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Au(III)/TPPMS-Catalyzed Benzylation of Indoles with Benzylic Alcohols in Water

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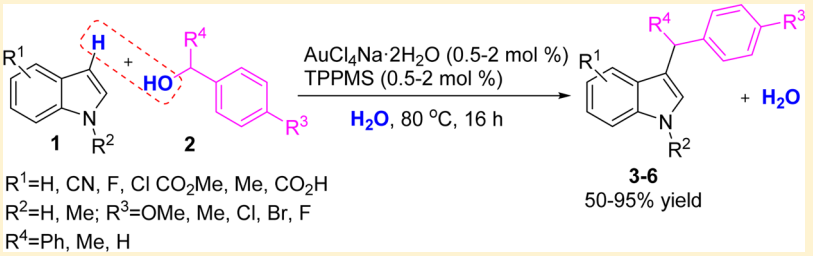
Supporting Information



ABSTRACT: A novel and efficient method for the Au(III)/TPPMS-catalyzed direct substitution reaction of benzhydryl and benzylic alcohols with indoles in water is developed. Au(III)/TPPMS is an effective catalyst for the benzylation of the strong π nucleophile 1-methylindole, while common Brønsted or Lewis acids are ineffective.

INTRODUCTION

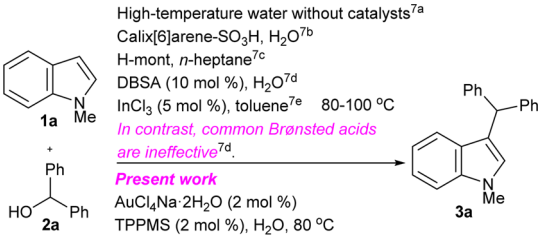
The reaction of benzylic alcohols as benzylating agents has attracted attention as an environmentally benign process, whereas benzylic halides are toxic and their use in benzylation produces large amounts of inorganic waste, which is undesirable from the standpoint of green chemistry. Therefore, the development of a direct substitution of benzylic alcohols, which generates only H_2O as the byproduct, is highly important.[1]

The gold-catalyzed direct substitution of benzylic alcohols with various nucleophiles provides a powerful methodology for the formation of carbon−carbon and carbon−nitrogen bonds.[2] Such efficiency is due to the σ-electrophilic Lewis acidic character and allows for the activation of several hydroxyl groups, thus promoting an environmentally benign chemical process.

We have been investigating benzylation using the (η^3-benzyl) palladium system from benzyl alcohol in water,[3] which activates the benzyl alcohol via hydration of the hydroxyl group. Recently, we reported the Au(III)/TPPMS-catalyzed chemoselective benzylation of unprotected anthranilic acids with benzhydryl alcohols in water,[4,5] which promises to generate further innovative direct transformation reactions. In our continuing effort to develop gold-catalyzed benzylation, we began to investigate indoles as nucleophiles.

The nucleophilic substitution of alcohols without added catalysts "on water" has been reported.[6] However, the reaction between the strong π nucleophile 1-methylindole (**1a**) and benzhydrol (**2a**) did not afford the benzylated product **3a** in water at 80 °C, and common Brønsted acids (AcOH or TFA) were also ineffective catalysts for this reaction in water.[7d] In high-temperature water (220 °C) the reaction proceeds without added catalysts since its physical properties are dramatically altered depending on temperature and pressure. To achieve the benzylation of 1-methylindole (**1a**) under mild conditions, several effective catalysts have been developed (Scheme 1).[7b−e]

Scheme 1. Benzylation of the Strong π Nucleophile 1-Methylindole (1a)



In those papers, surfactant-type Brønsted acids have been employed as nucleophilic partners. Liu and Wang reported calix[n]arene sulfonic acids.[7b] Kobayashi and co-workers reported DBSA-catalyzed dehydrative nucleophilic substitutions of alcohols in water.[7d] Although various efficient catalytic systems in water have been developed, the dehydration reaction in water is one of the most challenging research topics. Herein, we report the development of a water-soluble gold(III)-catalyzed direct substitution reaction of benzhydryl or benzylic alcohols with indoles in water. Notably, the protocol using $NaAuCl_4{\cdot}2H_2O$ in CH_2Cl_2[2,8] was ineffective for benzylation of the strong π nucleophile 1-methylindole (**1a**).[9]

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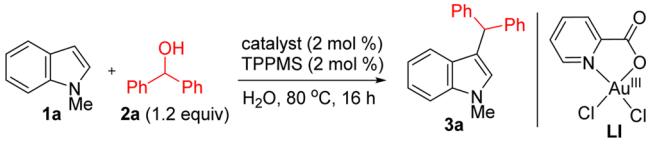
RESULTS AND DISCUSSION

First, we heated a mixture of 1-methylindole (**1a**) and **2a** (1.2 equiv) in the presence of $AuCl_4Na{\cdot}2H_2O$ (2 mol %) and sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 2 mol %) in water at 80 °C for 16 h under air. Benzylated **3a** was obtained in 73% yield (Table 1, entry 1). When $AuCl_4Na{\cdot}2H_2O$ (0.5 mol %) and TPPMS (0.5 mol %) were used, the reaction afforded the desired **3a** in only 18% yield (entry 2). Using only $AuCl_4Na{\cdot}2H_2O$ resulted in no reaction, and recovery of the starting material **1a** was detected by TLC analysis (entry 3). With regard to the gold catalyst, the use of $HAuCl_4{\cdot}3H_2O$ or $AuBr_3$ also gave the product **3a** in good yield (entry 4, 73%; entry 5, 73%). In contrast, when the Au(III)-picolinate complex **LI** or AuCl was used, the reaction did not proceed (entries 6 and 7). To compare $AuCl_4Na{\cdot}2H_2O$ with other efficient catalysts, we tested the reaction using Brønsted acids such as HCl and MsOH and effective Lewis acids in water such as $Sc(OTf)_3$ and $Hf(OTf)_4$. However, the reaction did not proceed (entries 8–11), clearly showing the superiority of water-soluble Au(III)/TPPMS for the benzylation of indole **1a** with benzhydrol (**2a**). Furthermore, using $AuCl_4Na{\cdot}2H_2O$ in organic solvents such as CH_2Cl_2, 1,4-dioxane, and toluene also resulted in no reaction (entries 12–14).[1] In a biphasic system such as toluene/H_2O or 1,4-dioxane/H_2O, the reaction also did not proceed (entries 15 and 16). In contrast, using EtOH resulted in good yield (entry 17).

Table 1. Effect of Catalysts and Solvents[a]



entry	catalyst	ligand	solvent	yield (%)
1	$AuCl_4Na{\cdot}2H_2O$	TPPMS	H_2O	73 (74)[d]
2[b]	$AuCl_4Na{\cdot}2H_2O$	TPPMS	H_2O	18
3	$AuCl_4Na{\cdot}2H_2O$	none	H_2O	trace[c]
4	$HAuCl_4{\cdot}3H_2O$	TPPMS	H_2O	73
5	$AuBr_3$	TPPMS	H_2O	73
6	Au(III)-picolinate **LI**	none	H_2O	trace[c]
7	AuCl	TPPMS	H_2O	trace[c]
8	HCl[e]	none	H_2O	trace[c]
9	MsOH[e]	none	H_2O	trace[c]
10	$Sc(OTf)_3$	none	H_2O	trace[c]
11	$Hf(OTf)_4$	none	H_2O	trace[c] (4)[d]
12	$AuCl_4Na{\cdot}2H_2O$	none	CH_2Cl_2[f]	trace[c]
13	$AuCl_4Na{\cdot}2H_2O$	none	1,4-dioxane	trace[c]
14	$AuCl_4Na{\cdot}2H_2O$	none	toluene	trace[c]
15	$AuCl_4Na{\cdot}2H_2O$	TPPMS	1,4-dioxane/H_2O (1/1)	trace[c]
16	$AuCl_4Na{\cdot}2H_2O$	TPPMS	toluene/H_2O (1/1)	trace[c]
17	$AuCl_4Na{\cdot}2H_2O$	TPPMS	EtOH	(73)[d]

[a]Reaction conditions: **1a** (131 mg, 1 mmol), catalyst (2 mol %), TPPMS (7.3 mg, 2 mol %), benzhydrol (**2a**; 221 mg, 1.2 mmol), solvent (4 mL), 80 °C, 16 h, in air. [b]$AuCl_4Na{\cdot}2H_2O$ (0.5 mol %) and TPPMS (0.5 mol %) were used. [c]By TLC analysis. [d]Conversion yield. [e]10 mol %. [f]At 40 °C (bp).

Results for the direct substitution reaction of several benzhydryl alcohols **2** with 1-methylindole (**1a**) using $AuCl_4Na{\cdot}2H_2O$ and TPPMS in water are summarized in Figure 1. The benzhydryl alcohols with electron-donating methoxy and methyl groups afforded products in excellent yields (**3b**, 95%; **3c**, 95%; **3d**, 84%). The reaction of benzhydryl alcohols with electron-withdrawing chloro, bromo, and fluoro groups proceeded to give benzylated products in moderate to good yields (**3e**, 54%; **3f**, 40%; **3g**, 83%). In contrast, trifluoromethyl and pentafluoro groups resulted in no reaction. Since electron-poor diarylmethanols **2c**,**d** failed to react with indole **1a** under the same conditions, the stability of the diaryl carbocation must be critical to the success of these reactions.

The scope of the reaction with respect to indoles **1** was further examined (Figure 2), and the reactions of 4,4′-dimethoxybenzhydrol (**2d**) and indoles **1** with cyano, fluoro, chloro, methyl carboxylate, and methoxy groups using $AuCl_4Na{\cdot}2H_2O$ (0.5 mol %) and TPPMS (0.5 mol %) resulted in excellent yields (**3h**, 93%; **3i**, 90%; **3j**, 95%; **3k**, 95%; **3l**, 66%). No isomers through *N*- or 2-benzylation were obtained. The unsubstituted indole **1b** also afforded benzylated **3m** in 95% yield. Furthermore, the sterically demanding 2-substituted indoles gave moderate to good yields (**3n**, 71%; **3o**, 70%; **3p**, 51%). 3-Methylindole (**1c**) afforded 2-benzylated **3q** in 86% yield. In contrast, *N*-tosylindole (**1d**) resulted in no reaction.

We became interested in further expanding the substrate scope of the Au(III)/TPPMS system to water-soluble unprotected indolecarboxylic acids **1**, since we have been studying the development of unprotected syntheses and selective reactions toward various reactive functional groups.[10] In general, unprotected syntheses represent a distinct challenge and have been met with a number of difficulties such as chemoselectivity. One of the most effective ways for achieving unprotected syntheses is the development of selective reactions toward various reactive functional groups.[11] Interestingly, the benzylation of indole-5-carboxylic acid afforded only C3-benzylated **4a** in 82% yield with the carboxyl group left intact (Figure 3). Furthermore, indole-2-carboxylic acids with several

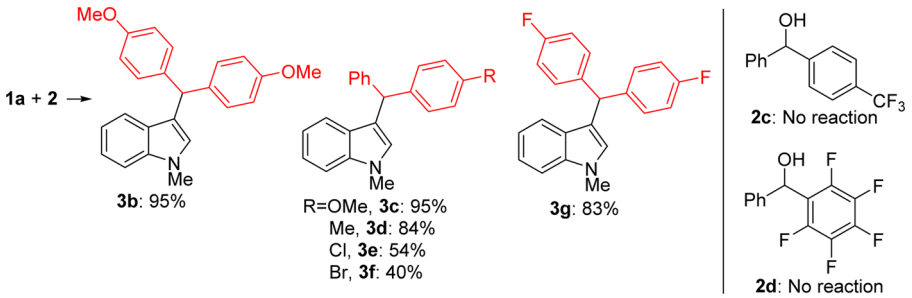


Figure 1. Scope of benzhydryl alcohols **2**. Reaction conditions: 1-methylindole **1a** (1 mmol), $AuCl_4Na{\cdot}2H_2O$ (2 mol %), TPPMS (2 mol %), benzhydryl alcohol **2** (1.2 equiv), H_2O (4 mL), 80 °C, 16 h.

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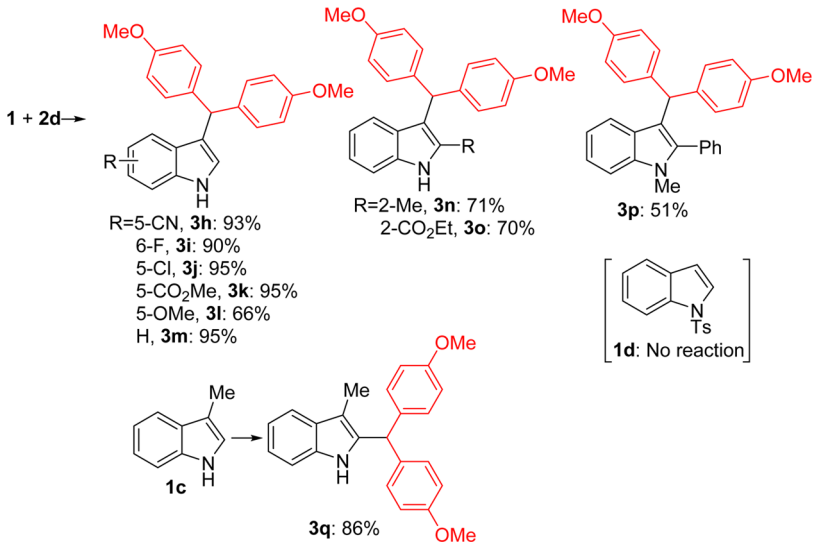

Figure 2. Scope of indole **1**. Reaction conditions: **1** (1.1 mmol), $AuCl_4Na{\cdot}2H_2O$ (0.5 mol %), TPPMS (0.5 mol %), 4,4′-dimethoxybenzhydrol (**2d**; 1 mmol), H_2O (4 mL), 80 °C, 16 h.

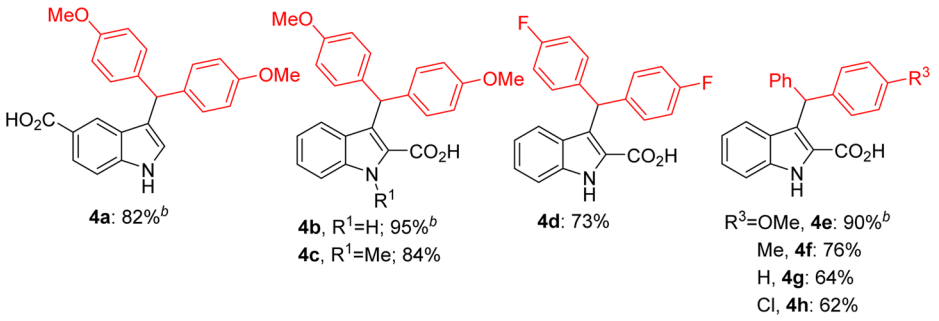

Figure 3. C3-Benzylation of indolecarboxylic acids **1**. Reaction conditions except where noted: **1** (1 mmol), $AuCl_4Na{\cdot}2H_2O$ (2 mol %), TPPMS (2 mol %), benzhydryl alcohol **2** (1.2 equiv), H_2O (4 mL), 80 °C, 16 h in a sealed tube. The superscript b indicates that $AuCl_4Na{\cdot}2H_2O$ (0.5 mol %) and TPPMS (0.5 mol %) were used.

benzhydryl alcohols **2** also resulted in moderate to excellent yields (**4b**, 95%; **4c**, 84%; **4d**, 73%; **4e**, 90%; **4f**, 76%; **4g**, 64%; **4h**, 62%).

Furthermore, direct substitution of 1-phenylethyl alcohols **2** also afforded the desired **5** in moderate to excellent yield (**5a**, 95%; **5b**, 55%; **5c**, 91% in Figure 4). Interestingly, simple

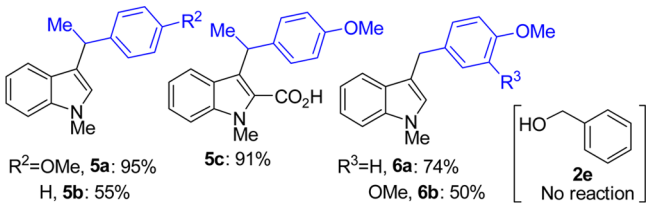

Figure 4. Scope of alcohols **2**. Reaction conditions: **1** (1 mmol), $AuCl_4Na{\cdot}2H_2O$ (2 mol %), TPPMS (2 mol %), benzhydryl alcohol **2** (1.2 equiv), H_2O (4 mL), 80 °C, 16 h in a sealed tube.

benzyl alcohols **2** with a methoxy group also resulted in moderate to good yield (**6a**, 74%; **6b**, 50%). In contrast, the reaction of the unsubstituted benzyl alcohol (**2e**) did not proceed.

We investigated the classical Friedel–Crafts reaction of 1,3-dimethoxybenzene (**7**) with benzhydrol (**2a**) (see Table S1 in the Supporting Information). While the use of HCl or $AuCl_4Na{\cdot}2H_2O$ and TPPMS resulted in no reaction or low yield, the use of $Hf(OTf)_4$ afforded benzylated **8a**,**b** in moderate yield. To our surprise, in the presence of 1-methylindole (**1a**), the $Hf(OTf)_4$-catalyzed Friedel–Crafts reaction did not proceed, suggesting that the strong π nucleophile 1-methylindole (**1a**) might suppress the acidity of $Hf(OTf)_4$. Thus, Au(III)/TPPMS is an effective catalyst for benzylation of indoles in water.

On the basis of our results and literature reports, the following mechanism can be suggested (Scheme 2). First, the water-soluble Au–benzhydryl alcohol complex **9** forms from benzhydryl alcohol **2** in the presence of $AuCl_4Na{\cdot}2H_2O$ and TPPMS. Next, the benzyl cation species **11** forms, followed by nucleophilic attack of the indole **1a**, to give benzylated **3**. In aqueous solution, carbocations tend to have very short lifetimes.[12] However, the lifetimes of carbocations can be increased by the introduction of electron-donating substituents on the aryl ring.[13] Figure 5 shows a good correlation between the $\log(k_X/k_H)$ vs the σ^+ value of the respective substituents. From the slope a negative ρ value of 2.74 is obtained, suggesting that there is a buildup of positive charge in the transition state. Indeed, benzylation using benzhydryl alcohol with the electron-withdrawing trifluoromethyl group **2c** or unsubstituted benzyl alcohol **2e** did not proceed, since alcohols **2c**,**e** could not form carbocationic intermediates in our catalytic system (see Figures 1 and 4).

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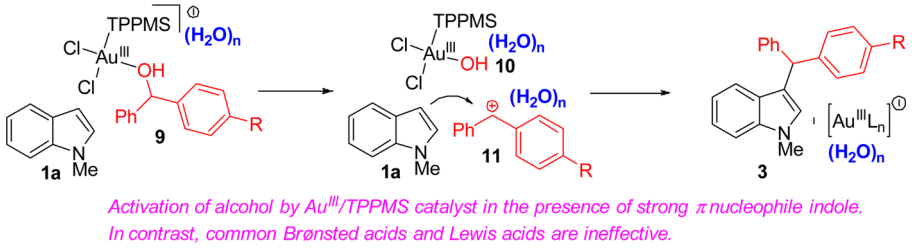
Scheme 2. Plausible Mechanism



Activation of alcohol by Au^{III}/TPPMS catalyst in the presence of strong π nucleophile indole. In contrast, common Brønsted acids and Lewis acids are ineffective.

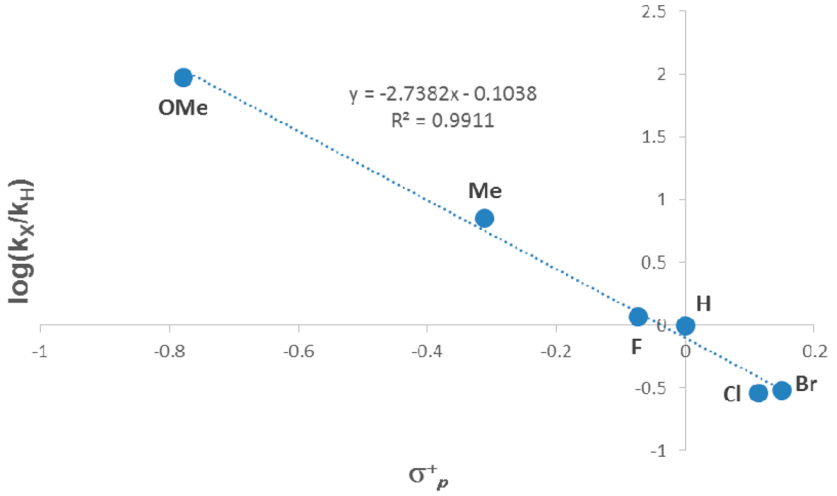
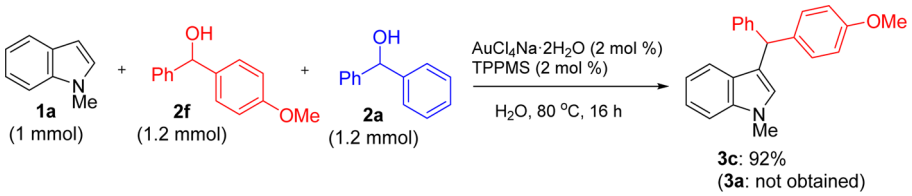


Figure 5. Brown−Okamoto plot for the rate constants of benzylation by various substituted alcohols. Reaction conditions: 1-methylindole **1a** (1 mmol), $AuCl_4Na·2H_2O$ (2 mol %), TPPMS (2 mol %), benzhydrol **2a** (1 mmol) and benzhydryl alcohols **2** (1 mmol), H_2O (4 mL), 80 °C, 30 min in a sealed tube (see Table S2 in the Supporting Information)

Scheme 3. Competition Experiment



Furthermore, a competition experiment using an equimolar amount of benzhydryl alcohols **2f** (R = OMe) and **2a** (R = H) gave only the OMe species **3c** in 92% yield (Scheme 3).

Water might play an important role in the smooth generation of intermediates **9**−**11**, which are stabilized by hydration.[6] Indeed, the reaction did not occur without water and water-soluble phosphine ligands, TPPMS (see Table 1). In addition, while the strong π nucleophile 1-methylindole (**1a**) might suppress the acidity of naked Au(III) catalyst in organic solvents, the water-soluble Au(III)/TPPMS active catalyst could form in water.

CONCLUSIONS

In summary, we developed the first direct substitution reaction of benzhydryl and benzylic alcohols with indoles using a water-soluble gold(III)/TPPMS catalyst system in water, one of the most efficient and environmentally friendly synthetic strategies for benzylation.

EXPERIMENTAL SECTION

General Considerations. All reagents and solvents were obtained commercially and used as received unless otherwise indicated. All melting points were determined on a Yanagimoto micromelting hot stage apparatus and are uncorrected. IR spectra were recorded as KBr tablets (unless otherwise stated). NMR spectra were recorded at 400 MHz for ^1H and 100 MHz for ^{13}C NMR with tetramethylsilane as the internal reference. The following abbreviations were used: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; m, multiplet. EI mass spectra and high-resolution mass spectra were measured using a direct inlet system. The mass analyzer type was a double-focusing magnetic sector mass spectrometer for the HRMS measurements.

General Procedure. A mixture of indoles **1** (1 mmol), $AuCl_4Na·2H_2O$ (0.5−2 mol %), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 0.5−2 mol %), and alcohols **2** (1.2 mmol) in H_2O (4 mL) was heated at 80 °C for 16 h in a sealed tube. After it was cooled, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes/EtOAc) to give the desired products **3**−**6**.

*3-Benzhydryl-1-methyl-1H-indole (**3a**; Table 1, Entry 1).*[7c] Following the general procedure, **3a** was obtained as a white solid:

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yield 217 mg (73%); mp 142−144 °C; IR (KBr) (cm^{-1}) 3056, 1482; ^1H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3H), 5.66 (s, 1H), 6.40 (s, 1H), 6.97 (dd, J = 7.8, 7.8 Hz, 1H), 7.10−7.40 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.8, 48.9, 109.2, 118.4, 118.9, 120.1, 121.7, 126.3, 127.5, 128.4, 128.8, 129.1, 137.5, 144.2; MS (EI) m/z 297 (M^+, 100).

*3-[Bis(4-methoxyphenyl)methyl]-1-methyl-1H-indole (**3b**; Figure 1).*[7d] Following the general procedure, **3b** was obtained as an off-white solid: yield 339 mg (95%); mp 107−109 °C; IR (KBr) (cm^{-1}) 2939, 1509; ^1H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3H), 3.77 (s, 6H), 5.56 (s, 1H), 6.39 (s, 1H), 6.81 (d, J = 8.7 Hz, 4H), 6.97 (dd, J = 7.1, 7.1 Hz, 1H), 7.12 (d, J = 8.7 Hz, 4H), 7.15−7.30 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.8, 47.2, 55.3, 109.2, 113.7, 118.8, 119.1, 120.2, 121.7, 127.4, 128.7, 129.9, 136.8, 137.6, 158.0; MS (EI) m/z (%) 357 (M^+, 100).

*3-[(4-Methoxyphenyl)(phenyl)methyl]-1-methyl-1H-indole (**3c**; Figure 1).*[14] Following the general procedure, **3c** was obtained as a white solid: yield 311 mg (95%); mp 116−118 °C; IR (KBr) (cm^{-1}) 3017, 1506; ^1H NMR (400 MHz, $CDCl_3$): δ 3.68 (s, 3H), 3.78 (s, 3H), 5.61 (s, 1H), 6.40 (s, 1H), 6.81 (dt, J = 8.5, 1.8 Hz, 2H), 6.97 (dd, J = 6.9, 6.9 Hz, 1H), 7.13 (dt, J = 8.7, 2.1 Hz, 2H), 7.16−7.30 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.8, 48.0, 55.3, 109.2, 113.7, 118.9, 120.1, 121.7, 126.2, 128.3, 128.8, 129.0, 130.0, 136.4, 144.6, 158.0; MS (EI) m/z 327 (M^+, 100).

*1-Methyl-3-[phenyl(p-tolyl)methyl]-1H-indole (**3d**; Figure 1).* Following the general procedure, **3d** was obtained as a white solid: yield 263 mg (84%); mp 114−116 °C; IR (KBr) (cm^{-1}) 3023, 2930, 1470; ^1H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 3.67 (s, 3H), 5.62 (s, 1H), 6.40 (d, J = 0.9 Hz, 1H), 6.96 (ddd, J = 8.7, 7.1, 0.9 Hz, 1H), 7.07 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 2H), 7.15−7.30 (m, 8H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0, 32.6, 48.4, 109.1, 118.4, 118.8, 120.0, 121.6, 126.1, 127.4, 128.2, 128.7, 128.8, 128.9, 135.6, 137.4, 141.1, 144.3; MS (EI) m/z (%) 311 (M^+, 100). Anal. Calcd for $C_{23}H_{21}N$: C, 88.71; H, 6.80; N, 4.50. Found: C, 88.58; H, 6.85; N, 4.46.

*3-[(4-Chlorophenyl)(phenyl)methyl]-1-methyl-1H-indole (**3e**; Figure 1).* Following the general procedure, **3e** was obtained as a white solid: yield 180 mg (54%); mp 140−142 °C; IR (KBr) (cm^{-1}) 3052, 1478; ^1H NMR (400 MHz, $CDCl_3$): δ 3.70 (s, 3H), 5.63 (s, 1H), 6.38 (s, 1H), 6.98 (ddd, J = 8.9, 8.0, 0.9 Hz, 1H), 7.10−7.32 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.7, 48.1, 109.2, 117.8, 118.9, 119.8, 121.8, 126.4, 127.1, 128.4, 128.7, 128.9, 130.3, 131.9, 137.4, 142.6, 143.6; MS (EI) m/z (%) 333 (M^+ + 2, 35), 331 (M^+, 100). Anal. Calcd for $C_{22}H_{18}ClN$: C, 79.63; H, 5.47; N, 4.22. Found: C, 79.74; H, 5.52; N, 4.26.

*3-[(4-Bromophenyl)(phenyl)methyl]-1-methyl-1H-indole (**3f**; Figure 1).* Following the general procedure, **3f** was obtained as a white solid: yield 150 mg (40%); mp 138−140 °C; IR (KBr) (cm^{-1}) 3054, 1478; ^1H NMR (400 MHz, DMSO-d_6): δ 3.71 (s, 3H), 5.68 (s, 1H), 6.71 (s, 1H), 6.90 (dd, J = 8.0, 8.0 Hz, 1H), 7.09−7.14 (m, 2H), 7.18 (d, J = 8.5 Hz, 1H), 7.20−7.26 (m, 4H), 7.30 (dd, J = 7.3, 7.3 Hz, 2H), 7.38 (d, J = 8.0 Hz, 1H), 7.48 (dt, J = 8.5, 2.5 Hz, 2H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 32.8, 47.8, 110.0, 117.1, 119.1, 119.7, 119.8, 121.8, 126.8, 127.2, 128.9, 129.1, 131.3, 131.7, 137.6, 144.2; MS (EI) m/z (%) 377 (M^+ + 2, 99), 375 (M^+, 100); HRMS (EI) m/z calcd for $C_{22}H_{18}NBr$ [M^+ + 2] 377.0602, found 377.0599.

*3-[Bis(4-fluorophenyl)methyl]-1-methyl-1H-indole (**3g**; Figure 1).*[7d] Following the general procedure, **3g** was obtained as a colorless oil: yield 277 mg (83%); IR (neat) (cm^{-1}) 3054, 1504; ^1H NMR (400 MHz, $CDCl_3$): δ 3.66 (s, 3H), 5.61 (s, 1H), 6.35 (s, 1H), 6.90−7.00 (m, 5H), 7.10−7.22 (m, 6H), 7.27 (d, J = 8.3 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 32.0, 46.6, 108.6, 114.5 (d, J = 21.0 Hz), 117.4, 118.4, 119.2, 121.2, 126.4, 128.0, 129.6 (d, J = 7.6 Hz), 136.9, 139.0, 160.8 (d, J = 243.1 Hz); MS (EI) m/z (%) 333 (M^+, 100).

*3-[Bis(4-methoxyphenyl)methyl]-1H-indole-5-carbonitrile (**3h**; Figure 2).* Following the general procedure, **3h** was obtained as a brown amorphous solid: yield 343 mg (93%); IR (KBr) (cm^{-1}) 3330, 2222, 1608, 1507, 1251; ^1H NMR (400 MHz, $CDCl_3$): δ 3.79 (s, 3H), 5.53 (s, 1H), 6.69 (dd, J = 2.3, 1.2 Hz, 1H), 6.82 (d, J = 8.7 Hz, 4H), 7.10 (d, J = 8.7 Hz, 4H), 7.39 (s, 2H), 7.56 (s, 1H), 8.30 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.0, 55.3, 102.4, 112.1, 113.6, 113.9, 121.8, 125.1, 125.8, 126.0, 126.9, 129.7, 132.4, 135.6, 138.6, 158.3; MS (EI) m/z 368 (M^+, 100); HRMS (EI) m/z calcd for $C_{24}H_{20}N_2O_2$ [M^+] 368.1525, found 368.1527.

*3-[Bis(4-methoxyphenyl)methyl]-6-fluoro-1H-indole (**3i**; Figure 2).* Following the general procedure, **3i** was obtained as a brown amorphous solid: yield 325 mg (90%); IR (KBr) (cm^{-1}) 3417, 1603, 1507; ^1H NMR (400 MHz, $CDCl_3$): δ 3.78 (s, 6H), 5.52 (s, 1H), 6.52 (dd, J = 2.1, 0.9 Hz, 1H), 6.73 (dt, J = 8.7, 2.5 Hz, 1H), 6.82 (d, J = 8.7 Hz, 4H), 7.01 (dd, J = 9.6, 2.1 Hz, 1H), 7.06−7.15 (m, 5H), 7.92 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.2, 55.3, 97.4 (d, J = 25.7 Hz), 108.1 (d, J = 24.8 Hz), 113.6, 113.7, 120.8 (d, J = 10.5 Hz), 120.9, 123.8, 124.2, 129.8, 132.4, 136.3, 136.8 (d, J = 12.4 Hz), 158.1, 160.0 (d, J = 236.5 Hz); MS (EI) m/z 361 (M^+, 100); HRMS (EI) m/z calcd for $C_{23}H_{20}NO_2F$ [M^+] 361.1478, found 361.1479.

*3-[Bis(4-methoxyphenyl)methyl]-5-chloro-1H-indole (**3j**; Figure 2).*[7d] Following the general procedure, **3j** was obtained as a brown amorphous solid: yield 359 mg (95%); IR (KBr) (cm^{-1}) 3355, 1587; ^1H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 6H), 5.50 (s, 1H), 6.58 (dd, J = 2.6, 1.3 Hz, 1H), 6.82 (d, J = 8.7 Hz, 4H), 7.05−7.15 (m, 5H), 7.19 (d, J = 2.1 Hz, 1H), 7.25 (d, J = 8.5 Hz, 1H), 7.98 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.9, 55.2, 112.1, 113.7, 119.3, 120.4, 122.4, 125.0, 125.2, 128.0, 129.7, 135.1, 136.1, 158.0; MS (EI) m/z (%) 379 (M^++2, 36), 377 (M^+, 100); HRMS (EI) m/z calcd for $C_{23}H_{20}NO_2Cl$ [M^+] 377.1183, found 377.1183.

*Methyl 3-[bis(4-methoxyphenyl)methyl]-1H-indole-5-carboxylate (**3k**; Figure 2).*[7d] Following the general procedure, **3k** was obtained as an off-white solid: yield 381 mg (95%); mp 151−153 °C; IR (KBr) (cm^{-1}) 3394, 1704; ^1H NMR (400 MHz, $CDCl_3$): δ 3.76 (s, 6H), 3.85 (s, 3H), 5.62 (s, 1H), 6.63 (d, J = 1.2 Hz, 1H), 6.81 (d, J = 8.7 Hz, 4H), 7.10 (d, J = 8.7 Hz, 4H), 7.34 (d, J = 8.5 Hz, 1H), 7.87 (dd, J = 8.5, 1.6 Hz, 1H), 8.05 (s, 1H), 8.18 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 46.7, 51.8, 55.2, 110.8, 113.7, 121.5, 122.1, 122.7, 123.5, 125.1, 126.7, 129.7, 136.2, 139.3, 158.0, 168.2; MS (EI) m/z 401 (M^+, 100). Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.79; H, 5.77; N, 3.49. Found: C, 74.89; H, 5.83; N, 3.45.

*3-[Bis(4-methoxyphenyl)methyl]-5-methoxy-1H-indole (**3l**; Figure 2).* Following the general procedure, **3l** was obtained as a white solid: yield 248 mg (66%); mp 118−120 °C; IR (KBr) (cm^{-1}) 3369, 1503; ^1H NMR (400 MHz, $CDCl_3$): δ 3.67 (s, 3H), 3.77 (s, 6H), 5.51 (s, 1H), 6.52−6.56 (m, 1H), 6.64 (d, J = 2.1 Hz, 1H), 6.81 (d, J = 8.5 Hz, 5H), 7.13 (d, J = 8.5 Hz, 4H), 7.22 (d, J = 8.7 Hz, 1H), 7.82 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.1, 55.2, 55.8, 102.1, 111.6, 112.0, 113.6, 120.3, 124.6, 127.4, 129.8, 131.9, 136.4, 153.7, 157.9; MS (EI) m/z (%) 373 (M^+, 100). Anal. Calcd for $C_{24}H_{23}NO_3$: C, 77.19; H, 6.21; N, 3.75. Found: C, 77.14; H, 6.28; N, 3.62.

*3-[Bis(4-methoxyphenyl)methyl]-1H-indole (**3m**; Figure 2).*[6a] Following the general procedure, **3m** was obtained as a pink solid: yield 326 mg (95%); mp 121−123 °C; IR (KBr) (cm^{-1}) 3419, 1509; ^1H NMR (400 MHz, $CDCl_3$): δ 3.77 (s, 6H), 5.56 (s, 1H), 6.54 (dd, J = 2.3, 1.1 Hz, 1H), 6.81 (d, J = 8.7 Hz, 4H), 6.98 (ddd, J = 8.0, 7.1, 0.9 Hz, 1H), 7.10−7.18 (m, 5H), 7.21 (d, J = 8.7 Hz, 1H), 7.33 (dt, J = 8.3, 0.7 Hz, 1H), 7.91 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 47.1, 55.2, 111.0, 113.6, 119.3, 120.0, 120.7, 122.0, 123.9, 127.0, 129.8, 136.5, 136.7, 157.9; MS (EI) m/z (%) 343 (M^+, 100).

*3-[Bis(4-methoxyphenyl)methyl]-2-methyl-1H-indole (**3n**; Figure 2).*[15] Following the general procedure, **3n** was obtained as a white solid: yield 253 mg (71%); mp 165−167 °C; IR (KBr) (cm^{-1}) 3416, 1505; ^1H NMR (400 MHz, DMSO-d_6): δ 2.18 (s, 3H), 3.70 (s, 6H), 5.60 (s, 1H), 6.73 (dd, J = 7.6, 7.6 Hz, 1H), 6.82 (d, J = 8.7 Hz, 4H), 6.88−6.93 (m, 2H), 7.04 (d, J = 8.7 Hz, 4H), 7.21 (d, J = 8.3 Hz, 1H), 10.8 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 12.4, 45.8, 55.5, 110.9, 113.7, 113.9, 118.6, 119.2, 120.2, 128.2, 130.1, 132.7, 135.8, 136.9, 157.8; MS (EI) m/z (%) 357 (M^+, 100).

*Ethyl 3-[Bis(4-methoxyphenyl)methyl]-1H-indole-2-carboxylate (**3o**; Figure 2).* Following the general procedure, **3o** was obtained as a white solid: yield 291 mg (70%); mp 213−125 °C; IR (KBr) (cm^{-1}) 3365, 1674, 1512; ^1H NMR (400 MHz, $CDCl_3$): δ 1.39 (t, J = 7.1 Hz, 3H), 3.74 (s, 6H), 4.38 (q, J = 7.1 Hz, 2H), 6.56 (s, 1H), 6.79 (d, J = 8.5 Hz, 4H), 6.89 (dd, J = 7.3, 7.3 Hz, 1H), 7.00 (d, J = 8.2 Hz, 1H),

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7.12 (d, J = 8.7 Hz, 4H), 7.23 (dd, J = 7.6, 7.6 Hz, 1H), 7.35 (d, J = 8.5 Hz, 1H), 8.82 (br s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.4, 45.6, 55.2, 61.0, 111.7, 113.5, 120.1, 123.6, 125.1, 126.7, 127.3, 130.1, 136.0, 136.1, 157.9, 162.1; MS (EI) m/z (%) 415 (M^+, 57), 369 (100). Anal. Calcd for $C_{26}H_{25}NO_4$: C, 75.16; H, 6.07; N, 3.37. Found: C, 74.87; H, 6.13; N, 3.39.

*3-[Bis(4-methoxyphenyl)methyl]-1-methyl-2-phenyl-1H-indole (**3p**; Figure 2).* Following the general procedure, **3p** was obtained as a white solid: yield 221 mg (51%); mp 203−205 °C; IR (KBr) (cm^{-1}) 2956, 1505; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.58 (s, 3H), 3.76 (s, 6H), 5.42 (s, 1H), 6.75 (d, J = 8.7 Hz, 4H), 6.93 (ddd, J = 8.0, 7.1, 0.9 Hz, 1H), 7.06 (d, J = 8.3 Hz, 4H), 7.13 (d, J = 7.8 Hz, 1H), 7.18 (ddd, J = 8.3, 7.1, 1.1 Hz, 1H), 7.25−7.29 (m, 2H), 7.33 (d, J = 8.3 Hz, 1H), 7.40−7.44 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.9, 46.5, 55.2, 109.3, 113.4, 115.7, 119.2, 121.3, 126.9, 128.2, 128.3, 130.0, 130.8, 136.9, 157.6; MS (EI) m/z (%) 433 (M^+, 100). Anal. Calcd for $C_{30}H_{27}NO_2$: C, 83.11; H, 6.28; N, 3.23. Found: C, 82.89; H, 6.35; N, 3.22.

*2-[Bis(4-methoxyphenyl)methyl]-3-methyl-1H-indole (**3q**; Figure 2).* Following the general procedure, **3q** was obtained as an off-white solid: yield 308 mg (86%); mp 119−121 °C; IR (KBr) (cm^{-1}) 3433, 1508; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.13 (s, 3H), 3.72 (s, 6H), 5.67 (s, 1H), 6.87 (d, J = 8.5 Hz, 4H), 6.93 (dd, J = 8.5, 8.5 Hz, 1H), 6.99 (dd, J = 8.5, 8.5 Hz, 1H), 7.09 (d, J = 8.5 Hz, 4H), 7.25 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 7.8 Hz, 1H), 10.4 (br s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 9.1, 46.7, 55.5, 106.4, 111.4, 114.2, 118.2, 118.6, 120.9, 129.1, 130.2, 135.3, 136.2, 137.3, 158.2; MS (EI) m/z (%) 357 (M^+, 100). Anal. Calcd for $C_{24}H_{23}NO_2$: C, 80.64; H, 6.49; N, 3.92. Found: C, 80.62; H, 6.50; N, 3.91.

*3-[Bis(4-methoxyphenyl)methyl]-1H-indole-5-carboxylic Acid (**4a**; Figure 3).* Following the general procedure, **4a** was obtained as a pink solid: yield 318 mg (82%); mp 260−262 °C; IR (KBr) (cm^{-1}) 3391, 1687; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (s, 6H), 5.62 (s, 1H), 6.74 (dd, J = 2.3, 0.7 Hz, 1H), 6.85 (d, J = 8.8 Hz, 4H), 7.12 (d, J = 8.8 Hz, 4H), 7.40 (dd, J = 8.5, 0.7 Hz, 1H), 7.68 (dd, J = 8.5, 1.6 Hz, 1H), 7.85 (d, J = 1.6 Hz, 1H), 11.2 (s, 1H), 12.3 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 46.6, 55.5, 100.0, 114.2, 120.5, 121.4, 122.4, 126.6, 129.9, 136.9, 139.8, 158.0, 168.8; MS (EI) m/z (%) 387 (M^+, 100). Anal. Calcd for $C_{24}H_{21}NO_4 \cdot 0.1H_2O$: C, 74.06; H, 5.49; N, 3.60. Found: C, 73.94; H, 5.62; N, 3.51.

*3-[Bis(4-methoxyphenyl)methyl]-1H-indole-2-carboxylic Acid (**4b**; Figure 3).* Following the general procedure, **4b** was obtained as a white solid: yield 325 mg (84%); mp 248−250 °C; IR (KBr) (cm^{-1}) 3457, 2939, 1664; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.70 (s, 6H), 6.61 (s, 1H), 6.79−6.88 (m, 5H), 6.95 (d, J = 8.3 Hz, 1H), 7.05 (d, J = 8.3 Hz, 4H), 7.14 (ddd, J = 8.3, 6.9, 1.1 Hz, 1H), 7.41 (d, J = 8.3 Hz, 1H), 11.6 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.0, 55.5, 113.2, 114.0, 119.8, 122.8, 124.6, 124.7, 125.2, 126.8, 130.2, 136.4, 137.0, 157.9, 163.9; MS (EI) m/z (%) 387 (M^+, 92), 369 (100). Anal. Calcd for $C_{24}H_{21}NO_4$: C, 74.40; H, 5.46; N, 3.62. Found: C, 74.28; H, 5.65; N, 3.64.

*3-[Bis(4-methoxyphenyl)methyl]-1-methyl-1H-indole-2-carboxylic Acid (**4c**; Figure 3).* Following the general procedure, **4c** was obtained as a white solid: yield 337 mg (84%); mp 227−229 °C; IR (KBr) (cm^{-1}) 2952, 1661; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.66 (s, 6H), 3.94 (s, 3H), 6.50 (s, 1H), 6.83 (d, J = 8.7 Hz, 4H), 6.87 (d, J = 8.0 Hz, 1H), 6.94 (d, J = 8.0 Hz, 1H), 7.01 (d, J = 8.5 Hz, 4H), 7.23 (dd, J = 7.3, 7.3 Hz, 1H), 7.52 (d, J = 8.5 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 32.6, 45.5, 55.5, 111.4, 114.0, 120.2, 122.9, 124.7, 125.3, 125.8, 127.0, 130.0, 130.1, 136.3, 139.0, 157.9, 164.1; MS (EI) m/z (%) 401 (M^+, 87), 383 (100). Anal. Calcd for $C_{25}H_{23}NO_4$: C, 74.80; H, 5.77; N, 3.49. Found: C, 74.72; H, 5.71; N, 3.47.

*3-[Bis(4-fluorophenyl)methyl]-1H-indole-2-carboxylic Acid (**4d**; Figure 3).* Following the general procedure, **4d** was obtained as a white solid: yield 267 mg (73%); mp 233−235 °C; IR (KBr) (cm^{-1}) 3448, 3067, 1667; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.65 (s, 3H), 6.90−7.00 (m, 6H), 7.16 (d, J = 8.3 Hz, 2H), 7.17 (d, J = 8.3 Hz, 2H), 7.29 (ddd, J = 8.0, 6.4, 1.4 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 8.89 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.3, 113.4, 115.5 (d, J = 21.0 Hz), 120.2, 122.3, 123.8, 124.7, 125.0, 126.6, 130.9 (d, J = 7.6 Hz), 137.0, 140.0, 161.2 (d, J = 241.2 Hz), 163.7; MS (EI) m/z (%) 363 (M^+, 68), 252 (100). Anal. Calcd for $C_{22}H_{15}F_2NO_2$: C, 72.72; H, 4.16; N, 3.85. Found: C, 72.72; H, 4.35; N, 3.94.

*3-[(4-Methoxyphenyl)(phenyl)methyl]-1H-indole-2-carboxylic Acid (**4e**; Figure 3).* Following the general procedure, **4e** was obtained as a white solid: yield 322 mg (90%); mp 234−236 °C; IR (KBr) (cm^{-1}) 3457, 3005, 1664; ^{1}H NMR (400 MHz, DMSO-d_6): δ 3.71 (s, 3H), 6.83 (s, 1H), 6.77−6.88 (m, 3H), 6.93 (d, J = 8.0 Hz, 1H), 7.05 (d, J = 8.7 Hz, 2H), 7.10−7.22 (m, 4H), 7.27 (dd, J = 7.3, 7.3 Hz, 2H), 7.41 (d, J = 8.3 Hz, 1H), 11.6 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 45.3, 55.0, 112.7, 113.6, 119.4, 122.2, 124.1, 124.2, 124.3, 126.0, 126.3, 128.1, 128.7, 129.7, 135.4, 136.4, 143.9, 157.5, 163.4; MS (EI) m/z (%) 357 (M^+, 87), 339 (100). Anal. Calcd for $C_{23}H_{19}NO_3 \cdot 0.1H_2O$: C, 76.91; H, 5.39; N, 3.90. Found: C, 76.85; H, 5.53; N, 3.78.

*3-[Phenyl(p-tolyl)methyl]-1H-indole-2-carboxylic Acid (**4f**; Figure 3).* Following the general procedure, **4f** was obtained as a white solid: yield 258 mg (76%); mp 242−244 °C; IR (KBr) (cm^{-1}) 3415, 3023, 1666; ^{1}H NMR (400 MHz, DMSO-d_6): δ 2.25 (s, 3H), 6.70 (s, 1H), 6.80 (dd, J = 7.3, 7.3 Hz, 1H), 6.93 (dd, J = 8.0, 8.0 Hz, 1H), 7.02 (d, J = 7.6 Hz, 2H), 7.07 (d, J = 7.6 Hz, 2H), 7.10−7.22 (m, 4H), 7.26 (dd, J = 7.3, 7.3 Hz, 2H), 7.41 (d, J = 8.3 Hz, 1H), 11.6 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 21.1, 46.2, 113.2, 119.9, 122.7, 124.5, 124.6, 124.9, 126.5, 126.8, 128.7, 129.2, 129.3, 135.5, 136.9, 141.0, 144.2, 163.9; MS (EI) m/z (%) 341 (M^+, 85), 323 (100). Anal. Calcd for $C_{23}H_{19}NO_2 \cdot 0.2H_2O$: C, 80.07; H, 5.67; N, 4.06. Found: C, 80.09; H, 5.82; N, 3.98.

*3-Benzhydryl-1H-indole-2-carboxylic Acid (**4g**; Figure 3).*[16] Following the general procedure, **4g** was obtained as a white solid: yield 208 mg (64%); mp 146−148 °C; IR (KBr) (cm^{-1}) 3452, 3049, 1665; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.71 (s, 1H), 6.76 (dt, J = 8.0, 0.7 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 7.07−7.18 (m, 8H), 7.23 (dd, J = 7.1, 7.1 Hz, 4H), 7.38 (d, J = 8.3 Hz, 1H), 11.6 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 46.7, 113.3, 119.9, 122.7, 124.3, 124.6, 125.0, 126.6, 126.9, 128.7, 129.3, 137.0, 144.0, 163.9; MS (EI) m/z (%) 327 (M^+, 100).

*3-[(4-Chlorophenyl)(phenyl)methyl]-1H-indole-2-carboxylic Acid (**4h**; Figure 3).* Following the general procedure, **4h** was obtained as a white solid: yield 225 mg (62%); mp 231−233 °C; IR (KBr) (cm^{-1}) 3431, 3053, 1667; ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.68 (s, 1H), 6.92 (dd, J = 7.7, 7.7 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 7.10−7.32 (m, 11H), 7.38 (d, J = 8.3 Hz, 1H), 8.89 (s, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ 46.1, 113.3, 120.1, 122.4, 123.7, 124.7, 125.0, 126.8, 128.7, 128.8, 129.2, 131.1, 131.2, 136.9, 143.1, 143.5, 163.8; MS (EI) m/z (%) 363 (M^++2, 34), 361 (M^+, 100). Anal. Calcd for $C_{22}H_{16}ClNO_2$: C, 73.03; H, 4.46; N, 3.87. Found: C, 73.01; H, 4.62; N, 3.87.

*3-[1-(4-Methoxyphenyl)ethyl]-1-methyl-1H-indole (**5a**; Figure 4).*[7d] Following the general procedure, **5a** was obtained as a colorless oil: yield 252 mg (95%); IR (neat) (cm^{-1}) 2960, 1471; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (d, J = 7.1 Hz, 3H), 3.59 (s, 3H), 3.67 (s, 3H), 4.28 (q, J = 7.1 Hz, 1H), 6.70−6.82 (m, 3H), 6.96 (dt, J = 8.0, 1.1 Hz, 1H), 7.10−7.23 (m, 4H), 7.35 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 31.8, 35.3, 54.4, 108.4, 112.9, 117.9, 119.1, 119.6, 120.8, 125.1, 127.6, 136.6, 138.4, 157.0; MS (EI) m/z (%) 265 (M^+, 42), 250 (100).

*1-Methyl-3-(1-phenylethyl)-1H-indole (**5b**; Figure 4).*[17] Following the general procedure, **5b** was obtained as a colorless oil: yield 130 mg (55%); IR (neat) (cm^{-1}) 2964, 1477; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.68 (d, J = 7.1 Hz, 3H), 3.69 (s, 3H), 4.35 (q, J = 7.1 Hz, 1H), 6.81 (s, 1H), 6.98 (ddd, J = 8.0, 7.1, 1.2 Hz, 1H), 7.10−7.32 (m, 7H), 7.35 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.7, 32.8, 37.1, 109.3, 118.8, 119.9, 120.1, 121.7, 126.0, 126.1, 127.4, 127.6, 127.8, 128.5, 137.5, 147.1; MS (EI) m/z (%) 235 (M^+, 78), 220 (100).

*3-(1-Phenylethyl)-1H-indole-2-carboxylic Acid (**5c**; Figure 4).* Following the general procedure, **5c** was obtained as a white solid: yield 282 mg (91%); mp 178−180 °C; IR (KBr) (cm^{-1}) 2967, 1666; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.70 (d, J = 7.3 Hz, 3H), 3.69 (s, 3H), 3.93 (s, 3H), 5.21 (q, J = 7.3 Hz, 1H), 6.81 (d, J = 8.7 Hz, 2H), 6.91 (dd, J = 7.6, 7.6 Hz, 1H), 7.20−7.30 (m, 3H), 7.33 (d, J = 8.4 Hz, 1H), 7.48 (d, J = 8.4 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6): δ

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19.8, 31.9, 33.4, 54.8, 110.7, 113.3, 119.2, 121.9, 124.1, 124.2, 125.5, 127.0, 127.9, 137.1, 138.4, 157.0, 163.7; MS (EI) m/z (%) 309 (M^+, 57), 294 (100); HRMS (EI) m/z calcd for $C_{19}H_{19}NO_3$ [M^+], 309.1365 found 309.1364.

*3-(4-Methoxybenzyl)-1-methyl-1H-indole (**6a**; Figure 4).*[18] Following the general procedure, **6a** was obtained as a colorless oil: yield 186 mg (74%); IR (neat) (cm^{-1}) 2905, 1471; ^1H NMR (400 MHz, $CHCl_3$): δ 3.63 (s, 3H), 3.70 (s, 3H), 4.00 (s, 2H), 6.65 (d, J = 2.3 Hz, 1H), 6.73−6.82 (m, 2H), 7.00−7.08 (m, 1H), 7.12−7.25 (m, 4H), 7.48 (dd, J = 7.8, 2.3 Hz, 1H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 30.9, 32.7, 55.4, 109.4, 114.0, 114.1, 115.0, 119.0, 119.5, 121.8, 127.3, 128.1, 129.8, 133.8, 137.4, 158.1; MS (EI) m/z (%) 251 (M^+, 100).

*3-(3,4-Dimethoxybenzyl)-1-methyl-1H-indole (**6b**; Figure 4).* Following the general procedure, **6b** was obtained as a colorless oil: yield 141 mg (50%); IR (neat) (cm^{-1}) 2938, 1512; ^1H NMR (400 MHz, $CHCl_3$): δ 3.64 (s, 3H), 3.78 (s, 3H), 3.80 (s, 3H), 4.02 (s, 2H), 6.65−6.90 (m, 4H), 7.05 (dd, J = 6.9, 6.9 Hz, 1H), 7.12−7.30 (m, 2H), 7.51 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CHCl_3$): δ 30.5, 31.9, 55.1, 55.2, 108.5, 110.4, 111.4, 113.9, 118.1, 118.5, 119.9, 120.9, 126.4, 133.3, 146.5, 148.1; MS (EI) m/z (%) 281 (M^+, 100); HRMS (EI) m/z calcd for $C_{18}H_{19}NO_2$ [M^+], 281.1416 found 281.1413.

Conversion Yields of 8a,b (Table S1, Supporting Information). A mixture of 1,3-dimethoxybenzene 7 (138.2 mg, 1.0 mmol), catalyst, and benzhydrol (**2a**; 221 mg, 1.2 mmol) in H_2O (4 mL) was heated at 80 °C for 36 h. After the reaction mixture was cooled, *p*-nitroanisole (153.1 mg, 1.0 mmol, internal standard) was added to the reaction mixture, which was extracted with $CDCl_3$ (8 mL), and then the organic layer was analyzed by ^1H NMR spectroscopy.

Preparation of 8a,b. A mixture of 1,3-dimethoxybenzene (7; 138.2 mg, 1.0 mmol), $Hf(OTf)_4$ (77 mg, 0.1 mmol), and benzhydrol (**2a**; 221 mg, 1.2 mmol) in H_2O (4 mL) was heated to 120 °C for 3 h. After it was cooled, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes/EtOAc) to give **8a** (75 mg, 0.25 mmol) and **8b** (60 mg, 0.13 mmol).

*[(2,4-Dimethoxyphenyl)methylene]dibenzene (**8a**):* white solid; yield 75 mg (25%); mp 126−127 °C (lit.[18] mp 120−121 °C); IR (KBr) (cm^{-1}) 2945, 1587, 1496, 1458; ^1H NMR (400 MHz, $CDCl_3$): δ 3.69 (s, 3H), 3.78 (s, 3H), 5.83 (s, 1H), 6.39 (dd, J = 8.5, 2.5 Hz, 1H), 6.46 (d, J = 2.5 Hz, 1H), 6.73 (d, J = 8.5 Hz, 1H), 7.06−7.12 (m, 4H), 7.18 (tt, J = 7.3, 1.4 Hz, 2H), 7.22−7.30 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.1, 55.3, 55.6, 98.6, 103.7, 125.2, 125.9, 128.1, 129.4, 130.7, 144.2, 158.0, 159.4; MS (EI) m/z (%) 304 (M^+, 100).

*[(4,6-Dimethoxy-1,3-phenylene)bis(methanetriyl)]tetrabenzene (**8b**):* white solid, 60 mg (13%); mp 139−141 °C (lit.[19] mp 154−155 °C); IR (KBr) (cm^{-1}) 3026, 1603, 1499, 1456; ^1H NMR (400 MHz, $CDCl_3$): δ 3.70 (s, 6H), 5.75 (s, 2H), 6.39 (s, 1H), 6.44 (s, 1H), 6.90−6.96 (m, 8H), 7.07−7.18 (m, 12H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.1, 55.9, 95.5, 124.0, 125.9, 128.0, 129.3, 132.8, 144.2, 156.4; MS (EI) m/z (%) 470 (M^+, 100).

General Procedure for Figure 1 and Table S2 (Supporting Information). A mixture of 1-methylindole (**1a**; 131 mg, 1.0 mmol), $AuCl_4Na{\cdot}2H_2O$ (8.0 mg, 2 mol %), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 7.3 mg, 2 mol %), benzhydrol (**2a**; 184 mg, 1 mmol) and alcohols **2x** (1 mmol) in H_2O (4 mL) was heated to 80 °C for 30 min in a sealed tube. After it was cooled, the reaction mixture was extracted with $CDCl_3$ (8 mL) and then the organic layer was determined by ^1H NMR.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Tables giving data for the Friedel-Crafts reaction of 1,3-dimethoxybenzene (7) and for the Brown−Okamoto plot for the rate constants of benzylation by various substituted alcohols and figures giving ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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