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Iron-Catalyzed Direct C3-Benzylation of Indoles with Benzyl Alcohols through Borrowing Hydrogen

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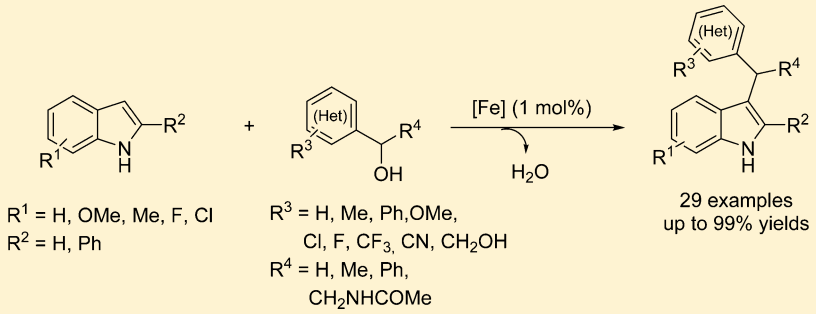
Supporting Information



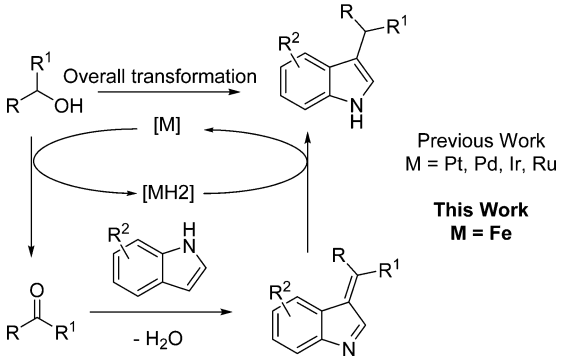
ABSTRACT: We present the coupling of primary and secondary benzyl alcohols with indoles to form 3-benzylated indoles and H_2O that is catalyzed, for the first time, by a complex of earth-abundant iron. This transformation accommodates a variety of substrates and is distinguished by its operational simplicity, sustainability, high functional-group tolerance, and amenability to gram-scale synthesis. On the basis of the preliminary experimental observations, we propose that the reaction proceeds through a borrowing hydrogen process.

The catalytic alkylation of indoles with alcohols represents an environmentally benign and atom-economic pathway for the synthesis of substituted indoles and indolenine, which have important synthetic applications in the synthesis of dyes, fragrances, pharmaceuticals (including controlling bacterial behavior), and agricultural chemicals.[1] In terms of sustainability, the choice of alcohols as substrates is highly desirable as they are readily available by a variety of industrial processes, inexpensive because they can be obtained renewably via fermentation or catalytic conversion of lignocellulosic biomass, relatively nontoxic, and easy to use.[2] The best known method for the alkylation of indoles is the Friedel−Crafts reaction with haloalkanes and related alkyl agents mediated by Lewis acid.[3] However, this method can be problematic due to over alkylation, toxic nature of many alkyl (pseudo)halides, and it also produces large amounts of inorganic salt. The so-called 'borrowing hydrogen methodology'[4] has aroused great interest in recent years and is an excellent protocol for the catalytic C-alkylation of ketones and related compounds, using nontoxic alcohols.[5] The catalytic cycle, for the indole alkylation, involves three or four successive steps: (i) acceptorless dehydrogenation of alcohols, (ii) alkylideneindolenine formation (which behaves as an actual vinylogous imine), and (iii) *in situ* hydrogenation of the double bond (borrowing hydrogen methodology) and aromatization generate the alkylated-indole compound. Key features are that the process is hydrogen neutral and that the only stoichiometric byproduct is water (Scheme 1).

Despite the significance of such coupling reactions, homogeneous and heterogeneous catalysts mostly employ precious metals such as Pt,[6] Pd,[7] Ir,[8] and Ru.[9] In comparison, the same reaction with catalysts that utilize nonprecious, less toxic earth-abundant metals[10] is much less developed. However, base metals have been found to readily oxidize alcohols via acceptorless dehydrogenation.[11]

On the other hand, the groups of Feringa and Barta, Wills, and Zhao have reported the alkylation of primary amines with alcohols to give secondary and tertiary amines by utilizing iron catalysts featuring functionalized cyclopentadienone or hydroxy

Scheme 1. Representative Reaction Pathway for the C3-Alkylation of Indoles by Transition-Metal-Catalyzed Borrowing Hydrogen Methodology



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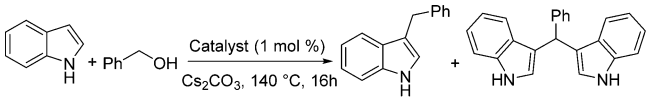
cyclopentadienyl ligands based on Knölker's complex or derivatives thereof.[12] Applications of this methodology based on an iron-catalyzed hydrogen-borrowing strategy process also include the formation of new carbon−carbon bonds.[13]

Inspired by these recent discoveries, we report herein a green, economical, and efficient iron-catalyzed C3-selective alkylation of indole. This reaction employs iron(II) phthalocyanine (Fe(II)Pc), an inexpensive commercially available compound that is typically used as an industrial additive for ink as well as photonic and optical material manufacturing. Of note, to date, Fe(II)Pc complexes have not been applied as catalysts for the formation of new carbon−carbon bonds via the borrowing hydrogen process.[14]

The reaction of unsubstituted indole (**1a**) with benzyl alcohol (**2a**) was selected as the model reaction to establish the best reaction conditions. Initially, the effect of various iron-based catalysts was investigated (Table 1). The reaction did not proceed without any catalyst in the presence of Cs_2CO_3, which excluded the contribution of the base itself as a catalyst (Table 1, entry 1).[15] The highest activity was observed with Fe(II)Pc and a stoichiometric amount of Cs_2CO_3 (Table 1, entries 5−7). Other iron salts were found to be ineffective and, not surprisingly, led to the formation of bis(indolyl)methane (**4**) in poor yields (Table 1, entries 2−4).[16] Due to its inherent redox properties, the iron(0)tricarbonyl complex such as the Knölker-type catalyst is widely known to activate inert substrates via dehydrogenation/hydrogenation reactions and has been reported previously for C−C bond formation.[17] Neither alone (Table 1, entry 8) nor in the presence of 10 mol % Me_3NO oxidant (to form active catalyst) and PPh_3 ligand did the alkylated product form (Table 1, entries 9 and 10). This solvent-free reaction with Fe(II)Pc as the catalyst was excellent in terms of both yield and selectivity as compared with the corresponding reaction in toluene (1.0 M, 54% yield; 0.5 M, 10% yield) or *tert*-amyl alcohol (at reflux under air atmosphere for 16 h afforded the desired alkylated product **3a** in 31% yield). The desired coupling product was also obtained in the absence of light as well as in the presence of radical scavengers such butylated hydroxytoluene (BHT), thus discarding the involvement of radical species in the reaction pathway (Table 1, entries 11 and 12).[18]

Table 1. Optimization of the Reaction Conditions for C3-Alkylation of Indole with Benzyl Alcohol



entry[a]	catalyst	yield of **3a**[b] (%)
1	–	–
2	$FeSO_4$[c]	–
3	$FeCl_2$[d]	–
4	$Fe(acac)_3$	–
5	Fe(II)Pc	99
6	Fe(II)Pc[e]	8
7	Fe(II)Pc[f]	trace
8	Fe-Knölker	–
9	Fe-Knölker with PPh_3	–
10	Fe-Knölker with Me_3NO	–
11	Fe(II)Pc in the dark	97
12	Fe(II)Pc with BHT	98

[a]Reaction conditions: indole (0.5 mmol), benzyl alcohol (1 mmol), Cs_2CO_3 (0.55 mmol), catalyst (1 mol %) at 140 °C for 16 h. [b]Isolated yield. [c]Only **4** was isolated in 13% yield [d]Only **4** was isolated in 21% yield [e]Cs_2CO_3 (0.05 mmol). [f]Without base.

Once the optimal reaction conditions were achieved, we examined the scope of the alkylation with respect to alcohols catalyzed by Fe(II)Pc, and these results are outlined in Scheme 2. The C3-alkylation of indole with primary benzylic alcohols bearing an electron-donating substituent such as methyl, phenyl, and methoxy groups afforded the corresponding products **3b−f** in 46−98% yields. Also, (2-aminophenyl)-methanol and 2-(hydroxymethyl)phenol provided the products **3g−h** in good yield, 56% and 42%, respectively. Similarly, electronically deactivated benzylic alcohols, which are very poor substrates in Lewis- or Brønsted acid-catalyzed Friedel−Crafts reactions,[19] bearing an electron-withdrawing group such as chloro, fluoro, cyano and trifluoromethyl groups were converted to the desired products **3i−m** in 37−71% yields. A trisubstituted benzyl alcohol, such as 3,4,5-trimethoxybenzyl alcohol, was successfully transformed to 3-(3,4,5-trimethoxybenzyl)-1*H*-indole in 62% yield. A naphthyl alcohol (naphthalen-2-ylmethanol), (3,5-dichlorophenyl)methanol, and benzo[1,3]dioxonyl were converted to give the corresponding alkylated indole products **3o−q** in good yields. Heteroaromatic alcohols with furanyl and thienyl groups were also tolerated, and the corresponding indoles **3r−s** were obtained in 95% and 78% yields, respectively.

This reaction sequence was demonstrated for the preparation of symmetrical bisindole compound **3t**, whereby indole, used in excess, was double alkylated with 1,3-phenylenedimethanol through a one-pot process in satisfactory yield. Moreover, sequential functionalization of diols is undoubtedly a valuable synthetic tool to obtain compounds with great diversity. We explored a selective iron-catalyzed method that allows for the preparation of nonsymmetrical, functionalized bisindoles. This reaction sequence was demonstrated for the preparation of compound **3u**, whereby 1,3-phenylenedimethanol was selectively monoalkylated with indole to form (3-((1*H*-indol-3-yl)methyl)phenyl)methanol and subsequently treated with 6-fluoroindole to provide **3u**.

Next, secondary benzylic alcohols, which are less prone to the condensation and hydrogenation step in comparison to primary ones, were used as the substrate. 1-Phenylethanol, diphenylmethanol, and 2-acetamido-1-phenylethanol reacted smoothly with indole, and the corresponding products **3v−x** were obtained in moderate to good yields.

When cinnamyl alcohol was utilized, the desired product was obtained in poor yield due to large contamination of saturated derivatives; whereas with aliphatic alcohols such as cyclohexanol, cyclopropyl methanol, and 1-octanol, the reaction failed.

Next, we examined some representative substituted indoles to explore the generality of this novel reaction. For example, the electron-rich and sterically hindered 4-methoxyindole was converted to the desired product **3x** in a very good yield and selectivity. The 6-methyl-, 5-fluoro-, and 6-chloroindole-benzylated derivatives **3z** and **3aa−3ab** were also obtained in decent yields, although the yields were lower than those of the 4-OMe analog. Pleasingly, the presence of a substituent at C2 did not impair the reaction, despite the potential steric crowding around the reaction site. Thus, 2-phenylindole reacted efficiently with benzyl alcohol to give the corresponding product **3ac**. Not surprisingly, *N*-methylindole proved to be

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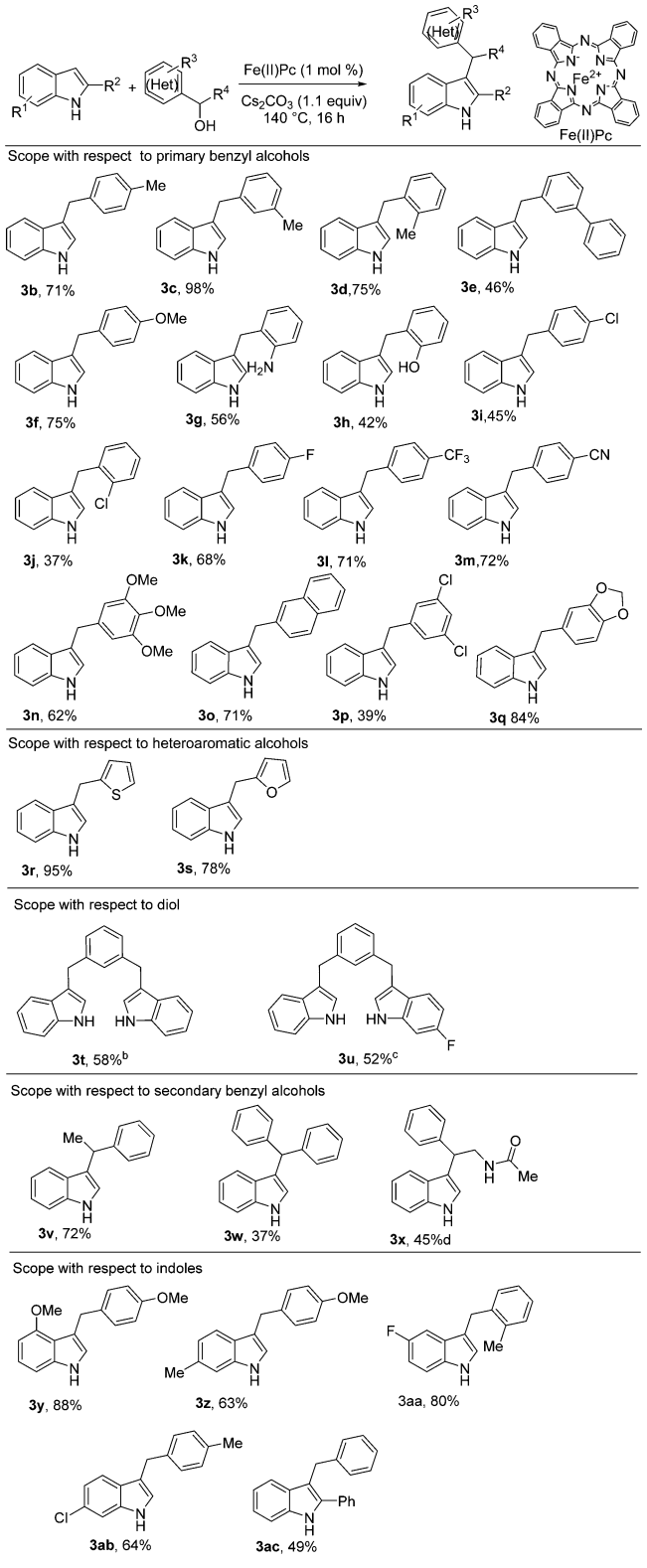
Scheme 2. Scope of C3-Alkylation of Indole with Benzyl Alcohol[a]



[a]Reaction conditions: indole (0.5 mmol), alcohol (1 mmol), Cs_2CO_3 (0.55 mmol), Fe(II)Pc (0.055 mmol) at 140 °C for 16 h. [b]Indole (1 mmol), alcohol (0.5 mmol). [c]1*H*-indole (0.5 mmol), 6-fluoro-1*H*-indole (0.5 mm0l), 2-(hydroxymethyl)phenol (0.5 mmol). [d]140 °C for 36h.

inert, suggesting the involvement of the indole N−H in a key interaction with the base during the rate-determining step. However, nearly complete recovery of the starting material was observed when C3-substituted indole, such as 3-methyl or 3-benzylindole, was allowed to react with benzyl alcohol under the reaction conditions reported above. Neither dearomatization of the indole nucleus to 3-benzylindolenine products nor C3- to C2-benzyl migration and rearomatization to afford 2,3-disubstituted indoles were detected, in spite of recent reports.[20] To highlight the synthetic utility of the present protocol, a gram-scale reaction with indole (**1a**) and benzylic alcohol (**2a**) was performed, and the efficiency of the small-scale reaction was retained upon scale-up, delivering **3a** in 92% yield.

To obtain insight into the reaction mechanism of the catalytic process, other experiments were carried out, thus providing significant evidence for a plausible borrowing hydrogen mechanism rather than a general acidic strategy involving the formation of a stabilized benzylic cation. The reaction of indole with benzyl bromide (2 equiv) under the optimized reaction conditions gave a mixture of 1-benzyl-1*H*-indole (45%) and 1,3-dibenzyl-1*H*-indole (28%). Then, we repeated the reaction using triphenylmethanol, and the starting unchanged indole was recovered, which is another indirect proof that the cationic benzyl intermediate is not involved. When benzylic alcohol was heated in the presence of Fe(II)Pc and cesium carbonate at 140 °C in a sealed tube for 16 h, formation of a small amount of benzaldehyde (11% according to GC-analysis of the crude mixture) was observed. Finally, the competitive reaction of indole with benzaldehyde and (4-methoxyphenyl)methanol (Scheme 3) gave a mixture 6:1 of 3-benzylated compounds (based on ^{1}H NMR spectra), in which the main product was that arising from the condensation with benzaldehyde followed by reduction of benzylideneindolenine (obviously, large formation of *p*-methoxybenzaldehyde was also observed). All of these data together with the presence of bisindole side product **4**, obtainable only in the presence of aldehyde on the reaction mixture, and the good yields obtained with electronpoor benzylic alcohols (compounds **3l**, **3m**) are confirming our initial borrowing hydrogen mechanistic hypothesis.

In conclusion, we have established, for the first time, a general methodology for the catalytic formation of value-added 3-benzylindoles through the use of indole and primary, secondary, and heteroaromatic benzyl alcohols using an easily handled, air- and moisture-stable earth-abundant iron complex catalyst that operates through a hydrogen-borrowing mechanism. Many synthetically challenging routes were systematically explored, starting from readily accessible substrates that do not require prior alcohol activation by stoichiometric methods. This included the one-pot synthesis of symmetrical bisindoles, the sequential functionalization of diols, and the use of a secondary alcohol coupling partner under the catalytic conditions, which then enabled the formation of the desired branched alkylated indole cross-coupled products.

EXPERIMENTAL SECTION

General Methods. All reactions were run in air unless otherwise noted. Column chromatography purifications were performed in flash chromatography conditions using 230−400 mesh silica gel. Analytical thin-layer chromatography (TLC) was carried out on silica gel plates (Silica Gel 60 F254) that were visualized by exposure to ultraviolet light and an aqueous solution of $KMnO_4$. ^{1}H NMR and ^{13}C NMR spectra were recorded on a 400 spectrometer, using $CDCl_3$ and

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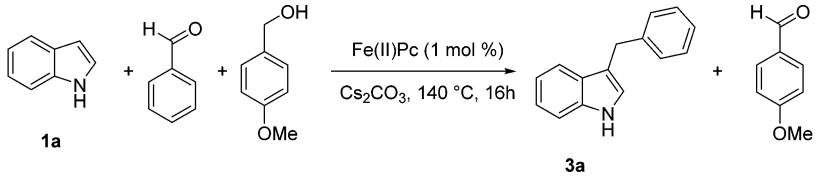
Scheme 3. Competitive Experiments between an Aldehyde and an Alcohol



acetone-d_6 as solvent. Chemical shifts (δ scale) are reported in parts per million (ppm) relative to the central peak of the solvent. Coupling constants (J values) are given in hertz (Hz). ESI-MS spectra were taken on a Waters Micromass ZQ instrument. IR spectra were obtained on FT-IR spectrometer, and absorbance is reported in cm^{-1}. Melting points were determined on a capillary melting point apparatus and are uncorrected. HRMS analysis was performed using a Q-TOF microTM mass spectrometer.

Starting Materials. 1*H*-indole, 6-fluoro-1*H*-indole, 4-methoxy-1*H*-indole, 6-methyl-1*H*-indole, 5-fluoro-1*H*-indole, 6-chloro-1*H*-indole, 2-phenyl-1*H*-indole, benzyl alcohol, *p*-tolylmethanol, *m*-tolylmethanol, *o*-tolylmethanol, biphenyl-3-ylmethanol, (*N*-(2-hydroxy-2-phenylethyl)acetamide, 4-methoxyphenyl)methanol, (2-aminophenyl)methanol, 2-(hydroxymethyl)phenol, (4-chlorophenyl)-methanol, (2-chlorophenyl)methanol, (4-fluorophenyl)methanol, (4-(trifluoromethyl)phenyl)methanol, 4-(hydroxymethyl)benzonitrile, (3,4,5-trimethoxyphenyl)methanol, naphthalen-2-ylmethanol, (3,5-dichlorophenyl)methanol, furan-2-ylmethanol, thiophen-2-ylmethanol, benzo[*d*][1,3]dioxol-5-ylmethanol, 1-phenylethanol, and diphenylmethanol are commercially available.

General Procedure for C3-Alkylation of Indole with Benzyl Alcohol. A vial was charged with the appropriate indole (0.5 mmol), the appropriate alcohol (1 mmol), iron(II) phthalocyanine (Fe(II)Pc) (3 mg, 0.005 mmol), and Cs_2CO_3 (179 mg, 0.55 mmol). The vial was immersed in a preheated (140 °C) oil bath and stirred at this temperature for 16 h. The reaction mixture was diluted with ethyl acetate and filtered over a plug of Celite. The solvent was evaporated under reduced pressure, and the residue obtained was purified by flash chromatography.

*3-Benzyl-1H-indole (**3a**).* The title compound was prepared according to the general procedure using 1*H*-indole and benzyl alcohol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give **3a** (102 mg, 99%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (br s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.33−7.30 (m, 4H), 7.24−7.14 (m, 2H), 7.12 (t, J = 7.0 Hz, 1H), 6.93 (s, 1H), 4.16 (s, 2H); HRMS (ESI) m/z calcd for $C_{15}H_{13}NNa$ $(M + Na)^+$ 230.0940; found 230.0946. The chemical-physical data are in accordance with literature.[21]

*3-(4-Methylbenzyl)-1H-indole (**3b**).* The title compound was prepared according to the general procedure using 1*H*-indole and *p*-tolylmethanol. The product was purified by flash chromatography (cyclohexane/EtOAc 9:1) to give **3b** (78 mg, 71%) as pinkish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (br s, 1H), 7.59 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.26−7.22 (m, 3H), 7.16−7.12 (m, 3H), 6.92−6.91 (m, 1H), 4.14 (s, 2H), 2.38 (s, 3H); HRMS (ESI) m/z calcd for $C_{16}H_{16}N$ $(M + H)^+$ 222.1277; found 222.1286. The chemical-physical data are in accordance with literature.[7a]

*3-(3-Methylbenzyl)-1H-indole (**3c**).* The title compound was prepared according to the general procedure using 1*H*-indole and *m*-tolylmethanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give **3c** (108 mg, 98%) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.76 (br s, 1H), 7.70 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.33 (t, J = 8.0 Hz, 2H), 7.27−7.23 (m, 3H), 7.17 (d, J = 7.0 Hz, 1H), 6.92 (s, 1H), 4.22 (s, 2H), 2.46 (s, 3H); HRMS (ESI) m/z calcd for $C_{16}H_{16}N$ $(M + H)^+$ 222.1277; found 222.1283. The chemical-physical data are in accordance with literature.[7a]

*3-(2-Methylbenzyl)-1H-indole (**3d**).* The title compound was prepared according to the general procedure using 1*H*-indole and *o*-tolylmethanol. The product was purified by flash chromatography (gradient from cyclohexane/EtOAc 8:2 to cyclohexane/EtOAc 7:3) to give **3d** (83 mg, 75%) as pinkish solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (br s, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.30−7.15 (m, 6H), 6.74 (s, 1H), 4.15 (s, 2H), 2.41 (s, 3H); HRMS (ESI) m/z calcd for $C_{16}H_{16}N$ $(M + H)^+$ 222.1277; found 222.1274. The chemical-physical data are in accordance with literature.[7a]

*3-(Biphenyl-3-ylmethyl)-1H-indole (**3e**).* The title compound was prepared according to the general procedure using 1*H*-indole and biphenyl-3-ylmethanol. The product was purified by flash chromatography (cyclohexane/EtOAc 9:1) to give **3e** (65 mg, 46%) as orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (br s, 1H), 7.61−7.57 (m, 3H), 7.53 (d, J = 8.0 Hz, 3H), 7.44 (t, J = 8.0 Hz, 2H), 7.40−7.32 (m, 3H), 7.24−7.20 (m, 1H), 7.14−7.10 (m, 1H), 6.98 (br s, 1H), 4.18 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 141.1, 140.4, 138.8, 136.4, 129.1, 128.7, 127.5, 127.1, 127.0, 122.4, 122.1, 119.4, 119.2, 115.7, 111.1, 31.2; mp 194−196 °C; IR (film): 3412, 3056 cm^{-1}; HRMS (ESI) m/z calcd for $C_{21}H_{18}N$ $(M + H)^+$ 284.1434; found 284.1439.

*3-(4-Methoxybenzyl)-1H-indole (**3f**).* The title compound was prepared according to the general procedure using 1*H*-indole and (4-methoxyphenyl)methanol. The product was purified by flash chromatography (gradient from cyclohexane/EtOAc 95:5 to cyclohexane/EtOAc 90:10) to give **3f** (89 mg, 75%) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (br s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 7.29−7.22 (m, 3H), 7.14 (t, J = 8.0 Hz, 1H), 6.93 (s, 1H), 6.88 (d, J = 8.0 Hz, 2H), 4.11 (s, 2H), 3.83 (s, 3H); HRMS (ESI) m/z calcd for $C_{16}H_{16}NO$ $(M + H)^+$ 238.1226; found 238.1221. The chemical-physical data are in accordance with literature.[8a]

*2-((1H-Indol-3-yl)methyl)aniline (**3g**).* The title compound was prepared according to the general procedure using 1*H*-indole and (2-aminophenyl)methanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give **3g** (62 mg, 56%) as off-white solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 10.05 (br s, 1H), 7.53−7.51 (m, 1H), 7.40 (dt, J = 8.0, 1.0 Hz, 1H), 7.13−7.05 (m, 3H), 7.01−6.95 (m, 2H), 6.72 (dd, J = 8.0, 1.5 Hz, 1H), 6.59 (dt, J = 7.5, 1.5 Hz, 1H), 4.40 (br s, 2H), 3.99 (s, 2H). ^{13}C NMR (101 MHz, Acetone-d_6) δ 146.0, 137.1, 129.7, 127.7, 126.8, 125.0, 122.9, 121.3, 118.8, 118.5, 117.1, 115.1, 113.0, 111.3, 27.4; HRMS (ESI) m/z calcd for $C_{15}H_{15}N_2$ $(M + H)^+$ 223.1230; found 223.1241. The chemical-physical data are in accordance with literature.[22]

*2-((1H-Indol-3-yl)methyl)phenol (**3h**).* The title compound was prepared according to the general procedure using 1*H*-indole and 2-(hydroxymethyl)phenol. The product was purified by flash chromatography (cyclohexane/EtOAc 1:1) to give **3h** (47 mg, 42%) as pale yellow solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 9.99 (br s, 1H), 8.28 (s, 1H), 7.57−7.54 (m, 1H), 7.38 (dt, J = 8.0, 1.0 Hz, 1H), 7.12−7.06 (m, 3H), 7.04−6.96 (m, 2H), 6.88 (dd, J = 8.0, 1.0 Hz, 1H), 6.71 (dt, J = 7.5, 1.0 Hz, 1H), 4.10 (s, 2H); HRMS (ESI) m/z calcd for $C_{15}H_{14}NO$ $(M + H)^+$ 224.1070; found 224.1079. The chemical-physical data are in accordance with literature.[23]

*3-(4-Chlorobenzyl)-1H-indole (**3i**).* The title compound was prepared according to the general procedure using 1*H*-indole and (4-chlorophenyl)methanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give **3i** (54 mg, 45%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.51 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.33−7.22 (m, 5H), 7.12 (t, J = 7.0 Hz, 1H), 6.93 (s, 1H), 4.12 (s, 2H); HRMS (ESI) m/z calcd for $C_{15}H_{13}ClN$ $(M + H)^+$ 242.0731; found 242.0726. The chemical-physical data are in accordance with literature.[2]

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*3-(2-Chlorobenzyl)-1H-indole (**3j**).* The title compound was prepared in according to the general procedure using 1*H*-indole and (2-chlorophenyl)methanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give **3j** (44 mg, 37%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98 (br s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.43−7.38 (m, 2H), 7.25−7.11 (m, 5H), 6.96 (s, 1H), 4.25 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 138.7, 136.4, 134.0, 130.6, 129.4, 127.4, 127.3, 126.7, 122.7, 122.1, 119.5, 119.1, 114.0, 111.1, 29.1; HRMS (ESI) m/z calcd for $C_{15}H_{13}ClN$ $(M + H)^+$ 242.0731; found 242.0742.

*3-(4-Fluorobenzyl)-1H-indole (**3k**).* The title compound was prepared according to the general procedure using 1*H*-indole and (4-fluorophenyl)methanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give **3k** (76 mg, 68%) as white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99 (br s, 1H), 7.58 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.23−7.14 (m, 3H), 7.13−6.99 (m, 4H), 4.15 (s, 2H); HRMS (ESI) m/z calcd for $C_{15}H_{13}FN$ $(M + H)^+$ 226.1027; found 226.1036. The chemical-physical data are in accordance with literature.[7a]

*3-(4-(Trifluoromethyl)benzyl)-1H-indole (**3l**).* The title compound was prepared according to the general procedure using 1*H*-indole and (4-(trifluoromethyl)phenyl)methanol. The product was purified by flash chromatography (cyclohexane/EtOAc 9:1) to give **3l** (97 mg, 71%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.49 (d, J = 8.0 Hz, 1H), 7.41−7.39 (m, 3H), 7.23 (t, J = 7.5 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 7.02−6.93 (m, 1H), 4.19 (s, 2H); HRMS (ESI) m/z calcd for $C_{16}H_{13}F_3N$ $(M + H)^+$ 276.0995; found 275.0988. The chemical-physical data are in accordance with literature.[7a]

*4-((1H-Indol-3-yl)methyl)benzonitrile (**3m**).* The title compound was prepared according to the general procedure using 1*H*-indole and 4-(hydroxymethyl)benzonitrile. The product was purified by flash chromatography (from cyclohexane/EtOAc 1:1 to cyclohexane/EtOAc 1:9) to give **3m** (83 mg, 72%) as off-white solid. ^{1}H NMR (400 MHz, acetone-d_6) δ 10.11 (br s, 1H), 7.86 (d, J = 8.0 Hz, 2H), 7.46 (d, J = 7.5 Hz, 1H), 7.46 (d, J = 8.0 Hz, 2H), 7.19−7.18 (m,1H), 7.11−7.07 (m,1H), 6.99−6.95 (m,1H), 4.18 (s, 2H); HRMS (ESI) m/z calcd for $C_{16}H_{13}N_2$ $(M + H)^+$ 233.1073; found 233.1068. The chemical-physical data are in accordance with literature.[24]

*3-(3,4,5-Trimethoxybenzyl)-1H-indole (**3n**).* The title compound was prepared according to the general procedure using 1*H*-indole and (3,4,5-trimethoxyphenyl)methanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give **3n** (92 mg, 62%) as orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (br s, 1H), 7.57 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.21 (t, J = 8.0 Hz, 1H), 7.11 (t, J = 8.0 Hz, 1H), 6.95 (s, 1H), 6.54 (s, 2H), 4.07 (s, 2H), 3.84 (s, 3H), 3.81 (s, 6H); HRMS (ESI) m/z calcd for $C_{18}H_{20}NO_3$ $(M + H)^+$ 298.1438; found 298.1435. The chemical-physical data are in accordance with literature.[21]

*3-(Naphthalen-2-ylmethyl)-1H-indole (**3o**).* The title compound was prepared according to the general procedure using 1*H*-indole and naphthalen-2-ylmethanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give **3o** (91 mg, 71%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (br s, 1H), 7.83−7.74 (m, 4H), 7.56 (dd, J = 8.0, 1.0 Hz, 1H), 7.46−7.41 (m, 3H), 7.39 (dt, J = 8.0, 1.0 Hz, 1H), 7.21 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 7.09 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 6.96−6.95 (m, 1H), 4.30 (s, 2H); HRMS (ESI) m/z calcd for $C_{19}H_{16}N$ $(M + H)^+$ 258.1277; found 258.1271. The chemical-physical data are in accordance with literature.[25]

*3-(3,5-Dichlorobenzyl)-1H-indole (**3p**).* The title compound was prepared according to the general procedure using 1*H*-indole and (3,5-dichlorophenyl)methanol. The product was purified by flash chromatography (cyclohexane/EtOAc 98:2) to give **3p** (53 mg, 39%) as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (br s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.29−7.12 (m, 5H), 6.98 (s, 1H), 4.08 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 136.4, 134.7, 127.14, 127.08, 126.2, 122.6, 122.4, 119.7, 118.9, 114.0, 111.2, 31.1; IR (film): 3170, 2949, 2824, 1555 cm^{-1}; HRMS (ESI) m/z calcd for $C_{15}H_{12}Cl_2N$ $(M + H)^+$ 276.0341; found 276.0334.

*3-(Benzo[d][1,3]dioxol-5-ylmethyl)-1H-indole (**3q**).* The title compound was prepared according to the general procedure using 1*H*-indole and benzo[*d*][1,3]dioxol-5-ylmethanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give **3q** (105 mg, 84%) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (br s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.13 (t, J = 8.0 Hz, 1H), 6.94 (s, 1H), 6.82−6.76 (m, 3H), 5.93 (s, 2H), 4.07 (s, 2H); HRMS (ESI) m/z calcd for $C_{16}H_{14}NO_2$ $(M + H)^+$ 252.1019; found 252.1013. The chemical-physical data are in accordance with literature.[8a]

*3-(Thiophen-2-ylmethyl)-1H-indole (**3r**).* The title compound was prepared according to the general procedure using 1*H*-indole and thiophen-2-ylmethanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give **3r** (101 mg, 95%) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.96 (s, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.25−7.21 (m, 1H), 7.16−7.11 (m, 2H), 7.06−7.05 (m, 1H), 6.95 (dd, J = 5.0, 4.0 Hz, 1H), 6.91−6.90 (m, 1H), 4.35 (s, 2H); HRMS (ESI) m/z calcd for: $C_{13}H_{12}NS$ $(M + H)^+$ 214.0685; found 214.0677. The chemical-physical data are in accordance with literature.[8a]

*3-(Furan-2-ylmethyl)-1H-indole (**3s**).* The title compound was prepared according to the general procedure using 1*H*-indole and furan-2-ylmethanol. The product was purified by flash chromatography (cyclohexane/EtOAc 95:5) to give **3s** (76 mg, 78%) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.45 (s, 1H), 7.34 (dt, J = 8.0, 7.6 Hz, 2H), 7.27−7.21 (m, 1H), 7.02 (s, 1H), 6.41 (dd, J = 3.0, 2.0 Hz, 1H), 6.16 (d, J = 3.0 Hz, 1H), 4.24 (s, 2H); HRMS (ESI) m/z calcd for $C_{13}H_{11}NONa$ $(M + Na)^+$ 220.0733; found 220.0737. The chemical-physical data are in accordance with literature.[8a]

*1,3-Bis((1H-indol-3-yl)methyl)benzene (**3t**).* The title compound was prepared according to the general procedure using 1*H*-indole (234 mg, 2 mmol) and 1,3-phenylenedimethanol (138 mg, 1 mmol). The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give **3t** (97 mg, 58%) as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (br s, 2H), 7.53 (d, J = 8.0 Hz, 2H), 7.35 (d, J = 8.0 Hz, 2H), 7.28 (br s, 1H), 7.23−7.19 (m, 3H), 7.15−7.04 (m, 4H), 6.87 (s, 2H), 4.09 (s, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 141.2, 136.4, 129.2, 128.3, 127.5, 126.3, 122.3, 122.0, 119.3, 119.2, 116.0, 111.1, 31.6; IR (film): 3165, 2929, 2820, 1556 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{21}N_2$ $(M + H)^+$ 337.1699; found 337.1691.

*3-(3-((1H-Indol-3-yl)methyl)benzyl)-6-fluoro-1H-indole (**3u**).* A vial was charged with 1*H*-indole (59 mg, 0.5 mmol), 1,4-phenylenedimethanol (69 mg, 1 mmol), iron(II) phthalocyanine (2.5 mg, 0.005 mmol), and Cs_2CO_3 (179 mg, 0.55 mmol). The vial was immersed in a preheated (140 °C) oil bath and stirred at this temperature for 16 h. Than the vial was removed from oil bath, and 6-fluoro-1*H*-indole (67 mg, 0.5 mmol) was added to the reaction mixture and stirred again for 16 h at 140 °C. The reaction mixture was diluted with ethyl acetate and filtered over a plug of silica gel. The solvent was evaporated under reduced pressure, and the residue obtained was purified by flash chromatography (cyclohexane/EtOAc 7:3) to give **3u** (93 mg, 52%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.93 (br s, 1H), 7.94 (br s, 1H), 7.49 (d, J = 8.0 Hz, 1H), 7.23−7.18 (m, 3H), 7.14−7.01 (m, 5H), 6.88−6.78 (m, 3H), 4.08 (s, 2H), 4.04 (s, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 159.9 (d, J = 236 Hz), 141.0 (d, J = 39 Hz), 136.43, 136.39, 136.3, 129.1, 128.3, 127.4, 126.4, 126.3, 126.2, 124.1, 122.5 (d, J = 3 Hz), 122.2, 122.0, 120.0, 119.9 (d, J = 10 Hz), 119.2 (d, J = 10 Hz), 116.0 (d, J = 12 Hz), 111.0, 108.0 (d, J = 25 Hz), 97.3 (d, J = 25 Hz), 31.59, 31.57; mp 166−168 °C; IR (film): 3161, 2932, 2816, 1549 cm^{-1}; HRMS (ESI) m/z calcd for $C_{24}H_{20}FN_2$ $(M + H)^+$ 355.1605; found 355.1611.

*3-(1-Phenylethyl)-1H-indole (**3v**).* The title compound was prepared according to the general procedure using 1*H*-indole and 1-phenylethanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give **3v** (79 mg, 72%) as yellowish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (br s, 1H), 7.45 (dd, J = 8.0, 2.5 Hz, 1H), 7.38−7.35 (m, 4H), 7.26−7.21 (m, 2H), 7.11−7.07 (m, 1H), 7.02 (s, 1H), 4.45 (q, J = 7.0 Hz, 1H), 1.78 (d, J = 7.0 Hz, 3H); HRMS

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(ESI) m/z calcd for $C_{16}H_{16}N$ $(M + H)^+$ 222.1277; found 222.1269. The chemical-physical data are in accordance with literature.[7a]

*3-Benzhydryl-1H-indole (**3w**).* The title compound was prepared according to the general procedure using 1*H*-indole and diphenylmethanol. The product was purified by flash chromatography (cyclohexane/EtOAc 9:1) to give **3w** (52 mg, 37%) as yellowish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.38−7.19 (m, 13H), 7.04 (dt, J = 7.5, 1.0 Hz, 1H), 6.57 (t, J = 2.0, 1.0 Hz, 1H), 5.73 (s, 1H); HRMS (ESI) m/z calcd for $C_{21}H_{18}N$ $(M + H)^+$ 284.1434; found 284.1439. The chemical-physical data are in accordance with literature.[7a]

*N-(2-(1H-indol-3-yl)-2-phenylethyl)acetamide (**3x**).* The title compound was prepared according to the general procedure using 1*H*-indole and *N*-(2-hydroxy-2-phenylethyl)acetamide. The product was purified by flash chromatography (EtOAc) to give **3x** (62 mg, 45%) as yellowish solid. ^{1}H NMR (400 MHz, CDCl3) δ 8.23 (br s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz, 1H), 7.32−7.31 (m, 4H), 7.24 (dd, J = 5.0, 4.0 Hz, 1H), 7.21−7.16 (m, 1H), 7.09 (br s, 1H), 7.07−7.03 (m, 1H), 5.51 (br s, 1H), 4.44 (t, J = 8.0 Hz, 1H), 4.11−4.04 (m, 1H), 3.86−3.79 (m, 1H), 1.91 (s, 3H); HRMS (ESI) m/z calcd for $C_{18}H_{19}N_2O$ $(M + H)^+$ 279.1492; found 279.1486. The chemical-physical data are in accordance with literature.[8d]

*4-Methoxy-3-(4-methoxybenzyl)-1H-indole (**3y**).* The title compound was prepared according to the general procedure using 4-methoxy-1*H*-indole and (3-((1*H*-indol-3-yl)methyl)phenyl)methanol. The product was purified by flash chromatography (gradient from cyclohexane/EtOAc 8:2 to cyclohexane/EtOAc 6:4) to give **3y** (117 mg, 88%) as brown oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (br s, 1H), 7.25 (d, J = 8.0 Hz, 2H), 7.11 (t, J = 8.0 Hz, 1H), 6.95 (d, J = 8.0, 1H), 6.87−6.85 (m, 2H), 6.64 (br s, 1H), 6.51 (d, J = 8.0 Hz, 1H), 4.26 (s, 2H), 3.90 (s, 3H), 3.82 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 157.6, 155.1, 138.1, 134.7, 129.8, 122.8, 120.9, 117.4, 117.2, 113.6, 104.4, 99.5, 55.3, 55.1, 32.2; IR (film): 3397, 2848,1387 cm^{-1}; HRMS (ESI) m/z calcd for: $C_{17}H_{18}NO_2$ $(M + H)^+$ 268.1332; found 268.1338.

*3-(4-Methoxybenzyl)-6-methyl-1H-indole (**3z**).* The title compound was prepared according to the general procedure using 6-methyl-1*H*-indole and (3-((1*H*-indol-3-yl)methyl)phenyl)methanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give **3z** (79 mg, 63%) as pinkish solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (br s, 1H), 7.45 (d, J = 8.0 Hz, 1H), 7.29−7.23 (m, 2H), 7.16 (s, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.88 (m, 2H), 6.84 (s, 1H), 4.09 (s, 2H), 3.83 (s, 3H), 2.51 (s, 3H); HRMS (ESI) m/z calcd for $C_{17}H_{18}NO$ $(M + H)^+$ 252.1383; found 252.1379. The chemical-physical data are in accordance with literature.[26]

*5-Fluoro-3-(2-methylbenzyl)-1H-indole (**3aa**).* The title compound was prepared according to the general procedure using 5-fluoro-1*H*-indole and (3-((1*H*-indol-3-yl)methyl)phenyl)methanol. The product was purified by flash chromatography (cyclohexane/EtOAc 9:1) to give **3aa** (95 mg, 80%) as orange solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.94 (br s, 1H), 7.30−7.26 (m, 2H), 7.23−7.14 (m, 4H), 6.95 (td, J = 9.0, 2.5 Hz, 1H), 6.80 (s, 1H), 4.03 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 157.8 (d, J = 234 Hz), 138.8, 136.5, 133.0, 130.3, 129.4, 128.0 (d, J = 10 Hz), 126.4, 126.1, 124.4, 115.3 (d, J = 5 Hz), 111.8 (d, J = 10 Hz), 110.4 (d, J = 26 Hz), 104.0 (d, J = 23 Hz), 29.3, 19.6; mp 65−66 °C; IR (film): 3310, 2901,1354 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{15}FN$ $(M + H)^+$ 240.1183; found 240.1180.

*6-Chloro-3-(4-methylbenzyl)-1H-indole (**3ab**).* The title compound was prepared according to the general procedure using 6-chloro-1*H*-indole and (3-((1*H*-indol-3-yl)methyl)phenyl)methanol. The product was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give **3ab** (82 mg, 64%) as brown solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (br s, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 2.0 Hz, 1H), 7.16 (d, J = 8.0 Hz, 2H), 7.10 (d, J = 8.0 Hz, 2H), 7.05 (dd, J = 8.0, 2.0 Hz, 1H), 6.92 (d, J = 1.0 Hz, 1H), 4.06 (s, 2H), 2.33 (s, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 137.7, 136.8, 135.5, 129.1, 128.5, 128.0, 126.1, 122.8, 120.1, 116.3, 110.9, 31.0, 21.0; mp 98−99 °C; IR (film): 3220, 2965, 2837, 1601 cm^{-1}; HRMS (ESI) m/z calcd for $C_{16}H_{15}ClN$ $(M + H)^+$ 256.0888; found 256.0895.

*3-Benzyl-2-phenyl-1H-indole (**3ac**).* The title compound was prepared according to the general procedure using 2-phenyl-1*H*-indole and benzyl alcohol. The product was purified by flash chromatography (cyclohexane/DCM 1:9) to give **3ac** (69 mg, 49%) as off-white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (br s, 1H), 7.55−7.52 (m, 2H), 7.46−7.44 (m, 4H), 7.38−7.31 (m, 2H), 7.26−7.16 (m, 5H), 7.10−7.06 (m, 1H), 4.29 (s, 2H); HRMS (ESI) m/z calcd for $C_{21}H_{18}N$ $(M + H)^+$ 284.1434; found 284.1438. The chemical-physical data are in accordance with literature.[27]

Procedure for Large-Scale Synthesis of Compound 3a. A 50 mL Schlenk flask equipped with a magnetic stir bar was charged with indole (1 g, 8.5 mmol), benzyl alcohol (1.8 g, 17 mmol), iron(II) phthalocyanine (48 mg, 0.085 mmol), and Cs_2CO_3 (3 g, 9.35 mmol). The reaction mixture was immersed in a preheated (140 °C) oil bath and stirred at this temperature for 16 h. The reaction mixture was diluted with ethyl acetate and filtered over a plug of Celite. The solvent was evaporated under reduced pressure, and the residue obtained was purified by flash chromatography (cyclohexane/EtOAc 8:2) to give **3a** (1.6 g, 92%) as white solid. The chemical-physical data are in accordance as reported above.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b01603.

Copies of ^{1}H NMR, ^{13}C NMR spectra for all compounds were reported (PDF)

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Notes

The authors declare no competing financial interest.

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