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Pinacolyl boronic esters as components in the Petasis reaction

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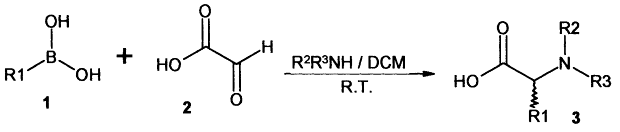
Abstract—The multicomponent reaction of boronic esters with imine or iminium species (generated in situ by reaction of amines with glyoxylic acid) has received little attention in the literature despite the current interest in the corresponding reactions of boronic acids (Petasis reaction). Moreover, the use of boronic esters in this reaction is particularly attractive since chiral esters could act as auxiliaries in a novel enantioselective process. We set out to establish whether boronic esters were general substrates in the Petasis reaction. Pinacolyl boronic esters were selected for study as a model substrate for more complex homochiral boronic esters because of their ease of synthesis and chemical stability. We found that pinacolyl boronic esters do not react with imines derived from primary amines and glyoxylic acid under standard conditions. By contrast, imines derived from secondary amines and glyoxylic acid react readily with vinylboronic esters but less readily with heteroaryl- or arylboronic esters. © 2002 Elsevier Science Ltd. All rights reserved.

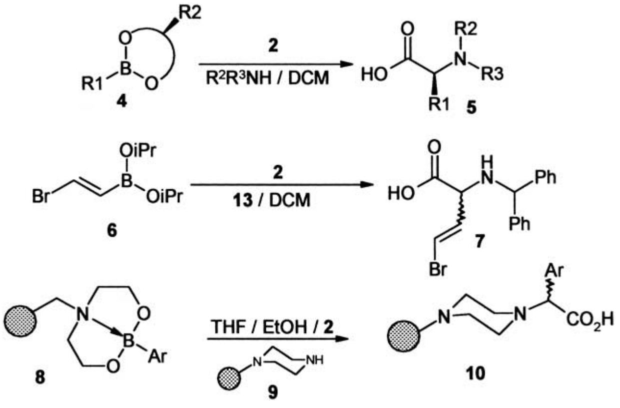
The Petasis multicomponent reaction of aryl- and vinylboronic acids with aldehydes and amines has recently been the subject of considerable attention.[1–3] Sometimes referred to as the boronic acid Mannich reaction, it provides a powerful and convenient method for the one-pot formation of unnatural amino acid derivatives. Thus (Scheme 1), simply stirring an aryl- (or vinyl)boronic acid **1** together with glyoxylic acid **2** and an amine in dichloromethane affords high yields of amino acid derivatives **3**. The reaction can also be used for preparation of α,α-disubstituted amines when aldehydes other than glyoxylic acid are used.[1] This approach is often substrate specific with respect to the aldehyde and appears to favour aldehydes containing an adjacent heteroatom.



Scheme 1.

Both Petasis and Harwood have developed diastereoselective methodologies by employing either homochiral aldehydes or amines as components in the reaction.[4,5] These approaches have met with considerable success but both suffer from the drawback that the chiral centre, which is responsible for chiral induction in the reaction, must also be present as a feature in the final product.

We reasoned (Scheme 2) that if the reaction could be extended to tolerate homochiral boronic esters (e.g. **4**), it should be possible to develop a generally enantioselective process utilising a chiral auxiliary group which



Scheme 2.

Keywords: boronic ester; Petasis reaction; amino acid.

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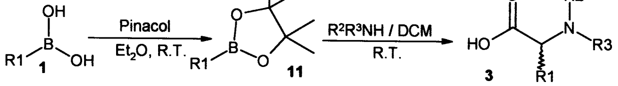
would be eliminated during the course of the reaction and therefore need not be present in the final product **5**.

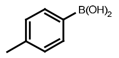
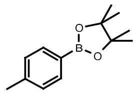
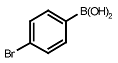
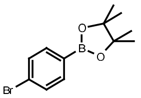
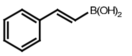
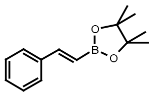
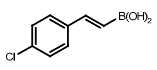
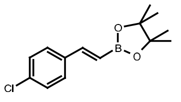
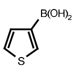
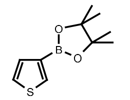
To our knowledge the literature contains only two isolated examples of boronic esters participating in this process. Thus, the non-chiral bis(isopropyl) bromovinylboronic ester **6** is reported to react smoothly with the primary amine 1,1-diphenylmethylamine **13** and glyoxylic acid at room temperature to afford the corresponding racemic amino acid derivative **7** in high yield (80%).[6] In a second, very recent example which appeared in the literature during preparation of this manuscript a resin tethered boronic ester **8** was shown to react with a solution of glyoxylic acid in THF/EtOH and a resin bound secondary amine **9**. This is a rather novel resin-to-resin transfer process involving deliberate disproportionation of the polymer supported boronic ester into a bis(ethyl) arylboronic ester which is released into solution to react further with a second resin bound species **9**.[7]

In view of the relative shortage of literature precedents concerning participation of boronic esters in the Petasis reaction, we set out to investigate whether boronic esters were general substrates with both primary and secondary amines. Initially we elected to study some non-chiral pinacolyl boronic esters **11** since these provide a good model system endowed with both chemical stability and steric bulk. These are properties which would ultimately be required if a suitable chiral auxiliary **4** were to be developed.



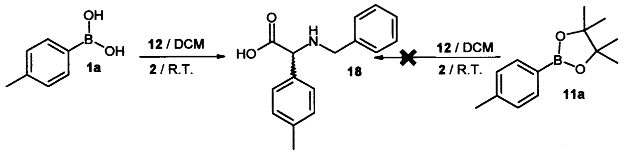
Scheme 3.

Table 1. Formation of pinacolyl boronic esters from boronic acids

Boronic Acid **1**	Boronic Ester **11**
 **1a**	 **11a** (97%)
 **1b**	 **11b** (97%)
 **1c**	 **11c** (100%)
 **1d**	 **11d** (88%)
 **1e**	 **11e** (76%)

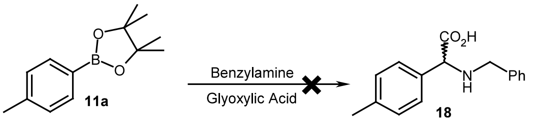
Formation (Scheme 3) of the required pinacolyl boronic esters **11** was extremely straightforward;[8] the results are summarised in Table 1. Reaction of the boronic acids **1a–e** with pinacol in ether afforded the requisite aryl- or vinylboronic esters **11a–e** directly. We found that simply washing the crude ether reaction mixture with water followed by evaporation of the solvent led to isolation of the pure product in high yields (76–100%).

Having found a reliable synthesis of pinacolyl boronic esters, we then set out to study their reactivities with amines and glyoxylic acid under standard Petasis conditions (Table 3). Surprisingly, treatment of boronic esters **11a–e** with glyoxylic acid and the primary amines **12–14** in DCM as solvent produced no observable reaction. This apparent lack of reactivity was quite unexpected and in contrast to prior literature precedents. We therefore carried out a study to determine if the corresponding reactions of the boronic acids **1a–e** would work (Scheme 4). When we treated 4-methylbenzeneboronic acid **1a** with benzylamine **12** and glyoxylic acid in dichloromethane at room temperature, the expected product **18** was formed in good yield (67%). We then evaluated the reaction of the corresponding pinacolyl ester derivative **11a** using a range of different solvents (DCM, THF, dioxane, toluene or DMF) and reaction temperatures. Conditions including both Lewis acid catalysis and microwave heating were also evaluated but in all cases studied, no product formation was observed. The results are summarised in Table 2.



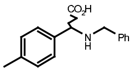
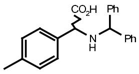
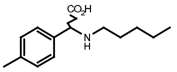
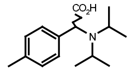
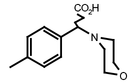
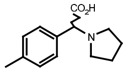
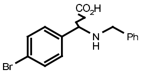
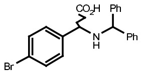
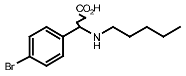
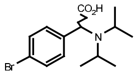
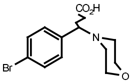
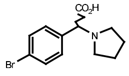
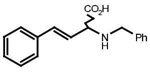
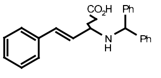
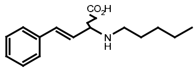
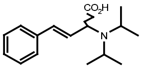
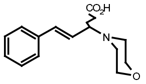
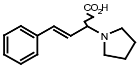
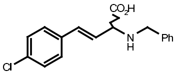
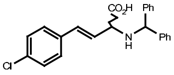
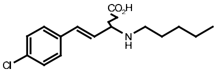
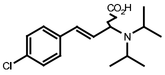
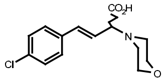
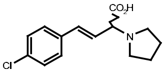
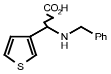
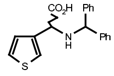
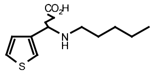
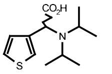
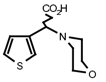
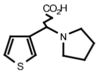
Scheme 4.

Table 2. Attempted reactions of **11a** with benzylamine and glyoxylic acid



DCM, rt	No reaction
DCM, $Yb(OTf)_3$, rt	No reaction
THF, reflux	No reaction
Dioxane, reflux	No reaction
Toluene, reflux	No reaction
DMF, 250°C (microwave)	No reaction

Table 3. Formation of amino acids **3** by reaction of pinacolyl boronic esters **11a**–**e** with glyoxylic acid **2** and amines **12**–**17**

Boronic Ester **11**	Benzylamine **12**	1,1-Diphenyl methylamine **13**	*n*-Pentylamine **14**	Diisopropylamine **15**	Morpholine **16**	Pyrrolidine **17**
11a	 **18** (Not detected)	 **23** (Not detected)	 **28** (Not detected)	 **33** (12%)	 **38** (12%)	 **43** (9%)
11b	 **19** (Not detected)	 **24** (Not detected)	 **29** (Not detected)	 **34** (6%)	 **39** (5%)	 **44** (5%)
11c	 **20** (Not detected)	 **25** (Not detected)	 **30** (Not detected)	 **35** (75%[a])	 **40** (82%)	 **45** (75%[a])
11d	 **21** (Not detected)	 **26** (Not detected)	 **31** (Not detected)	 **36** (70%[a])	 **41** (71%)	 **46** (70%[a])
11e	 **22** (Not detected)	 **27** (Not detected)	 **32** (Not detected)	 **37** (27%)	 **42** (25%)	 **47** (28%)

[a] Yields derived from HPLC.

By contrast, the reactions of boronic esters **11a**–**e** with secondary amines **15**–**17** and glyoxylic acid gave the expected products **33**–**47** (Table 3). In these cases we observed a striking reactivity pattern which was dependent on the nature of the boronic ester substrate. Under standard conditions the vinylic substrates **11c** and **11d** gave high yields (70–82%) of the expected amino-acid products with all secondary amines **15**, **16** and **17**. The heterocyclic thien-3-yl substrate **11e** gave only modest (25–28%) yields of products while aryl substituted boronic esters **11a** and **11b** were rather unreactive at room temperature and only low yields (5–12%) of products could be isolated by preparative HPLC. We believe that it will be possible to optimise these low yielding reactions but have not attempted this in the present study.

In summary we have demonstrated that pinacolyl boronic esters participate in the Petasis reaction with secondary amines but not with primary amines. The reasons for the failure of primary amines to take part in these reactions even under forcing conditions is not clear to us at present. We speculate that the previous literature example shown in Scheme 2 in which bis(isopropyl) vinylboronic ester **6** reacts with a primary amine (1,1-diphenylmethylamine) might involve the intermediacy of the corresponding boronic acid (**6**; H for ^{i}Pr) as the reacting species. Formation of the acid could be explained by slow disproportionation of the bis(isopropyl) ester under the reaction conditions (glyoxylic acid monohydrate). Certainly the stability of isopropyl boronic esters to traces of aqueous acid is expected to be much lower than their pinacolyl analogues.

In any case there are still facets to this reaction which are not well understood and these will doubtless become the subjects of future investigations in the literature. Our current focus is on developing the Petasis reaction to include chiral boronic esters so that their use as auxiliaries in this process can be evaluated. The results of our initial studies in this area are presented in the following communication.[9]

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