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Highly Enantiospecific Borylation for Chiral α-Amino Tertiary Boronic Esters

Qingqing Qi,[a] Xuena Yang,[a] Xiaoping Fu,[a] Shiqing Xu,*[a] and Ei-ichi Negishi*[a]

Abstract: Herein we report a highly efficient and enantiospecific borylation method to synthesize a wide range of enantiopure (>99% ee) α-amino tertiary boronic esters. The configurationally stable α-*N*-Boc substituted tertiary organolithium species and pinacolborane (HBpin) underwent enantiospecific borylation at -78 °C with the formation of a new stereogenic C−B bond. This reaction has a broad scope, enabling the synthesis of various α-amino tertiary boronic esters in excellent yields and, importantly, with universally excellent enantiospecificity (>99% es) and complete retention of configuration.

Chiral boronic acids and their derivatives are highly versatile building blocks in modern asymmetric synthesis. Their stereospecific conversion into a broad range of useful functional groups is a continually growing and important research area.[1] Additionally, many unique biological activities of boron-containing compounds have been revealed.[2] Among them, chiral α-aminoboronic acids have received significant attention since they are the key pharmacophores in protease inhibitions such as Bortezomib (Velcade, an anti-cancer drug and the first therapeutic proteasome inhibitor) and Ixazomib (Ninlaro, a drug for the treatment of multiple myeloma).[3] In addition, many other α-aminoboronic acid compounds showed excellent anticancer, antiviral, and antibacterial activities.[2,3] From the success of these compounds, there has been an increased interest in searching α-amino boronate-containing small bioactive molecules (Figure 1).

In view of their broad biological activities, substantial efforts have been made to develop synthetic methods for the asymmetric construction of α-aminoboronic acids and their derivatives.[4] Examples include Matteson's homologation,[5] sparteine-mediated enantioselective lithiation-borylation,[6] metal-catalyzed and metal-free borylation of imines,[7] Cu-catalyzed borylation of enamides,[8] Cu-catalyzed hydroamination of alkenyl dan-boronates,[9] Curtius rearrangement of chiral α-borylcarboxylic acid derivatives,[10] and Ni-catalyzed decarboxylative borylation.[11] These approaches by either use of chiral auxiliaries or asymmetric catalytic transformations have been utilized for the efficient preparation of a variety of α-aminoboronic acid derivatives, whereas they mainly limited to the construction of chiral α-amino secondary boronic esters.

Indeed, there have been only a limited number of reports on asymmetric approaches to more sterically congested α-amino tertiary boronic esters, which involves a particular challenge for

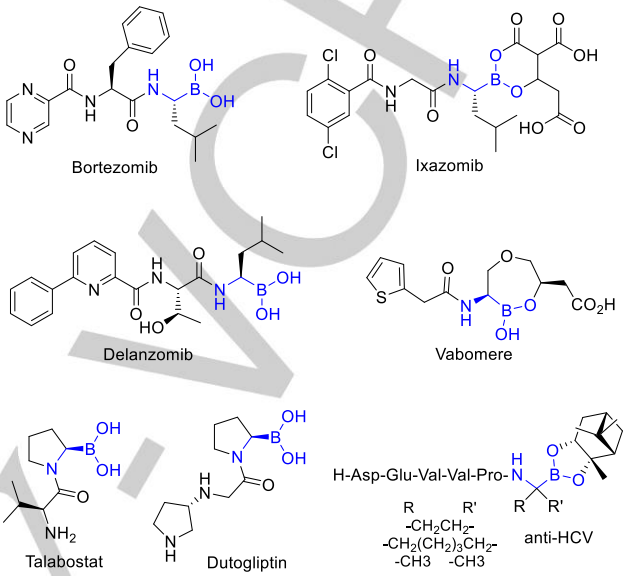

Figure 1. Examples of α-aminoboronate drugs and biologically active molecules.

the stereoselective construction of *N*-substituted quaternary carbon stereogenic centers (Scheme 1). For example, significant lower enantioselectivities were observed for the synthesis of sterically hindered α-amino tertiary boronic esters compared to secondary boronic esters by borylation of imines[7d] and Cu-catalyzed hydroamination of alkenyl dan-boronates[9]. Recently, Ellman reported a copper-catalyzed diastereoselective borylation of chiral *N*-tert-butanesufinyl ketimines with involvement of a chiral auxiliary to synthesize α-amino tertiary boronic esters (Scheme 1, eq 1).[7g] In another approach, Tang described an elegant enantioselective rhodium-catalyzed hydroboration of α-arylenamides (Scheme 1, eq 2).[12] Very recently, Ready and Studer developed transition-metal catalyzed enantioselective and diastereoselective multi-component coupling involving indolylboron ate complexes to provide α-substituted indoline boronic esters, respectively (Scheme 1, eq 3 and eq 4).[13]

Despite recent progress, there remains a great challenge for the synthesis of α-amino tertiary boronic esters with high enantiopurity in a general manner. Herein, we report a general method to prepare enantiopure (>99% ee) chiral α-amino tertiary boronic esters that makes use of the enantiospecific borylation of configurationally stable α-*N*-substituted tertiary organolithium species (Scheme 1, eq 5). This strategy is very attractive because: i) chiral amines are ubiquitous in natural products as well as in synthetic compounds, and numerous methods for chiral amine synthesis are well established;[14] ii) excellent enantiopurity is general and predictable that is independent of electronic and steric perturbations of substrates if the overall process proceeds with full stereospecificity.

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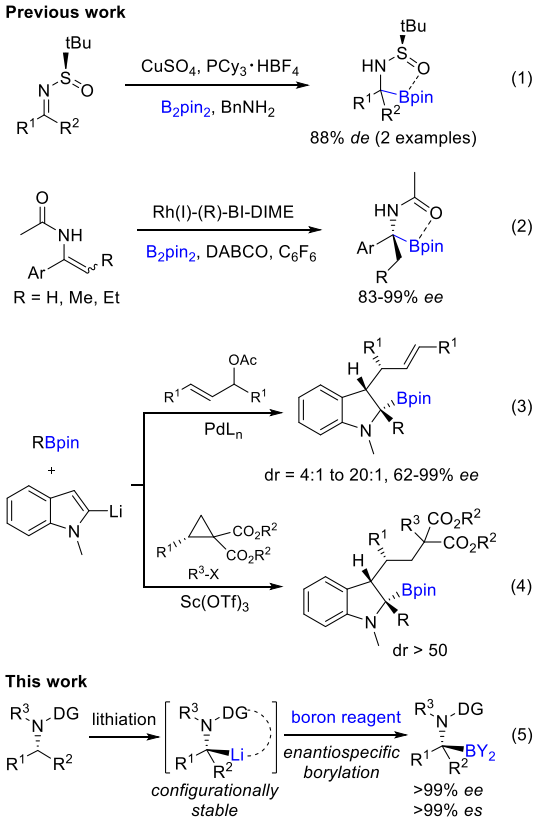
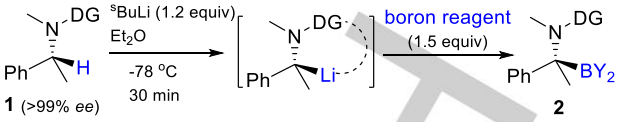


Scheme 1. Asymmetric approaches to α-amino tertiary boronic esters.

α-Lithiated tertiary *N*-benzylic carbamates have been reported as configurationally stable organolithium intermediates, which react with various electrophiles to generate a new C−C, C−Si, or C−Sn bond with the asymmetric formation of a quaternary stereocenter.[15] To the best of our knowledge, no such C−B bond formation has been reported for the synthesis of *N*-substituted tertiary α-aminoboronic esters with high enantiopurity. To check the feasibility of our strategy, we first used *N*-Boc-*N*-methyl-1-phenylethanamine **1** as the standard substrate for screening enantiospecific borylation (Table 1). The lithiation of **1** using sec-BuLi in Et_2O at -78 °C was completed in 30 min to generate the corresponding organolithium species with 100% retention of the stereoconfiguration. Then we focused on the examination of various conditions for the enantiospecific borylation of α-lithiated tertiary *N*-benzylic carbamate. We began our investigation by using iPrOBpin and MeOBpin as borylation reagents, but no borylation occurred at -78 °C (Table 1, entries 1 and 3). To facilitate the borylation, the reaction was carried out initially at -78 °C and slowly increased the reaction temperature to 23 °C in 12 h. In these cases, the desired borylated product **2a** (DG = Boc) was obtained in 55% and 56% yield, but only in 80% ee and 88% ee, respectively (Table 1, entries 2 and 4). The low enantiopurities are most likely to result from increasing reaction temperature to enable the sluggish desired borylation of the tertiary α-*N*-substituted organolithium species with less nucleophilicity due to the steric hindrance and the adjacent electron-withdrawing *N*-DG group. This problem could be circumvented by using less

Table 1. Optimization of the enantiospecific borylation[16]



Entry	DG	Boron reagent	Borylation condition	Yield [%][a]	*ee* [%][b]
1	Boc	iPrOBpin	-78°C, 2.5 h	<2	-
2	Boc	iPrOBpin	-78 to 23 °C slowly in 12 h	55	80
3	Boc	MeOBpin	-78°C, 2.5 h	<2	-
4	Boc	MeOBpin	-78 to 23 °C slowly in 12 h	56	88
5	Boc	$B(OMe)_3$	-78 °C, 2.5 h	75[c]	80[d]
6	**Boc**	**HBpin**	**-78 °C, 2.5 h**	**99**	**>99**
7	Boc	HBcat	-78 °C, 2.5 h	28[c]	-
8	$CON(^iPr)_2$	HBpin	-78 °C, 2.5 h	80	97

[a] Isolated yields. [b] Determined by HPLC-analysis on chiral stationary phase. [c] Determined by crude ^1H NMR analysis. [d] Determined by HPLC-analysis on chiral stationary phase of the corresponding pinacol boronic ester.

hindered and more reactive boron electrophile reagents to promote the borylation at low temperature with excellent enantiospecificity. We were very delighted to find that pinacolborane (HBpin)[17] reacted readily with α-*N*-substituted organolithium species in Et_2O at -78 °C to give exclusively a borylated product in 99% yield and >99% ee (Table 1, entry 6). When directing group of Boc was replaced with $CON(^iPr)_2$, the corresponding borylated product was obtained in 80% yield and 97% ee (Table 1, entry 8).

After establishing the optimal reaction conditions, we then looked into the substrate scope of this enantiospecific borylation. As can be seen in Scheme 2, various substituents of *N*-Boc protected amines, such as aryls with electron-withdrawing (Cl, F, CF_3) and electron-donating (OMe) groups, alkyls with OMe, Br, and double bond, can undergo lithiation−borylation process smoothly affording a series of α-amino tertiary boronic esters in excellent yields and extremely high enantiopurities. Notably, this enantiospecific borylation was also tolerant of *N*-Boc protected tetrahydroisoquinoline providing **2j** in 92% yield with >98% ee. In the case of **2c**, the lithiation occurred at both positions adjacent to nitrogen of *N*-Boc due to OMe group acting as an additional directing group for lithiation at C**H**$_2$N-Boc, thus furnishing an approximate 1:2 ratio of CH_2/benzylic borylated products. Switching s-BuLi to n-BuLi as the base resulted in a completely regioselective deprotonation at the benzylic position and subsequent addition of HBpin provided **2c** in 82% yield with complete stereocontrol (>99% ee).

The enantiospecific borylation process can be easily extended to the substrates with multiple chiral centers. As shown in Scheme 3, the reaction was tolerant of *N*-Boc protected amines containing various functional groups such as halides (**3a**, **3b**), olefin (**3d**-**e**, **3h**-**k**), alkyne (**3c**), OTBPDS (**3i**), hetero-rings (**3b**, **3f**, **3h**), and CF_3 (**3l**). In all cases, the desired α-amino tertiary boronic esters

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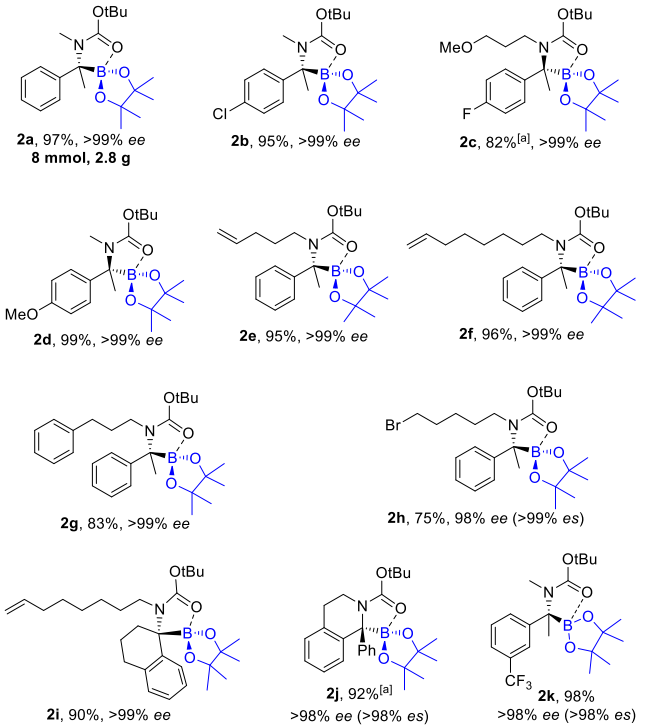
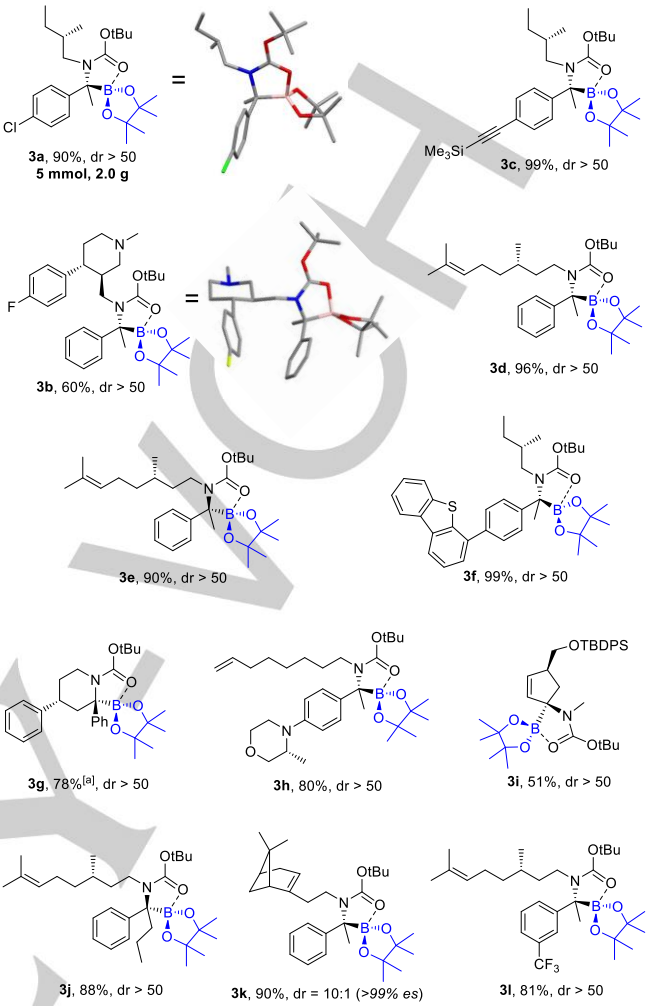


Scheme 2. Standard reaction conditions of the enantiospecific borylation: i) amine (0.25 mmol, 1.0 equiv), s-BuLi (1.2 equiv) in Et_2O at -78 °C for 0.5 h, ii) neat HBpin (1.5 equiv) at -78 °C for 2.5 h. [a] s-BuLi was replaced with n-BuLi.

3 were obtained in good to excellent yields and, importantly, with universally complete retention of configuration, as determined by X-ray crystallographic analysis of **3a** and **3b**.[18] The coordination between the boron atom and the carbonyl group of Boc makes such α-amino tertiary boronic esters highly stable. The absolute configuration of the other α-amino boronic esters is based on assumed retention at the organolithium center. Notably, both enantiopure α-amino tertiary boronic esters (*R*,*S*)-**3d** and (*S*,*S*)-**3e** were prepared from the corresponding (*R*,*S*)- and (*S*,*S*)-*N*-Boc amines with complete enantiospecificity in 96% and 90% yield, respectively. This result indicates that there is no matched/mismatched issue here, which can often complicate reaction outcomes.

It should be noted that the distinguish rotamers from diastereomers is critically important to determine the enantiospecificity of borylation in circumstances where the possibilities of both isomers exist. For example, during the synthesis of **3a**, the ^{11}B NMR spectrum (EtOAc as solvent) of the crude reaction mixture showed two peaks at 14.7, and 9.7 ppm (indicating the strong coordination between B and the carbonyl group of Boc). Furthermore, two new spots were observed in TLC which can be isolated by common silica gel column chromatography. Interestingly, the compound **3aa** of higher Rf value rapidly converts to the compound **3ab** of lower Rf value in d-chloroform in less than 5 minutes even at low temperature, whereas **3aa** is quite stable in other solvents such as hexanes, ethyl acetate, acetone, and acetonitrile. The ^1H and ^{13}C NMR (d-acetone) spectra of **3aa** indicate it is a mixture of several



Scheme 3. Standard reaction conditions of the enantiospecific borylation as shown in Scheme 2. [a] s-BuLi was replaced with n-BuLi and TMEDA (1.5 equiv).

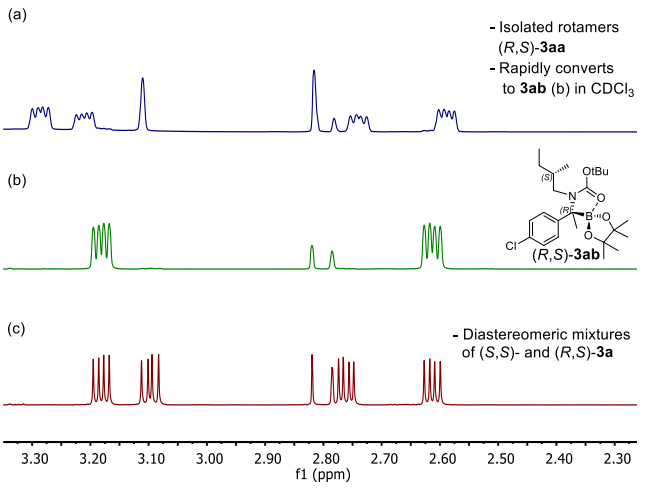


Figure 2. Comparison of rotamers and diastereomers of **3a** by ^1H NMR (d-acetone, a-c).

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isomers.[19] The fast conversion of **3aa** to **3ab** implies these compounds are rotamers since epimerization in neutral solvent is usually negligible. Comparison of the spectra of an intentionally prepared diastereomeric mixtures of (*S*,*S*)- and (*R*,*S*)-**3a** (Figure 2, c) with (*R*,*S*)-**3a** (Figure 2, b) further supports the conclusion about the identity of **3aa** and **3ab** as rotamers. The existence of highly stable and chromatographically separable rotamers is likely due to the energetic barriers for the pseudo-rotation of the boron-containing five-membered ring which was supported by the observation of a superstructure of **3c** with four rotamers A-D related by pseudo-rotation and pseudo-translation (Figure 3).[20]

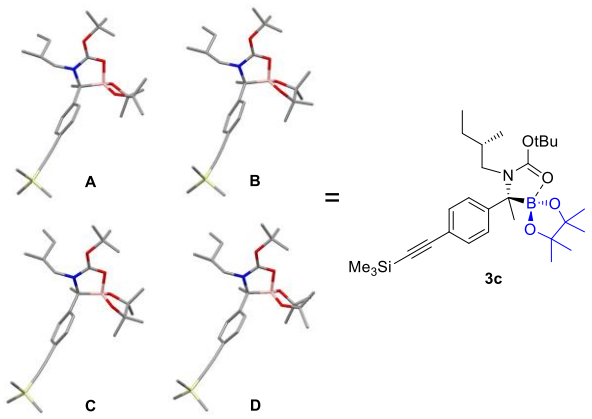
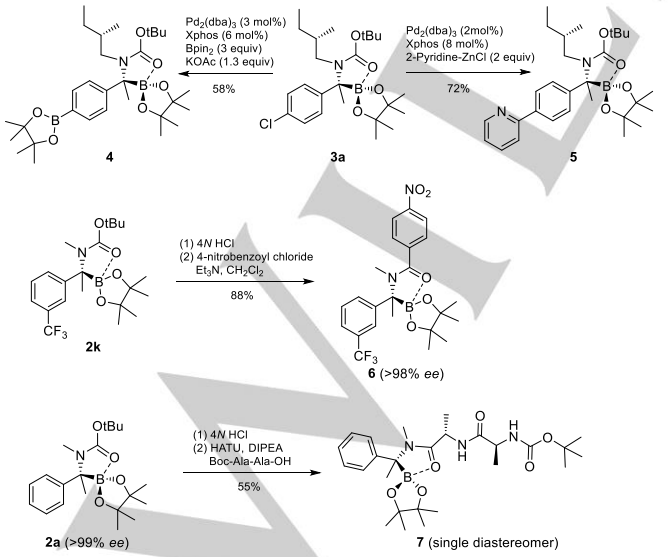


Figure 3. X-ray crystal structures of four different rotamers of α-amino tertiary boronic ester **3c**.

The chiral α-amino tertiary boronic esters can be employed for further transformations to synthesize various chiral compounds. For example, **3a** was transformed to **4** in 58% yield and **5** in 72% yield by Pd-catalyzed borylation[21] and Pd-catalyzed Negishi coupling[22], respectively. Treatment of **2k** with 4*N* HCl to remove the Boc group followed by amidation with 4-nitrobenzoyl chloride produced amide **6** in 88% yield over two steps. Similarly, peptide **7** was synthesized in 55% overall yield from **2a** of >99% ee, and importantly, only a single diastereomer was obtained.



Scheme 4. Derivatization of chiral α-amino tertiary boronic esters.

In conclusion, we have successfully developed a new and highly efficient enantiospecific borylation route to various chiral α-amino tertiary boronic esters. This route employs *N*-Boc protected amines which are lithiated at -78 °C to generate configurationally stable organolithium species followed by the treatment with HBpin to undergo enantiospecific borylation, enabling the synthesis of a series of enantiopure (>99% ee) α-amino tertiary boronic esters with the formation of a new stereogenic C−B bond. Importantly, universally excellent enantiospecificity (>99% es) and complete retention of configuration were observed. The current method is also applicable for gram-scale synthesis of **2a** and **3a** without erosion of enantiospecificity. The α-amino tertiary boronic esters can be further functionalized to provide various chiral compounds which hold a great potential for peptidomimetics of boron-based bioactive molecules.

Acknowledgements

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Keywords: α-aminoboronates • borylation • quaternary centers • asymmetric synthesis • rotamer

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[16] For details on the optimization of the reaction conditions, see the Supporting Information.

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[18] a) CCDC 1862092 (**3a**) and CCDC 1862091 (**3b**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

[19] The full spectra of rotamers **3aa** see supporting information.

[20] CCDC 1862090 (**3c**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre.

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Layout 2:

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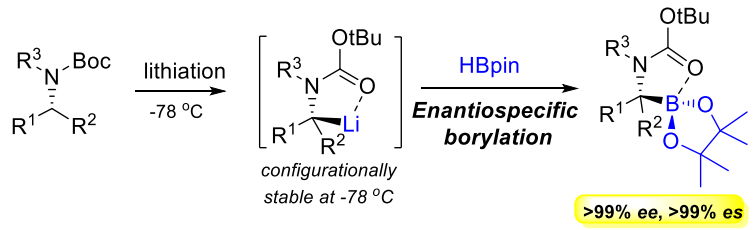

Qingqing Qi, Xuena Yang, Xiaoping Fu, Shiqing Xu, and Ei-ichi Negishi**

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Highly Enantiospecific Borylation for Chiral α-Amino Tertiary Boronic Esters

Enantiospecific borylation: A highly enantiospecific borylation of configurationally stable α-*N*-Boc substituted tertiary organolithium species and HBpin has been developed to synthesize various α-amino tertiary boronic esters through the formation of a new C−B bond with excellet enantiopurities and complete retention of configuration.