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# 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 pharmaceutically useful protease inhibitors such as bortezomib,<sup>1</sup> delanzomib,<sup>2</sup> and ixazomib.<sup>3</sup> In addition, their use in transition-metal-catalyzed stereospecific C–C bond forming reactions has also gained growing attention.<sup>4</sup> Therefore, significant efforts have been devoted to the development of efficient methods to synthesize chiral  $\alpha$ -amino boronate esters.<sup>5</sup> Most methods rely on a diastereoselective synthesis involving a stoichiometric amount of chiral auxiliaries.<sup>6</sup> 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.<sup>7</sup> In contrast, the direct catalytic asymmetric borylation towards cyclic chiral  $\alpha$ -amino boronate esters remains elusive,<sup>8</sup> although some of these molecules have shown promising bioactivities such as dipeptidyl peptidase-4 (DPP-4) inhibitors, *e.g.*, talabostat and dutogliptin.<sup>9</sup>

Dearomatization reactions have emerged as powerful approaches to convert readily available planar aromatic compounds into a plethora of three dimensional, highly functionalized cyclic products.<sup>10</sup> 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,<sup>11</sup> many systems including transition-metal catalysis and organocatalysis have been developed to achieve high chemo- and regioselectivity in this area.<sup>12</sup> The successes of most aforementioned reactions are probably due to the formation of stable N–B bonds.<sup>11b</sup> 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).<sup>13</sup> Subsequently, they developed one-pot sequential dearomative reduction/asymmetric borylation of pyridines and quinolines.<sup>14</sup> The reaction produced C3 borylated chiral piperidine derivatives with high diastereo- and

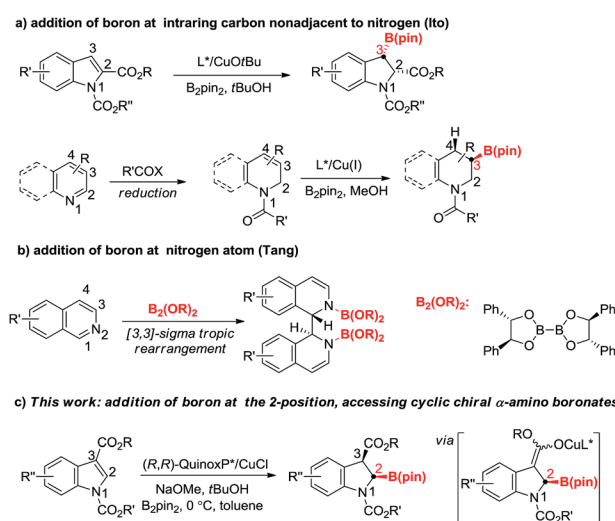


Fig. 1 Recent advances in asymmetric dearomative borylation of *N*-heteroarenes.

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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).<sup>15</sup> 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.<sup>16</sup> The lack of research probably arises from the instability of the product.<sup>14a</sup> However, the asymmetric nucleophilic addition of a boryl group at *N*-adjacent carbon could offer a straightforward method that leads to cyclic chiral  $\alpha$ -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).<sup>17</sup> The boron addition takes place regioselectively at the 2-position followed by diastereoselective protonation, affording a series of indoline-based cyclic chiral  $\alpha$ -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.<sup>18</sup> 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<sup>a</sup>

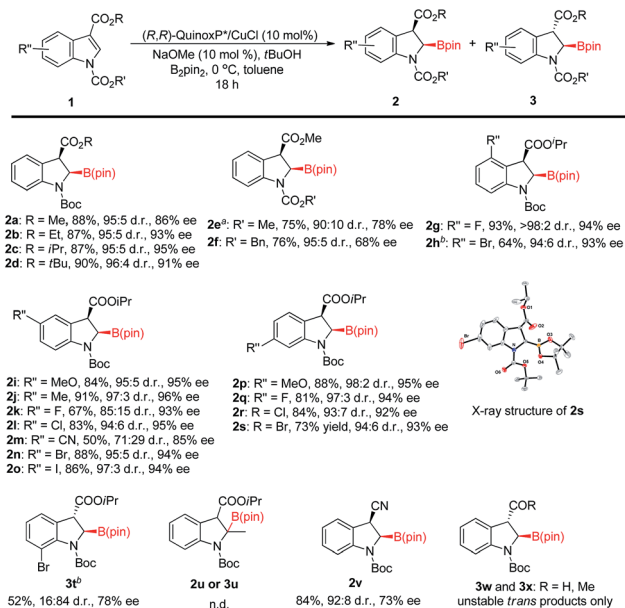
Entry	Ligand	1: R	Yield <sup>b</sup> (%)	d.r. <sup>c</sup>	ee <sup>d</sup> (%)
1	<b>L1</b>	<b>1a</b> : Me	Trace	n.d.	n.d.
2	<b>L2</b>	<b>1a</b> : Me	Trace	n.d.	n.d.
3	<b>L3</b>	<b>1a</b> : Me	44	45 : 55	92
4	<b>L4</b>	<b>1a</b> : Me	60	80 : 20	80
5	<b>L5</b>	<b>1a</b> : Me	90	92 : 8	86
6	<b>L5</b>	<b>1b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

<sup>a</sup> 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. <sup>b</sup> The yield of isolated *cis*-product **2**. <sup>c</sup> The diastereoselective ratio (*cis/trans*) was determined by <sup>1</sup>H NMR of crude reaction mixtures. <sup>d</sup> The enantiomeric excess was determined by HPLC on a chiral IE column. <sup>e</sup> MeOH was used instead of *t*BuOH. <sup>f</sup> EtOH was used instead of *t*BuOH. <sup>g</sup> *i*PrOH was used instead of *t*BuOH. <sup>h</sup> 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,<sup>19</sup> 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





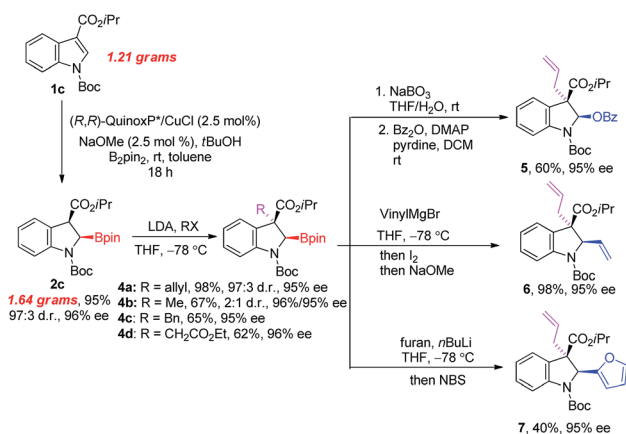
**Fig. 2** Substrate scope of reaction. Unless otherwise noted, all the reactions were carried out with **1** (0.2 mmol), (*R,R*)-QuinoxP\* (0.02 mol), CuCl (0.02 mmol), NaOMe (0.02 mmol), *t*BuOH (0.4 mmol), and B<sub>2</sub>pin<sub>2</sub> (0.3 mmol) in toluene (1 mL) at 0 °C for 18 h. The d.r. values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

excellent stereoselectivities (92–96% ee, ≥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 (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.<sup>20</sup> 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<sub>3</sub> 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.<sup>21</sup> The C–B bond in **4a** could be transformed to a C–O bond in the presence of NaBO<sub>3</sub>. 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<sub>2</sub> and NaOMe could provide 2-vinylindoline **6** in 98% yield with 95% ee.<sup>22</sup> 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.<sup>23</sup>

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 borylation of α,β-unsaturated carbonyl compounds.<sup>24</sup> The reaction of LCu–O*t*Bu (**A**) with B<sub>2</sub>pin<sub>2</sub> 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**.<sup>25</sup> 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**.



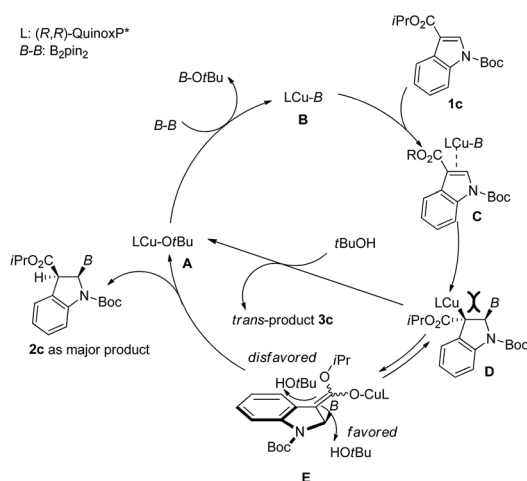


Fig. 4 Plausible reaction pathway of the current dearomative borylation.

## 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  $\alpha$ -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  $\alpha$ -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

- (a) J. Adams and M. Kauffman, *Cancer Invest.*, 2004, **22**, 304; (b) L. R. Dick and P. E. Fleming, *Drug Discovery Today*, 2010, **15**, 243.
- (a) E. Gallerani, M. Zucchetti, D. Brunelli, E. Marangon, C. Noberasco, D. Hess, A. Delmonte, G. Martinelli, S. Böhm, C. Driessen, F. De Braud, S. Marsoni, R. Cereda, F. Sala, M. D'Incalci and C. Sessa, *Eur. J. Cancer*, 2013, **49**, 290; (b) R. C. Roemmele and M. A. Christie, *Org. Process Res. Dev.*, 2013, **17**, 422.
- M. Gentile, M. Offidani, E. Vigna, L. Corvatta, A. G. Recchia, L. Morabito, F. Morabito and S. Gentili, *Expert Opin. Invest. Drugs*, 2015, **24**, 1287.
- (a) T. Ohmura, T. Awano and M. Sugimoto, *J. Am. Chem. Soc.*, 2010, **132**, 13191; (b) T. Awano, T. Ohmura and M. Sugimoto, *J. Am. Chem. Soc.*, 2011, **133**, 20738; (c) A. W. Buesking and J. A. Ellman, *Chem. Sci.*, 2014, **5**, 1983.
- P. Andres, G. Ballano, M. I. Calaza and C. Cativiela, *Chem. Soc. Rev.*, 2016, **45**, 2291.
- For a review, see: (a) D. S. Matteson, *Chem. Rev.*, 1989, **89**, 1535. For selected examples, see: (b) D. S. Matteson, K. M. Sadhu and G. E. Lienhard, *J. Am. Chem. Soc.*, 1981, **103**, 5241; (c) D. S. Matteson, D. Maliakal and L. J. Fabry-Asztalos, *Organomet. Chem.*, 2008, **693**, 2258; (d) Z. He, A. Zajdlík, J. D. St. Denis, N. Assem and A. K. Yudin, *J. Am. Chem. Soc.*, 2012, **134**, 9926; (e) A. Zajdlík, Z. Wang, J. L. Hickey, A. Aman, A. D. Schimmer and A. K. Yudin, *Angew. Chem., Int. Ed.*, 2013, **52**, 8411; (f) M. A. Beenen, C. An and J. A. Ellman, *J. Am. Chem. Soc.*, 2008, **130**, 6910; (g) A. W. Buesking, V. Bacauanu, I. Cai and J. A. Ellman, *J. Org. Chem.*, 2014, **79**, 3671; (h) J.-b. Xie, J. Luo, T. R. Winn, D. B. Cordes and G. Li, *Beilstein J. Org. Chem.*, 2014, **10**, 746. For substrate control, see: (i) C. Li, J. Wang, L. M. Barton, S. Yu, M. Tian, D. S. Peters, M. Kumar, A. W. Yu, K. A. Johnson, A. K. Chatterjee, M. Yan and P. S. Baran, *Science*, 2017, **356**, 1045.
- (a) C. Sole, H. Gulyas and E. Fernández, *Chem. Commun.*, 2012, **48**, 3769; (b) K. Hong and J. P. Morken, *J. Am. Chem. Soc.*, 2013, **135**, 9252; (c) S.-S. Zhang, Y.-S. Zhao, P. Tian and G.-Q. Lin, *Synlett*, 2013, **24**, 437; (d) D. Wang, P. Cao, B. Wang, T. Jia, Y. Lou, M. Wang and J. Liao, *Org. Lett.*, 2015, **17**, 2420; (e) D. Nishikawa, K. Hirano and M. Miura, *J. Am. Chem. Soc.*, 2015, **137**, 15620; (f) N. Hu, G. Zhao, Y. Zhang, X. Liu, G. Li and W. Tang, *J. Am. Chem. Soc.*, 2015, **137**, 6746; (g) A. López, T. B. Clark, A. Parra and M. Tortosa, *Org. Lett.*, 2017, **19**, 6272; (h) L. Chen, X. Zou, H. Zhao and S. Xu, *Org. Lett.*, 2017, **19**, 3676.
- Catalytic synthesis of cyclic chiral  $\alpha$ -amino boronates via 1,2-rearrangement of indol-2-yl boronates: (a) S. Panda and J. M. Ready, *J. Am. Chem. Soc.*, 2017, **139**, 6038; (b) S. Das, C. G. Daniliuc and A. Studer, *Angew. Chem., Int. Ed.*, 2018, **57**, 4053.
- (a) S. J. Baker, C. Z. Ding, T. Akama, Y.-K. Zhang, V. Hernandez and Y. Xia, *Future Med. Chem.*, 2009, **1**, 1275; (b) S. E. Poplawski, J. H. Lai, Y. Li, Y. Z. Jin, Y. Liu., W. Wu, Y. Wu, Y. Zhou, J. L. Sudmeier, D. G. Sanford and W. W. Bachovchin, *J. Med. Chem.*, 2013, **56**, 3467.
- (a) C.-X. Zhuo, C. Zheng and S.-L. You, *Acc. Chem. Res.*, 2014, **47**, 2558; (b) C.-X. Zhuo, W. Zhang and S.-L. You, *Angew. Chem., Int. Ed.*, 2012, **51**, 12662; (c) Q. Ding, X. Zhou and R. Fan, *Org. Biomol. Chem.*, 2014, **12**, 4807; (d) S. P. Roche, J.-J. Youte Tendoung and B. Tréguier, *Tetrahedron*, 2015, **71**, 3549.
- (a) M. Arrowsmith, M. S. Hill, T. Hadlington, G. Kociok-Köhn and C. Weetman, *Organometallics*, 2011, **30**, 5556; (b)



- K. Oshima, T. Ohmura and M. Suginome, *J. Am. Chem. Soc.*, 2011, **133**, 7324.
- 12 For transition-metal-catalyzed dearomative borylation, see: (a) K. Oshima, T. Ohmura and M. Suginome, *J. Am. Chem. Soc.*, 2012, **134**, 3699; (b) A. S. Dudnik, V. L. Weidner, A. Motta, M. Delferro and T. J. Marks, *Nat. Chem.*, 2014, **6**, 1100; (c) A. Kaithal, B. Chatterjee and C. Gunanathan, *Org. Lett.*, 2016, **18**, 3402; (d) F. Zhang, H. Song, X. Zhuang, C.-H. Tung and W. Wang, *J. Am. Chem. Soc.*, 2017, **139**, 17775. For dearomative borylation catalyzed by organocatalysts, see: (e) X. Fan, J. Zheng, Z. H. Li and H. Wang, *J. Am. Chem. Soc.*, 2015, **137**, 4916; (f) E. N. Keyzer, S. S. Kang, S. Hanf and D. S. Wright, *Chem. Commun.*, 2017, **53**, 9434; (g) T. Ohmura, Y. Morimasa and M. Suginome, *J. Am. Chem. Soc.*, 2015, **137**, 2852; (h) K. Oshima, T. Ohmura and M. Suginome, *Chem. Commun.*, 2012, **48**, 8571; (i) B. Rao, C. C. Chong and R. Kinjo, *J. Am. Chem. Soc.*, 2018, **140**, 652; (j) A. Jayaraman, L. C. Misal Castro, V. Desrosiers and F.-G. Fontaine, *Chem. Sci.*, 2018, **9**, 5057.
- 13 K. Kubota, K. Hayama, H. Iwamoto and H. Ito, *Angew. Chem., Int. Ed.*, 2015, **54**, 8809.
- 14 (a) K. Kubota, Y. Watanabe, K. Hayama and H. Ito, *J. Am. Chem. Soc.*, 2016, **138**, 4338; (b) K. Kubota, Y. Watanabe and H. Ito, *Adv. Synth. Catal.*, 2016, **358**, 2379.
- 15 D. Chen, G. Xu, Q. Zhou, L. W. Chung and W. Tang, *J. Am. Chem. Soc.*, 2017, **139**, 9767.
- 16 J. A. Bull, J. J. Mousseau, G. Pelletier and A. B. Charette, *Chem. Rev.*, 2012, **112**, 2642.
- 17 For selected reviews on Cu-catalyzed borylation, see: (a) K. Semba, T. Fujihara, J. Terao and Y. Tsuji, *Tetrahedron*, 2015, **71**, 2183; (b) J. A. Schiffner, K. Mütter and M. Oestreich, *Angew. Chem., Int. Ed.*, 2010, **49**, 1194; (c) E. C. Neeve, S. J. Geier, I. A. I. Mkhalid, S. A. Westcott and T. B. Marder, *Chem. Rev.*, 2016, **116**, 9091; (d) J. Cid, H. Gulyas, J. J. Carbo and E. Fernández, *Chem. Soc. Rev.*, 2012, **41**, 3558; (e) L. Dang, Z. Lin and T. B. Marder, *Chem. Commun.*, 2009, 3987; (f) V. Lillo, A. Bonet and E. Fernández, *Dalton Trans.*, 2009, 2899.
- 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.†
- 22 R. P. Sonawane, V. Jheengut, C. Rabalakos, R. Larouche-Gauthier, H. K. Scott and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2011, **50**, 3760.
- 23 A. Bonet, M. Odachowski, D. Leonori, S. Essafi and V. K. Aggarwal, *Nat. Chem.*, 2014, **6**, 584.
- 24 L. Dang, Z. Lin and T. B. Marder, *Organometallics*, 2008, **27**, 4443.
- 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.

