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Oligonucleotide modifications enhance probe stability for single cell transcriptome in vivo analysis (TIVA)

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Bifunctional thiourea-modified polymers of intrinsic microporosity for enantioselective α-amination of 3-aryl-2-oxindoles in batch and flow conditions

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Two novel polymers of intrinsic microporosity decorated with chiral thioureas have been used as recoverable organocatalysts in enantioselective α-amination of 3-aryl-substituted oxindoles, creating a quaternary stereocenter. Both catalysts were able to promote the reaction in excellent yields and good enantioselection. Catalyst **II**, with a pyridyl nucleus, was used in recycling experiments maintaining the activity without additional reactivation, and in flow processes allowing the synthesis of the amination product in multigram scale.

Introduction

Oxindoles with a quaternary stereocenter at C-3, specially 3-amino-3-substituted derivatives, are privileged scaffolds due to their possibility of application in different areas.[1] The synthesis of this kind of enantioenriched targets has attracted a lot of interest, and enantioselective metal-mediated[2] or organocatalytic[3] transformations have been developed to that end. With respect to the organocatalytic methodology, the addition of different nucleophiles to ketimines derived from isatin is the most thoroughly studied reaction. Chiral organocatalysts such as thioureas,[4] squaramides,[5] amines,[6] sulfonamides,[7] and phosphoric acids[8] provided good results in asymmetric Mannich-type reactions, cyanation,[9] or in the addition of phenols,[10] alcohols and thiols.[11]

The organocatalytic electrophilic α-amination of 3-substituted oxindoles is probably the most direct access to the enantioenriched derivatives, but this protocol has been much less studied.[12] Biscinchona alkaloids were first used as organocatalysts in the reaction of 3-substituted 2-oxindoles with different azodicarboxylates leading to the amination products in good yields and moderate to good enantioselectivities.[13] Chiral bifunctional thioureas,[14] amino acids-derived chiral bifunctional phosphine catalysts,[15] 2-aminobenzimidazoles,[16] and chiral bifunctional phase-transfer catalysts[17] have been also shown as excellent catalysts in the amination of 3-substituted oxindoles.

In spite of the problems associated with the recovery of the catalysts in the aforementioned transformations, we have only found two references on the use of easily recoverable and reusable organocatalysts able to promote the enantioselective electrophilic α-amination of 3-substituted oxindoles. In both cases, the heterogeneous organocatalysts derived from cinchona alkaloids, have been synthesized by Cu-catalyzed azide-alkyne cycloaddition, leading to materials very robust and active in the amination process, although using and important loading of catalyst.[18] However, some problems, probably associated with the presence of traces of copper in the catalysts resulting from the synthetic methodology, have been observed in organocatalytic heterogeneous aminations, for which reason it is convenient to avoid the metal in the preparation of the catalysts. [19]

Polymers of intrinsic microporosity (PIMs) are characterized for a high internal surface, and interconnected porous system, and they have been used for different applications.[20] Recently, we have synthesized chiral bifunctional thiourea **I** (Figure 1) by postmodification of PIM-1[21] and used it as an excellent organocatalyst in enantioselective nitro-Michael reaction.[22] Now we report on the synthesis of the novel bifunctional thiourea **II**, derived from **PIM-1n**,[23] and their use as catalysts in the enantioselective amination of 3-substituted oxindoles both in batch and flow conditions.
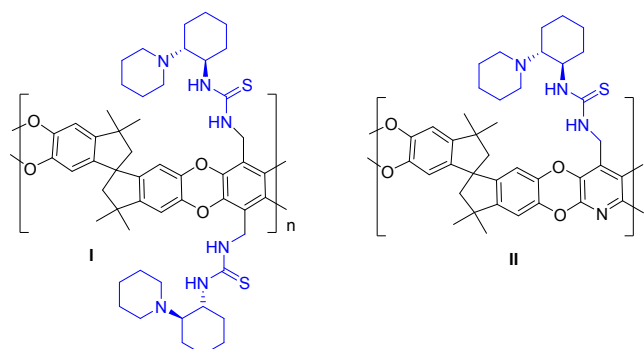
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Figure 1 Catalysts used in the enantioselective amination of 3-substituted oxindoles.

Results and discussion

Known **PIM-1n** was prepared by condensation of commercially available **1** and **2** in N, N-Dimethylformamide (DMF) at 70 °C in the presence of potassium carbonate, and was then transformed into bifunctional thiourea **II** in two steps as summarized in Scheme 1.
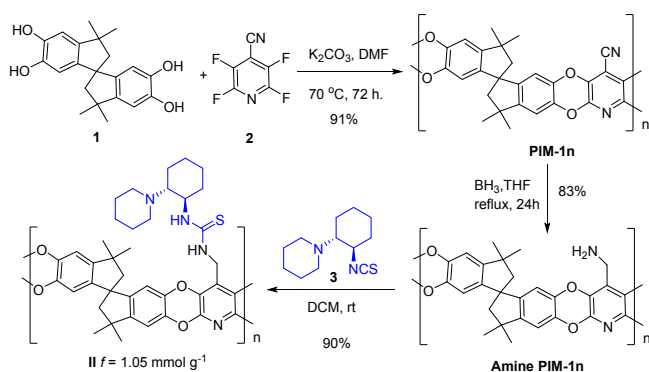

Scheme 1. Synthesis of polymeric thiourea **II**.

Reduction of PIM-1n with diborane in tetrahydrofuran (THF) at reflux[21b] for 24 h yielded **amine PIM-1n** in 83 % yield, which precipitates in the reaction medium. As described for amine PIM-1 counterpart, this amine is insoluble in common laboratory solvents. Then, **amine PIM-1n** was transformed into thiourea **II** in excellent yield (90 %) by condensation with chiral isothiocyanate **3**[24] derived from (1R,2R)-trans-2-(1-piperidinyl)cyclohexylamine in dichloromethane (DCM) at room temperature. Thiourea **II** was found to be insoluble in chloroform, dichloromethane, hexane, tetrahydrofuran, dimethylsulfoxide (DMSO), dimethylformamide, ethyl acetate, acetone, diethyl ether, toluene, 1,4-dioxane and methanol. A constant effective functionalization (f = 1.05 mmol g^{-1}) was determined for different batches on the basis of the sulfur content determined by elemental analysis. The synthesis and post-modifications of **PIM-1n** were monitored by infrared spectroscopy showing characteristics bands of nitrile, amine and thiourea groups (See ESI†). Thermal degradation behavior was also examined by thermogravimetric analysis (TGA) confirming the well-known high thermal stability of above 400 °C of these family of polymers[21c] and also the typical pattern of decomposition above 220 °C due to the presence of thiourea groups in the catalyst **II** (See ESI†). NMR spectroscopy together with the FTIR and elemental data analysis, confirmed that the **PIM-1n** and catalyst **II** were highly modified with the acquisition of nitrile and thiourea functionalities respectively. N$_2$ adsorption isotherms (See ESI†) of the dry powder thiourea **II,** before and after being used as a catalyst, showed low BET surface areas (2.16 and 1.75 m^2 g^{-1} respectively). Post-synthetic modification of PIMs is a useful method of tailoring its properties, but most of these modifications could lead to reducing microporosity. These studies of the N$_2$-adsortion

isotherms are in concordance with published results for amine-PIM-1[21b] which reveal reduced N$_2$ uptake that can be explained by formation of hydrogen-bonds, which frequently results in a reduction of the BET surface area. The morphology study of the dry powder thiourea **II** was carried out by scanning electron microscopy (SEM).[25] The SEM images (See ESI†) showed no differences in the appearance of rough surface topography, and also in their sizes, between samples before and after using them as organocatalysts. Nonetheless, these experiments have been carried out with dry samples that can collapse and this may not explain their porous behaviour when swollen in the solvent employed for the asymmetric reactions.

We started searching for the best experimental conditions (catalyst, solvent, and temperature) for the heterogeneous asymmetric amination of N-Boc-3-phenyl-2-oxindole (**4a**) with di-tert-butyl azodicarboxylate as a model (entries 1-8 in Table 1). The reactions were initially carried out by stirring a 0.1 M solution of oxindole **4a** with azodicarboxylate **5** (2 equiv) in the presence of 5 mol% of catalyst **I-II** in DCM or toluene until disappearance of **4a** in the reaction mixture (TLC). The reactions finished after 6 h at 25 °C, leading to **6a** in good yield, and moderate enantioselectivity (entries 1-4 in Table 1). Longer reaction times (10 h) were needed to complete the reaction at low temperature (-40 °C), but **6a** was isolated in excellent yields and better enantioselection (entries 5-8 in Table 1). Interestingly, our catalysts showed to be as active as the previously described dimeric Cinchona alkaloid organocatalyst anchored on polystyrene used in the α-amination of N-benzyl protected 2-oxindoles.[18] The nature of the solvent also affected the activity of the catalysts, but contrary to what has been previously described in reactions promoted by cinchona-derived organocatalysts,[13c] the best enantioselection was obtained by using the nonpolar and more benign toluene as solvent (Table 1, compare entries 1-2 or 5-6 versus 3-4 or 7-8, respectively). These observations led us to consider one of the main features associated with the required practical usage of the solid-supported catalysts that is their extended reuse. The recyclability of the best catalyst **II** was tested in the reaction of N-Boc-3-phenyl oxindole (**4a**) with di-tert-butyl azodicarboxylate (**5**) at 25 °C. Although the enantioselection was lower at that temperature, we selected these conditions because -40 °C is an inconvenient low temperature for practical applications. Catalyst **II** was recovered by filtration from the reaction mixture of **4a** with **5** (entry 4 in Table 1), washed successively with toluene and DCM, dried until constant weight, and reused in the next cycle. The data collected in Table 1 (entries 9-12) showed that both the activity and the enantioselection were maintained for five cycles without any additional reactivation described for unsupported and supported bifunctional thioureas used in other amination processes.[19, 26]

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Table 1 Optimization of the enantioselective α-amination conditions and recycling experiments [a]
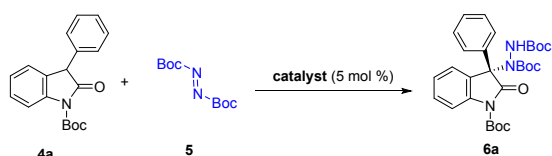
Entry[a]	Cat.	Solvent	T (°C)	t(h)	Yield[b] (%)	er[c]
1	I	DCM	25	6	70	66:34
2	II	DCM	25	6	85	77:23
3	I	PhMe	25	6	78	77:23
4	II	PhMe	25	6	80	82:18
5	I	DCM	-40	10	92	85:15
6	II	DCM	-40	10	97	88:12
7	I	PhMe	-40	10	88	94:6
8	II	PhMe	-40	10	91	94:6
9[d]	II	PhMe	25	6	87	85:15
10[d]	II	PhMe	25	6	84	83:17
11[d]	II	PhMe	25	6	82	82:18
12[d]	II	PhMe	25	6	84	83:17

[a]Reactions performed with 3-aryloxindole **4a** (0.1 mmol) and di-tert-butyl azodicarboxilate (0.2 mmol) in 1 mL of solvent at different temperatures in the presence of 5 mol% of catalyst. [b]Isolated yield. [c]Determined by chiral HPLC analysis. [d]Data for recycling (2-5) experiments of entry 4.

The scope of the reaction was studied in toluene as solvent and temperature of -40 ºC and the reaction was applied to different 3-aryl substituted oxindoles (**4b**-**4g**) in the presence of 5 mol% of catalysts **I** and **II** (determined on the basis of elemental analysis)(Table 2).
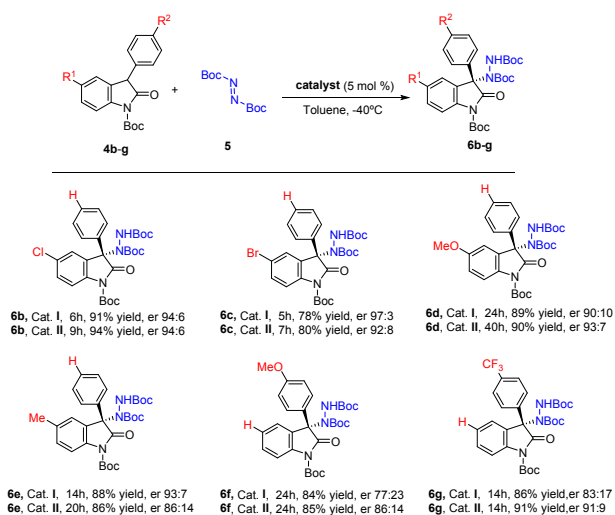

Table 2 Substrate scope of the reaction [a]

[a]Reaction conditions: 0.1 mmol (3-aryloxindole **4b-g**), 0.2 mmol (**5**), catalyst **I** or **II** (5 mol %), toluene (1 mL), -40°C.

Irrespective of the substituent at C-5 in the oxindole nucleus or at the *para* position in the phenyl group at C-3, the amination products **6a**-**g** were obtained in good yields and enantioselection. In general terms, it was observed that catalyst **I** was more active than **II** (shorter reaction times), but, except for **4c** and **4e**, less enantioselective. The electronic nature of the substituent at C-5 does not appreciably influence the reaction, but the presence of a donor methoxy group in the aryl substituent at C-3 decreased the enantioselectivity of the reaction for **6f**, as previously was observed for the amination promoted by supported cinchona catalysts. [18a]

To further explore the applicability of the novel supported thiourea **II** as enantioselective catalyst, we focused our attention on the continuous process. The system for the flow process was constituted of a chromatographic Omnifit column (6.6 mm ID) refilled with supported catalyst **II** (500 mg, f = 1.05 mmol g^{-1}) connected to a THALESNano micro HPLC pump (Table 3). Toluene was flushed for 60 min at 200 μL min^{-1} flow rate to swell the catalyst, and different mixtures of **4a** and **5** (unreactive in the absence of catalyst) were pumped through the reactor at 100 μL min^{-1} flow rate.

Initially, we studied the influence of the substrate concentration, and the ratio of the reagents in the continuous flow amination process. To this end, mixtures (5 mL) of different concentration, and ratio of oxindole **4a** and azodicarboxylate **5** in toluene were injected (100 μL min^{-1}, residence time 10 min) in the column, and the product **6a** was collected (Table 3, entries 1-4). The solid phase was washed with toluene for 30 min after each injection. Fortunately, decreasing the molar ratio **5**/**4a** from 2 to 1.2 equivalents did not modify either the conversion or the enantiomeric ratio of product **6a** (entries 1,2 in Table 3).

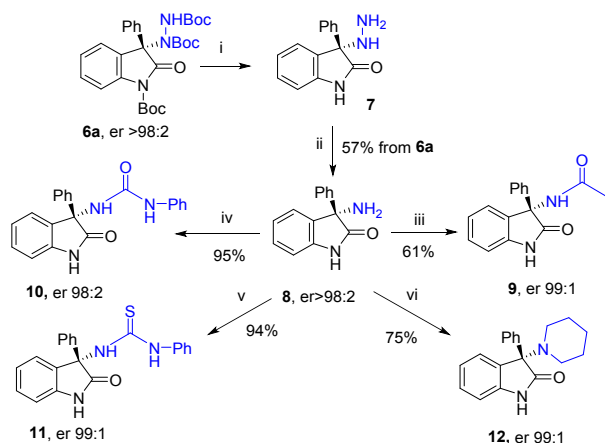**Table 3** α-Amination of oxindole **4a** with **5** in flow conditions.

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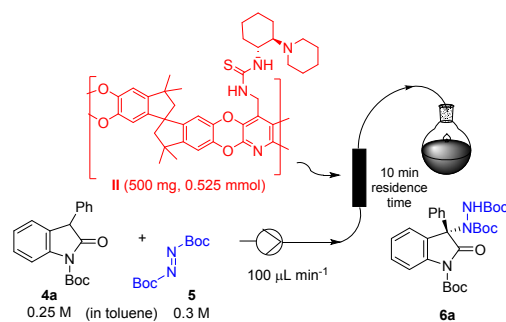
[a]Molar concentration of **4a**. [b]Determined by ^{1}H NMR in the reaction mixture. [c]Isolated yield after purification by flash chromatography. [d]Determined by HPLC on a chiral column.

The effect that the concentration (0.1-0.25 M) had on the reaction was also studied but no change was observed either in the substrate conversion, or in the enantioselectivity (entries 2-4 in Table 3). These facts led us to perform the reaction with less azodicarboxylate and solvent than previously described,[18a] facilitating the isolation and purification of the final product. Interestingly, the enantioselection in the flow experiments increased with respect to the batch reaction carried out under the same conditions (compare entry 1 in Table 3 with entries 4, 9-12 in Table 1).

Under the best reaction conditions (entry 4 in Table 3), we decided to scale the continuous-flow process to prepare enantioenriched **6a** in multigram quantity. A mixture of 3.25 g of **4a** and 2.90 g of **5** in 42 mL of toluene (0.25 M, and 0.30 M respectively for **4a** and **5**) was injected in the column previously used for seven hours (100 µL min^{-1}). The process was followed by ^{1}H NMR (conversion), and HPLC on a chiral column (enantioselection) of aliquots each 60 min. It was observed the total conversion, and a constant enantiomeric ratio (entries 5-10 in Table 3). The system was running for seven hours, and the final mixture was purified by flash chromatography to yield amination product **6a** in 82% yield (4.65 g, 8.62 mmol), and good enantioselectivity (er 87:13). The residence time was 10 min, the calculated productivity 2.35 mmol mmolcat^{-1}h^{-1}, and a TON of 16 (entry 11 in Table 3).

It is important to note that recrystallization of the mixture of enantiomers (er 87:13) from hexane-EtOAc allowed to obtain practically enantiopure **6a** (er ≥98:2) from the mother liquor in 85% yield.

The practical synthetic application of the amination process was demonstrated, as an example, by transformation of compound **6a** into a series of compounds **8**-**12** with potential pharmacological interest (Scheme 2).

Entry[a]	t (min)	C[a] (M)	Ratio 4a/5	Conversion[b] (Yield)[c]	er[d]
1	50	0.1	1:2	100 (80)	88:12
2	50	0.1	1:1.2	100 (84)	88:12
3	50	0.2	1:1.2	100 (84)	88:12
4	50	0.25	1:1.2	100 (85)	88:12
5	60	0.25	1:1.2	100	88:12
6	120	0.25	1:1.2	100	88:12
7	180	0.25	1:1.2	100	87:13
8	240	0.25	1:1.2	100	87:13
9	300	0.25	1:1.2	100	87:13
10	360	0.25	1:1.2	100	87:13
11	420	0.25	1:1.2	100 (82)	87:13

Amination product **6a** was deprotected with a 4M solution of HCl in dioxane into the hydrazine derivative **7**, which was transformed into almost enantiomerically pure (*S*)-3-amino-3-phenylindolin-2-one **8**[14] by stirring with Nickel Raney. Different 3-substituted amidoyloxindoles have been prepared to modulate their bioactivity in the racemic form,[27] and we transformed amine **8** into enantiopure acetamide **9** by refluxing in a mixture of Zn(OAc)$_2$ and acetic acid.[28]

Ureas and thioureas derived from oxindoles have been described as antitumoral,[29] and antimicrobial and antineoplastic agents[30] respectively. Urea **10** was obtained from **8** by reaction with phenyl isocyanate, whereas thiourea **11** was prepared by condensation with phenyl isothiocyanate, in excellent yields. Finally, (*S*)-3-phenyl-3-(piperidin-1-yl)indolin-2-one **12**, previously described as a racemic mixture,[31] was obtained practically enantiopure in 75% yield by reductive amination[32] of **8** with glutaraldehyde.

Conclusions

In summary, a novel chiral bifunctional thiourea has been prepared in few steps and high yield by modification of bottom-up synthesized polymer of intrinsic microporosity. Both the novel and the previously prepared thiourea **I** have been used as efficient organocatalysts for the enantioselective α-amination of 3-aryl-substituted oxindoles at room temperature, creating a quaternary stereocenter. Of special interest is the catalyst **II** which can be recycled or used in a flow process for long periods of time without observed deactivation or necessity of activation. The described protocol allows to prepare chiral 3-substituted 3-amino-2-oxindoles in multigram scale with very good yields and enantiomerically pure after a single recrystallization.

Experimental

General Information

^{1}H NMR (400 or 500 MHz) and ^{13}C NMR (100 or 126 MHz) spectra were recorded in CDCl$_3$ or DMSO-d$_6$ as solvent. Chemical shifts for protons are reported in ppm from TMS with the residual CHCl3 resonance as internal reference. Chemical shifts for carbons are reported in ppm from TMS and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d =

Scheme 2 Reagents and conditions: (i) 4M HCl/dioxane, rt, 6h. (ii) Raney Ni, EtOH/HOAc, rt, 8h. (iii) Zn(OAc)$_2$, HOAc, reflux, 10h. (iv) Phenyl isocyanate, MeCN, rt, 3h. (v) Phenyl isothiocyanate, CH$_2$Cl$_2$, rt, 5h. (vi) Glutaraldehyde, NaCNBH$_3$, EtOH, HOAc, 4˚C, 16h.

doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants in Hertz, and integration. Solid- state ^{13}C cross-polarization magic angle spinning NMR spectra (CP/ MAS ^{13}C NMR) were recorded on a Bruker Advance 400 spectrometer equipped with a 89 mm wide bore and a 9.4 T superconducting magnet. The spectrometer was operated at a Larmor frequency of 100 MHz using a contact time of 1 ms and a delay time of 3 s. All samples were spun at 11 kHz.

Specific rotations were measured on a Perkin-Elmer 341 digital polarimeter using a 1 mL cell with a 1-dm path length, and a sodium lamp, and concentration is given in g per 100 mL. Infrared spectra were recorded on a Perkin-Elmer Spectrum One FT-IR spectrometer and are reported in frequency of absorption (only the structurally most important peaks are given).

Flash chromatography was carried out using silica gel (230–240 mesh). TLC analysis was performed on glass-backed plates coated with silica gel 60 and an F254 indicator, and visualized by either UV irradiation or by staining with phosphomolybdic acid or potassium permanganate solutions. Melting points were obtained with open capillary tubes and are uncorrected. Chemical yields refer to pure isolated substances. Chiral HPLC analysis was performed on a JASCO HPLC system (JASCO PU-2089 pump and UV-2075 UV/Vis detector) and on a Hewlett-Packard 1090 Series II instrument equipped with a quaternary pump using Phenomenex Lux Amylose-1 (250 x 4.6 mm) and Lux Cellulose-1 (250 x 4.6 mm). Elemental analyses were carried out at the Elemental Analysis Center of the Complutense University of Madrid, using a LECO CHNS-932. ESI mass spectra were obtained on an Agilent 5973 inert GC/MS system. The molecular weight and molecular weight distributions for the starting soluble PIM-1n were measured by gel permeation chromatography (GPC) using Styragel columns and CHCl$_3$ as the eluent at a flow rate of 1mL min^{-1}. Thermogravimetric analysis (TGA) was performed under nitrogen, using a Mettler, Mod. TGA/ STDA 851e with a heating rate of 10 °C min^{-1} over a temperature range of 50-850 °C. Scanning electron microscopy (SEM) images were taken with a Hitachi S-8000 FE-SEM on Au-metallized samples (Polaron SC7640) operating under high vacuum at the ICTP-CSIC Electronic Microscopy facilities. BET surface area and pore size distribution analysis by N$_2$ gas adsorption were measured at −196 °C (77 K) in a volumetric device ASAP 2420 (Micromeritics) at the ICP-CSIC (Technical Research Support Unit). Samples were degassed at 120 °C for 16 h under vacuum, before the sorption measurements, to eliminate the sample humidity and any other adsorbed gases.

Commercially available reagents were used as purchased without further treatment. Solvents were dried and stored over microwave-activated 4 Å molecular sieves. Thiourea I[22] (f = 1.47 mmol g^{-1}) and isothiocyanate 3[24] were prepared as previously described. N-Boc-protected 3-aryloxindoles 4a,d-g[15] and 4b-c[33] were synthesized according to known literature procedures. Racemic reference samples were prepared using 1,4-diazabicyclo[2.2.2]octane (DABCO) in the same conditions that the asymmetric reaction.

PIM-1n.[23] A mixture of 5,5',6,6'-tetrahydroxy-3,3,3',3'-tetramethyl-1,1'-spirobisindane (1.0 g, 2.85 mmol, 1 equiv) and 2,3,5,6-tetrafluoro-4-pyridinecarbonitrile (0.50 g, 2.85 mmol, 1 equiv) was dissolved in anhydrous DMF (20 mL). Anhydrous K$_2$CO$_3$ powder (3.15 g, 22.8 mmol, 8 equiv) was added quickly and the mixture was stirred for 72h at 70 °C under nitrogen. Then the reaction was poured into water (50 mL) and the precipitate formed was collected by filtration. Repeated precipitations from acetone (150 mL) of the crude product dissolved in chloroform (50 mL) gave 1.13 g (2.59 mmol, 91% yield) of fluorescent yellow polymer after complete drying. M$_n$ = 9509 and M$_w$ = 36914 by GPC, calculated against polystyrene standards. ^1H NMR (400 MHz, CDCl$_3$): δ 6.75 (br, 2H), 6.38 (br, 2H), 2.7-1.9 (br, 4H), 1.31 (br, 12H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 149.2, 146.5, 141.7, 140.4, 140.3, 139.4, 139.3, 134.7, 112.5, 110.3, 109.0, 98.8, 59.1, 57.1, 43.4, 31.3, 29.9 ppm; IR (ATR): 2960, 2866, 2241, 1637, 1593, 1491, 1430, 1307, 1287, 1242, 1107, 1058, 997, 870 cm^{-1}. The effective functionalization, f = 2.2 mmol g^{-1}, was calculated on the basis of nitrogen elemental analysis: C: 70.83, H: 4.76, N: 6.16.

Amine-PIM-1n. PIM-1n (1.04 g, 2.29 mmol) was stirred in anhydrous THF (65 mL) under an inert atmosphere of nitrogen. The mixture was cooled to 0 °C and 1M borane-THF complex (6.41 mL, 6.41 mmol, 2.8 equiv) was added dropwise to the reaction mixture. The reaction was set to reflux overnight with constant stirring and the product was precipitating. After cooling, ethanol (40 mL) was added dropwise to remove excess borane. The solid was collected and stirred overnight in 1M methanolic HCl (60 mL), then collected by filtration and stirred in 5% aqueous NaOH solution (100 mL) for 3 h. The solid was washed repeatedly with water until neutral pH and acetone and dried under vacuum at 60 °C to give 840 mg of a pale yellow solid (83% yield). IR (ATR): 3359, 2955, 2866, 1629, 1597, 1486, 1417, 1307, 1291, 1258, 1107, 980 cm^{-1}. An effective functionalization, f = 2.075 mmol g^{-1}, was calculated on the basis of nitrogen elemental analysis: C: 67.93, H: 5.42, N: 5.81.

Polymeric thiourea II. To a suspension of **Amine PIM-1n** (544 mg, 1.13 mmol) in anhydrous CH$_2$Cl$_2$ (30 mL) was added a solution of isothiocyanate 3 (507 mg, 2.26 mmol, 2 equiv) in CH$_2$Cl$_2$ under nitrogen atmosphere, and the mixture was stirred for 24h at room temperature. The yellow solid was collected by filtration, washed with CH$_2$Cl$_2$, acetone and dried under vacuum to give 718 mg of grafted-thiourea **II** (90 % yield). ^{13}C-SS CP/MAS NMR analysis: δ 186.2, 149.5, 142.0, 133.8, 112.1, 57.9, 44.0, 30.9, 25.4 ppm; IR (ATR): 3323, 2931, 2853, 1637, 1597, 1523, 1486, 1429, 1413, 1311, 1295, 1250, 1213, 1107, 997 cm^{-1}. The effective functionalization, f = 1.05 mmol g^{-1}, was calculated on the basis of sulfur elemental analysis: C: 68.28, H: 6. 31, N: 7. 43, S: 3.35.

General procedure for the enantioselective α-amination reaction in batch conditions. To a solution of 3-aryl oxindole **4a-g** (0.1 mmol, 1 equiv) and di-tert-butyl-azodicarboxylate **5** (0.2 mmol, 2 equiv.) in toluene (1 mL) at the prescribed temperature was added the corresponding grafted PIM's catalyst **I** or **II** (5 mol %). The mixture was stirred until the

reaction was finished (TLC). The catalyst was collected by filtration and washed with toluene (2 × 0.5 mL) and dichloromethane (2 × 0.5 mL). The filtrate was concentrated under reduced pressure and the residue was directly purified by flash column chromatography (silica gel, hexane/diethyl ether 8:1 to 2:1) to give the pure α-amination products **6a-g**. For the recycled experiments with **II** (entries 9-12 in Table 1), the catalyst was washed with toluene and dichloromethane, dried under vacuum at 60 ºC until constant weight, and reused in the next experiment.

(*S*)-Di-tert-butyl-1-[1-(tert-butoxycarbonyl)-2-oxo-3-phenylindolin-3-yl]hydrazine-1,2-dicarboxylate (6a).[15] Product **6a** was prepared according to the general procedure, using oxindole **4a** (31 mg, 0.1 mmol), di-tert-butyl-azodicarboxylate **5** (46 mg, 0.2 mmol) and catalyst **II** (4.8 mg, 0.005 mmol) in toluene (1 mL) at -40 °C. The crude reaction mixture was purified by flash chromatography (hexane/diethyl ether: 5:1) leading to compound **6a** as a white solid (49 mg, 0.091 mmol, 91% yield, er: 94:6). $[\alpha]_D^{25}$ = + 27.6 (c = 0.7, CHCl$_3$) [Lit. [15] $[\alpha]_D^{25}$ = + 26.4 (c = 1.7, CHCl$_3$, 93% ee for (*S*) enantiomer]; Chiral HPLC analysis (Lux Amylose-1, hexane/2-propanol 95:5, λ = 220 nm, 0.7 mL min^{-1}): t_R = 43.1 min (major, *S*), t_R = 58.5 min (minor, *R*); ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.25 (d, *J* = 7.3 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.54 (br, 2H), 7.36-7.33 (m, 1H), 7.32-7.27 (m, 4H), 6.28 (s, 1H), 1.60 (s, 9H), 1.29 (s, 9H), 1.19 (s, 9H) ppm.

(*S*)-Di-tert-butyl-1-[1-(tert-butoxycarbonyl)-5-chloro-2-oxo-3-phenylindolin-3-yl]hydrazine-1,2-dicarboxylate(6b). Product **6b** was prepared according to the general procedure, using oxindole **4b** (34 mg, 0.1 mmol), di-tert-butyl-azodicarboxylate **5** (46 mg, 0.2 mmol) and catalyst **II** (4.8 mg, 0.005 mmol) in toluene (1.0 mL) at -40 ºC. The crude reaction mixture was purified by flash chromatography (hexane/diethyl ether: 4:1) leading to compound **6b** as a white solid (54 mg, 0.094 mmol, 94% yield, er: 94:6). $[\alpha]_D^{25}$ = +81.7 (c = 0.5, CHCl$_3$); Chiral HPLC analysis (Lux Amylose-1, hexane/2-propanol 90:10, λ = 220 nm, 0.7 mL min^{-1}): t_R = 26.5 min (minor, *R*), t_R = 35.4 min (major, *S*); m.p. 123-125 ˚C; ^{1}H-NMR (500 MHz, CDCl$_3$): δ 8.27 (br, 1H), 7.76 (d, *J* = 8.6 Hz, 1H), 7.53-7.49 (m, 2H), 7.33-7.28 (m, 4H), 6.27 (s, 1H), 1.59 (s, 9H), 1.29 (s, 9H), 1.23 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 173.4, 154.6, 153.0, 148.9, 137.3, 132.4, 131.1, 129.9, 129.5, 129.0, 128.9, 128.4, 126.4, 116.0, 84.6, 83.4, 81.1, 72.4, 31.5, 27.8, 22.6, 14.1 ppm; IR (ATR): 3336, 2976, 2935, 1778, 1729, 822, 729 cm^{-1}; HRMS (ESI): m/z calcd for C$_{29}$H$_{36}$ClN$_3$O$_7$: 596.2164 [M+Na]$^+$; found 596.2145.

(*S*)-Di-tert-butyl-1-[5-bromo-1-(tert-butoxycarbonyl)-2-oxo-3-phenylindolin-3-yl]hydrazine-1,2-dicarboxylate (6c). Product **6c** was prepared according to the general procedure, using oxindole **4c** (39 mg, 0.1 mmol), di-tert-butyl-azodicarboxylate **5** (46 mg, 0.2 mmol) and catalyst **I** (3.4 mg, 0.005 mmol, *f* =1.47 mmol g^{-1}) in toluene (1 mL) at -40 °C. The crude reaction mixture was purified by flash chromatography (hexane/diethyl ether: 4:1) leading to compound **6c** as a white solid (48 mg, 0.078 mmol, 78% yield, er: 97:3). $[\alpha]_D^{25}$ = +118.5 (c = 0.7, CHCl$_3$); Chiral HPLC analysis (Lux Amylose-1, hexane/2-propanol 90:10, λ = 220 nm, 0.7 mL min^{-1}): t_R =31.5 min (minor, *R*), t_R = 43.1 min (major, *S*); m.p. 133-135 ˚C; [1]H

NMR (400 MHz, CDCl$_3$): δ 8.37 (br, 1H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.50-7.47 (m, 2H), 7.35-7.26 (m, 4H), 6.25 (s, 1H), 1.57 (s, 9H), 1.28 (s, 9H), 1.22 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 173.3, 154.6, 153.0, 148.9, 137.8, 132.4, 131.8, 131.4, 129.5, 129.2, 129.0, 128.8, 128.4, 117.5, 116.9, 116.5, 84.7, 83.4, 81.1, 77.3, 31.6, 28.0, 27.9, 27.8, 22.6, 14.1 ppm; IR (ATR): 3336, 2980, 2935, 1778, 1729, 1470, 818, 725 cm^{-1}; HRMS (ESI): m/z calcd for C$_{29}$H$_{36}$BrN$_3$O$_7$: 640.1629 [M+Na]$^+$; found 640.1638.

(*S*)-Di-tert-butyl-1-[1-(tert-butoxycarbonyl)-5-methoxy-2-oxo-3-phenylindolin-3-yl]hydrazine-1,2-dicarboxylate(6d).[13,15] Product **6d** was prepared according to the general procedure, using oxindole **4d** (34 mg, 0.1 mmol), di-tert-butyl-azodicarboxylate **5** (46 mg, 0.2 mmol) and catalyst **II** (4.8 mg, 0.005 mmol) in toluene (1 mL) at -40 °C. The crude reaction mixture was purified by flash chromatography (hexane/diethyl ether: 8:1) leading to compound **6d** as a white solid (51 mg, 0.09 mmol, 90% yield, er: 93:7). $[\alpha]_D^{25}$ = + 68.2 (c = 0.7, CHCl$_3$) [Lit.[15] $[\alpha]_D^{25}$ = + 79.9 (c = 1.0, CHCl$_3$, 96% ee for (*S*) enantiomer)]; Chiral HPLC analysis (Lux Cellulose-1, hexane/2-propanol 99:1, λ = 220 nm, 1.0 mL min^{-1}): t_R = 24.2 min (major, *S*), t_R = 48.4 min (minor, *R*); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.92 (br, 1H), 7.71 (d, *J* = 8.9 Hz, 1H), 7.56-7.51 (m, 2H), 7.32-7.27 (m, 3H), 6.88 (dd, *J* = 8.8, 2.8 Hz, 1H), 6.26 (s, 1H), 3.88 (s, 3H), 1.59 (s, 9H), 1.29 (s, 9H), 1.22 (s, 9H) ppm.

(*S*)-Di-tert-butyl-1-(1-(tert-butoxycarbonyl)-5-methyl-2-oxo-3-phenylindolin-3-yl)hydrazine-1,2-dicarboxylate (6e).[15] Product **6e** was prepared according to the general procedure, using oxindole **4e** (32 mg, 0.1 mmol), di-tert-butyl-azodicarboxylate **5** (46 mg, 0.2 mmol) and catalyst **I** (3.4 mg, 0.005 mmol) in toluene (1 mL) at -40 °C. The crude reaction mixture was purified by flash chromatography (hexane/diethyl ether: 4:1) leading to compound **6e** as a white solid (49 mg, 0.088 mmol, 88% yield, er: 93:7). $[\alpha]_D^{25}$ = + 68.7 (c = 0.8, CHCl$_3$) [Lit.[15] $[\alpha]_D^{25}$ = + 67.2 (c = 2, CHCl$_3$, 96% ee for (*S*) enantiomer)]; Chiral HPLC analysis (Lux Cellulose-1, hexane/2-propanol 99:1, λ = 220 nm, 1.0 mL min^{-1}): t_R =13.8 min (major, *S*), t_R = 24.7 min (minor, *R*); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.98 (s, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.55 (br, 2H), 7.30-7.27 (m, 3H), 7.14 (dd, *J* = 8.3, 1.9 Hz, 1H), 6.28 (s, 1H), 2.45 (s, 3H), 1.60 (s, 9H), 1.30 (s, 9H), 1.20 (s, 9H) ppm.

(*S*)-Di-tert-butyl-1-(1-(tert-butoxycarbonyl)-3-(4-methoxyphenyl)-2-oxoindolin-3-yl)hydrazine-1,2-dicarboxylate (6f).[15] Product **6f** was prepared according to the general procedure, using oxindole **4f** (34 mg, 0.1 mmol), di-tert-butyl-azodicarboxylate **5** (46 mg, 0.2 mmol) and catalyst **II** (4.8 mg, 0.005 mmol) in toluene (1 mL) at -40 °C. The crude reaction mixture was purified by flash chromatography (hexane/diethyl ether: 3:1) leading to compound **6f** as a white solid (48 mg, 0.085 mmol, 85% yield, er: 86:14). $[\alpha]_D^{25}$ = +68.2 (c = 0.7, CHCl$_3$) [Lit.[15] $[\alpha]_D^{25}$ = + 38.7 (c = 2.1, CHCl$_3$, 95% ee for (*S*) enantiomer)]; Chiral HPLC analysis (Lux Amylose-1, hexane/2-propanol 90:10, λ = 220 nm, 1.0 mL min^{-1}): t_R = 26.5 min (major, *S*), t_R = 46.9 min (minor, *R*); ^{1}H NMR (500 MHz, CDCl$_3$): δ 8.25 (d, *J* = 7.3 Hz, 1H), 7.78 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.34-7.27 (m, 2H), 6.82 (d, *J* = 8.6 Hz, 2H),

6.26 (s, 1H), 3.77 (s, 3H), 1.60 (s, 9H), 1.31 (s, 9H), 1.18 (s, 9H) ppm.

(S)-Di-tert-butyl-1-(1-(tert-butoxycarbonyl)-2-oxo-3-(4 (trifluoromethyl)phenyl)indolin-3-yl)hydrazine-1,2-dicarboxylate (6g). Product **6g** was prepared according to the general procedure, using oxindole **4g** (38 mg, 0.1 mmol), di-tert-butyl azodicarboxylate **5** (46 mg, 0.2 mmol) and catalyst **II** (4.8 mg, 0.005 mmol) in toluene (1 mL) at -40 °C. The crude reaction mixture was purified by flash chromatography (hexane/diethyl ether: 4:1) leading to compound **6g** as a white solid (55 mg, 0.091 mmol, 91% yield, er: 91: 9). Chiral HPLC analysis (Lux Amylose-1, hexane/2-propanol 90:10, λ = 220 nm, 1.0 mL min^{-1}): t_R = 10.0 min (major, *S*), t_R = 31.3 min (minor, *R*); m.p. 117-119 ˚C; [α]$_D^{25}$ = +62.4 (c = 0.9, CHCl$_3$); ^{1}H NMR (500 MHz, CDCl$_3$): δ 7.82 (d, J = 8.1 Hz, 1H), 7.69 (d, J = 8.2 Hz, 1H), 7.56 (d, J = 8.6 Hz, 2H), 7.41-7.28 (m, 2H), 6.30 (s, 1H), 1.59 (s, 9H), 1.30 (s, 9H), 1.20 (s, 9H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$): δ 173.6, 154.8, 152.9, 148.9, 138.9, 137.2, 130.8 (q, $^2J_{C-F}$ = 32.7 Hz), 130.1, 129.3, 126.4, 125.0 (q, $^3J_{C-F}$ = 3.9 Hz), 124.7, 123.8 (q, $^1J_{C-F}$ = 272.3 Hz), 114.9, 84.6, 83.5, 81.3, 72.1, 28.0, 27.9, 27.7ppm. IR (ATR): 3332, 2978, 2952, 1777, 1732, 1480, 1366, 1325, 1252, 1154, 1102, 1064, 833, 755 cm^{-1}; HRMS (ESI): m/z calcd for C$_{30}$H$_{36}$F$_3$N$_3$O$_7$: 630.2403 [M+Na]$^+$; found 630.2403.

Experimental set-up for the continuous flow α-amination of N-Boc protected 3-phenyl oxindole 4a. For the continuous flow experiments, the instrumental is schematized in Table 3. The packed bed reactor consisted of a vertically mounted Omnifit column (6.6 internal diameter and 50 mm length) containing the grafted PIM's catalyst **II** (500 mg, f = 1.05 mmol g^{-1}, 0.525 mmol). The reactor inlet was connected to a THALESNano micro HPLC pump. First, toluene was flushed for 60 min at 200 μL min^{-1} flow rate to swell the catalyst. After that, the channel was fed with a solution of N-Boc 3-phenyloxindole **4a** (3.24 g, 10.5 mmol, 1.0 equiv, 0.25 M) and di-tert-butyl azodicarboxylate 5 (2.90 g, 12.6 mmol, 1.2 equiv, 0.30 M) in toluene (42 mL), which was pumped through the reactor at 100 μL min^{-1} flow rate (Table 3). The reactor outlet was connected to a flask, where the product was collected. Samples were collected each 60 min to determine conversion and enantiomeric ratio of the final product by ^{1}H NMR and HPLC analysis, respectively. The system was running for 7 h and the catalyst was washed with toluene for 60 min at 200 μL min^{-1} flow rate. Then, the solvent was removed under reduced pressure and the crude was purified by flash column chromatography on silica gel (hexane/diethyl ether, 5:1) to afford the final pure product as a white solid in 82% isolated yield (4.65 g, 8.62 mmol), er 87:13. Productivity: 2.345 mmol mmolcat^{-1} h^{-1}; TON: 16, residence time: 10 min.

A sample of **6a** (1.0 g, er: 87:13) was recrystallized from hexane/EtOAc (10:1) to afford 0.15 g of **6a** as white crystals (quasi-racemic mixture, er: 57:43) and 0.82 g of enantiomerically pure **6a** from the mother liquors (er ≥98:2). This last fraction was used to prepare compounds **8**-**12**.

(S)-3-Hydrazineyl-3-phenylindolin-2-one (7). To a solution of 4M HCl, in 1,4-dioxane (7.5 mL, 30 mmol) was added **6a** (469 mg, 0.87 mmol) in MeOH (5 mL) and the mixture was stirred for 6h at room temperature. The solvent was evaporated

under vacuum to give **7** as a colorless solid, which was used for the next step without purification. [α]$_D^{25}$ = -191.1 (c = 1.1, MeOH); ^{1}H NMR (400 MHz, DMSO-d$_6$): δ 10.92 (s, 1H), 9.05 (s, 1H), 7.46-7.25 (m, 7H), 7.03 (td, J = 7.6, 1.0 Hz, 1H), 6.95 (m, 1H), 3.55 (s, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 181.7, 147.3, 135.2, 134.0, 133.8, 133.4, 131.8, 130.9, 127.5, 115.8, 71.5 ppm; IR (ATR): 3057, 2943, 2859, 1701, 1621, 1469, 1333, 1223, 1181, 1113, 873, 754 cm^{-1}. HRMS (ESI): m/z calcd for C$_{14}$H$_{13}$N$_3$O: 240.1131 [M+H]$^+$; found 240.1135.

(S)-3-Amino-3-phenylindolin-2-one (8).[14] Crude **7** was dissolved in EtOH/HOAc = 3/2 (6.8 mL/4.5 mL), followed by the addition of Ni-Raney (230 mg) at room temperature under a nitrogen atmosphere. The resulting suspension was stirred for 8 h, and then filtered. The filtrate was treated with water (15 mL), and then made alkaline with saturated NaHCO$_3$ solution and extracted with CH$_2$Cl$_2$ (3 x 20 mL). The combined organic layers were dried with MgSO$_4$, filtered, and the organic solvent was evaporated under vacuum. The residue was purified by silica gel column chromatography (hexane/EtOAc from 5:1 to 1:1) to give **8** (white solid, 112 mg, 0.50 mmol, 57% yield, er: 99: 1); [α]$_D^{25}$ = -26.1 (c = 0.8, MeOH) [Lit.[14] [α]$_D^{20}$ = -26.7 (c = 1.2, MeOH, 88% ee for (*S*) enantiomer)]; Chiral HPLC analysis (Lux Cellulose-1, hexane/2-propanol 85:15, λ = 230 nm, 1.0 mL min^{-1}): t_R = 17.4 min (minor, *R*), t_R = 21.3 min (major, *S*); m.p. 261-263 ˚C; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 10.41 (br, 1H), 7.35-7.12 (m, 8H), 7.08 (m, 1H), 6.88 (m, 2H), 2.56 (br 2H) ppm.

(S)-N-(2-Oxo-3-phenylindolin-3-yl)acetamide (9). To a mixture of HOAc (0.5 mL) and zinc acetate (46 mg, 0.25 mmol) was added **8** (20 mg, 0.09 mmol). The reaction mixture was refluxed for 10h. After the reaction was completed, HOAc was removed under reduced pressure and the residue was purified by silica gel flash chromatography (Hexane/EtOAc 2:1) to afford **9** (pale yellow solid, 15 mg, 0.055 mmol, 61% yield, er: 99: 1); [α]$_D^{25}$ = +51.9 (c = 0.32, MeOH); Chiral HPLC analysis (Lux Amylose-1, hexane/2-propanol 70:30, λ = 254 nm, 1.0 mL min^{-1}): t_R = 6.7 min (minor, *R*), t_R = 12.1 min (major, *S*); m.p. 187-189˚C; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 10.27 (s, 1H), 8.88 (s, 1H), 7.36-7.31 (m, 3H), 7.29-7.25 (m, 2H), 7.21 (td, J = 7.6, 1.2 Hz, 1H), 7.17 (dd, J = 7.4, 1.2 Hz, 1H), 6.99 (td, J = 7.5, 1.0 Hz, 1H), 6.81 (dd, J = 7.8, 0.9 Hz, 1H), 1.84 (s, 3H) ppm; ^{13}C NMR (126 MHz, DMSO-d$_6$): δ 176.8, 169.4, 142.9, 138.6, 131.7, 128.9, 128.8, 128.7, 127.3, 122.0, 109.9, 64.8, 22.5 ppm; IR (ATR): 3252, 3061, 3028, 1717, 1654, 1620, 1489, 1472, 1371, 1242, 742 cm^{-1}; HRMS (ESI): m/z calcd for C$_{16}$H$_{14}$N$_2$NaO$_2$: 289.0947 [M+Na]$^+$; found 289.0953.

(S)-1-(2-Oxo-3-phenylindolin-3-yl)-3-phenylurea (10). A mixture of phenyl isocyanate (6.0 μL, 0.054 mmol) and **8** (10 mg, 0.045 mmol) in MeCN (1 mL) was stirred for 3h at room temperature. After that, the solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (Hexane/EtOAc 3:1) to afford **10** (white solid, 15 mg, 0.043 mmol, 95 % yield, er: 98: 2); [α]$_D^{25}$ = +108.7 (c = 0.3, MeOH); Chiral HPLC analysis (Lux Amylose-1, hexane/2-propanol 85:15, λ = 254 nm, 1.0 mL min^{-1}): t_R = 20.3 min (minor, *R*), t_R = 37.8 min (major, *S*); m.p 213-215 ˚C; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 10.35 (s, 1H), 8.68 (s, 1H), 7.40-

7.25 (m, 9H), 7.23 (td, J = 7.7, 1.2 Hz, 1H), 7.17 (dd, J = 8.5, 7.3 Hz, 2H), 6.99 (t, J = 7.3 Hz, 1H), 6.90-6.83 (m, 2H) ppm; ^{13}C NMR (100 MHz, DMSO-d$_6$): δ 177.6, 154.1, 142.7, 140.2, 139.3, 132.4, 129.1, 129.1, 128.9, 128.72, 126.8, 124.5, 121.8, 117.8, 110.1, 64.8 ppm; IR (ATR): 3374, 3319, 1735, 1668, 1601, 750 cm^{-1}; HRMS (ESI): m/z calcd for C$_{21}$H$_{17}$N$_3$O$_2$Na: 366.1213 [M+Na]$^+$; found 366.1229.

(S)-1-(2-Oxo-3-phenylindolin-3-yl)-3-phenylthiourea (11). A mixture of phenyl isothiocyanate (7 µL, 0.055 mmol) and **8** (10 mg, 0.045 mmol) in MeCN (1 mL) was stirred for 3h at room temperature. After that, the reaction mixture was stirred for 5h at room temperature. The solvent was removed under reduced pressure and the residue was purified by silica gel flash chromatography (Hexane/EtOAc 2:1) to afford **11** (white solid, 15 mg, 0.042 mmol, 94 %, er: 99 : 1); [α]$_D^{25}$ = -142.0 (c = 0.34, CH$_2$Cl$_2$); Chiral HPLC analysis (Lux Amylose-1, hexane/2-propanol 70:30, λ = 220 nm, 1.0 mL min^{-1}): t$_R$ = 12.1 min (minor, R), t$_R$ = 28.4 min (major, S); m.p. 223-225˚C; ^{1}H NMR (500 MHz, DMSO-d$_6$): δ 10.41 (s, 1H), 9.82 (s, 1H), 8.34 (s, 1H), 7.52 (m, 2H), 7.41-7.34 (m, 5H), 7.29-7.24 (m, 3H), 7.21 (td, J = 7.7, 1.3 Hz, 1H), 7.07-7.02 (m, 1H), 6.99 (td, J = 7.5, 1.0 Hz, 1H), 6.79 (dd, J = 7.7, 0.9 Hz, 1H) ppm; ^{13}C-NMR (100MHz, DMSO-d$_6$): δ 179.5, 175.9, 142.9, 139.9, 139.4, 130.8, 129.1, 128.9, 127.4, 124.2, 122.3, 121.8, 110.1, 67.4 ppm; IR (ATR): 3243, 3058, 3019, 1714, 1620, 750 cm^{-1}; HRMS (ESI): m/z calcd for C$_{21}$H$_{17}$N$_3$OSNa: 382.0985 [M+Na]$^+$; found 382.100.

(S)-3-Phenyl-3-(piperidin-1-yl)indolin-2-one (12). To a solution of glutaraldehyde (20 µL, 50% water, 0.11 mmol) was added a solution of **8** (20 mg, 0.09 mmol) in EtOH (1mL), and NaCNBH$_3$ (10 mg, 0.16 mmol) at 0 ˚C. The reaction mixture was adjusted to pH5 by addition of glacial HOAc and stirred for 16h at 4 ˚C. After the reaction was complete (TLC), NaHCO$_3$ solution (5 mL) was added and the organic phase extracted with EtOAc (3 x 2mL). The combined organic layers were washed with brine, dried over anhydrous MgSO$_4$, filtered, and the organic solvent was evaporated under vacuum. The residue was purified by silica gel column chromatography (eluent, hexane/EtOAc 5:1) to give **12** (white solid, 20 mg, 0.067 mmol, 75% yield, er: 99 : 1); [α]$_D$25 = +9.6 (c = 0.26, CDCl$_3$); Chiral HPLC analysis (Lux Cellulose-1, hexane/2-propanol 95:5, λ = 254 nm, 1.0 mL min^{-1}): t$_R$ = 7.2 min (minor, R), t$_R$ = 11.2 min (major, S); m.p. 265-267 ˚C [Lit.^{30} m.p. 246 °C (dec). for the racemic mixture]; ^{1}H NMR (400 MHz, CDCl$_3$): δ 8.21 (br, 1H), 7.54 (d, J = 7.4 Hz, 1H), 7.36-7.19 (m, 5H), 7.04 (t, J = 7.5Hz, 1H), 6.89 (d, J = 7.7Hz, 1H), 2.55 (m, 4H), 1.57 (m, 4H), 1.44 (m, 2H) ppm; ^{13}C NMR (100 MHz, CDCl$_3$) δ 178.3, 140.5, 139.3, 130.1, 128.5, 127.8, 127.5, 126.2, 122.5, 110.1, 75.2, 48.4, 29.7, 26.6, 24.7; IR (ATR): 3243, 2930, 2854, 2829, 2799, 1722, 1676, 1621, 742 cm^{-1}; HRMS (ESI): m/z calcd for C$_{19}$H$_{20}$N$_2$O: 293.3820 [M+H]$^+$; found 293.1653.

Conflicts of interest

There are no conflicts to declare.

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Table of contents entry

Catalyst II can be used in batch and flow conditions
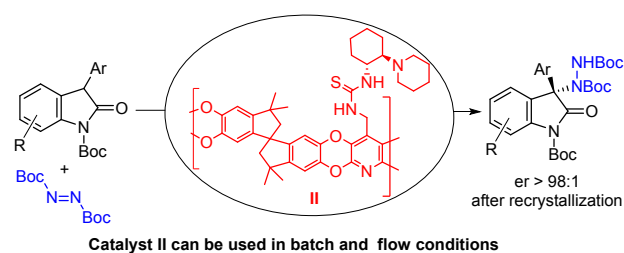
A multigram scale preparation of enantioenriched 3-aryl-3-amino-2-oxindoles promoted by a novel chiral bifunctional thiourea, readily prepared from polymers of intrinsic microporosity.