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Synthesis of Pyrido[1,2-*b*]indazoles via Aryne [3 + 2] Cycloaddition with *N*-Tosylpyridinium Imides

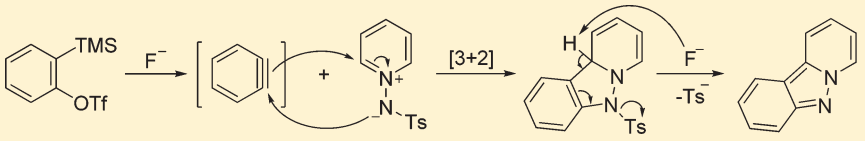
Jingjing Zhao,[†] Chunrui Wu,[*,†] Pan Li,[†] Wenying Ai,[†] Hongli Chen,[†] Chaojie Wang,[†] Richard C. Larock,[‡] and Feng Shi[*,†]

[†]Key Laboratory of Natural Medicine and Immuno-Engineering of Henan Province, Henan University, Jinming Campus, Kaifeng, Henan 475004, P. R. China

[‡]Department of Chemistry, Iowa State University, Ames, Iowa 50011, United States

Supporting Information

ABSTRACT:



The [3 + 2] cycloaddition of arynes with *N*-tosylpyridinium imides, followed by an elimination of Ts^-, affords pyrido[1,2-*b*]-indazoles under mild reaction conditions in good yields.

Pyrido[1,2-*b*]indazole is a class of fused polycyclic aromatics that has received relatively little attention since its early syntheses.[1] To date, not much is known about the physicochemical properties, synthetic utilities, and biological activities, presumably due, in part, to the synthetic challenges. As traditional syntheses involve multistep elaboration with toxic and hazardous materials, new and efficient routes are clearly in demand. Herein, we wish to report our approach using aryne [3 + 2] cycloaddition chemistry,[2−4] which hopefully will facilitate further studies of this heterocyclic system.

Our inspiration comes from an early report by Masumura and co-workers,[5] where aryne [3 + 2] cycloaddition with *N*-acylpyridinium imides **1** (also called *N*-iminopyridinium ylides[6,7]) afforded low yields of pyrido[1,2-*b*]indazole (**3a**) alongside a major product of *N*-acyl-2-(2-pyridyl)anilines (**2**) (Scheme 1, left side). Although further studies failed to improve the yield of **3a** to a synthetically meaningful range and no further studies followed, we envisioned that this reaction might serve as a potentially applicable route to **3a** upon a key modification of the substrate structure, particularly the electron-withdrawing group on the imide nitrogen. It is apparent from Masumura's report that although the acyl group or the alkoxycarbonyl group played a positive role in the [3 + 2] cycloaddition,[5] they adversely affected the formation of **3a** not only due to the problems associated to their removal and a necessitated subsequent oxidation, but also by turning the imide nitrogen into a fair leaving group, leading to the predominant formation of **2** (Scheme 1, left side). Nonetheless, unlike an acyl or alkoxycarbonyl group, a sulfonyl group, such as Ts, can behave as a leaving group itself. Thus, if one employs *N*-sulfonylpyridinium imides instead of *N*-acylpyridinium imides as the starting material, the [3 + 2] intermediate could eliminate a Ts^- to afford the desired product directly (Scheme 1, right side). Such a process would be much more facile than the removal of the acyl/alkoxycarbonyl group in the former case and would eliminate the need of the oxidation step as well, thus leading to a much improved system for the synthesis of **3a**. It should be noted that similar strategies have been utilized in some previous work on [3 + 2] cycloaddition reactions,[8] but they have not been systematically investigated or applied to reactions involving arynes.

In order to test our hypothesis, we first examined different electron-withdrawing groups on the imide nitrogen (Table 1). Acyl and alkoxycarbonyl groups, such as Bz, Piv, and Cbz, indeed led to complex mixtures with no more than 30% yields of **3a** (entries 1−3). A Boc group led to a much cleaner reaction, but the major product was **2** (entry 4).[9,10] In sharp contrast, a 65% yield of **3a** could be obtained upon switching to a Ts group (entry 5). A brief optimization discovered THF as the optimal solvent and the yield increased to 85% (entry 7). Thus, it can be clearly concluded that a sulfonyl group on the imide nitrogen was the key to the desired reaction. Noticeably, an additional equivalent of CsF was necessary to promote the elimination of Ts^-, as a control experiment with only 1.5 equiv of CsF led to significantly lower conversion of both **1a** and **4a** and the yield dropped to 34% (entry 8).

With these optimal conditions in hand, a range of *N*-tosylpyridinium imides (**1**) together with different aryne precursors (**4**)[11] was tested (Table 2). The symmetrical aryne generated from **4b** afforded the desired product **3b** in an 88% yield (entry 1). The unsymmetrical aryne from **4c** gave a 77% yield as a single regioisomer arising from attack of the imide nitrogen at the *meta*

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Scheme 1. Aryne [3 + 2] Cycloaddition Approaches to *N*-Acylpyridinium Imides: Mechanistic Considerations

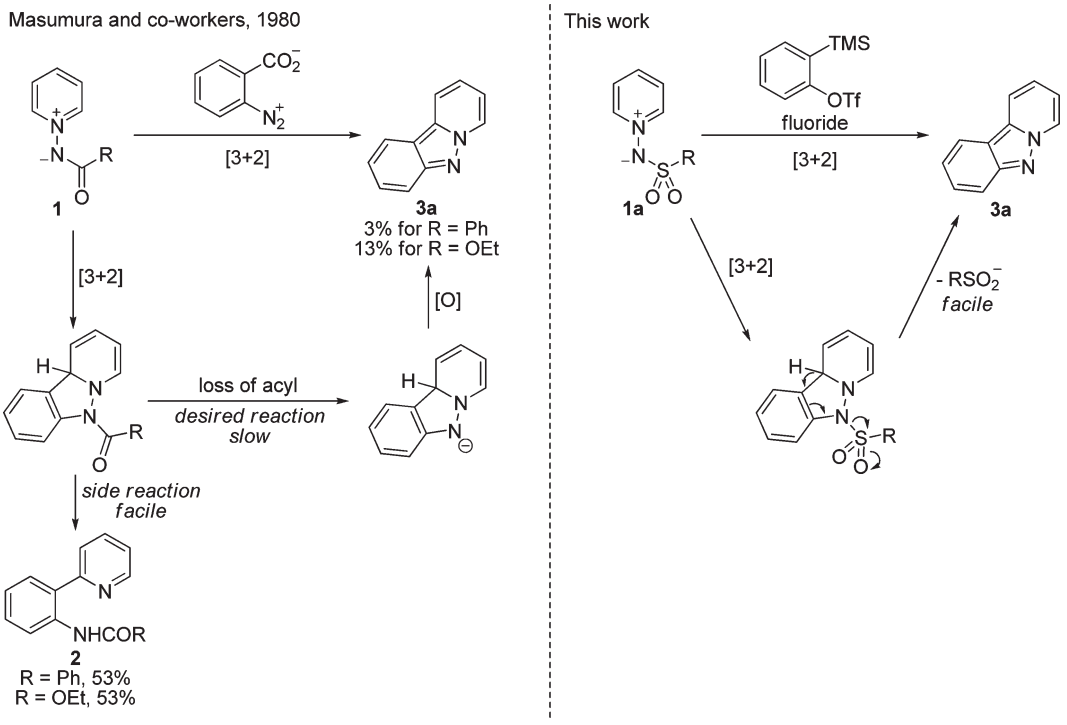
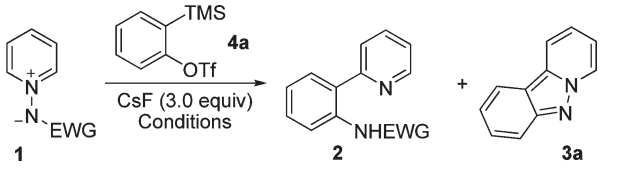


Table 1. Influence of Different Electron-Withdrawing Groups[a]



entry	EWG	reaction conditions	% yield[b] (2)	% yield[b] (3a)
1	Bz	MeCN, 50 °C, 16 h	0	24
2	Piv	MeCN, 50 °C, 16 h	complex mixture	
3	Cbz	MeCN, 50 °C, 16 h	7	30
4	Boc	MeCN, 50 °C, 16 h	86	10
5	Ts (**1a**)	MeCN, 50 °C, 16 h	0	65
6	Ts (**1a**)	THF, 70 °C, 24 h	0	83
7[c]	Ts (**1a**)	THF, 70 °C, 24 h	0	85
8[c,d]	Ts (**1a**)	THF, 70 °C, 24 h	0	34

[a] All reactions were carried out on a 0.3 mmol scale with 1.5 equiv of **4a** in 4 mL of solvent. [b] Isolated yields. [c] 1.2 equiv of **4a**. [d] 1.5 equiv of CsF.

position (with respect to the OMe group) of the aryne (entry 2). Unfortunately, attempts to employing α-naphthalyne as the aryne partner under the standard reaction conditions resulted in low conversions of both starting materials and low yields (<40%) of products with poor regioselectivity (not shown), which might suggest that the scope of the current reaction is limited to substituted benzynes. In terms of the scope of the *N*-tosylpyridinium imides, the reaction worked well with a 2-alkyl substituent,[12] such as in **1b** (entry 3), where cyclization took place cleanly at the 6 position. For 4-substituted pyridinium imides, high yields were only observed for those substituted with an alkyl (entry 4) or electron-withdrawing groups (entries 5 and 6). Imide **1f** derived from DMAP only afforded a 40% yield (entry 7). 3-Substituted pyridinium imides exhibited a similar trend. While substrates equipped with electron-withdrawing (entries 8−10) or alkyl groups (entry 11) afforded the desired products in high yields, a strong electron-donating group, such as a morpholino group (not shown) led to a complex mixture. Regretfully, 3-subsituted pyridinium imides exhibited poor regioselectivity between the 2- and 6-positions (entries 8−11). Neither electronic nor steric factors seem to be dominant in controlling such regioselectivity, similar to the early studies of related [3 + 2] cycloadditions.[13] In most cases, the two regioisomers can be easily distinguished by ^{1}H NMR spectroscopy using the multiplicity of 7-H. Beyond monosubstituted substrates, a 3,5-disubstituted pyridinium imide **1k** also afforded the desired product in a 73% yield (entry 12).[14,15] Other than pyridine-derived imides, those derived from related fused heterocycles, such as quinoline (compound **1l**) and isoquinoline (compound **1m**), were also suitable substrates, affording high yields of **3n** and **3o** (entries 13 and 14), respectively. More worth noting is that **1m** reacted with good regioselectivity in favor of the α-position (entry 14). Such polycyclic products are known to exhibit anticancer activities[16] and our method offers a fairly simple approach for the construction of such anticancer candidates.

The reaction of isoquinolinium imide **1m** provides a very effective route to indazolo[3,2-*a*]isoquinolines. Inspired by Wu and co-workers' Ag-catalyzed electrophilic cyclization that generates isoquinolinium imides in situ from *N*′-(2-alkynylbenzylidene)-hydrazides,[8,17] we conducted a preliminary study of this in situ generation of isoquinolinium imides (Scheme 2). Thus, upon AgOTf catalysis, hydrazone **5** underwent a *6-endo-dig* cyclization to afford imide **1n**. Without isolation and purification, the reaction

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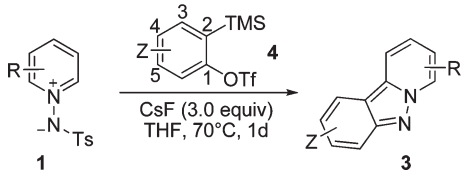
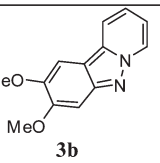
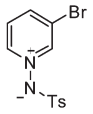
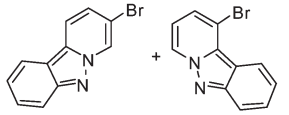
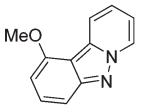
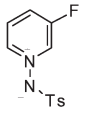
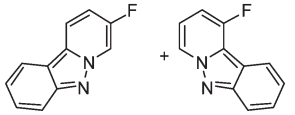
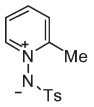
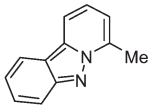
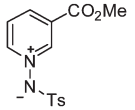
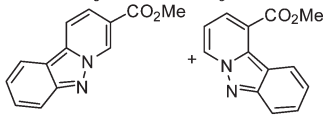
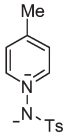
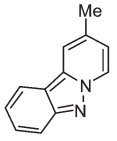
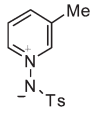
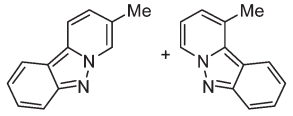
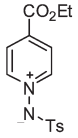
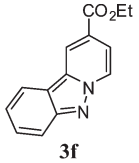
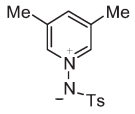
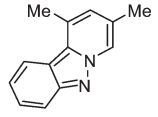
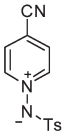
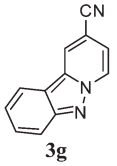
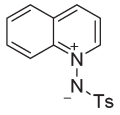
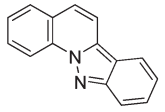
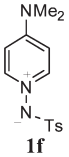
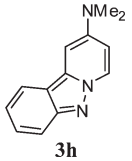
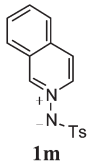
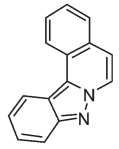
Table 2. Substrate scope[a]



entry	1	4	product	% yield[b]	entry	1	4	product	% yield[b]
1	**1a**	Z = 4,5-(MeO)$_2$ (**4b**)	 **3b**	88	8	 **1g**	**4a**	 **3i** **3i'**	29+62[d]
2	**1a**	Z = 3-(MeO) (**4c**)	 **3c**	77[c]	9[e]	 **1h**	**4a**	 **3j** **3j'**	24+45[f]
3	 **1b**	**4a**	 **3d**	93	10	 **1i**	**4a**	 **3k** **3k'**	52+47[d]
4	 **1c**	**4a**	 **3e**	90	11	 **1j**	**4a**	 **3l** **3l'**	88[d,g] (0.8:1)
5	 **1d**	**4a**	 **3f**	90	12	 **1k**	**4a**	 **3m**	73
6	 **1e**	**4a**	 **3g**	66	13	 **1l**	**4a**	 **3n**	92
7	 **1f**	**4a**	 **3h**	40	14	 **1m**	**4a**	 **3o**	87[h]

[a] All reactions were carried out on a 0.3 mmol scale in 4 mL of solvent. [b] Isolated yields. [c] NOESY experiments were carried out for further structure clarification. See the Supporting Information for spectra and analysis. [d] The two regioisomers can be easily distinguished by ^{1}H NMR spectroscopy. The H at 7-position has no *ortho* coupling for the 8-substituted isomer but has one *ortho* coupling for the 10-substituted isomer. See the Experimental Section for data. [e] 2.0 equiv of **4a** was employed. [f] The two regioisomers can be distinguished by ^{13}C NMR spectroscopy. See the Supporting Information for spectra and analysis. [g] The two regioisomers were inseparable, and the ratio was obtained by ^{1}H NMR spectroscopy. [h] The crude ^{1}H NMR spectrum revealed a trace quantity of the other regioisomer, but it was not isolable.

mixture containing **1n** was treated with aryne precursor **4a** and CsF, and the desired product **3p** was isolated cleanly in a 92% yield over two steps.

In summary, we have developed a facile, effective, and operationally simple route to pyrido[1,2-*b*]indazoles and analogues. The method involves an aryne [3 + 2] cycloaddition with *N*-tosylpyridinium imides and subsequent elimination of Ts^-. Although this methodology has limited substrate scope at present, it offers a much simpler route to the pyrido[1,2-*b*]indazole system than previous methods. Work continues on expanding

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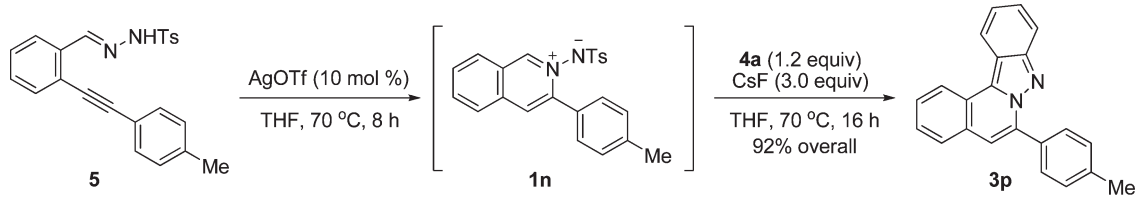
Scheme 2. One-Pot Synthesis of Indazolo[3,2-*a*]isoquinoline via Ag-Catalyzed Cyclization/Aryne Cycloaddition



the scope of this process, including the use of in situ generated isoquinolinium imides.

EXPERIMENTAL SECTION

General Procedures for the Preparation of the *N*-Tosylpyridinium Imides.[7a] To a mixture of H_2O and THF (0.4 mL each for each mmol of pyridine derivatives) was added the pyridine substrate, followed by *O*-(2,4-dinitrophenyl)hydroxylamine (1.1 equiv). The resultant suspension was stirred at 40 °C for 12 h before being cooled to room temperature. The dark red mixture was treated with NaOH (2.5 N, 5 mL for each mmol of pyridine derivatives), followed by TsCl (1.5 equiv, in 1.6 mL of THF for each mmol of pyridine derivatives) dropwise. After another 4 h, the reaction was diluted with H_2O and extracted with CH_2Cl_2. Combined extracts were washed with 2.5 N NaOH, dried over Na_2SO_4, filtered, and concentrated in vacuo. The residue was purified by column chromatography (CH_2Cl_2/MeOH) to afford the *N*-tosylpyridinium imides.

Compound 1a: yield 91%; yellow solid; mp 213 °C (lit.[12e] mp 215 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47−8.42 (m, 2 H), 7.99 (t, J = 7.8 Hz, 1 H), 7.64−7.57 (m, 4 H), 7.16 (d, J = 8.0 Hz, 2 H), 2.35 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.2, 141.6, 138.6, 138.5, 129.2, 127.0, 126.7, 21.4; LRMS (ESI) 249 (M + H).

Compound 1b: yield 58%; slightly yellow solid; mp 207−208 °C (lit.[18] mp 206 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, J = 6.4, 1.0 Hz, 1 H), 7.83 (td, J = 7.8, 1.4 Hz, 1 H), 7.56 (apparent d, J = 8.2 Hz, 2 H), 7.48 (dd, J = 8.1, 1.5 Hz, 1 H), 7.43 (td, J = 7.7, 1.8 Hz, 1 H), 7.19−7.12 (m, 2 H), 2.43 (s, 3 H), 2.36 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.3, 146.5, 141.3, 140.7, 138.0, 129.3, 128.0, 126.4, 123.9, 21.3, 19.9; LRMS (ESI) 285 (M + Na), 263 (M + H).

Compound 1c: yield 21%; slightly yellow solid; mp 180−181 °C (lit.[12e] mp 165 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.27 (d, J = 6.7 Hz, 2 H), 7.61 (d, J = 8.1 Hz, 2 H), 7.37 (d, J = 6.6 Hz, 2 H), 7.17 (d, J = 8.0 Hz, 2 H), 2.54 (s, 3 H), 2.37 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2, 144.8, 141.3, 138.9, 129.2, 127.2, 127.0, 21.5, 21.3; LRMS (ESI) 285 (M + Na), 263 (M + H).

Compound 1d. The title compound was obtained as a beige solid according to the general procedure, but a satd aq $NaHCO_3$ solution was used instead of the aqueous NaOH solution: yield 64%; mp 187 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.65−8.59 (m, 2 H), 8.07−8.03 (m, 2 H), 7.73−7.67 (m, 2 H), 7.20 (d, J = 7.9 Hz, 2 H), 4.44 (q, J = 7.1 Hz, 2 H), 2.37 (s, 3 H), 1.41 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.0, 142.6, 142.2, 138.0, 136.6, 129.4, 127.1, 126.4, 63.0, 21.4, 14.0; LRMS (ESI) 343 (M + Na), 321 (M + H).

Compound 1e. The title compound was obtained as a yellow solid according to the general procedure, but a satd aq $NaHCO_3$ solution was used instead of the aqueous NaOH solution: yield 17%; mp 201−202 °C (lit.[12e] mp 162 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71−8.67 (m, 2 H), 7.78−7.75 (m, 2 H), 7.70−7.66 (m, 2 H), 7.24 (d, overlapped with $CDCl_3$ residue, J unclear, 2 H), 2.39 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 140.4, 137.3, 129.7, 129.1, 127.3, 126.3, 114.5, 21.5; LRMS (ESI) 274 (M + H).

Compound 1f: yield 64%; white solid; mp 212 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 7.8 Hz, 2 H), 7.62 (d, J = 8.1 Hz, 2 H), 7.14 (d, J = 8.0 Hz, 2 H), 6.46 (d, J = 7.8 Hz, 2 H), 3.13 (s, 6 H), 2.35 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 154.3, 144.8, 140.8, 139.8, 129.0, 127.1, 106.6, 39.9, 21.3; LRMS (ESI) 292 (M + H).

Compound 1g: yield 61%; white solid; mp 197 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.64 (t, J = 1.6 Hz, 1 H), 8.43 (dt, J = 6.4, 1.4 Hz, 1 H), 8.02 (d, J = 8.3 Hz, 1 H), 7.65 (d, J = 8.3 Hz, 2 H), 7.44 (dd, J = 8.3, 6.4 Hz, 1 H), 7.20 (d, J = 8.4 Hz, 2 H), 2.37 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.1, 142.6, 142.0, 140.2, 138.2, 129.4, 127.1, 126.9, 121.3, 21.4; HRMS (ESI) calcd for $C_{12}H_{12}BrN_2O_2S$ (M + H) 326.9797, found 326.9793; LRMS (ESI) 349 (M + Na), 327 (M + H).

Compound 1h: yield 40%; beige solid; mp 233 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.59−8.51 (m, 1 H), 8.38 (d, J = 6.3 Hz, 1 H), 7.69−7.63 (m, 3 H), 7.61−7.50 (m, 1 H), 7.20 (d, J = 8.0 Hz, 2 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 159.4 (d, $^1J_{CF}$ = 252.7 Hz), 141.7 (d, $^4J_{CF}$ = 3.5 Hz), 141.2, 138.8, 134.9 (d, $^2J_{CF}$ = 36.7 Hz), 129.4, 128.2 (d, $^3J_{CF}$ = 8.5 Hz), 127.5 (d, $^2J_{CF}$ = 19.0 Hz), 126.7, 20.9; HRMS (ESI) calcd for $C_{12}H_{12}FN_2O_2S$ (M + H) 267.0598, found 267.0595.

Compound 1i. The title compound was obtained as a yellow solid according to the general procedure, but using a satd aq $NaHCO_3$ solution instead of the aqueous NaOH solution: yield 11%; mp 126 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1 H), 8.60 (d, J = 6.3 Hz, 1 H), 8.49 (d, J = 8.0 Hz, 1 H), 7.67 (dd, J = 6.5, 7.9 Hz, 1 H), 7.63 (d, J = 8.3 Hz, 2 H), 7.19 (d, J = 8.0 Hz, 2 H), 3.99 (s, 3 H), 2.36 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 161.8, 147.30, 147.28, 145.5, 141.9, 138.2, 130.0, 129.4, 127.0, 126.6, 53.5, 21.4; HRMS (ESI) calcd for $C_{14}H_{15}N_2O_4S$(M + H) 307.0747, found 307.0747; LRMS (ESI) 329 (M + Na), 307 (M + H).

Compound 1j: yield 50%; yellow solid; mp 192 °C (lit.[12e] mp 165 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (s, 1 H), 8.19 (d, J = 6.3 Hz, 1 H), 7.76 (d, J = 8.0 Hz, 1 H), 7.61 (d, J = 8.2 Hz, 2 H), 7.44 (dd, J = 6.4, 7.8 Hz, 1 H), 7.17 (d, J = 8.4 Hz, 2 H), 2.42 (s, 3 H), 2.36 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 145.0, 142.4, 140.8, 139.4, 138.1, 129.3, 126.7, 126.6, 20.9, 17.7; HRMS (ESI) calcd for $C_{13}H_{15}N_2O_2S$ (M + H) 263.0849, found 263.0849.

Compound 1k: yield 81%; white solid; mp 172−173 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (s, 2 H), 7.62 (d, J = 8.3 Hz, 2 H), 7.55 (brs, 1 H), 7.17 (d, J = 8.4 Hz, 2 H), 2.36 (s, 3 H), 2.34 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.1, 141.2, 140.3, 139.0, 136.9, 129.0, 126.9, 21.3, 18.2; HRMS (ESI) calcd for $C_{14}H_{17}N_2O_2S$ (M + H) 277.1005, found 277.1002; LRMS (ESI) 299 (M + Na), 277 (M + H).

Compound 1l: yield 17%; brown solid; mp 223 °C (lit.[12e] mp 225 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.07 (dd, J = 6.0, 1.2 Hz, 1 H), 8.61−8.56 (m, 1 H), 8.44 (d, J = 8.4 Hz, 1 H), 7.99−7.94 (m, 1 H), 7.74−7.66 (m, 2 H), 7.62 (dd, J = 8.4, 6.0 Hz, 1 H), 7.52 (d, J = 8.2 Hz, 2 H), 7.04 (d, J = 8.0 Hz, 2 H), 2.28 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.9, 141.2, 141.1, 139.7, 139.3, 133.2, 130.0, 129.5, 129.1, 128.4, 126.7, 121.0, 120.6, 21.3; LRMS (ESI) 299 (M + H).

Compound 1m. The title compound was obtained as a brown solid according to the general procedure, but TsCl was added first followed by the aq NaOH solution 30 min later: yield 23%; mp 220−221 °C (lit.[12e] mp 223−224 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.26 (s, 1 H), 8.11

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(dd, J = 7.0, 1.5 Hz, 1 H), 8.04 (d, J = 8.4 Hz, 1 H), 7.96−7.90 (m, 2 H), 7.85−7.79 (m, 2 H), 7.65 (d, J = 8.2 Hz, 2 H), 7.15 (d, J = 7.9 Hz, 2 H), 2.35 (s, 3 H); ^{13}C NMR (100 MHz, DMSO-d_6) δ 147.9, 140.8, 139.5, 137.8, 134.6, 134.4, 130.4, 129.2, 129.0, 127.8, 127.0, 126.6, 125.2, 20.9; LRMS (ESI) 321 (M + Na), 299 (M + H).

Compound 5. To a 10 mL microwave-adaptive vial equipped with a stir bar was added 925 mg of 2-bromobenzaldehyde (5 mmol), followed by 696 mg of 4-ethynyltoluene (6 mmol, 1.2 equiv). Et_3N (1 mL) and DMF (4 mL) were added, followed by $PdCl_2(PPh_3)_2$ (70 mg, 0.1 mmol, 2 mol %) and CuI (38 mg, 0.2 mmol, 4 mol %). The vial was sealed and irradiated with microwave at 100 °C for 2 h. The mixture was cooled to room temperature, poured into 50 mL of EtOAc, and washed three times with brine. The organic layer was dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (15:1 petroleum ether/EtOAc) to afford 850 mg of 2-(*p*-tolylethynyl)-benzaldehyde (77% yield) as a brown solid. This compound (2 mmol) was added to a 25 mL round-bottom flask equipped with a stir bar containing 409 mg of *p*-toluenesulfonyl hydrazide (2.2 mmol, 1.1 equiv) and 5 mL of absolute MeOH. The mixture was stirred at room temperature for 2 h, and the volatiles were evaporated in vacuo. The residue was recrystallized from a minimum amount of MeOH to afford 640 mg of *N*′-(2-alkynylbenzylidene)tosylhydrazides (82% yield) as white crystals: mp 159−161 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (s, 1 H), 7.97 (s, 1 H), 7.95−7.93 (m, 1 H), 7.89 (d, J = 8.3 Hz, 2 H), 7.52−7.46 (m, 1 H), 7.41 (d, J = 8.1 Hz, 2 H), 7.35−7.30 (m, 4 H), 7.17 (d, J = 7.9 Hz, 2 H), 2.40 (s, 3 H), 2.38 (s, 3 H); LRMS (ESI) 411 (M + Na), 389 (M + H).

General Procedures for the Preparation of the Pyrido[1,2-*b*]indazole. To a 10 mL round-bottom flask equipped with a stir bar was added *N*-tosylpyridinium imide **1** (0.3 mmol), followed by the aryne precursor **4** (0.36 mmol) and THF (4 mL). The mixture was briefly stirred before the addition of CsF (ca. 0.9 mmol). The flask was fitted with a reflux condenser and sealed with a septum. A balloon was added on top, and the mixture was stirred in a 70 °C oil bath for 24 h. Upon completion as judged by TLC, the mixture was diluted with EtOAc and brine. The layers were separated and the aqueous layer was extracted twice with EtOAc. Combined extracts were dried over $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography (petroleum ether/EtOAc) to afford the desired product.

Pyrido[1,2-*b*]indazole (3a): yield 43 mg (85%); light yellow solid; mp 85 °C (lit.[1d] mp 83−84 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (dt, J = 6.9, 1.0 Hz, 1 H), 8.17−8.06 (m, 2 H), 7.85 (dt, J = 8.7, 0.8 Hz, 1 H), 7.57 (ddd, J = 1.1, 6.8, 7.9 Hz, 1 H), 7.36 (ddd, J = 1.0, 6.9, 8.1 Hz, 1 H), 7.25−7.15 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.6, 135.4, 128.4, 127.9, 121.9, 119.8, 119.7, 117.9, 116.2, 115.5, 115.2; IR (KBr) 1644, 1604, 1510, 1430, 1360, 1213, 1141, 741, 718 cm^{-1}; HRMS (ESI) calcd for $C_{11}H_9N_2$ (M + H) 169.0760, found 169.0760.

2,3-Dimethoxypyrido[1,2-*b*]indazole (3b): yield 60 mg (88%); white solid; mp 132 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, J = 7.0 Hz, 1 H), 7.94 (d, J = 8.7 Hz, 1 H), 7.31 (s, 1 H), 7.27−7.22 (m, 1 H), 7.16 (s, 1 H), 7.02 (td, J = 6.9, 1.2 Hz, 1 H), 4.02 (s, 3 H), 4.01 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.4, 146.0, 134.7, 127.70, 127.67, 121.1, 116.9, 114.0, 108.0, 98.0, 94.8, 56.0, 55.8; HRMS (ESI) calcd for $C_{13}H_{13}N_2O_2$ (M + H) 229.0972, found 229.0968.

1-Methoxypyrido[1,2-*b*]indazole (3c): yield 46 mg (77%); off-white solid; mp 100 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.76 (dt, J = 6.9, 0.9 Hz, 1 H), 8.34 (dt, J = 8.4, 1.3 Hz, 1 H), 7.49−7.41 (m, 2 H), 7.34 (apparent t, J = 7.8 Hz, 1 H), 7.16 (td, J = 6.9, 1.5 Hz, 1 H), 6.53 (d, J = 7.3 Hz, 1 H), 4.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5, 151.2, 135.1, 129.2, 127.5, 122.3, 120.1, 115.6, 107.8, 107.0, 97.8, 55.4; HRMS (ESI) calcd for $C_{12}H_{11}N_2O$ (M + H) 199.0866, found 199.0861.

7-Methylpyrido[1,2-*b*]indazole (3d): yield 51 mg (93%); beige solid; mp 70 °C (lit.[5] mp 63−64 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 8.2 Hz, 1 H), 8.07 (d, J = 8.6 Hz, 1 H), 7.93 (d, J = 8.4 Hz, 1 H), 7.58 (t, J = 7.6 Hz, 1 H), 7.35−7.20 (m, 2 H), 7.06−7.04 (m, 1 H), 2.96 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 137.6, 135.7, 128.3, 121.9, 119.9, 119.5, 115.73, 115.67, 115.6, 115.4, 18.6; HRMS (ESI) calcd for $C_{12}H_{11}N_2$ (M + H) 183.0917, found 183.0912.

9-Methylpyrido[1,2-*b*]indazole (3e): yield 49 mg (90%); beige solid; mp 133 °C (lit.[5] mp 116−121 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.68 (d, J = 7.1 Hz, 1 H), 8.04 (dt, J = 8.2, 1.0 Hz, 1 H), 7.90 (quint, J = 0.9 Hz, 1 H), 7.79 (d, J = 8.7 Hz, 1 H), 7.54 (ddd, J = 8.6, 6.7, 1.1 Hz, 1 H), 7.18 (ddd, J = 8.1, 6.8, 0.8 Hz, 1 H), 7.02 (dd, J = 7.1, 1.9 Hz, 1 H), 2.55 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.0, 135.4, 133.0, 128.3, 127.2, 119.8, 119.1, 118.5, 116.8, 115.3, 114.5, 21.2; IR (KBr) 1648, 1608, 1356, 804, 747 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_{11}N_2$ (M + H) 183.0917, found 183.0912.

Ethyl pyrido[1,2-*b*]indazole-9-carboxylate (3f). yield 65 mg (90%); slightly yellow solid; mp 98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86−8.82 (m, 1 H), 8.76 (d, J = 7.2 Hz, 1 H), 8.16 (dd, J = 8.3, 0.9 Hz, 1 H), 7.91 (dd, J = 8.7, 0.7 Hz, 1 H), 7.77 (dd, J = 7.2, 1.9 Hz, 1 H), 7.66−7.58 (m, 1 H), 7.38−7.30 (m, 1 H), 4.46 (q, J = 7.1 Hz, 2 H), 1.46 (t, J = 7.1 Hz, 3 H); ^{13}C NMR (75 MHz, CDCl3) δ 164.9, 150.1, 134.3, 128.8, 127.3, 123.3, 121.4, 120.1, 119.7, 116.9, 116.4, 115.5, 61.6, 14.3; IR (KBr) 1605, 1278, 759, 714 cm^{-1}; HRMS (ESI) calcd for $C_{14}H_{13}N_2O_2$ (M + H) 241.0972, found 241.0968.

Pyrido[1,2-*b*]indazole-9-carbonitrile (3g): yield 38 mg (66%); yellow green solid; mp 65 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (dd, J = 7.2, 0.9 Hz, 1 H), 8.51 (dd, J = 1.9, 0.9 Hz, 1 H), 8.14 (dt, J = 8.3, 1.0 Hz, 1 H), 7.95 (d, J = 8.7 Hz, 1 H), 7.68 (ddd, J = 8.6, 6.8, 1.1 Hz, 1 H), 7.41 (ddd, J = 8.2, 6.8, 0.8 Hz, 1 H), 7.33 (dd, J = 7.2, 1.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 133.9, 129.5, 128.3, 123.4, 122.5, 119.5, 117.6, 116.7, 116.4, 116.3, 103.9; IR (KBr) 2225, 1523, 1451, 1361, 1284, 803, 753, 728, 718 cm^{-1}; HRMS (ESI) calcd for $C_{12}H_8N_3$ (M + H) 194.0713, found 194.0709.

***N*,*N*-Dimethylpyrido[1,2-*b*]indazol-9-amine (3h):** yield 25 mg (40%); yellow green solid; mp 170−171 °C ; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.57 (d, J = 7.7 Hz, 1 H), 7.94 (d, J = 8.2 Hz, 1 H), 7.65 (d, J = 8.6 Hz, 1 H), 7.46 (t, J = 7.5 Hz, 1 H), 7.03 (t, J = 7.4 Hz, 1 H), 6.98 (d, J = 2.5 Hz, 1 H), 6.73 (dd, J = 7.7, 2.8 Hz, 1 H), 3.09 (s, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 146.5, 137.3, 128.7, 128.2, 120.3, 117.5, 114.3, 114.0, 105.9, 95.0, 40.3; HRMS (ESI) calcd for $C_{13}H_{14}N_3$ (M + H) 212.1182, found 212.1176.

8-Bromopyrido[1,2-*b*]indazole (3i): yield 31 mg (29%); off-white solid; mp 103 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.93 (s, 1 H), 8.05 (d, J = 8.3 Hz, 1 H), 8.00 (d, J = 9.1 Hz, 1H), 7.85 (d, J = 8.7 Hz, 1 H), 7.59 (ddd, J = 1.0, 6.8, 7.9 Hz, 1 H), 7.44 (dd, J = 9.1, 1.6 Hz, 1 H), 7.30−7.25 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.7, 133.9, 128.7, 128.2, 125.1, 120.6, 119.5, 118.1, 115.9, 115.2, 110.9; HRMS (ESI) calcd for $C_{11}H_8BrN_2$ (M + H) 246.9865, found 246.9861.

10-Bromopyrido[1,2-*b*]indazole (3i′): yield 49 mg (62%); off-white solid; mp 141 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.78 (dd, J = 6.9, 0.8 Hz, 1 H), 8.63 (dt, J = 8.5, 1.0 Hz, 1 H), 7.87 (d, J = 8.7 Hz, 1 H), 7.61 (ddd, J = 8.7, 6.8, 1.1 Hz, 1 H), 7.55 (dd, J = 7.5, 0.7 Hz, 1 H), 7.31 (ddd, J = 8.4, 6.8, 0.9 Hz, 1 H), 7.05 (t, J = 7.2 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.9, 133.2, 128.7, 126.9, 125.3, 122.1, 120.4, 116.0, 115.7, 113.8; HRMS (ESI) calcd for $C_{11}H_8BrN_2$ (M + H) 246.9865, found 246.9868.

8-Fluoropyrido[1,2-*b*]indazole (3j): yield 13 mg (24%); white solid; mp 91−92 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.71 (dd, J = 4.3, 2.0 Hz, 1 H), 8.14−8.04 (m, 2 H), 7.85 (d, J = 8.7 Hz, 1 H), 7.61−7.54 (m, 1 H), 7.30−7.24 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.5 (d, $^1J_{CF}$ = 241.3 Hz), 150.1 (d, $^4J_{CF}$ = 2.1 Hz), 132.9, 128.1, 120.5, 119.3, 117.9 (d, $^3J_{CF}$ = 9.4 Hz), 115.6, 115.5 (d, $^2J_{CF}$ = 39.7 Hz), 115.3 (overlapped with the d at 115.5), 113.1 (d, $^2J_{CF}$ = 24.3 Hz); HRMS (ESI) calcd for $C_{11}H_8FN_2$ (M + H) 187.0666, found 187.0664.

10-Fluoropyrido[1,2-*b*]indazole (3j′): yield 25 mg (45%); white solid; mp 95−96 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.63

(d, J = 6.7 Hz, 1 H), 8.22 (d, J = 8.3 Hz, 1 H), 7.87 (d, J = 8.7 Hz, 1 H), 7.60 (ddd, J = 1.0, 6.7, 8.0 Hz, 1 H), 7.33−7.28 (m, 1H), 7.18−7.01 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 155.7 (d, $^1J_{CF}$ = 251.8 Hz), 149.3, 128.6, 127.2 (d, $^2J_{CF}$ = 34.0 Hz), 124.2 (d, $^4J_{CF}$ = 3.9 Hz), 121.3 (d, $^4J_{CF}$ = 3.4 Hz), 120.9, 115.6, 115.1 (d, $^3J_{CF}$ = 7.8 Hz), 113.8 (d, $^3J_{CF}$ = 4.5 Hz), 105.9 (d, $^2J_{CF}$ = 17.6 Hz); HRMS (ESI) calcd for $C_{11}H_8FN_2$ (M + H) 187.0660, found 187.0664.

Methyl pyrido[1,2-*b*]indazole-8-carboxylate (3k): yield 36 mg (52%); yellow solid; mp 172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.46 (s, 1 H), 8.12 (d, J = 9.0 Hz, 1 H), 8.07 (d, J = 8.3 Hz, 1 H), 7.89−7.84 (m, 2 H), 7.60 (t, J = 7.4 Hz, 1 H), 7.25 (t, J = 7.5 Hz, 1 H), 4.01 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.1, 151.2, 136.5, 131.2, 129.4, 121.4, 120.8, 120.1, 119.7, 117.3, 116.0, 115.0, 52.7; HRMS (ESI) calcd for $C_{13}H_{11}N_2O_2$ (M + H) 227.0815, found 227.0813.

Methyl pyrido[1,2-*b*]indazole-10-carboxylate (3k′): yield 33 mg (47%); yellow solid; mp 128 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.94 (d, J = 6.8 Hz, 1 H), 8.79 (d, J = 8.6 Hz, 1 H), 8.04 (d, J = 7.2 Hz, 1 H), 7.85 (d, J = 8.7 Hz, 1 H), 7.59 (t, J = 7.3 Hz, 1 H), 7.27 (t, J = 7.9 Hz, 1 H), 7.20 (t, J = 7.1 Hz, 1 H), 4.08 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.3, 150.7, 133.2, 131.7, 129.0, 126.4, 124.5, 123.6, 120.5, 115.6, 114.7, 114.5, 52.7; IR (KBr) 1720, 1647, 1302, 1089, 740 cm^{-1}; HRMS (ESI) calcd for $C_{13}H_{11}N_2O_2$ (M + H) 227.0815, found 227.0811.

10-Methylpyrido[1,2-*b*]indazole (3l) and 8-methylpyrido-[1,2-*b*]indazole (3l′): yield 64 mg (88% combined); yellow solid; major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.69 (d, J = 6.3 Hz, 1 H), 8.18 (d, J = 8.4 Hz, 1 H), 7.86 (d, J = 8.6 Hz, 1 H), 7.57 (t, J = 7.7 Hz, 1 H), 7.54 (t, J = 7.7 Hz, 1 H), 7.17−7.07 (m, 2 H), 2.90 (s, 3 H); minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.59 (s, 1 H), 8.05 (d, J = 8.2 Hz, 1 H), 8.01 (d, J = 8.8 Hz, 1 H), 7.82 (d, J = 8.6 Hz, 1 H), 7.25−7.18 (m, 3 H), 2.49 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 130.7, 128.0, 127.8, 126.6, 126.2, 125.7, 124.9, 122.5, 121.6, 119.7, 119.5, 119.5, 117.1, 116, 115.8, 115.4, 115.3, 115.1, 19.3, 18.6; HRMS (ESI) calcd for $C_{12}H_{11}N_2$ (M + H) 183.0917, found 183.0915.

8,10-Dimethylpyrido[1,2-*b*]indazole (3m): yield 43 mg (73%); slightly yellow solid; mp 116 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.47 (s, 1 H), 8.12 (d, J = 8.3 Hz, 1 H), 7.83 (d, J = 8.6 Hz, 1 H), 7.53 (ddd, J = 1.1, 6.8, 8.0 Hz, 1 H), 7.21 (ddd, J = 0.7, 6.7, 7.7 Hz, 1 H), 6.97 (s, 1 H), 2.82 (s, 3 H), 2.43 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.4, 133.1, 129.7, 127.4, 126.1, 125.4, 125.3, 124.0, 121.30, 119.4, 115.3, 19.1, 18.4; HRMS (ESI) calcd for $C_{13}H_{13}N_2$ (M + H) 197.1073, found 197.1069.

Indazolo[2,3-*a*]quinoline (3n): yield 60 mg (92%); beige solid; mp 98 °C (lit.[5] mp 107−109 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (d, J = 8.5 Hz, 1 H), 8.09 (d, J = 8.3 Hz, 1 H), 8.01−7.96 (m, 2 H), 7.92 (d, J = 8.0 Hz, 1 H), 7.80 (ddd, J = 1.3, 7.2, 8.5 Hz, 1 H), 7.67−7.54 (m, 3 H), 7.30−7.24 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 134.0, 132.23, 129.3, 128.3, 127.9, 125.9, 125.1, 123.0, 120.6, 119.6, 117.0, 116.6, 116.5, 115.4; HRMS (ESI) calcd for $C_{15}H_{11}N_2$ (M + H) 219.0917, found 219.0913; HRMS (ESI) calcd for $C_{15}H_{11}N_2$ (M + H) 219.0917, found 219.0913

Indazolo[3,2-*a*]isoquinoline (3o): yield 57 mg (87%); light-brown solid; mp 90−92 °C (lit[5] 90−91 °C); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 (d, J = 8.2 Hz, 1 H), 8.59 (d, J = 7.4 Hz, 1 H), 8.45 (d, J = 8.5 Hz, 1 H), 7.95 (d, J = 8.7 Hz, 1 H), 7.87 (d, J = 7.9 Hz, 1 H), 7.78−7.73 (m, 1 H), 7.64−7.54 (m, 2 H), 7.41−7.32 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.2, 130.5, 128.4, 128.2, 127.5, 127.4, 127.2, 126.4, 126.1, 122.9, 121.3, 121.1, 116.9, 116.4, 116.2; HRMS (ESI) calcd for $C_{15}H_{11}N_2$ (M + H) 219.0917, found 219.0912.

6-*p*-Tolylindazolo[3,2-*a*]isoquinoline (3p). To a 10 mL round-bottom flask equipped with a stir bar containing compound **5** (117 mg, 0.3 mmol) and CH_3CN (4 mL) was added AgOTf (ca. 8 mg, 0.03 mmol, 10 mol %). The reaction mixture was stirred at 80 °C for 6 h and cooled to ambient temperature. Aryne precursor (110 mg, 0.36 mmol, 1.2 equiv) was added followed by CsF (ca. 140 mg, 0.9 mmol, 3 equiv). The reaction mixture was again stirred at 80 °C for 12 h and cooled to room temperature. It was poured into brine and extracted three times with EtOAc. The combined extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (4:1 petroleum ether/EtOAc) to afford 85 mg of **3p** (92%) as a yellow solid: mp 178−179 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.75 (d, J = 8.3 Hz, 1 H), 8.52 (d, J = 8.5 Hz, 1 H), 7.97 (dt, J = 8.7, 0.9 Hz, 1 H), 7.94−7.87 (m, 3 H), 7.76 (ddd, J = 8.3, 7.2, 1.3 Hz, 1 H), 7.67−7.60 (m, 1 H), 7.54 (ddd, J = 8.7, 6.7, 1.0 Hz, 1 H), 7.44 (s, 1H), 7.42−7.37 (m, 2 H), 7.37−7.32 (m, 1 H), 2.48 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 139.5, 138.5, 131.3, 131.1, 129.5, 129.1, 128.6, 128.0, 127.5, 127.1, 127.0, 125.5, 122.6, 121.3, 121.1, 117.7, 116.7, 116.4, 21.5; IR (KBr) 1619, 1511, 1363, 1233, 809, 752, 724 cm^{-1}; HRMS (ESI) calcd for $C_{22}H_{17}N_2$ (M + H) 309.1386, found 309.1380.

■ ASSOCIATED CONTENT

Supporting Information. Copies of ^{1}H and ^{13}C NMR spectra for all products, including the 2D-NOESY spectrum. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*(C.W.) Tel: +86-378-286-4665. Fax: +86-378-286-4665. E-mail: cwu@henu.edu.cn; (F.S.) fshi@henu.edu.cn.

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(10) At least for the reaction of entry 4, Table 1, addition of base (Cs_2CO_3, for easier hydrolysis of the Boc−N bond) or oxidant (I_2, for easier oxidation) failed to significantly improve the yield of **3a**, and for unknown reasons, reactions performed at a lower temperature led to more of **3a**. However, in no case was the yield of **3a** higher than 50%.

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