Supporting Information

Asymmetric cascade Aza-Henry/lactamization reaction in the highly enantioselective organocatalytic synthesis of 3-(nitromethyl)isoindolin-1-ones from α-amido sulfones.

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General Information

Unless otherwise noted, all chemicals, reagents and solvents for the performed reactions are commercially available and were used without further purification. Phthalide, 5-bromo-phthalide, 3-hydroxyphthalide and 6-chloro-3-hydroxyphthalide were purchased from Fluorochem. Other phthalides and 2-formylbenzoate esters a-h were prepared according to literature procedures.® Catalysts I-IV are commercially available. Catalyst V was gently supplied by Prof. Mario Waser, Institute of Organic Chemistry, University of Linz, Austria. All the reactions were monitored by thin layer chromatography (TLC) on precoated silica gel plates (0.25 mm) and visualized by fluorescence quenching at 254 nm. Flash chromatography was carried out using silica gel 60 (70–230 mesh, Merck, Darmstadt, Germany). Yields are given for isolated products showing one spot on a TLC plate and no impurities were detectable in the NMR spectrum. The NMR spectra were recorded on Bruker DRX 600, 400, and 300 MHz spectrometers (600 MHz, 1H, 150 MHz, 13C; 400 MHz, 1H, 100 MHz; 13C, 300 MHz, 1H, 75 MHz, 13C). Internal reference was set to the residual solvent signals (δH 7.26 ppm, δC 77 ppm for CDCl3 and δH 2.50 ppm, δC 39 ppm for DMSO-d6). The 13C NMR spectra were recorded under broadband proton-decoupling. Spectra are reported only for unknown compounds. The following abbreviations are used to indicate the multiplicity in NMR spectra: s-singlet, d-doublet, t-triplet, q-quartet, dd-doublet of doublets, m-multiplet, brs-broad signal. Coupling constants (J) are quoted in Hertz. High resolution mass spectra (HRMS) were acquired using a Bruker SolariX XR Fourier transform ion cyclotron resonance mass spectrometer (Bruker Daltonik GmbH, Bremen, Germany) equipped with a 7T refrigerated actively-shielded superconducting magnet. For ionization of the samples electrospray ionization (ESI) or MALDI was applied.

Experimental procedures

Procedures for the synthesis of 6-iodophthalide

Synthesis of 6-nitrophthalide: Phthalide (2.0 g, 1.0 eq., 15.0 mmol) was dissolved in fuming nitric acid (2.0 mL) and concentrated sulfuric acid (2.3 mL) at 0 °C. The ice bath was then removed and the reaction stirred for 12 h. The reaction was then poured into an ice-H2O bath and collected via filtration to give the crude product as a white solid. Recrystallisation from Hexane/CHCl3 gave the title compound as white crystals (Yield= 1.630 mg, 61%). 1H NMR (400 MHz, CDCl3): δ 8.77 (d, J= 1.8 Hz, 1H), 8.59 (d, J= 8.3 Hz, 1H), 7.72 (d, J= 8.4 Hz, 1H), 5.46 (s, 2H). Mp and the obtained spectroscopic data were found in agreement with literature.®
Synthesis of 6-aminophthalide: To a solution of 6-nitrophthalide (1.0 g, 1 eq., 5.58 mmol) in methanol (33.0 mL) Zn (1.450 g, 4 eq., 22.3 mmol) and 37% HCl (6.25 mL) were added dropwise at 0° (ice bath) and the mixture stirred for 2 h. The mixture was then basified with sodium hydroxide and filtered. The aqueous layer was extracted with Ethyl acetate two times, dried in vacuo to yield the corresponding 6-aminophthalide as yellow solid. (Yield= 830 mg, 99%). $^1$H NMR (600 MHz, DMSO-$d_6$): $\delta$ 7.24 (d, $J = 7.8$ Hz, 1H), 6.98 (dd, $J_1 = 8.4$, $J_2 = 1.2$ Hz, 1H), 6.92 (s, 1H), 5.46 (s, 2H), 5.18 (s, 2H). Mp and the obtained spectroscopic data were found in agreement with literature.²

Synthesis of 6-iodophthalide: In an ice bath a solution of NaNO$_2$ (610 mg, 1.2 eq., 6.5 mmol) in H$_2$O (1.2 mL) was added dropwise to a suspension of 6-aminophthalide (800 mg, 1.0 eq., 5.4 mmol) in 37% HCl (3.5 mL) and the resulting mixture was stirred for 25 min at 0°C. Then, a solution of KI (4.5 g, 5.0 eq., 27.0 mmol) in H$_2$O (4.6 mL) was added dropwise. The mixture was stirred at room temperature for 18 h. Then, the aqueous suspension was extracted with Ethyl acetate and the combined organic layers were washed with saturated aq. Na$_2$S$_2$O$_3$ and brine (14.0 mL), dried over Na$_2$SO$_4$ and concentrated in vacuo. The residue was purified by silica gel column chromatography eluting with CHCl$_3$ to obtain the product as white solid. (Yield= 900 mg, 65%). $^1$H NMR (300 MHz, CDCl$_3$) $\delta$ 8.26 (d, $J = 1.5$ Hz, 1H), 7.99 (dd, $J_1 = 8.0$, $J_2 = 1.5$ Hz, 1H), 7.30 (d, $J = 8.0$ Hz, 1 H), 5.29 (s, 2 H). Mp and the obtained spectroscopic data were found in agreement with literature.³

Procedure for the synthesis of 6-methoxyphthalide

To a solution of 3-methoxybenzoic acid (1.520 g, 1.0 eq., 10.0 mmol) in glacial acetic acid (5 mL), 37% HCl (7.5 mL) and 30% formaldehyde (3 mL, 4.0 eq., 40.0 mmol) were added, and the reaction mixture was stirred at 100°C for 1 h in an oil bath. After cooling, a saturated solution of NaHCO$_3$ was added until pH=7. The resulting mixture was extracted with CH$_2$Cl$_2$ twice, the combined organic layers were dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (Hexane/Ethyl acetate, 7:1) to afford 6-methoxyphthalide as a gum. (Yield= 700 mg, 43%). $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36 (d, $J = 8.4$ Hz, 1H), 7.28 (d, $J = 2.2$ Hz, 1H), 7.23 (dd, $J_1 = 8.4$, $J_2 = 2.2$ Hz, 1H), 5.24 (s, 2H), 3.84 (s, 3H). The obtained spectroscopic data were found in agreement with literature.⁴
Procedure for the synthesis of 5-phenylphthalide

\[
\text{PhOH} + \text{BrO} \xrightarrow{\text{Pd(PPh}_3\text{)}_4, \text{Toluene/Na}_2\text{CO}_3, \text{N}_2/100^\circ\text{C}} \xrightarrow{\text{PhOH}} \text{PhO}
\]

Phenylboronic acid (340 mg, 1.0 eq., 2.8 mmol), 5-bromophthalide (600 mg, 1.0 eq., 2.88 mmol) and tetrakis(triphenylphosphine)palladium 1(0) (Pd(PPh\text{$_3$})\text{$_4$}) (130 mg, 4.0 mol%) were stirred in toluene (2.8 mL) and 2 M Na\text{$_2$}CO\text{$_3$} solution (2.24 mL) at 100°C in an oil bath for 3 h under nitrogen atmosphere. Then, the mixture was extracted with Ethyl acetate three times. The combined organic layer was washed with brine, dried over anhydrous Na\text{$_2$}SO\text{$_4$} and concentrated under reduced pressure. The crude product was purified by column chromatography on silica gel (Petroleum ether/Ethyl acetate, 8:1) affording 5-phenylphthalide as white solid (Yield= 600 mg, 99%). \text{\textsuperscript{1}H NMR (300 MHz, CDCl\textsubscript{3}} \delta 7.99 (d, J= 7.8 Hz, 1H), 7.77 (d, J= 7.9 Hz, 1H), 7.65 (m, 1H), 7.45 (m, 5H), 5.38 (s, 2H). Mp and the obtained spectroscopic data were found in agreement with literature.\textsuperscript{5}

General procedure for the synthesis of 3-hydroxy phthalide derivatives

\[
\text{R}_1 \xrightarrow{1) \text{NBS/AIBN, 1,2-Dichloroethane, reflux}} \xrightarrow{2) \text{H}_2\text{O, Reflux}} \text{OH}
\]

A mixture of phthalide (1.0 eq., 2.5 mmol), N-bromosuccinimide (NBS, 1.1 eq., 2.75 mmol) and azobisisobutyronitrile (AIBN, 0.04 eq., 0.10 mmol) in 1,2-dichloroethane (15.0 mL) was refluxed for 1-6 h in an oil bath. The reaction mixture was kept in an ice bath for 2 h and then filtered. The solvent was removed under reduced pressure and the crude was suspended in water (7.0 mL) and the resulting mixture was refluxed for 1 h. The reaction mixture was cooled to room temperature and extracted with Ethyl acetate three times. The combined organic phases were dried and concentrated under reduced pressure to give 3-hydroxyphtalide derivatives, which are known compounds.\textsuperscript{3,5,6}

5-bromo 3-hydroxy phthalide.\textsuperscript{5} White solid (470 mg, 82%). \text{\textsuperscript{1}H NMR (300 MHz, DMSO-\text{d}_6}} \delta 8.28 (d, J= 4.1 Hz, 1H), 7.96-8.00 (m, 1H), 7.63 (d, J= 7.7 Hz, 2H), 6.66 (d, J= 4.6 Hz, 1H).

3-hydroxy 6-methoxy phthalide.\textsuperscript{4} Reaction carried out on 4 mmol of respective phthalide. White solid (597 mg, 83%). \text{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}} \delta 7.54 (s, 1H), 7.29 (s, 2H), 6.53 (s, 1H), 5.57 (s, 1H), 3.88 (s, 3H)

3-hydroxy 6-iodophthalide.\textsuperscript{3} White solid (495 mg, 72%). \text{\textsuperscript{1}H NMR (300 MHz, DMSO-\text{d}_6}} \delta 8.26 (d, J= 7.0 Hz, 1H), 8.06-8.02 (m, 2H), 7.49 (d, J= 7.8 Hz, 1H), 6.44 (d, J= 7.6 Hz, 1H).

3-hydroxy 5-phenylphthalide.\textsuperscript{3} White solid (276 mg, 49%). \text{\textsuperscript{1}H NMR (600 MHz, CDCl\textsubscript{3}} \delta 7.98 (d, J= 7.6 Hz, 1H), 7.86 (d, J= 6.9 Hz, 2H), 7.66 (d, J= 7.6 Hz, 3H), 7.53 (t, J= 7.0 Hz, 2H), 7.47-7.49 (m, 1H), 6.71 (s, 1H).
Mp and the obtained spectroscopic data were found in agreement with literature.\(^3,5,6\)

**Procedure for the synthesis of 5-fluoro-3-hydroxyphthalide**

\[
\begin{align*}
\text{N-bromosuccinimide (1.440 mg, 2.5 eq., 8.1 mmol) and azobisisobutyronitrile (20 mg, 0.04 eq., 0.12 mmol)}
\end{align*}
\]

were added to a suspension of 4-fluoro-2-methylbenzoic acid (500 mg, 1.0 eq., 3.24 mmol) in CCl\(_4\) (13.0 mL) and refluxed for 4-6 h in an oil bath. Then the mixture was cooled to room temperature, and filtered. The resulting organic solution was evaporated in vacuo, the residue dissolved in a mixture of water/dioxane (1:1, 7.5 mL/7.5 mL) and refluxed for 8 h. Then dioxane was removed under reduced pressure and the aqueous layer extracted with Ethyl acetate twice to afford the resulting 5-fluoro-3-hydroxyphthalide as white solid. (Yield = 495 mg, >99%). \(^6\)\(\text{HNMR (400 MHz, DMSO-}d_6\text{) } \delta 8.30 (d, J = 7.3 \text{ Hz, } 1\text{H}), 7.90 (dd, J_1 = 8.1, J_2 = 4.8 \text{ Hz, } 1\text{H}), 7.54 (dd, J_1 = 8.0, J_2 = 1.6 \text{ Hz, } 1\text{H}), 7.55-7.44 (m, 1\text{H}), 6.65 (d, J = 7.1 \text{ Hz, } 1\text{H}).\)

Mp and the obtained spectroscopic data were found in agreement with literature.\(^6\)

**General procedure for the synthesis of 2-formyl benzoate esters a-h**

\[
\begin{align*}
\text{K}_2\text{CO}_3 \text{ (0.6 eq.) and Benzyl Bromide or iodomethane (1.2 eq.) were added to a suspension of 3-} \text{ hydroxyphthalide (1.0 eq.) in DMF (0.5 M). The resulting mixture was stirred for 16-18 h. Then the mixture}
\end{align*}
\]

was extracted with Ethyl acetate and water and the resulting organic layer washed with brine. The organic layer was dried over Na\(_2\)CO\(_3\) and evaporated under vacuo. The mixture was directly purified by flash chromatography on silica gel (Hexane/Ethyl acetate, 5:1) to give the resulting 2-formylbenzoate esters a-h. All the compounds a, d, f, g are known. The \(^1\)H NMR spectra of the products are consistent with the literature data.\(^7\) The compounds c, e and h are new. Their complete spectroscopic data and copies of NMR spectra are reported as supplementary materials.
Benzyl 2-formylbenzoate. (a)
Following the general procedure using 6.7 mmol of the respective of 3-hydroxyphthalide, the title compound was obtained as a colorless oil in 87% yield (1.4 g).

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 10.60 (s, 1H), 7.99-7.96 (m, 1H), 7.93-7.90 (m, 1H), 7.63-7.58 (m, 2H), 7.44-7.34 (m, 5H), 5.40 (s, 2H).

Methyl 2-formylbenzoate. (a-1)
Following the general procedure using 5.0 mmol of the respective of 3-hydroxyphthalide, the title compound was obtained as a colorless oil in 95% yield (780 mg).

$^1$H NMR (CDCl$_3$, 300 MHz): $\delta$ 10.60 (s, 1H), 7.98-7.90 (m, 2H), 7.66-7.62 (m, 2H), 3.96 (s, 3H).

Benzyl 4-fluoro-2-formylbenzoate. (c)
Following the general procedure using 2.2 mmol of the respective of 3-hydroxyphthalide, the title compound was obtained as a colorless oil in 80% yield (454 mg).

$^1$H NMR: (400 MHz, CDCl$_3$): $\delta$ 10.66 (s, 1H), 8.08 (dd, $J_1= 5.5$ Hz, $J_2= 2.9$ Hz, 1H), 7.62 (dd, $J_1= 5.5$ Hz, $J_2= 2.9$ Hz, 1H), 7.46-7.28 (m, 6H), 5.41 (s, 2H).

$^{13}$C NMR: (75 MHz, CDCl$_3$): $\delta$ 190.9, 165.2, 140.3, 135.3, 133.7 ($J_{C,F}= 8.5$ Hz), 128.9, 119.9 ($J_{C,F}= 22.2$ Hz), 115.4 ($J_{C,F}= 22.2$ Hz), 67.9.

HRMS (ESI-FT ICR): m/z calcd for C$_{15}$H$_{11}$FO$_3$ [M+Na]$^+$ = 281.0595, found: 281.0578.

Benzyl 5-chloro-2-formylbenzoate. (d)
Following the general procedure using 3.0 mmol of the respective of 3-hydroxyphthalide, the title compound was obtained as a colorless oil in 94% yield (772 mg).

$^1$H NMR (CDCl$_3$, 400 MHz) $\delta$ 10.56 (s, 1H), 7.93 (d, $J = 2.0$ Hz, 1H), 7.86 (d, $J = 8.4$ Hz, 1H), 7.56 (dd, $J_1= 8.4$ Hz, $J_2= 2.0$ Hz, 1H), 7.44-7.35 (m, 5H), 5.39 (s, 2H).

Benzyl 4-bromo-2-formylbenzoate. (e)

Following the general procedure using 2.0 mmol of the respective of 3-hydroxyphthalide, the title compound was obtained as a colorless oil in 87% yield (555 mg).
\[ ^1H \text{NMR:} \ (300 \text{ MHz, CDCl}_3) \delta 10.61 \ (s, 1H), 8.03 \ (d, J= 2.2 \text{ Hz, 1H}), 7.88 \ (d, J= 7.2 \text{ Hz, 1H}), 7.73 \ (dd, J_1= 7.2 \text{ Hz, } J_2= 2.2 \text{ Hz, 1H}), 7.44-7.37 \ (m, 5H), 5.40 \ (s, 2H). \]

\[ ^{13}C \text{NMR:} \ (75 \text{ MHz, CDCl}_3) \delta 190.8, 165.4, 138.7, 135.9, 135.2, 131.6, 130.5, 128.9, 128.7, 127.9, 68.0. \]

**HRMS (MALDI-FT ICR):** m/z calcd for C_{15}H_{11}BrO_{3} [M+Na]^+ = 340.9789, found: 340.9781.

**Benzyl 2-formyl-5-methoxybenzoate. (f)**

Following the general procedure using 3.0 mmol of the respective of 3-hydroxyphthalide, the title compound was obtained as a colorless oil in 35% yield (283 mg).

\[ ^1H \text{NMR (CDCl}_3, 400 \text{ MHz) \delta 10.54 \ (s, 1H), 7.82 \ (d, J= 8.0 \text{ Hz, 1H}), 7.74 \ (s, 1H), 7.46-7.31 \ (m, 6H), 5.37 \ (s, 2H), 3.88 \ (s, 3H).} \]

**Benzyl 2-formyl-4-iodobenzoate. (g)**

Following the general procedure using 1.0 mmol of the respective of 3-hydroxyphthalide, the title compound was obtained as a colorless oil in 85% yield (311 mg).

\[ ^1H \text{NMR (CDCl}_3, 400 \text{ MHz) \delta 10.57 \ (s, 1H), 8.33 \ (d, J= 1.7 \text{ Hz, 1H}), 8.01 \ (dd, J_1= 8.2, J_2= 1.5 \text{ Hz, 1H}), 7.64 \ (d, J= 8.2 \text{ Hz, 1H}), 7.48-7.34 \ (m, 5H), 5.43 \ (s, 2H).} \]

**Benzyl 3-formyl-[1,1'-biphenyl]-4-carboxylate. (h)**

Following the general procedure using 1.0 mmol of the respective of 3-hydroxyphthalide, the title compound was obtained as colorless oil in 63% yield (200 mg).

\[ ^1H \text{NMR:} \ (300 \text{ MHz, CDCl}_3) \delta 10.73 \ (s, 1H), 8.17 \ (d, J= 1.9 \text{ Hz, 1H}), 8.10 \ (d, J= 6.9 \text{ Hz, 1H}), 7.85 (dd, J_1= 6.9 \text{ Hz, } J_2= 1.9 \text{ Hz, 1H}), 7.66-7.63 \ (m, 2H), 7.49-7.38 \ (m, 8H), 5.44 \ (s, 2H). \]

\[ ^{13}C \text{NMR:} \ (75 \text{ MHz, CDCl}_3) \delta 192.4, 166.1, 145.5, 138.8, 137.9, 135.5, 131.5, 131.2, 130.4, 129.3, 128.9, 128.8, 128.6, 127.4, 127.0, 67.8. \]

**HRMS (MALDI-FT ICR):** m/z calcd for C_{21}H_{16}O_{3} [M+Na]^+ = 339.0991, found: 339.1027.
General procedure for the synthesis of the α-amido sulfones derivatives 1a-1i.

\[
\text{R} = \text{Bn, Me}
\]
\[\text{R}_1 = \text{H, F, Cl, Br, OMe, I, Ph}\]
\[\text{Pg} = \text{Boc,Cbz}\]

2-formyl benzoate esters a-h (1.0 eq., using 2.2 mmol of aldehyde a, R= Bn, R₁ = H) and formic acid (210 µL) were added at room temperature to a rapidly stirred suspension of t-butyl- or benzyl- carbamate (1.0 eq., 2.2 mmol) and p-toluenesulfonic acid sodium salt (1.3 eq., 2.9 mmol) in methanol/water (2:1, 2.5 mL/1.25 mL). The reaction mixture was vigorously stirred for three days and then filtered. The resulting white solid was washed with water and diethyl ether and then dried in vacuo to yield the pure sulfone that was then used without further purification. For the other compounds the reactions were performed on 0.80-2.2 mmol range. Characterization of compounds is reported in the main text. Copies of the spectra are reported below.

**General procedure for the asymmetric synthesis of N-protected 3-substituted isoindolin-1 ones 3a-3h**

\[
\text{R} = \text{Bn, Me}
\]
\[\text{R}_1 = \text{H, F, Cl, Br, OMe, I, Ph}\]
\[\text{Pg} = \text{Boc,Cbz}\]

*Compounds employed as crude starting materials.

In an ACE tube, α-amido sulfones 1a-1i (1.0 eq., 0.08 mmol), K₂CO₃ (55 mg, 5.0 eq., 4 mmol), nitromethane (21 µL, 5.0 eq., 0.4 mmol) and organocatalyst II (20 mol%) were stirred in at -40° in toluene (0.4 mL) until starting material was all converted in the intermediate. Then, the reaction mixture was allowed to slowly warm up to room temperature and the stirring was continued until the intermediate disappeared (48 h).
mixture was directly purified by flash chromatography on silica gel (Hexane/Ethyl acetate, 5:1). Characterization of compounds is reported in the main text. Copies of the spectra are reported below.

**Racemic procedure for the synthesis of compound 3a and 3e**

α-amido sulfones 1a or 1e (1.0 eq., 0.08 mmol), K₂CO₃ (55 mg, 5.0 eq., 0.4 mmol) and nitromethane (21 µL, 5.0 eq., 0.4 mmol) were stirred at room temperature in toluene (0.4 mL) until starting material was all converted in the intermediate. Then, the reaction mixture was allowed to slowly warm up to room temperature and the stirring was continued for 72 h. Purification by flash chromatography on silica gel (Hexane/Ethyl acetate, 5:1) afforded the racemic products 3a (10.5 mg, 45%) and 3e (11.8 mg, 40%).

**Asymmetric synthesis of tert-butyl 1-(1-nitroethyl)-3-oxoisooindoline-2-carboxylate. (4)**

![Chemical structure of compound 4]

In an ACE tube, α-amido sulfone 1a (27 mg, 1.0 eq., 0.08 mmol), K₂CO₃ (55 mg, 5.0 eq., 0.4 mmol), nitroethane (28 µL, 5.0 eq., 0.4 mmol) and organocatalyst II (20 mol%) were stirred in at -40° in toluene (0.4 mL) until starting material was all converted in the intermediate. Then, the reaction mixture was allowed to slowly warm up to room temperature and the stirring was continued until the intermediate disappeared (96 h). Then, the mixture was directly purified by flash chromatography on silica gel (Hexane/Ethyl acetate, 7:3). Yield= 14 mg, 54%. Characterization of compounds is reported in the main text. Copies of the spectra are reported below.

**Racemic procedure for the synthesis of compound 4.**

α-amido sulfones 1a (27 mg, 1.0 eq., 0.08 mmol), K₂CO₃ (55 mg, 5.0 eq., 0.4 mmol) and nitroethane (28 µL, 5.0 eq., 0.4 mmol) were stirred at room temperature in toluene (0.4 mL) until starting material was all converted in the intermediate. Then, the reaction mixture was allowed to slowly warm up to room temperature and the stirring was continued until the intermediate disappeared (110 h). Purification by flash chromatography on silica gel (Hexane/Ethyl acetate, 7:3) gave the racemic product. Yield= 8 mg, 33%.
Crystallographic data

Crystals of compound 3e suitable for single crystal X-ray diffraction analysis were obtained dissolving 14 mg of the compound in a mixture of chloroform (0.3 mL) and hexane (0.1 mL) at room temperature. After the complete dissolution, the saturated solution was cooled down to -18°C. Crystals were obtained after few days. For the measurement, a colourless prismatic crystal of 0.34 mm x 0.21 mm x 0.07 mm was selected and mounted on a cryoloop with paratone oil.

Data collection was performed at room temperature with a Bruker D8 QUEST diffractometer equipped with a PHOTON II detector using CuKα radiation (λ = 1.54178 Å).

Data indexing, integration and reduction were performed using CrysAlisPro ver. 1.171.41.122a. Empirical absorption correction was performed with CrysAlisPro ver. 1.171.41.122a using spherical harmonics, implemented in SCALE3 ABSPACK scaling algorithm. The structure was solved using SHELXS-97 and refined through full matrix least-squares based on F^2 using the program SHELXL.

Non-hydrogen atoms were refined anisotropically, hydrogen atoms were positioned geometrically and included in structure factors calculations but not refined.

The chirality on carbon atom C2 (R) was successfully assigned by anomalous-dispersion effects in diffraction measurements on the crystal (Flack parameter -0.025(14)).

ORTEP diagrams (Figure S1) was drawn using OLEX2. In Table S1 are reported the crystallographic data.

Figure S1. ORTEP drawings for compound 3e. Atom types: C grey, H white, Br orange, O red, N blue. Ellipsoids are drawn at 20% probability level. CCDC 2143635 contains the supplementary crystallographic data, which can be accessed available free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/structures.
Table S1. Crystallographic data for compound 3e.

|                  | 3e              |
|------------------|-----------------|
| T (K)            | 296             |
| Formula          | C_{14}H_{15}BrN_{2}O_{5} |
| Formula weight   | 371.18          |
| System           | Orthorhombic    |
| Space group      | P_{2}1_{2}1_{2}1 |
| a (Å)            | 6.50468(9)      |
| b (Å)            | 7.19264(8)      |
| c (Å)            | 33.7877(4)      |
| a (°)            | 90              |
| β (°)            | 90              |
| γ (°)            | 90              |
| V (Å³)           | 1580.79(3)      |
| Z                | 4               |
| D_{x} (g cm⁻³)  | 1.560           |
| λ (Å)            | 1.54178         |
| μ (mm⁻¹)         | 3.779           |
| F_{000}          | 752.0           |
| R1 (I > 2σI)     | 0.0379(2719)    |
| χ R2             | 0.1024(2861)    |
| N. of param.     | 203             |
| Goof             | 1.069           |
| Flack parameter  | -0.025(14)      |
| ρ_{min}, ρ_{max} (eÅ³) | -0.51, 0.40   |
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Copies of $^1$H NMR and $^{13}$C NMR Spectra of intermediates and starting materials.
$^{1}H$ NMR (300 MHz, CDCl$_3$)

$^{13}C^{(1)}H$ NMR (75 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (75 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$)
$^{1}H$ NMR (300 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (75 MHz, CDCl$_3$)
$\text{H NMR (400 MHz, CDCl}_3$)

$\text{C}^{13}\text{H NMR (100 MHz, CDCl}_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

**Compound 1f**

$^1$H NMR (300 MHz, CDCl$_3$)

**Compound 1h**
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (75 MHz, CDCl$_3$)
Copies of $^1$H NMR, $^{13}$CNMR spectra and HPLC traces of enantioenriched isoindolin-1-ones 3a-3h
| RT (min) | Area (a.u.) | % Area | Height (a.u.) | % Height |
|---------|-------------|--------|--------------|---------|
| 1       | 13.445      | 1.78   | 12299        | 3.46    |
| 2       | 21.413      | 99.24  | 340045       | 68.52   |
| RT (min) | Area (a.u.) | % Area | Height (a.u.) | % Height |
| 1       | 14.964      | 98.39  | 410021       | 98.12   |
| 2       | 22.172      | 1.61   | 7878         | 1.86    |
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (75 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$)
$^{1}H$ NMR (300 MHz, CDCl$_3$)

$^{13}C(^1H)$ NMR (150 MHz, CDCl$_3$)
$^{1}H$ NMR (300 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (75 MHz, DMSO-$d_6$)
$^1$H NMR (400 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (100 MHz, CDCl$_3$)
$^1$H NMR (300 MHz, CDCl$_3$)

$^{13}$C($^1$H) NMR (75 MHz, CDCl$_3$)
IR spectra of selected compounds