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Organocatalytic Asymmetric Synthesis of Bridged Acetals with Spirooxindole Skeleton

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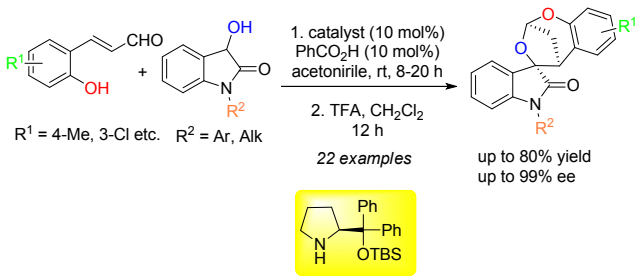


ABSTRACT: The first highly diastereo- and enantioselective synthesis of bridged *O*,*O*-acetals embedded with spirooxindoles has been developed. Dioxindoles and 2-hydroxy cinnamldehydes were employed as the reaction partners in this method. The desired products were obtained via diaryl prolinol TBS ether catalyzed Michael reaction followed by acetal formation with TFA.

Chiral *O*,*O*-acetals are important structural motifs present in a range of natural products and pharmaceuticals and display a wide range of bioactivities.[1] Thus considerable efforts have been devoted in the recent times for the asymmetric synthesis of these compounds.[2] Infact a number of convenient approaches has been developed for the synthesis of mono cyclic acetals,[3] fused acetals[4] and spiroketals.[5] For example, List and Čorić have elegantly developed asymmetric synthesis of

spiroacetals using imidophosphoric acid as catalyst.[5a] In contrary, the asymmetric synthesis of bridged *O*,*O*-acetals has been less developed though such skeleton is present in procyanidin A1,[6] epicoccolide A,[7] cholinesterase inhibitor[8] and other bioactive compounds (Figure 1).[9] Only Jørgensen[4a] and Franzén[10] recently reported organocatalytic synthesis of bridged acetals and Shi and co-workers[11] alternatively developed Pd-catalyzed synthesis of bridged [3,3,1]-ketals (Scheme 1). However, the structural variety and complexity of bridged acetals necessitate the development of efficient synthesis of them having diverse scaffolds.

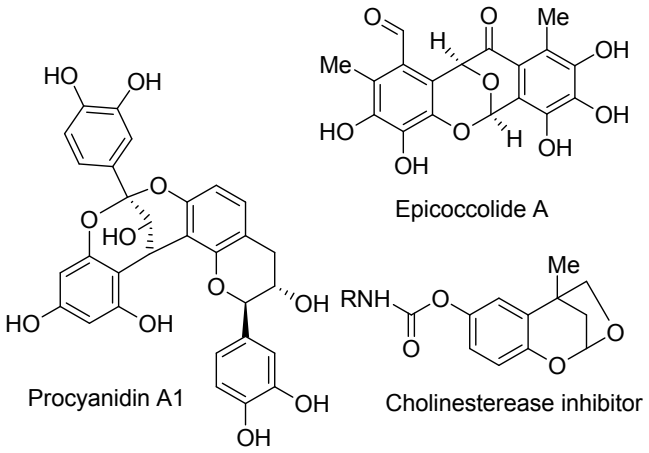
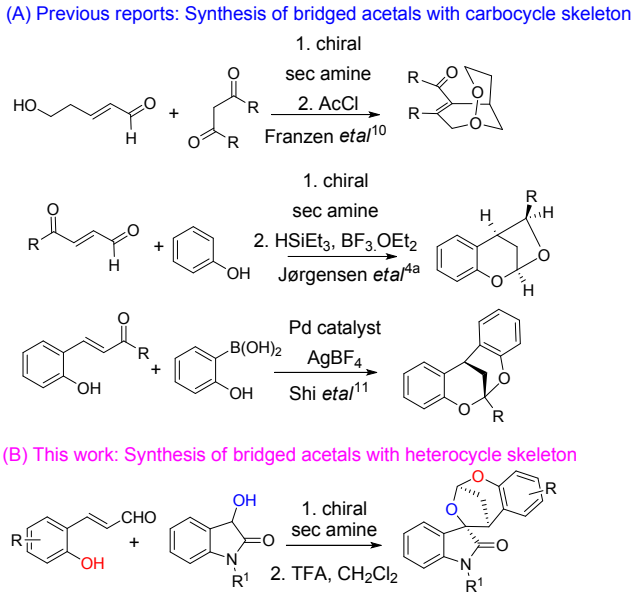


Figure 1. Representative bioactive bridged *O*,*O*-acetals

Spirocyclic oxindole frameworks have been frequently found in natural and unnatural compounds and demonstrate varied and extensive biological activities.[12] For this reason, extensive attention has been given to access to the enantiopure spirocyclic oxindole containing skeletons during the past decade. However, from the literature survey, it is evident that the most of the methods involve the construction of spirooxindoles having monocyclic or fused scaffolds.[13] Thus, the developement of a facile method for the creation of multi rings embedded complex chiral spiro oxindoles is a challenging task and only Chen, Wang and Feng demonstrated few examples.[14]

During the initiation of the project, Bu and co-workers reported triflic acid catalyzed synthesis of bridged ketals with spirooxindole motif[15] but a catalytic asymmetric synthesis of spirooxindoles having briged acetal structure is still not known despite high medical importance of bridged acetals and spirooxindoles individually.

Scheme 1. Catalytic asymmetric synthesis of bridged acetals.

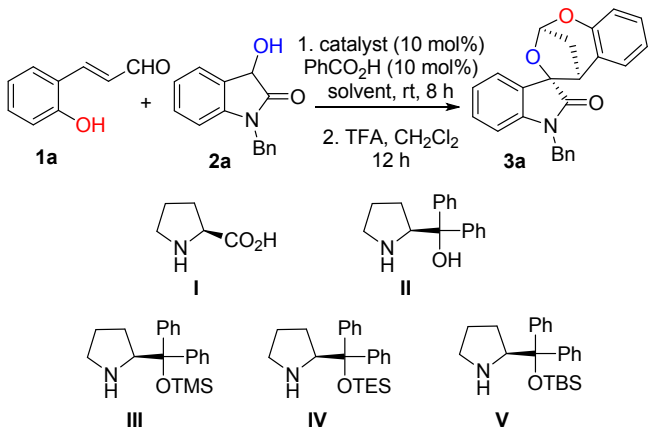


Dioxiindoles have earlier been employed as bidentate reagents in asymmetric oragnocatalysis by Melchiorre and co-workers for different conjugate addition reactions.[16] We envisaged that if *o*-hydroxy cinnamaldehydes are employed as a reaction partner, then the insitu formed hemi acetal from first Michael reaction could be converted to bridged acetal motif with acid. We thus became interested in developing a simple method for the asymmetric synthesis of bridged acetals having spirooxindole moiety.

We initiated our exploration by performing a reaction between *ortho*-hydroxy-cinnamaldehyde (**1a)** and *N*-benzyl dioxindole (**2a**) with proline in toluene (Table 1). However, no product formation was detected (entry 1). Interestingly, stirring with diphenyl prolinol in combination with

benzoic acid for 8 hours resulted in the formation of a hemicaetal which was converted to the desired acetal **3a** by further reaction with trifluoroacetic acid. Interestingly, only a single diatereomer was detected by ^{1}H NMR and the enantiomeric excess was 60%. Encouraged by this result, different secondary amine catalysts were screened. Gratifyingly, the enantisoelectivity got increased to 93% ee with Jørgesen-Hayshi catalyst **III**.[17] Then catalysts **IV** and **V** having OTES and OTBS groups respectively were employed in the reaction (entries 2-4). Interestingly, though catalyst **IV** could not enhance the enantioselectivity, higher enantiomeric excess (96% ee) was achieved with catalyst **V**. Then we turned our attention on solvent optimization. Halogenated solvent such as dichloromethane was not good for this reaction as poor conversion was seen. Gratifiyngly, slight enhancement in enantioselectivity was observed in α,α,α-trifluorotoluene and finally the best solvent emerged as acetonitrile in which 98% ee was achieved. Other acid additives were also screened but benzoic acid was found to be the best (see supporting information for details).

Table 1. Catalyst Screening and Optimization of Reaction Condition



entry[a]	catalyst	solvent	yield[b]	d.r[c]	ee[d]

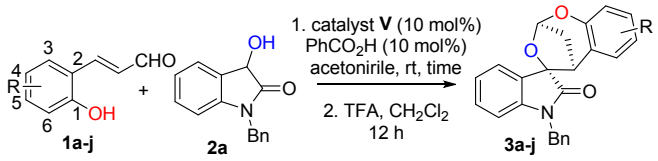
1	**I**	$PhCH_3$	0	>20:1	-
2	**II**	$PhCH_3$	55	>20:1	60
3	**III**	$PhCH_3$	70	>20:1	93
4	**IV**	$PhCH_3$	68	>20:1	93
5	**V**	$PhCH_3$	78	>20:1	96
6	**V**	CH_2Cl_2	20	>20:1	89
7	**V**	$PhCF_3$	65	>20:1	97
8	**V**	**CH_3CN**	**79**	**>20:1**	**98**

[a] All reactions were carried out with 0.12 mmol of **1a** with 0.1 mmol of **2a** in 0.5 ml solvent at room temperature. [b] Isolated yield after silica gel column chromatography. [c] Determined by ^1H NMR. [d] Determined by HPLC using stationary phase chiral column.

The scope of the reaction was then investigated by testing a variety of *o*-hydroxyaromatic *α,β*-unsaturated aldehydes **1** in this method and the results are shown in Table 2. To our delight, high enantioselectivities were obtained in all of the cases and excellent diastereoselectivities were maintained. At first, different 4-substituted *α,β*-unsaturated aldehydes **1b-1e** were screened and the corrseponding products were obtained in acceptable yields and with good stereoselectivities (entries 2-5). The electronic effects of the substituents did not influence much on the outcome of the reaction. Then 3-chloro and 5-methoxy substituted enals **1f** and **1g** were employed in the

reaction and high enantioselectivities were achieved for the corresponding products (entries 6-7). In particular, 99% ee was observed for product **3f** having 3-chloro substitution. Our methodology

Table 2. Scope of *o*-Hydroxyaromatic-*α,β*-unsaturated aldehydes



Entry[a]	R	Time (h)	Product	Yield (%)[b]	dr[c]	ee[d]
1	H	8	**3a**	79	>20:1	98
2	4-Me	10	**3b**	64	>20:1	97
3	4-OMe	12	**3c**	51	>20:1	98
4	4-Cl	12	**3d**	66	>20:1	97
5	4-Br	8	**3e**	57	>20:1	98
6	3-Cl	12	**3f**	61	>20:1	99
7	5-OMe	20	**3g**	62	>20:1	97
8	4,6-diCl	20	**3h**	34	>20:1	94
9	4,6-diBr	20	**3i**	23	>20:1	95
10	4-Cl, 6-Br	20	**3j**	32	>20:1	96
11	4-NHBoc	12	**3k**	47	>20:1	98

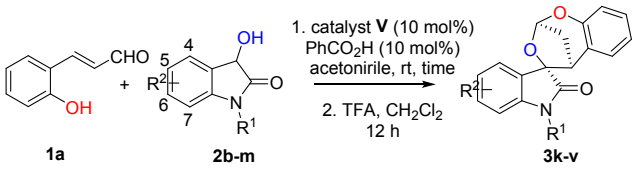
[a]All reactions were carried out with 0.12 mmol of **1** with 0.1 mmol of **2a** in 0.5 mL acetonitrile. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC using stationary phase chiral column.

is also suitable for 4,6-disubstituted enals and high diastereo- and enantioselectivities were observed albeit moderate yields were detected (entries 8-10). To our delight, substrate **1k** having 4-NHBoc group could also be employed in our methodology delivering product **3k** in excellent 98% ee (entry 11).

Next, the generatlity of the reaction was further extended by engaging a variety of dioxindoles (Table 3). Initially, different *N*-substitutions were checked and gratifyingly here also excellent results were achieved preserving high diastereomeric ratio. For example, 80% yield and 98% ee obtained for product **3l** having *N*-methyl substitution and 99% ee was observed for product **3m** having *N*-^{i}Bu substitution (entries 1-2). Dioxindole **2d** having *N*-allyl group and **2e** having *N*-prenyl group also participated in the reaction delivering products **3n** and **3o** respectively in excellent enantioselectivities (entries 3-4). Then dioxindole **2f** having *N*-4-CF_3benzyl group was employed in the reaction and smooth conversion was observed for **3p** with 98% ee (entry 5). Moreover our methodolgy was also suitable for *N*-unsbstituted oxindole **2g** delivering the product **3q** in 99% ee (entry 6). Then the aromatic part of the oxindole motif was varied and here also the results were unaffected. Initially, 5-halo substituted *N*-benzyl dioxindoles **2h**-**2j** were prepared and engaged in the reaction (entries 7-9). The desired products **3r**-**3t** were isolated in acceptable yields with excellent enantioselectivities. The reactions with dioxindolex **2k** and **2l** having 6-bromo and

7-chloro substitutions respectively was also satisfactory (entries 10-11). Finally 4-bromo substituted oxiindole **2m** participated in the reaction but the acetal formation was slow and only after heating at 40 °C, moderate yield was detected (entry 12). Nevertheless these products having halo substitutions are important as they can be elaborated easily by cross-coupling reactions.

Table 3. Scope of dioxindoles



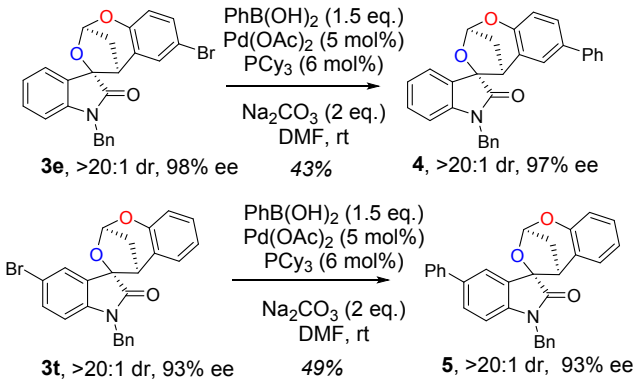
Entry[a]	R^1	R^2	Time (h)	Product	Yield(%)[b]	dr[c]	ee[d]
1	Me	H	10	**3l**	80	>20:1	98
2	^{i}Bu	H	12	**3m**	71	>20:1	99
3	allyl	H	8	**3n**	68	>20:1	98
4	prenyl	H	20	**3o**	65	>20:1	99
5	4-CF_3Bn	H	9	**3p**	51	>20:1	98
6	H	H	20	**3q**	64	>20:1	99
7	Bn	5-F	20	**3r**	59	>20:1	97
8	Bn	5-Cl	20	**3s**	46	>20:1	99
9	Bn	5-Br	20	**3t**	37	>20:1	93
10	Bn	6-Br	12	**3u**	49	>20:1	98

11	Bn	7-Cl	20	**3v**	55	>20:1	93
12	Bn	4-Br	10	**3w**	22	>20:1	85

[a]All reactions were carried out with 0.12 mmol of **1** with 0.1 mmol of **2a** in 0.5 mL acetonitrile. [b]Isolated yield after silica gel column chromatography. [c]Determined by ^{1}H NMR. [d]Determined by chiral HPLC using stationary phase chiral column.

The synthetic utility of our method was demonstrated by performing Suzuki coupling reactions on **3e** and **3t** (Scheme 2). Thus, when phenyl boronic acid was treated with **3e** and **3t** in the presence of palladium acetate and tricyclohexyl phosphine under basic conditions, the corresponding products **4** and **5** were formed in moderate yields. Delightfully, the enantiopurity was preserved for both products.

Scheme 2. Synthetic Transformations of 3e and **3s**.

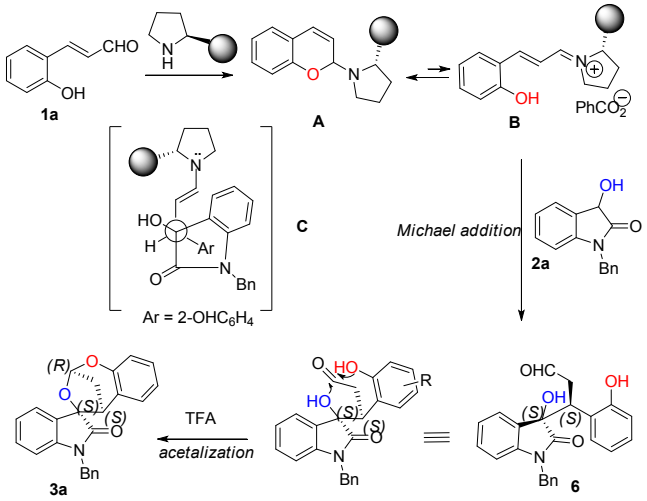


The absolute structure of product **3s** was solved by X-ray crystallography[18] and was found to be (*2R*,*3'S*,*5S*). The configuration of other products are expected to be same by analogy.

Based on the configuration, a plausible mechanism has been shown in Scheme 3. It is believed that catalyst **V** reacts with **1a** in the presence of benzoic acid to provide aminal **A**[19] whose presence was detected by NMR by stoichiometric mixing of **V** and **1a**. Interestingly intermediate **A** is

nucleophilic in nature and it must be in equilibrium with iminium ion **B** which is electrophilic and thus the active intermediate for our reaction. Since the *Si* face of the chiral iminium ion is blocked by bulky OTBS group, the conjugate addition of dioxindole **2a** takes place from the *Re* face to generate intermediate **6** after hydrolysis. A Newman projection **C** was also drawn to understand the diastereoselectivity of the reaction. The enamine group and the CONAr group orients in *anti*-fashion possibly due to steric interaction. Intermediate **6** then undergoes acetalization reaction diastereoselectively in the presence of TFA to deliver product **3a** (Scheme 3).

Scheme 3. The Proposed Mechanism



In summary, this paper reports the first catalytic asymmetric synthesis of bridged *O,O*-acetal with spirooxindole skeleton. The methodology involves amine catalyzed conjugated addition followed by diastereoselective acetalization with TFA. The desired spirooxindole products were obtained in good to high yields with high diastereo- and enantioselectivities in operationally simple reaction conditions. Also few products have been further functionalized via Suzuki coupling reaction. Given the high pharmaceutical significance of spirooxindoles and bridged acetals our products might be bioactive and such studies are currently in progress.

Experimental Section

General Information:

Chemicals and solvents were purchased from commercial suppliers and used as received. ^{1}H NMR spectra were recorded on 400 MHz, 500 MHz and 600 MHz spectrometer. ^{13}C NMR spectra were recorded on 100 MHz , 126 MHz and 150 MHz. Chemical shifts were reported in parts per million (ppm), and the residual solvent peak was used as an internal reference: proton (chloroform δ 7.260), carbon (chloroform δ 77.23). Multiplicity was indicated as follows**:** s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), dd (doublet of doublet), brs (broad singlet). Coupling constants were reported in Hertz (Hz). Using +ESI-TOF mode HRMS spectra were recorded. Enantiomeric ratios were determined by HPLC analysis performed on Chiral Columns using a Daicel Chiralpak IA Column. For visualizing the products UV light and I_2 were used. Melting points were measured using BüCHI melting point B-540 apparatus. All melting points were measured in open glass capillary and values are uncorrected. DCM was distilled over CaH_2 under argon and stored over 4A° molecular sieves. Silica gel (60-120 mesh size) was used for the column chromatography. Reactions were monitored by TLC on silica gel 60 F254 (0.25 mm).

General procedure for the synthesis of *ortho*-hydroxy-cinnamaldehydes:

Ortho-hydroxy-cinnamaldehydes were prepared according to reported procedure.[20]

In an oven dried round bottom flask, (triphenylphosphoranylidene) acetaldehyde (2 mmol, 1.0 eq.) was added to the stirred solution of salicylaldehyde (2 mmol) in dry THF (2 mL) and the resulting solution was heated at reflux overnight. Completion of reaction was checked by TLC (6–12 h). After the completion of reaction, solvent was evaporated and reaction mixture was purified by

flash column chromatography on silica gel eluting with hexane/ethyl acetate to afford desired products **1b-j**.

Characterisation of *ortho*-hydroxy-cinnamaldehydes:

((*E*)-3-(2-hydroxy-5-methylphenyl)acrylaldehyde) (1b)

The title compound was prepared as a dark yellow solid in 51% yield (165.4 mg) according to the general procedure, as described above. **^{1}H NMR (400 MHz, MeOD)** δ 9.59 (d, *J* = 8.0 Hz, 1H), 7.88 (d, *J* = 15.9 Hz, 1H), 7.35 (s, 1H), 7.10 (d, *J* = 8.3 Hz, 1H), 6.85 (dd, *J* = 16.0, 8.0 Hz, 1H), 6.78 (d, *J* = 8.3 Hz, 1H), 2.26 (s, 3H).

((*E*)-3-(2-hydroxy-5-methoxyphenyl)acrylaldehyde) (1c)

The title compound was prepared as a dark yellow solid in 52% yield (185.3 mg) according to the general procedure, as described above. **^{1}H NMR (400 MHz, MeOD)** δ 9.62 (d, *J* = 7.9 Hz, 1H), 7.92 (d, *J* = 16.0 Hz, 1H), 7.10 (d, *J* = 3.0 Hz, 1H), 6.87 (ddd, *J* = 13.9, 13.2, 7.1 Hz, 3H), 3.78 (s, 3H).

((*E*)-3-(5-chloro-2-hydroxyphenyl)acrylaldehyde) (1d)

The title compound was prepared as a yellow solid in 48% yield (175.3 mg) according to the general procedure, as described above. **^{1}H NMR (400 MHz, MeOD)** δ 9.61 (d, *J* = 7.8 Hz, 1H), 7.82 (d, *J* = 16.0 Hz, 1H), 7.56 (d, *J* = 2.2 Hz, 1H), 7.25 (d, *J* = 8.7 Hz, 1H), 6.92 – 6.80 (m, 2H).

((*E*)-3-(5-bromo-2-hydroxyphenyl)acrylaldehyde) (1e)

The title compound was prepared as a yellow solid in 77% yield (349.6 mg) according to the general procedure, as described above. **^{1}H NMR (400 MHz, MeOD)** δ 9.60 (d, *J* = 7.9 Hz, 1H), 7.80 (d, *J* = 16.0 Hz, 1H), 7.68 (d, *J* = 2.4 Hz, 1H), 7.37 (d, *J* = 8.7 Hz, 1H), 6.90 – 6.79 (m, 2H).

((*E*)-3-(2-chloro-6-hydroxyphenyl)acrylaldehyde) (1f)

The title compound was prepared as a pale yellow solid in 79% yield (288.5 mg) according to the general procedure, as described above. **^{1}H NMR (400 MHz, MeOD)** δ 9.63 (d, *J* = 8.0 Hz, 1H), 7.96 (d, *J* = 16.0 Hz, 1H), 7.30 – 7.17 (m, 2H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.85 (d, *J* = 8.3 Hz, 1H).

((*E*)-3-(2-hydroxy-4-methoxyphenyl)acrylaldehyde) (1g)

The title compound was prepared as a yellow solid in 54% yield (192.4 mg) according to the general procedure, as described above. **^{1}H NMR (600 MHz, MeOD)** δ 9.51 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 15.8 Hz, 1H), 7.49 (d, J = 8.7 Hz, 1H), 6.76 (dd, J = 15.8, 8.1 Hz, 1H), 6.50 (d, J = 8.7 Hz, 1H), 6.43 (d, J = 2.3 Hz, 1H), 3.80 (s, 3H).

((*E*)-3-(3,5-dichloro-2-hydroxyphenyl)acrylaldehyde) (1h)

The title compound was prepared as a pale yellow solid in 80% yield (347.2 mg) according to the general procedure, as described above. **^{1}H NMR (400 MHz, MeOD)** δ 9.66 (d, J = 7.7 Hz, 1H), 7.86 (d, J = 16.1 Hz, 1H), 7.58 (d, J = 2.5 Hz, 1H), 7.46 (d, J = 2.5 Hz, 1H), 6.87 (dd, J = 16.1, 7.7 Hz, 1H).

((*E*)-3-(3,5-dibromo-2-hydroxyphenyl)acrylaldehyde) (1i)

The title compound was prepared as a yellow solid in 78% yield (477.2 mg) according to the general procedure, as described above. **^{1}H NMR (400 MHz, MeOD)** δ 9.56 (d, *J* = 7.7 Hz, 1H), 7.76 (d, *J* = 16.0 Hz, 1H), 7.65 (dd, *J* = 5.8, 2.3 Hz, 2H), 6.76 (dd, *J* = 16.0, 7.7 Hz, 1H).

((*E*)-3-(3-bromo-5-chloro-2-hydroxyphenyl)acrylaldehyde) (1j)

The title compound was prepared as a pale yellow solid in 45% yield (235.3 mg) according to the general procedure, as described above. **^{1}H NMR (400 MHz, MeOD)** δ 9.69 (d, *J* = 7.7 Hz, 1H), 7.89 (d, *J* = 16.1 Hz, 1H), 7.60 (s, 1H), 7.49 (s, 1H), 6.90 (dd, *J* = 16.1, 7.7 Hz, 1H).

(tert-butyl (E)-(4-hydroxy-3-(3-oxoprop-1-en-1-yl)phenyl)carbamate) (1k)

The title compound was prepared as a pale yellow solid in 40% yield (210.6 mg) according to the general procedure, as described above. **^{1}H NMR (400 MHz, MeOD)** δ 9.61 (s, 1H), 7.91 (d, J = 16.0 Hz, 2H), 6.83 (dd, J = 8.4, 3.2 Hz, 3H), 1.53 (s, 9H).

General procedure for the synthesis of dioxindoles:

Dioxindoles were prepared according to reported procedures.[21]

In an oven dried round bottom flask, a solution of isatin (10 mmol) was slowly added to K_2CO_3 (25 mmol, 2.5 eq.) under argon atmosphere at 0 ºC. The reaction mixture was allowed to stir at 0 ºC for 10 minutes. Then, alkyl halide or benzyl halide (20 mmol, 2.0 eq.) was added to reaction mixture and allowed to stir at RT for 12 hours. Reaction mixture was filtered through Celite with about 50 mL DCM, dried over Na_2SO_4 and concentrated under reduced pressure. Water was added until precipitation of the N-protected isatin. Crystallization from hexane/ethyl acetate afforded the pure product.

N-protected isatins (10 mmol) were added in small portions to a stirred suspension of sodium borohydride (15 mmol, 1.5 eq.) in 60 mL of a 1:1 dichloromethane/ethanol mixture at 0 ºC. The mixture was vigorously stirred at this temperature until the suspension became colorless (about 5 min). Then water (1.0 mL) was added and the reaction mixture was stirred until bubbling stop. The mixture was extracted with dichloromethane (3 ×50 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The residue was used without further purification.

Characterisation of dioxindoles:

(3-hydroxy-1-methylindolin-2-one) (2b)

The title compound was prepared as a green solid in 68% yield (1.1 g) according to the general procedure, as described above. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.46 (d, *J* = 7.2 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.11 (t, *J* = 7.4 Hz, 1H), 6.83 (d, *J* = 7.7 Hz, 1H), 5.10 (s, 1H), 3.18 (s, 3H).

(3-hydroxy-1-isobutylindolin-2-one) (2c)

The title compound was prepared as a dark yellow solid in 75% yield (1.5 g) according to the general procedure, as described above. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.47 (d, *J* = 7.3 Hz, 1H), 7.31 (t, *J* = 7.8 Hz, 1H), 7.09 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 7.9 Hz, 1H), 5.11 (s, 1H), 3.54 (dd, *J* = 13.9, 7.6 Hz, 1H), 3.42 (dd, *J* = 13.9, 7.4 Hz, 1H), 2.13 (dt, *J* = 13.8, 7.0 Hz, 1H), 0.96 (d, *J* = 6.7 Hz, 6H).

(1-allyl-3-hydroxyindolin-2-one) (2d)

The title compound was prepared as an off-white solid in 79% yield (1.5 g) according to the general procedure, as described above. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.47 (d, *J* = 7.3 Hz, 1H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.83 (d, *J* = 7.8 Hz, 1H), 5.83 (ddd, *J* = 22.5, 10.5, 5.4 Hz, 1H), 5.25 (t, *J* = 12.7 Hz, 2H), 5.13 (s, 1H), 4.38 (d, *J* = 16.3 Hz, 1H), 4.27 (d, *J* = 16.3 Hz, 1H).

(3-hydroxy-1-(3-methylbut-2-en-1-yl) indolin-2-one) (2e)

The title compound was prepared as an orange solid in 85% yield (1.8 g) according to the general procedure, as described above. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.43 (d, *J* = 7.3 Hz, 1H), 7.25 (dd, *J* = 12.7, 4.9 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 7.8 Hz, 1H), 5.13 (t, *J* = 6.7 Hz, 1H), 5.08 (s, 1H), 4.30 (dd, *J* = 15.5, 6.6 Hz, 1H), 4.20 (dd, *J* = 15.5, 6.7 Hz, 1H), 1.78 (s, 3H), 1.68 (s, 3H).

(3-hydroxy-1-(4-(trifluoromethyl) benzyl) indolin-2-one) (2f)

The title compound was prepared as a green solid in 80% yield (2.5 g) according to the general procedure, as described above. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.58 (d, *J* = 8.1 Hz, 2H), 7.49 (d, *J* = 7.4 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.26 – 7.21 (m, 1H), 7.10 (t, *J* = 7.5 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 5.20 (s, 1H), 4.93 (q, *J* = 16.0 Hz, 2H).

(3-hydroxyindolin-2-one) (2g)

The title compound was prepared as a white solid in 78% yield (1.2 g) according to the general procedure, as described above. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.44 (d, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 7.7 Hz, 1H), 7.09 (t, *J* = 7.6 Hz, 1H), 6.86 (d, *J* = 7.8 Hz, 1H), 5.08 (s, 1H).

(1-benzyl-5-fluoro-3-hydroxyindolin-2-one) (2h)

The title compound was prepared as a green sticky solid in 70% yield (1.8 g) according to the general procedure, as described above. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.32 – 7.23 (m, 5H), 7.19 (d, *J* = 7.6 Hz, 1H), 6.88 (t, *J* = 8.9 Hz, 1H), 6.60 (dd, *J* = 8.6, 4.0 Hz, 1H), 5.16 (s, 1H), 4.90 (d, *J* = 15.7 Hz, 1H), 4.79 (d, *J* = 15.7 Hz, 1H).

(1-benzyl-5-chloro-3-hydroxyindolin-2-one) (2i)

The title compound was prepared as a brown sticky solid in 84% yield (2.3 g) according to the general procedure, as described above. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.44 (s, 1H), 7.35 – 7.26 (m, 5H), 7.18 (dd, *J* = 8.4, 2.1 Hz, 1H), 6.62 (d, *J* = 8.4 Hz, 1H), 5.17 (s, 1H), 4.91 (d, *J* = 15.5 Hz, 1H), 4.81 (d, *J* = 15.7 Hz, 1H).

(1-benzyl-5-bromo-3-hydroxyindolin-2-one) (2j)

The title compound was prepared as a green sticky solid in 76% yield (2.4 g) according to the general procedure, as described above. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.57 (s, 1H), 7.33 – 7.23

(m, 6H), 6.56 (d, *J* = 8.3 Hz, 1H), 5.19 (s, 1H), 4.89 (d, *J* = 15.5 Hz, 1H), 4.79 (d, *J* = 15.7 Hz, 1H).

(1-benzyl-6-bromo-3-hydroxyindolin-2-one) (2k)

The title compound was prepared as a green solid in 74% yield (2.3 g) according to the general procedure, as described above. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.28 (dt, *J* = 15.0, 6.4 Hz, 6H), 7.18 (d, *J* = 7.9 Hz, 1H), 6.84 (s, 1H), 5.11 (s, 1H), 4.87 (d, *J* = 15.7 Hz, 1H), 4.74 (d, *J* = 15.7 Hz, 1H).

(1-benzyl-7-chloro-3-hydroxyindolin-2-one) (2l)

The title compound was prepared as a yellowish green solid in 75% yield (2.0 g) according to the general procedure, as described above. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.41 (d, *J* = 7.3 Hz, 1H), 7.34 – 7.29 (m, 2H), 7.23 (dd, *J* = 14.3, 7.8 Hz, 4H), 7.06 – 7.01 (m, 1H), 5.33 (d, *J* = 5.0 Hz, 2H), 5.18 (s, 1H).

(1-benzyl-4-bromo-3-hydroxyindolin-2-one) (2m)

The title compound was prepared as a dark yellow solid in 76% yield (2.4 g) according to the general procedure, as described above. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.30 (dd, *J* = 13.3, 6.7 Hz, 5H), 7.17 (d, *J* = 8.2 Hz, 1H), 7.09 (t, *J* = 8.0 Hz, 1H), 6.65 (d, *J* = 7.7 Hz, 1H), 5.17 (s, 1H), 4.87 (d, *J* = 3.1 Hz, 2H).

General procedure for the synthesis of catalyst:

The catalyst (**III, IV** and **V**) was prepared according to reported procedures.[22, 23]

General procedure for the synthesis of compound 3:

In an oven dried round bottom flask, **1** (17.7 mg, 0.12 mmol), **2** (23.9 mg, 0.1 mmol), 10 mol% of catalyst (**V**) and 10 mol% of $PhCO_2H$ were taken. 0.5 mL of toluene was added to the reaction mixture and stirred at rt for 8-20 hours. Completion of reaction was checked by TLC. After the completion of reaction, solvent was concentrated and the reaction mixture was directly subjected to TFA.

Second step:

To the vacuum dried reaction mixture, DCM was added to the reaction mixture of first step and allowed to stir at rt. 1.5 eq of TFA was added; the reaction mixture was allowed to stir overnight. Progress of the reaction was monitored by TLC. After the completion of reaction, solvent was concentrated and reaction mixture was directly purified by column chromatography on silica gel eluting with hexane/ethyl acetate (10 %) to afford desired product **3a-v.**

Characterisation of the products:

((2'*R*,3*S*,5'*S*)-1-benzyl-5'H-spiro[indoline-3,4'[2,5]methanobenzo[d][1,3]dioxepin]-2-one)

(3a) was obtained as a light yellow solid in 79% yield (29.2 mg) after column chromatography. M.P. = 128-130 ^{o}C. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.32 – 7.18 (m, 6H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.90 (d, *J* = 8.1 Hz, 1H), 6.74 (t, *J* = 7.4 Hz, 1H), 6.61 (t, *J* = 7.3 Hz, 2H), 6.55 (d, *J* = 7.4 Hz, 1H), 6.04 (d, *J* = 3.5 Hz, 1H), 5.84 (d, *J* = 8.0 Hz, 1H), 4.88 (d, *J* = 15.6 Hz, 1H), 4.75 (d, *J* = 15.6 Hz, 1H), 3.62 (dt, *J* = 11.6, 3.9 Hz, 1H), 3.25 (d, *J* = 3.9 Hz, 1H), 2.42 (d, *J* = 11.6 Hz, 1H). **^{13}C {1H} NMR (151 MHz, Chloroform-*d*)** δ 175.5 , 151.8 , 143.0 , 135.6 , 130.1 , 129.7 , 129.0 , 128.9 , 127.9 , 127.4 , 125.9 , 125.7 , 125.5 , 122.6 , 120.8 , 116.5 , 109.1 , 101.3 , 90.8 , 45.1 , 43.9 , 31.4. **HPLC Analysis:** ee = 98%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10,

flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 11.0 min, t_{minor} = 21.3 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{20}NO_3[M+H]^+$ 370.1438, found 370.1439.

((2'*R*,3*S*,5'*S*)-1-benzyl-7'-methyl-5'H-spiro[indoline-3,4'[2,5]methanobenzo[d][1,3] dioxepin]-2-one) (3b) was obtained as light yellow semi solid in 64% (24.5 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.30 – 7.20 (m, 5H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.99 (d, *J* = 8.2 Hz, 1H), 6.78 (d, *J* = 8.2 Hz, 1H), 6.62 (t, *J* = 6.6 Hz, 2H), 6.36 (s, 1H), 6.02 (d, *J* = 3.5 Hz, 1H), 5.86 (d, *J* = 7.6 Hz, 1H), 4.88 (d, *J* = 15.6 Hz, 1H), 4.73 (d, *J* = 15.6 Hz, 1H), 3.60 (dt, *J* = 11.6, 3.9 Hz, 1H), 3.19 (d, *J* = 3.9 Hz, 1H), 2.39 (d, *J* = 11.6 Hz, 1H), 2.11 (s, 3H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 175.6 , 149.6 , 143.1 , 135.7 , 130.1 , 130.1 , 130.1 , 129.4 , 129.0 , 127.9 , 127.5 , 126.1 , 125.8 , 125.2 , 122.6 , 116.2 , 109.0 , 101.3 , 90.7 , 45.1 , 43.9 , 31.6 , 20.5. **HPLC Analysis:** ee = 97%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 9.9 min, t_{minor} = 15.8 min). **HRMS (+ESI-TOF)**: calcd. For $C_{25}H_{22}NO_3$ $[M+H]^+$ 384.1594, found 384.1603.

((2'*R*,3*S*,5'*S*)-1-benzyl-7'-methoxy-5'H-spiro[indoline-3,4'[2,5]methanobenzo[d][1,3] dioxepin]-2-one) (3c) was obtained as a yellow sticky solid in 51% (20.4 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.31 – 7.20 (m, 5H), 7.06 (t, *J* = 7.8 Hz, 1H), 6.82 (d, *J* = 8.8 Hz, 1H), 6.75 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.68 – 6.59 (m, 2H), 6.12 (d, *J* = 2.9 Hz, 1H), 6.01 (d, *J* = 3.5 Hz, 1H), 5.91 (d, *J* = 7.2 Hz, 1H), 4.86 (d, *J* = 15.6 Hz, 1H), 4.75 (d, *J* = 15.6 Hz, 1H), 3.65 – 3.55 (m, 4H), 3.18 (d, *J* = 3.9 Hz, 1H), 2.38 (d, *J* = 11.6 Hz, 1H). **^{13}C{1H} NMR (101 MHz, $CDCl_3$)** δ 175.5 , 153.7 , 145.7 , 143.0 , 135.7 , 130.1 , 129.0 , 127.9 , 127.5 , 126.0 , 125.7 , 122.8 , 117.0 , 114.9 , 114.6 , 109.1 , 101.2 , 90.6 , 76.9 , 56.1 , 45.3 , 43.9 , 31.60. **HPLC Analysis:** ee = 98%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0

mL/min, λ = 254 nm (t_{major} = 13.1 min, t_{minor} = 23.8 min). **HRMS (+ESI-TOF)**: calcd. For $C_{25}H_{22}NO_4$ $[M+H]^+$ 400.1543, found 400.1540.

((2'*R*,3*S*,5'*S*)-1-benzyl-7'-chloro-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3] dioxepin]-2-one) (**3d)** was obtained as a white semi solid in 66% (26.6 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.28 (dt, *J* = 15.3, 7.1 Hz, 5H), 7.17 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.84 (d, *J* = 8.6 Hz, 1H), 6.69 (t, *J* = 7.6 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 6.57 (d, *J* = 2.5 Hz, 1H), 6.03 (d, *J* = 3.5 Hz, 1H), 5.94 (d, *J* = 7.0 Hz, 1H), 4.88 (d, *J* = 15.6 Hz, 1H), 4.75 (d, *J* = 15.6 Hz, 1H), 3.64 (dt, *J* = 11.8, 3.9 Hz, 1H), 3.22 (d, *J* = 3.9 Hz, 1H), 2.37 (d, *J* = 11.7 Hz, 1H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 175.2 , 150.5 , 143.1 , 135.5 , 130.4 , 129.5 , 129.1 , 128.5 , 128.0 , 127.4 , 127.0 , 125.7 , 125.7 , 125.3 , 122.9 , 117.8 , 109.3 , 101.3 , 90.7 , 44.9 , 44.0 , 31.2 . **HPLC Analysis:** ee = 97%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 11.3 min, t_{minor} = 21.6 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{19}ClNO_3$ $[M+H]^+$ 404.1048, found 404.1055.

((2'*R*,3*S*,5'*S*)-1-benzyl-7'-bromo-5'H-spiro[indoline-3,4'[2,5]methanobenzo[d][1,3] dioxepin]-2-one) (3e) was obtained as a light yellow sticky solid in 57% (25.5 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.34 – 7.27 (m, 3H), 7.27 – 7.21 (m, 3H), 7.10 (t, *J* = 7.8 Hz, 1H), 6.79 (d, *J* = 8.6 Hz, 1H), 6.73 – 6.67 (m, 2H), 6.65 (d, *J* = 7.8 Hz, 1H), 6.03 (d, *J* = 3.5 Hz, 1H), 5.94 (d, *J* = 7.5 Hz, 1H), 4.88 (d, *J* = 15.6 Hz, 1H), 4.75 (d, *J* = 15.6 Hz, 1H), 3.64 (dt, *J* = 11.8, 3.9 Hz, 1H), 3.22 (d, *J* = 3.9 Hz, 1H), 2.37 (d, *J* = 11.7 Hz, 1H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 175.2 , 151.0 , 143.1 , 135.5 , 132.5 , 131.4 , 130.5 , 129.1 , 128.0 , 127.4 , 125.8 , 125.3 , 122.9 , 118.3 , 112.9 , 109.3 , 101.3 , 90.7 , 44.9 , 44.0 ,

31.2. **HPLC Analysis:** ee = 98%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 11.9 min, t_{minor} = 20.9 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{19}BrNO_3$ $[M+H]^+$ 448.0543, found 448.0542.

((2'*R*,3*S*,5'*S*)-1-benzyl-6'-chloro-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3] dioxepin]-2-one) (3f) was obtained as a light yellow semi solid in 61% (24.6 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.34 – 7.22 (m, 5H), 7.18 – 7.07 (m, 2H), 6.83 (dd, *J* = 10.5, 8.1 Hz, 2H), 6.66 (t, *J* = 7.6 Hz, 1H), 6.62 (d, *J* = 7.8 Hz, 1H), 6.06 (d, *J* = 3.5 Hz, 1H), 5.94 (d, *J* = 7.0 Hz, 1H), 4.96 (d, *J* = 15.9 Hz, 1H), 4.78 (d, *J* = 15.9 Hz, 1H), 3.89 (d, *J* = 4.1 Hz, 1H), 3.62 (dt, *J* = 11.8, 3.9 Hz, 1H), 2.36 (d, *J* = 11.8 Hz, 1H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175.2 , 152.9 , 142.9 , 135.5 , 133.5 , 130.2 , 129.8 , 129.0 , 127.8 , 127.1 , 125.3 , 124.8 , 123.8 , 122.8 , 121.6 , 115.2 , 109.3 , 101.2 , 90.8 , 43.8 , 42.0 , 30.7. **HPLC Analysis:** ee = 99%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 11.8 min, t_{minor} = 21.5 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{19}ClNO_3$ $[M+H]^+$ 404.1048, found 404.1051.

((2'*R*,3*S*,5'*S*)-1-benzyl-8'-methoxy-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3] dioxepin]-2-one) (3g) was obtained as a light yellow sticky solid in 62% (24.7 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.30 (ddd, *J* = 17.5, 12.7, 6.0 Hz, 6H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.74 – 6.64 (m, 2H), 6.55 – 6.47 (m, 2H), 6.35 (dd, *J* = 8.3, 2.5 Hz, 1H), 6.07 (d, *J* = 3.5 Hz, 1H), 5.98 (d, *J* = 7.5 Hz, 1H), 4.92 (d, *J* = 15.6 Hz, 1H), 4.79 (d, *J* = 15.6 Hz, 1H), 3.81 (s, 3H), 3.65 (dt, *J* = 11.6, 3.9 Hz, 1H), 3.25 (d, *J* = 3.9 Hz, 1H), 2.42 (d, *J* = 11.5 Hz, 1H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 175.7 , 161.0 , 152.8 , 143.2 , 135.8 , 130.2

, 129.5 , 129.2 , 128.0 , 127.6 , 126.2 , 126.0 , 122.8 , 118.0 , 109.2 , 106.7 , 102.2 , 101.4 , 91.1 , 55.7 , 44.7 , 44.0 , 32.0. **HPLC Analysis:** ee = 97%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 12.9 min, t_{minor} = 20.1 min). **HRMS (+ESI-TOF):** calcd. For $C_{25}H_{22}NO_4$ $[M+H]^+$ 400.1543, found 400.1548.

((2'*S*,3*S*,5'*S*)-1-benzyl-7',9'-dichloro-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3] dioxepin]-2-one) (3h) was obtained as a yellow sticky solid in 34% (15.0 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.34 (d, *J* = 2.4 Hz, 2H), 7.33 (s, 1H), 7.29 (d, *J* = 7.0 Hz, 3H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.77 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 7.9 Hz, 1H), 6.55 (d, *J* = 2.4 Hz, 1H), 6.20 (d, *J* = 3.4 Hz, 1H), 6.01 (d, *J* = 7.5 Hz, 1H), 4.93 (d, *J* = 15.6 Hz, 1H), 4.79 (d, *J* = 15.6 Hz, 1H), 3.73 (dt, *J* = 11.9, 3.8 Hz, 1H), 3.30 (d, *J* = 3.9 Hz, 1H), 2.42 (d, *J* = 11.9 Hz, 1H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 174.9 , 146.8 , 143.1 , 135.4 , 130.6 , 129.9 , 129.1 , 128.0 , 128.0 , 127.5 , 127.1 , 125.7 , 125.6 , 124.8 , 123.0 , 122.4 , 109.5 , 101.7 , 90.7 , 45.0 , 44.1 , 31.1 , 29.9. **HPLC Analysis:** ee = 94%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 11.0 min, t_{minor} = 19.5 min). **HRMS (+ESI-TOF):** calcd. For $C_{24}H_{18}Cl_2NO_3$ $[M+H]^+$ 438.0658, found 438.0655.

((2'*S*,3*S*,5'*S*)-1-benzyl-7',9'-dibromo-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3] dioxepin]-2-one) (3i) was obtained as a light yellow semi solid in 23% (12.1 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.64 (d, *J* = 2.2 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.28 (d, *J* = 16.5 Hz, 4H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.77 (t, *J* = 7.6 Hz, 1H), 6.74 – 6.67 (m, 2H), 6.20 (d, *J* = 3.3 Hz, 1H), 6.00 (d, *J* = 7.4 Hz, 1H), 4.93 (d, *J* = 15.6 Hz, 1H), 4.78 (d, *J* = 15.6 Hz, 1H), 3.72 (dt, *J* = 11.9, 3.8 Hz, 1H), 3.28 (d, *J* = 3.9 Hz, 1H), 2.41 (d, *J* = 11.8 Hz,

1H). **^{13}C {1H} NMR (101 MHz, Chloroform-*d*)** δ 174.9 , 148.4 , 143.1 , 135.4 , 130.7 , 130.6 , 129.1 , 128.4 , 128.0 , 127.5 , 125.8 , 124.8 , 123.0 , 112.8 , 109.5 , 101.8 , 90.7 , 45.0 , 44.0 , 31.1 , 29.9. **HPLC Analysis:** ee = 95%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 11.5 min, t_{minor} = 19.6 min). **HRMS (+ESI-TOF):** calcd. For $C_{24}H_{18}Br_2NO_3$ $[M+H]^+$ 525.9648, found 525.9647.

((2'*S*,3*S*,5'*S*)-1-benzyl-9'-bromo-7'-chloro-5'H-spiro[indoline-3,4'[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3j) was obtained as a light yellow semi solid in 32% (15.5 mg) yield after column chromatography. **^{1}H NMR (400 MHz, Chloroform-*d*)** δ 7.50 (d, *J* = 2.4 Hz, 1H), 7.38 – 7.32 (m, 2H), 7.28 (d, *J* = 16.3 Hz, 4H), 7.16 (t, *J* = 7.8 Hz, 1H), 6.77 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 6.58 (d, *J* = 2.4 Hz, 1H), 6.20 (d, *J* = 3.4 Hz, 1H), 6.00 (d, *J* = 7.0 Hz, 1H), 4.93 (d, *J* = 15.6 Hz, 1H), 4.78 (d, *J* = 15.6 Hz, 1H), 3.72 (dt, *J* = 11.9, 3.8 Hz, 1H), 3.28 (d, *J* = 3.8 Hz, 1H), 2.41 (d, *J* = 11.9 Hz, 1H). **^{13}C {1H} NMR (151 MHz, Chloroform-*d*)** δ 174.9 , 147.8 , 143.0 , 135.4 , 132.7 , 130.6 , 129.1 , 128.0 , 127.8 , 127.4 , 126.0 , 125.7 , 123.0 , 110.9 , 109.5 , 101.8 , 90.6 , 45.0 , 44.0 , 31.1. **HPLC Analysis:** ee = 96%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 10.8 min, t_{minor} = 20.9 min). **HRMS (+ESI-TOF):** calcd. For $C_{24}H_{18}BrClNO_3$ $[M+H]^+$ 482.0153, found 482.0157.

(tert-butyl((2'R,3S,5'S)-1-benzyl-2-oxo-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-7'-yl)carbamate) (3k) was obtained as a dark yellow semi solid in 47% (22.7 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.36 – 7.27 (m, 5H), 7.18 (d, *J* = 6.6 Hz, 1H), 7.11 (t, *J* = 7.8 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 6.72 – 6.64 (m, 3H), 6.05 (d, *J* = 3.5 Hz, 1H), 6.00 (d, *J* = 6.9 Hz, 1H), 4.92 (d, *J* = 15.6 Hz, 1H), 4.78 (d, *J* = 15.6 Hz, 1H), 3.64

(dt, *J* = 11.6, 3.9 Hz, 1H), 3.26 (d, *J* = 3.9 Hz, 1H), 2.42 (d, *J* = 11.5 Hz, 1H), 1.45 (s, 9H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175.5, 147.7, 143.1, 135.6, 131.5, 130.2, 129.1, 127.9, 127.4, 125.9, 125.8, 125.7, 122.8, 116.7, 109.2, 101.3, 90.6, 45.1, 44.0, 31.6, 28.5. **HPLC Analysis:** ee = 98%, Chiralpak LUX C1 Column, n-Hexane/i-PrOH = 70/30, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 22.4 min, t_{minor} = 9.5 min). **HRMS (+ESI-TOF):** calcd. For $C_{29}H_{28}N_2NaO_5$ $[M+Na]^+$ 507.1890, found 507.1876.

((2'*R*,3*S*,5'*S*)-1-methyl-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3l) was obtained as a yellow sticky solid in 80% (23.5 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.38 – 7.32 (m, 2H), 7.23 (t, *J* = 7.7 Hz, 1H), 7.06 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 8.0 Hz, 1H), 6.84 (dd, *J* = 13.3, 7.5 Hz, 2H), 6.78 (d, *J* = 7.4 Hz, 1H), 6.09 (d, *J* = 3.4 Hz, 1H), 3.28 – 3.25 (m, 1H), 3.09 (s, 3H), 2.93 (dt, *J* = 11.8, 3.8 Hz, 1H), 2.50 (d, *J* = 11.9 Hz, 1H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 174.1, 151.7, 143.2, 130.3, 129.5, 129.4, 126.9, 125.2, 123.4, 122.7, 121.0, 115.9, 108.6, 100.7, 90.7, 46.9, 33.1, 26.7. **HPLC Analysis:** ee = 98%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 9.2 min, t_{minor} = 17.3 min). **HRMS (+ESI-TOF):** calcd. For $C_{18}H_{16}NO_3$ $[M+H]^+$ 294.1125, found 294.1131.

((2'*R*,3*S*,5'*S*)-1-isobutyl-5'H-spiro[indoline-3,4'-[2,5] methanobenzo[d][1,3]dioxepin]-2-one) (3m) was obtained as a white semi solid in 71% (23.8 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.25 (dd, *J* = 10.6, 4.8 Hz, 1H), 7.20 (t, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.81 – 6.74 (m, 2H), 6.67 (t, *J* = 7.6 Hz, 1H), 6.59 (d, *J* = 7.4 Hz, 1H), 6.06 (d, *J* = 3.5 Hz, 1H), 5.88 (d, *J* = 7.5 Hz, 1H), 3.63 (dt, *J* = 11.6, 3.9 Hz, 1H), 3.54 (dd, *J* = 13.9, 7.8 Hz, 1H), 3.39 (dd, *J* = 13.9, 7.3 Hz, 1H), 3.22 (d, *J* = 4.0 Hz, 1H), 2.42 (d, *J* = 11.6 Hz, 1H), 2.19 –

2.10 (m, 1H), 0.98 (d, *J* = 6.7 Hz, 6H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175.6, 151.9, 143.7, 130.1, 129.6, 128.9, 125.9, 125.8, 125.6, 122.3, 120.8, 116.5, 108.6, 101.3, 90.7, 47.5, 45.2, 31.4, 27.1, 20.4. **HPLC Analysis:** ee = 99%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 5.8 min, t_{minor} = 8.7 min). **HRMS (+ESI-TOF)**: calcd. For $C_{21}H_{22}NO_3$ $[M+H]^+$ 336.1594, found 336.1598.

((2'*R*,3*S*,5'*S*)-1-allyl-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one) (3n) was obtained as a light yellow semi solid in 68% (21.7 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.25 (dd, *J* = 9.9, 5.7 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 6.94 (d, *J* = 8.0 Hz, 1H), 6.78 (dd, *J* = 13.5, 7.6 Hz, 2H), 6.69 (t, *J* = 7.6 Hz, 1H), 6.59 (d, *J* = 7.5 Hz, 1H), 6.06 (d, *J* = 3.5 Hz, 1H), 5.84 (ddd, *J* = 15.7, 12.0, 6.7 Hz, 2H), 5.30 – 5.22 (m, 2H), 4.35 (dd, *J* = 16.3, 5.3 Hz, 1H), 4.23 (dd, *J* = 16.3, 5.3 Hz, 1H), 3.62 (dt, *J* = 11.6, 3.9 Hz, 1H), 3.25 (d, *J* = 4.0 Hz, 3H), 2.43 (d, *J* = 11.6 Hz, 1H)**. ^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175.1, 151.8, 143.1, 131.3, 130.1, 129.7, 128.9, 125.9, 125.7, 125.5, 122.6, 120.8, 118.0, 116.5, 108.9, 101.3, 90.8, 45.1, 42.5, 31.4. **HPLC Analysis:** ee = 98%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 8.0 min, t_{minor} = 11.3 min). **HRMS (+ESI-TOF)**: calcd. For $C_{20}H_{18}NO_3$ $[M+H]^+$ 320.1281, found 320.1274.

(2'*R*,3*S*,5'*S*)-1-(3-methylbut-2-en-1-yl)-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3] dioxepin]-2-one (3o) was obtained as a light yellow semi solid in 65% (22.6 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.28 – 7.21 (m, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 6.93 (d, *J* = 8.1 Hz, 1H), 6.78 (t, *J* = 7.4 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.67 (t, *J* = 7.6 Hz, 1H), 6.59 (d, *J* = 7.4 Hz, 1H), 6.05 (d, *J* = 3.5 Hz, 1H), 5.87 (d, *J* = 7.5 Hz, 1H), 5.18 (t, *J* = 6.1

Hz, 1H), 4.31 (dd, *J* = 15.4, 6.4 Hz, 1H), 4.22 (dd, *J* = 15.5, 6.8 Hz, 1H), 3.62 (dt, *J* = 11.6, 3.9 Hz, 1H), 3.24 (d, *J* = 3.9 Hz, 1H), 2.42 (d, *J* = 11.6 Hz, 1H), 1.83 (s, 3H), 1.73 (s, 3H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 174.9, 151.9, 143.3, 137.1, 130.1, 129.6, 128.9, 125.9, 125.6, 122.4, 120.7, 118.1, 116.5, 108.8, 101.3, 90.9, 44.9, 38.3, 31.4, 25.8, 18.3. **HPLC Analysis:** ee = 99%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 6.7 min, t_{minor} = 12.4 min). **HRMS (+ESI-TOF)**: calcd. For $C_{22}H_{22}NO_3$ $[M+H]^+$ 348.1594, found 348.1596.

(2'*R*,3*S*,5'*S*)-1-(4-(trifluoromethyl)benzyl)-5'H-spiro[indoline-3,4'[2,5]methanobenzo [d][1,3]dioxepin]-2-one (3p) was obtained as a green semi solid in 51% (22.3 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.60 (d, *J* = 8.1 Hz, 2H), 7.41 (d, *J* = 8.0 Hz, 2H), 7.28 – 7.24 (m, 2H), 7.13 (t, *J* = 7.8 Hz, 1H), 6.95 (d, *J* = 8.0 Hz, 1H), 6.79 (t, *J* = 7.4 Hz, 1H), 6.69 (t, *J* = 7.3 Hz, 1H), 6.64 – 6.58 (m, 2H), 6.09 (d, *J* = 3.5 Hz, 1H), 5.90 (d, *J* = 7.0 Hz, 1H), 4.91 (q, *J* = 16.0 Hz, 2H), 3.64 (dt, *J* = 11.6, 3.9 Hz, 1H), 3.30 (d, *J* = 3.9 Hz, 1H), 2.48 (d, *J* = 11.6 Hz, 1H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175.6, 151.9, 142.7, 139.7, 130.2, 130.2(q, $J_{C\text{-}F}$ = 32.33 Hz), 129.8, 128.9, 127.7, 126.2, 126.1(q, $J_{C\text{-}F}$ = 3.03 Hz), 125.8, 125.5, 125.3, 124.1(q, $J_{C\text{-}F}$ = 272.70 Hz) 123.0, 120.9 116.6, 108.8, 101.3, 90.8, 45.2, 43.5, 31.5. **HPLC Analysis:** ee = 98%, Chiralpak IA Column Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 11.1 min, t_{minor} = 19.4 min). **HRMS (+ESI-TOF)**: calcd. For $C_{25}H_{19}F_3NO_3$ $[M+H]^+$ 438.1312, found 438.1312.

(2'*R*,3*S*,5'*S*)-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one (3q) was obtained as a light pink solid in 64% (17.9 mg) yield after column chromatography. M.P. = 115-117 °C. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 8.29 (s, 1H), 7.25 (dd, *J* = 9.5, 6.0 Hz, 1H), 7.16 (t, *J* =

7.7 Hz, 1H), 6.94 (d, *J* = 8.1 Hz, 1H), 6.80 (dd, *J* = 13.7, 7.4 Hz, 2H), 6.67 (t, *J* = 7.6 Hz, 1H), 6.58 (d, *J* = 7.4 Hz, 1H), 6.06 (d, *J* = 3.5 Hz, 1H), 5.87 (d, *J* = 7.6 Hz, 1H), 3.55 (dt, *J* = 11.6, 3.9 Hz, 1H), 3.31 (d, *J* = 3.9 Hz, 1H), 2.44 (d, *J* = 11.6 Hz, 1H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 177.8, 151.8, 140.9, 130.2, 129.7, 128.9, 126.2, 126.2, 125.4, 122.6, 120.8, 116.5, 110.1, 101.3, 91.2, 44.9, 31.2. **HPLC Analysis:** ee = 99%, Chiralpak IA Column n-Hexane/i-PrOH = 85/15, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 8.8 min, t_{minor} = 16.3 min). **HRMS (+ESI-TOF)**: calcd. For $C_{17}H_{14}NO_3$ $[M+H]^+$ 280.0968, found 280.0970.

(2'*R*,3*S*,5'*S*)-1-benzyl-5-fluoro-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one (3r) was obtained as a light grey semi solid in 59% (22.9 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.34 – 7.29 (m, 2H), 7.25 (dd, *J* = 12.0, 4.1 Hz, 4H), 6.93 (d, *J* = 8.0 Hz, 1H), 6.82 – 6.74 (m, 2H), 6.59 (d, *J* = 7.5 Hz, 1H), 6.54 (dd, *J* = 8.6, 4.1 Hz, 1H), 6.06 (d, *J* = 3.5 Hz, 1H), 5.55 (dd, *J* = 8.5, 2.6 Hz, 1H), 4.87 (d, *J* = 15.7 Hz, 1H), 4.77 (d, *J* = 15.7 Hz, 1H), 3.63 (dt, *J* = 11.7, 3.9 Hz, 1H), 3.28 (d, *J* = 3.9 Hz, 1H), 2.45 (d, *J* = 11.6 Hz, 1H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175.3, 158.9 (d, $J_{C\text{-}F}$ = 241.39 Hz), 151.7, 138.9, 138.9, 135.3, 130.0, 129.1, 128.9, 128.1, 127.6 (d, $J_{C\text{-}F}$ = 8.08 Hz), 127.4, 127.4, 124.9, 121.0, 116.7, 116.4 (d, $J_{C\text{-}F}$ = 24.24 Hz), 114.1 (d, $J_{C\text{-}F}$ = 26.26 Hz), 109.6 (d, $J_{C\text{-}F}$ = 8.08 Hz), 101.4, 90.8, 90.7, 45.2, 44.1, 31.4. **HPLC Analysis:** ee = 97%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 11.9 min, t_{minor} = 23.6 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{19}FNO_3$ $[M+H]^+$ 388.1343, found 388.1346.

(2'*R*,3*S*,5'*S*)-1-benzyl-5-chloro-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one (3s) was obtained as a light brown solid in 46% (18.6 mg) yield after column

chromatography. M.P. = 167-170 °C. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.34 (t, *J* = 7.3 Hz, 2H), 7.31 – 7.25 (m, 4H), 7.07 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.84 (td, *J* = 7.5, 1.0 Hz, 1H), 6.60 (d, *J* = 7.5 Hz, 1H), 6.57 (d, *J* = 8.3 Hz, 1H), 6.09 (d, *J* = 3.5 Hz, 1H), 5.75 (d, *J* = 2.1 Hz, 1H), 4.88 (d, *J* = 15.7 Hz, 1H), 4.80 (d, *J* = 15.7 Hz, 1H), 3.62 (dt, *J* = 11.7, 3.9 Hz, 1H), 3.29 (d, *J* = 3.9 Hz, 1H), 2.50 (d, *J* = 11.6 Hz, 1H). **^{13}C {1H} NMR (151 MHz, $CDCl_3$)** δ 175.0, 151.7, 141.4, 135.2, 130.0, 129.9, 129.1, 128.9, 128.1, 128.1, 127.5, 127.4, 126.5, 124.9, 121.0, 116.7, 110.0, 101.4, 90.7, 45.2, 44.0, 31.3. **HPLC Analysis:** ee = 99%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 12.6 min, t_{minor} = 25.1 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{19}ClNO_3$ $[M+H]^+$ 404.1048, found 404.1049.

(2'*R*,3*S*,5'*S*)-1-benzyl-5-bromo-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one (3t) was obtained as a light yellow sticky solid in 37% (16.6 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.27 (dd, *J* = 14.8, 7.2 Hz, 3H), 7.21 (t, *J* = 5.0 Hz, 3H), 7.16 (dd, *J* = 8.3, 2.0 Hz, 1H), 6.91 (d, *J* = 8.1 Hz, 1H), 6.79 (t, *J* = 7.5 Hz, 1H), 6.54 (d, *J* = 7.5 Hz, 1H), 6.46 (d, *J* = 8.3 Hz, 1H), 6.03 (d, *J* = 3.5 Hz, 1H), 5.82 (d, *J* = 2.0 Hz, 1H), 4.82 (d, *J* = 15.7 Hz, 1H), 4.74 (d, *J* = 15.7 Hz, 1H), 3.56 (dt, *J* = 11.7, 3.9 Hz, 1H), 3.23 (d, *J* = 3.9 Hz, 1H), 2.44 (d, *J* = 11.7 Hz, 1H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 174.9, 151.7, 141.9, 135.1, 132.8, 130.0, 129.3, 129.1, 128.9, 128.1, 127.8, 127.4, 124.9, 121.0, 116.8, 115.5, 110.5, 101.4, 90.7, 45.3, 44.0, 31.3. **HPLC Analysis:** ee = 93%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 13.5 min, t_{minor} = 26.0 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{19}BrNO_3$ $[M+H]^+$ 448.0543, found 448.0544.

(2'*R*,3*S*,5'*S*)-1-benzyl-6-bromo-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one (3u) was obtained as a light brown semi solid in 49% (22.0 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.84 – 7.78 (m, 2H), 7.78 – 7.67 (m, 4H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.29 – 7.21 (m, 3H), 7.05 (d, *J* = 7.5 Hz, 1H), 6.52 (d, *J* = 3.5 Hz, 1H), 6.16 (d, *J* = 8.6 Hz, 1H), 5.35 (d, *J* = 15.7 Hz, 1H), 5.20 (d, *J* = 15.7 Hz, 1H), 4.07 (dt, *J* = 11.7, 3.9 Hz, 1H), 3.72 (d, *J* = 3.9 Hz, 1H), 2.91 (d, *J* = 11.7 Hz, 1H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 175., 151.7, 144.3, 135.1, 129.9, 129.2, 128.9, 128.2, 127.4, 127.2, 125.6, 125.1, 124.7, 124.0, 121.0, 116.6, 112.5, 101.3, 90.4, 45.1, 44.0, 31.4. **HPLC Analysis:** ee = 98%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 9.7 min, t_{minor} = 20.9 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{19}BrNO_3$ $[M+H]^+$ 448.0543, found 448.0546.

(2'*R*,3*S*,5'*S*)-1-benzyl-7-chloro-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3] dioxepin]-2-one (3v) was obtained as a brown semi solid in 55% (22.2 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.32 (t, *J* = 7.2 Hz, 2H), 7.25 (dd, *J* = 14.3, 6.0 Hz, 5H), 7.09 (d, *J* = 8.2 Hz, 1H), 6.94 (d, *J* = 7.9 Hz, 1H), 6.79 (t, *J* = 7.4 Hz, 1H), 6.64 – 6.56 (m, 2H), 6.08 (d, *J* = 3.5 Hz, 1H), 5.87 (d, *J* = 7.5 Hz, 1H), 5.32 (s, 2H), 3.64 (dt, *J* = 11.7, 3.9 Hz, 1H), 3.28 (d, *J* = 3.9 Hz, 1H), 2.46 (d, *J* = 11.7 Hz, 1H). **^{13}C {1H} NMR (101 MHz, $CDCl_3$)** δ 176.2, 151.8, 139.0, 137.2, 132.7, 129.9, 129.0, 128.8, 128.8, 127.5, 126.6, 125.1, 124.5, 123.5, 120.9, 116.5, 115.4, 101.4, 90.2, 45.6, 45.1, 31.4. **HPLC Analysis:** ee = 93%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 8.8 min, t_{minor} = 15.9 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{19}ClNO_3$ $[M+H]^+$ 404.1048, found 404.1046.

(2'*R*,3*S*,5'*S*)-1-benzyl-4-bromo-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one (3w) was obtained as a yellow semi solid in 22% (10.0 mg) yield after column chromatography. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.35 (t, *J* = 7.4 Hz, 2H), 7.29 (dd, *J* = 15.2, 7.4 Hz, 3H), 7.22 (t, *J* = 7.8 Hz, 1H), 6.95 – 6.93 (m, 1H), 6.83 (d, *J* = 8.1 Hz, 1H), 6.76 (t, *J* = 7.4 Hz, 1H), 6.63 (dd, *J* = 8.6, 4.9 Hz, 1H), 6.56 (d, *J* = 7.5 Hz, 1H), 6.23 (d, *J* = 3.6 Hz, 1H), 5.00 (d, *J* = 15.7 Hz, 1H), 4.71 (d, *J* = 15.7 Hz, 1H), 3.71 (dt, *J* = 11.7, 3.8 Hz, 1H), 3.21 (d, *J* = 3.7 Hz, 1H), 2.24 (d, *J* = 11.7 Hz, 1H). **^{13}C {1H} NMR (151 MHz, $CDCl_3$)** δ 176.4, 153.4, 144.5, 135.3, 130.6, 130.2, 129.2, 128.5, 128.4, 128.1, 127.4, 125.9, 123.9, 121.5, 120.8, 117.0, 108.3, 102.3, 94.3, 47.2, 44.2, 29.8. **HPLC Analysis:** ee = 85%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 12.6 min, t_{minor} = 23.0 min). **HRMS (+ESI-TOF)**: calcd. For $C_{24}H_{19}BrNO_3$ $[M+H]^+$ 448.0543, found 448.0547.

General procedure for the preparation of compound 4/5:

In an oven dried round bottom flask, compound **3e/3t** (44.8 mg, 0.1 mmol), phenylboronic acid (1.5 eq), palladium (II) acetate (0.05eq), tricyclohexylphosphine (0.06eq) and Na_2CO_3 (2eq) were taken, flushed with argon and then dry DMF (0.1 mL) was added. The reaction mixture was allowed to stir for 3 days under argon atmosphere. The solvent was evaporated under reduced pressure. The obtained residue was purified by silica gel column chromatography using EtOAc-Hexane (1-2%) as eluent to afford the compound **4/5**.

(2'*R*,3*S*,5'*S*)-1-benzyl-7'-phenyl-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3] dioxepin]-2-one (4) was obtained as a light yellow sticky solid in 43% (19.1 mg) yield after column chromatography. **^{1}H NMR (400 MHz, $CDCl_3$)** δ 7.48 (dd, *J* = 8.4, 2.2 Hz, 1H), 7.40 –

7.26 (m, 11H), 7.10 (t, *J* = 7.3 Hz, 1H), 7.02 (d, *J* = 8.4 Hz, 1H), 6.80 (d, *J* = 2.2 Hz, 1H), 6.66 (dd, *J* = 17.4, 7.8 Hz, 2H), 6.13 (d, *J* = 3.5 Hz, 1H), 5.97 (d, *J* = 7.4 Hz, 1H), 4.93 (d, *J* = 15.6 Hz, 1H), 4.81 (d, *J* = 15.6 Hz, 1H), 3.72 (dt, *J* = 11.7, 3.9 Hz, 1H), 3.35 (d, *J* = 3.9 Hz, 1H), 2.51 (d, *J* = 11.7 Hz, 1H). **^{13}C {1H} NMR (151 MHz, $CDCl_3$)** δ 175.4, 151.4, 143.0, 140.7, 135.6, 134.2, 130.3, 129.1, 128.8, 128.4, 127.9, 127.7, 127.5, 127.0, 126.9, 126.0, 125.7, 125.6, 122.7, 116.8, 109.2, 101.4, 90.8, 45.3, 44.0, 31.5. **HPLC Analysis:** ee = 97%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 12.2 min, t_{minor} = 20.1 min). **HRMS (+ESI-TOF)**: calcd. For $C_{30}H_{24}NO_3$ $[M+H]^+$ 446.1751, found 446.1750.

(2'*R*,3*S*,5'*S*)-1-benzyl-5-phenyl-5'H-spiro[indoline-3,4'-[2,5]methanobenzo[d][1,3]dioxepin]-2-one (5) was obtained as a light yellow semi solid in 49% (21.8 mg) yield after column chromatography. **^{1}H NMR (600 MHz, $CDCl_3$)** δ 7.37 – 7.31 (m, 6H), 7.31 – 7.25 (m, 4H), 7.22 (t, *J* = 7.3 Hz, 1H), 7.07 (d, *J* = 7.2 Hz, 2H), 6.99 (d, *J* = 8.0 Hz, 1H), 6.87 (t, *J* = 7.4 Hz, 1H), 6.73 (d, *J* = 8.1 Hz, 1H), 6.69 (d, *J* = 7.4 Hz, 1H), 6.18 (d, *J* = 1.8 Hz, 1H), 6.11 (d, *J* = 3.5 Hz, 1H), 4.93 (d, *J* = 15.6 Hz, 1H), 4.86 (d, *J* = 15.6 Hz, 1H), 3.67 (dt, *J* = 11.7, 3.9 Hz, 1H), 3.36 (d, *J* = 4.0 Hz, 1H), 2.52 (d, *J* = 11.6 Hz, 1H). **^{13}C {1H} NMR (151 MHz, $CDCl_3$)** δ 175.5, 152.0, 142.2, 140.4, 135.8, 135.6, 129.7, 129.1, 129.1, 128.7, 128.6, 128.0, 127.5, 127.0, 126.7, 126.2, 125.6, 124.9, 121.0, 116.8, 109.3, 101.4, 90.7, 45.2, 44.1, 29.9. **HPLC Analysis:** ee = 94%, Chiralpak IA Column, n-Hexane/i-PrOH = 90/10, flow rate 1.0 mL/min, λ = 254 nm (t_{major} = 20.6 min, t_{minor} = 30.8 min). **HRMS (+ESI-TOF)**: calcd. For $C_{30}H_{24}NO_3$ $[M+H]^+$ 446.1751, found 446.1756.

ASSOCIATED CONTENT

Supporting Information

Optimization, X-ray crystal data, NMR spectra, and HPLC chromatograms (PDF), Crystal data for compound **3t** (CIF).

This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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