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Well-defined NHC–Pd complex-mediated intermolecular direct annulations for synthesis of functionalized indoles (NHC = *N*-heterocyclic carbene)

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As alternatives to the common tertiary phosphine/Pd systems, well-defined *N*-heterocyclic carbene–Pd complexes have been proven to be highly efficient precatalysts for intermolecular direct annalution of *o*-haloanilines and ketones at lower catalyst loadings. A highly efficient and practical protocol for synthesis of functionalized indoles was developed using (IPr)Pd(acac)Cl as catalyst. Both *o*-bromoanilines and *o*-chloroanilines gave rise to efficient coupling under the reaction conditions. Related to acyclic ones, cyclic ketones coupled more effectively with *o*-haloanilines. With [Pd(IPr)$_2$] as catalyst, the base-sensitive groups including OH and CO_2H groups could be tolerated.

Supporting information may be found in the online version of this article.

Keywords: indole synthesis; *N*-heterocyclic carbene; annulation; palladium

Introduction

Over the past decade, transition metal-mediated homogeneous catalysis using *N*-heterocyclic carbenes (NHCs) as supporting ligands has witnessed a vast development.[1] Although tertiary phosphines are still widely popular as ancillary ligands, the use of NHCs as alternative ligands in transition metal-catalyzed cross-coupling reactions is still steadily increasing.[2] The shielding steric substitutents in the heterocyclic backbone, high thermal stability and strong σ-donor character result in very high stability of the metal–NHC bond. Particularly in the field of Pd-catalyzed cross-coupling reactions, well-defined NHC-containing Pd(II) complexes have proven to be a superior alternative for catalytic systems of tertiary phosphines.[3]

Active pharmaceutical ingredients (APIs) and naturally occurring alkaloids,[4] which exhibit significant, diverse biological activities, are often found to share an indole unit as the central core in their skeletons. For this reason, indole synthesis, including both the construction of indole nucleus and the functionalization of the indole ring, has attracted remarkable attention from synthetic chemistry community.[5] Notwithstanding, many strategies suffer from lack of availability of the starting materials, harsh reaction conditions, multi-step reactions, low yields and resulting troublesome separation and purification. In this sense, Pd-catalyzed intermolecular direct annulation from the commercially available *o*-haloanilines and simple ketones appears to be a highly efficient and practical strategy for the construction of an indole nucleus (Scheme 1).[6] The tertiary phosphine/Pd complex [Pd(P*t*-Bu$_3$)$_2$] has recently proven to be a superior catalyst for this transformation.[7] The procedure is applicable for both *o*-chloroanilines and *o*-chloroaminopyridines. Unfortunately, high catalyst loading (10 mol% of substrate) and elevated reaction temperature (up to 140 °C) were required for efficient conversion. In addition, the extreme air-sensitivity and degradable property of the phosphine ligand at high temperatures,[8] together with phosphine ligand and ligand decomposition byproduct removal difficulties, seriously hampered application of the procedure in the fine chemical and pharmaceutical industries.

Very recently, it has been shown that well-defined NHC–Pd complex (NHC)Pd(allyl)Cl (NHC = SIPr) was able to catalyze the coupling of 3-bromo-2-aminopyridine and simple ketones to form the related azoindole derivatives.[9] However, high catalyst loading (up to 20 mol%) was needed for this transformation. Given the stringent US Food and Drug Administration (FDA) requirements on the amount of Pd and P present in pharmaceuticals, combined with the cost, product purity, toxicity and environmental concerns, reducing the amount of palladium to as little as possible in the catalytic process, particularly on an industrial scale, is also important.[10] In view of the robust catalytic performance of various well-defined NHC–Pd complexes, we are very interested in achieving this transformation at lower catalyst loadings by utilizing well-defined NHC–Pd complexes as an alternative to the common tertiary phosphine–Pd system. We herein report our investigation of catalytic performance of well-defined NHC–Pd

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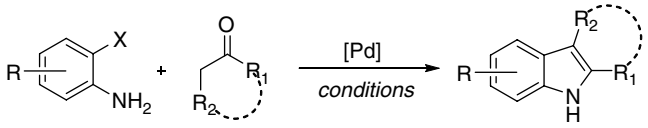


Scheme 1. Pd-catalyzed intermolecular direct annulations reaction.

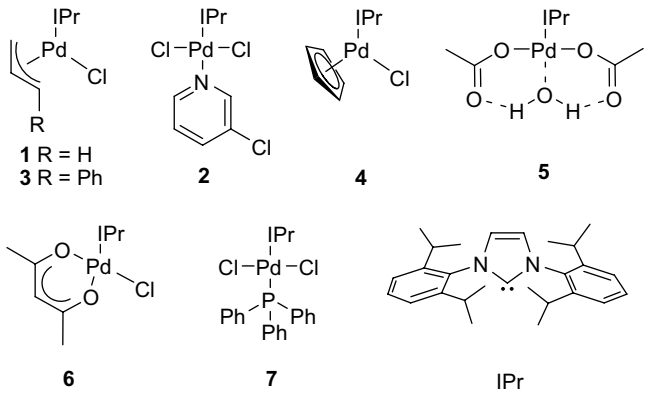
complexes in intermolecular direct annulation for the synthesis of functionalized indoles. In addition, the scope and limitations of substrates and reaction mechanism are also discussed.

Results and Discussion

Screening of Well-defined NHC–Pd Complexes for Direct Annulations Reactions

In recent years, structurally diverse well-defined NHC–Pd complexes have been developed for different synthetic utilizations.[11] These complexes show prominent catalytic activities in the broad cross-coupling reactions, including the Suzuki–Miyaura, Negishi, Kumada–Tamao–Corriu and Buchwald–Hartwig reactions, and α-arylation of ketones. They not only consist of an accurate ratio of the Pd/ligand that avoids the use of excess costly ligand, but generally also exhibit enhanced reactivity associated with easy access to a highly active low-coordinate [Pd^0L] species.[12]

Firstly, we examined the catalytic potential of the commercially available NHC–Pd complexes (NHC)Pd(allyl)Cl, **1**,[13] and PEPPSI, **2**,[14] in direct annulation reactions. In early experiments we used acetophenone and *o*-bromoaniline as the coupling substrates and established that annulation reactions were performed in the presence of 5 mol% NHC–Pd complex with KO^{t}Bu as base in toluene. We found that both compounds **1** and **2** could efficiently catalyze the transformation at 100 °C to give the corresponding 2-phenylindole. It has been demonstrated recently[15,16] that, in addition to the dominant NHC ligand, other ancillary ligands surrounding the Pd metal center also play a crucial role in their catalytic performance. As a result, a variety of NHC–Pd complexes stabilized by different anionic ligands, including cinnamyl, **3**,[17] and Cp, **4**,[18] OAc, **5**,[19] acac, **6**[20] and PPh_3, **7**,[21] were also prepared and their catalytic potential evaluated in direct annulation reactions of *o*-haloanilines and ketones (Scheme 2). We observed that, of the NHC–Pd complexes that we have examined thus far, all were able to catalyze conversion of acetophenone and *o*-bromoaniline into the desired 2-phenylindole to a certain extent with decreased catalyst loadings (5 mol%; entries 1–7, Table 1). Amongst them, the (IPr)Pd(acac)Cl, **6**, was found to give the best result (entry 6, Table 1).



Scheme 2. The structures of well-defined *N*-heterocyclic carbene–Pd complexes.

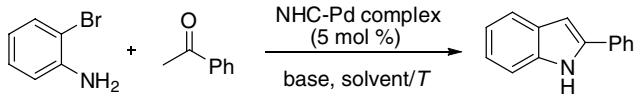
For optimizing reaction conditions, various bases were investigated. In addition to KO^{t}Bu, NaO^{t}Bu also proved to be effective, but to a lesser extent (entry 8, Table 1). In contrast, with Cs_2CO_3 as base, only 22% indole was obtained (entry 9, Table 1). Other bases, including inorganic bases LiOH, KF and KOAc, and organic base DBU, were completely ineffective. A survey of reaction solvent and temperature revealed that toluene (100 °C) was optimal, while other solvents, such as tetrahydrofuran (THF) (60 °C), 1,2-dimethoxyethane (DME, 80 °C) and 1,4-dioxane (100 °C), caused slightly lower yields. Meanwhile, elevated reaction temperature (140 °C in xylene) and longer reaction time (24 h) did not give an obviously higher yield (entries 13 and 14, Table 1). Additionally, it is noteworthy that, with further decreased catalyst loading (2 mol%), parallel yield could be also obtained, although a longer reaction time (36–48 h) was required for complete conversion (entry 15, Table 1).

Annulation Reaction of Ketones with *o*-Haloanilines

With optimized catalytic conditions in hand, we thus tested (NHC)Pd(acac)Cl, **6**, as a precatalyst in an intermolecular direct annulation reaction between a wide array of acyclic and cyclic ketones and *o*-bromoanilines at 5 mol% catalyst loadings. As shown in Table 2, both cyclic and acyclic ketones reacted well with *o*-bromoanilines under the present catalytic conditions. Among the ketones investigated, cyclic ones gave rise to more efficient annulation than the corresponding acyclic ones (entries 5, 11 and 16, Table 2). With regard to cyclic ketones, coupling reactions of six-membered cyclic ketones were more effective than those of five-membered analogs. For the aromatic ketones examined, both electron-donating and electron-withdrawing substituents in the aryl group had the same reactivity. For instance, the annulation reaction of *p*-F-acetophenone with 4-methyl-2-bromoaniline gave the desired indole in an isolated yield of 77% (entry 10, Table 2). Furthermore, it is remarkable that the steric effect on *o*-bromoaniline was not obvious and the sterically hindered 3-methyl-2-bromoaniline showed equally high reactivity to 2-bromoaniline (entries 14–16, Table 2).

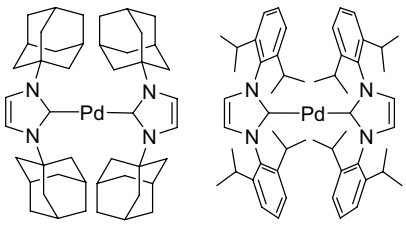
Unfortunately, owing to the base-sensitivity of the groups OH and CO_2H, using KOBu^t as a base in an attempt to achieve annulation between either *o*-bromoanilines or ketones incorporating such groups was unsuccessful and a complicated mixture was obtained. In the present catalytic system, the use of a strong base such as KOBu^t has two results: (1) activation of these well-defined NHC–Pd precatalysts to produce active [NHC–Pd^0] species in a catalytic cycle;[3] and (2) deprotonation of the enolizable ketone. Previous research by Nazare has demonstrated that mild bases such as K_3PO_4 are also effective for deprotonation of ketones.[7] Therefore, if an active NHC–Pd^0 catalyst, such as [Pd^0(NHC)$_2$],

Table 1. Catalytic activity of well-defined NHC–Pd complexes in the annulation reactions[a]



Entry	NHC–Pd complex	Base	Solvent/temperature (°C)	Yield (%)[b]
1	**1**	KO^{t}Bu	Toluene/100	52
2	**2**	KO^{t}Bu	Toluene/100	50
3	**3**	KO^{t}Bu	Toluene/100	45
4	**4**	KO^{t}Bu	Toluene/100	47
5	**5**	KO^{t}Bu	Toluene/100	43
6	**6**	KO^{t}Bu	Toluene/100	68
7	**7**	KO^{t}Bu	Toluene/100	44
8	**6**	NaO^{t}Bu	Toluene/100	62
9	**6**	Cs_2CO_3	Toluene/100	22
10	**6**	KO^{t}Bu	THF/60	47
11	**6**	KO^{t}Bu	DME/80	52
12	**6**	KO^{t}Bu	1,4-Dioxane/100	59
13	**6**	KO^{t}Bu	Xylene/140	67
14	**6**	KO^{t}Bu	Toluene/100	66[c]
15	**6**	KO^{t}Bu	Toluene/100	62[d]

[a] Reaction conditions: *o*-bromoaniline, 1.0 mmol; acetophenone, 3.0 mmol; NHC–Pd catalyst, 5 mol%; base, 4.0 mmol; $MgSO_4$, 1.0 mmol; solvent, 3 ml; reaction time *t*, 10 h unless indicated.
[b] Isolated yields based on the average of two runs.
[c] Reaction time, 24 h. 14
[d] 2 mol% **6** was used; reaction time, 36 h.



8a **8b**

Scheme 3. The structures of [Pd^0(NHC)$_2$] complexes.

8a[22] and **8b**[23] (Scheme 3), was employed, a strong base should be avoidable so as to broaden the scope of substrates. In fact, we have demonstrated that using mild K_3PO_4 as a base with 5 mol% NHC–Pd complex **8b** as the catalyst, *o*-bromoaniline could be efficiently coupled with pyruvic acid to give 2-indolecarboxylic acid in 89% yield (Scheme 4).

Owing to the increased availability and low cost of *o*-chloroanilines related to *o*-bromoanilines, using *o*-chloroanilines as the starting substrates remains a very attractive target in the industrial applicable process. Therefore, we further investigated the annulation reactions of *o*-chloroanilines with a variety of ketones utilizing (NHC)Pd(acac)Cl, **6**, as the catalyst. As expected, using the present catalytic protocol, *o*-chloroanilines showed the same reactivity and allowed for efficient annulation to produce the functionalized indoles (Table 2). Like that in *o*-bromoanilines, in general, cyclic ketones and aliphatic ketones gave rise to the corresponding indoles in higher yields than aromatic ketones (entries 5, 7 and 16, Table 2). Notably, heteroaromatic ketone exhibited prominent reactivity under the present catalytic system (entries 18 and 19, Table 2).

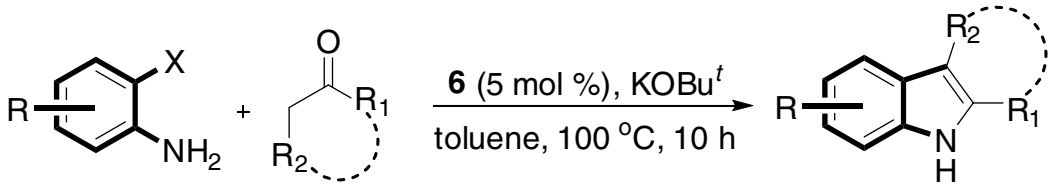
Mechanism

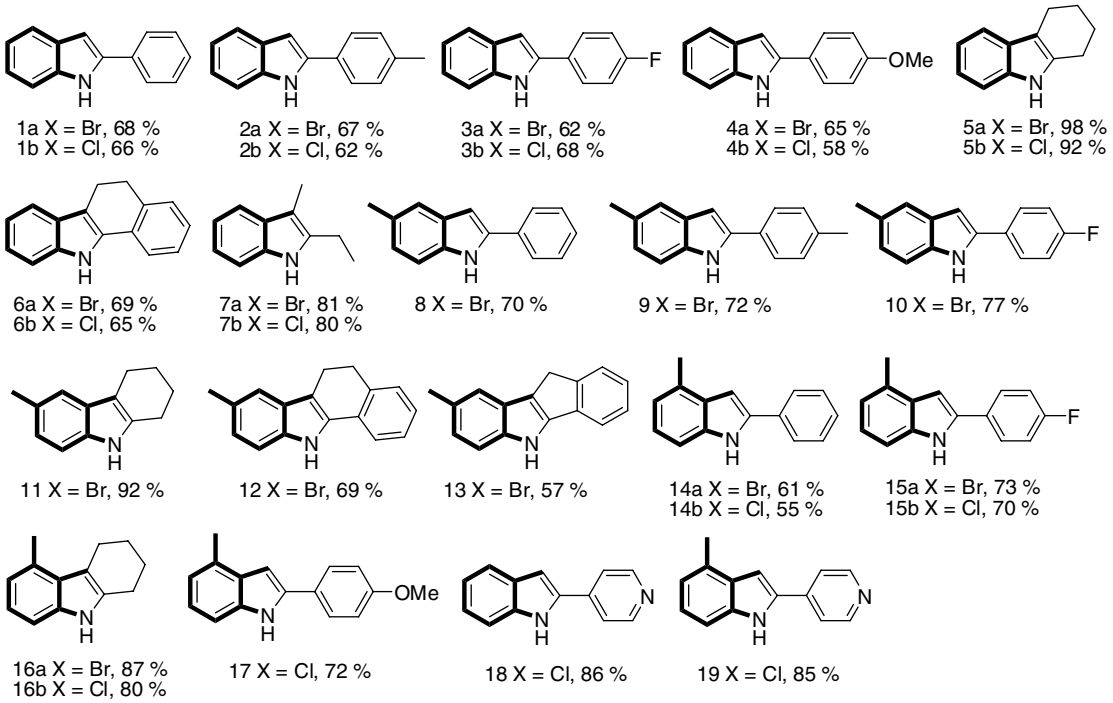
Theoretically, construction of indole nuclei by annulation between *o*-haloanilines and ketones may be achieved via two possible pathways: (1) an α-arylation reaction[24] of ketones followed by intramolecular dehydration cyclization process (*path a*); and (2) an enamine formation followed by an intramolecular Heck coupling reaction (*path b*; Scheme 5).[6] The previous study has showed that a lone, potentially reactive Cl substituent does not carry out relative α-arylation of ketone under those reaction conditions, which supports an enamine-Heck mechanism (*path b*).[7] In the present study, we observed further that isolated enamine, prepared by condensation of *o*-bromoanile with acetophenone mediated by a $TiCl_4$/TEA system,[25] was able to be cyclized to afford the 2-phenylindole in an overall yield of 72% by utilizing the present catalytic protocol (Scheme 6).

Conclusion

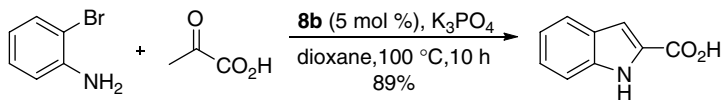
In conclusion, a variety of well-defined NHC–Pd complexes have been evaluated for their catalytic activity in direct annulations of *o*-haloanilines with ketones. We have demonstrated that, instead of common tertiary phosphine ligand, well-defined NHC–Pd complexes, such as (IPr)Pd(acac)Cl, **6**, can also be utilized as highly efficient and practical catalysts for intermolecular direct annulation reaction between *o*-haloanilines and ketones at lower catalyst loadings. Both *o*-bromoanilines and *o*-chloroanilines are applicable substrates under the present system. Cyclic ketones give rise to more effective coupling than acyclic ones. Moreover, using [Pd(IPr)$_2$], **8b**, as catalyst, the base-sensitive groups including OH and CO_2H group can be tolerated in this transformation. Relative to the common tertiary phosphine–Pd catalytic system,

Table 2. Annulation reaction of ketones with *o*-haloanilines[a,b]





[a] Reaction conditions: *o*-haloaniline, 1 mmol; ketone, 3 mmol; (NHC)Pd(acac)Cl, **6**, 5 mol%; KO^{t}Bu, 4 mmol; $MgSO_4$, 1 mmol; toluene, 3 ml; reaction temperature, *T*, 100 °C oil bath; reaction time, *t*, 10 h; reaction time not optimized.
[b] Isolated yield based on the average of two runs.



Scheme 4. Synthesis of 2-indole-carboxylic acid.

the strategy for indole synthesis described here represents a practically and industrially applicable alternative.

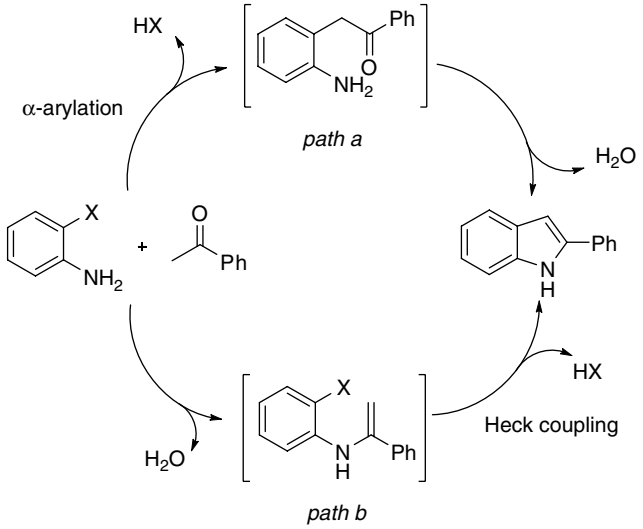
Experimental Section

General Comments

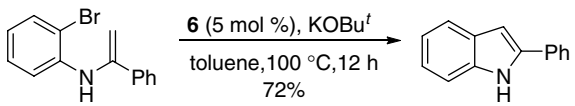
All reactions were carried out under an Ar_2 atmosphere unless indicated otherwise. Toluene, THF, DME, 1,4-dioxane and xylene were dried and distilled over Ph_2CO/Na prior to use. All ketones, *o*-bromoanilines and *o*-chloroanilines were used as received from commercial sources. Potassium *tert*-butoxide and sodium *tert*-butoxide was stored under argon in a desiccator. ^{1}H- and ^{13}C-NMR spectra were recorded on a Bruker 400 MHz spectrometer at ambient temperature in $CDCl_3$ (Cambridge Isotope Laboratories, Inc.). Melting points of compounds were recorded with uncorrected thermometers. Flash column chromatography was performed on silica gel 60 (230–400 mesh). Well-defined NHC–Pd complexes (NHC)Pd(allyl)Cl, **1**,[13b] and PEPPSI, **2**,[14d] are commercially available and could also be prepared easily according to the literature method. (NHC)Pd(cinnamyl)Cl, **3**,[17a] CpPd(NHC)Cl, **4**,[18] $Pd(OAc)_2$(NHC)(H_2O), **5**,[19] (NHC)Pd(acac)Cl, **6**[20b] and $PdCl_2$(IPr)(PPh_3), **7**,[21] were prepared following the literature procedures.

General Procedure for Annulation Reaction of *o*-Haloanilines with Ketones

In air, potassium *tert*-butoxide (4 mmol, 450 mg), (NHC)Pd(acac)Cl, **6** (5 mol%, 32 mg) and anhydrous $MgSO_4$ (1 mmol, 120 mg) were weighed into a 10 ml screw-cap threaded vial that was sealed with a septum and evacuated and backfilled with argon three times. The *o*-bromoaniline or *o*-chloroaniline (1 mmol), ketone



Scheme 5. Possible pathways for annulation to indoles.



Scheme 6. Catalytic synthesis of 2-phenyl indole.

(3 mmol, 3 equiv.) and toluene (3 ml) were added in turn via a syringe. The mixture was heated in an oil bath of 100 °C for 12 h. After cooling to room temperature the reaction mixture was filtered with celite, water (10 ml) was added to the filtrate and the mixture was abstracted with ethyl acetate (10 ml × 3). The combined organic phases were dried over anhydrous $MgSO_4$ and filtered. After removal of the solvents under reduced pressure, the residue was purified either by flash chromatography on silica or by recrystallization from *n*-hexane.

According to the above-mentioned general procedure, the following indole derivatives were obtained and their m.p., ^{1}H- and ^{13}C-NMR were identical to those described in the literature. 2-Phenyl-1*H*-indole (entry 1, Table 2, in 68 and 66% yield),[26] 2-(4′-methyl)phenyl-1*H*-indole (entry 2, Table 2, in 67 and 62% yield),[27] 2-(4′-fluoro)phenyl-1*H*-indole (entry 3, Table 2, in 62 and 68% yield),[27] 2-(4′-methoxy)phenyl-1*H*-indole (entry 4, Table 2, in 65 and 58% yield),[28] 2,3,4,9-tetrahydro-1*H*-carbazole (entry 5, Table 2, in 98 and 92% yield),[29] 6,11-dihydro-5*H*-benzo[*a*]carbazole (entry 6, Table 2, in 69 and 65% yield),[30] 2-ethyl-3-methyl-1*H*-indole (entry 7, Table 2, in 81 and 80% yield),[31] 5-methyl-2-phenyl-1*H*-indole (entry 8, Table 2, in 70% yield),[27] 5-methyl-2-(4′-methyl)phenyl-1*H*-indole (entry 9, Table 2, in 72% yield),[32] 5-methyl-2-(4′-fluoro)phenyl-1*H*-indole (entry 10, Table 2, in 77% yield),[33] 6-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (entry 11, Table 2, in 92% yield),[31] 8-methyl-6,11-dihydro-5*H*-benzo[*a*]carbazole (entry 12, Table 2, in 69% yield),[34] 8-methyl-5,10-dihydroindeno[1,2-*b*]indole (entry 13, Table 2, in 57% yield),[35] 4-methyl-2-phenyl-1*H*-indole (entry 14, Table 2, in 61 and 55% yield),[36] 5-methyl-2,3,4,9-tetrahydro-1*H*-carbazole (entry 16, Table 2, in 87 and 80% yield),[37] 2-(pyridin-4-yl)-1*H*-indole (entry 18, Table 2, in 86% yield).[38]

According to the same procedure, 4-methyl-2-(4′-fluoro)phenyl-1*H*-indole (entry 15, Table 2) was obtained from 3-methyl-2-bromoaniline or 3-methyl-2-chloroaniline and acetophenone in 73 and 70% yield, respectively. Colorless solid. M.p. 99–100 °C, ^{1}H NMR δ (ppm): 8.24 (br, 1H, NH), 7.63–7.60 (m, 2H, ArH), 7.23 (d, 1H, J = 8.4 Hz, ArH), 7.15–7.08 (m, 3H, ArH), 6.92 (d, 1H, J = 7.0 Hz, ArH), 6.76 (s, 1H, ArH), 2.57 (s, 3H, CH_3). ^{13}C NMR δ (ppm): 163.6, 161.1, 136.5, 136.4, 130.2, 129.2, 128.9, 128.8, 126.8, 126.7, 122.6, 120.5, 116.2, 115.9, 108.5, 98.5, 18.8. ESI-MS [M^+ + H]: 226. Anal. calcd $C_{15}H_{12}FN$: C, 79.98; H, 5.37; N, 6.22. Found: C, 79.95; H, 5.40; N, 6.21.

Similarly, 4-methyl-2-(4′-methoxy)phenyl-1*H*-indole (entry 17, Table 2) was obtained from 3-methyl-2-chloroaniline and 4-methoxyacetophenone in 72% yield. Colorless solid. M.p. 154–155 °C, ^{1}H NMR δ (ppm): 8.20 (br, 1H, NH), 7.56 (d, 2H, J = 8.5 Hz, ArH), 7.21 (d, 1H, J = 8.3 Hz, ArH), 7.09–7.05 (t, 1H, ArH), 6.95 (d, 2H, J = 8.5 Hz, ArH), 6.90 (d, 1H, J = 7.1 Hz, ArH), 6.71 (s, 1H, ArH), 3.82 (s, 3H, CH_3), 2.57 (s, 3H, CH_3). ^{13}C NMR δ (ppm): 159.3, 137.4, 136.3, 129.9, 129.3, 126.5, 125.3, 122.1, 120.3, 114.5, 108.4, 97.4, 55.4, 18.8. ESI-MS [M^+ + H]: 238. Anal. calcd $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90. Found: C, 80.90; H, 6.39; N, 5.89.

4-Methyl-2-(pyridin-4-yl)-1*H*-indole (entry 19, Table 2) was obtained from 3-methyl-2-chloroaniline and 4-acetylpyridine in 85% yield. Colorless solid. M.p. 210 °C, ^{1}H NMR δ (ppm): 8.78 (br, 1H, NH), 8.65 (d, 2H, J = 4.8 Hz, ArH), 7.55 (d, 2H, J = 4.9 Hz, ArH), 7.26 (d, 1H, J = 7.1 Hz, ArH), 7.18–7.14 (t, 1H, ArH), 7.07 (s, 1H, ArH), 6.95 (d, 1H, J = 7.0 Hz, ArH), 2.59 (s, 3H, CH_3). ^{13}C NMR δ (ppm): 150.4, 139.5, 137.1, 133.9, 131.0, 128.8, 123.9, 120.8, 119.0, 108.8, 101.5, 18.7. ESI-MS [M^+ + H]: 209. Anal. Calcd. $C_{14}H_{12}N_2$: C, 80.74; H, 5.81; N, 13.45. Found: C, 80.88; H, 5.80; N, 13.49.

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Supporting information

Supporting information may be found in the online version of this article.

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