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Organocatalyzed Petasis Reaction

Accessing New 5-α-(3,3-Disubstituted Oxindole)-Benzylamine Derivatives from Isatin: Stereoselective Organocatalytic Three Component Petasis Reaction

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Abstract: A one-step, three-component Petasis reaction of isatin derived 5-arylboronate-3-substituted oxindole derivatives with salicylaldehydes and secondary amines affords new enantiomerically pure structurally diverse 5-α-(3-substituted-oxindole)-benzylamine derivatives. The reaction shows good substrate and reagent scope affording the products with good to excellent yields (up to >99 % yield) and enantioselectivities (up to 99 % ee) using cheap and readily available (*R*)-BINOL as the organocatalyst. A diastereoselective version of the reaction was also developed where moderate yields (37 to 55 % yield), excellent enantioselectivities (up to 99 % ee) and good diastereoselectivities (up to 86 % de) were obtained for new 5-α-(3-hydroxy-oxindole)-benzylamine derivatives, having two stereocenters. The reaction is also feasible on gram-scale.

Introduction

The creation of new sustainable processes with high atom- and step-economy is currently a key objective for chemists. Multicomponent reactions, defined as one-pot processes that combine at least three reagents to give a single product containing essentially all the atoms of the starting materials, are increasingly appreciated as one the most efficient tools to rapidly access complex structural scaffolds, with step and process efficiency.[1] The number of drugs on the market and in clinical evaluation obtained by multicomponent processes has increased considerably over the last twenty years.[2] Examples are the calcium channel-blocker nifedipine,[3] the HIV drug indinavir (Crixivan®)[4] and the antiplatelet agent clopidogrel (Plavix®),[5] the world's second-highest-selling pharmaceutical in 2005. Like the two prior examples (see Figure 1), approximately 40 % of Active Pharmaceutical Ingredients (APIs) contain a chiral amine moiety, and this is the main reason why enantiomerically pure amines constitute an important class of chiral building blocks.[6]

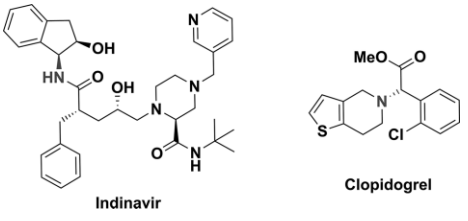

Figure 1. Representative examples of commercially available drugs possessing chiral amine moieties synthesized using multicomponent reactions.

Discovered in 1993, the Petasis reaction (PR), also known as the Petasis borono-Mannich reaction, is a three-component process involving the coupling of an aldehyde, an amine and a boronic acid to afford an amine-containing molecule.[7] It has been used very successfully for the synthesis of structurally diverse scaffolds and biologically interesting small molecules, including new catalysts and reagents. Asymmetric versions have also been developed.[8] In the case of these asymmetric versions most of the examples found in the literature involve the chiral-pool approach (asymmetric induction via chirality in the substrates). The use of a chiral catalyst or an auxiliary is a less common alternative.[8d,9] Schaus's group reported the first enantioselective and diastereoselective versions of the catalytic PR to access chiral α-amino acids, using chiral biphenols as catalysts, with styryl boronates, secondary amines and ethyl glyoxylates as reagents (Scheme 1(a)).[10] Shortly thereafter, Yuan's group found that chiral BINOL containing catalysts could efficiently catalyse the three-component Petasis reaction using salicylaldehydes, amines, and organoboronic acids, applying low reaction temperatures (Scheme 1(b)).[11] Despite all the elegant approaches to synthesize new families of oxindole-type derivatives,[12b–12d,13b–13c,14] very few examples using asymmetric methods are known. Nonetheless, one particular example comes from Zhang's group,[15a] who reported diastereoselective

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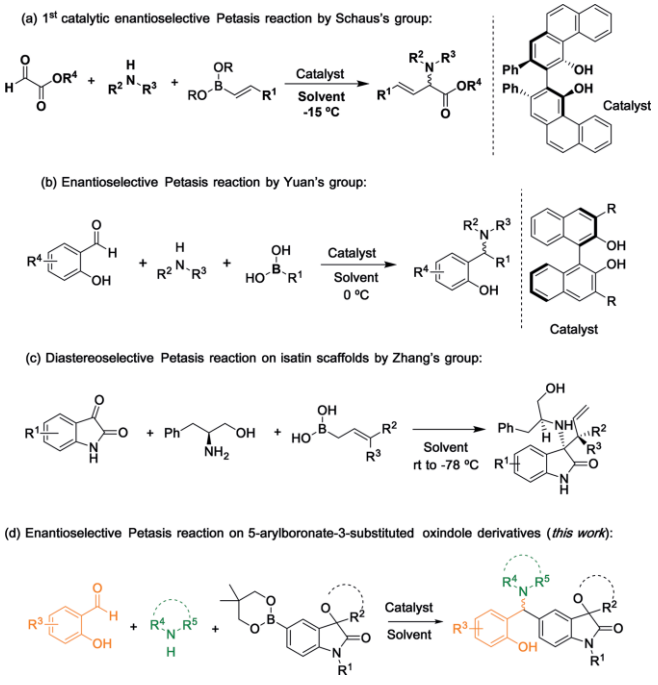
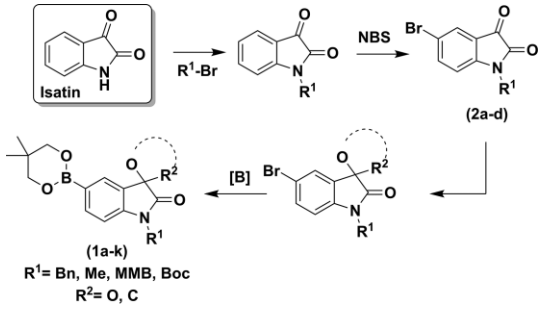
PRs using isatins, allylboronic acids and chiral amino alcohols (Scheme1(c)), and similar work reported by Huang's group,[15b] using *gem*-difluoroallylboronates.



Scheme 1. Petasis reactions affording chiral amine containing products.

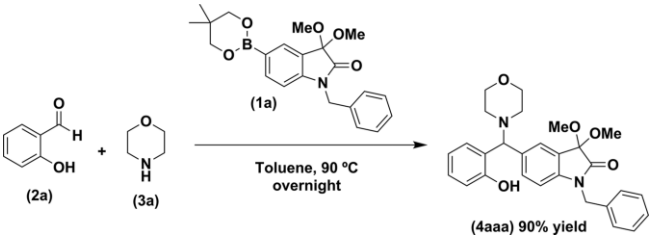
Over the last ten years we have been active in the synthesis of privileged heterocyclic scaffolds for application in medicinal chemistry,[12] mostly in the field of neurodegenerative diseases, like Alzheimer's disease.[13] We have focused particularly on 3,3-disubstituted oxindole derivatives[12b–12d,13b–13c] and aminodiarylmethane structural motifs[16] found in a variety of natural products and APIs.[6] The development of a novel PR by our group to give enantiomerically pure 5-α-(3-substituted-oxindole)-benzylamine derivatives (as shown Scheme 1(d)) leads to a new group of compounds with much potential in medicinal chemistry. A library of 5-arylboronate-3-substituted oxindole derivatives **(1a–k)** were obtained from cheap and commercially available isatin (Scheme 2, for further details see Supporting Information file).[12a,d,f,17,18]



Scheme 2. A 4-step synthesis of 5-arylboronate-3-substituted oxindole derivatives **(1a–k)**. [B]= borylation reaction; MMB= *meta*-methoxybenzyl.

Results and Discussion

Initially the 5-arylboronate-3-substituted oxindole derivative **(1a)**, salicylaldehyde **(2a)** (successfully applied in the PR due to the boron-activating hydroxyl group[8a,19]) and morpholine **(3a)** were selected as model reagents to explore and optimize the reaction conditions. We choose to use the 3-oxo acetal protected version, as the 5-arylboronate-non-protected 3-carbonyl group (that could potentially participate in this reaction as is the case of Zhang's methodology[15a] or in some Ugi 4-centre-3-component reactions[20]), failing to give the desired product. The corresponding racemic 5-α-(3,3-dimethoxy-substituted-oxindole)-benzylamine derivative **(4aaa)** was obtained in 90 % yield (Scheme 3).



Scheme 3. Initial PR using the 5-arylboronate-3-substituted oxindole derivative **(1a)**, salicylaldehyde **(2a)** and morpholine **(3a)**.

Motivated by this result we decided to optimize the reaction conditions and explore also the asymmetric version (Table 1). We decided to add 4Å activated molecular sieves (MS) in the reaction medium in order to improve the reaction rate and conversions.[19a] We started our screening tests using mild reaction conditions (CH_2Cl_2 as solvent, room temperature, absence of catalyst) and we noticed no formation of the desired product **(4aaa)** (Table 1, entry 1). A variety of organocatalysts were then investigated (see Supporting Information for further details); among them, (*R*)-BINOL[10a,10c,21] was used under the same reaction conditions and the product **(4aaa)** was obtained with a yield of 60 % and an excellent enantioselectivity (95 % ee, Table 1, entry 2). *L*-Proline and (*R*)-(–)-1,1′-binaphthyl-2,2′-diyl hydrogenphosphate ((*R*)-BNPPA) were also tested[22] but unfortunately led to significant decreases in both yield and enantioselectivity (Table 1, entries 3 and 4). We also noted a significant solvent effect. Upon screening several solvents, the best yields were obtained using THF and Me-THF (Table 1, entries 7 and 8) and moderate yields with 1,4-dioxane and dichloroethane (Table 1, entries 5 and 9, respectively). With regard to the enantioselectivity, curiously the best enantioselectivity was achieved using toluene as solvent (Table 1, entry 6), despite the moderate yield (this in fact could be an indication of key π–π interactions within the transition state complex during the crucial asymmetric induction step; see Scheme 6). This was followed by a study on the effect of temperature using Me-THF, a recognized green solvent[23] (Table 1, entries 14 to 16). We established 50 °C as the optimal temperature for this synthetic transformation (Table 1, entry 15, 17 and 18) and dichloromethane as the best solvent (Table 1, entry 17). We also looked at the effect of ligand loading on the reaction, by changing the quantity of ligand we observed no significant changes in the yield of **(4aaa)** (Table 1, entries 19 to 22). This was not true for the

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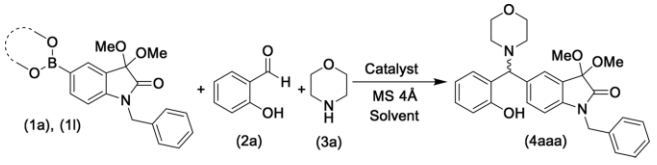
enantioselectivity, and we observed that 20 mol-% was the optimized loading (Table 1, entry 17).

Table 1. Optimization of reaction conditions.



Entry[a]	(1)	Catalyst	Solvent	Yield/%[b]	ee/%[c]
1	**(1a)**	–	CH_2Cl_2	0	–
2	**(1a)**	(*R*)-BINOL	CH_2Cl_2	60	95
3	**(1a)**	*L*-Proline	CH_2Cl_2	11	<5
4	**(1a)**	(*R*)-BNPPA	CH_2Cl_2	10	12
5	**(1a)**	(*R*)-BINOL	Dioxane	63	37
6	**(1a)**	(*R*)-BINOL	Toluene	48	86
7	**(1a)**	(*R*)-BINOL	THF	76	41
8	**(1a)**	(*R*)-BINOL	MeTHF	73	45
9	**(1a)**	(*R*)-BINOL	DCE	63	66
10	**(1a)**	(*R*)-BINOL	DME	35	36
11	**(1a)**	(*R*)-BINOL	CH_3CN	54	61
12	**(1a)**	(*R*)-BINOL	DMF	36	13
13	**(1a)**	(*R*)-BINOL	MeOH	55	20
14[d]	**(1a)**	(*R*)-BINOL	MeTHF	13	60
15[e]	**(1a)**	(*R*)-BINOL	MeTHF	95	53
16[f]	**(1a)**	(*R*)-BINOL	MeTHF	82	37
17[e]	**(1a)**	(*R*)-BINOL	CH_2Cl_2	85	81
18[e]	**(1a)**	(*R*)-BINOL	Toluene	85	69
19[e,g]	**(1a)**	(*R*)-BINOL	CH_2Cl_2	76	46
20[e,h]	**(1a)**	(*R*)-BINOL	CH_2Cl_2	77	70
21[e,i]	**(1a)**	(*R*)-BINOL	CH_2Cl_2	69	66
22[e,j]	**(1a)**	(*R*)-BINOL	CH_2Cl_2	77	87
23[e]	**(1l)**	(*R*)-BINOL	CH_2Cl_2	19	24
24	**(1l)**	(*R*)-BINOL	CH_2Cl_2	27	27

[a] Reaction conditions: **(1a)** (0.25 mmol), **(2a)** (0.25 mmol), **(3a)** (0.25 mmol), Catalyst (20 mol-%), 4Å MS (200 mg) and solvent (2 mL) were added to a Radley's® 12 position carousel reactor tube under a nitrogen atmosphere and stirred at room temperature for 24 hours. [b] Isolated yield. [c] Determined by chiral stationary phase HPLC (see Supporting Information for further details). [d] The reaction was performed at 0 °C. [e] The reaction was performed at 50 °C. [f] The reaction was performed at 85 °C. [g] 5 mol-% of (*R*)-BINOL was used. [h] 10 mol-% of (*R*)-BINOL was used. [i] 15 mol-% of (*R*)-BINOL was used. [j] 30 mol-% of (*R*)-BINOL was used.

To determine the reactivity effect of the boronic ester moiety on **(1)** we decided to synthesize the corresponding pinacol ester **(1l)** and screen it with morpholine **(3a)** and salicylaldehyde **(2a)** (Table 1, entry 23) using the previously optimized reaction conditions (Table 1, entry 17). A pronounced decrease in the reactivity and enantioselectivity of **(4aaa)** was observed, even testing the reaction at room temperature (Table 1, entry 24). Other amines were also tested using **(1l)** without promising results (see Supporting Information for further details). These studies demonstrated that the bulkier neopentyl-glycolate boronate was the boronic ester of choice. In fact, the pinacolboronate analogue is probably more stable and harder to cleave during the catalytic cycle (boronate cleavage is probably one of the rate-determining steps of this reaction, see Scheme 6).

We then studied the reaction scope by reacting 5-arylboronate-3-substituted oxindole derivatives **(1a–h)** with several aldehyde derivatives **(2)** and primary/secondary amines **(3)** using (*R*)-BINOL as catalyst (20 mol-% loading), dichloromethane as solvent, at 50° C during 24 h. The results can be seen in Scheme 4. We started by testing 5-arylboronate-3-substituted oxindole derivatives **(1a-d)** with salicylaldehyde **(2a)** and morpholine **(3a)** to evaluate the influence of the *N*-substituent in **(1)**. A significant drop in yield and enantioselectivity was noted when *N*-substituted methyl **(1b)**, MMB **(1c)** and Boc-protected **(1d)** groups were used (compare compounds **(4baa)**, **(4caa)** and **(4daa)** with **(4aaa)**, Scheme 4). Using **(1a)** and **(2a)** we decided to investigate the behaviour of the amine component **(3a–j)**. As expected,[11] the reaction failed when primary amines (like aniline **(3g)**, chiral (*R*)-(+)-α-methylbenzylamine **(3i)** and benzylamine **(3j)**) were used. There was also no reactivity when *N*-methylaniline **(3e)** and isopropylamine **(3h)** were used (see Supporting Information file for further details). Exploiting cyclic secondary amines **(3b-d)**, and also benzylmethylamine **(3f)**, the corresponding compounds **(4aab)**, **(4aac)**, **(4aad)** and **(4aaf)** were obtained in good to excellent yields and moderate enantioselectivities (Scheme 4). Exactly the same trend was observed when *N*-substituted cyclic acetals **(1e–h)** were used: showing the significant influence of *N*-substitution on the oxindole nitrogen (see compounds **(4eaa)**, **(4faa)** and **(4gaa)** in Scheme 4). Similar results concerning yield and enantioselectivity were obtained using cyclic secondary amines **(3c)** and **(3d)** and benzylmethylamine **(3f)**, with **(1e)** and **(2a)** (see Scheme 4, compounds **(4eac)**, **(4ead)** and **(4eaf)**). This finding may be a consequence of the basicity of the amine reagents, as the cyclic amines are more basic/nucleophilic than acyclic, on account of a more exposed nitrogen lone-pair orbital. Finally, using the 5-arylboronate-3-cyclic-acetal-oxindole derivative **(1e)** and morpholine **(3a)** we screened several aldehydes **(2)** (see Scheme 4 and Supporting Information file for further information). As expected, the reaction only works with salicylaldehyde derivatives **(2a–e)** (The phenol OH is required to complex with the transient boronate intermediate B as depicted in Scheme 6). No significant difference was noted using either electron-donating **(2d)** or -withdrawing **(2e)** substituents. Despite high enantioselectivity values being maintained (87 % ee), the yield decreased drastically when a substituted salicylaldehyde was used (see Scheme 4, compounds **(4eaa)**, **(4eda)** and **(4eea)**).

The structure of **(4aaa)** was unambiguously assigned by X-ray crystallography.[24] Unfortunately, the crystals were obtained as a racemic mixture and thus we were unable to unambiguously assign a stereochemical configuration to the major enantiomer (see section 2.2.3 of the Supporting Information file for further details and discussion). Moreover, we suspect that the racemate may have a higher lattice energy and be less soluble than either of the individual enantiomers.

In medicinal chemistry, it is generally observed that molecules with more than one stereogenic centre manifest significant biological activities. With an interest in forming derivatives of our products with more than one stereogenic centre and studying diastereoselective aspects of this reaction we decided to carry out the same reactions with chiral 3,3-aryl-hydroxy-oxindole derivatives.[12c] The chiral substrates **(1i–k)**[17b] (with one stereocenter) (see Supporting Information), salicylaldehyde **(2a)** and morpholine **(3a)** were tested in a putative diastereo-

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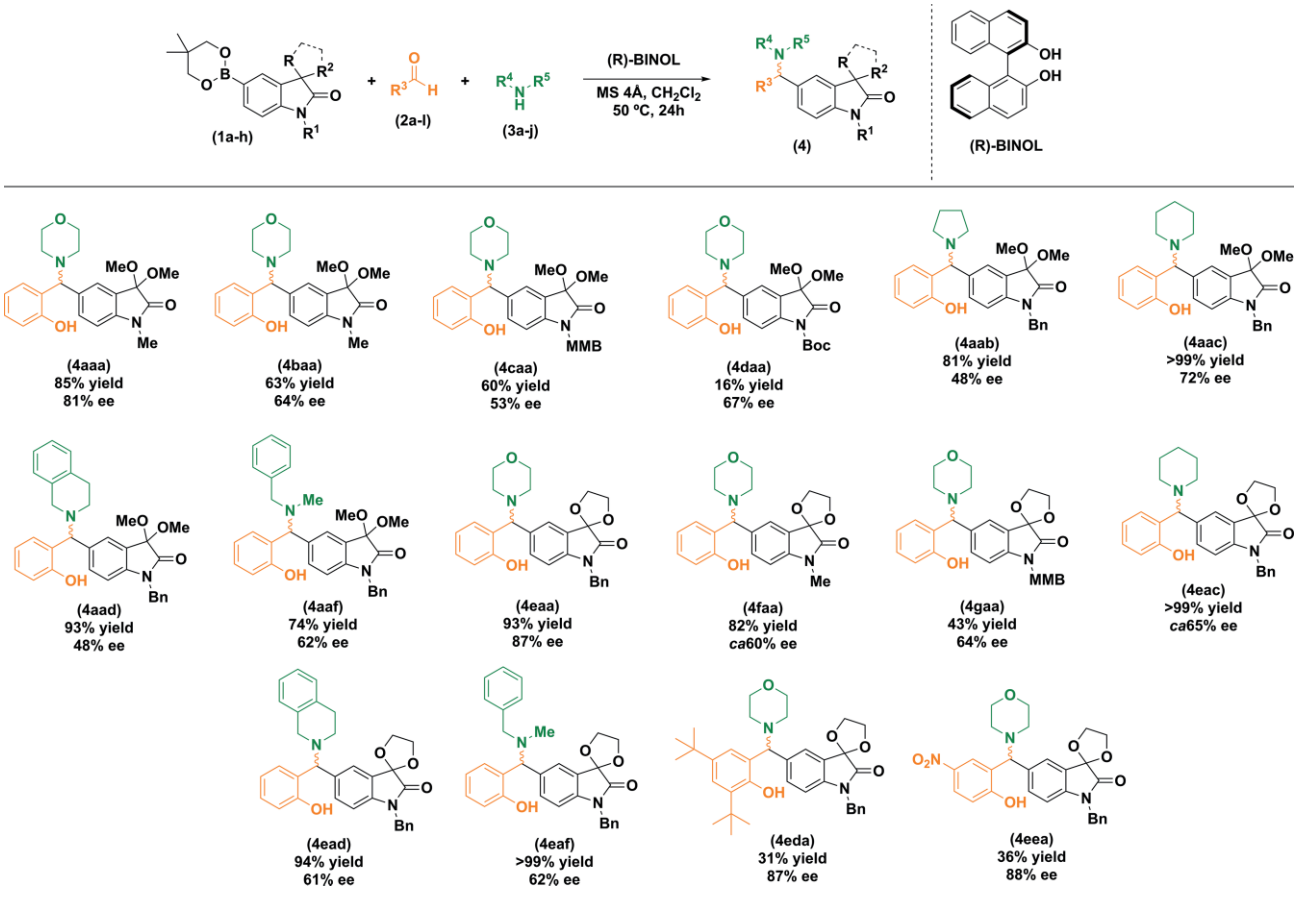
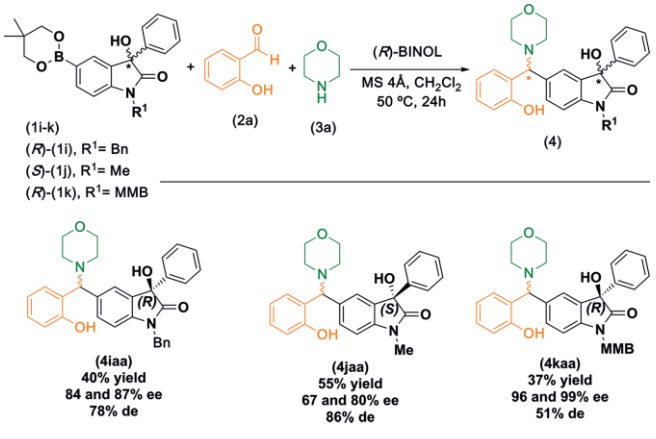


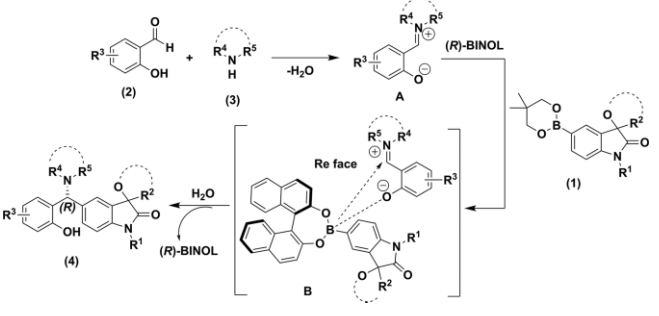
Scheme 4. Enantioselective PR between 5-arylboronate-3-substituted oxindole derivatives **(1a–h)**, aldehydes **(2a-l)** and amines **(3a–j)**; reaction scope.

selective PR. The results can be seen in Scheme 5. Gratifyingly, three new 5-α-(3-hydroxy-3-phenyl-oxindole)-benzylamine derivatives **(4iaa)**, **(4jaa)** and **(4kaa)** with two stereocenters were obtained. Despite the moderate yields, the enantioselectivities were very promising (best 99 % ee, Scheme 5) and the diastereoselectivities moderate to good (51 to 86 % de, Scheme 5). We found that when we used enantiomerically enriched starting boronic ester derivatives **(1i–k)** the diastereoselectivities significantly improved. For instance, when **(*S*)-(1j)** (with 86 % ee) was used, **(4jaa)** was obtained with 86 % de (Scheme 5). Moreover, when the reaction was conducted in the absence of (*R*)-BINOL the reaction was not diastereoselective and there was a noticeable decrease in both the enantioselectivity and yield. The same behaviour was observed when *rac*-**(1k)** was used (see further details in Supporting Information file).



Scheme 5. Diastereoselective PR using 5-arylboronate-3-oxindole derivatives **(1i–k)**.

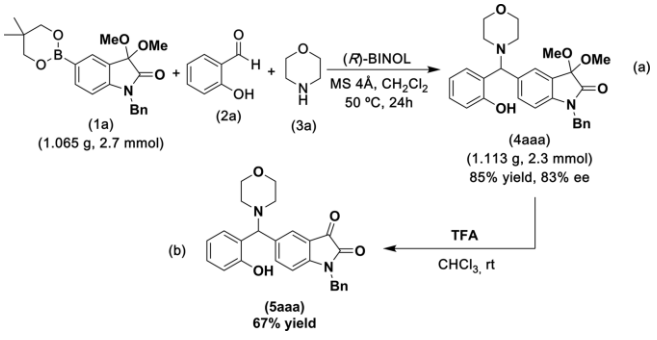
We propose the following mechanistic pathway which is based on Yuan's study[11] (Scheme 6). We suggest that the iminium intermediate **A** (Scheme 6) is formed from the nucleophilic addition of the amine **(3)** to salicylaldehyde **(2)**.[8,11] This is followed by exchange of the neopentyl-glycolate unit of **(1)** with (*R*)-BINOL to give intermediate **B**, that then undergoes nucleophilic attack on the *Re*-face of the iminium salt **A** affording the



Scheme 6. Proposed reaction mechanism for our (*R*)-BINOL catalysed PR.

desired product **(4)** with the *R*-configuration. Water would be essential for release (via hydrolysis) of the catalyst from the boron to start a new catalytic cycle, however, this still remains to be confirmed.[11]

Finally, two additional approaches were successfully made to highlight the synthetic value of the method (Scheme 7). The gram-scale preparation of **(4aaa)** was successfully conducted without any significant changes in yield and enantioselectivity (Scheme 7 (a)). Also, the 3-substituted oxo-acetal group of compound **(4aaa)** was successfully deprotected to give the corresponding isatin derivative **(5aaa)**, in 67 % yield, using trifluoroacetic acid under mild reaction conditions (Scheme 7 (b)).



Scheme 7. (a) Gram-scale preparation of **(4aaa)**; (b) deprotection of the 3-oxo acetal moiety of **(4aaa)** to give **(5aaa)**. TFA= trifluoroacetic acid.

Conclusions

In conclusion, we have developed an efficient novel enantio- and diastereoselective three-component Petasis Reaction (PR) using 5-arylboronate-3-substituted oxindole derivatives, salicylaldehydes, secondary amines and cheap and readily available chiral (*R*)-BINOL as catalyst. The reaction shows good scope, giving excellent yields (up to >99 %) and enantioselectivities (up to 98 % ee). A diastereoselective version using chiral 5-arylboronate-3-oxindole derivatives **(1i–k)** was also tested, and although the yields were only moderate (up to 55 %), excellent enantioselectivities (up to 99 % ee) and good diastereoselectivities (up to 86 % de) were obtained.

Experimental Section

General Remarks: Reagents were obtained from Sigma–Aldrich, Acros, Strem and Alfa Aesar and were used as received. The solvents used were dried using current laboratory techniques.[25] Petasis Reactions (PR) were conducted in a Radley's® 12-position carousel reactor under a nitrogen atmosphere or in round-bottom flasks. The 4Å molecular sieves (1–2 mm, 0.04–0.08 in were obtained from Alfa Aesar (used as received). Column chromatography was carried out on silica gel (Carlo Erba, 40–63 μm, 60Å). Thin-layer chromatography (TLC) was carried out on aluminum-backed Kieselgel 60 F254 plates (Merck and Machery Nagel). Plates were visualized either by UV light or with phosphomolybdic acid in ethanol. Melting points (m.p.) were determined with a Barnstead Electothermal 9100 apparatus and are uncorrected. NMR spectra were recorded with a Bruker Avance III instrument (400 MHz). The chemical shifts (δ) were quoted in parts per million (ppm) with respect to the solvent ($CDCl_3$, ^1H: δ = 7.26 ppm, ^{13}C: δ = 77.2 ppm; [D_6]DMSO, ^1H: δ = 2.50 ppm, ^{13}C: δ = 39.5 ppm). Coupling constants (*J*) are reported in Hz and refer to apparent peak multiplicities. Splitting patterns are reported as s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quadruplet; m, multiplet; br, broad. Mass spectra (MS) were recorded with a quadrupole mass spectrometer Waters ZQ4000. The ionization was performed by ESI and the samples were infused in methanol. Infra-red (IR) spectroscopy analysis measurements were performed on a Perkin Elmer Spectrum Two FT-IR Spectrometer with an ATR (Attenuated Total Reflectance) accessory. High-performance liquid chromatographic (HPLC) analysis was carried out with a Hitachi Primaide instrument, equipped with a 1410 series UV detector and an Agilent 1100 series instrument. Daicel Chiralpak AD-H column was used as stationary phase, *n*-hexane/*i*-propanol as mobile phase and 254 nm was used as wavelength in the UV light detector. An Oxford Diffraction Xcalibur system was used to collect X-ray diffraction data at room temperature using MoK_α radiation. ETG = Ethylene glycol; B_2NPG_2 = bis(neopentyl glycolato)diboron; MMB= *meta*-methoxybenzyl group; Boc= *tert*-butyloxycarbonyl group.

Synthesis of the Precursors for 5-Arylboronate-3,3-disubstituted-oxindole Derivatives (1a–k)

Synthesis of the 5-Br-*N*-Substituted Isatin Derivatives.

5-Bromoindoline-2,3-dione:[26a] In a round-bottom flask was added isatin (3 g, 20 mmol) and AcOH (41 mL) and the mixture was stirred at room temperature. Br_2 (1.1 mL, 22 mmol, 1.1 equiv.) was added in one portion and the mixture was left stirring at reflux temperature (oil bath, 120 °C) overnight. The reaction mixture was cooled down to room temperature and the precipitate washed with EtOH. After being well dried 5-bromoindoline-2,3-dione (3.66 g, 70 % yield) was obtained as an orange solid. ^1H NMR ([D_6]DMSO, 400 MHz): δ_H = 6.86–6.88 (d, *J* = 6 Hz, 1H), 7.65 (s, 1H), 7.72–7.74 (d, *J* = 8 Hz, 1H), 11.13 (s br, 1H).

1-Benzyl-5-bromoindoline-2,3-dione:[26b,26c] In a round-bottom flask was added 5-bromoindoline-2,3-dione (4.54 g, 20 mmol), CH_3CN (80 mL), K_2CO_3 (8.3 g, 60 mmol, 3 equiv.) and BnBr (2.4 mL, 20 mmol, 1 equiv.). The mixture was left stirring at 50 °C in an oil bath, overnight. After cooling down, the solvent was evaporated under reduced pressure and 50 mL of CH_2Cl_2 and 50 mL of H_2O was added to the crude solid mixture and extracted. The aqueous phase was washed with CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The corresponding 1-benzyl-5-bromoindoline-2,3-dione (5.95 g, 94 % yield) was obtained as an orange solid. ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 4.92 (s, 2H), 6.66–6.68 (d, *J* = 8 Hz, 1H), 7.30–7.36 (m, 5H), 7.57–7.59 (dd, *J* = 8 Hz, 1H), 7.71 (s, 1H); or: In a round-bottom flask was added 1-benzylindoline-2,3-dione (7.73 g, 32.6 mmol), CH_3CN (120 mL), NH_4OAc (276 mg, 3.59 mmol, 0.11 equiv.) and NBS (6.37 g, 35.9 mmol, 1.1 equiv.). The mixture was left stirring at room temperature overnight. After that the solvent was evaporated under reduced pressure and the crude mixture diluted with AcOEt (100 mL) and washed with brine (2 × 50 mL). The organic layer was dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford 1-benzyl-5-bromoindoline-2,3-dione (8.91 g, 86 % yield) as an orange solid.

1-Benzylindoline-2,3-dione:[26b] In a round-bottom flask was added isatin (5.0 g, 34 mmol), CH_3CN (100 mL), K_2CO_3 (14.09 g, 102 mmol, 3 equiv.) and BnBr (4.04 mL, 34 mmol, 1 equiv.). The mixture was left stirring at 50 °C in an oil bath, overnight. After cooling down, the solvent was evaporated under reduced pressure and 80 mL of CH_2Cl_2 and 80 mL of H_2O were added to the crude

solid mixture and extracted. The aqueous phase was washed with CH_2Cl_2 (2 × 50 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The corresponding 1-benzylindoline-2,3-dione (7.72 g, 88 % yield) was obtained as an orange solid. ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 4.93 (s, 3H), 6.77–6.79 (d, *J* = 8 Hz, 1H), 7.07–7.10 (t, *J* = 8 Hz, 1H), 7.30–7.34 (m, 5H), 7.46–7.50 (t, *J* = 8 Hz, 1H), 7.59–7.61 (d, *J* = 8 Hz, 1H).

5-Bromo-1-methylindoline-2,3-dione:[12b,26c] NaH (451 mg, 60 wt.-% in mineral oil, 11 mmol, 1.5 equiv.) was added portion-wise to a solution of 5-bromoindoline-2,3-dione (1.70 g, 7.5 mmol) in THF (70 mL) at 0 °C and the resulting mixture was stirred for 1 h at room temperature. CH_3I (0.7 mL, 11 mmol, 1.5 equiv.) was added and the mixture was stirred at 50 °C in an oil bath, overnight. After cooling to room temperature, the solvent was evaporated under reduced pressure and the reaction mixture was diluted with AcOEt and washed with H_2O. The organic layer was dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford 5-bromo-1-methylindoline-2,3-dione (0.53 g, 30 % yield) as an orange solid. ^1H NMR($CDCl_3$, 400 MHz): δ_H = 3.25 (s, 3H), 6.80–6.82 (d, *J* = 8 Hz, 1H), 7.71–7.75 (m, 2H); or: In a round-bottom flask was added 1-methylindoline-2,3-dione (2.44 g, 15 mmol), CH_3CN (70 mL), NH_4OAc (127.2 mg, 1.65 mmol, 0.11 equiv.) and NBS (2.93 g, 16.5 mmol, 1.1 equiv.). The mixture was left stirring at room temperature overnight. After that the solvent was evaporated under reduced pressure and the crude mixture diluted with AcOEt (80 mL) and washed with brine (2 × 30 mL). The organic layer was dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford 5-bromo-1-methylindoline-2,3-dione (2.96 g, 82 % yield) as an orange solid.

1-Methylindoline-2,3-dione:[26d] In a round-bottom flash were added isatin (5.0 g, 34 mmol), K_2CO_3 (11.7 g, 85 mmol, 2.5 equiv.), DMF (35 mL) and CH_3I (3.2 mL, 51 mmol, 1.5 equiv.). The mixture was left stirring at room temperature overnight. After that H_2O (50 mL) was added to the reaction flask. The mixture was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases washed with brine (50 mL). The organic layers were dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford 1-methylindoline-2,3-dione (5.79 g, 94 % yield) as an orange solid. ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 3.24 (s, 3H), 6.88–6.90 (d, *J* = 8 Hz, 1H), 7.10–7.14 (t, *J* = 8 Hz, 1H), 7.58–7.62 (m, 2H).

1-(3-Methoxybenzyl)indoline-2,3-dione:[26e] In a round-bottom flask was added isatin (2.0 g, 14 mmol), CH_3CN (50 mL), K_2CO_3 (5.8 g, 42 mmol, 3 equiv.) and MMBBr (2.0 mL, 14 mmol, 1 equiv.). The mixture was left stirring at 50 °C in an oil bath, overnight. After cooling down, the solvent was evaporated under reduced pressure and 50 mL of CH_2Cl_2 and 50 mL of H_2O were added to the crude solid mixture and extracted. The aqueous phase was washed with CH_2Cl_2 (2 × 30 mL). The combined organic phases were dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The corresponding 1-(3-methoxybenzyl)indoline-2,3-dione (3.56 g, 90 % yield) was obtained as an orange solid. ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 3.77 (s, 3H), 4.89 (s, 2H), 6.78–6.86 (m, 3H), 6.90–6.92 (d, *J* = 8 Hz, 1H), 7.07–7.11 (t, *J* = 8 Hz, 1H), 7.24–7.28 (t, *J* = 8 Hz, 1H), 7.46–7.50 (t, *J* = 8 Hz, 1H), 7.54–7.61 (d, *J* = 8 Hz, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 44.1, 55.4, 111.2, 113.3, 113.4, 117.7, 119.7, 123.99, 125.5, 130.2, 136.2, 138.5, 150.8, 158.3, 160.2, 183.3.

5-Bromo-1-(3-methoxybenzyl)indoline-2,3-dione: In a round-bottom flask was added 1-(3-methoxybenzyl)indoline-2,3-dione (3.56 g, 13.3 mmol), CH_3CN (70 mL), NH_4OAc (113 mg, 1.46 mmol, 0.11 equiv.) and NBS (2.60 g, 14.6 mmol, 1.1 equiv.). The mixture was left stirring at room temperature overnight. After that the solvent was evaporated under reduced pressure and the crude mixture diluted with AcOEt (80 mL) and washed with brine (2 × 30 mL). The organic layer was dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure to afford 5-bromo-1-(3-methoxybenzyl)indoline-2,3-dione (4.09 g, 89 % yield) as an orange solid. ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 3.69 (s, 3H), 4.99 (s, 2H), 6.72–6.78 (m, 3H), 7.11–7.14 (t, 1H), 7.48–7.51 (m, 2H), 7.63–7.65 (d, *J* = 8 Hz, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 44.2, 55.7, 111.3, 113.1, 114.3, 114.9, 117.8, 124.3, 125.6, 133.9, 134.5, 138.7, 150.6, 158.6, 159.6, 183.1.

***tert*-Butyl 5-Bromo-2,3-dioxoindoline-1-carboxylate:**[26f] In a round-bottom flask were added 5-Bromoindoline-2,3-dione (3.72 g, 16 mmol), THF (30 mL) and DMAP (196 mg, 1.6 mmol, 0.1 equiv.) and the mixture was stirred at 0 °C. $(Boc)_2O$ (4.19 g, 19.2 mmol, 1.2 equiv.) in 10 mL of THF was added slowly to the substrate solution. The reaction mixture was left stirring at room temperature overnight. The solvent was evaporated under reduced pressure and the crude mixture diluted with AcOEt (50 mL) and washed with H_2O (2 × 30 mL). The organic layer was dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by silica gel flash chromatography using hexane/AcOEt (5:1) and (1:1) as eluents. The corresponding *tert*-butyl 5-bromo-2,3-dioxoindoline-1-carboxylate was obtained (407.3 mg, 8 % yield) as a pale-yellow solid. ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 1.53 (s, 9H), 7.68–7.71 (m, 1H), 8.08–8.09 (m, 1H), 8.41–8.43 (d, *J* = 8 Hz, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 28.3, 82.1, 113.8, 118.3, 121.2, 135.9, 139.8, 142.7, 152.7, 163.8, 187.9.

Synthesis of the 5-Br-*N*-Substituted-3,3-disubstituted-oxindole Derivatives

3,3-OMe Acetal Derivatives.

General Procedure:[26g] In a round-bottom flask was added 1-substituted-5-bromoindoline-2,3-dione, MeOH, *p*TsOH (20 mol-%), and trimethyl orthoformate (TMOF, 5.2 equiv.) and the reaction stirred at 70 °C in an oil bath, overnight. The reaction was cooled down to room temperature and the MeOH evaporated under reduced pressure. The crude product was purified by silica gel flash chromatography using hexane/AcOEt (9:1), (5:1) and (1:1) as eluents.

1-Benzyl-5-bromo-3,3-dimethoxyindolin-2-one: 1-Benzyl-5-bromoindoline-2,3-dione (500 mg, 1.6 mmol), MeOH (30 mL), *p*TsOH (61 mg, 0.32 mmol, 20 mol-%), and TMOF (1.0 mL, 8.3 mmol, 5.2 equiv.) were used. The corresponding 1-benzyl-5-bromo-3,3-dimethoxyindolin-2-one was obtained as a pale orange solid (0.58 g, >99 % yield). ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 3.60 (s, 6H), 4.85 (s, 2H), 6.56–6.58 (d, *J* = 8 Hz, 1H), 7.24–7.37 (m, 6H), 7.53 (s, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 43.6, 51.1, 96.9, 111.5, 115.7, 127.0, 127.3, 128.0, 128.1, 129.1, 133.4, 134.9, 141.5, 170.4.

5-Bromo-3,3-dimethoxy-1-methylindolin-2-one: 5-Bromo-1-methylindoline-2,3-dione (500 mg, 2.1 mmol), MeOH (30 mL), *p*TsOH (80 mg, 0.42 mmol, 20 mol-%), and TMOF (1.2 mL, 11.0 mmol, 5.2 equiv.) were used. The corresponding 5-bromo-3,3-dimethoxy-1-methylindolin-2-one was obtained as a pale orange solid (378.6 mg, 61 % yield). ^1H NMR ($CDCl_3$, 400 MHz) δ_H: = 3.15 (s, 3H), 3.56 (s, 6H), 6.71–6.73 (d, *J* = 8 Hz, 1H), 7.49–7.52 (m, 2H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 26.1, 51.0, 96.8, 110.4, 115.6, 126.9, 128.0, 133.6, 142.5, 170.2.

5-Bromo-3,3-dimethoxy-1-(3-methoxybenzyl)indolin-2-one: 5-bromo-1-(3-methoxybenzyl)indoline-2,3-dione (4.09 g, 12 mmol), MeOH (70 mL), *p*TsOH (476 mg, 2.4 mmol, 20 mol-%), and TMOF (6.8 mL, 62.4 mmol, 5.2 equiv.) were used. The corresponding 5-bromo-3,3-dimethoxy-1-(3-methoxybenzyl)indolin-2-one was ob-

tained as a pale orange solid (3.99 g, 85 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ_H: = 3.61 (s, 6H), 3.64 (s, 3H), 4.92 (s, 2H), 6.61–6.62 (m, 1H), 6.66–6.69 (m, 2H), 7.06–7.09 (t, 1H), 7.24–7.28 (t, *J* = 8 Hz, 1H), 7.42–7.46 (m, 2H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 43.5, 51.1, 55.4, 97.3, 110.0, 113.1, 113.5, 114.9, 123.1, 124.9, 124.9, 130.9, 133.7, 135.2, 142.2, 159.5, 171.1.

***tert*-Butyl 5-Bromo-3,3-dimethoxy-2-oxoindoline-1-carboxylate:** *tert*-Butyl 5-bromo-2,3-dioxoindoline-1-carboxylate (407.3 mg, 1.2 mmol), MeOH (30 mL), *p*TsOH (48 mg, 0.24 mmol, 20 mol-%), and TMOF (0.7 mL, 6.24 mmol, 5.2 equiv.) were used. The corresponding *tert*-butyl 5-bromo-3,3-dimethoxy-2-oxoindoline-1-carboxylate was not obtained with this procedure, but 5-bromo-3,3-dimethoxyindolin-2-one was obtained as an orange solid (225.1 mg, 69 % yield) (deprotection of the Boc group). We used this compound (5-bromo-3,3-dimethoxyindolin-2-one, 225.1 mg, 0.83 mmol) along with DMAP (10.1 mg, 0.083 mmol, 0.1 equiv.), THF (15 mL) and $(Boc)_2O$ (216 mg, 1.0 mmol, 1.2 equiv.) to obtain the corresponding *tert*-butyl 5-bromo-3,3-dimethoxy-2-oxoindoline-1-carboxylate as a pale orange oil (229.2 mg, 74 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 1.62 (s, 9H), 3.53 (s, 6H), 7.52–7.56 (m, 2H), 7.81–7.83 (d, *J* = 8 Hz, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 28.2, 51.2, 85.2, 117.5, 117.7, 126.2, 127.9, 133.9, 138.7, 148.9, 168.2.

3,3-(1,3-Dioxolane) Derivatives.

General Procedure:[26c] In a round-bottom flask was added 1-substituted-5-bromoindoline-2,3-dione, toluene, *p*TsOH (0.05 equiv.) and ethylene glycol (ETG, 20 equiv.) and the reaction stirred at 120 °C in an oil bath, overnight. The reaction was cool down to room temperature and the toluene evaporated under reduced pressure. The crude mixture was diluted with CH_2Cl_2 and washed with $NaHCO_3$ aq. sat. solution. The organic layer was dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by silica gel flash chromatography using hexane/AcOEt (1:1) as eluent.

1-Benzyl-5-bromospiro[indoline-3,2′-[1,3]dioxolan]-2-one: 1-Benzyl-5-bromoindoline-2,3-dione (2.62 g, 8.3 mmol), toluene (50 mL), *p*TsOH (80 mg, 0.41 mmol, 0.05 equiv.) and ETG (9.3 mL, 166 mmol, 20 equiv.) were used. The corresponding 1-benzyl-5-bromospiro[indoline-3,2′-[1,3]dioxolan]-2-one was obtained as a white solid (1.75 g, 58 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 4.33–4.36 (m, 2H), 4.60–4.63 (m, 2H), 4.80 (s, 2H), 6.51–6.53 (d, *J* = 8 Hz, 1H), 7.24–7.36 (m, 6H), 7.49 (s, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 43.6, 66.2, 101.9, 111.4, 116.1, 126.1, 127.3, 128.0, 128.3, 129.1, 134.4, 134.8, 142.9, 172.9.

5-Bromo-1-methylspiro[indoline-3,2′-[1,3]dioxolan]-2-one:[26c] 5-Bromo-1-methylindoline-2,3-dione (1.26 g, 5.3 mmol), toluene (30 mL), *p*TsOH (50.4 mg, 0.26 mmol, 0.05 equiv.) and ETG (5.9 mL, 106 mmol, 20 equiv.) were used. The corresponding 5-bromo-1-methylspiro[indoline-3,2′-[1,3]dioxolan]-2-one was obtained as a white solid (1.23 g, 82 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 3.10 (s, 3H), 4.26–4.35 (m, 2H), 4.52–4.60 (m, 2H), 6.66–6.68 (d, *J* = 8 Hz, 1H), 7.47–7.50 (m, 3H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 26.0, 66.1, 101.8, 110.3, 115.9, 126.0, 128.2, 134.5, 143.8, 172.8.

5-Bromo-1-(3-methoxybenzyl)spiro[indoline-3,2′-[1,3]dioxolan]-2-one: 5-Bromo-1-(3-methoxybenzyl)indoline-2,3-dione (1.5 g, 4.3 mmol), toluene (30 mL), *p*TsOH (41 mg, 0.21 mmol, 0.05 equiv.) and ETG (4.8 mL, 86 mmol, 20 equiv.) were used. The corresponding 5-bromo-1-(3-methoxybenzyl)spiro [indoline-3,2′-[1,3]dioxolan]-2-one was obtained as a pale orange solid (1.32 g, 77 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 3.65 (s, 3H), 4.34–4.37 (m, 2H), 4.61–4.64 (m, 2H), 4.87 (s, 2H), 6.62–6.70 (m, 3H), 7.06–7.10 (t, *J* = 8 Hz, 1H), 7.25–7.29 (m, 1H), 7.39–7.40 (d, *J* = 8 Hz, 1H), 7.45–7.47 (d, *J* = 8 Hz, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 43.5, 55.5, 66.0, 102.4, 109.8, 112.9, 113.6, 114.8, 123.7, 123.9, 124.9, 131.9, 133.6, 135.1, 143.6, 159.4, 173.7.

5-Bromospiro[indoline-3,2′-[1,3]dioxolan]-2-one:[26h] 5-Bromoindoline-2,3-dione (1.0 g, 4.4 mmol), toluene (30 mL), *p*TsOH (42 mg, 0.22 mmol, 0.05 equiv.) and ETG (4.9 mL, 88 mmol, 20 equiv.) were used. The corresponding 5-bromospiro[indoline-3,2′-[1,3]dioxolan]-2-one was obtained as a pale orange solid (0.70 g, 54 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 4.28–4.36 (m, 2H), 4.50–4.56 (m, 2H), 6.72–6.74 (*d*, *J* = 8 Hz, 1H), 7.41–7.46 (m, 2H), 8.69 (sbr, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 66.1, 102.1, 112.5, 115.9, 126.5, 128.6, 134.5, 140.9, 175.4.

***tert*-Butyl 5-Bromo-2-oxospiro[indoline-3,2′-[1,3]dioxolane]-1-carboxylate:** 5-Bromospiro[indoline-3,2′-[1,3]dioxolan]-2-one (0.70 g, 2.6 mmol), DMAP (32 mg, 0.26 mmol, 0.1 equiv.), THF (25 mL) and $(Boc)_2O$ (680 mg, 3.12 mmol, 1.2 equiv.) were used to obtained the corresponding *tert*-butyl 5-bromo-2-oxospiro[indoline-3,2′-[1,3]dioxolane]-1-carboxylate as a pale orange oil (0.88 g, 92 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 1.61 (s, 9H), 4.31–4.35 (m, 2H), 4.54–4.58 (m, 2H), 7.53–7.55 (m, 2H), 7.79–7.81 (d, *J* = 8 Hz, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 28.1, 66.4, 85.1, 100.9, 117.5, 118.1, 125.1, 128.1, 134.9, 140.1, 148.8, 170.9.

3-OH-3-Aryl Derivatives

General Procedure (Racemic Reaction): Method A:[26i] In a Radley's® 12 position carousel reactor tube under a nitrogen atmosphere was added $Rh_2(OAc)_4$ (1.0 mol-%), $HPCy_3{\cdot}BF_4$ (2.5 mol-%), the corresponding 5-Br-*N*-substituted isatin derivative, $PhB(OH)_2$ (1.1 equiv.), K_2CO_3 (5.0 mol-%) and DME/H_2O (1:1). The reaction was left stirring at 90 °C for 18 h. AcOEt and H_2O were added to the reaction mixture and extracted. The organic layer was dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by silica gel flash chromatography using hexane/AcOEt (5:1) as eluent.

Method B: In a Radley's® 12 position carousel reactor tube under nitrogen atmosphere was added $[Rh(COD)Cl]_2$ (5.0 mol-%), $HPCy_3{\cdot}BF_4$ (10 mol-%), the corresponding 5-Br-*N*-substituted isatin derivative, $PhB(OH)_2$ (2 equiv.), K_2CO_3 (3 equiv.) and toluene. The reaction was left stirring at 80 °C for 18 h. After evaporation of the solvent, the crude product was purified by silica gel flash chromatography using $CHCl_3$/AcOEt (5:1) as eluent.

General Procedure (Chiral Reaction):[12c] In a round-bottom flask under a nitrogen atmosphere $Rh(acac)(C_2H_4)_2$ (3 mol-%), (*R*) or (*S*)-BINAP (6 mol-%) and CH_2Cl_2 (1 mL) were added. The mixture was stirred at room temperature for 1 h, then the solvent was removed on a rotary evaporator. Under a nitrogen atmosphere the following reagents were added sequentially: 5-Br-*N*-substituted isatin derivative, $PhB(OH)_2$ (2 equiv.), MeOH (2 mL) and DIPEA (0.5 equiv.). The mixture was stirred at 60 °C in an oil bath, during 18 h. After evaporation of the solvent, the crude product was purified by silica gel flash chromatography using $CHCl_3$/AcOEt (5:1) as eluent.

1-Benzyl-5-bromo-3-hydroxy-3-phenylindolin-2-one:[26j] **Racemic: Method A:** $Rh_2(OAc)_4$ (14.2 mg, 0.032 mmol, 1.0 mol-%), $HPCy_3{\cdot}BF_4$ (29.4 mg, 0.08 mmol, 2.5 mol-%), 1-benzyl-5-bromoindoline-2,3-dione (1.0 g, 3.2 mmol), $PhB(OH)_2$ (424.2 mg, 3.52 mmol, 1.1 equiv.), K_2CO_3 (22.2 mg, 0.16 mmol, 5.0 mol-%) and DME/H_2O (1:1) (14 mL) were used to obtain the corresponding *rac*-1-benzyl-5-bromo-3-hydroxy-3-phenylindolin-2-one (0.76 g, 57 % yield) as pale yellow foamy solid. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 3.49 (s, 1H), 4.81–4.85 (d, *J* = 16 Hz, 1H), 5.00–5.04 (d, *J* = 16 Hz, 1H), 6.64–6.66 (d, *J* = 8 Hz, 1H), 7.28–7.40 (m, 12H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 44.3, 78.1, 111.4, 116.4, 125.3, 127.4, 128.1, 128.4,

128.7, 128.9, 129.1, 132.7, 133.7, 135.0, 135.8, 139.6, 141.6, 177.3. **HPLC:** Daicel Chiralpak AD-H column, *n*-hexane/2-propanol (85:15), 0.6 mL/min, 254 nm, retention times: 27.060 min and 37.173 min.

Chiral: $Rh(acac)(C_2H_4)_2$ (5.0 mg, 0.019 mmol, 3 mol-%), (*S*)-BINAP (24 mg, 0.038 mmol, 6 mol-%), CH_2Cl_2 (1 mL), 1-benzyl-5-bromo-indoline-2,3-dione (200 mg, 0.63 mmol), $PhB(OH)_2$ (154 mg, 1.3 mmol, 2 equiv.), MeOH (2 mL) and DIPEA (0.06 mL, 0.32 mmol, 0.5 equiv.) were used to obtain the corresponding (*R*)-1-benzyl-5-bromo-3-hydroxy-3-phenylindolin-2-one (275.9 mg, 94 % yield, 81 % ee). **HPLC:** Daicel Chiralpak AD-H column AD-H column, *n*-hexane/2-propanol (85:15), 0.6 mL/min, 254 nm, retention times: 28.273 min (major, (*R*)) and 38.613 min (minor, (*S*)). The assigned stereochemical configuration was based on literature precedent.[12c]

5-Bromo-3-hydroxy-1-methyl-3-phenylindolin-2-one:[26k] **Racemic: Method B:** $[Rh(COD)Cl]_2$ (8.2 mg, 0.017 mmol, 5.0 mol-%), $HPCy_3{\cdot}BF_4$ (12.3 mg, 0.033 mmol, 10 mol-%), 5-bromo-1-methylindoline-2,3-dione (80 mg, 0.33 mmol), $PhB(OH)_2$ (81.2 mg, 0.66 mmol, 2 equiv.), K_2CO_3 (138 mg, 1.0 mmol, 3 equiv.) and toluene (2 mL) were used to obtain the corresponding *rac*-5-bromo-3-hydroxy-1-methyl-3-phenylindolin-2-one (79.2 mg, 62 % yield) as pale yellow foamy solid. ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 3.20 (s, 3H), 6.76–6.78 (d, *J* = 8 Hz, 1H), 7.30–7.38 (m, 6H), 7.44–7.47 (m, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 26.7, 78.1, 110.3, 116.3, 125.3, 128.3, 128.6, 128.8, 132.7, 133.7, 139.5, 142.5, 177.4. **HPLC:** Daicel Chiralpak AD-H column, *n*-hexane/2-propanol (85:15), 0.6 mL/min, 254 nm, retention times: 17.453 min and 20.467 min.

Chiral: $Rh(acac)(C_2H_4)_2$ (6.5 mg, 0.025 mmol, 3 mol-%), (*R*)-BINAP (31.1 mg, 0.05 mmol, 6 mol-%), CH_2Cl_2 (1 mL), 5-bromo-1-methylindoline-2,3-dione (200 mg, 0.83 mmol), $PhB(OH)_2$ (203 mg, 1.7 mmol, 2 equiv.), MeOH (2 mL) and DIPEA (0.07 mL, 0.42 mmol, 0.5 equiv.) were used to obtain the corresponding (*S*)-5-bromo-3-hydroxy-1-methyl-3-phenylindolin-2-one (250.6 mg, 88 % yield, 87 % ee). **HPLC:** Daicel Chiralpak AD-H column AD-H column, *n*-hexane/2-propanol (85:15), 0.6 mL/min, 254 nm, retention times: 18.062 min (minor, (*R*)) and 21.031 min (major, (*S*)). The assigned stereochemical configuration was based on literature precedent.[12c,13b]

5-Bromo-3-hydroxy-1-(3-methoxybenzyl)-3-phenylindolin-2-one: Racemic: Method B: $[Rh(COD)Cl]_2$ (12.8 mg, 0.044 mmol, 5.0 mol-%), $HPCy_3{\cdot}BF_4$ (19.2 mg, 0.087 mmol, 10 mol-%), 5-bromo-1-(3-methoxybenzyl) indoline-2,3-dione (300 mg, 0.87 mmol), $PhB(OH)_2$ (211 mg, 1.74 mmol, 2 equiv.), K_2CO_3 (359 mg, 2.61 mmol, 3 equiv.) and toluene (3 mL) were used to obtain the corresponding *rac*-5-bromo-3-hydroxy-1-(3-methoxybenzyl)-3-phenylindolin-2-one (284.5 mg, 73 % yield) as pale yellow foamy solid. ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 3.55 (s, 3H), 4.85–4.89 (d, *J* = 16 Hz, 1H), 5.04–5.09 (d, *J* = 20 Hz, 1H), 6.60–6.61 (d, *J* = 4 Hz, 1H), 6.68–6.71 (m, 1H), 6.75–6.77 (d, *J* = 8 Hz, 1H), 7.06–7.09 (m, 1H), 7.23–7.27 (m, 1H), 7.30–7.34 (m, 4H), 7.43–7.48 (m, 3H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 44.1, 55.4, 78.2, 109.9, 113.0, 113.1, 115.5, 123.9, 125.2, 125.6, 128.5, 128.8, 130.1, 131.5, 133.7, 135.3, 140.2, 142.4, 159.4, 177.9. **HPLC:** Daicel Chiralpak AD-H column, *n*-hexane/2-propanol (85:15), 0.6 mL/min, 254 nm, retention times: 23.560 min and 39.613 min.

Chiral: $Rh(acac)(C_2H_4)_2$ (6.7 mg, 0.026 mmol, 3 mol-%), (*S*)-BINAP (32.4 mg, 0.052 mmol, 6 mol-%), CH_2Cl_2 (1 mL), 5-bromo-1-(3-methoxybenzyl)indoline-2,3-dione (300 mg, 0.87 mmol), $PhB(OH)_2$ (211 mg, 1.74 mmol, 2 equiv.), MeOH (2 mL) and DIPEA (0.08 mL, 0.44 mmol, 0.5 equiv.) were used to obtain the corresponding (*R*)-5-bromo-3-hydroxy-1-(3-methoxybenzyl)-3-phenylindolin-2-one (337.2 mg, 86 % yield, 64 % ee). **HPLC:** Daicel Chiralpak AD-H column AD-H column, *n*-hexane/2-propanol (85:15), 0.6 mL/min, 254 nm, retention times: 23.833 min (major, (*R*)) and 40.527 min (minor, (*S*)). The assigned stereochemical configuration was based on literature precedent.[12c,13b]

Synthesis of the 5-Arylboronate-*N*-substituted-3,3-disubstituted-oxindole Derivatives (1a-k) (General Procedure):[17] In a round-bottom flask or in a Radley's® 12 position carousel reactor tube under nitrogen atmosphere was added the 5-Br-*N*-substituted-3,3-disubstituted-oxindole derivatives, B_2NPG_2 (1.1 equiv.), $PdCl_2$(dppf) (3 mol-%), KOAc (3 equiv.) and 1,4-dioxane. The reaction was stirred at 80 °C (in an oil bath when a round-bottom flask was used) overnight and monitored by TLC. After cooling down to room temperature, the reaction mixture was diluted with AcOEt and H_2O was added. The phases were separated, and the aqueous phase extracted with AcOEt. The combined organic layers were dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by silica gel flash chromatography using hexane/AcOEt (5:1), (1:1) as eluents.

1-Benzyl-5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-3,3-dimethoxyindol-*in*-2-one (1a): 1-Benzyl-5-bromo-3,3-dimethoxy-indolin-2-one (578.5 mg, 1.6 mmol), B_2NPG_2 (397 mg, 1.76 mmol, 1.1 equiv.), $PdCl_2$(dppf) (39.2 mg, 0.048 mmol, 3 mol-%), KOAc (471 mg, 4.8 mmol, 3 equiv.) and 1,4-dioxane (5 mL) were used to obtain the corresponding 1-benzyl-5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-3,3-dimethoxyindolin-2-one **(1a)** as a pale yellow solid (430.4 mg, 68 % yield). ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 0.99 (s, 6H), 3.62 (s, 6H), 3.73 (s, 4H), 4.87 (s, 2H), 6.69–6.71 (d, *J* = 8 Hz, 1H), 7.24–7.32 (m, 5H), 7.70–7.72 (d, *J* = 8 Hz, 1H), 7.86 (s, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 21.9, 31.9, 43.4, 51.0, 72.4, 97.1, 109.2, 124.2, 127.3, 127.7, 128.9, 130.2, 135.4, 136.8, 144.7, 171.3.

5-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-3,3-dimethoxy-1-methylindol-*in*-2-one (1b): 5-Bromo-3,3-dimethoxy-1-methylindolin-2-one (200 mg, 0.7 mmol), B_2NPG_2 (174 mg, 0.77 mmol, 1.1 equiv.), $PdCl_2$(dppf) (17.1 mg, 0.021 mmol, 3 mol-%), KOAc (206 mg, 2.1 mmol, 3 equiv.) and 1,4-dioxane (3 mL) were used to obtain the corresponding 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-3,3-dimethoxy-1-methylindolin-2-one **(1b)** as a white solid (144.5 mg, 59 % yield). ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 1.02 (s, 6H), 3.17 (s, 3H), 3.58 (s, 6H), 3.75 (s, 4H), 6.81–6.83 (d, *J* = 8 Hz, 1H), 7.82–7.84 (m, 2H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 21.9, 25.9, 31.9, 50.9, 72.4, 96.9, 108.2, 124.1, 130.0, 136.9, 145.5, 171.1.

5-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-3,3-dimethoxy-1-(3-methoxybenzyl)indolin-2-one (1c): 5-Bromo-3,3-dimethoxy-1-(3-methoxybenzyl) indolin-2-one (200 mg, 0.51 mmol), B_2NPG_2 (127 mg, 0.56 mmol, 1.1 equiv.), $PdCl_2$(dppf) (12.5 mg, 0.015 mmol, 3 mol-%), KOAc (150 mg, 1.53 mmol, 3 equiv.) and 1,4-dioxane (3 mL) were used to obtain the corresponding 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-3,3-dimethoxy-1-(3-methoxy benzyl)indolin-2-one **(1c)** as a white solid (127.5 mg, 58 % yield). ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 1.05 (s, 6H), 3.61 (s, 6H), 3.80 (s, 4H), 5.24 (s, 2H), 6.59–6.60 (m, 1H), 6.70–6.76 (m, 2H), 7.02–7.06 (t, *J* = 8 Hz, 1H), 7.18–7.22 (t, *J* = 8 Hz, 1H), 7.40–7.42 (d, *J* = 8 Hz, 1H), 7.80–7.82 (d, *J* = 8 Hz, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 22.0, 31.8, 42.8, 51.1, 55.0, 72.4, 97.5, 110.4, 111.4, 111.8, 122.7, 124.7, 125.0, 130.7, 137.7, 143.1, 143.6, 161.9, 171.3.

***tert*-Butyl 5-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-3,3-dimethoxy-2-oxoindoline-1-carboxylate (1d):** *tert*-Butyl 5-bromo-3,3-dimethoxy-2-oxoindoline-1-carboxylate (229.2 mg, 0.62 mmol), B_2NPG_2 (153 mg, 0.68 mmol, 1.1 equiv.), $PdCl_2$(dppf) (15.0 mg, 0.018 mmol, 3 mol-%), KOAc (181 mg, 1.86 mmol, 3 equiv.) and 1,4-dioxane (3 mL) were used to obtain the corresponding *tert*-butyl

5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-3,3-dimethoxy-2-oxoindoline-1-carboxylate **(1d)** as a white solid (140.6 mg, 56 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 1.02 (s, 6H), 1.63 (s, 9H), 3.54 (s, 6H), 3.76 (s, 4H), 7.86–7.87 (m, 3H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 22.0, 28.2, 32.0, 51.1, 67.2, 72.4, 84.8, 96.1, 114.8, 123.3, 130.2, 137.0, 147.7, 149.0, 169.2.

1-Benzyl-5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)spiro[indoline-3,2′-[1,3]dioxolan]-2-one (1e): 1-Benzyl-5-bromospiro[indoline-3,2′-[1,3]dioxolan]-2-one (687.9 mg, 1.9 mmol), B_2NPG_2 (475 mg, 2.09 mmol, 1.1 equiv.), $PdCl_2$(dppf) (46.5 mg, 0.057 mmol, 3 mol-%), KOAc (559 mg, 5.7 mmol, 3 equiv.) and 1,4-dioxane (5 mL) were used to obtain the corresponding 1-benzyl-5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)spiro[indoline-3,2′-[1,3]dioxolan]-2-one **(1e)** as a pale brown solid (501 mg, 67 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 0.98 (s, 6H), 3.72 (s, 4H), 4.33–4.36 (m, 2H), 4.59–4.63 (m, 2H), 4.83 (s, 2H), 6.64–6.66 (d, *J* = 8 Hz, 1H), 7.24–7.32 (m, 5H), 7.70–7.72 (d, *J* = 8 Hz, 1H), 7.82 (s, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 21.9, 32.0, 43.6, 66.1, 72.4, 109.1, 123.4, 127.3, 127.8, 128.9, 130.3, 135.4, 137.8, 146.1, 173.9.

5-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-1-methylspiro[indoline-3,2′-[1,3]dioxolan]-2-one (1f): 5-Bromo-1-methylspiro[indoline-3,2′-[1,3]dioxolan]-2-one (1.23 g, 4.4 mmol), B_2NPG_2 (1.09 g, 4.84 mmol, 1.1 equiv.), $PdCl_2$(dppf) (108 mg, 0.132 mmol, 3 mol-%), KOAc (1.3 g, 13.2 mmol, 3 equiv.) and 1,4-dioxane (10 mL) were used to obtain the corresponding 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-methylspiro[indoline-3,2′-[1, 3]dioxolan]-2-one **(1f)** as a pale brown solid (0.97 g, 69 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 1.00 (s, 6H), 3.12 (s, 4H), 3.74 (s, 3H), 4.26–4.35 (m, 2H), 4.51–4.59 (m, 2H), 6.76–6.78 (d, *J* = 8 Hz, 1H), 7.80–7.83 (m, 2H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 21.9, 25.9, 32.0, 65.9, 72.4, 102.3, 108.0, 123.3, 130.1, 137.9, 146.9, 173.7.

5-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-1-(3-methoxybenzyl)-spiro[indoline-3,2′-[1,3]dioxolan]-2-one (1g): 5-Bromo-1-(3-methoxybenzyl)spiro-[indoline-3,2′-[1,3]dioxolan]-2-one (500 mg, 1.3 mmol), B_2NPG_2 (319 mg, 1.43 mmol, 1.1 equiv.), $PdCl_2$(dppf) (31.8 mg, 0.039 mmol, 3 mol-%), KOAc (383 mg, 3.9 mmol, 3 equiv.) and 1,4-dioxane (3 mL) were used to obtain the corresponding 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-1-(3-methoxybenzyl)spiro-[indoline-3,2′-[1,3]dioxolan]-2-one **(1g)** as a white solid (343.2 mg, 61 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 1.05 (s, 6H), 3.67 (s, 4H), 3.79 (s, 3H), 4.33–4.36 (m, 2H), 4.61–4.65 (m, 2H), 5.18 (s, 2H), 6.63–6.66 (m, 2H), 7.01–7.07 (q, *J* = 8 HZ, 1H), 7.21–7.25 (m, 2H), 7.36–7.38 (d, *J* = 8 Hz, 1H), 7.80–7.82 (d, *J* = 8 Hz, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 22.0, 31.8, 42.9, 55.1, 66.0, 72.4, 102.5, 109.8, 110.3, 119.5, 123.2, 124.1, 127.7, 131.7, 136.9, 137.6, 143.5, 144.5, 161.9, 173.9.

***tert*-Butyl 5-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-2-oxospiro-[indoline-3,2′-[1,3]dioxolane]-1-carboxylate (1h):** *tert*-Butyl 5-bromo-2-oxospiro[indoline-3,2′-[1,3]dioxolane]-1-carboxylate (877.4 mg, 2.4 mmol), B_2NPG_2 (596 mg, 2.64 mmol, 1.1 equiv.), $PdCl_2$(dppf) (58.8 mg, 0.072 mmol, 3 mol-%), KOAc (706 mg, 7.2 mmol, 3 equiv.) and 1,4-dioxane (4 mL) were used to obtain the corresponding *tert*-butyl 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-2-oxospiro[indoline-3,2′-[1,3]- dioxolane]-1-carboxylate **(1h)** as a white solid (563.1 mg, 58 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 1.01 (s, 6H), 1.62 (s, 9H), 3.75 (s, 4H), 4.31–4.35 (m, 2H), 4.54–4.58 (m, 2H), 7.83–7.88 (m, 3H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 22.0, 28.2, 32.0, 66.1, 72.4, 84.7, 101.5, 114.8, 122.3, 130.5, 137.9, 143.1, 149.0, 172.0.

1-Benzyl-5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-3-hydroxy-3-phenyl-indolin-2-one (1i): 1-Benzyl-5-bromo-3-hydroxy-3-phenyl-indolin-2-one (577.4 mg, 1.5 mmol), B_2NPG_2 (373 mg, 1.65 mmol, 1.1 equiv.), $PdCl_2$(dppf) (37 mg, 0.045 mmol, 3 mol-%), KOAc (441 mg, 4.5 mmol, 3 equiv.) and 1,4-dioxane (6 mL) were used to obtain the corresponding 1-benzyl-5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-3-hydroxy-3-phenyl- indolin-2-one **(1i)** as a white solid (485.2 mg, 76 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 0.97 (s, 6H), 3.23 (s, 1H), 3.69 (s, 4H), 4.83–4.87 (d, *J* = 16 Hz, 1H), 5.02–5.06 (d, *J* = 16 Hz, 1H), 6.77–6.79 (d, *J* = 8 Hz, 1H), 7.28–7.36 (m, 9H), 7.35–7.43 (m, 2H), 7.71 (s, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 21.9, 31.9, 44.1, 72.4, 78.0, 109.2, 123.7, 125.4, 125.5, 127.4, 127.8, 128.3, 128.8, 128.8, 128.9, 129.0, 130.3, 131.0, 131.7, 135.6, 136.1, 140.3, 145.0, 178.0.

5-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-3-hydroxy-1-methyl-3-phenylindolin-2-one (1j): 5-Bromo-3-hydroxy-1-methyl-3-phenylindolin-2-one (321.1 mg, 1.0 mmol), B_2NPG_2 (251 mg, 1.1 mmol, 1.1 equiv.), $PdCl_2$(dppf) (24.5 mg, 0.03 mmol, 3 mol-%), KOAc (294 mg, 3.0 mmol, 3 equiv.) and 1,4-dioxane (4 mL) were used to obtain the corresponding 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-3-hydroxy-1-methyl-3-phenylindolin-2-one **(1j)** as a white solid (151.2 mg, 43 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 0.99 (s, 6H), 3.23 (s, 3H), 3.45 (s, 1H), 3.71 (s, 4H), 6.88–6.90 (d, *J* = 8 Hz, 1H), 7.27–7.33 (m, 3H), 7.38–7.40 (m, 2H), 7.71 (s, 1H), 7.81–7.83 (d, *J* = 8 Hz, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 22.0, 26.7, 31.9, 72.4, 77.9, 108.1, 125.6, 128.3, 128.6, 130.2, 130.9, 136.2, 140.3, 145.9, 177.9.

5-(5,5-Dimethyl-1,3,2-dioxaborinan-2-yl)-3-hydroxy-1-(3-methoxybenzyl)-3-phenylindolin-2-one (1k): 5-Bromo-3-hydroxy-1-(3-methoxybenzyl)-3-phenylindolin-2-one (284.5 mg, 0.67 mmol), B_2NPG_2 (166 mg, 0.74 mmol, 1.1 equiv.), $PdCl_2$(dppf) (16.4 mg, 0.02 mmol, 3 mol-%), KOAc (197 mg, 2.01 mmol, 3 equiv.) and 1,4-dioxane (3 mL) were used to obtain the corresponding 5-(5,5-dimethyl-1,3,2-dioxaborinan-2-yl)-3-hydroxy-1-(3-methoxybenzyl)-3-phenyl indolin-2-one **(1k)** as a white solid (228.8 mg, 75 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 1.06 (s, 6H), 3.58 (s, 4H), 3.80 (s, 3H), 5.22–5.26 (d, *J* = 16 Hz, 1H), 5.36–5.40 (d, *J* = 16 Hz, 1H), 6.61 (s, 1H), 6.80–6.82 (d, *J* = 8 Hz, 2H), 7.02–7.06 (t, *J* = 8 Hz, 1H), 7.28–7.36 (m, 5H), 7.46–7.48 (d, *J* = 8 Hz, 2H), 7.81–7.83 (d, *J* = 8 Hz, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 22.0, 31.8, 44.1, 54.9, 72.4, 78.3, 109.9, 111.1, 119.6, 123.5, 124.9, 125.4, 125.6, 128.7, 129.9, 131.7, 137.1, 137.7, 140.5, 143.7, 161.9, 178.1.

Synthesis of 1-Benzyl-3,3-dimethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-2-one (1l):[27] In a round-bottom flask under a nitrogen atmosphere was added 1-benzyl-5-bromo-3,3-dimethoxyindolin-2-one (1.08 g, 3.0 mmol), $PdCl_2(CH_3CN)_2$ (31.0 mg, 0.12 mmol, 4 mol-%), SPhos (123 mg, 0.3 mmol, 10 mol-%), NEt_3 (1.25 mL, 9.0 mmol, 3 equiv.), HBPin (0.65 mL, 4.5 mmol, 1.5 equiv.) and 1,4-dioxane (15 mL). The reaction was left stirring at 80 °C in an oil bath, overnight and monitored by TLC. After cooling down to room temperature, the reaction mixture was diluted with AcOEt and H_2O was added. The phases were separated, and the aqueous phase extracted with AcOEt. The combined organic layers were dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by silica gel flash chromatography using hexane/AcOEt (5:1), (1:1) as eluents. The corresponding 1-benzyl-3,3-dimethoxy-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)indolin-2-one **(1l)** was obtained as a pale yellow solid (0.97 g, 79 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 1.31 (s, 12H), 3.62 (s, 6H), 4.88 (s, 2H), 6.70–6.72 (d, *J* = 8 Hz, 1H), 7.24–7.32 (m, 5H), 7.71–7.73 (d, *J* = 8 Hz, 1H), 7.85 (s, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 24.9, 43.5, 51.1, 83.9, 97.0, 109.4, 124.5, 127.3, 127.8, 128.9, 130.9, 135.3, 137.9, 145.2, 171.2.

Synthesis of the 5-α-(3,3-Dimethoxy-substituted-oxindole)-benzylamine Derivatives (4)

Racemic Reaction (General Procedure): Method (A): In a Radley's® 12 position carousel reactor tube under nitrogen atmosphere was added the amine **(3)** (1.0 equiv.), the aldehyde **(2)** (1.2 equiv.) and toluene (2 mL). The mixture was left stirring at 90 °C during 30 min. After that the 5-arylboronate-*N*-substituted-3,3-disubstituted-oxindole derivatives **(1a–k)** (100 mg, 1.2 equiv.) were added to the reactor tube and the reaction stirred at 90 °C and monitored by TLC. When all the boronate specie **(1a–k)** were consumed the reaction was cooled down and the solvent evaporated under reduced pressure. The crude product was purified by silica gel flash chromatography using hexane/AcOEt (5:1), (1:1) as eluents.

Method (B): In a Radley's® 12 position carousel reactor tube under nitrogen atmosphere was added the 5-arylboronate-*N*-substituted-3,3-disubstituted-oxindole derivatives **(1a–k)** (100 mg, 1.0 equiv.), the aldehyde **(2)** (1.0 equiv.), the amine **(3)** (1.0 equiv.), MS 4Å (200 mg) and CH_2Cl_2 (2 mL). The reaction was stirred at 50 °C for 24 hours. After cooling down, the reaction mixture was filtered with a porous plate glass funnel packed with a celite layer and washed with CH_2Cl_2. The solvent was evaporated under reduced pressure and the crude product purified by silica gel flash chromatography using hexane/AcOEt (5:1), (1:1) as eluents.

1-Benzyl-5-((2-hydroxyphenyl)(morpholino)methyl)-3,3-dimethoxyin-dolin-2-one (4aaa): Method (A): **(1a)** (150 mg, 0.38 mmol, 1.2 equiv.), (**2a**) (0.04 mL, 0.38 mmol, 1.2 equiv.), **(3a)** (0.03 mL, 0.32 mmol, 1.0 equiv.) and toluene (2 mL) were used to obtain the corresponding **(4aaa)** as a white solid (161.6 mg, 90 % yield). M.p.= 163.8–164.0 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 2.43–2.57 (m, 4H), 3.53 (s, 3H), 3.60 (s, 3H), 3.73–3.76 (m, 4H), 4.36 (s, 1H), 4.81 (s, 2H), 6.64–6.66 (d, *J* = 8 Hz, 1H), 6.69–6.73 (t, *J* = 8 Hz, 1H), 6.82–6.84 (d, *J* = 8 Hz, 1H), 6.88–6.90 (d, *J* = 8 Hz, 1H), 7.09–7.13 (t, *J* = 8 Hz, 1H), 7.25–7.32 (m, 6H), 7.47 (s, 1H), 11.54 (s, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 43.7, 50.9, 66.9, 76.6, 100.1, 117.3, 119.9, 124.7, 127.5, 127.9, 128.9, 129.0, 129.4, 134.0, 135.3, 142.4, 156.0, 170.9. FTIR-ATR $\tilde{\nu}$ = 3670, 2974, 2904, 1730, 1620, 1070, 1046, 749 (cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{28}H_{31}N_2O_5$ $[M]^+$ 475.2227, found 475.2219.

5-((2-Hydroxyphenyl)(morpholino)methyl)-3,3-dimethoxy-1-methyl-indolin-2-one (4baa): Method (A): **(1b)** (157.7 mg, 0.49 mmol, 1.2 equiv.), **(2a)** (0.05 mL, 0.49 mmol, 1.2 equiv.), **(3a)** (0.04 mL, 0.41 mmol, 1.0 equiv.) and toluene (2 mL) were used to obtain the corresponding **(4baa)** as a pale yellow solid (116.0 mg, 59 % yield). M.p.= 73.7–75.0 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 2.45–2.61 (m, 4H), 3.12 (s, 3H), 3.49 (s, 3H), 3.56 (s, 3H), 3.75–3.77 (m, 4H), 4.41 (s, 1H), 6.71–6.78 (m, 2H), 6.85–6.87 (d, *J* = 8 Hz, 1H), 6.91–6.93 (d, *J* = 8 Hz, 1H), 7.10–7.15 (m, 1H), 7.44–7.47 (m, 2H), 11.59 (s br, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 26.0, 50.8, 67.0, 76.6, 117.3, 119.9, 124.7, 129.0, 129.4, 133.9, 143.3, 156.1, 170.7. FTIR-ATR $\tilde{\nu}$ = 2939, 2852, 1725, 1109, 1063, 753 (cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{22}H_{27}N_2O_5$ $[M]^+$ 399.1914, found 399.1908.

5-((2-Hydroxyphenyl)(morpholino)methyl)-3,3-dimethoxy-1-(3-methoxybenzyl)indolin-2-one (4caa): Method (B): **(1c)** (70.8 mg, 0.17 mmol), **(2a)** (0.02 mL, 0.17 mmol, 1.0 equiv.), **(3a)** (0.02 mL, 0.17 mmol, 1.0 equiv.), MS 4Å (200 mg) and CH_2Cl_2 (2 mL) were used to obtain the corresponding **(4caa)** as a white solid (46.2 mg, 55 % yield). M.p.= 67.9–71.0 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 2.48–2.64 (m, 4H), 3.62 (s, 3H), 3.63 (s, 3H), 3.68 (s, 3H), 3.73 (s br, 4H), 4.87 (s, 1H), 4.92–4.96 (d, *J* = 16 Hz, 1H), 5.15–5.19 (d, *J* = 16 Hz, 1H), 6.64 (s, 1H), 6.69–6.73 (t, *J* = 8 Hz, 2H), 6.78–6.81 (m, 1H), 6.83–6.85 (d, *J* = 8 Hz, 1H), 6.97–6.99 (m, 1H), 7.06–7.13 (m, 2H), 7.20–7.24 (t, *J* = 8 Hz, 1H), 7.44–7.46 (d, *J* = 8 Hz, 1H), 7.64–7.67 (m, 1H), 11.88 (s br, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 42.5, 50.9, 52.9, 55.2, 67.1, 96.9, 110.2, 113.9, 114.1, 117.4, 119.8, 123.1, 125.0, 125.1, 128.7, 129.2, 130.3, 130.8, 134.0, 142.4, 156.2, 159.1, 170.9. FTIR-ATR $\tilde{\nu}$ = 3670, 2972, 2904, 1725, 1610, 1056, 752 (cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{29}H_{33}N_2O_6$ $[M]^+$ 505.2333, found 505.2340.

***tert*-Butyl 5-((2-Hydroxyphenyl)(morpholino)methyl)-3,3-dimethoxy-2-oxoindoline-1-carboxylate (4daa):** Method (B): **(1d)** (140.6 mg, 0.35 mmol), **(2a)** (0.04 mL, 0.35 mmol, 1.0 equiv.), **(3a)** (0.03 mL, 0.35 mmol, 1.0 equiv.), MS 4Å (200 mg) and CH_2Cl_2 (2 mL) were used to obtain the corresponding **(4daa)** as a white solid (76.0 mg, 45 % yield). M.p.= 65.4–66.0 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 1.60 (s, 9H), 2.48 (m, 2H), 2.58 (m, 2H), 3.45 (s, 3H), 3.53 (s, 3H), 3.77 (m, 4H), 4.43 (s, 1H), 6.71–6.75 (t, *J* = 8 Hz, 1H), 6.85–6.87 (d, *J* = 8 Hz, 1H), 6.91–6.93 (d, *J* = 8 Hz, 1H), 7.11–7.15 (t, *J* = 8 Hz, 1H), 7.50 (m, 2H), 7.83–7.85 (d, *J* = 8 Hz, 1H), 11.51 (s br, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 28.1, 50.9, 51.0, 53.0, 66.9, 76.4, 85.1, 93.4, 116.2, 117.3, 119.9, 124.5, 125.9, 129.1, 129.3, 131.2, 135.8, 139.4, 148.8, 156.0, 168.8. FTIR-ATR $\tilde{\nu}$ = 3670, 2975, 2905, 1781, 1732, 1619, 1065, 755 (cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{26}H_{33}N_2O_7$ $[M]^+$ 485.2282, found 485.2288.

1-Benzyl-5-((2-hydroxyphenyl)(pyrrolidin-1-yl)methyl)-3,3-dimethoxyindolin-2-one (4aab): Method (B): **(1a)** (100 mg, 0.25 mmol), **(2a)** (0.03 mL, 0.25 mmol, 1.0 equiv.), **(3b)** (0.02 mL, 0.25 mmol, 1.0 equiv.), MS 4Å (200 mg) and CH_2Cl_2 (2 mL) were used to obtain the corresponding **(4aab)** as a pale orange solid (87 mg, 75 % yield). M.p.= 176.4–178.2 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 1.79–1.86 (m, 4H), 2.46–2.59 (m, 2H), 2.60–2.65 (m, 2H), 3.55 (s, 3H), 3.61 (s, 3H), 4.35 (s, 1H), 4.81 (s, 2H), 6.62–6.64 (d, *J* = 8 Hz, 1H), 6.68–6.72 (t, *J* = 8 Hz, 1H), 6.83–6.85 (d, *J* = 8 Hz, 1H), 6.91–6.94 (dd, *J* = 8 Hz, 1H), 7.07–7.11 (t, *J* = 8 Hz, 1H), 7.24–7.32 (m, 5H), 7.36–7.38 (d, *J* = 8 Hz, 1H), 7.55 (s, 1H), 12.06 (s br, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 23.5, 43.5, 50.8, 53.3, 75.3, 96.9, 109.9, 116.9, 119.3, 124.4, 125.2, 126.5, 127.4, 127.8, 128.2, 128.5, 128.9, 129.9, 135.3, 136.9, 141.9, 156.5, 170.9. FTIR-ATR $\tilde{\nu}$ = 3670, 2966, 2926, 1727, 1619, 1072, 1043, 747 (cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{28}H_{31}N_2O_4$ $[M]^+$ 459.2278, found 459.2281.

1-Benzyl-5-((2-hydroxyphenyl)(piperidin-1-yl)methyl)-3,3-dimethoxy-indolin-2-one (4aac): Method (B): **(1a)** (100 mg, 0.25 mmol), **(2a)** (0.03 mL, 0.25 mmol, 1.0 equiv.), **(3c)** (0.03 mL, 0.25 mmol, 1.0 equiv.), MS 4Å (200 mg) and CH_2Cl_2 (2 mL) were used to obtain the corresponding **(4aac)** as a white solid (72.9 mg, 54 % yield). M.p.= 124.1–125.9 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 1.40–1.46 (m, 2H), 1.56–1.68 (m, 5H), 2.20–2.41 (m, 3H), 3.56 (s, 3H), 3.62 (s, 3H), 4.45 (s, 1H), 4.82 (s, 2H), 6.66–6.70 (m, 2H), 6.83–6.86 (m, 2H), 7.08–7.12 (t, *J* = 8 Hz, 1H), 7.25–7.34 (m, 6H), 7.47 (s br, 1H), 12.42 (s br, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 24.1, 26.1, 43.5, 50.8, 53.9, 75.9, 96.9, 116.9, 119.1, 125.3, 127.4, 127.8, 128.5, 128.9, 129.0, 134.1, 135.3, 142.0, 156.9, 170.9. FTIR-ATR $\tilde{\nu}$ = 3670, 2934, 1727, 1618, 1071, 1042, 750 (cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{29}H_{33}N_2O_4$ $[M]^+$ 473.2435, found 473.2424.

1-Benzyl-5-((3,4-dihydroisoquinolin-2(1H)-yl)(2-hydroxyphenyl)methyl)-3,3-dimethoxyindolin-2-one (4aad): Method (B): **(1a)** (100 mg, 0.25 mmol), **(2a)** (0.03 mL, 0.25 mmol, 1.0 equiv.), **(3d)** (0.03 mL, 0.25 mmol, 1.0 equiv.), MS 4Å (200 mg) and CH_2Cl_2 (2 mL) were used to obtain the corresponding **(4aad)** as a pale yellow solid (142.4 mg, 84 % yield). M.p.= 91.0–93.5 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 2.81–3.08 (m, 4H), 3.63 (s, 3H), 3.66 (s, 3H), 3.72 (m, 2H), 4.64 (s, 1H), 4.87 (s, 2H), 6.73–6.80 (m, 2H), 6.89–6.98 (m, 3H), 7.07–7.20 (m, 4H), 7.22–7.38 (m, 5H), 7.43–7.49 (m, 1H), 7.64 (s, 1H), 11.80 (s br, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 28.6, 43.5, 50.8, 54.3, 75.3, 96.8, 110.0, 116.7, 117.2, 119.5, 120.5,

125.2, 125.5, 126.0, 126.7, 126.8, 127.4, 127.8, 128.6, 128.7, 128.9, 129.0, 133.3, 133.5, 134.7, 135.2, 142.2, 156.5, 170.8. FTIR-ATR $\tilde{\nu}$ = 2935, 1727, 1619, 1071, 1042, 743 (cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{33}H_{33}N_2O_4$ $[M]^+$ 521.2435, found 521.2418.

1-Benzyl-5-((benzyl(methyl)amino)(2-hydroxyphenyl)methyl)-3,3-dimethoxyindolin-2-one (4aaf): Method (A): **(1a)** (100 mg, 0.25 mmol, 1.2 equiv.), **(2a)** (0.03 mL, 0.25 mmol, 1.2 equiv.), **(3f)** (0.03 mL, 0.21 mmol, 1.0 equiv.) and toluene (2 mL) were used to obtain the corresponding **(4aaf)** as a pale yellow solid (86.1 mg, 66 % yield). M.p. = 64.0–65.2 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 2.17 (s, 3H), 3.60–3.62 (m, 8H), 4.69 (s, 1H), 4.85 (s, 1H), 6.71–6.76 (m, 2H), 6.90–6.92 (d, *J* = 8 Hz, 2H), 7.13–7.17 (t, *J* = 8 Hz, 1H), 7.27–7.40 (m, 11H), 7.57 (s, 1H), 12.20 (s br, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 39.2, 43.6, 50.9, 59.7, 75.0, 96.9, 109.9, 117.2, 119.4, 125.2, 125.5, 125.6, 127.4, 127.7, 127.9, 128.7, 128.9, 128.9, 129.0, 129.4, 135.2, 133.5, 135.3, 136.9, 142.3, 156.9, 170.9. FTIR-ATR $\tilde{\nu}$ = 3671, 2978, 2903, 1727, 1619, 1063, 745 (cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{32}H_{33}N_2O_4$ $[M]^+$ 509.2435, found 509.2424.

1-Benzyl-5-((2-hydroxyphenyl)(morpholino)methyl)spiro[indoline-3,2′-[1,3]dioxolan]-2-one (4eaa): Method (A): **(1e)** (101.3 mg, 0.26 mmol, 1.2 equiv.), **(2a)** (0.03 mL, 0.26 mmol, 1.2 equiv.), **(3a)** (0.02 mL, 0.21 mmol, 1.0 equiv.) and toluene (2 mL) were used to obtain the corresponding **(4eaa)** as a pale yellow solid (95.9 mg, 79 % yield). M.p.= 85.7–89.1 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 2.42–2.56 (m, 4H), 3.71–3.77 (m, 4H), 4.33–4.36 (m, 3H), 4.60–4.62 (m, 2H), 4.77 (s, 2H), 6.59–6.61 (d, *J* = 8 Hz, 1H), 6.69–6.73 (t, *J* = 8 Hz, 1H), 6.83–6.85 (d, *J* = 8 Hz, 1H), 6.88–6.90 (d, *J* = 8 Hz, 1H), 7.09–7.13 (t, *J* = 8 Hz, 1H), 7.27–7.33 (m, 6H), 7.41 (s br, 1H), 11.59 (s br, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 43.7, 65.9, 66.9, 76.6, 117.3, 119.9, 124.6, 127.4, 127.9, 128.9, 129.0, 129.5, 134.7, 135.2, 143.9, 156.0, 173.5. FTIR-ATR $\tilde{\nu}$ = 2968, 2850, 1730, 1627, 1112, 1033, 999, 747 (cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{28}H_{29}N_2O_5$ $[M]^+$ 473.2071, found 473.2064.

5-((2-Hydroxyphenyl)(morpholino)methyl)-1-methylspiro[indoline-3,2′-[1,3]dioxolan]-2-one (4faa): Method (A): **(1f)** (100 mg, 0.32 mmol, 1.2 equiv.), **(2a)** (0.03 mL, 0.32 mmol, 1.2 equiv.), **(3a)** (0.02 mL, 0.26 mmol, 1.0 equiv.) and toluene (2 mL) were used to obtain the corresponding **(4faa)** as a pale yellow solid (125.9 mg, 89 % yield). M.p.= 182.1–185.0 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 2.44–2.45 (m, 2H), 2.59–2.66 (m, 2H), 3.09 (s, 3H), 3.73–3.77 (m, 4H), 4.30–4.35 (m, 2H), 4.38 (s, 1H), 4.55–4.58 (m, 2H), 6.71–6.75 (m, 2H), 6.85–6.87 (d, *J* = 8 Hz, 1H), 6.90–6.92 (d, *J* = 8 Hz, 1H), 7.11–7.15 (m, 1H), 7.40–7.47 (m, 2H), 11.65 (s br, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 25.9, 65.8, 66.9, 66.9, 76.4, 102.0, 117.2, 118.0, 119.8, 124.5, 128.3, 128.9, 129.4, 132.7, 134.5, 144.7, 155.9, 173.3. FTIR-ATR $\tilde{\nu}$ = 3669, 2967, 2907, 1727, 1623, 1108, 1033, 1000, 753 (cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{22}H_{25}N_2O_5$ $[M]^+$ 397.1758, found 397.1748.

5-((2-Hydroxyphenyl)(morpholino)methyl)-1-(3-methoxybenzyl)spiro[indoline-3,2′-[1,3]dioxolan]-2-one (4gaa): Method (B): **(1g)** (70.3 mg, 0.17 mmol), **(2a)** (0.02 mL, 0.17 mmol, 1.0 equiv.), **(3a)** (0.01 mL, 0.17 mmol, 1.0 equiv.), MS 4Å (200 mg) and CH_2Cl_2 (2 mL) were used to obtain the corresponding **(4gaa)** as a pale yellow solid (43.1 mg, 52 % yield). M.p.= 61.0–63.5 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 2.47–2.61 (m, 4H), 3.67 (s, 3H), 3.71–3.74 (m, 4H), 4.34–4.37 (m, 2H), 4.60–4.63 (m, 2H), 4.86–4.90 (m, 2H), 5.10–5.14 (m, 1H), 6.61 (s br, 1H), 6.71–6.75 (m, 2H), 6.77–6.80 (dd, *J* = 4 Hz, 1H), 6.84–6.86 (d, *J* = 8 Hz, 1H), 6.98–7.00 (d, *J* = 8 Hz, 1H), 7.06–7.14 (m, 2H), 7.22–7.26 (t, *J* = 8 Hz, 1H), 7.41–7.43 (d, *J* = 8 Hz, 1H), 7.65–7.67 (d, *J* = 8 Hz, 1H), 11.87 (s br, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 55.2, 61.9, 65.9, 66.0, 67.1, 102.2, 109.9, 113.9, 114.1, 117.4, 119.8, 123.7, 124.1, 125.2, 128.7, 129.1, 130.4, 131.8, 133.9, 143.8, 156.2, 159.1, 173.6. FTIR-ATR $\tilde{\nu}$ = 2932, 1726, 1614, 1115, 1036, 753 (cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{29}H_{31}N_2O_6$ $[M]^+$ 503.2177, found 503.2167.

1-Benzyl-5-((2-hydroxyphenyl)(piperidin-1-yl)methyl)spiro[indoline-3,2′-[1,3]dioxolan]-2-one (4eac): Method (A): **(1e)** (123.7 mg, 0.32 mmol, 1.2 equiv.), **(2a)** (0.03 mL, 0.32 mmol, 1.2 equiv.), **(3c)** (0.03 mL, 0.26 mmol, 1.0 equiv.) and toluene (2 mL) were used to obtain the corresponding **(4eac)** as a pale orange solid (156.9 mg, 98 % yield). M.p.= 61.3–64.4 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 1.41–1.70 (m, 8H), 2.35 (m, 1H), 3.64–3.67 (m, 1H), 4.35 (m, 2H), 4.42 (s, 1H), 4.61–4.62 (m, 2H), 4.77 (s, 2H), 6.60–6.62 (d, *J* = 8 Hz, 1H), 6.65–6.69 (t, *J* = 8 Hz, 1H), 6.81–6.84 (m, 2H), 7.07–7.11 (t, *J* = 8 Hz, 1H), 7.23–7.38 (m, 7H), 12.47 (s br, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 24.1, 24.6, 26.1, 26.2, 43.6, 65.9, 76.1, 102.3, 117.1, 118.1, 118.5, 119.2, 125.2, 127.4, 127.9, 128.3, 128.5, 128.9, 129.2, 132.5, 134.7, 135.2, 143.6, 157.1, 173.6. FTIR-ATR $\tilde{\nu}$ = 3667, 2931, 2857, 1728, 1623, 1165, 1032, 750 (cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{29}H_{31}N_2O_4$ $[M]^+$ 471.2278, found 471.2281.

1-Benzyl-5-((3,4-dihydroisoquinolin-2(1H)-yl)(2-hydroxyphenyl)methyl)spiro[indoline-3,2′-[1,3]dioxolan]-2-one (4ead): Method (B): **(1e)** (100 mg, 0.25 mmol), **(2a)** (0.03 mL, 0.25 mmol, 1.0 equiv.), **(3d)** (0.03 mL, 0.25 mmol, 1.0 equiv.), MS 4Å (200 mg) and CH_2Cl_2 (2 mL) were used to obtain the corresponding **(4ead)** as a pale yellow solid (72.5 mg, 79 % yield). M.p.= 75.0–77.4 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 2.75–3.00 (m, 4H), 3.64 (m, 2H), 4.34–4.38 (m, 2H), 4.57 (s, 1H), 4.62–4.65 (m, 2H), 4.80 (s, 2H), 6.64–6.66 (d, *J* = 8 Hz, 1H), 6.72–6.76 (t, *J* = 8 Hz, 1H), 6.85–6.87 (d, *J* = 8 Hz, 1H), 6.93–6.95 (d, *J* = 8 Hz, 2H), 7.12–7.17 (m, 4H), 7.27–7.35 (m, 5H), 7.41–7.43 (d, *J* = 8 Hz, 1H), 7.50 (s, 1H), 11.79 (s br, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 28.8, 43.7, 65.9, 65.9, 75.4, 102.2, 110.1, 117.4, 119.6, 125.2, 125.3, 126.1, 126.8, 127.0, 127.5, 127.9, 128.7, 128.8, 129.0, 129.3, 131.8, 133.5, 133.7, 135.2, 135.3, 143.8, 156.5, 173.6. FTIR-ATR $\tilde{\nu}$ = 3670, 2977, 2903, 1729, 1624, 1052, 747 (cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{33}H_{31}N_2O_4$ $[M]^+$ 519.2278, found 519.2275.

1-Benzyl-5-((benzyl(methyl)amino)(2-hydroxyphenyl)methyl)spiro[indoline-3,2′-[1,3]dioxolan]-2-one (4eaf): Method (A): **(1e)** (100 mg, 0.25 mmol, 1.2 equiv.), **(2a)** (0.03 mL, 0.25 mmol, 1.2 equiv.), **(3f)** (0.03 mL, 0.21 mmol, 1.0 equiv.) and toluene (2 mL) were used to obtain the corresponding **(4eaf)** as a pale yellow solid (100.7 mg, 65 % yield). M.p.= 66.6–68.0 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 2.15 (s, 3H), 3.56–3.61 (m, 2H), 4.34–4.37 (m, 2H), 4.61–4.64 (m, 2H), 4.69 (s, 1H), 4.79 (s, 2H), 6.65–6.67 (d, *J* = 8 Hz, 1H), 6.71–6.75 (t, *J* = 8 Hz, 1H), 6.88–6.90 (m, 2H), 7.12–7.16 (t, *J* = 8 Hz, 1H), 7.27–7.35 (m, 11H), 7.46 (s, 1H), 12.21 (s br, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 39.1, 43.6, 59.6, 65.9, 74.9, 102.2, 109.9, 117.1, 119.4, 124.5, 125.1, 125.8, 127.4, 127.7, 127.9, 128.7, 128.8, 128.9, 129.1, 129.4, 132.3, 134.0, 135.2, 136.9, 143.8, 156.9, 173.5. FTIR-ATR $\tilde{\nu}$ = 3670, 2977, 2903, 1728, 1624, 1073, 1040, 745(cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{32}H_{31}N_2O_4$ $[M]^+$ 507.2278, found 507.2262.

1-Benzyl-5-((3,5-di-*tert*-butyl-2-hydroxyphenyl)(morpholino)methyl)spiro[indoline-3,2′-[1,3]dioxolan]-2-one (4eda): Method (A): **(1e)** (100 mg, 0.25 mmol, 1.2 equiv.), **(2d)** (59.5 mg, 0.25 mmol, 1.2 equiv.), **(3a)** (0.02 mL, 0.21 mmol, 1.0 equiv.) and toluene (2 mL) were used to obtain the corresponding **(4eda)** as a pale yellow solid (118.3 mg, 59 % yield). M.p.= >220 °C. ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 1.21 (s, 9H), 1.43 (s, 9H), 2.36–2.42 (m, 4H), 3.73 (m, 4H), 4.28 (s, 1H), 4.34–4.38 (m, 2H), 4.57–4.63 (m, 2H), 4.78 (s, 2H), 6.58–6.60 (d, *J* = 8 Hz, 1H), 6.72–6.73 (m, 1H), 7.15 (s, 1H), 7.28–7.31 (m, 6H), 7.53 (s, 1H), 11.77 (s br, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 29.6, 31.7, 32.0, 34.3, 43.7, 66.1, 66.9, 72.4, 77.3,

102.2, 109.1, 123.2, 123.7, 124.0, 127.3, 127.4, 127.9, 128.9, 129.0, 130.3, 135.1, 135.2, 136.4, 137.8, 141.1, 143.6, 152.5, 173.5. FTIR-ATR $\tilde{\nu}$ = 2958, 1734, 1616, 1116, 1032, 742 (cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{36}H_{45}N_2O_5$ $[M]^+$ 585.3323, found 585.3308.

1-Benzyl-5-((2-hydroxy-5-nitrophenyl)(morpholino)methyl)-spiro[indoline-3,2′-[1,3]dioxolan]-2-one (4eea): Method (A): **(1e)** (100 mg, 0.25 mmol, 1.2 equiv.), **(2e)** (42.4 mg, 0.25 mmol, 1.2 equiv.), **(3a)** (0.02 mL, 0.21 mmol, 1.0 equiv.) and toluene (2 mL) were used to obtain the corresponding **(4eea)** as a pale orange solid (111.4 mg, 63 % yield). M.p.= 83.8–85.0 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 2.43–2.61 (m, 4H), 3.71–3.75 (m, 4H), 4.33–4.38 (m, 2H), 4.46 (s, 1H), 4.58–4.64 (m, 2H), 4.78 (s, 2H), 6.62–6.64 (d, *J* = 8 Hz, 1H), 6.89–6.91 (d, *J* = 8 Hz, 1H), 7.24–7.33 (m, 6H), 7.37 (s, 1H), 7.85–7.86 (m, 1H), 8.02–8.05 (m, 1H), 13.09 (s br, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 43.7, 65.9, 66.7, 75.8, 100.1, 101.9, 117.9, 124.9, 125.3, 125.8, 127.4, 128.0, 129.1, 132.8, 134.9, 140.7, 144.5, 162.7, 173.4. FTIR-ATR $\tilde{\nu}$ = 2922, 2854, 1729, 1622, 1584, 1335, 1270, 1168, 729 (cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{28}H_{28}N_3O_7$ $[M]^+$ 518.1922, found 518.1922.

1-Benzyl-3-hydroxy-5-((2-hydroxyphenyl)(morpholino)methyl)-3-phenylindolin-2-one (4iaa): Method (A): ***rac*-(1i)** (100 mg, 0.23 mmol, 1.2 equiv.), **(2a)** (0.025 mL, 0.23 mmol, 1.2 equiv.), **(3a)** (0.02 mL, 0.20 mmol, 1.0 equiv.) and toluene (2 mL) were used to obtain the corresponding **(4iaa)** as a pale orange solid (85.9 mg, 69 % yield). M.p.= 82.9–87.0 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 2.23–2.47 (m, 4H), 3.62–3.66 (m, 4H), 4.30–4.33 (d, *J* = 12 Hz, 1H), 4.38 (s br, 1H), 4.69–4.74 (m, 1H), 4.94–5.00 (m, 1H), 6.64–6.68 (t, *J* = 8 Hz, 1H), 6.70–6.73 (m, 1H), 6.72–6.86 (m, 2H), 7.04–7.09 (m, 1H), 7.27–7.38 (m, 12H), 11.61 (s br, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 44.2, 66.8, 66.8, 76.1, 77.9, 117.1, 117.2, 124.6, 125.4, 125.5, 127.4, 127.5, 127.9, 128.4, 128.5, 128.70, 128.74, 128.8, 128.9, 129.3, 129.4, 132.2, 134.4, 134.6, 135.3, 140.0, 142.6, 155.9, 177.7. FTIR-ATR $\tilde{\nu}$ = 2929, 1728, 1623, 1335, 1270, 730 (cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{32}H_{31}N_2O_4$ $[M]^+$ 507.2278, found 507.2287. Note: only the major diastereomer was described.

3-Hydroxy-5-((2-hydroxyphenyl)(morpholino)methyl)-1-methyl-3-phenylindolin-2-one (4jaa): Method (A): ***rac*-(1j)** (151.2 mg, 0.43 mmol, 1.2 equiv.), **(2a)** (0.05 mL, 0.43 mmol, 1.2 equiv.), **(3a)** (0.03 mL, 0.36 mmol, 1.0 equiv.) and toluene (2 mL) were used to obtain the corresponding **(4jaa)** as a white solid (83.9 mg, 45 % yield). M.p.= 87.3–90.1 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 2.38–2.43 (m, 2H), 2.53–2.56 (m, 1H), 3.18–3.19 (d, *J* = 4 Hz, 3H), 3.68–3.74 (m, 5H), 3.82 (s br, 1H), 4.37–4.39 (d, *J* = 8 Hz, 1H), 6.67–6.71 (t, *J* = 8 Hz, 1H), 6.79–6.89 (m, 3H), 7.07–7.13 (m, 1H), 7.28–7.33 (m, 6H), 7.46–7.48 (m, 1H), 11.64 (s br, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 26.7, 66.8, 66.9, 76.3, 77.9, 117.2, 117.3, 119.8, 124.6, 125.4, 125.5, 128.5, 128.5, 128.7, 128.8, 128.9, 129.4, 129.4, 132.0, 134.6, 140.0, 143.5, 156.1, 177.5. FTIR-ATR $\tilde{\nu}$ = 3349, 2925, 2856, 1712, 1614, 1104, 755 (cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{26}H_{27}N_2O_4$ $[M]^+$ 431.1965, found 431.1954. Note: only the major diastereomer was described.

3-Hydroxy-5-((2-hydroxyphenyl)(morpholino)methyl)-1-(3-methoxy-benzyl)-3-phenylindolin-2-one (4kaa): Method (B): ***rac*-(1k)** (87.3 mg, 0.19 mmol), **(2a)** (0.02 mL, 0.19 mmol, 1.0 equiv.), **(3a)** (0.02 mL, 0.19 mmol, 1.0 equiv.), MS 4Å (200 mg) and CH_2Cl_2 (2 mL) were used to obtain the corresponding **(4kaa)** as a white solid (26.1 mg, 25 % yield). M.p.= 81.0–83.4 °C. ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 2.45–2.62 (m, 4H), 3.46–3.54 (m, 1H), 3.59–3.61 (d, *J* = 8 Hz, 3H), 3.70–3.74 (m, 4H), 4.93–4.95 (d, *J* = 8 Hz, 1H), 5.13 (s br, 1H), 6.63–6.74 (m, 3H), 6.77–6.80 (dd, *J* = 4 Hz, 1H), 6.83–6.87 (t, *J* = 8 Hz, 1H), 6.93–6.97 (t, *J* = 8 Hz, 1H), 7.07–7.13 (m, 2H), 7.21–7.25 (t, *J* = 8 Hz, 1H), 7.30–7.36 (m, 4H), 7.42–7.48 (m, 2H), 7.60–7.63 (m, 1H), 11.83 (s br, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 55.2, 61.9, 67.1, 71.2, 78.0, 109.9, 112.5, 117.4, 117.5, 119.8, 119.9, 123.9, 125.4, 125.5, 125.7, 125.8, 128.6, 128.8, 128.8, 128.85, 128.88, 129.5, 130.1, 131.1, 131.6, 134.4, 139.9, 142.8, 156.3, 159.3, 177.8. FTIR-ATR $\tilde{\nu}$ = 3341, 2923, 2856, 1715, 1610, 1108, 750 (cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{33}H_{33}N_2O_5$ $[M]^+$ 537.2384, found 537.2364. Note: only the major diastereomer was described.

Enantioselective Reaction (General Procedure): In a Radley's® 12 position carousel reactor tube under nitrogen atmosphere was added the 5-arylboronate-*N*-substituted-3,3-disubstituted-oxindole derivatives **(1a–m)** (100 mg, 1.0 equiv.), the aldehyde **(2a–e)** (1.0 equiv.), the amine **(3a–f)** (1.0 equiv.), catalyst (20 mol-%), MS 4Å (200 mg) and CH_2Cl_2 (2 mL). The reaction was stirred at 50 °C for 24 hours. After cooling down, the reaction mixture was filtered with a porous plate glass funnel packed with a celite layer and washed with CH_2Cl_2. The solvent was evaporated under reduced pressure and the crude product purified by silica gel flash chromatography using hexane/AcOEt (5:1), (1:1) as eluents. HPLC data of the 5-α-(3,3-dimethoxy-substituted-oxindole)-benzylamine derivatives **(4)** can be found in supporting information file.

Diastereoselective Reaction (General Procedure): In a Radley's® 12 position carousel reactor tube under nitrogen atmosphere was added the 5-arylboronate-*N*-substituted-3,3-disubstituted-oxindole derivatives **(1i–k)** (1.0 equiv.), **(2a)** (1.0 equiv.), **(3a)** (1.0 equiv.), (*R*)-BINOL (20 mol-%), MS 4Å (200 mg) and CH_2Cl_2 (2 mL). The reaction was stirred at 50 °C for 24 hours. After cooling down, the reaction mixture was filtered in a porous plate glass funnel packed with a celite layer and washed with CH_2Cl_2. The solvent was evaporated under reduced pressure and the crude product purified by silica gel flash chromatography using hexane/AcOEt (5:1), (1:1) as eluents. HPLC data of the 5-α-(3,3-dimethoxy-substituted-oxindole)-benzylamine derivatives **(4iaa)**, **(4jaa)** and **(4kaa)** can be found in supporting information file.

Synthesis of 1-Benzyl-5-((2-hydroxyphenyl)(morpholino)-methyl)indoline-2,3-dione (5aaa): 1-Benzyl-5-((2-hydroxyphenyl)-(morpholino)methyl)-3,3-dimethoxyin-dolin-2-one **(4aaa)** (102.4 mg, 0.26 mmol) was put into a round-bottomed flask containing a stirrer bar under air. $CHCl_3$ (2 mL) and TFA (3 mL) were added to the flask and the mixture was stirred overnight at room temperature. The reaction was quenched with saturated $NaHCO_3$ aqueous solution, carefully, to neutralize the acid. The resulting crude mixture was extracted with CH_2Cl_2. The combined organic layers were dried with $MgSO_4$, filtered and the solvent evaporated under reduced pressure. The crude product was purified by silica flash chromatography using hexane/AcOEt (5:1) and (1:1) as eluents. The corresponding **(5aaa)** was obtained as a red solid (74.6 mg, 67 % yield). ^{1}H NMR ($CDCl_3$, 400 MHz): δ_H = 2.42–2.43 (m, 2H), 2.54–2.58 (m, 2H), 3.73 (m, 4H), 4.35 (s, 1H), 4.86 (s, 2H), 6.72–6.75 (m, 2H), 6.82–6.84 (d, *J* = 8 Hz, 1H), 6.88–6.90 (m, 1H), 7.09–7.13 (t, *J* = 8 Hz, 1H), 7.28–7.31 (m, 5H), 7.58–7.60 (m, 1H), 7.65 (s, 1H), 11.35 (s, 1H). $^{13}C\{^1H\}$ APT NMR ($CDCl_3$, 100 MHz): δ_C = 44.2, 66.8, 75.9, 111.7, 117.5, 120.1, 123.9, 125.5, 127.6, 128.4, 129.1, 129.2, 129.3, 134.4, 135.6, 138.3, 150.5, 155.8, 158.2, 183.0. FTIR-ATR $\tilde{\nu}$ = 2923, 2855, 1734, 1618, 1112, 731 (cm^{-1}). HRMS (ESI-TOF) *m/z*: calcd. for $C_{26}H_{25}N_2O_4$ $[M]^+$ 429.1809, found 429.1812.

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