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# Comparative Study of the Kumada, Negishi, Stille, and Suzuki−Miyaura Reactions in the Synthesis of the Indole Alkaloids Hippadine and Pratosine

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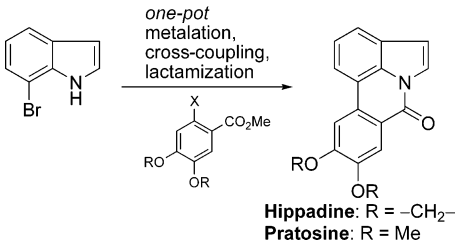
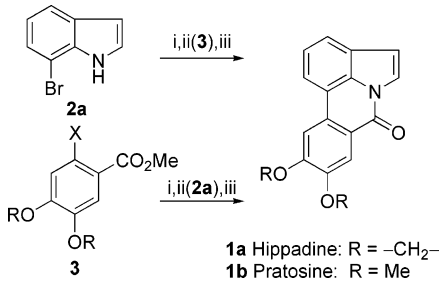



The total synthesis of hippadine by a tandem metalation/cross-coupling/lactamization strategy was investigated starting from either 7-bromoindole or a 6-halogenated methyl piperonate. The Kumada and Negishi cross-coupling reactions failed to provide any of the desired product. However, the Stille and Suzuki reactions furnished hippadine in low yields starting from the electron-deficient methyl 6-iodo- and 6-bromopiperonate, respectively. Starting from the metalated indole, only the Suzuki reaction occurred, affording hippadine in 67−74% and pratosine in 62% isolated yield.

Indole alkaloids containing the pyrrolophenanthridinone core have been the subject of many synthetic studies due to their interesting biological activities, such as cytotoxicity[1] and inhibition of male fertility.[2] This family of alkaloids is exemplified by hippadine and pratosine (Scheme 1). Previous syntheses of hippadine (**1a**) have focused on the connection of an indole/indoline moiety with a piperonal/piperonate derivative, and the key step in all the syntheses is formation of the C−C bond between the indole and the piperonate moieties. Except for three strategies involving radical chemistry,[3,4] oxidative cyclization,[5] and one [4 + 2] cycloaddition route,[6] this union has been achieved by the use of metal-mediated reactions. Thus, a modified Ullmann reaction,[7] a magnesium-mediated biaryl coupling,[8] and the palladium-mediated Heck-type,[9−11] Stille,[12−14] and Suzuki−Miyaura[15−17] reactions have been applied. However, all of the reported syntheses require a series of additional synthetic transformations either before or after the construction of the ring system.

**SCHEME 1. Strategy for the Construction of the Pyrrolophenanthridinone Core**




In our previous work in the indole alkaloids series,[18] we observed straightforward base-mediated formation of the tricyclic pyrroloquinolinone system from an appropriately 7-substituted indole, and we envisioned that this transformation could be used to prepare natural products, such as hippadine (**1a**) and pratosine (**1b**). As shown in Scheme 1, the pyrrolophenanthridinone ring system could be formed by a series of steps comprising (i) metalation of either of the two coupling partners **2a** and **3**, followed by (ii) a transition-metal-catalyzed cross-coupling, and finally (iii) a base-mediated lactamization.

For this strategy, the steric and electronic properties of the organometallic species involved in the cross-coupling step must be considered since it is usually preferable to have an electron-deficient aryl group for oxidative addition and an electron-rich aryl group for transmetalation. We would therefore expect to get the best results from the path in which the electron-rich indole is metalated and coupled with the electron-deficient piperonate ester.

Inspired by an elegant intermolecular tandem palladium-catalyzed borylation/Suzuki coupling,[20,21] and the corresponding intramolecular Stille variant,[12,22] the metalation of 7-bromoindole[23] was investigated (Scheme 2 and Table 1). To our disappointment, we were not able to introduce either zinc, magnesium, or tin into the indole 7-position, even though palladium-catalyzed stannylation of an indole with a triflate in

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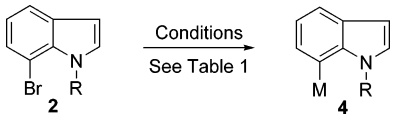
**TABLE 1. Metalation of 7-Bromoindoles**

| entry | component I | R | metalating reagent | M | reaction conditions | yield (%) | product |
|---|---|---|---|---|---|---|---|
| 1 | **2a** | H | HB(pin) | B(pin) | $Pd(OAc)_2$, **7**, $Et_3N$, 80 °C, 15 min | 93[a,b] | **4a** |
| 2 | **2a** | H | $B_2(pin)_2$ | B(pin) | $Pd(OAc)_2$, **7**, KOAc, 80 °C, 3 h | 54[a,c] | **4a** |
| 3 | **2a** | H | $B_2(pin)_2$ | B(pin) | $PdCl_2$, dppf, KOAc, 80 °C, 3 h | 50[a] | **4a** |
| 4 | **2a** | H | *i*-PrMgCl[d] | MgCl | −40, 0, 25 °C | | |
| 5 | **2b** | Bn | *i*-PrMgCl | MgCl | −40, 0, 25 °C | | |
| 6 | **2a** | H | $Bu_3SnSnBu_3$ | $SnBu_3$ | $PdCl_2(CH_3CN)_2$, 80 °C | | |
| 7 | **2a** | H | $Bu_3SnSnBu_3$ | $SnBu_3$ | $Pd(PPh_3)_4$, 80 °C | | |
| 8 | **2a** | H | $Bu_3SnSnBu_3$ | $SnBu_3$ | $PdCl_2(P(o\text{-}Tol)_3)_2$, 80 °C | | |
| 9 | **2b** | Bn | $Bu_3SnCl$ | $SnBu_3$ | *t*-BuLi, −78 °C | | |
| 10 | **2a** | H | Zn | ZnBr | $BrCH_2CH_2Br$, TMSCl, sonication, 0 or 25 °C | | |

[a] Determined by GCMS. [b] Isolated yield = 64% (partly decomposed during column chromatography). [c] Indole (46%) was formed by reductive dehalogenation. [d] With 2.1 equiv. HB(pin) = pinacolborane, **7** = 2-(dicyclohexylphosphine)biphenyl,[19] $B_2(pin)_2$ = bis(pinacolato)diborane, dppf = 1,1′-(diphenylphosphine)ferrocene.

**SCHEME 2. Metalation of 7-Bromoindoles**

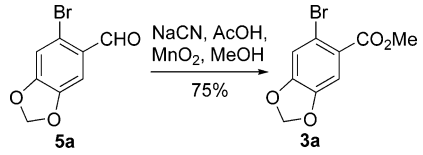



the 7-position[24] and lithium-mediated stannylation in the 7-position of indoline[14] have been reported. In the case of stannylation via halogen−lithium exchange followed by transmetalation to tin (entry 9), formation of the lithiated species was indicated by the product observed upon quenching with water; however, the stannylated product was not formed. To investigate if the unprotected indole nitrogen was causing the problems, the benzyl-protected 7-bromoindole (**2b**) was tested in the magnesiation and stannylation experiments (entries 5 and 9), but still without success.

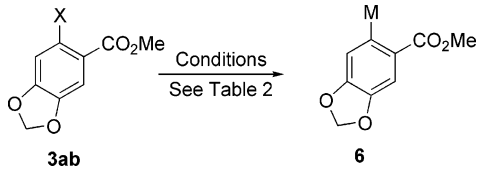
In agreement with earlier reports,[16,25,26] boron was readily inserted in the 7-position of the indole ring (entries 1−3), reflecting that the Pd-catalyzed borylation of aryl bromides is the only metalation strategy that prefers electron-rich substrates.[21,27] The Pd-catalyzed borylation reported by Baudoin and co-workers[20,21] using pinacolborane as the borylating agent and $Pd(OAc)_2$ in combination with 2-(dicyclohexylphosphine)-biphenyl[19] (**7**) as ligand and triethylamine as base turned out to be very efficient. Thus, a maximum of 93% borylation (**4a**) was achieved in 15 min using 1.5 equiv of triethylamine compared to 90% with the original 3−4 equiv.[20,21,27,28] Full conversion into product could not be achieved due to formation of indole by reductive dehalogenation of **2a**. Another versatile borylation reagent, bis(pinacolato)diborane,[29] was tested, but yields were significantly lower and formation of other byproducts was detected (entries 2 and 3).

For the investigations of the inverse strategy, we needed the aryl bromide **3a**. This was prepared from 6-bromopiperonal (**5a**) by a one-pot oxidation/esterification with $MnO_2$ and sodium cyanide.[30,31] The corresponding iodide **5b** was prepared following literature procedures from **5a** in a sequence of three steps[32] followed by the same oxidation/esterification to give **3b**.[31]

**SCHEME 3. Synthesis of 3a**




**SCHEME 4. Metalation of Piperonate Halides**




In the metalation of the electron-deficient piperonate moiety, we observed that all metals tested could be inserted with the exception of zinc, for which we could not isolate the intermediate or measure the degree of insertion (Scheme 4 and Table 2). The borylation was considerably slower than that in the indole case (60 vs 15 min) and also gave lower yields (77 vs 93%) of the aryl boronate (**6a**).

On the other hand, magnesiation[33,34] was extremely fast, giving >99% of the metalated compound (**6b**) after 1 min when the iodide **3b** was used (entries 2 and 3). Using the less reactive bromide led to formation of only 10% of **6b** after 2 h.

Stannylation via a lithiation route was not feasible, but by taking advantage of the smooth magnesiation, the transmetalation route via Mg to Sn afforded **6c** in 54% yield (entry 5). In the metalation/cross-coupling sequence, a Pd-catalyzed reaction would be preferable, and to our satisfaction, this could be achieved with $PdCl_2(CH_3CN)_2$ and hexabutylditin as stannylating reagent affording **6c** in an isolated yield of 68% (entry 6). Since we expected that $Pd(PPh_3)_4$ would be more efficient in the following cross-coupling,[22] this catalyst was also tested in the stannylation, but without success.

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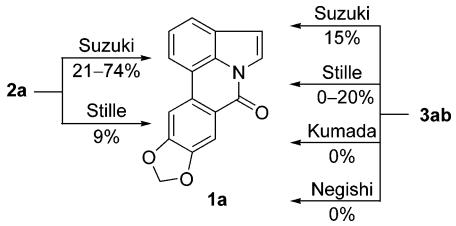
**TABLE 2. Metalation of Piperonate Halides**

| entry | component I | X | metalating reagent | M | reaction conditions | yield (%) | product |
|---|---|---|---|---|---|---|---|
| 1 | **3a** | Br | HB(pin) | B(pin) | $Pd(OAc)_2$, **7**, $Et_3N$, 80 °C, 60 min | 77[a,b] | **6a** |
| 2 | **3a** | Br | *i*-PrMgCl | MgCl | 2 h, −40 °C | <10[a,c] | **6b** |
| 3 | **3b** | I | *i*-PrMgCl | MgCl | 1 min, −40 °C | >99[a] | **6b** |
| 4 | **3b** | I | $Bu_3SnCl$ | $SnBu_3$ | *n*-BuLi, −78 → −40 °C | | |
| 5 | **3b** | I | $Bu_3SnCl$ | $SnBu_3$ | *i*-PrMgCl, −40 °C | 54 | **6c** |
| 6 | **3b** | I | $Bu_3SnSnBu_3$ | $SnBu_3$ | $PdCl_2(CH_3CN)_2$, rt | 68 | **6c** |
| 7 | **3b** | I | $Bu_3SnSnBu_3$ | $SnBu_3$ | $Pd(P(Ph)_3)_4$ | | |
| 8 | **3a** | Br | Zn | ZnBr | $BrCH_2CH_2Br$, TMSCl, sonication, 0 or 25 °C | | |

[a] Determined by GCMS. [b] Isolated yield = 74%. [c] The formation of several byproducts was observed during the reaction. HB(pin) = pinacolborane.

**SCHEME 5. Synthesis of Hippadine**




Direct zinc insertion could not be achieved on the bromide **3a**, and since the indirect metalation of the aryl iodide **3b** via magnesiation had shown such good results in the stannylation, this was the strategy chosen for the Negishi cross-coupling (see below). However, as the aryl zinc species (**6d**) could not be isolated, we were not able to measure the degree of zinc incorporation.

**The Suzuki Reaction.** With borylation as the best metalation procedure, we went on to see if the one-pot borylation/Suzuki reaction/lactamization would work in the hippadine system (Scheme 5 and Table 3). To our satisfaction, we observed the formation of hippadine when the borylation was conducted under optimal metalation conditions for 30 min, followed by addition of water (to quench excess pinacolborane), aryl bromide **3a**, and $Ba(OH)_2$ as the base necessary for transmetalation.[35]

Not surprisingly, it was found that use of 1.5 equiv of triethylamine provided higher yields of hippadine (67%) than when 4.0 equiv was used (entries 1 and 2), reflecting the previously mentioned formation of indole by reductive dehalogenation.

As we suspected that hydrolysis of the piperonate ester was responsible for the lower yields, we tested CsF as base in the Suzuki reaction. However, this did not lead to an improvement when the aryl bromide (**3a**) was employed (entry 3). Comparing the aryl bromide (**3a**) with the aryl iodide (**3b**) led to the expected increase in yields for the iodide (entries 5 and 6), with the interesting observation that CsF led to the highest observed yields of hippadine (74%) when **3b** was used as component II. The use of **3a** as component I also gave the product but in only 15% yield (entry 7).

**The Kumada Reaction.** Since magnesiation of the aryl ester (**3b**) was possible, its cross-coupling was now investigated. First, coupling was attempted with the catalyst system $Pd(dba)_2$/dppf, which is reported to be well suited for the Kumada reaction (Table 3, entries 8 and 9).[34] To avoid quenching of the organometallic species (**6b**), MgCl or benzyl was used as protection for the indole nitrogen.[33] Unfortunately, the only reaction observed was degradation of the aryl ester at 25 °C. The use of $Pd(OAc)_2$ in combination with ligand **7**, which had given good results in the Suzuki reaction (see above), was also unsuccessful (entry 10). The failure is probably due to poor reactivity at the low temperatures (−40 → 0 °C), which have to be employed to avoid reaction with the ester functionality.[33,34] In this temperature range, the oxidative addition of the electron-rich indole may be too slow for reaction to occur before degradation of the magnesiated aryl ester (**6b**).[33]

**The Stille Reaction.** Stannylation of the indole did not occur, but tin could be introduced in the aryl ester either via magnesiation followed by transmetalation to tin or via a palladium-catalyzed stannylation. It quickly became clear that different catalysts were necessary for stannylation and the cross-coupling, respectively. Stannylation worked well with $PdCl_2(CH_3CN)_2$, whereas cross-coupling preferred $Pd(PPh_3)_4$ or $PdCl_2(P(o\text{-}Tol)_3)_2$ (Table 3, entries 11−15). Isolation of the organostannane **6c** prior to cross-coupling led to the formation of hippadine in 20% isolated yield. Attempts to increase this by careful control of the inert atmosphere, addition of Cu(I) salts together with CsF[36] and LiCl[37] did not lead to better results. In fact, addition of more CuCl led to increased homocoupling. In the hope of achieving a one-pot stannylation/cross-coupling, $PdCl_2(CH_3CN)_2$ was employed with or without added ligand ($PBu_3$). Unfortunately, no cross-coupled product was observed. One example of a true one-pot tandem reaction was realized (entry 13) starting from the indole **2a** using $PdCl_2(P(o\text{-}Tol)_3)_2$. However, only 9% isolated yield of hippadine was obtained together with 31% homocoupled aryl ester, suggesting that the stannylated intermediate was actually **6c** and not the indole. Thus, the one-pot reaction with **2a** as component I furnished hippadine in 9% yield, whereas a maximum of 20% was obtained in a stepwise reaction sequence from **3a**.

**The Negishi Reaction.** Since the direct zinc insertion in the indole (**2a**) did not occur at room temperature or below, the Negishi cross-coupling was attempted on the presumed zincated aryl ester (**6d**), formed via transmetalation from the magnesiated species (**6b**). With $PdCl_2(o\text{-}Tol)_2$ as the catalyst, reaction at either room temperature or 60 °C did not lead to formation of the cross-coupling product. Instead, the metalated aryl ester slowly decomposed under the reaction conditions.

From the studies discussed above, it was evident that the Suzuki strategy was by far the best for synthesizing the pyrrolophenanthridinone system. The borylation/Suzuki/lactamization sequence was therefore applied to the synthesis of pratosine, with the electron-rich **2a** as component I and the electron-deficient methyl-2-bromo-4,5-dimethoxybenzoate (**3c**) as component II. As for the synthesis of hippadine, $Ba(OH)_2$ led to higher yields than CsF (62 vs 54%). In conclusion, by using

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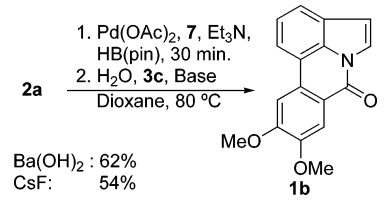
**TABLE 3. Tandem Metalation/Cross-Coupling/Lactamization**

| entry | component I/II | reaction conditions | yield (%) |
|---|---|---|---|
| 1 | **2a**/**3a** (Suzuki) | 1. $Pd(OAc)_2$ (5%), **7** (20%), $Et_3N$ (4.0 equiv), HB(pin) (3 equiv), dioxane, 80 °C, 30 min<br>2. $H_2O$, **3a**, $Ba(OH)_2 \cdot 8H_2O$ (3 equiv), 80 °C, 4 h | 61 |
| 2 | **2a**/**3a** (Suzuki) | 1. $Pd(OAc)_2$ (5%), **7** (20%), $Et_3N$ (1.5 equiv), HB(pin) (3 equiv), dioxane, 80 °C, 30 min<br>2. $H_2O$, **3a**, $Ba(OH)_2 \cdot 8H_2O$ (3 equiv), 80 °C, 4 h | 67 |
| 3 | **2a**/**3a** (Suzuki)[a] | 1. $Pd(OAc)_2$ (5%), **7** (20%), $Et_3N$ (1.5 equiv), HB(pin) (3 equiv), dioxane, 80 °C, 30 min<br>2. $H_2O$, **3a**, CsF (3 equiv), 80 °C, 4 h | 64 |
| 4 | **2a**/**3a** (Suzuki) | 1. $PdCl_2$ (5%), dppf (5%), KOAc, $B_2(pin)_2$ (3 equiv), dioxane, 80 °C, 3 h<br>2. $H_2O$, **3a**, $Ba(OH)_2 \cdot 8H_2O$ (3 equiv), 80 °C, 18 h | 21 |
| 5 | **2a**/**3b** (Suzuki) | 1. $Pd(OAc)_2$ (5%), **7** (20%), $Et_3N$ (1.5 equiv), HB(pin) (3 equiv), dioxane, 80 °C, 30 min<br>2. $H_2O$, **3b**, $Ba(OH)_2 \cdot 8H_2O$ (3 equiv), 80 °C, 4 h | 60 |
| 6 | **2a**/**3b** (Suzuki)[a] | 1. $Pd(OAc)_2$ (5%), **7** (20%), $Et_3N$ (1.5 equiv), HB(pin) (3 equiv), dioxane, 80 °C, 30 min<br>2. $H_2O$, **3b**, CsF (3 equiv), 80 °C, 4 h | 74 |
| 7 | **3a**/**2a** (Suzuki) | 1. $Pd(OAc)_2$ (5%), **7** (20%), $Et_3N$ (1.5 equiv), HB(pin) (3 equiv), dioxane, 80 °C, 60 min<br>2. $H_2O$, **2a**, $Ba(OH)_2 \cdot 8H_2O$ (3 equiv), 80 °C, 4 h | 15 |
| 8 | **3b**/**2a**[b] (Kumada) | 1. *i*-PrMgCl (1.1 equiv), THF, −40 °C, 10 min<br>2. **2a**, $Pd_2(dba)_3 \cdot CHCl_3$ (0.025 equiv), dppf (0.05 equiv), −40 or 0 °C for 7 h → 25 °C for 16 h | |
| 9 | **3b**/**2b** (Kumada) | 1. *i*-PrMgCl (1.1 equiv), THF, −40 °C, 10 min<br>2. **2b**, $Pd_2(dba)_3 \cdot CHCl_3$ (0.025 equiv), dppf (0.05 equiv), −40 or 0 °C for 7 h → 25 °C for 16 h | |
| 10 | **3b**/**2b** (Kumada) | 1. *i*-PrMgCl (1.1 equiv), THF, −40 °C, 10 min<br>2. **2b**, $Pd(OAc)_2$ (5%), **7** (20%), −40 or 0 °C for 7 h → 25 °C for 16 h | |
| 11 | **3a**[c]/**2a** (Stille)[a] | 1. **2a**, $Pd(PPh_3)_4$ (7%), CuI (0.2 equiv), CsF (2 equiv), DMSO, 80 °C, 16 h | 20 |
| 12 | **3a**[c]/**2a** (Stille)[a] | 1. **2a**, $Pd(PPh_3)_4$ (5%), CuCl (5 equiv), LiCl (6 equiv), DMSO, rt, 24 h → 80 °C, 24 h | 14 |
| 13 | **3b**/**2a** (Stille)[a] | 1. $PdCl_2(CH_3CN)_2$ (5%), DMF, 80 °C, 7 days<br>2. **2a**, CsF (3 equiv) | |
| 14 | **3b**/**2a** (Stille)[a] | 1. $PdCl_2(CH_3CN)_2$ (5%), DMF, 80 °C, 7 days<br>2. **2a**, $P(Bu)_3$ (20%), CsF (3 equiv) | |
| 15 | **2a**/**3a** (Stille)[a] | 1. $PdCl_2(P(o\text{-}Tol)_3)_2$ (5%), $Bu_3SnSnBu_3$ (1.2 equiv), DMSO, 80 °C, 16 h<br>2. **3a**, CuCl (5 equiv), LiCl (6 equiv), DMSO, 80 °C, 20 h | 9[d] |
| 16 | **3b**/**2a** (Negishi) | 1. *i*-PrMgCl, THF, −40 °C, 5 min<br>2. $ZnBr_2$, −40 → 25 °C, 2.5 h<br>3. **3a**, $PdCl_2(o\text{-}Tol)_2$ (10%), THF, 25 °C, 24 h, then more catalyst, 60 °C, 3 days | |

[a] In cases with no base present, $Ba(OH)_2$ was added after cross-coupling to ensure lactamization. [b] **2a** was deprotonated with *i*-PrMgCl prior to the cross-coupling attempt. [c] **6c** was isolated by column chromatography prior to cross-coupling. [d] Homocoupling (31%) of **3a** was observed.

**SCHEME 6. Synthesis of Pratosine**




the tandem borylation/Suzuki/lactamization strategy, it was possible to synthesize hippadine in two steps from commercially available starting materials. Of the different cross-coupling reactions, the Suzuki and Stille reactions were the only ones to provide the desired product, with the Suzuki reaction being best suited for the hippadine system. With an overall yield of 50% from 6-bromopiperonal (via **3a**), the route presented here is the shortest and most efficient synthesis of hippadine reported to date.

## Experimental Section

**Hippadine (1a) via Borylation and Suzuki−Miyaura Coupling (one pot).** $Et_3N$ (0.09 mL, 0.6 mmol), $Pd(OAc)_2$ (4.9 mg, 0.022 mmol), and 2-(dicyclohexylphosphino)biphenyl (31 mg, 0.088 mmol) were successively added to a solution of 7-bromoindole (**2a**) (86 mg, 0.44 mmol) in dioxane (1.0 mL). The solution was heated to 80 °C, and pinacolborane (0.19 mL, 1.3 mmol) was added dropwise. After 30 min, $H_2O$ (0.19 mL) was added dropwise followed by a solution of methyl-6-bromopiperonate (**3a**) (114 mg, 0.44 mmol) in dioxane (1.5 mL) and $Ba(OH)_2 \cdot 8H_2O$ (417 mg, 1.32 mmol). Stirring was continued at 80 °C until the reaction was complete (monitored by GCMS). The reaction mixture was diluted with $CH_2Cl_2$ (50 mL) and $H_2O$ (20 mL). The solution was filtered, and the dark precipitate was washed with $CH_2Cl_2$. The layers were separated, and the aqueous layer was extracted with $CH_2Cl_2$. The combined organic phases were dried ($Na_2SO_4$) and the solvents evaporated. Column chromatography (EtOAc/heptane 1:4) of the residue afforded the product as a light tan solid with spectroscopic data in accordance with previous reports.[6,7] Mp (MeOH): 207−208 °C (lit. 216−218 °C,[7] 207−209 °C[38]). Anal. Calcd for $C_{16}H_9NO_3$: C, 73.00; H, 3.45; N, 5.34. Found: C, 72.65; H, 3.13; N, 5.02.

**Hippadine (1a) via Stille Coupling.** A flask was charged with LiCl (36 mg, 0.85 mmol) and flame-dried under high vacuum. Upon cooling, $Pd(PPh_3)_4$ (16.5 mg, 0.014 mmol) and CuCl (70 mg, 0.71 mmol) were added, and the mixture was degassed (×4) under high vacuum. 7-Bromoindole (**2a**) (35 mg, 0.18 mmol) and the stannane **6c** (66 mg, 0.14 mmol) were dissolved in DMSO (1.5 mL), degassed, and added to the flask containing the salts. The resulting mixture was degassed (×3) by the freeze−thaw process (−78 °C → 20 °C, Ar). The reaction mixture was stirred overnight at 20 °C and again overnight at 80 °C in order to complete the reaction. $Ba(OH)_2 \cdot 8H_2O$ (131 mg, 0.415 mmol) was added, and after 2 h, workup of the reaction and purification as described above afforded the product (**1a**) as a solid (5 mg, 14%).

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**Supporting Information Available:** Experimental procedures and full spectroscopic data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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