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Factors affecting the efficiency and stereoselectivity of α-amino acid synthesis by the Petasis reaction

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Abstract—The use of chiral secondary amines containing only one branched substituent has been shown to give optimal yields and stereoselectivities in the preparation of α-amino acids using the Petasis reaction. While the use of chiral primary amines generally gives products in low to moderate diastereoselectivity, chiral secondary amines generally give products in >95:5 diastereoselectivity. Additionally, the use of amines with two chiral (and by definition, branched) *N*-alkyl substituents results in significantly reduced yields with respect to to secondary amines with one or no branched *N*-alkyl substituents.

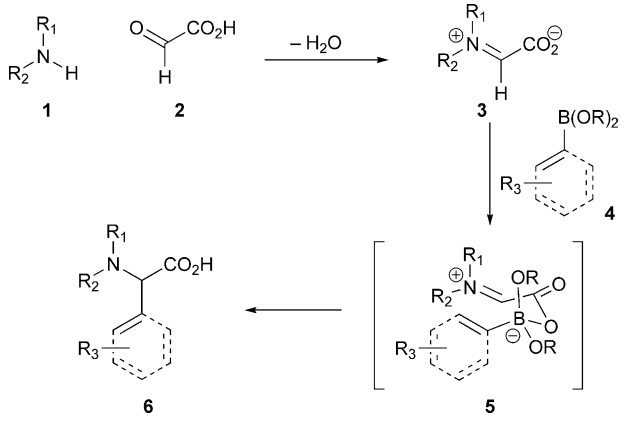
1. Introduction

The Petasis reaction, or boronic acid Mannich reaction, involves the three-component coupling of an amine, aldehyde and organoboronic acid, and has developed over the last few years into a powerful synthetic tool.[1–5] The methodology has been extended to the solid phase,[6–9] and tandem processes involving a Petasis reaction and subsequent Ugi[10–12] or palladium-catalysed process[13] have expanded the scope of the reaction. Recent advances in microwave conditions[14,15] and the use of fluorinated solvents[16] have allowed for high conversions within reasonable reaction times, which had remained one of the major limitations.

One of the most important uses of the Petasis reaction is the synthesis of α-amino acids using glyoxylic acid as the aldehyde component (Scheme 1). A wide range of aryl- and vinyl-boronic acids have been employed in such reactions, allowing the production of a wide variety of arylglycine and vinylglycine derivatives. The use of chiral amines allows the stereoselective production of α-amino acid derivatives, but the range of chiral amines investigated remains limited.

The Petasis reaction proceeds through condensation of the amine **1** and aldehyde to give the corresponding iminium ion **3**. It is believed that when glyoxylic acid (**2**) is employed as the aldehyde, the organoboron species **4** coordinates to the carboxylic acid group, with subsequent intramolecular transfer of the aryl/vinyl group from the activated 'ate'-complex (**5**) of the organoboronic acid yielding the amino acid product **6** (Scheme 1).[6]

Two general trends are apparent from the reported examples of Petasis reactions; vinylboronic acids are more reactive than arylboronic acids, and secondary amines generally give better yields than primary amines (though some branched primary amines appear to be suitable substrates for the reaction). However, despite the wide appeal of the Petasis reaction as a mild method for the preparation of α-amino



Scheme 1. α-Amino acid synthesis from the Petasis reaction.

Keywords: Amino acids; Petasis reaction; Multi-component coupling; Boronic acid Mannich reaction.
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acids, few systematic studies have been conducted to explore the scope and limitations of the process, particularly with regard to stereoselective reactions.

Scobie and co-workers[17] recently investigated the use of chiral boronate esters in the Petasis reaction, but the ee of the products obtained from chiral boronates were very low. However, it was not ascertained whether the low selectivity was due to low stereoinduction by the chiral boronate, or the result of the chiral boronates hydrolysing to the achiral boronic acids, which then dominate the reaction in a stereorandom manner. Scobie also investigated the use of pinacolyl boronate esters in Petasis reactions.[18] Whereas reactions of pinacolyl vinylboronates with secondary amines proceeded in good yield, the corresponding reactions of arylboronates proceeded in only low yield, and the reactions of all pinacolyl boronates with primary amines failed completely.

Given the enormous potential of the Petasis reaction as a general tool for the synthesis of α-amino acids, we have conducted a systematic study of the factors affecting the yield and stereoselectivity of the Petasis reaction, focussing on the effects of the nature and chirality of the amine and organoboron species used.

2. Results and discussion

2.1. Effect of boronate esters and amine

We initially sought to expand the scope of Scobie's study of the reactivity of organoboronate esters in Petasis reactions.[18] We speculated that two factors could result in the lower reactivity of pinacolyl boronate esters compared to the corresponding boronic acids. Pinacolyl boronates form tetrahedral 'ate'-complexes much less readily than boronic acids due to steric interactions between the boron ligand and the methyl groups of the pinacolyl group, which would impede formation of the active species **5**. Alternatively, the bulk of the pinacolyl group could simply hinder the approach of the organoboron group to the iminium ion and/or disrupt the conformation of the active species **5**. Ethyleneglycolyl boronates were therefore employed alongside pinacolyl boronates and boronic acids in order to provide organoboron reagents of intermediate steric bulk. It was expected that ethylene glycol boronates would form tetrahedral 'ate'-complexes relatively easily but experience a degree of steric clash during nucleophilic attack on the iminium ion intermediate between that of a boronic acid and a pinacolyl boronate ester.

An examination of the reactivity of glyoxylic acid **2** and benzylamine **1a** with phenylboronic acid **4a** and the corresponding ethyleneglycolyl and pinacolyl boronates, **4b** and **4c**, was undertaken. Additionally, the reactivity of styrenylboronic acid **7a** and the corresponding ethylene glycolyl and pinacolyl boronates, **7b** and **7c**, were investigated. Phenylboronic acid **4a** was found to react very slowly under standard conditions (room temperature, 48 h, CH_2Cl_2), giving the product *N*-benzylphenylglycine **6a** in low yield (10%) (Scheme 2 and Table 1, row 1). No product was obtained from the corresponding ethylene glycol boronate ester **4b**. The pinacolyl ester **4c** was not investigated given that this was expected to be less reactive than the ethyleneglycolyl ester, and that Scobie and co-workers demonstrated that such reagents are unreactive with primary amines. A similar trend was observed in reaction of the styrenylboron reagents **7a–c** with amine **1b**. As previously demonstrated by Petasis,[1] use of styrenylboronic acid **7a** gave vinylglycine derivative **8a** in good yield (Table 1, row 1). When the corresponding ethyleneglycolyl ester **7b** was employed, the product **8a** was obtained in considerably lower yield (20% cf. 79%). No product was obtained when the pinacolyl ester **7c** was employed, in accordance with the findings of Scobie and co-workers.[18]

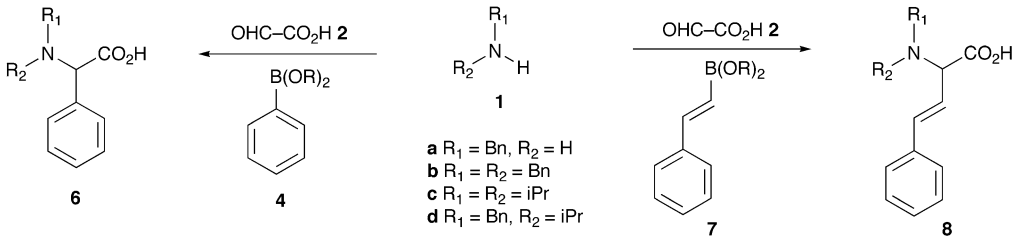
Importantly, the fact that **7b** affords the corresponding α-amino acid, albeit in low yield, indicates that it is possible for boronate esters to participate in the Petasis reaction with primary amines. This reaction proceeded in an identical manner in the presence of dehydrating agents (molecular sieves, magnesium sulfate), indicating that the boronate ester **7b** is participating in the reaction, with hydrolysis to the boronic acid **7a** not being a significant factor.

An analogous series of reactions was then performed with the secondary amine, dibenzylamine **1b**. Phenylboronic acid **4a** reacted in the presence of dibenzylamine **1b** to form the corresponding α-amino acid **6b** in good yield (Table 1, row 2). Both the ethyleneglycol boronate **4b** and pinacolyl boronate **4c** reacted with dibenzylamine **1b** to give the α-amino acid product **6b** in reasonable yield. This is in stark contrast to the result obtained from the reaction of boronate **4b** with benzylamine **1a**, where no product was obtained.

A similar contrast in reactivity was found when the styrenylboronate series **7a–c** was treated with dibenzylamine **1b** and glyoxylic acid **2**. Reactions of the boronic acid **7a**, ethyleneglycolyl boronate **7b** and pinacolyl boronate **7c** all proceeded to give the product **8b** in good yield. These results indicate that sterically demanding boronates can participate in the Petasis reaction providing a secondary amine is used, in accordance with the results of Scobie and co-workers.[18] Again, the addition of dehydrating agents (molecular sieves, magnesium sulfate), did not affect outcome of the reaction, suggesting that the boronate esters **7b**,**c** are participating directly in the reaction, rather than via hydrolysis to the corresponding boronic acid **7a**.

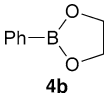
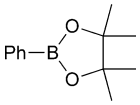
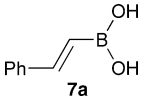
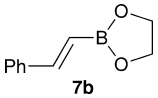
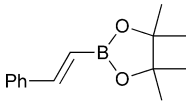
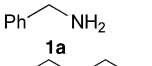
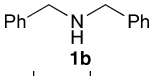
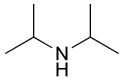
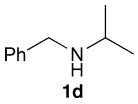
The reaction with diisopropylamine **1c** was next investigated. Phenylboronic acid **4a** reacted with diisopropylamine **1c** and glyoxylic acid **2** to afford the *N*,*N*-diisopropyl α-amino acid **6c** in high yield (84%). The ethyleneglycolyl boronate **4b** gave the product **6c** in low yield (19%). Furthermore, the pinacolyl boronate **4c** failed to react at all. Reaction of diisopropylamine **1c** with the styrenylboron reagents **7a–c** proceeded in an identical manner to the corresponding phenylboron reagents (Table 1, row 3).

A comparison of the yields obtained from diisopropylamine **1c** with those obtained from dibenzylamine **1b** shows that much lower yields of the amino acid product are isolated from reactions of diisopropylamine and boronate esters, particularly in the case of styrenyl pinacolyl boronate **7c** (0% cf. 90%, Table 1, column 6).[19] It is apparent, therefore,



Scheme 2. Preparation of phenylglycine derivatives **6** and styrenylglycine derivatives **8** using the Petasis reaction.

Table 1. Yields of phenylglycine derivatives **6a–d** and styrenylglycine derivatives **8a–d** from Petasis reaction (see Scheme 3)

	 4a	 4b	 4c	 7a	 7b	 7c
 1a	10	0	—	79	20	0
 1b	64	35	35	64	77	90
 1c	84	19	0	84	19	0
 1d	89	43	0	90	39	5

that an increased degree of branching in the iminium ion, in combination with increased steric bulk about the boron, results in a decrease in yield.

In order to gain a broader picture of the effect of branching upon the outcome of the Petasis reaction with boronates, the amine substrate *N*-isopropylbenzylamine **1d** was employed, since the degree of branching of **1d** can be viewed as intermediate between dibenzylamine **1b** and diisopropylamine **1c**. As shown in Table 1, row 4, the boronic acids **4a** and **7a** both afforded the corresponding α-amino acids **6d** and **8d** in high yield. When the ethylene glycol boronates **4b** and **7b** were used in place of the boronic acid, the products were formed in yields intermediate between those obtained from the corresponding reactions with diisopropylamine **1c** and dibenzylamine **1b**. The use of pinacolyl boronates **4c** and **7c** gave no product or only very low yield of the products. It is therefore apparent that monobranched amine substrates are tolerated by ethylene glycol boronates but not by pinacolyl boronates.

These results presented in Table 1 can be interpreted through three factors that influence the outcome of the Petasis reaction. Two of these effects have already been discussed: first, the reactivity of the organoboron species, with vinylboron reagents being more reactive than arylboron reagents, and second, the reactivity of the amine, with secondary amines being generally more reactive than primary amines. The third effect is a steric effect, being the combined effect of steric bulk of both the boronate and amine. It should be noted that the steric bulk of the boronate and degree of branching of the amine by themselves are not predictive of the reaction outcome, but must be considered in combination. That is, combination of a bulky boronate ester with a branched amine greatly reduces the yield of the Petasis reaction product. The ability of the organoboron reagent to form a tetrahedral 'ate'-complex appears not to be a critical factor in the progress of the Petasis reaction, given that pinacolyl boronates can give high yields under certain conditions.

2.2. Stereoselective reactions with chiral amines

We next investigated the effects of the amine and organoboron reagents on the stereoselectivity of Petasis reactions. The reaction of (*S*)-1-phenylethylamine **1e** with styrenylboronic acid **7a** yielded the Petasis reaction product **8e** in high yield (Scheme 3 and Table 2, row 1), as previously demonstrated by Petasis and co-workers.[1] The use of the corresponding ethylene glycol boronate **7b** afforded the product **8e** in moderate yield and with similar stereoselectivity to that obtained from the boronic acid **7a**. Use of the pinacolyl boronate **7c**, however, afforded the product **8e** in low yield and with poor stereoselectivity (Table 2, row 1). Most surprisingly, the direction of the diastereoselectivity was reversed. The major change in stereoselectivity when employing the pinacolylboronate presumably indicates a change in the reaction mechanism or conformation of the transition state. However, whether these results relate to the steric bulk around this system or its lack of propensity to form tetracoordinate species cannot be delineated at this time.

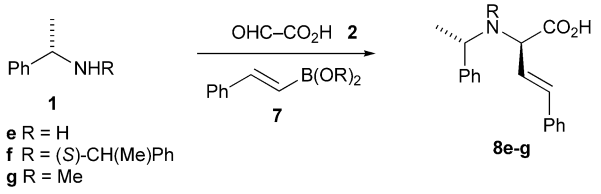
The use of the chiral secondary amine, *N*,*N*-bis-((*S*)-1-phenylethyl)amine **1f** as a substrate in the Petasis reaction was also investigated. Three-component coupling of **1f** with

glyoxylic acid **2** and styrenylboronic acid **7a** gave the product **8f** in moderate yield but with very high stereoselectivity. Only one diastereomer was observed by ^{1}H NMR spectroscopy, indicating the product **8f** was formed in >95:5 diastereomeric ratio. The corresponding ethylene glycol boronate **7b** afforded **8f** in low yield but again with very high stereoselectivity.

Although the stereoselectivity obtained in the reaction of the secondary amine **1f** is much greater that that from the primary amine **1e**, the yields are lower, consistent with the fact that secondary amine **1f** has a high degree of branching, similar to diisopropyl amine. Indeed, the isolated yield for the product formed from the boronic acid **7a** with amine **1f** is much lower than any other obtained from **7a** in this study.

Despite the poor yields obtained from amine **1f**, the high degree of stereoselectivity obtained prompted the investigation of a chiral secondary amine with a reduced degree of branching. Accordingly, a series of reactions with (*S*)-*N*-methyl-1-phenylethylamine **1g** was conducted (Scheme 3 and Table 2, row 3). The results from this series of reactions were very promising. Petasis reaction of amine **1g** with styrenylboronic acid **7a** and glyoxylic acid **2** gave the corresponding amino acid product **8g** in good yield (89%) and high stereoselectivity (>95:5) (Table 2). The yields from the corresponding ethylene glycolyl and pinacolyl boronates, **7b** and **7c**, reduced to moderate and poor, respectively, but the diastereoselectivity remained very high.

Similar results with chiral secondary amines have been observed by Nanda et al.,[16] in which the three-component coupling of phenylboronic acid, glyoxylic acid and various chiral 2-substituted pyrrolidines were studied. In all cases



Scheme 3. Chiral amines in diastereoselective α-amino acid synthesis.

the products were obtained in good yield and >95:5 diastereomeric ratio. Use of 2,5-dimethylpyrrolidine, however—containing two chiral (branched) substituents—resulted in no reaction.

In general, it is apparent that chiral secondary amines give Petasis reaction products in much greater stereoselectivity than reactions of related chiral primary amines. However, secondary amines containing two chiral alkyl substituents by definition have a high degree of branching, which leads to low yields. Nevertheless, we have shown that only one chiral alkyl substituent is required for high degree of stereoselectivity. Chiral secondary amines such as **1g**, containing one chiral alkyl substituent and one achiral (i.e., unbranched) substituent are the optimal reagents for Petasis reactions as they give rise to both high yields and high diastereoselectivities.

2.3. Combination of chiral amines and chiral boronates

While much attention has focused on the participation of chiral amines and aldehydes in the Petasis reaction very little has been placed upon the potential role of chiral boronates. Scobie and co-workers[17] have reported the use of chiral boronate esters such as tartrate- and pinanediol-derived boronates, **7d–f**, in enantioselective Petasis reactions with glyoxylic acid and morpholine. However, in all cases the ee of the amino acid products were very low (ee 6–15%). Despite the poor asymmetric induction provided by chiral boronate esters, we investigated the combination of chiral boronates and chiral amines in order to assess whether the establishment of matched/mismatched systems may lead to improvements in diastereoselectivity. Treatment of (*S*)-1-phenyl-ethylamine **1e** with the enantiomeric tartrate-derived boronates **7d** and **7e** under standard conditions gave the Petasis reaction product **8e** in moderate yield, with the major stereoisomer in each case being the same as that observed from the corresponding reaction with the boronic acid **7a** (Table 3). Use of the D-tartrate derivative **7d** gave the product in a 3.5:1 diastereomeric ratio, only slightly higher than that observed from the boronic acid **7a**. Use of the L-tartrate derivative **7e** gave the product with slightly lower diastereoselectivity (2.5:1). No reaction was observed when the pinane-diol derived

Table 2. Comparison of Petasis reaction yields and stereoselectivities with chiral amines **1e–g** (see Scheme 3)

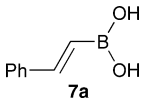
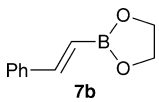
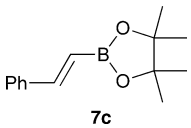
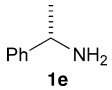
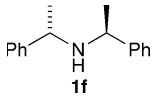
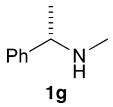
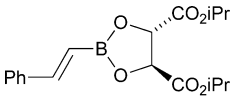
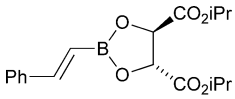
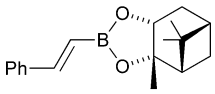
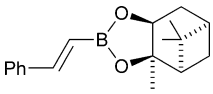
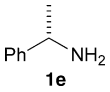
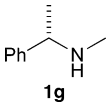
	 **7a**		 **7b**		 **7c**	
	Yield	dr	Yield	dr	Yield	dr
 **1e**	81	3.3:1	47	3.2:1	7	1:1.4
 **1f**	38	>95:5	13	>95:5	—	—
 **1g**	89	>95:5	49	>95:5	21	>95:5

Table 3. Comparison of yields and stereoselectivities of Petasis reaction of **2** and **1e**,**g** with chiral boronates **7d–g**

	 **7d**		 **7e**		 **7f**		 **7g**	
	Yield	dr	Yield	dr	Yield	dr	Yield	dr
 **1e**	75	3.5:1	55	2.5:1	—	—	—	—
 **1g**	60	>95:5	50	>95:5	7	>95:5	1	>95:5

boronates **7f**,**g** were used. Analogous reactions were conducted with the chiral secondary amine **1g**. In all cases the product was obtained in >95:5 diastereomeric ratio, consistent with other reactions of amine **1g**. Products were obtained from the tartrate-derived boronates in reasonable yield, while from the pinane-diol derived bornates the yields were very low. These results indicate that while the use of chiral boronates in combination with chiral amines does result in the generation of matched/mismatched systems, the effects of the chiral boronates are only small and the configuration of the amine dominates the stereochemical outcome of the reaction. However, the use of chiral boronates in the improvement of stereoselectivity of Petasis reactions may find use in limited cases.

3. Conclusion

In conclusion, the yield and stereoselectivity of a Petasis reaction is determined by an interplay of several factors, including the type of amine employed, either primary or secondary, the degree of branching in the amine reagent and the degree of steric hindrance which is imposed by the groups around boron.

The use of chiral secondary amines containing only one branched substituent has been shown to give optimal yields and stereoselectivities in the preparation of α-amino acids using the Petasis reaction. While the use of chiral primary amines generally gives products in low to moderate diastereoselectivity, chiral secondary amines generally give products in >95:5 diastereoselectivity. Additionally, the use of amines with two chiral (and by definition, branched) *N*-alkyl substitutents results in significantly reduced yields with respect to secondary amines with one or no branched *N*-alkyl substituents.

4. Experimental procedures

4.1. General

Infrared absorption spectra were acquired using a Perkin–Elmer 1600 FTIR spectrometer. Compounds were prepared as KBr discs or as thin films between sodium chloride plates. Absorption maxima are expressed in wavenumbers (cm^{-1}). ^1H nuclear magnetic resonance spectra were recorded using a Bruker AC 200B recorded at a frequency of 200.13 MHz or a Bruker Avance 300 recorded at a frequency of 300.13 MHz and are expressed as parts per million (ppm) downfield shift, with deuterochloroform (δ 7.26) as an internal reference, unless otherwise stated. The spectral data is recorded as chemical shift (δ_H), relative integral, multiplicity (s=singlet, br=broad, d=doublet, t=triplet, dd=doublet of doublets, dt=doublet of triplets, m=multiplet, app=apparent) and coupling constant (*J* Hz). ^{13}C nuclear magnetic resonance spectra were recorded using a Bruker AC 200B recorded at a frequency of 50.32 MHz or a Bruker Avance 300 recorded at a frequency of 75.47 MHz. The ^{13}C NMR data are recorded as parts per million (ppm) downfield shift with deuterochloroform (δ 77.2) as an internal reference, unless otherwise stated. Low resolution mass spectra were recorded on a Finnigan PolarisQ ion trap mass spectrometer using electron impact (EI) ionisation mode at 70 eV and a Finnigan LCQ ion trap mass spectrometer (ESI). The molecular ion, designated as $[M^{+\cdot}]$, major fragment peaks are quoted as percentages relative to the base peak intensity. High resolution mass spectra were recorded on a VG Autospec mass spectrometer using EI ionisation mode at 70 eV and a Bruker BioApex FTICR with an Analytica ESI source and magnet strength of 4.7 T. Melting points were determined on a Reichert hot stage microscope and are uncorrected.

Amines **1a–g** were obtained from Sigma–Aldrich. Compounds **4a**, **4c**, **7a** were obtained from BoronMolecular Pty. Ltd.

4.2. Preparation of boronate esters

Boronate esters **7d–g** were prepared according to the method of Scobie et al.[17,18] Other boronate esters were prepared by the following method: to a solution of the appropriate diol in diethyl ether (1 mL/mmol) was added the boronic acid (1 equiv) and dried magnesium sulfate (1 equiv) and the resulting mixture was stirred for 20 h. The mixture was filtered, the solid was washed with ether, and the filtrate concentrated in vacuo to yield the boronate ester.

4.2.1. 2-Phenyl-1,3,2-dioxaborolane (4b). Colourless oil, 90%; ^1H NMR (300 MHz, $CDCl_3$) δ 7.85–7.80 (2H, m), 7.49–7.35 (3H, m), 4.38 (4H, s); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.0, 131.6, 128.0, 66.2 (carbon bearing boron substituent not observed); data in accordance with literature values.[20]

4.2.2. 2-((*E*)-2-Phenylethenyl)-1,3,2-dioxaborolane (7b). Colourless liquid which solidified on standing, 93%; mp 47–48 °C; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.53–7.48 (3H, m), 7.39–7.32 (3H, m), 6.20 (1H, d, J=18.4 Hz), 4.29 (4H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 150.2, 129.1, 128.7, 127.2 65.7 (carbon bearing boron substituent not observed); MS *m/z* (EI) 173.9 [$M^{+\cdot}$] (100%); HRMS *m/z* (EI) found 174.0857, $C_{10}H_{11}BO_2$ requires 174.0852.

4.2.3. 4,4,5,5-Tetramethyl-2-((*E*)-2-phenylethenyl)-1,3,2-dioxaborolane (7c). Colourless liquid, 93%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.50–7.26 (6H, m), 6.17 (1H, d, J= 18.4 Hz), 1.30 (12H, s); ^{13}C NMR (50 MHz, $CDCl_3$) δ 149.6, 137.5, 128.9, 128.6, 127.1, 83.4, 24.8 (carbon bearing boron substituent not observed); MS *m/z* (EI) 230 [$M^{+\cdot}$] (20%), 129 (100), 144 (66); spectral data in accordance with literature values.[21]

4.3. Petasis reactions

Method A. To a suspension of glyoxylic acid monohydrate **2** (1 mmol) in dichloromethane (5 mL) was added the amine **1** (1 mmol) and organoboron reagent (1 mmol) and the reaction was stirred under N_2 for 48 h. The resulting precipitate was isolated by filtration and washed with dichloromethane to yield the product.

Method B. To a suspension of glyoxylic acid monohydrate **2** (1 mmol) in dichloromethane (5 mL) was added the amine (1 mmol) and organoboron reagent (1 mmol) and the reaction was stirred under N_2 for 48 h. The solvent was removed in vacuo and the crude product purified by chromatography on silica to yield the product.

4.3.1. *N*-Benzylphenylglycine (6a). *Method A*. White solid, 10%; mp 219–220 °C (lit.[22] 220–221 °C); ^{1}H NMR (200 MHz, $D_2O+K_2CO_3$) δ 7.45–7.34 (10H, m), 4.16 (1H, s), 3.70 (2H, m); data in accordance with literature values.[22]

4.3.2. *N*,*N*-Dibenzyl-α-phenylglycine (6b). *Method B*. Clear colourless oil, 64%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.61 (1H, br s), 7.53–7.25 (15H, m), 4.83 (1H, s), 4.02 (2H, d, J=13.7 Hz), 3.78 (2H, d, J=13.7 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 174.2, 137.0, 134.0, 130.2, 129.8, 129.2, 128.7, 128.6, 127.8, 67.1, 54.7; data in accordance with literature values.[23]

4.3.3. *N*,*N*-Diisopropyl-α-phenylglycine (6c). *Method A*. White solid, 94%; mp 135–136 °C; ^{1}H NMR (300 MHz, D_2O) δ 7.82–7.32 (5H, m), 5.08 (1H, s), 3.51 (2H, septet, J=6.5 Hz), 1.31 (12H, d, J=6.5 Hz); ^{13}C NMR (75 MHz, D_2O) δ 176.9, 134.3, 131.9, 131.8, 128.8, 63.2, 47.9, 18.9; IR ν_{max} (cm^{-1}) 3015, 2873, 1696, 1622; MS *m/z* (ESI) 236.1 [$M+H]^+$(100%); HRMS *m/z* (EI) found 235.1566, $C_{14}H_{22}NO_2$ requires 235.1572.

4.3.4. *N*-Benzyl-*N*-isopropyl-α-phenylglycine (6d). *Method A*. White solid, 99%; mp 101–102 °C; ^{1}H NMR (200 MHz, $D_2O+K_2CO_3$) δ 7.60–7.20 (10H, m), 5.09 (1H, br s), 3.82 (2H, br s), 2.94 (1H, septet, J=6.5 Hz), 1.05 (6H, d, J=6.5 Hz); ^{13}C NMR (75 MHz, d_6-DMSO) δ 177.5, 134.9, 133.5, 132.7, 130.6, 129.6, 129.5, 128.2, 126.9, 92.1, 50.2, 48.4, 19.6; IR ν_{max} (cm^{-1}) 2922, 1699; MS *m/z* (ESI) 284 [$M+H]^+$(100%); HRMS *m/z* (ESI) found 284.1650, $C_{18}H_{22}NO_2$ requires 284.1651.

4.3.5. *N*-Benzyl-α-(*E*)-phenylethenylglycine (8a). *Method A*. Off white solid, 79%; ^{1}H NMR (200 MHz, $D_2O+K_2CO_3$) δ 7.35–7.11 (10H, m), 6.47 (1H, d, J=15.9 Hz), 6.12 (1H, dd, J=8.2, 15.9 Hz), 3.70 (1H, d, J=8.1 Hz), 3.56 (2H, m); ^{13}C NMR (50 MHz, $D_2O+K_2CO_3$) δ 171.2, 136.1, 133.3, 129.0, 128.6, 128.5, 128.4, 128.2, 128.0, 127.7, 126.9, 63.5, 49.2; data in accordance with literature values.[1]

4.3.6. *N*,*N*-Dibenzyl-α-(*E*)-phenylethenylglycine (8b). *Method B*. Colourless oil, 64%; ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.26 (1H, br s), 7.45–7.24 (15H, m), 6.70 (1H, d, J=16.0 Hz), 6.38 (1H, dd, J=8.4, 16.0 Hz), 4.23 (1H, d, J=8.4 Hz), 4.06 (2H, d, J=13.5 Hz), 3.78 (2H, d, J=13.5 Hz); ^{13}C NMR (50 MHz, $CDCl_3$) δ 172.9, 138.1, 136.1, 136.0, 129.3, 128.9, 128.7, 128.5, 128.2, 126.9, 120.7, 65.5, 55.1; IR ν_{max} (cm^{-1}) 3021, 2849, 1711, 1628; HRMS *m/z* (ESI) found 358.1813, $C_{24}H_{24}NO_2$ requires 358.1807.

4.3.7. *N*,*N*-Diisopropyl-α-(*E*)-phenylethenylglycine (8c). *Method A*. White solid, 84%; mp 111–112 °C; ^{1}H NMR (300 MHz, D_2O) δ 7.61–7.41 (5H, m), 7.03 (1H, d, J=15.7 Hz), 6.36 (1H, dd, J=9.8, 15.7 Hz), 4.69 (1H, d, J=9.8 Hz), 3.90 (2H, br m), 1.48–1.37 (12H, m); ^{13}C NMR (75 MHz, D_2O) δ 173.3, 141.3, 136.0, 129.8, 129.6, 119.7, 65.7, 54.7, 20.1; IR ν_{max} (cm^{-1}) 3011, 2973, 1628, 1616; MS *m/z* (EI^+) 284.1 [$M+Na]^+$(100%); HRMS *m/z* (ESI) found 262.1810, $C_{16}H_{24}NO_2$ requires 262.1807.

4.3.8. *N*-Benzyl-*N*-isopropyl-α-(*E*)-phenylethenylglycine (8d). *Method A*. White solid, 90%; mp 116–117 °C; ^{1}H NMR (300 MHz, D_2O/DMSO + K_2CO_3) δ 7.17–6.85 (10H, m), 6.41 (1H, d, J=16.1 Hz), 6.04 (1H, dd, J=8.7, 16.1 Hz), 3.93 (1H, d, J=8.7 Hz), 3.57 (1H, d, J=15.0 Hz), 3.46 (1H, d, J=15.0 Hz), 3.04 (1H, septet, J=6.2 Hz), 0.92 (6H, m); ^{13}C NMR (75 MHz, D_2O/DMSO + K_2CO_3) δ 179.4, 141.5, 137.3, 132.7, 129.5, 129.3, 129.0, 128.6, 128.0, 127.0, 126.9, 71.4, 51.5, 51.1, 20.9; IR ν_{max} (cm^{-1}) 3029, 2983, 1621, 1616; MS *m/z* (ESI) 332.1 [$M+Na]^+$(100%); HRMS *m/z* (ESI) found 310.1810, $C_{20}H_{24}NO_2$ requires 310.1807.

4.3.9. *N*-((*S*)-1-Phenylethyl)-(*R*)-α-(*E*)-phenylethenylglycine (8e). *Method A*. White solid, 97%; ^{1}H NMR (200 MHz, $D_2O+K_2CO_3$) major isomer δ 7.55–7.35 (10H, m), 6.48 (1H, d, J=15.9 Hz), 6.22 (1H, dd, J=8.4, 15.9 Hz), 3.91 (1H, q, J=6.6 Hz), 3.70 (1H, d, J=8.4 Hz), 1.42 (3H, d, J=6.6 Hz); minor isomer δ 7.55–7.35 (10H, m), 6.53 (1H, d, J=16.0 Hz), 6.17 (1H, dd, J=8.0, 16.0 Hz), 3.89 (1H, q, J=6.6 Hz), 3.61 (1H, d, J=8.0 Hz), 1.44 (3H, d, J=6.6 Hz); ^{13}C NMR (75 MHz, D_2O/DMSO + K_2CO_3) major isomer δ 178.9, 144.3, 137.1, 134.2, 129.2, 129.1, 128.5, 128.2, 127.7, 127.3, 126.9, 64.2, 54.7, 24.0; minor isomer δ 179.5, 145.2, 137.1, 132.8, 129.2, 129.1, 128.5, 128.1, 127.5, 127.3, 126.9, 65.1, 55.9, 22.7; data in accordance with literature values.[1]

4.3.10. *N*,*N*-Bis-((*S*)-1-phenylethyl)-(*R*)-α-(*E*)-phenylethenylglycine (8f). *Method B*. Colourless oil, 38%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.47–7.22 (15H, m), 6.83 (1H, d, J=15.9 Hz), 6.46 (1H, dd, J=8.9, 15.9 Hz), 4.54 (2H, q, J=6.9 Hz), 4.39 (1H, d, J=8.9 Hz), 1.69 (6H, d, J=6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 141.5, 137.3, 136.2, 129.0, 128.8, 128.4, 128.2, 127.8, 126.7, 123.7, 62.5, 56.9, 17.6; IR ν_{max} (cm^{-1}) 3029, 2976, 1721, 1626; MS *m*/*z* (ESI) 386 (100%) $[M+H]^+$; HRMS *m*/*z* (ESI) found 386.2116, $C_{26}H_{28}NO_2$ requires 386.2120.

4.3.11. *N*-Methyl-*N*-((*S*)-1-phenylethyl)-(*R*)-α-(*E*)-phenylethenylglycine (8g). *Method A*. White solid, 81%; ^{1}H NMR (300 MHz, $D_2O+K_2CO_3$) δ 7.36–7.17 (10H, m), 6.41 (1H, d, J=15.9 Hz), 6.18 (1H, dd, J=8.7, 15.9 Hz), 3.93 (1H, q, J=6.8 Hz), 3.60 (1H, d, J=8.7 Hz), 2.12 (3H, s), 1.28 (3H, d, J=6.8 Hz).

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