Synthesis of cyclic chiral \(\alpha\)-amino boronates by copper-catalyzed asymmetric dearomative borylation of indoles†

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A copper(I)-catalyzed dearomative borylation of \(N\)-alkoxycarbonyl protected indole-3-carboxylates has been developed. The boron addition in this reaction occurred regioselectively at the 2-position of indoles followed by diastereoselective protonation, affording the corresponding stable cyclic chiral \(\alpha\)-amino boronates (2-borylindolines) in moderate to good yields with excellent diastereo- and enantioselectivities. The product 2c could be used as a versatile precursor to undergo subsequent stereoselective transformations, delivering highly functionalized 2,3,3-trisubstituted chiral indolines.

The importance of chiral \(\alpha\)-amino boronic acid derivatives has been demonstrated in pharmacologically useful protease inhibitors such as bortezomib,1 delanzomb,2 and ixazomb.3 In addition, their use in transition-metal-catalyzed stereospecific C–C bond forming reactions has also gained growing attention.4 Therefore, significant efforts have been devoted to the development of efficient methods to synthesize chiral \(\alpha\)-amino boronate esters.5 Most methods rely on a diastereoselective synthesis involving a stoichiometric amount of chiral auxiliaries.6 The recently emerged transition-metal-catalyzed asymmetric borylations by Fernández, Morken, Lin, Liao, Miura, Tang, Parra and Tortosa, and our group also provide efficient methods to access a number of acyclic chiral \(\alpha\)-amino boronate esters.7 In contrast, the direct catalytic asymmetric borylation towards cyclic chiral \(\alpha\)-amino boronate esters remains elusive,8 although some of these molecules have shown promising bioactivities such as dipeptidyl peptidase-4 (DPP-4) inhibitors, e.g., talabostat and dutogliptin.9

Dearomatization reactions have emerged as powerful approaches to convert readily available planar aromatic compounds into a plethora of three dimensional, highly functionalized cyclic products.10 Among them, dearomative borylation involving \(N\)-heteroarenes has gained increasing attention recently as it can provide saturated or partially saturated borylated \(N\)-heterocycles that are important building blocks for the synthesis of natural and bioactive compounds. Pioneered by Hill and Suginome,11 many systems including transition-metal catalysis and organocatalysis have been developed to achieve high chemoselectivity and regioselectivity in this area.12 The successes of most aforementioned reactions are probably due to the formation of stable N–B bonds.13 In stark contrast, only a few examples of asymmetric transformations have been documented. In 2015, the Ito group reported a copper-catalyzed asymmetric protoboration of 2-substituted indoles, delivering 3-borylindolines with high regio-, diastereo-, and enantioselectivity (Fig. 1a).14 Subsequently, they developed one-pot sequential dearomative reduction/asymmetric borylation of pyridines and quinolines.14 The reaction produced C3 borylated chiral piperidine derivatives with high diastereo- and

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Fig. 1 Recent advances in asymmetric dearomative borylation of \(N\)-heteroarenes.
enantioselectivity (Fig. 1a). Tang and coworkers recently reported chiral diboron templated dearomative reductive coupling of isoquinolines involving a diastereoselective concerted [3,3]-sigma rearrangement along with the formation of two N–B bonds (Fig. 1b). It is quite surprising that the direct asymmetric boryl addition to the carbon adjacent to the nitrogen of N-heteroarenes remains elusive although numerous examples have been shown with carbon nucleophiles. The lack of research probably arises from the instability of the product. However, the asymmetric nucleophilic addition of a boryl group at N-adjacent carbon could offer a straightforward method that leads to cyclic chiral α-amino boronate esters. Particularly, asymmetric dearomative borylation of the 2-position of 3-substituted indoles could also furnish potentially useful chiral 2,3-disubstituted indolines that may serve as key building blocks in drug discovery and natural product synthesis. In this communication, we disclose a copper(i)-catalyzed asymmetric dearomative borylation of N-alkoxycarbonyl protected indole-3-carboxylates by way of a borylcopper(i) species (Fig. 1c). The boryl addition takes place regioselectively at the 2-position followed by diastereoselective protonation, affording a series of indoline-based cyclic chiral α-amino boronate esters (2-borylindolines) with high diastereo- and enantioselectivity. Stereospecific transformations of the C–B bond of chiral 2-borylindoline have also been demonstrated.

To test our hypothesis, we began our reaction with an indole substrate with different combinations of substituents at 1 and 3 positions. The initial results showed that in the presence of dppe/CuCl (10 mol%), NaOEt (10 mol%) and tBuOH (2.0 equiv.), the reaction of N-alkoxycarbonyl methyl indole-3-carboxylates with bis(pinacolato)diboron (B2pin2) in THF at room temperature for 18 hours gave a significant amount of isolable cis-2-borylindoline whereas the other diastereomer was not stable towards purification. Particularly, the N-Boc methyl indole-3-carboxylate 1a gave the cis-isomer preferentially. With 1a in hand, we then turned our attention to the asymmetric version of this reaction. The reaction of 1a with B2pin2 in the presence of 10 mol% of the axially chiral ligand (S)-BINAP (L1) or bulky (R)-DTBM-SEGPHOS (L2) only gave a trace amount of the product (Table 1, entries 1 and 2). Fortunately, when the electron-rich ligand (R,R)-DuPhos (L3) was used, an appreciable amount of cis-product 2a was obtained with an excellent ee value (92%) albeit with almost no dia-stereoselectivity (45 : 55) (Table 1, entry 3). Encouraged by this, several electron-rich bidentate phosphines were investigated. For example, the use of (R,R)-Me-BPE resulted in a product with elevated diastereoselectivity (80 : 20) but decreased enantioselectivity (80%) compared to L3 (Table 1, entry 4). Gratifyingly, when the bulky electron-rich ligand (R,R)-Quinox® (L5) was used, the reaction proceeded smoothly, affording cis-2-borylindoline 2a in 90% yield with good stereoselectivity (86% ee, 92 : 8 d.r.; Table 1, entry 5). The size of R in the ester moiety also played an important role in controlling the stereoselectivity. For example, when R was ethyl (2b), an enhanced stereoselectivity was observed (91% ee, >98 : 2 d.r.; Table 1, entry 6). With the use of a substrate with R = iPr, the corresponding 2-borylindoline 2c could be obtained with 94% ee and good diastereoselectivity (94 : 6 d.r.; Table 1, entry 7). Further increasing the size of R such as Bu (2d) led to a diminished ee value (81%) and yield (72%) whereas good diastereoselectivity (97 : 3 d.r.; Table 1, entry 8) was maintained. Although the other applied alcohols such as MeOH, EtOH or iPrOH gave products with excellent enantiomeric excesses (96–97%), only moderate d.r. values (50 : 30–50 : 20) were achieved. When the reaction of 2c was carried out at 0 °C, the product was obtained with a slightly enhanced stereoselectivity (93% ee, 95 : 5 : d.r.; Table 1, entry 12).

With the optimized reaction conditions (Table 1, entry 12) in hand, we then explored the substrate scope of this reaction as illustrated in Fig. 2. Generally, the N-protecting group affected enantioselectivity significantly, with less influence on diastereoselectivity. For example, the smaller groups MeOOC and Cbz provided inferior results (78% and 68% ee, respectively; Fig. 2e and f) compared to the substrate with bulkier Boc (86% ee; Fig. 2a). The size of the ester at the 3-position of indole also played a pivotal role in chiral induction. The reaction with the substrate with R = iPr (1c) afforded corresponding cis-2-borylindoline (2c) with a superior ee value (91%) compared to those with R = Me (2a, 86% ee), Et (2b, 93% ee) and tBu (2d, 91% ee). In most cases, the reaction of N-Boc isopropyl indole-3-carboxylate 1 resulted in good yields (81–93%) with uniformly

### Table 1: Optimization of the reaction conditions for the asymmetric dearomative borylation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>R</th>
<th>Yield (%)</th>
<th>d.r. (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>1a: Me</td>
<td>Trace</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>L2</td>
<td>1a: Me</td>
<td>Trace</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>3</td>
<td>L3</td>
<td>1a: Me</td>
<td>44</td>
<td>45 : 55</td>
<td>92</td>
</tr>
<tr>
<td>4</td>
<td>L4</td>
<td>1a: Me</td>
<td>60</td>
<td>80 : 20</td>
<td>80</td>
</tr>
<tr>
<td>5</td>
<td>L5</td>
<td>1a: Me</td>
<td>90</td>
<td>92 : 8</td>
<td>86</td>
</tr>
<tr>
<td>6</td>
<td>L5</td>
<td>1b: Et</td>
<td>86</td>
<td>&gt;98 : 2</td>
<td>91</td>
</tr>
<tr>
<td>7</td>
<td>L5</td>
<td>1c: iPr</td>
<td>93</td>
<td>94 : 6</td>
<td>94</td>
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<tr>
<td>8</td>
<td>L5</td>
<td>1d: tBu</td>
<td>72</td>
<td>97 : 3</td>
<td>81</td>
</tr>
<tr>
<td>9</td>
<td>L5</td>
<td>1e: iPr</td>
<td>46</td>
<td>50 : 50</td>
<td>96</td>
</tr>
<tr>
<td>10</td>
<td>L5</td>
<td>1e: iPr</td>
<td>55</td>
<td>63 : 37</td>
<td>97</td>
</tr>
<tr>
<td>11</td>
<td>L5</td>
<td>1e: iPr</td>
<td>56</td>
<td>70 : 30</td>
<td>97</td>
</tr>
<tr>
<td>12</td>
<td>L5</td>
<td>1e: iPr</td>
<td>85</td>
<td>95 : 5</td>
<td>95</td>
</tr>
</tbody>
</table>

a Unless otherwise noted, all the reactions were carried out with 1 (0.2 mmol), L (0.02 mol), CuCl (0.02 mmol), NaOMe (0.02 mmol), alcohol (0.4 mmol), and B2pin2 (0.3 mmol) in toluene (1 mL) at 25 °C for 16 h. b The yield of isolated cis-product. c The diastereoselective ratio (cis/trans) was determined by 1H NMR of crude reaction mixtures. d The enantiomeric excess was determined by HPLC on a chiral IE column. e MeOH was used instead of tBuOH. f EtOH was used instead of tBuOH. g iPrOH was used instead of tBuOH. h The reaction was carried out at 0 °C for 18 h.
The reaction of 2c involved the sequential addition of methanolic solution of I$_2$ and NaOMe followed by the addition of electrophiles a to the C-O bond of the corresponding 2-borylindoline 4 in good yields with excellent stereoselectivities.$^{21}$ The C–B bond in 4a could be transformed to a C–O bond in the presence of NaBO$_2$. After benzoylation, the corresponding indolin-2-yl benzoate 5 was obtained in 60% overall yield (2 steps) with 95% ee. The C–B bond in 4a could also undergo stereospecific C–C bond forming reactions. For example, the reaction of 4a with vinylMgBr followed by the sequential addition of methanolic solution of I$_2$ and NaOMe could produce 2-vinylindoline 6 in 98% yield with 95% ee.$^{22}$ In addition, the arylation of 4a with furyl-2-lithium followed by the addition of NBS was able to produce 2-(2-furyl)-indoline 7 in 40% yield with 95% ee.$^{23}$

The plausible reaction mechanism for the current copper(i)-catalyzed dearomatic borylation of 3-substituted indoles is depicted in Fig. 4. Because the borylation only worked for indole with an EWG at its 3-position, the reaction should proceed in a similar way to the copper-catalyzed conjugate boration of a,$\beta$-unsaturated carbonyl compounds.$^{24}$ The reaction of LCu-OrBu (A) with B$_2$pin$_2$ would generate active species borylcopper(i) B. The coordination of complex B to the C$_2$–C$_3$ π bond of indole 1c followed by the subsequent syn-addition of the Cu–B bond to the C$_2$–C$_3$ π bond would give C-bound enolate D. The protolytic cleavage of the copper–carbon bond of D by BuOH would result in trans-product 3c, which is not consistent with the experimental outcome. To release large steric congestion between the Bpin group and LCu, D would isomerize into O-bound enolate E.$^{25}$ To avoid the steric repulsion between the Bpin group and bulky tBuOH, the protonation of E would take place from the opposite side of Bpin to liberate cis-product 2c and A for the next catalytic cycle.

![Fig. 2 Substrate scope of reaction. Unless otherwise noted, all the reactions were carried out with 1 (0.2 mmol), (R,R)-QuinoxP$_8$ (0.02 mol), CuCl (0.02 mmol), NaOMe (0.02 mmol), tBuOH (0.4 mmol), and B$_2$pin$_2$ (0.3 mmol) in toluene (1 mL) at 0 °C for 48 hours. The d.r. value was determined by GC of crude reaction mixtures. The enantiomeric excesses were determined by chiral HPLC. The reaction time was 48 hours.](image1)

![Fig. 3 Gram-scale synthesis and transformations of 2-borylindoline 2c.](image2)
Conclusions

In conclusion, we have developed a copper-catalyzed asymmetric dearomative borylation of N-alloxy carbonyl protected indole-3-carboxylates under mild reaction conditions, providing a straightforward method to achieve cyclic chiral ε-amino boronate esters with high diastereo- and enantioselectivity. The obtained products could undergo subsequent stereoselective transformations, affording highly functionalized 2,3,3-trisubstituted chiral indolines. This method provides not only a route to cyclic chiral ε-amino boronate esters but also a series of versatile chiral precursors for chiral indoline synthesis. The further application of chiral 2-borylindolines and the development of other dearomative process are currently underway in our laboratory.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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Notes and references

11 (a) M. Arrowsmith, M. S. Hill, T. Hadlington, G. Kocioak-Kön and C. Weetman, Organometallics, 2011, 30, 5556; (b)


18 For details see Table S1 in ESI†.

19 The relative configuration of major product was determined by 2D NMR NOSEY spectrum. For details see ESI†.

21 The reason we chose Table 1, entry 12 as optimal because enantioselectivities of most substrates were not satisfying when the reactions were carried out at room temperature.


25 Although conversion of C-bound enolate to O-bound enolate is disfavored in borylation of methyacrylate according to the calculations (ref. 24), the large steric congestion between substituents at 2- and 3-positions of D would probably force this conversion to occur in the current reaction.