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# Enantioselective Suzuki cross-coupling of 1,2-diboryl cyclopropanes†

Javier Teresa,<sup>a</sup> Marina Velado,<sup>b</sup> Roberto Fernández de la Pradilla,<sup>b</sup> Alma Viso,<sup>b</sup> Blanca Lozano<sup>a</sup> and Mariola Tortosa<sup>\*ac</sup>

Herein, we describe the catalytic enantioselective cross-coupling of 1,2-bisboronic esters. Prior work on group specific cross coupling is limited to the use of geminal bis-boronates. This desymmetrization provides a novel approach to prepare enantioenriched cyclopropyl boronates with three contiguous stereocenters, that could be further derivatized through selective functionalization of the carbon–boron bond. Our results suggest that transmetalation, which is the enantiodetermining step, takes place with retention of stereochemistry at carbon.

## Introduction

The Suzuki–Miyaura cross-coupling reaction is one of the main tools used in the pharmaceutical industry to forge carbon–carbon bonds.<sup>1</sup> A large variety of libraries of compounds are synthesized every year using this cross-coupling as a key point of diversification. In fact, a recent analysis showed that this transformation is the second most commonly used reaction in pharma, placed after amide coupling.<sup>2</sup> The robustness of the Suzuki cross-coupling has also made possible its use in automated settings<sup>3</sup> and in the synthesis of DNA encoded libraries.<sup>4</sup>

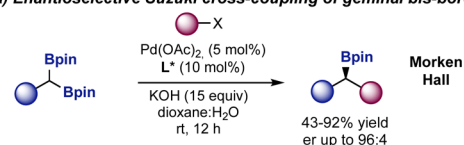
As the pharmaceutical industry is shifting from compounds with a strong  $sp^2$  character to libraries of compounds with increased three-dimensionality,<sup>5</sup> the need to develop robust stereoselective Suzuki cross-couplings to provide compounds with an increased  $sp^3$  character becomes apparent.<sup>6</sup> In this context, the development of enantioselective Suzuki–Miyaura cross-coupling reactions using prochiral bis-boronates remains largely unexplored.<sup>7,8</sup> Morken<sup>9</sup> and Hall<sup>10</sup> reported the enantioselective Suzuki cross-coupling reaction of symmetric geminal bis-boronates to prepare enantiomerically enriched boronic esters (Fig. 1a). However, despite the elegant strategies developed to selectively functionalize 1,2-bis-boronates,<sup>11,12</sup> the enantioselective desymmetrization of these species is still an unmet challenge (Fig. 1b). The degree of complexity in the

products, relative to those prepared from geminal bis-boronates, would be higher as two contiguous stereocenters are generated in the process.

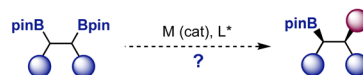
Following our interest in the functionalization of small rings<sup>13</sup> and inspired by the relevance of cyclopropanes in synthetic methodology and pharmaceutical industry,<sup>14</sup> we envisioned that symmetric bis-boryl cyclopropanes **I** could offer an ideal scenario to test this transformation (Fig. 1c). The products would be enantiomerically enriched cyclopropyl boronates,<sup>15</sup> with three substituents in a hindered *cis* orientation and a handle for further stereospecific C–B functionalization.<sup>16</sup>

We realized from the outset that the proposed desymmetrization was a challenging transformation from the point of view of asymmetric catalysis (Fig. 2). Under the basic conditions needed for the Suzuki reaction, the bis-boronic ester **I** is likely to be in equilibrium with the racemic mixture of monoacids **II** and

### a) Enantioselective Suzuki cross-coupling of geminal bis-boronates



### b) Enantioselective desymmetrization of 1,2-bis-boronates: Unknown



### c) This work: enantioselective cross-coupling of 1,2-diboryl/cyclopropanes

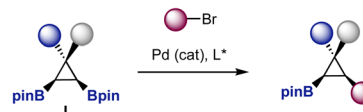


Fig. 1 Enantioselective Suzuki cross-coupling of prochiral bis-boronates.

<sup>a</sup>Organic Chemistry Department, Center for Innovation in Advanced Chemistry (ORFEO-CINQA), Universidad Autónoma de Madrid (UAM), 28049 Madrid, Spain. E-mail: mariola.tortosa@uam.es

<sup>b</sup>Instituto de Química Orgánica General (IQOG), CSIC, Juan de la Cierva 3, 28006 Madrid, Spain

<sup>c</sup>Institute for Advanced Research in Chemical Sciences (IAChem), Universidad Autónoma de Madrid (UAM), 28049 Madrid, Spain

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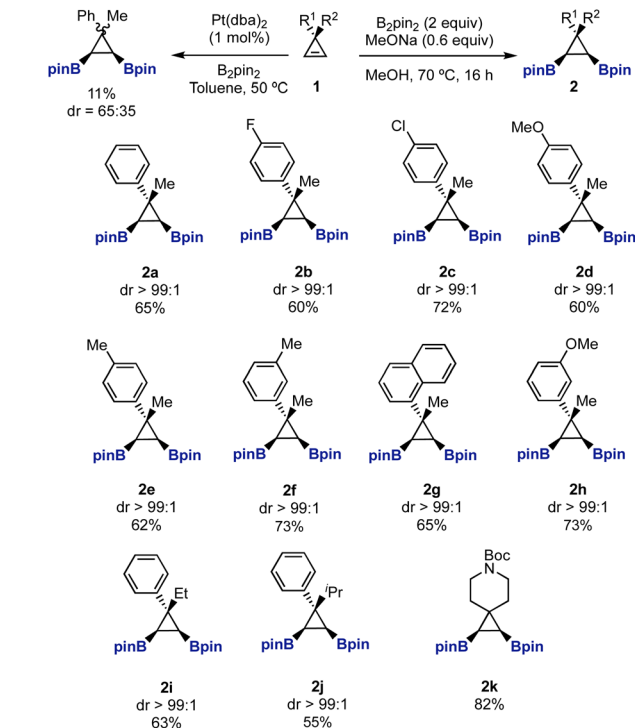
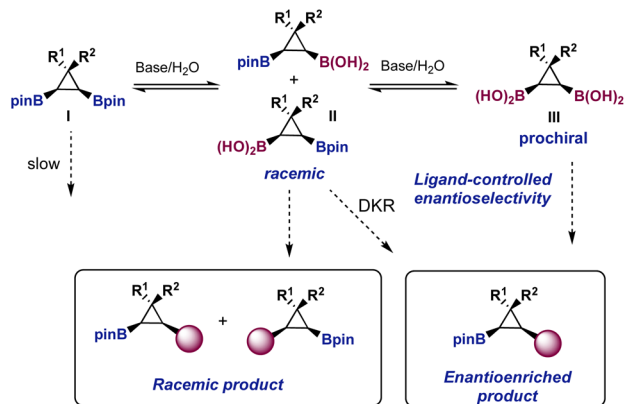


Fig. 2 Challenges involved in the proposed desymmetrization.

the prochiral bis-boronic acid **III**. If hydrolysis is a prerequisite for transmetalation, as it was proposed for geminal bis-boronates,<sup>9,10</sup> the chiral  $L^*PdAr(X)$  complex formed after oxidative addition would be exposed to mixtures of **II** and **III**. Although a dynamic kinetic resolution (DKR) could not be discarded, the reaction of a  $L^*PdAr(X)$  complex with racemic mixture **II** would likely provide racemic products, having a detrimental effect on the overall enantiocontrol. Therefore, we hypothesized that to maximize a potential ligand-controlled enantioselectivity the equilibria in Fig. 2 should be displaced towards bis-boronic acid **III**.

## Results and discussion

When we started our study, we realized that bis-boryl cyclopropanes such as **2** had not been prepared in the literature before.<sup>17,18</sup> We envisioned that diboration of readily available cyclopropenes **1** could provide easy access to these intermediates. Our first attempts using Pt-catalyzed diboration conditions<sup>19,20</sup> afforded a complex crude product from which we isolated a 65 : 35 mixture of diborylated diastereomers **2a/2a'** in 11% yield. Although we did not identify any other products, the dimerization of the cyclopropene under the reaction conditions could be a potential undesired reaction.<sup>13b,21</sup> Then, we turned our attention to the use of transition-metal free borylation conditions. We were pleased to find that heating cyclopropanes **1** in MeOH, in the presence of MeONa and  $B_2pin_2$ , provided exclusively 1,2-*syn*-diboryl cyclopropanes **2a–2k** in good yields as single diastereomers (Scheme 1).<sup>22,23</sup>

With a method to prepare diboryl cyclopropanes in hand, we started to explore the feasibility of the enantioselective Suzuki cross-coupling using cyclopropane **2a**, bromobenzene, and NaOH as the base, in the presence of 5 mol% of  $Pd(OAc)_2$ . Chiral bidentate ligands commonly used in palladium-catalyzed asymmetric transformations (not shown) consistently provided a racemic mixture of **3a** in variable yields.<sup>24</sup> A key observation was that in the absence of an added ligand, we observed exclusive formation of the protodeboronation product (Table 1, entry 1).<sup>25</sup> Indeed, we soon realized that the inhibition of this background reaction was one of the main challenges in this cross-coupling

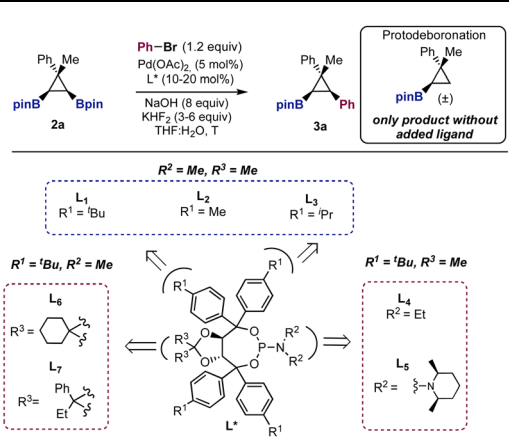
Scheme 1 Base-promoted diboration of cyclopropenes.

reaction. We then moved to explore the reactivity of monodentate ligands, hoping that three-coordinate  $LPdAr(X)$  complexes would show enhanced selectivity.

After extensive experimentation, we found that TADDOL derived phosphoramidites ( $L_1–L_7$ , Table 1) showed encouraging results. Using bromobenzene, 5 mol% of  $Pd(OAc)_2$ , NaOH (8 equiv.) and chiral ligand  $L_1$ , at 60 °C, cross-coupling product **3a** was obtained in 66% yield with a promising enantiomeric ratio ( $er = 83 : 17$ , Table 1, entry 2). It is known that the addition of a fluoride source helps to increase the rate of the Suzuki cross-coupling reaction.<sup>26</sup> In our case, the addition of  $KHF_2$  (Table 1, entry 3) had a positive effect on controlling the protodeboronation and, therefore, increasing the yield up to 78%. Using 6 equiv. of  $KHF_2$  the yield was further improved to 85% without reducing the enantiomeric ratio ( $er = 83 : 17$ ). Less bulky groups in the *para* position of the aromatic rings of the ligands provided lower stereocontrol ( $L_2–L_3$ , Table 1, entries 5–6). Tuning of the substituents at nitrogen ( $L_4–L_5$ , Table 1, entries 7–8) and the acetal backbone ( $L_6–L_7$ , Table 1, entries 9–10) did not improve the results obtained with  $L_1$ . While at room temperature the cross-coupling did not occur, at 40 °C compound **3a** was obtained with higher enantioselectivity ( $er = 86 : 14$ , Table 1, entry 11). Additionally, the use of 20 mol% of  $L_1$  had a beneficial effect on both the yield and the enantiomeric ratio (89%,  $er = 87 : 13$ , Table 1, entry 12). This is probably due to the inhibition of the background protodeboronation. According to this result, the use of 5 mol% of  $L_1$  was detrimental to the yield and the enantioselectivity (Table 1, entry 13). Aryl iodides (Table 1, entry 14) afforded compound **3a** with poorer results. Finally, entries 15–17 show that the use of a large excess of base was necessary. Using 1



Table 1 Optimization of the enantioselective Suzuki cross-coupling



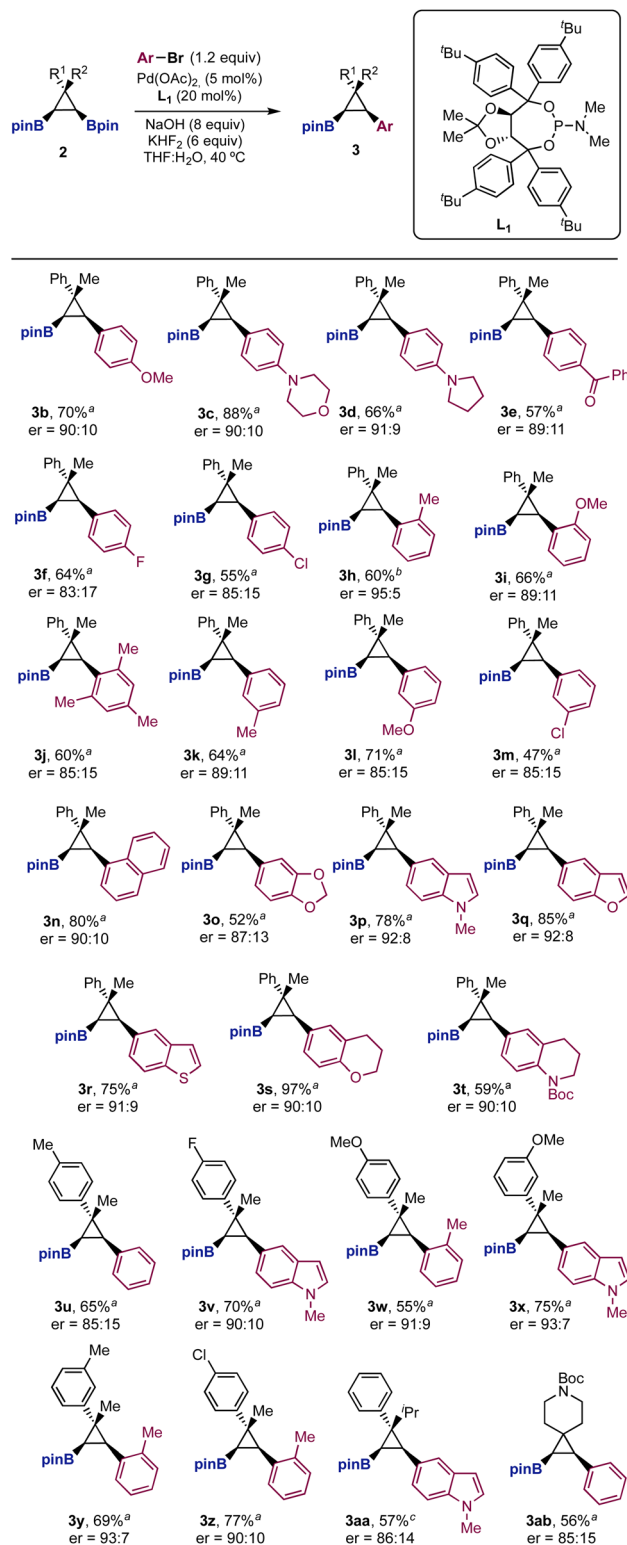
| Entry           | L              | Equiv. NaOH | Equiv. KHF <sub>2</sub> | T  | Yield 3a <sup>b</sup> (%) | er <sup>c</sup> |
|-----------------|----------------|-------------|-------------------------|----|---------------------------|-----------------|
| 1               | —              | 8           | —                       | 60 | —                         | —               |
| 2 <sup>a</sup>  | L <sub>1</sub> | 8           | —                       | 60 | 66                        | 83 : 17         |
| 3 <sup>a</sup>  | L <sub>1</sub> | 8           | 3                       | 60 | 78                        | 82 : 18         |
| 4 <sup>a</sup>  | L <sub>1</sub> | 8           | 6                       | 60 | 85                        | 83 : 17         |
| 5 <sup>a</sup>  | L <sub>2</sub> | 8           | 6                       | 60 | 72                        | 70 : 30         |
| 6 <sup>a</sup>  | L <sub>3</sub> | 8           | 6                       | 60 | 65                        | 79 : 21         |
| 7 <sup>a</sup>  | L <sub>4</sub> | 8           | 6                       | 60 | 54                        | 80 : 20         |
| 8 <sup>a</sup>  | L <sub>5</sub> | 8           | 6                       | 60 | 59                        | 73 : 27         |
| 9 <sup>a</sup>  | L <sub>6</sub> | 8           | 6                       | 60 | 74                        | 83 : 17         |
| 10 <sup>a</sup> | L <sub>7</sub> | 8           | 6                       | 60 | 66                        | 84 : 16         |
| 11 <sup>a</sup> | L <sub>1</sub> | 8           | 6                       | 40 | 75                        | 86 : 14         |
| 12 <sup>d</sup> | L <sub>1</sub> | 8           | 6                       | 40 | 89                        | 87 : 13         |
| 13 <sup>e</sup> | L <sub>1</sub> | 8           | 6                       | 40 | 68                        | 84 : 16         |
| 14 <sup>f</sup> | L <sub>1</sub> | 8           | 6                       | 40 | 46                        | 72 : 28         |
| 15 <sup>g</sup> | L <sub>1</sub> | 1           | 6                       | 40 | NR                        | —               |
| 16 <sup>g</sup> | L <sub>1</sub> | 4           | 6                       | 40 | Traces                    | —               |
| 17 <sup>g</sup> | L <sub>1</sub> | 15          | 6                       | 40 | 65                        | 88 : 12         |

<sup>a</sup> Reaction conditions: **2a** (0.1 mmol), PhBr (1.2 equiv.), Pd(OAc)<sub>2</sub> (5 mol%), L\* (10 mol%), NaOH (8 equiv.), KHF<sub>2</sub> (0–6 equiv.), THF : H<sub>2</sub>O (10 : 1, 0.1 M), and 16 h. <sup>b</sup> Yield calculated by <sup>1</sup>H NMR using an internal standard. <sup>c</sup> Enantiomeric ratio determined by chiral-phase HPLC. <sup>d</sup> 20 mol% of L<sub>1</sub> used. <sup>e</sup> 5 mol% L<sub>1</sub> used. <sup>f</sup> PhI was used instead of PhBr. <sup>g</sup> Reaction conditions [a] except for the equiv. of NaOH.

and 4 equiv. of NaOH we did not observe product formation. Increasing the amount of base to 15 equiv. maintained the level of stereocontrol (er = 88 : 12) but also increased the protodeboration, lowering the yield of **3a** to 65% (Table 1, entry 17). The use of other bases, Pd precatalysts or solvents were not found to be beneficial.<sup>24</sup>

It should be highlighted that compound **3a** was obtained as a single *syn*-diastereomer. Assuming that the reductive elimination step occurs with retention, this result suggests that the transmetallation step takes place with retention of stereochemistry at carbon. This is in contrast with the results observed in the enantioselective cross-coupling with 1,1-diboronates, in which the transmetallation seems to proceed with inversion.<sup>9</sup>

We next studied the structural scope of the enantioselective Suzuki cross-coupling reaction (Scheme 2). We were pleased to find that the reaction was quite general for different aryl



Scheme 2 Scope of the enantioselective desymmetrization. <sup>a</sup>Reaction conditions: **2** (0.2 mmol), PhBr (1.2 equiv.), Pd(OAc)<sub>2</sub> (5 mol%), L\* (20 mol%), NaOH (8 equiv.), KHF<sub>2</sub> (6 equiv.), THF : H<sub>2</sub>O (10 : 1, 0.1 M), 40 °C, and 16 h. <sup>b</sup>15 equiv. of NaOH were used. <sup>c</sup>8 equiv. of NaOH were used at 60 °C.

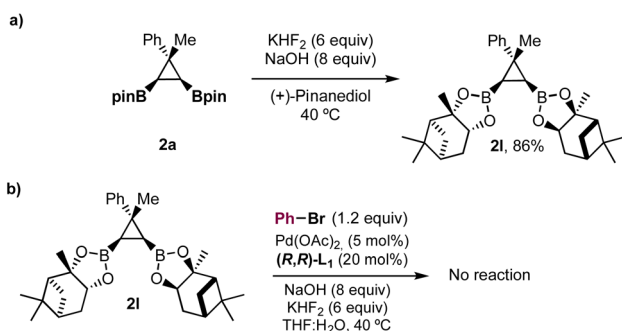


bromides (**3b–3t**) and cyclopropanes (**3u–3ab**). Importantly, in many cases the enantioselectivity was higher than that observed for bromobenzene. Aryl bromides with electron donating groups in the *para* and *ortho* positions provided the cross-coupling products (**3b–3d** and **3h–3l**) in good yields and high enantiomeric ratios (up to 95 : 5 for **3h**). Aryl bromides with electron-withdrawing substituents afforded arylated boryl cyclopropanes with similar stereoselectivities (**3e–3g**). Electrophiles with substituents in the *meta* position (**3k–3m**), sterically hindered aryl bromides (**3j**), as well as naphthalene (**3n**) and methylenedioxy derivatives (**3o**) were well tolerated. Heterocycles such as indole (**3p**), benzofuran (**3q**), thiobenzofuran (**3r**), chromane (**3s**) and tetrahydroquinoline (**3t**) worked particularly well, providing cross-coupling products in good yields and enantiomeric ratios higher to that observed for bromobenzene. Finally, the method allowed structural modifications on the aryl and methyl groups of the diboryl cyclopropane framework (**3u–3ab**). In those cases, the cross-coupling products were prepared with comparable efficiencies to those shown with the Ph/Me substitution pattern.

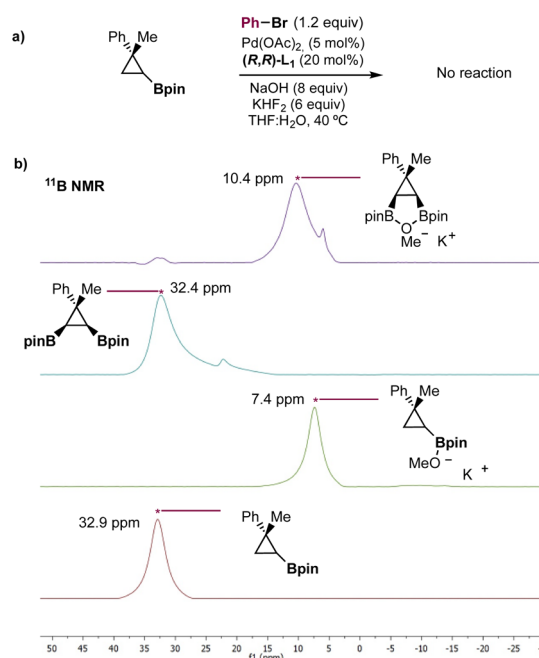
To gain insight into the boron species formed under the reaction conditions, we mixed pinacol ester **2a** with (+)-pinanediol with  $\text{KHF}_2$  (6 equiv.) and  $\text{NaOH}$  (8 equiv.) at 40 °C, in the absence of  $\text{Pd}(\text{OAc})_2$  and bromobenzene (Scheme 3). We observed immediate disappearance of compound **2a** by TLC and transesterified pinanediol derivative **2l** was obtained in 86% yield. It is known that pinacol boronic esters form potassium trifluoroborate salts in the presence of  $\text{KHF}_2$ , and that these salts are hydrolyzed to boronic acids<sup>27</sup> in the basic aqueous media used in Suzuki cross-coupling reactions. Therefore, the experiment in Scheme 3 supports the *in situ* formation of bis-boronic acids but does not rule out the formation of transient trifluoroborate salts that could also participate in the equilibria shown in Fig. 2. According to our results, the use of  $\text{KHF}_2$  has a positive effect on controlling the protodeboronation without compromising the enantioselectivity. Although the exact role of  $\text{KHF}_2$  is not clear at this point, the *in situ* formation of trifluoroborate salts could provide a slower release of the bis-boronic acid<sup>28</sup> and fluoride<sup>26</sup> under the basic aqueous conditions, minimizing the protodeboronation and increasing the rate of the cross-coupling. Bis-ester **2l** did not react under the optimized conditions. Since pinanediol boronic esters are more robust towards hydrolysis, this result further supports the

participation of a bis-boronic acid **III** (Fig. 2) as an intermediate in the reaction.

Another question that emerged from our study was the role played by the second boryl moiety. Morcken has reported that the presence of a vicinal pinacol boronic ester may have an activating effect towards transmetalation in Suzuki cross-coupling reactions.<sup>12g</sup> More recently, Morcken has also shown that terminal 1,2-diboronic esters, in the presence of potassium methoxide, form a 5-membered heterocycle with a single oxygen atom bridging both boron atoms.<sup>29</sup> This chelated cyclic ate complex seemed to play a key role in the transmetalation with a copper complex. We were intrigued to compare the behavior of our 1,2-bisboryl cyclopropanes with that observed by Morcken with terminal 1,2-bisboronates. We checked the reactivity of a monoborylated derivative (Scheme 4a) under the optimized reaction conditions and no product was observed after 16 hours. This result indicates that the presence of the adjacent boryl moiety is necessary for the transmetalation to take place. Additionally, we studied by  $^{11}\text{B}$  NMR spectroscopy the alkoxide complexation of mono- and diborylated cyclopropane (Scheme 4b). The treatment of the monoborylated derivative (32.9 ppm) with 1 equivalent of KOMe resulted in complete conversion to a compound with an upfield shifted resonance (7.4 ppm), which is in agreement with the formation of a  $\text{sp}^3$  hybridized borate complex. When we treated diborylated cyclopropane **2a** (32.4 ppm) with 1 equivalent of KOMe, we observed an almost quantitative upfield shift of the  $^{11}\text{B}$  NMR peak to 10.4 ppm. The smaller peak at 7.4 ppm corresponds to the borate complex of the residual protodeboronation product. Considering that we are using 0.5 equivalents of KOMe relative to the total amount of boron, the signal at 10.4 ppm suggests a chelation similar to that proposed by Morcken for acyclic terminal 1,2-diboronates. Although the conditions used for the  $^{11}\text{B}$  NMR



Scheme 3 Support for the *in situ* hydrolysis of diboronic ester **2a**.



Scheme 4 Role of the vicinal boryl moiety.



experiments (THF and KOMe) are not those used in the Suzuki cross coupling reaction (THF:H<sub>2</sub>O, NaOH, and KHF<sub>2</sub>), these results suggest that chelated cyclic ate complexes could potentially participate in our catalytic cycle. These observations could open the door to the design of further desymmetrizations.

The reaction was scaled up to 1 mmol with diboryl cyclopropane **2a** and 5-bromoindole, affording cyclopropane **3p** in similar yield and enantioselectivity to those observed before (Scheme 5). From boronate **3p**, we performed the oxidation of the C–B bond followed by benzylation to obtain benzoate **4**. The recrystallization of **4** provided crystals of high enantiopurity (er = 97 : 3), which allowed us to assign the absolute configuration of the products in Table 1 and Scheme 2.<sup>30</sup>

Finally, we showed the synthetic potential of the Suzuki cross-coupling products **3** with further stereospecific functionalization of the remaining boryl unit (Scheme 5). The transformation of the pinacol ester in the potassium trifluoroborate salt took place in high yield. Zweifel and Matteson homologations provided the desired products (**6** and **7**) in excellent yields, even though the

boryl unit is placed in a crowded environment, surrounded by two substituents in *syn* relative distribution. The Matteson homologation product **7** is especially interesting as it still preserves the boryl unit for further transformations. A second sp<sup>2</sup>–sp<sup>3</sup> Suzuki cross-coupling from **7** afforded trisubstituted cyclopropane **9** in 80% yield. Additionally, Zweifel homologation from **7** provided allylcyclopropane **8** in high yield. Finally, we briefly explored the synthetic potential of diboryl cyclopropanes **2** with reactions different than the Suzuki cross-coupling. Selective mono-oxidation of **2a** afforded boryl cyclopropanol **11** as a single diastereomer. Moreover, double Matteson homologation provided symmetric bisboronate **10**, which could be used to explore further desymmetrizations.

## Conclusions

In summary, we have developed the first enantioselective desymmetrization of a 1,2-bisboronic ester. Prior work on group specific cross coupling has focused on geminal bis-boronates. Therefore, our study might pave the road to develop further desymmetrizations of prochiral 1,2-bis-boronates. This strategy allows for the preparation of highly functionalized enantioenriched boryl cyclopropanes with three stereocenters, one of them being quaternary. The products still preserve one boryl unit that can be used to design further stereospecific transformations. We believe that this methodology provides a useful tool for industrial and medicinal chemists to introduce functionalized three-membered rings into libraries of compounds.

## Data availability

All the data supporting the findings of this study are available in the ESI† Crystallographic data for compound **4** has been deposited in the Cambridge Crystallographic Data Centre under accession number CCDC 21910290.

## Author contributions

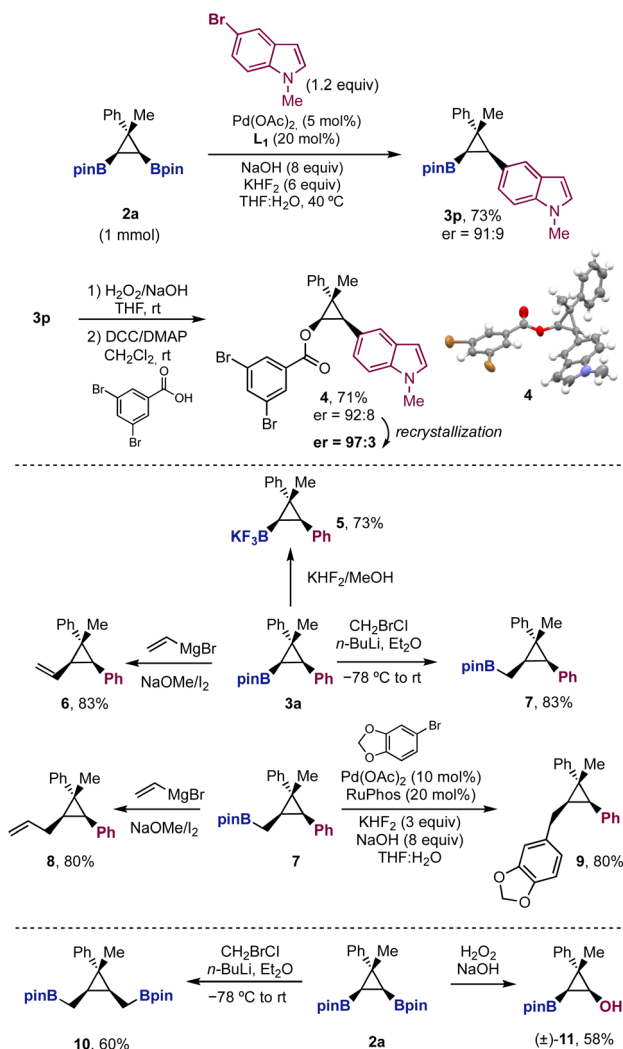
J. T., M. V., R. F., A. V. and B. L. performed the experiments, wrote the ESI† and participated in discussions. M. T. conceived and directed the project and wrote the manuscript.

## Conflicts of interest

There are no conflicts to declare.

## Acknowledgements

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Scheme 5 Assignment of the absolute stereochemistry and C–B bond functionalizations.



## Notes and references

- 1 (a) B. S. Takale, F.-Y. Kong and R. R. Thakore, *Organics*, 2022, **3**, 1–21; (b) M. J. Blanco and M. J. Buskes, *Molecules*, 2020, **25**, 3493–3515; (c) J. Magano and J. R. Dunetz, *Chem. Rev.*, 2011, **111**, 2177–2250.
- 2 D. G. Brown and J. Boström, *J. Med. Chem.*, 2016, **59**, 4443–4458.
- 3 (a) D. J. Blair, S. Chitti, M. Trobe, D. M. Kostyra, H. M. S. Haley, R. L. Hansen, S. G. Ballmer, T. J. Woods, W. Wang, V. Mubayi, M. J. Schmidt, R. W. Pipal, G. F. Morehouse, A. M. E. Palazzolo Ray, D. L. Gray, A. L. Gill and M. D. Burke, *Nature*, 2022, **604**, 92–97; (b) J. Li, S. G. Ballmer, E. P. Gillis, S. Fujii, M. J. Schmidt, A. M. E. Palazzolo, J. W. Lehmann, G. F. Morehouse and M. D. Burke, *Science*, 2015, **347**, 1221–1226.
- 4 (a) F. Lovering, *MedChemComm*, 2013, 515–519; (b) F. Lovering, J. Bikker and C. Humblet, *J. Med. Chem.*, 2009, **52**, 6752–6756.
- 5 (a) J. Li and H. Huang, *Bioconjugate Chem.*, 2018, **29**, 3841–3846; (b) Y. Ding and M. A. Clark, *ACS Comb. Sci.*, 2015, **17**, 1–4.
- 6 Recent reviews on enantioselective and stereospecific Suzuki cross-coupling: (a) X. Ma, B. Murray and M. R. Biscoe, *Nat. Rev. Chem.*, 2020, **4**, 584–599; (b) J. P. G. Rygus and C. M. Crudden, *J. Am. Chem. Soc.*, 2017, **139**, 18124–18137; (c) A. H. Cherney, N. T. Kadunce and S. E. Reisman, *Chem. Rev.*, 2015, **115**, 9587–9652.
- 7 For a pioneering desymmetrization involving distal boranes in an intramolecular Suzuki cross-coupling, see: S. Y. Cho and M. Shibasaki, *Tetrahedron: Asymmetry*, 1998, **9**, 3751–3754.
- 8 Recent reviews on enantioselective metal-catalyzed transformations of geminal bisboronates: (a) Y. Lee, S. Han and S. H. Cho, *Acc. Chem. Res.*, 2021, **54**, 3917–3929; (b) C. Zhang, W. Hu and J. P. Morken, *ACS Catal.*, 2021, **11**, 10660–10680.
- 9 (a) C. Sun, B. Potter and J. P. Morken, *J. Am. Chem. Soc.*, 2014, **136**, 6534–6537; (b) B. Potter, A. A. Szymaniak, E. K. Edelstein and J. P. Morken, *J. Am. Chem. Soc.*, 2014, **136**, 17918–17921.
- 10 H. Sun, K. Kubota and D. G. Hall, *Chem. –Eur. J.*, 2015, **21**, 19186–19194.
- 11 Recent review on selective functionalization of 1,2-bisboronates: A. Viso, R. Fernández de la Pradilla and M. Tortosa, *ACS Catal.*, 2022, **12**, 10603–10620.
- 12 Selected recent examples of selective functionalization of 1,2-bis-boronates: (a) N. Xu, Z. Kong, J. Z. Wang, G. J. Lovinger and J. P. Morken, *J. Am. Chem. Soc.*, 2022, **144**, 17815–17823; (b) H. Wang, W. Han, A. Noble and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2022, **61**, e202207988; (c) H. Wang, J. Wu, A. Noble and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2022, **61**, e202202061; (d) D. Kaiser, A. Noble, V. Fasano and V. K. Aggarwal, *J. Am. Chem. Soc.*, 2019, **141**, 14104–14109; (e) A. Fawcett, D. Nitsch, M. Ali, J. M. Bateman, E. L. Myers and V. K. Aggarwal, *Angew. Chem., Int. Ed.*, 2016, **55**, 14663–14667; (f) C. M. Crudden, C. Ziebenhaus, J. P. G. Rygus, K. Ghazati, P. J. Unsworth, M. Nambo, S. Voth, M. Hutchinson, V. S. Laberge, Y. Maekawa and D. Imao, *Nat. Commun.*, 2016, **7**, 11065; (g) S. N. Mlynarski, C. H. Schuster and J. P. Morken, *Nature*, 2014, **505**, 386–390.
- 13 (a) L. Nóvoa, L. Trulli, A. Parra and M. Tortosa, *Org. Lett.*, 2021, **23**(19), 7434–7438; (b) L. Nóvoa, L. Trulli, A. Parra and M. Tortosa, *Angew. Chem., Int. Ed.*, 2021, **60**, 11763–11768; (c) L. Amenós, L. Trulli, L. Nóvoa, A. Parra and M. Tortosa, *Angew. Chem., Int. Ed.*, 2019, **58**, 3188–3192; (d) M. Guisan-Ceinos, A. Parra, V. Martin-Heras and M. Tortosa, *Angew. Chem., Int. Ed.*, 2016, **55**, 6969–6972; (e) A. Parra, L. Amenós, M. Guisan-Ceinos, A. López, J. L. Garcia-Ruano and M. Tortosa, *J. Am. Chem. Soc.*, 2014, **136**, 15833–15836.
- 14 (a) M.-R. Sun, H.-L. Li, M.-Y. Ba, W. Cheng, H.-L. Zhu and Y.-T. Duan, *Mini-Rev. Med. Chem.*, 2021, **21**, 150–170; (b) T. T. Talele, *J. Med. Chem.*, 2016, **59**, 8712–8756; (c) Y. Cohen and I. Marek, *Acc. Chem. Res.*, 2022, **55**, 2848–2868.
- 15 Recent selected stereoselective synthesis of cyclopropylboronates: (a) A. U. Augustin, S. Di Silvio and I. Marek, *J. Am. Chem. Soc.*, 2022, **144**, 16298–16302; (b) Y. Shi, Y. Yang and S. Xu, *Angew. Chem., Int. Ed.*, 2022, **61**, e202201463; (c) H. Iwamoto, Y. Ozawa, Y. Hayashi, T. Imamoto and H. Ito, *J. Am. Chem. Soc.*, 2022, **144**, 10483–10494; (d) N. Hanania, M. Nassir, N. Eghbarieh and A. Masarwa, *Chem. –Eur. J.*, 2022, e202202748; (e) G. Benoit and A. B. Charette, *J. Am. Chem. Soc.*, 2017, **139**, 1364–1367; (f) B. Tian, Q. Liu, X. Tong, P. Tian and G.-Q. Lin, *Org. Chem. Front.*, 2014, **1**, 1116–1122; (g) C. Zhong, S. Kunii, Y. Kosaka, M. Sawamura and H. Ito, *J. Am. Chem. Soc.*, 2010, **132**, 11440–11442; (h) M. Rubina, M. Rubin and V. Gevorgyan, *J. Am. Chem. Soc.*, 2003, **125**, 7198–7199.
- 16 D. G. Hall, *Boronic Acids: Preparation and Application in Organic Synthesis, Medicine and Materials*, Wiley-VCH, Boston, 2nd edn, 2011.
- 17 Synthesis of related 1,2-diboryl cyclopropanes, see: (a) F.-P. Wu, X. Luo, U. Radius, T. B. Marder and X.-F. Wu, *J. Am. Chem. Soc.*, 2020, **142**, 14074–14079; (b) M. Mali, G. V. Sharma, S. Ghosh, T. Roisnel, B. Carboni and F. Berrée, *J. Org. Chem.*, 2022, **87**, 7649–7657.
- 18 (a) For an early review on transition metal catalyzed diboration, see: T. B. Marder and N. C. Norman, *Top. Catal.*, 1998, **5**, 63–73; (b) For a review on the reactivity of diboron compounds, see: E. C. Neeve, S. J. Geier, I. A. I. Mkhaliid, S. A. Westcott and T. B. Marder, *Chem. Rev.*, 2016, **116**, 9091–9161.
- 19 For pioneering work on Pt-catalyzed diboration: (a) T. Ishiyama, M. Yamamoto and N. Miyaura, *Chem. Commun.*, 1997, 689–690; (b) C. N. Iverson and M. R. Smith III, *Organometallics*, 1997, **16**, 2757–2759. For relevant work on Pt-catalyzed 1,2-diboration of alkenes using chiral diboron reagents: (c) T. B. Marder, N. C. Norman and C. R. Rice, *Tetrahedron Lett.*, 1998, **39**, 155–158; (d) L. T. Kliman, S. N. Mlynarski and J. P. Morken, *J. Am. Chem. Soc.*, 2009, **131**, 13210–13211; (e) L. T. Kliman, S. N. Mlynarski, G. E. Ferris and J. P. Morken, *Angew.*



- Chem., Int. Ed.*, 2012, **51**, 521–524; (f) J. R. Coombs, F. Haeffner, L. T. Kliman and J. P. Morken, *J. Am. Chem. Soc.*, 2013, **135**, 11222–11231; (g) J. R. Coombs, L. Zhang and J. P. Morken, *J. Am. Chem. Soc.*, 2014, **136**, 16140–16143.
- 20 For the first metal-catalyzed 1,2-diboration of alkenes, see: (a) R. T. Baker, P. Nguyen, T. B. Marder and S. A. Westcott, *Angew. Chem., Int. Ed.*, 1995, **34**, 1336; for a pioneering example of Rh(I) catalyzed 1,2-diboration of alkenes with B<sub>2</sub>cat<sub>2</sub>, see: (b) C. Dai, E. G. Robins, A. J. Scott, W. Clegg, D. S. Yufit, J. A. K. Howard and T. B. Marder, *Chem. Commun.*, 1998, 1983. For enantioselective Rh(I) catalyzed 1,2-diboration of alkenes, see: (c) J. B. Morgan, S. P. Miller and J. P. Morken, *J. Am. Chem. Soc.*, 2003, **125**, 8702; (d) S. Trudeau, J. B. Morgan, M. Shrestha and J. P. Morken, *J. Org. Chem.*, 2005, **70**, 9538; (e) K. Toribatake and H. Nishiyama, *Angew. Chem., Int. Ed.*, 2013, **52**, 11011.
- 21 W. M. Sherrill and M. Rubin, *J. Am. Chem. Soc.*, 2008, **130**, 13804.
- 22 Base-promoted 1,2-diboration of alkenes: (a) A. Bonet, C. Pubill-Ulldemolins, C. Bo, H. Gulyás and E. Fernández, *Angew. Chem., Int. Ed.*, 2011, **50**, 7158–7161; (b) T. P. Blaisdell, T. C. Caya, L. Zhang, A. Sanz-Marco and J. P. Morken, *J. Am. Chem. Soc.*, 2014, **136**, 9264–9267; (c) A. Bonet, C. Sole, H. Gulyás and E. Fernández, *Org. Biomol. Chem.*, 2012, **10**, 6621–6623; (d) L. Fang, L. Yan, F. Haeffner and J. P. Morken, *J. Am. Chem. Soc.*, 2016, **138**, 2508–2511; (e) A. J. Vendola, C. Allais, A.-M. R. Dechert-Schmitt, J. T. Lee, R. A. Singer and J. P. Morken, *Org. Lett.*, 2021, **23**, 2863–2867.
- 23 S. Pietsch, E. C. Neeve, D. C. Apperley, R. Bertermann, F. Mo, D. Qiu, M. S. Cheung, L. Dang, J. Wang, U. Radius, Z. Lin, C. Kleeberg and T. B. Marder, *Chem. –Eur. J.*, 2015, **21**, 7082–7098.
- 24 For optimization full details see the ESI.†
- 25 (a) P. A. Cox, A. G. Leach, A. D. Campbell and G. C. Lloyd-Jones, *J. Am. Chem. Soc.*, 2016, **138**, 9145–9157; (b) H. L. D. Hayes, R. Wei, M. Assante, K. J. Geogheghan, N. Jin, S. Tomasi, G. Noonan, A. G. Leach and G. C. Lloyd-Jones, *J. Am. Chem. Soc.*, 2021, **143**, 14814–14826.
- 26 C. Amatore, A. Jutand and G. Le Duc, *Angew. Chem., Int. Ed.*, 2012, **51**, 1379–1382.
- 27 A. J. J. Lennox and G. C. Lloyd-Jones, *J. Am. Chem. Soc.*, 2012, **134**, 7431–7441.
- 28 A. J. J. Lennox and G. C. Lloyd-Jones, *Isr. J. Chem.*, 2010, **50**, 664–674.
- 29 N. Xu, Z. Kong, J. Z. Wang, G. J. Lovinger and J. P. Morken, *J. Am. Chem. Soc.*, 2022, **144**, 17815–17823.
- 30 The absolute configuration of the cross-coupling products was established from compound **4** by single crystal X-ray crystallography. CCDC 2191020 contains the supplementary crystallographic data for **4**.†

