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Access to Spirocyclized Oxindoles and Indolenines via Palladium-Catalyzed Cascade Reactions of Propargyl Carbonates with 2-Oxotryptamines and Tryptamines

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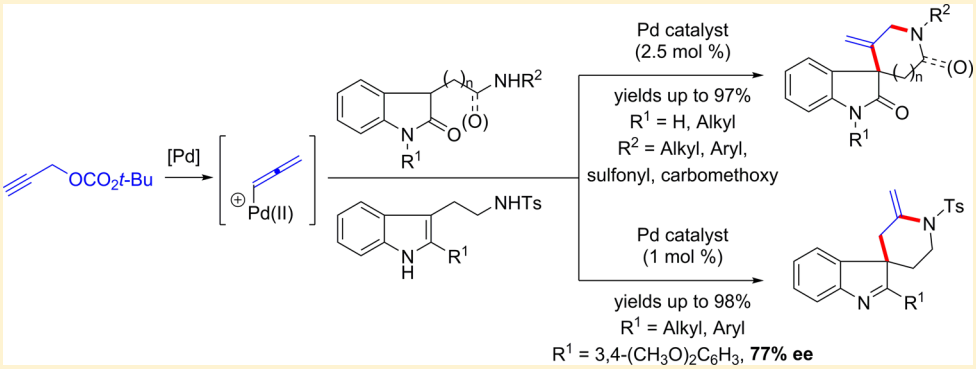
Supporting Information



ABSTRACT: Reported here are methods for the direct construction of a range of spirocyclized oxindoles and indolenines in good to excellent yields. Specifically, we report the palladium-catalyzed reactions of oxindoles and indoles, both functioning as bis-nucleophiles, with propargyl carbonates to afford spirocyclic products having an exocyclic double bond on the newly formed ring. The reaction proceeds through a process wherein the first nucleophilic unit on the oxindole or indole reacts with an allenyl-palladium species, formed from oxidative addition of Pd(0) to propargyl carbonates, to generate a π-allyl palladium intermediate that then reacts further with the second nucleophilic component of the oxindole or indole. The cascade process forges two bonds en route to spirocyclized oxindole and indolenine products. The use of chiral phosphines renders the cyclization sequence enantioselective, providing spirocyclic products with modest to good enantioselectivities.

INTRODUCTION

Natural products hold a great fascination for synthetic organic chemists. The intricate connectivity of the different atoms in a natural product, even a simple one, can inspire the conception of diverse strategies for its synthesis, with individual steps either grounded on established precedents or guided by reactivity principles. Given the subtle interplay between structure and reactivity, particularly in a complex setting, it is often the case that methods shown to be effective in one substrate can fail completely in another seemingly similar substrate. While a source of frustration, these failures serve as beacons to point out the limitations of available methodology and thereby spur the development of new solutions to the challenges at hand. In this way, a complex molecule synthesis exercise can have an impact well beyond what may be anticipated upon conception of a project. We describe below the results of a methodology study that had its origins precisely as described above, motivated by difficulties encountered with a simple allylation reaction during a total synthesis program.

Over the years, our research group has pursued the synthesis of several families of monoterpene indole alkaloids such as strychnine (**1**), vindoline (**2**), geissoschizine (**3**), and strictamine (**4**) (Figure 1). A route that was conceived to strictamine

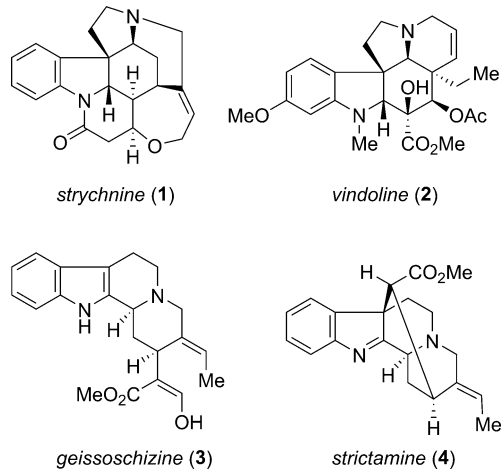


Figure 1. Indole-alkaloid natural products.

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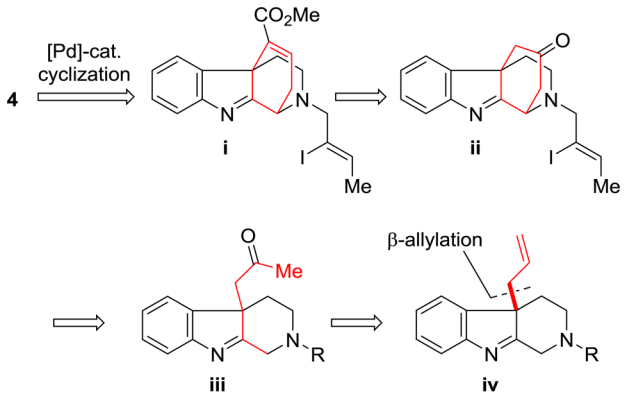
capitalized on palladium-catalyzed C−C bond-forming processes, such as the Heck or enolate alkenylation reaction. Both transformations were selected for their ability to maintain the defined stereochemistry of an alkenyl chain during the bond-forming step.[1] In one of the approaches explored, the Heck cyclization precursor was expected to be prepared from methyl ketone **iii**, which in turn would originate from **iv**, the product of *β*-allylation of a tryptoline precursor (Scheme 1).[2]

Scheme 1. Retrosynthesis of 4



The regioselectivity of alkylation in simple indoles (i.e., *N*-− vs C-3-alkylation) was known to be controllable through judicious selection of reactants and reaction conditions, in line with the hard−soft acid−base (HSAB) heuristic used to predict such selectivity in ambident reactants.[3] When appropriate conditions were examined for the *β*-allylation of simple 3-substituted indoles, the results were variable and quite poor for 2,3-disubstituted indole derivatives such as *β*-carbolines. This limitation in available methodology provided an opportunity to explore alternate methods for the desired *β*-allylation, and initiated our studies of palladium catalysis as an effective means to functionalize indole derivatives.

In 2006, when we began our study of palladium-catalyzed *β*-allylation of indoles, there were few reports of this process, with most giving primarily, or only, *N*-allylation.[4] The one exception was the pioneering work of Bandini and Umani-Ronchi, who reported selective *β*-allylation of *β*-unsubstituted indoles.[5] With 2,3-disubstituted indoles required for our planned synthesis, the published methods gave the *β*-allylation products in only modest or low yields and so motivated the development of a palladium-catalyzed decarboxylative *β*-allylation of 2,3-disubstituted indoles (Figure 2, eq a).[6] The mild reaction conditions and broad functional group tolerance of the allylation chemistry that we developed then inspired the examination of the corresponding *β*-benzylation reaction of indoles (eq b).[7,8] More recently, we reported a useful variant of these two reactions, wherein the *N*-alloc and *N*-Cbz indoles are transformed to the C-3-allyl and C-3-benzyl indolenine derivatives, respectively (eq c).[9] Success with allylation and benzylation of indole substrates set the stage for the investigation of the analogous propargylation reaction.[7b,10−12] In contrast to the first two processes, the palladium-catalyzed propargylation did not give the expected propargylated indole derivative (eq d). Unlike the intermediates formed from the oxidative addition of palladium to allyl and benzyl carbonates, which are capable of reacting with one nucleophile, the intermediate from propargyl carbonate has the capacity to react twice with nucleophiles. With this in mind, we examined the reaction of indolic substrates having in place a second nucleophilic group and obtained spirocyclized products arising from reaction with both nucleophilic units (eq e).[13,14]

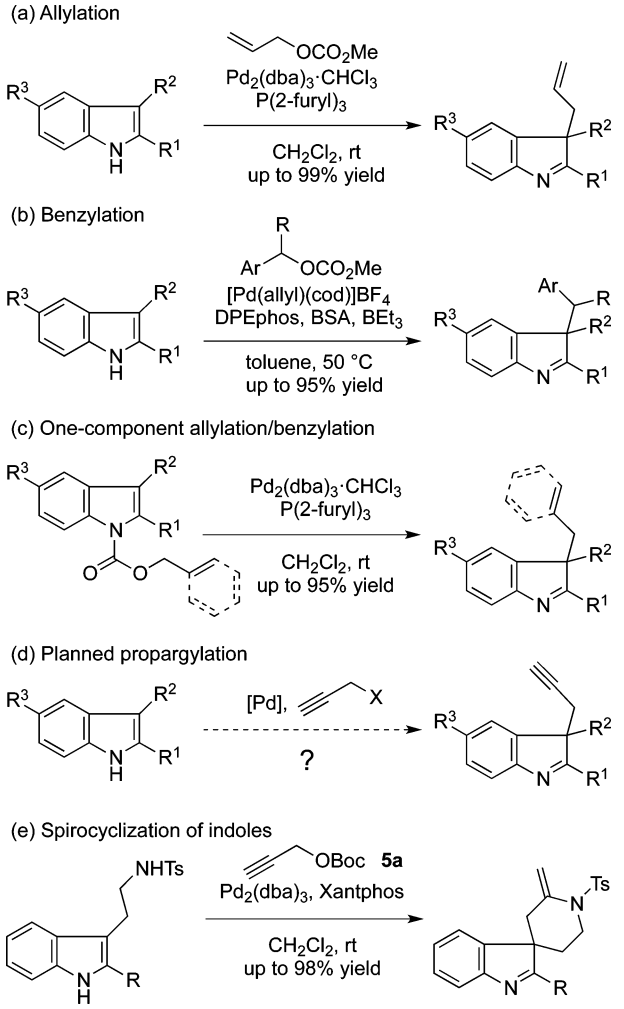


Figure 2. Pd-catalyzed *β*-functionalization of indoles.

We report here the results of further studies on the palladium-catalyzed reaction of propargyl carbonates with indole bis-nucleophiles, in addition to new studies with oxindole bis-nucleophiles. The reactions are high-yielding and furnish the desired spirocyclic products under mild conditions and at low catalyst loadings. Also described are the results of a study of enantioselective spirocyclization of propargyl carbonates with oxindole and indole substrates in the presence of chiral phosphine ligands.

RESULTS AND DISCUSSION

Since tryptamine derivatives were competent bis-nucleophiles for the spirocyclization reaction, we hypothesized that 2-oxotryptamine derivatives would perform comparably, possibly better. We were pleased to find that the optimized reaction conditions used for indole substrates also worked well for oxindole **6a** and produced the spirooxindole **7a** in 83% yield, although requiring a significantly longer reaction time (Table 1, entry 1).[15] The reaction conditions originally employed for the attempted propargylation of 2,3-dimethylindole gave an appreciably faster reaction rate with oxindole **6a** (entry 2). By changing the ligand to dppb, we noted a major improvement in rate, with the reaction proceeding to completion after only 40 min at ambient temperature (97%, entry 3). As seen previously,[13]

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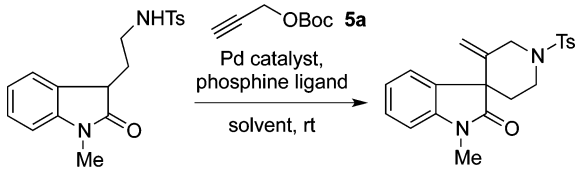
Table 1. Optimization of Oxindole Spirocyclization[a]



entry	[Pd]	ligand	solvent	5a (equiv)	time (h)	yield[b]
1	$Pd_2(dba)_3{\cdot}CHCl_3$	Xantphos	CH_2Cl_2	1.3	18	83
2	$Pd_2(dba)_3{\cdot}CHCl_3$	DPEphos	THF	1.1	0.75	83
3	$Pd_2(dba)_3{\cdot}CHCl_3$	dppb	THF	1.1	0.75	97[c]
4	$Pd_2(dba)_3{\cdot}CHCl_3$	none	THF	1.1	0.75	0
5	$Pd_2(dba)_3{\cdot}CHCl_3$	PPh_3	THF	1.1	4	0
6[d]	$Pd(OAc)_2$	dppb	THF	1.1	0.75	10
7	$Pd_2(dba)_3{\cdot}CHCl_3$	dppb	CH_2Cl_2	1.1	0.5	84
8	$Pd_2(dba)_3{\cdot}CHCl_3$	dppb	EtOAc	1.1	0.75	92
9[e]	$Pd_2(dba)_3{\cdot}CHCl_3$	dppb	THF	1.1	0.75	0
10	$Pd_2(dba)_3{\cdot}CHCl_3$	dppb	THF	1.5	0.33	98
11[f]	**$Pd_2(dba)_3{\cdot}CHCl_3$**	**dppb**	**THF**	**1.5**	**2**	**98**[c]
12[g]	$Pd_2(dba)_3{\cdot}CHCl_3$	dppb	THF	1.5	6	95[c]

[a]Reaction conditions: [Pd] (5.0 mol %), ligand (5.5 mol %), **6a** (0.1 M in solvent), N_2 atmosphere, 23 °C. [b]NMR yield calculated using 1,3,5-trimethoxybenzene as an internal standard; see Experimental Section for details. [c]Isolated yield for a single run. [d]dppb (11 mol %). [e]Reaction run under ambient atmosphere. [f][Pd] (2.0 mol %), dppb (2.2 mol %). [g][Pd] (1.0 mol %), dppb (1.1 mol %).

the reaction did not proceed in the absence of a phosphine ligand (entry 4), nor when monodentate ligands were employed (entry 5). Other palladium sources were examined and offered no significant improvement (entry 6). We found polar aprotic solvents (entries 3, 7, and 8) to be superior to either nonpolar or protic solvents. Use of excess propargyl carbonate **5a** led to a significant reduction in reaction time, giving full conversion to the product after 20 min (entry 10). Importantly, the spirocyclization proceeded in high yields even with reduced catalyst loadings (entries 11 and 12). In order to have common conditions for a range of substrates, 5 mol % of the palladium catalyst was used for examining the substrate scope.

With optimized conditions in hand, we proceeded to survey the substrate scope for the oxindole spirocyclization. Our studies initially focused on the N^{10}-Ts oxindoles (Table 2, entries 1−3) with the N^1-methyl and N^1-benzyl substrates both giving the desired product in excellent yield (entries 1, 2). Interestingly, oxindole substrates lacking a substituent at N^1 reacted significantly slower, though still gave the expected cyclized product in near-quantitative yield (entry 3). Tryptophan-derived oxindole **6d** gave spirooxindole **7d** in good yield as a mixture of diastereomers (entry 4), and 2-propylamine oxindole **6e** gave the corresponding seven-membered spirocycle (entry 5). However, the reaction of oxindole carbamate **6f** under the optimized reaction conditions produced a significant quantity of oligomeric products. The problem was minimized by using a dilute reaction concentration, elevated temperature, and slow addition of the oxindole to the reaction mixture,[16] which increased the yield of the cyclized product from 18% to 68% (entry 6). Under similar reaction conditions, N^{10}-Ph acetamide **6g** provided spirocycle **7g** in good yield (entry 7). Interestingly, the N^{10}-Me acetamide **6h** provided the isomeric eneamide **7h** in good yield (entry 8). As expected, phenol **6i** formed the tetracyclic product **7i** in excellent yield (entry 9).

In order to further explore the scope of these spirocyclization reactions, we also examined the reaction of substituted propargyl carbonates (Figure 3). A series of *tert*-butyl propargyl carbonates containing substitution at the 1- and/or 3-positions was synthesized and subjected to the reaction conditions.

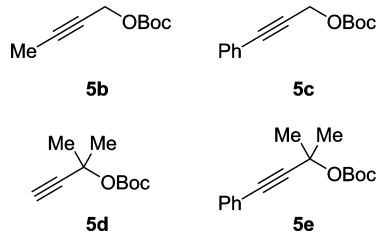


Figure 3. Substituted propargyl carbonates.

Under the optimized reaction conditions, the substituted propargyl carbonates **5b**−**5d** produced the expected spirocyclic products as inseparable mixtures of regioisomers or olefin isomers. A notable exception was the geminal-dimethyl substituted carbonate **5e**, which afforded spirooxindole **7j** in excellent yield and with minimal formation of the isomeric addition product (Scheme 2).

A brief evaluation of the carbonate substrate scope was carried using substituted propargyl carbonates **5b**−**5g** and tryptamine sulfonamide **8a**. Methyl-substituted propargyl carbonates **5b** or **5d** gave complex mixtures of stereoisomers, and trisubstituted propargyl carbonate **5e** gave no product, even on heating to 40 °C for 72 h. The phenyl-substituted propargyl carbonate **5c** gave

Scheme 2. Selective Spirocyclization Reaction Using Trisubstituted Propargyl Carbonate 5e

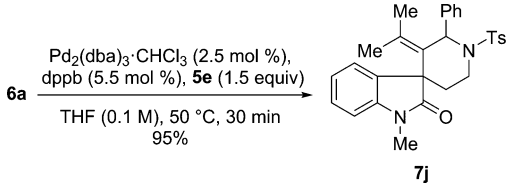


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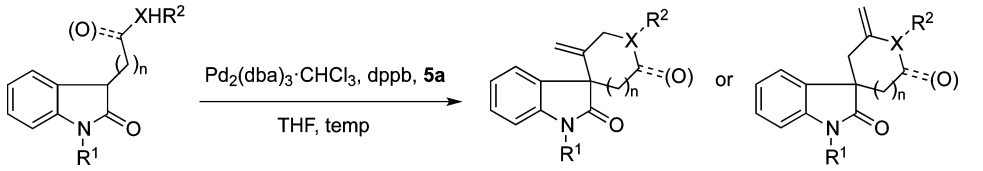
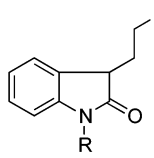
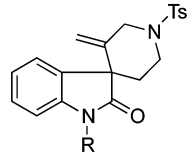
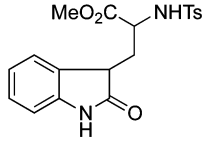
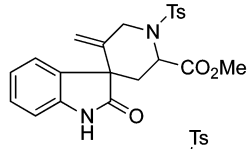
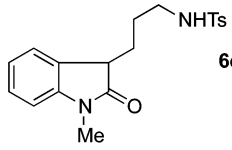
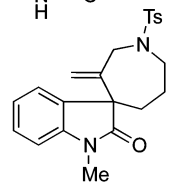
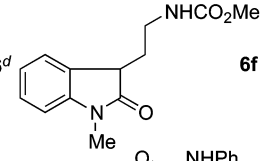
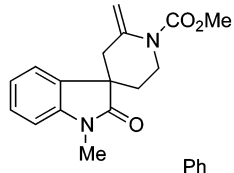
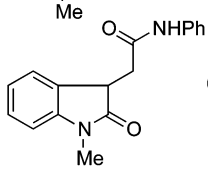
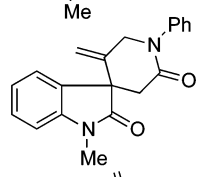
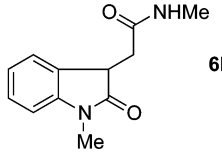
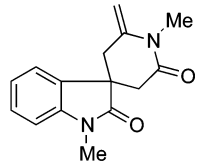
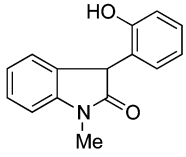
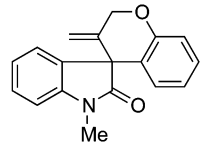
Table 2. Substrate Scope for Oxindole Spirocyclization[a]



entry	substrate	conc. (M)	temp (°C)	time (h)	product	yield (%)[b]
1	 **6a**	0.1	23	0.33	 **7a**, R = Me	97
2	**6b**	0.1	23	0.5	**7b**, R = Bn	92
3	**6c**	0.1	23	14	**7c**, R = H	95
4	 **6d**	0.1	23	7	 **7d**	78[c] (59:41 dr)
5	 **6e**	0.1	23	0.33	 **7e**	78
6[d]	 **6f**	0.01	50	15	 **7f**	68
7	 **6g**	0.01	50	0.5	 **7g**	77
8	 **6h**	0.01	50	0.5	 **7h**	73
9	 **6i**	0.1	23	0.5	 **7i**	95

[a]Reaction conditions: oxindole **6** (0.2 mmol), **5a** (1.5 equiv), $Pd_2(dba)_3$·$CHCl_3$ (2.5 mol %), dppb (5.5 mol %), **6** (0.1 M in THF), 23 °C. [b]Isolated yield for a single run. [c]Diastereomer ratio determined by ^{1}H NMR. Isolated as 48% and 30%. [d]Solution of **6f** (0.2 mmol) in THF (1 mL) at 50 °C added by syringe pump over 1 h.

the product as a single constitutional isomer, as a 4:1 mixture of diastereomers. Interestingly, the isomeric propargyl carbonate **5f** yielded the same product, with comparable diastereoselectivity (Scheme 3). These results suggest the involvement of a common reaction intermediate that is converted into spiroindolenine **9a** with near-identical diastereoselectivity (see Scheme 4). Finally, when disubstituted propargyl carbonate **5g** was used, the reaction generated spiroindolenine **9b** as a single product in moderate yield and with excellent diastereoselectivity (32% yield, 18:1 dr).

Although we have not studied the mechanism of this reaction, a reasonable catalytic cycle for these spirocyclizations can be proposed in analogy with mechanisms presented for related Pd-catalyzed reactions (Figure 4).[10,17] Decarboxylative oxidative addition of Pd(0) to the propargyl carbonate generates a *tert*-butoxide anion and Pd-allene **I**.[18] The *tert*-butoxide anion may serve as the endogenous base that deprotonates oxindole **6**. Given the similarity in their pK_a values,[17c−e,19] deprotonation at *C*-3 (to give enolate **II**) or *N*[10] (to give amide anion **VI**) are both feasible, and the two anions are expected to be in dynamic equilibrium. At this point, nucleophilic addition by enolate **II** would generate palladium carbene **III**,[11a−c,20] whereas amide anion **VI** would give palladium carbene **VII**. Subsequent protonation would form the corresponding Pd-π-allyl species

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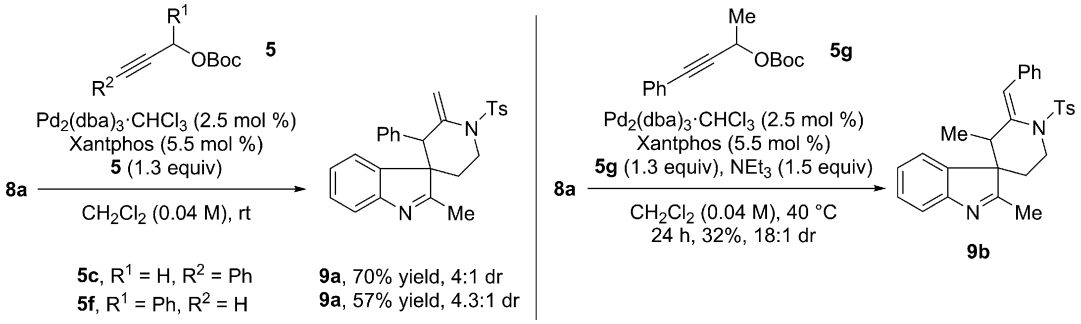
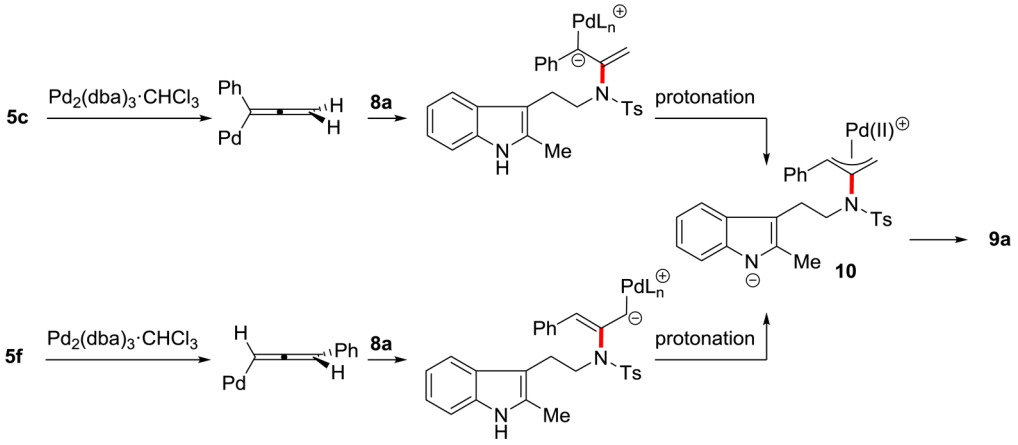
Scheme 3. Reaction of Substituted Propargyl Carbonates with Tryptamine Sulfonamide 8a



Scheme 4. Mechanistic Rationale for the Stereoconvergent Synthesis of 9a



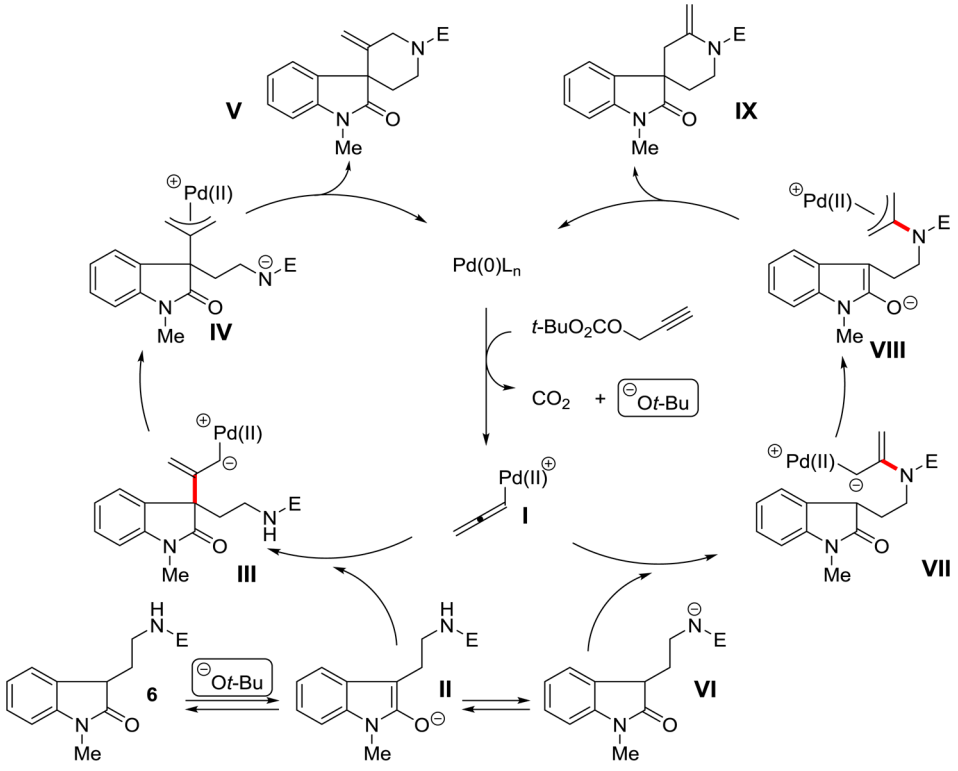


Figure 4. Reaction catalytic cycles.

IV or **VIII**, respectively. Intramolecular allylation of **IV** by *N*[10] would give spirooxindole **V**, whereas the same process on **VIII** would occur at C3 to give **IX**.[10a,21] Both processes give rise to Pd(0), thereby enabling continuation of the catalytic cycle.

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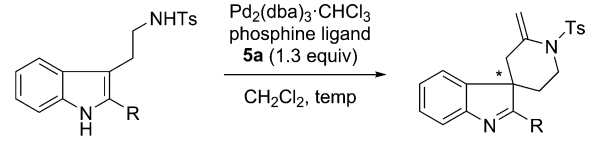
The suggested mechanistic scheme accounts for the formation of isomeric spirooxindoles, depending on the withdrawing group present on the N^{10} nitrogen. A strong electron-withdrawing group such as tosyl on the side-chain nitrogen would render the resulting anion less nucleophilic, thus favoring initial addition of the oxindole enolate to the allenyl palladium species (Figure 4, species **III**). On the other hand, with a less powerful withdrawing group such as carbomethoxy, the resulting nitrogen-based anion would be more nucleophilic and give initial C−N bond formation (Figure 4, species **VII**). We have not been able to correlate more precisely the product outcome with the nature of the side chain and its pK_a,[22] presumably because other factors such as relative nucleophilicity and steric considerations also play an important role in determining the product outcome.

The reaction of tryptamine sulfonamide **8a** with substituted propargyl carbonate **5c** or **5f** to give nearly the same diastereomeric ratio of spiro product **9a** (Scheme 3) can be understood as follows. The reaction of the two propargyl carbonates with Pd(0) would give Pd-allenyl species that are constitutional isomers (Scheme 4). Subsequent addition of the sulfonamide nucleophile would form two isomeric Pd-carbenoids that on protonation would produce isomeric σ-allyl intermediates, capable of interconversion through a common π-allyl species **10**. In order for **5c** and **5f** to generate the same product, the rate of the interconversion must be faster than the rate of C−C bond formation.

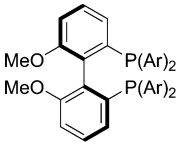
A natural progression of the Pd-catalyzed allylation, benzylation, and spirocyclization reactions is to render the processes enantioselective. Toward this end we examined a focused collection of chiral phosphine ligands for the spirocyclization reactions of indole substrates (Table 3).[7b] (*R*)-BINAP gave the spiroindolenine product **11a** in good yield but low, albeit promising, enantioselectivity (entry 1). Modifying the quantity of chiral ligand or reaction temperature or utilizing a more hindered phosphine (entries 2−4) gave only minor improvements to the selectivity. Use of a monodentate ligand gave no conversion to product (entry 5). Employment of BIPHEP-type ligands improved the enantioselectivity and yield modestly (entry 6). Encouragingly, switching the aryl substituent on the ligand from phenyl to furyl improved the results measurably (entry 7). An even greater increase in enantioselectivity was observed using the bulkier 4-Me-furyl ligand (41% ee, entry 8). Unfortunately, the use of benzofuran-substituted BIPHEP did not enhance selectivity (entry 9). The most promising selectivities were observed for 2-aryl tryptamine sulfonamide substrates. When paired with L^2, 2-phenylindolenine **11b** was formed with 53% ee (entry 10). The dimethoxyphenyl indolenine **11c** was formed with 66% ee under the same reaction conditions, and in higher yield (entry 11). Finally, use of the bulkier ligand L^3 with dimethoxyphenylindole **8c** produced indolenine **11c** with 77% ee (entry 12).

A brief examination of the enantioselective spirocyclization of oxindole substrates has proven less fruitful (Scheme 5). A number of chiral phosphine ligands were examined for the reaction, but most did not afford the product at ambient temperature. The cyclization did proceed at elevated temperatures and with an extended reaction time (20 h), but gave the product in just 8% yield and with 32% ee. It is interesting to note that, despite the ease of the racemic spirocyclization reactions of oxindoles with propargyl carbonates (ambient temperature, generally less than 30 min), rendering these reactions highly enantioselective has, to date, proven difficult.

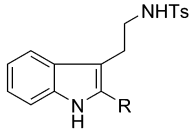
Table 3. Investigation of Chiral Phosphine Ligands for the Indole Spirocyclization[a]



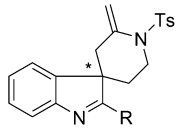
entry	ligand	substrate	temp (°C)	time (h)	yield (%)[b]	ee (%)[c]
1	(*R*)-BINAP	**8a**	rt	12	80	12
2	(*R*)-BINAP	**8a**	rt	2	77	15
3	(*R*)-BINAP	**8a**	0	16	25	16
4	(*R*)-T-BINAP	**8a**	rt	18	68	15
5	QUINAP	**8a**	rt	18	0	0
6	L^1	**8a**	rt	24	86	16
7	L^2	**8a**	rt	2	68	34
8	L^3	**8a**	rt	16	69	41
9	L^4	**8a**	rt	24	65	20
10	L^2	**8b**	rt	24	70	53
11	L^2	**8c**	rt	24	83	66
12	L^3	**8c**	rt	40	73	77



L^1, Ar = 4-F-Ph
L^2, Ar = 2-furyl
L^3, Ar = 4-Me-2-furyl
L^4, Ar = benzofuran



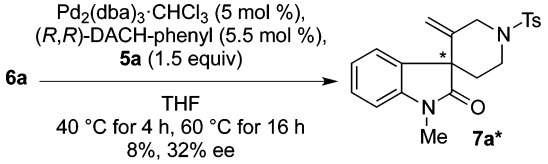
8a, R = Me
8b, R = Ph
8c, R = 3,4-$(CH_3O)_2C_6H_3$



11a, R = Me
11b, R = Ph
11c, R = 3,4-$(CH_3O)_2C_6H_3$

[a]Reaction conditions: [Pd] (5 mol %), phosphine ligand (5.5 mol %), **5a** (1.3 equiv), **8** (0.04 M in CH_2Cl_2). [b]Isolated yield for a single run. [c]Determined by chiral stationary phase HPLC. [d](*R*)-BINAP (10 mol %).

Scheme 5. Investigation of Chiral Phosphine Ligands for the Oxindole Spirocyclization



CONCLUSION

Inspired by methodology needs arising from a natural product total synthesis project, we have investigated and developed mild methods for the C-3 functionalization of oxindoles and indoles. In the present study, we focused on the palladium-catalyzed decarboxylative spirocyclization reactions of 2-oxotryptamine derivatives possessing two nucleophilic sites, which afforded intricate, spirocyclized products. The transformation involves the reaction of propargyl carbonate with Pd(0) to generate a Pd-allenyl species that reacts with the first nucleophilic unit on the oxindole substrate to generate, after protonation, a π-allyl palladium intermediate, which then reacts further with the

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second nucleophilic component. The cascade process forges two bonds (C−C and C−N) en route to spirocyclized oxindole products. Depending on the nature of the nitrogen nucleophile, either the C−C or the C−N bond is formed first, thereby giving with high selectivity 3′- or 2′-methylene spirocyclic products, respectively. Substituted propargyl carbonates were examined and found to react successfully with oxindole and indole substrates, in some cases giving a single product. The enantioselective variant of these spirocyclization reactions was also examined for tryptamine substrates and provided the corresponding spirocyclic products with modest to good enantioselectivities.

EXPERIMENTAL SECTION

General Information. Reactions were run in oven-dried glassware under a N_2 atmosphere. Reactions were monitored by TLC on silica gel 60 Å F254 plates, visualized by UV florescence quenching (254 nm), I_2/SiO_2, PMA, Seebach's stain, or Hanessian's staining solution. Flash column chromatography (EtOAc/Hexanes or MeOH/CH_2Cl_2) was performed with silica gel (40−63 μm). NMR spectra were measured at 500 MHz for ^{1}H spectra and 125 MHz for ^{13}C spectra. ^{1}H spectra were calibrated from internal standard TMS (δ 0.0) or solvent resonance ($CHCl_3$: 7.26, DMSO: 2.5). ^{13}C spectra were calibrated from solvent resonance ($CHCl_3$: 77.0, DMSO: 39.52). NMR data are reported as chemical shift (parts per million, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, m = multiplet, br = broad signal), coupling constant (Hz), and integration. High-resolution mass spectral analysis was measured on TOF LC/MS (positive electrospray ionization). Enantiomeric excess was determined by chiral HPLC analysis using an HPLC instrument with a Chiralcel OD-H or ChiralPak AD-H or AS-H column (250 mm × 10 mm, 4.6 μm particle size, 1.0 mL/min flow rate) equipped with a guard column, employing a mixture of isopropanol and hexanes. Melting points were measured using a capillary melting point apparatus.

Methylene chloride (CH_2Cl_2), tetrahydrofuran (THF), toluene, and dimethylformamide (DMF) were purified by passage over activated alumina, using a solvent purification system. All other solvents were purchased from commercial suppliers and used as received. $Pd_2(dba)_3$·$CHCl_3$ and $Pd(OAc)_2$ were purchased from commercial suppliers and used as received. Xantphos, DPEphos, dppb, (*R*,*R*)-DACH, PPh_3, (*R*)-T-BINAP, QUINAP, and (*R*)-BINAP were purchased from commercial suppliers and used as received. BIPHEP ligands L^1, L^2, L^3, and L^4 were prepared according to previously published procedures.[7b] *tert*-Butyl prop-2-yn-1-yl carbonate, 4-methyl-*N*-(2-(2-methyl-1*H*-indol-3-yl)-ethyl)benzenesulfonamide, 4-methyl-*N*-(2-(2-phenyl-1*H*-indol-3-yl)-ethyl)benzenesulfonamide, and *N*-(2-(2-(3,4-dimethoxyphenyl)-1*H*-indol-3-yl)ethyl)-4-methylbenzenesulfonamide were prepared according to previously published procedures.[13] Unless otherwise noted, tryptamine, propargyl alcohols, and all other materials were purchased from commercial suppliers and used as received.

General Procedure for *tert*-Butyl Propargyl Carbonates. Method A: Prepared according to Chalasani and co-workers.[23] To a solution of propargyl alcohol in anh. CH_2Cl_2 maintained under a positive pressure of nitrogen were added N(*i*-Pr)$_2$Et and DMAP. The reaction mixture was cooled to 0 °C, and di-*tert*-butyl dicarbonate was added either portionwise over two min or dropwise as a solution in CH_2Cl_2. The reaction mixture was slowly warmed to ambient temperature (23 °C) over 3 h. The reaction mixture was diluted with CH_2Cl_2 and washed with water, 10% aq. HCl, sat. aq. $NaHCO_3$, and brine. The organic layer was then dried over anh. $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography to give the desired product. Method B: Prepared according to Stambasky and co-workers.[24] To a suspension of 60% w/w NaH in THF maintained under a positive pressure of nitrogen was added the propargyl alcohol. This mixture was allowed to stir at ambient temperature for 30 min and was then cooled to 0 °C. To this mixture was added a solution of Boc_2O in THF over 1 h, and the mixture was allowed to warm to ambient temperature. After consumption of the starting material, the reaction mixture was concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 and washed with water. The aqueous phase was extracted with CH_2Cl_2, and the combined organic layers were washed with brine. The organic layer was dried with anh. $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography to give the desired product.

But-2-yn-1-yl *tert*-butyl Carbonate (5b). Prepared according to Method B using 2-butyn-1-ol (1.9 mL, 25 mmol), 60% w/w NaH (1.43 g, 35.7 mmol), Boc_2O (5.2 g, 23.8 mmol), and THF (250 mL) for 16 h. Purified by filtration over a short plug of SiO_2 and the method by Basel and Hassner[25] (for the destruction of excess Boc_2O) to afford **5b** (1.08 g, 63%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.63 (q, J = 2.4 Hz, 2H), 1.85 (t, J = 2.4 Hz, 3H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.9, 83.4, 82.4, 72.8, 55.0, 27.6, 3.4; HRMS (ESI) calcd for $(C_9H_{14}O_3Na)^+$ $[M + Na]^+$: 193.0835, found: 193.0837.

***tert*-Butyl (3-Phenylprop-2-yn-1-yl) Carbonate (5c).** Step 1: Prepared according to procedure by Panteleev and co-workers.[26] $Pd(PPh_3)_2Cl_2$ (35 mg, 50 μmol) and CuI (19 mg, 0.1 mmol) were suspended in NEt_3 (20 mL, 0.275 M) under a positive pressure of nitrogen. To this suspension was added iodobenzene (560 μL, 5.0 mmol) and propargyl alcohol (320 μL, 5.5 mmol). The reaction was stirred for 16 h at ambient temperature. Any precipitate matter was removed by filtration through a plug of Celite, which was then washed with NEt_3 (2 × 10 mL). The reaction mixture was passed through a plug of silica and concentrated *in vacuo*. This residue was used without further purification. Step 2: Prepared according to Method B using 60% w/w NaH (320 mg, 8.0 mmol) in THF (15 mL), the unpurified Sonogashira product (5.0 mmol) as a solution in THF (10 mL), and Boc_2O (982 mg, 4.5 mmol) in THF (25 mL). Purified by flash column chromatography (10% EtOAc/Hexanes) to afford **5c** (929 mg, 73% over both steps) as a red/brown liquid. Analytical data (^{1}H NMR, ^{13}C NMR, and HRMS) match those reported in the literature.[27] A ^{1}H NMR spectrum is provided to demonstrate purity.

***tert*-Butyl (2-Methylbut-3-yn-2-yl) Carbonate (5d).** Prepared according to Method B using 2-methyl-3-butyn-ol (1.02 mL, 10.5 mmol), 60% w/w NaH (0.62 g, 15.5 mmol), Boc_2O (2.18 g, 10.0 mmol), and THF (100 mL) for 16 h. Purified by filtration over a short plug of SiO_2 to afford **5d** (1.05 g, 57%) as a colorless liquid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.56 (s, 1H), 1.69 (s, 6H), 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) 151.13, 84.22, 81.86, 72.56, 72.33, 28.66, (×2) 27.60 (×3); HRMS (ESI) calcd for $(C_{10}H_{17}O_3)^+$ $[M + H]^+$: 185.1172, found: 185.1169.

***tert*-Butyl (2-Methyl-4-phenylbut-3-yn-2-yl) Carbonate (5e).** Step 1: Prepared according to a procedure by Li and co-workers.[28] To a 125 mL flame-dried round bottom flask (RBF) were added $HNEt_2$ (125 mL), PhBr (7.6 mL, 60 mmol), 2-methyl-3-butyn-2-ol (4.9 mL, 50 mmol), PPh_3 (197 mg, 0.75 mmol), CuI (95 mg, 0.5 mmol), and $Pd(OAc)_2$ (56 mg, 0.25 mmol). The mixture was sparged with N_2 for 30 min, and then the RBF was fitted with a reflux condenser and sparged for an additional 5 min. The reaction was allowed to reflux for 22 h. After cooling to ambient temperature, the mixture was concentrated *in vacuo*. Purified by flash column chromatography (10% EtOAc/Hexanes) to afford the Sonogashira product (6.98 g, 87%) as a tan solid. Analytical data (^{1}H and ^{13}C NMR) match those reported in the literature.[28] ^{1}H NMR spectrum is provided to demonstrate purity. Step 2: Prepared according to Method B using Sonogashira product (1.76 g, 11 mmol), 60% w/w NaH (840 mg, 21 mmol), Boc_2O (2.29 g, 10.5 mmol), and THF (110 mL). Purified by flash column chromatography (10% EtOAc/Hexanes) and the method by Basel and Hassner[25] (for the destruction of excess Boc_2O) to afford **5e** (1.67 g, 61%) as a light yellow solid. Mp: 46−47 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.45−7.40 (m, 2H), 7.33−7.27 (m, 3H), 1.78 (s, 6H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.3, 131.6 (×2), 128.2, 128.1 (×2), 122.6, 89.9, 84.0, 81.8, 73.7, 28.9 (×2), 27.7 (×3); HRMS (ESI) calcd for $(C_{16}H_{20}O_3Na)^+$ $[M + Na]^+$: 283.1305, found: 283.1294.

***tert*-Butyl (1-Phenylprop-2-yn-1-yl) Carbonate (5f).** Prepared according to Method A using 1-phenylprop-2-yn-1-ol (920 μL, 7.57 mmol), Boc_2O (2.2 g, 9.9 mmol), N(*i*-Pr)$_2$Et (3.3 mL, 18.9 mmol), DMAP (93 mg, 0.76 mmol), and CH_2Cl_2 (640 μL). Purified by flash column chromatography (10% EtOAc/Hexanes) to afford **5f** (1.54 g,

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88%) as a red/brown liquid. Analytical data (^{1}H NMR, ^{13}C NMR, HRMS) match those reported in the literature.[27] A ^{1}H NMR spectrum is provided to demonstrate purity.

***tert*-Butyl (4-Phenylbut-3-yn-2-yl) Carbonate (5g).** Prepared according to Method A using 4-phenyl-3-butyn-2-ol (1.11 mL, 7.6 mmol), Boc_2O (2.2 g, 9.9 mmol), N(*i*-Pr)$_2$Et (3.3 mL, 18.9 mmol), DMAP (93 mg, 0.76 mmol), and CH_2Cl_2 (0.64 mL) for 16 h. Purified by filtration over a short plug of SiO_2 to afford **5g** (2.01 g, 99%) as a pale yellow liquid. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46−7.41 (m, 2H), 7.33−7.27 (m, 3H), 5.50 (q, J = 6.7 Hz, 1H), 1.62 (d, J = 6.7 Hz, 3H), 1.51 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3, 131.6, 128.3, 128.0 (×2), 122.1, 87.0, 84.8, 82.2, 63.4, 27.6, 27.5 (×3), 21.3; HRMS (ESI) calcd for $(C_{15}H_{18}O_3Na)^+$ $[M + Na]^+$: 269.1148, found: 269.1152.

Preparation of *N*^{1}-Alkyl Tryptamines and Tryptamine Derivatives: 2-(1-Methyl-1*H*-indol-3-yl)ethanamine (SI-1). Step1: Prepared according to Feldman and co-workers.[29] To a 250 mL RBF were added tryptamine (3.52 g, 22 mmol), 1,4-dioxane (18.3 mL), and Et_3N (6.13 mL, 44 mmol). A solution of Boc_2O (4.37 g, 20 mmol) in 1,4-dioxane (18.3 mL) was added dropwise via addition funnel over 10 min. After 18 h, the mixture was poured into a separatory funnel, diluted with CH_2Cl_2, and washed three times with 1.0 M aq. HCl. The organic layer was backextracted once with CH_2Cl_2, and the combined organic layers were washed once with brine, dried over anh. Na_2SO_4, and concentrated *in vacuo*. The dark red-brown residue was used without further purification. Step 2: Prepared according to Song and co-workers.[30] To a 250 mL RBF containing unpurified Boc-tryptamine were added CH_2Cl_2 (110 mL), $TBAHSO_4$ (1.49 g, 4.39 mmol), powdered NaOH (10.6 g, 26.5 mmol), and MeI (2.74 mL, 44 mmol). The mixture was stirred for 15 h, then diluted with water, and stirred vigorously for 30 min. The organic layer was separated, washed three times with water, and backextracted once with CH_2Cl_2. The combined organic layers were washed once with brine, dried over anh. Na_2SO_4, and concentrated *in vacuo*. Purified by flash column chromatography (20% EtOAc/Hexanes) to remove most of the $TBAHSO_4$. The resulting residue was used without further purification. Step 3: Prepared according to a modified procedure by Song and co-workers.[30] To a 500 mL RBF containing *N*-methyl Boc tryptamine was added CH_2Cl_2 (100 mL). This solution was cooled with an ice/water bath, and a solution of 50/50 v/v TFA/CH_2Cl_2 (15.3 mL) was added dropwise over 30 min via an addition funnel. The reaction mixture was stirred for 10 min at 0 °C, then the ice/water bath was removed, and the reaction mixture was allowed to warm to ambient temperature. After 16.5 h, the reaction mixture was cooled with an ice/water bath and slowly neutralized with sat. aq. $NaHCO_3$. The resulting mixture was poured into a separatory funnel, and the organic layer was separated. The aqueous layer was extracted twice with CH_2Cl_2, washed once with brine, dried over Na_2SO_4, and concentrated *in vacuo* to afford **SI-1** (2.82 g, 82%) as a dark-brown solid foam. Analytical data (^{1}H and ^{13}C NMR) match those reported in the literature.[31] A ^{1}H NMR spectrum is provided to demonstrate purity.

Methyl (2-(1*H*-Indol-3-yl)ethyl)carbamate (SI-2). Step 1: Prepared according to a procedure by Fong and Copp.[32] To a mixture of tryptamine (3.20 g, 20 mmol) in EtOAc (40 mL) were added 1.0 M NaOH (25 mL) and methyl chloroformate (2 mL, 26 mmol). After 14 h at ambient temperature (23 °C), the reaction mixture was poured into a separatory funnel. The organic layer was separated, washed once with water, dried over anh. Na_2SO_4, and concentrated *in vacuo*. The residue was used without further purification. Step 2: Prepared according to Method B with tryptamine carbamate (20 mmol), CH_2Cl_2 (100 mL), $TBAHSO_4$ (1.36 g, 4 mmol), powdered NaOH (9.6 g, 400 mmol), and MeI (2.5 mL, 40 mmol) at ambient temperature for 19 h. Afterwards, analysis by TLC indicated that the reaction had not gone to completion. Additional powdered NaOH (9.6 g, 400 mmol) was added. TLC after an additional 9 h indicated that the reaction had gone to completion. The reaction mixture was diluted with water and poured into a separatory funnel. The organic layer was separated and washed twice with 1.0 M HCl. The organic layer was washed once with brine and dried over anh. Na_2SO_4. Purified by flash column chromatography (3 → 4% MeOH/CH_2Cl_2) to afford **SI-2** (2.65 g, 57%) as a red-orange oil that solidified on standing. Analytical data (^{1}H and ^{13}C NMR) match those reported in the literature.[33] A ^{1}H NMR spectrum is provided to demonstrate purity.

Preparation of C-3-Alkyl Sulfonamides. To a solution of tryptamine (5 mmol) in anh. CH_2Cl_2 (8 mL) maintained under a positive pressure of nitrogen was added NEt_3 (10.0 mmol) and cooled to 0 °C. To the stirred solution was added tosyl or mesyl chloride (5.5 mmol) in one portion, and the reaction was allowed to slowly warm to ambient temperature. The reaction was allowed to stir an additional 12 h. The solution was then diluted with CH_2Cl_2 (10 mL), washed with 10% aq. HCl (2 × 10 mL), aq. $NaHCO_3$ (15 mL), and brine. The organic layer was passed through a plug of silica, which was washed with CH_2Cl_2 (3 × 15 mL). The combined organic portions were dried over anh. $MgSO_4$ or anh. Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography to give the desired products.

***N*-(2-(1*H*-Indol-3-yl)ethyl)-4-methylbenzenesulfonamide (SI-3).** Prepared according to the general procedure using tryptamine (2.4 g, 15 mmol), CH_2Cl_2 (24 mL), Et_3N (2.3 mL, 16.5 mmol), and TsCl (3.43 g, 18 mmol) for 16 h at 0 → rt. Purified by flash column chromatography (5% MeOH/CH_2Cl_2) to afford **SI-3** (4.13 g, 88%) as a pale orange solid. Analytical data (^{1}H and ^{13}C NMR) match those reported in the literature.[34] A ^{1}H NMR spectrum is provided to demonstrate purity.

4-Methyl-*N*-(2-(1-methyl-1*H*-indol-3-yl)ethyl)benzenesulfonamide (SI-4). Prepared according to the general procedure using tryptamine **SI-1** (310 mg, 1.63 mmol), CH_2Cl_2 (8.2 mL), NEt_3 (450 μL, 3.3 mmol), and TsCl (370 mg, 2.0 mmol) for 12 h at ambient temperature. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **SI-4** (1.01 g, 62% over two steps) as a yellow oil. Analytical data (^{1}H NMR, ^{13}C NMR, HRMS) match those reported in the literature.[35] A ^{1}H NMR spectrum is provided to demonstrate purity.

***N*-(2-(1-Benzyl-1*H*-indol-3-yl)ethyl)-4-methylbenzenesulfonamide (SI-5).** Step 1: Prepared according to a procedure by Feng and co-workers.[36] To a 250 mL RBF were added tryptamine (4.81 g, 30 mmol), phthalic anhydride (4.58 g, 30.9 mmol), and toluene (176 mL). The RBF was fitted with a reflux condenser and brought to reflux. After 13 h, the reaction mixture was cooled and concentrated *in vacuo*. Purified by trituration from CH_2Cl_2 and Hexanes to afford tryptamine phthalimide (7.77 g, 89%) as a light-yellow solid after three triturations. Analytical data (^{1}H, ^{13}C NMR) match those reported in the literature.[36] A ^{1}H NMR spectrum is provided to demonstrate purity. HRMS (ESI) calcd for $(C_{18}H_{15}N_2O_2)^+$ $[M + H]^+$: 291.1128, found: 291.1129. Step 2: Prepared according to Zhai and co-workers.[37] To a suspension of 60% w/w NaH (488 mg, 12.2 mmol) in DMF (87 mL) was added a solution of tryptamine phthalimide (2.61 g, 6.12 mmol) in DMF (44 mL). Benzyl bromide (2.5 mL, 20.8 mmol) was added to the mixture, which was then heated at 60 °C for 14.5 h. At this point, TLC indicated incomplete consumption of starting material, so additional NaH (488 mg, 12.2 mmol) was added. After an additional 2 h, the reaction was cooled to ambient temperature. The mixture was poured over $NaHCO_3$, into EtOAc, washed five times with water, once with brine, and dried over anh. Na_2SO_4. The orange-sherbert-colored solid was used without further purification. Step 3: The protected tryptamine (6.12 mmol) was dissolved in EtOH (100 mL) and heated to 70 °C. After 10 min, 50−60% hydrazine hydrate (1.9 mL) was added. After 18.5 h, the mixture was cooled to ambient temperature and filtered through a cotton plug. The filtrate was diluted with 1.0 M aq. NaOH and extracted three times with 4:1 $CHCl_3$/*i*-PrOH and dried over anh. Na_2SO_4. The solvent was concentrated to afford a light yellow oil, which was used without further purification. Step 4: Prepared according to the general procedure using unpurified tryptamine precursor (6.12 mmol), CH_2Cl_2 (9.9 mL), NEt_3 (938 μL, 6.73 mmol), and TsCl (1.4 g, 7.34 mmol) for 17.5 h at ambient temperature. Purified by flash column chromatography (30 → 40% EtOAc/Hexanes) to afford **SI-5** (2.05 g, 83% over two steps) as an off-white solid. Mp: 118 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.62 (d, J = 8.3 Hz, 2H), 7.42 (d, J = 7.9 Hz, 1H), 7.34−7.28 (m, 2H), 7.28−7.24 (m, 2H), 7.20 (d, J = 8.1 Hz, 2H), 7.19−7.16 (m, 1H), 7.10 (d, J = 6.8 Hz, 2H), 7.05 (ddd, J = 7.8, 7.0, 1.0 Hz, 1H), 6.86 (s, 1H), 5.25 (s, 2H), 4.33 (t, J = 6.1 Hz, 1H), 3.28 (q, J = 6.5 Hz, 2H), 2.92 (t, J = 6.6 Hz, 2H), 2.39 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.0, 137.3, 136.8, 136.6, 129.4 (×2), 128.5 (×2), 127.5, 127.4, 126.8 (×2), 126.7 (×2), 126.4,

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121.7, 119.0, 118.6, 110.7, 109.7, 49.7, 43.1, 25.3, 21.3; HRMS (ESI) calcd for $(C_{24}H_{25}N_2O_2S)^+$ $[M + H]^+$: 405.1631, found: 405.1624.

Methyl 3-(1*H*-Indol-3-yl)-2-(4-methylphenylsulfonamido)-propanoate (SI-6). Prepared according to the general procedure using L-tryptophan methyl ester hydrochloride (2.0 g, 7.9 mmol), CH_2Cl_2 (15.7 mL), Et_3N (3.3 mL, 23.6 mmol), and TsCl (1.65 g, 8.6 mmol) for 12 h at ambient temperature. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **SI-6** (2.05 g, 70%) as a white powder. Analytical data (^{1}H NMR, ^{13}C NMR, HRMS) match those reported in the literature.[38] A ^{1}H NMR spectrum is provided to demonstrate purity.

4-Methyl-*N*-(3-(1-methyl-1*H*-indol-3-yl)propyl)benzene-sulfonamide (SI-7). Step 1: Prepared according to a modified procedure by Kuehne and co-workers.[39] To a 20 mL Ace Glass pressure tube was added indole (4.69 g, 40 mmol), acrylonitrile (4.4 mL, 66.8 mmol), $Cu(OAc)_2$ (80 mg, 0.4 mmol), $B(OH)_3$ (25 mg, 0.4 mmol), and toluene (2.9 mL). The vessel was sealed and heated to 135 °C behind a blast shield. After 48 h, the reaction was cooled to ambient temperature. The reaction mixture was poured into a separatory funnel and diluted with water, and the aqueous layer was extracted three times with CH_2Cl_2. The combined organic layers were dried over anh. Na_2SO_4. Purified by flash column chromatography (10 → 20% EtOAc/Hexanes) to afford the nitrile (4.24 g, 62%) as an off-white solid. Analytical data (^{1}H NMR, ^{13}C NMR, HRMS) matched those reported in the literature.[40] A ^{1}H NMR spectrum is provided to demonstrate purity. Step 2: Prepared according to a modified procedure by Kuehne and co-workers.[39] To a 200 mL RBF fitted with a reflux condenser under a positive pressure of nitrogen was added lithium aluminum hydride (25.9 mL of 1.0 M solution in THF, 25.9 mmol) followed by cooling to 0 °C. A solution of the nitrile (2.0 g, 11.8 mmol) in THF (35.6 mL) was added to the cooled reaction flask dropwise via cannula over 10 min. The reaction flask was then warmed to room temperature, heated to reflux using an oil bath, and allowed to reflux for 5 h. The reaction mixture was then allowed to cool to room temperature and was worked up using the Fieser method. The resulting residue was purified by flash column chromatography (5% MeOH/CH_2Cl_2) to afford the amine (1.05 g, 51% yield) as a yellow oil. The oil was used without further purification. Step 3: Prepared according to a modified procedure by Meijere and co-workers.[31] To a solution of the crude amine (0.42 g, 2.4 mmol) in DMF (6 mL) 60% w/w NaH (116 mg, 2.9 mmol) was added portionwise over 5 min. This was allowed to stir at ambient temperature for 30 min under a positive pressure of nitrogen. To the stirring solution was added a solution of MeI (0.18 mL, 2.9 mmol) in DMF (6 mL) dropwise over 15 min. The resulting solution was allowed to stir for an additional 18 h. The reaction solution was poured into water and diluted with CH_2Cl_2. The organic layer was separated and washed 5 times with H_2O, once with brine, dried over $MgSO_4$, and concentrated *in vacuo*. The residue was purified by flash column chromatography (10% EtOAc/Hexanes) to afford the alkylated homotryptamine (0.31 g, 68%) as a pale-yellow oil. Step 4: Prepared according to the general procedure using the homotryptamine precursor (0.23 g, 1.2 mmol), CH_2Cl_2 (2.4 mL), Et_3N (0.2 mL, 1.44 mmol), and TsCl (0.27 g, 1.44 mmol) for 18 h at ambient temperature. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **SI-7** (0.23 g, 59%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (d, J = 8.2 Hz, 2H), 7.46 (dd, J = 7.9, 1.1 Hz, 1H), 7.31−7.24 (m, 3H), 7.21 (ddd, J = 8.1, 6.9, 1.1 Hz, 1H), 7.07 (ddt, J = 8.0, 7.0, 1.1 Hz, 1H), 6.76 (s, 1H), 4.41 (br s, 1H), 3.72 (s, 3H), 3.01 (q, J = 6.6 Hz, 2H), 2.74 (t, J = 7.3 Hz, 2H), 2.41 (s, 3H), 1.85 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.2, 137.0, 129.6 (×2), 127.6, 127.1 (×3), 126.4, 121.5, 118.7, 118.6, 113.3, 109.2, 42.8, 32.5, 29.9, 21.9, 21.5; HRMS (ESI) calcd for $(C_{19}H_{23}N_2O_2S)^+$ $[M + H]^+$: 343.1475, found: 343.1475.

Preparation of Indole 3-Acetamides. To a 100 mL RBF was added indole acetic acid and CH_2Cl_2. Et_3N was added, followed by EDCI. The mixture was allowed to stir for a few minutes, and then the amine was added. Upon consumption of starting material, the reaction was diluted with water. The mixture was poured into a separatory funnel and washed with 1.0 M NaOH several times and brine and dried over anh. Na_2SO_4. The residue was purified by flash column chromatography to give the desired products.

2-(1-Methyl-1*H*-indol-3-yl)-*N*-phenylacetamide (SI-8). Prepared according to the general procedure using 1-methyl-3-indoleacetic acid (1.89 g, 10 mmol), CH_2Cl_2 (33 mL), NEt_3 (3.1 mL, 22 mmol), EDCI (2.3 g, 12 mmol), and aniline (1 mL, 11 mmol) for 15 h at ambient temperature. Purified by flash column chromatography (0 → 2% MeOH/CH_2Cl_2) to afford **SI-8** (1.20 g, 45%) as a tan solid. Analytical data (^{1}H and ^{13}C NMR) match those reported in the literature.[41] A ^{1}H NMR spectrum is provided to demonstrate purity.

***N*-Methyl-2-(1-methyl-1*H*-indol-3-yl)acetamide (SI-9).** Prepared according to the general procedure using 1-methyl-3-indoleacetic acid (1.89 g, 10 mmol), CH_2Cl_2 (33 mL), NEt_3 (3.1 mL, 22 mmol), EDCI (2.3 g, 12 mmol), and $MeNH_2$ (5.5 mL, 2.0 M in THF) for 18 h at ambient temperature. Purified by flash column chromatography (5 → 30% MeOH/CH_2Cl_2) to afford **SI-9** (1.06 g, 52%) as an orange-brown solid. Analytical data (^{1}H NMR, ^{13}C NMR, HRMS) match those reported in the literature.[42] A ^{1}H NMR spectrum is provided to demonstrate purity.

General Procedure for Indole Oxidation. To a solution of tryptamine in DMSO at ambient temperature (23 °C) was added 12.1 M HCl dropwise. After the oxidation was completed, the reaction mixture was neutralized with sat. aq. $NaHCO_3$ and extracted with CH_2Cl_2. The combined organic layers were washed with water and brine and dried over anh. $MgSO_4$ or anh. Na_2SO_4. The organic extract was then concentrated *in vacuo*. The residue was purified by flash column chromatography to give the desired products.

4-Methyl-*N*-(2-(1-methyl-2-oxoindolin-3-yl)ethyl)benzene-sulfonamide (6a). Prepared according to the general procedure using sulfonamide **SI-4** (320 mg, 1.0 mmol), DMSO (1.7 mL 24.3 mmol), and 12.1 M HCl (3.4 mL, 41.6 mmol) at ambient temperature. Methanol (1 mL) was added to keep solids solubilized. Purified by flash column chromatography (30% EtOAc/Hexanes) to afford **6a** (170 mg, 55%) as a white solid. Mp: 132−133 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.74 (d, J = 8.2 Hz, 2H), 7.33−7.27 (m, 3H), 7.17 (d, J = 7.3 Hz, 1H), 7.07 (t, J = 7.7 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 5.52 (br s, 1H), 3.45 (dd, J = 8.8, 5.1 Hz, 1H), 3.26 (ddd, J = 12.8, 7.1, 5.6 Hz, 1H), 3.22−3.11 (m, 1H), 3.19 (s, 3H), 2.42 (s, 3H), 2.25−2.16 (m, 1H), 1.91 (dddd, J = 14.3, 8.8, 7.1, 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.8, 143.9, 143.1, 137.2, 129.6, 128.2 (×2), 128.2, 127.0 (×2), 123.6, 122.7, 108.2, 43.5, 40.9, 30.3, 26.2, 21.4.; HRMS (ESI) calcd for $(C_{18}H_{21}N_2O_3S)^+$ $[M + H]^+$: 345.1267, found: 345.1253.

***N*-(2-(1-Benzyl-2-oxoindolin-3-yl)ethyl)-4-methylbenzene-sulfonamide (6b).** Prepared according to the general procedure using sulfonamide **SI-5** (331 mg, 0.82 mmol), DMSO (291 μL, 4.09 mmol), and 12.1 M HCl (676 μL, 8.18 mmol) at ambient temperature for 24 h. Analysis by TLC indicated the reaction was not yet complete, so additional DMSO (291 μL, 4.09 mmol) and 12.1 M HCl (676 μL, 8.18 mmol) were added to the reaction mixture, which was stirred for an additional 10 h. Purified by flash column chromatography (40% EtOAc/Hexanes) to afford **6b** (279 mg, 81%) as an off-white solid. Mp: 118 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.75 (d, J = 8.2 Hz, 2H), 7.36−7.23 (m, 7H), 7.22−7.13 (m, 2H), 7.03 (td, J = 7.6, 1.0 Hz, 1H), 6.76−6.68 (m, 1H), 5.57−5.46 (m, 1H), 4.91 (d, J = 15.7 Hz, 1H), 4.85 (d, J = 15.6 Hz, 1H), 3.55 (dd, J = 8.7, 5.1 Hz, 1H), 3.37−3.25 (m, 1H), 3.20 (ddt, J = 12.8, 7.1, 5.7 Hz, 1H), 2.42 (s, 3H), 2.25 (ddt, J = 14.4, 7.1, 5.5 Hz, 1H), 1.95 (dddd, J = 14.0, 8.5, 7.0, 5.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.8, 143.0, 142.9, 137.1, 135.6, 129.5 (×2), 128.6 (×2), 128.1, 128.0, 127.5, 127.1 (×2), 126.9 (×2), 123.8, 122.6, 109.1, 43.6, 43.2, 40.6, 30.5, 21.3; HRMS (ESI) calcd for $(C_{24}H_{22}N_2O_2SNa)^+$ $[M - H_2O + Na]^+$: 425.1300, found: 425.1300.

4-Methyl-*N*-(2-(2-oxoindolin-3-yl)ethyl)benzenesulfonamide (6c). Prepared according to the general procedure using sulfonamide **SI-3** (1.12 g, 3.56 mmol), DMSO (909 μL, 12.8 mmol), and 12.1 M HCl (1.06 mL, 12.8 mmol) at ambient temperature for 22 h. Purified by flash column chromatography (10% MeOH/CH_2Cl_2) to afford **6c** (768 g, 65%) as a light purple solid. Mp 160−161 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 10.39 (s, 1H), 7.69 (s, 1H), 7.66 (d, J = 8.2 Hz, 2H), 7.39 (d, J = 8.1 Hz, 2H), 7.16 (t, J = 7.7 Hz, 1H), 7.13 (d, J = 7.4 Hz, 1H), 6.93 (t, J = 7.5 Hz, 1H), 6.80 (d, J = 7.7 Hz, 1H), 3.43 (t, J = 6.7 Hz, 1H), 3.35 (br s, 1 H), 2.93−2.81 (m, 2H), 2.38 (s, 3H), 1.91 (ddt, J = 13.3, 8.8, 6.7 Hz, 1H), 1.81 (ddt, J = 13.3, 8.5, 6.4 Hz, 1H); ^{13}C NMR (125 MHz,

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DMSO-d_6): δ 178.5, 142.6, 142.5, 137.5, 129.6 (×2), 129.1, 127.7, 126.4 (×2), 123.8, 121.2, 109.2, 42.5, 40.0, 30.3, 20.9; HRMS (ESI) calcd for $(C_{17}H_{18}N_2O_3S)^+$ $[M + H]^+$: 331.1111, found: 331.1094.

Methyl 3-(1-Methyl-2-oxoindolin-3-yl)-2-(4-methylphenylsulfonamido)propanoate (6d). Prepared according to the general procedure using sulfonamide **SI-6** (1.9 g, 5.0 mmol), DMSO (8.5 mL, 120 mmol), and 12.1 M HCl (17 mL, 205 mmol) at ambient temperature for 12 h. Purified by flash column chromatography (30% EtOAc/Hexanes) to afford **6d** (1.3 g, 66%) as a white solid. Mp: 97−98 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.72 (br s, min), 8.59 (br s, maj), 7.78 (d, J = 8.2 Hz, maj), 7.64 (d, J = 8.2 Hz, min), 7.33 (d, J = 7.5 Hz, min), 7.30 (d, J = 8.0 Hz, maj), 7.23 (d, J = 6.7 Hz, 2H), 7.20 (d, J = 7.0 Hz, 2H), 7.08−7.02 (m, 2H), 6.90 (d, J = 7.8 Hz, maj), 6.87 (d, J = 7.7 Hz, min), 6.41 (d, J = 10.1 Hz, min), 6.15 (d, J = 8.8 Hz, maj), 4.30 (td, J = 9.1, 5.0 Hz, maj), 4.22 (td, J = 9.9, 4.2 Hz, min), 3.72−3.66 (m, 1H), 3.62 (dd, J = 7.9, 3.3 Hz, 1H), 3.46 (s, maj), 3.43 (s, min), 2.41 (s, maj), 2.38 (s, min), 2.33 (ddd, J = 14.4, 9.2, 3.7 Hz, maj), 2.19 (ddd, J = 14.1, 8.2, 4.9 Hz, min); ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7, 171.4, 143.6, 143.3, 141.8, 141.3, 137.0, 136.7, 129.6, 129.4, 128.8, 128.3, 128.2, 127.3, 127.1, 124.4, 123.8, 122.6, 122.4, 110.3, 110.1, 53.9, 53.7, 52.4, 52.3, 42.7, 42.2, 34.1, 32.4, 21.5, 21.4; HRMS (ESI) calcd for $(C_{19}H_{21}N_2O_5S)^+$ $[M + H]^+$: 389.1166, found: 389.1159.

4-Methyl-*N*-(3-(1-methyl-2-oxoindolin-3-yl)propyl)benzenesulfonamide (6e). Prepared according to the general procedure using unpurified tryptamine **SI-7** (0.23 g, 0.67 mmol), DMSO (1.2 mL, 16.1 mmol), and 12.1 M HCl (2.3 mL, 27.5 mmol) at ambient temperature for 12 h. Purified by flash column chromatography (50% EtOAc/Hexanes) to afford **6e** (0.16 g, 68%) as a brown solid. Mp: 129−130 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, J = 8.2 Hz, 2H), 7.35−7.24 (m, 3H), 7.17 (d, J = 7.5 Hz, 1H), 7.04 (td, J = 7.5, 1.0 Hz, 1H), 6.81 (d, J = 7.8 Hz, 1H), 4.85 (t, J = 6.2 Hz, 1H), 3.42 (t, J = 6.0 Hz, 1H), 3.16 (s, 3H), 2.99−2.84 (m, 2H), 2.42 (s, 3H), 2.02−1.84 (m, 2H), 1.61−1.49 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.6, 144.2, 143.2, 137.0, 129.6 (×2), 128.5, 128.0, 127.0 (×2), 123.7, 122.5, 108.0, 44.7, 42.9, 27.3, 26.1, 25.8, 21.5; HRMS (ESI) calcd for $(C_{19}H_{23}N_2O_3S)^+$ $[M + H]^+$: 359.1424, found: 359.1408.

Methyl (2-(1-Methyl-2-oxoindolin-3-yl)ethyl)carbamate (6f). Prepared according to the general procedure using tryptamine **SI-2** (1.43 g, 6.16 mmol), DMSO (2.2 mL, 30.8 mmol), and 12.1 M HCl (5.1 mL, 61.6 mmol) at ambient temperature for 21 h. Purified by flash column chromatography (40 → 50% EtOAc/Hexanes), followed by trituration with CH_2Cl_2/Et_2O to afford **6f** (515 mg, 34%) as a light gray powder. Mp: 98 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34−7.27 (m, 2H), 7.08 (td, J = 7.5, 1.0 Hz, 1H), 6.83 (d, J = 7.8 Hz, 1H), 5.27 (br s, 1H), 3.65 (s, 3H), 3.48 (t, J = 6.7 Hz, 1H), 3.46−3.34 (m, 2H), 3.21 (s, 3H), 2.25−2.16 (m, 1H), 2.03 (dt, J = 14.0, 7.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.7, 157.0, 144.0, 128.5, 128.0, 123.8, 122.6, 108.0, 51.9, 43.4, 38.5, 30.6, 26.1; HRMS (ESI) calcd for $(C_{13}H_{17}N_2O_3)^+$ $[M + H]^+$: 249.1234, found: 249.1232.

2-(1-Methyl-2-oxoindolin-3-yl)-*N*-phenylacetamide (6g). Prepared according to the general procedure using tryptamine **SI-8** (1.02 g, 3.86 mmol), DMSO (1.4 mL, 19.3 mmol), and 12.1 M HCl (3.2 mL, 38.6 mmol) at ambient temperature for 16 h. Purified by flash column chromatography (2.5% MeOH/CH_2Cl_2) to afford **6g** (849 mg, 79%) as a straw-colored solid. Mp: 58−59 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.06 (br s, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.40−7.29 (m, 4H), 7.16−7.06 (m, 2H), 6.87 (d, J = 7.7 Hz, 1H), 3.96 (t, J = 6.7 Hz, 1H), 3.27 (s, 3H), 3.05 (dd, J = 15.8, 7.8 Hz, 1H), 2.79 (dd, J = 15.7, 5.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.9, 168.6, 143.7, 138.1, 128.9 (×2), 128.3, 128.1, 124.2, 124.1, 123.0, 119.9 (×2), 108.2, 42.2, 38.4, 26; HRMS (ESI) calcd for $(C_{17}H_{14}N_2ONa)^+$ $[M-H_2O+Na]^+$: 285.1004, found: 285.1015.

***N*-Methyl-2-(1-methyl-2-oxoindolin-3-yl)acetamide (6h).** Prepared according to the general procedure using indole acetamide **SI-9** (1.06 g, 5.24 mmol), DMSO (1.9 mL, 26.2 mmol), and 12.1 M HCl (4.4 mL, 52.4 mmol) at ambient temperature for 26.5 h. Purified by flash column chromatography (5 → 10% MeOH/CH_2Cl_2) to afford **6h** (589 mg, 52%) as a pale-yellow powder. Mp: 157−158 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 7.30 (t, J = 7.5 Hz, 2H), 7.07 (t, J = 7.6 Hz, 1H), 6.84 (d, J = 7.7 Hz, 1H), 6.52 (br s, 1H), 3.87 (t, J = 6.8 Hz, 1H), 3.23 (s, 3H), 2.91−2.83 (m, 1H), 2.87 (d, J = 4.7 Hz, 3 H), 2.58 (dd, J = 15.5, 6.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.6, 170.7, 143.8, 128.4, 128.1, 124.1, 122.6, 108.0, 42.2, 37.0, 26.3, 26.2; HRMS (ESI) calcd for $(C_{12}H_{15}N_2O_2)^+$ $[M + H]^+$: 219.1128, found: 219.1129.

3-(2-Hydroxyphenyl)-1-methylindolin-2-one (6i). Step 1: Prepared according to a procedure by Basavaiah and co-workers.[43] To a 250 mL RBF was added isatin (2.94 g, 20 mmol), Na_2CO_3 (5.30 g, 50 mmol), acetone (100 mL), and Me_2SO_4 (2.85 mL, 30 mmol). The RBF was fitted with a reflux condenser and heated at reflux for 42.5 h. After cooling to ambient temperature, the bright-orange suspension was vacuum-filtered and the filtrate was concentrated. Purified by flash column chromatography (0 → 2.5% EtOAc/Hexanes) to afford methyl isatin (2.92 g) as a bright red-orange oil that consisted of a mixture of product and some Me_2SO_4. The residue was used without further purification. Step 2: The 100 mL RBF containing the aforementioned methyl isatin was purged with N_2, and anh. CH_2Cl_2 (20 mL) and cyclohexenone (1.94 mL, 20 mmol) were added. The mixture was cooled with an ice/water bath, and $TiCl_4$ (20 mL, 1.0 M in CH_2Cl_2) was added. The reaction was allowed to warm to ambient temperature. After 3.5 h, the reaction mixture was cooled with an ice/water bath and quenched with water, extracted three times with CH_2Cl_2, and dried over anh. Na_2SO_4. The combined organic layers were reduced *in vacuo*. Purified by flash column chromatography (5% MeOH/CH_2Cl_2) to afford the hydroxyoxindole (1.68 g, 33% over two steps) as a light-yellow solid foam. A ^{1}H NMR spectrum is provided to demonstrate purity. Step 3: To a 100 mL RBF containing the hydroxyoxindole (852 mg, 3.31 mmol) was added 1,2-dichloroethane (3.3 mL) and 48% aq. HBr (1.9 mL). The reaction mixture was refluxed for 15.5 h and then cooled to ambient temperature. The reaction mixture was diluted with water and extracted three times with CH_2Cl_2, and the combined organic layers were dried over anh. Na_2SO_4 and concentrated *in vacuo*. Purified by flash column chromatography (50−75% EtOAc/Hexanes) to afford **6i** (551 mg, 70%) as an off-white solid. Analytical data (^{1}H and ^{13}C NMR) match those reported in the literature.[43] A ^{1}H NMR spectrum is provided to demonstrate purity.

General Procedure for the Calculation of NMR Yields. The crude reaction mixture was concentrated *in vacuo*, and the residue was dissolved in an appropriate deuterated solvent (1 mL). To this solution was added 1,3,5-trimethoxybenzene (0.33 equiv), followed by stirring until all solids were completely dissolved. An aliquot was removed and subjected to ^{1}H NMR analysis (d1 relaxation time is set to 5) wherein the integration value of the 1,3,5-trimethoxybenzene signal at δ 6.08 (s, 3H) was compared to the integration values of several peaks corresponding to the desired product. With this information the NMR yield was determined by using the following equations:

$$\text{NMR yield} = \frac{P}{\text{SM}}$$

$$P = \frac{3x}{y} * \text{mmol of (1, 3, 5-trimethoxybenzene)}$$

P = calculated mmol of product; SM = mmol of starting material; x = a normalized average of three aromatic signals corresponding to the product; and y = integration value of 1,3,5-trimethoxybenzene peak at δ 6.08.

General Procedure for the Pd-Catalyzed Spirocyclization of Oxindole-Based Bis-nucleophiles. Oxindole substrate **6** (0.20 mmol), $Pd_2(dba)_3$·$CHCl_3$ (5 mg, 5.0 μmol, 5 mol % Pd), and dppb (5 mg, 11 μmol) were added to an oven-dried 16 × 100 borosilicate test tube. The test tube was covered with a rubber septum and sealed with Teflon tape or parafilm. The test tube was purged with N_2, anhydrous THF (2 mL) was added, and the mixture was maintained under a positive pressure of nitrogen. The reaction was either heated or maintained at ambient temperature (23 °C) as indicated. After 15 min the propargyl *tert*-butyl carbonate **5** (0.30 mmol) was added to the reaction mixture. After consumption of starting material as judged by TLC, the reaction mixture was filtered through a pipet plug of Celite and concentrated. The residue was purified by flash column chromatography to give the desired products.

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1-Methyl-3′-methylene-1′-tosylspiro[indoline-3,4′-piperidin]-2-one (7a). Prepared according to the general procedure using oxindole **6a** (69 mg, 0.20 mmol), propargyl carbonate **5a** (47 mg, 0.30 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (2 mg, 2 μmol), dppb (2 mg, 4.4 μmol), and anh. THF (2 mL) at ambient temperature for 20 min. Purified by flash column chromatography (30% EtOAc/Hexanes) to afford **7a** (75 mg, 98%) as a white solid. Mp: 194 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.72 (d, *J* = 8.0 Hz, 2H), 7.36 (d, *J* = 8.0 Hz, 2H), 7.31 (ddd, *J* = 8.1, 6.9, 2.1 Hz, 1H), 7.14−7.06 (m, 2H), 6.84 (d, *J* = 7.8 Hz, 1H), 5.06 (s, 1H), 4.55 (s, 1H), 4.28 (dd, *J* = 12.8, 1.7 Hz, 1H), 3.88 (d, *J* = 12.7 Hz, 1H), 3.79 (dq, *J* = 9.8, 2.4 Hz, 1H), 3.42 (td, *J* = 12.4, 2.9 Hz, 1H), 3.10 (s, 3H), 2.46 (s, 3H), 2.19 (td, *J* = 13.2, 4.8 Hz, 1H), 1.78 (dt, *J* = 13.7, 2.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ176.7, 143.5, 143.2, 139.3, 133.7, 130.5, 129.7 (×2), 128.5, 127.7 (×2), 124.3, 122.7, 114.2, 108.3, 51.1, 49.6, 41.6, 34.0, 26.0, 21.5; HRMS (ESI): Mass calcd for $(C_{21}H_{23}N_2O_3S)^+$ $[M + H]^+$: 383.1424; found: 383.1429.

1-Benzyl-3′-methylene-1′-tosylspiro[indoline-3,4′-piperidin]-2-one (7b). Prepared according to the general procedure using oxindole **6b** (84 mg, 0.20 mmol), propargyl carbonate **5a** (47 mg, 0.30 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5 μmol), dppb (5 mg, 11 μmol), and anh. THF (2 mL) at ambient temperature for 30 min. Purified by flash column chromatography (20 → 30% EtOAc/Hexanes) to afford **7b** (85 mg, 92%) as a white solid foam. Mp: 158−159 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.0 Hz, 2H), 7.31−7.21 (m, 3H), 7.18 (td, *J* = 7.6, 1.6 Hz, 1H), 7.16−7.12 (m, 2H), 7.12−7.04 (m, 2H), 6.71 (d, *J* = 7.8 Hz, 1H), 5.10 (s, 1H), 4.83 (d, *J* = 15.8 Hz, 1H), 4.74 (d, *J* = 15.8 Hz, 1H), 4.59 (s, 1H), 4.32 (dd, *J* = 12.8, 1.6 Hz, 1H), 3.91 (d, *J* = 12.7 Hz, 1H), 3.83 (ddt, *J* = 11.9, 4.6, 2.2 Hz, 1H), 3.46 (td, *J* = 12.3, 2.8 Hz, 1H), 2.45 (s, 3H), 2.25 (ddd, *J* = 13.9, 12.7, 4.9 Hz, 1H), 1.85 (dt, *J* = 13.8, 2.7 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 176.8, 143.6, 142.3, 139.4, 135.5, 133.6, 130.5, 129.7 (×2), 128.7 (×2), 128.4, 127.7 (×2), 127.5, 126.7 (×2), 124.4, 122.8, 114.5, 109.3, 51.0, 49.7, 43.1, 41.7, 34.0, 21.5; HRMS (ESI): Mass calcd for $(C_{27}H_{26}N_2O_3SNa)^+$ $[M + Na]^+$: 481.1556; found: 481.1557.

3′-Methylene-1′-tosylspiro[indoline-3,4′-piperidin]-2-one (7c). Prepared according to the general procedure using oxindole **6c** (66 mg, 0.20 mmol), propargyl carbonate **5a** (47 mg, 0.30 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5 μmol), dppb (5 mg, 11 μmol), and anh. THF (2 mL) at ambient temperature for 14 h. Purified by flash column chromatography (30% EtOAc/Hexanes) to afford **7c** (70 mg, 95%) as a white solid. Mp: 205−207 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 7.75 (br s, 1H), 7.73 (d, *J* = 8.3 Hz, 2H), 7.36 (d, *J* = 7.9 Hz, 2H), 7.24 (tt, *J* = 7.5, 1.3 Hz, 1H), 7.11−7.02 (m, 2H), 6.83 (d, *J* = 7.7 Hz, 1H), 5.08 (s, 1H), 4.59 (s, 1H), 4.28 (dd, *J* = 12.9, 1.5 Hz, 1H), 3.88 (dd, *J* = 12.9, 1.4 Hz, 1H), 3.82−3.73 (m, 1H), 3.42 (td, *J* = 12.4, 2.9 Hz, 1H), 2.47 (s, 3H), 2.20−2.10 (m, 1H), 1.83 (dt, *J* = 13.8, 2.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): 178.7, 143.6, 140.3, 139.1, 133.9, 131.2, 129.7 (×2), 128.5, 127.8 (×2), 124.8, 122.8, 114.6, 109.8, 51.4, 49.6, 41.6, 34.0, 21.6; HRMS (ESI): Mass calcd for $(C_{20}H_{21}N_2O_3S)^+$ $[M + H]^+$: 369.1267; found: 369.1266.

Methyl 5′-Methylene-2-oxo-1′-tosylspiro[indoline-3,4′-piperidine]-2′-carboxylate (7d). Prepared according to the general procedure using oxindole **6d** (78 mg, 0.20 mmol), propargyl carbonate **5a** (47 mg, 0.30 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5 μmol), dppb (5 mg, 11 μmol), and anh. THF (2 mL) at ambient temperature for 8 h. Purified by flash column chromatography (5 → 50% EtOAc/Hexanes) to afford diastereomer **7d major** (41 mg, 48%) as a white solid, mp: 213−214 °C, and diastereomer **7d minor** (25 mg, 30%) as a white solid. Mp: 213−214 °C; **7d major**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.56 (br s, 1H), 7.83 (d, *J* = 8.2 Hz, 2H), 7.37 (d, *J* = 8.1 Hz, 2H), 7.30−7.20 (m, 1H), 7.10 (d, *J* = 7.9 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 5.06 (s, 1H), 4.72−4.65 (m, 1H), 4.63 (s, 1H), 4.24 (d, *J* = 13.5 Hz, 1H), 4.13 (d, *J* = 13.5 Hz, 1H), 3.77 (s, 3H), 2.49−2.44 (m, 1H), 2.46 (s, 3H), 2.20 (ddd, *J* = 14.1, 4.6, 1.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.8, 171.4, 143.8, 140.3, 138.4, 134.5, 131.2, 129.6 (×2), 128.7, 128.3 (×2), 124.6, 122.8, 115.1, 110.2, 54.9, 52.6, 51.4, 48.9, 36.1, 21.6; HRMS (ESI): Mass calcd for $(C_{22}H_{23}N_2O_5S)^+$ $[M + H]^+$: 427.1322; found: 427.1327. **7d minor**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.14 (br s, 1H), 7.82 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 7.9 Hz, 2H), 7.24 (td, *J* = 7.8, 1.3 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 6.83 (d, *J* = 7.4 Hz, 1H), 5.04 (s, 1H), 4.89 (d, *J* = 6.2 Hz, 1H), 4.59 (d, *J* = 14.9 Hz, 1H), 4.51 (s, 1H), 4.38 (d, *J* = 15.0 Hz, 1H), 3.67 (s, 3H), 2.52−2.48 (m, 1H), 2.48 (s, 3H), 2.17 (dd, *J* = 14.2, 7.2 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.6, 169.9, 143.4, 140.6, 138.6, 137.5, 130.7, 129.5 (×2), 128.8, 127.6 (×2), 124.6, 122.7, 114.2, 110.0, 53.3, 52.3, 51.2, 46.0, 34.4, 21.5; HRMS (ESI): Mass calcd for $(C_{22}H_{23}N_2O_5S)^+$ $[M + H]^+$: 427.1322; found: 427.1324.

1′-Methyl-3-methylene-1-tosylspiro[azepane-4,3′-indolin]-2′-one (7e). Prepared according to the general procedure using oxindole **6e** (61 mg, 0.17 mmol), propargyl carbonate **5a** (41 mg, 0.26 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (4 mg, 4.3 μmol), dppb (4 mg, 9.4 μmol), and anh. THF (1.7 mL) at ambient temperature for 20 min. Purified by flash column chromatography (30% EtOAc/Hexanes) to afford **7e** (53 mg, 78%) as a white solid. Mp: 161 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.34 (d, *J* = 8.0 Hz, 2H), 7.30 (t, *J* = 7.7 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.85 (d, *J* = 7.8 Hz, 1H), 5.25 (s, 1H), 4.61 (s, 1H), 4.42 (dd, *J* = 14.0, 1.5 Hz, 1H), 3.92 (d, *J* = 13.9 Hz, 1H), 3.90−3.82 (m, 1H), 3.17 (s, 3H), 2.97 (ddd, *J* = 12.5, 8.4, 3.6 Hz, 1H), 2.46 (s, 3H), 2.16−2.07 (m, 2H), 2.04−1.91 (m, 1H), 1.85−1.74 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.6, 144.1, 143.2, 142.9, 136.3, 133.8, 129.7 (×2), 128.1, 127.3 (×2), 124.3, 122.8, 119.9, 108.2, 55.3, 51.9, 48.9, 35.0, 26.3, 24.4, 21.5; HRMS (ESI): Mass calcd for $(C_{22}H_{25}N_2O_3S)^+$ $[M + H]^+$: 397.1580; found: 397.1592.

Methyl 1-Methyl-2′-methylene-2-oxospiro[indoline-3,4′-piperidine]-1′-carboxylate (7f). To a 50 mL RBF were added $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5 μmol) and dppb (5 mg, 11 μmol). The flask was purged with N_2, and anh. THF (20 mL) was added. After 5 min, propargyl carbonate **5a** (47 mg, 0.30 mmol) was added and then stirred at ambient temperature for 5 min. After heating to 50 °C for 15 min, a solution of oxindole **6f** (50 mg, 0.20 mmol) in THF (1 mL) was added dropwise via syringe pump over 1 h. After 15 h, the reaction was cooled to ambient temperature, filtered over a Celite pipet plug, and concentrated *in vacuo*. Purified by flash column chromatography (40% EtOAc/Hexanes) to afford **7f** (39 mg, 68%) as an amber residue. NOTE: The exocyclic olefin product slowly isomerizes to an endocyclic olefin product at ambient temperature; purified **7f** is stored at −78 °C to slow/halt this process. Analytical data for **7f**: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (d, *J* = 7.4 Hz, 1H), 7.32 (t, *J* = 7.7 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.89 (d, *J* = 7.8 Hz, 1H), 5.20 (s, 1H), 4.93 (s, 1H), 4.22 (dt, *J* = 13.4, 5.2 Hz, 1H), 3.78 (s, 3H), 3.67 (ddd, *J* = 13.6, 9.8, 3.7 Hz, 1H), 3.23 (s, 3H), 2.73 (d, *J* = 13.6 Hz, 1H), 2.23 (d, *J* = 13.6 Hz, 1H), 2.12 (ddd, *J* = 14.0, 9.7, 4.5 Hz, 1H), 1.67 (dt, *J* = 13.7, 4.8 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.6, 155.2, 142.7, 139.1, 132.8, 128.1, 123.9, 122.3, 109.3, 108.1, 52.8, 46.7, 41.2, 39.3, 32.0, 26.3; HRMS (ESI): Mass calcd for $(C_{16}H_{19}N_2O_3)^+$ $[M + H]^+$: 287.1390; found: 287.1392.

1-Methyl-5′-methylene-1′-phenylspiro[indoline-3,4′-piperidine]-2,2′-dione (7g). To a 50 mL RBF were added oxindole **6g** (56 mg, 0.20 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5 μmol), and dppb (5 mg, 11 μmol). The flask was purged with N_2, and anh. THF (20 mL) was added. The flask was immediately immersed in a 50 °C oil bath. After heating for 15 min, propargyl carbonate **5a** (47 mg, 0.30 mmol) was added in one portion. After 30 min, the reaction mixture was cooled to ambient temperature, filtered over a Celite pipet plug, and concentrated *in vacuo*. Purified by flash column chromatography (50 → 70% EtOAc/Hexanes) to afford **7g** (49 mg, 77%) as an off-white solid foam. Mp: 63−64 °C; NOTE: The exocyclic olefin product slowly isomerizes to the endocyclic olefin product at ambient temperature; purified **7g** is stored at −78 °C to slow/halt this process. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.50−7.40 (m, 4H), 7.36 (t, *J* = 7.7 Hz, 1H), 7.34−7.28 (m, 1H), 7.28−7.23 (m, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 5.14 (s, 1H), 4.83 (d, *J* = 14.5 Hz, 1H), 4.79 (s, 1H), 4.35 (d, *J* = 14.5 Hz, 1H), 3.26 (s, 3H), 2.96 (d, *J* = 16.3 Hz, 1H), 2.79 (d, *J* = 16.3 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.1, 167.6, 143.1, 142.1, 139.5, 130.6, 129.2 (×2), 128.8, 127.0, 126.0 (×2), 123.9, 123.1, 113.2, 108.6, 55.2, 52.4, 40.5, 26.4; HRMS (ESI): Mass calcd for $(C_{20}H_{19}N_2O_2)^+$ $[M + H]^+$: 319.1441; found: 319.1437.

1,1′-Dimethyl-2′-methylenespiro[indoline-3,4′-piperidine]-2,6′-dione (7h). To a 50 mL RBF were added oxindole **6h** (44 mg, 0.20 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5 μmol), and dppb (5 mg, 11 μmol). The flask was purged with N_2, and anh. THF (20 mL) was added. The

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flask was immediately immersed in a 50 °C oil bath. After heating for 15 min, propargyl carbonate **5a** (47 mg, 0.30 mmol) was added in one portion. After 30 min, the reaction mixture was cooled to ambient temperature, filtered over a Celite pipet plug, and concentrated *in vacuo*. Purified by flash column chromatography (0 → 5% MeOH/CH_2Cl_2) to afford **7h** (37 mg, 73%) as an amber residue that slowly crystallized on standing. Mp: 139−140 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 7.32 (td, J = 7.7, 1.3 Hz, 1H), 7.03 (td, J = 7.5, 1.0 Hz, 1H), 6.96 (dd, J = 7.5, 1.2 Hz, 1H), 6.90 (d, J = 7.8 Hz, 1H), 4.52 (t, J = 1.7 Hz, 1H), 4.20 (t, J = 1.6 Hz, 1H), 3.34 (s, 3H), 3.25 (s, 3H), 3.05 (d, J = 17.4 Hz, 1H), 3.03 (dt, J = 14.5, 1.8 Hz, 1H), 2.49 (dd, J = 17.3, 2.8 Hz, 1H), 2.41 (dd, J = 14.6, 2.9 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.0, 167.0, 142.6, 141.6, 130.7, 128.7, 123.2, 122.8, 108.4, 94.5, 45.0, 39.1, 37.2, 29.6, 26.4; HRMS (ESI): Mass calcd for $(C_{15}H_{17}N_2O_2)^+$ $[M + H]^+$: 257.1285; found: 257.1277.

1′-Methyl-3-methylenespiro[chroman-4,3′-indolin]-2′-one (7i). Prepared according to the general procedure using oxindole **6i** (48 mg, 0.20 mmol), propargyl carbonate **5a** (47 mg, 0.30 mmol), $Pd_2(dba)_3$·$CHCl_3$ (5 mg, 5 μmol), dppb (5 mg, 11 μmol), and anh. THF (2 mL) at ambient temperature for 20 min. Purified by flash column chromatography (10 → 30% EtOAc/Hexanes) to afford **7i** (52 mg, 95%) as a pale-yellow powder. Mp: 97−98 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (td, J = 7.7, 1.3 Hz, 1H), 7.14 (ddd, J = 8.6, 7.2, 1.6 Hz, 1H), 7.10 (td, J = 7.5, 1.0 Hz, 1H), 7.02 (dd, J = 7.4, 1.3 Hz, 1H), 6.95 (td, J = 8.3, 1.0 Hz, 2H), 6.73 (ddd, J = 8.3, 7.2, 1.3 Hz, 1H), 6.41 (dd, J = 7.8, 1.7 Hz, 1H), 5.35 (dd, J = 11.9, 1.3 Hz, 1H), 5.17 (d, J = 1.3 Hz, 1H), 4.68 (d, J = 12.0 Hz, 1H), 4.65 (s, 1H), 3.25 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.7, 155.6, 144.5, 139.3, 132.3, 128.8, 128.7, 127.9, 125.5, 123.3, 121.8, 121.1, 117.4, 113.6, 108.2, 68.4, 55.5, 26.6; HRMS (ESI): Mass calcd for $(C_{18}H_{16}NO_2)^+$ $[M + H]^+$: 278.1176; found: 278.1165.

1-Methyl-2′-phenyl-3′-(propan-2-ylidene)-1′-tosylspiro-[indoline-3,4′-piperidin]-2-one (7j). Prepared according to the general procedure using oxindole **6a** (69 mg, 0.20 mmol), propargyl carbonate **5e** (78 mg, 0.30 mmol, as a 0.30 M solution in THF), $Pd_2(dba)_3$·$CHCl_3$ (5 mg, 5 μmol), dppb (5 mg, 11 μmol), and anh. THF (2 mL) at 50 °C for 30 min. Purified by flash column chromatography (20 → 25% EtOAc/Hexanes) to afford **7j** (92 mg, 95%) as an amorphous bright orange-yellow solid foam. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (t, J = 7.1 Hz, 3H), 7.44−7.37 (m, 2H), 7.36−7.29 (m, 4H), 7.19 (d, J = 8.1 Hz, 2H), 7.08 (t, J = 7.6 Hz, 1H), 6.82 (d, J = 7.8 Hz, 1H), 4.14−4.07 (m, 1H), 3.16 (s, 3H), 2.64−2.53 (m, 2H), 2.45−2.39 (m, 2H), 2.36 (s, 3H), 1.53 (s, 3H), 0.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.5, 144.1, 142.9, 136.8, 131.4 (×2), 129.4 (×2), 129.0, 128.4, 128.2 (×2), 127.9, 126.9 (×2), 124.8, 123.2, 122.3, 107.9, 94.3, 82.7, 55.5, 39.9, 38.6, 32.0, 26.0, 24.6, 23.8, 21.3; HRMS (ESI): Mass calcd for $(C_{29}H_{31}N_2O_3S)^+$ $[M + H]^+$: 487.2050; found: 487.2052.

General Procedure for the Pd-Catalyzed Spirocyclization of Indole-Based Bis-nucleophiles. Tryptamine sulfonamide **8** (0.20 mmol), $Pd_2(dba)_3$·$CHCl_3$ (5 mg, 5.0 μmol, 5 mol % Pd), and Xantphos (6 mg, 11 μmol) were added to an oven-dried 16 × 100 borosilicate test tube. The test tube was covered with a rubber septum and sealed with Teflon tape or parafilm. The test tube was purged with N_2, anhydrous CH_2Cl_2 (5 mL) was added, and the mixture was maintained under a positive pressure of nitrogen. After 15 min, *tert*-butyl propargyl carbonate **5** (0.26 mmol) was added to the reaction mixture. After consumption of starting material as judged by TLC, the reaction was filtered through a pipet plug of Celite and concentrated. The residue was purified by flash column chromatography to give the desired products.

2-Methyl-2′-methylene-3′-phenyl-1′-tosylspiro[indole-3,4′-piperidine] (9a). Prepared according to the general procedure using sulfonamide **8a** (66 mg, 0.20 mmol), propargyl carbonate **5c** (60 mg, 0.26 mmol), $Pd_2(dba)_3$·$CHCl_3$ (5 mg, 5.0 μmol), Xantphos (6 mg, 11.0 μmol), and anh. CH_2Cl_2 (5 mL) at 23 °C for 24 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **9a** (59 mg, 70%, 4:1 dr) as an off-white solid. Mp: 78−80 °C; ^{1}H NMR (500 MHz, $CDCl_3$) (major): 7.94−7.85 (m, 2H), 7.70 (d, J = 7.4 Hz, 1H), 7.53−7.43 (m, 3H), 7.41 (td, J = 7.6, 1.1 Hz, 1H), 7.27−7.20 (m, 1H), 7.10−7.01 (m, 2H), 6.95 (t, J = 7.7 Hz, 2H), 6.29 (br s, 2H), 5.50 (d, J = 1.7 Hz, 1H), 4.53 (ddd, J = 14.6, 5.2, 2.0 Hz, 1H), 3.90 (ddd, J = 14.7, 13.4, 3.1 Hz, 1H), 3.43 (s, 1H), 2.53 (s, 3H), 2.19 (td, J = 13.3, 5.1 Hz, 1H), 1.91 (d, J = 0.9 Hz, 3H), 1.14 (ddd, J = 13.4, 3.2, 2.2 Hz, 1H). ^{13}C NMR analytical data and HRMS data match those reported below.

2-Methyl-2′-methylene-3′-phenyl-1′-tosylspiro[indole-3,4′-piperidine] (9a). Prepared according to the general procedure using sulfonamide **8a** (66 mg, 0.20 mmol), propargyl carbonate **5f** (60 mg, 0.26 mmol), $Pd_2(dba)_3$·$CHCl_3$ (5 mg, 5.0 μmol), Xantphos (6 mg, 11.0 μmol), and anh. CH_2Cl_2 (5 mL) at 23 °C for 18 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **9a** (51 mg, 57%, 4.3:1 dr) as an off-white solid. Mp: 78−80 °C; ^{1}H NMR (500 MHz, $CDCl_3$) (major): 7.92−7.86 (m, 2H), 7.70 (dd, J = 7.5, 1.0 Hz, 1H), 7.49−7.43 (m, 3H), 7.41 (td, J = 7.7, 1.1 Hz, 1H), 7.24 (t, J = 7.2 Hz, 1H), 7.09−7.00 (m, 2H), 6.95 (t, J = 7.6 Hz, 2H), 6.29 (br s, 2H), 5.51 (d, J = 1.7 Hz, 1H), 4.60 (d, J = 1.9 Hz, 1H), 4.53 (ddd, J = 14.5, 5.2, 2.0 Hz, 1H), 3.90 (ddd, J = 14.6, 13.3, 3.1 Hz, 1H), 3.43 (s, 1H), 2.52 (s, 3H), 2.19 (td, J = 13.3, 5.2 Hz, 1H), 1.91 (s, 3H), 1.71 (dt, J = 14.4, 4.0 Hz, 1H), 1.14 (dt, J = 13.3, 2.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 183.2, 155.0, 154.9, 144.0, 143.9, 142.1, 139.6, 138.0, 135.2, 129.8, 129.6, 129.5, 128.7, 128.6, 128.3, 128.1, 128.0, 127.8, 127.6, 127.3, 127.2, 125.1, 124.7, 124.5, 121.0, 120.8, 120.0, 116.5, 60.8, 53.4, 51.5, 43.1, 43.1, 32.2, 32.2, 31.5, 29.7, 22.0, 21.6, 15.6; HRMS (ESI): Mass calcd for $(C_{27}H_{27}N_2O_2S)^+$ $[M + H]^+$: 443.1788; found: 443.1789.

2′-Benzylidene-1,3′-dimethyl-1′-tosylspiro[indoline-3,4′-piperidin]-2-one (9b). Prepared according to the general procedure using sulfonamide **8a** (66 mg, 0.20 mmol), propargyl carbonate **5g** (64 mg, 0.26 mmol), $Pd_2(dba)_3$·$CHCl_3$ (5 mg, 5.0 μmol), Xantphos (6 mg, 11.0 μmol), triethylamine (30 mg, 0.3 mmol), and anh. CH_2Cl_2 (5 mL) at 40 °C for 24 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **9b** (29.4 mg, 32%, 18:1 dr) as a pale-yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.96 (d, J = 8.3 Hz, min), 7.55 (d, J = 7.6 Hz, 1H, maj), 7.52 (d, J = 8.3 Hz, 2H, maj), 7.40 (dd, J = 7.5, 2.0 Hz, 2H, maj), 7.34 (d, J = 7.4 Hz, 1H, maj), 7.33−7.29 (m, 1H, maj), 7.26−7.22 (m, J = 1.4 Hz, 2H, maj), 7.20 (d, J = 7.8 Hz, min), 7.11 (d, J = 8.4 Hz, 2H, maj), 7.05 (t, J = 7.5 Hz, 1H, maj), 6.96 (t, J = 7.5 Hz, min), 6.70 (d, J = 7.4 Hz, min), 6.48 (d, J = 7.7 Hz, min), 6.26 (s, 1H, maj), 5.45 (d, J = 7.0 Hz, min), 4.35 (dd, J = 5.0, 15.0 Hz, min), 4.28 (dd, J = 14.7, 3.5 Hz, 1H, maj), 3.79−3.71 (m, 1H, maj), 3.09−2.97 (m, 1H, maj), 2.65 (s, min), 2.57 (s, min), 2.42−2.32 (m, 1H, maj), 2.37 (s, 3H, maj), 2.15 (s, 3H, maj), 1.77 (dd, J = 6.9, 2.0 Hz, min), 1.13 (d, J = 13.3 Hz, 1H, maj), 0.53 (d, J = 6.7 Hz, 3H, maj); ^{13}C NMR (126 MHz, $CDCl_3$) δ 184.22, 155.03, 143.53, 139.24, 137.16, 136.40, 135.05, 129.29 (×2), 129.00 (×2), 128.63, 128.29 (×2), 128.25, 127.83 (×2), 127.58, 124.73, 123.82, 120.54, 63.00, 44.23, 38.88, 30.86, 21.45, 15.37, 11.94; HRMS (ESI): Mass calcd for $(C_{28}H_{29}N_2O_2S)^+$ $[M + H]^+$: 457.1944; found: 457.1947.

General Procedure for the Enantioselective Pd-Catalyzed Spirocyclization of Indole-Based Bis-nucleophiles. Tryptamine sulfonamide **8**[13] (0.20 mmol), $Pd_2(dba)_3$·$CHCl_3$ (5 mg, 5.0 μmol, 5 mol % Pd), and chiral ligand (11 μmol) were added to an oven-dried 16 × 100 borosilicate test tube. The test tube was covered with a rubber septum and sealed with Teflon tape or parafilm. The test tube was purged with N_2, anhydrous CH_2Cl_2 (5 mL) was added, and the mixture was maintained under a positive pressure of nitrogen. After 15 min, *tert*-butyl propargyl carbonate **5a** (0.26 mmol) was added to the reaction mixture. After consumption of starting material as judged by TLC, the reaction was filtered through a pipet plug of Celite and concentrated. The residue was purified by flash column chromatography to give the desired products.

2-Methyl-2′-methylene-1′-tosylspiro[indole-3,4′-piperidine] (11a). Prepared according to the general procedure using tryptamine **8a** (66 mg, 0.20 mmol), propargyl carbonate **5a** (41 mg, 0.26 mmol), $Pd_2(dba)_3$·$CHCl_3$ (5 mg, 5 μmol), 2,2′-Bis(di-2-(4-methylfuranyl)-phosphino)-6,6′-dimethoxy-1,1′-biphenyl (6 mg, 11 μmol), and CH_2Cl_2 (5 mL) at ambient temperature for 16 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **11a** (51 mg, 69%, 41% ee) as a white solid. Analytical data (^{1}H NMR, ^{13}C NMR, and HRMS) match those previously reported in the literature.[13] A ^{1}H NMR spectrum is provided to demonstrate purity. The enantiomeric ratio was measured by HPLC (Chiralpak AD-H, 25% *i*-PrOH/Hexanes, 1 mL/min, Rt_1 = 10.30, Rt_2 = 16.4).

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2′-Methylene-2-phenyl-1′-tosylspiro[indole-3,4′-piperidine] (11b). Prepared according to the general procedure using tryptamine **8b** (39 mg, 0.10 mmol), propargyl carbonate **5a** (20 mg, 0.13 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (3 mg, 2.5 μmol), 2,2′-Bis(di-2-furanylphosphino)-6,6′-dimethoxy-1,1′-biphenyl (3 mg, 5.5 μmol), and anh. CH_2Cl_2 (2.5 mL) at ambient temperature for 18 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **11b** (30 mg, 70%, 53% ee) as a white solid. Analytical data (^{1}H NMR,^{13}C NMR, and HRMS) match those previously reported in the literature.[13] A ^{1}H NMR spectrum is provided to demonstrate purity. The enantiomeric ratio was measured by HPLC (Chiralcel OD-H, 2.5% *i*-PrOH/Hexanes, 1 mL/min, Rt_1 = 34.8, Rt_2 = 38.2).

2-(3,4-Dimethoxyphenyl)-2′-methylene-1′-tosylspiro-[indole-3,4′-piperidine] (11c). Prepared according to the general procedure using tryptamine **8c** (45 mg, 0.10 mmol), propargyl carbonate **5a** (20 mg, 0.13 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (3 mg, 2.5 μmol), 2,2′-Bis(di-2-(4-methylfuranyl)phosphino)-6,6′-dimethoxy-1,1′-biphenyl (3 mg, 5.5 μmol), and anh. CH_2Cl_2 (2.5 mL) at ambient temperature for 24 h. Purified by flash column chromatography (20% EtOAc/Hexanes) to afford **11c** (36 mg, 73%, 77% ee) as a white solid. Analytical data (^{1}H NMR, ^{13}C NMR, and HRMS) match those previously reported in the literature.[13] A ^{1}H NMR spectrum is provided to demonstrate purity. The enantiomeric ratio was measured by HPLC (Chiralcel AD-H, 10% *i*-PrOH/Hexanes, 1 mL/min, Rt_1 = 24.3, Rt_2 = 57.4).

1-Methyl-3′-methylene-1′-tosylspiro[indoline-3,4′-piperidin]-2-one (7a*). Prepared according to a modification of the general procedure using oxindole **6a** (69 mg, 0.20 mmol), propargyl carbonate **5a** (47 mg, 0.30 mmol), $Pd_2(dba)_3{\cdot}CHCl_3$ (5 mg, 5.0 μmol), (*R*,*R*)-DACH-phenyl (7 mg, 11 μmol), and anh. THF (2 mL) at 40 °C for 4 h, followed by heating to 60 °C for 16 h. Purified by flash column chromatography (25% EtOAc/Hexanes) to afford **7a*** (6 mg, 8%, 32% ee) as a white solid. Analytical data (^{1}H NMR, ^{13}C NMR, and HRMS) match those reported in this document for **7a**. A ^{1}H NMR spectrum is provided to demonstrate purity. The enantiomeric ratio was measured by HPLC (Chiralpak AS-H, 10% *i*-PrOH/Hexanes, 1 mL/min, Rt_1 = 22.8, Rt_2 = 26.0).

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

^{1}H and ^{13}C NMR, HRMS, and melting point ranges of new compounds, 2-D NMR for **9b**, and pK_a table. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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