Palladium-Catalyzed Heteroannulation Approach to 1,2-Bis(3-indolyl)ethanes

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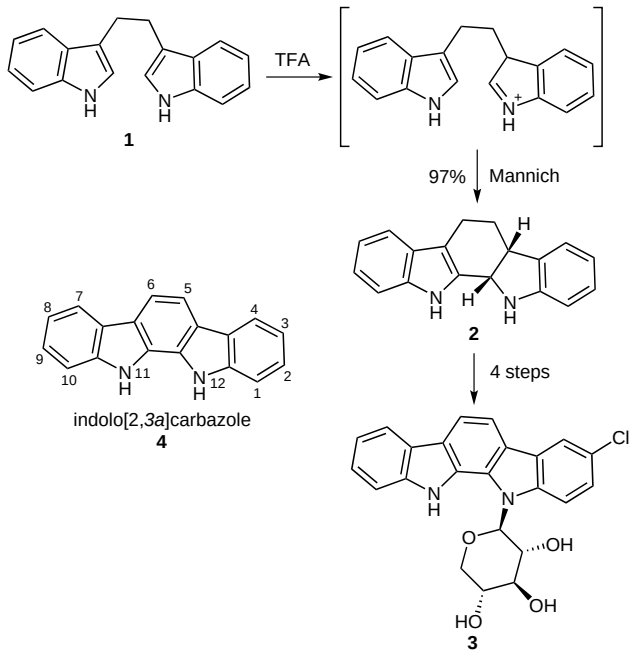
Abstract: Palladium-catalyzed heteroannulation between indole-3-butanal and various *o*-iodoanilines provides a straightforward synthesis of 1,2-bis(3-indolyl)ethanes, which are useful precursors to valued indolo[2,3*a*]carbazoles. 1,2-Bis(3-indolyl)ethanes bearing a variety of substituents are available by using this methodology, with one transformed into the natural product 1,2-bis(3-indolyl)ethane-1,2-dione through a novel double Yonemitsu oxidation.

Key words: indole, heteroannulation, indole derivatives, palladium, natural products

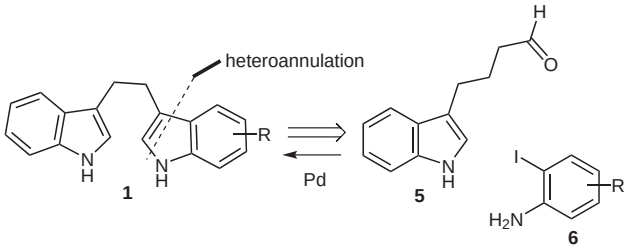
The Mannich cyclization of 1,2-bis(3-indolyl)ethane (**1**) provides tetrahydroindolocarbazole (**2**), a key intermediate in the total synthesis of (+)-tjipanazole F2 (**3**; Scheme 1).[1,2] Although the chemistry outlined in Scheme 1 facilitates easy access to indolo[2,3*a*]carbazoles[3] **4**, unsubstituted at C5 and C6, most synthetic routes to these compounds ignore this methodology and rely on Fischer indolizations[4] or the cyclization of an appropriately substituted 2,2′-bisindole.[5]



Scheme 1 Van Vranken's total synthesis of (+)-tjipanazole F2 (**3**)

The limited applications of the chemistry outlined in Scheme 1 is presumably due to the lack of synthetic methods[6] available to access 1,2-bis(3-indolyl)ethanes of type **1**, making it particularly unappealing when a structurally diverse series of indolocarbazoles are desired. To make this methodology more attractive for indolocarbazole synthesis programmes, including our own, a facile synthesis of 1,2-bis(3-indolyl)ethanes **1** was sought.

The palladium-catalyzed heteroannulation of *o*-iodoanilines with carbonyl compounds is a mild and straightforward method for the synthesis of indoles.[7] This reaction was envisaged as the defining step in the synthesis of 1,2-bis(3-indolyl)ethanes **1** from indole-3-butanal (**5**) and *o*-iodoanilines **6** (Scheme 2).



Scheme 2 Proposed synthesis of 1,2-bis(3-indolyl)ethanes **1**

Although it has been reported that aldehyde **5** is available by reducing the ethyl ester of butyric acid **7**,[8] this was not selective in our hands and a two-step reduction–oxidation sequence was employed (Scheme 3). Carboxylic acid **7** was reduced to the alcohol **8**,[9,10] which, upon oxidation with 2-iodoxybenzoic acid (IBX), delivered aldehyde **5**,[8,11] which could not be purified due to its instability and had to be used immediately in the subsequent heteroannulation.

Upon subjecting freshly prepared aldehyde **5** and *o*-iodoaniline **6a** to the heteroannulation conditions reported by Chen,[7b] 1,2-bis(3-indolyl)ethane (**1a**) was isolated in decent overall yield (Table 1, entry 1). With this pleasing result in hand, the scope of the reaction was investigated with a range of *o*-iodoanilines[12] (Table 1). The methodology can be used to access unsymmetrical 1,2-bis(3-indolyl)ethanes[13] bearing electron-donating alkyl (entry 2) and alkoxy substituents (entry 3). Chlorinated (entry 4) and fluorinated (entry 5) products are also available, as are those possessing trifluoromethyl (entry 6), nitrile (entry 7) and nitro (entry 8) substituents. 1,2-Bis(3-indolyl)ethanes possessing more than one substituent are also readily available (entry 9).

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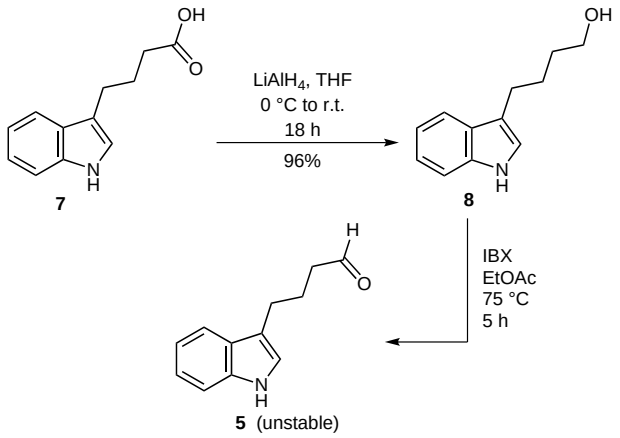
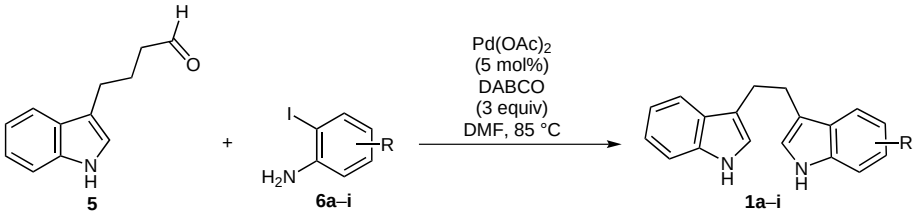


Scheme 3 Synthesis of indole-3-butanal (**5**)

A minor drawback of this methodology is the extended times required for the heteroannulation to reach completion (Table 1). Attempts to address this issue by increasing the reaction temperature resulted in significantly reduced yields due to degradation of indole-3-butanal (**5**) at temperatures above 85 °C. We felt that faster reactions may be possible by using the more reactive *o*-bromoaniline (**9**) in the reaction, however, because the mild, ligandless conditions used in Table 1 fail to effect heteroannulation of aldehydes with *o*-bromoanilines, the modified conditions reported by Zhu[7d] were employed (Scheme 4). Unfortunately, no reaction occurred between **5** and **9** at 85 °C and attempts to heat the reaction further caused degradation of **5**. Thus, it appears that *o*-iodoanilines cannot be replaced by other haloanilines in this process.

Table 1 Synthesis of 1,2-Bis(3-indolyl)ethanes **1a–i**



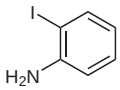
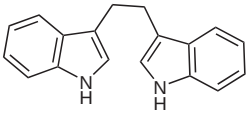
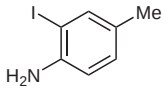
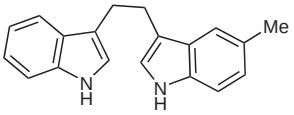
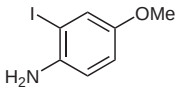
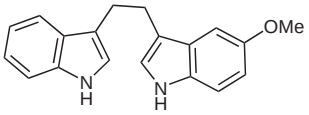
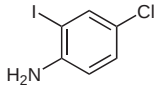
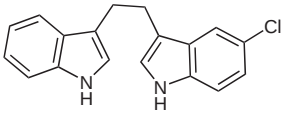
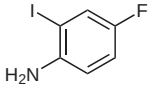
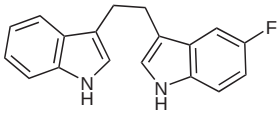
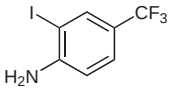
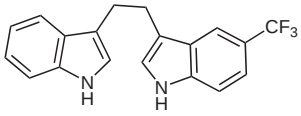
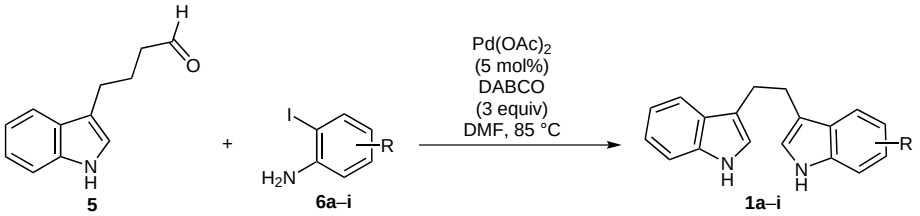
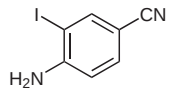
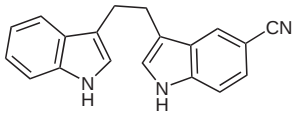
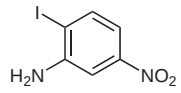
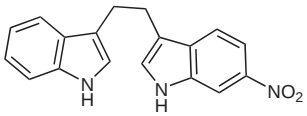
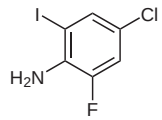
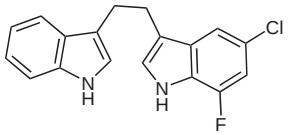
Entry	**6** (1.1 equiv)	Time (h)	Product	Yield (%)[a]
1	 **6a**	60	 **1a**	19
2	 **6b**	42	 **1b**	26
3	 **6c**	17	 **1c**	22
4	 **6d**	18	 **1d**	17
5	 **6e**	60	 **1e**	21
6	 **6f**	21	 **1f**	33

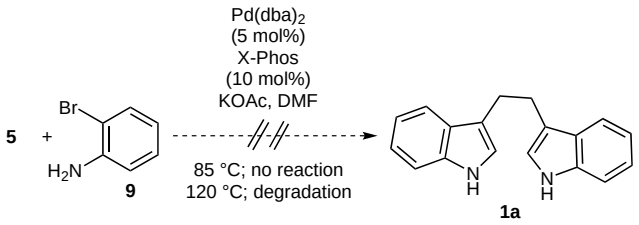
Table 1 Synthesis of 1,2-Bis(3-indolyl)ethanes **1a–i** (continued)



5 + **6a–i** → **1a–i**

Entry	**6** (1.1 equiv)	Time (h)	Product	Yield (%)[a]
7	 **6g**	90	 **1g**	32
8	 **6h**	20	 **1h**	50
9	 **6i**	19	 **1i**	51

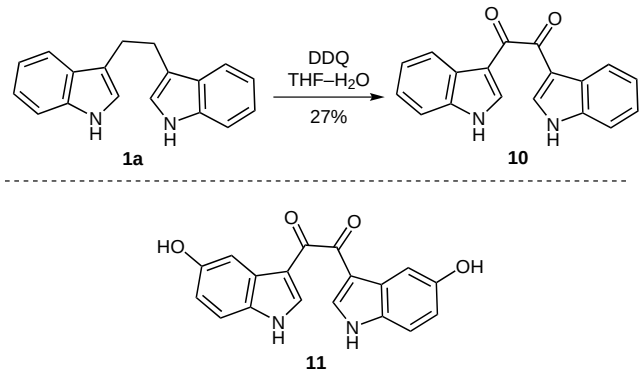
[a] Yield over two steps from alcohol **8**.



5 + **9** → **1a**

Scheme 4 Failed heteroannulation with *o*-bromoaniline (**9**)

In a related project, we wished to investigate whether the double Yonemitsu oxidation[14] of **1a** would furnish 1,2-bis(3-indolyl)ethane-1,2-dione (**10**), an alkaloid from the marine sponge *Smenospongia* sp.[15] and the core structure of the natural product hyrtiosin B[16] (**11**), itself a potent inhibitor of isocitrate lyase from *Candida albicans*.[17] Upon treating **1a** with an excess of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in aqueous tetrahydrofuran (THF), double Yonemitsu oxidation successfully occurred to afford the natural product **10** (Scheme 5).[18]



1a → **10**

1a → **11**

Scheme 5 A double Yonemitsu oxidation

In conclusion, the palladium-catalyzed heteroannulation between **5** and various *o*-iodoanilines **6a–i** provides a general synthetic route to 1,2-bis(3-indolyl)ethanes. The 1,2-bis(3-indolyl)ethanes reported herein possess a range of substituents, many of which constitute useful handles upon which to conduct further synthetic manipulations. Because this reaction relies on readily available substrates,[12,19] it is anticipated that this methodology can be extended to examples well beyond those reported herein. It has also been demonstrated that **1a** can be transformed into the natural product **10** by a novel double Yonemitsu oxidation.

Acknowledgment

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(10) **Indole-3-butanol (8):** To a solution of indole-3-butyric acid (**7**; 0.50 g, 2.46 mmol) in THF (30 mL) at 0 °C was slowly added $LiAlH_4$ (0.47 g, 12.31 mmol) and the reaction mixture was allowed to warm to r.t. over 18 h. EtOAc (10 mL) was added slowly followed by H_2O (10 mL) and the mixture was poured onto a solution of Rochelle's salt (40 mL). The resulting suspension was extracted with EtOAc (3 × 40 mL) and the combined organic extracts were dried ($MgSO_4$), filtered and concentrated in vacuo. Purification by filtration through a short plug of silica gel (hexanes–EtOAc, 1:3) gave the title compound as a yellow oil (0.45 g, 2.36 mmol, 96%). Spectroscopic data were consistent with literature data.[9] IR: 3385, 3288, 2927, 1455, 1423, 1340, 1225, 1091, 1062, 1047, 1033, 1007, 984, 932, 911, 749, 739, 687, 667, 615 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.93 (br s, 1 H, NH), 7.61 (d, *J* = 7.9 Hz, 1 H, ArH), 7.35 (d, *J* = 8.0 Hz, 1 H, ArH), 7.19 (td, *J* = 7.6, 1.1 Hz, 1 H, ArH), 7.12 (td, *J* = 7.6, 1.1 Hz, 1 H, ArH), 6.98 (s, 1 H, ArH), 3.69 (t, *J* = 6.5 Hz, 2 H, CH_2OH), 2.81 (t, *J* = 7.3 Hz, 2 H, CH_2), 1.74 (m, 4 H, 2 × CH_2); OH not observed. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 136.5 (C), 127.7 (C), 122.0 (CH), 121.3 (CH), 119.3 (CH), 119.1 (CH), 116.8 (C), 111.2 (CH), 63.1 (CH_2), 32.8 (CH_2), 26.4 (CH_2), 25.0 (CH_2). ESI-MS: *m*/*z* (%) = 212 (100) $[M + Na]^+$, 196 (8), 190 (5). ESI-HRMS: *m*/*z* $[M + Na]^+$ calcd for $[C_{12}H_{15}NO + Na]^+$: 212.1046; found: 212.1047.

(11) **Indole-3-butanal (5):** A solution of indole-3-butanol (**8**; 0.10 g, 0.53 mmol) and IBX (0.59 g, 2.11 mmol) in EtOAc (15 mL) was heated to 75 °C for 5 h. The reaction mixture was cooled, filtered through a short plug of Celite, and the cake was washed with EtOAc (10 mL). The filtrate was then concentrated in vacuo to afford aldehyde **5** (ca. 100 mg) as an unstable yellow oil which was used *immediately* in the subsequent heteroannulation. *Note*: Using aldehyde **5** that has been stored in a freezer under argon leads to significantly reduced yields in the heteroannulation reaction.

(12) *o*-Iodoanilines **6a–i** were purchased from commercial sources.

(13) **Synthesis of 1,2-bis(3-indolyl)ethanes 1a–i; Heteroannulation General Procedure:** A quantitative yield for the oxidation step (**8**→**5**)[16] is presumed and hence the molar amounts of each reagent are based on alcohol **8**. A sealed tube charged with DMF (1–2 mL) was degassed with nitrogen for 30 min. Freshly prepared aldehyde **5** (0.15–0.26 mmol) was added, followed by the appropriate *o*-iodoaniline **6a–i** (0.17–0.29 mmol), DABCO (0.45–0.79 mmol) and $Pd(OAc)_2$ (5 mol%). The tube was then sealed under a blanket of nitrogen and stirred at 85 °C for 18–90 h. The cooled solution was poured onto H_2O (10 mL) and extracted with Et_2O (3 × 10 mL). The combined organic extracts were dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (hexanes–EtOAc) gave the desired products **1a–i**, the yields of which were calculated over two steps from alcohol **8**.

Compound 1a: According to the general procedure, a mixture of aldehyde **5**, 2-iodoaniline (**6a**; 60 mg, 0.27 mmol), DABCO (83 mg, 0.74 mmol) and $Pd(OAc)_2$ (3 mg, 0.012 mmol, 5 mol%) in DMF (2.0 mL) was heated at 85 °C for 60 h. The title compound (12 mg, 0.046 mmol, 19% over two steps) was obtained after flash chromatography (4:1) as a yellow solid; mp 210 –220 °C (dec.) [Lit.[6e] 263–265 °C (MeCN)], (Lit.[6f] 161–162 °C). IR: 3390, 3049, 2900, 2847, 1618, 1456, 1423, 1355, 1337, 1301, 1267, 1248, 1220, 1090, 1051, 1007, 930, 808, 766, 738 cm^{-1}. ^1H NMR [400 MHz, $(CD_3)_2CO$]: δ = 10.74 (br s, 2 H, 2 × NH), 7.56 (d, *J* = 7.8 Hz, 2 H, 2 × ArH), 7.33 (d, *J* = 8.1 Hz, 2 H, 2 × ArH), 7.15 (d, *J* = 2.0 Hz, 2 H, 2 × ArH), 7.06 (td, *J* = 7.4, 1.0 Hz, 2 H, 2 × ArH), 6.98 (td, *J* = 7.4, 1.0 Hz, 2 H, 2 × ArH), 3.06 (s, 4 H, 2 × CH_2). ^{13}C NMR [100 MHz, $(CD_3)_2CO$]: δ = 136.3 (2 × C), 127.2 (2 × C), 122.2 (2 × CH), 120.8 (2 × CH), 118.3 (2 × CH), 118.1 (2 × CH), 114.8 (2 × C), 111.3 (2 × CH), 25.9 (2 × CH_2). ESI-MS: *m*/*z* (%) = 283 (100) $[M + Na]^+$, 156 (80), 144 (13), 130 (80). ESI-HRMS: *m*/*z* $[M + Na]^+$ calcd for $[C_{18}H_{16}N_2 + Na]^+$: 283.1206; found: 283.1197.

Compound 1b: According to the general procedure, a mixture of aldehyde **5**, 2-iodo-4-methylaniline (**6b**; 68 mg, 0.29 mmol), DABCO (89 mg, 0.79 mmol) and $Pd(OAc)_2$ (3 mg, 0.013 mmol, 5 mol%) in DMF (2.0 mL) was heated at 85 °C for 42 h. The title compound (19 mg, 0.069 mmol, 26% over two steps) was obtained after flash

chromatography (7:3) as a brown solid; mp 193–196 °C. IR: 3393, 2918, 2848, 1483, 1456, 1423, 1330, 1230, 1250, 1223, 1182, 1090, 1047, 1005, 927, 874, 794, 771, 742, 694 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 9.91 (br s, 1 H, NH), 9.77 (br s, 1 H, NH), 7.64 (d, *J* = 7.8 Hz, 1 H, ArH), 7.39 (m, 2 H, 2 × ArH), 7.26 (d, *J* = 8.2 Hz, 1 H, ArH), 7.15 (d, *J* = 2.2 Hz, 1 H, ArH), 7.10 (m, 2 H, 2 × ArH), 7.02 (td, *J* = 7.4, 1.0 Hz, 1 H, ArH), 6.93 (dd, *J* = 8.3, 1.0 Hz, 1 H, ArH), 3.14 (m, 4 H, 2 × CH_2), 2.41 (s, 3 H, Me). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 137.8 (C), 136.2 (C), 128.9 (C), 128.7 (C), 128.0 (C), 123.6 (CH), 122.8 (CH), 122.7 (CH), 122.0 (CH), 119.4 (CH), 119.3 (CH), 119.1 (CH), 116.7 (C), 116.2 (C), 112.1 (CH), 111.8 (CH), 27.11 (CH_2), 27.07 (CH_2), 21.7 (Me). ESI-MS: *m/z* (%) = 297 (100) $[M + Na]^+$, 170 (9). ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $[C_{19}H_{18}N_2 + Na]^+$: 297.1362; found: 297.1366.

Compound 1c: According to the general procedure, a mixture of aldehyde **5**, 2-iodo-4-methoxylaniline (**6c**; 72 mg, 0.29 mmol), DABCO (89 mg, 0.79 mmol) and $Pd(OAc)_2$ (3 mg, 0.013 mmol, 5 mol%) in DMF (2.0 mL) was heated at 85 °C for 17 h. The title compound (17 mg, 0.059 mmol, 22% over two steps) was obtained after flash chromatography (4:1) as a brown solid; mp 136 –140 °C. IR: 3400, 1484, 1454, 1435, 1335, 1294, 1266, 1207, 1168, 1093, 1052, 1030, 1008, 967, 923, 829, 811, 795, 770, 747 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 10.73 (s, 1 H, NH), 10.57 (s, 1 H, NH), 7.57 (d, *J* = 7.8 Hz, 1 H, ArH), 7.34 (d, *J* = 8.0 Hz, 1 H, ArH), 7.22 (d, *J* = 8.7 Hz, 1 H, ArH), 7.13 (m, 2 H, 2 × ArH), 7.07 (td, *J* = 7.5, 0.9 Hz, 1 H, ArH), 6.97 (m, 2 H, 2 × ArH), 6.70 (dd, *J* = 8.7, 2.4 Hz, 1 H, ArH), 3.72 (s, 3 H, OMe), 3.05 (m, 4 H, 2 × CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 152.9 (C), 136.3 (C), 131.4 (C), 127.6 (C), 127.3 (C), 122.9 (CH), 122.3 (CH), 120.8 (CH), 118.3 (CH), 118.1 (CH), 114.8 (C), 114.6 (C), 111.9 (CH), 111.3 (CH), 110.9 (CH), 100.2 (CH), 55.3 (OMe), 25.8 (2 × CH_2). ESI-MS: *m/z* (%) = 313 (100) $[M + Na]^+$, 143 (9). ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $[C_{19}H_{18}N_2O + Na]^+$: 313.1311; found: 313.1315.

Compound 1d: According to the general procedure, a mixture of aldehyde **5**, 4-chloro-2-iodoaniline (**6d**; 49 mg, 0.193 mmol), DABCO (60 mg, 0.535 mmol) and $Pd(OAc)_2$ (2 mg, 0.009 mmol, 5 mol%) in DMF (1.3 mL) was heated at 85 °C for 18 h. The title compound (9 mg, 0.031 mmol, 17% over two steps) was obtained after flash chromatography (7:3) as a brown solid; mp 175 –178 °C (Lit.[1b] 178–180 °C). IR: 3397, 2907, 1454, 1421, 1394, 1328, 1299, 1283, 1251, 1214, 1091, 1043, 1007, 927, 895, 871, 797, 777, 768, 738 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 10.96 (s, 1 H, NH), 10.74 (s, 1 H, NH), 7.55 (m, 2 H, 2 × ArH), 7.34 (m, 2 H, 2 × ArH), 7.24 (d, *J* = 2.2 Hz, 1 H, ArH), 7.15 (d, *J* = 2.0 Hz, 1 H, ArH), 7.06 (m, 2 H, 2 × ArH), 6.97 (td, *J* = 7.3, 0.7 Hz, 1 H, ArH), 3.04 (s, 4 H, 2 × CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 136.2 (C), 134.6 (C), 128.4 (C), 127.2 (C), 124.2 (CH), 122.8 (C), 122.3 (CH), 120.8 (CH), 120.7 (CH), 118.3 (CH), 118.1 (CH), 117.6 (CH), 114.8 (C), 114.5 (C), 112.8 (CH), 111.3 (CH), 25.8 (CH_2), 25.5 (CH_2). ESI-MS: *m/z* (%) = 317 (100) $[M + Na]^+$, 143 (18). ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $[C_{18}H_{15}{}^{35}ClN_2 + Na]^+$: 317.0816; found: 317.0807. Spectroscopic data is consistent with the literature.[1b]

Compound 1e: According to the general procedure, a mixture of aldehyde **5**, 4-fluoro-2-iodoaniline (**6e**; 46 mg, 0.194 mmol), DABCO (60 mg, 0.535 mmol) and $Pd(OAc)_2$ (2 mg, 0.009 mmol, 5 mol%) in DMF (1.3 mL) was heated at 85 °C for 60 h. The title compound (10 mg, 0.037 mmol, 21% over two steps) was obtained after flash chromatography (7:3) as a brown solid; mp 200 – 220 °C (dec.). IR: 3401, 1579, 1483, 1453, 1423, 1358, 1332, 1260, 1215, 1167, 1092, 1041, 1008, 938, 866, 797, 769, 739, 695, 610 cm^{-1}. ^1H NMR [400 MHz, $(CD_3)_2CO$]: δ = 10.02 (br s, 1 H, NH), 9.92 (br s, 1 H, NH), 7.63 (d, *J* = 8.0 Hz, 1 H, ArH), 7.37 (m, 2 H, 2 × ArH), 7.29 (dd, *J* = 10.0, 2.5 Hz, 1 H, ArH), 7.23 (d, *J* = 2.3 Hz, 1 H, ArH), 7.15 (d, *J* = 2.3 Hz, 1 H, ArH), 7.09 (td, *J* = 7.5, 1.2 Hz, 1 H, ArH), 7.02 (td, *J* = 7.5, 1.0 Hz, 1 H, ArH), 6.88 (td, *J* = 9.1, 2.5 Hz, 1 H, ArH), 3.13 (m, 4 H, 2 × CH_2). ^{13}C NMR [100 MHz, $(CD_3)_2CO$]: δ = 158.3 (d, $J_{C–F}$ = 231.4 Hz, C), 137.8 (C), 134.3 (C), 129.0 (d, $J_{C–F}$ = 9.4 Hz, C), 128.7 (C), 125.0 (CH), 122.8 (CH), 122.0 (CH), 119.4 (CH), 119.3 (CH), 116.9 (d, $J_{C–F}$ = 4.9 Hz, C), 116.5 (C), 112.9 (d, $J_{C–F}$ = 9.7 Hz, CH), 112.1 (CH), 109.9 (d, $J_{C–F}$ = 26.4 Hz, CH), 104.0 (d, $J_{C–F}$ = 23.2 Hz, CH), 26.9 (2 × CH_2). ESI-MS: *m/z* (%) = 301 (100) $[M + Na]^+$, 242 (4), 210 (3). ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $[C_{18}H_{15}FN_2 + Na]^+$: 301.1111; found: 301.1124.

Compound 1f: According to the general procedure, a mixture of aldehyde **5**, 2-iodo-4-(trifluoromethyl)aniline (**6f**; 47 mg, 0.165 mmol), DABCO (51 mg, 0.450 mmol) and $Pd(OAc)_2$ (2 mg, 0.008 mmol, 5 mol%) in DMF (1.1 mL) was heated at 85 °C for 21 h. The title compound (16 mg, 0.049 mmol, 33% over two steps) was obtained after flash chromatography (7:3) as a brown solid; mp 142–145 °C. IR: 3388, 1458, 1328, 1282, 1261, 1215, 1153, 1130, 1096, 1080, 1044, 1026, 1006, 904, 891, 802, 771, 751, 714, 661 cm^{-1}. ^1H NMR [400 MHz, $(CD_3)_2CO$]: δ = 10.38 (br s, 1 H, NH), 9.92 (br s, 1 H, NH), 7.93 (s, 1 H, ArH), 7.61 (d, *J* = 7.9 Hz, 1 H, ArH), 7.56 (d, *J* = 8.7 Hz, 1 H, ArH), 7.37 (d, *J* = 8.2 Hz, 2 H, 2 × ArH), 7.33 (s, 1 H, ArH), 7.14 (d, *J* = 2.1 Hz, 1 H, ArH), 7.08 (td, *J* = 7.4, 0.8 Hz, 1 H, ArH), 7.00 (t, *J* = 7.4 Hz, 1 H, ArH), 3.19 (m, 4 H, 2 × CH_2); ^{13}C NMR [100 MHz, $(CD_3)_2CO$]: δ = 139.1 (C), 137.8 (C), 128.6 (C), 128.0 (CF_3), 125.1 (CH), 125.0 (C), 122.9 (CH), 122.0 (CH), 121.3 (C), 119.3 (2 × CH), 118.5 (d, $J_{C–F}$ = 3.5 Hz, CH), 117.9 (C), 117.1 (q, $J_{C–F}$ = 4.2 Hz, CH), 116.3 (C), 112.7 (CH), 112.1 (CH), 27.0 (CH_2), 26.6 (CH_2). ESI-MS: *m/z* (%) = 351 (100) $[M + Na]^+$, 250 (7). ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $[C_{19}H_{15}F_3N_2 + Na]^+$: 351.1080; found: 351.1076.

Compound 1g: According to the general procedure, a mixture of aldehyde **5**, 4-amino-3-iodobenzonitrile (**6g**; 71 mg, 0.29 mmol), DABCO (89 mg, 0.79 mmol) and $Pd(OAc)_2$ (3 mg, 0.013 mmol, 5 mol%) in DMF (2.0 mL) was heated at 85 °C for 90 h. The title compound (24 mg, 0.085 mmol, 32% over two steps) was obtained after flash chromatography (3:2) as a brown solid; mp 162–165 °C. IR: 3406, 2223, 1614, 1469, 1456, 1422, 1361, 1322, 1221, 1098, 1082, 1066, 1008, 883, 827, 813, 801, 787, 764, 737 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 11.36 (s, 1 H, NH), 10.74 (s, 1 H, NH), 8.05 (s, 1 H, ArH), 7.53 (m, 2 H, 2 × ArH), 7.37 (m, 3 H, 3 × ArH), 7.15 (s, 1 H, ArH), 7.06 (t, *J* = 7.5 Hz, 1 H, ArH), 6.97 (t, *J* = 7.5 Hz, 1 H, ArH), 3.08 (m, 4 H, 2 × CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 137.9 (C), 136.2 (C), 127.2 (C), 127.1 (C), 125.0 (CH), 124.3 (CH), 123.5 (CH), 122.4 (CH), 121.0 (C), 120.8 (CH), 118.4 (CH), 118.1 (CH), 116.2 (C), 114.4 (C), 112.5 (CH), 111.3 (CH), 100.2 (C), 25.8 (CH_2), 25.4 (CH_2). ESI-MS: *m/z* (%) = 308 (100) $[M + Na]^+$. ESI-HRMS: *m/z* $[M + Na]^+$ calcd for $[C_{19}H_{15}N_3 + Na]^+$: 308.1158; found: 308.1153.

Compound 1h: According to the general procedure, a mixture of aldehyde **5**, 2-iodo-5-nitroaniline (**6h**; 77 mg, 0.29 mmol), DABCO (89 mg, 0.79 mmol) and $Pd(OAc)_2$ (3 mg, 0.013 mmol, 5 mol%) in DMF (2.0 mL) was heated at 85 °C for 20 h. The title compound (40 mg, 0.131 mmol, 50% over two steps) was obtained after flash chromatography (7:3) as an orange solid; mp 170–173 °C.

IR: 3416, 3218, 1494, 1458, 1420, 1345, 1310, 1291, 1241, 1216, 1124, 1105, 1095, 1076, 1053, 1010, 865, 815, 782, 738, 724, 665 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 11.58 (s, 1 H, NH), 10.75 (s, 1 H, NH), 8.31 (d, *J* = 1.9 Hz, 1 H, ArH), 7.86 (dd, *J* = 8.9, 1.9 Hz, 1 H, ArH), 7.70 (d, *J* = 8.9 Hz, 1 H, ArH), 7.62 (s, 1 H, ArH), 7.56 (d, *J* = 8.0 Hz, 1 H, ArH), 7.34 (d, *J* = 8.0 Hz, 1 H, ArH), 7.14 (s, 1 H, ArH), 7.07 (t, *J* = 7.5 Hz, 1 H, ArH), 6.97 (t, *J* = 7.5 Hz, 1 H, ArH), 3.10 (m, 4 H, 2 × CH_2). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 141.7 (C), 136.3 (C), 134.5 (C), 131.9 (C), 129.8 (CH), 127.2 (C), 122.3 (CH), 120.8 (CH), 118.6 (CH), 118.3 (CH), 118.1 (CH), 116.3 (C), 114.3 (C), 113.4 (CH), 111.3 (CH), 108.2 (CH), 25.8 (CH_2), 25.4 (CH_2). ESI-MS: *m*/*z* (%) = 328 (100) $[M + Na]^+$. ESI-HRMS: *m*/*z* $[M + Na]^+$ calcd for $[C_{18}H_{15}N_3O_2 + Na]^+$: 328.1056; found: 328.1063.

Compound 1i: According to the general procedure, a mixture of aldehyde **5**, 4-chloro-2-fluoro-6-iodoaniline (**6i**; 79 mg, 0.29 mmol), DABCO (89 mg, 0.79 mmol) and $Pd(OAc)_2$ (3 mg, 0.013 mmol, 5 mol%) in DMF (2.0 mL) was heated at 85 °C for 19 h. The title compound (42 mg, 0.134 mmol, 51% over two steps) was obtained after flash chromatography (3:1) as a yellow solid; mp 132–135 °C. IR: 3386, 1474, 1457, 1435, 1363, 1297, 1221, 1085, 1071, 1061, 1008, 968, 890, 862, 855, 821, 812, 772, 746, 705 cm^{-1}. ^1H NMR [400 MHz, $(CD_3)_2CO$]: δ =10.56 (br s, 1 H, NH), 9.93 (br s, 1 H, NH), 7.61 (d, *J* = 7.6 Hz, 1 H, ArH), 7.43 (d, *J* = 2.0 Hz, 1 H, ArH), 7.38 (d, *J* = 8.3 Hz, 1 H, ArH), 7.30 (d, *J* = 1.9 Hz, 1 H, ArH), 7.14 (d, *J* = 2.2 Hz, 1 H, ArH), 7.09 (td, *J* = 7.6, 1.2, 1 H, ArH), 7.01 (td, *J* = 7.6, 1.0 Hz, 1 H), 6.93 (dd, *J* = 10.8, 1.7 Hz, 1 H, ArH), 3.15 (s, 4 H, 2 × CH_2). ^{13}C NMR [100 MHz, $(CD_3)_2CO$]: δ =150.0 (d, $J_{C–F}$ = 246.3 Hz, C), 137.8 (C), 132.9 (d, $J_{C–F}$ = 6.5 Hz, C), 128.6 (C), 125.7 (CH), 124.1 (C), 123.9 (d, $J_{C–F}$ = 8.6 Hz, C), 129.9 (CH), 122.0 (CH), 119.33 (CH), 119.31 (CH), 117.8 (d, $J_{C–F}$ = 5.9 Hz, C), 116.2 (C), 115.3 (d, $J_{C–F}$ = 3.2 Hz, CH), 112.2 (CH), 107.7 (d, $J_{C–F}$ = 20.4 Hz, CH), 26.9 (CH_2), 26.6 (CH_2). ESI-MS: *m*/*z* (%) = 335 (100) $[M + Na]^+$, 278 (23). ESI-HRMS: *m*/*z* $[M + Na]^+$ calcd for $[C_{18}H_{14}{}^{35}ClFN_2 + Na]^+$: 335.0722; found: 335.0734.

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(18) **1,2-Bis(3-indol-3-yl)ethane-1,2-dione (10):** To a mixture of **1a** (30 mg, 0.12 mmol) in THF–H_2O (3 mL, 9:1) at 0 °C was added DDQ (58 mg, 0.25 mmol) and the reaction mixture was stirred at r.t. for 2.5 h. A second portion of DDQ (58 mg, 0.25 mmol) was added and the reaction mixture stirred for a further 2.5 h. The mixture was poured onto a saturated solution of $NaHCO_3$ (20 mL) and extracted with EtOAc (20 mL). The organic extract was further washed with a saturated solution of $NaHCO_3$ (5 × 20 mL), dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel (hexanes–EtOAc, 1:1) gave the title compound (9 mg, 0.031 mmol, 27%) as an orange solid; mp 278–280 °C [Lit.[6a] 278–280 °C]. Spectroscopic data is consistent with the literature.[6a] IR: 3297, 1595, 1505, 1454, 1430, 1410, 1357, 1336, 1308, 1237, 1115, 1098, 1084, 1009, 874, 775, 757, 745, 732 cm^{-1}. ^1H NMR (400 MHz, DMSO-d_6): δ = 12.22 (s, 2 H, 2 × NH), 8.27 (m, 2 H, 2 × ArH), 8.22 (d, *J* = 2.8 Hz, 2 H, 2 × ArH), 7.54 (m, 2 H, 2 × ArH), 7.29 (m, 4 H, 4 × ArH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 188.8 (2 × C), 137.3 (2 × CH), 136.7 (2 × C), 125.6 (2 × C), 123.4 (2 × CH), 122.4 (2 × CH), 121.3 (2 × CH), 112.54 (2 × CH), 112.47 (2 × C). ESI-MS: *m*/*z* (%) = 311 (100) $[M + Na]^+$, 178 (36), 109 (9). ESI-HRMS: *m*/*z* $[M + Na]^+$ calcd for $[C_{18}H_{12}N_2O_2 + Na]^+$: 311.0791; found: 311.0787.

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