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Enantioselective preparation and chemoselective cross-coupling of 1,1-diboron compounds

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The simplicity, efficiency and generality of the transition-metal-catalysed Suzuki–Miyaura cross-coupling reaction has led to its application in the preparation of a wide variety of organic compounds. Cross-coupling of alkylboron derivatives, however, remains a major challenge, in particular with regard to stereochemical control. Here, we describe the preparation and reaction of highly optically enriched 1,1-diboron compounds. A catalytic asymmetric conjugate borylation of β-boronylacrylates provided geminal diboronate products that feature two distinct boronyl units, in 99% enantiomeric excess. Chemoselective cross-coupling of one-boronyl unit, a trifluoroborate salt, occurred stereospecifically via inversion of its configuration to generate enantioenriched benzylic or allylic boronates. The difficult transmetallation in the Suzuki–Miyaura catalytic reaction cycle is believed to be facilitated by a stabilization effect from the second boronyl unit, and internal coordination by the oxygen of the proximal carboxyester. We also explored subsequent functionalization of the second boronyl unit.

Cross-coupling reactions have become ubiquitous in the elaboration of carbon–carbon bonds in synthetic organic chemistry[1–4]. These reactions have been widely studied, developed and utilized for the generation of novel organic molecules in the pharmaceutical, agrochemical and materials industries. Indeed, the significance of this class of reactions was recognized in the attribution of the 2010 Nobel Prize in Chemistry to Richard Heck, Ei-ichi Negishi and Akira Suzuki for their contributions in developing palladium-catalysed cross-coupling reactions. Efficient catalysts and conditions exist for the preparation of unsaturated compounds by coupling of sp^2- and sp-hybridized carbon centres. Although coupling of sp^3 centres using the Suzuki–Miyaura cross-coupling of primary alkylboranes is also well known[5], it is only recently that notable advances have been reported for the coupling of organoboronates[6–8]. The comparatively slow development of cross-coupling methodology with alkylboronates is associated with difficulties such as slow transmetallation[9] and side reactions like β-hydride elimination and protodeboronation. These issues add more complications to the significant challenge of stereoselective cross-coupling of alkylboron derivatives. In spite of these hurdles, it has now become possible to conduct stereoselective cross-couplings through either a dynamic kinetic resolution of secondary alkyl halides[10–13], stereospecific cross-coupling of optically pure alkyl triflate[14], or a stereospecific cross-coupling of secondary alkylboronates. The first stereospecific cross-coupling of optically enriched benzylic boronates was demonstrated by Crudden and co-workers[6]. Suginome and co-workers extended those findings to α-(acylamino)benzylboronic esters[7]. More recently, Molander and co-workers provided the first example of stereospecific cross-coupling of a non-benzylic, secondary alkylboron derivative (Fig. 1a)[8].

An attractive, logical evolution of this powerful approach would consist in achieving stereospecific coupling of optically pure 1,1-diboronyl esters (that is, geminal alkyl diboronic esters)[15]. Shibata and co-workers recently demonstrated that achiral 1,1-diboronyl esters undergo cross-coupling in a chemoselective fashion, affording only the mono-coupled product (as a racemate). These important results suggest that one boronyl unit can serve as an activating group for cross-coupling of the other one, suggesting promise for the stereospecific cross-coupling of optically pure 1,1-diboronyl esters. We therefore realized that the carbon atom of 1,1-diboronyl esters could be made stereogenic through the use of two different boronate adducts (Fig. 1b). To date, however, there have been no known examples of optically enriched 1,1-diboronyl esters. Herein, we report the first preparation of an optically pure 1,1-diboronyl compound, together with its use in stereoselective cross-coupling chemistry. Beyond their fundamental importance in the field of stereochemistry, these findings are significant from a practical standpoint. In addition to the potential of delivering optically enriched diarylmethane units via sequential cross-couplings of both boronyl units, it is also possible to plan sequential cross-coupling/allylation, cross-coupling/oxidation or cross-coupling/1,2-addition sequences towards the construction of a variety of synthetically valuable enantioenriched intermediates.

Results and discussions

Preparation of optically enriched 1,1-diboronyl compounds. Based on our recent report describing the preparation of optically pure boronic esters via a copper-catalysed conjugate addition of organomagnesium reagents onto 1,8-diaminonaphthalenyl (dan) 3-boronyl enoate **1a**[16], we envisioned that an asymmetric conjugate borylation of **1** with B_2pin_2 could deliver the desired, chiral 1,1-diboronyl ester **2** with high enantioselectivity (Table 1)[17]. By screening known reaction conditions[18–20], the protocol developed by Yun and co-workers quickly allowed access to the desired 3,3-diboronyl carboxyester **2a** with good yield, albeit with a low enantioselectivity when (*R*)–(*S*)-Josiphos **4** was used as the ligand (entry 2, Table 1). A more thorough evaluation of various chiral diphosphine ligands was therefore conducted. Taniaphos **5** was found to be ineffective, whereas (*R*)-tol-BINAP **6** afforded a much improved enantiomeric excess (e.e.) at 79% (Table 1, entries 3 and 4, respectively). The enantioselectivity could be improved to 82% using Walphos **7** (Table 1, entry 5). Following a systematic evaluation of commercial chiral ferrocene-type ligands, we were delighted to find that the

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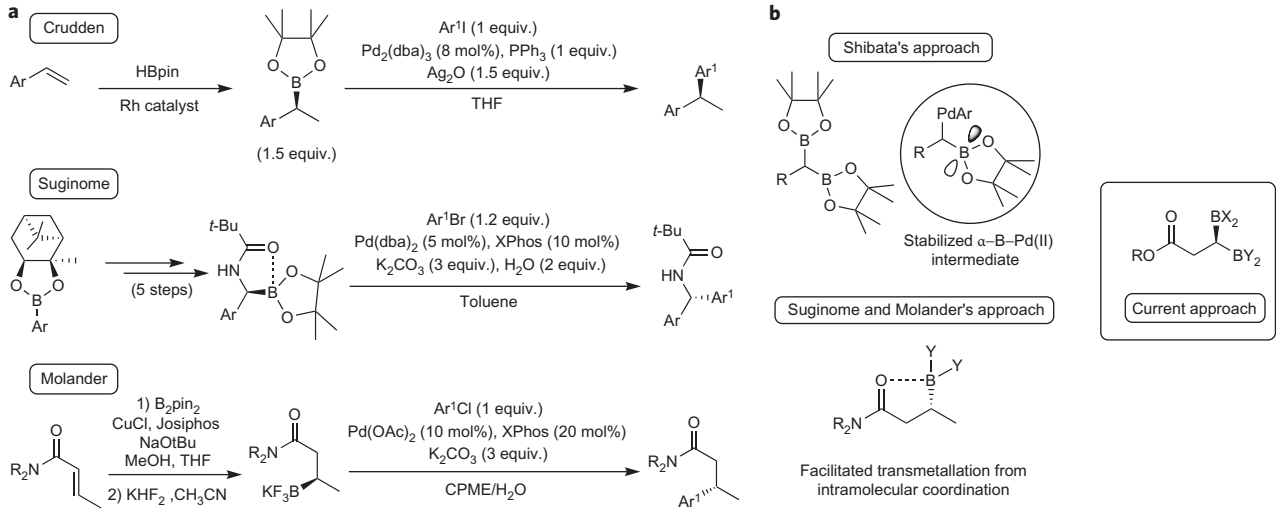
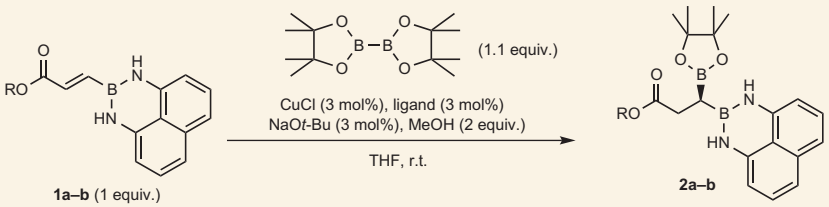
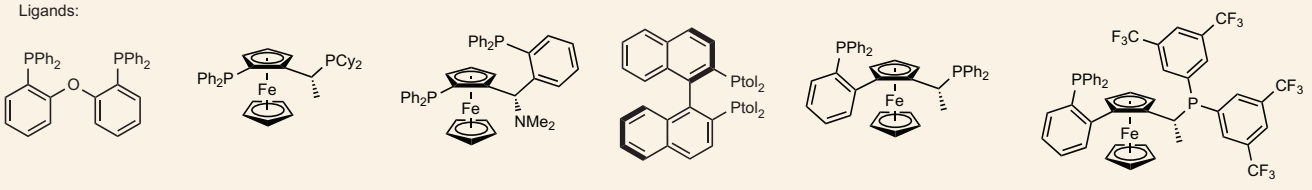


Figure 1 | Suzuki–Miyaura cross-coupling reactions with enantioenriched secondary alkyl boronate derivatives. a, Recent advances using either benzylic boronates or β-boronyl amide as the cross-coupling partners. Crudden and co-workers successfully cross-coupled optically enriched pinacol boronate with retention of stereochemistry[6]. Suginome and Molander's groups, on the other hand, cross-coupled optically enriched pinacol boronates and trifluoroborate salts with an inversion of stereochemistry[7,8]. All of the above methods, however, are restricted to the use of substrates that are either benzylic boronates or that have a strongly coordinating amide β to the boron atom. **b**, Current approach using the strong stabilization from the α-boronyl–Pd(II) intermediate discovered by Shibata and co-workers[15] and the intramolecular carbonyl coordination to further expand the concept of stereoselective cross-coupling reactions. CPME, cyclopentylmethyl ether.

Table 1 | Optimization of reaction conditions for the preparation of chiral 3,3-diboronyl carboxyesters.



Ligands:



3 DPEphos **4** (*R*)-(*S*)-Josiphos **5** (*S*)-(*S*)-Taniaphos **6** (*R*)-tol-BINAP **7** (*R*)-(*R*)-Walphos **8** (*R*)-(*R*)-Walphos (CF_3)

Entry	R	Ligand	Product	Yield (%)	e.e. (%)*
1	Me, **1a**	**3**	**2a**	90	0
2	Me, **1a**	**4**	**2a**	86	−13
3	Me, **1a**	**5**	**2a**	88	0
4	Me, **1a**	**6**	**2a**	91	−79
5	Me, **1a**	**7**	**2a**	74	82
6	Me, **1a**	**8**†	**2a**	88	99
7	CH_2(*o*-Br)C_6H_4, **1b**	**8**†	**2b**	81	99

Reaction conditions: RB(dan) (0.5 mmol), CuCl (15 μmol), Ligand (15 μmol), NaO*t*-Bu (15 μmol), B_2pin_2 (0.55 mmol), MeOH (1.0 mmol) in THF (1 ml) at room temperature. *Measured by chiral HPLC. Configuration assigned by X-ray crystallographic analysis of compound **2b**. †Solvias SL-W001-1.

trifluoromethyl-substituted Walphos ligand **8** provided the desired enantioenriched 3,3-diboronyl carboxyester **2a** with 99% e.e. (Table 1, entry 6). This enantioenriched 3,3-diboronyl carboxyester **2a** is stable to silica column chromatography and could be recrystallized from hot methanol to give X-ray quality crystals, which were successfully analysed by X-ray diffraction (Fig. 2). The absolute stereochemistry of 3,3-diboronyl carboxyester **2a**, when using (*R*)–(*R*)-CF_3-Walphos **8**, was assigned the (*R*) configuration based on X-ray crystallography of brominated derivative **2b**. Compound **2b** crystallized in the chiral space group *P*1. The high quality of the diffraction data and the presence of a bromine atom in the molecule allowed its absolute configuration to be reliably determined using anomalous dispersion methods, and the final value of the Flack absolute structure parameter[21–23] was determined to be 0.016(6).

Chemoselective cross-coupling of optically enriched 1,1-diboronyl compounds. The X-ray crystallographic structure of **2a** revealed that the carbonyl oxygen of the methyl ester is much closer to the boron atom of the pinacolate unit (distance of

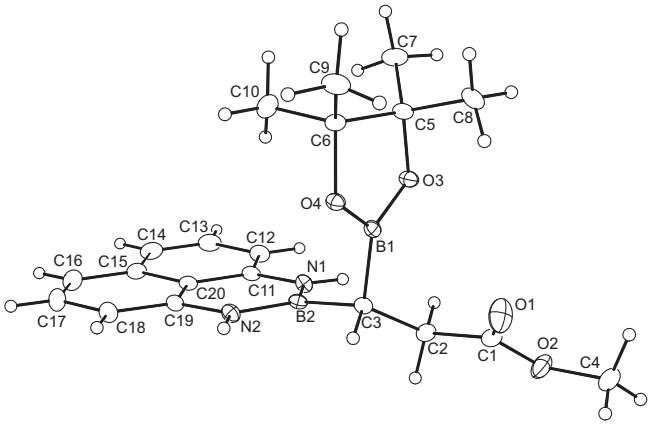
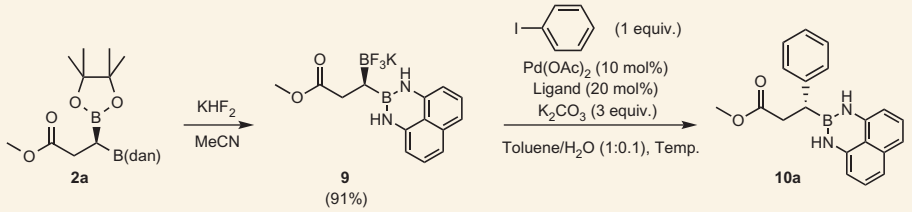


Figure 2 | X-ray crystallographic structure of chiral 3,3-diboronyl carboxyester 2a.

2.94 Å) than to the boron atom of the Bdan unit (distance of 4.41 Å). These data suggest that the boron pinacolate could be the active unit participating in the subsequent Suzuki–Miyaura cross-coupling reaction. Moreover, the longer B–O bond lengths (1.376 Å and 1.369 Å) compared to the standard B–O bond lengths of tricoordinate pinacol esters (usually ~1.31–1.32 Å)[24] are indicative of a weaker π-overlap between the oxygens of the boronic ester and the boron atom in **2a**. This comparison further supports the possibility for coordination between the carbonyl oxygen of the methyl ester and the boron atom. In addition, the torsional angles of the boron pinacolate unit between C6–O4–B1–O3 and C5–O3–B1–O4 are 13.75° and 4.81°, respectively. These data suggest that the boron pinacolate is slightly distorted from planarity, possibly because of the coordination with the carbonyl oxygen. On the other hand, the torsional angles for the Bdan unit, B2–N1–N2–C11 and B2–N1–N2–C19, are 4.0° and 3.7°, respectively, indicate that the Bdan unit is nearly trigonal planar. These observations and the reported inertness of the Bdan unit in cross-coupling reactions[25,26] made us confident that the pinacol boronate unit could be cross-coupled selectively. We then initiated model cross-coupling experiments with the 3,3-diboronyl carboxyester **2a**. Although we were able to obtain the desired product in good yield, under all conditions attempted (see Supplementary Information) we were only able to obtain the desired cross-coupled product as a racemate, implying that the reaction went through a transient intermediate that lost its stereochemical integrity. Because trifluoroborate salts are known to be potent cross-coupling partners, we prepared the corresponding trifluoroborate salt **9** from the 3,3-diboronyl carboxyester **2a** in hand. Using conditions similar to the method developed by Molander and co-workers[8], we were pleased to isolate product **10a** stereoselectively, with preservation of stereochemical integrity (Table 2, entry 1). The absolute configuration of **10a** was confirmed to be (*R*) by comparison with the reported optical rotation of the corresponding alcohol[27]. Combining this result with the (*R*) stereochemistry of 3,3-diboronyl carboxyester **2a** (vide supra), it can be concluded that the observed cross-coupling product **10a** underwent a complete inversion of stereochemistry, similar to that observed in the Suginome and Molander examples[7,8]. A screening of various ligands indicated that XPhos was the most effective in promoting the cross-coupling reactions (Table 2, entries 3–5). The temperature and stoichiometry of the diboronyl substrate **9** also play very important roles in ensuring high yields, resulting in 78% product formation when the reaction was executed in toluene at 80 °C with 1.5 equiv. of the 3,3-diboron reagent (Table 2, entries 6 and 7). After changing the electrophile from phenyl iodide to phenyl bromide, the reaction yield could be further improved to 92% (Table 2, entry 8), and it was later found that only 1.2 equiv. of the 3,3-diboron reagent was needed to achieve a high yield of the cross-coupled product (Table 2, entry 9). The main by-product observed in these cross-coupling reactions is the protodeboronated product, so a slight excess of the diboron reagent is necessary to ensure a high yield for the coupling process. This remarkable result constitutes another advance in the Suzuki–Miyaura cross-coupling of alkyl boronates. Indeed, in their previous communication[8], Molander and co-workers mentioned that a direct cross-coupling reaction with a β-boronyl carboxy ester was not possible, and a stronger coordinating amide was necessary. Consequently, our results with 3,3-diboronyl carboxyesters demonstrate that a strong cooperative effect is at play, which facilitates the transmetallation step through both the coordination of the methyl ester to the boron atom and the stabilization of the α-borylated, Pd(II) intermediate (Fig. 1).

Scope of chemo- and stereoselective cross-coupling of 3,3-diboronyl carboxyester 9. Using this optimized procedure, we

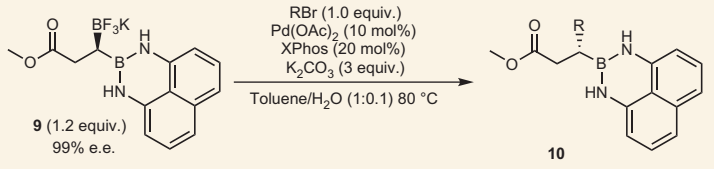
Table 2 | Optimization of reaction conditions for the cross-coupling of 3,3-diboronyl carboxyester 9.

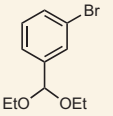
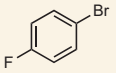
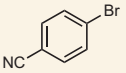
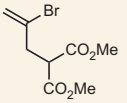
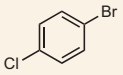
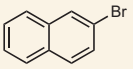
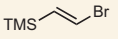
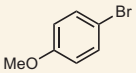
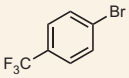


Entry	Equiv. (9)	Temp. (°C)	Ligand	Yield (%)	e.e. (%)*
1	1.1	95	XPhos	39	99
2	1.1	95	XPhos	23†	ND
3	1.1	95	SPhos	24	ND
4	1.1	95	RuPhos	13	ND
5	1.1	95	P*t*-Bu$_3$	37	ND
6	1.1	80	XPhos	53	ND
7	1.5	80	XPhos	78	ND
8	1.5	80	XPhos	92‡	99
9	1.2	80	XPhos	89‡	99

Reaction conditions: RBF_3K (0.11–0.15 mmol), phenyl iodide (0.1 mmol), $Pd(OAc)_2$ (10 μmol), Ligand (20 μmol), K_2CO_3 (0.3 mmol) in toluene (1 ml) and H_2O (0.1 ml) at the indicated temperature. †CPME was used as the solvent. ‡Phenyl bromide was used as the electrophile. *The e.e. of **10** was measured by chiral HPLC. The absolute configuration was assigned by comparison with the optical rotation of the corresponding alcohol[27]. ND = Not Determined.

Table 3 | Reaction scope for the cross-coupling of 3,3-diboronyl carboxyester 9.



Entry	RBr	Product	Yield (%)	e.e. (%)*	Entry	RBr	Product	Yield (%)	e.e. (%)*	Entry	RBr	Product	Yield (%)	e.e. (%)*
1		**10b**	83	99	6		**10g**	85	97	10†		**10k**	66	95
2		**10c**	86	99	7		**10h**	0	-	11†		**10l**	81	99
3		**10d**	85	99	8		**10i**	79	97	12†		**10m**	51	91
4		**10e**	88	99	9		**10j**	71	97	13†		**10n**	33	88
5		**10f**	84	98										

Reaction conditions: RBF_3K (0.12–0.15 mmol), phenyl bromide (0.1 mmol), $Pd(OAc)_2$ (10 μmol), XPhos (20 μmol), K_2CO_3 (0.3 mmol) in toluene (1 ml) and H_2O (0.1 ml) at 80 °C. *The e.e. of **10** was measured by chiral HPLC. †1.5 equiv of RBF_3K was used.

examined the scope of substrates for cross-coupling reactions with the 3,3-diboronyl carboxyester **9**. Most of the coupling reactions with aryl electrophiles proceeded efficiently, leading to high yields and almost complete enantiomeric inversion while tolerating various functional groups (Table 3, entries 1–6). Surprisingly, a nitrile-substituted electrophile did not fare well and afforded a mixture of protodeboronated side products (Table 3, entry 7). It is interesting to note here that when the aromatic ring system bears a nitrile group such as in **10h**, the Bdan unit is no longer stable and protodeboronation product is observed. The reaction tolerates various ortho- or meta-substituted aryl electrophiles, demonstrating that sterics is not a major factor in these cross-coupling reactions (Table 3, entries 1 and 6). Furthermore, naphthalene derivatives or heteroaromatics such as thiophene can also undergo the desired reactions to give the corresponding products **10i** and **10j** in good yields (Table 3, entries 8 and 9). To our satisfaction, not only aryl electrophiles, but also alkenyl electrophiles, could be cross-coupled with the diboronyl reagent. This approach constitutes a new way of preparing enantioenriched α-substituted allylic boronates[28–32], which can undergo carbonyl allylation reactions to form valuable carbon–carbon bonds (Table 3, entries 10–13)[33–35]. Coupling of **9** with alkenyl electrophiles, however, is slower than cross-coupling reactions with aryl electrophiles. The reaction requires 1.5 equiv. of the diboron reagent and tends to lead to lower product yields (Table 3, entries 10–13). A particularly interesting example is the cross-coupling reaction of diboron reagent **9** with 2-trimethylsilyl-bromoethene. The resulting product represents a Type I double allylation reagent that is capable of undergoing sequential allylation or oxidation reactions leading to different functionalities (Table 3, entry 12)[36–39].

Mechanistic proposal for the cross-couplings. The mechanism of these stereospecific cross-coupling reactions probably follows a pathway similar to that suggested previously by Suginome, Molander and Shibata[7,8,15]. Subsequent to the oxidative addition of Pd(0) into the C–X bond, the resulting intermediate is surmised to readily transmetallate by inversion of configuration with the borate to provide a σ-alkyl–Pd(II)Ar intermediate through a transition structure **13** (Fig. 3a). This key transmetallation step is known to be notoriously difficult for alkyl boronates due to potential β–H elimination and protodeboronation side reactions. Despite this apprehension, the desired cross-coupled products were obtained in high yields. Thus, we believe that the second boronyl unit, Bdan, stabilizes the α-B–Pd(II) intermediate (see Fig. 1b) in a manner similar to Shibata's work with bis-pinacolates, even though the 1,8-diaminonaphthalene protecting group partially suppresses the Lewis acidity of the boron atom. In addition, the facile transmetallation step is also probably facilitated by internal coordination between the carbonyl oxygen and the boron atom in **13** (Fig. 3a). This internal coordination becomes much more evident in the trifluoroborate salt **9** than in pinacolate **2**, probably due to the formation of the boronic acid intermediate reported to be the active species in cross-coupling reactions of trifluoroborate salts[40]. The dual stabilization effect greatly facilitates the transmetallation step for the 1,1-diboronic ester. The resulting σ-alkyl–Pd(II)Ar could then undergo reductive elimination to afford products **10** while regenerating the Pd(0) catalyst.

Applications of the cross-coupled products. To demonstrate the versatility of the products obtained in these stereospecific cross-couplings, we then attempted the second cross-coupling with the

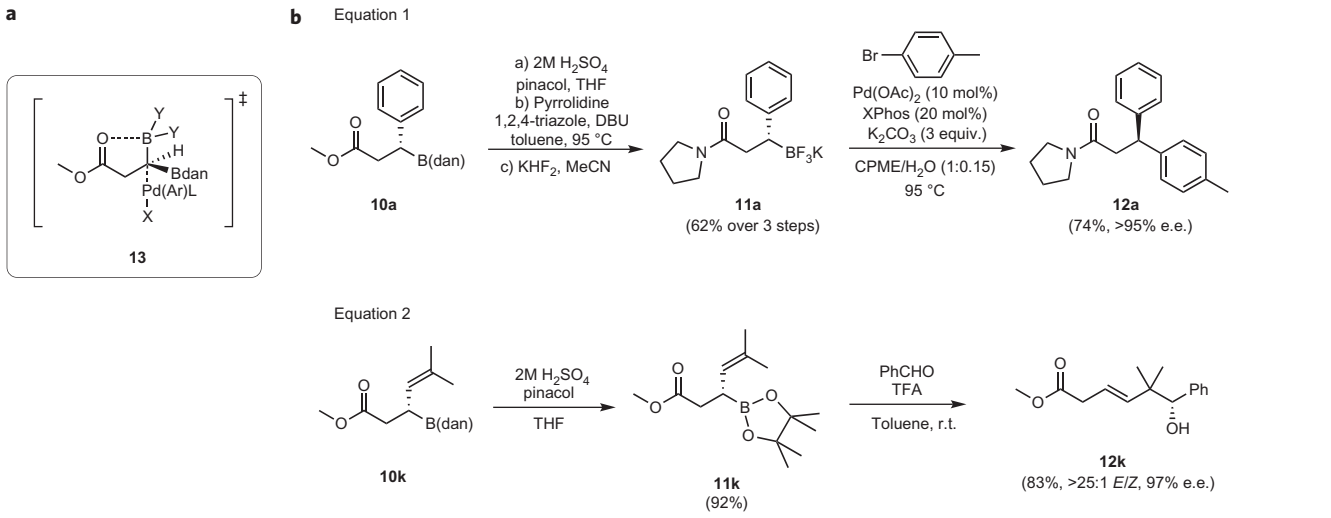


Figure 3 | Proposed transition state for the stereospecific cross-coupling reaction of 3,3-diboronyl carboxyester 9 and applications of mono cross-coupled products 10. a, Proposed transition state (Y = F or OH) for the key transmetallation step with inversion of stereochemistry during the cross-coupling reaction. The transition state is believed to be stabilized both by the neighbouring empty *p*-orbital from the boron atom and the coordination effect from the oxygen of the carboxyester. **b**, Equation 1: iterative cross-coupling sequence for the synthesis of enantioenriched diarylmethane units **12a**. This enantioenriched diarylmethane core structure is an important pharmacophore and the approach presented here demonstrates a potential method for diversity-oriented synthesis towards the discovery of various pharmaceuticals. Equation 2: carbonyl allylboration reaction to synthesize enantioenriched homoallylic alcohol **12k**. The resulting enantioenriched homoallylic alcohol moiety is a common entity in various biologically active natural products, thus demonstrating the importance of the optically enriched 1,1-diboronyl compounds **2** and **9** synthesized in this study.

chiral boronate **10** acquired from the first coupling. However, it was not possible to cross-couple the boronate **10a** directly, even after transforming the 1,8-diaminonaphthalene protecting group to the trifluoroborate salt. We found it necessary to transform the carboxyester to the amide to effect the desired reaction. As shown in Fig. 3b (equation 1), following the conversion of the Bdan unit to the boronic acid pinacol ester, we applied the protocol developed by Yang and Birman to form the corresponding amide[41]. Trifluoroborate salt formation afforded **11a**, and this compound could be cross-coupled successfully with *p*-bromotoluene to afford the enantioenriched diarylmethane **12a**. The enantioenriched diarylmethane core structure is an important pharmacophore, and 1,1-diboryls could serve as a universal template for their synthesis[42]. Our method represents a new way to prepare these synthetic intermediates where both of the aryl groups can be assembled through simple cross-coupling reactions with readily available aryl bromides.

Another synthetically valuable application of the mono cross-coupled products is the subsequent allylboration reaction. Once the Bdan group was removed to provide access to allyl boronic acid pinacol ester **11k**, a Brønsted-acid-catalysed allylboration reaction could be achieved to afford the homoallylic alcohol **12k**[43,44]. The e.e., as measured by chiral high-performance liquid chromatography (HPLC) analysis, was found to be fully retained in the alcohol product **12k** (equation 2, Fig. 3b). Based on the excellent enantiomeric retention and the *E*/*Z* ratio, the reaction most likely proceeded through the expected chair-like transition state[35,45–48]. All these preliminary applications demonstrate the potential value of enantioenriched 3,3-diboronyl carboxyesters as intermediates in organic synthesis.

In summary, we have reported the first syntheses of enantiomerically pure 3,3-diboronyl carboxyesters and shown their intriguing physical properties through X-ray crystallographic analysis. We have demonstrated that the enantioenriched diboronyl esters can be cross-coupled chemoselectively and stereoselectively with various organic electrophiles. Both the coordination of the carbonyl oxygen to the boron atom and the stabilization provided by the second boronyl unit in the α-B–Pd(II) complex are thought to assist the transmetallation process, thus facilitating this notoriously difficult mechanistic step in cross-coupling reactions of alkyl boronates. The cross-coupling reactions reported herein represent a rare example of the successful use of non-benzylic secondary alkylboronates, which occur with preservation of stereochemical integrity. The resulting enantioenriched benzylic or allylic boronates can undergo a plethora of reactions including a second iterative cross-coupling, carbonyl allylation and oxidation reactions. These applications highlight the versatility of chiral boronates and demonstrate the numerous synthetic possibilities associated with enantioenriched 1,1-diboronyl compounds.

Methods

3,3-Diboronyl carboxyester 2a. CuCl (1.5 mg, 15 μmol), Solvias SL-W001-1 ligand **8** (10 mg, 15 μmol) and NaOtBu (1.4 mg, 15 μmol) were dissolved in dry tetrahydrofuran (THF, 0.4 ml) and stirred at room temperature for 30 min before the addition of bis-pinacolato diboron (140 mg, 0.550 mmol) in THF (0.3 ml). The reaction was stirred further for 10 min, and boronate **1a** (126 mg, 0.500 mmol) was then added with THF (0.3 ml) followed by dropwise addition of MeOH (41 μl, 1.00 mmol). After 12 h of stirring, the reaction mixture was evaporated *in vacuo* and purified directly by silica column chromatography (EtOAc/hexanes = 1:4) to give **2a** (167 mg, 88%) as a white solid. The product could be recrystallized from hot MeOH to give X-ray quality crystals (72%) (see Supplementary Information).

General procedure for stereoselective cross-coupling reactions with 3,3-diboronyl carboxyester 9. $Pd(OAc)_2$ (10 μmol), XPhos (20 μmol), K_2CO_3 (0.30 mmol), aromatic or alkenyl bromide (0.10 mmol) and 1,1-diboronyl ester **9** (0.12 or 0.15 mmol) were stirred in toluene (1.0 ml) and H_2O (0.10 ml) at 80 °C for 6 h. The reaction mixture was then cooled and evaporated *in vacuo*. The crude reaction mixture was purified with column chromatography to afford the purified product.

X-ray crystallographic data. CCDC 816515 contains the crystallographic data for compound **2a**. CCDC 826384 contains the crystallographic data for compound **2b**. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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Author contributions

J.C.H.L. performed the experiments. R.M. performed the X-ray crystallographic analysis of **2b**. D.G.H. directed the project. The manuscript was co-written by J.C.H.L. and D.G.H.

Additional information

The authors declare no competing financial interests. Supplementary information and chemical compound information accompany this paper at www.nature.com/naturechemistry. Reprints and permission information is available online at http://www.nature.com/reprints. Correspondence and requests for materials should be addressed to D.G.H.

CORRIGENDUM

Enantioselective preparation and chemoselective cross-coupling of 1,1-diboron compounds

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In the version of this Article originally published, in Table 1, the ferrocene-based ligands 4, 5, 7 and 8 should have had 1,2-substituted cyclopentadienyl rings rather than 1,3-substituted. This error has been corrected in the HTML and PDF versions of this Article.