Efficient Reagents for the Synthesis of 5-, 7-, and 5,7-Substituted Indoles Starting from Aromatic Amines: Scope and Limitations

Jesús Ezquerra, Concepción Pedregal, and Carlos Lamas*

Centro de Investigación Lilly, S. A., Paseo de la Cruz s/n. 28130 Valdeolmos, Madrid, Spain

José Barluenga,* Marta Pérez, Miguel Angel García-Martín, and José M. González

Instituto Universitario de Química Organometálica "Enrique Moles"—Unidad Asociada al CSIC, C/Julián Clavería 8, Universidad de Oviedo, 33071 Oviedo, Spain

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Upon reaction with IPy_2BF_4, 4-substituted anilines give regioselectively the corresponding *o*-iodoanilines in nearly quantitative yield, in a process that can be carried out on a multigram scale. Palladium-catalyzed coupling of the resulting 2-iodoanilines with (trimethylsilyl)acetylene (TMSA), followed by efficient CuI-mediated nitrogen cyclization onto alkynes with concurrent elimination of the TMS substituent, allows a straightforward elaboration of 5-mono- and 5,7-disubstituted indoles from aromatic amines. This new approach to the aforementioned indoles does not requires protective groups on nitrogen at any step and can be adapted for preparing related 7-monosubstituted indoles. Moreover, examples iterating the process are given, allowing bis-annulation and sequential double annulation and resulting in synthesis of benzodipyrroles. Additionally, suitable conditions for iodination of some of the target indoles with IPy_2BF_4 are discussed.

Introduction

The substituted indole nucleus is prevalent in natural products[1] and important in medicinal chemistry.[2] Many procedures are known for preparing indoles;[3] the availability of the starting material and its compatibility with the reaction conditions generally dictate the method of choice for synthesizing a target molecule. Several factors account for the current interest in new and selective syntheses of the indole ring.[4] Among them are unavailability of some patterns of indole substitution using classic methods[5] and the search for efficient ways to synthesize more elaborate structures possessing biological activity.[6] Known procedures for the preparation of 7-monosubstituted[4c,5s−u,7,8] or 5,7-disubstituted indoles[9]

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are scant and poor yielding. Moreover, transition metal-assisted organic transformations have become useful tools for the synthesis and functionalization of heterocycles,[10] and palladium complexes have proven to be very efficient catalysts for indole ring elaboration.[11,12] We now report a novel approach to 5-monosubstituted and 5,7-disubstituted indoles from 4-substituted aromatic amines, most of which are commercially available. This method is amenable to the synthesis of related 7-monosubstituted compounds. Significantly, the procedure affords free N−H indoles, without requiring the use of cumbersome nitrogen-protective groups along the reaction path.

Results and Discussion

The synthetic strategy described herein relies on selective reactions: ortho iodination of substituted anilines **1**,[13] palladium-catalyzed coupling of the iodinated amines **2** with (trimethylsilyl)acetylene (TMSA, **3**), and treatment of the resulting arylacetylenes **4** with CuI, giving directly desilylated indoles **5** (Scheme 1).

Iodination of Aromatic Amines. The iodination of arenes with bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4) was previously reported.[14] Unprotected aniline and *N*,*N*-dimethylaniline furnish the corresponding *p*-iodo derivatives in a clean process, without evidence of polyiodination taking place under the reported conditions.[14b] For synthesizing the target indoles **5**, we started from amines **1** with $R^2 \neq H$ for preparing *o*-iodoanilines **2**, as outlined in Scheme 1. The reaction of these unprotected anilines with IPy_2BF_4 affords the related 2-iodo derivatives **2** as the single reaction product, in nearly quantitative yields as evidenced ^1H NMR and/or GC/EM analyses of the crude reaction mixtures. The generality of the reaction is shown in Table 1.

The iodination always takes place at room temperature. For entries a, c, and f in Table 1, the reaction is completed after simply mixing in CH_2Cl_2 the amine and

Scheme 1

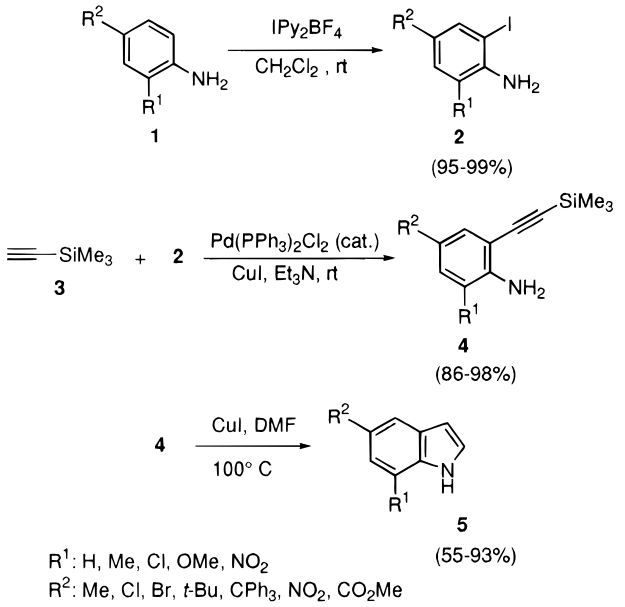

Table 1. Iodination of 4-Substituted Anilines with IPy_2BF_4

entry	R^1	R^2	**2** (%)[a]
a	Me	Me	99
b	Cl	Me	99[b]
c	H	Me	99
d	H	Cl	99[b]
e	Cl	Br	95[b]
f	Cl	^{t}Bu	98
g	OMe	CPh_3	95[b]
h	NO_2	Br	95[b]
i	OMe	NO_2	95[b]
j	OMe	CO_2Me	99[b]
k	Me	CO_2Me	99[b]

[a] Isolated yield. [b] Acid (HBF_4 or CF_3SO_3H) was added to the solution to activate the iodinating agent (for more details, see discussion in the text).

the iodinating agent in an equimolar ratio. This experimental protocol works well for multigram quantities; for instance, the iodination of **1a** was run on a 25 g scale. Other iodinating reagents, such as CF_3COOAg/I_2,[15] were ineffective for the direct iodination of these substrates, delivering oxidation products. Attempts to prepare **2a** by iodination with $BnMe_3NICl_2$[16] were less efficient (70% yield) than those with IPy_2BF_4 (99% yield). Moreover, for entries b, d, e, and g in Table 1, the iodination was optimized by activating the iodinating reagent by addition of HBF_4 (54% ethereal solution, IPy_2BF_4/HBF_4 1:2), in addition to increasing the reaction time up to 0.3 h. Finally, for entries h−k, triflic acid (CF_3SO_3H) results in higher reaction rates than HBF_4 and was the acid of choice, although specific conditions were needed, depending on the starting amine. Thus, for accomplishing quantitative iodination, **1h** requires reaction for 3 days at rt, using the molar ratio amine/IPy_2BF_4/CF_3SO_3H 1:2:4; however, **2i** required 24 h (amine/IPy_2BF_4/CF_3SO_3H 1:1.5:3), and for **2j** and **2k** only 16 h was needed, without excess of the iodinating reagent (amine/IPy_2BF_4/CF_3SO_3H 1:1:2). Though the results reported in Table 1 were obtained using CH_2Cl_2 as solvent, AcOEt was also tested as an alternative in the iodination of some amines. For

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Table 2. Palladium-Catalyzed TMSA Coupling with 2-Iodoanilines and CuI-Mediated Cyclization of the Resulting 2-Alkynylanilines, Furnishing Indoles

entry	R^1	R^2	**4** (%)	**5** (%)
a	Me	Me	98	82
b	Cl	Me	94	65
c	H	Me	97	55
d	H	Cl	92	65
e	Cl	Br	94	55
f	Cl	^{t}Bu	95	75
g	OMe	CPh_3	86	93
h	NO_2	Br	89	55
i	OMe	NO_2	98	60
j	OMe	CO_2Me	90	69
k	Me	CO_2Me	90	60

instance, comparable results were obtained in the preparation of **2b** using IPy_2BF_4 in both solvents. The degree of purity shown by the iodoamines in the crude products allows their use in the following step of the indole synthesis without further purification, enhancing the synthetic convenience of this procedure. Importantly, other reagents either fail to iodinate aniline itself[17] or give lower yield and/or poor regioselectivity.[18] For instance, using ICl, a reputed halogenating agent,[19] iodination of **1d** gives 68% of **2d** and 7% of the 2,6-diiodo derivative and requires a 4:1 molar ratio of 4-chloroaniline to ICl,[20] while IPy_2BF_4 gives almost quantitative conversion of **1d** to **2d**, using equimolar ratios of the amine and the iodinating reagent.

Synthesis of *o*-[(Trimethylsilyl)ethynyl]anilines 4. The *o*-iodoanilines **2** were transformed into indoles **5** by the two-step reaction sequence depicted in Scheme 1. First, the palladium-catalyzed cross-coupling reaction of amines **2** with (trimethylsilyl)acetylene (**3**), using the experimental conditions previously described by Hagihara et al. for simple aryl halides,[21] provides access to the key intermediates, the *o*-alkynylanilines **4**, in excellent yield (Table 2).

Thus, reaction of *o*-iodoanilines with TMSA (1.2 equiv) and catalytic amounts of the $Pd(PPh_3)_2Cl_2$−CuI system (0.05 equiv) in Et_3N under N_2, from 0 °C to rt, furnishes *o*-[(trimethylsilyl)alkynyl]anilines **4** as the single reaction products. TLC monitoring of the reaction showed its progress (a new spot of higher R_f value than that of the starting *o*-iodoaniline was noticed), while the reaction time was determined as a function of the disappearance of the starting material. Minor amounts of bis(trimethylsilyl)-1,3-butadiyne were detected in some cases by NMR analysis of the crude reaction mixtures as the only byproduct. This compound, easily removed by column chromatography or sublimation, arises from self-coupling of two TMSA molecules. Nitrogen protection is not needed in order to carry out the coupling of 2-iodoanilines **2** with TMSA, as first reported Hagihara et al. in related studies using *p*-iodoaniline.[21] The examples described herein significantly broaden the scope of the substitution pattern previously described for related reactions.[12e,22] On this basis, this reaction is superior to other procedures addressing the preparation of **4**.[23] Also, the reaction shows total chemoselectivity with respect to the nature of the halogen atom, as depicted in Table 2 (entries b, d, f, h, and especially e).

Ring Closure of Alkynylanilines Mediated by CuI: Formation of Indoles 5. Palladium chloride is a well-established catalyst for converting 2-alkynylanilines into 2-substituted indoles through N−C_2 ring closure. However, this salt does not promote cyclization onto trimethylsilyl-substituted alkynes, starting from either unsubstituted or *N*-protected anilines, leading instead to recovery of the starting material or to decomposition products.[12d,f] Moreover, copper iodide-mediated intramolecular cyclization of *o*-alkynylanilines was first reported by Castro et al.[24] as a useful approach to prepare 2-substituted indoles.[25] More recently, Yamanaka et al.[12g] have reported on the use of $Pd(PPh_3)_2Cl_2$ and/or CuI as efficient catalysts for related cyclization reactions, starting from alkynylanilines protected as *N*-methanesulfonamides. Besides, addition of CuI produces intramolecular cyclization of *o*-[(trimethylsilyl)ethynyl]aniline upon thermal treatment in DMF−Et_3N, providing 2-TMS-substituted indole as the major component of the crude material, together with minor amounts of the desilylated adduct. $Pd(PPh_3)_2Cl_2$−CuI as catalyst furnished only the 2-TMS-substituted indole, although in significantly lower overall yield. Similar cyclization to indole with concomitant elimination of the TMS group was previously noticed in the formation of 1-benzylindole[13g] and in the synthesis of 7-azaindoles.[26] We found that addition of 2 equiv of CuI promotes heteroannulation of **4**, providing an easy entry into indoles **5** in moderate to excellent yields, furthermore, without requiring a second step to remove the silane[27] (Scheme 1, Table 2). The reaction takes place in anhydrous DMF, and the mixture is heated at 100 °C under N_2, typically over a period of 2.5−3 h. In general, longer reaction times were ineffective at improving the yield, resulting instead in the formation of decomposition products. The degree of purity of the starting alkynylaniline also influences the yield and must be high to accomplish satisfactorily the synthesis of the reported indoles. Cyclizations were succesfully run on a 4 g scale (yields in Table 2 were recorded starting from 15 mmol of the corresponding amine **4** and are based on pure isolated compounds); larger excesses gave significantly lower yields of indole under similar conditions. For instance, for **5a**, the yield was in the 90% range starting from 1 g of **4a**; conversely, it was lower than 20% when 8 g of starting material was used (unoptimized process). Increasing the CuI/amine ratio to 2.5:1 still allows cyclization to take place in moderate yield, but besides indoles **5**, significant amounts of their corresponding 3-iodo derivatives are formed. For instance, reaction of **4d** with CuI in DMF at 100 °C produces **5d** and its 3-iodo derivative in 4:1 ratio. The latter was the only product

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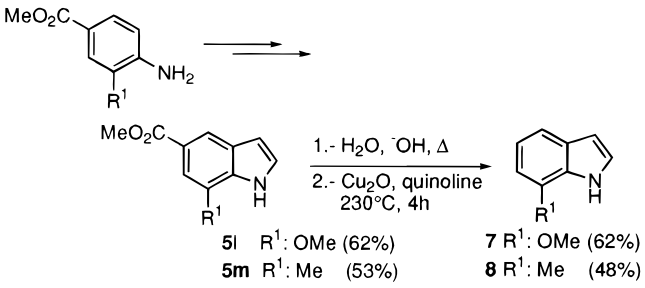
Scheme 2

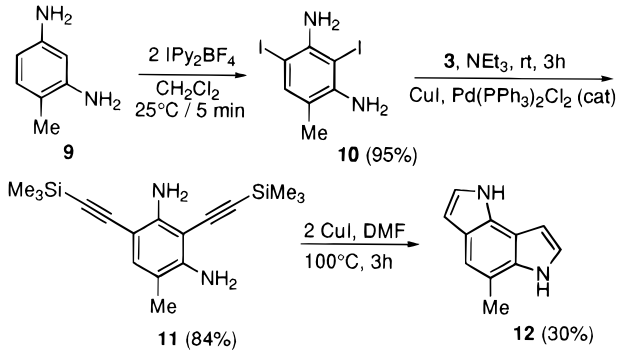


isolated—but in low yield—when larger excesses of CuI were used. Attempts were made to find appropriate experimental conditions to carry out the conversion of the 2-iodoanilines to indoles in a single step. Partial success was achieved in some cases, though, at present, the reaction is not general and requires optimizing the conditions for every starting material. So, **2c** gives a 60% isolated yield of **5c** after reaction with TMSA in DMF at 100 °C over 24 h, in the presence of 2 equiv of CuI and catalytic amounts of the palladium salt and Et_3N. Under these conditions, 15% of **4c** was also recovered from the reaction mixture. Nevertheless, starting from **2a**, the iodoaniline was consumed after 1.5 h; TLC also indicates the formation of the alkynylamine in this period. After reaction for 4 h, some indole **5a** was formed, but still significant amounts of the 2-alkynyl compound were present. After 7 h, the reaction gave only decomposition products. Finally, the cyclization conditions described previously to elaborate *N*-benzylindoles from related systems[13g] were also tested. In this regard, the most remarkable result comes from the reaction of **4c** with CuI (0.5 equiv) and $CaCO_3$ (1 equiv) in DMF at 120 °C for 2 h, affording **5c** in 70% yield, and showing that this modification of the original Castro coupling conditions is also compatible with the cyclization of unprotected nitrogen alkynylamines. Although no general conditions were traced for this approach to cyclize alkynylanilines to indoles, its consideration might open alternative ways to optimize the yield for some target molecule.

In summary, the method reported herein for the synthesis of aryl-substituted indoles is highly efficient and good yielding, does not require the use of protective groups at any step, and competes well with previously reported methods to prepare 5-mono-[28] and 5,7-disubstituted indoles. In this approach, a new example of the efficient use of TMSA as a masked source of acetylene itself is given; in this regard, the results depicted in Table 2 can, formally, complement those obtained from the insertion reaction of internal alkynes into 2-iodoanilines catalyzed by palladium salts.[12c]

So far, this method has proven very efficient to obtain 5-mono- and 5,7-disubstituted indoles. However, to illustrate its utility to prepare 7-substituted derivatives, 5,7-disubstituted indoles bearing substituents at C-5 that can be removed using simple procedures are necessary. In this regard, we have chosen amines with $R^2 = CO_2Me$ as adequate synthons to prepare 7-monosubstituted indoles, including the relevant 7-methoxyindole, as depicted in Scheme 2.

Scheme 3



Indeed, starting from indoles **5j**,**k**, the corresponding 7-monosubstituted indoles were readily accesible (**7**, $R^1 = OCH_3$; **8**, $R^1 = CH_3$). Upon hydrolysis, the corresponding indolic acids **5l**,**m** were subjected to decarboxylation conditions, providing an easy path to the related 7-substituted indoles.

Preparation of Benzodipyrroles. To further explore the scope of the above-described methodology, we investigated the feasibility of applying it for preparing benzodipyrroles.[29] Reaction of diamine **9** with 2 equiv of IPy_2BF_4 at rt led instantaneously to the diiodo derivative **10** in quantitative yield. Coupling of **10** with TMSA furnishes the dialkynyldiamine **11** in excellent yield under standard conditions (Scheme 3). Finally, bisannulation of **11** affords the desired compound in moderate yield. Although cyclization conditions leading to **12** have not been optimized, this preparation clearly opens up a new and extremely short pathway to easily elaborate this class of interesting structures from simple amines.

The feasibility of a sequential double-annulation approach was also tested starting from indole **5i**, which is readily available from the commercial amine **2i** following the protocol described in Scheme 1. After conventional nitrogen protection and reduction steps, the aminoindole **13** was obtained in good overall yield (Scheme 4). Reaction of this indole with IPy_2BF_4 yields the iodo derivative **14** almost quantitatively. Remarkably, the combination of the electronic effects of the amine substituent and the protecting group on the indolic nitrogen totally overrides incorporation of electrophiles at the C-3 position in the indole ring, otherwise anticipated according to the general rules controlling the electrophilic substitution on indole. Successful alkyne coupling gave nicely indole **15**, and CuI-mediated annulation furnished the elaborate structure of **16**, in a satisfactory 45% yield without optimization.

These examples further enlarge the scope of the method reported herein for preparing indoles with patterns of substitution otherwise difficult to elaborate from simple anilines; additionally, some distinctive features of the reagents employed to approach this synthetic problem are given.

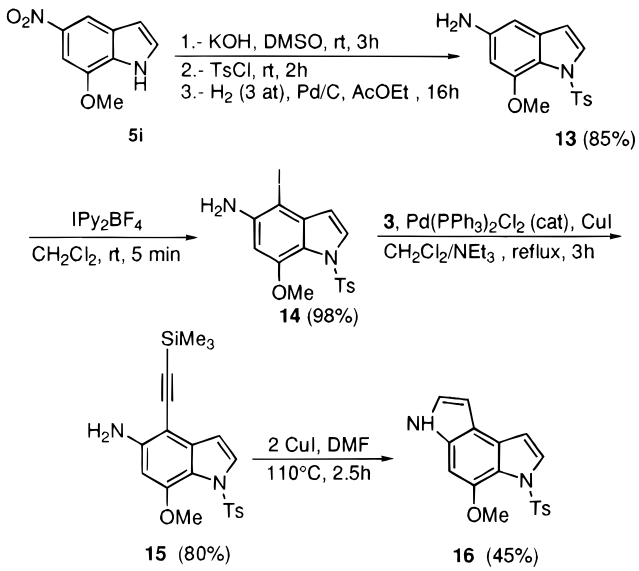
Indole Iodination Reactions with IPy_2BF_4.[30] We have already shown that indole can be smoothly iodin-

(28) For recent methods of the basic indole skeleton synthesis, including examples of substitution at C-5, see refs 8, 12h, and 13g in this paper and the following: (a) Sakamoto, T.; Hosoda, I.; Kikugawa, Y. *J. Heterocycl. Chem.* **1988**, *25*, 1279. (b) Kasahara, A.; Izumi, T.; Kikuchi, T.; Xiao-ping, L. *J. Heterocycl. Chem.* **1987**, *24*, 1555. (c) Kawase, M.; Sinhababu, A. K.; Borchardt, R. T. *J. Heterocycl. Chem.* **1987**, *24*, 1499.

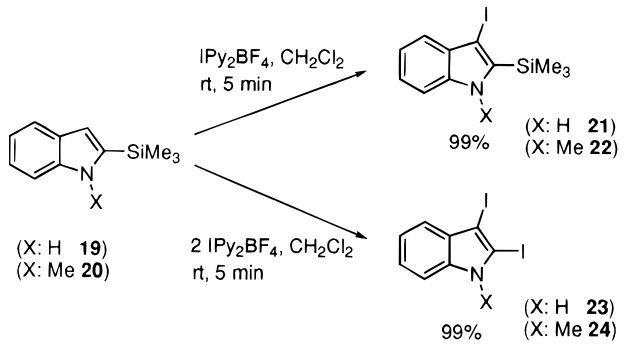
(29) See, for instance: (a) Sundberg, R. J.; Hamilton, G. S.; Laurino, J. P. *J. Org. Chem.* **1988**, *53*, 976 and references therein. (b) Rawal, V. H.; Jones, R. J.; Cava, M. P. *Heterocycles* **1987**, *25*, 701. (c) Berlin, A.; Bradamante, S.; Ferraccioli, R.; Pagani, G. A; Sannicolò, F. *J. Chem. Soc., Chem. Commun.* **1987**, 1176.

(30) Recent iodination reaction of indole, see: (a) Bergman, J.; Venelmalm, L. *J. Org. Chem.* **1992**, *57*, 2495. (b) Bocchi, V.; Palla, G. *Synthesis* **1982**, 1096. (c) Saulmier, M. G.; Gribble, G. W. *J. Org. Chem.* **1982**, *47*, 757.

Scheme 4



Scheme 5



ated at the C-3 position by reaction with IPy_2BF_4.[14b] We also attempted the iodination of indoles **5a**,**d** using this reagent and catalytic amounts of HBF_4. We found almost instantaneous and quantitative conversion into the corresponding 3-iodo indoles **17** and **18** at rt. Furthermore, 2-(trimethysilyl)indole (**19**) and its *N*-methylated derivative (**20**) were prepared by alternative routes,[31] and their reactions with IPy_2BF_4 were also investigated (Scheme 5).

The formation of 3-iodo-2-(trimethylsilyl)indoles **21** and **22** takes place in quantitative yield using equimolar ratios of the iodinating reagent and the corresponding indole, while 2 equiv of IPy_2BF_4 affords 2,3-diiodoindoles **23** and **24** as the only reaction products, respectively. The manifold, selectivity, and efficiency of this reaction are very useful, enabling selective functionalization on indole for further synthetic purposes.

Additional Data on 2-TMS-Substituted Indoles Concerning the Cyclization Process. Our study was synthetically oriented from its begining, and detailed mechanistic studies were not undertaken at present. However, we were curious about the influence that several factors could have in the evolution of the alkynylanilines to the cyclization products. Certainly, on the basis of the available information, mechanistic interpretations would be speculative, but additional data might provide some indication and could be useful for further studies in the field. The degree of compatibility of CuI with 2-TMS-substituted indoles was examined. For both unprotected indole **19** and its corresponding *N*-methyl derivative **20**, unchanged starting material was recovered upon heating at 100 °C for 3 h with different excesses of CuI in DMF (up to 1:4 molar ratios), without noticeable changes taking place after chromatographic purification. This provides some argument against the possibility of products **5** arising from cyclization resulting in 2-(trimethylsilyl)indoles, followed by loss of silicon along the purification step. The reaction was not affected by addition of small amounts of an antioxidant agent, 2,6-di-*tert*-butyl-4-methylphenol (BHT).[32] The cyclization was fully suppressed when the TMS group was replaced by either H or *tert*-butyldimethylsilyl (TBDMS) on the starting alkynylamine, giving only unchanged starting material without formation of indole. Longer reaction times were not efficient to promote cyclization in these cases. Thus, no significant formation of indole[33] from TBDMS-substituted 2-alkynylaniline was observed, even after reaction for 24 h. Also, it could be conceived the role of CuI might go beyond its initially postulated implication in the ring closure,[24] considering recent findings showing large differences in its behavior in the Stille coupling, depending on the experimental protocol.[34]

Conclusions

The results reported herein offer a solid body of simple and straightforward preparations of compounds belonging to scarcely reported classes of indoles. The success of this method relies on the use of efficient and selective reagents in every step that, as a common feature, can be carried out without the use of protective groups. This procedure can be adapted for easily synthesizing benzodipyrroles by the same experimental protocol, by means of bisannulation or sequential double-annulation strategies, starting from simple amines.

Experimental Section

General Methods. Melting points are uncorrected. NMR experiments were run in $CDCl_3$ unless otherwise noted. Analytical TLC was performed using commercially available silica gel 60 F_{254} precoated plates from E. Merck. Flash column chromatography[35] was performed with silica gel (230−400 mesh). Bulb-to-bulb distillations of the Kügelrohr type were conducted at the pressures and oven temperatures (uncorrected) reported. General spectroscopic equipments and procedures have been previously reported.[36] Where DEPT experiments were carried out with ^{13}C NMR acquisitions, the carbon multiplicities are listed as (0) quaternary, (1) methine, (2) methylene, and (3) methyl.

Materials. Commercially available anilines were of the best grade and were used without prior purification. Amine **1f** was prepared from *o*-chloroacetanilide by reaction with *t*-BuCl (3 equiv) and $AlCl_3$ (2 equiv) in $PhNO_2$ at 140 °C for 18 h in a sealed tube, in 45% yield. Amine **1g** was prepared

(31) (a) Indole **20** was prepared from indole by using the protocol previously described to prepare 2-substituted indoles, see: Katritzky, A. R.; Akutagawa, K. *Tetrahedron Lett.* **1985**, *26*, 5935. (b) Indole **21** was prepared according to early work on the activation of C-2 in *N*-methylindole, see: Shirley, D. A.; Rousell, P. A. *J. Am. Chem. Soc.* **1953**, *75*, 375.

(32) Janzen, E. G.; Wilcox, A. L.; Manoharan, V. *J. Org. Chem.* **1993**, *58*, 3597.

(33) For the synthesis of 2-(*tert*-butyldimethylsilyl)indole for test experiments, see: Sundberg, R. J.; Russell, H. F. *J. Org. Chem*, **1973**, *38*, 3324. (b) Wright, A.; Ling, D.; Boudjouk, P.; West, R. *J. Am. Chem. Soc.* **1972**, *94*, 4784.

(34) Farina, V.; Kapadia, S.; Krishnan, B.; Wang, C.; Liebeskind, L. S. *J. Org. Chem.* **1994**, *59*, 5905.

(35) Still, W. C.; Kahn, M.; Mitra, A. *J. Org. Chem.* **1978**, *43*, 2923.

(36) Barluenga, J.; Campos, P. J.; González, J. M.; Suarez, J. L.; Asensio, G. *J. Org. Chem.* **1991**, *56*, 2234.

according to the literature procedure.[37] Amines **1j**,**k** were prepared from commercial 4-amino-3-methoxybenzoic acid and 4-amino-3-methylbenzoic acid by reaction in CH_3OH with $SOCl_2$ (2.5 equiv, slow addition), stirring the mixture at rt for 2 h. Hydrolysis, followed by extraction with ether at basic pH, evaporation of solvents at reduced pressure, and purification by column chromatography on silica gel (hexane/AcOEt 5:1), furnished the desired esters **1j**,**k**. Tetrafluoroboric acid (HBF_4) was used as an ethereal solution (54%), available from Merck. (Trimethylsilyl)ethyne (TMSA) was purchased from Lancaster. Bis(pyridine)iodonium(I) tetrafluoroborate (IPy_2BF_4) was prepared as previously reported.[38] Bis(triphenylphosphine)-palladium(II) chloride [$Pd(PPh_3)_2Cl_2$] was prepared according to the literature procedure.[39] Dichloromethane (CH_2Cl_2) was distilled under N_2 from P_2O_5 prior to its use. Triethylamine (Et_3N) was distilled under N_2 from KOH pellets prior to its use. DMF was distilled from CaH_2 and stored under N_2 in the presence of molecular sieves.

Representative Procedure for the Iodination of Anilines 1a,c,f (Scheme 1, Table 1). IPy_2BF_4 (7.44 g, 20 mmol) was added to a solution of the starting aniline (20 mmol) in CH_2Cl_2 (∼50 mL), and the resulting mixture was magnetically stirred at rt for 5 min. The solution was then treated with H_2O (20 mL). After extraction with CH_2Cl_2 (2 × 20 mL), the combined organic layers were washed with aqueous $Na_2S_2O_3$ and dried over anhydrous Na_2SO_4, and the solvents removed under vacuum. The residue was subjected to chromatography (SiO_2, hexane/AcOEt, mixtures of increasing polarity), affording the corresponding anilines **2a**,**c**,**f**, which were further purified by high-vacuum distillation or sublimation.

Iodination of 1b,d,e,g (Scheme 1, Table 1). To a solution of the starting aniline (20 mmol) in CH_2Cl_2 (∼50 mL) were added IPy_2BF_4 (7.44 g, 20 mmol) and HBF_4 (5.43 mL of 54% ethereal solution, 40 mmol). The mixture was stirred for 20 min at rt. Hydrolysis, workup, and purification as described above furnished the corresponding iodinated anilines **2b**,**d**,**e**,**g**.

Iodination of Anilines 2h−k (Scheme 1, Table 1). To the starting aniline (20 mmol) in CH_2Cl_2 (∼50 mL) were added IPy_2BF_4 (7.44 g, 20 mmol for **2j**,**k**; 11.16 g, 30 mmol for **2i**; 14.88 g, 40 mmol for **2h**) and CF_3SO_3H (3.54 mL, 40 mmol for **2j**,**k**; 5.31 mL, 60 mmol for **2i**; 7.08 mL, 80 mmol for **2h**). The resulting mixtures were magnetically stirred at rt (16 h for **2j**,**k**; 24 h for **2i**; 72 h for **2h**). Hydrolysis, workup, and purification as described above furnished the corresponding iodinated anilines **2b**,**d**,**e**,**g**.

4,6-Dimethyl-2-iodoaniline (2a): white solid, mp 64−65 °C (lit.[40] mp 65 °C); IR (KBr) ν 3397, 3314, 1281; ^{1}H NMR δ 2.18 (s, 3H), 2.19 (s, 3H), 3.75 (s br, 2H), 6.83 (s, 1H), 7.35 (s, 1H); ^{13}C NMR δ 18.8 (3), 19.7 (3), 84.6 (0), 122.3 (0), 129.0 (0), 131.2 (1), 136.6 (0), 142.2 (0); MS *m*/*e* 247 (M^+), 120.

2-Chloro-6-iodo-4-methylaniline (2b): white solid, mp 57−59 °C (lit.[41] mp 59−60 °C); IR (KBr) ν 3413, 3314, 1293; ^{1}H NMR δ 2.20 (s, 3H), 4.30 (s br, 2H), 7.07 (d, J = 0.8 Hz, 1H), 7.39 (d, J = 0.8 Hz, 1H); ^{13}C NMR δ 19.6 (3), 83.4 (0), 117.4 (0), 129.5 (0), 130.0 (1), 137.6 (1), 140.7 (0); MS *m*/*e* 247 (M^+), 120.

2-Iodo-4-methylaniline (2c): white solid, mp 37 °C (lit.[40] mp 37−39 °C); IR (KBr) ν 3416, 3337, 1155; ^{1}H NMR δ 2.21 (s, 3H), 3.93 (s br, 2H), 6.66 (d, J = 8.1 Hz, 1H), 6.95 (dd, J = 1.37, 8.1 Hz, 1H), 6.95 (dd, J = 1.4, 8.1 Hz, 1H), 7.48 (d, J = 1.3 Hz, 1H); ^{13}C NMR δ 19.7 (3), 84.2 (0), 114.6 (1), 129.4 (0), 130.0 (1), 139.0 (1), 144.3 (0); MS *m*/*e* 233 (M^+), 106.

4-Chloro-2-iodoaniline (2d): white solid, mp 44 °C (lit.[42] mp 41 °C); IR (KBr) ν 3389, 3298, 3181; ^{1}H NMR δ 3.96 (s br, 2H), 6.66 (d, J = 8.6 Hz, 1H), 7.10 (dd, J = 2.4, 8.6 Hz, 1H), 7.61 (d, J = 2.4 Hz, 1H); ^{13}C NMR δ 83.4 (0), 114.9 (1), 122.9 (0), 129.0 (1), 137.5 (1), 145.3 (0); MS *m*/*e* 255 (M^+ + 2), 253 (M^+), 126.

4-Bromo-2-chloro-6-iodoaniline (2e): white solid, mp 95−96 °C; IR (KBr) ν 3300, 3294; ^{1}H NMR δ 4.54 (s br, 2H), 7.39 (d, J = 2 Hz, 1H), 7.66 (d, J = 2 Hz, 1H); ^{13}C NMR δ 83.0 (0), 109.0 (0), 117.8 (0), 131.7 (1), 139.0 (1), 142.5 (0); MS *m*/*e* 335 (M^+ + 4, 24), 333 (M^+ + 2, 100), 331 (M^+, 75), 206; HRMS calcd for $C_6H_4BrClIN$ (M^+) 330.8260, found 330.8256.

4-*tert*-Butyl-2-chloro-6-iodoaniline (2f): dark red oil, chromatographed on silica gel 20:1 hexane/AcOEt; IR (NaCl) ν 3472, 3376, 1260; ^{1}H NMR δ 1.26 (s, 9H), 4.39 (s br, 2H), 7.26 (d, J = 2 Hz, 1H), 7.55 (d, J = 2 Hz, 1H); ^{13}C NMR δ 31.2 (3), 33.9 (0), 83.7 (0), 117.4 (0), 126.7 (1), 134.4 (1), 140.7 (0), 143.3 (0); MS *m*/*e* 311 (M^+ + 2, 9), 309 (M^+, 26) 294, 167.

6-Iodo-2-methoxy-4-tritylaniline (2g): light pink solid, mp 122−123 °C; IR (KBr) ν 3453, 3368, 1213; ^{1}H NMR (DMSO-d_6) δ 3.50 (s, 3H), 4.80 (s br, 2H), 6.56 (d, J = 1.6 Hz, 1H), 7.03 (d, J = 1.6 Hz, 1H), 7.41−7.22 (m, 15 H); ^{13}C NMR (DMSO-d_6) δ 55.5, 63.7, 81.3, 113.8, 126.0, 127.6, 127.8, 130.4, 131.6, 136.4, 144.8, 146.3; MS *m*/*e* 491 (M^+), 414, 365, 288. Anal. Calcd for $C_{26}H_{22}INO$: C, 63.55; H, 4.51; N, 2.85. Found: C, 63.78; H, 4.63; N, 2.84.

4-Bromo-2-nitro-6-iodoaniline (2h): yellow solid, mp 147−148 °C; IR (KBr) ν 3459, 3347, 1343, 1240; ^{1}H NMR δ 6.69 (s br, 2H), 8.02 (d, J = 2.3 Hz, 1H), 8.32 (d, J = 2.3 Hz, 1H); ^{13}C NMR δ 87.8 (0), 107.8 (0), 129.1 (1), 131.6 (0), 143.0 (0), 147.3 (1); MS *m*/*e* 344 (M^+ + 2, 96), 342 (M^+, 100), 296; HRMS calcd for $C_6H_4BrIN_2O_2$ (M^+) 341.8500, found 341.8499.

4-Nitro-2-methoxy-6-iodoaniline (2i): yellow solid, mp 158−160 °C; IR (KBr) ν 3497, 3385, 1283, 1227; ^{1}H NMR δ 3.93 (s, 3H), 5.0 (s br, 2H), 7.61 (d, J = 1.4 Hz, 1H), 8.25 (d, J = 1.4 Hz, 1H); ^{13}C NMR δ 56.2 (3), 78.1 (0), 105.1 (1), 127.8 (1), 138.6 (0), 143.7 (0), 144.1 (0); MS *m*/*e* 294 (M^+, 100), 279; HRMS calcd for $C_7H_7IN_2O_3$ (M^+) 293.9501, found 293.9504.

Methyl 4-amino-3-methoxy-5-iodobenzoate (2j): yellow solid, mp 117−118 °C; IR (KBr) ν 3495, 3393, 1296, 1215; ^{1}H NMR δ 3.87 (s, 3H), 3.90 (s, 3H), 4.70 (s br, 2H), 7.39 (d, J = 1 Hz, 1H), 8.00 (d, J = 1 Hz, 1H); ^{13}C NMR δ 51.8 (3), 55.8 (3), 80.3 (0), 110.3 (1), 120.0 (0), 132.9 (1), 141.6 (0), 144.8 (0), 165.9 (0); MS *m*/*e* 307 (M^+, 100), 292.

Methyl 4-amino-3-iodo-5-methylbenzoate (2k): yellow solid, mp 81−82 °C; IR (KBr) ν 3455, 3358, 1708, 1302, 1262; ^{1}H NMR δ 2.16 (s, 3H), 3.80 (s, 3H), 4.55 (s br, 2H), 7.61 (d, J = 1.7 Hz, 1H), 8.15 (d, J = 1.7 Hz, 1H); ^{13}C NMR δ 18.4 (3), 51.5 (3), 82.2 (0), 120.1 (0), 120.6 (0), 131.5 (1), 138.5 (1), 148.7 (0), 165.6 (0); MS *m*/*e* 291 (M^+, 100), 260. Anal. Calcd for $C_9H_{10}INO_2$: C, 37.13; H, 3.46; N, 4.81. Found: C, 37.22; H, 3.48; N, 4.68.

Cross-Coupling Reaction of *o*-Iodoanilines 2 with (Trimethylsilyl)ethyne (Scheme 1, Table 2). The corresponding *o*-iodoaniline **2** (40 mmol), $Pd(PPh_3)_2Cl_2$ (1.4 g, 2 mmol), and CuI (381 mg, 2 mmol) were placed in an oven-dried flask under N_2. Dry Et_3N was added, and the resulting suspension was cooled at 0 °C and magnetically stirred. Upon dropwise addition of (trimethylsilyl)acetylene (**3**, 4.3 g, 44 mmol), the mixture was stirred at rt until TLC showed the disappearance of the starting aniline (∼3 h). Solvents and volatiles were then removed at reduced pressure, and ether was added to the resulting residue. After filtration over Celite, the organic extract was washed with a saturated aqueous solution of NaCl and dried over Na_2SO_4. Solvents were removed at reduced pressure, giving a residue containing compounds **4**, which were chromatographed and further purified by either distillation or recrystallization.

4,6-Dimethyl-2-[2-(trimethylsilyl)ethynyl]aniline (4a): oil, chromatographed on silica gel 10:1 hexane/AcOEt, and distilled at 110 °C (10^{-2} mmHg); IR (NaCl) ν 3478, 3385, 2141, 1250; ^{1}H NMR δ 0.26 (s, 9H), 2.13 (s, 3H), 2.13 (s, 3H), 2.18 (s, 3H), 4.07 (s br, 2H), 6.84 (s, 1H), 7.02 (s, 1H); ^{13}C NMR δ 0.1 (3), 17.4 (3), 20.1(3), 98.9 (0), 102.3 (0), 107.3 (0), 121.5 (0), 126.4 (0), 129.8 (1), 131.9 (1), 144.0 (0); MS *m*/*e* 217 (M^+, 90), 202 (100), 187, 172; HRMS calcd for $C_{13}H_{19}NSi$ (M^+) 217.1287, found 217.1289.

6-Chloro-4-methyl-2-[2-(trimethylsilyl)ethynyl]-aniline (4b): white solid, mp 32−33 °C; IR (NaCl) ν 3488,

(37) Benkeser, R.; Gosnell, R. B. *J. Org. Chem.* **1957**, *22*, 327.
(38) Barluenga, J.; Rodríguez, M. A.; Campos, P. J. *J. Org. Chem.* **1990**, *55*, 3104.
(39) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic: London, 1985; p 18.
(40) Kajigaeshi, S.; Kakinami, T.; Yamasaki, H.; Fujisaki, S.; Okamoto, T. *Bull. Chem. Soc. Jpn.* **1988**, *61*, 601.
(41) Adams, R.; Holmes, R. R. *J. Am. Chem. Soc.* **1952**, *74*, 3038.
(42) Berliner, E. *J. Am. Chem. Soc.* **1956**, *78*, 3632.

3387, 2147, 1250; ^{1}H NMR δ 0.28 (s, 9H), 2.19 (s, 3H), 4.48 (s br, 2H), 7.05 (s, 2H); ^{13}C NMR δ −0.5 (3), 19.9 (3), 100.2 (0), 101.0 (0), 108.6 (0), 118.4 (0), 127.0 (0), 130.4 (1), 130.8 (1), 142.4 (0); MS *m/e* 239 ($M^+ + 2$, 36), 237 (M^+, 100), 222, 207, 186; HRMS calcd for $C_{12}H_{16}ClNSi$ (M^+) 237.0741, found 237.0742.

4-Methyl-2-[2-(trimethylsilyl)ethynyl]aniline (4c): white solid, mp 54−56 °C; IR (KBr) ν 3484, 3385, 2143; ^{1}H NMR δ 0.28 (s, 9H), 2.21 (s, 3H), 4.11 (s br, 2H), 6.22 (d, J = 8.3 Hz, 1H), 6.95 (dd, J = 2, 8.3 Hz, 1H), 7.14 (d, J = 2 Hz, 1H); ^{13}C NMR δ 0.1 (3), 20.1 (3), 99.3 (0), 101.9 (0), 107.7 (0), 114.3 (1), 126.9 (0), 130.6 (1), 132.2 (1), 145.8 (0); MS *m/e* 203 (M^+, 72), 188 (100); HRMS calcd for $C_{12}H_{17}NSi$ (M^+) 203.1130, found 203.1132.

4-Chloro-2-[2-(trimethylsilyl)ethynyl]aniline (4d): light yellow oil, chromatographed on silica gel 20:1 hexane/AcOEt, and distilled at 85 °C (10^{-2} mmHg); IR (NaCl) ν 3484, 3387, 2153, 1250; ^{1}H NMR δ 0.28 (s, 9H), 4.25 (s br, 2H), 6.61 (d, J = 8.6 Hz, 1H), 7.07 (dd, J = 2.4, 8.6 Hz, 1H), 7.28 (d, J = 2.4 Hz, 1H); ^{13}C NMR δ −0.1 (3), 100.2 (0), 100.9 (0), 108.9 (0), 115.2 (1), 121.7 (0), 129.7 (1), 131.3 (1), 146.7 (0); MS *m/e* 225 ($M^+ + 2$, 17), 223 (M^+, 50), 208 (100); HRMS calcd for $C_{11}H_{14}ClNSi$ (M^+) 223.0584, found 223.0583.

4-Bromo-6-chloro-2-[2-(trimethylsilyl)ethynyl]aniline (4e): colorless oil, chromatographed on silica gel 20:1 hexane/AcOEt, and distilled at 105 °C (10^{-2} mmHg); IR (NaCl) ν 3489, 3389, 2155, 1250; ^{1}H NMR δ 0.27 (s, 9H), 4.63 (s br, 2H), 7.33 (s, 2H); ^{13}C NMR δ −0.1 (3), 99.2 (0), 102.1 (0), 107.6 (0), 110.1 (0), 119.1 (0), 132.0 (1), 132.8 (1), 143.8 (0); MS *m/e* 305 ($M^+ + 4$, 22), 303 ($M^+ + 2$, 80), 301 (M^+, 61), 288 (100), 207.

4-*tert*-Butyl-6-chloro-2-[2-(trimethylsilyl)ethynyl]aniline (4f): colorless oil, after column chromatography on silica gel 20:1 hexane/AcOEt; IR (KBr) ν 3489, 3388, 2151, 1250; ^{1}H NMR δ 0.28 (s, 9H), 1.26 (s, 9H), 4.50 (s br, 2H), 7.24 (s, 2H); ^{13}C NMR δ 0.0 (3), 31.2 (3), 33.9 (0), 99.9 (0), 101.4 (0), 108.3 (0), 118.4 (0), 127.2 (1), 127.2 (1), 140.9 (0), 142.3 (0); MS *m/e* 281 ($M^+ + 2$, 8), 279 (M^+, 4), 264 (100).

2-Methoxy-6-[2-(trimethylsilyl)ethynyl]-4-tritylaniline (4g): white solid, mp 159−160 °C; IR (KBr) ν 3472, 3378, 2133, 1283; ^{1}H NMR δ 0.29 (s, 9H), 3.60 (s, 3H), 4.39 (s br, 2H), 6.54 (d, J = 2 Hz, 1H), 6.92 (d, J = 2 Hz, 1H), 7.28 (m, 15 H); ^{13}C NMR δ 0.1, 55.4, 64.4, 99.4, 102.0, 105.7, 115.0, 125.2, 125.7, 127.3, 131.0, 135.4, 137.2, 145.5, 146.7; MS *m/e* 461 (M^+, 51), 384 (100), 165.

4-Bromo-2-nitro-6-[2-(trimethylsilyl)ethynyl]aniline (4h): yellow solid, mp 123−124 °C; IR (KBr) ν 3493, 3372, 2155; ^{1}H NMR δ 0.31 (s, 9H), 6.75 (s br, 2H), 7.65 (d, J = 2.3 Hz, 1H), 8.27 (d, J = 2.3 Hz, 1H); ^{13}C NMR δ −0.3 (3), 97.3 (0), 105.0 (0), 106.3 (0), 113.9 (0), 128.8 (1), 130.1 (0), 140.7 (1), 144.3 (0); MS *m/e* 314 ($M^+ + 2$, 100), 312 (M^+, 100). Anal. Calcd for $C_{11}H_{13}BrN_2O_2Si$: C, 42.18; H, 4.18; N, 8.94. Found: C, 42.34; H, 4.02; N, 9.04.

4-Nitro-2-methoxy-6-[2-(trimethylsilyl)ethynyl]aniline (4i): yellow solid, mp 156−158 °C; IR (KBr) ν 3505, 3393, 2151; ^{1}H NMR δ 0.28 (s, 9H), 3.92 (s, 3H), 5.12 (s br, 2H), 7.57 (d, J = 1.6 Hz, 1H), 7.94 (d, J = 1.6 Hz, 1H); ^{13}C NMR δ −0.2 (3), 56.0 (3), 98.8 (0), 101.8 (0), 105.0 (0), 105.2 (1), 121.6 (1), 137.3 (0), 144.7 (0), 144.9 (0); MS *m/e* 264 (M^+, 100), 249, 234; HRMS calcd for $C_{10}H_{16}N_2O_3Si$ (M^+) 264.0930, found 264.0931.

Methyl 4-amino-3-methoxy-5-[2-(trimethylsilyl)ethynyl]benzoate (4j): white solid, mp 105−106 °C; IR (KBr) ν 3486, 3366, 2149; ^{1}H NMR δ 0.28 (s, 9H), 3.88 (s, 3H), 3.91 (s, 3H), 4.82 (s br, 2H), 7.40 (d, J = 2.2 Hz, 1H), 7.72 (d, J = 2.2 Hz, 1H); ^{13}C NMR δ −0.1 (3), 51.7 (3), 55.6 (3), 100.1 (0), 100.4 (0), 105.9 (0), 110.7 (1), 118.0 (0), 126.9 (1), 143.0 (0), 145.4 (0), 166.7 (0); MS *m/e* 277 (M^+, 100), 247; HRMS calcd for $C_{14}H_{19}NO_3Si$ (M^+) 277.1134, found 277.1135.

Methyl 4-amino-5-methyl-3-[2-(trimethylsilyl)ethynyl]benzoate (4k): light yellow solid, mp 100 °C; IR (KBr) ν 3488, 3389, 2143; ^{1}H NMR δ 0.21 (s, 9H), 2.05 (s, 3H), 3.75 (s, 3H), 4.70 (s br, 2H), 7.59 (d, J = 1.9 Hz, 1H), 7.84 (d, J = 1.9 Hz, 1H); ^{13}C NMR δ −0.3, 16.9, 51.0, 99.5, 100.8, 106.1, 118.0, 120.1, 128.2, 131.9, 150.2, 166.2; MS *m/e* 261(M^+, 100), 246; HRMS calcd for $C_{14}H_{19}NO_2Si$ (M^+) 261.1157, found 261.1154.

Representative Procedure for the Cyclization of [(Trimethylsilyl)ethynyl]anilines 4, Giving Indoles 5 (Scheme 1, Table 2). The *o*-[(trimethylsilyl)ethynyl]aniline **4** (15 mmol) and CuI (30 mmol) were placed under N_2 in an oven-dried flask fitted with a condeser, and DMF (4 mL/mmol of **4**) was added. The mixture was heated at 100 °C until TLC showed the disappearance of the starting aniline (∼2.5 h), and then the mixture was cooled at rt. After addition of ether (a large excess) and filtration over Celite (washing solids several times with more ether), the combined ethereal solution was washed with a saturated aqueous solution of NaCl and dried over Na_2SO_4. The remaining solution was evaporated and chromatographed, yielding indoles **5**, which were further purified by vacuum distillation or recrystallization.

5,7-Dimethyl-1*H*-indole (5a): colorless oil, chromatographed on silica gel 7:1 hexane/AcOEt, and distilled at 90 °C (10^{-1} mmHg); IR (NaCl) ν 3418, 2918, 1109, 843, 725; ^{1}H NMR δ 2.59 (s, 3H), 2.71 (s, 3H), 6.72 (m, 1H), 7.11 (s, 1H), 7.16 (m, 1H), 7.30 (s, 1H), 7.54 (s br, 1H); ^{13}C NMR δ 16.4 (3), 21.3 (3), 102.4 (1), 117.9 (1), 119.8 (0), 123.9 (0), 124.2 (1), 127.6 (0), 129.1 (1), 133.6 (0); MS *m/e* 145 (M^+, 100), 130, 115, 102; HRMS calcd for $C_{10}H_{11}N$ (M^+) 145.0892, found 145.0893.

7-Chloro-5-methyl-1*H*-indole (5b): light yellow oil, chromatographed on silica gel 20:1 hexane/AcOEt; IR (NaCl) ν 3322, 2918, 1314, 841, 723; ^{1}H NMR δ 2.58 (s, 3H), 6.64 (m, 1H), 7.17 (m, 1H), 7.22 (s, 1H), 7.48 (s, 1H), 8.19 (s br, 1H); ^{13}C NMR δ 21.1 (3), 102.8 (1), 115.9 (0), 118.9 (1), 122.6 (1), 124.8 (1), 129.2 (0), 130.1 (0), 131.2 (0); MS *m/e* 167 ($M^+ + 2$, 21), 165 (M^+, 72), 130 (100), 102; HRMS calcd for C_9H_8ClN (M^+) 165.0345, found 165.0344.

5-Methyl-1*H*-indole (5c): white solid, mp 60 °C (lit.[43] mp 58 °C); IR (NaCl) ν 3387, 2917, 1341, 799, 762, 718; ^{1}H NMR δ 2.45 (s, 3H), 6.47 (m, 1H), 7.02 (d, J = 7.5 Hz, 1H), 7.17 (m, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.43 (m, 1H), 8.05 (s br, 1H); ^{13}C NMR δ 21.3 (3), 101.6 (1), 110.6 (1), 120.1 (1), 123.4 (1), 124.2 (1), 127.8 (0), 128.8 (0), 133.8 (0); MS *m/e* 131 (M^+, 68), 130 ($M^+ - 1$, 100), 103.

5-Chloro-1*H*-indole (5d): white solid, mp 67−69 °C (lit.[7a] mp 65 °C); IR (KBr) ν 3385, 3106, 1094, 1065, 876, 801, 762, 735; ^{1}H NMR δ 6.52 (m, 1H), 7.15−7.32 (m, 3H), 7.64 (m, 1H), 8.19 (s br, 1H); ^{13}C NMR δ 102.2 (1), 111.9 (1), 119.9 (1), 122.1 (1), 125.2 (0), 125.5 (1) 128.7 (0), 133.9 (0); MS *m/e* 153 ($M^+ + 2$, 33), 151 (M^+, 100), 124, 116, 89.

5-Bromo-7-chloro-1*H*-indole (5e): light yellow oil, chromatographed on silica gel 5:1 hexane/AcOEt; IR (NaCl) ν 3439, 1188, 762, 721, 710; ^{1}H NMR δ 6.54 (m, 1H), 7.25 (m, 1H), 7.34 (s, 1H), 7.69 (s, 1H), 8.48 (s br, 1H); ^{13}C NMR δ 103.1 (1), 112.2 (0), 117.1 (0), 121.8 (1), 123.7 (1), 125.8 (1), 130.2 (0), 133.4 (0); MS *m/e* 233 ($M^+ + 4$, 24), 231 ($M^+ + 2$, 100), 229 (M^+, 76), 150; HRMS calcd for C_8H_5BrClN (M^+) 228.9294, found 228.9296.

5-*tert*-Butyl-7-chloro-1*H*-indole (5f): colorless oil, chromatographed on silica gel 20:1 hexane/AcOEt; IR (NaCl) ν 3434, 2963, 1479, 1312, 862, 723; ^{1}H NMR δ 1.38 (s, 9H), 6.55 (m, 1H), 7.20 (m, 1H), 7.28 (d, J = 1.6 Hz, 1H), 7.55 (d, J = 1.6 Hz, 1H), 8.32 (s br, 1H); ^{13}C NMR δ 31.8 (3), 34.7 (0), 103.5 (1), 115.1 (1), 116.0 (0), 119.7 (1), 124.8 (1), 128.9 (0), 131.2 (0), 144.1 (0); MS *m/e* 209 ($M^+ + 2$, 9), 207 (M^+, 29), 192 (100); HRMS calcd for $C_{12}H_{14}ClN$ ($M^+ + 2$) 209.0785, found 209.0781.

7-Methoxy-5-trityl-1*H*-indole (5g): light pink solid, mp 173−174 °C; IR (KBr) ν 3457, 3416, 1478, 1082, 723, 702; ^{1}H NMR δ 3.67 (s, 3H), 6.42 (d, J = 12.7 Hz, 1H), 7.14−7.31 (m, 18H), 8.32 (s br, 1H); ^{13}C NMR δ 55.1, 65.2, 103.3, 107.3, 115.1, 123.5, 124.6, 125.6, 127.2, 127.7, 131.3, 139.2, 144.7, 147.3; MS *m/e* 389 (M^+, 68), 312 (100). Anal. Calcd for $C_{28}H_{23}NO$: C, 86.34; H, 5.95; N, 3.60. Found: C, 86.52; H, 5.78; N, 3.62.

5-Bromo-7-nitro-1*H*-indole (5h): yellow solid, mp 208−209 °C; IR (KBr) ν 3381, 1292; ^{1}H NMR (DMSO-d_6) δ 6.80 (d, J = 3 Hz 1H), 7.67 (d, J = 3 Hz, 1H), 8.21 (d, J = 1.3 Hz, 1H), 8.33 (d, J = 1.3 Hz, 1H); 12.7 (s br, 1H); ^{13}C NMR (DMSO-d_6) δ 102.8 (1), 109.6 (0), 120.1 (1), 127.1 (0), 130.3 (1), 130.6 (1), 132.9 (0), 133.8 (0); MS *m/e* 242 ($M^+ + 2$, 100), 240 (M^+, 98); HRMS calcd for $C_8H_5BrN_2O_2$ (M^+) 239.9531, found 239.9534.

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7-Methoxy-5-nitro-1*H*-indole (5i): yellow solid, mp 154 °C; IR (KBr) ν 3376, 2924, 1337; ^{1}H NMR δ 4.03 (s, 3H), 6.70 (dd, J = 1.4, 2 Hz, 1H), 7.32 (t, J = 2 Hz, 1H), 7.53 (d, J = 1.2 Hz, 1H), 8.29 (d, J = 1.2 Hz, 1H), 8.73 (s br, 1H); ^{13}C NMR δ 55.8 (3), 97.2 (1), 105.4 (1), 111.7 (1), 126.2 (1), 127.1 (0), 129.6 (0), 142.4 (0), 145.3 (0); MS *m/e* 192 (M^+, 100), 146; HRMS calcd for $C_9H_8N_2O_3$ (M^+) 192.0536, found 192.0535.

Methyl 7-methoxy-1*H*-indole-5-carboxylate (5j): white solid, mp 176−177 °C; IR (KBr) ν 3349, 1684, 1269; ^{1}H NMR (DMSO-d_6) δ 3.96 (s, 3H), 4.08 (s, 3H), 6.69 (m, 1H), 7.35 (s, 1H), 7.47 (m, 1H), 8.08 (s, 1H), 11.74 (s br, 1H); ^{13}C NMR (DMSO-d_6) δ 51.7, 55.2, 101.4, 103.2, 116.6, 121.2, 126.5, 128.5, 128.9, 145.8, 167.4; MS *m/e* 205 (M^+, 100); HRMS calcd for $C_{11}H_{11}NO_3$ (M^+) 205.0741, found 205.0739.

Methyl 7-methyl-1*H*-indole-5-carboxylate (5k): white solid, mp 169−170 °C; IR (KBr) ν 3381, 1694, 1269; ^{1}H NMR (DMSO-d_6) δ 3.52 (s, 3 H), 3.91 (s, 3H), 6.67 (t, J = 2.6 Hz, 1H), 7.53 (t, J = 2.6 Hz, 1H), 7.63 (s, 1H), 8.21 (s, 1H), 11.54 (s br, 1H); ^{13}C NMR (DMSO-d_6) δ 16.8, 51.6, 103.1, 120.5, 120.6, 120.7, 122.0, 126.8, 126.9, 138.1, 167.4; MS *m/e* 189 (M^+, 100), 158; HRMS calcd for $C_{11}H_{11}NO_2$ (M^+) 189.0787, found 189.0789.

Elaboration of 7-Substituted Indoles (Scheme 2). The preparation of 7-substituted indoles **7** and **8** was accomplished in two steps from **5j** and **5k**, respectively.

Hydrolysis of 5j and 5k.[44] To a solution of the corresponding esters in ethanol was added aqueous KOH (20%), and the mixture was refluxed for 24 h. After extraction and evaporation of solvents, the indolic acids **5l** and **5m** were isolated as white solids in 95% and 96% yield, respectively. These indoles were taken to the next step without further purification.

7-Methoxy-1*H*-indole-5-carboxylic acid (5l): white solid, mp 221 °C, 95% yield; IR (KBr) ν 3457, 2924, 1672; ^{1}H NMR (DMSO-d_6) δ 4.06 (s, 3H), 6.65 (m, 1H), 7.30 (s, 1H), 7.44 (m, 1H), 8.01 (s, 1H), 11.66 (s, 1H), 12.50 (s br, 1H); ^{13}C NMR (DMSO-d_6) δ 55.2, 101.7, 103.2, 116.6, 122.3, 126.4, 128.5, 128.8, 145.7, 168.6; MS *m/e* 191 (M^+, 100), 176 (33). Anal. Calcd for $C_{10}H_9NO_3$: C, 62.84; H, 4.74; N, 7.32. Found: C, 63.02; H, 4.83; N, 7.04.

7-Methyl-1*H*-indole-5-carboxylic acid (5m): white solid, mp 160 °C, 96% yield; IR (KBr) ν 3358, 2922, 1659; ^{1}H NMR (DMSO-d_6) δ 3.62 (s, 3H), 6.68 (d, J = 2 Hz, 1H), 7.52 (d, J = 2 Hz, 1H), 7.61 (s, 1H), 8.18 (s, 1H), 11.50 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 16.9, 103.0, 120.5, 120.8, 121.6, 122.5, 126.6, 126.9, 138.1, 168.6; MS *m/e* 175 (M^+, 100), 158; HRMS calcd for $C_{10}H_9NO_2$ (M^+) 175.0633, found 175.0633.

7-Methoxy-1*H*-indole (7): brownish oil, 65% yield, from the decarboxylation[9,45] of **5l** (180 mg, 0.94 mmol) over Cu_2O (14 mg, 0.1 equiv) by heating at 230 °C over a period of 4 h under N_2 in quinoline (10 mL), purified by column chromatography on silica gel 10:1 hexane/AcOEt; IR (KBr) ν 2924, 1258, 1090, 1024; ^{1}H NMR (DMSO-d_6) δ 4.0 (s, 3H), 6.48 (dd, J = 1.6, 2.8 Hz, 1H), 6.72 (d, J = 7.8 Hz, 1H), 7.00 (t, J = 7.8 Hz, 1H), 7.22 (d, J = 7.8 Hz, 1H), 7.32 (t, J = 1.6 Hz, 1H), 11.25 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 55.0, 101.3, 101.4, 112.8, 119.3, 124.7, 126.0, 129.1, 146.2; MS *m/e* 147 (M^+, 100); HRMS calcd for C_9H_9NO (M^+) 147.0682, found 147.0684.

7-Methyl-1*H*-indole (8): white solid, mp 79−80 °C (lit.[9] 81−83 °C), 50% yield from the decarboxylation[9,45] of **5m** (190 mg, 1.08 mmol) over Cu_2O (25 mg, 0.17 mmol) by heating at 230 °C over a period of 4 h under N_2 in quinoline (10 mL), purified by column chromatography on silica gel 20:1 hexane/AcOEt; IR (KBr) ν 3412, 2926, 1341; ^{1}H NMR δ 2.53 (s, 3H), 6.59 (dd, J = 1.9, 3.0 Hz, 1H), 7.05 (m, 2H), 7.24 (m, 1H), 7.53 (d br, J = 7.0 Hz, 1H), 8.10 (s br, 1H); ^{13}C NMR δ 16.6, 103.0, 113.3, 118.3, 119.9, 122.4, 123.7, 127.3, 135.3; MS *m/e* 147 (M^+, 100).

Preparation of Benzodipyrroles 12 and 15 (Schemes 3 and 4). The synthesis of these compounds was carried out by an adaptation of the general method described for indole synthesis in this paper.

1,3-Diamino-2,4-diiodo-6-methylbenzene (10). Double iodination was done in one pot, following method I described in this paper, in 95% yield, by simply doubling the amount of IPy_2BF_4: white solid, mp 105−106 °C dec; IR (KBr) ν 3410, 3320, 1603, 1456; ^{1}H NMR δ 2.14 (s, 3 H), 4.16 (s br, 2H), 4.48 (s br, 2H), 7.31 (s, 1H); ^{13}C NMR δ 17.6 (3), 66.7 (0), 73.2 (0), 114.4 (0), 138.9 (1), 144.4 (0), 145.7 (0); MS m/z 374 (M^+, 100), 274, 120. Anal. Calcd for $C_7H_8N_2I_2$: C, 22.48; H, 2.16; N, 7.49. Found: C, 22.31; H, 2.16; N, 7.48.

1,3-Diamino-6-Methyl-2,4-bis[2-(trimethylsilyl)ethynyl]-benzene (11): white solid, mp 133 °C, chromatographed on silica gel 50:1 hexane/AcOEt, and sublimed at 100 °C (10^{-2} mmHg); IR (KBr) ν 3464, 3370, 2135; ^{1}H NMR δ 0.25 (s, 9H), 0.29 (s, 9H), 2.03 (s, 3H), 4.33 (s br, 2H), 4.65 (s br, 2 H), 6.98 (s, 1H); ^{13}C NMR δ 0.2, 16.4, 92.7, 96.2, 97.2, 98.4, 102.4, 105.5, 110.5, 133.9, 147.5, 149.2; MS *m/e* 314 (M^+, 100), 284; HRMS calcd for $C_{17}H_{26}N_2Si_2$ (M^+) 314.1668, found 314.1669.

5-Methyl-1,6-dihydrobenzo[1,2-*b*:3,4-*b*′]dipyrrole (12): from 1.3 g (4.14 mmol) of **11** and 3.15 g (16.56 mmol) of CuI under the above-described conditions for cyclizing to indoles, giving 212 mg of a white solid, mp 149−151, 30% yield, purified by column chromatography on silica gel 5:1 hexane/AcOEt; IR (KBr) ν 3381, 1109, 721; ^{1}H NMR (DMSO-d_6) δ 3.66 (s, 3H), 6.46 (t, J = 2 Hz, 1H), 6.77 (m, 1H), 7.15 (m, 1H), 7.3 (t, J = 2 Hz, 1H), 11.04 (s br, 1H), 11.18 (s br, 1H); ^{13}C NMR (DMSO-d_6) δ 17.6, 98.7, 101.9, 113.3, 113.7, 114.3, 120.1 (2 peaks), 122.1, 127.6, 132.5; MS *m/e* 171 (M^+ + 1, 13), 170 (M^+, 100); HRMS calcd for $C_{11}H_{10}N_2$ (M^+) 170.0846, found 170.0844.

***N*-Tosyl-5-amino-7-methoxyindole (13).** To a solution of **5i** in DMSO was added KOH (2 equiv). The mixture was stirred at rt for 3 h, and the solution became deep red. After addition of TsCl (1.5 equiv), the solution turned colorless. After 2 h, the reaction mixture was diluted with H_2O. Upon extraction with ether, the organic layer was dried over Na_2SO_4, and the solvents were removed under vacuum. Chromatography on silica gel with 20:1 hexane/AcOEt furnished the *N*-tosylated derivative as an orange solid. Reduction with hydrogen in an autoclave, using Pd on carbon as catalyst, was run in AcOEt for 16 h. Filtration over Celite and evaporation of solvents afforded indole **13**, in 85% overall yield for the two steps after chromatographic purification: white solid, mp 118−119 °C; IR (KBr) ν 3441, 3376, 1593, 1169; ^{1}H NMR δ 2.37 (s, 3H), 3.5 (s br, 2 H), 3.62 (s, 3H), 6.08 (d, J = 1.7 Hz, 1H), 6.40 (d, J = 1.7 Hz, 1H), 6.44 (d, J = 3 Hz, 1H), 7.25 (d, J = 6.9 Hz, 2H), 7.69 (d, J = 6.9 Hz, 2H), 7.71 (d, J = 6.9 Hz, 1H); ^{13}C NMR δ 21.4, 55.2, 97.1, 98.2, 106.6, 118.4, 127.1, 129.0, 129.1, 134.4, 137.0, 143.4, 143.8, 147.6; MS *m/e* 316 (M^+, 39), 161 (100). Anal. Calcd for $C_{16}H_{16}N_2O_3S$: C, 60.74; H, 5.10; N, 8.85. Found: C, 60.34; H, 5.12; N, 8.68.

***N*-Tosyl-5-amino-4-Iodo-7-methoxyindole (14):** iodination of **13** (0.14 g, 1.26 mmol) with IPy_2BF_4 (0.8 g, 2.15 mmol) in 98% yield, white solid, mp 94−96 °C; IR (KBr) ν 3360, 2926, 1595, 1364, 1171; ^{1}H NMR δ 2.37 (s, 3H), 3.6 (s, 3H), 6.19 (s, 1H), 6.47 (d, J = 3.7 Hz, 1H), 7.23 (d, J = 8.3 Hz, 2H), 7.67 (d, J = 8.3 Hz, 2H), 7.76 (d, J = 3.7 Hz, 1H); ^{13}C NMR δ 21.5, 55.3, 64.3, 96.0, 110.1, 117.5, 123.6, 127.1, 128.8, 129.2, 136.0, 143.8, 144.2, 149.5; MS *m/e* 442 (M^+, 33), 316, 287; HRMS calcd for $C_{16}H_{15}IN_2O_3S$ (M^+) 441.9848, found 441.9837.

***N*-Tosyl-5-amino-4-[2-(trimethylsilyl)ethynyl]-7-methoxyindole (15).** To a solution of **14** (600 mg, 1.36 mmmol) and (trimethylsilyl)acetylene (0.21 mL, 1.49 mmol) under N_2 at rt in dry Et_3N and CH_2Cl_2 (Et_3N/CH_2Cl_2 1:80, 40 mL) were added $Pd(PPh_3)_2Cl_2$ (48 mg, 5 mol %) and CuI (13 mg, 5 mol %). The mixture was heated at reflux until TLC showed the disappearance of the starting indole (~2 h). Solvents and volatile compounds were removed under vacuum. The residue was taken up in ether, and the remaining solids were eliminated by filtration over Celite. Solvent evaporation at reduced pressure and chromatography on silica gel 3:1 hexane/AcOEt furnished indole **15** as an oil, which was crystallized from ether, 448 mg, (80%): white solid, mp 71−73 °C; IR (KBr) ν 3478, 3381, 2959, 2137; ^{1}H NMR δ 0.29 (s, 9H), 2.37 (s, 3H), 3.62 (s, 3H), 4.21 (s br, 2H), 6.03 (s, 1H), 6.67 (d, J = 3.8 Hz, 1H), 7.22 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 8.3 Hz, 2H), 7.76 (d, J = 3.8 Hz, 1H); ^{13}C NMR δ 0.20, 21.4, 55.0, 91.5, 95.3, 99.6, 101.4, 106.4, 117.5, 127.0, 129.2, 135.4, 136.7, 144.0, 146.7,

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148.4; MS *m/e* 412 (M^+, 34), 257 (100); HRMS calcd for $C_{21}H_{24}N_2O_3SSi$ (M^+) 412.1277, found 412.1288.

4-Methoxy-3-tosyl-3,6-dihydrobenzo[1,2-*b*:4,3-*b*′]dipyrrole (16). The cyclization of **15** (370 mg, 0.9 mmol), mediated by CuI (342 mg, 1.8 mmol), as previously described in the general procedure, modifying the reaction time to only 25 min, gave, after chromatography on silica gel 3:1 hexane/AcOEt and recrystallization from CH_2Cl_2/hexane, 138 mg (45%) of **16**: white solid, mp 73−74 °C; IR (KBr) ν 3408, 2926, 1169; ^{1}H NMR δ 2.4 (s, 3 H), 3.65 (s, 3H), 6.68 (m, 1H), 6.70 (s, 1H), 6.89 (d, J = 3.4 Hz, 1H), 7.13 (m, 1H), 7.23 (d, J = 8.3 Hz, 2H), 7.70 (d, J = 8.3 Hz, 2H), 7.90 (d, J = 3.4 Hz, 1H), 8.18 (s br, 1H); ^{13}C NMR δ 21.5, 55.7, 91.3, 100.9, 105.6, 114.3, 121.0, 122.2, 125.3, 126.9, 128.0, 129.2, 132.2, 137.6, 143.7, 144.8; MS *m/e* 340 (M^+, 48), 157 (100); HRMS calcd for $C_{18}H_{16}N_2O_3S$ (M^+) 340.0882, found 340.0885.

Iodination of Indoles (Scheme 5). **Preparation of 2-(Trimethylsilyl)-1*H*-indole (19).** The literature procedure for the C-2 substitution on indole[31a] was modified as follows: to a solution of 1*H*-indole (1g, 8.5 mmol) in THF (15 mL), cooled to −78 °C, was added BuLi dropwise (3.5 mL of 2.5 M solution in hexane) under N_2. After being stirred at −78 °C for an additional 30 min, the mixture was purged in the vacuum line, and a stream of CO_2 gas was passed over the suspension for 15 min. Upon stirring the reaction for 1 h at rt, a white solid was obtained. Volatiles were removed in the vacuum line. The resulting solid was suspended in dry THF (20 mL) and cooled to −70 °C, and then *t*-BuLi (5.2 mL of 1.7 M solution in pentane) was added. The solution became yellow and was further stirred for 1 h at the same temperature. After addition of TMSCl, the mixture turned white, and the stirring was prolonged for 1.5 h at −70 °C. Water (1 mL) was added while the reaction gradually warmed to rt. The mixture was treated with a saturated aqueous solution of NH_4Cl, vigorously stirred for 5 min, and extracted with ether, and the combined organic layers were dried over Na_2SO_4. Solvents were evaporated under vacuum, and the residue was purified by column chromatography 40:1 hexane/AcOEt, yielding 0.71 g (44%) of the desired 2-(trimethylsilyl)indole as a light yellow oil: IR (NaCl) ν 3420, 2957, 1251, 1102, 841; ^{1}H NMR δ 0.75 (s, 9H), 7.19 (d, J = 0.7 Hz, 1H), 7.5−7.7 (m, 3H), 8.13 (d, J = 7.3 Hz, 1H), 8.30 (s br, 1H); ^{13}C NMR δ −1.3, 110.8, 111.2, 119.5, 120.4, 122.0, 128.5, 138.1, 138.6; MS *m/e* 189 (M^+, 53), 174 (100).

***N*-Methyl-2-(trimethylsilyl)indole (20):**[31b] light yellow oil, chromatographed on silica gel 50:1 hexane/AcOEt; IR (NaCl) ν 2957, 1466, 1358, 1250, 845; ^{1}H NMR δ 0.55 (s, 9H), 3.97 (s, 3H), 6.86 (s, 1H), 7.27 (td, J = 0.7, 8.1 Hz, 1H), 7.37 (td, J = 0.7, 8.1 Hz, 1H), 7.41 (d, J = 8.1 Hz, 1H), 7.77 (d, J = 8.1 Hz, 1H); ^{13}C NMR δ −0.6, 32.8, 108.9, 111.2, 119.0, 120.6, 121.9, 128.2, 140.0, 140.9; MS *m/e* 203 (M^+, 48), 188 (100).

The iodination of indoles was carried out according to the experimental procedure previously described to iodinate indole with IPy_2BF_4.[14b]

3-Iodo-5,7-dimethyl-1*H*-indole (17): from **5a** (99%), brown oil; IR (NaCl) ν 3407, 2917, 1595, 1460, 1148, 1115, 847, 793; ^{1}H NMR δ 2.44 (s, 1H), 2.55 (s, 3H), 6.96 (s, 1H), 7.16 (s, 1H), 7.20 (s, 1H), 8.15 (s br, 1H); ^{13}C NMR δ 16.0 (3), 21.3 (3), 57.1 (0), 117.9 (1), 120.1 (0), 125.2 (1), 128.1 (1), 129.3 (0), 130.2 (0), 133.2 (0); MS *m/e* 271 (M^+, 100), 144, 115.

3-Iodo-5-chloro-1*H*-indole (18): from **5d** (99%), brown oil; IR (NaCl) ν 3407, 2924, 1454, 1099, 799; ^{1}H NMR δ 7.18 (d, J = 2.1 Hz, 1H), 7.24 (d, J = 2.1 Hz, 1H), 7.28 (t, J = 2.1 Hz, 1H), 7.42 (d, J = 2.1 Hz, 1H), 8.92 (s br, 1H); ^{13}C NMR δ 56.2 (0), 112.4 (1), 120.2 (1), 123.2 (1), 126.2 (0), 129.8 (1), 130.7 (0), 133.9 (0); MS *m/e* 379 (M^+ + 2, 32), 277 (M^+, 100), 150.

3-Iodo-2-(trimethylsilyl)-1*H*-indole (21): from **19** (99%), colorless oil; IR (NaCl) ν 3439, 2955, 1250, 1102, 843. ^{1}H NMR δ 0.64 (s, 9H), 7.3−7.5 (m, 3H), 7.66 (m, 1H), 8.55 (s br, 1H); ^{13}C NMR δ −1.4, 68.4, 110.9, 120.4, 120.7, 123.2, 131.4, 137.4, 138.6; MS *m/e* 315 (M^+, 100); HRMS calcd for $C_{11}H_{14}SiIN$ 314.9942, found 314.9940.

***N*-Methyl-3-iodo-2-(trimethylsilyl)indole (22):** from **20** (99%), white solid, mp 64 °C; IR (KBr) ν 2953, 1462, 1348, 1252, 845, 739; ^{1}H NMR δ 0.77 (s, 9H), 3.98 (s, 3H), 7.37−7.47 (m, 3H), 7.70 (d, J = 1.6, 7 Hz, 1H); ^{13}C NMR δ 1.7, 33.7, 68.4, 109.0, 119.9, 121.4, 123.1, 131.3, 139.5, 139.7; MS *m/e* 329 (M^+, 100), 314, 187.

2,3-Diiodo-1*H*-indole (23): from **21** (99%), white solid, mp 132 °C (lit.[30a] mp 130−131 °C); IR (KBr) ν 3363, 1437, 1302, 748; ^{1}H NMR δ 7.15 (m, 2H), 7.31 (d, J = 8.5 Hz, 1H), 7.43 (d, J = 7.5 Hz, 1H), 12.0 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 71.6, 91.1, 111.1, 119.9, 120.4, 122.4, 130.9, 139.0; MS *m/e* 369 (M^+, 100), 241, 115.

***N*-Methyl-2,3-diiodoindole (24):** from **22** using 2 equiv of IPy_2BF_4 and catalytic amounts of HBF_4 (99%), white solid, mp 76−78 °C; IR (KBr) ν 1452, 1416, 1323, 1227, 739; ^{1}H NMR (DMSO-d_6) δ 3.89 (s, 3H), 7.1−7.4 (m, 3H), 7.48 (dd, J = 1.8, 7.5 Hz, 1H); ^{13}C NMR (DMSO-d_6) δ 35.9, 71.6, 99.5, 110.7, 120.3, 120.6, 122.5, 130.9, 137.8; MS *m/e* 383 (M^+, 100), 368, 256, 129.

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Supporting Information Available: Copies of NMR spectra (44 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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