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A Cascade Synthesis of Indoles

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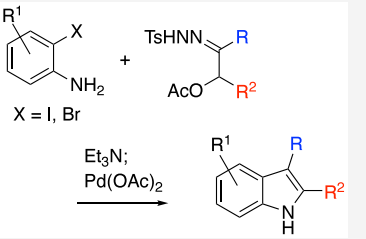
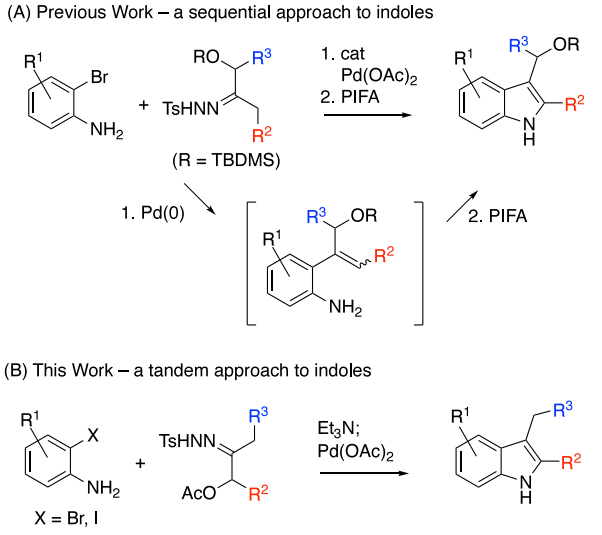
ABSTRACT: We report herein an expedient method for the regioselective synthesis of indoles from *o*-haloanilines and *α*-ketol-derived *N*-tosylhydrazones. This two-step, modular synthesis of *N*-H indoles can be carried out conveniently without purification of intermediates.



INTRODUCTION

The indole nucleus is among the most frequently encountered heterocycles in natural products. There is a continuing interest in the development of new synthetic methods for functionalized indoles.[1] The union of two readily available fragments is an effective strategy to construct the indole skeleton. Of burgeoning interest are inherently advantageous cascade reactions that allow indole synthesis in a single operation from simple starting materials.[2] We recently described indole synthesis by the sequential implementation of Pd-catalyzed cross-coupling of *o*-haloanilines with *N*-tosylhydrazones and oxidative cyclization of the resulting 2-alkenylanilines (Scheme 1A).[3] We report a variant for the convenient construction of mono- and disubstituted indoles with predetermined regiochemistry (Scheme 1B). This method features an intramolecular Barluenga–Valdés cross-coupling reaction, which, to our knowledge, has not been reported previously. A highlight is the regiochemical outcome of our indole syntheses that is complementary to the venerable Fischer indole synthesis and related variants with respect to the starting keto substrates, offering greater flexibility in synthetic planning.[4] Direct preparation of *N*-H indoles with no *N*-protecting group is also advantageous.

Scheme 1. Sequential and Tandem Approaches to Indoles



RESULTS AND DISCUSSION

Our previously reported synthesis of indoles proceeded in good overall yields.[3] Clean regioselectivity was observed in favor of the 2-alkenylanilines at the less substituted *α*-carbon (e.g., a methylene or methyl position in preference to the methine), when the starting *N*-tosylhydrazones are substituted at the *α* position. There was a clear limitation with unsymmetrical *N*-tosylhydrazones having no alpha-substituents, which proceeded with low regioselectivity. A solution was found in the use of an *α*-siloxy tosylhydrazone to secure regioselective formation of 2-alkenylanilines by the Barluenga–Valdés cross-coupling reaction[5] with *o*-bromoaniline (Scheme 1A). The corresponding *α*-acyloxy substrate was projected to display a new reaction manifold with complete regiocontrol (Scheme 1B). *α*-Acetoxy-*N*-tosylhydrazone **1** (prepared from the known acetate of propioin) and *o*-bromoaniline (**2**) were subjected to the Barluenga reaction under Houpis–Chen's modified conditions [$Pd(OAc)_2$, $tBu_2MeP{\cdot}HBF_4$, and K_2CO_3 in DMA].[6a] The desired indole **3** was obtained in 48% yield, together with 2-(4-methylphenyl)aniline (19%):[3,6b] the preliminary (unoptimized) result gave a modest yield, in part

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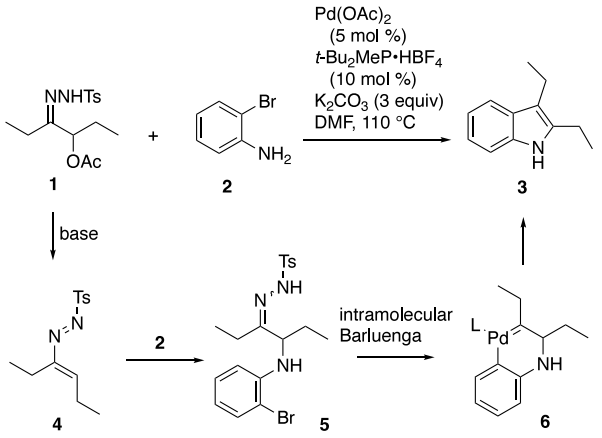
due to the known formation of the latter side-product. However, the formation of **3** as a single regioisomer was notable (Scheme 2). Tosylhydrazone **1** was chosen as an initial

Scheme 2. A Cascade Reaction Mechanism



substrate to shed light on the mechanistic pathways. Formation of **3** as a single regioisomer was in accord with the intermediacy of sulfonylazoalkene **4** (triggered by 1,4-elimination of acetate), followed by the aza-Michael reaction of aniline **2** and cyclization (**5** → **6** → **3**).[7]

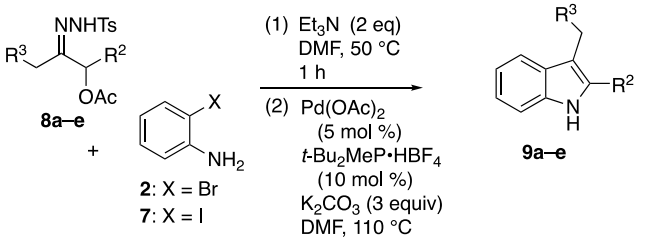
1,4-Elimination reactions of *N*-tosylhydrazones bearing a potential nucleofuge, such as halides or epoxides, at the α-carbon were well-known.[8,9] In addition to the venerable Eschenmoser fragmentation,[10] their useful synthetic applications involved conjugate addition reactions of carbon nucleophiles (e.g., cuprates) to the resulting *N*-sulfonyl azoalkenes and Diels–Alder reactions.[9,11] In marked contrast, only a handful of examples involving an acyloxy group as a leaving group were documented under somewhat harsh conditions (thermally or with base), along with thermal decomposition to alkynes or allenes.[12] Additionally, 1,4-elimination of α-acyloxy tosylhydrazones was not used to trigger a tandem reaction sequence.

In support of the initial 1,4-elimination reaction, the trapping product **5** was obtained cleanly in 90% yield by the action of triethylamine (which was superior to K_2CO_3) as a base at 50 °C. When **5** was then subjected to Houpis–Chen's conditions, the indole formation, an intramolecular Barluenga–Valdés reaction, proceeded cleanly in 81% yield. The indole **3** was also synthesized conveniently without the purification of intermediates in a comparable 70% yield.

This cascade synthesis of indoles was validated by a set of examples, in which the yield for each step of the two-step tandem sequence was determined to ascertain its efficiency (Scheme 3). Indoles **9a–c** were prepared in good yields from α-acetoxy tosylhydrazones **8a–c** and *o*-bromoaniline (**2**) under the aforementioned conditions.[13] Similarly, the coupling of **8c–e** and *o*-iodoaniline (**7**) (see below) also proceeded cleanly. As was the case with the synthesis of **3**, comparable yields were obtained when the intermediates were not purified (e.g., 80% and 82% for **9a** and **9b**, respectively).

However, it was surprising that **8f** failed to afford **9f**; instead, ketone **11** was isolated in a nearly quantitative yield (Scheme 4).[14] Also unanticipated was the exclusive formation of **12** with trace amounts of **9g** from **8g**: the Barluenga reaction pathway was surprisingly slower than the Bamford–Stevens-type

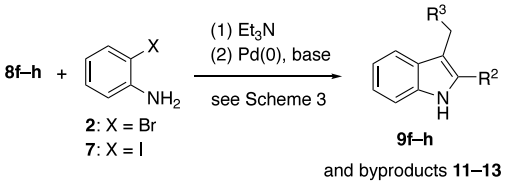
Scheme 3. Additional Indole Syntheses



with **2**:
a: R^2 = Et, R^3 = CH_2Ph
b: R^2 = *i*-Bu, R^3 = CH_2Ph
c: R^2 = *i*-Bu, R^3 = $(CH_2)_4CH_3$
with **7**:
c: R^2 = *i*-Bu, R^3 = $(CH_2)_4CH_3$
d: R^2 = Et, R^3 = $(CH_2)_4CH_3$
e: R^2 = $(CH_2)_5CH_3$, R^3 = CH_2Ph

with **2**:
a: (1) 88%; (2) 90%
b: (1) 94%; (2) 92%
c: (1) 88%; (2) 86%
with **7**:
c: (1) 91%; (2) 90%
d: (1) 88%; (2) 86%
e: (1) 90%; (2) 92%

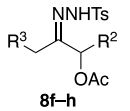
Scheme 4. Comparison of *o*-Bromoaniline and *o*-Iodoaniline

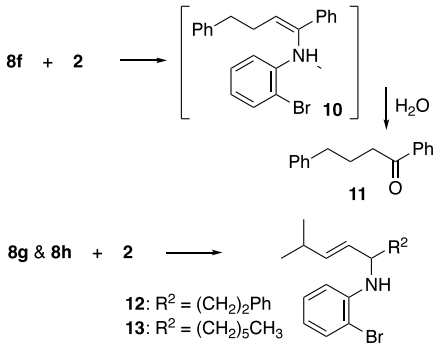


and byproducts **11–13**

SM	indole	yields (%) step (1)	yields (%) indole + byproduct
8f	**2**	88	**9f** (~0) + **11** (100)
8g	**2**	91	**9g** (~0) + **12** (100)
8h	**2**	91	**9h** (~50) + **13** (~50)
8f	**7**	88	**9f** (85) + **11** (0)
8g	**7**	88	**9g** (86) + **12** (0)
8h	**7**	94	**9h** (90) + **13** (0)

8f: R^2 = Ph, R^3 = CH_2Ph
8g: R^2 = $(CH_2)_2Ph$, R^3 = *i*-Pr
8h: R^2 = $(CH_2)_5CH_3$, R^3 = *i*-Pr





reaction. Similarly, the corresponding reaction of **8h** was plagued by the formation of a ~1:1 mixture of **9h** and **13**.[15] It was gratifying that an effective solution to the unforeseen side-reaction was found in the use of *o*-iodoaniline (**7**), where faster oxidative addition enabled the preparation of **9f** from **8f** in 85% yield. When **7** was utilized in place of **2**, clean formation of **9g** and **9h** was also observed in good yields.

Adaptation of the identical procedure also afforded tri- and tetracyclic indoles **15–18** smoothly (Scheme 5). These polycyclic indoles were synthesized in support of the projected

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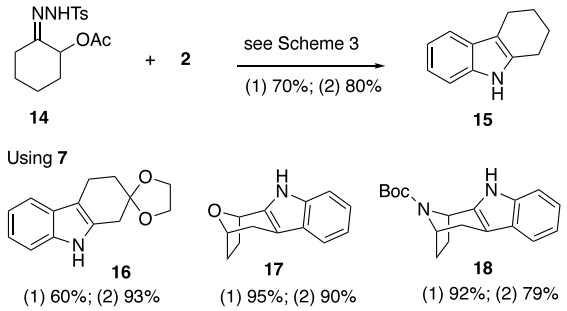
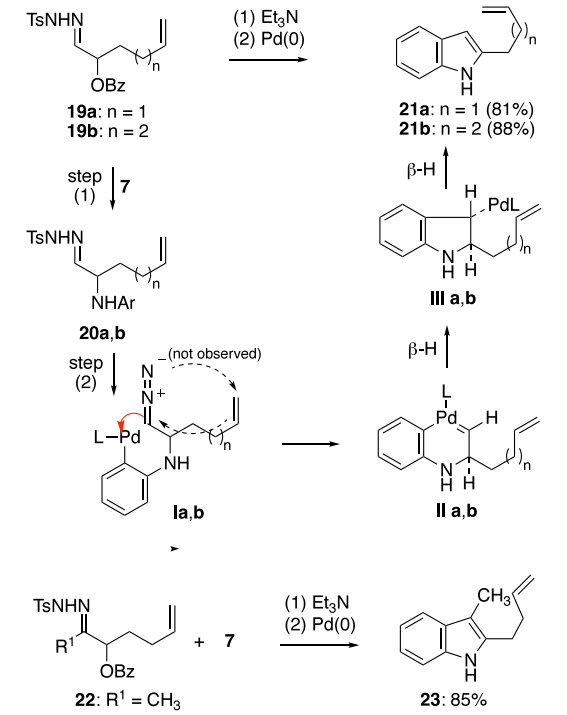
total synthesis studies toward structurally complex natural products.[16]

Scheme 5. Synthesis of Tri- and Tetracyclic Indoles



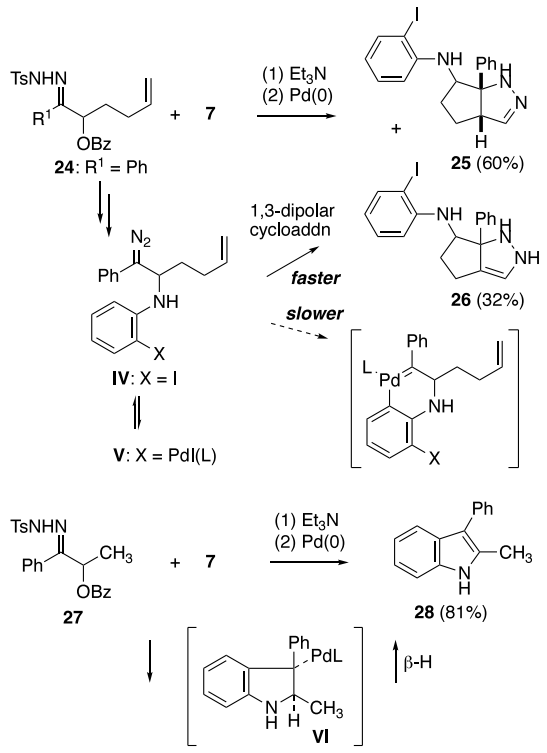
Frequent applications of the Barluenga reaction in the preparation of various olefins and heterocycles notwithstanding,[5] only a few computational reports have appeared.[17] To gain mechanistic insight into the hitherto unknown energetics of the key migratory insertion and rate-determining steps, the competition experiments of the diazo intermediate (from base-induced decomposition of an *N*-tosylhydrazone) between its subsequent reaction with the presumed arylpalladium intermediate and the competing 1,3-dipolar cycloaddition to the tethered olefin were carried out (Scheme 6). *N*-Tosylhydrazones **19a,b** (n = 1 and 2) derived from the corresponding aldehydes afforded indoles **21a,b**, via anilines **20a,b**, in excellent yields under standard conditions: as indicated with the red arrow in **Ia,b**, the reaction of the diazo group with the arylpalladium complex (from oxidative addition), **Ia,b** → **IIa,b**, proceeded cleanly with no 1,3-dipolar cycloadduct.[18,19a] Additionally, the intramolecular nature of the second step (Barluenga reaction) allowed determining the stereochemical outcome of **IIa,b** → **IIIa,b**, since the latter must be capable of syn β-H elimination leading to the indole products. Similarly, indole **23** was obtained in a comparable yield from **22** having the methyl group (R^1 = Me).[19b]

Scheme 6. Competition Experiments with 19a,b and 22



Interestingly, the corresponding tosylhydrazone **24** possessing the phenyl moiety (R^1 = Ph vs Me or H in Scheme 6) afforded no indole product (Scheme 7). The Barluenga reaction pathway of the diazo intermediate **V** was completely outcompeted by the diazo 1,3-dipolar cycloaddition to furnish a mixture of **25** and **26** in excellent yield. This result was attributed to the phenyl group impeding the key reaction step of **V** between the diazo group and the arylpalladium intermediate. In a control experiment with **27** lacking the butenyl side-chain, clean (81%) formation of indole **28** was observed, supporting the indicated stereochemistry of the presumed alkylpalladium intermediate **VI** to set the stage for the final syn β-H elimination step.

Scheme 7. Competition Experiments with 24



Taken together, these competition experiments corroborate the premise that the reaction between the diazo intermediate and the arylpalladium complex (from oxidative addition) is the rate-determining step in the Barluenga reaction and that the oxidative addition step is reversible (**IV** ⇄ **V**) with **V** being the catalyst resting state.[20]

CONCLUSIONS

In conclusion, we have developed a convenient synthesis of indoles from *o*-haloanilines and α-acyloxy-*N*-tosylhydrazones by the sequential orchestration of the base-induced 1,4-elimination, the aza-Michael reaction, and the intramolecular Pd-catalyzed cross-coupling reaction. This cascade variant can be carried out in good to excellent yields without isolating reaction intermediates. Advantages over our previous synthesis (involving the Barluenga reaction and subsequent PIFA

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oxidation)[3] are the predetermined regiochemistry, especially regarding unsymmetrical *N*-tosylhydrazone substrates having no alpha-substituents (e.g., having two different methylene groups); and the absence of the 2-(4-methylphenyl)aniline side-product derived from the toluenesulfonyl fragment, obviating the use of the nitrobenzenesulfonyl hydrazones.[6b] Both synthetic methods utilize the identical ketone starting materials (as the corresponding *N*-tosylhydrazones), which are regioisomers of those required for the Fischer indole synthesis and its variants. Finally, the intramolecular nature of the Pd-catalyzed cross-coupling (Barluenga) reaction is exploited to probe the hitherto unknown stereochemical outcome of the widely accepted alkylpalladium intermediates.

EXPERIMENTAL SECTION

General. Unless otherwise noted, reagents were obtained from commercial sources and were used without further purification. All glassware, syringes, needles, and magnetic stirring bars used in moisture-sensitive reactions were oven-dried and stored in desiccators prior to use. All moisture- or oxygen-sensitive reactions were conducted under an atmosphere of argon. Upon workup, solvents were evaporated by using a rotary evaporator. All solvents were purified prior to use. Ether and tetrahydrofuran were dried through alumina columns.

NMR spectra were measured on commercially available spectrometers (^{1}H at 400 and ^{13}C at 100 MHz) in $CDCl_3$ unless stated otherwise. Low- and high-resolution mass spectra were measured by the GC−MS and QTof ionization methods, respectively.

Analytical thin layer chromatography (TLC) was performed by using Merck 60 F254 glass plates precoated with a 0.25 mm thickness of silica gel. TLC plates were visualized with UV light (254 nm) and phosphomolybdic acid, anisaldehyde, I_2, or ninhydrin staining solutions. Column chromatography was performed on Kiesel gel 60 (70−230 mesh) silica gel. Unless otherwise noted, all compounds purified by chromatography were sufficiently pure (>95%) by ^{1}H NMR analysis.

Representative Procedure for the Preparation of o-Bromoaniline Trapping Products from α-Acyloxy-N-tosylhydrazones. In an oven-dried flask under an argon atmosphere were placed 2-bromoaniline (35.2 mg, 0.20 mmol) and tosylhydrazone **8c** (70 mg, 0.17 mmol), followed by DMF (0.8 mL). After the mixture had been heated at 50 °C, a solution of NEt_3 (0.05 mL, 0.34 mmol) in DMF (1 mL) was added dropwise (by syringe pump) over 1 h. The reaction mixture was then stirred at the same temperature for an additional 3 h. The reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (3 × 15 mL). The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (1:4 EtOAc−hexane) to afford the corresponding *o*-bromoaniline trapping product (78 mg, 88%) as a white solid: R_f = 0.3 (4:1 hexane−EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.2 Hz, 2H), 7.75 (br s, 1H), 7.34 (dd, J = 7.6, 1.5 Hz, 1H), 7.29 (d, J = 8.2 Hz, 2H), 6.83 (t, J = 8.3 Hz, 1H), 6.49 (td, J = 7.6 Hz, 1.5 Hz, 1H), 6.36 (dd, J = 8.3, 1.5 Hz, 1H), 4.38 (d, J = 6.7 Hz, 1H), 3.96 (q, J = 6.8 Hz, 1H), 2.44 (s, 3H), 2.04 (td, J = 7.4, 5.8, 2.5 Hz, 2H), 1.50−1.44 (m, 2H), 1.32−1.03 (m, 9H), 0.88−0.78 (m, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.6, 143.9, 143.8, 135.4 132.2, 129.5, 128.3, 128.0, 117.9, 112.0, 109.5, 57.6, 42.4, 31.2, 29.6, 25.8, 25.0, 24.7, 22.6, 22.4, 22.3, 21.6, 13.9; HRMS (ESI): m/z calcd for $C_{25}H_{36}BrN_3O_2S$: 522.1790 $[M + H]^+$; found: 522.1801.

Representative Procedure for the Preparation of Indole Products from o-Bromoaniline Trapping Products. A mixture of $Pd(OAc)_2$ (1.2 mg, 5 μmol), tBu$_2$MeP·HBF$_4$ (2.8 mg, 0.01 mmol), and K_2CO_3 (47.6 mg, 0.34 mmol) in DMF (1 mL) was heated to 110 °C under an argon atmosphere. A solution of the *o*-bromoaniline trapping product (60 mg, 0.114 mmol) in DMF (1 mL) was added dropwise (by syringe pump) over 1 h. The reaction mixture was then stirred at 110 °C for an additional 3 h. The reaction mixture was cooled to rt, and water (10 mL) was added. The mixture was extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with brine (6 mL), dried with Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (1:9 EtOAc−hexane) to afford the indole product **9c** (25.4 mg, 86%) as a waxy solid: R_f = 0.3 (4:1 hexane−EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (br s, 1H), 7.52 (dd, J = 7.4, 1.4 Hz, 1H), 7.27 (d, J = 7.4 Hz, 1H), 7.12−7.04 (m, 2H), 2.71−2.64 (m, 2H), 2.59 (d, J = 7.3 Hz, 2H), 2.00−1.91 (m, 1H), 1.67−1.58 (m, 2H), 1.40−1.22 (m, 6H), 0.97 (d, J = 6.6 Hz, 6H), 0.89 (t, J = 5.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 135.3, 134.2, 128.7, 120.7, 118.8, 118.4, 113.1, 110.1, 35.4, 31.8, 30.9, 29.5, 29.3, 24.3, 22.7, 22.6, 14.1; HRMS (ESI): m/z calcd for $C_{18}H_{27}N$: 258.2222 $[M + H]^+$; found: 258.2229.

Representative Procedure for the Preparation of o-Iodoaniline Trapping Products from α-Acyloxy-N-tosylhydrazones. In an oven-dried flask under an argon atmosphere were placed 2-iodoaniline (38.4 mg, 0.17 mmol), tosylhydrazone **8c** (60 mg, 0.14 mmol), and DMF (0.7 mL). After the mixture had been heated at 50 °C, a solution of NEt_3 (0.04 mL, 0.28 mmol) in DMF (1 mL) was added dropwise (by syringe pump) over 1 h. The reaction mixture was then stirred at the same temperature for an additional 3 h. The reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (3 × 15 mL). The organic extracts were washed with brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography (1:4 EtOAc−hexane) to afford the corresponding *o*-iodoaniline trapping product (75.7 mg, 91%) as a white solid: R_f = 0.3 (9:1 hexane−EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 8.1 Hz, 2H), 7.58 (dd, J = 7.6, 1.5 Hz, 1H), 7.30 (d, J = 8.1 Hz, 2H), 6.85 (dt, J = 8.3, 1.4 Hz, 1H), 6.36 (dt, J = 7.6, 1.5 Hz, 1H), 6.29 (dd, J = 8.3, 1.4 Hz, 1H), 4.24 (d, J = 6.6 Hz, 1H), 3.96 (q, J = 6.6 Hz, 1H), 2.44 (s, 3H), 2.08−1.99 (m, 2H), 1.54−1.42 (m, 3H), 1.28−1.07 (m, 8H), 0.86 (d, J = 5.4 Hz, 3H), 0.81 (dd, J = 6.4, 2.8 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.5, 146.0, 143.9, 138.8, 135.4, 129.5, 129.3, 128.0, 118.8, 111.3, 85.2, 58.0, 42.4, 31.2, 29.6, 25.7, 25.0, 24.8, 22.6, 22.4, 22.3, 21.6, 13.9; HRMS (ESI): m/z calcd for $C_{25}H_{36}IN_3O_2S$: 570.1651 $[M + H]^+$; found: 570.1649.

Representative Procedure for the Preparation of Indole Products from o-Iodoaniline Trapping Products. A mixture of $Pd(OAc)_2$ (1 mg, 4 μmol), tBu$_2$MeP·HBF$_4$ (2.1 mg, 8 μmol), and K_2CO_3 (36.4 mg, 0.26 mmol) in DMF (0.7 mL) was heated to 110 °C under an argon atmosphere. A solution of the *o*-iodoaniline trapping product (50 mg, 0.088 mmol) in DMF (0.7 mL) was added dropwise (by syringe pump) over 1 h. The reaction mixture was then stirred at 110 °C for an additional 3 h. The reaction mixture was cooled to rt, and water (10 mL) was added. The mixture was extracted with ethyl acetate (3 × 15 mL). The organic layer was washed with brine (6 mL), dried with Na_2SO_4, filtered, and concentrated. The residue was purified by flash chromatography (1:9 EtOAc−hexane) to afford the indole product **9c** (20.3 mg, 90%).

Representative Procedure for the "One-Pot" Preparation (Without Purifying the Trapping Products) of Indole Products. In an oven-dried flask under an argon atmosphere were placed 2-iodoaniline (56 mg, 0.25 mmol), tosylhydrazone **8c** (100 mg, 0.24 mmol), and DMF (1 mL). After the mixture had been heated at 50 °C, a solution of NEt_3 (0.07 mL, 0.48 mmol) in DMF (1 mL) was added dropwise (by syringe pump) over 1 h. The reaction mixture was then stirred at the same temperature for an additional 3 h. The reaction mixture was quenched with water (10 mL) and extracted with ethyl acetate (3 × 20 mL). The organic extracts were washed with brine, dried over Na_2SO_4, concentrated, and used for the next step without further purification.

A solution of the aforementioned *o*-iodoaniline trapping product in DMF (1 mL) was added dropwise (by syringe pump) over 1 h to a mixture of $Pd(OAc)_2$ (1.3 mg, 0.006 mmol), tBu$_2$MeP·HBF$_4$ (2.8 mg, 0.011 mmol), and K_2CO_3 (47.3 mg, 0.34 mmol) in DMF (1 mL) heated to 110 °C under an argon atmosphere. The reaction mixture was then stirred at 110 °C for an additional 2 h. The reaction mixture was cooled to rt, and water (10 mL) was added. The mixture was extracted with ethyl acetate (3 × 20 mL). The organic layer was washed with brine (6 mL), dried with Na_2SO_4, filtered, and

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concentrated. The residue was purified by flash chromatography (1:9 EtOAc−hexane) to afford the indole product **9c** (32.6 mg, 92%).

■ 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.4c01190.

Reaction mechanism; characterization data for all new compounds; ^{1}H and ^{13}C NMR spectra (PDF)

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Notes

The authors declare no competing financial interest.

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