JOC The Journal of Organic Chemistry

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Synthesis of Polysubstituted 5-Azaindoles via Palladium-Catalyzed Heteroannulation of Diarylalkynes

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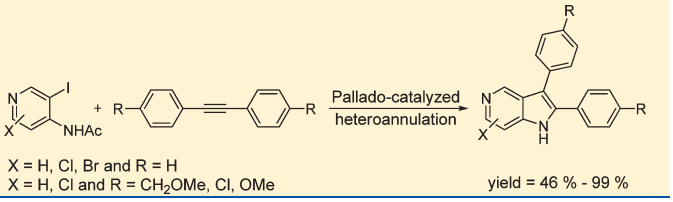
Supporting Information

ABSTRACT: A general and efficient procedure for the synthesis of functionalized 5-azaindoles through the catalyzed heteroannulation of 4-acetamido-3-iodopyridines and diarylalkynes is described. The reaction allows the preparation of a variety of substituted 2,3-diaryl-5-azaindoles in good to excellent yields.



Azaindoles,[1−3] also known as pyrrolopyridines or diazaindenes, constitute an important class of heterocyclic compounds possessing a broad range of biological activities. While acting as indole isosteres, or as tryptophan and purine base analogues, the extra nitrogen atom usually brings to these scaffolds a better solubility and often a better bioavailability than their indole counterparts. Recently, azaindoles have been established as very promising candidates in the drug discovery of anthelmintic agents,[4] angiotensin inhibitors,[5] dopamine D4 ligands,[6] thrombin inhibitors,[7] coagulation factors inhibitors (Xa, VIIa),[8,9] kinase inhibitors (p38, VEGFR, MK-2, Chk1, B-Raf),[10−14] 5-HT$_6$ receptor ligands,[15,16] HIV-1 inhibitors,[17] and CB$_2$ agonists.[18]

Although many efficient synthetic strategies have been devoted to the preparation of indole derivatives,[19] the preparation of their aza analogs remains particularly challenging due to the electron-deficient nature of the pyridine ring. Among the azaindole family, the 5-azaindoles are even more difficult to synthesize.[1−3] Almost all the methods currently employed for the preparation of the indole core, such as the Madelung reaction,[20] the Fischer synthesis,[21,22] the Leimbruger−Batcho reaction,[23] the Bischler−Napieralski reaction,[24] or the Hemetsberger−Knittel reaction,[25,26] cannot be efficiently transposed to 5-azaindoles as they usually proceed with low yields and/or cannot be generalized.

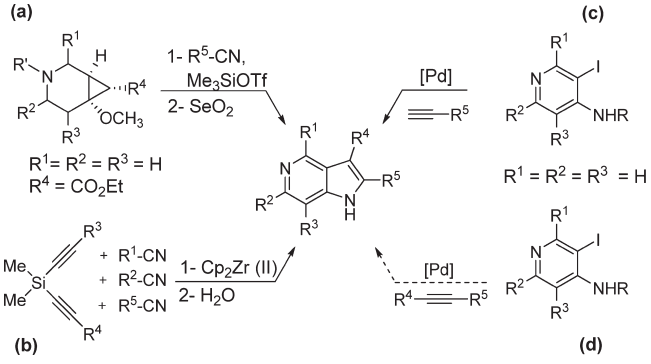
In our ongoing research project aiming at the evaluation of 2,3-diaryl-5-azaindoles (R^4 = R^5 = aryl) as kinase inhibitors, we required a straightforward, efficient, and flexible access to these structures. Very recently, some improved methods have been reported for the synthesis of 5-azaindoles: on one hand, the [3 + 2] dipolar cycloaddition between nitriles and a 3,4-cyclopropanopiperidine, followed by SeO_2 oxidation (Scheme 1, path a),[27] and, on the other hand, the zirconocene coupling of Si-tethered diyne with three molecules of organonitriles (Scheme 1, path b).[28,29] However, neither of these methods were suitable for us as they either require the synthesis of complex starting materials or are not flexible enough.

We thus turned our attention to potentially more straightforward palladium-catalyzed processes, well-known for the synthesis of indole derivatives,[30−32] starting from easily available aminoiodo- or aminobromopyridines. Nevertheless, the tandem Sonogashira/5-endo cyclization (Scheme 1, path c) does not allow introducing the required aryl substituent in the 3 position (R^4).[33,34] For these reasons, we decided to focus on the Larock type heteroannulation with diarylalkynes (Scheme 1, path d).[35] To the best of our knowledge, the single example reported in literature shows a quite sluggish reactivity of a diarylacetylene with 3-iodo-4-aminopyridine, the corresponding 3,4-diphenyl-5-azaindole being obtained in low yield (22%).[36] Another reported application of Larock heteroannulation led to the formation of tricyclic or tetracyclic 5-azaindoles.[37,38] We wish to report here an efficient and easy access to functionalized 5-azaindoles through the heteroannulation of 3-iodo-4-acetamidopyridines with diarylalkynes.

At the outset of our study, we investigated the reaction of 4-acetamido-3-iodopyridine (**1**) and diphenylacetylene (**2**) (5 equiv) with Pd(OAc)$_2$ (5 mol %), a base (5 equiv), and an additive (1 equiv) in DMF at 100 °C (Table 1) during 48 h.[39] Using either LiCl or *n*-Bu$_4$NCl as additives, several bases were evaluated. No conversion or poor yields were observed when potassium carbonate, potassium acetate, or sodium acetate were used as base (Table 1, entries 1−5). Unexpectedly, although usually poorly efficient for indole synthesis, sodium carbonate proved to be the most efficient base,[39] as the 5-azaindole **3** was obtained in reasonable yields of 52% and 58%, respectively, with *n*-Bu$_4$NCl and LiCl (Table 1, entries 6 and 7). It is noteworthy that, under the same reaction conditions, unprotected, mesylated, and tosylated 3-iodo-4-aminoaminopyridines are completely unreactive, thus confirming the decisive influence of the *N*-protecting group.[40]

Received: March 4, 2011
Published: April 18, 2011

Scheme 1. Recent Methods for 5-Azaindole Synthesis

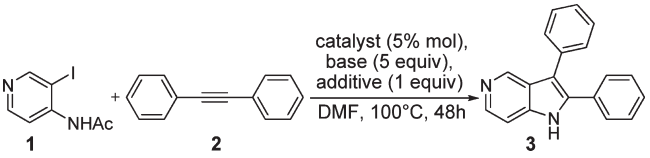


No conversion was observed when DMF was substituted by a less polar solvent like toluene. The influence of the halide source was then investigated. Pleasingly, when LiCl was substituted by either LiBr or LiI the reaction was achieved in very good yield of 89% and 83%, respectively (Table 1, entries 8 and 9).[41] We pursued our studies by optimization of the palladium catalyst and concentration of the aminopyridine. The use of $PdCl_2(PhCN)_2$ afforded the desired 5-azaindole **3** in good yield (84%), comparable to that obtained with $Pd(OAc)_2$ (Table 1, entry 10). On the other hand, a quantitative yield was obtained when using the triphenylphosphine-stabilized palladium complex $PdCl_2(PPh_3)_2$ (Table 1, entry 11). The substrate concentration also plays a significant role in this process. The reaction was not complete when the concentration was lower than 0.2 M (Table 1, entries 14 and 15) and degradation was observed when the concentration was higher than 0.5 M (Table 1, entry 13). We next evaluated the impact of decreasing the stoichiometry of the alkyne using either LiCl or LiBr as additives. Using 3 equiv of alkyne **2**, the desired 5-azaindole **3** was obtained in excellent yields of 89% (LiCl) and 95% (LiBr) (Table 1, entries 16 and 19); the conversion became incomplete with a lower amount of alkyne (Table 1, entries 17, 18, 20, and 21).

With these optimized reaction conditions in hand (Table 1, entry 19), we next examined the reactivity of chlorine or bromine substituted 3-iodo-4-(acetamido)pyridines **4**−**9** (Table 2). When the substrate bore a chlorine in position 2, the corresponding azaindole **10** was obtained in a good yield of 80% (Table 2, entry 1), whereas a bromine in the same position led to an incomplete conversion and afforded **11** in 42% yield (Table 2, entry 2). 5- and 6-chloro-substituted substrates **6** and **8** led to 5-azaindoles **12** and **14** in good to excellent yields of 79% and 99%, respectively (Table 2, entries 3 and 5). Although 5- and 6-bromo compounds **7** and **9** were more slugglish to react, the corresponding 5-azaindoles **13** and **15** were obtained in satisfactory yields. In view of these results, it seems that chloro-substituted acetamidopyridines are better substrates than their bromo counterparts, which may be explained by a better chemoselectivity during the palladium(0) oxidative addition. Nonetheless, our reaction conditions allow the introduction of chlorine or bromine in every positions of the pyridine ring, thus opening the door to further functionalization of the 5-azaindole core through SNAr reactions or metal-catalyzed coupling processes.[42−44]

We next turned our attention to the synthesis of azaindoles with functionalized diarylacetylenes. For this study, alkynes **16**−**18** were prepared possessing either withdrawing or donating

Table 1. Optimization of the Heteroannulation Reaction between 4-Acetamido-3-iodopyridine (1) and Diphenylacetylene (2)



entry	base	additive	catalyst	[1] M	2 (equiv)	yield (%)
1	K_2CO_3	*n*-Bu_4NCl	$Pd(OAc)_2$	0.2	5	0[a]
2	K_2CO_3	LiCl	$Pd(OAc)_2$	0.2	5	0[a]
3	KOAc	*n*-Bu_4NCl	$Pd(OAc)_2$	0.2	5	24[b]
4	KOAc	LiCl	$Pd(OAc)_2$	0.2	5	28[b]
5	NaOAc	LiCl	$Pd(OAc)_2$	0.2	5	30[b]
6	Na_2CO_3	*n*-Bu_4NCl	$Pd(OAc)_2$	0.2	5	52[b]
7	Na_2CO_3	LiCl	$Pd(OAc)_2$	0.2	5	58[b]
8	Na_2CO_3	LiBr	$Pd(OAc)_2$	0.2	5	89[b]
9	Na_2CO_3	LiI	$Pd(OAc)_2$	0.2	5	83[b]
10	Na_2CO_3	LiCl	$PdCl_2(PhCN)_2$	0.2	5	84[b]
11	Na_2CO_3	LiCl	$PdCl_2(PPh_3)_2$	0.2	5	99
12	Na_2CO_3	LiCl	$PdCl_2(PPh_3)_2$	0.5	5	96
13	Na_2CO_3	LiCl	$PdCl_2(PPh_3)_2$	1	5	29[c]
14	Na_2CO_3	LiCl	$PdCl_2(PPh_3)_2$	0.1	5	86[b]
15	Na_2CO_3	LiCl	$PdCl_2(PPh_3)_2$	0.05	5	62[b]
16	Na_2CO_3	LiCl	$PdCl_2(PPh_3)_2$	0.2	3	89[b]
17	Na_2CO_3	LiCl	$PdCl_2(PPh_3)_2$	0.2	2	42[b]
18	Na_2CO_3	LiCl	$PdCl_2(PPh_3)_2$	0.2	1	24[b]
19	Na_2CO_3	LiBr	$PdCl_2(PPh_3)_2$	0.2	3	95
20	Na_2CO_3	LiBr	$PdCl_2(PPh_3)_2$	0.2	2	80[b]
21	Na_2CO_3	LiBr	$PdCl_2(PPh_3)_2$	0.2	1	50[b]

[a] Starting material was recovered. [b] Incomplete conversion. [c] Partial degradation was observed.

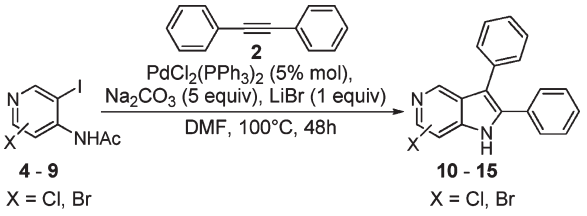
electronic effects. When the aromatic rings possessed a chlorine (**16**) or a methoxy group (**17**), the corresponding azaindoles were obtained in good yields of 76% and 85%, respectively (Table 3, entries 1−2). However, the use of the very electron-deficient bis-nitroalkyne did not promote the desired heteroannulation, probably because of its poor ability to complex palladium (Table 3, entry 3). Notably, we could combine the use of chloro-substituted acetamidopyridines with the electron-rich 1,2-bis(4-methoxyphenyl)alkyne and could obtain the corresponding functionalized 5-azaindoles **22** and **23** in good yields (Table 3, entries 4 and 5).

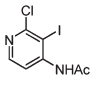
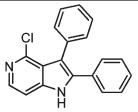
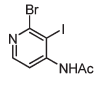
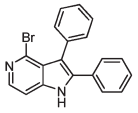
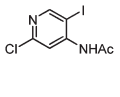
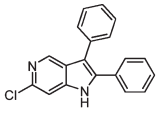
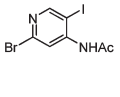
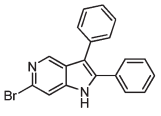
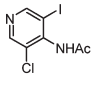
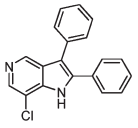
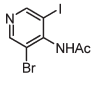
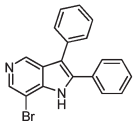
Finally, in order to evaluate the regioselectivity of this process, the reaction was carried out with unsymmetrical alkynes. The desired 5-azaindoles were obtained with good yields of 77%, 89%, and 87% for the methoxymethyl, chlorine, and methoxy groups, respectively (Table 4, entries 1−3). Similar to the use of symmetrical alkynes, the substitution of an aromatic ring by a nitro group was detrimental to the reaction (Table 4, entry 4). In all cases, products were formed without any regioselectivity and the azaindoles isolated as a mixture of both regioisomers.

In summary, we have developed a straightforward and efficient access to functionalized 5-azaindoles through the palladium-catalyzed heteroannulation of 3-iodoacetamidopyridines with diarylalkynes. This process allows the preparation of a wide

dx.doi.org/10.1021/jo200480h |*J. Org. Chem.* 2011, 76, 4734–4740

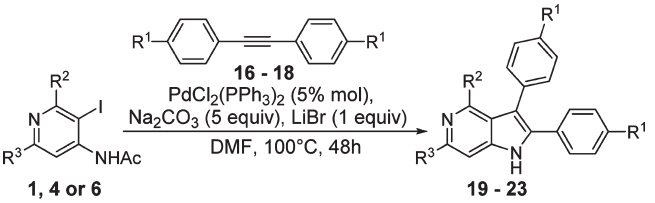
Table 2. Heteroannulation Reaction between Halogenated 4-Acetamido-3-iodopyridines 4−9 and Diphenylacetylene (2)



entry	aminopyridine	azaindole	Yield (%)
1	4 	10 	80
2	5 	11 	42[a]
3	6 	12 	79
4	7 	13 	60
5	8 	14 	99
6	9 	15 	79

[a] Isolated as a mixture with **5**.

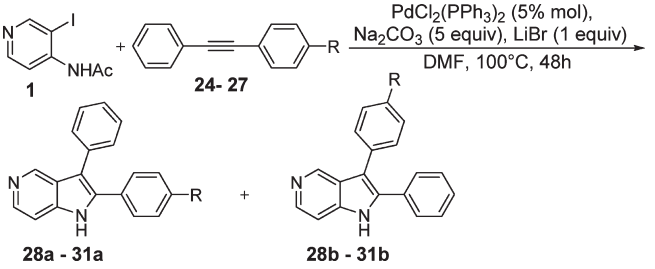
Table 3. Heteroannulation Reaction between 4-Acetamido-3-iodopyridines 1, 4, and 6 and Symmetrical Diarylacetylenes 16−18



entry	R^1	R^2	R^3	product	yield (%)
1	Cl	H	H	**19**	76
2	OMe	H	H	**20**	85
3	NO_2	H	H	**21**	[a]
4	OMe	Cl	H	**22**	46
5	OMe	H	Cl	**23**	66

[a] Starting material was recovered.

Table 4. Heteroannulation Reaction between 4-Acetamido-3-iodopyridine (1) and Unsymmetrical Diarylacetylenes 24−27



entry	alkyne	R	products	ratio[a]	yield (%)
1	**24**	CH_2OMe	**28a/28b**	1/1	77
2	**25**	Cl	**29a/29b**	1/1	89
3	**26**	OMe	**30a/30b**	1/1	87
4	**27**	NO_2	**31a/31b**		[b]

[a] Determined by ^{1}H NMR spectroscopy. [b] Degradation of the reaction mixture

range of 5-azaindoles possessing various substituents on both the pyridine and the pyrrole rings. The diversification of these scaffolds through palladium-catalyzed cross-coupling reactions is currently being evaluated. All the compounds prepared in this study are currently being evaluated as kinase inhibitors, and their biological activities will be reported in due course.

EXPERIMENTAL SECTION

***N*-(3-Iodopyridin-4-yl)acetamide (1).** Under an argon atmosphere, acetic anhydride (0.77 mL, 6.74 mmol) and triethylamine (1.41 mL, 10.11 mmol) were added to a solution of 4-amino-3-iodopyridine (1.48 g, 6.74 mmol) in CH_2Cl_2 (13.5 mL). The mixture was then stirred for 18 h at room temperature. After concentration under vacuum, the crude product was purified by chromatography (silica gel, EtOAc/cyclohexane 80:20 to 90:10) to give 1.58 g of a mixture of *N*-(3-iodopyridin-4-yl)acetamide and *N*-acetyl-*N*-(3-iodopyridin-4-yl)acetamide. This fraction was hydrolyzed with lithium hydroxide (0.21 g, 5.07 mmol) in 6 mL of H_2O/THF 1:1 (v:v) for 30 min. When the hydrolysis was complete, the solution was extracted with EtOAc (3 × 6 mL), and the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum to yield 1.27 g (72%) of the title compound as a white solid. Mp: 115 °C (recrystallized from a mixture of EtOAc/heptane). R_f = 0.31 (EtOAc). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.82 (s, 1H), 8.41 (d, J = 5.4 Hz, 1H), 8.34 (d, J = 5.4 Hz, 1H), 7.61 (br s, 1H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 168.6, 157.1, 150.1, 144.7, 115.0, 87.2, 25.0. IR (NaCl, thin film) ν (cm^{-1}): 2921, 1704, 1572, 1496, 1399, 1302, 1237, 1012, 751. LRMS (ES^+): m/z = 263.0 ($[M + H]^+$, 100). HRMS (ES^+): calcd for $C_7H_8N_2OI$ $[M + H]^+$: 262.9681, found 262.9691.

***N*-(2-Chloro-3-iodopyridin-4-yl)acetamide (4).** General procedure A for acetylation reaction: Under argon atmosphere, 4-amino-2-chloro-3-iodopyridine (3.00 g, 11.76 mmol) was added to a stirred solution of sodium hydride (3.02 g, 70.56 mmol) in THF (12 mL). After 5 min, acetyl chloride (5.00 mL, 70.56 mmol) was added, and the

dx.doi.org/10.1021/jo200480h |*J. Org. Chem.* 2011, 76, 4734–4740

solution was warmed to room temperature until completion. The mixture was cooled at 0 °C, and then MeOH (5 mL) followed by H_2O (5 mL) were added. The aqueous layer was extracted with EtOAc (3 × 10 mL), and the combined organic layers were concentrated under vacuum. The fraction composed of *N*-(2-chloro-3-iodopyridin-4-yl)acetamide and *N*-acetyl-*N*-(2-chloro-3-iodopyridin-4-yl)acetamide was hydrolyzed with lithium hydroxide (0.33 g, 7.97 mmol) in 14 mL of H_2O/THF 1:1 (v/v) for 30 min. When the hydrolysis was complete, the solution was extracted with EtOAc (3 × 30 mL), the combined organic layers were dried over $MgSO_4$, and concentrated under vacuum. The crude product was purified by chromatography (silica gel, cyclohexane/EtOAc 50:50) to give 1.79 g (51%) of the desired compound as a white solid. Mp: 149 °C (recrystallized from a mixture of EtOAc/heptane). R_f = 0.33 (EtOAc/cyclohexane 4/6). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.20 (d, J = 5.5 Hz, 1H), 8.15 (d, J = 5.5 Hz, 1H), 7.85 (br s, 1H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 168.3, 155.1, 149.2, 147.8, 112.4, 88.9, 25.0. IR (NaCl, thin film) ν (cm^{-1}): 3300, 1680, 1560, 1493, 1348, 764, 750. LRMS (ES$^+$): m/z = 295.0 ([M + H]$^+$, 64), 297.0 (22). HRMS (ES$^-$): calcd for $C_7H_5N_2OClI$ [M]$^-$ 294.9135, found 294.9130.

***N*-(2-Bromo-3-iodopyridin-4-yl)acetamide (5).** Compound **5** was prepared following the general procedure A with 387 mg (1.29 mmol) of 4-amino-2-bromo-3-iodopyridine. The crude product was purified by chromatography (silica gel, cyclohexane/EtOAc 60:40) to give 277 mg (63%) of compound **5** as a white solid. Mp: 170 °C (recrystallized from a mixture of EtOAc/heptane). R_f = 0.27 (cyclohexane/EtOAc: 6/4). ^{1}H NMR (MeOD, 300 MHz) δ (ppm): 8.19 (d, J = 5.4 Hz, 1H), 7.89 (d, J = 5.4 Hz, 1H), 2.25 (s, 3H). ^{13}C NMR (MeOD, 75 MHz) δ (ppm): 171.7, 151.1, 150.6, 150.1, 117.6, 97.1, 24.2. IR (CH_2Cl_2), ν (cm^{-1}): 3361, 2932, 2857, 1718, 1558, 1488, 1343, 1242. LRMS (ES$^-$): m/z = 338.8 ([M − H]$^-$, 100), 340.8 (67); HRMS (ES$^+$): calcd for $C_7H_7N_2OBrI$ [M + H]$^+$ 340.8787, found 340.8802.

***N*-(2-Chloro-5-iodopyridin-4-yl)acetamide (6).** Compound **6** was prepared following the general procedure A with 501 mg (1.97 mmol) of 4-amino-2-chloro-5-iodopyridine. The crude product was purified by chromatography (silica gel, cyclohexane/EtOAc 80:20 to 70:30) to give 366 mg (63%) of compound **6** as a white solid. Mp: 181 °C (recrystallized from a mixture of EtOAc/heptane). R_f = 0.24 (cyclohexane/EtOAc 6/4). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.55 (s, 1H), 8.40 (s, 1H), 7.62 (br s, 1H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 168.7, 156.2, 153.0, 146.4, 114.8, 85.0, 25.2. IR (NaCl, thin film) ν (cm^{-1}): 3284, 2924, 1679, 1555, 1480, 1350, 1261, 1101. LRMS (ES$^+$): m/z = 297.1 ([M + H]$^+$, 13), 299.0 (31). HRMS (ES$^+$): calcd for $C_7H_7N_2OClI$ [M + H]$^+$ 296.9292, found 296.9300.

***N*-(2-Bromo-5-iodopyridin-4-yl)acetamide (7).** Compound **7** was prepared following the general procedure A with 363 mg (1.21 mmol) of 4-amino-2-bromo-5-iodopyridine. The crude product was purified by chromatography (silica gel, cyclohexane/EtOAc 80:20 to 60:40) to give 210 mg (51%) of compound **7** as a white solid. Mp: 202 °C (recrystallized from a mixture of EtOAc/heptane). R_f = 0.32 (cyclohexane/EtOAc 6/4). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.57 (s, 1H), 8.54 (s, 1H), 7.59 (br s, 1H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ (ppm): 168.6, 156.6, 146.0, 143.3, 118.4, 85.9, 25.1. IR (CH_2Cl_2) ν (cm^{-1}): 3283, 1676, 1549, 1341, 1277, 1091. LRMS (ES$^+$): m/z = 340.9 ([M + H]$^+$, 100), 342.9 (96). HRMS (ES$^+$): calcd for $C_7H_7N_2OBrI$ [M + H]$^+$ 340.8787, found 340.8781.

***N*-(3-Chloro-5-iodopyridin-4-yl)acetamide (8).** Compound **8** was prepared following the general procedure A with 1.84 g (7.22 mmol) of 4-amino-3-chloro-5-iodopyridine. The crude product was purified by chromatography (silica gel, cyclohexane/EtOAc 60:40 to 20:80) to give 1.39 g (65%) of compound **8** as a white solid. Mp: 204 °C (recrystallized from a mixture of EtOAc/heptane). R_f = 0.17 (cyclohexane/EtOAc 6/4). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 8.85 (s, 1H), 8.56 (s, 1H), 7.04 (br s, 1H), 2.27 (s, 3H). ^{13}C NMR (MeOD, 75 MHz) δ (ppm): 171.3, 157.3, 150.3, 146.9, 131.9, 99.5, 22.7. IR (CH_2Cl_2) ν (cm^{-1}): 3184, 1667, 1538, 1492, 1396, 1227. LRMS (ES$^+$): m/z = 296.9 ([M + H]$^+$, 100), 298.9 (34). HRMS (ES$^+$): calcd for $C_7H_7N_2OClI$ [M + H]$^+$ 296.9292, found 296.9297.

***N*-(3-Bromo-5-iodopyridin-4-yl)acetamide (9).** Compound **9** was prepared following the general procedure A with 1.08 g (3.62 mmol) of 4-amino-3-bromo-5-iodopyridine. The crude product was purified by chromatography (silica gel, cyclohexane/EtOAc 70:30 to 30:70) to give 553 mg (45%) of compound **9** as a white solid. Mp: 221 °C (recrystallized from a mixture of EtOAc/heptane). R_f = 0.18 (cyclohexane/EtOAc: 6/4). ^{1}H NMR (MeOD, 300 MHz) δ (ppm): 8.82 (s, 1H), 8.62 (s, 1H), 2.12 (s, 3H). ^{13}C NMR (MeOD, 75 MHz) δ (ppm): 171.3, 157.9, 152.9, 148.4, 122.4, 99.9, 22.8. IR (CH_2Cl_2) ν (cm^{-1}): 3194, 1668, 1538, 1494, 1276. LRMS (ES$^+$): m/z = 340.8 ([M + H]$^+$,100), 342.8 (98). HRMS (ES$^+$): calcd for $C_7H_7N_2OBrI$ [M + H]$^+$ 340.8787, found 340.8800.

2,3-Diphenyl-1*H*-pyrrolo[3,2-*c*]pyridine (3). General procedure B for heteroannulation reaction: Under argon atmosphere, to a solution of 4-acetamido-2-iodopyridine (86 mg, 0.32 mmol), $PdCl_2(PPh_3)_2$ (11 mg, 0.016 mmol), lithium bromide (28 mg, 0.32 mmol), and sodium carbonate (170 mg, 1.6 mmol) in anhydrous DMF (1.6 mL) was added diphenylacetylene **2** (171 mg, 0.96 mmol). The mixture was stirred at 100 °C for 48 h and then cooled to room temperature and hydrolyzed with 2 mL of water. After extraction with EtOAc (3 × 4 mL), the combined organic layers were dried over $MgSO_4$ and concentrated under vacuum. The purification of the residue by chromatography (silica gel, methanol/EtOAc/cyclohexane 0:70:30 to 10:90:00) afforded 82 mg (95%) of the 5-azaindole **3** as a white solid. Mp: 228 °C (recrystallized from methanol). R_f = 0.28 (EtOAc/methanol: 9/1). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 12.11 (s, 1H), 8.81 (s, 1H), 8.27 (d, J = 5.7 Hz, 1H), 7.45 (d, J = 5.7 Hz, 1H), 7.51−7.29 (m, 10H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 141.9, 140.9, 139.5, 135.0, 134.0, 131.6, 129.7 (2C), 128.7 (2C), 128.6 (2C), 128.4 (2C), 128.1, 126.5, 124.9, 112.6, 106.6. IR (CH_2Cl_2) ν (cm^{-1}): 3446, 3043, 1465, 1262, 752, 699. LRMS (ES$^+$): m/z = 271.1 ([M + H]$^+$, 100); HRMS (ES$^+$): calcd for $C_{19}H_{15}N_2$ [M + H]$^+$ 271.1235, found 271.1235.

4-Chloro-2,3-diphenyl-1*H*-pyrrolo[3,2-*c*]pyridine (10). Compound **10** was prepared following the general procedure B with 1.00 g (3.28 mmol) of *N*-(2-chloro-3-iodopyridin-4-yl)acetamide **4**. The crude product was purified by chromatography (silica gel, cyclohexane/EtOAc 90:10 to 70:30) to give 0.82 g (80%) of compound **10** as a yellow solid. Mp: 249 °C. R_f = 0.29 (EtOAc/methanol 9/1). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 12.38 (s, 1H), 7.99 (d, J = 5.7 Hz, 1H), 7.45 (d, J = 5.7 Hz, 1H), 7.46−7.29 (m, 10H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 142.0, 140.9, 139.5, 136.5, 134.1, 131.7 (2C), 131.1, 128.4 (2C), 128.1 (3C), 127.8 (2C), 127.2, 121.6, 113.3, 107.0. IR (NaCl, thin film) ν (cm^{-1}): 3640, 3056, 1444, 1260, 765, 750, 697. LRMS (ES$^+$): m/z = 305.1 ([M + H]$^+$, 100), 307.1 (36). HRMS (ES$^+$): calcd for $C_{19}H_{14}N_2Cl$ [M + H]$^+$ 305.0846, found 305.0854.

4-Bromo-2,3-diphenyl-1*H*-pyrrolo[3,2-*c*]pyridine (11). Compound **11** was prepared following the general procedure B with 78 mg (0.23 mmol) of *N*-(2-bromo-3-iodopyridin-4-yl)acetamide **5**. The crude product was purified by chromatography (silica gel, cyclohexane/EtOAc 90:10 to 70:30) to give 34 mg (42%) of compound **11** in mixture with starting material. The yield was evaluated by NMR. R_f = 0.24 (cyclohexane/EtOAc: 6/4). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 12.37 (s, 1H), 7.95 (d, J = 5.4 Hz, 1H), 7.46 (d, J = 5.4 Hz, 1H), 7.37−7.27 (m, 10H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 150.0, 141.2, 140.9, 137.5, 134.8, 133.8, 133.0 (2C), 132.0, 129.3 (2C), 129.0 (2C), 128.6 (2C), 128.2, 124.6, 114.8, 108.1. IR (CH_2Cl_2) ν (cm^{-1}): 3442, 3049, 1557, 1440, 1262, 755, 701. LRMS (ES$^+$): m/z = 349.0 ([M + H]$^+$, 43), 351.0 (99). HRMS (ES$^+$): calcd for $C_{19}H_{14}N_2Br$ [M + H]$^+$ 349.0340, found 349.0356.

6-Chloro-2,3-diphenyl-1*H*-pyrrolo[3,2-*c*]pyridine (12). Compound **12** was prepared following the general procedure B with 100 mg (0.34 mmol) of *N*-(2-chloro-5-iodopyridin-4-yl)acetamide **6**. The crude product was purified by chromatography (silica gel, cyclohexane/EtOAc 90:10 to 70:30) to give 81 mg (79%) of compound **12** as a yellow solid. Mp: 262 °C. R_f = 0.55 (cyclohexane/EtOAc: 6/4). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 12.22 (s, 1H), 8.54 (s, 1H), 7.47−7.39 (m, 11H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 141.9, 141.5, 141.0, 136.4, 133.3, 131.0, 129.5 (2C), 128.8 (2C), 128.6 (2C), 128.4, 128.3 (2C), 126.8, 124.6, 112.6, 105.6. IR (NaCl, thin film) ν (cm^{-1}): 3062, 1600, 1459, 1268, 1061, 765, 696, 614. LRMS (ES$^+$): m/z = 305.1 ([M + H]$^+$, 100), 307.1 (33); HRMS (ES$^+$): calcd for $C_{19}H_{14}N_2Cl$ [M + H]$^+$ 305.0846, found 305.0858.

6-Bromo-2,3-diphenyl-1*H*-pyrrolo[3,2-*c*]pyridine (13). Compound **13** was prepared following the general procedure B with 80 mg (0.23 mmol) of *N*-(2-bromo-5-iodopyridin-4-yl)acetamide **7**. The crude product was purified by chromatography (silica gel, cyclohexane/EtOAc 90:10 to 70:30) to give 49 mg (60%) of compound **13** as a yellow solid. Mp: 238 °C. R_f = 0.52 (cyclohexane/EtOAc: 6/4). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 12.22 (s, 1H), 8.52 (s, 1H), 7.57 (s, 1H), 7.45−7.36 (m, 10H). ^{13}C NMR (DMSO-d_6, 75 MHz), δ (ppm): 141.6, 141.5, 136.3, 133.2, 132.0, 131.0, 129.6 (2C), 128.8 (2C), 128.6 (2C), 128.5, 128.4 (2C), 126.8, 124.9, 112.5, 109.4. IR (CH_2Cl_2) ν (cm^{-1}): 3442, 2928, 1556, 1460, 1268, 1049, 765, 696. LRMS (ES$^+$): m/z = 349.0 ([M + H]$^+$, 100), 351.0 (100). HRMS (ES$^+$): calcd for $C_{19}H_{14}N_2Br$ [M + H]$^+$ 349.0340, found 349.0348.

7-Chloro-2,3-diphenyl-1*H*-pyrrolo[3,2-*c*]pyridine (14). Compound **14** was prepared following the general procedure B with 82 mg (0.28 mmol) of *N*-(3-chloro-5-iodopyridin-4-yl)acetamide **8**. The crude product was purified by chromatography (silica gel, cyclohexane/EtOAc 90:10 to 70:30) to give 85 mg (99%) of compound **14** as a yellow solid. Mp: 210 °C. R_f = 0.34 (cyclohexane/EtOAc: 6/4). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 12.40 (s, 1H), 8.70 (d, J = 1.8 Hz, 1H), 8.29 (d, J = 1.8 Hz, 1H), 7.50−7.35 (m, 10H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 140.3, 139.1, 137.0, 136.6, 133.3, 130.8, 129.6 (2C), 129.3 (2C), 128.8 (2C), 128.4, 128.3 (2C), 126.8, 126.2, 114.1, 113.6. IR (CH_2Cl_2) ν (cm^{-1}): 3430, 2927, 1716, 1462, 1266, 1230, 756, 708. LRMS (ES$^+$): m/z = 305.0 ([M + H]$^+$, 100), 307.0 (37); HRMS (ES$^+$): calcd for $C_{19}H_{14}N_2Cl$ [M + H]$^+$ 305.0846, found 305.0856.

7-Bromo-2,3-diphenyl-1*H*-pyrrolo[3,2-*c*]pyridine (15). Compound **15** was prepared following the general procedure B with 110 mg (0.32 mmol) of *N*-(3-bromo-5-iodopyridin-4-yl)acetamide **9**. The crude product was purified by chromatography (silica gel, cyclohexane/EtOAc 90:10 to 70:30) to give 89 mg (79%) of compound **15** as a yellow solid. Mp: 248 °C. R_f = 0.37 (cyclohexane/EtOAc: 6/4). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 12.28 (s, 1H), 8.72 (s, 1H), 8.37 (s, 1H), 7.49−7.32 (m, 10H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 141.5, 140.7, 138.1, 137.0, 133.3, 130.8, 129.6 (2C), 129.4 (2C), 128.8 (2C), 128.4, 128.3 (2C), 126.8, 126.1, 113.7, 102.7. IR (CH_2Cl_2) ν (cm^{-1}): 3428, 2929, 1716, 1462, 1267, 756, 697. LRMS (ES$^+$): m/z = 349.0 ([M + H]$^+$, 100), 351.0 (100); HRMS (ES$^+$): calcd for $C_{19}H_{14}N_2Br$ [M + H]$^+$ 349.0340, found 349.0348.

1-(Methoxymethyl)-4-(phenylethynyl)benzene (24). Under argon atmosphere, ethynylbenzene (250 μL, 2.3 mmol) was added to a mixture of 1-iodo-4-(methoxymethyl)benzene (538 mg, 2.2 mmol), $PdCl_2(PPh_3)_2$ (15 mg, 0.02 mmol), CuI (17 mg, 0.88 mmol), and triethylamine (445 μL, 3.3 mmol) in anhydrous THF (5.5 mL). The mixture was stirred at room temperature until the reaction was complete and then filtered over Celite and concentrated under vacuum. The crude product was purified by chromatography (silica gel, pentane/Et_2O 95:5) to give 455 mg (94%) of compound **24** as a yellow oil. R_f = 0.29 (cyclohexane/EtOAc: 95/5). ^{1}H NMR ($CDCl_3$, 300 MHz) δ (ppm): 7.58−7.53 (m, 4H), 7.39−7.26 (m, 5H), 4.48 (s, 2H), 3.42 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ (ppm): 138.4, 131.6 (2C), 131.5 (2C), 128.3 (2C), 128.2, 127.5 (2C), 123.2, 122.4, 89.3, 89.2, 74.2, 58.1. IR (CH_2Cl_2) ν (cm^{-1}): 2929, 1510, 1263, 1098,732, 718, 736. LRMS (MALDI): m/z = 222.1 (M$^+$, 100). HRMS (MALDI): calcd for $C_{16}H_{14}O$ [M]$^+$ 222.1039, found 222.1037.

Alkynes **16**,[45] **17**,[46] **18**,[47] **25**,[48] **26**,[49] and **27**[50] were prepared as previously described.

2,3-Bis(4-chlorophenyl)-1*H*-pyrrolo[3,2-*c*]pyridine (19). Compound **19** was prepared following the general procedure B with 81 mg (0.3 mmol) of *N*-(3-iodopyridin-4-yl)acetamide **1** and 222 mg (0.9 mmol) of 1,2-bis(4-chlorophenyl)ethyne **16**. The crude product was purified by chromatography (silica gel, cyclohexane/EtOAc/methanol 30:70:0 to 0:90:10) to give 77 mg (76%) of compound **19** as a yellow solid. Mp: 227 °C. R_f = 0.33 (EtOAc/methanol 9/1). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 12.15 (s, 1H), 8.78 (s, 1H), 8.27 (d, J = 4.2 Hz, 1H), 7.52−7.39 (m, 9H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 142.8, 142.1, 140.4, 135.0, 133.9, 133.5, 132.3 (3C), 131.1 (3C), 129.9 (2C), 129.8 (2C), 125.4, 112.6, 107.6. IR (CH_2Cl_2) ν (cm^{-1}): 3444, 2929, 1464, 1262, 751, 708. LRMS (ES$^+$): m/z = 339.1 ([M + H]$^+$, 100), 341.1 (73). HRMS (ES$^+$): calcd for $C_{19}H_{13}N_2Cl_2$ [M + H]$^+$ 339.0456, found 339.0466.

2,3-Bis(4-methoxyphenyl)-1*H*-pyrrolo[3,2-*c*]pyridine (20). Compound **20** was prepared following the general procedure B with 124 mg (0.47 mmol) of *N*-(3-iodopyridin-4-yl)acetamide **1** and 336 mg (1.41 mmol) of 1,2-bis(4-methoxyphenyl)ethyne **17**. The crude product was purified by chromatography (silica gel, cyclohexane/EtOAc/methanol 30:70:0 to 0:90:10) to give 132 mg (85%) of compound **20** as a yellow solid. Mp: 212 °C. R_f = 0.24 (EtOAc/methanol: 9/1). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 11.85 (s, 1H), 8.69 (s, 1H), 8.19 (d, J = 3.9 Hz, 1H), 7.42−7.29 (m, 5H), 7.00−6.95 (m, 4H), 3.79 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 159.0, 157.8, 141.5, 140.5, 139.1, 134.5, 130.7 (2C), 129.5 (2C), 126.2 (2C), 125.2, 124.0 (2C), 114.2, 114.1, 111.2, 106.4, 55.1, 55.0. IR (CH_2Cl_2) ν (cm^{-1}): 3449, 2966, 1521, 1499, 1466, 1262, 1178, 1033, 736, 722. LRMS (ES$^+$): m/z = 331.2 ([M + H]$^+$, 100). HRMS (ES$^+$): calcd for $C_{21}H_{19}N_2O_2$ [M + H]$^+$ 331.1447, found 331.1463.

4-Chloro-2,3-bis(4-methoxyphenyl)-1*H*-pyrrolo[3,2-*c*]-pyridine (22). Compound **22** was prepared following the general procedure B with 184 mg (0.62 mmol) of *N*-(2-chloro-3-iodopyridin-4-yl)acetamide **4** and 443 mg (1.26 mmol) of 1,2-bis(4-methoxyphenyl)ethyne **17**. The crude product was purified by chromatography (silica gel, cyclohexane/EtOAc 80:20 to 60:40) to give 104 mg (46%) of compound **22** as a yellow solid. Mp: 210 °C. R_f = 0.19 (cyclohexane/EtOAc 6/4). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 12.21 (br s, 1H), 7.95 (d, J = 5.6 Hz, 1H), 7.41 (d, J = 5.6 Hz, 1H), 7.30 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.2 Hz, 2H), 6.94 (d, J = 9.2 Hz, 2H), 6.91 (d, J = 9.2 Hz, 2H), 3.79 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 159.0, 158.2, 141.7, 140.7, 139.1, 136.4, 132.8 (2C), 129.3 (2C), 126.2, 123.5, 121.5, 113.9 (2C), 113.2 (2C), 111.8, 106.7, 55.1, 54.9. IR (CH_2Cl_2) ν (cm^{-1}): 3444, 2963, 1614, 1496, 1441, 1248, 1102, 1032, 760, 744. LRMS (ES$^-$): m/z = 363.1 ([M-H]$^-$, 100), 365.1 (34); HRMS (ES$^-$): calcd for $C_{21}H_{16}N_2O_2Cl$ [M − H]$^-$ 363.0900, found 363.0915.

6-Chloro-2,3-bis(4-methoxyphenyl)-1*H*-pyrrolo[3,2-*c*]-pyridine (23). Compound **23** was prepared following the general procedure B with 734 mg (2.48 mmol) of *N*-(2-chloro-5-iodopyridin-4-yl)acetamide **6** and 1.97 g (7.44 mmol) of 1,2-bis(4-methoxyphenyl)ethyne **17**. The crude product was purified by chromatography (silica gel, cyclohexane/EtOAc 80:20 to 70:30) to give 595 mg (66%) of compound **23** as a yellow solid. Mp: 119 °C. R_f = 0.36 (cyclohexane/EtOAc: 6/4). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 12.04 (br s, 1H), 8.46 (s, 1H), 7.44−7.23 (m, 4H), 7.39 (s, 1H), 7.02−6.89 (m, 4H), 3.77 (s, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 160.1, 158.9, 142.5, 142.2, 141.5, 136.9, 131.6 (2C), 130.5 (2C), 126.5, 126.0, 124.4, 115.2 (2C), 115.0 (2C), 112.2, 106.3, 56.0, 55.9. IR (CH_2Cl_2) ν (cm^{-1}): 3444, 2930, 1611, 1464, 1217, 1178, 1030, 832. LRMS

(ES$^+$): m/z = 365.0 ([M + H]$^+$, 100), 367.0 (36). HRMS (ES$^+$): calcd for $C_{21}H_{18}N_2O_2Cl$ [M + H]$^+$ 365.1057, found 365.1065.

2-(4-(Methoxymethyl)phenyl)-3-phenyl-1*H*-pyrrolo[3,2-*c*]-pyridine (28a) and 3-(4-(Methoxymethyl)phenyl)-2-phenyl-1*H*-pyrrolo[3,2-*c*]pyridine (28b). Compounds **28a** and **28b** were prepared following the general procedure B with 101 mg (0.37 mmol) of *N*-(3-iodopyridin-4-yl)acetamide **1** and 247 mg (1.11 mmol) of 1-(methoxymethyl)-4-(phenylethynyl)benzene **24**. The crude product was purified by chromatography (silica gel, cyclohexane/EtOAc/methanol 30:70:0 to 0:90:10) to give 90 mg (77%) of an inseparable mixture of compounds **28a** and **28b**. R_f = 0.27 (EtOAc/methanol: 9/1). ^{1}H NMR (DMSO-d_6, 300 MHz), δ (ppm): 12.00 (br s, 2H), 8.76 (s, 1H), 8.75 (s, 1H), 8.23 (d, J = 5.7 Hz, 2H), 7.47−7.31 (m, 20H), 4.44 (s, 1H), 4.41 (s, 1H), 3.33 (s, 3H), 3.30 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz), δ (ppm): 141.8, 141.7, 140.8, 139.4, 138.2, 136.5, 135.0, 134.8, 133.9, 133.0, 132.0, 131.6, 131.5, 131.4, 130.7, 129.6 (2C), 129.4 (2C), 128.8 (2C), 128.6 (2C), 128.4 (2C), 128.2 (2C), 128.1, 128.0 (2C), 127.7 (2C), 126.5, 124.8, 112.5, 112.3, 106.6 (2C), 73.5, 73.2, 57.6 (2C). IR (CH_2Cl_2) ν (cm^{-1}): 3446, 2929, 1466, 1262, 1099, 756, 719. LRMS (ES$^+$): m/z = 315.2 ([M + H]$^+$, 100); HRMS (ES$^+$): calcd for $C_{21}H_{19}N_2O$ [M + H]$^+$ 315.1497, found 315.1492.

2-(4-Chlorophenyl)-3-phenyl-1*H*-pyrrolo[3,2-*c*]pyridine (29a) and 3-(4-Chlorophenyl)-2-phenyl-1*H*-pyrrolo[3,2-*c*]-pyridine (29b). Compounds **29a** and **29b** were prepared following the general procedure B with 82 mg (0.31 mmol) of *N*-(3-iodopyridin-4-yl)acetamide **1** and 195 mg (0.92 mmol) of 1-chloro-4-(phenylethynyl)-benzene **25**. The crude product was purified by chromatography (silica gel, cyclohexane/EtOAc/methanol 30:70:0 to 0:90:10) to give 84 mg (89%) of an inseparable mixture of compounds **29a** and **29b**. R_f = 0.33 (EtOAc/methanol: 9/1). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 12.08 (br s, 2H), 8.78 (s, 1H), 8.76 (s, 1H), 8.25 (d, J = 5.4 Hz, 2H), 7.47−7.34 (m, 20H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 141.9, 141.7, 141.0, 140.9, 139.4, 135.4, 133.7, 133.6, 132.9, 132.8, 132.0, 131.5, 131.3 (2C), 131.1, 130.4, 130.0 (2C), 129.6 (2C), 128.9 (2C), 128.8 (3C), 128.7 (3C), 128.5 (2C), 128.3, 126.7, 124.7, 124.5, 113.1, 111.2, 106.7 (2C). IR (CH_2Cl_2) ν (cm^{-1}): 3444, 3043, 1503, 1464, 1265, 1094, 831, 732, 717. LRMS (ES$^+$): m/z = 305.1 ([M + H]$^+$, 100), 307.1 (82). HRMS (ES$^+$): calcd for $C_{19}H_{14}N_2Cl$ [M + H]$^+$ 305.0846, found 305.0855.

2-(4-Methoxyphenyl)-3-phenyl-1*H*-pyrrolo[3,2-*c*]pyridine (30a) and 3-(4-methoxyphenyl)-2-phenyl-1*H*-pyrrolo[3,2-*c*]-pyridine (30b). were prepared following the general procedure B with 97 mg (0.36 mmol) of *N*-(3-iodopyridin-4-yl)acetamide **1** and 225 mg (1.08 mmol) of 1-methoxy-4-(phenylethynyl)benzene **26**. The crude product was purified by chromatography (silica gel, cyclohexane/EtOAc/methanol 30:70:0 to 0:90:10) to give 94 mg (87%) of an inseparable mixture of compounds **30a** and **30b**. R_f = 0.28 (EtOAc/methanol: 9/1). ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 11.93 (br s, 1H), 11.91 (br s, 1H), 8.72 (s, 2H), 8.21 (d, J = 3.9 Hz, 2H), 7.62−7.28 (m, 16H), 6.98 (d, J = 7.5 Hz, 2H), 6.95 (d, J = 7.8 Hz, 2H), 3.78 (s, 3H), 3.77 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz) δ (ppm): 160.0, 158.9, 142.7, 142.3, 141.6, 141.5, 140.2, 136.0, 135.4, 135.1, 134.3, 132.9, 132.6, 132.4, 132.3, 131.7 (2C), 130.6, 130.5, 129.7 (3C), 129.5 (3C), 129.2 (2C), 128.9, 127.3, 126.9, 125.9, 124.7, 115.2, 115.0, 113.3, 112.5, 107.4 (2C), 56.1, 55.9. IR (CH_2Cl_2) ν (cm^{-1}): 3446, 2964, 1515, 1466, 1261, 1034, 836, 756, 717. LRMS (ES$^+$): m/z = 301.2 ([M + H]$^+$, 100). HRMS (ES$^+$): calcd for $C_{20}H_{17}N_2O$ [M + H]$^+$ 301.1341, found 301.1347.

■ ASSOCIATED CONTENT

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

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■ ACKNOWLEDGMENT

G.C. thanks the Association pour la Recherche sur le Cancer (ARC) for a postdoctoral grant. We thank Dr. J.-C. Florent and Dr. P. Belmont for fruitful discussions and Delphine Naud-Martin for technical assistance.

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