

Cite this: *Chem. Sci.*, 2018, 9, 5855Received 20th April 2018
Accepted 8th June 2018DOI: 10.1039/c8sc01815d
rsc.li/chemical-science

Synthesis of cyclic chiral α -amino boronates by copper-catalyzed asymmetric dearomative borylation of indoles†

Lili Chen,^a Jun-Jian Shen,^a Qian Gao^a and Senmiao Xu^{id} *^{ab}

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 Suginome,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

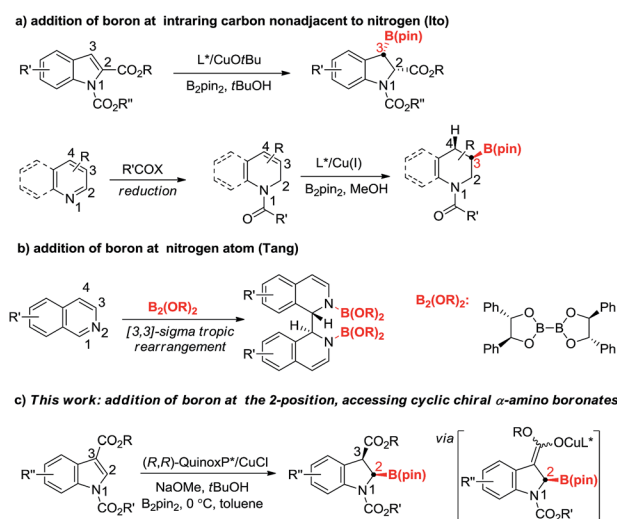


Fig. 1 Recent advances in asymmetric dearomative borylation of *N*-heteroarenes.

^aState Key Laboratory for Oxo Synthesis and Selective Oxidation, Centre for Excellence in Molecular Synthesis, Suzhou Research Institute, Lanzhou Institute of Chemical Physics, University of Chinese Academy of Sciences, Chinese Academy of Sciences, Lanzhou 730000, China. E-mail: senmiaoxu@licp.cas.cn

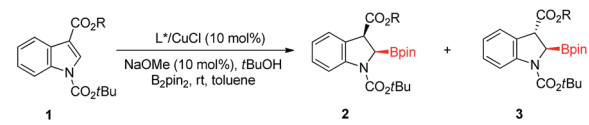
^bKey Laboratory of Organosilicon Chemistry and Material Technology of Ministry of Education, Hangzhou Normal University, Hangzhou 311121, China

† Electronic supplementary information (ESI) available. CCDC 1836254. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c8sc01815d

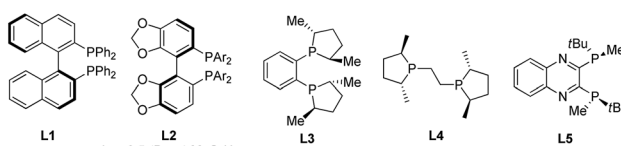
enantioselectivity (Fig. 1a). Tang and coworkers recently reported chiral diboron templated dearomative reductive coupling of isoquinolines involving a diastereoselective concerted [3,3]-sigma rearrangement along with the formation of two N-B bonds (Fig. 1b).¹⁵ It is quite surprising that the direct 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



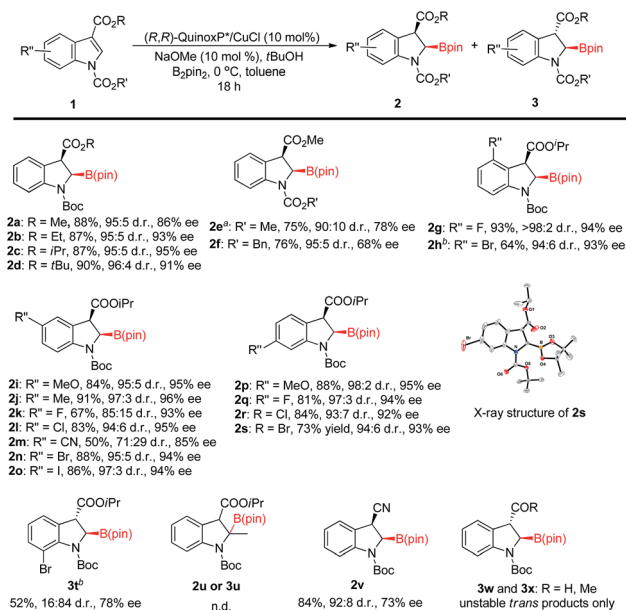


Fig. 2 Substrate scope of reaction. Unless otherwise noted, all the reactions were carried out with **1** (0.2 mmol), (R,R) -QuinoxP* (0.02 mol), CuCl (0.02 mmol), NaOMe (0.02 mmol), t BuOH (0.4 mmol), and B_2pin_2 (0.3 mmol) in toluene (1 mL) at 0 °C for 18 h. The d.r. values (*cis/trans*) were determined 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 borylation 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.

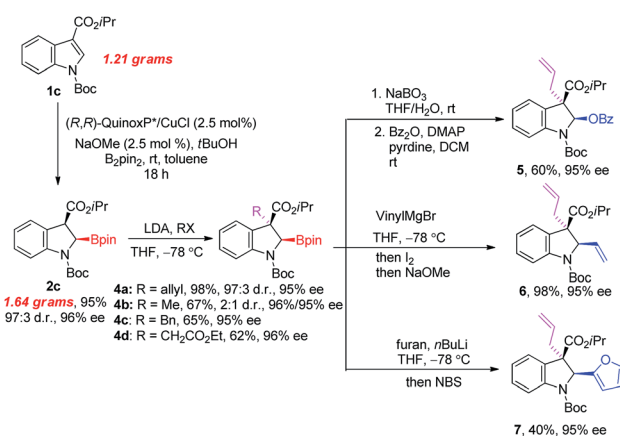


Fig. 3 Gram-scale synthesis and transformations of 2-borylindoline **2c**.



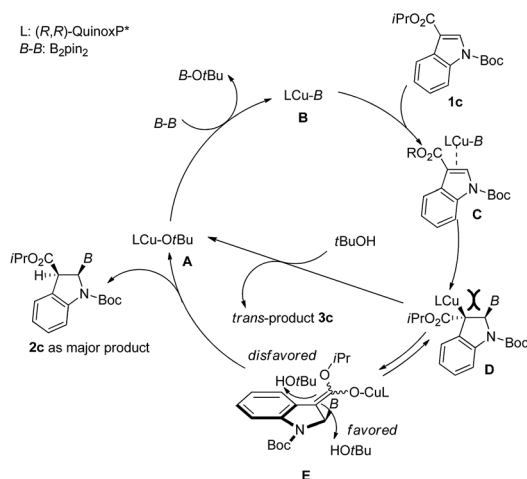


Fig. 4 Plausible reaction pathway of the current dearomative borylation.

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

We thank the 1000-Youth Talents Plan, a Start-up Grant from the Lanzhou Institute of Chemical Physics, National Natural Science Foundation of China (21573262) and Natural Science Foundation of Jiangsu Province (BK20161259, BK20170422) for generous financial support.

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 α -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. Sugimoto, *J. Am. Chem. Soc.*, 2011, **133**, 7324.
- 12 For transition-metal-catalyzed dearomative borylation, see: (a) K. Oshima, T. Ohmura and M. Sugimoto, *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. Sugimoto, *J. Am. Chem. Soc.*, 2015, **137**, 2852; (h) K. Oshima, T. Ohmura and M. Sugimoto, *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.

