Diindolylamine Preparation and Stability Investigations

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ABSTRACT: The synthesis of diindolylamines via the palladium-catalyzed cross-coupling of aminoidoles and bromoidoles has been investigated, and efficient coupling conditions using BrettPhos, Pd(OAc)$_2$, K$_2$CO$_3$, and tBuOH have been identified. The diindolylamines were found to be unstable in ambient conditions. Blocking the reactive 3-position of the bromoidole coupling partner with a tert-butyl group results in a diindolylamine with improved air stability. NMR, CV, and UV–vis studies on an asymmetrically substituted 3-tert-butyl-3'H-diindolylamine indicate that the instability of the diindolylamine substrates is likely due to oxidative oligomerization. Literature conditions used for the preparation of 3-tert-butylindoles afforded only the indole tetramer. The presence of water during the alkylation reaction was identified as the cause of the formation of the tetramer. Replacing hygroscopic tBuOH with nonhygroscopic tBuCl as the alkylating reagent provided access to 7-bromo-3-tert-butyl indole.

INTRODUCTION

Diindolylamine structures wherein the indolyl moieties are connected through an amine substituent on the benzene ring (Scheme 1, compound 1) are of interest in drug discovery and organic electronics. They have been investigated on their own and as part of larger molecules for uses in medicinal therapy areas, such as oncology and Alzheimer’s disease, and as hole transport agents and organic electroluminescent materials (Figure 1). During our investigations into the design of new chromophores for metal complexation, we required a synthesis of structural motifs of this type, specifically derivatives of 1 in which $R = R' = H$.

We envisioned the preparation of the diindolylamines via palladium-catalyzed cross-coupling Buchwald–Hartwig amination of the appropriate bromoidole and aminoidole compounds (Scheme 1). The position of the halide and amine on the indole partners would dictate the connectivity of the indole halves in the diindolylamines, and because many bromo- and aminoidoles are commercially available or are relatively easy to access synthetically, a wide variety of derivatives could potentially be accessed by this methodology. Reported examples for the preparation of diindolylamine-type structures that contain synthetic procedures and specific experimental details are limited. In cases where $R' = H$, the preparation of the diindolyl structures via Buchwald–Hartwig amination (BHA) using two indole coupling partners has been reported, albeit uncommonly. Almost all the literature examples involve the coupling of indoles where the indole nitrogen on at least one, and usually both, coupling partners has been protected. In cases where $R' = alkyl$ or aryl, synthesis is most often performed by first forming a secondary amine 3, which consists of an indole and the alkyl or aryl group, and then attaching the second indole ring via cross-coupling of the secondary amine and a bromoidole.

We ideally wished to perform the BHA reaction on unprotected indoles, thereby avoiding extra protection and deprotection steps. However, the lack of examples using unprotected indoles could indicate that protection of the indole nitrogen on one or both coupling partners is necessary for reasons of selectivity and reactivity. Indoles contain two reactive sites, the indole N–H and the C-3 position, that can compete with the intended reaction between the aniline moiety and the aryl bromide. This presents a potential selectivity problem during the coupling reaction. Literature reports of unwanted C–C coupling at the C-3 exist, but it tends to occur under specific combinations of catalyst and ligand and appears to be most problematic with highly hindered (o-substituted) anilines.

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since many examples of this type of reaction are found in the literature. There are also potential issues inherent in the structure of the diindolylamine products where \( R = H \). The structure of these compounds makes them prospective ligands (Figure 2). Under basic conditions in the presence of a metal, i.e., the BHA reaction environment, the diindolylamines may form coordination complexes with the metal, effectively poisoning the BHA catalyst and stalling the reaction.

Because the nature of the coupling partners, the precatalyst, ligand, solvent, and base can all vastly affect the outcome of the Buchwald–Hartwig amination reaction, a wide variety of catalysts, ligands, and reaction conditions have been developed for this transformation. While this introduces challenges in the selection of reagents and conditions for previously unreported coupling partners, it has given a broad scope to the reaction, and we felt that a judicious choice of the metal catalyst and ligands could effectively control the selectivity of the reaction with unprotected indoles and could also minimize coordination of the diindolyl product.

### RESULTS AND DISCUSSION

To evaluate whether protection of the indoles was necessary for the success of the proposed synthetic methodology, BHA reactions involving both two unprotected indoles and one protected and one unprotected indole were investigated. Because of the commercial availability of the starting bromo and aminoindoles, the 6,6′- and 7,7′-diindolyl systems (Table 1 compounds 8a, 8b, 9a, and 9b, respectively) were chosen as the target molecules for this exploratory chemistry.

#### Protection of Bromoindoles

Protection of the bromoindole was implemented in preference to the aminoindole because of potential difficulties in selectively protecting the indole nitrogen in the presence of an aniline nitrogen. A tert-butyl silyl ether protecting group was chosen because its stability under basic conditions and heat might allow the protected derivatives to remain intact during the Buchwald–Hartwig coupling reaction.

### Table 1. Identification of Reaction Conditions for the Formation of Diindolylamines using Buchwald–Hartwig Amination

| entry | NH₂ | Br | precatalyst | ligand | base   | solvent | products* |
|-------|-----|----|-------------|--------|--------|---------|-----------|
| 1     | 7   | 5a | Pd(dppf)Cl₂| dppf   | NaO₂Bu | 1,4-dioxane | N.R.      |
| 2     | 7   | 5a | Pd(OAc)₃   | XPhos  | Co₂(CO)₆ | t-BuOH | N.R.      |
| 3     | 7   | 5a | Pd₂(dba)₂  | XPhos  | NaO₂Bu | t-BuOH | N.R.      |
| 4     | 7   | 5a | Pd(OAc)₃   | XPhos  | K₂CO₃  | t-BuOH | 9a (incomplete conversion) |
| 5     | 6   | 4b | Pd(OAc)₃   | XPhos  | K₂CO₃  | t-BuOH | 8b        |
| 6     | 6   | 4b | Pd(OAc)₃   | XPhos  | KO₂Bu | t-BuOH | 4a major  |
| 7     | 6   | 4b | Pd(OAc)₃   | XPhos  | K₂CO₃ /Bt₃N| t-BuOH | 8a trace and unknown |
| 8     | 6   | 4b | Pd(OAc)₃   | BrettPhos | K₂CO₃  | t-BuOH | 8a        |
| 9     | 7   | 5a | Pd(OAc)₃   | BrettPhos | K₂CO₃  | t-BuOH | 9a major  |

*N.R., no reaction.
Treatment of 6-bromoindole 4a with NaH, followed by tert-butylimethylsilyl chloride (TBDMSCl), gave the desired compound 4b in a 55% yield after 15 min at room temperature (Scheme 2). Longer reaction times and the addition of extra NaH were explored to try to drive the reaction to completion; however, these attempts resulted in lower yields. Monitoring the reaction using TLC showed that the product was formed and then decomposed back to the starting material, implying that unreacted H\(^+\) deprotected the silyl ether in a manner similar to F\(^-\).\(^{22}\) The formation of the TBDMS-protected 7-bromoindole 5b was also successful; however, the reaction required overnight reflux and still resulted in an incomplete reaction. The sluggish reaction was attributed to the added steric hindrance imparted by the 7-position substituent.

**Buchwald–Hartwig Amination Conditions for Diindolylamine Synthesis.** Exploration of the BHA reaction conditions was initiated using the unprotected 7-substituted indoles. Two promising sets of conditions were identified on the basis of literature precedence. The first combination was based on a reported example of BHA coupling using unprotected 7-aminooindole.\(^{23}\) The conditions use a Josiphos-type (Pd(dppf)Cl\(_2\)) ligand—catalyst system, NaOtBu, and dioxane. This ligand—metal combination is rarely reported for indolyl N–H coupling; when it is reported for indolyl N–H coupling, the base is a weak inorganic base such as Cs\(_2\)CO\(_3\) or K\(_2\)CO\(_3\),\(^{24}\) which could indicate that selective coupling is possible for this system when two unprotected indoles are used. The second set of conditions was based on reported examples of diindolyl formation using protected indoles and on the publications of Buchwald et al. Reported metal—ligand systems for diindolyl formation are palladium and either XPhos\(^3\)—5 or XantPhos.\(^3\) We also considered BrettPhos as a potentially a better ligand choice as it is known to be useful for BHA with primary amines.\(^25\) Buchwald et al. have developed ligands other than BrettPhos to perform the arylation of indole N–H,\(^{26}\) which suggested that the BrettPhos–Pd ligand—metal system might be selective for the desired aniline coupling on the unprotected indoles.

**Table 1** summarizes the initial exploration of the BHA reaction conditions. Despite the literature precedence for the BHA of 7-aminooindole 7 using Pd(dppf)Cl\(_2\), these BHA conditions resulted in no observed reaction (entry 1). Likewise, reactions using either Pd(OAc)\(_2\) or Pd(dbta)\(_2\) as the metal source, Xphos as the ligand, and either Cs\(_2\)CO\(_3\) or NaOtBu also resulted in the recovery of starting materials (entry 2 and 3, respectively). However, upon changing the base to K\(_2\)CO\(_3\), a slow, incomplete reaction was observed (entry 4). Using the same conditions with 6-aminooindole 6 and TBDMS-protected 6-bromoindole 4b in a 55% yield, an incomplete reaction was observed (entry 5). The ratio of coupled product to deprotected bromide varied with the number of equivalents of ligand used. Higher ligand loadings resulted in a larger ratio of coupled product to deprotected bromide. However, because ligand loadings of 0.3 equiv (relative to the aminoindole) still produced mixtures of products, an alternative was necessary. Different bases, including KOtBu and triethylamine, were explored but did not yield better outcomes (entries 6 and 7, respectively).

When 6-aminooindole and 6-bromo-1-TBDMS indole 4b were submitted to a reaction with Pd(OAc)\(_2\), BrettPhos, and K\(_2\)CO\(_3\) in refluxing iBuOH, the products of the reaction were found to be deprotected bromide 4a and the unprotected 6,6′-aminodiindole 8a (entry 8). This suggested that when BrettPhos was used as the ligand, coupling of the unprotected bromoindole and unprotected aminooindole might be occurring. When these reaction conditions were used on the unprotected 7-amino and 7-bromoindoles, consumption of the starting material was observed, and the major product of the reaction (by TLC) was the desired 7,7′-aminodiindole 9a (entry 9).

Identification of the aminodiindole products during reaction optimization was done primarily using \(^1\)H NMR spectroscopy because the products were isolated in small amounts, which was initially attributed to the small scale of the reactions and low yields resulting from incomplete reactions and the formation of mixtures of products. However, upon scale-up of the reactions, it became clear that instability of the aminodiindoles themselves was also an issue. During workup and purification, the disappearance of the desired product was noted by TLC, and a dark precipitate formed. The isolated desired product was also observed to change from a soluble colorless compound to a dark insoluble compound over minutes to days (depending on the substitution pattern of the diindole system and whether the indole was protected). The instability was greatest in solution, which prevented full characterization of these compounds.

We hypothesized that oxidation of the diindolylamine compounds to a diindolylmethene-type structure (Figure 3) might be occurring in the presence of air. Because of their extended conjugation, the oxidized compounds could adopt a planar structure, causing them to be insoluble. To prevent oxidation upon characterization, the completed reaction was transferred to a glovebox following solvent removal on the Schlenk line. NMR characterization of the crude reaction mixture was done using this method, yet even under these rigorously air-free conditions the formation of a dark precipitate was observed. The need for column chromatography to purify the diindolylamines 8a, 8b, and 9a meant that isolation of clean material for characterization was not possible.

**Preparation of 3-tert-Butyl Indole.** The insoluble nature of the bluish-black precipitate that formed following the palladium-catalyzed cross-coupling of 7-bromoindole and 7-aminooindole prompted consideration of solubilizing substituents that could be directly installed on the indole starting materials. tert-Butyl groups were selected because they could be introduced to the ring by electrophilic aromatic substitution. Electrophilic aromatic substitution at the 3-
position of the indole ring is favored electronically, but competing substitution at the 2-position and 1-position can be problematic. Many protocols for the Friedel–Crafts alkylation of indoles suffer from poor yields due to the formation of mixtures of products and consequently difficult chromatographic separations. However, the selective installation of tert-butyl groups at the 3-position of indoles using unconventional Friedel–Crafts conditions has been reported. The described alkylation employs K-10 montmorillonite clay and tert-butanol under solvent-free microwave conditions and was reported to afford isolated yields of 47–73% for a variety of indoles.

However, when we submitted 7-bromoindole 5a to these reaction conditions, the desired 3-tert-butyl-substituted product was isolated only as a very minor product. The major product of the reaction was a relatively insoluble white powder with a 1H NMR spectrum that was incompatible with the structure of the desired compound. The spectrum displayed two distinct indole N–H signals, indicating the presence of chemically inequivalent indole rings. The spectrum also exhibited a total of seven aromatic signals and no tert-butyl signals. Taken together, this presented the possibility that a dimerization or oligomerization reaction was occurring.

Further evidence for oligomerization was obtained from the 13C NMR spectra, which showed a total of 16 signals, all aromatic, and from COSY and TOCSY NMR spectroscopy, which elucidated two sets of coupled protons and revealed that one indole ring contained a hydrogen at the C2-position while the other indole ring did not. This pointed to a more complex structure than a simple dimer, and single-crystal X-ray analysis revealed the compound to be the indole tetramer 10 (Figure 4 and Tables S1–S3).

![Figure 4. Chemical structure (left) and X-ray crystal structure (right) of the 7-bromoindole tetramer 10. Ellipsoids are represented at the 50% probability level. Hydrogen atoms (except N–H hydrogens) have been removed for clarity.](image)

While compounds similar to 10 have occasionally been reported, in one case as the product of a traditional Friedel-Crafts alkylation, the literature did not provide insight into the cause of the tetramer formation under our conditions. Since the only byproducts in the original paper describing the alkylation using tert-butanol were those resulting from N-alkylation of the indole, the experimental conditions were scrutinized for potential differences between the literature and the preparative conditions. One possible discrepancy was the introduction of water to the reaction during the weighing and addition of tert-butanol. The tert-butanol was highly deliquescent when handled in our ambient conditions, but no mention of hygroscopic behavior was made in the reported procedure.

Three reactions were performed to test the effect of water on the reaction. In the first, no alkylation reagent was used and water was added to the reaction. In the second, tert-butanol was used and additional water was added (21.7 equiv). In the third, tert-butanol was replaced with 2-chloro-2-methylpropane (a nonhygroscopic alkyl source). The outcomes of all three reactions indicated that water was involved in the oligomerization reaction. In the reaction with added water but no alkylation agent, the only product observed was the tetramer (isolated in a 30% yield). Likewise, only the tetramer was formed during the reaction using tert-butanol and added water. In contrast, in the reaction using 2-chloro-2-methylpropane, the desired 3-substituted indole 11 was the major product, and no tetramer was observed. While these studies implicate water in the formation of the tetramer, it is also possible that adventitious oxygen may be at least partially involved, as per previous reports.

The alkylation using 2-chloro-2-methylpropane was then modified to minimize the formation of di- and trialkylated byproducts that were observed when 2-chloro-2-methylpropane was used. The dialkylated compound was tentatively assigned to 3,5-di-tert-butylindoline on the basis of 1H and COSY NMR spectra. The structure of the trialkylated compound was not identified. The formation of these compounds was likely a consequence of a number of coinciding factors, including high temperatures, higher than stoichiometric equivalents of the alkylation agent, and the increased electrophilicity of the indole upon the introduction of the first tert-butyl substituent. Lowering the reaction temperature by 20 °C and decreasing the reaction time eliminated the formation of the trialkylated product and reduced the amount of dialkylated product created. Surprisingly, lowering the amount of 2-chloro-2-methylpropane appeared to have an effect opposite what was desired, as the amount of dialkylated product increased from 7% to 15% (by NMR) when the number of equivalents of 2-chloro-2-methylpropane was lowered from 1.5 to 1.0. Under the optimized conditions, the desired 3-tert-butyl-7-bromoindole was isolated in a 36% yield following column chromatography (Scheme 3).

![Scheme 3. Optimized Conditions for the Formation of 7-Bromo-3-tert-butylindole 11](image)

**Synthesis of 7,7′-Amino-3-tert-butylidindole 12 and Stability Investigations.** The previously established palladium-catalyzed cross-coupling conditions for the 6,6′-diindolylamine and unsubstituted 7,7′-diindolylamine systems were applied to the reaction of 7-aminoindole with 7-bromo-3-tert-butylindole (Scheme 4). This provided one major product, which was isolated after column chromatography in 59% yield as a slightly grayish oil that solidified upon exposure to
Scheme 4. Palladium-Catalyzed Cross-Coupling Reaction of 7 and 11 to Form 7,7′-Amino-3-tert-butyl-diindole 12

![Scheme 4](image)

deuterated chloroform. The 1H NMR spectrum of the material was consistent with the desired compound 12, but the 13C spectrum appeared to lack one aromatic quaternary carbon signal. DEPT135, HSQC, and HMBC NMR experiments were performed to verify the structure. These experiments revealed overlapping 13C carbon signals for the 7 and 7′ carbon atoms and confirmed the assignment of the product as the 7,7′-amino-3-tert-butyl-diindole 12.

In contrast to the unsubstituted diindolylamine compounds 8a, 8b, 9a, and 9b, the tert-butyl substituted compound 12 exhibited substantially improved stability in air. In the solid phase, the compound was stable for several months at room temperature or below. However, as an oil or in solution the compound completely decomposed in days to weeks, even when stored at subzero Celsius temperatures. The instability of the compound in solution prevented the acquisition of a single-crystal X-ray structure of diindolylamine 12, as attempts to grow crystals invariably led to decomposition.

With the diindolylamine 12 in hand, the nature of the diindolylamine instability was explored. The suspected two electron, two proton oxidation to form the diindolylmethene 13 was investigated using DDQ as the oxidant. The addition of DDQ to a solution of 12 at room temperature immediately afforded a dark precipitate, and TLC indicated the complete consumption of the starting material within 10 min. The precipitate was isolated as a black solid, which dissolved in d6-acetone to give a dark blue solution. The product structure was not able to be confirmed by 1H NMR spectroscopy as the spectrum displayed very broad peaks, which could be indicative of a number of phenomena, including (i) aggregation, (ii) slow tautomerization of diindolylmethene 13 on the NMR time scale (Figure 5), or (iii) formation of oligomers during the oxidation reaction. Mass spectroscopy was also inconclusive, providing no [M + H] peak but instead a possible [2M + H] peak. In order to elucidate whether tautomerization was occurring, attempts were made to N-alkylate or metalate the presumed 13. However, treating the precipitate with sodium hydride and iodomethane or with triethylamine and either PtCl2(PhCN)2 or PtCl2(COD)2 resulted in mixtures of unidentified products.

Oxidation of 12 using Ag2O in dichloromethane resulted in a much slower reaction (consumption of starting material in five days) than with DDQ and yielded a qualitatively more soluble black product. The 1H NMR spectrum of the product was again very broad, and UV–visible-NIR absorption spectra of the products of the two oxidation reactions (DDQ and Ag2O) were obtained for comparative identification (Figure 6).

![Figure 6](image)

The absorption spectra of the two products are demonstrably different, although they share similar features. Both absorb most strongly in the UV, and have a broad, relatively shapeless absorption band across the rest of the spectral region examined. These features, along with the trailing absorption past 1100 nm, suggest that oligomerization is the outcome of the oxidation of 12. The differences in the absorption spectra could be the result of the two oxidation reactions generating mixtures of oligomers that have different product distributions.

Cyclic voltammetry experiments on 7,7′-amino-3-tert-butyl-diindole 12 provided further evidence that oligomerization was occurring during oxidation. The diindolylamine 12 has an irreversible one-electron oxidation at a relatively mild potential of 0.165 V vs Fc/Fc+ and a multielectron irreversible oxidation at 0.99–1.29 V vs Fc/Fc+ (Figure 7). When the switching potential was set lower than the potential of the second oxidation, the first oxidation wave was still irreversible. The first oxidation presumably happens with the loss of a proton, and repeated cycling showed no change in the shape, indicating that oligomerization is not an issue in the first oxidation (Figure 8). The second oxidation does show

![Figure 7](image)

Figure 5. Possible tautomerization of asymmetric diindolylmethene 13.

Figure 6. UV–vis-NIR absorption spectra of the products of the oxidation of 12 with DDQ (dashed black line) and Ag2O (solid blue line).

Figure 7. Cyclic voltammogram of 7,7′-amino-3-tert-butyl-diindole 12. The concentration of the analyte in dichloromethane is ~1 mM. The standard is Fc/Fc+, the electrolyte is 0.1 M Bu4NPF6, and the scan rate is 100 mV s⁻¹.

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and 5 sites on the indoles) should be considered when the substituents to block reactive sites on the rings (namely the 3 be necessary for similar compounds, and the consideration of toward oxidative oligomerization inherent in these structures. chemists wishing to prepare and use diindolyl compounds of electron-donating group (an amine) as a substituent. Thus, is not surprising. Indoles are already generally electron rich being less prone to oligomerization than diindolylamines corresponding 7,7′-amino-3-tert-butyl-diindole 12 have been attributed to oxidation-induced oligomerization based on evidence from 1H NMR spectroscopy, UV–visible absorption spectroscopy, and cyclic voltammetry. The introduction of a tert-butyl group at the C3 position of the bromoindole was proven to be synthetically viable and resulted in the corresponding 7,7′-amino-3-tert-butyl diindolylamine 12 is less prone to oligomerization than diindolylamines without substituents at the reactive sites.

In retrospect, the reactive nature of the diindolyl compounds is not surprising. Indoles are already generally electron rich compounds, and the diindolyl structure places a powerful electron-donating group (an amine) as a substituent. Thus, chemists wishing to prepare and use diindolyl compounds of the type described herein should be aware of the tendency toward oxidative oligomerization inherent in these structures. Rigorous air-free reaction, workup, and storage conditions may be necessary for similar compounds, and the consideration of substituents to block reactive sites on the rings (namely the 3 and 5 sites on the indoles) should be considered when the design of the final compounds allows such substitution.

■ METHODS

General Methods. The reagents used were commercially available. Commercially available reagents were used as received with the exception of tert-butanol, which was dried and stored over 4 Å molecular sieves. Reactions under an inert atmosphere were performed using a Schlenck manifold, equipment, and techniques unless otherwise indicated. Concentration of liquids was accomplished by rotary evaporation unless stated otherwise. 1H NMR and 13C NMR were recorded at ambient temperature at frequencies of 500, 360, or 300 and 125, 90, or 75 MHz, respectively, unless otherwise noted. The data are reported as follows: proton multiplicities (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent), coupling constants, and integration. Microanalyses were performed by Canadian Microanalytical Services Ltd., Vancouver, BC, Canada. Mass spectrometry was performed by the UBC Mass Spectrometry Center. Melting points are reported uncorrected. Flash chromatography was performed using the indicated solvent system on Caledon Laboratories silica gel (SiO2) 60 (70–230 mesh) or Alfa Aesar neutral activated aluminum oxide (Al2O3), Brockman grade 1, 58 Å (60 mesh). Infrared spectra were recorded using a PerkinElmer Spectrum One instrument. Cyclic voltammetry (CV) experiments were performed with a Bioanalytical Systems CV50 voltammetric analyzer. CV experiments were performed using a three-electrode setup consisting of a glassy carbon working electrode, a platinum electrode, and a silver quasi-reference electrode. Ferrocene was used as an internal reference. The electrolyte (tetraethylammonium hexafluorophosphate) was obtained from a commercial supplier and used as received. Ground-state absorption spectra were obtained using an Agilent 8453 UV–vis spectrophotometer.

Synthesis. 6-Bromo-1-tert-butyl(dimethyl)silyl indole (4b). Tetrahydrofuran (6 mL) and 6-bromoindole (250 mg, 1.3 mmol) were added to a round-bottom flask under ambient conditions. NaH (60% in mineral oil, 60 mg, 1.5 mmol) was added in portions, resulting in a clear, reddish-orange mixture which was aged for ten minutes. Tert-butyl(dimethyl)silyl chloride (211 mg, 1.4 mmol) was added and the reaction immediately became cloudy and yellow. After 15 min, the reaction was quenched with water, followed by ethyl acetate. The mixture was transferred to a separatory funnel, and the organic layer was washed twice with water. The organic layer was dried over anhydrous sodium sulfate, decanted, and concentrated to a faintly brown oil. Column chromatography using silica gel (0.5 in. × 8 in.) and 1:4 ethyl acetate/hexanes afforded the desired compound as a white solid (220 mg, 55%). 1H NMR (300 MHz, CDCl3) δ 7.63 (s, 1H), 7.47 (d, J = 8.3 Hz, 1H), 7.21 (dd, J = 8.4, 1.7 Hz, 1H), 7.15 (d, J = 3.2 Hz, 1H), 6.78 (dd, J = 3.2, 0.8 Hz, 1H), 0.93 (s, 9H), 0.60 (s, 6H). 13C NMR (90 MHz, CDCl3) δ 141.9, 131.6, 130.2, 123.0, 121.7, 116.6, 115.0, 104.8, 26.2, 19.4; −40.0; IR (solid-ATR) 2927, 2855, 1147, 803, 789 cm−1; HRMS (ESI-TOF) m/z [M + H]+ calcd for C16H23BrNsi4 310.0627.

7-Bromo-1-tert-butyl(dimethyl)silyl indole (5b). Tetrahydrofuran (5 mL) and 7-bromoindole (250 mg, 1.3 mmol) were added to a round-bottom flask under N2. The homogeneous solution was cooled to 0 C in an ice–water bath, and NaH (60% in mineral oil, 62 mg, 1.6 mmol) was added in portions. The reaction mixture was aged for 10 min, then tert-butyl(dimethyl)silyl chloride (211 mg, 1.4 mmol) was added to the mixture and the ice bath was removed. After 4 h, only a trace amount of product was observed by TLC. The reaction was heated to reflux and aged overnight. The reaction was cooled to room temperature before water was added,
followed by dichloromethane. The organic layer was washed twice with water, dried over anhydrous sodium sulfate, decanted, and concentrated to a reddish oil. Column chromatography using silica gel (0.5 in. × 8 in.) and 1:4 ethyl acetate/hexanes gave the desired compound as a pale yellow oil (105 mg, 24%). $^1$H NMR (300 MHz, CDCl$_3$) δ 7.55 (dd, $J = 7.8, 1.2$ Hz, 1H), 7.39−7.37 (m, 2H), 6.95 (t, $J = 7.7$ Hz, 1H), 6.63 (d, $J = 3.4$ Hz, 1H), 0.98 (s, 9H), 0.72 (s, 6H).

**Di(1H-indol-6-yl)amine (8a).** Brett-Phos (8 mg, 0.015 mmol), Pd(OAc)$_2$ (1.5 mg, 0.007 mmol), and tert-butanol ($≈$1 mL) were added to a Schlenk flask. The reaction was sealed with a rubber septum and stirred with N$_2$ for 4 min. The reaction vessel was sealed with a rubber septum, then placed in an approximately 110 °C sand bath for 3 min until the reaction became dark brown and homogeneous. The reaction was removed from the sand bath and 6-bromo-1-tert-butyldimethylsilyl-6-indolyl-6-amine (40 mg, 0.13 mmol), 6-aminoindole (20 mg, 0.075 mmol), and potassium carbonate (20 mg, 0.145 mmol) were added under a steady N$_2$ stream. The reaction mixture was stirred and a heterogeneous mixture was stirred and filtered, and the filtrate was concentrated by rotary evaporation. Column chromatography using silica gel and 1:4 ethyl acetate/hexanes afforded the desired compound as a viscous oil. Because the isolated compound decomposed rapidly, the compound was not fully characterized. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.93 (s, br, 2H), 7.52 (d, $J = 8.4$ Hz, 2H), 7.13 (d, $J = 0.8$ Hz, 2H), 5.09 (dd, $J = 2.8, 2.4$ Hz, 2H), 6.90 (dd, $J = 8.4, 1.9$ Hz, 2H), 6.48 (m, 2H), 5.68 (s, br, 1H).

**1H-Indol-N-(1-tert-butyl(dimethyl)silyl-6-indolyl)-6-amine (8b).** X-Phos (12 mg, 0.03 mmol), Pd(OAc)$_2$ (2.0 mg, 0.01 mmol), and tert-butanol ($≈$3 mL) were added to a Schlenk flask. The reaction was sealed with a rubber septum, then evacuated and backfilled with N$_2$ 4 times. The reaction was placed in an approximately 110 °C sand bath for 3 min until the reaction became yellow and homogeneous. The reaction was removed from the sand bath and 6-bromoindole (13 mg, 0.065 mmol), 6-aminoindole (10 mg, 0.075 mmol), and potassium carbonate (20 mg, 0.145 mmol) were added under a steady N$_2$ stream. The reaction was carefully evacuated and backfilled with N$_2$ 3 times. The side arm tap was closed, and the septum and tap were parafilmmed in place. The reaction was placed in the 110 °C sand bath and aged overnight. The reaction vessel was removed from the sand bath, and the mixture was diluted with ethyl acetate, filtered, and concentrated using rotary evaporation. Column chromatography using silica gel (0.25 in. × 7 in.) and 1:4 ethyl acetate/hexanes, followed by 100% ethyl acetate, followed by dichloromethane/hexanes, followed by 100% ethyl acetate, afforded the desired compound as a viscous gray oil. Because the isolated compound decomposed rapidly, the compound was not fully characterized. $^1$H NMR (300 MHz, CDCl$_3$) δ 7.9 (s, br, 2H), 7.5 (d, $J = 8.4$ Hz, 2H), 7.3 (d, $J = 2.8$ Hz, 2H), 6.9 (d, $J = 2.4$ Hz, 2H), 6.48 (m, 2H), 5.68 (s, br, 1H).

**Di(1H-indol-6-yl)amine (9a).** Brett-Phos (8 mg, 0.015 mmol), Pd(OAc)$_2$ (1.5 mg, 0.007 mmol) and tert-butanol ($≈$1.5 mL) were added to a Schlenk flask. The reaction was sealed with a rubber septum and evacuated and backfilled with N$_2$ four times. The flask was placed in an approximately 110 °C sand bath for 3 min until the reaction became reddish-brown and homogeneous. The flask was removed from the sand bath and 7-bromoindole (13 mg, 0.065 mmol), 7-aminoindole (10 mg, 0.075 mmol), and potassium carbonate (20 mg, 0.145 mmol) were added under a steady N$_2$ stream. The reaction was carefully evacuated and backfilled with N$_2$ 3 times. The side arm tap was closed, and the septum and tap were parafilmmed in place. The reaction was placed in the 110 °C sand bath and aged overnight. The reaction was removed from the sand bath, was diluted with ethyl acetate, filtered, and concentrated using rotary evaporation. Column chromatography using silica gel and 1:4:1 ethyl acetate/hexanes/aceton took behind the desired compound as a viscous white solid, (30 mg, 30%). $^1$H NMR (500 MHz, d$_6$-acetone) δ 10.35 (s, 2H), 10.29 (br s, 2H), 7.35 (d, $J = 7.9$ Hz, 2H), 7.32 (d, $J = 7.6$ Hz, 2H), 7.21 (d, $J = 7.5$ Hz, 2H), 7.12−7.11 (m, 4H), 6.92 (t, $J = 7.8$ Hz, 2H), 6.69 (t, $J = 7.8$ Hz, 2H); $^{13}$C NMR (125 MHz, d$_6$-acetone) δ 136.1, 135.5, 133.7, 132.3, 128.4, 126.4, 124.6, 121.43, 121.36, 120.1, 119.6, 110.5, 108.7, 104.9, 104.1; IR (KBr) 3414, 3369, 2921, 1718 (br), 1433, 1314, 1205, 777, 742 cm$^{-1}$; HRMS (ESI-TOF) m/z [M − H]$^+$ calcd for C$_9$H$_7$Br$_2$N$_4$: 772.8187, found 772.8201.

**7-Bromo-3-tert-butylindole (11).** Dichloromethane (10 mL) and 7-bromoindole (1.00 g, 5.1 mmol) were added to a round-bottom flask. The solution was mixed until homogeneous. K-10 montmorillonite clay (254 mg), and water (0.1 mL) was added, the solution was thoroughly mixed and then concentrated until no dichloromethane remained. The reaction was microwaved on high power for 10 min. Then, another 0.1 mL of water was added, and the reaction was microwaved for another 5 min. The reaction was allowed to cool to room temperature. Dichloromethane was added, the heterogeneous mixture was stirred and filtered. The filtrate was concentrated to dryness. Treatment of the crude product with a mixture of dichloromethane and hexanes removed a colored oil, leaving behind the desired compound as a white solid, (30 mg, 30%). $^1$H NMR (500 MHz, d$_6$-acetone) δ 10.35 (s, 2H), 10.29 (br s, 2H), 7.35 (d, $J = 7.9$ Hz, 2H), 7.32 (d, $J = 7.6$ Hz, 2H), 7.21 (d, $J = 7.5$ Hz, 2H), 7.12−7.11 (m, 4H), 6.92 (t, $J = 7.8$ Hz, 2H), (6.69 (t, $J = 7.8$ Hz, 2H); $^{13}$C NMR (125 MHz, d$_6$-acetone) δ 136.1, 135.5, 133.7, 132.3, 128.4, 126.4, 124.6, 121.43, 121.36, 120.1, 119.6, 110.5, 108.7, 104.9, 104.1; IR (KBr) 3414, 3369, 2921, 1718 (br), 1433, 1314, 1205, 777, 742 cm$^{-1}$; HRMS (ESI-TOF) m/z [M − H]$^+$ calcd for C$_9$H$_7$Br$_2$N$_4$: 772.8187, found 772.8201.

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TOF) m/z [M – H]– calc for C_{20}H_{22}N_{3} 304.1814, found 304.1811.

ASSOCIATED CONTENT

Supporting Information
The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.1c06289.

NMR spectra of numbered compounds, X-ray crystallographic data for compound 10, and cyclic voltammetry of compound 12 (PDF)

Indole tetramer 10 (CIF)

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Notes
The authors declare no competing financial interest.

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