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Ruthenium(II)-Catalyzed C–H Methylation with Trifluoroborates

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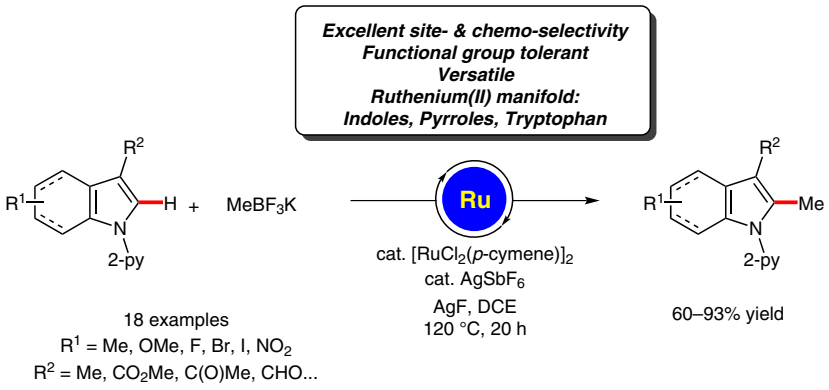
Dedicated to Professor Dieter Enders



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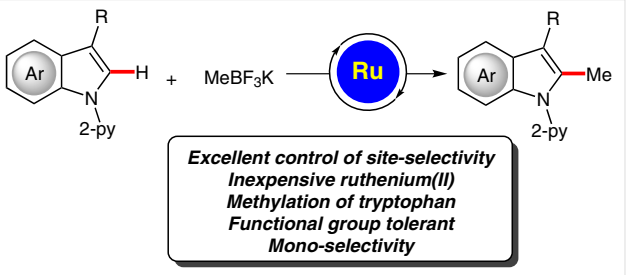
Abstract A cationic ruthenium(II)-complex enabled unprecedented C–H methylations on indoles and pyrroles. The versatile catalyst proved to be widely applicable and delivered the methylated heteroarenes with excellent levels of positional selectivity and ample substrate scope. The robustness of the catalysts was reflected by the challenging racemization-free C–H methylation of (*S*)-tryptophan.

Key words amino acids, C–H activation, heteroarenes, methylation, ruthenium, tryptophan

The methyl group constitutes an omnipresent structural feature in compounds of relevance for agrochemical and pharmaceutical industries. Thus, the introduction of a methyl group frequently improves the bioactivities and physical properties of pharmacologically active drug molecules.[1] For instance, the methyl substituent enhances the hydrophobicity of organic compounds and thereby its binding affinities at biomolecules.[2] This *magic methyl effect* can thus stimulate a hundredfold boost in effectiveness, translating into a significantly improved IC_{50} value.[1,3]

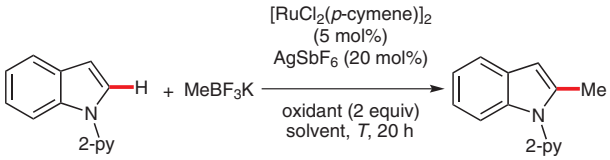
In addition to traditional stoichiometric deprotonative approaches,[4] transition-metal catalysis has proven to be instrumental in the development of synthetically meaningful alkylation and methylation reactions.[5] However, the step-economy of conventional cross-coupling methylations is compromised by the requirement for both coupling partners to undergo elements of prefunctionalization. Thus, focus has shifted in the past few years towards C–H functionalization[6] strategies that minimize the number of synthetic operations in an environmentally benign and economically attractive fashion.[7] Yet, despite significant advances in metal-catalyzed C–H methylations,[8] ruthenium(II)-catalyzed[9] C–H methylations have unfortunately proven elusive. Within our program on ruthenium(II)-catalyzed C–H functionalizations[10] for direct alkylations, we have now devised reaction conditions for unprecedented C–H methylations by means of versatile ruthenium(II) catalysis (Scheme 1), on which we report herein. Notable features of our study include (i) expedient C–H methylations on diversely decorated indoles and pyrroles, (ii) a removable[11] directing group strategy, (iii) key mechanistic insights, and (iv) racemization-free C–H functionalization on tryptophan derivatives.



Scheme 1 C–H methylation by ruthenium(II) catalysis

We commenced our studies by testing various reaction conditions for the envisioned C–H methylation of indole **1a** with trifluoroborate **2** (Table 1). Thus, among a set of representative sacrificial oxidants, silver(I) salts provided optimal results (entries 1–7). While a variety of solvents ranging from apolar toluene to polar *N*,*N*-dimethylformamide (DMF) could be utilized, the ruthenium(II)-catalyzed C–H methylation was most effective in 1,2-dichloroethane (DCE) (entries 7–14). The C–H functionalization proved viable at various reaction temperatures, with the best catalytic performance being achieved at 120 °C (entries 10–14). The key importance of the ruthenium catalyst in the C–H methylation manifold was verified by probing the transformation in the absence of the ruthenium catalyst under otherwise identical reaction conditions (entries 13 and 14).

Table 1 Optimization of the Ruthenium(II)-Catalyzed C–H Methylation[a]



1a 2 3a

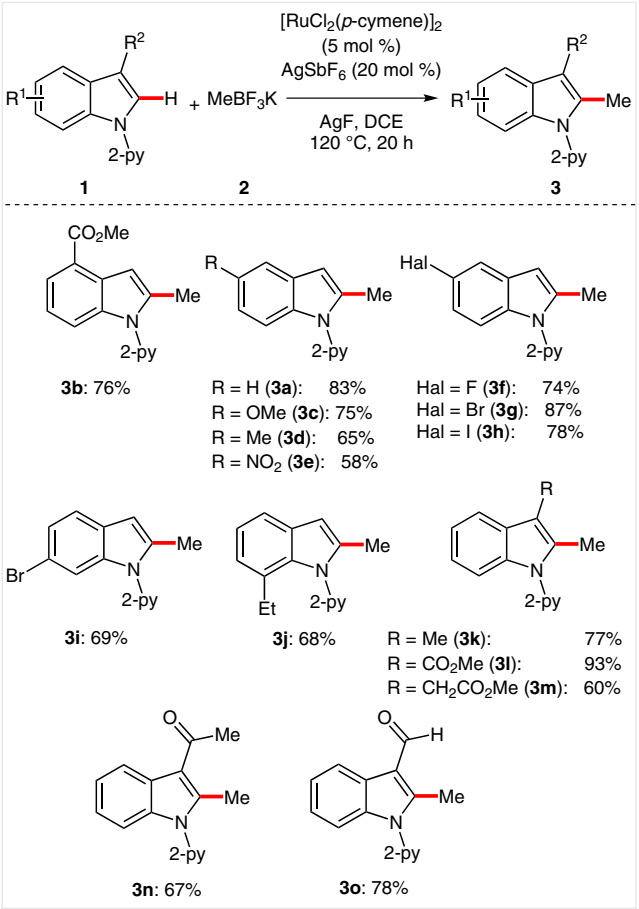
Entry	Oxidant	*T* (°C)	Solvent	**3a** (%)[a]
1	1,4-benzoquinone	120	DCE	traces
2	O_2 (1 atm)	120	DCE	20
3	$K_2S_2O_8$	120	DCE	29
4	$Cu(OAc)_2·H_2O$	120	DCE	37
5	Oxone	120	DCE	41
6	Ag_2O	120	DCE	79[b]
7	AgF	120	toluene	35
8	AgF	120	1,4-dioxane	56
9	AgF	120	DMF	63
10	AgF	60	DCE	71
11	AgF	80	DCE	73
12	AgF	100	DCE	76
13	AgF	120	DCE	–[c]
14	AgF	120	DCE	83

[a] Reaction conditions: **1a** (0.50 mmol), **2** (1.00 mmol), $[RuCl_2(p\text{-cymene})]_2$ (5 mol%), $AgSbF_6$ (20 mol%), oxidant (2 equiv), solvent (1.0 mL), T, 20 h.
[b] Ag_2O (1 equiv).
[c] Without $[RuCl_2(p\text{-cymene})]_2$, C-3-substituted **3a′** product was obtained in 21%.

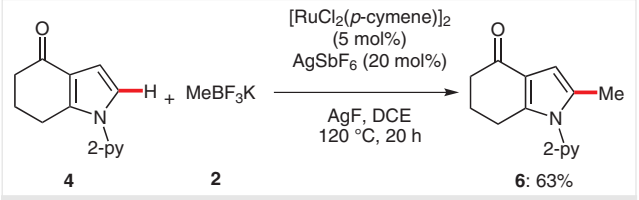
With the optimized catalytic system in hand, we explored its versatility in the C–H methylation of diversely decorated indoles **1** (Scheme 2). Thereby, substrates possessing substituents on all positions of the aromatic backbone were efficiently transformed into the desired products **3a–j**. Importantly, more sterically encumbered 3-substituted heteroarenes **1k–o** also proved to be viable substrates. The robustness of the ruthenium(II) C–H methylation manifold was reflected by fully tolerating valuable functional groups, including nitro, bromo, iodo, ester, ketone, and aldehyde groups, which should prove invaluable for further post-synthetic diversification.

The versatile ruthenium(II) catalyst was not restricted to indole substrates **1**, but enabled the step-economical C–H methylation on pyrrole **4** likewise (Scheme 3).

The late-stage modification of amino acids bears great potential for the synthesis of non-natural amino acids and peptide diversification.[12] Therefore, we were particularly delighted to observe that the effective C–H methylation on tryptophan derivative **7** proved viable for the first time

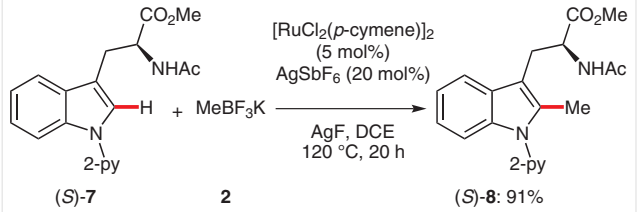


Scheme 2 Ruthenium(II)-catalyzed C–H methylation of indoles **1**

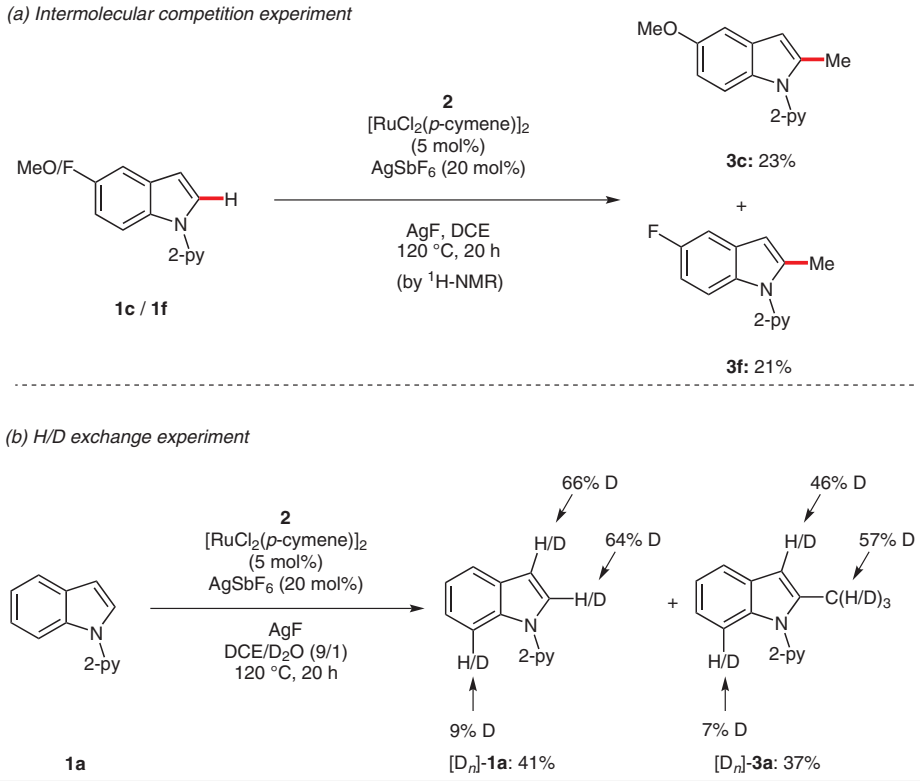


Scheme 3 Ruthenium(II)-catalyzed C–H methylation of pyrrole **4**

(Scheme 4). In this context it is noteworthy that the C–H functionalization occurred without any racemization of the stereogenic center.



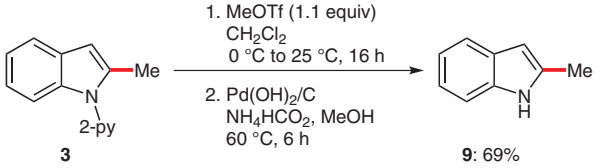
Scheme 4 Tryptophan (*S*)-**7** modification by ruthenium(II)-catalyzed C–H methylation



Scheme 5 Summary of key mechanistic findings

In consideration of the unique synthetic utility of the ruthenium(II)-catalyzed C–H methylation, we were intrigued by its mode of action. To investigate this aspect of the reaction, we performed intermolecular competition experiments, with the results indicating only a slight preference for more electron-rich substrates (Scheme 5a). Moreover, C–H methylation in the presence of an isotopically labeled co-solvent provided evidence for a facile C-2 C–H cyclometallation step (Scheme 5b). While the additional H/D exchange in the C-3 position can be rationalized in terms of an electrophilic activation mode, the notable, albeit minor, deuteration at the C-7 position highlights the potential of our strategy for C–H functionalizations by six-membered ruthenacycles.

Finally, the synthetic power of the ruthenium(II)-catalyzed C–H methylation strategy was reflected by the removal of the pyridyl group in a traceless fashion, thereby delivering the methylated NH-free indole **9** (Scheme 6).



Scheme 6 Traceless removal of the pyridyl group

In summary, we have reported on the first ruthenium(II)-catalyzed C–H methylation by chelation assistance. Thus, a cationic ruthenium(II) catalyst formed in situ enabled C–H functionalizations with methytrifluoroborates on heteroarenes with high levels of positional selectivity. The versatility of the ruthenium(II) catalysis regime set the stage for efficient C–H methylations on indoles and pyrroles with excellent functional group tolerance. The bioorthogonal nature of the C–H functionalization further enabled the direct modification of tryptophan derivatives, indicating the potential of our approach for the late-stage diversification of amino acids and peptides.[13]

All catalytic reactions were carried out under N_2 in predried glassware. Anhydrous DCE was obtained by distillation over CaH_2 under reduced pressure. Yields refer to isolated compounds, estimated to be >95% pure as determined by ^{1}H NMR and GC analysis. Melting points were obtained with a Stuart® SMP3 melting point apparatus, and the values are uncorrected. TLC were recorded with detection under UV light at 254 nm. Chromatographic separations were carried out on Merck silica gel 60 (0.040–0.063 mm, 70–230 mesh ASTM). All IR spectra were recorded with a Bruker Alpha-P spectrometer. EI-MS were obtained with a Finnigan MAT 95 (70 eV). ESI-MS were obtained with a Finnigan LCQ. High-resolution mass spectrometry (HRMS) were obtained with a APEX IV 7T FTICR, Bruker Daltonic. ^{1}H, ^{13}C, ^{19}F, and ^{11}B NMR spectra were recorded at 300, 400, 500, 600 (^{1}H), 100,

125 [^{13}C, APT (Attached Proton Test)] and 283 MHz (^{19}F), with Varian Unity-300 (600) and AMX 300 instruments in $CDCl_3$ solutions; chemical shifts (δ) are given in ppm.

1-(Pyridin-2-yl)-1*H*-indole (1a); Typical Procedure

A mixture of 1*H*-indole (3.52 g, 30 mmol) and KOH (4.21 g, 75 mmol) in DMSO (30 mL) was stirred and heated at 120 °C for 15 min, then 2-bromopyridine (6.64 g, 42 mmol) was added. After 30 h, the mixture was cooled to ambient temperature, diluted with EtOAc (120 mL) and washed with H_2O (3 × 50 mL). The product was extracted with EtOAc (3 × 100 mL), the organic layer was dried over Na_2SO_4, and the solvent was removed in vacuo. The crude product was purified by chromatography on silica gel (*n*-hexane/EtOAc, 20:1) to afford **1a**.

Yield: 5.36 g (92%); yellow oil.

IR (ATR): 3052, 1587, 1470, 1449, 1433, 1317, 1240, 729 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.57 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1 H), 8.23 (d, *J* = 8.3 Hz, 1 H), 7.81 (ddd, *J* = 8.2, 7.4, 2.0 Hz, 1 H), 7.73 (d, *J* = 3.5 Hz, 1 H), 7.66 (dd, *J* = 7.7, 1.2 Hz, 1 H), 7.48 (d, *J* = 8.2 Hz, 1 H), 7.33–7.27 (m, 1 H), 7.22–7.19 (m, 1 H), 7.15 (dd, *J* = 7.4, 4.9 Hz, 1 H), 6.72 (dd, *J* = 3.5, 0.9 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 152.0 (C_q), 148.4 (CH), 137.9 (CH), 134.7 (C_q), 130.1 (C_q), 125.6 (CH), 122.8 (CH), 121.0 (CH), 119.5 (CH), 113.9 (CH), 113.0 (CH), 112.9 (CH), 105.2 (CH).

MS (EI): *m*/*z* (%) = 194 (100) [M]$^+$, 167 (30).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{13}H_{10}N_2$: 194.0844; found: 194.0841.

The analytical data are in accordance with those reported in the literature.[12b]

2-Methyl-1-(pyridin-2-yl)-1*H*-indole (3a)

A suspension of 1-(pyridin-2-yl)-1*H*-indole (**1a**; 97.1 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol%), $AgSbF_6$ (34.4 mg, 20 mol%), AgF (127 mg, 1.00 mmol) and potassium methyltrifluoroborate (**2**; 122 mg, 1.00 mmol) in DCE (1.0 mL) was stirred and heated at 120 °C for 20 h. At ambient temperature, the reaction mixture was diluted with H_2O (10.0 mL) and extracted with EtOAc (3 × 25 mL), and the combined organic layers were dried with Na_2SO_4. After filtration and evaporation of the solvents in vacuo, the crude product was purified by column chromatography (*n*-hexane/EtOAc/CH_2Cl_2, 26:3:1) to afford **3a**.

Yield: 86.5 mg (83%); yellow oil.

IR (ATR): 3052, 1581, 1468, 1455, 1432, 776, 734 cm^{-1}.

^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.66–8.65 (m, 1 H), 7.87–7.84 (m, 1 H), 7.56–7.54 (m, 1 H), 7.41 (dd, *J* = 8.0, 0.9 Hz, 1 H), 7.39–7.34 (m, 1 H), 7.29 (ddd, *J* = 7.5, 4.9, 0.8 Hz, 1 H), 7.14–7.11 (m, 2 H), 6.42 (dd, *J* = 0.9, 0.9 Hz, 1 H), 2.46 (d, *J* = 0.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.3 (C_q), 149.4 (CH), 138.0 (CH), 137.0 (C_q), 136.7 (C_q), 128.6 (C_q), 121.7 (CH), 121.4 (CH), 120.7 (CH), 120.5 (CH), 119.6 (CH), 110.1 (CH), 103.2 (CH), 14.0 (CH_3).

MS (EI): *m*/*z* (%) = 208 (100) [M]$^+$, 130 (30).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{12}N_2$: 209.1073; found: 209.1079.

The analytical data are in accordance with those reported in the literature.[8c]

Methyl 2-Methyl-1-(pyridin-2-yl)-1*H*-indole-4-carboxylate (3b)

The representative procedure was followed using methyl 1-(pyridin-2-yl)-1*H*-indole-4-carboxylate (**1b**; 126 mg, 0.50 mmol) and potassium methyltrifluoroborate (**2**; 122 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/CH_2Cl_2, 1:1) afforded **3b**.

Yield: 101 mg (76%); yellow oil.

IR (ATR): 1707, 1585, 1434, 1261, 1135, 727 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.66 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1 H), 7.90 (dd, *J* = 7.6, 1.0 Hz, 1 H), 7.87 (ddd, *J* = 8.0, 7.5, 2.0 Hz, 1 H), 7.54 (dt, *J* = 8.2, 0.9 Hz, 1 H), 7.36 (dt, *J* = 8.0, 1.0 Hz, 1 H), 7.32 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1 H), 7.14 (dd, *J* = 8.2, 7.6 Hz, 1 H), 7.09 (t, *J* = 0.9 Hz, 1 H), 3.99 (s, 3 H), 2.48 (d, *J* = 1.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 168.1 (C_q), 151.0 (C_q), 149.8 (CH), 139.4 (C_q), 138.4 (CH), 138.1 (C_q), 128.6 (C_q), 124.0 (CH), 122.4 (CH), 121.1 (CH), 120.8 (CH), 120.6 (C_q), 115.1 (CH), 104.5 (CH), 51.8 (CH_3), 14.0 (CH_3).

MS (EI): *m*/*z* (%) = 266 (100) [M]$^+$, 207 (67).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{16}H_{14}N_2O_2$: 266.1055; found: 266.1053.

5-Methoxy-2-methyl-1-(pyridin-2-yl)-1*H*-indole (3c)

The representative procedure was followed using 5-methoxy-1-(pyridin-2-yl)-1*H*-indole (**1c**; 112 mg, 0.50 mmol) and potassium methyltrifluoroborate (**2**; 122 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc/CH_2Cl_2, 10:1:1) afforded **3c**.

Yield: 89.0 mg (75%); light-brown oil.

IR (ATR): 1588, 1470, 1435, 1372, 907, 781, 728 cm^{-1}

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.53 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1 H), 7.74 (td, *J* = 7.8, 2.0 Hz, 1 H), 7.28 (dt, *J* = 8.1, 1.0 Hz, 1 H), 7.20 (d, *J* = 9.1 Hz, 1 H), 7.18–7.14 (m, 1 H), 6.93 (d, *J* = 2.5 Hz, 1 H), 6.68 (dd, *J* = 8.9, 2.5 Hz, 1 H), 6.25 (q, *J* = 1.0 Hz, 1 H), 3.75 (s, 3 H), 2.35 (d, *J* = 1.0 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 154.9 (C_q), 151.6 (C_q), 149.5 (CH), 138.3 (CH), 137.5 (C_q), 132.3 (C_q), 129.4 (C_q), 121.7 (CH), 120.9 (CH), 111.2 (CH), 111.1 (CH), 103.4 (CH), 102.1 (CH), 55.9 (CH_3), 14.2 (CH_3).

MS (EI) *m*/*z* (%) = 238 (100) [M]$^+$, 223 (54).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}N_2O$: 238.1106; found: 238.1099.

The analytical data are in accordance with those reported in the literature.[8c]

2,5-Dimethyl-1-(pyridin-2-yl)-1*H*-indole (3d)

The representative procedure was followed using 5-methyl-1-(pyridin-2-yl)-1*H*-indole (**1d**; 104 mg, 0.50 mmol) and potassium methyltrifluoroborate (**2**; 122 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc/CH_2Cl_2, 20:1:1) afforded **3d**.

Yield: 72.2 mg (65%); brown oil.

IR (ATR): 1469, 1433, 1202, 1173, 1033, 770, 727 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.63 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1 H), 7.83 (td, *J* = 7.7, 2.0 Hz, 1 H), 7.39 (dd, *J* = 8.0, 1.0 Hz, 1 H), 7.35–7.32 (m, 1 H), 7.30–7.22 (m, 2 H), 6.94 (dd, *J* = 8.4, 1.7 Hz, 1 H), 6.34 (t, *J* = 1.0 Hz, 1 H), 2.45 (d, *J* = 1.0 Hz, 3 H), 2.43 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 151.7 (C_q), 149.6 (CH), 138.2 (CH), 137.0 (C_q), 135.6 (C_q), 130.0 (C_q), 129.1 (C_q), 123.1 (CH), 121.7 (CH), 120.6 (CH), 119.7 (CH), 110.0 (CH), 103.1 (CH), 21.5 (CH_3), 14.2 (CH_3).

MS (EI) *m*/*z* (%) = 222 (100) [M]$^+$, 207 (18).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{15}H_{14}N_2$: 222.1157; found: 222.1152.

2-Methyl-5-nitro-1-(pyridin-2-yl)-1*H*-indole (3e)

The representative procedure was followed using 5-nitro-1-(pyridin-2-yl)-1*H*-indole (**1e**; 120 mg, 0.50 mmol) and potassium methyltrifluoroborate (**2**; 122 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc/CH_2Cl_2, 26:3:1) afforded **3e**.

Yield: 73.0 mg (58%); off-white solid; mp 143–145 °C.

IR (ATR): 1587, 1565, 1511, 1467, 1339, 1322, 774, 744 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.70–8.68 (m, 1 H), 8.48 (d, *J* = 2.3 Hz, 1 H), 8.01 (ddd, *J* = 9.1, 2.3, 0.7 Hz, 1 H), 7.95 (tdd, *J* = 7.7, 2.0, 0.8 Hz, 1 H), 7.42–7.40 (m, 2 H), 7.33 (dd, *J* = 9.0, 0.7 Hz, 1 H), 6.56 (s, 1 H), 2.44 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.3 (C_q), 150.0 (CH), 142.4 (C_q), 140.4 (C_q), 140.1 (C_q), 138.7 (CH), 128.1 (C_q), 123.1 (CH), 121.1 (CH), 117.3 (CH), 116.7 (CH), 110.3 (CH), 104.7 (CH), 14.1 (CH_3).

MS (EI): *m*/*z* (%) = 253 (100) $[M]^+$, 207 (50).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{11}N_3O_2$: 253.0851; found: 253.0853.

5-Fluoro-2-methyl-1-(pyridin-2-yl)-1*H*-indole (3f)

The representative procedure was followed using 5-fluoro-1-(pyridin-2-yl)-1*H*-indole (**1f**; 106 mg, 0.50 mmol) and potassium methyltrifluoroborate (**2**; 122 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc/CH_2Cl_2, 26:3:1) afforded **3f**.

Yield: 84.0 mg (74%); yellow oil.

IR (ATR): 1583, 1468, 1433, 1383, 1176, 772, 588 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.64 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1 H), 7.87 (ddd, *J* = 8.0, 7.5, 2.0 Hz, 1 H), 7.38 (dt, *J* = 8.0, 1.0 Hz, 1 H), 7.31–7.25 (m, 2 H), 7.17 (dd, *J* = 9.4, 2.5 Hz, 1 H), 6.83 (td, *J* = 9.1, 2.5 Hz, 1 H), 6.36 (dd, *J* = 0.9, 0.9 Hz, 1 H), 2.43 (d, *J* = 0.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 158.5 (C_q, $^1J_{C-F}$ = 234.0 Hz), 151.4 (C_q), 149.7 (CH), 138.5 (C_q), 138.3 (CH), 133.7 (C_q), 129.3 (C_q, $^3J_{C-F}$ = 9.9 Hz), 122.1 (CH), 120.8 (CH), 111.1 (CH, $^3J_{C-F}$ = 9.8 Hz), 109.5 (CH, $^2J_{C-F}$ = 26.1 Hz), 104.9 (CH, $^2J_{C-F}$ = 23.6 Hz), 103.4 (CH, $^4J_{C-F}$ = 4.5 Hz), 14.3 (CH_3).

^{19}F NMR (282 MHz, $CDCl_3$): δ = –124.1.

MS (EI): *m*/*z* (%) = 226 (100) $[M]^+$, 148 (30).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{11}FN_2$: 226.0906; found: 226.0904.

5-Bromo-2-methyl-1-(pyridin-2-yl)-1*H*-indole (3g)

The representative procedure was followed using 5-bromo-1-(pyridin-2-yl)-1*H*-indole (**1g**; 137 mg, 0.50 mmol) and potassium methyltrifluoroborate (**2**; 122 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc/CH_2Cl_2, 26:3:1) afforded **3g**.

Yield: 124 mg (87%); off-white solid; mp 53–55 °C.

IR (ATR): 2920, 1557, 1468, 1436, 773, 743 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.64 (ddd, *J* = 4.8, 2.0, 0.8 Hz, 1 H), 7.86 (t, *J* = 7.7 Hz, 1 H), 7.65 (s, 1 H), 7.36–7.30 (m, 2 H), 7.24–7.16 (m, 2 H), 6.34 (s, 1 H), 2.43 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.0 (C_q), 149.7 (CH), 138.4 (CH), 138.2 (C_q), 135.9 (C_q), 130.5 (C_q), 124.3 (CH), 122.3 (CH), 122.3 (CH), 120.8 (CH), 113.8 (C_q), 111.8 (CH), 102.8 (CH), 14.2 (CH_3).

MS (EI): *m*/*z* (%) = 286 (100) $[M(^{79}Br)]^+$, 207 (60).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{11}{}^{79}BrN_2$: 287.0178; found: 287.0172.

5-Iodo-2-methyl-1-(pyridin-2-yl)-1*H*-indole (3h)

The representative procedure was followed using 5-iodo-1-(pyridin-2-yl)-1*H*-indole (**1h**; 160 mg, 0.50 mmol) and potassium methyltrifluoroborate (**2**; 122 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc/CH_2Cl_2, 26:3:1) afforded **3h**.

Yield: 130 mg (78%); colorless oil.

IR (ATR): 1585, 1469, 1439, 1384, 1371, 779 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.64 (ddd, *J* = 4.8, 2.0, 0.8 Hz, 1 H), 7.89–7.81 (m, 2 H), 7.37–7.27 (m, 3 H), 7.12 (dt, *J* = 8.7, 0.8 Hz, 1 H), 6.32 (dd, *J* = 0.9, 0.9 Hz, 1 H), 2.42 (s, *J* = 0.9 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 150.8 (C_q), 149.5 (CH), 138.2 (CH), 137.7 (C_q), 136.2 (C_q), 131.1 (C_q), 129.7 (CH), 128.3 (CH), 122.1 (CH), 120.6 (CH), 112.2 (CH), 102.3 (CH), 84.1 (C_q), 13.9 (CH_3).

MS (EI) *m*/*z* (%) = 334 (100) $[M]^+$, 256 (10), 207 (50), 128 (10).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{11}IN_2$: 333.9067; found: 333.9060.

6-Bromo-2-methyl-1-(pyridin-2-yl)-1*H*-indole (3i)

The representative procedure was followed using 6-bromo-1-(pyridin-2-yl)-1*H*-indole (**1i**; 137 mg, 0.50 mmol) and potassium methyltrifluoroborate (**2**; 122 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/CH_2Cl_2, 1:1) afforded **3i**.

Yield: 98.7 mg (69%); yellow oil.

IR (ATR): 1585, 1459, 1428, 1383, 1337, 808, 780 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.66 (dd, *J* = 4.7, 1.9 Hz, 1 H), 7.87 (td, *J* = 7.7, 2.0 Hz, 1 H), 7.54 (d, *J* = 1.7 Hz, 1 H), 7.41 (d, *J* = 8.3 Hz, 1 H), 7.39–7.35 (m, 1 H), 7.32 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1 H), 7.24 (dd, *J* = 8.4, 1.8 Hz, 1 H), 6.39 (dd, *J* = 0.9, 0.9 Hz, 1 H), 2.43 (d, *J* = 1.1 Hz, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 150.9 (C_q), 149.8 (CH), 138.5 (CH), 138.0 (C_q), 137.6 (C_q), 127.6 (C_q), 123.9 (CH), 122.4 (CH), 121.0 (CH), 120.8 (CH), 115.1 (C_q), 113.4 (CH), 103.3 (CH), 14.0 (CH_3).

MS (EI): *m*/*z* (%) = 286 (94) $[M(^{79}Br)]^+$, 207 (65).

HRMS (EI): *m*/*z* $[M + H]^+$ calcd for $C_{14}H_{11}{}^{79}BrN_2$: 286.0106; found: 286.0106

7-Ethyl-2-methyl-1-(pyridin-2-yl)-1*H*-indole (3j)

The representative procedure was followed using 7-ethyl-1-(pyridin-2-yl)-1*H*-indole (**1j**; 110 mg, 0.50 mmol) and potassium methyltrifluoroborate (**2**; 122 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc/CH_2Cl_2, 26:3:1) afforded **3j**.

Yield: 79.0 mg (68%); red oil.

IR (ATR): 1684, 1583, 1566, 1466, 739 cm^{-1}.

^1H NMR (500 MHz, $CDCl_3$): δ = 8.64 (ddd, *J* = 4.9, 2.0, 0.8 Hz, 1 H), 7.86 (td, *J* = 7.7, 2.0 Hz, 1 H), 7.41–7.37 (m, 2 H), 7.33 (dt, *J* = 7.8, 1.0 Hz, 1 H), 7.06 (dd, *J* = 7.5, 7.5 Hz, 1 H), 6.94 (dd, *J* = 7.3, 1.0 Hz, 1 H), 6.39 (s, 1 H), 2.20–2.16 (m, 5 H), 0.94 (t, *J* = 7.5 Hz, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 153.7 (C_q), 149.3 (CH), 137.9 (CH), 137.8 (C_q), 136.2 (C_q), 129.7 (C_q), 127.5 (C_q), 124.0 (CH), 123.4 (CH), 122.1 (CH), 120.7 (CH), 117.8 (CH), 102.6 (CH), 25.0 (CH_2), 14.7 (CH_3), 13.6 (CH_3).

MS (EI): *m*/*z* (%) = 236 (100) $[M]^+$, 221 (70), 206 (30).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{16}N_2$: 236.1313; found: 236.1305.

2,3-Dimethyl-1-(pyridin-2-yl)-1*H*-indole (3k)

The representative procedure was followed using 3-methyl-1-(pyridin-2-yl)-1*H*-indole (**1k**; 104 mg, 0.50 mmol) and potassium methyltrifluoroborate (**2**; 122 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc/CH_2Cl_2, 26:3:1) afforded **3k**.

Yield: 85.5 mg (77%); colorless oil.

IR (ATR): 1586, 1470, 1459, 1435, 1317, 783 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.64 (ddd, *J* = 4.9, 1.9, 0.8 Hz, 1 H), 7.84 (d, *J* = 8.1, 7.6, 2.0 Hz, 1 H), 7.56–7.47 (m, 1 H), 7.43–7.35 (m, 2 H), 7.26 (ddd, *J* = 7.3, 4.9, 1.0 Hz, 1 H), 7.18–7.06 (m, 2 H), 2.39 (s, 3 H), 2.31 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 151.7 (C_q), 149.4 (CH), 138.0 (CH), 136.3 (C_q), 132.3 (C_q), 129.5 (C_q), 121.6 (CH), 121.4 (CH), 120.7 (CH), 120.1 (CH), 118.0 (CH), 109.9 (CH), 109.9 (C_q), 11.4 (CH_3), 8.8 (CH_3).

MS (EI) *m*/*z* (%) = 222 (100) $[M]^+$, 207 (50), 144 (25).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{15}H_{14}N_2$: 222.1157; found: 222.1146.

The analytical data are in accordance with those reported in the literature.[14]

Methyl 2-Methyl-1-(pyridin-2-yl)-1*H*-indole-3-carboxylate (3l)

The representative procedure was followed using methyl 1-(pyridin-2-yl)-1*H*-indole-3-carboxylate (**1l**; 122 mg, 0.50 mmol) and potassium methyltrifluoroborate (**2**; 127 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc/CH_2Cl_2, 10:3:1) afforded **3l**.

Yield: 124 mg (93%); white solid; mp 97–98 °C.

IR (ATR): 1691, 1467, 1431, 1397, 776, 757 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.69 (ddd, *J* = 4.8, 2.0, 0.8 Hz, 1 H), 8.15 (d, *J* = 7.9 Hz, 1 H), 7.91 (td, *J* = 7.7, 1.9 Hz, 1 H), 7.41–7.37 (m, 2 H), 7.26–7.23 (m, 1 H), 7.20–7.14 (m, 2 H), 3.95 (s, 3 H), 2.69 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.4 (C_q), 150.1 (C_q), 150.0 (CH), 145.1 (C_q), 138.6 (CH), 136.6 (C_q), 126.7 (C_q), 123.4 (CH), 122.8 (CH), 122.4 (CH), 122.1 (CH), 121.5 (CH), 110.4 (CH), 106.2 (C_q), 51.0 (CH_3), 13.4 (CH_3).

MS (EI) *m*/*z* (%) = 266 (100) $[M]^+$, 251 (50), 235 (50), 206 (40).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{14}N_2O_2$: 266.1055; found: 266.1051.

The analytical data are in accordance with those reported in the literature.[15]

Methyl 2-[2-Methyl-1-(pyridin-2-yl)-1*H*-indol-3-yl]acetate (3m)

The representative procedure was followed using methyl 2-(1-(pyridin-2-yl)-1*H*-indol-3-yl)acetate (**1m**; 133 mg, 0.50 mmol) and potassium methyltrifluoroborate (**2**; 122 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc/CH_2Cl_2, 10:3:1) afforded **3m**.

Yield: 84 mg (60%); red oil.

IR (ATR): 1732, 1584, 1469, 1458, 1435, 1161, 733 cm^{-1}.

^1H NMR (600 MHz, $CDCl_3$): δ = 8.64 (ddd, *J* = 4.8, 2.0, 0.8 Hz, 1 H), 7.86 (td, *J* = 7.7, 2.0 Hz, 1 H), 7.58 (dd, *J* = 7.0, 1.6 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 7.35–7.34 (m, 1 H), 7.29 (ddd, *J* = 7.5, 4.8, 1.0 Hz, 1 H), 7.17–7.11 (m, 2 H), 3.76 (s, 2 H), 3.67 (s, 3 H), 2.42 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.2 (C_q), 151.4 (C_q), 149.6 (CH), 138.2 (CH), 136.4 (C_q), 134.4 (C_q), 128.6 (C_q), 122.0 (CH), 121.9 (CH), 121.1 (CH), 120.7 (CH), 118.2 (CH), 110.2 (CH), 107.2 (C_q), 52.1 (CH_3), 30.7 (CH_2), 11.8 (CH_3).

MS (EI): *m*/*z* (%) = 280 (40) $[M]^+$, 221 (100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{17}H_{16}N_2O_2$: 280.1212; found: 280.1205.

1-[2-Methyl-1-(pyridin-2-yl)-1*H*-indol-3-yl]ethan-1-one (3n)

The representative procedure was followed using 1-(1-(pyridin-2-yl)-1*H*-indol-3-yl)ethan-1-one (**1n**; 118 mg, 0.50 mmol) and potassium methyltrifluoroborate (**2**; 122 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc/CH_2Cl_2, 10:1:1) afforded **3n**.

Yield: 83.8 mg (67%); white solid; mp 126–127 °C.

IR (ATR): 1684, 1631, 1465, 1421, 1397, 1204, 742 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.69 (ddd, *J* = 4.8, 2.0, 0.8 Hz, 1 H), 8.05 (dt, *J* = 7.0, 0.8 Hz, 1 H), 7.96–7.89 (m, 1 H), 7.42 (ddd, *J* = 7.6, 4.9, 1.0 Hz, 1 H), 7.38 (dt, *J* = 7.9, 1.0 Hz, 1 H), 7.29–7.23 (m, 1 H), 7.19–7.13 (m, 2 H), 2.70 (s, 3 H), 2.60 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 194.7 (C_q), 149.9 (CH), 149.8 (C_q), 144.2 (C_q), 138.5 (CH), 136.7 (C_q), 126.4 (C_q), 123.4 (CH), 122.6 (CH), 122.5 (CH), 122.2 (CH), 120.7 (CH), 115.9 (C_q), 110.6 (CH), 31.7 (CH_3), 14.1 (CH_3).

MS (EI): *m*/*z* (%) = 250 (55) $[M]^+$, 235 (100), 205 (20).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{14}N_2O$: 250.1106; found: 250.1100.

2-Methyl-1-(pyridin-2-yl)-1*H*-indole-3-carbaldehyde (3o)

The representative procedure was followed using 1-(pyridin-2-yl)-1*H*-indole-3-carbaldehyde (**1o**; 111 mg, 0.50 mmol) and potassium methyltrifluoroborate (**2**; 122 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc/CH_2Cl_2, 26:3:1) afforded **3o**.

Yield: 92.0 mg (78%); white solid; mp 110–111 °C.

IR (ATR): 3054, 2823, 2727, 1649, 747 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 10.3 (s, 1 H), 8.72–8.70 (m, 1 H), 8.31 (dt, *J* = 7.8, 1.1 Hz, 1 H), 7.96 (td, *J* = 7.6, 2.0 Hz, 1 H), 7.46–7.42 (m, 2 H), 7.31–7.24 (m, 2 H), 7.20 (t, *J* = 0.9 Hz, 1 H), 2.67 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 185.0 (CH), 150.2 (CH), 149.8 (C_q), 147.7 (C_q), 138.8 (CH), 137.0 (C_q), 125.9 (C_q), 123.8 (CH), 123.7 (CH), 123.4 (CH), 121.8 (CH), 121.1 (CH), 115.8 (C_q), 110.5 (CH), 11.8 (CH_3).

MS (EI): *m*/*z* (%) = 236 (90) $[M]^+$, 207 (40).

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{12}N_2O$: 237.1022; found: 237.1023.

6,7-Dihydro-2-methyl-1-(pyridin-2-yl)-1*H*-indol-4(5*H*)-one (6)

The representative procedure was followed using 6,7-dihydro-1-(pyridin-2-yl)-1*H*-indol-4(5H)-one (**4**; 107 mg, 0.50 mmol) and potassium methyltrifluoroborate (**2**; 122 mg, 1.00 mmol). Purification by column chromatography (EtOAc/*n*-hexane, 5:1) afforded **6**.

Yield: 71.9 mg (63%); off-white solid; mp 131–133 °C.

IR (ATR): 1645, 1587, 1466, 1433, 1173, 782, 579 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 8.56 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1 H), 7.83 (td, *J* = 7.7, 2.0 Hz, 1 H), 7.32 (ddd, *J* = 7.5, 4.9, 1.0 Hz, 1 H), 7.20 (dt, *J* = 8.0, 1.0 Hz, 1 H), 6.31 (q, *J* = 1.1 Hz, 1 H), 2.60 (t, *J* = 6.1 Hz, 2 H), 2.41 (dd, *J* = 7.5, 6.1 Hz, 2 H), 2.09 (d, *J* = 1.1 Hz, 3 H), 2.02 (tt, *J* = 7.5, 5.8 Hz, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 194.6 (C_q), 150.5 (C_q), 149.8 (CH), 144.3 (C_q), 138.5 (CH), 131.0 (C_q), 123.4 (CH), 121.5 (CH), 120.9 (C_q), 104.7 (CH), 38.0 (CH_2), 24.0 (CH_2), 23.2 (CH_2), 13.0 (CH_3).

MS (EI): *m*/*z* (%) = 226 (82) $[M]^+$, 170 (100).

HRMS (EI): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{14}N_2O$: 226.1106; found: 226.1098.

Methyl (*S*)-2-Acetamido-3-[2-methyl-1-(pyridin-2-yl)-1*H*-indol-3-yl]propanoate (8)

The representative procedure was followed using methyl (*S*)-N^{α}-acetyl-1-(pyridin-2-yl)-tryptophanate (**7**; 169 mg, 0.50 mmol) and potassium methyltrifluoroborate (**2**; 122 mg, 1.00 mmol). Purification by column chromatography (*n*-hexane/EtOAc/CH_2Cl_2, 3:1:1) afforded **8**.

Yield: 159 mg (91%); off-white solid; mp 59–61 °C.

IR (ATR): 3277, 2959, 1739, 1651, 1584, 1469, 1434, 739 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.64 (ddd, *J* = 4.9, 2.0, 0.9 Hz, 1 H), 7.87 (ddd, *J* = 8.0, 7.5, 2.0 Hz, 1 H), 7.48–7.42 (m, 1 H), 7.39 (dt, *J* = 8.0, 1.0 Hz, 1 H), 7.34–7.28 (m, 2 H), 7.15–7.07 (m, 2 H), 6.08 (d, *J* = 8.0 Hz, 1 H), 4.93 (dt, *J* = 8.0, 5.4 Hz, 1 H), 3.66 (s, 3 H), 3.33 (d, *J* = 5.4 Hz, 2 H), 2.32 (s, 3 H), 1.95 (s, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 172.5 (C_q), 169.6 (C_q), 151.4 (C_q), 149.6 (CH), 138.3 (CH), 136.6 (C_q), 134.7 (C_q), 129.1 (C_q), 122.1 (CH), 122.1 (CH), 121.1 (CH), 120.7 (CH), 118.0 (CH), 110.3 (CH), 108.4 (C_q), 53.0 (CH), 52.6 (CH_3), 27.3 (CH_2), 23.5 (CH_3), 11.8 (CH_3).

MS (EI): *m*/*z* (%) = 351 (5) [M]$^+$, 221 (100).

HRMS (EI): *m*/*z* [M]$^+$ calcd for $C_{20}H_{21}N_3O_3$: 351.1583; found: 351.1593.

H/D-Exchange Studies

The representative procedure was followed using 1-(pyridin-2-yl)-1*H*-indole (**1a**; 97.1 mg, 0.50 mmol), $[RuCl_2(p\text{-cymene})]_2$ (15.3 mg, 5.0 mol%), $AgSbF_6$ (34.4 mg, 20 mol%), AgF (127 mg, 1.00 mmol) and potassium methyltrifluoroborate (**2**; 122 mg, 1.00 mmol) in DCE (0.9 mL) and D_2O (0.1 mL). Purification by column chromatography (*n*-hexane/EtOAc/CH_2Cl_2, 26:3:1) afforded [D_n]-**1a** (40.4 mg, 41%) and [D_n]-**3a** (39.0 mg, 37%).

Removal of Directing Group

2-Methyl-1*H*-indole (9)

To a solution of **3** (115 mg, 0.55 mmol) in CH_2Cl_2 (2.00 mL) was added MeOTf (103 mg, 69.0 µL, 0.63 mmol, 1.15 equiv) dropwise at 0 °C. After 30 min, the mixture was allowed to warm to 25 °C and stirred for 16 h. After removal of the solvent in vacuo, $Pd(OH)_2$/C (20.2 mg, 10 wt.-%) and ammonium formate (347 mg, 5.50 mmol, 10 equiv) were added. The mixture was diluted with MeOH (2.00 mL) and stirred at 60 °C for 6 h. After addition of EtOAc (10.0 mL) at ambient temperature, the mixture was filtered through a short pad of Celite and the solvents were removed in vacuo. The crude mixture was purified by flash column chromatography on silica gel (*n*-hexane/EtOAc, 10/1) to afford **9**.

Yield: 49.2 mg (69%); pale-yellow solid; mp 56–57 °C.

IR (ATR): 3384, 1579, 1404, 1364, 1306, 781, 734 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.67 (br. s, 1 H), 7.57 (dd, *J* = 7.7, 1.8 Hz, 1 H), 7.28–7.24 (m, 1 H), 7.18–7.12 (m, 2 H), 6.26 (dd, *J* = 0.9, 0.9 Hz, 1 H), 2.42 (s, 3 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.1 (C_q), 135.2 (C_q), 129.1 (C_q), 121.0 (CH), 119.7 (CH), 110.3 (CH), 100.3 (CH), 13.7 (CH_3).

MS (EI) *m*/*z* (%) = 131 (80) [M]$^+$, 103 (10), 77 (15).

The analytical data are in accordance with those reported in the literature.[16]

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Supporting Information

Supporting information for this article is available online at http://dx.doi.org/10.1055/s-0036-1588890.

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