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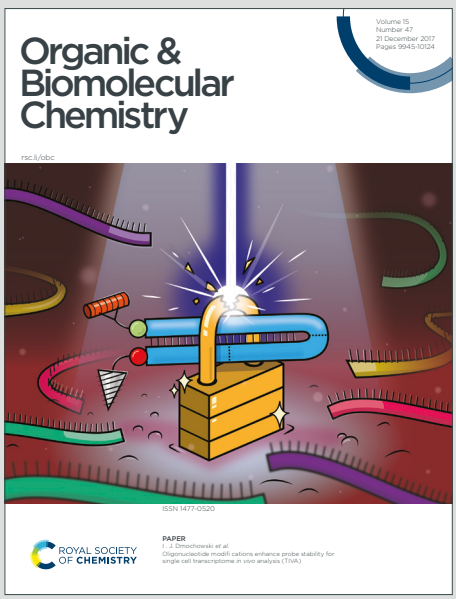




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ARTICLE

# Highly diastereoselective entry to chiral oxindole-based β-amino boronic acids and spiro derivatives

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Marco Manenti, Stefano Gazzotti, Leonardo Lo Presti, Giorgio Molteni and Alessandra Silvani*

**We here describe the first Cu-catalysed, diastereoselective 1,2-addition of 1,1-diborylmethane to chiral ketimines for the synthesis of quaternary stereocenters and spiro compounds. The method provides easy access to a range of chiral, highly functionalized compounds, namely oxindole-based β,β'-disubstituted β-amino boronates, boron-containing peptidomimetics and six-, seven-membered spirocyclic hemiboronic esters. Such unprecedented compounds are mostly obtained in high yields and easily isolated as single diastereoisomers, paving the way to a more intense exploitation of boron-containing compounds in diversity-oriented chemistry and drug-discovery programs. Concerning stereochemistry, the application of Ellman's auxiliary strategy allows in principle to access both steric series of target compounds.**

## Introduction

In recent years, aminoboronic acids have gained unprecedented value as synthetic precursors, biochemical probes and drugs. In addition to the wide applicability of boron-containing compounds[1] due to the peculiar properties of electrophilic boron and nucleophilic C–B bond,[2] the rationale for the biological relevance of aminoboronic acids relies on bioisosterism with amino acids.[3,4] Depending on the state and hybridization of boron, several possibilities of reversible covalent interactions with nucleophilic amino acid residues are possible, supporting the possible use of aminoboronic acids as drugs. Most developments aim at the use of aminoboronic acids in the field of protease inhibition. In 2003, the first boron-containing agent, the proteasome inhibitor bortezomib, gained FDA approval and entered the market for the treatment of multiple myeloma (Figure 1).[5] Since then, the analogous mechanism of inhibition in serine proteases has led to a wide range of compounds endowed of pharmacologically relevant properties, mainly anticancer,[6] antiviral,[7] and antibacterial,[8,9] with several drug candidates in various phases of clinical trials. Boron-containing peptidomimetics have also been described to interact effectively with the binding site of SARS-CoV-2 main protease,[10] suggesting the testing of available boron-containing drugs in patients with severe symptoms of COVID-19 infection.[11]

Just as more common α-aminoboronic acids[12] are bioisosteres of α-amino acids, β-aminoboronic derivatives can be considered bioisosteres of β-amino acids, which suggests significant potential in drug discovery. Indeed, as incorporation of β-amino acids into peptides is an effective way to create peptidomimetics that display various biological activities, in a similar way β-amino boronate peptidomimetics can be developed, taking also further advantage from the better stability of free β-amino boronic acids, with respect to α- ones.[13] The first proof-of-concept for the use of β-amino boronic acids in drug discovery was brought in 2013, when a variety of peptidyl β-aminoboronic derivatives were described to display relevant antitubercular activity.[14] Since then, some reliable and efficient synthetic strategies for their preparation have been described,[15,16] but they still need to be developed in order to have an impact in drug discovery programs.

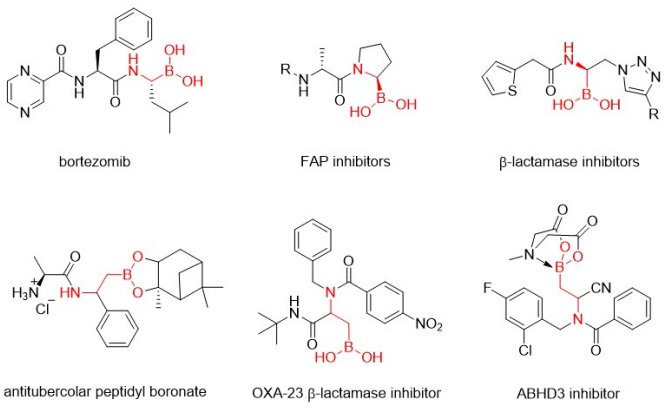


**Figure 1**. Examples of biologically relevant compounds containing the α- and β-amino boronic moiety

*Dipartimento di Chimica, Università degli Studi di Milano, Via Golgi 19, Milano, 20133, Italy. E-mail: alessandra.silvani@unimi.it.*

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Within this context, our long-standing studies on the asymmetric synthesis of 3,3-disubstituted oxindole derivatives and related spiro compounds,[17] combined with the growing interest in β-amino boronic acids as therapeutic agents,[18] inspired us to a molecular hybridization strategy, that is to merge the two biologically relevant oxindole and β-amino boronic moieties into a new scaffold, with the aim to access unexplored and potentially drug-like chemical space. Incorporation of boron atom within chiral oxindoles has been reported only quite recently, exploiting Cu-catalyzed enantioselective intramolecular transformations.[19]

Relying on our previous experience with isatin-derived, optically pure sulfinyl ketimines, we looked at the nucleophilic addition of 1,1-diborylalkane-derived organometallic derivatives, as a way to access oxindole-based β-aminoboronates. In 2016 Cho and co-workers reported the first diastereoselective Cu-catalyzed 1,2-addition of 1,1-diborylmethane to Ellman's chiral imines,[20] while the first diastereoselective addition of lithiated 1,1-diborylalkanes onto sulfinyl aldimines was described by Li and Hall in 2018.[21]

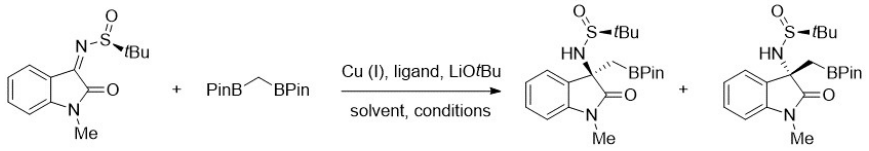
Although the application of both these strategies is remarkable, to the best of our knowledge, no diastereoselective reactions have been described for the preparation of β,β-disubstituted β-aminoboronates, which means employing ketimines as substrates. Herein we first demonstrate the suitability of chiral, isatin-derived tert-butanesulfinyl ketimines for reaction with 1,1-diborylmethane-derived organometallic derivatives, applying these reactions to the synthesis of unprecedented, enantiopure 3-amino, 3-boromethyl-oxindoles and derived spiro hemiboronic heterocycles.

## Results and Discussion

We began our investigation using the known (*S*)-1-methyl-isatin-derived *N-tert*-butanesulfinyl ketimine **1a**, 1,1-diborylmethane, lithium tert-butoxide and various Cu catalysts and ligands, as reported in Table 1.

The first reaction was carried out at 50 °C in toluene, with CuCl and 1,2-bis(diphenylphosphino)benzene (DPPBn), as described by Cho and co-workers, and the desired β-amino-boronate was isolated in 80% yield, with a slight prevalence of diastereoisomer **2aa** (entry 1). Since the reaction proved to proceed smoothly also at room temperature (entry 2), we next considered the role of the solvent, switching first to 1,4-dioxane and THF (entries 3 and 4) and finally to the optimal 1:1 mixture of THF and toluene (entry 5). From a mechanistic perspective, we could verify that, in absence of both the Cu catalyst and the ligand, the reaction did not lead to any product, dispelling the doubt that the poor diastereoselectivity could be due to the competitive reaction of the α-borylcarbanion (generated from 1,1-diborylmethane and LiO*t*Bu) in a metal-free process (entry 6).

**Table 1**. Survey of the reaction conditions for the reaction of isatin ketimine **1a** with 1,1-diborylmethane in the presence of Cu catalysts.[a]




**1a** **2aa** **2ab**

| Entry | Cu (I) | ligand[e] | Solvent | temperature | time | yield[b] (%) | dr[c] (**2aa** : **2ab**) |
|---|---|---|---|---|---|---|---|
| 1 | CuCl | 1,2-Bis(diphenylphosphino)benzene | toluene | 50°C | 4h | 80 | 58:42 |
| 2 | CuCl | 1,2-Bis(diphenylphosphino)benzene | toluene | r.t. | 4h | 84 | 61:39 |
| 3 | CuCl | 1,2-Bis(diphenylphosphino)benzene | 1,4-dioxane | r.t. | 4h | 93 | 54:46 |
| 4 | CuCl | 1,2-Bis(diphenylphosphino)benzene | THF | r.t. | 4h | 95 | 56:44 |
| 5 | CuCl | 1,2-Bis(diphenylphosphino)benzene | THF/toluene (1:1) | r.t. | 4h | 96 | 63:37 |
| 6 | - | 1,2-Bis(diphenylphosphino)benzene | THF/toluene (1:1) | r.t. | 18h | n.d. | n.d. |
| 7 | CuCl | 1,2-Bis(diphenylphosphino)benzene | THF/toluene (1:1) | 0 °C | 4h | 46 | 26:74 |
| **8** | **CuCl** | **Tricyclohexylphosphine** | **THF/toluene (1:1)** | **0 °C** | **1h** | **97** | **5:95** |
| 9[d] | CuCl | Tricyclohexylphosphine | THF/toluene (1:1) | 0 °C (to rt) | 3h | 84 | 80:20 |
| 10 | CuCl | PhDavePhos | THF/toluene (1:1) | 0 °C (to rt) | 18h | 5 | 50:50 |
| 11 | CuCl | Xantphos | THF/toluene (1:1) | 0 °C (to rt) | 48h | n.d. | n.d. |
| 12 | CuCl | 2,2'-bipyridine | THF/toluene (1:1) | 0 °C (to rt) | 48h | n.d. | n.d. |
| 13 | CuCl | (±)-BINAP | THF/toluene (1:1) | 0 °C (to rt) | 4h | 44 | 78:22 |
| 14 | CuCl | Tri(2-furyl)phosphine | THF/toluene (1:1) | 0 °C (to rt) | 18h | n.d. | n.d. |
| 15 | CuCl | 2'-(diphenylphosphino)-N,N-dimethyl[1,1'-binaphtalen]-2-amine | THF/toluene (1:1) | 0 °C (to rt) | 3h | 72 | 52:48 |
| 16 | CuCl | Tris(o-tolyl)phosphine | THF/toluene (1:1) | 0 °C (to rt) | 6h | <5 | 50:50 |
| 17 | CuCl | Tri-tert-butylphosphine | THF/toluene (1:1) | 0 °C (to rt) | 6h | 53 | 83:17 |
| 18 | CuI | Tricyclohexylphosphine | THF/toluene (1:1) | 0 °C | 1h | 45 | 22:78 |

**Table 1**: [a] Reagents and conditions: **1a** (0.2 mmol), $CH_2(BPin)_2$ (1.5 equiv), Cu salt (10%), Ligand (10%), LiOtBu (3.0 equiv) in solvent (0.4M). [b] isolated yields. [c] Determined by $^1H$ NMR of the crude material. [d] Reaction conduced with 5% of both CuCl and $P(Cy)_3$. [e] For ligands' chemical structures, see supporting information (SI).

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In our ongoing screening of reaction conditions, we realized that, by lowering the reaction temperature to 0 °C, the β-amino-boronate was achieved in a lower yield but in higher dr, with reversal of the stereochemical outcome and prevalence of diastereoisomer **2ab** (entry 7). Encouraged by the rise of diastereoselectivity at 0°C but needing to increase the reactivity of the organometallic species, we set up to investigate the effect of alternative phosphine ligands. Turning from DPPBn to monodentate and electron-rich tricyclohexylphosphine ($P(Cy)_3$), the reaction was complete within one hour, with the de raising up to 90% (entry 8). Also, the direction of asymmetric induction was confirmed opposite to that observed at room temperature, thus suggesting a kinetic diastereocontrol for this reaction at 0°C. Given such a short reaction time, we considered reducing the molar percentage of phosphine ligand and Cu catalyst, with respect to substrate **1a**. However, when $P(Cy)_3$ and CuCl was lowered from 10 to 5% mol, the reaction became slower and, upon raising at room temperature, a drop of dr was observed (entry 9). Next, we evaluated various commercially available phosphines, both monodentate and bidentate, in combination with CuCl, but in all cases yields decreased and diastereoselectivity was poor (entries 10-17). Finally, switching from CuCl to CuI, in the presence of the most performing $P(Cy)_3$ ligand, resulted in lower yield and diastereoselectivity (entry 18).

As usual for these kinds of studies, we also proceeded to a scale-up experiment, employing 2 mmol of ketimine **1a** (reaction conditions as reported in Table 1, entry 8). After one hour, the desired β-amino-boronate **2ab** was obtained almost quantitatively, in the optimal diastereoisomeric ratio, identical to that on the small scale.

With the best conditions reported in entry 8 in hands, the scope of the reaction with respect to the *N-tert*-butanesulfinyl imine substrate was next explored (Table 2).

In general, the nature of the protecting group on the oxindole nitrogen was found to have a moderate effect on both yields and drs (**2a-d**), with best diastereoselectivities achieved with allyl (**2b**) and trityl (**2d**) $R^1$ substituents. Evidently, more cumbersome groups at that position, with respect to methyl, have a steric matching effect with the chiral auxiliary *tert*-butanesulfinyl moiety. Moving to N-methyl ketimines substrates bearing substituents on the aromatic ring, moderate to good yields of the corresponding β-amino-boronates were achieved in the presence of a variety of substituents, including alkyl groups (**2e**), electron-donating groups (**2f**) and halogen substituents (**2g**, **2h**, **2j**), with lower diastereoselectivity in the case of the 6-OMe oxindole derivative. Substitutions at all C4, C5, C6 and C7-aromatic ring position were evaluated and found compatible with the good performance of the reaction. Slightly lower yields were obtained with the Cl-substituent at C4 (**2g**), likely for reasons of steric hindrance, and with both substituents at C7 (**2i**, **2j**). In the latter cases, some traces of not containing boron, unidentified by-products were detected during the reaction. Anyhow, acceptable results were also obtained in the presence of the pharmaceutically relevant, but significantly electron-withdrawing, $CF_3$ group at C7 position (**2i**).

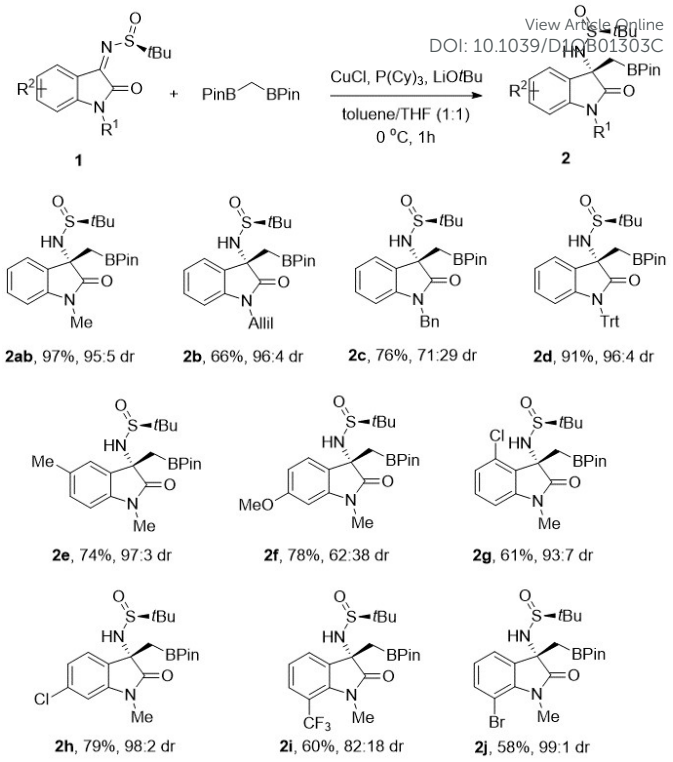
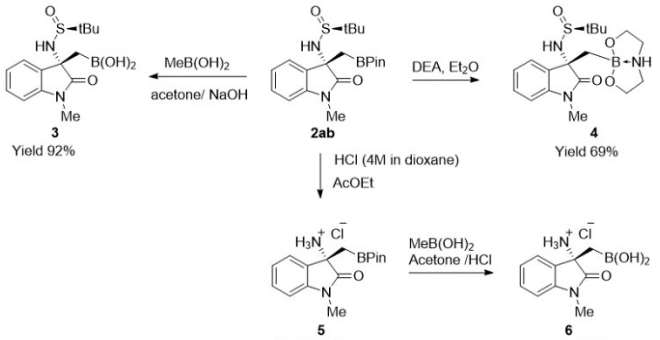



**Table 2**. Substrate scope of the CuCl-catalysed reaction of isatin ketimines 1 with 1,1-diborylmethane

To demonstrate the synthetic utility of β-amino-boronates **2**, both exploiting the C-3 amino group and the boronic acid functionality, a series of transformations were pursued, as reported in Scheme 1. Starting from compound **2ab**, deprotection of boron pinacolate with methyl boronic acid in basic conditions afforded the quite stable, β-amino-boronic acid derivative **3**, while transesterification with diethanolamine (DEA) provided cleanly the nitrogen-coordinating cyclic boronic diester **4**. DEA boronic esters were developed quite recently by AstraZeneca as promising large-scale alternative to pinacol boronic esters, thanks to their facile preparation, remarkable air stability and favourable solubility profile. On the other hand, selective removal of the sulfinyl moiety from **2ab** afforded amine hydrochloride **5** and can be followed by treatment with methyl boronic acid in acidic conditions, to provide the completely deprotected β-amino-boronic acid hydrochloride **6**.




**Scheme 1**. Selective auxiliary and protective groups removal on β-amino boronate **2ab**

Since β-amino-boronates **2** and derivatives failed to provide adequate crystals, due to a high solubility in a range of organic solvents, the determination of the quaternary C-3 oxindole absolute configuration was carried out through the Mosher NMR protocol, starting from amine **5**. From NMR data of the corresponding Mosher (*R*)- methoxy-α-trifluoromethyl-α-phenylacetic acid (MTPA) and (*S*)-MTPA derivatives, the C-3 (*S*)-configuration can be unambiguously assigned (see SI for details).

In order to elucidate such stereochemical outcome, we refer to the established mechanism for copper-catalysed additions of organoboron reagents to C=N bonds. On the basis of the observed diastereoselectivity, a chair-like six-membered cyclic transition state (TS) was considered, in accordance with the one proposed by Cho and co-workers for addition to aldimines[20a] (Figure 2). In this model, the boron atom of the 1-copper-1-borylmethane intermediate, arising from the initial, base-promoted reaction between 1,1-diborylmethane and copper(I) catalyst, may coordinate to the oxygen atom of the sulfinyl moiety. The observed remarkable diastereoselectivity can then be accounted for by considering the steric congestion caused by both the phosphine ligands bound to the copper and the pinacolate boronic ester, as well as taking into account the stereodirecting effect of the *tert*-butyl group. Indeed, all these bulky substituents should be able to impart a certain degree of structural rigidity to the TS, which is necessary in order to achieve a high stereoselectivity. Within this picture, the C-nucleophile attack occurs from the less hindered *Re*-face of the ketimine, then originating the (*S*)-stereocenter in the 3-position of the oxindole nucleus.

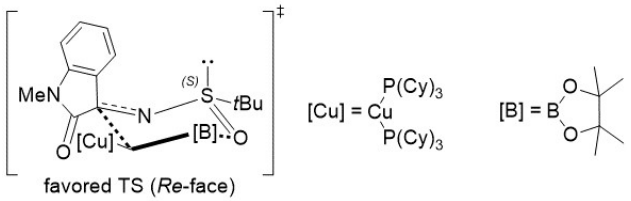
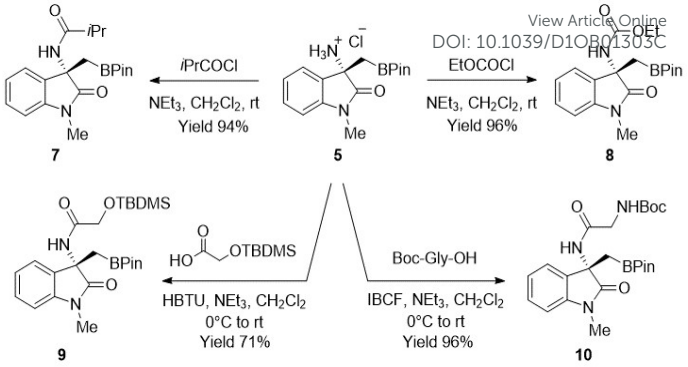



**Figure 2**. Plausible rationale for the observed stereochemical outcome

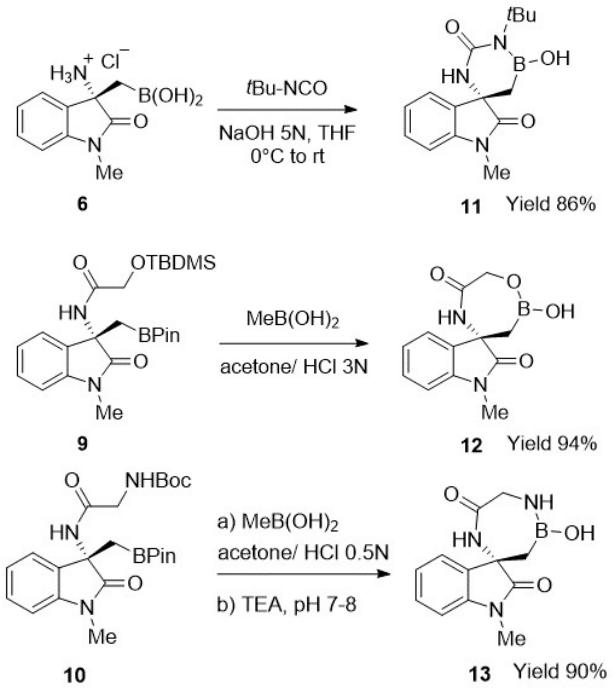
Going on with post transformation reactions, the amine hydrochloride **5** proved to be a versatile intermediate, well suited for condensation reactions, acquiring huge potential as a privileged motif in boron-containing peptidomimetic chemistry. As shown in Scheme 2, compound **5** was found to react smoothly with acyl chlorides, affording the synthetically useful amide and carbamate derivatives **7** and **8** in high yields. Further, it could be easily condensed with both OH-protected glycolic acid and N-Boc glycine, allowing to obtain the highly functionalized, quite stable derivatives **9** and **10**, respectively (Scheme 2).




**Scheme 2.** Condensation reactions starting from amine hydrochloride **5**

Finally, being aware of the growing importance of saturated boron heterocycles, recently highlighted by the approval of the antibiotic vaborbactam,[22] the conversion of 3,3-disubstituted derivatives into different spiro compounds was pursued.

Starting from the completely deprotected β-amino-boronic acid hydrochloride **6**, reaction with *t*-butyl isocyanate led smoothly to the formation of the six-membered, hemiboronic spiro-heterocycle **11** (Scheme 3). Treatment of compound **9** with methyl boronic acid, followed by HCl 3N, efficiently removed protecting groups and afforded the seven-membered cyclic boronic ester **12**. Analogously, peptidomimetic derivative **10** could be easily converted into the corresponding seven-membered spiro-derivative **13**, definitely highlighting the versatility of the oxindole-based β-amino boronic acids in the synthesis of boron heterocycles (Scheme 3).




**Scheme 3**. Synthesis of spirooxindole-based boron heterocycles

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## Conclusions

An efficient asymmetric preparation of unprecedented, chiral oxindole-based β-amino boronic acids and spiro derivatives has been developed, based on a diastereoselective, Cu-catalysed addition of 1,1-diborylmethane to isatin ketimines. The method provides easy access to a range of highly functionalized compounds, which are obtained in high yields and easily isolated as single diastereoisomers. By taking advantage of chiral auxiliary removal and subsequent condensation reactions, the rapid construction of various boron-containing peptidomimetic derivatives was demonstrated. Finally, for the first time, spirocyclic, six- and seven-membered hemiboronic esters were easily achieved. Relying on these results, further work is currently underway, aimed at establishing oxindole-based β-amino boronic acids and corresponding spiro derivatives as possible lead compounds for drug discovery programs.

## Conflicts of interest

There are no conflicts to declare.

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