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Synthesis of α-aminoboronic acids

Patricia Andrés, Gema Ballano, M. Isabel Calaza and Carlos Cativiela*

This review describes available methods for the preparation of α-aminoboronic acids in their racemic or in their enantiopure form. Both, highly stereoselective syntheses and asymmetric procedures leading to the stereocontrolled generation of α-aminoboronic acid derivatives are included. The preparation of acyclic, carbocyclic and azacyclic α-aminoboronic acid derivatives is covered. Within each section, the different synthetic approaches have been classified according to the key bond which is formed to complete the α-aminoboronic acid skeleton.

1. Introduction

In the last few decades important biomedical applications[1] have been established for compounds containing α-aminoboronic acids in their structure (Fig. 1). Most developments aimed at the use of α-aminoboronic acids in the area of protease inhibition.[1] In this context, the discovery of bortezomib (Fig. 1) represented a very significant advance and it presently constitutes an important treatment for multiple myeloma and mantle cell lymphoma. The α-aminoboronic acid residue in bortezomib, L-boroleucine,[2] is key for its proteasome-inhibitory activity.[3] It forms tetrahedral adducts with the hydroxyl groups of threonine residues at the catalytic sites of 20S proteasome that block the enzymatic activity. Such adducts are considered transition state analogues for deacylation reactions that occur during proteasome-dependent proteolysis. The clinical efficacy of bortezomib encouraged further studies for its optimal delivery to tumours,[4] as well as the development of new analogues,[5] such as orally active ixazomib[5a] (Ninlaro® has recently been granted approval by FDA) and delanzomib,[5b,c] which preserve the key α-aminoboronic residue (Fig. 1).

The analogous mechanism of inhibition in serine proteases has led to a wide range of compounds with pharmacologically relevant properties (Fig. 2).[1,6–9] Among the targeted enzymes[1] are thrombin, dipeptidyl peptidases (DPPs),[6] β-lactamases,[7] penicillin-binding proteins (PBPs), HCV NS3/4A protease, enteropeptidase, and mycosin-1 protease.[8,9] In this context, the most significant advances have been achieved in the development of compounds with anticancer, antiviral, and antibacterial activities, which are in various phases of clinical trials (Fig. 2).

The increasing interest in α-aminoboronic acids is also linked to their utility as building blocks[10] and their potential use in sensing applications.[11] In fact, boroglycine constitutes

Departamento de Química Orgánica, Instituto de Síntesis Química y Catálisis Homogénea (ISQCH), CSIC–Universidad de Zaragoza, 50009 Zaragoza, Spain. E-mail: cativiela@unizar.es; Tel: +34 976761210

Patricia Andrés

Patricia Andrés graduated in Chemistry from the University of Zaragoza in 2011, and completed her Master's Thesis in Organic Chemistry one year later. She is currently a PhD student in the group of Prof. C. Cativiela at the same university. Her research focuses on the development of synthetic methodologies for the preparation of α-aminoboronic acids.

Gema Ballano

Gema Ballano received her PhD in Chemistry in 2006 from the University of Zaragoza under the supervision of Prof. C. Cativiela. She conducted postdoctoral research in the laboratories of Prof. C. Toniolo at the University of Padova (Italy). In 2012, she joined Rolabo Outsourcing S.L. (Zaragoza) and works in collaboration with the University of Zaragoza. Her research interests include the synthesis of non-proteinogenic amino acids and their incorporation into peptides.

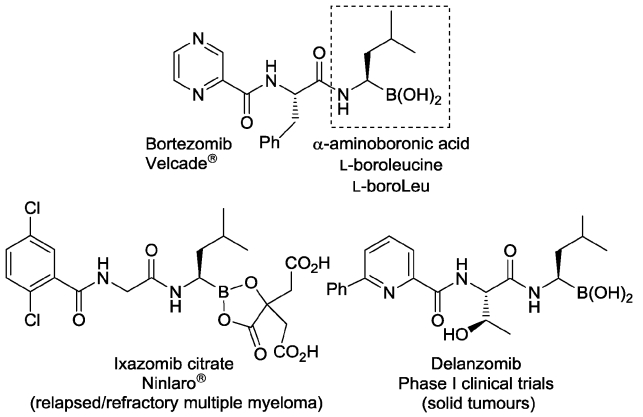


Fig. 1 Proteasome inhibitors that contain an α-aminoboronic acid in their structure.

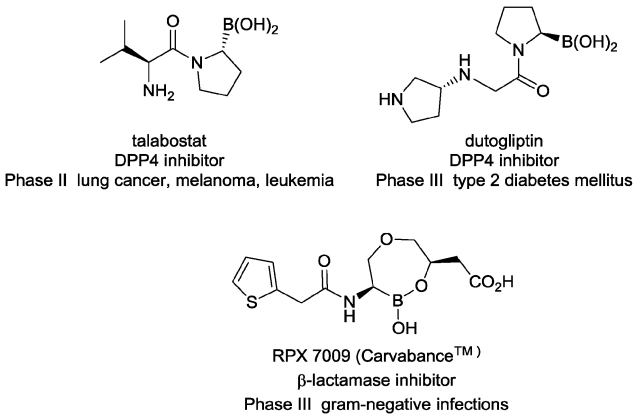


Fig. 2 Boron-based serine protease inhibitors that exhibit pharmacologically relevant properties.

the key recognition part of a fluorescent tracer (Fig. 3) for binding assays that are aimed at the identification of inhibitors

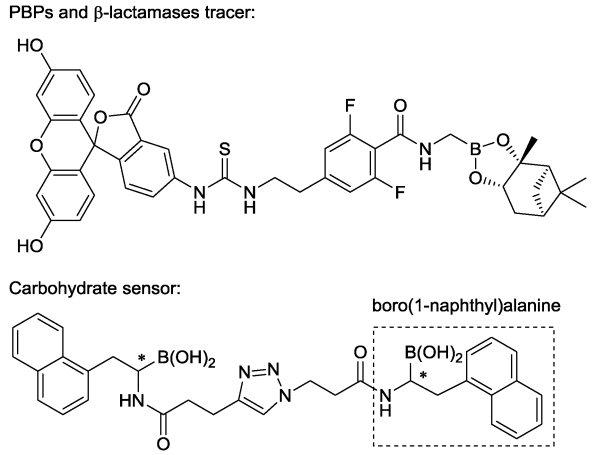


Fig. 3 α-Aminoboronic acid-based investigational fluorescent sensors.

of PBPs and β-lactamases.[11a] Besides, boronic acid analogues of L- and D-1-naphthylalanine,[11b] and their bisboronic acid derivatives (Fig. 3),[11c] are being examined as carbohydrate sensors, due to their significant fluorescent property changes upon sugar binding, and their water solubility.

The enormous potential of α-aminoboronic acids has stimulated a great deal of innovation on synthetic methods for their preparation.[12] The difficulties associated with their isolation, which are due to the reactivity of the C–B bond, constitute a major synthetic issue.[12b] The electron-deficient nature of the boron atom in its trivalent form enables it to form a three-membered ring adduct with the nitrogen atom. Such an adduct is subsequently protonated at carbon with concomitant C–B bond cleavage. For this reason, the preparation of suitable protected α-aminoboronic acid derivatives is assumed.

Herein, we wish to illustrate the progress of synthetic methods utilized for the construction of α-aminoboronic acid derivatives. Specifically, the preparation of acyclic, carbocyclic and azacyclic α-aminoboronic acid derivatives is covered.

M. Isabel Calaza

M. Isabel Calaza obtained her PhD in Chemistry from the University of Santiago de Compostela in 2000. She conducted post-doctoral research in the group of Prof. P. Knochel at the Ludwig Maximilians University of Munich. In 2004, she joined the Medicinal Chemistry Department at AstraZeneca R&D Mölndal. In 2007, she moved to the University of Zaragoza where she is an Assistant Professor. Her research interests include the synthesis of proline analogues for structural analysis and α-aminoboronic acids.

Carlos Cativiela

Carlos Cativiela is Full Professor of Organic Chemistry at the University of Zaragoza since 1996. His scientific activity started in the field of asymmetric synthesis and is oriented to the synthesis of non-proteinogenic amino acids in enantiomerically pure form. He has developed different methodologies for the synthesis of a wide variety of enantiopure non-coded constrained amino acids either by enantio-/diastereoselective syntheses or by chromatographic resolution procedures. Current research interests involve the incorporation of such amino acids into peptides of structural, medical or agrochemical interest. He is the author of more than 400 papers and several review articles on the synthesis of amino acids.

The different synthetic approaches, within each section, have been classified according to the bond which is formed to complete the α-aminoboronic acid skeleton.

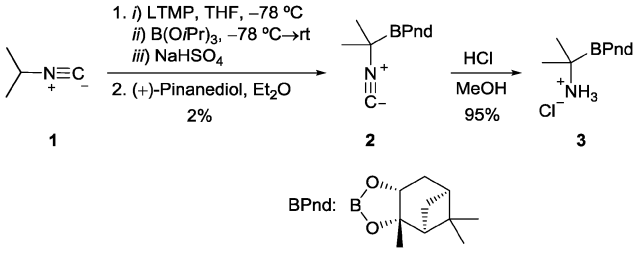
2. Synthesis of acyclic α-aminoboronic acids

2.1. Formation of the C–B bond

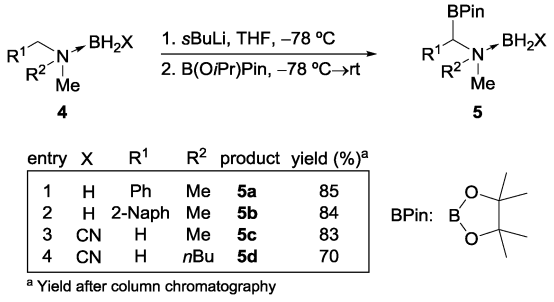
2.1.1. Addition of α-amino organometallic compounds to boron-containing electrophiles. Synthetic routes towards acyclic α-aminoboronic acids that involve the borylation of α-amino metalated species are scarce in the literature.[13,14] In 2000, Priestley and Decicco[13] described the preparation of acyclic (Scheme 1) and carbocyclic (*vide infra*) α-aminoboronic acid esters by the reaction of metalated isocyanides with trialkyl borate esters. Regrettably, the boronic analogue of α-aminoisobutyric acid (**3**, Scheme 1) was obtained in very low yield by reaction of the metalated isocyanide with triisopropyl borate, followed by acid hydrolysis. Such a low yield was attributed to the instability of the resulting α-isocyanoboronic ester under basic reaction conditions.

More recently, Srebnik and Shibli[14] reported the use of aminoboranes and aminocyanoboranes (**4**, Scheme 2) as precursors for the preparation of α-aminoboronic esters **5**. The borane and cyanoborane groups inductively facilitate the selective α-deprotonation of the tertiary amines. The resulting lithiated complexes reacted readily with the boron-containing electrophile and furnished racemic α-alkylaminoboronic acid esters **5** in good yields.

2.1.2. Addition of nucleophilic boron reagents to imines. By contrast, nucleophilic borylations[15] of imines have emerged as very efficient approaches for the preparation of highly enantioenriched α-aminoboronic acid derivatives. In this context, the stereocontrol has been either achieved by the presence of a chiral auxiliary at the aldimine, or employing chiral catalysts with achiral substrates.



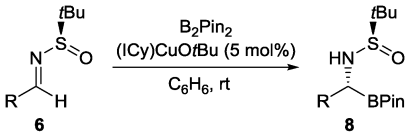
Scheme 1



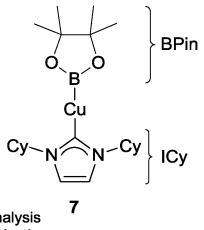
entry	X	R^1	R^2	product	yield (%)[a]
1	H	Ph	Me	**5a**	85
2	H	2-Naph	Me	**5b**	84
3	CN	H	Me	**5c**	83
4	CN	H	*n*Bu	**5d**	70

[a] Yield after column chromatography

Scheme 2



imine	R	product	yield (%)	*dr*
6a	$(CH_3)_2CHCH_2$	**8a**	74	>98:2[b]
6b	Bn	**8b**	59	>98:2[b]
6c	$(CH_3)_2CH$[a]	**8c**	88	>98:2[c]
6d	4-MeO-Ph	**8d**	57	>98:2[b]
6e	$TBDPSOCH_2$	**8e**	75	>99:1[b]
6f	$(CH_3)_3C$	**8f**	75	96:4[c]
6g	Ph	**8g**	54	99:1[b]



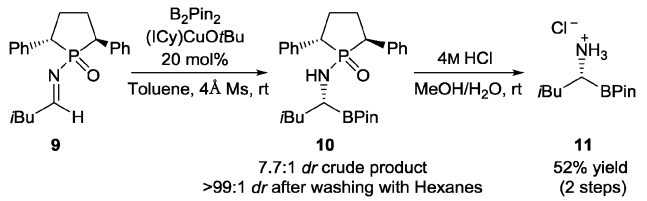
[a] Absolute configuration determined by X-ray diffraction analysis
[b] Determined by ^{19}F NMR of (*R*)- and (*S*)-MTPA amide derivatives
[c] Determined by ^{1}H and ^{13}C NMR of an authentic mixture of diastereoisomers

Scheme 3

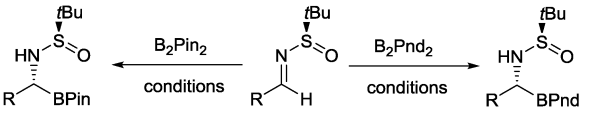
2.1.2.1. Substrate-controlled approach. In 2008, Ellman *et al.* reported the first stereoselective borylation of chiral sulfinylimines **6** (Scheme 3),[16a] on the basis of preceding studies of diboration of racemic *N*-aryl aldimines.[16b] Ellman's procedure involved *in situ* generation of a copper(I) boryl complex **7** (Scheme 3) by the treatment of bis(pinacolate)diboron (B_2Pin_2) with (1,3-dicyclohexylimidazol-2-ylidene)copper(I) *tert*-butoxide, also named as Sadighi's catalyst. The reaction of the active catalytic species (**7**) with sulfinylimines **6** proceeded at room temperature with good yield and high diastereoselectivity for a wide range of substrates (Scheme 3). The transformation was also achieved at 0 °C albeit with higher catalyst loading. The stereoselectivity observed was consistent with coordination of **7** from the least hindered face of the aldimine. Selective removal of the *N*-sulfinyl group under acidic conditions enabled the production of highly enantioenriched α-aminoboronic ester derivatives.

The same catalyst was applied by Li *et al.* to the asymmetric borylation of imine **9** that bears a chiral *N*-phosphinyl auxiliary (Scheme 4).[17] This group anchored onto the aldimine displayed good asymmetric induction in the borylation reaction and facilitated the isolation of the desired product by avoiding conventional purification methods (group-assisted purification concept). Thus, diastereomerically pure **10** was obtained by washing the crude reaction mixture with hexanes, and the chiral *N*-phosphinyl auxiliary was readily recovered after the subsequent deprotection step.

In recent work, the reactivity of copper(I) boryl complexes supported by different N-heterocyclic carbene (NHC) ligands



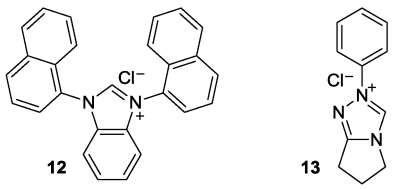
Scheme 4



A: **12** (10 mol%), CuCl (10 mol%), NaO*t*Bu (10 mol%), Toluene, rt
B: **13** (10 mol%), CuCl (10 mol%), Cs_2CO_3 (10 mol%), Toluene or C_6H_6, rt
C: $CuSO_4/PCy_3{\cdot}HBF_4$ (1.2 mol%), $BnNH_2$ (5 mol%), Toluene/H_2O, rt

entry	imine	R	conditions	product	yield (%)	*dr*	ref.
1	**6a**	$(CH_3)_2CHCH_2$	A	**8a**	89	99:1[a]	18a
2	**6b**	Bn	A	**8b**	85	98:2[a]	18a
3	**6d**	4-MeO-Ph	A	**8d**	80	99:1[a]	18a
4	**6f**	$(CH_3)_3C$	A	**8f**	86	>99:1[a]	18a
5	**6c**	$(CH_3)_2CH$	B	**14c**	88	99:1[b]	18b
6	**6b**	Bn	B	**14b**	89	99:1[b]	18b
7	**6g**	Ph	B	**14g**	86	99:1[b]	18b
8	**6h**	$Cl(CH_2)_3$	B	**14h**	86	99:1[b]	18b
9	**6a**	$(CH_3)_2CHCH_2$	C	**8a**	82	94:6[b]	19
10	**6i**	$CbzHN(CH_2)_2$	C	**8i**	60	>95:5[b]	19
11	**6j**	4-CH_3-Ph	C	**8j**	75	94:6[b]	19
12	**6k**	Cy	C	**8k**	86	96:4[b,c]	19

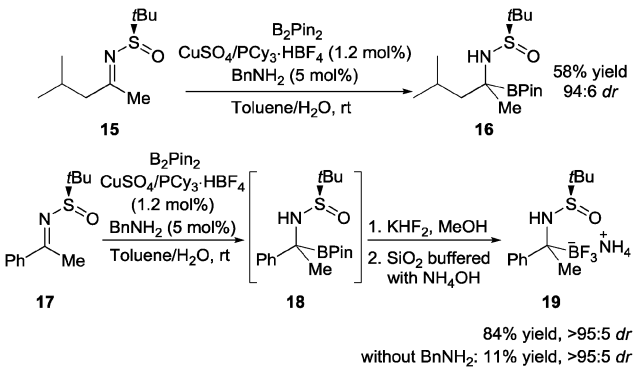
[a] Determined by ^{19}F NMR of (*R*)- and (*S*)-MTPA amide derivatives
[b] Determined by ^{1}H NMR of the crude product
[c] Reaction conducted from 0 °C to rt



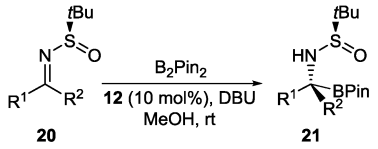
Scheme 5

is described.[18,19] Benzimidazole-[18a] and triazine-[18b] based N-heterocyclic carbene (NHC) precursors (**12** and **13** respectively, Scheme 5) lead to copper(I) boryl complexes that proved quite efficient catalysts for borylations of chiral sulfinylimines **6** (Scheme 5, entries 1–8). Remarkably, these reactions took place in a one-pot procedure without the need of a glove box as it was required with Sadighi's catalyst (Scheme 3).[16a]

In addition to this, Ellman *et al.*[19] developed an air- and moisture-stable copper(II) catalytic system for the borylation of **6** (Scheme 5, conditions C). It is worth noting that not only sulfinylimines (Scheme 5, entries 9–12), but also ketimines (Scheme 6) reacted readily to provide access to α-sulfinamido boronate esters in good yields and with high stereoselectivities. The stereocontrol achieved with the catalytic system $CuSO_4/PCy_3{\cdot}HBF_4$



Scheme 6



entry	R^1	R^2	yield (%)	*dr*[a]
1	CH_3	H	85	>99:1
2	4-Cl-Ph	H	83	>99:1
3	4-MeO-Ph	H	82	99:1
4	$(CH_3)_3C$	H	88	>99:1
5	Ph	CH_3	68	69:31
6	$Ph(CH_2)_2$	Ph	65	71:29

[a] Determined by ^{19}F NMR of (*R*)- and (*S*)-MTPA amide derivatives

Scheme 7

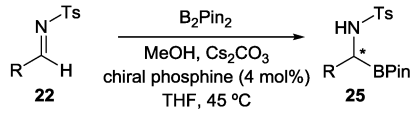
was shown to be dependent on the nature of the phosphorus ligand, the ligand to copper ratio and the solvent mixture. It was found that the use of benzylamine as an additive was not essential for the phosphine salt selected but it proved beneficial for the borylation of challenging substrates such as **17** (Scheme 6).

Alternatively, the addition of boron to *N-tert*-butanesulfinyl aldimines and ketimines **20** was possible in the absence of a transition metal complex as a catalyst (Scheme 7).[20] In this procedure, it was the *in situ* generated methoxide anion which was responsible to activate the diboron reagent and to promote the addition in the presence of an N-heterocyclic carbene as a ligand. The sp^2 boron atom in the adduct gains a nucleophilic character whereas the one that interacts with methoxide anion loses electron density because of the lack of electron donation from the oxygen atoms of its pinacolate moiety.[21] Specifically, the use of carbene precursor **12** (Scheme 5), with a benzimidazole core, allowed the reaction to be performed without requiring an inert atmosphere.

2.1.2.2. Reagent-controlled approach. The first catalytic enantioselective approach for the synthesis of α-aminoboronic esters was reported by Fernández *et al.*, who conducted nucleophilic boron addition to tosylaldimines **22** in the presence of chiral phosphines as ligands (Scheme 8).[22] The use of such phosphines proved to be essential for enantiofacial differentiation in the course of the reaction, even though aliphatic tosylaldimines gave low enantioselectivities (entries 7 and 8).

Later, enantioselective copper-catalyzed boryl additions to *N*-benzoyl[23] and *N-tert*-butoxycarbonyl (*N*-Boc)[10e] aldimines were accomplished (Scheme 9). On one hand, the asymmetric addition of B_2Pin_2 to *N*-benzoyl aldimines (entry 1) involved the use of NHC–Cu complexes *in situ*-generated by the treatment of **27** with sodium *tert*-butoxide and copper chloride.[23] The reaction proceed smoothly and gave excellent yields and high enantioselectivities for a broad scope of 4-substituted benzaldimines regardless of their electronic nature. However, some erosion in enantioselectivity was observed for sterically hindered 2- or 3-substituted benzaldimines. Alkyl aldimines were also effective under the reaction conditions but they were generated *in situ* by the treatment of α-tosylamine precursors with a base, in order to avoid their decomposition.

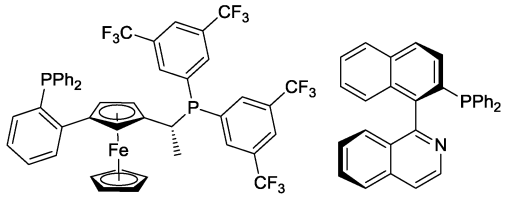
On the other hand, Liao *et al.*[10e] reported a highly enantioselective copper(I)-catalyzed boryl addition to *N*-Boc aldimines



22 25

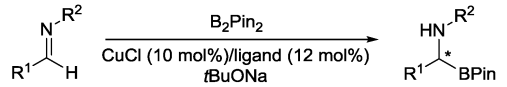
entry	R	chiral phosphine	product	conv.[a] (%)	*ee*[b] (%)
1	Ph	**23**	**25a**	56[c]	99
2	Ph	**24**	**25a**	45[c]	99
3	4-MeO-Ph	**23**	**25b**	83	75
4	4-MeO-Ph	**24**	**25b**	74	55
5	4-CF_3-Ph	**23**	**25c**	95	71
6	4-CF_3-Ph	**24**	**25c**	90	52
7	C_6H_{13}	**23**	**25d**	97	24
8	C_6H_{13}	**24**	**25d**	99	14

[a] Determined by ^{1}H NMR spectroscopy
[b] Determined by HPLC–TOF
[c] 25 °C



23 **24**

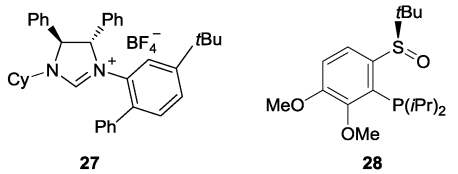
Scheme 8



26 **29**

entry	R^1	R^2	ligand	additive	product	yield (%)	*ee* (%)[a]
1	Ar, Cy[b], *i*Bu[b]	Bz	**27**	-	(*R*)-**29**	29–94	41–86
2	Ar	Boc	**28**	-	(*S*)-**29**	45–65	72–96
3	Ar	Boc	**28**	NaBARF[c]	(*R*)-**29**	46–64	82–96

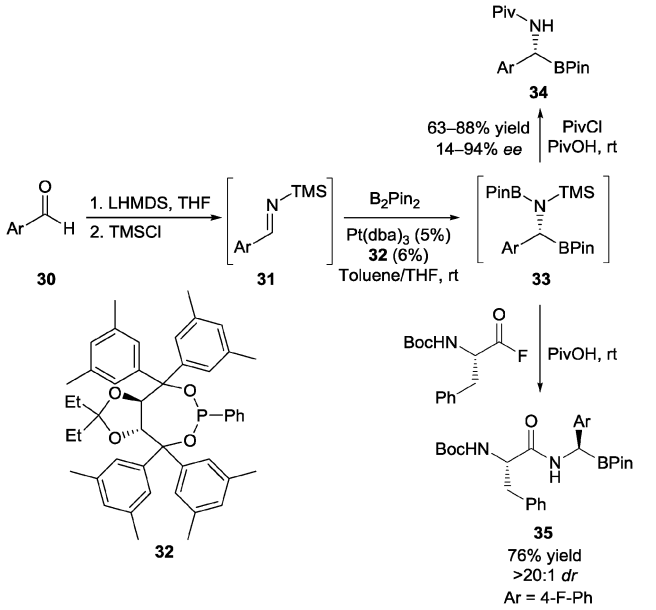
[a] Determined by chiral HPLC analysis
[b] Aldimine generated *in situ* by treatment of α-tosylamine precursor with Cs_2CO_3
[c] Sodium tetrakis[(3,5-trifluoromethyl)phenyl]borate



27 **28**

Scheme 9

(Scheme 9, entries 2 and 3) by using chiral sulfoxide-dialkylphosphine **28** as a ligand. Remarkably, both enantiomers of α-aminoboronic esters **29** were obtained through a counteranion switch in the cationic copper(I) catalyst that was *in situ*-generated. The boryl copper species generated from precatalyst **28**-Cu-O*t*Bu underwent addition from the *Si*-face of the imine and afforded the (*S*)-products (entry 2). Conversely, the cationic copper complex with a larger anion, (**28**-Cu)$^+$ BARF$^-$, induced the opposite absolute configuration of **29** (entry 3). It was reasoned by the authors that the pinacolboryl moiety approaches the cationic copper complex from the back side of the BARF anion. As a consequence of this, the boryl-copper species underwent addition from the *Re*-face of the imine due to its coordination *trans* to the *tert*-butylsulfinyl group.



30 **31** **33** **34**

32

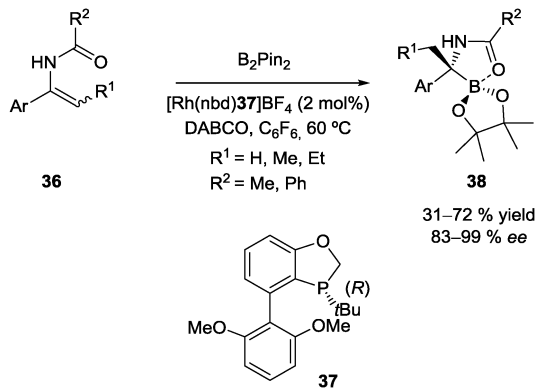
35
76% yield
>20:1 *dr*
Ar = 4-F-Ph

Scheme 10

The reaction gave high enantioselectivities for a broad scope of benzaldimines. Only low enantioselectivities were observed for *ortho*-substituted aryl aldimines when NaBARF was used as an additive and for alkyl aldimines with both catalytic systems.

In a related work, Morken and Hong[24] showed the diboration of *in situ*-generated silyl imines with B_2Pin_2 in the presence of a Pt–phosphonite catalyst made, in turn, from **32** (Scheme 10). The resulting diboration adducts **33** were directly acylated, thus providing straightforward access to *N*-acyl α-aminoboronic esters **34** or peptide derivatives such as **35**.

2.1.3. Hydroboration of enamides. It is only very recently that Tang *et al.* described the first enantioselective synthesis of α-amino tertiary boronic esters by rhodium-catalyzed hydroboration of α-arylenamides (Scheme 11).[10d] The treatment of the latter with B_2Pin_2 in the presence of a rhodium complex, generated from phosphorous-chiral ligand **37**, yielded α-aminoboronic esters **38** in good yields and excellent enantioselectivities. The regiocontrol achieved was shown to be due to the presence of a carbonyl directing group in the starting substrates.



36 **38**

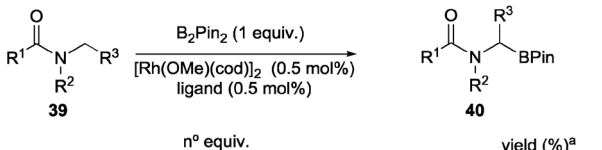
37

Scheme 11

Under optimized conditions of solvent, base and ligand, the hydroboration was broad in scope, particularly regarding the electronic properties and the substitution pattern of the aryl group (Ar) in **36**. Experimental studies supported the hydroboration reaction pathway and allowed to discard the tautomerization of **36** followed by diboration of the resultant acyl imine as an alternative mechanism. The catalytic cycle of the hydroboration involved oxidative addition of bis(pinacolate)diboron to the rhodium complex, reaction with the N–H of **36** to yield boryl rhodium hydride species, olefin insertion to the Rh–H bond, and reductive elimination.

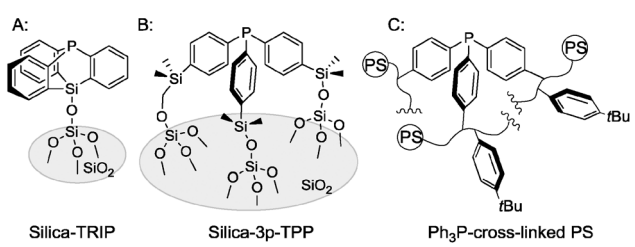
2.1.4. C(sp^3)–H borylation reactions. The direct C(sp^3)–H borylation α to a *N* atom certainly is a straightforward approach for synthesizing α-aminoboronic acid derivatives (Scheme 12). This type of C–B bond assembly has been recently achieved by using a diboron reagent in the presence of different heterogeneous catalytic systems.[25] The combination of $[Rh(OMe)(cod)]_2$ with silica-supported triarylphosphanes (A and B, Scheme 12) gave mono(phosphane)–metal complexes that enabled the selective borylation of *N*-adjacent C(sp^3)–H bonds of amides and ureas **39** under quite mild reaction conditions.[25a,c] According to the authors, the tryptycene-type cage structure featured by triarylphosphanes A and B and their immobilization proved critical factors for borylation activity. Such structural features resulted in an efficient isolation of each phosphane center, thus allowing the selective 1 : 1 metal-phosphane coordination.

Furthermore, Sawamura *et al.*[25b] described the catalytic application of a polystyrene-phosphane covalently bound hybrid (C, Scheme 12) for Rh-catalyzed *N*-adjacent C(sp^3)–H borylations.

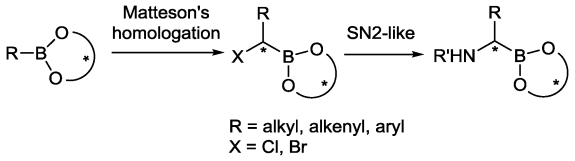


R^1	R^2	R^3	nº equiv. **39**	ligand	solvent	T (ºC)	product	yield (%)[a] based on B
Me	Me	H	2	A	Hexane	25	**40a**	80
Me	Me	H	2	A	Hexane	60	**40a**	126[c]
Me	Me	H	2	B[b]	Hexane	60	**40a**	69 (50)
*t*Bu	Me	H	2	A	Hexane	80	**40b**	84 (70)
*t*Bu	Et	Ph	2	A	Hexane	50	**40c**	139 (139)[c]
NEt_2	Me	H	2	A	Hexane	70	**40d**	92 (90)
$-(CH_2)_5-$		H	2	A	Hexane	40	**40e**	117 (86)
$-(CH_2)_5-$		H	2	B[b]	Hexane	60	**40e**	116 (106)[c]
$-N(Me)CH_2CH_2CH_2-$		H	2	B[b]	Hexane	40	**40f**	100 (75)
$-N(Me)CH_2CH_2CH_2-$		H	8	C[d]	THF	70	**40f**	73

[a] Determined by ^{1}H NMR or GC analysis (a small % of geminal bisborylation product was detected in the crude product mixture); isolated yield is given in parenthesis
[b] 0.7 mol% of ligand
[c] Yield >100% indicates that the byproduct HBPin also worked as a borylating reagent
[d] 1 mol% of catalyst



Scheme 12



Scheme 13

In this case, the three-fold cross-linking increases the density of the polymer around the phosphane core, thus achieving 1 : 1 metal-phosphane ligation, and generates a ligand steric effect moderate enough to ensure catalytic performance.

These procedures gave access to boroglycine and borophenylglycine derivatives (Scheme 12) in good yields based on boron. The required excess of substrate against the boron reagent constitutes an undesirable feature if the activation of more laborious substrates is pursued. However, the applicability of the methodology for the preparation of additional acyclic α-aminoboronic acid derivatives has not yet been explored.

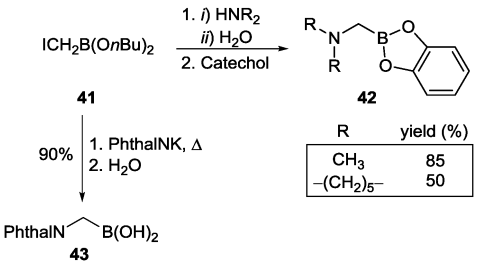
2.2. Formation of the C–N bond

2.2.1. S_N2-like nucleophilic displacements. A great deal of research has been devoted to the preparation of α-aminoboronic acid derivatives by reaction of (α-haloalkyl)boronic esters with nitrogen-based nucleophiles. This strategy was initiated by Matteson for the synthesis of α-aminomethylboronic esters (boroglycinates)[26] and further developed for the preparation of α-alkyl, α-alkenyl, and α-arylaminoboronic acid derivatives in racemic or enantioenriched form (Scheme 13).[12e,27]

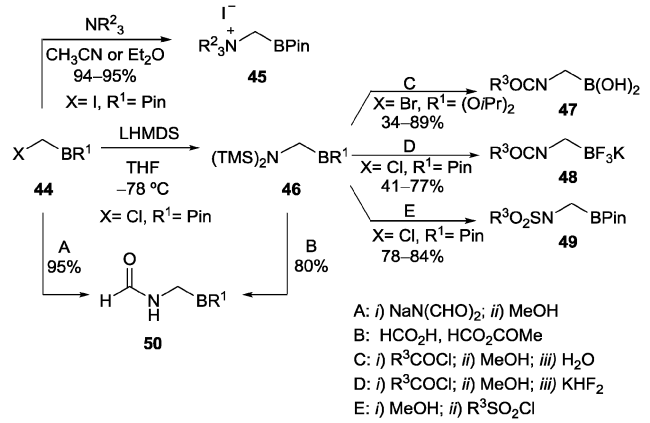
The displacement of iodide from α-iodomethylboronate ester **41** by nitrogen-based nucleophiles was first reported in 1968 (Scheme 14).[26] Secondary amines reacted readily with **41** and furnished α-aminoboronic acids that were isolated as catechol ester derivatives. In addition, deprotonated amides provided compounds such as phthalimidomethaneboronic acid **43**.

Besides, tertiary amines[28] and lithiohexamethyldisilazane[29–31] reacted with α-halomethylboronic esters **44** and produced stable quaternary ammonium boronate salts **45** and silylated aminoboronic esters **46**, respectively (Scheme 15). The latter were used as intermediates for the preparation of formamido-,[29] acylamino-,[30] and sulfonamidemethylboronic esters.[31]

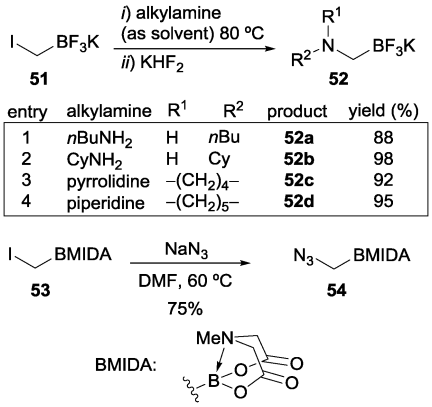
More recently, nucleophilic substitutions of α-halomethylboronic esters equipped with a tetracoordinated boron center have been described (Scheme 16).[32] According to the authors, substitutions of trifluoroborate **51** by alkylamines follow a pure



Scheme 14



Scheme 15

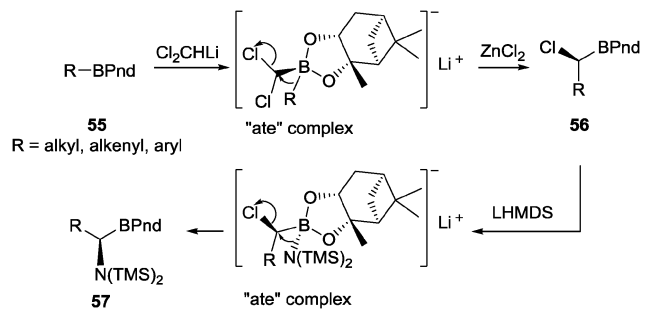


entry	alkylamine	R^1	R^2	product	yield (%)
1	$nBuNH_2$	H	*n*Bu	**52a**	88
2	$CyNH_2$	H	Cy	**52b**	98
3	pyrrolidine	$-(CH_2)_4-$		**52c**	92
4	piperidine	$-(CH_2)_5-$		**52d**	95

Scheme 16

S_N2 mechanism.[32a] By contrast, the nucleophilic displacement of the halide in a substrate with sp^2 hybridization at the boron atom involves the generation of an intermediate ''ate'' complex that undergoes migration of the nitrogen to the neighboring carbon atom (Scheme 17).[12e,27]

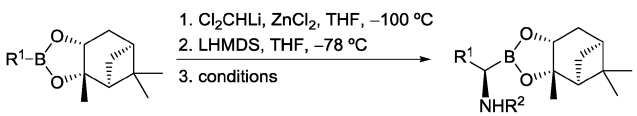
The mechanism *via* an ''ate''-type intermediate is at the base of Matteson's homologation methodology (Scheme 17), which involves the one-carbon chain extension of a sp^2-boronic ester.[12e,27] Such a procedure has been a standard method for the synthesis of racemic[12e,27,33,34] and enantioenriched α-alkyl-, α-alkenyl- and α-arylaminoboronic acid derivatives.[7a,10a,11c,12e,27,33,35]



Scheme 17

Specifically, addition of (dichloromethyl)lithium to a pinanediol boronic ester **55** (Scheme 17) places the group on the less hindered face of the chiral director. Rearrangement of the resulting ''ate''-complex produces (α-chloroalkyl)boronic ester **56** in high diastereomeric purity.[12e] Subsequent treatment of **56** with lithiohexamethyldisilazane furnishes the *N*-silylated derivative with inversion of the configuration. The experimental conditions for this chain-extending process have been optimized.[36] It was found that the presence of zinc chloride in the mixture enhances the stereoselectivity attained during the migration step (generally formed in ~90–95% if the only cation is lithium and ≥99% if zinc chloride is used).[12e,36] This effect was attributed to the ability of the Lewis acid to act as a promoter of the rearrangement and as a scavenger of the chlorine ion that might cause epimerization at the α-carbon of **56**. In addition, the use of diethyl ether as a solvent, instead of tetrahydrofuran, ensured reproducibility on a large-scale manufacturing process.[36]

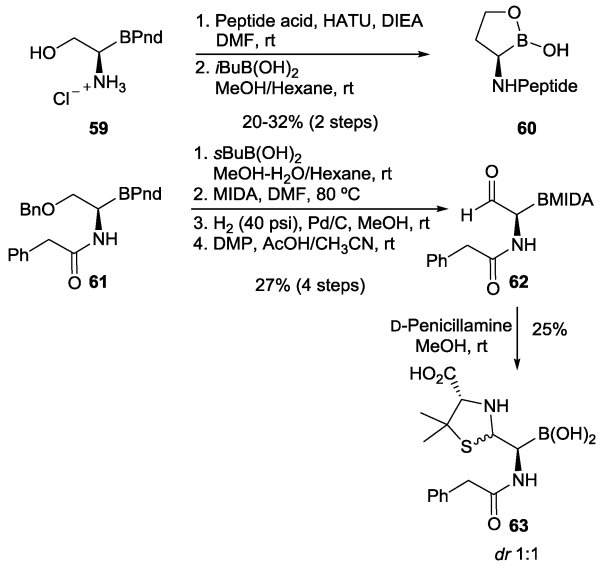
As already mentioned, the isolation of *N*-silylated derivatives is usually eluded and *N*-acyl (Scheme 18, entries 1–6), *N*-sulfonyl (Scheme 18, entry 14), and α-aminoboronic esters bearing tertiary amino groups (Scheme 18, entries 7–13) are produced.[7a,10a,11c,12e,27,33,35] Alternatively, *bis*(trimethylsilyl)-amino boronic esters **57** (Scheme 17) have been desilylated and reacted immediately for the preparation of peptidyl derivatives.[37] Mattesson's homologation proceeded with high diastereoselectivity for a broad scope of pinanediol boronic esters **55** (Scheme 18), generated, in turn, from aryl- and alkyl-Grignard reagents. Among others, the process gave access to



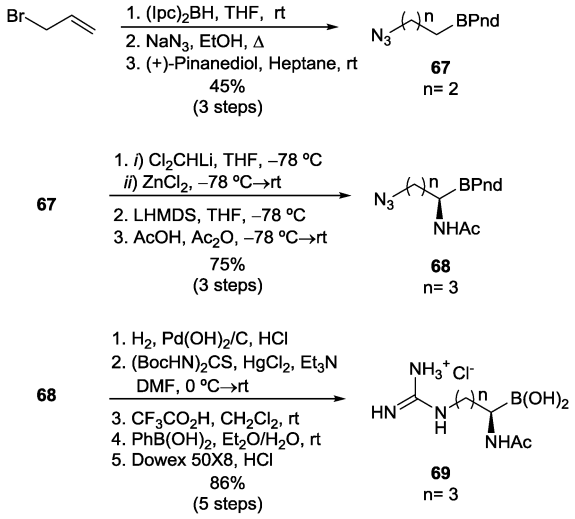
entry	R^1	R^2	conditions	product	yield (%)	ref.
1	Bn	Ac	A	**58a**	63[a]	27
2	Bn	Cbz-Ala	B	**58b**	25–35[b]	33c
3	Bn	Bz	B	**58c**	35[b]	33c
4	Ph	Cbz-Ala	B	**58d**	25[b]	33c
5	$(CH_3)_2CH$	Cbz-Ala	C	**58e**	42[b]	33c
6	N_3CH_2	Ac	D	**58f**	60[a,c]	7a
7	$(CH_3)_2CH$	$H{\cdot}CF_3CO_2H$	E	**58g**	43[d]	33b
8	Bn	$H{\cdot}CF_3CO_2H$	E	**58h**	58	35r
9	4-MeO-$PhCH_2$	$H{\cdot}CF_3CO_2H$	E	**58i**	78[e]	35k
10	CH_3	H·HCl	F	**58j**[f]	32	35l
11	$PMBO(CH_2)_2$	H·HCl	F	**58k**[g]	66	35m
12	$(CH_3)_2CHCH_2$	H·HCl	F	**58l**	65[e]	35p
13	$(CH_3)_2CH$	H·HCl	F	**58m**	60[e]	35q
14	Bn	SO_2Bn	G	**58n**	20	31b

[a] Isolated yield prior to recrystallization. [b] Recrystallyzed solid. [c] Step 2 performed at –100 °C to minimize elimination; >98% *de*. [d] 88% *dr* determined by ^{19}F NMR of MTPA amide derivative. [e] THF/Et_2O as solvent in step 2. [f] The enantiomer is described. [g] $R^1 = HO(CH_2)_2-$.

Scheme 18



Scheme 19



Scheme 21

boroalanine, boroleucine, borovaline, borophenylalanine and boroserine derivatives.

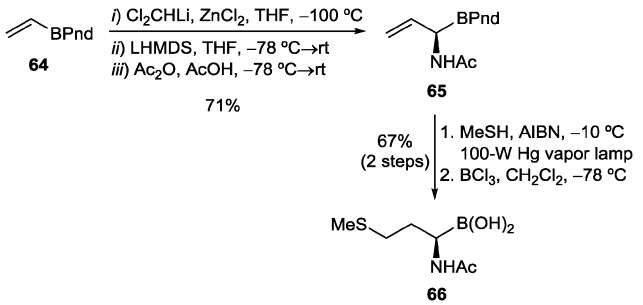
Interestingly, (α-azidoalkyl)-[7a,38] (entry 6, Scheme 18) and (α-hydroxyalkyl)amino boronic esters[35m,39] (Scheme 19) proved useful intermediates for the preparation of bioactive molecules, such as α-(triazolyl)amino boronic acids,[7a] α-amino cyclic boronates **60**,[35m] and α-(2-thiazolidinyl)amino boronic acids **63**.[39]

In addition to aryl- and alkylboronic esters, Mattesson's homologation has been applied to α-alkenylboronic esters[34b,40] such as **64**[40] (Scheme 20). Subsequent desilylation and acylation gave α-(acetamido)allylboronate **65** that, in turn, underwent radical addition of methanethiol to give boromethionine derivative **66**.

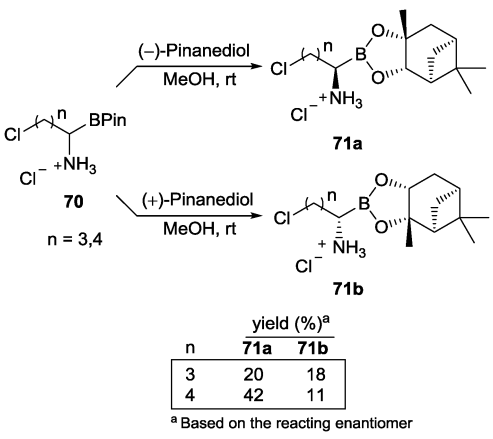
On the other hand, the hydroboration of allyl bromide furnished an haloalkyl-substituted boronate that proved a convenient precursor for azidoalkyl-substituted **67** (Scheme 21).[41,42] This substrate gave access to boroornithine[41a] and boroarginine[41b] derivatives when subjected to Matteson's homologation.

Interestingly, the preparation of boroarginine- and borolysine-containing peptides[42] has often involved the incorporation of a haloalkyl-substituted α-aminoboronic acid precursor in the peptide chain, followed by the side-chain transformations needed. Due to their utility as synthetic intermediates, a few haloalkyl-substituted α-aminoboronic esters have been isolated in diastereomerically pure form by transesterification of racemic precursors **70** with chiral pinanediols under selective crystallization conditions (Scheme 22).[43]

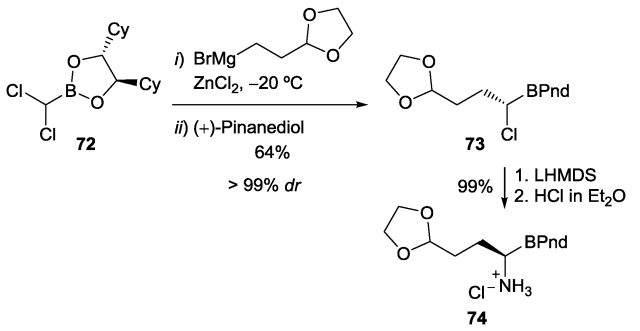
The synthetic versatility of chiral (α-haloalkyl)boronic esters (**56**, Scheme 17) stimulated the development of additional methods for their preparation.[12e,44–46] The preparative pathways include the reaction of dichloromethylboronic esters of C_2-symmetrical chiral diols with organometallic reagents (Scheme 23),[12e,45] and enantioselective hydrogenations of 1-chloro-1-alkenylboronic esters (Scheme 24).[46] Matteson reported the use of dichloromethylboronic esters of C_2 symmetric diols for chiral induction in the synthesis of (α-chloroalkyl)boronic esters.[12e,44] This methodology was applied by Mantri *et al.* to the preparation of **74** (Scheme 23), which is a precursor of boroornithine.[45] A high asymmetric induction (>99% dr) was achieved during the reaction of **72** with the dioxolane Grignard at a reaction temperature readily practicable for large scale synthesis. The resulting compound was transesterified to pinanediol ester due to good stability for projected boropeptide chemistry. The treatment of (α-chloroalkyl)boronic ester **73** with lithium



Scheme 20



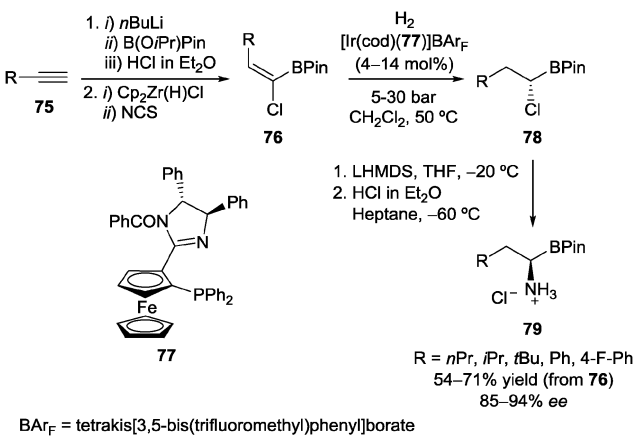
Scheme 22



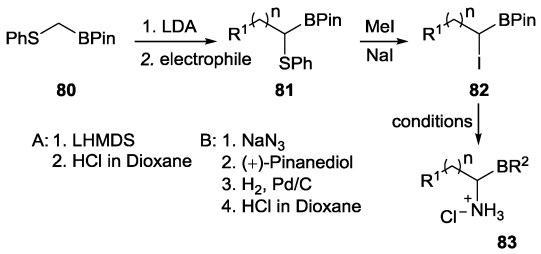
Scheme 23

bis(trimethylsilyl)amide (LHMDS) produced an amine that underwent deprotection in dry ethereal hydrogen chloride solution to generate hydrochloride salt **74**. It should be noted that pinanediol (dichloromethyl)boronate was also used as a means of expanding the variety of side-chains to be incorporated during the synthesis of (α-chloroalkyl)boronic esters.[47] However, the resulting diastereomeric "ate"-complexes show quite different levels of stereocontrol during the subsequent migration step, thus leading to poor diastereomeric ratios of (α-chloroalkyl)boronic esters.[12e]

The route towards (α-chloroalkyl)boronic esters **78** (Scheme 24) based on the asymmetric catalytic hydrogenation of 1-chloro-1-alkenylboronates **76** was reported by Časar *et al.* in 2012.[46a,b] A range of substrates **76** were hydrogenated in the presence of a P^N ligand-based iridium catalyst. The stereoelectronic features of the chiral ligand and the substrate concentration were found to have a significant influence in the reaction outcome. Under optimized conditions, the transformation occurred without significant dehalogenation for all substrates. Excellent conversions and good enantioselectivities were obtained, albeit higher catalyst loadings were required to achieve full conversions for substrates bearing bulky alkyl moieties or aryl substituents. In a later report, the same authors found that 1-bromo-1-alkenylboronic appear to be less reactive towards hydrogenation with a number of iridium–P^N complexes.[46c] In spite of this, the study demonstrated that high chemoselectivities and enantioselectivities of up to 73% ee,



Scheme 24



entry	electrophile	n	R^1	R^2	conditions	yield (%) 81	82	83
1	F_2HC–Br	1	CHF_2	Pin	A	56	49	52
2	$tBuO_2C$–Br	1	CO_2tBu	Pnd	B	35	-	47[a]
3	MeO_2C–	2	CO_2Me	Pnd	B	21	38	23

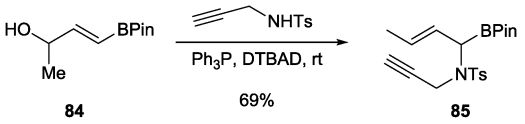
[a] Yield from **81**

Scheme 25

along with full conversions could be obtained for hydrogenation of acyclic alkyl substituted derivatives.

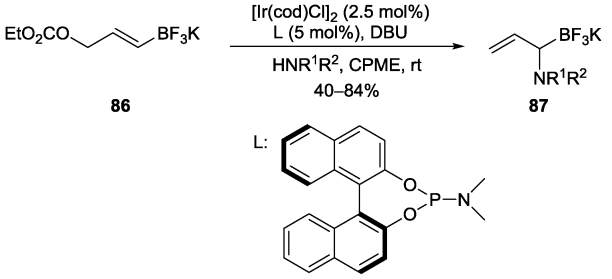
In addition to the aforementioned methods, a few strategies that provide access to racemic (α-haloalkyl)boronic esters have been reported.[48–50] Methods available include chlorination of α-alkoxyboronic esters generated, in turn, by borylation of α-alkoxyorganolithium reagents,[48] cleavage of a carbon–zirconium bond in boron–zirconium *gem*-bimetallic species with *N*-halosuccinimides (*vide infra*),[49] and the preparation of (α-haloalkyl)boronic esters under conditions amenable to the introduction of side chains as electrophiles (Scheme 25).[50] In the latter case, alkyl bromides and methyl acrylate were allowed to react with the stabilized anion of (phenylthio)methylboronate **80**. The resulting (α-phenylthioalkyl)boronic esters **81** were converted to the corresponding sulfonium salts by alkylation with excess methyl iodide. Such salts in the presence of sodium iodide produced α-iodo derivatives **82**. The latter gave access to α-aminoboronic esters **83** by conventional methods. In some cases racemic pinacol boronic esters were transesterified to (+)-pinanediol esters, and enantiomerically pure isomers could be separated by chromatography. This strategy proved particularly valuable with side chains that contain functionalities which are sensitive to basic conditions, thus being complementary to those procedures that involve the use of Grignard reagents. Among others, the methodology provided access to the boronic analogues of aspartic and glutamic acid.

2.2.2. Allylic aminations. In 2009 Carboni *et al.* studied Mitsunobu reactions of (3-hydroxy-buten-1-yl)boronic acid ester **84** with various nucleophiles, and found that the boronic ester moiety governed the regio- and stereochemical course of the amination.[51] Specifically, the use of *N*-tosylpropargylamine as the nucleophile gave access to α-aminoboronic ester **85** (Scheme 26). On the basis of the regio- and stereoselectivity observed a plausible reaction mechanism was proposed. It involved *in situ* generation of the leaving group, as in the classical Mitsunobu reaction, the formation of a borate by addition of the nucleophile to the boron atom, and 1,2-migration of the nitrogenated group in an S_N2' manner. The formation of a single isomer (*E*) was rationalized through a transition state that places the migrating substituent in *anti* to the leaving group and arranges for the least possible allylic 1,3-strain.



84 85

Scheme 26



86 87

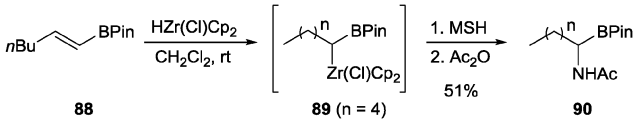
HNR^1R^2 : morpholine, piperidine, pirimidines, pirazines, tetrahydroisoquinolines, *N*-benzylmethylamine

Scheme 27

The allylic amination of alkenylboronic esters **86** catalyzed by chiral iridium complexes was later investigated by the same group (Scheme 27).[52] In this case, the nature of the boronic ester directed the regioselectivity of the process. The use of trifluoroborates **86** led to α-aminoboronate **87** as the only product, while pinacol boronic esters preferentially gave the linear allylic amine. The inversion of regioselectivity was attributed to the electronic effect of the trifluoroborate group on the (π-allyl)Ir intermediate. Under optimized conditions of the solvent and base, the allylic amination was broad in scope for cyclic amines, but only suited to acyclic amines endowed with a small cone angle, such as benzylethylamine. Unfortunately, no data were provided by the authors regarding the enantiomeric excess of allylic substitution products due to the lack of a suitable analytical method.

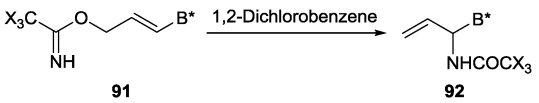
2.2.3. Electrophilic aminations. Sbrenik and Zheng[49] reported the preparation of α-aminoboronic ester **90**, in the racemic form, by electrophilic amination of boron–zirconium *gem*-bimetallic species **89** (Scheme 28). This species was generated through the regioselective hydrozirconation of alkenylboronic ester **88** by using Schwartz's reagent. Subsequent selective cleavage of the carbon–zirconium bond with *O*-mesitylsulfonyl hydroxylamine (MSH)[53] as the electrophilic aminating reagent provided α-aminoboronic ester **90** in a reasonable yield.

2.2.4. [3,3]-Sigmatropic rearrangements. Pietruszka *et al.*[54] investigated [3,3]-sigmatropic rearrangements of trichloro- and trifluoroacetimidates **91** as an entry to enantiopure α-aminoboronic acid derivatives **92** (Scheme 29). However, it was found



88 89 (n = 4) 90

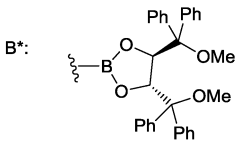
Scheme 28



91 92

X	T (°C)	[91] (mM)	product	yield (%)	*dr*
Cl	170	30	**92a**	52	59:41
Cl	170[a]	5	**92a**	67	59:41
F	176	17	**92b**	20	55:45

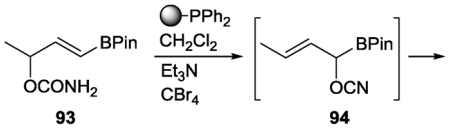
[a] Microwave heating



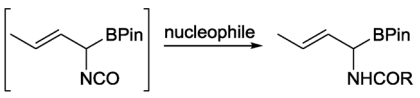
Scheme 29

that the rearrangement required a very high temperature to occur and led to **92** as mixtures of diastereoisomers that were determined to be close to 60 : 40 in all cases. Unfortunately, the separation of diastereoisomers was unsuccessful and, therefore, no further attempts to pursue the approach were made by the authors.

More recently, Carboni's group carried out the synthesis of allylic α-aminoboronic esters **96** *via* a [3,3]-sigmatropic cyanate–isocyanate rearrangement of racemic carbamate **93** (Scheme 30).[55] Dehydration of **93** with triphenylphosphine, carbon tetrabromide and triethylamine gave cyanate **94**, which underwent [3,3]-sigmatropic rearrangement at room temperature. The resulting allyl isocyanate **95** was transformed *in situ* by reaction with a variety of nucleophiles. It was suggested that the rearrangement occurs through a cyclic transition state of six centers with the boronate and methyl groups in pseudoequatorial positions, which helps to explain the detection of a single geometric isomer of *E* configuration.



93 94

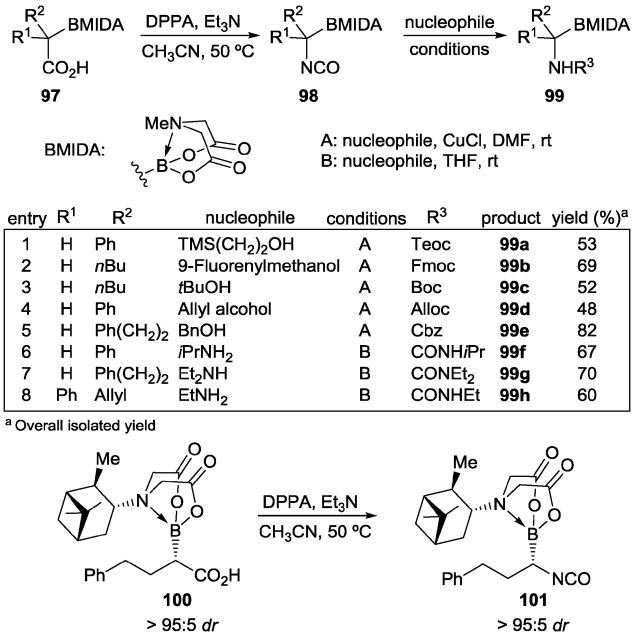


95 96

nucleophile	product	R	yield (%)
MeOH	OMe	**96a**	81
pyrrolidine	$N(CH_2)_4$	**96b**	80
piperidine	$N(CH_2)_5$	**96c**	76
$BnNH_2$	NHBn	**96d**	78
Gly-OMe·HCl[a]	Gly-OMe	**96e**	70
L-AlaOMe·HCl[a]	L-Ala-OMe	**96f**	60
AcSH	Me	**96g**	63
		96h	

[a] In the presence of a supplementary equivalent of Et_3N

Scheme 30



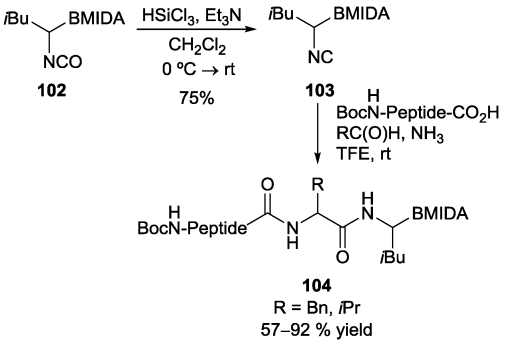
entry	R^1	R^2	nucleophile	conditions	R^3	product	yield (%)[a]
1	H	Ph	$TMS(CH_2)_2OH$	A	Teoc	**99a**	53
2	H	*n*Bu	9-Fluorenylmethanol	A	Fmoc	**99b**	69
3	H	*n*Bu	*t*BuOH	A	Boc	**99c**	52
4	H	Ph	Allyl alcohol	A	Alloc	**99d**	48
5	H	$Ph(CH_2)_2$	BnOH	A	Cbz	**99e**	82
6	H	Ph	$iPrNH_2$	B	CONH*i*Pr	**99f**	67
7	H	$Ph(CH_2)_2$	Et_2NH	B	$CONEt_2$	**99g**	70
8	Ph	Allyl	$EtNH_2$	B	CONHEt	**99h**	60

[a] Overall isolated yield

Scheme 31

2.2.5. Curtius rearrangement of α-borylcarboxylic acids. Yudin *et al.* reported an attractive boroalkyl group migration that provides access to α-aminoboronic acid derivatives (Scheme 31).[56] The procedure[56a,b] involved the preparation of α-borylisocyanates **98** *via* Curtius rearrangement of α-borylcarboxylic acids **97**.[57] The thermal decomposition of the intermediate carboxylic azides worked well with aryl- or alkyl-substituted precursors (entries 1–7) and with α,α-disubstituted analogues (entry 8). In addition, α-borylcarboxylic acid **100** was used for the stereochemical investigation of the migratory process that it was found to occur with complete retention of the configuration. The resulting α-borylisocyanates **98** have enabled the synthesis of α-aminoboronic acid derivatives **99** by reaction with amine and alcohol nucleophiles at the isocyanate group.

In addition, the deoxygenation of isocyanates **102** (Scheme 32) furnished isocyanides **103** that enabled the preparation of boropeptides through a multicomponent approach.[56c]



Scheme 32

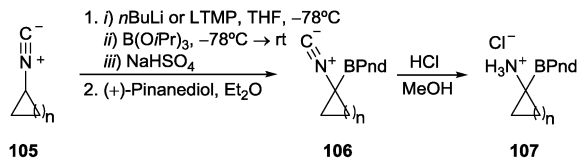
3. Synthesis of carbocyclic α-aminoboronic acids

As mentioned in Section 2.1.1, Priestley and Decicco[13] reported the preparation of carbocyclic α-aminoboronic acid esters through borylation of α-amino metalated species. Specifically, three- and six-membered carbocyclic α-aminoboronates **107** (Scheme 33) were obtained through a three-step sequence that involved the addition of metalated isocyanides to triisopropyl borate, esterification of the boronic acids isolated after the hydrolytic work-up, and acid-catalyzed hydrolysis of isocyanides **106.**

4. Synthesis of azacyclic α-aminoboronic acids

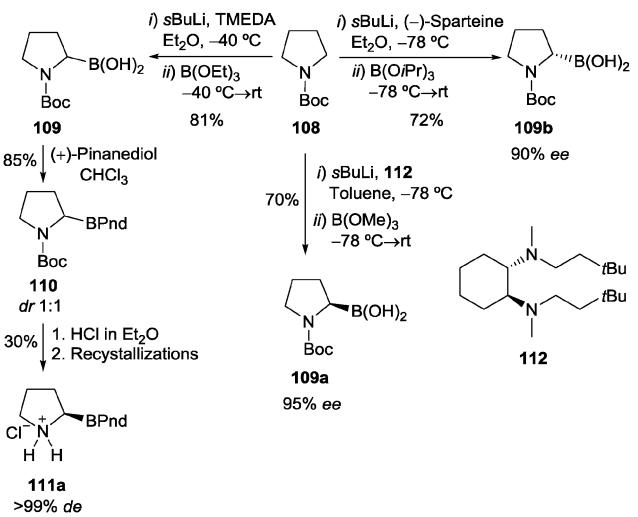
4.1. Formation of the C–B bond

4.1.1. Addition of α-amino organometallic compounds to boron-containing electrophiles. The ease of the lithiation of *N*-Boc-pyrrolidine **108** has been applied to the preparation of boroproline both in racemic[58] and enantioenriched forms[59] (Scheme 34). Treatment of **108** with *sec*-butyllithium in the presence of tetramethylethylenediamine (TMEDA) generated α-anionic species that efficiently reacted with trimethyl borate.[58a] The resulting boroprolinate was hydrolysed during the work-up to give **109** in high yield. Diastereochemically pure **111a** was



n	yield (%) 106	107
1	33	96
4	14	95

Scheme 33



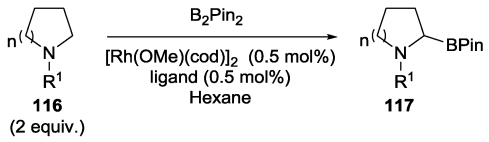
Scheme 34

produced through a sequence[60] that involved esterification of the racemic precursor **109** with (+)-pinanediol, deprotection of the amine functionality under acidic conditions, and sequential selective crystallizations of the resulting amine hydrochloride (Scheme 34). The absolute configuration of the new stereogenic center was assigned as *R* on the basis of X-ray diffraction analysis of **111a**. Scale-up of the overall process engaged several modifications for the α-metalation step, such as avoidance of TMEDA as an additive, and improvements for recycling the chiral auxiliary that is employed as a resolving agent.[58b]

Alternatively, highly enantioselective syntheses of *N*-Boc protected boroproline have been accomplished by asymmetric directed α-metalations of **108** (Scheme 34).[59] Specifically, (−)-sparteine-mediated lithiation of **108** and subsequent treatment with triisopropyl borate yielded (*S*)-configured boroproline **109b** with 90% ee.[59a] In contrast, the use of diamine **112** for the generation of the chiral lithium–carbanion pair furnished (*R*)-configured boroproline **109a** with 95% ee.[59b]

More recently, Lai *et al.* described the preparation of the *cis* stereoisomer of 4-hydroxy-l-boroproline **115** (Scheme 35) for designing dipeptidyl peptidase IV inhibitors for the treatment of type II diabetes.[61] The lithiation of pyrrolidinol **113** required the use of an additional equivalent of *sec*-butyllithium and to raise the temperature to −46 °C for two hours. After treatment with triisopropyl borate and hydrolytic work-up the crude mixture was esterified with (+)-pinanediol. Diastereochemically pure **115** was isolated in 35% yield by crystallization of the diastereoisomeric mixture. The stereochemistry and regiochemistry of the process were unambiguously assigned by 2D NMR of cyclic dipeptide derivatives.

4.1.2. C(sp^3)–H borylation reactions. Rh-catalyzed *N*-adjacent C(sp^3)–H borylation through heterogeneous approaches were also applicable to the preparation of racemic α-aminoboronic ester derivatives with azacyclic structure (Scheme 36).[25] The catalytic species generated from silica-supported phosphane ligands[25a,c] enabled the selective borylation of amides and ureas **116** (entries 1 and 2, respectively) under mild reaction conditions. The selectivity for ring borylation was not limited to the use of *N*-acyl groups as catalyst directing groups, but also to N-heterocyclic groups. In fact, pyridine worked well as a directing group for catalysts generated from silica-,[25a,c] or polystyrene-supported[25b] phosphane ligands and azacyclic α-aminoboronic esters were obtained from saturated cyclic amines with different ring sizes (entries 3–7).



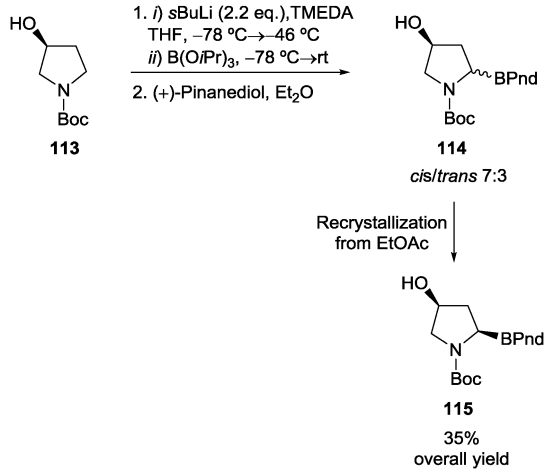
entry	R^1	n	ligand	T (°C)	product	yield (%) based on B[a]
1	Piv	1	Silica-TRIP	80	**117a**	122 (107)
2	C(O)NEt$_2$	1	Silica-TRIP	60	**117b**	184 (154)
3	2-Pyridyl	1	Silica-TRIP	80	**117c**	152 (125)
4	2-Pyridyl	2	Silica-TRIP	80	**117d**	153 (130)
5	2-Pyridyl	2	Silica-3p-TPP	80	**117d**	154 (117)[b]
6	2-Pyridyl	2	Ph_3P-cross-linked PS	80	**117d**	(90)[c]
7	2-Pyridyl	3	Silica-TRIP	100	**117e**	112 (101)

[a] Yields based on B_2Pin_2 determined by ^{1}H NMR and GC; isolated yields are given in parenthesis; yields >100% indicate that the byproduct HBPin also worked as a borylating reagent
[b] 0.7 mol% of ligand
[c] 8 equiv. of **116**, 1 mol% of Rh, 1 mol% of ligand

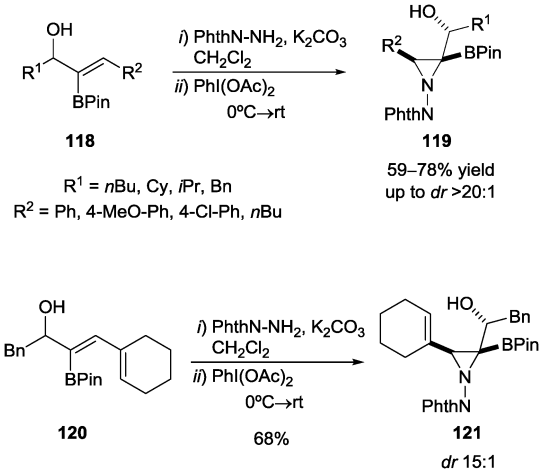
Scheme 36

4.2. Formation of the C–N bond

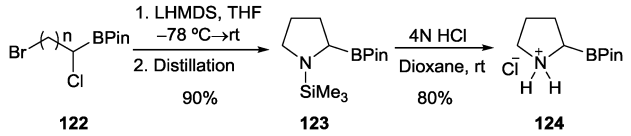
4.2.1. Two-component cyclizations. In 2011, Walsh *et al.* reported the synthesis of boron-substituted aziridines **119** by the treatment of BPin-substituted allylic alcohols **118** with *N*-aminophthalimide as the nitrogen source in the presence of di(acetoxyiodo)benzene (Scheme 37).[62] The nitrene, which is generated by the action of this oxidant, produced BPin-substituted aziridines **119** in good yields with high levels of diastereoselectivity. The nature of the solvent, the presence of a base, and the order of addition of reagents were found to have a significant influence on the reaction outcome. The *syn* relative stereochemistry between the aziridine ring and the hydroxyl group was confirmed by X-ray diffraction analysis of **119** (R^1 = iPr, R^2 = 4-MeO-Ph). The chemoselectivity attained with dyene **120**



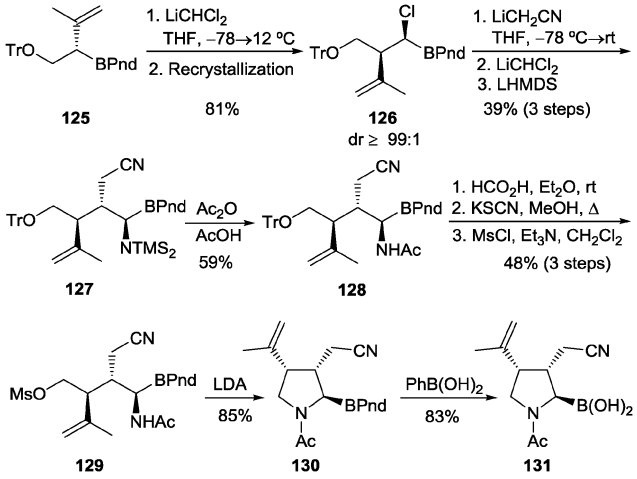
Scheme 35



Scheme 37



Scheme 38



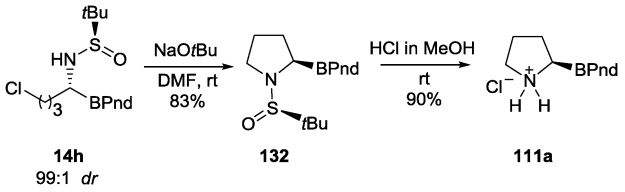
Scheme 39

suggested the reactions being accelerated and directed by the allylic hydroxyl group.

4.2.2. Intramolecular C–N cyclization. In 1990, the procedure developed by Matteson for the synthesis of α-aminoboronic acids was applied to the synthesis of racemic boroproline derivatives (Scheme 38).[63] The pyrrolidine ring was assembled by intramolecular C–N cyclization of a halogen-substituted α-aminoboronic ester. The latter was obtained by the treatment of **122** with LHMDS. The cyclization reaction took place by distillation of the crude *N*-silylated α-aminoboronic ester intermediate.

This type of chain-extension methodology was later applied by Matteson and Lu to the asymmetric synthesis of **131**, which is an analogue of kainic acid having cyano and boronic acid moieties in place of the two carboxylic acid groups (Scheme 39).[64] The cyanomethyl and bis(trimethylsilyl)amino substituents were sequentially incorporated into pinanediol boronate **125**. According to the authors, all of the boronic ester intermediates were produced in high diastereomeric purity, with the exception of **126**. In this case, reaction of **125** with (dichloromethyl)lithium gave better yield when conducted without zinc chloride. The major isomer of the diastereomeric mixture (dr ~ 10 : 1) was obtained by crystallization. The deprotection of the oxygen group in **128** involved the generation of a formate ester that was subsequently treated with potassium thiocyanate. The resulting hydroxyl group was mesylated under standard conditions. The pyrrolidine ring formation took place rapidly by the treatment of **129** with lithium diisopropylamide.

More recently, Sun *et al.* reported[18b] the asymmetric synthesis of **14h** by copper(I)-catalyzed borylation of a chiral sulfinylimine precursor (Section 2.1.2.1, Scheme 5). The tolerance of this methodology to the presence of a chloride group in the starting



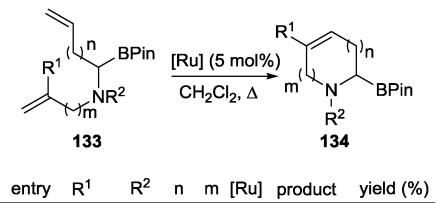
Scheme 40

sulfinylimine was further exploited for the preparation of the cyclic derivative (Scheme 40). Thus, the treatment of **14h** with base led to intramolecular cyclization and gave **132** in high diastereomeric purity. Removal of the *N*-protecting group gave boroproline ester **111a**.

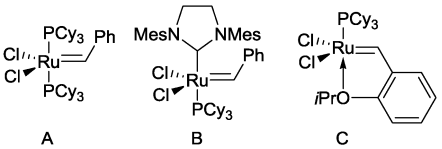
4.3. Intramolecular C–C bond formation

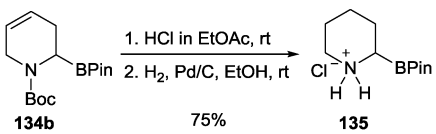
4.3.1. Ring-closing metathesis. In 2004, Carboni *et al.* reported ruthenium catalyzed ring-closing metathesis as the key step for the synthesis of cyclic α-aminoboronic esters **134**, in racemic form (Scheme 41).[65] The Grubbs catalyst was found to be effective for six- and seven-membered ring formation from *N*-Boc- or *N*-tosylaminoboronates **133** (entries 2–5). In addition, substrates with 1,1-disubstituted double bonds gave moderate yields of cyclic α-aminoboronic esters, such as **134f**, in the presence of second-generation Grubbs catalysts. Instead, five-membered ring-closing proved difficult due to the instability of the products in the presence of either catalyst, and only a moderate yield of **134a** (entry 1) was obtained with catalyst C. Deprotection and hydrogenation of the double bond in **134b** gave access to the boronic acid analogue of pipecolic acid.

4.3.2. Tandem carbene addition/cyclopropanation. The same group[66] explored the preparation of strained bicyclic

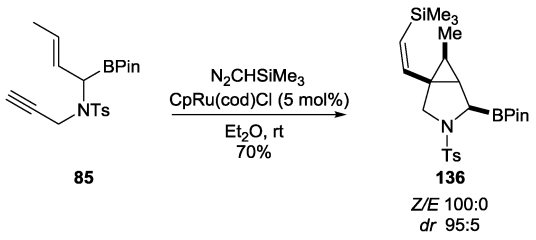


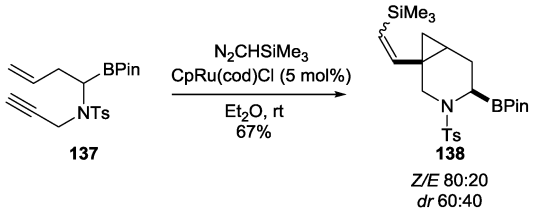
entry	R^1	R^2	n	m	[Ru]	product	yield (%)
1	H	Ts	0	1	C	**134a**	42
2	H	Boc	1	1	A	**134b**	87
3	H	Ts	1	1	A	**134c**	90
4	H	Boc	1	2	A	**134d**	85
5	H	Boc	2	1	A	**134e**	58
6	Me	Boc	1	1	B	**134f**	40



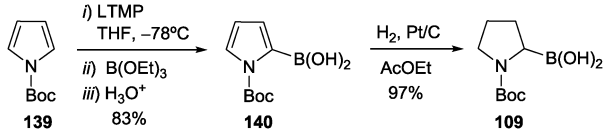


Scheme 41





Scheme 42



Scheme 43

α-aminoboronic esters by reaction of 1,6- and 1,7-enynes **85** and **137** (Scheme 42) with trimethylsilyldiazomethane in the presence of a ruthenium catalyst. The carbene addition/cyclopropanation sequence took place under mild conditions and furnished racemic **136** and **138** in good yields. The major isomer exhibited a *cis* configuration of the vinyl and ester group along with high *Z*-stereoselectivity for the created alkenyl chain.

4.4. Synthesis from aromatic heterocycles

In 1993, Kelly *et al.* reported an efficient route for the preparation of multigram quantities of racemic *N*-Boc protected boroproline **109** (Scheme 43), that was resolved as previously described (Scheme 34 in Section 4.1.1).[60] The synthetic procedure involved the lithiation–borylation–reduction of *N*-Boc protected pyrrole **139**.[58a,60,67] Treatment of the latter with lithium tetramethylpiperidide (LTMP) generated the α-anion that reacted with triethylborate. Hydrolytic work-up produced free boronic acid **140** that was readily hydrogenated by using Pt/C as a catalyst.

5. Concluding remarks

In this review we have tried to provide a general perspective of methodologies for the preparation of α-aminoboronic acid derivatives in either racemic or enantiopure form. A variety of valuable protocols have been established depending upon the acyclic, carbocyclic and azacyclic nature of the targeted structures. Among the implemented methods, the most widely-applied for the preparation of acyclic α-aminoboronic acids, Matteson's methodology, relied on the highly stereoselective chain-extension of a chiral boronic ester, followed by the addition of a nitrogen-nucleophile to the electrophilic boron atom, and stereospecific 1,2-migration of the amino function. This methodology, wherein the selection of the chiral director sets up the final stereochemistry, gave efficient access to a broad scope of highly enantioenriched α-aminoboronic acids. More recently, nucleophilic borylations of aldimines and rearrangements of chiral boronates of α-borylcarboxylic acids have delivered noteworthy contributions for the preparation of this type of compounds. On the other hand, the preparation of azacyclic analogues has largely addressed the isolation of boroproline in enantiomerically pure form, as it is part of serine protease inhibitors with important pharmacological properties. Best results were accomplished through highly enantioselective lithiation–borylation of a pyrrolidine precursor, intramolecular cyclization of α-aminoboronic esters generated by borylation of a chiral aldimine, and chemical resolution processes.

There is no doubt that the results achieved will encourage further investigations focusing on the refinement of the processes in an effort to improve the enantiomeric purity of the resulting α-aminoboronic acids. In some cases, the optical purity and absolute configuration of the final compound has not been established largely due to the limitations for their separation and analysis.

Acknowledgements

Financial support from Ministerio de Economía y Competitividad (CTQ2010-17436, CTQ2013-40855-R; FPI fellowship to P. A.) and Gobierno de Aragón – Fondo Social Europeo (research group E40) is gratefully acknowledged.

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