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Palladium-catalyzed tandem addition/cyclization in aqueous medium: synthesis of 2-arylindoles†

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An efficient protocol to construct 2-arylindoles was developed through palladium-catalyzed tandem addition/cyclization of potassium aryltrifluoroborates with aliphatic nitriles in aqueous medium. The use of water as the reaction medium makes the synthesis process environmentally benign. A plausible mechanism for the formation of 2-arylindoles involving sequential nucleophilic addition followed by an intramolecular cyclization is proposed. Moreover, the utility of this catalytic tandem transformation was also demonstrated in an efficient gram-scale synthesis. This method provides an alternative synthetic tool for accessing a more diverse array of 2-arylindoles.

Introduction

Nitrogen-containing heterocycles are ubiquitous in a wide variety of bioactive natural products and biological molecules that may be good drug candidates.[1] In particular, 2-arylindoles and their derivatives represent a medicinally and pharmaceutically important class of heterocyclic motifs that are found as the core structural skeletons in a variety of drug molecules such as zindoxifene,[2] NSC-370875,[3] and L-838751[4] (Fig. 1). Not only indole motifs are present in a variety of products with functional significance, but they can be used as an important class of molecular building blocks in organic chemistry for the synthesis of other N-heterocycles.[5] Therefore, the development of effective methods for the preparation of 2-arylindoles has received much attention during the past several decades. In this context, two strategies for the synthesis of 2-arylindoles have been developed: first, the introduction of substituents by direct selective C-2 arylation of a preexisting indole ring;[6] second, the assembly of the functionalized pyrrole nucleus on a benzenoid scaffold.[7]

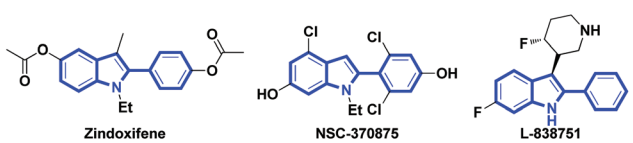

Fig. 1 Representative bioactive 2-arylindole derivatives.

Transition-metal-catalyzed transformations of the readily available nitriles would provide an attractive route for the formation of novel carbon–carbon and carbon–heteroatom bonds in both the organic chemistry research and fine chemical industry.[8] It is well known, however, that nitriles (*e.g.* acetonitrile or benzonitrile) have been used as solvents or ligands in organometallic reactions presumably due to the inherently inert nature of nitriles.[9] Inspired by the pioneering works of Larock[10] concerning the addition of arylpalladium species to the cyano group and remarkable progress in recent years,[11] we envisioned that 2-arylindoles might be assembled by Pd-catalyzed tandem addition/cyclization of functionalized nitriles with arylation reagents. Recently, we have also developed the palladium-catalyzed synthesis of alkyl aryl ketones,[12a,b] benzofurans,[12a–c] 2-aminobenzophenones[12d] and N-heterocyclic compounds[12e–g] by catalytic carbopalladation of nitriles. However, the use of nitriles as reaction partners in the synthesis of indoles has rarely been reported,[13] even though the prevalence of transformation of nitriles into a wide range of functional groups has been well-established.

Although arylboronic acids have advantages of low toxicity, air- and moisture-stability, they often dimerize and trimerize to the corresponding anhydrides and boroxines with loss of water, which result in difficulties in purification and determination of precise stoichiometry.[14] Additionally, a large excess of arylboronic acids is often required because they easily generate protodeboronation and homocoupling products. Recently, potassium aryltrifluoroborates have been focused as attractive and promising alternatives to arylboronic acids because of their superior features. Perhaps most importantly, the tetracoordinate nature of potassium aryltrifluoroborates, anchored by exceptionally strong boron–fluorine bonds, makes them inherently inert to many of the most common reagents utilized

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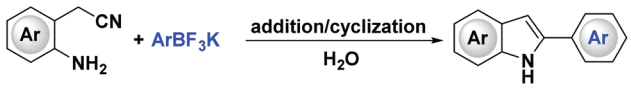


Scheme 1 Palladium-catalyzed one-pot synthesis of 2-arylindoles.

in organic synthesis. To our knowledge, the application of potassium aryltrifluoroborates in transition-metal-catalyzed addition of nitriles for the synthesis of 2-arylindoles has not been reported thus far.

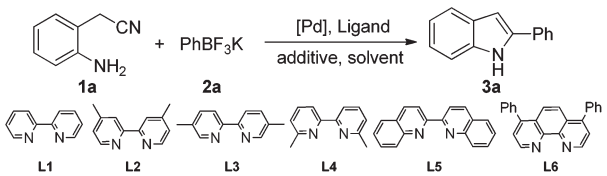
Additionally, water as a reaction medium for green chemistry has recently attracted considerable attention in organic synthesis due to its environmental acceptability, abundance, safety and low cost, and would thus be highly advantageous alternatives to organic solvents from both economical and ecological standpoints.[15] This work forms part of the continuing efforts in our laboratory toward the development of novel transition metal-catalyzed addition or coupling reactions with organoboron reagents[12,16] and the synthesis of N-heterocycles.[17] Herein, we report a simple and efficient protocol for the synthesis of 2-arylindoles by palladium-catalyzed tandem addition/cyclization of 2-(2-aminoaryl)acetonitriles with potassium aryltrifluoroborates in aqueous medium (Scheme 1).

Results and discussion

We started our investigation employing readily available 2-(2-aminophenyl)acetonitrile (**1a**) and potassium phenyltrifluoroborate (**2a**) as model substrates to obtain the optimal reaction conditions (Table 1).

Encouragingly, we found that the model reaction proceeded in the presence of $Pd(OAc)_2$, 2,2′-bipyridine (**L1**) and *p*-toluenesulfonic acid monohydrate ($TsOH{\cdot}H_2O$) in toluene to give the desired product **3a** in 21% yield (entry 1). Through further optimization of the reaction conditions, we discovered that the yield of **3a** was improved to 71% when 4,4′-dimethyl-2,2′-bipyridine (**L2**) was used as the ligand in water (entry 7). Other larger steric bidentate nitrogen ligands, such as 6,6′-dimethyl-2,2′-bipyridine (**L4**) and 2,2′-biquinoline (**L5**) affected the tandem reaction adversely (entries 9 and 10). Replacement of $TsOH{\cdot}H_2O$ with other additives, including CH_3CO_2H, CF_3CO_2H, CF_3SO_3H (TfOH), *p*-nitrobenzenesulfonic acid (NsOH), D-camphorsulfonic acid (CSA) and HCl, led to lower yields (entries 12–17). A variety of Pd(II) salts are reactive, with $Pd(acac)_2$ being the optimal choice (entries 18–20). In contrast, this reaction did not work using Pd(0) such as $Pd(dba)_2$ or $Pd(PPh_3)_4$ as a catalyst (entries 21 and 22). Decreasing the amount of TsOH afforded the desired product **3a** in lower yield (entry 20). We were delighted to find that the yield increased to 85–92% when the reaction was run at higher concentration by reducing the quantity of the solvent (entries 23 and 24). The reaction failed to improve the yield of **3a** in air (entry 25). It should also be noted that no reactivity was observed in the absence of either $Pd(acac)_2$ or the ligand.

Table 1 Optimization of reaction conditions[a]

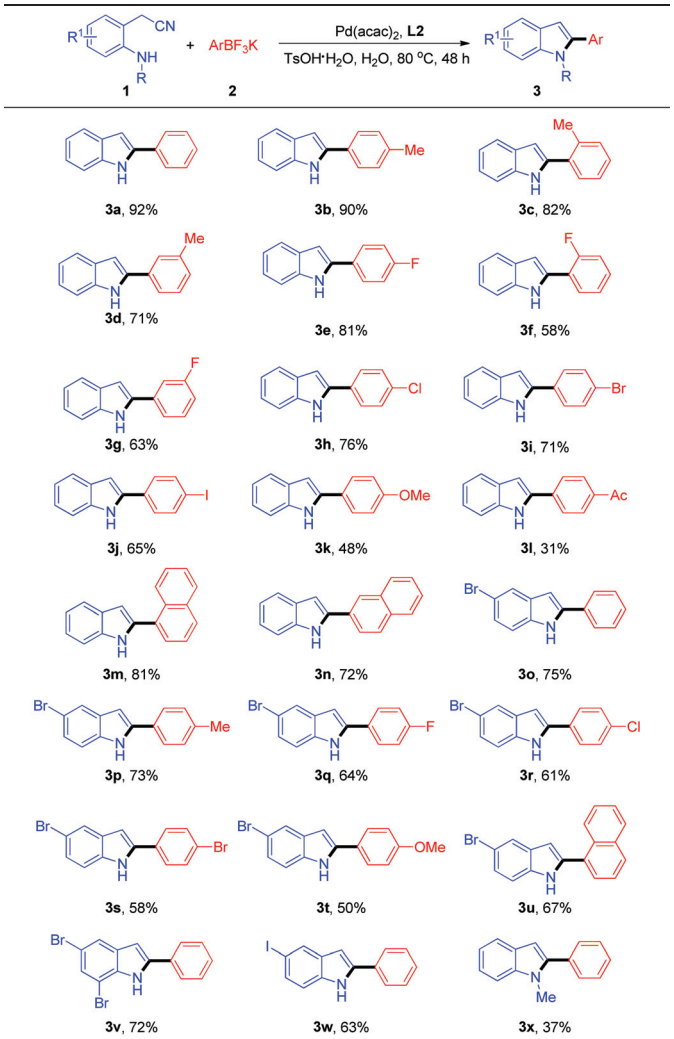


Entry	[Pd]	Ligand	Additive	Solvent	Yield[b] (%)
1	$Pd(OAc)_2$	**L1**	$TsOH{\cdot}H_2O$	Toluene	21
2	$Pd(OAc)_2$	**L1**	$TsOH{\cdot}H_2O$	DMF	24
3	$Pd(OAc)_2$	**L1**	$TsOH{\cdot}H_2O$	THF	35
4	$Pd(OAc)_2$	**L1**	$TsOH{\cdot}H_2O$	THF/H_2O	48[c]
5	$Pd(OAc)_2$	**L1**	$TsOH{\cdot}H_2O$	$EtOH/H_2O$	52[c]
6	$Pd(OAc)_2$	**L1**	$TsOH{\cdot}H_2O$	H_2O	65
7	$Pd(OAc)_2$	**L2**	$TsOH{\cdot}H_2O$	H_2O	71
8	$Pd(OAc)_2$	**L3**	$TsOH{\cdot}H_2O$	H_2O	69
9	$Pd(OAc)_2$	**L4**	$TsOH{\cdot}H_2O$	H_2O	0
10	$Pd(OAc)_2$	**L5**	$TsOH{\cdot}H_2O$	H_2O	Trace
11	$Pd(OAc)_2$	**L6**	$TsOH{\cdot}H_2O$	H_2O	26
12	$Pd(OAc)_2$	**L2**	CH_3CO_2H	H_2O	Trace
13	$Pd(OAc)_2$	**L2**	CF_3CO_2H	H_2O	19
14	$Pd(OAc)_2$	**L2**	TfOH	H_2O	38
15	$Pd(OAc)_2$	**L2**	NsOH	H_2O	62
16	$Pd(OAc)_2$	**L2**	CAS	H_2O	37
17	$Pd(OAc)_2$	**L2**	HCl	H_2O	Trace
18	$PdCl_2$	**L2**	$TsOH{\cdot}H_2O$	H_2O	51
19	$Pd(CF_3CO_2)_2$	**L2**	$TsOH{\cdot}H_2O$	H_2O	72
20	$Pd(acac)_2$	**L2**	$TsOH{\cdot}H_2O$	H_2O	75 (52[d], 83[e])
21	$Pd(PPh_3)_4$	**L2**	$TsOH{\cdot}H_2O$	H_2O	0
22	$Pd(dba)_2$	**L2**	$TsOH{\cdot}H_2O$	H_2O	0
23	$Pd(acac)_2$	**L2**	$TsOH{\cdot}H_2O$	H_2O	85[f]
24	$Pd(acac)_2$	**L2**	$TsOH{\cdot}H_2O$	H_2O	92[g]
25	$Pd(acac)_2$	**L2**	$TsOH{\cdot}H_2O$	H_2O	71[h]

[a] Conditions: **1a** (0.3 mmol), **2a** (0.6 mmol), [Pd] (5 mol%), ligand (10 mol%), additive (10 equiv.), solvent (3 mL), 80 °C, 48 h, N_2. [b] Isolated yield. [c] THF or EtOH (2.5 mL)/H_2O (0.5 mL). [d] $TsOH{\cdot}H_2O$ (5 equiv.). [e] $TsOH{\cdot}H_2O$ (15 equiv.). [f] H_2O (2 mL). [g] H_2O (1 mL). [h] In air.

With the optimized reaction conditions in hand, we next proceeded to examine the substrate scope (Table 2). First, the reaction of various potassium aryltrifluoroborates with 2-(2-aminophenyl)acetonitrile (**1a**) was investigated under standard conditions (**3a–3n**). A wide variety of substituted potassium aryltrifluoroborates are reactive. The reactivity of *para*-, *meta*-, and *ortho*-tolyltrifluoroborate were evaluated, and the results demonstrated that steric effects of substituents had some effects on the reaction. For example, the reaction of **1a** with *para*-tolyltrifluoroborate gave 90% yield of **3b**, while the *ortho*- and *meta*-tolyltrifluoroborate afforded the desired products **3c** and **3d** with diminished yields of 82% and 71%, respectively. The same phenomenon was observed in the reaction of **1a** with *para*-, *ortho*-and *meta*-fluorophenyltrifluoroborate, affording the desired products **3e**, **3f** and **3g** in 81%, 58% and 63% yields, respectively. Electron deficient potassium aryltrifluoroborates bearing fluoro (**3e–3g**), chloro (**3h**), bromo (**3i**) and iodo (**3j**) groups reacted under these conditions to afford the desired products in moderate to good yields. Both strongly electron-donating (*e.g.*, –OMe) and electron-withdrawing (*e.g.*, –Ac) groups were compatible with this reaction, affording the corresponding products **3k** and **3l** in 48% and 31% yields,

Table 2 Synthesis of 2-arylindoles[a]



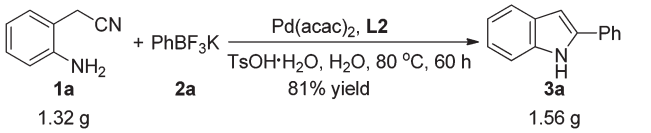
[a] Conditions: **1** (0.3 mmol), **2** (0.6 mmol), $Pd(acac)_2$ (5 mol%), **L2** (10 mol%), $TsOH{\cdot}H_2O$ (10 equiv.), H_2O (1 mL), 80 °C, 48 h, N_2. Isolated yield.

respectively. Notably, the treatment of naphthyl-substituted substrates with **1a** also proceeded smoothly and delivered the desired product **3m** and **3n** in 81% and 72% yields, respectively. Next, we turned our attention to the scope of other 2-(2-aminoaryl)acetonitriles under the standard conditions (**3o–3x**). As shown in Table 2, the reaction worked well with bromo or iodo-substituted substrates (commonly used for cross-coupling reactions), and gave the corresponding products **3o–3w** in 50–75% yields. It is worth noting that the presence of the halogen (Br, I) in the products is very useful for further synthetic elaborations. Finally, the reaction between 2-(2-(methylamino)phenyl)acetonitrile and **2a** was performed, affording the desired product **3x** in 37% yield.

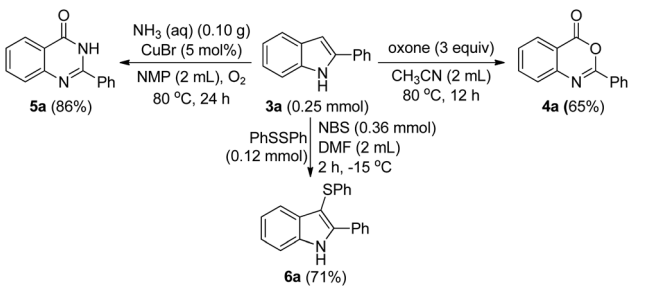
Additionally, the efficiency of this catalytic system was further demonstrated by running the reaction on a laboratory preparative scale. For example, we conducted the reaction on a gram scale (10 mmol), and **3a** was obtained in 81% isolated yield, albeit with a prolonged reaction time (60 h) (Scheme 2).

The 2-arylindoles produced by this chemistry should be amenable for further synthetic applications. For example, substrate **3a** smoothly underwent the Baeyer–Villiger oxidation,[5d] Baeyer–Villiger oxidation/amination[5e] and sulfenylation[18] (Scheme 3), affording the corresponding products 2-phenylbenzoxazinone (**4a**), 2-phenylquinazolinone (**5a**) and 2-phenyl-3-(phenylthio)-1*H*-indole (**6a**) in moderate to good yields.

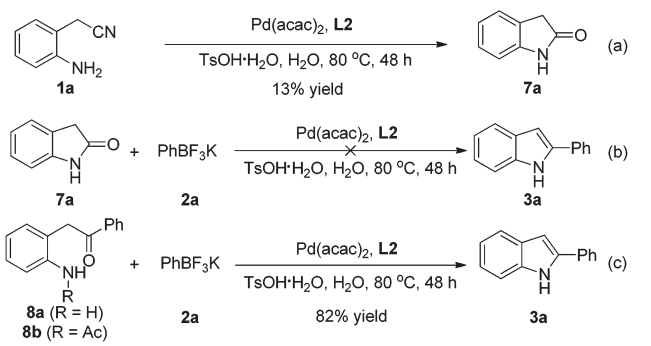
To elucidate the reaction mechanism of the formation of 2-arylindoles, several control experiments were performed under the standard conditions as shown in Scheme 4. We found that indolin-2-one (**7a**) was obtained in 13% yield if potassium aryltrifluoroborate was absent (Scheme 4a). However, the reaction failed to afford the desired product **3a** when the reaction of **7a** with **2a** was performed (Scheme 4b). Our efforts to isolate the ketone intermediate 2-(2-aminophenyl)-1-phenylethan-1-one (**8a**) have been unsuccessful. Alternatively, acetylation substrate *N*-(2-(2-oxo-2-phenylethyl)phenyl)acetamide (**8b**) was prepared according to the literature procedure.[19] The



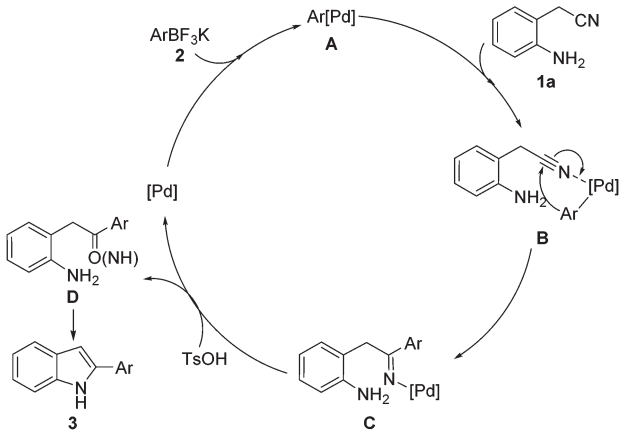
Scheme 2 Gram-scale synthesis of **3a**.



Scheme 3 Applications in organic synthesis.



Scheme 4 Control experiments.



Scheme 5 Possible mechanism for the formation of 2-arylindoles.

desired product **3a** was obtained in good yield *via* cyclization/deacetylation using **8b** as a surrogate of **8a** (Scheme 4c).

On the basis of the above experimental results and relevant reports in the literature, a possible reaction mechanism for the formation of 2-arylindoles is illustrated in Scheme 5 (**1a** as a representative example). The following key steps are included in the catalytic pathway: (i) transmetallation between the palladium catalyst and potassium aryltrifluoroborates **2** to form the palladium-aryl species **A**, which was followed by (ii) the coordination of **1a** to generate intermediate **B**; (iii) carbopalladation of **1a** to give the corresponding ketimine palladium intermediate **C**; (iv) protonation of the intermediate **C** by TsOH to afford the ketone or ketimine intermediate **D** and regenerates an active palladium species. Finally, intramolecular cyclization of the intermediate **D** under acidic conditions readily achieves 2-arylindoles **3** as the desired products. A plausible mechanism for the formation of 2-arylindoles involving sequential nucleophilic addition followed by an intramolecular cyclization is proposed. However, a detailed mechanism of this transformation remains unclear at the current stage.

Conclusions

In conclusion, we have developed a Pd-catalyzed tandem addition/cyclization of potassium aryltrifluoroborates with aliphatic nitriles in aqueous medium. This protocol provides an alternative synthetic pathway to access 2-arylindoles. Further studies to extend this catalytic system to the preparation of other useful N-heterocyclic compounds are currently underway in our laboratories.

Experimental section

General methods

All commercial reagents were used without further purification unless otherwise noted. Melting points are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 500 MHz spectrometer using DMSO-d_6 or $CDCl_3$ as the solvent with tetramethylsilane (TMS) as an internal standard at room temperature. Chemical shifts are given in δ relative to TMS, and the coupling constants J are given in hertz. High-resolution mass spectrometry (HRMS) was performed with a TOF MS instrument with an ESI source. *N*-(2-(2-Oxo-2-phenylethyl)phenyl) acetamide was prepared according to the literature procedures.[19] Other commercially obtained reagents were used without further purification. Column chromatography was performed using EM silica gel 60 (300–400 mesh).

General procedure for palladium-catalyzed tandem synthesis of 2-arylindoles

Under a N_2 atmosphere, 2-(2-aminophenyl)acetonitriles **1** (0.3 mmol), potassium aryltrifluoroborates **2** (0.6 mmol), $Pd(acac)_2$ (5 mol%), **L2** (10 mol%), $TsOH{\cdot}H_2O$ (10 equiv.), and H_2O (1 mL) were successively added into a Schlenk reaction tube. The reaction mixture was stirred vigorously at 80 °C for 48 h. After the reaction reached equilibrium, the mixture was poured into ethyl acetate, which was washed with saturated $NaHCO_3$ (2 × 10 mL) and then brine (1 × 10 mL). After the aqueous layer was extracted with ethyl acetate, the combined organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum. The filtrate was concentrated *in vacuo* and purified by a silica gel packed flash chromatography column with petroleum ether/ethyl acetate (8 : 1) as the eluent to afford the desired products.

2-Phenyl-1*H*-indole (3a). White solid (53.4 mg, 92%), mp 189–190 °C (lit.[20] 186–188.6 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.68–7.64 (m, 3H), 7.47–7.41 (m, 3H), 7.34 (t, J = 7.5 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.14 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9, 136.8, 132.4, 129.3, 129.0, 127.7, 125.2, 122.4, 120.7, 120.3, 110.9, 100.0.

2-(*p*-Tolyl)-1*H*-indole (3b). White solid (56.0 mg, 90%), mp 219.6–220 °C (lit.[20] 217.9–219.5 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.37 (d, J = 8.5 Hz, 1H), 7.25–7.23 (m, 2H), 7.18 (t, J = 8.0 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 6.78 (s, 1H), 2.38 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 137.7, 136.7, 129.7, 129.6, 129.4, 125.1, 122.1, 120.5, 120.2, 110.8, 99.4, 21.3.

2-(*o*-Tolyl)-1*H*-indole (3c). White solid (51.0 mg, 82%), mp 93–94 °C (lit.[21] 92–93 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.67–7.64 (m, 1H), 7.47–7.45 (m, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.32–7.27 (m, 3H), 7.23–7.19 (m, 1H), 7.15–7.12 (m, 1H), 6.61 (s, 1H), 2.50 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 136.2, 136.1, 132.7, 131.1, 129.0, 128.9, 128.0, 126.1, 122.1, 120.6, 120.1, 110.8, 103.0, 21.1.

2-(*m*-Tolyl)-1*H*-indole (3d). Pale-yellow solid (44.2 mg, 71%), mp 138–139 °C (lit.[22] 140–142 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.34 (s, 1H), 7.64 (d, J = 7.5 Hz, 1H), 7.50–7.47 (m, 2H), 7.41 (d, J = 8.0 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 7.21 (t, J = 7.5 Hz, 1H), 7.17–7.12 (m, 2H), 6.83 (d, J = 2.0 Hz, 1H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7, 138.1, 136.8, 132.3, 129.3, 128.9, 128.6, 125.9, 122.3, 122.2, 120.6, 120.2, 110.9, 99.9, 21.5.

2-(4-Fluorophenyl)-1*H*-indole (3e). White solid (51.5 mg, 81%), mp 188–189 °C (lit.[23] 185 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.64–7.60 (m, 3H), 7.40 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 7.0 Hz, 1H), 7.17–7.13 (m, 3H), 6.77–6.76 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.4, 161.4, 137.0, 136.8, 129.3, 128.7, 126.8, 126.9, 122.4, 120.7, 120.4, 116.2, 116.0, 110.9, 110.0.

2-(2-Fluorophenyl)-1*H*-indole (3f). White solid, (36.9 mg, 58%), mp 96–97 °C (lit.[24] 97–98.5 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.53 (s, 1H), 7.93 (s, 1H), 7.58–7.34 (m, 5H), 7.14–6.93 (m, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.9, 157.9, 136.7, 131.3, 129.0, 128.9, 128.3, 127.7, 124.9, 122.0, 120.3, 120.1, 119.4, 116.5, 111.4, 102.5, 102.4.

2-(3-Fluorophenyl)-1*H*-indole (3g). White solid, (40.2 mg, 63%), mp 142–143 °C (lit.[23] 144 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.24 (s, 1H), 7.62 (d, J = 8.0 Hz, 1H), 7.39–7.34 (m, 3H), 7.31–7.29 (m, 1H), 7.20 (t, J = 7.5 Hz, 1H), 7.12 (t, J = 7.0 Hz, 1H), 7.01–6.97 (m, 1H), 6.81 (d, J = 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.3, 162.3, 137.0, 136.7, 136.6, 134.6, 134.5, 130.6, 130.5, 129.1, 122.9, 120.9, 120.8, 120.7, 120.5, 114.6, 114.4, 112.2, 112.0, 111.1, 100.9.

2-(4-Chlorophenyl)-1*H*-indole (3h). White solid (52.1 mg, 76%), mp 202–203 °C (lit.[20] 206.3–209 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (s, 1H), 7.64 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.5 Hz, 2H), 7.42–7.39 (m, 3H), 7.23–7.20 (m, 1H), 7.14 (t, J = 8.0 Hz, 1H), 6.82 (d, J = 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 136.7, 133.6, 130.9, 129.1, 129.2, 126.3, 122.7, 120.8, 120.5, 111.0, 100.5.

2-(4-Bromophenyl)-1*H*-indole (3i). White solid (58.0 mg, 71%), mp 211–212 °C (lit.[25] 212–213 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.58–7.52 (m, 4H), 7.40 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 6.83 (d, J = 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.9, 136.7, 132.2, 131.4, 129.2, 126.6, 122.7, 121.5, 120.8, 120.5, 110.9, 100.6.

2-(4-Iodophenyl)-1*H*-indole (3j). White solid (61.9 mg, 65%), mp 234–235 °C (lit.[26] 220–222 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.31 (s, 1H), 7.76 (d, J = 8.5 Hz, 2H), 7.63 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.5 Hz, 3H), 7.23–7.20 (m, 1H), 7.13 (t, J = 7.5 Hz, 1H), 6.84 (d, J = 2.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.1, 136.9, 136.7, 131.9, 129.2, 126.8, 122.8, 120.8, 120.5, 111.0, 100.6, 92.8.

2-(4-Methoxyphenyl)-1*H*-indole (3k). Pale-yellow solid (32.3 mg, 48%), mp 228–229 °C (lit.[20] 227.4–230.8 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.40 (s, 1H), 7.79 (d, J = 9.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.07–7.02 (m, 3H), 6.98–6.95 (m, 1H), 6.76 (s, 1H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.8, 137.7, 136.9, 128.8, 126.3, 124.9, 121.0, 119.6, 119.2, 114.3, 111.0, 97.3, 55.2.

1-(4-(1*H*-Indol-2-yl)phenyl)ethan-1-one (3l). Pale-yellow solid (22.0 mg, 31%), mp 203–204 °C (lit.[20] 200.9–202.3 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.69 (s, 1H), 8.04 (d, J = 8.0 Hz, 2H), 8.00 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 1H), 7.43 (d, J = 8.5 Hz, 1H), 7.14 (t, J = 8.0 Hz, 1H), 7.09 (s, 1H), 7.02 (t, J = 7.5 Hz, 1H), 2.60 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.1, 137.6, 136.4, 136.3, 135.3, 128.9, 128.5, 124.8, 122.4, 120.4, 119.6, 111.5, 100.8, 26.6.

2-(Naphthalen-1-yl)-1*H*-indole (3m). Pale-yellow solid (59.3 mg, 81%), mp 100–101 °C (lit.[27] 97–99 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.54 (s, 1H), 8.33–8.31 (m, 1H), 8.04–8.02 (m, 1H), 7.98 (d, J = 8.0 Hz, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.64–7.58 (m, 4H), 7.45 (d, J = 8.0 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 7.06 (t, J = 7.5 Hz, 1H), 6.73 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 136.7, 136.4, 133.6, 130.9, 130.8, 128.4, 128.3, 128.1, 127.2, 126.6, 126.1, 125.4, 121.2, 120.0, 119.2, 111.3, 102.4.

2-(Naphthalen-2-yl)-1*H*-indole (3n). White solid (52.7 mg, 72%), mp 167–168 °C (lit.[28] 163–165 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.74 (s, 1H), 8.40 (s, 1H), 8.05–8.03 (m, 1H), 7.98–7.91 (m, 3H), 7.58–7.54 (m, 2H), 7.52–7.46 (m, 2H), 7.14 (t, J = 7.0 Hz, 1H), 7.05–7.02 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 137.6, 137.4, 133.3, 132.3, 129.7, 128.7, 128.4, 127.8, 127.7, 126.7, 126.0, 123.8, 122.8, 121.8, 120.1, 119.4, 111.3, 99.6.

5-Bromo-2-phenyl-1*H*-indole (3o). White solid (61.3 mg, 75%), mp 192–193 °C (lit.[25] 195–196 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.76 (s, 1H), 7.86 (d, J = 7.5 Hz, 2H), 7.72 (s, 1H), 7.48 (d, J = 8.0 Hz, 2H), 7.37–7.33 (m, 2H), 7.22–7.20 (m, 1H), 6.90 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 139.1, 135.8, 131.6, 130.5, 128.9, 127.8, 125.2, 123.9, 122.1, 113.2, 111.8, 98.2.

5-Bromo-2-(*p*-tolyl)-1*H*-indole (3p). White solid (62.9 mg, 73%), mp 239–240 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.70 (s, 1H), 7.75 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 1.5 Hz, 1H), 7.34 (d, J = 8.5 Hz, 1H), 7.28 (d, J = 7.5 Hz, 2H), 7.18 (dd, J_1 = 2.0 Hz, J_2 = 8.5 Hz, 1H), 6.83 (d, J = 1.5 Hz, 1H), 2.34 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 139.3, 137.3, 135.6, 130.6, 129.5, 128.8, 125.1, 123.7, 121.9, 113.1, 111.7, 97.6, 20.8. IR (KBr): 3444, 1540, 1497, 1444, 1308, 1278, 1049, 907, 875, 824, 798, 776, 734, 663, 650 cm^{-1}. HRMS (ESI) calcd for $C_{15}H_{12}BrN$ $[M + H]^+$: 286.0226, found 286.0232.

5-Bromo-2-(4-fluorophenyl)-1*H*-indole (3q). White solid (55.8 mg, 64%), mp 179–180 °C (lit.[29] 178–179 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.75 (s, 1H), 7.91–7.88 (m, 2H), 7.71 (d, J = 2.0 Hz, 1H), 7.36–7.31 (m, 3H), 7.21 (dd, J_1 = 2.0 Hz, J_2 = 8.5 Hz, 1H), 6.86 (d, J = 2.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 162.8, 160.8, 138.2, 135.8, 130.5, 128.3, 127.3, 127.2, 124.0, 122.1, 116.0, 115.8, 113.2, 111.9, 98.2.

5-Bromo-2-(4-chlorophenyl)-1*H*-indole (3r). White solid (56.1 mg, 61%), mp 188.5–189 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.81 (s, 1H), 7.88 (d, J = 8.5 Hz, 2H), 7.72 (d, J = 1.5 Hz, 1H), 7.54 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.5 Hz, 1H), 7.21 (dd, J_1 = 1.5 Hz, J_2 = 8.5 Hz, 1H), 6.92 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 137.9, 135.8, 132.3, 130.5, 130.4, 129.0, 126.8, 124.3, 122.2, 113.3, 112.0, 98.8. IR (KBr): 3437, 1533, 1480, 1454, 1444, 1411, 1314, 1278, 1172, 1099, 1049, 1003, 908, 864, 791, 721, 665 cm^{-1}. HRMS (ESI) calcd for $C_{14}H_9BrClN$ $[M + H]^+$: 305.9680, found 305.9682.

5-Bromo-2-(4-bromophenyl)-1*H*-indole (3s). White solid, (61.2 mg, 58%), mp 161.7–162 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.82 (s, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.70

(d, J = 1.5 Hz, 1H), 7.66 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.5 Hz, 1H), 7.22 (dd, J_1 = 1.5 Hz, J_2 = 8.5 Hz, 1H), 6.90 (d, J = 1.5 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 137.9, 135.9, 131.9, 130.9, 130.4, 127.1, 124.3, 122.2, 120.8, 113.3, 112.0, 98.9. IR (KBr): 3450, 1530, 1487, 1454, 1417, 1314, 1179, 1076, 1046, 1006, 907, 869, 791, 736, 706, 665 cm^{-1}. HRMS (ESI) calcd for $C_{14}H_9Br_2N$ [M + H]$^+$: 349.9175, found 349.9182.

5-Bromo-2-(4-methoxyphenyl)-1*H*-indole (3t). Pale-yellow solid (45.4 mg, 50%), mp 224–225 °C (lit.[30] not reported). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.64 (s, 1H), 7.79 (d, J = 8.5 Hz, 2H), 7.66 (d, J = 2.0 Hz, 1H), 7.32 (d, J = 8.5 Hz, 1H), 7.16 (dd, J_1 = 2.0 Hz, J_2 = 8.5 Hz, 1H), 7.04 (d, J = 8.5 Hz, 2H), 6.75 (d, J = 2.0 Hz, 1H), 3.80 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 159.1, 139.3, 135.6, 130.7, 126.6, 124.2, 123.4, 121.7, 114.4, 112.9, 111.7, 96.9, 55.2.

5-Bromo-2-(naphthalen-1-yl)-1*H*-indole (3u). Oil (64.9 mg, 67%). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.83 (s, 1H), 8.29–8.27 (m, 1H), 8.04–7.99 (m, 2H), 7.82–7.81 (m, 1H), 7.72–7.71 (m, 1H), 7.64–7.58 (m, 3H), 7.42 (d, J = 8.5 Hz, 1H), 7.27 (dd, J_1 = 2.0 Hz, J_2 = 8.5 Hz, 1H), 6.74 (d, J = 2.0 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 138.5, 135.8, 134.0, 131.1, 130.8, 130.7, 129.0, 128.9, 127.9, 127.3, 126.7, 126.0, 125.7, 124.3, 122.7, 113.8, 112.2, 102.5. IR (KBr): 3411, 1729, 1437, 1391, 1321, 1298, 1116, 1049, 902, 869, 804, 788, 781, 686, 665 cm^{-1}. HRMS (ESI) calcd for $C_{18}H_{12}BrN$ [M + H]$^+$: 322.0226, found 322.0223.

5,7-Bibromo-2-phenyl-1*H*-indole (3v). White solid (79.9 mg, 72%), mp 163–164 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.60 (s, 1H), 7.98 (d, J = 7.0 Hz, 2H), 7.76 (s, 1H), 7.49–7.46 (m, 3H), 7.38 (t, J = 7.5 Hz, 1H), 6.99 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 141.0, 134.6, 131.5, 131.0, 128.7, 128.3, 126.3, 125.9, 121.6, 111.7, 104.7, 100.2. IR (KBr): 3427, 2922, 2364, 1742, 1561, 1457, 1340, 1303, 1180, 1072, 897, 842, 759, 724, 680, 514, 484, 442 cm^{-1}. HRMS (ESI) calcd for $C_{14}H_9Br_2N$ [M + H]$^+$: 349.9175, found 349.9175.

5-Iodo-2-phenyl-1*H*-indole (3w). White solid (60.3 mg, 63%), mp 237–238 °C. ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.72 (s, 1H), 7.89 (s, 1H), 7.85 (d, J = 8.5 Hz, 2H), 7.47 (t, J = 8.0 Hz, 2H), 7.36–7.32 (m, 2H), 7.26 (d, J = 8.0 Hz, 1H), 6.86 (s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 138.7, 136.1, 131.6, 131.4, 129.4, 128.9, 128.3, 127.8, 125.2, 113.7, 97.9, 83.0. IR (KBr): 3432, 2922, 2809, 2318, 1451, 1388, 796, 761, 505 cm^{-1}. HRMS (ESI) calcd for $C_{14}H_{10}IN$ [M + H]$^+$: 319.9931, found 319.9935.

1-Methyl-2-phenyl-1*H*-indole (3x). Yellow solid (23.2 mg, 37%), mp 100.5–101 °C (lit.[31] 100–101 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.61–7.56 (m, 3H), 7.54–7.49 (m, 3H), 7.45 (t, J = 7.5 Hz, 1H), 7.19 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 6.59 (s, 1H), 3.75 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 141.0, 138.1, 132.2, 129.0, 128.6, 127.9, 127.4, 121.4, 120.0, 119.5, 110.1, 101.1, 31.1.

2-Phenyl-4*H*-benzo[*d*][1,3]oxazin-4-one (4a). White solid (36.3 mg, 65%), mp 112–113 °C (lit.[5d] not reported). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.32–8.30 (m, 2H), 8.25–8.23 (m, 1H), 7.85–7.81 (m, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.58–7.56 (m, 1H), 7.64–7.50 (m, 3H).

2-Phenylquinazolin-4(3*H*)-one (5a). White solid (47.8 mg, 86%), mp 245–246 °C (lit.[5e] 245–246 °C). ^{1}H NMR (500 MHz, $CDCl_3$) δ 11.05 (s, 1H), 8.34–8.33 (m, 1H), 8.21–8.19 (m, 2H), 7.85–7.80 (m, 2H), 7.61–7.58 (m, 3H), 7.53–7.50 (m, 1H).

2-Phenyl-3-(phenylthio)-1*H*-indole (6a).[18] Oil (53.5 mg, 71%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07–7.10 (m, 1H), 7.14–7.16 (m, 2H), 7.18–7.22 (m, 3H), 7.31 (t, J = 7.5 Hz, 1H), 7.38–7.46 (m, 4H), 7.68 (d, J = 8.0 Hz, 1H), 7.77–7.78 (m, 1H), 8.60 (s, 1H).

Indolin-2-one (7a). White solid, (5.3 mg, 13%), mp 127–128 °C (lit.[32] 128 °C). ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.38 (s, 1H), 7.20–7.14 (m, 2H), 6.92 (t, J = 7.5 Hz, 1H), 6.80 (d, J = 7.5 Hz, 1H), 3.46 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 177.4, 142.4, 127.9, 125.3, 124.7, 122.4, 109.6, 36.2.

***N*-(2-(2-Oxo-2-phenylethyl)phenyl)acetamide (8b).** White solid, mp 99–100 °C (lit.[19] not reported). ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.35 (s, 1H), 8.01 (d, J = 7.5 Hz, 2H), 7.65 (t, J = 7.5 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.23 (t, J = 7.5 Hz, 2H), 7.13 (t, J = 7.5 Hz, 2H), 4.40 (s, 2H), 1.92 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 197.4, 168.2, 136.8, 136.7, 133.1, 131.2, 129.8, 128.6, 128.1, 126.9, 125.4, 125.0, 41.3, 23.1.

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