Supporting Information

Pd-Catalyzed C-H Activation in Water: Synthesis of Bis(Indolyl)methanes from Indoles and Benzyl Alcohols

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**General procedure:** A mixture of indole 1 (0.5 mmol), palladium(II) acetate (6 mg, 0.025 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 18 mg, 0.05 mmol) and benzyl alcohol 2 (1.5 mmol) in H2O (2 mL) was heated at 60 °C for 16 h in a sealed tube. After cooling, the reaction mixture was poured into water and extracted with EtOAc. The organic layer was washed with brine, dried over MgSO4 and concentrated in vacuo. The residue was purified by flash column chromatography (silica gel, hexanes/EtOAc) to give desired product 3.

**Bis(5-methoxyindol-3-yl)(phenyl)methane 3a**
Following the general procedure, 3a was obtained as a white solid. 77 mg (81%); mp 213-216 °C; IR (KBr) (cm⁻¹) 3392, 3319; ¹H NMR (400 MHz, CDCl₃): δ 3.69 (s, 6H), 5.77 (s, 1H), 6.66 (dd, J=4.0, 2.0 Hz, 2H), 6.78-6.84 (m, 4H), 7.18-7.30 (m, 5H), 7.33-7.37 (m, 2H), 7.81 (burs, 2H); ¹³C NMR (100 MHz, DMSO-d₆): δ 40.3, 55.8, 102.0, 111.7, 111.9, 119.3, 124.4, 126.1, 127.5, 128.2, 128.7, 131.9, 143.9, 153.7; MS (EI): m/z (%) 382 (M⁺, 100).

**Bis(5-methoxyindol-3-yl)(4-methylphenyl)methane 3b**
Following the general procedure, 3b was obtained as a pale yellow solid. 59 mg (60%); mp 202-204 °C; IR (KBr) (cm⁻¹) 3348; ¹H NMR (400 MHz, CDCl₃): δ 2.32 (s, 3H), 3.69 (s, 6H), 5.73 (s, 1H), 6.66 (s, 2H), 6.80 (m, 4H), 7.08 (d, J=8.0 Hz, 2H), 7.20-7.25 (m, 4H), 7.80 (burs, 2H); ¹³C NMR (100 MHz, CDCl₃): δ ; 21.1, 39.9, 55.9, 102.0, 111.6, 111.8, 119.5, 124.4, 127.5, 128.6, 128.9, 131.9, 135.4, 140.9, 153.7; MS (EI): m/z (%) 396 (M⁺, 100).

**Bis(5-methoxyindol-3-yl)(4-ethylphenyl)methane 3c**
Following the general procedure, 3c was obtained as a white solid. 100 mg (97%); mp 180-182 °C; IR (KBr) (cm⁻¹) 3402; ¹H NMR (400 MHz, CDCl₃): δ 1.21 (t, J=8.0 Hz, 3H), 2.62 (q, J=8.0 Hz, 2H), 3.68 (s, 6H), 5.73 (s, 1H), 6.66 (d, J=4.0 Hz, 2H), 6.78-6.84 (m, 4H), 7.10 (d, J=8.0 Hz, 2H), 7.20-7.28 (m, 4H), 7.79 (burs, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 15.6, 28.5, 39.9, 55.8, 102.0, 111.6, 111.8, 119.6, 124.4, 127.6, 127.7, 128.6, 131.9, 141.1, 141.9, 153.7; MS (EI): m/z (%) 410 (M⁺, 100). Anal. Calcd for C₂₇H₂₆N₂O₂: C, 79.00; H, 6.38; N, 6.82. Found: C, 78.83; H, 6.43; N, 6.71.

**Bis(5-methoxyindol-3-yl)(4-methoxyphenyl)methane 3d**
Following the general procedure, 3d was obtained as an off-white solid. 67 mg (65%); mp 186-188 °C; IR (KBr) (cm⁻¹) 3332; ¹H NMR (400 MHz, DMSO-d₆): δ 3.59 (s, 6H), 3.71 (s, 3H), 5.68 (s, 1H), 6.65-7.00 (m, 8H), 7.20-7.30 (m, 4H), 10.6 (burs, 2H); ¹³C NMR (100 MHz, DMSO-d₆): δ 54.9, 55.2, 101.5, 110.4, 111.9, 113.3, 118.0, 124.2, 127.0, 129.2, 131.8, 137.0, 152.6, 157.3; MS (EI): m/z (%) 412 (M⁺, 100).
Bis(5-methoxyindol-3-yl)(3-methylphenyl)methane 3e
Following the general procedure, 3e was obtained as a white solid. 93 mg (94%); mp 193-195 °C; IR (KBr) (cm⁻¹) 3394; ¹H NMR (400 MHz, CDCl₃): δ 2.29 (s, 3H), 3.69 (s, 6H), 5.72 (s, 1H), 6.66 (dd, J=2.0, 0.4 Hz, 2H), 6.80-6.84 (m, 4H), 7.01 (t, J=6.8 Hz, 1H), 7.10-7.20 (m, 3H), 7.20-7.26 (m, 2H), 7.80 (brs, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 21.5, 40.2, 55.9, 102.0, 111.6, 111.8, 119.4, 124.4, 125.7, 126.9, 127.6, 128.1, 129.4, 131.9, 137.6, 143.8, 153.7; MS (EI): m/z (%) 396 (M⁺, 100); HRMS-EI: m/z (%) calcd for C₂₆H₂₄N₂O₂ 396.1838, found 396.1837.

Bis(5-methoxyindol-3-yl)(4-fluorophenyl)methane 3f
Following the general procedure, 3f was obtained as a pale yellow solid. 73 mg (73%); mp 145-147 °C; IR (KBr) (cm⁻¹) 3461, 3405; ¹H NMR (400 MHz, CDCl₃): δ 3.69 (s, 6H), 5.75 (s, 1H), 6.63 (d, J=2.0 Hz, 2H), 6.77 (d, J=4.0 Hz, 2H), 6.84 (dd, J=8.0, 4.0 Hz, 2H), 6.96 (t, J=8.0 Hz, 2H), 7.20-7.35 (m, 2H), 7.83 (brs, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 39.5, 55.9, 101.9, 111.7, 112.0, 114.8, 115.1, 119.1, 124.4, 127.4, 130.0, 131.9, 139.6, 139.6, 139.6, 153.8, 160.2, 162.6; MS (EI): m/z (%) 400 (M⁺, 100).

Bis(5-methoxyindol-3-yl)(2-methylphenyl)methane 3g
Following the general procedure, 3g was obtained as a white solid. 86 mg (87%); mp 177-179 °C; IR (KBr) (cm⁻¹) 3419; ¹H NMR (400 MHz, CDCl₃): δ 2.38 (s, 3H), 3.69 (s, 6H), 5.89 (s, 1H), 6.57 (d, J=2.0 Hz, 2H), 6.76 (d, J=2.4 Hz, 2H), 6.83 (dd, J=8.8, 2.4 Hz, 2H), 7.00-7.15 (m, 3H), 7.15-7.25 (m, 3H), 7.79 (brs, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 19.6, 36.4, 55.9, 102.0, 111.6, 111.7, 118.7, 124.7, 125.8, 126.1, 127.6, 128.4, 130.2, 131.9, 136.0, 141.9, 153.7; MS (EI): m/z (%) 396 (M⁺, 100); Anal. Calcd for C₂₆H₂₄N₂O₂: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.49; H, 6.11; N, 6.83.

Bis(5-methoxyindol-3-yl)(2-thienyl)methane 3h
Following the general procedure, 3h was obtained as an off-white solid. 54 mg (56%); mp 190-192 °C; IR (KBr) (cm⁻¹) 3390, 3325; ¹H NMR (400 MHz, CDCl₃): δ 3.71 (s, 6H), 6.05 (s, 1H), 6.80-6.86 (m, 4H), 6.88 (d, J=2.4 Hz, 2H), 6.90-6.95 (m, 2H), 7.15 (dd, J=4.4, 1.6 Hz, 1H), 7.24 (dd, J=8.4, 0.4 Hz, 2H), 7.84 (brs, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 35.4, 55.9, 101.8, 111.8, 112.0, 119.3, 123.6, 124.0, 125.2, 126.4, 127.2, 131.8, 148.6, 153.8; MS (EI): m/z (%) 388 (M⁺, 100); Anal. Calcd for C₂₃H₂₀N₂O₂S: C, 71.11; H, 5.19; N, 7.21. Found: C, 70.76; H, 5.09; N, 6.98.

Bis(indol-3-yl)(phenyl)methane 3i
Following the general procedure, 3i was obtained as a brown solid. 47 mg (58%); mp 141-143 °C; IR (KBr) (cm⁻¹) 3398; ¹H NMR (400 MHz, CDCl₃): δ 5.87 (s, 1H), 6.59 (s, 2H), 6.99 (dd, J=8.0, 8.0 Hz, 2H), 7.15 (dd, J=8.0, 8.0 Hz, 2H), 7.18-7.40 (m, 9H), 7.78 (brs, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 40.2, 111.0, 119.2, 119.7, 119.9, 121.9, 123.6, 126.1, 127.1, 128.2, 128.7, 136.7, 144.0; MS (EI): m/z (%) 322
Bis(5-methylindol-3-yl)(phenyl)methane 3j
Following the general procedure, 3j was obtained as a brown solid. 65 mg (74%); mp 183-185 °C; IR (KBr) (cm⁻¹) 3422; ¹H NMR (400 MHz, CDCl₃): δ 2.34 (s, 6H), 5.82 (s, 1H), 6.57 (d, J=4.0 Hz, 2H), 6.99 (d, J=8.0 Hz, 2H), 7.15-7.40 (m, 9H), 7.79 (brs, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 21.5, 40.0, 110.7, 119.3, 119.5, 123.5, 123.9, 126.0, 127.3, 128.2, 128.4, 128.7, 135.0, 144.2; MS (EI): m/z (%) 350 (M⁺, 100).

Bis(5-fluoroindol-3-yl)(phenyl)methane 3k
Following the general procedure, 3k was obtained as an off-white solid. 50 mg (56%); mp 169-171 °C; IR (KBr) (cm⁻¹) 3465, 3424; ¹H NMR (400 MHz, CDCl₃): δ 5.73 (s, 1H), 6.72 (s, 2H), 6.90 (td, J=9.2, 2.4 Hz, 2H), 6.98 (dd, J=9.2, 2.4 Hz, 2H), 7.20-7.35 (m, 7H), 7.93 (brs, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 40.2, 104.7, 104.9, 110.3, 110.5, 111.6, 111.7, 119.5, 119.9, 125.2, 126.4, 127.3, 127.4, 128.4, 128.6, 133.2, 143.2, 156.4, 158.7; MS (EI): m/z (%) 358 (M⁺, 100); HRMS-EI: m/z (M⁺) calcd for C₂₃H₁₆F₂N₂ 358.1282, found 358.1283.

Bis(5-cyanoindol-3-yl)(phenyl)methane 3l
Following the general procedure, 3l was obtained as an off-white solid. 84 mg (90%); mp 246-249 °C; IR (KBr) (cm⁻¹) 3319, 2220; ¹H NMR (400 MHz, CDCl₃): δ 5.84 (s, 1H), 6.81 (s, 2H), 7.25-7.35 (m, 5H), 7.40-7.45 (m, 4H), 7.67 (s, 2H), 8.34 (brs, 2H); ¹³C NMR (100 MHz, CDCl₃): δ 40.0, 102.7, 112.2, 119.9, 120.7, 125.2, 125.5, 126.6, 127.0, 128.4, 128.7, 138.4, 142.2; MS (EI): m/z (%) 372 (M⁺, 100).

Bis(5-carbomethoxyindol-3-yl)(phenyl)methane 3m
Following the general procedure, 3m was obtained as an off-white solid. 92 mg (84%); mp 226-228 °C; IR (KBr) (cm⁻¹) 3325, 1689; ¹H NMR (400 MHz, DMSO-d₆): δ 3.76 (s, 6H), 6.02 (s, 1H), 6.88 (s, 2H), 7.21 (dd, J=7.2, 7.2 Hz, 1H), 7.30 (dd, J=7.6, 7.6 Hz, 2H), 7.35 (d, J=7.2 Hz, 2H), 7.45 (d, J=8.8 Hz, 2H), 7.70 (dd, J=8.4, 1.2 Hz, 2H), 8.02 (s, 2H), 11.3 (brs, 2H); ¹³C NMR (100 MHz, DMSO-d₆): δ 51.6, 111.5, 119.4, 119.8, 121.7, 122.1, 125.6, 126.1, 126.1, 128.2, 139.3, 144.2, 167.2; MS (EI): m/z (%) 438 (M⁺, 100); HRMS-EI: m/z (M⁺) calcd for C₂₇H₂₂N₂O₄ 438.1580, found 438.1579.

Bis(2-methylindol-3-yl)(phenyl)methane 3n
Following the general procedure, 3n was obtained as a brown solid. 86 mg (98%); mp 251-254 °C; IR (KBr) (cm⁻¹) 3395; ¹H NMR (400 MHz, CDCl₃): δ 2.06 (s, 6H), 6.00 (s, 1H), 6.85 (dd, J=8.0, 8.0 Hz, 2H), 6.97 (d, J=8.0 Hz, 2H), 7.03 (dd, J=8.0, 8.0 Hz, 2H), 7.20-7.30 (m, 7H), 7.73 (brs, 2H); ¹³C NMR (100  

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Bis(1-methylindol-3-yl)(phenyl)methane 3o\textsuperscript{5}

Following the general procedure, 3l was obtained as an off-white solid. 64 mg (73%); mp 199-201 °C; IR (KBr) (cm\textsuperscript{-1}) 1473; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 3.66 (s, 6H), 5.88 (s, 1H), 6.52 (s, 2H), 6.98 (dd, \(J\)=8.0, 6.0 Hz, 2H), 7.16-7.30 (m, 7H), 7.32-7.40 (m, 4H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 32.7, 40.1, 190.0, 118.2, 118.6, 120.0, 121.4, 126.0, 127.4, 128.2, 128.2, 128.7, 137.4, 144.4; MS (EI): \(m/z\) (%) 350 (M\textsuperscript{+}, 100).

References


Scheme 2. C-H bond Activation at the C3-position of indole 1a.

A mixture of 1a (37 mg, 0.25 mmol), palladium(II) acetate (3 mg, 0.0125 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 9 mg, 0.025 mmol) and benzyl alcohol 2a (54 mg, 0.5 mmol) in D$_2$O (0.75 mL) was heated at 60 °C for 30 min in a sealed tube. After cooling, the reaction mixture was extracted with CDCl$_3$ (8 mL), then the organic layer was analyzed by $^1$H-NMR spectroscopy.

0.03H: 97% D incorporation
Scheme 3 (A). $^1$H NMR experiments to monitor the reaction.

A mixture of 1a (74 mg, 0.5 mmol), palladium(II) acetate (6 mg, 0.025 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 18 mg, 0.05 mmol) and benzyl alcohol 2a (108 mg, 1.0 mmol) in H$_2$O (2 mL) was heated at 60 ºC for 5 h in a sealed tube. After cooling, the reaction mixture was extracted with CDCl$_3$ (8 mL), then the organic layer was analyzed by $^1$H-NMR spectroscopy.

Product ratio was determined by integration.

<table>
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<th>desired 3a</th>
<th>3-benzylated 4a</th>
<th>toluene 5</th>
<th>benzaldehyde 6</th>
<th>PhCH$_2$OH 2a</th>
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<tr>
<td>Signal δ</td>
<td>5.76 (methine-H)</td>
<td>3.79 (OCH$_3$)</td>
<td>2.35 (CH$_3$)</td>
<td>10.0 (CHO)</td>
<td>4.69 (CH$_2$)</td>
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<tr>
<td>Integral value</td>
<td>1.00 (1H)</td>
<td>0.33 (3H)</td>
<td>2.00 (3H)</td>
<td>0.53 (1H)</td>
<td>5.93 (2H)</td>
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<tr>
<td>Calculated ratio</td>
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<td>0.1</td>
<td>0.7</td>
<td>0.5</td>
<td>3</td>
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</table>
Scheme 3 (A)

PhCH$_2$OH

PhCHO

PhCH$_3$

3a

Electronic Supplementary Material (ESI) for RSC Advances

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### Scheme 3 (A) (Expansion)

\(^1\)H-NMR spectrum in Scheme 3 (A) was expanded for detection of 3-benzyl-5-methoxy-1\(\text{H}\)-indole 4a.


**3-Benzyl-5-methoxy-1\(\text{H}\)-indole**

\(^1\)H NMR (500 MHz, CDCl\(\text{3}\)):  3.78 (s, 3H, CH\(\text{3}\)), 4.06 (s, 2H, CH\(\text{2}\)), 6.81 (d, 1H, \(J = 2.1\) Hz), 6.83 (dd, 1H, \(J = 2.1, 8.8\) Hz), 6.94 (d, 1H, \(J = 2.1\) Hz), 7.19-7.16 (m, 2H), 7.28-7.24 (m, 4H), 7.76 (br s, 1H, NH)
Scheme 3 (B). $^1$H NMR experiments to monitor the reaction.

A mixture of 3-benzylindole $4b$ (26 mg, 0.125 mmol), $1b$ (30 mg, 0.25 mmol), palladium(II) acetate (3 mg, 0.0125 mmol), sodium diphenylphosphinobenzene-3-sulfonate (TPPMS, 9 mg, 0.025 mmol) and benzyl alcohol $2a$ (77 $\mu$L, 0.7 mmol) in H$_2$O (2 mL) was heated at 60 $^\circ$C for 16 h in a sealed tube. After the reaction mixture was cooled, $p$-nitroanisole (19 mg, 0.125 mmol, internal standard) was added to the reaction mixture, which was extracted with CDCl$_3$ (10 mL), then the organic layer was analyzed by $^1$H-NMR spectroscopy.

Conversion yield and recovery were calculated by integration.

<table>
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<th>Signal $\delta$</th>
<th>3-benzylindole $4b$</th>
<th>$p$-nitroanisole internal standard</th>
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<tbody>
<tr>
<td>Integral value</td>
<td>0.78 (1H)</td>
<td>1.92 (2H)</td>
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<td>19 mg (0.125 mmol)</td>
<td>2.0 (2H)</td>
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<tr>
<td>Calculated ratio</td>
<td>0.098 mmol</td>
<td>0.12 mmol</td>
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<tr>
<td>78% from $1b$</td>
<td>96% recovery</td>
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</tbody>
</table>

$\delta$ 5.89 (methine-H) 4.12 (CH$_2$) 8.21 (Ar-Hx2)
**p-nitroanisole**  
(internal standard)  

**desired 3b**  

**indole 1b**  

**3-benzylindole 4b**  

**Scheme 3 (B)**
single pulse decoupled gated NOE
single pulse decoupled gated NOE

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single_pulse
single pulse decoupled gated NOE
single pulse decoupled gated NOE

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**EXMOD** carbon.jsp
**OBFRQ** 100.53 MHz
**OBSET** 5.35 KHz
**OBFIN** 5.86 Hz
**POINT** 26214
**FREQU** 25125.63 Hz
**SCANS** 1024
**ACQTM** 1.0433 sec
**PD** 2.0000 sec
**PW1** 2.67 usec
**IRNUC** 1H
**CTEMP** 22.3 c
**SLVNT** DMSO
**EXREF** 39.50 ppm
**BF** 1.20 Hz
**RGAIN** 60

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