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Construction of Azacycles by Intramolecular Amination of Organoboronates and Organobis(boronates)

Peilin Xu, Mingkai Zhang, Bryan Ingoglia, Christophe Allais, Anne-Marie R. Dechert-Schmitt, Robert A. Singer, and James P. Morken*

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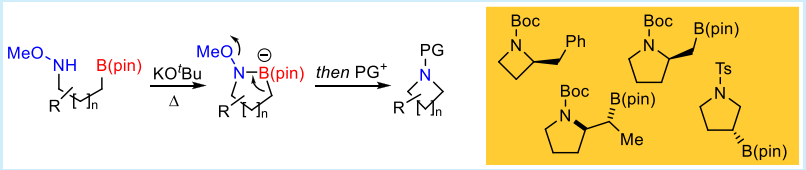
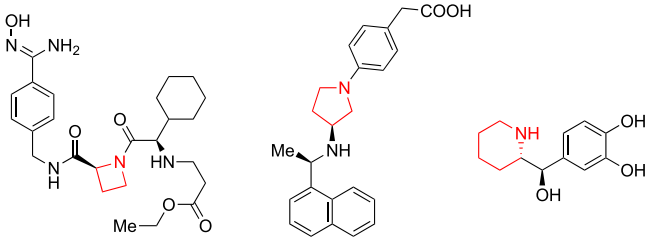


ABSTRACT: Intramolecular amination of organoboronates occurs with a 1,2-metalate shift of an aminoboron "ate" complex to form azetidines, pyrrolidines, and piperidines. Bis(boronates) undergo site-selective amination to form boronate-containing azacycles. Enantiomerically enriched azacycles are formed with high stereospecificity.

Saturated nitrogen-containing heterocycles, such as azetidines, pyrrolidines, and piperidines, are important structures in natural product alkaloids,[1] in pharmaceutical targets,[2] and as catalysts in organocatalytic synthesis[3] (Scheme 1). In this connection, C−N bond formation is one of the most common strategies to prepare such heterocycles, and within that framework a straightforward method employed is nucleophilic displacement of a leaving group by a nitrogen nucleophile.[4] However, with challenging ring closures such as those that involve the formation of strained rings or that require substitution at hindered electrophilic carbons, competitive β-elimination of the leaving group can pose a problem.[4a,b] As an alternative route to the construction of azacycles, and one that capitalizes on recent advances[5] in the construction of chiral enantiomerically enriched organoboronic esters, we undertook a study of intramolecular boronate amination.

Scheme 1. Pharmaceutical Targets Containing Saturated Azacycles



Stereospecific amination of organoboron compounds with electrophilic nitrogen-based reagents can be brought about by the formation of an aminoboron "-ate" complex, followed by a 1,2-metalate shift to establish the C−N bond (Scheme 2a). To affect such an amination, a range of reagents have been developed, including hydroxylamine-*O*-sulfonic acid,[6] organic azides,[7] methoxyamine,[8] and aminoazanium ions.[9] When the electrophilic amine is tethered to the organoboron motif, intramolecular amination can lead to azacyclic compounds. This approach was first established by Evans[10a] for the synthesis of substituted proline derivatives (Scheme 2b) and subsequently adopted by a number of groups for construction of pyrrolidine and piperidine ring systems.[10] Notably, Aggarwal and co-workers established that the intramolecular reaction could be applied to tertiary boronic esters (Scheme 2c) by employing a synthesis sequence that proceeds by way of an intermediate trifluoroborate salt.[7f] The examples described, however, remain largely limited to the reaction between alkyl azides and highly electrophilic trialkyl- or dihaloborane substrates, with the latter compounds often generated *in situ* through the use of caustic reagents. Processes that directly employ boronic esters and that can enable the synthesis of strained ring systems have not been well developed.

To accomplish stereospecific amination of a range of primary and secondary alkylboronic esters, without the use of highly Lewis acidic reagents, the use of methoxyamine pretreated with either *n*-BuLi or KO*t*-Bu is effective.[8] The scope of this amination has been found to include tertiary

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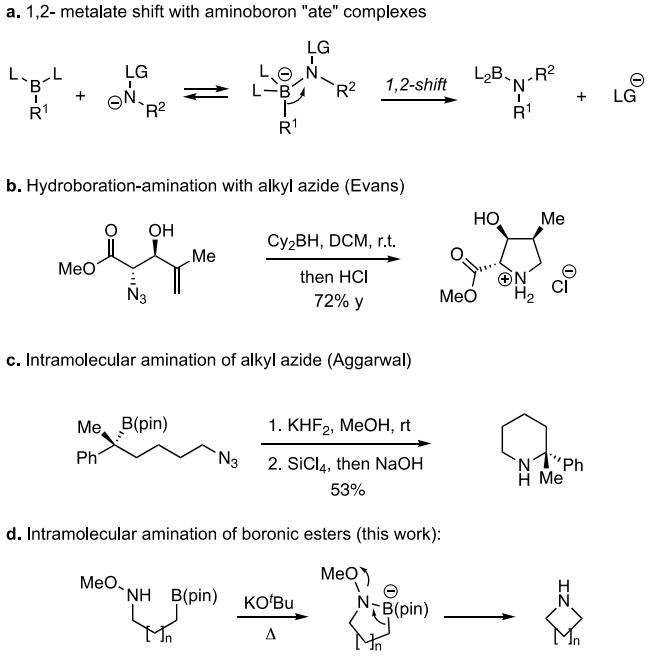
Scheme 2. Intramolecular Amination via a 1,2-Metalate Shift of the Aminoboron "-Ate" Complex

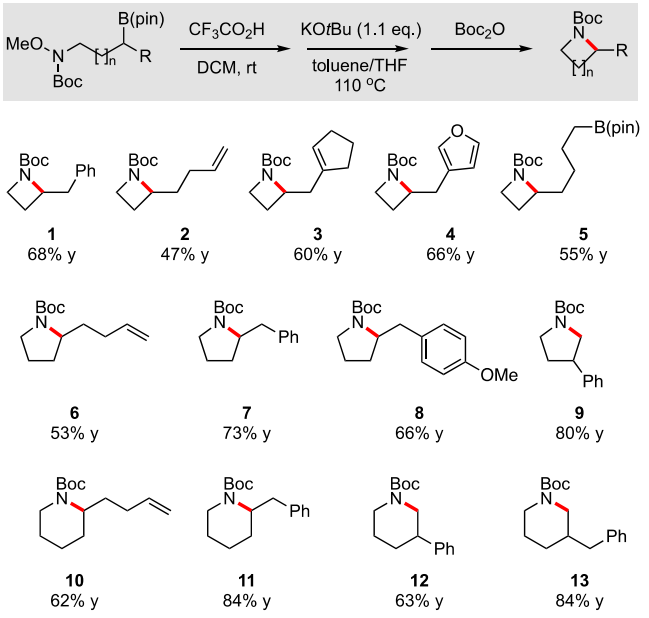


boronates and, in one case, has been employed to prepare a piperidine ring.[11] Within this framework, we set out to explore whether more challenging strained rings might be prepared by intramolecular amination and whether site selectivity and stereospecificity might be possible when multiple boronic esters are present in a substrate.

As shown in Scheme 3, initial experiments showed that a variety of substituted azacycles can be prepared with ease by intramolecular amination between an organoboronic ester and a tethered methoxyamine group. An appealing feature of this process is that the methoxyamine functional group is readily introduced by reaction of BocNH(OMe) and either alkyl halides (base promotion) or aliphatic alcohols (Mitsunobu reaction). Prior to amination, the Boc group is removed with CF_3CO_2H, the residue evaporated to dryness, and the intermediate then heated in THF/toluene in the presence of potassium *tert*-butoxide. As shown in Scheme 3, the transformation applies to the synthesis of substituted azetidines and can tolerate the presence of several useful malleable functional groups, including an alkene (**2**, **3**), a furan ring (**4**), and a boronic ester (**5**). The formation of pyrrolidines and piperidines is also easily accomplished from appropriate precursor boronic ester derivatives. As depicted in Scheme 3, a range of 2- or 3-substituted pyrrolidine motifs (**6**–**9**) can be prepared in an efficient and simple fashion from the corresponding δ-methoxyamino boronate derivatives, whereas the analogous 1,5-methoxyamino boronates deliver 2- or 3-substitued chiral piperidines (**10**–**13**).

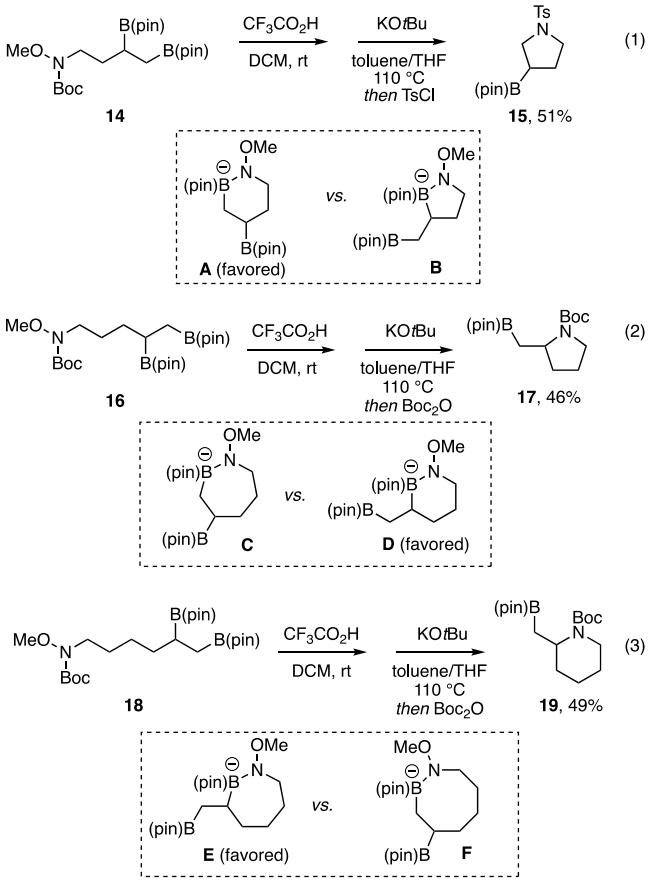
Because vicinal diboron compounds are readily prepared by diboration[12] of alkenes, we considered whether sequential diboration and site-selective amination might deliver boron-containing azacycles that could be useful for the preparation of diverse sets of heterocyclic building blocks (Scheme 4). The requisite substrates are readily prepared by diboration of olefins bearing a tethered Boc-protected methoxyamine group.[13] Subsequent deprotection with TFA does not perturb

Scheme 3. Synthesis of Azetidine, Pyrrolidine, and Piperidine Rings by Intramolecular Amination of Boronic Esters[a]



[a]Yields refer to isolated yields of purified material and are an average of two experiments.

Scheme 4. Chemoselectivity in Intramolecular Amination of Vicinal Bis(boronic) Esters



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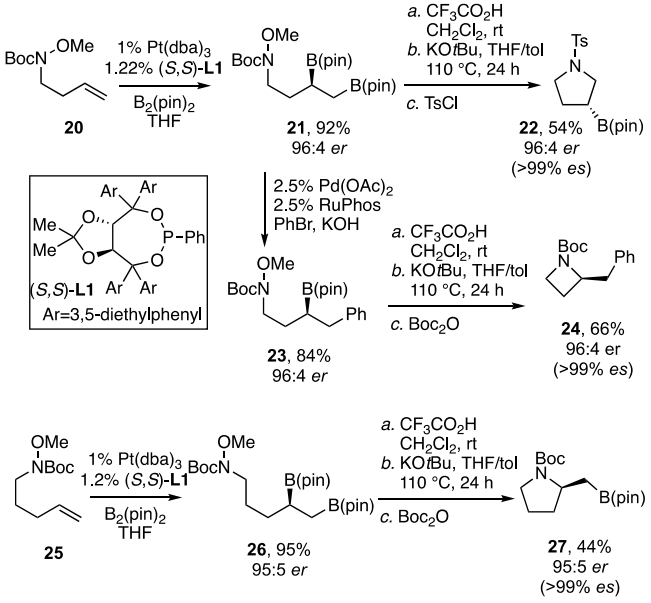
the vicinal bis(boronate) motif. As depicted in eq 1, given a choice between forming an azetidine or a pyrrolidine ring during the course of amination, the five-membered ring is preferred and provides 3-borylpyrrolidine **15**.[14] Because there are unlikely to be significant differences in strain between the five- and six-membered chelated structures **A** and **B** (inset, Scheme 4), it is plausible that the selectivity in eq 1 arises from the rate of 1,2-metalate shift, with the formation of the pyrrolidine occurring faster. A homologous substrate provides the opportunity to form either a pyrrolidine or piperidine derivative, and as shown in eq 2, the pyrrolidine is again favored. Presumably selectivity in this case arises from a more favorable six-membered chelate size (**D**) that furnishes the five-membered ring product. When the substrate is configured in a way that either the six- or seven-membered rings are prospective products, the reaction is site-selective and favors formation of the piperidine derivative (eq 3), likely a result of the favorable formation of the seven-membered chelate (**E**) over the eight-membered complex (**F**).

Enantiomerically enriched vicinal diboron compounds can be synthesized using platinum-catalyzed enantioselective diboration, and this strategy provides an opportunity to examine whether the amination can occur with stereospecificity even for strained ring systems.[15] As depicted in Scheme 5, diboration of **20** provides **21** with good yield and

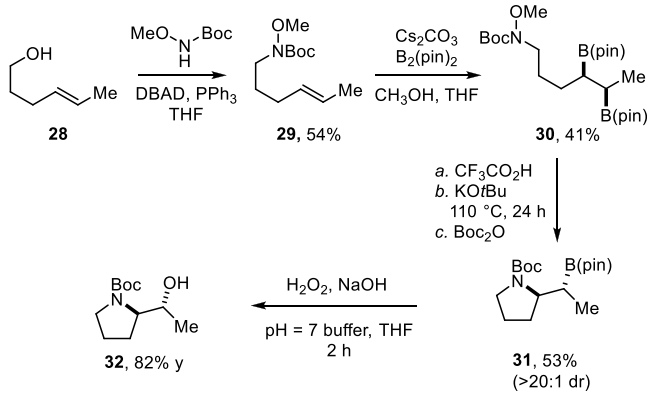
Scheme 5. Intramolecular Amination of Enantiomerically Enriched Boronic Esters



enantiomeric excess. Direct chemoselective amination to give **22** was found to occur with complete preservation of the enantiomeric purity of the substrate such that **22** is accessed with high selectivity. In addition, site-selective Suzuki−Miyaura coupling of **21** gives **23**, and amination of **23** furnishes the azetidine derivative **24** with complete enantiospecificity. Of note, compound **24**, in its Boc-free form, is a known bioactive compound with good affinity toward the TAAR1 receptor.[16] Lastly, enantioselective diboration of **25** furnishes **26**, and this vicinal bis(boronate) was also found to participate in stereospecific amination to provide boron-containing pyrrolidine **27** with good enantiomeric purity.

As described above, the intramolecular amination can be conducted with good chemoselectivity and enantiospecificity for a range of substrates. Given the importance of proline derivatives as catalysts, ligands, and building blocks for the synthesis of alkaloids, it was of interest to learn whether compounds bearing two contiguous stereocenters might be available by the diboration/amination reaction sequence. As depicted in Scheme 6, alcohol **28** was converted to protected

Scheme 6. Construction of a Pyrrolidine with an Exocyclic Stereogenic Center by Selective Amination



methoxyamine **29** by a Mitsunobu reaction. Subsequent Cs_2CO_3-catalyzed diboration furnished **30**, which was subjected to nitrogen deprotection, amination, and Boc protection, thereby furnishing **31** as a single stereoisomer. Subsequent oxidation provides **32**, a compound found in the construction of a KRas G12C inhibitor.[17]

In conclusion, we have developed a method to synthesize azacycles of ring sizes 4−6 via intramolecular amination reaction of methoxyamine-containing boronic esters. Boronate-containing azacycles can be formed with high regioselectivity from bis(boronates). In addition, the method can be utilized to deliver enantiomerically enriched azacyclic compounds with excellent enantiospecificity.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.1c00856.

Procedures, characterization, and spectral data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

James P. Morken − *Department of Chemistry, Merkert Chemistry Center, Boston College, Massachusetts 02467, United States;* orcid.org/0000-0002-9123-9791; Email: morken@bc.edu

Authors

Peilin Xu − *Department of Chemistry, Merkert Chemistry Center, Boston College, Massachusetts 02467, United States*

Mingkai Zhang − *Department of Chemistry, Merkert Chemistry Center, Boston College, Massachusetts 02467, United States*

Bryan Ingoglia − *Department of Chemistry, Merkert Chemistry Center, Boston College, Massachusetts 02467, United States*

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Christophe Allais − *Pfizer Worldwide Research and Development, Groton, Connecticut 06340, United States;* orcid.org/0000-0002-3443-9391
Anne-Marie R. Dechert-Schmitt − *Pfizer Worldwide Research and Development, Groton, Connecticut 06340, United States*
Robert A. Singer − *Pfizer Worldwide Research and Development, Groton, Connecticut 06340, United States;* orcid.org/0000-0001-9730-1261

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.1c00856

Notes

The authors declare the following competing financial interest(s): C.A., A.R.D., and R.A.S. are employees and stockholders of Pfizer Inc.
Several of the boron-containing compounds reported in this manuscript will be accessible from Enamine.

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