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Diastereo- and Enantioselective Synthesis of β-Aminoboronate Esters by Copper(I)-Catalyzed 1,2-Addition of 1,1-Bis[(pinacolato)boryl]alkanes to Imines

Jeongho Kim, Kwangwook Ko, and Seung Hwan Cho*[a]

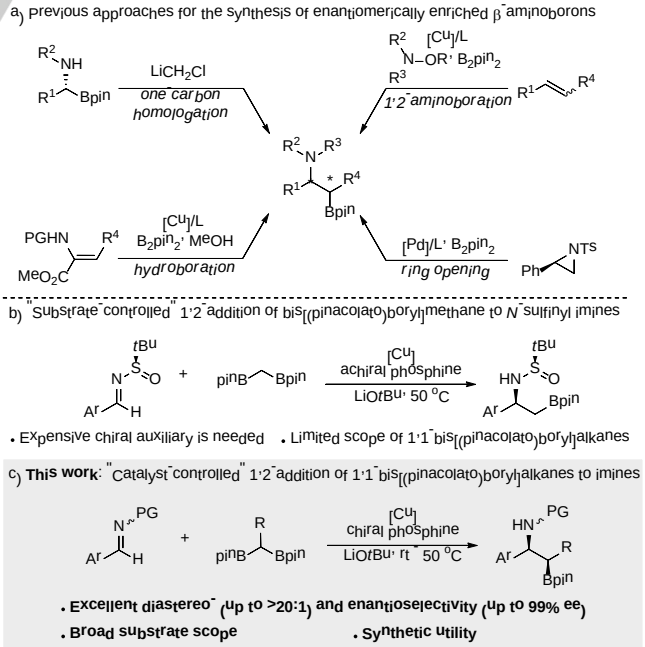
This work is dedicated to professor Jaiwook Park on the occasion of his 60th birthday

Abstract: We report an efficient Cu(I)-catalytic system for the diastereo- and enantioselective 1,2-addition of 1,1-bis[(pinacolato)boryl]alkanes to protected imines to afford synthetically valuable enantioenriched β-aminoboron compounds bearing contiguous stereogenic centers. The reaction exhibits a broad scope with respect to protected imines and 1,1-bis[(pinacolato)boryl]alkanes, providing β-aminoboronate esters with excellent diastereo- and enantioselectivity. The synthetic utility of the obtained β-aminoboronate ester was also demonstrated.

Chiral organoborons are an important class of synthetic intermediates that can undergo a range of carbon-carbon and carbon-heteroatom bond-forming reactions via stereospecific couplings.[1] The synthesis of such compounds containing a nitrogen functionality at the β-position of the chiral boron unit is of significant importance in synthetic chemistry because they serve as versatile building blocks in many biologically active compounds.[2] Consequently, several synthetic methods have been developed to afford chiral β-aminoborons (Scheme 1a). A typical approach for the synthesis of a chiral β-aminoboron involves a one-carbon homologation reaction of chiral β-aminoborons with $LiCH_2Cl$.[3] However, this method requires harsh reaction conditions and shows limited substrate scope. In this context, several elegant catalytic enatioselective methods have emerged for the preparation of chiral β-aminoborons under mild conditions. For examples, Miura[4] and others[5] described a diastereo- and enantioselective inter- or intramolecular copper-catalyzed 1,2-aminoboration of unactivated alkenes employing bis(pinacolato)diboron and hydroxylamines as coupling partners. Lin and co-workers demonstrated a copper-catalyzed hydroboration of *N*-protected dehydroamino esters to afford β-boron-α-amino acids with excellent enantioselectivity and low diastereoselectivity.[6] A palladium-catalyzed borylated ring-opening reaction of chiral 2-arylaziridines was also documented.[7] Despite these advances, the development of a new approach from readily accessible imines remains elusive but is highly desirable.

Recently, our group[8] and others[9-11] reported chemo- and stereoselective coupling of 1,1-bis[(pinacolato)boryl]alkanes with suitable electrophiles. In particular, we described a copper-catalyzed diastereoselective 1,2-addition of diborylmethane to *N*-*tert*-butanesulfinyl imines, providing access to enantiomerically enriched β-aminoboronate esters with high efficiency (Scheme 1b).[8c] Although this protocol constitutes an efficient approach to prepare enantioenriched β-aminoboronate esters, the reaction required the use of a stoichiometric amount of a chiral auxiliary and displayed limited scope of 1,1-bis[(pinacolato)boryl]alkanes. Therefore, we decided to investigate a more broadly applicable chiral catalytic system for the 1,2-addition of imines with 1,1-bis[(pinacolato)boryl]alkanes. Herein, we report a highly diastereo- and enantioselective synthesis of β-aminoboronate esters by the copper-catalyzed 1,2-addition reaction of 1,1-bis[(pinacolato)boryl]alkanes to *N*-protected imines (Scheme 1c). Moreover, we demonstrate that the obtained β-aminoboronate ester serve as a useful synthetic intermediate, which can undergo oxidations and C-C bond formations to generate synthetically valuable compounds with two vicinal stereocenters.

At the outset of our study, we initially focused on the reaction of 1,1-bis[(pinacolato)boryl]ethane (**2a**) and cyclic aldimine **1a**, which has been reported to be an effective substrate for transition-metal-catalyzed 1,2-addition reactions with organoboron compounds,[12] in the presence of CuBr (5 mol %), an (*R*)-BINOL



Scheme 1. Strategies for the synthesis of enantioenriched β-aminoborons.

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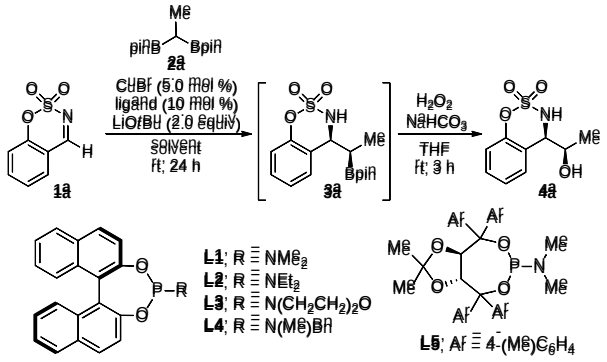
Table 1. Evaluation of reaction conditions[a]



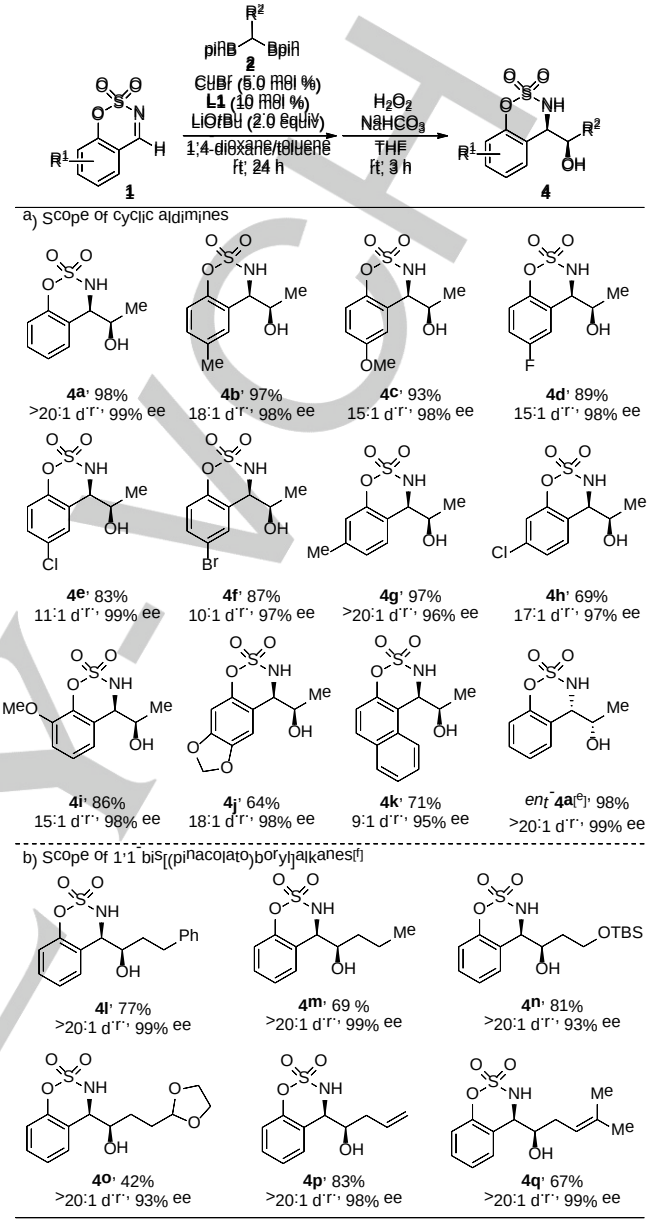
Entry	L	Solvent	Yield of **4a** [%][b]	dr[c]	ee [%][d]
1	**L1**	dioxane	94	14:1	98
2	**L1**	THF	93	11:1	99
3	**L1**	dioxane/toluene (1:1)	98(98)[e]	>20:1	99
4	**L2**	dioxane/toluene (1:1)	87	>20:1	98
5	**L3**	dioxane/toluene (1:1)	95	>20:1	99
6	**L4**	dioxane/toluene (1:1)	94	>20:1	98
7	**L5**	dioxane/toluene (1:1)	<1	n.d.	n.d.

[a] Reaction conditions: **1** (0.20 mmol), **2a** (1.5 equiv), CuBr (5.0 mol %), ligand (10 mol %), base (2.0 equiv) in solvent (0.4 mL) at rt for 24 h and then $NaHCO_3$ and H_2O_2 in THF at rt for 3 h. [b] The yield was determined by ^{1}H NMR analysis [c] Diastereomeric ratio was determined by ^{1}H-NMR analysis of the crude mixture. [d] Enantiomeric excess (% ee) was determined by HPLC analysis. [e] Isolated yield is given in parentheses. n.d. = not determined

-derived phosphoramidite ligand (**L1,** 10 mol %) and LiO*t*Bu as a base in dioxane at room temperature. We found that a 14:1 diastereomeric mixture of β-amino alcohol **4a** was obtained in 94% yield with 98% ee (Table 1, entry 1) after oxidation of the Bpin unit of **3a** in the presence of H_2O_2 and $NaHCO_3$. Switching the solvent from 1,4-dioxane to THF provided **4a** with a slightly lower diastereoselectivity (93% yield, 11:1 d.r., 99% ee, entry 2). We were pleased to observe that the use of an equal mixture of 1,4- dioxane and toluene as a solvent gave the desired product**4a** in 97% yield with >20:1 d.r. and 99% ee (entry 3), whereas the reaction in toluene led to no additional product formation.[13] Chiral phosphoramidite ligands with varying amino groups (**L2**-**L4**) were also effective (entries 4-6) in this transformation, furnishing **4a** with excellent diastereo- and enantioselectivities. The reaction of **1a** with **2a** in the presence of CuBr with a taddol-derived phosphoramidite ligand (**L5**) did not provide the desired product (entry 7). Because chiral ligand **L1** is commercially available, we chose CuBr and **L1** as our standard catalytic system. The absolute and relative configurations of product **3a** were assigned as (*S*, *R*), as determined by single-crystal X-ray analysis.

Having identified an efficient catalytic system for the copper-catalyzed diastereo- and enantioselective 1,2-addition reaction of **1a** with **2a**, we investigated the scope of cyclic aldimines with **2a** (Table 2). Cyclic aldimines containing electron-donating

Table 2. Scope of cyclic aldimines and 1,1-bis[(pinacolato)boryl]alkanes[a]-[d]



[a] Reaction conditions: **1** (0.20 mmol), **2** (1.5 equiv), CuBr (5.0 mol %), **L1** (10 mol %), base (2.0 equiv) in 1,4-dioxane/toluene (0.4 mL, 1:1) at rt for 24 h and then $NaHCO_3$ and H_2O_2 in THF at rt for 3 h. [b] Diastereomeric ratio was determined by ^{1}H-NMR analysis of the crude mixture. [c] Enantiomeric excess (% ee) was determined by HPLC analysis. [d] Isolated yields are given. [e] *ent*-**L1** was used as a ligand instead of **L1**. [f] Experiments were performed at 50 ° C in the presence of 2 equivalents of **2**.

substituents on the arene ring (**4b**, **4c** and **4g**) underwent the 1,2-addition reactions in excellent yields with high diastereoselectivity (>20:1-15:1 d.r.) and enantioselectivity (>96% ee). The reactions of cyclic aldimines bearing halides, such as fluoro (**4d**), chloro (**4e** and **4h**) and bromo (**4f**) groups, remained intact in this reaction, and the corresponding β-amino alcohols were formed in good yields (69-89%) with high diastereo- (>10:1) and enantioselectivity (>97% ee). The cyclic aldimine containing substituent at the 8-position was also a suitable electrophile,

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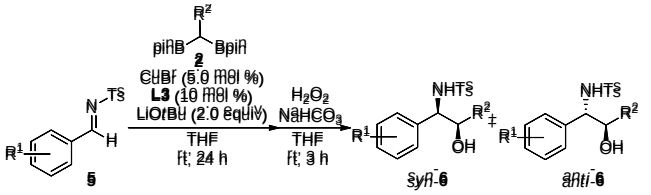
Table 3. Scope of *N*-Ts imines and 1,1-bis[(pinacolato)boryl]alkanes[a]



Entry	R^1	R^2	Yield [%][b]	dr[c]	Product	ee [%][d]
1	H	Me	92	3.2:1	**6a**	94(67)
2[e]	H	*n*-Pr	67	3.5:1	**6b**	98(91)
3[e]	H	$(CH_2)_2Ph$	53	4.9:1	**6c**	98(94)
4	4-Me	Me	72	3.6:1	**6d**	96(76)
5	4-Cl	Me	65	3.2:1	**6e**	96(77)

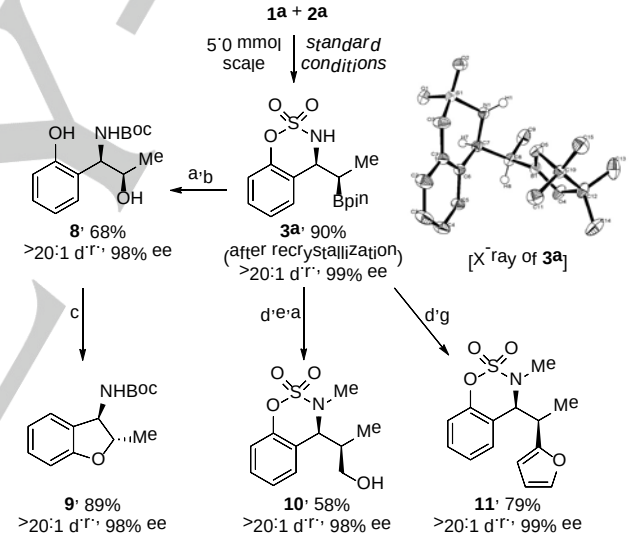
[a] Reaction conditions: **5** (0.20 mmol), **2** (1.5 equiv), CuBr (5.0 mol %), **L3** (10 mol %), LiO*t*Bu (2.0 equiv) in THF (1.0 mL) at rt for 24 h and then $NaHCO_3$ and H_2O_2 in THF at rt for 3 h. [b] Combined isolated yields of the two diastereomers are given. [c] Diastereomeric ratio was determined by ^{1}H-NMR analysis of the crude mixture. [d] Enantiomeric excess was determined by HPLC analysis. Values in parenthesis indicated the enantiomeric excess of *anti*-isomer [e] Experiments were performed at 50 °C in the presence of 2.0 equivalents of **2**.

providing **4i** in 86% yield with 15:1 d.r. and 98% ee. Protected catechol- and naphthyl-containing cyclic aldimines also underwent the 1,2-addition process, giving **4j** and **4k** in moderateto good yields with good diastereo- and enantioselectivity (18:1 and 9:1 d.r. and 98% ee and 95% ee, respectively). Finally, the opposite enantiomer of **4a** was obtained in 98% yield with >20:1 d.r. and 99% ee when the reaction was conducted with the (*S*)-BINOL-derived phosphoramidite ligand (*ent*-**L1**).

The standard 1,2-addition reaction conditions were then applied to the reaction of a range of 1,1-bis[(pinacolato)boryl]alkanes with **1a**. However, when **1a** was reacted with 1,1-bis[(pinacolato)boryl]propylbenzene (**2b**), the desired enantioenriched β-aminoboronate ester **4l** was formed only in 23% yield. Further examination of the reaction temperature revealed that the

reaction performed at 50 °C provided **4l** in 77% yield with excellent diastereo- (>20:1) and enantioselectivity (>99% ee). Under this slightly modified conditions, various 1,1-bis[(pinacolato)boryl]alkanes underwent the reaction with **1a** to generate addition products in good yields with high stereoselectivity. For example, the reaction of **1a** with 1,1-bis[(pinacolato)boryl]butane (**3c**) afforded the product **4m** in 69% yield with >20:1 d.r. and 99% ee. Additionally, a 1,1-bis[(pinacolato)boryl]alkane-containing TBS-protected alcohol and masked aldehyde underwent the 1,2-addition process, forming **4n** and **4o** in good yields with high stereoselectivity (>20:1 d.r., 93% ee). Finally, the 1,1-bis[(pinacolato)boryl]alkanes possessing an alkene moiety reacted with **1a** in 83% and 67% yields (**4p** and **4q**) with excellent diastereo- (>20:1 d.r.) and enantioselectivity (>98% ee). Note that the enantioenriched β-amino boronate esters **3** obtained in this study could be isolated by recrystallization.[13]

Next, we studied the feasibility of the 1,2-addition reaction with other *N*-protected imine electrophiles (Table 3). Although no reactions took place when *N*-phosphinoyl- or *N*-Boc-protected imines were used as substrates, the reaction of an *N*-tosyl-protected imine (**5a**) catalyzed by CuBr/**L3** in THF at room temperature gave the corresponding 1,2-amino alcohol in 92% yield (Table 3, entry 1) with moderate levels of diastereoselectivity (3.2:1 d.r.), forming *syn*-**6a** as the major isomer.[13],[14] In this case, *syn*-**6a** was highly enantioenriched (94% ee), while *anti*-**6a** was formed in moderate ee (67% ee). The reactions with other 1,1-bis[(pinacolato)boryl]alkanes **2** also provided the corresponding products **6b** (entry 2) and **6c** (entry 3) at 50 °C in good to moderate yields with increase of diastereo- and enantioselectivity. Interestingly, the enantiomeric exess of *anti*-**6b** and *anti*-**6c** products was higher than that of *anti*-**6a**, indicating that the chain length of the substituent (R^2) of **2** has an effect on the enantiselectivity of 1,2-addition process. The reactions of *N*-tosyl-protected imines bearing electron-donating (entry 4) or electron-withdrawing (entry 5) substituents at the 4-position on the arene ring with **2a** also furnished the products **6d** and **6e** at room temperature in good yields with moderate diastereoselectivity and good enantioselectivity.



Scheme 2. Reaction conditions: [a] H_2O_2, $NaHCO_3$, THF, rt for 3 h. [b] $LiAlH_4$, THF, 60 °C for 2 h and then Boc_2O at rt for 1 h. [c] DEAD, PPh_3, CH_2Cl_2, 0 °C to rt, 10 h. [d] MeI, K_2CO_3, CH_3CN, rt, 12 h. [e] $ClCH_2I$, *n*-BuLi, THF, -78 °C for 4 h. [g] furan, *n*-BuLi, NBS, THF, -78 °C for 5 h.

The reaction of **1a** with **2a** can be scaled up (5.0 mmol) with good efficiency, producing the enantiopure β-aminoboronate ester **3a** in 90% yield (>20:1 d.r., 99% ee) after recrystallization from a mixture of *n*-hexane and diethyl ether at -20 °C. We demonstrated the utility of the obtained product **3a** as illustrated in Scheme 2. After the oxidation of the Bpin unit of **3a** with H_2O_2, a desulfonylation reaction was achieved upon treatment with $LiAlH_4$ followed by Boc protection of the amino group, furnishing 2-(1-amino-2-hydroxypropyl)phenol **8** in 68% yield (2 steps; >20:1 d.r., 98% ee).[15] Treatment of **8** with diethyl azodicarboxylate (DEAD) and PPh_3 at 0 °C to room temperature gave the corresponding 3-amino-2-methylcoumaran derivative **9** in 89% yield (>20:1 d.r., 98% ee).[16] The product **3a** was also utilized for

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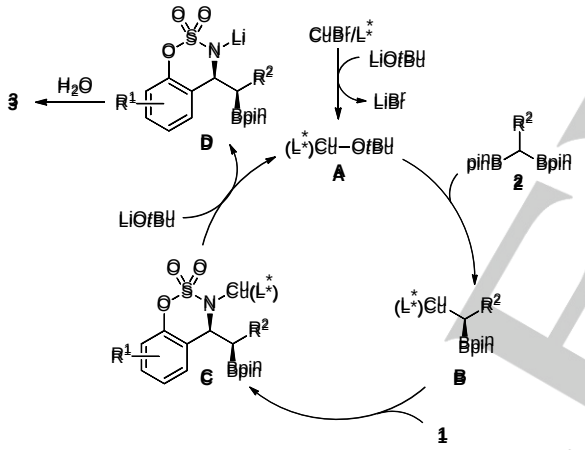
carbon-carbon bond forming reactions. After protection of the amine moiety of **3a** with methyl iodide, a one-carbon homologation with $LiCH_2Cl$ and oxidation gave the corresponding γ-amino alcohol **10** in moderate yield (58% in 2 steps; >20:1 d.r., 98% ee). Moreover, when the reaction of **4a** with 2-lithiated furan was conducted under the reaction conditions reported by Aggarwal,[17] the arylated product **11** was obtained in 76% yield with preservation of the optical purity.

Scheme 3 represents our proposed reaction pathway for the developed transformation. First, an anion exchange between CuBr ligated by the chiral phosphoramidite ligand and Li*O*t*Bu affords the copper species **A**. Based on the literature precedents,[10a,d,e] the formation of chiral α-boryl-alkyl-copper species **B** is expected to occur by an enantioselective transmetalation of 1,1-bis[(pinacolato)boryl]alkane with **A**. A subsequent nucleophilic addition of the chiral copper species **B** to cyclic aldimines **1** forms **C**. Finally, a transmetalation between **C** and Li*O*t*Bu regenerates the active copper species **A** with concomitant generation of the product **D** and the hydrolysis of **D** by workup converts **D** to **3**. The observed high levels of diastereoselectivity in this study is presumably determined by the facial selectivity in the addition of copper species **B** to cyclic aldimine **1**.



Scheme 3. Proposed catalytic cycle.

In summary, we have developed a copper-catalyzed, highly diastereo- and enantioselective 1,2-addition of 1,1-bis[(pinacolato)boryl]alkanes to *N*-protected imines. With CuBr/chiral phosphoramidite as a catalyst and Li*O*t*Bu as a base, the 1,2-addition reactions proceed to generate a broad range of β-aminoboronate esters with contiguous stereocenteres in high yields. The products are highly synthetically useful, as demonstrated by further functionalizations of the Bpin unit to form new C-O or C-C bonds upon C-B bond cleavage. Efforts to expand the scope of the diastereo- and enantiostereoselective 1,2-addition employing 1,1-bis[(pinacolato)boryl]alkanes are currently underway in our laboratory.

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Keywords: copper • imines • enantioselective • chiral β-aminoboronate esters • 1,1-bis[(pinacolato)boryl]alkanes

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[13] See the Supporting Information for details.

[14] The absolute and relative configuration of the major and minor stereoisomers of **6a** was assigned by comparison of their HPLC with that of authentic samples. We assigned the absolute and relative stereochemistry of **6b**-**6e** by analogy. See the Supporting Information for details.

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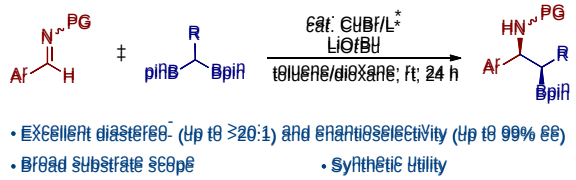

We report an efficient Cu(I)-catalytic system for the diastereo- and enantioselective 1,2-addition of 1,1-bis[(pinacolato)boryl]alkanes to protected imines to afford synthetically valuable enantioenriched β-aminoboron compounds bearing contiguous stereogenic centers.

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Diastereo- and Enantioselective Synthesis of β-Aminoboronates by Cu(I)-Catalyzed 1,2-Addition of 1,1-bis[(pinacolato)boryl]alkanes to Imines**