Boronic Acids and Esters in the Petasis-Borono Mannich Multicomponent Reaction

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1. Introduction

Organoboron reagents have been widely explored in organic synthesis as a suitable tool for the formation of new C−C bonds. Such compounds are captivating not only because of their ready availability but also, and most importantly, because of their stability toward air and water, as well as the low toxicity and tolerance to several functional groups. These reagents have gained a special notoriety because of their employment in the Suzuki−Miyaura reaction, but they are also used in other reactions, such as allylboration, rhodium-catalyzed additions to carbonyl compounds and alkenes, copper(II) catalyzed heteroatom couplings, and multicomponent Petasis-borono Mannich reaction (PBM).[1] Multicomponent reactions (MCR) are one of the best tools available for the preparation of large libraries of compounds, once the simple modification of a substituent can lead to a diverse set of new molecules.[2] The incorporation of most reactants' atoms in the final product, the simultaneously addition of all reactants and easy purification procedures have made these reactions to be worth of attention by the organic chemists community. MCR can be divided in three types according to the number of reversible steps, as pointed by Dömling and Ugi.[3] Hence, type I MCR are characterized by multiple equilibria among all reactants and intermediates, type II have one irreversible step leading to the product and type III MCR have only irreversible steps and are usually related to cascade or domino reactions (Scheme 1).

Type II reactions, which comprise one irreversible step, are the most desirable in the context of organic synthesis. The Ugi, Passerini and Biginelli reactions are some examples of this type.[2,3] Through the employment of boronic acids as reactants in processes involving the adducts of amines with aldehydes, Petasis and co-workers developed a new versatile type II MCR reaction, where the irreversible step is the formation of a new C−C bond.

The present review, which is intended to cover and update the previous reviews on this topic, by Batey[1] and Petasis,[2] will be organized according to the aldehyde framework, divided into preparation of α-amino acids (starting from glyoxylic acid and derivatives), preparation of α-hydroxyl amines and 2-hydroxyl morpholines (starting from glycolaldehyde and derivatives), preparation of alkylaminophenols (starting from salicylaldehyde and derivatives), and the use of miscellaneous aldehydes. A section comprising the asymmetric version of this reaction will be presented, and finally, a section concerning the reports of reactions related with PBM transformation will be presented. The preparation of 2*H*-chromenes will also be focused on this last part.

2. Mechanistic Considerations

After the pioneer work by Petasis and co-workers on the discovery of the borono-Mannich reaction, the first mechanistic proposal was advanced. According to Petasis, the reaction consists in the formation of an imine or an iminium **4** after condensation of an aldehyde **2** with a primary or secondary amine **1**, respectively. This C−N double bond further reacts with the boronic acid **3** to yield the secondary or tertiary amine **6**. The first report on this reaction consisted in the preparation of tertiary allylamines starting from paraformaldehyde and was applied to the preparation of naftifine in 82% yield in dioxane at 90 °C.[4] Despite the inertness of the boronic acid towards the aldehyde functional group, the reaction between this and the iminium or the imine (Scheme 2) is extremely facilitated by the presence of an adjacent OH functional group that activates the boronic acid via the formation of a tetrahedron boronate salt **5**.[1,5] This quaternary boron salt **5** has been referred to as the "ate complex", which is able to transfer the boron substituent to the imine or iminium moiety. Although most of the reports on this reaction display the use of aldehydes containing a hydroxyl or carboxyl group suitable for the ate complex

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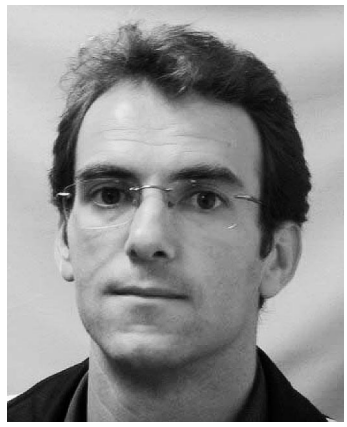


Nuno R. Candeias was born in Lisbon (Portugal) in 1981. He graduated in Applied Chemistry from New University of Lisbon (2004) and started his PhD in chemistry titled "Intramolecular C−H Insertion of α-Diazoacetamides in Water" under the supervision of Professor Carlos A. M. Afonso at Technical University of Lisbon (2005−2008). He worked for 6 months as an Invited Assistant Professor at Cooperativa de Ensino Egas Moniz. Currently, he is working as a postdoctoral research fellow at the Pharmacy Faculty of the Lisbon University under the supervision of Dr. Pedro M. P. Góis and at Scripps Research Institute under the supervision of Professor Carlos F. Barbas III. In 2010, he received an Honor Mention in the Portuguese Young Chemists Award. His current interests are the development of synthetic methodologies and sustainable chemistry, particularly the use of multicomponent reactions as a synthetic utility and organocatalysis.

Francesco Montalbano was born in Palermo, Italy, in 1981. He graduated in Chemistry and Pharmaceutical Technology from Pharmacy University of Palermo (2008) and started his PhD in chemistry under the supervision of Dr. Pedro Gois and Professor Rui Moreira at Pharmacy Faculty of Lisbon University. His current interests are the development of multicomponent reactions, boron chemistry and the use of water as a reaction media.

formation, Petasis reported the use of paraformaldehyde, lacking such type of substituents.[4] The Petasis-borono Mannich multicomponent reaction has been evaluated in the preparation of several small organic molecules with distinct functional groups such as functionalized α-amino acids,[6] α-hydroxyl amines, 2-hydroxyl morpholines, alkylaminophenols, and 2*H*-chromenes.

Several studies based on this mechanism and focusing different aldehydes have been reported. Density Functional Theory (DFT) studies have been used as a valuable tool in the mechanistic elucidation, and the most relevant results will be presented next.

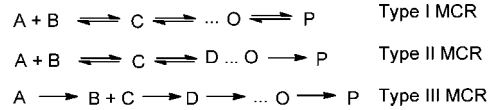
Starting from the use of glyoxylic acid as the aldehyde component, Gois et al. have recently performed a DFT study of this reaction at the PBE1PBE/6-31G(d,p) level of theory, based on the Petasis' proposal presented in Scheme 2.

Pedro M. S. D. Cal was born in Lisbon, Portugal, in 1985. He is a master's student of Pharmaceutical Sciences from University of Lisbon. He works in the medicinal chemistry laboratory under the supervision of Dr. Pedro M. P. Gois at Pharmacy Faculty of the University of Lisbon. His current interests are the development of synthetic methodologies and chemical manipulation of biomolecules.

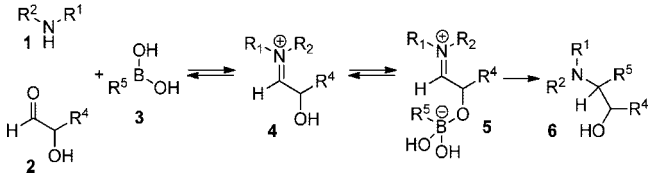
Pedro M. P. Gois was born in Lisbon, Portugal, in 1977. He studied chemistry at the New University of Lisbon from where he also received in 2005 his PhD in organic chemistry under the supervision of Prof. Dr. Carlos Afonso. From May 2005 to May 2008 he worked as a postdoctoral research fellow at the University of Sussex with Prof. Dr. F. Geoffrey N. Cloke FRS, at the University College of London with Prof. Dr. Stephen Caddick and at the Instituto Superior Técnico (Technical University of Lisbon) with Prof. Dr. Carlos Afonso. In 2008, he joined the Pharmacy Faculty of the Lisbon University (iMed.UL—Research Institute for Medicines and Pharmaceutical Sciences) as an assistant research fellow. His research encompasses the development of new methodologies mediated by metal and/or organo-catalysts, the study of multicomponent reactions and the use of water as a reaction media for organic synthesis. In 2001, he received a school merit award in chemistry from the Faculty of Sciences and Technology of the New University of Lisbon and in October 2008 he received an Honor Mention in the Young Research Award of the Technical University of Lisbon (in the area of Environmental Eng., Chemical Eng., Material Sciences, Nanomaterial Sciences and Nanotechology).

Starting the study from ate complex formation **A** resulting from the iminium and boronic acid, an energy barrier for the boronic acid substituent migration of 10 kcal/mol and a five-membered transition state **B** (Scheme 3, energies in kcal/mol and bond distances in Å) were disclosed.[7] Experimental evidence concerning the formation of a quaternary boron salt was reported by Hansen and co-workers, who observed a

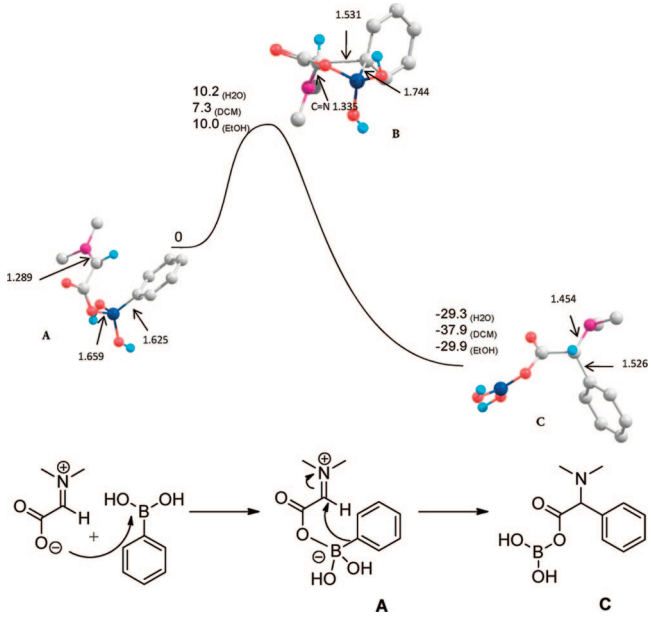
Scheme 1



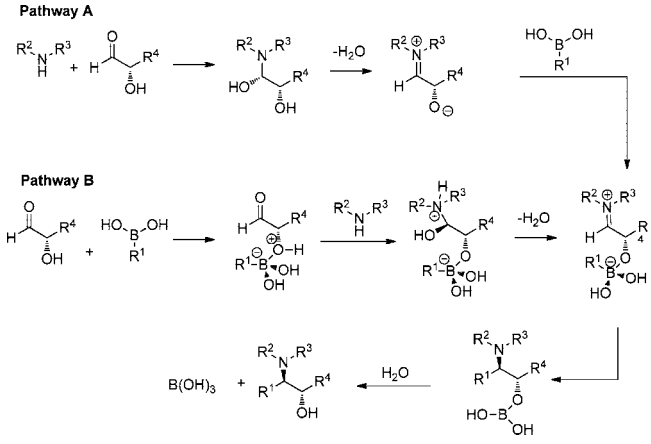
Scheme 2



Scheme 3



Scheme 4

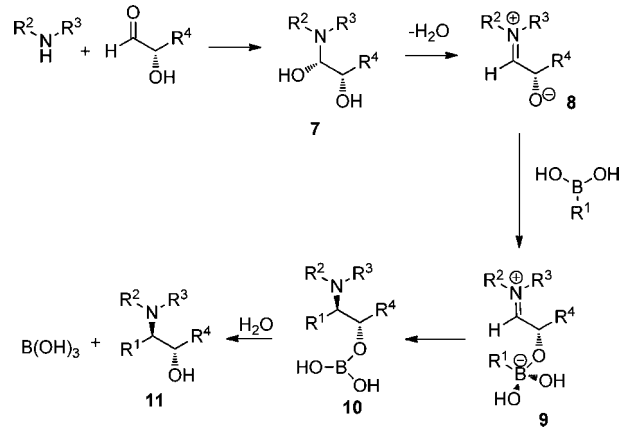


^{11}B NMR upfield chemical shift of the boron species after addition of glyoxylic acid to a solution of phenylboronic acid, even before the addition of the amine.[8]

In the case of α-hydroxy aldehydes, two different mechanistic pathways were proposed, although only recently DFT calculations were performed to support one of the pathways. Tao and Li[9] compared these mechanisms pointed by Petasis,[10] Schlienger,[8] and Voisin.[11] While Petasis indicated the formation of the ate complex after dehydration and concomitant formation of the iminium (pathway A, Scheme 4), Schlienger and Voisin suggested this formation starting from the aldehyde itself, and iminium's generation was the second step (pathway B, Scheme 4).

Despite inherent difficulties in the use of continuum solvation models, which do not take into account plausible hydrogen bonds between the solvent and the species involved

Scheme 5



in the reaction, the authors considered ethanol as solvents. The crucial importance of the solvent nature on this reaction was displayed on this computational study and experimentally demonstrated using salicylaldehyde (*vide infra*).[12] The comparison of the energies for transitions states of both mechanisms, pointed that pathway A was the most reliable. Furthermore, it was observed that the coordination of the aldehyde to the boronic acid would only be possible by a dehydration mechanism, without the formation of a boron tetravalent species.

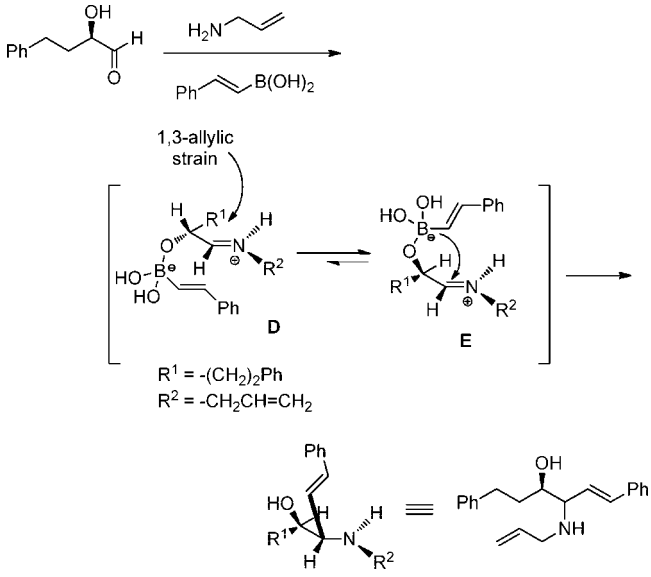
The pathway previously described by Petasis was indicated as the most favorable but with some slight changes. Instead of the prior formation of the iminium and consequent complexation of the alcohol to the boronic acid, as reported by Petasis and supported by DFT calculation for the salicylaldehyde and glyoxylic acid cases,[7] Tao et al. found the conversion of carbinolamine intermediate **7** into a possible zwitterion species **8** by dehydration via a five membered ring transition state (Scheme 5).[9] This zwitterion species was presented as an epoxide species from geometry optimization.

For the whole reaction, the rate-determining step was proposed to be C−C bond formation, with closely related transition states by both studies, with different hybrid functional (PBE1PBE/6-31G(d,p)[7] and B3LYP/6-31G(d,p)[9]). Hence, the PBM reaction mechanism for the glycolaldehyde, according to the authors, consists of (Scheme 5) (i) nucleophilic addition of the amine to the aldehyde to form the carbinolamine **7**, (ii) dehydration of the carbinolamine to produce an iminium intermediate **8**, (iii) coordination of the iminium species by the styrylboronic acid to generate the tetra-coordinated boronate intermediate **9**, (iv) C−C bond formation by the intramolecular transfer of the styryl group, and (v) hydrolysis of the resulting intermediate **10** to give the final products.[9]

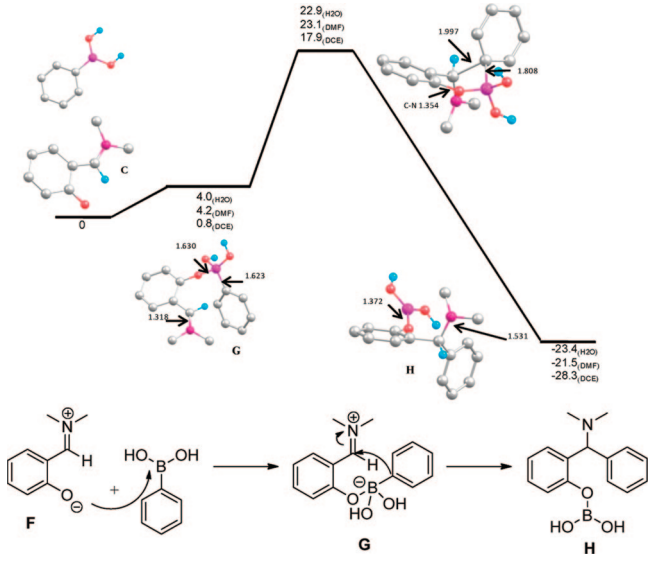
This transformation is highly stereocontrolled as reported by Petasis and Zavialov in their pioneer work on the use of α-hydroxy aldehydes. The exclusive formation of the anti-*β*-amino alcohols diastereomer was observed starting from racemic α-hydroxy aldehydes, while a single enantiomer was formed from enantiomerically pure analogues.[13] Pyne and co-workers, suggested that, for the case of vinyl boronic acids, the diastereocontrol arises from the reactive conformation **E** of the ate complex, where the 1,3-allylic strain is minimized (Scheme 6).[5,14]

Considering the use of salicylaldehyde, a generally accepted mechanism is supported on the formation of a boron tetrahedron ate complex, as assumed for other aldehydes.

Scheme 6



Scheme 7



Such mechanism was evaluated by DFT calculations and a concordance between the experimental results and the theoretical calculations was obtained. After the iminium formation and complexation of the phenyl boronic acid to yield an ate complex **G**, the aryl migration toward the electrophilic carbon was determined to be sensitive to the solvent nature, being 5 kcal/mol smaller for dichloroethane than for water (Scheme 7). The introduction of a 4-methoxy substituent on the phenyl boronic acid was found to decrease the transition state energy barrier, increasing the migrating ability of the aryl substituent.[7,12]

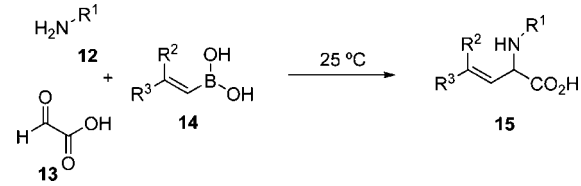
A complete study of three different aldehydes demonstrated the following order of reactivity: glycolaldehyde > glyoxylic acid > salicylaldehyde.[7] In addition to the choice of the aldehyde, the reaction success is also dependent on the nature of the other two components used. Despite the higher reactivity of secondary amines toward PBM reaction, bulky primary amines were reported to be a good choice as well. Regarding the nature of the boronic acids employed in the reaction, vinyl boronic acids are in general more reactive than their aryl counterparts. Such fact is probably related to the higher migration ability of that moiety, once the boronic substituent migration seems to be the higher energy demanding step.

3. Glyoxylic Acid

3.1. β,γ-Unsaturated α-Amino Acids

Vinyl glycine analogues were successfully prepared by Petasis and Zavialov through the condensation of an organoboronic acid or boronate with an amine and glyoxylic acid. A variety of solvents, such as ethanol, toluene, and dichloromethane were explored, and the desired β,γ-unsaturated α-amino acids were obtained in good yields by simple stirring of the three components at 25−50 °C over 12−48 h. The methodology was applied to primary and secondary amines, and bulky amines were also reported to react under these conditions. To prepare free amino acids, trityl amine (Table 1, entry 3) and bis(4-methoxyphenyl)methylamine (Table 1, entry 5) were used anticipating a suitable amine deprotecting procedure by acidic hydrolysis. The use of morpholine as the amine component required the use of ethanol and higher temperature (50 °C) to induce the condensation with 4-methylstyrylboronic acid with a 76%

Table 1



entry	R^1	R^2	R^3	solvent	product	yield (%)
1	$PhCH_2$	H	Ph	EtOH	**15a**	87
2	Ph_2CH	H	Ph	toluene	**15b**	94
3	Ph_3C	H	Ph	EtOH	**15c**	54
4	$HOCH_2CH_2$	H	Ph	EtOH	**15d**	82
5	$(4\text{-}MeOC_6H_4)_2CH$	H	Ph	toluene	**15e**	92
6	$4\text{-}MeOC_6H_4$	H	Ph	EtOH	**15f**	94
7	adamantyl	H	Ph	CH_2Cl_2	**15g**	96
8	Ph_2CH	Br	Ph	toluene	**15h**	87
9	Ph_2CH	H	Br	CH_2Cl_2	**15i**	80

Scheme 8

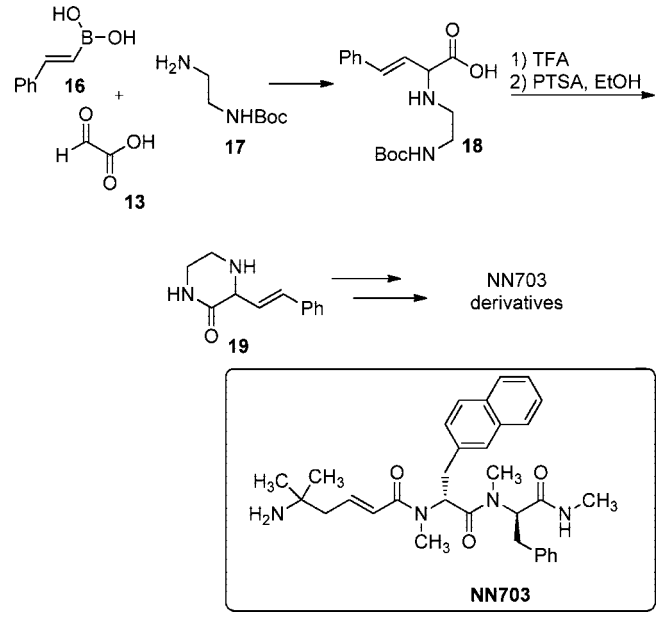
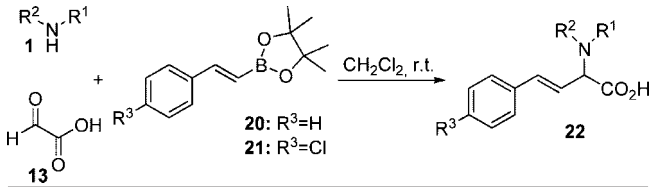


Table 2



entry	R^1	R^2	R^3	product	yield (%)
1	H	$PhCH_2$	H	**22a**	not detected
2	H	$PhCH_2$	Cl	**22b**	not detected
3	H	Ph_2CH	H	**22c**	not detected
4	H	Ph_2CH	Cl	**22d**	not detected
5	H	$CH_3CH_2CH_2CH_2CH_2$	H	**22e**	not detected
6	H	$CH_3CH_2CH_2CH_2CH_2$	Cl	**22f**	not detected
7	*i*-Pr	*i*-Pr	H	**22g**	75
8	*i*-Pr	*i*-Pr	Cl	**22h**	70
9	morpholine		H	**22i**	82
10	morpholine		Cl	**22j**	71
11	pyrrolidine		H	**22k**	75
12	pyrrolidine		Cl	**22l**	70

yield.[15] Gois et al. recently demonstrated that this reaction can also be efficiently performed in water, without loss of selectivity, although higher temperatures are needed for the success of the reaction (50 or 80 °C).[7]

To obtain constrained versions of orally active growth hormone secretagogue NN703, particularly, *N*-terminal, central or *C*-terminal constraints, Hansen and co-workers adopted the PBM reaction as a crucial step in the preparation of 3-alkylated piperazones. The vinyl amino acid was prepared through the use of Boc monoprotected diamine which after deprotection was cyclized in the presence of a catalytic amount of *para*-toluenesulfonic acid (PTSA) to yield the desired piperazone **19** in 64% yield (Scheme 8).[16]

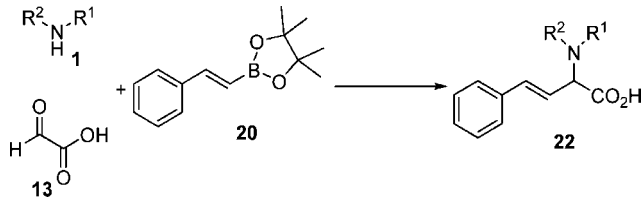
Considering the preparation of β,γ-unsaturated α-amino acids and envisioning the creation of a stereogenic center, boronic esters have been tested as possible components of this reaction. A variety of boronic esters were prepared by simple reaction of the corresponding boronic acid with pinacol in ethyl ether. Taking advantage of their high stability and steric bulkiness, pinacol boronic ester derivatives were combined in the reaction with primary and secondary amines (Table 2). From all the examples reported, several conclusions were drawn. Vinyl boronic esters were determined to be the most reactive when compared with their aryl and thienyl counterparts. An important finding was the absence of reactivity of the primary amines (Table 2, entries 1−6), and the desired amino acids were obtained only when using secondary amines (Table 2, entries 7−12).[17]

Recently, Piettre and co-workers observed that the lack of reactivity of primary amines could be avoided by the use of protic solvents. As a matter of fact, the use of methanol allowed the formation of α-amino acid **22a** in 65% after 24 h at room temperature. Furthermore, the substitution of methanol by hexafluoro-*iso*-propanol (HFIP) shortened the reaction time to 4 h and **22a** was obtained in 85% yield. Hence, these conditions were used on a semiautomated synthesizer generating a small library of α-amino acids, starting from primary amines (Table 3, entries 1−5).[18] Different diastereoisomeric ratios for the two solvents were determined when starting from enantiomerically pure α-methylbenzylamine (entry 4). Secondary amines were also tested in this reaction and the corresponding tertiary amino acids were obtained in better yields when using HFIP as the solvent. In order to obviate the utilization of this expensive solvent, microwave irradiation (MWI) was used to promote the reaction in MeOH. Despite the shorter reaction times (10 min under MWI), the yields remained lower than the ones obtained in HFIP.[18]

3.2. α-Aryl Glycines

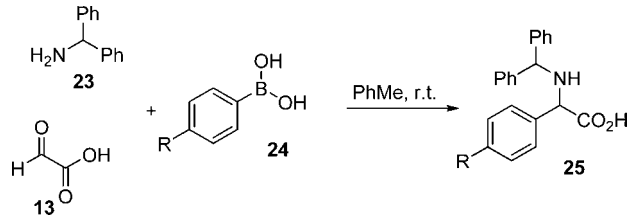
Vinyl boronic acids are among the most reactive boronic acids used in the Petasis-borono Mannich reaction, though these are not the only boronic acids used in this reaction. Aryl boronic acids and heterocyclic derivatives, such as thienyl and pyridyl boronic acids, can also be used as the boron component.

Table 3



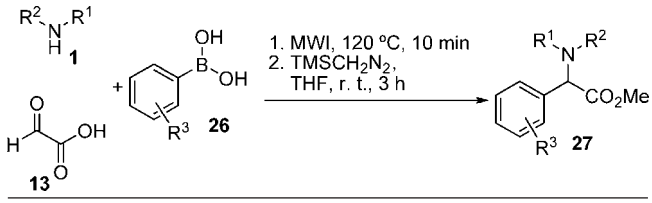
Entry	R^1	R^2	Product	MeOH Conditions	Yield (%)	HFIP Conditions	Yield (%)
1	$PhCH_2$	H	**22a**	r. t.	67	r. t.	85
2	$CH_3CH_2CH_2CH_2$	H	**22m**	r. t.	66	r. t.	77
3	Ph_2CH	H	**22c**	r. t.	64	r. t.	92
4		H	**22n**	r. t.	70 (*de*=33 %)	r. t.	77 (*de*=81 %)
5	C_6H_{11}	H	**22o**	r. t.	60	r. t.	78
6	Piperidine		**22p**	MWI (120°C)	89	r. t.	90
7	Morpholine		**22i**	MWI (120°C)	85	r. t.	97
8	$PhCH_2$	$PhCH_2$	**22q**	MWI (120°C)	67	r. t.	97

Table 4



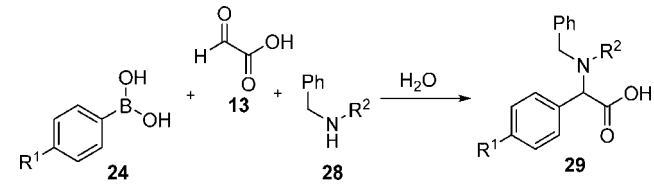
entry	R	product	yield (%)
1	H	**25a**	84
2	F	**25b**	50
3	Br	**25c**	71
4	OMe	**25d**	85
5	CH=CH$_2$	**25e**	90

Table 5



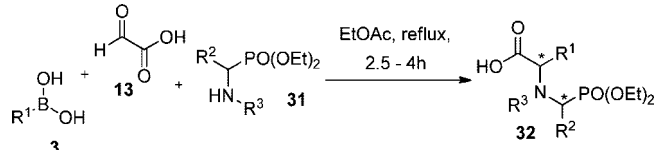
entry	R^1	R^2	R^3	product	conversion (%)	yield (%)
1		morpholine	H	**27a**	63	40
2		morpholine	3-MeO	**27b**	78	42
3		morpholine	4-Br	**27c**	60	35
4		morpholine	4-F	**27d**	53	34
5		morpholine	4-*t*-Bu	**27e**	78	31
6	H	Ph$_2$CH	H	**27f**	50	17
7	CH$_3$CH$_2$	CH$_3$CH$_2$	H	**27g**	54	18
8	PhCH$_2$	PhCH$_2$	H	**27h**	82	83
9	H	4-MeOC$_6$H$_4$	H	**27i**	52	27

Table 6



entry	R^1	R^2	conditions	product	yield (%)
1	H	CH$_2$Ph	50 °C, 24 h	**29a**	86
2	Me	Me	80 °C, 36 h	**29b**	65

Table 7



Entry	R^1	R^2	R^3	Product	Yield	dr
1	Ph	4-MeOC$_6$H$_4$	H	**32a**	75	9:1
2	4-MeOC$_6$H$_4$	4-MeOC$_6$H$_4$	H	**32b**	76	9:1
3	O, O	4-MeOC$_6$H$_4$	H	**32c**	53	9:1
4	S	4-MeOC$_6$H$_4$	H	**32d**	43	9:1
5	Ph	Ph	CH$_2$Ph	**32e**	80	>95:5
6	4-MeOC$_6$H$_4$	Ph	CH$_2$Ph	**32**	95	>95:5
7	O, O	Ph	CH$_2$Ph	**32g**	88	>95:5
8	S	Ph	CH$_2$Ph	**32h**	69	>95:5

Bearing in mind α-arylglycines as agonists and antagonists of the glutamate receptors of the central nervous system,[84] these molecules were prepared by Petasis through the condensation of imines with boronic acids. Bulky primary amines, namely, aminodiphenylmethane **23** and the corresponding bis(*p*-methoxy) derivative, were employed in the three component condensation reaction (Table 4). Concerning the use of aminodiphenylmethane **23**, the desired α-arylglycines were obtained in high yields using boronic acids with different substituents in the aromatic ring.[19] Villalgordo and co-workers employed this protocol in the preparation of pyrimidinyl arylglycines based on subsequent Mitsunobu and Petasis reactions. Secondary and sterically hindered primary amines were used and the desired products were obtained in reasonable to good yields (50−94%), after the esterification of the carboxylic acid.[20] Recently, Tye and co-workers developed a protocol based on a microwave irradiation method for the preparation of α-arylglycines ester derivatives in dichloromethane at 120 °C. The isolated yields of the corresponding ester after column chromatography, however, were only moderate and dependent upon the substituent in the aromatic ring of the boronic acid (Table 5).[21]

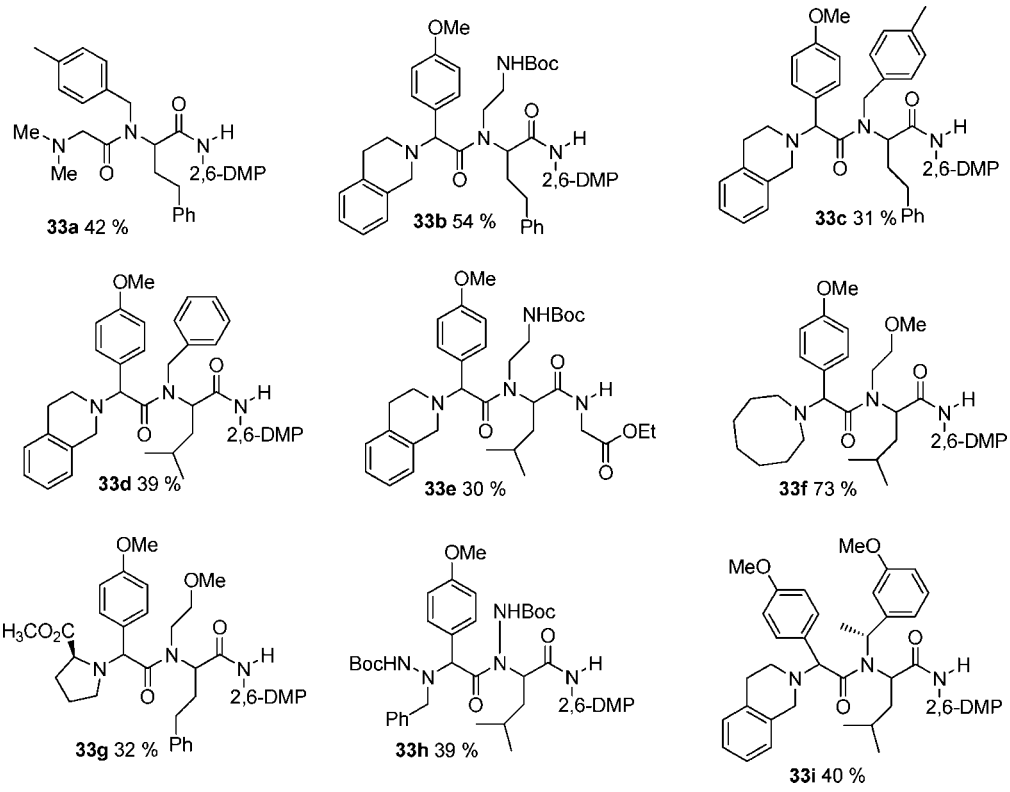
In the course of the evaluation of water as a suitable reaction medium for the PBM reaction, some arylglycines derived from benzyl amines were obtained in good yields after simple precipitation from the reaction mixture (Table 6).[7]

N-phosphomethylglycine derivatives **32** were recently prepared using aminophosphonates **31** as the amine component in the PBM reaction. Electron rich boronic acids were shown to be the most reactive, while the use of phenyl boronic acid led only to trace amounts of the product. The reaction with primary amines was observed to be successful, though when using secondary amines better yields and diastereoselectivities were obtained. The product was achieved in a 75% yield in ethyl acetate (entry 1, Table 7); however, solvents with high dielectric constants such as water, ethanol, acetonitrile and THF were observed to be worst. Sterically hindered tetraethyl (pyrrolidine-2,2-diyl)biphosphonate was also observed to react with some boronic acids yielding the corresponding biphosphonate derivatives in good yields (47−80%).[22]

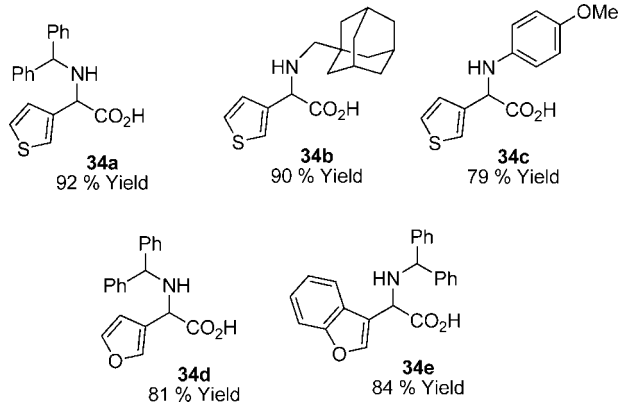
To increase the molecular diversity achieved with a multicomponent reaction, Portlock and co-workers attached the 4-component Ugi reaction to the PBM reaction in a tandem fashion resulting in a six component condensation (Scheme 9).[23] A wide variety of compounds was achieved with this method, although in low yields in most cases.

Analogously to the condensation with phenyl boronic acid derivatives (Table 4), heteroaryl amino acids **34a**−**e** were also obtained in good yields from heteroaryl boronic acids in dichloromethane or ethanol at room temperature (Scheme 10). These boronic acids were reported to be more reactive than their aryl counterparts and were combined with several alkylamines such as 1-adamantanemethyl amine and with aryl amines such as 4-methoxyaniline.[19] Using MWI induced conditions and employing 2-thienyl, 2-benzofuranyl and 1-naphthyl boronic acids in the presence of morpholine, the corresponding amino acids were achieved in good conversions (66−100% conversions).[21]

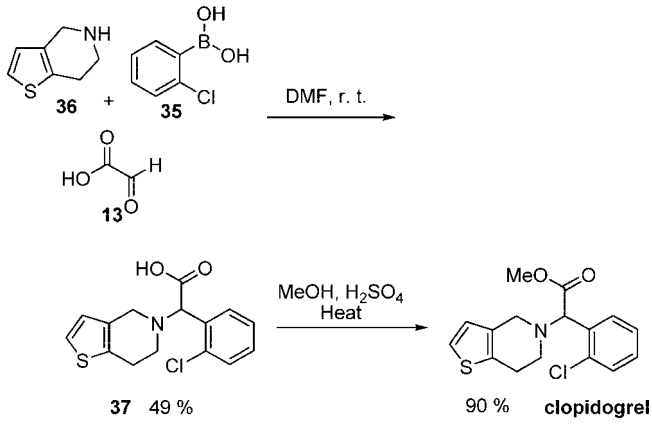
Scheme 9



Scheme 10

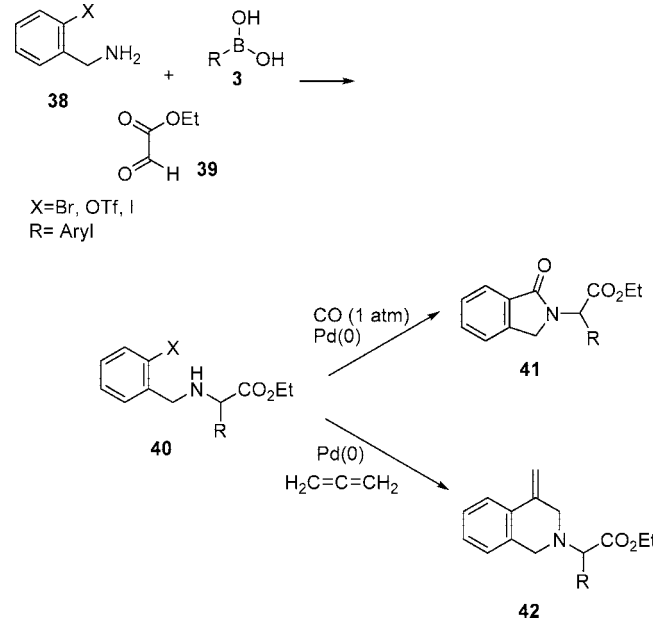


Scheme 11



Kalinski and co-workers studied the use of several MCR as a method for the preparation of antiplatelet agent clopidogrel in the racemic form. Despite the better yields achieved through the use of Ugi 3-component reaction, the PBM reaction allowed the preparation of the precursor in 49% yield. Subsequent esterification afforded the desired product in 44% overall yield (Scheme 11).[24]

Scheme 12



The PBM reaction can be coupled to other reactions to increase the structural diversity of the reaction products. For instance, this reaction was successfully applied to a palladium catalyzed process in a one-pot sequential fashion in order to obtain nonproteinogenic amino acids **41** and **42** (Scheme 12). A particular feature of this process is the use of ethyl glyoxalate **39** instead of the usual glyoxylic acid. The PBM reaction was coupled with palladium catalyzed carbonylation/amination (54−62% yield) and allenylation/amination processes (46−72% yield). The condensation reaction was

Scheme 13

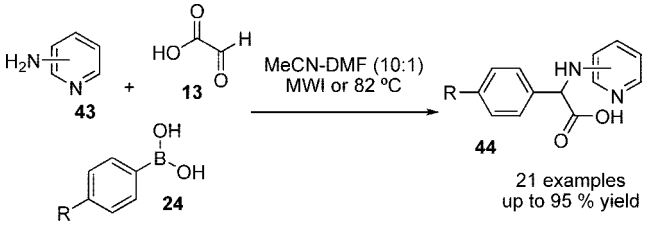
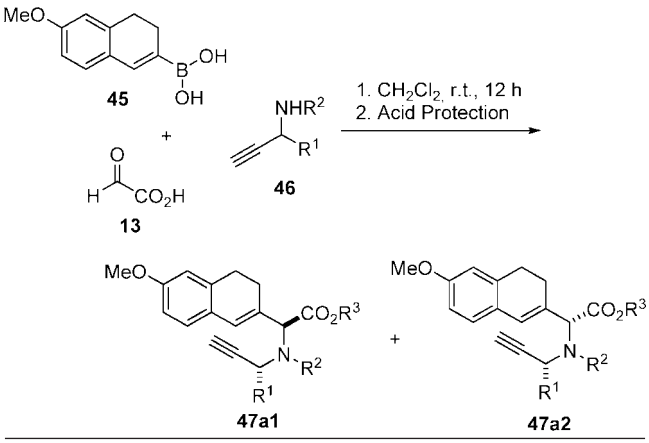


Table 8



entry	R^1	R^2	R^3	product	yield (%)	diasteriomeric ratio
1	H	CH_2Ph	Me	**47aa**	92	–
2	Me	Me	Me	**47ab**	92	1:1
3	Me	Me	Bn	**47ac**	87	1:1

achieved by placing the reaction mixture at 45−50 °C in toluene for 24 h, while harsh conditions were needed for the palladium-catalyzed processes.[25]

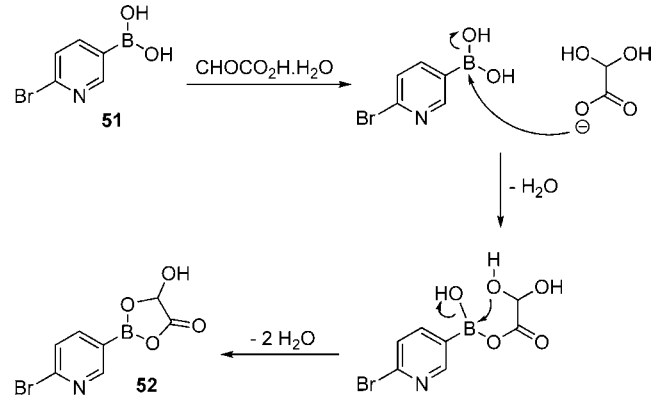
Microwave irradiation methods were applied to the PBM reaction, using electron-poor aromatic amines such as aminopyridines (Scheme 13). This study demonstrated that electron rich boronic acids as well as some heterocyclic boronic acids such as benzothiophene and indole derived can be successfully employed in PBM reaction. Sterically hindered and very electron-poor amines did not react under these conditions. This methodology was compared with classical heating conditions (82 °C), and in most cases, similar results were obtained for both methods, despite the shorter reaction times under MWI (5−10 min vs 0.5−4 h at 82 °C).[26]

To check the viability of intramolecular Pauson−Khand reaction to *N*-propargyl dihydronaphthalenyl amino acid derivatives, Jiang and Xu prepared a series of derivatives through PBM reaction in good yields, although as a 1:1 diastereoselectivity mixture. Propargyl amines **46** were made to react with glyoxylic acid and dihydronaphthalenyl boronic acids **45** in dichloromethane at room temperature, followed by protection of the carboxylic acid functional group (Table 8).[27]

Table 9

entry	R	product	yield (%)
1	4-MeC_6H_4	**50a**	85
2	2-MeC_6H_4	**50b**	73
3	4-$MeOC_6H_4$	**50c**	>95
4	4-BrC_6H_4	**50d**	10
5	1-Naph	**50e**	90
6	*E*-HC═CH(Bu)	**50f**	>95

Scheme 15



Aryl glycine derivatives can be prepared by a resin-to-resin method, which consists in the reaction of an iminium intermediate (formed from the condensation of glyoxylic acid and resins functionalized with a secondary amine) with a supported boronic acid, as illustrated in Scheme 14. The methodology was applied in the preparation of several aryl glycine derivatives, where electron-rich boronic acids were needed to achieve good yields (Table 9).[28]

Boronic acids bearing a strong electron-poor aromatic group such as pyridinyl boronic acid were reported to lack reactivity toward the Petasis reaction, when the standard conditions were tested (dichloromethane, 25 °C). The addition order of the reactants was studied, and the formation of a boronate ester from condensation of the boronic acid with glyoxylic acid in ethyl acetate was detected. This procedure was not observed to be general, since phenyl boronic acid

Scheme 14

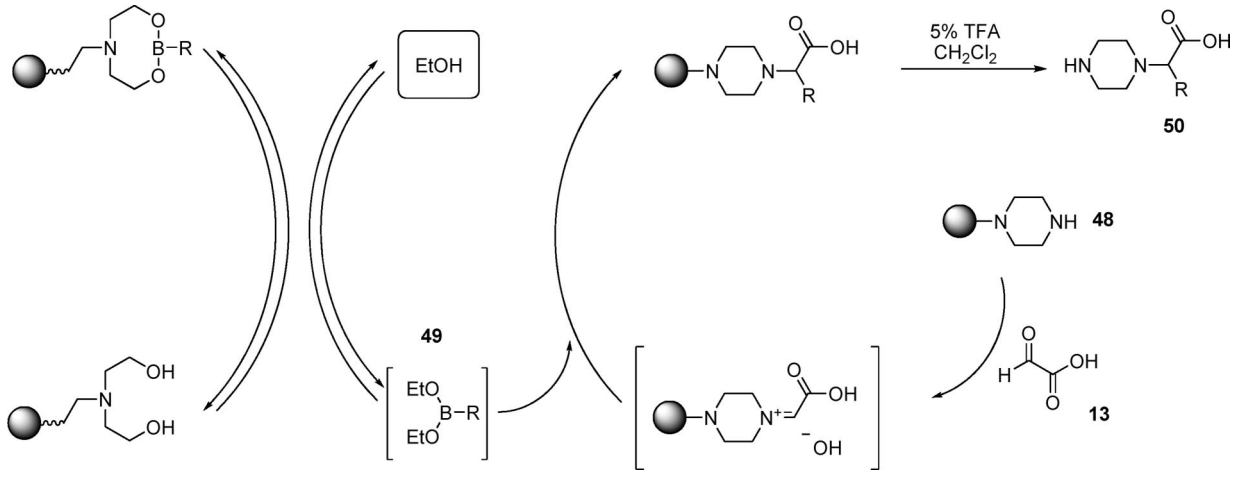
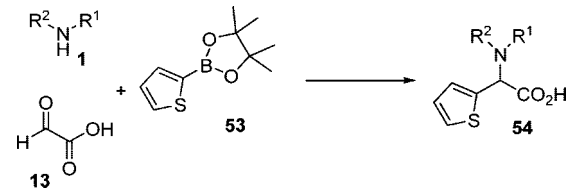
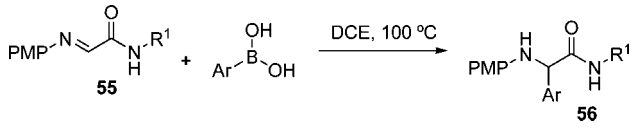


Table 10



				MeOH		HFIP	
entry	R^1	R^2	product	conditions	yield (%)	conditions	yield (%)
1	$PhCH_2$	H	**54a**	rt	40	rt	90
2	$CH_3CH_2CH_2CH_2$	H	**54b**	rt	68	rt	83
3	Ph_2CH	H	**54c**	rt	78	rt	79
4	C_6H_{11}	H	**54d**	rt	35	rt	75
5	piperidine		**54e**	MWI	88	rt	85
6	morpholine		**54f**	MWI	92	rt	89
7	Boc-piperazine		**54g**	MWI	89	rt	86
8	$PhCH_2$	$PhCH_2$	**54h**	MWI	78	rt	85

Table 11



entry	R^1	Ar	product	yield (%)
1	CH_2Ph	Ph	**56a**	65
2	CH_2Ph	4-$MeOC_6H_4$	**56b**	97
3	CH_2Ph	4-ClC_6H_4	**56c**	78
4	CH_2Ph	2-MeC_6H_4	**56d**	56
5	CH_2Ph	2-naphthyl	**56e**	99
6	Me	Ph	**56f**	96
7	Me	4-$MeOC_6H_4$	**56g**	81
8	Me	4-BrC_6H_4	**56h**	82
9	Me	2-naphthyl	**56i**	94
10	Ph	Ph	**56j**	17
11	CH_2CO_2Et	Ph	**56k**	81
12	CH_2CO_2Et	2-MeC_6H_4	**56l**	64
13	CH_2CO_2Et	2-furanyl	**56m**	73
14	CH_2CO_2Et	2-thienyl	**56n**	41
15	CH_2CO_2Et	4-$MeOC_6H_4$	**56o**	82
16	CH_2CO_2Et	4-ClC_6H_4	**56p**	50

does not lead to the formation of the analogous complex. A mechanism for the formation of the boronate species was advanced by the authors (Scheme 15).[11]

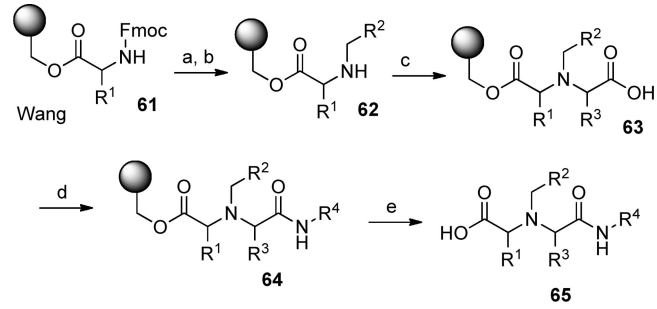
Using boronic esters, Pietre and co-workers used 2-thienyl boronates **53** and several primary amines in methanol and HFIP at room temperature, while MWI and methanol or HFIP at room temperature was needed for secondary amines (Table 10).[18]

N-Phenylimino amides **55** were reported to react with arylboronic acids under harsh conditions (dichloroethane at 100 °C) to yield α-functionalized glycine derivatives **56**. Electron-rich boronic acids were observed to be more reactive than their electron-deficient or sterically hindered counterparts (Table 11).[29]

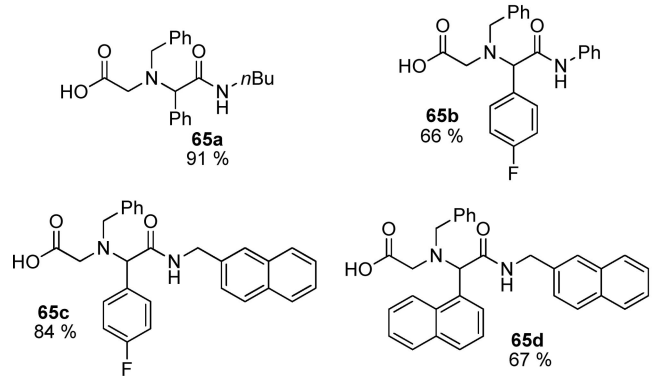
3.3. Other Skeletons Derived from Glyoxylic Acid

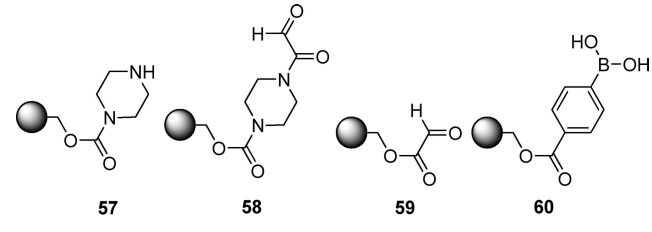
In an attempt to develop a suitable method for the automated generation of combinatorial libraries, Hansen and co-workers immobilized each one of the three components on an insoluble support. Resin-bound amine **57**, resin-bound glyoxylic acid derivatives **58** and **59**, and resin-bound 4-carboxyphenylboronic acid **60** were prepared and tested with the remaining components in a DMF/1,2-dichloroethane solvent mixture. Wang polystyrene was used as the starting material. The use of several aldehydes demonstrated the need of an α-hydroxyl group or an α-heteroatom in the aldehyde.[8]

Scheme 16



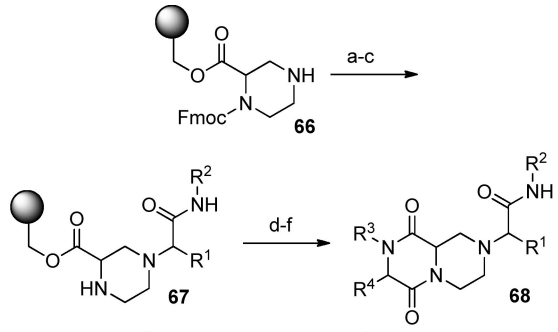
a) 25 % Pip/DMF; b) R^2CHO, 1 % AcOH/TMOF, $NaCNBH_3$;
c) $R^3B(OH)_2$, Glyoxylic acid, DCM; d) DIC, HOBt, R^4NH_2; e) 95:5 TFA:H_2O





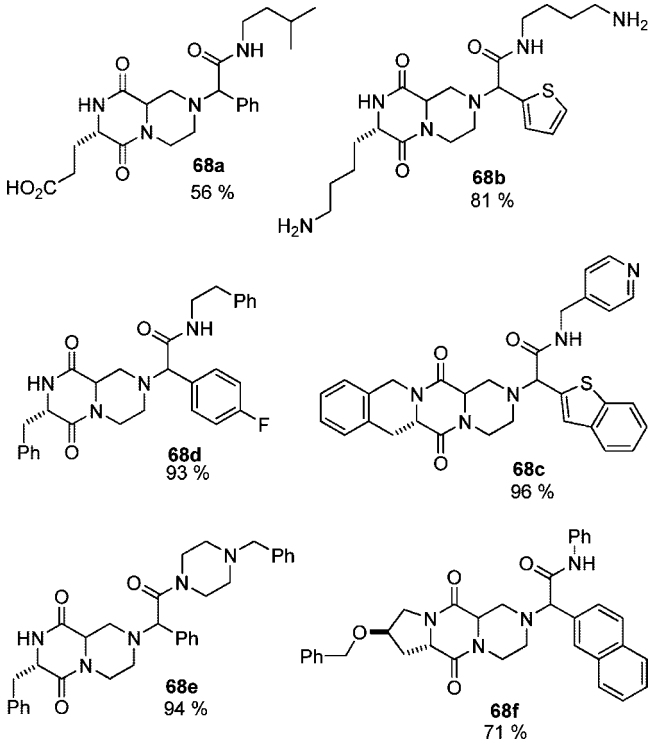
Peptide mimetics **65** can be efficiently prepared through the Petasis-borono Mannich reaction in solid phase synthesis. Large numbers of pharmaceutically relevant compounds for high-throughput screening can be prepared using this protocol. Some of the reported compounds are represented in Scheme 16.[30]

Scheme 17



a) $OHCCO_2H.H_2O$, $R^1B(OH)_2$, DCM; b) DIC, R^2NH_2, DCM;
c) piperidine/DMF 25 % sol.; d) *N*-BOC-α-amino acid, PyBOP, DMF, r. t.;
e) TFA/DCM 25 %, r.t., 1h; f) 2 M AcOH in *i*-BuOH, 50 ºC, 24 h

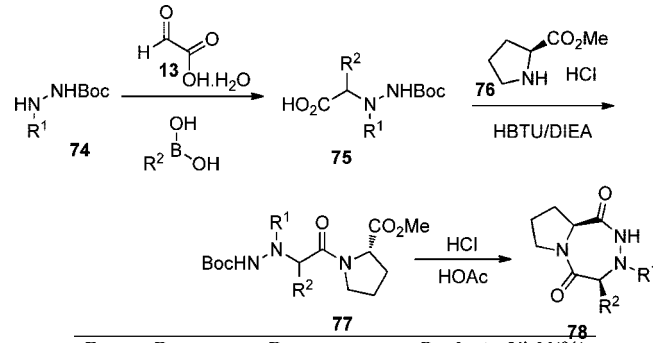
Scheme 18



The solid-phase synthetic methodology was also applied in the preparation of β-turn mimetics via the Petasis reaction/diketopiperazine formation. The high-throughput organic synthesis of bicyclic diketopiperazines was achieved starting from Merrifield resin-bound piperazine 2-carboxylic acid **66**. The amide and α-carbonyl substituents were introduced via the Petasis reaction and the resultant solid supported product was further transformed through usual synthetic transformations (Scheme 17). The process optimization afforded the desired products in high yields and purity, allowing the biological evaluation of the crude samples (Scheme 18). Despite the good yields reported for several examples, boronic acids containing a basic nitrogen atom did not result in product formation (e.g., pyridine-4-boronic acid).[31] This procedure was also applied in the preparation of constrained β-turn mimetics incorporating a byciclic turn inducer.[32]

A solid supported synthetic procedure for the preparation of β-turn mimetics **70** based on 2,5-diketopiperazine skeleton was recently developed (Scheme 19). Optically pure (*S*)-piperazine-2-carboxylic acid dihydrochloride **69** was converted into an orthogonally protected, resin-bound amino

Table 12



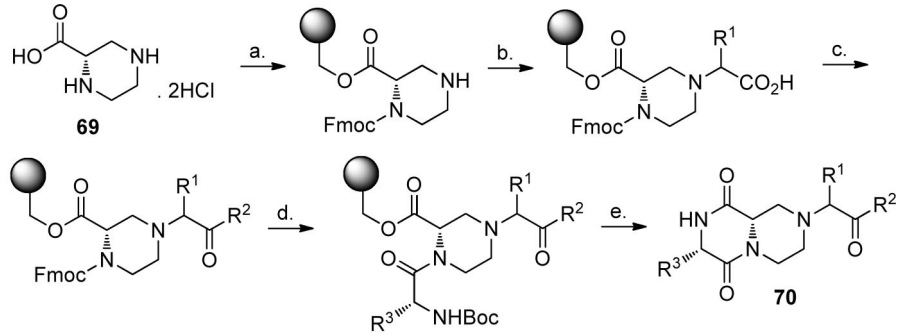
Entry	R_1	R_2	Product	Yield(%)
1	CH_2Ph	4-$MeOC_6H_4$	**78a**	42
2	CH_2Ph	4-$MeSC_6H_4$	**78b**	50
3	CH_2Ph	3,4-$(MeO)_2C_6H_3$	**78c**	45
4	CH_2Ph		**78d**	36
5		Ph	**78e**	48
6		4-$MeOC_6H_4$	**78f**	43
7	CH_2CO_2Me		**78g**	45
8	Ph	3,4-$(MeO)_2C_6H_3$	**78h**	40
9	4-FC_6H_4		**78i**	46
10	2-MeC_6H_4	3-$MeOC_6H_4$	**78j**	44
11	Ph	4-$MeSC_6H_4$	**78k**	39
12	Ph	4-$MeOC_6H_4$	**78l**	43
13	CH_2Ph	3-MeO,4-FC_6H_3	**78m**	54

derivative, and further reacted with glyoxylic acid and an aryl boronic acid **71** in a PBM fashion. Several boronic acids, amines, and α-amino acids were used as building blocks, resulting in a large library of β-turn mimetics in up to 47% overall yield. Concerning the PBM reaction step, the substituents' nature of the boronic acid was observed to be crucial for the reaction's success. Phenylboronic acids containing electron-donating groups led to higher yields than unsubstituted boronic acid and the introduction of electron-withdrawing groups like chlorine and OCF_3 did not lead to the desired products.[33]

Another pathway to prepare β-turn mimetics was disclosed by Naskar and co-workers, based on Petasis reaction followed by coupling reaction in the presence of HBTU ((2-(1*H*-Benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate) and DIEA (*N*,*N*-Diisopropylethylamine). *N*-1-Boc-*N*-2-(alkyl)-hydrazines **74** were used in the Petasis-borono Mannich reaction and L-proline methyl ester•hydrochloride **76** was sequentially reacted with the PBM product in the presence of HBTU/DIEA, affording 4,5-bridged 1,2,5-triazepine-3,6-diones in moderate yield (36−54%) (Table 12). Changing the order of the reactants between the first and second step, 1,2,5-triazepine 3,7-diones heterocyles **81** were synthesized in moderate yields (32−48%) (Table 13).[34]

N-Substituted indoles **82** were reported to be suitable alternatives of the amine component in the Petasis reaction. Several substituted indoles were obtained in modest yields

Scheme 19



a. (i) Boc_2O, aq NaOH, dioxane-H_2O(2:1), 0 ºC-r.t., then FmocCl, Na_2CO_3 (ii) DEAD, Ph_3P, THF-CH_2Cl_2 (3:1), 0 ºC-r.t.; (iii) 40 % TFA-CH_2Cl_2; b. $OHCCO_2H.H_2O$, $R^1B(OH)_2$ **71**, CH_2Cl_2-MeOH (4:1), r.t.; c. DIC, HOBt, Amine **72**, DMF; d. (i) 25 % piperidine-DMF, r.t. (ii) DIC, HOBt, $R^3NH(Boc)CO_2H$, α-amino acid **73**, DMF, r.t. (iii) 25 % TFA-CH_2Cl_2; e. 10 % AcOH-*i*-PrOH, 50 ºC

Building Blocks

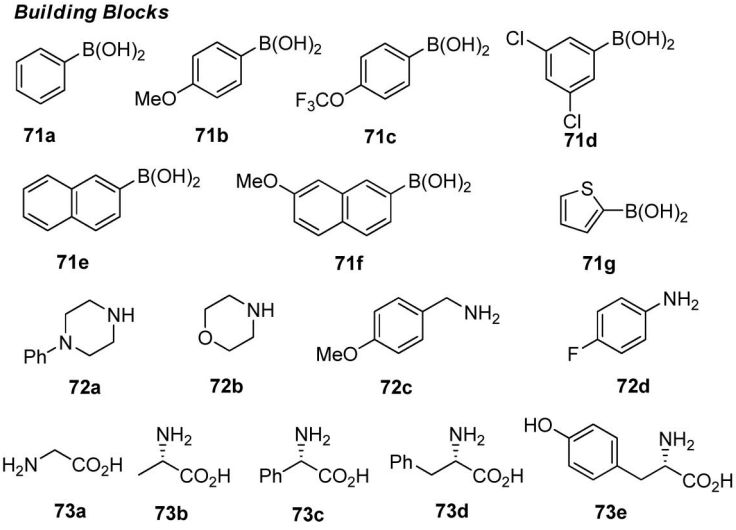
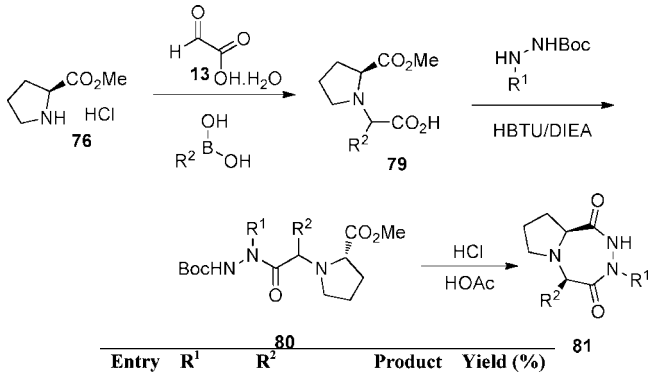


Table 13



Entry	R^1	R^2	Product	Yield (%)
1	CH_2Ph		**81a**	48
2	CH_2Ph	4-$MeOC_6H_4$	**81b**	34
3		Ph	**81c**	32
4		4-$MeOC_6H_4$	**81d**	32

in refluxing dioxane for 12 h. The presence of a substituent in the nitrogen atom of the indole ring was observed to be crucial to success of the reaction. In the absence of such a substituent, low yields of the corresponding product were obtained. The advanced mechanism for this reaction comprises the nucleophilic attack of the indole's 3-position to the aldehyde, formation of an ate complex with the carboxylic acid functional group, dehydration of the ate complex, and concomitant migration of the aryl substituent from the boronic acid to the sp^2 carbon (Scheme 20). Boronic acids, such as styryl, 3-thienyl, 2-benzothiophenyl, and the ones shown in Table 14, afforded the desired reaction products in moderate yields (45−51%).[35]

Scheme 20

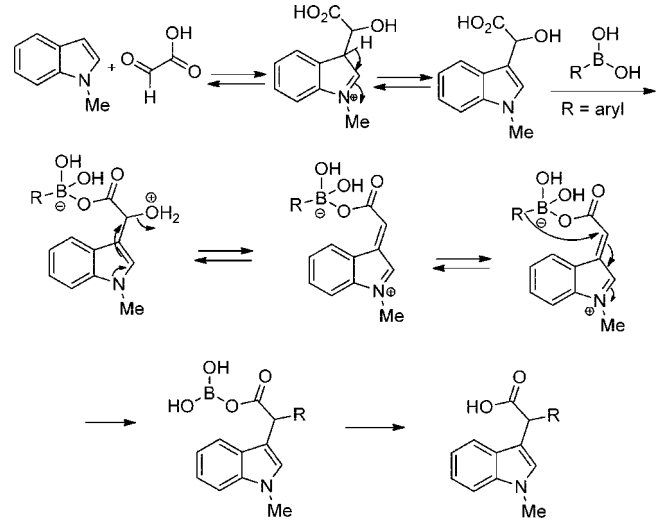
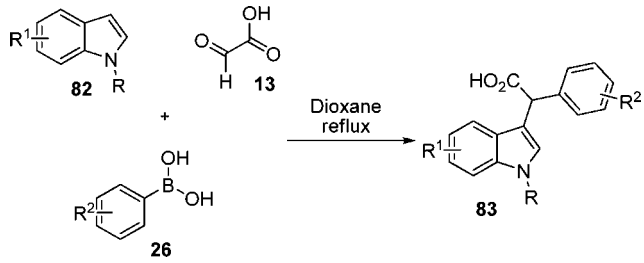
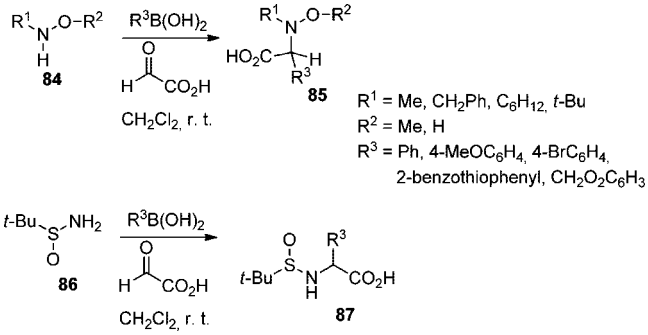


Table 14



entry	R	R^1	R^2	product	yield (%)
1	Me	H	4-MeO	**83a**	60
2	Me	H	3,4-$(MeO)_2$	**83b**	50
3	Me	H	4-MeS	**83c**	49
4	Me	H	4-Br	**83d**	48
5	Me	H	4-F	**83e**	42
6	Me	6-Br	4-OMe	**83f**	70
7	Et	6-Br	4-OMe	**83g**	68
8	*i*-Pr	6-Br	4-OMe	**83h**	60
9	Me	5-Br	4-OMe	**83i**	62
10	H	H	4-OMe	**83j**	26

Scheme 21

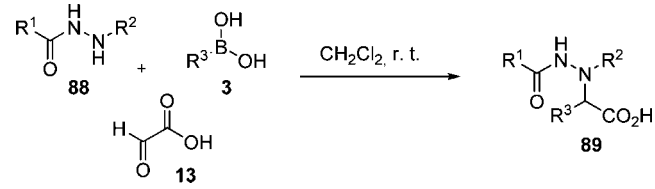


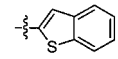
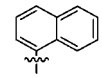
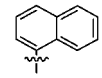
N-Hydroxy or alkoxy-α-aminocarboxylic acids **85** and *N*-(*tert*-butyl sulfinyl)-α-amino carboxylic acids **87** have been prepared from *N,O*-alkyl or hydroxylamines **84** and *tert*-butyl sulfinamide **86** as an alternative amine component in the Petasis reaction (Scheme 21). The reaction products were obtained in good yields, regardless of the electronic nature of the aryl substituent in the boronic acid moiety (41−96% yield).[36]

Substituted hydrazines **88** have been used as the amine component in the Petasis-borono Mannich reaction, leading to the preparation of biologically important α-hydrazinocarboxylic acids **89**. These carboxylic acid derivatives have been reported to be antibiotics, protease inhibitors,[37] antivirals,[38] and building blocks for the synthesis of peptidomimetics.[39] Equimolar amounts of glyoxylic acid **13**, hydrazine **88**, and a boronic acid **3** were reported to undergo the condensation reaction in dichloromethane at room temperature. Despite the lack of influence of the boronic acid substituent in the success of the reaction, the substituent of the hydrazine was seen to be of pivotal importance since an electron-withdrawing substituent decreased the efficacy of the process (Table 15, entries 10 and 11).[40]

Following his work in the exploitation of the three component condensation reaction with boronic acids, Petasis and co-workers demonstrated the preparation of piperazinones **91** and benzopiperazinones **94** using 1,2-diamines **90**. A dual role was attributed to the boronic acid, serving both as reactant and as catalyst for the subsequent cyclization step (Scheme 22). While secondary 1,2-diamines led to the

Table 15



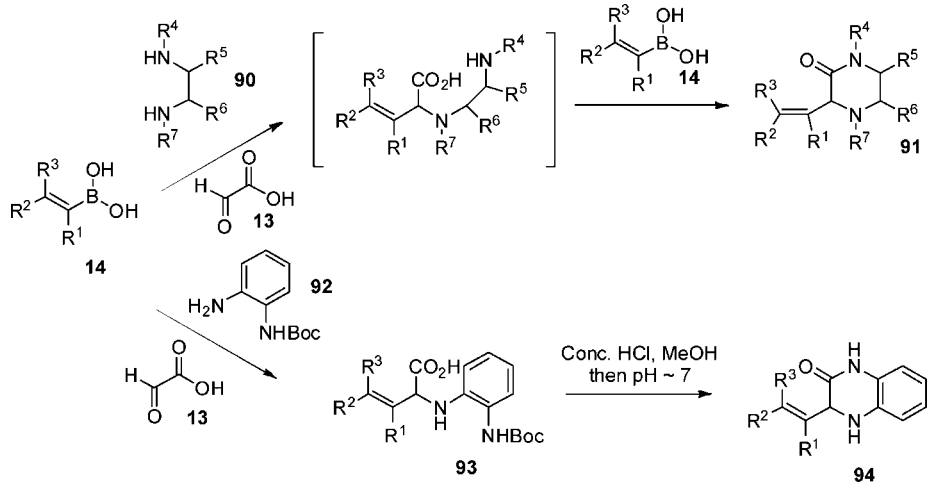
Entry	R^1	R^2	R^3	Product	Yield (%)
1	*t*-BuO		4-$MeOC_6H_4$	**89a**	99
2	*t*-BuO		4-$CH_3C_6H_4$	**89b**	74
3	*t*-BuO		CH=CHPh	**89c**	86
4	*t*-BuO		Ph	**89d**	89
5	*t*-BuO			**89e**	60
6	*t*-BuO	CH_2CO_2Me		**89f**	70
7	*t*-BuO	CH_2Ph	4-$CH_3OC_6H_4$	**89g**	86
8	*t*-BuO	Ph	4-$CH_3OC_6H_4$	**89h**	99
9	*t*-BuO	4-MeC_6H_4		**89i**	85
10	*t*-BuO	4-$NO_2C_6H_4$	4-$CH_3OC_6H_4$	**89j**	34
11	*t*-BuO		4-$CH_3OC_6H_4$	**89k**	0
12	*t*-BuO	H	4-$CH_3OC_6H_4$	**89l**	71
13	$PhCH_2O$	CH_2CO_2Et	4-$CH_3OC_6H_4$	**89m**	60
14	H_2N	Ph	4-$CH_3OC_6H_4$	**89n**	20

formation of the desired product in good yields, primary 1,2-diamines afforded the reaction product in somewhat lower yields.[41]

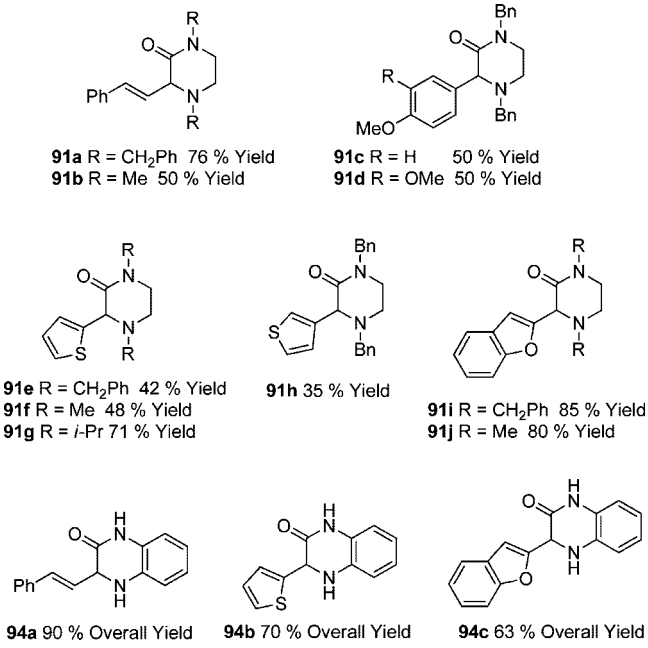
An extensive study on the solvent influence on the piperazinone formation was performed, where dichloromethane, methanol, acetonitrile, or toluene were tested at different reaction temperatures. Refluxing acetonitrile was determined to be the best way to accomplish this transformation. The use of benzyl protected 1,2-diamines was justified by the easy deprotection of the piperazinones prepared (Scheme 23). Despite the success of this reaction with alkyl 1,2-diamines, the analogous product was not obtained when using 1,2-phenylenediamine. However, the Boc-monoprotected 1,2-phenylenediamine **92** allowed the formation of several benzopiperazinones **94** after acidic treatment of the condensation product (Schemes 22 and 23).[41]

A novel Petasis-borono Mannich reaction of tertiary aromatic amines with glyoxylic acid was reported by Naskar and co-workers. α-(4-*N,N*-Dialkylamino-2-alkyloxyphenyl)-carboxylic acids **96** were prepared after refluxing the reactants in dioxane for 24 h (Scheme 24). The use of α-keto acids instead of glyoxylic acid, was not detrimental for the

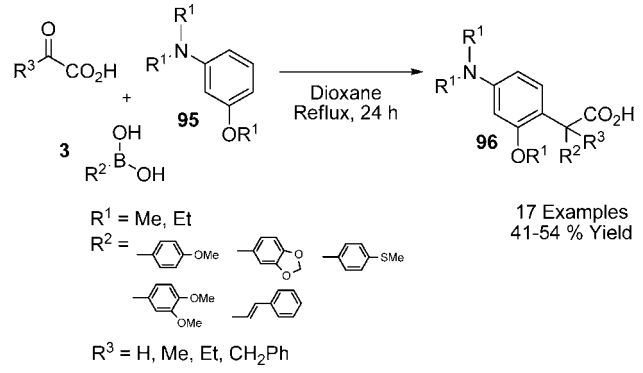
Scheme 22



Scheme 23



Scheme 24



reaction, and the products were obtained in the same yields as their homologues.[42] 1,3,5-Trioxygenated benzene derivatives were tested as substrates for the preparation of carboxylic acids without the amino group. Despite the harsh conditions employed (dioxane at reflux), the corresponding carboxylic acids were obtained in reasonable yields (40−62%).[43]

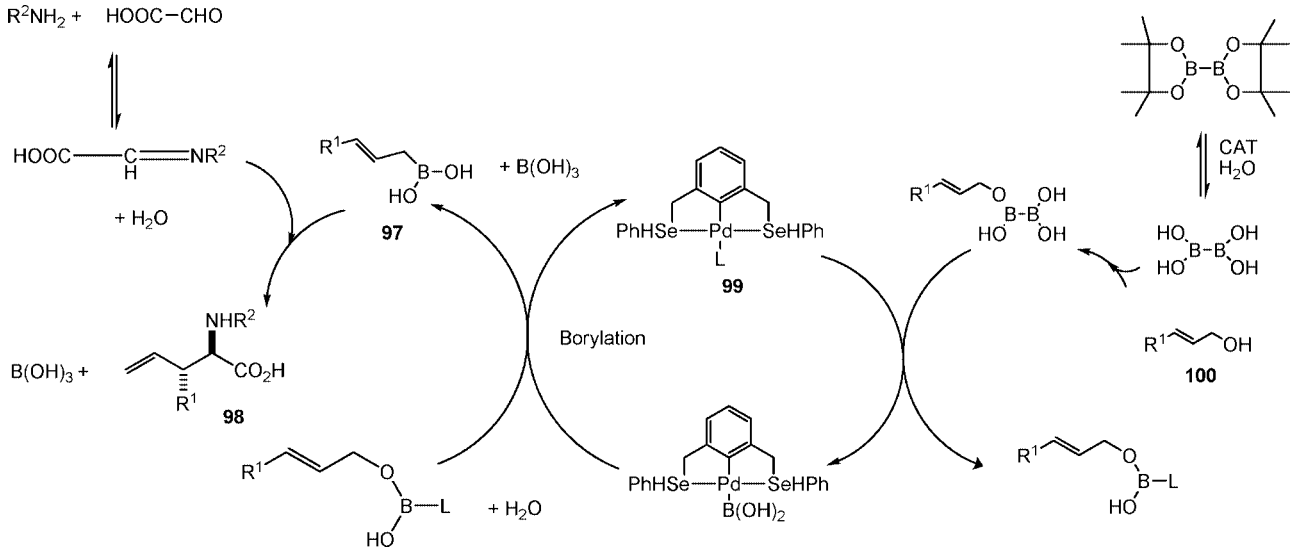
Considering the relatively low stability of functionalized allyl boronates, their isolation and purification often becomes a major issue. Szabó and co-workers disclosed a new procedure for the one-pot synthesis of *R*-amino acids and homoallyl alcohols from easily available allyl alcohol, amine, aldehyde, or ketone substrates. In this procedure, the active allylating agents are in situ generated allyl boronic acid derivatives, and the transformation is achieved by integration of the pincer−complex-catalyzed borylation of allyl alcohols. Diboronic acid or in situ hydrolyzed diboronate ester are used as the boronate source of the reaction, ensuring that the waste product of the reaction is the nontoxic boric acid. The most important differences from the classical Petasis reaction are: the Szabó procedure is a four-component coupling (involving in situ generation of the allyl boronate component) and the amines and glyoxylic acid are not added at the beginning of the coupling reaction but after the allotted times required for the borylation process. Addition of the amine component at the beginning of the reaction, probably could lead to a coordination between the nitrogen atom and palladium causing the deactivation of catalyst **99** and thus preventing the formation of **97**. The regio- and stereoselectivity of the reaction is excellent, as almost all products were obtained as single regio- and stereoisomers, with reasonable to good yields (52−80%) (Scheme 25).

When allyl alcohol was employed as the reagent, the primarily formed amino carboxylate intermediate underwent lactam formation. Accordingly, the reaction of Pd-pincer-complex **99**, diboronic acid, 1-phenylbenzilamine, and β-hydroxy acid, triggers a four-step cascade, which can be performed as a one-pot reaction (Scheme 26).[44]

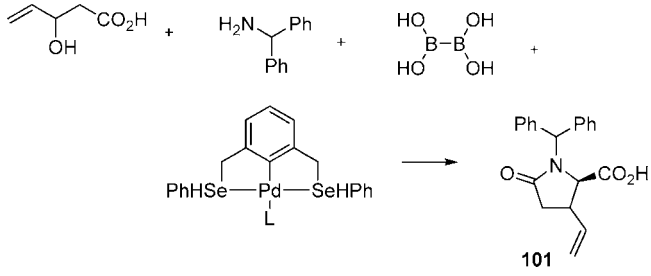
4. Glycolaldehyde and Derivatives

As aforementioned, the presence of a hydroxyl group or an heteroatom (vide infra) in the aldehyde is almost imperative for the success of the PBM reaction. Following this guideline, Petasis and co-workers tested glycolaldehyde derivatives **2** as the aldehyde component aiming to reach a new synthetic method for the preparation of β-amino alcohols. In this case, the reaction proceeded with high levels of diastereocontrol, yielding exclusively the anti-isomer, and no racemization is observed when optically pure α-hydroxyl aldehydes were used (Scheme 27).[13]

Scheme 25



Scheme 26



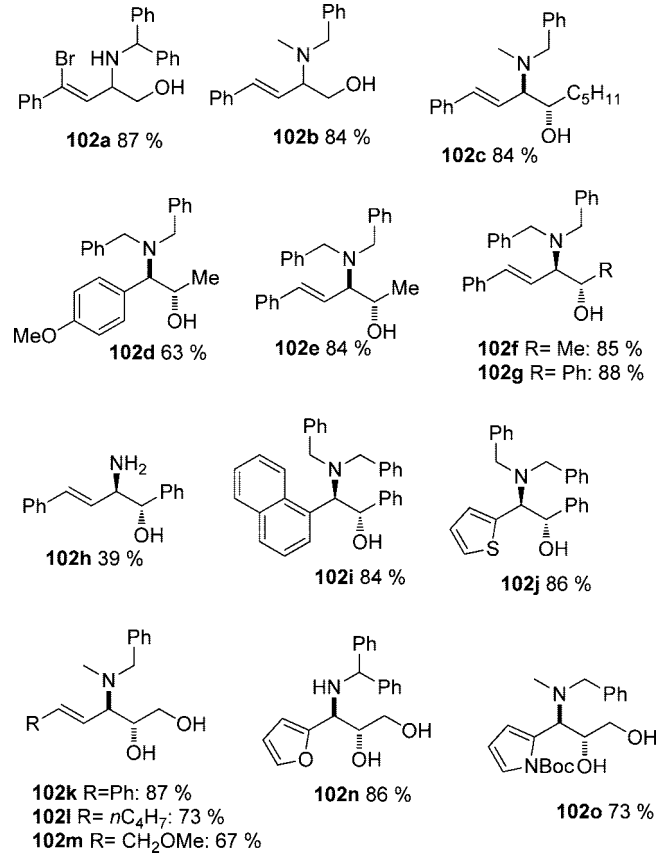
Later this reaction was coupled to an amine propargylation reaction to yield a diverse collection of small molecules. To obtain it, the secondary amine resultant from the PBM reaction was subsequently reacted with propargyl bromide and then submitted to several transformations, namely palladium cycloisomerization or the cobalt-catalyzed Pauson−Khand reaction.[45]

In the development of his work, Petasis and co-workers reported a short route to *anti*-α-trifluoromethyl-*β*-amino alcohols **104** via 3,3,3-trifluorolactic aldehyde **103** (Scheme 28). The oligomeric form of the aldehyde was observed to react with several boronic acids at room temperature in excellent diastereoselectivity, yielding the anti-diastereoisomer in >99% *de*.[46]

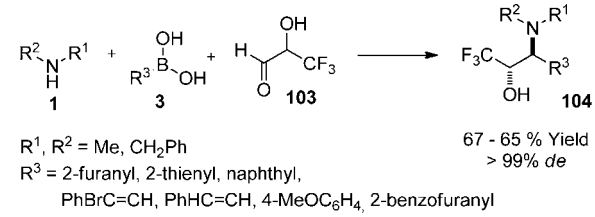
This one step three-component methodology was used for the preparation of *anti*-α-(difluoromethyl)-*β*-amino alcohols **110,** and was included as a key step in the synthesis of chemotherapeutic agents, fluorinated amino acids. The hydroxyl aldehyde **109** was prepared from ethyl difluoroacetate **105**, after conversion to the enantiomerically pure acetylenic alcohol **107** (Scheme 29). Alkenyl, aryl, and heteroaryl boronic acids were tested in the PBM reaction, leading to better results after purification by recrystallization of the commercially available boronic acids. Secondary amines were observed to be better partners than their primary counterparts, as previously reported.[47]

The PBM reaction has been successfully applied as a key step in the preparation of the immunosuppressive agent FTY720 starting from 4-octylbenzaldehyde. Combining (*E*)-2-(4-octylphenyl)ethenylboronic acid **112**, dihydroxyacetone **111** and benzylamine in ethanol at room temperature allowed the preparation of the amine diol **113** in 40% yield (Scheme 30).[48]

Scheme 27

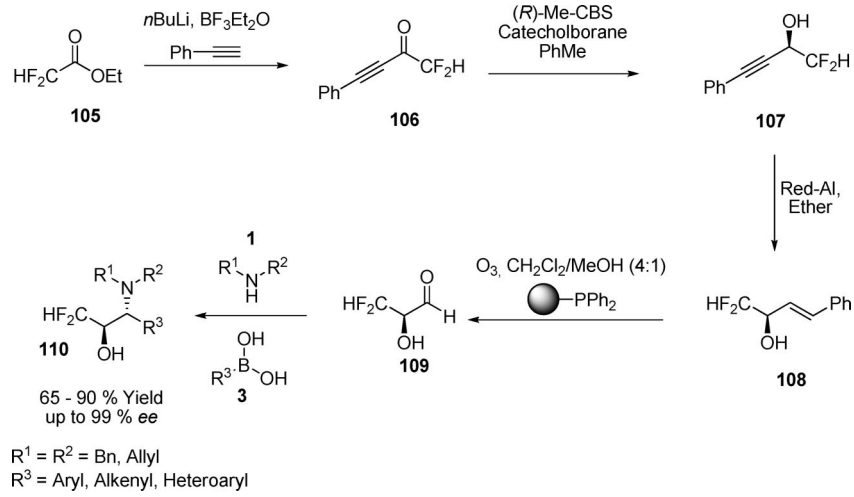


Scheme 28

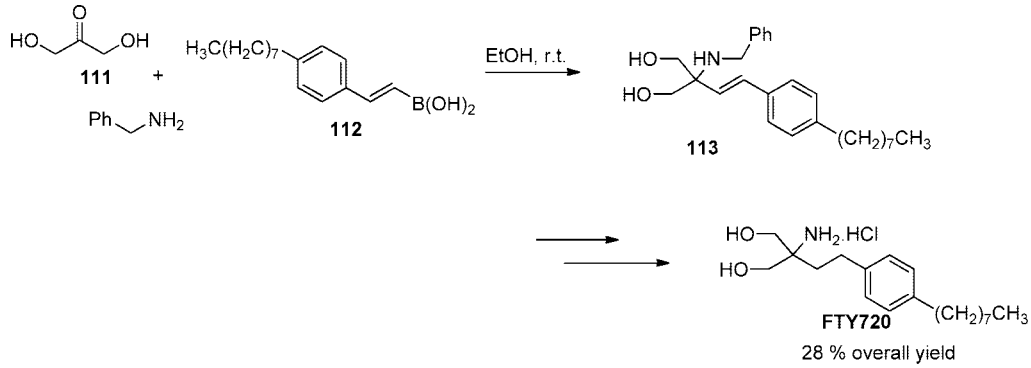


Recently, the use of glycolaldehyde derivatives **117** in the PBM reaction allowed the preparation of polycyclic heterocycles **120**. Supported reagents were used to achieve a high-

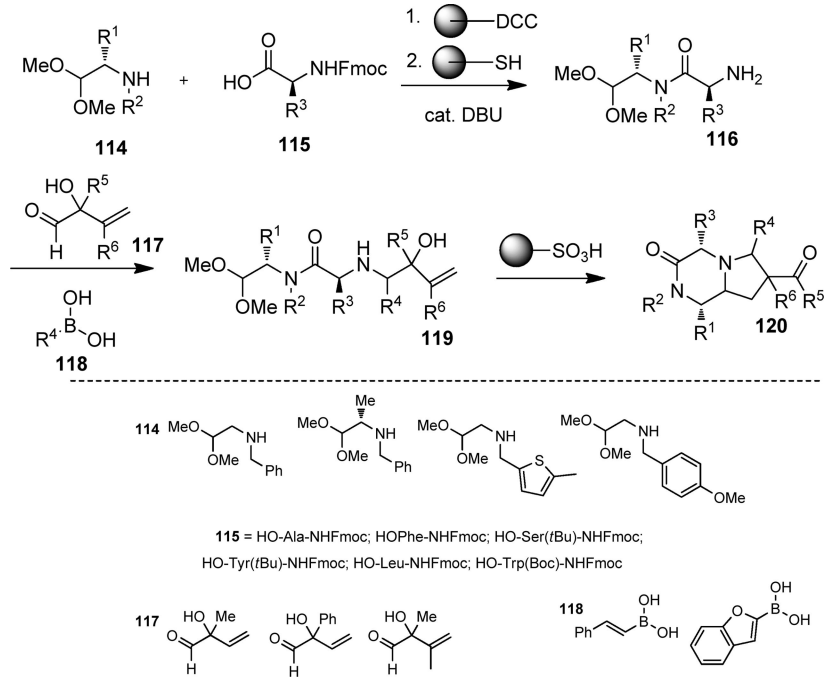
Scheme 29



Scheme 30



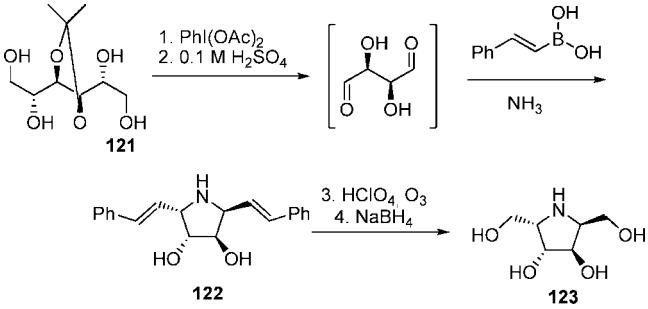
Scheme 31



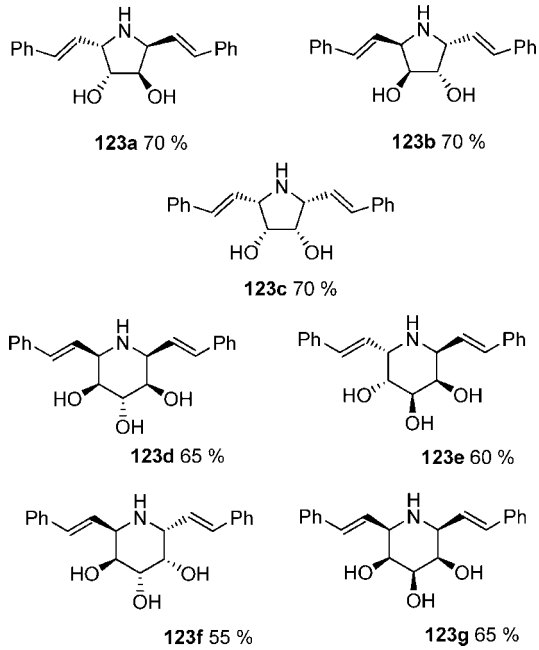
throughput synthesis, facilitating the isolation of the reaction products. The Petasis method afforded the secondary amines **119** in good to high yields (83−96% yield), and the amines formed were then used in an aza-Cope-Mannich reaction (36−77% yield) using sulfonic acid resin (Scheme 31).[49]

After the successful preparation of sialic acids using boronic esters,[50] metabolically inert iminocyclitols have been prepared by Wong and co-workers.[51] This family of compounds is known to exhibit strong binding affinity to glycosidases and glycotransferases and has been evaluated

Scheme 32



Scheme 33



for antivirial, anticancer, and antidiabetic properties. The preparation of these compounds can be achieved via the oxidation of polyhydroxyl dialdehydes **121** with $PhI(OAc)_2$, followed by Petasis reaction using ammonia and then ozonolysis (Scheme 32). The method was applied to the preparation of both 5- and 6-membered iminocyclitols in reasonable yields (44−60%) (Scheme 33).[51]

To develop a new synthetic strategy for the preparation of the purported structure of uniflorine A, Pyne and co-workers used a sugar as the aldehyde component. An efficient 8-step synthesis of purported uniflorine A from L-xylose was developed, by using the Petasis-borono Mannich reaction and ring-closing metathesis as key steps.[5] This strategy was recently applied in the preparation of the correct structure of uniflorine A (Scheme 34)[14b,52] and related pyrrolizidine alkaloids[52b] and castanospermine,[53] with the PBM reaction being the first synthetic step yielding the tetrahydroxy amine with the desired configurations.

Following their work in the use of PBM reaction as a crucial step in the synthesis of natural compounds, Pyne and co-workers achieved the short formal synthesis of (−)-swainsonine. Chiral α-hydroxy aldehyde **127** and **129** were generated in situ by the Sharpless asymmetric dihydroxylation reaction of vinyl sulfones **126** and further reacted in the presence of a primary amine and *β*-styrenyl boronic acid to give *anti*-1,2-amino alcohols **128** and **130** with high *ee*'s (Table 16). The reaction was much less successful when the secondary amine morpholine and 4-methoxyaniline were

Scheme 34

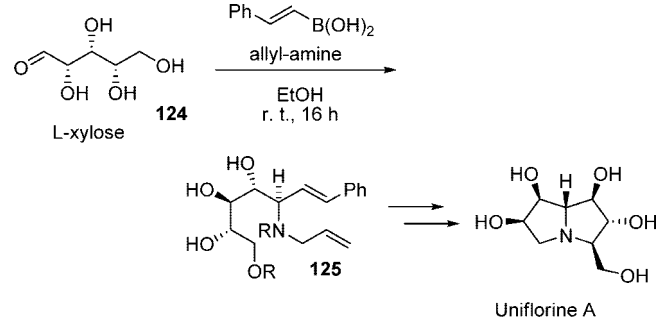
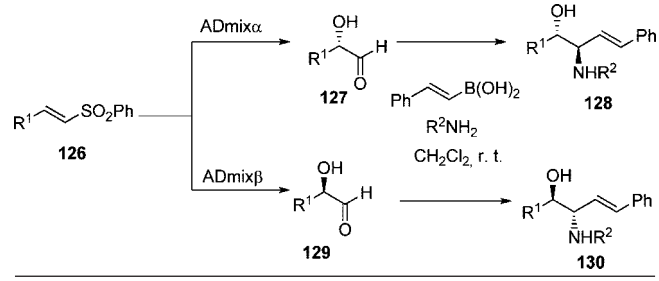


Table 16[a]



entry	R^1	ADmix	R^2	product	yield (%)	ee (%)
1	$Ph(CH_2)_2$	α	$H_2C{=}CH$	**128a**	44	91
2	$Ph(CH_2)_2$	*β*	$H_2C{=}CH$	**130a**	51	94
3	$Ph(CH_2)_2$	α	$4\text{-}OMeC_6H_4CH_2$	**128b**	46	91
4	$Ph(CH_2)_2$	*β*	$4\text{-}OMeC_6H_4CH_2$	**130b**	43	95
5	$TBDPSO(CH_2)_2$	α	$H_2C{=}CH$	**128c**	35	83
6	$TBDPSO(CH_2)_2$	*β*	$H_2C{=}CH$	**130c**	38	93

[a] TBDPSO = *tert*-butyldiphenylsilyl.

used, with the former yielding the product only in 12% and the latter completely failing to react.[14a,54] This method has been applied to the synthesis of hyacinthacine B_3 and purported hyacinthacine B_7.[54]

5. Salicylaldehyde and Derivatives

Proceeding his work, Petasis and co-workers,[10] simultaneously with Wang and Finn,[55] observed that the easily formed iminium ion of salicylaldehyde reacted with boronic acids affording the aminomethylphenol derivatives **132** (Scheme 35). As previously observed in the case of glyoxylic acid, the reaction has a broader application with secondary amines, while primary amines afforded the expected product in modest yields. Supporting the thesis of a required hydroxyl group in the aldehyde to activate the boronic acid, the use of benzaldehyde and other aldehydes lacking an OH group in position 2 failed to deliver the desired product. Tertiary amines were obtained in good yields after 24−36 h at room temperature in ethanol.[10]

Recently, Gois et al. demonstrated that water can be used as a good medium for this type of reactions. Several salicylaldehyde derivatives were combined with different amines and boronic acids and the corresponding tertiary amines were obtained in good to excellent yields, after 24 h at 80 °C.[7] Water was compared with several organic solvents, such as DMF, DME, toluene and DCE. No rate acceleration effect due to water was observed, despite the reaction proceeding in a heterogeneous phase (Table 17). The procedure was found to be applicable to bulky amines, such as dibenzylamine, and diallyl amine was shown to be an excellent partner for this purpose (Scheme 36).[12]

Scheme 35

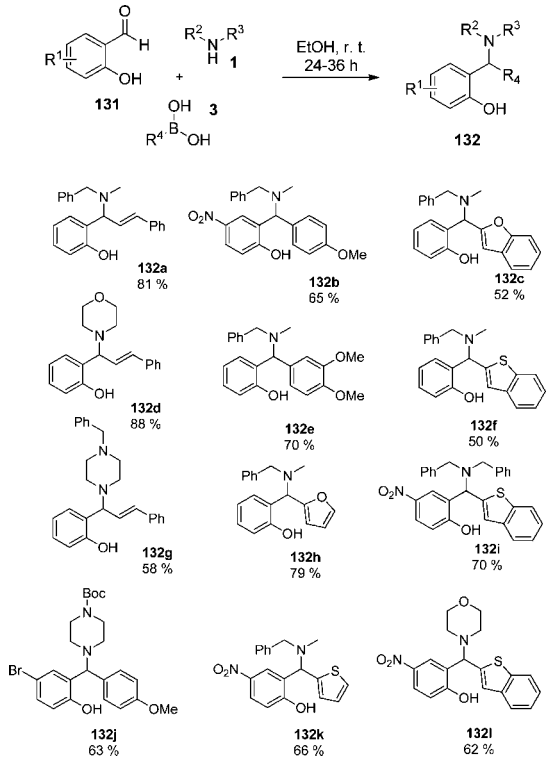
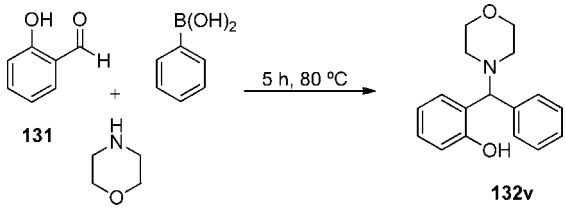
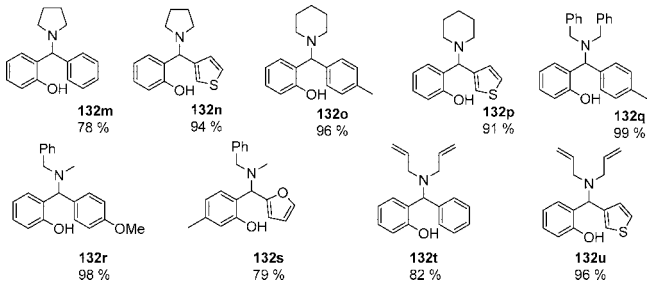


Table 17



entry	solvent	yield (%)
1	H_2O	53
2	DME	69
3	DMF	41
4	toluene	75
5	DCE	77

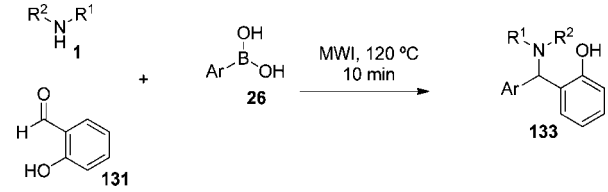
Scheme 36



As mentioned previously for glyoxylic acid, microwave irradiation was used to induce the PBM reaction using salicylaldehyde, and the corresponding phenols were obtained in reasonable yields (Table 18). Formation of imines was observed after the use of primary amines, but the aryl migration from the boronic acid to the imine was not observed.[21]

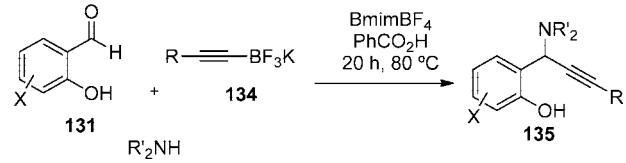
After the successful implementation of potassium organotrifluoroborates as a component of the Petasis-borono Mannich reaction, several other examples have been reported.

Table 18



entry	amine	aryl	product	yield (%)
1	morpholine	Ph	**133a**	76
2	dibenzylamine	Ph	**133b**	50
3	morpholine	3-$MeOC_6H_4$	**133c**	62
4	morpholine	4-FC_6H_4	**133d**	75
5	morpholine	2-benzofuranyl	**133e**	23

Table 19



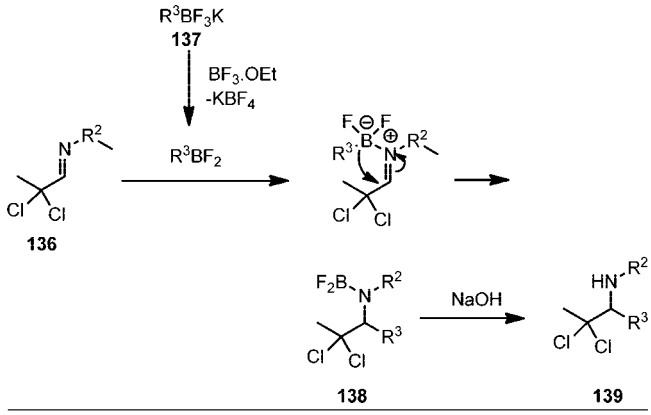
entry	R	amine	X	product	yield (%)
1	$CH_3CH_2CH_2CH_2$	dibenzylamine	H	**135a**	81
2	$CH_3CH_2CH_2CH_2$	dibenzylamine	5-NO_2	**135b**	83
3	$CH_3CH_2CH_2CH_2$	morpholine	H	**135c**	76
4	$CH_3CH_2CH_2CH_2$	morpholine	3-CH_3	**135d**	63
5	$CH_3CH_2CH_2CH_2$	morpholine	5-*t*-Bu	**135e**	76
6	$CH_3CH_2CH_2CH_2$	morpholine	5-Cl	**135f**	53
7	C_6H_5	dibenzylamine	H	**135g**	81
8	C_6H_5	morpholine	5-NO_2	**135h**	79
9	4-$CH_3C_6H_4$	morpholine	5-NO_2	**135i**	78
10	*t*-Bu	morpholine	H	**135j**	72
11	C_6H_{11}	morpholine	H	**135k**	78

Raeppel and co-workers demonstrated that the presence of a Lewis acid (BF_3•OEt_2) was essential for the efficient use of trifluoroborates salts. From the several types of aldehydes used, it was observed that an α or ortho activating group was necessary for the success of the reaction (as previously observed for boronic acids).[56]

Yadav and co-workers have recently explored the use of ionic liquid [butyl methylimidazole] with tetrafluoroborate counterion ($BmimBF_4$) as Petasis reaction media. Better yields and enhanced reaction rates were observed compared to those reactions just using common organic solvents. The ionic liquid could be reused four to five times without apparent loss of activity. The reactions proceeded at room temperature, and after 3 h the alkyl amino phenols were obtained in good to excellent yields by simple extraction of the reaction media with diethyl ether. Several aryl boronic acids, secondary amines and salicylaldehyde derivatives were tested demonstrating the advantages on the utilization of a more sustainable reaction solvent.[57] Previously, Kabalka et al. observed that in $BmimBF_4$, alkynyltrifluoroborates react with amines and salicylaldehydes to afford the corresponding propargylamines in good yields. The use of benzoic acid enhanced the reaction yields, which was assigned to the easy formation of the iminium ion driven from the acidic catalysis (Table 19).[58]

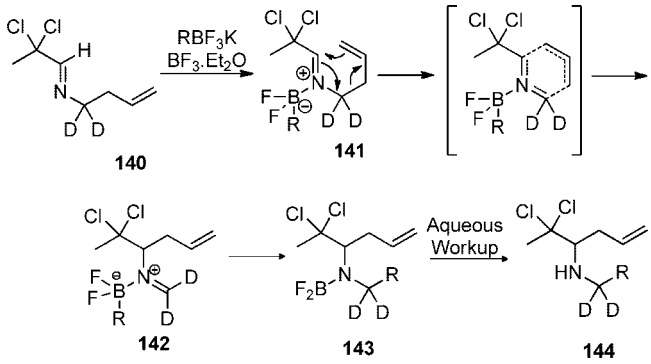
The use of alkynyltrifluoroborates in the presence of BF_3.OEt_2 was reported as another method for the preparation of propargylamines. Starting from fluoroaziridines, monofluorinated propargylamines can be obtained (30−66% yield) after in situ generation of the imine from reaction of the aziridine with SbF_3.[59] Organotrifluoroborates were observed

Table 20



entry	R^2	R^3	product	yield (%)
1	$PhCH_2$	PhCH=CH	**139a**	24
2	$PhCH_2$	PhC≡C	**139b**	81
3	*t*-Bu	PhCH=CH	**139c**	20
4	*i*-Pr	PhCH=CH	**139d**	21−37
5	*i*-Pr	PhC≡C	**139e**	72
6	*n*-Pr	PhCH=CH	**139f**	27
7	*n*-Pr	PhC≡C	**139g**	78
8	Allyl	PhCH=CH	**139h**	44
9	Allyl	PhC≡C	**139i**	83
10	Et	PhCH=CH	**139j**	32
11	Et	4-MeC_6H_4CH=CH	**139k**	60
12	Et	4-ClC_6H_4CH=CH	**139l**	23
13	Et	(*Z*)-MeCH=CH	**139m**	30
14	Et	PhC≡C	**139n**	80
15	Me	PhCH=CH	**139o**	20
16	*n*-Pr	3-$MeOC_6H_4$C≡C	**139p**	88
17	*n*-Pr	4-EtC_6H_4C≡C	**139q**	90
18	*n*-Pr	$MeOCH_2$C≡C	**139r**	44

Scheme 37



to react with *N*-3-butenyl-(2,2-dichloro-1-propylidene)amine **136** leading to a new stable class of functionalized propargylamines and allylamines. This procedure involves the formed imines and 1,1,1,3,3,3-hexa- fluoroisopropanol (HFIP) as cosolvent instead of amines and aldehydes (iminium percursors). It is supposed that the acidic HFIP accelerates the formation of the iminium species, which might then be attacked by organoboronic acids. In fact, when HFIP is used, the yields are much higher than when the same reaction takes place in pure CH_2Cl_2 (Table 20).[60]

In continuation of their work, the authors observed the reaction of organotrifluoroborates with *N*-3-butenyl-(2,2-dichloro-1-propylidene)amine leading to an interesting tandem cationic 2-aza-Cope rearrangement. Geminally dichlorinated secondary homoallylamines **144** formed through the combination of an aza-Cope rearrangement with a modified Petasis reaction. The use of a deuterated imine allowed the elucidation of the reaction mechanism (Scheme 37).[61] This methodology was extended to the use of α,α-dichloro-acetaldimines, which in presence of alkoxide bases were reported to form α-chloroketimines that can be further hydrolyzed into the corresponding α-chloro-ketones.[62]

6. Miscellaneous Aldehydes

2-Hydroxymorpholines **147** can be easily prepared through the condensation of 1,2-aminoalcohol **145**, an organoboronic acid and a glyoxal derivative (Scheme 38).[63] The stereoselective synthesis of hydroxymorpholines can be achieved by employing chiral 1,2-aminoalcohols.[64] Starting from glyoxal, 1,2-aminoalcohols, boronic acids, and aliphatic or aromatic amines, 2-aminomorpholines can be prepared in a few minutes under microwave irradiation. The reaction involves first a Petasis reaction, yielding product **147**, followed by a microwave promoted hydroxyl displacement by the amine.[65]

One of the many advantages of the utilization of water as solvent of a reaction is the possibility of an easy purification of the reaction products. When the preparation of hydroxymorpholines was combined with the use of water, the products were simply purified by extraction of the reaction mixture. When the reaction was performed in organic solvents, chromatography was needed resulting in lower yields, probably because of the lack of stability of the products to chromatographic conditions (Table 21).[7]

Schlienger et al. demonstrated that heterocyclic aldehydes could be used leading to the desired products in low yields after reaction with phenylalkenyl boronic acid. When employing alkenyl trifluoroborate salt **137**, morpholine, and pyridine-2-carboxaldehyde derivatives **148**, the product yield increased up to 54% (Table 22).[66]

Kobayashi and co-workers successfully disclosed the possibility of reacting several aldehydes using ammonia as the nitrogen source with the allyl boronate **150** (Scheme 39). A large excess of ammonia (satured in the solvent) was found to be crucial to obtain high chemoselectivity.[67]

The stereochemical implications of the reaction were investigated based on the reaction with (*Z*)- or (*S*)-crotylboronates. (*Z*)-Crotylboronate **152b** afforded syn-adduct **153b**, whereas *anti*-**153a** was obtained from (*E*)-**152a**. The authors noted that the stereochemical outcome of this reaction is not the same as that of crotylation of most N-substituted

Scheme 38

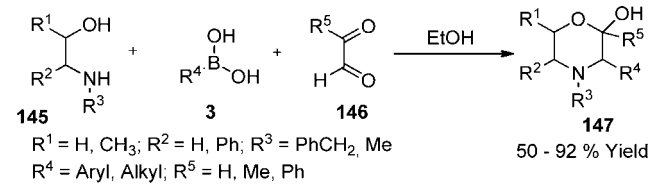
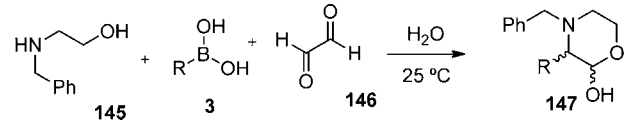
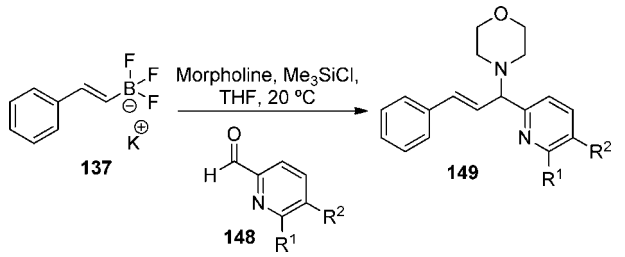


Table 21



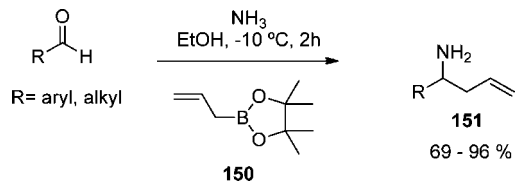
entry	R	reaction time (h)	product	de (%)	yield (%)
1	Ph	24	**147a**	54	97
2	4-MeC_6H_4	48	**147b**	67	93
3	4-$MeOC_6H_4$	24	**147c**	61	94
4	CH=CHPh	48	**147d**	5	89

Table 22

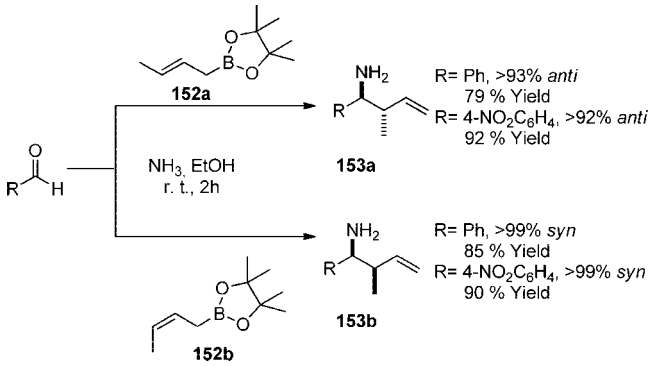


entry	R^1	R^2	product	yield (%)
1	H	H	**149a**	54
2	Br	H	**149b**	28
3	OMe	H	**149c**	40
4	H	CO_2Me	**149d**	31

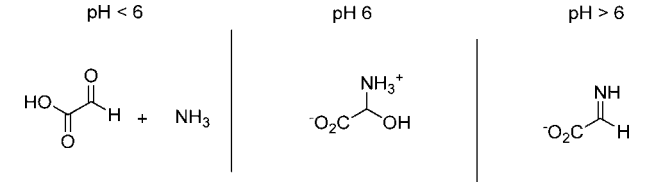
Scheme 39



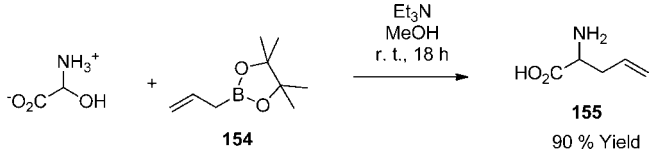
Scheme 40



Scheme 41



Scheme 42



imines, instead being similar to that of aldehydes which react via cyclic transition states (Scheme 40).[67]

An extension of this methodology concerning the use of hydroxyglycine as the carbonyl source allowed the synthesis of unnatural unprotected α-amino acids. The key step was to take advantage of the nature of amino acids at different pH values. Indeed, if the solution was maintained above pH 6, using a tertiary amine, then hydroxyglycine exists predominantly as the iminoacetate (Scheme 41), which should facilitate the chemoselective allylation of the imine and allow access to unprotected amino acids (Scheme 42).[68]

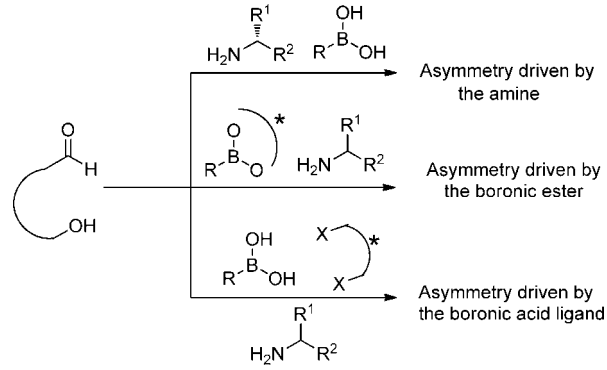
7. Asymmetric Petasis-Borono Mannich Reaction

The ultimate goal on the discovery of new reactions and new synthetic methods is the functionalization or introduction of new asymmetric centers in a molecule. Hence, the Petasis reaction has been tested for this proposal in three different approaches. The first comprises the use of a stereogenic carbon in the amine that can induce some regioselectivity on the formation of the new carbon−nitrogen bond. In this case, the enantiomerically pure compound is obtained only after amine deprotection. The second method uses an enantiopure or enantioenriched boronic ester, resulting in the formation of an enantiomerically pure side product. A more elegant process is the use of a chiral ligand that can complex with the boronic ester leading to a diastereoisomeric transition state that further results in the formation of an enantioenriched product (Scheme 43).

The first report in the asymmetric version of this reaction was made by Petasis, using an enantiomerically pure amine with two different boronic acids. In both cases, the secondary aryl glycine was obtained in reasonable yields, although in poor diastereoselectivity. In fact, the use of α-methylbenzyl amine with 4-methoxyphenylboronic acid or 4-allyl phenylboronic acid resulted in the formation of the arylglycine derivatives in only 35 and 28% *de*, respectively.[19] In the first report made by Petasis on the preparation of vinyl glycine derivatives, the use of enantiomerically pure primary amines was tested. While in the case of α-methylbenzylamine the product **156** was obtained in only 66% *de*, the use of (S)-2-phenylglycinol was much more effective and the resultant vinylglycine **157** was obtained as a single diastereomer in 78% yield (Scheme 44).[15a]

Jiang and co-workers tested this same reaction in the preparation of optically active indolyl *N*-substituted glycines

Scheme 43



Scheme 44

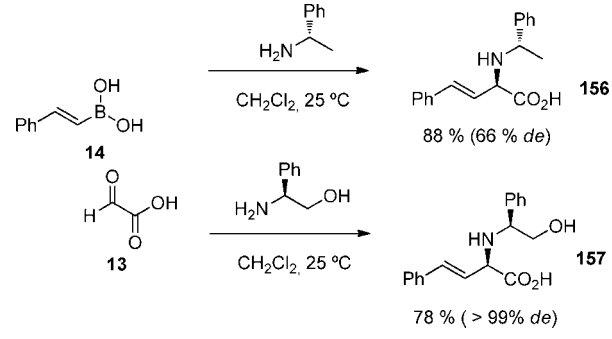
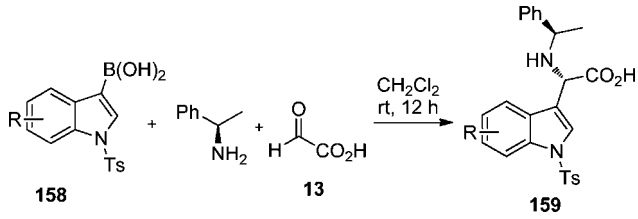
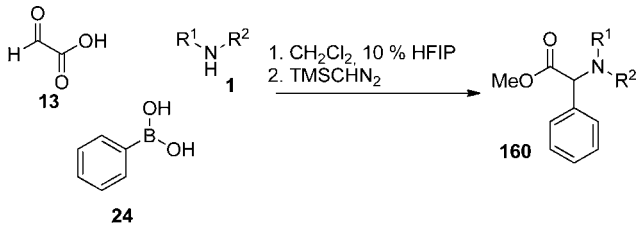


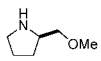
Table 23



entry	R	yield (%)	product	*de* (%)
1	H	77	**159a**	99
2	5-O CH_2Ph	68	**159b**	99
3	5-Br	64	**159c**	99
4	6-Br	71	**159d**	99

Table 24



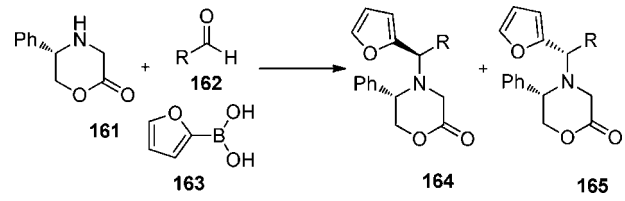
Entry	Amine	Time (h)	Diastereomeric Ratio	Product	Yield (%)
1		22	> 95:5	**160a**	80
2		19	> 95:5	**160b**	90
3		7	> 95:5	**160c**	96
4		24	> 95:5	**160d**	85
5		24	-		No Reaction
6		24	-		No Reaction
7		24	50: 50	**160e**	80

159. *N*-tosyl-3-indolylboronic acid **158** reacted with glyoxylic acid using chiral methylbenzylamine as the chiral auxiliary and the secondary amines were obtained exclusively as one diastereoisomer in reasonable yields (Table 23).[69]

A similar procedure was adopted for the preparation of pyrrolidine-derived arylglycines **160** in high diastereoselectivity. The use of hexafluoroisopropanol as an additive in dichloromethane was found to accelerate the reaction while preserving the yield and the stereoselectivity observed in neat dichloromethane. Concerning the scope of the reaction, the authors observed that the reaction proceed efficiently using electron-rich and sterically hindered aryl boronic acids, unlike the introduction of electron-deficient boronic acids which led to absence of reaction. Hindered pyrrolidine and less basic piperidine were observed to be inert under the reaction conditions, while others afforded the desired products in good diastereoselectivities (Table 24, entries 5 and 6).[70]

Employing (*S*)-5-phenylmorpholin-2-one **161** as a chiral template and 2-furylboronic acid **163**, a series of enantiomerically pure α-amino acids were prepared after successive modifications on the Petasis-borono Mannich reaction products. Considering the aldehydes studied, it was possible to observe that the reaction is prone to steric constraints in the aldehyde, despite the high diastereoselectivity obtained (Table 25).[71]

Table 25



		yield (%)		
entry	R	**164**	**165**	*de* (%)
1	H	69		
2	Pr	59	2	93
3	Bu	69	5	90
4	$Ph(CH_2)_2$	66	4	89
5	$PhCH_2OCH_2$	64	3	86
6	*i*-Bu	71	3	92
7	*t*-$BuCH_2$	75	3	92
8	*c*-C_6H_{11}	6		>95
9	*i*-Pr	7		>95

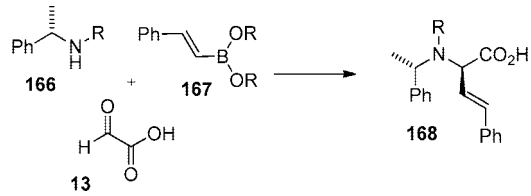
As aforementioned, another way to achieve enantiomerically enriched Petasis reaction products is through the use of a homochiral boronic acid derivative. In fact, Scobie and co-workers developed a methodology for the preparation of 2-morpholin-1-yl-4-phenylbut-3-enoic acids, where chiral boronic esters were employed as the chiral inductor component. Despite the very good yields achieved (59−81%), the α-amino acids were obtained in low enantioselectivity (up to 15% *ee*). However, it should be noticed that the boronic ester herein described can be easily prepared through the condensation between *trans*-2-phenylvinylboronic acid and several diols at room temperature in ethyl ether (yields up to 92%).[72] Recently Southwood and co-workers performed an exhaustive study on the use of boronic esters as components of the Petasis reaction. In such study it was observed that a combination of a bulky boronate ester with a branched amine greatly reduces the yield of the reaction product. *N*,*N*-bis-((*S*)-1-phenylethyl)amine was used in the asymmetric version of this reaction, leading to the exclusive formation of only one diasterioisomer. The conjugation between the chiral boronate and chiral amine elucidated the absence of a matched/mismatched system and the chiral amine was observed to be responsible for the stereochemical outcome (Table 26).[73]

Lou and Schaus recently reported the use of chiral biphenols as effective catalysts for the asymmetric Petasis reaction. From the several BINOL derivatives tested, (*S*)-VAPOL was reported to be the most efficient and the protocol was extended to the use of several heteroaromatic substituted alkenyl boronates and different amines (Table 27). The ^{11}B NMR analysis demonstrated the formation of a tetravalent boronate species.[74]

8. Related Reactions

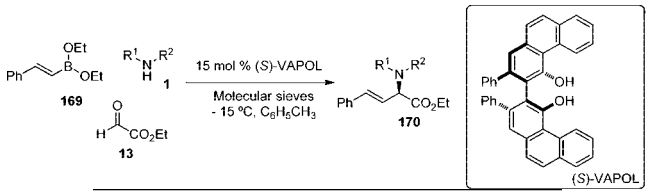
As aforementioned, the PBM reaction is a three component reaction between an aldehyde, an amine, and a boronic acid. However, several other reactions concerning the addition of a boronic acid moiety to iminium ions or imines have been

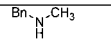
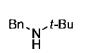
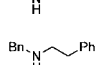
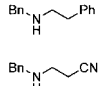
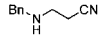
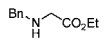
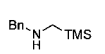
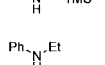
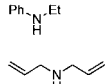
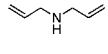
Table 26



	Yield (%)	*dr*	Yield (%)	*dr*	Yield (%)	*dr*	Yield (%)	*dr*
	75	3.5:1	55	2.5:1	-	-	-	-
	60	>95:5	50	>95:5	7	>95:5	1	>95:5

Table 27

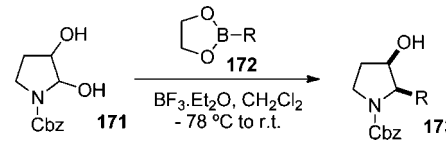


Entry	Amine	Product	Yield (%)	*er*
1		**170a**	81	95:5
2		**170b**	73	93:7
3		**170c**	82	97:3
4		**170d**	80	98.5:1.5
5		**170e**	94	95:5
6		**170f**	84	95.5:4.5
7		**170g**	74	89:11
8		**170h**	87	97:3
9		**170i**	81	*dr* 90:10
10		**170j**	89	*dr* 84:16

developed and will be covered in this section. Preparation of 2*H*-chromenes, consisting in the cyclization of the product resulting from the PBM reaction, will also be covered.

In situ generated *N*-acyliminium ions also react with alkenyl- and arylboronates as reported for the case of pyrrolidine derivatives. The stereochemistry of the alkene is retained in the product and *cis*-2,3-disubstituted pyrrolidines **173** were exclusively formed in good to excellent yields (Table 28).[75] The diastereoselectivity of this transformation allowed the authors to envision a total synthesis of (±)-6-deoxycastanospermine in 32% overall yield (7 steps) in which the addition of organoboronates to *N*-acyliminium ions plays a crucial role. The total synthesis also comprised a alkene dihydroxylation and ring-closing reductive amination as key steps.[76]

Table 28



Entry	R	Product	Yield (%)
1		**173a**	91
2		**173b**	81
3		**173c**	64
4		**173d**	80
5	Ph	**173e**	70
6	4-MeOC$_6$H$_4$	**173f**	83
7		**173g**	98
8		**173h**	77
9		**173i**	99
10		**173j**	81

Using a similar strategy, Pyne and co-workers expanded the previous reaction to enantiomerically enriched cyclic hemiaminals having an *endo*-cyclic *N*-acyl group. The borono-Mannich addition of boronic acids to enantiomerically enriched **174**, led to the *cis*-diastereoselective formation of the product **175** in a 77% yield. Such diastereoselectivity is consistent with the formation of an initial boronate complex **176**, formed with the 5-hydroxy group, followed by intramolecular delivery of the sp^2 hybridized boron ligand to the same face of the iminium ion intermediate (Scheme 45). Boronates were also reported to add to five and six-membered ring *N*-acyliminium ions, in the same diastereoselective fashion, providing 5- and 6-substituted 4-hydroxypyrrolidin-2-ones and 5-hydroxypiperidin-2-ones, respectively. However such procedure is limited to reactive, electron-rich boronic acids.[77]

Starting from a previously formed iminolactone, PBM reaction was successfully applied to the preparation of morpholin-2-ones **178**. The procedure was tested using aryl

Scheme 45

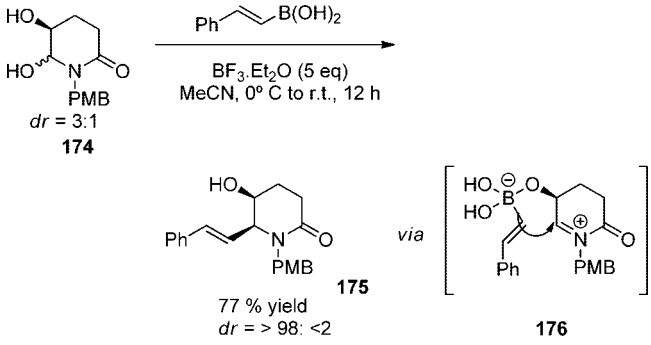
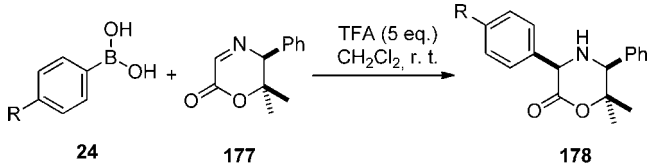
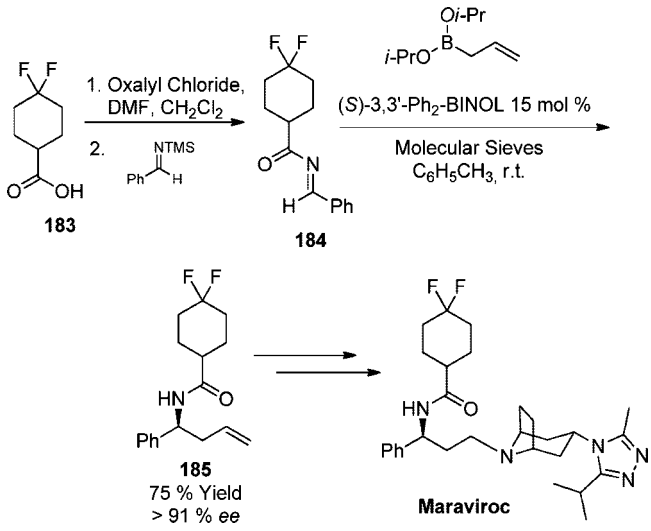


Table 29



entry	R	reaction time (h)	product	yield (%)
1	$PhCH_2O$	1.5	**178a**	94
2	MeO	3.5	**178b**	85

Scheme 46



boronic acids under mild conditions in the presence of trifluoroacetic acid, forming the desired product in good yields as a single diastereomer (Table 29).[78]

Envisioning the preparation of a new class of compounds for HIV therapy that targets the human protein responsible for recognition of the virus, CCR5 antagonist Maraviroc, the asymmetric allylboration of benzoyl imines was developed (Scheme 46). Lou et al. achieved this goal using BINOL derivatives, where (*S*)-3,3′-Ph_2-BINOL was determined to be the most effective catalyst. The interruption of hydrogen bonding or ligand exchange between the boronate **179** and the diol catalyst in Lewis basic solvent was advanced as a possible explanation for the slower reaction rates and lower enantioselectivities in electron donating solvents (THF and Et_2O). Polar noncoordinating solvents gave faster rates and higher selectivities. The addition of molecular sieves to the reaction medium is desirable for the prevention of unstable acyl imine decomposition. An exhaustive study on the reaction mechanism indicates that a dissymmetrical boronate

Scheme 47

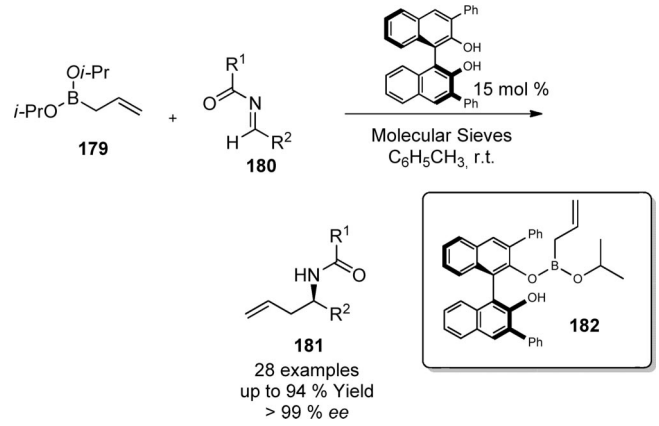
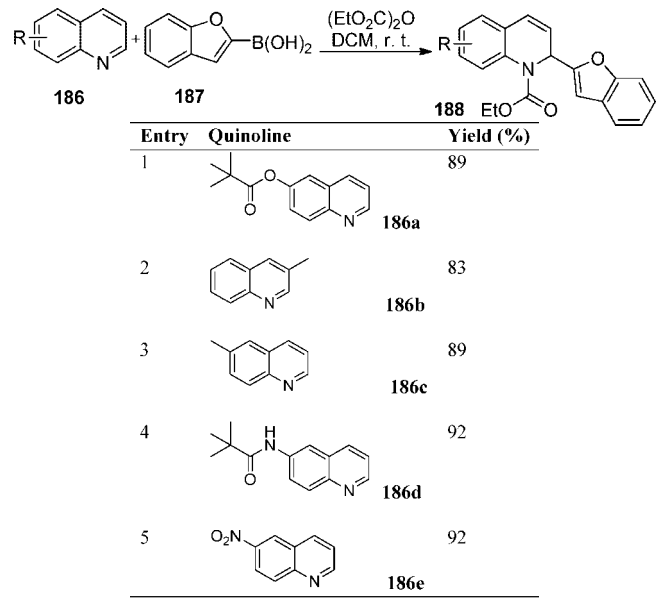


Table 30

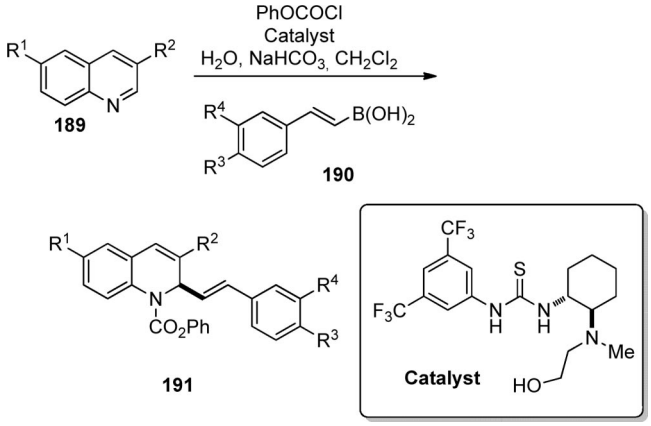


complex **182** without the formation of the corresponding cyclic boronate is the responsible species for the enantioselectivity of the transformation (Scheme 47).[79]

A method for the preparation of 1,2-dihydroquinoline and 1,2-dihydroisoquinoline derivatives was recently reported by Yoon and co-workers. After the observation that 2-ethoxy-1-ethoxycarbonyl-1,2-dihydroquinoline and its isoquinoline isomer reacted with electron sufficient boronic acids, diethyl pyrocarbonate was employed as the activating reagent to achieve the in situ formation of these reactants, starting from quinoline and isoquinoline, respectively. The coupling reaction with 2-benzofuranboronic acid **187** led to the formation of the desired heterocycles in good to excellent yields (Table 30).[80]

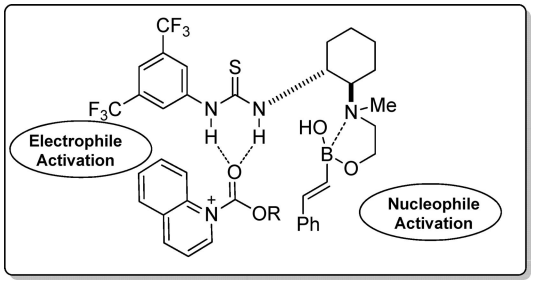
Concerning stereospecific reactions related with the Petasis reaction, the best enantioselectivities were reported by Takemoto and co-workers in the addition of boronic acids to *N*-acylated quinoline salts, using a newly designed thiourea organocatalyst (Table 31). The activating reagent was observed to affect the reaction enantioselectivity and phenyl chloroformate was determined to be better when compared with ethyl and benzyl analogues. The reaction consists in the in situ formation of the *N*-acylated quinoline and further addition of the alkyl moiety of the boronic acid. The thiourea catalyst stands for the formation of a chiral complex as well

Table 31



entry	R^1	R^2	R^3	R^4	T (°C)	product	yield (%)	ee (%)
1	Me	H	H	H	−65	**191a**	75	95
2	H	Me	H	H	−78	**191b**	70	96
3	Cl	H	H	H	−65	**191c**	63	94
4	Br	H	H	H	−65	**191d**	78	95
5	*t*-$BuCO_2$	H	H	H	−65	**191f**	61	96
6	H	H	OMe	H	−78	**191g**	70	97
7	H	H	OCH_2O		−78	**191h**	59	82
8	H	H	OMe	OMe	−78	**191i**	60	89
9	H	H	Me	H	−65	**191j**	60	91
10	H	H	CF_3	H	−40	**191k**	28	95

Scheme 48



as for the dual activation of the nucleophile and the electrophile (Scheme 48).[81]

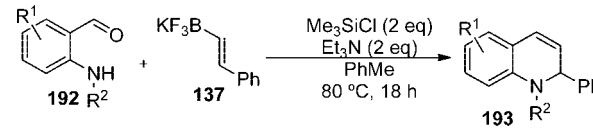
Using trimethylsilyl chloride as a Lewis acid, allowed the preparation of 1,2-dihydroquinolines **193** starting from 2-sulfamidobenzaldehydes **192** in the presence of triethylamine (Table 32). The 1,2-dihydroquinoline sulfamides obtained were further converted into either 2-substituted quinolines or 2-substituted 1,2,3,4-tetrahydroquinolines.[82]

8.1. Preparation of 2*H*-Chromenes

Wang and Finn demonstrated that the use of vinyl boronic acids allows the facile preparation of 2*H*-chromenes **199**. The use of 5 mol % of dibenzylamine in dioxane at 90 °C was found to be enough to promote the product formation in excellent yields in 12 h. The mechanism proposed for this reaction (Scheme 49) involves the iminium ion **195** formation and coordination of the boronic acid to the phenolate oxygen. After the intramolecular transference of the vinyl group, the boronic acid is hydrolyzed, and the cyclization step is promoted by the amine protonation and regeneration of the catalytic dibenzylamine **194**.[55]

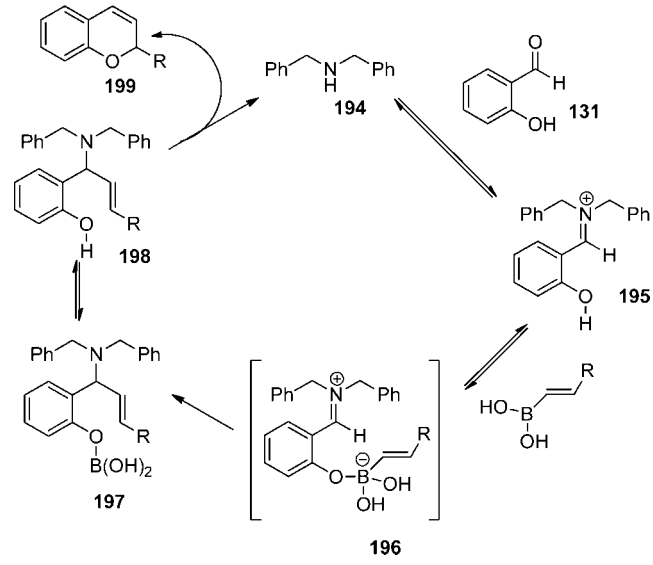
The use of *N*-benzylaminomethyl polystyrene **201** allowed the procedure to be applied in the preparation of several 2*H*-chromenes **202**−**204**, in dioxane at 90 °C for 24 h, where the aldehyde and the boronic acid substituents were studied

Table 32

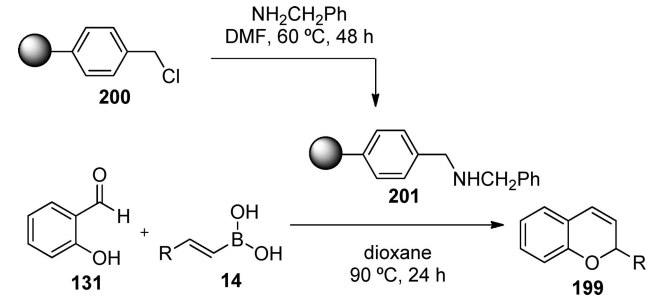


Entry	Product	Yield (%)
1	**193a**	59
2	**193b**	36
3	**193c**	59
4	**193d**	46
5	**193e**	53

Scheme 49



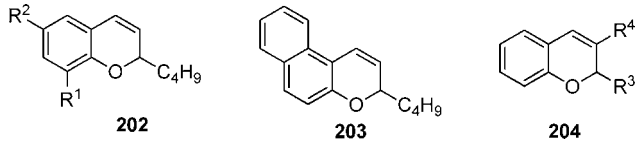
Scheme 50

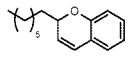


(Scheme 50, Table 33). The reaction was observed to proceed quite well for aryl vinyl boronic acids, as well as for alkyl vinyl homologues, yielding the reaction product after simple filtration of the reaction medium.[55]

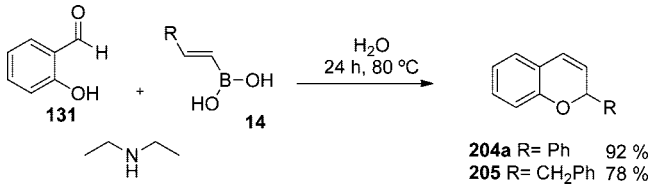
The use of vinyl boronic acids in water also allowed the preparation of 2*H*-chromenes as previously obtained by

Table 33

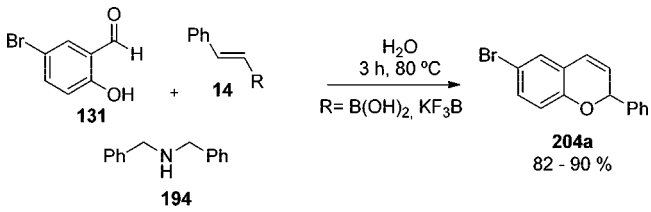


Entry	R^1	R^2	R^3	R^4	Product	Yield (%)
1	H	H	-	-	**202a**	99
2	OH	H	-	-	**202b**	88
3	OMe	H	-	-	**202c**	91
4	H	Br	-	-	**202d**	90
5	Cl	Cl	-	-	**202e**	91
6	*t*-Bu	*t*-Bu	-	-	**202f**	85
7	-	-	-	-	**203**	93
8	-	-	Ph	H	**204a**	96
9	-	-	*t*-Bu	H	**204b**	96
10	-	-	Ph	Me	**204d**	75
11	-	-	$(CH_2)_6CCH$	H	**204e**	95
12	-	-		H	**204f**	91

Scheme 51

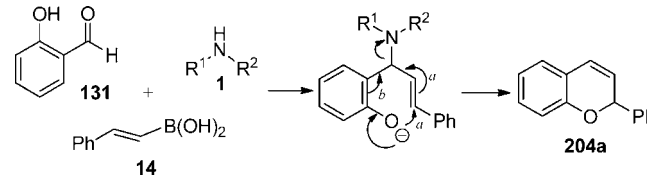


Scheme 52



Wang.[55] However, a stoichiometric amount of amine was necessary to achieve an efficient transformation, and diethylamine was the most competent among several secondary amines tested (Scheme 51).[12] Simultaneously, Petasis and co-workers demonstrated that the cyclization step could be efficiently performed in protic solvents, namely, water and ethanol, with alkenyl boronic acids or alkenyl trifluoroborates in the presence of dibenzylamine (Scheme 52). Despite being less effective, tertiary amines were documented to mediate this process as well, supporting a mechanistic pathway where an ion pair consisting of an electrophilic ammonium species and a nucleophilic borate species are involved.[82] 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[55] (Scheme 53, pathway a) or an 6π-electrocyclization (Scheme 53, pathway b). Bearing this in mind, Gois et al. tested the use of a chiral amine in order to obtain some enantioselectivity in the chromene formation. Since this was not observed,

Scheme 53



using half equivalent of (*S*)-α,α-diphenylprolinol at 80 °C for 24 h, in water at least, the reaction probably proceeds via pathway b.[7]

Analogously to the use of vinyl boronic acids, potassium vinylfluoroborates were explored as efficient components in the preparation of 2*H*-chromenes. In this study, dibenzylamine was used in a catalytic amount (20 mol %), and several salicylaldehyde derivatives were tested in DMF at 80 °C. The desired 2*H*-chromenes were obtained in reasonable to good yields (51−90%).[83]

9. Conclusions and Future Perspectives

The Petasis-borono Mannich reaction has proven to be very versatile, allowing a myriad of different families of compounds to be obtained. Concerning the reactivity of the components used in this reaction, there are some conclusions that can be easily drawn. The use of secondary amines is desirable when compared to primary ones, since the latter usually results in low yields because of the lower reactivity of the imine compared to the iminium formed from the former. Nonetheless, bulky primary amines can be employed and usually the yields obtained are good. Concerning the boronic component, vinyl boronic acids are the most reactive, usually affording the desired products in good to high yields. About the nature of the aldehyde, the three most used aldehydes in the PBM reaction here focused tend to follow the next trend in reactivity: glycolaldehyde > glyoxylic acid > salicylaldehyde.

Regarding the asymmetric version, and despite all the efforts employed, no suitable chiral catalyst has been developed for the general reaction. The upcoming years will certainly bring us some news on this aspect, particularly taken in consideration the recent developments on the field of organocatalysis. One other aspect that seems to be prominent is the discovery of substitutes for each component of the reaction, particularly the discovery of new suitable aldehydes without the need of a hydroxyl group for the boron activation.

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11. Note Added after ASAP Publication

This paper was published on the Web on August 2, 2010. Several changes were made to the text, Tables 3 and 5, and references 1, 2, and 84. The corrected version was reposted on August 23, 2010.

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