

Iron(II) Chloride–1,1'-Binaphthyl-2,2'-diamine (FeCl₂–BINAM) Complex Catalyzed Domino Synthesis of Bisindolylmethanes from Indoles and Primary Alcohols

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Abstract: Biologically important bisindolylmethanes are synthesized in a domino fashion by using an iron(II) chloride–(±)-1,1'-binaphthyl-2,2'-diamine [FeCl₂–(±)-BINAM] complex as the catalyst. This method proceeds via oxidation of a primary alcohol into the corresponding aldehyde followed by nucleophilic addition of an indole in the presence of the catalyst. A reaction intermediate is synthesized separately and converted into the bisindolylmethane product under the same reaction conditions as support for the proposed mechanism.

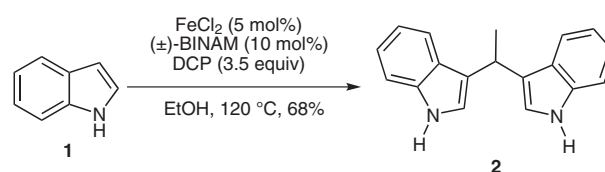
Key words: bisindolylmethanes, iron catalysts, alcohol oxidation, domino reactions, BINAM ligand

1,1-Bisindolylmethanes and their derivatives are known to have a broad spectrum of biological and pharmacological activities.¹ They are active against human breast cancer cells and are found to activate a specific estrogen receptor.² These compounds show growth inhibitory activity toward lung cancer cells,³ inhibit bladder cancer growth⁴ and have antimicrobial,⁵ antifungal,⁶ antibacterial⁷ and antitumor activities.⁸ In addition, 1,1-bisindolylmethane derivatives are used as human dietary supplements.⁹ The oxidized forms of 1,1-bisindolylmethanes have been reported as chromogenic-sensing molecules.¹⁰ As a result of their potential value in pharmaceuticals and materials, the synthesis of this class of compounds has attracted significant interest from synthetic chemists.¹¹ 1,1-Bisindolylmethanes have been isolated from metabolites of terrestrial and marine origin,¹² and various protocols have been adopted for their synthesis.¹³ Most of the common methods involve the addition of indoles to aldehydes or ketones in the presence of a Lewis acid,¹⁴ a Bronsted acid,¹⁵ transition metals,¹⁶ rare earth catalysts¹⁷ or zeolites.¹⁸ However, many of these methods suffer from the disadvantages of using stoichiometric amounts of acids, expensive metal catalysts and easily oxidizable aldehyde precursors. There have been very few reports in the literature on the synthesis of 1,1-bisindolylmethanes from alcohols.¹⁹ Yokoyama et al. reported the synthesis of 1,1-bisindolylmethanes from benzyl alcohol using a palladium catalyst.²⁰ Although, this method worked well, the protocol utilized costly palladium as the catalyst and was limited to benzylic alcohols as

substrates. Hence, there is a need for an efficient, economic and ecofriendly catalyst for the synthesis of 1,1-bisindolylmethanes starting from primary alcohols.

Iron is an attractive alternative catalyst because of its abundance, low price and environmentally benign character.²¹ Unlike other metals, iron is involved as a key element in various biological systems, particularly in oxidations. Due to its ability to undergo facile changes in oxidation state and because of its distinct Lewis acid character, iron catalysts enable a broad range of synthetic transformations such as oxidation, cross-coupling, alkylation and addition reactions.²² In continuation of our research on environmentally friendly iron-catalyzed reactions,²³ herein, we report an efficient iron(II) chloride–(±)-1,1'-binaphthyl-2,2'-diamine [FeCl₂–(±)-BINAM] complex catalyzed synthesis of 1,1-bisindolylmethanes from primary alcohols and indoles in a domino fashion.²⁴

In our preliminary studies, the synthesis was carried out starting from ethanol via a domino alcohol oxidation in the presence of the FeCl₂–BINAM complex as the catalyst and dicumyl peroxide (DCP), followed by condensation of the resulting aldehyde with indole (**1**) in ethanol, at 120 °C. To our surprise, the bisindolyl product was formed in 68% isolated yield after eight hours (Scheme 1). It is noteworthy that the reaction did not proceed without the iron catalyst.



Scheme 1 Synthesis of bisindolylmethane **2** from indole

In order to improve the reaction efficiency, several BINAM-derived and other ligands were screened, but none of them provided a better yield compared to BINAM (**L1**) (Figure 1). When the reaction was carried out with iron(II) chloride, but without a ligand, only a 27% yield of the product was obtained.

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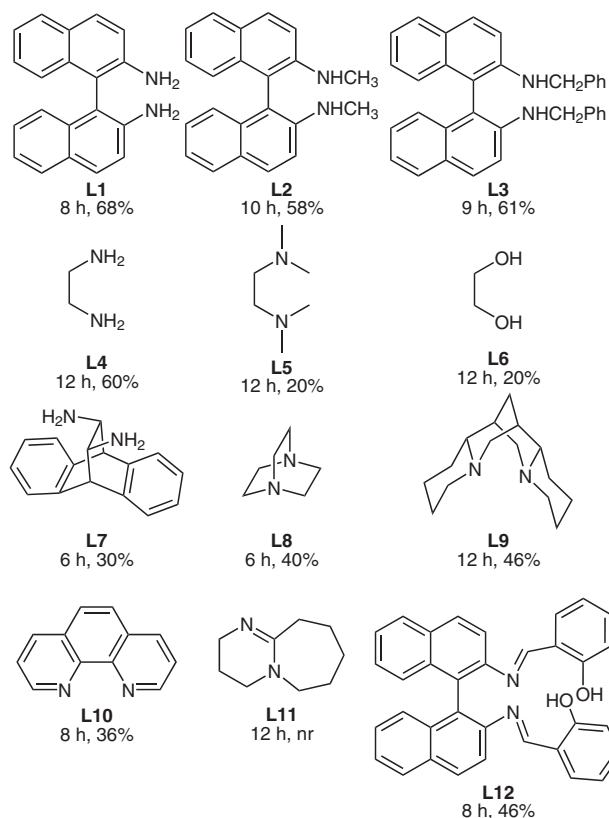
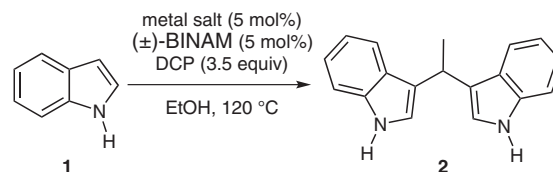


Figure 1 Ligand screening for the domino synthesis of **2**

To optimize the conditions in terms of the yield, we screened several other metal salts in combination with BINAM (**L1**) as the ligand in this domino reaction (Table 1). Although copper, cobalt and zinc salts catalyzed the reaction, none of them provided better yields than iron(II) chloride. It was found that when a higher oxidation state iron catalyst (Fe^{3+}) was used, no product formation was observed. The best result was obtained with iron(II) chloride (5 mol%), which gave bisindolylmethane **2** in 75% yield after six hours. The results are summarized in Table 1.

Next, different types of oxidizing agents were examined. Oxidants including hydrogen peroxide (H_2O_2), *tert*-butyl hydroperoxide (*t*-BuOOH) and benzoyl peroxide were less effective for the formation of product **2** when compared with dicumyl peroxide (DCP). The reaction was also attempted with 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO) and molecular oxygen as the oxidant, however, there was no product formation. The number of equivalents of dicumyl peroxide used was important with 3.5 equivalents giving the best result.

Table 1 Screening of Metal Salts for the Synthesis of **2**



Entry	Metal salt	Time (h)	Yield (%) ^a
1	FeCl_2	6	68
2	$\text{Fe}(\text{OAc})_2$	16	40
3	FeSO_4	16	15
4	FeCl_3	24	0
5	FeBr_3	20	0
6	$\text{Fe}(\text{ClO}_4)_2$	15	0
7	CuCl_2	12	14
8	$\text{Cu}(\text{OAc})_2$	12	42
9	$\text{Cu}(\text{OTf})_2$	12	45
10	CuI	24	25
11	$\text{Co}(\text{OAc})_2$	12	20
12	$\text{Ni}(\text{OAc})_2$	24	20
13	$\text{Zn}(\text{OAc})_2$	16	38
14	FeCl_2	8	50 ^b
15	FeCl_2	6	75^c
16	FeCl_2	8	69 ^d
17	FeCl_2	12	70 ^e

^a Yield of isolated product.

^b FeCl_2 (2.5 mol%).

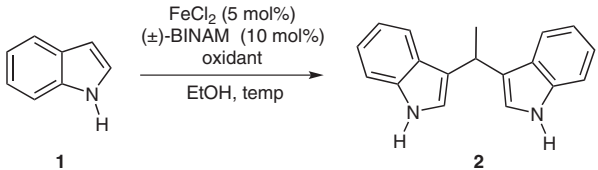
^c FeCl_2 (5 mol%) and **L1** (10 mol%).

^d FeCl_2 (10 mol%) and **L1** (10 mol%).

^e FeCl_2 (10 mol%) and **L1** (20 mol%).

Since the temperature plays a major role in catalyst efficiency, the reaction was examined at different temperatures. When the temperature was lowered to 80 °C, the yield of product **2** (76%) remained almost the same (Table 2, entry 9). However, when the temperature was reduced to 60 °C, the yield decreased to 62% (Table 2, entry 10).

From the optimization studies the best catalytic system was found to be: iron(II) chloride (5 mol%), 1,1'-binaphthyl-2,2'-diamine (**L1**) (10 mol%), dicumyl peroxide (3.5

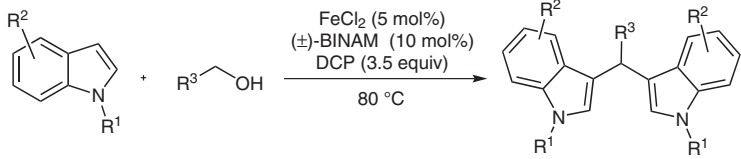
Table 2 Screening of Oxidants for the Synthesis of **2**


Entry	Oxidant	Temp (°C)	Time (h)	Yield (%) ^a
1	DCP	120	6	75
2	H ₂ O ₂	120	16	0
3	<i>t</i> -BuOOH	120	16	0
4	(PhCO ₂) ₂	120	18	trace
5	TEMPO	120	40	0 ^b
6	DCP	120	48	0 ^c
7	DCP	120	18	55 ^d
8	DCP	100	10	72
9	DCP	80	6	76
10	DCP	60	12	62
11	DCP	r.t.	24	0

^a Yield of isolated product.^b O₂ was used as a co-oxidant.^c TEMPO (1.0 equiv) was added.^d DCP (2.0 equiv).

equiv), 80 °C. The substrate scope of this methodology was evaluated using the optimized reaction conditions and the results are summarized in Table 3. Notably, indole reacted with ethanol to give the important natural product, vibrindole A (**2**) (Table 3, entry 1). For substituted indoles, it was found that the presence of an electron-releasing group on the nitrogen atom resulted in a good yield of the corresponding product (Table 3, entry 2). However, electron-withdrawing groups on the indole nitrogen atom, such as tosyl, completely inhibited the reaction (Table 3, entry 8), whilst an electron-withdrawing group on the benzene ring reduced the yield (Table 3, entry 5).

Increasing the length of the aliphatic chain of the alcohol led to reduced yields; when the alkyl chain was more than three carbon atoms long, the reaction did not take place. In the case of benzyl alcohol the reaction required a longer time than aliphatic alcohols (Table 3, entries 11–14).

Table 3 Iron-Catalyzed Domino Synthesis of Bisindolylmethanes from Indoles and Alcohols


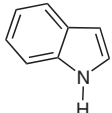

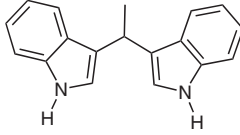
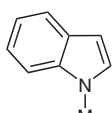

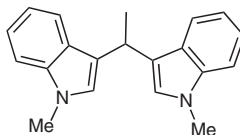
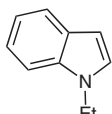

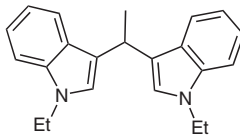
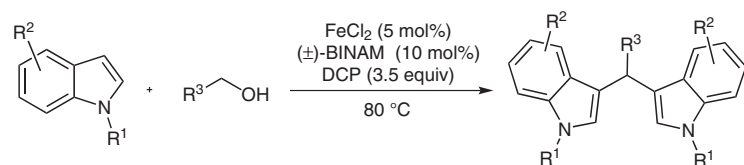
Entry	Indole	Alcohol	Product	Time (h)	Yield (%)
1				6	76 ^a
2				6	80
3				24	62
4					

Table 3 Iron-Catalyzed Domino Synthesis of Bisindolylmethanes from Indoles and Alcohols (continued)

Entry	Indole	Alcohol	Product	Time (h)	Yield (%)
4				12	70
5				36	63
6				15	63
7				48	54
8				24	0
9				10	85
10				36	62

11

Table 3 Iron-Catalyzed Domino Synthesis of Bisindolylmethanes from Indoles and Alcohols (continued)

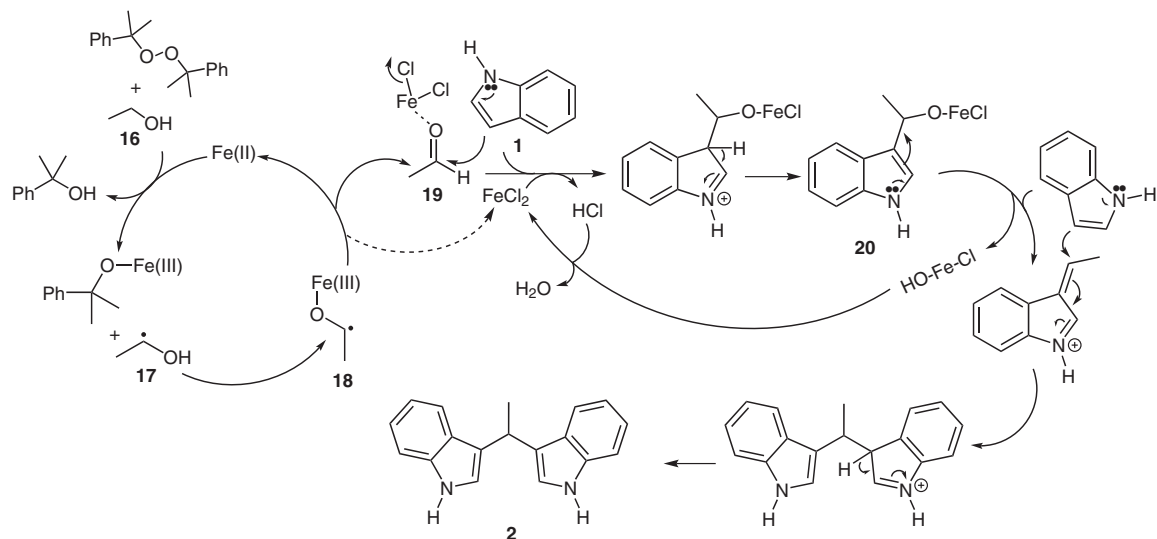
Entry	Indole	Alcohol	Product	Time (h)	Yield (%)
11				36	60 ^{b,c}
12				48	62 ^{b,c}
13				48	58 ^{b,c}
14				36	59 ^{b,c}

^a Yield of isolated product.^b *tert*-Butyl hydroperoxide was used as the oxidant.^c *tert*-Butyl alcohol (2 mL) was used as the solvent.

The reaction was completely suppressed by adding one equivalent of TEMPO (with respect to FeCl₂), a radical trapping agent, to the reaction mixture. These results indicate that a radical intermediate is most likely involved in the initial steps of the domino transformation. This explains the observed fact that aliphatic alcohols are more reactive than benzyl alcohol, since benzylic radicals are stabilized by resonance effects. When a secondary alcohol was subjected to the optimized conditions there was no reaction at all. These observations prove that the first step involves oxidation of the alcohol into an aldehyde. More importantly, there was no product formation at all when the strongly electron-deficient indole, *N*-tosylindole was used. The second step might involve nucleophilic attack

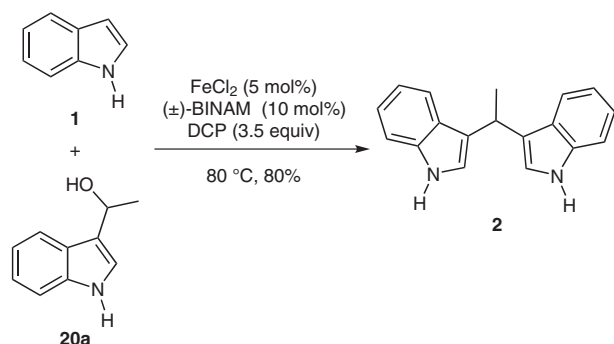
of indole, which is directed by the lone pair of electrons on the nitrogen of the indole.

Based on these observations, a plausible mechanism for the domino synthesis of bisindolylmethanes, using **2** as an example, is suggested (Scheme 2). Two catalytic cycles are proposed in the mechanism. In the first cycle, the primary alcohol **16** is oxidized by iron(II) chloride and dicumyl peroxide to give the corresponding aldehyde **19** through the radical intermediates **17** and **18**. In the second cycle, nucleophilic addition of indole (**1**) to the iron(II) chloride activated aldehyde **19** (which is formed in first the cycle) affords secondary alcohol **20a** (see Scheme 3). The secondary alcohol is further activated by iron(II)



Scheme 2 A plausible mechanism for the domino synthesis of bisindolylmethanes

chloride and undergoes a second addition of indole to give the bisindolylmethane **2**. We anticipated that the reaction proceeded through the secondary alcohol **20a** of the intermediate **20**, and we thus carried out a control experiment to understand the mechanism. The intermediate **20a** was synthesized by the reduction of 3-acetylindole using sodium borohydride,²⁵ and then subjected to our standard conditions for the preparation of bisindolylmethanes. As expected, the reaction took place smoothly and afforded an 80% isolated yield of compound **2** (Scheme 3). The instability of the intermediate **20a** explains the adverse effect of high temperature on this reaction.²⁶



Scheme 3 Synthesis of bisindolylmethane **2** from indole and the secondary alcohol **20a**

In summary, an efficient, cost-effective, and environmentally friendly iron-catalyzed domino synthesis of bisindolylmethanes and their derivatives from indoles and primary alcohols has been reported. A plausible mechanism has been proposed for this domino process. In support of the mechanism, one of the postulated reaction intermediates was independently synthesized and converted into the corresponding bisindolylmethane under the same reaction conditions.

All reactions were carried out in screw-cap pressure tubes under N_2 . All the solvents used for the reactions were obtained from Merck, India and were dried according to standard procedures. EtOH was purchased from Changshu Yangyuan Chemical, China, and dried over 4 Å molecular sieves. Reactions were monitored by thin-layer chromatography (TLC) using Merck silica gel 60 F254 pre-coated plates (0.25 mm), and samples were made visual by UV fluorescence. Silica gel (particle size: 100–200 mesh) was purchased from SRL India and was used for column chromatography using appropriate mixtures of hexanes–EtOAc as the eluent. $FeCl_2$ was obtained from Sigma-Aldrich Company. Other chemicals were purchased: indole from Spectrochem Pvt. Ltd., Mumbai, India (AR), dicumyl peroxide from Acros Organics, and 1,1'-binaphthyl-2,2'-diamine (BINAM) ligand **L1** was purchased from GERCHEM chemicals, Hyderabad, India. Reaction temperatures were controlled using a Varivolt temperature modulator. Melting points were obtained using a Toshniwal melting point apparatus and are uncorrected. FTIR spectra were recorded on a Nicolet 6700 spectrometer and absorptions are reported in wavenumbers (cm^{-1}). 1H and ^{13}C NMR spectra were recorded on Bruker 400 or 500 MHz instruments. 1H NMR spectra are reported relative to Me_4Si (δ 0.0) or residual $CHCl_3$ (δ 7.26). ^{13}C NMR are reported relative to $CDCl_3$ (δ 77.16). High-resolution mass spectra (HRMS) were recorded on Q-Tof Micro mass spectrometer.

3,3'-(Ethane-1,1-diyl)bis(1*H*-indole) (**2**);²⁷ Typical Procedure

An oven-dried, screw-cap pressure tube containing a magnetic stir bar was charged with $FeCl_2$ (3.2 mg, 0.025 mmol), 1,1'-binaphthyl-2,2'-diamine (BINAM) (14.2 mg, 0.05 mmol), dicumyl peroxide (DCP) (473.2 mg, 1.75 mmol) and indole (**1**) (58.6 mg, 0.5 mmol). The pressure tube was evacuated and back-filled with N_2 . Anhydrous EtOH (2 mL) was added and the mixture was stirred at 80 °C for 6 h. After the complete disappearance of indole (the progress of the reaction was monitored by TLC), the mixture was allowed to cool to r.t. and the EtOH was evaporated under reduced pressure using a rotary evaporator. Next, H_2O (15 mL) was added, and the product was extracted with EtOAc (3×10 mL) and dried over anhydrous Na_2SO_4 . The solvent was evaporated and the residue purified by column chromatography on silica gel (EtOAc–hexane, 12:88) to afford pure product **2**.

Yield: 49.8 mg (76%); light yellow solid; mp 148 °C (Lit.²⁷ 158–160 °C); $R_f = 0.39$ (20% EtOAc in hexane).

IR (neat): 3413, 3053, 2969, 2871, 1456, 1417, 1340, 1221, 1092, 1012, 746, 585 cm^{-1} .

¹H NMR (400 MHz, CDCl₃): δ = 1.83 (d, *J* = 7.2 Hz, 3 H), 4.70 (q, *J* = 7.2 Hz, 1 H), 6.89 (d, *J* = 2.4 Hz, 2 H), 7.08 (td, *J* = 8, 0.8 Hz, 2 H), 7.20 (td, *J* = 8.0, 0.8 Hz, 2 H), 7.34 (d, *J* = 8 Hz, 2 H), 7.61 (d, *J* = 8.4 Hz, 2 H), 7.80 (br s, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 21.9, 28.3, 111.2, 119.1, 119.9, 121.3, 121.8, 121.9, 127.0, 136.8.

HRMS (ESI, +): *m/z* [M + Na]⁺ calcd for C₁₈H₁₆N₂Na: 283.1211; found: 283.1220.

3,3'-(Ethane-1,1-diyl)bis(1-methyl-1*H*-indole) (3)

Yield: 58.4 mg (80%); colorless oil; *R*_f = 0.77 (20% EtOAc in hexane).

IR (neat): 2925, 1612, 1469, 739 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 1.71 (d, *J* = 7.0 Hz, 3 H), 3.63 (s, 6 H), 4.59 (q, *J* = 7.1 Hz, 1 H), 6.71 (s, 2 H), 6.96 (t, *J* = 7.0 Hz, 2 H), 7.12 (td, *J* = 7.0, 1.1 Hz, 2 H), 7.20 (t, *J* = 8.2 Hz, 2 H), 7.51 (d, *J* = 8 Hz, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 22.5, 28.3, 32.9, 109.4, 118.7, 120.1, 120.6, 121.6, 126.3, 127.6, 137.6.

HRMS (ESI, +): *m/z* [M + H]⁺ calcd for C₂₀H₂₁N₂: 289.1705; found: 289.1714.

3,3'-(Ethane-1,1-diyl)bis(1-ethyl-1*H*-indole) (4)

Yield: 49.7 mg (62%); pale brown solid; mp 101 °C; *R*_f = 0.54 (5% EtOAc in hexane).

IR (KBr): 2929, 2869, 1607, 1547, 1462, 1394, 1334, 931, 819 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 1.33 (t, *J* = 7 Hz, 6 H), 1.72 (d, *J* = 7 Hz, 3 H), 4.02 (dq, *J* = 7.0, 1.5 Hz, 4 H), 4.59 (q, *J* = 7.5 Hz, 1 H), 6.77 (s, 2 H), 6.95 (t, *J* = 7 Hz, 2 H), 7.10 (t, *J* = 7.5 Hz, 2 H), 7.23 (d, *J* = 8.5 Hz, 2 H), 7.50 (d, *J* = 8 Hz, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 15.5, 22.2, 28.2, 40.8, 109.2, 118.3, 120.0, 121.1, 124.3, 125.6, 127.9, 136.3.

HRMS (ESI, +): *m/z* [M + K]⁺ calcd for C₂₂H₂₄N₂K: 355.1577; found: 355.1589.

3,3'-(Propane-1,1-diyl)bis(5-methoxy-1*H*-indole) (5)

Yield: 58.2 mg (70%); brown solid; mp 121 °C; *R*_f = 0.41 (30% EtOAc in hexane).

IR (KBr): 3409, 2924, 2853, 1617, 1452, 1309, 1089, 878, 800, 760 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 1.02 (t, *J* = 7.2 Hz, 3 H), 2.23 (quin, *J* = 7.2 Hz, 2 H), 3.77 (s, 6 H), 4.27 (t, *J* = 7.2 Hz, 1 H), 6.81 (dd, *J* = 8, 2 Hz, 2 H), 6.99 (d, *J* = 1.6 Hz, 2 H), 7.03 (d, *J* = 2 Hz, 2 H), 7.22 (d, *J* = 8 Hz, 2 H), 7.81 (br s, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 13.3, 28.2, 55.7, 56.0, 102.1, 111.7, 118.8, 122.4, 128.3, 128.4, 144.6, 158.0.

3,3'-(Ethane-1,1-diyl)bis(5-bromo-1-methyl-1*H*-indole) (6)²⁸

Yield: 65.8 mg (63%); brown solid; mp 112 °C; *R*_f = 0.41 (10% EtOAc in hexane).

IR (neat): 3114, 2968, 2821, 1611, 1535, 1420, 1366, 907, 866, 790 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 1.66 (d, *J* = 7.0 Hz, 3 H), 3.62 (s, 6 H), 4.44 (q, *J* = 7.0 Hz, 1 H), 6.69 (s, 2 H), 7.07 (d, *J* = 8.5 Hz, 2 H), 7.19 (dd, *J* = 8.5, 2.0 Hz, 2 H), 7.57 (d, *J* = 2 Hz, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 22.1, 28.0, 32.9, 110.8, 112.2, 119.6, 122.3, 124.4, 127.3, 128.9, 136.2.

3,3'-(Ethane-1,1-diyl)bis(5-methoxy-1*H*-indole) (7)²⁸

Yield: 50.6 mg (63%); brown sticky solid; *R*_f = 0.43 (30% EtOAc in hexane).

IR (KBr): 3412, 2954, 2830, 1619, 1479, 1361, 1212, 805, 739 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 1.79 (d, *J* = 7.2 Hz, 3 H), 3.77 (s, 6 H), 4.57 (q, *J* = 6.8 Hz, 1 H), 6.83 (d, *J* = 9.2 Hz, 2 H), 6.92 (s, 2 H), 7.01 (s, 2 H), 7.23 (s, 2 H), 7.81 (s, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 21.6, 28.2, 56.0, 101.9, 111.7, 111.8, 121.3, 122.2, 127.4, 132.0, 153.6.

3,3'-(Ethane-1,1-diyl)bis[1-(4-methoxyphenyl)-1*H*-indole] (8)

Yield: 63.7 mg (54%); brown solid; mp 89 °C; *R*_f = 0.46 (10% EtOAc in hexane).

IR (KBr): 3049, 2925, 2838, 1607, 1457, 1370, 1246, 834, 743 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 1.80 (d, *J* = 7.5 Hz, 3 H), 3.77 (s, 6 H), 4.69 (q, *J* = 7 Hz, 1 H), 6.91 (d, *J* = 8.5 Hz, 4 H), 7.02 (m, 4 H), 7.11 (t, *J* = 7 Hz, 2 H), 7.29 (d, *J* = 9 Hz, 4 H), 7.37 (d, *J* = 8.5 Hz, 2 H), 7.59 (d, *J* = 8 Hz, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 22.0, 28.2, 55.7, 110.5, 114.7, 119.5, 120.0, 121.9, 122.2, 125.6, 125.9, 128.1, 133.2, 136.9, 158.0.

HRMS (ESI, +): *m/z* [M + Na]⁺ calcd for C₃₂H₂₈N₂O₂Na: 495.2048; found: 495.2068.

3,3'-(Propane-1,1-diyl)bis(1*H*-indole) (10)²⁹

Yield: 58.2 mg (85%); colorless oil; *R*_f = 0.45 (20% EtOAc in hexane).

¹H NMR (500 MHz, CDCl₃): δ = 0.93 (t, *J* = 7.4 Hz, 3 H), 2.16 (quin, *J* = 7.4 Hz, 2 H), 4.29 (t, *J* = 7.4 Hz, 1 H), 6.87 (d, *J* = 2.2 Hz, 2 H), 6.95 (t, *J* = 7.1 Hz, 2 H), 7.06 (t, *J* = 7.6 Hz, 2 H), 7.22 (d, *J* = 8.1 Hz, 2 H), 7.51 (d, *J* = 8 Hz, 2 H), 7.75 (s, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 13.2, 28.8, 36.0, 111.1, 119.1, 119.8, 120.4, 121.5, 121.8, 127.3, 136.7.

3,3'-(Propane-1,1-diyl)bis(1-methyl-1*H*-indole) (11)

Yield: 46.5 mg (62%); dark red solid; *R*_f = 0.56 (10% EtOAc in hexane).

IR (KBr): 2923, 1607, 1465, 1370, 1086, 747 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 0.93 (t, *J* = 7.5 Hz, 3 H), 2.14 (q, *J* = 7.5 Hz, 2 H), 3.64 (s, 6 H), 4.29 (t, *J* = 7.0 Hz, 1 H), 6.77 (s, 2 H), 6.94–6.97 (m, 2 H), 7.09–7.12 (m, 2 H), 7.18 (s, 2 H), 7.53 (d, *J* = 8 Hz, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 13.3, 29.4, 32.8, 35.9, 109.2, 118.5, 119.1, 119.9, 121.3, 126.4, 127.7, 137.4.

HRMS (ESI, +): *m/z* [M + Na]⁺ calcd for C₂₁H₂₂N₂Na: 325.1681; found: 325.1696.

3,3'-(Phenylmethane-1,1-diyl)bis(1*H*-indole) (12)³⁰

Yield: 48.3 mg (60%); pink solid; mp 139 °C (Lit.³⁰ 141–142 °C); *R*_f = 0.49 (20% EtOAc in hexane).

IR (KBr): 3409, 2924, 2853, 1605, 1455, 1198, 744 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 5.80 (s, 1 H), 6.55 (d, *J* = 1.6 Hz, 2 H), 6.92 (t, *J* = 7.2 Hz, 2 H), 7.06–7.14 (m, 3 H), 7.19 (t, *J* = 7.2 Hz, 2 H), 7.25–7.27 (m, 4 H), 7.31 (d, *J* = 8 Hz, 2 H), 7.79 (s, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 40.2, 111.0, 119.2, 119.9, 121.9, 123.6, 126.1, 127.1, 128.2, 128.7, 133.7, 136.7, 144.0.

3,3'-(Phenylmethane-1,1-diyl)bis(1-methyl-1*H*-indole) (13)²⁷

Yield: 54.2 mg (59%); dark red solid; mp 163 °C; *R*_f = 0.43 (10% EtOAc in hexane).

IR (KBr): 3020, 2927, 1607, 1547, 1472, 1366, 744, 700 cm⁻¹.

¹H NMR (400 MHz, CDCl₃): δ = 3.66 (s, 6 H), 5.87 (s, 1 H), 6.52 (d, *J* = 0.8 Hz, 2 H), 6.96–7.00 (m, 2 H), 7.16–7.21 (m, 3 H), 7.24–7.29 (m, 4 H), 7.33–7.35 (m, 2 H), 7.38 (d, *J* = 7.6 Hz, 2 H).

¹³C NMR (100 MHz, CDCl₃): δ = 32.8, 40.2, 109.2, 118.4, 118.8, 120.2, 121.5, 126.1, 127.6, 128.3, 128.4, 128.8, 137.5, 144.6.

HRMS (ESI, +): *m/z* [M + Na]⁺ calcd for C₂₅H₂₂N₂Na: 373.1681; found: 373.1696.

3,3'-(Phenylmethane-1,1-diyl)bis(5-methoxy-1H-indole) (14)²⁸
Yield: 55.4 mg (58%); red solid; mp 198 °C; R_f = 0.56 (30% EtOAc in hexane).

IR (KBr): 3004, 2934, 1619, 1586, 1484, 1448, 1208, 1028, 799 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 3.61 (s, 6 H), 5.69 (s, 1 H), 7.11–7.22 (m, 7 H), 7.27 (d, J = 7.2 Hz, 2 H), 7.39 (t, J = 7.6 Hz, 2 H), 7.76 (s, 2 H), 8.04 (d, J = 7.6 Hz, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 40.4, 56.0, 102.2, 111.8, 112.0, 119.5, 124.6, 126.2, 128.3, 128.6, 128.9, 130.3, 132.0, 133.8.

HRMS (ESI, +): m/z [M + Na]⁺ calcd for C₂₅H₂₂N₂O₂Na: 405.1579; found: 405.1566.

3,3'-(Phenylmethane-1,1-diyl)bis(5-bromo-1H-indole) (15)³¹

Yield: 59.1 mg (59%); dark red solid; mp 223 °C; R_f = 0.55 (30% EtOAc in hexane).

IR (KBr): 3416, 3068, 2927, 2859, 1592, 1558, 1449, 976, 775 cm⁻¹.

¹H NMR (500 MHz, CDCl₃): δ = 5.75 (s, 1 H), 6.65 (d, J = 1.5 Hz, 2 H), 7.23–7.24 (m, 4 H), 7.26 (s, 2 H), 7.29–7.30 (m, 4 H), 7.47 (d, J = 0.5 Hz, 2 H), 7.99 (s, 2 H).

¹³C NMR (125 MHz, CDCl₃): δ = 40.0, 112.7, 112.8, 119.2, 122.4, 124.9, 125.1, 126.7, 128.6, 128.7, 128.8, 135.5, 143.1.

HRMS (ESI, +): m/z [M + H]⁺ calcd for C₂₃H₁₇N₂Br₂: 478.9758; found: 478.9743.

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- (26) The reaction intermediate might be unstable at 100 °C and may decompose before it reacts. This speculation might explain the low yield at 100 °C. Intermediate **20a** might be somewhat stable at 80 °C, the temperature at which it gives the maximum yield. At lower temperature, product formation may be sluggish.
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