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One-Pot and Regiospecific Synthesis of 2,3-Disubstituted Indoles from 2-Bromoanilides via Consecutive Palladium-Catalyzed Sonogashira Coupling, Amidopalladation, and Reductive Elimination

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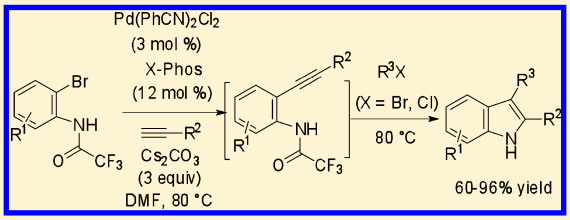
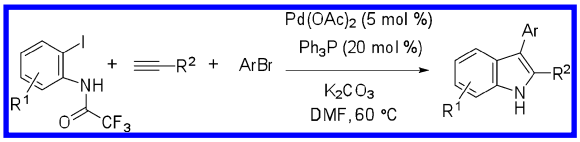
Supporting Information

ABSTRACT: A practical one-pot and regiospecific three-component process for the synthesis of 2,3-disubstituted indoles from 2-bromoanilides was developed via consecutive palladium-catalyzed Sonogashira coupling, amidopalladation, and reductive elimination.



The indole motif is a ubiquitous feature of alkaloid natural products and represents a privileged structural element for pharmaceutically active compounds.[1] Despite the plethora of methodologies developed for synthesis of this heterocyclic system,[2] efficient general methods for *regioselective* preparation of highly substituted indoles are limited.[3] As a program of developing practical and economical processes, we have reported several efficient methods for the regioselective synthesis of a variety of indole skeletons,[4] including the recently communicated one-pot *regiospecific* synthesis of 2,3-disubstituted indoles from 2-iodoanilides, terminal alkynes, and aryl bromides via the domino Sonogashira[5]−Cacchi reactions[6] (Scheme 1). Although this three-component cascade reaction

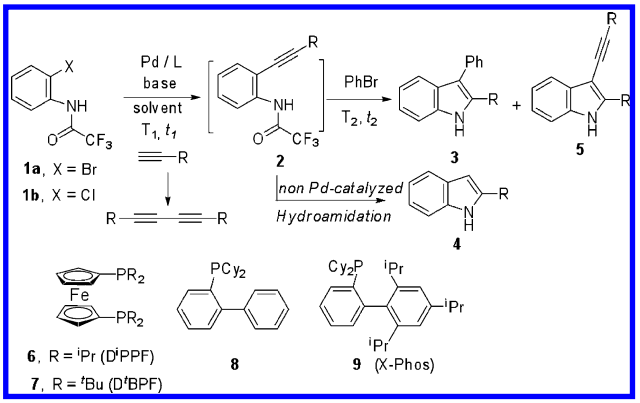
Scheme 1. One-Pot Process for Preparation of 2,3-Disubstituted Indoles from 2-Iodoanilides via Domino Sonogashira and Cacchi Reactions



allows access to a variety of multisubstituted indoles under mild conditions, the use of 2-iodoanilides as the starting material is not ideal from a production perspective because of throughput consideration and the currently prohibitive iodine cost. We sought therefore to modify our initial strategy accordingly.

Our goal became to extend the scope of this one-pot, three-component protocol to aryl bromides or chlorides, which are significantly less expensive and more throughput efficient than the corresponding iodides. However, the major anticipated hurdle of using the rather unreactive and stereohindered 2-bromo- or chloroanilides as the starting material would be the harsh reaction conditions needed for the Sonogashira coupling, which would result in the undesired intramolecular hydroamidation of the primary product, *o*-alkynylanilides **4** (Scheme 2).[7] In fact, efficient Sonogashira couplings of unreactive aryl

Scheme 2. One-Pot Domino Process for Preparation of 2,3-Disubstituted Indoles from 2-Bromo- or Chloroanilides, Terminal Alkynes, and Aryl Bromides or Chlorides



halides bearing *ortho* substituents such as 2-bromo- or 2-chloroanilides are rarely reported,[8] despite the remarkable progress in the utilization of unreactive aryl chlorides in Pd-catalyzed C−C bond formations.[9] In addition, in order to minimize the hydroamidation of intermediate **2**, use of copper salts as cocatalyst, strong base, or high temperature in the Sonogashira coupling must be avoided.[10] Herein we report the development of this new one-pot approach to 2,3-disubstituted indoles from 2-bromoanilides, terminal alkynes, and aryl bromides or chlorides.

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Table 1. Reaction Conditions for the One-Pot, Three-Component Reaction of 2-Bromoanilide 1a, Phenylacetylene, and Bromobenzene[a]

entry	catalyst/ligand	base/solvent	T_1/t_1 (°C/h) T_2/t_2 (°C/h)	**2**/**3**/**4**[b]
1	$Pd(OAc)_2/Cy_3P$	K_2CO_3/DMF	80/1.2;	trace of **2**
2	$Pd(^tBu_3P)_2$ (3 mol %)	K_2CO_3/DMF	60/1.5; 60/23	10/11/79
3	$Pd(OAc)_2$ (3 mol %)/**6** (6 mol %)	K_2CO_3/DMF	80/23	58% **2**
4	$Pd(OAc)_2$ (3 mol %)/**7** (6 mol %)	K_2CO_3/DMF	80	trace of **2**
5	$Pd(PhCN)_2Cl_2$/**8**	Cs_2CO_3/DMF	100/1	82/0/18
6	$Pd(PhCN)_2Cl_2$/**9**	K_2CO_3/DMF	80/1; 80/1	0/86/14 (68%)[c]
7	$Pd(PhCN)_2Cl_2$/**9**	Cs_2CO_3/DMF	80/1.2; 80/2	0/94/6
8	$Pd(PhCN)_2Cl_2$/**9**	KOAc/DMF	80/1.2	10% **2**; 48% **4**
9	$Pd(PhCN)_2Cl_2$/**9**	*n*-Bu_4NOAc/DMF	80/1.2	33% **2**; 32% **4**
10	$Pd(OCOCF_3)_2$/**9**	Cs_2CO_3/DMF	80/1.2; 80/1.2	27/70/3
11	$Pd(OAc)_2$/**9**	Cs_2CO_3/DMF	80/1.5; 80/2	19/77/4
12	$PdCl_2$/**9**	Cs_2CO_3/DMF	80/1.5; 80/2	39/58/3
13[d]	$Pd(PhCN)_2Cl_2$/**9**	Cs_2CO_3/DMF	80/5; 80/8	20/55/25
14	$Pd(PhCN)_2Cl_2$/**9**	Cs_2CO_3/MeCN	80/1.2; 80/2	88/4/8
15	$Pd(PhCN)_2Cl_2$/**9**	Cs_2CO_3/NMP	80/1.2; 80/2	79/13/8
16	$Pd(PhCN)_2Cl_2$/**9**	Cs_2CO_3/toluene	80/1.2;	trace **2**
17[e]	$Pd(PhCN)_2Cl_2$/**9**	Cs_2CO_3 /DMF	80/1.2; 80/5	20/75/5

[a]Unless otherwise noted, all reactions were run by using 3 mol % of palladium precatalyst, 12 mol % of ligand, 1.2 equiv of phenylacetylene, 1.0 equiv of **1a**, and 3.0 equiv of base in the specified solvent (c = 0.2 M). 1.2 equiv of bromobenzene was added once the bromoanilide **1a** was consumed completely. [b]Measured by HPLC at wavelength of 248 μm. [c]Solution yield of **3** (measured by quantitative HPLC). [d]The reaction was run under otherwise identical conditions except using 1 mol % of $Pd(PhCN)_2Cl_2$ and 4 mol % of **9**. [e]The reaction was run under otherwise identical conditions except using 2.2 equiv of Cs_2CO_3.

Our investigation started with the Sonogashira coupling of 2-bromo-*N*-trifluoroacetylanilide (**1a**) with phenylacetylene, followed by addition of bromobenzene for the Cacchi cyclization (R = Ph). Important parameters including base, solvent, temperature, and ligand were examined. No copper salts were used. The results are summarized in Table 1.

First, several bulky and electron-rich phosphines as ligand were evaluated using K_2CO_3 as base in DMF. Preliminary results showed that besides the expected non-Pd-catalyzed side product **4**, a new impurity, identified as **5**, was observed; its formation could be explained assuming some 1,3-diyne, formed by homocoupling of the alkyne, may undergo a Larock-like insertion with the bromoanilide.[11] With $Pd(OAc)_2$ and Cy_3P as the catalyst,[12] the Sonogashira coupling of phenylacetylene with **1a** did not occur at 80 °C (entry 1, Table 1). Using $Pd(t\text{-}Bu_3P)_2$ as the catalyst,[13] the Sonogashira coupling reaction was completed in 1.5 h at 60 °C; however, the subsequent Cacchi cyclization was extremely slow, resulting in the formation of 2-phenyl indole **4** as the major product after prolonged reaction time (entry 2, Table 1). When D^{i}PPF **6** was used as ligand, the Sonogashira coupling was incomplete even after 23 h at 80 °C, while no reaction occurred by using D^{t}BPF **7** as the ligand, probably due to the steric hindrance of the bulky ligand (entries 3 and 4, Table 1). With biarylphosphine **8** as ligand and Cs_2CO_3 as base, the Sonogashira coupling did not proceed until the temperature was elevated to 100 °C. The coupling reaction was completed in 1 h at this temperature, giving the desired product **2** and the byproduct **4** in a ratio of 82/18 (entry 5, Table 1). Finally, using X-Phos **9** as ligand,[14] the Sonogashira coupling in DMF was completed in 1.5 h at 80 °C, affording **2** as the only product. After addition of bromobenzene, the Cacchi cyclization proceeded smoothly, affording the desired product **3** and byproduct **4** in a ratio of 86/14 (entry 6, Table 1). The ratio of **3** to **4** was further improved to 94/6 by using Cs_2CO_3 as base under otherwise identical conditions (entry 7, Table 1). On the other hand, noticeable amounts of byproduct **4** were observed during the Sonogashira coupling when KOAc or *n*-Bu_4NOAc was used as base (entries 8 and 9, Table 1).

Next, several Pd precatalysts, such as $Pd(OAc)_2$, $PdCl_2$, and $Pd(OCOCF_3)_2$, were evaluated in comparison with $Pd(PhCN)_2Cl_2$ (entries 10−12, Table 1). Although the major side product **4** was still under control in these cases, the Cacchi cyclization was slower, *suggesting a shorter lifetime of the catalyst formed from these Pd species*. The deactivation of the catalyst was further evidenced when the reaction was performed under reduced catalyst loading. With 1 mol % of $Pd(PhCN)_2Cl_2$ and 4 mol % of X-Phos (**9**) in DMF, the Sonogashira coupling took 5 h to reach completion, whereas the subsequent Cacchi cyclization did not reach completion after 8 h, resulting in the significant formation of byproduct **4** (entry 13, Table 1). We speculated that the deactivation of the catalyst might be attributed to the low solubility of the ligand X-Phos in DMF, resulting in the formation of palladium black. Other solvents were examined (entries 14−16, Table 1). While the Sonogashira coupling proceeded smoothly in both acetonitrile and NMP, the Cacchi cyclization was significantly retarded in both solvents. No reaction occurred in toluene, probably due to poor solubility of the base. It is worthy of notice that a *total of 3 equiv of* Cs_2CO_3 is required to complete the reaction, as evidenced by the incomplete Cacchi cyclization when 2.2 equiv of the base was used (entry 17, Table 1). Attempt to extend the reaction to 2-chloroanilide **1b** using 3 mol % of $PdCl_2(PhCN)_2$, 12 mol % of X-Phos **9**, 1.2 equiv of phenylacetylene, and 3.0 equiv of Cs_2CO_3 in DMF (c = 0.2 M) at 80 °C met with no success.

The deactivation of the Pd catalyst became more severe when alkylalkyne **10** was used under the same conditions, resulting in incomplete Sonogashira coupling reaction (Scheme 3). With 3 mol % of Pd catalyst, the Sonogashira coupling proceeded very rapidly at the beginning, with about 50% conversion in just 10 min at 80 °C. However, the reaction rate slowed afterward. Addition of an extra equivalent of the alkyne

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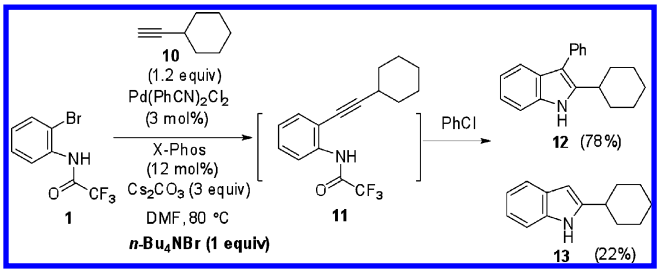
Scheme 3. Domino Sonogashira Coupling, Amidopalladation, and Cyclization Using Alkylalkyne

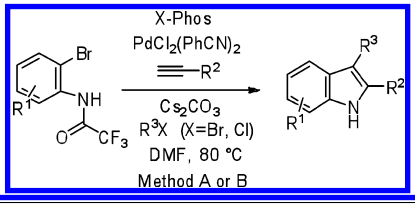


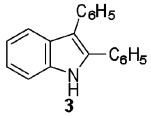
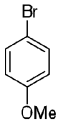
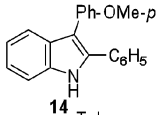
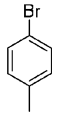
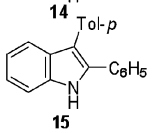
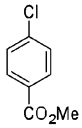
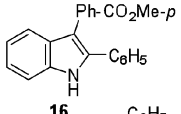
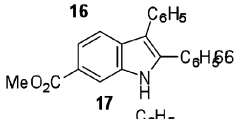
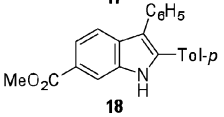
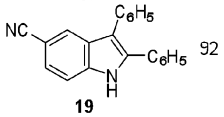
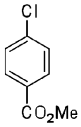
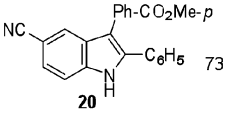
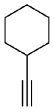
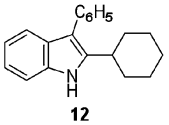
did not enhance the reaction rate, indicating that the sluggishness was not due to potential consumption of the alkyne **10** via homocoupling but rather to catalyst instability. The Sonogashira coupling took over 12 h to complete, but subsequent addition of bromobenzene did not lead to cyclization, showing that no active catalyst was available at this stage. However, to our delight, addition of 1 equiv of *n*-Bu_4NBr (TBAB) significantly stabilized the catalyst, producing the desired product **12** in good yield. The rate of the cyclization depended on the concentration of chlorobenzene. With 1.5 equiv of chlorobenzene, the reaction took 10 h to complete, giving **12** and **13** in a ratio of 76: 24. With 3 equiv of chlorobenzene, the reaction took only 1 h to complete, affording **12** and **13** in a ratio of 78:22. Employment of more chlorobenzene did not further improve the ratio. We speculated that the effect of TBAB on stabilizing the active palladium catalyst might be related to formation of colloidal palladium nanoparticles under the current reaction conditions.[15] The same effect was achieved by using *n*-Bu_4NCl as additive.

To evaluate the scope of this one-pot process, a variety of indoles were synthesized from 2-bromoanilides. Two procedures were used: in the cases when there is competing oxidative insertion of LPd(0) to both the 2-bromoanilides and the aryl halides (reactive ones like bromobenzene), the aryl halides were added after the Sonogashira coupling was complete (Method A); in the cases when there are no competing oxidative insertion of LPd(0), the aryl halides were added in one-pot at the beginning, thus eliminating the need to monitor the progress of the Sonogashira coupling before proceeding to the next step (Method B). The results are summarized in Table 2. Since the problem related to the Sonogashira coupling with alkylalkynes is uniquely demanding, all the 2,3-diarylindoles were prepared under the normal conditions, without addition of *n*-Bu_4NBr. Even without this beneficial additive, good to excellent yields were achieved in all cases examined. 2-Bromoanilides bearing a carboxylate at the C6 position gave only moderate yield, mainly due to the hydroamidation side reaction (entries 5 and 6, Table 2). Also, with substrates bearing a nitrile group at the C5 position, the Sonogashira coupling was significantly slower. Nevertheless, the overall yields for the two steps are not compromised in these cases (entries 7 and , Table 2).

In summary, we have developed a regiospecific one-pot process for rapid access to a variety of 2,3-disubstituted indoles from aryl bromides via consecutive palladium-catalyzed Sonogashira coupling, amidopalladation, and reductive elimination This mild method provides a complementary tool for the regiospecific synthesis of highly substituted indoles.

Table 2. Synthesis of 2,3-Disubstituted Indoles via the One-Pot Three-Component Sonogashira–Cacchi Domino Reaction[a]



entry	starting materials: alkynes	RX	conditions (time)	product	yield (%)[b]
1	Ph	PhBr	A (1.5 h)	 **3**	83
		PhCl	B (11 h)		78[c]
2	Ph		A (2 h)	 **14**	74
3	Ph		A (1.5 h)	 **15**	81
4	Ph		A (1.5 h)	 **16**	96
5	Ph	PhCl	B (2.5 h)	 **17**	66
6	*p*-Tol	PhCl	B (1 h)	 **18**	60
7	Ph	PhCl	B (7 h)	 **19**	92
8	Ph		B (5 h)	 **20**	73
9[c]		PhCl	B (h)	 **12**	72

[a]Method A: The reactions were run by mixing 3 mol % of $PdCl_2(PhCN)_2$, 12 mol % of X-Phos **9**, 1.2 equiv of alkyne, and 1.0 equiv of the anilide and 3.0 equiv of Cs_2CO_3 in DMF (c = 0.2 M) at 80 °C. After the bromoanilide was consumed completely, 1.2 equiv of aryl bromide or chloride was added at 80 °C. Method B: The reactions were run by mixing 3 mol % of $PdCl_2(PhCN)_2$, 12 mol % of X-Phos **9**, 1.2 equiv of alkyne, 1.2 equiv of the aryl chloride, and 1.0 equiv of the anilide and 3.0 equiv of Cs_2CO_3 in DMF (c = 0.2 M) at 80 °C. [b]Isolated yield. [c]3.0 equiv of PhCl, 2.0 equiv of acetylene, and 1.0 equiv of *n*-Bu_4NBr were used under otherwise identical conditions.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out in oven-dried glassware sealed with rubber septa under an inert atmosphere of argon. All commercial materials were used without further purification. HPLC conditions for reaction monitoring and quantitation: column

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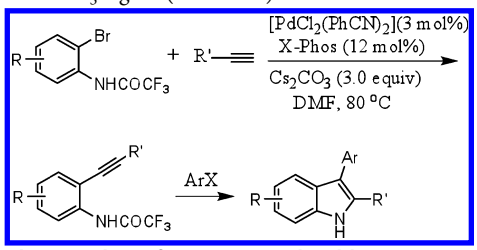
Zorbax Eclipse XDB-C8, 4.6 × 150 mm, 5 μm particle size, column temperature at 40 °C, mobile phase A (0.1% trifluoroacetic acid in water), mobile phase B (0.1% trifluoroacetic acid in acetonitrile), flow rate: 2.0 mL min^{-1}, gradient program 30% B to 95% B in 10 min, to 100% B in 3 min, hold at 100% B for 3 min, λ = 248 nm. The samples for HPLC were diluted with CH_3CN. Chemical shifts are reported in δ (ppm) relative to TMS in $CDCl_3$ as internal standard (^1H NMR) or the residual $CHCl_3$ signal (^{13}C NMR).

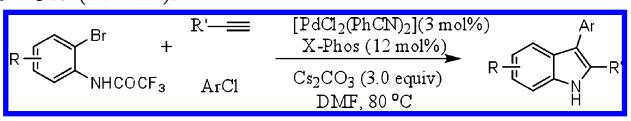


General Procedure for *Sequential Addition* Reaction Conditions (Method A). *2,3-Diphenyl-1H-indole (**3**).*[16] A 10 mL, three-neck flask, equipped with a magnetic-stirring bar, thermocouple, and argon inlet, was charged 2-bromo-*N*-trifluoroacetylanilide **1** (209 mg, 0.78 mmol, 1.0 equiv), $PdCl_2(PhCN)_2$ (8.9 mg, 0.02 mmol, 3 mol %), X-Phos **9** (44 mg, 0.09 mmol, 12 mol %), and cesium carbonate (753 mg, 2.31 mmol, 3 equiv), followed by addition of 3 mL of anhydrous DMF. The reaction mixture was stirred at room temperature for 10 min and added with phenylacetylene (95 mg, 0.93 mmol, 1.2 equiv). The mixture was heated at 80 °C until the Sonogashira reaction was complete, judged by the disappearance of the bromoanilide **1**, followed by addition of bromobenzene (146 mg, 0.93 mmol, 1.2 equiv). The reaction mixture was stirred at 80 °C until the *o*-alkynylanilide intermediate was completely consumed. The mixture was quenched with water and diluted with EtOAc. The organic phase was separated and the aqueous layer was extracted with EtOAc two times. The combined organic layers were washed with brine and dried over Na_2SO_4. After removal of solvents, the crude product was purified by column chromatography on silica gel to afford the desired product **3** as an off-white solid (174 mg, 83% yield): mp 108−110 °C; ^1H NMR (400 MHz, DMSO-d_6) δ 11.55 (s, 1H), 7.46−6.90 (m, 14H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 135.9, 135.1, 134.1, 132.7, 130.2, 128.8, 128.7, 128.5, 128.2, 127.7, 126.2, 122.7, 120.4, 119.7, 115.1, 110.9; LC-MSD (API-ES, positive) m/z = 270 ($M + H^+$).

*2-Phenyl-3-(p-methoxyphenyl)-1H-indole (**14**).*[17] The experiment was performed in the same way as described above, using 2-bromo-*N*-trifluoroacetylanilide **1** (209 mg, 0.78 mmol, 1.0 equiv), $PdCl_2(PhCN)_2$ (8.9 mg, 0.02 mmol, 3 mol %), X-Phos (**9**) (44 mg, 0.09 mmol, 12 mol %), Cs_2CO_3 (753 mg, 2.31 mmol, 3 equiv), phenylacetylene (95 mg, 0.93 mmol, 1.2 equiv), and *p*-bromoanisole (174 mg, 0.93 mmol, 1.2 equiv). The desired compound **14** was obtained as a pale brown solid (173 mg, 74% yield): mp 185−187.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.44−6.92 (m, 12 H), 3.85 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 158.2, 135.9, 133.7, 132.8, 131.2, 129.0, 128.7, 128.0, 127.6, 127.3, 122.6, 121.0, 119.7, 114.73, 114.1, 110.8, 55.2.

*2-Phenyl-3-(p-methylphenyl)-1H-indole (**15**).*[17] The experiment was performed in the same way as described above, using 2-bromo-*N*-trifluoroacetylanilide **1** (209 mg, 0.78 mmol, 1.0 equiv), $PdCl_2(PhCN)_2$ (8.9 mg, 0.02 mmol, 3 mol %), X-Phos (**9**) (44 mg, 0.09 mmol, 12 mol %), Cs_2CO_3 (753 mg, 2.31 mmol, 3 equiv), phenylacetylene (95 mg, 0.93 mmol, 1.2 equiv), and *p*-bromotoluene (159 mg, 0.93 mmol, 1.2 equiv). The desired compound **15** was obtained as an off-white solid (179 mg, 81% yield).

*2-Phenyl-3-(p-methoxycarbonylphenyl)-1H-indole (**16**).*[18] The experiment was performed in the same way as described above, using 2-bromo-*N*-trifluoroacetylanilide **1** (209 mg, 0.78 mmol, 1.0 equiv), $PdCl_2(PhCN)_2$ (8.9 mg, 0.02 mmol, 3 mol %), X-Phos (**9**) (44 mg, 0.09 mmol, 12 mol %), Cs_2CO_3 (753 mg, 2.31 mmol, 3 equiv), phenylacetylene (95 mg, 0.93 mmol, 1.2 equiv), and methyl 4-chlorobenzoate (159 mg, 0.93 mmol, 1.2 equiv). The desired compound **16** was obtained as a pale brown solid (245 mg, 96% yield): mp 155−157 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.34 (s, 1H), 8.03 (d, J = 8.4 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), 7.53−7.21 (m, 10H), 3.93 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.3, 140.3, 136.0, 135.1, 132.3, 129.9, 128.9, 128.4, 128.3, 128.1, 127.7, 126.9, 123.0, 120.9, 119.5, 114.0, 111.1, 52.0; LC-MSD (API-ES, positive) m/z = 328 ($M + H^+$).



General Procedure for *One-Pot* Reaction Conditions (Method B). The reaction was performed under the same conditions as described above in method A, except that *bromobenzene* (1.2 equiv) was replaced with *chlorobenzene* (3 equiv) and added *at the beginning*. There is no need to monitor the Sonogashira coupling reaction. After the reaction went to completion with the time indicated in the text, the product was purified by column chromatography on silica gel to afford the desired product.

*2-Cyclohexyl-3-phenyl-1H-indole (**12**).* The reaction was performed under the same conditions as described above, using 2-bromo-*N*-trifluoroacetylanilide **1** (206 mg, 0.77 mmol, 1.0 equiv), $PdCl_2(PhCN)_2$ (8.7 mg, 0.02 mmol, 3 mol %), X-Phos **9** (44 mg, 0.09 mmol, 12 mol %), Cs_2CO_3 (753 mg, 2.31 mmol, 3 equiv), cyclohexylacetylene (166 mg, 1.5 mmol, 2.0 equiv), chlorobenzene (260 mg, 2.3 mmol, 3 equiv), and *n*-Bu_4NBr (248 mg, 0.77 mmol, 1.0 equiv). The desired compound **12** was obtained as an off-white solid (152 mg, 72% yield): ^1H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.62 (bs, 1H), 7.47−7.40 (m, 4H), 7.34−7.26 (m, 2H), 7.21−7.07 (m, 2H), 3.03 (t, 1H, J = 12 Hz), 1.97−1.81 (m, 2H), 1.76−1.62 (m, 2H), 1.54−1.20 (m, 5H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 140.7, 135.6, 135.0, 129.8, 128.5, 128.0, 125.9, 121.6, 119.9, 119.0, 113.2, 110.5, 35.5, 33.8, 26.5, 22.8; HRMS m/z ($M + H^+$) calcd for $C_{20}H_{22}N$ 276.1747, found 276.1748.

*Methyl 6-(2,3-Diphenylindolyl)carboxylate (**17**).*[19] The reaction was performed under the same conditions as described above, using methyl 4-bromo-3-(trifluoroacetylamino)benzoate (326 mg, 1.0 mmol, 1.0 equiv), $PdCl_2(PhCN)_2$ (12 mg, 0.03 mmol, 3 mol %), X-Phos **9** (57 mg, 0.12 mmol, 12 mol %), Cs_2CO_3 (977 mg, 3.0 mmol, 3 equiv), phenylacetylene (122 mg, 1.2 mmol, 1.2 equiv), and chlorobenzene (338 mg, 3.0 mmol, 3 equiv). The desired compound **17** was obtained as pale brown solid (216 mg, 66% yield): mp 234−236 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.59 (bs, 1H), 8.20 (s, 1H), 7.84−7.68 (m, 2H), 7.47−7.34 (m, 10H), 3.95 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 168.1, 137.5, 135.1, 134.4, 132.3, 132.1, 130.1, 128.2, 128.9, 128.7, 128.3, 126.6, 124.2, 121.5 119.2, 115.4, 113.3, 52.0; LC-MSD (API-ES, positive) m/z = 328 ($M + H^+$).

*Methyl 6-[2-(p-Methylphenyl)-3-phenylindolyl]carboxylate (**18**).*[4c] The reaction was performed under the same conditions as described above, using methyl 4-bromo-3-(trifluoroacetylamino)-benzoate (326 mg, 1.0 mmol, 1.0 equiv), $PdCl_2(PhCN)_2$ (12 mg, 0.03 mmol, 3 mol %), X-Phos **9** (57 mg, 0.12 mmol, 12 mol %), Cs_2CO_3 (977 mg, 3.0 mmol, 3 equiv), *p*-methylphenylacetylene (139 mg, 1.2 mmol, 1.2 equiv), and chlorobenzene (338 mg, 3.0 mmol, 3 equiv). The desired compound **18** was obtained as a pale brown solid (205 mg, 60% yield): mp 227−229 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 8.45 (s, 1H), 8.18 (bs, 1H), 7.83−7.81 (m, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.43−7.28 (m, 7H), 7.15 (d, J = 8.0 Hz, 2H), 3.93 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (400 MHz, $CDCl_3$) δ 168.3, 138.3, 137.7, 135.1, 134.6, 132.4, 130.1, 129.5, 129.1, 128.7, 128.2, 126.5, 123.9, 121.4, 119.1, 115.0, 113.2, 52.0, 21.3; LC-MSD (API-ES, positive) m/z = 342 ($M + H^+$).

*2,3-Diphenyl-5-cyano-1H-indole (**19**).*[4c] The reaction was performed under the same conditions as described above, using 3-bromo-4-(trifluoroacetylamino)benzonitrile (293 mg, 1.0 mmol, 1.0 equiv), $PdCl_2(PhCN)_2$ (12 mg, 0.03 mmol, 3 mol %), X-Phos **9** (57 mg, 0.12 mmol, 12 mol %), Cs_2CO_3 (977 mg, 3.0 mmol, 3 equiv), phenylacetylene (122 mg, 1.2 mmol, 1.2 equiv), and chlorobenzene (338 mg, 3.0 mmol, 3 equiv). The desired compound **19** was obtained as a pale brown solid (270 mg, 92% yield): decomposed at 157 °C. ^1H NMR (400 MHz, DMSO-d_6) δ 12.20 (s, 1H), 7.89 (s, 1H), 7.62−7.30 (m, 12H); ^{13}C NMR (400 MHz, DMSO-d_6) δ (ppm) 137.7, 136.5,

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133.7, 131.3, 129.7, 128.8, 128.6, 128.3, 128.2, 127.6, 126.6, 124.6, 124.0, 120.4, 113.8, 112.7, 101.8.

*2-Phenyl-3-(p-methoxycarbonylphenyl)-5-cyano-1H-indole (**20**).* The reaction was performed under the same conditions as described above, using 3-bromo-4-(trifluoroacetylamino)benzonitrile (293 mg, 1.0 mmol, 1.0 equiv), $PdCl_2(PhCN)_2$ (12 mg, 0.03 mmol, 3 mol %), X-Phos **9** (57 mg, 0.12 mmol, 12 mol %), Cs_2CO_3 (977 mg, 3.0 mmol, 3 equiv), phenylacetylene (122 mg, 1.2 mmol, 1.2 equiv), and methyl 4-chlorobenzoate (512 mg, 3.0 mmol, 3 equiv). The desired compound **20** was obtained as a pale brown solid (257 mg, 73% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.90 (s, 1H), 8.08−7.97 (m, 3H), 7.63−7.31 (m, 9H), 3.95 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 167.0, 138.8, 137.6, 137.1, 131.2, 130.2, 129.8, 129.1, 128.9, 128.5, 128.4, 128.3, 125.7, 125.1, 120.5, 114.4, 112.05, 104.0, 52.2; HRMS *m*/*z* (M + H$^+$) calcd for $C_{23}H_{17}N_2O_2$ 353.1285, found 353.1282.

■ ASSOCIATED CONTENT

Supporting Information

Copies of ^{1}H and ^{13}C NMR of all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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