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Friedel–Crafts Hydroxyalkylation of Indoles Mediated by Trimethylsilyl Trifluoromethanesulfonate

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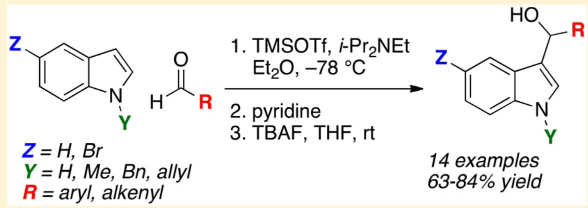
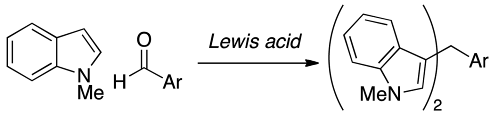
Supporting Information

ABSTRACT: Indoles and N-alkylindoles undergo Friedel–Crafts addition to aldehydes in the presence of trimethylsilyl trifluoromethanesulfonate and a trialkylamine to produce 3-(1-silyloxyalkyl)-indoles. Neutralization of the reaction mixture with pyridine followed by deprotection under basic conditions with tetrabutylammonium fluoride provides the 1:1 adduct as the free alcohol. This method prevents spontaneous conversion of the desired products to the thermodynamically favored bisindolyl(aryl)methanes, a process typically observed when indoles are reacted with aldehydes under acidic conditions.

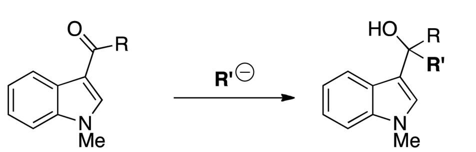


The condensation of N-alkylindoles with aryl aldehydes has been known since the 19th century, when Fischer observed the formation of triarylmethane products in the presence of Lewis acids (eq 1).[1] These bisindolyl products result from the rapid conversion of the initial alcohol product to a stabilized carbocation, which is subsequently attacked by a second indole. The isolation of 1:1 indole:aldehyde adducts has been reported for very electron-poor electrophiles, such as when the carbonyl acceptor features an α-trifluoromethyl group[2] and, in rare cases, when the indole nitrogen is unprotected.[3] To our knowledge, however, no general method exists for the synthesis of the corresponding N-alkylated derivatives via a convergent Friedel–Crafts route. In this note, we report the Friedel–Crafts silyloxyalkylation of indoles and N-alkylated indoles with aldehydes mediated by trimethylsilyl trifluoromethanesulfonate (TMSOTf) and i-Pr_2NEt.



(1)

Fischer, 1886



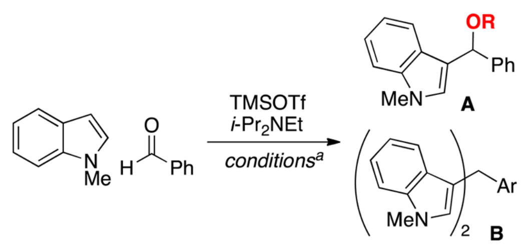
(2)

R, R' = H, aryl

The most commonly used methods for the generation of 3-(1-hydroxyalkyl)indoles require highly basic conditions such as reduction of the corresponding ketone with lithium aluminum hydride[4] or Grignard[5] addition to relatively expensive indole-carboxaldehydes (eq 2). The unusual potential of TMSOTf to act as a Lewis acid *and* to generate an ionization-resistant O-silylated product appeared to be perfectly suited for this reaction. The Lewis acidity of the silicon center provides a classic catalyst for electrophilic aromatic substitution, and the bulk of the trimethylsilyl-protected product should slow undesired ionization and decomposition processes. Development of such a method was made more attractive by the utility of the products, which show significant promise as (1-indolyl)-alkylating agents under mild conditions.[6]

We began our discovery and optimization process with representative substrates *N*-methylindole and benzaldehyde (Table 1). To begin, the reactants were dissolved in methylene chloride and treated with TMSOTf and i-Pr_2NEt for 1 h at −78 °C. During preliminary purification via silica gel filtration,

Table 1. Optimization of the Synthesis of 1:1 Adduct A



entry	OR	solvent	T (°C)	quench	A:B[b]
1	OTMS	CH_2Cl_2	−78	pyridine	0:100
2	OTMS	Et_2O	−78	none	0:100
3	**OTMS**	$\mathbf{Et_2O}$	**−78**	pyridine	**98:02**
4	OTMS	Et_2O	0	pyridine	90:10
5	OMe[c]	Et_2O	−78	pyridine	0:100

[a]Reaction conditions: (1) 0.2 mmol of *N*-methylindole, 0.28 mmol of benzaldehyde, 0.3 mmol of TMSOTf, 0.28 mmol of i-Pr_2NEt, 2 mL of Et_2O, − 78 °C, 1 h; (2) 0.5 mmol of pyridine. [b]Ratio determined by ^1H NMR spectroscopy. [c]Benzaldehyde was replaced with benzaldehyde dimethyl acetal.

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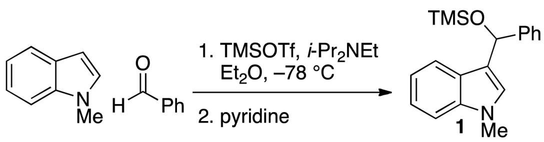
however, the color of the reaction mixture rapidly changed from orange to pink, and NMR analysis revealed the formation of triarylmethane **B**. The same color change was observed at extended reaction times, even at low temperatures. Addition of pyridine to quench the reaction mixture, a method employed in previous studies to prevent TMSOTf-mediated decomposition reactions,[7] did not prevent triarylmethane formation when methylene chloride was used as solvent (entry 1). When methylene chloride was replaced with diethyl ether as the reaction solvent, the reaction became noticeably heterogeneous, an observation consistent with the precipitation of mildly acidic trialkylammonium salts. Nonetheless, a color change to pink was still observed during workup (entry 2). When both diethyl ether *and* the pyridine quench were employed, the color change was prevented, and observation of the silyloxyalkylation adduct (**A**) was confirmed by NMR spectroscopy (entry 2). Purification on silica gel deactivated by triethylamine provided the desired product in 76% yield (eq 3).

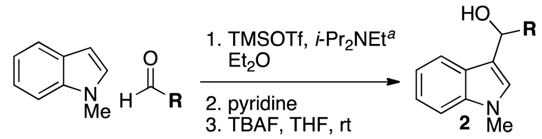


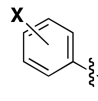
76% yield (3)

Despite existing as the protected trimethylsilyl ether rather than the free alcohol, adduct **1** proved to be quite prone to decomposition. Warmer temperatures or the omission of the pyridine quench resulted in significant to complete degradation of the desired product to 2:1 adduct **B** (Table 1, entries 2 and 4). At lower temperatures, however, it appears that the large silyl group significantly slows coordination of Lewis acidic species to the silyloxy group, preventing ionization and eventual conversion to the bisindolyl byproduct. The effectiveness of the pyridine quench, which likely sequesters any silyl cations in solution as well as lowers the pH of the solution, provides some support for this hypothesis. Removal of the TMS group under acidic conditions (methanol, trifluoroacetic acid) resulted in complete conversion to the thermodynamically favored 2:1 adduct **B**, further demonstrating the sensitivity of the desired product to acids. When benzaldehyde was replaced with benzaldehyde dimethyl acetal under otherwise optimized reaction conditions, only adduct **B** was observed (Table 1, entry 5). Presumably, the small methoxy group in the desired product coordinates readily with Lewis acidic species present in solution (e.g., TMSOTf, R_3NH^+), leading to rapid ionization. Indeed, we have previously observed the activation of certain methyl ethers with TMSOTf, leading to C-alkylation by suitable nucleophiles.[8]

With the reaction conditions for carbon−carbon bond formation optimized, we focused on the synthesis of a wider range of hydroxyalkylated indoles. Although acid-catalyzed removal of the trimethylsilyl group resulted in decomposition (vide supra), deprotection was readily achieved under basic conditions through treatment of the unpurified product with tetrabutylammonium fluoride (TBAF). Thus, reaction of *N*-methylindole with various aldehydes provided the hydroxyalkylation product in good yields (Table 2). A variety of electron-poor aromatic aldehydes performed well under the reaction conditions (entries 3−5), but the product derived from the electron-rich anisaldehyde was too prone to ionization for the 1:1 adduct to be isolated (entry 2). Larger aromatic groups and heterocyclic groups, however, were well-tolerated in

Table 2. Addition of *N*-Methylindole to Aldehydes

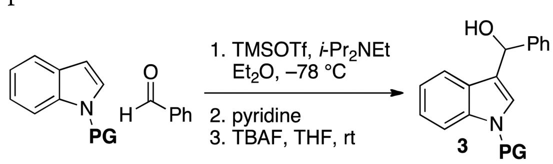


entry	R		product	T (°C)	yield (%)[b]
1		**X** = H	**2a**	−78	68
2		**X** = 4-MeO	**2b**	−78	0[c]
3		**X** = 4-NO_2	**2c**	−10	71[d]
4		**X** = 4-F	**2d**	−78	79
5		**X** = 4-Br	**2e**	−78	78
6	2-naphthyl		**2f**	−78	77
7	2-furyl		**2g**	−78	71
8	2-thiophenyl		**2h**	−48	84
9	cinnamyl		**2i**	−48	63

[a]Reaction conditions: (1) 1.0 mmol of *N*-methylindole, 1.4 mmol of aldehyde, 1.5 mmol of TMSOTf, 1.4 mmol of *i*-Pr$_2$NEt, 10 mL of Et$_2$O, − 78 °C, 1 h; (2) 2.6 mmol of pyridine; (3) 1.1 mmol of TBAF, 10 mL of THF. [b]Isolated yield after chromatography. [c]2:1 adduct observed exclusively. [d]1.6 mmol of *i*-Pr$_2$NEt used.

the aldehyde reaction partner (entries 6−8). Cinnamaldehyde also gave satisfactory results. Attempts to add *N*-methylindole to aliphatic aldehydes were disappointing, however. Under the reaction conditions, enolizable aldehydes such as isobutyraldehyde and cyclohexanecarboxaldehyde were rapidly transformed into enol silanes and did not undergo addition.

When the nitrogen-protecting group on the indole was replaced with synthetically convenient benzyl or allyl groups, reactivity was maintained and good yields were observed (eq 4). These compounds appeared to be somewhat more robust with respect to product decomposition and formation of the 2:1 adducts than the N-methylated series. In contrast, replacement of TMSOTf with TESOTf or TBSOTf resulted in lower conversion to the desired product and a significant increase in the generation of 2:1 adducts. This change in reactivity may be caused by a significantly slower rate of addition of indole to the silyl triflate-activated aldehyde, allowing ionization of the desired product to become kinetically competitive under the reaction conditions.



(4)

3a: *PG = Bn, 75% yield*
3b: *PG = allyl, 80% yield*

Given the success of various N-protected indoles under the optimized reaction conditions, we were intrigued by the potential application to unprotected indoles and the challenge of accommodating an N−H bond under silylating conditions. Although Friedel−Crafts additions of free indoles to aromatic aldehydes have been reported previously, known methods are low yielding,[2c] require a large excess of indole,[2a,b] or are mostly limited to very electron-poor aldehydes.[2a,c] Unfortunately, when free indole was treated with benzaldehyde under our standard reaction conditions (1.5 equiv of TMSOTf, 1.4 equiv of *i*-Pr$_2$NEt), Friedel−Crafts addition was significantly outperformed by competing silylation at the indole nitrogen.

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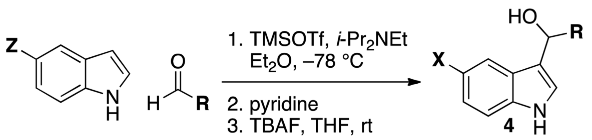
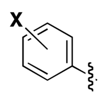
By increasing the stoichiometry of the TMSOTf and base,[9] however, conversion to the desired products **4** was clearly observed. A very brief survey of the reaction scope of free indoles is described in Table 3. Of particular interest are brominated adducts **4b** and **4c**, which provide the possibility of further elaboration by cross-coupling reactions.[10]

Table 3. Addition of Free Indoles to Aldehydes[a]



entry	Z	R		product	yield (%)[b]
1	H		X = H	**4a**	73
2	Br		X = H	**4b**	72
3	H		X = Br	**4c**	87
4	H	2-naphthyl		**4d**	77[c]

[a]Reaction conditions: (1) 1.0 mmol of indole, 1.4 mmol of aldehyde, 2.2 mmol of TMSOTf, 2.5 mmol of i-Pr_2NEt, 10 mL of Et_2O, − 78 °C, 1 h; (2) 2.6 mmol of pyridine; (3) 2.1 mmol of TBAF, 10 mL of THF. [b]Isolated yield after chromatography, adjusted for residual solvent. [c]Product yield adjusted for approximately 10% impurities as determined by ^{1}H NMR spectroscopy.

In summary, we have described the Friedel−Crafts silyloxyalkylation of indoles and their subsequent deprotection to yield hydroxyalkylated products. These 1:1 adducts of indoles and aldehydes have largely eluded researchers for over a century, but the unique ability of TMSOTf to act as both a Lewis acid and a protecting agent provides convenient access to this decomposition-prone class of compounds. The products may be isolated in either the hydroxyalkylated or silyloxyalkylated form. Their use as efficient electrophiles under related conditions remains to be explored.

■ EXPERIMENTAL SECTION

General Methods. Reactions were carried out under an atmosphere of nitrogen with a septum cap in oven-dried glassware with magnetic stirring. Diethyl ether was purified by passage through a bed of activated alumina.[11] Trimethylsilyl trifluoromethanesulfonate (TMSOTf) was stored in a Schlenk flask under an inert atmosphere. Hunig's base (i-Pr_2NEt) was distilled from calcium hydride and stored in a Schlenk flask under an inert atmosphere. *N*-Methylindole was passed through a plug of silica with ether and concentrated in vacuo. Benzaldehyde, 4-fluorobenzaldehyde, 4-methoxybenzaldehyde, 2-furanaldehyde, 2-thiophenecarboxaldehyde, and cinnamaldehyde were distilled prior to use. All other chemicals were used as received. Purification of reaction products was carried out by flash chromatography using silica gel (230−400 mesh). Analytical thin-layer chromatography was performed on silica gel plates. Visualization was accomplished with UV light and phosphomolybdic acid stain, followed by heating. Infrared spectra were recorded on an FT-IR spectrometer. ^{1}H NMR spectra were recorded on a 500 or 300 MHz spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 7.28 ppm). Data are reported as (ap = apparent, s = singlet, d = doublet, t = triplet, q = quartet, sx = sextet, sp = septet, m = multiplet, b = broad; coupling constant(s) in Hz; integration). Proton-decoupled ^{13}C NMR spectra were recorded on a 125 or 75 MHz spectrometer and are reported in ppm using solvent as an internal standard ($CDCl_3$ at 77.0 ppm). High-resolution mass spectra were obtained by electrospray ionization unless otherwise indicated. Melting points were determined using a capillary melting point apparatus.

General Procedure A. *Friedel–Crafts Silyloxyalkylation of N-Alkylindoles.* To an oven-dried round-bottomed flask under a N_2 atmosphere were added diethyl ether (10 mL), *N*-alkylindole (1.0 mmol), i-Pr_2NEt (250 μL, 186 mg, 1.44 mmol), and aldehyde (1.40 mmol). The reaction mixture was cooled to −78 °C in a dry ice/acetone bath, and trimethylsilyl trifluoromethanesulfonate (270 μL, 332 mg, 1.50 mmol) was added dropwise. The orange reaction mixture was stirred for 1 h and then quenched with pyridine (210 μL). The reaction mixture was passed through a column of silica (2 cm × 1 cm) with Et_2O. The solvent was removed in vacuo, and the residue was redissolved in tetrahydrofuran (10 mL). To the solution was added tetrabutylammonium fluoride as a 1.0 M solution in THF (1.10 mL, 1.10 mmol). The reaction mixture was stirred for 5 min and then partitioned between diethyl ether (20 mL) and saturated sodium bicarbonate (20 mL). The layers were separated, and the organic layer was washed with water (20 mL). The organic layer was diluted with hexanes (60 mL) and dried with sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated in vacuo. Column chromatography of the residue (0−20% EtOAc/hexanes with 1% diethylamine) provided the product, which was stored at −20 °C after isolation.

General Procedure B. *Friedel–Crafts Silyloxyalkylation of Free Indoles.* To an oven-dried round-bottomed flask under a N_2 atmosphere were added diethyl ether (10 mL), free indole (1.0 mmol), i-Pr_2NEt (437 μL, 324 mg, 2.51 mmol), and aldehyde (1.40 mmol). The reaction mixture was cooled to −78 °C in a dry ice/acetone bath, and trimethylsilyl trifluoromethanesulfonate (398 μL, 489 mg, 2.20 mmol) was added dropwise. The orange reaction mixture was stirred for 1 h and then quenched with pyridine (210 μL). The reaction mixture was passed through a column of silica (2 cm × 1 cm) with Et_2O. The solvent was removed in vacuo, and the residue was redissolved in tetrahydrofuran (10 mL). To the solution was added tetrabutylammonium fluoride as a 1.0 M solution in THF (2.10 mL, 2.10 mmol). The reaction mixture was stirred for 5 min and then partitioned between diethyl ether (20 mL) and saturated sodium bicarbonate (20 mL). The layers were separated, and the organic layer was washed with water (20 mL). The organic layer was diluted with hexanes (60 mL) and dried with sodium sulfate. The sodium sulfate was removed by filtration, and the filtrate was concentrated in vacuo. Column chromatography of the residue (0−20% EtOAc/hexanes with 1% diethylamine) provided the product, which was stored at −20 °C after isolation.

1-Methyl-3-(phenyl((trimethylsilyl)oxy)methyl)-1*H*-indole (1). The title compound[12] was prepared similarly to General Procedure A: To an oven-dried round-bottomed flask under a N_2 atmosphere were added diethyl ether (10 mL), *N*-methylindole (125 μL, 131 mg 1.0 mmol), i-Pr_2NEt (210 μL, 156 mg, 1.21 mmol), and benzaldehyde (140 μL, 146 mg, 1.40 mmol). The reaction mixture was cooled to −78 °C in a dry ice/acetone bath, and trimethylsilyl trifluoromethanesulfonate (270 μL, 332 mg, 1.50 mmol) was added dropwise. The orange reaction mixture was stirred for 1 h and then quenched with pyridine (210 μL). The reaction mixture was passed through a column of silica (2 cm × 1 cm) with Et_2O. The solvent was removed in vacuo. Column chromatography of the residue (0−10% EtOAc/hexanes with 1% diethylamine) provided the product as a colorless oil (235 mg, 76%), which was stored at −20 °C after isolation: IR (film) 3058, 3016, 2959, 2150, 1081, 1046, 1012, 885, 838, 738, 702 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.66 (d, J = 7.9 Hz, 1H), 7.63 (d, J = 7.4 Hz, 2H), 7.49−7.43 (m, 2H), 7.42−7.34 (m, 2H), 7.31 (ddd, J = 8.2, 7.0, 1.2 Hz, 1H), 7.16 (ddd, J = 7.9, 7.0, 1.0 Hz, 1H), 7.03 (s, 1H), 6.27 (s, 1H), 3.80 (s, 3H), 0.26 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2, 137.5, 128.1, 127.1, 127.0, 126.6, 126.3, 121.6, 119.9, 119.1, 119.0, 109.3, 71.0, 32.6, 0.0; HRMS (EI, TOF) exact mass calcd for $C_{16}H_{14}N$ [M − $OSiMe_3$]$^+$, 220.1121; found, 220.1124.

(1-Methyl-1*H*-indol-3-yl)(phenyl)methanol (2a). The title compound[4a] was prepared according to General Procedure A, using *N*-methylindole (128 μL, 135 mg 1.03 mmol) and benzaldehyde

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(140 μL, 146 mg, 1.40 mmol). The product was isolated as a yellow solid (164 mg, 68%): mp 65−70 °C; IR (film) 3420, 2939, 2863, 1469, 1371, 1330, 1241, 1194, 1059, 1033, 801, 740, 702 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.61 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.58−7.53 (m, 2H), 7.45−7.39 (m, 2H), 7.38−7.32 (m, 2H), 7.27 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.11 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.91 (s, 1H), 6.17 (s, 1H), 3.76 (s, 3H), 2.44 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2, 137.5, 128.2, 127.3, 127.2, 126.4, 126.3, 121.8, 120.0, 119.6, 119.2, 118.4, 109.4, 70.1, 32.6; HRMS (EI, TOF) exact mass calcd for $C_{16}H_{15}NONa$ [M + Na]$^+$, 260.1046; found, 260.1043; exact mass calcd for $C_{16}H_{14}N$ [M − OH]$^+$, 220.1121; found, 220.1124.

(1-Methyl-1*H*-indol-3-yl)(4-nitrophenyl)methanol (2c). The title compound[12] was prepared according to General Procedure A, using *N*-methylindole (128 μL, 135 mg 1.03 mmol) and 4-nitrobenzaldehyde (211 mg, 1.40 mmol), except that a different amount of *i*-Pr_2NEt was used (292 μL, 217 mg 1.68 mmol). The product was isolated as a pale brown solid (206 mg, 71%): mp 123−127 °C; IR (film) 3524, 310, 3043, 2928, 1593, 1507, 1331, 1042, 805, 741, 718 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.25−8.19 (m, 2H), 7.76−7.71 (m, 2H), 7.55 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.36 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.26 (ddd, *J* = 8.2, 7.0, 1.1 Hz, 1H), 7.10 (ddd, *J* = 8.0, 7.0, 1.0 Hz, 1H), 6.94 (s, 1H), 6.26 (s, 1H), 3.78 (s, 3H), 2.50 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.4, 147.1, 137.5, 127.7, 127.0, 125.8, 123.3, 122.1, 119.5, 119.3, 117.0, 109.6, 69.2, 32.7; HRMS (EI, TOF) exact mass calcd for $C_{16}H_{13}N_2O_3$ [M − H]$^+$, 281.0921 (weak peak observed only at 130 °C); found, 281.0927; exact mass calcd for $C_{16}H_{13}N_2O_2$ [M − OH]$^+$, 265.0972; found, 265.0960.

(4-Fluorophenyl)(1-methyl-1*H*-indol-3-yl)methanol (2d). The title compound[12] was prepared according to General Procedure A, using *N*-methylindole (128 μL, 135 mg 1.03 mmol) and 4-fluorobenzaldehyde (150 μL, 174 mg, 1.40 mmol). The product was isolated as an off-white solid (183 mg, 79%): mp 87−92 °C; IR (film) 3339, 3054, 2921, 1594, 1506, 1466, 1218, 1154, 979, 817, 740 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.56 (dt, *J* = 8.1, 1.1 Hz, 1H), 7.55−7.48 (m, 2H), 7.36 (d, *J* = 8.3 Hz, 1H), 7.26 (ddd, *J* = 8.2, 6.9, 1.2 Hz, 1H), 7.14−7.05 (m, 3H), 6.90 (s, 1H), 6.15 (s, 1H), 3.77 (s, 3H), 2.40 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0 (d, J_F 244.2 = Hz), 140.0 (d, J_F 3.0 = Hz), 137.5, 128.1 (d, J_F = 8.0 Hz), 127.3, 126.1, 121.9, 119.5, 119.2, 118.2, 114.9 (d, J_F = 21.4 Hz), 109.4, 69.5, 32.6; HRMS (EI, TOF) exact mass calcd for $C_{16}H_{14}NOFNa$ [M + Na]$^+$, 278.0952; found, 278.0954; exact mass calcd for $C_{16}H_{13}NF$ [M − OH]$^+$, 238.1027; found, 238.1037.

(4-Bromophenyl)(1-methyl-1*H*-indol-3-yl)methanol (2e). The title compound[12] was prepared according to General Procedure A, using *N*-methylindole (128 μL, 135 mg 1.03 mmol) and 4-bromobenzaldehyde (259 mg, 1.40 mmol). The product was isolated as an off-white solid (254 mg, 78%): mp 90−92 °C; IR (film) 3360, 3047, 2936, 1558, 1479, 1337, 1235, 1068, 1011, 811, 741 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.59 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.57−7.51 (m, 2H), 7.45−7.40 (m, 2H), 7.37 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.29 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.13 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 6.87 (s, 1H), 6.09 (s, 1H), 3.75 (s, 3H), 2.65 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3, 137.5, 131.2, 128.2, 127.5, 126.1, 122.0, 120.8, 119.5, 119.3, 117.8, 109.5, 69.4, 32.6; HRMS (EI, TOF) exact mass calcd for $C_{16}H_{13}NOBr$ [M − H]$^+$, 314.0175, 316.0154; found, 314.0163, 316.0158 (weak peaks observed only at 130 °C); exact mass calcd for $C_{16}H_{13}NBr$ [M − OH]$^+$, 298.0226, 300.0207; found, 298.0212, 300.0195.

(1-Methyl-1*H*-indol-3-yl)(naphthalen-2-yl)methanol (2f). The title compound[12] was prepared according to General Procedure A, using *N*-methylindole (128 μL, 135 mg 1.03 mmol) and 2-naphthaldehyde (219 mg, 1.40 mmol). The product was isolated as brown solid (227 mg, 77%): mp 54−57 °C; IR (film) 3364, 3048, 1473, 1424, 1329, 1240, 1155, 1028, 996, 818, 738 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.12 (bs, 1H), 7.95 (ddd, *J* = 6.8, 5.3, 2.7 Hz, 2H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.69 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.63 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.62−7.56 (m, 2H), 7.39 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.32 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.16 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 6.90 (s, 1H), 6.33 (s, 1H), 3.71 (s, 3H), 2.90 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8, 137.6, 133.4, 132.9, 128.1, 127.8, 127.7, 127.6, 126.4, 126.1, 125.8, 125.2, 124.6, 121.9, 119.7, 119.3, 118.2, 109.5, 70.1, 32.6; HRMS (EI, TOF) exact mass calcd for $C_{20}H_{17}NONa$ [M + Na]$^+$, 310.1202; found, 310.1190; exact mass calcd for $C_{20}H_{15}N$ [M − OH]$^+$, 270.1277; found, 270.1268.

Furan-2-yl(1-methyl-1*H*-indol-3-yl)methanol (2g). The title compound[12] was prepared according to General Procedure A, using *N*-methylindole (128 μL, 135 mg, 1.03 mmol) and 2-furanaldehyde (128 μL, 134 mg, 1.40 mmol). The product was isolated as a dark red oil (165 mg (*corrected to account for residual diethyl ether*), 71%): IR (film) 3386, 3052, 2967, 2932, 2874, 1551, 1474, 1329, 1191, 1063, 1009, 993, 784, 733 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.71 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.52 (dd, *J* = 1.8, 0.9 Hz, 1H), 7.42 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.36 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H), 7.22 (ddd, *J* = 7.9, 7.0, 1.1 Hz, 1H), 7.13 (s, 1H), 6.48 (dd, *J* = 3.2, 1.9 Hz, 1H), 6.39 (dt, *J* = 3.2, 0.8 Hz, 1H), 6.17 (s, 1H), 3.77 (s, 3H), 3.01 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.7, 142.0, 137.4, 127.5, 126.3, 121.9, 119.7, 119.3, 115.2, 110.3, 109.5, 106.7, 64.2, 32.6.; HRMS (EI, TOF) exact mass calcd for $C_{14}H_{13}NO_2Na$ [M + Na]$^+$, 250.0839; found, 250.0844; exact mass calcd for $C_{14}H_{12}NO$ [M − OH]$^+$, 210.0913; found, 210.0908.

(1*H*-Indol-3-yl)(thiophen-2-yl)methanol (2h). The title compound[12] was prepared according to General Procedure A, using *N*-methylindole (128 μL, 135 mg, 1.03 mmol) and 2-thiophenecarboxaldehyde (131 μL, 157 mg, 1.40 mmol). The product was isolated as a pale brown solid (210 mg, 84%): IR (film) 3360, 3047, 2923, 2872, 1609, 1549, 1473, 1423, 1329, 1239, 1155, 1131, 1063, 1024, 978, 853, 764, 739, 701 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.61 (dt, *J* = 8.0, 0.9 Hz, 1H), 7.38 (dt, *J* = 8.3, 0.9 Hz, 1H), 7.32 (dd, *J* = 5.0, 1.3 Hz, 1H), 7.27 (ddd, *J* = 8.2, 7.1, 1.1 Hz, 1H), 7.14−7.10 (m, 2H), 7.07 (dt, *J* = 3.5, 1.1 Hz, 1H), 7.02 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.40 (s, 1H), 3.79 (s, 3H), 2.57 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.8, 137.5, 127.2, 126.6, 126.0, 124.6, 124.3, 121.9, 119.6, 119.3, 117.6, 109.5, 66.6, 32.7; HRMS (EI, TOF) exact mass calcd for $C_{14}H_{13}NOSNa$ [M + Na]$^+$, 266.0610; found, 266.0614; exact mass calcd for $C_{14}H_{13}NS$ [M − OH]$^+$, 226.0685; found, 226.0678.

(*E*)-1-(1-Methyl-1*H*-indol-3-yl)-3-phenylprop-2-en-1-ol (2i). The title compound[12] was prepared according to General Procedure A, using *N*-methylindole (128 μL, 135 mg, 1.03 mmol) and *trans*-cinnamaldehyde (176 μL, 185 mg, 1.40 mmol). The product was isolated as an orange-brown oil (172 mg (*yield corrected for presence of residual diethyl ether*), 63%): IR (film) 3364, 3050, 3021, 2926, 2863, 1548, 1473, 1447, 1328, 1242, 1154, 1112, 1066, 1012, 962, 737, 692 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.83 (dt, *J* = 8.0, 1.0 Hz, 1H), 7.55−7.47 (m, 2H), 7.44−7.36 (m, 3H), 7.35−7.28 (m, 2H), 7.19 (ddd, *J* = 8.0, 7.0, 1.1 Hz, 1H), 7.13 (s, 1H), 6.85 (d, *J* = 16.0, 1H), 6.69 (dd, *J* = 15.9, 6.1 Hz, 1H), 5.74 (d, *J* = 6.1 Hz, 1H), 3.79 (s, 3H), 2.33 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5, 137.1, 131.9, 129.6, 128.6, 127.5, 126.8, 126.5, 126.3, 121.8, 119.7, 119.2, 116.9, 109.5, 68.7, 32.6; HRMS (EI, TOF) exact mass calcd for $C_{18}H_{16}NO$ [M − H]$^+$, 262.1226; found, 262.1218 (weak peak observed only at 130 °C); exact mass calcd for $C_{18}H_{16}N$ [M − OH]$^+$, 246.1277; found, 246.1274.

(1-Benzyl-1*H*-indol-3-yl)(phenyl)methanol (3a). The title compound[5] was prepared according to General Procedure A, using *N*-benzylindole (206 mg, 1.00 mmol) and benzaldehyde (142 μL, 149 mg, 1.40 mmol). The product was isolated as a pale yellow oil (235 mg, 75%): IR (film) 3343, 1636, 1550, 1452, 1332, 1264, 1170, 1032, 990, 731, 695 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.66 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 2H), 7.55−7.32 (m, 7H), 7.32−7.18 (m, 3H), 7.14 (t, *J* = 7.5 Hz, 1H), 7.07 (s, 1H), 6.21 (s, 1H), 5.31 (s, 2H), 2.58 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 137.7, 137.1, 128.7, 128.3, 127.6, 127.3, 126.8, 126.8, 126.8, 126.6, 126.5, 122.1, 119.9, 119.5, 119.1, 110.0, 70.3, 50.1; HRMS (EI, TOF) exact mass calcd for $C_{22}H_{19}NONa$ [M + Na]$^+$, 336.1359; found, 336.1357.

(1-Allyl-1*H*-indol-3-yl)(phenyl)methanol (3b). The title compound[12] was prepared according to General Procedure A, using *N*-allylindole (160 mg, 1.02 mmol) and benzaldehyde (145 μL, 152 mg, 1.43 mmol). The product was isolated as a yellow oil

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(205 mg, 76%): IR (film) 3343, 1643, 1550, 1465, 1332, 1264, 1177, 989, 919, 813, 735, 697 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 7.58 (dt, J = 8.0, 1.0 Hz, 1H), 7.56−7.52 (m, 2H), 7.43−7.37 (m, 2H), 7.36−7.29 (m, 2H), 7.21 (ddd, J = 8.3, 7.0, 1.1 Hz, 1H), 7.07 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 6.97 (s, 1H), 6.18 (d, J = 3.9 Hz, 1H), 6.03 (ddt, J = 17.1, 10.2, 5.5 Hz, 1H), 5.22 (dq, J = 10.3, 1.4 Hz, 1H), 5.12 (dq, J = 17.1, 1.6 Hz, 1H), 4.72 (dt, J = 5.5, 1.6 Hz, 2H), 2.30 (d, J = 4.1 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.1, 136.9, 133.5, 128.2, 127.2, 126.4, 126.4, 126.3, 121.8, 119.7, 119.3, 118.8, 117.0, 109.8, 70.2, 48.8; HRMS (EI, TOF) exact mass calcd for $C_{18}H_{17}NONa$ $[M + Na]^+$, 286.1202; found, 286.1197.

(1*H*-Indol-3-yl)(phenyl)methanol (4a). The title compound[3a] was prepared according to General Procedure B, using indole (117 mg, 1.00 mmol) and benzaldehyde (142 μL, 149 mg, 1.40 mmol). The product was isolated as a white solid (163 mg (*yield corrected for residual diethyl ether*), 73%): mp 80−83 °C; IR (film) 3536, 3408, 3305, 3060, 2925, 2848, 1548, 1493, 1455, 1420, 1338, 1227, 1101, 989, 741, 699 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.30 (s, 1H), 7.61 (dq, J = 8.0, 0.9 Hz, 1H), 7.58−7.49 (m, 2H), 7.46−7.32 (m, 4H), 7.23 (ddd, J = 8.3, 7.0, 1.2 Hz, 1H), 7.11 (ddd, J = 8.0, 7.0, 1.0 Hz, 1H), 6.99 (dd, J = 2.5, 0.8 Hz, 1H), 6.18 (s, 1H), 2.52 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0, 136.7, 128.2, 127.3, 126.5, 125.8, 122.8, 122.2, 119.7, 119.6, 119.5, 111.3, 70.3; HRMS (EI, TOF) exact mass calcd for $C_{15}H_{13}NONa$ $[M + Na]^+$, 246.0889; found, 246.0887; exact mass calcd for $C_{15}H_{12}N$ $[M - OH]^+$, 206.0964; found, 206.0954.

(5-Bromo-1*H*-indol-3-yl)(phenyl)methanol (4b). The title compound[3c] was prepared according to General Procedure B, using 5-bromoindole (196 mg, 1.00 mmol) and benzaldehyde (142 μL, 149 mg, 1.40 mmol). The product was isolated as an off-white solid (223 mg (*yield corrected for residual ethyl acetate*), 72%): mp 35−38 °C; IR (film) 3422, 3297, 2870, 1450, 1223, 1099, 983, 952, 881, 794, 732, 699 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.47 (s, 1H), 7.76 (d, J = 1.6 Hz, 1H), 7.53−7.48 (m, 2H), 7.45−7.39 (m, 2H), 7.38−7.33 (m, 1H), 7.29 (dd, J = 8.6, 1.9 Hz, 1H), 7.23 (dd, J = 8.6, 0.6 Hz, 1H), 6.94 (d, J = 2.5 Hz, 1H), 6.10 (s, 1H), 2.69 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.5, 135.3, 128.4, 127.6, 127.5, 126.4, 125.0, 124.1, 122.1, 119.2, 112.9, 112.8, 70.1; HRMS (EI, TOF) exact mass calcd for $C_{15}H_{11}NOBr$ $[M - H]^+$, 300.0019, 301.9999 (weak peaks observed only at 130 °C); found, 300.0010, 302.0025; exact mass calcd for $C_{15}H_{11}NBr$ $[M - OH]^+$, 284.0069, 286.0050; found, 284.0069, 286.0043.

(4-Bromophenyl)(1*H*-indol-3-yl)methanol (4c). The title compound[6a] was prepared according to General Procedure B, using indole (117 mg, 1.00 mmol) and 4-bromobenzaldehyde (259 mg, 1.40 mmol). The product was isolated as a white solid (287 mg (*yield corrected for residual ethyl acetate*), 87%): mp 38−42 °C; IR (film) 3403, 3312, 3058, 2928, 2858, 1485, 1420, 1338, 1232, 1069, 819, 778, 741 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.37 (s, 1H), 7.58 (d, J = 8.1 Hz, 1H), 7.56−7.49 (m, 2H), 7.42−7.33 (m, 3H), 7.25 (ddd, J = 8.3, 7.0, 1.2 Hz, 1H), 7.13 (ddd, J = 8.1, 7.0, 1.0 Hz, 1H), 6.89 (d, J = 2.5 Hz, 1H), 6.09 (s, 1H), 2.84 (bs, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0, 136.7, 131.2, 128.2, 125.5, 122.8, 122.4, 120.9, 119.8, 119.5, 119.3, 111.3, 69.6; HRMS (EI, TOF) exact mass calcd for $C_{15}H_{11}NOBr$ $[M - H]^+$, 300.0019, 301.9999; found, 300.0025, 301.9963 (weak peaks observed only at 130 °C); exact mass calcd for $C_{15}H_{11}NBr$ $[M - OH]^+$, 284.0069, 286.0050; found, 284.0074, 286.0061.

(1*H*-Indol-3-yl)(naphthalen-2-yl)methanol (4d). The title compound[3b] was prepared according to General Procedure B, using indole (117 mg, 1.00 mmol) and 2-naphthaldehyde (219 mg, 1.40 mmol). The product was isolated as a pinkish white solid, although purity appears to be only ~90% by ^{1}H NMR spectroscopy (254 mg (*yield corrected for residual ethyl acetate and trace impurities*), 77%): mp 136−138 °C °C; IR (film) 3433, 3337, 3052, 1664, 1544, 1459, 1339, 1250, 1116, 1007, 827, 787, 748 cm^{-1}; ^{1}H NMR (500 MHz, CD_2Cl_2) δ 8.27 (bs, 1H), 8.08 (s, 1H), 7.95−7.82 (m, 3H), 7.64−7.57 (m, 2H), 7.56−7.49 (m, 2H), 7.42 (dt, J = 8.2, 0.9 Hz, 1H), 7.20 (ddd, J = 8.3, 7.1, 1.2 Hz, 1H), 7.11 (dd, J = 2.5, 0.8 Hz, 1H), 7.07 (ddd, J = 8.1, 7.1, 1.0 Hz, 1H), 6.36 (s, 1H), 2.46 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.4, 136.7, 133.3, 132.9, 128.0, 127.8, 127.6, 126.0, 125.8, 125.7, 125.0, 124.6, 122.8, 122.3, 119.7 (double intensity), 119.5, 111.2, 70.3; HRMS (EI, TOF) exact mass calcd for $C_{19}H_{15}NONa$ $[M + Na]^+$, 296.1046; found, 296.1048; exact mass calcd for $C_{19}H_{14}N$ $[M - OH]^+$, 256.1121; found, 256.1110.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.5b01681.

Spectral data (PDF).

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Notes

The authors declare no competing financial interest.

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