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Synthesis of Indoles from *o*-Haloanilines

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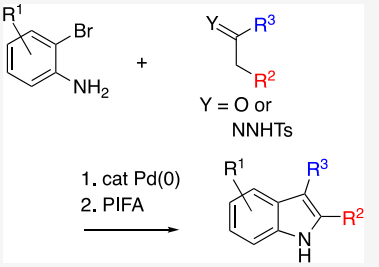
ABSTRACT: A convenient method for the synthesis of indoles has been developed by the sequential orchestration of the cross-coupling reaction of *o*-haloaniline and PIFA oxidation of the resulting 2-alkenylanilines. A highlight of this two-step indole synthesis is a modular strategy which is applicable to both acyclic and cyclic starting materials. Particularly noteworthy is the regiochemistry that is complementary to the Fischer indole synthesis and related variants. Direct preparation of *N*−H indoles with no *N*-protecting group is also advantageous.



INTRODUCTION

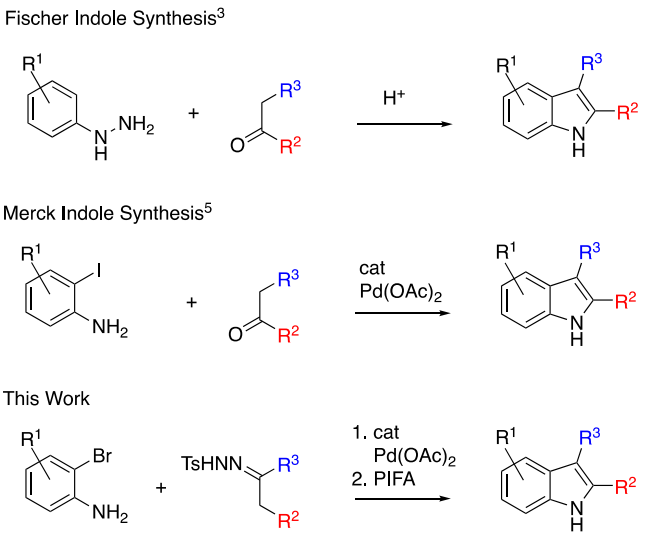
The indole ring motif is found in a large number of natural products and medicinally relevant compounds. The importance of indoles, coupled with a broad range of structural complexities, has spurred the development of many synthetic methods.[1,2] The venerable Fischer indole reaction is a classical method for preparing indoles from carbonyl compounds.[3] The palladium-catalyzed coupling reactions of *o*-haloaniline derivatives offer valuable alternatives to the Fischer indole synthesis.[4,5] As part of the projected total syntheses of structurally complex indole alkaloids, a flexible method for installing an indole scaffold to an advanced intermediate at a late stage of synthesis was required; and a new approach of employing ketones or aldehydes that are regioisomeric to the substrates for the Fischer indole synthesis and variants was highly desirable.[3,5] An operationally expedient method for preparing *N*−H indoles without the use of an *N*-protecting group, while accessing all substitution patterns was also ideal. Toward this end, an effective strategy was recently found in oxidative cyclization of 2-alkenylanilines,[6] which were easily accessible from *o*-haloanilines. We report herein a convenient synthesis of indoles by the sequential implementation of Pd-catalyzed cross-coupling reactions of *o*-haloanilines and oxidative cyclization of the resulting 2-alkenylanilines (Scheme 1).

RESULTS AND DISCUSSION

Our work commenced with the construction of a tricyclic indole nucleus possessing a five-membered or six-membered ring, as this motif is frequently embedded in structurally complex natural products.[1,7] The known 2-cyclopentenyl and 2-cyclohexenyl anilines **3a** and **3b** were prepared in 82−86% yields by the Suzuki coupling reaction according to literature procedures (Scheme 2A).[8] When a THF solution of **3a** and **3b** was next treated with $PhI(OCOCF_3)_2$ (PIFA) (1 equiv) at rt, oxidative cyclization proceeded cleanly to afford indoles **5a** and **5b** in 80 and 73% yields, respectively, requiring no *N*-protection. Cyclization was facile and took ≤10 min. In the literature, other hypervalent iodines or other oxidants had been employed for oxidative cyclization of typically *N*-protected aniline derivatives (e.g., Cbz, Bz, or Ts),[9] but commercially available PIFA proved to be effective.

During an initial phase of this work the Suzuki coupling of **1** or the Stille reaction of vinyl stannanes (when readily

Scheme 1. Representative Synthetic Methods for Indoles



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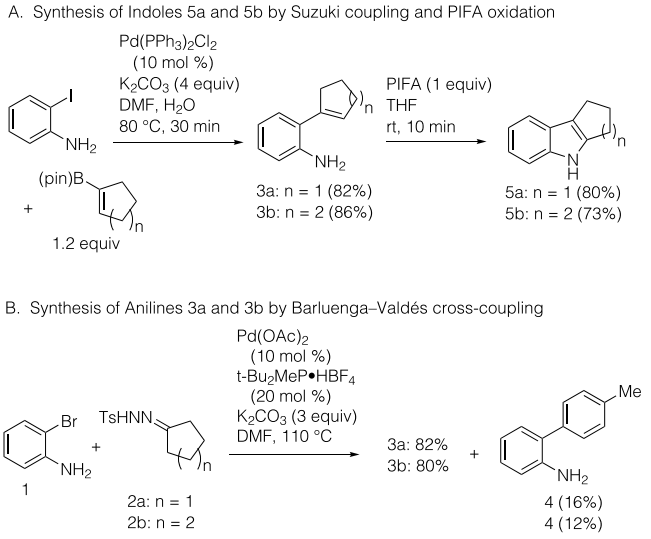
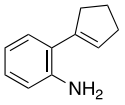
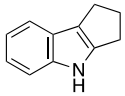
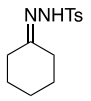
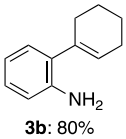
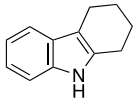
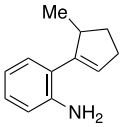
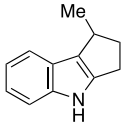
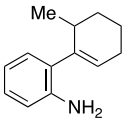
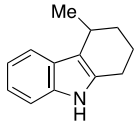
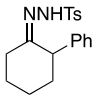
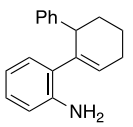
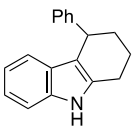
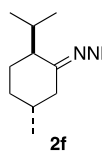
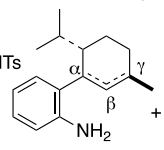
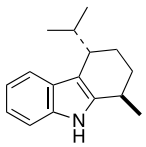
Scheme 2. Suzuki and Barluenga–Valdés Coupling toward Indoles



available) was employed for the preparation of the requisite 2-alkenylanilines.[6] Our attention was shifted to a more expedient option of the Barluenga–Valdés cross-coupling reaction involving typically crystalline tosylhydrazones to bypass the otherwise necessary pre-functionalization (e.g., the intermediacy of enol triflates and/or boronates) of carbonyl compounds.[10,11] Barluenga's seminal application of tosylhydrazones as diazo precursors[12] provides new routes to an array of alkenes. However, we were concerned that the presence of an unprotected amine ortho to the bromide might be problematic;[13] only one example had been reported for coupling of *o*-bromo-*N*-methylaniline.[10e] An effective solution was found in the Houpis–Chen protocol [$Pd(OAc)_2$, $tBu_2MeP{\cdot}HBF_4$, and K_2CO_3 in DMA], which was designed specifically for cross-coupling of *o*-halo unprotected aniline derivatives: its adaptation to **2a** and **2b** indeed afforded **3a** and **3b** in good yields (Scheme 2B).[14,15,16a] In accordance with previous observations by the Janssen team, 4′-methylbiphenyl-2-amine (**4**) was also obtained in significant amounts (16 and 12%, respectively). The formation of this *p*-tolyl adduct, derived from the tosylhydrazone moiety, seems to be a general limitation for Janssen's reaction conditions designed for aryl halide coupling partners having an o-nitrogen functionality. A hydrazone containing an electron-withdrawing group (e.g., *p*-nitrosulfonylphenylhydrazones) was reported to offer an effective solution to avert the formation of 4.[14] Importantly, however, the formation of this side product in the Barluenga coupling reaction interfered with neither subsequent PIFA oxidation of 2-alkenylanilines **3a**/**3b**, nor the isolation of pure indole products.[16b] Since our overriding objective was the indole synthesis by the sequential implementation of the key steps, inexpensive costs prompted us to employ tosylhydrazones.

The scope of our indole synthesis was next examined with cyclopentanone- and cyclohexanone-derived tosylhydrazones with particular emphasis on regioselective formation of the indole products **5a**–**5f** (Table 1). Coupling of 2-alkyl substituted derivatives proceeded with complete regioselectivity to afford the less substituted alkenes **3c**–**3f** as the sole regioisomers, resulting in regioselective formation of indoles **5c**–**5f**. The latter is illustrative of the synthetic utility of this

Table 1. Additional Tricyclic Indoles

2a–2f	anilines 3a–3f[a]	indoles 5a–5f[b]
 **2a**	 **3a**: 82% + **4** (16%)	 **5a**: 80%
 **2b**	 **3b**: 80% + **4** (12%)	 **5b**: 73%
 **2c**	 **3c**: 75% + **4** (13%)	 **5c**: 76%
 **2d**	 **3d**: 76% + **4** (18%)	 **5d**: 69%
 **2e**	 **3e**: 71% + **4** (19%)	 **5e**: 83%
 **2f**	 **3f** (α,β) + **3f′** (β,γ): 74%, 9:1 + **4** (14%)	 **5f**: 68%

[a] **1** (1 equiv), **2a**–**2f** (1.2 equiv), $Pd(OAc)_2$ (10 mol %), $^tBu_2MeP{\cdot}HBF_4$ (20 mol %), K_2CO_3 (3 equiv), DMF, 90–110 °C, 5–6 h. [b] PIFA (1 equiv), THF (0.3 M), rt, 10 min.

method, compared to the Fischer indole synthesis and its Merck's variant (Scheme 3).[3,5a,17] Particularly noteworthy are the different regiochemical outcomes of the latter procedure and our method, leading to the constitutional indole isomers starting from the same ketone substrates. The alternative regioselectivity would be valuable in synthetic planning of complex indole alkaloids, as it offers greater flexibility.

The formation of dehydroindoles (dihydrocarbazoles) was next probed starting from cyclohexenone-derived tosylhydrazones via oxidative cyclization of 1,3-dienyanilines **3g**–**3i** (Table 2). Not surprisingly, indole formation was accompanied by over-oxidation to the corresponding carbazoles (e.g., **5g** + **5g′** and **5i** + **5i′**: **5g** was separated from **5g′**). In the case of **2i** the first (coupling) step produced the over-oxidation product **3i′** in 16% yield in addition to the desired product **3i** (72%). When the latter was subjected to PIFA oxidation, an inseparable mixture of **5i** and **5i′** was obtained in a combined yield of 79%. These results suggest that related application of

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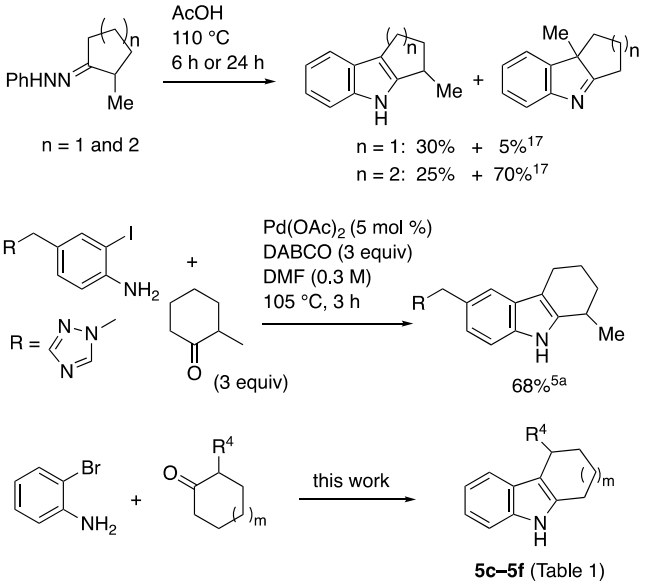
Scheme 3. Comparison of Regiochemical Outcomes in the Indole Synthesis

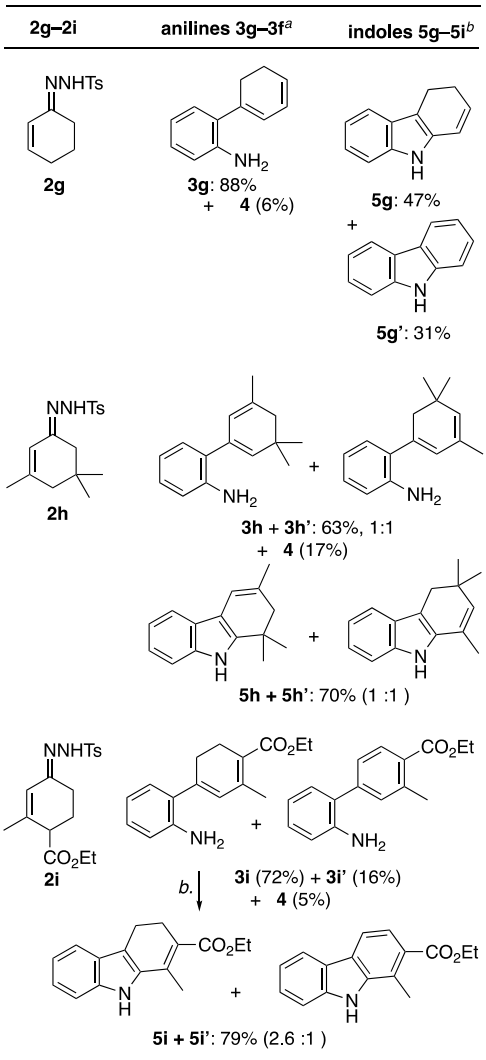


cyclohexenone derivatives could offer new access to carbazoles, as a useful alternative to oxidative cyclization of 2-amino-biaryls, which recently attracted extensive attention.[18,19]

The regioselective formation of **3g** was in accordance with the intermediacy of the pi-allyl palladium complex (Scheme 4).[10b,c] Several known examples notwithstanding,[10] the cross-coupling reaction of cyclohexenones is under-explored. For example, no examples were previously reported in the literature for the Barluenga coupling of 3-alkylcyclohexenone (e.g., endocyclic enone having a 3-alkyl substituent) tosylhydrazones.[10,20] We note, in passing, that the Suzuki coupling reaction of a 2-dioxaborolany-1,3-cyclohexadiene[21] would afford the cyclohexadienyl aniline, which is regioisomeric to **3g** (corresponding to the coupling methods **A** and **B** in Scheme 2); a judicious choice of cross-coupling reactions would thus provide a regiodivergent route to both dehydroindoles, which underscores the versatility of the centerpiece method.

Finally, the formation of indoles **5j**−**5m** from acyclic substrates was examined to establish the broad substrate scope (Table 3); overall yields were comparable to those of the aforementioned synthesis of tricyclic indoles (Tables 1 and 2).[22] Indole **5j** was prepared uneventfully. As expected, **3k** having the less substituted terminal alkene (from beta-hydride elimination at the methyl position with preference to the methine position) was obtained in 78% yield; and the corresponding indole **5k** was next obtained in 81% yield. A low level of regioselectivity was observed for the corresponding coupling of **2l** to afford a mixture of **3l** and **3l′** (an *E*/*Z* mixture) (∼1 + 1.4 in 61% yield). Regioselectivity for a methyl vs a methylene position (∼2:3) was generally poor.[10a] These results are in sharp contrast to the exclusive preference for a methyl or methylene position over a methine position (e.g., **2k** → **3k** in addition to **2c**−**2f** → **3c**−**3f**). The use of an *α*-siloxy group was next examined as a regiocontrol element that is suitable for subsequent elaboration and indeed afforded **3m** as a single regioisomer (as 3:2 geometrical isomers) in 74% yield. Since the *N*−H indole product was expected to be prone to elimination of the siloxy moiety, PIFA oxidation of the corresponding *N*-sulfonamide was carried out to deliver **5m** in 77% yield: this oxidation expectedly took longer (5 h) compared to that of *N*−H anilines (10 min), but PIFA was equally effective. Ultimately, Suzuki coupling could be relied on to achieve a regioselective synthesis of indoles from acyclic

Table 2. Tricyclic Dehydroindoles



[a]**1** (1 equiv), **2a**−**2f** (1.2 equiv), $Pd(OAc)_2$ (10 mol %), $^tBu_2MeP{\cdot}HBF_4$ (20 mol %), K_2CO_3 (3 equiv), DMF, 90−110 °C, 5−6 h. [b]PIFA (1 equiv), THF (0.3 M), rt, 10 min.

Scheme 4. Mechanism for the Synthesis of 3g

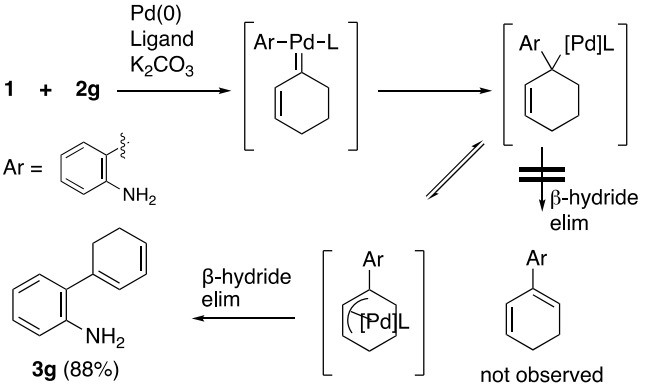


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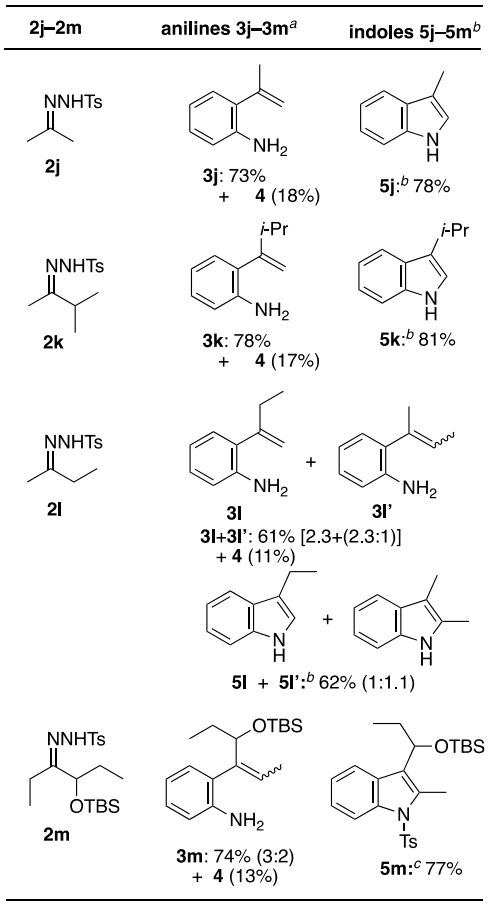
Table 3. Indoles from Acyclic Ketones



[a]**1** (1 equiv), **2a**–**2f** (1.2 equiv), $Pd(OAc)_2$ (10 mol %), $^tBu_2MeP{\cdot}HBF_4$ (20 mol %), K_2CO_3 (3 equiv), DMF, 90–110 °C, 5–6 h. [b]PIFA (1 equiv), THF (0.3 M), rt, 10 min. [c]PIFA (3 equiv), THF (0.3 M), rt, 5 h.

substrates (involving a methyl vs methylene position of ketones) by regioselective formation of the prefabricated enol boronates.[8,21]

CONCLUSIONS

In conclusion we have developed an expedient method for the synthesis of indoles by the sequential implementation of the Pd-catalyzed cross-coupling reaction of *o*-haloaniline and PIFA oxidation of the resulting 2-alkenylanilines. Highlights of this modular synthesis include the regiochemical outcome that is complementary to the Fischer indole synthesis and related variants, and direct preparation of free *N*–H indoles without requiring an *N*-protecting group. Application in total synthesis of structurally complex indole alkaloids will be reported in due course.

EXPERIMENTAL SECTION

All materials were obtained from commercial vendors and used without further purification unless otherwise noted. Air- and moisture-sensitive manipulations were carried out under a nitrogen or argon atmosphere using oven-dried glassware and standard syringe/septa techniques. Thin-layer chromatography (TLC) analysis was run on SiO_2 TLC plates that were visualized with UV light (254 nm) and phosphomolybdic acid, anisaldehyde, I_2, or a ninhydrin staining solution. Column chromatography was performed with silica gel 60 (70–230 mesh). The ^1H and ^{13}C NMR spectra were measured at 400 and 100 MHz in $CDCl_3$, respectively. The chemical shifts (δ) of the ^1H and ^{13}C NMR spectra were reported with reference to the NMR solvent signals at 7.26 and 77.2 ppm, respectively. High resolution mass spectra were obtained with an Orbitrap mass analyzer.

Representative Procedure for the Preparation of 2-Alkenylanilines. *Representative Procedure for the Suzuki Coupling Reaction.* A suspension of $Pd(PPh_3)_2Cl_2$ (0.28 g, 0.40 mmol), K_2CO_3 (2.21 g, 16.00 mmol), and *o*-iodoaniline (0.941 g, 4.3 mmol) in a 2:1 DMF/H_2O mixture (15 mL) was stirred at rt, followed by addition of cyclopenten-1-yl boronic acid pinacol ester (1.0 g, 5.1 mmol) in DMF (3 mL). The reaction mixture was heated in an oil bath to 80 °C for 30 min. The reaction was quenched with water (10 mL), and the resulting mixture was extracted with diethyl ether (10 mL × 3). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered, and concentrated under reduced pressure. The residue was purified with column chromatography using 8:1 hexane–EtOAc (R_f 0.30) to give 562 mg (82%) of **3a**[8] as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$): δ 7.12 (dd, J = 7.6, 1.3 Hz, 1H), 7.04 (td, J = 7.6, 1.4 Hz, 1H), 6.76–6.70 (m, 2H), 6.00 (t, J = 1.8 Hz, 1H), 3.93 (br s, 2H), 2.72–2.68 (m, 2H), 2.58–2.54 (m, 2H), 1.97 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 144.0, 141.3, 128.3, 128.2, 127.6, 123.7, 118.2, 115.8, 36.4, 33.9, 23.2; MS (EI) m/z: 159 (M, 100), 144 (49), 130 (67), 117 (18), 103 (9), 90 (6), 77 (12), 63 (5), 50 (2).

Similarly, 597 mg (86%) of **3b**[8] was prepared as a colorless oil: ^1H NMR (400 MHz, $CDCl_3$) δ 7.04 (td, J = 7.6, 1.5 Hz, 1H), 6.98 (dd, J = 7.6, 1.5 Hz, 1H), 6.74–6.68 (m, 2H), 5.75 (m, 1H), 3.76 (br, 2H), 2.26–2.22 (m, 2H), 2.20–2.12 (m, 2H), 1.78–1.74 (m, 2H), 1.72–1.66 (m, 2H); $^{13}C\{^1H\}$ NMR (100 MHz, $CDCl_3$): δ 143.2, 136.5, 130.5, 128.7, 127.5, 126.8, 118.3, 115.4, 29.4, 25.5, 23.2, 22.2; MS (EI) m/z: 173 ($[M]^+$, 100), 144 (100), 119 (26), 93 (7), 77 (12), 51 (4).

Representative Procedure for the Barluenga–Valdés Coupling Reaction. 2 mmol-Scale Experiment. A solution of $Pd(OAc)_2$ (26.6 mg, 0.12 mmol), $^tBu_2MeP{\cdot}HBF_4$ (63.6 mg, 0.26 mmol), and K_2CO_3 (828 mg, 6 mmol) was placed in degassed DMF (1.6 mL) under an atmosphere of argon. *o*-Bromoaniline (**1**) (224 ml, 2 mmol) was then added. The reaction mixture was placed under vacuum and backfilled with argon. After the mixture had been heated to 110 °C, a solution of tosylhydrazone **2a** (604 mg, 2.4 mmol) in degassed DMF (2 mL) was added over 2 h by using a syringe pump. The resulting mixture was stirred at 110 °C in an oil bath for an additional 5 h (until the stating aniline **1** was consumed). The reaction mixture was then cooled to rt and water (6 mL) was added. The mixture was extracted with EtOAc (2 × 15 mL). The organic extracts were washed with brine (6 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash silica gel column chromatography using 9:1 hexane/EtOAc as the eluent to afford 245 mg (78%) of aniline **3a** as a colorless oil.

0.5 mmol-Scale Experiment. A solution of $Pd(OAc)_2$ (11.2 mg, 0.05 mmol), $^tBu_2MeP{\cdot}HBF_4$ (26.5 mg, 0.10 mmol), and K_2CO_3 (207 mg, 1.5 mmol) was placed in degassed DMF (0.4 mL) under an atmosphere of argon. *o*-Bromoaniline (**1**) (56 μL, 0.5 mmol) was then added. The reaction mixture was placed under vacuum and backfilled with argon. After the mixture had been heated to 110 °C, a solution of tosylhydrazone **2a** (151 mg, 0.6 mmol) in degassed DMF (0.8 mL) was added over 1 h by using a syringe pump. The resulting mixture was stirred at 110 °C in an oil bath for an additional 5 h (until the stating aniline **1** was consumed). The reaction mixture was then cooled to rt and water (2 mL) was added. The mixture was extracted with EtOAc (2 × 8 mL). The organic extracts were washed with brine (3 mL), dried over Na_2SO_4, and concentrated under vacuum. The residue was purified by flash silica gel column chromatography using 9:1 hexane/EtOAc as the eluent to afford 64 mg (82%) of aniline **3a** as a colorless oil.

Representative Procedure for Oxidative Cyclization with PIFA. *0.36 mmol Scale Experiment.* A solution of bis-(trifluoroacetoxy)iodo)benzene (PIFA) (162 mg, 0.36 mmol) in THF (1.2 mL) was added dropwise (over a 5 min period) to a solution of *o*-cyclopentenylaniline (**3a**) (60 mg, 0.36 mmol) in THF

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(1.2 mL) under an atmosphere of argon. The resulting mixture was stirred at rt for an additional 5 min (until TLC indicated the disappearance of **3a**), filtered through a short pad of silica gel, and concentrated under reduced pressure to give 31 mg (80%) of indole **5a**[23] as a white solid by flash column chromatography using hexane/EtOAc (9:1): mp 106−107 °C; R_f 0.4 (hexane/EtOAc 9:1); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83 (br s, 1H), 7.43 (dd, J = 6.6, 2.2 Hz, 1H), 7.3 (dd, J = 6.4, 2.0 Hz, 1H), 7.10−7.06 (m, 2H), 2.88−2.85 (m, 2H), 2.83 (m, 2H), 2.57−2.51 (m, 2H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$): δ 143.6, 141.0, 124.7, 120.5, 119.8, 119.4, 118.4, 111.2, 28.6, 25.8, 24.4; MS (EI) m/z: 157 ([M]$^+$, 100), 130 (25), 115 (4), 102 (4), 77 (8), 65 (4).

1 mmol Scale Experiment. A solution of bis(trifluoroacetoxy)-iodo)benzene (PIFA) (430 mg, 3.5 mmol) in THF (3.5 mL) was added dropwise (over a 5 min period) to a solution of *o*-isopropenylaniline (**3j**) (133 mg, 1 mmol) in THF (3.5 mL) under an atmosphere of argon. The resulting mixture was stirred at rt for an additional 5 min (until TLC indicated the disappearance of **3j**), filtered through a short pad of silica gel, and concentrated under reduced pressure to give 105 mg (80%) of indole **5j**[30] as a white solid by flash column chromatography using hexane/EtOAc (9:1): mp 95−96 °C; R_f 0.4 (hexane/EtOAc 9:1). The characterization data are listed below. An initial experiment in a smaller (0.35 mmol) scale experiment afforded 78% yield (as shown in Table 1).

Indole **5b**.[24] 13 mg (73%) as a white solid by flash column chromatography using hexane/EtOAc (9:1); R_f 0.4 (hexane/EtOAc 9:1); ^{1}H NMR ($CDCl_3$): δ 7.67 (br s, 1H), 7.46 (d, J = 7.0 Hz, 1H), 7.28 (d, J = 8.1 Hz, 1H), 7.09 (dt, J = 7.0, 1.3 Hz, 2H), 2.75−2.70 (m, 4H), 1.90 (m, 4H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 138.7, 135.6, 134.0, 127.8, 121.0, 119.1, 117.7, 110.2, 23.3, 23.2, 23.1, 20.9.

Indole **5c**.[25] 29 mg (76%) as a white solid by flash column chromatography using hexane/EtOAc (9:1); R_f 0.4 (hexane/EtOAc 9:1); ^{1}H NMR ($CDCl_3$): δ 7.78 (br, 1H), 7.48 (d, J = 8.2 Hz, 1H), 7.30 (dd, J = 7.2, 1.5 Hz, 1H), 7.07−7.05 (m, 2H), 3.36 (m, 1H), 2.89 (m, 1H), 2.81 (m, 1H), 2.73 (m, 1H), 2.03 (m, 1H), 1.36 (d, J = 6.8 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 142.9, 141.1, 124.8, 124.6, 120.6, 119.6, 118.3, 111.5, 38.3, 33.4, 25.6, 21.5.

Indole **5d**.[26] 28 mg (69%) as a white solid by flash column chromatography using hexane/EtOAc (9:1); R_f 0.4 (hexane/EtOAc 9:1); ^{1}H NMR ($CDCl_3$): δ 7.65 (br s, 1H) 7.56 (dd, J = 7.8, 1.4 Hz, 1H), 7.28 (dt, J = 8.1, 0.9 Hz, 1H), 7.13−7.03 (m, 2H), 3.11 (m, 1H), 2.72−2.69 (m, 2H), 2.02−1.94 (m, 2H), 1.81 (m, 1H), 1.58 (m, 1H), 1.37 (d, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 136.0, 134.0, 127.6, 121.0, 119.2, 118.9, 115.3, 110.6, 32.3, 27.3, 23.7, 21.4, 20.6.

Indole **5e**.[27] 45 mg (83%) as a white solid by flash column chromatography using hexane/EtOAc (8:1); R_f 0.5 (hexane/EtOAc 9:1); ^{1}H NMR ($CDCl_3$): δ 7.79 (br s, 1H), 7.31−7.22 (m, 3H), 7.22−7.17 (m,3H), 7.05 (ddd, J = 8.2, 6.7, 1.5 Hz, 1H), 6.89−6.80 (m, 2H), 4.21 (m, 1H), 2.92−2.74 (m, 2H), 2.24 (m, 1H), 2.00 (m, 1H), 1.89−1.79 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 146.3, 136.0, 135.6, 128.4, 128.3, 127.6, 126.1, 121.1, 119.4, 119.2, 112.2, 110.4, 40.0, 34.6, 23.6, 21.3.

Indole **5f**. 12 mg (68%) as a brown solid by flash column chromatography using hexane/EtOAc (9:1); R_f 0.4 (hexane/EtOAc 9:1); ^{1}H NMR ($CDCl_3$): δ 7.77 (br s, 1H), 7.60 (d, J = 7.9 Hz, 1H), 7.30 (d, J = 8.0 Hz, 1H), 7.10 (dd, J = 7.9, 6.8 Hz, 1H), 7.03 (dd, J = 8.0, 7.9 Hz, 1H), 2.99−2.90 (m, 2H), 2.63 (dt, J = 11.7, 6.8 Hz, 1H), 2.09 (m, 1H), 1.89 (m, 1H), 1.60 (m, 1H), 1.39 (m, 1H), 1.28 (d, J = 6.9 Hz, 3H), 1.08 (d, J = 6.9 Hz, 3H), 0.70 (d, J = 6.9 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 124.9, 123.0, 120.6, 119.6, 118.9, 110.5, 110.4, 109.4, 39.4, 31.1, 28.9, 22.7, 22.0, 21.1, 20.0, 17.0; HRMS (ESI) m/z: calcd for $C_{16}H_{21}N$ [M]$^+$, calcd 227.1674; found, 227.1621.

Indole **5g**.[28] 27 mg (47%) as a white solid by flash column chromatography using hexane/EtOAc (9:1); R_f 0.4 (hexane/EtOAc 9:1); ^{1}H NMR ($CDCl_3$): δ 7.80 (br s, 1H) 7.7.48 (m, 1H), 7.29 (m, 1H), 7.12−7.07 (m, 2H), 6.42 (d, J = 9.7 Hz, 1H), 5.97 (dt, J = 9.7, 4.4 Hz, 1H), 2.90 (t, J = 9.2 Hz, 2H), 2.51 (m, 2H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 128.3, 126.0, 121.5, 120.5, 119.9, 119.6, 118.7, 118.4, 111.1, 110.7, 24.5, 19.3.

Indoles **5h** + **5h′**. 37 mg (70%) as a brown waxy solid by flash column chromatography using hexane/EtOAc (9:1); R_f 0.4 (hexane/EtOAc 9:1); ^{1}H NMR ($CDCl_3$): δ 7.34 (dd, J = 16.8, 8.5 Hz, 4H), 7.16 (d, J = 8.5 Hz, 1H), 7.13−7.08 (m, 2H), 6.70 (d, J = 8.5 Hz, 1H), 5.77 (s, 1H), 5.55 (s, 1H), 5.35 (s, 1H), 4.69 (s, 1H), 2.35−2.16 (m, 4H), 1.68 (s, 3H), 1.66 (s, 3H), 1.24 (s, 3H), 1.22 (s, 3H), 1.14 (s, 3H) 1.12 (s, 3H); ^{13}C{^{1}H} NMR (of one regioisomer) ($CDCl_3$): δ 137.2, 136.5, 130.3, 129.6, 126.9, 124.0, 123.73, 120.1, 82.02, 77.4, 45.7, 33.4, 32.8, 29.3, 18.4; HRMS (ESI) m/z: calcd for $C_{15}H_{17}N$ [M]$^+$, calcd 211.1361; found, 227.1309.

Indoles **5i** + **5i′**.[29] 33 mg (in 57 and 22% yields) as a yellow waxy solid by flash column chromatography using hexane/EtOAc (9:1); R_f 0.4 (hexane/EtOAc 9:1); for **5i**: ^{1}H NMR ($CDCl_3$): δ 8.16 (br s, 1H), 7.55 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.19 (m, 1H), 7.12 (m, 1H), 4.26 (q, J = 7.1 Hz, 2H), 2.84 (m, 1H), 2.77 (s, 3H), 2.50−2.48 (m, 3H), 1.36 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 168.1, 130.8, 127.0, 121.0, 120.2, 119.7, 119.4, 114.6, 113.1, 111.2, 110.8, 60.7, 25.8, 22.1, 19.3, 15.2; for **5i′**: ^{1}H NMR ($CDCl_3$): δ 8.09 (d, J = 8.2 Hz, 1H), 7.93 (m, 1H), 7.51−7.44 (m, 2H), 7.28−7.22 (m, 2H), 4.42 (q, J = 7.1 Hz, 2H), 2.77 (s, 3H), 1.44 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 168.3, 141.0, 139.3, 126.8, 126.6, 125.4, 123.1, 122.6, 121.9, 121.1, 119.9, 117.2, 110.9, 60.1, 14.8, 14.4; HRMS (ESI) m/z: calcd for $C_{16}H_{17}NO_2$ [M]$^+$, calcd 255.1259; found, 255.1252.

Indole **5j**.[30] 19 mg (78%) as a white solid by flash column chromatography using hexane/EtOAc (9:1); R_f 0.4 (hexane/EtOAc 9:1); ^{1}H NMR ($CDCl_3$): δ 7.87 (br s, 1H), 7.59 (d, J = 7.9 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.19 (ddd, J = 8.0, 7.0, 1.3 Hz, 1H), 7.12 (ddd, J = 7.9, 7.0, 1.1 Hz, 1H), 6.97 (m, 1H), 2.34 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 136.5, 128.5, 122.0, 121.7, 119.3, 119.0, 111.9, 111.1, 9.8.

Indole **5k**.[30] 35 mg (81%) as a white solid by flash column chromatography using hexane/EtOAc (9:1); R_f 0.4 (hexane/EtOAc 9:1); ^{1}H NMR ($CDCl_3$): δ 7.88 (br s, 1H), 7.66 (d, J = 7.8 Hz, 1H), 7.36 (d, J = 8.1 Hz, 1H), 7.18 (ddd, J = 8.1, 7.0, 1.3 Hz, 1H), 7.11 (ddd, J = 7.8, 7.0, 1.1 Hz, 1H), 6.96 (d, J = 2.3 Hz, 1H), 3.22 (m, 1H), 1.37 (d, J = 6.9 Hz, 6H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 127.0, 124.3, 122.0, 119.6, 119.4, 119.2, 114.6, 111.3, 25.6, 23.5.

Indoles **5l** + **5l′**.[30,31] 37 mg (62%) as a white waxy solid by flash column chromatography using hexane/EtOAc (9:1); R_f 0.4 (hexane/EtOAc 9:1); for **5l**: ^{1}H NMR ($CDCl_3$): δ 7.66 (br s, 1H), 7.62 (d, J = 7.8 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.19 (ddd, J = 8.1, 7.0, 1.2 Hz, 1H) 7.14−7.04 (m, 2H), 6.98 (s, 1H), 2.80 (q, J = 7.6 Hz, 2H), 1.34 (t, J = 7.6 Hz, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 135.4, 130.8, 129.6, 129.6, 120.6, 119.1, 118.1, 110.1, 11.7, 8.6; for **5l′**: ^{1}H NMR ($CDCl_3$): δ 7.88 (br s, 1H), 7.25 (d, J = 7.3 Hz, 1H), 7.46 (dd, J = 6.9, 1.9 Hz, 1H), 7.14−7.04 (m, 2H), 2.37 (s, 3H), 2.23 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 136.6, 127.6, 122.1, 121.1, 119.2, 119.2, 119.1, 111.2, 18.5, 14.6.

Indole **5m**. 45 mg (77%) as a white solid by flash column chromatography using hexane/EtOAc (9:1); R_f 0.4 (hexane/EtOAc 9:1); ^{1}H NMR ($CDCl_3$): δ 8.17 (dd, J = 8.0, 1.2 Hz, 1H), 7.69 (d, J = 7.7 Hz, 1H), 7.55 (dd, J = 8.2 Hz, 2H), 7.24−7.17 (m, 2H), 7.14 (d, J = 8.2 Hz, 2H), 4.73 (t, J = 7.0 Hz, 1H), 2.54 (s, 3H), 2.32 (s, 3H), 1.90 (m, 1H), 1.70 (m, 1H), 0.81−0.78 (m, 3H), 0.77 (s, 9H), −0.06 (s, 3H), −0.38 (s, 3H); ^{13}C{^{1}H} NMR ($CDCl_3$): δ 144.4, 136.8, 136.3, 131.9, 129.6, 129.0, 126.1, 123.8, 123.7, 123.0, 120.7, 114.7, 70.1, 31.3, 25.7, 21.4, 18.1, 13.1, 10.4, −5.3, −5.2; HRMS (ESI) m/z: calcd for $C_{19}H_{20}NO_2S$ [M − OTBS]$^+$, calcd 326.1215; found, 326.1302.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.3c01047.

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Representative procedures, spectral listing, and NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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(16) (a) In small-scale experiments, 10 mol % of $Pd(OAc)_2$ and 20 mol % of $^tBu_2MeP{\cdot}HBF_4$ were used to ensure accurate weighing. In turn, the addition time (via a syringe pump) of tosylhydrazones was reduced to 1 h from Jassen chemists' 3 h.[14] A larger scale coupling reaction afforded comparable yields at reduced loadings [e.g., 6 mol % of $Pd(OAc)_2$] (3 mol % was employed in ref 14). See the Supporting Information for representative experimental procedures. (b) A one-pot protocol of combining both the cross-coupling and PIFA oxidation reactions seemed possible, but was not pursued: although PIFA oxidation did not require column chromatography, it became clean when simple filtration through a pad of silica gel was undertaken.

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