

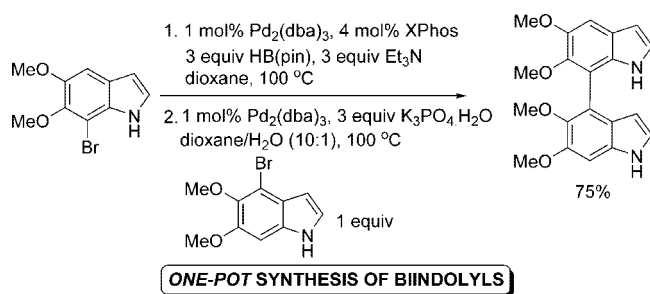
Synthesis of Biindolyls via Palladium-Catalyzed Reactions

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An unprecedented synthesis of a range of high value homo- and heterobiindolyls is presented. The one-pot Miyaura borylation and subsequent Suzuki–Miyaura coupling sequence allows for the construction of the highly sterically congested C–C bond between two bromoindoles in modest to good overall yields.

Indoles are undoubtedly one of the most important structural classes of compounds found in nature. The recurring prominence in bioactive natural products as well as commercial drugs has earned this structural motif a place as a “privileged structure” in drug discovery.¹ Indole oligomers such as biindolyls may also serve as the backbone of chiral chelating diphosphine ligands, which have played an important role in asymmetric catalysis (i.e., BINAP),² making use of their atropisomeric biaryl scaffold.³ An interesting natural polymer that is derived from indolic subunits is eumelanin. Eumelanin is a key brown/black pigment, whose central role in man is believed to be photoprotection.⁴ While it is well-established that the monomeric units

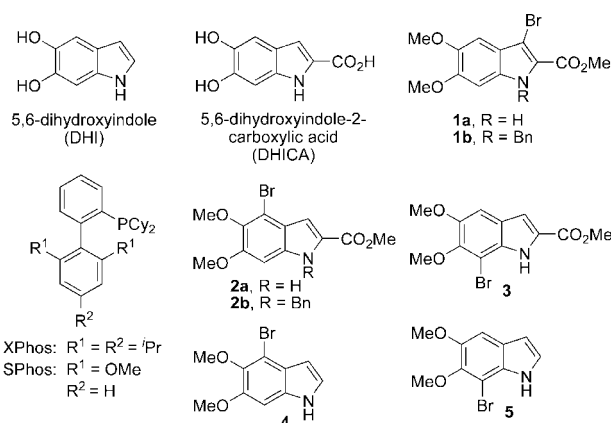


FIGURE 1. Indoles and ligands relevant to this study.

of eumelanin are 5,6-dihydroxyindole (DHI) and 5,6-dihydroxyindole-2-carboxylic acid (DHICA) (Figure 1), the precise structure of the natural material has not been elucidated. However, some insight has been gained from the study of a series of DHI and DHICA biindolyls.⁵ Given the importance of biindolyls, we sought to develop methodology for their construction.

We envisioned that the Pd-catalyzed Suzuki–Miyaura coupling could be a powerful method for the construction of different C–C bonds between indole units.⁶ The requisite boronic acid/ester coupling partner could be prepared in several ways. Methods involving transmetalation between aryl magnesium or lithium intermediates and boron compounds were avoided due to the extreme basic conditions that could lead to unwanted side reactions.⁷ A recent advance in the preparation of indolyl boronates is Ir-catalyzed C–H borylation.^{8,9} However, this method is limited to C2 and C7 functionalization. An alternative, mild method is via the Miyaura palladium catalyzed

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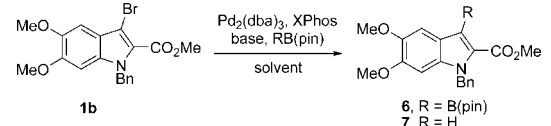
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TABLE 1. Screening Conditions for Borylation of Indoles^a


entry	bases	RB(pin)	solvents	conv (%) ^b	6 (%) ^b	7 (%) ^b
1	Et ₃ N	HB(pin)	toluene	100	74	8
2 ^c	Et ₃ N	HB(pin)	toluene	100	60	11
3 ^d	Et ₃ N	HB(pin)	toluene	16	0	13
4 ^e	Et ₃ N	HB(pin)	toluene	63	40	0
5	Et ₃ N	HB(pin)	dioxane	100	84	11
6	K ₃ PO ₄	HB(pin)	dioxane	31	10	16
7	K ₃ PO ₄	B ₂ (pin) ₂	dioxane	29	22	5
8	KOAc	B ₂ (pin) ₂	dioxane	9	0	0

^a **1b** (0.1 M), Pd₂(dba)₃ (1 mol %), XPhos (4 mol %), base (0.3 M), RB(pin) (0.3 M), 110 °C, 14 h. ^b Determined by GC with naphthalene as an internal standard. ^c SPhos was used instead of XPhos. ^d No ligand was used. ^e Reaction was run at rt.

borylation of bromoindoles and this was considered appropriate for application in the current study.¹⁰

Buchwald and co-workers recently reported that the combination of their dialkylphosphinobiphenyl ligands (e.g., XPhos and SPhos) (Figure 1) and a suitable Pd source efficiently catalyzed the coupling of hindered arylboronic acids and aryl halides.¹¹ The substrate scope was later extended to include heteroaryl halides and heteroaryl boronic acids/esters.¹² We have found that highly congested biindolyis (homo- and heterodimers) can also be conveniently prepared from bromoindoles via sequential borylation and Suzuki–Miyaura cross-coupling.^{13,14} Herein, we report the first directed synthesis of the positional isomers of the homo- and heterodimers of DHI and DHICA derivatives **1–5** (Figure 1).¹⁵ Our study demonstrates the synthesis of diverse, sterically hindered biindolyl systems and for the first time, verifies the feasibility of constructing protected DHI and DHICA oligomers via a transition metal mediated cross-coupling protocol. Furthermore, this work showcases the application of Pd-catalyzed reactions in forging the aryl–aryl σ -linkage of highly substituted biaryl compounds (i.e., those containing four

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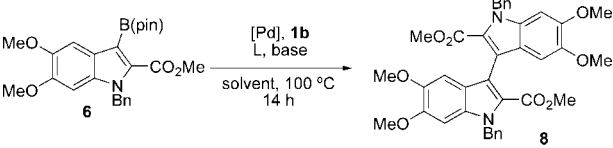
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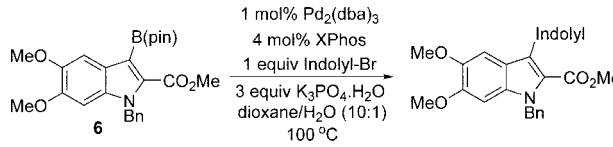
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TABLE 2. Screening Conditions for Suzuki–Miyaura Coupling To Prepare Biindolyis^a


entry	L	bases	solvents	conv (%) ^b	8 (%) ^{b,c}
1	XPhos	K ₃ PO ₄ ·H ₂ O	dioxane/H ₂ O (10:1)	100	67
2	XPhos	K ₃ PO ₄	dioxane/H ₂ O (10:1)	100	61
3	XPhos	Cs ₂ CO ₃	dioxane/H ₂ O (10:1)	100	67
4	XPhos	Et ₃ N	dioxane/H ₂ O (10:1)	64	35
5	XPhos	K ₃ PO ₄	dioxane	100	trace
6	SPhos	K ₃ PO ₄ ·H ₂ O	dioxane/H ₂ O (10:1)	94	53
7 ^d	SPhos	K ₃ PO ₄ ·H ₂ O	dioxane/H ₂ O (10:1)	100	48
8	XPhos	K ₃ PO ₄ ·H ₂ O	toluene/H ₂ O (10:1)	100	9
9	XPhos	K ₃ PO ₄ ·H ₂ O	DMF/H ₂ O (10:1)	100	11

^a **1b** (0.1 M), **6** (0.1 M), Pd₂(dba)₃ (1 mol %), L (4 mol %), base (0.3 M). ^b Determined by ¹H NMR with ferrocene as an internal standard. ^c The mass balance could be accounted for by the formation of **7**. ^d 2 mol % Pd(OAc)₂ was used instead of Pd₂(dba)₃.

TABLE 3. Suzuki–Miyaura Coupling of Boronate **6** with Bromoindoles^a


Entry	Bromoindoles	Biindolyis	Yields (%)
1	1b	8	60
2	2b	9	85
3	5	10	73

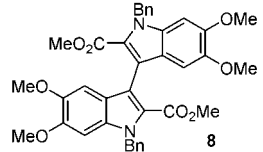
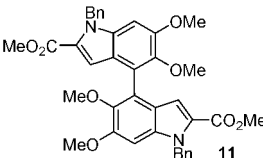
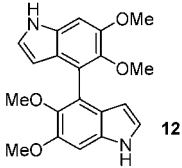
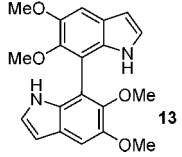
^a **6** (0.1 M), Indolyl-Br (0.1 M), Pd₂(dba)₃ (1 mol %), XPhos (4 mol %), K₃PO₄·H₂O (0.3 M), dioxane/H₂O (10:1), 100 °C.

ortho substituents), a construction that has been a persistent focus of interest for synthetic chemists.^{2,16}

At the outset, we explored the synthesis of the requisite indolyl boronate coupling partners via a Miyaura borylation reaction. With use of indole **1b** as a representative precursor for borylation, different reaction parameters, including Pd sources, ligands, borylating reagents, bases, and solvents, were screened (Table 1). Running the reaction in toluene in the presence of triethylamine (3 equiv), pinacolborane (3 equiv), and catalytic amounts of Pd₂(dba)₃ and XPhos resulted in a good

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TABLE 4. Dimerization of Bromoindoles^a

Entry	Bromoindoles	Biindolyis	Yields (%)
1	1b		49
2	2b		71
3 ^b	4		54
4	5		60

^a Indolyl¹-Br (0.1 M), Pd₂(dba)₃ (1 mol %), XPhos (4 mol %), K₃PO₄·H₂O (0.3 M), B₂(pin)₂ (0.05 M), dioxane/H₂O (10:1), 100 °C.
^b 2 mol % Pd₂(dba)₃ and 8 mol % XPhos were employed.

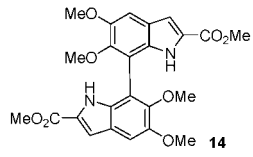
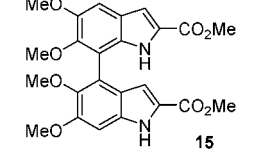
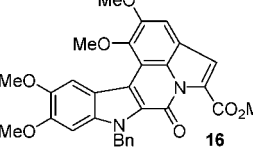
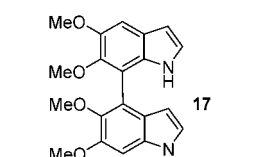
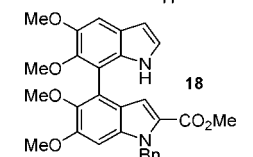
yield of the desired borylated indole **6** with concomitant formation of a small amount of the undesired product **7**, resulting from hydrodehalogenation of **1b** (entry 1). Under this condition (entry 1), bromoindole **1b** was converted to **6** in 74% GC yield and in 75% isolated yield. Reactions run in the presence of SPhos as ligand (entry 2), without any ligand (entry 3), or at room temperature (entry 4) all resulted in lower yields of **6**. A higher yield of **6** was obtained when dioxane was employed as solvent instead of toluene (entry 5 vs entry 1). Conditions reported by Buchwald et al.^{14e} for borylation of aryl chlorides only resulted in low yields of **6** (entries 7 and 8).

The pinacolboronates derived from other indoles, such as **2b** and **5**, can also be synthesized with this method as confirmed by ESI-LC/MS and ¹H NMR spectroscopy. However, attempts to isolate these boronates met with little success as they readily decomposed during column chromatography on silica gel.

Conditions for the Suzuki–Miyaura coupling of **1b** and **6** were then investigated (Table 2).^{11,12} The best yield of **8** was obtained when the reaction was run in a mixture of dioxane/H₂O (10:1) in the presence of 1 mol % of Pd₂(dba)₃, 4 mol % of XPhos, and 3 equiv of K₃PO₄·H₂O (entry 1). The use of anhydrous K₃PO₄ (entry 2) or Cs₂CO₃ (entry 3) instead of K₃PO₄·H₂O did not affect the reaction yields to any significant extent. The use of triethylamine (entry 4) or strictly anhydrous conditions (entry 5) resulted in the formation of **7** as the major product and low yields of **8**. The use of SPhos instead of XPhos (entry 6) or Pd(OAc)₂ instead of Pd₂(dba)₃ (entry 7) gave lower yields of **8**. Dioxane/water as solvent was superior to toluene/water (entry 8) and DMF/water mixtures (entry 9). The latter two solvent mixtures resulted in extensive formation of undesired **7** at the expense of dimer **8**.

Under our optimized Suzuki–Miyaura coupling conditions, boronate **6** was coupled with bromides **1b**, **2b**, and **5** to afford

TABLE 5. Sequential One-Pot Two-Step Sequence Leading to Homo- and Heterocoupled Biindolyis^a

Entry	Bromoindoles	Biindolyis	Yields (%)
1	Indolyl ¹ -Br = 3 Indolyl ² -Br = 3		75
2	Indolyl ¹ -Br = 2a Indolyl ² -Br = 3		37
3	Indolyl ¹ -Br = 1b Indolyl ² -Br = 3		55
4	Indolyl ¹ -Br = 5 Indolyl ² -Br = 4		75
5	Indolyl ¹ -Br = 5 Indolyl ² -Br = 2b		72

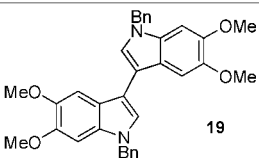
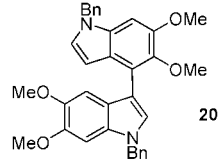

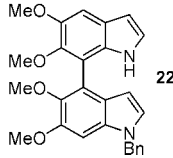
^a (1) Indolyl¹-Br (0.1 M), Pd₂(dba)₃ (1 mol %), XPhos (4 mol %), Et₃N (0.3M), HB(pin) (0.3 M), dioxane, 100 °C; (2) Pd₂(dba)₃ (1 mol %), Indolyl²-Br (0.1 M), K₃PO₄·H₂O (0.3 M), dioxane/H₂O (10:1), 100 °C.

dimers **8**, **9**, and **10** in 60%, 85%, and 73% yield, respectively (Table 3). The pentacyclic adduct **10** resulted from an in situ intramolecular lactamization event postformation of the heterocoupled dimer.¹⁷

Gratifyingly, the homocoupled products could be prepared via a one-pot, tandem borylation/Suzuki–Miyaura coupling reaction in dioxane/H₂O (10:1) (Table 4).^{14e} Modest to good overall yields of homodimers were obtained. Dimerization of the 5,6-dimethoxyindole carboxylates **1b** and **2b** gave rise to dimers **8** (49%) and **11** (71%) (entries 1 and 2), respectively. The one-pot procedure could be applied to the direct synthesis of dimers **12** and **13**, starting from the respective 5,6-dimethoxyindoles **4** and **5** (entries 3 and 4). A higher catalyst loading (2 mol %) was required for >90% conversion of indole **4** to the desired dimer. In contrast, **1a**, **2a**, and **3** almost exclusively gave rise to hydrodehalogenated products as observed by GC-MS analysis of the reaction mixtures. It is possible that the presence of the electron-withdrawing ester functional

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TABLE 6. Synthesis of DHI-Dimers via Saponification^a and Decarboxylation^b Sequence

Entry	Bromoindoles	Biindolyls	Yields (%)
1	8		61
2	9		45
3	11		71
4	18		59

^a LiOH (15 equiv), THF/H₂O/MeOH (3:1:1). ^b Microwave, 250 °C.

group in these nonprotected indoles facilitates the competing hydrodehalogenation reaction.¹⁸

To avoid the need to isolate indolyl boronates, a one-pot sequential coupling procedure was developed for the construction of homo- and heterodimers (Table 5). For example, at the completion of the borylation reaction of bromoindole **3** in dioxane (entry 1), water (10% v/v) was added followed by bromoindole **3** (1 equiv), K₃PO₄·H₂O (3 equiv), and Pd₂(dba)₃ (1 mol %). After the reaction, purification by chromatography afforded the homodimer **14** in 75% yield over two steps (entry 1). It should be noted that decomposition of Pd(0) as black precipitate was observed during the first step (borylation). Thus, a new batch of Pd(0) was needed in the Suzuki coupling step. In a similar manner, mixed dimers **15** and **16** were obtained in 37% and 55% yield (entries 2 and 3). The sequential addition of **5** and **4** led to the dimethoxyindole dimer **17** in 75% yield over two steps (entry 4). A mixed dimethoxyindole–dimethoxyindole carboxylate dimer **18** was also prepared in 72% yield over 2 steps (entry 5). These examples demonstrate that *N*-protecting groups can be avoided under these coupling conditions.

An alternative method to prepare dimethoxyindole homodimers would be via saponification followed by decarboxylation of dimethoxyindole carboxylate homodimers or mixed dimethoxyindole–dimethoxyindole carboxylate dimers. To demonstrate this, compounds **19**, **20**, **21**, and **22** were prepared in modest yields from dimers **8**, **9**, **11**, and **18**, respectively (Table 6).

In conclusion, the methodology reported herein has allowed, for the first time, homo- and heterobiindolyls (i.e., positional permutations of dimers of DHI and DHICA derivatives **1–5**)

to be readily prepared from bromoindoles. Significantly, highly sterically hindered biindolyls could be obtained conveniently in modest to good yields with or without *N*-protecting groups. Applications of this methodology in the preparation of biologically interesting compounds as well as unique biindolyl ligands for catalysis are ongoing in our laboratories and the results will be reported in due course.

Experimental Section

General Procedure for the Dimerization of Bromoindoles.

An oven-dried 10-mL Schlenk flask was charged with bromoindole, bis(pinacolato)diboron (0.05 equiv), K₃PO₄·H₂O (3 equiv), Pd₂(dba)₃ (1 mol %), and XPhos (4 mol %). The flask was evacuated and refilled with argon three times. Dioxane and degassed water were added and the flask was equipped with a reflux condenser. The reaction mixture was heated at reflux overnight. Purification on silica gel column chromatography afforded the desired coupling product.

Methyl 3-(2-(Methoxycarbonyl)-1-benzyl-5,6-dimethoxy-1H-indol-3-yl)-1-benzyl-5,6-dimethoxy-1H-indole-2-carboxylate, 8. ¹H NMR (400 MHz, acetone-*d*₆, ppm) δ 7.32–7.28 (m, 4H), 7.23–7.21 (m, 2H), 7.16–7.13 (m, 6H), 6.73 (s, 2H), 6.07 (d, 2H, 16 Hz), 5.85 (d, 2H, 16 Hz), 3.85 (s, 6H), 3.64 (s, 6H), 3.42 (s, 6H); ¹³C {¹H} NMR (100 MHz, acetone-*d*₆, ppm) δ 163.4, 151.5, 147.5, 140.1, 134.8, 129.3, 127.8, 127.2, 124.6, 120.7, 118.3, 103.3, 94.4, 56.3, 56.2, 51.3, 48.6; IR (cm⁻¹, CH₂Cl₂ film) 2988, 2949, 1697; LC-HRMS calcd for C₃₈H₃₆N₂O₈ ([M + Na]⁺) 671.23639, obsd 671.23496; mp 205.8–206.2 °C. Anal. Calcd for C₃₈H₃₆N₂O₈: C, 70.36; H, 5.59; N, 4.32. Found: C, 70.41; H, 5.67; N, 4.25.

General Procedure for Sequential One-Pot Two-Step Coupling Leading to Homo- and Heterocoupled Biindolyls. An oven-dried 10-mL Schlenk flask was charged with the first bromoindole, Pd₂(dba)₃ (1 mol %), and XPhos (4 mol %). The flask was evacuated and refilled with argon three times. Dioxane, triethylamine (3 equiv), and pinacolborane (3 equiv) were added and the flask was equipped with a reflux condenser. The reaction mixture was heated at reflux for 2 h. After the reaction mixture was cooled to rt, degassed water (10% v/v) was added. A solution of the second bromoindole (1 equiv) in dioxane was added followed by Pd₂(dba)₃ (1 mol %) and K₃PO₄·H₂O (3 equiv). The reaction mixture was heated at reflux overnight. Purification on silica gel column chromatography afforded the desired coupling product.

Dimethyl 5,5',6,6'-Tetramethoxy-1H,1'H-7,7'-biindole-2,2'-dicarboxylate, 14. ¹H NMR (400 MHz, CD₂Cl₂, ppm) δ 9.37 (s, 2H), 7.21 (s, 2H), 7.01 (d, 2H, 2.0 Hz), 3.97 (s, 6H), 3.64 (s, 6H), 3.55 (s, 6H); ¹³C {¹H} NMR (100 MHz, CD₂Cl₂, ppm) δ 162.5, 149.7, 147.7, 131.7, 127.5, 123.3, 111.8, 109.2, 103.8, 61.4, 56.2, 52.0; IR (cm⁻¹, CH₂Cl₂ film) 3260, 2925, 1685; LC-HRMS calcd for C₂₄H₂₄N₂O₈ ([M + Na]⁺) 491.14249, obsd 491.14124; mp 222.2–223.0 °C. Anal. Calcd for C₂₄H₂₄N₂O₈: C, 61.53; H, 5.16; N, 5.98. Found: C, 61.48; H, 5.28; N, 5.94.

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Supporting Information Available: Experimental procedures and ¹H, ¹³C NMR, and IR data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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