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Communication

Boronic Esters

Copper-Catalyzed Borylation of Cyclic Sulfamidates: Access to Enantiomerically Pure (β-and γ-Aminoalkyl)boronic Esters

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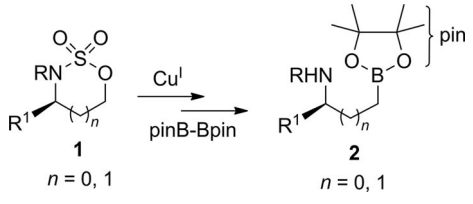
Abstract: Cyclic sulfamidates undergo borylation under copper-catalyzed conditions using B_2pin_2 to give enantiomerically (and diasteromerically) defined (aminoalkyl)boronic esters. External iodide is essential, but the intermediacy of simple alkyl iodides has been excluded; *N*-sulfated intermediates are key in the borylation sequence. Based on stereochemical studies and trapping experiments, the involvement of carbon-centered radicals under these copper-catalyzed conditions appears likely.

Introduction

Alkyl (i.e. sp^3) boronic esters, together with the corresponding boronic acids and trifluoroborates, represent a versatile class of cross-coupling agents that have extended significantly the utility and scope of Suzuki–Miyaura-type cross-coupling reactions to encompass sp^3–sp^2 and sp^3–sp^3 processes.[1–3] Alkyl halides (as well as pseudohalides such as tosylates) provide access to the requisite sp^3-based boron reagents by Pd- or Ni-,[4a–4c] Zn-,[4d] Fe-[4e,4f] or (and perhaps of most versatility) the Cu-catalyzed borylation processes[5] described first by Marder and Lin.[5d,5f]

Our interest in this area has centered on the use of stable and readily available 1,2- and 1,3-cyclic sulfamidates **1**, which have already found extensive utility as electrophiles to construct C–C, C–N and C–O bonds within heterocyclic synthesis.[6] However, their utility in either direct or indirect sp^3-based cross-coupling reactions is essentially unexplored.[7]

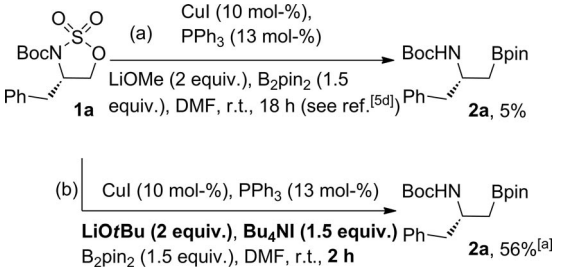
Here we report on the application of cyclic sulfamidates **1** as substrates for Cu-catalyzed borylation to provide access to a range of stereochemically defined and enantiomerically pure (aminoalkyl)boronic esters **2**[8] (Scheme 1). In mechanistic terms, however, cyclic sulfamidates, which can be viewed as alkyl pseudohalides, are differentiated from more conventional substrates, such as alkyl halides or tosylates, under Cu-mediated borylation conditions.



Scheme 1.

Results and Discussion

We evaluated initially a series of metals (Pd, Ni, Zn, Fe) to promote borylation, but did not achieve good turnover and yields. Copper, which is also attractive for reasons of scalability, cost and low toxicity, however, proved effective with cyclic sulfamidates.[9] The (*S*)-phenylalanine-derived substrate **1a**[6b] was screened against Marder's efficient room-temperature Cu-catalyzed conditions for borylation of alkyl halides (Scheme 2).[5d] The target boronate ester **2a** was isolated by using these conditions but in poor yield (5 %) and only after an extended reaction time. Following an extensive evaluation of reaction conditions, we identified two necessary modifications: the optimal base (LiO*t*Bu) and – more critically – the presence of an external iodide source (e.g. Bu_4NI). Use of these modified conditions provided boronic ester **2a**[10] in 56 % yield at room temperature after a reaction time of 2 h.



Scheme 2. Cu-catalyzed borylation of **1a** under (a) Marder's conditions for alkyl halides and (b) with key modifications including an external iodide source to provide boronic ester **2a**. [a] Enantiomeric purity of **2a** was determined by using (±)-**2a** from (±)-**1a** as a standard, and no erosion of stereochemical integrity was detected by chiral HPLC.

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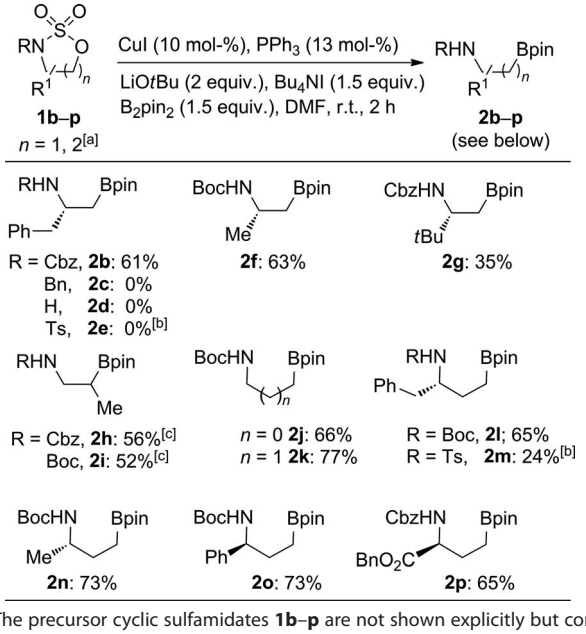
Replacing CuI with either Pd_2dba_3 or NiI_2 gave no trace of **2a**, and the combination of CuI and PPh_3 was crucial for conversion; **2a** was not observed in the absence of either of these reagents. Addition of Bu_4NI, which had been applied successfully[5d] (but also without PPh_3) to the borylation of alkyl tosylates, improved significantly the yield of **2a**, and the presence of this external iodide source was critical.[11]

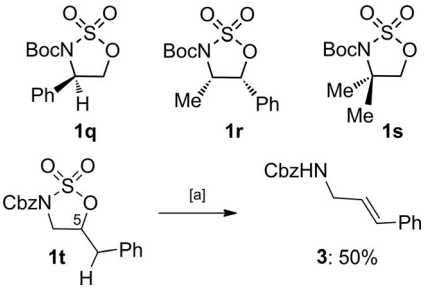
Using the iodide-mediated conditions shown in Scheme 2, we have assessed the scope of this reaction with respect to 1,2- and 1,3-cyclic sulfamidates. A range of substrates across **1b**–**p** function to provide (β- and γ-aminoalkyl)boronic esters **2b**–**p** (Scheme 2, Table 1). These include substrates with a substituent at the reacting center (and disubstituted variants) as an entry to secondary boronic esters (see also Scheme 4).

Table 1. Synthetic scope of cyclic sulfamidates for (β- and γ-aminoalkyl)-boronic esters **2b**–**p**.



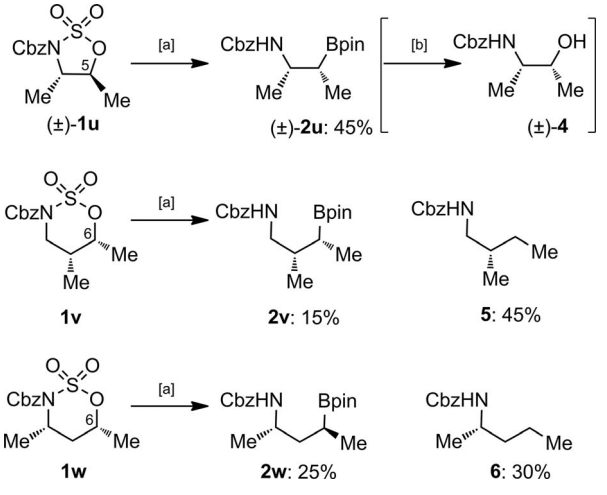
[a] The precursor cyclic sulfamidates **1b**–**p** are not shown explicitly but correspond directly to the products **2b**–**p** seen here. [b] The feasibility of a sulfonamide-based substrate depends on ring size (compare **2e** and **2m**). [c] Product **2h** was racemic (see text), and **2i** was assumed to be racemic.

A number of constraints and limitations were also apparent. Electron-withdrawing carbonyl-based *N*-protecting groups (Boc, Cbz) were highly preferred and essential within 1,2-cyclic sulfamidates for effective conversion. In these cases, the corresponding *N*-benzyl, N-H and *N*-sulfonyl variants failed to give the desired boronic esters **2c**–**e**. Conventionally, 1,2-cyclic sulfamidates are more reactive (e.g., towards ring-opening with nucleophiles[6]) than the 1,3-homologues; therefore, it was interesting that here the 1,3-series **1** (n = 1) proved in general to be somewhat better substrates for Cu-catalyzed borylation (compare yields of **2a** and **2l**; **2f** and **2n**). Certain benzylic substrates, such as **1q** and **1r**, underwent rapid decomposition (likely oxidation or elimination), but the location of the benzyl moiety is important (compare **1o** to give **2o**; Table 1). Sterically demanding substrates, such as the 4,4-dimethyl variant **1s**, failed to react, and subjecting the 5-benzyl sulfamidate **1t** to the optimized borylation conditions led only to allylic amine **3**[12] by competing elimination (Scheme 3).



Scheme 3. Substrates that failed to undergo Cu-catalyzed borylation. [a] General Cu-catalyzed borylation conditions as in Table 1.

Disubstituted cyclic sulfamidates **1u**–**w** provide stereochemically defined products but, to date, are less efficient in terms of conversion and yield (Scheme 4). In these cases, the major byproducts observed, **5** and **6**, resulted from C–O reduction.[13] Nevertheless, these substrates also reflect on the nature of the mechanism of Cu-catalyzed borylation, which is discussed below.



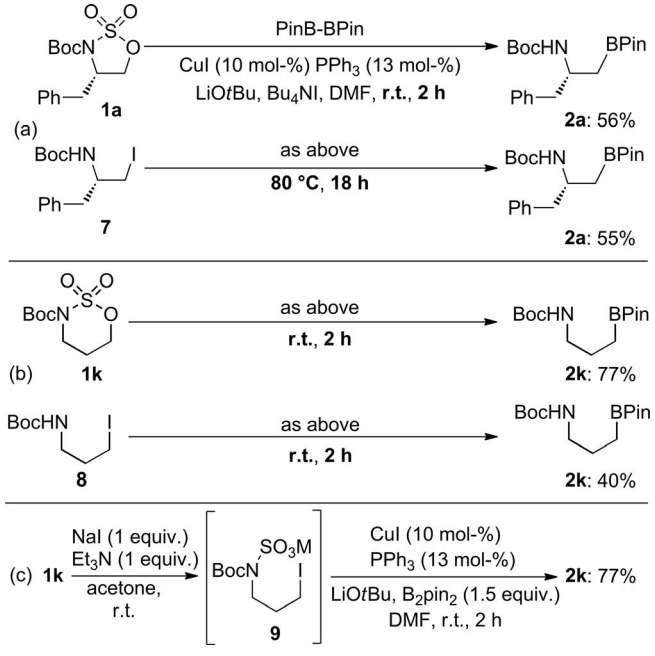
Scheme 4. Stereochemical outcomes for disubstituted 1,2- and 1,3-cyclic sulfamidates. [a] General Cu-catalyzed borylation conditions as in Table 1. [b] Stereochemistry of **2u**–**w** was determined by oxidation (NaOH, H_2O, H_2O_2, 0 °C) to give the corresponding secondary alcohol as illustrated by the conversion of **2u** to **4**. Analogous transformations (leading to either the same amino alcohol used to prepare the starting cyclic sulfamidate or its diastereomer) secured the stereochemistry of boronic esters **2v** and **2w** (see Supporting Information).

In the cases of the product boronic esters **2u**–**w**, the stereochemistry of the borylation process was determined by oxidation of the boronic esters to the corresponding (and known) secondary alcohols. This process proceeds with retention of stereochemistry at the reacting center and is illustrated here for **2u**.

Given our initial assumptions as to the alkyl pseudohalide character of cyclic sulfamidates but their failure, for example, to undergo borylation under otherwise well-established condi-

tions, we have carried out a series of experiments to gain some insight into the mechanism of Cu-catalyzed borylation of **2**. The role for an external iodide source was explored, prompting the obvious explanation that facile nucleophilic opening of the cyclic sulfamidate provides directly a simple alkyl iodide that reacts as expected on the basis of Marder's earlier work.[5d]

Two substrates were investigated by directly comparing the reactivity of the cyclic sulfamidate and the equivalent alkyl iodide (Scheme 5). As discussed above, 1,2-cyclic sulfamidate **1a** underwent Cu-mediated borylation to give **2a** in 56 % yield at room temperature after 2 h [Scheme 5 (a)]. The corresponding primary iodide **7** failed to react appreciably at room temperature; however, boronic ester **2a** was obtained in essentially the same yield following heating at 80 °C for 18 h.

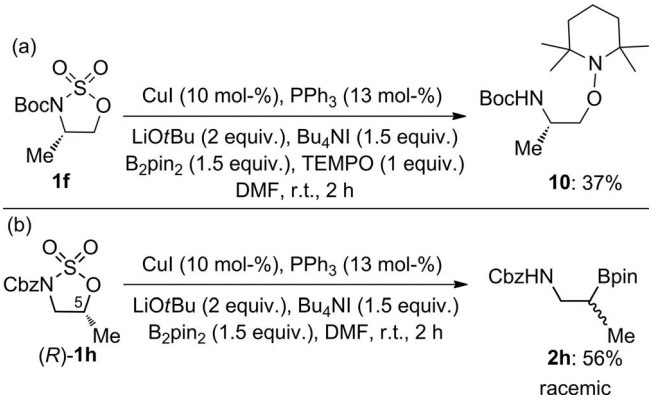


Scheme 5. Cyclic sulfamidate vs. alkyl iodide; comparison of relative reaction rates and yields. (a) Differences in time/reaction temperature to achieve the same conversion. (b) Differential yields at room temperature after a fixed time (2 h). (c) Generation, isolation of *N*-sulfate **9** and conversion to boronic ester **2k**.

The 1,3-variant **1k** provided an alternative perspective of this differential reactivity. While **1k** gave boronic ester **2k** in 77 % yield at room temperature after 2 h, the corresponding alkyl iodide **8** led to 40 % of **2k** under the same conditions but with added iodide [Scheme 5 (b)]. These results both suggest that a simple alkyl iodide (**7** or **8**) is not an intermediate in the conversion of cyclic sulfamidates to the corresponding boronic esters.

Further insight into this process was gleaned from closer study of the initial reaction of the cyclic sulfamidate with iodide. Exposure of **1k** to NaI (in the presence of Et_3N, which was essential to retain the *N*-sulfate unit) in anhydrous acetone gave the hydrolytically sensitive *N*-sulfate **9** as a colorless solid [Scheme 5 (c)]. Subsequent exposure of isolated **9**[14] to the standard Cu-mediated borylation procedure gave **2k** in 77 % yield, which parallels the observation in Scheme 5 (b). From this we conclude that the *N*-sulfated iodide **9** is the key intermediate and, additionally, that the presence of the *N*-sulfate moiety favorably influences the subsequent Cu-catalyzed borylation, based on the comparison to a simple primary alkyl iodide.

The mechanism of Cu-catalyzed borylation of aryl and alkyl halides has been probed,[15] and there is some but not definitive evidence for the intermediacy of alkyl radicals. Our studies support the likely involvement of radical species, at least with respect to the carbon center. Using 1 equiv. of TEMPO as a radical trap with **1f** as the cyclic sulfamidate substrate, we isolated adduct **10** in 37 % yield and observed no borylation (i.e. ester **2f**) product [Scheme 6 (a)]. Cyclohexa-1,4-diene also completely suppressed boronic ester formation from **1f**, although we were unable to isolate an adduct in this case.[13]



Scheme 6. (a) Use of TEMPO as a C-radical trap and (b) loss of enantiomeric integrity for a 5-methyl-1,2-cyclic sulfamidate on borylation.

Further support for a radical mechanism comes from use of enantiomerically pure 5-substituted 1,2-cyclic sulfamidate **1h** [Scheme 6 (b)]. Copper-catalyzed borylation of (*R*)-**1h** under standard conditions gave a 56 % isolated yield of racemic secondary boronic ester **2g**, a result that was confirmed by using racemic **1h** as a control to validate chiral HPLC analysis of the products.[14] It is also pertinent to reflect on the stereochemical results shown in Scheme 4 for disubstituted 1,2- and 1,3-cyclic sulfamidates. Borylation of *trans*-**1u** gave boronic ester **2u** in 45 % yield, the stereochemistry of which was established by stereospecific oxidation to give the known alcohol **4**. In this case, although stereochemically clean, the original configuration at the C-5 stereocenter was lost. Similarly, the *cis*-configured 1,3-cyclic sulfamidates **1v** and **1w** gave retention and inversion, respectively, at the borylating center (C-6), where the outcome at the intermediate carbon radical is subject to a high level of internal diasteromeric control. In these latter cases, although yields were moderate (and competitive reduction was seen), no trace of the diastereomeric boronic esters was detected.

Conclusions

We have developed a variant of copper-catalyzed borylation that is suited to the exploitation of readily available cyclic sulfamidates and extends the scope of the copper-based proce-

dures to synthesize stereochemically defined alkylboronic esters. Cyclic sulfamidates are readily available and offer access to enantiomerically (or diastereomerically) pure (aminoalkyl)-boronic esters suitable for further exploitation in cross-coupling processes. While our initial premise was that cyclic sulfamidates would perform as pseudohalides (cf., tosylates) and undergo borylation under well-established conditions, that proved not to be the case. There are substrate-specific features, such as the intermediacy of an *N*-sulfated iodide that clearly imbue cyclic sulfamidates with major advantages over the corresponding (i.e., simple amino-based) alkyl halides. Another important aspect is the key requirement of an *N*-acylated cyclic sulfamidate; *N*-alkyl/benzyl or *N*-sulfonyl analogues are not efficient substrates in our hands. Further studies are required to probe the role of the *N*-acyl moiety, but this may, like the *N*-sulfate, serve to activate the reacting C–O bond and/or provide a ligand for any intermediate copper species. The involvement of radical intermediates in this chemistry can lead to loss of stereochemistry at the reacting C–O center, but the outcome is substrate-dependent and can provide good overall levels of stereocontrol.

CCDC 1433121 (for **2a**) 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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Keywords: Cyclic sulfamidates · Boron · Copper · Radical reactions · (Aminoalkyl)boronic esters

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[8] Achiral (aminoalkyl)boronic esters and related derivatives have been reported by metal-catalyzed borylation by Fu,[4b] Marder,[4d,5d] Chung[5b] and Cook;[4f] for other synthetic approaches, including examples of amino acid derived variants, see: a) D. N. Butler, A. H. Soloway, *J. Am. Chem. Soc.* **1964**, *86*, 2961; b) D. N. Butler, A. H. Soloway, *J. Am. Chem. Soc.* **1966**, *88*, 484–487; c) A. Dicko, M. Montury, M. Baboulene, *Synth. Commun.* **1988**, *18*, 459–463; d) I. Georgiou, A. Whiting, *Eur. J. Org. Chem.* **2012**, 4110–4113; e) J. E. Harvey, M. N. Kenworthy, R. J. K. Taylor, *Tetrahedron Lett.* **2004**, *45*, 2467–2471; f) C. P. Decicco, D. J. Nelson, Y. Luo, L. Shen, K. Y. Horiuchi, K. M. Amsler, L. A. Foster, S. M. Spitz, J. J. Merrill, C. F. Sizemore, K. C. Rogers, R. A. Copeland, M. R. Harpel, *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2561–2564; g) V. Denniel, P. Bauchat, D. Danion, R. Danion-Bougot, *Tetrahedron Lett.* **1996**, *37*, 5111–5114.

[9] By using **1a**, Pd-catalyzed borylation was extensively screened. Despite evaluating a wide range of catalyst/ligand combinations and reaction conditions, we were able to obtain **2a** (from **1a**) but in (at best) 28 % yield. This result was achieved by using Biscoe's conditions:[4a] Pd_2dba_3 (0.5 mol-%), $tBu_2MePHBF_4$ (3 mol-%), $K_3PO_4{\cdot}H_2O$ (2 equiv.), B_2pin_2 (1.2 equiv.), H_2O (15 equiv.), *t*BuOH, 60 °C, 18 h.

[10] X-ray crystallography also served to confirm the structure of **2a**; see Supporting Information.

[11] Cu-catalyzed borylation of **1a** also works with Bu_4NBr, but the yield of **2a** dropped to 29 %. All optimization details (Cu, halide sources, solvents etc.) are available in the Supporting Information.

[12] Cyclic sulfamidate **1t** (and other *N*-substituted analogues) is sensitive to base-mediated elimination and are therefore useful to employ[6b] as test substrates to help to define the limits of a methodology under study.

[13] Preliminary efforts to suppress the formation of reduction products such as **5** and **6** centered on the choice of solvent, and DMF proved to be the most effective; see Supporting Information.

[14] Molecular ion peak for *N*-sulfate intermediate **9** was observed by negative-ion ESI-MS. A change in the C=O stretching frequency of the Boc group was also seen by IR spectroscopy. Bu_4NI did not affect the conversion of iodide **9** into boronic ester **2k**.

[15] The mechanism of Cu-catalyzed borylation has been studied by Marder,[5d,5f] Chung[5b] and Ito,[5e] and various options have been recognised. Chung observed ring opening of cyclopropylmethyl bromide [to give the corresponding (3-butenyl)boronate]. Marder has reported that borylation of 6-bromohex-1-ene leads to cyclopentylmethyl boronate (via a cyclopentylmethyl radical?), but attempts to scavenge a radical

intermediate by using cyclohexa-1,4-diene failed. We have been able to suppress borylation using two radical traps (TEMPO and cyclohexa-1,4-diene), and the consequences adjacent to the reacting C–O bond – **2u** and **2w** both show a change in the stereochemistry at the reacting center; Schemes 4 and 6 (b) – support the participation of a carbon-centered radical under these Cu-catalyzed conditions. Under Pd-mediated borylation conditions, (*R*)-**1h** gave a poor (18 %) yield of **2h** but as a single enantiomer by HPLC, although the absolute configuration of this product has not yet been determined.

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Copper-catalyzed borylation of 1,2- and 1,3-cyclic sulfamidates provides stereochemically defined (β- and γ-aminoalkyl)boronate esters; iodide is essential but borylation is accelerated by the presence of the *N*-sulfate moiety.

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