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An efficient, mild, and selective Ullmann-type N-arylation of indoles catalyzed by copper(I) complex

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ABSTRACT

A wide range of *N*-arylated indoles are selectively synthesized through intermolecular C(aryl)–N bond formation from the corresponding aryl iodides and indoles through Ullmann-type coupling reactions in the presence of a catalytic amount of easily available *N*,*N*,*N*′,*N*′-tetramethyl-BINAM–CuI complex under very mild reaction conditions.

1. Introduction

Nitrogen containing heterocycles are found in numerous natural products and biologically active pharmaceutical products. Particularly, *N*-arylated indole motifs are very important molecules as they exhibit nanomolar affinity for α_1-adrenoceptors in addition to their affinities for dopamine D_2 and serotonin 5-HT_{2A} receptors.[1] Also, *N*-arylated indoles are prevalent in compounds that are materials of interest.[2] The palladium-catalyzed N-arylation of indoles from the corresponding aryl halides and indoles used to be the method of choice.[3] However, the high cost of palladium salts, high oxophilicity associated with phosphine ligands, C-3 arylation through π-complex formation, and tedious multistep processes involved in the synthesis of these phosphine ligands have rendered Pd unpopular, particularly for large scale reactions. Copper-catalyzed Ullmann coupling between an aryl halide and indole is the alternate method for palladium-catalyzed N-arylation of indole.[4] However, copper-catalyzed Ullmann reaction also suffers from several limitations such as high reaction temperatures (often 150 °C or as high as 200 °C), use of stoichiometric amounts of copper reagents, moderate yields, and poor substrate generality. In fact, only some of the efforts taken to improve the efficiency of this reaction started to bear fruit(s) with the use of copper salts with several ligands such as racemic *trans*-1,2-cyclohexyldiamine,[5] 1,10-phenanthroline,[6] diimine ligands,[7] L-proline,[8] and *N*-hydroxyimides.[9]

However, this advance in the field of Ullmann coupling is not sufficient as most of the reactions still require longer reaction time, high reaction temperature (more than 100 °C), and in some cases high catalytic loading. Therefore a mild, economic, and efficient catalytic system is still desirable for this process.

As a part of our ongoing research toward copper-catalyzed oxidation chemistry,[10] very recently we reported 1,1′-binaphthyl-2,2′-diamine (BINAM)–Cu$(OTf)_2$ as an efficient catalyst for the synthesis of diaryl ethers and aryl alkyl ethers via Ullmann-type coupling.[11] In this direction, for the first time we report our initial finding regarding *N*,*N*,*N*′,*N*′-tetramethyl-BINAM–copper complex catalyzed Ullmann type of coupling of indoles with aryl iodides under very mild reaction conditions.

2. Results and discussion

In preliminary studies, we used 20 mol % 1,1′-binaphthyl-2,2′-diamine (BINAM) **L1** (Fig. 1) as ligand with 20 mol % of CuI for the coupling of iodobenzene with indole in toluene at 110 °C. After 24 h the coupling reaction provided 89% isolated yield for the corresponding *N*-arylated indole and not even trace amount of *C*-arylated product was isolated (Table 1, entry 1). When the BINAM **L1** was replaced with *N*,*N*′-dibenzyl-BINAM **L2**, the yield for the coupling reaction was reduced to 61% (entry 2). Usage of *N*,*N*′-dimethyl-BINAM **L3** as ligand with CuI further reduced the yield to 21% (entry 3). Surprisingly, when *N*,*N*,*N*′,*N*′-tetramethyl-BINAM **L4** was used as ligand along with CuI it provided quantitative isolated yield for

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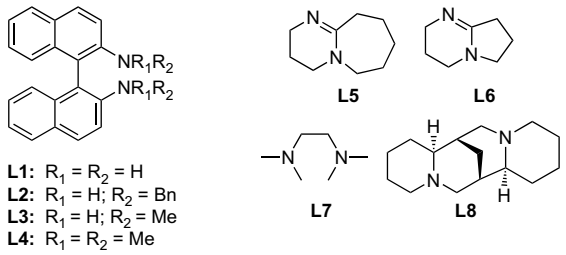


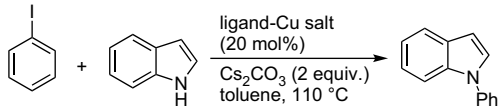
Figure 1. Ligands for Cu-catalyzed N-arylation of indoles.

arylated indole through C–N bond formation and the reaction took 24 h for completion at 110 °C (entry 4). When **L4** was replaced with other commercially available nitrogen based ligands such as DBU (**L5**), DBN (**L6**), *N*,*N*,*N*′,*N*′-tetramethyl ethylenediamine (TMEDA, **L7**), and (−)-sparteine (**L8**), the isolated yield for the N-arylation of indole reduced by 11–28%. Then the reaction was further screened with different copper salts along with ligand **L4** to reduce the reaction temperature and reaction time. From the screening of copper salts we found out CuI to be the best choice in view of reaction time and yields. The other copper salts took relatively longer reaction time and poor yields of *N*-arylated indoles.

The reaction was screened with various solvents and different bases to increase the efficiency of the coupling reactions and the results are summarized in Table 2. The reaction was taking place in several solvents and acetonitrile turned out to be the best among those examined. In acetonitrile the reaction took place at 82 °C and the reaction time was reduced to 18 h and it provided quantitative amount of isolated yield for *N*-arylated indole (entry 3). Further, the reaction was carried out with different ratios of ligand **L4** and CuI complex and it was found that 10 mol % ligand–copper combination also works efficiently to produce quantitative yield of *N*-arylated indole at 82 °C by taking slightly more time (entry 3 vs 10). Replacement of expensive and strong base Cs_2CO_3 by K_2CO_3 also gave identical results and low cost of K_2CO_3 made us to choose it for this coupling reaction (entry 10 vs 13).

Using the above-mentioned optimized conditions, we initiated our investigations into the scope of the **L4**–CuI catalyzed Ullmann-type coupling reaction and the results are summarized in Table 3. Various aryl iodides and indoles reacted to give the corresponding *N*-arylated indoles under mild reaction conditions. We found that

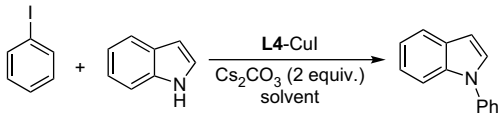
Table 1
Effect of different ligands and copper salts in N-arylation of indole



Entry	Ligand	Cu salt	Time (h)	Yield[a] (%)
1	**L1**	CuI	24	89
2	**L2**	CuI	40	61
3	**L3**	CuI	40	21
4	***L4***	*CuI*	*24*	*99*
5	**L5**	CuI	30	83
6	**L6**	CuI	30	88
7	**L7**	CuI	28	71
8	**L8**	CuI	48	78
9	**L4**	CuBr	40	46
10	**L4**	CuCl	72	52
11	**L4**	$Cu(OTf)_2$	40	19
12	**L4**	$Cu(OAc)_2 \cdot H_2O$	72	58
13	**L4**	$CuCl_2 \cdot 2H_20$	72	67
14	**L4**	$Cu(BF_4)_2 \cdot xH_2O$	72	66
15	**L4**	$CuSO_4$	72	60

[a] Isolated yield.

Table 2
Effect of solvents, ratio of catalyst and bases



Entry	**L4**	CuI	Solvent	Temp	Time (h)	Yield[a] (%)
1	20 mol %	20 mol %	Toluene	110 °C	24	99
2	20 mol %	20 mol %	DMF	110 °C	15	96
3	20 mol %	20 mol %	CH_3CN	82 °C	18	99
4	20 mol %	20 mol %	DMSO	110 °C	24	86
5[b]	20 mol %	20 mol %	THF	90 °C	48	67
6[b]	20 mol %	20 mol %	Benzene	90 °C	72	76
7	20 mol %	20 mol %	Dioxane	110 °C	72	46
8	5 mol %	5 mol %	CH_3CN	82 °C	36	87
9	10 mol %	5 mol %	CH_3CN	82 °C	30	71
10	10 mol %	10 mol %	CH_3CN	82 °C	26	99
11	20 mol %	10 mol %	CH_3CN	82 °C	30	82
12[c]	10 mol %	10 mol %	CH_3CN	82 °C	48	62
13[d]	*10 mol %*	*10 mol %*	*CH_3CN*	*82 °C*	*26*	*99*
14[e]	10 mol %	10 mol %	CH_3CN	82 °C	26	97
15	—	10 mol %	CH_3CN	82 °C	36	30
16	—	—	CH_3CN	82 °C	48	00

[a] Isolated yield.
[b] Reactions were carried out in pressure tube.
[c] Na_2CO_3 was used as base.
[d] K_2CO_3 was used as base.
[e] K_3PO_4 was used as base.

iodobenzene containing electron releasing groups as well as electron withdrawing groups reacted with indoles to give corresponding *N*-arylated indoles. Yields were different with electron rich and electron deficient indoles and iodobenzenes.

Presence of electron releasing groups such as methyl and methoxy groups on aryl iodide at *para* and *meta* position decreased the yield of the coupling reaction by 10–25% and the reaction took longer time for completion (entry 1 vs 7–9), where as an electron withdrawing groups such as keto group and nitro groups on iodobenzene increased reaction rate and yield for the N-arylation reaction (entry 5 vs 15 and 1 vs 13). It is very important to mention that under the reaction condition, the acid and base sensitive ester functional group remains intact (entries 3, 12, and 14). Bromobenzene did not provide any *N*-arylated indole in the presence of CuI-tetramethyl-BINAM complex under the optimized conditions. It is very important to mention that the reaction is very selective to give only *N*-arylated product and in none of these cases C-arylation of indole was observed.

3. Conclusion

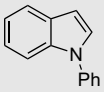
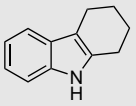
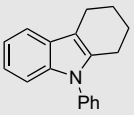
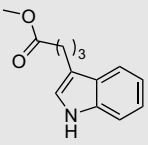
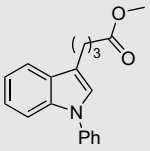
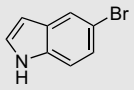
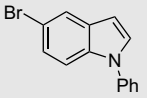
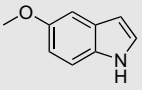
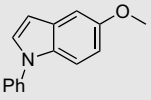
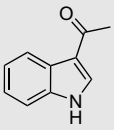
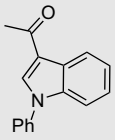
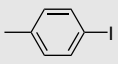
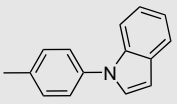
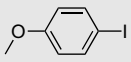
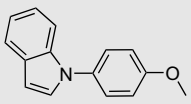
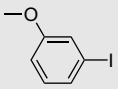
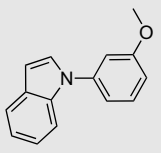
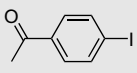
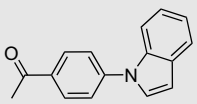
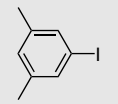
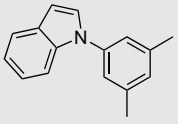
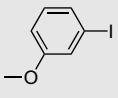
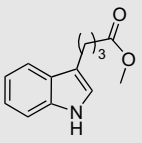
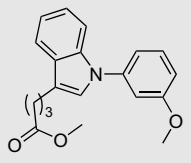
In summary, we have developed an efficient, very mild, experimentally simple, and economically attractive copper-catalyzed N-arylation of indoles with aryl iodides. Presence of electron releasing groups in aryl iodide decreases reaction rate and the yield of the coupling reaction whereas presence of an electron withdrawing group increases reaction rate and yield of the N-arylation reaction. The optimized reaction condition is highly selective to give only *N*-arylated indoles as in none of these cases *C*-arylated product was isolated.

4. Experimental

4.1. General

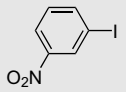
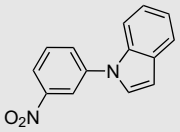
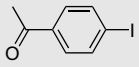
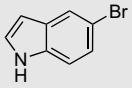
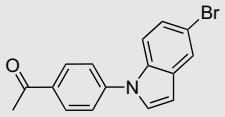
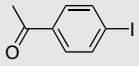
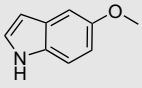
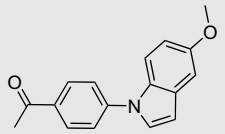
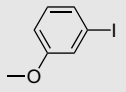
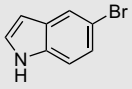
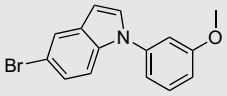
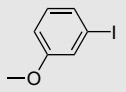
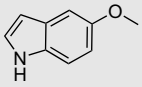
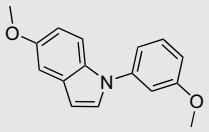
All reactions were carried out in reaction tubes under nitrogen atmosphere. Ligands **L2**, **L3**, and **L4** were made using literature procedure.[12] Copper(I) iodide was purchased from Aldrich

Table 3
Ullmann coupling of aryl iodide with indoles in the presence of **L4**–CuI catalyst at 82 °C

Entry	Aryl iodides	Indoles	Product	Time (h)	Yield[a] (%)
1				26	99
2				36	72
3				30	65
4				36	34
5				36	66
6				48	38
7				36	76
8				36	76
9				40	90
10				28	94
11				36	60
12				48	82

(*continued on next page*)

Table 3 (*continued*)

Entry	Aryl iodides	Indoles	Product	Time (h)	Yield[a] (%)
13				20	95
14				24	93
15				18	98
16				72	65
17				72	97

[a] Isolated yield.

Chemical Company. Potassium carbonate and indoles were purchased from Spectrochem India Private Limited and used without further purification. All other reagents are commercially available and used without further purification. Acetonitrile was purchased from SRL Chemicals, India and dried over CaH_2. Reaction temperatures were controlled by Varivolt temperature modulator. Thin-layer chromatography (TLC) was performed using Merck silica gel 60 F_{254} precoated plates (0.25 mm) and visualized by UV fluorescence quenching on UV analysis cabinet, Deep Vision. Silica gel (particle size 100–200 mesh) purchased from SRL India was used for chromatography. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker 400 MHz instrument, Department of Chemistry, IIT Madras. ^{1}H NMR spectra were reported relative to Me_4Si (δ 0.0 ppm) or residual $CHCl_3$ (δ 7.26 ppm). ^{13}C NMR were reported relative to $CDCl_3$ (δ 77.16 ppm). FTIR spectra were recorded on a Nicolet 6700 spectrometer, Department of Chemistry, IIT Madras and are reported in frequency of absorption (cm^{-1}). High resolution mass spectra (HRMS) were recorded on Q-Tof Micro mass spectrometer, Department of Chemistry, IIT Madras.

4.2. Typical experimental procedure (Table 3, entry 1)

N,*N*,*N*′,*N*′-Tetramethyl-BINAM **L4** (17 mg, 0.05 mmol), CuI (9.5 mg, 0.05 mmol), indole (58.6 mg, 0.5 mmol), and K_2CO_3 (138.2 mg, 1 mmol) were taken in a 10 mL reaction tube equipped with a septum. The reaction tube was evacuated and back-filled with nitrogen. Acetonitrile (2.2 mL) was added to the reaction mixture at room temperature. To the resulting solution was added iodobenzene (153 mg, 0.75 mmol), and then the reaction tube was sealed with glass stopper and the reaction mixture was heated for 26 h at 82 °C. The reaction mixture was allowed to cool to room temperature and the solvent was evaporated. The crude residue was directly purified by column chromatography on silica gel using ethyl acetate/hexanes as the eluent to afford 1-phenyl-indole[7] 95.2 mg, 99% (Table 3, entry 1). Colorless oil; R_f 0.63 (1:20 ethyl acetate/hexanes); FTIR (neat): 3052, 2922, 1593, 1502, 1451, 736, 690 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, J=3.6 Hz, 1H), 7.20–7.29 (m, 2H), 7.38–7.42 (m, 2H), 7.54–7.57 (m, 4H), 7.62 (d, J=8 Hz, 1H), 7.73–7.75 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.7, 110.6, 120.5, 121.3, 122.5, 124.5, 126.6, 128.1, 129.5, 129.7, 136.0, 139.9; MS (EI, m/z) 194 $[MH]^+$; HRMS $[MH]^+$ calculated for $C_{14}H_{12}N$ 194.0970, found 194.0974.

4.3. 9-Phenyl-2,3,4,9-tetrahydro-1*H*-carbazole (Table 3, entry 2)[13]

Colorless liquid; R_f 0.60 (1:19 ethyl acetate/hexanes); FTIR (neat) 3055, 2923, 2856, 1597, 1494, 1449, 744, 696 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.78 (m, 4H), 2.49 (br s, 2H), 2.70 (br s, 2H), 7.00–7.01 (m, 2H), 7.09–7.14 (m, 1H), 7.23–7.27 (m, 3H), 7.35–7.45 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 23.3, 23.4, 23.6, 110.0, 111.1, 117.9, 119.7, 121.4, 127.1, 127.4, 127.9, 129.4, 135.9, 137.4, 138.2.

4.4. Methyl 4-(1-phenyl-1*H*-indol-3-yl)-butanoate (Table 3, entry 3)

Colorless liquid; R_f 0.58 (1:9 ethyl acetate/hexanes); FTIR (neat) 3051, 2924, 2852, 1732, 1599, 1499, 1451, 1219, 738, 694 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.98–2.05 (m, 2H), 2.35 (t, J=7.4 Hz, 2H), 2.78 (t, J=7.4 Hz, 2H), 3.58 (s, 3H), 7.07–7.16 (m, 3H), 7.23–7.25 (m, 1H), 7.38–7.44 (m, 4H), 7.47 (d, J=8.0 Hz, 1H), 7.56 (d, J=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 25.4, 33.9, 51.5, 110.6, 116.9, 119.4, 120.0, 122.6, 124.3, 125.4, 126.2, 129.1, 129.7, 136.4, 140.1, 174.2; MS (EI, m/z) 294 $[MH]^+$; HRMS $[MH]^+$ calculated for $C_{19}H_{20}NO_2$ 294.1494, found 294.1492.

4.5. 5-Bromo-1-phenyl-1*H*-indole (Table 3, entry 4)[14]

Colorless liquid; R_f 0.76 (1:9 ethyl acetate/hexanes); FTIR (neat) 3057, 2923, 1593, 1501, 1448, 788, 751, 705 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.53 (t, J=2.4 Hz, 1H), 7.16–7.51 (m, 8H), 7.72 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 103.1, 112.1, 113.7, 123.7, 124.5,

125.3, 127.0, 129.2, 129.9, 131.1, 134.8, 139.5; MS (EI, *m*/*z*) 272 $[MH]^+$; HRMS $[MH]^+$ calculated for $C_{14}H_{11}NBr$ 272.0075, found 272.0080.

4.6. 5-Methoxy-1-phenyl-1*H*-indole (Table 3, entry 5)[15]

Colorless liquid; R_f 0.78 (1:9 ethyl acetate/hexanes); FTIR (neat) 2931, 2835, 1594, 1487, 1463, 1444, 1254, 1151, 799, 754, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.92 (s, 3H), 6.66 (d, *J*=2.8 Hz, 1H), 6.94 (dd, *J*=2.4, 8.8 Hz, 1H), 7.20 (d, *J*=2.4 Hz, 1H), 7.35–7.38 (m, 2H), 7.51–7.54 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 56.0, 102.9, 103.4, 111.5, 112.6, 124.2, 126.4, 128.5, 129.7, 130.0, 131.2, 140.1, 154.7; MS (EI, *m*/*z*) 224 $[MH]^+$; HRMS $[MH]^+$ calculated for $C_{15}H_{14}NO$ 224.1075, found 224.1072.

4.7. 1-(1-Phenyl-1*H*-indol-3-yl)-ethanone (Table 3, entry 6)[15]

Colorless solid, mp 143–145 °C (lit.[15] 145 °C); R_f 0.48 (1:1 ethyl acetate/hexanes); FTIR (neat) 3096, 3045, 1639, 1595, 1530, 1494, 1223, 748, 693 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.59 (s, 3H), 7.28–7.37 (m, 2H), 7.45–7.49 (m, 2H), 7.52–7.60 (m, 4H), 7.94 (s, 1H), 8.45–8.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 27.9, 110.9, 118.8, 122.9, 123.3, 124.1, 125.1, 126.7, 128.2, 130.1, 134.8, 137.2, 138.6, 193.5; MS (EI, *m*/*z*) 258 $[MNa]^+$; HRMS $[MH]^+$ calculated for $C_{16}H_{14}NO$ 236.1075, found 236.1074.

4.8. 1-*p*-Tolyl-1*H*-indole (Table 3, entry 7)[3b]

Colorless liquid; R_f 0.67 (1:19 ethyl acetate/hexanes); FTIR (neat) 3039, 2921, 1514, 1454, 1329, 730 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 3H), 6.57 (d, *J*=2.8 Hz, 1H), 7.05–7.14 (m, 2H), 7.20–7.22 (m, 3H), 7.29 (d, *J*=8.0 Hz, 2H), 7.44 (d, *J*=8.0 Hz, 1H), 7.59 (d, *J*=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.2, 103.3, 110.6, 120.3, 121.2, 122.3, 124.5, 128.2, 129.3, 130.3, 136.2, 136.4, 137.4; MS (EI, *m*/*z*) 208 $[MH]^+$; HRMS $[MH]^+$ calculated for $C_{15}H_{14}N$ 208.1126, found 208.1124.

4.9. 1-(4-Methoxyphenyl)-1*H*-indole (Table 3, entry 8)[3b]

White solid, mp 57–59 °C (lit.[16] 59.5–60.5 °C); R_f 0.68 (1:19 ethyl acetate/hexanes); FTIR (neat) 3051, 2924, 2838, 1511, 1456, 1289, 1241, 1027, 833, 734 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 6.57 (d, *J*=3.1 Hz, 1H), 6.93–6.96 (m, 2H), 7.05–7.14 (m, 2H), 7.19 (d, *J*=3.2 Hz, 1H), 7.30–7.34 (m, 2H), 7.37 (d, *J*=8.2 Hz, 1H), 7.60 (d, *J*=7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 103.0, 110.5, 114.9, 120.2, 121.2, 122.3, 126.2, 128.4, 129.1, 133.1, 136.6, 158.5; MS (EI, *m*/*z*) 224 $[MH]^+$; HRMS $[MH]^+$ calculated for $C_{15}H_{14}NO$ 224.1075, found 224.1079.

4.10. 1-(3-Methoxyphenyl)-1*H*-indole (Table 3, entry 9)[16]

Colorless liquid; R_f 0.63 (1:19 ethyl acetate/hexanes); FTIR (neat) 3055, 2946, 2835, 1595, 1483, 1458, 1208, 1040, 731, 688 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.77 (s, 3H), 6.59 (d, *J*=3.2 Hz, 1H), 6.81 (dd, *J*=1.6, 8.4 Hz, 1H), 6.97 (t, *J*=2.0 Hz, 1H), 7.01 (d, *J*=8.0 Hz, 1H), 7.06–7.15 (m, 2H), 7.25 (d, *J*=3.2 Hz, 1H), 7.32 (t, *J*=8.0 Hz, 1H), 7.51 (d, *J*=8.4 Hz, 1H), 7.59 (d, *J*=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 103.7, 110.3, 110.8, 112.1, 116.7, 120.5, 121.3, 122.5, 128.0, 129.5, 130.4, 135.9, 141.1, 160.7; MS (EI, *m*/*z*) 224 $[MH]^+$; HRMS $[MH]^+$ calculated for $C_{15}H_{14}NO$ 224.1075, found 224.1071.

4.11. 1-(4-(1*H*-Indol-1-yl)phenyl)-ethanone (Table 3, entry 10)[17]

White solid 84–86 °C (lit.[18] 85–87 °C); R_f 0.42 (1:9 ethyl acetate/hexanes); FTIR (neat) 3057, 2922, 1671, 1595, 1512, 1454, 1269, 731 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.52 (s, 3H), 6.61 (d, *J*=3.6 Hz, 1H), 7.07–7.17 (m, 2H), 7.24 (d, *J*=3.2 Hz, 1H), 7.47 (d, *J*=8.4 Hz, 2H), 7.52 (d, *J*=8.0 Hz, 1H), 7.58 (d, *J*=7.6 Hz, 1H), 7.98 (d, *J*=8.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.6, 105.2, 110.7, 121.2, 121.5, 123.0, 123.4, 127.4, 130.0, 130.1, 134.8, 135.6, 143.9, 196.7; MS (EI, *m*/*z*) 236 $[MH]^+$; HRMS $[MH]^+$ calculated for $C_{16}H_{14}NO$ 236.1075, found 236.1067.

4.12. 1-(3,5-Dimethylphenyl)-1*H*-indole (Table 3, entry 11)[18]

Colorless liquid; R_f 0.50 (hexanes); FTIR (neat) 3046, 2921, 2854, 1599, 1467, 1208, 732, 705 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.28 (s, 6H), 6.55 (d, *J*=3.2 Hz, 1H), 6.88 (s, 1H), 7.01–7.11 (m, 4H), 7.20 (d, *J*=3.2 Hz, 1H), 7.46 (d, *J*=8.4 Hz, 1H), 7.57 (d, *J*=7.6 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.5, 103.3, 110.8, 120.3, 121.2, 122.2, 122.3, 128.1, 128.2, 129.4, 136.0, 139.5, 139.8; MS (EI, *m*/*z*) 222 $[MH]^+$; HRMS $[MH]^+$ calculated for $C_{16}H_{16}N$ 222.1283, found 222.1287.

4.13. Methyl 4-(1-(3-methoxyphenyl)-1*H*-indol-3-yl)-butanoate (Table 3, entry 12)

Colorless viscous liquid; R_f 0.45 (1:9 ethyl acetate/hexanes); FTIR (neat) 2948, 2848, 1732, 1594, 1492, 1460, 1204, 1176, 1044, 779, 740, 694 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.10 (m, 2H), 2.44 (t, *J*=7.4 Hz, 2H), 2.86 (t, *J*=7.6 Hz, 2H), 3.67 (s, 3H), 3.87 (s, 3H), 6.86–6.89 (m, 1H), 7.03–7.04 (m, 1H), 7.07–7.09 (m, 1H), 7.15–7.24 (m, 3H), 7.4 (t, *J*=8.0 Hz, 1H), 7.59 (d, *J*=8.4 Hz, 1H), 7.64 (d, *J*=8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 24.6, 25.4, 33.9, 51.6, 55.6, 110.1, 110.8, 111.8, 116.5, 116.9, 119.4, 120.1, 122.6, 125.4, 129.2, 130.4, 136.3, 141.2, 160.8, 174.2; MS (EI, *m*/*z*) 346 $[MNa]^+$; HRMS $[MNa]^+$ calculated for $C_{20}H_{21}NO_3Na$ 346.1419, found 346.1419.

4.14. 1-(3-Nitrophenyl)-1*H*-indole (Table 3, entry 13)[19]

Pale yellow solid, mp 66–68 °C (lit.[19] 67–68 °C); R_f 0.45 (1:19 ethyl acetate/hexanes); FTIR (neat) 3090, 2923, 2358, 1525, 1483, 1451, 1341, 1206, 727, 677 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.68 (d, *J*=2.8 Hz, 1H), 7.13–7.23 (m, 2H), 7.29 (d, *J*=3.6 Hz, 1H), 7.49–7.52 (m, 1H), 7.63 (t, *J*=8.0 Hz, 2H), 7.78–7.81 (m, 1H), 8.11–8.13 (m, 1H), 8.31–8.32 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 105.5, 110.1, 118.9, 121.0, 121.4, 121.7, 123.4, 127.4, 129.7, 129.8, 130.7, 135.6, 141.1, 149.3; MS (EI, *m*/*z*) 239 $[MH]^+$; HRMS $[MH]^+$ calculated for $C_{14}H_{10}N_2O_2$ 239.0821, found 239.0824.

4.15. 1-(4-(5-Bromo-1*H*-indol-1-yl)phenyl)-ethanone (Table 3, entry 14)

Pale brown solid, mp 112–114 °C; R_f 0.42 (1:9 ethyl acetate/hexanes); FTIR (neat) 3108, 2922, 1678, 1599, 1517, 1449, 1266, 841, 761, 721 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.66 (s, 3H), 6.67 (d, *J*=3.2 Hz, 1H), 7.34 (dd, *J*=2.0, 8.8 Hz, 1H), 7.37 (d, *J*=3.6 Hz, 1H), 7.49 (d, *J*=8.8 Hz, 1H), 7.58 (d, *J*=8.4 Hz, 2H), 7.82 (d, *J*=1.6 Hz, 1H), 8.13 (d, *J*=8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 104.5, 112.1, 114.3, 123.5, 124.0, 125.9, 128.7, 130.3, 131.6, 134.3, 135.1, 143.4, 196.9; MS (EI, *m*/*z*) 314 $[MH]^+$; HRMS $[MH]^+$ calculated for $C_{16}H_{13}BrNO$ 314.0181, found 314.0176.

4.16. 1-(4-(5-Methoxy-1*H*-indol-1-yl)phenyl)-ethanone (Table 3, entry 15)

Colorless solid, mp 99–101 °C; R_f 0.32 (1:9 ethyl acetate/hexanes); FTIR (neat) 3096, 2921, 2852, 1665, 1593, 1509, 1463, 1260, 1150.0, 840, 805, 758, 725 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 2.65 (s, 3H), 3.88 (s, 3H), 6.66 (d, *J*=3.2 Hz, 1H), 6.91 (dd, *J*=2.4, 8.8 Hz, 1H), 7.14 (d, *J*=2.4 Hz, 1H), 7.36 (d, *J*=3.2 Hz, 1H), 7.54 (d, *J*=8.8 Hz, 1H), 7.58–7.61 (m, 2H), 8.09–8.12 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 26.7, 56.0, 103.3, 105.0, 111.6, 113.0, 123.0, 127.9, 130.2,

130.6, 130.7, 134.5, 144.1, 155.1, 196.9; MS (EI, *m*/*z*) 266 $[MH]^+$; HRMS $[MH]^+$ calculated for $C_{17}H_{16}NO_2$ 266.1181, found 266.1175.

4.17. 5-Bromo-1-(3-methoxyphenyl)-1*H*-indole (Table 3, entry 16)

Pale brown solid, mp 69–71 °C; R_f 0.65 (1:9 ethyl acetate/hexanes); FTIR (neat) 2925, 2839, 1595, 1483, 1451, 1208, 1171, 1042, 785, 703 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.85 (s, 3H), 6.59 (d, J=3.2 Hz, 1H), 6.89–6.92 (m, 1H), 6.99–7.05 (m, 2H), 7.27–7.32 (m, 2H), 7.39–7.44 (m, 2H), 7.79 (d, J=1.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.7, 103.2, 110.5, 112.2, 112.5, 113.7, 116.7, 123.7, 125.3, 129.2, 130.6, 131.2, 134.7, 140.6, 160.8; MS (EI, *m*/*z*) 301 $[M]^+$; HRMS $[M]^+$ calculated for $C_{15}H_{12}BrNO$ 301.0102, found 301.0107.

4.18. 5-Methoxy-1-(3-methoxyphenyl)-1*H*-indole (Table 3, entry 17)[3c]

Colorless liquid; R_f 0.51 (1:9 ethyl acetate:hexanes); FTIR (neat) 2945, 2841, 1601, 1485, 1445, 1222, 795, 733 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 3.87 (s, 3H), 3.88 (s, 3H), 6.60 (d, J=3.2 Hz, 1H), 6.89 (dd, J=2.0, 9.2 Hz, 2H), 7.04 (t, J=2.0 Hz, 1H), 7.08–7.10 (m, 1H), 7.14 (d, J=2.4 Hz, 1H), 7.33 (d, J=3.2 Hz, 1H), 7.41 (t, J=8.0 Hz, 1H), 7.51 (d, J=9.2 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 56.0, 102.8, 103.4, 110.0, 111.6, 111.9, 112.6, 116.4, 128.4, 130.0, 130.5, 131.1, 141.2, 154.7, 160.7; MS (EI, *m*/*z*) 254 $[MH]^+$; HRMS $[MH]^+$ calculated for $C_{16}H_{16}NO_2$ 254.1181, found 254.1181.

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