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Stereochemical implications in the synthesis of 3,3′-spirocyclopropyl oxindoles from β-aryl/alkyl-substituted alkylidene oxindoles

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ABSTRACT

3,3′-Spirocyclopropane oxindoles were synthesized in good to excellent yield and diastereoselectivity employing a Kukhtin–Ramirez reaction between readily accessible *E*-alkylidene oxindoles, commercially available $P(NMe_2)_3$, and α-keto esters. The stereoselectivity in the cyclopropanation event can be traced to the starting alkylidene geometry and the propensity of the exocyclic alkene to undergo isomerization in the presence of an electron rich phosphine.

1. Introduction

The spirooxindole framework has remained a synthetically challenging and privileged architectural motif that is prevalent in many pharmaceuticals and bioactive natural products.[1] In particular, the 3,3′-spirocyclopropyl oxindole core has recently generated considerable synthetic interest as an intriguing pharmacophore in medicinal discovery chemistry.[2] Additionally, this spirooxindole core is a versatile synthetic intermediate toward the 3,3′-spiropyrrolidinyl oxindole ring system, a prevalent substructure in numerous naturally occurring alkaloids (Fig. 1).[3] For example, the spirocyclopropyl oxindole motif has been implemented in the activity of NNRT HIV-1 and polo-like kinase inhibitors (Fig. 1).[2c,d,4] Furthermore, Carreira has elegantly demonstrated how Lewis-acid assisted ring openings of 3,3′-spirocyclopropyl oxindoles provide the corresponding spiropyrrolidinyl oxindole core in horsfiline and spirotryprostatin,[5] which displayed an array of biological activities, such as anticancer and anti-migraine properties as well as contraceptive activity.[5,6]

Due to the stereochemically dense framework of the spirocyclopropyl oxindoles, which contain at least one quaternary stereogenic center, combined with the potential for discovering new biologically active small molecules, we became interested in developing an efficient route toward this bicyclic motif. We envisioned that the two-carbon component necessary to form the

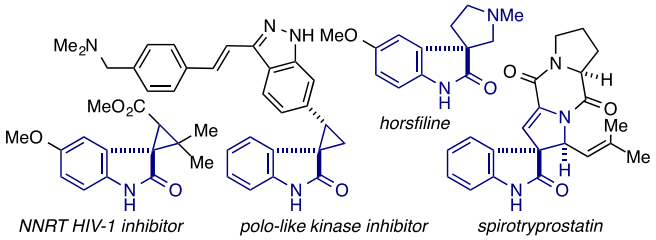

Fig. 1. Biologically active 3,3′-spirooxindoles.

cyclopropane could be installed via a reductive condensation of an α-keto ester, with the third carbon unit coming from a readily available alkylidene oxindole (Fig. 2a). Recently, the Kukhtin–Ramirez reaction of a trivalent phosphorus reagent to an α-keto ester has experienced a renaissance due to the inherent advantages of generating an intermediate dioxaphospholene **2b** in equilibrium with its more reactive zwitterionic form **2a** that exhibits ambiphilic reactivity under exceptionally mild reaction conditions.[7] We speculated that the soft anionic reactivity of this dioxaphospholene would add selectively to the β-position of an alkylidene oxindole **1** that would then set the stage for an intramolecular displacement of phosphine oxide via *C*-**4** to form the desired cyclopropane **5**.[8] Ultimately, the carbene-like reactivity of phospholene **2** enables the ketone precursor to serve as a diazo surrogate in this formal [2+1] cycloaddition.[2a,9] Recently, He and

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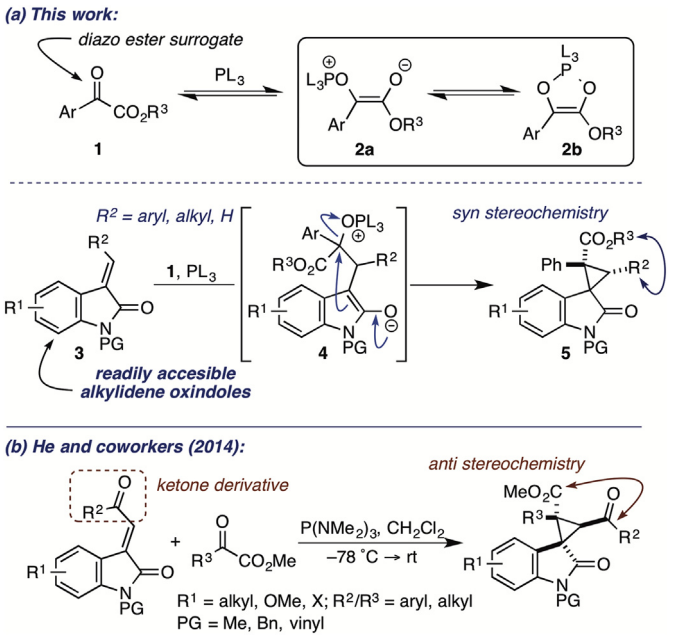
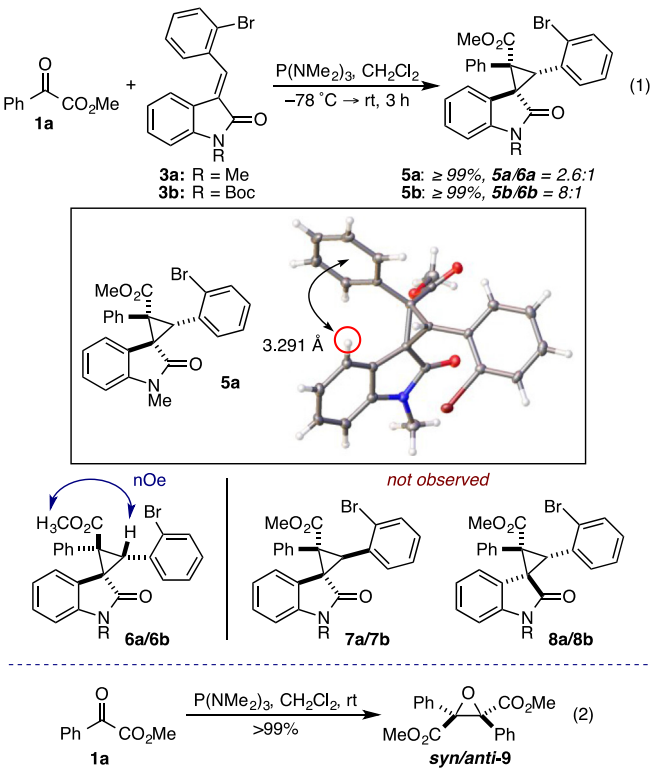


Fig. 2. Kukhtin–Ramirez condensation of alkylidene oxindoles.

co-workers demonstrated the utility of this approach toward alkylidene oxindoles bearing an electron withdrawing ketone at the β-position to provide the *anti* spriocyclopropane selectively (Fig. 2b).[10,11] We speculated that the absence of an electron withdrawing carbonyl group on the alkylidene would lead to conjugate addition of **2** to initially generate the tertiary cyclopropane stereocenter and subsequent oxindole spirocyclization. In contrast to He's proposal wherein the addition of **2** occurs at C3 of the oxindole ring, this mechanistic divergence should provide the *syn* spirocyclopropyl oxindole **5** preferentially. Additionally, this structural modification would also provide greater substrate flexibility for enhanced product diversity. Herein, we describe the successful application of this approach employing β-alkyl and β-aryl substituted alkylidene oxindoles to provide the corresponding *syn*-spirocyclopropyl oxindoles and mechanistic insights into the stereochemical outcome of C–C bond formation.

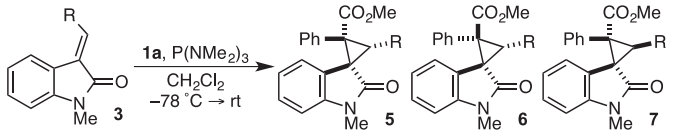
2. Results and discussion

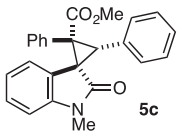
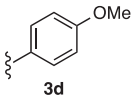
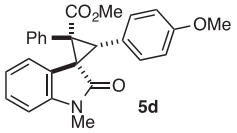
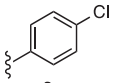
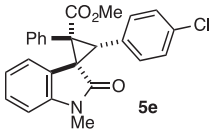
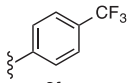
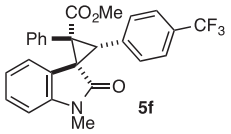
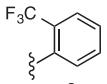
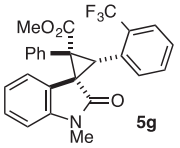
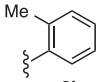
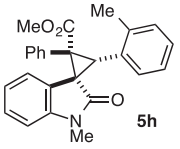
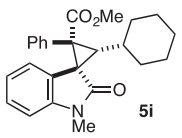
In his seminal work nearly 50 years ago on dioxaphospholene synthesis, Ramirez discovered that more sterically hindered phosphines exhibited greater nucleophilicity.[7a,12] Consequently, he surmised that this was due to a prevalence of the zwitterionic species **2a** over the more stable heterocyclic form **2b**.[13] These findings have since provided a basis for recent work by our group[14] and those of others,[15] in particular the elegant work by Radosevich and coworkers on the α-acetoxylation and α-amination of α-keto esters.[2a,9c,16] Therefore, our initial foray into the synthesis of 3,3′-spirocyclopropyl oxindoles began by examining the efficacy of hexamethylphosphorus triamine ($P(NMe_2)_3$) to mediate the cyclopropanation of alkylidene oxindoles. Thus, treatment of methylbenzoyl formate **1a** and (*E*)-*o*-bromophenylalkylidene *N*-methyloxindole **3a** with $P(NMe_2)_3$ in CH_2Cl_2 at −78 °C to room temperature for 3 h afforded the highly substituted spirocyclopropyl oxindole **5a** in quantitative yield and in a 2.6:1 ratio to **6a**. Interestingly, stereoisomers **7a**/**8a** were not observed.[17] The major diastereomer **5a** was unambiguously identified by single crystal X-ray diffraction while the relative configuration of **6a** was determined by NOE experiments. The X-ray crystal structure of **5a** revealed that the proton at C4 on the benzenoid ring of the spirooxindole was a mere 3.291 Å from the center of the phenyl ring originating from **1a**. This proximity results in a distinct shielding of the nucleus and a marked upfield shift in the ^1H NMR (5.71 ppm) that is in contrast to the comparable proton in **6a** (6.93 ppm).[18] While the corresponding *N*-Boc protected alkylidene oxindole **3b** underwent cyclopropanation in comparable yield, the ratio of spirooxindoles **5b**/**6b** improved to 8:1. Other phosphorus reagents (e.g., PPh_3, $P(OMe)_3$, etc.) exhibited poor reactivity leading to little cyclopropane formation (<5%). An examination of $P(NMe_2)_3$ stoichiometry revealed that employing a slight excess of phosphine and α-keto ester (1.1 equiv) resulted in incomplete conversion of the alkylidene oxindole. However, using 1.5 equiv resulted in 100% conversion of the starting material. It is important to note that conducting the reaction at ambient temperatures led to a significant decrease in the yield of **5**. After careful examination, we discovered that this loss in yield was due to the formation of *cis*/*trans* epoxides **9** (Eq. 2).[19] Minimization of this undesired by product was achieved by the addition of $P(NMe_2)_3$ to **1a** and **3a** at −78 °C before allowing the mixture to warm. Presumably, by keeping the reaction temperature low, the addition of **2** to **1a** is mitigated.[9c]



With optimal conditions in hand, we turned our attention toward evaluating the substitution pattern and functional group tolerance within alkylidene oxindole **3**. In general, a variety of aryl- and alkyl-substituted alkylidene oxindoles **3** provided high yields of the corresponding spirocyclopropyl oxindoles **5** (Table 1). While phenyl-substituted alkylidene **3c** provided the corresponding oxindole **5c** in high yield, a third diastereomer **7c** was now formed in the cyclopropanation reaction with **1a** (entry 1).[20] The diastereoselectivity for the major diastereomer **5c** was comparable to what we observed in the formation of **5a** albeit with less facial selectivity for the dioxaphospolene upon initial alkylidene addition. Electron rich aryl alkylidene **3d** and electron poor substrates **3e** and **3f** bearing electron donating and electron withdrawing groups at the *para* positions, respectively, proceeded in high yields and comparable diastereoselectivities (entries 2–4). Likewise, an *ortho*-CF_3 substituent on aryl alkylidene **3g** underwent cyclopropanation to

Table 1
Alkylidene oxindole structural variability[a]



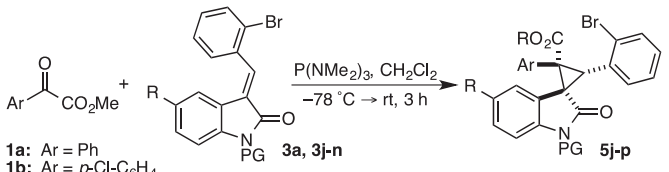
Entry	R	Major product **5**[b]	Yield[c]	**5**:**6**:**7**[d]
1	 **3c**	 **5c**	94%	5:1:1.5
2	 **3d**	 **5d**	≥99%	6:1:2
3	 **3e**	 **5e**	91%	5:1:2
4	 **3f**	 **5f**	80%	5:1:2
5	 **3g**	 **5g**	98%	4:1:0
6	 **3h**	 **5h**	21%	2:1:0
7	 **3i**	 **5i**	76%	≥98:1

[a] Reaction conditions: 0.15 mmol of **3**, 0.23 mmol of $P(NMe_2)_3$, and 0.23 mmol of **1a** in CH_2Cl_2 (0.25 M).
[b] Major isomer isolated.
[c] Combined yield of diastereomers.
[d] Diastereomeric ratio determined by ^1H NMR (500 MHz) of the crude reaction mixture.

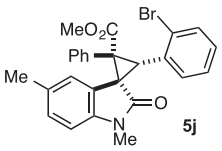
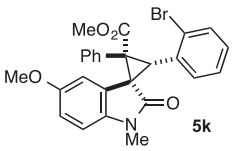
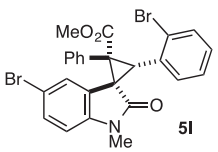
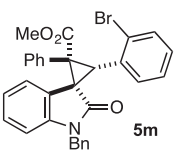
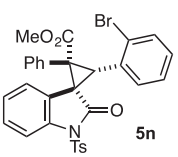
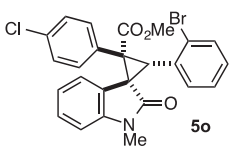
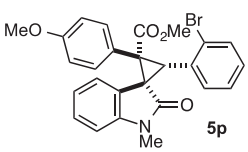
provide **5g** in 98% yield and as a 4:1:0 ratio of diastereomers (entry 5). However, in contrast to the oxindoles **3a** and **3g**, alkylidene **3h** bearing a methyl group at the *ortho* position underwent cyclopropanation in relatively low yield to provide adduct **5h** as the major diastereomer in a 2:1:0 diastereomeric ratio (entry 6). This result would indicate that while *ortho* substitution may inhibit the conjugate addition of the dioxaphospholene from **1a**, the steric hindrance is mitigated by the presence of an electron withdrawing group. Interestingly, in contrast to the aryl alkylidene oxindoles, cyclohexyl alkylidene oxindole **3i** underwent smooth conversion to the spirocyclopropyl oxindole **5i** in 76% yield as a *single diastereomer* (entry 7). These results underscore the impact that subtle stereoelectronic effects within alkylidene oxindole **3** can have on the yield and diastereoselectivity of cyclopropanations with α-keto esters when mediated by a bulky electron rich phosphine.

To explore how oxindole substitution can impact the efficiency of the cyclopropanation event, we chose to evaluate the performance of oxindole **3a** derivatives under our standard reaction

Table 2
Examination of 1,2-dicarbonyls **1** with alkylidenes **3**[a]



1a: Ar = Ph
1b: Ar = *p*-Cl-C_6H_4
1c: Ar = *p*-MeO-C_6H_4

Entry	**1**	**3**	Major product **5**[b]	Yield[c]	**5**:**6**:**7**[d]
1	**1a**	**3j**: R=Me PG=Me	 **5j**	91%	2:1:0
2	**1a**	**3k**: R=OMe PG=Me	 **5k**	94%	4:1:0
3	**1a**	**3l**: R=Br PG=Me	 **5l**	≥99%	4:1:0
4	**1a**	**3m**: R=H PG=Bn	 **5m**	≥99%	6:1:0
5	**1a**	**3n**: R=H PG=Ts	 **5n**	85%	3:1:0
6	**1b**	**3a**	 **5o**	≥99%	3:1:1
7	**1c**	**3a**	 **5p**	65%	3:1:1

[a] Reaction conditions: 0.15 mmol of **3**, 0.23 mmol of $P(NMe_2)_3$, and 0.23 mmol of **1** in CH_2Cl_2 (0.25 M).
[b] Major isomer isolated.
[c] Combined yield of diastereomers.
[d] Diastereomeric ratio determined by ^1H NMR (500 MHz) of the crude reaction mixture.

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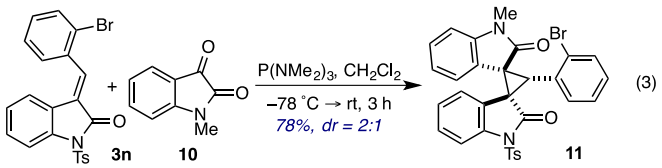
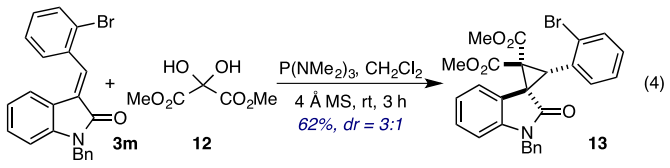
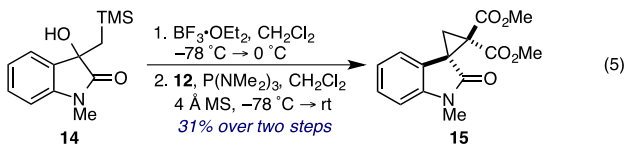
conditions (Table 2). In general, C5-substituted alkylidene oxindoles **3j**–**l** underwent cyclopropanation with **1a** and $P(NMe_2)_3$ in good to excellent yields and proceeded with comparable diastereoselectivity from what we observed with **3a** (entries 1–3). The reaction conditions also tolerated a variety of *N*-substituted oxindoles. Both *N*-benzyl and *N*-tosyl protected oxindoles **3m** and **3n** were efficiently converted to the corresponding spirocyclopropyl oxindoles **5m** and **5n** in 85% and quantitative yields and with better diastereoselectivity than **3a**, respectively (entries 4 and 5). Not surprisingly, substitution of the oxindole nitrogen proved critical, as we observed no product formation in cases where the free N–H was present. Additionally, the reaction proved tolerant, yet sensitive to electronic variations on the aryl α-keto ester **1**. Treatment of oxindole **3a** with α-keto ester **1b** bearing a chloride in the 4-position of the phenyl ring provided spirocyclopropyl oxindole **5o** in near quantitative yield (entry 6). However, *p*-methoxyphenyl α-keto ester **1c** gave the corresponding penta-substituted cyclopropane **5p** in only 65% yield (entry 7). The diminished yield of **5p** when compared to **5a** and **5o** is consistent with a mechanism involving nucleophilic addition of $P(NMe_2)_3$ to the α-keto ester, which should be favored for more electron deficient substrates.

Given the emergence of natural products and pharmaceutically relevant targets bearing the 1,2-bisoxindole motif,[21] we sought to expand this method to include isatin derivatives as the 1,2-dicarbonyl component. Thus, treatment of alkylidene oxindole **3m** and *N*-methyl isatin **10** with $P(NMe_2)_3$ provided the corresponding bis-spirooxindole cyclopropane **11** in 78% yield albeit in 2:1 diastereoselectivity (Eq. 3). Remarkably only two stereoisomers of this highly substituted cyclopropane were observed from this reaction. Additionally, 1,2,3-tricarbonyls proved competent under these reaction conditions. For example, dihydroxymalonate **12**[22] underwent dehydration in the presence of 4 Å molecular sieves followed by phospholene formation and addition to alkylidene **3m** to yield the diester substituted spirocyclopropyl oxindole **13** in 62% yield and 3:1 diastereoselectivity (Eq. 4). Likewise, unsubstituted alkylidene oxindoles participated in the cyclopropanation event with malonate **12**. Peterson olefination of β-silanol **14** followed by treatment with **12** and $P(NMe_2)_3$ in the presence of 4 Å MS provided cyclopropane **15** in 31% yield over two steps (Eq. 5).

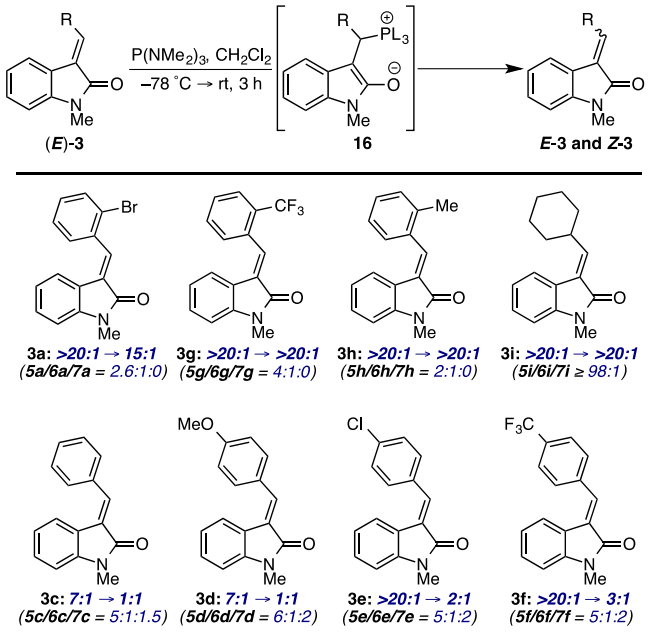






Irrespective of the oxindole protecting group, we observed overall that *o*-substituted aryl alkylidene oxindoles (**3a**, **3g**, and **3h**) or bulky alkyl substitutions (**3i**) seemed to provide spirocyclopropanes with superior diastereoselectivities. Hypothesizing that the stereoselectivity of this reaction is influenced by the geometry of the starting alkylidene upon addition of the intermediate **2**, we decided to examine the tendency of the *E*-alkylidene oxindoles to isomerize in the presence of the nucleophilic phosphorus reagent $P(NMe_2)_3$ (Table 3). Rather than allowing the

Table 3
Alkylidene isomerization of oxindole **3**[a,b,c]

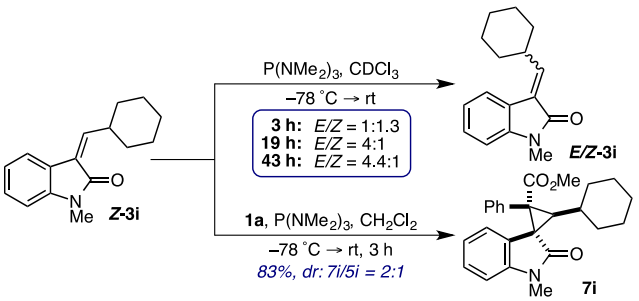


[a]Reaction conditions: 0.15 mmol of **3** and 0.23 mmol of $P(NMe_2)_3$ in CH_2Cl_2 (0.25 M). [b]Ratio of alkene isomers determined by ^1H NMR (500 MHz) of the crude reaction mixture. [c]Diastereoselectivities in the cyclopropanation of each alkylidene oxindole with **1a** are provided for comparison.

substrate to reach equilibrium, we chose to measure the alkylidene geometry after 3 h given that the cyclopropanation event is complete over this period of time. Exposing electron deficient, *ortho*-substituted alkylidenes **3a** and **3g** to 1.5 equiv of $P(NMe_2)_3$ in CH_2Cl_2 at −78 °C, allowing the reaction to warm to room temperature, and stirring for an additional 3 h led to a slight erosion in the ratio of *E*/*Z*-alkylidenes for **3a** while **3g** retained the corresponding *E*-isomer. *E*-Alkylidene oxindoles **3h** and **3i** also proved resilient to isomerization showing no erosion in alkene geometry under the reaction conditions. However, independent treatment of a 7:1 *E*/*Z* mixture of alkylidenes **3c** and **3d** led to significant isomerization of the double bond resulting in a 1:1 ratio after 3 h. Additionally, electron deficient *E*-alkylidenes **3e** and **3f** bearing *para* substitution underwent isomerization to provide a 2:1 and 3:1 mixture of *E*- and *Z*-alkenes, respectively. These results would seem to indicate a correlation between the propensity of the *E*-alkylidene oxindole to isomerize under the reaction conditions and the formation of the minor spirocyclopropyl oxindole diastereomer **7**. More specifically, we conclude that the minor diastereomer **7** arises from phospholene addition to the corresponding *Z*-alkylidene.

With increasing evidence that the propensity for isomerization under the reaction conditions of the double bond in the starting alkylidene oxindole played an important role in the diastereoselectivity of the cyclopropanation event, we next sought to evaluate how the stereochemical outcome is affected when the reaction is performed on the corresponding *Z*-alkylidene. Thus, we chose to examine oxindole **3i**, based on its apparent strong preference for the *E*-isomer, by first evaluating the extent of double bond isomerization when subjecting alkylidene *Z*-**3i** to $P(NMe_2)_3$ in CH_2Cl_2 from −78 °C to room temperature (Scheme 1). What we discovered was that *Z*-**3i** and $P(NMe_2)_3$ led to a 1:1.3 ratio of *E*/*Z* alkylidenes after 3 h that continued to isomerize to 4:1 over the course of an additional 16 h. The *E*/*Z* ratio of alkylidenes did not change significantly after allowing the mixture to stir at room temperature for 43 h. Treatment of *Z*-**3i** to the cyclopropanation

reaction conditions in the presence of α-keto ester **1a** gave spirocyclopropyl oxindole **7i** as the major diastereomer in 83% yield and in a ratio of **7i**/**5i**/**6i**=2:1:0. Formation of cyclopropane **7i** as the major isomer, which is epimeric at the former β-carbon, from oxindole *Z*-**3i** is consistent with our hypothesis that the alkylidene geometry influences the diastereoselectivity in the cyclopropanation event.



Scheme 1. Impact of *Z*-**3i** alkylidene geometry on the diastereoselectivity.

Overall, we were highly encouraged by the ease of this process as the reaction typically produced a high yield of the corresponding spirocyclopropyl oxindole and exhibited interesting trends in diastereoselectivity based on the geometry of the starting alkylidene oxindole. Based on these findings, our working mechanistic hypothesis involves initial formation of phosphine adducts **2a** and **2b** resulting from the addition of $P(NMe_2)_3$ to α-keto ester **1a**.[7a,9c] In contrast to He's proposed initial enone conjugate addition, subsequent 1,4-addition to the alkylidene oxindole **3** affords oxindole enolate intermediates **17a**–**c** via the corresponding transition states **16a**–**c** (Fig. 3).[10,23] Finally, C-alkylation and displacement of $O{=}PL_3$ provides the corresponding spirocyclopropyl oxindoles **5a**, **6a** and **7a**.[24] In light of our studies on the propensity of *ortho*-substituted aryl substituents alkylidenes to be resistant to alkene isomerization under the reaction conditions, and the resulting correlation to the formation of cyclopropane diastereomers, it seems prudent to speculate that steric interactions in the initial C–C bond forming event impact the stereoselectivity of the cyclopropanation event. If we assume that the initial phospholene addition is reversible,[16b] then minimization of gauche interactions in transition state **16a** and intermediate **17a** over those present in **16b**/**16c** and **17b**/**17c** lead to the observed preference for formation of cyclopropane **5a** over diastereomers **6a** or **7a**. However, double bond isomerization is kept at bay with sterically encumbered alkylidenes, thereby enabling the formation of cyclopropane **5a** to predominate.

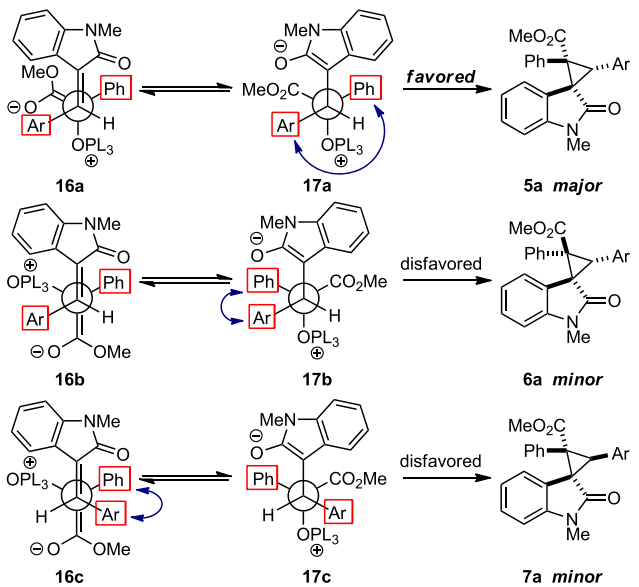


Fig. 3. Proposed origin of diastereoselectivity in the cyclopropanation.

3. Conclusion

In summary, we have developed an efficient approach toward the synthesis of the 3,3′-spirocyclopropane oxindole core via mild enolate generation using a Kukhtin–Ramirez condensation event with a broad range of aryl alkylidenes. Overall, high yields were obtained of the cyclopropanes with electron-deficient, *o*-substituted aryl alkylidenes affording particularly high diastereoselectivity. Mechanistic studies indicate a strong correlation between the substitution on the alkylidene, tendency of the alkylidene to undergo *E*/*Z* isomerization under the reaction conditions, and the diastereoselectivity of the cyclopropanation event. Further studies on expanding this method to a catalytic enantioselective variant, as well as the application of this reaction for the synthesis of biologically active natural products is currently being pursued, and will be reported in due course.

4. Experimental section

4.1. General

All solvents and reagents were ACS reagent grade, obtained from commercial sources, and used without further purification unless otherwise stated. Acetonitrile (CH_3CN), dimethylformamide (DMF), toluene (PhMe), tetrahydrofuran (THF), dichloromethane (CH_2Cl_2) and diethyl ether (Et_2O) were passed through a column of molecular sieves and stored under argon. Chlorobenzene (C_6H_5Cl) was distilled over CaH_2 and stored over 4 Å molecular sieves. All reactions were carried out in oven-dried glassware under nitrogen unless otherwise specified. Alkylidene oxindoles **3a**,[25] **3c**–**f**,[26] **3h**,[25] and **3i**,[26] methylbenzoyl formate derivatives **1b**–**c**,[27] *N*-methyl isatin **10**,[28] hydrate **12**,[29] and β-silanol **14**[30] were prepared according to the literature and spectral data (^1H NMR and ^{13}C NMR) were consistent with reported data.

^1H nuclear magnetic resonance (NMR) spectra were obtained at either 300, 400, 500 or 600 MHz. ^{13}C NMR were obtained at 100, 125 or 150 MHz. Chemical shifts are reported in parts per million (ppm, δ), and referenced from the solvent or tetramethylsilane (TMS). Coupling constants are reported in Hertz (Hz). Spectral splitting patterns are designated as s, singlet; d, doublet; t, triplet; q, quartet; p, pentet; m, multiplet; comp, complex; app, apparent; hom, higher order multiplet; and br, broad. Infrared (IR) spectra were obtained using a Thermo Electron Nicolet 380 FT-IR using a silicon (Si) crystal in an attenuated total reflectance (ATR) tower and reported as wavenumbers (cm^{-1}). High and Low resolution electrospray ionization (ESI) measurements were made with a Bruker MicroTOF II mass spectrometer. Analytical thin layer chromatography (TLC) was performed using EMD 250 micron 60 F_{254} silica gel plates, visualized with UV light and stained with either *p*-anisaldehyde, ceric ammonium nitrate (CAN) or potassium permanganate ($KMnO_4$) solutions. Flash column chromatography was performed according to Still's procedure using EMD 40–63 μm 60 Å silica gel.[31]

4.2. *tert*-Butyl (*E*)-3-(2-bromobenzylidene)-2-oxoindoline-1-carboxylate ((*E*)-3b)

To a solution of (*E*)-3-(2-bromobenzylidene)indolin-2-one[32] (510 mg, 1.7 mmol) in CH_2Cl_2 (8.5 mL) at 0 °C was added NaH (82 mg, 2.0 mmol, 60% mineral oil dispersion) and stirred for 30 min at which point hydrogen gas evolution had ceased. Then

DMAP (10.4 mg, 0.09 mmol) was added in one portion followed by Boc_2O (445 mg, 2.0 mmol) portionwise over 5 min. The resulting mixture was allowed to warm to room temperature by removal of the ice bath, and stirred for 20 min. The residual NaH was quenched by the addition of water (5 mL) and the layers separated. The organic phase was washed with saturated aqueous NaCl (10 mL), dried ($MgSO_4$), and then concentrated under reduced pressure. The resulting crude mixture was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to provide 626 mg (94%) of (*E*)-**3b** as an orange solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.92 (d, *J*=7.8 Hz, 1H), 7.83 (s, 1H), 7.70 (d, *J*=8.4 Hz, 1H), 7.62 (d, *J*=7.2 Hz, 1H), 7.39 (t, *J*=7.2 Hz, 1H), 7.32–7.29 (m, 3H), 6.94 (t, *J*=7.2 Hz, 1H), 1.67 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 166.2, 149.5, 136.8, 135.5, 133.5, 131.2, 130.6, 130.1, 127.5, 124.3, 124.0, 122.8, 121.3, 115.5, 84.5, 28.3; IR (neat) 3084, 2959, 2886, 1752, 1720, 1460, 1372, 1363, 1333, 1304, 1291, 1249, 1159, 1088, 1063, 1043, 1026, 1002, 769, 755, 745 cm^{-1}; HRMS (ESI) *m*/*z*=422.0388 [$C_{20}H_{18}BrNaNO_3$ (M+Na) requires 422.0368]; mp=112–116 °C.

4.3. (*E*)-1-Methyl-3-(2-(trifluoromethyl)benzylidene)indolin-2-one ((*E*)-3g)

To a solution of (*E*)-3-(2-(trifluoromethyl)benzylidene)indolin-2-one[33] (300 mg, 1.04 mmol) in DMF (5.2 mL) at 0 °C was added NaH (50 mg, 1.25 mmol, 60% mineral oil dispersion) and stirred for 30 min at which point hydrogen gas evolution had ceased. Then methyl iodide (177 mg, 1.25 mmol) was added dropwise. The resulting mixture was allowed to warm to room temperature by removal of the ice bath, and stirred for 20 min. The residual NaH was quenched by the addition of saturated NH_4Cl (5 mL) and the layers were separated. The organic phase was washed with saturated aqueous NaCl (10 mL), dried ($MgSO_4$), and then concentrated under reduced pressure. The resulting crude mixture was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to provide 195 mg (62%) of (*E*)-**3g** as an orange solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.97 (app d, *J*=2.4 Hz, 1H), 7.79 (d, *J*=8.4 Hz, 1H), 7.67 (app d, *J*=7.8 Hz, 1H), 7.61 (t, *J*=7.2 Hz, 1H), 7.55 (t, *J*=7.8 Hz, 1H), 7.24 (dt, *J*=1.2, 7.8 Hz, 1H), 6.93 (t, *J*=7.8 Hz, 1H), 6.81 (d, *J*=7.8 Hz, 1H), 6.78 (dt, *J*=1, 7.2 Hz, 1H), 3.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 167.8, 134.1, 134.1, 133.1, 132.0, 132.0, 130.4, 130.4, 129.8, 129.3, 129.2, 129.0, 126.6 (q, *J*=5.1 Hz), 124.9, 123.2, 123.0, 122.1, 120.9, 108.5, 26.4; IR (neat) 3023, 2923, 1701, 1609, 1484, 1466, 1376, 1335, 1311, 1298, 1170, 1163, 1124, 1103, 1058, 1023, 776, 749, 650 cm^{-1}; HRMS (EI) *m*/*z*=303.0873 [$C_{17}H_{12}F_3NO$ (M) requires 303.0871]; mp=122–127 °C.

4.4. (*E*)-1-Benzyl-3-(2-bromobenzylidene)indolin-2-one ((*E*)-3m)

To a solution of (*E*)-3-(2-bromobenzylidene)indolin-2-one[32] (831 mg, 2.77 mmol) in DMF (14 mL) at 0 °C was added NaH (133 mg, 3.32 mmol, 60% mineral oil dispersion) and stirred for 30 min at which point hydrogen gas evolution had ceased. Then benzyl bromide (497 mg, 2.90 mmol) was added dropwise. The resulting mixture was allowed to warm to room temperature by removal of the ice bath, and stirred for 20 min. The residual NaH was quenched by the addition of saturated NH_4Cl (10 mL) and the layers were separated. The organic phase was washed with saturated aqueous NaCl (10 mL), dried ($MgSO_4$), and then concentrated under reduced pressure. The resulting crude mixture was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to provide 294 mg (27%) of (*E*)-**3m** as an orange solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.71 (dt, *J*=1.2, 8.4 Hz, 2H), 7.39 (dt, *J*=1.0, 7.2 Hz, 1H), 7.37–7.28 (comp, 7H), 7.16 (dt, *J*=1.2, 7.8 Hz, 1H), 6.79 (dt, *J*=1.2, 7.8 Hz, 1H), 6.72 (d, *J*=7.8 Hz, 1H), 5.0 (s, 2H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 168.2, 143.7, 136.1, 136.1, 135.8, 133.4, 131.0, 130.5, 130.3, 129.0, 128.5, 127.8, 127.6, 127.4, 124.4, 123.2, 122.1, 121.2, 109.5, 44.0; IR (neat) 3063, 2920, 1709, 1609, 1463, 1341, 1179, 1015, 733, 692 cm^{-1}; HRMS (ESI) *m*/*z*=412.0332 [$C_{22}H_{16}BrNNaO$ (M+Na) requires 412.0307]; mp=106–110 °C.

4.5. (*E*)-3-(2-Bromobenzylidene)-1-tosylindolin-2-one ((*E*)-3n)

To a solution of (*E*)-3-(2-bromobenzylidene)indolin-2-one[32] (1.50 g, 5.0 mmol) in THF (14 mL) at 0 °C was added NaH (260 mg, 6.5 mmol, 60% mineral oil dispersion) and stirred for 30 min at which point hydrogen gas evolution had ceased. Then tosyl chloride (1.04 g, 5.5 mmol) was added dropwise. The resulting mixture was allowed to warm to room temperature by removal of the ice bath, and stirred for overnight at room temperature. The residual NaH was quenched by the addition of saturated water (50 mL) and the layers were separated. The organic phase was washed with saturated aqueous NaCl (10 mL), dried ($MgSO_4$), and then concentrated under reduced pressure. The resulting crude mixture was purified by flash chromatography hexanes/EtOAc (3:1) to afford 1.37 g (60%) of (*E*)-**3n** as an orange solid. ^{1}H NMR (500 MHz, THF-d_8) δ 8.05 (d, *J*=8 Hz, 2H), 8.02 (d, *J*=8 Hz, 1H), 7.75 (d, *J*=8 Hz, 1H), 7.69 (d, *J*=8 Hz, 1H), 7.68 (s, 1H), 7.46–7.30 (m, 6H), 6.96 (t, *J*=8 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (125 MHz, THF-d_8) δ 165.2, 145.7, 140.1, 136.3, 135.1, 133.4, 132.5, 131.5, 130.8, 130.2, 128.2, 128.1, 127.7, 126.7, 123.9, 123.8, 123.0, 121.5, 113.8, 20.8; IR (neat) 2955, 2923, 2854, 2359, 1743, 1714, 1630, 1596, 1454, 1366, 1312, 1294, 1234, 1186, 1174, 1159, 1138, 1116, 1084 cm^{-1}; HRMS (ESI) *m*/*z*=454.0122 [$C_{22}H_{17}BrNO_3S$ (M+H) requires 454.0107]; mp=156–159 °C.

4.6. General procedure for the preparation of alkylidene oxindoles 3j–l

To a solution of the corresponding oxindole (1.0 equiv) in EtOH (0.7 M) at room temperature was added sequentially 2-bromobenzaldehyde (1.2 equiv) and piperidine (0.1 equiv). The reaction mixture was heated to reflux and stirred until the starting oxindole was consumed as judged by TLC (ca. ~4 h). The reaction was allowed to cool to room temperature by removal of the oil bath, and then concentrated under reduced pressure. The crude mixture was purified by flash chromatography eluting with hexanes/EtOAc at the indicated ratio to afford the title compound.

*4.6.1. (E)-3-(2-Bromobenzylidene)-1,5-dimethylindolin-2-one (**3j**).* Conversion of the corresponding oxindole[34] was performed on a 4.0 mmol scale and purified with hexanes/EtOAc (4:1) to afford 450 mg (34%) of **3j** as a red oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.78 (s, 1H), 7.70 (d, *J*=8 Hz, 1H), 7.66 (dd, *J*=7.6, 2 Hz, 1H), 7.38 (td, *J*=7.5, 1 Hz), 7.30 (td, *J*=7.5, 2 Hz, 1H), 7.06 (comp, 2H), 6.70 (d, *J*=8.5 Hz, 1H), 3.26 (s, 3H), 2.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.1, 142.5, 135.9, 135.4, 133.4, 131.4, 130.9, 130.7, 130.5, 128.9, 127.3, 124.4, 123.8, 121.0, 108.2, 26.4, 21.3; IR (neat) 2926, 2857, 1706, 1644, 1617, 1491, 1435, 1105, 1023, 802, 750 cm^{-1}; HRMS (ESI) *m*/*z*=328.0349 [$C_{17}H_{15}BrNO$ (M+H) requires 328.0332].

*4.6.2. (E)-3-(2-Bromobenzylidene)-5-methoxy-1-methylindolin-2-one (**3k**).* Conversion of the corresponding oxindole[34] was performed on a 3.2 mmol scale and purified with hexanes/EtOAc (4:1) to afford 419 mg (38%) of **3k** as an orange solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (s, 1H), 7.69 (dd, *J*=9.2, 1.1 Hz, 1H), 7.65 (dd, *J*=7.6, 1.5 Hz, 1H), 7.39 (td, *J*=7.6, 1.1 Hz, 1H), 7.28 (td, *J*=9.2, 1.5 Hz, 1H), 6.85 (d, *J*=2.5 Hz, 1H), 6.8 (dd, *J*=8.5, 2.5 Hz, 1H), 6.70 (d, *J*=8.5 Hz, 1H), 3.62 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.9, 155.3, 138.6, 135.9, 135.7, 133.4, 131.0, 130.4, 129.1, 127.4, 124.3, 121.9, 114.9, 110.3, 108.7, 55.9, 26.4; IR (neat) 3055, 3002, 2932, 2829,

1844, 1698, 1643, 1600, 1488, 1434, 1367, 1225, 1104, 1026 cm^{-1}; HRMS (ESI) m/z=344.0262 [$C_{17}H_{15}BrNO_2$ (M+H) requires 344.0281]; mp=150–152 °C.

*4.6.3. (E)-5-Bromo-3-(2-bromobenzylidene)-1-methylindolin-2-one (**3l**).* Conversion of the corresponding oxindole[35] was performed on a 0.68 mmol scale and purified with hexanes/EtOAc (3:1) to afford 196 mg (73%) of **3l** as a yellow solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.71 (dd, J=8.2, 1.1 Hz, 1H), 7.62 (dd, J=7.7, 1.4 Hz, 1H), 7.41 (td, J=7.6, 0.7 Hz, 1H), 7.39–7.34 (m, 2H), 7.31 (comp, J=0.7 Hz, 1H), 6.70 (d, J=8.2 Hz, 1H), 3.27 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5, 143.5, 137.4, 135.2, 133.6, 132.9, 131.4, 130.3, 127.6, 127.6, 125.9, 124.4, 122.8, 114.7, 109.9, 26.5; IR (neat) 3056, 2967, 1889, 1868, 1843, 1698, 1603, 1461, 1365, 1322, 1253, 1105, 1026 cm^{-1}; HRMS (ESI) m/z=391.9281 [$C_{16}H_{12}Br_2NO$ (M+H) requires 391.9280]; mp=163–165 °C.

4.7. General procedure for the phosphine-mediated cyclopropanation of alkylidene oxindoles

To a solution of **3** (1 equiv) and **1** (1.5 equiv) in CH_2Cl_2 (0.25 M) at −78 °C was added $P(NMe_2)_3$ (1.5 equiv) dropwise. The reaction was allowed to warm to room temperature over 3 h and stirring continued until full consumption of the starting materials was indicated by TLC analysis (ca. 2 h). The solvent was removed under reduced pressure and the resulting crude reaction mixture was purified by flash chromatography eluting with hexanes/EtOAc (3:1) to give the title spirocyclopropane oxindoles. The ratio of diastereomers was determined ^1H NMR (500 or 600 MHz) of the crude reaction mixture.

*4.7.1. Methyl-3-(2-bromophenyl)-1′-methyl-2′-oxo-2-phenylspiro[cyclopropane-1,3′-indoline]-2-carboxylate (**5a**–**7a**).* Cyclopropanation of (*E*)-**3a** with **1a** was performed on a 0.16 mmol scale over 3 h to provide 73 mg (>99%) of **5a** and **6a** in a ratio of 2.6:1. The ratio of diastereomers was determined by comparing the integrations of peaks at 5.71 ppm and 6.93 ppm in the ^1H NMR of the crude reaction mixture. **5a**: White solid. ^1H NMR (600 MHz, $CDCl_3$) δ 8.31 (d, J=6.5 Hz, 2H), 7.51–7.49 (m, 3H), 7.38–7.36 (m, 4H), 7.22 (t, J=6.5 Hz, 1H), 7.15 (t, J=6.5 Hz, 1H), 6.89 (d, J=6.5 Hz, 1H), 6.73 (t, J=6.5 Hz, 1H), 5.71 (d, J=6 Hz, 1H), 3.59 (s, 3H), 3.53 (s, 1H), 3.25 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 167.8, 144.6, 135.3, 133.2, 132.7, 132.3, 130.9, 128.9, 128.6, 128.6, 128.5, 127.8, 127.5, 127.3, 126.8, 126.2, 125.6, 122.1, 121.3, 52.5, 51.5, 44.7, 41.0, 26.6; IR (neat) 3016, 2928, 1740, 1707, 1615, 1470, 1378, 1343, 1252, 1132, 745, 699 cm^{-1}; HRMS (ESI) m/z=462.0674 [$C_{25}H_{21}BrNO_3$ (M+1) requires 462.0699]; mp=174–179 °C. **6a**: Yellow solid. Isolated as an inseparable mixture with epoxide **9**. ^1H NMR (500 MHz, $CDCl_3$) δ 7.39–7.37 (m, 2H), 7.28–7.26 (m, 6H), 7.08 (d, J=1.0, 7.5 Hz, 1H), 7.06–7.04 (m, 2H), 6.93 (d, J=8 Hz, 1H), 4.46 (s, 1H), 3.54 (s, 3H), 3.26 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 170.1, 167.8, 143.6, 132.5, 131.7, 130.9, 129.9, 128.8, 128.4, 128.3, 127.9, 127.9, 127.8, 127.8, 127.7, 127.5, 127.4, 122.2, 119.8, 108.1, 69.2, 53.4, 53.2, 52.5, 44.6, 40.5, 26.8; IR (neat) 3053, 2956, 1727, 1710, 1612, 1494, 1469, 1446, 1432, 1376, 1344, 1170, 1043, 1025, 742, 696 cm^{-1}; mp=195–200 °C.

*4.7.2. 1′-(tert-Butyl)-2-methyl-3-(2-bromophenyl)-2′-oxo-2-phenylspiro[cyclopropane-1,3′-indoline]-1′,2-dicarboxylate (**5b**).* Cyclopropanation of (*E*)-**3b** with **1a** was performed on a 0.13 mmol scale over 3 h to provide 59 mg (>99%) of **5b** and unprotected (N–H) **6b** in a ratio of 8:1. The ratio of diastereomers was determined by comparing the integrations of peaks at 5.71 ppm and 6.90 ppm in the ^1H NMR of the crude reaction mixture. **5b**/**6b**: White solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.89 (d, J=5.5 Hz, 1H), 7.51 (dd, J=2.0, 5.0, 7.3 Hz, 1H), 7.46–7.44 (m, 2H), 7.40–7.29 (m, 3H), 7.26–7.22 (m, 1H), 7.18–7.13 (m, 2H), 7.07–7.03 (ddd, J=1 Hz), 6.82 (t, J=7.6 Hz, 1H), 5.71 (d, J=7.6 Hz, 1H), 4.41 and 3.49 (s, 1H), 3.61 and 3.51 (s, 3H), 1.61 (s, 9H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 169.2, 168.3, 167.6, 149.5, 149.3, 140.7, 139.9, 134.7, 133.5, 132.8, 132.6, 132.2, 132.1, 132.0, 131.9, 131.1, 130.1, 129.3, 129.1, 128.8, 128.8, 128.5, 128.4, 128.3, 128.2, 127.6, 127.2, 127.0, 126.8, 125.9, 125.9, 125.4, 124.2, 123.4, 122.1, 120.3, 114.8, 114.7, 84.5, 84.2, 54.9, 53.3, 53.2, 52.8, 45.9, 43.1, 41.5, 40.5, 28.6, 28.4, 28.3; IR (neat) 3058, 2923, 2853, 1709, 1619, 1471, 1434, 1339, 1262, 1234, 1156, 1030, 751, 715 cm^{-1}; HRMS (ESI) m/z=570.0909 [$C_{29}H_{26}BrNNaO_5$ (M+Na) requires 570.0887]; mp=215–220 °C. **6b**: White solid. ^1H NMR (500 MHz, $CDCl_3$) 8.1 (s, 1H), 7.39–7.37 (m, 2H), 7.34–7.32 (m, 2H), 7.29–7.24 (m, 4H), 7.13 (d, J=7.5 Hz, 1H), 7.09–7.03 (m, 3H), 6.9 (d, J=7.5 Hz, 1H), 4.43 (s, 1H), 3.55 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.8, 169.3, 140.6, 132.5, 132.3, 131.8, 131.8, 130.2, 128.6, 128.2, 127.8, 127.4, 126.8, 126.5, 122.1, 120.8, 109.5, 53.3, 53.0, 42.7, 40.3, 29.7; IR (neat) 3057, 2980, 1788, 1758, 1726, 1608, 1465, 1349, 1295, 1249, 1148, 1098, 1026, 1002, 749, 697 cm^{-1}; HRMS (ESI) m/z=448.0569 [$C_{24}H_{19}BrNO_3$ (M+1) requires 448.0543]; mp=81–85 °C.

*4.7.3. Methyl-1′-methyl-2′-oxo-2,3-diphenylspiro[cyclopropane-1,3′-indoline]-2-carboxylate (**5c**–**7c**).* Cyclopropanation of (*E*)-**3c** with **1a** was performed on a 0.21 mmol scale over 3 h to provide 77 mg (94%) of **5c**–**7c** in a ratio of 4.7:1.4:1. The ratio of diastereomers was determined by comparing the integrations of peaks at 5.82 ppm, 5.69 ppm and 6.94 ppm in the ^1H NMR of the crude reaction mixture. **5c**/**7c**: White solid. ^1H NMR (500 MHz, $CDCl_3$) δ 7.53–7.33 (m, 1H), 7.26–7.17 (m, 10H), 6.95 and 6.92 (d, J=8.0 Hz, 1H), 6.72 and 6.67 (t, J=7.5 Hz, 1H), 5.82 and 5.69 (d, J=7.5 Hz, 1H), 4.13 and 3.64 (s, 1H), 3.73 and 3.58 (s, 3H), 3.37 and 3.33 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.3, 171.9, 170.7, 167.9, 144.8, 144.2, 135.5, 132.6, 132.4, 132.1, 131.2, 130.9, 130.8, 130.7, 128.7, 128.7, 128.4, 128.1, 128.1, 127.8, 127.7, 127.5, 127.4, 127.3, 127.1, 126.6, 123.4, 122.1, 121.5, 120.9, 108.1, 107.9, 53.1, 52.5, 51.9, 50.6, 44.9, 42.4, 41.3, 40.1, 27.0, 26.8; IR (neat) 3057, 2853, 1726, 1698, 1608, 1494, 1471, 1455, 137, 1253, 1229, 698 cm^{-1}; HRMS (ESI) m/z=384.1620 [$C_{25}H_{22}NO_3$ (M+1) requires 384.1594]; mp=151–156 °C. **6c**: Yellow solid. Isolated as an inseparable mixture with epoxide **9**. ^1H NMR (500 MHz, $CDCl_3$) δ 7.41–7.16 (comp, 11H), 7.11–7.09 (m, 2H), 6.94 (d, J=7.5 Hz, 1H), 4.04 (s, 1H), 3.57 (s, 3H), 3.28 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 170.1, 167.8, 143.6, 132.5, 131.7, 130.9, 129.9, 128.8, 128.4, 128.3, 127.9, 127.9, 127.8, 127.7, 127.7, 127.5, 127.4, 122.2, 119.8, 108.1, 69.2, 53.4, 53.2, 52.5, 44.6, 40.5, 26.8; IR (neat) 3062, 2925, 2850, 1746, 1727, 1604, 1492, 1441, 1335, 1251, 697 cm^{-1}; HRMS (ESI) m/z=384.1622 [$C_{25}H_{22}NO_3$ (M+1) requires 384.1594]; mp=149–156 °C.

*4.7.4. Methyl-3-(4-methoxyphenyl)-1′-methyl-2′-oxo-2-phenylspiro[cyclopropane-1,3′-indoline]-2-carboxylate (**5d**–**7d**).* Cyclopropanation of (*E*)-**3d** with **1a** was performed on a 0.18 mmol scale over 3 h to provide 72 mg (>99%) of **5d**–**7d** in a ratio of 5.5:1:1.8. The ratio of diastereomers was determined by comparing the integrations of peaks at 5.83 ppm, 5.67, and 6.90 ppm in the ^1H NMR of the crude reaction mixture. **5d**/**7d**: Orange oil. ^1H NMR (500 MHz, $CDCl_3$) δ 7.45–7.43 (m, 1H), 7.36–7.33 (m, 1H), 7.26–7.18 (m, 4H), 7.12 (d, J=8.5 Hz, 2H), 6.94 and 6.91 (d, J=8.0 Hz, 1H), 6.87 and 6.73 (d, J=8.0 Hz, 2H), 6.68 (t, J=7.5 Hz), 5.83 and 5.67 (d, J=7.5 Hz, 1H), 4.07 and 3.56 (s, 1H), 3.80 and 3.74 (s, 3H), 3.72 and 3.56 (s, 3H), 3.36 and 3.32 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.4, 171.9, 171.4, 167.9, 158.8, 158.7, 144.8, 144.2, 135.6, 132.7, 132.0, 131.9, 131.2, 130.9, 128.7, 128.6, 128.4, 128.1, 127.6, 127.5, 127.0, 126.7, 124.3, 124.1, 123.5, 122.1, 121.5, 120.8, 113.5, 113.3, 108.1, 107.9, 60.6, 55.3, 52.5, 51.9, 50.6, 44.5, 42.0, 41.4, 40.2, 30.8, 27.0, 26.8, 21.2, 19.3, 14.4, 13.9; IR (neat) 3053, 2947, 1733, 1709, 1610, 1514, 1469, 1247, 1225, 1177, 1030, 1012, 750, 733, 697 cm^{-1}; HRMS (ESI) m/z=414.1668 [$C_{26}H_{24}NO_4$ (M+1) requires 414.1700]. **6d**: Yellow solid. Isolated as an inseparable mixture with epoxide **9**. ^1H NMR (500 MHz, $CDCl_3$)

δ 7.38–7.28 (m, 6H), 7.22–7.20 (m, 2H), 7.07–706 (m, 2H), 6.90 (d, *J*=7.8 Hz, 1H), 6.72 (d, *J*=8.6 Hz, 2H), 3.98 (s, 1H), 3.74 (s, 3H), 3.53 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.5, 158.8, 143.4, 140.1, 134.3, 133.7, 132.5, 128.9, 128.7, 128.4, 128.3, 128.3, 127.9, 127.8, 127.4, 123.9, 122.1, 119.6, 55.2, 53.9, 53.4, 53.0, 51.3, 43.9, 26.6; IR (neat) 3016, 2950, 1724, 1705, 1610, 1514, 1469, 1375, 1341, 1260, 1226, 1186, 1060, 1031, 833, 697 cm^{-1}; HRMS (ESI) *m*/*z*=436.1520 [$C_{26}H_{23}NaNO_4$ (M+Na) requires 436.1519]; mp=177–181 °C.

*4.7.5. Methyl-3-(4-chlorophenyl)-1′-methyl-2′-oxo-2-phenylspiro[cyclopropane-1,3′-indoline]-2-carboxylate (**5e**–**7e**).* Cyclopropanation of (*E*)-**3e** with **1a** was performed on a 0.19 mmol scale over 3 h to provide 86 mg (91%) of **5e**–**7e** in a ratio of 3:1:1. The ratio of diastereomers was determined by comparing the integrations of peaks at 5.77 ppm and 6.97 ppm in the ^{1}H NMR of the crude reaction mixture. **5e**: White solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.27–7.19 (m, 7H), 7.18–7.14 (m, 4H), 6.95 (d, *J*=7.8 Hz, 1H), 6.69 (dt, *J*=1, 7.8 Hz, 1H), 5.77 (dd, *J*=1, 7.8 Hz, 1H), 4.07 (s, 1H), 3.72 (s, 3H), 3.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.9, 170.3, 144.6, 133.1, 132.4, 132.1, 130.8, 130.4, 128.4, 128.1, 128.1, 127.7, 126.8, 122.9, 120.8, 108.1, 53.0, 50.3, 41.4, 41.0, 26.9; IR (neat) 3013, 2884, 1731, 1702, 1605, 1493, 1466, 1433, 1374, 1349, 1315, 1254, 1231, 1085, 1013, 821, 765 cm^{-1}; HRMS (ESI) *m*/*z*=418.1190 [$C_{25}H_{21}ClNO_3$ (M+1) requires 418.1204]; mp=167–169 °C. **6e**: Yellow oil. Isolated as an inseparable mixture with epoxide **9**. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.36–7.27 (m, 6H), 7.18–7.12 (m, 4H), 7.08–7.04 (m, 2H), 6.97 (d, *J*=7.8 Hz, 1H), 3.96 (s, 1H), 3.53 (s, 3H), 3.25 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.0, 169.7, 143.4, 133.2, 132.8, 132.2, 130.8, 129.2, 128.6, 128.4, 127.9, 127.8, 127.5, 122.1, 119.6, 108.1, 53.2, 52.2, 43.6, 40.2, 26.6; IR (neat) 3063, 2991, 1725, 1703, 1613, 1493, 1470, 1434, 1375, 1343, 1252, 1225, 1171, 1128, 1090, 1003, 746 cm^{-1}; HRMS (ESI) *m*/*z*=418.1226 [$C_{25}H_{21}ClNO_3$ (M+1) requires 418.1204].

*4.7.6. Methyl-1′-methyl-2′-oxo-2-phenyl-3-(4-(trifluoromethyl)phenyl) spiro[cyclopropane-1,3′-indoline]-2-carboxylate (**5f**–**7f**).* Cyclopropanation of (*E*)-**3f** with **1a** was performed on a 0.17 mmol scale over 3 h to provide 74 mg (>99%) of **5f**–**7f** in a ratio of 3:1:1. The ratio of diastereomers was determined by comparing the integrations of peaks at 5.79 ppm and 6.96 ppm in the ^{1}H NMR of the crude reaction mixture. **5f**: Orange solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.46 (d, *J*=8.4 Hz, 2H), 7.35 (d, *J*=8.4 Hz, 2H), 7.29–7.26 (m, 2H), 7.23–7.19 (m, 4H), 6.97 (d, *J*=8.4 Hz, 1H), 6.71 (t, *J*=7.2 Hz, 1H), 5.79 (d, *J*=7.2 Hz, 1H), 4.13 (s, 1H), 3.74 (s, 3H), 3.78 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.8, 170.2, 144.7, 136.6, 132.3, 131.0, 130.2, 129.4, 129.2, 128.5, 128.1, 127.9, 126.7, 124.8 (q, *J*=3.9 Hz), 122.7, 120.9, 108.2, 53.1, 50.3, 41.6, 41.1, 26.9; IR (neat) 3057, 2988, 1731, 1716, 1612, 1495, 1471, 1432, 1375, 1325, 1167, 1123, 1067, 1009, 853, 749, 731 cm^{-1}; HRMS (ESI) *m*/*z*=452.1449 [$C_{26}H_{21}F_3NO_3$ (M+1) requires 452.1468]; mp=147–151 °C. **6f**: Yellow solid. Isolated as an inseparable mixture with epoxide **9**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (d, *J*=10.8 Hz, 2H), 7.44 (d, *J*=10.2 Hz, 2H), 7.24–7.16 (m, 1H), 7.43–7.31 (comp, 5H), 7.12–7.09 (m, 2H), 6.96 (d, *J*=9.0 Hz, 1H), 4.06 (s, 1H), 3.57 (s, 3H), 3.29 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 169.6, 167.5, 143.4, 136.4, 132.2, 131.8, 130.7, 129.7, 129.2, 129.0, 128.6, 128.5, 128.4, 128.2, 128.1, 128.0, 127.9, 127.8, 127.7, 127.5, 127.4, 127.1, 124.1, 124.1, 122.2, 119.6, 108.1, 108.0, 68.9, 53.2, 53.0, 52.4, 43.6, 40.4, 26.6, 24.4; IR (neat) 3063, 2960, 1746, 1740, 1725, 1614, 1471, 1436, 1378, 1277, 1197, 1111, 1063, 1017, 961, 822, 676 cm^{-1}; HRMS (EI) *m*/*z*=451.1427 [$C_{26}H_{20}F_3NO_3$ (M) requires 451.1434]; mp=173–176 °C.

*4.7.7. Methyl-1′-methyl-2′-oxo-2-phenyl-3-(2(trifluoromethyl)phenyl)spiro[cyclopropane-1,3′-indoline]-2-carboxylate (**5g**–**7g**).* Cyclopropanation of (*E*)-**3g** with **1a** was performed on a 0.17 mmol scale over 3 h to provide 72 mg (>99%) of **5g** and **6g** in a ratio of 4:1. The ratio of diastereomers was determined by comparing the integrations of peaks at 5.78 ppm and 6.94 ppm in the ^{1}H NMR of the crude reaction mixture. **5g**: White solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.56 (d, *J*=7.8 Hz, 1H), 7.61–7.58 (m, 2H), 7.43–7.32 (m, 7H), 7.22 (dt, *J*=1.2, 7.8 Hz, 1H), 6.89 (d, *J*=7.8 Hz, 1H), 6.72 (dt, *J*=1, 7.2 Hz, 1H), 5.78 (d, *J*=7.8 Hz, 1H), 3.81 (s, 1H), 3.62 (s, 3H), 3.21 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.1, 168.3, 144.6, 135.7, 133.2, 131.7, 131.6, 130.9, 129.3, 129.1, 128.9, 128.7, 127.7, 127.7, 126.2 (q, *J*=5.9 Hz), 126.1, 122.3, 121.5, 107.9, 52.8, 51.1, 41.5, 41.4, 26.6; IR (neat) 3047, 2984, 1739, 1702, 1614, 1493, 1470, 1375, 1309, 1258, 1141, 1121, 1037, 1006, 767, 729 cm^{-1}; HRMS (ESI) *m*/*z*=474.1286 [$C_{26}H_{20}F_3NaNO_3$ (M+Na) requires 474.1287]; mp=177–180 °C. **6g**: Yellow solid. Isolated as an inseparable mixture with epoxide **9**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 (d, *J*=8.4 Hz, 1H), 7.55 (d, *J*=9.0 Hz, 1H), 7.39–7.33 (comp, 5H), 7.29–7.26 (comp, 3H), 7.11–7.71 (m, 2H), 6.94 (d, *J*=8.4 Hz, 1H), 4.48 (s, 1H), 3.57 (s, 3H), 3.26 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 167.8, 143.7, 132.5, 132.3, 130.9, 130.6, 130.0, 128.8, 128.6, 128.1, 127.9, 127.8, 127.1, 126.9, 125.9, 122.4, 120.2, 108.2, 53.4, 53.3, 40.6, 38.4, 26.8; IR (neat) 3066, 2960, 1747, 1726, 1705, 1614, 1448, 1378, 1260, 1168, 1120, 1062, 1041, 1001, 822, 747, 695 cm^{-1}; HRMS (EI) *m*/*z*=451.1432 [$C_{26}H_{20}F_3NO_3$ (M) requires 451.1434]; mp=123–128 °C.

*4.7.8. Methyl-1′-methyl-2′-oxo-2-phenyl-3-(o-tolyl)spiro[cyclopropane-1,3′-indoline]-2-carboxylate (**5h**–**6h**).* Cyclopropanation of (*E*)-**3h** with **1a** was performed on a 0.24 mmol scale over 3 h to provide 22 mg (21%) of **5h** and **7h** in a ratio of 2:1. The ratio of diastereomers was determined by comparing the integrations of peaks at 5.71 ppm and 5.61 ppm in the ^{1}H NMR of the crude reaction mixture. **5h**/**7h**: Yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 (dd, *J*=1.2, 7.2 Hz, 1H), 7.49–7.48 (m, 2H), 7.38–7.32 (m, 3H), 7.24–7.19 (m, 4H), 7.15–7.12 (m, 3H), 6.99 (d, *J*=7.8 Hz, 1H minor), 6.94 (d, *J*=7.8 Hz, 1H minor), 6.94 and 6.92 (d, *J*=7.8 Hz, 1H), 6.73 and 6.62 (dt, *J*=1.2, 7.8 Hz, 1H), 5.71 and 5.61 (d, *J*=7.2 Hz, 1H), 4.03 and 3.53 (s, 1H), 3.76 and 3.60 (s, 3H), 3.37 and 3.29 (s, 3H), 2.58 and 2.06 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.2, 171.9, 170.6, 167.9, 144.5, 144.1, 139.4, 137.9, 135.6, 131.9, 131.7, 131.3, 131.2, 131.1, 130.9, 1304, 129.8, 128.7, 128.5, 128.4, 128.2, 128.0, 127.5, 127.4, 127.3, 126.4, 126.2, 125.3, 125.1, 123.5, 121.9, 121.4, 120.7, 107.9, 107.7, 52.9, 52.4, 51.6, 50.2, 43.6, 41.2, 40.5, 40.3, 29.7, 26.9, 26.6, 20.4, 20.3; IR (neat) 3054, 2979, 1733, 1708, 1652, 1612, 1540, 1492, 1343, 1221, 1001, 728 cm^{-1}; HRMS (ESI) *m*/*z*=398.1727 [$C_{26}H_{24}NO_3$ (M+1) requires 398.1751]; mp=136–141 °C.

*4.7.9. Methyl-3-cyclohexyl-1′-methyl-2′-oxo-2-phenylspiro[cyclopropane-1,3′-indoline]-2-carboxylate (**5i**).* Cyclopropanation of (*E*)-**3i** with **1a** was performed on a 0.18 mmol scale over 3 h to provide 52 mg (76%) of **5i** in a ratio of >20:1. **5i**: ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.34–7.21 (m, 6H), 6.91 (d, *J*=7.2 Hz, 1H), 6.73 (t, *J*=7.8 Hz, 1H), 5.93 (d, *J*=7.8 Hz, 1H), 3.67 (s, 3H), 3.31 (s, 3H), 2.62 (d, *J*=9.6 Hz, 1H), 2.40–2.38 (m, 1H), 1.85 (d, *J*=13.2 Hz, 1H), 1.59 (d, *J*=13.2 Hz, 1H), 1.54–1.47 (m, 2H), 1.43–1.41 (m, 1H), 1.31–1.26 (m, 1H), 1.19–1.13 (m, 1H), 0.95–0.85 (m, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.6, 170.4, 144.2, 131.9, 131.3, 128.3, 128.2, 127.0, 124.5, 124.4, 121.0, 107.9, 52.7, 50.6, 44.9, 39.4, 33.9, 33.4, 31.5, 26.7, 26.1, 25.9, 25.6; IR (neat) 3062, 2922, 1731, 1701, 1608, 1494, 1468, 1375, 1348, 1256, 1216, 1162, 1013, 752 cm^{-1}; HRMS (ESI) *m*/*z*=390.2083 [$C_{25}H_{28}NO_3$ (M+1) requires 390.2064]; mp=165–170 °C.

*4.7.10. Methyl-3-(2-bromophenyl)-1′,5′-dimethyl-2′-oxo-2-phenylspiro[cyclopropane-1,3′-indoline]-2-carboxylate (**5j**).* Cyclopropanation of (*E*)-**3j** with **1a** was performed on a 0.38 mmol scale over 3 h to provide 165 mg (91%) of **5j** and **6j** in a ratio of 2.15:1. The ratio of diastereomers was determined by comparing the integrations of peaks at 5.47 ppm and 6.96 ppm in the ^{1}H NMR of the crude reaction mixture. **5j**: White solid. ^{1}H NMR

(500 MHz, $CDCl_3$) δ 8.30 (d, J=7.8 Hz, 1H), 7.49 (m, 3H), 7.35 (m, 4H), 7.14 (td, J=8.1, 1.0 Hz, 1H), 7.01 (dd, J=7.8, 1.0 Hz, 1H), 6.77 (d, J=7.9 Hz, 1H), 5.47 (s, 1H), 3.59 (s, 3H), 3.49 (s, 1H), 3.23 (s, 3H), 2.04 (s, 3H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.8, 168.0, 142.5, 135.6, 133.4, 133.0, 132.5, 131.2, 130.8, 129.1, 128.8, 128.6, 127.8, 127.0, 126.5, 125.9, 123.4, 107.5, 52.7, 51.5, 44.8, 41.2, 26.8, 21.3; IR (neat) 3023, 2948, 1733, 1706, 1622, 1600, 1497, 1432, 1365, 1348, 1256, 1214, 1027, 748 cm^{-1}; HRMS (ESI) m/z=476.0835 [$C_{26}H_{23}BrNO_3$ (M+1) requires 476.0856]; mp=115–120 °C. **6j**: Yellow solid. Isolated as an inseparable mixture with epoxide **9**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (comp, 1H), 7.38 (comp, 1H), 7.29–7.26 (m, 5H), 7.12 (comp, 1H), 7.04 (comp, 2H), 6.96 (s, 1H), 6.81 (d, J=7.9 Hz, 1H), 4.41 (s, 1H), 3.55 (s, 3H), 3.24 (s, 3H), 2.37 (s, 3H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.3, 169.7, 141.6, 132.7, 132.6, 132.2, 132.1, 131.8, 130.4, 128.7, 128.4, 128.3, 128.0, 127.8, 127.2, 127.0, 126.6, 121.2, 107.9, 53.1, 53.0, 42.5, 40.2, 26.9, 21.5; mp=145–150 °C.

*4.7.11. Methyl-(2-bromophenyl)-5′-methoxy-1′-methyl-2′-oxo-2-phenylspiro[cyclopropane-1,3′-indoline]-2-carboxylate (**5k**).* Cyclopropanation of (*E*)-**3k** with **1a** was performed on a 0.26 mmol scale over 3 h to provide 121 mg (94%) of **5k** and **6k** in a ratio of 3.76:1. The ratio of diastereomers was determined by comparing the integrations of peaks at 3.52 ppm and 4.41 ppm in the ^{1}H NMR of the crude reaction mixture. **5k**: White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.29 (dd, J=7.8, 1.1 Hz, 1H), 7.52–7.49 (m, 3H), 7.37–7.34 (m, 4H), 7.15 (td, 8.0, 1.6 Hz, 1H), 6.79–6.74 (comp, 2H), 5.29 (dd, J=2.1 Hz, 1H), 3.61 (s, 3H), 3.52 (s, 1H), 3.50 (s, 3H), 3.23 (s, 3H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 168.0, 155.0, 138.5, 135.5, 133.4, 132.9, 132.5, 131.2, 129.1, 128.9, 128.7, 127.7, 127.0, 125.9, 112.9, 109.2, 108.2, 55.7, 52.7, 51.6, 45.1, 41.5, 26.9, IR (neat) 3057, 2979, 2944, 1735, 1707, 1604, 1496, 1434, 1366, 1251, 1202, 1027, 751 cm^{-1}; HRMS (ESI) m/z=492.0788 [$C_{26}H_{23}BrNO_4$ (M+1) requires 492.0805]; mp=155–163 °C. **6k**: Yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (comp, J=9.3 Hz, 1H), 7.37 (comp, J=9.3 Hz, 1H), 7.29–7.26 (m, 5H), 7.05–7.03 (m, 2H), 6.85 (comp, 1H), 6.83 (s, 1H), 6.80 (comp, 1H), 4.41 (s, 1H), 3.82 (s, 3H), 3.58 (s, 3H), 3.23 (s, 3H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 169.7, 156.0, 137.7, 132.7, 132.6, 132.2, 132.1, 130.8, 130.4, 128.7, 128.4, 128.0, 127.1, 126.6, 112.8, 108.4, 108.0, 56.2, 53.3, 53.1, 42.7, 40.5, 26.9; mp=149–154 °C.

*4.7.12. Methyl-5′-bromo-3-(2-bromophenyl)-1′-methyl-2′-oxo-2-phenylspiro[cyclopropane-1,3′-indoline]-2-carboxylate (**5l**).* Cyclopropanation of (*E*)-**3l** with **1a** was performed on a 0.19 mmol scale over 3 h to provide 102 mg (>99%) of **5l** and **6l** in a ratio of 3.97:1. The ratio of diastereomers was determined by comparing the integrations of peaks at 3.51 ppm and 4.41 ppm in the ^{1}H NMR of the crude reaction mixture. **5l**: White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (dd, J=7.8, 1.3 Hz, 1H), 7.50 (dd, J=8.0, 1.3, Hz, 1H), 7.45 (comp, 2H), 7.41–7.37 (m, 4H), 7.33 (dd, J=8.2, 2.0, Hz, 1H), 7.16 (td, J=8.0, 0.8 Hz, 1H), 6.76 (d, J=8.2 Hz, 1H), 5.74 (d, J=2.0 Hz, 1H), 3.61 (s, 3H), 3.51 (s, 1H), 3.22 (s, 3H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 167.6, 143.8, 135.0, 133.4, 132.5, 132.5, 131.0, 130.3, 129.3, 129.2, 128.9, 128.6, 127.1, 125.8, 125.5, 114.1, 109.2, 52.8, 52.1, 45.3, 41.2, 26.9; IR (neat) 3058, 2980, 2884, 1733, 1715, 1609, 1488, 1431, 1249, 1138, 1096, 751 cm^{-1}; HRMS (ESI) m/z=539.9776 [$C_{25}H_{20}Br_2NO_3$ (M+1) requires 539.9804]; mp=112–120 °C. **6l**: Yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (comp, 1H), 7.46 (dd, J=8.3, 1.9 Hz, 1H), 7.35 (comp, 1H), 7.31–7.26 (m, 6H), 7.06–7.04 (m, 2H), 6.80 (d, J=8.3 Hz, 1H), 4.41 (s, 1H), 3.60 (s, 3H), 3.24 (s, 3H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 169.5, 143.0, 132.7, 132.2, 132.1, 132.0, 130.9, 130.0, 129.2, 128.9, 128.5, 128.1, 127.0, 126.6, 123.7, 115.0, 109.5, 53.4, 53.4, 43.0, 40.0, 26.9; mp=140–144 °C.

*4.7.13. Methyl-1′-benzyl-3-(2-bromophenyl)-2′-oxo-2-phenylspiro[cyclopropane-1,3′-indoline]-2-carboxylate (**5m**).* Cyclopropanation of (*E*)-**3m** with **1a** was performed on a 0.13 mmol scale over 3 h to provide 68 mg (>99%) of **5m** and **6m** in a ratio of 6:1. The ratio of diastereomers was determined by comparing the integrations of peaks at 5.73 ppm and 6.97 ppm in the ^{1}H NMR of the crude reaction mixture. **5m**: Yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.38 (d, J=7.8 Hz, 1H), 7.48–7.47 (hom, 3H), 7.39–7.32 (comp, 7H), 7.28–7.26 (m, 2H), 7.11 (dt, J=1, 7.8 Hz, 1H), 7.18–7.17 (m, 1H), 6.81 (d, J=7.8 Hz, 1H), 6.69 (dt, J=1, 7.8 Hz, 1H), 5.73 (d, J=7.8 Hz, 1H), 5.10 (d, J=15.6 Hz, 1H), 4.78 (d, J=15.6 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9, 167.7, 143.6, 136.4, 135.1, 133.2, 132.7, 132.2, 130.9, 128.9, 128.7, 128.6, 128.5, 127.6, 127.4, 127.3, 126.8, 126.1, 125.6, 122.2, 121.2, 108.6, 52.5, 51.9, 44.5, 43.9, 41.0; IR (neat) 3032, 1968, 1734, 1705, 1614, 1491, 1469, 1231, 1126, 1104, 1002, 751 cm^{-1}; HRMS (ESI) m/z=538.0986 [$C_{31}H_{25}BrNO_3$ (M+1) requires 538.1012]; mp=159–164 °C.

*4.7.14. Methyl 3-(2-bromophenyl)-2′-oxo-2-phenyl-1′-tosylspiro[cyclopropane-1,3′-indoline]-2-carboxylate (**5n**).* Cyclopropanation of (*E*)-**3n** with **1a** was performed on a 0.30 mmol scale over 3 h to provide 171 mg (95%) of **5n** and **6n** in a ratio of 3:1. The ratio of diastereomers was determined by comparing the integrations of peaks at 3.40 ppm and 4.22 ppm in the ^{1}H NMR of the crude reaction mixture. **5n**/**6n**: White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32 (d, J=7.8 Hz, 1H), 8.10 (d, J=8.3 Hz, 1H minor), 8.03 (d, J=8.2 Hz, 1H), 7.90 (d, J=8.4 Hz, 2H), 7.85 (d, J=8.4 Hz, 1H), 7.41–7.32 (m, 10H), 7.32–7.23 (m, 7H), 7.23–7.15–7.08 (m, 7H), 7.01 (comp, 1H), 6.82 (t, J=7.6 Hz, 1H), 5.65 (d, J=7.6 Hz, 1H), 4.22 (s, 1H minor), 3.51 (s, 3H), 3.50 (s, 3H minor), 3.40 (s, 1H), 2.44 (s, 3H), 2.44 (s, 3H minor); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.8, 167.0, 145.3, 140.0, 135.3, 134.2, 133.3, 132.5, 132.1, 131.7, 131.6, 130.8, 130.2, 129.7, 129.6, 129.6, 129.3, 129.2, 128.8, 128.8, 128.7, 128.7, 128.5, 128.3, 128.2, 128.1, 127.9, 127.7, 127.2, 126.8, 125.7, 125.5, 124.6, 123.7, 122.4, 120.5, 113.8, 133.3, 53.7, 53.3, 52.81, 46.12, 43.7, 41.1, 21.88, 21.85; IR (neat) 3103, 2952, 1750, 1733, 1706, 1607, 1461, 1376, 1231, 945, 812 cm^{-1}; HRMS (ESI) m/z=602.0608 [$C_{31}H_{25}BrNO_5S$ (M+1) requires 602.0631]; mp=155–158 °C.

*4.7.15. Methyl-3-(2-bromophenyl)-2-(4-chlorophenyl)-1′-methyl-2′-oxospiro[cyclopropane-1,3′-indoline]-2-carboxylate (**5o**).* Cyclopropanation of (*E*)-**3a** with **1b** was performed on a 0.16 mmol scale over 3 h to provide 78 mg (>99%) of **5o** and **6o** in a ratio of 3:1:1. The ratio of diastereomers was determined by comparing the integrations of peaks at 3.48 ppm and 4.45 ppm in the ^{1}H NMR of the crude reaction mixture. **5o**: Yellow solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.23 (d, J=7.7 Hz, 1H), 7.51 (dd, J=1.0, 8.0 Hz, 1H), 7.45 (d, J=8.3 Hz, 2H), 7.35 (dd, J=1.0, 7.6 Hz, 1H), 7.33 (d, J=8.7 Hz, 2H), 7.24 (dt, J=1.0, 7.8 Hz, 1H), 7.15 (m, 1H), 6.91 (d, J=7.7 Hz, 1H), 6.78 (dt, J=1.0, 7.6 Hz, 1H), 5.79 (s, J=7.8 Hz, 1H), 3.59 (s, 3H), 3.48 (s, 1H), 3.26 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 167.5, 162.9, 144.6, 134.7, 133.8, 133.1, 132.4, 132.3, 129.0, 128.7, 127.6, 126.8, 125.8, 125.6, 122.1, 121.5, 107.8, 52.6, 50.7, 44.6, 40.9, 26.6; IR (neat) 3032, 2852, 1751, 1738, 1715, 1492, 1469, 1374, 1343, 1247, 1213, 1087, 1012, 752 cm^{-1}; HRMS (ESI) m/z=496.0338 [$C_{25}H_{20}BrClNO_3$ (M+1) requires 496.0310]; mp=159–163 °C. **6o**: Yellow solid. Isolated as an inseparable mixture with epoxide **9**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.59–7.57 (m, 1H), 7.36–7.30 (m, 5H), 7.23 (d, J=8.9 Hz, 2H), 7.17 (d, J=8.8 Hz, 2H), 7.11–7.05 (m, 2H), 6.94 (d, J=7.8 Hz, 1H), 4.45 (s, 1H), 3.55 (s, 3H), 3.27 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 174.4, 170.3, 169.1, 143.9, 140.2, 134.4, 134.4, 133.4, 132.9, 132.3, 132.1, 129.1, 128.9, 128.9, 128.6, 128.3, 127.0, 126.7, 122.4, 120.7, 54.1, 53.3, 52.2, 42.6, 40.5, 26.9; IR (neat) 3053, 2950, 1729, 1709, 1612, 1491, 1471, 1434, 1346, 1255, 1225, 1172, 1091, 1066, 1014, 829, 747 cm^{-1}; HRMS (ESI) m/z=496.0315 [$C_{25}H_{20}BrClNO_3$ (M+1) requires 496.0310]; mp=165–168 °C.

4.7.16. Methyl-3-(2-bromophenyl)-2-(4-methoxyphenyl)-1′-methyl-2′-oxospiro[cyclopropane-1,3′-indoline]-2-carboxylate

(***5p***). Cyclopropanation of (*E*)-**3a** with **1c** was performed on a 0.16 mmol scale over 3 h to provide 52 mg (65%) of **5p** and **6p** in a ratio of 3:1:1. The ratio of diastereomers was determined by comparing the integrations of peaks at 5.80 ppm and 6.96 ppm in the ^{1}H NMR of the crude reaction mixture. **5p**: Yellow oil. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.29 (d, J=8.4 Hz, 1H), 7.5 (d, J=7.8 Hz, 1H), 7.41 (d, J=6.5 Hz, 2H), 7.35 (t, J=7.2 Hz, 1H), 7.22 (t, J=7.2 Hz, 1H), 7.14 (t, J=7.2 Hz, 1H), 6.89 (d, J=7.8 Hz, 1H), 6.86 (d, J=8.4 Hz, 2H), 6.76 (t, J=7.2 Hz, 1H), 5.80 (d, J=7.2 Hz, 1H), 3.83 (s, 3H), 3.58 (s, 3H), 3.49 (s, 3H), 3.25 (s, 3H), ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.9, 168.2, 159.9, 144.8, 133.4, 133.0, 132.5, 132.3, 129.1, 127.6, 127.5, 127.0, 126.5, 125.8, 122.4, 121.5, 114.0, 107.8, 100.0, 60.6, 55.5, 52.6, 51.0, 45.1, 41.3, 26.8, 21.3, 14.4; IR (neat) 3056, 2935, 1735, 1709, 1609, 1510, 1470, 1434, 1375, 1346, 1248, 1175, 1163, 1027, 834, 751, 729 cm^{-1}; HRMS (ESI) m/z=492.0804 [$C_{26}H_{23}BrNO_4$ (M+1) requires 492.0805] mp=149–156 °C.

*4.7.17. 3′-(2-Bromophenyl)-1-methyl-1″-tosyldispiro[indoline-3,1′-cyclopropane-2′,3″-indoline]-2,2″-dione (**11**).* Cyclopropanation of (*E*)-**3n** with **10** was performed on a 0.20 mmol scale over 3 h to provide 113 mg (95%) of **11** in a ratio of 3:1. The ratio of diastereomers was determined by comparing the integrations of peaks at 4.13 ppm and 4.09 ppm in the ^{1}H NMR of the crude reaction mixture. **11**: White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ (mixture of major and minor diastereomers) 8.03 (dd, J=7.9, 1.0, Hz, 1H), 7.95 (d, J=8.3 Hz, 1H, minor), 7.92 (d, J=8.2 Hz, 1H), 7.88 (d, J=8.4 Hz, 1H), 7.82 (d, J=7.8 Hz, 1H, minor), 7.76 (d, J=8.4 Hz, 2H), 7.43 (comp, 2H), 7.38–7.33 (m, 2H), 7.31–7.27 (m, 2H), 7.24–7.10 (m, 10H), 7.04 (dd, J=7.9, 1 Hz, 1H, minor), 6.99 (comp, 1H), 6.95–6.88 (m, 2H), 6.83 (comp, 2H), 4.13 (s, 1H), 4.09 (s, 1H, minor), 3.22 (s, 3H), 3.14 (s, 3H, minor), 2.38 (s, 3H), 2.38 (s, 3H, minor), ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.7, 170.2, 167.5, 145.7, 145.4, 144.4, 143.9, 139.4, 135.1, 132.9, 132.9, 132.6, 132.2, 129.8, 129.8, 129.7, 129.6, 129.6, 129.0, 128.9, 128.4, 128.0, 128.0, 126.8, 126.7, 126.0, 125.8, 125.5, 124.2, 123.9, 123.6, 122.4, 122.1, 121.3, 120.8, 113.1, 113.0, 107.9, 107.8, 49.3, 47.2, 41.7, 41.2, 27.1, 26.8, 21.9; IR (neat) 3053, 2954, 1751, 1712, 1610, 1460, 1374, 1233, 1176, 1142, 1086, 1027, 950, 749 cm^{-1}; HRMS (ESI) m/z=599.0608 [$C_{31}H_{24}BrN_2O_4S$(M+1) requires 599.0635] mp=172–178 °C.

*4.7.18. Dimethyl-1′-benzyl-3-(2-bromophenyl)-2′-oxospiro[cyclopropane-1,3′-indoline]-2,2-dicarboxylate (**13**).* Cyclopropanation of (*E*)-**3m** with **12** was performed on a 0.35 mmol scale over 3 h to provide 113 mg (62%) of **11** in a ratio of 3:1. The ratio of diastereomers was determined by comparing the integrations of peaks at 4.72 ppm and 4.13 ppm in the ^{1}H NMR of the crude reaction mixture. **13**: White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (dt, J=1, 8.0 Hz, 1H), 7.55 (dd, J=1.0, 8.0 Hz, 1H), 7.50 (dd, J=1.0, 7.5 Hz, 1H), 7.37–7.25 (m, 7H), 7.24–7.15 (m, 1H), 7.05 (t, J=8 Hz, 1H), 6.83 (d, J=7.5 Hz, 1H), 5.10 (d, J=16 Hz, 1H), 4.72 (d, J=16 Hz, 1H), 4.13 (s, 1H), 3.82 (s, 3H), 3.65 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.6, 166.7, 164.8, 144.2, 136.1, 133.2, 132.5, 132.4, 131.6, 131.5, 129.6, 129.3, 128.9, 128.8, 128.6, 128.5, 127.9, 127.8, 1277, 127.5, 126.9, 125.7, 125.0, 123.5, 122.5, 109.2, 109.2, 53.9, 53.4, 53.3, 52.9, 50.2, 44.5, 44.2, 42.4, 42.2, 40.9; IR (neat) 3063, 2971, 1713, 1748, 1611, 1468, 1430, 1245, 1176, 1133, 749, 696 cm^{-1}; HRMS (ESI) m/z=520.0779 [$C_{27}H_{23}BrNO_5$ (M+1) requires 520.0754]; mp=156–159 °C.

*4.7.19. Dimethyl 1′-methyl-2′-oxospiro[cyclopropane-1,3′-indoline]-2,2-dicarboxylate (**15**).* Freshly distilled $BF_3{\cdot}OEt_2$ (1.22 mL, 9.62 mmol) was added to a solution of **14**[30] (500 mg, 2.0 mmol) in CH_2Cl_2 (40 mL) at −78 °C. The reaction was allowed to warm to 0 °C by replacing the dry ice/acetone bath with an ice water bath, and stirred for 1 h. The resulting mixture was transferred slowly to a flask containing saturated aqueous $NaHCO_3$ (50 mL), the layers were separated, and the organic phase was extracted with CH_2Cl_2 (4×50 mL). The organic extracts were combined and then partially concentrated under reduced pressure to a total volume of ~5 mL. To this crude reaction mixture was added sequentially **12** (656 mg, 4 mmol), $P(NMe_2)_3$ (0.726 mL, 4 mmol), and 4 Å molecular sieves. The mixture was stirred for 18 h at room temperature, then filtered to remove the precipitate that had formed, and the filtrate concentrated under reduced pressure. The residue was purified by flash chromatography eluting with hexanes/ethyl acetate (3:1) to provide 179 mg (31%) of **15** as a light yellow solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.35 (d, J=8.4 Hz, 1H), 7.31 (t, J=7.2 Hz, 1H), 7.01 (t, J=7.8 Hz, 1H), 6.89 (d, J=8.4 Hz, 1H), 3.79 (s, 3H), 3.74 (s, 3H), 3.26 (s, 3H), 2.49 (d, J=4.8 Hz, 1H), 2.45 (d, J=4.8 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.56, 166.03, 165.84, 144.73, 128.54, 124.36, 123.15, 122.35, 108.30, 53.32, 53.11, 45.35, 38.02, 26.76, 24.40; IR (neat) 3102, 3013, 2953, 2849, 1749, 1732, 1608, 1549, 1494, 1467, 1433, 1381, 1343, 1249, 1185, 1162, 1147, 1125, 1107, 1044, 1010; HRMS (ESI) m/z 290.1023 [$C_{15}H_{16}NO_5$ (M+H) requires 290.1040]; mp=146–148 °C.

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Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.tet.2015.06.004.

References and notes

1. (a) Xia, M.; Ma, R.-Z. *J. Heterocycl. Chem.* **2014**, *51*, 539; (b) Cheng, D.; Ishihara, Y.; Tan, B.; Barbas, C. F. *ACS Catal.* **2014**, *4*, 743; (c) Trost, B. M.; Bringley, D. A.; Zhang, T.; Cramer, N. *J. Am. Chem. Soc.* **2013**, *135*, 16720; (d) Hanhan, N. V.; Ball-Jones, N. R.; Tran, N. T.; Franz, A. K. *Angew. Chem., Int. Ed.* **2012**, *51*, 989; (e) Dugal-Tessier, J.; O'Bryan, E. A.; Schroeder, T. B. H.; Cohen, D. T.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2012**, *51*, 4963; (f) Ball-Jones, N. R.; Badillo, J. J.; Franz, A. K. *Org. Biomol. Chem.* **2012**, *10*, 5165; (g) Madin, A.; O'Donnell, C. J.; Oh, T.; Old, D. W.; Overman, L. E.; Sharp, M. J. *J. Am. Chem. Soc.* **2005**, *127*, 18054.
2. (a) Zhao, W.; Fink, D. M.; Labutta, C. A.; Radosevich, A. T. *Org. Lett.* **2013**, *15*, 3090; (b) Jiang, X.; Cao, Y.; Wang, Y.; Liu, L.; Shen, F.; Wang, R. *J. Am. Chem. Soc.* **2010**, *132*, 15328; (c) Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Wu, T. Y.-H.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2105; (d) Jiang, T.; Kuhen, K. L.; Wolff, K.; Yin, H.; Bieza, K.; Caldwell, J.; Bursulaya, B.; Tuntland, T.; Zhang, K.; Karanewsky, D.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2109; (e) 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.
3. (a) Galliford, C. V.; Scheidt, K. A. *Angew. Chem., Int. Ed.* **2007**, *46*, 8748; (b) Lerchner, A.; Carreira, E. M. *Chem.—Eur. J.* **2006**, *12*, 8208.
4. Sampson, P. B.; Liu, Y.; Patel, N. K.; Feher, M.; Forrest, B.; Li, S.-W.; Edwards, L.; Laufer, R.; Lang, Y.; Ban, F.; Awrey, D. E.; Mao, G.; Plotnikova, O.; Leung, G.; Hodgson, R.; Mason, J.; Wei, X.; Kiarash, R.; Green, E.; Qiu, W.; Chirgadze, N. Y.; Mak, T. W.; Pan, G.; Pauls, H. W. *J. Med. Chem.* **2015**, *58*, 130.
5. (a) Meyers, C.; Carreira, E. M. *Angew. Chem., Int. Ed.* **2003**, *42*, 694; (b) Fischer, C.; Meyers, C.; Carreira, E. M. *Helv. Chim. Acta* **2000**, *83*, 1175; (c) Alper, P. B.; Meyers, C.; Lerchner, A.; Siegel, D. R.; Carreira, E. M. *Angew. Chem., Int. Ed.* **1999**, *38*, 3186.
6. Marti, C.; Carreira, E. M. *J. Am. Chem. Soc.* **2005**, *127*, 11505.
7. (a) Ramirez, F. *Acc. Chem. Res.* **1968**, *1*, 168; (b) Ramirez, F.; Kugler, H. J.; Smith, C. P. *Tetrahedron* **1968**, *24*, 1931.
8. (a) Ramirez, F.; Kugler, H. J.; Smith, C. P. *Tetrahedron* **1968**, *24*, 3153; (b) Ramirez, F.; Loewengart, G. V.; Tsolis, E. A.; Tasaka, K. *J. Am. Chem. Soc.* **1972**, *94*, 3531.
9. (a) Cao, Z.-Y.; Zhou, F.; Yu, Y.-H.; Zhou, J. *Org. Lett.* **2013**, *15*, 42; (b) Cao, Z.-Y.; Wang, X.; Tan, C.; Zhao, X.-L.; Zhou, J.; Ding, K. *J. Am. Chem. Soc.* **2013**, *135*, 8197; (c) Miller, E. J.; Zhao, W.; Herr, J. D.; Radosevich, A. T. *Angew. Chem., Int. Ed.* **2012**, *51*, 10605.
10. Zhou, R.; Yang, C.; Liu, Y.; Li, R.; He, Z. *J. Org. Chem.* **2014**, *79*, 10709.
11. Ito, Y.; Ueda, M.; Miyata, O. *Heterocycles* **2014**, *89*, 2029.
12. (a) Ramirez, F.; Bhatia, S. B.; Smith, C. P. *J. Am. Chem. Soc.* **1967**, *89*, 3026; (b) Ramirez, F.; Patwardhan, A. V.; Smith, C. P. *J. Org. Chem.* **1966**, *31*, 474.
13. (a) Ramirez, F.; Desai, N. B. *J. Am. Chem. Soc.* **1963**, *85*, 3252; (b) Ramirez, F.; Patwardhan, A. V.; Smith, C. P. *J. Org. Chem.* **1965**, *30*, 2575.

14. (a) Chavannavar, A. P.; Oliver, A. G.; Ashfeld, B. L. *Chem. Commun.* **2014**, 10853; (b) Haugen, K. C.; Rodriguez, K. X.; Chavannavar, A. P.; Oliver, A. G.; Ashfeld, B. L. *Tetrahedron Lett* **2015**, *56*, 3527.
15. (a) Tang, X.; Chapman, C.; Whiting, M.; Denton, R. *Chem. Commun.* **2014**, 7340; (b) Nikitin, K.; Müller-Bunz, H.; Gilheany, D. *Chem. Commun.* **2013**, 1434; (c) Kenny, N. P.; Rajendran, K. V.; Jennings, E. V.; Gilheany, D. G. *Chem.—Eur. J.* **2013**, *19*, 14210; (d) Headley, C. E.; Marsden, S. P. *J. Org. Chem.* **2007**, *72*, 7185.
16. (a) Zhao, W.; Yan, P. K.; Radosevich, A. T. *J. Am. Chem. Soc.* **2015**, *137*, 616; (b) Zhao, W.; McCarthy, S. M.; Lai, T. Y.; Yennawar, H. P.; Radosevich, A. T. *J. Am. Chem. Soc.* **2014**, *136*, 17634.
17. Diastereomeric ratios were determined by analysis of the crude reaction mixture prior to chromatographic purification. Although Z. He and co-workers (see Ref. 10) reported higher diastereoselectivities with β-ester substituted alkylidene oxindoles, the ratios of stereoisomers reported were of samples obtained after chromatographic purification. Additionally, the major stereoisomer they obtained corresponded to the relative configuration observed in **6** rather than **5** as we observed.
18. The observed shielding effect of the aryl ring *syn* to the C4 oxindole proton, along with single crystal X-ray analysis and NOE measurements, were used as a basis for subsequent structural assignments of the isolated major and minor diastereomers.
19. Ramirez, F.; Gulati, A. S.; Smith, C. P. *J. Org. Chem.* **1968**, *33*, 13.
20. See Supplementary data for full experimental details.
21. (a) Lanka, S.; Thennarasu, S.; Perumal, P. T. *Tetrahedron Lett.* **2014**, *55*, 2585; (b) Liu, Y.-L.; Wang, X.; Zhao, Y.-L.; Zhu, F.; Zeng, X.-P.; Chen, L.; Wang, C.-H.; Zhao, X.-L.; Zhou, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 13735; (c) Ahadi, S.; Khavasi, H. R.; Bazgir, A. *Chem.—Eur. J.* **2013**, *19*, 12553.
22. (a) Gui, H.; Dong, L.; Zhou, Q.; Hu, X. *Wuhan Univ. J. Nat. Sci.* **2011**, *16*, 271; (b) Smith, A. B.; Liu, Z. *Org. Lett.* **2008**, *10*, 4363; (c) Wasserman, H. H.; Han, W. T. *Tetrahedron Lett.* **1984**, *25*, 3743; (d) Astin, S.; Newman, A. C. C.; Riley, H. L. *J. Chem. Soc.* **1933**, 391.
23. (a) Simón, L.; Paton, R. S. *J. Org. Chem.* **2015**, *80*, 2756; (b) Lee, J. M.; Helquist, P.; Wiest, O. *J. Am. Chem. Soc.* **2012**, *134*, 14973.
24. An, J.; Denton, R. M.; Lambert, T. H.; Nacsa, E. D. *Org. Biomol. Chem.* **2014**, *12*, 2993.
25. Teichert, A.; Jantos, K.; Harms, K.; Studer, A. *Org. Lett.* **2004**, *6*, 3477.
26. Lubkoll, J.; Millemaggi, A.; Perry, A.; Taylor, R. J. K. *Tetrahedron* **2010**, *66*, 6606.
27. Wu, H.-L.; Wu, P.-Y.; Shen, Y.-Y.; Uang, B.-J. *J. Org. Chem.* **2008**, *73*, 6445.
28. Li, J.; Wang, N.; Li, C.; Jia, X. *Chem.—Eur. J.* **2012**, *18*, 9645.
29. Tietze, L. F.; Bratz, M. *Org Synth* **1993**, *71*, 214–219.
30. Loreto, M. A.; Migliorini, A.; Tardella, P. A.; Gambacorta, A. *Eur. J. Org. Chem.* **2007**, *2007*, 2365.
31. Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.
32. Wang, G.; Liu, X.; Huang, T.; Kuang, Y.; Lin, L.; Feng, X. *Org. Lett.* **2013**, *15*, 76.
33. Zhang, W.; Go, M.-L. *Bioorg. Med. Chem.* **2009**, *17*, 2077.
34. Lian, Z.; Friis, S. D.; Skrydstrup, T. *Angew. Chem., Int. Ed.* **2014**, *53*, 9582.
35. Prandi, C.; Occhiato, E. G.; Tabasso, S.; Bonfante, P.; Novero, M.; Scarpi, D.; Bova, M. E.; Miletto, I. *Eur. J. Org. Chem.* **2011**, *2011*, 3781.

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