## 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 ${ }^{1} H$ NMR, ${ }^{13} \mathrm{C}$ NMR and HPLC traces

Experimental part ..... S2
${ }^{1} \mathrm{H}$ NMR copies, ${ }^{13} \mathrm{C}$ NMR copies ..... S7
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 , $300 \mathrm{MHz}, 250 \mathrm{MHz},{ }^{1} \mathrm{H} ; 100 \mathrm{MHz}, 75 \mathrm{MHz}, 62.5 \mathrm{MHz}{ }^{13} \mathrm{C}$ ). Spectra were referenced to residual $\mathrm{CHCl}_{3}\left(7.26 \mathrm{ppm},{ }^{1} \mathrm{H}, 77.23 \mathrm{ppm},{ }^{13} \mathrm{C}\right.$ ) 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. ${ }^{1}[\alpha]_{\mathrm{D}}{ }^{21}=+58(\mathrm{c}=$ $1.00, \mathrm{CHCl}_{3}$ ). ${ }^{1} \mathrm{H}$ NMR ( $300 \mathrm{MHz}, \delta, \mathrm{CDCl}_{3}, 298 \mathrm{~K}$ ): 1.32-1.46 (m, 1H), 1.52-2.10 (m, 5H), 2.15$2.28(\mathrm{~m}, 1 \mathrm{H}), 2.55-2.67(\mathrm{~m}, 1 \mathrm{H}), 3.15(\mathrm{~s}, 3 \mathrm{H}), 3.25(\mathrm{~s}, 3 \mathrm{H}), 4.31-4.48(\mathrm{~m}, 1 \mathrm{H}), 4.62-4.75(\mathrm{~m}, 1 \mathrm{H})$, $5.30(\mathrm{~d}, 1 \mathrm{H}, J=13.0 \mathrm{~Hz}), 5.38(\mathrm{~d}, 1 \mathrm{H}, J=13.0 \mathrm{~Hz}), 7.55(\mathrm{~d}, 1 \mathrm{H}, J=9.6 \mathrm{~Hz}), 7.75(\mathrm{~d}, 2 \mathrm{H}, J=9.2$ $\mathrm{Hz}), 7.98(\mathrm{~s}, 1 \mathrm{H}), 8.01(\mathrm{~s}, 2 \mathrm{H}), 8.16(\mathrm{~d}, 2 \mathrm{H}, J=9.2 \mathrm{~Hz}), 9.21(\mathrm{~s}, 1 \mathrm{H}) \mathrm{ppm} .{ }^{13} \mathrm{C}$ NMR ( $75 \mathrm{MHz}, \delta$, $\mathrm{CDCl}_{3}, 298 \mathrm{~K}$ ): 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, $133.3(\mathrm{q}, J=34 \mathrm{~Hz}), 142.6,145.3,154.8 \mathrm{ppm} .{ }^{19} \mathrm{~F}$ NMR $(282 \mathrm{MHz}, \delta$, $\mathrm{CDCl}_{3}, 298 \mathrm{~K}$ ): -63.0 ppm. IR (film): $\bar{\nu}=3265,3206,3150,3083,3053,2940,2864,2324,1696$, $1613,1599,1553,1505,1373,1329,1279,1175,1134,1109,921,850,752,710,682,495,411$ $\mathrm{cm}^{-1}$. HRMS (ESI): $\mathrm{m} / \mathrm{z}$ calcd for $\mathrm{C}_{24} \mathrm{H}_{27} \mathrm{~F}_{6} \mathrm{~N}_{4} \mathrm{O}_{3}{ }^{+}: 533.1982$ [M ${ }^{+}$]; found: 533.1993
(S)-Dimethyl 2-(1-oxoisoindolin-3-yl)malonate (7). A mixture of 2-cyanobenzaldehyde 5 (262 $\mathrm{mg}, 2 \mathrm{mmol}), \mathrm{K}_{2} \mathrm{CO}_{3}(276 \mathrm{mg}, 2 \mathrm{mmol})$ and $(R, R)$-catalyst $8 \mathrm{a}(27 \mathrm{mg}, 0.05 \mathrm{mmol}, 2.5 \mathrm{~mol} \%)$ was dissolved in dichloromethane ( $30 \mathrm{~mL}, 0.066 \mathrm{M}$ ) and cooled to $-10^{\circ} \mathrm{C}$ with stirring. Within a period of 2 minutes dimethyl malonate $\mathbf{6}(245 \square \mathrm{~L}, 2.4 \mathrm{mmol}, 1.2$ equiv) was added. After 10 h (reaction monitored by TLC) the reaction mixture was filtrated through a plug of $\mathrm{Na}_{2} \mathrm{SO}_{4}$. 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 $\mathrm{mg}, 1.96 \mathrm{mmol}$ ) and ee $78 \%$. Chiralcel AD-H, $n$-hexane $/ \mathrm{iPrOH} 70: 30,1.0 \mathrm{~mL} / \mathrm{min}, 10^{\circ} \mathrm{C}, 12.3 \mathrm{~min}$
(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 $-20^{\circ} \mathrm{C}$. 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 ( $400 \mathrm{mg}, 1.51 \mathrm{mmol}$, ee $95 \%$ ). Spectroscopic data are in agreement with those reported in literature. ${ }^{2}$ Chiralpack AD column, hexane $/ \mathrm{iPrOH} 8: 2,0.8 \mathrm{~mL} / \mathrm{min}, \lambda=254 \mathrm{~nm}, t=19.4 \mathrm{~min}, t=$ 29.3 min .
(S)-2-(1-Oxoisoindolin-3-yl)malonic acid (10). To a solution of isoindolinone 7 ( $40 \mathrm{mg}, 0.15$ mmol ) in a mixture of dichloromethane/methanol 9:1 ( 1 mL ) was added $\mathrm{NaOH} 2 \mathrm{M}(500 \mu \mathrm{~L})$ 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 $\left(\mathrm{MgSO}_{4}\right)$, and the solvent was evaporated to give the pure compound. White solid ( $35 \mathrm{mg}, 0.149 \mathrm{mmol}, 99 \%$ ). M.p. $176-177^{\circ} \mathrm{C}$ (from $\mathrm{Et}_{2} \mathrm{O}$ ). ESI (m/z): $234.2(\mathrm{M}-\mathrm{H})^{-} .[\alpha]_{\mathrm{D}}{ }^{22}=-6.3(\mathrm{c}$ 0.1 M in methanol). Anal. calcd for $\mathrm{C}_{11} \mathrm{H}_{9} \mathrm{NO}_{5}$. Calcd: C, 56.17 ; H, 3.86; N, 5.96. Found: C, 56.35; H, 4.04; N, 6.02. ${ }^{1} \mathrm{HNMR}\left(300 \mathrm{MHz}, \mathrm{D}_{2} \mathrm{O}\right) \delta 7.72(\mathrm{~d}, 1 \mathrm{H}, J=6.87 \mathrm{~Hz}), 7.63-7.59(\mathrm{~m}, 1 \mathrm{H}), 7.54-$ $7.49(\mathrm{~m}, 2 \mathrm{H}) 5.21(\mathrm{~d}, 1 \mathrm{H}, J=8.55 \mathrm{~Hz}) 3.68(\mathrm{~d}, 1 \mathrm{H}, J=8.55 \mathrm{~Hz}) .{ }^{13} \mathrm{CNMR}\left(100 \mathrm{MHz}\right.$, DMSO-d $\left.\mathrm{d}_{6}\right) \delta$ 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 $\mathbf{1 2}$.
(S)-2-(1-Oxoisoindolin-3-yl)acetic acid (9) from 7. A flask containing a solution of isoindolinone $7(320 \mathrm{mg}, 1.20 \mathrm{mmol})$ and $\mathrm{HCl} 6 \mathrm{M}(2 \mathrm{~mL})$ was immersed in an oil bath preheated to $150{ }^{\circ} \mathrm{C}$ and the solution was refluxed for 30 minutes. The mixture was extracted with ethyl acetate ( $3 \times 15 \mathrm{~mL}$ ). The combined organic layers were dried $\left(\mathrm{MgSO}_{4}\right)$, and the solvent was evaporated to give compounds 9 which were purified on silica gel using ethyl acetate. White solid ( $208 \mathrm{mg}, 1.09$ $\mathrm{mmol}, 90 \%$ ). M.p $170-171^{\circ} \mathrm{C}$ (from ethyl acetate). ESI (m/z): $190.2(\mathrm{M}-\mathrm{H})^{-} \cdot[\alpha]_{\mathrm{D}}{ }^{22}=-21$ (c 1.0 in methanol). Anal. calcd for $\mathrm{C}_{10} \mathrm{H}_{9} \mathrm{NO}_{3}$. Calcd: C, $62.82 ; \mathrm{H}, 4.74 ; \mathrm{N}, 7.33$. Found: C, 62.72; $\mathrm{H}, 4.78$; $\mathrm{N}, 7.01 .^{1} \mathrm{HNMR}\left(300 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) 7.76(\mathrm{~d}, 1 \mathrm{H}, J=7.5 \mathrm{~Hz}), 7.65-7.53(\mathrm{~m}, 2 \mathrm{H}), 7.51-7.48(\mathrm{~m}$, $1 \mathrm{H})$, 5.09-4.99 (m, 1H), 2.97-2.89 (m, 1H), 2.68-2.48 (m, 1H). ${ }^{13} \mathrm{CNMR}\left(100 \mathrm{MHz}, \mathrm{CD}_{3} \mathrm{OD}\right) \delta$ $172.6,171.2,146.8,131.9,131.3,128.1,122.9,122.6,53.4,38.3$. Enantiomeric excesses were determined by derivatization of the compound into methyl ester $\mathbf{1 2}$ or amide $\mathbf{1 6}$.
(S)-2-(1-Oxoisoindolin-3-yl)acetic acid (9) from 10. A flask containing a solution of malonic acid $\mathbf{1 0}(30 \mathrm{mg}, 0.12 \mathrm{mmol})$ and $\mathrm{HCl} 6 \mathrm{M}(0.5 \mathrm{~mL})$ was immersed in an oil bath preheated to $150^{\circ} \mathrm{C}$ and the solution was refluxed for 15 minutes. The mixture was extracted with ethyl acetate ( $3 \times 15 \mathrm{~mL}$ ) . The combined organic layers were dried $\left(\mathrm{MgSO}_{4}\right)$, and the solvent was evaporated to give compound 9 which were purified on silica gel using ethyl acetate. White solid ( $23 \mathrm{mg}, 0.11 \mathrm{mmol}$, $97 \%$ ). M.p. $170-171{ }^{\circ} \mathrm{C}$ (from ethyl acetate). ESI (m/z): $190.2(\mathrm{M}-\mathrm{H})^{-} \cdot[\alpha]_{\mathrm{D}}{ }^{22}=-23$ (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 $\mathrm{K}_{2} \mathrm{CO}_{3}$ ( 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 $145.6-147.7^{\circ} \mathrm{C}$ (from ethyl acetate/petroleum ether); $[\alpha]_{\mathrm{D}}{ }^{22}=-9.4$ (c 1.0 in $\left.\mathrm{CHCl}_{3}\right)$. ESI $(\mathrm{m} / \mathrm{z})=206.2(\mathrm{M}+\mathrm{H})^{+}$. Anal. Calcd for $\mathrm{C}_{11} \mathrm{H}_{11} \mathrm{NO}_{3}: \mathrm{C}, 64.38 ; \mathrm{H}, 5.40 ; \mathrm{N}, 6.83$. 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- $i \operatorname{PrOH} 8 / 2,0.6 \mathrm{~mL} / \mathrm{min}, \lambda=254 \mathrm{~nm} \mathrm{t}=16.1 \mathrm{~min}$ and 20.3 min ). Using acid 9 ( $20 \mathrm{mg}, 0.104 \mathrm{mmol}$ ) obtained from 10, yield $96 \%$, ( $20 \mathrm{mg}, 0.099 \mathrm{mmol}$ ), ee. $95 \%$; mp $145^{\circ}-147^{\circ} \mathrm{C}$ (from ethyl acetate/petroleum ether); $[\alpha]_{\mathrm{D}}{ }^{22}=-9.7$ (c 1.0 in $\mathrm{CHCl}_{3}$ ).

## Synthesis of Belliotti (S)-PD 172938

(S)-3-(2-Hydroxyethyl)isoindolin-1-one (13). A solution of ester $\mathbf{1 2}$ ( $40 \mathrm{mg}, 0.2 \mathrm{mmol}$ ) in freshly distilled THF ( 1 mL ) was stirred under nitrogen atmosphere. Then a solution of $\mathrm{LiBH}_{4} 2 \mathrm{M}$ in THF $(150 \mu \mathrm{~L}, 0.30 \mathrm{mmol})$ 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 ( $31 \mathrm{mg}, 0.175 \mathrm{mmol}, 88 \%$ ), ee $95 \%$. $[\alpha]_{\mathrm{D}}{ }^{22}=-9.6$ (c $0.25 \mathrm{in} \mathrm{CHCl}_{3}$ ). $\mathrm{ESI}(\mathrm{m} / \mathrm{z})$ : $178.2(\mathrm{M}+\mathrm{H})^{+} .{ }^{1} \mathrm{HNMR}\left(300 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) 7.85(\mathrm{~d}, 1 \mathrm{H}, J=7.5 \mathrm{~Hz}), 7.57-7.43(\mathrm{~m}, 3 \mathrm{H}), 4.75(\mathrm{~d}$ app, $1 \mathrm{H}, J=6.1 \mathrm{~Hz}$ ), 3.997-3.93 (m, 2H), $2.80(\mathrm{br} \mathrm{s}, 1 \mathrm{H}), 2.28-2.24(\mathrm{~m}, 1 \mathrm{H}), 1.73(\mathrm{~m}, 1 \mathrm{H}) .{ }^{13} \mathrm{CNMR}$ ( $60 \mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 170.8,147.7,132.1,131.9,128.4,124.1,122.6,61.0,56.2,37.2$. Anal. calcd for $\mathrm{C}_{10} \mathrm{H}_{11} \mathrm{NO}_{2 . .}$ 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- $\operatorname{PrOH} 8 / 2,0.6 \mathrm{~mL} / \mathrm{min}, \lambda=254 \mathrm{~nm} \mathrm{t}=30.4 \mathrm{~min}$ and 34.4 min ).
(S)-2-(1-Oxoisoindolin-3-yl)ethyl methansulfonate (14). Under nitrogen atmosphere to a solution of alcohol $13(20 \mathrm{mg}, 0.12 \mathrm{mmol})$ and $\mathrm{Et}_{3} \mathrm{~N}(18 \mathrm{mg}, 0.18 \mathrm{mmol}, 24 \mu \mathrm{~L})$ in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ was added methansulfonyl chloride ( $16 \mathrm{mg}, 0.14 \mathrm{mmol}, 12 \mu \mathrm{~L}$ ) 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 ( $26 \mathrm{mg}, 0.101 \mathrm{mmol}, 88 \%$ ). M.p. $131-133{ }^{\circ} \mathrm{C}$ (from ethyl acetate), ee $95 \% .[\alpha]_{\mathrm{D}}{ }^{22}=-33.6$ (c 0.5 in $\mathrm{CHCl}_{3}$ ). ESI ( $\mathrm{m} / \mathrm{z}$ ): 256.2 $(\mathrm{M}+\mathrm{H})^{+} .{ }^{1} \mathrm{HNMR}\left(400 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 7.83(\mathrm{~d}, 1 \mathrm{H}, J=7.3 \mathrm{~Hz}), 7.63-7.53(\mathrm{~m}, 1 \mathrm{H}), 7.51-7.47$ $(\mathrm{m}, 3 \mathrm{H}), 4.83(\mathrm{br} \mathrm{s} 1 \mathrm{H}), 4.42-4.41(\mathrm{~m}, 2 \mathrm{H}), 3.03(\mathrm{~s}, 3 \mathrm{H}), 2.51-2.49(\mathrm{~m}, 1 \mathrm{H}), 2.00-1.97(\mathrm{~m} 1 \mathrm{H})$. ${ }^{13} \mathrm{CNMR}\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right.$ ) $\delta 171.0,146.4,132.3,128.6,124.0,122.5,66.6,53.6,37.4,34.2$. Anal. calcd for $\mathrm{C}_{11} \mathrm{H}_{13} \mathrm{NO}_{4} \mathrm{~S}$. 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 $\mathbf{1 4}(20 \mathrm{mg}, 0.07 \mathrm{mmol})$ and $\mathrm{Et}_{3} \mathrm{~N}(18 \mathrm{mg}, 0.18 \mathrm{mmol}$, $24 \mu \mathrm{~L}$ ) in $\mathrm{CH}_{2} \mathrm{Cl}_{2}$ was added 1-(3,4 dimethylphenyl)piperazine ( $15,16 \mathrm{mg}, 0.08 \mathrm{mmol}$ ) 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 , $0.06 \mathrm{mmol}, 87 \%$ ), ee $95 \%$. $[\mathrm{a}]_{\mathrm{D}}=-17$ (c $0.75, \mathrm{CHCl}_{3}$ ). ESI ( $\mathrm{m} / \mathrm{z}$ ): $350.1(\mathrm{M}+\mathrm{H})^{+} .{ }^{1} \mathrm{HNMR}(250$ $\left.\mathrm{MHz}, \mathrm{CDCl}_{3}\right) 7.85(\mathrm{~d}, 1 \mathrm{H}, J=7.2 \mathrm{~Hz}), 7.57-7.42(\mathrm{~m}, 4 \mathrm{H}), 7.02(\mathrm{~d}, 1 \mathrm{H}, J=8.1 \mathrm{~Hz}), 6.75-6.68(\mathrm{~m}$, $1 \mathrm{H}+\mathrm{NH}), 4.63(\mathrm{~d} \mathrm{app}, 1 \mathrm{H}, J=9.3 \mathrm{~Hz}), 3.20-3.16(\mathrm{~m}, 4 \mathrm{H}), 2.75-2.54(\mathrm{~m}, 6 \mathrm{H}), 2.23-2.18(\mathrm{~s}+\mathrm{m}$, $7 \mathrm{H}), 1.80-1.72(\mathrm{~m}, 1 \mathrm{H}) .{ }^{13} \mathrm{CNMR}\left(100 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 170.7,170.3,149.5,149.4,147.5,137.1$, 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 $\mathrm{C}_{22} \mathrm{H}_{27} \mathrm{~N}_{3} \mathrm{O}_{2}$. Calcd: C, $75.61 ; \mathrm{H}, 7.79 ; \mathrm{N}, 12.02$. Found: C, $75.58 ; \mathrm{H}, 7.66 ; \mathrm{N}, 11.97$. Chiralpack IA3 column, hexane-i-PrOH $8 / 2,0.6 \mathrm{~mL} / \mathrm{min}, \lambda=254 \mathrm{~nm} \mathrm{t}=13.2 \mathrm{~min}$ and 15.5 min .

## Synthesis of benzodiazepine-receptor agonists derivatives

(S)-3-\{2-[4-(4-Methylphenyl)piperazin-1-yl]-2-oxoethyl\}-2,3-dihydro-1H-isoindol-1-one (17).

Compound 9 ( $60 \mathrm{mg}, 0.31 \mathrm{mmol}$ ), 1-(4-methylphenyl)piperazine dihydrochloride ( $\mathbf{1 6}, 53 \mathrm{mg}, 0.31$ mmol ), $N$-(3-dimethylaminopropyl)- $N$-ethylcarbodiimide hydrochloride ( $58 \mathrm{mg}, 0.31 \mathrm{mmol}$ ), 1 hydroxybenzotriazole hydrate ( $41 \mathrm{mg}, 0.31 \mathrm{mmol}$ ) and triethylamine ( $100 \mathrm{mg}, 1 \mathrm{mmol}, 138 \mu \mathrm{~L}$ ) in THF ( 4 mL ) were stirred at $25^{\circ} \mathrm{C}$ for 16 h , and the reaction mixture then concentrated under reduced pressure. The resulting residue was purified by chromatography on silica gel
$\left(\mathrm{CHCl}_{3} /\right.$ methanol $\left.95 / 5\right)$. Yellow oil ( $96 \mathrm{mg}, 0.28 \mathrm{mmol}, 87 \%$ ), ee $95 \%$. $[\alpha]_{\mathrm{D}}{ }^{22}=-57$ (c 1.0 in $\mathrm{CHCl}_{3}$ ). ESI $(\mathrm{m} / \mathrm{z}) 350.2(\mathrm{M}+\mathrm{H})^{+} .{ }^{1} \mathrm{HNMR}\left(250 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 8.06(\mathrm{~d}, 1 \mathrm{H}, J=7 \mathrm{~Hz}) 7.76-7.61$ $(\mathrm{m}, 3 \mathrm{H}) 7.60(\mathrm{~s}, 1 \mathrm{H}) 7.27(\mathrm{~d}, 2 \mathrm{H}, \quad J=8.3 \mathrm{~Hz}) 7.02(\mathrm{~d}, 2 \mathrm{H}, J=8.4 \mathrm{~Hz}) 5.24(\mathrm{~d}, 1 \mathrm{H} J=10 \mathrm{~Hz}), 4.04-$ $4.00(\mathrm{~m}, 2 \mathrm{H}), 3.76-3.72(\mathrm{~m}, 2 \mathrm{H}), 3.33-3.24(\mathrm{~m}, 5 \mathrm{H}), 2.71-2.60(\mathrm{~m}, 1 \mathrm{H}), 2.46(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{CNMR}(60$ $\mathrm{MHz}, \mathrm{CDCl}_{3}$ ) $\delta 170.3,168.8,148.7,146.6,132.2,132.1,130.7,130.0,128.8,124.3,122.5,117.3$, 53.6, 50.4, 50.1, 45.5, 41.9, 39.1, 20.6. Anal. Calcd for $\mathrm{C}_{21} \mathrm{H}_{23} \mathrm{~N}_{3} \mathrm{O}_{2}$. 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 $8 / 2,0.6$ $\mathrm{mL} / \mathrm{min}, \lambda=254 \mathrm{~nm} \mathrm{t}=33.4 \mathrm{~min}, \mathrm{t}=37.5 \mathrm{~min})$.

## General procedure for the arylation of isoindolinones

A Schlenk tube was charged with $\mathrm{CuI}(0.05 \mathrm{mmol})$ and $\mathrm{K}_{3} \mathrm{PO}_{4}(0.23 \mathrm{mmol})$, evacuated and backfilled with nitrogen. 2-Iodo-5-nitropyridine or 2-iodopyridine or $\mathbf{1 8}$ or $\mathbf{1 9}$ ( 0.17 mmol ), $\mathrm{N}, \mathrm{N}$ dimethylethylenediamine ( $\mathbf{2 0}, 0.07 \mathrm{mmol}$ ), and 3-substituted isoindolinones $\mathbf{1 2}$ or $\mathbf{1 7}(0.15 \mathrm{mmol})$ dissolved in dioxane ( 1 mL ) were added under a nitrogen atmosphere. The reaction mixture was heated at $80^{\circ} \mathrm{C}$ 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 ( $53 \mathrm{mg}, 0.112 \mathrm{mmol}, 75 \%$ ). ee $95 \%$. $[\alpha]_{\mathrm{D}}{ }^{22}=+45$ (c $0.1 \mathrm{in} \mathrm{CHCl}_{3}$ ). m.p. $188^{\circ}-189^{\circ} \mathrm{C}$ (from ethyl acetate /petroleum ether). ESI $(\mathrm{m} / \mathrm{z})=472.5(\mathrm{M}+\mathrm{H})^{+} .{ }^{1} \mathrm{HNMR}\left(250 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta$ $9.28(\mathrm{~s}, 1 \mathrm{H}), 8.88(\mathrm{~d}, 1 \mathrm{H}, J=9.3 \mathrm{~Hz}), 8.53(\mathrm{~d}, 1 \mathrm{H}, J=9.3 \mathrm{~Hz}), 7.77-7.50(\mathrm{~m}, 4 \mathrm{H}), 7.07(\mathrm{~d}, 2 \mathrm{H}, J=8$ $\mathrm{Hz}), 6.81(\mathrm{~d}, 2 \mathrm{H}, J=8 \mathrm{~Hz}), 6.17(\mathrm{~d}, 1 \mathrm{H} J=9.55 \mathrm{~Hz}) 3.85-3.84(\mathrm{~m}, 2 \mathrm{H}), 3.55-3.51(\mathrm{~m}, 3 \mathrm{H}), 3.16-$ $3.00(\mathrm{~m}, 4 \mathrm{H}), 2.60-2.49(\mathrm{~m}, 1 \mathrm{H}), 2.26(\mathrm{~s}, 3 \mathrm{H}) .{ }^{13} \mathrm{CNMR}\left(60 \mathrm{MHz}, \mathrm{CDCl}_{3}\right) \delta 168.3,168.2,155.0$, $148.8,146.2,144.6,140.2,134.2,133.6,130.6,130.0,129.2,124.8,124.3,117.2,114.3,57.9,50.4$, 50.2, 45.7, 42.0, 37.5, 20.6. Anal. Calcd for $\mathrm{C}_{26} \mathrm{H}_{25} \mathrm{~N}_{5} \mathrm{O}_{4}$. 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 $8 / 2,0.6 \mathrm{~mL} / \mathrm{min}, \lambda=254 \mathrm{~nm}$ $\mathrm{t}=30.02 \mathrm{~min}, \mathrm{t}=35.8 \mathrm{~min})$.
(S)-Methyl 2-[1-oxo-2-(pyridin-2-yl)isoindolin-3-yl]acetate (22). White solid ( $35 \mathrm{mg}, 0.12 \mathrm{mmol}$, $78 \%$ ), ee $95 \% .[\alpha]_{\mathrm{D}}{ }^{22}=+4.6$ (c 1.6 in $\mathrm{CHCl}_{3}$ ). ). ESI (m/z): $283.12(\mathrm{M}+\mathrm{H})^{+}$. Anal. Calcd for $\mathrm{C}_{16} \mathrm{H}_{14} \mathrm{~N}_{2} \mathrm{O}_{3}$. Calcd: C, 68.07 ; H, 5.00; N, 9.92. Found: C, $68.38 ; \mathrm{H}, 5.16 ; \mathrm{N}, 9.87$. Spectroscopic
data are in agreement with those reported in literature. ${ }^{4}$ Chiralpack IA3 column, hexane- $i \operatorname{PrOH} 8 / 2$, $0.6 \mathrm{~mL} / \mathrm{min}, \lambda=254 \mathrm{~nm} \mathrm{t}=12.4 \mathrm{~min}$ and 13.4 min$)$.

## References

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| No. | Ret.Time <br> min | Peak Name | Height <br> mAU | Area <br> mAU*min | Rel.Area <br> $\%$ | Amount | Type |
| :---: | :---: | :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 12,28 | n.a. | 523,708 | 216,532 | 49,98 | n.a. | BMB |
| 2 | 25,89 | n.a. | 258,334 | 216,724 | 50,02 | n.a. | BMB |
| Total: |  |  | 782,041 | 433,256 | 100,00 | 0,000 |  |

Chiralcel AD-H, $n$-hexane: i-PrOH $=70: 30,1.0 \mathrm{~mL} / \mathrm{min}, 10^{\circ} \mathrm{C}$

$\begin{array}{|c|cccrcrc|}\hline \text { No. } & \begin{array}{c}\text { Ret.Time } \\ \text { min }\end{array} & & \text { Peak Name } & \begin{array}{c}\text { Height } \\ \text { mAU }\end{array} & \begin{array}{c}\text { Area } \\ \text { mAU*min }\end{array} & \begin{array}{c}\text { Rel.Area } \\ \%\end{array} & \text { Amount }\end{array}$ Type $)$

HPLC after reaction

Chiralpack AD column, hexane-i-PrOH 8: 2, $0.8 \mathrm{~mL} / \mathrm{min}, \lambda=254 \mathrm{~nm}$


HPLC after crystallization



|  | RT <br> $(\mathrm{min})$ | Area <br> $(\mathrm{V}$ sec $)$ | \% Area | Height <br> $(\mathrm{V})$ | \% <br> Height |
| :--- | :--- | :--- | ---: | ---: | ---: |
| 1 | 16.203 | 1716997 | 49.65 | 64395 | 54.82 |
| 2 | 20.703 | 1741279 | 50.35 | 53067 | 45.18 |





|  | RT <br> $(\mathrm{min})$ | Area <br> $(\vee * \mathrm{sec})$ | \% Area | Height <br> $(\mathbb{V})$ | $\%$ <br> Height |
| :--- | :---: | :---: | ---: | ---: | ---: |
| 1 | 33.440 | 252691 | 2.67 | 4091 | 3.89 |
| 2 | 37.496 | 9202492 | 97.33 | 101024 | 96.11 |



|  | RT <br> $(\mathrm{min})$ | Area <br> $(\mathrm{V} * \mathrm{sec})$ | \% Area | Height <br> $(\mathrm{V})$ | \% <br> Height |
| :--- | :---: | :---: | ---: | ---: | ---: |
| 1 | 30.981 | 6448090 | 49.73 | 53696 | 50.44 |
| 2 | 37.804 | 6519007 | 50.27 | 52751 | 49.56 |



|  | RT <br> $(\mathrm{min})$ | Area <br> $\left(\mathrm{V}^{\star} \mathrm{sec}\right)$ | \% Area | Height <br> $(\mathrm{V})$ | \% <br> Height |
| :--- | :--- | :---: | ---: | ---: | ---: |
| 1 | 30.028 | 791221 | 2.42 | 5522 | 2.46 |
| 2 | 35.853 | 31964886 | 97.58 | 218918 | 97.54 |



|  | RT <br> $(\mathrm{min})$ | Area <br> $\left(V^{*} \mathrm{sec}\right)$ | \% Area | Height <br> $(\mathbb{V})$ | $\%$ <br> Height |
| :---: | :---: | :---: | :---: | :---: | :---: |
| 1 | 12.411 | 1033486 | 50.42 | 68160 | 52.07 |
| 2 | 13.416 | 1016469 | 49.58 | 62730 | 47.93 |



|  | RT <br> $(\mathrm{min})$ | Area <br> $\left(\mathbb{V}^{*} \mathrm{sec}\right)$ | \% Area | Height <br> $(\mathbb{V})$ | \% <br> Height |
| :--- | :--- | ---: | ---: | ---: | ---: |
| 1 | 12.347 | 68590 | 2.43 | 1254 | 3.08 |
| 2 | 13.343 | 2754186 | 97.57 | 39510 | 96.92 |





|  | RT <br> $(\mathrm{min})$ | Area <br> $(\mathrm{V} * \mathrm{sec})$ | \% Area | Height <br> $(\mathrm{V})$ | \% <br> Height |
| :--- | :---: | :---: | :---: | :---: | :---: |
| 1 | 13.553 | 2362551 | 50.05 | 75579 | 53.56 |
| 2 | 16.289 | 2358183 | 49.95 | 65524 | 46.44 |



|  | RT <br> $(\mathrm{min})$ | Area <br> $\left(\mathrm{V}^{\star} \mathrm{sec}\right)$ | \% Area | Height <br> $(\mathrm{V})$ | $\%$ <br> Height |
| :--- | :--- | :---: | ---: | ---: | ---: |
| 1 | 13.211 | 1691049 | 2.62 | 86528 | 4.01 |
| 2 | 15.528 | 62959216 | 97.38 | 2070560 | 95.99 |

