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Stereodivergent Asymmetric Synthesis of α,β-Disubstituted β-Aminoalkylboronic Acid Derivatives via Group-Selective Protodeboronation Enabling Access to the Elusive anti Isomer

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ABSTRACT: Chiral β-aminoalkylboronates generate growing interest as versatile synthetic building blocks to access β-aminoalcohols and other useful compounds, and also as bioisosteres of β-aminoacids in drug discovery. In this study, the lack of methodology to access both syn and anti diastereomers of optically enriched, acyclic α,β-disubstituted β-aminoalkylboronates is addressed with the development of a divergent, diastereoselective strategy for the monoprotodeboration of β-amino *gem*-bis(boronate) precursors. To this end, new reaction conditions were successfully optimized to provide the elusive anti diastereomer by inverting a sequence of desulfinylation and protodeboronation. The desired syn or anti isomers are isolated independently in good yields and excellent diastereoselectivity (up to >20:1 dr) for a wide scope of substituents. The diastereotopic group selectivity of the new conditions yielding the anti isomer is rationalized by invoking a reactive rotamer featuring two ammonium-boronate hydrogen bonds, which enables phosphate coordination to boron with a concomitant, stereoretentive protonation of the C–B bond. The accessibility and utility of both diastereomers of these α,β-disubstituted β-aminoalkylboronates is exemplified with the functionalization of the amino group, stereospecific oxidation to β-amino alcohols and C–C bond transformations of the secondary alkylboronate, and the preparation of free boronic acids and hemiboronic heterocycles.

INTRODUCTION

Controlling the absolute stereochemistry of organic molecules is a crucial endeavor in drug discovery, one that is made possible by advances in enantioselective synthetic methods achieved in the past decades.[1] Diastereoselectivity is equally important, and it is often more challenging to control.[2] This paradox is well exemplified by the longstanding '*anti* aldol problem' that long plagued propionate synthesis using enantiocontrolled chiral auxiliary methods,[3] and, more recently, with organocatalysis.[4] In this regard, methods that can supply all stereoisomers of a compound independently from the same precursor constitute an ideal that is rarely achieved. This concept – stereodivergence – is particularly useful when applied to biologically relevant molecules.[5] The preparation of optically enriched and diastereomerically pure α,β-disubstituted β-aminoalkylboronates presents such a challenge. Like their lower α homologs, β-aminoalkylboronates are viewed as bioisosteres of the corresponding β-aminoacids (Figure 1a). Bioisosterism of α-aminoacids has inspired the rich chemistry of α-aminoalkylboronic acids and a variety of preparative methods to access these compounds,[6] which culminated in the commercialization of the anticancer agent bortezomib[7] and the antibiotic vaborbactam.[8] Though less studied, interest in β-aminoalkylboronic acids is surging owing to their potential applications as synthetic intermediates, in catalysis, and drug discovery.[9] Deplorably, further progress is hampered by the scarcity of selective methods to prepare both syn and anti diastereomers of optically enriched α,β-disubstituted β-aminoalkylboronates. An elegant stereodivergent methodology was developed by Meek and co-workers for synthesizing *syn*- and *anti*-α,β-disubstituted β-hydroxyalkylboronates,[10] however, it is not applicable to the analogous β-aminoalkylboronates. Efficient methods exist to prepare *syn*-α,β-disubstituted β-aminoalkylboronates in high enantioselectivity.[11] In contrast, only a single method was reported to access cyclic anti diastereomers; a kinetic resolution restricted to a niche class of

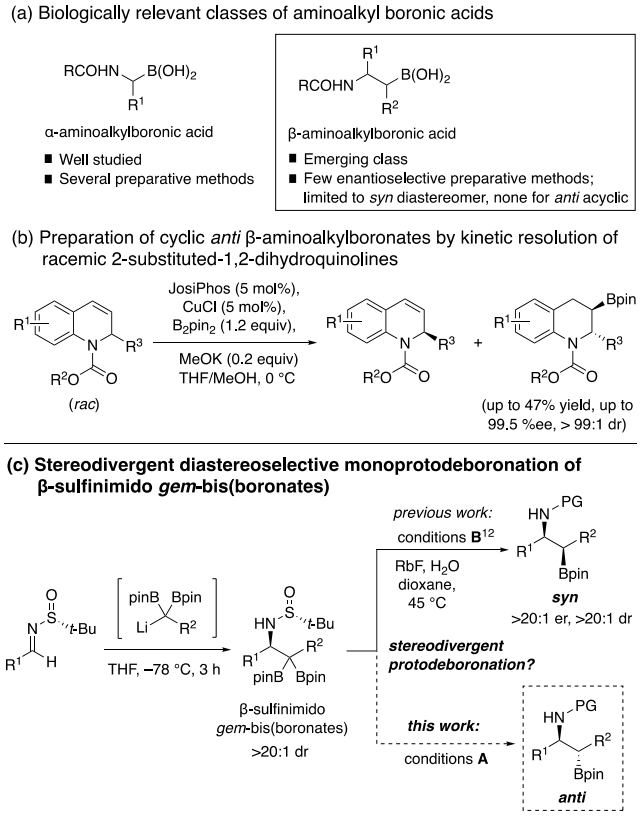


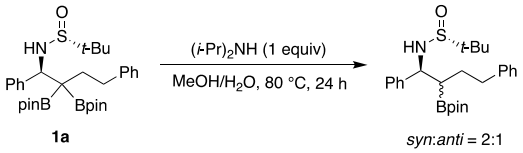
Figure 1. α,β-Disubstituted β-aminoalkylboronic acids/esters: (a) Structure; (b)-(c) Preparation.

tetrahydroquinolines (Figure 1b).[12] Recently, we reported a new synthetic strategy to prepare acyclic *syn*-α,β-disubstituted β-aminoalkylboronates based on the highly stereoselective addition of lithiated *gem*-diborylalkanes onto chiral sulfinylimines.[13,14] The resulting β-sulfinimido *gem*-diboronates can be monoprotodeboronated to form the *syn*-β-aminoalkylboronates in high yield and excellent diastereoselectivity for a wide scope of substituents (Figure 1c). To make this deboronation strategy truly general and versatile, it is essential to develop a complementary variant to prepare the anti diastereomers. Herein, we report a divergent set of highly diastereoselective reaction conditions to access both *syn*- and *anti*-α,β-disubstituted β-aminoalkylboronates, independently, in good yields and high selectivity.

RESULTS AND DISCUSSION

Optimization of Reaction Conditions. In the course of our previous optimization of the monoprotodeboronation of β-sulfinimido *gem*-bis(boronates) to access *syn*-α,β-disubstituted β-aminoalkylboronates,[13] no satisfactory conditions were identified to provide the anti diastereomers. No better than a 2:1 ratio (*syn*:*anti*) could be obtained, wherein the syn isomer is still the dominant product (Scheme 1).

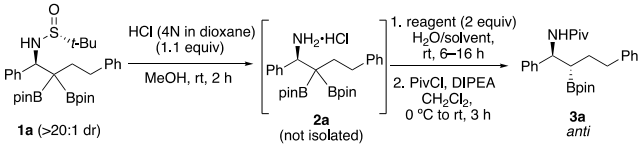
Scheme 1. Initial Efforts Towards anti-selective Monoprotodeboronation using β-Sulfinimido *gem*-Bis(boronate) 1a



Thus, to design a complementary method favoring the *anti*-β-aminoalkylboronates, we reasoned that the steps of protodeboronation and deprotection of the *N*-sulfinyl amine could be inverted. To this end, our initial study employed *N*-*tert*-butanesulfinyl β-amino *gem*-bis(boronate) **1a**, which was first desulfinylated using anhydrous HCl to provide after simple evaporation the amine salt **2a** as the model substrate (Table 1). For ease of isolation, the amine of the first-formed deboronated product was transformed into a pivaloyl amide (**3a**). As it ensued, when employing the protodeboronation conditions previously optimized to provide the syn diastereomer,[13] **2a** afforded a low yield of product **3a** favoring the anti isomer in a 5:1 ratio (entry 1). Screening of solvents revealed that use of CH_2Cl_2 increased the diastereoselectivity to 9:1 (entry 4) while other solvents such as MeOH and *n*-hexane were less effective (entries 2–3). Switching the reagent from RbF to TBAF led to a higher yield (81%) with slightly higher diastereoselectivity (10:1 dr; entry 5).

To further improve the diastereoselectivity, the nature of the counteranion of the tetrabutylammonium reagent was examined. Evaluation of the various tetrabutylammonium reagents confirmed that the counteranion exerts a significant impact on the diastereoselectivity (entries 6–12). Tetrabutylammonium reagents including TBAOH (entry 6), TBA(OSO_2CF_3) (entry 7), TBA(OC_6H_4p-NO_2) (entry 8) and TBA(OCOPh) (entry 9) were found to be less effective than TBAF. Gratifyingly, the use of tetrabutylammonium acetate increased the diastereoselectivity (13:1 dr) (entry 10). Evaluation of larger tetrabutylammonium carboxylates (entries 11 and 12) revealed that tetrabutylammonium phenylacetate (entry 12) delivered an excellent diastereoselectivity (>20:1 dr) with a good yield (63%; entry 12). Aiming to enhance the yield, the reaction was attempted at a lower (entry 13) or higher (entry 14) temperature, however, they both resulted in a decrease in yield. The yield further improved upon conducting the reaction using tetrabutylammonium phosphates (entries 15 and 16), with tetrabutylammonium dibenzylphosphate delivering 75% yield with excellent diastereoselectivity (>20:1 dr; entry 16). Increasing the amount of tetrabutylammonium dibenzylphosphate to 2.5 equivalents eventually led to the highest yield (82%) with excellent diastereoselectivity (>20:1 dr; entry 17). The anti stereochemistry of β-aminoalkylboronate **3a** and other analogues in this study was determined based on the X-ray crystallographic analysis of an optically enriched crystalline derivative (**10**, c.f., Scheme 4a).[15]

Table 1. Optimization of the Reaction Conditions[a]



entry	reagent	H_2O (equiv)	solvent	yield [%][b]	dr[c]
1	RbF	2	dioxane	25	5:1
2	RbF	2	*n*-hexane	32	3:1
3	RbF	2	MeOH	33	1:1
4	RbF	2	CH_2Cl_2	24	9:1
5	TBAF•3H_2O	–	CH_2Cl_2	81	10:1
6	TBAOH	6	CH_2Cl_2	76	4:1
7	TBA(OSO_2CF_3)	6	CH_2Cl_2	N.R.	–
8	TBA(OC_6H_4p-NO_2)	6	CH_2Cl_2	75	10:1
9	TBA(OCOPh)	6	CH_2Cl_2	70	10:1
10	TBA(OCOMe)	6	CH_2Cl_2	66	13:1
11	TBA(OCO^{i}Pr)	6	CH_2Cl_2	70	12:1
12	TBA(OCOBn)	6	CH_2Cl_2	63	>20:1
13[d]	TBA(OCOBn)	6	CH_2Cl_2	8	>20:1
14[e]	TBA(OCOBn)	6	CH_2Cl_2	48	>20:1
15	TBAOP(O)(O^nBu)$_2$	6	CH_2Cl_2	74	15:1
16	TBAOP(O)(OBn)$_2$	6	CH_2Cl_2	75	>20:1
17[f]	**TBAOP(O)(OBn)$_2$**	**6**	**CH_2Cl_2**	**82(77)[g]**	**>20:1**

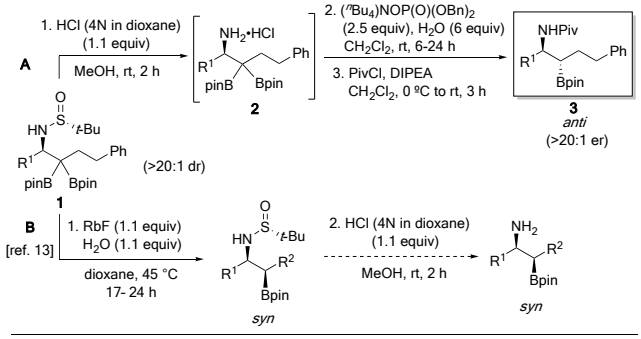
[a]Reactions performed on a 0.1 mmol scale under N_2 atm. [b]Yield determined by ^{1}H NMR analysis using dibromomethane as the internal standard. [c]dr determined by peak heights of isolated resonances by ^{1}H NMR of the crude reaction mixture. [d]Reaction performed at 0 ºC. [e]Reaction performed at 40 ºC. [f]With 2.5 equiv of TBAOP(O)(OBn)$_2$. [g]Isolated yield of the *anti* diastereomer. TBA = tetrabutylammonium. dioxane = 1,4-dioxane. N.R. = no reaction.

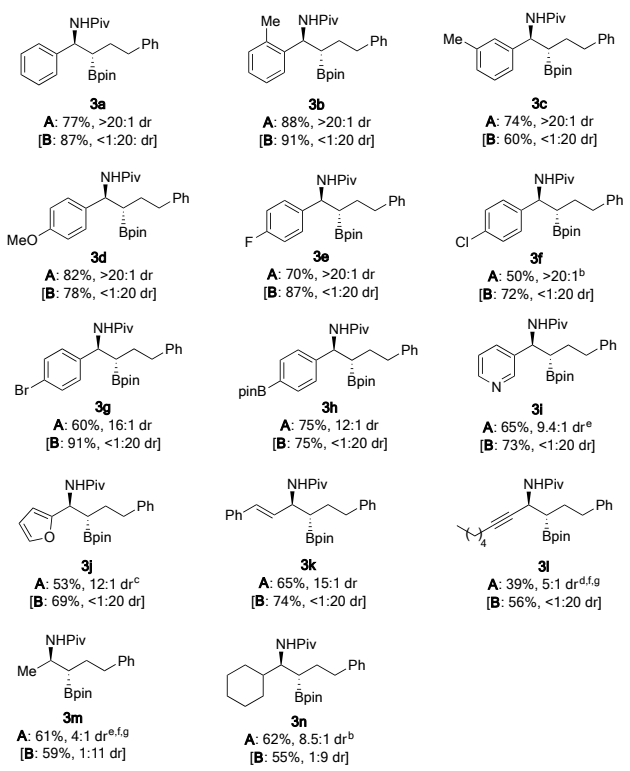
Reaction Scope. With the optimized protodeboronation conditions of Table 1 (entry 17) in hand, we examined the substrate scope by engaging a large selection of α,β-disubstituted β-sulfinimido *gem*-bis(boronates) reported in our

previous study.[13] Remarkably, together with the previous protodeboronation conditions to access the syn isomers, protodeboronation of β-amino *gem*-bis(boronates) allows the stereodivergent synthesis of both diastereomers of α,β-disubstituted β-aminoalkylboronates. As shown in Table 2, using sequence **A**, the simple three-step transformation of β-sulfinimido *gem*-bis(boronates) containing various aryl (R^1) substituted groups at the *ortho*, *meta* or *para* positions was found to be effective, producing the corresponding *anti*-β-aminoalkylboronates (**3b-h**) in good to high yields (50–88%) with good to excellent diastereoselectivity (up to >20:1 dr). Under the standard conditions, monoprotodeboronation of heteroaryl substituted (R^1) β-amino *gem*-bis(boronates) **2i** and **2j** gave only moderate conversions. However, it was discovered that by employing a larger amount of $(^nBu)_4NOP(O)(OBn)_2$, **2i** and **2j** were monoprotodeboronated to respectively yield *anti*-β-aminoalkylboronates **3i** and **3j** in good yields with good diastereoselectivity. *gem*-Bis(boronate) **1k** bearing an alkenyl group as the R^1 substituent was also found to be a suitable substrate, producing *anti*-β-aminoalkylboronates **3k** in 65% yield with high diastereoselectivity(15:1 dr) by employing sequence **A**. Alkynyl- and alkyl-substituted (R^1) β-sulfinimido *gem*-bis(boronates) also underwent the three-step sequence **A** to deliver the *anti*-β-aminoalkylboronates (**3l-n**) in moderate to good yields with moderate to good diastereoselectivity under modified conditions.

Besides β-sulfinimido *gem*-bis(boronate) substrates with a phenyl-containing R^2 substituent (**1a**; Table 3), the sequence is also compatible with other R^2 substituents containing alkenyl and cyclohexyl, forming the expected *anti*-β-aminoalkylboronates (**3o** and **3p**) without problems (Table 3). Unfortunately, a silyl ether-containing substrate (**1q**) failed to provide any desired β-aminoalkylboronate likely due to the desulfinylation conditions. In addition, a silyl-containing β-sulfinimido *gem*-bis(boronate) **1r** was synthesized through the 1,2-addition reaction.[13,15] *gem*-Bis(boronate) **1r** was found to be a suitable substrate for both sequence **A** and **B**, respectively affording the synthetically useful *anti*- and *syn*-silyl-containing β-aminoalkylboronates[16] in good to high yields with high levels of diastereoselectivity (>20:1 dr).

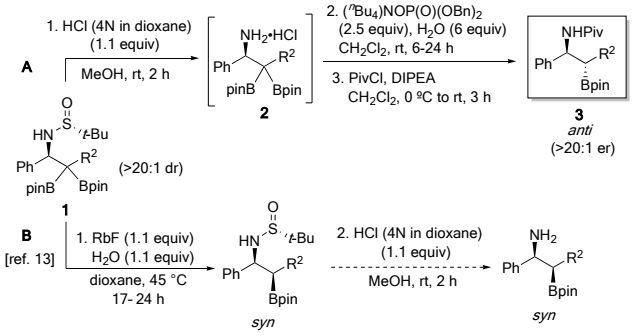
Table 2. Scope with Respect to the R^1 Substituent of the Diastereodivergent Synthesis of α,β-Disubstituted β-Aminoalkylboronates[a]

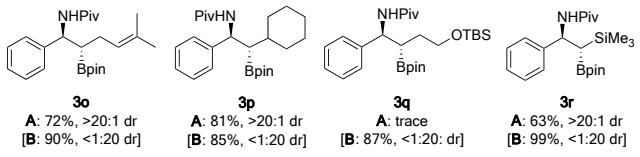




[a]Reactions performed on a 0.3 mmol scale under N_2 atm. Yields of isolated products are given. dr determined by peak heights of isolated resonances by ^1H NMR of the crude reaction mixture. For conditions B (ref. 13), the indicated dr is *anti*:*syn*. Yield and dr refer to the N-sulfinyl product. [b]With 3 equiv of $(^nBu)_4NOP(O)(OBn)_2$. [c]With 3.5 equiv of $(^nBu)_4NOP(O)(OBn)_2$. [d]With 4 equiv of $(^nBu)_4NOP(O)(OBn)_2$. [e]With 5 equiv of $(^nBu)_4NOP(O)(OBn)_2$. [f]At 60 ºC. $CHCl_3$ used as the solvent. [g]Isolated as a mixture of anti and syn diastereomers.

Table 3. Scope with Respect to the R^2 Substituent of the Diastereodivergent Synthesis of α,β-Disubstituted β-Aminoalkylboronates[a]

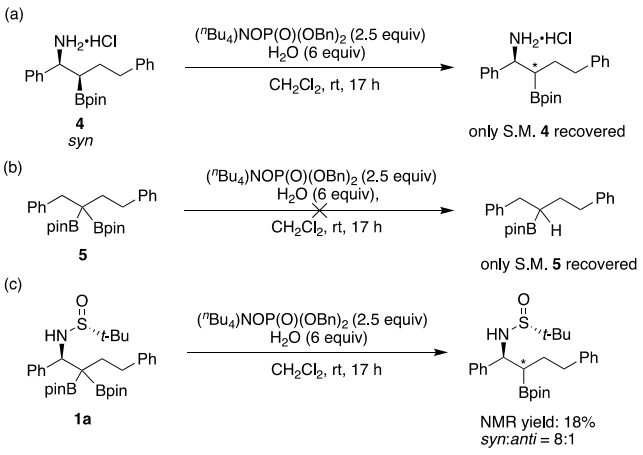




[a]Reactions performed on a 0.3 mmol scale under N_2 atm. Yields of isolated products are given. dr determined by peak heights of isolated resonances by ^1H NMR of the crude reaction mixture. For conditions B (ref. 13), the indicated dr is *anti*:*syn*; yield and dr refer to the N-sulfinyl product.

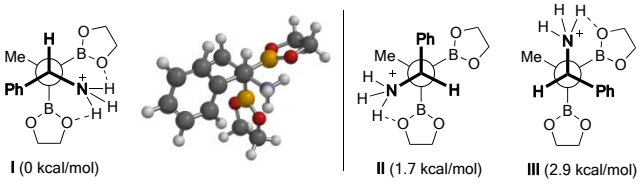
Mechanistic Studies. To understand the observed anti diastereoselectivity in the protodeboronation step, a *syn*-β-aminoalkylboronate **4** with a primary ammonium unit was prepared using our reported procedure.[13] When **4** was subjected to the standard protodeboronation conditions, no epimerization occurred (Scheme 2a). This result implies that there is no equilibration and the *anti*-β-aminoalkylboronate **3a** is a kinetically favored product. We also investigated the role of the primary ammonium units of β-amino *gem*-bis(boronates) **2**. The poor reactivity of *gem*-bis(boronates) **5** (Scheme 2b) and sulfinimide **1a** (Scheme 2c) confirms that the primary ammonium unit is essential for the high reactivity and anti-selectivity in the protodeboronation of β-amino *gem*-bis(boronates) **2**. This observation is consistent with our previous study[13] where sulfinyl NH···OB hydrogen bonding was determined to be important

Scheme 2. Control Experiments for the anti-Selective Monoprotodeboronation.



for the reactivity and syn-selectivity. Thus, in this anti-selective protodeboronation variant, it is reasonable that the same type of NH···OB hydrogen-bonding interaction occurs with both Bpin units since there are three available ammonium N–H bonds in *gem*-bis(boronates) **2**. To support this notion, the three staggered rotamers **I-III** of a prototypic compound were minimized by DFT in a nonpolar solvent model.[15] Rotamer **I** with two NH···OB bonds (1.95, 2.00 Å) was indeed found to be largely favored compared to rotamers **II** and **III** with only one NH···OB bond (Figure 2).

Figure 2. Energy of DFT Minimized Rotamers of a Model α,β-Disubstituted β-Amino *gem*-bis(boronate)



The question of identifying a reactive conformation is further complicated by the matter of stereochemistry in the protonation of the C–B bond. Specifically, the monoprotodeboronation of *gem*-bis(boronates) **1** and **2** with two Bpin groups can produce the same diastereomer by two distinct mechanisms. For example, as shown conceptually in Figure 3, deboronation of B^1pin by retention of stereochemistry and deboronation of B^2pin by inversion of stereochemistry both provide the anti diastereomer. Without labeling the Bpin groups, these two pathways are indistinguishable. Selectivelabeling of these diastereotopic Bpin groups and their stereochemical assignment is a daunting problem in such acyclic systems. However, because reported instances of protodeboronation with chiral organoboron compounds support a retentive mechanism of protonation of the C–B bond, it is reasonable to assume a similar course with *gem*-bis(boronates).[17,18]

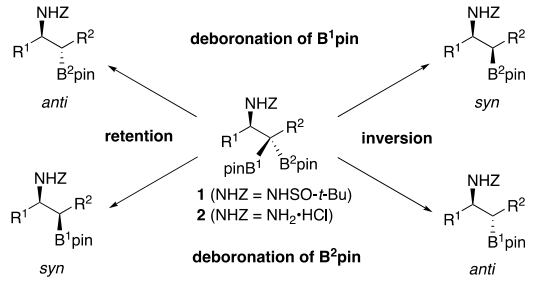
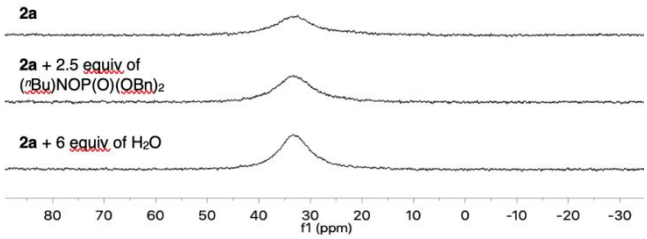


Figure 3. Possible stereochemical courses for the monoprotodeboronation of β-amino *gem*-bis(boronates) **1** and **2**.

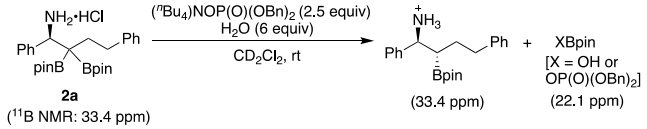
The mechanism of monoprotodeboronation of *gem*-bis(boronates) **2** was explored using ^{11}B NMR spectroscopy (Figure 4). Contrasting with previous studies on protodeboronation,[13,17] no tetrahedral boron intermediate was observed when *gem*-bis(boronates) **2a** and water or tetrabutylammonium dibenzylphosphate were mixed (Figure 4a). Moreover, when monitored by ^{11}B NMR spectroscopy, mixing

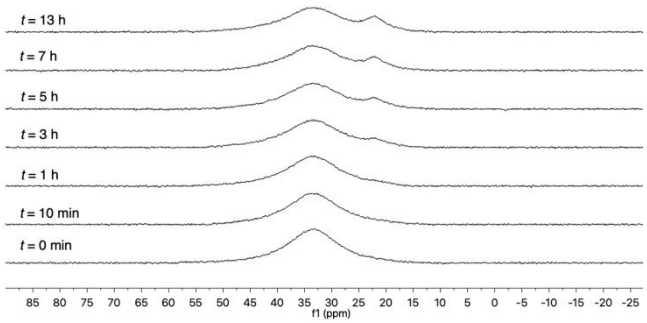
Figure 4. ^{11}B NMR Studies of the Deboronation of 2a.

(a) ^{11}B NMR spectra after mixing β-amino *gem*-bis(boronate) **2a** with water (H_2O) or tetrabutylammonium dibenzylphosphate



(b) Monitoring of the monoprotodeboronation at room temperature using ^{11}B NMR spectroscopy

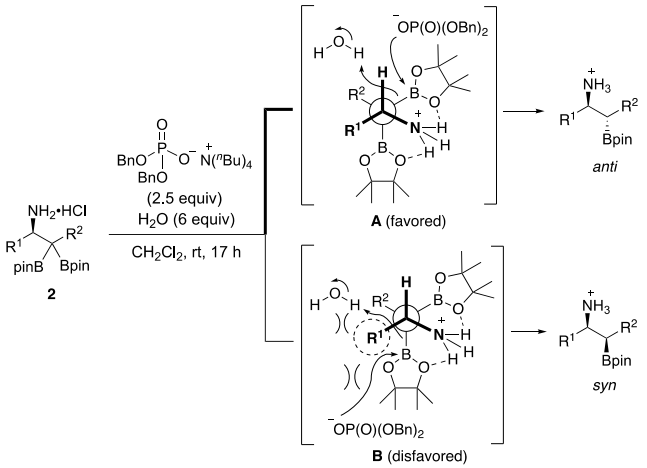




all the reagents and solvent together only gave rise to a signal at 33.4 ppm that can be assigned to the non-quaternized Bpin groups of **2a** (Figure 4b). As the reaction proceeds, a new signal appears at 22.1 ppm, which can be attributed to the BpinOH or Bpin[OP(O)(OBn)$_2$] by-product,[19] and it increased in intensity with time (Figure 4b). This ^{11}B NMR study suggests that *gem*-bis(boronates) **2** undergo protodeboronation through the trimolecular process shown in Scheme 3, which circumvents the formation of a discrete Lewis acid-base boronate complex.

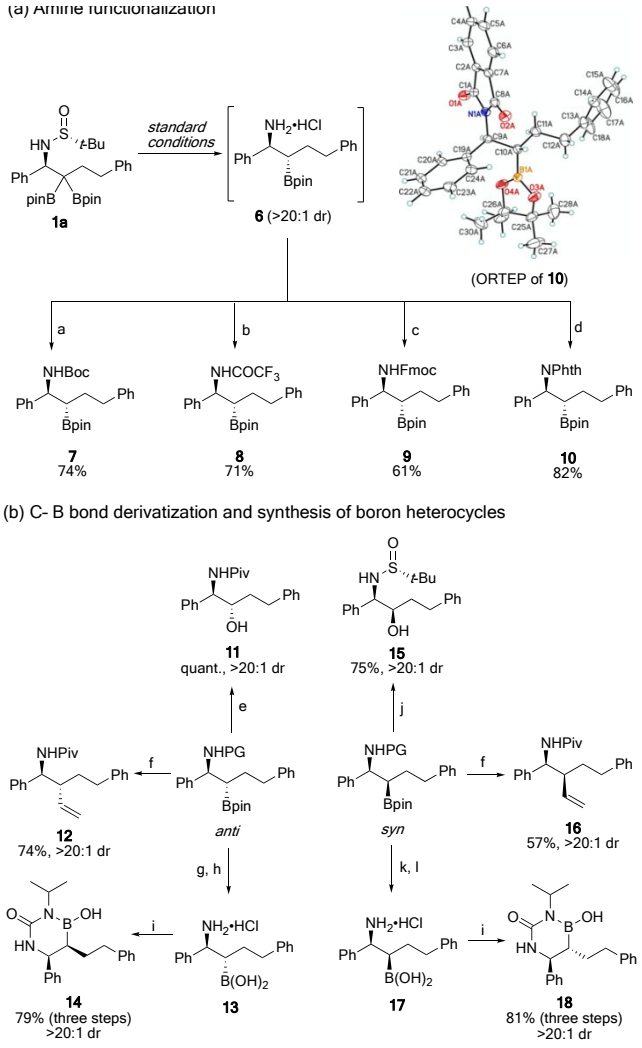
To explain the anti-selectivity, we favor model **A** with a reactive conformer similar to rotamer **I** (c.f., Figure 2), rigidified by two ammonium NH···OB hydrogen bonds activating both Bpin units (Scheme 3). In this rotamer, the least sterically hindered boryl group is exposed to a nucleophilic attack by the bulky dibenzylphosphate anion onto the boron atom, with concomitant stereoretentive protonolysis of the C–B bond by water to form the *anti*-α,β-disubstituted β-aminoalkylboronate products. Model **B**, which leads to the syn diastereomer according to the same assumption of a stereoretentive protodeboronation, is less favorable because the leaving Bpin group is much less approachable as a result of steric hindrance from the
the R^1 (R^1 ≠ H) group.

Scheme 3. Proposed anti-Selective Monoprotodeboronation Mechanism.



Synthetic Applications. The potential utility of α,β-disubstituted β-aminoalkylboronates was demonstrated with examples of selective transformations (Scheme 4). Besides the *N*-pivaloylation, the amino group of β-aminoalkylboronate intermediate **6** can also be protected in good yields into Boc (**7**), CF_3CO (**8**), Fmoc (**9**) and Phth (**10**) derivatives (Scheme 6a). Furthermore, both β-aminoalkylboronate diastereomers are amenable to C–O bond and C–C bond forming reactions by way of stereospecific C–B bond manipulations. As shown in Scheme 6b, oxidation of *anti*- and *syn*-β-aminoalkylboronates with H_2O_2/NaOH respectively furnished the *anti*- and *syn*-β-amino alcohols (**11** and **15**) in excellent yield. Of note, currently reported approaches to enantiomerically pure β-amino alcohols are still rare and often are associated with limitations including limited substrate scope and low stereoselectivity.[20] Using modified Zweifel olefination conditions,[21] both β-aminoalkylboronate isomers underwent stereospecific vinylation to afford the respective *anti*- and *syn*-homoallylic amines **12** and **16**. Finally, the potential utility of the β-aminoalkylboronates was also highlighted in the synthesis of boron heterocycles.[22] Removal of the Boc or sulfinyl moiety of both β-aminoalkylboronate isomers followed by deprotection of the Bpin unit afforded the *anti*- and *syn*-β-aminoboronic acids **13** and **17**. Addition of the isolated β-aminoboronic acids to isopropyl isocyanate produced the six-membered hemiboronic heterocycles **14** and **18** in 79% and 81% yield, respectively, over three steps. The importance of saturated boron heterocycles of this sort is highlighted by the recent approval of the antibiotic vaborbactam.[8]

Scheme 4. Synthetic Applications of α,β-Disubstituted β-Aminoalkylboronates.



[a]Boc_2O, NEt_3, CH_2Cl_2, rt. [b]TFAA, pyridine, CH_2Cl_2, rt. [c]FmocCl, DIPEA, CH_2Cl_2, rt. [d]Phthalic anhydride, NEt_3, toluene, Dean-Stark. [e]PG = Piv (**3a**), H_2O_2, NaOH, THF/H_2O, 0 ºC to rt. [f]PG = Piv (**3a**), CH_2=CHMgBr, I_2, NaOMe, THF/MeOH, –78 ºC to rt. [g]PG = Boc (**7**), HCl (4N in dioxane), CH_2Cl_2, 0 ºC to rt. [h]$PhB(OH)_2$, Et_2O/H_2O, rt. [i]Isopropyl isocyanate, $NaOH_{aq}$ (5N), THF, 0 ºC to rt. [j]PG = S(O)(*t*-Bu), see ref. 13. [k]PG = S(O)(*t*-Bu), HCl (4N in dioxane), MeOH, rt. [l]HCl_{aq} (3N), 100 ºC.

CONCLUSION

In summary, using the diastereotopic group-selective monoprotodeboronation strategy, a stereodivergent set of practical reaction conditions were established to access both *syn*- and *anti*- α,β-disubstituted β-aminoalkylboronates from β-amino *gem*-bis(boronates). Theoretically, by using the antipode of the chiral sulfinyl group of the readily available β-sulfinimido *gem*-bis(boronates), all four stereoisomers of α,β-disubstituted β-aminoalkylboronates can be prepared independently in high (>95:5) selectivity. A series of mechanistic studies revealed that the anti-selective monoprotodeboronation proceeds through a concerted trimolecular mechanism, and the NH···OB hydrogen-bonding interaction with both Bpin units of the *N*-desulfinylated β-amino *gem*-bis(boronates) plays a key role for the high reactivity and anti-selectivity. The general accessibility of both diastereomers of these β-aminoalkylboronates will not only benefit their potential application in drug discovery, typically as free boronic acids or hemiboronic heterocycles, but also in organic synthesis where the versatility of the C–B bond can be exploited in stereoselective transformations.

ASSOCIATED CONTENT

Supporting Information

Experimental details, analytical data and spectral reproductions for all new compounds; further reaction optimization studies; details of mechanistic studies and molecular modeling; X-ray crystallographic details. The Supporting Information is available free of charge on the ACS Publications website.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.

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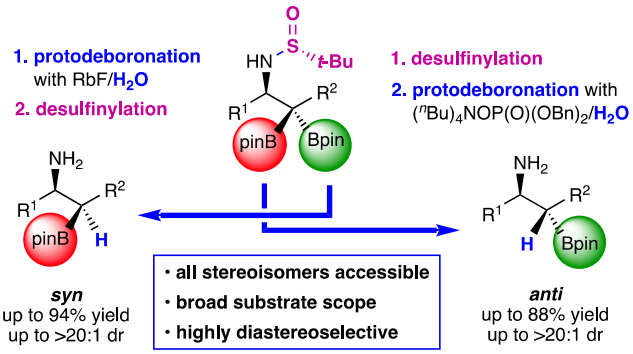
1. protodeboronation
with RbF/H2O
2. desulfinylation
1. desulfinylation
2. protodeboronation with
(nBu)4NOP(O)(OBn)2/H2O
t-Bu
pinB
Bpin
NH2
R1
R2
H
syn
up to 94% yield
up to >20:1 dr
anti
up to 88% yield
up to >20:1 dr
• all stereoisomers accessible
• broad substrate scope
• highly diastereoselective