A palladium-catalyzed dearomative arylation of indoles is reported, which provides straightforward access to structurally diverse indolines bearing vicinal tetrasubstituted and borylated trisubstituted stereocenters in moderate to good yields with excellent diastereoselectivities. By using a BiNOL-based chiral phosphoramidite ligand and an sp²–sp³ mixed-boron reagent, an enantioselective dearomative arylation was achieved and chiral boron-containing products were accessed in up to 94% ee. Synthetic transformations of the resulting organoborons were conducted to afford a number of unique indoline derivatives.

Boron containing molecules serve as important building blocks due to their capability of participating in carbon–carbon and carbon–heteroatom bond forming reactions and thus are ubiquitous intermediates in the synthesis of various natural products and bioactive compounds.¹ The palladium-catalyzed 1,2-difunctionalization of olefins involving Heck/anionic-capture sequences has been intensely studied and proceeds via a carbopalladation followed by the capture of the alkyl-Pd species with a variety of nucleophiles.² Domino Heck-arylation reactions employing boron reagents as nucleophiles have enabled an efficient method to synthesize Csp³-based organoboron compounds (Scheme 1a).³ It is worthwhile to extend this methodology to the synthesis of structurally diverse, chiral organoboron heterocycles.

The transition-metal-catalyzed dearomative functionalization of aromatics has recently emerged as a useful approach to the synthesis of unique aliphatic cyclic molecules.³ In this context, dearomative functionalization of indoles has rendered the synthesis of indolines, a frequently occurring key substructure of natural products and alkaloids, extremely straightforward and efficient.⁴ Documented reports include the intramolecular C3-arylation of an indolic enolate,⁵ the Heck arylation of N-tethered 2,3-disubstituted indoles,⁶ and the reductive-Heck reaction,⁷ which results in the dearomative mono-functionalization of indole derivatives. Furthermore, the dearomative difunctionalization of indoles was realized through the trapping of the benzyl-Pd intermediate of aryl-palladation using a series of trapping agents, such as cyanoëîd,⁸ boroxines,⁹ terminal alkynes,¹⁰ propionic acid,¹¹ and heteroarenes,¹² efficiently delivering 2,3-disubstituted indolines. While the formation of the C–H and C–C bonds is documented in the aforementioned reports, there are no examples reported for C–B bond formation to afford chiral organoboron compounds. We envisioned a dearomative Heck-borylation domino reaction of indole to provide benzylic-boron indolines; the protocol mainly relies on the capture of the in situ generated benzyl-Pd species with diboron compounds. Herein, we report this dearomative arylation reaction using bis(pinacolato)diboron (B₂pin₂), and its enantioselective variant with a pre-activated sp²–sp³ mixed-boron reagent and a new BINOL-based chiral phosphoramidite ligand, which leads to a series of structurally unique tetrcyclic indolines in moderate to good yields, excellent diastereoselectivities, and good to excellent enantioselectivities (Scheme 1b).

**Scheme 1** Palladium-catalyzed arylylation of C≡C bonds.
The reaction of 1a with B₂pin₂ 2 was chosen as the starting condition for optimization. An initial test using Pd(OAc)₂ (5 mol%), PPh₃ (10 mol%), and 1BuOLi (2.0 equiv.) in CH₂Cl₂ (0.2 M) at 100 °C led to the desired arylborylation product 3a in 25% yield with >20 : 1 dr (Table 1, entry 1). To improve the yield, some bases were screened (entries 2–5). A poor yield was observed when using 1BuOK (Table 1, entry 2), while K₃PO₄, K₂CO₃, and Na₂CO₃ significantly improve the yield of 3a isolated in 66% in the case of K₂CO₃ (Table 1, entries 3–5). Other commercially available ligands, such as P(p-tolyl)₃, P'Bu₃, and PCy₃ were then tested, none of which increased the yield (Table 1, entries 6–8). Moreover, poor yields were also observed for bidentate phosphine ligands, e.g. dppe and xantphos. A lower yield was observed when changing the catalyst from Pd(OAc)₂ to Pd(dbta)₂ (Table 1, entry 9). Higher yields could be obtained by lowering the temperature and 3a was isolated in 83% yield when the reaction was run at 60 °C (Table 1, entries 10 and 11). Finally, the solvent effect was examined (Table 1, entries 12–15). Comparable yields were observed in toluene and CH₄CN, while the best yield of 3a was achieved in DCE solvent (Table 1, entry 15).

With the optimal conditions in hand, we then examined the scope of the reaction by varying the substituents on the halobenzene and indole rings. As shown in Scheme 2, substituent effect was examined (Table 1, entries 1–5). Other commercially available ligands, such as P(p-tolyl)₃, P'Bu₃, and PCy₃ were then tested, none of which increased the yield (Table 1, entry 9). Higher yields could be obtained by lowering the temperature and 3a was isolated in 83% yield when the reaction was run at 60 °C (Table 1, entries 10 and 11). Finally, the solvent effect was examined (Table 1, entries 12–15). Comparable yields were observed in toluene and CH₄CN, while the best yield of 3a was achieved in DCE solvent (Table 1, entry 15).

**Table 1** Optimization of the reaction conditions

| Entry | Base   | L       | T (°C) | Solvent | Yield (%) |
|-------|--------|---------|--------|---------|-----------|
| 1     | 1BuOLi | PPh₃    | 100    | CH₂Cl₂ | 25        |
| 2     | 1BuOK  | PPh₃    | 100    | CH₂Cl₂ | 27        |
| 3     | K₃PO₄ | PPh₃    | 100    | CH₂Cl₂ | 57        |
| 4     | K₂CO₃ | PPh₃    | 100    | CH₂Cl₂ | 66        |
| 5     | Na₂CO₃ | PPh₃    | 100    | CH₂Cl₂ | 43        |
| 6     | K₂CO₃ | P(p-tolyl)₃ | 100 | CH₂Cl₂ | 35        |
| 7     | K₂CO₃ | P'Bu₃₂HBF₄ | 100 | CH₂Cl₂ | 24        |
| 8     | K₂CO₃ | PCy₂·HBF₄ | 100 | CH₂Cl₂ | 17        |
| 9     | K₂CO₃ | PPh₃    | 100    | CH₂Cl₂ | 38        |
| 10    | K₂CO₃ | PPh₃    | 80     | CH₂Cl₂ | 74        |
| 11    | K₂CO₃ | PPh₃    | 60     | CH₂Cl₂ | 83        |
| 12    | K₂CO₃ | PPh₃    | 60     | THF    | 68        |
| 13    | K₂CO₃ | PPh₃    | 60     | toluene | 84        |
| 14    | K₂CO₃ | PPh₃    | 60     | MeCN   | 83        |
| 15    | K₂CO₃ | PPh₃    | 60     | DCE    | 87        |

* Reaction conditions: 1a (0.2 mmol), 2 (2 eq.), 5 mol% Pd(OAc)₂, 10 mol% ligand, and 2 eq. base in solvent (2 mL) at 100 °C; isolated yield, dr > 20 : 1; DCE = 1,2-dichloroethane. b 5 mol% Pd(dbta)₂ was used.

electron-withdrawing substituent (3e and 3g vs. 3b–3d and 3f).

Product 3h having two methoxyl groups was isolated in 92% yield. Of note, 3b, having a sterically congested methyl group at the C3 position of the bromobenzoyl moiety, was obtained in 78% yield. Next, the substituent effect on the indole ring was examined. A range of C2-alkylated and C2-arylated indoles were subjected to the reaction at 70 °C, which led to the arylborylated products 3i–3n in moderate yields. In contrast, the yields of these borylated indolines were lower than those achieved for 2-methyl products 3a–3h. It is noteworthy that the reaction of a 2-furyl indole substrate successfully delivered 3n in 53% yield. Moreover, the substituent at the C5-position of 2-substituted indoles was examined and the reactions of substrates having MeO, iPr, and Me groups afforded 3o–3q in moderate yields.

To demonstrate the synthetic utility of this reaction, a gram-scale reaction (4.0 mmol) was carried out under the optimal conditions and afforded 3a in 77% yield (Scheme 3). Synthetic transformations of 3a were then conducted. Oxidation of 3a using NaBO₂·4H₂O in THF/H₂O led to alcohol 4 as a single isomer in almost quantitative yield. Compound 4 was further
oxidized to ketone 5 in 85% yield with PCC as an oxidant at room temperature. Subjecting 3a to KHF₂ in THF/H₂O led to the corresponding potassium trifluoroborate 6 in 91% yield. Compound 6 was further converted to amide 7 in MeCN with 64% yield, as a single isomer through a Cu(OAc)₂-promoted oxidative nucleophilic substitution. The relative configurations of alcohol 4 and amide 7 were determined from their 2D-NOESY spectra.

An enantioselective Heck/borylation reaction of 1a was then investigated using phosphoramidite L₁ as the chiral ligand (Table 2, for more details see the ESI†). Early on, we observed that the benzylic boron was susceptible to inorganic-base promoted proto-deborylation at the high temperatures necessary for this metal–ligand system (vide infra). In order to avoid the use of the inorganic base necessary to activate B₂Pin₂ we utilized an sp²–sp³ mixed boron reagent first reported by Santos for copper-catalyzed hydroboration reactions. To the best of our knowledge, this reagent has not been used in palladium-catalyzed borylations. It was necessary to change the solvent from DCE to MTBE since the former was not efficient in the enantioselective variant (Table 2, entry 1 and 2). Although the bromo- and iodo-substrates 1a and 1a” delivered product in higher yields than the aryl-chloride, it was evident that the smaller halide improved the enantioselectivities (Table 2, entries 2–4). The absolute stereochemistry of 3a was assigned by single-crystal X-ray analysis.¹⁸

In the case of aryl-chloride, there was no reaction using B₂Pin₂ (Table 2, entry 5). We employed an organic base to neutralize the by-product of the boron-reagent and the conversion was improved to 50% while maintaining the ee (Table 2, entry 6). Further increasing the steric bulk of the ligand improved the yield of the reaction (Table 2, entry 7). Other amines (Table 2, entry 8) or lowering the temperature (Table 2, entry 9) were not effective. By increasing ligand and reagent loading the product was delivered in 74% yield and 94% ee (Table 2, entry 10 and 11). With respect to the ligand, the nitro variant L₃ was not an effective ligand for the transformation (Table 2, entry 12). The 3,3'-orthoanisole ligand L₄ also did not improve the yield (Table 2, entry 13). The importance of the 3,3' rings was evident as the simple BINOL-derived phosphoramidite L₅ did not produce the product (Table 2, entry 14). Contrary to the dearomative reductive-Heck,⁹ BINAP was not effective in catalyzing the reaction (Table 2, entry 15).

Table 2: Optimization of the enantioselective arylborylation

| Entry | X   | Additive   | Changes to condition | Yield (%) | ee (%) |
|-------|-----|------------|----------------------|-----------|-------|
| 1     | Br  | None       | None                 | 73        | 64    |
| 2     | Br  | None       | DCE as solvent       | 34        | 20    |
| 3     | I   | None       | None                 | 40        | 50    |
| 4     | Cl  | None       | None                 | 15        | 88    |
| 5     | Cl  | K₂CO₃ (2 eq.) | B₂Pin₂ (2 eq.)     | n.r.      | —     |
| 6     | Cl  | NEt₃ (3 eq.) | using L₂             | 50        | 88    |
| 7     | Cl  | NEt₃ (3 eq.) |                       | 65        | 88    |

Entries 8–11 using L₂

| Entry | X | Additive   | Changes to condition | Yield (%) | ee (%) |
|-------|---|------------|----------------------|-----------|-------|
| 8     | Cl | Pr₂NEt (3 eq.) | None                 | 27        | —     |
| 9     | Cl | NEt₃ (3 eq.) | 80 °C                | n.r.      | —     |
| 10    | Cl | NEt₃ (3 eq.) | 10 mol% L₂           | 68        | 91    |
| 11    | Cl | NEt₃ (5 eq.) | 3 eq. mixed-boron reagent | 74        | 94    |

Entries 12–15 using conditions in entry 11

| Entry | X | Additive   | Changes to condition | Yield (%) | ee (%) |
|-------|---|------------|----------------------|-----------|-------|
| 12    | Cl | NEt₃ (5 eq.) | L₃                   | 17        | 78    |
| 13    | Cl | NEt₃ (5 eq.) | L₄                   | 70        | 91    |
| 14    | Cl | NEt₃ (5 eq.) | L₅                   | Trace     | —     |
| 15    | Cl | NEt₃ (5 eq.) | L₆                   | Trace     | —     |

* Standard conditions: 1 (0.2 mmol), mixed-boron reagent (2 eq.), 5 mol% Pd(dba)₂, 6 mol% L₁, and additive in MTBE (2 mL) at 100 °C for 18 h; isolated yield; ee was determined by chiral HPLC; TMG = tetramethyl guanidine; n.r. = no reaction.
We then examined the scope of the Heck/borylation on various aryl-chloride substrates (Scheme 4). The steric influence at the halide (3r), as well as functionalities para to the amide tether (3d and 3s) provided products in diminished enantioselectivities. In contrast, the substitution para to chloride (3t) or on the indole moiety yielded 3t-3v in moderate yields and excellent enantioselectivities. The aryl functionality at R² resulted in 3j and 3w in moderate and good yields with excellent enantioselectivities. Finally, heterocycle containing scaffold 3x was accessed in good yield albeit in a diminished enantioselectivity. Oxidation of compound 3a provided the chiral alcohol (+)-4 and ketone (+)-5 with no loss in enantiomeric excess.

Conclusions

In conclusion, we have developed a dearomative difunctionalization of indoles through a palladium-catalyzed intramolecular arylborylation reaction. Indoles possessing vicinal borylated trisubstituted and tetrasubstituted stereocenters were accessed in good yields and excellent diastereoselectivities. The asymmetric variant of this reaction was explored with a new BINOL-based chiral phosphoramidite ligand and moderate to excellent enantioselectivities were obtained (up to 94% ee). Transformations of the benzylic boron to alcohol and amide were presented to show the synthetic utilities of this reaction.

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