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Diindolylamine Preparation and Stability Investigations

Geneviève N. Boice, Brian O. Patrick, and Robin G. Hicks*

Cite This: *ACS Omega* 2022, 7, 5197−5205

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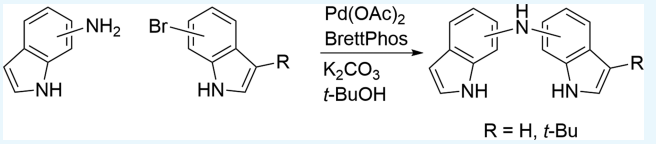
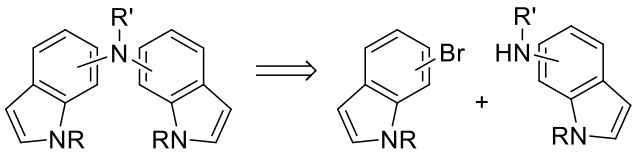
ABSTRACT: The synthesis of diindolylamines via the palladium-catalyzed cross-coupling of aminoindoles and bromoindoles has been investigated, and efficient coupling conditions using BrettPhos, $Pd(OAc)_2$, K_2CO_3, and tBuOH have been identified. The diindolylamines were found to be unstable in ambient conditions. Blocking the reactive 3-position of the bromoindole 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 *t*BuOH with nonhygroscopic *t*BuCl 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[1−3] and Alzheimer's disease,[4,5] and as hole transport agents[6] and organic electroluminescent materials (Figure 1).[7−10] 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.

Scheme 1. General Retrosynthetic Plan for the Synthesis of Diindolylamines 1



1 **2** **3**

We envisioned the preparation of the diindolylamines via palladium-catalyzed cross-coupling Buchwald−Hartwig amination of the appropriate bromoindole and aminoindole 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 aminoindoles 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.[4,5] 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 bromoindole.[7,11]

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.[12,13] 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.[14] C−N coupling between the aryl bromide and the indole N−H is of greater concern,

Received: November 8, 2021
Accepted: December 16, 2021
Published: February 4, 2022

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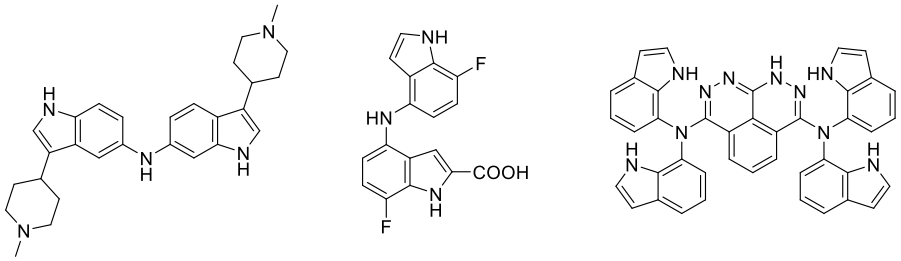


Figure 1. Examples of diindolyl amine-containing structures investigated for medicinal therapies and electroluminescent devices.

since many examples of this type of reaction are found in the literature.[15] There are also potential issues inherent in the structure of the diindolylamine products **1** where R = H. The structure of these compounds makes them prospective ligands (Figure 2). Under basic conditions in the presence of a metal,

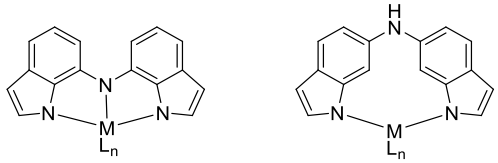


Figure 2. Examples of diindolylamine structures that can potentially serve as ligands for metal complexation.

i.e., the BHA reaction environment, the diindolylamines may form coordination complexes with the metal, effectively poisoning the BHA catalyst and stalling the reaction.

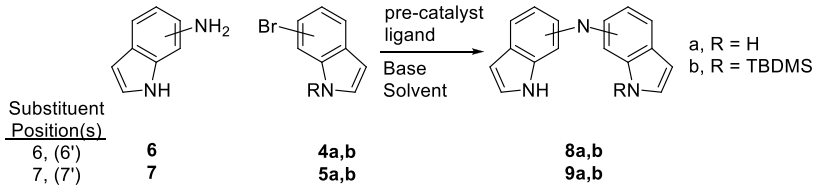
Because the nature of the coupling partners, the precatalyst, ligand, solvent, and base can all vastly affect the outcome of the Buchwald–Hartwig amination reaction, a wide variety of catalysts, ligands, and reaction conditions have been developed for this transformation.[15−19] While this introduces challenges in the selection of reagents and conditions for previously unreported coupling partners, it has given a broad scope to the reaction,[20,21] 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



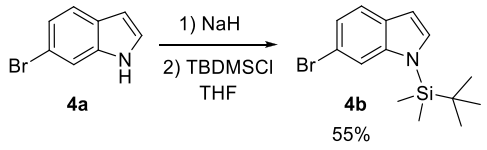
	reaction conditions						
	indole		catalyst				
entry	NH_2	Br	precatalyst	ligand	base	solvent	products[a]
1	**7**	**5a**	$Pd(dppf)Cl_2$	dppf	NaO*t*Bu	1,4-dioxane	N.R.
2	**7**	**5a**	$Pd(OAc)_2$	XPhos	Cs_2CO_3	*t*-BuOH	N.R.
3	**7**	**5a**	$Pd_2(dba)_2$	XPhos	NaO*t*Bu	*t*-BuOH	N.R.
4	**7**	**5a**	$Pd(OAc)_2$	XPhos	K_2CO_3	*t*-BuOH	**9a** (incomplete conversion)
5	**6**	**4b**	$Pd(OAc)_2$	XPhos	K_2CO_3	*t*-BuOH	**8b** **4a**
6	**6**	**4b**	$Pd(OAc)_2$	XPhos	KO*t*Bu	*t*-BuOH	**4a** major **8b** trace
7	**6**	**4b**	$Pd(OAc)_2$	XPhos	K_2CO_3/Et_3N	*t*-BuOH	**8a** trace and unknown
8	**6**	**4b**	$Pd(OAc)_2$	BrettPhos	K_2CO_3	*t*-BuOH	**8a** **4a**
9	**7**	**5a**	$Pd(OAc)_2$	BrettPhos	K_2CO_3	*t*-BuOH	**9a** major

[a]N.R., no reaction.

https://doi.org/10.1021/acsomega.1c06289
ACS Omega 2022, 7, 5197−5205

Treatment of 6-bromoindole **4a** with NaH, followed by *tert*-butyldimethylsilyl 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

Scheme 2. Conditions for the TBDMS Protection of 6-Bromoindole 4a



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-aminoindole.[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_2CO_3 or K_2CO_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 X-Phos[3−5] or XantPhos.[3] We also considered BrettPhos as potentially a better ligand choice as it is known to be useful for BHA with primary anilines.[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-aminoindole **7** using $Pd(dppf)Cl_2$, these BHA conditions resulted in no observed reaction (entry 1). Likewise, reactions using either $Pd(OAc)_2$ or $Pd(dba)_2$ as the metal source, Xphos as the ligand, and either Cs_2CO_3 or NaO*t*Bu also resulted in the recovery of starting materials (entry 2 and 3, respectively). However, upon changing the base to K_2CO_3, a slow, incomplete reaction was observed (entry 4). Using the same conditions with 6-aminoindole **6** and TBDMS-protected 6-bromoindole **4b** resulted in formation of the desired product along with deprotection of the 6-bromoindole **4b** (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 KO*t*Bu and triethylamine, were explored but did not yield better outcomes (entries 6 and 7, respectively).

When 6-aminoindole and 6-bromo-1-TBDMS indole **4b** were submitted to a reaction with $Pd(OAc)_2$, Brett-Phos, and K_2CO_3 in refluxing *t*BuOH, 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 Brett-Phos was used as the ligand, coupling of the unprotected bromoindole and unprotected aminoindole 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 ^1H 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)

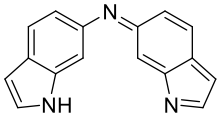


Figure 3. Diindolylmethene derivative of 6,6′-diindolylamine **8a**.

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-aminoindole 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-

https://doi.org/10.1021/acsomega.1c06289
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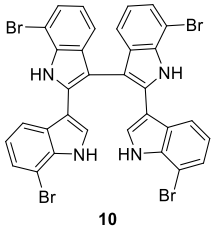
position of the indole ring is favored electronically,[27] but competing substitution at the 2-position and 1-position can be problematic.[28] Many protocols for the Friedel−Crafts alkylation of indoles suffer from poor yields due to the formation of mixtures of products and consequently difficult chromatographic separations. However, the selective installation of *tert*-butyl groups at the 3-position of indoles using unconventional Friedel−Crafts conditions has been reported.[29] 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 ^{1}H 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 ^{13}C 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).



10

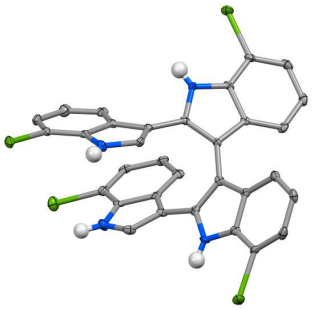


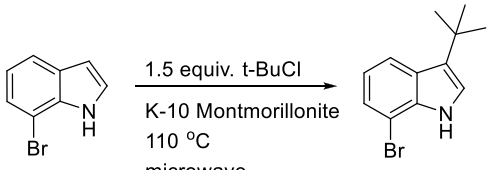
Figure 4. Chemical structure (left) and X-ray crystal structure (right) of the 7-bromoindole tetramer **10**. Ellipsoids are represented at the 50% probability level. Hydrogen atoms (except N−H hydrogens) have been removed for clarity.

While compounds similar to **10** have occasionally been reported,[30,31] in one case as the product of a traditional Freidel-Crafts alkylation,[32] 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 alkylating 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 alkylating 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.[31]

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*-butylindole on the basis of ^{1}H 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 alkylating 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



5a 11 36%

Synthesis of 7,7′-Amino-3-*tert*-butyldiindole 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

https://doi.org/10.1021/acsomega.1c06289
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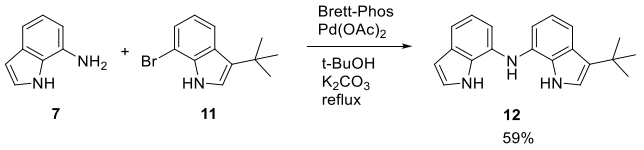
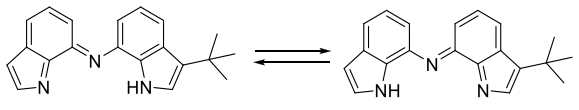
Scheme 4. Palladium-Catalyzed Cross-Coupling Reaction of 7 and 11 to Form 7,7′-Amino-3-*tert*-butyl-diindole 12



deuterated chloroform. The ^{1}H NMR spectrum of the material was consistent with the desired compound **12**, but the ^{13}C 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 ^{13}C carbon signals for the 7 and 7′ carbon atoms and confirmed the assignment of the product as the 7,7′-amino-3-*tert*-butyldiindole **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 d_6-acetone to give a dark blue solution. The product structure was not able to be confirmed by ^{1}H 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



13

Figure 5. Possible tautomerization of asymmetric diindolylmethene **13**.

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 $PtCl_2(PhCN)_2$ or $PtCl_2(COD)_2$ resulted in mixtures of unidentifiable products.

Oxidation of **12** using Ag_2O 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 ^{1}H 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 Ag_2O) were obtained for comparative identification (Figure 6).

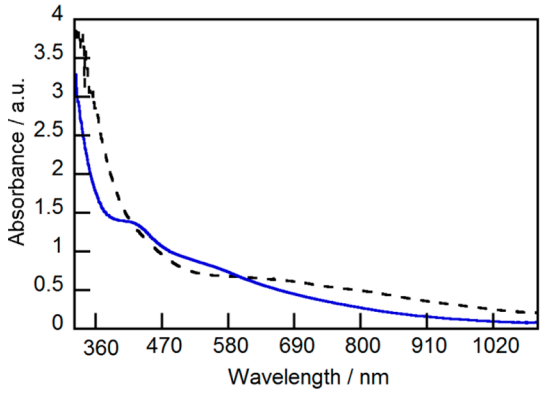


Figure 6. UV−vis-NIR absorption spectra of the products of the oxidation of **12** with DDQ (dashed black line) and Ag_2O (solid blue line).

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

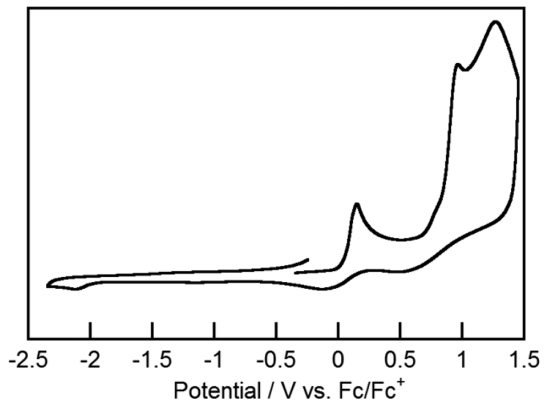


Figure 7. Cyclic voltammogram of 7,7′-amino-3-*tert*-butyl-diindole **12**. The concentration of the analyte in dichloromethane is ∼1 mM. The standard is Fc/Fc^{+}, the electrolyte is 0.1 M Bu_4NPF_6, and the scan rate is 100 mV s^{-1}.

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

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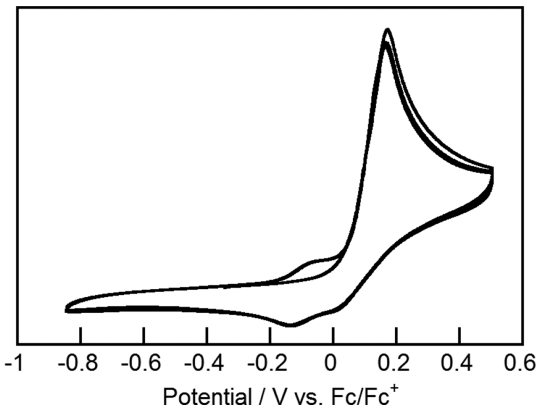

Figure 8. Cyclic voltammogram of 7,7′-amino-3-*tert*-butyl-diindole **12** cycled six times. The concentration of the analyte in dichloromethane is ∼1 mM. The standard is Fc/Fc^+, the electrolyte is 0.1 M Bu_4NPF_6, and the scan rate is 250 mV s^{-1}.

evidence of oligomerization, with the shape of the wave changing dramatically with repeat cycling (Figure S1) and the concurrent deposition of a dark glossy material on the carbon working electrode. These observations are consistent with oxidative oligomerization in the *tert*-butyldiindolylamine compound **12** and suggest that the dark insoluble precipitates formed during preparation and isolation of the unsubstituted diindolylamines **8a**, **8b**, **9a**, and **9b** were in fact mixtures of oligomers formed through air oxidation.

CONCLUSION

Buchwald−Hartwig amination conditions have been identified for the coupling of unprotected bromo indoles and amino indoles. The conditions are selective for reaction of the aryl bromide and anilino groups in the presence of the unprotected indole N−H moiety. The conditions appear to be amenable to coupling reactions using N-protected indoles as well. The facile and problematic oxidation of the aminodiindolyl products has been investigated, and the resulting insoluble precipitates have been attributed to oxidation-induced oligomerization based on evidence from ^{1}H 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** being 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.

^{1}H NMR and ^{13}C NMR were recorded at ambient temperature at frequencies of 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 (SiO_2) 60 (70−230 mesh) or Alfa Aesar neutral activated aluminum oxide (Al_2O_3), 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 (tetrabutylammonium 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-butyldimethylsilyl 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*-butyldimethylsilyl 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%). ^{1}H NMR (300 MHz, $CDCl_3$) 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), 6.58 (dd, J = 3.2, 0.8 Hz, 1H), 0.93 (s, 9H), 0.60 (s, 6H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 141.9, 131.6, 130.2, 123.0, 121.7, 116.6, 115.0, 104.8, 26.2, 19.4; −4.0; IR (solid-ATR) 2927, 2855, 1147, 803, 789 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd for $C_{14}H_{21}BrNSi$ 310.0627.

*7-Bromo-1-tert-butyldimethylsilyl indole (**5b**).* Tetrahydrofuran (5 mL) and 7-bromoindole (250 mg, 1.3 mmol) were added to a round-bottom flask under N_2. 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*-butyldimethylsilyl 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,

https://doi.org/10.1021/acsomega.1c06289
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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 (≈1.5 mL)were added to a Schlenk flask. The flask 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 dark brown and homogeneous. The flask 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 flask was carefully evacuated and backfilled with N_2 three times. The side arm tap was closed, and the septum and tap were parafilmed in place. The reaction was placed in the 110 °C sand bath and was 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, 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 7.93 (s, br, 2H), 7.52 (d, J = 8.4 Hz, 2 H), 7.13 (d, J = 0.8 Hz, 2H), 7.09 (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-butyldimethylsilyl-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 flask was sealed with a rubber septum, then 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 yellow and homogeneous. The flask was removed from the sand bath and 6-bromo-1-tertbutyldimethylsilyl indole **4.15b** (40 mg, 0.13 mmol), 6-aminoindole (20 mg, 0.15 mmol), and potassium carbonate (40 mg, 0.29 mmol) were added under a steady N_2 stream. The flask was carefully evacuated and backfilled with N_2 three times. The side arm tap was closed, and the septum and tap were parafilmed in place. The reaction was placed in the 110 °C sand bath and aged for 60 h. The reaction vessel was removed from the sand bath, and the reaction was diluted with ethyl acetate and water. The layers were separated, and the organic layer was concentrated using rotary evaporation. Column chromatography using silica gel (1 in. × 4 in.) and 1:4 ethyl acetate/hexanes gave the desired compound as a vanishingly small amount of oil. Because the isolated compound decomposed rapidly, the compound was not fully characterized. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (s, br, 1H), 7.51 (d, J = 8.3 Hz, 1 H), 7.50 (d, J = 8.4 Hz, 1 H), 7.30 (d, J = 1.0 Hz, 1H), 7.08−7.05 (m, 3H), 6.89 (app dt, J = 8.3, 2.0 Hz, 2H), 6.55 (dd, J = 3.2, 0.8 Hz, 1H), 6.49−6.46 (m, 1H), 5.68 (s, br, 1H), 0.92 (s, 9H), 0.53 (s, 6H).

*Di(1H-indol-7-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 flask 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 flask was carefully evacuated and backfilled with N_2 three times. The side arm tap was closed, and the septum and tap were parafilmed 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/acetone 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 8.06 (s, br, 2H), 7.37 (d, J = 7.9 Hz, 2H), 7.08 (app t, J = 2.8 Hz, 2H), 7.03 (t, J = 7.7 Hz, 2H), 6.74 (dd, J = 7.5, 0.6 Hz, 2H), 6.54 (dd, J = 3.1, 2.1 Hz, 2H), 5.80 (s, br, 1H).

*7,7′,7″,7‴-Tetrabromo-1H,1′H,1″H,1‴H-3,2′:3′,3″:2″,3‴tetraindole (**10**).* Dichloromethane (3 mL) and 7-bromoindole (100 mg, 0.51 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, 124.9, 124.6, 121.43, 121.36, 120.1, 119.6, 110.5, 108.7, 104.9, 104.8; IR (KBr) 3414, 3369, 2921, 1718 (br), 1433, 1314, 1205, 777, 742 cm^{-1}; HRMS (ESI-TOF) m/z [M − H]$^-$ calcd for $C_{32}H_{17}Br_4N_4$ 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 (2.0 g) was added, the solution was thoroughly mixed and then concentrated to dryness. The resulting tan solid was transferred to a microwave vial. 2-chloro- 2-methylpropane (0.83 mL, 7.7 mmol) was added, and the mixture was thoroughly combined. The reaction was heated in a microwave at 110 °C for 5 min and then allowed to cool to room temperature. Dichloromethane was added and the heterogeneous mixture was stirred, filtered, and the filtrate was concentrated to an oil. After purification by column chromatography using silica gel and hexanes, the title compound was obtained as a colorless oil (0.463 g, 36%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.06 (br s, 1H), 7.77 (d, J = 8.0 Hz, 1H), 7.34 (dd, J = 7.6, 0.6 Hz, 1H), 7.02−6.97 (m, 2H), 1.46 (s, 9H); ^{13}C NMR (90 MHz, $CDCl_3$) δ 135.9, 128.2, 127.3, 123.9, 120.6, 120.04, 119.96, 105.1, 31.9, 30.8; IR (liquid-ATR) 3427, 2962, 1691, 778, 737 cm^{-1}; HRMS (ESI-

https://doi.org/10.1021/acsomega.1c06289
ACS Omega 2022, 7, 5197−5205

TOF) m/z $[M - H]^-$ calcd for $C_{12}H_{14}NBr$ 250.0231; found 250.0231.

*3-(Tert-butyl)-N-(1H-indol-7-yl)-1H-indol-7-amine (**12**).* Brett-Phos (78 mg, 0.15 mmol), $Pd(OAc)_2$ (16 mg, 0.070 mmol), and *tert*-butanol (≈8 mL) were added to a Schlenk flask. The flask was sealed with a rubber septum and evacuated and backfilled with N_2 three times. The flask was placed in an approximately 100 °C sand bath for several minutes until the reaction became dark reddish-brown and homogeneous. The flask was removed from the sandbath and 7-bromo-3-*tert*-butylindole **11** (160 mg, 0.64 mmol dissolved in approximately 6 mL *tert*-butanol), 7-aminoindole (84 mg, 0.64 mmol), and potassium carbonate (193 mg, 1.4 mmol) were added under a steady N_2 stream. The flask was carefully evacuated and backfilled with N_2 three times. The side arm tap was closed, and the septum and tap were parafilmed in place. The reaction was placed in the sandbath, and the reaction was aged overnight. The reaction was transferred from the Schlenk flask to a round-bottom flask using dichloromethane and then was concentrated to a dark oily solid. The mixture was preabsorbed onto silica gel and purified by column chromatography using 4:1 dichloromethane/hexanes as the eluent. This afforded the desired compound as a foam, which became a pale gray solid upon treatment with $CDCl_3$ (115 mg, 59%). ^1H NMR (360 MHz, $CDCl_3$) δ 9.09 (br s, 1H), 8.80 (br s, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.26 (d, J = 7.9 Hz, 1H), 7.22 (app t, J = 2.8 Hz, 1H), 6.97−6.90 (m, 3H), 6.66 (d, J = 7.2 Hz, 1H), 6.65 (d, J = 7.4 Hz, 1H), 6.50 (dd, J = 2.0, 3.1 Hz, 1H), 6.37 (br s, 1H), 1.45 (s, 9H); ^{13}C NMR (125 MHz, CD_3CN) δ131.1, 130.4, 130.1, 129.7, 128.2, 127.4, 125.3, 121.0, 120.4, 120.0, 115.9, 115.0, 111.3, 111.1, 103.2, 32.2, 31.1; IR (solid-ATR) 3407, 3385, 2959, 1572, 1415, 1340, 722 cm^{-1}; HRMS (ESI-TOF) m/z $[M + H]^+$ calcd 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 voltammogram of compound **12** (PDF)

Indole tetramer **10** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

Robin G. Hicks − *Department of Chemistry, University of Victoria, Victoria, BC V8W2Y2, Canada;* orcid.org/0000-0002-4613-4616; Email: rhicks@uvic.ca

Authors

Geneviève N. Boice − *Department of Chemistry, University of Victoria, Victoria, BC V8W2Y2, Canada;* orcid.org/0000-0002-3083-6162

Brian O. Patrick − *Crystallography Laboratory, Department of Chemistry, University of British Columbia, Vancouver, BC V6T1Z1, Canada;* orcid.org/0000-0002-2921-8439

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.1c06289

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was supported by the Natural Sciences and Engineering Research Council of Canada (NSERC Discovery Grants and an Alexander Graham Bell Canada Graduate Scholarship). R.G.H. and G.N.B. wish to thank Cornelia Bohne for providing access to instrumentation and Chris Barr for assistance with NMR instrumentation and theory.

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