Supporting Information

for

Bifunctional phase-transfer catalysis in the asymmetric synthesis of biologically active isoindolinones

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Complete experimental details and procedures, spectroscopic data, copies of ¹H NMR, ¹³C NMR and HPLC traces

Experimental part	S2
¹ H NMR copies, ¹³ C NMR copies	S 7
HPLC traces	S15

Experimental part

Materials and methods

All reactions were performed using commercially available compounds without further purification. Column chromatographic purification of products was carried out using silica gel 60 (70–230 mesh, Merck). The NMR spectra were recorded on Bruker DRX 400, 300, 250 spectrometers (400 MHz, 300 MHz, 250 MHz, ¹H; 100 MHz, 75 MHz, 62.5 MHz ¹³C). Spectra were referenced to residual CHCl₃ (7.26 ppm, ¹H, 77.23 ppm, ¹³C) or other not deuterated residual solvents. Coupling constants *J* are reported in Hz. Yields are given for isolated products showing one spot on a TLC plate and no impurities detectable in the NMR spectrum. HPLC analyses were performed using a Waters instrument on a chiral column. Mass spectral analyses were carried out using an Waters 4 micro quadrupole electrospray spectrometer. Elemental analyses for CHNS-O were performed with a FLASHEA 1112 series-Thermo Scientific apparatus.

Catalyst 8a. Obtained as a colourless oil using the strategy described recently.¹ $[\alpha]_D^{21} = +58$ (c = 1.00, CHCl₃). ¹H NMR (300 MHz, δ , CDCl₃, 298 K): 1.32-1.46 (m, 1H), 1.52-2.10 (m, 5H), 2.15-2.28 (m, 1H), 2.55-2.67 (m, 1H), 3.15 (s, 3H), 3.25 (s, 3H), 4.31-4.48 (m, 1H), 4.62-4.75 (m, 1H), 5.30 (d, 1H, *J* = 13.0 Hz), 5.38 (d, 1H, *J* = 13.0 Hz), 7.55 (d, 1H, *J* = 9.6 Hz), 7.75 (d, 2H, *J* = 9.2 Hz), 7.98 (s, 1H), 8.01 (s, 2H), 8.16 (d, 2H, *J* = 9.2 Hz), 9.21 (s, 1H) ppm. ¹³C NMR (75 MHz, δ , CDCl₃, 298 K): 24.6, 25.0, 27.3, 35.9, 48.6, 50.6, 50.8, 65.4, 78.2, 117.8, 117.8, 122.5 (q, *J* = 275 Hz), 125.2, 130.0, 133.2, 133.3 (q, *J* = 34 Hz), 142.6, 145.3, 154.8 ppm. ¹⁹F NMR (282 MHz, δ , CDCl₃, 298 K): -63.0 ppm. IR (film): $\overline{\nu}$ = 3265, 3206, 3150, 3083, 3053, 2940, 2864, 2324, 1696, 1613, 1599, 1553, 1505, 1373, 1329, 1279, 1175, 1134, 1109, 921, 850, 752, 710, 682, 495, 411 cm⁻¹. HRMS (ESI): *m*/*z* calcd for C₂₄H₂₇F₆N₄O₃⁺: 533.1982 [M⁺]; found: 533.1993

(*S*)-Dimethyl 2-(1-oxoisoindolin-3-yl)malonate (7). A mixture of 2-cyanobenzaldehyde 5 (262 mg, 2 mmol), K₂CO₃ (276 mg, 2 mmol) and (*R*,*R*)-catalyst 8a (27 mg, 0.05 mmol, 2.5 mol %) was dissolved in dichloromethane (30 mL, 0.066 M) and cooled to -10 °C with stirring. Within a period of 2 minutes dimethyl malonate 6 (245 \Box L, 2.4 mmol, 1.2 equiv) was added. After 10 h (reaction monitored by TLC) the reaction mixture was filtrated through a plug of Na₂SO₄. The solvent was removed under reduced pressure. The crude product was purified by column chromatography (silica gel, heptanes/ethyl acetate 1:1) giving the product obtained as a colourless oil in 98% yield (520 mg, 1.96 mmol) and ee 78%. Chiralcel AD-H, *n*-hexane/iPrOH 70:30, 1.0 mL/min, 10 °C, 12.3 min

(minor; *R*-enantiomer), 25.5 min (major; *S*-enantiomer). The product was dissolved in a mixture of dichloromethane (6 mL) and heptanes (4 mL) and after crystallization overnight at -20 °C. The solid was filtered off and the solution containing the enantioriched compound was evaporated and analyzed by chiral HPLC afforded enantio-enriched product as a colourless oil in 77% overall yield (400 mg, 1.51 mmol, ee 95%). Spectroscopic data are in agreement with those reported in literature.² Chiralpack AD column, hexane/iPrOH 8:2, 0.8 mL/min, $\lambda = 254$ nm, t = 19.4 min, t = 29.3 min.

(*S*)-2-(1-Oxoisoindolin-3-yl)malonic acid (10). To a solution of isoindolinone 7 (40 mg, 0.15 mmol) in a mixture of dichloromethane/methanol 9:1 (1 mL) was added NaOH 2 M (500 μ L) in methanol and stirred overnight. The solvent was removed and ethyl acetate added. The aqueous layer was acidified till pH 2 and extracted four times with diethyl ether. The combined organic layers were dried (MgSO₄), and the solvent was evaporated to give the pure compound. White solid (35 mg, 0.149 mmol, 99%). M.p. 176-177 °C (from Et₂O). ESI (m/z): 234.2 (M-H)⁻. [α]_D²²= - 6.3 (c 0.1 M in methanol). Anal. calcd for C₁₁H₉NO₅. Calcd: C, 56.17; H, 3.86; N, 5.96. Found: C, 56.35; H, 4.04; N, 6.02. ¹HNMR (300 MHz, D₂O) δ 7.72 (d, 1H, *J* = 6.87 Hz), 7.63-7.59 (m, 1H), 7.54-7.49 (m, 2H) 5.21 (d, 1H, *J* = 8.55 Hz) 3.68 (d, 1H, *J* = 8.55 Hz). ¹³CNMR (100 MHz, DMSO-d₆) δ 169.7, 169.2, 168.8, 145.8, 133.0, 131.5, 128.7, 124.0, 123.1, 55.8, 55.1. Enantiomeric excesses were determined by derivatization of the compound into methyl ester **12**.

(*S*)-2-(1-Oxoisoindolin-3-yl)acetic acid (9) from 7. A flask containing a solution of isoindolinone 7 (320 mg, 1.20 mmol) and HCl 6 M (2 mL) was immersed in an oil bath preheated to 150 °C and the solution was refluxed for 30 minutes. The mixture was extracted with ethyl acetate (3 × 15 mL). The combined organic layers were dried (MgSO₄), and the solvent was evaporated to give compounds 9 which were purified on silica gel using ethyl acetate. White solid (208 mg, 1.09 mmol, 90%). M.p 170-171 °C (from ethyl acetate). ESI (m/z): 190.2 (M-H)⁻. $[\alpha]_D^{22}$ = -21 (c 1.0 in methanol). Anal. calcd for C₁₀H₉NO₃. Calcd: C, 62.82; H, 4.74; N, 7.33. Found: C, 62.72; H, 4.78; N, 7.01. ¹HNMR (300 MHz, CD₃OD) 7.76 (d, 1H, *J* = 7. 5 Hz), 7.65-7.53 (m, 2H), 7.51-7.48 (m, 1H), 5.09-4.99 (m, 1H), 2.97-2.89 (m, 1H), 2.68-2.48 (m, 1H).¹³CNMR (100 MHz, CD₃OD) δ 172.6, 171.2, 146.8, 131.9, 131.3, 128.1, 122.9, 122.6, 53.4, 38.3. Enantiomeric excesses were determined by derivatization of the compound into methyl ester **12** or amide **16**.

(*S*)-2-(1-Oxoisoindolin-3-yl)acetic acid (9) from 10. A flask containing a solution of malonic acid 10 (30 mg, 0.12 mmol) and HCl 6 M (0.5 mL) was immersed in an oil bath preheated to 150 °C and the solution was refluxed for 15 minutes. The mixture was extracted with ethyl acetate (3×15 mL). The combined organic layers were dried (MgSO₄), and the solvent was evaporated to give compound 9 which were purified on silica gel using ethyl acetate. White solid (23 mg, 0.11 mmol, 97%). M.p. 170-171 °C (from ethyl acetate). ESI (m/z): 190.2 (M-H)⁻. [α]_D²²= -23 (c 1.0 in methanol). Enantiomeric excesses were determined by derivatization of the compound into methyl ester 12.

(*S*)-Methyl 2-(-oxoisoindolin-3-yl)acetic acid (12). In a round botton flask compound 9 (120 mg, 0.63 mmol, 1 equiv) and K₂CO₃ (1.5 equiv) were dissolved in DMF (3 mL). After 30 minutes iodomethane (2 equiv) were added and the mixture was stirred overnight at room temperature. The solvent was removed under reduced pressure and the residue was purified on silica gel using ethyl acetate/petroleum ether 7:3 to give a white solid. Using acid 9 obtained from 7, yield 98%: (125 mg, 0.61 mmol), ee 95%; mp 145.6–147.7 °C (from ethyl acetate/petroleum ether); $[\alpha]_D^{22}$ = -9.4 (c 1.0 in CHCl₃). ESI (*m*/*z*) = 206.2 (M+H)⁺. Anal. Calcd for C₁₁H₁₁NO₃: C, 64.38; H, 5.40; N, 6.83. Found: C, 64.42; H, 5.30; N, 6.78. Spectroscopic data are in agreement with those reported in literature.³ Chiralpack IA3 column, hexane–*i*PrOH 8/2, 0.6 mL/min, λ = 254 nm t= 16.1 min and 20.3 min). Using acid 9 (20 mg, 0.104 mmol) obtained from 10, yield 96%, (20 mg, 0.099 mmol), ee. 95%; mp 145°–147°C (from ethyl acetate/petroleum ether); $[\alpha]_D^{22}$ = -9.7 (c 1.0 in CHCl₃).

Synthesis of Belliotti (S)-PD 172938

(*S*)-3-(2-Hydroxyethyl)isoindolin-1-one (13). A solution of ester 12 (40 mg, 0.2 mmol) in freshly distilled THF (1 mL) was stirred under nitrogen atmosphere. Then a solution of LiBH₄ 2 M in THF (150 μ L, 0.30 mmol) was added and the mixture was stirred for 2 h, the solvent was removed under reduced pressure. Purification of the residue (ethyl acetate/methanol 95:5) gave the pure compound as an oil. Yellow oil (31 mg, 0.175 mmol, 88%), ee 95%. [α]_D²²= - 9.6 (c 0.25 in CHCl₃). ESI (m/z): 178.2 (M+H)⁺. ¹HNMR (300 MHz, CDCl₃) 7.85 (d, 1H, *J* =7. 5 Hz), 7.57-7.43 (m, 3H), 4.75 (d app, 1H, *J* =6.1 Hz), 3.997-3.93 (m, 2H), 2.80 (br s, 1H), 2.28-2.24 (m, 1H), 1.73 (m, 1H).¹³CNMR (60 MHz, CDCl₃) δ 170.8, 147.7, 132.1, 131.9, 128.4, 124.1, 122.6, 61.0, 56.2, 37.2. Anal. calcd for C₁₀H₁₁NO_{2.} Calcd: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.76; H, 6.36; N, 7.87. Chiralpack IE3 column, hexane–i-PrOH 8/2, 0.6 mL/min, λ = 254 nm t=30.4 min and 34.4 min).

(*S*)-2-(1-Oxoisoindolin-3-yl)ethyl methansulfonate (14). Under nitrogen atmosphere to a solution of alcohol 13 (20 mg, 0.12 mmol) and Et₃N (18 mg, 0.18 mmol, 24 µL) in CH₂Cl₂ was added methansulfonyl chloride (16 mg, 0.14 mmol, 12 µL) and the mixture was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue purified on silica gel (ethyl acetate) to give the pure compound as white solid (26 mg, 0.101 mmol, 88%). M.p. 131-133 °C (from ethyl acetate), ee 95%. $[\alpha]_D^{22}$ = - 33.6 (c 0.5 in CHCl₃). ESI (m/z): 256.2 (M+H)⁺. ¹HNMR (400 MHz, CDCl₃) δ 7.83 (d, 1H, *J* = 7. 3 Hz), 7.63-7.53 (m, 1H), 7.51-7.47 (m, 3H), 4.83 (br s 1H), 4.42-4.41 (m, 2H), 3.03 (s, 3H), 2.51-2.49 (m, 1H), 2.00-1.97 (m 1H). ¹³CNMR (100 MHz, CDCl₃) δ 171.0, 146.4, 132.3, 128.6, 124.0, 122.5, 66.6, 53.6, 37.4, 34.2. Anal. calcd for C₁₁H₁₃NO₄S Calcd: C, 51.75; H, 5.13; N, 5.49.Found: C, 51.68; H, 5.16; N, 5.57.

(*S*)-(2-(4-(3,4-Dimethylphenyl)piperazin-1-yl)ethyl)isoindolin-1-one (*S*)-PD 172938 (3). Under nitrogen atmosphere to a solution of mesylate 14 (20 mg, 0.07 mmol) and Et₃N (18 mg, 0.18 mmol, 24 μL) in CH₂Cl₂ was added 1-(3,4 dimethylphenyl)piperazine (15, 16 mg, 0.08 mmol) and the mixture was stirred under reflux overnight. The solvent was removed under reduced pressure and the residue purified on silica gel (ethyl acetate) to give the pure compound as wax like solid (21 mg, 0.06 mmol, 87%), ee 95%. [a]_D= - 17 (c 0.75, CHCl₃). ESI (m/z): 350.1 (M+H)⁺. ¹HNMR (250 MHz, CDCl₃) 7.85 (d, 1H, *J* =7.2 Hz), 7.57-7.42 (m, 4H), 7.02 (d, 1H, *J* = 8.1 Hz), 6.75-6.68 (m, 1H + NH), 4.63 (d app, 1H, *J* = 9.3 Hz), 3.20-3.16 (m, 4H), 2.75-2.54 (m, 6H), 2.23-2.18 (s + m, 7H), 1.80-1.72 (m, 1H).¹³CNMR (100 MHz, CDCl₃) δ 170.7, 170.3, 149.5, 149.4, 147.5, 137.1, 132.0, 131.7, 130.2, 128.3, 123.8, 122.3, 118.3, 114.0, 57.1, 56.5, 53.4, 49.8, 31.3, 20.2, 18.8. Anal. calcd for C₂₂H₂₇N₃O₂. Calcd: C, 75.61; H, 7.79; N, 12.02. Found: C, 75.58; H, 7.66; N, 11.97. Chiralpack IA3 column, hexane–i-PrOH 8/2, 0.6 mL/min, λ = 254 nm t=13.2 min and 15.5 min.

Synthesis of benzodiazepine-receptor agonists derivatives

(*S*)-3-{2-[4-(4-Methylphenyl)piperazin-1-yl]-2-oxoethyl}-2,3-dihydro-1*H*-isoindol-1-one (17). Compound **9** (60 mg, 0.31 mmol), 1-(4-methylphenyl)piperazine dihydrochloride (16, 53 mg, 0.31 mmol), *N*-(3-dimethylaminopropyl)-*N*-ethylcarbodiimide hydrochloride (58 mg, 0.31 mmol), 1-hydroxybenzotriazole hydrate (41 mg, 0.31 mmol) and triethylamine (100 mg, 1 mmol, 138 μ L) in THF (4 mL) were stirred at 25 °C for 16 h, and the reaction mixture then concentrated under reduced pressure. The resulting residue was purified by chromatography on silica gel (CHCl₃/methanol 95/5). Yellow oil (96 mg, 0.28 mmol, 87%), ee 95%. $[\alpha]_D^{22}$ = -57 (c 1.0 in CHCl₃). ESI (*m*/*z*) 350.2 (M+H)⁺. ¹HNMR (250 MHz, CDCl₃) δ 8.06 (d,1H, *J*= 7 Hz) 7.76-7.61 (m, 3H) 7.60 (s, 1H) 7.27(d, 2H, *J*= 8.3 Hz) 7.02 (d, 2H, *J*= 8.4Hz) 5.24 (d, 1H *J*= 10Hz), 4.04-4.00 (m, 2H), 3.76-3.72 (m, 2H), 3.33-3.24 (m, 5H), 2.71-2.60 (m, 1H), 2.46 (s, 3H). ¹³CNMR (60 MHz, CDCl₃) δ 170.3, 168.8, 148.7, 146.6, 132.2, 132.1, 130.7, 130.0, 128.8, 124.3, 122.5, 117.3, 53.6, 50.4, 50.1, 45.5, 41.9, 39.1, 20.6. Anal. Calcd for C₂₁H₂₃N₃O₂. Calcd: C, 72.18; H,6.63; N, 12.03. Found: C, 71.99; H, 6.62; N, 11.93. Chiralpack IA3 column, hexane–i-PrOH 8/2, 0.6 mL/min, λ = 254 nm t = 33.4 min, t = 37.5 min).

General procedure for the arylation of isoindolinones

A Schlenk tube was charged with CuI (0.05 mmol) and K_3PO_4 (0.23 mmol), evacuated and backfilled with nitrogen. 2-Iodo-5-nitropyridine or 2-iodopyridine or **18** or **19** (0.17 mmol), *N*,*N*-dimethylethylenediamine (**20**, 0.07 mmol), and 3-substituted isoindolinones **12** or **17** (0.15 mmol) dissolved in dioxane (1 mL) were added under a nitrogen atmosphere. The reaction mixture was heated at 80 °C for 24 h. The resulting pale-brown suspension was cooled to room temperature. After removing the solvent, the residues were separated by chromatography on silica gel to afford the desired compounds.

(S)-2-(5-Nitropyridin-2-yl)-3-(2-oxo-2-(4-p-tolylpiperazin-1-yl)ethyl)isoindolin-1-one (21).

Yellow solid (53 mg, 0.112 mmol, 75%). ee 95%. $[\alpha]_D^{22} = +45$ (c 0.1 in CHCl₃). m.p. 188°-189°C (from ethyl acetate /petroleum ether). ESI (*m*/*z*) = 472.5 (M+H)⁺. ¹HNMR (250 MHz, CDCl₃) δ 9.28 (s, 1H), 8.88 (d, 1H, *J*= 9.3 Hz), 8.53 (d, 1H, *J*= 9.3 Hz), 7.77-7.50 (m, 4H), 7.07 (d, 2H, *J*= 8 Hz), 6.81 (d, 2H, *J*= 8 Hz), 6.17 (d, 1H *J*= 9.55 Hz) 3.85-3.84 (m, 2H), 3.55-3.51 (m, 3H), 3.16-3.00 (m, 4H), 2.60-2.49 (m, 1H), 2.26 (s, 3H). ¹³CNMR (60 MHz, CDCl₃) δ 168.3, 168.2, 155.0, 148.8, 146.2, 144.6, 140.2, 134.2, 133.6, 130.6, 130.0, 129.2, 124.8, 124.3, 117.2, 114.3, 57.9, 50.4, 50.2, 45.7, 42.0, 37.5, 20.6. Anal. Calcd for C₂₆H₂₅N₅O₄. Calcd: C, 66.23; H, 5.34; N, 14.85. Found: C, 66.11; H, 5.19; N, 14.73. Chiralpack IA3 column, hexane–i-PrOH 8/2, 0.6 mL/min, λ = 254 nm t= 30.02 min, t = 35.8 min).

(*S*)-Methyl 2-[1-oxo-2-(pyridin-2-yl)isoindolin-3-yl]acetate (22). White solid (35 mg, 0.12 mmol, 78%), ee 95%. $[\alpha]_D^{22} = + 4.6$ (c 1.6 in CHCl₃).). ESI (m/z): 283.12 (M+H)⁺. Anal. Calcd for C₁₆H₁₄N₂O₃. Calcd: C, 68.07; H, 5.00; N, 9.92. Found: C, 68.38; H, 5.16; N, 9.87. Spectroscopic

data are in agreement with those reported in literature.⁴ Chiralpack IA3 column, hexane–*i*PrOH 8/2, 0.6 mL/min, λ = 254 nm t=12.4 min and 13.4 min).

References

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S13



S14



S15

HPLC traces



Chiralcel AD-H, *n*-hexane: i-PrOH = 70:30, 1.0 mL/min, 10 °C



HPLC after reaction





HPLC after crystallization







16.101	245628	2.62	1163	4.00
20.290	9120278	97.38	27940	96.00





	RT (min)	Area (⊉*sec)	% Area	Height (⊉)	% Height
1	33.440	252691	2.67	4091	3.89
2	37.496	9202492	97.33	101024	96.11















