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Water as the reaction medium for multicomponent reactions based on boronic acids

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ABSTRACT

Water is a suitable medium for the Petasis-borono-Mannich multicomponent reaction. Salicylaldehyde, glyoxalic acid, glycoaldehyde and glyoxal were reacted with several boronic acids and different amines affording alkylaminophenols, 2*H*-chromenes, α-amino acids, α-amino alcohols and 2-hydroxylmorpholines in good to high yields. An efficient new one-pot method for the assembly of boron-heterocycles based on amino-acids, boronic acids and salicylaldehyde using water as the reaction media is presented. The mechanisms of these reactions were studied by means of DFT calculations, and the effect of solvent on the calculated energy barriers was addressed, for different aldehydes.

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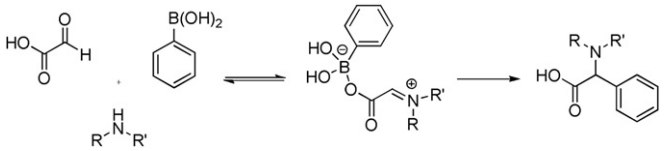
1. Introduction

The emerging of high-throughput screening of drug candidates in pharmaceutical industries has brought the concept of Multicomponent reactions (MCR) into the limelight of organic synthesis.[1] MCRs are one of the best tools available for the preparation of large libraries of diverse and structurally distinct molecules in a time and cost effective way.[1]

The use of water as solvent in organic reactions has been successfully reported for several examples. The low cost, the lack of inflammability, explosive, mutagenic, and carcinogenic properties are some of the economic and environmental benefits that have been associated to this solvent. In addition to this, the network of hydrogen bonds, the large surface tension, the high specific heat capacity, the high cohesive energy and the high polarity have been highlighted as some of the unique properties of water that can dramatically influence the transformations performed in this media.[2,3] In addition the necessity of exploring alternatives to conventional organic solvents, have lead, over the last decade, to a considerable increment in the number of reactions that may use water as solvent.[4] Conceptually, multicomponent reactions are potential candidates for the use of water as solvent since the multiple hydrophobic reactants are brought in closer proximity due to hydrophobic interactions. Furthermore these reactions typically have a negative transition molar volume and for that reason may be accelerated due to the hydrophobic effect.[5–7]

Boronic acids are ideal partners in MCR as they are generally stable and soluble in aqueous media. Furthermore, many different molecular structures are commercially available, which is particularly noteworthy when designing reactions targeting high levels of molecular diversity. Considering MCRs in which the boronic acids is used as a potential nucleophilic species generated without the use of metal catalysts, Petasis and co-workers developed a protocol in which the irreversible step is the formation of a new C–C bond.[8] The reaction proceeds via the formation of an imine or an iminium species, which reacts with the boronic acid to yield secondary or tertiary amines (Scheme 1). The success of this protocol resides in the fact that the boronic acid is completely inert towards the aldehyde though it efficiently traps the iminium or the imine bond. This process depends on the existence of an adjacent hydroxyl group that reacts with the boronic acid to form a more nucleophilic tetrahedron boronate species ('ate complex'), which is able to transfer the boron substituent to the imine or iminium bond.



Scheme 1. Example of a Petasis-borono-Mannich reaction.

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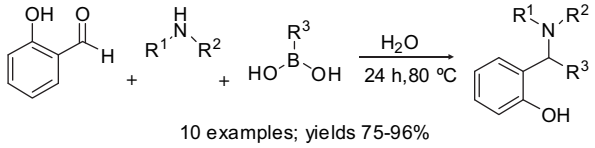
Following our preliminary report on the use of water as solvent for the Petasis-BMR,[9] we now present a detailed synthetic and mechanistic study on this topic.

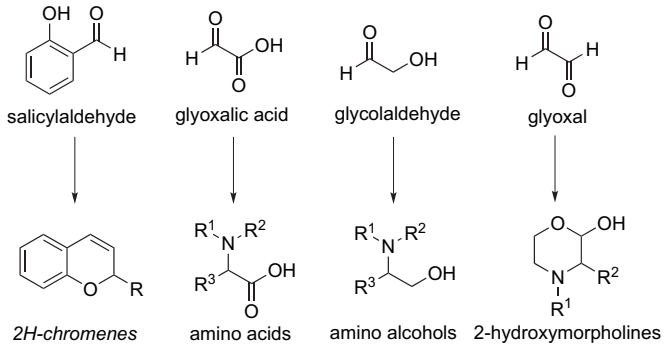
2. Results and discussion

Depending on the aldehyde (aldehyde+activating group), the Petasis-BMR may be used to prepare several synthetic valuable compounds such as α-amino acids[8a,10], α-amino alcohols[8b,11], 2*H*-chromenes[12], α-hydrazinocarboxylic acids[13], 2-hydroxymorpholines and aminodiols[14], 2-aminomorpholines[15] among others. Therefore in our first communication on the use of water as solvent for the Petasis-BMR we disclosed the preparation of alkylaminophenols in yields up to 96% based on the combination of different salicylaldehydes with a variety of secondary amines and boronic acids (Scheme 2).



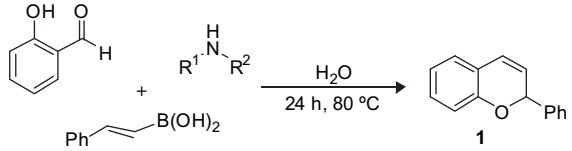
Scheme 2. Petasis-borono-Mannich reaction with salicylaldehydes.

Despite the success achieved when using salicylaldehyde, we became interested in understanding if water could be used as a general solvent for the Petasis-BMR. Therefore, different aldehydes were tested in the MCR using water as solvent (Scheme 3). Accompanying this synthetic study, the efficiency of the different activating groups (phenol, carboxylic acid and alcohol) was evaluated using DFT calculations.



Scheme 3. Petasis-BMR using different aldehydes.

Among the methodologies described in the literature, the one disclosed by Finn and co-workers, which combines an amine, salicylaldehydes and vinylboronic acids remains as one of the most efficient protocols to prepare 2*H*-chromenes.[12a] In this reaction after the three components condensation, occurs an intramolecular cyclisation promoted by the phenol hydroxyl group with consequent ejection of the amine moiety. In water the desired 2*H*-chromenes were obtained in good yields using 40 mol% of amine (Scheme 4, Table 1, entries 4 and 5) though when using 1.2 equiv of amine the yields of 2*H*-chromenes **1** and **2** were improved up to 92%. Among the amines tested, diethyl amine was the most competent, (Table 1, entries 2 and 3). Using the optimized reaction conditions 2*H*-chromenes **2** and **3** were obtained in 92% and 78% yield, respectively.



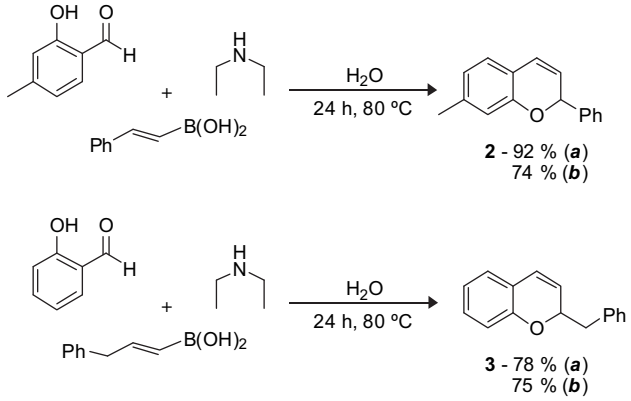
Scheme 4. 2*H*-Chromene preparation using the Petasis-BMR.

Table 1
2*H*-Chromene synthesis via the Petasis-BMR

Entry	Amine	Yield[a] (%)
1	Dimethyl amine·HCl (1.2 equiv) and NaOH (2 equiv)	79
2	Dibenzylamine (1.2 equiv)	58
3	Diethyl amine (1.2 equiv)	92
4	Diethyl amine (20 mol%)	49
5	Diethyl amine (40 mol%)	71

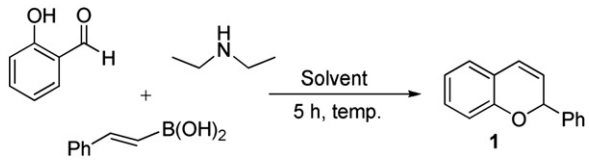
[a] Isolated yield.

Almost simultaneously with our first communication on this topic, Petasis and co-workers reported the use of water as solvent in the preparation of 2*H*-chromenes.[12b] In this study was shown that dibenzylamine was the best amine to promote the cyclisation. Differently, in our hands the same reaction afforded only 58% of compound **1** (Table 1, entry 2). This lower yield may be related with the reaction stirring as in our reaction conditions the stirring stopped frequently due to product **1** precipitation (Scheme 4 and Scheme 5).



Scheme 5. 2*H*-Chromenes preparation using the optimized reaction conditions using 1.2 equiv of amine (a) and using 40 mol% of amine (b).

In 2005 Pirrung and co-workers described an Ugi four-centre three-component reaction (U-4C-3CR) to construct β-lactams in which a considerable acceleration effect was detected when using water as solvent. This observation was rationalized considering the hydrophobic effect and the negative activation volume of the cyclisation step leading to the heterocyclic formation.[6c] Taking this precedent in consideration, we envisioned that water could exert a similar effect over the synthesis of 2*H*-chromenes as it involves an intramolecular cyclisation step as well. Therefore water, 1,2-dichloroethane and dioxane were evaluated in the preparation of compound **1** (Scheme 6, Table 2). When comparing with the other



Scheme 6. 2*H*-Chromene preparation in different solvents using the Petasis-BMR.

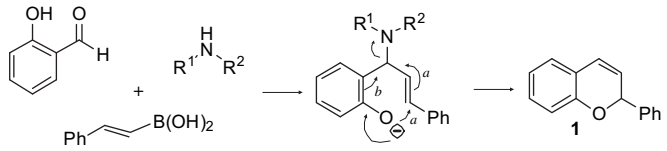
Table 2
Solvent comparison in the preparation of 2*H*-chromene via the Petasis-BMR

Entry	Solvent	Temperature (°C)	Yield[a] (%)
1	Water	80	66
2	Water	50	58
3	1,2-DCE	80	62
4	Dioxane	80	60

[a] Isolated yields.

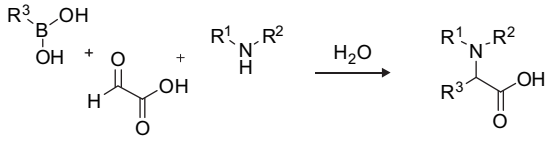
organic solvents typically used for this transformation, water exerted only a modest acceleration effect over the synthesis of 2*H*-chromene **1** (Scheme 6,Table 2).

The two proposed mechanisms for the formation of 2*H*-chromene using the Petasis-MCR involve either an intramolecular nucleophilic displacement of an ammonium leaving group[12a] (Scheme 7, *pathway a*) or an 6π-electrocyclisation (Scheme 7, *pathway b*). Bearing this in mind, we envisioned that if the reaction proceeds via *pathway a* we could probably induce some enantioselectivity in the process using a chiral amine. Therefore we attempted the enantioselectivity synthesis of **1** using half equivalent of (*S*)-α,α-diphenylprolinol at 80 °C for 24 h. A racemic mixture of 2*H*-chromene **1** was obtained in 36% yield, which indicates that, at least in water, the reaction probably proceeds via *pathway b*.



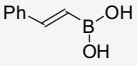
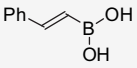
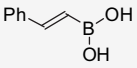
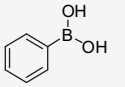
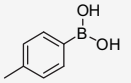
Scheme 7. Possible pathways for the preparation of 2*H*-chromenes.

Regarding the efficiency of salicylaldehyde to promote the Petasis-BMR in water, we extend the protocol to the preparation of α-amino acids using glyoxalic acid as the carbonyl component. The reaction of glyoxalic acid with stoichiometric amounts of boronic acids and secondary amines afforded the corresponding amino acids in yields up to 86%. These results are comparable with those described when using ethanol as solvent.[8a] The products obtained, were simply isolated via filtration after precipitation from the reaction media (Scheme 8, Table 3).



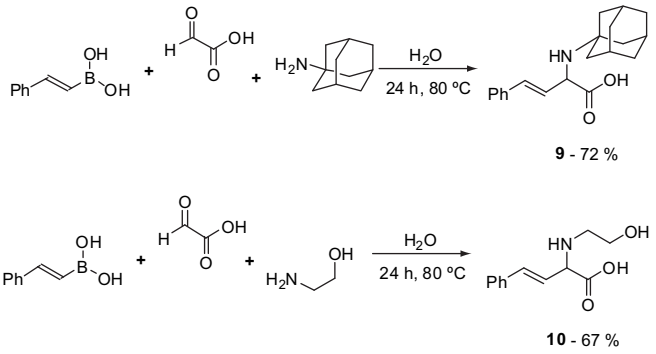
Scheme 8. Petasis borono-Mannich with glyoxalic acid.

Table 3
Petasis borono-Mannich with glyoxalic acid

Entry	Boronic Acid	Amine	Reaction conditions	Product	Yield[a] (%)
1			50 °C 24 h	**4**	67
2			50 °C 24 h	**5**	75
3			50 °C 36 h	**6**	77
4			50 °C 24 h	**7**	86
5			80 °C 36 h	**8**	65

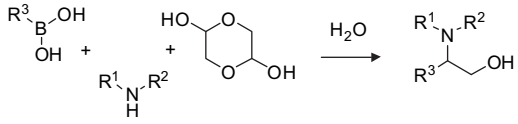
[a] Isolated yield after precipitation in water and filtration.

As shown in Scheme 9, the reaction also proceeds satisfyingly when using primary amines regardless their hydrophobic nature. For instance, the bulky hydrophobic adamantylamine afforded product **9** in 72% yield at the same time that the water soluble ethanolamine afforded the corresponding amino acid in 67% yield.



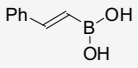
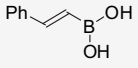
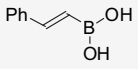
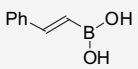
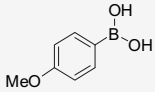
Scheme 9. Petasis borono-Mannich with glyoxalic acid and primary amines, with reaction products purified by precipitation.

Once established the synthesis of amino acids, the preparation of amino alcohols was studied. Hence, glycolaldehyde (dimer) was reacted with secondary amines and *trans*-2-phenylvinylboronic acid. This methodology afforded the expected α-amino alcohols at room temperature in yields up to 69% (Scheme 10, Table 4, entries 1–3). Interestingly 1,2,3,4-tetrahidroquinoline proved to be a very useful amine for this reaction affording the amino alcohols in good yields despite using vinyl or phenylboronic acid (Scheme 10, Table 4, entries 4 and 5).



Scheme 10. Petasis borono-Mannich with glycolaldehyde dimer.

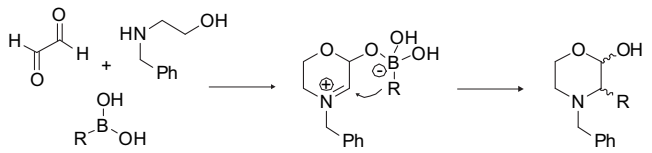
Table 4
Petasis borono-Mannich with glycolaldehyde dimer

Entry	Boronic Acid	Amine	Reaction conditions	Product	Yield[a] (%)
1			25 °C 48 h	**11**	62
2			25 °C 48 h	**12**	64
3			25 °C 48 h	**13**	69
4			50 °C 24 h	**14**	75
5			50 °C 48 h	**15**	74

[a] Isolated yields, except entry 2 where the product was extracted from the reaction medium with Et_2O.

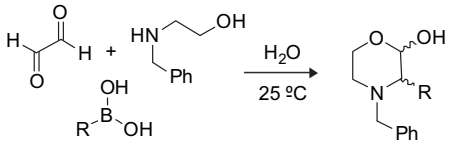
2-Hydroxymorpholines are important synthetic motifs present in a variety of biologically active molecules. This structure can be assessed reacting glyoxal with substituted ethanolamine in the presence of boronic acids (Scheme 11).[14]

In water this protocol proved to be quite efficient affording the 2-hydroxymorpholines in high yields at room temperature conveniently using an aqueous solution of glyoxal and benzylethanolamine (Scheme 12, Table 5). Interestingly, when the



Scheme 11. Preparation of 2-hydroxymorpholines in water.

reaction products were isolated by preparative TLC, the yields obtained were similar to those reported by Berrée and co-workers[14] (35–67%). Though, simply extracting the reaction mixture with ethyl ether led to a remarkable improvement of the isolated yields (89–97%). When using water as solvent no chromatographic steps were required to purify the products as they were extracted almost selectively, considering their ^{1}H and ^{13}C NMR (Table 5).



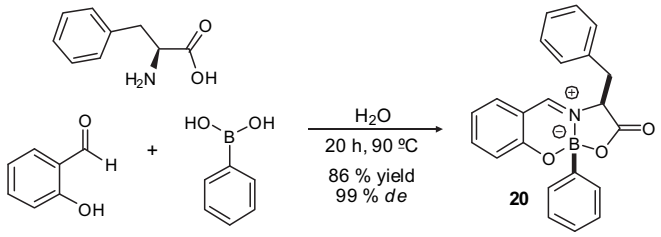
Scheme 12. Preparation of 2-hydroxymorpholines in water.

Table 5
Preparation of 2-hydroxymorpholines by Petasis borono-Mannich in water

Entry	R	Time (h)	Product	Diastereoisomeric ratio	Yield[a] (%)
1	Ph	24	**16**	1:0.3	97
2	4-MeC_6H_4	48	**17**	1:0.2	93
3	4-MeOC_6H_4	24	**18**	1:0.24	94
4	CH=CHPh	48	**19**	1:0.9	89

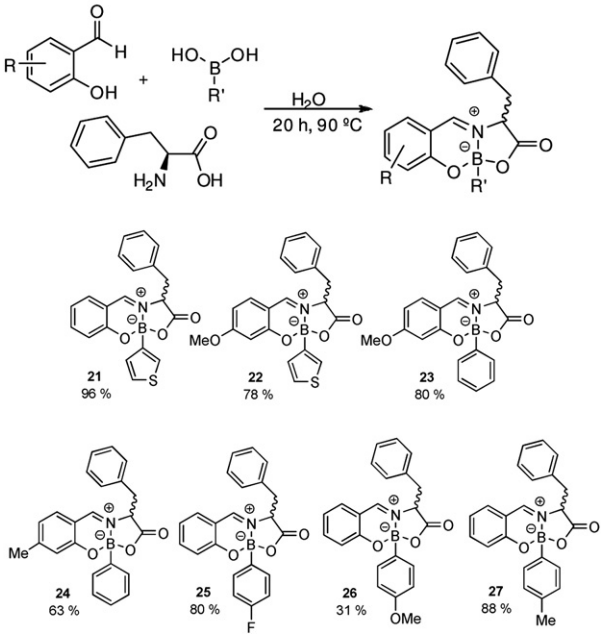
[a] Isolated yields after extraction of the reaction product with Et_2O.

Finally we decided to extend this protocol to the use of amino acids as the source of the amino component. Therefore we perform the reaction of L-phenylalanine and salicylaldehyde with phenylboronic acid in water. Rather surprisingly after 20 h reacting at 90 °C instead of the expected product we obtained the boron-complex **20** in 86% yield and with 99% de. Very conveniently, the complex isolation was considerably facilitated because it completely precipitated from the reaction mixture (Scheme 13).



Scheme 13. Self assembly of boron-complexes in water.

Several boronate complexes similar to **20** and generated from *N*,*O*,*O*-tridentate ligands may be found in the literature including those resulting from the combination of boronic acids with salicylaldehydes and amino-alcohols, amino-phenols or *N*-(2-hydroxybenzyl)-α-amino-acids.[16] Though their synthesis generally involves a multistep approach and organic solvents as the reaction media.[17] As far as our knowledge goes these complexes have never been prepared in one-pot using water as the reaction media. Therefore, and encouraged by the high yield obtained in the synthesis of complex **20**, as well as the complex high thermal and hydrolytic stability we extend the protocol to the preparation of different boron-complexes. Hence, combining L-phenylalanine with different salicylaldehydes and boronic acids afforded complexes **21**–**27** in yields up to 96%. Rather surprising, and despite our attempts, we were unable to improve the yield of complex **26** prepared using 4-metoxy-phenylboronic acid. Apart from this case, the substitutions either in the salicylaldehyde or the boronic acid had little effect on the overall good yields obtained (Scheme 14).



Scheme 14. Scope of the methodology using L-phenylalanine, different salicylaldehydes and boronic acids.

Suitable crystals for X-ray analysis were obtained for complexes **20**, **21**, **25** and **26**. Despite the different boronic acids used to prepare **20**, **21** and **25** they all display similar N–B dative bond distances (1.577(2) Å (**20**), 1.574(3) Å (**21**) and 1.569(4) Å (**25**)) and this fact most probably results from stereo constrains imposed by the tridentate ligand (Fig. 1).

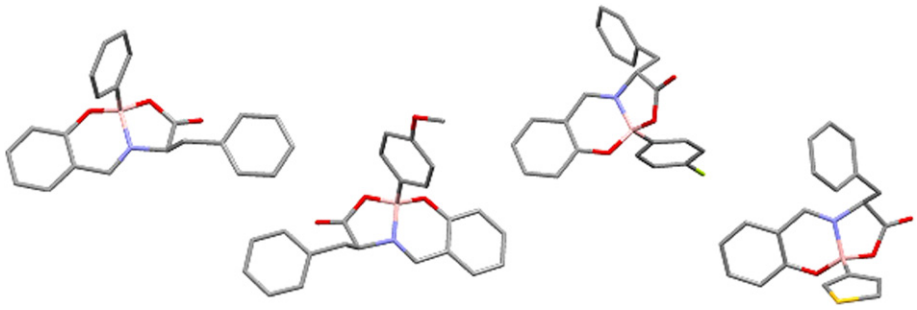


Figure 1. Molecular diagrams of the complexes **20**, **26**, **25** and **21** (from left to right) obtained by X-ray diffraction.

The structural features of selected boron-complexes were studied by means of DFT calculations,[18] with emphasis on the nature of the B–N bond. All complexes with determined X-ray structure were addressed, and the corresponding optimised geometry calculated (see Computational details). The calculated B–N distance is similar for all complexes (1.58 Å), in good agreement with the experimental bond lengths determined for complexes **20**, **21** and **25** (within 0.01 Å), and ca. 0.05 Å longer than the experimental B–N separation observed in the X-ray structure of complex **26** (1.530(7) Å). The similarity observed in the B–N bond lengths calculated for all species is reinforced by the corresponding Wiberg indices,[19] with a value of 0.61 in all cases, indicating comparable bond strength. In addition, the atomic charge (NPA,[20] see Computational details) calculated for the B-atom is also equal for all species (1.02) showing, once again, a general equivalence between the electronic structure of the complexes studied. These results indicate that the significantly shorter B–N bond distance observed in the X-ray structure of complex **26**, when compared with the remaining species, is most probably due to a solid-state effect. The relative positioning of the different B substituent implies a different conformational geometry, noticed in the angle between the planes sharing the B–N edge (36.05(6), 33.28(7), 38.79(8) and 41.1(3)° for complexes **20**, **21**, **25** and **26**, respectively) thus entailing distinct crystal packing arrangements.(see Fig. in Supplementary data).

The mechanism generally assumed for the Petasis-borono-Mannich reaction involves the formation of a tetrahedric boron complex, denominated as ate complex, after the activation of the boron atom by the hydroxyl functional group. This complex then transfers the aryl moiety to the iminium or imine bond. The aryl transfer does not occur in the absence of such hydroxyl group, supporting the need of a boronic acid activating agent in the molecule. After our previous work based on Density Functional Theory (DFT)[18] calculations for the reaction of salycilaldehyde,[9] we now report a comparative study including the reactions of glyoxalic acid and glycoaldehyde.

The DFT calculations on the mechanism of the Petasis reaction used dimethylamine, phenylboronic acid and three aldehydes (salicylaldehyde, glyoxalic acid and glyoxaldehyde) as model reactants. The effect of solvent was accounted for by means of the polarisable continuum model PCM (see Computational details). The corresponding results are presented as Supplementary data, but, for simplification sake, the following discussion will be based on the results obtained for water. For the three reactions studied, the phenyl migration step was investigated in two different conditions: starting from a boronic acid activated through the formation of an ate complex, or in the absence of such activation. In all cases, the ate complexes lead to lower energy barriers and, thus, these will be the mechanisms discussed here. The energy profiles associated with the alternative pathways, without previous activation of the boronic acid, are presented as Supplementary data.

Concerning the reaction of salicylaldehyde, it was previously found[9] that the ate complex formation should occur by the interaction of the boronic acid with a zwiterionic species resultant from the deprotonation of the iminium (Fig. 2). The transition state for the migration of phenyl (**TS1**) demands an energetic barrier of 18.9 kcal/mol and corresponds to an intermediate geometry between the ate complex (**ATE1**) and the tertiary amine (**TA1**). The long distance and the Wiberg index (WI)[19] associated with the formation of the new C–C bond (d=2.00 Å, WI=0.47), as well as the values relative to the C–B bond break (d=1.81 Å, WI=0.51), indicate an early transition state with only incipient C–C bond formation and C–B bond breaking.

Interestingly, the energy barrier was calculated to be ca. 2 kcal/mol smaller for dichloroethane, than for the other two solvent tested (water and dimethylformamide).

Analogously to the previous mechanism, glyoxalic acid was considered as the aldehyde component and a new mechanistic

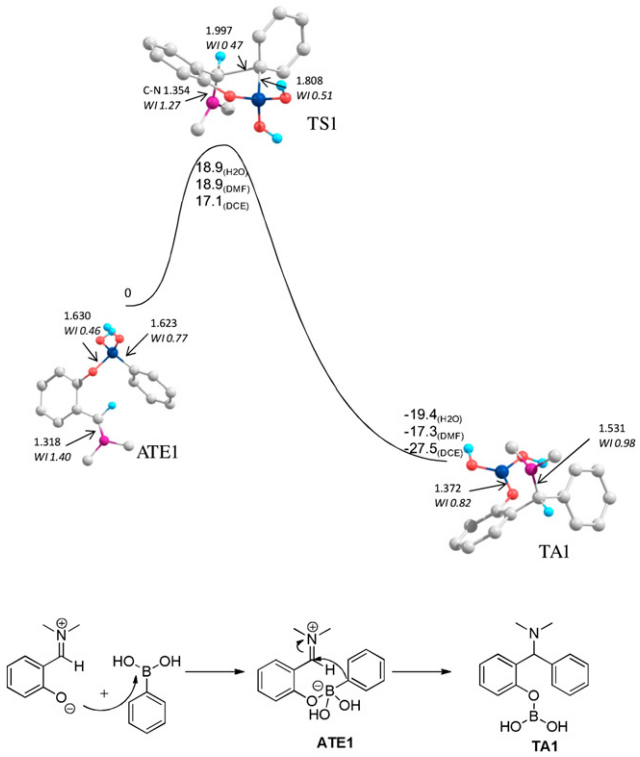


Figure 2. Energy profile calculated for Petasis reaction between dimethylamine, salicylaldehyde and phenylboronic acid. The relevant bond distances (Å) are indicated, as well as the respective Wiberg indices (WI, italics). The minima and the transition state were optimized and the energy values (kcal/mol) are referred to ate complex. H-atoms on the phenyl and methyl substituents are omitted for clarity.

study was performed (Fig. 3). The ate complex formed from glyoxalic acid is equivalent to the previous one, derived from salicylaldehyde, as shown by a comparison of the relevant B–O bond, i.e, the one that links together the iminium and the boronic acid: d=1.63 Å, WI=0.46 for salicylaldehyde and d=1.66 Å, WI=0.46 for

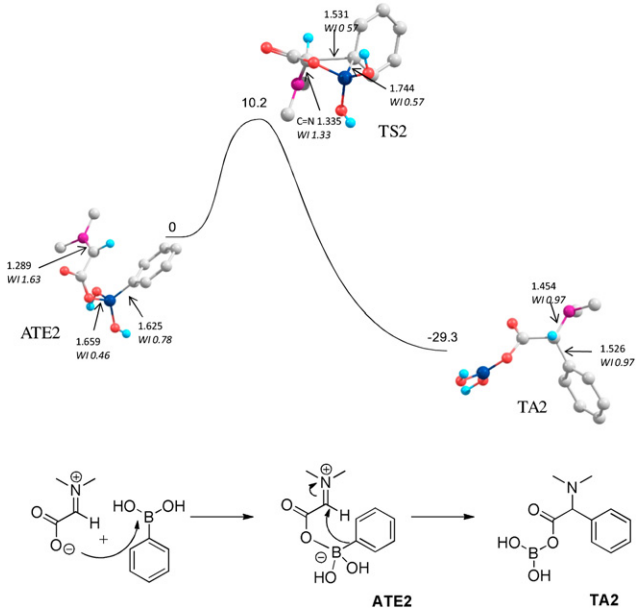


Figure 3. Energy profile calculated for Petasis reaction between dimethylamine, glyoxalic acid and phenylboronic acid. The relevant bond distances (Å) are indicated, as well as the respective Wiberg indices (WI, italics). The minima and the transition state were optimized and the energy values (kcal/mol) in water (PCM) are referred to the ate complex. H-atoms on the phenyl and methyl substituents are omitted for clarity.

glyoxalic acid. Again, the transition state determined for this mechanism (**TS2**) has an intermediate geometry between the ate complex (**ATE2**) and the tertiary amine (**TA2**). In **TS2**, the process of C–B bond breaking is incipient (d=1.74 Å, WI=0.57), while the new C–C bond is almost formed (d=1.53 Å, WI=0.57). Comparing both mechanisms, the smaller energetic barrier to achieve the transition state for the reaction of glyoxalic acid (10.2 kcal/mol) is in good agreement with the experimental results. For the case of the acid, the reaction can be performed at 50 °C, while a temperature of 80 °C is needed for the case of the aromatic aldehyde.

In the case of glycoaldehyde it was not possible to optimize the geometry of free deprotonated iminium alkoxide. All attempts leaded to alternative undesired geometries, reflecting the instability of that intermediate. However, both the corresponding ate complex, as well as the mechanism of phenyl migration from the ate complex to the amine, could be calculated (Fig. 4), similarly to what happened with the two former substrates, salicylaldehyde and glyoxalic acid, allowing, this way, the comparison between all three calculated paths.

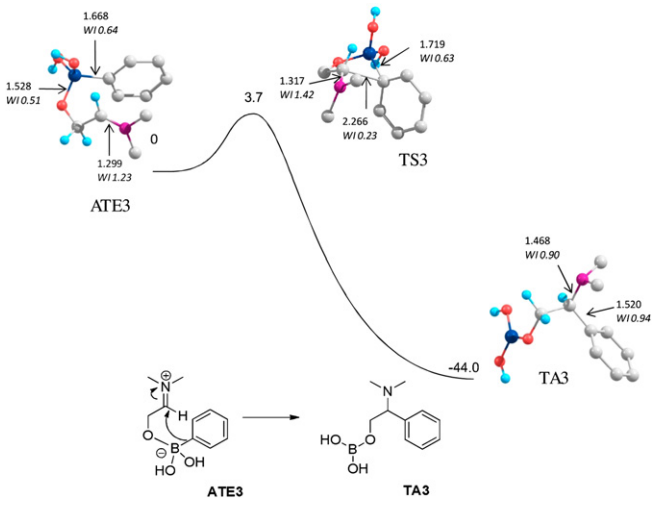


Figure 4. Energy profile calculated for Petasis reaction between dimethylamine, glycoaldehyde acid and phenylboronic acid. The relevant bond distances (Å) are indicated, as well as the respective Wiberg indices (WI, italics). The minima and the transition state were optimized and the energy values (kcal/mol) in water (PCM) are referred to the ate complex. H-atoms on the phenyl and methyl substituents are omitted for clarity.

Comparing the ate complex (**ATE3**) with the ones previously obtained, the relevant B–O bond—arising from the formation of the ate complex—is stronger (d=1.53 Å, WI=0.51) than the B–O bonds of the other ate complexes, **ATE1** and **ATE2** (see above). This bond strengthening is a direct consequence of the increased O-basicity in the case of glycoaldehyde, compared to the former two substrates. In other words, the O-atom belonging to the stronger base (glycoaldehyde) binds more strongly to the acidic boron center in the ate complex. In the calculated mechanism (Fig. 4), the transition state (**TS3**) is an early one since both the formation of the new C–C bond (d=2.27, WI=0.23), as well as the breaking of the C–B bond (d=1.72, WI=0.63), are only starting, once **TS3** is reached. This is a ground state effect, reflecting a weaker B–C(Ph) bond in the case of **ATE3**, compared with **ATE1** and **ATE2**, as shown by the corresponding distances and Wiberg indices (Figs. 2–4). As a consequence, the energy barrier calculated for this reaction is quite small (3.7 kcal/mol), in good agreement with the experimental results, since this kind of reaction proceeds at room temperature.

Considering that the deprotonation of the alcohol and subsequent formation of the ate complex should be a difficult process, due to the alcohol pKa high value, an alternative mechanism was investigated in which there is no deprotonation of the initial iminium reactant, and the ate complex is formed via dehydration of the boronic acid. This hypothesis was also tested for the other aldehydes and the corresponding profiles are presented as Supplementary data.

In the mechanism represented in Figure 5, there are two consecutive steps. The first step corresponds to the formation of an ate complex and, thus, to the activation of the boronic acid, while in the second step, there is phenyl migration from the boron to the C-atom of the iminium, with formation of the product. In the first step, proton transfer from the OH group in the iminium to one OH group of the boronic acid, allows to the formation of the B–O bond between the two reagents and the formation of the ate complex with one water molecule coordinating the B-atom (**ATE4**). In the second step phenyl migration occurs, in the ate complex, yielding the final product, the O-protonated tertiary amine **TA4**. This second step is equivalent, in its general features, to the mechanisms discussed above, based on the deprotonated ate complexes.

In the mechanism of Figure 5 the rate limiting step is the formation of the ate complex, with a very high activation energy of 30.4 kcal/mol. In addition, the energy barrier associated with phenyl migration (13.9 kcal/mol), is significantly higher than the one calculated for the mechanism involving the deprotonated ate complex (Fig. 4). This indicates that the mechanism depicted in Figure 4 is not competitive and hints that the reaction should proceed via a deprotonated ate complex.

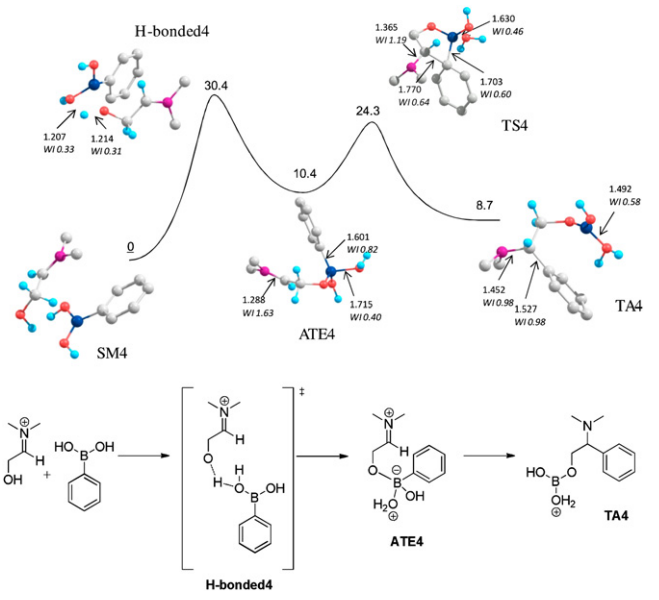


Figure 5. Energy profiles calculated for Petasis reaction between dimethylamine, glycoaldehyde and phenylboronic acid via dehydration. The geometries optimized are presented, and the relevant bond distances (Å) are indicated, as well as the respective Wiberg indices (WI, italics). The minima and the transition states were optimized and the energy values (kcal/mol) in water (PCM) are referred to the dimethyliminium and phenylboronic acid reactants. H-atoms on the phenyl and methyl substituents are omitted for clarity.

3. Conclusions

Water was successfully used as solvent for the Petasis-borono-Mannich reaction, using structurally different aldehydes such as salicylaldehyde, glyoxalic acid and glycoaldehyde. The products low solubility generally allowed simple isolation protocol based on extractions or filtrations. Therefore 2*H*-chromenes (78–92% yields), α-amino acids (65–86% yields), α-amino alcohols (62–75% yields) and 2-hydroxymorpholines (89–97% yields) have been prepared in good to excellent yields. In addition, we established a new

methodology for the one-pot assembly of boron heterocycles based on boronic acids, salicylaldehydes and aminoacids. Most of the complexes were obtained in good to excellent yields (up to 96%). The isolation protocol for these boron-heterocycles was considerably facilitated due to complex precipitation from water. DFT calculations were performed in order to establish the Petasis-BMR mechanism and the results obtained corroborate the generally accepted mechanism for this multicomponent transformation.

4. Experimental section

4.1. General information

Dichloromethane (DCM), 1,2-dimethoxyethane (DME) were freshly distilled over calcium hydride prior to use. Ethyl acetate was distilled over potassium carbonate. All reactions were performed in oven-dried glassware under nitrogen atmosphere. Preparative thin layer chromatography plates were prepared with silica gel 60 GF_{254} Merck (Ref. 1.07730.1000). Reaction mixtures were analysed by TLC using ALUGRAM® SIL G/UV_{254} from MN (Ref. 818133, silica gel 60), and visualisation of TLC spots was effected using UV and phosphomolybdic acid solution. NMR spectra were recorded in a Bruker AMX 300 or 400 using $CDCl_3$ as solvent and $(CH_3)_4Si$ (^1H) as internal standard. All coupling constants are expressed in hertz. The aldehydes and boronic acids were purchased from Aldrich and used without further purification. The amines were distilled prior to use.

4.2. Computational details

All calculations were performed using the Gaussian 03 software package,[21] and the PBE1PBE functional, without symmetry constraints. That functional uses a hybrid generalised gradient approximation (GGA), including 25% mixture of Hartree-Fock[22] exchange with DFT[18] exchange-correlation, given by Perdew, Burke and Ernzerhof functional (PBE).[23] The optimised geometries were obtained with a standard 6-31G(d,p)[24] basis set. Transition state optimisations were performed with the Synchronous Transit-Guided Quasi-Newton Method (STQN) developed by Schlegel et al.[25] Frequency calculations were performed to confirm the nature of the stationary points, yielding one imaginary frequency for the transition states and none for the minima. Each transition state was further confirmed by following its vibrational mode downhill on both sides, and obtaining the minima presented on the energy profile. A Natural Population Analysis (NPA)[20] and the resulting Wiberg indices[19] were used to study the electronic structure and bonding of the optimised species.

4.3. Crystallographic details

*4.3.1. Crystallographic data for complex **20**.* $C_{22}H_{18}BNO_3$, fw=355.18, monoclinic, space group $P2_1/c$, a=15.3476(8) Å, b=5.9084(4) Å, c=19.1585(12) Å, b=90.983(2)°, V=1737.03(18) Å^3, Z=4, d_{calcd}=1.358 mg m^{-3}, m=0.089 mm^{-1}, F(000)=744. Of 16,270 reflections collected, 3565 were independent (Rint=0.0654); final R indices R1=0.0445, wR2 (all data)=0.1057, GOF=0.985.

*4.3.2. Crystallographic data for complex **21**.* $C_{20}H_{16}BNO_3S$, fw=361.21, orthorhombic, space group $P2_12_12_1$, a=9.8260(2) Å, b=10.9220(2) Å, c=16.5660(3) Å, V=1777.86(6) Å^3, Z=4, d_{calcd}=1.349 mg m^{-3}, m=0.202 mm^{-1}, F(000)=752. Of 16,804 reflections collected, 4342 were independent (Rint=0.0445); final R indices R1=0.0602, wR2 (all data)=0.1868, GOF=1.069.

*4.3.3. Crystallographic data for complex **25**.* $C_{22}H_{17}BFNO_3$, fw=373.18, monoclinic, space group $P2_1/n$, a=10.470(1) Å, b=9.715(1) Å, c=18.653(2) Å, b=93.322(4)°, V=894.1(4) Å^3, Z=4, d_{calcd}=1.309 mg m^{-3}, m=0.093 mm^{-1}, F(000)=776. Of 16,174 reflections collected, 3576 were independent (Rint=0.1268); final R indices R1=0.0547, wR2 (all data)=0.1246, GOF=0.856.

*4.3.4. Crystallographic data for complex **26**.* $C_{22}H_{20}BNO_4$, fw=385.21, monoclinic, space group $P2_1/n$, a=16.444(6)(12) Å, b=5.923(4) Å, c=21.162(3) Å, b=109.378(8)°, V=1944.4(15) Å^3, Z=4, d_{calcd}=1.316 mg m^{-3}, m=0.089 mm^{-1}, F(000)=808. Of 9358 reflections collected, 3362 were independent (Rint=0.2346); final R indices R1=0.0669, wR2 (all data)=0.1494, GOF=0.670. Crystallographic data for the above mentioned compounds have been deposited in the Cambridge Crystallographic Data Centre with deposition numbers CCDC 766931 to CCDC 766934.

The energy values reported result from single point energy calculations using a 6-311+G(d,p)[26] basis set and the geometries optimised at the PBE1PBE/6-31G(d,p) level. Solvent effects were considered in the PBE1PBE/6-311++G(d,p)//PBE1PBE/6-31G(d,p) energy calculations using the Polarizable Continuum Model (PCM) initially devised by Tomasi and co-workers[27] as implemented on Gaussian 03,[28] and, thus, the energy barriers can be taken as free energy.[29] The molecular cavity was based on the united atom topological model applied on UAHF radii, optimized for the HF/6-31G(d) level.

4.4. Experimental procedure for the Petasis-Borono-Mannich reactions with glyoxalic acid

A round bottom flask equipped with a magnetic stirrer was charged with boronic acid (1.0 equiv), glyoxalic acid (1.0 equiv) and distilled water (2.0 mL). This suspension was stirred at 50 or 80 °C for 5 min after which the amine (0.41 mmol) was added. The mixture was stirred at 50 or 80 °C for 24 h or 36 h after which the reaction mixture was cooled at 4 °C and the reaction product filtered and washed with water. Products **9** and **10** were obtained with the same spectral characterization as previously described in Ref. 6a, product **7** as described in Ref. 10b, and products **4–6** as described in Ref. 10c.

Compound **8** was obtained in 65% after 36 h at 80 °C (0.068 g); ^1H NMR (400 MHz, DMSO-d_6): δ 2.09 (s, 3H, CH_3), δ 2.30 (s, 3H, NCH_3), δ 3.49–3.63 (m, 2H, NCH_2Ph), δ 4.20 (s, 1H, NCHCO$_2$), 7.13–7.69 (m, 5H, *Ph*), δ 8.20 (br s, 1H, CO$_2H$); ^{13}C NMR (125 MHz, $CDCl_3$): 21.19 (*C*H$_3$), 21.64 (NCH_3), 58.22 (NCH_2Ph), 72.21 (NCHCO$_2$), 127.59, 128.50, 128.68, 129.13, 129.21, 129.42, 134.31, 134.66 (Ph), 137.68 (Ph, quaternary), 138.74 (Ph, quaternary), 139.81 (Ph, quaternary), 172.90 (*C*O$_2$H). MS (EI): m/z=224, 132, 91. HMRS (EI): m/z calcd [M+1H] 270.1494, found [M+1H] 270.1495.

4.5. Experimental procedure for the Petasis-Borono-Mannich reactions with glycolaldehyde dimer

A round bottom flask equipped with a magnetic stirrer was charged with glycolaldehyde dimer (0.5 equiv), boronic acid (1.0 equiv) and distilled water (2.0 mL). This suspension was stirred at room temperature or 50 °C for 5 min after which the amine (0.41 mmol) was added. The mixture was stirred at room temperature or 50 °C for 24 h or 48 h after which the water was evaporated under reduced pressure and the reaction product isolated by preparative thin layer chromatography (AcOEt/Hexane). Product **13** was obtained pure by extraction of the reaction mixture with ethyl ether (3×3 mL), with no need of further purification. Product **11** was obtained with the same spectral characterization as previously described in Ref. 8b.

Compound **12** was obtained in 64% after 48 h at room temperature and isolated by PTLC, AcOEt/Hex (1:1) (0.091 g); ^1H NMR (400 MHz, $CDCl_3$): δ 3.33 (d, J=13.3, 2H, NCH_2Ph), δ 3.38–3.43 (m, 2H, NCHCH_2OH), δ 4.03 (d, J=9.4, 1H, NCHCO$_2$), 3.84 (d, J=13.3, 2H, NCH_2Ph), 6.09–6.15 (m, 1H, C*H*CHPh), 6.44 (d, J=16.0, NCHC*H*Ph), 7.14–7.35 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$): 53.56 (NCH_2Ph),

61.05 ($NCHCH_2OH_2$), 61.71 ($NCHCH_2OH$), 123.26 (*C*HCHPh), 126.52, 127.35, 128.07, 128.62, 128.75, 129.04 (*Ph*), 135.83 (CH*C*HPh), 136.48, 139.04 (*Ph*, quaternary). MS (EI): *m*/*z*=312, 220, 91. HMRS (EI): *m*/*z* calcd [M+1H] 344.2014, found [M+1H] 344.2006.

Compound **13** was obtained in 69% after 48 h at room temperature and isolated extraction of the reaction medium (0.084 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.00–3.06 (m, 2H, NCH_2CHCH_2), δ 3.48–3.49 (m, 2H, NCH_2CHCH_2), δ 3.60–3.70 (m, 1H, $NCHCH_2OH$), δ 5.21–5.27 (m, 4H, NCH_2CHCH_2), δ 5.82–5.92 (m, 2H, NCH_2CHCH_2), 6.12 (dd, *J*=16.0, *J*=7.3, 1H, *CH*CHPh), 6.54 (d, *J*=16.0, 1H, *CH*CHPh), 7.27–7.42 (m, 5H, *Ph*); ^{13}C NMR (125 MHz, $CDCl_3$): 52.54 (NCH_2CHCH_2), 61.03 ($NCHCH_2OH$), 62.67 ($NCHCH_2OH$), 118.17 (NCH_2CHCH_2), 123.38 (*C*HCHPh), 126.38, 128.02, 128.68 (Ph), 135.35 ($NCHCHCH_2$), 135.69 (CH*C*HPh), 136.40 (Ph, quaternary). MS (EI): *m*/*z*=244, 212, 172, 129, 115, 91. HMRS (EI): *m*/*z* calcd [M+1H] 244.1701, found [M+1H] 244.1702.

Compound **14** was obtained in 75% after 24 h at 50 °C and isolated by PTLC, AcOEt/Hex (1:4) (0.086 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.94–2.01 (m, 2H, $NCH_2CH_2CH_2$), δ 2.81–2.86 (m, 2H, $NCH_2CH_2CH_2$), δ 3.31 (t, *J*=5.6, 2H, $NCH_2CH_2CH_2$), δ 3.88–4.00 (m, 2H, $NCHCH_2OH$), δ 4.71–4.73 (m, 1H, $NCHCH_2OH$), 6.22–6.27 (m, 1H, *CH*CHPh), 6.58 (dd, *J*=16.2, *J*=5.8, 1H, CH*CH*Ph), 6.70–7.34 (m, 9H, Aryl); ^{13}C NMR (125 MHz, $CDCl_3$): 23.50 ($NCH_2CH_2CH_2$), 28.21 ($NCH_2CH_2CH_2$), 42.63 ($NCH_2CH_2CH_2$), 60.96 ($NCHCH_2OH$), 61.79 ($NCHCH_2OH$), 112.40, 117.22 (*Ar*), 124.31 (*C*HCHPh), 124.81, 126.41, 127.18, 127.85, 128.63, 129.52, 132.79 (*Ar*), 136.52 (CH*C*HPh), 145.76 (*Ar*). MS (EI): *m*/*z*=279, 248, 170, 91. HMRS (EI): *m*/*z* calcd [M+1H] 280.1701, found [M+1H] 280.1697.

Compound **15** was obtained in 74% after 48 h at 50 °C and isolated by PTLC, AcOEt/Hex (1:4) (0.086 g); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.83–1.87 (m, 2H, $NCH_2CH_2CH_2$), δ 2.81 (t, *J*=6.3, 2H, $NCH_2CH_2CH_2$), δ 3.13–3.16 (m, 1H, $NCH_2CH_2CH_2$), δ 3.27–3.32 (m, 1H, $NCH_2CH_2CH_2$), δ 3.83 (s, 3H, OCH_3), δ 4.13 (d, *J*=7.8, 2H, $NCHCH_2OH$), δ 5.15 (t, *J*=7.3, 1H, $NCHCH_2OH$), 6.69 (t, *J*=7.3, 1H, *Ar*), 6.89–7.24 (m, 7H, *Ar*); ^{13}C NMR (125 MHz, $CDCl_3$): 22.33 ($NCH_2CH_2CH_2$), 28.46 ($NCH_2CH_2CH_2$), 42.83 ($NCH_2CH_2CH_2$), 55.29 (OCH_3), 61.42 ($NCHCH_2OH$), 61.78 ($NCHCH_2OH$), 111.91, 114.05, 116.58, 123.57, 127.20, 128.48, 129.04, 129.51, 129.70, 130.07, 146.14, 158.89 (*Ar*). MS (EI): *m*/*z*=281, 252, 161, 132, 121. HMRS (EI): *m*/*z* calcd [M+1H] 284.1651, found [M+1H] 284.1656.

4.6. Experimental procedure for the Petasis-Borono-Mannich reactions with glyoxal and amino alcohols

A round bottom flask equipped with a magnetic stirrer was charged with boronic acid (1.0 equiv) distilled water (2.0 mL) and glyoxal 40% aqueous solution (1 equiv). To this suspension was added the amino alcohol (0.41 mmol) and mixture stirred at room temperature for 24 or 48 h. The reaction products were extracted from the reaction media with ethyl ether extraction (3×3 mL) and after the evaporation of the solvent under reduced pressure, the products were obtained with no need of further purification. Product **16** was obtained with a diasterioisomeric ratio 1:0.3 with the same spectral characterization as previously described in Ref. 14.

Compound **17** was obtained in 93% and a 1:0.2 *trans*:*cis* diastereoisomeric ratio after 48 h at room temperature (0.109 g); *trans* diasterioisomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H, CH_3), 2.74 (d, *J*=11.8, 1H, NCH_2CH_2O), 2.95 (d, *J*=7.6, 1H, NCH_2CH_2O), 3.14 (d, *J*=7.1, 1H, NCHC*H*O), 3.77–3.95 (m, 4H, NCH_2CH_2O, NCH_2Ph), 4.77 (d, *J*=7.2, 1H, NC*H*CHO), 7.24–7.48 (m, 9H, *Ph*); ^{13}C NMR (125 MHz, $CDCl_3$): 21.23 (CH_3), 50.56 (NCH_2CH_2O), 58.76 (NCH_2CH_2O), 64.49 (NCH_2Ph), 72.58 (N*C*HCHO), 97.83 (N*C*HCHO), 127.03, 128.26, 128.31, 128.91, 129.37 (Ar), 135.84, 137.61, 138.55 (Ar, quaternary); Relevant signals for the *cis* diasterioisomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.03 (br s, 1H, NC*H*CHOH). MS (EI): *m*/*z*=265, 236, 208, 192, 118, 91. HMRS (EI): *m*/*z* calcd [M+1H] 284.1651, found [M+1H] 284.1651.

Compound **18** was obtained in 94% and a 1:0.2 *trans*:*cis* diastereoisomeric ratio after 24 h at room temperature (0.116 g); *trans* diasterioisomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.72 (d, *J*=16.0, 2H, NCH_2CH_2O), δ 2.94 (d, J=17.6, 2H, NCH_2CH_2O), 3.09 (d, *J*=9.6, 1H, NCHC*H*OH), 3.74–4.08 (m, overlapped signals, 5H, NCH_2Ph, OCH_3), 4.72 (d, *J*=9.6, NC*H*CHOH), 6.96 (d, *J*=11.2, 2H, *Ph*), 7.26–7.48 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 50.42 (NCH_2CH_2O), 55.19 (OCH_3), 58.54 (NCH_2CH_2O), 64.05 (NCH_2Ph), 72.00 (NCH*C*HOH), 97.64 (N*C*HCHOH), 113.96 (*Ar*), 127.27, 128.29, 128.54, 128.71, 128.93, 128.96, 129.87 (Ar), 135.50, 138.26, 159.23 (*Ar*, quaternary); Relevant signals for the *cis* diasterioisomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.31 (br s, 1H, NC*H*CHOH); ^{13}C NMR (125 MHz, $CDCl_3$): δ 70.06 (NCH*C*HOH), 93.46 (N*C*HCHOH). MS (EI): *m*/*z*=252, 149, 135, 91. [M+1H] 300.1600, found [M+1H] 300.1592.

Compound **19** was obtained in 89% and a 1:0.9 diastereoisomeric ratio after 48 h at room temperature (0.109 g); *trans* diasterioisomer: ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30–2.39 (m, 2H, NCH_2CH_2O), δ 2.75–2.85 (m, 2H, NCH_2CH_2O), δ 3.04–3.41 (m, 1H, NCHC*H*OH), 3.88–4.13 (m, 2H, NCH_2Ph), 4.84–4.85 (m, 1H, NC*H*CHOH), 4.98 (m, 1H, NC*H*CHOH), 6.31–6.48 (m, 1H, NCHC*H*CHPh), 6.69–6.71 (m, 1H, NCHCHC*H*Ph), 7.28–7.53 (m, 10H, *Ph*); ^{13}C NMR (125 MHz, $CDCl_3$): δ 48.27, 50.02 (NCH_2CH_2O), 59.04, 60.00 (NCH_2Ph), 60.64, 60.74 (NCH_2CH_2O), 67.81, 68.84 (NCH*C*HOH), 93.76, 94.52 (N*C*HCHOH), 126.50, 126.55, 127.19, 128.00, 128.29, 128.34, 128.57, 128.96, 129.02, 135.71, 135.94, 136.14, 136.35, 137.71 (NCHCHCH*Ph*, *Ph*). MS (EI): *m*/*z*=277, 249, 204, 158, 115, 91. [M+1H] 295.1651, found [M+1H] 296.1646.

4.7. Experimental procedure for the reactions for the preparation of boron heterocycles

A round bottom flask equipped with a magnetic stirrer was charged with amino acid (2.0 equiv), aldehyde (1.5 equiv) and distilled water (2.0 mL). This suspension was stirred at 90 °C for 1 h, after which the boronic acid (0.41 mmol) was added. The mixture was stirred at 90 °C for 20 h and the product was filtered and washed with water, hexane and was recovered with dichloromethane.

Compound **20** was obtained in 86% after 20 h at 90 °C (0.125 g); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 2.71 (t, 1H, J_H: 13.2, –CHC*H*$_2$Ph), 3.41 (dd, 1H, J_H: 3.6, 14.0, –CHC*H*$_2$Ph), 4.34 (dd, 1H, J_H: 3.6, 12.4, –NC*H*COCH$_2$–), 6.87–6.95 (m, 3H), 7.02–7.05 (m, 1H), 7.11–7.16 (m, 2H), 7.27–7.34 (m, 6H), 7.43–7.55 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 37.73 (–CH*C*H$_2$Ph), 66.92 (–NCHCOCH$_2$–), 117.57, 120.19, 120.32, 127.79, 127.90, 128.58, 129.16, 129.21, 130.55, 131.45, 135.11, 139.04 (Ph), 159.95 (Ar*C*HN–), 160.43(Ar, quaternary), 170.22 (–CH*C*OO–). HMRS (EI): *m*/*z* calcd [M+1H] 356.1458, found [M+1H] 356.1466.

Compound **21** was obtained in 96% after 20 h at 90 °C (0.142 g); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 2.76 (t, 1H, J_H: 13.2, –CHC*H*$_2$Ph), 3.49 (dd, 1H, J_H: 3.6, 14.0, –CHC*H*$_2$Ph), 4.33 (dd, 1H, J_H: 3.6, 12.4, –NC*H*COCH$_2$–), 6.82–7.59 (m, 13H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 38.22 (–CH*C*H$_2$Ph), 66.45(–NCHCOCH$_2$–), 117.66, 120.39, 120.43, 125.83, 127.88, 128.02, 129.20, 129.32, 129.71, 131.35 (Aryl), 135.00 (Ar, quaternary), 138.97 (Aryl), 159.63 (Ar*C*HN–), 170.38 (–CH*C*OO–). HMRS (EI): *m*/*z* calcd [M+1H] 362.1022, found [M+1H] 362.1035.

Compound **22** was obtained in 78% after 20 h at 90 °C (0.125 g), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 2.73 (t, 1H, J_H: 13.0, –CHC*H*$_2$Ph), 3.44 (dd, 1H, J_H: 3.6, 14.0, –CHC*H*$_2$Ph), 3.85 (s, 3H, –Ar*OCH*$_3$). 4.31 (dd, 1H, J_H: 3.4, 12.2, –NC*H*COCH$_2$–), 6.47–6.52 (m, 2H), 6.95–7.04 (m, 5H), 7.28–7.40 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 38.22 (–CH*C*H$_2$Ph), 55.89 (–Ar*O*C*H*$_3$), 66.02 (–NCHCOCH$_2$–), 102.72, 110.19, 111.50, 125.71, 127.70, 127.75, 129.11, 129.34, 129.80, 132.82, 135.32 (Aryl), 158.24 (Ar*C*HN–), 162.34 (Ar, quaternary), 168.70 (Ar, quaternary), 171.05 (–CH*C*OO–). HMRS (EI): *m*/*z* calcd [M+1H] 392.1128, found [M+1H] 392.1138.

Compound **23** was obtained in 88% after 20 h at 90 °C (0.133 g), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 2.69 (t, 1H, J_H: 13.0, –CHC*H*$_2$Ph),

3.39 (dd, 1H, J_H: 3.6, 14.0, –CHCH_2Ph), 3.84 (s, 3H, –ArOCH_3), 4.31 (dd, 1H, J_H: 3.2, 12.4, –NC*H*COCH$_2$–), 6.45–6.50 (m, 2H), 6.97–7.09 (m, 4H), 7.28–7.48 (m, 6H), 7.49–7.50 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 37.78 (–CHCH_2Ph), 55.87 (–ArOCH_3), 66.54 (–NCHCOCH_2–), 102.62, 110.12, 111.47, 127.65, 127.88, 128.42, 129.10, 129.24, 130.57, 132.88, 135.47 (Aryl), 158.98 (ArCHN–), 162.65 (Ar, quaternary), 168.80 (Ar, quaternary), 170.91 (–CHCOO–). HMRS (EI): *m*/*z* calcd [M+1H] 386.1564, found [M+1H] 386.1571.

Compound **24** was obtained in 63% after 20 h at 90 °C (0.095 g), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 2.35 (s, 3H, –ArCH_3), 2.70 (t, 1H, J_H: 12.0, –CHCH_2Ph), 3.41 (dd, 1H, J_H: 2.0, 14.0, –CHCH_2Ph), 4.34 (dd, 1H, J_H: 4.0, 12.0, –CHCH_2Ph), 6.73 (d, 1H, J_H: 8.0 Hz), 6.85 (s, 1H), 6.97–7.03 (m, 3H), 7.12 (s, 1H), 7.28–7.38 (m, 6H), 7.45–7.47 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 22.50 (–ArCH_3), 37.75(–CHCH_2Ph), 66.75 (–NCHCOCH_2–), 115.41, 120.38, 121.74, 127.74, 127.88, 128.48, 129.14, 129.24, 130.58, 131.23, 135.28 (Aryl), 151.41 (Ar, quaternary), 159.95 (Ar, quaternary), 159.99 (ArCHN–), 170.58 (–CHCOO–). HMRS (EI): *m*/*z* calcd [M+1H] 370.1614, found [M+1H] 370.1615.

Compound **25** was obtained in 80% after 20 h at 90 °C (0.122 g), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 2.68 (t, 1H, J_H: 13.2, –CHCH_2Ph), 3.45 (dd, 1H, J_H: 3.4, 13.8, –CHCH_2Ph), 4.36 (dd, 1H, J_H: 3.2, 12.4, –NC*H*COCH$_2$–), 6.80–7.71 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 37.79 (–CHCH_2Ph), 66.87 (–NCHCOCH_2–), 114.74, 114.94, 117.47, 120.32, 120.38, 127.91, 129.16, 129.24, 131.53,132.34, 132.41, 134.97, 139.23 (Aryl), 159.84 (Ar, quaternary), 160.56 (Ar, quaternary), 170.13 (–CHCOO–). HMRS (EI): *m*/*z* calcd [M+1H] 374.1364, found [M+1H] 374.1367.

Compound **26** was obtained in 31% after 20 h at 90 °C (0.048 g), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 2.72 (t, 1H, J_H: 13.0, –CHCH_2Ph), 3.42 (dd, 1H, J_H: 3.2, 13.6, –CHCH_2Ph), 3.81 (s, 3H, –ArOCH_3), 4.34 (dd, 1H, J_H: 3.2, 12.4, –NC*H*COCH$_2$–), 6.80–7.35 (m, 14H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 37.87 (–CHCH_2Ph), 55.04 (–ArOCH_3), 66.82 (–NCHCOCH$_2$–), 113.42, 117.55, 120.15, 120.27, 127.80, 129.16, 129.28, 131.48, 131.96, 135.14, 138,92 (Ph), 159.94 (ArCHN–), 159.98, 160.22 (Ar, quaternary), 170.42 (–CHCOO–). HMRS (EI): *m*/*z* calcd [M+1H] 386.1564, found [M+1H] 386.1556.

Compound **27** was obtained in 83% after 20 h at 90 °C (0.126 g), ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C, TMS): δ 2.34 (s, 3H, –ArCH_3), 2.73 (t, 1H, J_H: 12.0, –CHCH_2Ph), 3.42 (dd, 1H, J_H: 4.0, 14.0, –CHCH_2Ph), 4.35 (dd, 1H, J_H: 4.0, 12.0, –NC*H*COCH$_2$–), 6.91 (t, 1H, J_H: 8.0), 6.99–7.04 (m, 3H), 7.12–7.16 (m, 4H), 7.28–7.38 (m, 5H), 7.50–7.56 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C, TMS): δ 21.44 (–ArCH_3), 37.78 (–CHCH_2Ph), 66.90 (–NCHCOCH_2–), 117.62, 120.14, 120.32, 127.80, 128.67, 129.16, 129.28, 130.61, 131.46, 135.21, 138.19, 138.94 (Aryl), 159.94 (Ar, quaternary), 160.35 (ArCHN–), 170.35 (–CHCOO–). HMRS (EI): *m*/*z* calcd [M+1H] 370.1614, found [M+1H] 370.1620.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2010.01.084.

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