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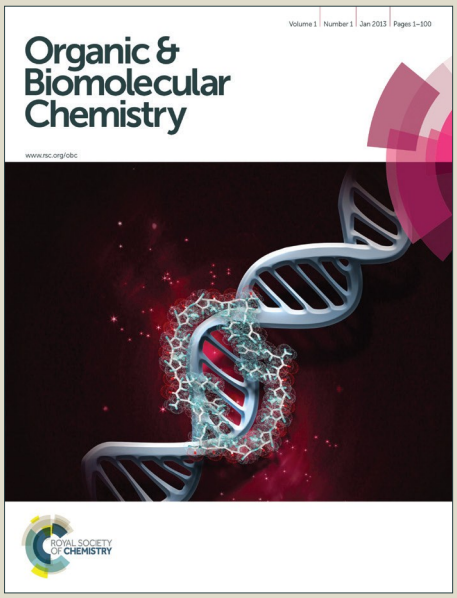

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Organocatalytic Vinylogous Mannich Reaction of Trimethylsiloxyfuran with Isatin-derived Benzhydryl-Ketimines

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Abstract

A family of chiral quaternary 3-aminooxindole butenolides have been synthesized, by BINOL-derived phosphoric acid-catalyzed addition of trimethylsiloxyfuran to isatin-derived ketimines. Such vinylogous Mannich-type reaction was found to produce the diastereoisomeric butenolides in good yields and in most cases high enantiomeric excesses. The configurational assignment of the obtained products was safely performed by chemical correlation. A computational study of the transition state allowed to rationalize the obtained stereochemical outcome, highlighting the possible binding modes of the catalyst-imine-nucleophile transition complex.

Introduction

Optically active δ-amino-α,β-unsaturated carbonyl compounds, particularly those bearing the γ-butenolide skeleton, are receiving considerable attention due to their broad application in the synthesis of biologically active compounds. The butenolide ring is in fact one of the most ubiquitous structures found in natural products and its incorporation into more complex heterocyclic architectures has continuously attracted the attention from a pharmaceutical point of view.[1]
The vinylogous Mannich-type reaction of imines with a dienolate equivalent, such as trimethylsiloxyfuran (TMSOF), is a useful mean to prepare γ-butenolide derivatives bearing an amine functionality.[2] Metal complexes and organocatalysts promote efficiently asymmetric vinylogous Mannich (AVM) reactions of aldimines, affording optically active δ-amino-α,β-unsaturated carbonyl compounds in high yields and enantiomeric excesses. With regard to catalytic methods, a milestone was placed in 2006 by Hoveyda,[3,4] who reported the first highly diastereo- and enantioselective protocol for such reaction. The AVM was catalyzed by a silver salt and an easily accessible chiral phosphine, and only aromatic aldimines were employed. More recently, a new Ag(I)-monophosphine complex was developed by Xu, displaying wide aldimine versatility, excellent yield and diastereoselectivity, and moderate enantioselectivity.[5] Among organocatalytic, metal-free methods, a iodine-substituted chiral phosphoric acid was demonstrated by Akiyama to efficiently catalyze the AVM of aliphatic as well aromatic aldimines.[6]
Application of the vinylogous Mannich-type reaction to ketimines is more challenging, due to the lower reactivity of ketimines compared with aldimines and to the steric challenge inherent in the stereocontrolled formation of a quaternary stereocenter consecutive with a bulky tertiary one. To date, there are only few reports on the AVM of TMSOF with ketimines, to give chiral δ-amino-α,β-unsaturated carbonyl compounds having a quaternary carbon center. Besides the successful Ag-catalyzed process, applied by Hoveyda[7] also to α-ketimine esters, relevant is the contribution from Nakamura,[8] who reported a Cinchona alkaloid amide/copper (II) catalyzed diastereo- and enantioselective Mannich reaction of ketimines. Quite recently, the strictly related Cinchona alkaloid amide/zinc (II) system was also developed by the same author,[9] and applied to the similar Mannich reaction employing γ-butenolide instead of TMSOF as nucleophile. Given the relevance of chiral δ-amino-α,β-unsaturated carbonyl compounds having a quaternary carbon center, the development of novel stereoselective methods for the construction of this attractive framework in an asymmetric manner is highly desirable.
As part of our interest in the asymmetric synthesis of 3,3-disubstituted oxindole derivatives and related spiro-compounds,[10] we recently turned our attention to BINOL-derived phosphoric acids as useful chiral Brønsted acid catalysts for the Biginelli reaction applied to isatin, allowing the synthesis of spiro(indoline-pyrimidine)-diones derivatives.[11] Chiral Brønsted acid catalysts have recently emerged as a new class of environmentally benign chiral catalysts for a number of enantioselective reactions.[12] Herein, our ongoing interest was extended to the asymmetric preparation of quaternary 3-aminooxindole butenolides, which can be considered an intriguing combination of pharmacologically interesting γ-butenolide and oxindole motifs. A racemic preparation of such compounds in excellent yields and diastereoselectivities was realized by Deng,[13] employing AgOAc as the catalyst. A highly practical, sulfinyl amine chiral auxiliary-based approach was also recently developed,[14] based on a simple Lewis acid mediated diastereoselective vinylogous Mannich process.
At the best of our knowledge, no organocatalytic methods employing TMSOF have been reported for the preparation of such scaffolds. Only a related AVM was recently realized, based on a bifunctional quinidine-derived catalyst and 3,4-dichlorofuran-2(5*H*)-one as the nucleophile.[15] Herein, we report the BINOL-derived phosphoric acid-catalyzed asymmetric synthesis of quaternary 3-aminooxindole butenolides via a vinylogous Mannich-type reaction, consisting in the enantioselective addition of TMSOF to isatin-derived ketimines (Scheme 1).

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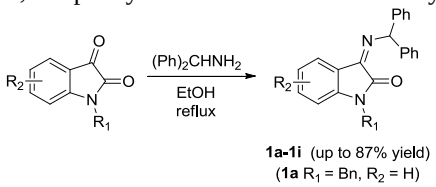
Results and discussion

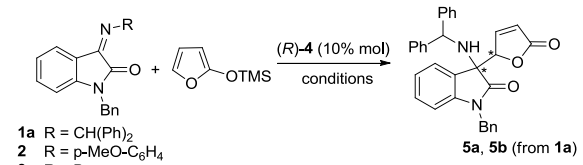
We began our investigation using *N*-diphenylmethyl ketimine **1a**, obtained as the only product in the reaction between C,C-diphenyl-methanamine and *N*-benzyl-isatin (Scheme 1), and two well-known isatin-derived ketimines, **2** and **3**.

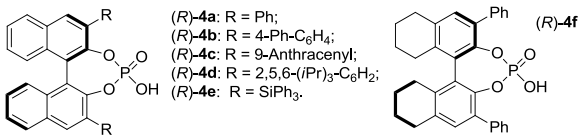


Scheme 1. Synthesis of isatin-based *N*-benzydryl ketimines **1**.

Reaction of **1a**, **2** and **3** with TMSOF, initially carried out at room temperature, using THF as the solvent and 10 mol % of catalyst **4a**, proved to be completely ineffective. Reasoning that the addition of a protic cosolvent to the reaction mixture could be essential for the onset of the catalytic cycle, we repeated the reaction by adding MeOH (1% vol). In such conditions, all three ketimines proved to be reactive, affording the corresponding 3-aminooxindole butenolides with variable yields, up to 84% (Table 1, entries 1-3). We assumed that probably the protic cosolvent suppresses the undesired retroaddition reaction by rapidly converting the silylated butenolide ring into the final product, while also enabling the isolation of the adduct formed under conditions of kinetic control.[16] In addition, we can also suppose that, in absence of a protic source, the catalytic BINOL-derived phosphoric acid might be converted to the corresponding O-silylated BINOL-phosphate, evidently not able to promote the AVM reaction as the phosphoric acid form.[17]
Ketimine **1a**, performing to the best, was then chosen for subsequent conditions and catalyst screening, also in the light of the potential greater versatility of the obtained products, due to the easy removal of the protective diphenyl-methyl group. The temperature proved to be a key parameter for the asymmetric induction of this reaction. At room temperature (entry 1), the reaction proceeds to give **5** as a 75/25 mixture of the **5a** and **5b** diastereoisomers, each of which with a negligible enantiomeric excess. Upon lowering the reaction temperature (entries 4-7), we noticed a substantial maintenance of the obtained yields, with a collapse of diastereoselectivity and an overall improvement of the enantioselectivity for both **5a** and **5b** diastereoisomers. In particular, carrying out the reaction at - 40 °C, both diastereoisomers could be recovered in almost equal quantities (80% overall yield, **5a**/**5b** 52:48), showing excellent enantioselectivities (ee **5a** 90%, ee **5b** 92%). Changing the solvent to toluene (entry 8) or dichloromethane (entry 9) entailed a significant negative effect on the chemical conversion, demonstrating that the originally chosen THF was the optimal solvent for this reaction. Screening of more hindered catalysts **4b-e**, aimed to evaluate the impact of the 3,3'-substitution, and of octahydro-BINOL-based **4f** was performed (entries 10-14). Increasing the size of the 3,3'-substitents on the phosphoric acid proved detrimental for the chemical conversion, with only catalysts **4b** and **4f** able to afford product **5**, with maintenance of the same level of diastereo- and lower enantioselectivity with respect to catalyst **4a**, and in definitely decreased yields.

Table 1. Optimization of the asymmetric AVM reaction.[a]





entry	R (ketimine)	catalyst	solvent	temp., time	yield %[b]	*dr* (**5a:5b**)[c]	*ee* % **5a**[d]	*ee* % **5b**[d]
1	$CH(Ph)_2$	**4a**	THF	rt, 10 min	84	75:25	0	25
2	p-MeO-C_6H_5	**4a**	THF	rt, 20 min	60	61:39	2	10
3	Boc	**4a**	THF	rt, 8h	15	51:49	5	7
4	$CH(Ph)_2$	**4a**	THF	0 °C, 40 min	87	69:31	1	31
5	$CH(Ph)_2$	**4a**	THF	- 20 °C, 1h	85	57:43	47	69
6	**$CH(Ph)_2$**	**4a**	**THF**	**- 40 °C, 7h**	**80**	**52:48**	**90**	**92**

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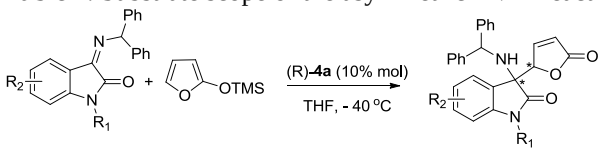
7	$CH(Ph)_2$	**4a**	THF	- 78 °C, 48h	68	51:49	90	92
8	$CH(Ph)_2$	**4a**	Toluene	- 40 °C, 48h	35	53:47	89	93
9	$CH(Ph)_2$	**4a**	CH_2Cl_2	- 40 °C, 48h	27	55:45	90	93
10	$CH(Ph)_2$	**4b**	THF	- 40 °C, 48h	50	57:43	57	66
11	$CH(Ph)_2$	**4c**	THF	- 40 °C, 48h	nr	-	-	-
12	$CH(Ph)_2$	**4d**	THF	- 40 °C, 48h	nr	-	-	-
13	$CH(Ph)_2$	**4e**	THF	- 40 °C, 48h	nr	-	-	-
14	$CH(Ph)_2$	**4f**	THF	- 40 °C, 48h	41	50:50	67	78

[a] Reactions were performed with 0.12 mmol of ketimine and 0.14 mmol of TMSOF, in 1.2 mL of solvent; MeOH was used as additive (1% vol). [b]Isolated yield. [c]Determined by ^{1}H NMR (from integration of olefinic protons). [d]Determined by chiral HPLC analysis. nr = no reaction.

After having established **4a** as the catalyst of choice and to work in THF at - 40 °C as the optimal conditions, the substrate scope of the AVM reaction was surveyed, by evaluating differently *N*-substituted isatins and the presence of substituents at 5- or 6-position of the isatin nucleus. (**Table 2**).

Table 2. Substrate scope of the asymmetric AVM reaction catalyzed by **4a**.[a]



1a-1i 5a,b-13a,b

entry	R_1	R_2	yield %[b]	*dr*[c]	*ee* % **5a-13a**[d]	*ee* % **5b-13b**[d]
1 (**1a**)	Bn	H	80	**5a:5b** 52:48	90	92
2 (**1b**)	H	H	78	**6a:6b** 63:37	80	88
3 (**1c**)	Me	H	81	**7a:7b** 55:45	91	68
4 (**1d**)	PMB	H	79	**8a:8b** 55:45	84	89
5 (**1e**)	Tr	H	81	**9a:9b** 47:53	4	96
6 (**1f**)	Bn	5-F	45	**10a:10b** 72:28	1	15
7 (**1g**)	Bn	5-Cl	42	**11a:11b** 70:30	26	74
8 (**1h**)	Bn	6-Br	65	**12a:12b** 70:30	31	42
9 (**1i**)	Me	6-Br	68	**13a:13b** 62:38	32	31

[a] Reactions were performed with 0.12 mmol of ketimine and 0.14 mmol of TMSOF, in 1.2 mL of solvent; MeOH was used as additive (1% vol). [b] Isolated yield. [c] Determined by ^{1}H NMR (from integration of olefinic protons); for relative and absolute configurational assignment of diastereoisomeric products, see below. [d] Determined by chiral HPLC analysis.

In general, all isatins readily undergo this reaction, to afford the desired products **5-13** in moderate to high yields, with a good degree of enantioselectivity (entries 1-5). The presence of a halogen substituent on the oxindole (entries 6-9) results in a lowering of yield and enantiomeric excess, with a slight increase of diastereoselectivity.
Since diastereoisomers **7a** and **7b** (entry 3) proved to be readily separable by flash chromatography, we selected them for the determination of absolute and relative stereochemistry. However, neither of them proved to be suitable for X-ray analysis. Thus, starting from the major **7a**, we performed a chemical correlation based on the literature compound **14**, as depicted in Scheme 2. From NMR and $[\alpha]_D$ comparison of compound **15**, derived from **14**, and compound **15'**, derived from **7a**, the (*R*,*R*) *anti* configuration could be safely assigned to **7a**.

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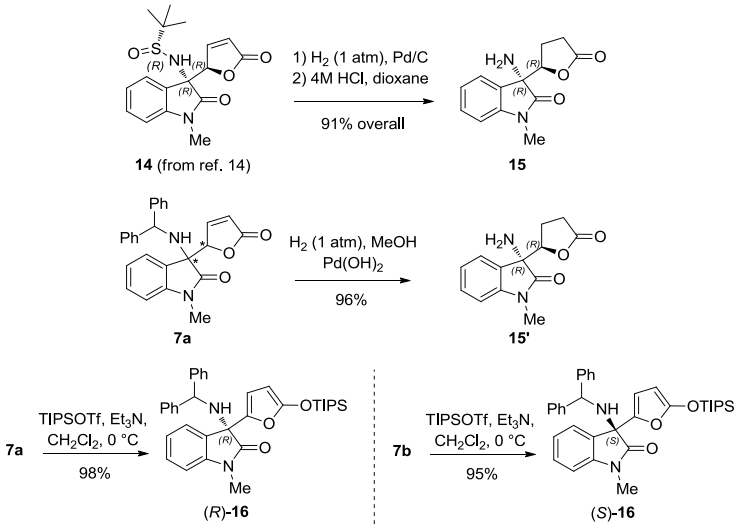

Scheme 2. Chemical correlations for the configurational assignment of **7a** and **7b**.

For the configurational assignment of minor diastereoisomer **7b**, still we relied on a chemical correlation, performing on both **7a** and **7b** the same reaction to give the silyl enol ether derivative **16**. Since **16** was obtained as opposite enantiomer starting from **7a** and **7b**, we could assign the (*S*,*R*) *syn* configuration to **7b**.

In order to propose a possible explanation of the stereochemical outcome, a preliminary investigation of the transition state organization was performed by means of computational tools. The theoretical study of this reaction is complicated by a number of factors, namely, the size of the system, the possible approach *endo* or *exo* of the nucleophile, with respect to both the *re* and *si* face of the imine and the several competing H-bonding possibilities in the assembly of the transition state. We were aware that also the *E*/*Z* geometry of the imine might play an important role in the enantioselection. However, since NMR analysis of starting imine **1c** showed the presence of a major isomer (9:1) and theoretical DFT calculations indicated the *Z*-**1c** imine more stable than the corresponding *E* isomer by 4.38 kcal/mol, we decided to consider only the *Z* geometry in our further studies.

In accordance with the enantioselectivity of the reaction, in the proposed model[18] the major enantiomer (3*R*,2'*R*)-**7a** is achieved through **TS-A**, whereas **TS-C** would lead to the diastereoisomeric (3*S*,2'*R*)-**7b**. To support this hypothesis, we calculated the energy for **TS-C** and **TS-D** at the B3LYP/6-31G(d) level (see SI for details).[19] **TS-C** resulted to be lower in energy for 0.6 kcal/mol at 233 K, with respect to **TS-D** , in agreement with the measured 68% ee. In such favored **TS-C**, the 2-hydroxyfuran is coordinated to the catalyst **4a** through the OH hydrogen and it prefers to assume the *endo* orientation with respect to the imine as the third component (the opposite *exo* orientation is present in **TS-D**). The same considerations apply to **TS-A** (favored) and **TS-B**. The orientation of the imine is less significant, probably due to the great steric hindrance around both faces of the imine double bond.

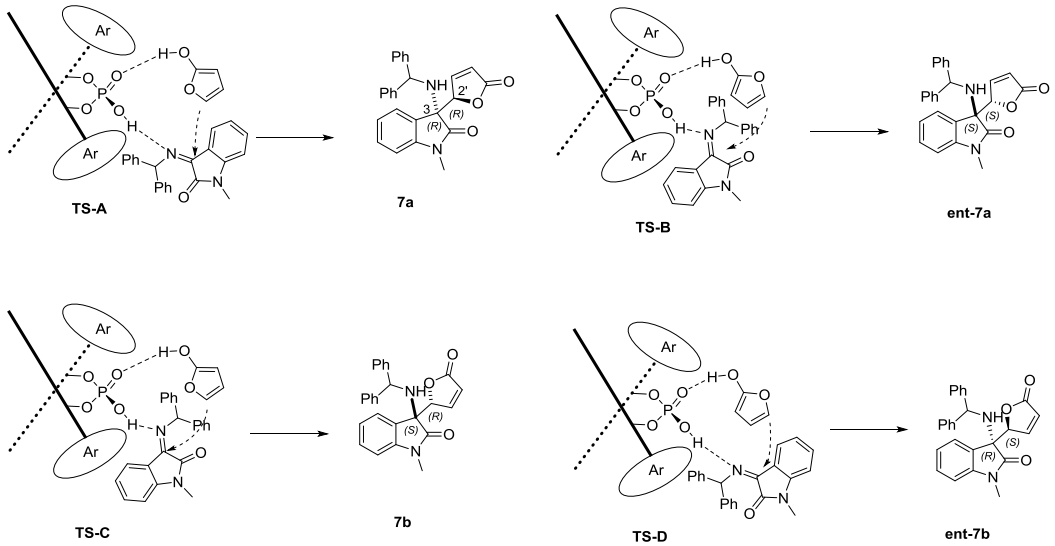

Figure 1. Possible binding modes of the catalyst **4a** - 2-hydroxyfuran - imine **1c** transition complex.

Conclusions

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In summary, an organocatalytic approach for the asymmetric synthesis of quaternary 3-aminooxindole butenolides has been developed. The method exploits the vinylogous Mannich reaction of TMSOF with various isatin-derived benzhydryl-ketimines, affording diastereoisomeric products in good yields and in most cases high enantiomeric excesses. The obtained products, containing a quaternary stereocenter consecutive with a bulky tertiary one, are suitable for further transformations, as demonstrated in the performed chemical correlation study. The stereochemical outcome was also rationalized by means of a computational study, which allowed to propose the most favoured binding modes of reaction components in the transition state.

Experimental section

General Information

All commercial materials (Aldrich, Fluka) were used without further purification. All solvents were of reagent grade or HPLC grade. All reactions were carried out under a nitrogen atmosphere unless otherwise noted. All reactions were monitored by thin layer chromatography (TLC) on precoated silica gel 60 F254; spots were visualized with UV light or by treatment with ninhydrin solution in ethanol. Products were purified by flash chromatography (FC) on silica gel 60 (230–400 mesh). ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on 300 and 400 MHz spectrometers. Chemical shifts are reported in parts per million relative to the residual solvent. ^{13}C NMR spectra have been recorded using the APT pulse sequence. Multiplicities in ^{1}H NMR are reported as follows: s = singlet, d = doublet, t = triplet, m = multiplet, br s = broad singlet. High-resolution MS spectra were recorded with a Waters Micromass Q-ToF micro TM mass spectrometer, equipped with an ESI source. Chiral HPLC analysis was performed on Jasco PU-2080 (UV Detector and binary HPLC pump) at 254 nm. Chiralcel ODH and AD columns were purchased from Daicel Chemical Industries®. Optical rotator power $[\alpha]^{T}_{D}$ was measured with a Jasco P-1030 polarimeter, endowed with a cell of 1 dm pathlength and 1 mL capacity. The light used has a wavelength of 589 nm (Sodium D line). All the *N*-substituted isatins[20] and BINOL-derived phosphoric acids[21] were synthetized according to reported literature.

General procedure A for the synthesis of isatins-derived benzhydryl imines (GP-A)

To a suspension of appropriate substituted isatin (1.5 mmol) in absolute EtOH (5 mL), under a nitrogen atmosphere, benzhydryl amine (1.5 mmol) was added in one portion and the mixture was refluxed for 24 hours. The reaction was cooled to room temperature and stirred for 2 hours.

3-(Benzhydrylimino)-1-benzylindolin-2-one (1a)

Prepared according to **GP-A** using 1-benzyl isatin. The desired product **1a** was collected by filtration; yield: 494 mg, 82%; yellow foam; ^{1}H NMR (300 MHz, $CDCl_3$, 9:1 mixture of imine isomers) δ 7.87 (s, 0.9H), 7.77 (d, *J* = 7.5 Hz, 0.9H), 7.61-7.46 (m, 4H), 7.45-7.14 (m, 12.1H), 7.05 (t, *J* = 7.5 Hz, 0.9H), 6.98 (t, *J* = 7.5 Hz, 0.1H), 6.75 (d, *J* = 7.8 Hz, 0.1H), 6.66 (d, *J* = 7.8 Hz, 0.9H), 6.56 (s, 0.1H), 4.97 (s, 0.2H), 4.89 (s, 1.8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.9, 151.8, 144.6 and 143.0 (1C), 144.2 (2C), 135.3, 133.3 and 132.7 (1C), 128.9-127.1 (15C), 123.2, 122.9 and 122.5 (1C), 122.0, 110.3 and 109.3 (1C), 69.9 and 65.5 (1C), 43.9 and 43.5 (1C); HRMS (ESI) calcd for $C_{28}H_{22}N_2NaO^+$ $[MNa]^+$ 425.1624, found 425.1632.

3-(Benzhydrylimino)indolin-2-one (1b)

Prepared according to **GP-A** using isatin. The desired product was collected by filtration; yield: 407 mg, 87%; yellow foam; ^{1}H NMR (300 MHz, $CDCl_3$, 4:1 mixture of imine isomers) δ 8.83 (m, br, 0.2H), 7.98 (m, br, 0.8H), 7.83-7.69 (m, 2H), 7.52 (d, br, *J* = 7.8 Hz, 3.2H), 7.46 (d, br, *J* = 7.7 Hz, 0.8H), 7.38-7.13 (m, 7H), 7.06 (t, *J* = 7.5 Hz, 0.8H), 7.00 (t, *J* = 7.5 Hz, 0.2H), 6.92 (d, *J* = 7.6 Hz, 0.2H), 6.78 (d, *J* = 7.6 Hz, 0.8H), 6.53 (s, br, 0.2H); ^{13}C NMR (75 MHz, CD_2Cl_2+1%DMSO-d_6) δ 160.9, 153.6, 144.8 (2C), 143.8, 133.8 and 133.2 (1C), 128.9-127.2 (10C), 122.8, 122.7, 122.5, 111.8 and 110.8 (1C), 69.9 and 65.1 (1C); HRMS (ESI) calcd for $C_{21}H_{16}N_2NaO^+$ $[MNa]^+$ 335.1155, found 335.1144.

3-(Benzhydrylimino)-1-methylindolin-2-one (1c)

Prepared according to **GP-A** using 1-methyl isatin. The desired product was collected by filtration; yield: 367 mg, 75%; yellow foam; ^{1}H NMR (400 MHz, CD_2Cl_2, 9:1 mixture of imine isomers) δ 7.83 (s, 0.9H), 7.78 (d, br, *J* = 7.5 Hz, 0.9H), 7.76 (d, br, *J* = 7.5 Hz, 0.1H), 7.57 (d, br, *J* = 7.7 Hz, 3.6H), 7.52 (d, br, *J* = 7.8 Hz, 0.4H), 7.47 (dt, *J* = 7.8 and 1.5 Hz, 0.9H), 7.46 (dt, *J* = 7.7 and 1.5 Hz, 0.1H), 7.41-7.24 (m, 6H), 7.16 (dt, *J* = 7.6, 1.0 Hz, 0.9H), 7.06 (dt, *J* = 7.8, 1.0 Hz, 0.1H), 6.92 (d, br, *J* = 7.8 Hz, 0.1H), 6.86 (d, br, *J* = 7.8 Hz, 0.9H), 6.57 (s, 0.1H), 3.27 (s, 0.3H), 3.22 (s, 2.7H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.9, 152.3, 145.7 and 143.3 (1C), 144.4 (2C), 133.5 and 132.9 (1C), 128.6-127.3 (10C), 122.9, 122.5, 121.7, 109.2 and 108.4 (1C), 69.7 and 65.4 (1C), 26.0 and 25.5 (1C); HRMS (ESI) calcd for $C_{22}H_{18}N_2NaO^+$ $[MNa]^+$ 349.1311, found 349.1322.

3-(Benzhydrylimino)-1-(4-methoxybenzyl)indolin-2-one (1d)

Prepared according to **GP-A** using 1-4-methoxybenzyl isatin. The desired product was collected by filtration; yield: 486 mg, 75%; yellow foam; ^{1}H NMR (400 MHz, CD_2Cl_2, 9:1 mixture of imine isomers) δ 7.88 (s, br, 0.9H), 7.79 (d, br, *J* = 7.6 Hz, 0.9H), 7.76 (d, br, *J* = 7.7 Hz, 0.1H), 7.59 (d, br, *J* = 7.4 Hz, 3.6H), 7.54 (d, br, *J* = 7.4 Hz, 0.4H), 7.44-7.23 (m, 9H), 7.12 (t, *J* = 7.6, 0.9H), 7.03 (t, *J* = 7.7, 0.1H), 6.88 (d, br, *J* = 8.0, 2H), 6.84 (d, br, *J* = 7.8, 0.1H), 6.78 (d, br, *J* = 7.8, 0.9H), 6.57 (s, br, 0.1H), 4.93 (s, 0.2H), 4.87 (s, 1.8H), 3.80 (s, 3H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ 159.9, 159.4, 152.9, 145.5, 145.0 (2C), 144.0, 134.0 and 133.4 (1C), 129.4-127.6 (12C), 123.7 and 123.3 (1C), 122.6, 122.7, 114.8 (2C), 110.9 and 110.0 (1C), 70.5 and 66.1 (1C), 55.9, 43.9 and 43.5 (1C); HRMS (ESI) calcd for $C_{29}H_{24}N_2NaO_2^+$ $[MNa]^+$ 455.1730, found 455.1742.

3-(Benzhydrylimino)-1-tritylindolin-2-one (1e)

Prepared according to **GP-A** using 1-trityl isatin. The desired product was collected by filtration; yield: 498 mg, 60%; pale yellow foam; ^{1}H NMR (300 MHz, $CDCl_3$, 9:1 mixture of imine isomers) δ 7.82-7.69 (m, 1.9H), 7.61-7.37 (m, 10H), 7.35-7.17 (m, 15H), 7.04-6.83 (m, 2H), 6.50 (s, br, 0.1H), 6.38 (d, *J* = 7.8 Hz, 0.1H), 6.16 (d, *J* = 7.8 Hz, 0.9H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 160.3, 151.8, 145.3, 144.5 (2C), 141.9 (3C), 131.6 and 131.2 (1C), 129.6-126.9 (25C), 123.4, 122.6, 122.2 and 122.8 (1C), 117.2 and 115.7 (1C), 74.7, 69.7 and 64.4 (1C); HRMS (ESI) calcd for $C_{40}H_{30}N_2NaO^+$ $[MNa]^+$ 577.2250, found 577.2239.

3-(Benzhydrylimino)-1-benzyl-5-fluoroindolin-2-one (1f)

Prepared according to **GP-A** using 5-fluoro-1-benzyl isatin. The desired product was collected by filtration; yield: 428 mg, 68%; yellow foam; ^{1}H NMR (400 MHz, CD_2Cl_2, 9:1 mixture of imine isomers) δ 7.88 (s, 0.9H), 7.63-7.50 (m, 4H), 7.47-7.26 (m, 11H), 7.07 (dt, *J* = 8.0, 2.8 Hz, 1H), 6.75 (dd, *J* = 8.0, 4.2 Hz, 0.1H), 6.68 (dd, *J* = 8.0, 3.9 Hz, 0.9H), 6.50 (s, 0.1H), 4.99 (s, 0.2H), 4.93 (s, 1.9H). ^{13}C NMR (101 MHz, CD_2Cl_2) δ 160.1 (d, *J* = 241.6Hz, 1C), 159.4, 152.4, 144.8 (2C), 143.7 and 141.5 (1C), 135.9, 131.0-127.8 (15C), 123.8 (d, *J* = 8.5Hz, 1C), 120.3 (d, *J* = 24.0Hz) and 119.6 (d, *J* = 24.0Hz) (1C), 116.0 (d, *J* = 24.0Hz) and 110.3 (d, *J* = 24.0Hz) (1C), 111.6 (d, *J* = 7.1Hz) and 111.0 (d, *J* = 7.1Hz) (1C), 70.6 and 66.4 (1C), 44.5 and 44.2 (1C); HRMS (ESI) calcd for $C_{28}H_{21}FN_2NaO^+$ $[MNa]^+$ 443.1530, found 443.1515.

3-(Benzhydrylimino)-1-benzyl-5-chloroindolin-2-one (1g)

Prepared according to **GP-A** using 5-chloro-1-benzyl isatin. The desired product was collected by filtration; yield: 458 mg, 70%; yellow foam; ^{1}H NMR (400 MHz, CD_2Cl_2, 19:1 mixture of imine isomers) δ 7.86 (s, br, 0.95H), 7.81 (d, br, *J* = 1.6 Hz, 0.95H), 7.78 (d, br, *J* = 1.6 Hz, 0.05H), 7.60 (d, br, *J* = 7.5 Hz, 3.8H), 7.55 (d, br, *J* = 7.5 Hz, 0.2H), 7.46-7.26 (m, 12H), 6.76 (d, *J* = 8.5 Hz, 0.05H), 6.69 (d, *J* = 8.5 Hz, 0.95H), 6.53 (s, br, 0.05H), 5.00 (s, 0.1H), 4.93 (s, 1.9H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.4, 151.2, 144.1 (2C), 143.3, 135.1, 132.9 and 132.3 (1C), 130.4-127.1 (16C), 123.3, 122.4, 111.3 and 110.6 (1C), 70.0 and 65.9 (1C), 43.9 and 43.6 (1C); HRMS (ESI) calcd for $C_{28}H_{21}ClN_2NaO^+$ $[MNa]^+$ 459.1234, found 459.1245.

3-(Benzhydrylimino)-1-benzyl-6-bromoindolin-2-one (1h)

Prepared according to **GP-A** using 6-bromo-1-benzyl isatin. The desired product was collected by filtration; yield: 562 mg, 78%; yellow foam; ^{1}H NMR (400 MHz, CD_2Cl_2, 85:15 mixture of imine isomers) δ 7.83 (s, 0.85H), 7.68 (d, *J* = 7.7 Hz, 0.85H), 7.66-7.50 (m, 4.15H), 7.47-7.25 (m, 11.85H), 7.19 (dd, *J* = 7.8 and 1.2 Hz, 0.15H), 6.99 (d, *J* = 1.2 Hz, 0.15H), 6.93 (s, br, 0.85H), 6.51 (s, br, 0.15H), 4.98 (s, 0.3H), 4.91 (s, 1.7H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 158.6, 151.2, 145.9, 144.1 (2C), 135.0, 128.9-125.7 (17C), 123.4, 120.9, 113.5 and 112.7 (1C), 70.1 and 65.8 (1C), 43.9 and 43.6 (1C); HRMS (ESI) calcd for $C_{28}H_{21}BrN_2NaO^+$ $[MNa]^+$ 503.0729, found 503.0713.

3-(Benzhydrylimino)-6-bromo-1-methylindolin-2-one (1i)

Prepared according to **GP-A** using 6-bromo-1-methyl isatin. The desired product was collected by filtration; yield: 424 mg, 70%; yellow foam; ^{1}H NMR (400 MHz, CD_2Cl_2, 85:15 mixture of imine isomers) δ 7.78 (s, br, 0.85H), 7.66 (d, *J* = 7.8 Hz, 0.85H), 7.61-7.46 (m, 4.15H), 7.44-7.19 (m, 7H), 7.10 (s, br, 0.15H), 7.03 (s, br, 0.85H), 6.48 (s, br, 0.15H), 3.25 (s, 0.45H), 3.20 (s, 2.55H); ^{13}C NMR (101 MHz, CD_2Cl_2) δ 159.2, 152.1, 147.3, 144.8 (2C), 131.1-123.9 (13C), 121.3, 113.5 and 112.7 (1C), 70.6 and 66.3 (1C), 26.9 and 26.4 (1C); HRMS (ESI) calcd for $C_{22}H_{17}BrN_2NaO^+$ $[MNa]^+$ 427.0416, found 427.0411.

General procedure B for the asymmetric organocatalyzed synthesis of compounds 5-13 (GP-B)

To a solution of isatin-derived imine **1a-i** (0.12 mmol, 1eq) and trimethylsilyloxyfuran (TMSOF) (0.14 mmol, 1.16eq) in tetrahydrofuran (1 mL) cooled to -40 °C, a solution of catalyst (*R*)-**4a** (10% mol) in MeOH (25 µL) and tetrahydrofuran (200 µL) was slowly added. The resulting mixture was stirred at the same temperature for 7 hours. The reaction was quenched by adding $NaHCO_3$ saturated aq. (1 mL) and the product was extracted with EtOAc (2 x 5 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated under reduced pressure. The residue was purified by FC, as indicated below.

3-(Benzhydrylamino)-1-benzyl-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (5a,b)

Prepared according to **GP-B** using 3-(benzhydrylimino)-1-benzylindolin-2-one (**1a**); FC: *n*-Hexane:EtOAc, 7:3; yield: 47 mg, 80%; pale orange solid; ^{1}H NMR (300 MHz, $CDCl_3$, mixture of diasteroisomers *syn*:*anti*, 48:52) δ 7.83 (dd, *J* = 5.8 and 1.7 Hz, 0.52H), 7.43-7.13 (m, 15H), 7.10 (dd, *J* = 5.9 and 1.5 Hz, 0.48H), 7.08-6.91 (m, 2.48H), 6.87 (td, *J* = 7.6 and 1.0 Hz, 0.52H), 6.65 (d, *J* = 7.8 Hz, 0.48H), 6.59 (d, *J* = 7.8 Hz, 0.52H), 6.25 (dd, *J* = 5.8, 1.9 Hz, 0.52H), 5.97 (dd, *J* = 5.9, 2.2 Hz, 0.48H), 5.48 (t, br, *J* = 1.8 Hz, 0.48H), 5.26 (t, br, *J* = 1.7 Hz, 0.52H), 4.81 (d, *J* = 15.9 Hz, 0.52H), 4.73 (s, br, 0.48H), 4.72 (s, br, 0.52H), 4.65 (d, *J* = 15.4 Hz, 0.48H), 4.25 (d, *J* = 15.9 Hz, 0.52H), 4.10 (d, *J* = 15.4 Hz, 0.48H), 3.03-2.41 (m, br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*, 48:52) δ 176.0 and 174.3 (1C), 165.0 and 163.2 (1C), 152.4 and 151.1 (1C), 143.6 and 143.3 (2C), 142.2 and 141.8 (1C), 135.5 and 135.3 (1C), 130.1 and 129.9 (1C), 128.8-1258(17C), 124.2 and 123.9 (1C), 122.9 and 122.1 (1C), 109.6 and 109.5 (1C), 86.1 and 85.2 (1C), 68.1 and 67.3 (1C), 63.0 and 62.3 (1C), 43.9; HRMS (ESI) calcd for $C_{32}H_{26}N_2NaO_3^+$ $[MNa]^+$ 509.1836, found 509.1828; enantiomeric excess: *syn* 92%, *anti* 90%, determined by HPLC (Chiracel-AD, *n*-hexane:isopropanol = 1:1, flow rate 0.6 mL/min): t_R = 10.33 min (*anti*, minor), t_R = 11.75 min (*syn*, major); t_R = 14.27 min (*syn*, minor), t_R = 66.85 min (*anti*, major).

3-(Benzhydrylamino)-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (6a,b)

Prepared according to **GP-B** using 3-(benzhydrylimino)indolin-2-one (**1b**); FC: dichlorometane:MeOH, 99:1; yield: 37 mg, 78%; pale yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$+1% CD_3OD, mixture of diasteroisomers *syn:anti*, 37:63) δ

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7.73 (d, br, *J* = 5.8 Hz, 0.63H), 7.32-6.82 (m, 15H), 6.81-6.62 (m, 1.37H), 6.16 (dd, *J* = 5.9 and 1.9 Hz, 0.63H), 5.92 (dd, *J* = 5.8 and 1.9 Hz, 0.37H), 5.34 (t, br, *J* = 1.8 Hz, 0.37H), 5.16 (t, br, *J* = 1.8 Hz, 0.63H), 4.64 (s, 0.37H), 4.62 (s, 0.63H); ^{13}C NMR (75 MHz, $CDCl_3$+1% CD_3OD, mixture of diasteroisomers *syn:anti*, 37:63) δ 178.1, 172.6 and 172.3 (1C), 153.1 and 151.7 (1C), 143.6 and 143.4 (2C), 142.6 and 142.0 (1C), 129.9-121.6 (15C), 110.3, 86.0 and 85.2 (1C), 66.0 and 64.8 (1C), 62.9 and 62.2 (1C); HRMS (ESI) calcd for $C_{25}H_{20}N_2NaO_3^+$ $[MNa]^+$ 419.1366, found 419.1354; enantiomeric excess: *syn* 88%, *anti* 80%, determined by HPLC (Chiracel-AD, *n*-hexane:isopropanol = 4:1, flow rate 0.7 mL/min): t_R = 10.58 min (*syn*, minor), t_R = 11.38 min (*syn*, major), t_R = 13.61 min (*anti*, minor), t_R = 63.13 min (*anti*, major).

3-(Benzhydrylamino)-1-methyl-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (7a) and (7b)

Prepared according to **GP-B** using 3-(benzhydrylimino)-1-methylindolin-2-one (**1c**); FC: *n*-Hexane:EtOAc, 7:3.

(**7a**) yield: 22 mg, 45%; orange foam; $[\alpha]^{20}_D$ –24.6 (*c* 0.2, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, *anti* diasteroisomer) δ 7.88 (dd, *J* = 5.6 and 1.5 Hz, 1H), 7.43-7.13 (m, 10H), 6.97 (t, *J* = 7.6 Hz, 1H), 6.87- 6.80 (m, 2H), 6.70 (d, *J* = 7.6 Hz, 1H), 6.27 (dd, *J* = 5.6 and 1.5 Hz, 1H), 5.16 (t, *J* = 1.5 Hz, 1H), 4.68 (s, br, 1H), 2.81 (s, 3H), 2.71-2.45 (m, br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.7, 171.8, 152.6, 144.5, 143.3, 141.9, 130.2, 128.5-126.8 (11C), 124.0, 123.1, 122.1, 108.5, 85.1, 67.0, 62.2, 26.1; HRMS (ESI) calcd for $C_{26}H_{22}N_2NaO_3^+$ $[MNa]^+$ 433.1523, found 433.1529; enantiomeric excess: 91%, determined by HPLC (C-ODH, *n*-hexane:isopropanol = 4:1, flow rate 0.7 mL/min): t_R = 5.51 min (minor), t_R = 15.34 min (major).

(**7b**) yield: 19 mg, 36%; orange foam; $[\alpha]^{20}_D$ + 115.2 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, *syn* diasteroisomer) δ 7.42-7.07 (m, 11H), 7.03 (t, br, *J* = 7.8 Hz, 1H), 6.94-6.86 (m, 2H), 6.64 (d, br, *J* = 7.8 Hz, 1H), 5.93 (dd, *J* = 5.9, 2.0 Hz, 1H), 5.41 (s, 1H), 4.64 (s, 1H), 3.21-2.74 (m, br, 1H), 2.68 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 172.1, 151.2, 143.6, 143.5, 141.4, 130.0, 128.4-127.1 (10C), 125.7, 123.9, 123.7, 122.9, 108.6, 86.0, 67.9, 63.1, 25.9; HRMS (ESI) calcd for $C_{26}H_{22}N_2NaO_3^+$ $[MNa]^+$ 433.1523, found 433.1531; enantiomeric excess: 68%, determined by HPLC (C-AD, *n*-hexane:isopropanol = 4:1, flow rate 0.7 mL/min): t_R = 11.28 min (major), t_R = 13.51 min (minor).

3-(Benzhydrylamino)-1-(4-methoxybenzyl)-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (8ab)

Prepared according to **GP-B** using 3-(benzhydrylimino)-1-(4-methoxybenzyl)indolin-2-one (**1d**); FC: *n*-Hexane:EtOAc, 7:3; yield: 51 mg, 79%; ^{1}H NMR (300 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*, 45:55) δ 7.73 (d, *J* = 4.9 Hz, 0.55H), 7.32-6.74 (m, 17.45H), 6.63 (d, br, *J* = 7.8 Hz, 0.45H), 6.58 (d, br, *J* = 7.8 Hz, 0.55H), 6.20 (d, br, *J* = 5.8 Hz, 0.55H), 5.93 (d, br, *J* = 5.9 Hz, 0.45H), 5.45 (s, br, 0.45H), 5.31 (s, br, 0.55H), 4.80-4.64 (m, 1.55H), 4.56 (d, *J* = 14.7 Hz, 0.45H), 4.15 (d, *J* = 15.8 Hz, 0.55H), 3.99 (d, *J* = 14.7 Hz, 0.45H), 3.75 (s, 3H), 3.34-2.47 (m, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*, 45:55) δ 175.2 and 174.0 (1C), 172.0 and 171.6 (1C), 159.2, 152.2 and 151.1 (1C), 143.5 and 143.4 (1C), 142.9, 141.6, 130.2 and 129.9 (1C), 128.8-127.2 (14C), 125.7 and 124.2 (1C), 122.8 and 122.2 (1C), 122.4, 114.2, 111.3, 109.6 and 109.5 (1C), 86.0 and 84.8 (1C), 68.0 and 67.3 (1C), 63.0 and 62.6 (1C), 55.3, 43.4 and 43.3 (1C); HRMS (ESI) calcd for $C_{33}H_{28}N_2NaO_4^+$ $[MNa]^+$ 539.1941, found 539.1950; enantiomeric excess: *syn* 89%, *anti* 84%, determined by HPLC (Chiracel-AD, *n*-hexane:isopropanol = 9:1, flow rate 1.0 mL/min): t_R = 30.00 min (*anti* minor), t_R = 40.25 min (*syn* major), t_R = 42.46 min (*syn* minor), t_R = 112.89 min (*anti* major).

3-(Benzhydrylamino)-3-(5-oxo-2,5-dihydrofuran-2-yl)-1-tritylindolin-2-one (9ab)

Prepared according to **GP-B** using 3-(benzhydrylimino)-1-tritylindolin-2-one (**1e**); FC: n-Hexane:EtOAc, 4:1; yield: 64mg, 81%; pale orange solid; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*, 53:47) δ 7.81 (dd, *J* = 5.9 and 1.5 Hz, 0.47H), 7.67-6.99 (m, 23H), 6.95 (d, br, *J* = 7.7 Hz, 0.47H), 6.88 (t, br, *J* = 7.7 Hz, 0.47H), 6.81-6.86 (m, 3.06H), 6.55 (dd, *J* = 5.9 and 1.5 Hz, 0.53H), 6.41-6.27 (m, 2H), 6.22 (dd, *J* = 5.8 and 1.9 Hz, 0.47H), 5.83 (dd, *J* = 5.9 and 2.2 Hz, 0.53H), 5.35 (t, br, *J* = 1.7 Hz, 0.53H), 5.24 (t, br, *J* = 1.7 Hz, 0.47H), 4.60 (s, br, 0.53H), 4.17 (s, br, 0.47H), 3.47-2.32 (m, br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*, 53:47) δ 178.6 and 175.6 (1C), 172.0 and 171.4 (1C), 153.0 and 151.7 (1C), 144.1 and 144.0 (1C), 143.5 and 143.4 (1C), 143.3 and 143.2 (1C), 142.2 and 141.9 (3C), 129.2, 129.3-126.9 (26C), 126.5 and 125.4 (1C), 125.2, 123.9 and 123.2 (1C), 122.4 and 121.0 (1C), 116.0 and 115.8 (1C), 86.5 and 85.2 (1C), 75.4 and 75.2 (1C), 68.8 and 68.4 (1C), 62.9 and 62.6 (1C); HRMS (ESI) calcd for $C_{44}H_{34}N_2NaO_3^+$ $[MNa]^+$ 661.2462, found 661.2455; enantiomeric excess: *syn* 96%, *anti* 4%, determined by HPLC (Chiracel-AD, *n*-hexane:isopropanol = 17:1, flow rate 0.7 mL/min): t_R = 15.85 min (*anti* minor), t_R = 24.13 min (*syn* minor), t_R = 27.90 min (*anti* major), t_R = 33.83 min (*syn* major).

3-(Benzhydrylamino)-1-benzyl-5-fluoro-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (10ab)

Prepared according to **GP-B** using 3-(benzhydrylimino)-1-benzyl-5-fluoroindolin-2-one (**1f**); FC: *n*-Hexane:EtOAc, 7:3; 29 mg, yield: 45%; pale orange solid; ^{1}H NMR (300 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*, 28:72) δ 7.81 (d, br, *J* = 4.9 Hz, 0.72H), 7.52-6.76 (m, 16.56H), 6.69 (d, br, *J* = 7.8 Hz, 0.72H), 6.57-6.42 (m, 1H), 6.25 (d, br, *J* = 5.8 Hz, 0.72H), 5.99 (d, br, *J* = 5.8 Hz, 0.28H), 5.42 (s, br, 0.28H), 5.21 (s, br, 0.72H), 4.81 (d, *J* = 15.7 Hz, 0.72H), 4.72-4.60 (m, 1.28H), 4.30 (d, *J* = 15.7 Hz, 0.72H), 4.11 (d, *J* = 15.7 Hz, 0.28H), 3.01-2.66 (m, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*, 28:72) δ 175.8 and 174.1 (1C), 158.9 (d, *J* = 239.9Hz) and 158.1 (d, *J* = 244.0Hz) (1C), 152.1 and 150.8 (1C), 143.3 and 142.9 (1C), 142.1 and 141.8 (1C), 139.3 and 138.7 (1C), 135.1 and 134.9 (1C), 128.9- 127.1 (16C), 125.3 and 124.6 (1C), 124.4 and 124.0 (1C), 116.6-116.1 (m, 1C), 114.9 (d, *J* = 26.2Hz) and 113.8 (d, *J* = 22.8Hz) (1C), 110.0 (d, *J* = 8.7Hz) (1C), 85.8 and 84.8 (1C), 68.3 and 67.7 (1C), 63.1 and 62.5 (1C), 44.0; HRMS (ESI) calcd for $C_{32}H_{25}FN_2NaO_3^+$ $[MNa]^+$ 527.1741, found 527.1752; enantiomeric excess: *syn* 15%, *anti* 1%, determined by HPLC (C-ODH, *n*-hexane:isopropanol = 4:1, flow rate 0.7 mL/min): t_R = 25.91 min (*syn* major), t_R = 32.60 min (*syn* minor), t_R = 35.53 min (*anti* major), t_R = 57.56 min (*anti* minor).

3-(Benzhydrylamino)-1-benzyl-5-chloro-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (11ab)
Prepared according to **GP-B** using 3-(benzhydrylimino)-1-benzyl-5-chloroindolin-2-one (**1g**); FC: *n*-Hexane:EtOAc, 7:3; yield: 27 mg, 42%; pale orange solid; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*, 3:7) δ 7.83 (dd, *J* = 5.8, 1.2 Hz, 0.7H), 7.46-6.98 (m, 16.6H), 6.92 (d, , *J* = 2.0 Hz, 0.7H) 6.54 (d, *J* = 8.4 Hz, 0.3H), 6.50 (d, *J* = 8.4 Hz, 0.7H), 6.29 (dd, *J* = 5.8, 1.7 Hz, 0.7H), 6.06 (dd, *J* = 5.8, 1.9 Hz, 0.3H), 5.44 (t, *J* = 1.5 Hz, 0.3H), 5.24 (t, *J* = 1.5 Hz, 0.7H), 4.84 (d, *J* = 15.8 Hz, 0.7H), 4.76-4.62 (m, 1.3H), 4.34 (d, *J* = 15.8 Hz, 0.7H), 4.14 (d, *J* = 15.8 Hz, 0.3H), 3.11-2.68 (m, br, 1H); ^{13}C NMR (101 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*, 3:7) δ 176.4 and 174.7 (1C), 172.2 and 172.0 (1C), 152.7 and 151.5 (1C), 143.8-142.1 (3C), 135.7 and 135.6 (1C), 130.7 and 130.5 (1C), 129.6 to 126.8 (17C), 126.6 and 125.2 (1C), 125.1 and 124.8 (1C), 111.1, 86.5 and 85.4 (1C), 68.9 and 68.3 (1C), 63.8 and 63.3 (1C), 44.8 and 44.7 (1C); HRMS (ESI) calcd for $C_{32}H_{25}ClN_2NaO_3^+$ $[MNa]^+$ 543.1446, found 543.1454; enantiomeric excess: *syn* 74%, *anti* 26%, determined by HPLC (C-AD, *n*-hexane:isopropanol = 9:1 to 3:7, flow rate 1.0 mL/min): t_R = 18.02 min (*syn* major), t_R = 19.84 min (*anti* major), t_R = 37.38 min (*syn* minor), t_R = 57.02 min (*anti* minor).

3-(Benzhydrylamino)-1-benzyl-6-bromo-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (12ab)
Prepared according to **GP-B** using 3-(benzhydrylimino)-1-benzyl-6-bromoindolin-2-one (**1h**); FC: *n*-Hexane:EtOAc, 7:3; yield: 44 mg, 65%; orange solid; ^{1}H NMR (400 MHz, $CDCl_3$, mixture of diasteroisomers 3:7) δ 7.83 (d, br, *J* = 5.6 Hz, 0.7H), 7.46-7.02 (m, 14.6H), 7.01-6.94 (m, 2H), 6.86 (d, br, *J* = 7.9 Hz, 0.7H), 6.79 (s, br 0.3H), 6.74 (s, br, 0.7H), 6.26 (dd, *J* = 5.6, 1.5 Hz, 0.7H), 6.00 (dd, *J* = 5.8, 1.9 Hz, 0.3H), 5.44 (s, br, 0.3H), 5.22 (s, br, 0.7H), 4.79 (d, *J* = 15.8 Hz, 0.7H), 4.72- 4.58 (m, 1.3H), 4.25 (d, *J* = 15.8 Hz, 0.7H), 4.08 (d, *J* = 15.8 Hz, 0.3H), 3.10-2.69 (m, br, 1H). ^{13}C NMR (101 MHz, $CDCl_3$, mixture of diasteroisomers *syn:anti*, 3:7) δ 176.6 and 174.9 (1C), 172.3 and 172.0 (1C), 152.8 and 151.4 (1C), 145.5-142.2 (4C), 135.6 and 135.4 (1C), 129.7 to 127.6 (15C), 126.5 and 125.7 (1C), 125.0 and 124.9 (1C), 124.6 and 124.4 (1C), 123.6 and 123.5 (1C), 113.5, 86.4 and 85.4 (1C), 68.5 and 67.9 (1C), 63.8 and 63.1 (1C), 44.7; HRMS (ESI) calcd for $C_{32}H_{25}BrN_2NaO_3^+$ $[MNa]^+$ 587.0941 found 587.0944. enantiomeric excess: *syn* 42%, *anti* 31%, determined by HPLC (C-AD, *n*-hexane:isopropanol = 9:1, flow rate 1.0 mL/min): t_R = 16.04 min (*anti* minor), t_R = 17.91 min (*syn* major), t_R = 24.31 min (*syn* minor), t_R = 63.35 min (*anti* major).

3-(Benzhydrylamino)-6-bromo-1-methyl-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (13a) and (13b)
Prepared according to **GP-B** using 3-(benzhydrylimino)-6-bromo-1-methylindolin-2-one (**1i**); FC: *n*-Hexane:EtOAc, 7:3.
(**13a**) yield: 25 mg, 42%; orange foam; $[\alpha]^{20}_D$ – 18.4 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, *anti* diasteroisomer) δ 7.84 (dd, *J* = 5.8, 1.9 Hz, 1H), 7.24-7.10 (m, 8H), 7.06 (d, br, *J* = 7.8 Hz, 1H), 6.98 (d, *J* = 7.8 Hz, 1H), 6.88-6.80 (m, 3H), 6.25 (dd, *J* = 5.8, 1.9 Hz, 1H), 5.12 (s, br, 1H), 4.61 (s, 1H), 2.78 (s, 3H), 2.72-2.06 (m, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 171.6, 152.3, 145.7, 142.8, 141.6, 128.3-127.1 (11C), 125.0, 124.3, 124.1, 121.9, 112.1, 84.6, 66.9, 62.3, 26.2; HRMS (ESI) calcd for $C_{26}H_{21}BrN_2NaO_3^+$ $[MNa]^+$ 511.0628, found 511.0637; enantiomeric excess: *anti* 32%, determined by HPLC (C-ODH, *n*-hexane:isopropanol = 4:1, flow rate 0.7 mL/min): t_R = 23.33 min (major), t_R = 75.68 min (minor).
(**13b**) yield: 15 mg, 26%; orange foam; $[\alpha]^{20}_D$ – 2.82 (*c* 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$, *syn* diasteroisomer) δ 7.44-7.03 (m, 11H), 7.01-6.90 (m, 2H), 6.80 (d, *J* = 1.4 Hz, 1H), 5.97 (dd, *J* = 5.8, 2.0 Hz, 1H), 5.39 (s, br, 1H), 4.62 (s, 1H), 2.68 (s, 3H), 2.16-1.77 (m, br, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 171.7, 150.9, 144.9, 142.8, 140.9, 128.3-126.9 (11C), 125.8, 124.2, 123.9, 122.5, 112.2, 85.5, 67.8, 63.4, 26.1; HRMS (ESI) calcd for $C_{26}H_{21}BrN_2NaO_3^+$ $[MNa]^+$ 511.0628, found 511.0633; enantiomeric excess: *syn* 31%, determined by HPLC (C-ODH, *n*-hexane:isopropanol = 4:1, flow rate 0.7 mL/min): t_R = 14.81 min (major), t_R = 23.13 min (minor).

Post-transformation reactions

3-Amino-1-methyl-3-(5-oxotetrahydrofuran-2-yl)indolin-2-one (15)
To a solution of Mannich adduct **14** (100 mg, 0.29 mmol) in EtOAc (3 mL), 10% Pd/C (10% w/w) was added. The reaction mixture was degassed *in vacuo*, placed under an atmosphere of H_2 (g), stirred at rt and the conversion was monitored by TLC. The mixture was filtered through a pad of Celite eluting with EtOAc (10 mL) and the solvent was concentrated *in vacuo*. The crude residue was dissolved in dry MeOH (1 mL) followed by the dropwise addition of HCl solution (0.5 mL, 4M HCl in dioxane) and the resulting mixture was stirred at room temperature for 4h. After quenching with saturated aq $NaHCO_3$ (2 mL), and dilution with CH_2Cl_2 (2 mL), the aqueous phase was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layer was washed with saturated aq $NaHCO_3$, dried over anhydrous Na_2SO_4 and the solvent was removed under reduce pressure. The crude was subjected to FC (dichlorometane:MeOH, 95:5) giving the desired product **15**, as a white foam (65 mg, 91% overall yield).
$[\alpha]^{20}_D$ – 83.3 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.46 (d, br, *J* = 7.8 Hz, 1H), 7.36 (t, br, *J* = 7.6 Hz, 1H), 7.09 (t, br, *J* = 7.7 Hz, 1H), 6.86 (d, br, *J* = 7.8 Hz, 1H), 4.62 (dd, br, *J* = 7.8 and 5.9 Hz, 1H), 3.21 (s, 3H), 2.58-2.33 (m, 4H), 1.88 (m, br, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.7, 176.6, 143.7, 130.1, 128.2, 124.8, 123.2, 108.7, 82.4, 62.1, 28.0, 26.5, 21.7; HRMS (ESI) calcd for $C_{13}H_{14}N_2NaO_3^+$ $[MNa]^+$ 269.0897, found 269.0908.

3-Amino-1-methyl-3-(5-oxotetrahydrofuran-2-yl)indolin-2-one (15')
Palladium hydroxide (20 wt.% on carbon, 12 mg) was added to a solution of vinylogous Mannich-adduct **7a** (82 mg, 0.20 mmol) in MeOH (1 mL). The reaction mixture was degassed *in vacuo*, placed under an atmosphere of H_2 (g), stirred at rt and the conversion was monitored by TLC. The mixture was filtered through a pad of Celite eluting with MeOH (10 mL), and the solvent was concentrated *in vacuo*. The crude was subjected to FC (dichlorometane:MeOH, 95:5) to give **15'** as a white foam (47 mg, 96%).

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$[\alpha]^{20}_D$ – 90.6 (*c* 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) were identical to those of compound **15**. HRMS (ESI) calcd for $C_{13}H_{14}N_2NaO_3^+$ $[MNa]^+$ 269.0897, found 269.0879.

3-(Benzhydrylamino)-1-methyl-3-(5-((triisopropylsilyl)oxy)furan-2-yl)indolin-2-one (16)

To a solution of 3-(benzhydrylamino)-1-methyl-3-(5-oxo-2,5-dihydrofuran-2-yl)indolin-2-one (**7a** or **7b**) (60 mg, 0.15 mmol) in anhydrous dichloromethane (1.5 mL) cooled to 0 °C, anhydrous trimethylamine (0.15 mmol, 1eq) and TIPSOTf (0.17 mmol, 1.1 eq) were added. The solution was stirred at the same temperature for 1 hour (monitored by TLC). The reaction was quenched by adding water (1.5 mL). The organic phase was separated, dried over anhydrous Na_2SO_4 and the solvent was evaporated *in vacuo* to give **16** as a viscous oil.

Compound **(*R*)-16** from **7a**:

Yield: 72 mg, 98%; $[\alpha]^{20}_D$ – 33.2 (*c* 1.0, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.10 (m, 12H), 6.90 (t, *J* = 7.4 Hz, 1H), 6.69 (d, *J* = 7.7 Hz, 1H), 6.13 (d, br, *J* = 2.9 Hz, 1H), 5.04 (d, br, *J* = 2.9 Hz, 1H), 4.79 (s, 1H), 3.07-2.95 (m, br, 1H), 2.72 (s, 3H), 1.22 (hept, *J* = 7.8 Hz, 3H), 1.04 (d, *J* = 7.8 Hz,18H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.7, 157.1, 144.2, 143.4, 142.5, 141.1, 128.1-126.9 (12C), 123.1, 122.2, 109.7, 109.0, 84.3, 71.7, 62.6, 25.2, 17.5 (6C), 12.2 (3C); HRMS (ESI) calcd for $C_{35}H_{42}N_2NaO_3Si^+$ $[MNa]^+$ 589.2857, found 589.2866.

Compound **(*S*)-16** from **7b**:

Yield: 69 mg, 95%; $[\alpha]^{20}_D$ + 31.8 (*c* 0.9, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) and ^{13}C NMR (75 MHz, $CDCl_3$) were identical to those of compound **(*R*)-16**; HRMS (ESI) calcd for $C_{35}H_{42}N_2NaO_3Si^+$ $[MNa]^+$ 589.2857, found 589.2869.

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