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Improved indole syntheses from anilines and vicinal diols by cooperative catalysis of ruthenium complex and acid†

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By developing a new and efficient dinuclear catalyst $[Ru(CO)_2(Xantphos)]_2$ [Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethyl-9*H*-xanthene], an improved synthesis of indole from vicinal diols and anilines by cooperative catalysis of ruthenium complex and *p*-TSA (*para*-toluenesufonic acid) has been demonstrated. The presented synthetic protocol allows assembling a wide range of products in an efficient manner. Comparing to the existed protocols, our indole syntheses can be achieved at lower reaction temperature, in shorter reaction time, and with improved substrate tolerance.

Introduction

The development of efficiently catalytic system to convert abundant feedstocks into valuable products under milder conditions is of significant importance in modern synthetic chemistry.[1] The advantages of such a goal are generally associated with lower reaction temperature, faster reaction rate, broader substrate scope, and improved selectivity.

Indole derivatives constitute a significant important class of heterocycles distributing in natural and synthetic products. Among numerous structurally diverse indoles, many of them possess interestingly biological activity.[2] Hence, the indole skeleton is found to be a frequently occurring structural unit in many marketing drugs.[3] Additionally, indoles serve as versatile intermediates for the preparation of dyes[4] and functionalized materials.[5] Owing to these interesting functions, great efforts have been contributed to the synthesis of various types of indoles in the past more than one century. Apart from the classical name reactions such as the Fischer,[6a] Madelung,[6b] Bischler,[6c] Nenitzescu[6d] and other syntheses,[6e] the recently developed methodologies including the inter-[7] and intra-molecular[8] cyclization processes have also showed elegant pathways to the related end. Nevertheless, many of these syntheses require pre-functionalized or unreadily available starting materials. In some cases, halogen waste-generating reagents are essential for the cyclization processes. From the viewpoint of atom economy and environmental concerns, the development of atom-economic and direct methods for indole syntheses still remains a demanding goal.

It is noteworthy that the transition-metal catalyzed direct transformation of vicinal diols and anilines into indole derivatives has provided an alternative pathway for elaboration of various indoles. Interestingly, such a reaction releases only two molecules of water and one molecule of hydrogen. And the synthesis has the merits of environmental compatibility, high atom-efficiency, cheap and easily accessible starting materials, so it is of potential value in industrial application. The early examples were achieved by using $RuCl_2(PPh_3)_3$ catalyst at 180 °C[9] and $IrCl_3{\cdot}3H_2O$/BINAP catalyst system at 169 °C[10] in the presence of excessive amount of anilines. Alternatively, aminoalcohols were also proved to be suitable coupling partners for accessing the related goal at 180 °C.[11] However, such a synthetic protocol requires a key pre-treatment to convert aminoalcohols into their salts. Moreover, an additional stoichiometric amount of $SnCl_2{\cdot}2H_2O$ is essential for the electrophilic ring-closure. More recently, the group of Madsen has described an elegant synthesis of 2,3-disubstituted indoles from anilines and 1,2-diols in the presence of catalytic amounts of $[Cp^*IrCl_2]_2$/MsOH (MsOH = methanesulfonic acid) or $RuCl_3$/phosphine (phosphine = PPh_3 or Xantphos) at 170 °C.[12] However, all these reported protocols were performed at high temperature (>169 °C), and some of them require either long reaction time (1–2 days) or excessive use of reagents. Problematically, high temperature intolerant substrates could lead to low product yields or failure of product formation.

Drawing from the useful functions of indole derivatives and our continuous research interests in developing ruthenium-catalyzed heterocycle syntheses,[13] we were interested in exploring an efficient ruthenium catalytic system for indole

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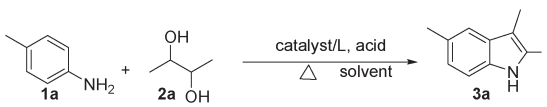
syntheses from vicinal diols and anilines. Our goal is aimed at lowering the reaction temperature, shortening the reaction time, obtaining improved substrate compatibility as well. Herein, we wish to report an improved indole synthesis by cooperative catalysis of $[Ru(CO)_2(Xantphos)]_2$ and *para*-toluenesufonic acid (*p*-TSA). To the best of our knowledge, the direct use of such a catalyst for indole syntheses from anilines and vicinal diols has not been reported yet.

Results and discussion

In order to develop an efficient catalytic system, the synthesis of 2,3,5-trimethyl-1*H*-indole **3a** from *p*-toluidine **1a** and butane-2,3-diol **2a** was chosen as a model reaction to evaluate the influence of different catalysts, solvents, temperatures on the reaction efficiency. Drawing from the combinations of diphosphine ligands with ruthenium catalyst precursors leading to active catalytic systems for alcohol activation,[14] we initiated our investigations by testing various ruthenium catalysts in combination with Xantphos (**L1**) for the formation of product **3a** (Table 1, entries 1–6). By performing the reactions at 120 °C for 24 h using *t*-amyl alcohol as the reaction solvent and *para*-toluenesufonic acid as the co-catalyst, $Ru_3(CO)_{12}$ gave a best result in 80% yield (Table 1, entry 6). Under the same reaction conditions employed, several other diphosphine ligands gave lower product yields (Table 1, entries 7–11). The use of $Ru_3(CO)_{12}$ catalyst in the absence of Xantphos or *p*-TSA gave only trace amount product (Table 1, entries 12–13), indicating that Xantphos and *p*-TSA are crucial factors for forming an efficient catalytic system. Further investigations showed that other acids such as sulfamic acid and methanesulfonic acid were not as efficient as *p*-TSA (Table 1, entries 14–15). Decreasing the reaction temperature from 120 °C to 115 or 110 °C led to decreased product yields (Table 1, entries 16–17). However, an increase of reaction temperature to 130 °C did not improve the product yield significantly (Table 1, entry 18).

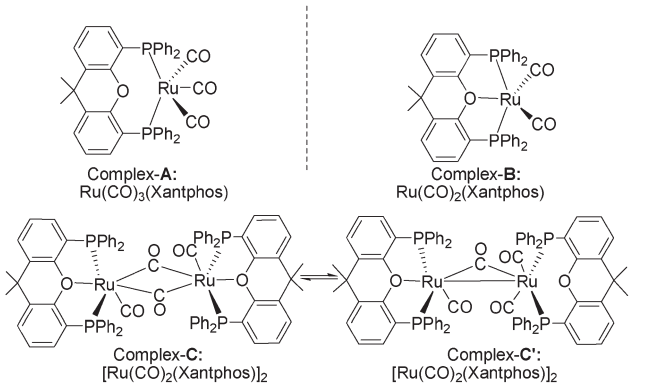
Inspired by the best yield obtained (Table 1, entry 6), we wish to obtain the active ruthenium catalyst precursor from $Ru_3(CO)_{12}$ and Xantphos. Considering Xantphos is a wide bite angle diphosphine that can act as a bidentate or tridentate bound ligand,[15] and the P?P and P?O?P coordination complexes might be isolated by partial dissociation of CO ligand from $Ru_3(CO)_{12}$ (Scheme 1, see complex-**A** and complex-**B**). In order to test these speculations, the mixture of equimolar $Ru_3(CO)_{12}$ and Xantphos in *t*-amyl alcohol was stirred at 120 °C for 24 h, an orange solid product was obtained in high yield after purification. However, it was found that the product is difficult to characterize by means of X-ray diffraction or NMR analysis owing to the existence of equilibrium of the isomers. Gratifyingly, the high resolution mass spectroscopy clearly indicates its formula is two times of complex-**B** and the elemental analysis shows it has high purity. On the basis of the early contributions on CO-bridged ruthenium complexes,[16] two possible dinuclear structures were proposed in Scheme 1 (see complex-**C** and complex-**C**′). Subsequently, this dinuclear product was directly employed as a catalyst for the model reaction without introduction of additional ligand. Interestingly, an improved product yield was obtained in only 16 h (Table 1, entry 19). However, changing *t*-amyl alcohol to other polar or less polar solvent led to lower

Table 1 Optimization of reaction conditions[a]



Entry	Ru cat./ligand/solvent	Acid	Yield% of **3a**[b]
1	$RuCl_3$/**L1**/*t*-amyl alcohol	*p*-TSA	<5
2	$RuCl_2(PPh_3)_3$/**L1**/*t*-amyl alcohol	*p*-TSA	<5
3	$RuHCl(CO)(PPh_3)_3$/**L1**/*t*-amyl alcohol	*p*-TSA	31
4	$[RuCl_2(p\text{-Cymene})]_2$/**L1**/*t*-amyl alcohol	*p*-TSA	76
5	Cp*RuCl(COD)/**L1**/*t*-amyl alcohol	*p*-TSA	<10
6	$Ru_3(CO)_{12}$/**L1**/*t*-amyl alcohol	*p*-TSA	80
7	$Ru_3(CO)_{12}$/**L2**/*t*-amyl alcohol	*p*-TSA	25
8	$Ru_3(CO)_{12}$/**L3**/*t*-amyl alcohol	*p*-TSA	<5
9	$Ru_3(CO)_{12}$/**L4**/*t*-amyl alcohol	*p*-TSA	12
10	$Ru_3(CO)_{12}$/**L5**/*t*-amyl alcohol	*p*-TSA	<5
11	$Ru_3(CO)_{12}$/**L6**/*t*-amyl alcohol	*p*-TSA	42
12	$Ru_3(CO)_{12}$/—/*t*-amyl alcohol	*p*-TSA	<10
13	$Ru_3(CO)_{12}$/**L1**/*t*-amyl alcohol	—	Trace
14	$Ru_3(CO)_{12}$/**L1**/*t*-amyl alcohol	NH_2SO_3H	12
15	$Ru_3(CO)_{12}$/**L1**/*t*-amyl alcohol	$MeSO_3H$	20
16[c]	$Ru_3(CO)_{12}$/**L1**/*t*-amyl alcohol	*p*-TSA	<5
17[d]	$Ru_3(CO)_{12}$/**L1**/*t*-amyl alcohol	*p*-TSA	53
18[e]	$Ru_3(CO)_{12}$/**L1**/*t*-amyl alcohol	*p*-TSA	81
19[f]	$[Ru(CO)_2(Xantphos)]_2$/*t*-amyl alcohol	*p*-TSA	88
20[f]	$[Ru(CO)_2(Xantphos)]_2$/diglyme	*p*-TSA	22
21[f]	$[Ru(CO)_2(Xantphos)]_2$/toluene	*p*-TSA	<1
22[f]	$[Ru(CO)_2(Xantphos)]_2$/DMSO	*p*-TSA	<10

[a] Reaction conditions: Unless otherwise specified, all reactions were carried out without inert gas protection by using **1a** (1.2 mmol), **2a** (1 mmol), catalyst (mono-nuclear one: 0.02 mmol; di-nuclear one: 0.01 mmol; tri-nuclear one: 0.0067 mmol), ligand (0.02 mmol), acid (0.1 mmol), solvent (1 mL), temperature (120 °C), reaction time (24 h). [b] GC yield using hexadecane as a internal standard. [c] Reaction temperature: 110 °C. [d] Reaction temperature: 115 °C. [e] Reaction temperature: 130 °C. [f] Reaction time: 16 h.



Scheme 1 Possible coordination modes of Xantphos with $Ru_3(CO)_{12}$.

product yields (Table 1, entries 20–22). Thus, the optimal reaction conditions are summarized as follows: 1 mol% of $[Ru(CO)_2(Xantphos)]_2$, 5 mol% of *p*-TSA in *t*-amyl alcohol, and at 120 °C for 16 h (Table 1, see entry 19).

With the optimal reaction conditions in hand, we then examined the generality and limitations of our synthetic protocol. Firstly, we tested the indole syntheses by using various anilines and symmetrically vicinal diols. As shown in Table 2, all the reactions proceeded smoothly and furnished desired products in moderate to excellent isolated yields (Table 2, entries 1–12). It was found that the substituents on the aryl ring of anilines have significant influence in the formation of products. Comparing to weak electron-withdrawing group (*i.e.* –Cl, entry 11), anilines having electron-donating ones (*i.e.* –OMe and –Me) gave the products in relatively higher yields (Table 2, entries 1–3 and 7–9). Notably, aniline bearing a strong electron-withdrawing group (*i.e.* $-NO_2$ or $-CF_3$) failed to yield the expected products, which is rationalized as the nucleophilicity of the aryl ring is insufficient to complete the electrophilic ring-closure. Clearly, these results are well consistent with the mechanism proposed in the previous literatures.[9–12] Among different anisidines employed (Table 2, entry 2–4 and 8), the *ortho*-substituted one gave the product in relatively lower yield, which is associated with the effect of steric hindrance (Table 2, entry 4). Unsymmetrical aniline *m*-anisidine **1c** was examined to investigate the regioselectivity of the reaction (Table 2, entry 3), which could lead to two possible regioisomers. However, the results showed that only one regioisomer was observed. 2,3,6-trisubstituted indole **3c** was obtained in 81% yield upon isolation, and the cyclization step only occurs at sterically less hindered position of aniline. Thus, the steric effect is considered as a major contributor to site the reaction regioselectivity. Interestingly, the reactions using cyclohexane-1,2-diol **2b** resulted in tetrahydrocarbazoles **3g–3k**, respectively. These examples demonstrate the extended potential of our synthetic protocol for the construction of various annulated heterocyclic compounds. Notably, simple but high temperature intolerant ethylene glycol **2c** in combination with alkyl-substituted aniline **1i** could also be applied to construct 2,3-nonsubstituted indole **3l** (Table 2, entry 12). However, the reaction using aniline **1e** and **2c** failed to afford non-substituted product **3m** (Table 2, entry 13). Complementarily, this goal can be achieved by replacing **2c** with triethanolammonium **2d** in the presence of one equivalent of *p*-TSA (Table 2, entry 14).

Drawing from the contributions of the group of Madsen and others,[9–12] the indole syntheses using mono-substituted vicinal diols gave either low product yields or failure of product formation due to the instability of substrates at high temperature. We thought that this presented problem might be solved under milder conditions. Herein, we were interested in exploring our synthetic protocol to tested several representative unsymmetrical vicinal diols for the formation of indoles. Clearly, two regioisomeric products (**4** and **4′**) can result from these reactions, which would obviously lower the synthetic usefulness of the protocol. However, in all cases studied, 1-phenylethane-1,2-diol **2d** and 1-phenylpropane-1,2-diol **2e** were well tolerated to afford 2-aryl substituted products exclusively in moderate to good yields (Table 3, entries 1–5 and 7). It indicates that the bulky groups in vicinal diols are mainly introduced into position-2 of the indole skeleton. Notably, propane-1,2-diol **2f** was also efficiently transformed into the corresponding products with high regioselectivity (entry 6 : 11 : 3), it is a significant improvement over the early reported example.[9a]

Conclusions

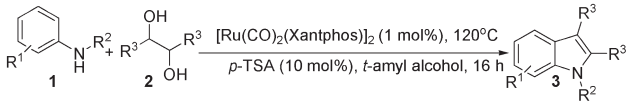
We have developed an improved synthesis of indole derivatives from anilines and vicinal diols by cooperative catalysis of $[Ru(CO)_2(Xantphos)]_2$ and *p*-TSA. The cyclocondensation process proceeded smoothly and furnished the products in an efficient manner. Comparing to the previously reported systems, the formation of indole products with our synthetic protocol could be achieved at lower reaction temperature and in shorter reaction time. Moreover, some high temperature intolerant substrates could also be transformed the corresponding products. Interestingly, the reactions using unsymmetrical anilines or vicinal diols could afford the products regioselectively. Considering various advantages of this protocol, we are convinced that it is of practical value for the preparation of various indoles since different sites in the indole skeleton can be varied, which is important for applications in biological, organic and material chemistry.

Experimental

General information

All the reactions for indole syntheses were carried out without inert gas protection. Chemicals were purchased from Aldrich, Acros and Strem and unless otherwise noted were used without further purification. Liquid amines and diols were distilled under argon. Except easily and commercially available product **3m** and **4f**, all other compounds were characterized by ^1H NMR, ^{13}C NMR, MS, HRMS spectroscopy and mp (melting points for solid products). ^1H and ^{13}C NMR spectra were recorded on Bruker AV 300. The ^1H and ^{13}C NMR chemical shifts are reported relative to the center of solvent resonance [$CDCl_3$: 7.18 (^1H), 77.0 (^{13}C)]. EI mass spectra were recorded on an MAT 95XP spectrometer (70 eV, Thermo ELECTRON CORPORATION). ESI high resolution mass spectra were recorded on an Agilent Technologies 6210 TOF LC/MS using H_2O + 0.1% formic acid (10%) and methanol (90%) as eluent. Melting points were recorded on a Galen-3 micromelting point apparatus and uncorrected.

Table 2 Selective synthesis of indoles using symmetrically vicinal diols[a]



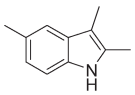
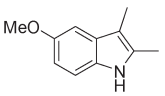
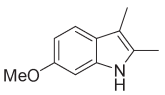
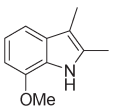
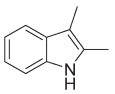
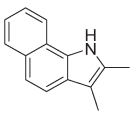
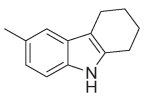
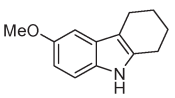
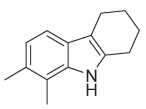
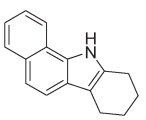
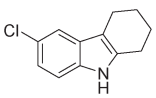
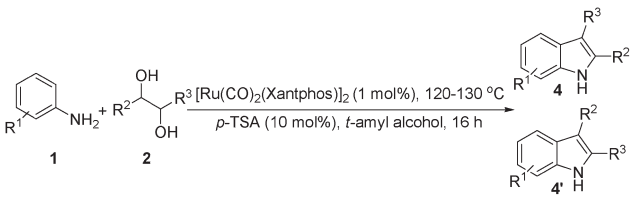
Entry	Aniline **1**	Diol **2**	Product	**3**, Yield%[b]
1	**1a:** R^1 = 4-Me; R^2 = H	 **, 2a**		**3a,** 79
2	**1b**: R^1 = 4-OMe; R^2 = H	**2a**		**3b,** 82
3	**1c:** R^1 = 3-OMe; R^2 = H	**2a**		**3c,** 81
4	**1d:** R^1 = 2-OMe; R^2 = H	**2a**		**3d,** 65
5	**1e:** R^1 = H; R^2 = H	**2a**		**3e,** 66
6	**1f:** 	**2a**		**3f,** 73
7	**1a:**	 **, 2b**		**3g,** 75
8	**1b**:	**2b**		**3h,** 73
9	**1g,** R^1 = 2,3-2Me; R^2 = H	**2b**		**3i,** 74
10	**1f:**	**2b**		**3j,** 66
11	**1h:** R^1 = 4-Cl; R^2 = H	**2b**		**3k,** 53
12	**1i:** R^1 = H; R^2 = Me	**2c,** 		**3l,** 53
13	**1e**	**2c,** 		**3m,** —

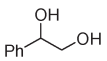
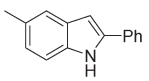
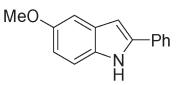
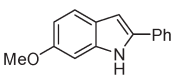
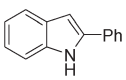
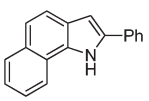
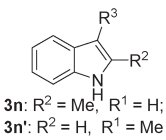
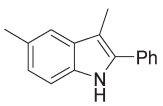
Table 2 (*Continued*)

Entry	Aniline **1**	Diol **2**	Product	**3**, Yield%[b]
14	**1e**	**2d** 		**3m**, 42[c]

[a] Reaction conditions: Unless otherwise specified, all reactions were carried out without inert gas protection by using aniline **1** (1.2 mmol), diol **2** (1 mmol), catalyst (0.01 mmol, 11.5 mg), *p*-TSA (0.1 mmol, 19 mg), solvent (1 mL), temperature: 120 °C, reaction time: 15 h. [b] Isolated yield. [c] *p*-TSA: 1 mmol; temperature: 130 °C.

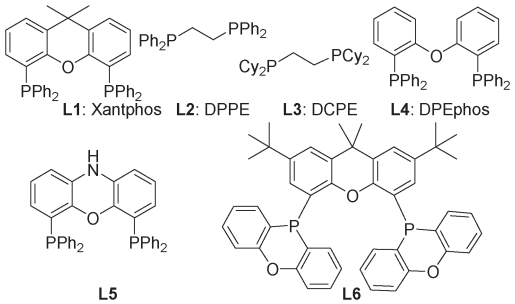
Table 3 Selective synthesis of indoles using unsymmetrically vicinal diols[a]



Entry	Aniline **1**	Diol **2**	Product	**4**, Yield% [b]
1	**1a**	 , **2d**		**4a**, 72
2	**1b**:	**2d**		**4b**, 75
3	**1c**	**2d**		**4c**, 71
4	**1e**	**2d**		**4d**, 68
5 [c]	**1f**	**2d**		**4e**, 46
6	**1e**	**2f**:R^2 = Me; R^3 = H	 **3n**: R^2 = Me, R^1 = H; **3n'**: R^2 = H, R^1 = Me	(**4f** : **4f'** = 11 : 3), 62[d]
7	**1a**	**2e**:R^2 = Ph; R^3 = Me		**4g**, 61

[a] Reaction conditions: Unless otherwise specified, all reactions were carried out without inert gas protection by using aniline **1** (1.2 mmol), diol **2** (1 mmol), catalyst (0.01 mmol, 9.5 mg), *p*-TSA (0,1 mmol, 19 mg), solvent (1 mL), temperature: 120 °C, reaction time: 15 h. [b] Isolated yield; By means of GC and GC-MS analysis, the product configuration was identified by comparing the retention time of product with the one of known compound. [c] Reaction temperature: 130 °C. [d] Total yield of two isomers, the ratio is determined by GC analysis.

Diphosphine ligands employed for optimization of reaction conditions



Preparation of $[Ru(CO)_2(Xantphos)]_2$

Under argon atmosphere, the mixture of $Ru_3(CO)_{12}$ (0.2 mmol, 128.0 mg), Xantphos (0.6 mol, 347 mg) in *t*-amyl alcohol (5 mL) was stirred in a Schlenk tube (25 mL) at 120 °C for 24 h, the color of the reaction mixture changed from brown to orange-red gradually. At the end of the reaction the orange precipitate appeared, it was collected by suction filtration. The crude product was then purified by flash chromatography eluting with hexane : dichloromethane (25 : 1) to give an orange and air-stable solid product (342 mg, 72%) after removing the eluting solvents. HRMS (ESI): Calcd. for $C_{82}H_{64}O_6P_4Ru_2$ $[M]^+$: 1472.17; found: 1472.17735. Elemental analysis: Calcd. for $C_{82}H_{64}O_6P_4Ru_2$: C, 66.93; H, 4.38; O, 6.52. Found: C, 67.08; H, 4.47; O, 6.32.

Typical procedure for the preparation of 3a

In a glass pressure tube (25 mL) equipped with a magnetic stirrer bar, $[Ru(CO)_2(Xantphos)]_2$ (0.01 mmol, 14.7 mg), *p*-TSA·H_2O (0.1 mmol, 19 mg), *p*-toluidine **1a** (1.2 mmol, 128.4 mg), butane-2,3-diol **2a** (1 mmol, 90 mg) and *t*-amyl alcohol (1 mL) were introduced successively. The pressure tube was closed with a Teflon cap and the resulting mixture was stirred at 120 °C for 16 h without inert gas protection. After cooling down to room temperature, the reaction solvent was removed under vacuum. The residue was directly purified by flash chromatography on silica gel eluting with heptane : ethyl acetate (25 : 1) to give 2,3,5-trimethyl-1*H*-indole **3a** as a white solid (126 mg, 79%).

Analytic data of obtained compounds

2,3,5-Trimethyl-1*H*-indole (3a). White solid, mp 118–120 °C (lit.[12] 115–120 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.48 (br, 1H), 7.17–7.18 (m, 1H), 7.06 (d, J = 8.1 Hz, 1H), 6.83–6.87 (m, 1H), 2.37 (s, 3H), 2.26 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 133.5, 130.8, 129.7, 128.2, 122.4, 117.8, 109.7, 106.7, 21.5, 11.6, 8.5; MS (EI, *m*/*z*): 159 $[M]^+$; HRMS (ESI): Calcd. for $C_{11}H_{14}N$ $[M+H]^+$: 160.11262; found: 160.11173.

5-Methoxy-2,3-dimethyl-1*H*-indole (3b). Yellow solid, mp 109–112 °C (lit.[12] 105–108 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.50 (br, 1H), 7.07 (d, J = 8.7 Hz, 1H), 6.85 (d, J = 2.4 Hz, 1H), 6.68 (dd, J = 2.4 Hz, 1H), 3.79 (s, 3H), 2.27 (s, 3H), 2.12 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.8, 131.7, 130.3, 129.8, 110.7, 110.5, 107.0, 100.4, 56.0, 11.7, 8.5; MS (EI, *m*/*z*): 175 $[M]^+$; HRMS (ESI): Calcd. for $C_{11}H_{14}NO$ $[M+H]^+$: 176.10753; found: 176.10723.

6-Methoxy-2,3-dimethyl-1*H*-indole (3c). White solid, mp 128–130 °C (lit.[12] 129–132 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (br, 1H), 7.24 (d, J = 9.0 Hz, 1H), 6.62–6.69 (m, 2H), 3.74 (s, 3H), 2.30 (s, 3H), 2.10 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.8, 135.9, 129.4, 124.0, 118.5, 108.3, 106.8, 94.5, 55.8, 11.5, 8.6; MS (EI, *m*/*z*): 175 $[M]^+$; HRMS (ESI): Calcd. for $C_{11}H_{14}NO$ $[M+H]^+$: 176.10753; found: 176.10723.

7-Methoxy-2,3-dimethyl-1*H*-indole (3d). Light yellow oil (lit.[12]); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.82 (br, 1H), 7.00 (d, J = 8.1 Hz, 1H), 6.91 (t, J = 7.8 Hz, 1H), 6.51 (d, J = 7.8 Hz, 1H), 3.86 (s, 3H), 2.27 (s, 3H), 2.13 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 145.4, 130.7, 130.3, 125.3, 119.3, 111.0, 107.6, 101.3, 55.3, 11.5, 8.7; MS (EI, *m*/*z*): 175 $[M]^+$; HRMS (ESI): Calcd. for $C_{11}H_{14}NO$ $[M+H]^+$: 176.10753; found: 176.10702.

2,3-Dimethyl-1*H*-indole (3e). White solid, mp 105–108 °C (lit.[17a] 106–107 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.59 (br, 1H), 7.37–7.41 (m, 1H), 7.16–7.19 (m, 1H), 6.97–7.06 (m, 2H), 2.20 (s, 3H), 2.16 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.2, 130.7, 129.5, 120.9, 119.0, 118.0, 110.0, 11.6, 8.5; MS (EI, *m*/*z*): 145 $[M]^+$; HRMS (ESI): Calcd. for $C_{10}H_{12}N$ $[M+H]^+$: 146.09697; found: 146.09667.

2,3-Dimethyl-1*H*-benzo[*g*]indole (3f). White solid, mp 149–151 °C (lit.[12] 149 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.33 (br, 1H), 7.83 (t, J = 8.1 Hz, 2H), 7.52 (d, J = 8.7 Hz, 1H), 7.37–7.42 (m, 2H), 7.25–7.31 (m, 1H), 2.38 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 130.0, 129.2, 128.9, 128.8, 125.1, 124.9, 123.1, 121.3, 119.8, 119.1, 118.7, 109.0, 11.7, 8.6; MS (EI, *m*/*z*): 195 $[M]^+$; HRMS (ESI): Calcd. for $C_{14}H_{14}N$ $[M+H]^+$: 196.11262; found: 196.11172.

3-Methyl-6,7,8,9-tetrahydro-5*H*-carbazole (3g). Light yellow solid, mp 137–138 °C (lit.[17b] 138–140 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37 (br, 1H), 7.15–7.16 (m, 1H), 7.02 (d, J = 8.1 Hz, 1H), 6.84 (dd, J = 1.2 Hz, 1H), 2.54–2.61 (m, 4H), 2.35 (s, 3H), 1.74–1.81 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.3, 134.0, 128.3, 128.1, 122.4, 117.6, 110.1, 109.7, 23.4, 23.3, 21.6, 21.0; MS (EI, *m*/*z*): 185 $[M]^+$; HRMS (ESI): Calcd. for $C_{13}H_{16}N$ $[M+H]^+$: 186.12827; found: 186.12750.

3-Methoxy-6,7,8,9-tetrahydro-5*H*-carbazole (3h). White solid, mp 108–109 °C (lit.[17c] 107.9–109.8 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.42 (br, 1H), 7.05 (d, J = 8.4 Hz, 1H), 6.84 (d, J = 2.4 Hz, 1H), 6.69 (dd, J = 2.4 Hz, 1H), 3.77 (s, 3H), 2.56–2.60 (m, 4H), 1.75–1.82 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 153.9, 143.9, 135.1, 130.8, 128.2, 111.0, 110.6, 100.3, 56.0, 23.4, 23.3, 23.2, 21.0; MS (EI, *m*/*z*): 201 $[M]^+$; HRMS (ESI): Calcd. for $C_{13}H_{16}NO$ $[M+H]^+$: 202.12318; found: 202.12278.

1,2-Dimethyl-6,7,8,9-tetrahydro-5*H*-carbazole (3i). Light yellow oil; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40 (br, 1H), 7.10 (d, J = 8.0 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 2.57–2.62 (m, 4H), 2.29 (s, 3H), 2.24 (s, 3H), 1.75–1.87 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.8, 133.3, 128.4, 125.8, 121.8, 117.5, 114.9, 110.7, 23.4, 23.3, 21.1, 19.4, 13.1; MS (EI, *m*/*z*): 199 $[M]^+$; HRMS (ESI): Calcd. for $C_{14}H_{18}N$ $[M+H]^+$: 200.14392; found: 200.14371.

8,9,10,11-Tetrahydro-7*H*-benzo[*a*]carbazole (3j). White solid, mp 137–139 °C (lit.[17d] 138–139.5 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.29 (br, 1H), 7.80–7.84 (m, 2H), 7.51 (d, J = 8.4 Hz, 1H), 7.36–7.41 (m, 2H), 7.25–7.30 (m, 1H), 2.68–2.76 (m, 4H),

1.80–1.89 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 132.3, 130.1, 129.7, 128.9, 125.1, 123.3, 123.1, 121.5, 119.8 119.2, 118.5, 112.0, 23.4, 21.1; MS (EI, *m*/*z*): 221 $[M]^+$; HRMS (ESI): Calcd. for $C_{16}H_{16}N$ $[M+H]^+$: 222.12827; found: 222.12796.

3-Chloro-6,7,8,9-tetrahydro-5*H*-carbazole (3k). White solid, mp 146–148 °C (lit.[17d] 146–147 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.61 (br, 1H), 7.33 (d, *J* = 1.5 Hz, 1H), 7.09 (d, *J* = 8.4 Hz, 1H), 6.97 (dd, *J* = 1.5 Hz, 1H), 2.56–2.66 (m, 4H), 1.75–1.87 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 135.8, 134.0, 129.0, 124.8, 121.1, 117.4, 111.2, 110.2, 23.3, 23.2, 23.1, 20.8; MS (EI, *m*/*z*): 205 $[M]^+$; HRMS (ESI): Calcd. for $C_{12}H_{12}NCl$ $[M+H]^+$: 205.06582; found: 205.06533.

1-Methyl-1*H*-indole (3l). Yellow oil; yellow liquid; 7.71–7.74 (m, 1H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.27–7.35 (m, 1H), 7.18–7.24 (m, 1H), 7.12 (d, *J* = 3.0 Hz, 1H), 6.57–6.59 (m, 1H), 3.84 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.8, 128.9, 128.5, 121.6, 120.9, 119.3, 109.3, 100.9, 32.8; MS (EI, *m*/*z*): 131 $[M]^+$; HRMS (ESI): Calcd. for $C_9H_{10}N$ $[M+H]^+$: 132.08132; found: 132.08056.

5-Methyl-2-phenyl-1*H*-indole (4a). White solid, mp 209–210 °C (lit.[17e] 211–213 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (br, 1H), 7.54–7.59 (m, 2H), 7.09–7.12 (m, 3H), 7.19–7.26 (m, 2H), 6.94 (dd, *J* = 1.2 Hz, 1H), 6.66–6.68 (m, 1H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 138.0, 135.2, 132.6, 129.6, 129.5, 129.0, 127.6, 125.1, 124.0, 120.4, 110.6, 99.6, 21.5; MS (EI, *m*/*z*): 207 $[M]^+$; HRMS (ESI): Calcd. for $C_{15}H_{14}N$ $[M+H]^+$: 208.11262; found: 208.11173.

5-Methoxy-2-phenyl-1*H*-indole (4b). White solid, mp 160–162 °C (lit.[17e] 160–162 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.15 (br, 1H), 7.54–7.58 (m, 2H), 7.33–7.39 (m, 2H), 7.19–7.27 (m, 2H), 7.02 (d, *J* = 2.1 Hz, 1H), 6.78 (dd, *J* = 2.7 Hz, *J* = 2.4 Hz, 1H), 6.67–6.69 (m, 1H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 154.6, 138.7, 132.5, 132.1, 129.8, 129.1, 127.7, 125.1, 112.7, 111.7, 102.3, 99.9, 55.9; MS (EI, *m*/*z*): 223 $[M]^+$; HRMS (ESI): Calcd. for $C_{15}H_{14}NO$ $[M+H]^+$: 224.10753; found: 224.10723.

6-Methoxy-2-phenyl-1*H*-indole (4c). White solid, mp 172–174 °C (lit.[17e] 173–176 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.16 (br, 1H), 7.52–7.56 (m, 2H), 7.32–7.44 (m, 3H), 7.18–7.24 (m, 1H), 6.82 (d, *J* = 2.4 Hz, 1H), 6.72 (dd, *J* = 2.4 Hz, *J* = 2.4 Hz, 1H), 6.67–6.69 (m, 1H), 3.79 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 156.8, 137.7, 136.9, 132.6, 129.0, 127.3, 124.8, 123.6, 121.3, 110.3, 99.9, 94.5, 55.7; MS (EI, *m*/*z*): 223 $[M]^+$; HRMS (ESI): Calcd. for $C_{15}H_{14}NO$ $[M+H]^+$: 224.10753; found: 224.10736.

2-Phenyl-1*H*-indole (4d). White solid, mp 188–190 °C (lit.[17e] 187–188 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.23 (br, 1H), 7.54–7.59 (m, 3H), 7.21–7.39 (m, 4H), 7.01–7.16 (m, 2H), 6.75 (dd, *J* = 1.2 Hz, *J* = 1.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.9, 136.9, 132.4, 129.3, 129.1, 127.8, 125.2, 122.4, 120.7, 120.3, 111.0, 100.0; MS (EI, *m*/*z*): 193 $[M]^+$; HRMS (ESI): Calcd. for $C_{14}H_{12}N$ $[M+H]^+$: 194.09697; found: 194.09624.

2-Phenyl-1*H*-benzo[*g*]indole (4e). White solid, mp 166–167 °C (lit.[17f] 165–167 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.00 (br, 1H), 7.96 (d, *J* = 8.1 Hz, 1H), 7.83 (d, *J* = 8.1 Hz, 1H), 7.60–7.64 (m, 3H), 7.20–7.48 (m, 6H), 6.86 (d, *J* = 2.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 136.3, 132.5, 131.4, 130.6, 129.1, 129.0, 127.5, 125.6, 125.3, 125.0, 124.0, 121.6, 121.2, 120.7, 119.4, 101.7; MS (EI, *m*/*z*): 243 $[M]^+$; HRMS (ESI): Calcd. for $C_{18}H_{14}N$ $[M+H]^+$: 244.11262; found: 244.11248.

Mixture of 2-methyl-1*H*-indole (4f) and 3-methyl-1*H*-indole (4f′). The ratio of **4f** and **4f′** was determined by GC and GC analysis using hexadecane as an internal standard. **4f** : **4f′** = 11 : 3.

3,5-Dimethyl-2-phenyl-1*H*-indole (4g). White solid, mp 100–102 °C (lit.[17g] 102–103 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.85 (br, 1H), 7.49–7.52 (m, 2H), 7.37–7.42 (s, 2H), 7.19–7.31 (m, 3H), 7.00 (dd, *J* = 8.1 Hz, 1H), 2.41 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 134.2, 133.5, 130.3, 128.8, 128.7, 127.7, 127.2, 123.9, 118.7, 110.3, 108.3, 21.6, 9.7; MS (EI, *m*/*z*): 221 $[M]^+$; HRMS (ESI): Calcd. for $C_{16}H_{15}N$ $[M+H]^+$: 221.12044; found: 221.12012.

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