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SYNTHETIC APPROACHES TO 3,3'-BIINDOLYL AND 3,3'-BIINDAZOLYL DERIVATIVES

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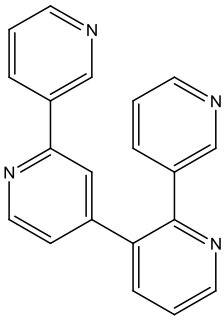
Abstract – In this paper new syntheses of 3,3'-biindolyl and 3,3'-biindazolyl derivatives are described. Formation of 3,3'-biindolyl derivatives by oxidative coupling of *N*-acetylindole with $TeCl_4$ gave a good yield, while attempt to use the same reaction conditions for synthesis of 3,3'-biindazolyl derivatives failed. However, conversion of 3-haloindazole derivatives to its trimethylstannane derivative, followed by palladium-catalyzed Stille cross-coupling reaction, resulted in formation of 3,3'-biindazolyl derivatives.

INTRODUCTION

Many naturally existing compounds include aromatic biheterocycles[1] as sub-units (Figure 1).

The tetra-pyridine derivative nemertelline **1** is illustrative. This molecule was originally isolated from the marine hoplonemertine worm.[2] This compound can be used as an antifouling agent for boats and other marine equipments.[3] Another interesting biheterocycle is the classical molecule indigo **2**, which is naturally obtained from plants of the genus *Indigofera*. It has a distinctive blue color and it is primarily used as a dye for cotton fabrics and blue jeans. Furthermore, indolocarbazole derivatives (*e.g.*, staurosporine **3**)[4] constitute a class of compounds with broad biological activities.[5] These 2,2'-biindole derivatives have shown potential in cancer treatment. Interest in these compounds has led to several attempts to produce them synthetically by diverse routes.



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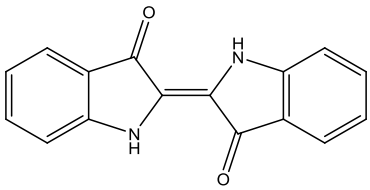

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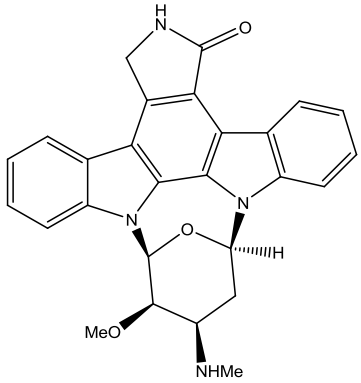

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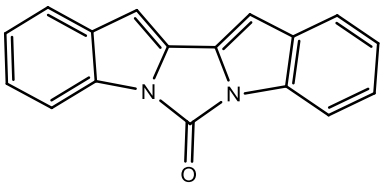
Figure 1

One of the most common uses of biheterocycles is as chelating ligands in organometallic chemistry. These biheterocycles have also been used as components in many large supermolecular species such as dendrimers, rotaxanes and catenanes. Although these types of compounds have proven useful in many different fields, detailed knowledge of many other biheterocycle derivatives are limited. This paper describes synthetic approaches to 3,3'-biindolyl and 3,3'-biindazolyl derivatives.

RESULTS AND DISCUSSION

Coupling (spontaneous or induced) via organotellurium compounds are known[6] in the literature. Furthermore, Clive[7] as reported facile couplings of benzyl halides (to bibenzyls) and allyl halides upon treatment with Te^{2-}. Another interesting oxidative coupling induced by $Pd(OAc)_2$ on indoles and *N*-acylindoles have earlier been reported.[8] For example coupling of *N*,*N*'-carbonylindole yielded compound **4** in a reasonable yield. Similar results have been obtained by Itahara[9] using related systems.



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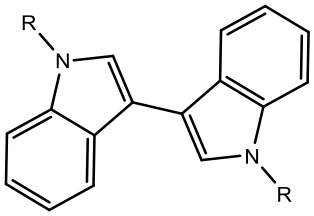
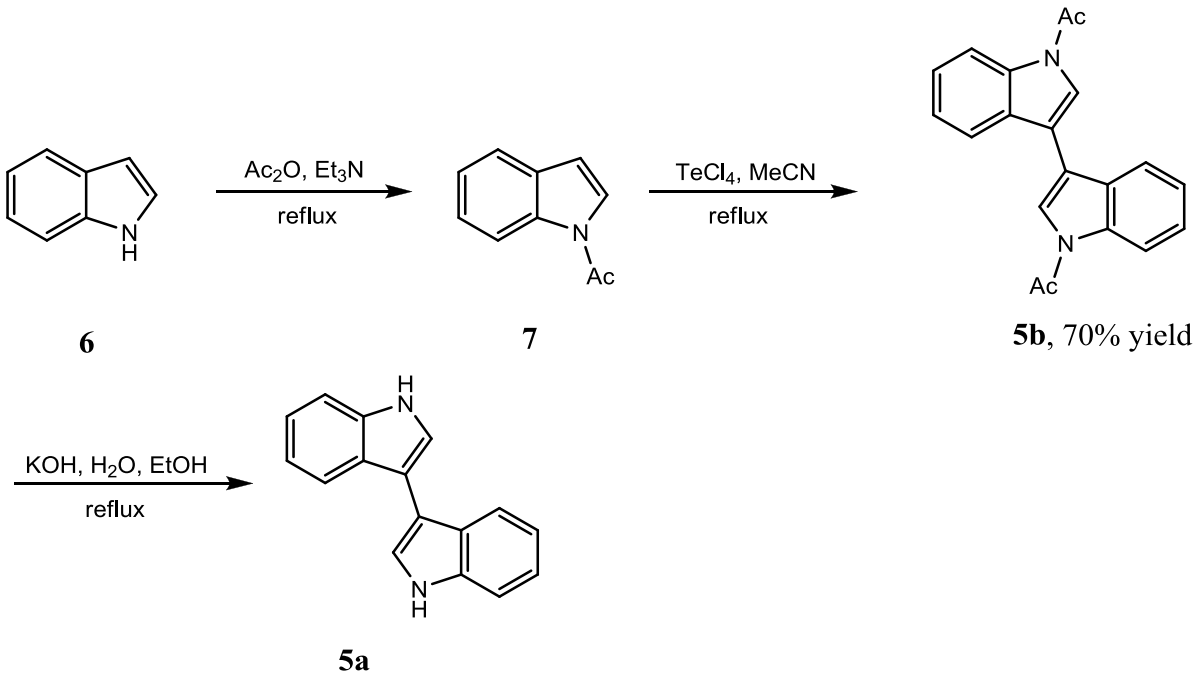


5a R=H
5b R=Ac
5c R=SO_2Ph

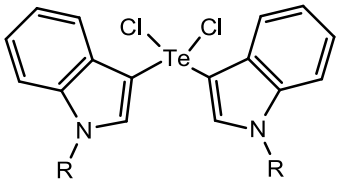
Figure 2

The 3,3'-biindolyl **5a** was first prepared by Gabriel *et al*. as early as in 1923[10] and since then, several approaches for the preparation of its derivatives have been reported.[1,11-15] Our initial attempts in this project was to investigate the possibility of synthesizing 3,3'-biindolyl derivatives **5** and in this context we contemplated a methodology based on oxidative coupling reaction of indole derivatives with $TeCl_4$. This general synthetic approach for the preparation of 3,3'-biindolyl **5** is summarized in Scheme 1.



Scheme 1

The interaction of $TeCl_4$ with *N*-acetylindole **7** readily afforded *N*,*N*'-diacetyl-3,3'-biindolyl **5b** in a good yield. Mild hydrolysis of **5b** delivered the well-known[12] and readily prepared compound 3,3'-biindolyl **5a**. Considering the relatively high price of $TeCl_4$ this procedure is suitable only for small scale preparations. *N*-Benzensulfonylindole did not similarly give the known[16] compound **5c**. It is not clear if **5b** was formed by a direct coupling or via an intermediate organotellurium compound such as di-*N*-acetyl-indolyl tellurium dichloride **8a**. Only a few indole derivatives, (*e.g.*, bis[*N*-(benzenesulfonyl)-2-indolyl] telluride[17] and bis(*N*-tosyl-2-indolyl) ditelluride[18]) containing tellurium have been published and repeated attempts now made to prepare **8a** or **8b** failed. It might be added that di(3-indolyl) ditelluride has earlier been prepared (unpublished results) in this laboratory in a low yield by treating indole with $TeCl_4$ in pyridine followed by a reductive work-up.



8a R=Ac
8b R=H

Figure 3

A logical extension of the presented results was to introduce *N*-acetylpyrrole, rather than *N*-acetylindole, as a reactant. Preliminary experiments using this reactant resulted in formation of *N*-acetylpolypyrroles **9**. We can therefore assume that polypyrrole derivatives **9** can be prepared by this procedure. Polypyrrole itself has been known since 1915.[19]

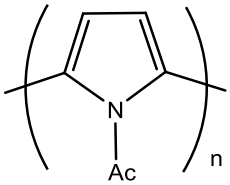


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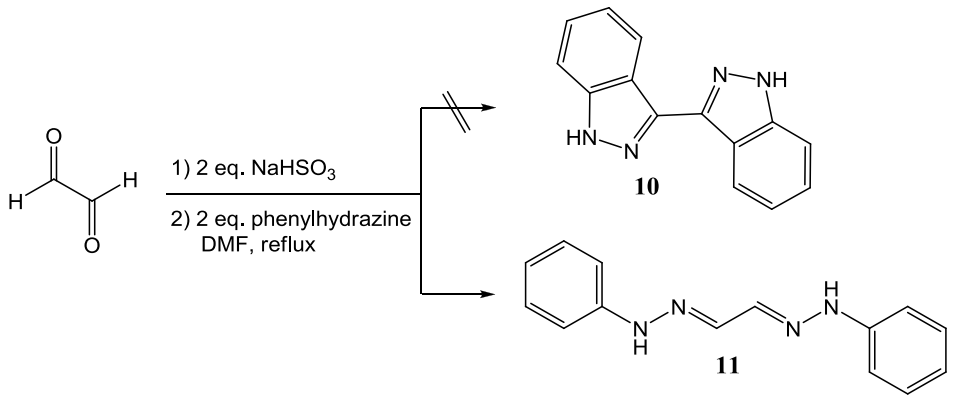
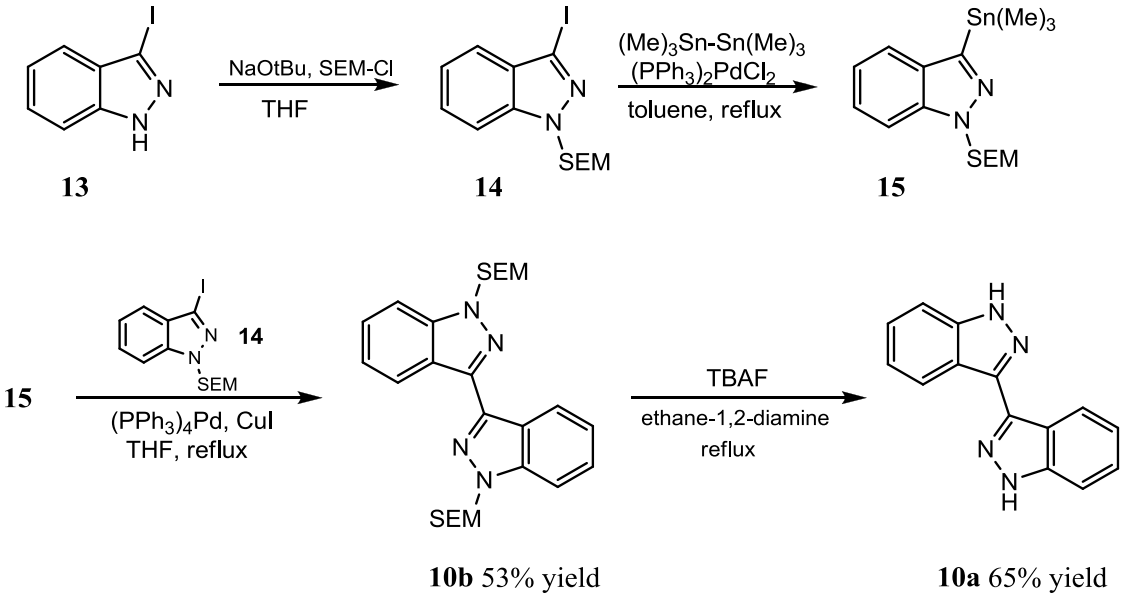
Figure 4

To explore the scope of the methodology, we also introduced this method on an azaindole ring system, namely indazole. Despite the fact that indazole is the 2-azabioisostere of indole, repeated attempts to synthesis of 3,3'-biindazolyl derivatives **10** via oxidative coupling with $TeCl_4$ failed. 3,3'-Biindazolyl **10a** was first prepared by Hill *et al*. as early as in 1971.[20] They reported two different routes for synthesis of this compound; dehydrogenation of 3,3-bi-tetrahydroindazole, made in two steps from cyclohexanone, and isomerization and cyclization of *N*,*N*'-dinitroso-2,2'-diacetamidobibenzyl. Unfortunately, both these approaches failed in our hands. Much later, Servi *et al*. claimed that reaction between the bisulfite adduct of benzaldehyde and phenylhydrazine, delivers 3,3'-biindazolyl **10a** in a high yield (Scheme 2).[21] However, since the spectral data (NMR and IR) and the melting point reported by Servi were in strong disagreement with the data reported by Hill, we repeated this reaction and found that the product was in fact the non-cyclic compound **11**. This known molecule[22-24] could also be made from glyoxal **12** and phenylhydrazine without use of sodium bisulfite.



Scheme 2

The Ullmann reaction also failed, when 3-iodoindazoles (N-substituted or not) were used with copper in DMF. Recently, isolation of protected indazolylboronic esters from haloindazoles and bis(pinacolato)diboron have been reported.[25] However, the only position that was not claimed was the 3-position of the indazole. Attempts to introduce boronic esters to 3-halo-indazole derivatives using the same conditions were unsuccessful. In contrast, conversion of 3-haloindazole derivatives to its trimethylstannane derivative, followed by palladium-catalyzed Stille cross-coupling reaction has been reported in a German patent.[26] Although tin compounds are not convenient to use because of high toxicity, they have become an asset to indazole chemistry. In the absence of other efficient synthetic routes for the synthesis of the 3,3-biindazolyl **10a**, we chose to prepare this compound via 3-(trimethylstannyl)indazole derivatives. The synthetic approach is summarized in Scheme 3.



Scheme 3

Thus, compound **13**[27] was treated with sodium *tert*-butoxide and 2-(trimethylsilanyl)-ethoxymethyl chloride (SEM-Cl) in THF to afford SEM protected 3-iodoindazole **14**.[25] Treatment of this molecule with hexamethylditin and a suitable palladium catalyst, delivered compound **15**. Further, using standard conditions for palladium catalyzed Stille coupling reaction between compound **15** and **14**, gave the desired product **10b** in accepyable yield. The SEM protected groups could easily be removed using standard basic conditions, TBAF in THF, which resulted in compound **10a** in a acceptable yield. It has recently been reported that when 3-iodoindazoles and methyl 2-(acetylamino)acrylate were used in palladium-catalyzed Heck cross-coupling reactions the biindazolyl derivatives (of type **10b**) were isolated as by-products in low yields.[28] However, since the color of the product and the melting point reported by Crestey *et al*. were in disagreement with our data, our product was therefore subjected to an X-ray analysis which gave conclusive evidence for structure **10b**. A Chem3D representation of the molecule is shown in Figure 5.

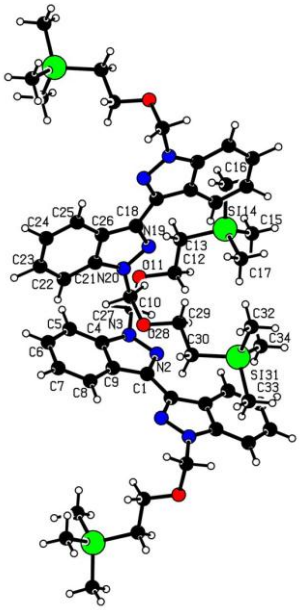


Figure 5. The crystal structure of 1,1´-bis[2-(trimethylsilanyl)etoxymethyl]-[3,3´]biindazolyl **10b**

In conclusion, the work described here presents synthesis of 3,3´-biindolyl derivatives via oxidative coupling induced by $TeCl_4$. However, attempts to achieving 3,3´-biindazolyl derivatives using $TeCl_4$ failed. In addition, the 3,3´-biindazolyl could be isolated using Stille coupling reaction and the structure of 1,1´-bis[2-(trimethylsilanyl)ethoxymethyl]-[3,3´]biindazolyl was confirmed by X-ray analysis.

EXPERIMENTAL

General experimental procedures

NMR Data were recorded on a Bruker DPX 300 instrument operating at 300.1 MHz for ^{1}H and 75.5 MHz for ^{13}C, respectively, using the residual solvent signal as reference. Assignments are based on standard ^{1}H, ATP, ^{13}C high power decoupling (HPDEC) and 1D NOE-DIFF experiments. IR spectra were acquired on a Thermo Nicolet Avatar 330 FT-IR instrument. Chromatographic separations were performed on silica gel 60 (40-63 µm). HRMS-determintions (FAB) were recorded by Einar Nilsson, University of Lund, Sweden. Elemental analyses were performed by LSM Lab, Uppsala, Sweden. Chemicals and solvents were obtained from commercial sources and used as received with the exception of THF, which was distilled from sodium and benzophenone and 1,4-dioxane and Et_2O, which were stored over sodium.

***N*-Acetylindole (7).**[29,30] Indole (35.1 g, 0.3 mol) in acetic anhydride (40 mL) and triethylamine (10 mL) was heated to reflux temperature for 8 h, whereupon the reaction mixture was concentrated and treated with water and Et_2O. The combined organic solvents were washed with a saturated solution of sodium hydrogencarbonate, dried with Na_2SO_4, filtered and evaporated. The crude product was purified by distillation at 153-154 ºC/15 torr (156 ºC/16 torr)[30] to yield **7** (40.9 g, 86%) as an oil. IR (neat) 1698, 1450, 1382, 1366, 1321, 1207, 932, 746 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.34 (d, *J*=7.8 Hz, 1H), 7.84 (d, *J*=3.5 Hz, 1H), 7.61 (d, *J*=7.8 Hz, 1H), 7.38-7.19 (m, 2H), 6.73 (d, *J*=3.5 Hz, 1H), 2.65 (s, 3H); ^{13}C NMR (DMSO-d_6) δ 169.6 (s), 134.9 (s), 130.3 (s), 127.2 (d), 124.5 (d), 123.4 (d), 120.9 (d), 115.9 (d), 108.2 (d), 23.8 (q).

***N,N*'-Diacetyl-3,3'-biindolyl (5b)** To a solution of *N*-acetylindole (2.0 g, 12.6 mmol) and MeCN (25 mL) was $TeCl_4$ (6.8 g, 25.1 mmol) added and the mixture heated to reflux for 2 h. The dark suspension was filtered thought a pad of celite twice and the remaining dark solution was left at rt overnight leading to precipitation of the product. This material was crystallized from MeCN to afford 2.8 g (70%) light green crystalline material, mp 225 °C; IR (neat) 1703, 1530, 1444, 1372, 1327, 1223, 944, 733 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.47 (d, *J*=7.4 Hz, 2H), 8.17 (s, 2H), 7.94 (d, *J*=7.4 Hz, 2H), 7.50-7.34 (m, 4H), 2.78 (s, 6H); ^{13}C NMR (DMSO-d_6) δ 169.7 (s), 135.3 (s), 128.8 (s), 125.3 (d), 124.6 (d), 123.8 (d), 120.3 (d), 116.1 (d), 113.4 (s), 24.0 (q). Anal. Calcd for $C_{20}H_{16}N_2O_2$: C, 75.93; H, 5.10; N, 8.86. Found: C, 75.89; H, 5.02, N, 8.76.

3,3'-Biindolyl (5a) mp 280-281 °C (lit. 284-286 °C)[11]; IR (neat) 3390, 1454, 1409, 1334, 1238, 1109, 1012, 736 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 11.15 (br. s, 1H), 7.78 (d, *J*=7.8 Hz, 1H), 7.63 (d, *J*=2.4 Hz, 1H), 7.45 (d, *J*=8.0 Hz, 1H), 7.19-7.11 (m, 1H), 7.10-7.02 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 136.4 (s), 126.0 (s), 121.8 (d), 121.2 (d), 119.6 (d), 118.8 (d), 111.5 (d), 109.7 (s).

3-Iodoindazole (13)[27] This compound was prepared from indazole (5.0 g, 42.3 mmol) according to ref.[27] The product was obtained as a yellow solid (8.7 g, 84%), mp 139-140 °C (lit. 141 °C)[27]; IR (neat) 3152, 3088, 2970, 2932, 1620, 1472, 1238, 1012 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 13.50 (br. s, 1H), 7.58-7.52 (m, 1H), 7.46-7.39 (m, 2H), 7.23-7.16 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 140.4 (s), 127.2 (d), 126.8 (s), 121.2

(d), 120.4 (d), 110.5 (d), 93.4 (s).

1-((2-Trimethylsilyl)ethoxy)methyl-3-iodo-1*H*-indazole (14)[27] To a solution of 3-iodoindazole (2 g, 8.2 mmol) in anhydrous THF (25 mL) at 0 °C under Ar-gas was NaO*t*Bu (0.95 g, 9.8 mmol) added. After stirring at 0 °C for 30 min, SEM-Cl (1.74 mL, 9.8 mmol) was added slowly. After complete addition, the mixture was stirred at 0 °C for 1 h and thereafter an additional hour at room temperature. The mixture was diluted with E*t*OAc and quenched with water. The layers were separated, and the organic layer was washed with brine, dried over $MgSO_4$, filtered, and concentrated. The residue was purified using column chromatography (gradient: 0-15% hexane/E*t*OAc) to afford **14** (1.9 g, 61%) as a pale yellow oil. IR (neat) 2951, 1614, 1459, 1315, 1247, 1076, 832, 742 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 7.75 (d, *J*=8.5 Hz, 1H), 7.57-7.42 (m, 2H), 7.27 (t, *J*=7.5 Hz, 1H), 5.75 (s, 2H), 3.57-3.45 (m, 2H), 0.84-0.73 (m, 2H), -0.12 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 140.2 (s), 128.2 (s), 127.8 (d), 122.1 (d), 120.9 (d), 110.3 (d), 94.7 (s), 76.8 (t), 65.7 (t), 17.1 (t), -1.4 (q).

1-((2-Trimethylsilyl)ethoxy)methyl-3-(trimethylstannyl)-1*H*-indazole (15) A mixture of **14** (0.8 g, 2.9 mmol), hexamethyldistannane (1.05 g, 3.2 mmol) and $(PPh_3)_2PdCl_2$ (41 mg, 0.06 mmol) in dry toluene (10 mL) was heated to reflux for 45 min under argon gas. The suspension was filtered through a layer of celite and removal of the solvent left a crude product, which was purified by column chromatography (hexane/E*t*OAc) to afford **15** (0.83 g, 70%) as an unstable solid. IR (*neat*) 2952, 1460, 1304, 1248, 1167, 1073, 833, 741 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.75 (d, *J*=8.2 Hz, 1H), 7.60 (d, *J*=8.2 Hz, 1H), 7.45-7.36 (m, 1H), 7.22-7.13 (m, 1H), 5.80 (s, 2H), 3.63-3.53 (m, 2H), 0.95-0.85 (m, 2H), 0.48 (s, with small side signals, 9H), -0.06 (s, 9H); ^{13}C NMR ($CDCl_3$) δ 148.9 (s), 139.9 (s), 132.8 (s), 126.3 (d), 122.1 (d), 120.7 (d), 109.7 (d), 77.3 (t), 66.3 (t), 17.8 (t), -1.4 (q), -8.8 (q).

1,1´-Bis[2-(trimethylsilanyl)ethoxymethyl][3,3´]biindazolyl (10b) A mixture of **15** (0.83 g, 2.03 mmol), **14** (0.61 g, 2.23 mmol), $(PPh_3)_4Pd$ (120 mg, 0.1 mmol) and CuI (40 mg, 0.2 mmol) in anhydrous THF (10 mL) was heated to reflux overnight under argon gas. The dark suspension was filtered thought a pad of celite and removal of the solvent left a crude product, which was purified by column chromatography (gradient: 0-15% hexane/E*t*OAc) to afford **10b** (0.53 g, 53%) as a white solid, mp 90.5-92.2 °C (lit. 82-84 °C)[28]; IR (neat) 2952, 1612, 1463, 1297, 1247, 1073, 831, 742 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 8.47 (d, *J*=8.1 Hz, 1H), 7.83 (d, *J*=8.1 Hz, 1H), 7.58-7.50 (m, 1H), 7.37-7.29 (m, 1H), 5.91 (s, 2H), 3.66 (t, *J*=8.0 Hz, 2H), 0.86 (t, *J*=8.0 Hz, 2H), -0.13 (s, 9H); ^{13}C NMR (DMSO-d_6) δ 140.6 (s), 138.9 (s), 127.2 (d), 122.4 (d), 121.9 (d), 121.9 (s), 110.2 (d), 76.8 (t), 65.8 (t), 17.1 (t), -1.5 (q).

3,3'-Biindazolyl (10a)[20] To a mixture of **10b** (0.2 g, 0.4 mmol) and ethane-1,2-diamine (0.27 mL, 4.0 mmol) was TBAF (1M in THF, 8.0 mL, 8.0 mmol) added and the mixture was refluxed overnight. The reaction mixture was diluted with E*t*OAc (30 mL) and washed with H_2O (2 x 40 mL) and brine (30 mL).

The organic layer was dried ($MgSO_4$), filtered and concentrated in vacuo. The residue was purified using column chromatography (hexane/E*t*OAc) to afford **10a** (61 mg, 65%) as a yellow solid mp 330-332 °C (lit. 328-330 °C).[20] ^{1}H NMR (DMSO-d_6) δ 13.27 (br. s, 1H), 8.45 (d, *J*=8.1 Hz, 1H), 7.61 (d, *J*=8.4 Hz, 1H), 7.48-7.38 (m, 1H), 7.28-7.20 (m, 1H); ^{13}C NMR (DMSO-d_6) δ 140.8 (s), 139.5 (s), 126.4 (d), 122.3 (d), 120.9 (d), 120.6 (s), 110.2 (d).

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