'PrOH 70:30, 1.5 mL/min, major enantiomer $t_r = 15.8$ min, minor enantiomer $t_r = 11.5$ min.

White oil, $[\alpha]_{D}^{20}$ +42.9 (*c* 0.215, MeOH) (85% *ee*); ¹H NMR (300 MHz, CDCl₃) δ 8.21 (s, 1H), 7.75 – 7.68 (m, 1H), 739 – 7.24 (m, 8H), 7.23 – 7.17 (m, 2H), 7.04 (td, *J* = 76, 1.0 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 6.52 (ddd, *J* = 3.1, 2.0, 0.9 Hz, 1H), 5.06 (d, *J* = 15.7 Hz, 1H), 4.87 (d, *J* = 15.7 Hz, 1H), 3.28 (s, 1H).; ¹³C NMR (75.5 MHz, CDCl₃) δ 178.1 (C), 142.6 (C), 135.64 (C), 135.58 (C), 132.1 (C), 131.6 (C), 129.5 (CH), 128.8 (CH), 127.8 (C), 127.7 (CH), 127.3 (CH), 125.1 (CH), 124.9 (CH), 123.4 (CH), 119.6 (CH), 117.8 (CH), 111.4 (CH), 109.6 (CH), 103.1 (CH), 78.3 (C), 44.0 (CH₂) ppm; HRMS (ESI) *m/z*: 353.1284 [M - H]⁻, C₂₃H₁₇N₂O₂ requires 353.1290.

X-ray Crystallography data of compound 3ac:



<u>X-ray data for compound **3ac**</u>: crystallized from DCM:Hexanes; C₂₃H₁₇ClN₂O₃; Mr=404.84; orthorhombic; space group= $P2_12_12_1$; *a*=8.8120(2), *b*=11.4950(4); *c*=19.1110(5) Å; V=1935.83(10) Å³; Z=4; $\rho_{calcd}=1.389$ Mg m⁻³; μ =0.225 mm⁻¹; F(000)=840. A colorless crystal of 0.04x0.06x0.08 mm³ was used; 4428 [R(int)=0.0682] independent reflections were collected on a Enraf Nonius CCD diffractomer by using graphite monochromator and Mo K α (λ = 0.71073 Å). The structures were solved by using direct methods with SHELXS-2014 and refined by using full matrix least squares on F^2 with SHELXL-2014. Non-hydrogen atoms were refined anisotropically, and hydrogen atoms were placed in calculated positions refined by using idealized geometries (riding model) and assigned fixed isotropic displacement parameters. Final R(ω R) values were R=0.0430 and ω R=0.0976. CCDC-1530502 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

References

- ¹ Li, H.; Wang, Y.; Tang, L.; Deng, L. J. Am. Chem. Soc. 2004, 126, 9906–9907.
- ² Li, H.; Wang, B.; Deng, L. J. Am. Chem. Soc. 2006, 128, 732-733.
- ³ Vakulya, B.; Varga, S.; Csámpai, A.; Soós, T. Org. Lett. 2005, 7, 1967–1969.
- ⁴ Yang, W.; Du, D.-M. Org. Lett. 2010, 12, 5450–5453.

NMR spectra







































































HPLC Traces









Retention Time	Area	Area Percent
54,32	402843402	93,062
63,37	30034908	6,938















1: 225 nm, 4 nm Results		
Retention Time	Area	Area Percent
17,50	164056528	90,024
21,26	18180641	9,976







Retention Time	Area	Area Percent
25,34	482278648	98,07
36,19	9443663	1,921







2: 300 nm, 4 nm Results		
Retention Time	Area	Area Percent
15,18	55695344	96,952
29,44	1750829	3,048







3: 245 nm, 4 nm Results		
Retention Time	Area	Area Percent
20,59	52767156	94,293
73,69	3193659	5,707







3: 260 nm, 4 nm Results		
Retention Time	Area	Area Percent
14,31	63258620	92,373
56,18	5223110	7,627









Retention Time	Area	Area Percent
18,87	491481038	93,214
23,50	35781599	6,786





Minutes

3: 245 nm, 4 nm Results		
Retention Time	Area	Area Percent
28,20	309404277	87,234
73,05	45279042	12,766







1: 243 nm, 4 nm Results		
Retention Time	Area	Area Percent
21,32	6531067	0,933
26,05	693261741	99,067

