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Synthesis of cyclic chiral α -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 α -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 α -amino boronic acid derivatives has been demonstrated in pharmaceutically useful protease inhibitors such as bortezomib,¹ delanzomib,² and ixazomib.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 α -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 α -amino boronate esters.⁷ In contrast, the direct catalytic asymmetric borylation towards cyclic chiral α -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 Sugimoto,¹¹ many systems including transition-metal catalysis and organocatalysis have been developed to achieve high chemo- and regioselectivity in this area.¹² The successes of most aforementioned reactions are probably due to the formation of stable N–B bonds.^{11b} 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).¹³ 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

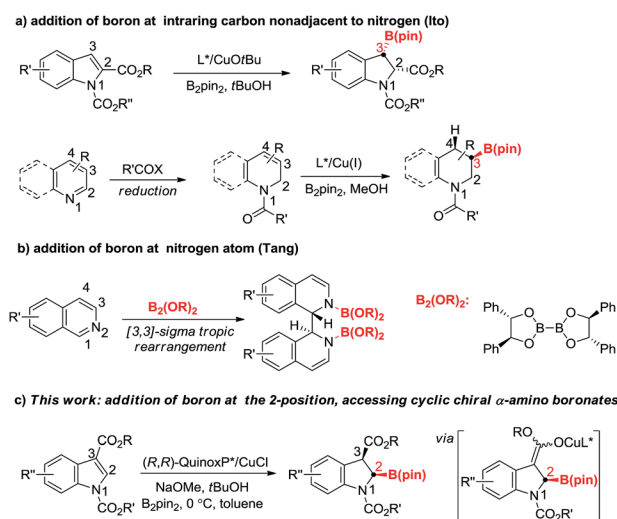


Fig. 1 Recent advances in asymmetric dearomative borylation of *N*-heteroarenes.

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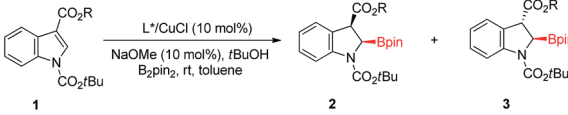
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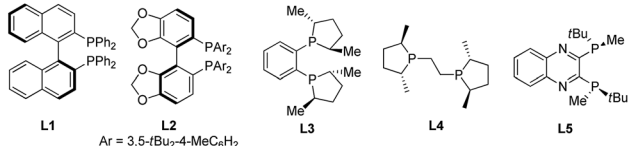
enantioselectivity (Fig. 1a). Tang and coworkers recently reported chiral diboron templated dearomative reductive coupling of isoquinolines involving a diastereoselective concerted [3,3]-sigma rearrangement along with the formation of two N-B bonds (Fig. 1b).¹⁵ It is quite surprising that the direct asymmetric boryl addition to the carbon adjacent to the nitrogen of *N*-heteroarenes remains elusive although numerous examples have been shown with carbon nucleophiles.¹⁶ The lack of research probably arises from the instability of the product.^{14a} 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).¹⁷ The boron 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%), NaOMe (10 mol%) and *t*BuOH (2.0 equiv.), the reaction of *N*-alkoxycarbonyl methyl indole-3-carboxylates with bis(pinacolato)diboron (B_2pin_2) 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.¹⁸ 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 B_2pin_2 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*)-QuinoxP* (**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* = *i*Pr, the corresponding 2-borylindoline **2c** could be obtained with 94% ee and good diastereoselectivity

Table 1 Optimization of the reaction conditions for the asymmetric dearomative borylation^a



Entry	Ligand	1: R	Yield ^b (%)	d.r. ^c	ee ^d (%)
1	L1	1a : Me	Trace	n.d.	n.d.
2	L2	1a : Me	Trace	n.d.	n.d.
3	L3	1a : Me	44	45 : 55	92
4	L4	1a : Me	60	80 : 20	80
5	L5	1a : Me	90	92 : 8	86
6	L5	1b : Et	86	>98 : 2	91
7	L5	1c : <i>i</i> Pr	93	94 : 6	94
8	L5	1d : <i>t</i> Bu	72	97 : 3	81
9 ^e	L5	1c : <i>i</i> Pr	46	50 : 50	96
10 ^f	L5	1c : <i>i</i> Pr	55	63 : 37	97
11 ^g	L5	1c : <i>i</i> Pr	56	70 : 30	97
12 ^h	L5	1c : <i>i</i> Pr	85	95 : 5	95



^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 B_2pin_2 (0.3 mmol) in toluene (1 mL) at 25 °C for 16 h. ^b The yield of isolated *cis*-product **2**. ^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 *t*BuOH. ^f EtOH was used instead of *t*BuOH. ^g *i*PrOH was used instead of *t*BuOH. ^h The reaction was carried out at 0 °C for 18 h.

(94 : 6 d.r.; Table 1, entry 7). Further increasing the size of *R* such as *t*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 *i*PrOH gave products with excellent enantiomeric excesses (96–97%), only moderate d.r. values (50 : 50–70 : 30) were achieved. When the reaction of **2c** was carried out at 0 °C, the product was obtained with a slightly enhanced stereoselectivity (95% ee, 95 : 5 d.r.; Table 1, entry 12).

With the optimized reaction conditions (Table 1, entry 12) in hand,¹⁹ 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 MeOCO 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 of the substrate with *R* = *i*Pr (**1c**) afforded corresponding *cis*-2-borylindoline (**2c**) with a superior ee value (95%) compared to those with *R* = Me (**2a**, 86% ee), Et (**2b**, 93% ee) and *t*Bu (**2d**, 91% ee). In most cases, the reaction of *N*-Boc isopropyl indole-3-carboxylate **1** resulted in good yields (81–93%) with uniformly



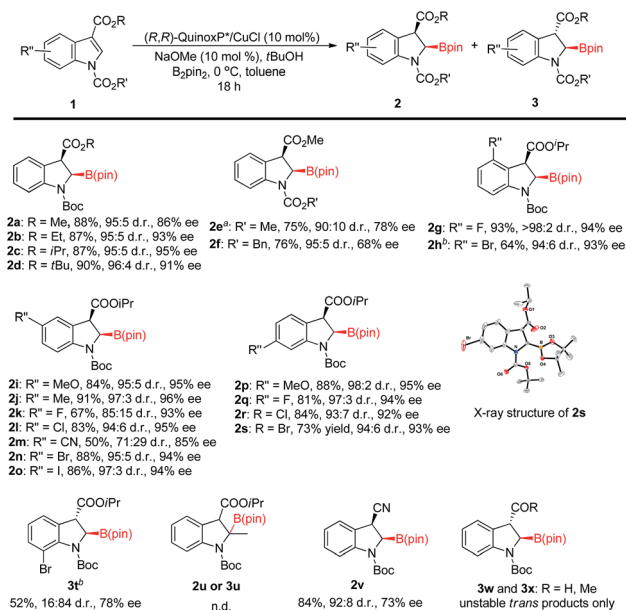


Fig. 2 Substrate scope of reaction. Unless otherwise noted, all the reactions were carried out with **1** (0.2 mmol), (R,R) -QuinoxP* (0.02 mol), CuCl (0.02 mmol), NaOMe (0.02 mmol), t BuOH (0.4 mmol), and B_2pin_2 (0.3 mmol) in toluene (1 mL) at 0 °C for 18 h. The d.r. values (*cis/trans*) were determined by 1H NMR of crude reaction mixtures. The enantiomeric excesses were determined by chiral HPLC. ^aThe d.r. value was determined by GC of crude reaction mixtures. ^bThe reaction time was 48 hours.

excellent stereoselectivities (92–96% ee, $\geq 94 : 6$ d.r.). The use of an electron-withdrawing group such as F or cyano at the 5-position in **1** afforded a decreased yield (67% and 50%, respectively) and stereoselectivity (**2k**: 93% ee, 85 : 15 d.r.; **2m**: 85% ee, 71 : 29 d.r.). Interestingly, when 7-bromo indole **1t** was employed, the reaction gave *trans*-product **3t** predominantly (*cis/trans* = 16 : 84) with 78% ee. The destruction of coplanarity of Boc and indole caused by steric repulsion between bromo and Boc may give rise to reversed diastereoselectivity. The proton might approach the copper O-bound enolate intermediate from the opposite side of Boc's t Bu group that would be in the *trans* position of the boryl group, thereby leading to *trans*-2-borylindoline **3t** as the major product. 2-Methylindole (**1u**) failed to yield any product (**2u** or **3u**). The reaction of 3-cyano indole **1v** could also give a *cis*-product in good yield with reasonable stereoselectivity (**2v**: 92 : 8 d.r., 73% ee). However, when the EWG was formyl or acetyl, only a labile *trans*-product was observed (**3w** and **3x**). The absolute configuration of **2s** was determined to be 2*R*, 3*R* by X-ray analysis.²⁰ The configurations of the other products were provisionally assigned as the same by analogy. Because the proton at the 3 position of product **2** is relatively acidic, we tested the stability of its stereochemistry. The results of control experiments clearly show that no isomerization was observed when **2c** was subjected to reaction conditions at 40 °C for 18 hours or in its $CDCl_3$ solution at room temperature for 24 hours (see the ESI† for more information).

To demonstrate the practicality of our method, a gram-scale reaction and synthetic applications of **2c** were performed as

illustrated in Fig. 3. Firstly, the current method could be amendable to the gram-scale with reduced catalyst loading (2.5 mol%) and elevated temperature. The reaction of **1c** (1.21 grams, 4.0 mmol) at room temperature for 18 hours gave corresponding 2-borylindoline **2c** (1.64 grams, 3.8 mmol) in 95% yield with excellent stereoselectivity (97 : 3 d.r. and 96% ee). The acidity of the C3 proton allows further functionalization at this position. The deprotonation of **2c** with LDA at –78 °C in THF followed by the addition of electrophiles afforded 2,3,3-trisubstituted 2-borylindolines **4** in good yields with good stereoselectivities.²¹ The C–B bond in **4a** could be transformed to a C–O bond in the presence of $NaBO_3$. After benzylation, 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 provide 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 dearomative 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 α,β -unsaturated carbonyl compounds.²⁴ The reaction of $LCu-OtBu$ (**A**) with B_2pin_2 would generate active species borylcopper(i) **B**. The coordination of complex **B** to the C2–C3 π bond of indole **1c** followed by the subsequent *syn*-addition of the Cu–B bond to the C2–C3 π bond would give C-bound enolate **D**. The protolytic cleavage of the copper–carbon bond of **D** by t 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 t BuOH, 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.

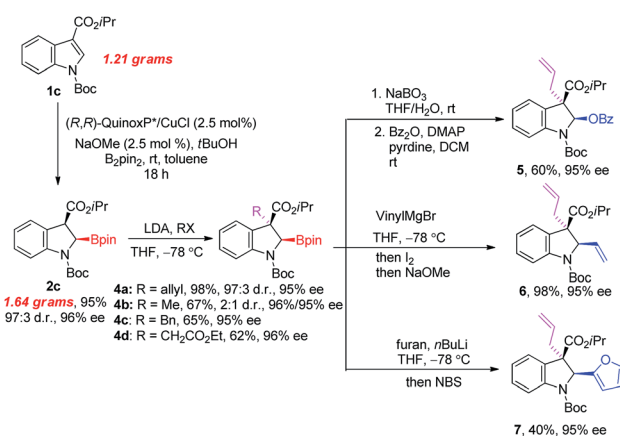


Fig. 3 Gram-scale synthesis and transformations of 2-borylindoline **2c**.

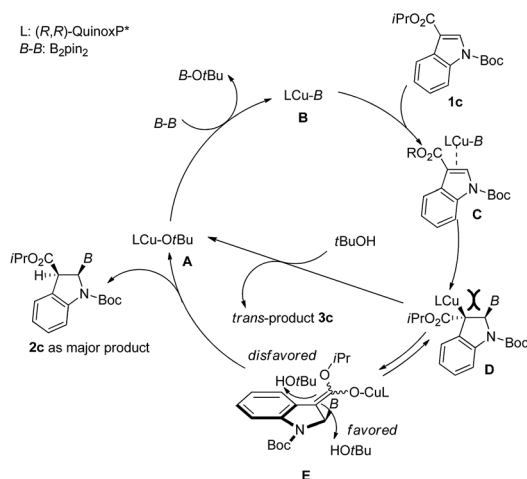


Fig. 4 Plausible reaction pathway of the current dearomative borylation.

Conclusions

In conclusion, we have developed a copper-catalyzed asymmetric dearomative borylation of *N*-alkoxycarbonyl protected indole-3-carboxylates under mild reaction conditions, providing a straightforward method to achieve cyclic chiral α -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 α -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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- 18 For details see Table S1 in ESI.†
- 19 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.
- 20 Crystallographic data for **2s** could be found in the ESI.† CCDC 1836254 contains the supplementary crystallographic data for this paper.
- 21 The relative configuration of major product was determined by 2D NMR NOSEY spectrum. For details see ESI.†
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- 25 Although conversion of C-bound enolate to O-bound enolate is disfavored in borylation of methacrylate 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.

