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PALLADIUM-CATALYZED ONE-POT APPROACH TO 3-(1,3-DIARYLPROP- 2-YN-1-YLIDENE)OXINDOLES

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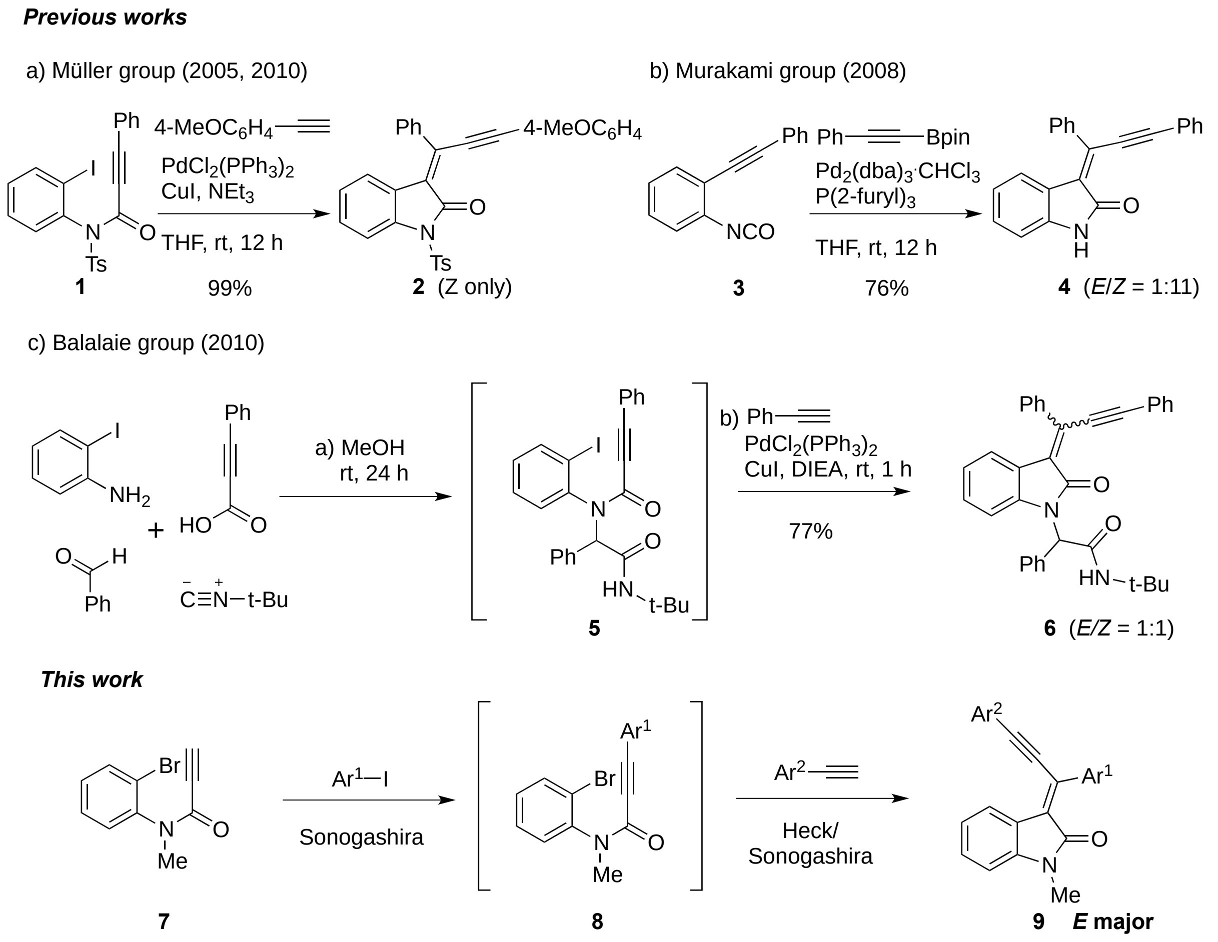
Abstract − An efficient and stereoselective one-pot approach for synthesizing 3-(1,3-diarylprop-2-yn-1-ylidene)oxindoles has been developed, starting from propiolamide, aryl iodides and arylacetylenes and utilizing two palladium-catalyzed reactions: the Sonogashira and Heck reactions. This method produced (*E*)-3-(1,3-diarylprop-2-yn-1-ylidne)oxindoles as the major stereoisomers. This is the first time an effective synthetic method for (*E*)-isomer of these compounds has been reported.

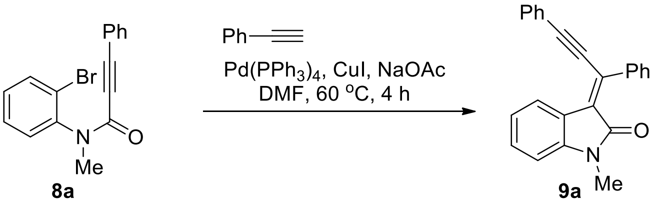
3-Methyleneoxindole is a representative skeleton of the oxindole family and has been identified in numerous natural products,[1] drugs[2] and synthetic intermediates.[3] 3-(Diarylmethylene)oxindoles in particular are attracting significant attention among synthetic chemists for their novel biological activities, including 5'-adenosine monophosphate-activated kinase activation[4] and anti-breast-cancer activity.[5] The ability to modify the basic 3-methyleneoxindole skeleton would be highly valuable, particularly to increase the use of 3-(diarylmethylene)oxindoles in drug development. One of the most useful structures to address this issue is 3-(1,3-diarylprop-2-yn-1-ylidene)oxindole, which has an acetylene linker between one of the aryl substituents and the 3-methyleneoxindole core. Despite the many reports of synthetic approaches for 3-methyleneoxindole derivatives,[6] very few synthetic methods for the intriguing structure of 3-(1,3-diarylprop-2-yn-1-ylidene)oxindole have been reported until now (Scheme 1). In 2005, Müller and co-workers reported the first synthesis of 3-(1,3-diarylprop-2-yn-1-ylidene)oxindole **2** using a Heck/Sonogashira domino reaction of *N*-tosylpropiolamide **1**.[7a] Despite the high yield and exquisite stereoselectivity of the reaction, only one example was presented, and the stereochemical assignment of **2** was corrected from *E* to *Z* in their subsequent paper in 2010.[7b] In another report of *Z*-selective synthesis of 3-(1,3-diarylprop-2-yn-1-ylidene)oxindole **4** by the Murakami group in 2008, palladium-catalyzed oxidative cyclization of 2-(alkynyl)aryl isocyanate **3**, followed by a Suzuki–Miyaura reaction with alkynyl boronate, was performed.[8a] This unique synthetic approach was developed by modification of on a Yamamoto group's seminal work in 2005, in which 3-(1-alkyl-3-arylprop-2-yn-1-ylidene)oxindoles were successfully prepared through intramolecular vinylpalladium addition to isocyanate. However, Yamamoto's condition was not suitable for preparation of diaryl-substituted compounds. Murakami's modification was able to afford diaryl-substituted compound **4**, but it is the only one example and no further studies on substrate scope were performed. In 2010, Balalaie and co-workers successfully used a four-component Ugi reaction to form propiolamide **5**, which was converted to 3-(1,3-diarylprop-2-yn-1-ylidene)oxindole **6** via a domino Heck/Sonogashira reaction.[9] This synthetic method was highly efficient but had low stereoselectivity (*E*/*Z* ratio = 1:1). As described above, the substrate scope of previous methods has not been well studied, and the *E*-stereoselective synthesis of 3-(1,3-diarylprop-2-yn-1-ylidene)oxindole has not yet been reported. This prompted us to devise a novel one-pot approach for synthesis of (*E*)-3-(1,3-diarylprop-2-yn-1-ylidene)oxindole **9**, based on our previous work related to the syntheses of other 3-methyleneoxindole derivatives.[10] This strategy consists of the Sonogashira reaction of propiolamide **7** and a domino Heck/Sonogashira reaction of the resulting Sonogashira adduct **8**.



Scheme 1. Synthetic approaches for 3-(1,3-diarylprop-2-yn-1-ylidene)oxindoles

First, we examined the Sonogashira reaction conditions used in our previous work and confirmed that they were suitable for successive domino Heck/Sonogashira reactions (Table 1). Potential intermediate **8a** was exposed to these conditions, originally developed by Zhu and co-workers for the Sonogashira reaction of electron-deficient acetylene substrates (Table 1, entry 1).[6f] Under these conditions, the desired product **9a** was obtained at a low yield (36%) with moderate *E*-stereoselectivity (*E*/*Z* ratio = 4.0:1). The stereochemistry of **(*E*/*Z*)-9a** was unambiguously determined by extensive NMR studies including ROESY. The reaction did not go to completion, with more than half of **8a** left unreacted. By-product analysis identified 1,4-diphenyl-1,3-butadiyne as a major by-product, probably due to dimerization of phenylacetylene. To decrease the formation of by-products, the reaction mixture was degassed by a freeze–pump–thaw method before temperature elevation, giving an increased yield and identical stereoselectivity (Entry 2: 46% yield, *E*/*Z* ratio = 4.0:1). Increasing the amount of phenylacetylene also resulted in higher yield but less stereoselectivity (Entries 3 and 4). The addition of two equivalents of phenylacetylene drove the reaction to completion, resulting in a high yield of the product with moderate stereoselectivity (Entry 4: 93% yield, *E*/*Z* ratio = 1.9:1). In our previous work, we found that the addition of a silver salt enhanced the stereoselectivity of the reaction by forcing the reaction to follow a cationic pathway, which decreased stereoisomerizaton of the vinylpalladium intermediate.[10] In this reaction, however, addition of Ag_3PO_4 gave a slightly lower yield with a similar *E*/*Z* ratio (Entry 5: 70% yield, *E*/*Z* ratio = 2.0:1). The above results imply that the one-pot successive reaction is both highly feasible, and that the reaction should be *E*-stereoselective.

Table 1. Feasibility test of Heck/Sonogashira reaction[a)]

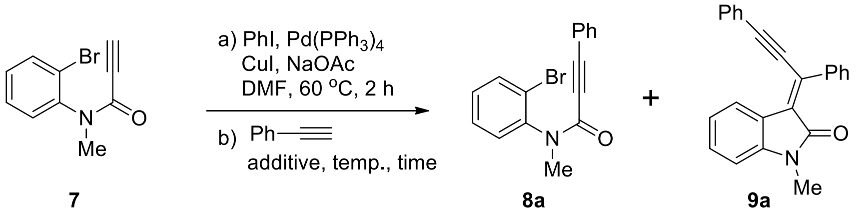


Entry	Phenylacetylene (eq)	Recovered **8a** (%)	**9a**	
			Yield[b)] (%)	*E*/*Z* ratio
1	1.2	60	36	4.0:1
2[c)]	1.2	49	46	4.0:1
3[c)]	1.5	39	54	3.8:1
4[c)]	2.0	-	93	1.9:1
5[c),d)]	2.0	-	70	2.0:1

[a)] Reagents and conditions: **8a** (0.17 mmol), phenylacetylene, $Pd(PPh_3)_4$ (10 mol%), CuI (5 mol%), NaOAc (3.0 eq), DMF(3.0 mL), 60 °C, 4 h. [b)] Combined isolated yield of *E*- and *Z*-isomers. [c)] Reaction mixture was degassed by freeze-pump-thaw method before heating. [d)] Ag_3PO_4 (1.1 eq) was added.

Based on these promising results, we aimed to identify the optimal conditions for the one-pot Sonogashira/Heck/Sonogashira reactions (Table 2). Propiolamide **7** was exposed to Zhu's Sonogashira reaction conditions [phenyl iodide (1.1 eq), $Pd(PPh_3)_4$ (10 mol%), CuI (5 mol%), NaOAc (3.0 eq), DMF, 60 °C, 2 h]. After the addition of phenylacetylene (2.0 eq), the reaction mixture was stirred for 4 h at the same temperature (Entry 1). The reaction had not gone to completion, resulting in a 45% yield of the desired product, **9a**, with good stereoselectivity (*E*/*Z* ratio = 8.0:1). Increasing the reaction time (Entry 2: 6 h) and the amount of phenylacetylene (Entry 3: 3 eq) did not significantly increase the yield. Elevating the reaction temperature to 90 °C, significantly enhanced the reaction rate, resulting in a good yield of **9a** with lower stereoselectivity (Entry 4: 84% yield, *E*/*Z* ratio = 2.2:1). A longer reaction time at 90 °C reduced the stereoselectivity of the product (Entry 5: *E*/*Z* ratio = 1.3:1). To increase the stereoselectivity, the silver salt effect was evaluated again (Entries 6 and 7). In agreement with our hypothesis, addition of Ag_3PO_4 to the reaction increased the *E*/*Z* ratio to 4.1:1 (Entry 6). Finally, the optimal conditions were identified as 4.0 eq phenylacetylene, 1.1 eq Ag_3PO_4, 90 °C, and 1.5 h, which provided a high product yield and good stereoselectivity (Entry 7: 84% yield, *E*/*Z* ratio = 4.2:1).

Table 2. Optimization of one-pot Sonogashira/Heck/Sonogashira reaction[a)]

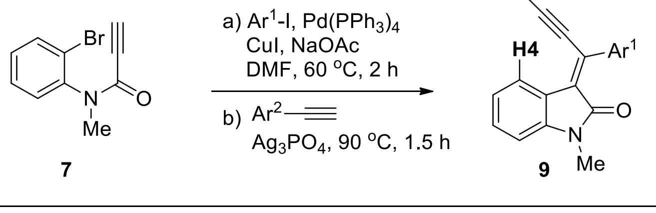


Entry	Phenylacetylene (eq)	Additive	Temp (°C)	Time (h)	**8a** (%)	**9a** Yield[b)] (%)	**9a** *E*/*Z* ratio
1	2.0	-	60	4	49	45	8.0:1
2	2.0	-	60	6	48	50	4.0:1
3	3.0	-	60	4	37	56	5.4:1
4	3.0	-	90	1	6	84	2.2:1
5	3.0	-	90	2	2	87	1.3:1
6	4.0	Ag_3PO_4[c)]	90	1	24	69	4.1:1
7	4.0	Ag_3PO_4[c)]	90	1.5	7	84	4.2:1

[a)] Reagents and conditions: **7** (0.17 mmol), $Pd(PPh_3)_4$ (10 mol%), CuI (5 mol%), NaOAc (3.0 eq), DMF (3.0 mL), degassed; phenyl iodide (1.1 eq), 60 °C, 2 h; phenylacetylene, additive, temp., time. [b)] Combined isolated yield of *E*- and *Z*-isomers. [c)] 1.1 equivalent of Ag_3PO_4 was added.

Having established the optimal conditions, we then screened the substrate scope of the one-pot Sonogashira/Heck/Sonogashira reactions (Table 3). Whereas reaction with 4-methoxyphenylacetylene resulted in **9b** at a moderate yield and stereoselectivity (Entry 1: 68% yield, *E*/*Z* ratio = 5.4:1), 4-chlorophenylacetylene was not a good substrate, providing **9c** at a somewhat low yield and stereoselectivity (Entry 2: 56% yield, *E*/*Z* ratio = 1.8:1). This is probably due to the lower reactivity of electron-deficient acetylenes towards the Sonogashira reaction. 4-Chlorophenyl iodide was a suitable substrate for the reaction with both phenylacetylene and 4-methoxyphenylacetylene (Entry 3: 81% yield, *E*/*Z* ratio = 7.1:1; Entry 4: 87% yield, *E*/*Z* ratio = 6.7:1), although the reaction with 4-chlorophenylacetylene resulted in a low yield and stereoselectivity (Entry 5: 35% yield, *E*/*Z* ratio = 3.9:1). Electron-sufficient 4-methoxyphenyl iodide showed similar results to those of 4-chlorophenyl iodode (Entries 6–8). The reaction with phenylacetylene produced a slightly lower *E*/*Z* ratio (2.9:1) (Entry 6). This result could be explained by the enhanced effect of the 4-methoxy group on *E*/*Z* isomerization of vinylpalladium species, as demonstrated in our previous works.[10] However, the negative effect of 4-methoxyphenyl iodide on stereoselectivity was compromised by the increased activity of 4-methoxyphenylacetylene on the last Sonogashira reaction (Entry 7: 74% yield, *E*/*Z* ratio = 6.4:1). The combination of 4-methoxyphenyl iodide and 4-chlorophenylacetylene resulted in a moderate yield (50%) and *E*/*Z* ratio (3.6:1) (Entry 8). Most of the structures of **9b-i** were elucidated by the aid of NMR studies. And we found that the chemical shift of hydrogen at 4-position (H4) in ^{1}H NMR lies within a certain range depending of *E*/*Z* stereochemistry of compounds. H4 of (*E*)-isomers is found in the narrow range of 8.36–8.44 ppm in ^{1}H NMR, whereas those of (*Z*)-isomers appear in relatively broad range of 6.48–6.73 ppm. This chemical shift tendency of H4 was applied to determine the stereochemistry of compounds for which 2D NMR is not available or correlations in 2D NMR were not clear enough to define stereochemistry. These results demonstrate that this novel one-pot Sonogashira/Heck/Sonogashira reaction is compatible with various substituents on aryl iodides and arylacetylenes, excluding electron-withdrawing groups in arylacetylenes which decreased both the yield and stereoselectivity.

Table 3. Substrate scope of one-pot Sonogashira/Heck/Sonogashira reaction[a)]



chemical shift of H4
(*E*)-9: δ 8.36~8.44
(*Z*)-9: δ 6.48~6.73

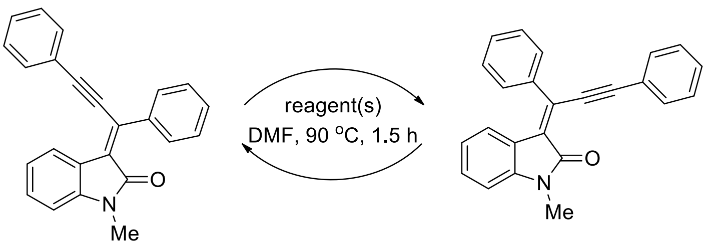
Entry	Ar^{1}	Ar^{2}	**9**	Yield$^{b)}$ (%)	*E*/*Z* ratio
1	C_6H_5	4-MeOC_6H_4	**9b**	68	5.4:1

2	C_6H_5	4-ClC_6H_4	**9c**	56	1.8:1
3	4-ClC_6H_4	C_6H_5	**9d**	81	7.1:1
4	4-ClC_6H_4	4-$MeOC_6H_4$	**9e**	87	6.7:1
5	4-ClC_6H_4	4-ClC_6H_4	**9f**	35	3.9:1
6	4-$MeOC_6H_4$	C_6H_5	**9g**	84	2.9:1
7	4-$MeOC_6H_4$	4-$MeOC_6H_4$	**9h**	74	6.4:1
8	4-$MeOC_6H_4$	4-ClC_6H_4	**9i**	50	3.6:1

$^{a)}$Reagents and conditions: **7** (0.17 mmol), $Pd(PPh_3)_4$ (10 mol%), CuI (5 mol%), NaOAc (3.0 eq), DMF (3.0 mL), degassed: Ar^1-I (1.1 eq) 60 °C, 2 h; Ar^2-acetylene (4.0 eq), Ag_3PO_4 (1.1 eq), 90 °C, 1.5 h. $^{b)}$Combined isolated yield of *E*- and *Z*-isomers.

E-Stereoselectivity of our one-pot approach is mainly due to *syn* addition mechanism of acetylene to arylpalladium bond at the Heck reaction. This affords the corresponding (*E*)-vinylpalladium species, which react with arylacetylenes to predominantly give (*E*)-isomers. However, moderate to poor stereoselectivity of our results implies existence of the other mechanism or *E*/*Z* isomerizations in the reaction conditions. *E*/*Z* isomerization of vinylpalladium species are already discussed and proved by silver salt effect by the addition of Ag_3PO_4. Thus, we decided to examine the possibility of *E*/*Z* isomerization of products under reaction conditions (Table 4). When **(*E*)-9a** and **(*Z*)-9a** were re-exposed to the reaction conditions, *E*/*Z* isomerization was detected with 19% and 21% conversion rate respectively (Entries 1 and 2). To verify the effect of each reagent on isomerization, separate experiments were conducted (Entries 3–10). These results show that $Pd(PPh_3)_4$, despite the small amount, is the major contributor to *E*/*Z* isomerization of products. This might be due to palladium's coordination effect on products or addition/elimination mechanism of phosphine ligands proposed by Yamamoto and co-workers.[8b]

Table 4. *E*/*Z* Isomerization Study$^{a)}$



(*E*)-9 **(*Z*)-9**

Entry	Starting Material	Reagent(s)	Conversion Rate (%)$^{a)}$
1	**(*E*)-9**	reagents for optimal conditions$^{b)}$	19
2	**(*Z*)-9**	reagents for optimal conditions$^{b)}$	22

3	**(*E*)-9**	$Pd(PPh_3)_4$ (10 mol%)	43
4	**(*Z*)-9**	$Pd(PPh_3)_4$ (10 mol%)	46
5	**(*E*)-9**	CuI (5 mol%)	10
6	**(*Z*)-9**	CuI (5 mol%)	14
7	**(*E*)-9**	NaOAc (3.0 eq)	16
8	**(*Z*)-9**	NaOAc (3.0 eq)	22
9	**(*E*)-9**	Ag_3PO_4 (1.1 eq)	11
10	**(*Z*)-9**	Ag_3PO_4 (1.1 eq)	14

[a] Rate was determined by ^1H NMR of the crude mixture. [b] $Pd(PPh_3)_4$ (10 mol%), CuI (5 mol%), NaOAc (3.0 eq), Ag_3PO_4 (1.1 eq).

In summary, we have developed an efficient method for the synthesis of 3-(1,3-diarylprop-2-yn-1-ylidene)oxindoles from three simple components (propiolamide, aryl iodide, and arylacetylene). This reaction is compatible with most substituents found on aryl substrates. Stereoselectivity of the reaction ranges from moderate to good, but the *E*-isomer is always the major isomer, which has not been easily accessible by previous literature methods. Currently, we are working on the development of tandem reaction conditions for the same conversion.

EXPERIMENTAL

All reactions were performed under an argon atmosphere with anhydrous DMF. All commercially available reagents were purchased and used without further purification. Purification of products was conducted by column chromatography through silica gel 60 (0.060–0.200 mm). Melting points of all solid compounds were determined by Buchi M-565. NMR spectra were obtained on Bruker AVANCE III 500 MHz using residual undeuterated solvent as an internal reference. IR spectra were recorded on a Jasco P-2000 FT-IR spectrometer. High-resolution mass spectra (HR-MS) were recorded on a JEOL JMS-700 using EI (electron impact).

General Procedure for One-Pot Sonogashira/Heck/Sonogashira Reaction

To a solution of propiolamide **7**[10a] (40.0 mg, 0.168 mmol) in anhydrous DMF (3.0 mL) were added, CuI (1.6 mg, 0.0084 mmol, 5 mol%), NaOAc (41.3 mg, 0.503 mmol, 3.0 equiv) and $Pd(PPh_3)_4$ (19.8 mg, 0.0171 mmol, 10 mol%). The reaction mixture was degassed by freeze-pump-thaw method. After addition of the corresponding aryl iodide (0.188 mmol, 1.1 equiv), the reaction mixture was stirred at 60 °C for 2 h. Heating source was removed and to the mixture were added Ag_3PO_4 (77.3 mg, 0.185 mmol, 1.1 equiv) and the corresponding arylacetylene (0.672 mmol, 4.0 equiv). The mixture was stirred at 90 °C for 1.5 h. The mixture was cooled to 25 °C and diluted with EtOAc (100 mL). Organic layer was washed with H_2O (15 mL x 3) and brine (15 mL), then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexanes/EtOAc) to yield 3-(1,3-diarylprop-2-yn-1-ylidene)oxindole **9**.

(*E*)-3-(1,3-Diphenylprop-2-yn-1-ylidene)-1-methylindolin-2-one ((*E*)-9a)

Orange solid; mp 143.3 °C; R_f = 0.29 (silica gel, hexanes:EtOAc 4:1); IR (film) 3053, 2927, 2185, 1701, 745 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.43 (dd, *J* = 7.7, 0.6 Hz, 1H), 7.64–7.62 (m, 2H), 7.59–7.57 (m, 2H), 7.46–7.40 (m, 6H), 7.32 (td, *J* = 7.7, 1.1 Hz, 1H), 7.09 (td, *J* = 7.7, 1.0 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 3.18 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2, 143.6, 136.9, 132.1, 131.9, 130.0, 129.8, 129.3, 129.2, 128.8, 128.0, 123.7, 123.2, 122.5, 122.1, 107.8, 105.2, 91.2, 25.9 ppm; HRMS (EI): calcd for $C_{24}H_{17}NO$ [M^+]: 335.1310, found 335.1310.

(*Z*)-3-(1,3-Diphenylprop-2-yn-1-ylidene)-1-methylindolin-2-one ((*Z*)-9a)

Orange solid; mp 39.0 °C; R_f = 0.29 (silica gel, hexanes:EtOAc 4:1); IR (film) 3053, 2926, 2182, 1701, 747 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.64–7.62 (m, 2H), 7.57–7.55 (m, 2H), 7.52–7.49 (m, 3H), 7.36–7.37 (m, 3H), 7.18 (td, *J* = 7.7, 1.1 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.67 (td, *J* = 7.7, 1.0 Hz, 1H), 6.51 (d, *J* = 7.3 Hz, 1H), 3.31 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.7, 143.1, 138.3, 132.6, 131.6, 130.7, 129.8, 129.4, 129.3, 129.2, 128.5, 128.4, 123.6, 123.1, 122.1, 121.6, 107.9, 105.5, 91.2, 26.1 ppm; HRMS (EI): calcd for $C_{24}H_{17}NO$ [M^+]: 335.1310, found 335.1313.

(*E*)-3-(3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-ylidene)-1-methylindolin-2-one ((*E*)-9b)

Orange solid; mp 159.0 °C; R_f = 0.33 (silica gel, hexanes:EtOAc 3:1); IR (film) 2918, 2849, 2194, 1697, 1251 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.44 (d, *J* = 7.6 Hz, 1H) , 7.63–7.61 (m, 2H), 7.52 (d, *J* = 8.5 Hz, 1H), 7.44–7.43 (m, 2H), 7.32 (t, *J* = 7.6 Hz, 1H), 7.10 (t, *J* = 7.6 Hz, 1H), 6.93 (d, *J* = 8.4 Hz, 2H), 6.81 (d, *J* = 7.6 Hz, 1H) , 3.85 (s, 3H), 3.18 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.3, 161.0, 143.5, 137.2, 133.9, 132.5, 129.8, 129.4, 129.2, 129.1, 128.00, 127.96, 123.6, 123.4, 122.0, 114.6, 114.5 107.7, 106.1, 90.8, 55.6, 25.9 ppm; HRMS (EI): calcd for $C_{25}H_{19}NO_2$ [M^+]: 365.1416, found 365.1419.

(*Z*)-3-(3-(4-Methoxyphenyl)-1-phenylprop-2-yn-1-ylidene)-1-methylindolin-2-one ((*Z*)-9b)

Orange solid; mp 43.5 °C; R_f = 0.27 (silica gel, hexanes:EtOAc 3:1); IR (film) 2924, 2851, 1701, 1251 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.59–7.57 (m, 2H), 7.55–7.54 (m, 2H), 7.52–7.49 (m, 3H), 7.18 (t, *J* = 7.7 Hz, 1H), 6.87–6.85 (m, 2H), 6.78 (d, *J* = 7.8 Hz, 1H) , 6.67 (t, *J* = 7.7 Hz, 1H) , 6.48 (d, *J* = 7.8 Hz, 1H), 3.88 (s, 3H), 3.31 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.9, 160.8, 142.9, 138.6, 134.4, 132.2, 129.8, 129.5, 129.24, 129.18, 128.4, 123.4, 122.3, 121.5, 115.4, 114.2, 107.9, 106.5, 90.9, 55.5, 26.0 ppm; HRMS (EI): calcd for $C_{25}H_{19}NO_2$ [M^+]: 365.1416, found 365.1415.

(*E*)-3-(3-(4-Chlorophenyl)-1-phenylprop-2-yn-1-ylidene)-1-methylindolin-2-one ((*E*)-9c)

Orange solid; mp 169.0 °C; R_f = 0.33 (silica gel, hexanes:EtOAc 4:1); IR (film) 3053, 2922, 2187, 1697, 1092 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.36 (dd, *J* = 7.8, 0.4 Hz, 1H), 7.61–7.59 (m, 2H), 7.51–7.48

(m, 2H), 7.46–7.41 (m, 3H), 7.39–7.37 (m, 2H), 7.33 (td, *J* = 6.1, 4.5 Hz, 1H), 7.08 (td, *J* = 7.7, 0.5 Hz, 1H), 6.82 (d, *J* = 7.8 Hz, 1H), 3.17 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.1, 143.7, 136.7, 136.1, 133.3, 131.5, 130.2, 129.31, 129.29, 129.2, 128.1, 123.7, 123.1, 122.1, 121.0, 107.9, 103.7, 92.0, 25.9 ppm; HRMS (EI): calcd for $C_{24}H_{16}ClNO$ [M$^+$]: 369.0920, found 369.0919.

(*Z*)-3-(3-(4-Chlorophenyl)-1-phenylprop-2-yn-1-ylidene)-1-methylindolin-2-one ((*Z*)-9c)

Orange solid; mp 49.8 °C; R_f = 0.43 (silica gel, hexanes:EtOAc 4:1); IR (film) 3060, 2918, 2185, 1704, 1093 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.57–7.49 (m, 7H), 7.33–7.30 (m, 2H), 7.18 (td, *J* = 7.7, 1.0 Hz, 1H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.67 (td, *J* = 7.7, 0.8 Hz, 1H), 6.50 (d, *J* = 7.7 Hz, 1H), 3.31 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.7, 143.2, 138.1, 135.6, 133.8, 131.13, 131.07, 130.0, 129.4, 1129.3, 128.9, 128.4, 123.7, 122.0, 121.81, 121.66 108.0, 103.8, 92.0, 26.1 ppm; HRMS (EI): calcd for $C_{24}H_{16}ClNO$ [M$^+$]: 369.0920, found 369.0923.

(*E*)-3-(1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-ylidene)-1-methylindolin-2-one ((*E*)-9d)

Orange solid; mp 134.8 °C; R_f = 0.42 (silica gel, hexanes:EtOAc 4:1); IR (film) 3053, 2920, 2186, 1694, 1608 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 7.7 Hz, 1H), 7.58–7.56 (m, 4H), 7.43–7.39 (m, 5H), 7.32 (td, *J* = 7.7, 1.0 Hz, 1H), 7.08 (td, *J* = 7.7, 1.0 Hz, 1H), 6.81 (d, *J* = 7.7 Hz, 1H), 3.17 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.1, 143.6, 135.28, 135.26, 132.1, 130.9, 130.4, 130.3, 129.9, 129.1, 128.8, 128.3, 123.8, 123.1, 122.3, 122.2, 107.9, 105.4, 90.9, 25.9 ppm; HRMS (EI): calcd for $C_{24}H_{16}ClNO$ [M$^+$]: 369.0920, found 369.0923.

(*Z*)-3-(1-(4-Chlorophenyl)-3-phenylprop-2-yn-1-ylidene)-1-methylindolin-2-one ((*Z*)-9d)

Dark orange solid; mp 122.8 °C; R_f = 0.35 (silica gel, hexanes:EtOAc 4:1); IR (film) 3053, 2922, 2183, 1701, 1608 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.63–7.61 (m, 2H), 7.52–7.48 (m, 4H), 7.38–7.32 (m, 3H), 7.20 (td, *J* = 7.7, 1.0 Hz, 1H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.72 (td, *J* = 7.7, 1.0 Hz, 1H), 6.59 (d, *J* = 7.4 Hz, 1H), 3.31 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.6, 143.3, 136.8, 135.4, 132.6, 130.9, 130.1, 130.04, 130.00, 129.6, 129.5, 28.5, 123.5, 123.0, 121.8, 121.7, 108.1, 105.7, 91.0, 26.1 ppm; HRMS (EI): calcd for $C_{24}H_{16}ClNO$ [M$^+$]: 369.0920, found 369.0917.

(*E*)-3-(1-(4-Chlorophenyl)-3-(4-methoxyphenyl)prop-2-yn-1-ylidene)-1-methylindolin-2-one ((*E*)-9e)

Orange solid; mp 179.4 °C; R_f = 0.20 (silica gel, hexanes:EtOAc 4:1); IR (film) 2929, 2176, 1697, 1603, 1575 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.40 (d, *J* = 7.6 Hz, 1H), 7.56 (d, *J* = 8.4 Hz, 2H), 7.50 (d, *J* = 8.8 Hz, 2H), 7.39 (d, *J* = 8.4 Hz, 2H), 7.32 (t, *J* = 7.4 Hz, 1H), 7.09 (t, *J* = 7.4 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 2H), 6.80 (d, *J* = 7.8 Hz, 1H), 3.84 (s, 3H), 3.16 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2, 161.1, 143.5, 135.5, 135.1, 133.9, 130.90, 130.85, 130.0, 128.2, 128.1, 123.6, 123.2, 122.1, 114.6, 114.3, 107.8, 106.3, 90.4, 55.5, 25.9 ppm; HRMS (EI): calcd for $C_{25}H_{18}ClNO_2$ [M$^+$]: 399.1026, found 399.1025.

(*Z*)-3-(1-(4-Chlorophenyl)-3-(4-methoxyphenyl)prop-2-yn-1-ylidene)-1-methylindolin-2-one ((*Z*)-9e)

Orange solid; mp 131.2 °C; R_f = 0.37 (silica gel, hexanes:EtOAc 4:1); IR (film) 2923, 2178, 1701, 1604, 1577 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.58–7.56 (m, 2H), 7.51–7.47 (m, 4H), 7.19 (td, *J* = 7.7, 0.9 Hz, 1H), 6.88–6.86 (m, 2H), 6.79 (d, *J* =7.8 Hz, 2H), 6.71 (td, *J* = 7.7, 0.9 Hz, 1H), 6.56 (d, *J* = 7.8 Hz, 1H), 3.83 (s, 3H), 3.31 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5, 143.3, 136.5, 135.8, 135.5, 133.8, 131.3, 130.3, 130.0, 129.6, 129.5, 128.9, 123.6, 121.8, 121.7, 121.5, 108.2, 104.0, 91.7, 26.1 ppm; HRMS (EI): calcd for $C_{25}H_{18}ClNO_2$ [M$^+$]: 399.1026, found 399.1025.

(*E*)-3-(1,3-Bis(4-chlorophenyl)prop-2-yn-1-ylidene)-1-methylindolin-2-one ((*E*)-9f)

Orange solid; mp 173.0 °C; R_f = 0.28 (silica gel, hexanes:EtOAc 6:1); IR (film) 2920, 2850, 2188, 1733 1610 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.33 (d, *J* = 7.7 Hz, 1H), 7.56–7.54 (m, 2H), 7.50–7.49 (m, 2H), 7.41–7.39 (m, 4H), 7.35 (t, *J* = 7.7 Hz, 1H), 7.10 (t, *J* = 7.7 Hz, 1H), 6.82 (d, *J* = 7.7 Hz, 1H), 3.18 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.1, 143.8, 136.3, 135.4, 135.1, 133.3, 130.8, 130.5, 129.9, 129.4, 129.3, 128.4, 123.7, 123.0, 122.2, 120.8, 108.0, 103.8, 91.6, 26.0 ppm; HRMS (EI): calcd for $C_{24}H_{15}Cl_2NO$ [M$^+$]: 403.0531, found 403.0533.

(*Z*)-3-(1,3-Bis(4-chlorophenyl)prop-2-yn-1-ylidene)-1-methylindolin-2-one ((*Z*)-9f)

Orange solid; mp 142.1 °C; R_f = 0.28 (silica gel, hexanes:EtOAc 6:1); IR (film) 2922, 2851, 2185, 1725, 1609 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.55–7.54 (m, 2H), 7.49 (s, 4H), 7.33–7.31 (m, 2H), 7.22 (t, *J* = 7.7 Hz, 1H), 6.79 (d, *J* = 7.7 Hz, 1H), 6.73 (t, *J* = 7.7 Hz, 1H), 6.58 (d, *J* = 7.7 Hz, 1H), 3.30 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.5, 143.3, 136.5, 135.8, 135.5, 133.8, 131.3, 130.3, 130.0, 129.6, 129.5, 128.9, 123.6, 121.8, 121.7, 121.5, 108.5, 104.0, 91.7, 26.1 ppm; HRMS (EI): calcd for $C_{24}H_{15}Cl_2NO$ [M$^+$]: 403.0531, found 403.0530.

(*E*)-3-(1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-ylidene)-1-methylindolin-2-one ((*E*)-9g)

Orange solid; mp 121.2 °C; R_f = 0.28 (silica gel, hexanes:EtOAc 4:1); IR (film) 3053, 2926, 2849, 2188, 1605 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 8.41 (d, *J* = 7.6 Hz, 1H), 7.66 (d, *J* = 8.6 Hz, 2H), 7.58–7.57 (m, 2H), 7.41–7.40 (m, 3H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.08 (t, *J* = 7.6 Hz, 1H), 6.95 (d, *J* = 8.6 Hz, 2H), 6.79 (d, *J* = 7.7 Hz, 1H), 3.85 (s, 3H), 3.18 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2, 160.8, 143.3, 132.1 132.0, 131.5, 129.7, 129.6, 128.9, 128.8, 127.7, 123.5, 122.5, 122.0, 113.3, 107.7, 104.6, 91.4, 55.4, 25.9 ppm; HRMS (EI): calcd for $C_{25}H_{19}NO_2$ [M$^+$]: 365.1416, found 365.1415.

(*Z*)- 3-(1-(4-Methoxyphenyl)-3-phenylprop-2-yn-1-ylidene)-1-methylindolin-2-one ((*Z*)-9g)

Dark orange solid; mp 121.5 °C; R_f = 0.37 (silica gel, hexanes:EtOAc 4:1); IR (film) 3052, 2923, 2851, 2183, 1604 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.64–7.62 (m, 2H), 7.54–7.52 (m, 2H), 7.35–7.33 (m, 3H), 7.30 (t, *J* = 7.6 Hz, 1H), 7.03–7.00 (m, 2H), 6.79–6.71 (m, 3H), 3.90 (s, 3H), 3.31 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.9, 160.7, 143.0, 132.6, 131.6, 130.6, 130.3, 130.1, 129.6, 129.4, 128.5, 123.4, 123.3, 122.3, 121.5, 114.5, 107.9, 105.0, 91.5, 55.6, 26.1 ppm; HRMS (EI): calcd for $C_{25}H_{19}NO_2$ [M$^+$]: 365.1416, found 365.1416.

(*E*)-3-(1,3-Bis(4-methoxyphenyl)prop-2-yn-1-ylidene)-1-methylindolin-2-one ((*E*)-9h)

Orange solid; mp 164.5 °C; R_f = 0.15 (silica gel, hexanes:EtOAc 4:1); IR (film) 3050, 2925, 2848, 2171, 1508 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.42 (d, *J* = 7.6 Hz, 1H), 7.66–7.64 (m, 2H), 7.53–7.51 (m, 2H), 7.28 (td, *J* = 7.6, 0.9 Hz, 1H), 7.07 (td, *J* = 7.6, 0.8 Hz, 1H), 6.96–6.91 (m, 4H), 6.80 (d, *J* = 7.8 Hz, 1H), 3.86 (s, 3H), 3.84 (s, 3H), 3.18 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.4, 161.0, 160.8, 143.1, 133.8, 132.6, 131.5, 129.3, 129.1, 126.9, 123.7, 123.4, 121.9, 114.7, 114.5, 113.3, 107.6, 105.5, 90.9, 55.5, 55.4, 25.9 ppm; HRMS (EI): calcd for $C_{26}H_{21}NO_3$ [M^+]: 395.1521, found 395.1520.

(*Z*)-3-(1,3-Bis(4-methoxyphenyl)prop-2-yn-1-ylidene)-1-methylindolin-2-one ((*Z*)-9h)

Orange solid; mp 130.6 °C; R_f = 0.27 (silica gel, hexanes:EtOAc 4:1); IR (film) 3050, 2928, 2837, 2177, 1508 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.59–7.58 (m, 2H), 7.53–7.52 (m, 2H), 7.20–7.17 (m, 1H), 7.02–7.00 (m, 2H), 6.87–6.86 (m, 2H), 6.78 (d, *J* = 7.8 Hz, 1H), 6.73–6.70 (m, 2H), 3.90 (s, 3H), 3.83 (s, 3H), 3.31 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 167.0, 160.7, 160.6, 142.8, 134.4, 132.2, 130.8, 130.3, 129.3, 129.1, 123.2, 122.5, 121.4, 115.4, 114.4, 114.2, 107.8, 106.0, 91.1, 55.54, 55.47, 26.0 ppm; HRMS (EI): calcd for $C_{26}H_{21}NO_3$ [M^+]: 395.1521, found 395.1519.

(*E*)-3-(3-(4-Chlorophenyl)-1-(4-methoxyphenyl)prop-2-yn-1-ylidene)-1-methylindolin-2-one ((*E*)-9i)

Orange solid; mp 159.9 °C; R_f = 0.28 (silica gel, hexanes:EtOAc 4:1); IR (film) 3053, 2918, 2849, 2188, 1695 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.34 (d, *J* = 7.7 Hz, 1H), 7.65–7.62 (m, 2H), 7.51–7.49 (m, 2H), 6.97–6.94 (m, 2H), 7.30 (td, *J* = 7.8,1.0 Hz, 1H), 7.06 (td, *J* = 7.8, 1.0 Hz, 1H), 7.55–7.54 (m, 2H), 6.81 (d, *J* = 7.7 Hz, 1H), 3.86 (s, 3H), 3.19 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2, 160.9, 143.4, 136.0, 133.3, 131.5, 131.4, 129.8, 129.2, 128.7, 128.0, 123.5, 122.0, 121.0, 113.4, 107.8, 103.1, 92.2, 55.4, 25.9 ppm; HRMS (EI): calcd for $C_{25}H_{18}ClNO_2$ [M^+]: 399.1026, found 399.1029.

(*Z*)-3-(3-(4-Chlorophenyl)-1-(4-methoxyphenyl)prop-2-yn-1-ylidene)-1-methylindolin-2-one ((*Z*)-9i)

Orange solid; mp 48.7 °C; R_f = 0.35 (silica gel, hexanes:EtOAc 4:1); IR (film) 3052, 2924, 2852, 2185, 1700 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.57–7.55 (m, 2H), 7.53–7.50 (m, 2H), 7.34–7.31 (m, 2H), 7.19 (td, *J* = 7.5, 1.3 Hz, 1H), 7.03–7.00 (m, 2H), 6.79 (d, *J* = 7.8 Hz, 1H), 6.76–6.71 (m, 2H), 3.91 (s, 3H), 3.31 (s, 3H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.8, 160.7, 143.1, 135.5, 133.8, 131.1, 130.4, 130.28, 130.26, 129.8, 128.9, 123.5, 122.2, 121.8, 121.6, 114.5, 108.0, 103.4, 92.3 55.6, 29.9 ppm; HRMS (EI): calcd for $C_{25}H_{18}ClNO_2$ [M^+]: 399.1026, found 399.1029.

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