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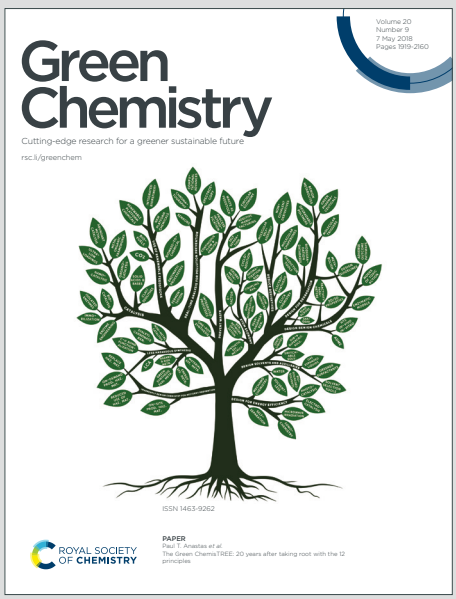

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Concise synthesis of *α*-amino cyclic boronates *via* multicomponent coupling of salicylaldehydes, amines, and $B_2(OH)_4$

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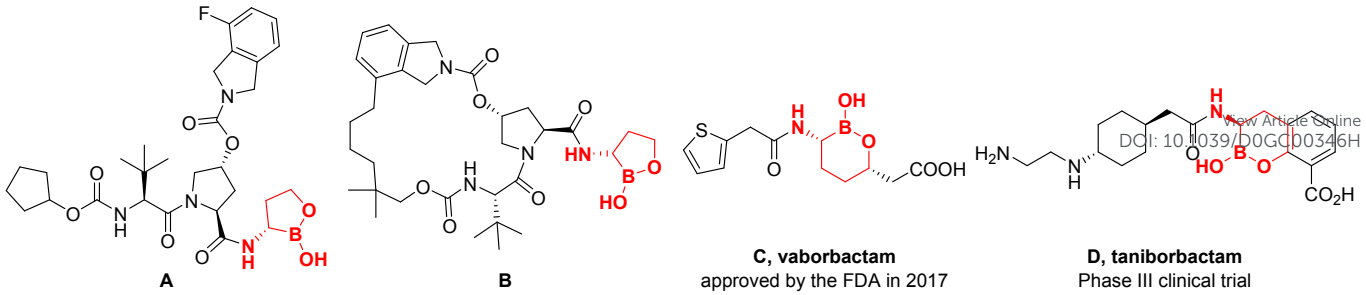
KEYWORDS: aminoboronic acids · benzoxaboroles · borylation · catalyst-free · cyclic boronic acids

Abstract: We report here a concise synthesis of *α*-amino cyclic boronates *via* multicomponent coupling of readily available salicylaldehydes, amines, and $B_2(OH)_4$. The process can be carried out at room temperature in ethanol, does not require catalysts or additives, and is easy to scale up. Aminals and ligated boroxines are intermediates in this reaction.

Organoboron compounds have numerous applications in organic synthesis, pharmaceuticals and functional materials.[1] In particular, *α*-aminoboronic acids and their derivatives are important due to their roles as bio-active agents, functional materials, and synthetic building blocks.[2] For example, *α*-amino cyclic boronate **A**, and its macrocyclic derivative **B**, are HCV NS3 serine protease inhibitors (IC_{50} 23 nM and 43 nM, respectively) (Scheme 1).[3] Vaborbactam, approved by the FDA in 2017, is a *β*-lactamase inhibitor based on a cyclic boronic acid pharmacophore. It has been used in trials investigating the treatment of bacterial infections in subjects with varying degrees of renal insufficiency (Scheme 1, **C**).[4] Taniborbactam is a new-generation cyclic boronate *β*-lactamase inhibitor, which has a unique broad-spectrum activity, covering both serine-*β*-lactamases and metallo-*β*-lactamases (Scheme 1, **D**).[5]

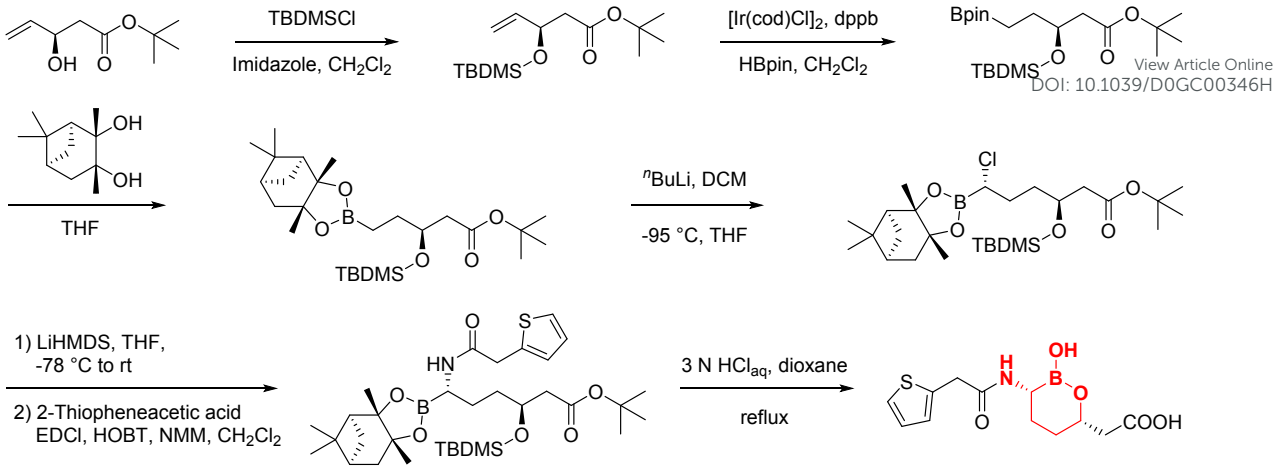


Scheme 1 Examples of enzyme inhibitors possessing an *α*-amino cyclic boronate motif.

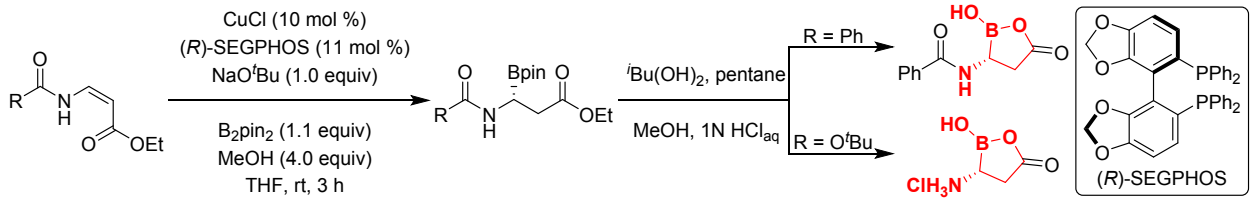
The therapeutic potential of *α*-amino cyclic boronates provides a driving force to develop and refine efficient and green methods for their synthesis. However, compared with their non-cyclic derivatives,[6] relatively few methods are available for the preparation of *α*-amino cyclic boronates. Traditional synthetic methods are based on multi-step reactions, including Ir-catalysed borylation, Matteson's boronic ester homologation, nucleophilic amination, cyclization, *etc.* (Scheme 2a).[4a,7] In 2017, Parra, Tortosa and coworkers synthesized a series of chiral *α*-aminoboronic esters by a Cu-catalysed asymmetric hydroboration of *β*-amidoacrylates. With these borylated products in hand, hemiboronates were prepared by hydrolysis of the pinacol boronic ester, and an *N*-Boc protected derivative was transformed into a primary *α*-aminoboronate (Scheme 2b).[8] These useful methods require harsh conditions, multi-step procedures, and/or metal catalysts. Additionally, the starting materials usually require several steps to prepare. Thus, development of efficient and versatile chemical transformations for synthesizing *α*-amino cyclic boronates from readily available starting materials is highly desirable.

Aldehydes and amines have been widely utilised in multicomponent Mannich, Strecker, and Petasis reactions, *etc.*, and are ideal starting materials as they are abundant, inexpensive and readily available from commercial suppliers. Bypassing the isolation of imine or iminium intermediates increases the product scope, reduces the number of steps, and is thus more economical and sustainable.

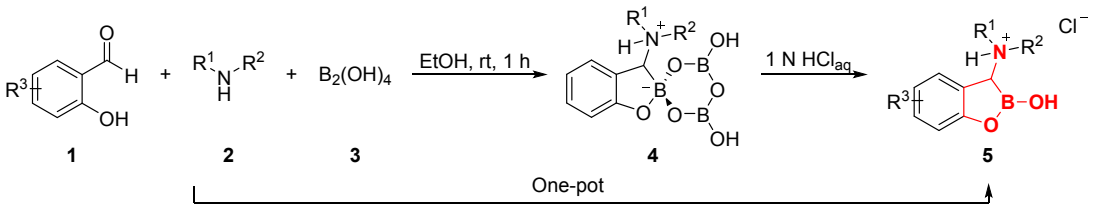
a) Reported synthetic route to Vaborbactam.[4a,7]



b) Parra and Tortosa's protocol to synthesize *α*-amino cyclic boronates.[8]



c) Catalyst- and additive-free synthesis of *α*-amino cyclic boronates *via* multicomponent coupling (this work).

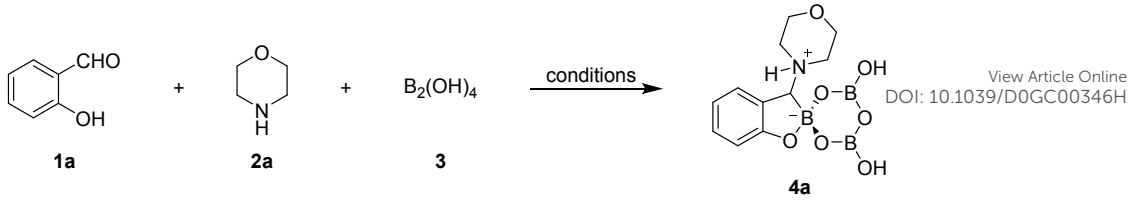


Scheme 2 Previously reported methods for the synthesis *α*-amino cyclic boronates, and our method.

We report here the synthesis of diverse *α*-amino cyclic boronates *via* the multicomponent coupling of commercially available salicylaldehydes, amines, and tetrahydroxydiboron [$B_2(OH)_4$]. The process is simple, can be run in a green solvent, and does not require catalysts or additives (Scheme 2c).

Our initial studies showed that a novel ligated boroxine **4a** was formed in 24 h, when salicylaldehyde **1a**, morpholine **2a** and $B_2(OH)_4$ were mixed in toluene at room temperature (Table 1, Entry 1). Optimisation of the reaction showed that polar solvents were better than non-polar ones, giving the product in 94% isolated yield, when CH_3CN was used (Entries 2-7). Compound **4a** was formed in 93% yield in only 12 h (Entry 8) and, due to its low solubility in CH_3CN, the product can be easily separated *via* filtration.

Table 1 The development of optimized conditions for ligated boroxine formation[a]



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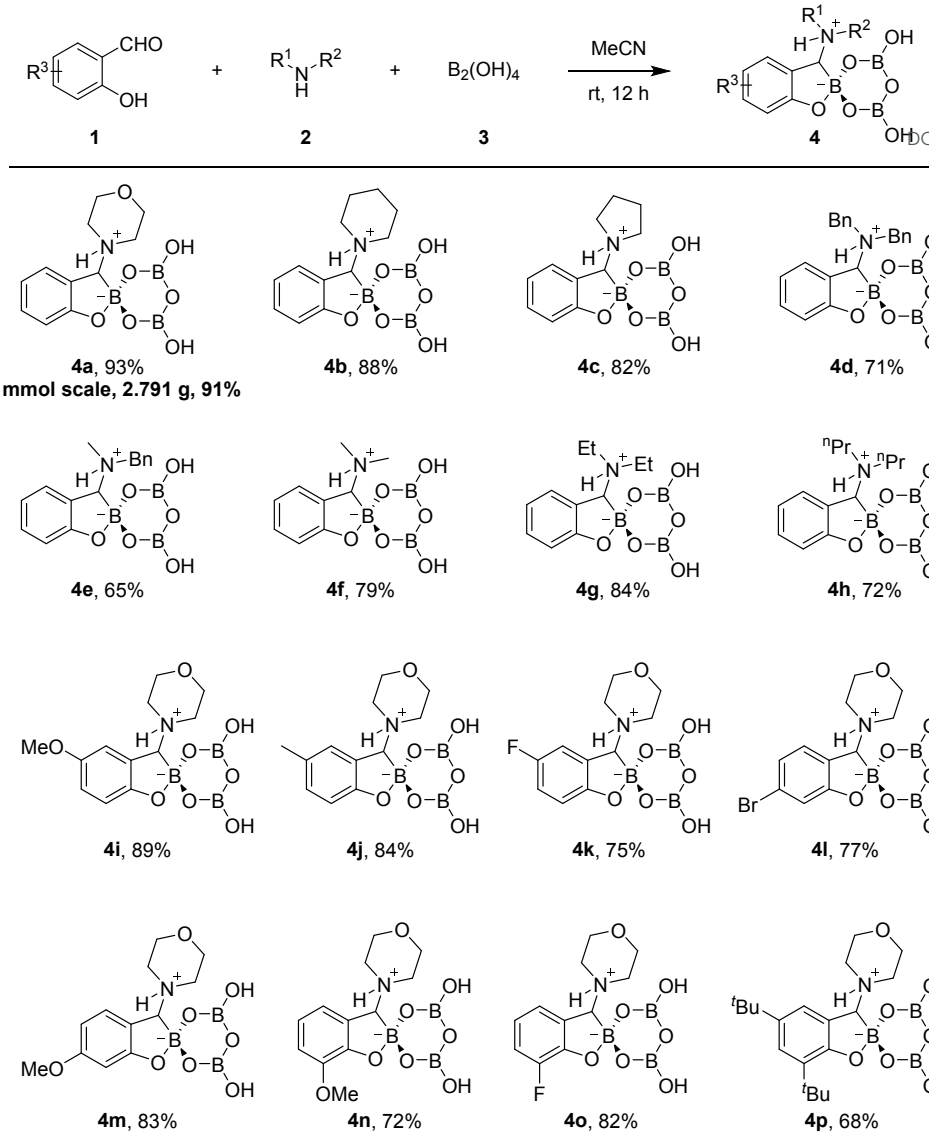
Entry	Solvent	Time (h)	Yield (%)
1	toluene	24	49
2	Et_2O	24	38
3	CH_2Cl_2	24	65
4	THF	24	68
5	EtOAc	24	72
6	acetone	24	89
7	MeCN	24	94
8	**MeCN**	**12**	**93**
9	MeCN	6	72

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol, 1.0 equiv), **3** (0.75 mmol, 1.5 equiv), solvent (2 mL), in air at ambient temperature, with isolated yields of product.

With optimised conditions in hand, the substrate scope was then systematically studied, and the results are compiled in Scheme 3. Secondary aliphatic amines, including piperidine, pyrrolidine, Bn_2NH, BnMeNH, Me_2NH, Et_2NH, and $^nPr_2NH$ were suitable substrates for this reaction. Both electron-donating methyl, methoxy, and *t*-butyl, and electron-withdrawing bromide and fluoride substituents on the salicylaldehyde were tolerated (Scheme 3). A convenient gram-scale reaction (10 mmol) of **1a** gives **4a** in 91% yield (2.791 g). The structures of the products were exemplified by single-crystal X-ray diffraction studies of **4a**, **4d**, and **4p** (Figure 1).



Reaction conditions: **1** (0.5 mmol, 1.0 equiv), **2** (0.5 mmol, 1.0 equiv) and 3 (0.75 mmol, 1.5 equiv) in MeCN (2 mL) in air at ambient temperature unless otherwise specified, with isolated yields of target product.

Scheme 3 Substrate scope of synthesis of boroxines.

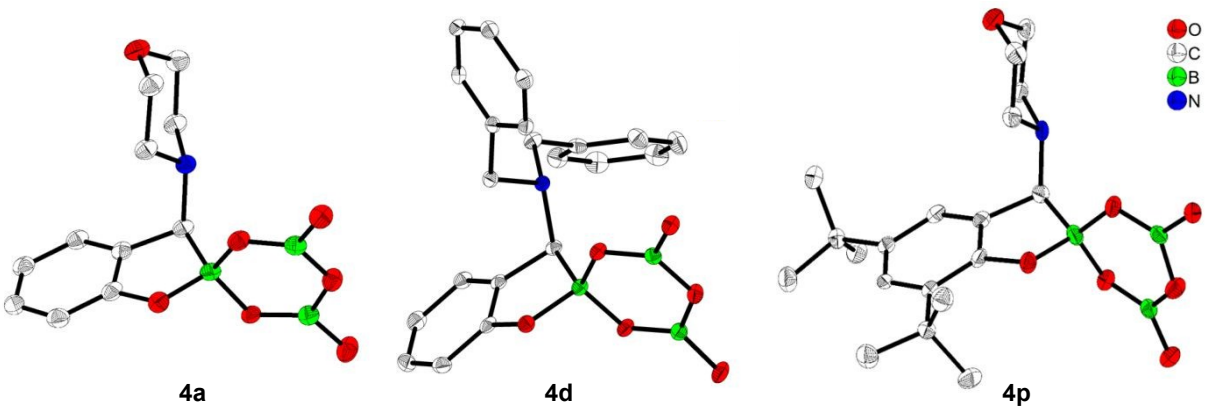
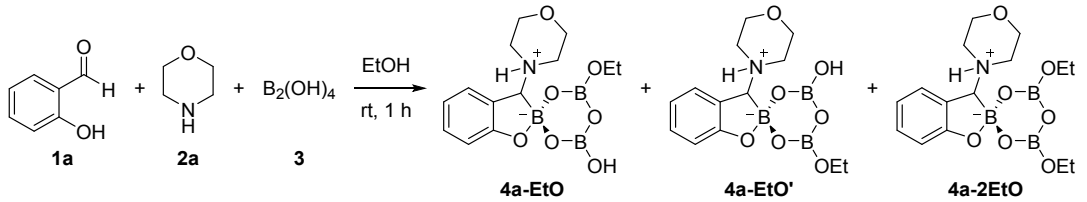


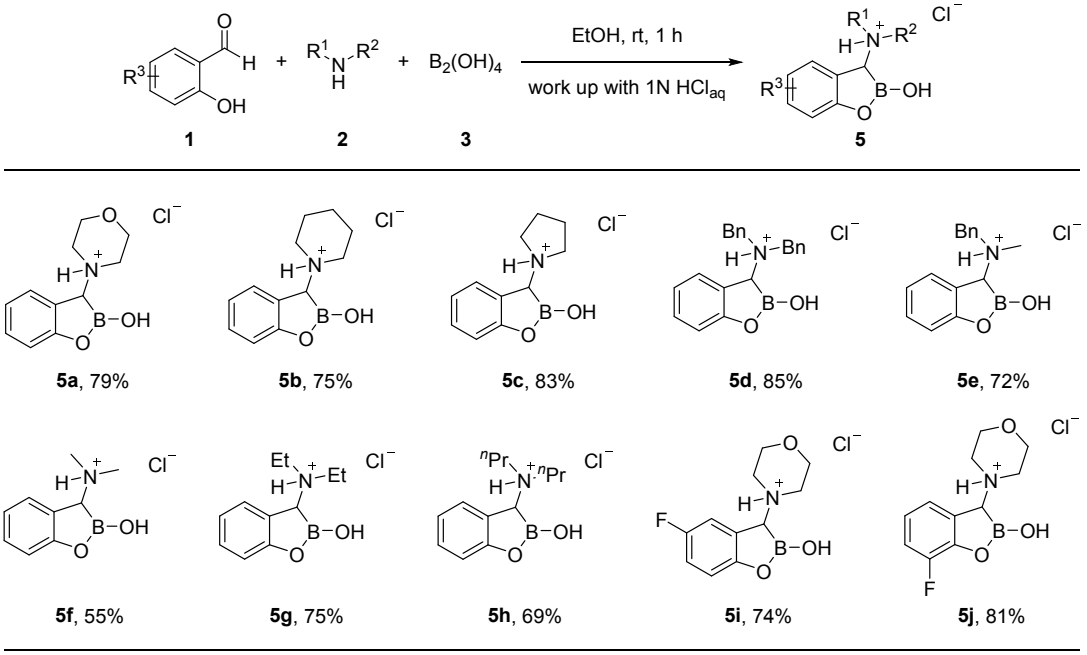
Figure 1. Molecular structures of **4a**, **4d**, and **4p**.

Given its low price, low boiling point and low toxicity, ethanol is widely used as a green solvent in organic synthesis.[9] With ethanol as the solvent for our reaction, one or both hydroxyls were substituted by EtO^-,

as confirmed by NMR spectroscopy and HRMS (Scheme 4 and Figures S7 to S11). However, the products were formed faster and in higher yields and, after work up with 1N HCl_{aq}, a benzoxaborole-derived *α*-amino cyclic boronate was isolated in 79% yield.[10,11] As depicted in Scheme 5, a series of *α*-amino cyclic boronates were prepared *via* this multicomponent reaction.



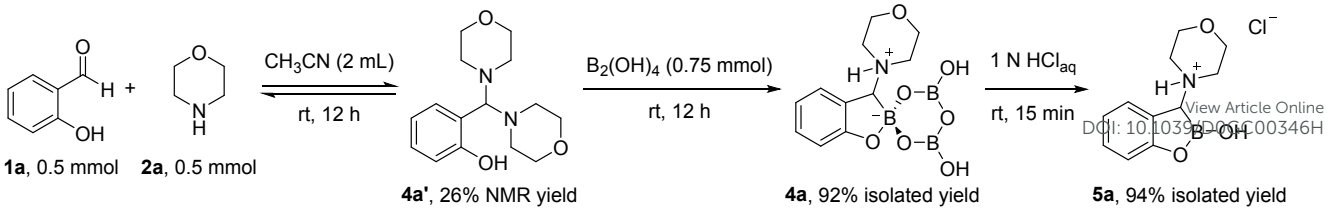
Scheme 4 Reaction conducted in ethanol.



Reaction conditions: **1** (0.5 mmol), **2** (0.5 mmol, 1.0 equiv) and **3** (0.75 mmol, 1.5 equiv), ethanol (2 mL), in air under ambient temperature for 1h, then 2 mL 1N HCl_{aq} was added, with isolated yields of target product.

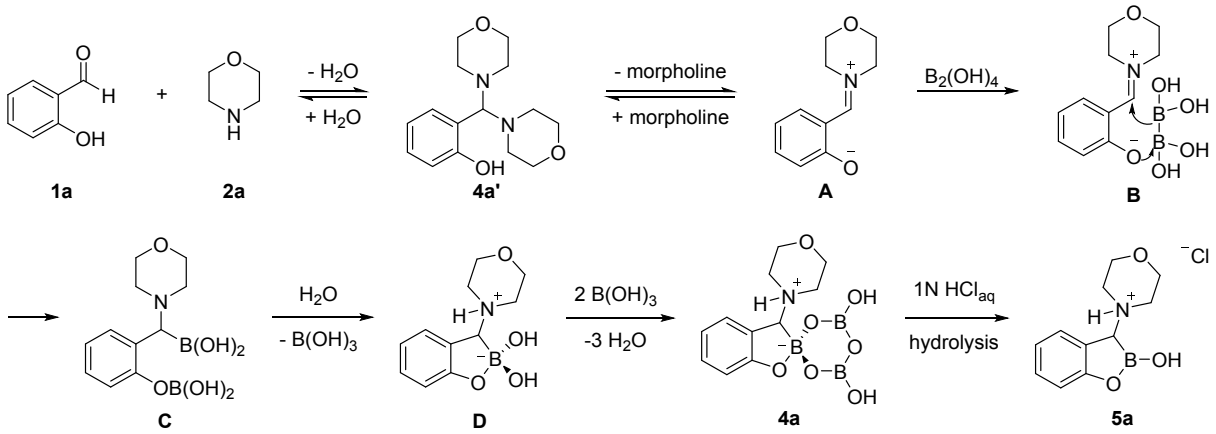
Scheme 5 Substrate scope of the one-pot synthesis of *α*-amino cyclic boronates.

To gain insight into the mechanism, the reaction was conducted stepwise, and aminal intermediate **4a'** was formed in 26% yield immediately upon mixing salicylaldehyde **1a** and morpholine **1b** in CH_3CN, confirmed by ^1H NMR spectroscopy (Figure S1). Prolonging the reaction time to 12 h did not lead to an improvement in the yield of **4a'**, indicating that the formation of aminals is reversible (Figures S2–S6). $B_2(OH)_4$ was then added to the reaction mixture, and boroxine **4a** was isolated in 92% yield after stirring for 12 h. Then, **4a** was hydrolysed with 1N HCl_{aq} to give *α*-amino cyclic boronate **5a** in 94% yield (Scheme 6).



Scheme 6 Stepwise reaction process; the yield of intermediate **4a'** was monitored by ^{1}H NMR spectroscopy (300 MHz, $CDCl_3$, rt) using 1,3,5-trimethoxybenzene as an internal standard.

The Petasis three-component reaction between an amine, an aldehyde and an organoboron compound, has evolved into a versatile process for the synthesis of amino acids, amino alcohols, and various heterocycles.[12] Matteson first reported ligand-facilitated trimerisation of arylboronic acids as early as 1962, when they prepared the 1 : 1 pyridine complex of vinylboronic acid anhydride, the boroxine being generated spontaneously in a high yield.[13]



Scheme 7 Proposed mechanism.

Based on the above, and our observations, we propose the mechanism for this multicomponent coupling reaction shown in Scheme 7. Salicylaldehyde **1a** reacts with morpholine **1b** to form aminal intermediate **4a'**. The key intermediate **B** is assembled by formation of iminium ion **A**, and coordination of its phenolate oxygen to $B_2(OH)_4$.[1d,14] Intramolecular boryl group transfer provides **C**, the immediate precursor to ligated *α*-aminoboronic acid **D**, which can react with boric acid to give boroxine **4a**. Finally, hydrolysis with 1N HCl_{aq} affords *α*-amino cyclic boronate **5a**.

In conclusion, we have developed a green and economical process for the synthesis of *α*-amino cyclic boronates. The desired products can be obtained via a one-step multicomponent reaction from the readily available starting materials, salicylaldehydes, amines, and $B_2(OH)_4$. Our protocol has several advantages over previous routes including mild reaction conditions (room temperature, in air), no catalysts or additives, easy product isolation, and green solvents (ethanol and water). Further explorations of the

scope of this multicomponent reaction and applications of the benzoxaborole-derived *α*-amino cyclic boronates are currently underway, and will be reported in due course.

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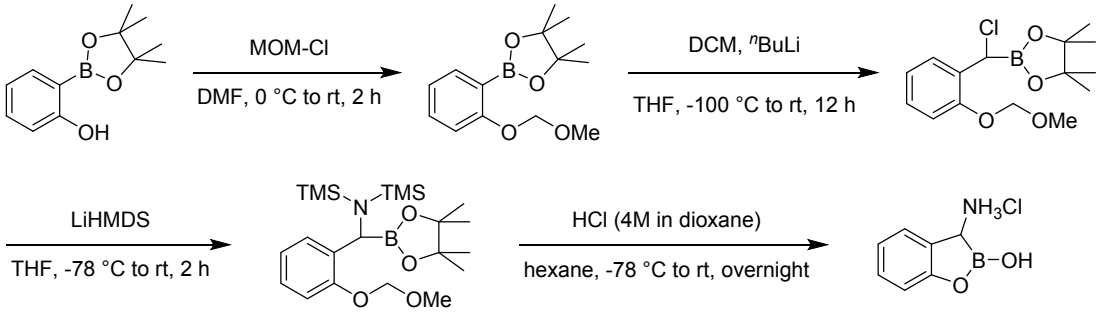
11. A reported synthetic route[7] to benzoxaborole-derived *α*-amino cyclic boronates is outlined below.



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