

# Cascade carbopalladation-annulation approach toward polycyclic derivatives of indole and indolizine

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**Dedicated to William F. Bailey on the occasion of his 65<sup>th</sup> anniversary**

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## Abstract

A convenient method for construction of polycyclic fused nitrogen-containing heterocycles has been developed. The methodology involves palladium-catalyzed intermolecular carbopalladation-annulation cascade reaction of haloaryl heterocyclic derivatives with different alkynes under relatively mild reaction conditions. Thus, the palladium-catalyzed cascade cyclization of bromophenyl derivatives of indolizine and indole with alkynes afforded tetracycles, possessing a newly formed fused six-membered ring. The reaction of 3-(2-iodobenzyl)-indoles with a variety of alkynes afforded polycyclic compounds with fused seven-membered rings. Annulation with unsymmetrical alkynes exhibited varied regioselectivity. Overall, this approach allows for quick and efficient assembly of polycyclic derivatives of indole and indolizine from easily available precursors.

**Keywords:** Heterocycles, annulation, palladium, alkynes

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## Introduction

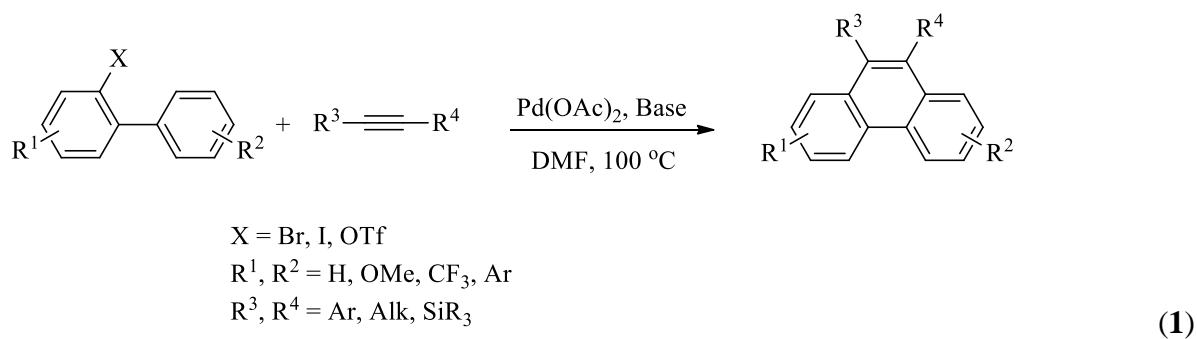
Polycyclic derivatives of indole<sup>1</sup> and indolizine<sup>2</sup> are important scaffolds, widely found in natural and unnatural bioactive molecules. Thus, indole derivatives exhibit antioxidant and membrane stabilizing properties<sup>1a,b</sup> and also protect against chemical mediated chemotoxicity.<sup>1c</sup> Tricyclic and tetracyclic derivatives of indole, possessing seven-membered ring, are used as direct precursors in synthesis of antihistaminic and anti-inflammatory compounds.<sup>1h-k</sup> Heterocycles, possessing indolizine core have also found numerous applications in synthesis of biologically active compounds. In addition, partially or completely reduced indolizine analogs are widely used in synthesis of indolizidine alkaloids and related unnatural products.<sup>3</sup> Moreover, polycyclic analogs of indole and indolizine have found a broad application as heterocyclic analogs of fluorene and indene

in the synthesis of ligands for transition metal complexes.<sup>1d-g</sup> Although the numerous methods have been developed for assembly of these polycyclic frameworks, they are generally lengthy or require employment of stoichiometric amounts of organometallic reagents, which largely limits their synthetic usefulness.<sup>4,5,6</sup> Accordingly, development of alternative catalytic methods for construction of these important heterocyclic cores is warranted. Herein we wish to report the palladium-catalyzed intermolecular cascade annulation reactions of bromophenyl and iodobenzyl derivatives of indole and indolizine with alkynes leading to the formation of polycyclic fused six and seven-membered heterocycles.

## Results and Discussion

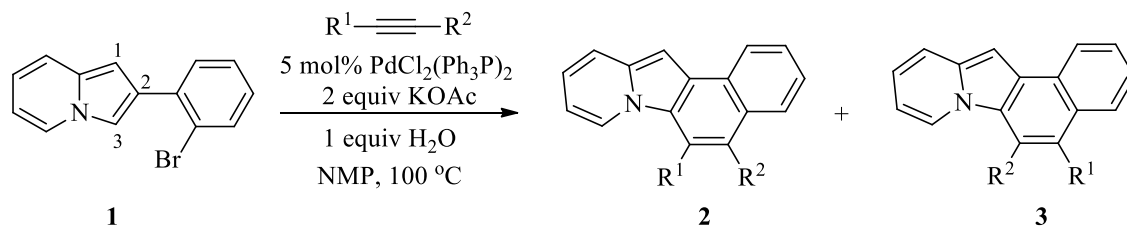
### Synthesis of fused six-membered heterocycles

The palladium-catalyzed intermolecular reaction of *o*-halobiaryls with alkynes, developed by Larock,<sup>7</sup> represents a powerful methodology for construction of fused aromatic systems. The process can be described as a cascade consisting of the carbopalladation across the triple bond followed by a C-H coupling with the adjacent aromatic ring of biphenyl leading to the phenanthrene frameworks (equation 1). The reaction is known to proceed efficiently on polysubstituted electron-rich *o*-halobiaryls, however, to the best of our knowledge, this annulation strategy has never been used for the construction of fused heterocyclic frameworks. Thus, we explored this concept toward assembly of fused derivatives of indole and indolizine.



Accordingly, the reaction of indolizine **1**<sup>8</sup> with different alkynes under palladium catalysis toward tetracyclic indolizine derivative **2** was tested first (Table 1). After brief catalyst screening, we found that our standard catalytic conditions<sup>9</sup> (5 mol% PdCl<sub>2</sub>(Ph<sub>3</sub>P)<sub>2</sub>, 2 equiv. KOAc, 1 equiv. H<sub>2</sub>O) allowed for efficient arylation/annulations cascade of 2-(2-bromophenyl)indolizine **1** with 5-decyne leading to tetracyclic indolizine **2a** in 70% yield (Table 1, entry 1). Likewise, diphenylacetylene reacted smoothly in this annulation cascade, producing **2b** in 85% yield (Table 1, entry 2). Reaction with unsymmetrical alkynes proceeded with varied regioselectivity. Thus, reaction of **1** with propynylbenzene resulted in the formation of 1:1 mixture of **2c** and **3c** in 76% overall yield (entry 3). Annulations with ethyl butynoate afforded a 56:44 mixture of **2d** and **3d** in

64% overall yield (entry 4). Somewhat similar selectivity was observed in the case of ethyl 3-phenylprop-2-ynoate (entry 5). Finally, the reaction with dibutyldiyne led to the formation of annulated products **2e** and **3e** in moderate yield, though with better regioselectivity (Table 1, entry 6).



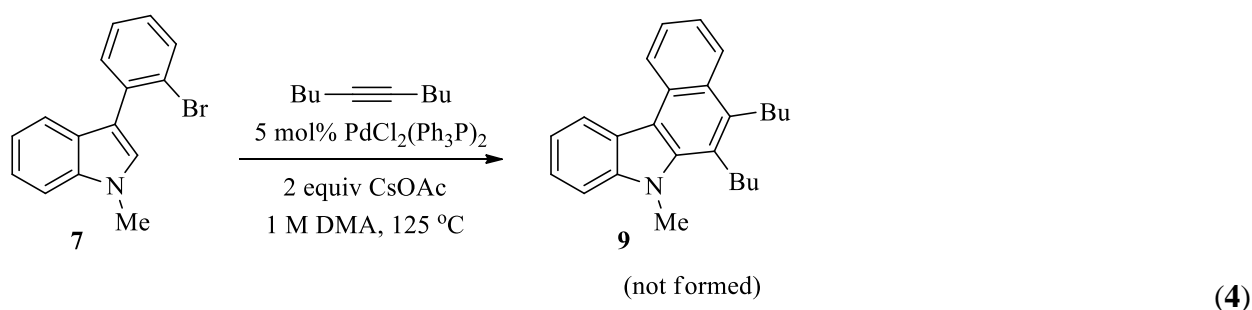
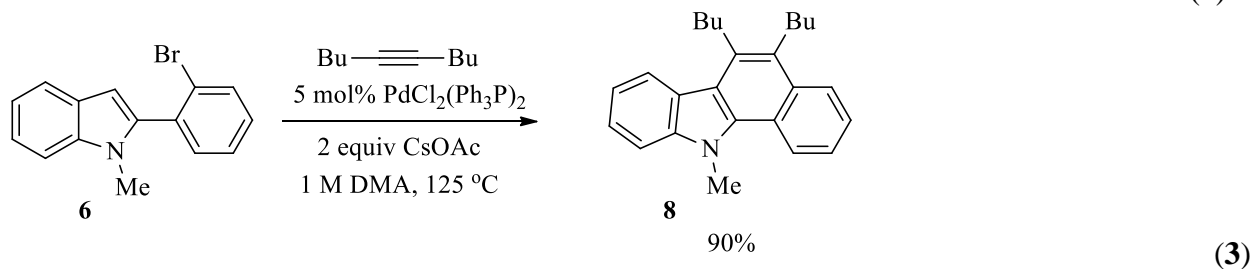
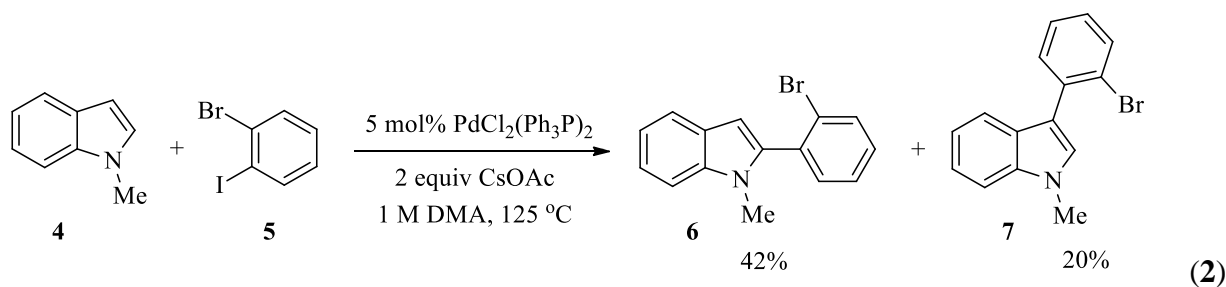
**Table 1.** Synthesis of tetracycles via palladium-catalyzed cascade carbopalladation /annulation reaction of indolizine **1** with alkynes

Entry	R <sup>1</sup>	R <sup>2</sup>	Product	Combined Yield (%) <sup>b</sup>
1	Bu	Bu	<b>2a</b>	70
2	Ph	Ph	<b>2b</b>	85
3	Me	Ph	<b>2c</b> + <b>3c</b> (50 : 50) <sup>a</sup>	76
4	CO <sub>2</sub> Et	Me	<b>2d</b> + <b>3d</b> (56 : 44) <sup>a</sup>	67
5	CO <sub>2</sub> Et	Ph	<b>2e</b> + <b>3e</b> (66 : 34) <sup>a</sup>	44
6	BuCC	Bu	<b>2f</b> + <b>3f</b> (89 : 11) <sup>a</sup>	56

<sup>a</sup>Ratio of products was determined by <sup>1</sup>H NMR analysis of crude reaction mixtures.

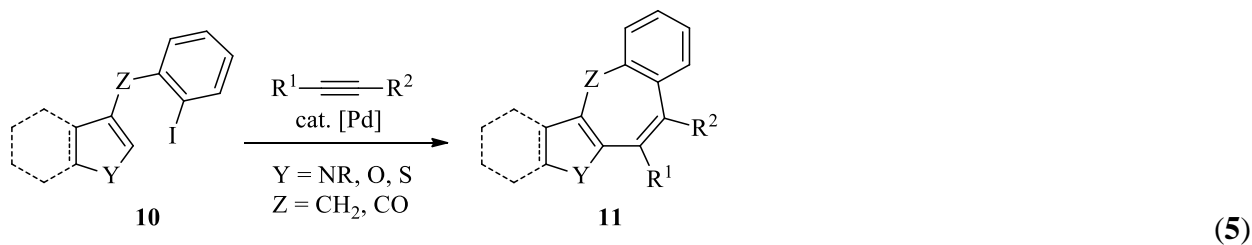
<sup>b</sup>Isolated yield.

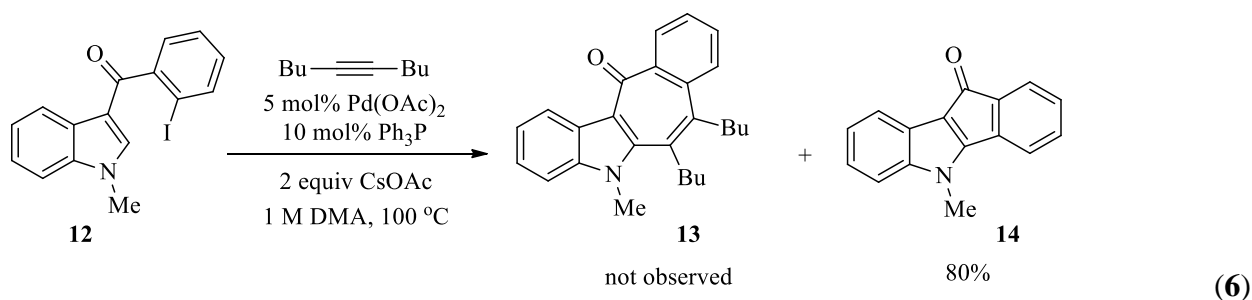
Next, a possibility of the analogous cascade annulation was examined in indole series. The bromoarylindole derivative **6** was synthesized via a direct C-H arylation of *N*-methyl indole **4** with 2-iodobromobenzene in 42% yield (equation 2), accompanied by a small amount of 3-aryl derivative **7**.<sup>10</sup> The regioisomers **6** and **7** were readily separated by column chromatography. First, *N*-methyl-2-(*o*-bromophenyl)indole **6** was subjected to the cascade annulations/cyclization reaction with 5-decyne in the presence of 5 mol% PdCl<sub>2</sub>(Ph<sub>3</sub>P)<sub>2</sub> and 2 equivalents of CsOAc. This cyclization led to the formation of the desired polycyclic carbazole derivative **8** in 90% (equation 3). Unexpectedly, attempts on analogous cyclization on *N*-methyl-3-(*o*-bromophenyl)indole **7** toward tetracycle **9** were unsuccessful resulting in a total decomposition of the starting material (equation 4).



### Synthesis of fused seven-membered heterocycles

Next, the possibility of the construction of fused seven-membered rings using carbopalladation/annulations strategy was explored. Generally, synthetic methods towards heterocycles containing fused seven-membered rings involve various intramolecular annulations, including acylation reactions of carboxylic acids and their derivatives,<sup>6</sup> radical cyclizations of alkyl halides,<sup>5or</sup> palladium catalyzed carbopalladation of aryl halide with alkyne tether.<sup>6h</sup> Thus, we envisioned that the intermolecular cascade arylation/cyclization reaction of haloaryl heterocycles **10** with alkynes might be an attractive alternative for construction of polycyclic compounds possessing a fused seven-membered ring **11** (equation 5).



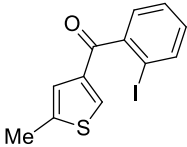
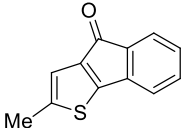
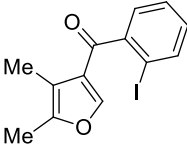
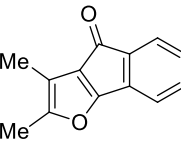


Towards this goal, 3-benzoyl derivative **12** was examined in arylation/cyclization reaction with 5-decyne. However, formation of the targeted seven-membered heterocycle **13** was not observed. Instead, tetracyclic indenone **14**, a product of intramolecular arylation, was obtained in 80% yield (equation 6).

All attempts on changing the chemoselectivity of the reaction were unsuccessful, and in all cases, the intramolecular arylation was a predominant process. It deserves mentioning, that a related reaction on indole derivatives is precedented. Thus, it was reported that isomeric 2-benzoyl indole undergoes intramolecular cyclization under palladium catalysis to produce indenoindolone.<sup>11</sup> Although, acyl-tethered derivatives **12** did not undergo intermolecular arylation-cyclization cascade with alkynes, we explored the scope of this novel mode of intramolecular arylation reaction (Table 2).<sup>12</sup> Thus, cyclization of **12** provided slightly better yields of **14** (entry 1) compared to that in the presence of alkyne (equation 6). It was found that unprotected indole **15**, in the presence of 5 mol% of PdCl<sub>2</sub>(Ph<sub>3</sub>P)<sub>2</sub> and CsOAc, produces indeno[1,2]indole-10(5H)-one **16** in nearly quantitative yield (entry 2). *N*-Phenylindole derivative **17** also cyclized uneventfully. Analogously, carbonyl derivatives of thiophene (entry 4), benzofuran (entry 5), and furan (entry 6) produced tetracyclic indenones in very good yields.

**Table 2.** Synthesis of heterocycles via intramolecular cyclization reaction of *o*-iodobenzoyl heterocycles<sup>a</sup>

Entry	Compound	Product	Yield(%) <sup>b</sup>
1			85
2			99
3			82

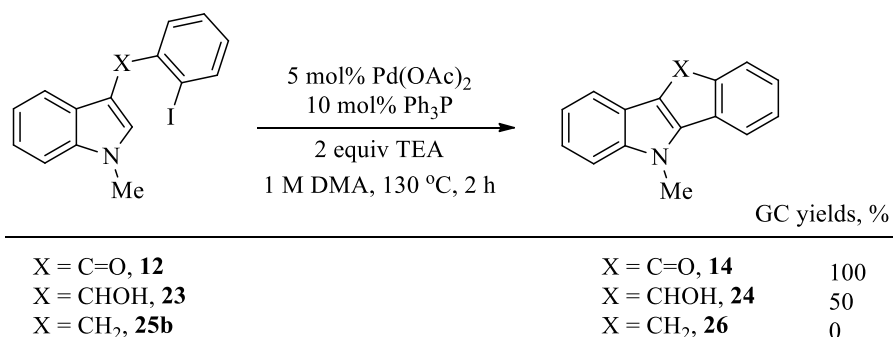
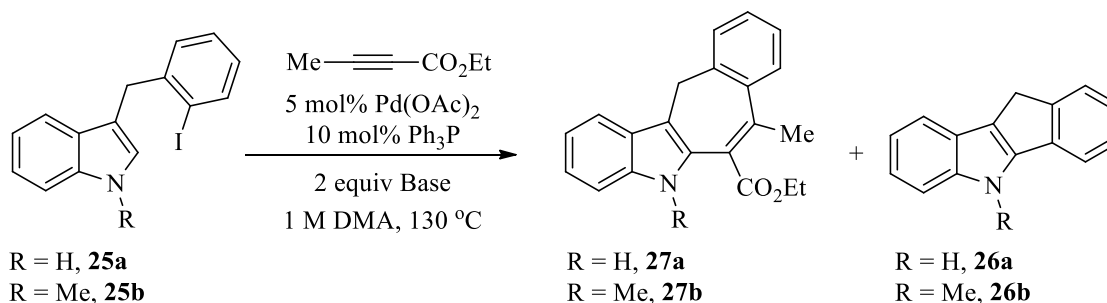
4		<b>19</b>		<b>20</b>	81
5		<b>21</b>		<b>22</b>	71

<sup>a</sup>Conditions: 5 mol% Pd(OAc)<sub>2</sub>, 10 mol% Ph<sub>3</sub>P, 2 equiv. CsOAc, 1M DMA, 100 °C, 12h.

<sup>b</sup>Isolated yields.

To gain insight into the origins of high propensity of carbonyl derivatives toward intramolecular arylation, we evaluated arylation of differently tethered indole derivatives **12**, **23**, and **25b** (Scheme 1). It was found that the carbonyl derivative **12** (X = CO) underwent the fastest intramolecular arylation reaction producing indeno[1,2]indole-10(5*H*)-one **12** in quantitative yield. Hydroxymethyl derivative **23** gave 50% yield of **24**, whereas no product formation was observed in the case of benzyl derivative **25b** (X=CH<sub>2</sub>) (Scheme 1). These results uncovered that the electronic effect of the carbonyl group at the C-3 position is responsible for the observed exclusive intramolecular cyclization of the carbonyl derivatives over the intermolecular arylation/cyclization reaction.<sup>13</sup> These observations, in turn, indicated that 3-benzyl indole derivative **25b**, unreactive in intramolecular arylation, might be a suitable substrate for the intermolecular carbopalladation/annulations cascade toward polycyclic frameworks possessing seven-membered rings.

Next, the influence of different bases on the chemoselectivity of this reaction was examined. First, 3-benzyl derivative **25a** was tested in annulation reaction with but-2-ynoate in the presence of catalytic amounts of PdCl<sub>2</sub>(Ph<sub>3</sub>P)<sub>2</sub> and 2 equivalents of CsOAc, the desired tetracycle **27a** was not formed (Table 3, entry 1). Employment of KOAc led to formation of equal amounts of **27a** and **27b** (entry 2). Delightfully, use of triethylamine resulted in exclusive formation of the desired heterocycle **27a** (entry 3). Analogous annulation of *N*-Me derivative **27b**, in the presence of different bases, was examined, as well. Accordingly, employment of CsOAc led to formation of seven-membered tetracycle **27b** together with significant amounts of chemoisomer **26b** (entry 4). Surprisingly, annulation reaction in the presence of KOAc resulted in exclusive formation of tetracycle **27b** in excellent yield (entry 5).<sup>12</sup>

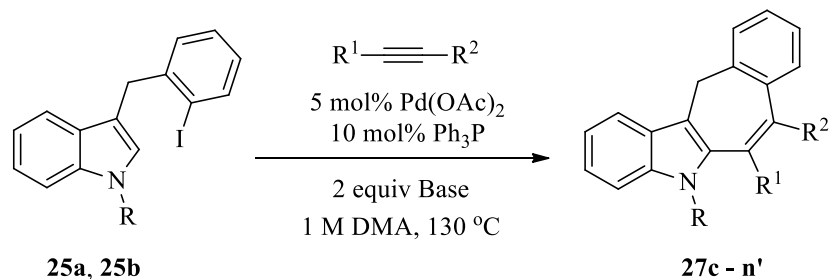
**Scheme 1.** Relative reactivities of indole derivatives in intramolecular arylation reaction.**Table 3.** Base optimization for cascade carbopalladation-annulation of indole derivatives

Entry	Substrate	Base	Ratios <sup>a</sup>
			<b>27a:26a/27b:26b</b>
1	<b>25a</b>	CsOAc	0:100
2	<b>25a</b>	KOAc	50:50
3	<b>25a</b>	TEA	100:0
4	<b>25b</b>	CsOAc	60:40
5	<b>25b</b>	KOAc	100:0

<sup>a</sup>The ratios were determined by GC-MS analysis of the crude reaction mixtures.

With the optimized conditions in hand, we examined this cascade transformation of indoles **25a,b** with different alkynes (Table 4). To our delight, a variety of alkynes, possessing electron-rich and electron-deficient triple bonds, were efficient partners in this annulations reaction, leading to the formation of fused heterocycles in good yields. Thus, reaction of **25a** with 5-decyne gave **27c** in 98% isolated yield (Table 4, entry 1). Reaction with diphenylalkyne produced polyaromatic tetracycle **27c** in 78% yield (entry 2). MOM protected but-2-yne-1,4-diol led to the formation of **29d** in 76% yield (entry 2). Annulation of **27a** with unsymmetrical ethyl phenylprop-2-ynoate led to a 70:30 mixture of regioisomers **27e** and **27e'** in 73% overall yield (entry 3). Reaction with propynylbenzene resulted in the formation of a similar mixture of **27f** and **27f'** in somewhat lower yield (entry 4). Protected indole derivative **25b** showed slightly lower reactivity with 5-decyne, producing polycycle **27g** in 70% yield (entry 5). Reaction of **25b** with MOM protected acetylene led to the formation of **27h** if 76% yield (entry 6). Ethyl 3-(trimethylsilyl)prop-2-ynoate and

trimethylsilylprop-2-yne smoothly reacted with N-methyl indole derivative **25b** leading to the formation of silylated tetracycles **27i** and **27j** (entries 7 and 8). On the other hand, reaction of **25b** with bis-trimethylsilylacetylene produced monodesilylated **27k** (entry 9). Analogously, annulation of **25b** with aryltrimethylsilyl alkynes resulted in the formation of monodesilylated seven-membered tetracycles **27l** and **27m** (entries 10 and 11).<sup>14</sup> In all cases, formation of only one regioisomer was observed. Similarly to **25a**, the reaction of compound **26b** with unsymmetrical ethyl phenylprop-2-ynoate resulted in 90:10 mixture of regioisomers **27n** and **27n'** in 65% overall yield (entry 12).<sup>12</sup>



**Table 4.** Synthesis of tetracycles via palladium-catalyzed cascade carbopalladation /annulation reaction of indole derivatives with alkynes

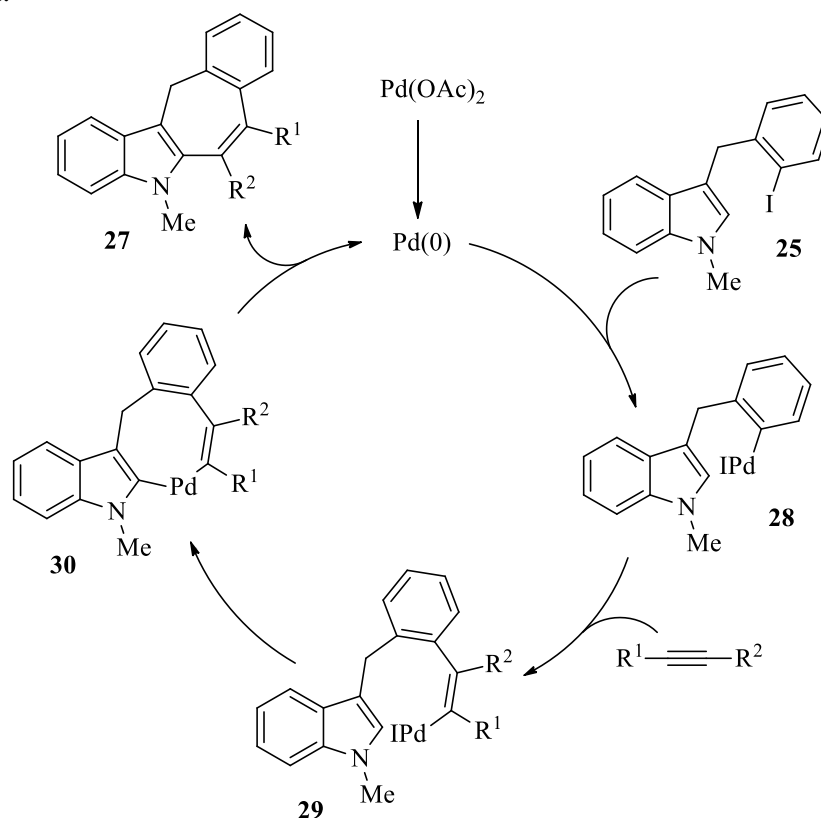
Entry	Alkyne	Base	Product			Yield, % <sup>a</sup>
			R	R <sup>1</sup>	R <sup>2</sup>	
1	Bu—C≡C—Bu	Et <sub>3</sub> N	H	Bu	Bu	<b>27c</b> 98
2	Ph—C≡C—Ph	Et <sub>3</sub> N	H	Ph	Ph	<b>27d</b> 78
3	Ph—C≡C—CO <sub>2</sub> Et	Et <sub>3</sub> N	H	CO <sub>2</sub> Et Ph	Ph CO <sub>2</sub> Et	<b>27e</b> 73 <b>27e'</b> (70 : 30) <sup>b</sup>
4	Ph—C≡C—Me	Et <sub>3</sub> N	H	Ph Me	Me Ph	<b>27f</b> 53 <b>27f'</b> (80 : 20) <sup>b</sup>
5	Bu—C≡C—Bu	KOAc	Me	Bu	Bu	<b>27g</b> 70
6	MOMO—C≡C—OMOM	KOAc	Me	CH <sub>2</sub> OMOM	CH <sub>2</sub> OMOM	<b>27h</b> 76
7	TMS—C≡C—CO <sub>2</sub> Et	KOAc	Me	TMS	CO <sub>2</sub> Et	<b>27i</b> 75
8	TMS—C≡C—Me	KOAc	Me	TMS	Me	<b>27j</b> 75
9	TMS—C≡C—TMS	KOAc	Me	H	TMS	<b>27k</b> 75
10	TMS—C≡C—Ph	KOAc	Me	H	Ph	<b>27l</b> 71
11	TMS—C≡C—C <sub>6</sub> H <sub>4</sub> OMe- <i>p</i>	KOAc	Me	H	C <sub>6</sub> H <sub>4</sub> OMe- <i>p</i>	<b>27m</b> 75
12	Ph—C≡C—CO <sub>2</sub> Et	KOAc	Me	CO <sub>2</sub> Et Ph	Ph CO <sub>2</sub> Et	<b>27n</b> 65 <b>27n'</b> (90 : 10) <sup>b</sup>



<sup>a</sup>Isolated yields. <sup>b</sup>Ratio of products was determined by <sup>1</sup>H NMR analysis of crude reaction mixtures.

### Mechanistic considerations

We believed that the mechanism of the presented herein intermolecular cascade arylation/cyclization reaction of the indole and indolizine derivatives follows the path proposed by Larock for the cascade cyclization of *o*-haloaryls.<sup>7</sup> It starts with the oxidative addition of the Pd(0) to iodobenzylindole **25** generating the arylpalladium complex **28** (Scheme 2). Carbopalladation of the alkyne triple bond produces the vinylpalladium intermediate **29**, which undergoes intermolecular electrophilic carbopalladation at the C-2 position of the indole to form the palladacycle **30**, which, upon reductive elimination, produces tetracyclic product **27** and regenerates the Pd(0) catalyst.<sup>15</sup>



**Scheme 2.** Plausible mechanism for the annulation reaction of indole heterocycles.

### Conclusions

In summary, we have developed an efficient methodology for construction of fused polycyclic indole and indolizine heterocyclic cores from easily available starting materials via the palladium-catalyzed cascade annulations/cyclization reaction with both electron rich and electron deficient alkynes. The method allows for the construction of fused heterocycles with six and seven-membered rings from bromophenyl and iodobenzyl derivatives of indole and indolizine in good

yields under relatively mild reaction conditions. It was found that in cyclization of the iodobenzyl derivative **25a,b**, the base used had a dramatic effect on the chemoselectivity of the intramolecular cyclization versus the intermolecular carbopalladation/intramolecular cyclization cascade. Thus, the fused five-membered tetracycle **26a** was a sole product in the presence of CsOAc, whereas the exclusive formation of seven-membered **27a** was observed in the presence of triethylamine. It was also found that the acyl-tethered heterocyclic substrates do not undergo intermolecular annulations, but rather the intramolecular cyclization reaction, producing tetracyclic indenones in very good yields.

## Experimental Section

**General.** All manipulations with transition metal catalysts were conducted under inert atmosphere using a combination of glovebox and standard Schlenk techniques. Anhydrous tetrahydrofuran, ether, and 1,2-dichloroethane purchased from Aldrich were additionally purified on PureSolv PS-400-4 by Innovative Technology, Inc. purification system and/or stored over calcium hydride. All other reagents were purchased from various commercial sources and used without additional purification. NMR spectra were recorded on Bruker Avance DRX-500 (500 MHz) and DPX-400 (400 MHz) instruments. GC/MS analyses were performed on a Hewlett Packard Model 6890 GC interfaced to a Hewlett Packard Model 5973 mass selective detector (15 m — 0.25 mm capillary column, HP-5MS). Column chromatography was carried out employing Merck silica gel (Kieselgel 60, 63-200  $\mu\text{m}$ ), ICN silica gel (ICN SiliTech, 63-200  $\mu\text{m}$ ), and SiliCycle silica gel (40-63  $\mu\text{m}$ ). Analytical thin-layer chromatography (TLC) was performed on 0.2 mm precoated Silica gel plates (60 F254).

### General procedure for the palladium-catalyzed annulation-cyclization reaction of *o*-bromophenylindolizines with alkynes

To a solution of 10 mmol 2-(2-bromophenyl)indolizine in 1 mL of NMP was added PdCl<sub>2</sub>(Ph<sub>3</sub>P)<sub>2</sub> (5 mol%), 20 mmol KOAc and 20 mmol of alkyne under inert atmosphere. The mixture was stirred at 100 °C for 10 minutes prior addition of 180  $\mu\text{L}$  of water. The reaction was stirred at 100 °C until full consumption of starting material. When reaction was complete, the resulting solution was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over the sodium sulfate and concentrated under reduced pressure. Resulting crude product was purified via column chromatography on silica gel (Hexanes/EtOAc).

**5,6-Di-*n*-butylbenzopyrido[1,2-*a*]indole (2a).** Brown oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>):  $\delta$  ppm 8.61 (d, *J* = 7.34 Hz, 1 H), 8.44 (dd, 1 H), 8.14 (dd, *J* = 6.42, 3.12 Hz, 1 H), 7.54 - 7.59 (m, 2 H), 7.31 (s, 1 H), 6.87 (dd, 1 H), 6.53 - 6.64 (m, 1 H), 3.18 - 3.24 (m, 2 H), 2.95 - 3.48 (m, 2 H), 1.81 (s, 2 H), 1.58 - 1.76 (m, 6 H), 1.11 (t, *J* = 7.34 Hz, 3 H), 1.07 (t, *J* = 7.34 Hz, 3 H), 0.91 - 1.04 (m, 1 H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>):  $\delta$  ppm 135.7 (s), 129.4 (s), 129.0 (s), 127.0 (s), 126.2 (s), 126.2 (s), 125.6 (s), 125.4 (s), 124.9 (s), 124.7 (s), 124.5 (s), 124.2 (s), 119.8 (s), 119.0 (s), 109.0 (s), 92.3 (s), 32.4 (s), 29.0 (s), 28.2 (s), 23.4 (s), 23.1 (s), 14.1 (s), 14.0 (s). Anal. HR EI MS *m/z* Calcd for C<sub>24</sub>H<sub>27</sub>N (M<sup>+</sup>): 329.2143. Found: 329.2142.

**5,6-Di-phenylbenzopyrido[1,2-*a*]indole (2b).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  ppm 8.52 (d,  $J = 8.1$  Hz, 1H), 7.62 (ddd,  $J = 1.1$  Hz, 7.0 Hz, 8.1 Hz, 1H), 7.58-7.53 (m, 3H), 7.42 (m, 1H), 7.39 (s, 1H), 7.34-7.36 (m, 1H), 7.32-7.28 (m, 2H), 7.23-7.26 (m, 3H), 7.22 (m, 1H), 7.15-7.21 (m, 3H), 6.79 (ddd,  $J = 1.1$  Hz, 6.2 Hz, 9.2 Hz, 1H), 6.12 (ddd,  $J = 1.5$  Hz, 6.2 Hz, 7.7 Hz, 1H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  ppm 151.8, 138.4, 131.8, 131.6, 130.5, 128.35, 127.6, 127.3, 126.2, 126.0, 124.9, 123.7, 120.1, 119.3, 108.3, 91.9. Anal. HR EI MS  $m/z$  Calcd for  $\text{C}_{28}\text{H}_{19}\text{N}$  ( $\text{M}^+$ ): 369.1517. Found: 369.1515.

**5,6-Dibutyl-11-methyl-11-*H*-benzo[*a*]carbazole (6).** Wheaton 1 mL mininert vial was charged with  $\text{Pd}(\text{OAc})_2$  (9 mg, 5 mol%), triphenylphosphine (36 mg, 20 mol%), cesium acetate (276 mg, 1.44 mmol, 2 equiv.), 5 (206 mg, 0.72 mmol) under inert gas atmosphere. The mixture was dissolved in 0.5 mL of DMA followed by addition of alkyne (1.08 mmol, 1.5 equiv.). The vial was sealed with an open-top cap fitted with Teflon septa. The reaction mixture was heated at 125 °C for 12 h. Then it was cooled to room temperature, diluted with 10 mL of water and extracted with EtOAc. The organic extracts were dried over the sodium sulfate and evaporated under the reduced pressure. The resulting crude mixture was purified by column chromatography on silica gel using Hexanes/EtOAc as eluent (gradient 20% to 10%). The resulting 5,6-Dibutyl-11-methyl-11-*H*-benzo[*a*]carbazole 7 was obtained as light brown oil, yield 90%, 223 mg.  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  ppm 8.75 (dd,  $J = 1.1$  Hz, 8.4 Hz, 1H), 8.25 (m, 2H), 7.61-7.50 (m, 3H), 7.38-7.30 (m, 2H), 4.40 (s, 3H), 3.75-3.85 (m, 2H), 3.46-3.40 (m, 2H), 3.25-3.19 (m, 2H), 1.90-1.82 (m, 2H), 1.78-1.68 (m, 2H), 1.67-1.59 (m, 2H), 1.12-1.05 (m, 6H).  $^{13}\text{C}$  NMR (126 MHz,  $\text{CDCl}_3$ ):  $\delta$  ppm 141.2, 135.1, 134.3, 132.0, 128.8, 127.4, 127.3, 125.3, 124.8, 124.0, 123.6, 122.8, 122.2, 121.8, 119.5, 109.1, 34.6, 33.5, 32.2, 30.5, 28.0, 23.5, 23.5, 14.2, 14.1. Anal. HR EI MS  $m/z$  Calcd for  $\text{C}_{25}\text{H}_{29}\text{N}$  ( $\text{M}^+$ ): 343.2297. Found: 343.2300.

### General procedure for the palladium-catalyzed annulation-cyclization reaction of *o*-bromophenylindolizines with alkynes

To a solution of 10 mmol 2(2-bromophenyl)indolizine in 1 mL of NMP was added  $\text{PdCl}_2(\text{Ph}_3\text{P})_2$  (5 mol%), 20 mmol KOAc and 20 mmol of alkyne under inert atmosphere. The mixture was stirred at 100 °C for 10 minutes prior addition of 10 mmol of water. The reaction was stirred at 100 °C for the desired time. When it was completed the resulting solution was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over the sodium sulfate and concentrated under reduced pressure. Resulting crude mixture was purified via column chromatography on silica gel.

**5-Phenylindeno[1,2-*b*]indol-10(5*H*)-one (18).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  ppm 7.74 (m, 1H), 7.37 (dd,  $J = 0.7$  Hz, 7.7 Hz, 1H), 7.25-7.10 (m, 6H), 3.83 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  184.9, 158.8, 142.9, 141.2, 134.8, 131.8, 129.6, 123.4, 123.1, 123.0, 122.8, 120.6, 118.3, 114.9, 110.5, 31.6. Anal. HR EI MS  $m/z$  Calcd for  $\text{C}_{21}\text{H}_{13}\text{NO}$  ( $\text{M}^+$ ): 295.0097. Found: 295.0096.

**2-Methyl-4*H*-indeno[1,2-*b*]thiophen-4-one (20).**  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  ppm 7.42 (d,  $J = 7.0$  Hz, 1H), 7.27 (dd,  $J = 1.2$  Hz, 7.6 Hz, 1H), 7.13 (d,  $J = 7.0$  Hz, 1H), 7.08 (d,  $J = 7.6$  Hz, 1H), 6.81 (s, 1H), 2.55 (s, 3H).  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  188.8, 159.1, 156.3, 139.8, 137.7, 134.3,

133.3, 128.0, 123.7, 119.3, 119.0, 16.7. Anal. HR EI MS  $m/z$  Calcd for  $C_{12}H_8OS$  ( $M^+$ ): 200.0296. Found: 200.0294.

**2,3-Dimethyl-4*H*-indeno[1,2-*b*]furan-4-one (22).**  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  ppm 7.31 (d,  $J = 7.7$  Hz, 1H), 7.21 (dd,  $J = 1.1$  Hz, 8.1 Hz, 1H), 7.09 (dd,  $J = 0.7$  Hz, 8.1 Hz, 1H), 6.98 (d,  $J = 7.7$  Hz, 1H), 2.30 (s, 3H), 2.11 (s, 3H).  $^{13}C$  NMR (125 MHz,  $CDCl_3$ ):  $\delta$  177.3, 160.8, 148.9, 136.4, 135.9, 132.7, 129.0, 128.3, 123.6, 119.2, 113.7, 12.4, 8.9. Anal. HR EI MS  $m/z$  Calcd for  $C_{13}H_{10}O_2$  ( $M^+$ ): 198.0681. Found: 198.0683.

### General procedure for the palladium-catalyzed annulation-cyclization reaction of 3-(2-iodobenzyl)indole derivatives with alkynes

To a solution of 10 mmol 3-(2-iodobenzyl)indole derivative in 1 mL of DMA was added  $PdCl_2(Ph_3P)_2$  (5 mol%), 20 mmol of the corresponding base (see Table 5 for details) and 20 mmol of alkyne under inert atmosphere. The reaction was stirred at 100 °C until full consumption of starting indole derivative. When it was completed the resulting solution was diluted with water (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic extracts were dried over the sodium sulfate and concentrated under reduced pressure. Resulting crude product was purified via column chromatography on silica gel (Hexanes/EtOAc).

**8,9-Di-(*n*-butyl)-5,12-dihydrobenzo[4.5]cyclohept[1,2-*b*]indole (27c).** Brown oil.  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  ppm 7.86 (br. s., 1H), 7.67 - 7.71 (m, 1 H), 7.43 (d,  $J = 7.70$  Hz, 1 H), 7.28 (s, 1 H), 7.23 (d,  $J = 6.60$  Hz, 1 H), 7.17 (s, 1 H), 7.12 (s, 3 H), 2.88 (s, 2 H), 2.18 (s, 3 H), 1.36 - 1.49 (m, 8 H), 1.26 (s, 1 H), 0.95 (t,  $J = 7.34$  Hz, 3 H), 0.90 (t,  $J = 7.15$  Hz, 3 H).  $^{13}C$  NMR (126 MHz,  $CDCl_3$ ):  $\delta$  ppm 142.4 (s), 139.7 (s), 138.7 (s), 136.6 (s), 134.1 (s), 129.1 (s), 127.2 (s), 126.3 (s), 125.9 (s), 124.9 (s), 121.7 (s), 119.3 (s), 117.9 (s), 116.8 (s), 110.6 (s), 33.5 (s), 33.0 (s), 32.5 (s), 32.0 (s), 30.8 (s), 30.4 (s), 22.9 (s), 22.9 (s), 14.0 (s), 13.9 (s). Anal. HR EI MS  $m/z$  Calcd for  $C_{25}H_{29}N$  ( $M^+$ ): 343.23000. Found: 343.22973.

**8,9-Diphenyl-5,12-dihydrobenzo[4.5]cyclohept[1,2-*b*]indole (27d).** Dark brown solid.  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  ppm 7.77 - 7.82 (m, 1 H), 7.73 (s, 1 H), 7.39 (d,  $J = 7.60$  Hz, 1 H), 7.18 - 7.30 (m, 7 H), 7.04 - 7.15 (m, 9 H), 4.07 (s, 2 H).  $^{13}C$  NMR (126 MHz,  $CDCl_3$ ):  $\delta$  ppm 142.6 (s), 141.6 (s), 140.2 (s), 138.5 (s), 137.1 (s), 132.8 (s), 131.2 (s), 130.6 (s), 129.5 (s), 128.4 (s), 127.3 (s), 127.2 (s), 126.9 (s), 126.2 (s), 125.1 (s), 122.4 (s), 119.5 (s), 118.4 (s), 115.6 (s), 110.8 (s), 31.0 (s). Anal. HR ESI MS  $m/z+1$  Calcd for  $C_{29}H_{22}N$  ( $M^{++1}$ ): 384.1752. Found: 384.1743.

***N*-Methyl-(8,9-di(*n*-butyl)-5,12-dihydrobenzo[4.5]cyclohept[1,2-*b*]indole (27g).** Brown oil.  $^1H$  NMR (500 MHz,  $CDCl_3$ ):  $\delta$  ppm 7.70 (d,  $J = 7.70$  Hz, 1 H), 7.43 (s, 1 H), 7.24 - 7.27 (m, 1 H), 7.20 (s, 1 H), 7.16 - 7.19 (m, 1 H), 7.11 - 7.16 (m, 3 H), 3.92 (d,  $J = 13.57$  Hz, 1 H), 3.67 (s, 3 H), 3.35 (d, 1 H), 2.93 - 3.02 (m, 2 H), 2.74 - 2.83 (m, 1 H), 2.65 - 2.72 (m, 1 H), 1.34 - 1.50 (m, 8 H), 0.96 (t,  $J = 6.97$  Hz, 3 H), 0.91 (t,  $J = 6.97$  Hz, 3 H).  $^{13}C$  NMR (126 MHz,  $CDCl_3$ ):  $\delta$  ppm 144.4 (s), 141.6 (s), 139.0 (s), 138.8 (s), 136.4 (s), 129.6 (s), 127.4 (s), 127.1 (s), 125.9 (s), 125.2 (s), 124.9 (s), 121.3 (s), 118.9 (s), 118.2 (s), 117.9 (s), 109.1 (s), 34.2 (s), 33.1 (s), 32.4 (s), 32.3 (s), 30.3 (s), 23.2 (s), 22.9 (s), 14.0 (s). Anal. HR EI MS  $m/z$  Calcd for  $C_{26}H_{31}N$  ( $M^+$ ): 357.2456. Found: 357.2451.

***N*-Methyl-(8,9-di(monomethoxymethyl)-5,12-dihydrobenzo[4.5]cyclohept[1,2-*b*]indole (27h).**

Yellow oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ ppm 7.71 (d, *J* = 7.89 Hz, 1H), 7.56 (d, *J* = 8.25 Hz, 1H), 7.10-7.26 (m, 6H), 4.83 – 4.94 (m, 3H), 4.66-4.77 (m, 5H), 4.02 (d, *J* = 13.75 Hz, 1H), 3.77 (s, 3H), 3.45 (s, 3H), 3.41 (s, 3H), 3.33 (d, *J* = 13.75 Hz, 1H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ ppm 143.3, 140.4, 139.3, 136.8, 134.7, 129.6, 128.3, 127.7, 126.4, 125.1, 124.9, 122.2, 119.2, 118.3, 109.3, 99.5, 96.4, 95.8, 67.2, 66.3, 56.1, 55.6, 31.9, 30.3. Anal. HR EI MS *m/z* Calcd for C<sub>24</sub>H<sub>27</sub>NO<sub>4</sub> (M<sup>+</sup>): 393.1940. Found: 393.1940.

***N*-Methyl-8-(trimethylsilyl)-9-ethoxycarbonyl-5,12-dihydrobenzo[4.5]cyclohept[1,2-*b*]indole (27i).**

Brown oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ ppm 8.53 (s, 1 H), 8.18 (dd, *J* = 14.03, 8.16 Hz, 2H), 8.05 (d, *J* = 8.07 Hz, 1H), 7.56 (s, 2H), 7.41 - 7.45 (m, 1H), 7.36 - 7.39 (m, 1H), 4.62 (s, 2H), 4.23 (q, 2H), 4.18 (s, 3H), 1.26 (t, *J* = 7.15 Hz, 3H), 0.08 (s, 9H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ ppm 172.1 (s), 144.9 (s), 140.2 (s), 135.2 (s), 132.4 (s), 129.0 (s), 128.4 (s), 127.4 (s), 126.3 (s), 125.7 (s), 122.8 (s), 122.7 (s), 120.5 (s), 119.3 (s), 118.6 (s), 108.7 (s), 108.5 (s), 104.3 (s), 61.2 (s), 34.0 (s), 33.4 (s), 14.2 (s), 1.0 (s). Anal. HR EI MS *m/z* Calcd for C<sub>24</sub>H<sub>27</sub>NO<sub>2</sub>Si (M<sup>+</sup>): 389.18111. Found: 389.18178.

***N*-Methyl-8-(trimethylsilyl)-9-methyl-5,12-dihydrobenzo[4.5]cyclohept[1,2-*b*]indole (27j).**

Dark brown oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ ppm 7.64 - 7.68 (m, 1H), 7.42 (s, 1H), 7.20 - 7.22 (m, 1H), 7.17 (s, 3H), 7.10 - 7.14 (m, 2H), 3.88 (d, *J* = 13.57 Hz, 1H), 3.56 (s, 3H), 3.38 (d, *J* = 13.39 Hz, 1 H), 2.59 (s, 3H), 0.36 (s, 9H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ ppm 150.4 (s), 144.9 (s), 139.7 (s), 139.3 (s), 138.6 (s), 129.6 (s), 128.0 (s), 127.7 (s), 126.2 (s), 125.6 (s), 125.1 (s), 120.6 (s), 118.9 (s), 117.6 (s), 115.4 (s), 109.1 (s), 32.3 (s), 30.4 (s), 25.6 (s), 1.3 (s). Anal. HR EI MS *m/z* Calcd for C<sub>22</sub>H<sub>25</sub>NSi (M<sup>+</sup>): 331.17563. Found: 331.17523.

***N*-Methyl-9-(trimethylsilyl)-5,12-dihydrobenzo[4.5]cyclohept[1,2-*b*]indole (27k).**

Dark brown oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ ppm 7.62 (s, 1 H), 7.47 - 7.51 (m, 1 H), 7.30 (s, 1 H), 7.16 - 7.24 (m, 3 H), 7.07 - 7.15 (m, 2 H), 6.88 (s, 1 H), 4.29 (s, 2 H), 3.75 (s, 3 H), 0.25 (s, 9 H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ ppm 143.9 (s), 137.1 (s), 132.4 (s), 128.9 (s), 128.6 (s), 127.9 (s), 127.3 (s), 125.7 (s), 122.4 (s), 121.5 (s), 119.4 (s), 119.3 (s), 118.8 (s), 118.7 (s), 113.6 (s), 109.1 (s), 104.2 (s), 98.5 (s), 91.3 (s), 91.2 (s), 32.6 (s), 29.9 (s), 29.7 (s). Anal. HR EI MS *m/z* Calcd for C<sub>21</sub>H<sub>23</sub>NSi (M<sup>+</sup>): 317.1600. Found: 317.1598.

***N*-Methyl-9-phenyl-5,12-dihydrobenzo[4.5]cyclohept[1,2-*b*]indole (27l).**

Brown oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ ppm 7.74-7.80 (m, 1H), 7.52-7.57 (m, 2H), 7.41-7.46 (m, 2H), 7.35-7.41 (m, 2H), 7.27-7.34 (m, 2H), 7.19-7.24 (m, 2H), 7.15 (ddd, *J* = 7.89 Hz, *J* = 6.88 Hz, *J* = 7.89 Hz), 7.04-7.10 (m, 2H), 3.90 (s, 2H), 3.80 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ ppm 144.5, 144.6, 140.5, 138.6, 137.1, 133.9, 130.3, 129.2, 129.1, 128.4, 127.6, 127.5, 125.4, 125.0, 122.0, 119.2, 118.3, 118.0, 115.2, 109.0, 31.0, 29.9. Anal. HR EI MS *m/z* Calcd for C<sub>24</sub>H<sub>19</sub>N (M<sup>+</sup>); 321.1517. Found: 321.1516.

***N*-Methyl-9-(*p*-methoxyphenyl)-5,12-dihydrobenzo[4.5]cyclohept[1,2-*b*]indole (27m).**

Dark brown oil. <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ ppm 7.76 (d, *J* = 7.70 Hz, 1H), 7.45-7.49 (m, 2H), 7.35-7.38 (m, 1H), 7.25-7.33 (m, 2H), 7.19-7.23 (m, 1H), 7.16-7.17 (m, 1H), 7.05-7.15 (m, 3H), 6.95-6.99 (m, 2H), 3.87-3.91 (m, 5H), 3.79 (s, 3H). <sup>13</sup>C NMR (126 MHz, CDCl<sub>3</sub>): δ ppm 159.2, 144.2, 138.6, 137.3, 137.1, 134.1, 130.3, 129.1, 127.6, 125.3, 125.4, 124.9, 121.8, 119.1, 118.2, 117.0,

115.0, 113.8, 109.0, 101.0, 55.4, 31.0, 29.9. Anal. HR EI MS  $m/z$  Calcd for C<sub>25</sub>H<sub>21</sub>NO (M<sup>+</sup>): 351.1623. Found: 351.1621.

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