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Supported bifunctional chiral thioureas as catalysts in the synthesis of 3-amino-2-oxindoles through enantioselective aza-Friedel-Crafts reaction. Application in continuous flow processes.

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Abstract. Novel supported cinchone-derived thioureas promote highly enantioselective aza-Friedel-Crafts reaction of different naphthols with a variety of N-Boc ketimines derived from isatin. The catalysts are recoverable and reusable, and one of the supported catalyst has been used in a flow process allowing the synthesis of 3-amino-2-oxindole derivatives in multigram scale with high yield and enantioselectivity.

Keywords: Asymmetric catalysis; chiral 3-amino oxindoles; aza Friedel-Crafts reaction; bifunctional thioureas; flow chemistry; supported catalysts.

Introduction

Metal-transition complexes or organocatalytic-promoted asymmetric *aza*-Friedel-Crafts reaction using imines as electrophiles provides a rapid access to important enantioenriched amine derivatives.[1] Former examples of those organocatalyzed reactions refer to the additions to aldimines promoted by chiral BINOL-derived carboxylic[2] or phosphoric acids,[3] and cinchona derivatives.[4] More recently, chiral phosphoric acids have been also used as organocatalysts to promote the addition of aldimines,[5] and ketimines,[6] including isatin-derived ketimines.[7] Moreover, major attention has attracted heteroaromatic systems such as indoles,[8] pyrroles,[7,9] and furans[10] as donors. The lower reactivity of arenes as nucleophiles has made their reactivity less explored, although electron-reach phenols, and naphthols have been used in the organocatalyzed *aza*-Friedel-Crafts reaction with aldimines.[11]

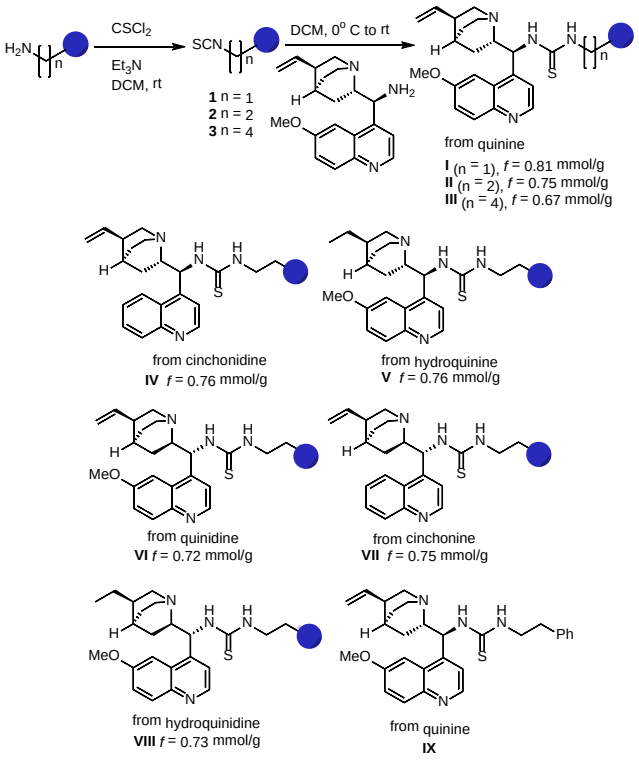
Recently, the first stereoselective reaction of naphthols with ketimines derived from isatin promoted by quinine-derived thioureas has been reported to yield the addition products with excellent enantioselection.[12] After that, taking advantage of the directing ability of the hydroxy group, thioureas and squaramides derived from quinine have been used as organocatalysts in the *aza*-Friedel-Crafts aminoalkylation of hydroxyindoles in the carbocyclic ring with ketimines derived from isatins,[13] and cyclic imines.[14] In a similar approach, bulky squaramides derived from quinine, are able to promote the same reaction on phenol derivatives.[15]

The use of ketimines derived from isatins as electrophiles in the asymmetric *aza*-Friedel-Crafts is especially interesting because it allows the synthesis of bioactive[16] 3-substituted-3-aminooxindoles with a predetermined stereochemistry at C-3, which is the responsible of the activity of these compounds.[17] All the described organocatalyzed reactions have been performed under homogeneous conditions, and the recovery of the catalysts presents problems associated with chromatographic separations. As a part of our program directed to the synthesis of easily recoverable and reusable chiral bifunctional organocatalysts[18] we decided to prepare a series of novel supported thioureas derived from cinchona alkaloids. These catalysts have been tested in the enantioselective *aza*-Friedel-Crafts reaction of different naphthols and isatin-derived ketimines in batch and, more important, flow conditions.

Results and Discussion

Eight supported bifunctional thioureas (**I-VIII**) derived from cinchona alkaloids were prepared, in two steps, as previously described[19] (Scheme 1). The reaction of commercially available methyl-, ethyl- and *n*-butylamino polystyrene with thiophosgene lead to isothiocyanates **1-3** in near quantitative yield. The condensation of these intermediates with the corresponding cinchona-derived primary amines gave the supported thioureas with excellent yield and high

effective functionalization calculated on the basis of the sulfur content in the final materials. Previously prepared[20] thiourea **IX**, molecular homolog of polymeric thiourea **II**, was also used in the reaction in homogeneous conditions for comparative purposes.



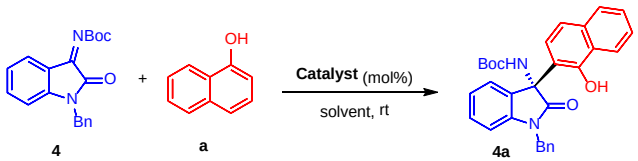
Scheme 1. Two steps synthesis of supported catalysts **I-VIII**, and molecular catalyst **IX**.

Catalysts **I-III** derived from quinine differ in the length of the tether of the chain joining the active thiourea with the polymeric material. Taking into account that the best results with these catalysts were obtained for the aminoethyl polystyrene (**II**), we prepared the related catalyst **IV**,[19] derived from cinchonidine, and **V** (from hydroquinine), which bear different functionalization in the aromatic or the bicyclic system respectively. Additionally, the pseudoenantiomeric catalysts were also synthesized from isothiocyanate **2** and quinidine (**VI**), cinchonine (**VII**),[19] and hydroquinidine (**VIII**) derivatives, respectively.

The reaction of isatin-derived ketimine (**4**) with 1-naphthol (**a**), catalyzed by polymeric materials **I-VIII** was selected to establish the best catalysts and reaction conditions (Table 1). First, the influence of the tether length between the thiourea and the polymer was determined using thioureas **I-III** as catalyst. All these catalysts were very active in toluene, yielding the aza-Friedel-Crafts product **4a** in excellent conversion, but catalyst **II** provided better enantioselection (entries 8, 11, and 12 in Table 1). Fortunately, supported catalyst **II** provides similar results in heterogeneous reaction than its molecular homolog **IX** in homogeneous conditions. Only a slight decrease in the enantioselection was observed in the reaction promoted by the polymeric catalyst (compare entries 8 *versus* 18 in Table 1).

The reaction conditions were initially studied by using **II** as catalyst in the reaction of ketimine **4** with 1.2 equivalents of 1-naphthol (**a**) at room temperature. It is interesting to note that in ethereal or polar solvents the reaction occurs in good to moderate yield, although as racemic mixtures (entries 1-4).

Table 1. Screening of conditions and catalysts.[a]



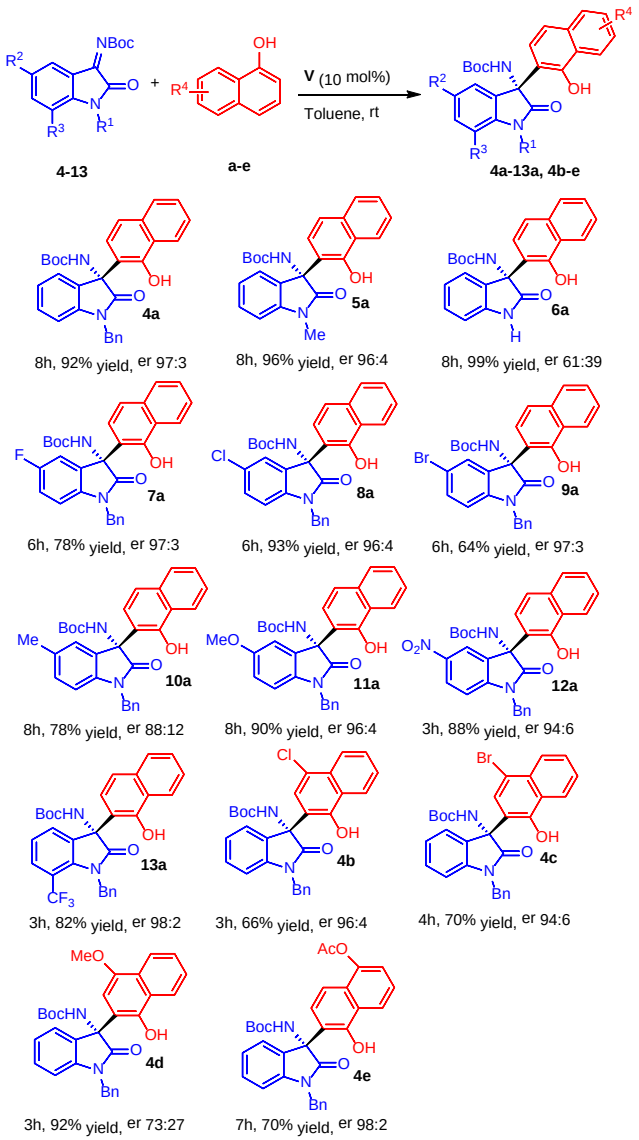
Entry	Catalyst (mol%)	Time (h)	Solvent	Conv. [b]	Er [c]
1	**II** (10)	8	CH_3CN	79	50:50
2	**II** (10)	8	Dioxane	27	51:49
3	**II** (10)	8	TBME	72	51:49
4	**II** (10)	8	THF	60	51:49
5	**II** (10)	8	$CHCl_3$	98	84:16
6	**II** (10)	8	DCM	77	82:18
7	**II** (10)	8	DCE	98	79:21
8	**II** (10)	8	Toluene	96	93:7
9	**II** (5)	24	Toluene	93	88:12
10[d]	**II** (10)	24	Toluene	88	76:24
11	**I** (10)	8	Toluene	100	90:10
12	**III** (10)	8	Toluene	96	81:19
13	**IV** (10)	8	Toluene	97	90:10
14	**V** (10)	8	Toluene	100	97:3
15	**VI** (10)	8	Toluene	91	11:89
16	**VII** (10)	8	Toluene	98	22:78
17	**VIII** (10)	8	Toluene	97	5:95
18	**IX** (10)	8	Toluene	98	99:1
19[e]	**V** (10)	8	Toluene	100	96:4
20[e]	**V** (10)	8	Toluene	100	96:4
21[e]	**V** (10)	8	Toluene	100	95:5
22[e]	**V** (10)	8	Toluene	100	97:3

[a] Unless stated otherwise, the reactions were carried out with **4** (0.1 mmol), **a** (0.12 mmol) and catalyst (0.01 mmol) in toluene (1.5 mL) at rt. [b] Conversion was determined by ^{1}HNMR of the crude mixtures. [c] Determined by HPLC on chiral columns. [d] Reaction performed at 0 ºC. [e] Entries 19-22 correspond to the recycling experiments (2-5) for entry 14.

Nearly quantitative yield but moderate enantioselection was obtained in halogenated solvents (entries 5, 7). Excellent yield (96% conversion), and very good enantioselection (93:7 er) were reached in toluene (entry 8), and the catalyst loading can be decreased to 5 mol% although the er was slightly lower and the reaction time increased to 24 h (entry 9). A drop in the conversion and in the enantioselection was observed when the reaction was carried out at 0 ºC (entry 10). Because the best results

were obtained with catalyst **V** in toluene as solvent (entry 14 in Table 1), we studied the evolution of the reaction of ketimine **4** with naphthol **a** with time (see Table S-1 in SI). We observed that the conversion increased with time, and the process was completed after 8 h of reaction, maintaining the enantioselection along the time. For comparative purposes this time was maintained constant for reactions carried out with different solvents and catalysts in Table 1.

Next we tested the ability of all the catalysts to promote the reaction in the best conditions. Catalyst **IV**, derived from cinchonidine, promoted the formation of **4a** in very high yield but lower stereoselection. The best catalyst was supported thiourea **V** derived from hydroquinine (compare entries 8, 13, and 14 in Table 1). The opposite enantiomer was obtained when pseudo enantiomeric thioureas (**VI-VIII**) were used as the catalysts (entries 15-17). It is noteworthy that only thiourea **VIII**, derived from hydroquinidine, maintains the chiral discrimination with respect to its pseudo-enantiomer (entries 14, 17 in Table 1), while **VI** and **VII** provide the enantiomer obtained with **II** and **IV** but with lower enantioselection (entries 15, 16 versus 8, 13 in Table 1).



Scheme 2. Scope of the aza-Friedel-Crafts for different imines and 1-naphthols.

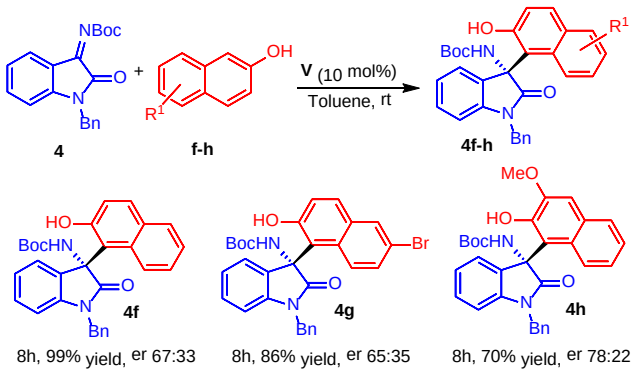
The recyclability of the catalyst was tested for the most active thiourea **V** (entries 19-22). The results showed that the catalyst could be recovered and reused for five cycles without loss of activity.

The scope of the reaction was studied with ketimines (**4-13**) and 1-naphthols (**a-e**), both bearing different substituents. The reactions were carried out by stirring, at room temperature, a mixture of ketimine (0.10 mmol), 1-naphthol (0.12 mmol) and catalyst **V** (10 mol%) in toluene (1.5 mL), until disappearance of ketimine (TLC) (Scheme 2). The reaction worked very well for N-benzyl- and N-methyl-substituted ketimines **4** and **5**, but N-unsubstituted derivative **6** yielded the aza-Friedel-Crafts product **6a** in excellent yield, but very poor enantioselectivity.

The presence of halogens at C-5 in the ketimine is well tolerated leading to products **7a-9a** with excellent to good yields and very good enantioselectivities. However, 5-methyl substituted

compound was found to be less reactive, leading to **10a**, with similar yield but moderate er (88:12).
Both, electron donating (**11**) or electron withdrawing (**12-13**) substituted ketimines also afforded the expected products **11a** and **12a-13a** with excellent results. The reactions of different substituted 1-naphthols (**b-e**) were highly enantioselective although the products were formed in lower yield, except 4-methoxy-1-naphthol (**d**), which lead to the aza-Friedel-Crafts product **4d** in excellent yield but poor enantioselectivity.

We extended our method to different substituted 2-naphthol derivatives (**f-h**) as nucleophiles in the described reaction conditions. The products **4f-h** were obtained in good yields, but contrary to described for the homogeneous organocatalyzed reaction,[12a] the enantioselection was very poor (Scheme 3).



Scheme 3. Scope of the reaction of ketimine **4** with different 2-naphthols.

The absolute configuration of the created stereocenter was established as *R* by comparison of the sign of the optical rotation of the known compounds, [12] and by X-ray analysis of a single crystal of **12a** (Figure 1). [21]

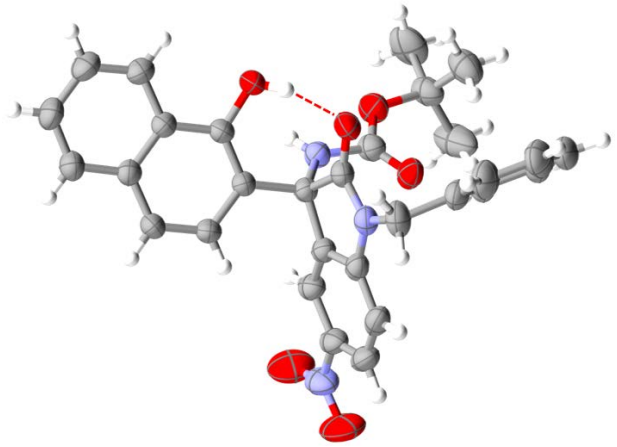
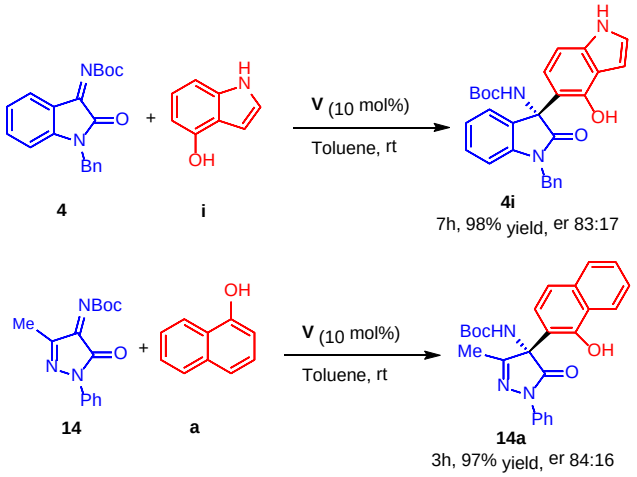


Figure 1. X-ray structure of **12a** (ellipsoids at 50% probability)

To further explore the applicability of the novel supported thiourea **V** as enantioselective catalyst, we studied two different transformations, previously described in homogeneous conditions (Scheme 4). The first one refers to the important enantioselective functionalization at the carbocyclic ring of N-unsubstituted 4-hydroxyindoles.[13] Based on the known directing effect of the hydroxyl group at the carbocyclic ring,[22] the reaction of ketimine **4** with 4-hydroxyindole **i**, catalysed by **V** yielded the 5-functionalized-4-hydroxyindole **4i** in nearly quantitative yield, complete regioselectivity, and enantioselectivity slightly lower than that described for the reaction in homogeneous conditions.



Scheme 4. Additional enantioselective transformations promoted by **V**.

Recently, it has been reported the enantioselective aza-Friedel-Crafts functionalization of 1-naphthols and hydroxyindoles by reaction with different ketimines derived from pyrazolinones in homogeneous conditions promoted by cinchone-derived squaramides.[23] In our case, N-Boc ketimine derived from pyrazolin-5-one **14**[24] reacted with 1-naphthol **a** in presence of supported thiourea **V** leading to the aza-Friedel-Crafts product **14a** in excellent yield and good enantioselectivity, although lower than for the reaction promoted by the squaramide derivative.

Continuous-flow transformations offer several advantages with respect to the same reactions in batch conditions, such as increasing efficiency and sustainability. Recently, these processes have attracted a great attention,[25] and due to the robustness of our catalysts we decided to test supported thiourea **V** as organocatalyst in the continuous-flow synthesis of enantioenriched compounds **12a** and **13a** in multigram scale.

To this end, 400 mg (f = 0.76 mmolg^{-1}, 0.3 mmol) of **V** were placed in a Teflon column (6.6 mm ID), and two different solutions of imines **12** or **13** (20 or 40 mL, respectively, 0.14M in toluene) and 1-

naphthol **a** (20 or 40 mL, 0.20 M in toluene) were individually injected (0.1 mLmin^{-1}) at room temperature, with a two ways syringe pump, and the products **12a** and **13a** was collected in a flask cooled to -15 ^{o}C to avoid further background reaction of the residual reagents (Figure 2).

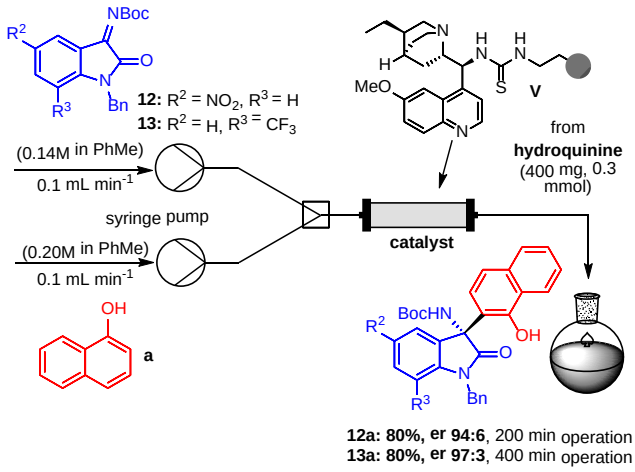


Figure 2. Continuous flow organocatalytic synthesis of **12a** and **13a**.

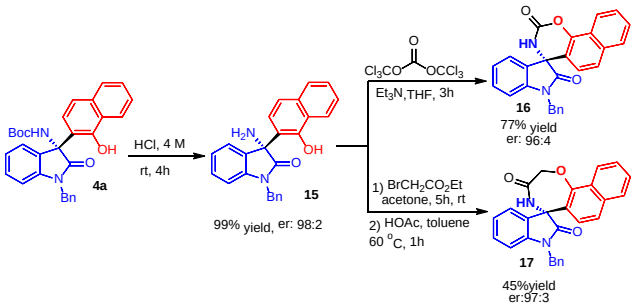
Aliquots were taken each 30 min for the reaction of **12** or 60 min for **13** to follow the reactions, and the results are collected in Table 2. It is important to note that both the activity and the enantioselection were maintained along both reactions. The systems were running for 200 min or 400 min, respectively, and final solutions were purified by flash chromatography after elimination of toluene. Products **12a** and **13a** were obtained in 80% yield (1.18 g, 2.25 mmol for **12a**, and 2.45 g, 4.47 mmol for **13a**) with 94:6, and 97:3 enantiomeric ratio, respectively. The data show an effective catalyst loading of 10 mol%, an accumulated TON of 7.4, and a productivity of 2.2 mmol mmol$_{cat}^{-1}$ h^{-1} for the synthesis of **12a**. For the formation of **13a,** the catalyst loading was 5 mol%, the accumulated TON was 14.7, and the productivity 2.2 mmol mmol$_{cat}^{-1}$ h^{-1}. The residence time, under these flow conditions, was 10.3 min, in sharp contrast with the reaction time for full conversion in batch operation (3h), in both cases.

Table 2. Continuous flow evolution of the reaction of **12** and **13** with **a**.

Entry	Reagents	Time (min)	Conversion (%)[a]	Er[b]
1	**12** + **a**	30	92	96:4
2	**12** + **a**	60	97	96:4
3	**12** + **a**	90	97	95:5
4	**12** + **a**	120	97	95:5
5	**12** + **a**	150	97	94:6
6	**12** + **a**	180	97	95:5
7	**13** + **a**	60	82	98:2
8	**13** + **a**	120	83	98:2
9	**13** + **a**	180	83	98:2
10	**13** + **a**	240	84	97:3
11	**13** + **a**	300	83	98:2
12	**13** + **a**	360	85	97:3
13	**13** + **a**	400	85	97:3

[a] Conversion was determined by ^{1}HNMR. [b] Determined by HPLC on a chiral column.

Natural and synthetic structures with spirooxindole core present interesting biological activity, and their synthesis has attracted continuous interest. [26] As an example, we have transformed amine **15**, obtained in excellent yield by Boc-deprotection of **4a**,[12a] into spirooxindole carbamate **16** and spiro oxazepinone **17** as summarized in Scheme 5.



Scheme 5. Synthesis of spirooxindole derivatives.

Spirooxindole **16** was obtained in one step, with very good yield by reaction of **15** with triphosgene, whereas **17** was synthesized, in moderate yield, by reaction with ethyl bromoacetate, followed by lactamization in the presence of acetic acid. In both processes the stereochemical integrity of the final products was totally maintained.

Conclusion

In summary, we have prepared eight novel supported bifunctional thioureas derived from cinchone alkaloids and used as promoter in enantioselective aza-Friedel-Crafts reaction by using isatin N-Boc ketimines as electrophiles. The best supported thiourea **V** has been recycled and reused without loss of activity, and it was used as catalyst in continuous flow conditions. The obtained results show that the supported catalysts present similar results in terms of yield and enantioselection to those presented by analogous ones used in homogeneous conditions.[12]

Experimental Section

General information

^{1}H NMR (400 or 500 MHz), ^{13}C NMR (100 MHz) and ^{19}F NMR (376 MHz) spectra were recorded in $CDCl_3$ as solvent. Chemical shifts for protons are reported in ppm from TMS with the residual $CHCl_3$ 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 = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants in Hertz, and integration.

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 F254 indicator, and visualized by either UV irradiation or by staining with phosphomolybdic acid solution. Chiral HPLC analysis was performed on a JASCO HPLC system (JASCO PU-2089 and UV-2075 UV/Vis detector) with a quaternary pump, using Phenomenex Lux-amylose-1, Lux-i-amylose-1 and Lux-i-cellulose-5 analytical columns (250 × 4.6 mm). Detection was monitored at 254 nm. Elemental analyses were carried out at the Elemental Analysis Center of the Complutense University of Madrid, using a Perkin Elmer 2400 CHN. ESI mass spectra were obtained on an Agilent 5973 inert GC/MS system.

Commercially available organic and inorganic compounds were used without further purification. Solvents were dried and stored over microwave-activated 4 Å molecular sieves. Aminomethyl polystyrene resin (particle size: 160−200 μm, *f* = 1.11 mmol/g), aminoethyl polystyrene resin (particle size: 160−200 μm, *f* = 1.05 mmol/g), and 4-aminobutyl polystyrene (particle size: 160−200 μm, *f* = 1.01 mmol/g) are commercially available. Supported isothiocyanate **2**,[19] thiourea **IX**,[20] and ketimines **4**-**13**,[27] and **14**[24] were prepared as previously described. Naphthols **a**-**h** are commercially available, except 1-naphthol derivative **e**, which was prepared as described in the literature.[12a] Amino cinchona derivatives were obtained from the corresponding alkaloids as previously described.[28]

Isothiocyanate 1. A suspension of aminomethyl polystyrene resin (400 mg, 0.44 mmol) in dichloromethane (16 mL) was stirred for 30 min at room temperature. Triethylamine (0. 25 mL, 1.76 mmol, 4 equiv) and thiophosgene (0.04 mL, 0.53 mmol, 1.2 equiv) were added dropwise to the previous suspension and the reaction mixture was stirred overnight at room temperature. After that time, the suspension was filtered and washed with dichloromethane (5 x 20 mL), THF (3 x 20 mL) and dichloromethane (3 x 20 mL). The resin was dried under vacuum obtaining 419 mg of polymer (100% yield). IR (ATR): 3027, 2921, 2852, 2168, 2082, 1598, 1488, 1451, 1333, 755, 694, 543 cm^{-1}. The effective functionalization (*f* = 0.81 $mmolg^{-1}$) was calculated on the basis of the sulphur elemental analysis: C: 85.99, H: 7.32, N: 1.63, S: 2.61.

Isothiocyanate 3. This resin was prepared from 4-aminobutyl polystyrene (400 mg, 0.40 mmol) as described for **1** to give 381 mg of polymer in 91% yield. IR (ATR): 3027, 2921, 2852, 2176, 2090, 1598, 1492, 1447, 1064, 755, 694, 539 cm^{-1}. The effective functionalization (*f* = 0.90 $mmolg^{-1}$) was calculated on the basis of the sulphur elemental analysis: C: 85.00, H: 7.53, N: 2.22, S: 2.87.

General procedure for the preparation of supported thioureas.[19] To a cooled (0 ºC) suspension of polystyrene isocyanate **1**-**3** (0.42 mmol) in dry DCM (6 mL) was added a solution of the corresponding amine (0.63 mmol, 1.5 equiv) in dry DCM (4 mL). The resulting mixture was stirred at room temperature for 48 h. The solid was collected by filtration, washed with DCM (5 x 20 mL), and dried under vacuum until constant weight.

Thiourea I. Prepared from isothiocyanate **1** and 9-amino-epi-quinine as described before in 98% yield. IR (ATR): 3027, 2921, 2856, 1622, 1598, 1508, 1492, 1447, 1345, 1223, 1028, 910, 844, 751, 694, 539 cm^{-1}. The effective functionalization (*f* = 0.81 $mmolg^{-1}$) was calculated on the basis of the sulphur elemental analysis: C: 81.99, H: 7.26, N: 4.43, S: 2.61.

Thiourea II. Prepared from isothiocyanate **2** and 9-amino-epi-quinine as described before in 92% yield. IR (ATR): 3026, 2918, 2857, 1620, 1597, 1489, 1446, 1225, 1023, 915, 840, 755, 694, 539 cm^{-1}. The effective functionalization (*f* = 0.75 $mmolg^{-1}$) was calculated on the basis of the sulphur elemental analysis: C: 81.91, H: 7.32, N: 4.24, S: 2.39.

Thiourea III. Prepared from isothiocyanate **3** and 9-amino-epi-quinine, as described before in 86% yield. IR (ATR): 3023, 2921, 2856, 1618, 1598, 1496, 1447, 1227, 1068, 1028, 905, 828, 755, 694, 543 cm^{-1}. The effective functionalization (*f* = 0.67 $mmolg^{-1}$) was calculated on the basis of the sulphur elemental analysis: C: 80.85, H: 7.41, N: 4.20, S: 2.15.

Thiourea IV. Prepared from isothiocyanate **2** and and 9-amino-epi-cinchonidine as described before in a 98% yield. IR (ATR): 3023, 2921, 2856, 1492, 1451, 905, 800, 751, 698, 539 cm^{-1}. The effective functionalization (*f* = 0.76 $mmolg^{-1}$) was calculated on the basis of the sulphur elemental analysis: C: 80.95, H: 7.26, N: 4.11, S: 2.44.

Thiourea V. Prepared from isothiocyanate **2** and 9-amino-epi-hydroquinine as described in 90% yield. IR (ATR): 3027, 2921, 2856, 1622, 1598, 1492, 1451, 1337, 1227, 1024, 905, 820, 755, 702, 535 cm^{-1}. The effective functionalization (*f* = 0.76 $mmolg^{-1}$) was calculated on the basis of the sulphur elemental analysis: C: 81.31, H: 7.37, N: 4.21, S: 2.44.

Thiourea VI. Prepared from isothiocyanate **2** and 9-amino-epi-quinidine (95% yield). IR (ATR): 3027, 2921, 2860, 1622, 1606, 1508, 1492, 1455, 1231, 1028, 914, 853, 755, 698, 539 cm^{-1}. The effective functionalization (*f* = 0.72 $mmolg^{-1}$) was calculated on the basis of the sulphur elemental analysis: 82.22, H: 7.26, N: 4.39, S: 2.32.

Thiourea VII. Prepared from isothiocyanate **2** and 9-amino-epi-cinchonine as described before in 98% yield. IR (ATR): 3023, 2921, 2852, 1537, 1488, 1451, 1024, 910, 844, 755, 694, 539 cm^{-1}. The effective functionalization (*f* = 0.75 $mmolg^{-1}$) was calculated on the basis of the sulphur elemental analysis: 82.28, H: 7.23, N: 4.17, S: 2.39.

Thiourea VIII. Prepared from isothiocyanate **2** and 9-amino-epi-hydroquinidine as described before in 90% yield. IR (ATR): 3024, 2918, 2859, 1621, 1602, 1511, 1488, 1449, 1343, 1225, 1030, 759, 696, 544 cm^{-1}. The effective functionalization (*f* = 0.73 $mmolg^{-1}$) was calculated on the basis of the sulphur elemental analysis: C: 82.22, H: 7.46, N: 4.32, S: 2.34.

General procedure for the enantioselective aza-Friedel-Crafts reaction in batch conditions. A mixture of *N*-Boc ketimine **4**-**13** (0.10 mmol), naphthol **a**-**h** (0.12 mmol) and the corresponding supported thiourea (**I**-**VIII**) (10 mol%) in toluene (1.5 mL) was placed in a vial, and the mixture was stirred at room temperature until the reaction was finished (TLC). The catalyst was filtered and the filtrate was purified by flash chromatography. For the recycled experiments with **V** (entries 19-22 in Table 1), the catalyst was washed with toluene, dried until constant weight, and reused in the next experiment.

(*R*)-*tert*-Butyl-(1-benzyl-3-(1-hydroxynaphthalen-2-yl)-2-oxoindolin-3-yl) carbamate (4a).[12a] This product was prepared according the general procedure. The crude reaction mixture was purified by flash chromatography

(silica gel, Hexane/Et_2O 95:5 to 80:20) obtaining a white solid (44 mg, 0.09 mmol, 92 % yield). $[\alpha]_D^{20}$ = + 354.5 (*c* = 0.99, $CHCl_3$) [Lit.[12a] $[\alpha]_D^{20}$ = +359.6 (*c* = 0.44, $CHCl_3$, 99% *ee* for (*R*) enantiomer)]; ^1H NMR (500 MHz, $CDCl_3$): δ 1.33 (s, 9H), 4.85 (br d, 1H), 5.07 (d, *J* = 15.8 Hz, 1H), 5.80 (s, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 1H), 7.18–7.27 (m, 7H), 7,31 (t, *J* = 7.7 Hz, 1H), 7,43 (d, *J* = 7.3 Hz, 1H), 7.50–7.54 (m, 2H), 7.70–7.75 (m, 1H), 8.45–8.50 (m, 1H), 10.82 (s, 1H). HPLC (Lux-amylose-1, hexane/isopropanol 70:30, λ = 230 nm, 1.0 mL/min): t_R = 11.7 (minor, *S*), t_R = 52.6 (major, *R*) (er: 97:3).

(*R*)-*tert*-Butyl-(3-(1-hydroxynaphthalen-2-yl)-1-methyl-2-oxoindolin-3-yl) carbamate (5a).[12a] This product was prepared according the general procedure. The crude reaction mixture was purified by flash chromatography (silica gel, Hexane/Et_2O 70:30) obtaining a white brownish solid (39 mg, 0.09 mmol, 96 % yield). $[\alpha]_D^{20}$ = + 333.7 (*c* = 1.01, $CHCl_3$) [Lit.[12a] $[\alpha]_D^{20}$ = +390.8 (*c* = 0.42, $CHCl_3$, 96% *ee* for (*R*) enantiomer)]; ^1H NMR (400 MHz, $CDCl_3$): δ 1.27 (s, 9H), 3.23 (s, 3H), 5.67 (br s, 1H), 6.80 (d, *J* = 8.8 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 7.16 (d, *J* = 8.9 Hz, 1H), 7.23-7.30 (m, 1H), 7.39-7.44 (m, 2H), 7.45-7.51 (m, 2H), 7.65-7.71 (m, 1H), 8.40-8.47 (m, 1H), 10.83 (bs, 1H). HPLC (Lux-amylose-1, hexane/isopropanol 70:30, λ = 254 nm, 1.0 mL/min): t_R = 7.8 (major, *R*), t_R = 8.8 (minor, *S*) (er: 96:4).

(*R*)-*tert*-Butyl-(3-(1-hydroxynaphthalen-2-yl)-2-oxoindolin-3-yl)carbamate (6a). [12b] This product was prepared according the general procedure. The crude reaction mixture was purified by flash chromatography (silica gel, Hexane/EtOAc 4:1 to 2:1) obtaining a white solid (39 mg, 0.1 mmol, 99 % yield). $[\alpha]_D^{20}$ = + 92.7 (*c* = 1.09, $CHCl_3$) [Lit.[12b] $[\alpha]_D^{20}$ = +341.0 (*c* = 0.45, $CHCl_3$, 63% *ee* for (*R*) enantiomer)]; ^1H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 9H), 5.72 (s, 1H), 6.81 (d, *J* = 8.7 Hz, 1H), 6.92 (d, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.8 Hz, 1H), 7.21–7.27 (m, 1H), 7.33–7.41 (m, 2H), 7.46–7.52 (m, 2H), 7.58 (s, 1H), 7.66–7.72 (m, 1H), 8.40–8.45 (m, 1H), 10.50 (s, 1H). HPLC (Lux-i-amylose-1, hexane/isopropanol 90:10, λ = 254 nm, 0.8 mL/min): t_R = 18.3 (minor, *S*), t_R = 20.8 (major, *R*) (er: 61:39).

(*R*)-*tert*-Butyl-(1-benzyl-5-fluoro-3-(1-hydroxynaphthalen-2-yl)-2-oxoindolin-3-yl) carbamate (7a). [12b] This product was prepared according the general procedure. The crude reaction mixture was purified by flash chromatography (silica gel, Hexane/Et_2O 95:5 to 70:30) obtaining a white solid (39 mg, 0.08 mmol, 78 % yield). $[\alpha]_D^{20}$ = + 333.6 (*c* = 1.04, $CHCl_3$) [Lit.[12b] $[\alpha]_D^{20}$ = +382.2 (*c* = 0.42, $CHCl_3$, 96% *ee* for (*R*) enantiomer)]; ^1H NMR (400 MHz, $CDCl_3$): δ 1.35 (s, 9H), 4.78–4.92 (m, 1H), 4.93–5.06 (m, 1H), 5.81 (s, 1H), 6.67 (dd, *J* = 8.6, 4.1 Hz, 1H), 6.78 (d, *J* = 8.9 Hz, 1H), 6.95–7.02 (m, 1H), 7.16 (dd, *J* = 7.6, 2.5 Hz, 1H), 7.19–7.26 (m, 6H), 7.48–7.54 (m, 2H), 7.69–7.74 (m, 1H), 8.42–8.48 (m, 1H), 10.74 (s, 1H). HPLC (Lux-i-amylose-1, hexane/isopropanol 85:15, λ = 254 nm, 0.7 mL/min): t_R = 15.1 (minor, *S*), t_R = 49.3 (major, *R*) (er: 97:3).

(*R*)-*tert*-Butyl-(1-benzyl-5-chloro-3-(1-hydroxynaphthalen-2-yl)-2-oxoindolin-3-yl) carbamate (8a). [12a] This product was prepared according the general procedure. The crude reaction mixture was purified by flash chromatography (silica gel, Hexane/Et_2O 95:5 to 70:30) obtaining a white solid (48 mg, 0.09 mmol, 93 % yield). $[\alpha]_D^{20}$ = + 346.1 (*c* = 1.03, $CHCl_3$) [Lit.[12a] $[\alpha]_D^{20}$ = +412.5 (*c* = 0.35, $CHCl_3$, 98% *ee* for (*R*) enantiomer)]; ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 9H), 4.79–5.03 (m, 2H), 5.81 (s, 1H), 6.67 (d, *J* = 8.5 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 1H), 7.19–7.28 (m, 7H), 7.37–7.41 (m, 1H), 7.49–7.55 (m, 2H), 7.70–7.75 (m, 1H), 8.42–8.48 (m, 1H), 10.65 (s, 1H). HPLC (Lux-amylose-1, hexane/isopropanol 80:20, λ = 254 nm, 1 mL/min): t_R = 13.3 (minor, *S*), t_R = 42.8 (major, *R*) (er: 96:4).

(*R*)-*tert*-Butyl-(1-benzyl-5-bromo-3-(1-hydroxynaphthalen-2-yl)-2-oxoindolin-3-yl) carbamate (9a). [12a] This product was prepared according the general procedure. The crude reaction mixture was purified by flash chromatography (silica gel, Hexane/Et_2O 95:5 to 70:30) obtaining a white solid (36 mg, 0.06 mmol, 64 % yield). $[\alpha]_D^{20}$ = + 324.7 (*c* = 1.02, $CHCl_3$) [Lit.[12a] $[\alpha]_D^{20}$ = +419.2 (*c* = 0.27, $CHCl_3$, 95% *ee* for (*R*) enantiomer)]; ^1H NMR (400 MHz, $CDCl_3$): δ 1.36 (s, 9H), 4.79–5.03 (m, 2H), 5.80 (s, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 6.78 (d, *J* = 8.8 Hz, 1H), 7.19–7.26 (m, 6H), 7.38–7.42 (m, 1H), 7.49–7.54 (m, 3H), 7.70–7.75 (m, 1H), 8.42–8.47 (m, 1H), 10.63 (s, 1H). HPLC (Lux-amylose-1, hexane/isopropanol 70:30, λ = 254 nm, 1 mL/min): t_R = 9.7 (minor, *S*), t_R = 30.7 (major, *R*) (er: 97:3).

(*R*)-*tert*-Butyl-(1-benzyl-3-(1-hydroxynaphthalen-2-yl)-5-methyl-2-oxoindolin-3-yl) carbamate (10a). This product was prepared according the general procedure. The crude reaction mixture was purified by flash chromatography (silica gel, Hexane/Et_2O 95:5 to 80:20) obtaining a white solid (24 mg, 0.05 mmol, 78 % yield). Mp = 209–210 ºC; $[\alpha]_D^{20}$ = + 298.2 (*c* = 1.2, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 9H), 2.40 (s, 3H), 4.76–7.90 (m, 1H), 5.00 (d, *J* = 15.2 Hz, 1H), 5.76 (br s, 1H), 6.64 (d, *J* = 8.0 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 1H), 7.07 (d, *J* = 8.0 Hz, 1H), 7.15–7.26 (m, 7H), 7.46–7.53 (m, 2H), 7.68–7.74 (m, 1H), 8.43–8.48 (m, 1H), 10.86 (br s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.3, 28.6 (3C), 44.4, 66.2, 80.7, 110.1, 114.7, 119.6, 123.2, 125.2, 125.6, 126.1, 126.9 (2C), 127.0, 127.1, 127.4, 127.6, 128.7 (2C), 128.8, 129.7, 133.1, 134.8, 134.9, 140.1, 153.9, 154.1, 179.6. IR (ATR): 3450, 2922, 1717, 1675, 1477, 1379, 1160, 805, 699 cm^{-1}. HPLC (Lux-amylose-1, hexane/isopropanol 70:30, λ = 254 nm, 1 mL/min): t_R = 9.7 (minor, *S*), t_R = 46.1 (major, *R*) (er: 88:12). HRMS (ESI^+): *m/z* $[M+Na]^+$ Calculated for $C_{31}H_{30}N_2O_4Na$ 517.2098; Found 517.2104.

(*R*)-*tert*-Butyl-(1-benzyl-3-(1-hydroxynaphthalen-2-yl)-5-methoxy-2-oxoindolin-3-yl) carbamate (11a). [12a] This product was prepared according the general procedure. The crude reaction mixture was purified by flash chromatography (silica gel, Hexane/Et_2O 95:5 to 70:30) obtaining a brownish white solid (46 mg, 0.09 mmol, 90 % yield). $[\alpha]_D^{20}$ = + 332.7 (*c* = 1.02, $CHCl_3$) [Lit.[12a] $[\alpha]_D^{20}$ = +385.9 (*c* = 0.325, $CHCl_3$, 99% *ee* for (*R*) enantiomer)]; ^1H NMR (400 MHz, $CDCl_3$): δ 1.33 (s, 9H), 3.81 (s, 3H), 4.74–4.91 (m, 1H), 4.93–5.06 (m, 1H), 5.77 (s, 1H), 6.65 (d, *J* = 8.5 Hz, 1H), 6.79 (dd, *J* = 8.7, 2.0 Hz, 1H), 6.84 (d, *J* = 8.8 Hz, 1H), 7.01 (d, *J* = 2.1 Hz, 1H), 7.17–7.26 (m, 6H), 7.47–7.53 (m, 2H), 7.68–7.74 (m, 1H), 8.42–8.48 (m, 1H), 10.88 (s, 1H). HPLC (Lux-amylose-1, hexane/isopropanol 70:30, λ = 254 nm, 1 mL/min): t_R = 13.6 (minor, *S*), t_R = 141.8 (major, *R*) (er: 96:4).

(*R*)-*tert*-Butyl-(1-benzyl-3-(1-hydroxynaphthalen-2-yl)-5-nitro-2-oxoindolin-3-yl)carbamate (12a).[12a] This product was prepared according the general procedure. The crude reaction mixture was purified by flash chromatography (silica gel, Hexane/Et_2O 80:20 to 70:30) obtaining a yellow solid (46 mg, 0.09 mmol, 88 % yield).$[\alpha]_D^{20}$ = +392.6 (*c* = 1.01, $CHCl_3$) [Lit.[12a] $[\alpha]_D^{20}$ = +498.5 (*c* = 0.25, $CHCl_3$, 97% *ee* for (*R*) enantiomer)]; ^1H NMR (500 MHz, $CDCl_3$): δ 1.39 (s, 9H), 5.01 (s, 2H), 5.95 (s, 1H), 6.70 (d, *J* = 8.8 Hz, 1H), 6.85 (d, *J* = 8.7 Hz, 1H), 7.23–7.28 (m, 6H), 7.53–7.57 (m, 2H), 7.73–7.77 (m, 1H), 8.26 (dd, *J* = 8.7, 2.3 Hz, 1H), 8.32 (d, *J* = 2.3 Hz, 1H), 8.45–8.49 (m, 1H), 10.33 (s, 1H). HPLC (Lux-amylose-1, hexane/isopropanol 75:25, λ = 254 nm, 1 mL/min): t_R = 16.8 (minor, *S*), t_R = 36.1 (major, *R*) (er: 94:6).

(*R*)-*tert*-Butyl-(1-benzyl-3-(1-hydroxynaphthalen-2-yl)-2-oxo-7-(trifluoromethyl) indolin-3-yl)carbamate (13a). This product was prepared according the general procedure. The crude reaction mixture was purified by flash column chromatography (silica gel, DCM) obtaining a white solid (45 mg, 0.08 mmol, 82 % yield). Mp = 180–181 ºC; $[\alpha]_D^{20}$ = + 307.2 (*c* = 1.01, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$):

δ 1.35 (s, 9H), 5.11 (d, *J* = 16.7 Hz, 1H), 5.31 (d, *J* = 16.7 Hz, 1H), 5.88 (br s, 1H), 6.66 (d, *J* = 8.8 Hz, 1H), 6.98–7.16 (m, 5H), 7.22 (d, *J* = 8.7 Hz, 1H), 7.38 (dd, *J* = 7.8, 7.8 Hz, 1H), 7.49–7.56 (m, 2H), 7.63 (d, *J* = 7.2 Hz, 1H), 7.69–7.75 (m, 2H), 8.40–8.45 (m, 1H), 10.38 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1 (3C), 46.3, 64.4, 81.3, 113.8, 113.9, 120.0, 123.0, 123.1 (q, *J* = 274.0 Hz), 123.2, 124.4, 125.4, 125.9, 126.8, 127.1 (2C), 127.7 (2C), 128.3 (2C), 128.9, 132.4, 134.9, 135.5, 140.7, 140.7, 153.7, 154.2, 181.3. ^{19}F NMR (376 MHz, $CDCl_3$): δ –54.6. IR (ATR): 3328, 2922, 1730, 1701, 1333, 1164, 1122, 796, 690 cm^{-1}. HPLC (Lux-amylose-1, hexane/isopropanol 70:30, λ = 254 nm, 1 mL/min): t_R = 7.3 (minor, *S*), t_R = 18.5 (major, *R*) (er: 98:2). HRMS (ESI$^+$): *m/z* $[M+Na]^+$ Calculated for $C_{31}H_{27}F_3N_2O_4Na$ 571.1815; Found 571.1823.

(*R*)-*tert*-Butyl-(1-benzyl-3-(4-chloro-1-hydroxynaphthalen-2-yl)-2-oxoindolin-3-yl) carbamate (4b). [12a] This product was prepared according the general procedure. The crude reaction mixture was purified by flash chromatography (silica gel, Hexane/Et_2O 95:5 to 70:30) obtaining a white solid (34 mg, 0.07 mmol, 66 % yield). $[\alpha]_D^{20}$ = +249.5 (*c* = 1.05, $CHCl_3$) [Lit.[12a] $[\alpha]_D^{20}$ = +332.1 (*c* = 0.35, $CHCl_3$, 97% *ee* for (*R*) enantiomer)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.32 (s, 9H), 4.80–4.95 (m, 1H), 4.98–5.10 (m, 1H), 5.75 (s, 1H), 6.81 (d, *J* = 7.8 Hz, 1H), 6.94 (s, 1H), 7.21–7.29 (m, 6H), 7.33 (ddd, *J* = 7.8, 7.8, 1.4 Hz, 1H), 7.43 (dd, *J* = 7.3, 1,1 Hz, 1H), 7.58 (ddd, *J* = 8.4, 6.7, 1.3 Hz, 1H), 7.64 (ddd, *J* = 8.5, 6.8, 1.4 Hz, 1H), 8.11 (d, *J* = 8.4 Hz, 1H), 8.50 (d, *J* = 8.5 Hz, 1H), 10.98 (s, 1H). HPLC (Lux-i-amylose-1, hexane/isopropanol 70:30, λ = 254 nm, 1 mL/min): t_R = 6.5 (minor, *S*), t_R = 11.7 (major, *R*) (er: 96:4).

(*R*)-*tert*-Butyl-(1-benzyl-3-(4-bromo-1-hydroxynaphthalen-2-yl)-2-oxoindolin-3-yl)carbamate (4c). This product was prepared according the general procedure. The crude reaction mixture was purified by flash chromatography (silica gel, Hexane/Et_2O 95:5 to 70:30) obtaining a white solid (39 mg, 0.07 mmol, 70 % yield). Mp = 115–116 °C; $[\alpha]_D^{20}$ = +209.0 (*c* = 0.95, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.32 (s, 9H), 4.88 (d, *J* = 15.8 Hz, 1H), 5.03 (d, *J* = 15.8 Hz, 1H), 5.79 (s, 1H), 6.81 (d, *J* = 7.6 Hz, 1H), 7.13 (s, 1H), 7.21–7.30 (m, 6H), 7.33 (ddd, *J* = 7.7, 7.7, 1.2 Hz, 1H), 7.43 (dd, *J* = 7.3, 1.4 Hz, 1H), 7.56 (ddd, *J* = 8.7, 6.8, 1.2 Hz, 1H), 7.63 (ddd, *J* = 8.7, 6.8, 1.3 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 8.48 (d, *J* = 8.2 Hz, 1H), 11.04 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.1 (3C), 44.6, 65.7, 80.9, 110.5, 112.7, 115.3, 123.7, 123.8, 125.2, 126.4, 126.5, 127.1 (2C), 127.7, 128.2, 128.5, 128.6, 128.8, 128.8 (2C), 129.8, 133.0, 134.7, 142.6, 153.7, 154.1, 179.5. IR (ATR): 3340, 2926, 1713, 1684, 1616, 1485, 1371, 1160, 754, 695 cm^{-1}. HPLC (Lux-i-amylose-1, hexane/isopropanol 70:30, λ = 254 nm, 1 mL/min): t_R = 6.2 (minor, *S*), t_R = 10.3 (major, *R*) (er: 94:6). HRMS (ESI$^+$): *m/z* $[M+Na]^+$ Calculated for $C_{30}H_{27}BrN_2O_4Na$ 581.1046;Found 581.1061.

(*R*)-*tert*-Butyl-(1-benzyl-3-(1-hydroxy-4-methoxynaphthalen-2-yl)-2-oxoindolin-3-yl) carbamate (4d). [12b] This product was prepared according the general procedure. The crude reaction mixture was purified by flash chromatography (silica gel, Hexane/Et_2O 80:20) obtaining a dark solid (47 mg, 0.09 mmol, 92 % yield). $[\alpha]_D^{20}$ = +47.3 (*c* = 1.1, $CHCl_3$) [Lit.[12b] $[\alpha]_D^{20}$ = +301.1 (*c* = 0.35, $CHCl_3$, 97% *ee* for (*R*) enantiomer)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.34 (s, 9H), 3.62 (s, 3H), 4.81–4.95 (m, 1H), 4.99–5.10 (m, 1H), 5.89 (s, 1H), 6.15 (s, 1H), 6.79 (d, *J* = 7.9 Hz, 1H), 7.19–7.34 (m, 7H), 7.45 (d, *J* = 7.3 Hz, 1H), 7.50–7.58 (m, 2H), 8.10–8.13 (m, 1H), 8.41–8.44 (m, 1H), 10.31 (s, 1H). HPLC (Lux-i-amylose-1, hexane/isopropanol 70:30, λ = 254 nm, 0.7 mL/min): t_R = 9.3 (minor, *S*), t_R = 21.3 (major, *R*) (er: 73:27).

(*R*)-6-(1-Benzyl-3-((*tert*-butoxycarbonyl)amino)-2-oxoindolin-3-yl)-5-hydroxynaphthalen-1-yl acetate (4e).[12a] This product was prepared according the general procedure. The crude reaction mixture was purified by flash chromatography (silica gel, DCM) obtaining a white solid (37 mg, 0.07 mmol, 70 % yield). $[\alpha]_D^{20}$ = +303.2 (*c* = 1.02, $CHCl_3$) [Lit.[12a] $[\alpha]_D^{20}$ = +300.3 (*c* = 0.25, $CHCl_3$, 99% *ee* for (*R*) enantiomer)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (s, 9H), 2.39 (s, 3H), 4.76–4.94 (m, 1H), 4.99–5.13 (m, 1H), 5.78 (s, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.88 (d, *J* = 8.9 Hz, 1H), 7.15–7.33 (m, 9H), 7.41 (d, *J* = 7.4 Hz, 1H), 7.50 (dd, *J* = 8.0, 8.0 Hz, 1H), 8.39 (d, *J* = 8.6 Hz, 1H), 10.94 (s, 1H). HPLC (Lux-i-cellulose-5, hexane/isopropanol 80:20, λ = 254 nm, 1 mL/min): t_R = 15.8 (major, *S*), t_R = 30.0 (minor, *R*) (er: 98:2).

(*R*)-*tert*-Butyl-(1-benzyl-3-(2-hydroxynaphthalen-1-yl)-2-oxoindolin-3-yl) carbamate (4f).[12a] This product was prepared according the general procedure. The crude reaction mixture was purified by flash chromatography (silica gel, Hexane/Et_2O 70:30 to 40:60) obtaining a brown solid (47 mg, 0.01 mmol, 99 % yield). $[\alpha]_D^{20}$ = –3.5 (*c* = 1.03, $CHCl_3$) [Lit.[12a] $[\alpha]_D^{20}$ = –14.8 (*c* = 0.25, $CHCl_3$, 91% *ee* for (*R*) enantiomer)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (s, 9H), 4.85 (d, *J* = 16.0 Hz, 1H), 5.16 (d, *J* = 16.0 Hz, 1H), 5.85 (s, 1H), 6.79 (d, *J* = 7.6 Hz, 1H), 6.91–6.99 (m, 1H), 7.03 (dd, *J* = 7.5, 7.5 Hz, 1H), 7.13–7.35 (m, 10H), 7.65 (dd, *J* = 9.8, 9.8 Hz, 2H), 9.98 (s, 1H). HPLC (Lux-amylose-1, hexane/isopropanol 80:20, λ = 254 nm, 1 mL/min): t_R = 19.4 (minor, *S*), t_R = 40.4 (major, *R*) (er: 67:33).

(*R*)-*tert*-Butyl-(1-benzyl-3-(6-bromo-2-hydroxynaphthalen-1-yl)-2-oxoindolin-3-yl) carbamate (4g).[12a] This product was prepared according the general procedure. The crude reaction mixture was purified by flash chromatography (silica gel, Hexane/Et_2O 40:60) obtaining a yellowish white solid (48 mg, 0.08 mmol, 86 % yield). $[\alpha]_D^{20}$ = –3.7 (*c* = 1.09, $CHCl_3$) [Lit.[12a] $[\alpha]_D^{20}$ = +4.3 (*c* = 0.325, $CHCl_3$, 86% *ee* for (*R*) enantiomer)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 9H), 4.84 (d, *J* = 15.9 Hz, 1H), 5.16 (d, *J* = 15.9 Hz, 1H), 5.82 (s, 1H), 6.60–6.71 (m, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 7.00–7.07 (m, 2H), 7.17–7.33 (m, 8H), 7.55 (d, *J* = 8.9 Hz, 1H), 7.81 (d, *J* = 2.3 Hz, 1H), 10.12 (s, 1H). HPLC (Lux Amylose-1, hexane/isopropanol 80:20, λ = 254 nm, 1 mL/min): t_R = 11.2 (major, *R*), t_R = 16.7 (minor, *S*) (er: 65:35).

(*R*)-*tert*-Butyl-(1-benzyl-3-(2-hydroxy-3-methoxynaphthalen-1-yl)-2-oxoindolin-3-yl)carbamate (4h).[12a] This product was prepared according the general procedure. The crude reaction mixture was purified by flash chromatography (silica gel, Hexane/Et_2O 40:60) obtaining a red solid (36 mg, 0.07 mmol, 70 % yield). $[\alpha]_D^{20}$ = –261.5 (*c* = 1.00, $CHCl_3$) [Lit.[12a] $[\alpha]_D^{20}$ = -410.7 (*c* = 0.55, $CHCl_3$, 99% *ee* for (*R*) enantiomer)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33 (s, 9H), 3.88 (s, 3H), 5.03 (d, *J* = 15.9 Hz, 1H), 5.10 (d, *J* = 15.9 Hz, 1H), 5.91 (s, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.88 (ddd, *J* = 8.3, 8.3, 0.9 Hz, 1H), 6.97 (s, 1H), 7.15 (ddd, *J* = 8.2, 8.2, 1.1 Hz, 1H), 7.25-7.29 (m, 2H), 7.32–7.38 (m, 3H), 7.38–7.44 (m, 1H), 7.52 (d, *J* = 7.4 Hz, 2H), 7.56 (d, *J* = 7.5 Hz, 1H), 7.68 (ddd, *J* = 8.1, 1.3 Hz, 1H), 8.75 (s, 1H). HPLC (Lux i-cellulose-5, hexane/isopropanol 80:20, λ = 254 nm, 1 mL/min): t_R = 20.7 (minor, *S*), t_R = 24.1 (major, *R*) (er: 78:22).

***tert*-Butyl (*R*)-(1-benzyl-3-(4-hydroxy-1*H*-indol-5-yl)-2-oxoindolin-3-yl)carbamate (4i)**.[13] This product was prepared according the general procedure. The crude reaction mixture was purified by flash chromatography (silica gel, Hexane/Et_2O 70:30) obtaining a colorless solid (46 mg, 0.098 mmol, 98 % yield). $[\alpha]_D^{20}$ = +164.7 (*c* = 0.68, $CHCl_3$) [Lit.[13] $[\alpha]_D^{20}$ = +251.6 (*c* = 0.23, $CHCl_3$, 99% *ee* for (*R*) enantiomer)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.31 (s, 9H), 4.72–4.90 (m, 1H), 5.03 (bd, *J* = 14.5 Hz, 1H), 5.80 (s, 1H), 6.54 (d, *J* = 8.7 Hz, 1H), 6.73 (t, *J* = 8.6 Hz, 2H), 6.77–6.80 (m, 1H), 7.10–7.13 (m, 1H), 7.15–7.29 (m, 8H), 7.40 (dd, *J* = 7.3, 1.0 Hz, 1H), 8.19 (s, 1H), 10.47 (s, 1H). HPLC (Lux-amylose-1, hexane/isopropanol 70:30, λ = 254 nm, 1 mL/min): t_R = 10.3 (minor, *S*), t_R = 23.7 (major, *R*) (er: 83:17).

***tert*-Butyl (*S*)-(4-(1-hydroxynaphthalen-2-yl)-3-methyl-5-oxo-1-phenyl-4,5-dihydro-1*H*-pyrazol-4-yl)carbamate (14a).**[23a] This product was prepared according the general procedure. The crude reaction mixture was purified by flash chromatography (silica gel, Hexane/Et_2O 80:20) obtaining a colorless solid (42 mg, 0.097 mmol, 97 % yield). $[\alpha]_D^{20}$ = +289.8 (*c* = 0.62, $CHCl_3$) [Lit.[23a] $[\alpha]_D^{20}$ = +416.3 (*c* = 0.9, $CHCl_3$, 96% *ee* for (*S*) enantiomer)]; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.41 (s, 9H), 2.38 (s, 3H), 5.69 (bs, 1H), 6.98 (d, *J* = 8.8 Hz, 1H), 7.16 (t, *J* = 8.2 Hz, 1H), 7.32–7.39 (m, 3H), 7.49–7.54 (m, 2H), 7.70–7.75 (m, 1H), 7.85 (d, *J* = 8.7 Hz, 2H), 8.36–8.42 (m, 1H), 9.97 (s, 1H). HPLC (Lux-i-amylose-1, hexane/isopropanol 80:20, λ = 230 nm, 1 mL/min): t_R = 7.2 (minor, *R*), t_R = 19.2 (major, *S*) (er: 84:16).

(*R*)-3-Amino-1-benzyl-3-(1-hydroxynaphthalen-2-yl)indolin-2-one (15).[12a] Compound **4a** (90 mg, 0.18 mmol) was dissolved in HCl 4M solution in 1,4-dioxane (4 mL) and stirred at room temperature for 5 h. The volatiles were removed under reduced pressure and the reaction mixture was diluted in dichloromethane and quenched with K_2CO_3 10% w/v solution in water (7 mL). The aqueous phase was washed with dichloromethane (3 x 10 mL) and dried over $MgSO_4$. The solvent was evaporated and the final product was obtained as a white solid in a 99% yield (68 mg, 0.178 mmol). $[\alpha]_D^{20}$ = –402.7 (*c* = 1.05, $CHCl_3$) [Lit.[12a] $[\alpha]_D^{20}$ = -391.0 (*c* = 1.07, $CHCl_3$, 99% *ee* for (*R*) enantiomer)]; ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.79–4.97 (m, 1H), 5.00–5.14 (m, 1H), 6.70–6.82 (m, 2H), 6.96 (t, *J* = 7.3 Hz, 1H), 7.14–7.20 (m, 2H), 7.27–7.48 (m, 7H), 7.64–7.74 (m, 2H), 8.30–8.37 (m, 1H). HPLC (Lux-amylose-1, hexane/isopropanol 80:20, λ = 254 nm, 1 mL/min): t_R = 20.7 (minor, *S*), t_R = 24.8 (major, *R*) (er 98:2).

Synthesis of (*R*)-1-Benzylspiro[indoline-3,4'-naphtho[2,1-e][1,3]oxazine]-2,2'(3'*H*)-dione (16). Compound **15** (60 mg, 0.16 mmol) was dissolved in anhydrous THF (3 mL) under inert atmosphere. The solution was cooled to 0 ºC and triphosgene (57 mg, 0.19 mmol, 1.2 equiv) was added slowly. The mixture was allowed to stir at the same temperature for 10 min followed by addition of Et_3N (0.8 mL, 0.56 mmol, 3.5 equiv). The reaction mixture was stirred at room temperature for 3 h, water (4 mL) was added and the mixture was concentrated under vacuum. The product was extracted with ethyl acetate (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated. The crude was purified by column chromatography (silica gel, Hexane/EtOAc 1:1) and the final product was isolated as a foamy white solid (50 mg, 0.12 mmol, 77% yield). Mp = 125–127 ºC; $[\alpha]_D^{20}$ = + 60.0 (*c* = 1.06, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.78 (d, *J* = 15.5 Hz, 1H), 5.05 (d, *J* = 15.5 Hz, 1H), 6.50 (d, *J* = 8.6 Hz, 1H), 6.58 (s, 1H), 6.88 (d, *J* = 7.9 Hz, 1H), 7.10 (dd, *J* = 7.6, 7.6 Hz, 1H), 7.26–7.36 (m, 7H), 7.46 (d, *J* = 8.6 Hz, 1H), 7.54–7.63 (m, 2H), 7.77 (d, *J* = 8.2 Hz, 1H), 8.39 (d, *J* = 8.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.3, 64.1, 110.0, 112.6, 120.6, 121.7, 123.4, 124.1, 124.8, 125.4, 127.1, 127.4, 127.5 (2C), 127.6, 128.0, 128.9 (2C), 129.3, 131.0, 134.2, 135.2, 142.9, 145.7, 150.1, 175.1. IR (ATR): 1722, 1612, 1468, 1329, 1193, 1172, 745, 699 cm^{-1}. HPLC (Lux-i-amylose-1, hexane/isopropanol 80:20, λ = 254 nm, 1 mL/min): t_R = 42.6 (major, *R*), t_R = 68.5 (minor, *S*) (er 96:4). HRMS (ESI^+): *m/z* $[M+Na]^+$ Calculated for $C_{26}H_{18}N_2O_3Na$ 429.1210; Found 429.1218.

Synthesis of (*R*)-1-benzyl-2'H-spiro[indoline-3,5'-naphtho[2,1-f][1,4]oxazepine]-2,3'(4'*H*)-dione (17). To a solution of amine **15** (121 mg, 0.32 mmol) in acetone (1 mL) was sequentially added K_2CO_3 (48 mg, 0.35 mmol, 1.1 equiv) and ethyl bromoacetate (35 µL, 0.32 mmol, 1 equiv). The mixture was stirred at room temperature for 3 h. After this time, the solution was filtered to eliminate the solids and the filtrate was concentrated under reduced pressure. The resulting oil was dissolved in ethyl acetate and washed with sat. NaCl (3 x 10 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated under reduced pressure. The residue was dissolved in toluene (3 mL), added acetic acid (0.2 mL) and heated at 60 ºC for 1 h. The solvent was evaporated under reduced pressure and the residue was dissolved in dichloromethane (10 mL) and washed with sat. $NaHCO_3$ (2 x 10 mL). The organic phase was dried over $MgSO_4$, filtered and concentrated. The crude mixture was purified by column chromatography on silica gel using Hexane/ EtOAc 1:1 as eluent. The final product was isolated as a foamy white solid in a 45% yield (60 mg, 0.14 mmol). Mp = 123–124 ºC; $[\alpha]_D^{20}$ = + 92.3 (*c* = 1.03, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.82 (d, *J* = 15.5 Hz, 1H), 4.90 (d, *J* = 15.0 Hz, 1H), 5.10 (d, *J* = 15.5 Hz, 1H), 5.52 (d, *J* = 15.0 Hz, 1H), 6.25 (s, 1H), 6.58 (d, *J* = 8.8 Hz, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 7.07 (dd, *J* = 7.7, 7.7 Hz, 1H), 7.24–7.38 (m, 7H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.50-7.59 (m, 2H), 7.74 (d, *J* = 8.1 Hz, 1H), 8.33 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.4, 65.4, 73.2, 109.9, 120.7, 122.3, 123.4, 124.3, 124.7, 125.2, 126.6, 127.3, 127.4, 127.5, 127.6, 128.0, 128.8, 129.0 (2C), 130.5, 132.3, 134.1, 135.1, 142.0, 154.6, 174.0, 175.5. IR (ATR): 1722, 1663, 1608, 1371, 1341, 1109, 809, 745, 695 cm^{-1}. HPLC (Lux-i-amylose-1, hexane/isopropanol 70:30, λ = 254 nm, 1 mL/min): t_R = 25.8 (major, *R*), t_R = 50.1 (minor, *S*) (er 97:3). HRMS (ESI^+): *m/z* $[M+Na]^+$ Calculated for $C_{27}H_{20}N_2O_3Na$ 443.1366;Found 443.1374.

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