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Spirocycles Hot Paper

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Stereoselective Diboration of Spirocyclobutenes: A Platform for the Synthesis of Spirocycles with Orthogonal Exit Vectors

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In memory of Professor Kilian Muñiz (1970–2020)

Abstract: *The diastereo- and enantioselective diboration of spirocyclobutenes provides a platform for the rapid preparation of a wide variety of chiral spirocyclic building blocks. The chemoselective functionalization of the carbon-boron bond in the products, including a stereospecific sp^3-sp^2 Suzuki–Miyaura cross-coupling reaction, provides a powerful tool to control the directionality and the nature of the exit vectors in the spirocyclic framework.*

Spirocyclic compounds, especially those containing small rings, are witnessing increasing attention in drug discovery programs.[1] Among them, spirocyclobutanes are particularly attractive scaffolds as they hold well-defined exit vectors that rigorously shape their three-dimensionality (Scheme 1).[2] They provide access to unexplored regions of chemical space offering new opportunities for intellectual property. Moreover, they offer complementary tools to modulate physicochemical and pharmacokinetic properties such as lipophilicity, solubility and metabolic stability.[1b,2] Common strategies to prepare these compounds include intramolecular S_N2 reactions or addition of a nucleophile to a carbonyl to build either ring of the spirocycle,[3] cycloaddition reactions starting from an exocyclic alkene[4] and ring expansion strategies.[5] Ideally, from a drug discovery perspective, a synthetic method should offer control on the different points of diversification (exit vectors) in the spirocyclic scaffold, which could be critical in a lead optimization program. While with the existing methods it is relatively easy to place exit vectors on terminal heteroatoms, there is a lack of strategies to introduce orthogonal exit vectors on carbon atoms (Figure 1).

Inspired by our recent work on the desymmetrization of meso cyclobutenes,[6] we envisioned that spirocyclobutenes **I** could offer a platform to tackle this challenge. We thought that diboration of a spirocyclobutene would provide a bisorganometallic intermediate **II** in which the two boryl units could act as orthogonal exit vectors through selective carbon-boron bond functionalization. To succeed in this approach several difficulties needed to be overcome, such as feasibility and control in the diastereo- and enantioselectivity of the diboration and chemoselective manipulation of the two boron atoms in the diborylated products. If successful, it would provide a unique way to control the directionality and the nature of the exit vectors in the spirocyclic framework, allowing access to multiple compounds from a common intermediate.

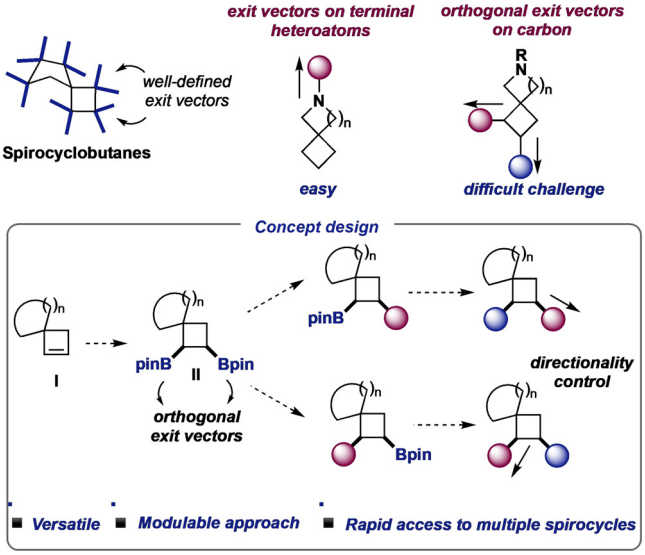

Figure 1. Design of spirocycles with orthogonal exit vectors.

To test the viability of our approach we needed to have easy access to diborylated compounds **II**, which had not been previously synthesized. The diboration of alkenes has been described under transition-metal[7–10] and base-promoted conditions.[11] However, despite the progress in the field, the diboration of cyclobutenes remains unknown. We chose to explore the base-promoted diboration to prepare racemic diborylated spirocycles **II** (Scheme 1). Under conditions described for the diboration of cyclohexene[11a] (conditions A, Scheme 1) we obtained bisboronic ester **2a** in low yield. After some optimization, we found that heating a solution of cyclobutene **1a** and B_2pin_2 in MeOH in the presence of NaOMe, afforded spirocycle **2a** as a single *syn* diastereomer in 78% isolated yield.[12] Importantly, the reaction could be scaled up to prepare 1.6 g of **2a** without compromising the yield.

These conditions allowed us to easily prepare a collection of novel diborylated chiral building blocks in a straightforward manner (Scheme 1). We prepared spirocycles containing the

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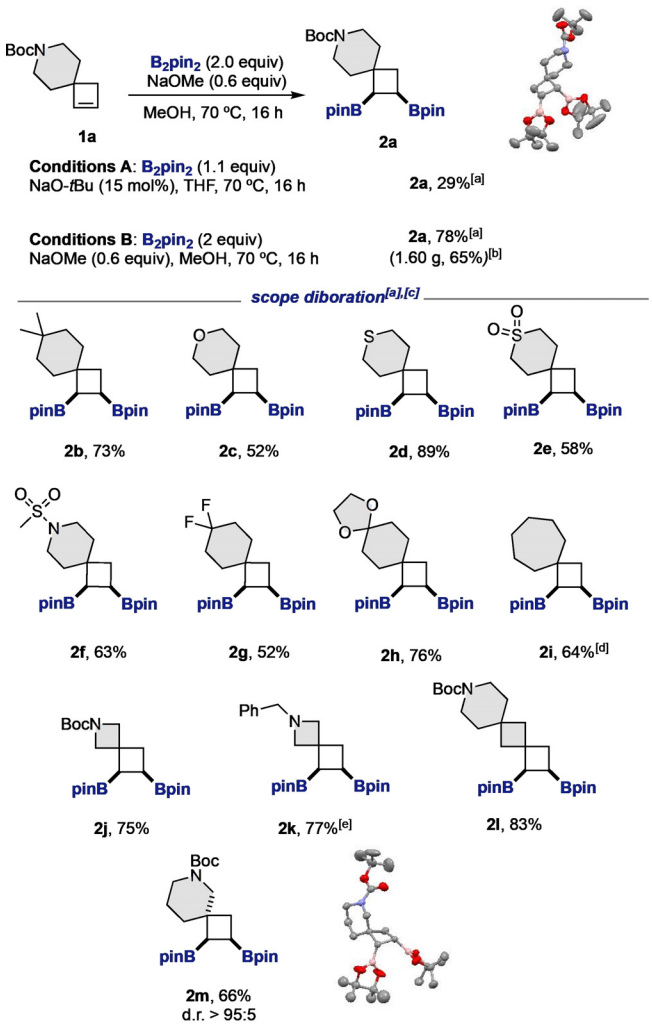
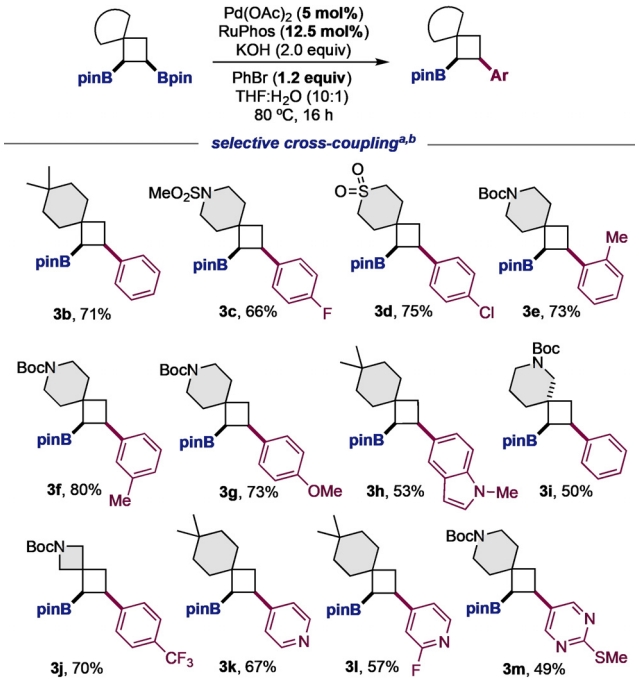


Scheme 1. Based-promoted diboration. [a] Isolated yields. [b] Starting from 1 g of **1a**. [c] Reaction conditions: **1** (0.2 mmol), B_2pin_2 (0.4 mmol), NaOMe (0.12 mmol), MeOH (0.2 M), 70 °C, 16 h. [d] $T = 85$ °C. [e] Yield calculated by ^1H NMR owing to instability of **2k**.



Scheme 2. Selective Suzuki–Miyaura cross-coupling. [a] Reaction conditions: **2** (0.1 mmol), $Pd(OAc)_2$ (5 mol%), RuPhos (12.5 mol%), KOH (2.0 equiv), ArBr (1.2 equiv), THF:H_2O (10:1, 0.1 M), 80 °C, 16 h. [b] Isolated yields.

spiro[3.5]nonane ring system with different functional groups as connectors: carbon chain (**2b**), ether (**2c**), thioether (**2d**), sulfone (**2e**), sulfonamide (**2f**), CF_2 (**2g**) and acetal (**2h**). Additionally, compounds with the spiro[3.3]heptane (**2j**, **2k**, **2l**) and the spiro[3.6]decane (**2i**) ring systems were successfully synthesized. Remarkably, a non-symmetric spirocyclobutene afforded diborylated spirocycle **2m** as a single diastereomer.[12]

With an easy access to diborylated spirocycles **2** in hand, we focused on the possibility of performing chemo- and stereospecific transformations on the two C–B bonds. One of our ambitious goals was to use them in selective Suzuki–Miyaura cross-coupling reactions, as it would provide a convenient tool to introduce the spirocyclic scaffold into existing libraries of compounds. While the use of cyclobutyl boronic acids[13] and trifluoroborate salts[14] as nucleophiles in Suzuki–Miyaura cross-coupling reactions is well-documented, the use of cyclobutyl pinacol boronic ester derivatives is scarce.[15] Inspired by the pioneering work of Morken with 1,2-terminal diboronic pinacol esters,[16] we envisioned that a second boronic ester in an adjacent carbon of the cyclobutane could act as a Lewis acid coordinating to the oxygen atom of the neighboring pinacolato (Scheme 2, **III**). This coordination, could increase the Lewis acidity of the external boron atom, facilitating the transmetalation step. It should be pointed out that all previous reported examples describing selective cross-coupling of 1,2-diboronic esters are described with terminal acyclic substrates and distinguish between a primary boronic ester and a secondary boryl unit.[10,11b,16,17] With the exception of examples that require the use of directing groups,[18] there are no reports of Suzuki–Miyaura cross-coupling reactions discriminating between two secondary alkyl boronic esters. Therefore, there is little information about the regioselectivity and the stereochemical outcome in this kind of orthogonal cross-coupling.

To test this hypothesis, we chose spirocycle **2a** as a model substrate and PhBr as electrophile, in the presence of $Pd(OAc)_2$ and an electron-rich monodentate phosphine (Table 1). Disappointingly, using a 1 mol% of $Pd(OAc)_2$ and RuPhos as ligand in a 1:1 ratio,[16] 9% of cyclobutene **1a** was obtained along with unreacted starting material (entry 1). Increasing the amount of palladium and ligand to 5 mol% only increased the yield of cyclobutene **1a** (entry 2). This is in contrast with previous reports of terminal 1,2-diboronates for which alkene formation is not observed. We reasoned that **1a** could be formed through an unusual β-boryl elimination process,[19] favored by the rigid *syn* disposition of the palladium and the adjacent boron atom after transmetalation. After some experimentation, we found that increasing the ligand:palladium ratio from 1:1 to 2.5:1 was

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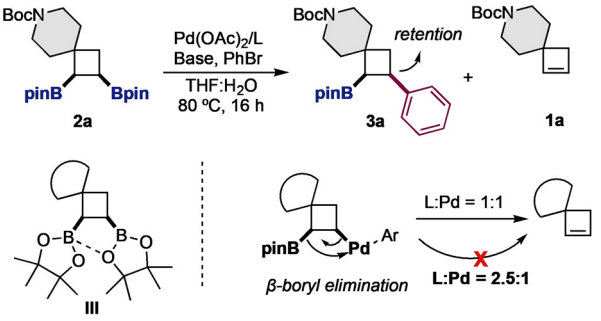
Table 1: Optimization of the selective cross-coupling.



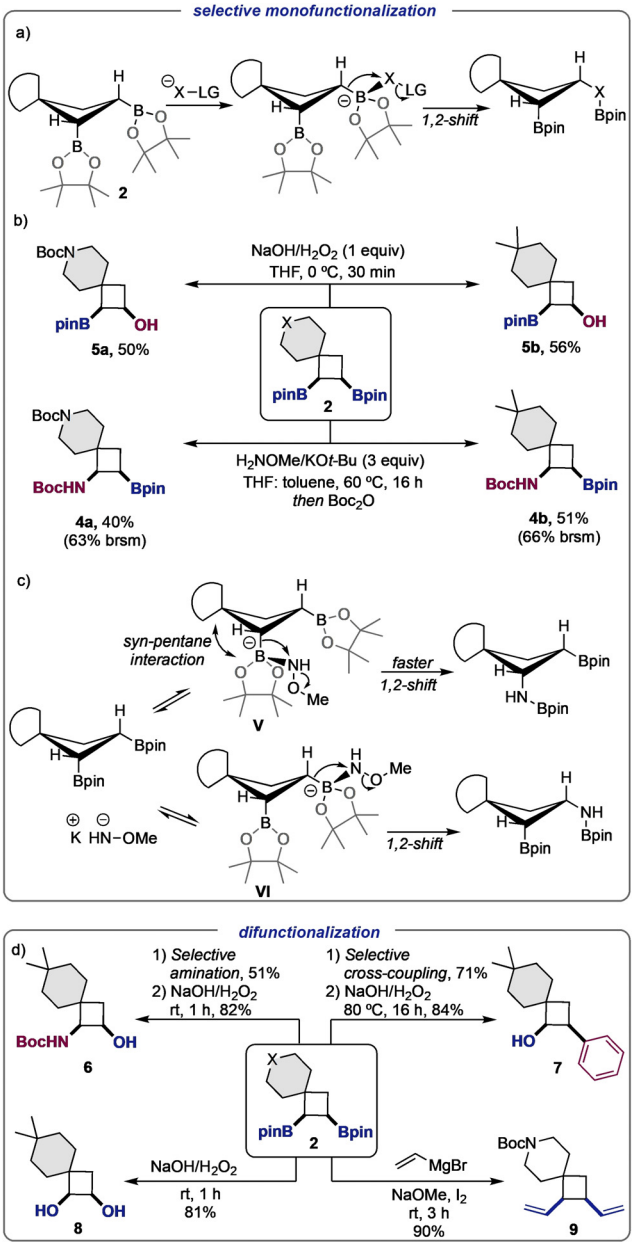
Entry	$Pd(OAc)_2$ [mol%]	Ligand [mol%]	Base	Yield **3a** [%][c]	Yield **1a** [%]
1[a]	1	RuPhos 1%	KOH	–	9[c]
2[a]	5	RuPhos 5%	KOH	–	45[c]
3[a]	5	RuPhos 10%	KOH	59	4[d]
4[a]	**5**	**RuPhos 12.5%**	**KOH**	**66**	–
5[a]	5	SPhos 12.5%	KOH	65	6[d]
6[a]	5	cataXium 12.5%	KOH	30	1[d]
7[a]	5	XPhos 12.5%	KOH	52	7[d]
8[b]	5	RuPhos 12.5%	K_2CO_3	32	–
9[b]	**5**	**RuPhos 12.5%**	**KOH**	**77**[e]	–

[a] Reaction conditions: **2a** (0.1 mmol), $Pd(OAc)_2$, Ligand, KOH (2.0 equiv), ArBr (1.5 equiv), $THF:H_2O$ (10:1, 0.1 M), 80 °C, 16 h. [b] ArBr (1.2 equiv). [c] Isolated yields. [d] Yield calculated by ^1H NMR. [e] 91% yield calculated by ^1H NMR.

key to suppress the β-boryl elimination affording the monoarylated product in good yield as a single regio- and diastereoisomer (entry 4). Other electron-rich monodentate phosphines (entries 5–7) or a different base (entry 8) provided inferior results. Notably, the amount of aryl bromide could be reduced to 1.2 equivalents (entry 9). The *syn* relative stereochemistry between the aryl ring and the boryl moiety in **3a** suggests that the transmetalation step takes place with retention of the configuration.[20]

The cross-coupling reaction worked with exquisite regioselectivity with different spiro ring systems (Scheme 2, **3b**–**3m**). Additionally, the scope in the aryl electrophile was very broad including aryl rings with electron withdrawing (**3c**, **3d**, **3j**) and electron donating groups (**3g**), ortho-substituted rings (**3e**) and, often challenging, nitrogen-containing heterocycles (**3h**, **3k**, **3l**, **3m**).

Along with transition-metal-catalyzed transformations, the most common reactions of boronic esters involve the coordination of a Lewis base to the boron atom, followed by a stereospecific 1,2-shift of the boryl moiety. The favored conformer in **2** should place the external boron atom in a pseudoecuatorial position ($\mathbf{B}_{ec}$) in a puckered conformation to avoid 1,3-diaxial interactions with the substituents of the spiro carbon [Scheme 3, Eq. (a)]. We hypothesized that if the coordination of the Lewis base to the boron atoms in **2** was rate-limiting, steric effects could favor coordination of $\mathbf{B}_{ec}$ over the axial ($\mathbf{B}_{ax}$). Additionally, coordination of the oxygen of the pinacolato in $\mathbf{B}_{ec}$ with $\mathbf{B}_{ax}$, could increase the Lewis acidity of $\mathbf{B}_{ec}$. Following this hypothesis, we found that it is possible to oxidize selectively $\mathbf{B}_{ec}$ in spirocycles **2** controlling the amount of oxidant (H_2O_2, 1 equiv), the temperature (0 °C)



Scheme 3. Selective functionalization of the C–B bonds.

and the reaction time (30 min). Hydroxy boronates **5a** and **5b** were obtained as the only oxidized products [Scheme 3, Eq. (b)].

Surprisingly, selective amination of $\mathbf{B}_{ax}$ in **2** was achieved by heating a toluene solution of **2a** or **2b** at 60 °C in the presence of methoxyamine and KO*t*-Bu.[21] Compounds **4a** and **4b** were obtained as single regioisomers. To the best of our knowledge this is the first example of selective monoamination of a diboronic ester. A plausible explanation for the selective formation of products **4a** and **4b** could imply a reversible coordination of the nucleophilic nitrogen to the boron atoms in **2** under the reaction conditions [Scheme 3, Eq. (c)] to form boronate complexes **V** and **VI**. Boronate complex **V** presents a destabilizing interaction between the equatorial substituent of the spiro carbon and the pinacol

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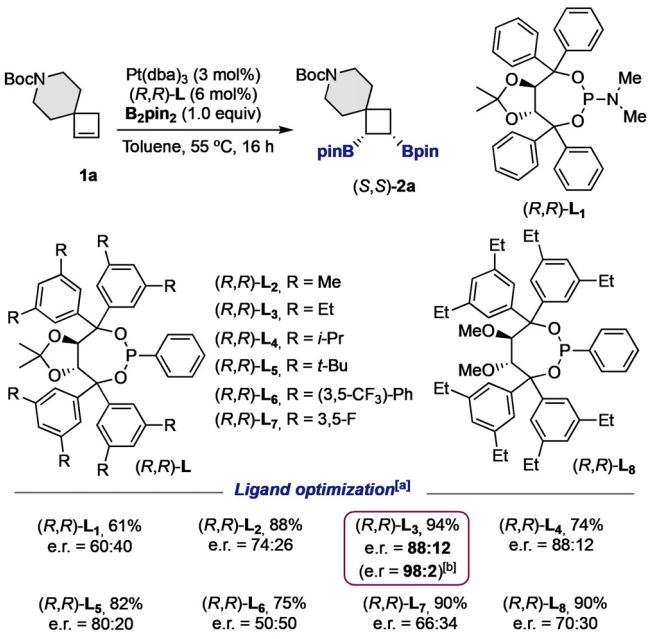
moiety after sp^3-hybridation of the boron (*syn* pentane type interaction). This interaction is not present in boronate complex **VI**. The relief of steric strain[22] in **V** could explain a faster 1,2-shift than in **VI**, leading to the selective amination of $\mathbf{B}_{ax}$.

Once we controlled the monofunctionalization of diboronates **2**, selective difunctionalizations could be designed [Scheme 3, Eq. (c)]. Starting from spirocyclo **2b**, sequential cross-coupling/oxidation provided spirocyclobutanol **7** as single product in good overall yield. Moreover, amination followed by oxidation of **2b** afforded spirocyclic amino-alcohol **6**. These transformations represent formal diastereoselective hydroxy-arylation and amino-hydroxylation reactions of the cyclobutene. Finally, compounds **8** and **9** were prepared in high yields by double oxidation and Zweifel olefination, respectively.[23]

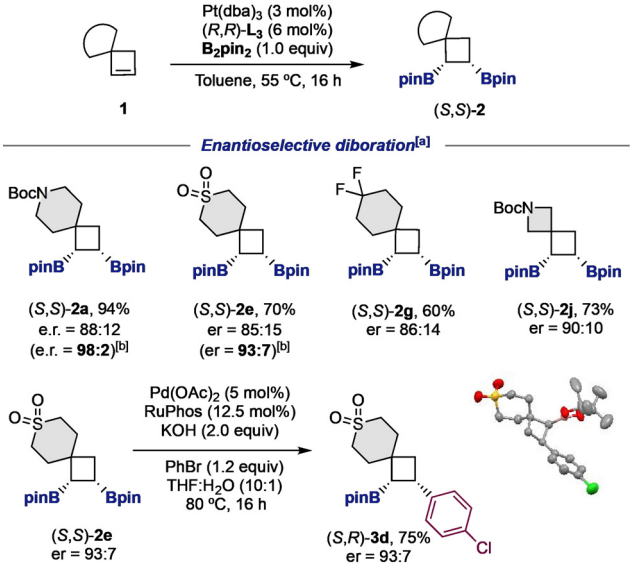
Schemes 2 and 3 show that the diboration of spirocyclobutenes **1** is a powerful tool for the assembly of spirocycles libraries with controlled vectorization. Since the reactions shown in Scheme 2 and 3 are stereospecific, the development of an enantioselective diboration of spirocyclobutenes would provide access to a broad variety of enantioenriched novel spirocyclic building blocks. To accomplish this goal, we turned our attention to the use of platinum complexes.[8] The Pt-catalyzed enantioselective 1,2-diboration of alkenes has been only reported for terminal olefins.[8] It has been shown that disubstituted alkenes prevent the diboration. Interestingly, this lack of reactivity has been observed even in strained alkenes such as norbornene.[8c] Therefore, at the outset of the project, we were skeptical about the development of a platinum catalyzed enantioselective diboration of cyclobutenes **1**. We chose spirocyclobutene **1a** as a model substrate and taddol-derived phosphoramidites and phosphonites as ligands (Scheme 4), due to their success in the diboration of terminal alkenes. Phosphoramidite (*R*,*R*)-$\mathbf{L_1}$ provided the desired compound with moderate yield and low enantiomeric ratio. Switching to phosphonite (*R*,*R*)-$\mathbf{L_2}$ improved the yield and the enantioselectivity. After a fine tuning of the R group on the aromatic rings of the ligand ($\mathbf{L_2}$–$\mathbf{L_7}$), and the groups on the diol back-bond ((*R*,*R*)-$\mathbf{L_8}$) we found the best results using (*R*,*R*)-$\mathbf{L_3}$ (R = Et). Heating a solution of **1a**, $Pt(dba)_3$ (3 mol%), (*R*,*R*)-$\mathbf{L_3}$ (6 mol%), B_2pin_2 (1 equiv) in toluene at 55 °C smoothly afforded (*S*,*S*)-**2a** in excellent yield and good levels of enantiocontrol. We were pleased to find that a single recrystallization increased the enantiomeric ratio up to 98:2.

Compounds (*S*,*S*)-**2e**, (*S*,*S*)-**2g** and (*S*,*S*)-**2j** were prepared as representative examples of spirocycles with different connectors and different ring sizes, with enantiomeric ratios comparable to that observed for (*S*,*S*)-**2a** (Scheme 5). The enantiomeric ratio of compound (*S*,*S*)-**2e** was increased to 93:7 through a single recrystallization. Selective Suzuki–Miyaura cross-coupling reaction of (*S*,*S*)-**2e** provided enantiomerically enriched (*S*,*R*)-**3d** with perfect chirality transfer.[24]

In summary, we have disclosed the ability of spirocyclobutenes to provide a platform for the preparation of chiral spirocycles, through the diastereo- and enantioselective diboration of the double bond. Selective manipulation of the boryl moieties in the products allows unique control on the directionality and nature of the substituents on the spirocycle framework. This approach provides facile access to a wide variety of novel building blocks from a common intermediate. Further catalytic transformations of the spirocyclobutenes are ongoing and will be reported in due course.



Scheme 4. Preliminary validation of the enantioselective diboration. [a] Reaction conditions: **1** (0.1 mmol), B_2pin_2 (0.1 mmol), $Pt(dba)_3$ (3 mol%), (*R*,*R*)-Ligand (6 mol%), toluene (0.2 M), 55 °C, 16 h. Yield of isolated (*S*,*S*)-**2a**. e.r. determined by chiral-phase HPLC. [b] e.r. after a single recrystallization.



Scheme 5. Enantioselective diboration. [a] Reaction conditions: **1** (0.1 mmol), B_2pin_2 (0.1 mmol), $Pt(dba)_3$ (3 mol%), (*R*,*R*)-$\mathbf{L_3}$ (6 mol%), toluene (0.2 M), 55 °C, 16 h. Yield of isolated **2**. e.r. determined by chiral-phase HPLC. [b] e.r. after a single recrystallization.

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Conflict of interest

The authors declare no conflict of interest.

Keywords: boronic esters · cyclobutenes · exit vectors · spirocycles · Suzuki–Miyaura cross-coupling

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