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Synthesis of Boronic Ester γ-Lactam Building Blocks

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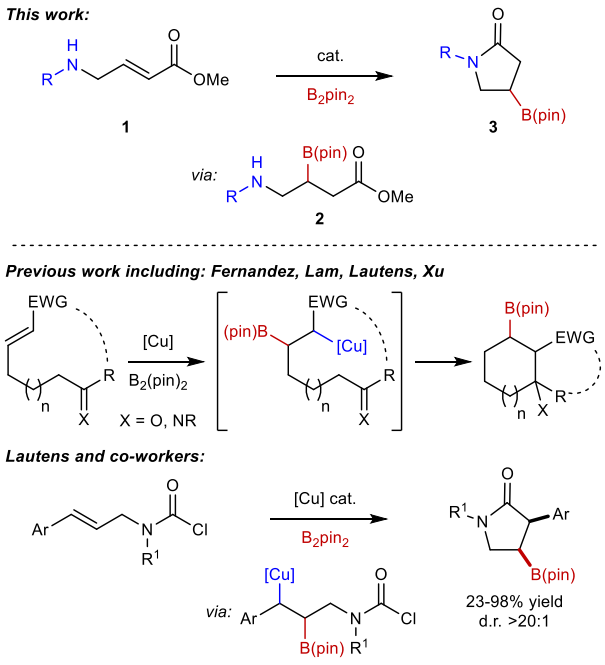
Abstract. Saturated heterocycles are found widely in biologically active compounds such as medicinal drugs and agrochemicals. However, boronic acid-derived building blocks for these structures have limited availability, particularly in comparison to heteroaromatic boronic acids. We report the preparation of boronic ester γ-lactams through a Cu-catalysed conjugate borylation-cyclisation protocol. Using a chiral catalyst, this can be performed in high enantioselectivity. Exploration of the further transformations of these reagents suggest that the boronic esters have much potential as chemical building blocks.

Keywords: boron; lactams; copper; building blocks; cross-coupling.

Boronic acids are valuable chemical building blocks, which are used in a broad range of disciplines from medicinal chemistry to materials science.[1] Heteroaromatic boronic acids, and their derivatives, are particularly useful for the preparation of biologically active molecules through reactions such as the Suzuki-Miyaura cross-coupling[2] and the Chan-lam reaction.[3] This is further enabled by the wide commercial availability and ease of preparation of a broad range of hetereoaromatic boronic acids and derivatives. Conversely, the corresponding boronic acid-containing saturated heterocycles have limited availability, despite the prevalence of such heterocycles in pharmaceutical drugs.[4] To illustrate this, at the time of publication Merck Sigma-Aldrich sold only 4 pyrrolidine- or piperidine-based boronic acids and derivatives.[5] There are a growing number of transformations of alkylboron reagents.[6] However, in order for such methods to be taken up widely by both academia and industry, access to a broader range of alkylboron building blocks is required.

As part of an ongoing research programme into the chemistry of alkylboronic esters,[7] we envisaged that beta-boronic ester γ-lactams could be prepared through conjugate borylation[8] of an *E*-amino enoate (scheme 1). Borylation would break the unsaturation of the enoate, allowing the pendent amine to form the lactam. Previous conjugate borylation-cyclisation strategies have instead involved C-C bond formation through reaction of an *in situ* formed enolate with a pendent electrophile.[9] This work complements recent reports from Lautens and co-workers, who have developed a borylation-acylation strategy of styrene-containing carbamoyl chlorides to form lactams.[10]



Scheme 1. Examples of borylation-cyclisation strategies to form saturated carbo- and heterocyclic boronic esters.

We started this investigation by subjecting enoate **1a** to a B_2Pin_2 in the presence of CuI as a catalyst (scheme 2). It was found that borylation proceeded smoothly to give boronic ester **2a** in good yield. Interestingly, the reaction was complete within 1 h, whereas the borylation of ethyl cinammate under the same reaction conditions requires >12 h reaction time. Boronic ester **2a** did not lactamize spontaneously,

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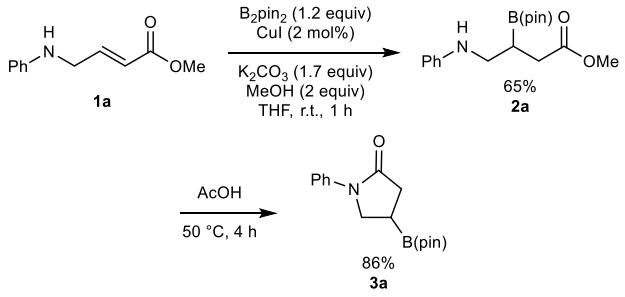
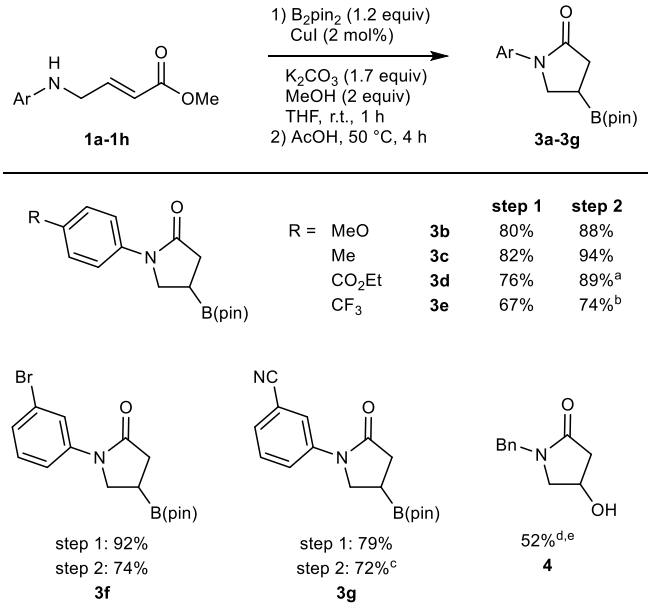
presumably due to the relatively low nucleophilicity of the aniline nitrogen. Attempts to induce cylisation under mildly basic conditions were successful, but was accompanied by a small amount of a degradation product from protodeboronation of the boronic ester. Instead, treatment of boronic ester **2a** with acetic acid gave the corresponding lactam **3a**, without need for further purification. While the process can be telescoped, purification after conjugate borylation was found to be more successful.



Scheme 2. Borylation and cyclisation of enoate **1a**.

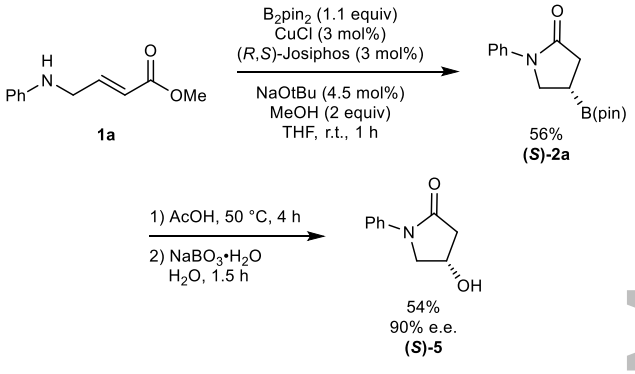
We next subjected our protocol to the formation of a range of boronic ester-containing lactams (scheme 3). The method is tolerant to functional groups including esters, nitriles and aryl bromides. Lactamisation of anilines substituted with electron withdrawing groups required longer reaction times (**3d**, **3e**, **3g**). Both steps of the protocol could be performed on multigram scale.[11]



Scheme 3. Scope of boronic ester lactams. Yields are of isolated material unless otherwise state. a) 24 h reaction time for step 2. b) 9 h reaction time for step 2. c) 5 h reaction time for step 2. d) isolated as a 1:1 mixture with pinacol. e) oxidation of the crude material using H_2O_2/NaOH was carried out. See the supporting information for full details.

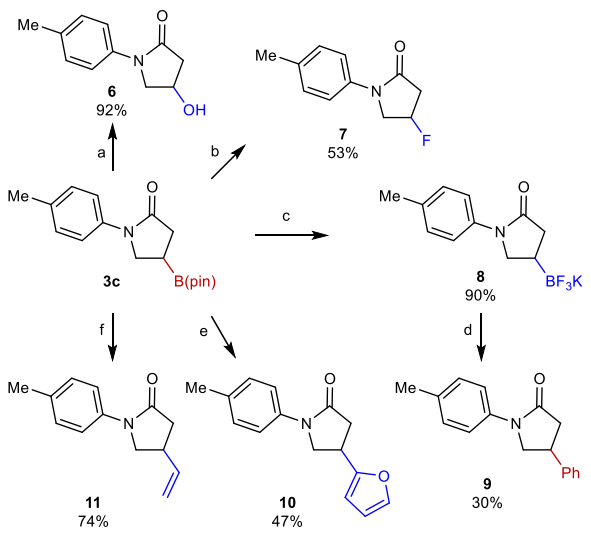
When *N*-benzyl enoate **1h** was subjected to conjugate borylation, the linear boronic ester underwent cyclisation *in situ*. This is presumably due to the higher nucleophilicity of alkyl amines versus anilines. While the boronic ester was formed in good yield, attempts at purification led to significant decomposition of the product. Instead, to give an indication of the efficiency of the reaction, oxidation of the boronic ester was performed to give alcohol **4**.

Access to enantiomerically enriched boronic ester **(*S*)-2a** was achieved using a catalyst derived from CuCl and (*R*,*S*)-Josiphos as a ligand[12] to give **(*S*)-2a** in 56% yield. Cyclisation followed by oxidation of the C-B bond gave alcohol **(*S*)-5** in 90% e.e.. The absolute configuration of **(*S*)-5** was confirmed through X-ray crystallography.[11,13]



Scheme 4. Enantioselective borylation-cyclisation and oxidation. e.e. determined by HPLC analysis of **(*S*)-5**.

To demonstrate the utility of boronic ester lactams, we explored their further reactivity. Oxidation of the boronic ester to alcohol **6**, using $NaBO_3 \cdot H_2O$, and fluoride **7**, using $AgNO_3$ and Selectfluor,[14] proceeded smoothly. Zweifel olefination and Aggarwal arylation[15] were both successful, despite the presence of enolizable protons from the lactam. Suzuki-Miyaura cross coupling could be carried out using the corresponding trifluoroborate salt **8**, albeit in moderate yield.[16]



Scheme 5. Transformations of boronic ester lactams. a) $NaBO_3 \cdot H_2O$, THF/H_2O. b) $AgNO_3$ Selectfluor, TFA, CH_2Cl_2/H_2O, 60 °C. c) KHF_2, MeOH. d) PhBr, cataCXium A Pd G3 (5 mol%), Cs_2CO_3, $PhMe/H_2O$, 110 °C. e) i) furan, nBuLi, THF, −78 °C ii) **3c**, iii) NBS, THF, −78 °C-RT. f) i) vinyl MgBr, THF, −78 °C, ii) I_2, MeOH, −78 °C, iii) NaOMe, MeOH, −78 °C-RT.

In summary, we have developed a protocol for the preparation of γ-lactams containing an alkylboronic ester handle. These boronic esters have much potential as heterocyclic chemical building blocks, demonstrated by a range of further transformations of the boronic ester moeity. Further methods to produce boronic ester heterocycles are underdevelopment and will be reported in due course.

Experimental Section

General procedure for the preparation of γ-lactam boronic esters (**3**):

An oven dried Schlenk flask was charged with B_2pin_2 (0.305 g, 1.20 mmol), CuI (4.0 mg, 0.020 mmol), K_2CO_3 (0.235 g, 1.70 mmol) and backfilled with Ar. Anhydrous THF (2 mL) was added, and the mixture was stirred for 10 mins. A solution of the enoate **1** (1.00 mmol) in anhydrous THF (1.3 ml) and methanol (0.08 ml, 2 mmol) was added, and the mixture stirred for 1 h. The mixture was passed through a plug of celite, and the solution was concentrated *in vacuo*. The crude material was purified by either chromatography or recrystallisation to give boronic ester **2**.

Boronic ester **2** (0.5 mmol) was stirred in AcOH (1 ml, 0.5 M) at 50 °C for 4 h. The mixture was quenched with saturated aqueous Na_2CO_3 (10.0 ml), and extracted with CH_2Cl_2 (3 × 15.0 ml). The combined organic phases were dried ($MgSO_4$), filtered, and concentrated *in vacuo* to give lactam **3**.

Acknowledgements

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[13] CCDC 2041142 (**(*S*)-5**) 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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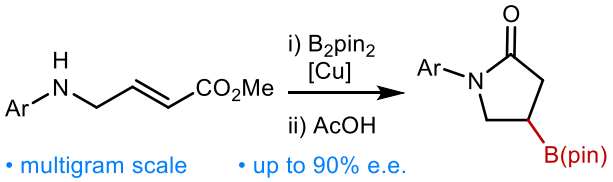

• multigram scale • up to 90% e.e.
• potential as chemical building blocks