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Synthesis of new boron analogues of cyclic carboxylic α-amino acids using ring-closing metathesis reactions

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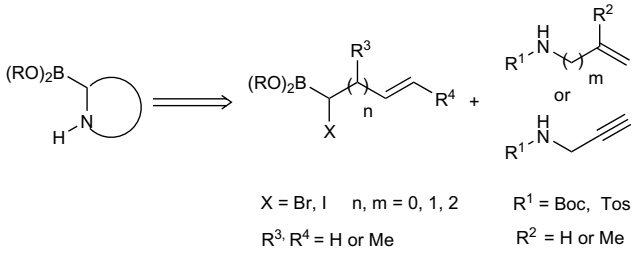
Abstract—Ruthenium catalyzed ring-closing metathesis has been used as a key step for the synthesis of cyclic α-aminoboronic esters as, for example, boron-containing mimics of pipecolic, 2-azepanecarboxylic acid or baikiain.

The enzyme inhibiting activity of boronic acid derivatives was first discovered three decades ago with (*S*)-*N*-acetyl-borophenyl-alanine.[1] This compound acts as a reversible transition state analogue inhibitor of chymotrypsin due to the close similarity between a tetrahedral borate fragment and the key intermediate in the enzymatic sequence.[2] Since these pioneering works, there was an intense interest in synthesizing new other amidoboronic acids and derivatives and examining their biological properties.[3] Thus, Velcade®, a boropeptide, has recently received approval from the US Food and Drug Administration for the treatment of multiple myeloma. This class of compounds has also been examined as carriers of ^{10}B for treatment of cancer in boron neutron capture therapy (BNCT) strategy.[4]

Cyclic carboxylic α-amino acids, as proline or pipecolic acid for example, display significant biological activities and are valuable constituents in peptides. To our knowledge, boroproline, prepared by borylation of N-Boc-pyrrolidine or pyrrole,[5] and an analogue of *N*-acetyl-kainic acid, obtained by an intramolecular nucleophilic substitution reaction,[6] were the only boron analogues of cyclic carboxylic α-amino acid described in the literature.

However, the reported syntheses of these compounds seem restricted to some isolated examples. The transition metal-mediated cyclization reactions have drawn a lot of attention for the construction of nitrogen-containing systems.[7] Thus, ring-closing metathesis became a major tool in synthetic organic chemistry and was shown to tolerate a range of functional groups.[8]

In the present work, we investigated the synthesis of new α-amino boronic esters using this reaction as key step (Scheme 1). Besides the potential biological interest of these mimics of carboxylic amino acids, it seems also important to determine the stability of the B–C–N linkage in such a catalytic process.



Scheme 1. Access to boron analogues of cyclic α-amino acids.

Starting α-bromoboronates were first prepared in good yields, either from pinacol dibromomethylboronate by reaction with an unsaturated organomagnesium compound (**1a**–**c**) or by insertion of a CHBr moiety into the carbon–boron bond of an ω-alkenylboronic ester (**1d**).[9] The reactivity of **1** in the amidation reaction was found to be low, except for **1a** where the halogen is in an allylic position.

Keywords: Aminoboronic esters; Ring-closing metathesis; Aminoacids analogues.
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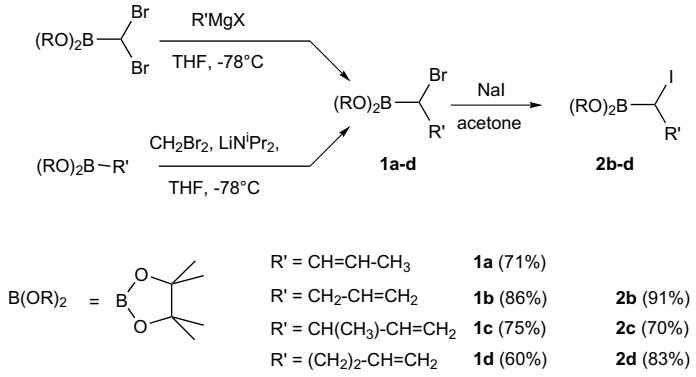
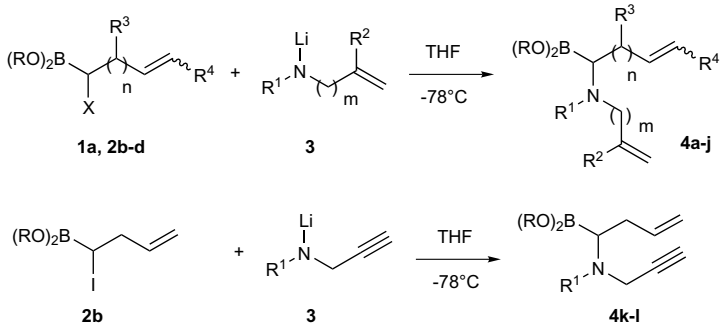


Scheme 2. Synthesis of α-haloboronates **1a–d** and **2b–d**.



Scheme 3. Synthesis of dienes **4a–j** and enynes **4k–l**.

To overcome this difficulty, bromine/iodide exchange was performed by treatment with NaI in acetone at reflux for 12 h (Scheme 2).

Having in hand the α-halogenoboronates **1a** and **2b–d**, we then examined their reactivity toward the lithium salts of N-Boc- or N-Tos-allyl- and propargylamines **3**.[10] N-Boc- or N-tosyl-aminoboronates **4b–i** and **4k–l** were obtained in reasonable to good yields after purification by chromatography on silica gel (Scheme 3, Table 1). In our hands, **2c**, with a methyl group α to the iodine atom, afforded only traces of **4j**, while α-bromoallylboronic ester **1a** gave **4a** in a disappointing and unoptimized 23% yield.

Table 1. Synthesis of α-amidoboronic esters **4a–l**

Product	X	R^1	R^2	R^3	R^4	*n*	*m*	Yield (%)
4a	Br	Tos	H	H	Me	0	1	23
4b	I	Boc	H	H	H	1	1	78
4c	I	Tos	H	H	H	1	1	82
4d	I	Boc	H	H	H	1	2	64
4e	I	Tos	H	H	H	1	2	67
4f	I	Boc	Me	H	H	1	1	56
4g	I	Tos	Me	H	H	1	1	60
4h	I	Boc	H	H	H	2	1	55
4i	I	Tos	H	H	H	2	1	68
4j	I	Tos	H	Me	H	1	1	Traces
4k	I	Boc	—	—	—	—	—	75
4l	I	Tos	—	—	—	—	—	92

Next, we turned our attention to the ring-closing reactions. Three different catalysts were used (Fig. 1). The results are summarized in Scheme 4 and Table 2.

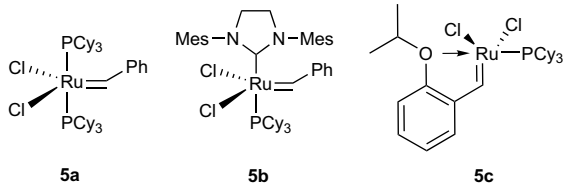
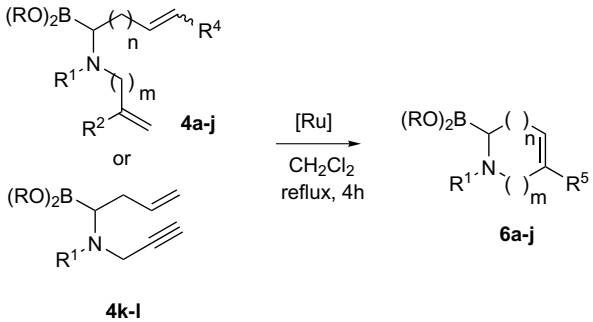


Figure 1. Ruthenium catalysts.

Ruthenium catalyst **5a** was found to be effective for six- and seven-membered ring α-amidoboronic esters **6b–e** and **6h–k**, which were isolated in 54–90% yields in



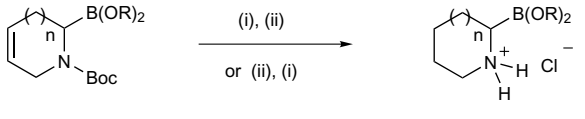
Scheme 4. Ring-closing metathesis of **4a–l**.

CH_2Cl_2 at reflux for 4 h.[11] Tetrahydropyridines **6f–g** with a 1,1-disubstitution on the initial double bond were only obtained, respectively, in 55% and 40% yields, in the presence of second-generation Grubbs catalyst **5b**. In contrast, the B–C–N linkage is not stable in the presence of these catalysts and we were unable to obtain any pyrroline starting from **4a** in the presence of **5a** or **5b**. No starting material was recovered under these reaction conditions. Gratifyingly, the cyclization has been realized with Hoveyda catalyst **5c**, albeit in a low yield. The difficulties observed in this reaction are in agreement with previous observations related to the carboxylic analogue.[12]

Table 2. Synthesis of cyclic α-amidoboronic esters **6**

Product	Cat.	R^1	R^5	*n*	*m*	Yield (%)
6a	**5c**	Tos	H	0	1	42
6b	**5a**	Boc	H	1	1	87
6c	**5a**	Tos	H	1	1	90
6d	**5a**	Boc	H	1	2	85
6e	**5a**	Tos	H	1	2	86
6f	**5b**	Boc	Me	1	1	40
6g	**5b**	Tos	Me	1	1	55
6h	**5a**	Boc	H	2	1	58
6i	**5a**	Tos	H	2	1	54
6k	**5a**	Boc	$CH{=}CH_2$	1	1	67
6l	**5a**	Tos	$CH{=}CH_2$	1	1	75

Since the synthesis of boropeptides required the NH derivative of aminoboronic esters,[5] deprotections of **6b** and **6h**, selected as examples, were easily carried out with HCl in diethylether (Scheme 5). Hydrogenation of the double bond occurred in the presence of Pd/C to give the corresponding saturated heterocycles, respectively, in 75% and 86% overall yields.[13] The order of these two steps can be reversed with no significant modification in terms of purity and yield.



6b (n=1), **6h** (n=2) **7b** (75%) **7h** (86%)

Scheme 5. Synthesis of aminoboronate hydrochlorides **7**. Reagents and conditions: (i) HCl, EtOAc, 2 h, rt; (ii) H_2, Pd/C, EtOH, 10 atm.

In conclusion, we have demonstrated a feasible route into a variety of new N-protected cyclic α-aminoboronates. In addition, the cleavage of the N-Boc group provided the corresponding boron analogues of carboxylic amino esters that could be further engaged in boropeptide synthesis. Further studies including the development of an asymmetric version using enantiomerically pure α-haloboronate as starting material and the incorporation of the corresponding α-aminoboronic acids in peptidic chains are currently under investigation.

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11. Typical procedure for the ring closing metathesis: To a solution of diene **4b** (113 mg, 0.335 mmol) in CH_2Cl_2 (5 mL) was added $Cl_2(Pcy_3)_2RuCHPh$ (**5a**, 14 mg, 0.017 mmol). The solution was refluxed under argon for 3 h. The solvent was evaporated and the residue was purified by flash chromatography on silica gel (10% ethyl acetate in cyclohexane) to give **6b** as a light yellow oil (90 mg, 87%). ^1H NMR (300 MHz, $CDCl_3$): δ 5.92–5.81 (m, 1H), 5.53–5.42 (m, 1H), 3.89–3.75 (dm, J = 17.7 Hz, 1H), 3.53–3.42 (dm, J = 17.7 Hz 1H), 2.43 (dd, J = 3.3 and 6.4 Hz, 1H), 2.33–2.18 (m, 1H), 2.01–1.87 (m, 1H), 1.43 (s, 9H), 1.11 (s, 12H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 160.2, 127.8, 120.7, 86.0, 80.1, 41.0, 28.2, 25.7, 25.1, 24.8.
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13. Amine deprotection: **6b** (81 mg, 0.28 mmol) was treated with a saturated solution of HCl in diethylether (10 mL) with stirring at 0 °C for 12 h. The solvent was evaporated to yield the corresponding hydrochloride. ^1H NMR (300 MHz, $CDCl_3$): ^1H NMR (300 MHz, $CDCl_3$): δ 9.60–9.46 (m, 1H), 9.34–9.20 (m, 1H), 6.02–5.90 (m, 1H), 5.70–5.58 (m, 1H), 4.00–3.83 (m, 1H), 3.72–3.55 (m, 1H), 3.22–3.10 (m, 1H), 2.72–2.54 (m, 1H), 2.50–2.32 (m, 1H), 1.22 (s, 12H). ^{13}C NMR (75.5 MHz, $CDCl_3$): δ 126.1, 120.3, 85.2, 41.2, 29.6, 24.8, 24.7. Hydrogenation: The crude hydrochloride (74 mg, 0.24 mmol) was dissolved in ethanol (10 mL). The reaction mixture was stirred in the presence of Pd/C 5% (10 mg) under H_2 (10 atm.) for 4 h. After filtration through Celite, the solvent was evaporated to give **7b** (65 mg, 75%). ^1H NMR (300 MHz, $CDCl_3$): δ 9.20 (bs, 1H), 8.72 (bs, 1H), 3.52–3.38 (m, 1H), 3.18–2.98 (m, 2H), 2.10–1.40 (m, 6H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 85.2, 44.2, 29.7, 24.9, 24.6, 22.6, 22.4.