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One-Pot Synthesis of Camalexins and 3,3′-Biindoles by the Masuda Borylation–Suzuki Arylation (MBSA) Sequence

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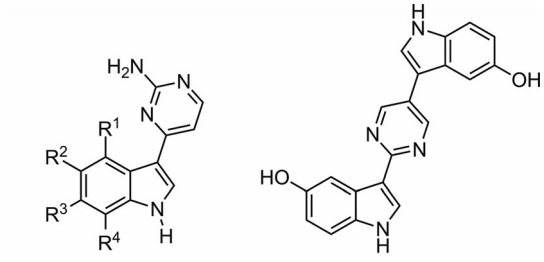
Dedicated to Professor Dr. Manfred Braun on the occasion of his 65th birthday

Keywords: Synthetic methods / C–C coupling / Arylation / Palladium / Boron / Alkaloids

The Masuda borylation/Suzuki arylation (MBSA) sequence starting from *N*-protected 3-iodoindoles has successfully been extended to the coupling of five-membered heterocycles and indoles in the arylation step, which could not be achieved with previously developed MBSA methods. By this approach the one-pot nature of the method as well as the use of a simple catalyst system has been retained. The applicability of the method has been demonstrated by the facile synthesis of camalexins and 3,3′-biindoles, compounds of special interest due to their pronounced antifungal, antimicrobial and cytotoxic activities.

Introduction

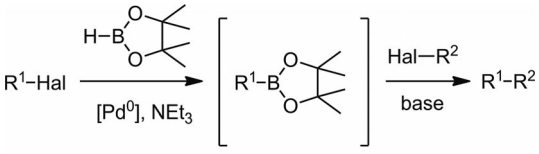
Indoles bearing heteroaromatic substituents at the 3-position are commonly encountered scaffolds with remarkable biological activities and significant prevalence in nature.[1] As a consequence, this structural motif has received considerable attention in the development of leads in medicinal chemistry addressing a wide spectrum of pharmaceutical activity. For example, structurally simple marine indole alkaloids such as meridianins and hyrtinadine A (Figure 1) bear pyrimidinyl substituents and display remarkable cytotoxicity against several cancer cell lines.[2]



A: R^1 = OH, R^2 = R^3 = R^4 = H
G: R^1 = R^2 = R^3 = R^4 = H

Figure 1. 3-Heteroaryl-substituted indoles as structural motifs in natural products.

As part of our program to develop user-friendly one-pot methods to access such substance classes, we are particularly interested in the conceptual development of sequential Pd-catalyzed processes.[3] Within this approach, the consecutive one-pot cross-coupling of two aryl halides by the Masuda borylation/Suzuki arylation (MBSA) sequence in the presence of a single Pd catalyst without further catalyst addition and by using equimolar amounts of reactants appears to be challenging and rewarding (Scheme 1).[4] In addition, Miyaura borylation/Suzuki arylation reactions have also been considered and developed.[5]



R^1, R^2 = (hetero)aryl
Hal = Br, I

Scheme 1. Sequential Pd-catalyzed one-pot Masuda borylation/Suzuki arylation (MBSA) sequence.

Starting from iodo-(7-aza)indoles, furans, thiophenes, pyrroles, and arenes, a plethora of six-membered halogenated carbo- and heterocycles can be cross-coupled in a one-pot manner by using the same simple catalyst system without the need for further catalyst addition in the concluding Suzuki step.[6] In addition, this straightforward protocol has been successfully applied to the concise total syntheses of the marine indole alkaloids meridanin A and G and the marine bis-indole alkaloid hyrtinadine A.[6,7] However, under the standard conditions, the use of five-membered heterocycles as coupling partners in the Suzuki step

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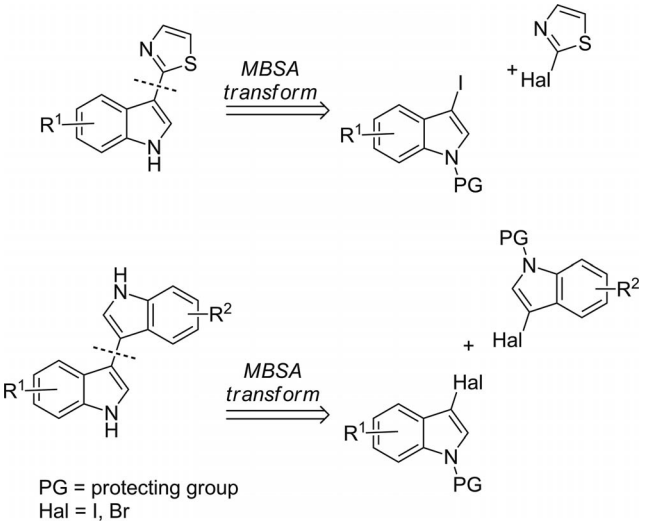
astoundingly only proceeded in low yield or did not occur at all in the case of Boc-protected 3-iodoindoles.

The loss of crops due to infection with pathogens has become a serious problem worldwide. One answer to this could be the utilization of phytoalexins,[8] secondary metabolites that are produced as part of a plant's defense against abiotic stress or infection. However, many of these small molecules are also known to show significant antioxidant, anticarcinogenic, or anti-inflammatory activity. The detoxification of phytoalexins by pathogens has become a major problem for plants, which are left defenseless against infection.

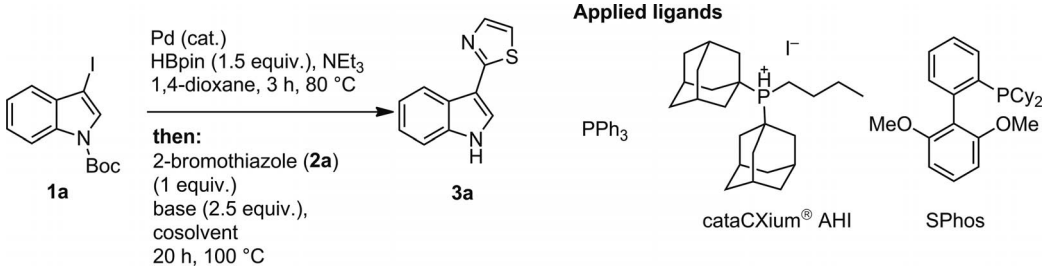
Among the known phytoalexins, camalexin[9] has been intensively studied. First isolated together with 6-methoxycamalexin from *Camelina sativa* infected with *Alternaria brassicae*, it can also be found in various other *Cruciferae*[10] and shows interesting antifungal,[11] antimicrobial,[9] and cytotoxic activity against various human cancer cell lines including the human breast cancer cell line SKBr3 (IC_{50} = 2.7 μM).[12] Several total syntheses of camalexin based on organometallic (Kharasch,[13] Negishi,[14] and McMurry[15] coupling reactions) and biomimetic key steps[16] have been reported.

3,3′-Biindoles are scaffolds in natural products such as rivilarine C,[17] folicanthine, and chimonanthine.[18] In particular, 1*H*,1′*H*-3,3′-biindole, a secondary metabolite isolated from the fungus *Gliocladium catenulatum*,[19] has shown very promising biological activity against *Paenibacillus larvae*, which is responsible for the American foulbrood disease among honey bees, a significant factor in commercial apiculture due to the lack of specific antibiotic treatment. Furthermore, unsymmetrically substituted 3,3′-biindoles have been studied for treating protein folding disorder, for example, in Alzheimer's disease, dementia, Parkinson's disease, Huntington's disease, and Creutzfeldt-Jakob's disease.[20]

Published syntheses of 3,3′-biindoles most often use the isatin route.[21] In addition, Pd-catalyzed cross-coupling, including a one-pot symmetrical dimerization by Miyaura borylation and Suzuki coupling,[22] Pd-catalyzed cyclization,[23] and the reductive cyclization of substituted indole derivatives,[24] have also been applied to the synthesis of the 3,3′-biindole scaffold.



Scheme 2. Retrosynthetic analysis of camalexins and 3,3′-biindoles based upon the MBSA sequence.



Scheme 3. Synthesis of camalexin (**3a**) in a one-pot reaction.

Table 1. Optimization of the reaction conditions for the MBSA synthesis of camalexin (**3a**) in a one-pot reaction.

Entry	Conditions for the Masuda borylation[a]	Conditions for the Suzuki arylation	Isolated yield of **3a** [%]
1	3 mol-% $[Pd(PPh_3)_4]$, 1.0 mL NEt_3	2.5 equiv. Cs_2CO_3, MeOH	41
2	3 mol-% $[PdCl_2(PPh_3)_2]$, 1.0 mL NEt_3	2.5 equiv. Cs_2CO_3, MeOH	10
3	3 mol-% $[PdCl_2(PPh_3)_2]$, 0.5 mL NEt_3	2.5 equiv. Na_2CO_3, MeOH	29
4	3 mol-% $[PdCl_2(PPh_3)_2]$, 0.5 mL NEt_3	2.5 equiv. CsF, MeOH	20
5	3 mol-% $[Pd(PPh_3)_4]$, 0.5 mL NEt_3	2.5 equiv. Na_2CO_3, H_2O	65[b]
6	3 mol-% $[PdCl_2(PPh_3)_2]$, 0.5 mL NEt_3	2.5 equiv. Na_2CO_3, H_2O	n.i.[c]
7	3 mol-% $[Pd(PPh_3)_4]$, 6 mol-% PPh_3, 0.5 mL NEt_3	2.5 equiv. Na_2CO_3, H_2O	39
8	3 mol-% $[Pd(PPh_3)_4]$, 0.5 mL NEt_3	2.5 equiv. Na_2CO_3, 6 mol-% PPh_3, H_2O	74
9	2 mol-% $PdCl_2$, 4 mol-% cataCXium® AHI, 0.5 mL NEt_3	2.5 equiv. Na_2CO_3, H_2O	n.i.[d]
10	3 mol-% $[PdCl_2(CH_3CN)_2]$, 12 mol-% SPhos, 0.5 mL NEt_3	2.5 equiv. Na_2CO_3, H_2O; then 24 h, 110 °C	n.i.[e]

[a] An excess of 3.6 or 7.2 equiv. NEt_3 was used. [b] The reaction mixture contained many byproducts (monitored by TLC). [c] The reaction mixture appeared to be similar to that of entry 5 (monitored by TLC), but isolation was not attempted. [d] A mixture of starting material and products was formed according to TLC and GC-MS; no isolation was attempted. [e] The desired product **3a** was formed in only trace amounts with the dehalogenated indole the major product (monitored by TLC).

Herein we report the extension of the MBSA sequence to bromothiazoles and iodoindoles as representative coupling partners in the final Suzuki step illustrating this methodology with one-pot syntheses of the indole alkaloids camalexin, 6-methoxycamalexin, and 3,3′-biindole.

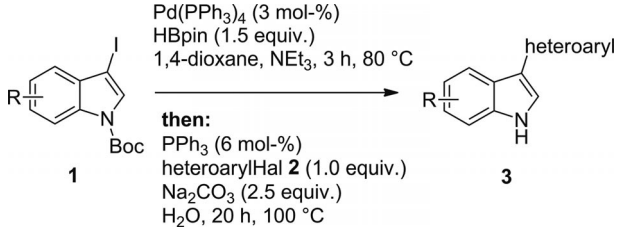
Results and Discussion

The retrosynthetic scheme for the Masuda borylation/Suzuki arylation sequence with concomitant Boc cleavage as the key step for the synthesis of camalexins and 3,3′-biindoles is shown in Scheme 2.

Based upon our experience of the MBSA sequence with brominated pyrimidines or dihalogenated diazines as Suzuki substrates we set up a model reaction to optimize the synthesis of camalexin (**3a**) by using *tert*-butyl 3-iodo-1*H*-indole-1-carboxylate (**1a**) and 2-bromothiazole (**2a**) (Scheme 3, Table 1).

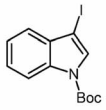
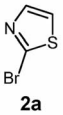
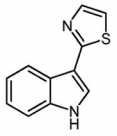
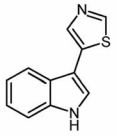
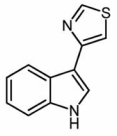
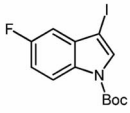
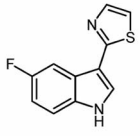
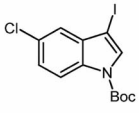
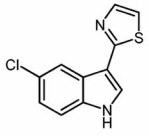
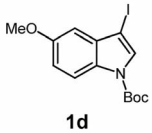
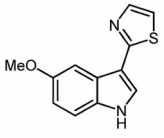
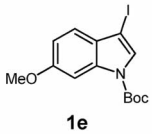
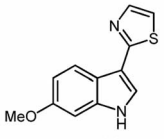
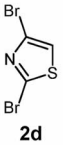
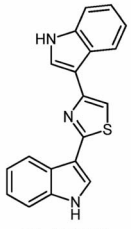
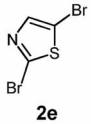
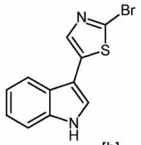
First, the standard conditions[6,7] were applied to give compound **3a** in a moderate 41% yield (Table 1, entry 1). Upon changing the precatalyst to $[PdCl_2(PPh_3)_2]$, the yield of **3a** decreased considerably (Table 1, entry 2). In the course of our work we found that concomitant Boc deprotection significantly affected the Suzuki coupling if the rate of this reaction was lower than the base-mediated deprotection. However, variation of the base under otherwise the same conditions revealed that sodium carbonate as base gave higher yields (Table 1, entries 3, 5, 7, and 8). In addition, the use of methanol as co-solvent in the final step to quench excessive pinacolborane and to enhance the solubility of the base was replaced by water (Table 1, entries 5–10). Finally, the addition of catalytic amounts of triphenylphosphane to prevent precipitation of palladium in the second step led to the formation of camalexin (**3a**) in 74% isolated yield (Table 1, entry 8). Note that two other tested precatalyst systems based upon sterically hindered phosphane ligands that have proven to considerably accelerate cross-coupling in many other cases[25] completely failed in the MBSA sequence (Table 1, entries 9 and 10).

With the optimized conditions in hand (Table 1, entry 8), camalexin analogues **3** were synthesized in a concise one-pot manner, always maintaining an equimolar ratio of the iodoindoles **1** and the bromothiazoles **2**. The reaction of variously substituted, easily accessible *N*-Boc-3-iodoindoles **1**[26] with pinacolborane (HBpin) and subsequent Suzuki arylation with bromothiazoles **2** furnished camalexin analogues **3** in good overall yields (Scheme 4, Table 2).



Scheme 4. MBSA one-pot synthesis of camalexin derivatives **3**.

Table 2. MBSA one-pot synthesis of camalexin derivatives **3**.

Entry	3-Iodoindole **1**	Bromothiazole **2**	Camalexin derivative **3** (isolated yield %)
1	 **1a**	 **2a**	 **3a** (74 %)
2	**1a**	 **2b**	 **3b** (75 %)
3	**1a**	 **2c**	 **3c** (65 %)
4	 **1b**	**2a**	 **3d** (69 %)
5	 **1c**	**2a**	 **3e** (31 %)
6	 **1d**	**2a**	 **3f** (51 %)
7	 **1e**	**2a**	 **3g** (62 %)
8[a]	**1a**	 **2d**	 **3h** (52 %)
9[a]	**1a**	 **2e**	 **3i** (69 %)[b]

[a] The reaction was performed with 1.0 equiv. indole and 0.5 equiv. dibromothiazole. [b] The desired bis-indole was formed in only trace amounts (by HRMS).

Table 3. Optimization of the reaction conditions for the one-pot synthesis of 3,3′-biindole (**5a**).

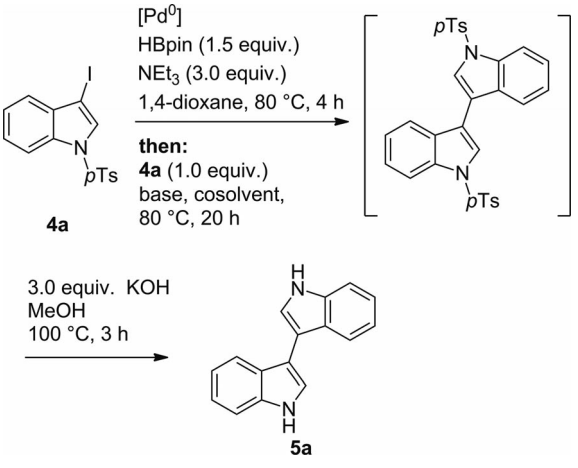
Entry	Conditions for the Masuda borylation	Conditions for the Suzuki arylation	Isolated yield of **5a** [%]
1	2 mol-% $PdCl_2$, 4 mol-% cataCXium® AHI, 60 °C, 4 h	2.5 equiv. Cs_2CO_3, MeOH, 80 °C, 20 h	n.i.[a]
2	2 mol-% $PdCl_2$, 4 mol-% cataCXium® AHI, 80 °C, 4 h	2.5 equiv. Na_2CO_3, H_2O, 80 °C, 20 h	n.i.[a]
3	2 mol-% $PdCl_2$, 4 mol-% cataCXium® AHI, 80 °C, 4 h	2.0 equiv. Ag_2O, MeOH, 80 °C, 20 h	n.i.[a]
4	2 mol-% $PdCl_2$, 4 mol-% cataCXium® AHI, 80 °C, 4 h	2.0 equiv. CsF, MeOH, 80 °C, 20 h	n.i.[a]
5	2 mol-% $PdCl_2$, 4 mol-% cataCXium® AHI, 80 °C, 4 h	2.0 equiv. KF, MeOH, 80 °C, 20 h	n.i.[a]
6	2 mol-% $PdCl_2$, 4 mol-% cataCXium® AHI, 80 °C, 4 h	2.0 equiv. K_3PO_4, MeOH, 80 °C, 20 h	n.i.[a]
7	3 mol-% $[Pd(PPh_3)_4]$, 80 °C, 4 h	2.5 equiv. Cs_2CO_3, MeOH, 80 °C, 20 h	83

[a] No product was observed (monitored by GC–MS). Therefore deprotection was not performed.

In addition to camalexin (**3a**), the 4-thiazolyl isomer **3b** and the hitherto unknown isomer **3c** were synthesized in comparable good yields (Table 2, entries 1–3). Furthermore, the fluoro- (**3d**), chloro- (**3e**), and methoxy-substituted (**3f** and **3g**) derivatives of camalexin were readily obtained (Table 2, entries 4–7). The thiazole analogue **3h** of the biologically highly active marine alkaloid nortopsentin[27] is a thiazole-bridged bis-indole derivative that was also isolated in good yield (Table 2, entry 8). Interestingly, the regioisomeric 2,5-dibromothiazole (**2e**) only furnished the corresponding bis-indole in trace amounts; the main product was the monocoupled bromo derivative **3i** (Table 2, entry 9).

All attempts to use *N*-Boc-protected 7-azaindoles in the Masuda borylation or *N*-Boc-protected pyrroles in the Suzuki arylation met with failure.

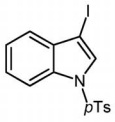
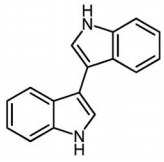
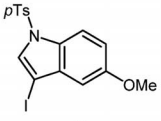
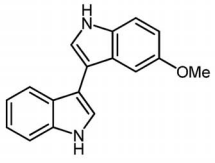
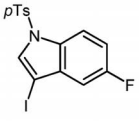
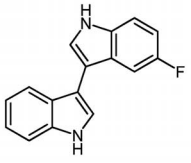
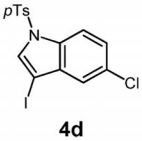
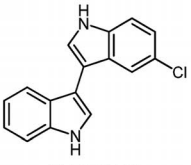
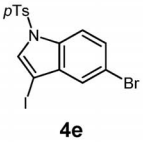
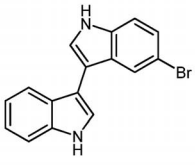
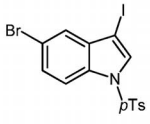
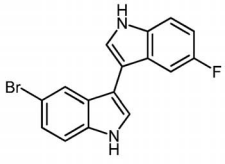
The desired 3,3′-biindoles could not be isolated with *N*-Boc-protected 3-iodoindoles **1** as coupling partners in the terminal Suzuki step. Therefore we reasoned that the fragile Boc group should be replaced by the Suzuki coupling-robust tosyl group. For optimization studies, the stepwise homocoupling of *N*-tosyl-3-iodoindole **4a**[28] to furnish 3,3′-biindole (**5a**) was chosen (Scheme 5, Table 3). For subsequent detosylation in the same reaction vessel, KOH and methanol were added and the mixture was heated at 100 °C for 3 h.



Scheme 5. One-pot synthesis of 3,3′-biindole **5a**.

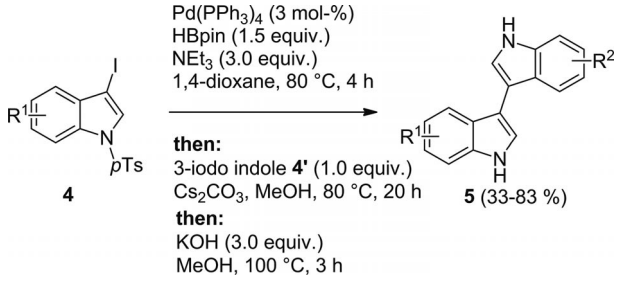
First, the precatalyst system based upon the ligand cataCXium® AHI with $PdCl_2$ as the palladium source was screened and the bases and solvent additives in the Suzuki step were varied (Table 3, entries 1–6). Monitoring the reaction by GC–MS showed that the borylation step was successful, but the Suzuki arylation failed under these conditions. Even the modified conditions for the Suzuki arylation as established for the synthesis of camalexins **3** did not fur-

Table 4. MBSA one-pot synthesis of 3,3′-biindoles **5**.

Entry	Indole **4**	Indole **4'**	3,3'-Biindole **5** (isolated yield %)
1	 **4a**	**4a**	 **5a** (83 %)
2	**4a**	 **4b**	 **5b** (56 %)
3	**4a**	 **4c**	 **5c** (58 %)
4	**4a**	 **4d**	 **5d** (55 %)
5	**4a**	 **4e**	 **5e** (50 %)
6	 **4e**	**4c**	 **5f** (33 %)

nish 3,3′-biindole (**5a**). Returning to the original precatalyst [$Pd(PPh_3)_4$] without additional ligands led to the isolation of the detosylated compound **5a** in 83% yield (Table 3, entry 7).

These optimized conditions (Table 3, entry 7) were applied to a three-step, one-pot MBSA sequence for the synthesis of unsymmetrically substituted 3,3′-biindoles **5** in a very straightforward fashion and in good overall yields (Scheme 6, Table 4).



Scheme 6. MBSA one-pot synthesis of 3,3′-biindoles **5**.

Conclusions

The Masuda borylation/Suzuki arylation (MBSA) sequence starting from *N*-Boc- and *N*-tosyl-3-iodoindoles has been successfully extended to the coupling of five-membered heterocycles in the Suzuki step, as illustrated by the synthesis of camalexin analogues and symmetrically and unsymmetrically substituted 3,3′-biindoles. A detailed screening of the reaction conditions showed that a simple commercial precatalyst system could be successfully used. However, it was necessary to modify the additives and bases as well as co-solvents. In the case of the synthesis of 3,3′-biindoles, the traditional Boc protecting group had to be replaced by the more robust *N*-tosyl group. The ease of performing this sequential palladium-catalyzed one-pot sequence as well as the building block character of the strategy and the equimolar ratio of the reactants ensure that it is highly sustainable. This straightforward methodology has potential applications in alkaloid synthesis and medicinal chemistry, especially because no complex ligands are required and the access to starting materials is short and elaborated. Further studies on one-pot sequences based upon the Masuda borylation/Suzuki arylation as a key step are underway.

Experimental Section

General Procedure for the Synthesis of Camalexin Derivatives 3 by the MBSA Sequence: [$Pd(PPh_3)_4$] (35 mg, 0.03 mmol) was placed under argon in a dry screw-cap vessel equipped with a septum. The *tert*-butyl 3-iodo-1*H*-indole-1-carboxylate **1** (1.0 mmol) was dissolved in dry 1,4-dioxane (5.0 mL) and added to the catalyst. The mixture was degassed with argon for 5 min. Dry triethylamine (0.5 mL) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.22 mL, 1.50 mmol) were successively added to the mixture, which was then stirred at 80 °C (preheated oil bath) for 3 h (monitored by TLC). Then, after cooling to room temperature (water bath), water (5.0 mL), Na_2CO_3 (266 mg, 2.5 mmol), triphenylphosphane (16 mg, 0.06 mmol), and heteroaryl halide **2** (1.0 mmol) were successively added. The mixture was stirred at 100 °C for 20 h (preheated oil bath). After cooling to room temperature, the solvents were removed under reduced pressure. The residue was absorbed onto Celite® and purified chromatographically on silica gel (for experimental details and analytical data, see the Supporting Information).

General Procedure for the Synthesis of 3,3′-Biindoles 5 by the MBSA Sequence: [$Pd(PPh_3)_4$] (35 mg, 0.03 mmol) and the 3-iodo-1-tosyl-1*H*-indole **4** (1.0 mmol) were placed under argon in a dry screw-cap vessel equipped with septum and dissolved in dry 1,4-dioxane (2.0 mL). Dry triethylamine (0.5 mL) and 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (0.22 mL, 1.50 mmol) were successively added to the mixture, which was then stirred at 80 °C (preheated oil bath) for 4 h (monitored by TLC). Then, after cooling to room temperature (water bath), dry methanol (2.0 mL), Cs_2CO_3 (815 mg, 2.5 mmol), and another 3-iodo-1-tosyl-1*H*-indole **4′** (1.0 mmol) were successively added. The mixture was stirred at 80 °C for 20 h (preheated oil bath). After cooling to room temperature (water bath), potassium hydroxide (198 mg, 3.0 mmol) and dry methanol (2.0 mL) were successively added to the reaction mixture, which was then sealed and stirred at 100 °C for 3 h (preheated oil bath). Finally, after cooling to room temperature, 0.1 N aqueous HCl (30 mL) was added to the reaction mixture. A colorless precipitate was formed. The aqueous phase was then extracted with dichloromethane (3× 35 mL, monitored by TLC). The combined organic layers were dried with anhydrous sodium sulfate and the solvents were removed under reduced pressure. The residue was adsorbed onto Celite® and purified chromatographically on silica gel (for experimental details and analytical data, see the Supporting Information).

Supporting Information (see footnote on the first page of this article): Experimental details for the synthesis of compounds **3** and **5**, ^1H, ^{13}C, and 135-DEPT NMR spectra of compounds **3** and **5**.

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