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Palladium-catalyzed sequential indole synthesis using sterically hindered amines

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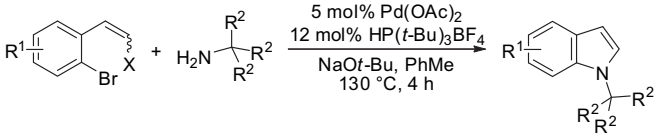
ABSTRACT

A palladium catalyst derived from a bulky *N*-heterocyclic carbene ligand enabled a modular synthesis of indoles bearing sterically hindered *N*-alkyl or *N*-aryl substituents through a reaction sequence comprising an intermolecular N-arylation and an intramolecular hydroamination.

1. Introduction

Indoles are arguably the most abundant heterocyclic structural motifs in drug discovery.[1,2] Therefore, a continued strong demand exists for the development of generally applicable syntheses of this heteroarene.[1–5] While the preparation of regioselectively substituted indole derivatives remains challenging via classical methods, significant progress has been accomplished more recently through transition metal-catalysis.[6–13] Despite these advances the synthesis of indoles displaying sterically hindered *N*-substituents continued to constitute a considerable challenge. Indeed, for example, simple substitution reactions at nitrogen of free (NH)-indoles are hampered by their relatively low nucleophilicities. A remarkable breakthrough was, however, recently achieved by Willis through an application of his elegantly developed N-annulation strategy[14] to the conversion of dihalogenated styrenes **1** with sterically demanding primary amines **2** (Scheme 1).[15]



1 2 3

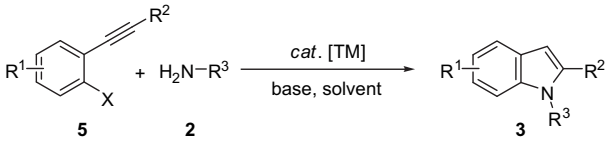
Scheme 1. Palladium-catalyzed N-annulation route to indoles **3** with sterically demanding *N*-substituents.

Thereafter, Schirok devised a transition metal-free microwave-assisted protocol for the preparation of N-*sec*- and N-*tert*-alkylated indoles **3**.[16] Thus, *ortho*-(fluoroaryl)oxiranes **4** served as substrates for a domino reaction relying on an intermolecular ring opening of an oxirane, an intramolecular nucleophilic aromatic substitution and a final dehydration, albeit at a relatively high reaction temperature of 240 °C (Scheme 2).

4 2 3

Scheme 2. Microwave-assisted synthesis of indoles **3**.

In recent years, we exploited alkenyl or aryl *vic*-dihalides for modular syntheses of heteroarenes, such as inter alias pyrroles[17] or benzo[*b*]furans.[18] Furthermore, we established reaction conditions for palladium-[19,20] or copper-catalyzed[19,21] syntheses of diversely substituted indoles[22] starting from *ortho*-alkynylhaloarenes **5**. Thus, reaction sequences involving intermolecular N-arylations[23] and intramolecular hydroaminations[24,25] set the stage for efficient approaches to *N*-substituted indoles (Scheme 3).



5 2 3

Scheme 3. Palladium-catalyzed N-arylation/hydroamination sequence for indole syntheses.

Given the important biological activities of indoles with sterically hindered *N*-substituents,[26] we became interested in employing our protocol for the more challenging conversion of bulky alkyl amines.[27] Herein, we wish to present a full account on a modular palladium-catalyzed sequential synthesis of indoles displaying sterically hindered substituents, which also proved broadly applicable to the use of less nucleophilic anilines.

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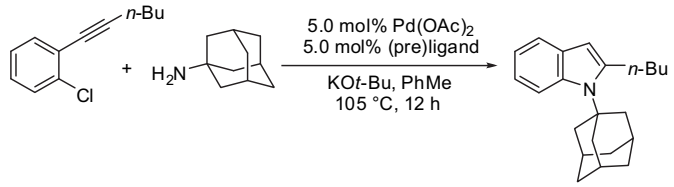
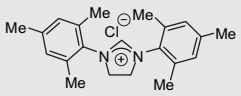
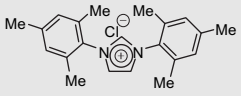
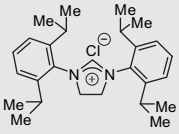
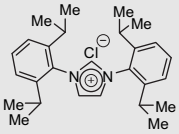
2. Results and discussion

In initial studies, we probed in situ generated palladium complexes derived from various phosphine or *N*-heterocyclic carbene[28,29] ligands for the challenging preparation of indole **3aa** (Table 1). Unfortunately, diphosphines **6** and **7** provided only unsatisfactory conversions of sterically demanding amine **2a** (entries 2 and 3). On the contrary, electron-rich monophosphines **8**, and **9a–d**[30] led to improved isolated yields of desired product **3aa** (Fig. 1, and entries 4–8).

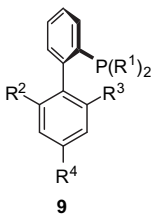
Table 1
Optimization of the palladium catalyst[a]



5a **2a** **3aa**

Entry	(Pre)ligand		Isolated yield (%)
1	—	—	—
2	dppf	**6**	—
3	BINAP	**7**	5[b]
4	PCy_3	**8**	38
5	R^1=*i*-Pr, R^2=H, R^3=H, R^4=H	**9a**	30
6	R^1=Cy, R^2=NMe_2, R^3, R^4=H	**9b**	51
7	R^1=Cy, R^2, R^3=OMe, R^4=H	**9c**	59
8	R^1=Cy, R^2, R^3, R^4=*i*-Pr	**9d**	45
9		**10**	—
10		**11**	9[b]
11		**12**	39
12		**13**	62
13			74[c]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.6 mmol), $Pd(OAc)_2$ (5.0 mol %), (pre)ligand (5.0 mol %), KO*t*-Bu (1.5 mmol), PhMe (1.5 mL), 105 °C, 12 h; yields of isolated products.
[b] GC-conversion.
[c] 120 °C.

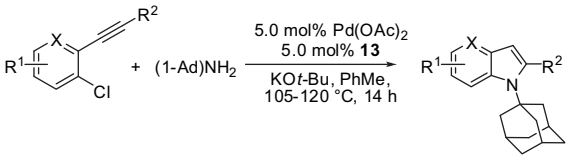


9

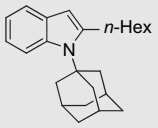
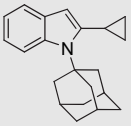
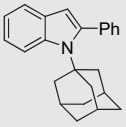
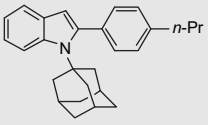
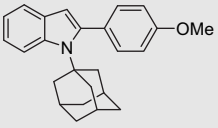
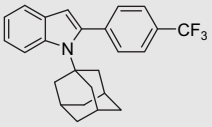
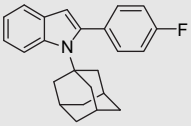
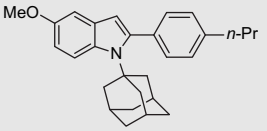
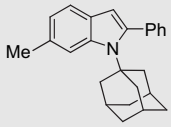
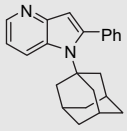
Figure 1. General structure of biaryl monophosphine ligands **9**.

However, superior results were accomplished when using *N*-heterocyclic carbene precursors. Interestingly, palladium complexes derived from imidazolinium chlorides **10** and **12** (entries 9

Table 2
Palladium-catalyzed sequential synthesis of indoles using amine **2a**[a]



5 **2a** **3**

Entry	R^1	R^2	X			Isolated yield (%)
1	H	*n*-Hex	CH	**5b**		**3ab** 59[b]
2	H	*c*-Pr	CH	**5c**		**3ac** 80[b]
3	H	Ph	CH	**5d**		**3ad** 83
4	H	4-*n*-PrC_6H_4	CH	**5e**		**3ae** 88
5	H	4-$MeOC_6H_4$	CH	**5f**		**3af** 79
6	H	4-$CF_3C_6H_4$	CH	**5g**		**3ag** 83
7	H	4-FC_6H_4	CH	**5h**		**3ah** 94
8	4-MeO	4-*n*-PrC_6H_4	CH	**5i**		**3ai** 55
9	5-Me	Ph	CH	**5j**		**3aj** 94
10	H	Ph	N	**5k**		**3ak** 46[c]

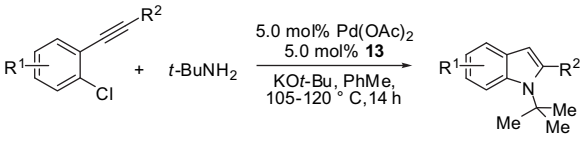
[a] Reaction conditions: **5** (0.5–1.0 mmol), **2a** (0.6–1.2 mmol), $Pd(OAc)_2$ (5.0 mol %), **13** (5.0 mol %), KO*t*-Bu (1.5–3.0 mmol), PhMe (1.5–3.0 mL), 120 °C, 14 h.
[b] 105 °C.
[c] GC-conversion.

and 11) displayed considerably lower catalytic activities than the ones generated from the corresponding imidazolium salts **11** and **13**, respectively (entries 10 and 12). Thus, optimal yields were obtained with sterically hindered unsaturated imidazolium salt **13** as preligand (entry 12). The isolated yield of product **3aa** was further found improved at a slightly higher reaction temperature (entry 13).

With this optimized catalytic system in hand, we explored its scope in the synthesis of indoles **3** using sterically hindered amine 1-AdNH$_2$ (**2a**) as starting material (Table 2). Thus, alkyl-substituted alkynes **5b** and **5c** yielded efficiently the desired products **3ab** and **3ac**, respectively (entries 1 and 2). Additionally, differently aryl-substituted derivatives **5d**–**k** enabled the regioselective synthesis of the corresponding indoles (entries 3–9), notably, including azaindole **3ak** (entry 10). On the contrary, a TMS-substituted alkyne did not deliver the corresponding 2-silylated indole.

Our protocol was not restricted to the use of amine **2a** as sterically hindered coupling partner, but allowed for an efficient indole formation also with bulky *t*-BuNH$_2$ (**2b**) (Table 3). Thereby, products **3** bearing either aliphatic (entries 1 and 2) or aromatic groups (entries 3–6) in position C-2 were obtained selectively. Generally, slightly lower yields of indoles **3** were obtained in transformations of alkynes **5** with primary alkyl-substituents, which was due to an incomplete intramolecular hydroamination of the quantitatively formed secondary amine.

Table 3
Scope of palladium-catalyzed indole synthesis with amine **2b**[a]

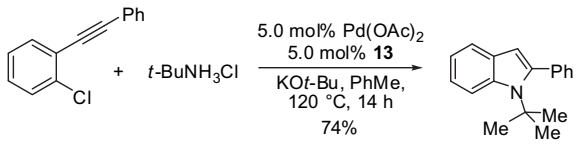


5 **2b** **3**

Entry	R^1	R^2			Isolated yield (%)
1	H	*n*-Bu	**5a**	**3al**	63
2	H	*c*-Pr	**5c**	**3am**	87
3	H	Ph	**5d**	**3an**	55
4	H	4-*n*-PrC$_6$H$_4$	**5e**	**3ao**	84[b]
5	4-MeO	4-*n*-PrC$_6$H$_4$	**5i**	**3ap**	65[b]
6	5-Me	Ph	**5j**	**3aq**	90[b]

[a] Conditions: **5** (0.5–1.0 mmol), **2b** (0.6–3.0 mmol), Pd(OAc)$_2$ (5.0 mol %), **13** (5.0 mol %), KO*t*-Bu (1.5–3.0 mmol), PhMe (1.5–3.0 mL), 105 °C, 14 h.
[b] 120 °C.

Given the relatively low boiling point of amine **2b**, we were delighted to note that ammonium salt **14** could be employed as a more convenient *N*-nucleophile as well (Scheme 4).

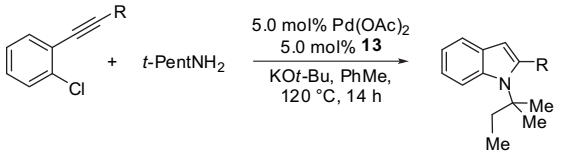


5d **14** **3an**

Scheme 4. Indole synthesis with ammonium salt **14**.

Likewise, sterically hindered amine **2c** turned out to be a suitable substrate for N-annulations, thereby, providing indoles **3ar**–**au** (Table 4).

Table 4
Palladium-catalyzed sequential indole synthesis with amine **2c**[a]



5 **2c** **3**

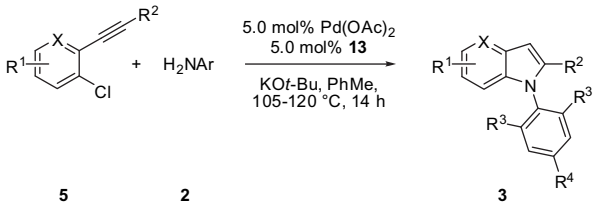
Entry	R			Isolated yield (%)
1	*n*-Bu	**5a**	**3ar**	43
2	4-*n*-PrC$_6$H$_4$	**5e**	**3as**	92
3	4-CF$_3$C$_6$H$_4$	**5g**	**3at**	80
4	3-MeC$_6$H$_4$	**5l**	**3au**	85

[a] Conditions: **5** (0.5–1.0 mmol), **2c** (0.6–1.2 mmol), Pd(OAc)$_2$ (5.0 mol %), **13** (5.0 mol %), KO*t*-Bu (1.5–3.0 mmol), PhMe (3.0–6.0 mL), 120 °C, 14 h.

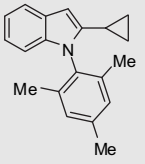
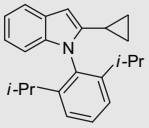
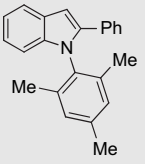
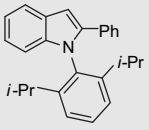
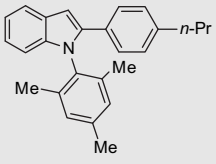
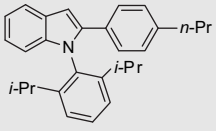
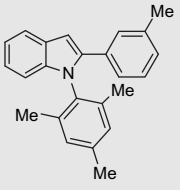
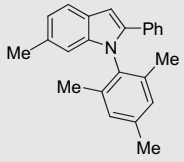
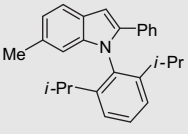
Considering the remarkable efficacy of our catalytic system in the synthesis of *N*-alkyl-substituted indoles, we became interested in submitting sterically demanding aniline derivatives to the optimized reaction conditions (Table 5). Thus, less nucleophilic amines **2d** and **2e** led to 2-alkyl- (entries 1 and 2) or 2-aryl-substituted indoles **3** (entries 3–11) in high yields. Interestingly, excellent chemoselectivies were observed when using substrate **5m** bearing an unprotected hydroxyl-group (entries 10, and 11), a valuable asset for further applications of our protocol to sustainable syntheses of serotonin analogues. Additionally, pyridine **5n** provided direct access to 4-azaindole **3bf** through our N-annulation strategy (entry 12).

Various naturally occurring indole derivatives feature reverse-prenyl substituents. For example, fungal natural products asterriquinones[26] exhibit valuable biological—including antitumour—activities, and are decorated with an *N*-reverse-prenyl group. As a consequence, we submitted amine **2f** to our optimized reaction conditions, and were delighted to observe the regioselective formation of indole **3bh** (Scheme 5).

Table 5
Palladium-catalyzed preparation of indoles **3** with sterically hindered anilines **2**[a]

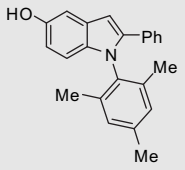
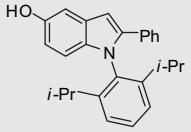
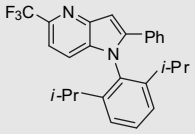


5 **2** **3**

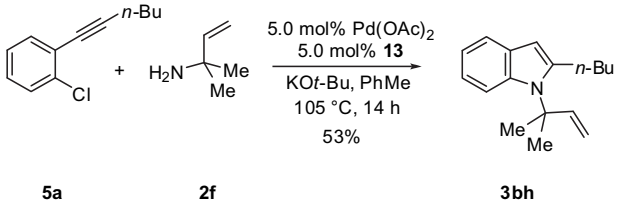
Entry	R^1	R^2	X		Ar				Isolated yield (%)
1	H	*c*-Pr	CH	**5c**	2,4,6-$Me_3C_6H_2$	**2d**		**3av**	85[b]
2	H	*c*-Pr	CH	**5c**	2,6-(*i*-Pr)$_2C_6H_3$	**2e**		**3aw**	82[b]
3	H	Ph	CH	**5d**	2,4,6-$Me_3C_6H_2$	**2d**		**3ax**	91
4	H	Ph	CH	**5d**	2,6-(*i*-Pr)$_2C_6H_3$	**2e**		**3ay**	94
5	H	4-*n*-PrC_6H_4	CH	**5e**	2,4,6-$Me_3C_6H_2$	**2d**		**3az**	95
6	H	4-*n*-PrC_6H_4	CH	**5e**	2,6-(*i*-Pr)$_2C_6H_3$	**2e**		**3ba**	88
7	H	3-MeC_6H_4	CH	**5l**	2,4,6-$Me_3C_6H_2$	**2d**		**3bb**	91
8	5-Me	Ph	CH	**5j**	2,4,6-$Me_3C_6H_2$	**2d**		**3bc**	56
9	5-Me	Ph	CH	**5j**	2,6-(*i*-Pr)$_2C_6H_3$	**2e**		**3bd**	91

(*continued on next page*)

Table 5 (*continued*)

Entry	R^1	R^2	X		Ar				Isolated yield (%)
10	4-OH	Ph	CH	**5m**	2,4,6-$Me_3C_6H_2$	**2d**		**3be**	75
11	4-OH	Ph	CH	**5m**	2,6-(*i*-Pr)$_2C_6H_3$	**2e**		**3bf**	71
12	6-CF_3	Ph	N	**5n**	2,6-(*i*-Pr)$_2C_6H_3$	**2e**		**3bg**	64[b,c]

[a] Reaction conditions: **5** (0.5–1.0 mmol), **2** (0.6–1.2 mmol), $Pd(OAc)_2$ (5.0 mol %), **13** (5.0 mol %), KO*t*-Bu (1.5–3.0 mmol), PhMe (1.5–6.0 mL), 120 °C, 14 h.
[b] 105 °C.
[c] GC-conversion.



5a **2f** **3bh**

Scheme 5. Synthesis of indole **3bh** bearing an *N*-reverse-prenyl group.

3. Conclusions

In summary, we disclosed a protocol for a modular synthesis of (aza)indoles bearing sterically hindered aliphatic or aromatic *N*-substituents. Namely, a palladium-catalyzed reaction sequence consisting of an intermolecular N-arylation and an intramolecular hydroamination allowed for a regioselective N-annulation, which proved applicable to the preparation of an *N*-reverse-prenyl-substituted indole.

4. Experimental section

4.1. General

All reactions were carried out on a 0.5–1.0 mmol scale under N_2 using pre-dried glassware. Chemicals were obtained from commercial sources, and were used without further purification. PhMe was distilled from sodium under nitrogen and stored over molecular sieves (4 Å). Yields refer to isolated compounds, estimated to be >95% pure as determined by ^{1}H NMR and GC. Flash chromatography: Merck silica gel 60 (230–400 mesh). NMR: Spectra were recorded on a Varian Unity 300, Varian Mercury 300, or a Varian Inova 500 in the solvent indicated; chemical shifts (δ) are given in parts per million, coupling constants (J) in hertz.

4.2. Representative procedure for palladium-catalyzed indole synthesis: 1-(1-adamantyl)-2-*n*-butyl-1*H*-indole (3aa)

To a suspension of **2a** (91.0 mg, 0.60 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), **13** (10.6 mg, 0.025 mmol) and KO*t*-Bu (168 mg, 1.50 mmol) in dry PhMe (1.5 mL) was added **5a** (96.0 mg, 0.50 mmol) and the resulting reaction mixture was stirred for 14 h at 120 °C. Then, H_2O (25 mL) was added at ambient temperature. The aqueous layer was extracted with Et_2O (3×30 mL), the combined organic layers were dried over Na_2SO_4 and concentrated in vacuo. The remaining residue was purified by column chromatography on silica gel (*n*-hexane→*n*-hexane/EtOAc 100:1) to yield **3aa** (113 mg, 74%) as a white solid. Mp: 143–145 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (d, J=8.1 Hz, 1H), 7.51–7.48 (m, 1H), 7.08–6.98 (m, 2H), 6.29 (s, 1H), 3.01 (t, J=7.2 Hz, 2H), 2.59 (d, J=3.0 Hz, 6H), 2.27 (s, 3H), 1.81–1.68 (m, 8H), 1.49–1.39 (m, 2H), 0.98 (t, J=7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.8, 136.4, 129.2, 119.8, 119.3, 118.4, 115.2, 103.0, 61.0, 42.3, 36.4, 33.2, 32.0, 30.3, 22.9, 14.2. IR (KBr): 3429, 2918, 2855, 2361, 2337, 1653, 1457, 777, 746, 731 cm^{-1}. MS (EI) m/z (relative intensity): 307 (22) [M^+], 265 (6), 135 (100), 107 (5). HRMS (ESI) m/z calcd for $C_{22}H_{30}N$ 308.2373, found 308.2374.

4.3. 1-(1-Adamantyl)-2-*n*-hexyl-1*H*-indole (3ab)

Following the general procedure, **2a** (184 mg, 1.20 mmol), **5b** (220 mg, 1.00 mmol), **13** (21.2 mg, 0.05 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), KO*t*-Bu (336 mg, 3.00 mmol) were stirred in PhMe (3.0 mL) for 12 h at 105 °C. Indole **3ab** (200 mg, 59%) was obtained as a white solid after purification by column chromatography on silica gel (*n*-hexane). Mp: 129–131 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77 (md, J=7.8 Hz, 1H), 7.51–7.48 (m, 1H), 7.08–6.98 (m, 2H), 6.29 (s, 1H), 3.00 (t, J=7.6 Hz, 2H), 2.59 (d, J=3.0 Hz, 6H), 2.27 (s, 3H), 1.88–1.69 (m, 8H), 1.46–1.32 (m, 6H), 0.92 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.0, 136.4, 129.2, 119.9, 119.4, 118.5, 115.3, 102.9, 61.0, 42.2, 36.3, 32.2, 31.8, 30.9, 30.2, 29.4, 22.6, 14.1. IR (KBr): 3419, 2959, 2915, 2852, 2361, 1653, 1457, 772, 744, 729 cm^{-1}. MS (EI) m/z (relative intensity): 335 (23) [M^+], 265 (8), 135 (100). HRMS (ESI) m/z calcd for $C_{24}H_{34}N$ 336.2686, found 336.2686.

4.4. 1-(1-Adamantyl)-2-cyclopropyl-1*H*-indole (3ac)

Following the general procedure, **2a** (91.0 mg, 1.20 mmol), **5c** (87.0 mg, 0.494 mmol), **13** (10.6 mg, 0.025 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), KO*t*-Bu (168 mg, 1.50 mmol) were stirred in PhMe (1.5 mL) for 14 h at 105 °C. Indole **3ac** (117 mg, 80%) was obtained as a white solid after purification by column chromatography on silica gel (*n*-hexane). Mp: 211.4 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.78–7.75 (m, 1H), 7.50–7.47 (m, 1H), 7.10–6.98 (m, 2H), 6.23 (s, 1H), 2.71 (d, J=3.0 Hz, 6H), 2.28 (s, 3H), 2.21–2.12 (m, 1H),

1.90–1.78 (m, 6H), 0.99–0.83 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.7, 136.4, 128.7, 120.2, 119.8, 118.5, 115.0, 102.5, 60.7, 42.1, 36.3, 30.2, 13.5, 9.7. IR (KBr): 2913, 2361, 2338, 1653, 1635, 1558, 1540, 1457, 1314, 1271, 1228, 1100, 727 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 291 (44) [M$^+$], 156 (2), 135 (100), 107 (7), 93 (11), 79 (14). HRMS (ESI) *m*/*z* calcd for $C_{21}H_{26}N$ 292.2060, found 292.2060.

4.5. 1-(1-Adamantyl)-2-phenyl-1*H*-indole (3ad)

Following the general procedure, **2a** (91.0 mg, 0.60 mmol), **5d** (102 mg, 0.481 mmol), **13** (10.6 mg, 0.025 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), KO*t*-Bu (168 mg, 1.50 mmol) were stirred in PhMe (3.0 mL) for 14 h at 120 °C. Indole **3ad** (131 mg, 83%) was obtained as a white solid after purification by column chromatography on silica gel (*n*-hexane/Et_2O 100:1). Mp: 200–201 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84–7.82 (m, 1H), 7.59–7.55 (m, 1H), 7.42–7.38 (m, 2H), 7.35–7.32 (m, 3H), 7.15–7.06 (m, 2H), 6.28 (s, 1H), 2.30 (d, *J*=3.0 Hz, 6H), 2.09 (s, 3H), 1.72–1.63 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.5, 138.7, 136.5, 130.2, 129.2, 127.3, 127.2, 120.6, 120.3, 119.3, 115.7, 106.7, 60.9, 43.5, 36.2, 30.2. IR (KBr): 3420, 2901, 2849, 2361, 2339, 1653, 1448, 1296, 774, 736 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 327 (32) [M$^+$], 193 (9), 165 (10), 135 (100), 11 (19). HRMS (ESI) *m*/*z* calcd for $C_{24}H_{26}N$ 328.2060, found 328.2060.

4.6. 1-(1-Adamantyl)-2-(4-*n*-propylphenyl)-1*H*-indole (3ae)

Following the general procedure, **2a** (91.0 mg, 0.60 mmol), **5e** (127 mg, 0.50 mmol), **13** (10.6 mg, 0.025 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), KO*t*-Bu (168 mg, 1.50 mmol) were stirred in PhMe (3.0 mL) for 14 h at 120 °C. Indole **3ae** (162 mg, 88%) was obtained as a white solid after purification by column chromatography on silica gel (*n*-pentane/Et_2O 100:1). Mp: 144–145 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.86–7.83 (m, 1H), 7.60–7.57 (m, 1H), 7.33–7.31 (m, 2H), 7.19–7.07 (m, 4H), 6.29 (d, *J*=0.6 Hz, 1H), 2.66 (t, *J*=7.2 Hz, 2H), 2.31 (d, *J*=2.7 Hz, 6H), 2.11 (s, 3H), 1.75–1.65 (m, 8H), 0.99 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.7, 141.6, 136.4, 135.8, 129.9, 129.1, 127.2, 120.5, 120.0, 119.1, 115.6, 106.4, 60.8, 43.3, 37.9, 36.3, 30.3, 24.5, 13.9. IR (film): 2960, 2912, 2854, 2361, 2253, 1499, 1450, 1335, 1296, 1103, 909, 738, 650 cm^{-1}. MS (ESI) *m*/*z* (relative intensity): 370 (100) [M+H$^+$], 301 (2), 269 (6), 211 (4). HRMS (ESI) *m*/*z* calcd for $C_{27}H_{32}N$ 370.2535, found 370.2529.

4.7. 1-(1-Adamantyl)-2-(4-methoxyphenyl)-1*H*-indole (3af)

Following the general procedure, **2a** (91.0 mg, 0.60 mmol), **5f** (125 mg, 0.517 mmol), **13** (10.6 mg, 0.025 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), KO*t*-Bu (168 mg, 1.50 mmol) were stirred in PhMe (3.0 mL) for 14 h at 120 °C. Indole **3af** (147 mg, 79%) was obtained as an off-white solid after purification by column chromatography on silica gel (*n*-pentane/Et_2O 50:1→20:1→5:1). Mp: 193–194 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83–7.80 (m, 1H), 7.60–7.54 (m, 1H), 7.30 (ddd, *J*=9.0, 5.1, 2.7 Hz, 2H), 7.14–7.05 (m, 2H), 6.86 (ddd, *J*=8.7, 5.1, 3.0 Hz, 2H), 6.25 (d, *J*=0.9 Hz, 1H), 3.85 (s, 3H), 2.28 (d, *J*=3.0 Hz, 6H), 2.10 (s, 3H), 1.72–1.63 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.9, 141.2, 136.3, 131.2, 130.9, 129.1, 120.4, 120.1, 119.1, 115.7, 112.6, 106.4, 60.8, 55.2, 43.3, 36.2, 30.2. IR (film): 2907, 2853, 2253, 1612, 1499, 1450, 1283, 1245, 1174, 1104, 1028, 908, 734 cm^{-1}. MS (ESI) *m*/*z* (relative intensity): 358 (100) [M+H$^+$], 242 (13), 211 (5). HRMS (ESI) *m*/*z* calcd for $C_{25}H_{28}NO$ 358.2171, found 358.2165.

4.8. 1-(1-Adamantyl)-2-(4-trifluoromethylphenyl)-1*H*-indole (3ag)

Following the general procedure, **2a** (91.0 mg, 0.60 mmol), **5g** (166 mg, 0.509 mmol), **13** (10.6 mg, 0.025 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), KO*t*-Bu (168 mg, 1.50 mmol) were stirred in PhMe (3.0 mL) for 14 h at 120 °C. Indole **3ag** (167 mg, 83%) was obtained as a white solid after purification by column chromatography on silica gel (*n*-pentane/Et_2O 100:1). Mp: 205 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.84–7.82 (m, 1H), 7.60–7.50 (m, 5H), 7.20–7.07 (m, 2H), 6.28 (d, *J*=0.6 Hz, 1H), 2.26 (d, *J*=3.3 Hz, 6H), 2.11 (s, 3H), 1.73–1.63 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.5, 139.7, 136.9, 130.2, 129.4 ($^2J_{C-F}$=32 Hz), 129.0, 124.3 ($^3J_{C-F}$=4 Hz), 124.2 ($^1J_{C-F}$=272 Hz), 120.8, 120.8, 119.6, 115.8, 107.6, 61.0, 43.6, 36.1, 30.2. ^{19}F NMR (275 MHz, $CDCl_3$): δ −62.4 (s). IR (Nujol): 2921, 2361, 2338, 1734, 1717, 1699, 1653, 1558, 1506, 1458, 1377, 1162, 722 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 396 (25) [M$^+$], 368 (2), 311 (4), 261 (4), 233 (4), 204 (2), 188 (4), 135 (100), 119 (16). HRMS (ESI) *m*/*z* calcd for $C_{25}H_{25}NF_3$ 396.1934, found 396.1932.

4.9. 1-(1-Adamantyl)-2-(4-fluorophenyl)-1*H*-indole (3ah)

Following the general procedure, **2a** (91.0 mg, 0.60 mmol), **5h** (122 mg, 0.530 mmol), **13** (10.6 mg, 0.025 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), KO*t*-Bu (168 mg, 1.50 mmol) were stirred in PhMe (3.0 mL) for 14 h at 120 °C. Indole **3ah** (173 mg, 94%) was obtained as a white solid after purification by column chromatography on silica gel (*n*-pentane/Et_2O 100:1). Mp: 210 °C (decomp.). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.83–7.80 (m, 1H), 7.57–7.54 (m, 1H), 7.27–7.32 (m, 2H), 7.15–6.93 (m, 4H), 6.26 (d, *J*=0.6 Hz, 1H), 2.26 (d, *J*=3.0 Hz, 6H), 2.10 (s, 3H), 1.72–1.67 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 162.2 ($^1J_{C-F}$=247 Hz), 140.2, 136.5, 134.6, 131.7 ($^4J_{C-F}$=4 Hz), 130.8, 129.0, 120.5 ($^3J_{C-F}$=7 Hz), 119.3, 115.7, 114.2 ($^2J_{C-F}$=22 Hz), 106.9, 60.9, 43.5, 36.2, 30.2. ^{19}F NMR (275 MHz, $CDCl_3$): δ −114.7 (tt, *J*=9.1, 5.4 Hz). IR (KBr): 2906, 2361, 2338, 1699, 1653, 1635, 1540, 1496, 1456, 1296, 847, 791, 737 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 345 (52) [M$^+$], 311 (1), 211 (6), 183 (6), 135 (100), 107 (4). HRMS (ESI) *m*/*z* calcd for $C_{24}H_{25}NF$ 346.1966, found 346.1965.

4.10. 1-(1-Adamantyl)-5-methoxy-2-(4-*n*-propylphenyl)-1*H*-indole (3ai)

Following the general procedure, **2a** (91.0 mg, 0.60 mmol), **5i** (145 mg, 0.512 mmol), **13** (10.6 mg, 0.025 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), KO*t*-Bu (168 mg, 1.50 mmol) were stirred in PhMe (3.0 mL) for 14 h at 120 °C. Indole **3ai** (113 mg, 55%) was obtained as a light yellow solid after purification by column chromatography on silica gel (*n*-pentane/Et_2O 100:1→50:1). Mp: 125–126 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71 (d, *J*=9.0 Hz, 1H), 7.31–7.28 (m, 2H), 7.14–7.12 (m, 2H), 7.02 (d, *J*=2.7 Hz, 1H), 6.80 (dd, *J*=9.0, 2.7 Hz, 1H), 6.20 (s, 1H), 3.85 (s, 3H), 2.64 (t, *J*=7.5 Hz, 2H), 2.26 (d, *J*=2.7 Hz, 6H), 2.08 (s, 3H), 1.72–1.63 (m, 8H), 0.97 (t, *J*=7.5 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.4, 142.1, 141.7, 135.7, 131.5, 129.9, 129.5, 127.1, 116.2, 110.2, 106.0, 101.8, 60.6, 55.7, 43.4, 37.8, 36.3, 30.3, 24.5, 13.9. IR (film): 2912, 2253, 1616, 1466, 1435, 1358, 1342, 1302, 1215, 1162, 1121, 1035, 909, 840, 737 cm^{-1}. MS (ESI) *m*/*z* (relative intensity): 822 (55) [2M+Na$^+$], 422 (33) [M+Na$^+$], 400 (100) [M+H$^+$], 284 (15). HRMS (ESI) *m*/*z* calcd for $C_{28}H_{34}NO$ 400.2640, found 400.2635.

4.11. 1-(1-Adamantyl)-6-methyl-2-phenyl-1*H*-indole (3aj)

Following the general procedure, **2a** (91.0 mg, 0.60 mmol), **5j** (113 mg, 0.513 mmol), **13** (10.6 mg, 0.025 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), KO*t*-Bu (168 mg, 1.50 mmol) were stirred in PhMe (3.0 mL) for 14 h at 120 °C. Indole **3aj** (164 mg, 94%) was obtained as a pale brown solid after purification by column chromatography on silica gel (*n*-pentane/Et_2O 100:1). Mp: 176–177 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.50–7.33 (m, 6H), 6.96 (d, *J*=7.8 Hz, 1H), 6.26 (s, 1H), 2.55 (s, 3H), 2.31 (s, 6H), 2.13 (s, 3H), 1.71–1.41 (m, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.8, 138.8, 137.0, 130.0, 129.6, 127.1, 127.1, 126.9, 120.8, 120.1, 115.7, 106.5, 60.7, 43.4, 36.3, 30.3, 22.5. IR (film): 3054, 3025, 2912, 2854, 2252, 1483, 1445, 1300,

1262, 1103, 1028, 909, 805, 734 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 341 (67) [M^+], 235 (3), 206 (18), 179 (5), 135 (100), 107 (4), 93 (11). HRMS (ESI) *m*/*z* calcd for $C_{25}H_{28}N$ 342.2216, found 342.2217.

4.12. 1-*tert*-Butyl-2-*n*-butyl-1*H*-indole (3al)

Following the general procedure, **2b** (262 mg, 3.00 mmol), **5a** (192 mg, 1.00 mmol), **13** (21.2 mg, 0.05 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), KO*t*-Bu (336 mg, 3.00 mmol) were stirred in PhMe (3.0 mL) for 12 h at 105 °C. Purification by column chromatography on silica gel (*n*-hexane) yielded indole **3al** (144 mg, 63%) as an orange oil. ^1H NMR (300 MHz, C_6D_6): δ 7.67–7.64 (m, 1H), 7.57–7.54 (m, 1H), 7.19–7.12 (m, 2H), 6.33 (d, *J*=0.9 Hz, 1H), 2.73 (t, *J*=9.0 Hz, 2H), 1.64–1.54 (m, 2H), 1.45 (s, 9H), 1.33–1.20 (m, 2H), 0.85 (t, *J*=7.5 Hz, 3H). ^{13}C NMR (75 MHz, C_6D_6): δ 142.5, 138.0, 130.2, 120.5, 120.4, 119.2, 114.8, 103.8, 58.5, 33.1, 31.6, 31.4, 23.0, 14.1. IR (film): 2957, 2930, 2871, 1653, 1455, 1400, 1369, 1287, 776, 732 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 229 (5) [M^+], 173 (5), 131 (18). HRMS (ESI) *m*/*z* calcd for $C_{16}H_{24}N$ 230.1903, found 230.1905.

4.13. 1-*tert*-Butyl-2-cyclopropyl-1*H*-indole (3am)

Following the general procedure, **2b** (44.0 mg, 0.60 mmol), **5c** (84.0 mg, 0.48 mmol), **13** (10.6 mg, 0.025 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), KO*t*-Bu (168 mg, 1.50 mmol) were stirred in PhMe (1.5 mL) for 14 h at 105 °C. Indole **3am** (89 mg, 87%) was obtained as a colourless oil after purification by column chromatography on silica gel (*n*-pentane). ^1H NMR (300 MHz, $CDCl_3$): δ 7.69–7.66 (m, 1H), 7.51–7.48 (m, 1H), 7.11–7.00 (m, 2H), 6.24 (s, 1H), 2.16–2.04 (m, 1H), 1.94 (s, 9H), 1.01–0.84 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.9, 137.1, 128.5, 120.1, 120.0, 118.6, 114.3, 102.3, 58.7, 31.3, 13.0, 9.5. IR (film): 3053, 2986, 2361, 1456, 1420, 1371, 1304, 1265, 1204, 896, 739, 705 cm^{-1}. MS (ESI) *m*/*z* (relative intensity): 236 (9) [M+Na^+], 214 (36) [M+H^+], 158 (100). HRMS (ESI) *m*/*z* calcd for $C_{15}H_{20}N$ 214.1596, found 214.1590.

4.14. 1-*tert*-Butyl-2-phenyl-1*H*-indole (3an)

Following the general procedure, **2b** (262 mg, 3.00 mmol), **5d** (212 mg, 1.00 mmol), **13** (21.2 mg, 0.05 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), KO*t*-Bu (336 mg, 3.00 mmol) were stirred in PhMe (3.0 mL) for 12 h at 105 °C. Purification by column chromatography on silica gel (*n*-hexane) yielded indole **3an** (136 mg, 55%) as a white solid. Mp: 105–107 °C. ^1H NMR (300 MHz, C_6D_6): δ 7.66–7.59 (m, 2H), 7.34–7.31 (m, 2H), 7.24–7.16 (m, 2H), 7.09–7.07 (m, 3H), 6.41 (s, 1H), 1.34 (s, 9H). ^{13}C NMR (75 MHz, C_6D_6): δ 141.7, 138.8, 138.0, 130.4, 130.0, 127.9, 127.6, 121.2, 121.2, 119.9, 115.3, 107.1, 58.6, 31.9. IR (KBr): 3441, 2362, 2339, 1653, 1635, 1450, 1292, 782, 736, 673 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 249 (14) [M^+], 193 (100), 165 (9). HRMS (EI) *m*/*z* calcd for $C_{18}H_{19}N$ 249.1517, found 249.1513. The spectral data are in accordance with those reported in the literature.[31]

4.15. 1-*tert*-Butyl-2-(4-*n*-propylphenyl)-1*H*-indole (3ao)

Following the general procedure, **2b** (44.0 mg, 0.60 mmol), **5e** (128 mg, 0.504 mmol), **13** (10.6 mg, 0.025 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), KO*t*-Bu (168 mg, 1.50 mmol) were stirred in PhMe (3.0 mL) for 14 h at 120 °C. Indole **3ao** (122 mg, 84%) was obtained as a pale yellow solid after purification by column chromatography on silica gel (*n*-pentane/Et_2O 100:1). Mp: 36.5 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.79–7.76 (m, 1H), 7.64–7.61 (m, 1H), 7.38–7.35 (m, 2H), 7.23–7.13 (m, 4H), 6.36 (d, *J*=0.9 Hz, 1H), 2.69 (t, *J*=7.5 Hz, 2H), 1.86–1.60 (m, 11H), 1.03 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.0, 141.9, 137.1, 135.3, 130.0, 129.0, 127.4, 120.4, 120.4, 119.2, 114.9, 105.9, 58.8, 37.8, 32.0, 24.5, 13.8. IR (film): 2962, 2933, 2873, 2246, 1499, 1450, 1336, 1293, 1202, 1024, 909, 789, 735, 650 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 291 (28) [M^+], 235 (100), 217 (1), 206 (60), 178 (4), 165 (1). HRMS (ESI) *m*/*z* calcd for $C_{21}H_{26}N$ 292.2060, found 292.2061.

4.16. 1-*tert*-Butyl-5-methoxy-2-(4-*n*-propylphenyl)-1*H*-indole (3ap)

Following the general procedure, **2b** (44.0 mg, 0.60 mmol), **5i** (143 mg, 0.503 mmol), **13** (10.6 mg, 0.025 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), KO*t*-Bu (168 mg, 1.50 mmol) were stirred in PhMe (3.0 mL) for 14 h at 120 °C. Indole **3ap** (104 mg, 65%) was obtained as a yellow solid after purification by column chromatography on silica gel (*n*-pentane/Et_2O 100:1→50:1). Mp: 75–76 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.62–7.59 (m, 1H), 7.30 (ddd, *J*=8.1, 3.6, 1.8 Hz, 2H), 7.15 (ddd, *J*=8.0, 3.5, 1.8 Hz, 2H), 7.03 (d, *J*=2.4 Hz, 1H), 6.82 (dd, *J*=9.0, 2.7 Hz, 1H), 6.22 (d, *J*=0.6 Hz, 1H), 3.85 (s, 3H), 2.64 (t, *J*=7.5 Hz, 2H), 1.78–1.62 (m, 2H), 1.57 (s, 9H), 0.97 (t, *J*=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.5, 142.5, 141.9, 135.2, 132.3, 129.9, 129.4, 127.3, 115.5, 110.5, 105.5, 101.7, 58.7, 55.8, 37.8, 32.1, 24.5, 13.9. IR (film): 2960, 2933, 2873, 2361, 2253, 1466, 1344, 1297, 1214, 1130, 1043, 907, 735, 650 cm^{-1}. MS (ESI) *m*/*z* (relative intensity): 344 (100) [M+Na^+], 322 (51) [M+H^+], 266 (91), 167 (10). HRMS (ESI) *m*/*z* calcd for $C_{22}H_{28}NO$ 322.2171, found 322.2165.

4.17. 1-*tert*-Butyl-6-methyl-2-phenyl-1*H*-indole (3aq)

Following the general procedure, **2b** (44.0 mg, 0.60 mmol), **5j** (117 mg, 0.518 mmol), **13** (10.6 mg, 0.025 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), KO*t*-Bu (168 mg, 1.50 mmol) were stirred in PhMe (3.0 mL) for 14 h at 120 °C. Indole **3aq** (123 mg, 90%) was obtained as a pale yellow solid after purification by column chromatography on silica gel (*n*-pentane/Et_2O 100:1). Mp: 136 °C. ^1H NMR (300 MHz, $CDCl_3$): δ 7.54–7.34 (m, 7H), 6.98–6.95 (m, 1H), 6.27 (s, 1H), 2.54 (s, 3H), 1.61 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.2, 138.3, 137.7, 130.1, 130.1, 127.3, 126.8, 126.8, 121.0, 120.1, 115.1, 106.0, 58.7, 32.0, 22.3. IR (film): 3421, 3003, 2968, 2918, 2356, 1653, 1540, 1443, 1332, 1206, 1104, 1028, 814, 705, 607 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 263 (22) [M^+], 235 (4), 220 (4), 207 (100), 178 (5), 152 (2). HRMS (ESI) *m*/*z* calcd for $C_{19}H_{21}NNa$ 286.1566, found 286.1567. The spectral data are in accordance with those reported in the literature.[31]

4.18. 2-*n*-Butyl-1-*tert*-pentyl-1*H*-indole (3ar)

Following the general procedure, **2c** (104 mg, 1.19 mmol), **5a** (193 mg, 1.00 mmol), **13** (21.2 mg, 0.05 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), KO*t*-Bu (337 mg, 3.00 mmol) were stirred in PhMe (3.0 mL) for 14 h at 120 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 400:1) yielded indole **3ar** (104 mg, 43%) as a yellow oil. ^1H NMR (300 MHz, $CDCl_3$): δ 7.74–7.62 (m, 1H), 7.56–7.46 (m, 1H), 7.12–6.97 (m, 2H), 6.32 (s, 1H), 2.96 (t, *J*=7.7 Hz, 2H), 2.19 (q, *J*=7.3 Hz, 2H), 1.86 (s, 6H), 1.83–1.70 (m, 2H), 1.57–1.39 (m, 2H), 1.00 (t, *J*=7.3 Hz, 3H), 0.69 (t, *J*=7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.7, 137.3, 129.1, 119.6, 119.6, 118.5, 114.2, 102.5, 62.1, 34.6, 32.6, 31.4, 30.0, 22.9, 14.1, 8.8. IR (film): 3104, 3065, 2959, 2872, 1577, 1539, 1455, 1379, 1285, 1230, 1190, 1086, 1055, 1028, 922, 807, 776, 747, 732, 699 cm^{-1}. MS (EI) *m*/*z* (relative intensity): 243 (48) [M^+], 173 (31), 131 (100), 58 (17), 43 (62). HRMS (ESI) *m*/*z* calcd for $C_{17}H_{26}N$ 244.2060, found 244.2060.

4.19. 1-*tert*-Pentyl-2-(4-*n*-propylphenyl)-1*H*-indole (3as)

Following the general procedure, **2c** (101 mg, 1.16 mmol), **5e** (257 mg, 1.01 mmol), **13** (21.2 mg, 0.05 mmol), $Pd(OAc)_2$ (11.2 mg,

0.05 mmol), KO*t*-Bu (365 mg, 2.98 mmol) were stirred in PhMe (6.0 mL) for 14 h at 120 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 500:1) yielded indole **3as** (282 mg, 92%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72 (d, J=8.3 Hz, 1H), 7.61–7.54 (m, 1H), 7.36–7.28 (m, 2H), 7.21–7.05 (m, 4H), 6.29 (s, 1H), 2.64 (t, J=7.5 Hz, 2H), 2.12 (q, J=7.3 Hz, 2H), 1.69 (sext., J=7.3 Hz, 2H), 1.48 (s, 6H), 0.97 (t, J=7.3 Hz, 3H), 0.61 (t, J=7.3 Hz, 3H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.8, 141.9, 137.1, 135.4, 130.0, 128.9, 127.3, 120.4, 120.3, 119.2, 114.7, 105.9, 62.1, 37.9, 34.6, 30.6, 24.5, 13.9, 8.6. IR (film): 3044, 3017, 2963, 2930, 2872, 1499, 1450, 1393, 1377, 1336, 1299, 1280, 1189, 1025, 844, 826, 756, 752, 734, 682 cm^{-1}. MS (EI) m/z (relative intensity): 305 (18) [M$^+$], 235 (100), 206 (67), 178 (4), 43 (11). HRMS (ESI) m/z calcd for $C_{22}H_{28}N$ 306.2216, found 306.2217.

4.20. 1-*tert*-Pentyl-2-(4-trifluoromethylphenyl)-1*H*-indole (3at)

Following the general procedure, **2c** (52.0 mg, 0.60 mmol), **5g** (143 mg, 0.51 mmol), **13** (10.6 mg, 0.025 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), KO*t*-Bu (168 mg, 1.50 mmol) were stirred in PhMe (3.0 mL) for 14 h at 120 °C. Purification by column chromatography on silica gel (*n*-pentane/MTBE 200:1→150:1) yielded indole **3at** (146 mg, 80%) as a light yellow solid. Mp: 103–104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.74–7.71 (m, 1H), 7.62–7.51 (m, 5H), 7.21–7.09 (m, 2H), 6.30 (d, J=0.6 Hz, 1H), 2.12 (q, J=7.5 Hz, 2H), 1.48 (s, 6H), 0.59 (t, J=7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.0, 141.0, 137.6, 130.3, 129.6 ($^2J_{C-F}$=33 Hz), 128.9, 124.3 ($^3J_{C-F}$=4 Hz), 124.2 ($^1J_{C-F}$=272 Hz), 121.2, 120.6, 119.7, 114.9, 107.0, 62.3, 34.5, 30.8, 8.5. ^{19}F NMR (275 MHz, $CDCl_3$): δ −62.4 (s). IR (KBr): 2973, 2938, 1931, 1804, 1614, 1448, 1378, 1299, 1098, 1062, 1021, 847, 784, 752, 736 cm^{-1}. MS (EI) m/z (relative intensity): 331 (14) [M$^+$], 302 (1), 261 (100), 242 (4), 233 (4). HRMS (ESI) m/z calcd for $C_{20}H_{21}NF_3$ 332.1621, found 332.1621.

4.21. 1-*tert*-Pentyl-2-(3-methylphenyl)-1*H*-indole (3au)

Following the general procedure, **2c** (103 mg, 1.18 mmol), **5l** (228 mg, 1.01 mmol), **13** (21.2 mg, 0.05 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), KO*t*-Bu (336 mg, 3.00 mmol) were stirred in PhMe (5.0 mL) for 14 h at 120 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 500:1) yielded indole **3au** (236 mg, 85%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.77–7.68 (m, 1H), 7.62–7.54 (m, 1H), 7.30–7.05 (m, 6H), 6.28 (s, 1H), 2.38 (s, 3H), 2.12 (q, J=7.6 Hz, 2H), 1.50 (s, 6H), 0.61 (t, J=7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 142.9, 138.2, 137.2, 136.8, 130.9, 129.0, 128.2, 127.4, 127.1, 120.5, 120.4, 119.3, 114.8, 105.9, 62.1, 34.5, 30.6, 21.4, 8.5. IR (film): 3014, 2970, 2935, 2877, 1606, 1450, 1393, 1373, 1338, 1300, 1281, 1226, 1189, 1091, 1026, 784, 752, 735, 709 cm^{-1}. MS (EI) m/z (relative intensity): 277 (14) [M$^+$], 207 (100), 86 (5), 84 (8), 43 (4). HRMS (ESI) m/z calcd for $C_{20}H_{23}NNa$ 300.1723, found 300.1723.

4.22. 2-Cyclopropyl-1-(2,4,6-trimethylphenyl)-1*H*-indole (3av)

Following the general procedure, **2d** (81.0 mg, 0.60 mmol), **5c** (87.0 mg, 0.494 mmol), **13** (10.6 mg, 0.025 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), KO*t*-Bu (168 mg, 1.50 mmol) were stirred in PhMe (1.5 mL) for 14 h at 105 °C. Indole **3av** (117 mg, 85%) was obtained as a colourless oil after purification by column chromatography on silica gel (*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57–7.54 (m, 1H), 7.10–7.00 (m, 4H), 6.77–6.74 (m, 1H), 6.16 (s, 1H), 2.39 (s, 3H), 1.88 (s, 6H), 1.45–1.38 (m, 1H), 0.84–0.72 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 143.8, 138.1, 137.6, 137.0, 133.1, 128.9, 128.0, 120.7, 119.6, 119.6, 109.4, 95.3, 21.1, 17.4, 7.9, 7.5. IR (film): 3009, 2919, 1653, 1611, 1557, 1489, 1457, 1302, 1219, 1012, 883, 854, 772 cm^{-1}. MS (EI) m/z (relative intensity): 275 (100) [M$^+$], 260 (8), 246 (33), 218 (10), 204 (2), 158 (5), 133 (7). HRMS (ESI) m/z calcd for $C_{20}H_{22}N$ 276.1747, found 276.1747.

4.23. 2-Cyclopropyl-1-(2,6-di-*iso*-propylphenyl)-1*H*-indole (3aw)

Following the general procedure, **2e** (106 mg, 0.60 mmol), **5c** (84.0 mg, 0.477 mmol), **13** (10.6 mg, 0.025 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), KO*t*-Bu (168 mg, 1.50 mmol) were stirred in PhMe (1.5 mL) for 14 h at 105 °C. Indole **3aw** (125 mg, 82%) was obtained as a colourless solid after purification by column chromatography on silica gel (*n*-pentane). Mp: 124.6 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.57–7.46 (m, 2H), 7.34–7.31 (m, 2H), 7.10–6.98 (m, 2H), 6.77–6.75 (m, 1H), 6.12 (s, 1H), 2.30 (sept., J=6.0 Hz, 2H), 1.45–1.36 (m, 1H), 1.14 (d, J=6.0 Hz, 6H), 0.97 (d, J=6.0 Hz, 6H), 0.87–0.75 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 148.6, 145.1, 138.5, 132.6, 129.4, 127.7, 123.9, 120.6, 119.7, 119.4, 110.1, 94.3, 28.1, 24.7, 23.7, 9.3, 7.8. IR (KBr): 2962, 2926, 2865, 2360, 2340, 1473, 1457, 1400, 1381, 1358, 1298, 1215, 805, 775, 737 cm^{-1}. MS (ESI) m/z (relative intensity): 340 (5) [M+Na$^+$], 318 (100) [M+H$^+$], 223 (1), 163 (4). HRMS (ESI) m/z calcd for $C_{23}H_{28}N$ 318.2222, found 318.2216.

4.24. 1-(2,4,6-Trimethylphenyl)-2-phenyl-1*H*-indole (3ax)

Following the general procedure, **2d** (81.0 mg, 0.60 mmol), **5d** (106 mg, 0.50 mmol), **13** (10.6 mg, 0.025 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), KO*t*-Bu (168 mg, 1.50 mmol) were stirred in PhMe (3.0 mL) for 14 h at 105 °C. Indole **3ax** (143 mg, 91%) was obtained as a colourless oil after purification by column chromatography on silica gel (*n*-hexane). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72–7.69 (m, 1H), 7.32–7.11 (m, 7H), 6.96 (s, 2H), 6.88–6.83 (m, 2H), 2.36 (s, 3H), 1.84 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.5, 138.0, 137.9, 136.9, 133.8, 132.8, 129.2, 128.2, 128.2, 127.5, 127.2, 122.1, 120.3, 120.2, 110.5, 102.0, 21.1, 17.7. IR (film): 3053, 2985, 2305, 1653, 1558, 1489, 1457, 1375, 1322, 1265, 1210, 1029, 896, 857 cm^{-1}. MS (EI) m/z (relative intensity): 311 (100) [M$^+$], 296 (4), 218 (4), 140 (2). HRMS (ESI) m/z calcd for $C_{23}H_{22}N$ 312.1747, found 312.1747.

4.25. 2-Phenyl-1-(2,6-di-*iso*-propylphenyl)-1*H*-indole (3ay)

Following the general procedure, **2e** (106 mg, 0.60 mmol), **5d** (106 mg, 0.500 mmol), **13** (10.6 mg, 0.025 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), KO*t*-Bu (168 mg, 1.50 mmol) were stirred in PhMe (3.0 mL) for 14 h at 120 °C. Indole **3ay** (167 mg, 94%) was obtained as a colourless solid after purification by column chromatography on silica gel (*n*-hexane). Mp: 83–84 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.71–7.68 (m, 1H), 7.49–7.44 (m, 1H), 7.29–7.24 (m, 4H), 7.22–7.07 (m, 5H), 6.93 (d, J=0.9 Hz, 1H), 6.85–6.82 (m, 1H), 2.34 (sept., J=6.0 Hz, 2H), 0.96 (d, J=6.0 Hz, 6H), 0.84 (d, J=6.0 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.7, 140.8, 139.6, 133.6, 132.4, 129.4, 128.0, 127.7, 127.6, 127.1, 124.2, 121.9, 120.2, 120.2, 111.1, 101.8, 28.2, 25.1, 23.2. IR (KBr): 3048, 2961, 2925, 2866, 1487, 1458, 1442, 1352, 1331, 1176, 1055, 801, 747, 668 cm^{-1}. MS (EI) m/z (relative intensity): 353 (98) [M$^+$], 338 (12), 310 (8), 280 (5), 220 (11), 204 (6), 165 (100), 105 (23). HRMS (ESI) m/z calcd for $C_{26}H_{28}N$ 354.2216, found 354.2217.

4.26. 2-(4-*n*-Propylphenyl)-1-(2,4,6-trimethylphenyl)-1*H*-indole (3az)

Following the general procedure, **2d** (161 mg, 1.19 mmol), **5e** (256 mg, 1.00 mmol), **13** (21.2 mg, 0.05 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), KO*t*-Bu (336 mg, 3.00 mmol) were stirred in PhMe (6.0 mL) for 14 h at 120 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 500:1) yielded indole **3az** (335 mg,

95%) as a white solid. Mp: 125 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72–7.63 (m, 1H), 7.22–6.99 (m, 6H), 6.94 (s, 2H), 6.86–6.76 (m, 2H), 2.52 (t, J=8.3 Hz, 2H), 2.35 (s, 3H), 1.82 (s, 6H), 1.61 (sext., J=7.5 Hz, 2H), 0.92 (t, J=7.3 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 141.8, 140.7, 138.0, 137.1, 134.1, 130.2, 129.2, 128.4, 128.3, 127.3, 121.9, 120.2, 120.1, 110.4, 101.6, 37.7, 24.2, 21.1, 17.7, 13.8. IR (KBr): 3020, 2956, 2918, 2865, 2361, 1488, 1470, 1452, 1415, 1372, 1354, 1316, 1301, 857, 840, 827, 780, 750, 734, 611 cm^{-1}. MS (EI) m/z (relative intensity): 353 (100) [M$^+$], 324 (29), 57 (7), 43 (18). HRMS (ESI) m/z calcd for $C_{26}H_{28}N$ 354.2216, found 354.2215.

4.27. 2-(4-*n*-Propylphenyl)-1-(2,6-di-*iso*-propylphenyl)-1*H*-indole (3ba)

Following the general procedure, **2e** (208 mg, 1.17 mmol), **5e** (253 mg, 0.99 mmol), **13** (21.2 mg, 0.05 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), KO*t*-Bu (337 mg, 3.00 mmol) were stirred in PhMe (6.0 mL) for 14 h at 120 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 500:1) yielded indole **3ba** (348 mg, 88%) as a white solid. Mp: 104 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.73–7.64 (m, 1H), 7.46 (t, J=7.7 Hz, 1H), 7.32–6.76 (m, 10H), 2.49 (t, J=7.2 Hz, 2H), 2.33 (sept., J=7.2 Hz, 2H), 1.57 (sext., J=7.7 Hz, 2H), 1.01–0.75 (m, 15H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.9, 141.8, 141.1, 139.6, 129.8, 129.4, 128.2, 127.8, 127.7, 124.2, 121.7, 120.2, 120.1, 111.0, 101.3, 37.5, 28.1, 25.0, 24.3, 23.1, 13.7. IR (KBr): 3049, 2961, 2926, 2867, 1497, 1468, 1416, 1383, 1360, 1314, 1255, 1191, 829, 800, 784, 756, 746, 734, 608, 427 cm^{-1}. MS (EI) m/z (relative intensity): 395 (100) [M$^+$], 267 (26), 252 (10), 236 (14), 191 (22), 165 (14), 111 (9), 97 (15), 91 (15), 69 (20), 57 (34), 43 (26). HRMS (ESI) m/z calcd for $C_{29}H_{34}N$ 396.2686, found 396.2684.

4.28. 2-(3-Methylphenyl)-1-(2,4,6-trimethylphenyl)-1*H*-indole (3bb)

Following the general procedure, **2d** (163 mg, 1.21 mmol), **5l** (217 mg, 0.96 mmol), **13** (21.2 mg, 0.05 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), KO*t*-Bu (338 mg, 3.01 mmol) were stirred in PhMe (6.0 mL) for 14 h at 120 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 333:1) yielded indole **3bb** (285 mg, 91%) as a white solid. Mp: 90 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.72–7.62 (m, 1H), 7.20–6.77 (m, 10H), 2.34 (s, 3H), 2.26 (s, 3H), 1.82 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 140.7, 138.0, 137.9, 137.8, 137.0, 134.0, 132.7, 129.1, 129.1, 128.5, 128.2, 128.1, 124.4, 122.0, 120.3, 120.2, 110.5, 101.9, 21.5, 21.1, 17.7. IR (KBr): 2917, 2371, 1604, 1485, 1456, 1373, 1353, 1315, 1299, 1214, 1010, 850, 799, 781, 750, 767, 694, 669, 615, 449 cm^{-1}. MS (EI) m/z (relative intensity): 325 (100) [M$^+$], 310 (13), 234 (7), 131 (14), 84 (8), 57 (8). HRMS (ESI) m/z calcd for $C_{24}H_{24}N$ 326.1903, found 326.1904.

4.29. 6-Methyl-2-phenyl-1-(2,4,6-trimethylphenyl)-1*H*-indole (3bc)

Following the general procedure, **2e** (81 mg, 0.60 mmol), **5j** (115 mg, 0.51 mmol), **13** (10.6 mg, 0.025 mmol), $Pd(OAc)_2$ (5.5 mg, 0.025 mmol), KO*t*-Bu (170 mg, 1.52 mmol) were stirred in PhMe (1.5 mL) for 14 h at 120 °C. Purification by column chromatography on silica gel (*n*-pentane/Et_2O 200:1) yielded indole **3bc** (91 mg, 56%) as a yellow solid. Mp: 48 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.56 (d, J=7.0 Hz, 1H), 7.29–7.14 (m, 5H), 7.01–6.89 (m, 3H), 6.80 (s, 1H), 6.60 (s, 1H), 2.38 (s, 3H), 2.34 (s, 3H), 1.82 (s, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.9, 138.3, 137.9, 136.9, 134.0, 132.9, 131.9, 129.1, 128.1, 127.3, 127.0, 126.0, 122.0, 120.0, 110.2, 101.9, 21.9, 21.2, 17.8. IR (KBr): 3020, 2946, 2916, 1616, 1602, 1486, 1456, 1437, 1372, 1346, 1322, 1302, 1028, 854, 810, 759, 744, 694, 611, 604 cm^{-1}. MS (EI) m/z (relative intensity): 325 (100) [M$^+$], 310 (6), 294 (4), 148 (5). HRMS (ESI) m/z calcd for $C_{24}H_{24}N$ 326.1903, found 326.1911.

4.30. 6-Methyl-2-phenyl-1-(2,6-di-*iso*-propylphenyl)-1*H*-indole (3bd)

Following the general procedure, **2e** (109 mg, 0.61 mmol), **5j** (114 mg, 0.51 mmol), **13** (21.2 mg, 0.025 mmol), $Pd(OAc)_2$ (6.0 mg, 0.027 mmol), KO*t*-Bu (170 mg, 1.52 mmol) were stirred in PhMe (1.5 mL) for 14 h at 120 °C. Purification by column chromatography on silica gel (*n*-pentane/Et_2O 200:1) yielded indole **3bd** (168 mg, 91%) as a yellow solid. Mp: 105 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (d, J=8.3 Hz, 1H), 7.48 (t, J=7.5 Hz, 1H), 7.32–7.11 (m, 7H), 7.03–6.88 (m, 2H), 6.64 (s, 1H), 2.45–2.30 (m, 5H), 0.98 (d, J=6.8 Hz, 6H), 0.85 (d, J=6.8 Hz, 6H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.8, 140.2, 140.1, 133.7, 132.6, 131.8, 129.3, 128.0, 127.6, 126.9, 125.5, 124.2, 122.0, 119.8, 110.9, 101.7, 28.2, 25.1, 23.2, 21.9. IR (KBr): 2961, 2924, 2845, 1617, 1599, 1468, 1381, 1346, 1315, 1255, 1176, 1057, 812, 790, 759, 742, 693, 608, 589 cm^{-1}. MS (EI) m/z (relative intensity): 367 (100) [M$^+$], 352 (7), 325 (14), 232 (5). HRMS (ESI) m/z calcd for $C_{27}H_{30}N$ 368.2373, found 368.2375.

4.31. 5-Hydroxy-2-phenyl-1-(2,4,6-trimethylphenyl)-1*H*-indole (3be)

Following the general procedure, **2d** (130 mg, 0.96 mmol), **5m** (177 mg, 0.77 mmol), **13** (16.3 mg, 0.039 mmol), $Pd(OAc)_2$ (8.5 mg, 0.04 mmol), KO*t*-Bu (261 mg, 2.32 mmol) were stirred in PhMe (1.0 mL) for 14 h at 120 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 15:1) yielded indole **3be** (190 mg, 75%) as a brown solid. Mp: 72 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28–7.17 (m, 5H), 7.10–7.08 (m, 1H), 6.93 (s, 2H), 6.73 (s, 1H), 6.71–6.65 (m, 2H), 4.73 (br s, 1H), 2.33 (s, 3H), 1.82 (s, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.8, 141.3, 138.0, 136.9, 133.9, 133.4, 132.7, 129.1, 128.7, 128.2, 127.3, 127.2, 111.7, 111.1, 104.7, 101.3, 21.2, 17.7. IR (KBr): 3059, 3027, 2951, 2917, 2855, 2733, 2361, 2338, 1650, 1619, 1580, 1539, 1465, 1372, 1279, 1211, 1139, 1027, 1028, 951, 867, 848, 793, 759, 735, 694, 601 cm^{-1}. MS (EI) m/z (relative intensity): 327 (100), 312 (16), 250 (9), 228 (8), 148 (5). HRMS (ESI) m/z calcd for $C_{23}H_{22}NO$ 328.1696, found 328.1695.

4.32. 5-Hydroxy-2-phenyl-1-(2,6-di-*iso*-propylphenyl)-1*H*-indole (3bf)

Following the general procedure, **2e** (211 mg, 1.20 mmol), **5m** (229 mg, 1.00 mmol), **13** (21.2 mg, 0.05 mmol), $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), KO*t*-Bu (339 mg, 3.02 mmol) were stirred in PhMe (2.0 mL) for 14 h at 120 °C. Purification by column chromatography on silica gel (*n*-hexane/EtOAc 15:1) yielded indole **3bf** (262 mg, 71%) as a white solid. Mp: 155 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.49–7.41 (m, 1H), 7.31–7.12 (m, 7H), 7.12–7.06 (m, 1H), 6.83 (s, 1H), 6.69 (s, 2H), 4.67 (br s, 1H), 2.34 (sept., J=6.9 Hz, 2H), 0.96 (d, J=6.8 Hz, 6H), 0.88 (d, J=6.9 Hz, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 149.8, 147.8, 141.7, 135.3, 133.6, 132.3, 129.3, 128.2, 128.0, 127.6, 127.1, 124.2, 111.7, 111.7, 104.5, 101.1, 28.2, 25.1, 23.1. IR (KBr): 3060, 2962, 2926, 2866, 2361, 2338, 1617, 1600, 1523, 1470, 1437, 1373, 1313, 1205, 1174, 1143, 1118, 842, 805, 761, 737, 695 cm^{-1}. MS (EI) m/z (relative intensity): 369 (100), 354 (11), 326 (10), 248 (5), 194 (6), 171 (5). HRMS (ESI) m/z calcd for $C_{26}H_{28}NO$ 370.2165, found 370.2165.

4.33. 2-*n*-Butyl-1-(2-methylbut-3-en-2-yl)-1*H*-indole (3bh)

Following the general procedure, **2f** (51.1 mg, 0.60 mmol), **5a** (91.0 mg, 0.474 mmol), **13** (10.6 mg, 0.025 mmol), $Pd(OAc)_2$ (5.6 mg, 0.025 mmol), KO*t*-Bu (168 mg, 1.50 mmol) were stirred in PhMe (1.5 mL) for 14 h at 105 °C. Indole **3bh** (60 mg, 53%) was obtained as a yellow oil after purification by column chromatography on silica gel (*n*-pentane/Et_2O 100:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.67–7.61 (m, 1H), 7.50–7.46 (m, 1H), 7.04–6.99 (m, 2H), 6.38–6.28 (m, 2H),

5.16–5.10 (m, 2H), 2.90 (t, J=7.2 Hz, 2H), 1.87–1.68 (m, 8H), 1.49–1.39 (m, 2H), 0.97 (t, J=7.5 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 147.4, 143.2, 137.3, 128.9, 119.8, 119.5, 118.8, 114.5, 111.4, 102.4, 62.0, 32.2, 30.8, 29.5, 22.8, 14.0. IR (KBr): 3048, 2959, 2932, 2872, 1456, 1379, 1291, 1265, 1184, 918, 778, 738, 704 cm^{-1}. MS (EI) m/z (relative intensity): 241 (60) [M^+], 190 (9), 173 (29), 131 (100), 115 (2). HRMS (ESI) m/z calcd for $C_{17}H_{24}N$ 242.1903, found 242.1906.

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