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The synthesis of C-3β functionalized indoles via a hydroboration/Suzuki–Miyaura coupling sequence

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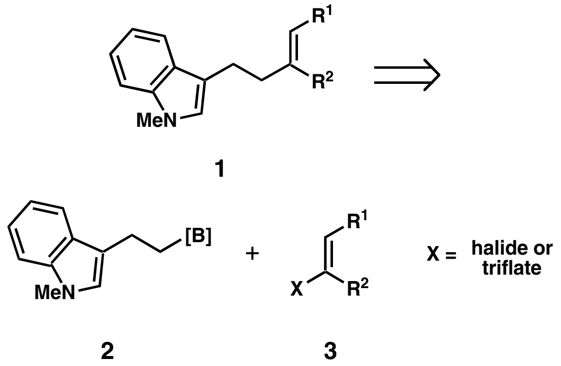
Abstract—A method for the functionalization of C-3β of vinyl indoles is described. The procedure involves a hydroboration, followed by a Suzuki–Miyaura cross-coupling with the intermediate alkyl borane. Triflates, bromides, and iodides are suitable coupling partners, allowing access to a variety of elaborated indole compounds.

Indoles are important structural moieties in a number of biologically relevant compounds.[1] The development of synthetic methods involving indole-containing compounds remains an active area of research.[1a,2] During the course of our studies on the palladium-catalyzed oxidative annulation of indoles,[3] it became necessary to synthesize substrates with olefin tethers at the C-3 position. Specifically, we desired compounds where the indole tethers had olefins attached to the β carbon. We envisioned that indoles of this type could arise via sp^2–sp^3 palladium-catalyzed cross coupling chemistry. The Suzuki–Miyaura reaction has proven widely effective in the construction of carbon–carbon bonds.[4] We anticipated that a sequence consisting of a hydroboration of a 3-vinyl indole followed by a palladium-catalyzed cross coupling with a halide or triflate would afford the desired indole products (Scheme 1).



Scheme 1.

The regioselectivity of a hydroboration on a vinyl indole compound was uncertain at the beginning of this study. Styrenyl compounds generally react with hydroborating agents to afford compounds with boron substitution at the terminal (β) position, although functionalization of the internal carbon is often observed in catalytic reactions. The hydroboration of more electron-rich heteroarenes, however, could potentially be complicated by the numerous nucleophilic sites. It could be envisioned that the hydroboration of *N*-methyl-3-vinyl indole would result in boron substitution at four different sites, C-2, C-3, C-3α, and C-3β, the desired location (Scheme 2).

In the event, the hydroboration/Suzuki–Miyaura coupling sequence proved to be remarkably effective (Scheme 3). Starting with *N*-methyl-3-vinyl indole (**4**), hydroboration with 9-BBN afforded *B*-alkyl intermediate **9**, which was treated with triflate **10** under standard Suzuki–Miyaura coupling conditions.[5] After the reaction was completed, analysis of the crude material revealed that there was only one compound present arising from boron substitution at C-3β (**11**). No products arising from hydroboration at any other sites on **4** were observed. This outcome is strongly suggestive that the regioselectivity of the hydroboration event

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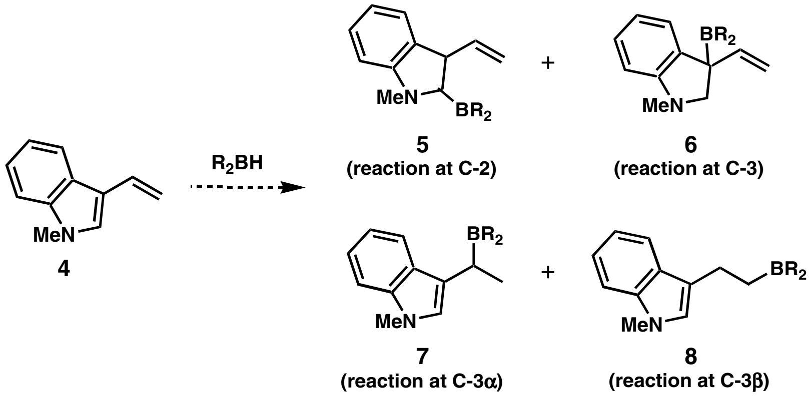
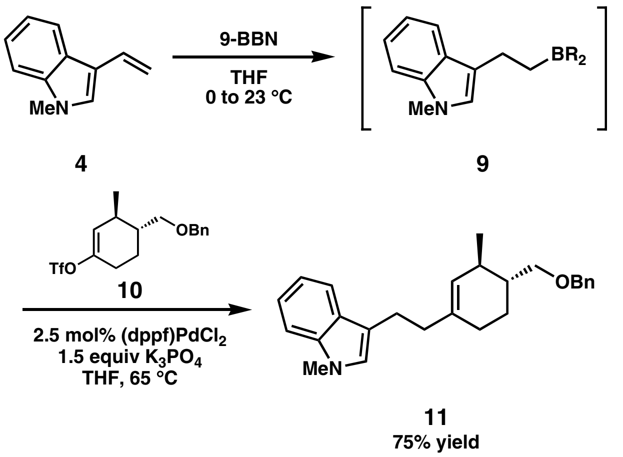


Scheme 2.



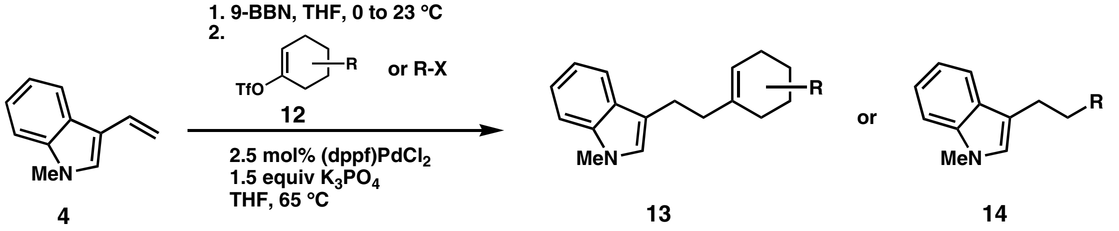
Scheme 3.

was extremely high for the terminal position of the vinyl group.

A variety of C-3β substituted indoles can be synthesized via this hydroboration/Suzuki–Miyaura method (Table 1). Triflates derived from cyclohexanone derivatives are efficient coupling partners for this reaction (entries 1–6). Vinyl and aryl halides are also viable substrates for the construction of C-3β substituted indoles (entries 7–9).

A representative procedure is as follows: 9-BBN dimer (203 mg, 0.830 mmol) was dissolved in THF (1.66 mL) at 23 °C under an argon atmosphere. Following dissolution, the reaction mixture was cooled to 0 °C, and to the solution was added a solution of vinyl indole **4** (261 mg, 1.66 mmol) in THF (1.66 mL). The reaction mixture was warmed to 23 °C, stirred for 3 h, and then treated with a solution of triflate **10** (552 mg, 1.51 mmol) in THF (7.55 mL), (dppf)$PdCl_2$ (30.8 mg, 0.0378 mmol), and K_3PO_4 (482 mg, 2.27 mmol). The reaction mixture was heated to 65 °C, and after 5 h, the reaction was cooled to 23 °C and treated with 1 mL NaOH (3.0 M aq) and 1 mL 30% H_2O_2, and the resulting mixture was stirred 1 h. The mixture was then partitioned between Et_2O (50 mL) and water (40 mL), and the aqueous phase was extracted with Et_2O (1 × 50 mL). The combined organic phases were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. Purification of the

Table 1. C-3β Substituted indoles via a hydroboration/Suzuki–Miyaura coupling sequence



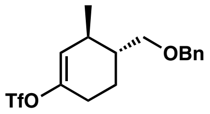
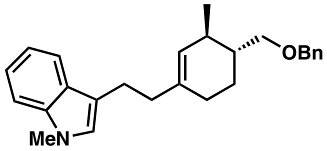
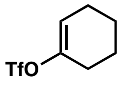
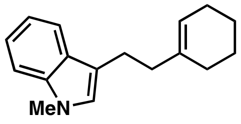
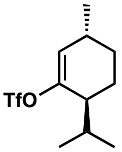
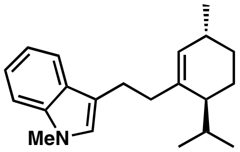
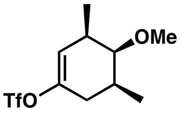
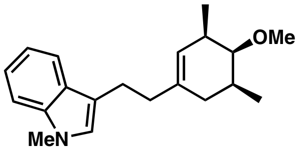
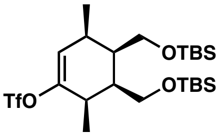
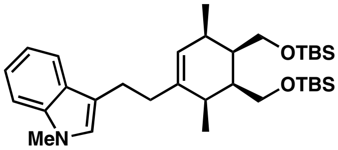
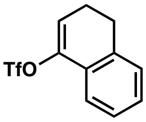
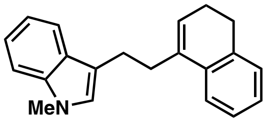
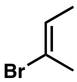
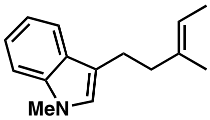
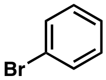
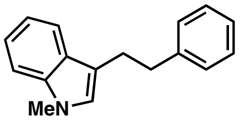
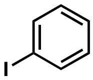
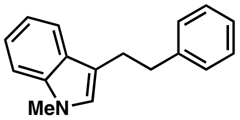
Entry	Triflate or R–X	Product	Yield[a] (%)
1			75
2			46

Table 1 (*continued*)

Entry	Triflate or R–X	Product	Yield[a] (%)
3			56
4			61
5			73
6[b]			72
7			57
8[b]			63
9[b]			56

[a] Isolated yield.

[b] A minor amount (~5%) of the coupling product arising from boron substitution at C-3α was observed.

residue by flash chromatography (2:1 → 1:1 hexanes/CH_2Cl_2 eluent) afforded Suzuki product **11** (467 mg, 75% yield, $R_F = 0.20$ in 4:1 hexanes/CH_2Cl_2) as a colorless oil.

In summary, a hydroboration/Suzuki–Miyaura method was utilized to functionalize 3-vinyl indoles. An array of indole-containing compounds arising from triflates or halides can be synthesized via this protocol. It is anticipated that this method could be applied to the synthesis of a number of biologically interesting compounds featuring the indole nucleus.

Acknowledgments

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References and notes

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4. For reviews of the Suzuki–Miyaura reaction, see: (a) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, 2419–2440; (b) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457–2483.
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