Efficient Preparation of Polyfunctional Indoles via a Zinc Organometallic Variation of the Fischer Indole Synthesis

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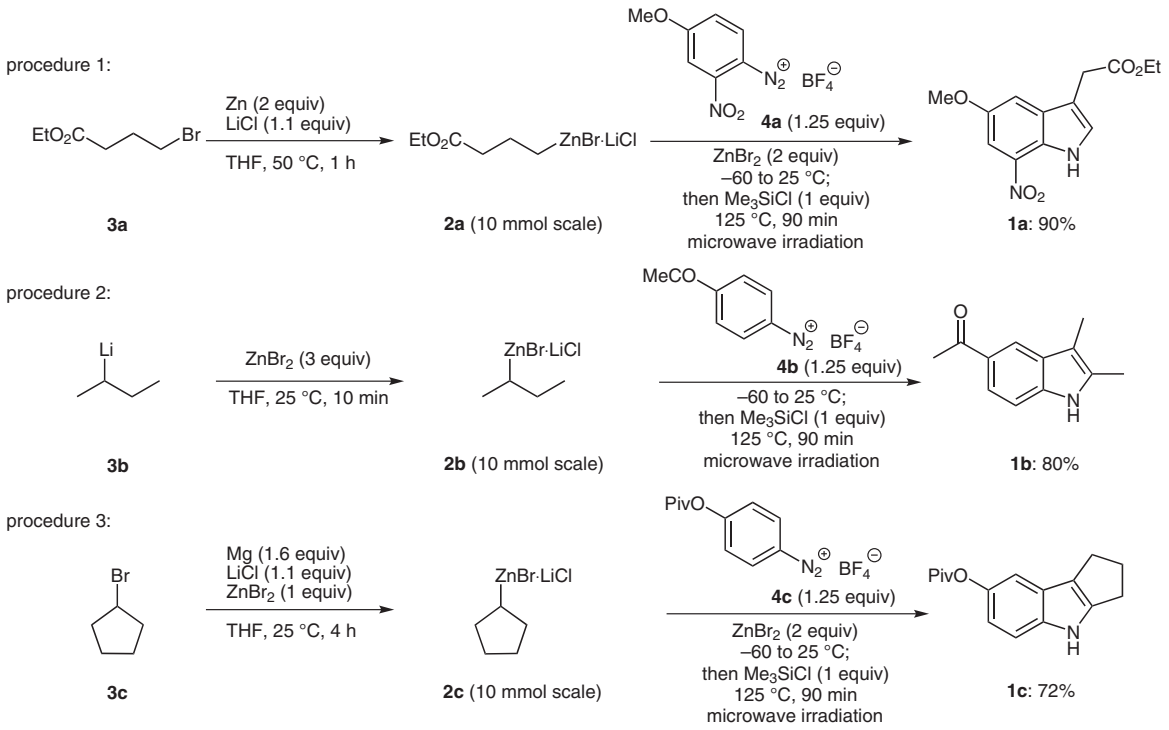
Abstract: Functionalized organozinc reagents readily react with various aryldiazonium salts furnishing regioselectively polyfunctional indoles after heating with microwave irradiation. This new organometallic variation of the Fischer indole synthesis tolerates a wide range of functional groups and can be readily scaled up.

Key words: organozinc reagents, indoles, regioselectivity, Fischer indole synthesis, N-heterocycles



Scheme 1

Introduction

Polyfunctional indoles are privileged structures in drug discovery and are present in numerous natural products.[1] The direct synthesis of polysubstituted indole derivatives has proven to be highly challenging due to the need of harsh and acidic reaction conditions (Fischer indole synthesis)[2,3] or expensive transition metal catalysis.[4] Moreover, by means of classical approaches, regioisomeric mixtures are often obtained.[2] Recently, we have reported a new strategy for the regioselective preparation of polysubstituted indoles of type **1** from functionalized primary or secondary alkylzinc reagents of type **2**. This organometallic variation of the Fischer indole synthesis tolerates a broad spectrum of functional groups (Scheme 1, Procedures 1–3).[5,6] Due to the good availability of functionalized organozincs,[7,8] the efficiency, and practicability of the reaction, large-scale procedures should be possible. We report herein our efforts to prepare various polyfunctional indole derivatives in 10–20 mmol scale using this new method. Furthermore, we have applied the large-scale procedure to the preparation of the antidepressant iprindole (**6**) (4 g scale).

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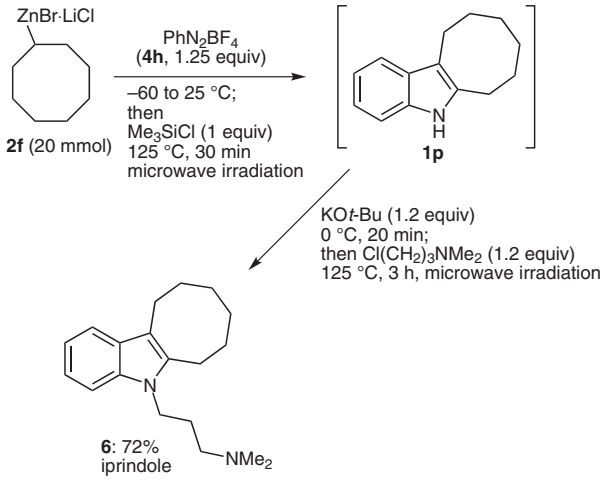
Scope and Limitations

A variety of functionalized primary or secondary alkylzinc bromides of type **2** are readily available via direct zinc insertion[9] or direct magnesium insertion[10] in the presence of $ZnBr_2$ from the corresponding alkyl bromides such as **3a** or **3c** or via transmetalation of *s*-BuLi with $ZnBr_2$ such as **3b**. Addition to aryldiazonium tetrafluoroborates[11] of type **4** led to the polyfunctional indoles of type **1** (Scheme 1).

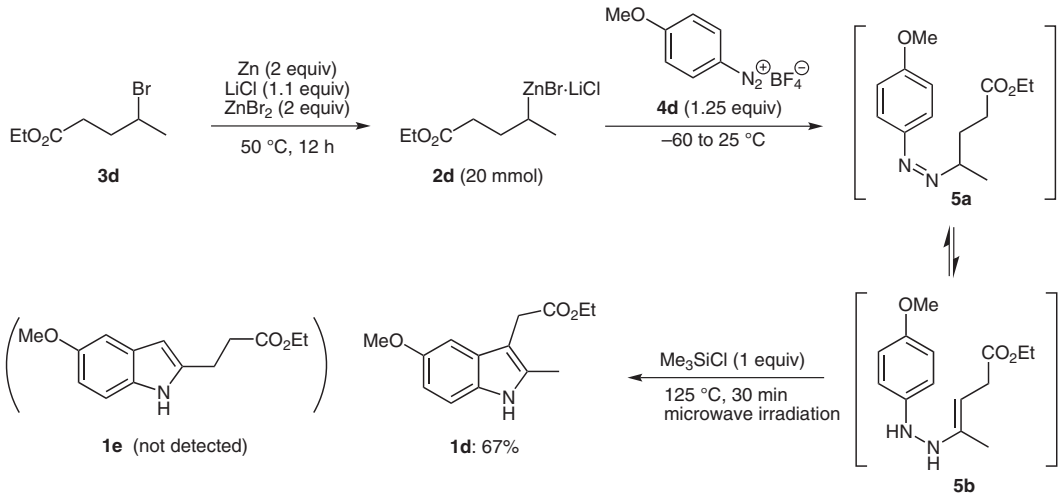
Similarly, the secondary alkylzinc bromide **2d** obtained after direct zinc insertion[9] with the reagent **3d** [Zn (2 equiv), LiCl (1.1 equiv), $ZnBr_2$ (2 equiv), 50 °C, 12 h] added smoothly to a substituted aryldiazonium salt[11] such as **4d** (–60 °C to 25 °C) providing the azo compound **5a**. After isomerization to the unsaturated hydrazine **5b**, induced by addition of Me_3SiCl (1 equiv), heating by microwave irradiation (125 °C, 30 min) furnished regioselectively the polyfunctional indole **1d** in 67% yield (Scheme 2). No regioisomer like the indole **1e** was detected. The presence of additional $ZnBr_2$ (2.0 equiv) proved to be essential to ensure a selective reaction with the diazonium salt in the next reaction step. In the absence of $ZnBr_2$, double addition products to diazonium salts were detected. The primary alkylzinc bromide **2a** reacted with the aryldiazonium salt **4a** (–60 to 25 °C) providing after microwave irradiation [Me_3SiCl (1 equiv), 125 °C, 90 min], the indole **1a** in 90% yield (Table 1, entry 1). Furthermore, the ester-substituted secondary alkylzinc bromide **2d** added to the aryldiazonium tetrafluoroborate **4c** furnishing under our standard conditions the 3-substituted indole **1f** in 63% yield (Table 1, entry 2). Similarly, *s*-BuZnBr·LiCl added to various polyfunctional aryldiazonium salts (**4a**,**b** and **4e**,**f**) affording regioselectively the functionalized 2,3-dimethylindole derivatives **1b** and **1g–i** in 68–80% yield (Table 1, entries 3–6). Under the same reaction conditions, cyclopentylzinc bromide (**2c**) and substituted aryldiazonium salts such as **4a** and **4c** led to the corresponding indoles **1j** and **1c** in 68 and 72% yield, respectively (Table 1, entries 7, 8). The secondary alkylzinc reagent *c*-HexZnBr·LiCl (**2e**) added to readily available functionalized aryldiazonium tetrafluoroborates (**4a**,**b**, **4d**, **4f**,**g**) and provided polyfunctional tetrahydro-1*H*-carbazoles **1k–o** in 73–91% yields (Table 1, entries 9–13). Besides microwave irradiation, conventional heating was also successfully used in the case of electron-rich substrates; however, this required longer reaction time for the cyclization step to form the corresponding indole derivatives.

As an application of this method, the pharmaceutical iprindole,[12] a tricyclic antidepressant, was prepared in a one-pot procedure on a 20 mmol scale. Thus, cyclooctylzinc bromide (**2f**) added smoothly to phenyldiazonium tetrafluoroborate (**4h**) (–60 to 25 °C) leading after microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (1 equiv) to the indole derivative **1p**. Subsequent N-alkylation of the intermediate **1p** [*t*-BuOK (1.2 equiv), 0 °C, 20 min; then $Cl(CH_2)_3NMe_2$ (1.2 equiv), 125 °C, 3 h] provided iprindole (**6**) in 72% yield (Scheme 3).

In summary, we have demonstrated an efficient and regioselective preparation of polyfunctional indoles using readily available functionalized primary and secondary

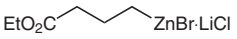
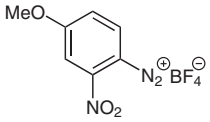
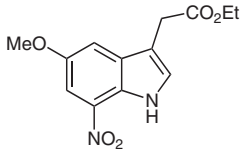
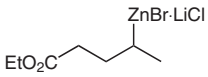
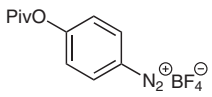
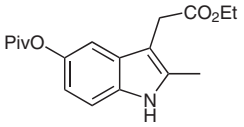
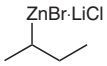
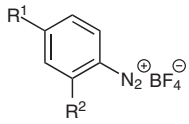
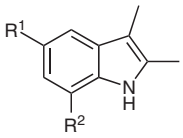
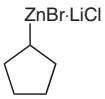
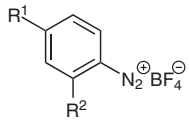
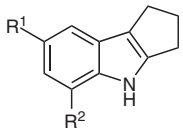
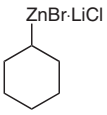
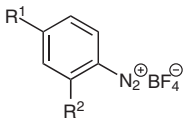
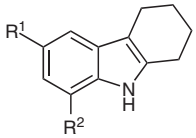


Scheme 3



Scheme 2

Table 1 Preparation of Polyfunctional Indole Derivatives of Type **1** on a 10 mmol Scale

Entry	Alkylzinc reagent	Aryldiazonium salt	Product	Yield (%)[a]
1	 **2a**	 **4a**	 **1a**	90
2	 **2d**	 **4c**	 **1f**	63
				
3	**2b**	**4b** R^1 = COMe, R^2 = H	**1b**	80
4	**2b**	**4a** R^1 = OMe, R^2 = NO_2	**1g**	80
5	**2b**	**4e** R^1 = F, R^2 = H	**1h**	68
6	**2b**	**4f** R^1 = Br, R^2 = H	**1i**	80
				
7	**2c**	**4a** R^1 = OMe, R^2 = NO_2	**1j**	68
8	**2c**	**4c** R^1 = OPiv, R^2 = H	**1c**	72
				
9	**2e**	**4a** R^1 = OMe, R^2 = NO_2	**1k**	91
10	**2e**	**4b** R^1 = COMe, R^2 = H	**1l**	73
11	**2e**	**4d** R^1 = OMe, R^2 = H	**1m**	80
12	**2e**	**4f** R^1 = Br, R^2 = H	**1n**	80
13	**2e**	**4g** R^1 = CN, R^2 = H	**1o**	80

[a] Isolated yield of analytically pure product as determined by ^{1}H NMR spectroscopy.

alkylzinc reagents and substituted aryldiazonium salts. During the new indole synthesis, a range of sensitive functional groups such as nitro, ester, cyano, and keto groups are well tolerated. As an application of this method, the antidepressant iprindole was prepared on a four-gram scale. We have extended the reaction scope and improved the reaction conditions for the preparation of synthetically interesting indoles. The reactions could be performed with standard laboratory glassware and did not require the use of expensive chemicals or catalysts.

All reactions were carried out under argon atmosphere in dried glassware. All starting materials were purchased from commercial suppliers and used without further purification, unless otherwise stated. The functionalized aryldiazonium tetrafluoroborates **4a–h** were prepared according to literature procedures.[11] THF was continuously refluxed and freshly distilled from sodium benzophenone ketyl under N_2. The cyclization reaction induced by microwave irradiation was performed in a Biotage Initiator Unit (Biotage, Uppsala, Sweden) in a closed-vessel system. Flash column chromatography was performed using Al_2O_3 from Merck (Al_2O_3 90 active, activity grade II–III, 70–230 mesh ASTM). Yields refer to isolated compounds estimated to be >95% pure as determined by ^{1}H NMR spectroscopy and capillary GC analysis.

Zinc Bromide Solution (1 M) in Tetrahydrofuran

A dry, argon-flushed 1 L Schlenk flask, equipped with a magnetic stirring bar and a septum was charged with $ZnBr_2$ (113 g, 0.5 mol) and heated to 150 °C for 5 h. After cooling to 25 °C under argon, anhyd THF (500 mL) was added slowly and stirred continuously until the salts had dissolved. The reagent $ZnBr_2$ (1 M in THF) was obtained as a colorless solution.

(4-Ethoxy-4-oxobutyl)zinc Bromide (2a); Typical Procedure 1 for Direct Zinc Insertion

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with Zn dust (2.54 g, 40 mmol) and dry LiCl (dried in vacuo with a heat gun at 450 °C for 5 min; 933 mg, 22 mmol). After the addition of THF (10 mL), Zn dust was activated with 1,2-dibromoethane (2 mol%) and Me_3SiCl (5 mol%). After stirring for 5 min, ethyl 4-bromobutanoate (**3a**; 3.9 g, 20 mmol) in THF (20 mL) was added at 25 °C to the suspension and the reaction mixture was stirred for 1 h at 50 °C. The supernatant solution was then cannulated into a new dry, argon-flushed Schlenk flask and titrated against I_2. The active alkylzinc reagent **2a** was obtained with a concentration of 0.74 M in THF.[9]

Cyclopentylzinc Bromide (2c); Typical Procedure 2 for Direct Magnesium Insertion in the Presence of Zinc Bromide

A dry, argon-flushed Schlenk flask equipped with a magnetic stirring bar and a septum was charged with Mg turnings (768 mg, 32 mmol) and LiCl (dried in vacuo with a heat gun at 450 °C for 5 min; 933 mg, 22 mmol). After the addition of THF (20 mL), the Mg was activated with 1,2-dibromoethane (2 mol%) and Me_3SiCl (5 mol%). After stirring for 5 min, $ZnBr_2$ (20 mmol, 20 mL, 1 M in THF) was added to the mixture. Thereafter, the suspension was cooled to 0 °C, cyclopentyl bromide (**3c**; 2.98 g, 20 mmol) in THF (20 mL) was added, and the reaction mixture was stirred for 4 h at 25 °C. The supernatant solution was then cannulated into a new dry, argon-flushed Schlenk flask and titrated against I_2. The active alkylzinc reagent **2c** was obtained with a concentration of 0.36 M in THF.[10]

Ethyl (5-Methoxy-7-nitro-1*H*-indol-3yl)acetate (1a); Typical Procedure 3

In a flame-dried and argon-flushed Schlenk flask, a solution of **2a** (10 mmol, 13.5 mL, 0.74 M in THF) prepared via typical procedure 1 from ethyl 4-bromobutanoate (**3a**) was added dropwise to a solution of $ZnBr_2$ (20 mmol, 20 mL, 1 M in THF) at 25 °C. After stirring at 25 °C for 10 min, the organozinc reagent was transferred slowly to a solution of 4-methoxy-2-nitrobenzenediazonium tetrafluoroborate (**4a**; 3.34 g, 12.5 mmol) in THF (50 mL) at –60 °C. The reaction mixture was allowed to slowly warm to 25 °C. Subsequently, the solvent volume was reduced by half, Me_3SiCl (1.08 g, 10 mmol) was added, and the mixture was heated by microwave irradiation for 90 min at 125 °C. After the reaction mixture had cooled to 25 °C, the resulting solution was diluted with Et_2O (20 mL), and quenched with brine (50 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic phases were dried (Na_2SO_4) and concentrated in vacuo. Purification by flash column chromatography (Al_2O_3; pentane–EtOAc–MeOH, 95:5:0.3) afforded **1a** as a red solid (2.50 g, 90%); mp 121.6–122.6 °C.

IR (ATR): 3390, 2940, 2854, 1708, 1584, 1562, 1512, 1476, 1440, 1410, 1362, 1308, 1266, 1208, 1192, 1130, 1090, 1040, 1022, 948, 932, 842 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.65 (br s, 1 H), 7.77 (d, *J* = 2.3 Hz, 1 H), 7.51 (d, *J* = 2.1 Hz, 1 H), 7.35 (d, *J* = 1.7 Hz, 1 H), 4.19 (q, *J* = 7.0 Hz, 2 H), 3.92 (s, 3 H), 3.76 (s, 2 H), 1.28 (t, *J* = 7.0 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 171.3, 153.0, 132.4, 131.5, 126.4, 125.3, 112.2, 109.5, 106.5, 61.0, 56.4, 31.1, 14.2.

MS (70 eV, EI): *m*/*z* (%) = 278 (M^+, 29), 206 (11), 205 (100), 159 (17).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{14}N_2O_5$: 278.0903; found: 278.0895.

1-(2,3-Dimethyl-1*H*-indol-5-yl)ethanone (1b)

s-BuZnBr (**2b**; 10 mmol, 38.5 mL, 0.26 M in THF) was prepared via addition of *s*-BuLi (**3b**, 10 mmol, 8.33 mL, 1.2 M in hexane) to a solution of $ZnBr_2$ (30 mmol, 30 mL, 1 M in THF) at 0 °C with continuous stirring for 10 min. Following typical procedure 3, the resulting alkylzinc reagent was reacted with 4-acetylbenzenediazonium tetrafluoroborate (**4b**; 12.5 mmol, 2.92 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was purified after the usual workup by flash column chromatography (Al_2O_3; pentane–EtOAc–MeOH, 95:5:0.3) to give **1b** as a pale yellow solid (1.49 g, 80%); mp 179.0–181.0 °C.

IR (ATR): 3286, 1654, 1612, 1578, 1458, 1356, 1264, 1232, 1142, 970, 898, 794, 692, 648 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.27 (br s, 1 H), 8.14 (s, 1 H), 7.77 (d, *J* = 8.4 Hz, 1 H), 7.24 (d, *J* = 8.4 Hz, 1 H), 2.67 (s, 3 H), 2.33 (s, 3 H), 2.25 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.7, 138.1, 132.4, 129.0, 129.0, 121.5, 119.9, 109.8, 108.7, 26.6, 11.5, 8.3.

MS (70 eV, EI): *m*/*z* (%) = 188 (16), 187 (M^+, 87), 186 (20), 173 (14), 172 (100), 144 (51), 143 (20), 85 (13), 83 (12), 77 (14), 71 (27), 57 (36), 55 (23), 43 (32).

HRMS (EI): *m*/*z* $[M]^+$ for $C_{12}H_{13}NO$: 187.0997; found: 187.0990.

1,2,3,4-Tetrahydrocyclopenta[*b*]indol-7-yl Pivalate (1c)

Following typical procedure 3, cyclopentylzinc bromide (**2c**; 10 mmol, 27.7 mL, 0.36 M in THF), prepared from cyclopentyl bromide (**3c**) via typical procedure 2 (25 °C, 4 h) using $ZnBr_2$ (20 mmol, 20 mL, 1 M in THF), was reacted with 4-[(2,2-dimethylpropanoyl)oxy]benzenediazonium tetrafluoroborate (**4c**; 12.5 mmol, 3.64 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 60 min) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was purified after the usual workup by flash column chromatography (Al_2O_3; pentane–EtOAc–MeOH, 96:4:0.2) to give **1c** as a white powder (1.86 g, 72%); mp 141.5–142.9 °C.

IR (ATR): 3392, 2950, 2851, 1730, 1623, 1580, 1475, 1461, 1162, 1137, 1112, 786, 625 cm^{-1}.

^1H NMR (300 MHz): δ = 7.89 (br s, 1 H), 7.15 (d, *J* = 8.7 Hz, 1 H), 7.08 (d, *J* = 2.4 Hz, 1 H), 6.73 (dd, *J* = 5.7 Hz, 2.4 Hz, 1 H), 2.84–2.75 (m, 4 H), 2.55–2.46 (m, 2 H), 1.40 (s, 9 H).

^{13}C NMR (75 MHz): δ = 178.15, 145.27, 144.51, 138.75, 124.94, 119.87, 113.98, 111.46, 110.51, 39.03, 28.59, 27.29, 25.86, 24.35.

MS (70 eV, EI): *m*/*z* (%) = 257 (M^+, 32), 174 (14), 173 (100), 172 (42).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{16}H_{19}NO_2$: 257.1416; found: 257.1412.

Ethyl (5-Methoxy-2-methyl-1*H*-indol-3-yl)acetate (1d)

Following typical procedure 3, the alkylzinc reagent **2d** (20 mmol, 22.2 mL, 0.90 M in THF), prepared from ethyl 4-bromopentanoate (**3d**) via typical procedure 1 (25 °C, 12 h) using $ZnBr_2$ (40 mmol, 40 mL, 1 M in THF), was reacted with 4-methoxybenzenediazonium tetrafluoroborate (**4d**; 25 mmol, 5.55 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 90 min) in the presence of Me_3SiCl (2.17 g, 20 mmol). The crude product was purified after the usual workup by flash column chromatography

(Al_2O_3; isohexane–EtOAc–MeOH, 96:4:0.3) to give **1d** as a pale yellow solid (3.35 g, 67%); mp 69.0–70.9 °C.

IR (ATR): 3314, 2976, 2924, 2832, 1708, 1588, 1486, 1454, 1370, 1320, 1264, 1216, 1172, 1124, 1102, 1030, 790, 686, 632 cm^{-1}.

^1H NMR (300 MHz): δ = 7.81 (br s, 1 H), 7.10 (d, *J* = 8.6 Hz, 1 H), 7.00 (d, *J* = 2.2 Hz, 1 H), 6.76 (dd, *J* = 8.8, 2.4 Hz, 1 H), 4.12 (q, *J* = 7.1 Hz, 2 H), 3.82 (s, 3 H), 3.63 (s, 2 H), 2.35 (s, 3 H), 1.24 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz): δ = 172.0, 154.1, 133.5, 130.1, 128.9, 110.9, 110.8, 104.5, 100.5, 60.6, 55.9, 30.6, 14.2, 11.7.

MS (70 eV, EI): *m*/*z* (%) = 247 (27), 175 (10), 174 (100), 131 (7).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{17}NO_3$: 247.1208; found: 247.1204.

3-(2-Ethoxy-2-oxoethyl)-2-methyl-1*H*-indol-5-yl Pivalate (1f)

Following typical procedure 3, the zinc reagent **2d** (10 mmol, 11.1 mL, 0.90 M in THF), prepared from ethyl 4-bromopentanoate (**3d**) via typical procedure 1 (50 °C, 12 h) using $ZnBr_2$ (20 mmol, 20 mL, 1 M in THF), was reacted with **4c** (12.5 mmol, 3.65 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 1 h) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was purified after the usual workup by flash column chromatography (Al_2O_3; pentane–EtOAc–MeOH, 90:10:0.5) to give **1f** as a pale yellow solid (2.00 g, 63%); >250 °C (dec.).

IR (ATR): 3372, 2976, 2936, 1728, 1590, 1480, 1458, 1368, 1278, 1170, 1122, 1030, 900, 786 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 8.17 (br s, 1 H), 7.14 (s, 1 H), 6.92 (d, *J* = 8.6 Hz, 1 H), 6.68 (d, *J* = 8.6 Hz, 1 H), 4.11 (q, *J* = 7.1 Hz, 2 H), 3.59 (s, 2 H), 2.22 (s, 3 H), 1.39 (s, 9 H), 1.22 (t, *J* = 7.1 Hz, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 178.2, 172.0, 144.4, 134.3, 132.8, 128.6, 114.6, 110.6, 109.8, 104.3, 60.6, 38.9, 30.4, 27.2, 14.1, 11.4.

MS (70 eV, EI): *m*/*z* (%) = 317 (M^+, 24), 244 (15), 233 (32), 161 (9), 160 (100), 159 (10), 131 (6), 57 (18).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{18}H_{23}NO_4$: 317.1627; found: 317.1622.

5-Methoxy-2,3-dimethyl-7-nitro-1*H*-indole (1g)

s-BuZnBr (**2b**; 10 mmol, 38.6 mL, 0.26 M in THF) was prepared via the addition of *s*-BuLi (**3b**, 10 mmol, 8.3 mL, 1.2 M in hexane) to a solution of $ZnBr_2$ (30 mmol, 30 mL, 1 M in THF) at 0 °C with continuous stirring for 10 min. The resulting alkylzinc reagent was reacted, according to typical procedure 3, with **4a** (12.5 mmol, 3.33 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 2 h). The crude product was purified after the usual workup by flash column chromatography (Al_2O_3; pentane–EtOAc–MeOH, 96:4:0.5) to give **1g** as a red solid (1.77 g, 80%); mp 153.0–154.0 °C.

IR (ATR): 3420, 3370, 3110, 3024, 2914, 2836, 1604, 1576, 1502, 1474, 1458, 1388, 1364, 1330, 1288, 1192, 1178, 1140, 1082, 1044, 966, 878, 834, 756, 700, 606 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.25 (br s, 1 H), 7.61 (d, *J* = 2.2 Hz, 1 H), 7.30 (d, *J* = 2.2 Hz, 1 H), 3.89 (s, 3 H), 2.39 (s, 3 H), 2.19 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.6, 134.8, 133.8, 131.3, 124.8, 111.8, 107.9, 103.9, 56.4, 11.6, 8.3.

MS (70 eV, EI): *m*/*z* (%) = 221 (13), 220 (M^+, 100), 219 (20), 205 (24), 174 (17), 159 (39), 131 (14), 130 (10).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{11}H_{12}N_2O_3$: 220.0848; found: 220.0834.

5-Fluoro-2,3-dimethyl-1*H*-indole (1h)

s-BuZnBr (**2b**; 10 mmol, 38.6 mL, 0.26 M in THF) was prepared via addition of *s*-BuLi (**3b**, 10 mmol, 8.3 mL, 1.2 M in hexane) to a solution of $ZnBr_2$ (30 mmol, 30 mL, 1 M in THF) at 0 °C with continuous stirring for 10 min. The resulting alkylzinc reagent was reacted according to typical procedure 3 with 4-fluorobenzenediazonium tetrafluoroborate (**4e**; 12.5 mmol, 2.62 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 90 min). The crude product was purified after the usual workup by flash column chromatography (Al_2O_3; pentane–EtOAc–MeOH, 96:4:0.2) to give **1h** as a pale yellow solid (1.11 g, 68%); mp 98.2–99.0 °C.

IR (ATR): 3408, 2916, 2862, 1628, 1586, 1482, 1442, 1386, 1288, 1228, 1184, 1130, 944, 792, 702 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.64 (br s, 1 H), 7.06–7.17 (m, 2 H), 6.83 (dd, *J* = 8.8, 2.6 Hz, 1 H), 2.35 (s, 3 H), 2.17 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.7 (d, *J* = 233.4 Hz), 132.7, 131.5, 129.9 (d, *J* = 9.5 Hz), 110.4 (d, *J* = 9.8 Hz), 108.8 (d, *J* = 26.1 Hz), 107.5, 103.0 (d, *J* = 23.3 Hz), 11.6, 8.4.

MS (70 eV, EI): *m*/*z* (%) = 163 (M^+, 18), 162 (24), 148 (15), 71 (54), 70 (18), 57 (75), 65 (38), 55 (26), 44 (32), 43 (100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{10}FN$: 163.0797; found: 163.0796.

5-Bromo-2,3-dimethyl-1*H*-indole (1i)

s-BuZnBr (**2b**; 10 mmol, 38.6 mL, 0.26 M in THF) was prepared via addition of *s*-BuLi (**3b**, 10 mmol, 8.3 mL, 1.2 M in hexane) to a solution of $ZnBr_2$ (30 mmol, 30 mL, 1 M in THF) at 0 °C with continuous stirring for 10 min. The resulting alkylzinc reagent reacted according to typical procedure 3 with 4-bromobenzenediazonium tetrafluoroborate (**4f**; 12.5 mmol, 3.38 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 90 min). The crude product was purified after the usual workup by flash column chromatography (Al_2O_3; isohexane–EtOAc–MeOH, 95:5:0.5) to give **1i** as a pale yellow solid (1.79 g, 80%); mp 152.6–154.1 °C.

IR (ATR): 3396, 2914, 1572, 1466, 1426, 1386, 1302, 1274, 1238, 1044, 1002, 966, 898, 864, 798, 744, 668 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.62 (br s, 1 H), 7.59 (d, *J* = 1.7 Hz, 1 H), 7.19 (dd, *J* = 8.6, 1.7 Hz, 1 H), 7.07 (d, *J* = 8.3 Hz, 1 H), 2.33 (s, 3 H), 2.18 (s, 3 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 133.7, 132.2, 131.2, 123.4, 120.5, 112.2, 111.4, 106.9, 11.5, 8.3.

MS (70 eV, EI): *m*/*z* (%) = 226 (24), 225 (M^+, 65), 224 (95), 223 (M^+, 81), 222 (69), 210 (42), 208 (45), 143 (62), 115 (26), 89 (17), 75 (22), 71 (56), 57 (42), 44 (32), 43 (100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{10}H_{10}{}^{79}BrN$: 222.9997; found: 222.9974.

7-Methoxy-5-nitro-1,2,3,4-tetrahydrocyclopenta[*b*]indole (1j)

Following typical procedure 3, cyclopentylzinc bromide (**2c**; 10 mmol, 27.7 mL, 0.36 M in THF), prepared from cyclopentyl bromide (**3c**) via typical procedure 1 (25 °C, 4 h) using $ZnBr_2$ (20 mmol, 20 mL, 1 M in THF), was reacted with **4a** (12.5 mmol, 3.33 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 90 min) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was purified after the usual workup by flash column chromatography (Al_2O_3; pentane–EtOAc–MeOH, 96:4:0.2) to give **1j** as a red solid (1.56 g, 68%); mp 138.0–139.0 °C.

IR (ATR): 3472, 2960, 2932, 2856, 1570, 1510, 1464, 1372, 1326, 1274, 1194, 1178, 1154, 1088, 1032, 836, 758 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 9.45 (br s, 1 H), 7.61 (d, *J* = 2.2 Hz, 1 H), 7.27 (d, *J* = 2.1 Hz, 1 H), 3.88 (s, 3 H), 2.85–2.99 (m, 2 H), 2.72–2.85 (m, 2 H), 2.46–2.69 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.8, 147.8, 132.0, 130.0, 128.6, 120.4, 112.1, 103.7, 56.4, 28.7, 25.9, 24.1.

MS (70 eV, EI): *m*/*z* (%) = 233 (14), 232 (M^+, 100), 231 (38), 186 (14), 185 (11), 171 (18), 143 (9).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{12}N_2O_3$: 232.0848; found: 232.0864.

6-Methoxy-8-nitro-2,3,4,9-tetrahydro-1*H*-carbazole (1k)

Following typical procedure 3, cyclohexylzinc bromide (**2e**; 10 mmol, 27 mL, 0.37 M in THF), prepared from cyclohexyl bromide via typical procedure 2 (25 °C, 4 h) using $ZnBr_2$ (20 mmol, 20 mL, 1 M in THF), was reacted with **4a** (12.5 mmol, 3.33 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was purified after the usual workup by flash column chromatography (Al_2O_3; pentane–EtOAc–MeOH, 95:4:0.5) to give **1k** as a red solid (2.25 g, 91%); mp 137.1–138.6 °C.

IR (ATR): 3424, 2934, 2844, 1734, 1604, 1574, 1508, 1466, 1440, 1382, 1278, 1194, 1134, 1036, 834, 758, 648, 606 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 9.27 (br s, 1 H), 7.62 (d, *J* = 2.1 Hz, 1 H), 7.29 (d, *J* = 2.1 Hz, 1 H), 3.89 (s, 3 H), 2.77 (t, *J* = 5.9 Hz, 2 H), 2.65 (t, *J* = 5.9 Hz, 2 H), 1.89–2.00 (m, 2 H), 1.80–1.89 (m, 2 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 152.7, 138.1, 132.3, 131.5, 125.3, 111.7, 110.9, 103.9, 56.4, 23.2, 22.9, 22.8, 20.6.

MS (70 eV, EI): *m*/*z* (%) = 246 (10), 247 (M^+, 78), 245 (11), 219 (11), 218 (100), 203 (8).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{14}N_2O_3$: 246.1004; found: 246.0997.

1-(2,3,4,9-Tetrahydro-1*H*-carbazol-6-yl)ethanone (1l)

Following typical procedure 3, cyclohexylzinc bromide (**2e**; 10 mmol, 27 mL, 0.37 M in THF), prepared from cyclohexyl bromide via typical procedure 2 (25 °C, 4 h) using $ZnBr_2$ (20 mmol, 20 mL, 1 M in THF), was reacted with **4b** (12.5 mmol, 3.33 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was purified after the usual workup by flash column chromatography (Al_2O_3; pentane–EtOAc–MeOH, 90:10:0.5) to give **1l** as a pale yellow solid (1.56 g, 73%); mp 122.5–124.0 °C.

IR (ATR): 3286, 2926, 2854, 1652, 1614, 1578, 1460, 1354, 1232, 1122, 812, 798, 686, 648 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.12 (s, 1 H), 8.09 (br s, 1 H), 7.78 (d, *J* = 8.5 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 1 H), 2.73 (t, *J* = 5.9 Hz, 4 H), 2.65 (s, 3 H), 1.78–2.01 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 198.5, 138.5, 135.8, 129.2, 127.5, 121.7, 119.7, 111.8, 110.0, 62.7, 26.6, 23.2, 23.0, 20.8.

MS (70 eV, EI): *m*/*z* (%) = 214 (19), 213 (M^+, 100), 212 (11), 198 (51), 185 (42), 170 (18), 142 (8).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{14}H_{15}NO$: 213.1154; found: 213.1151.

6-Methoxy-2,3,4,9-tetrahydro-1*H*-carbazole (1m)

Following typical procedure 3, cyclohexylzinc bromide (**2e**; 10 mmol, 27 mL, 0.37 M in THF), prepared from cyclohexyl bromide via typical procedure 2 (25 °C, 4 h) using $ZnBr_2$ (20 mmol, 20 mL, 1 M in THF), was reacted with **4d** (12.5 mmol, 2.77 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was purified after the usual workup by flash column chromatography (Al_2O_3; pentane–EtOAc–MeOH, 95:4:0.5) to give **1m**[13] as a pale yellow solid (2.25 g, 80%); mp 107.9–109.8 °C.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 7.56 (br s, 1 H), 7.15 (d, *J* = 8.6 Hz, 1 H), 6.95 (d, *J* = 2.4 Hz, 1 H), 6.88 (dd, *J* = 8.6 Hz, 2.4 Hz, 1 H), 3.87 (s, 3 H), 2.73–2.69 (m, 4 H), 2.67–1.89 (m, 4 H).

6-Bromo-2,3,4,9-tetrahydro-1*H*-carbazole (1n)

Following typical procedure 3, cyclohexylzinc bromide (**2e**; 10 mmol, 27 mL, 0.37 M in THF), prepared from cyclohexyl bromide via typical procedure 2 (25 °C, 4 h) using $ZnBr_2$ (20 mmol, 20 mL, 1 M in THF), was reacted with **4f** (12.5 mmol, 3.38 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was purified after the usual workup by flash column chromatography (Al_2O_3; isohexane–EtOAc–MeOH, 95:5:0.5) to give **1n** as a pale yellow solid (2.00 g, 80%); mp 152.6–154.1 °C.

IR (ATR): 3400, 2938, 2906, 2848, 1578, 1434, 1310, 1232, 1046, 974, 862, 796 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.63 (br s, 1 H), 7.58 (d, *J* = 1.8 Hz, 1 H), 7.19 (dd, *J* = 8.4 Hz, 1.8 Hz, 1 H), 7.11 (d, *J* = 8.4 Hz, 1 H), 2.73–2.64 (m, 4 H), 1.95–1.84 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 135.60, 134.26, 129.68, 123.59, 120.42, 112.32, 111.71, 110.01, 23.22, 23.14, 23.06, 20.76.

MS (70 eV, EI): *m*/*z* (%) = 252 (10), 251 (M^+, 76), 250 (26), 249 (M^+, 81), 248 (16), 224 (12), 223 (98), 221 (100), 168 (19), 167 (15), 142 (11), 115 (12).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{12}H_{12}{}^{79}BrN$: 249.0153; found: 249.0137.

2,3,4,9-Tetrahydro-1*H*-carbazole-6-carbonitrile (1o)

Following typical procedure 3, cyclohexylzinc bromide (**2e**; 10 mmol, 27 mL, 0.37 M in THF), prepared from cyclohexyl bromide via typical procedure 2 (25 °C, 4 h) using $ZnBr_2$ (20 mmol, 20 mL, 1 M in THF), was reacted with 4-cyanobenzenediazonium tetrafluoroborate (**4g**; 12.5 mmol, 2.71 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (1.08 g, 10 mmol). The crude product was purified after the usual workup by flash column chromatography (Al_2O_3; isohexane–EtOAc–MeOH, 95:6:1) to give **1o** as a pale yellow solid (1.56 g, 80%); mp 124.0–125.0 °C.

IR (ATR): 3314, 2926, 2846, 2216, 1686, 1622, 1478, 1318, 1236, 1180, 872, 806, 798, 626 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.13 (br s, 1 H), 7.76 (s, 1 H), 7.19–7.49 (m, 2 H), 2.74 (t, *J* = 5.7 Hz, 2 H), 2.67 (t, *J* = 5.8 Hz, 2 H), 1.75–2.03 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 137.4, 136.6, 127.7, 124.1, 123.1, 121.2, 111.0, 111.0, 101.7, 23.1, 22.9, 22.8, 20.6.

MS (70 eV, EI): *m*/*z* (%) = 197 (11), 196 (M^+, 79), 195 (17), 169 (12), 168 (100).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{12}N_2$: 196.1000; found: 196.0997.

[3-(6,7,8,9,10,11-Hexahydro-5*H*-cycloocta[*b*]indol-5-yl)propyl]dimethylamine (6, Iprindole)

Following typical procedure 3, cyclooctylzinc bromide (**2f**; 20 mmol, 57 mL, 0.35 M in THF), prepared from cyclooctyl bromide via typical procedure 2 (25 °C, 4 h) using $ZnBr_2$ (40 mmol, 40 mL, 1 M in THF), was reacted with phenyldiazonium tetrafluoroborate (**4h**; 25 mmol, 4.80 g). The hydrazone intermediate was heated by microwave irradiation (125 °C, 30 min) in the presence of Me_3SiCl (2.17 g, 20 mmol). After cooling to 0 °C, *t*-BuOK (24 mmol, 2.29 g) was slowly added. The reaction mixture was stirred for 20 min at 0 °C followed by the addition of (3-chloropropyl)dimethylamine (24 mmol, 2.92 g). The resulting solution was heated by microwave irradiation (125 °C, 3 h) and quenched with brine (50 mL). The

aqueous phase was extracted with EtOAc (3 × 50 mL). The combined organic phases were dried (Na_2SO_4) and the solvent was removed in vacuo. The crude product was purified by flash column chromatography (Al_2O_3; pentane–EtOAc–MeOH, 97:3:0.3) to give iprindole (**6**) as a yellow oil (4.09 g, 72%).

IR (ATR): 3050, 2920, 2848, 2814, 2764, 1464, 1370, 1338, 1316, 1180, 1040, 734, 696 cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 7.50 (d, *J* = 7.3 Hz, 1 H), 7.29 (d, *J* = 7.8 Hz, 1 H), 7.10 (t, *J* = 7.9 Hz, 1 H), 7.01–7.08 (m, 1 H), 4.12 (t, *J* = 7.6 Hz, 2 H), 2.79–2.95 (m, 4 H), 2.30 (t, *J* = 6.9 Hz, 2 H), 2.23 (s, 6 H), 1.83–1.97 (m, 2 H), 1.64–1.78 (m, 4 H), 1.35–1.47 (m, 4 H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 136.6, 136.0, 127.5, 120.1, 118.4, 117.6, 111.8, 108.9, 56.8, 45.4, 40.9, 30.4, 29.3, 28.7, 26.1, 25.9, 23.0, 22.9.

MS (70 eV, EI): *m*/*z* (%) = 284 (M^+, 57), 213 (33), 212 (20), 198 (20), 185 (21), 184 (20), 171 (21), 170 (73), 157 (21), 156 (26), 145 (22), 144 (24), 71 (15), 58 (100), 43 (58), 41 (48).

HRMS (EI): *m*/*z* $[M]^+$ calcd for $C_{19}H_{28}N_2$: 284.2252; found: 284.2246.

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