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Copper-catalyzed *N*-alkylation of indoles by *N*-tosylhydrazones†

Li Ling, [ab] Jing Cao,[a] Jianfeng Hu[ab] and Hao Zhang ⋆[abc]

An efficient method for the direct *N*-alkylation of indoles *via* copper-catalyzed reductive cross coupling between *N*-tosylhydrazones and indole reagents has been developed. The reaction was performed in the presence of copper iodide and potassium hydroxide by utilization of tri(*p*-tolyl)phosphine as a ligand. A wide variety of *N*-alkylated indoles were obtained in moderate to good yields. The application of the current method to the synthesis of biologically active *N*-alkylated indole derivatives has also been demonstrated.

Introduction

The indole core is one of the most prevalent architectures found in a myriad of biologically active natural and synthesized compounds.[1] For over 100 years, substituted indoles have remained preferred structures in the creation of new potential drugs, due to their high affinity to bind with many biological targets.[2] Hence, enormous efforts have been devoted to the preparation and direct functionalization of indoles.[3] However, the direct *N*-alkylation of indoles remains challenging due to the inertness of the indole nitrogen atom toward electrophilic reagents, despite the structural novelties and attractive biological activities of *N*-alkylated indoles. Some biologically active *N*-alkylated indole derivatives are shown in Fig. 1.

One of the common methods for alkylation of indoles is a Mitsunobu reaction of indole derivatives with alcohol (Scheme 1).[4] However, electron withdrawing substituents at position 2 or position 3 are needed to increase NH acidity in this reaction. Chen *et al.* reported the use of Morita–Baylis–Hillman carbonates in asymmetric *N*-allylic alkylation of indoles.[5] Trost *et al.* and Hartwig *et al.* developed palladium-catalyzed and iridium-catalyzed *N*-allylic alkylation of indoles, respectively.[6] Nevertheless, only *N*-allylation products were obtained through these methods. Therefore, it would be highly desirable to develop a new method for the mild and efficient direct introduction of alkyl substituents at the nitrogen atoms of indoles.

On the other hand, *N*-tosylhydrazones, which are readily prepared from carbonyl compounds, have been used as a source for the safe generation of diazo compounds and carbenes.[7] They have emerged as a new type of cross-coupling partner in C–C(X) bond formation, including in reactions with aryl halides,[8]
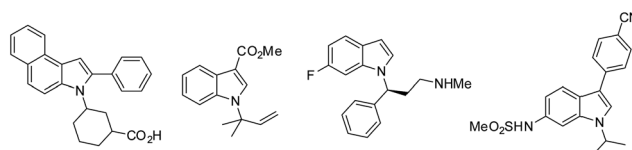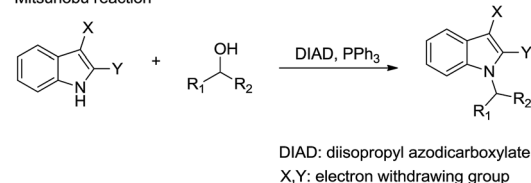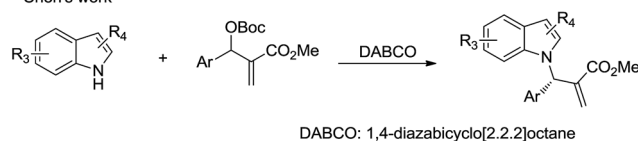

Fig. 1 Representative biologically active *N*-alkylated indole derivatives.
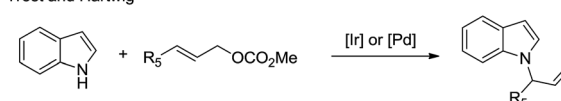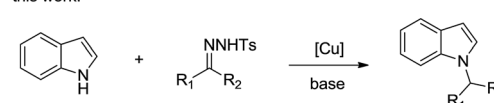
Scheme 1 Synthesis of *N*-alkylated indoles.

[a]College of Chemistry & Chemical Engineering, Inner Mongolia University, Hohhot 010021, P. R. China. E-mail: haozhang@imu.edu.cn

[b]Inner Mongolia Key Laboratory of Fine Organic Synthesis, Hohhot 010021, P. R. China

[c]State Key Laboratory of Polymer Physics and Chemistry, Changchun Institute of Applied Chemistry, Chinese Academy of Sciences, Changchun 130022, P. R. China

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arylsulfonates,[9] alkynes,[10] H-phosphonates,[11] azoles,[12] arylboronic acids,[13] benzylic halides,[14] and amines.[15]

Herein, *N*-alkylated indoles were synthesized through the Cu-catalyzed reductive cross coupling of *N*-tosylhydrazones with indoles using potassium hydroxide as a base. Various *N*-branched alkylated and *N*-benzylated indoles were obtained through this method.

Results and discussion

We selected alkylation of indole with acetyl benzene-derived tosylhydrazone **1a** as the model reaction for optimization (Table 1). Initial screening of Cu catalysts revealed that CuI provided the best activity, with 31% yield of **3a** (Table 1, entry 7). Several phosphine ligands, including triphenylphosphine, tri(*p*-tolyl)phosphine, tris(4-methoxyphenyl)phosphine and tricyclohexylphosphine were examined. Tri(*p*-tolyl)phosphine and tris(4-methoxyphenyl)phosphine were shown to be the most efficient ligands in terms of reactivity, giving the product **3a** in 30–31% yield (Table 1, entries 7 and 10). The best result was obtained with KOH as the base, giving **3a** in 68% yield (Table 1, entry 12). Further screening of solvents did not improve the results (Table 1, entries 14–16). In the control experiment, 42% yield of product **3a** was detected under conditions in which the phosphine ligand was absent (Table 1, entry 17). Thus, optimized reaction conditions were obtained as follows: 10 mol% of CuI, 10 mol% of tri(*p*-tolyl)phosphine, 2.5-equivalent of KOH, in dioxane at 100 °C under argon (Table 1, entry 12).

Under the above optimized reaction conditions, we next examined the scope of this reaction (Table 2). *N*-Alkylation of indole proceeded with a wide range of *N*-tosylhydrazones in good yields. Electron-donating groups at the *ortho*, *meta* or *para* position on the phenyl ring of acetyl benzene-derived *N*-tosylhydrazones led to increased yields (**3b** to **3f**), while strong electron withdrawing groups decreased the reaction efficiency to some extent (**3j** and **3k**). Halogen groups and heteroaryl groups were well tolerated (**3g** to **3j**, **3p**), generating product in 58–80% yields. Benzophenone-derived *N*-tosylhydrazones with methyl or chloro substituents reacted with indoles to give *N*-alkylation products in good yield (**3m** to **3o**). More importantly, alkyl ketone-derived *N*-tosylhydrazones could be effective alkylation substrates (**3q** to **3s**). Alkylation of indoles with benzaldehyde-derived *N*-tosylhydrazone was examined (**3t** and **3u**), giving products in 82–86% yield. Substituted indoles with an electron-donating group at the 5-position increased the product yield to 85% (**3w**) and electron withdrawing group at the 5-position caused a small decrease in production yield to 64% (**3v**). Finally, pyrrole and carbazole also reacted well with *N*-tosylhydrazones giving products (**3x** to **3z**, **3aa**) in 41–78% yield.

The synthetic value of our method was demonstrated by the synthesis of *N*-alkylated indole derivative **6**, which has been shown to have activity in treatment of Alzheimer's disease (Scheme 2).[16] The reaction of 2-phenylbenz[*e*]indole **4** with 3-(methoxycarbonyl)cyclohexanone-derived tosylhydrazone **5** under the current conditions proceeded smoothly to give *N*-alkylated product in 71% yield. Following hydrolysis of the ester

Table 1 Optimization of reaction conditions[a]
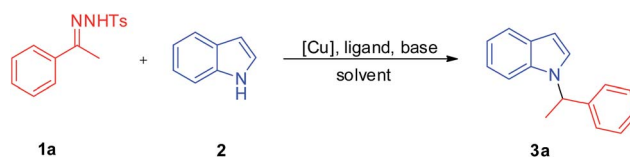
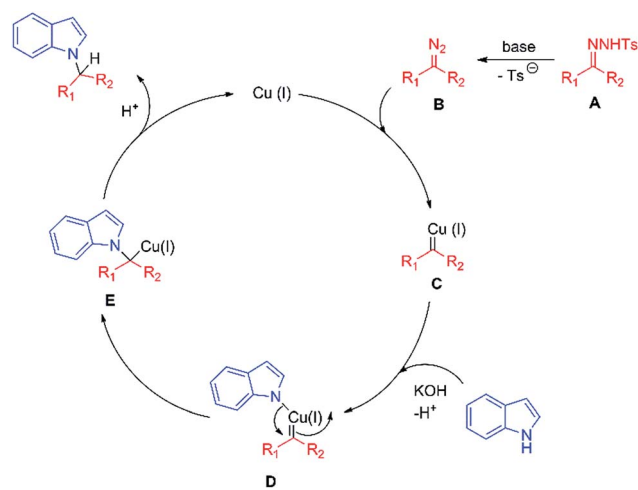| Entry	Catalyst (10 mol%)	Ligand (10 mol%)	Solvent	Base (2.5 equiv.)	Yield[b] (%)
1	Cu(acac)$_2$	P(*p*-tolyl)$_3$	Dioxane	Cs$_2$CO$_3$	Trace
2	Cu(OTf)$_2$	P(*p*-tolyl)$_3$	Dioxane	Cs$_2$CO$_3$	18
3	Cu(OAc)$_2$	P(*p*-tolyl)$_3$	Dioxane	Cs$_2$CO$_3$	Trace
4	CuBr	P(*p*-tolyl)$_3$	Dioxane	Cs$_2$CO$_3$	20
5	CuCl	P(*p*-tolyl)$_3$	Dioxane	Cs$_2$CO$_3$	19
6	Cu$_2$O	P(*p*-tolyl)$_3$	Dioxane	Cs$_2$CO$_3$	10
7	CuI	P(*p*-tolyl)$_3$	Dioxane	Cs$_2$CO$_3$	31
8	CuI	PPh$_3$	Dioxane	Cs$_2$CO$_3$	28
9	CuI	P(*p*-OMePh)$_3$	Dioxane	Cs$_2$CO$_3$	30
10	CuI	PCy$_3$	Dioxane	Cs$_2$CO$_3$	21
11	CuI	P(*p*-tolyl)$_3$	Dioxane	LiO^{t}Bu	25
12	**CuI**	**P(*p*-tolyl)$_3$**	**Dioxane**	**KOH**	**68**
13	CuI	P(*p*-tolyl)$_3$	Dioxane	LiOH	Trace
14	CuI	P(*p*-tolyl)$_3$	Toulene	KOH	Trace
15	CuI	P(*p*-tolyl)$_3$	CH$_3$CN	KOH	Trace
16	CuI	P(*p*-tolyl)$_3$	DMF	KOH	Trace
17	CuI	P(*p*-tolyl)$_3$	Dioxane	KOH	42

[a] Reactions were carried out with 0.33 mmol of **1a** and 0.50 mmol of **2** in the presence of 10 mol% of catalyst, 10 mol% of ligand, 2.5 equiv. of base and 2 mL solvent under an argon atmosphere for 12 h. [b] Isolated yield.

Table 2 Cu-catalyzed *N*-alkylation of indoles with tosylhydrazones[a,b]

3a, 68% · 3b, 71% · 3c, 78% · 3d, 81% · 3e, 65% · 3f, 84% · 3g, 67% · 3h, 73% · 3i, 80% · 3j, 65% · 3k, 33% · 3l, 72% · 3m, 75% · 3n, 64% · 3o, 63% · 3p, 58% · 3q, 81% · 3r, 79% · 3s, 75% · 3t, 82% · 3u, 86% · 3v, 64% · 3w, 85% · 3x, 55% · 3y, 76% · 3z, 41% · 3aa, 78%

[a] Reactions were carried out with 0.33 mmol of **1** and 0.50 mmol of **2** in the presence of 10 mol% of CuI, 10 mol% of P(*p*-tolyl)$_3$, 0.83 mmol of KOH and 2 mL of dioxane at 100 °C under an argon atmosphere for 12 h. [b] Isolated yield after chromatography.
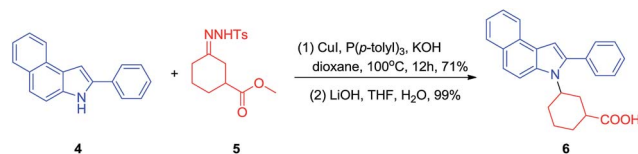
Scheme 2 Application of current method to synthesis of biologically active *N*-alkylated indole derivative.

group, the biologically active indole derivative **6** was obtained in 70% yield over two steps.

A plausible mechanism for this Cu-catalyzed reductive coupling is proposed on the basis of transition metal-catalyzed cross-coupling reactions of *N*-tosylhydrazones in the literature (Scheme 3).[7b,17] First, the diazo compound **B** is formed by decomposition of the tosylhydrazone **A** in the presence of base. Subsequently, reaction of copper salt and diazo compound **B** leads to the copper-carbene species **C**. Then, deprotonation of indole in basic conditions followed by coordination with Cu(I) generates the intermediate **D**. Next, migratory insertion of the indole group gives Cu(I) species **E**. Finally, protonation of intermediate **E** affords the product and regenerates the Cu(I) catalyst.

Scheme 3 Proposed reaction mechanism.

Conclusions

In conclusion, we have described a new procedure for the direct *N*-alkylation of indoles by reductive coupling of *N*-tosylhydrazones with indoles in the presence of KOH and a catalytic amount of CuI and tri(*p*-tolyl)phosphine. Various *N*-branched alkylated and *N*-benzylated indoles could be obtained in moderate to good yield. Notably, the starting materials in this method are readily available, since *N*-tosylhydrazones are easily prepared from the corresponding aldehydes or ketones. Additionally, the reaction procedure has functional group compatibility and operational simplicity, and may have potential use in the synthesis of biologically important *N*-alkylated indoles.

Experimental section

General experimental methods

All reactions were carried out in oven dried glassware under argon unless otherwise specified. All NMR experiments were carried out on a Bruker AVANCE 500 MHz nuclear magnetic resonance spectrometer using $CDCl_3$ or DMSO-d_6 as the solvent with tetramethylsilane as the internal standard. Chemical shift values (δ) are given in parts per million. HRMS data were obtained on a Bruker QTOF mass spectrometer. The melting points were determined on an X-4 binocular microscope melting point apparatus and uncorrected. Dioxane, toluene, DMF and acetonitrile were dried according to literature techniques.

General procedure for preparation of N-alkylindoles

The indoles (0.50 mmol, 1.5 equiv.), N-tosylhydrazones (0.33 mmol, 1.0 equiv.), potassium hydroxide (0.83 mmol, 2.5 equiv.), copper iodide (0.03 mmol, 10 mol%), P(p-tolyl)$_3$ (0.03 mmol, 10 mol%) and 2 mL dioxane were mixed in a dry reaction tube. The mixture was stirred at 100 °C under an argon atmosphere for 12 hours. When the reaction was completed, the crude reaction mixture was allowed to reach room temperature, and the solvent was eliminated. Then ethyl acetate and ammonia were added and the layers were separated. The aqueous phase was extracted three times with ethyl acetate. The combined organic layers were washed with water and then dried over $MgSO_4$ and filtered. The solvents were evaporated under reduced pressure and the residue was purified by flash chromatography on silica gel.

1-(1-Phenylethyl)-1H-indole (3a).[18] Yellow oil, 52.2 mg (68% yield); Rf (petroleum ether) = 0.6. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.71 (d, J = 7.3 Hz, 1H), 7.32 (d, J = 17.5, 11.8, 6.3 Hz, 5H), 7.25–7.13 (m, 4H), 6.65 (t, J = 4.3 Hz, 1H), 5.73 (d, J = 13.8, 6.8 Hz, 1H), 1.98 (t, J = 6.3 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 149.2, 148.5, 147.5, 139.1, 123.4, 115.8, 113.8, 69.7, 69.0, 66.9. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for C$_{16}$H$_{15}$N 222.1283; found: 222.1283.

1-(1-(o-Tolyl)ethyl)-1H-indole (3b). Yellow oil, 55.2 mg (71% yield); Rf (petroleum ether) = 0.6. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.62 (d, J = 7.8 Hz, 1H), 7.21–7.14 (m, 4H), 7.13–7.06 (m, 4H), 6.50 (d, J = 3.0 Hz, 1H), 5.78 (q, J = 6.9 Hz, 1H), 2.24 (s, 3H), 1.84 (d, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 140.1, 136.0, 135.7, 130.8, 128.8, 127.7, 126.6, 125.4, 125.1, 121.5, 121.0, 119.6, 109.7, 101.3, 51.8, 20.5, 19.1. HRMS (ESI-TOF) m/z: [M]$^+$ calcd for C$_{17}$H$_{17}$N 235.1361; found: 235.1356.

1-(1-(m-Tolyl)ethyl)-1H-indole (3c). Yellow oil, 60.5 mg (78% yield); Rf (petroleum ether) = 0.5. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.51 (d, J = 20.3 Hz, 2H), 8.24 (d, J = 8.2 Hz, 1H), 8.02–7.79 (m, 1H), 7.36 (d, J = 6.8, 5.2 Hz, 1H), 4.85 (s, 2H), 4.37 (s, 2H), 4.13 (s, 5H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 142.7, 138.4, 136.2, 128.8, 128.6, 128.3, 126.7, 125.0, 123.1, 121.5, 120.9, 119.6, 110.1, 101.4, 54.8, 21.9, 21.6. HRMS (ESI-TOF) m/z: [M]$^+$ calcd for C$_{17}$H$_{17}$N 235.1361; found: 235.1358.

1-(1-(p-Tolyl)ethyl)-1H-indole (3d). Yellow oil, 62.9 mg (81% yield); Rf (petroleum ether) = 0.5. ^{1}H NMR (500 MHz, CDCl$_3$)

δ 8.51 (d, J = 20.3 Hz, 2H), 8.24 (d, J = 8.2 Hz, 1H), 8.02–7.79 (m, 1H), 7.36 (dd, J = 6.8, 5.2 Hz, 1H), 4.85 (s, 2H), 4.37 (s, 2H), 4.13 (s, 5H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 139.7, 137.1, 136.1, 129.4, 128.8, 125.9, 124.9, 121.5, 120.9, 119.5, 110.1, 101.4, 54.6, 21.8, 21.1. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for C$_{17}$H$_{17}$N 236.1439; found: 236.1442.

1-(1-(2-Methoxyphenyl)ethyl)-1H-indole (3e). Yellow oil, 51.4 mg (65% yield); Rf (petroleum ether) = 0.4. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.61 (d, J = 7.7 Hz, 1H), 7.38 (d, J = 3.2 Hz, 1H), 7.22 (d, J = 8.0 Hz, 1H), 7.16 (s, 1H), 7.13–7.00 (m, 2H), 6.84 (d, J = 8.1 Hz, 1H), 6.76 (d, J = 6.6 Hz, 2H), 6.54 (d, J = 3.1 Hz, 1H), 6.03 (q, J = 7.0 Hz, 1H), 3.83 (s, 3H), 1.84 (d, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 156.2, 136.1, 131.3, 128.7, 128.5, 126.0, 125.1, 121.3, 120.8, 119.4, 110.5, 110.3, 101.0, 55.5, 49.2, 20.5. HRMS (ESI-TOF) m/z: [M]$^+$ calcd for C$_{17}$H$_{17}$NO 251.1310; found: 251.1305.

1-(1-(4-Methoxyphenyl)ethyl)-1H-indole (3f). Yellow oil, 64.1 mg (81% yield); Rf (petroleum ether) = 0.4. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.69 (d, J = 7.5 Hz, 1H), 7.30 (t, J = 6.4 Hz, 2H), 7.19 (t, J = 7.5 Hz, 1H), 7.13 (d, J = 15.2, 7.8 Hz, 3H), 6.86 (d, J = 8.7 Hz, 2H), 6.60 (d, J = 3.2 Hz, 1H), 5.68 (q, J = 7.0 Hz, 1H), 3.80 (s, 3H), 1.93 (d, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 158.9, 136.0, 134.7, 128.8, 127.2, 124.9, 121.4, 120.9, 119.5, 114.0, 110.1, 101.4, 55.3, 54.3, 21.7. HRMS (ESI-TOF) m/z: [M]$^+$ calcd for C$_{17}$H$_{17}$NO 251.1310; found: 251.1305.

1-(1-(2-Chlorophenyl)ethyl)-1H-indole (3g). Yellow oil, 49.8 mg (63% yield); Rf (petroleum ether) = 0.5. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.67–7.56 (m, 1H), 7.36 (dd, J = 18.9, 5.6 Hz, 2H), 7.16–7.05 (m, 4H), 7.02 (d, J = 14.8, 7.4 Hz, 1H), 6.74 (d, J = 7.8 Hz, 1H), 6.58 (d, J = 3.2 Hz, 1H), 6.02 (q, J = 7.0 Hz, 1H), 1.86 (d, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 140.7, 136.1, 132.1, 129.7, 128.9, 128.7, 127.6, 126.5, 124.7, 121.7, 120.9, 119.8, 110.1, 101.6, 52.1, 20.5. HRMS (ESI-TOF) m/z: [M]$^+$ calcd for C$_{16}$H$_{14}$NCl 255.0815; found: 255.0809.

1-(1-(3-Chlorophenyl)ethyl)-1H-indole (3h). Yellow oil, 57.7 mg (73% yield); Rf (petroleum ether) = 0.5. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.63 (d, J = 7.4 Hz, 1H), 7.17 (d, J = 9.1, 7.9 Hz, 3H), 7.12 (d, J = 25.6, 11.7, 4.2 Hz, 4H), 6.92 (d, J = 7.2, 1.1 Hz, 1H), 6.57 (s, 1H), 5.59 (t, J = 6.9 Hz, 1H), 1.86 (d, J = 7.1, 1.6 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 145.0, 136.0, 134.7, 130.1, 128.9, 127.7, 126.1, 124.7, 124.3, 121.1, 121.1, 120.0, 110.0, 102.0, 54.4, 21.8. HRMS (ESI-TOF) m/z: [M]$^+$ calcd for C$_{16}$H$_{14}$NCl 255.0815; found: 255.0812.

1-(1-(4-Chlorophenyl)ethyl)-1H-indole (3i). Yellow oil, 65.7 mg (83% yield); Rf (petroleum ether) = 0.5. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.63 (d, J = 7.1 Hz, 1H), 7.23 (d, J = 15.1, 5.9 Hz, 3H), 7.19–7.04 (m, 3H), 7.01 (d, J = 8.4 Hz, 2H), 6.57 (d, J = 3.2 Hz, 1H), 5.60 (q, J = 7.1 Hz, 1H), 1.87 (d, J = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.4, 136.0, 133.2, 128.9, 127.3, 124.7, 121.7, 121.1, 119.8, 110.0, 101.8, 54.3, 21.7. HRMS (ESI-TOF) m/z: [M]$^+$ calcd for C$_{16}$H$_{14}$NCl 255.0815; found: 255.0809.

1-(1-(4-Fluorophenyl)ethyl)-1H-indole (3J). White solid, 61.7 mg (79% yield); mp 72–73 °C; Rf (petroleum ether) = 0.4. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.63 (d, J = 7.3 Hz, 1H), 7.22 (d, J = 3.0 Hz, 1H), 7.17 (d, J = 7.7 Hz, 1H), 7.14–7.06 (m, 2H), 7.03 (d, J = 8.3, 5.5 Hz, 2H), 6.95–6.88 (m, 2H), 6.55 (d, J = 3.1 Hz, 1H), 5.59 (q, J = 7.0 Hz, 1H), 1.84 (d, J = 7.1 Hz, 3H). ^{13}C NMR (126

MHz, CDCl$_3$) δ 163.0, 161.0, 138.5, 138.5, 136.0, 128.9, 127.6, 127.6, 124.7, 121.6, 121.0, 119.7, 115.7, 115.5, 110.0, 101.7, 54.2, 21.8. HRMS (ESI-TOF) *m/z*: [M]$^+$ calcd for C$_{16}$H$_{14}$NF 239.1110; found: 239.1105.

1-(1-(4-(Trifluoromethyl)phenyl)ethyl)-1*H*-indole (3k). White oil, 26.7 mg (33% yield); Rf (petroleum ether) = 0.4. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.66 (d, *J* = 6.8, 2.0 Hz, 1H), 7.54 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 3.3 Hz, 1H), 7.20 (d, *J* = 8.4 Hz, 2H), 7.18–7.09 (m, 3H), 6.62 (d, *J* = 3.2 Hz, 1H), 5.72 (q, *J* = 7.1 Hz, 1H), 1.96 (d, *J* = 7.1 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 136.0, 128.9, 126.2, 125.8, 124.6, 121.8, 121.2, 119.9, 110.0, 102.1, 100.1, 54.6, 21.8. HRMS (ESI-TOF) *m/z*: [M]$^+$ calcd for C$_{17}$H$_{14}$NF$_3$ 239.1110; found: 239.1105.

1-(1-Phenylpropyl)-1*H*-indole (3l). Yellow oil, 63.7 mg (82% yield); Rf (petroleum ether) = 0.6. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.62 (d, *J* = 7.8 Hz, 1H), 7.29 (d, *J* = 3.1 Hz, 2H), 7.25–7.10 (m, 6H), 7.07 (t, *J* = 7.6 Hz, 1H), 6.56 (d, *J* = 3.2 Hz, 1H), 5.32 (d, *J* = 8.7, 6.7 Hz, 1H), 2.36–2.24 (m, 2H), 0.94 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.7, 136.5, 128.7, 128.7, 127.5, 126.5, 125.0, 121.5, 121.0, 119.5, 110.0, 101.7, 61.4, 28.5, 11.6. HRMS (ESI-TOF) *m/z*: [M]$^+$ calcd for C$_{17}$H$_{17}$N 235.1361; found: 235.1362.

1-(Diphenylmethyl)-1*H*-indole (3m).[19] White solid, 60.7 mg (75% yield); mp 91–92 °C; Rf (petroleum ether) = 0.5. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.63 (d, *J* = 5.8, 2.9 Hz, 1H), 7.35–7.16 (m, 7H), 7.11 (d, *J* = 14.5, 11.7, 7.9 Hz, 7H), 6.85–6.78 (m, 2H), 6.48 (d, *J* = 3.1 Hz, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 139.9, 136.6, 129.0, 128.7, 128.6, 128.5, 128.2, 128.0, 127.0, 125.9, 121.7, 121.0, 119.9, 110.3, 101.5, 63.7. HRMS (ESI-TOF) *m/z*: [M]$^+$ calcd for C$_{21}$H$_{17}$N 283.1361; found: 283.1356.

1-(Di-*p*-tolylmethyl)-1*H*-indole (3n). White solid, 69.0 mg (84% yield); mp 111–113 °C; Rf (petroleum ether) = 0.6. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.72 (d, *J* = 6.2, 2.4 Hz, 1H), 7.31 (d, *J* = 7.2 Hz, 1H), 7.18 (t, *J* = 6.3 Hz, 6H), 7.06 (d, *J* = 8.0 Hz, 4H), 6.92 (d, *J* = 3.3 Hz, 1H), 6.84 (s, 1H), 6.56 (d, *J* = 3.1 Hz, 1H), 2.40 (s, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 137.6, 137.2, 136.6, 129.4, 129.0, 128.3, 127.0, 121.5, 120.9, 119.7, 110.3, 101.2, 63.2, 21.2. HRMS (ESI-TOF) *m/z*: [M]$^+$ calcd for C$_{23}$H$_{21}$N 311.1674; found: 311.1669.

1-((4-Chlorophenyl) (phenyl)methyl)-1*H*-indole (3o). Yellow oil, 68.4 mg (83% yield); Rf (petroleum ether) = 0.5. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.77–7.70 (m, 1H), 7.40 (d, *J* = 6.2 Hz, 3H), 7.36 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 6.4 Hz, 1H), 7.22 (d, *J* = 9.4, 5.7 Hz, 2H), 7.19–7.15 (m, 2H), 7.08 (d, *J* = 8.4 Hz, 2H), 6.91–6.84 (m, 2H), 6.60 (d, *J* = 3.1 Hz, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 139.3, 138.5, 136.5, 133.8, 129.7, 129.0, 128.9, 128.9, 128.5, 128.2, 126.7, 121.8, 121.1, 120.0, 110.1, 101.8, 63.0. HRMS (ESI-TOF) *m/z*: [M]$^+$ calcd for C$_{21}$H$_{16}$NCl 317.0971; found: 317.0970.

1-(1-(Thiophen-2-yl)ethyl)-1*H*-indole (3p).[20] Yellow oil, 44.8 mg (58% yield); Rf (petroleum ether) = 0.5. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.66 (d, *J* = 7.9 Hz, 1H), 7.40 (d, *J* = 8.3 Hz, 1H), 7.22 (t, *J* = 3.7 Hz, 3H), 7.14 (t, *J* = 7.4 Hz, 1H), 6.98–6.86 (m, 2H), 6.57 (d, *J* = 3.2 Hz, 1H), 5.93 (q, *J* = 7.0 Hz, 1H), 1.99 (d, *J* = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 146.1, 135.8, 128.8, 126.8, 124.8, 124.5, 121.6, 121.2, 119.7, 109.7, 102.1, 50.8, 22.3. HRMS (ESI-TOF) *m/z*: [M]$^+$ calcd for C$_{14}$H$_{13}$NS 227.0769; found: 227.0763.

1-(Pentan-3-yl)-1*H*-indole (3q). Yellow oil, 59.5 mg (81% yield); Rf (petroleum ether) = 0.6. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.63 (d, *J* = 7.8 Hz, 1H), 7.37 (d, *J* = 8.3 Hz, 1H), 7.18 (d, *J* = 13.7, 5.6 Hz, 1H), 7.12 (d, *J* = 3.2 Hz, 1H), 7.08 (t, *J* = 7.1 Hz, 1H), 6.54 (d, *J* = 3.0 Hz, 1H), 4.17–4.04 (m, 1H), 1.91–1.82 (m, 4H), 0.75 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 136.9, 128.4, 124.4, 121.1, 120.9, 119.1, 109.7, 101.4, 59.7, 29.8, 28.6, 11.0. HRMS (ESI-TOF) *m/z*: [M]$^+$ calcd for C$_{13}$H$_{17}$N 187.1361; found: 187.1356.

1-(4-Phenylbutan-2-yl)-1*H*-indole (3r). Yellow oil, 38.5 mg (49% yield); Rf (petroleum ether) = 0.5. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.64 (d, *J* = 7.8 Hz, 1H), 7.30–7.25 (m, 2H), 7.20 (d, *J* = 12.6, 5.2 Hz, 3H), 7.08 (t, *J* = 7.0 Hz, 3H), 6.56 (d, *J* = 2.8 Hz, 1H), 4.48 (d, *J* = 14.3, 6.8 Hz, 1H), 2.50 (d, *J* = 8.2 Hz, 2H), 2.32–2.22 (m, 1H), 2.19–2.08 (m, 1H), 1.51 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.3, 136.0, 128.4, 126.1, 124.0, 121.3, 121.0, 119.3, 109.6, 101.8, 509, 38.7, 32.6, 21.5. HRMS (ESI-TOF) *m/z*: [M + H]$^+$ calcd for C$_{18}$H$_{19}$N 250.1596; found: 250.1570.

1-Cyclohexyl-1*H*-indole (3s). Yellow oil, 27.6 mg (37% yield); Rf (petroleum ether) = 0.7. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.61 (t, *J* = 6.7 Hz, 1H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.17 (d, *J* = 8.0, 5.3 Hz, 2H), 7.11–7.04 (m, 1H), 6.49 (d, *J* = 3.2 Hz, 1H), 4.18 (t, *J* = 11.9, 3.7 Hz, 1H), 2.12 (d, *J* = 1.7 Hz, 2H), 1.90 (d, *J* = 13.6 Hz, 2H), 1.70–1.61 (m, 2H), 1.47 (t, *J* = 13.2, 6.6 Hz, 2H), 1.35–1.16 (m, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 135.9, 135.6, 128.8, 128.5, 126.7, 124.1, 121.6, 121.0, 119.7, 119.2, 111.1, 109.5, 102.0, 101.0, 55.1, 33.6, 29.8, 28.9, 26.0, 25.7, 24.6, 23.0, 22.0. HRMS (ESI-TOF) *m/z*: [M]$^+$ calcd for C$_{14}$H$_{17}$N 199.1361; found: 199.1356.

1-Benzyl-1*H*-indole (3t).[21] Yellow oil, 61.9 mg (82% yield); Rf (petroleum ether) = 0.4. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.68 (d, *J* = 7.8 Hz, 1H), 7.34–7.27 (m, 4H), 7.22–7.17 (m, 1H), 7.17–7.12 (m, 4H), 6.58 (d, *J* = 3.1, 0.6 Hz, 1H), 5.35 (s, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 137.6, 136.4, 128.8, 128.8, 128.3, 127.7, 126.8, 121.8, 121.0, 119.6, 109.8, 101.8, 50.1. HRMS (ESI-TOF) *m/z*: [M]$^+$ calcd for C$_{15}$H$_{13}$N 207.1048; found: 207.1043.

1-(4-Methylbenzyl)-1*H*-indole (3u).[22] Yellow oil, 65.9 mg (86% yield); Rf (petroleum ether) = 0.4. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.63 (d, *J* = 7.8 Hz, 1H), 7.18–6.96 (m, 8H), 6.52 (d, *J* = 3.1 Hz, 1H), 5.23 (s, 2H), 2.28 (s, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 137.3, 136.3, 134.5, 129.5, 128.8, 128.3, 126.9, 121.7, 121.0, 119.5, 109.8, 101.6, 49.9, 21.1. HRMS(ESI-TOF) *m/z*: [M]$^+$ calcd for C$_{15}$H$_{13}$N 221.1204; found: 221.1199.

5-Fluoro-1-(pentan-3-yl)-1*H*-indole (3v). Yellow oil, 43.4 mg (64% yield); Rf (petroleum ether) = 0.4. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.30–7.26 (m, 1H), 7.25–7.23 (m, 1H), 7.22–7.20 (m, 1H), 6.96–6.90 (m, 1H), 6.47 (d, *J* = 3.1 Hz, 1H), 4.59–4.32 (m, 1H), 1.93–1.70 (m, 4H), 0.88 (t, *J* = 7.4 Hz, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 157.8 (d, *J* = 233.6 Hz), 132.7, 128.6 (d, *J* = 10.1 Hz), 125.7, 110.1 (d, *J* = 9.7 Hz), 109.7 (d, *J* = 26.3 Hz), 105.6 (d, *J* = 23.1 Hz), 101.4 (d, *J* = 4.7 Hz), 51.8, 39.5, 14.0. HRMS (ESI-TOF) *m/z*: [M + Na]$^+$ calcd for C$_{13}$H$_{16}$FN 228.1164; found: 228.1165.

5-Methoxy-1-(pentan-3-yl)-1*H*-indole (3w). Colorless oil, 61.0 mg (85% yield); Rf (petroleum ether) = 0.4. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.28–7.25 (m, 1H), 7.15 (d, *J* = 3.1 Hz, 1H), 7.09

(d, J = 2.4 Hz, 1H), 6.88–6.83 (m, 1H), 6.44 (d, J = 3.1 Hz, 1H), 4.49–4.33 (m, 1H), 3.85 (s, 3H), 2.02–1.62 (m, 4H), 0.87 (t, J = 7.4 Hz, 6H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 153.9, 131.4, 128.8, 124.7, 111.7, 110.3, 102.6, 100.9, 56.0, 51.6, 29.9, 14.0. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for C$_{14}$H$_{19}$NO 218.1545; found: 218.1551.

1-Benzhydryl-1H-pyrrole (3x). Colorless oil, 42.3 mg (55% yield); Rf (petroleum ether) = 0.5. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.35–6.99 (m, 10H), 6.76 (t, J = 2.1 Hz, 2H), 6.19 (t, J = 2.1 Hz, 2H), 5.33–5.24 (m, 1H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 143.7, 133.4, 129.6, 128.8, 128.5, 127.6, 127.5, 127.2, 126.0, 119.7, 108.2, 58.3. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for C$_{17}$H$_{15}$N 234.1283; found: 234.1281.

1-(1-Ferrocenylethyl)-1H-pyrrole (3y). Yellow oil, 70.0 mg (76% yield); Rf (petroleum ether) = 0.5. ^{1}H NMR (500 MHz, CDCl$_3$) δ 6.76–6.60 (m, 2H), 6.20–5.96 (m, 2H), 5.07 (d, J = 7.0 Hz, 1H), 4.20–4.18 (m, 1H), 4.17–4.10 (m, 7H), 4.10–4.06 (m, 1H), 1.78 (d, J = 7.0 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 119.1, 107.6, 90.8, 69.0, 68.3, 67.8, 67.8, 66.2, 54.5, 22.5. HRMS (ESI-TOF) m/z: [M]$^+$ calcd for C$_{16}$H$_{17}$FeN 279.0710; found: 279.0723.

9-(4-Phenylbutan-2-yl)-9H-carbazole (3z). Yellow oil, 38.7 mg (41% yield); Rf (petroleum ether : ethyl acetate = 100 : 1) = 0.4. ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.68 (d, J = 7.8 Hz, 1H), 7.30 (d, J = 8.0 Hz, 3H), 7.22 (d, J = 8.5 Hz, 3H), 7.12 (t, J = 7.7 Hz, 3H), 6.59 (d, J = 2.9 Hz, 1H), 4.51 (d, J = 6.8 Hz, 1H), 2.54 (d, J = 5.9 Hz, 2H), 2.30 (d, J = 6.2 Hz, 1H), 2.16 (d, J = 6.0 Hz, 1H), 1.54 (d, J = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 141.2, 128.5, 126.0, 125.5, 120.4, 118.7, 50.6, 36.6, 33.0, 19.3. HRMS (ESI-TOF) m/z: [M]$^+$ calcd for C$_{22}$H$_{21}$N 299.1674; found: 299.1670.

9-Benzhydryl-9H-carbazole (3aa). White solid, 74.1 mg (78% yield); mp 170–173 °C; Rf (petroleum ether : ethyl acetate = 100 : 1) = 0.6. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.22 (d, J = 7.6 Hz, 2H), 7.38 (d, J = 3.7 Hz, 7H), 7.36–7.27 (m, 8H), 7.18 (d, J = 8.2 Hz, 2H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 140.7, 138.9, 128.7, 128.4, 127.9, 125.6, 123.6, 120.2, 119.3, 110.8, 62.3. HRMS (ESI-TOF) m/z: [M + Na]$^+$ calcd for C$_{25}$H$_{19}$N 356.1415; found: 356.1406.

3-(2-Phenyl-3H-benzo[e]indol-3-yl)cyclohexanecarboxylic acid (6).[16] White oil, 85.3 mg (70% yield); Rf (petroleum ether) = 0.7. ^{1}H NMR (500 MHz, CDCl$_3$) δ 8.30–8.25 (m, 1H), 8.10–8.05 (m, 2H), 7.84–7.88 (m, 2H), 7.55–7.44 (m, 6H), 7.02–6.98 (m, 1H), 4.54–4.31 (m, 1H), 2.94–1.51 (m, 9H). ^{13}C NMR (126 MHz, CDCl$_3$) δ 185.1, 138.9, 136.0, 133.1, 131.3, 130.9, 128.5, 128.2, 127.5, 126.5, 126.4, 126.1, 124.9, 120.5, 110.7, 95.0, 43.1, 38.0, 32.5, 25.8, 20.3. HRMS (ESI-TOF) m/z: [M + H]$^+$ calcd for C$_{25}$H$_{23}$NO$_2$ 370.1729; found: 370.1739.

Acknowledgements

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