Copper catalyzed borylative ring closing C-C coupling toward spiro- and dispiroheterocycles.

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ABSTRACT: The synthesis of novel spiroheterocyclic structures with a pendant methylene boronate substituent has been accomplished to promote further functionalization. A Cu-catalyzed borylative ring closing C-C coupling of an alkenyl halide is the key step towards the synthesis of [m.n]-spirocycles (m,n = 3−5). Computational studies on the mechanism reproduced all the experimental trends and explain the enhanced reactivity of systems leading to strained smaller rings. The optimized protocol also gives access to dispirocycle scaffolds, fully characterized by X-ray diffraction.

KEYWORDS spiroheterocyclic structures, borylative cyclization, DFT study, dispirocycle scaffolds, functionalization.

The synthesis and application of spirocyclic scaffolds are witnessing exponential growth due to their exclusive properties as dense and rigid structures with well-defined exit vectors that rigorously populate the three-dimensional chemical space.[1,2] Spirocyclic compounds have a high sp^3/sp^2 ratio thus facilitating the design of new classes of biologically-active molecules with improved properties. In general, the reduced lipophilicity of spirocyclic compounds compared to analogous cyclic molecules is related to their compactness, and can be even lowered by the presence of heteroatoms in the spirocycles. In addition spiroheterocycles have shown to be superior to traditional saturated heterocycles because of their unique structural advantages both in physicochemical properties and pharmacokinetic effects.[3]

As a privileged class of spirocycles, in this work we focus on the synthesis of [m.n]-spiroheterocyclic structures (m,n = 3−5) with a methylene boronate substituent bound to an all-carbon cyclic backbone, aiming to expand the pharmacopeia's chemical space of multifunctional cores. For the preparation of the target spiroheterocyclic structures we envisaged a synthetic strategy whereby an *O*- or *N*-containing heterocycle is already present in the starting material. The spirocylce would then be formed through a Cu-catalyzed borylative ring closing C-C coupling of an alkenyl halide moiety (Figure 1). Despite the fact that Cu-catalyzed borylative exo-cyclization had been previously explored to build spirocyclobutane rings onto saturated carbocycles,[4] only a single example leading to a spirocyclobutylpiperidine-based skeleton was reported.[4,5] In addition to cover the gap on spiroheterocyclic synthesis, we assume potential difficulties to form 5- and 6-membered spirocyclic rings. Density functional theory calculations (DFT) accompany the experiments to shed light to the reaction mechanism.

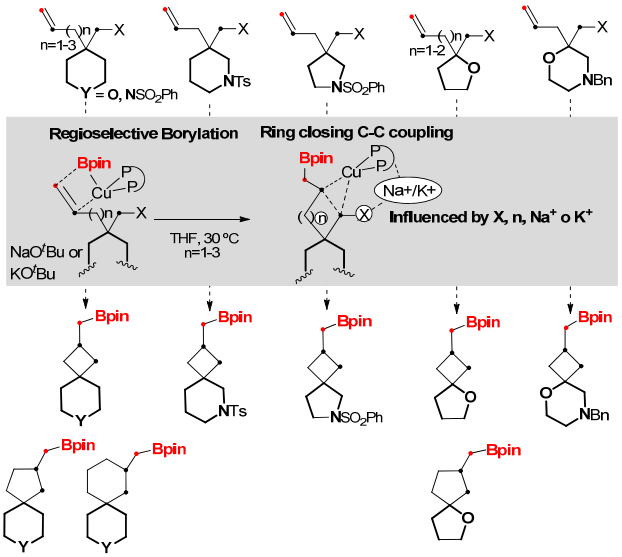
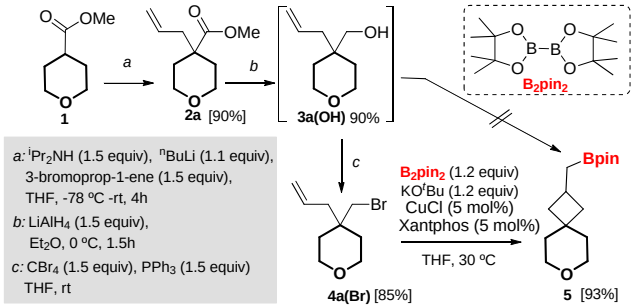


Figure 1. Synthesis of target spiroheterocyclic structures with a pendant methylene boronate substituent for subsequent functionalization

Once suitable conditions could be identified, this strategy would offer a route to prepare [m.n]-spiroheterocyclic structures (m,n= 3−5) with a methylene boronate substituent that could be used as a handle for functionalization towards primary

alcohols, aldehydes, acids and esters, or olefination using *gem*-bisborylsilyl methane species. Furthermore, attempts to synthesize dispirocyclic compounds by assembly of three different cyclic systems are also explored.

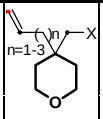
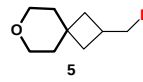
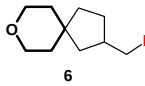
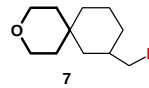
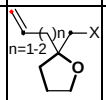
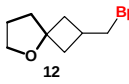
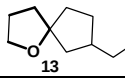
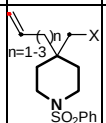
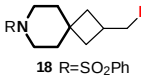
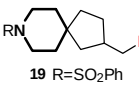
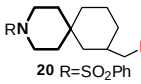
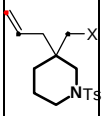
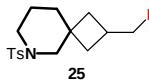
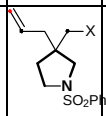
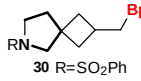
We started with the preparation of 2-methylboryl-7-oxaspiro[3.5]nonane (**5**) from the commercially available methyl tetrahydro-2H-pyran-4-carboxylate (**1**) via Cu-catalyzed borylative ring closing C-C coupling of the alkenyl halide intermediate (**4a(Br)**) (Scheme 1). Initially substrate **1** was alkylated with 3-bromoprop-1-ene, to form intermediate **2a** that was subsequently reduced to afford the OH functionality in **3a(OH)** (Scheme 1). Since the Cu/Xantphos-catalyzed borylative ring closing C-C coupling of **3a(OH)** was unsuccessful, we addressed the preparation of the corresponding alkyl halide. Gratefully, the brominated intermediate **4a(Br)** underwent the expected borylative exo-cyclization, producing 93% of target product **5** (Table 1, entry1). The borylative cyclization was found to compete with the borylative debromination,[6] observing the corresponding by-product in less than 5% yield. Switching from the originally used Xantphos ligand to PCy_3 or ^{t}Bu-Xantphos led to comparable isolated yields of the target spirocycle **5** (80% and 85%, respectively). The use of carbene ligands, such as 1,3-bis(2,6-diidopropylphenyl)-1,3-dihydro-2*H*-imidazol-2-ylidene (IPr), was unfavorable for the borylative cyclization leading to 67% isolated yield of **5**, (see SI). The use of other diboron reagents was also explored, however the borylative cyclization proved less efficient. Thus, the product **5(hex)**, derived from the reaction of **4a(Br)** with B_2hex_2 (hex= hexyleneglycolato), was isolated in 65% yield, whereas the use of B_2neop_2 (neop= neopentaneglycolato) led to compound **5(neop)** in 54% yield, (see SI).



Scheme 1. Synthesis of 2-methylboryl-7-oxaspiro[3.5]nonane (**5**) from methyl tetrahydro-2H-pyran-4-carboxylate (**1**). Isolated yields in brackets

The efficiency of the C-C coupling reaction to form a spirocyclic 5-membered ring (**6**) dropped to 45% from substrate with X=Br, (Table 1, entry 2). Nevertheless, the use of the corresponding iodinated intermediate accelerates the transformation, providing a higher isolated yield, namely 65% after 4h, which could be improved up to 80% after a prolonged reaction time of 16h (Table 1, entry 2). A similar effect had been reported in the palladium-catalyzed ring-forming aromatic C−H alkylations with unactivated alkyl halides.[7] The C-C coupling reaction to form the spirocyclic 6-membered ring in 8-methylboryl-3-oxaspiro[5.5]undecane (**7**) proved to be more challenging, and both brominated and iodated intermediates led to the target compound in moderate yields (Table 1, entry 3, 20-36%). However, it should be highlighted that the formation of **7** represents the first example of the Cu-catalyzed borylative ring closing C-C coupling leading to the formation of a 6-membered ring. The borylative spirocyclization reaction was also successfully carried out onto tetrahydrofurane rings. Thus, 2-methylboryl-5-oxaspiro[3.4]octane (**12**) and 7-methyl-1-oxaspiro[4.4]nonane derivatives (**13**) were prepared with comparable moderate isolated yields (Table 1, entries 4, 5).

Table 1. Synthetic approach to tetrahydropirane-, tetrahydrofurane-, piperidine- and pyrrolidine-containing spirocyclic compounds.[a]

Entry[a]	Substrate	n/X	Product	Time (h)	Yield [%][b]
1		n=1/ X=Br	 **5**	4	93%
2		n=2/ X=Br n=2/ X=I n=2/ X=I	 **6**	4 4 16	45% 65% 80%
3		n=3/ X=Br n=3/ X=I n=3/ X=I	 **7**	4 4 16	20% 28% 36%
4		n=1/ X=I	 **12**	16	45% (1:1 dr)
5		n=2/ X=I	 **13**	16	54% (6:1 dr)
6		n=1/ X=Br	 **18** R=SO_2Ph	4	93%
7		n=2/ X=Br n=2/ X=Br n=2/ X=I	 **19** R=SO_2Ph	4 16 4	42% 55% 60%
8		n=3/ X=Br	 **20** R=SO_2Ph	4	35%
9		n=1/ X=Br	 **25**	4	62% (1:1 dr)
10		n=1/ X=Br	 **30** R=SO_2Ph	4	60% (1:1 dr)

[a]Conditions for the whole sequence of reactions as shown in Scheme 1: *alkylation*: ^{i}Pr$_2$NH (1.5 equiv), ^{n}BuLi (1.1 equiv), 3-bromoalk-1-ene (1.5 equiv), THF, -78 ºC-rt, 4h. *reduction*: $LiAlH_4$ (1,5 equiv), Et_2O, 0 ºC, 1.5h; *bromination*: CBr_4 (1.1 equiv), PPh_3 (1.1 equiv), THF, 0 ºC-rt, 12h. *iodination*: I_2 (1.05 equiv), imidazole (1.05 equiv), PPh_3 (1.5 equiv), THF, 80 ºC, 12h. For Cu-catalyzed borylative ring closing C-C coupling: substrate (0.2 mmol), B_2pin_2 (1.2 equiv), CuCl (5 mol%) Xantphos (5 mol%), KO^{t}Bu (1.2 equiv), THF, 30 ºC, t. [b]Isolated yield

The formation of new spiro-fused rings based on a piperidine and pyrrolidine backbones has also been studied. The reactivity of these compounds followed a similar trend to

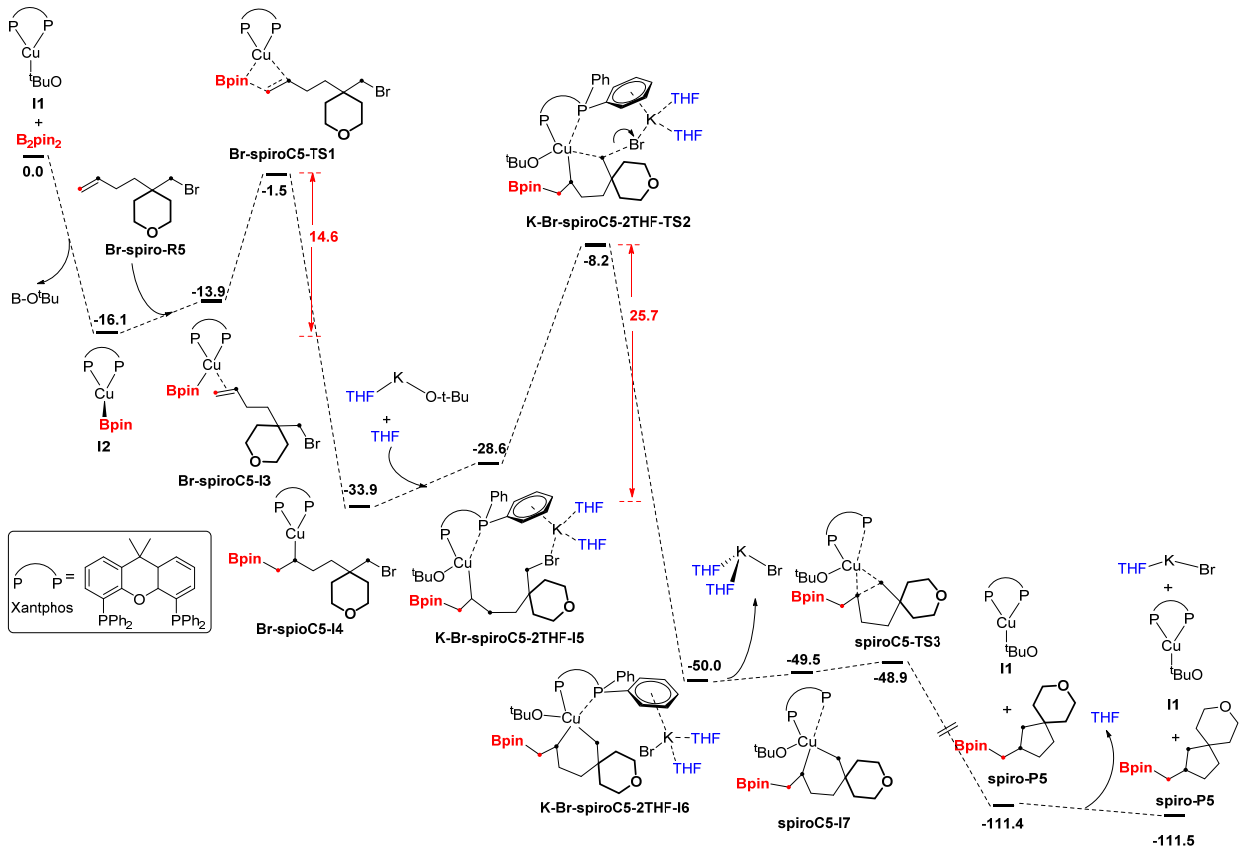
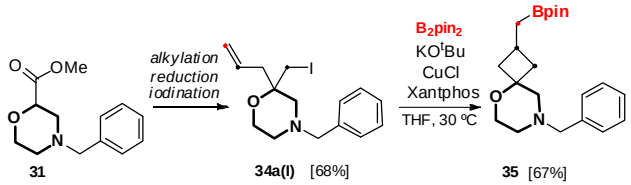


Figure 2. Computed free energy profile (in kcal mol^{-1}) for the formation of the 5-membered ring product **6** in Table 1(entry 2) with Br as the leaving group and KO^{t}Bu as base (with the coordination of two THF).

that observed for the cyclic ethers and again while the formation of the four, five[8] and six membered ring could be achieved, the cyclization efficiency decreased with increasing target ring size (Table 1, entries 6-8). As far as the base is concerned, KO^{t}Bu was found to be optimal, since the related NaO^{t}Bu proved to be less efficient, leading to increased amounts of the borylative debromination by-product. Negligible conversion towards the spiricyclization product was observed with LiO^{t}Bu. The use of the alkenyl iodide favours the Cu-catalyzed borylative ring closing C-C coupling, in comparison to the alkenyl bromide derivative (Table 1, entry 7). To study the effect of the N position in the heterocycle, we conducted the synthetic sequence from ethyl 1-tosylpiperidine-3-carboxylate **21** and ethyl 1-(phenylsulfonyl)pyrrolidine-3-carboxylate **26**, showing that the spiroheterocyclic compounds **25** and **30** can be obtained in similar moderate yields (62% and 60%, respectively, Table 1, entries 9 and 10).



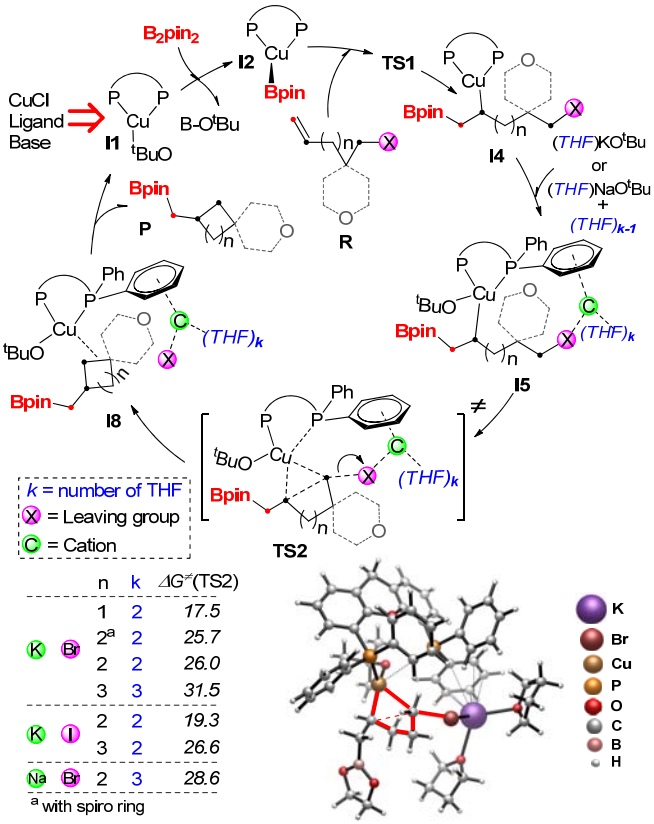
Scheme 2. Synthesis of 8-benzyl-2-methylboryl-5-oxa-8-azaspiro[3.5]nonane (**35**). Isolated yields in brackets, conditions for alkylation, reduction and iodination as in Table 1.

Next, we conducted the synthesis of a spirocyclized morpholine derivative starting from methyl 4-benzylmorpholine-2-carboxylate (**31**) (Scheme 2). Alkylation with 3-bromoprop-1-ene, followed by reduction of the ester group and iodination, allowed the access to the key intermediate **34a(I)**. This species successfully underwent the Cu-catalyzed borylative exo-cyclization to furnish the 8-benzyl-2-methylboryl-5-oxa-8-azaspiro[3.5]nonane (**35**) in 67% isolated yield.

The reactivity is shown thus to depend non-trivially on a variety of factors, which prompted us to carry out a DFT study on the reaction mechanism.[9-11] Calculations in solution (THF) were carried out with the ωB97X-D functional and a valence triple-ζ basis set complemented with polarization and diffuse functions.[12] A data set collection of computational results is available in the ioChem-BD repository.[13] A total of 28 different free energy profiles (Figures S1 to S28 in the Supporting Information) were computed varying the nature of the organic reactant **R**, the leaving group **X**, the counter-ion **C** in the base as well as the number of explicit THF molecules in the calculation. We constrained our study to systems with one single copper center and one single alkaline cation. We admit more complex polynuclear systems may be at play, but we expect the behaviour of these systems to be representative.

A representative free energy profile is presented in Figure 2, and the general features of the mechanism, which are in all cases similar are shown in the reaction diagram in Figure 3. The starting point is intermediate **I1,** the diphosphine copper(I) alkoxide complex that must be readily obtained upon mixing CuCl, the base and the Xantphos ligand. The corresponding Cu-B species **I2** would then form readily through a reaction of **I1**

with B_2pin_2. The key steps in the catalytic cycle are the insertion of the C=C double bond of reactant **R** into the Cu-B bond *via* transition state **TS1**, and the mostly concerted step consisting of halogen abstraction and ring closure through transition state **TS2**. Remarkably, we were able to optimize the Cu(III) intermediate proposed by Ito and co-workers[4,5] in approximately half of the systems (Figures S1-S8, S17-S20), and it corresponded in all cases to a shallow well. This intermediate is shown in Figure 2 as intermediate **I7**, and contains the expected two Cu-C bonds. It has a barrier of less than 2 kcal mol-1 for reductive elimination, so it is not kinetically relevant. The highest barrier in the catalytic cycle is measured as the difference between **TS2** and **I4**, and decides the overall efficiency of the process. It is worth noting the presence of the alkaline cation in **TS2**. Alternative mechanisms without involvement of the cation were found to have significantly higher barriers. We considered also the possibility of a Heck-type mechanism,[14-15] with initial activation of the substrate through the C-X bond rather than from the double bond. The free energy profile corresponding to the activation of the C-Br bond in **Br-spiro-R5** (Figure 2) by **I2** indicates a barrier of 34.5 kcal mol^{-1} (see Figure S29), much higher than that for the mechanism in Figures 2 and 3.



	n	k	$\Delta G^{\neq}$(TS2)
K Br	1	2	17.5
	2[a]	2	25.7
	2	2	26.0
	3	3	31.5
K I	2	2	19.3
	3	2	26.6
Na Br	2	3	28.6

[a] with spiro ring

Figure 3. Computed overall mechanism of the Cu-catalyzed exo-cyclization process and reaction barriers (kcal mol^{-1}) for the rate determining step (**I4** → **TS2**)

Our first set of calculations (Figure 2 and Figures S1-S4) was carried out on the experimental system leading to the formation of the 5-membered ring spirocyclic product **6**, shown in Table 1, entry 2. We evaluated the validity of our model by introducing different numbers of solvation molecules, and we found the case with two THF units to be favored, with an associated free energy barrier of 25.7 kcal mol^{-1} (Figure S3). This value is in line with a reaction producing a 45% yield after 4 h at 30 °C. We then checked the role of the connected spiro ring by replacing it by two hydrogen atoms, and found a very minor effect in the barrier, which increased only by 0.3 kcal mol^{-1} (*i.e.* to 26.0 kcal mol^{-1}, Figure S7). Thus, subsequent calculations on other systems were carried out with a simplified model lacking the spiro connection. The resulting barriers are summarized in the Table included in Figure 3.

The overall barriers corresponding to the formation of the 4- and 6-membered ring products with the same leaving group and base are 17.5, and 31.5 kcal mol^{-1}, respectively. The experimental trend in favor of smaller rings (93%, 45%, and 20% yields for 4-, 5-, 6-membered rings) is clearly followed qualitatively by the computed barriers of 17.5, 26.0 and 31.5 kcal mol^{-1}. Differences in barriers are certainly larger than expected, but we must mention that the isolated yield of 93% for the 4-member ring corresponds in practice to quantitative conversion, and the 20% observed for the 6-membered ring may come from a different reaction path. A simple qualitative explanation on the preference for the more strained small rings can be made from inspection of the 3-D drawing in Figure 3. The increasing negative charge of the leaving bromide group is stabilized by the nearby presence of the potassium cation, which is also interacting with phenyl rings attached to the phosphines. The formation of the 4-membered ring brings naturally the bromide in the vicinity of potassium. This is not the case for the transition states leading to the 5- and 6-membered rings. The organic chains in these systems have to distort, with the subsequent energy penalty, to keep the attractive interactions.

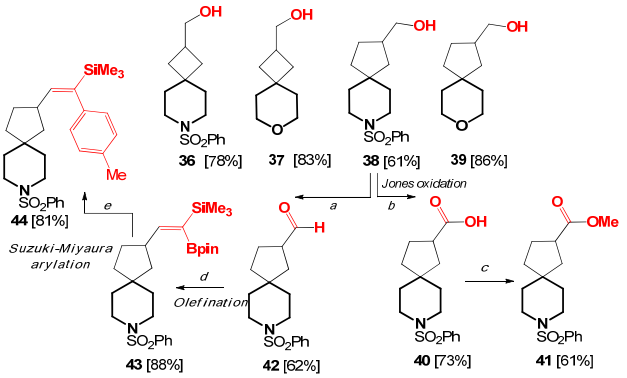
Next, we analyzed the influence of the leaving group by replacing bromide by iodide. As summarized in Figure 3, the barriers of the rate determining steps for the formation of the 5- and 6-membered ring products are 19.3 and 26.6 kcal mol^{-1}, which are lower than those reported above using Br as the leaving group (26.0 and 31.5 kcal mol^{-1}, respectively). This correlates well with the increased experimental reactivity of the iodinated systems. We attribute this result to the lower strength of the C-I bond. Finally, we studied computationally the role of the alkaline ion through the replacement of potassium by sodium. For the system leading to the formation of a 5-membered ring (n=2), the barrier increases by 2.6 kcal mol^{-1}, going from 26.0 to 28.6 kcal/mol. This reproduces the experimental sluggishness of the reaction conducted using NaO*t*Bu as base, and confirms the relevance of the cation in the key transition state **TS2**. The 3-D drawing in Figure 3 indicates that the size of the cation is important for the interactions, highlighting that potassium seems more adequate for these particular systems.

It would be certainly interesting to have direct experimental proof of the involvement of the alkaline cations in the reaction mechanism through characterization of the corresponding adducts. However, according to the free energy profile in Figure 2, these complexes are transient species with very short life time in the reaction media, thus very difficult to characterize.

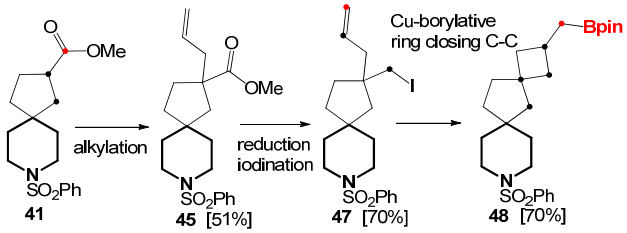
To demonstrate the potential avenue to functionalize the newly formed spiroheterocyclic boronate compounds, we conducted the oxidative work-up thereby producing the corresponding hydroxylated products **36**-**39** in high isolated yields (Scheme 3). Further functionalization can be carried out by oxidizing the primary alcohol to an aldehyde,[16] acid[2] or ester group,[17] as can be seen in the transformation of **38** into products **40**-**42**. The aldehyde **42** was conveniently transformed into the poly-substituted olefin through recently described olefination

strategy that is based on the deprotonation of $HC(Bpin)_2(SiMe_3)$ species to generate a boron and silicon stabilized carbanion, able to add to the carbonyl functionality on **42**.[18] Upon such addition the B-O elimination took place to give the *gem*-silaborated structure **43**. Finally, a Suzuki–Miyaura cross coupling of **43** with 4-iodotoluene, in the presence of $Pd(PPh_3)_4$, KOH, in 1,4-dioxane as solvent, at 90 ºC over 16 h, produced the corresponding multisubstituted olefin **44** with total control of the setereoselectivity (Scheme 3).[19-21]

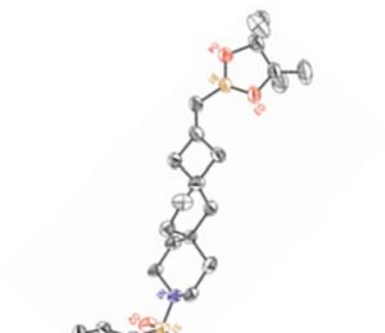
Finally, given that dispirocycle scaffolds are present in many natural products with biological activity we became interested in applying the iterative Cu-catalyzed borylative ring closing C-C coupling to form a dispirocyclic motif containing a methylboronate functionality and 3 different sized rings, one of which would be heterocyclic. Indeed, the spirocyclic ester **41** could be further elaborated through alkylation, reduction and iodination, into compound **47**, which underwent intramolecular borylative cyclization to form a new 4-membered ring (Scheme 4). The structure of product **48**, was fully characterized by standard analysis and X-ray diffraction (Scheme 5) confirming the presence of the spiro-fused four-, five-, and six-membered rings. Notably the last piperidine core is a heterocyclic motif ubiquitously present in most common dispirocycles employed in medicinal chemistry and agrochemicals.[22-25]



Scheme 3. Functionalization of spiroheterocyclic boronate copounds towards alcohols, aldehydes, acids and esters, as well as trisubstituted olefins. Isolated yields in brackets.



Scheme 4. Isolated yields in brackets, conditions for alkylation, reduction, iodination and Cu-borylative ring closing C-C, as Table 1.



Scheme 5. ORTEP of the X-ray diffraction analysis for dispirocycle **48**.

Through the present study, it can be concluded that Cu-catalyzed borylative ring closing C-C coupling of alkenyl halides allows for the synthesis of target [m.n]-spiro *O*- or *N*-containing heterocyclic structures (m,n = 3−5) bearing a methylene boronate substituent suitable for further functionalization. Computational studies identify the key steps in the catalytic cycle and rationalize the preference of the reactions leading to the strained smaller rings. The optimized protocol gives access to a dispirocyclic tricyclic structure that could be fully characterized by X-ray diffraction.

ASSOCIATED CONTENT

Supporting Information includes Experimental Procedures and Spectra data, ^{1}H, ^{13}C and ^{11}B spectra images, Computational Studies and X-Ray Diffraction data. This material is available free of charge via the Internet at http://pubs.acs.org.

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