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Palladium-Catalyzed Cross-Coupling of 1-Aminoazoles with Aryl Chlorides: Application to the Synthesis of Unsymmetrical *N,N′*-Diaryl-1-aminoindoles

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Abstract: An efficient method for the selective mono-N-arylation of 1-aminoazoles to provide a range of *N*-aryl-1-aminoazoles in good yields is described. This process based on the use of tris(dibenzylideneacetone)dipalladium associated to Xphos as the catalyst system is general, and allows the coupling to proceed, for the first time, with a variety of cheaper and less reactive aryl chlorides. The sequential combination of selective monoarylation using aryl chlorides and a second N-arylation reaction using (hetero)aryl bromides and iodides proved to be useful for the rapid construction of non-symmetrical *N,N′*-diaryl-1-aminoindoles in good yields.

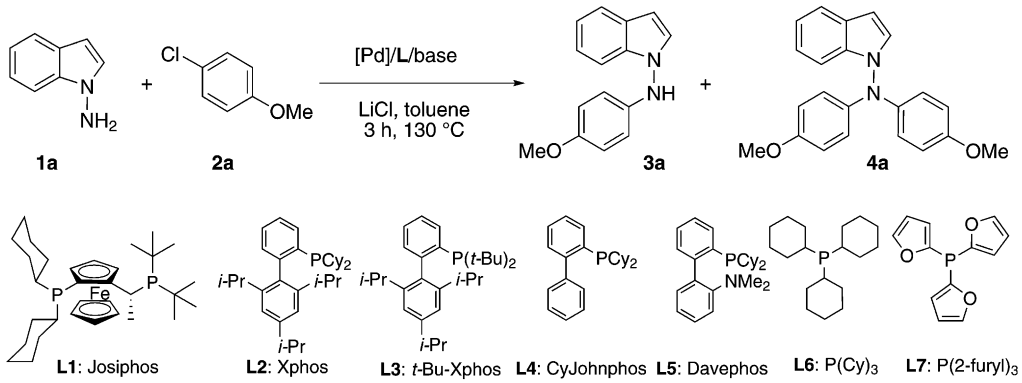
Keywords: 1-aminoazoles; aryl chlorides; C–N bond formation; palladium catalysis

Introduction

The indole unit is a heterocyclic privileged structure.[1] It probably represents the most important of all structural classes in drug discovery.[2] One of the most important subfamilies of indoles is *N*-substituted-1-aminoindoles, whose derivatives exhibit promising biological activities,[3] including antidepressant,[4] tyrosine hydroxylase inductors,[5] aromatase,[6] and acetylcholinesterase inhibitors.[7] In addition, these compounds are highly valuable intermediates in the synthesis of a number of important nitrogen-containing heterocyclic frameworks.[8] While *N*-substituted-1-aminoindoles clearly hold great potential in organic synthesis, a careful examination of the literature reveals a lack of methods for their preparation. They have been synthesized by electrolysis,[9] or Pd-catalyzed cyclization of *N,N′*-dimethyl-*o*-chloroarylacetaldehyde hydrazones.[10] Alternative routes consist in a Cu-catalyzed intramolecular cyclization of a suitable Boc-protected enehydrazine and subsequent deprotection,[11] or the Pd-catalyzed N-arylation of phenylhydrazines[12] followed by an intramolecular cyclization process.[13] All these multistep procedures are often moderate to low yielding, and the variety of substituents on the nitrogen atom is, however, limited. Therefore, the search for new selective and simple procedures that accommodates a wider combination of aryl and heteroaryl groups at the nitrogen atom of the 1-aminoindoles presents an interesting challenge. To address these issues, we decided to explore the ability of 1-aminoindole derivatives **1** to participate as nucleophiles in a palladium-catalyzed C–N[14] cross-coupling reaction with various (hetero)aryl halides.[15] In these instances, the challenge is to develop a valuable palladium catalyst system that allows, firstly, selective monoarylation of 1-aminoindoles and, secondly, prevents metal-mediated N–N bond cleavage,[16] thus resulting in the formation of undesired indole by-products.

In our preliminary study,[17] difficulties associated with challenging 1-aminoindoles have been addressed by the use of Josiphos ligand in combination with $Pd_2(dba)_3$ in the presence of *t*-BuOK as the base and LiCl as the additive. Under these conditions, 1-aminoindoles **1** were selectively coupled with the more reactive organic halides, aryl iodides and bromides to provide a variety of *N*-(hetero)aryl-1-aminoindoles **3**. In addition, we reported one example where the newly developed catalyst system also enabled, for the first time, efficient reactions with the cheap and less reactive aryl chlorides (Table 1, entry 1). On the basis of

Table 1. Optimization of the coupling reaction of **1a** with 4-chloroanisole under various conditions.[a]



Entry	[Pd]	[L]	Base	Solvent	Conversion[b] [%]	Yield[c] [%]	
						3a	**4a**
1	$Pd_2(dba)_3$	**L1**	*t*-BuOK	toluene	100	76	0
2	**$Pd_2(dba)_3$**	**L2**	***t*-BuOK**	**toluene**	**100**	**82**[d]	**0**
3	$Pd_2(dba)_3$	**L3**	*t*-BuOK	toluene	10	–	–
4	$Pd_2(dba)_3$	**L4**	*t*-BuOK	toluene	90	25	0
5	$Pd_2(dba)_3$	**L5**	*t*-BuOK	toluene	100	46	0
6	$Pd_2(dba)_3$	**L6**	*t*-BuOK	toluene	100	5	56
7	$Pd_2(dba)_3$	**L7**	*t*-BuOK	toluene	100	2	60
8	$Pd(OAc)_2$	**L2**	*t*-BuOK	toluene	30	–	–
9	$Pd_2(dba)_3$	**L2**	*t*-BuONa	toluene	100	51	0
10	$Pd_2(dba)_3$	**L2**	*t*-BuOK	anisole	100	65	0
11	$Pd_2(dba)_3$	**L2**	*t*-BuOK	dioxane	10	–	–
12	$Pd_2(dba)_3$	**L2**	*t*-BuOK	THF	13	–	–

[a] Reactions of **1a** (0.25 mmol) with 4-chloroanisole **2a** (0.5 mmol) were performed in a sealed Schlenk tube in toluene (2 mL) by using [Pd] (2.5 mol%), ligand (5 mol%), LiCl (0.5 mmol) and base (0.375 mmol).

[b] Conversion was determined by ^{1}H NMR in the crude reaction mixture based on the chemical shift of the proton signal (ppm) at the 2-position (**1a**: $\delta = 6.41$, **3a**: $\delta = 6.55$, **4a**: $\delta = 6.45$).

[c] Yield of isolated product.

[d] For control experiments, no conversion at all was observed in the absence of $Pd_2(dba)_3$ or **L2**, and in the absence of $Pd_2(dba)_3$ and **L2**.

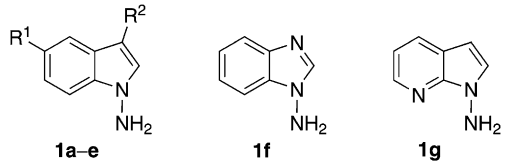
these preliminary results, we sought to improve three aspects of the scope of the (hetero)arylation of 1-aminoindoles **1**. First, because the high cost of Josiphos ligand (446 $/gram, Aldrich), we sought to investigate the scope of this coupling with cheaper ligands. Second, we sought to conduct the coupling with various aryl chlorides and to take advantage of the lower cost of these haloarenes without offsetting their cost advantage by using large amounts of catalyst. Third, we sought to couple 1-aminoindoles with high selectivity for mono(hetero)arylation but also to define conditions allowing access to non-symmetrical *N*,*N*′-diaryl-1-aminoindoles **6**. Each of these goals was met with success by using the $Pd_2(dba)_3$/Xphos combination. Herein we wish to disclose our full results that extend the scope of our earlier communication.[17]

Results and Discussion

To establish the appropriate conditions for the monoarylation reaction, 1-aminoindole **1a** and 4-chloroanisole **2a** were selected as model substrates. The coupling was investigated under our previously reported conditions,[17] using *t*-BuOK (2 equiv.) as the base, LiCl (2 equiv.) as the additive, and $Pd_2(dba)_3$ (2.5 mol%) as the catalyst in the presence of various ligands (5 mol%). As summarized in Table 1, screening of phosphine ligands revealed that they play an important role in the reaction selectivity. Thus, tricyclohexylphosphine (**L6**) and tri-2-furylphosphine (**L7**) gave mainly symmetrical *N*,*N*-diarylated product **4a** (entries 6 and 7), whereas dialkylbiarylphosphine ligands (**L2**, **L4**, and **L5**) selectively provided monoarylated 1-aminoindole **2a** (entries 2, 4 and 5). The use of the monodentate phosphine ligand, Xphos (66 $/gram, Aldrich) in combination with $Pd_2(dba)_3$ in toluene at 130 °C for 3 h proved to be superior to all other choices, providing exclusively **3a** in 82% yield

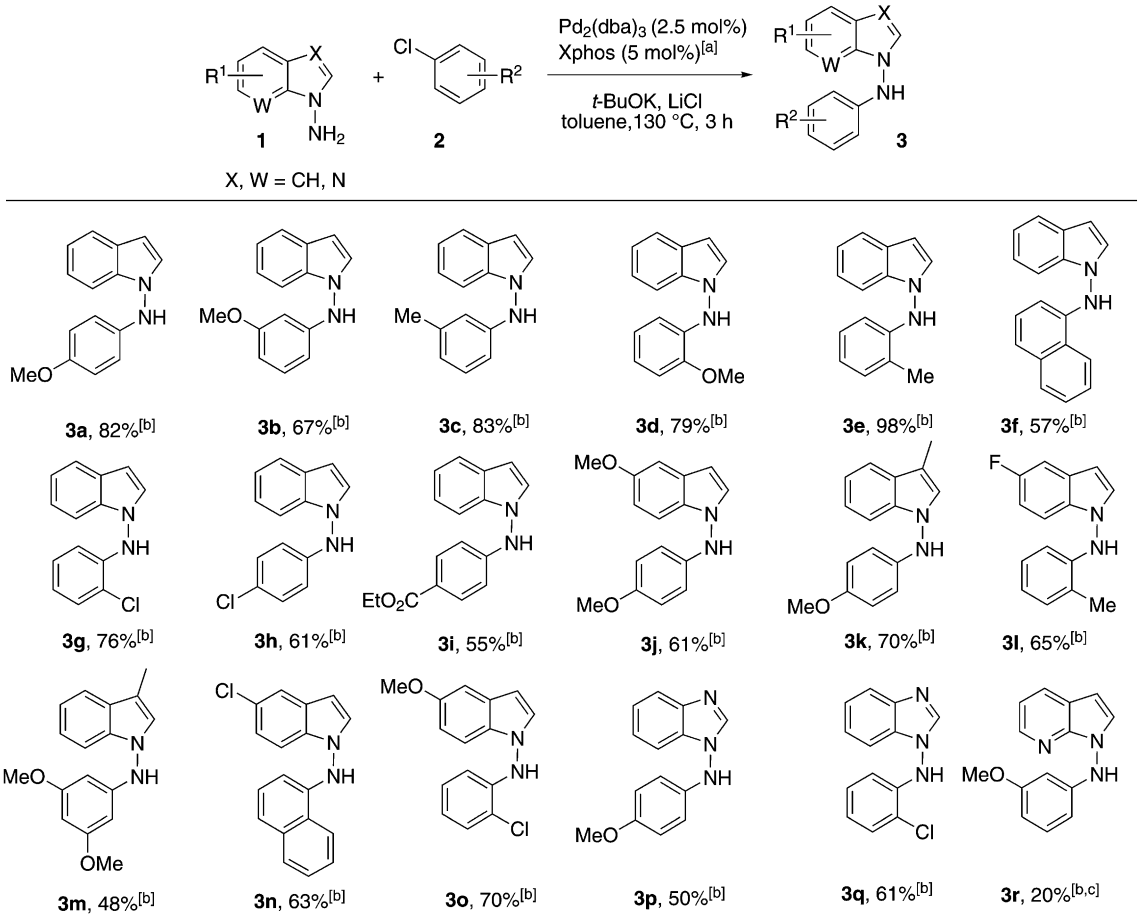
(compare entries 2 and 4, 5). Changing $Pd_2(dba)_3$ to $Pd(OAc)_2$ induced a lowering of the conversion rate (entry 8). Other parameters, for example, base and solvent were investigated. *t*-BuONa was also effective, albeit affording **3a** with slighly diminished yield (entry 9). Of the several solvents tested anisole, a non common solvent used for the N-arylation reaction, proved also to be effective providing **3a** but in a slightly lower yield (entry 10). It should be noted that this coupling of **1a** with 4-chloroanisole is not limited to a small scale (0.25 mmol) as it could be conveniently performed on a 1-g scale (5 mmol; 20-fold scale up) in 75% yield.

Motivated by these results, we next explored the scope of the reaction with various *N*-aminoazoles **1a–g** (Figure 1). Interestingly, attempts to expand the generality and applicability of the reaction proved to be successful and a wide range of aromatic moieties were incorporated, thus providing a functional handle for further manipulation. As depicted in Scheme 1, **1a** was readily reacted with functionalized aryl chlorides having *para*- and *meta*-electron-donating or electron-withdrawing substituents on the aryl ring to give the corresponding products **3a–c** and **3h, i** in good yields. In addition, the sterically demanding *ortho* substitution pattern was tolerated toward the coupling reaction of **1a**, leading to *N*-aryl-1-aminoindoles **3d–g** in



a: $R^1 = R^2 = H$
b: $R^1 = OMe$, $R^2 = H$
c: $R^1 = H$, $R^2 = Me$
d: $R^1 = F$, $R^2 = H$
e: $R^1 = Cl$, $R^2 = H$

Figure 1. 1-Aminoazoles used in this study.

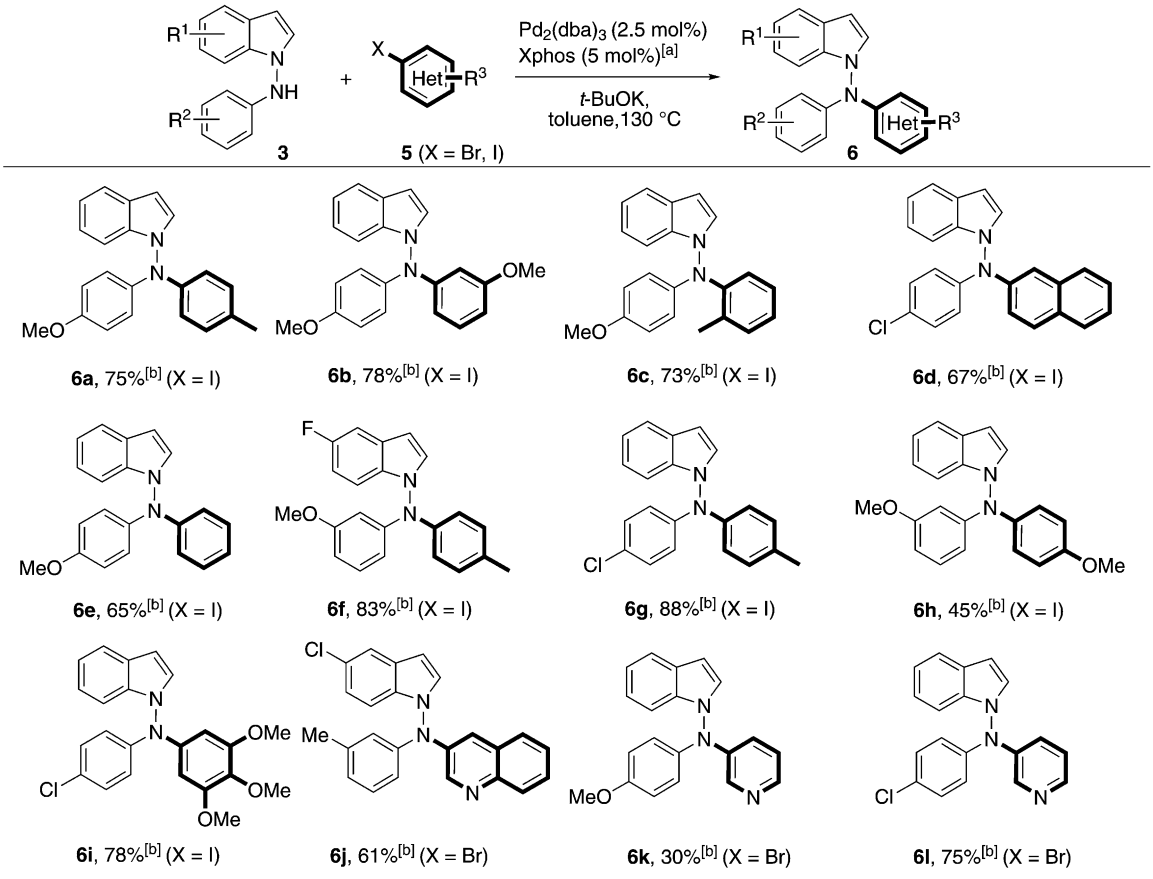


[a] Reactions of **1b–d** (0.25 mmol) with aryl chloride **2a** (0.5 mmol) were performed in a sealed Schlenk tube at 130 °C for 3 h in toluene (2 mL) in the presence of Pd_2dba_3 (2.5 mol%), Xphos (5 mol%), and *t*-BuOK (0.375 mmol).
[b] Yield of isolated product.
[c] The reaction was carried out with Josiphos as the ligand (5 mol%).

Scheme 1. Palladium-catalyzed monoarylation of 1-aminoazoles **1** with aryl chlorides **2**.

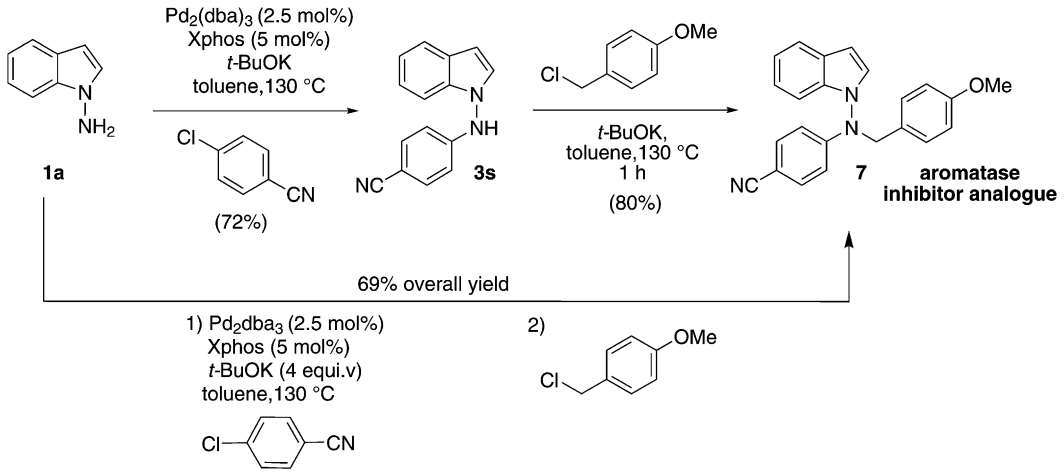
yields ranging from 57 to 98%, regardless of the electronic nature of the substituents. It is interesting to note that dichloro-substituted coupling partners 1,2- and 1,4-dichlorobenzene successfully underwent selective reaction, affording in good yields products **3g** and **3h**, respectively, without the competitive reaction on the remaining C–Cl bond. To expand the scope of our method further, a range of substituted *N*-aminoindoles **1b–e** as well as related azoles, such as *N*-aminobenzimidazole **1f**, and *N*-aminoazaindole **1g** were subjected to the coupling protocol with aryl chlorides (Scheme 1). We were pleased to observe that *N*-aminoindoles having an electron-donating or electron -withdrawing group on the aromatic nucleus, or at the C-3 position of the indole moiety led to the formation of the corresponding products **3j–o** in good yields. Interestingly, product **3n** revealed an excellent chemical selectivity of 1-chloronaphthalene over the C–Cl bond of 5-chloro-1-aminoindole **1e**, which could enjoy further metal-catalyzed functionalization processes.[18] Finally, this reaction was not limited to 1-aminoindole derivatives, since 1-aminobenzimidazole **1f**, and 1-aminoazaindole **1g** also afforded the coupling products **3p–r** in acceptable yields.

Given the high efficiency of our protocol for the selective preparation of *N*-aryl-1-aminoindoles **3**, we expected that the newly developed procedure would serve as an extremely useful and quick route to obtain non-symmetrical *N*,*N*′-diaryl-1-aminoindole derivatives **6** (Scheme 2). These classes of substituted heterocyclic compounds offer a high degree of structural diversity and have proven to be broadly useful as biologically active compounds.[19] In this context, we were pleased to observe that the optimal reaction conditions for the selective monoarylation of 1-aminoindoles **1** with aryl chlorides were found to be similar to those of the second N-arylation reaction of *N*-aryl-1-aminoindoles **3**, using $Pd_2(dba)_3$ as the palladium source, Xphos as the ligand, *t*-BuOK as the base and toluene as the solvent. These conditions proved to be effective with a wide range of (hetero)aryl bromides and iodides[20] **5** furnishing non-symmetrical *N*,*N*′-diaryl-1-aminoindoles **6a–l** in good yields, regardless of the electronic nature of the substituents in



[a] Reactions of **3** (0.25 mmol) with aryl halide (0.5 mmol) were performed in a sealed Schlenk tube at 130 °C in toluene (2 mL) in the presence of Pd_2dba_3 (2.5 mol%), Xphos (5 mol%), and *t*-BuOK (0.375 mmol).
[b] Yield of isolated product.

Scheme 2. Palladium-catalyzed synthesis of non-symmetrical *N*,*N*′-diaryl-1-aminoindoles **6**.



Scheme 3. Synthesis of the aromatase inhibitor analogue **7**.

both coupling partners **3** and **5** (Scheme 2). In addition, the steric effect of *ortho* substituents on the aryl halides had no impact on the outcome of the present reaction, since diaryl-1-aminoindole **6c** was formed in a good 73% yield. Interestingly, the reaction was found to proceed successfully when heterocyclic halides were used, such as 3-bromoquinoline and 2-bromopyridine, furnishing the desired *N*,*N*′-di-(hetero)aryl-1-aminoindoles **6j–l** in acceptable to good yields.

To illustrate the synthetic potential of our protocol, the 1-aminoindole **1a** enables the synthesis of aromatase inhibitor[21] analogue **7** having on the nitrogen atom an aryl nucleus and a benzyl unit (Scheme 3). Reaction of **1a** with 4-chlorobenzonitrile under our optimized conditions gave selectively **3s** in 72% yield. Further alkylation with 4-methoxybenzyl chloride in the presence of *t*-BuOK as the base and toluene as the solvent furnished the desired aromatase inhibitor analogue **7** in 80% yield. Because the base (*t*-BuOK) and solvent (toluene) used in both steps are similar, we decided to carry out in a one-pot fashion this transformation as it would be economically and environmentally advantageous over the multistep syntheses. Typically, in the first step, **1a** was reacted with 4-chlorobenzonitrile under the optimal reaction conditions. After completion, 4-methoxybenzyl chloride (2 equiv.) was introduced at room temperature and the medium was heated at 130 °C for 1 h. Under this protocol the desired product **7** was formed in 69% overall yield.

Conclusions

In summary, we have demonstrated that *N*-aminoindoles can be selectively arylated with a variety of cheaper and generally more available aryl chlorides using $Pd_2(dba)_3$/Xphos as the catalyst system, in the presence *t*-BuOK as the base and toluene as the solvent. To the best of our knowledge, this is the first general method for the arylation of 1-aminoazoles with aryl chlorides to provide selectively *N*-aryl-1-aminoindoles **3** in good to excellent yields. Sequential selective N-arylation reactions using aryl chlorides and then aryl bromides or iodides proved to be useful for the rapid construction of non-symmetrical *N*,*N*′-di-(hetero)aryl-1-amino-indoles **6** in good yields. We believe that this methodology should find broad applications in synthetic organic chemistry, as well as in the combinatorial and pharmaceutical sciences.

Experimental Section

General Experimental Methods

The compounds were all identified by the usual physical methods, that is, ^{1}H NMR, ^{13}C NMR (J-MOD), IR, MS (ESI). ^{1}H and ^{13}C NMR spectra were measured in $CDCl_3$ or DMSO-d_6 with a Bruker Avance-300. ^{1}H chemical shifts are reported in ppm from an internal standard TMS or of residual chloroform (7.27 ppm). The following abreviations are used: m (multiplet), s (singlet), bs (broad singlet), d (doublet), t (triplet) dd (doublet of doublet), td (triplet of doublet), q (quadruplet), qui (quintuplet), sex (sextuplet). ^{13}C chemical shifts are reported in ppm from the central peak of deuteriochloroform (77.14). IR spectra were measured on a Bruker Vector 22 spectrophotometer. MS were recorded on a Micromass spectrometer. Analytical TLC was performed on Merck precoated silica gel 60F plates. Merck silica gel 60 (0.015–0.040 mm) was used for column chromatography. Melting points were recorded on a Büchi B-450 apparatus and are uncorrected.

General Procedure for Palladium-Catalyzed Monoarylation of 1-Aminoazoles 1 with Aryl Chlorides 2

A flame-dried resealable Schlenk tube was charged with Pd_2dba_3 (2.5 mol%), Xphos (5 mol%), 1-aminoazole **1** (0.25 mmol), aryl chloride **2** (0.5 mmol), LiCl (0.5 mmol) and *t*-BuOK (0.375 mmol). The Schlenk tube was capped with a rubber septum, evacuated and backfilled with argon; then toluene (2 mL) was added through the septum. The septum was replaced with a teflon screwcap. The Schlenk tube was sealed, and the mixture was stirred at 130 °C for 3 h. The resulting suspension was cooled to room temperature and filtered through celite eluting with ethyl acetate. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product.

Analytical Data for *N*-Aryl-1-aminoazoles 3

***N*-(4-Methoxyphenyl)-1*H*-indol-1-amine (3a):** Yield: 78% (70 mg), white-yellow solid, mp 105–107 °C, $R_f = 0.53$ (cyclohexane/EtOAc 8:2); IR (neat): $\nu = 3457$, 3417, 3348, 3319, 3232, 2268, 2193, 2171, 2023, 1929, 1509, 1453, 1293, 1236, 1214, 1180, 1033, 8826, 763, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.65$ (d, $J = 6.9$ Hz, 1H), 7.32–7.23 (m, 1H), 7.24–7.08 (m, 3H), 6.76 (d, $J = 9.0$ Hz, 2H), 6.57–6.42 (m, 4H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 154.55$ (C), 141.11 (C), 135.86 (C), 128.70 (CH), 126.63 (C), 122.33 (CH), 121.08 (CH), 120.26 (CH), 114.77 (2CH), 114.25 (2CH), 109.50 (CH), 100.58 (CH), 55.63 (CH_3); MS (ESI positive): $m/z = 239$ $[M+H]^+$; HR-MS (APCI positive): $m/z = 239.1180$, calcd. for $C_{15}H_{14}N_2O$ (M+H): 239.1179.

***N*-(3-Methoxyphenyl)-1*H*-indol-1-amine (3b):** Yield: 67% (60 mg), white-yellow oil, $R_f = 0.53$ (cyclohexane/EtOAc 8:2); IR (neat): $\nu = 3309$, 3056, 2834, 2359, 2270, 2229, 2155, 2140, 2085, 2023, 1598, 11502, 1457, 1387, 1328, 1283, 1265, 1223, 1208, 1192, 1152, 1091, 1008 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.74$ (d, $J = 8.3$ Hz, 1H), 7.43–7.12 (m, 5H), 6.62 (d, $J = 3.4$ Hz, 1H), 6.61 (s, NH), 6.54 (dd, $J = 8.2$, 2.3 Hz, 1H), 6.28–6.11 (m, 2H), 3.75 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 160.94$ (C), 148.94 (C), 135.98 (C), 130.39 (CH), 128.79 (CH), 126.69 (C), 122.55 (CH), 121.19 (CH), 120.48 (CH), 109.53 (CH), 106.36 (CH), 105.46 (CH), 100.96 (CH), 99.11 (CH), 55.28 (OMe); MS (ESI positive): $m/z = 239$ $[M+H]^+$; HR-MS (ESI positive): $m/z = 239.1192$, calcd. for $C_{15}H_{14}N_2O$ (M+H): 239.1184.

***N*-(*m*-Tolyl)-1*H*-indol-1-amine (3c):** Yield: 83% (70 mg), brown oil, $R_f = 0.70$ (CH_2Cl_2/EtOAc 8:2); IR (neat): $\nu = 3465$, 3342, 3317, 3292, 2550, 2372, 2331, 2255, 2163, 2053, 1990, 1976, 1611, 1595, 1507, 1489, 1454, 1329, 1245, 1219, 1150, 1124, 1090, 1044, 1008 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.70$–7.66 (m, 1H), 7.36–7.28 (m, 1H), 7.25–7.16 (m, 3H), 7.10 (t, $J = 7.8$ Hz, 1H), 6.75 (d, $J = 7.5$ Hz, 1H), 6.57 (dd, $J = 3.3$, 0.8 Hz, 1H), 6.52 (bs, 1H), 6.38 (bs, 1H), 6.33 (dd, $J = 8.0$, 2.0 Hz, 1H), 2.26 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 147.40$ (C), 139.39 (C), 135.92 (C), 129.24 (CH), 128.68 (CH), 126.54 (C), 122.37 (CH), 122.06 (CH), 121.02 (CH), 120.28 (CH), 113.30 (CH), 109.90 (CH), 109.44 (CH), 100.72 (CH), 21.50 (CH_3); MS (ESI positive): $m/z = 223$ $[M+H]^+$; HR-MS (APCI positive): $m/z = 223.1244$, calcd. for $C_{15}H_{14}N_2$ (M+H): 223.1230.

***N*-(2-Methoxyphenyl)-1*H*-indol-1-amine (3d):** Yield: 79% (71 mg), white-yellow solid, mp 80–82 °C, $R_f = 0.50$ (cyclohexane/EtOAc 8:2); IR (neat): $\nu = 3480$, 3447, 3159, 2834, 2790, 2360, 2270, 2250, 2198, 2148, 2114, 2014, 1961, 1921, 1900, 1600, 1502, 1460, 1429, 1328, 1292, 1249, 1211, 1175, 1153, 11126, 1114, 1089, 1047, 1027, 913 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.65$ (d, $J = 8.2$ Hz, 1H), 7.35–7.09 (m, 5H), 6.96–6.80 (m, 2H), 6.71 (t, $J = 7.5$ Hz, 1H), 6.55 (d, $J = 3.3$ Hz, 1H), 6.10 (d, $J = 7.9$ Hz, 1H), 3.99 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 146.41$ (C), 136.84 (C), 135.99 (C), 128.99 (CH), 126.75 (C), 122.43 (CH), 121.47 (CH), 121.16 (CH), 120.92 (CH), 120.36 (CH), 112.72 (CH), 110.20 (CH), 109.49 (CH), 100.77 (CH), 55.78 (OMe); MS (ESI positive): $m/z = 239$ $[M+H]^+$; HR-MS (ESI): $m/z = 239.1182$, calcd. for $C_{15}H_{14}N_2O$ (M+H): 239.1184.

***N*-(*o*-Tolyl)-1*H*-indol-1-amine (3e):** Yield: 98% (80 mg), white-yellow solid, mp 98–100 °C, $R_f = 0.39$ (cyclohexane/EtOAc 9:1); IR (neat): $\nu = 3481$, 3351, 3328, 3084, 2947, 2360, 2330, 2134, 1996, 1504, 1245, 742, 714, 647, 632 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.81$ (s, 1H), 7.76–7.62 (m, 1H), 7.52 (d, $J = 7.6$ Hz, 1H), 7.33–7.14 (m, 4H), 7.06 (t, $J = 7.5$ Hz, 1H), 6.89 (t, $J = 7.5$ Hz, 1H), 6.61 (d, $J = 3.3$ Hz, 1H), 6.12 (d, $J = 8.1$ Hz, 1H), 2.54 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 147.54$ (C), 139.56 (C), 136.11 (CH), 129.41 (CH), 128.82 (CH), 126.73 (C), 122.55 (CH), 122.27 (CH), 121.19 (C), 120.46 (CH), 113.48 (CH), 110.08 (CH), 109.59 (CH), 100.92 (CH), 21.65 (CH_3); MS (ESI positive): $m/z = 223$ $[M+H]^+$; HR-MS (ESI): $m/z = 223.1228$, calcd. for $C_{15}H_{14}N_2$ $(M+H)^+$: 223.1235.

***N*-(Naphthalen-1-yl)-1*H*-indol-1-amine (3f):** Yield: 57% (56 mg), white-yellow oil, $R_f = 0.49$ (cyclohexane/EtOAc 9:1); IR (neat): $\nu = 2936$, 2210, 2173, 2037, 2020, 1984, 1590, 1504, 1486, 1462, 1449, 1425, 1410, 1353, 1325, 1264, 1234, 1209, 1180 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.07$–7.83 (m, 2H), 7.78–7.68 (m, 1H), 7.66–7.51 (m, 2H), 7.44 (d, $J = 8.2$ Hz, 1H), 7.34–7.11 (m, 6H), 6.64 (d, $J = 3.3$ Hz, 1H), 6.13 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 142.08$ (C), 135.79 (C), 134.19 (C), 128.99 (CH), 128.80 (CH), 126.82 (C), 126.37 (CH), 126.30 (CH), 125.85 (CH), 122.62 (CH), 122.26 (C), 121.38 (CH), 121.34 (CH), 120.58 (CH), 119.63 (CH), 109.50 (CH), 107.45 (CH), 101.18 (CH); MS (ESI positive): $m/z = 259$ $[M+H]^+$; HR-MS (ESI): $m/z = 259.1234$, calcd. for $C_{18}H_{14}N_2$ $(M+H)^+$: 259.1235.

***N*-(2-Chlorophenyl)-1*H*-indol-1-amine (3g):** Yield: 76% (70 mg), white-yellow solid, mp 75–77 °C, $R_f = 0.67$ (cyclohexane/EtOAc 8:2); IR (neat): $\nu = 3315$, 2178, 2153, 1593, 1514, 1491, 1453, 1389, 1329, 1296, 1238, 1216, 1132, 1088, 1052, 1035, 1009, 931 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.81$–7.68 (m, 1H), 7.44 (dd, $J = 7.9$, 1.3 Hz, 1H), 7.37–7.18 (m, 4H+NH), 7.06 (t, $J = 8.0$ Hz, 1H), 6.90 (td, $J = 7.8$, 1.5 Hz, 1H), 6.65 (d, $J = 3.3$ Hz, 1H), 6.18 (d, $J = 8.1$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 143.31$ (C), 135.72 (C), 129.47 (CH), 128.70 (CH), 128.16 (CH), 126.80 (C), 122.77 (CH), 121.53 (CH), 121.31 (CH), 120.72 (CH), 118.08 (C), 113.63 (CH), 109.32 (CH), 101.37 (CH); MS (ESI positive): $m/z = 243$ $[M+H]^+$; HR-MS (ESI positive): $m/z = 243.0690$, calcd. for $C_{14}H_{11}ClN_2$ (M+H): 243.0689.

***N*-(4-Chlorophenyl)-1*H*-indol-1-amine (3h):** Yield: 61% (56 mg), white-yellow solid, mp 103–105 °C, $R_f = 0.50$ (cyclohexane/EtOAc 9:1); IR (neat): $\nu = 3447$, 3338, 3132, 3058, 2330, 2124, 1597, 1514, 1490, 1453, 1327, 1282, 1243, 1216, 1173, 1125, 1089, 1045, 1007, 929 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$): $\delta = 7.74$–7.59 (m, 1H), 7.35–7.02 (m, 6H), 6.61 (s, 1H), 6.55 (dd, $J = 3.4$, 0.7 Hz, 1H), 6.44 (d, $J = 8.9$ Hz, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 146.08$ (C), 135.77 (C), 129.48 (2CH), 128.56 (CH), 126.83 (C), 126.14 (C), 122.74 (CH), 121.36 (CH), 120.70 (CH), 114.08 (2CH), 109.43 (CH), 101.29 (CH); MS (APCI negative): $m/z = 241$ $[M-H]^-$; HR-MS (APCI negative): $m/z = 241.0525$, calcd. for $C_{14}H_{11}ClN_2$ (M−H): 241.0527.

Ethyl 4-[(1*H*-indol-1-yl)amino]benzoate (3i): Yield: 55% (60 mg), white-yellow solid, mp 165–167 °C, $R_f = 0.50$ (cyclohexane/EtOAc 8:2); IR (neat): $\nu = 3469$, 3421, 3368, 3184, 3105, 2357, 2211, 2016, 1964, 1713, 1688, 1605, 1511, 1367, 1278, 1254, 1217, 1172, 1106, 766 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.89$ (d, $J = 8.8$ Hz, 2H), 7.72–7.59 (m, 1H), 7.24–7.13 (m, 4H), 6.92 (s, NH), 6.57 (d, $J = 3.2$ Hz, 1H), 6.49 (d, $J = 8.8$ Hz, 2H), 4.32 (q, $J = 7.1$ Hz, 2H), 1.35 (t, $J = 7.1$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.31$ (C), 151.05 (C), 135.57 (C), 131.45 (2CH), 128.35 (CH), 126.64 (C), 123.01 (C), 122.70 (CH), 121.24 (CH), 120.67 (CH), 111.63 (2CH), 109.20 (CH), 101.41 (CH), 60.58 (CH_2), 14.35 (CH_3); MS (ESI positive): $m/z = 281$ $[M+H]^+$; HR-MS (ESI): $m/z = 281.1290$, calcd. for $C_{17}H_{16}N_2O_2$ (M+H): 281.1299.

5-Methoxy-*N*-(4-methoxyphenyl)-1*H*-indol-1-amine (3j): Yield: 61% (50 mg), white-yellow solid, mp 74–76 °C, $R_f = 0.43$ (cyclohexane/EtOAc 8:2); IR (neat): $\nu = 3312$, 3240, 2833, 2363, 2180, 2001, 1622, 1587, 1509, 1489, 1469, 1433, 1325, 1287, 1243, 1229, 1210, 1180, 1147, 1090, 1031, 937, 823, 800 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.17$ (m, 2H), 7.11 (d, $J = 2.3$ Hz, 1H), 6.84 (dd, $J = 9.0$, 2.3 Hz, 1H), 6.76 (d, $J = 9.0$ Hz, 2H), 6.52–6.42 (m, 4H), 3.86 (s, 3H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 154.59$ (C), 154.52 (C), 141.19 (C), 130.98 (C), 129.20 (CH), 127.04 (C), 114.75 (2CH), 114.18 (2CH), 112.54 (CH), 110.26 (CH), 102.78 (CH), 100.03 (CH), 55.82 (OMe), 55.61 (OMe); MS (APCI positive): $m/z = 269$ $[M+H]^+$; HR-MS (APCI): $m/z = 269.1279$, calcd. for $C_{16}H_{16}N_2O_2$ (M+H): 269.1285.

***N*-(4-Methoxyphenyl)-3-methyl-1*H*-indol-1-amine (3k):** Yield: 70% (59 mg), white-yellow solid, mp 115–117 °C, $R_f = 0.33$ (cyclohexane/EtOAc 9:1); IR (neat): $\nu = 3429$, 2338, 2321, 2246, 2207, 2164, 2060, 2043, 2023, 1984, 1941, 1510, 1453, 1237, 1180, 1033, 824, 741, 703 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.60$ (dd, $J = 6.5$, 1.7 Hz, 1H), 7.29–7.24 (m, 1H), 7.22–7.10 (m, 2H), 6.96 (d, $J = 0.9$ Hz, 1H), 6.76 (d, $J = 8.9$ Hz, 2H), 6.50 (d, $J = 8.9$ Hz, 2H), 6.40 (s, NH), 3.74 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 154.64$ (C), 141.52 (C), 136.49 (C), 127.10 (C), 126.10 (CH), 122.43 (CH), 119.71 (CH), 119.12 (CH), 114.91 (2CH), 114.38 (2CH), 110.09 (C), 109.44 (CH), 55.78 (OMe), 9.75 (CH_3); MS (ESI positive): $m/z = 253$ $[M+H]^+$; HR-MS (ESI): $m/z = 253.1347$, calcd. for $C_{16}H_{16}N_2O$ $(M+H)^+$: 253.1341.

5-Fluoro-*N*-(*o*-tolyl)-1*H*-indol-1-amine (3l): Yield: 48% (46 mg), orange oil, $R_f = 0.46$ (cyclohexane/EtOAc 9:1); IR (neat): $\nu = 3361$, 2174, 2040, 1589, 1501, 1469, 1442, 1364, 1335, 1300, 1274, 1229, 1124, 1047, 945, 863 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.43$ (dd, $J = 9.4$, 2.3 Hz, 1H), (dd, 7.32 (dd, $J = 9.4$, 2.3 Hz, 1H), 7.25 (d, $J = 3.3$ Hz, 1H), 7.23–7.10 (m, 2H), 7.05–6.92 (m, 2H), 6.95–6.78 (m, 2H), 6.53 (d, $J = 3.4$ Hz, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 158.45$ (C) (d, $J = 234.9$ Hz), 145.0 (C), 132.49 (C), 130.69 (CH), 130.44 (CH), 127.43 (CH), 126.88 (d, $J = 10.3$ Hz), 121.58 (C), 121.08 (CH), 111.89 (CH), 110.94 (d, $J = 26.4$ Hz), 110.18 (d, $J = 9.7$ Hz), 106.08 (d, $J = 23.7$ Hz), 100.82 (d, $J = 4.4$ Hz), 17.19 (CH_3); ^{19}F NMR (188 MHz, $CDCl_3$): $\delta = -122.3$ (s); MS (APCI positive): $m/z = 241$ $[M+H]^+$; HR-MS (APCI positive): $m/z = 241.1143$, calcd. for $C_{15}H_{13}FN_2$ (M+H): 241.1136.

***N*-(3,5-Dimethoxyphenyl)-3-methyl-1*H*-indol-1-amine (3m):** Yield: 48% (46 mg), white-yellow oil, $R_f = 0.30$ (cyclohexane/EtOAc 9:1); IR (neat): $\nu = 3489$, 3342, 2837, 2162, 2059, 2021, 1621, 1596, 1509, 1478, 1459, 1416, 1343, 1309, 1229, 1204, 1149, 1111, 1068, 1059, 11010, 993 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.58$ (d, $J = 7.0$ Hz, 1H), 7.42–7.04 (m, 3H), 6.93 (s, 1H), 6.49 (s, 1H), 6.03 (s, 1H), 5.72 (d, $J = 2.0$ Hz, 2H), 3.68 (s, 6H), 2.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 161.91$ (2C), 149.90 (C), 136.54 (C), 127.05 (C), 126.06 (CH), 122.53 (CH), 119.80 (CH), 119.10 (CH), 110.31 (C), 109.33 (CH), 92.93 (CH), 91.70 (CH), 55.38 (2OMe), 9.77 (CH_3); MS (ESI positive): $m/z = 283$ $[M+H]^+$; HR-MS (ESI positive): $m/z = 283.1448$, calcd. for $C_{17}H_{18}N_2O_2$ (M+H): 283.1447.

5-Chloro-*N*-(naphthalen-1-yl)-1*H*-indol-1-amine (3n): Yield: 63% (60 mg), white-yellow oil, $R_f = 0.47$ (cyclohexane/EtOAc 9:1) ; IR (neat): $\nu = 3471$, 3449, 3418, 3347, 3256, 3233, 3075, 2361, 2246, 2216, 2189, 2163, 2072, 2043, 2024, 1598, 1581, 1526, 1507, 1481, 1457, 1403, 1271, 1205, 1153, 1093, 1058, 905 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.05$–7.83 (m, 2H), 7.67 (d, $J = 1.8$ Hz, 1H), 7.63–7.51 (m, 2H), 7.45 (d, $J = 8.2$ Hz, 1H), 7.28 (d, $J = 3.3$ Hz, 1H), 7.24–7.09 (m, 4H), 6.56 (dd, $J = 3.3$, 0.7 Hz, 1H), 6.08 (d, $J = 7.6$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 141.80$ (C), 134.29 (C), 134.22 (C), 130.09 (CH), 129.04 (CH), 127.74 (C), 126.41 (CH), 126.28 (CH), 126.01 (CH), 123.02 (CH), 122.28 (C), 121.72 (CH), 120.77 (CH), 119.53 (CH), 110.61 (CH), 107.44 (CH), 100.87 (CH); MS (ESI positive): $m/z = 293$ $[M+H]^+$; HR-MS (APCI positive): $m/z = 293.0814$, calcd. for $C_{18}H_{13}ClN_2$ (M+H): 293.0820.

***N*-(2-Chlorophenyl)-5-methoxy-1*H*-indol-1-amine (3o):** Yield: 70% (59 mg), white-yellow oil, $R_f = 0.69$ (cyclohexane/EtOAc 8:2); IR (neat): $\nu = 3423$, 3337, 2832, 2361, 2163, 2145, 2013, 1961, 1623, 1595, 1494, 1476, 1442, 1385, 1362, 1343, 1301, 1284, 1251, 1229, 1202, 1146, 1127, 1089, 1053, 1032, 936 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.35$ (d, $J = 7.9$ Hz, 1H), 7.21–7.08 (m, 4H), 7.00 (t, $J = 7.8$ Hz, 1H), 6.92–6.75 (m, 2H), 6.49 (d, $J = 3.2$ Hz, 1H), 6.10 (d, $J = 8.1$ Hz, 1H), 3.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 154.82$ (C), 143.26 (C), 130.69 (C), 129.31 (CH), 129.10 (CH), 128.03 (CH), 127.12 (C), 121.37 (CH), 117.89 (C), 113.47 (CH), 112.83 (CH), 109.98 (CH), 102.90 (CH), 100.74 (CH), 55.81 (OMe); MS (ESI positive): $m/z = 273$ $[M+H]^+$; HR-MS (ESI positive): $m/z = 273.0806$, calcd. for $C_{15}H_{13}ClN_2O$ (M+H): 273.0795.

***N*-(2-Chlorophenyl)-1*H*-benzo[*d*]imidazol-1-amine (3p):** Yield: 50% (45 mg), white-yellow oil, $R_f = 0.54$ (EtOAc 100%); IR (neat): $\nu = 3419$, 3398, 3351, 2365, 2242, 2174, 2025, 1606, 1510, 1478, 1450, 1306, 1277, 1236, 1204, 1175, 1119, 1071, 1032, 1002 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.05$ (s, 1H), 7.82 (d, $J = 7.6$ Hz, 1H), 7.38–7.22 (m, 3H), 6.78 (d, $J = 9.0$ Hz, 2H), 6.78 (s, NH), 6.58 (d, $J = 9.0$ Hz, 2H), 3.74 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 155.36$ (C), 142.12 (C), 139.71 (C), 133.22 (C), 123.80 (CH), 122.96 (CH), 120.94 (CH), 115.02 (5CH), 109.90 (CH), 55.74 (CH_3); MS (ESI positive): $m/z = 240$ $[M+H]^+$; HR-MS (ESI

positive): $m/z = 240.1141$, calcd. for $C_{14}H_{13}N_3O$ (M+H): 240.1137.

***N*-(2-Chlorophenyl)-1*H*-benzo[*d*]imidazol-1-amine (3q):** Yield: 30% (25 mg), white-yellow oil, $R_f = 0.28$ (cyclohexane/EtOAc 8:2); IR (neat): $n = 3441$, 3415, 3394, 3377, 3345, 3314, 3258, 3189, 3113, 3063, 2951, 2811, 2360, 2282, 2207, 2177, 2154, 2131, 2073, 2019, 1988, 1968, 1923, 1594, 837, 817, 742 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.07$ (s, 1H), 7.87–7.81 (m, 1H), 7.41 (d, $J = 1.4$ Hz, 1H), 7.37–7.19 (m, 4H), 7.08–7.00 (m, 1H), 6.91 (td, $J = 7.7$, 1.5 Hz, 1H), 6.20 (dd, $J = 8.1$, 1.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta =$ 143.97 (CH), 142.07 (C), 142.07 (C), 132.90 (C), 129.80 (CH), 128.36 (CH), 124.16 (CH), 123.29 (CH), 122.65 (CH), 121.17 (CH), 118.90 (C), 113.86 (CH), 109.56 (CH); MS (ESI positive): $m/z = 244$ $[M+H]^+$; HR-MS (ESI positive): $m/z = 244.0640$, calcd. for $C_{13}H_{10}ClN_3$ (M+H): 244.0642.

***N*-(3-Methoxyphenyl)-1*H*-pyrrolo[2,3-*b*]pyridin-1-amine (3r):** Yield: 20% (10 mg), white-yellow oil, $R_f = 0.50$ (cyclohexane/EtOAc 9:1); IR (neat): $\nu = 3488$, 3202, 2931, 2334, 2187, 2159, 2133, 1931, 1608, 1591, 1515, 1493, 1465, 1420, 1360, 1326, 1291, 1270, 1254, 1217, 1180, 1048, 894, 797, 762, 689 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.38$ (dd, $J = 4.7$, 1.5 Hz, 1H), 7.96 (dd, $J = 7.8$, 1.6 Hz, 1H), 7.51 (d, $J =$ 3.6 Hz, 1H), 7.47–7.30 (m, 3H), 7.13 (dd, $J = 7.8$, 4.7 Hz, 1H), 6.89 (ddd, $J = 8.1$, 2.5, 1.0 Hz, 1H), 6.62 (d, $J = 3.7$ Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 160.44$ (C), 147.66 (C), 143.74 (CH), 139.73 (C), 130.19 (CH), 129.18 (CH), 128.03 (CH), 121.75 (C), 116.82 (CH), 116.34 (CH), 112.01 (CH), 110.21 (CH), 101.75 (CH), 55.58 (CH_3); MS (ESI positive): $m/z = 240$ $[M+H]^+$; HR-MS (ESI positive): $m/z = 240.1133$, calcd. for $C_{14}H_{13}N_3O$ (M+H): 240.1131.

4-[(1*H*-Indol-1-yl)amino]benzonitrile (3s): Yield: 72% (64 mg), white-yellow solid, mp 140–142 °C, $R_f = 0.50$ (cyclohexane/EtOAc 8:2); IR (neat): $\nu = 3370$, 3127, 2437, 2361, 2343, 2220, 2197, 2158, 2124, 2107, 22082, 2061, 2020, 1995, 1947, 1908, 1606, 1512, 1455, 1216, 830 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.72$–7.61 (m, 1H), 7.47 (d, $J =$ 8.8 Hz, 2H), 7.24–7.12 (m, 4H), 6.99 (s, 1H), 6.59 (d, $J =$ 3.4 Hz, 1H), 6.51 (d, $J = 8.8$ Hz, 2H) ; ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 150.87$ (C), 135.56 (C), 134.05 (2CH), 128.17 (C), 123.14 (CH), 121.57 (CH), 121.11 (CH), 119.41 (CH), 112.54 (CH), 109.15 (CH), 103.90 (C), 102.12 (CH); MS (APCI positive): m/z = 234 $[M+H]^+$; HR-MS (APCI positive): $m/z = 234.1011$, calcd. for $C_{15}H_{11}N_3$ (M+H): 234.1026.

General Procedure for Palladium-Catalyzed Synthesis of Unsymmetrical *N*,*N*′-Diaryl-1-aminoindoles 6

A flame-dried resealable Schlenk tube was charged with Pd_2dba_3 (2.5 mol%), Xphos (5 mol%), *N*-aryl-1-aminoazole **3** (0.25 mmol), aryl halide **5** (0.5 mmol) and *t*-BuOK (0.375 mmol). The Schlenk tube was capped with a rubber septum, evacuated and backfilled with argon; then, toluene (2 mL) was added through the septum. The septum was replaced with a teflon screwcap. The Schlenk tube was sealed, and the mixture was stirred at 130 °C. The resulting suspension was cooled to room temperature and filtered through celite eluting with ethyl acetate. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product.

Analytical Data for Non-Symmetrical *N*,*N*′-Di(hetero)aryl-1-aminoindoles 6

***N*-(4-Methoxyphenyl)-*N*-(*p*-tolyl)-1*H*-indol-1-amine (6a):** Yield: 75% (52 mg), white-yellow oil, $R_f = 0.67$ (cyclohexane/EtOAc 95:5); IR (neat): $\nu = 3487$, 3459, 3411, 3370, 3344, 3313, 3213, 33184, 3120, 2904, 2565, 22533, 2474, 2364, 2213, 2187, 2133, 2107, 2062, 2043, 2006, 1506, 1246, 1176, 809 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.67$ (d, $J =$ 7.6 Hz, 1H), 7.41 (d, $J = 8.0$ Hz, 1H), 7.29 (d, $J = 3.4$ Hz, 1H), 7.24–7.13 (m, 2H), 7.11 (d, $J = 9.1$ Hz, 2H), 7.03 (d, $J =$ 8.7 Hz, 2H), 6.83 (d, $J = 9.1$ Hz, 2H), 6.73 (d, $J = 8.6$ Hz, 2H), 6.60 (dd, $J = 3.4$, 0.8 Hz, 1H), 3.78 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 156.30$ (C), 144.24 (C), 138.82 (C), 135.48 (C), 131.37 (C), 129.69 (2CH), 127.59 (CH), 126.20 (C), 122.67 (CH), 122.49 (2CH), 121.09 (CH), 120.46 (CH), 117.02 (2CH), 114.58 (2CH), 109.81 (CH), 101.57 (CH), 55.51 (OMe), 20.58 (CH_3); MS (ESI positive): $m/z = 329$ $[M+H]^+$; HR-MS (ESI positive): $m/z = 329.1669$, calcd. for $C_{22}H_{20}N_2O$ (M+H): 329.1654.

***N*-(3-Methoxyphenyl)-*N*-(4-methoxyphenyl)-1*H*-indol-1-amine (6b):** Yield: 78% (56 mg), white-yellow oil, $R_f = 0.50$ (cyclohexane/EtOAc 95:5); IR (neat): $\nu = 3371$, 3000, 2835, 2371, 2332, 2285, 2194, 2089, 2022, 1977, 1961, 1599, 1581, 1507, 1490, 1452, 1437, 1329, 1245, 1210, 1183, 1151, 1088, 1033, 1008, 830 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.66$ (d, $J = 7.3$ Hz, 1H), 7.42 (d, $J = 8.2$ Hz, 1H), 7.33–6.99 (m, 6H), 6.85 (d, $J = 9.0$ Hz, 2H), 6.59 (d, $J = 3.4$ Hz, 1H), 6.53–6.43 (m, 1H), 6.34–6.24 (m, 2H), 3.78 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 160.62$ (C), 157.11 (C), 148.39 (C), 138.06 (C), 135.54 (C), 130.04 (CH), 127.63 (CH), 126.34 (C), 124.30 (2CH), 122.86 (CH), 121.25 (CH), 120.64 (CH), 114.79 (2CH), 109.87 (CH), 108.62 (CH), 106.30 (CH), 102.33 (CH), 101.86 (CH), 55.62 (OMe), 55.29 (OMe); MS (ESI positive): $m/z = 345$ $[M+H]^+$; HR-MS (ESI positive): $m/z = 345.1586$, calcd. for $C_{22}H_{20}N_2O_2$ (M+H): 345.1603.

***N*-(4-Methoxyphenyl)-*N*-(*o*-tolyl)-1*H*-indol-1-amine (6c):** Yield: 73% (50 mg), white-yellow oil, $R_f = 0.84$ (cyclohexane/EtOAc 9:1); IR (neat): $\nu = 3457$, 3384, 3058, 2927, 2198, 2176, 2147, 1969, 1505, 1451, 1243, 1211, 1180, 1126, 1034, 826, 762 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.63$ (d, $J =$ 7.1 Hz, 1H), 7.38 (d, $J = 7.8$ Hz, 1H), 7.29–7.05 (m, 7H), 6.73 (d, $J = 9.1$ Hz, 2H), 6.55 (d, $J = 3.4$ Hz, 1H), 6.51 (d, $J =$ 9.1 Hz, 2H), 3.74 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 155.02$ (C), 144.49 (C), 141.23 (C), 135.64 (C), 133.51 (C), 131.64 (CH), 127.55 (CH), 127.20 (CH), 126.14 (C), 125.75 (CH), 123.48 (CH), 122.68 (CH), 121.19 (CH), 120.45 (CH), 118.78 (2CH), 114.54 (2CH), 110.18 (CH), 101.36 (CH), 55.65 (OMe), 19.18 (CH_3); MS (APCI positive): $m/z = 329$ $[M+H]^+$; HR-MS (APCI positive): $m/z =$ 329.1637, calcd. for $C_{22}H_{20}N_2O$ (M+H): 329.1648.

***N*-(4-Chlorophenyl)-*N*-(naphthalen-2-yl)-1*H*-indol-1-amine (6d):** Yield: 67% (51 mg), white-yellow oil, $R_f = 0.77$ (cyclohexane/EtOAc 95:5); IR (neat): $\nu = 1631$, 1591, 1513, 1488, 1308, 1287, 1261, 1226, 1163, 1129, 1091, 1072, 1045, 1013, 994, 976, 869, 852, 820, 801, 766, 745 cm^{-1}; ^1H NMR (300 MHz, acetone-d_6): $\delta = 7.77$–7.66 (m, 2H), 7.62–7.51 (m, 2H), 7.45 (d, $J = 3.4$ Hz, 1H), 7.37 (d, $J = 2.3$ Hz, 1H), 7.34–7.23 (m, 3H), 7.20 (d, $J = 9.1$ Hz, 2H), 7.12 (dd, $J = 9.0$, 2.4 Hz, 1H), 7.07–6.94 (m, 2H), 6.87 (d, $J = 9.0$ Hz, 2H), 6.55 (dd, $J = 3.4$, 0.9 Hz, 1H); ^{13}C NMR (75 MHz, acetone-

d_6): δ = 149.78 (C), 147.95 (C), 140.58 (C), 139.34 (C), 135.83 (C), 134.68 (CH), 134.52 (2CH), 133.16 (C), 133.16 (CH), 132.80 (CH), 132.43 (CH), 131.93 (CH), 131.77 (C), 130.24 (CH), 128.10 (CH), 126.48 (CH), 125.98 (CH), 125.35 (2CH), 125.18 (CH), 120.77 (CH), 114.62 (CH), 107.31 (CH); MS (ESI positive): m/z = 369 $[M+H]^+$; HR-MS (APCI positive): m/z = 369.1107, calcd. for $C_{24}H_{17}ClN_2$ (M+H): 369.1121.

***N*-(4-Methoxyphenyl)-*N*-phenyl-1*H*-indol-1-amine (6e):** Yield: 65% (40 mg), white-yellow oil, R_f = 0.87 (cyclohexane/EtOAc 9:1); IR (neat): ν = 3323, 3274, 2962, 2360, 2265, 1594, 1507, 1491, 11455, 1246, 1182, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.65 (d, J = 7.0 Hz, 1H), 7.39 (d, J = 7.5 Hz, 1H), 7.28 (d, J = 3.3 Hz, 1H), 7.23–7.09 (m, 6H), 6.91 (t, J = 8.3 Hz, 1H), 6.87–6.80 (m, 2H), 6.72 (dd, J = 7.7, 1.1 Hz, 2H), 6.62–6.56 (m, 1H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 156.96 (C), 146.91 (C), 138.29 (C), 135.54 (C), 129.27 (2CH), 127.68 (CH), 126.37 (C), 123.82 (2CH), 122.87 (CH), 121.50 (CH), 121.27 (CH), 120.67 (CH), 116.10 (2CH), 114.81 (2CH), 109.91 (CH), 101.85 (CH), 55.66 (OMe); MS (ESI positive): m/z = 315 $[M+H]^+$.

5-Fluoro-*N*-(3-methoxyphenyl)-*N*-(*p*-tolyl)-1*H*-indol-1-amine (6f): Yield: 83% (40 mg), white-yellow solid, mp 80–82 °C, R_f = 0.60 (cyclohexane/EtOAc 9:1); IR (neat): ν = 3454, 3428, 3374, 3349, 3279, 2158, 2037, 2001, 1986, 1601, 1510, 1491, 1469, 1443, 1251, 1229, 1154, 1119, 1042, 946 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.33–7.22 (m, 3H), 7.16–7.05 (m, 3H), 7.01 (d, J = 8.6 Hz, 2H), 6.92 (td, J = 9.1, 2.4 Hz, 1H), 6.56–6.49 (m, 2H), 6.45–6.35 (m, 2H), 3.69 (s, 3H), 2.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.48 (C), 159.99 (C), 147.27 (C), 142.39 (C), 133.88 (C), 131.94 (C), 129.94 (2CH), 129.28 (CH), 126.41 (C), 120.62 (2CH), 111.17 (CH, d, J = 26.5 Hz), 110.44 (CH, d, J = 9.6 Hz), 109.89 (CH), 107.23 (CH), 106.03 (CH, d, J = 23.5 Hz), 103.65 (CH), 101.61 (CH), 101.55 (CH), 55.20 (OMe), 20.76 (CH_3); ^{19}F NMR (188 MHz, $CDCl_3$): δ = −124.5 (s); MS (APCI positive): m/z = 347 $[M+H]^+$; HR-MS (APCI positive): m/z = 347.1543, calcd. for $C_{22}H_{19}FN_2O$ (M+H): 347.1554.

***N*-(4-Chlorophenyl)-*N*-(*p*-tolyl)-1*H*-indol-1-amine (6g):** Yield: 88% (40 mg), white-yellow oil, R_f = 0.50 (cyclohexane); IR (neat): ν = 3494, 3479, 3455, 3421, 3388, 3327, 3294, 3267, 3081, 2364, 2342, 2329, 2286, 2237, 2211, 2184, 2170, 2144, 2082, 2038, 2013, 1992, 1978, 1942, 1913, 1510, 1488, 1008 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.70–7.62 (m, 1H), 7.37–7.29 (m, 1H), 7.27–7.12 (m, 5H), 7.09 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 6.79 (d, J = 9.1 Hz, 2H), 6.61 (dd, J = 3.4, 0.9 Hz, 1H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.74 (C), 142.30 (C), 135.30 (C), 134.04 (C), 130.06 (2CH), 129.18 (2CH), 127.45 (CH), 127.01 (C), 126.32 (C), 122.94 (CH), 121.26 (CH), 120.75 (CH), 120.51 (2CH), 118.51 (2CH), 109.65 (CH), 102.04 (CH), 20.77 (CH_3); MS (APCI positive): m/z = 333 $[M+H]^+$; HR-MS (APCI positive): m/z = 333.1138, calcd. for $C_{21}H_{17}ClN_2$ (M+H): 333.1153.

***N*-(3-Methoxyphenyl)-*N*-(4-methoxyphenyl)-1*H*-indol-1-amine (6h):** Yield: 61% (44 mg), white-yellow oil, R_f = 0.50 (cyclohexane/EtOAc 95:5); IR (neat): ν = 3371, 3000, 2835, 2371, 2332, 2285, 2194, 2089, 2022, 1977, 1961, 1599, 1581, 1507, 1490, 1452, 1437, 1329, 1245, 1210, 1183, 1151, 1088, 1033, 1008, 830 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.66 (d, J = 7.3 Hz, 1H), 7.42 (d, J = 8.2 Hz, 1H), 7.33–6.99 (m, 6H), 6.85 (d, J = 9.0 Hz, 2H), 6.59 (d, J = 3.4 Hz, 1H), 6.53–6.43 (m, 1H), 6.34–6.24 (m, 2H), 3.78 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.62 (C), 157.11 (C), 148.39 (C), 138.06 (C), 135.54 (C), 130.04 (CH), 127.63 (CH), 126.34 (C), 124.30 (2CH), 122.86 (CH), 121.25 (CH), 120.64 (CH), 114.79 (2CH), 109.87 (CH), 108.62 (CH), 106.30 (CH), 102.33 (CH), 101.86 (CH), 55.62 (OMe), 55.29 (OMe); MS (ESI positive): m/z = 345 $[M+H]^+$; HR-MS (ESI positive): m/z = 345.1586, calcd. for $C_{22}H_{20}N_2O_2$ (M+H): 345.1603.

***N*-(4-Chlorophenyl)-*N*-(3,4,5-trimethoxyphenyl)-1*H*-indol-1-amine (6i)** : Yield: 78% (65 mg), white-yellow oil, R_f = 0.54 (cyclohexane/EtOAc 9:1); IR (neat): ν = 3461, 33358, 3258, 3225, 3199, 2361, 22217, 2190, 1989, 1590, 1504, 1427, 1234 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 7.67–7.64 (m, 1H), 7.36–7.32 (m, 1H), 7.26–7.16 (m, 5H), 6.80 (d, J = 9.1 Hz, 2H), 6.61 (dd, J = 3.4, 0.9 Hz, 1H), 6.33 (s, 1H), 3.81 (s, 3H), 3.69 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.90 (2C), 144.70 (C), 140.97 (C), 135.48 (C), 135.04 (C), 129.36 (2CH), 127.47 (CH), 127.47 (C), 126.40 (C), 123.17 (CH), 121.45 (CH), 120.96 (CH), 119.08 (2CH), 109.69 (CH), 102.36 (CH), 98.43 (2CH), 61.08 (CH_3), 56.24 ($2CH_3$); MS (ESI positive): m/z = 409 $[M+H]^+$; HR-MS (APCI positive): m/z = 409.1282, calcd. for $C_{23}H_{21}ClN_2O_3$ (M+H): 409.1313.

***N*-(5-Chloro-1*H*-indol-1-yl)-*N*-(*m*-tolyl)quinolin-3-amine (6j):** Yield: 61% (48 mg), white-yellow oil, R_f = 0.21 (cyclohexane/EtOAc 9:1); IR (neat): ν = 3495, 3428, 3407, 3331, 3254, 3207, 3188, 3139, 3124, 3070, 3021, 2529, 2361, 2189, 2170, 2147, 2104, 2036, 2013, 1990, 1970, 1601, 1489, 1454, 775 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.65 (d, J = 2.7 Hz, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.57 (d, J = 1.8 Hz, 1H), 7.53–7.44 (m, 2H), 7.42–7.33 (m, 1H), 7.27 (dd, J = 8.9, 3.0 Hz, 2H), 7.18 (d, J = 4.2 Hz, 1H), 7.12 (t, J = 7.8 Hz, 1H), 7.06 (dd, J = 8.7, 1.9 Hz, 1H), 6.91–6.74 (m, 3H), 6.52 (d, J = 3.4 Hz, 1H), 2.20 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 144.60 (C), 144.48 (C), 144.22 (CH), 139.91 (C), 139.18 (C), 133.67 (C), 129.61 (CH), 129.14 (CH), 128.71 (CH), 128.71 (C), 128.34 (C), 127.92 (CH), 127.40 (CH), 127.00 (CH), 126.74 (C), 125.58 (CH), 123.60 (CH), 120.90 (CH), 120.64 (CH), 120.05 (CH), 116.67 (CH), 110.62 (CH), 102.12 (CH), 21.54 (CH_3); MS (ESI positive): m/z = 384 $[M+H]^+$; HRMS (ESI positive): m/z = 384.1268, calcd. for $C_{24}H_{18}ClN_3$ (M+H): 384.1268.

***N*-(4-Methoxyphenyl)-*N*-(pyridin-2-yl)-1*H*-indol-1-amine (6k):** Yield: 30% (20 mg), white-rose solid, mp 119–121 °C, R_f = 0.84 (cyclohexane/EtOAc 9:1); IR (neat): ν = 2358, 2043, 1587, 1568, 1507, 1467, 1431, 1329, 1285, 1246, 1213, 1188, 1151, 1125, 1032, 985, 883 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 8.25 (d, J = 4.2 Hz, 1H), 7.67 (d, J = 7.8 Hz, 1H), 7.50–7.07 (m, 7H), 6.87 (d, J = 8.9 Hz, 2H), 6.83–6.74 (m, 1H), 6.63 (d, J = 3.2 Hz, 1H), 6.06 (d, J = 8.5 Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.98 (C), 157.45 (C), 147.94 (CH), 138.32 (CH), 136.35 (C), 135.21 (C), 127.60 (CH), 126.60 (C), 125.10 (2CH), 123.12 (CH), 121.44 (CH), 120.91 (CH), 116.35 (2CH), 114.52 (CH), 109.67 (CH), 108.66 (CH), 102.39 (CH), 55.59 (OMe); MS (ESI positive): m/z = 316 $[M+H]^+$; HR-MS (ESI positive): m/z = 316.1452, calcd. for $C_{20}H_{17}N_3O$ (M+H): 316.1450.

***N*-(4-Chlorophenyl)-*N*-(pyridin-2-yl)-1*H*-indol-1-amine (6l):** Yield: 75% (50 mg), white-yellow oil, R_f = 0.57 (cyclohexane/EtOAc 9:1); IR (neat): ν = 3372, 2365, 2331, 2232, 2172, 2150, 2008, 1982, 1587, 1489, 1469, 1432, 1325, 1212,

1188, 1152, 1092, 1051, 1010, 821, 765, 743 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.28$ (ddd, $J = 4.9$, 1.9, 0.8 Hz, 1H), 7.76–7.61 (m, 1H), 7.43 (ddd, $J = 8.5$, 7.3, 1.9 Hz, 1H), 7.32–7.11 (m, 8H), 6.86 (ddd, $J = 7.3$, 4.9, 0.8 Hz, 1H), 6.66 (dd, $J = 3.4$, 0.7 Hz, 1H), 6.10 (d, $J = 8.5$ Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 157.11$ (C), 147.75 (CH), 141.91 (C), 138.70 (CH), 135.10 (C), 129.69 (C), 129.12 (2CH), 127.60 (CH), 126.69 (C), 123.44 (CH), 122.60 (2CH), 121.59 (CH), 121.27 (CH), 117.57 (CH), 110.04 (CH), 109.54 (CH), 102.90 (CH); MS (ESI positive): $m/z = 320$ $[M+H]^+$; HR-MS (ESI positive): $m/z = 320.0965$, calcd. for $C_{19}H_{14}ClN_3$ (M+H): 320.0955.

General Procedure for the Sequential Synthesis of 7

A flame-dried resealable Schlenk tube was charged with *N*-aryl-1-aminoazole **3s** (0.25 mmol), 1-(chloromethyl)-4-methoxybenzene (0.5 mmol) and *t*-BuOK (0.5 mmol). The Schlenk tube was capped with a rubber septum, evacuated and backfilled with argon; then, toluene (2 mL) was added through the septum. The septum was replaced with a teflon screwcap. The Schlenk tube was sealed, and the mixture was stirred at 130 °C for 1 h. The resulting suspension was cooled to room temperature and filtered through celite eluting with ethyl acetate. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product.

General Procedure for the One-Pot Synthesis of 7

A flame-dried resealable Schlenk tube was charged with Pd_2dba_3 (2.5 mol%), Xphos (5 mol%), 1-aminoindole **1a** (0.25 mmol), 4-chlorobenzonitrile (0.5 mmol), LiCl (0.5 mmol) and *t*BuOK (1 mmol). The Schlenk tube was capped with a rubber septum, evacuated and backfilled with argon; then, toluene (2 mL) was added through the septum. The septum was replaced with a teflon screwcap. The Schlenk tube was sealed, and the mixture was stirred at 130 °C for 3 h. Then, the resulting suspension was cooled to room temperature and 1-(chloromethyl)-4-methoxybenzene (0.5 mmol) was added through the septum. The septum was replaced with a teflon screwcap and the reaction vessel was sealed, and then heated at 130 °C for 1 h. The resulting suspension was cooled to room temperature and filtered through celite eluting with ethyl acetate. The filtrate was concentrated and purification of the residue by silica gel column chromatography gave the desired product.

4-[(1*H*-Indol-1-yl)(4-methoxybenzyl)amino]benzonitrile (7): Yield: 69% (53 mg), white-yellow oil, $R_f = 0.42$ (cyclohexane/EtOAc 8:2); IR (neat): $\nu = 3420$, 2364, 1595, 1507, 1492, 1453, 1245, 1213, 1182, 1033 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.69$–7.58 (m, 1H), 7.44 (d, $J = 9.1$ Hz, 2H), 7.22–7.09 (m, 5H), 6.93 (d, $J = 3.4$ Hz, 1H), 6.83 (d, $J = 8.7$ Hz, 2H), 6.60–6.43 (m, 3H), 5.09 (d, $J = 15.3$ Hz, 1H), 4.79 (d, $J = 15.3$ Hz, 1H), 3.78 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 159.60$ (C), 152.04 (C), 134.08 (C), 133.89 (2CH), 129.22 (2CH), 127.81 (C), 127.50 (CH), 126.78 (C), 123.03 (CH), 121.66 (CH), 121.07 (CH), 119.64 (C), 114.37 (2CH), 112.69 (2CH), 109.48 (CH), 102.46 (C), 101.98 (CH), 56.50 (CH_2), 55.42 (CH_3); MS (ESI positive): 354 $[M+H]^+$; HR-MS (ESI positive): $m/z = 320.0965$, calcd. for $C_{23}H_{19}N_3O$ (M+H): 320.0955.

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