

Phosphine-Catalyzed Synthesis of 3,3-Spirocyclopenteneoxindoles from γ -Substituted Allenates: Systematic Studies and Targeted Applications

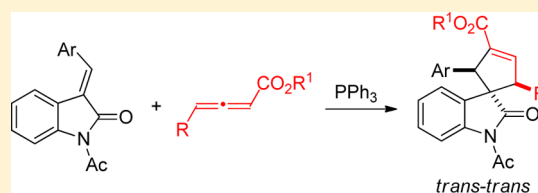
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Supporting Information

ABSTRACT: The phosphine-promoted [3 + 2] cyclizations between γ -substituted allenates and arylideneoxindoles have been applied to the stereoselective synthesis of spiro(cyclopentene)oxindoles with trisubstituted cyclopentene units. It has been demonstrated that PPh₃ operates a very efficient control of the relative stereochemistry of the three stereogenic centers of the final spiranic products. Focused experiments have been carried out then so as to access carbocyclic analogues of an important series of anticancer agents inhibiting MDM2-p53 interactions.

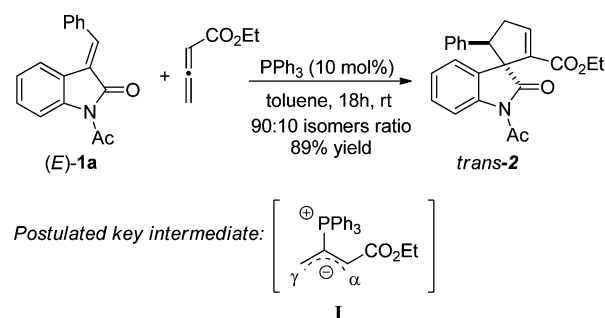


INTRODUCTION

Spirocyclic oxindoles are common scaffolds for natural products as well as privileged core elements of medicinal agents largely inspired by those natural products. In particular, spirooxindoles with carbocyclic five-membered rings are featured in some series of naturally occurring products including citrinadins, cyclopiamines, and notoamides as well as in synthetic bioactive compounds.¹ For the synthesis of these challenging substructures, organocatalytic approaches have been eagerly sought in recent years.² Our contribution to this effort has been to define an efficient access to 3-cyclopentene-spirooxindoles under phosphine catalysis, based on Lu's [3 + 2] cyclization³ between electron-poor olefins and allenes.⁴ Starting from arylideneoxindoles and 2,3-butadienoates, our method affords multifunctional 2,5-disubstituted cyclopentene units in a diastereoselective and highly enantioselective manner (Scheme 1). Later, Wei and Shi adapted the same [3 + 2] cyclization

strategy to isatin-derived enones;⁵ these doubly activated substrates reacted properly with ethyl 2,3-pentadienoate via a supposed γ -addition process while they afforded intractable mixtures in their reactions with ethyl 2,3-butadienoate. Other phosphine-promoted annulations have been also applied to the synthesis of spirocyclic oxindoles, including the reaction of arylidene oxindoles with Morita–Baylis–Hillman adducts⁶ and other 1,3-dipolar cycloadditions.⁷ Given the significance and biological relevance of the spiro-cyclopentane core structures, as well as the potential synthetic usefulness of our organocatalytic method above, we decided to expand its scope so as to access spiranes with trisubstituted cyclopentene units, starting from 3-arylidene oxindoles and 4-substituted allenates. Through systematic studies, we have demonstrated that these reactions take place with different regio- and stereochemical control, with respect to those described by Wei and Shi.⁵ Moreover, we have demonstrated that the method enables the synthesis of new carbon analogues of a well-known series of P53-MDM2 inhibitors, via a simple, three-step reaction sequence. The method thus affords a new starting point for the synthesis of bioinspired compound collections. The main results of these studies are summarized hereafter.

Scheme 1. Phosphine-Promoted Synthesis of 2,5-Disubstituted Spiro(cyclopentene)oxindoles⁴



RESULTS AND DISCUSSION

The phosphine-based organocatalytic cyclization methods known so far to access spirocyclopentene oxindoles, afford complementary series of spiranic derivatives whose specific substitution patterns depend on the substrate pairs and cyclization modes.^{5–8} The [3 + 2] cyclizations of 2,3-

Received: November 23, 2012

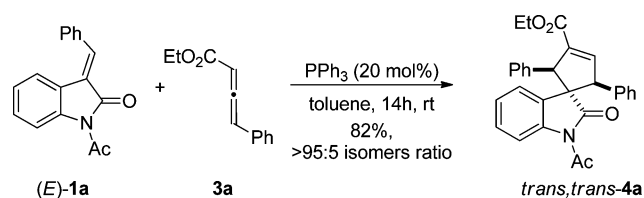
Published: January 23, 2013

butadienoates with 3-arylideneoxindoles developed in our previous work (Scheme 1)⁴ give 5-substituted cyclopentene units bearing an ester function on their 2-positions as the major products. This means that the preferred cyclization mode involves a Michael-type addition of the key zwitterionic intermediate **I** through its γ -carbon to the electron-poor olefin (γ -addition).

In these cyclization reactions, the final product displays a cyclopentene unit with *trans*-configuration of the two contiguous stereogenic centers (Ph *trans* to the carbonyl function of the oxindole unit). The high regio- and stereochemical control of these cyclizations encouraged us to expand the scope of the reaction to γ -substituted allenates, with the aim of obtaining spirocyclic oxindoles with trisubstituted five-membered rings.

As a model reaction we have considered the [3 + 2] cyclization of (*E*)-*N*-acetyl-3-benzylideneoxindole (**1a**) with 4-phenyl-2,3-butadienoate (**3a**), shown in Scheme 2. Under PPh₃

Scheme 2. Synthesis of 4a by PPh₃-Promoted [3 + 2] Annulation



catalysis, the reaction occurs at room temperature leading to the spirooxindole **4a** as the major product, together with a <5% amount of a minor isomer (82% total yield). The reaction thus proceeds with excellent regio- and diastereoselectivity.

Compound **4a** results from the α -addition of the allenate to the arylidene oxindole **1a**, which is in agreement with previous studies showing that α -addition is favored for [3 + 2] cyclizations involving γ -substituted allenates or the corresponding alkynes.⁹ The observed α -addition mode should have here mainly steric origins, as far as the γ -substituent of the allenate might disfavor a γ -addition mode. The X-ray crystal structure of **4a** (see Supporting Information) confirms the structural assignment and demonstrates the *trans,trans* configuration of the trisubstituted cyclopentene.^{10,11} The observed stereochemistry is consistent with that of analogous cyclizations on simple α,β -unsaturated ketones which also afforded

cyclopentenones with a *trans* arrangements of the two ring substituents with respect to the carbonyl function.^{9b,c}

The preference for α -adducts with *trans,trans* stereochemistry has been confirmed through more extended studies by which variously substituted substrates have been combined in the presence of PPh₃. In a first series of experiments, the benzylidene oxindole (*E*)-**1a** has been reacted with allenates with alkyl substituents on the γ -carbon (Table 1). All these

Table 1. Synthesis of the 2,3,5-Trisubstituted Spiro(cyclopentene)oxindoles 4 and 5 from γ -Substituted Allenates under PPh₃ Catalysis

entry	substrate	R ¹	R	product	dr	yield (%)
1	3b	Et	<i>n</i> -Pr	4b	90:10	82
2	3c	Et	<i>i</i> -Pr	4c	88:12	71
3	3d	Et	CH ₂ CH ₂ Ph	4d	95:5	65
4	3e	Et	CH ₂ - <i>t</i> -Bu	4e	>95:5	68
5	3f	Et	CH ₂ -cyclo-C ₅ H ₉	4f^a	95:5	55
6	3g	Et	CH ₂ CH ₂ CO ₂ Me	4g^a	95:5	51
7	3h	Bn	<i>n</i> -Pr	5	95:5	67

^aSmall amounts of a minor isomer (<10%) have been observed in the crude reaction mixture.

reactions afforded the corresponding *trans,trans* cycloadducts **4b–g** in very high isomer ratios (>8:1) for both linear and branched γ -substituents. Changing the ester group R¹ from ethyl to benzyl does not change the isomer ratio significantly (entry 1 vs 7).

Similarly, 4-phenyl-2,3-butadienoate was reacted with a variety of (*E*)-arylideneoxindoles in the presence of PPh₃ as the catalysts to afford the spirocyclic compounds **6–10** shown in Figure 1. The desired spiro(cyclopentene)oxindoles have been obtained from arylidene oxindoles with ethoxycarbonyl as the nitrogen protecting group (**6**), with substituted aromatic and heteroaromatic groups as the olefin substituent (**7a–c**, **10**), and with oxindole units functionalized at their 5- and 6-positions (**8–10**). Good yields and diastereomeric ratios >95:5

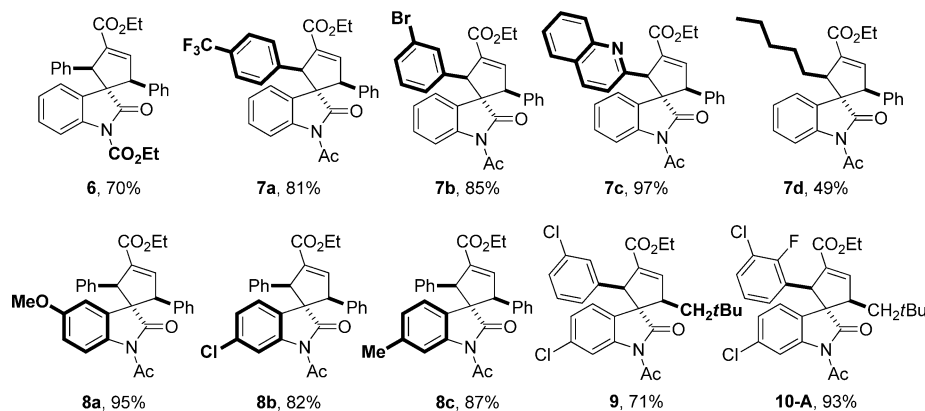
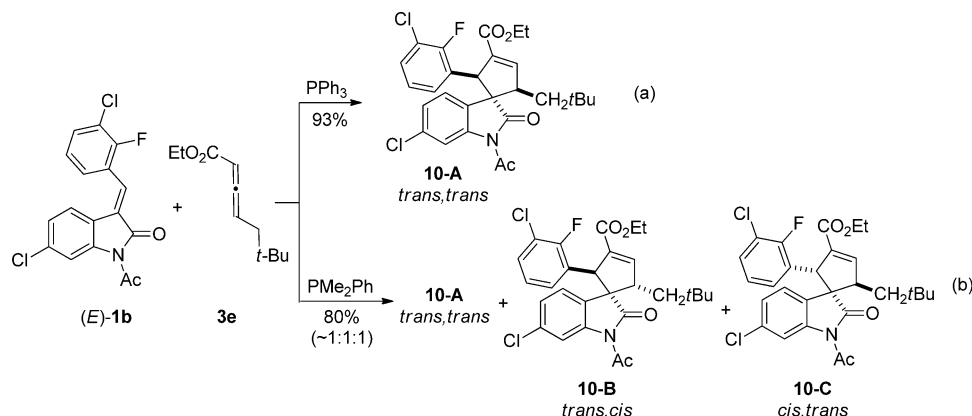


Figure 1. Trisubstituted spiro(cyclopentene)oxindoles.

Scheme 3. Synthesis of the Diastereomeric Spiranes 10



Conditions: **1b**, 0.5 mmol; **3e**, 0.75 mmol; toluene, 2.5 mL; PR_3 , 20 mol%, rt, 12–24 h, under Ar.

have been obtained for the whole series. The reaction also applies to alkylideneoxindoles as shown by the synthesis of **7d**.

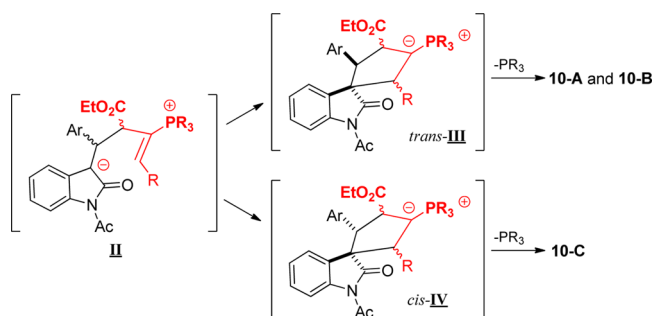
The results above demonstrate that the cyclization takes place with extremely high regio- and diastereoselectivity when PPh_3 is used as the catalyst. More extended studies have shown then that the stereochemical course of the reaction is highly dependent on the nature of the phosphorus catalyst. A representative example is shown in Scheme 3 below: the reaction between the arylidene oxindole (*E*)-**1b** and allenoate **3e** promoted by PMe_2Ph affords a mixture of three isomeric spiranes in approximately equal amounts (Scheme 3 b). Besides the expected *trans,trans* isomer **10-A**, the *trans,cis* and *cis,trans* isomers, **10-B** and **10-C**, have been isolated and fully characterized. Their stereochemistry has been secured by X-ray diffraction studies (see Supporting Information). The *cis,cis* isomer has not been detected in these reactions.¹²

Among the other phosphorus catalysts tested so far, 1,2-diphenylphosphinoethane (dppe) and PBU_3 give mixtures of **10-A** and **10-C**, while $\text{P}(p\text{-MeOC}_6\text{H}_4)_3$, $\text{P}(p\text{-FC}_6\text{H}_4)_3$, and PPhCy_2 afford **10-A** selectively, albeit in lower yields compared to PPh_3 .

According to theoretical mechanistic studies on phosphine-promoted [3 + 2] cyclizations between allenes and olefins,¹³ these are assumed to be stepwise processes in which the zwitterionic phosphine allenoate adduct undergoes at first a Michael-type addition to the olefin, followed by a cyclization step. Although these theoretical studies mainly relate to reactions between methyl 2,3-butadienoate and methyl acrylate, we can assume that stepwise mechanisms operate also in reactions involving substituted substrates, as typified in this work. Accordingly, the key reaction intermediates can be drawn as shown in Scheme 4. An α -addition of the phosphine-allenoate adduct to the olefin affords **II**, and then a cyclization step occurs by which the relative stereochemistry of the final product will be determined.¹⁴ Thus, it can be reasonably anticipated that the nature of the phosphorus catalysts will affect the stereochemical course of the reaction, as far as it might control the relative stabilities (or the relative rates of formation) of intermediates **III** and **IV**. The favored intermediate, *trans*-**III**, accounts for the final product of eq (a) in Scheme 3 (**10-A**) as well as for 2/3 of the final products of eq (b) (**10-A** + **10-B**), while the spirooxindole **10-C** is produced from *cis*-**IV**.

Previous literature reports on [3 + 2] cyclizations involving γ -substituted allenoates (or the corresponding alkynes) and 1,2-

Scheme 4. Postulated Reaction Intermediates



disubstituted olefins (mainly (*E*)-enones) are still rare.^{9b,c} They highlight the selective formation of *trans,trans* isomers of the final cyclopentenes, with only trace amounts of other diastereomers: overall the (*E*)-configuration of the starting enones translates apparently into the final product. A notable exception to this general trend can be noticed in the above-mentioned work of Wei and Shi,⁵ which shows formation of several stereoisomers in the [3 + 2] cyclization of ethyl 2,3-pentadienoate with isatin-derived 3-(2-oxopropylidene)indolin-2-ones. This paper also highlights a very efficient control of the product distribution by an appropriate choice of the phosphorus catalyst: the electron-poor $\text{P}(p\text{-FC}_6\text{H}_4)_3$ catalyst gives the *trans,trans* diastereomer with total diastereoselectivity, while PBU_3 affords a mixture of *trans,trans* and *cis,trans* isomers in a 1:2 ratio. The stereochemical control of these reactions cannot be compared effectively to that of reactions in Scheme 3 as far as γ -additions are postulated by Shi,¹⁵ while α -additions occur in our experiments. Most certainly, additional systematic studies are required to enlighten the mechanisms and the stereochemical courses of these reactions, as well as the role of the phosphorus catalyst in their stereocontrol.

From a synthetic point of view, the key information afforded by reactions in Schemes 2–4 is that triphenylphosphine affords a stereoselective access to the *trans,trans* stereoisomers of the trisubstituted spirocyclopentenes **4**–**10**, while other stereoisomers are available by using PMe_2Ph as the phosphorus catalyst, although this last reaction is not selective. Both the stereochemical control of these cyclizations and the opportunity to access various stereoisomers will be of prime importance when targeted syntheses are envisioned. In spite of the remarkable synthetic potential of the method, so far only

a few articles report on the use of phosphine-promoted [3 + 2] cyclizations in the synthesis of targeted cyclopentene or cyclopentane derivatives.¹⁶ The pioneering work of Pyne has shown the suitability of the method to the synthesis of conformationally restricted L-glutamate analogues,^{9a,17} while Xiao, Chen,¹⁸ Jørgensen,¹⁹ and Shi²⁰ have developed stereo-selective accesses to non-natural amino acids, including cyclic analogues of aspartic acid. In addition, phosphine-promoted [3 + 2] cyclizations have been envisioned as key steps in the formal or total synthesis of natural products and bioactive compounds, namely for the synthesis of carbocyclic analogues of the potent herbicide hydatocidin,²¹ for the total syntheses of (–)-hinesol²² and (+)-geniposide,²³ as well as for the formal synthesis of hirsutene.²⁴

In this work also, the [3 + 2] cyclization reactions above have been considered as a suitable tool for the synthesis of targeted analogues of known bioactive compounds. Thus, the cyclization reactions in Scheme 3 have been specifically inspired by recent studies by Wang on a series of potent anticancer agents which display a 3-pyrrolidine–spirooxindole scaffold.²⁵ These compounds, typified by **11** in Figure 2, are selective inhibitors of the

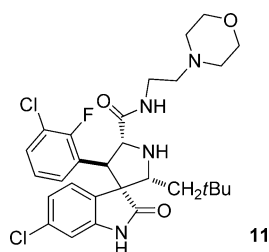


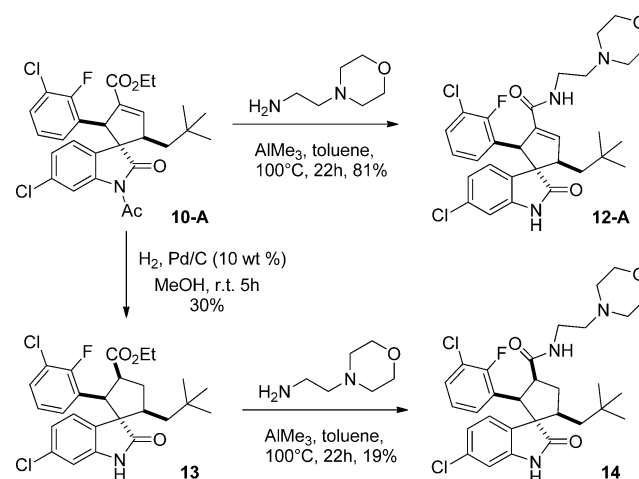
Figure 2. Representative example of the Wang's MDM2 inhibitors displaying spiro(pyrrolidine)oxindole core structures.²⁵

MDM2-p53 interaction, giving excellent inhibition of the proliferation of cancer cells with wild-type p53 status and minimal toxicity to normal cells. We envisioned that the organocatalytic, phosphine-based methodology would be perfectly suitable to access new carbocyclic analogues of these bioactive compounds, with various relative stereochemistries of their stereogenic centers.

In a preliminary study oriented toward this target, the reaction sequence shown in Scheme 5 has been implemented to convert the spiro(cyclopentene)oxindole ester *trans,trans*-**10-A** into the corresponding saturated amide **14**. The sequence involves at first catalytic hydrogenation of **10-A** in MeOH, with Pd/C under an H₂ atmosphere, to afford the saturated spiranic derivative **13**. The acetyl *N*-protecting group was also removed under these reaction conditions. The molecular structure of **13** and the *all-trans* stereochemistry of the cyclopentane unit have been unambiguously established by X-ray diffraction studies (X-ray data for this compound are given as Supporting Information). In the second step, ester **13** was transformed into the corresponding amide **14** by reaction with 2-aminoethylmorpholine in the presence of AlMe₃.

Moreover, starting from **10-A**, an unsaturated analogue of **11**, i.e. compound **12-A**, has been prepared in 81% yield by amidation with 2-aminoethylmorpholine (Scheme 5). Similarly, other unsaturated analogues of **11** have been prepared which display different relative stereochemistries of the 2- and 5-carbon centers, with respect to the quaternary carbon at the ring junction. Amidation of esters **10-B** and **10-C** with 2-

Scheme 5. Synthesis of the Spirocyclopentane Oxindole **14**, a Carbocyclic Analogue of **11**



aminoethylmorpholine in the presence of AlCl₃ afforded **12-B** and **12-C** in 62% and 69% yields, respectively (Figure 3).

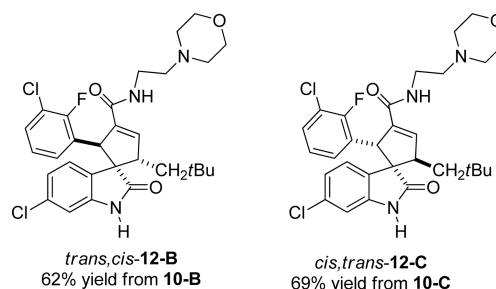


Figure 3. Unsaturated carbocyclic analogues of **11**.

Compounds **12** and **14** are the first representatives of a new class of carbocyclic analogues of the bioactive pyrrolidine–spirooxindoles **11**. The experiments above demonstrate that these phosphine-promoted [3 + 2] cyclizations on arylideneoxindoles can be successfully employed as key steps in the synthesis of highly functionalized, specifically targeted molecules.

In conclusion, this work expands the scope of the phosphine-promoted [3 + 2] cyclizations between allenates and arylideneoxindoles to the stereoselective synthesis of spiro(cyclopentene)oxindoles with trisubstituted cyclopentene units. It has been demonstrated that PPh₃ operates a very efficient control of the relative stereochemistry of the three stereogenic centers of the final products. After a systematic screening of a range of substrates, focused experiments have been carried out so as to access specifically targeted spiranic scaffolds. In particular, we have demonstrated the suitability of these phosphine-promoted cyclizations for the straightforward synthesis of carbocyclic analogues of an important series of inhibitors of MDM2-p53 interactions with anticancer properties. Ongoing studies are oriented toward asymmetric variants of these reactions.

EXPERIMENTAL SECTION

General Procedures. All non-aqueous reactions were run under an inert atmosphere (argon) by using standard techniques for manipulating air-sensitive compounds. Anhydrous solvents were obtained by filtration through drying columns (THF, toluene,

CH_2Cl_2). All reagents and solvents were of commercial quality and were used without further purification. Analytical thin-layer chromatography (TLC) was performed on plates precoated with silica gel layers. Visualization of the developed chromatogram was followed by UV absorbance. Flash column chromatography was performed using 40–63 mesh silica. NMR spectra (^1H , ^{13}C) were recorded at 500 or 300 MHz spectrometers. IR spectra were recorded with a FT-IR spectrophotometer and are reported in reciprocal centimeters (cm^{-1}). High-resolution mass spectrometry (HRMS) was performed using electrospray ionization (ESI) and time-of-flight (TOF) analyzer, in positive-ion or negative-ion detection mode.

Synthesis of Substrates. Ethyl 5-*tert*-Butylpenta-2,3-dienoate (3e). A solution of acrylic acid (2.75 mL, 40.0 mmol) in tetrahydrofuran (220 mL) was cooled to -78°C and added slowly to a *tert*-butyllithium (1.75 M, 50.0 mL, 88.0 mmol) solution in tetrahydrofuran (60 mL) at -78°C . After 2 h at -78°C , the yellow mixture was stirred for 12 h at room temperature. Water (300 mL) was added at 0°C , and the solvent was partly evaporated under reduced pressure. The residue was extracted with TBME. The aqueous layer was acidified under stirring and ice-cooling by slow addition of concentrated hydrochloric acid and extracted with ethyl acetate (2×250 mL), and the organic layer was dried. Evaporation of the solvent afforded the desired 4,4-dimethylpentanoic acid which was used in the next step without further purification. To the acid (2.2 g, 16.9 mmol) in dichloromethane (80 mL) was added slowly at room temperature SOCl_2 (1.48 mL, 20.0 mmol) and 0.5 mL of DMF. The resulting mixture was stirred at reflux for 3 h. After evaporation of the solvent, the crude acyl chloride was used in the next step. Triethylamine (1.7 mL, 12.0 mmol) was added to a solution of (carbethoxymethylene)-triphenylphosphorane (3.8 g, 11.0 mmol) in dichloromethane (20 mL) under argon at room temperature. After 10 min, a solution of crude 4,4-dimethylpentanoyl chloride (1.6 g, 11.0 mmol) in dichloromethane (17 mL) was added. During the addition, the color of the reaction changed to orange. The mixture was stirred for 18 h and concentrated to afford a gummy residue which was purified by flash chromatography on silica gel (1% MTBE/pentane) to furnish the desired compound **3e** (1.12 g, 37% yield, over two steps, colorless oil): ^1H NMR (300 MHz, CDCl_3) δ 5.60–5.50 (m, 2H), 4.25–4.10 (m, 2H), 2.04–1.99 (m, 2H), 1.26 (t, $J = 7.1$ Hz, 3H), 0.95 (s, 9H); ^{13}C NMR (75 MHz, CDCl_3) δ 213.1 (C), 166.6 (C), 92.2 (CH), 87.2 (CH), 60.8 (CH_2), 42.4 (CH_2), 29.5 (C), 29.1 (CH_3), 14.3 (CH_3); IR $\nu_{\text{max}} = 2956, 1741, 1366, 1258, 1163, 1030, 801$ cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{19}\text{O}_2$ [$\text{M} + \text{H}$] $^+$ 183.1385, found 183.1375.

(*E*)-6-Chloro-3-(3-chloro-2-fluorobenzylidene)-*N*-acetylindolin-2-one ((*E*)-1b). Piperidine (59 μL , 0.6 mmol) was added dropwise to a mixture of 6-chlorooxindole (500 mg, 3.0 mmol) and 3-chloro-2-fluorobenzaldehyde (0.39 mL, 3.3 mmol) in ethanol (4 mL). The mixture was heated at 80°C for 2 h. The yellow solid was filtered and washed with ethanol to afford 6-chloro-3-(3-chloro-2-fluorobenzylidene)indolin-2-one (861 mg, 94%). This compound was dissolved in tetrahydrofuran (3 mL) and treated with acetic anhydride (1.6 mL, 16.8 mmol) and sodium carbonate (1.8 g, 16.8 mmol). The mixture was stirred for 12 h at room temperature, diluted with water (20 mL), and extracted with ethyl acetate (50 mL). The combined organic layers were washed with water (50 mL) and brine (50 mL) and dried over MgSO_4 . The crude mixture was concentrated in vacuo and purified by flash chromatography on silica gel (10% EtOAc/heptanes) to furnish the desired compound (*E*)-1b (841 mg, 86%, yellow powder, mp = 138 – 140°C): R_f 0.20 (10% EtOAc/heptanes); ^1H NMR (300 MHz, CDCl_3) δ 8.38 (d, $J = 2.0$ Hz, 1H), 7.79 (bs, 1H), 7.52 (t, $J = 7.5$ Hz, 2H), 7.34 (d, $J = 8.2$ Hz, 1H), 7.20 (t, $J = 7.5$ Hz, 1H), 7.04 (dd, $J = 8.2, 2.0$ Hz, 1H), 2.76 (s, 3H); IR $\nu_{\text{max}} = 1746, 1714, 1597, 1451, 1424, 1373, 1316, 1282, 1262, 1165, 930, 765$ cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{11}\text{Cl}_2\text{FNO}_2$ [$\text{M} + \text{H}$] $^+$ 350.0151, found 350.0150.

(*Z*)-6-Chloro-3-(3-chloro-2-fluorobenzylidene)-*N*-acetylindolin-2-one ((*Z*)-1b). 6-Chlorooxindole (2.0 g, 12.0 mmol) was dissolved in tetrahydrofuran (40 mL) and treated with acetic anhydride (6.7 mL, 71.0 mmol) and sodium carbonate (7.6 g, 106.0 mmol). The mixture was stirred for 12 h at room temperature, diluted with water (80 mL),

and extracted with ethyl acetate. The combined organic phases were washed with water, brine, dried over MgSO_4 , and evaporated. 3-Chloro-2-fluorobenzaldehyde (1.5 mL, 13.0 mmol) and piperidine (0.2 mL, 24.0 mmol) were added dropwise to the crude *N*-acetylindolinone dissolved in ethanol (16 mL). The mixture was heated at 80°C for 24 h. After cooling to rt, the precipitate was filtered and recrystallized in chloroform. The isolated solid contained mainly (*E*)-1b. (*Z*)-1b was obtained by evaporation of the filtrate (0.89 g, 22%, yellow powder, mp $>200^\circ\text{C}$): R_f 0.25 (10% EtOAc/heptanes); ^1H NMR (300 MHz, CDCl_3) δ 8.34 (d, $J = 1.8$ Hz, 1H), 8.17 (t, $J = 7.8$ Hz, 1H), 7.71 (s, 1H), 7.55 (d, $J = 8.4$ Hz, 1H), 7.49 (t, $J = 7.8$ Hz, 1H), 7.23 (m, 1H), 7.19 (t, $J = 7.8$ Hz, 1H), 2.69 (s, 3H); IR $\nu_{\text{max}} = 1742, 1714, 1602, 1471, 1452, 1373, 1282, 1263, 1157, 931, 921, 818$ cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{11}\text{Cl}_2\text{FNO}_2$ [$\text{M} + \text{H}$] $^+$ 350.0151, found 350.0148.

Procedure for the Catalytic [3 + 2] Annulations. Degassed toluene (0.50 mL) was added to a mixture of arylidene oxindole **1** (0.5 mmol), allenone **3** (0.75 mmol, 1.5 equiv), and PPh_3 (0.1 mmol, 20 mol %) under an argon atmosphere. The solution was stirred at room temperature for 12–24 h. The crude mixture was concentrated in vacuo, and the final product was purified by flash chromatography on silica gel (EtOAc/heptanes).

Ethyl 1'-acetyl-2'-oxo-2,5-diphenylspiro[cyclopent[3]ene-1,3'-indoline]-3-carboxylate (4a): 186 mg, 82% yield, dr $> 95:5$; R_f 0.26 (15% EtOAc/heptanes); ^1H NMR (500 MHz, CDCl_3) δ 7.81 (d, $J = 8.1$ Hz, 1H), 7.34 (t, $J = 2.4$ Hz, 1H), 7.14–6.92 (m, 8H), 6.9–6.8 (m, 3H), 6.54 (td, $J = 7.5, 0.9$ Hz, 1H), 6.33 (dd, $J = 7.5, 0.9$ Hz, 1H), 4.95 (t, $J = 2.4$ Hz, 1H), 4.84 (t, $J = 2.4$ Hz, 1H), 4.30–4.05 (m, 2H), 2.80 (s, 3H), 1.13 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 181.2 (C), 170.6 (C), 164.4 (C), 143.9 (CH), 139.4 (C), 138.2 (C), 137.10 (C), 137.06 (C), 128.4 (CH), 128.2 (CH), 128.1 (CH), 128.07 (CH), 127.9 (CH), 127.5 (CH), 127.1 (CH), 126.9 (CH), 125.8 (C), 123.3 (CH), 115.5 (CH), 65.8 (C), 60.8 (CH_2), 60.7 (CH), 59.1 (CH), 27.1 (CH_3), 14.1 (CH_3); IR $\nu_{\text{max}} = 1748, 1713, 1464, 1463, 1370, 1274, 1171, 1099, 1015, 755, 699$ cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{24}\text{NO}_4$ [$\text{M} - \text{H}$] $^-$ 450.1705, found 450.1722.

Ethyl 1'-acetyl-2'-oxo-2-phenyl-5-propylspiro[cyclopent[3]ene-1,3'-indoline]-3-carboxylate (4b): 82% yield, dr = 90/10; R_f 0.30 (15% EtOAc/heptanes); ^1H NMR (300 MHz, CDCl_3) δ 7.97 (d, $J = 8.4$ Hz, 1H), 7.10–6.98 (m, 5H), 6.92–6.84 (m, 2H), 6.83–6.75 (m, 2H), 4.79 (t, $J = 2.5$ Hz, 1H), 4.20–4.00 (m, 2H), 3.43 (br, 1H), 2.73 (s, 3H), 1.50–1.40 (m, 1H), 1.35–1.20 (m, 1H), 1.20–1.00 (m, 2H), 1.08 (t, $J = 7.2$ Hz, 3H), 0.76 (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 181.1 (C), 170.8 (C), 164.6 (C), 146.3 (CH), 139.7 (C), 137.0 (C), 135.9 (C), 128.5 (CH), 128.1 (CH), 127.8 (CH), 127.1 (CH), 126.3 (CH), 126.1 (C), 123.8 (CH), 116.1 (CH), 64.4 (C), 61.2 (CH), 60.6 (CH_2), 53.3 (CH), 32.7 (CH_2), 27.0 (CH_3), 21.1 (CH_2), 14.1 (CH_3), 14.0 (CH_3); IR $\nu_{\text{max}} = 1748, 1711, 1463, 1368, 1256, 1168, 1096, 930, 758, 739, 700$ cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{26}\text{NO}_4$ [$\text{M} - \text{H}$] $^-$ 416.1862, found 416.1876. The minor isomer observed in the crude mixture has been tentatively assigned as a diastereomer of **4b**, based on the ^1H NMR signals for the cyclopentene CH groups: ^1H NMR (300 MHz, CDCl_3) δ 4.60 (t, $J = 2.5$ Hz, 1H), 3.37 (br, 1H) ppm.

Ethyl 1'-acetyl-5-isopropyl-2'-oxo-2-phenylspiro[cyclopent[3]ene-1,3'-indoline]-3-carboxylate (4c): 71% yield, dr = 88/12; R_f 0.32 (15% EtOAc/heptanes); ^1H NMR (500 MHz, CDCl_3) δ 7.86 (d, $J = 8.5$ Hz, 1H), 7.24 (d, $J = 7.5$ Hz, 1H), 7.14 (t, $J = 2.5$ Hz, 1H), 7.07 (t, $J = 8.0$ Hz, 1H), 6.97–6.90 (4H), 6.75–6.70 (m, 2H), 4.83 (t, $J = 3.0$ Hz, 1H), 4.15–4.0 (m, 2H), 3.24 (d, $J = 11.5$ Hz, 1H), 2.72 (s, 3H), 1.80–1.70 (m, 1H), 1.11 (d, $J = 6.5$ Hz, 3H), 1.04 (t, $J = 7.0$ Hz, 3H), 0.39 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 180.9 (C), 170.6 (C), 164.8 (C), 145.3 (CH), 139.4 (C), 136.0 (C), 135.9 (C), 128.6 (CH), 127.9 (CH), 127.6 (CH), 127.0 (CH), 126.3 (C), 125.4 (CH), 123.8 (CH), 116.2 (CH), 65.6 (C), 62.9 (CH), 60.6 (CH_2), 60.4 (CH), 28.2 (CH_3), 26.9 (CH_3), 22.0 (CH), 20.6 (CH_3), 14.1 (CH_3); HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{26}\text{NO}_4$ [$\text{M} - \text{H}$] $^-$ 416.1862, found 416.1870. A small sample of the minor isomer of **4c** has been isolated by HPLC: ^1H NMR (500 MHz, CDCl_3) δ 8.01 (d, $J = 7.5$ Hz, 1H), 7.50–7.44 (m, 1H), 7.35–7.28 (m, 2H), 7.15–7.05 (m, 4H),

6.66 (br, 2H), 4.54 (t, J = 3.0 Hz, 1H), 4.20–4.02 (m, 2H), 3.09 (dt, J = 11.0, 2.5 Hz, 1H), 2.22–2.14 (m, 1H), 2.06 (s, 3H), 1.12 (d, J = 6.5 Hz, 3H), 1.09 (t, J = 7.0 Hz, 3H), 0.38 (d, J = 6.5 Hz, 3H) ppm.

Ethyl 1'-acetyl-2'-oxo-5-phenethyl-2-phenylspiro[cyclopent[3]ene-1,3'-indoline]-3-carboxylate (4d): 65% yield, dr = 95/5; R_f 0.24 (15% EtOAc/heptanes); ^1H NMR (500 MHz, CDCl_3) δ 8.01 (d, J = 8.1 Hz, 1H), 7.25–7.10 (m, 4H), 7.08–7.00 (m, 4H), 6.95–6.86 (m, 4H), 6.85–6.76 (m, 2H), 4.82 (t, J = 2.5 Hz, 1H), 4.20–4.00 (m, 2H), 3.55–3.45 (m, 1H), 2.73 (s, 3H), 2.55–2.45 (m, 1H), 2.30–2.20 (m, 1H), 1.90–1.76 (m, 1H), 1.60–1.48 (m, 1H), 1.08 (t, J = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 181.0 (C), 170.7 (C), 164.5 (C), 145.8 (CH), 140.9 (C), 139.7 (C), 136.9 (C), 136.2 (C), 128.63 (CH), 128.56 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.2 (CH), 126.3 (CH), 126.2 (CH), 125.8 (C), 123.9 (CH), 116.2 (CH), 64.2 (C), 61.2 (CH), 60.7 (CH₂), 53.0 (CH), 34.2 (CH₂), 32.6 (CH₂), 27.0 (CH₃), 14.1 (CH₃); IR ν_{max} = 1749, 1711, 1463, 1371, 1339, 1268, 1173, 1114, 1014, 911, 758, 729, 700 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{28}\text{NO}_4$ [$\text{M} - \text{H}$] $^-$ 478.2018, found 478.2036.

Ethyl 1'-acetyl-5-isopropyl-2'-oxo-2-phenylspiro[cyclopent[3]ene-1,3'-indoline]-3-carboxylate (4e): 68% yield, dr > 95/5; R_f 0.36 (15% EtOAc/heptanes); ^1H NMR (500 MHz, CDCl_3) δ 7.91 (d, J = 8.7 Hz, 1H), 7.10–6.88 (m, 7H), 6.82–6.74 (m, 2H), 4.82 (t, J = 2.7 Hz, 1H), 4.2–4.0 (m, 2H), 3.54 (dd, J = 9.6, 2.4 Hz, 1H), 2.71 (s, 3H), 1.37 (dd, J = 14.5, 9.6 Hz, 1H), 1.06 (t, J = 6.9 Hz, 3H), 0.84 (s, 9H), 0.71 (dd, J = 14.5, 1.8 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 180.4 (C), 170.7 (C), 164.8 (C), 147.9 (CH), 139.6 (C), 136.7 (C), 135.9 (C), 128.5 (CH), 128.0 (CH), 127.7 (CH), 127.0 (CH), 126.5 (C), 125.8 (CH), 123.9 (CH), 116.1 (CH), 67.0 (C), 60.8 (CH), 60.6 (CH₂), 49.0 (CH), 43.9 (CH₂), 30.8 (C), 29.5 (CH₃), 26.9 (CH₃), 14.1 (CH₃); IR ν_{max} = 1750, 1712, 1464, 1370, 1287, 1273, 1233, 1173, 1159, 1116, 1017, 911, 758, 730, 700 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{30}\text{NO}_4$ [$\text{M} - \text{H}$] $^-$ 444.2175, found 444.2194.

Ethyl 1'-acetyl-5-(cyclopentylmethyl)-2'-oxo-2-phenylspiro[cyclopent[3]ene-1,3'-indoline]-3-carboxylate (4f): 55% yield, dr = 95/5; R_f 0.36 (15% EtOAc/heptanes); ^1H NMR (500 MHz, CDCl_3) δ 7.97 (d, J = 8.1 Hz, 1H), 7.14–7.06 (m, 2H), 7.05–6.98 (m, 3H), 6.95–6.85 (m, 2H), 6.83–6.75 (m, 2H), 4.79 (t, J = 2.7 Hz, 1H), 4.20–4.00 (m, 2H), 3.55–3.45 (m, 1H), 2.72 (s, 3H), 1.80–1.70 (m, 1H), 1.65–1.40 (m, 8H), 1.08 (t, J = 6.9 Hz, 3H), 0.95–0.85 (m, 2H); ^{13}C NMR (75 MHz, CDCl_3) δ 181.0 (C), 170.8 (C), 164.6 (C), 146.5 (CH), 139.7 (C), 137.0 (C), 135.8 (C), 128.4 (CH), 128.1 (CH $\times$ 2), 127.8 (CH $\times$ 2), 127.1 (CH), 126.3 (CH), 126.1 (C), 123.7 (CH), 116.0 (CH), 64.6 (C), 61.1 (CH), 60.6 (CH₂), 52.4 (CH), 38.2 (CH), 36.8 (CH₂), 33.0 (CH₂), 32.6 (CH₂), 27.0 (CH₃), 25.3 (CH₂), 25.0 (CH₂), 14.1 (CH₃); IR ν_{max} = 1749, 1711, 1464, 1371, 1309, 1270, 1171, 1111, 1014, 910, 758, 728, 700 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{30}\text{NO}_4$ [$\text{M} - \text{H}$] $^-$ 456.2175, found 456.2194.

Ethyl 1'-acetyl-5-(3-methoxy-3-oxopropyl)-2'-oxo-2-phenylspiro[cyclopent[3]ene-1,3'-indoline]-3-carboxylate (4g): 51% yield, dr = 95/5; R_f 0.20 (25% EtOAc/heptanes); ^1H NMR (500 MHz, CDCl_3) δ 7.98 (d, J = 8.1 Hz, 1H), 7.10 (t, J = 7.8 Hz, 1H), 7.06–6.98 (m, 4H), 6.89 (t, J = 7.6 Hz, 1H), 6.85 (d, J = 6.8 Hz, 1H), 6.82–6.75 (m, 2H), 4.79 (t, J = 2.5 Hz, 1H), 4.20–4.05 (m, 2H), 3.61 (s, 3H), 3.45 (t, J = 8.0 Hz, 1H), 2.73 (s, 3H), 2.20–2.00 (m, 2H), 1.90–1.80 (m, 1H), 1.55–1.45 (m, 1H), 1.08 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 180.7 (C), 172.9 (C), 170.7 (C), 164.4 (C), 144.8 (CH), 139.7 (C), 136.8 (C), 136.6 (C), 128.8 (CH), 128.1 (CH $\times$ 2), 127.9 (CH $\times$ 2), 127.2 (CH), 126.2 (CH), 125.5 (C), 124.0 (CH), 116.2 (CH), 64.1 (C), 61.2 (CH), 60.7 (CH₂), 52.5 (CH₃), 51.9 (CH), 32.0 (CH₂), 26.9 (CH₃), 25.7 (CH₂), 14.1 (CH₃); IR ν_{max} = 1738, 1713, 14643, 1371, 1339, 1269, 1172, 1116, 912, 759, 730, 702 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{27}\text{H}_{26}\text{NO}_6$ [$\text{M} - \text{H}$] $^-$ 460.1760, found 460.1783.

Benzyl 1'-acetyl-2'-oxo-2-phenyl-5-propylspiro[cyclopent[3]ene-1,3'-indoline]-3-carboxylate (5): 67% yield, dr = 95/5; R_f 0.30 (15% EtOAc/heptanes); ^1H NMR (300 MHz, CDCl_3) δ 7.99 (d, J = 8.1 Hz, 1H), 7.28–7.20 (m, 3H), 7.15–6.96 (m, 7H), 6.94–6.75 (m, 4H), 5.17 (d, J = 12.3 Hz, 1H), 5.02 (d, J = 12.3 Hz, 1H), 4.85 (t, J = 2.7 Hz, 1H), 3.50–3.40 (m, 1H), 2.74 (s, 3H), 1.50–1.25 (m, 2H), 1.20–1.00 (m, 2H), 0.78 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ

181.0 (C), 170.8 (C), 164.4 (C), 147.1 (CH), 139.7 (C), 137.0 (C), 135.7 (C), 135.6 (C), 128.5 (CH), 128.3 (CH $\times$ 2), 128.2 (CH $\times$ 2), 128.1 (CH), 127.97 (CH $\times$ 2), 127.95 (CH $\times$ 2), 127.2 (CH), 126.3 (CH), 126.0 (C), 123.7 (CH), 116.1 (CH), 66.4 (CH₂), 64.4 (C), 61.2 (CH), 53.3 (CH), 32.7 (CH₂), 27.0 (CH₃), 21.1 (CH₂), 14.0 (CH₃); IR ν_{max} = 1749, 1713, 1464, 1372, 1339, 1267, 1170, 1098, 1017, 913, 737, 701 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{31}\text{H}_{28}\text{NO}_4$ [$\text{M} - \text{H}$] $^-$ 478.2018, found 478.2037.

Diethyl 2'-oxo-2,5-diphenylspiro[cyclopent[3]ene-1,3'-indoline]-1',3'-dicarboxylate (6): 70% yield, dr > 95/5; R_f 0.26 (15% EtOAc/heptanes); ^1H NMR (500 MHz, CDCl_3) δ 7.46 (d, J = 8.1 Hz, 1H), 7.32 (t, J = 2.4 Hz, 1H), 7.15–6.95 (m, 8H), 6.92–6.80 (m, 3H), 6.50 (td, J = 7.5, 0.9 Hz, 1H), 6.31 (d, J = 7.8 Hz, 1H), 4.97 (t, J = 2.4 Hz, 1H), 4.85 (t, J = 2.4 Hz, 1H), 4.49 (q, J = 7.2 Hz, 2H), 4.25–4.05 (m, 2H), 1.48 (t, J = 7.2 Hz, 3H), 1.11 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 178.8 (C), 164.5 (C), 150.8 (C), 144.0 (CH), 138.7 (C), 138.3 (C), 137.3 (C), 137.2 (C), 128.35 (CH $\times$ 2), 128.31 (CH $\times$ 2), 128.2 (CH $\times$ 2), 128.0 (CH), 127.9 (CH $\times$ 2), 127.4 (CH), 127.2 (CH), 127.0 (CH), 125.8 (C), 122.9 (CH), 114.0 (CH), 65.7 (C), 63.7 (CH₂), 60.8 (CH₂), 60.6 (CH), 59.1 (CH), 14.4 (CH₃), 14.1 (CH₃); IR ν_{max} = 2982, 1734, 1719, 1466, 1371, 1290, 1238, 1163, 1097, 1047, 754, 700 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{30}\text{H}_{26}\text{NO}_5$ [$\text{M} - \text{H}$] $^-$ 480.1811, found 480.1830.

Ethyl 1'-acetyl-2'-oxo-5-phenyl-2-(4-(trifluoromethyl)phenyl)-spiro[cyclopent[3]ene-1,3'-indoline]-3-carboxylate (7a): 81% yield, dr > 95/5; R_f 0.23 (15% EtOAc/heptanes); ^1H NMR (500 MHz, CDCl_3) δ 7.82 (d, J = 8.0 Hz, 1H), 7.40 (t, J = 2.4 Hz, 1H), 7.34–7.24 (m, 2H), 7.15–7.05 (m, 3H), 7.02–6.92 (m, 4H), 6.90 (d, J = 8.0 Hz, 1H), 6.58 (t, J = 7.5 Hz, 1H), 6.33 (d, J = 7.5 Hz, 1H), 5.00 (bs, 1H), 4.86 (bs, 1H), 4.25–4.10 (m, 2H), 2.80 (s, 3H), 1.15 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 180.9 (C), 170.5 (C), 164.0 (C), 144.9 (CH), 141.4 (C), 139.4 (C), 137.4 (C), 136.7 (C), 128.6 (CH $\times$ 2), 128.51 (CH), 128.49 (CH $\times$ 2), 128.2 (CH $\times$ 2), 127.7 (CH), 126.6 (CH), 125.3 (C), 124.9 (q, J = 3.5 Hz, CH $\times$ 2), 123.5 (CH), 115.8 (CH), 65.7 (C), 61.1 (CH₂), 60.2 (CH), 59.3 (CH), 27.1 (CH₃), 14.1 (CH₃); IR ν_{max} = 1749, 1715, 1465, 1372, 1325, 1277, 1169, 1115, 1069, 1017, 756 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{30}\text{H}_{23}\text{F}_3\text{NO}_4$ [$\text{M} - \text{H}$] $^-$ 518.1579, found 518.1581.

Ethyl 1'-acetyl-2-(3-bromophenyl)-2'-oxo-5-phenylspiro[cyclopent[3]ene-1,3'-indoline]-3-carboxylate (7b): 85% yield, dr > 95/5; R_f 0.23 (15% EtOAc/heptanes); ^1H NMR (300 MHz, CDCl_3) δ 7.83 (d, J = 8.4 Hz, 1H), 7.37 (t, J = 2.4 Hz, 1H), 7.18–7.05 (m, 4H), 7.00 (t, J = 1.5 Hz, 1H), 6.98–6.85 (m, 4H), 6.75 (d, J = 7.7 Hz, 1H), 6.61 (dt, J = 7.6, 0.8 Hz, 1H), 6.34 (d, J = 7.5 Hz, 1H), 4.88 (bs, 1H), 4.84 (bs, 1H), 4.30–4.10 (m, 2H), 2.79 (s, 3H), 1.16 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 180.9 (C), 170.6 (C), 164.1 (C), 144.7 (CH), 139.5 (C), 139.4 (C), 137.5 (C), 136.8 (C), 131.4 (CH), 130.2 (CH), 129.5 (CH), 128.5 (CH $\times$ 3), 128.2 (CH $\times$ 2), 127.7 (CH), 126.77 (CH), 126.74 (CH), 125.4 (C), 125.3 (CH), 122.0 (C), 115.7 (CH), 65.9 (C), 61.0 (CH₂), 60.2 (CH), 59.0 (CH), 27.0 (CH₃), 14.2 (CH₃); IR ν_{max} = 1749, 1713, 1477, 1371, 1266, 1171, 1102, 1015, 736, 701 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{23}\text{BrNO}_4$ [$\text{M} - \text{H}$] $^-$ 528.0810, found 528.0831.

Ethyl 1'-acetyl-2'-oxo-5-phenyl-2-(quinolin-2-yl)spiro[cyclopent[3]ene-1,3'-indoline]-3-carboxylate (7c): 97% yield, dr > 95/5; R_f 0.27 (25% EtOAc/heptanes); ^1H NMR (500 MHz, CDCl_3) δ 7.92 (d, J = 8.5 Hz, 1H), 7.80–7.72 (m, 2H), 7.66–7.58 (m, 2H), 7.41 (t, J = 7.5 Hz, 1H), 7.31 (bs, 1H), 7.16–7.00 (m, 5H), 6.79 (d, J = 8.5 Hz, 1H), 6.72 (t, J = 7.5 Hz, 1H), 6.32 (t, J = 7.5 Hz, 1H), 6.23 (d, J = 7.5 Hz, 1H), 5.26 (bs, 1H), 4.86 (bs, 1H), 4.25–4.10 (m, 2H), 2.87 (s, 3H), 1.10 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 181.2 (C), 170.8 (C), 164.7 (C), 157.6 (C), 147.3 (C), 143.0 (CH), 139.4 (C), 138.1 (C), 136.9 (C), 135.7 (CH), 129.4 (CH), 129.1 (CH), 128.7 (CH $\times$ 2), 128.2 (CH $\times$ 2), 128.0 (CH), 127.5 (CH), 127.4 (CH), 126.8 (CH), 126.7 (C), 126.2 (CH), 125.7 (C), 123.3 (CH), 120.9 (CH), 115.3 (CH), 64.5 (C), 62.3 (CH), 60.7 (CH₂), 60.1 (CH), 27.0 (CH₃), 14.2 (CH₃); IR ν_{max} = 1750, 1713, 1600, 1464, 1371, 1266, 1171, 1099, 1015, 737, 701 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{32}\text{H}_{25}\text{N}_2\text{O}_4$ [$\text{M} - \text{H}$] $^-$ 501.1814, found 501.1833.

Ethyl 1'-acetyl-2'-oxo-2-pentyl-5-phenylspiro[cyclopent[3]ene-1,3'-indoline]-3-carboxylate (7d): 49% yield, dr > 95:5; R_f 0.32 (20% EtOAc/heptanes); ^1H NMR (300 MHz, CDCl_3) δ 7.93 (d, J = 8.1 Hz, 1H), 7.12–7.00 (m, 5H), 6.96 (t, J = 2.4 Hz, 1H), 6.93 (d, J = 7.2 Hz, 1H), 6.90–6.82 (m, 2H), 4.65 (t, J = 2.8 Hz, 1H), 4.40–4.20 (m, 2H), 3.74 (dq, J = 11.7, 3.0 Hz, 1H), 2.74 (s, 3H), 2.20–2.05 (m, 1H), 1.37 (t, J = 7.2 Hz, 3H), 1.30–1.22 (m, 1H), 1.10–0.85 (m, 5H), 0.64 (t, J = 6.6 Hz, 3H), 0.60–0.48 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 181.2 (C), 170.7 (C), 164.8 (C), 142.2 (CH), 139.6 (C), 139.5 (C), 136.5 (C), 128.5 (CH), 128.2 (CH $\times$ 2), 128.0 (CH $\times$ 2), 127.5 (CH), 126.0 (C), 125.6 (CH), 123.8 (CH), 116.1 (CH), 65.0 (C), 60.83 (CH₂), 60.78 (CH), 53.5 (CH), 31.2 (CH₂), 28.2 (CH₂), 27.0 (CH₃), 26.5 (CH₂), 22.0 (CH₂), 14.4 (CH₃), 13.8 (CH₃); IR ν_{max} = 2956, 2929, 2858, 1750, 1713, 1464, 1371, 1285, 1197, 1168, 1095, 1014, 755, 700 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{32}\text{NO}_4$ [$\text{M} + \text{H}$] $^+$ 446.2331, found 446.2316.

Ethyl 1'-acetyl-5'-methoxy-2'-oxo-2,5-diphenylspiro[cyclopent[3]ene-1,3'-indoline]-3-carboxylate (8a): 95% yield, dr > 95:5; R_f 0.15 (25% EtOAc/heptanes); ^1H NMR (500 MHz, CDCl_3) δ 7.82 (d, J = 8.5 Hz, 1H), 7.35 (s, 1H), 7.20–7.08 (m, 3H), 7.07–7.02 (m, 3H), 6.94 (d, J = 6.5 Hz, 2H), 6.84 (d, J = 6.5 Hz, 2H), 6.42 (dd, J = 8.5, 2.0 Hz, 1H), 5.37 (d, J = 2.0 Hz, 1H), 4.85 (s, 1H), 4.73 (s, 1H), 4.25–4.10 (m, 2H), 3.15 (s, 3H), 2.77 (s, 3H), 1.14 (t, J = 7.0 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 181.6 (C), 170.5 (C), 164.2 (C), 155.4 (C), 143.9 (C), 138.4 (C), 137.6 (C), 137.3 (C), 133.1 (C), 128.6 (CH $\times$ 2), 128.3 (CH $\times$ 4), 128.0 (CH $\times$ 2), 127.6 (CH), 127.2 (CH), 127.1 (C), 116.3 (CH), 114.2 (CH), 112.4 (CH), 64.4 (C), 60.9 (CH₂), 60.1 (CH), 59.1 (CH), 55.2 (CH₃), 26.9 (CH₃), 14.1 (CH₃); IR ν_{max} = 1750, 1711, 1485, 1453, 1372, 1269, 1207, 1177, 1098, 1018, 700 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{30}\text{H}_{26}\text{NO}_5$ [$\text{M} - \text{H}$] $^-$ 480.1811, found 480.1826.

Ethyl 1'-acetyl-6'-chloro-2'-oxo-2,5-diphenylspiro[cyclopent[3]ene-1,3'-indoline]-3-carboxylate (8b): 82% yield, dr > 95:5; R_f 0.29 (25% EtOAc/heptanes); ^1H NMR (500 MHz, CDCl_3) δ 7.90 (d, J = 2.1 Hz, 1H), 7.31 (t, J = 2.4 Hz, 1H), 7.16–7.08 (m, 3H), 7.08–7.01 (m, 3H), 6.98–6.90 (m, 2H), 6.88–6.80 (m, 2H), 6.50 (dd, J = 8.4, 2.1 Hz, 1H), 6.14 (d, J = 8.4 Hz, 1H), 4.92 (t, J = 2.4 Hz, 1H), 4.80 (t, J = 2.4 Hz, 1H), 4.25–4.10 (m, 2H), 2.79 (s, 3H), 1.13 (t, J = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 180.9 (C), 170.5 (C), 164.2 (C), 143.7 (CH), 140.1 (C), 138.3 (C), 136.9 (C), 136.8 (C), 133.8 (C), 128.6 (CH $\times$ 2), 128.2 (CH $\times$ 2), 128.1 (CH $\times$ 2), 128.0 (CH $\times$ 2), 127.8 (CH), 127.7 (CH), 127.4 (CH), 124.4 (C), 123.5 (CH), 116.1 (CH), 65.3 (C), 60.9 (CH₂), 60.6 (CH), 59.1 (CH), 26.9 (CH₃), 14.1 (CH₃); IR ν_{max} = 1754, 1715, 1602, 1474, 1421, 1372, 1335, 1282, 1236, 1169, 1100, 931, 737, 701 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{29}\text{H}_{23}\text{ClNO}_4$ [$\text{M} - \text{H}$] $^-$ 484.1316, found 484.1331.

Ethyl 1'-acetyl-6'-methyl-2'-oxo-2,5-diphenylspiro[cyclopent[3]ene-1,3'-indoline]-3-carboxylate (8c): 87% yield, dr = 90:10; R_f 0.28 (15% EtOAc/heptanes); ^1H NMR (500 MHz, CDCl_3) δ 7.59 (bs, 1H), 7.28–7.22 (m, 1H), 7.05–6.98 (m, 3H), 6.97–6.90 (m, 3H), 6.88–6.82 (m, 2H), 6.80–6.70 (m, 2H), 6.26 (d, J = 7.5 Hz, 1H), 6.05 (d, J = 7.8 Hz, 1H), 4.82 (bs, 1H), 4.71 (bs, 1H), 4.15–4.00 (m, 2H), 2.70 (s, 3H), 2.00 (s, 3H), 1.05 (t, J = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, CDCl_3) δ 181.7 (C), 170.7 (C), 164.4 (C), 144.0 (CH), 139.4 (C), 138.3 (C), 138.1 (C), 137.3 (C), 137.2 (C), 128.4 (CH $\times$ 2), 128.3 (CH $\times$ 2), 128.2 (CH $\times$ 2), 127.9 (CH $\times$ 2), 127.4 (CH), 127.1 (CH), 126.6 (CH), 124.1 (CH), 122.7 (C), 116.1 (CH), 65.6 (C), 60.8 (CH₂), 60.6 (CH), 59.1 (CH), 27.1 (CH₃), 21.8 (CH₃), 14.1 (CH₃); IR ν_{max} = 1748, 1713, 1371, 1287, 1266, 1177, 1100, 737, 702 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{30}\text{H}_{26}\text{NO}_4$ [$\text{M} - \text{H}$] $^-$ 464.1862, found 464.1872.

Ethyl 1'-acetyl-2'-oxo-2-(3-chlorophenyl)-5-neopentylspiro[cyclopent[3]ene-6'-chloro-3'-indoline]-3-carboxylate (9): 71% yield, dr > 95:5; ^1H NMR (500 MHz, CDCl_3) δ 8.02 (s, 1H), 7.02 (t, J = 2.3 Hz, 1H), 7.00–6.90 (m, 4H), 6.78 (t, J = 1.9 Hz, 1H), 6.65 (d, J = 7.6 Hz, 1H), 4.77 (t, J = 2.4 Hz, 1H), 4.20–4.03 (m, 2H), 3.52 (ddd, J = 9.7, 5.2, 2.4 Hz, 1H), 2.70 (s, 3H), 1.33 (dd, J = 14.4, 9.7 Hz, 1H), 1.09 (t, J = 7.1 Hz, 3H), 0.84 (s, 9H), 0.66 (dd, J = 14.4, 2.4 Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 179.7 (C), 170.3 (C), 164.3 (C), 148.3 (CH), 140.4 (C), 138.7 (C), 135.2 (C), 134.5 (C), 133.9

(C), 129.2 (CH), 128.2 (CH), 127.5 (CH), 126.4 (CH), 126.1 (CH), 124.6 (C), 124.2 (CH), 116.9 (CH), 66.7 (C), 60.8 (CH₂), 60.2 (CH), 49.1 (CH), 43.9 (CH₂), 30.9 (C), 29.5 (CH₃ $\times$ 3), 26.8 (CH₃), 14.1 (CH₃); IR ν_{max} = 2957, 1753, 1713, 1600, 1573, 1474, 1421, 1370, 1336, 1283, 1257, 1232, 1198, 1162, 1121, 1081, 1020, 930, 733 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{29}\text{Cl}_2\text{NNaO}_4$ [$\text{M} + \text{Na}$] $^+$ 536.1371, found 536.1349.

Ethyl 1'-acetyl-2'-oxo-2-(3-chloro-2-fluorophenyl)-5-neopentylspiro[cyclopent[3]ene-6'-chloro-3'-indoline]-3-carboxylate (10-A): 248 mg, 93%, white solid; mp 119–121 $^\circ\text{C}$; R_f 0.45 (15% EtOAc/heptanes); ^1H NMR (300 MHz, CDCl_3) δ 8.06 (s, 1H), 7.08 (td, J = 7.5, 1.7 Hz, 1H), 7.04–7.00 (m, 1H), 6.95–6.89 (m, 2H), 6.78 (t, J = 8.0 Hz, 1H), 6.69 (td, J = 7.0, 1.5 Hz, 1H), 5.03 (bs, 1H), 4.20–4.05 (m, 2H), 3.57 (dd, J = 9.8, 2.4 Hz, 1H), 2.71 (s, 3H), 1.32 (dd, J = 14.5, 9.8 Hz, 1H), 1.11 (t, J = 7.1 Hz, 3H), 0.84 (s, 9H), 0.66 (dd, J = 14.5, 1.7 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 179.6 (C), 170.6 (C), 164.2 (C), 157.7 (C), 154.4 (C), 148.1 (CH), 140.6 (C), 134.6 (C), 129.7 (CH), 128.1 (d, J = 3.3 Hz, CH), 126.2 (CH), 126.0 (C), 124.7 (C), 124.1 (CH), 123.8 (CH), 116.9 (CH), 65.3 (C), 60.9 (CH₂), 53.8 (CH), 49.2 (CH), 44.0 (CH₂), 30.9 (C), 29.5 (CH₃ $\times$ 3), 26.6 (CH₃), 14.1 (CH₃); IR ν_{max} = 2964, 1760, 1712, 1640, 1602, 1473, 1456, 1367, 1338, 1279, 1265, 1252, 1160, 1116, 1020, 930, 772, 759 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{27}\text{Cl}_2\text{FNO}_4$ [$\text{M} - \text{H}$] $^-$ 530.1301, found 530.1299.

Ethyl 1'-acetyl-2'-oxo-2-(3-chloro-2-fluorophenyl)-5-neopentylspiro[cyclopent[3]ene-6'-chloro-3'-indoline]-3-carboxylate (10-B and 10-C). A solution of ethyl 5-tert-butylpenta-2,3-dienoate (3e) (137 mg, 0.75 mmol) in toluene (1.5 mL) was added under argon to a solution of the (*E*)-arylideneoxindole 1b (175 mg, 0.5 mmol) and dimethylphenylphosphine (0.1 mmol) in toluene (1 mL). The solution was stirred for 24 h at room temperature. The crude mixture was concentrated in vacuo and purified by flash chromatography on silica gel (10% EtOAc/heptanes) to furnish a mixture of 10-A, 10-B, and 10-C (210 mg, 80%, white powder). Pure isomers have been obtained from this mixture by HPLC separation (heptane/EtOAc 0–15% gradient).

Compound 10-B: ^1H NMR (300 MHz, CDCl_3) δ 8.28 (s, 1H), 7.30 (t, J = 7.1 Hz, 1H), 7.23–7.20 (m, 1H), 7.11 (t, J = 7.7 Hz, 1H), 7.08–7.02 (m, 1H), 6.80 (d, J = 7.7 Hz, 1H), 5.83 (d, J = 7.7 Hz, 1H), 4.69 (br s, 1H), 4.20–4.10 (m, 2H), 3.17 (d, J = 9.7 Hz, 1H), 2.71 (s, 3H), 1.62 (dd, J = 13.8, 10.4 Hz, 1H), 1.19 (t, J = 7.2 Hz, 3H), 0.77 (s, 9H), 0.75–0.70 (m, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 178.5 (C), 170.8 (C), 163.5 (C), 157.4 (C), 155.4 (C), 148.3 (CH), 141.4 (C), 134.9 (C), 134.8 (C), 130.3 (CH), 125.9 (CH), 125.0 (C), 124.6 (CH $\times$ 2), 124.3 (CH), 122.0 (d, J = 11.0 Hz, C), 116.9 (CH), 62.6 (C), 61.0 (CH₂), 50.6 (CH), 50.0 (CH), 41.4 (CH₂), 29.9 (C), 29.4 (CH₃ $\times$ 3), 26.9 (CH₃), 14.3 (CH₃); IR ν_{max} = 2956, 1756, 1713, 1602, 1458, 1421, 1371, 1336, 1282, 1257, 1242, 1202, 1161, 1112, 1078, 1026, 930, 735 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{27}\text{Cl}_2\text{FNO}_4$ [$\text{M} - \text{H}$] $^-$: 530.1301, found 530.1304.

Compound 10-C: ^1H NMR (300 MHz, CDCl_3) δ 8.32 (d, J = 1.8 Hz, 1H), 7.31 (td, J = 8.1, 1.8 Hz, 1H), 7.28–7.20 (m, 2H), 7.15 (dd, J = 8.1, 1.8 Hz, 1H), 7.15–7.07 (m, 1H), 7.02–6.95 (m, 1H), 4.51 (bs, 1H), 4.22–4.05 (m, 2H), 3.46 (d, J = 9.4 Hz, 1H), 2.44 (s, 3H), 1.32–1.22 (m, 1H), 1.19 (t, J = 7.1 Hz, 3H), 0.82 (s, 9H), 0.62 (d, J = 12.2 Hz, 1H); ^{13}C NMR (75 MHz, CDCl_3) δ 176.4 (C), 170.7 (C), 163.4 (C), 156.8 (C), 154.7 (C), 150.1 (CH), 140.0 (C), 134.8 (C), 134.5 (C), 130.1 (CH), 129.6 (C), 126.6 (CH), 125.6 (CH), 124.7 (d, J = 4.3 Hz, CH), 123.4 (CH), 117.3 (CH), 63.6 (C), 61.1 (CH₂), 54.2 (CH), 48.4 (CH), 42.7 (CH₂), 30.9 (C), 29.5 (CH₃ $\times$ 3), 26.3 (CH₃), 14.2 (CH₃); IR ν_{max} = 2953, 1763, 1708, 1628, 1601, 1457, 1421, 1371, 1337, 1286, 1263, 1227, 1208, 1160, 1106, 1059, 1023, 928, 768 cm^{-1} ; HRMS (ESI) calcd for $\text{C}_{28}\text{H}_{27}\text{Cl}_2\text{FNO}_4$ [$\text{M} - \text{H}$] $^-$ 530.1301, found 530.1317.

Compound 10-D: ^1H NMR (500 MHz, CDCl_3) δ 8.15 (s, 1H), 7.43 (d, J = 8.1 Hz, 1H), 7.29 (d, J = 8.1 Hz, 1H), 7.24–7.18 (m, 1H), 7.08 (bs, 1H), 6.98–6.90 (m, 2H), 4.84 (bs, 1H), 4.18–4.05 (m, 2H), 3.33 (dt, J = 8.5 Hz, 1H), 2.27 (s, 3H), 1.68 (dd, J = 13.8, 10.0 Hz, 1H), 1.12 (t, J = 7.1 Hz, 3H), 0.92–0.87 (m, 1H), 0.82 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 175.5 (C), 170.4 (C), 163.9 (C), 157.3

(C), 155.4 (C), 147.8 (CH), 140.7 (C), 134.9 (C), 129.9 (CH), 128.8 (C), 127.9 (C), 125.9 (CH), 125.7 (d, $J = 8.3$ Hz, C), 123.9 (CH), 123.8 (CH), 123.4 (CH), 116.9 (CH), 65.4 (C), 60.8 (CH₂), 55.3 (CH), 50.3 (CH), 42.8 (CH₂), 30.9 (C), 29.5 (CH₃ × 3), 26.3 (CH₃), 14.2 (CH₃); IR $\nu_{\max} = 2955, 1755, 1716, 1634, 1601, 1473, 1458, 1421, 1371, 1337, 1279, 1256, 1225, 1200, 1158, 1118, 1075, 1024, 930, 778$ cm⁻¹; HRMS (ESI) calcd for C₂₈H₂₇Cl₂FNO₄ [M - H]⁻ 530.1301, found 530.1300.

Ethyl 2'-Oxo-2-(3-chloro-2-fluorophenyl)-5-neopentylspiro[cyclopentane-6'-chloro-3'-indoline]-3-carboxylate (13). Compound **10-A** (121 mg, 0.23 mmol) was hydrogenated over Pd/C (10%, 12 mg) in 11 mL of MeOH at room temperature for 5 h. The resulting mixture was filtered on Celite and washed with methanol twice. The filtrate was concentrated under reduced pressure and purified by column chromatography on silica gel (0–10% EtOAc/heptanes), affording compound **13** (36 mg, 30%, white powder, mp 188–190 °C): R_f 0.27 (15% EtOAc/heptanes); ¹H NMR (300 MHz, CDCl₃) δ 8.29 (s, 1H), 7.86 (d, $J = 8.2$ Hz, 1H), 7.13–7.05 (m, 2H), 6.84 (d, $J = 1.9$ Hz, 1H), 6.62 (td, $J = 8.0, 1.1$ Hz, 1H), 6.45 (td, $J = 6.5, 1.5$ Hz, 1H), 4.57 (d, $J = 12.0$ Hz, 1H), 3.87–3.79 (m, 1H), 3.72–3.59 (m, 2H), 2.61–2.49 (m, 3H), 0.93–0.87 (m, 1H), 0.81 (t, $J = 6.9$ Hz, 3H), 0.79 (s, 9H), 0.65 (d, $J = 14.0$, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 180.1 (C), 174.2 (C), 155.0 (C), 142.1 (C), 134.2 (C), 129.3 (CH), 128.6 (CH), 127.2 (d, $J = 2.6$ Hz, CH), 126.8 (C), 126.2 (d, $J = 13.2$ Hz, C), 123.7 (d, $J = 4.8$ Hz, CH), 122.5 (CH), 120.9 (d, $J = 19.5$ Hz, C), 110.7 (CH), 63.7 (C), 60.8 (CH₂), 46.9 (CH), 46.7 (d, $J = 3.2$ Hz, CH), 46.5 (CH), 44.1 (CH₂), 36.8 (CH₂), 30.4 (C), 29.9 (CH₃ × 3), 13.7 (CH₃); IR $\nu_{\max} = 2955, 1725, 1716, 1614, 1487, 1458, 1328, 1192, 1076, 916, 731$ cm⁻¹; HRMS (ESI) calcd for C₂₆H₂₇Cl₂FNO₃ [M - H]⁻: 490.1352, found 490.1365.

N-2-Morpholinoethyl 2'-Oxo-2-(3-chloro-2-fluorophenyl)-5-neopentylspiro[cyclopentane-6'-chloro-3'-indoline]-3-carboxamide (14). 4-(2-Aminoethyl)morpholine (53 μ L, 0.41 mmol) was dissolved in toluene (0.2 mL), and then a solution of trimethylaluminum 2 M (0.4 mL, 0.81 mmol) was added dropwise at 0 °C. The mixture was stirred for 30 min, and a solution of substrate **13** (31 mg, 0.06 mmol) in toluene (0.3 mL) was added. After 22 h of stirring at 100 °C, the solution was treated with citric acid 10% (10 mL) and extracted with EtOAc (2 × 10 mL). The combined organic extracts were washed with H₂O (2 × 30 mL), dried over MgSO₄, and concentrated under reduced pressure. The crude mixture was purified by flash chromatography on silica gel (0 to 2% MeOH/CH₂Cl₂) to give the desired amide **14** (7 mg, 19%, white powder): R_f 0.31 (5% MeOH/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 7.67 (s, 1H), 7.28 (s, 1H), 7.13 (td, $J = 7.6, 1.8$ Hz, 1H), 7.03 (dd, $J = 8.0, 1.9$ Hz, 1H), 6.85 (td, $J = 6.9, 1.8$ Hz, 1H), 6.80–6.75 (m, 1H), 6.71 (d, $J = 1.9$ Hz, 1H), 5.88 (bs, 1H), 4.25 (d, $J = 11.8$ Hz, 1H), 3.66–3.59 (m, 1H), 3.56 (t, $J = 4.6$ Hz, 4H), 3.35–3.18 (m, 2H), 2.96 (qd, $J = 9.8, 1.8$ Hz, 1H), 2.89–2.78 (m, 1H), 2.36–2.19 (m, 6H), 2.17–2.07 (m, 1H), 0.91–0.86 (m, 1H), 0.82 (s, 9H), 0.72 (dd, $J = 13.9, 1.8$ Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 178.5 (C), 172.9 (C), 158.4 (C), 155.0 (C), 142.0 (C), 137.7 (C), 134.2 (C), 129.9 (CH), 128.2 (d, $J = 3.3$ Hz, CH), 126.7 (CH), 126.3 (C), 125.4 (d, $J = 12.7$ Hz, C), 124.2 (d, $J = 3.9$ Hz, CH), 122.0 (CH), 110.6 (CH), 66.9 (CH₂), 56.9 (CH₂), 53.3 (CH₂), 51.5 (CH), 48.8 (CH), 46.1 (CH₂), 44.2 (CH), 36.5 (CH₂), 35.8 (CH₂), 30.7 (C), 30.0 (CH₃); IR $\nu_{\max} = 2955, 2928, 2855, 1713, 1646, 1615, 1548, 1485, 1455, 1365, 1335, 1309, 1264, 1245, 1142, 1116, 1072, 916, 733$ cm⁻¹; HRMS (ESI) calcd for C₃₀H₃₇Cl₂FN₃O₃ [M + H]⁺ 576.2196, found 576.2191.

N-2-Morpholinoethyl 2'-Oxo-2-(3-chloro-2-fluorophenyl)-5-neopentylspiro[cyclopent[3]ene-6'-chloro-3'-indoline]-3-carboxamide (12-A). Compound **12-A** was prepared from **10-A** (100 mg, 0.19 mmol) by following the same procedure as for **14**. The crude mixture was purified by flash chromatography on silica gel (1% MeOH/CH₂Cl₂) to afford **12-A** in 81% yield (89 mg): R_f 0.26 (5% MeOH/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 8.77 (s, 1H), 7.11 (td, $J = 8.0, 1.9$ Hz, 1H), 6.95–6.80 (m, 4H), 6.75–6.68 (m, 2H), 5.99 (bs, 1H), 5.02 (bs, 1H), 3.70–3.59 (m, 1H), 3.57–3.41 (m, 4H), 3.38–3.20 (m, 2H), 2.38–2.24 (m, 3H), 2.11–1.95 (m, 3H), 1.29 (dd, $J = 14.3, 9.8$ Hz, 1H), 0.83 (s, 9H), 0.68 (dd, $J = 14.3, 1.9$ Hz, 1H); ¹³C

NMR (75 MHz, CDCl₃) δ 180.6 (C), 164.1 (C), 157.9 (C), 154.7 (C), 141.9 (C), 136.9 (C), 134.2 (C), 129.9 (CH), 129.1 (d, $J = 3.5$ Hz, CH), 127.2 (CH), 126.0 (d, $J = 13.9$ Hz, C), 125.8 (C), 124.0 (d, $J = 4.9$ Hz, CH), 121.4 (CH), 121.1 (d, $J = 18.8$ Hz, C), 110.5 (CH), 66.9 (CH₂ × 2), 56.5 (CH₂), 53.1 (2 × CH₂, C), 51.9 (CH), 48.3 (CH), 44.0 (CH₂), 35.4 (CH₂), 30.8 (C), 29.5 (CH₃ × 3); IR $\nu_{\max} = 2957, 1721, 1654, 1614, 1516, 1484, 1457, 1367, 1327, 1238, 1143, 1118, 1070, 924, 750$ cm⁻¹; HRMS (ESI) calcd for C₃₀H₃₅Cl₂FN₃O₃ [M + H]⁺ 574.2040, found 574.2057.

N-2-Morpholinoethyl 2'-Oxo-2-(3-chloro-2-fluorophenyl)-5-neopentylspiro[cyclopent[3]ene-6'-chloro-3'-indoline]-3-carboxamide (12-B). Compound **12-B** was obtained from **10-B** (45 mg, 0.08 mmol) by the same procedure as for **14** (30 mg, 62% yield): R_f 0.21 (5% MeOH/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 8.60 (s, 1H), 7.32 (td, $J = 7.3, 1.7$ Hz, 1H), 7.21–7.08 (m, 3H), 6.88 (d, $J = 1.6$ Hz, 1H), 6.61 (dd, $J = 8.0, 1.6$ Hz, 1H), 6.28 (bs, 1H), 5.73 (d, $J = 8.0$ Hz, 1H), 4.62 (bs, 1H), 3.57–3.39 (m, 4H), 3.37–3.20 (m, 2H), 3.13 (d, $J = 9.5$ Hz, 1H), 2.48–2.38 (m, 1H), 2.37–2.26 (m, 3H), 2.22–2.12 (m, 2H), 1.66 (dd, $J = 13.9, 10.3$ Hz, 1H), 0.83–0.76 (m, 1H), 0.76 (s, 9H); ¹³C NMR (75 MHz, CDCl₃) δ 180.0 (C), 163.2 (C), 158.1 (C), 154.8 (C), 144.9 (CH), 142.6 (C), 136.9 (C), 134.4 (C), 130.3 (CH), 126.7 (CH), 126.4 (C), 124.9 (CH), 124.8 (d, $J = 4.7$ Hz, CH), 121.9 (d, $J = 18.0$ Hz, C), 121.8 (CH), 110.4 (CH), 66.9 (CH₂ × 2), 62.9 (C), 56.5 (CH₂), 53.2 (CH₂ × 2), 49.3 (CH), 48.8 (CH), 41.5 (CH₂), 35.6 (CH₂), 30.7 (C), 29.5 (CH₃ × 3); IR $\nu_{\max} = 2955, 1714, 1653, 1615, 1514, 1486, 1457, 1366, 1329, 1235, 1141, 1117, 1069, 914, 730$ cm⁻¹; HRMS (ESI) calcd for C₃₀H₃₅Cl₂FN₃O₃ [M + H]⁺ 574.2040, found 574.2047.

N-2-Morpholinoethyl 2'-Oxo-2-(3-chloro-2-fluorophenyl)-5-neopentylspiro[cyclopent[3]ene-6'-chloro-3'-indoline]-3-carboxamide (12-C). Compound **12-C** was obtained from **10-C** (86 mg, 0.16 mmol) by the same procedure as for **12-A** (64 mg, 69% yield): R_f 0.38 (5% MeOH/CH₂Cl₂); ¹H NMR (300 MHz, CDCl₃) δ 8.99 (s, 1H), 7.45–7.35 (m, 1H), 7.27 (dd, $J = 10.9, 2.3$ Hz, 2H), 7.19–7.13 (m, 2H), 7.00 (dd, $J = 8.0, 2.3$ Hz, 1H), 6.80 (d, $J = 1.7$ Hz, 1H), 6.06 (bs, 1H), 4.49 (bs, 1H), 3.55–3.36 (m, 5H), 3.35–3.21 (m, 2H), 2.45–2.36 (m, 1H), 2.34–2.21 (m, 3H), 2.19–2.09 (m, 2H), 1.25 (dd, $J = 13.4, 9.3$ Hz, 1H), 0.86 (s, 9H), 0.67 (d, $J = 13.4$ Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 177.7 (C), 163.0 (C), 158.3 (C), 155.0 (C), 147.1 (CH), 141.5 (C), 136.9 (C), 134.2 (C), 130.3 (CH), 127.8 (CH), 125.2 (d, $J = 14.4$ Hz, C), 124.8 (d, $J = 4.6$ Hz, CH), 124.1 (CH), 122.5 (CH), 121.3 (d, $J = 18.1$ Hz, C), 110.9 (CH), 66.8 (CH₂ × 2), 63.7 (C), 56.4 (CH₂), 53.1 (CH₂ × 2), 52.0 (CH), 47.6 (CH), 42.5 (CH₂), 35.5 (CH₂), 30.8 (C), 29.5 (CH₃ × 3); IR $\nu_{\max} = 2956, 1721, 1650, 1614, 1513, 1485, 1457, 1366, 1321, 1272, 1233, 1142, 1116, 1069, 923, 735$ cm⁻¹; HRMS (ESI) calcd for C₃₀H₃₅Cl₂FN₃O₃ [M + H]⁺ 574.2040, found 574.2044.

■ ASSOCIATED CONTENT

● Supporting Information

¹H and ¹³C NMR spectra. X-ray crystal data for compounds **4a**, **10-A**, **13**, **10-B**, **10-C**, and **10-D** (CCDC deposit nos. 890163, 890164, 890165, 890166, 890167, and 890168). 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.

■ ACKNOWLEDGMENTS

We thank Sanofi for a grant to C.G. and Carlos Garcia-Echeverria for his kind support. The Cost actions ORCA (CM0905) and PhoSciNet (CM0802) are warmly acknowledged.

REFERENCES

- (1) (a) Bond, R. F.; Boeyens, J. C. A.; Holzapfel, C. W.; Steyn, P. S. *J. Chem. Soc., Perkin Trans. 1* **1979**, 1751–1760. (b) Polonsky, J.; Merrien, M. A.; Prangé, T.; Pascard, C.; Moreau, S. *J. Chem. Soc., Chem. Commun.* **1980**, 601. (c) Mugishima, T.; Tsuda, M.; Kasai, Y.; Ishiyama, H.; Fukushi, E.; Kawabata, J.; Watanabe, M.; Akao, K.; Kobayashi, J. *J. Org. Chem.* **2005**, *70*, 9430–9435. (d) Greshock, T. J.; Grubbs, A. W.; Jiao, P.; Wicklow, D. T.; Gloer, J. B.; Williams, R. M. *Angew. Chem., Int. Ed.* **2008**, *47*, 3573–3577. (e) Fensome, A.; Adams, W. R.; Adams, A. L.; Berrodin, T. J.; Cohen, J.; Huselton, C.; Illenberger, A.; Kern, J. C.; Hudak, V. A.; Marella, M. A.; Melenski, E. G.; McComas, C. C.; Mugford, C. A.; Slayden, O. D.; Yudit, M.; Zhang, Z.; Zhang, P.; Zhu, Y.; Winneker, R. C.; Wrobel, J. E. *J. Med. Chem.* **2008**, *51*, 1861–1873. (f) Eastwood, P. R.; Gonzalez Rodriguez, J.; Giulio Matassa, V. (Almirall S.A.) WO2009/132774, 2009. (g) Liu, J.-J. (Hoffmann-La Roche Inc.) US 2009/0239889, 2009. (h) Tsukamoto, S.; Kawabata, T.; Kato, H.; Greshock, T. J.; Hirota, H.; Ohta, T.; Williams, R. M. *Org. Lett.* **2009**, *11*, 1297–1300. (i) Finefield, J. M.; Kato, H.; Greshock, T. J.; Sherman, D. H.; Tsukamoto, S.; Williams, R. M. *Org. Lett.* **2011**, *13*, 3802–3805. (j) Eastwood, P.; González, J.; Gómez, E.; Vidal, B.; Caturla, F.; Roca, R.; Balagué, C.; Orellana, A.; Domínguez, M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 4130–4133. (k) Guerrero, C. A.; Sorensen, E. J. *Org. Lett.* **2011**, *13*, 5164–5167.
- (2) (a) Aroyan, C. E.; Dermenci, A.; Miller, S. J. *Tetrahedron* **2009**, *65*, 4069–4084. (b) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *Nature Chem.* **2011**, *3*, 473–477. (c) Peng, J.; Huang, X.; Jiang, L.; Cui, H.-L.; Chen, Y.-C. *Org. Lett.* **2011**, *13*, 4584–4587. (d) Li, Y.-M.; Li, X.; Peng, F.-Z.; Li, Z.-Q.; Wu, S.-T.; Sun, Z.-W.; Zhang, H.-B.; Shao, Z.-H. *Org. Lett.* **2011**, *13*, 6200–6203. (e) Sun, W.; Zhu, G.; Wu, C.; Hong, L.; Wang, R. *Chem.—Eur. J.* **2012**, *18*, 6737–6741. (f) Jiang, K.; Tiwari, B.; Chi, Y. R. *Org. Lett.* **2012**, *14*, 2382–2385. (g) Albertshofer, K.; Tan, B.; Barbas, C. F., III. *Org. Lett.* **2012**, *14*, 1834–1837. (h) Sun, W.; Zhu, G.; Wu, C.; Hong, L.; Wang, R. *Chem.—Eur. J.* **2012**, *18*, 13959–13963. (i) Dalpozzo, R.; Bartoli, G.; Bencivenni, G. *Chem. Soc. Rev.* **2012**, *41*, 7247–7290.
- (3) (a) Zhang, C.; Lu, X. *J. Org. Chem.* **1995**, *60*, 2906–2908. (b) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535–544. (c) Methot, J. L.; Roush, W. R. *Adv. Synth. Catal.* **2004**, *346*, 1035–1050. (d) Ye, L.-W.; Zhou, J.; Tang, Y. *Chem. Soc. Rev.* **2008**, *37*, 1140–1152. (e) Cowen, B. J.; Miller, S. J. *Chem. Soc. Rev.* **2009**, *38*, 3102–3116. (f) Marinetti, A.; Voituriez, A. *Synlett* **2010**, 174–194.
- (4) Voituriez, A.; Pinto, N.; Neel, M.; Retaillieu, P.; Marinetti, A. *Chem.—Eur. J.* **2010**, *16*, 12541–12544.
- (5) Zhang, X.-C.; Cao, S.-H.; Wei, Y.; Shi, M. *Chem. Commun.* **2011**, 47, 1548–1550.
- (6) (a) Tan, B.; Candeias, N. R.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 4672–4675. (b) Zhong, F.; Han, X.; Wang, Y.; Lu, Y. *Angew. Chem., Int. Ed.* **2011**, *50*, 7837–7841. (c) Deng, H.-P.; Wei, Y.; Shi, M. *Org. Lett.* **2011**, *13*, 3348–3351.
- (7) (a) Selvakumar, K.; Vaithyanathan, V.; Shanmugam, P. *Chem. Commun.* **2010**, 46, 2826–2828. (b) Wang, Y.; Liu, L.; Zhang, T.; Zhong, N.-J.; Wang, D.; Chen, Y.-J. *J. Org. Chem.* **2012**, *77*, 4143–4147.
- (8) Yong, S. R.; Williams, M. C.; Pyne, S. G.; Ung, A. T.; Skelton, B. W.; White, A. H.; Turner, P. *Tetrahedron* **2005**, *61*, 8120–8129.
- (9) (a) Pyne, S. G.; Schafer, K.; Skelton, B. W.; White, A. H. *Chem. Commun.* **1997**, 2267–2268. (b) Cowen, B. J.; Miller, S. J. *J. Am. Chem. Soc.* **2007**, *129*, 10988–10989. (c) Sampath, M.; Loh, T.-P. *Chem. Sci.* **2010**, *1*, 739–742. (d) Fujiwara, Y.; Fu, G. C. *J. Am. Chem. Soc.* **2011**, *133*, 12293–12297.
- (10) The *cis*, *trans* stereochemical labels indicate the arrangements of the two phenyl groups at C2 and C5, with respect to the carbonyl group at the C1 position.
- (11) The minor isomer, formed in <5% amount, has been tentatively assigned as an isomer of the α -adduct **4a** by ^1H NMR analysis of the mixture.
- (12) A very small amount of the *cis,cis* isomer **10-D** has been isolated when the reaction was carried out at 80 °C in the presence of PMe_2Ph . X-ray data are given as Supporting Information.
- (13) (a) Dudding, T.; Kwon, O.; Mercier, E. *Org. Lett.* **2006**, *8*, 3643–3646. (b) Mercier, E.; Fonovic, B.; Henry, C.; Kwon, O.; Dudding, T. *Tetrahedron Lett.* **2007**, *48*, 3617–3620. (c) Xia, Y.; Liang, Y.; Chen, Y.; Wang, M.; Jiao, L.; Huang, F.; Liu, S.; Li, Y.; Yu, Z.-X. *J. Am. Chem. Soc.* **2007**, *129*, 3470–3471. (d) Liang, Y.; Liu, S.; Xia, Y.; Li, Y.; Yu, Z.-X. *Chem.—Eur. J.* **2008**, *14*, 4361–4373.
- (14) It is worth noting here that approximately the same product distribution was observed in the crude reaction mixtures when either (Z)- or (E)-**1b** were subjected to [3 + 2]-cyclizations in the presence of PPh_3 or PMe_2Ph . This is consistent with the postulated stepwise mechanism in Scheme 4, although isomerization of (Z)-**1b** into (E)-**1b** under phosphine catalysis might also account for this result.
- (15) The postulated γ -addition mode, as well as the rationale afforded in this paper to account for the observed selectivity, are rather speculative.
- (16) Gomez, C.; Betzer, J.-F.; Voituriez, A.; Marinetti, A. *ChemCatChem* DOI: 10.1002/cctc.201200442.
- (17) Ung, A. T.; Schafer, K.; Lindsay, K. B.; Pyne, S. G.; Amornraksa, K.; Wouters, R.; Van der Linden, I.; Biesmans, I.; Lesage, A. S. J.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2002**, *67*, 227–233.
- (18) Zou, Y.-Q.; Li, C.; Rong, J.; Yan, H.; Chen, J.-R.; Xiao, W.-J. *Synlett* **2011**, 1000–1004.
- (19) Steurer, M.; Jensen, K. L.; Worgull, D.; Jørgensen, K. A. *Chem.—Eur. J.* **2012**, *18*, 76–79.
- (20) Wang, D.; Wei, Y.; Shi, M. *Chem. Commun.* **2012**, 48, 2764–2766.
- (21) (a) Pham, T. Q.; Pyne, S. G.; Skelton, B. W.; White, A. H. *Tetrahedron Lett.* **2002**, *43*, 5953–5956. (b) Pham, T. Q.; Pyne, S. G.; Skelton, B. W.; White, A. H. *J. Org. Chem.* **2005**, *70*, 6369–6377.
- (22) Du, Y.; Lu, X. *J. Org. Chem.* **2003**, *68*, 6463–6465.
- (23) Jones, R. A.; Krische, M. J. *Org. Lett.* **2009**, *11*, 1849–1851.
- (24) Wang, J.-C.; Krische, M. J. *Angew. Chem., Int. Ed.* **2003**, *42*, 5855–5857.
- (25) (a) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Qiu, S.; Ding, Y.; Gao, W.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Tomita, Y.; Parrish, D. A.; Deschamps, J. R.; Wang, S. *J. Am. Chem. Soc.* **2005**, *127*, 10130–10131. (b) Ding, K.; Lu, Y.; Nikolovska-Coleska, Z.; Wang, G.; Qiu, S.; Shangary, S.; Gao, W.; Qin, D.; Stuckey, J.; Krajewski, K.; Roller, P. P.; Wang, C. *J. Med. Chem.* **2006**, *49*, 3432–3435. (c) Shangary, S.; Qin, D.; McEachern, D.; Liu, M.; Miller, R. S.; Qiu, S.; Nikolovska-Coleska, Z.; Ding, K.; Wang, G.; Chen, J.; Bernard, D.; Zhang, J.; Lu, Y.; Gu, Q.; Shah, R. B.; Pienta, K. J.; Ling, X.; Kang, S.; Guo, M.; Sun, Y.; Yang, D.; Wang, S. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 3933–3938. (d) Yu, S.; Qin, D.; Shangary, S.; Chen, J.; Wang, G.; Ding, K.; McEachern, D.; Qiu, S.; Nikolovska-Coleska, Z.; Miller, R.; Kang, S.; Yang, D.; Wang, S. *J. Med. Chem.* **2009**, *52*, 7970–7973. (e) Wang, S.; Zhao, Y.; Sun, W.; Kumar, S.; Leopold, L.; Debussche, L.; Barrere, C.; Carry, J.-C.; Amaning, K. WO Patent 2012065022 A2, 18 May 2012.