Palladium-Catalyzed Direct Arylation-Based Domino Synthesis of Annulated *N*-Heterocycles Using Alkenyl or (Hetero)Aryl 1,2-Dihalides

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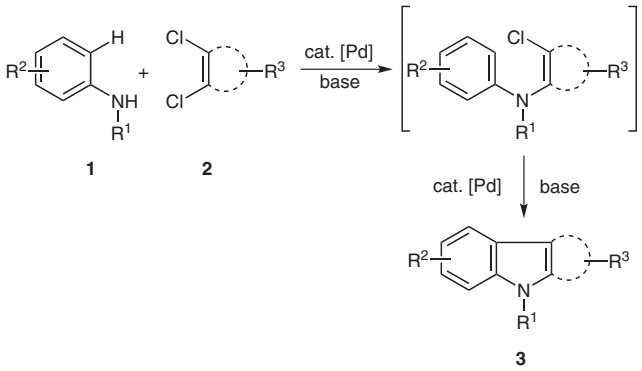
Abstract: A palladium-catalyzed reaction sequence consisting of an intermolecular amination and an intramolecular direct arylation enabled highly regioselective syntheses of functionalized indoles or carbazoles and proved to be amenable to the use of inexpensive 1,2-dichloroarenes as electrophiles.

Key words: arylation, catalysis, heterocycles, palladium, sequential reaction

Because of their ecologically sound and economically attractive nature, direct arylations of (hetero)arenes are attractive alternatives to cross-coupling reactions with stoichiometric amounts of organometallic reagents.[1,2] Until now, these challenging C–H bond functionalization reactions have predominantly been accomplished with catalysts based on palladium,[3,4] rhodium,[5] ruthenium[6,7] or other metals.[8] After pioneering contributions by Ames[9–11] and Ohta,[12–14] palladium-catalyzed direct arylations with aryl iodides, triflates, or bromides as electrophiles have proved to be increasingly useful tools for efficient syntheses of heterocycles.[15] However, among the aryl halides, chlorides are arguably the most useful single class of electrophilic substrates because of their lower costs and the wide diversity of compounds that are commercially available.[16,17] Therefore, the recent development of methods for the general use of readily available, but less reactive, aryl chlorides as electrophilic reagents in both intramolecular[18–25] and intermolecular[7b,e,i,26,27] transformations[3,6] represents significant progress in direct arylation chemistry.

The overall efficiency of direct arylation-based synthesis strategies could be considerably improved by their use in combination with mechanistically distinct catalytic processes in one-pot procedures. Interestingly, these more-sustainable sequential catalyses have been accomplished almost exclusively by using palladium catalysts.[28,29] Hence, Bedford and co-workers developed an elegant direct arylation-based consecutive palladium-catalyzed domino reaction using 2-chloroanilines and bromoarenes.[18,20,23,24] We, on the other hand, were attracted toward the design of reaction conditions for the direct conversion of easily accessible anilines **1** and 1,2-dihalo(hetero)arenes[30] **2** into the corresponding indole[2i,31–35] or carbazole[36,37] derivatives **3** through a domino[38] approach consisting of an intermolecular amination[39] and an intramolecular direct arylation with a chloride (Scheme 1). Here, we present a full account[40] of the development, scope, and limitations of a protocol that allows the use of inexpensive 1,2-dichloroarenes **2** as electrophilic starting materials in a highly regioselective[41] synthesis of carbazoles **3**.



Scheme 1 Direct arylation-based domino synthesis of N-heterocycles **3**

At the outset of our studies, we optimized the reaction conditions for the domino synthesis of *N*-phenylcarbazole (**3a**) from 1,2-dibromobenzene (**2a**) (Table 1). Thus, representative in situ generated carbenes (entries 1–4) or phosphines (entries 5–7) were probed as (pre)ligands; the imidazolium salt **7** (entry 4) and the phosphines **8** (entry 5) or **10** (entry 7) gave satisfactory results. Among a variety of bases, sodium *tert*-butoxide proved to be beneficial for the preparation of *N*-substituted carbazole **3a** (entries 7–10).

Having identified a highly active catalytic system, we explored its scope and limitations for the synthesis of N-substituted carbazoles **3** (Table 2). Importantly, the use of the electron-rich tertiary phosphine **10** as the ligand allowed not only for the use of bromides or iodides as electrophiles (entries 1 and 2), but also set the stage for an efficient intramolecular direct arylation with aryl chlorides (entries 3 and 4). Potentially problematic dichlorides with Lewis-basic functionalities were also converted efficiently (entries 5 and 6).

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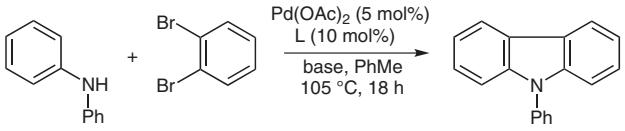
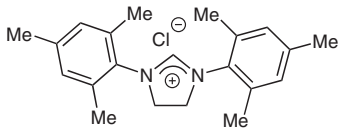
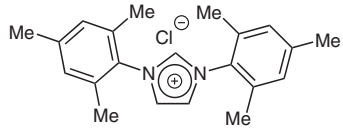
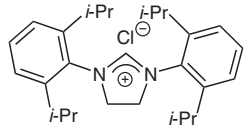
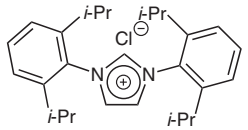
Table 1 Optimization Studies for the Synthesis of N-Substituted Carbazole **3a**



1a **2a** **3a**

Entry[a]	L		Base	Yield (%)[b]
1		**4**	NaO*t*-Bu	9[c]
2		**5**	NaO*t*-Bu	6[c]
3		**6**	NaO*t*-Bu	80
4		**7**	NaO*t*-Bu	94
5	PPh_3	**8**	NaO*t*-Bu	94
6	P(*o*-Tol)$_3$	**9**	NaO*t*-Bu	6[c]
7	PCy_3	**10**	NaO*t*-Bu	96
8	PCy_3	**10**	KOAc	–
9	PCy_3	**10**	K_2CO_3	–
10	PCy_3	**10**	K_3PO_4	8[c]

[a] Reaction conditions: **1a** (1.2 mmol), **2a** (1.0 mmol), $Pd(OAc)_2$ (5.0 mol%), L (10.0 mol%), base (3.0 mmol), toluene (10.0 mL), 105 °C, 18 h.
[b] Yield of isolated product (except where otherwise stated).
[c] GC conversion.

Notably, the reaction of a substituted 2,3-dichloropyridine proceeded with excellent regioselectivity to give carbazole **3c**, the molecular structure of which was verified by X-ray diffraction analysis (Figure 1). Additionally, our protocol proved to be applicable to the synthesis of the annulated indole **3d** from a cyclic 1,2-dibromoalkene (entry 7). On the other hand, an acyclic alkenylic dihalide did not lead to the desired product **3e** because competitive β-elimination occurred (entry 8). Finally, the use of *N*-benzylaniline failed to provide carbazole **3f** under our optimized reaction conditions (entry 9) as a result of β-hydride elimination from the corresponding palladium amide complex, which resulted in a reduction of the electrophile.

Numerous biologically active carbazoles **3** contain a free N–H moiety.[36] Consequently, we became interested in submitting primary anilines to the reaction conditions optimized for the synthesis of N-substituted carbazoles. Unfortunately, the product of palladium-catalyzed intermolecular amination was selectively formed in this case (Table 3, entry 1). Subsequent studies revealed that the use of polar-aprotic solvents, along with weaker inorganic bases, allowed for more-satisfactory catalysis to proceed. Indeed, when *N*,*N*-dimethylacetamide was used as the solvent, carbazole **3g** was formed with good selectivities (entries 2–4), particularly with potassium phosphate as the inorganic base (entry 4). Conversely, reactions performed in *N*,*N*-dimethylformamide or 1,3-dimethyltetrahydropyrimidin-2(1*H*)-one as the solvent gave lower conversions to the desired product **3g** (entries 5, and 6). However, superior results were obtained with *N*-methylpyrrolidin-2-one as solvent, with K_3PO_4 again being the base of choice (entries 7, and 8). A reaction conducted at a lower reaction temperature of 100 °C provided product **3g** in 53% yield (entry 9). Finally, the molarity of the substrate also had a marked effect on the outcome of the catalytic reaction (entries 7, 10, and 11).

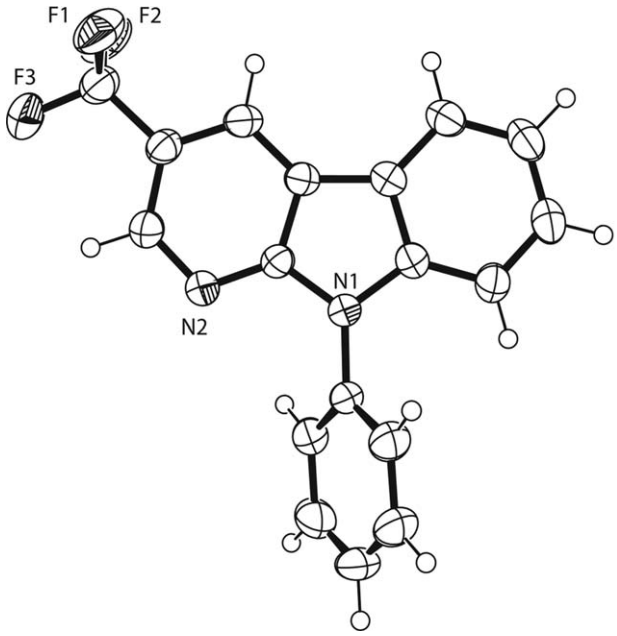
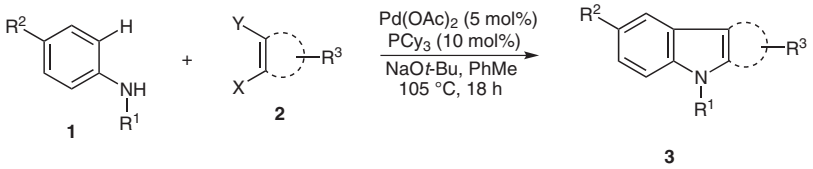
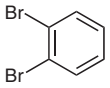
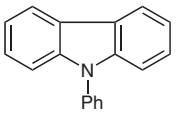
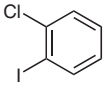
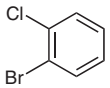
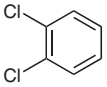
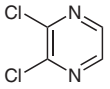
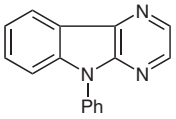
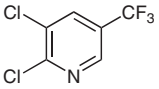
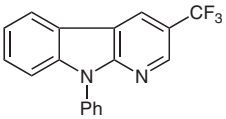
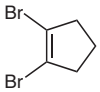
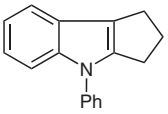
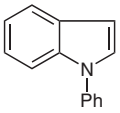
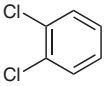
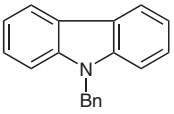


Figure 1 Molecular structure of crystalline carbazole **3c**

Subsequently, we applied the optimal reaction conditions to the conversion of various substituted primary anilines with unsubstituted 1,2-dihaloarenes (Table 4). Notably, the catalytic system was again not limited to the use of iodides or bromides as leaving groups (entries 1 and 3), but also enabled the use of less-expensive 1,2-dichlorobenzene (entries 2 and 4). This reactivity profile was also reflected by transformations with anilines with either electron-donating (entries 5–14) or electron-withdrawing substituents (entry 15). Hence, a reaction of an *ortho*-fluoroaniline displayed a noteworthy chemoselectivity that permitted the preparation of fluorinated[24] carbazole **3n** (entry 15). Unfortunately, our reaction conditions did not permit the domino synthesis of the *N*-unsubstituted α-carboline **3o** (entry 16).

Table 2 Synthesis of N-Substituted Carbazoles **3**



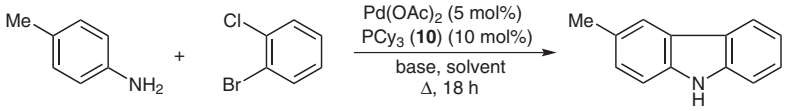
Entry[a]	R^1	**2**	Product		Yield (%)[b]
1	Ph			**3a**	96
2	Ph				83
3	Ph				88
4	Ph				85
5	Ph			**3b**	93
6	Ph			**3c**	93
7	Ph			**3d**	77[c]
8	Ph			**3e**	–
9	Bn			**3f**	–

[a] Reaction conditions: **1** (1.2 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (5.0 mol%), PCy_3 (**10**) (10.0 mol%), NaO*t*-Bu (3.0 mmol), toluene (10.0 mL), 105 °C, 18 h.
[b] Yields of isolated products.
[c] A 78% yield was obtained when **7** (10.0 mol%) was used instead of PCy_3 (**10**).

We then probed the chemo- and regioselectivity[41] of our domino carbazole synthesis by using unsymmetrically substituted 1,2-dihaloarenes (Table 5). Thus, the intermolecular amination of an electrophile bearing both a bromo and a chloro substituent occurred chemoselectively at the former functionality, thereby leading to carbazole **3p** in high yields (entry 1). More importantly, high selectivities were also observed when using unsymmetrically substituted 1,2-dichloroarenes as substrates (entries 2–6). Thus, electrophiles bearing an ester, a ketone, or an amide as a functional group gave carbazoles **3q**–**u**, respectively, in high yields. Whereas the molecular structures of products **3p**, **3r**, and **3u** were unambiguously established by X-ray diffraction analyses (Figures 2– 4), the exact reason why regioisomer **3u** was selectively formed is, as yet, not fully understood.

Finally, we exploited our protocol for an effective synthesis of naturally occurring[36] murrayafoline A (**3v**; 1-methoxy-3-methyl-9*H*-carbazole) (Scheme 2). Easily accessible 2-methoxy-4-methylaniline[42] gave to the desired product **3v** in high yields through the palladium-catalyzed reaction sequence, also when inexpensive 1,2-dichlorobenzene was used as the electrophile.

Table 3 Optimization Studies for the Synthesis of N-Unsubstituted Carbazole **3g**

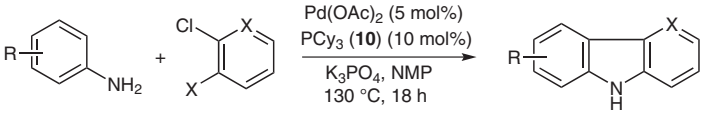


1b **2b** **3g**

Entry[a]	Solvent	Base	Temp. (°C)	Yield (%)[b]
1	Toluene (0.1 M)	NaO*t*-Bu	105	–[c]
2	DMA (0.1 M)	K_2CO_3	130	60
3	DMA (0.1 M)	Cs_2CO_3	130	51
4	DMA (0.1 M)	K_3PO_4	130	79
5	DMF (0.1 M)	K_3PO_4	130	6[d]
6	DMPU (0.1 M)	K_3PO_4	130	<2[d]
7	NMP (0.1 M)	K_3PO_4	130	81
8	NMP (0.1 M)	K_2CO_3	130	76
9	NMP (0.1 M)	K_3PO_4	100	53
10	NMP (0.5 M)	K_3PO_4	130	69
11	NMP (1.0 M)	K_3PO_4	130	25[d]

[a] Reaction conditions: **1b** (1.2 mmol), **2b** (1.0 mmol), $Pd(OAc)_2$ (5.0 mol%), PCy_3 (**10**) (10.0 mol%), base (2.2 mmol), solvent, 100–130 °C, 18 h.
[b] Yields of isolated products (except where stated otherwise).
[c] The product of intermolecular amination was isolated in 94% yield.
[d] GC conversion.

Table 4 Synthesis of N-Unsubstituted Carbazoles **3** from Unsubstituted 1,2-Dihaloarenes **2**



1 **2** **3**

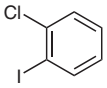
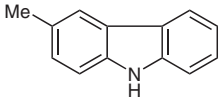
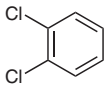
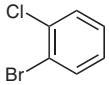
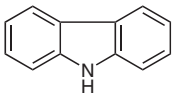
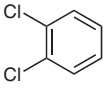
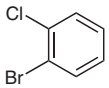
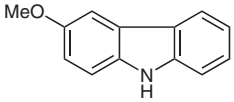
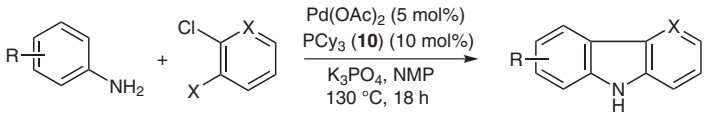
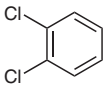
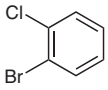
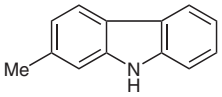
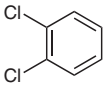
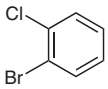
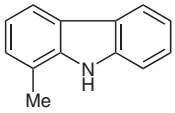
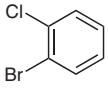
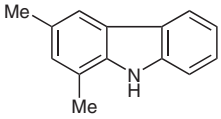
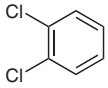
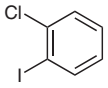
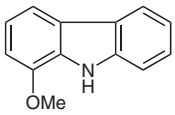
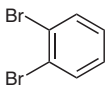
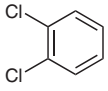
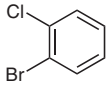
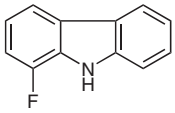
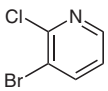
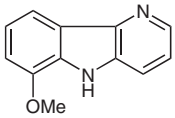
Entry[a]	R	**2**	**3**		Yield[b] (%)
1	4-Me			**3g**	53
2	4-Me				77
3	H			**3h**	67
4	H				81
5	4-MeO			**3i**	74

Table 4 Synthesis of N-Unsubstituted Carbazoles **3** from Unsubstituted 1,2-Dihaloarenes **2** (continued)



1 **2** **3**

Entry[a]	R	2	3		Yield[b] (%)
6	4-MeO				71
7	3-Me			**3j**	63
8	3-Me				75
9	2-Me			**3k**	56
10	2,4-Me_2			**3l**	66
11	2,4-Me_2				63
12	2-MeO			**3m**	69
13	2-MeO				68
14	2-MeO				64
15	2-F			**3n**	80
16	2-OMe			**3o**	–[c]

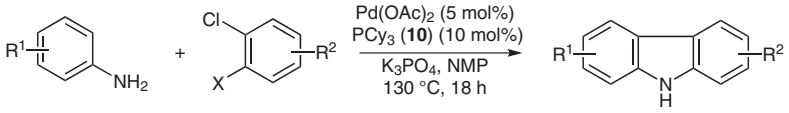
[a] Reaction conditions: **1** (1.2 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (5.0 mol%), PCy_3 (**10**) (10.0 mol%), K_3PO_4 (3.0 mmol), NMP (10.0 mL), 130 °C, 18 h.

[b] Yields of isolated products.

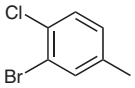
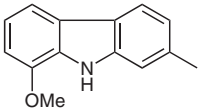
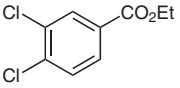
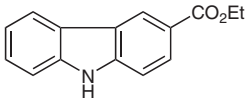
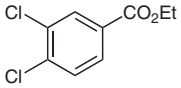
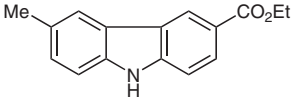
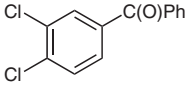
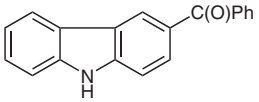
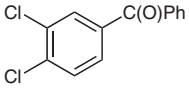
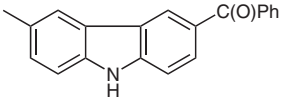
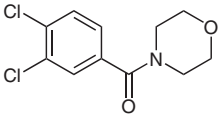
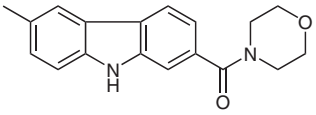
[c] The product of intermolecular amination was formed in 91% yield (GC).

In summary, we report on the development, scope, and limitations of a palladium-catalyzed domino synthesis of annulated heterocycles employing readily available anilines and 1,2-dihalo(hetero)arenes. This strategy involves an intermolecular amination and an intramolecular direct arylation, which proved to be applicable to electrophilic substrates bearing chlorides as the sole leaving groups. The efficiency of the protocol was further highlighted by an economical synthesis of murrayafoline A from inexpensive 1,2-dichlorobenzene.

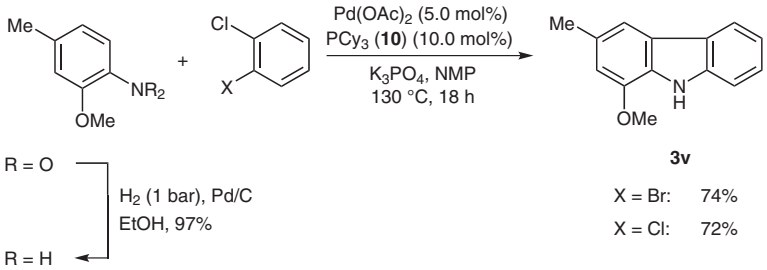
Table 5 Synthesis of N-Unsubstituted Carbazole **3** from Substituted 1,2-Dihaloarenes **2**



1 2 3

Entry[a]	2	3		Yield[b] (%)
1			**3p**	80%
2			**3q**	62%
3			**3r**	57%
4			**3s**	77%
5			**3t**	76%
6			**3u**	71%

[a] Reaction conditions: **1** (1.2 mmol), **2** (1.0 mmol), $Pd(OAc)_2$ (5.0 mol%), PCy_3 (**10**) (10.0 mol%), K_3PO_4 (3.0 mmol), NMP (10.0 mL), 130 °C, 18 h.
[b] Yields of isolated products.



Scheme 2 Efficient synthesis of murrayafoline A (**3v**)

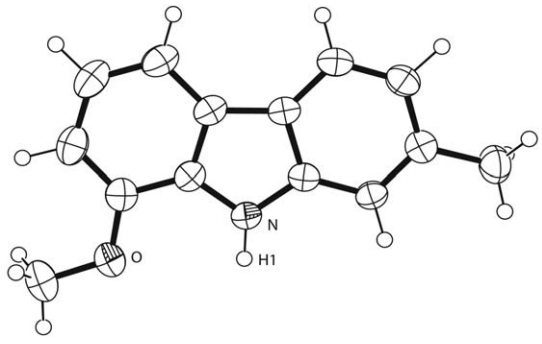


Figure 2 Molecular structure of crystalline carbazole **3p**

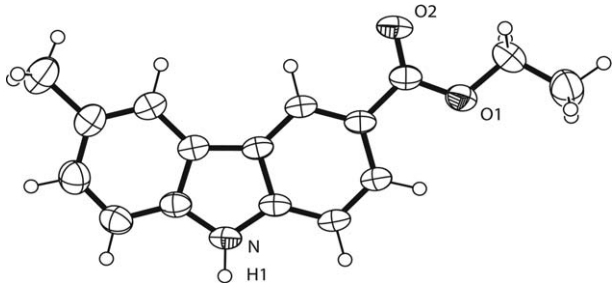


Figure 3 Molecular structure of crystalline carbazole **3r**

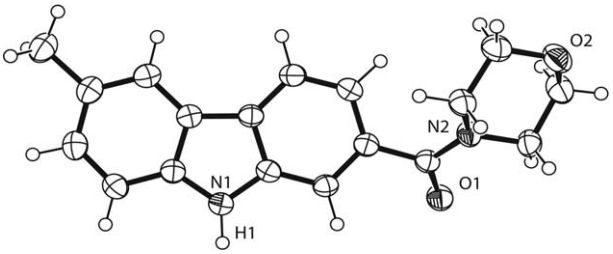


Figure 4 Molecular structure of crystalline carbazole **3u**

All catalytic reactions were carried out on a 1-mmol scale under N_2 in dry glassware. Anilines were purified by column chromatography before use. Dry NMP (H_2O: < 50 ppm) was used as obtained from Acros. Toluene was freshly distilled over Na/benzophenone. Yields refer to isolated compounds, estimated to be > 95% pure as judged by ^1H NMR and GC analyses. Flash chromatography was conducted on Macherey-Nagel silica gel 60 (70–230 mesh). ATR-IR = attenuated total reflection IR. NMR spectra were recorded on a Bruker ARX 300, a Varian VXR 400, or a Varian NMR-system 600 MHz instrument in the solvent indicated; chemical shifts (δ) are given in ppm.

Crystallographic data for compounds **3c**, **3p**, **3r**, and **3u** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publications CCDC 730830, 730832, 730831 and 730829, respectively; copies can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033 or email: deposit@ccdc.cam.ac. uk].

N-Phenylcarbazole (3a); Typical Procedure for the Synthesis of N-Substituted Carbazoles

A soln of $[Pd(OAc)_2]$ (11.2 mg, 0.05 mmol, 5.0 mol%), PCy_3 (**10**; 28.9 mg, 0.10 mmol, 10 mol%), NaO*t*-Bu (288 mg, 3.00 mmol), Ph_2NH (**1a**; 203 mg, 1.20 mmol), and 1,2-dichlorobenzene (147 mg, 1.00 mmol) in dry toluene (10.0 mL) was stirred for 18 h at 105 °C under N_2. Et_2O (25 mL) and H_2O (25 mL) were added to the mixture at r.t., and the separated aqueous phase was extracted with Et_2O (2 × 75 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography (silica gel, pentane) to give a light-yellow solid; yield: 206 mg (85%); mp 91.2–91.6 °C. The spectral data were in accordance with those reported in the literature.[42]

IR (ATR): 3791, 3640, 3035, 1934, 1585, 1491, 1475, 1335, 1232, 1027 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.19–8.17 (m, 2 H), 7.66–7.57 (m, 4 H), 7.52–7.46 (m, 1 H), 7.44–7.41 (m, 4 H), 7.34–7.29 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 140.9, 137.7, 129.8, 127.3, 127.1, 125.9, 123.2, 120.3, 119.9, 109.7.

MS (EI, 70 eV): *m/z* (%) = 243 (100) $[M]^+$, 242 (14), 241 (14), 166 (2), 121 (2).

HRMS (EI): *m/z* calcd for $C_{18}H_{13}N$: 243.1048; found: 243.1022.

5-Phenyl-5*H*-pyrazino[*2,3-b*]indole (3b)

The representative procedure was followed using Ph_2NH (**1a**; 203 mg, 1.20 mmol) and 2,3-dichloropyrazine (156 mg, 1.05 mmol) to give **3b** as a yellow solid; yield: 239 mg (93%); mp 162.7–163.7 °C.

IR (ATR): 2923, 1620, 1594, 1499, 1452, 1405, 1325, 1169, 1103, 746, 693 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.56 (d, *J* = 2.8 Hz, 1 H), 8.43 (md, *J* = 7.9 Hz, 1 H), 8.39 (d, *J* = 2.8 Hz, 1 H), 7.66–7.46 (m, 7 H), 7.43 (dt, *J* = 7.3, 1.6 Hz, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.0, 141.7, 140.1, 137.8, 136.8, 135.2, 130.0, 129.6, 128.3, 127.3, 122.0, 121.9, 120.2, 110.9.

MS (EI, 70 eV): *m/z* (%) = 245 (100) $[M^+]$, 217 (4), 190 (6), 164 (3), 144 (2), 122 (12).

HRMS (EI): *m/z* calcd for $C_{16}H_{11}N_3$: 245.0953; found: 245.0955.

9-Phenyl-2-(trifluoromethyl)-9*H*-pyrido[2,3-*b*]indole (3c)

The representative procedure was followed using Ph_2NH (**1a**; 203 mg, 1.20 mmol) and 2,3-dichloro-5-(trifluoromethyl)pyridine (220 mg, 1.00 mmol) to give **3c** as a light-yellow solid; yield: 289 mg (93%); mp 108.3–109.6 °C.

IR (ATR): 3147, 3059, 2890, 1600, 1501, 1407, 1340, 1266, 1144, 1101 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.75 (m, 1 H), 8.61 (s, 1 H), 8.18–8.16 (m, 1 H), 7.65–7.63 (m, 4 H), 7.55–7.49 (m, 3 H), 7.43–7.38 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.1, 143.6 (q, *J* = 4.1 Hz), 135.5, 129.8, 128.2, 128.0, 128.3 (d, *J* = 272.2 Hz), 127.3, 125.5 (q, *J* = 4.1 Hz), 123.0, 121.6, 121.3, 120.2, 119.1 (d, *J* = 32.1 Hz), 115.7, 110.9.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –60.4.

MS (EI, 70 eV): *m/z* (%) = 312 (84), 311 (100), 293 (8), 242 (18), 156 (15), 146 (11).

HRMS (EI): *m/z* calcd for $C_{18}H_{11}F_3N_2$: 312.0874; found: 312.0886.

4-Phenyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole (3d)

The representative procedure was followed using Ph_2NH (**1a**) (203 mg, 1.20 mmol) and 1,2-dibromocyclopentene (230 mg, 1.00 mmol) to give **3d** as a yellow solid; yield: 175 mg (77%); mp 91.2–92.0 °C. The spectral data were in accordance with those reported in the literature.[43]

IR (ATR): 3043, 2960, 2903, 2848, 1597, 1498, 1446, 1371, 1075, 758 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 7.53–7.50 (m, 3 H), 7.47–7.45 (m, 3 H), 7.36–7.33 (m, 1 H), 7.17–7.12 (m, 2 H), 2.95–2.90 (m, 4 H), 2.57 (quint, *J* = 7.1 Hz, 2 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 145.6, 140.9, 129.4, 129.0, 126.1, 125.0, 124.8, 120.9, 120.4, 120.1, 118.6, 110.8, 28.3, 26.2, 25.6.

MS (EI, 70 eV): *m/z* (%) = 233 (100) $[M]^+$, 232 (72), 218 (11), 217 (11), 128 (3).

HRMS (EI): *m/z* calcd for $C_{17}H_{15}N$: 233.1204; found: 233.1202.

3-Methyl-9*H*-carbazole (3g); Typical Procedure for the Synthesis of N-Unsubstituted Carbazoles

A soln of $[Pd(OAc)_2]$ (11.2 mg, 0.05 mmol, 5.0 mol%), PCy_3 (**10**; 28.9 mg, 0.10 mmol, 10 mol%), finely powdered K_3PO_4 (637 mg, 3.00 mmol), 4-methylaniline (**1b**; 129 mg, 1.20 mmol), and 1,2-dichlorobenzene (147 mg, 1.00 mmol) in dry NMP (10.0 mL) was stirred for 18 h at 130 °C under N_2. Et_2O (25 mL) and H_2O (25 mL) were added to the mixture at r.t., and the separated aqueous phase was extracted with Et_2O (2 × 75 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$), and concentrated in vacuo. The residue was purified by column chromatography [silica gel, pentane–Et_2O (100:1 to 30:1)] to give **3g** as a light brown solid; yield: 140 mg (77%); mp 205.4–207.0 °C. The spectral data were in accordance with those reported in the literature.[44]

IR (ATR): 3853, 3402, 2915, 1826, 1457, 1333, 1239, 1026, 804 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.05 (d, *J* = 8.4 Hz, 1 H), 7.92 (br s, 1 H), 7.88 (s, 1 H), 7.40 (d, *J* = 4.0 Hz, 2 H), 7.32 (d, *J* = 7.9 Hz, 1 H), 7.25–7.21 (m, 2 H), 2.54 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.8, 137.7, 128.7, 127.1, 125.6, 123.5, 123.2, 120.2, 120.2, 119.2, 110.5, 110.2, 21.4.

MS (EI, 70 eV): *m/z* (%) = 181 (100), $[M]^+$, 180 (81), 178 (8), 152 (13), 91 (9), 77 (6).

HRMS (EI): *m/z* calcd for $C_{13}H_{11}N$: 181.0891; found: 181.0886.

9*H*-Carbazole (3h)

The representative procedure was followed using $PhNH_2$ (112 mg, 1.20 mmol) and 1,2-dichlorobenzene (138 mg, 0.94 mmol) to give **3h** as a colorless solid; yield: 127 mg (81%); mp 246.2–246.8 °C. The spectral data were in accordance with those reported in the literature.[44]

IR (ATR): 3414, 3050, 1601, 1450, 1325, 1233, 1068, 746 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (d, *J* = 7.9 Hz, 2 H), 8.06 (br s, 1 H), 7.48 (br s, 1 H), 7.47–7.45 (m, 3 H), 7.33–7.25 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.5, 125.8, 123.4, 120.3, 119.4, 110.6.

MS (EI, 70 eV): *m/z* (%) = 167 (100) $[M]^+$, 91 (23), 65 (4).

HRMS (EI): *m/z* calcd for $C_{12}H_9N$: 167.0735; found: 167.0763.

3-Methoxy-9*H*-carbazole (3i)

The representative procedure was followed using 4-methoxyaniline (148 mg, 1.20 mmol) and 1,2-dichlorobenzene (147 mg, 1.00 mmol) to give **3i** as a blue solid; yield: 140 mg (71%); mp 140 °C (decomp.). The spectral data were in accordance with those reported in the literature.[44]

IR (ATR): 3419, 2932, 1457, 1280, 1198, 1166, 1033, 818, 746 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.06 (d, *J* = 7.9 Hz, 1 H), 7.89 (br s, 1 H), 7.56 (d, *J* = 2.6 Hz, 1 H), 7.41–7.39 (m, 2 H), 7.31 (d, *J* = 8.8 Hz, 1 H), 7.26–7.19 (m, 1 H), 7.08 (dd, *J* = 1.8 Hz, 1 H), 3.94 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 153.9, 140.3, 134.4, 125.8, 123.8, 123.3, 120.2, 119.0, 115.0, 111.3, 110.7, 103.2, 56.1.

MS (EI, 70 eV): *m/z* (%) = 197 (79) $[M]^+$, 182 (100), 154 (32), 127 (10), 69 (2).

HRMS (EI): *m/z* calcd for $C_{13}H_{11}NO$: 197.0841; found: 197.0849.

2-Methyl-9*H*-carbazole (3j)

The representative procedure was followed using 3-methylaniline (129 mg, 1.20 mmol) and 1,2-dichlorobenzene (147 mg, 1.00 mmol) to give **3j** as a colorless solid; yield: 136 mg (75%); mp 230 °C (dec). The spectral data were in accordance with those reported in the literature.[45]

IR (ATR): 3396, 2912, 1605, 1459, 1439, 1325, 1241, 997, 725 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 7.9 Hz, 1 H), 7.95 (d, *J* = 7.9 Hz, 1 H), 7.89 (br s, 1 H), 7.39 (d, *J* = 3.5 Hz, 1 H), 7.27–7.24 (m, 1 H), 7.21 (s, 1 H), 7.20 (m, 1 H), 7.08 (d, *J* = 7.9 Hz, 1 H), 2.54 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.9, 139.5, 136.0, 125.3, 123.4, 121.0, 121.0, 120.0, 120.0, 119.3, 110.7, 110.5, 22.0.

MS (EI, 70 eV): *m/z* (%) = 181 (100), 152 (13), 127 (8), 90 (6), 63 (5).

HRMS (EI): *m/z* calcd for $C_{13}H_{11}N$: 181.0891; found: 181.0873.

1-Methyl-9*H*-carbazole (3k)

The representative procedure was followed using 2-methylaniline (129 mg, 1.20 mmol) and 1-bromo-2-chlorobenzene (200 mg, 1.04 mmol) to give **3k** as a brownish solid; yield: 105 mg (56%); mp 123.5–124.5 °C. The spectral data were in accordance with those reported in the literature.[44]

IR (ATR): 3407, 2970, 1863, 1604, 1450, 1322, 1233, 1117, 749 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.09 (d, *J* = 8.4 Hz, 1 H), 7.97–7.90 (m, 2 H), 7.48–7.45 (m, 1 H), 7.44 (dt, *J* = 7.2, 1.0 Hz, 1 H), 7.28–7.24 (m, 2 H), 7.20–7.17 (m, 1 H), 2.59 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 139.6, 139.1, 126.6, 125.9, 124.1, 123.1, 120.7, 120.0, 119.8, 119.7, 118.2, 110.9, 17.1.

MS (EI, 70 eV): *m/z* (%) = 181 (27) $[M^+]$, 169 (100), 131 (41), 119 (33).

HRMS (EI): *m/z* calcd for $C_{13}H_{11}N$: 181.0891; found: 181.0895.

1,3-Dimethyl-9*H*-carbazole (3l)

The representative procedure was followed using 2,4-dimethylaniline (145 mg, 1.20 mmol) and 1,2-dichlorobenzene (147 mg, 1.00 mmol) to give **3l** as an off-white solid; yield: 123 mg (63%); mp 91.1–91.6 °C. The spectral data were in accordance with those reported in the literature.[46]

IR (ATR): 3750, 3410, 3049, 2963, 2917, 2852, 2732, 1844, 1733, 1495, 1449, 1229, 1012, 743 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.04 (d, *J* = 8.8 Hz, 1 H), 7.86 (br s, 1 H), 7.74 (s, 1 H), 7.45–7.43 (m, 1 H), 7.40 (ddd, *J* = 7.1, 0.8 Hz, 1 H), 7.24–7.21 (m, 1 H), 7.08 (s, 1 H), 2.54 (s, 3 H), 2.52 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 139.7, 137.1, 128.9, 127.9, 124.5, 123.7, 123.0, 120.3, 119.3, 119.2, 117.8, 110.6, 21.4, 16.8.

MS (EI, 70 eV): *m/z* (%) = 195 (100) $[M]^+$, 194 (51), 180 (34), 97 (5), 77 (2).

HRMS (EI): *m/z* calcd for $C_{14}H_{13}N$: 195.1048; found: 195.1045.

1-Methoxy-9*H*-carbazole (3m)

The representative procedure was followed using 2-methoxyaniline (148 mg, 1.20 mmol) and 1,2-dichlorobenzene (150 mg, 1.02 mmol) to give **3m** as a colorless solid; yield: 129 mg (64%); mp 172.6–174.4 °C. The spectral data were in accordance with those reported in the literature.[47]

IR (ATR): 3853, 3412, 3005, 2604, 1889, 1577, 1434, 1254, 1094, 853 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.26 (br s, 1 H), 8.04 (d, *J* = 8.4 Hz, 1 H), 7.70 (d, *J* = 7.9 Hz, 1 H), 7.49–7.40 (m, 2 H), 7.24 (m, 1 H), 7.18 (t, *J* = 7.9 Hz, 1 H), 6.92 (d, *J* = 7.5 Hz, 1 H), 4.03 (s, 3 H).

^{13}C NMR (150 MHz, $CDCl_3$): δ = 145.7, 139.2, 129.8, 125.7, 124.3, 123.7, 120.5, 119.7, 119.4, 112.8, 110.9, 105.9, 55.5.

MS (EI, 70 eV): *m/z* (%) = 197 (100), 182 (69), 166 (9), 154 (46), 139 (9), 127 (6).

HRMS (EI): *m/z* calcd for $C_{13}H_{11}NO$: 197.0841; found: 197.0821.

1-Fluoro-9*H*-carbazole (3n)

The representative procedure was followed using 2-fluoroaniline (133 mg, 1.20 mmol) and 1-bromo-2-chlorobenzene (192 mg, 1.00 mmol) to give **3n** as a colorless solid; yield: 148 mg (80%); mp 164 °C (dec).

IR (ATR): 3394, 1581, 1454, 1391, 1313, 1246, 1149, 1051, 739 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14 (br s, 1 H), 8.06 (d, *J* = 7.9 Hz, 1 H), 7.86–7.98 (m, 1 H), 7.45 (d, *J* = 4.4 Hz, 2 H), 7.27 (dd, *J* = 7.9, 4.4 Hz, 1 H), 7.16–7.12 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 149.1 (q, *J* = 242.7 Hz), 139.5, 127.9, 126.9 (q, *J* = 25.2 Hz), 126.5, 123.2, (q, *J* = 4.2 Hz), 120.6, 120.0, 119.7 (q, *J* = 7.3 Hz), 115.9 (q, *J* = 3.3 Hz), 111.0, 110.8.

^{19}F NMR (282 MHz, $CDCl_3$): δ = –133.3.

MS (EI, 70 eV): *m/z* (%) = 185 (100) $[M]^+$, 164 (21), 158 (13), 92 (7).

HRMS (EI): *m/z* calcd for $C_{12}H_8FN$: 185.0651; found: 185.0638.

1-Methoxy-7-methyl-9*H*-carbazole (3p)

The representative procedure was followed using 2-methoxyaniline (148 mg, 1.20 mmol) and 1-bromo-2-chloro-5-methylbenzene (147 mg, 0.94 mmol) to give **3p** as a colorless solid; yield: 172 mg (80%); mp 172.6–174.4 °C.

IR (ATR): 3401, 2833, 1576, 1504, 1436, 1323, 1241, 1100, 933 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.15 (br s, 1 H), 7.94 (d, *J* = 7.4 Hz, 1 H), 7.65 (d, *J* = 7.4 Hz, 1 H), 7.25 (s, 1 H), 7.15 (t, d, *J* = 8.2 Hz, 1 H), 7.07 (d, *J* = 8.2 Hz, 1 H), 6.89 (d, *J* = 7.4 Hz, 1 H), 4.02 (s, 3 H), 2.54 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.6, 139.6, 135.8, 129.6, 124.4, 121.4, 120.9, 120.2, 119.6, 112.6, 111.0, 105.5, 55.5, 22.0.

MS (EI, 70 eV): *m/z* (%) = 212 (14), 211 (100) $[M]^+$, 197 (10), 196 (68), 168 (53), 167 (15), 138 (5), 83 (8).

HRMS (EI): *m/z* calcd for $C_{14}H_{13}NO$: 211.0997; found: 211.0984.

Ethyl 9*H*-Carbazole-3-carboxylate (3q)

The representative procedure was followed using $PhNH_2$ (112 mg, 1.20 mmol) and ethyl 3,4-dichlorobenzoate[40] (219 mg, 1.00 mmol) to give **3q** as a colorless solid; yield: 148 mg (62%); mp 162.1–163.0 °C. The spectral data were in accordance with those reported in the literature.[48]

IR (ATR): 3287, 2979, 1681, 1599, 1364, 1334, 1263, 1100, 1032, 910, 724 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.78 (s, 1 H), 8.39 (br s, 1 H), 8.13–8.05 (m, 2 H), 7.43–7.31 (m, 3 H), 7.27–7.21 (m, 1 H), 4.42 (q, *J* = 7.1 Hz, 2 H), 1.41 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 194.1, 167.5, 142.3, 139.9, 127.4, 126.5, 123.2, 122.8, 121.7, 120.6, 120.2, 111.0, 110.2, 60.7, 14.5.

MS (EI, 70 eV): *m/z* (%) = 239 (91) $[M]^+$, 224 (13), 211 (27), 194 (100), 166 (44), 139 (22).

HRMS (EI): *m/z* calcd for $C_{15}H_{13}NO_2$: 239.0946; found: 239.0933.

Ethyl 6-Methyl-9*H*-carbazole-3-carboxylate (3r)

The representative procedure was followed using 4-methylaniline (219 mg, 1.20 mmol) and ethyl 3,4-dichlorobenzoate[40] (219 mg, 1.00 mmol) to give **3r** as an orange solid; yield: 136 mg (57%); mp 166.8–168.9 °C.

IR (ATR): 3302, 2979, 1680, 1606, 1365, 1289, 1260, 1136, 1021 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.73 (m, 1 H), 8.26 (br s, 1 H), 8.08–8.05 (m, 1 H), 7.86 (s, 1 H), 7.34–7.29 (m, 1 H), 7.28–7.19 (m, 2 H), 4.39 (q, *J* = 7.1 Hz, 2 H), 2.48 (s, 3 H), 1.40 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 167.5, 142.5, 138.1, 129.7, 127.8, 127.2, 123.5, 122.9, 122.7, 121.4, 120.5, 110.5, 110.0, 60.7, 21.4, 14.5.

MS (EI, 70 eV): *m/z* (%) = 253 (100) $[M]^+$, 238 (10), 225 (45), 208 (90), 180 (81), 164 (3), 152 (23), 103 (7).

HRMS (EI): *m/z* calcd for $C_{16}H_{15}NO_2$: 253.1103; found: 253.1123.

9*H*-Carbazol-3-yl(phenyl)methanone (3s)

The representative procedure was followed using $PhNH_2$ (112 mg, 1.20 mmol) and 3,4-dichlorobenzophenone[40] (251 mg, 1.00 mmol) to give **3s** as a yellow solid; yield: 209 mg (77%); mp 162.1–163.0 °C. The spectral data were in accordance with those reported in the literature.[49]

IR (ATR): 3238, 3060, 1566, 1409, 1327, 1268, 1234, 1069, 1015, 783 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.59 (d, *J* = 1.6 Hz, 1 H), 8.43 (br s, 1 H), 8.08 (d, *J* = 7.3 Hz, 1 H), 8.01–7.97 (m, 1 H), 7.87 (m, 1 H), 7.85–7.84 (m, 1 H), 7.61 (ddd, *J* = 7.3, 2.4 Hz, 1 H), 7.55–7.46 (m, 5 H), 7.31–7.27 (m, 1 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.7, 138.9, 131.7, 129.9, 129.2, 128.6, 128.2, 126.6, 123.9, 123.4, 123.0, 120.7, 120.4, 111.0, 110.2.

MS (EI, 70 eV): *m/z* (%) = 271 (100) $[M]^+$, 242 (11), 194 (83), 166 (56), 139 (41), 121 (13).

HRMS (EI): *m/z* calcd for $C_{19}H_{13}NO$: 271.0997; found: 271.0994.

(6-Methyl-9*H*-carbazol-3-yl)(phenyl)methanone (3t)

The representative procedure was followed using 4-methylaniline (129 mg, 1.20 mmol) and 3,4-dichlorobenzophenone[40] (251 mg, 1.00 mmol) to give **3t** as a yellow solid; yield: 218 mg (76%); mp 217.4–219.6 °C. The spectral data were in accordance with those reported in the literature.[49]

IR (ATR): 3254, 1642, 1567, 1442, 1312, 1290, 1276, 1169, 1078, 807 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.51 (s, 1 H), 8.29 (br s, 1 H), 7.94 (d, *J* = 8.6 Hz, 1 H), 7.86–7.79 (m, 3 H), 7.59–7.21 (m, 6 H), 2.48 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 196.7, 142.5, 139.0, 138.2, 131.7, 129.9, 129.0, 128.8, 128.4, 128.2, 128.0, 124.0, 123.6, 122.8, 120.6, 110.6, 110.2, 21.4.

MS (EI, 70 eV): *m/z* (%) = 285 (85) $[M]^+$, 208 (100), 180 (45), 152 (17), 105 (7), 77 (9).

HRMS (EI): *m/z* calcd for $C_{20}H_{15}NO$: 285.1154; found: 285.1167.

(6-Methyl-9*H*-carbazol-3-yl)(morpholin-4-yl)methanone (3u)

The representative procedure was followed using 4-methylaniline (129 mg, 1.20 mmol) and (3,4-dichlorophenyl)(morpholin-4-yl)methanone[40] (260 mg, 0.94 mmol) to give **3u** as a colorless solid; yield: 209 mg (71%); mp 261.8–263.2 °C.

IR (ATR): 3157, 2985, 2916, 2850, 1599, 1579, 1452, 1435, 1359, 1271, 1109, 805 cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 11.3 (s, 1 H), 8.10 (d, *J* = 8.2 Hz, 1 H), 7.94 (m, 1 H), 7.48–7.47 (m, 1 H), 7.41 (d, *J* = 8.2 Hz, 1 H), 7.26–7.23 (m, 1 H), 7.15 (dd, *J* = 8.2, 1.6 Hz, 1 H), 3.62 (m, 8 H), 3.35 (s, 3 H).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 169.8, 139.2, 138.6, 132.2, 127.5, 127.4, 123.0, 121.9, 120.1, 119.8, 117.2, 110.8, 109.8, 66.1, 66.1, 21.0.

MS (EI, 70 eV): *m/z* (%) = 294 (38) $[M]^+$, 208 (100), 180 (35), 152 (13), 77 (6).

HRMS (EI): *m/z* calcd for $C_{18}H_{18}N_2O_2$: 294.1368; found: 294.1350.

Murrayafoline A (3v; 1-Methoxy-3-methyl-9*H*-carbazole)

The representative procedure was followed using 2-methoxy-4-methylaniline (165 mg, 1.20 mmol) and 1,2-dichlorobenzene

(147 mg, 1.00 mmol) to give **3v** as an off-white solid; yield: 152 mg (72%); mp 52.3–53.1 °C. The spectral data were in accordance with those reported in the literature.[42]

IR (ATR): 3414, 3054, 2917, 1587, 1503, 1449, 1303, 1228, 1104, 825 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.20 (br, s, 1 H), 8.08 (d, *J* = 7.7 Hz, 1 H), 7.54 (s, 1 H), 7.48–7.23 (m, 3 H), 6.79 (s, 1 H), 4.04 (s, 3 H), 2.60 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 145.3, 139.4, 129.4, 127.9, 125.4, 124.3, 123.5, 120.4, 119.1, 112.5, 110.9, 107.6, 55.4, 21.9.

MS (EI, 70 eV): *m/z* (%) = 211 (100) $[M]^+$, 196 (77), 168 (42), 166 (29), 139 (5), 105 (7).

HRMS (EI): *m/z* calcd for $C_{14}H_{13}NO$: 211.0997; found: 211.0975.

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