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Enantio- and diastereoselective synthesis of β-substituted-δ-aminoboronic esters from nitriles ☆

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ABSTRACT

The first stereocontrolled synthesis of the title δ-aminoboronic esters—proceeding from commercially available nitriles—via a reduction, Brown's 'allyl' boration reaction, a Boc-protection, a hydroboration, an oxidative elimination of α-pinene, and an esterification reaction, has been reported in excellent enantio- and diastereoselectivities.

Aminoboronic acids have been shown capable of mimicking natural amino acids, and have also been demonstrated to act as bioisosteres in many biochemical reactions.[1,2] These unusual amino acid mimetics can function as potent inhibitors of several enzymes, and can also effectively serve as immunosuppressants. α-Aminoboronic acids have also recently acquired special pharmaceutical significance with the recent approval of bortezomib (Velcade™) (Fig. 1), the first boron-containing compound to be approved for pharmaceutical use by the FDA. Indeed, bortezomib has shown its potential to function as a successful proteasome inhibitor.[3] Owing to the clear and growing importance of aminoboronic acids in various areas of medicinal chemistry, several classes of these important molecules have been synthesized.[3,4] Despite this recent interest, there remains only a limited amount of literature precedence for the asymmetric preparation of aminoboronic acids.[5]

The preparation of functionalized aminoboronic acids has remained challenging. While a few methods have been reported for the preparation of α-,[6] β-,[7] and γ-aminoboronic acids,[7] the preparation of δ-aminoboronic acids and esters remains almost entirely unexplored. In perhaps the most significant example of the latter, Vaultier and co-workers reported the preparation of simple δ-aminoboronic acids by the reduction of azide-containing boronic esters in a series of two papers.[8] Their synthetic route, shown in Scheme 1, involved the hydrodibromoboration of a halide-containing alkene, followed by hydrolysis, azidation, and hydrogenative reduction. One consequence of this synthetic route is that the use of primary azides necessitates that the resultant δ-aminoboronic acids remain achiral.

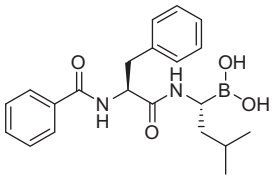

Figure 1. Bortezomib (Velcade™).

It is not inconceivable that this group of interesting compounds remains underreported in the literature because their synthesis can be difficult. Quite possibly, this is due to the fact that these compounds are often unstable, and to the incompatibility of the varying functional groups that are needed to serve as synthetic handles during their synthesis.[9]

As part of a separate research project in our laboratory, we recently developed and reported a number of convenient syntheses for a series of aldimine–borane and *N*-aluminoimine complexes.[10] Their subsequent allyl-, crotyl-, and methoxyallylborations provide access to homoallylic amines in high yields and very good to excellent enantio- and diastereoselectivities. We envisaged that the use of these homoallylic amines as synthons could provide easy access through a novel route to a new class of functionalized, chiral

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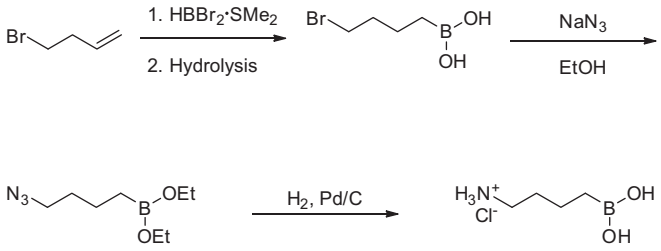
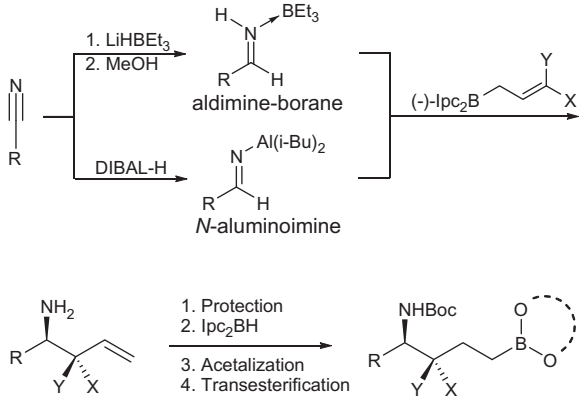


Scheme 1. δ-Aminoboronic acid production by Vaultier and co-workers by means of an azide-containing pathway.



Scheme 2. Synthetic route employed in the production of δ-aminoboronic esters.[11]

δ-aminoboronic esters and their substituted analogs. The synthetic approach to this class of compounds is outlined in Scheme 2.

The hydroboration of functionalized olefins can lead to the synthesis of a variety of substituted alkylborons and boron-containing heterocycles, and also to those alcohols and functionalities that result from the oxidation and further synthetic manipulation of these borane intermediates.[12] We believed that the application of this hydroboration methodology to (aminoalkyl)-ω-olefins would necessarily lead to the production of amino-ω-borylated compounds. For our purposes, we were interested in investigating the hydroboration of 1-aminobut-3-enes, as we considered that they could provide direct access to the desired δ-aminoboranes, which, upon oxidative elimination of α-pinene and esterification, would furnish the desired δ-aminoboronic esters.

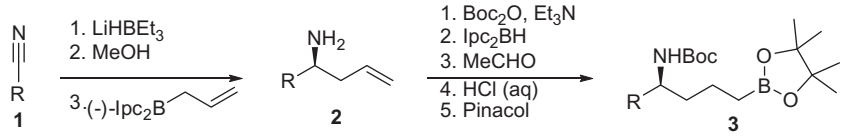
We began our efforts by searching for a method that would allow for both the symmetric and asymmetric production of the requisite 1-aminobut-3-enes. To this end, we decided to extend our previous methodology[10] in which we had described a one-pot process of imine allylation. In that case, metalated imines were produced in situ by the reduction of a variety of substituted nitriles.

Building on our previous work, these 1-substituted-1-aminobut-3-enes were then protected at the amine position with the *tert*-butoxycarbonyl group. The resultant Boc-protected homoallylic amines were then subjected to hydroboration conditions, thereby furnishing the expected alkylamines possessing the desired ω-boryl group. Oxidation of the two boron diisopinocamphenyl ligands with acetaldehyde (akin to a DIP-Cl® reduction),[13] followed by hydrolysis with diluted mineral acid provided the desired δ-boronic acids. Unfortunately, these products were not readily purifiable. As such, these compounds were directly converted into their ester analogs by esterification with pinacol. In this way, the pinacolato δ-aminoboronic esters were prepared in very good overall yields.

The use of Brown's chiral isopinocampheyl ligand[14] during the allylboration stage was found to provide excellent enantiomeric ratios of the desired 1-substituted-1-aminobut-3-enes. Expectedly, this high enantiomeric enrichment was carried through to the boronic esters, providing, to the best of our knowledge, the first such stereocontrolled synthesis of δ-aminoboronic acids and esters. Generally speaking, enantiomeric ratios of between 6:1 and 99:1 were obtained with this process (Table 1).

The synthesis of a series of N-protected-1-aryl-1-amino-δ-boronic esters was then performed as follows (Table 1). An aromatic nitrile (**1**) was first reduced with lithium triethylborohydride to furnish the lithium triethyl(alkylidenylamino)borate complex. After a controlled protonation with methanol, the resulting imminium–borane adduct was allylated with (-)-B-allyldiisopinocampheylborane [(-)-Ipc_2B(allyl)] which, upon oxidative workup and column chromatography, provided the intermediate homoallylic amines **2** in very good yields and excellent enantiomeric ratios. After protection of the amine functionality by reaction with di(*t*-butyloxycarbonyl) anhydride, hydroboration with the

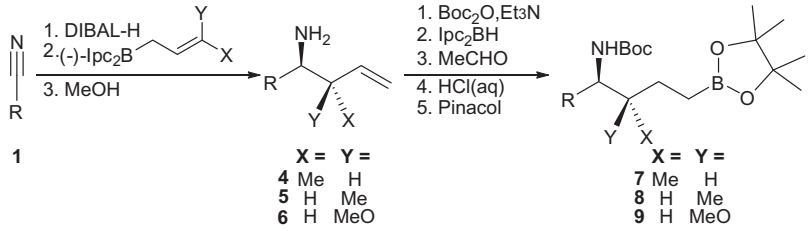
Table 1
Asymmetric synthesis of Boc-protected δ-aminoboronic esters



Entry	Nitrile		Homoallylic amine		δ-Aminoboronic ester		
	No.	R=	No.	Yield[a] (%)	No.	Yield[b] (%)	er[c]
1	**1a**	C_6H_5–	**2a**	79[d]	**3a**	59	96:4
2	**1b**	4-Me-C_6H_4–	**2b**	86[d]	**3b**	67	97:3
3	**1c**	4-MeO-C_6H_4–	**2c**	90[d]	**3c**	65	97:3
4	**1d**	2-Thiophenyl–	**2d**	82[d]	**3d**	55	>99:1
5	**1e**	2-F-C_6H_4–	**2e**	71[e]	**3e**	54	88:12

[a] Yields refer to analytically pure material (flash chromatography) after three steps.
[b] Yields refer to analytically pure material (flash chromatography) after five steps.
[c] Enantiomeric ratios were determined by Mosher amide analysis using ^{19}F NMR.
[d] Yields are from previous report.[11]
[e] Reduction was performed using DIBAL-H.

Table 2
Asymmetric synthesis of methylated and methoxylated δ-aminoboronic esters



	Nitrile		Homoallylic amine		δ-Aminoboronic ester			
Entry	No.	R=	No.	Yield[a] (%)	No.	Yield[b] (%)	dr[c]	er[d]
1	**1b**	4-Me-C_6H_4–	**4b**	69	**7b**	64	>99:1	95:5
2	**1b**	4-Me-C_6H_4–	**5b**	56	**8b**	52	>99:1	93:7
3	**1b**	4-Me-C_6H_4–	**6b**	63	**9b**	53	98:2	>99:1
4	**1c**	4-MeO-C_6H_4–	**4c**	59	**7c**	57	>99:1	84:16
5	**1c**	4-MeO-C_6H_4–	**5c**	63	**8c**	58	>99:1	84:16
6	**1c**	4-MeO-C_6H_4–	**6c**	56	**9c**	51	99:1	94:6

[a] Yields refer to analytically pure material (flash chromatography) after three steps.
[b] Yields refer to analytically pure material (flash chromatography) after five steps.
[c] Diastereomeric ratios were determined by ^{1}H NMR analysis of the crude reaction mixture.
[d] Enantiomeric ratios were determined by Moscher amide analysis of the major diastereomer using both ^{1}H and ^{19}F NMR.

bulky Ipc_2BH,[15] followed by oxidation with excess acetaldehyde, hydrolysis with dilute hydrochloric acid, and esterification with pinacol provided the product 1-aryl-1-amino-δ-boronic esters **3** in very good overall yields and excellent enantiomeric ratios. The product boronate esters, which were stable under conditions of column chromatography, were obtained as the major enantiomer shown in Table 1. A comparison with literature values of similar compounds[11,16] was used as confirmation that the stereochemical outcome was the one expected for imine allylation. This stereochemistry, when considered in the context of the stereochemical consistency of other reports of analogous imine allylations,[17] is very reasonable.

The application of these conditions to Brown's crotyl-[18] and methoxyallylboration[19] reactions was also studied. These synthetic analogs provide an excellent means to introduce further substitutions or functionalities vicinal to the amine. We initially explored these reactions, again using lithium triethylborohydride as the nitrile reductant. We found, however, that the use of the less expensive diisobutylaluminum hydride (DIBAL-H)[10] offered comparably high enantio- and diastereoselectivities at the expense of only a slight decrease in isolated yield (Table 2).

By following a methodology similar to that above, the formation of crotyl-derived amines was realized. For example, the use of 4-methyl and 4-methoxybenzonitriles, when subjected to the sequential reduction and crotylation conditions, resulted in the formation of the expected products. Again, protection, followed by hydroboration, controlled ligand oxidation, hydrolysis, and esterification, furnished the desired δ-aminoboronic esters. In these cases, the use of the chiral isopinocampheyl ligand provided very high levels of stereoinduction, with enantiomeric ratios as high as 99:1 or better. As expected, the crotylation of the imines proceeded with excellent diasteromeric ratios.[10,17]

In conclusion, we have presented herein the first synthesis of δ-aminoboronic esters in a fully stereocontrolled manner.[20] The very high levels of enantio- and diastereoselectivity, when considered in the context of the high synthetic yields obtained, make this a very attractive methodology, and opens a new route for the exploration of these potentially useful δ-aminoboronic esters.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.076.

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15. Racemic Ipc_2BH was used for hydroboration. Although hydroboration with Br_2BH followed by hydrolysis can be used (Ref. 8a,b), we opted instead for the use of Ipc_2BH, followed by oxidative elimination with acetaldehyde, since this protocol is more economical on a molar basis (Sigma–Aldrich chemical catalog). Furthermore, α-pinene is completely eliminated and is recoverable during this process.

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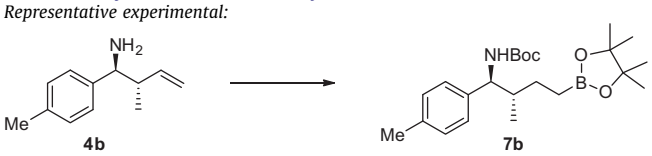
20. *Representative experimental:*



4b **7b**

A RB flask was charged with 176 mg KO-*t*-Bu dissolved in 3 mL THF and cooled to −78 °C. 0.34 mL of *E*-2-butene (2.5 equiv) was added to the solution, and the mixture was stirred for 5 mins. 0.63 mL of *n*-butyllithium (1.3 equiv) was then added, and the mixture was stirred for 45 mins at −55 °C. After re-cooling to −78 °C, 1.5 equiv (−)-*B*-methoxydiisopinocamphenylborane (1.44 M in THF) was added, and the mixture was stirred for 1 h. Subsequently, 1.0 equiv *N*-aluminoimine (1 M in THF) was added, followed by the slow addition of 0.05 mL methanol. After stirring for 4 h at −78 °C, 0.8 mL 3 M NaOH (aq) and 0.5 mL H_2O_2 (30%) were added sequentially to the mixture. The mixture was warmed to 25 °C over 12 h while maintaining a N_2 atmosphere. The product was extracted with Et_2O, and the solvent was removed in vacuo. The crude product **4b** was then isolated via column chromatography in 69% yield. The material (1.0 equiv) was then transferred into a RB flask, and dissolved in Et_2O (0.19 M). To this was added 1.1 equiv Boc_2O, followed by 1.2 equiv Et_3N. After stirring for 6 h, the solvent was removed in vacuo. The crude material was dissolved in THF (1 M), then was transferred into a suspension of 1.5 equiv diisopinocampheylborane in THF (0.84 M). The reaction was stirred for 4 h, then excess acetaldehyde was added. After stirring for 36 h, 1 M HCl (aq) was added, then the product was then extracted with Et_2O. The organic layer was concentrated in vacuo, then 1.5 equiv pinacol were added. After stirring for an additional 12 h, the product was extracted with Et_2O, and the combined organic layers were washed with brine, dried with Na_2SO_4, filtered, and concentrated. Purification via column chromatography then furnished the desired **(1*S*,2*S*)-*N*-(*t*-butoxycarbonyl)-2-methyl-1-(4-methylphenyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butan-1-amine** product **7b** in 64% yield.