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J. Am. Chem. Soc., **Just Accepted Manuscript** • Publication Date (Web): 10 Dec 2019

Just Accepted

is published by the American Chemical Society. 1155 Sixteenth Street N.W., Washington, DC 20036

Asymmetric Synthesis of α-Aminoboronates via Rhodium-Catalyzed Enantioselective C(sp^3)–H Borylation

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KEYWORDS: a-aminoboronic acids, borylation, asymmetric synthesis, C–H activation

ABSTRACT: α-Aminoboronic acids, isostructural boron analogues of α-amino acids, have received much attention because of the important biomedical applications implicated for compounds containing this structure. Additionally, the inherent versatility of α-aminoboronic acids as synthetic intermediates through diverse carbon–boron bond transformations make the efficient synthesis of these compounds highly desirable. Here, we present a Rh-monophosphite chiral catalytic system that enables a highly efficient enantioselective borylation of N-adjacent C(sp^3)–H bonds for a range of substrate classes including 2-(*N*-alkylamino)heteroaryls and N-alkanoyl or aroyl-based secondary or tertiary amides, some of which are pharmaceutical agents or related compounds. Various stereospecific transformations of the enantioenriched α-aminoboronates including Suzuki–Miyaura coupling with aryl halides and the Rh-catalyzed reaction with an isocyanate derivative of α-amino acid affording a new peptide chain elongation method have been demonstrated. As a highlight of this work, the borylation protocol was successfully applied to the catalyst-controlled site- and stereoselective C(sp^3)–H borylation of an unprotected dipeptidic compound allowing remarkably streamlined synthesis of the anti-cancer drug molecule bortezomib, offering a straightforward route for the synthesis of privileged molecular architectures.

INTRODUCTION

Organoboronic acids represent an interesting class of enzyme inhibitors prominently in the area of protease inhibition.[1] The emergence of isostructural boron analogues of α-amino acids (Figure 1A), collectively called α-aminoboronic acids or boro(amino acid)s,[2,3] has resulted in the enhancement of the specificity and potency. A variety of alkyl- or arylboronic acids including peptidylboronic acid analogues have been implicated in numerous therapeutic interventions.[1] Among these, *bortezomib* finds particularly significant clinical applications as an anti-cancer drug as it reversibly inhibits the action of 26S proteasome with remarkable selectivity and potency through covalent boron–oxygen bond formation between the boronate moiety and the *N*-terminal threonine residue at the chymotrypsin-like active site of the protein.[4,5] Moreover, *ValboroPro* and *ProboroPro* are successful inhibitors of dipeptidyl peptidase IV (DPP IV) providing a strategy for the treatment of type-2 diabetes (Figure 1B).[6,7]

Such growing demands for pharmaceutically active boron-containing compounds amplify the necessity to develop practical strategies for synthesizing α-chirogenic α-aminoboronic acid derivatives.[8,9] Furthermore, alkylboronates participate in a number of transformations to give an array of products resulting from the intrinsic versatility of boronic acids and their derivatives as fundamental intermediates in synthesis, giving access to highly functionalized molecules including intermediate metabolites, amine-derived organocatalysts, and N-α-substituted compounds that have found widespread application in asymmetric synthesis as salient chirogenic auxiliaries (Figure 1A).[10–12]

Established protocols to access enantioenriched α-aminoboronates often heavily rely on the utilization of diastereoselective chemical reactions requiring stoichiometric amount of chiral auxiliaries including the classical Matteson's one-carbon homologation of optically active pinanediol-based boronates using α-halocarbanions.[13] Among the limited success on catalytic asymmetric synthesis of α-aminoboronates, enantioselective boryl addition to N-protected imines[14–16] are notable, while the applicability to aliphatic substrates has not been satisfactory.[17–19] One desirable but unmet method is the direct asymmetric borylation of N-adjacent C(sp^3)–H bonds that discriminates between the two hydrogen atoms on a single carbon center.

We recently reported the synthesis of enantioenriched α-chirogenic alkylboronates via the iridium-catalyzed asymmetric borylation of unactivated methylene C(sp^3)–H bonds using a triisopropylsilyloxy(TIPS)-modified BINOL-based monophosphite ligand (*R*, *R*)-**L***.[20] Quantum chemical calculations using the artificial force induced reaction (AFIR) method[21,22] suggested that the interplay between the substrate and the catalytic system through multiple noncovalent interactions within a chiral narrow reaction pocket was crucial to achieve the observed catalytic activity and enantioselectivity.

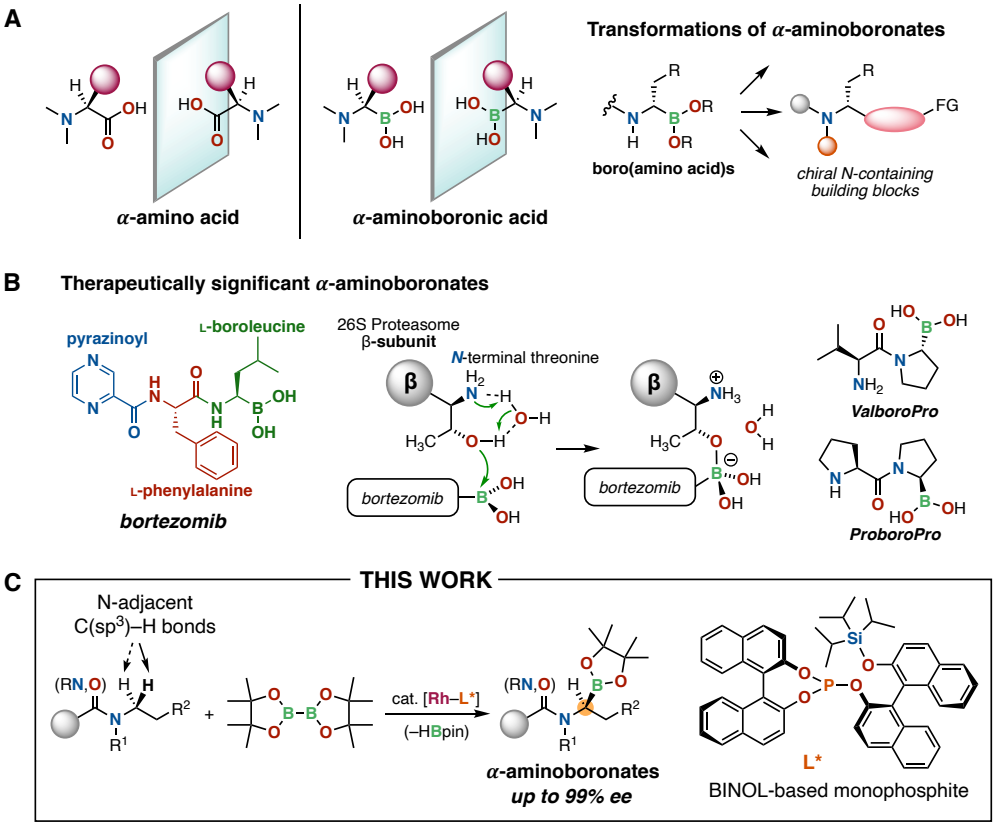


Figure 1. N-adjacent C–H bond functionalization. (A) Isostructural boron analogues of α-amino acids, boro(amino acid)s are indispensable bioactive compounds and are versatile intermediates in synthesis. (B) Representative examples of α-aminoboronates exhibiting significant therapeutic activities as proteasome inhibitors. The boron atom in *bortezomib* binds with the active site of 26S proteasome with remarkable affinity and specificity leading to the overall proteasome inhibition. (C) Catalytic borylation of N-adjacent C(sp^3)–H bonds providing a direct access to α-aminoboronic acid derivatives.

Herein, we report our finding that a rhodium catalyst system with the identical chiral phosphite ligand **L*** enabled a highly enantioselective borylation of N-adjacent C(sp^3)–H bonds allowing the direct asymmetric synthesis of chiral α-aminoboronates (Figure 1C). Importantly, the protocol was applicable not only to N-heteroarylamines but also to *N*-alkanoyl or aroyl-based secondary or tertiary amides. The extended substrate scope led us to propose an interesting mechanistic feature of this catalysis that the amide substrates were favorably bound to the catalyst with the crucial participation of dispersive noncovalent interactions that occur between an aromatic group of the substrate and the concave surface of the catalyst. Remarkably, the aromatic rings as noncovalent interaction donors could be situated in various regions in the substrate including the *N*-heteroaromatic moiety, *N*-acyl group and *N*-alkyl substituent such as a benzyl group. Stereospecific transformations of carbon–boron bonds of the C–H borylation products allow a direct route for the utilization of these α-aminoboronates including their use as building blocks for a new peptide elongation strategy. Moreover, a straightforward synthesis of the anti-cancer drug molecule *bortezomib* through late stage site- and stereoselective borylation of the N-adjacent C(sp^3)–H bond in the proboroleucine residue of the parent dipeptidic compound has been achieved, overturning the strenuous manipulations of sensitive organoboron compounds, collectively embodying the versatility and potential of the asymmetric borylation presented herein.

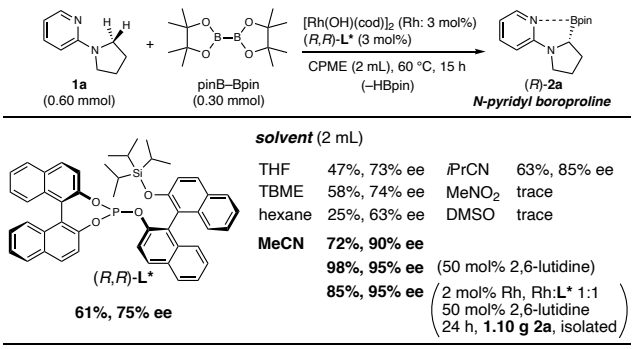
RESULTS AND DISCUSSION

Reaction development (Table 1)**.** We initially investigated the synthesis of an *N*-pyridyl boroproline derivative from 2-(pyrrolidine-1-yl)pyridine (**1a**) via the borylation of the N-adjacent methylene C(sp^3)–H bond of the pyrrolidinyl moiety using bis(pinacolato)diboron (pinB–Bpin) under Ir or Rh catalysis [cyclopentylmethyl ether (CPME) 2 mL as solvent, 60 °C, 15 h] (Table 1). However, the initial investigation on iridium catalysis (3 mol% Ir, Ir/P 1:1) utilizing (*R, R*)-**L*** resulted in merely low substrate conversion. In stark contrast, the use of $[Rh(OH)(cod)]_2$ satisfyingly promoted the N-adjacent C(sp^3)–H borylation of **1a** giving the boroproline derivative **2a** in moderate yield with a promising enantiomeric excess (ee) of 75%, favoring the *R* isomer. These observed contrasting activities between Ir and Rh catalysis is analogous to our previous observation with achiral Silica-TRIP and chiral phosphoramidite ligands.[23,24] We have also examined other variants of the biaryl monophosphite ligand, showing that the combination of (*R, R*)-**L*** and $[Rh(OH)(cod)]_2$ provided the best catalytic system (see Supporting Information, Table S1–S4).

The solvent has a strong impact on both the reactivity and enantioselectivity (Table 1). Ethereal solvents like THF and *t*-butyl methyl ether (TBME) were useful while non-polar solvents like hexane led to diminished reactivities and enantioselectivities. Replacing CPME with acetonitrile showed a marked improvement giving (*R*)-**2a** at an enhanced yield (72%) and enantioselectivity

(90% ee). The use of isobutyronitrile likewise exhibited favorable effects although less pronounced (63%, 85% ee) compared with MeCN. Other polar aprotic solvents like nitromethane and DMSO led to the loss of reactivity.

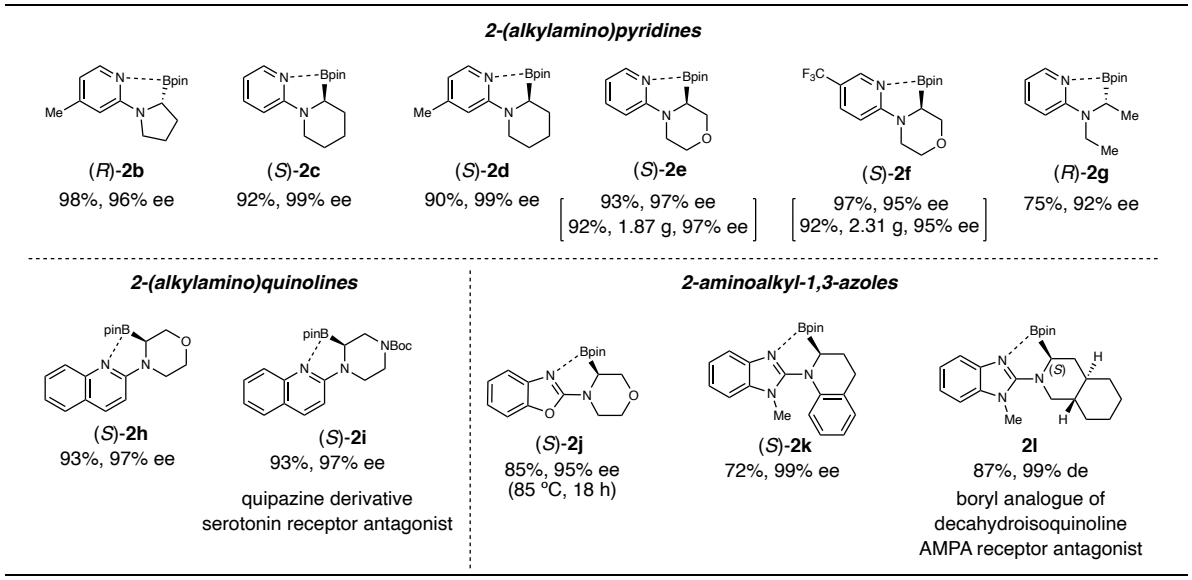
Table 1. Asymmetric borylation of N-adjacent methylene C(sp³)–H bond of 2-pyrrolidinopyridine (1a): Optimization of reaction conditions



We then explored the utilization of additives that can trap the in situ generated HBpin and at the same time compete with the undesired substrate–boron interactions based on our knowledge of favorable additive effects in our recent work[20] (Table S2, Figure S4). The use of 2,6-lutidine (50 mol%) as an additive led to optimal results delivering the product (*R*)-**2a** at 98% yield with an excellent enantioselectivity of 95% ee, even allowing a gram-scale preparation without detrimental effects on the enantioselectivity (Table 1). Notably, the reaction using 1 equiv each of **1a** and 2,6-lutidine relative to pinB–Bpin gave the product at a comparable enantiomeric excess (93% ee) and a moderate yield [68% (^{1}H NMR), 53% (isolated) based on **1a**] (Table S3), but, for easier product separation, we used 2 equiv of alkylamine substrates for further exploration of the substrate scope.

***N*-Heteroarene substrates** (Table 2)**.** The suitability of this protocol was examined across a variety of different substrate classes. At first, we explored 2-(*N*-alkylamino)pyridines including azacycloalkane frameworks that are common synthetic building blocks, and are reminiscent of natural alkaloids and bioactive compounds. Thus, the 4-methylpyridine-substituted pyrrolidine also gave the corresponding *N*-pyridyl boroproline derivative (*R*)-**2b** in excellent yield and enantioselectivity (96% ee). Expansion of the azacycloalkyl group with the piperidinyl moiety delivered the boron analogue of L-homoproline esters (*S*)-**2c** and (*S*)-**2d** with excellent enantioselectivity (99% ee), providing a derivative of pipecolic acid that is implicated as a diagnostic marker of pyridoxine-dependent epilepsy.[25] Likewise, the borylation of 2-morpholinopyridines provided the 2-(pinacolatoboryl)morpholine derivatives (*S*)-**2e** (97% ee) and (*S*)-**2f** (95% ee) even withstanding a gram-scale preparation. This protocol was also useful for acyclic amine system as exemplified by the synthesis of the enantioenriched (*R*)-**2g** (92% ee) from the monoborylation of N-adjacent C–H bond in 2-(*N*,*N*-diethylamino)pyridine.

Table 2. Asymmetric synthesis of α-aminoboronates by Rh-catalyzed borylation of N-adjacent C(sp³)–H bonds[a]



[a]Reaction conditions: pinB–Bpin (0.30 mmol), substrates **1b–l** (2 equiv, 0.60 mmol), [Rh(OH)(cod)]$_2$ (3 mol% Rh), (*R*,*R*)-**L*** (3 mol%), 2,6-lutidine (50 mol%), MeCN (2 mL), 60 °C, 15 h. Yields given are isolated yields of the product. Enantiomeric excess was determined by chiral HPLC analysis. Absolute configurations of the products were determined by the preparation of authentic samples, comparison and/or structural correlation with known compounds.

We then used several azacycloalkane derivatives bound to the pharmaceutically important quinoline scaffold (Table 2).[26] Thus, the diversely bioactive 2-morpholinoquinoline underwent the N-adjacent methylene C–H borylation to give the corresponding product (*S*)-**2h** (97% ee). An *N*-Boc-quipazine derivative, a piperazine-based nonselective serotonin receptor antagonist known for its antidepressant and oxytocic activity,[27a] also showed reactivity giving (*S*)-**2i** (97% ee).

Next, we evaluated substrates bearing 1,3-azole units as these heteroaromatic cores are also frequently encountered in natural products and pharmacologically active compounds (Table 2). 2-Morpholinobenzoxazole gave the enantioenriched product (*S*)-**2j** (95% ee), while benzimidazole derivatives proved to be viable substrates as demonstrated by the isolation of the α-tetrahydroquinoline boronate (*S*)-**2k** (99% ee). This result is indicative of the applicability of the protocol towards anilide derivatives. Likewise, a benzimidazolyl substrate bearing *trans*-decahydroisoquinoline moiety gave the borylated product **2l** with exclusive diastereoselectivity (>99% de), giving access to the boronate analogue of decahydroisoquinoline-3-carboxylic acid, the fundamental scaffold in numerous putative AMPA receptor antagonist.[27b]

As described above, the C–H borylation protocol exhibited excellent enantioselection ability toward various 2-(*N*-alkylamino)heteroaryl compounds, while the sense of stereoselection depended on the substrate structure and is not easily predictable.

Amide substrates (Table 3)**.** Considering the general pharmacological significance of amides, we investigated the propensity of using *N*-alkanoyl (**3a**-**k**) and *N*-aroyl derivatives (**3l**-**q**). The initial assessment of amide substrates with simple *N*-alkanoyl groups such as **3a**-**e** resulted in poor reactivities. We argued that the low reactivity of amides **3a**-**e** is presumably because of the weaker coordinating ability of the amide motif and also due to the simplicity of the substrate lacking an additional moiety that can facilitate interaction with the catalytic system.[28] In contrast, however, the tertiary amide *N*,*N*-dibenzylpivalamide **3f** with a more sterically demanding *N*-alkanoyl group gave the borophenylglycine derivative **4f** in 81% yield at enantioselectivity as high as 88% ee, favoring the *R* configuration. Furthermore, the use of *N*,*N*-dibenzyladamantanecarboxamide **3g** with an even bulkier alkanoyl group led to much higher enantioselectivity (**4g**, 95% ee, *R*), demonstrating the crucial role of the extended bulky substituents in the *N*-alkanoyl moieties.

Surprisingly, the borylation of *N*-benzyl-*N*-ethylpivalamide **3h** occurred at the *N*-ethyl arm rather than at the benzylic position with exclusive site-selectivity to give **4h** (89% ee, *R*), while the reactivity was completely lost using substrate **3i** with an *N*,*N*-diethylamino moiety (Table 3). This means that the *N*-benzyl groups did not present a reactive C–H bond but induced the reactivity of the N-adjacent C–H bond in the *N*-ethyl group, suggesting the occurrence of a favorable noncovalent interactions, most probably a ligand–substrate π/ π interaction, provided by the aromatic ring of the *N*-benzyl group. In fact, the same observation was elicited using the adamantane carboxamide derivatives **3j** and **3k**. Thus, substrate **3j** bearing an *N*-benzyl-*N*-ethyl adamantane carboxamide gave product **4j** (90% ee, *R*) with exclusive site-selectivity towards the *N*-ethyl arm, while substrate **3k** with a *N*,*N*-diethylamino group failed in delivering the corresponding product **4k**.

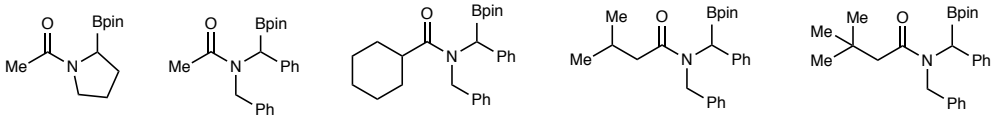
Following this lead, the potency of pharmacologically important *N*-aroyl-*N*,*N*-dialkylamines[29] towards asymmetric N-adjacent C–H borylation was explored (Table 3). Replacing the pivaloyl group in **4f** to an *o*-methoxy-substituted benzoyl group in **3l** delivered a borophenylglycine derivative **4l** with an enhanced enantioselectivity (92% ee, *R*), suggesting that an aromatic environment is favored near the coordinating donor atom. This feature implies the existence of substrate–ligand π/π interactions as in the previously reported Ir-catalyzed asymmetric borylation of unactivated C(sp^3)–H bonds.[20] Notably, the C(sp^2)–H bond ortho to the carbonyl directing group remained untouched. A *m*-methylbenzamide derivative **3m** containing an *N*-benzyl-*N*-ethyl moiety delivered the boroalanine derivative **4m** (91% ee, *R*). Introducing an *N*-isopentyl arm as a replacement to the *N*-ethyl group in **3n** maintained the observed site preference favoring the N-adjacent methylene C–H bond (75%, ^{1}H NMR) in the isopentyl chain rather than benzylic C–H bond (7%, ^{1}H NMR), providing **4n** (90% ee, *R*) despite the steric bulk imposed by the elongated branched substituent. The borophenylglycine derivative **4o** with a naphthamide core, common in natural products and pharmaceutical molecules, was obtained with excellent enantioselectivity (96% ee, *R*). A structurally related functional component of the coenzyme NAD, *N*,*N*-diethylnicotinamide **3p**, delivered the desired product **4p** (92% ee, *R*) efficiently. The borylation of indole derived tubulin inhibitor[30] **3q** that exhibits anti-mitotic activity gave the indole carboxamide boronate **4q** as the only product (93% ee, *R*) demonstrating another case of anilide borylation [c.f. Table 2, (*S*)-**2k**].

In contrast to the reactivity trend with the *N*-alkanoyl derivatives, the *N*-aroyl derivatives underwent site-selective C–H borylation at the aliphatic *N*-substituents regardless of the existence or absence of the *N*-benzyl group. This should be due to the existence of the aromatic ring in the *N*-aroyl group as a π-donor moiety.

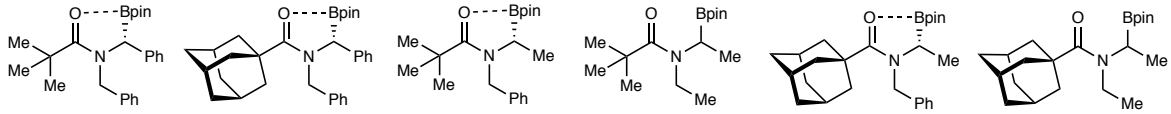
Gratifyingly, the synthetic significance of this reaction protocol was substantially enhanced as even secondary amides were amenable to the borylation reaction as exemplified by the production of **4r** (98% ee, *S*) starting from *N*-benzylbenzamide **3r** in a straightforward manner (Table 3). Notably, compound **4r** was previously accessed through multistep diastereoselective synthesis involving Matteson homologation reaction of optically active pinanediol phenylboronate.[31–33] Furthermore, we applied the present protocol for the borylation of bioactive compounds. Hence, the reaction of the antidepressant drug molecule *moclobemide* (**3s**)[34] gave compound **4s** as the sole product (95% ee, *S*) from the selective borylation of the N-adjacent C–H bond in the (2-morpholinoethyl)amine chain. In a similar fashion, the extensively used antiemetic drug molecule *trimethobenzamide* (**3t**)[35] having a terminal *N*,*N*-dimethylamino group gave the boronate **4t** exclusively with excellent enantioselectivity (93% ee, *S*). Note that all the tested secondary amide substrates were converted into the *S*-configurated borylation products, while the borylation products **4l**–**4q** from the tertiary amides had the *R* configuration.

Table 3. Rh-catalyzed borylation of N-adjacent C(sp^3)–H bonds in *N*-alkanoyl or *N*-aroyl *N,N*-dialkylamines and secondary benzamide derivatives[a]

N-alkanoyl-N,N-dialkylamines

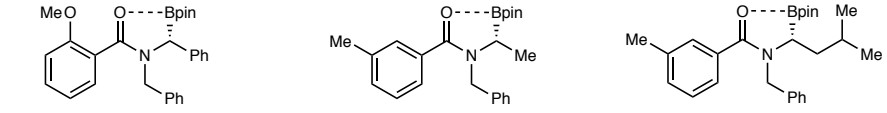


4a 0% | **4b** trace | **4c** 5% (^{1}H NMR) | **4d** 7% (^{1}H NMR) | **4e** 12% (^{1}H NMR)

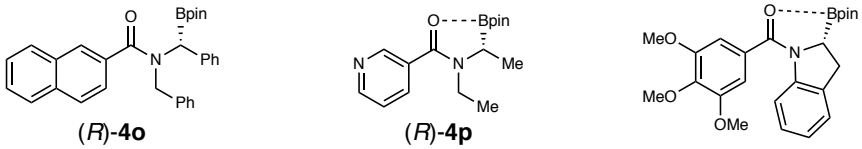


(*R*)-**4f** 81%, 88% ee | (*R*)-**4g** 63%, 95% ee | (*R*)-**4h** 95%, 89% ee | **4i** 0% | (*R*)-**4j** 89%, 90% ee | **4k** 5% (^{1}H NMR)

N-aroyl-N,N-dialkylamines

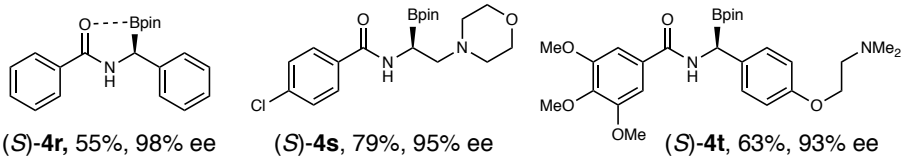


(*R*)-**4l** 88%, 92% ee | (*R*)-**4m** 81%, 91% ee | (*R*)-**4n** 72%, 90% ee



(*R*)-**4o** 92%, 96% ee | (*R*)-**4p** 65%, 92% ee | (*R*)-**4q**, 74%, 93% ee
borylation of a *tubulin inhibitor*: anti-mitotic agent

secondary benzamide derivatives

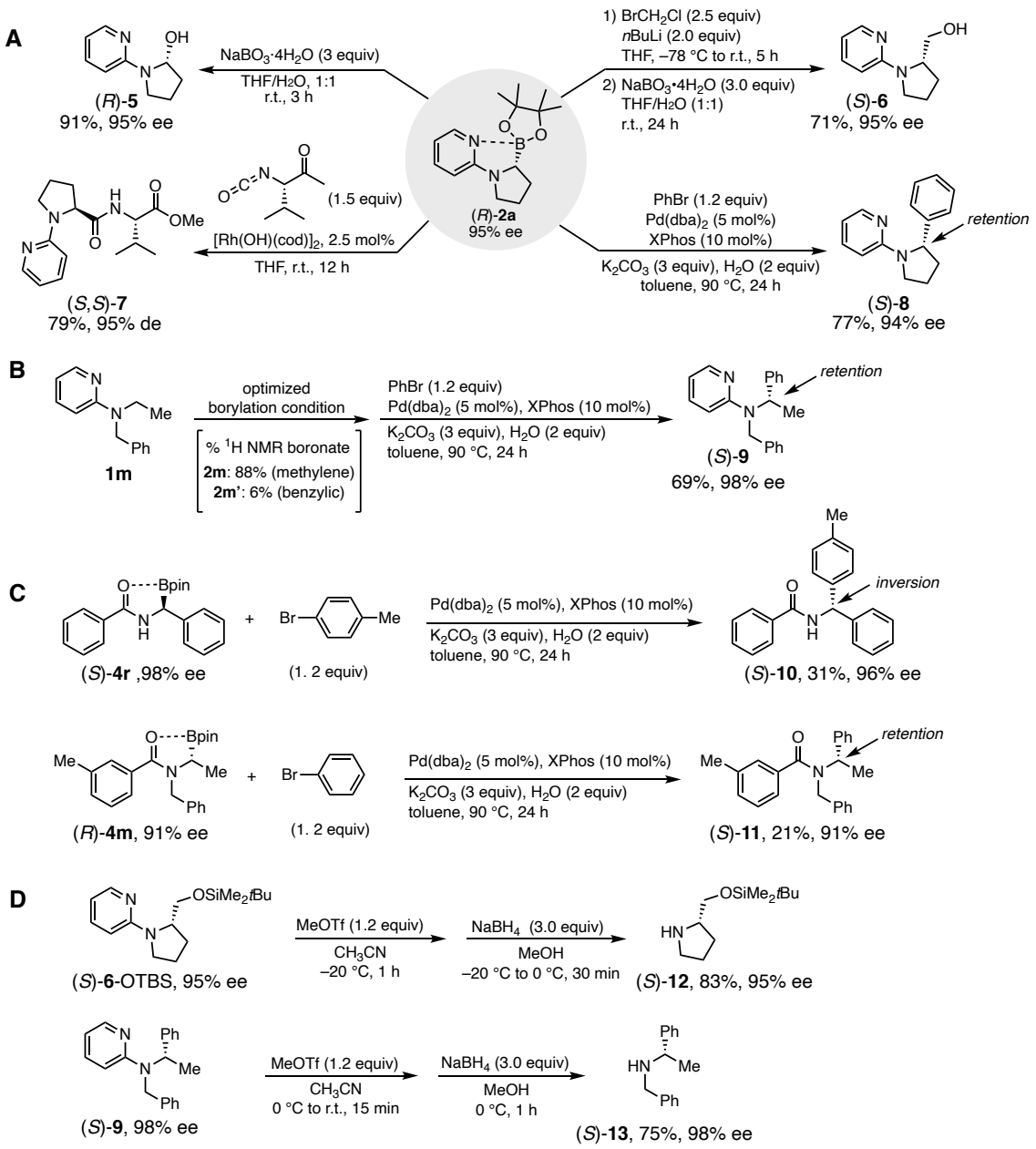


(*S*)-**4r,** 55%, 98% ee | (*S*)-**4s**, 79%, 95% ee
borylation of *moclobemide*: monoamine oxidase inhibitor with antidepressant activity | (*S*)-**4t**, 63%, 93% ee
borylation of *trimethobenzamide*: antiemetic drug

Reaction conditions: pinB–Bpin (0.30 mmol), substrate (2 equiv, 0.60 mmol), $[Rh(OH)(cod)]_2$ (3 mol% Rh), (*R,R*)-**L*** (3 mol%), 2,6-lutidine (50 mol%), MeCN (2 mL), 60 °C, 15 h. Yields given are isolated yields of the product unless otherwise indicated. Enantiomeric excess was determined by chiral HPLC analysis. Absolute configurations of the products were determined by the preparation of authentic samples, comparison and/or structural correlation with known compounds.

Synthetic transformations (Scheme 1)**.** Oxidation of the *N*-pyridyl boroproline derivative (*R*)-**2a** with sodium perborate gave the corresponding 2-hydroxypyrrolidine derivative (*R*)-**5** with complete retention of configuration (Scheme 1A). The boroproline derivative **2a** also underwent a facile stereoretentive one-carbon homologation with bromochloromethane/BuLi reagent furnishing the N-adjacent secondary alkylboronate (87% ^{1}H NMR yield) followed by direct oxidation with $NaBO_3$, delivering the pyridyl prolinol derivative (*S*)-**6**. Moreover, the Rh-catalyzed addition of organoboronates to isocyanates, which was previously demonstrated only with combinations of arylboronic acid derivatives and achiral isocyanates by Murakami and co-workers,[36] has been applied to the reaction between (*R*)-**2a** and an isocyanate derivative of L-valine to provide the dipeptide (*S,S*)-**7** with no epimerization at the both stereogenic centers, demonstrating the potential of α-aminoboronates as a new type of building blocks for peptide chain elongation to be studied in the future.

Scheme 1. Synthetic transformations and functionalizations



(A) Transformations of the boroproline derivative **2a** at mild reaction conditions gave the corresponding α-amino alcohol **5**, pyridyl prolinol derivative **6**, dipeptide **7** from the direct addition of **2a** to an isocyanate derivative of L-valine, and α-arylation product **8** formed through Suzuki–Miyaura cross-coupling. **(B)** One-pot borylation/cross-coupling protocol provided access to an acylic α-functionalized amino derivative. **(C)** Stereospecific cross-coupling reaction of the α-aminoboronates derived from amides. **(D)** Removal of the pyridine directing group via a quaternization–hydride reduction protocol allowed the isolation of the enantioenriched free amine. All reactions were carried out at 0.20–0.50 mmol scale.

Meanwhile, we sought the utility of (*R*)-**2a** towards N-adjacent arylation via a Suzuki–Miyaura-type cross-coupling reaction employing the reaction conditions previously reported by Ohmura and Suginome[31,32] in the cross-coupling between α-(*N*-acylamino)benzylboronic esters and bromobenzene with a $Pd(dba)_2$/XPhos catalyst system (Scheme 1A). In fact, this reaction occurred similarly but in contrast to the reported case, *with retention of configuration*, affording the coupling product (*S*)-**8** with almost completely preserved enantiomeric purity (94% ee).[37] A one-pot borylation/cross-coupling transformation was also explored (Scheme 1B). Thus, starting from substrate **1m**, the enantioselective borylation of the N-adjacent C–H bond of the *N*-ethyl moiety (**2m**, 88% ^{1}H NMR) followed by the Suzuki–Miyaura cross-coupling reaction afforded product **9** with 98% ee (*S*) in 69% overall yield. This successful borylation–arylation sequence further highlight the synthetic significance of the present protocol allowing

the asymmetric arylation of N-adjacent C(sp^3)–H bonds, as only a few notable strategies for such functionalization have been reported so far.[38–40]

As described above, in contrast to Ohmura and Suginome's report, the cross-coupling reaction of the α-aminoboronate (*R*)-**2a** derived from a 2-(*N*,*N*-dialkylamino)pyridine derivative proceeded with stereoretention (see Scheme 1A). To delve into this, we have performed a cross-coupling reaction with the highly enantioenriched borophenylglycine **4r** (98% ee, *S*) derived from a secondary amide, confirming the stereochemical inversion as previously disclosed by Ohmura and Suginome with the identical substrate with a moderate enantiomeric purity (Scheme 1C, 87% ee, *S*).[31,32] In direct contrast, the cross-coupling reaction of the tertiary amide boronate (*R*)-**4m** proceeded *with complete stereoretention* similar to the observed stereochemical outcome in the cross-coupling of (*R*)-**2a**. These contrasting observations with the secondary and tertiary amide boronates support an assumption that the stereoinvertive cross-coupling with the secondary amide occurred though deprotonation of the NH moiety under the basic conditions.

We also assessed the feasibility of removing the pyridyl group by exploiting a reported quaternization–hydride reduction strategy (Scheme 1D).[41] Thus, the TBS-protected pyrrolidinyl α-amino alcohol **6**-OTBS (95% ee, *S*) was treated with slight excess of methyl triflate to give an *N*-methylpyridinium salt which was subsequently reduced using $NaBH_4$ under mild conditions, resulting in the isolation of the prolinol product **12** (95% ee, *S*).[42] Likewise, removal of the pyridyl group to isolate the free amine in product (*S*)-**9** gave the corresponding enantioenriched *N*-benzyl-1-phenylethan-1-amine [(*S*)-**13**] without erosion of the enantiomeric purity (98% ee).[43]

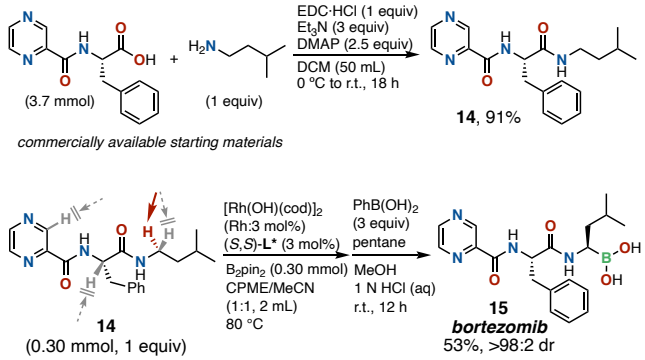
Synthesis of *bortezomib*. On the basis of the observed broad substrate scope, we sought to demonstrate the versatility of the present borylation methodology by the synthesis of the anti-cancer drug molecule *bortezomib*,[4] an L-boroleucine derivative and the first therapeutic proteasome inhibitor. *Bortezomib* consists of three structural units linked together by peptide bonds: pyrazinoyl, L-phenylalanyl, and the α-aminoboronic acid unit L-boroleucine (see Figure 1B). Industrially, *bortezomib* is prepared through a multistep sequence[16,44] which suffers from drawbacks connected to the utilization of protecting groups, process complexity, and stereocontrol. Thus, we contemplated the synthesis of *bortezomib* through a direct, site- and stereoselective borylation of the N-adjacent C–H bond of the pro-boroleucine residue of the parent dipeptidic compound (**14**), which was prepared from *N*-(pyrazinoyl)-L-phenylalanine and isopentylamine, both commercially available (Scheme 2).[45]

To our delight, the reaction of **14** with the modified borylation protocol using the antipode of the monophosphite ligand [(*S*,*S*)-**L***] (3 mol% Rh-L*, **14**/B_2pin_2 1:1, MeCN/CPME 1:1, 80 °C, 36 h) occurred cleanly with the desired site- and stereoselectivities, furnishing spectroscopically pure *bortezomib* (**15**, >98:2 dr) in 53% yield upon transesterification[46] of the pinacol ester with phenylboronic acid (Scheme 2). Remarkably, the reaction required neither an excessive amount of the substrate **14** nor any additive such as 2,6-lutidine. Furthermore, the protection or pre-functionalization of the secondary amide NH groups within the dipeptide chain was unnecessary while the other N-adjacent C(sp^3)–H bonds present in the phenylalanine residue, which are more acidic than those in the *N*-isopentyl group, remained intact.

The observed stereoselectivity of the C–H borylation of **14** with the Rh-(*S*,*S*)-**L*** catalyst system was due to catalyst control as the reaction with (*R*,*R*)-**L*** resulted in a reversed selectivity (dr 10:90) and a lower chemical yield (31%) for a diastereomeric mixture of **15**. The use of the supported achiral ligand Silica-TRIP[23] resulted in the formation of a complex mixture with a low conversion of **14** (7%). Considering the general importance of the aromatic moiety in the substrates indicated throughout this study, participation of the aromatic ring in the phenylalanine residue of **14** in ligand–substrate noncovalent interactions is strongly suggested in the catalysis with (*S*,*S*)-**L***.

The synthesis of *bortezomib* described herein represents an innovative advancement from previously reported methodologies[16,44] in lieu of a straightforward C–H borylation strategy enabling the late-stage installation of the boryl group, and thus eliminating tedious synthesis routes and circumventing the laborious manipulations of sensitive organoboron compounds. In view of this reactivity, we envisage the potential of the present protocol for the borylation and functionalization of more complex systems including peptidic substrates and for the diversification of a broad spectrum of pharmaceutical compounds and natural products.

Scheme 2. Synthesis of *bortezomib*



CONCLUSION

Herein, we showed a direct synthesis of enantioenriched α-aminoboronates from the corresponding achiral *N*-alkylamine derivatives through the highly enantioselective Rh-catalyzed borylation of N-adjacent C(sp^3)–H bonds. The reaction protocol presents multifold synthetic advantages, providing a direct catalytic route for the preparation of α-aminoboronates and allowing the preparation of bioactive compounds and chiral α-aminoboronic acids. The chiral monophosphite ligand enabled the asymmetric discrimination of N-adjacent enantiotopic C(sp^3)–H bonds across a wide-range of substrate classes under the rhodium catalysis through catalyst–substrate noncovalent interactions in a well-defined catalytic pocket, demonstrating the versatility of the monophosphite ligand, which similarly allowed the borylation of unactivated methylene C–H bonds under the iridium catalysis.[20] We envisage that the exceptional and unparalleled site-and stereoselectivities demonstrated in this work will provide opportunities for the development of synthetically useful transformations that will have rippling effects in the creation of novel molecules from simple and readily available starting materials.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and the characterization of all new compounds are provided in the Supporting Information. The Supporting Information is available free of charge on the ACS Publications website.

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Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENT

This work was supported by JST ACT-C Grant Number JPMJCR12YN, MEXT KAKENHI Grant Number JP15H05801 in Precisely Designed Catalysts with Customized Scaffolding, and JSPS KAKENHI Grant Number JP18H03906 in Grant-in-Aid for Scientific Research (A) to M.Sawamura. R.L. thanks the Japanese Government (MEXT) scholarship for the support during his Ph.D. studies.

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