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Enantioselective N-Heterocyclic Carbene-Catalyzed Synthesis of Spirocyclic Oxindole-benzofuroazepinones

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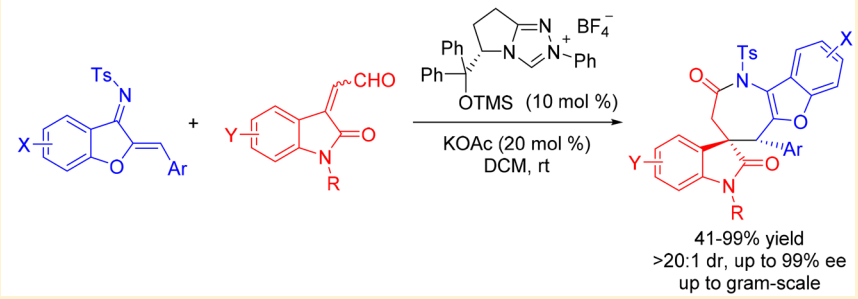
Supporting Information



ABSTRACT: Herein, we report an enantioselective synthesis of azepinones via the *N*-heterocyclic carbene (NHC) catalyzed [3+4] annulation reaction of isatin-derived enals and aurone-derived azadienes. The corresponding spirocyclic oxindole-benzofuroazepinones were obtained in good yields, with excellent diastereo- and enantioselectivities. The resulted azepinones were evaluated for their in vitro cytotoxic activities against six human tumor cell lines, with two compounds showing significant inhibitory activity comparable with that of cisplatin.

INTRODUCTION

Spirocyclic oxindoles have been found as a core structure of many alkaloids, bioactive molecules, and pharmaceuticals, and often find applications for the treatment of human cancers and neurodegenerative diseases.[1] Due to the prominent pharmacological activities, spirocyclic oxindoles have been important synthetic targets for drug discovery. Several approaches for the construction of spirocyclic oxindoles with a three- to six-membered spiro ring fused at the C-3 position of the oxindole core have been reported.[2] However, the synthesis of spirocyclic oxindoles with seven-membered heterocycles (ε-lactones and azepinones, etc.) have been far less developed.[3]

N-Heterocyclic carbenes (NHCs)[4] are powerful organocatalysts for the umpolung of aldehydes via the Breslow intermediate. In 2004, Glorius et al. and Bode et al. independently reported the pioneering NHC-catalyzed extended umpolung of enals (a^3 to d^3) for the annulation reactions via a homoenolate intermediate.[5] The NHC-catalyzed generation of homoenolate and the following [3+2],[6] [3+3][7] annulation and related cascade reactions[8] to give cyclic compounds are extremely successful. In 2013, Scheidt and our group independently reported the NHC-catalyzed [3+4] annulations of enals with *o*-quinomethides to give seven-membered lactones (ε-lactones).[9] Subsequently, NHC-catalyzed [3+4] cycloaddition reactions via a homoenolate intermediate were recognized as an effective approach to seven-membered heterocycles. Compared with ε-lactones,[3b,c,10] construction of azepinones via the NHC-catalyzed homoenolate pathway was rarely developed. In 2016, Enders et al.[3a] disclosed reactions of isatin-derived enals with the in situ-generated azoalkenes to prepare benzazepinones in good yields (Scheme 1, reaction a). In the same year, Glorius et al.[11] exploited an elegant cooperative palladium/NHC catalysis strategy for the synthesis of benzazepinones via an allylic palladium species and homoenolate intermediate (Scheme 1, reaction b). Generally, NHC-catalyzed reactions of enals with azadienes (α,β-unsaturated imines) failed to give access to azepinones but afforded β-lactam[12] (Scheme 1, reaction c) or enaminone[13] (Scheme 1, reaction d) as the final product. Herein, we report a facile, efficient, and straightforward annulation methodology utilizing aurone-derived azadienes[14] and isatin-derived enals[15] under NHC catalysis to afford the corresponding spirocyclic oxindole-benzofuroazepinones with highly potential bioactivities (Scheme 1, reaction e).

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Scheme 1. NHC-Catalyzed Enantioselective Synthesis of Azepinones and Related Reactions

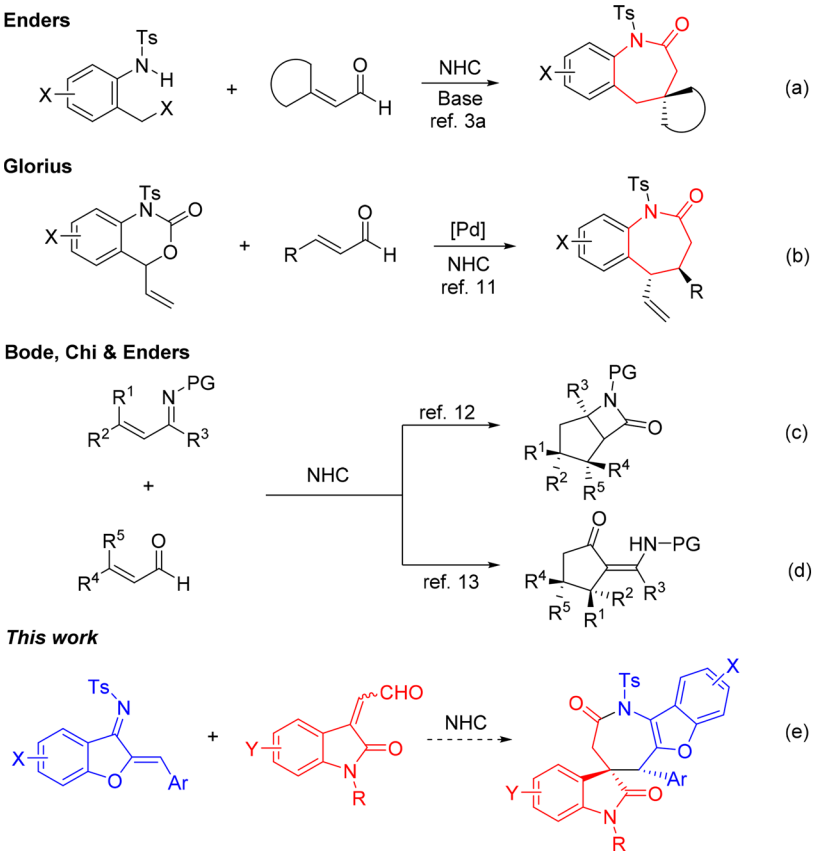
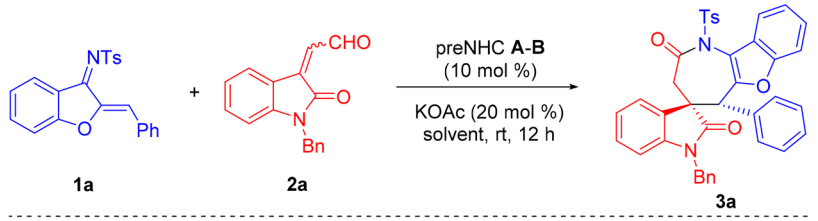


Table 1. Condition Optimization for the Reaction of Isatin-Derived Enals.[a]



A1: R = TBS, R = Ph
A2: R = TMS, R = Ph
A3: R = TBS, R = 2-*i*PrC$_6$H$_4$

B1: Ar = Mes
B2: Ar = C$_6$F$_5$

entry	preNHC	solvent	yield (%)[b]	dr[c]	ee (%)[d]
1	**A1**	1,4-dioxane	66	13:1	84
2	**A2**	1,4-dioxane	46	>20:1	84
3	**A3**	1,4-dioxane	92	>20:1	68
4	**B1**	1,4-dioxane	40	>20:1	75
5	**B2**	1,4-dioxane	46	1:1	
6	**A2**	toluene	58	>20:1	84
7	**A2**	THF	trace		
8	**A2**	CH_3CN	63	>20:1	94
9	**A2**	DCM	90	>20:1	96

[a]General conditions: **1a** (0.1 mmol), **2a** (0.12 mmol), preNHC **A,B** (10 mol %), KOAc (20 mol %), solvent (2 mL), and rt. [b]Isolated yields. [c]Determined by ^{1}H NMR spectroscopy of the crude reaction mixture. [d]Determined by HPLC analysis.

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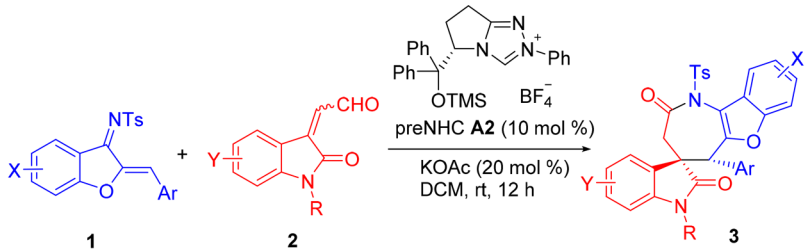
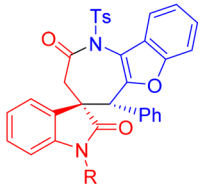
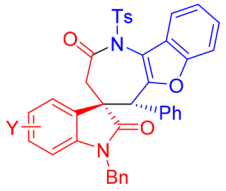
Scheme 2. Substrate Scope

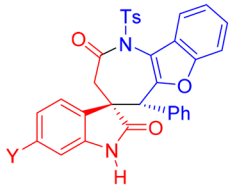




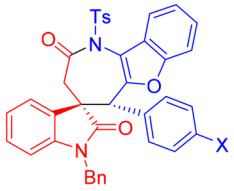
3a (R = Bn) 90%, >20:1 dr, 96% ee
3b (R = CH_3) 99%, >20:1 dr, 93% ee
3c (R = *i*Pr) 84%, >20:1 dr, 92% ee
3d (R = Ph) 92%, >20:1 dr, 92% ee
3e (R = 4-tol) 97%, >20:1 dr, 92% ee



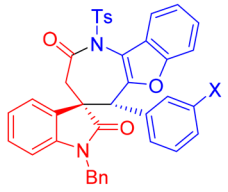
3f (Y = 5-CH_3) 61%, >20:1 dr, 95% ee
3g (Y = 5-CH_3O) 86%, >20:1 dr, 91% ee
3h (Y = 7-CH_3) 41%, >20:1 dr, 93% ee
3i (Y = 6-Cl) 77%, >20:1 dr, 90% ee
3j (Y =6-Br) 58%, >20:1 dr, 87% ee



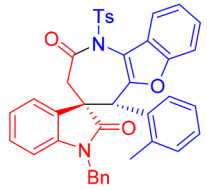
3k (Y = H) 89%, >20:1 dr, 93% ee
3l (Y = Cl)71%, >20:1 dr, 89% ee
3m (Y = Br) 47%, >20:1 dr, 90% ee



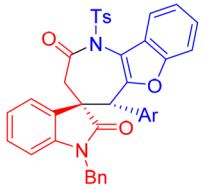
3n (X = F) 95%, >20:1 dr, 94% ee
3o (X = Br) 80%, >20:1 dr, 93% ee
3p (X = CH_3) 92%, >20:1 dr, 92% ee
3q (X = CH_3O) 85%, >20:1 dr, 95% ee



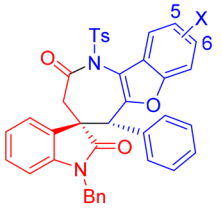
3r (X = Cl) 96%, >20:1 dr, 92% ee
3s (X = CH_3O) 95%, >20:1 dr, 87% ee



3t 99%, >20:1 dr, 80% ee



3u Ar = 2-thienyl 86%, >20:1 dr, 94% ee
3v Ar = 1-naphthyl 94%, >20:1 dr, 85% ee



3w (X = 5-F) 94%, >20:1 dr, 96% ee
3x (X = 6-F) 98%, >20:1 dr, 91% ee
3y (X = 5-CH_3) 65%, >20:1 dr, 93% ee

RESULTS AND DISCUSSION

Initially, isatin-derived enal **2a** was selected as the model substrate for the reaction with azadiene **1a** (Table 1). When the reaction was conducted in 1,4-dioxane using TBS-protected preNHC **A1** as the catalyst at room temperature, the desired cycloadduct **3a** was obtained in 66% yield, with 13:1 dr and 84% ee (Table 1, entry 1). The TMS-protected preNHC **A2** led to excellent diastereoselectivity but a decreased yield (entry 2). The TBS-protected preNHC **A3** with an *N*-2-isopropylphenyl substituent gave the final product in good yield but with decreased enantioselectivity (entry 3). Further screening of preNHCs with a tetracyclic core (**B1** and **B2**)[16] did not give satisfying results (entries 4−5). Thus, preNHC **A2** was selected for further optimization. To our delight, solvent screening revealed that the reaction performed best in dichloromethane, providing the desired spirocyclic azepinone **3a** in 90% yield, with >20:1 dr and 96% ee (entries 6−8 vs 9).

Under the optimized reaction conditions, the scope of isatin-derived enals were then explored (Scheme 2, **3a**−**3m**). Different *N*-protecting groups (R = benzyl, methyl, isopropyl, phenyl, and *p*-tolyl) on isatin-derived enals were all tolerated, giving the corresponding products (**3a**−**3e**) in good yields with excellent diastereo- and enantioselectivities. Isatin-derived enals with both electron-donating and electron-withdrawing groups (5-

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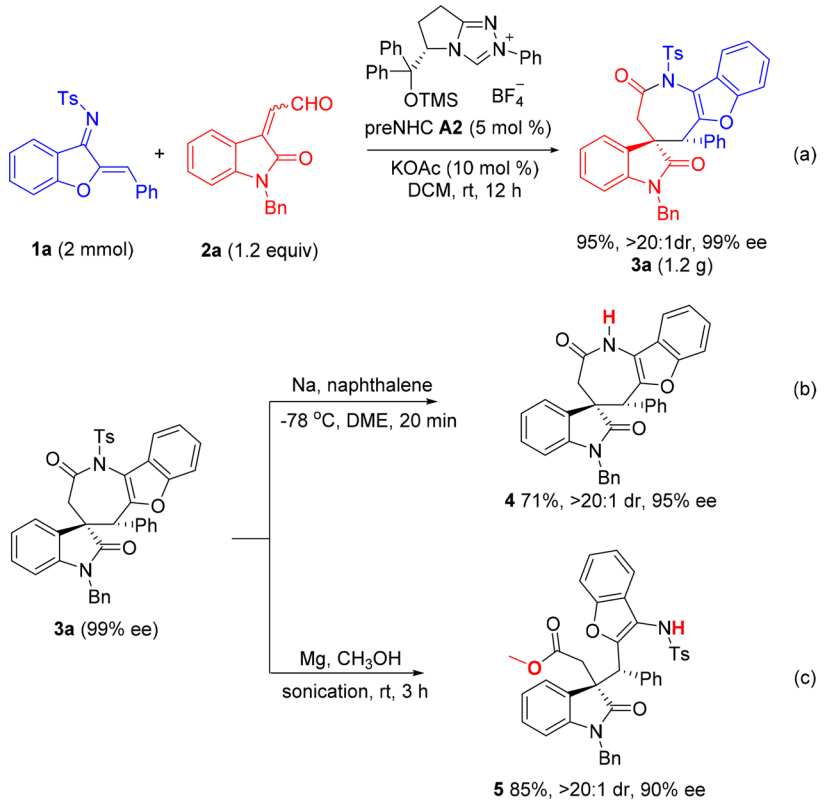
Scheme 3. Gram-Scale Reaction and Further Transformations



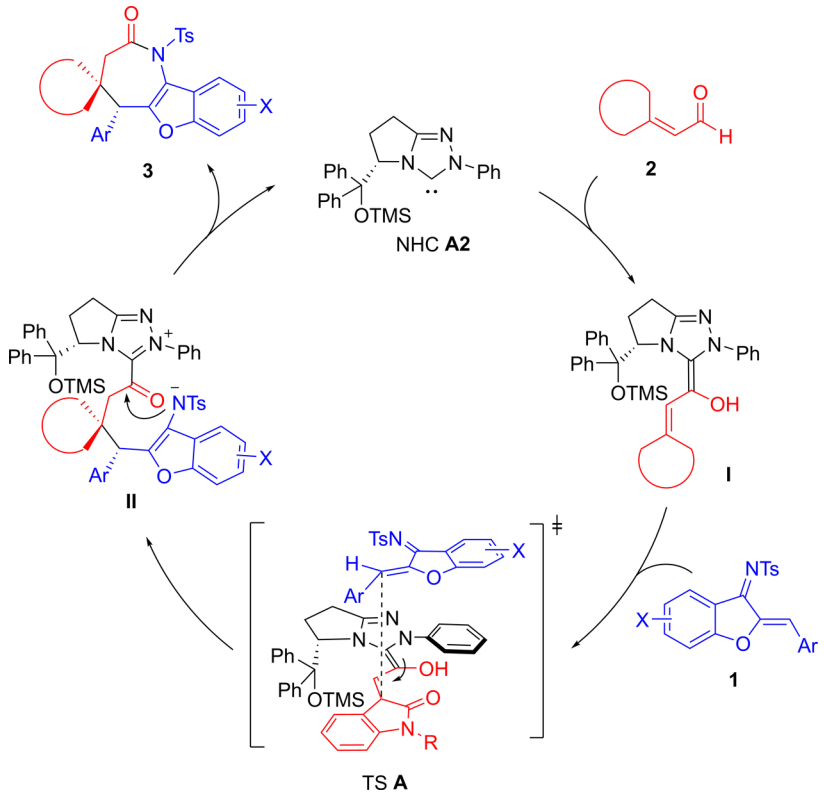


Figure 1. Proposed catalytic cycle.

CH_3, 5-CH_3O, 7-CH_3, 6-Cl, and 6-Br) on the aryl ring gave the products (**3f**–**3j**) in moderate to good yields with excellent stereoselectivities. Surprisingly, the unprotected isatin-derived enal worked as well to provide the desired cycloadduct **3k** in 89% yield with >20:1 dr and 93% ee. The reaction of unprotected 6-chloro or 6-bromo isatin-derived enals afforded

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Table 2. Cytotoxic Activities of Benzofuroazepinones against Six Human Tumor Cell Lines.[a,b]

compound	Jurkat	SMMC-7721	A549	MCF-7	SW480	MDA-MB-231
3b	10.7	11.1	6.6	21.2	17.0	18.8
3d	34.2	13.9	10.3	20.2	22.7	22.1
3k	13.9	10.0	6.5	21.2	25.1	14.0
3l	4.9	4.5	6.0	4.5	6.6	3.8
3m	8.1	4.1	4.7	5.1	6.2	4.3
DDP	2.2	9.3	5.6	19.6	6.8	3.1
paclitaxel	<0.008	<0.008	<0.008	<0.008	<0.008	<0.008

[a]Results are expressed as IC_{50} values in μM. Cell lines: Jurkat, T-cell leukemia; SMMC-7721, hepatie cancer; A-549, lung cancer; MCF-7, breast cancer; SW-480, colon cancer; and MDA-MB-231, breast cancer. [b]DDP (cisplatin) and paclitaxel were used as positive controls.

the spirocyclic azepinones (**3l** and **3m**) in moderate yields with excellent diastereo- and enantioselectivities.

The scope of azadienes for the reaction with isatin-derived enal was also evaluated (Scheme 2, **3n**−**3y**). Both electron-withdrawing and electron-donating groups (Ar = 4-FC_6H_4, 4-BrC_6H_4, 4-$CH_3C_6H_4$, and 4-$CH_3OC_6H_4$) on the *para*-position of the aryl of azadienes were all tolerated to give the corresponding cycloadducts (**3n**−**3q**) in good yields with excellent stereoselectivities. Azadienes with a *meta*-substituted aryl (Ar = 3-ClC_6H_4 and 3-$CH_3OC_6H_4$) also worked well (**3r** and **3s**). The reaction of azadiene with *ortho*-substituted aryl (Ar = 2-$CH_3C_6H_4$) gave the corresponding spirocyclic azepinone (**3t**) in quantitative yield and excellent diastereoselectivity, albeit with decreased enantioselectivity, probably owing to the steric effect of the *ortho*-substituent. 2-Thienyl or 1-naphthyl azadienes gave the corresponding annulation products (**3u** and **3v**) in good yields with excellent stereocontrol. In addition, the reactions of azadienes with substituents on the benzofuran ring (5-F, 6-F, and 5-CH_3) were also successful to afford the desired azepinones (**3w**−**3y**) in 65−98% yields, with excellent diastereo- and enantioselectivities.

The reactions of isatin-derived enals with azadienes could be scaled up without loss of yield and stereoselectivity. For instance, the desired spirocyclic azepinone **3a** could be obtained in 95% yield (1.2 g), with >20:1 dr and 99% ee, when the reaction was scaled up with 2 mmol of azadiene **1a** and 1.2 equiv of isatin-derived enal **2a** using a decreased catalyst loading of 5 mol % of preNHC **A2** and 10 mol % of KOAc (Scheme 3, reaction a). The resulting azepinones are structurally interesting and ready for further chemical transformations. The *N*-tosyl group could be removed by Na/naphthalene in 1,2-dimethoxyethane (DME) at −78 °C within 20 min to give the unprotected azepinone **4** in 71% yield, with >20:1 dr and 95% ee (Scheme 3, reaction b). The azepinone **3a** could be ring-opened with methanol to furnish the corresponding methyl ester **5** in 85% yield, with >20:1 dr and a slightly decreased enantioselectivity (90% ee) (Scheme 3, reaction c).

The absolute configuration of benzofuroazepinone **3o** was established by the X-ray analysis of its single crystal (see Figure S1).

A possible mechanism for this asymmetric [3+4] annulation is shown in Figure 1. The addition of NHC to enals generates the vinyl Breslow intermediate **I**, which attacks from the less hindered face of azadiene **1** (*exo*-transition state, TS **A**). Further lactamization affords the desired [3+4] cycloadduct benzofuroazepinones **3** and regenerates the NHC catalyst.

The reaction products possess an azepinone motif that is widely present in various bioactive natural and unnatural molecules. We are interested in antitumor activities of these obtained azepinones for exploitation of potential anticancer drugs.

The azepinones were then evaluated for their in vitro cytotoxic activities against six human tumor cell lines, including Jurkat, SMMC-7721, A-549, MCF-7, SW-480, and MDA-MB-231, using the (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium (MTS) method[17] with cisplatin (DDP) and paclitaxel as positive controls (Table 2, for detailed results see Table S1). Compounds **3l** and **3m** displayed significant inhibitory activity, with IC_{50} values ranging from 3.8 to 8.1 μM for all tested cell lines, which were comparable to that of cisplatin, while compounds **3b**, **3d**, and **3k** exhibited moderate cytotoxic potency. The remaining twenty-one azepinones were noncytotoxic against these tested systems (IC_{50} > 40 μM). The structure−activity relationship (SAR) analysis suggests that small or non-*N*-protecting groups on the oxindole motif as well as the halogen substitution at C-6 may contribute to the cytotoxicity. Thus, compounds **3b** and **3k** showed moderate cytotoxicity, while **3a** and **3c**−**3e** were inactive. Moreover, electron-deficiency or hydrophobic effect due to the halogen substitution at C-6 results in the increase of proliferation inhibitory activity, as in **3l** and **3m**.

CONCLUSION

In conclusion, we have developed an NHC-catalyzed asymmetric formal [3+4] annulation reaction of enals and azadienes, giving a series of benzofuroazepinones in good yields, with excellent diastereo- and enantioselectivities. The benzofuroazepinones obtained were evaluated for their in vitro cytotoxic activities against six human tumor cell lines, with two compounds showing significant cytotoxicity comparable with that of cisplatin. Further investigations on the related NHC-catalyzed annulation reactions to afford heterocycles and the anticancer mechanism of these bioactive compounds are underway in our laboratory.

EXPERIMENTAL SECTION

General Information. Unless otherwise indicated, all reactions were carried out under an N_2 atmosphere with magnetic stirring. Anhydrous THF, ether, 1,4-dioxane, and toluene were distilled from sodium and benzophenone. Anhydrous CH_2Cl_2 and acetonitrile were distilled from CaH_2. Chiral triazolium salts **A**,**B**;[16b,18] aurone-derived azadienes **1**;[19] and isatin-derived enals **2**[20] were prepared according to the literatures. HRMS were obtained with the mass analyzer of an orbitrap. Column chromatography was performed on silica gel 200−300 mesh. Cytotoxicity of all benzofuroazepinones was determined by the MTS method.[17] The IC_{50} values were calculated from the appropriate dose−response curves.

General Procedure for NHC-Catalyzed [3+4] Annulation of Isatin-Derived Enals with Aurone-Derived Azadienes. An oven-dried 25 mL Schlenk tube was charged with aurone-derived azadienes **1**

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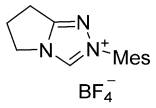
(0.1 mmol), enals **2** (0.12 mmol, 1.2 equiv), NHC precursor **A2** (5.27 mg. 0.01 mmol), and KOAc (1.96 mg. 0.02 mmol), and freshly distilled DCM (2 mL) was added. The reaction mixture was stirred at rt until the full consumption of the aurone-derived azadienes (typically 12 h). The reaction mixture was concentrated under reduced pressure, and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc as the eluent, typically 15:1 to 4:1) to furnish the desired cycloadducts **3a**−**3y**.

The procedure for gram-scaled annulation to afford **3a** is similar to the general procedure, except for lower catalyst (5 mol %) and base (10 mol %) loading.

Racemic samples for the chiral phase HPLC analysis were prepared using triazolium **C** as the pre-NHC under the same conditions.



C

*(4R,5R)-1′-Benzyl-5-phenyl-1-tosyl-1,5-dihydrospiro[benzofuro-[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3a**).* 57.3 mg. >20:1 dr. 90% yield. White solid. mp 100−102 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ + 14.1 (*c* 0.36, $CHCl_3$). HPLC analysis: 96% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 16.1 min (major), 24.7 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.12 (d, *J* = 8.0 Hz, 2H), 7.89 (d, *J* = 6.9 Hz, 1H), 7.59 (d, *J* = 7.6 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.41−7.39 (m, 2H), 7.22 (t, *J* = 6.5 Hz, 1H), 7.17−7.08 (m, 7H), 7.01 (t, *J* = 7.6 Hz, 1H), 6.89 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 7.4 Hz, 2H), 6.46 (d, *J* = 7.4 Hz, 1H), 6.29 (d, *J* = 7.8 Hz, 1H), 4.61 (d, *J* = 16.0 Hz, 1H), 4.51 (d, *J* = 16.0 Hz, 1H), 4.03 (s, 1H), 3.21 (d, *J* = 12.4 Hz, 1H), 2.57 (s, 3H), 2.18 (d, *J* = 12.4 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, δ): 174.7, 170.1, 154.3, 151.3, 145.9, 141.8, 135.5, 134.7, 130.8, 130.7, 129.7, 129.5, 129.0, 128.9, 128.6, 128.13, 128.08, 127.4, 126.8, 125.2, 124.8, 124.0, 123.6, 122.7, 120.6, 117.5, 112.2, 109.3, 62.0, 47.9, 43.8, 43.7, 21.8. IR (KBr): 2918, 1712, 1612, 1384, 1174, 749. HRMS (ESI): [M + Na]$^+$ calcd for $C_{39}H_{30}N_2O_5SNa$, 661.1768; found, 661.1762.

*(4R,5R)-1′-Methyl-5-phenyl-1-tosyl-1,5-dihydrospiro[benzofuro-[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3b**).* 55.7 mg. >20:1 dr. 99% yield. White solid. mp 118−120 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ −18.9 (*c* 1.09, $CHCl_3$). HPLC analysis: 93% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 11.4 min (major), 22.1 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.09 (d, *J* = 8.3 Hz, 2H), 7.90−7.88 (m, 1H), 7.58−7.56 (m, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.42−7.36 (m, 2H), 7.17−7.14 (m, 1H), 7.12−7.07 (m, 3H), 6.97 (d, *J* = 7.4 Hz, 2H), 6.94−6.91 (m, 1H), 6.55 (d, *J* = 7.4 Hz, 1H), 6.39 (d, *J* = 7.7 Hz, 1H), 3.87 (s, 1H), 3.18 (d, *J* = 12.5 Hz, 1H), 2.79 (s, 3H), 2.55 (s, 3H), 2.19 (d, *J* = 12.5 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, δ): 174.5, 170.6, 154.3, 151.2, 145.9, 142.5, 135.4, 130.5, 130.3, 129.6, 129.4, 129.2, 128.9, 128.2, 127.6, 125.1, 124.8, 124.0, 123.5, 122.8, 120.6, 117.4, 112.2, 107.9, 61.9, 48.7, 42.6, 25.9, 21.8. IR (KBr): 2926, 1712, 1611, 1142, 747. HRMS (ESI): [M + Na]$^+$ calcd for $C_{33}H_{26}N_2O_5SNa$, 585.1455; found, 585.1456.

*(4R,5R)-1′-Isopropyl-5-phenyl-1-tosyl-1,5-dihydrospiro-[benzofuro[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3c**).* 49.8 mg. >20:1 dr. 84% yield. White solid. mp 102−103 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ −5.5 (*c* 0.24, $CHCl_3$). HPLC analysis: 92% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 9.9 min (major), 18.9 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.10 (d, *J* = 8.3 Hz, 2H), 7.89−7.87 (m, 1H), 7.59−7.57 (m, 1H), 7.47 (d, *J* = 8.3 Hz, 2H), 7.40−7.37 (m, 2H), 7.16−7.15 (m, 1H), 7.12−7.07 (m, 3H), 7.04 (d, *J* = 7.3 Hz, 2H), 6.88 (t, *J* = 7.6 Hz, 1H), 6.59 (d, *J* = 7.9 Hz, 1H), 6.45 (d, *J* = 7.6 Hz, 1H), 4.29−4.26 (m, 1H), 3.91 (s, 1H), 3.15 (d, *J* = 12.4 Hz, 1H), 2.56 (s, 3H), 2.13 (d, *J* = 12.4 Hz, 1H), 1.19 (d, *J* = 7.0 Hz, 3H), 0.98 (d, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, δ): 174.1, 170.4, 154.2, 151.3, 145.9, 141.2, 135.5, 130.70, 130.65, 129.62, 129.57, 129.47, 128.6, 128.1, 127.8, 125.1, 124.8, 124.0, 123.8, 122.1, 120.6, 117.4, 112.2, 109.7, 61.4, 48.3, 43.7, 43.2, 21.8, 19.1, 18.5. IR (KBr): 2922, 1708, 1605, 1120, 1042. HRMS (ESI): [M + Na]$^+$ calcd for $C_{35}H_{30}N_2O_5SNa$, 613.1768; found, 613.1764.

*(4R,5R)-1′,5-diphenyl-1-tosyl-1,5-dihydrospiro[benzofuro[3,2-b]-azepine-4,3′-indoline]-2,2′(3H)-dione (**3d**).* 57.3 mg. >20:1 dr. 92% yield. White solid. mp 83−85 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ −6.0 (*c* 1.16, $CHCl_3$). HPLC analysis: 92% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 11.3 min (major), 16.3 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.12 (d, *J* = 8.4 Hz, 2H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.52−7.48 (m, 3H), 7.40−7.31 (m, 5H), 7.25−7.22 (m, 1H), 7.14 (t, *J* = 7.6 Hz, 2H), 7.08−7.02 (m, 3H), 6.96 (t, *J* = 7.6, Hz, 1H), 6.83 (d, *J* = 7.5 Hz, 2H), 6.62 (d, *J* = 7.5 Hz, 1H), 6.35 (d, *J* = 7.8 Hz, 1H), 3.99 (s, 1H), 3.27 (d, *J* = 12.4 Hz, 1H), 2.57 (s, 3H), 2.36 (d, *J* = 12.4 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, δ): 173.9, 170.5, 154.3, 151.1, 145.9, 142.6, 135.4, 133.5, 130.7, 130.6, 129.7, 129.50, 129.47, 129.0, 128.9, 128.3, 127.9, 126.2, 125.2, 124.8, 124.0, 123.8, 123.2, 120.6, 117.5, 112.2, 109.2, 62.0, 48.9, 43.0, 21.9. IR (KBr): 2924, 1716, 1610, 1180, 745. HRMS (ESI): [M + Na]$^+$ calcd for $C_{38}H_{28}N_2O_5SNa$, 647.1611; found, 647.1609.

*(4R,5R)-5-Phenyl-1′-(p-tolyl)-1-tosyl-1,5-dihydrospiro[benzofuro-[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3e**).* 61.7 mg. >20:1 dr. 97% yield. White solid. mp 150−152 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ −22.3 (*c* 1.07, $CHCl_3$). HPLC analysis: 92% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 11.5 min (major), 16.1 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.11 (d, *J* = 8.2 Hz, 2H), 7.89 (d, *J* = 7.5 Hz, 1H), 7.51−7.47 (m, 3H), 7.40−7.35 (m, 2H), 7.24−7.21 (m, 1H), 7.17−7.12 (m, 4H), 7.08−7.01 (m, 3H), 6.95 (t, *J* = 7.6 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 2H), 6.60 (d, *J* = 7.5 Hz, 1H), 6.33 (d, *J* = 7.8 Hz, 1H), 3.97 (s, 1H), 3.26 (d, *J* = 12.4 Hz, 1H), 2.57 (s, 3H), 2.36−2.33 (m, 4H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, δ): 174.0, 170.5, 154.3, 151.1, 145.9, 142.8, 138.3, 135.4, 130.8, 130.7, 130.6, 130.1, 129.7, 129.5, 129.0, 128.9, 128.3, 127.9, 126.0, 125.2, 124.8, 124.0, 123.8, 123.1, 120.6, 117.5, 112.2, 109.2, 62.0, 48.9, 43.0, 21.9, 21.2. IR (KBr): 2923, 1715, 1611, 1176, 750. HRMS (ESI): [M + Na]$^+$ calcd for $C_{39}H_{30}N_2O_5SNa$, 661.1768; found, 661.1767.

*(4R,5R)-1′-Benzyl-5′-methyl-5-phenyl-1-tosyl-1,5-dihydrospiro-[benzofuro[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3f**).* 39.9 mg. >20:1 dr. 61% yield. White solid. mp 69−71 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ + 30.8 (*c* 0.92, $CHCl_3$). HPLC analysis: 95% ee [Daicel CHIRALPAK IB column, 20 °C, 254 nm, hexane/*i*-PrOH = 85:15, 1.0 mL/min, 13.2 min (major), 16.7 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.13 (d, *J* = 8.1 Hz, 2H), 7.90−7.88 (m, 1H), 7.58−7.56 (m, 1H), 7.50 (d, *J* = 8.1 Hz, 2H), 7.40−7.37 (m, 2H), 7.22−7.21 (m, 1H), 7.15−7.08 (m, 7H), 6.79 (d, *J* = 7.9 Hz, 1H), 6.66 (d, *J* = 7.0 Hz, 2H), 6.18−6.15 (m, 2H), 4.60 (d, *J* = 16.0 Hz, 1H), 4.46 (d, *J* = 16.0 Hz, 1H), 4.00 (s, 1H), 3.20 (d, *J* = 12.4 Hz, 1H), 2.57 (s, 3H), 2.22 (s, 3H), 2.14 (d, *J* = 12.4 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 174.6, 170.0, 154.2, 151.3, 145.8, 139.4, 135.8, 134.9, 132.1, 131.0, 130.8, 129.7, 129.6, 129.2, 129.0, 128.6, 128.1, 127.4, 126.8, 125.1, 124.9, 124.3, 124.0, 120.6, 117.6, 112.2, 109.0, 62.0, 47.9, 43.8, 43.7, 21.8, 21.0. IR (KBr): 2923, 1710, 1602, 1172, 749. HRMS (ESI): [M + Na]$^+$ calcd for $C_{40}H_{32}N_2O_5SNa$, 675.1924; found, 675.1917.

*(4R,5R)-1′-Benzyl-5′-methoxy-5-phenyl-1-tosyl-1,5-dihydrospiro-[benzofuro[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3g**).* 57.7 mg. >20:1 dr. 86% yield. White solid. mp 151−153 °C. R_f = 0.2 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ + 56.0 (*c* 0.97, $CHCl_3$). HPLC analysis: 91% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 18.3 min (major), 23.7 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.10 (d, *J* = 8.2 Hz, 2H), 7.90−7.88 (m, 1H), 7.59−7.57 (m, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.40−7.37 (m, 2H), 7.25−7.23 (m, 1H), 7.16−7.12 (m, 7H), 6.68 (d, *J* = 6.8 Hz, 2H), 6.51 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.17 (d, *J* = 8.5 Hz, 1H), 6.08 (d, *J* = 2.5 Hz, 1H), 4.59 (d, *J* = 16.0 Hz, 1H), 4.48 (d, *J* = 16.0 Hz, 1H), 4.00 (s, 1H), 3.69 (s, 3H), 3.21 (d, *J* = 12.4 Hz, 1H), 2.55 (s, 3H), 2.17 (d, *J* = 12.4 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 174.4, 170.1, 156.0, 154.3, 151.2, 146.0, 135.6, 135.1, 134.8, 130.9, 130.7, 130.3, 129.7, 129.4, 128.6, 128.1, 127.4, 126.8, 125.2, 124.8, 124.0, 120.6, 117.6, 113.3, 112.2, 111.1, 109.7, 62.4, 55.7, 48.0, 43.8, 43.7,

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21.8. IR (KBr): 2919, 1709, 1598, 1172, 748. HRMS (ESI): $[M + Na]^+$ calcd for $C_{40}H_{32}N_2O_6SNa$, 691.1873; found, 691.1870.

(4R,5R)-1′-Benzyl-7′-methyl-5-phenyl-1-tosyl-1,5-dihydrospiro-[benzofuro[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3h**). 26.5 mg. >20:1 dr. 41% yield. White solid. mp 153−154 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ + 21.9 (*c* 0.45, $CHCl_3$). HPLC analysis: 93% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 14.2 min (major), 22.4 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.13 (d, *J* = 8.2 Hz, 2H), 7.88−7.87 (m, 1H), 7.57−7.55 (m, 1H), 7.50 (d, *J* = 8.2 Hz, 2H), 7.41−7.35 (m, 2H), 7.27−7.26 (m, 1H), 7.17−7.10 (m, 7H), 6.82−6.81 (m, 2H), 6.53 (d, *J* = 6.8 Hz, 2H), 6.29−6.28 (m, 1H), 4.88 (d, *J* = 17.1 Hz, 1H), 4.80 (d, *J* = 17.1 Hz, 1H), 4.07 (s, 1H), 3.20 (d, *J* = 12.3 Hz, 1H), 2.58 (s, 3H), 2.17 (d, *J* = 12.3 Hz, 1H), 1.92 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 175.7, 169.9, 154.2, 151.4, 145.9, 140.0, 136.8, 135.6, 132.9, 131.1, 130.9, 129.7, 129.6, 129.5, 128.7, 128.2, 128.1, 127.0, 125.3, 125.1, 124.8, 124.0, 122.7, 121.6, 120.5, 119.8, 117.4, 112.2, 61.5, 47.8, 45.0, 44.4, 21.8, 18.3. IR (KBr): 2919, 1713, 1605, 1171, 738. HRMS (ESI): $[M + Na]^+$ calcd for $C_{40}H_{32}N_2O_5SNa$, 675.1924; found, 675.1921.

(4R,5R)-1′-Benzyl-6′-chloro-5-phenyl-1-tosyl-1,5-dihydrospiro-[benzofuro[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3i**). 51.5 mg. >20:1 dr. 77% yield. White solid. mp 101−102 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ + 11.4 (*c* 0.33, $CHCl_3$). HPLC analysis: 90% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 13.2 min (major), 19.3 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.10 (d, *J* = 8.1 Hz, 2H), 7.90−7.88 (m, 1H), 7.59−7.57 (m, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.42−7.37 (m, 2H), 7.26−7.23 (m, 1H), 7.20−7.12 (m, 5H), 7.08 (d, *J* = 7.4 Hz, 2H), 6.88 (dd, *J* = 8.0, 1.9 Hz, 1H), 6.68 (*J* = 7.0 Hz, 2H), 6.38 (d, *J* = 8.0 Hz, 1H), 6.30 (d, *J* = 1.9 Hz, 1H), 4.58 (d, *J* = 16.0 Hz, 1H), 4.47 (d, *J* = 16.0 Hz, 1H), 3.96 (s, 1H), 3.18 (d, *J* = 12.4 Hz, 1H), 2.56 (s, 3H), 2.12 (d, *J* = 12.4 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 174.7, 169.9, 154.3, 150.9, 146.0, 143.0, 135.5, 134.8, 134.1, 130.6, 130.5, 129.6, 129.5, 128.8, 128.33, 128.26, 127.7, 127.5, 126.8, 125.3, 124.7, 124.5, 124.1, 122.7, 120.6, 117.6, 112.2, 109.9, 61.6, 47.8, 43.9, 43.6, 21.8. IR (KBr): 2921, 1713, 1607, 1175, 750. HRMS (ESI): $[M + Na]^+$ calcd for $C_{39}H_{29}ClN_2O_5SNa$, 695.1378; found, 695.1375.

(4R,5R)-1′-Benzyl-6′-bromo-5-phenyl-1-tosyl-1,5-dihydrospiro-[benzofuro[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3j**). 41.5 mg. >20:1 dr. 58% yield. White solid. mp 123−124 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ + 16.5 (*c* 0.17, $CHCl_3$). HPLC analysis: 87% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 14.6 min (major), 20.3 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.10 (d, *J* = 8.4 Hz, 2H), 7.90−7.88 (m, 1H), 7.59−7.57 (m, 1H), 7.48 (d, *J* = 8.4 Hz, 2H), 7.41−7.39 (m, 2H), 7.27−7.24 (m, 1H), 7.19−7.13 (m, 5H), 7.08−7.03 (m, 3H), 6.69 (d, *J* = 7.1 Hz, 2H), 6.45 (d, *J* = 1.7 Hz, 1H), 6.32 (d, *J* = 8.0 Hz, 1H), 4.58 (d, *J* = 16.0 Hz, 1H), 4.47 (d, *J* = 16.0 Hz, 1H), 3.96 (s, 1H), 3.18 (d, *J* = 12.4 Hz, 1H), 2.57 (s, 3H), 2.13 (d, *J* = 12.4 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, δ): 174.6, 169.9, 154.3, 150.9, 146.0, 143.1, 135.4, 134.1, 130.6, 130.5, 129.7, 129.5, 128.8, 128.4, 128.3, 128.0, 127.7, 126.8, 125.7, 125.3, 124.9, 124.7, 124.1, 122.7, 120.6, 117.6, 112.6, 112.2, 61.7, 47.7, 43.9, 43.6, 21.9. IR (KBr): 2919, 1714, 1604, 1180, 771. HRMS (ESI): $[M + Na]^+$ calcd for $C_{39}H_{29}BrN_2O_5SNa$, 739.0873; found, 739.0867.

(4R,5R)-5-Phenyl-1-tosyl-1,5-dihydrospiro[benzofuro[3,2-b]-azepine-4,3′-indoline]-2,2′(3H)-dione (**3k**). 48.6 mg. >20:1 dr. 89% yield. White solid. mp 193−194 °C. R_f = 0.2 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ −21.1 (*c* 0.24, $CHCl_3$). HPLC analysis: 93% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 11.5 min (major), 20.2 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.09 (d, *J* = 8.3 Hz, 2H), 7.87 (d, *J* = 7.0 Hz, 1H), 7.74 (s, 1H), 7.47 (d, *J* = 8.2 Hz, 2H), 7.40−7.33 (m, 2H), 7.21−7.18 (m, 1H), 7.13−7.00 (m, 4H), 6.99 (t, *J* = 8.3 Hz, 1H), 6.87 (t, *J* = 7.6 Hz, 1H), 6.42 (t, *J* = 6.8 Hz, 2H), 3.92 (s, 1H), 3.07 (d, *J* = 12.4 Hz, 1H), 2.57 (s, 3H), 2.15 (d, *J* = 12.4 Hz, 1H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 176.5, 170.2, 154.2, 151.2, 145.9, 139.5, 135.4, 130.6, 130.5, 129.6, 129.54, 129.48, 128.9, 128.2, 127.9, 125.1, 124.8, 124.0, 123.8, 122.7, 120.6, 117.4, 112.2, 109.7, 62.2, 48.2, 43.2, 21.8. IR (KBr): 2920, 1713, 1620, 1186, 746. HRMS (ESI): $[M + Na]^+$ calcd for $C_{32}H_{24}N_2O_5SNa$, 571.1298; found, 571.1295.

(4R,5R)-6′-Chloro-5-phenyl-1-tosyl-1,5-dihydrospiro[benzofuro-[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3l**). 41.2 mg. >20:1 dr. 71% yield. White solid. mp 163−165 °C. R_f = 0.2 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ + 18.1 (*c* 0.52, $CHCl_3$). HPLC analysis: 89% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 11.5 min (major), 17.5 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.08 (d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 7.4 Hz, 1H), 7.72 (s, 1H), 7.53 (d, *J* = 7.9 Hz, 1H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.42−7.36 (m, 2H), 7.22 (t, *J* = 7.2 Hz, 1H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.05−7.02 (m, 2H), 6.86 (dd, *J* = 8.1, 1.1 Hz, 1H), 6.47 (s, 1H), 6.35 (d, *J* = 8.0 Hz, 1H), 3.87 (s, 1H), 3.04 (d, *J* = 12.5 Hz, 1H), 2.58 (s, 3H), 2.12 (d, *J* = 12.5 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, δ): 176.3, 170.1, 154.2, 150.8, 146.0, 140.5, 135.3, 134.7, 130.5, 130.3, 129.7, 129.5, 128.4, 128.1, 128.0, 125.3, 124.8, 124.7, 124.1, 122.7, 120.7, 117.4, 112.2, 110.4, 61.9, 48.2, 43.0, 21.9. IR (KBr): 2923, 1715, 1612, 1086, 748. HRMS (ESI): $[M + Na]^+$ calcd for $C_{32}H_{23}ClN_2O_5SNa$, 605.0908; found, 605.0905.

(4R,5R)-6′-Bromo-5-phenyl-1-tosyl-1,5-dihydrospiro[benzofuro-[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3m**). 29.7 mg. >20:1 dr. 47% yield. White solid. mp 148−150 °C. R_f = 0.2 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ + 18.7 (*c* 0.55, $CHCl_3$). HPLC analysis: 90% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 11.9 min (major), 16.6 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.08 (d, *J* = 8.1 Hz, 2H), 7.89−7.87 (m, 1H), 7.63 (s, 1H), 7.56−7.54 (m, 1H), 7.47 (d, *J* = 8.1 Hz, 2H), 7.41−7.38 (m, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 2H), 7.05−7.02 (m, 3H), 6.65 (d, *J* = 1.7 Hz, 1H), 6.32 (d, *J* = 8.0 Hz, 1H), 3.86 (s, 1H), 3.08 (d, *J* = 12.4 Hz, 1H), 2.58 (s, 3H), 2.15 (d, *J* = 12.4 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, δ): 176.2, 170.0, 154.2, 150.7, 146.0, 140.7, 135.3, 130.5, 130.2, 129.7, 129.5, 128.51, 128.45, 128.1, 125.7, 125.3, 125.2, 124.7, 124.1, 122.6, 120.7, 117.5, 113.1, 112.2, 61.9, 48.1, 43.0, 21.9. IR (KBr): 2924, 1714, 1609, 1176, 747. HRMS (ESI): $[M + Na]^+$ calcd for $C_{32}H_{23}BrN_2O_5SNa$, 649.0403; found, 649.0400.

(4R,5R)-1′-Benzyl-5-(4-fluorophenyl)-1-tosyl-1,5-dihydrospiro-[benzofuro[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3n**). 62.5 mg. >20:1 dr. 95% yield. White solid. mp 160−162 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ + 7.5 (*c* 0.24, $CHCl_3$). HPLC analysis: 94% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 15.0 min (major), 25.7 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.12 (d, *J* = 8.1 Hz, 2H), 7.89−7.87 (m, 1H), 7.59−7.57 (m, 1H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.43−7.38 (m, 2H), 7.21−7.15 (m, 3H), 7.08−7.04 (m, 3H), 6.91 (t, *J* = 7.5 Hz, 1H), 6.77 (t, *J* = 8.6 Hz, 2H), 6.72 (d, *J* = 6.9 Hz, 2H), 6.46 (d, *J* = 7.4 Hz, 1H), 6.37 (d, *J* = 7.8 Hz, 1H), 4.64 (d, *J* = 15.9 Hz, 1H), 4.50 (d, *J* = 15.9 Hz, 1H), 4.06 (s, 1H), 3.19 (d, *J* = 12.4 Hz, 1H), 2.57 (s, 3H), 2.17 (d, *J* = 12.4 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, δ): 174.5, 170.0, 162.5 (J_{CF} = 247.9 Hz), 154.2, 150.9, 146.0, 141.8, 135.5, 134.6, 132.4 (J_{CF} = 8.1 Hz), 129.6, 129.5, 129.1, 128.9, 128.6, 127.6, 126.9, 126.6 (J_{CF} = 3.2 Hz), 125.3, 124.7, 124.1, 123.6, 122.9, 120.6, 117.5, 115.0 (J_{CF} = 21.4 Hz), 112.2, 109.4, 61.9, 47.1, 43.8, 43.6, 21.8. ^{19}F NMR (376 MHz, $CDCl_3$): −113.4 (Ar−F). IR (KBr): 2920, 1714, 1610, 1175, 771. HRMS (ESI): $[M + Na]^+$ calcd for $C_{39}H_{29}FN_2O_5SNa$, 679.1673; found, 679.1668.

(4R,5R)-1′-Benzyl-5-(4-bromophenyl)-1-tosyl-1,5-dihydrospiro-[benzofuro[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3o**). 57.6 mg. >20:1 dr. 80% yield. White solid. mp 146−147 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ + 17.5 (*c* 0.24, $CHCl_3$). HPLC analysis: 93% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 15.1 min (major), 25.9 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.11 (d, *J* = 8.0 Hz, 2H), 7.89−7.88 (m, 1H), 7.58−7.57 (m, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.43−7.38 (m, 2H), 7.26−7.21 (m, 5H), 7.06 (t, *J* = 7.7 Hz, 1H) 6.96−6.90 (m, 3H), 6.70−6.69 (m, 2H), 6.47 (d, *J* = 7.4 Hz, 1H), 6.38 (d, *J* = 7.8 Hz, 1H), 4.73 (d, *J* = 16.0 Hz, 1H), 4.46 (d, *J* = 16.0 Hz, 1H), 4.01 (s, 1H), 3.18 (d, *J* = 12.4 Hz, 1H), 2.56 (s, 3H), 2.16 (d, *J* = 12.4 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, δ): 174.4, 169.9, 154.2, 150.6, 145.9, 141.8, 135.5, 134.5, 132.3, 131.3, 129.8, 129.6, 129.5, 129.1, 128.72, 128.68, 127.6, 126.8, 125.3, 124.7, 124.1, 123.5, 122.9, 122.6,

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120.6, 117.6, 112.2, 109.5, 61.7, 47.2, 43.8, 43.7, 21.8. IR (KBr): 2921, 1713, 1612, 1174, 770. HRMS (ESI): $[M + Na]^+$ calcd for $C_{39}H_{29}BrN_2O_5SNa$, 739.0873; found, 739.0866.

(4R,5R)-1′-Benzyl-5-(p-tolyl)-1-tosyl-1,5-dihydrospiro[benzofuro-[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3p**). 59.9 mg. >20:1 dr. 92% yield. White solid. mp 135−136 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ + 10.6 (*c* 0.26, $CHCl_3$). HPLC analysis: 92% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 14.9 min (major), 20.7 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.10 (d, *J* = 8.3 Hz, 2H), 7.89−7.88(m, 1H), 7.58−7.56 (m, 1H), 7.48 (d, *J* = 8.1 Hz, 2H), 7.40−7.38 (m, 2H), 7.18−7.16 (m, 1H), 7.13−7.11 (m, 2H), 7.03−7.00 (m, 1H), 6.97 (d, *J* = 8.2 Hz, 2H), 6.92−6.89 (m, 3H), 6.71 (d, *J* = 7.1 Hz, 2H), 6.44 (d, *J* = 7.7, 1H), 6.31 (d, *J* = 7.8 Hz, 1H), 4.69 (d, *J* = 16.0 Hz, 1H), 4.48 (d, *J* = 16.0 Hz, 1H), 3.97 (s, 1H), 3.19 (d, *J* = 12.3 Hz, 1H), 2.56 (s, 3H), 2.27 (s, 3H), 2.16 (d, *J* = 12.3 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, δ): 174.8, 170.2, 154.2, 151.5, 145.9, 141.8, 137.9, 135.5, 134.8, 130.6, 129.7, 129.5, 129.2, 128.8, 128.5, 127.7, 127.4, 126.9, 125.1, 124.8, 124.0, 123.6, 122.7, 120.6, 117.3, 112.2, 109.3, 61.9, 47.4, 43.8, 43.7, 21.8, 21.2. IR (KBr): 2923, 2851, 1714, 1618, 1175. HRMS (ESI): [M + Na]$^+$ calcd for $C_{40}H_{32}N_2O_5SNa$, 675.1924; found, 675.1917.

(4R,5R)-1′-Benzyl-5-(4-methoxyphenyl)-1-tosyl-1,5-dihydrospiro-[benzofuro[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3q**). 56.5 mg. >20:1 dr. 85% yield. White solid. mp 132−133 °C. R_f = 0.2 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ + 24. (*c* 0.27, $CHCl_3$). HPLC analysis: 95% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 16.3 min (major), 28.5 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.11 (d, *J* = 8.0 Hz, 2H), 7.88 (d, *J* = 7.1 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 2H), 7.42−7.37 (m, 2H), 7.17−7.11 (m, 3H), 7.04−7.01 (m, 3H), 6.89 (t, *J* = 7.6 Hz, 1H), 6.68 (d, *J* = 7.3 Hz, 2H), 6.63 (d, *J* = 8.3 Hz, 2H), 6.42 (d, *J* = 7.5 Hz, 1H), 6.31 (d, *J* = 7.8 Hz, 1H), 4.69 (d, *J* = 16.0 Hz, 1H), 4.49 (d, *J* = 16.0 Hz, 1H), 4.01 (s, 1H), 3.74 (s, 3H), 3.19 (d, *J* = 12.4 Hz, 1H), 2.57 (s, 3H), 2.16 (d, *J* = 12.4 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, δ): 174.7, 170.1, 159.3, 154.2, 151.6, 145.9, 141.8, 135.5, 134.7, 131.8, 129.6, 129.5, 129.2, 128.8, 128.5, 127.4, 126.8, 125.1, 124.8, 124.0, 123.5, 122.73, 122.67, 120.5, 117.2, 113.4, 112.2, 109.3, 62.0, 55.1, 47.0, 43.7, 43.6, 21.8. IR (KBr): 2923, 2852, 1714, 1612, 1175, 748. HRMS (ESI): [M + Na]$^+$ calcd for $C_{40}H_{32}N_2O_6SNa$, 691.1873; found, 691.1868.

(4R,5R)-1′-Benzyl-5-(3-chlorophenyl)-1-tosyl-1,5-dihydrospiro-[benzofuro[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3r**). 64.6 mg. >20:1 dr. 96% yield. White solid. mp 73−74 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ + 14.9 (*c* 0.27, $CHCl_3$). HPLC analysis: 92% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 14.4 min (major), 26.0 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.10 (d, *J* = 8.1 Hz, 2H), 7.90−7.89 (m, 1H), 7.61−7.59 (m, 1H), 7.49 (d, *J* = 8.0 Hz, 2H), 7.42−7.40 (m, 2H), 7.20−7.16 (m, 4H), 7.07−7.03 (m, 3H), 6.93 (t, *J* = 7.2 Hz, 2H), 6.81−6.79 (m, 2H), 6.51 (d, *J* = 7.4 Hz, 1H), 6.36 (d, *J* = 7.9 Hz, 1H), 4.61 (d, *J* = 15.9 Hz, 1H), 4.56 (d, *J* = 15.9 Hz, 1H), 3.87 (s, 1H), 3.18 (d, *J* = 12.4 Hz, 1H), 2.58 (s, 3H), 2.20 (d, *J* = 12.4 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, δ): 174.5, 170.1, 154.3, 150.5, 146.1, 141.7, 135.3, 134.7, 133.7, 132.8, 130.8, 129.7, 129.4, 129.3, 129.2, 128.8, 128.7, 128.6, 128.4, 127.6, 126.9, 125.4, 124.7, 124.2, 123.6, 122.9, 120.7, 117.6, 112.3, 109.4, 61.8, 47.5, 43.9, 43.7, 21.8. IR (KBr): 2920, 1714, 1611, 1180, 749. HRMS (ESI): [M + Na]$^+$ calcd for $C_{39}H_{29}ClN_2O_5SNa$, 695.1378; found, 695.1373.

(4R,5R)-1′-Benzyl-5-(3-methoxyphenyl)-1-tosyl-1,5-dihydrospiro-[benzofuro[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3s**). 63.4 mg. >20:1 dr. 95% yield. White solid. mp 230−231 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ + 22.5 (*c* 0.73, $CHCl_3$). HPLC analysis: 87% ee [Daicel CHIRALPAK IB column, 20 °C, 254 nm, hexane/*i*-PrOH = 85:15, 1.0 mL/min, 18.6 min (major), 23.5 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.12 (d, *J* = 8.1 Hz, 2H), 7.90−7.88 (m, 1H), 7.59−7.57 (m, 1H), 7.49 (d, *J* = 8.1 Hz, 2H), 7.42−7.37 (m, 2H), 7.17−7.12 (m, 3H), 7.05−7.00 (m, 2H), 6.89 (t, *J* = 7.6 Hz, 1H), 6.77 (dd, *J* = 8.2, 2.5 Hz, 1H), 6.72−6.69 (m, 3H), 6.64 (s, 1H), 6.44 (d, *J* = 7.4 Hz, 1H), 6.32 (d, *J* = 7.8 Hz, 1H), 4.67 (d, *J* = 16.0 Hz, 1H), 4.50 (d, *J* = 16.0 Hz, 1H), 4.00 (s, 1H), 3.59 (s, 3H), 3.20 (d, *J* = 12.4 Hz, 1H), 2.56 (s, 3H), 2.17 (d, *J* = 12.4 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, δ): 174.7, 170.1, 159.0, 154.3, 151.2, 145.9, 141.9, 135.5, 134.8, 132.2, 129.7, 129.5, 129.1, 129.0, 128.9, 128.6, 127.4, 126.7, 125.2, 124.8, 124.0, 123.6, 123.0, 122.7, 120.6, 117.5, 116.2, 114.1, 112.2, 109.4, 61.9, 55.1, 47.8, 43.8, 21.8. IR (KBr): 2923, 1712, 1610, 1175, 749. HRMS (ESI): [M + Na]$^+$ calcd for $C_{40}H_{32}N_2O_6SNa$, 691.1873; found, 691.1874.

(4R,5R)-1′-Benzyl-5-(o-tolyl)-1-tosyl-1,5-dihydrospiro[benzofuro-[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3t**). 64.5 mg. >20:1 dr. 99% yield. White solid. mp 154−155 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ −32.0 (*c* 0.84, $CHCl_3$). HPLC analysis: 80% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 14.5 min (major), 22.2 min (minor)]. ^{1}H NMR (400 MHz, $CDCl_3$, δ): 8.18 (d, *J* = 8.1 Hz, 2H), 8.03−8.00 (m, 1H), 7.92−7.90 (m, 1H), 7.52 (d, *J* = 7.3 Hz, 1H), 7.45 (d, *J* = 8.1 Hz, 2H), 7.40−7.35 (m, 2H), 7.17−7.09 (m, 5H), 7.02 (t, *J* = 7.7 Hz, 1H), 6.91−6.82 (m, 5H), 6.34 (d, *J* = 7.8 Hz, 1H), 4.81 (s, 1H), 4.69 (d, *J* = 15.9 Hz, 1H), 4.60 (d, *J* = 15.9 Hz, 1H), 3.25 (d, *J* = 12.4 Hz, 1H), 2.52 (s, 3H), 2.19 (d, *J* = 12.4 Hz, 1H), 1.62 (s, 3H). ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$, δ): 175.4, 170.2, 154.1, 151.2, 145.8, 141.8, 136.4, 135.5, 134.8, 131.5, 130.4, 129.8, 129.6, 129.4, 129.1, 128.7, 128.0, 127.5, 127.1, 126.0, 125.1, 124.8, 124.2, 123.9, 122.5, 120.8, 117.1, 112.2, 109.2, 62.3, 44.3, 44.0, 41.8, 21.8, 19.7. IR (KBr): 2920, 1710, 1611, 1174, 749. HRMS (ESI): [M + Na]$^+$ calcd for $C_{40}H_{32}N_2O_5SNa$, 675.1924; found, 675.1924.

(4R,5R)-1′-Benzyl-5-(thiophen-2-yl)-1-tosyl-1,5-dihydrospiro-[benzofuro[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3u**). 55.7 mg. >20:1 dr. 86% yield. White solid. mp 216−217 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ + 28.4 (*c* 1.25, $CHCl_3$). HPLC analysis: 94% ee [Daicel CHIRALPAK IB column, 20 °C, 254 nm, hexane/*i*-PrOH/MeOH = 90:8:2, 1.0 mL/min, 22.8 min (major), 29.5 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.09 (d, *J* = 8.3 Hz, 2H), 7.90−7.88 (m, 1H), 7.63−7.61 (m, 1H), 7.48 (d, *J* = 8.3 Hz, 2H), 7.43−7.39 (m, 2H), 7.17−7.14 (m, 4H), 7.09−7.07 (m, 2H), 6.93 (t, *J* = 7.6 Hz, 1H), 6.87−6.85 (m, 1H), 6.76−6.74 (m, 2H), 6.39 (d, *J* = 7.8 Hz, 2H), 4.69 (d, *J* = 16.0 Hz, 1H), 4.52 (d, *J* = 16.0 Hz, 1H), 4.30 (s, 1H), 3.14 (d, *J* = 12.4 Hz, 1H), 2.54 (s, 3H), 2.17 (d, *J* = 12.4 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, δ): 174.6, 169.9, 154.3, 150.2, 146.1, 142.2, 135.3, 134.8, 131.1, 129.8, 129.3, 129.2, 129.1, 128.7, 127.5, 127.0, 126.9, 125.38, 125.37, 124.8, 124.2, 123.5, 122.9, 120.6, 117.5, 112.3, 109.4, 61.9, 43.8, 43.5, 42.7, 21.8. IR (KBr): 2920, 1714, 1612, 1174, 748. HRMS (ESI): [M + Na]$^+$ calcd for $C_{37}H_{28}N_2O_5S_2Na$, 667.1332; found, 667.1329.

(4R,5R)-1′-Benzyl-5-(naphthalen-1-yl)-1-tosyl-1,5-dihydrospiro-[benzofuro[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3v**). 64.7 mg. >20:1 dr. 94% yield. White solid. mp 228−230 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ −104.4 (*c* 0.73, $CHCl_3$). HPLC analysis: 85% ee [Daicel CHIRALPAK IB column, 20 °C, 254 nm, hexane/*i*-PrOH/MeOH = 90:8:2, 1.0 mL/min, 21.8 min (major), 26.2 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.30 (d, *J* = 7.4 Hz, 1H), 8.21 (d, *J* = 8.0 Hz, 2H), 7.94 (d, *J* = 7.5 Hz, 1H), 7.71 (d, *J* = 8.2 Hz, 1H), 7.67 (d, *J* = 8.1 Hz, 1H), 7.56−7.51 (m, 3H), 7.41−7.35 (m, 3H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.18−7.10 (m, 4H), 7.04 (d, *J* = 8.7 Hz, 1H), 6.79−6.76 (m, 4H), 6.70 (t, *J* = 7.5 Hz, 1H), 6.16 (d, *J* = 7.7 Hz, 1H), 5.43 (s, 1H), 4.64 (d, *J* = 15.9 Hz, 1H), 4.56 (d, *J* = 15.9 Hz, 1H), 3.35 (d, *J* = 12.3 Hz, 1H), 2.64 (s, 3H), 2.27 (d, *J* = 12.3 Hz, 1H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$, δ): 175.4, 170.3, 154.2, 151.1, 145.7, 141.5, 135.8, 134.8, 133.5, 131.4, 130.0 129.9, 129.8, 128.89, 128.87, 128.7, 127.5, 127.0, 126.7, 125.4, 125.2, 125.1, 124.9, 124.3, 124.0, 122.5, 122.3, 120.9, 117.5, 112.2, 109.0, 62.7, 44.4, 43.9, 39.9, 22.1. IR (KBr): 2920, 1711, 1612, 1174, 749. HRMS (ESI): [M + Na]$^+$ calcd for $C_{43}H_{32}N_2O_5SNa$, 711.1924; found, 711.1927.

(4R,5R)-1′-Benzyl-9-fluoro-5-phenyl-1-tosyl-1,5-dihydrospiro-[benzofuro[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3w**). 61.9 mg. >20:1 dr. 94% yield. White solid. mp 116−118 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ + 10.0 (*c* 0.99, $CHCl_3$). HPLC analysis: 96% ee [Daicel CHIRALPAK IA column, 20 °C, 210 nm, hexane/*i*-PrOH = 80:20, 1.0 mL/min, 16.4 min (major), 25.4 min (minor)]. ^{1}H NMR (500 MHz, $CDCl_3$, δ): 8.10 (d, *J* = 8.0 Hz, 2H), 7.56−7.48 (m, 4H), 7.24−7.21 (m, 1H), 7.17−7.05 (m, 8H), 7.01 (t, *J*

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= 7.8 Hz, 1H), 6.90 (t, J = 7.4 Hz, 1H), 6.71 (d, J = 7.1 Hz, 2H), 6.48 (d, J = 7.4 Hz, 1H), 6.30 (d, J = 7.8 Hz, 1H), 4.61 (d, J = 15.9 Hz, 1H), 4.52 (d, J = 15.9 Hz, 1H), 3.99 (s, 1H), 3.19 (d, J = 12.4 Hz, 1H), 2.57 (s, 3H), 2.19 (d, J = 12.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, δ): 174.7, 169.9, 159.8 (J_{CF} = 239.4 Hz), 153.2, 150.4, 146.1, 141.8, 135.3, 134.7, 130.6, 130.5, 129.7, 129.5, 129.0, 128.9, 128.6, 128.2, 128.1, 127.5, 126.9, 125.7 (J_{CF} = 11.2 Hz), 123.6, 122.8, 117.6 (J_{CF} = 3.8 Hz), 113.2 (J_{CF} = 19.2 Hz), 113.1, 109.4, 106.5 (J_{CF} = 26.4 Hz), 61.8, 47.9, 43.8, 43.6, 21.8. ^{19}F NMR (376 MHz, $CDCl_3$): −118.4 (Ar−F). IR (KBr): 2920, 1711, 1609, 1176, 750. HRMS (ESI): $[M + Na]^+$ calcd for $C_{39}H_{29}FN_2O_5SNa$, 679.1673; found, 679.1674.

*(4R,5R)-1′-Benzyl-8-fluoro-5-phenyl-1-tosyl-1,5-dihydrospiro-[benzofuro[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3x**).* 64.3 mg. >20:1 dr. 98% yield. White solid. mp 118−121 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ + 17.7 (c 0.87, $CHCl_3$). HPLC analysis: 91% ee [Daicel CHIRALPAK IA column, 20 °C, 210 nm, hexane/i-PrOH = 80:20, 1.0 mL/min, 17.5 min (major), 29.6 min (minor)]. ^1H NMR (500 MHz, $CDCl_3$, δ): 8.10 (d, J = 7.9 Hz, 2H), 7.82 (dd, J = 8.7, 5.3 Hz, 1H), 7.49 (d, J = 8.0 Hz, 2H), 7.31 (d, J = 8.6 Hz, 1H), 7.24−7.09 (m, 7H), 7.05−7.00 (m, 3H), 6.89 (t, J = 7.6 Hz, 1H), 6.71 (d, J = 7.3 Hz, 2H), 6.45 (d, J = 7.3 Hz, 1H), 6.30 (d, J = 7.6 Hz, 1H), 4.61 (d, J = 16.0 Hz, 1H), 4.52 (d, J = 16.0 Hz, 1H), 3.96 (s, 1H), 3.19 (d, J = 12.4 Hz, 1H), 2.57 (s, 3H), 2.19 (d, J = 12.4 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, δ): 174.7, 170.0, 161.2 (J_{CF} = 243.9 Hz), 154.1 (J_{CF} = 13.7 Hz), 151.9 (J_{CF} = 3.8 Hz), 146.1, 141.8, 135.3, 134.7, 130.6, 130.0, 129.7, 129.5, 129.0, 128.9, 128.6, 128.2, 128.1, 128.0, 127.5, 126.9, 123.5, 122.8, 121.3 (J_{CF} = 10.1 Hz), 117.4, 112.6 (J_{CF} = 24.2 Hz), 109.4, 100.0 (J_{CF} = 26.9 Hz), 62.0, 47.9, 43.8, 43.7, 21.8. ^{19}F NMR (376 MHz, $CDCl_3$): −115.7 (Ar−F). IR (KBr): 2924, 1714, 1611, 1175, 750. HRMS (ESI): $[M + Na]^+$ calcd for $C_{39}H_{29}FN_2O_5SNa$, 679.1673; found, 679.1673.

*(4R,5R)-1′-Benzyl-9-methyl-5-phenyl-1-tosyl-1,5-dihydrospiro-[benzofuro[3,2-b]azepine-4,3′-indoline]-2,2′(3H)-dione (**3y**).* 42.7 mg. >20:1 dr. 65% yield. White solid. mp 270−271 °C. R_f = 0.3 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ + 27.7 (c 0.30, $CHCl_3$). HPLC analysis: 93% ee [Daicel CHIRALPAK IA column, 20 °C, 210 nm, hexane/i-PrOH = 80:20, 1.0 mL/min, 17.8 min (major), 26.6 min (minor)]. ^1H NMR (500 MHz, $CDCl_3$, δ): 8.11 (d, J = 8.0 Hz, 2H), 7.67 (s, 1H), 7.49−7.45 (m, 3H), 7.25−7.06 (m, 9H), 6.99 (t, J = 7.8 Hz, 1H), 6.87 (t, J = 7.5 Hz, 1H), 6.68 (d, J = 7.1 Hz, 2H), 6.40 (d, J = 7.4 Hz, 1H), 6.28 (d, J = 7.8 Hz, 1H), 4.61 (d, J = 16.0 Hz, 1H), 4.50 (d, J = 16.0 Hz, 1H), 3.98 (s, 1H), 3.19 (d, J = 12.3 Hz, 1H), 2.57 (s, 3H), 2.52 (s, 3H), 2.16 (d, J = 12.3 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, δ): 174.7, 170.2, 152.8, 151.3, 145.9, 141.8, 135.5, 134.7, 133.7, 130.9, 130.7, 129.6, 129.5, 129.1, 128.9, 128.6, 128.10, 128.06, 127.4, 126.8, 126.6, 124.8, 123.6, 122.7, 120.2, 117.2, 111.8, 109.3, 62.0, 47.9, 43.8, 43.6, 21.8, 21.6. IR (KBr): 2921, 1713, 1610, 1176, 749. HRMS (ESI): $[M + Na]^+$ calcd for $C_{40}H_{32}N_2O_5SNa$, 675.1924; found, 675.1920.

*(4R,5R)-1′-Benzyl-5-phenyl-1,5-dihydrospiro[benzofuro[3,2-b]-azepine-4,3′-indoline]-2,2′(3H)-dione (**4**).* To a solution of naphthalene (128 mg. 1 mmol, 10.0 equiv) in DME (4 mL) was added sodium (23 mg. 1 mmol, 10.0 equiv) at room temperature. The reaction mixture was stirred for 3 h at room temperature and then cooled down to −78 °C. Compound **3a** (63.8 mg. 99% ee, 0.1 mmol, 1.0 equiv) in DME (2 mL) was added to the above mixture at −78 °C. After being stirred for 20 min, the reaction was quenched with water, and the mixture was extracted with DCM. The organic extracts were washed with brine and dried over Na_2SO_4. The solvent was removed, and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 10:1−2:1 as the eluent) to afford **4** as a white solid. 34.4 mg. >20:1 dr. 71% yield. mp 159−160 °C. R_f = 0.2 (petroleum ether/ethyl acetate 2:1). $[\alpha]_D^{23}$ −79.3 (c 0.30, $CHCl_3$). HPLC analysis: 95% ee [Daicel CHIRALPAK IB column, 20 °C, 254 nm, hexane/i-PrOH = 70:30, 1.0 mL/min, 14.9 min (minor), 18.2 min (major)]. ^1H NMR (500 MHz, $CDCl_3$, δ): 8.60 (brs, 1H), 7.64 (d, J = 6.5 Hz, 1H), 7.44−7.42 (m, 1H), 7.28−7.24 (m, 3H), 7.20−7.17 (m, 1H), 7.16−7.12 (m, 3H), 7.08 (t, J = 7.4 Hz, 2H), 7.02 (t, J = 7.6 Hz, 2H), 6.81 (d, J = 7.6 Hz, 2H), 6.46 (d, J = 7.4 Hz, 2H), 6.39−6.37 (m, 1H), 4.95 (s, 1H), 4.79 (d, J = 16.0 Hz, 1H), 4.23 (d, J = 16.0 Hz, 1H), 3.54 (d, J = 14.2 Hz, 1H), 2.88 (d, J = 14.2 Hz, 1H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, δ): 174.1, 170.6, 152.9, 142.4, 142.2, 136.0, 134.9, 132.8, 129.7, 128.9, 128.5, 128.1, 127.6, 127.1, 126.6, 125.1, 123.5, 122.9, 122.8, 122.6, 118.2, 118.0, 111.3, 109.6, 52.4, 51.9, 44.4, 43.6. IR (KBr): 2921, 1714, 1614, 1162, 750. HRMS (ESI): $[M + H]^+$ calcd for $C_{32}H_{25}N_2O_3$, 485.1860; found, 485.1858.

*Methyl 2-((R)-1-Benzyl-3-((R)-(3-((4-methylphenyl)sulfonamido)-benzofuran-2-yl)(phenyl)methyl)-2-oxoindolin-3-yl)acetate (**5**).* To a dry Schlenk tube equipped with a magnetic stir bar was added **3a** (63.8 mg. 0.1 mmol) and Mg-powder (14.4 mg. 6 equiv). The tube was sealed with a septum, evacuated, and refilled with nitrogen 3 times. Then, absolute MeOH (2 mL) was added, and the reaction was sonicated at room temperature until no more starting material remained, which was monitored by TLC (around 5 h). The reaction mixture was diluted with DCM and vacuum filtered through Celite, the filtrate was removed under reduced pressure, and the residue was purified by chromatography on silica gel (petroleum ether/EtOAc 6:1) to afford product **5**. 55.3 mg. >20:1 dr. 83% yield. White solid. mp 80−82 °C. R_f = 0.1 (petroleum ether/ethyl acetate 3:1). $[\alpha]_D^{23}$ + 7.2 (c 0.38, $CHCl_3$). HPLC analysis: 90% ee [Daicel CHIRALPAK IA column, 20 °C, 254 nm, hexane/i-PrOH = 60:40, 1.0 mL/min, 17.7 min (minor), 53.8 min (major)]. ^1H NMR (500 MHz, $CDCl_3$, δ): 7.68 (d, J = 6.9 Hz, 1H), 7.53 (d, J = 8.0 Hz, 2H), 7.31−7.19 (m, 5H), 7.13−6.96 (m, 9H), 6.89−6.84 (m, 3H), 6.70 (d, J = 7.5 Hz, 2H), 6.41 (d, J = 7.8 Hz, 1H), 4.66 (d, J = 15.8 Hz, 1H), 4.43 (d, J = 15.8 Hz, 1H), 4.23 (s, 1H), 3.29 (s, 3H), 3.03 (d, J = 16.0 Hz, 1H), 2.67 (d, J = 16.0 Hz, 1H), 2.34 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$, δ): 179.8, 169.4, 153.4, 150.0, 143.7, 143.4, 136.6, 134.8, 133.7, 130.9, 129.7, 128.8, 128.5, 128.1, 127.9, 127.8, 127.24, 127.16, 126.7, 125.4, 125.0, 124.9, 123.4, 122.1, 121.2, 115.5, 111.1, 109.4, 53.6, 51.7, 48.2, 44.4, 40.6, 21.6. IR (KBr): 2919, 1714, 1654, 1166, 1040. HRMS (ESI): $[M + Na]^+$ calcd for $C_{40}H_{34}N_2O_6SNa$, 693.2030; found, 693.2031.

Cytotoxic Activities of Benzofuroazepinones against Six Human Tumor Cell Lines. Cytotoxicity of all benzofuroazepinones was determined by the MTS method. Briefly, 5×10^3 cells were plated in 96-well plates 12 h before treatment and continuously exposed to test compounds for 48 h. Then, (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium, MTS) (Promega) was added to each well. The samples were incubated at 37 °C for 1−4 h, and the optical density (OD) was measured at 490 nm using a microplate reader (PerkinElmer). The IC_{50} values were calculated from the appropriate dose−response curves.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.8b02497.

Full cytotoxic activity; X-ray data; and copies of ^1H, ^{13}C, and ^{19}F NMR, and HPLC spectra (PDF)

X-ray crystallographic data for compound **3o** (CIF)

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Notes

The authors declare no competing financial interest.

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