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Access to Cyclic Amino Boronates via Rhodium-Catalyzed Functionalization of Alkyl MIDA Boronates

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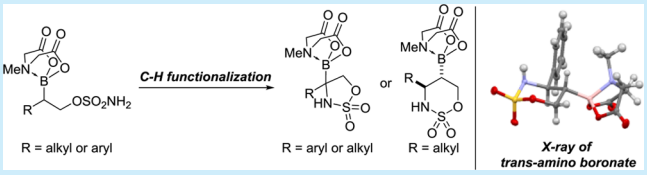
Supporting Information

ABSTRACT: Herein, we describe the rhodium-catalyzed C−H amination reaction of 1,2-boryl sulfamate esters derived from amphoteric α-boryl aldehydes. Depending on the substitution pattern of the boryl sulfamate ester, a diverse range of five- or six-membered ring heterocycles are accessible using this transformation. The highly chemoselective nature of the C−H functionalization reaction preserves the alkyl boronate functional group, which enables the synthesis of B−C−N and B−C−C−N motifs that are present in a number of hydrolase inhibitors.



Alkyl and arylboronic acids are known to interact covalently with a number of enzymes including thrombin, β-lactamase, HCV NS3/4A protease, and the 20S proteasome.[1] As shown by Matteson and Leinhard, α-amino alkylboronic acids mimicking the native peptide substrates confer greater specificity and higher potency of inhibition.[2] The mechanism of protease inhibition is based on the favored interaction between the nucleophilic amino acid residues, typically serine and threonine residues, and the boron center.[3] Lewis acid/base interaction forms the sp^3-boronate that acts as the transition-state analogue for amide bond cleavage. Thus, α-amino boronates are important motifs that have been incorporated into several classes of protease inhibitors.[4] Bortezomib (Velcade), an FDA-approved treatment for multiple myeloma, exhibits high selectivity as a reversible, covalent inhibitor for the 20S proteasome.[5] Another peptidase inhibitor, Val-boroPro (Talabostat), contains an exocyclic boronic acid that has been successful through Phase II clinical trials.[6] From the success of these compounds, there has been an increased interest in other α-amino boronate-containing small molecules for the identification and elucidation of biological activity (Figure 1).

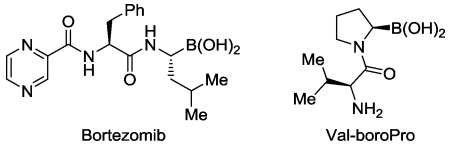


Figure 1. Selected biologically active amino boronates.

In contrast to the large number of studies into the biological properties of α-amino boronates, there are few general methods for the synthesis of α-amino boronates using late-stage introduction of the boron functional group. The most common process utilizes metalated amines for halide displacement of α-halo alkyl boronates.[7] While effective for simple alkyl boronates, the strongly basic conditions present chemoselectivity issues and limit functional group compatibility. Recently, the diastereoselective copper-catalyzed addition of B_2Pin_2 to Ellman imines and enamides (*N*-*tert*-butylsulfinylimines and -enamides) has provided a convenient entry into secondary and tertiary amino boronates.[8] An enantioselective platinum-catalyzed variant has also been reported;[8e] however, these methods are ineffective for the synthesis of cyclic derivatives.

Our synthetic studies of the amino boronate motif have uncovered that α-*N*-methyliminodiacetyl (MIDA) boryl acyl azides undergo a concerted carbon−boron bond transposition to afford the linear α-amino boronic acid derivatives.[9] Since this initial disclosure, our group has been interested in other processes that introduce amine functional groups to alkyl MIDA boronates. Herein, we describe the rhodium-catalyzed amination of alkyl MIDA boronates to afford borylated heterocycles (Figure 2).

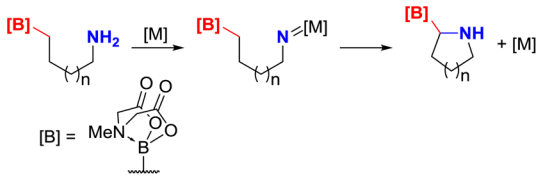


Figure 2. Intramolecular insertion of [M]-nitrenoid to alkyl boronates.

In an effort to evaluate the amination process, we sought to utilize alkyl MIDA boryl sulfamate esters as substrates. Previously reported α-MIDA boryl aldehydes served as appropriate starting materials for the synthesis of the sulfamate esters.[10] The 1,2-boryl alcohol is a sensitive functional group

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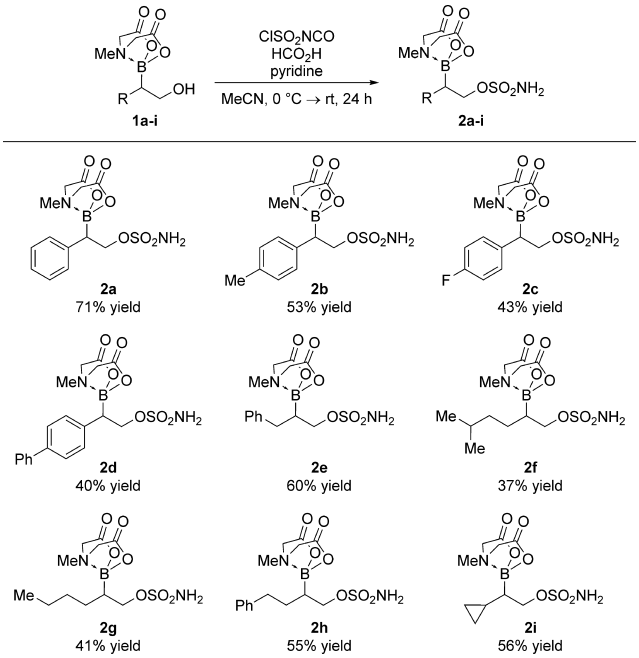
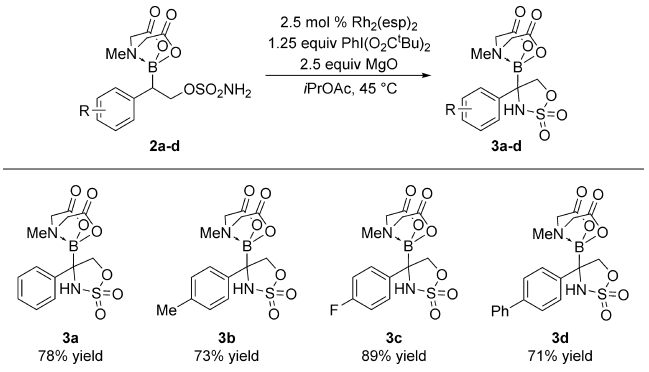
due to the facile borono-Peterson elimination;[11] however, the reduction of the starting boryl aldehyde with $NaBH(OAc)_3$ afforded the desired 1,2-MIDA boryl alcohol as a white solid (see the Supporting Information). The increased stability of this motif is attributed to the MIDA ligand on the boron atom. Synthesis of the requisite sulfamate ester was next attempted with a mixture of $ClSO_2NCO$/formic acid.[12] Initially, the formation of the sulfamate was accompanied by the production of the corresponding formate ester.[13] However, we later found that ester formation could be suppressed by quenching the reaction with water prior to removal of the solvent. As a result of the modified workup, the desired boryl sulfamate esters were obtained in good yields (Scheme 1).

Scheme 1. Synthesis of the 1,2-Borysulfamate Ester



With the boryl sulfamate ester **2a** in hand, we sought to promote the C−N bond formation via Rh^{II} catalysis. The initial attempt with 5 mol % of $Rh_2(OAc)_4$ in the presence of $PhI(OAc)_2$ afforded the quaternary α-amino boronate (**3a**) in 56% conversion by ^1H NMR. The reduced conversion is attributed to the decomposition of the catalyst.[14] Exchanging $Rh_2(OAc)_4$ for Du Bois' $Rh_2(esp)_2$ system resulted in the formation of **3a** in 78% yield (Table 1, entry 4). Application of the optimized reaction conditions to other boryl sulfamates found no observable influence of the aryl substituent on the recovered yields of the cyclic α-amino boronate (Scheme 2, **2a−d**).[15] In addition, we did not detect any products from C−B bond engagement, which underscores that the MIDA ligand is inhibiting transmetalation to the rhodium center.[16]

Scheme 2. Five-Membered Borylated Heterocycles via C−H Amination



In contrast to boryl sulfamates **2a−d**, alkyl-substituted sulfamates **2e−h** possess multiple reactive C−H bonds. To probe the regioselectivity of the alkyl boronate amination process, benzyl boryl sulfamate (**2e**) was subjected to the optimized reaction conditions, which resulted in the isolation of the β-amination product, and the relative stereochemistry was confirmed by single-crystal X-ray analysis (Scheme 3, **3e**). Other alkyl-substituted boryl sulfamates (**2f−h**) afforded a mixture of 5- and 6-membered ring products.[17] Attempts to ring-open the cyclic products with a variety of nucleophiles resulted in a complex reaction mixture or recovered starting material.

A mixture of regioisomers obtained for **3f−h** from the C−H amination reaction is thought to result from a radical intermediate.[18,19] This intermediate is proposed given that α-boryl radicals are reactive species and have been utilized in oxygenation,[20a] photoredox alkylation,[20b] and halogenation reactions.[21] To provide insight, we exposed the cyclopropylboryl sulfamate ester (**2i**) to the optimized reaction conditions. Analysis of the crude material by ^1H NMR found

Table 1. Optimization of C−H Amination Reaction[a]

entry	catalyst	oxidant	solvent	time (h)	conversion[b] (%)	yield (%)
1	$Rh_2(OAc)_4$	$PhI(OAc)_2$	*i*-PrOAc	18	56	ND
2	$Rh_2(esp)_2$	$PhI(OAc)_2$	DCM	6	38	ND
3	$Rh_2(esp)_2$	$PhI(OAc)_2$	*i*-PrOAc	6	83	ND
4[c]	$Rh_2(esp)_2$	$PhI(O_2C$-*t*-$Bu)_2$	*i*-PrOAc	18	100	78
5[c,d]	$Rh_2(esp)_2$	$PhI(O_2C$-*t*-$Bu)_2$	*i*-PrOAc/MeCN	10	85	40
6	none	$PhI(O_2C$-*t*-$Bu)_2$	*i*-PrOAc	10	0	ND

[a]Reaction conditions: 1.25 equiv of oxidant, 2.5 equiv of MgO, in N_2-sparged anhydrous solvent. [b]Measured by comparison of corresponding NCH_3 of SM/product by crude ^1H NMR. [c]2.5 mol % of $Rh_2(esp)_2$. [d]4:1 *i*-PrOAc/MeCN. ND = not determined.

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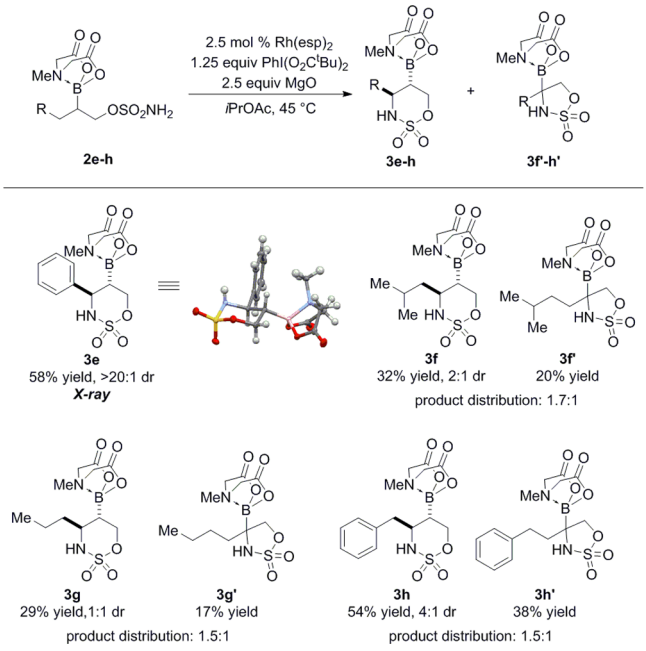
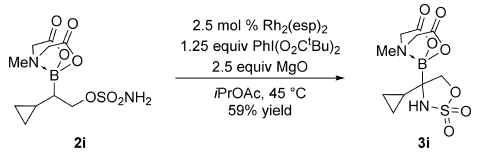
Scheme 3. Boryl Sulfamate Cyclization



no discernible cyclopropane fragmentation products, and product **3i** was obtained in 59% yield (Scheme 4). This suggests that the amination reaction does not proceed via long-lived α-boryl radical species.

Scheme 4. Radical Clock Experiment



The absence of radical fragmentation products suggests that the C−H amination reaction of boryl sulfamate esters is heterolytic.[22,23] In this process, hydride is transferred to the electrophilic rhodium nitrene, resulting in a transient positive charge at the reactive carbon.[24] Therefore, substitution of electron-rich groups at the reactive site is typically beneficial.[25] In addition to benzylic cation stabilization (for aryl substituents), the electron-rich sp^3-boron center is proposed to stabilize the α- and β-cations via hyperconjugation (Figure 3A,B).[26] This is similarly invoked in the C−H amination of mannose-derived sulfamate esters (Figure 3B)[27] as well as [1,2]-boryl migration of oxiranyl-MIDA boronates (Figure 3C).[9a,28] These factors presumably contribute to the single regioisomer (**3e**). In contrast to **2e**, sulfamates **2f−h** lack the reinforcing aryl substitution, and a mixture of α- and β-regioisomers was obtained (Scheme 3, **3f−h**). Further efforts into understanding the factors affecting the regioselectivity are ongoing.

In summary, we have developed the first example of a chemoselective C−H amination of alkyl boronates that provides access to heterocyclic boronates. The use of the MIDA boronate functional group not only enables the synthesis of the necessary intermediates but also inhibits rhodium engagement of the C−B bond. In the case of aryl boryl sulfamates, a single regioisomer is isolated whereas alkyl

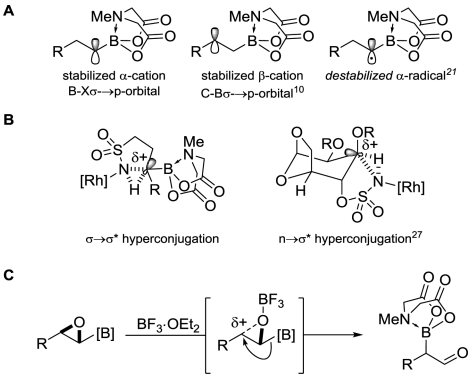


Figure 3. (A) α- and β-boryl cation stabilization and α-boryl radical destabilization. (B) Proposed stabilization of incipient α-cation by electron-rich sp^3-boronate and n → σ* hyperconjugation observed by Davis and co-workers that favors five-membered ring formation.[27] (C) Formation of β-carbocation results in [1,2]-boryl migration to quench electron deficiency.

sulfamate esters provide a mixture of five and six-membered ring products. This chemistry should provide access to other boron-containing functional group arrays that are difficult to synthesize via other methods.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.5b02861.

X-ray crystallographic data for **1c** (CIF)
X-ray crystallographic data for **3e** (CIF)
Experimental data; HRMS and ^{1}H, ^{11}B, and ^{13}C NMR spectra of all novel products (PDF)

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Notes

The authors declare no competing financial interest.

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