Exploring the Petasis reaction through amino acid synthesis

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Abstract

The Petasis reaction was reviewed and shown to be a versatile and efficient reaction for the synthesis of nitrogen containing compounds and α-amino acids.

Many different amines and amine equivalents can be used in the Petasis reaction, in conjunction with a wide variety of aryl and vinyl boronic acids and esters, and a small selection of aldehydes. Chiral reagents can enforce stereochemical control in the reaction. Certain chiral amines and chiral amine equivalents give the highest selectivity.

Several limitations remained for the Petasis reaction: yields were low with sterically small amines and the organoborons were largely limited to aryl, heteroaryl and vinyl derivatives. These limitations were addressed to make the Petasis reaction a more well-rounded and useful synthetic method.

tert-Butyl sulfinamide was explored as an amine equivalent and the kinetics of the Petasis reaction with this reagent were investigated through the use of in situ FT-IR and $^1$H NMR spectroscopy analysis. tert-Butyl sulfinamide and glyoxylic acid both had rate orders of one, whereas styrenyl boronic acid had a rate order of two. This accounted for an observed dramatic increase in reaction rate. A mechanism for this reaction system was proposed, in which the boronic acid acts as both a reagent and as a Lewis acid catalyst.

Allyl boronic acid pinacol esters were synthesised by palladium catalysed borylation of allyl alcohols, and then reacted with tert-butyl sulfinamide and glyoxylic acid to yield allyl glycine derivatives. Isolated yields of the final amino acids were excellent, but the diastereoselective ratios achieved were low to moderate. The addition of scandium(III) triflate to the allyl-Petasis reaction gave excellent control over the syn/anti configuration of the product, resulting in diastereomeric ratios in the order of >20:1. However, stereochemical control at the α-carbon was still moderate. A mechanism was devised to explain this observation and several supporting reactions were conducted.
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*N*-Methyl tert-butyl sulfinamide was synthesised racemically in a single step from the commercially available tert-butyl sulfinyl chloride and methylamine solution. The product was isolated in a pure yield of 98%. Racemic *N*-methyl tert-butyl sulfinamide was applied to a modified allyl-Petasis reaction, which employed molecular sieves to promote the formation of the initial iminium ion, to yield *N*-methyl amino acids in a quick and efficient manner. The use of scandium(III) triflate gave excellent control of the syn/anti configurations. Enantiopure *N*-methyl tert-butyl sulfinamide was also synthesised and applied to the Petasis reaction, resulting in excellent yields and stereochemical control.

This work demonstrated the robust and widely applicable nature of the Petasis reaction as a method to synthesise α-amino acids in an efficient manner. The Petasis reaction can therefore be utilised in the chemical total synthesis of more complex natural products containing unusual amino acids residues.
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Declaration

This is to certify that:

i. the thesis comprises only my original work towards the PhD except where indicated in the main text;

ii. due acknowledgement has been made in the text to all other material used;

iii. the thesis is fewer than 100,000 words in length, exclusive of tables, maps, bibliographies and appendices.

________________________________
Lucie Bradley
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Abbreviations

°C degrees Celsius
Å Angstrom/Ångström
Ac acetate
acac acetylacetonate
Ar aryl
Bn benzyl
Boc tert-butyloxycarbonyl
Bu butyl
cm centimetres
dba dibenzylideneacetone
DCE dichloroethane
de diastereomeric excess
DFT density functional theory
DMA dimethylacetamide
dMAP 4-dimethylaminopyridine
DMF dimethylformamide
DMSO dimethyl sulfoxide
dr diastereomeric ratio
eee enantiomeric excess
eq equivalents
ESI electron spray ionisation
Et ethyl
FT-IR Fourier transform infrared spectroscopy
g grams
h hours
HFIP hexafluoro-iso-propanol
HPLC high-performance liquid chromatography
Hz hertz
i iso
kJ kilojoules
L litres
M molar
Me methyl
mim methyl imidazole
min minutes
mol moles
mm millimetres
MS mass spectrometry
n normal
NMR nuclear magnetic resonance
p para
Ph phenyl
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pin  pinacolato  
ppm  parts per million  
Pr  propyl  
quant.  quantitative  
R  Re 
Rf  retention factor  
rt  room temperature  
S  Si  
s  seconds  
t  tertiary  
tert  tertiary  
Tf  triflate  
TFA  trifluoroacetic acid  
THF  tetrahydrofuran  
TLC  thin layer chromatography  
TMS  tetramethylsilane  
Ts  tosyl  
μw  microwave
Chapter 1: Introduction
Exploring the Petasis reaction through amino acid synthesis
1. Introduction

1.1. Amino acids in nature

Amino acids, along with sugars and nucleotides, are the most fundamental building blocks of life, giving rise to proteins and executing the work of the genetic code.

There are 20 common $\alpha$-amino acids present in humans and hundreds more that arise through the modification of these or from de novo biosynthesis. These $\alpha$-amino acids, as part of larger peptides or other natural products, often exhibit pharmacological activity, opening up the possibility of creating new drug scaffolds. Hence, the synthesis of these moieties in a chemical laboratory is highly desirable for the purpose of drug discovery and development.

![Echinocandin B - antifungal](image1)

![Mycocyclosin - *Mycobacterium tuberculosis* metabolite](image2)

![TMC-95A - proteosome inhibitor](image3)

**Figure 1: Peptidic natural products**

Echinocandin B,$^1$ mycocyclosin$^2$ and TMC-95A$^3$ (Figure 1) are examples of peptidic natural products and offer a small insight into the diversity possible for these
compounds. Mycocyclosin is a small molecule that is of importance to the viability of *Mycobacterium tuberculosis*, whereas echinocandin B and TMC-95A are both large cyclic peptides, which function as antifungal and anticancer compounds, respectively.

### 1.2. Amino acid synthesis

Any approach to the synthesis of complex peptides must address the preparation of highly functionalised α-amino acid components.

![General retrosynthetic routes to α-amino acids](image)

**Figure 2: General retrosynthetic routes to α-amino acids**

There are many different strategies and starting points for the chemical synthesis of α-amino acids, but in general there are four main routes (Figure 2): the electrophilic or nucleophilic alkylation of glycine (a); the addition of cyanide to imines (b); the substitution of α-halo acids (c); and the reduction of α-imino acids or dehydroamino acids (d). Most routes require the separate preparation of the necessary precursor; for example the synthesis of an α-halo acid from the analogous carboxylic acid or the synthesis of an α-imino acid from its corresponding α-keto acid. These processes can be time consuming and cumbersome.
Multicomponent reactions offer a more effective route to the synthesis of amino acids because multiple key bonds are made in a single step. In addition these reactions are often highly atom efficient and can be used to quickly build up large compound libraries.

1.2.1. The Strecker and Ugi reactions

One of the first multicomponent synthetic methods to be developed was the Strecker reaction (Scheme 1).4 The reaction is a three-component coupling, beginning with the condensation of an aldehyde and amine (or ammonia) to generate an imine or iminium ion. Nucleophilic attack by cyanide generates an α-amino nitrile and hydrolysis of this nitrile in aqueous media liberates a carboxylic acid, ultimately yielding an α-amino acid.

The Ugi reaction5,6 is the four-component coupling of an amine, aldehyde, carboxylic acid and isonitrile (Scheme 2). This reaction also proceeds through the formation of an iminium ion, with the subsequent attack of the electrophilic carbon by the isonitrile. The α-amino nitrilium intermediate is attacked by the carboxylic acid, followed by an O→N acyl transfer. As with all multicomponent couplings, the Ugi reaction is an efficient reaction and it is specifically used to generate an α-amino acid containing two amide groups.

\[
\text{Scheme 1: The Strecker reaction}^4
\]
Although both the Strecker and Ugi reactions can produce complex amino acids in a single step, they require harsh conditions, such as the use of cyanide, high temperatures and strong acids, which are frequently incompatible with other functional groups. A popular alternative is to use the Petasis reaction, which yields similar products but requires considerably milder conditions.

### 1.3. The Petasis reaction

The Petasis reaction was first reported as the boronic acid Mannich reaction by Petasis and Akritopoulou in 1993. The three-component reaction employs an amine, an aldehyde and an organoboron reagent (Scheme 3). The reaction allows for the concise synthesis of nitrogen-containing compounds and was initially used as a method for the formation of geometrically pure allyl amines.

**Scheme 3: Initial Petasis reaction with paraformaldehyde**

Conditions: a) dioxane, 90 °C, 10 min; b) dioxane, 90 °C, 30 min, 75-96%.
Organoboron reagents provide an attractive choice of nucleophile. Vinyl and aryl boronic acids (and their boronate esters) are frequently used in organic synthesis, having gained popularity through their application in the Suzuki-Miyaura reaction,\textsuperscript{8} as air and moisture stable reagents that are also tolerant of a broad range of functional groups. The Petasis reaction does not require any harsh reagents or conditions and the organoboron reagents are generally of low toxicity, making the reaction widely applicable and safe.

The Petasis reaction can provide a route to the synthesis of isomers that are unattainable by other methods, such as electrophilic aromatic substitution. This is because the site of attack in the Petasis reaction is directed by the boron, instead of the electronic effects of other substituents (Scheme 4).\textsuperscript{9}

![Scheme 4: Potential retrosynthesis of a tertiary amine](image)

A further benefit of the Petasis reaction is the exclusive preference of the boronic acid to attack the imine carbon-nitrogen double bond, over any carbon-oxygen double bonds that may be present. The vinyl-Petasis reaction also proceeds with retention of the double bond geometry.\textsuperscript{7}

### 1.3.1. Mechanism of the Petasis reaction

The Petasis reaction, as with the Ugi and Strecker reactions, is categorised as a Type II multicomponent reaction. These reactions consist of an unspecified number of reversible steps and an irreversible step. Type II multicomponent reactions are generally versatile and efficient. For the Petasis reaction, the irreversible step is the formation of the new carbon-carbon bond at the α-position, created by the migration of the organoboron substituent to the electrophilic carbon of the imine or iminium ion. This is also the rate limiting step.
It was initially proposed that the mechanism of the Petasis reaction begins with the formation of the imine or iminium ion, by condensation of the amine and aldehyde components. This intermediate would coordinate to the organoboron reagent, creating a tetracoordinate boron species, in one of two ways (Scheme 5): coordination through an α-heteroatom (Pathway A), or coordination to the nitrogen (Pathway B). The rate limiting carbon-carbon bond formation would occur by migration of the boronic acid substituent to the electropositive carbon. The final product would be liberated by hydrolysis of the boronic anhydride.\(^7\)

*Scheme 5: Initial proposed mechanism for the Petasis reaction*\(^7\)

It has been observed that the Petasis reaction is often facilitated by the presence of a nucleophilic functional group, frequently a hydroxyl, at the α-position of the aldehyde. In these situations the reactions are likely to proceed through Pathway A (Scheme 5). The functional group would aid the reaction by coordinating to the electron deficient organoboron reagent, creating a tetracoordinate boronate salt.

An alternative mechanism, beginning with the donating group on the aldehyde coordinating to the organoboron reagent, was proposed.\(^{10,11}\) The boronate-aldehyde
complex would then undergo an amine-aldehyde condensation, followed by migration of the boron substituent to the electropositive carbon (Scheme 6).

Scheme 6: Alternative mechanism of the Petasis reaction

Experimental evidence for this mechanism (Scheme 6) has been found by the observation of an upfield chemical shift in the $^{11}$B NMR spectrum of the boron species after addition of the aldehyde, but before addition of the amine. However, it is not clear how this reaction pathway would proceed in cases such as Petasis and co-workers’ initial paraformaldehyde reactions (Scheme 3), in which there is no donating group on the aldehyde to form the aldehyde-boron intermediate.

All mechanistic pathways (Scheme 5 and Scheme 6) utilise a quaternary boron complex. A comparison of the energies of the transition states for these mechanisms shows that the original mechanism (Scheme 5), using either pathway, is more likely. An analysis of the Petasis reaction mechanism, through computational density functional theory (DFT) calculations, further supports the mechanism originally proposed (Scheme 5).

Substituent migration from the boron to the electropositive carbon, after formation of the boronate complex, requires the surmounting of a 42.8 kJ mol$^{-1}$ energy barrier. This migration is solvent sensitive and, in general, protic solvents hinder the reaction, with water giving a 20.9 kJ mol$^{-1}$ penalty compared with dichloroethane. This has been demonstrated by conducting reactions in water, which required temperatures of up to
80 °C, whereas analogous reactions in non-protic solvents proceeded at room temperature.\textsuperscript{13}

The use of hexafluoro-iso-propanol (HFIP) has been shown to promote the Petasis reaction in a number of cases, shortening the reaction time and increasing yields.\textsuperscript{15-18} However, because HFIP is an expensive solvent its use is not ideal. Microwave irradiation has also been used to enhance the rate of reaction, although complementary improvements in total yields were not observed.\textsuperscript{15}

Recent years have seen the emergence of ionic liquids as an alternative reaction medium. Yadav and co-workers\textsuperscript{19} have used the ionic liquid butyl methyl imidazole with the counterion tetrafluoroborate (BmimBF\textsubscript{4}) as a solvent in the Petasis reaction (Scheme 7). In their reactions to produce alkyl amino phenols both the rate of reaction and corresponding yields obtained were improved: most reactions reached completion in just three hours at room temperature and gave excellent yields. Furthermore, after extraction with diethyl ether the ionic liquid could be reused four or five times without any loss of activity. This reaction medium was shown to be appropriate for a range of aryl boronic acids, secondary amines and salicylaldehyde derivatives.

![Scheme 7: Use of ionic liquids in the Petasis reaction\textsuperscript{19}](image)

**Scheme 7: Use of ionic liquids in the Petasis reaction\textsuperscript{19}**

**Conditions:** a) BmimBF\textsubscript{4}, rt or 80 °C, 5 h, 70-85%.

The migration of the boron substituent is aided by neighbouring electron donating groups. For example, the reaction with 4-methoxyphenylboronic acid proceeded faster than the reaction with phenylboronic acid. The migrating substituent in the Petasis reaction is a carbon nucleophile: if this substituent has greater electron density it is a stronger nucleophile, promoting the migration.
1.3.2. Variation at the amine

The variety of amines that have been used in the Petasis reaction is extensive and includes primary and secondary amines, as well as amine equivalents such as amino acids and hydrazine derivatives.

![Chemical structure of the Petasis reaction]

<table>
<thead>
<tr>
<th>Primary amine</th>
<th>Yield %</th>
<th>Secondary amine</th>
<th>Yield %</th>
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<tr>
<td>PhNH₂</td>
<td>87</td>
<td>PhNPh</td>
<td>64</td>
</tr>
<tr>
<td>PhNH₂</td>
<td>94</td>
<td>i-PrNHi-Pr</td>
<td>84</td>
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<tr>
<td>PhNH₂</td>
<td>54</td>
<td>PhN'Pr</td>
<td>90</td>
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Table 1: Effect of alkyl amines in the Petasis reaction

The synthesis of styrenyl amino acids 1 from styrenyl boronic acid 2 and glyoxylic acid 3 with primary and secondary amines can be achieved in good to excellent yields, with secondary amines proving most effective.\(^{13,15,20-25}\) Sterically small primary amines (e.g. methylamine) give no reaction unless forcing conditions, such as high temperatures, microwave irradiation or the use of HFIP, are employed (section 1.3.1).\(^{15-18,22}\) However, a large steric bulk around the nitrogen results in reduced yields,\(^{13,20,21}\) as seen by the large drop in yield between di- and triphenyl methylamine (Table 1).
The Petasis reaction is tolerant of a variety of functionalised amines (Table 2). Alkyl amines (including adamantyl amine), anilines, allyl amines and \( \beta \)-oxy amines, such as morpholine, all provide Petasis products in high yields.\(^{13,20} \) Primary and secondary propargyl amines have also been used in the Petasis reaction giving excellent yields.\(^{26,27} \)

The sterically bulky adamantyl amine and electron rich 4-aminophenol gave excellent yields (row 2, Table 2). Reactions with morpholine frequently required the addition of heat, due to the decreased electron density about morpholine compared with piperidine. For example, in the reaction of morpholine with glyoxylic acid 3 and 4-methoxystyrenyl boronic acid a temperature of 50 °C was required to produce the product in 76% yield, whereas analogous reactions with piperidine occurred at room temperature.\(^{20} \) Morpholines have also been synthesised through the use of a \( \beta \)-hydroxyamine and an \( \alpha \)-hydroxy aldehyde (Scheme 8).\(^ {28} \) In these examples the
Petasis product underwent a spontaneous cyclisation to produce a substituted morpholine in a single step.

Scheme 8: Synthesis of morpholines by using the Petasis reaction

Conditions: a) EtOH, rt, 24 h, 50-92%.

Other types of amines and amine equivalents have been used in the Petasis reaction with varying success (Table 3).
Aminophosphonates have participated in the Petasis reaction akin to regular amines, with the use of secondary aminophosphonates proceeding in higher yields than their primary counterparts.\textsuperscript{30} Hydrazine derivatives have also been used with simple alkyl or aryl hydrazine bases providing Petasis adducts in good yields. However, incorporation of electron withdrawing substituents reduced the yields, with no reaction observed with the pyridinyl hydrazone.\textsuperscript{31} This problem is also observed with electron deficient amines such as simple amino pyridines.\textsuperscript{32}

Although secondary amines tend to give higher yields in the Petasis product than primary amines, ammonia has also been used in the reaction. However, it was found that the Petasis reactions with ammonia were generally low yielding,\textsuperscript{33} or required an extremely large excess of ammonia to provide chemoselectivity and acceptable yields. Even with a vast excess of ammonia the undesired allylic alcohol, formed by the direct
allylation of the aldehyde without incorporating the nitrogen, was isolated or detected as a by-product in all cases in up to 12% yield (Scheme 9).\textsuperscript{34,35}

\begin{center}
\begin{align*}
\text{O} & \quad + \\
\text{H} \quad \text{R}^1 & \quad \text{Bpin} \quad \xrightarrow{\text{a}} \\
\text{NH}_2 & \quad \text{OH} \\
\text{R}^1 & \quad \text{R}^1
\end{align*}
\end{center}

\textbf{Scheme 9: Petasis reaction with ammonia}\textsuperscript{34,35}

\textbf{Conditions: a) 20\% NH}_3 \text{ in MeOH, rt, 18 h, 66-93\%.}

\(\alpha\)-Amino acids\textsuperscript{10,36} have been employed as the amine component of the Petasis reaction with some success. These reactions can be prone to oligomerisation under certain conditions, but by tethering the amino acid to a resin this has been reduced.\textsuperscript{10}

Other solid supported amines can also be used in the Petasis reaction including piperazine.\textsuperscript{10} For reactions in which both the boronic acid and aldehyde were electron rich no reaction occurred, whereas if just one of the components had high electron density the reaction proceeded in moderate (electron rich boronic acids) to high (electron rich aldehydes) yields. It was hypothesised that this may be due to an electronically induced destabilisation of the activated intermediate. However, a complementary result with electron poor reagents was not observed.

The primary amine equivalent tert-butyl sulfinamide 4 is an effective ammonia substitute and can give excellent yields in the Petasis reaction.\textsuperscript{29,37,38}

\textbf{1.3.2.1. Amine-directed stereocontrol}

Many different chiral amines have been used in attempts to control the stereoselectivity of the Petasis reaction (Table 4).
In general, chiral secondary amines provide higher selectivities than primary amines. For example, α-methyl-benzylamine gave a diastereomeric ratio of just 3.3:1 on reaction with styrenyl boronic acid 2 and glyoxylic acid 3, whereas N-methyl α-methyl-benzylamine gave a diastereomeric ratio in excess of 95:5 (row 1, Table 4). By using the more sterically hindered di(α-methyl benzyl)amine the yield dropped to just 38% but the diastereomeric ratio observed remained in excess of 95:5.21 In reactions with primary chiral amines the use of a sterically larger boronic acid improved the stereocontrol of the Petasis reaction; diastereomeric ratios of up to 88:12 were observed with α-methyl-benzylamine.42 Alternatively, changing the solvent to HFIP increased the diastereomeric ratio to 90:10.15

Both primary and secondary chiral aminophosphonates have been shown to give excellent stereoselectivity30 and there are many other chiral amines that have

### Table 4: Chiral amines in the Petasis reaction

<table>
<thead>
<tr>
<th>Amine</th>
<th>Yield</th>
<th>dr</th>
<th>Amine</th>
<th>Yield</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="PhNH2" /></td>
<td>81</td>
<td>3.3:1</td>
<td><img src="image2.png" alt="NHMe" /></td>
<td>89</td>
<td>&gt;95:5</td>
</tr>
<tr>
<td><img src="image3.png" alt="PO(OEt)2" /></td>
<td>80</td>
<td>&gt;95:5</td>
<td><img src="image4.png" alt="PhNMe" /></td>
<td>59&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt;95:5&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td><img src="image5.png" alt="MeN" /></td>
<td>80</td>
<td>&gt;95:5</td>
<td><img src="image6.png" alt="BocHN" /></td>
<td>80</td>
<td>1:1</td>
</tr>
<tr>
<td><img src="image7.png" alt="HO-N" /></td>
<td>62&lt;sup&gt;b&lt;/sup&gt;</td>
<td>95:5&lt;sup&gt;b&lt;/sup&gt;</td>
<td><img src="image8.png" alt="O" /></td>
<td>97</td>
<td>&gt;20:1</td>
</tr>
</tbody>
</table>

<sup>a</sup> with butanal; <sup>b</sup> with oxaldehyde.21,29,30,39-41
enforced stereocontrol. For example, (S)-5-phenylmorpholin-2-one has provided high diastereoselectivities and it was found that the nature of the aliphatic aldehydes used in the reactions made little difference to the stereochemical outcome, although more sterically hindered aldehydes resulted in poor yields. For example, upon reaction with butanal, (S)-5-phenylmorpholin-2-one gave a yield of 59% and diastereomeric ratio of 96:4, whereas with iso-butanal it gave a 7% yield but a diastereomeric ratio of greater than 98:2. Pyrrolidines with an α-branch also gave good to excellent stereochemical results and this was further improved by using HFIP. If the α-substituent of the pyrrolidine was removed there was no stereochemical control. For example, racemic 2-methyl pyrrolidine gave a diastereomeric ratio of >95:5, but racemic 3-methyl pyrrolidine gave a ratio of just 1:1 (row 3, Table 4).

Stereochemical control by using chiral propargyl amines has been attempted but was unsuccessful. Solid supported piperazine, in which the chiral centre was in the β-position also failed, presumably because the directing group was too far away to control the stereochemistry of the reaction.

The primary chiral amine 2-phenylglycinol 5 has been used in the asymmetric Petasis reaction with varying success (Scheme 10).

![Scheme 10: The use of phenylglycinol 5 in the Petasis reaction](image)

**Conditions:**
- a) styrenyl boronic acid, OHCCO₂H, CH₂Cl₂, rt, 12 h, 78%, dr >99:1;
- b) i) H₂, Pd/C; ii) HCl, MeOH, Et₂O, 76%, dr >99:1.

The addition of a β-hydroxyl group to the amine has been found to improve the stereochemical control of reactions with primary amines. For example, a comparison of α-methyl-benzylamine and N-benzyl-phenylglycinol under similar reaction conditions gave diastereomeric ratios of 67:33 and >99:1 respectively. This large
increase in stereocontrol is thought to arise through a 6-membered chair type transition state, which reduces the 1,3-allylic strain and is stabilised by hydrogen bonding (Figure 3).

![Proposed transition state for Petasis reactions with phenylglycinol 5](image)

**Figure 3: Proposed transition state for Petasis reactions with phenylglycinol 5**

By using a secondary amine and increasing the steric bulk, this conformation was disrupted and selectivities dropped. However, other reactions with N-benzyl-phenylglycinol progressed with poor diastereoselectivity. If aryl boronic acids are used the facile epimerisation of α-aryl glycines may contribute to poor selectivities, but in vinyl systems this is harder to explain.

A limitation of using chiral amines such as phenylglycinol 5 in the Petasis reaction is that the benzyl groups must be removed by hydrogenation if the free amine is desired. This also reduces any olefins in the molecule (Scheme 10). For the asymmetric synthesis of unsaturated amino acids a different auxiliary is required.

**tert-Butyl sulfinamide 4** has been shown to be an effective chiral amine substitute in the Petasis reaction. The *tert*-butyl sulfinyl auxiliary can be removed under mild acidic conditions, which leaves any olefins in the molecule intact (Scheme 11).

![Scheme 11: tert-Butyl sulfinamide 4 in the Petasis reaction](image)

**Scheme 11: tert-Butyl sulfinamide 4 in the Petasis reaction**  
Conditions: a) R′B(OH)2, OHCCO2H; b) H⁺.

In reactions with aryl boronic acids, α-aryl glycine derivatives were synthesised in good yields, but as racemic mixtures. Conversely, in the synthesis of styrenyl amino acids 1, the use of *tert*-butyl sulfinamide 4 resulted in good to excellent
stereoselectivity, from 10:1 up to and surpassing 20:1, depending on the identity of the phenyl ring substituent on the organoboronate.\textsuperscript{29}

Expanding on this work, tert-butyl sulfinyl imino esters have been used in the asymmetric synthesis of amino acid derivatives.\textsuperscript{38,42} By combining tert-butyl sulfinamide 4 with a Lewis acid catalyst, such as indium(III) bromide or iron(III) chloride, a greater level of stereochemical control was enforced over the Petasis reaction (Table 5).

![Reaction Diagram]

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Loading mol%</th>
<th>Yield %</th>
<th>dr</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>-</td>
<td>87</td>
<td>91:9</td>
</tr>
<tr>
<td>In(OTf)\textsubscript{3}</td>
<td>10</td>
<td>64</td>
<td>96:4</td>
</tr>
<tr>
<td>FeCl\textsubscript{3}</td>
<td>10</td>
<td>43</td>
<td>&gt;98:2</td>
</tr>
<tr>
<td>InCl\textsubscript{3}</td>
<td>10</td>
<td>84</td>
<td>95:5</td>
</tr>
<tr>
<td>InBr\textsubscript{3}</td>
<td>10</td>
<td>53</td>
<td>99:1</td>
</tr>
<tr>
<td>InBr\textsubscript{3}</td>
<td>20</td>
<td>50</td>
<td>99:1</td>
</tr>
<tr>
<td>InBr\textsubscript{3}</td>
<td>5</td>
<td>71</td>
<td>&gt;97:3</td>
</tr>
</tbody>
</table>

Table 5: Different Lewis acids and catalyst loading in the asymmetric Petasis reaction\textsuperscript{38}

Conditions: a) CH\textsubscript{2}Cl\textsubscript{2}, rt, 8-12 h.

Addition of the inexpensive iron(III) chloride gave a diastereomeric ratio of above 98:2 if used at 10 mol\% (row 3, Table 5). Increasing the catalyst loading on indium(III) bromide to 20 mol\% gave no improvements to the reaction, whereas lowering the loading to 5 mol\% resulted in a small drop in the selectivity, to give a diastereomeric ratio of approximately 97:3. However, there was an increase in reaction rate and yield. This stereochemical control was applicable across a range of styrenyl boronic acids 2.\textsuperscript{38}
A transition state was proposed in which the imine nitrogen and carbonyl oxygen of the quaternary boronate intermediate were coordinated to the Lewis acid metal (Figure 4). To minimise steric repulsion between the aryl substituent of the boronic acid and the sulfur-oxygen double bond the migrating group prefers to approach from the Re face, if using (S)-tert-butyl sulfinamide 4. This preference for the conformation of the transition state gives the observed stereochemical control for the reaction, in this case resulting in the (R)-product. The absolute stereochemistry of the product was determined by removing the N-sulfinyl group under acidic conditions and comparing the optical rotation of the resulting material with the known compound.38

![Figure 4: Proposed transition state for the asymmetric Petasis reaction](image)

1.3.3. Variation at the boron

Many different organoboron reagents have been shown to be viable Petasis reaction partners with a variety of aldehydes and amines. These include aryl and heteroaryl boronic acids, as well as vinyl boronic acids. By using aryl and heteroaryl boronic acids in the Petasis reaction with an amine and glyoxylic acid 3, aryl glycine derivatives can be synthesised.
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The Petasis reaction with aryl and heteroaryl boronic acids tends to provide higher yields if the boronic acid is electron rich (Table 6). This is because there is greater electron density about the π-system and migrating substituent (section 1.3.1). For example, the reaction of benzhydryl amine, glyoxylic acid 3 and phenylboronic acid gave a yield of 84%, whereas the use of para-fluoro phenylboronic acid gave just 50% yield. The addition of an electron donating substituent such as a para-methoxy or alkenyl group improved the yield to 85% and 90% respectively (Table 6).

Electron deficient boron reagents can also catalyse side reactions, for example those leading to the formation of amides or imino dicarboxylic acids (Scheme 12), which would further reduce the yield of the desired product. For the reactions in Table 6 a bulky diaryl amine was used to prevent these side reactions.

Table 6: Aryl and heteroaryl boronic acids in the Petasis reaction

<table>
<thead>
<tr>
<th>Aryl boronic acid</th>
<th>Yield %</th>
<th>Heteroaryl boronic acid</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>PhB(OH)₂</td>
<td>90</td>
<td>PhB(OH)₂</td>
<td>92</td>
</tr>
<tr>
<td>MeO-PhB(OH)₂</td>
<td>85</td>
<td>F-PhB(OH)₂</td>
<td>84</td>
</tr>
<tr>
<td>PhB(OH)₂</td>
<td>84</td>
<td>PhB(OH)₂</td>
<td>81</td>
</tr>
<tr>
<td>OMe-PhB(OH)₂</td>
<td>50</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>29</td>
</tr>
</tbody>
</table>

9
Vinyl boronic acids have been commonly used in the Petasis reaction, including those with alkyl, aryl and heteroatom substituents. Styrenyl boronic acids have been used particularly frequently (Table 7).

<table>
<thead>
<tr>
<th>Vinyl boronic acid</th>
<th>Yield %</th>
<th>Styrenyl boronic acid</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br B(O-i-Pr)_2</td>
<td>80(^a)</td>
<td>MeO B(OH)_2</td>
<td>99(^c)</td>
</tr>
<tr>
<td>B(OEt)_2</td>
<td>74(^b)</td>
<td>B(OH)_2</td>
<td>94(^c)</td>
</tr>
<tr>
<td>O-Bn</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bu B(OEt)_2</td>
<td>73(^b)</td>
<td>F B(OH)_2</td>
<td>90(^c)</td>
</tr>
</tbody>
</table>

\(^{a} R^{1} = \text{Ph}, R^{2} = R^{5} = \text{H}^{20}, ^{b} R^{1} = \text{Bn}, R^{5} = \text{Et}^{56}, ^{c} R^{1} = \text{tBuS(O)}, R^{2} = R^{5} = \text{H}^{29}\)

Vinyl boronic acids are viable Petasis reaction partners and even those with electron withdrawing groups give good yields (Table 7). Styrenyl boronic acids give excellent yields and as before, greater electron density correlates to higher yields, although the
effect of phenyl substituents has less effect on the final yields than with aryl systems. For example, styrenyl boronic acid 2 gave a yield of 94%, compared to a yield of 90% from para-fluoro styrenyl boronic acid.\textsuperscript{29}

Overall styrenyl boronic acids give the highest yields (90% from para-fluoro styrenyl boronic acid, Table 7), followed by vinyl boronic acids (80% from trans-bromo alkenyl boronic ester, Table 7) and then aryl boronic acids (50% from para-fluoro phenylboronic acid, Table 6).

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|}
\hline
Aryl boronic acid or ester & Yield & Styrenyl boronic acid or ester & Yield \\
\hline
\includegraphics[width=0.2\textwidth]{image1.png} & 89 & \includegraphics[width=0.2\textwidth]{image2.png} & 90 \\
\includegraphics[width=0.2\textwidth]{image3.png} & 43 & \includegraphics[width=0.2\textwidth]{image4.png} & 39 \\
\includegraphics[width=0.2\textwidth]{image5.png} & 0 & \includegraphics[width=0.2\textwidth]{image6.png} & 5 \\
\hline
\end{tabular}
\caption{The effect of esterification\textsuperscript{21}}
\end{table}

The use of phenylboronate esters compared with the free boronic acids resulted in lower yields for the Petasis products (Table 8).\textsuperscript{20-22,36} This is due to the relative steric bulk of the boronic acid or ester. It is more difficult to form the activated tetracoordinate boron intermediate with sterically hindered boronate esters. For
example, a yield of 89% was acquired from phenylboronic acid but no reaction was observed with phenylboronic acid pinacol ester.21

To improve the yields obtained from electron deficient boronic acids, trifluoroborates can be used with boron trifluoride diethyl etherate (Scheme 13).47 An activating group α to the boron is also vital for the success of these reactions.

Scheme 13: Effect of trifluoroborates on the Petasis reaction
Conditions: a) morpholine, 2-pyridine carbaldehyde, DMF/CH$_2$Cl$_2$ (4:6), 50 °C, 48 h, 10%; b) morpholine, 2-pyridine carbaldehyde, THF, Me$_3$SiCl, 20 °C, 16 h, 54%.

More recently, allyl amino acids 6 have been synthesised by using the Petasis reaction. Following an initial screen of allyl metal species with benzaldehyde and ammonia, allyl boronic acid pinacol ester was shown to be the most efficient allylating agent.34 These reactions used ammonia with glyoxylic acid 3,48 2,2-dihydroxyacetic acid34 or hydroxyglycine 735 (Scheme 14).

Scheme 14: Formation of allyl amino acids by Kobayashi et al.34,35
Conditions: a) allyl metal, EtOH, rt, 2 h, 69%-quant; b) i) MeOH; ii) allyl metal, Et$_3$N (20 mol%), MeOH, rt, 18 h, 90%.

Due to the instability of allyl boronic acids 8 Szabó and co-workers49 developed a palladium pincer catalyst for their synthesis from the corresponding allyl alcohol 9 and a diboronic acid or ester. Although this reaction is conducted in situ the other Petasis partners are added after the boronic acid 8 has been formed, because it is thought...
that the amine could interfere with the palladium and result in catalyst deactivation (Scheme 15).

![Scheme 15: Formation of allyl boronic acid 8 in situ for use in the Petasis reaction](image)

**Conditions:**

- **a)** DMSO/MeOH (1:1), catalyst, 40-50 °C, 4-16 h;
- **b)** R^2NH, OHCCO_H, rt, 8-24 h, 52-83%.

Resin-bound boronic acids have been used in the Petasis reaction and follow the trends highlighted previously. For example, in the synthesis of β-mimetics on solid support electron rich boronic acids gave high yields (e.g. 95% with 4-methoxyphenylboronic acid compared with trace product with unsubstituted phenylboronic acid) and the presence of electron withdrawing groups on the boronic acid prevented any reaction from occurring. Sterically hindered boronic acids also gave low yields in these reactions. A resin-to-resin approach, utilising both resin-bound boron reagents and resin-bound amines simultaneously, is also possible for reactions with unstable reagents, or to reduce cleavage and transfer steps. However, with aryl boron reagents these reactions were slow to proceed and the use of solid supports means that the reactions suffer from atom inefficiency.

### 1.3.3.1. Boronic acid-directed stereocontrol

Chiral esters of boronic acids can be used as stereo-directing participants in the Petasis reaction. The directing group on the boronic acid would be removed in the final stage of the reaction, thus acting as a chiral auxiliary.

The reaction of homochiral styrenyl boronic esters (synthesised by the condensation of styrenyl boronic acid 2 with chiral 1,2-diols) provided only low enantioselectivities in the final substituted glycines. Although enantioselectivity was improved by using...
esters with more rigidity, the best selectivity remained low, at just 15% enantiomeric excess (Table 9).

\[
\begin{align*}
R^1 & \quad N \quad R^2 + \quad \begin{array}{c}
\text{Ph} \\
\text{O}_{\text{t-Bu}}
\end{array} \quad B(\text{OR}^3)_2 + \quad \begin{array}{c}
\text{Ph} \\
\text{H}
\end{array} \quad \text{CO}_2\text{H} \rightarrow \quad \begin{array}{c}
\text{Ph} \\
\text{N}\quad \text{R}^1 \quad \text{R}^2
\end{array} \quad \text{CO}_2\text{H}
\end{align*}
\]

<table>
<thead>
<tr>
<th>Boronic ester</th>
<th>ee %</th>
<th>Boronic ester</th>
<th>dr</th>
</tr>
</thead>
</table>
| \begin{array}{c}
\text{Ph} \\
\text{O}_{\text{t-Bu}}
\end{array} \quad B(\text{OR}^3)_2 \quad \begin{array}{c}
\text{Ph} \\
\text{H}
\end{array} \quad \text{CO}_2\text{H} | 6.5^a | \begin{array}{c}
\text{Ph} \\
\text{O}_{\text{t-Bu}}
\end{array} \quad B(\text{CO}_2)^j\text{-Pr} \quad \begin{array}{c}
\text{Ph} \\
\text{H}
\end{array} \quad \text{CO}_2\text{H} | 3.5:1^b |
| \begin{array}{c}
\text{Ph} \\
\text{O}_{\text{t-Bu}}
\end{array} \quad B(\text{OR}^3)_2 \quad \begin{array}{c}
\text{Ph} \\
\text{H}
\end{array} \quad \text{CO}_2\text{H} | 15.3^a | \begin{array}{c}
\text{Ph} \\
\text{O}_{\text{t-Bu}}
\end{array} \quad B(\text{CO}_2)^j\text{-Pr} \quad \begin{array}{c}
\text{Ph} \\
\text{H}
\end{array} \quad \text{CO}_2\text{H} | >95:5^c |

Table 9: Chiral boronic esters in the Petasis reaction

^a^ morpholine;^b^ (S)-1-phenylethanamine;^c^ (S)-N-methyl-1-phenylethanamine.

The use of chiral boronate esters in combination with chiral amines has been shown to produce both matched and mismatched systems.\(^{21}\) For example, two enantiomers of a styrenyl boronate tartrate ester (column 2, Table 9) gave diastereomeric ratios of 3.5:1 and 2.5:1 on reaction with (S)-1-phenylethanamine and glyoxylic acid 3. However, the stereochemical preference of the amine had the most effect on this reaction as changing to the more stereodirecting (S)-N-methyl-1-phenylethanamine gave diastereomeric ratios in excess of 95:5 for both boronic acids.
The reactions of substituted allyl boronates in the Petasis reaction by Kobayashi and co-workers\textsuperscript{34,35} displayed good diastereoselectivity. It was found that the (Z)- and (E)-crotyl boronates gave the anti- and syn-adducts, respectively (Scheme 16), which is the opposite selectivity to that usually seen with the addition of an α-branched allyl group to a nitrogen. In the addition of allyl metals to N-substituted imines, a cyclic transition state promotes the selective formation of the syn-isomer from the (E)-allyl metal and the anti-isomer from the (Z)-allyl metal.\textsuperscript{52} It was hypothesised that the selectivity observed in the reactions of Kobayashi and co-workers was enforced by an α-amino alcohol hemiacetal intermediate (Figure 5). The proposed hemiacetal intermediate for the allyl-Petasis reaction would prevent the reaction from proceeding through the usual cyclic transition state. This gives rise to the observed stereoselectivity, which is the same as for the crotylation of aldehydes.\textsuperscript{53}

**Scheme 16: Substituted allyl boronates in the Petasis reaction\textsuperscript{34,35}**

**Conditions:** a) i) MeOH; ii) Et$_3$N (20 mol%), MeOH, rt, 18 h;

*syn*-product 73%, *anti*-product 65%.

**Figure 5: Proposed hemiacetal intermediate**

$X = O$ or $N$. 
1.3.4. Variation at the aldehyde

The range of aldehydes used in the Petasis reaction has been mostly limited to salicylaldehydes and glyoxylic acid 3.

A scan of aldehydes with different functionalities at the α-position has shown that the presence of a heteroatom adjacent to the aldehyde is extremely beneficial for the Petasis reaction. This is presumably because the heteroatom can coordinate to the boronic acid (section 1.3.1) facilitating the coordination of the boronate to the intermediate imine, although it is possible to form some Petasis products under forcing conditions if this heteroatom is absent (Scheme 3, section 1.3.1). The syntheses of functionalised amino alkyl phenols from salicylaldehydes, however do not proceed with unfunctionalised benzaldehydes.\(^{54}\)

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Cyclic system</th>
<th>Yield %</th>
<th>Glycolaldehyde</th>
<th>Yield %</th>
<th>Glyoxylic acid</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Structure 1" /></td>
<td>88(^a)</td>
<td><img src="image" alt="Structure 2" /></td>
<td>87(^b)</td>
<td><img src="image" alt="Structure 3" /></td>
<td>94(^c)</td>
</tr>
<tr>
<td><img src="image" alt="Structure 4" /></td>
<td>85(^a)</td>
<td><img src="image" alt="Structure 5" /></td>
<td>84(^b)</td>
<td><img src="image" alt="Structure 6" /></td>
<td>76(^d)</td>
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<tr>
<td><img src="image" alt="Structure 7" /></td>
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<td><img src="image" alt="Structure 8" /></td>
<td>84(^a)</td>
<td><img src="image" alt="Structure 9" /></td>
<td></td>
</tr>
</tbody>
</table>

Table 10: The use of α-hydroxy- and α-keto aldehydes or pseudo-aldehydes in Petasis reactions

\(^{a}\) \(R^1 = R^2 = \text{Bn}, \text{Ar} = \text{Ph}\); \(^{b}\) \(R^1 = \text{Bn}, R^2 = \text{Me}, \text{Ar} = \text{Ph}\); \(^{c}\) \(R^1 = \text{Ph}_2\text{CH}, R^2 = \text{H}, \text{Ar} = \text{Ph}\); \(^{d}\) \(R^1 = \text{Ph}_2\text{CH}, R^2 = \text{H}, \text{Ar} = \text{para-methyl phenyl}\).
A range of hydroxy- and α-keto aldehydes have been used in the Petasis reaction (Table 10).

The exact identity of the reagent has little effect on the final outcome of the reaction, unless the electrophilic nature of the carbonyl or pseudo-carbonyl carbon is reduced, or the carbon atom is sterically hindered. Sugars and hydroxyglycine have also been used with similar results.

For cyclic and heterocyclic aldehydes, reduced electron density correlates with lower yields (Table 11). For example, the reaction of 2-pyridine carbaldehyde with styrenyl boronic acid gave low yields, of 10% or less. To improve these yields styrenyl trifluoroborate was used (section 1.3.3). However, even with trifluoroborates the maximum yield was just 54% and the viable aromatic aldehydes remained limited to salicylaldehyde and a small number of derivatives, particularly 2-pyridine carbaldehydes.
To expand the scope of viable aldehydes under catalyst free conditions the reaction between 2-pyridine carbaldehyde with dibenzylamine and styrenyl boronic acid 2 was probed. In accordance with previous literature (section 1.3.1), protic solvents seriously hindered the reaction, whereas dichloromethane and HFIP were much more successful. Acetonitrile promoted the reaction considerably, although no explanation or hypothesis for this result could be offered. Under optimised conditions, of 0.2 M at reflux for 3-15 hours, Petasis products were achieved in 11-96% (Table 12).

![Reaction diagram]

<table>
<thead>
<tr>
<th>Aldehyde</th>
<th>Yield</th>
<th>Aldehyde</th>
<th>Yield</th>
<th>Aldehyde</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image" alt="Pyridine carbaldehyde" /></td>
<td>96</td>
<td><img src="image" alt="Pyridine carbaldehyde with chlorine" /></td>
<td>74</td>
<td><img src="image" alt="Pyridine carbaldehyde with methoxy" /></td>
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</tr>
<tr>
<td><img src="image" alt="Pyridine carbaldehyde with bromine" /></td>
<td>91</td>
<td><img src="image" alt="Pyridine carbaldehyde with pyrrole" /></td>
<td>35</td>
<td><img src="image" alt="Pyridine carbaldehyde with quinoline" /></td>
<td>11</td>
</tr>
</tbody>
</table>

Table 12: Catalyst free Petasis reaction with 2-pyridine carbaldehydes

Aldehydes with mildly electron donating groups gave the highest yields due to the increased electrophilicity of the reactive carbon atom. Steric hindrance about the carbonyl and α-heteroatom caused large drops in yields (Table 12). Other heteroatomic aldehydes that incorporated an additional basic nitrogen, including those with pyridine, pyrrole, imidazole and quinoline functionalities, showed either no reaction, or a complicated mixture of products – a result that could not be explained.
For the use of other types of aldehydes in the Petasis reaction, a general trend of increased yields with glyoxylic acid 3 compared with salicylaldehydes has been observed (Table 13).

<table>
<thead>
<tr>
<th>Salicylaldehyde(^a)</th>
<th>Yield %</th>
<th>Glyoxylic acid 3(^b)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>68</td>
<td></td>
<td>82</td>
</tr>
</tbody>
</table>

Table 13: Comparison of salicylaldehyde and glyoxylic acid 3 in the Petasis reaction
\(^a\) R\(^1\) = H; \(^b\) R\(^1\) = pinacol ester.\(^{22}\)

As for the other reaction partners, resin-bound aldehydes have been applied to the Petasis reaction. For alkyl, aryl and heterocyclic aldehydes, only those with an α-hydroxyl substituent were successful, whereas resin-bound glyoxylic acid 3, either with or without a linker, was more viable.\(^{10}\)

1.3.4.1. Aldehyde-directed stereocontrol

Through the use of optically pure α-hydroxy aldehydes excellent diastereoselectivities can be achieved. In the synthesis of β-amino alcohols only the anti-isomers were created and no racemisation or epimerisation was observed (Scheme 17). The products were formed with excellent control of stereochemistry, in which enantiomeric excesses were greater than 99%.\(^{55}\)
Chiral aldehydes have also been used in the solid supported Petasis reaction but diastereoselectivity varied wildly, although reactions were generally more selective with salicylaldehydes.\textsuperscript{10}

### 1.4. Other variations in Petasis and Petasis-like reactions

The Petasis reaction has been coupled with other reactions to yield libraries of compounds and products with alternative functionalities.

#### 1.4.1. Tandem reactions

Wiatrowska and co-workers\textsuperscript{58} used the Petasis reaction, coupled with the Pomeranz-Fritsch-Bobbitt method as a way to synthesise tetrahydroisoquinoline compounds \textsuperscript{10}. By using glyoxylic acid \textsuperscript{3} with an amino acetal \textsuperscript{11} and an aryl boron reagent the Petasis products were formed in good yields. The subsequent cyclisation reactions, utilising the acetal functionality on the amine fragment, gave the desired quinoline derivatives \textsuperscript{10} (Scheme 18).

In keeping with previous literature reports (section 1.3.2) unhindered secondary amines gave the best yields, whereas small primary amines gave the lowest yields (e.g.
96% from 2,2-dimethoxy-N-methylethanamine compared with 69% from 2,2-dimethoxyethanamine). Variations in the boronic acid component also followed the general reaction trends described previously (section 1.3.3), with yields for the Petasis products dropping with decreasing electron density around the boronic acid (e.g. 96% from 3,4-dimethoxyphenylboronic acid compared with 52% from phenylboronic acid). The Petasis reaction-cyclisation combination can also give piperazinones and related compounds in a similar fashion. Excess boronic acid can be used to drive the Petasis reaction and catalyse the following cyclisation (Scheme 19).

![Scheme 19: Piperazinone synthesis using the Petasis reaction](image)

A tandem Petasis-Ugi condensation reaction has been developed to create a six-component system, although reported yields were fairly low (Scheme 20). In subsequent studies aza-β-lactams were synthesised by the combined Petasis-Ugi reaction followed by a condensation step (Scheme 20).

![Scheme 20: A combined Petasis-Ugi reaction system](image)

Conditions: a) CH₂Cl₂, rt, 48 h; b) MeOH, rt, 24 h, 30-73% over two steps.
Other reactions that have been combined with the Petasis reaction include amine propargylation,\textsuperscript{61} palladium-catalysed cycloisomerisation,\textsuperscript{61,62} the Pauson-Khand reaction\textsuperscript{27,61} and amide couplings.\textsuperscript{43}

Hulme and co-workers\textsuperscript{63} investigated the use of the Petasis reaction followed by a key cyclodehydration to synthesise quinoxalines 12 (Scheme 21). The initial 84\% yield was boosted to 98\% under microwave irradiation.

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\includegraphics[width=0.5\textwidth]{reaction.png}};
\end{tikzpicture}
\end{center}

\textbf{Scheme 21: Synthesis of quinoxalines 12 by Hulme and co-workers}\textsuperscript{63}

\textbf{Conditions:}
\begin{itemize}
\item[a)] $\text{ArB(OH)}_2$, OHCCPhO, CH$_2$Cl$_2$, $\mu$w, 120 °C, 15 min;
\item[b)] 20\% TFA/DCE, rt, 18 h, 77-98\%.
\end{itemize}

A wide range of aldehydes and boronic acids were successful in this reaction although, as expected, increasing the steric hindrance of the aldehyde was detrimental to the final yield. In an unusual observation non-aryl boronic acids, such as styrenyl boronic acid 2, gave low yields, as did pyrazines.\textsuperscript{63}

\section*{1.4.2. Petasis-like reactions}

Portlock and co-workers\textsuperscript{64} have used tertiary aromatic amines in a Petasis-like reaction. The three-component reaction took place upon heating tertiary amines in dioxane with glyoxylic acid 3 or $\alpha$-keto acids, however the products were only synthesised in low to moderate yields (Scheme 22). These reactions proceeded through attack of the aldehyde from the carbon at the 4-position on the aromatic ring to yield \textit{para}-aminobenzoic acids 13.
1,3,5-Tri-oxygenated benzenes have been used to produce analogous compounds, incorporating an oxygen atom in place of nitrogen in the final product,\textsuperscript{64} and indoles have also been used in pseudo-Petasis reactions (Scheme 23).\textsuperscript{65}

Scheme 23: Indoles in a pseudo-Petasis reaction\textsuperscript{65}

Conditions: a) R\textsuperscript{2}B(OH)\textsubscript{2}, OR\textsuperscript{2}CCO\textsubscript{2}H, dioxane, reflux, 12 h, 26-70%.

1.5. Summary

The Petasis reaction has been shown to be a versatile and efficient reaction for the synthesis of nitrogen containing compounds and α-amino acids.

An extensive review of the available literature has shown that a wide range of amines can be used in the Petasis reaction, including primary and secondary alkyl, aryl and heteroaryl amines. Secondary amines gave higher yields than their primary amine counterparts. However, bulky primary amines have been almost or equally as successful, depending upon the nature of the substituents. Extremely sterically hindered amines gave low yields.

Many different alkyl, aryl, allyl and propargyl amines, as well as β-hydroxy amines, provided high yields in the Petasis reaction. Functionalised amines including aminophosphonates, hydrazine derivatives and amino acids are also viable partners,
although yields varied. In general, more electron poor amines gave lower yields. Ammonia and solid supported amines have also been used in the Petasis reaction with moderate success.

Amines such as (S)-5-phenylmorpholin-2-one have shown great success as chiral templates in the Petasis reaction, whereas others, such as α-methyl-benzylamine and (S)-2-phenylglycinol, show variable results. The presence of a branched substituent in the α-position was key to providing good stereoselectivity in the reaction. tert-Butyl sulfinamide 4 has been used as a chiral amine substitute and the ease of removal of the tert-butyl sulfinyl group made it a powerful auxiliary. tert-Butyl sulfinamide 4 has also been used in conjunction with a Lewis acid catalyst to enforce diastereomeric ratios of up to 98:2 in the Petasis reaction, depending upon the nature of the reagents used.

Aryl and vinyl boronic acids are the most commonly used organoborons in the Petasis reaction. A general trend is observed, in which reactions with vinyl boronic acids, and particularly styrenyl boronic acids, gave higher yields than reactions with aryl boronic acids. Electron rich boronic acids provided higher yields, due to the increased nucleophilicity of the migrating substituent. This observation was supported by DFT calculations, which found that increasing the electron density on the boron substituent led to a reduction in the energy needed for the associated migration.13

Boronate esters gave lower yields than free boronic acids due to the increased steric hindrance around the boron, which negatively affected the formation of the tetravalent boronate complex. Nevertheless, boronate esters can be useful in the Petasis reaction; chirality in the ester region of organoboronates has enforced stereochemical control over the Petasis reaction, without the need for the chiral directing group to remain in the final product. Several different reports have documented the use of chiral boronates, however the stereoselective success of these reagents has been limited and the potential directing power of the amine was much more prominent.
For the aldehyde, a wide range of carbonyl compounds are viable Petasis reaction partners. An α-heteroatom was extremely valuable to the reaction for coordination to the boronic acid component. Sterically hindered aldehydes performed less well, providing lower yields, and the presence of electron withdrawing groups hindered boron coordination, although electron rich aldehydes may be less reactive to the initial condensation step with the amine. It has been found that glycolaldehydes provide the highest yields, followed by glyoxylic acid 3 and then salicylaldehydes. For the latter group of compounds the effect of the solvent was found to be quite dramatic, with acetonitrile providing excellent yields in most cases. Literature reports to date on the use of chiral aldehydes in the asymmetric Petasis reaction have had varying success.

A range of synthetic methods have been combined with the Petasis reaction to increase the diversity of attainable products. Amongst these are the Pomeranz-Fritsch-Bobbitt method to synthesise tetrahydroisoquinoline compounds 10 from amino acetics 11, Ugi reactions and palladium-catalysed couplings and cyclisations. Petasis-like reactions have also been developed for aromatic substitution.

1.6. Project aims

A full analysis of the available literature regarding the Petasis reaction has highlighted that although extensive research has been completed there are several limitations of this otherwise useful reaction. The use of different amines and boronic acids in the Petasis reaction has been studied extensively, but small amines have tended to fail and the organoborons have been limited to aryl, heteroaryl and vinyl derivatives.

This thesis aims to expand upon the current literature knowledge of the function, mechanism and scope of the Petasis reaction, specifically as a method for the synthesis of α-amino acids.

The kinetics of the Petasis reaction will be explored and the scope of the reaction will be probed in an attempt to expand its capacity. In particular, the use of allyl boronic acids and tert-butyl sulfinamide 4 will be investigated.
Chapter 2: Vinyl systems
Exploring the Petasis reaction through amino acid synthesis
2. Vinyl systems

Vinyl and aryl boronic acids are the most utilised organoboron reagents in the Petasis reaction. Vinyl boronic acids are particularly valuable reagents, providing higher yields and faster reaction times than their aryl counterparts.

Previous studies in the Hutton group\(^{29}\) have found that the outcome of the Petasis reactions employing tert-butyl sulfinamide 4 were dependent on the concentration of the reaction. With all reagents (tert-butyl sulfinamide 4, styrenyl boronic acid 2 and glyoxylic acid 3) at 0.20 M the product was formed in a yield of 55% (70% conversion) after 48 hours. However, at 0.33 M the reaction had reached completion after just 12 hours and an isolated yield of 94% was achieved. Hence, this 1.65-fold increase in concentration resulted in an approximate four-fold boost in the rate, as well as a considerable rise in the final yield. This dramatic increase in rate suggests that this particular Petasis system may not be a first-order reaction.

The mechanism for the synthesis of styrenyl amino acid derivatives 1 from tert-butyl sulfinamide 4 was therefore investigated to further understand the role each reagent plays in the kinetics of the system.

2.1. ReactIR™ studies

Reaction analysis by in situ Fourier Transform Infra-Red (FT-IR) allows for the real time monitoring of a reaction. It was hoped that the various components of the reaction (Scheme 24) would be distinguishable by FT-IR analysis and the rate could be monitored by the increase or decrease of a chosen FT-IR peak, by using ReactIR™.
An analysis of: the solvent, dichloromethane; the starting materials tert-butyl sulfinamide 4, styrenyl boronic acid 2 and glyoxylic acid 3; and imine intermediate 14 – prepared from a 1:1 mixture of tert-butyl sulfinamide 4 and glyoxylic acid 3 – each dissolved in dichloromethane, revealed a peak that is specific to the imine 14 at a wavelength of 1732 cm\(^{-1}\) (Graph 1). The nearest neighbouring peak, at 1636 cm\(^{-1}\), was deemed far enough away to avoid interfering with the relative height of the imine 14 stretch.

A test reaction was performed at a concentration of 0.125 M for each reagent in dichloromethane. The tert-butyl sulfinamide 4 and glyoxylic acid 3 were stirred together at room temperature for 30 minutes before the boronic acid 2 was added.
Analysis of the FT-IR traces acquired from this reaction, at specific time points after the addition of the boronic acid, (Graph 2) showed a decrease in the imine 14 peak at 1732 cm\(^{-1}\), presumably due to the formation of the product.

By monitoring the change in height of the peak at 1732 cm\(^{-1}\) over time, an initial increase in the height of the peak was observed. As the reaction progressed, the peak at 1732 cm\(^{-1}\) decreased in height, corresponding to a decrease in the amount of imine 14 in the reaction. A series of reactions were then performed by varying the concentration of one reagent between 0.031-0.625 M, whilst keeping the other reactants at 0.125 M.

By using the ConcIRT™ data treatment of the iC IR™ program, the change in height of the peak at 1732 cm\(^{-1}\) was monitored over time, relative to the baseline at 1833 cm\(^{-1}\). Analysis of a plot of the data showed that the initial rates did not follow a clear trend and it was hypothesised that this was caused by poor solubility. In addition, the volatility of dichloromethane was a problem; the reaction vessel could not be fully sealed if the probe was in use and, given the small scale of the reactions, any evaporation would affect the concentration and reaction rate significantly.
To address these issues the solvent was changed to methanol, because of its lower volatility and the improved reaction homogeneity. Reactions were also run at a higher concentration (reagent concentration varied between 0.039-0.781 M and control reagents held at 0.156 M), leading to shorter reaction times, which further reduced problems caused by solvent evaporation. An analysis of the solvent, starting materials and intermediate 14 were conducted, as before (Graph 1), to identify a peak belonging to intermediate 14 to monitor.

Data analysis showed a change in rate with an increase in the concentration of boronic acid 2 (Graph 3). This data was analysed according to an exponential function (Equation 1), in which $k$ was the initial rate of reaction.

\[ y = y_0 + Ae^k \]

**Graph 3: Decrease in imine 14 FT-IR peak over time with various amounts of boronic acid 2**

**Conditions:** (S)-t-BuSONH$_2$, styrenyl boronic acid, OHCO$_2$H, MeOH, rt.

Despite promising preliminary results the values acquired for $k$ from these reactions did not follow a trend (Graph 4).
Chapter 2 | Vinyl systems

It was determined that the initial decrease in the intensity of the imine 14 peak (time 15-65 seconds, Graph 3) was due to the dilution effect of the addition of the boronic acid 2 solution. This meant that the initial rate could not be monitored. The remainder of the reaction continued with a slow rate of reaction, because the protic solvent hindered the reaction, as has been found in the literature (section 1.3.1). These rates did not provide robust values for $k$. Furthermore, in methanol the carbonyl FT-IR stretch of glyoxylic acid 3 became much more prominent and overlapped slightly with the imine 14 stretch, thus interfering with the data analysis.

2.2. $^1$H NMR studies

Due to the problems with ReactIR™, investigations shifted to use $^1$H NMR spectroscopy as the analytical tool, because reactions could be conducted in sealed tubes to avoid any loss of solvent. A series of Petasis reactions was conducted in deuterated chloroform and a $^1$H NMR spectrum was obtained approximately every 2.5 minutes for the first hour. A subsequent spectrum was taken several hours later (Figure 6).
The Petasis reaction (Scheme 24) gives the product 1 as a 10:1 mixture of diastereomers. The α-proton can be seen at δ 4.70 ppm as a doublet of doublets, with $J$ values of 6.3 Hz and 5.3 Hz, whereas the vinylic protons, Hb and Hc, appear in the spectrum between δ 6.8-6.2 ppm (Figure 6). For the major isomer, Hb can be seen as a doublet of doublets at δ 6.21 ppm, with $J$ values of 15.8 Hz and 6.3 Hz (corresponding to the trans and vicinal couplings), and Hc appears at δ 6.72 ppm as a doublet with a $J$ value of 15.8 Hz (for the trans coupling). In the minor diastereomer Hb appears as doublet of doublets at δ 6.35 ppm, with $J$ values of 15.8 Hz and 6.9 Hz (for the trans and vicinal couplings), whereas Hc is a doublet with a $J$ value of 15.8 Hz (for the trans coupling) at δ 6.78 ppm.

The reaction progress could be monitored by analysing the increase in the integration of a known product peak. The γ-vinyl proton ‘Hc’ was observed as an unobstructed doublet in a 10:1 ratio of diastereomers (Figure 6) and was therefore chosen for monitoring the reaction rate and for determining the diastereomeric ratio. The
integration of the γ-vinyllic proton (Hc) at δ 6.7-6.8 ppm was compared with the total integration of all the tert-butyl protons between δ 1.2-1.3 ppm. These peaks were caused by the tert-butyl protons of the sulfinamide starting material 4, intermediates and the product 1 and therefore remained constant, at nine protons, throughout the experiment. The relative integrations of these two proton environments were used to calculate the increase of product over time, and hence the rate of reaction. The linear slope at the origin was used to calculate the initial rate.

It was found that reactions conducted at 0.33 M proceeded too quickly to monitor the initial rate, as did those at 0.20 M. This is because of the limitations of the machinery; each 1H NMR spectrum took two minutes to be acquired, whereas an FT-IR spectrum could be acquired every 15 seconds. Furthermore, reactions above 0.125 M were heterogeneous, due to the limited solubility of the boronic acid 2. Attempts to improve reagent solubility with either 5% deuterated methanol or deuterated DMSO decreased the rate of reaction, in accordance with literature reports.13,14 Hence, the study was conducted by varying the concentration of one reagent between 0.050-0.125 M, with the other reagents held at 0.050 M (Table 14).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Sulfanamide 4 (M)</th>
<th>Boronic acid 2 (M)</th>
<th>Glyoxylic acid 3 (M)</th>
<th>Initial rate (mol L^{-1}s^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>S1</td>
<td>0.025</td>
<td>0.050</td>
<td>0.050</td>
<td>1.4 x 10^6</td>
</tr>
<tr>
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<td>0.075</td>
<td>0.050</td>
<td>0.050</td>
<td>4.0 x 10^6</td>
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<tr>
<td>S3</td>
<td>0.100</td>
<td>0.050</td>
<td>0.050</td>
<td>5.7 x 10^6</td>
</tr>
<tr>
<td>S4</td>
<td>0.125</td>
<td>0.050</td>
<td>0.050</td>
<td>4.8 x 10^6</td>
</tr>
<tr>
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<td>0.025</td>
<td>0.050</td>
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<td>0.075</td>
<td>0.050</td>
<td>2.8 x 10^6</td>
</tr>
<tr>
<td>B3</td>
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<td>0.100</td>
<td>0.050</td>
<td>9.9 x 10^6</td>
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<tr>
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<td>0.050</td>
<td>0.125</td>
<td>9.2 x 10^6</td>
</tr>
</tbody>
</table>

Table 14: Initial rates of the Petasis reaction

Conditions: (S)-BuSONH₂, styrenyl boronic acid, OHCCO₂H, CH₂Cl₂, rt.

Initial rate was plotted as a function of concentration. In a zero-order reaction, rate is independent of reagent concentration, resulting in a horizontal plot of rate versus concentration. A first-order system results in a linear plot and second-order gives an exponential plot (Graph 5).
Graph 5: Idealised rate curves for zero-, first- and second-order reactions

A comparison of these idealised plots (Graph 5) with the data collected from the kinetics study strongly suggests that the Petasis reaction may be proceeding with a rate order of one with respect to both the glyoxylic acid 3 and tert-butyl sulfinamide 4, and with a rate order of two with respect to the boronic acid 2. That is, the reaction is second-order in the boronic acid 2 (Graph 6).

Graph 6: Calculated rates for the Petasis reaction as a function of changing concentrations
A mathematical analysis of the data gathered from the experiments with changing boronic acid 2 concentration was conducted. This analysis showed that the data points fit an exponential equation with an $R^2$ value of 0.8554. This number is a mathematical depiction of how closely the experimental values conform to an ideal set of data for the desired equation. Thus, a value of $R^2$ that is close to 1.0 is given by data that exactly fits the ideal plot.

Fitting the data for changing boronic acid 2 concentration to a linear equation resulted in an $R^2$ value of 0.8130. This smaller figure confirms that the data is more suited to an exponential plot and thus follows second-order kinetics.

It is proposed that the boronic acid 2 acts as both a nucleophile and as a Lewis acid catalyst in the Petasis reaction with tert-butyl sulfinamide 4, resulting in second-order kinetics. In these reactions the boronic acid 2 coordinates to the sulfinyl oxygen of the imine species 14, thereby making the reactive carbon more electrophilic and increasing the rate of transfer of the vinylic group from the organoboron species (Scheme 25).

Scheme 25: Proposed mechanism, showing different components throughout the Petasis reaction

Conditions: a) CH$_2$Cl$_2$, rt, 12 h, 89%.
There is also the possibility that the boronic acid 2 could act as a hydrogen-bonding catalyst, in which one of the hydroxyl groups on the boron would bond to the sulfinyl oxygen in place of the Lewis acidic boron.

Due to the trends displayed by the results acquired, in addition to the limited solubility of the reagents in deuterated chloroform and the time intensive nature of the kinetics experiments, further data was not collected.

**2.3. Conclusions**

Vinyl boronic acids are valuable organoboron partners for the Petasis reaction. This is largely due to the fast reaction rates and high yields obtained, and the reagents’ good stability and ease of handling.

The kinetics of the Petasis reaction with tert-butyl sulfinamide 4, styrenyl boronic acid 2 and glyoxylic acid 3 were investigated.

The use of in situ FT-IR analysis proved unsuccessful due to poor reagent solubility, peak overlap and slow reaction times. Therefore the reaction was monitored by $^1$H NMR spectroscopy and analysis of the results suggested that the tert-butyl sulfinamide 4 and glyoxylic acid 3 both had rate orders of one, whereas the boronic acid 2 had a rate order of two, accounting for the dramatic increase in reaction rate that had been observed.

A mechanism for the Petasis reaction with tert-butyl sulfinamide 4 has been proposed, in which the boronic acid 2 acts as both a nucleophile and as a Lewis acid catalyst.
Chapter 3: Allyl systems
Exploring the Petasis reaction through amino acid synthesis
3. Allyl systems

Allylic amino acids are often found in natural products and act as key intermediates for the synthesis of more complex amino acids and peptides. However their synthesis is frequently laborious. Current procedures take several steps to individually add each component, and oxidise or reduce functional groups as appropriate.

The use of allyl boron reagents in the Petasis reaction offers a practical solution to this problem and simultaneously expands the scope of the Petasis reaction, which has thus far focused predominantly on aryl and vinyl boronic acids.

Due to the limited research into the single step preparation of allylic amino acids the scope of the Petasis reaction was expanded to include the use of allyl boronates. In addition, a more advanced method for the stereoselective synthesis of allyl amino acids was investigated.

3.1. Optimising the allyl-Petasis reaction

Following on from previous work regarding the use of tert-butyl sulfinamide in Petasis reactions, the use of allyl boronic acids was investigated. Employing standard Petasis conditions, racemic tert-butyl sulfinamide, allyl boronic acid pinacol ester and glyoxylic acid were reacted in a ratio of 1:1.2:1 to yield the tert-butyl sulfinyl-protected allyl glycine in a yield of 41% (Scheme 26 and entry A, Table 15).

![Scheme 26: Allyl boronic acid pinacol ester 15 with tert-butyl sulfinamide 4 in the Petasis reaction](image)

*Conditions: a) CH₂Cl₂, rt, 12 h, 41%.*
To optimise the reaction a variety of solvents, concentrations, temperatures and times were compared (Table 15). Despite previous work\(^{29}\) discovering no advantage to conducting the reaction with molecular sieves, Shi et al.\(^{67}\) later reported the acceleration of the Petasis reaction by using dry conditions. Hence molecular sieves were also used as a variable in this reaction, as was the Lewis acid catalyst copper(II) acetate.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Concentration</th>
<th>Temperature</th>
<th>Time h</th>
<th>% Conversion</th>
</tr>
</thead>
<tbody>
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<td>CH(_2)Cl(_2)</td>
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<td>rt</td>
<td>12</td>
<td>41</td>
</tr>
<tr>
<td>B</td>
<td>MeOH</td>
<td>0.25</td>
<td>rt</td>
<td>11</td>
<td>44</td>
</tr>
<tr>
<td>C</td>
<td>MeOH</td>
<td>0.25</td>
<td>rt</td>
<td>48</td>
<td>50</td>
</tr>
<tr>
<td>D(^a)</td>
<td>MeOH</td>
<td>0.25</td>
<td>rt</td>
<td>23</td>
<td>39</td>
</tr>
<tr>
<td>E</td>
<td>EtOH</td>
<td>0.25</td>
<td>70</td>
<td>21</td>
<td>Quant.</td>
</tr>
<tr>
<td>F</td>
<td>MeCN</td>
<td>0.25</td>
<td>rt</td>
<td>23</td>
<td>0</td>
</tr>
<tr>
<td>G</td>
<td>DMF</td>
<td>0.25</td>
<td>rt</td>
<td>23</td>
<td>Trace</td>
</tr>
<tr>
<td>H</td>
<td>Toluene</td>
<td>0.25</td>
<td>rt</td>
<td>21</td>
<td>77</td>
</tr>
<tr>
<td>I</td>
<td>EtOAc</td>
<td>0.25</td>
<td>rt</td>
<td>21</td>
<td>Quant.</td>
</tr>
<tr>
<td>J</td>
<td>CH(_2)Cl(_2)</td>
<td>0.33</td>
<td>rt</td>
<td>12</td>
<td>67</td>
</tr>
<tr>
<td>K</td>
<td>CH(_2)Cl(_2)</td>
<td>0.33</td>
<td>rt</td>
<td>17</td>
<td>Quant.</td>
</tr>
<tr>
<td>L</td>
<td>CH(_2)Cl(_2)</td>
<td>0.25</td>
<td>rt</td>
<td>21</td>
<td>Quant.</td>
</tr>
<tr>
<td>M(^b)</td>
<td>CH(_2)Cl(_2)</td>
<td>0.25</td>
<td>rt</td>
<td>21</td>
<td>42</td>
</tr>
</tbody>
</table>

Table 15: Optimisations for the Petasis reaction with allyl boronic acid pinacol ester 15

\(^a\) with Cu(OAc)\(_2\) catalyst; \(^b\) with molecular sieves;

% conversion determined by \(^1\)H NMR spectroscopy.

Several sets of conditions for the allyl-Petasis reaction gave quantitative conversions (entries E, I, K and L, Table 15) and as dichloromethane gave cleaner and higher yielding reactions (entries K and L, Table 15) it was chosen as the solvent. It was found that increasing the concentration of the reaction from 0.33 M (entry K, Table 15) gave no significant difference in time or conversion, but the product was less pure by both TLC and \(^1\)H NMR spectroscopy analysis. Notably, neither the addition of molecular
sieves nor a Lewis acid catalyst gave any advantage. Hence, the optimum reaction conditions chosen were a concentration of 0.25 M in dichloromethane at room temperature (approximately 21-25 °C) for 21 hours (entry L, Table 15).

Once the optimised reaction conditions had been determined an appropriate purification method was sought. The product 16 proved extremely difficult to handle and TLC analysis failed to find a suitable solvent system for purification by column chromatography. This was presumably because of the free carboxylic acid. Additionally, the similar solubilities of the product, by-products and any residual starting materials made purification by recrystallisation, trituration or extraction extremely difficult.

Accordingly, the product 16 was converted to the methyl ester 17 by reaction with either trimethylsilyl diazomethane or diazomethane generated in situ by the decomposition of diazald with sodium hydroxide (Scheme 27).

\[
\text{Conditions: a) TMSCHN}_2 \text{ in Et}_2\text{O, CH}_2\text{Cl}_2, \text{ rt, 2 h, 8%; or CH}_3\text{N}_2 \text{ (from diazald, EtOH, NaOH, rt), CH}_2\text{Cl}_2, \text{ rt, 2 h, 9%}.}
\]

The methyl ester 17 was confirmed by mass spectrometry and by the presence of a singlet at δ 3.75 ppm in the $^1$H NMR spectrum. However, the product 17 still proved difficult to purify by conventional methods and a significant amount of material was isolated in which the tert-butyl sulfinyl group had been cleaved. Attempts to benzylate the carboxylic acid with benzyl bromide were also unsuccessful (Scheme 28).
It was discovered that addition of diethyl ether to a solution of the product 16 in methanol caused the precipitation of a small amount of white product. Analysis by $^1$H NMR spectroscopy showed this to be a pure sample of allyl glycine 6 and it was concluded that some of the tert-butyl sulfinyl group had been cleaved from the amine during the reaction or work-up. This was confirmed by the observation of a major peak in the mass spectrum at an $m/z$ value of 116.07 (116.07 required for C$_5$H$_{10}$NO$_2$ [M+H]$^+$).

Given the problems in the purification of sulfinyl amino acids or amino esters it was decided to isolate allyl glycine adducts 6 as free amino acids. Hence, a simple route to fully remove the tert-butyl sulfinyl group was required. Following previous work in the Hutton group, the crude product was heated for one hour at 40 °C in 50:50 6 M hydrochloric acid and THF. The desired product 6 was isolated in 97% yield over two steps (the Petasis reaction and the deprotection) after precipitation with diethyl ether.

### 3.2. Synthesis of allyl boronates

After optimal reaction conditions and a route to the deprotection and purification of the free amino acid products 6 had been determined, the effect of substituted allyl boronates on the Petasis reaction was studied.

The first allyl boronate desired was cinnamyl boronic acid pinacol ester 15f (Figure 7).
Two methods for the conversion of cinnamyl alcohol 18 to the boronate ester 15f were considered: proceeding through the chloride 19 or the acetate 20. The commercially available cinnamyl alcohol 18 was treated with thionyl chloride to afford cinnamyl chloride 19 in 88% crude yield. The product proved extremely difficult to purify and so the material was taken forward in its crude form and reacted with bis(pinacolato)diboron (B\(_2\)pin\(_2\)) in the presence of tris(dibenzylidene acetone) dipalladium(0) (Pd(dba)\(_3\)). Unfortunately the desired product was not formed and degradation of the starting material was observed (Scheme 29).

The borylation was then attempted with alternative transition metal catalysts, including rhodium(II) and nickel(II) biscyclooctadiene catalysts, and different phosphorous ligands under a variety of conditions. However, each set of reaction conditions failed to give the desired product, with either the starting materials recovered or degradation observed.

Borylation by using lithium-halogen exchange had been previously attempted in-house but had been unsuccessful. The use of n-butyl lithium and trimethyl boronate gave no reaction under the majority of conditions attempted, and finally led to compound degradation as the conditions became more forcing (Table 16).
<table>
<thead>
<tr>
<th>Entry</th>
<th>Method</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Starting material and n-butyl lithium reacted at -78 °C for 30 minutes. Boronate added and reacted for 30 minutes. Reaction warmed to room temperature.</td>
<td>Starting material recovered</td>
</tr>
<tr>
<td>B</td>
<td>Starting material and n-butyl lithium reacted at -78 °C for 30 minutes and at 0 °C for 30 minutes. Reaction cooled to -78 °C, boronate added and reacted at -78 °C for 30 minutes. Reaction warmed to room temperature.</td>
<td>Starting material recovered</td>
</tr>
<tr>
<td>C</td>
<td>Starting material and n-butyl lithium reacted at -78 °C for 30 minutes and at room temperature for 30 minutes. Reaction cooled to -78 °C, boronate added and reacted at -78 °C for 30 minutes. Reaction warmed to room temperature.</td>
<td>Starting material recovered</td>
</tr>
<tr>
<td>D</td>
<td>Starting material and n-butyl lithium reacted at -78 °C for 30 minutes and at room temperature for 30 minutes. Reaction cooled to -78 °C, boronate added and reacted at -78 °C for 30 minutes. Reaction warmed slowly to 60 °C and reacted at 60 °C for two hours.</td>
<td>Decomposition</td>
</tr>
</tbody>
</table>

Table 16: Conditions for attempted borylation with "BuLi"

Cross coupling methods from the chloride were also attempted by using tris(dibenzylidene acetone) dipalladium(0) and bis(pinacolato)diboron under a number of conditions but no conditions led to the formation of the desired product. Due to these failures, focus was redirected to synthesise the desired compound 15f from cinnamyl acetate 20.

Treatment of cinnamyl alcohol 18 with a mixture of acetic anhydride, triethylamine and a catalytic amount of DMAP in dichloromethane at room temperature for five hours, resulted in quantitative conversion to the acetate 20 (Scheme 30). The product 20 was collected in high purity following aqueous work-up.
With the allyl acetate 20 in hand the next step was to exchange the acetate group for a boronic acid pinacol ester. Treatment of allyl acetate 20 with rhodium(II) bis(cyclooctadiene)boron tetrafluoride, tricyclohexyl phosphine and bis(pinacolato)-diboron after two days at 60 °C produced no product and the starting material was recovered. Palladium cross-coupling reactions, using tris(dibenzylidene acetone) dipalladium(0) under a variety of conditions, were attempted but each time no reaction was observed, even after several days, with complete recovery of the starting material (Scheme 31).

An alternative method for the direct borylation of allylic alcohols, by using a palladium catalyst 21, has been reported by Aggarwal and co-workers (Figure 8).

Accordingly, treatment of cinnamyl alcohol 18 with catalyst 21, a catalytic amount of para-toluene sulfonic acid and bis(pinacolato)diboron provided the desired boronic
acid pinacol ester 15f in quantitative yield and a high level of purity (Scheme 32). A shift of the allylic protons from δ 4.03 ppm (adjacent to oxygen) to δ 1.73 ppm (adjacent to boron) was observed, and the presence of a peak in the mass spectrum at an m/z value of 245.17 confirmed the identity of the product (245.17 required for C\textsubscript{15}H\textsubscript{22}BO\textsubscript{2} [M+OH]).

\[
\begin{align*}
\text{OH} & \quad \longrightarrow & \quad \text{Bpin} \\
\text{Ph} & \quad & \quad \text{Ph} \\
18 & \quad & \quad 15f
\end{align*}
\]

**Scheme 32: Borylation of cinnamyl alcohol 18 by using palladium catalyst 21**

**Conditions:** a) B\textsubscript{2}pin\textsubscript{2}, p-TsOH, 21, DMSO, MeOH, 50 °C, 16 h, quant.

This methodology was then applied to other allylic alcohols to give the corresponding boronic acid pinacol esters 15a-g in quantitative conversion (Figure 9).

<table>
<thead>
<tr>
<th>Compound</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>R\textsuperscript{3}</th>
</tr>
</thead>
<tbody>
<tr>
<td>15a</td>
<td>H</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>15b</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>15c</td>
<td>H</td>
<td>H</td>
<td>CO\textsubscript{2}Et</td>
</tr>
<tr>
<td>15d</td>
<td>Me</td>
<td>H</td>
<td>H</td>
</tr>
<tr>
<td>15e</td>
<td>H</td>
<td>Me</td>
<td>H</td>
</tr>
<tr>
<td>15f</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
</tr>
<tr>
<td>15g</td>
<td>H</td>
<td>Pr</td>
<td>H</td>
</tr>
</tbody>
</table>

**Figure 9: Boron compounds 15a-g synthesised by using the method of Aggarwal and co-workers\textsuperscript{70}**

It was found that this route was extremely selective for allylic alcohols, leaving alkynyl and alkyl alcohols unchanged – no reaction was observed with propargyl alcohol or hex-3-en-1-ol. In addition, the catalyst 21 yielded the terminal boronates exclusively.
Hence, if a mixture of allylic alcohol isomers were treated by this method, only one product was observed, still in quantitative yield overall. For example, a mixture of hex-2-en-1-ol and hex-1-en-3-ol gave only hex-2-enyl boronic acid pinacol ester 15g. These results are consistent with findings published by Aggarwal and co-workers.\(^\text{70}\)

### 3.3. Effect of substituted allyl boronates

With the allyl boronic acid pinacol esters 15a-g in hand Petasis reactions were conducted with tert-butyl sulfinamide 4 and glyoxylic acid 3. Diastereomeric ratios were determined from the crude \(^1\)H NMR spectra and then removal of the tert-butyl sulfinyl group in aqueous acid liberated the free allylic amino acid derivatives 6a-g. Diastereomeric ratios of the final products were also determined from the crude \(^1\)H NMR spectra (Table 17).

It was found that the allyl boronates 15a-g, synthesised from the corresponding allylic alcohols, could be taken through to the Petasis reaction in their crude form. No loss of yield or stereoselectivity in the final products 6a-g was observed, in comparison to reactions that were conducted with commercially available organoboronates 15a,d-e.
Diastereomeric ratios were determined by comparing the integrations of the γ-vinylic proton (Hc, Figure 10), the resonances for which were distinct in all products. For compounds 16a-c there are two stereogenic centres: the sulfur and the α-carbon. The observed diastereomeric ratios for compounds 16a-c, and hence the selectivity enforced at α-position by the sulfinyl stereocenter, were moderate, at 3:1 to 4:1.

Compounds 16d-g contain an additional stereogenic centre at the β-position. Analysing the 1H NMR spectra of these compounds revealed one major isomer, one minor isomer and a trace amount of the remaining two potential diastereomers. The signals from these diastereomers overlapped in the 1H NMR spectrum (Figure 10), making it difficult to confidently integrate the minor isomers separately. Hence reported diastereomeric ratios combine the minor diastereomers if appropriate.

<table>
<thead>
<tr>
<th>Compound</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>dr of 16a</th>
<th>dr of 6</th>
<th>Two-step yield of 6b</th>
</tr>
</thead>
<tbody>
<tr>
<td>15a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>4:1</td>
<td>-</td>
<td>97</td>
</tr>
<tr>
<td>15b</td>
<td>Me</td>
<td>Me</td>
<td>H</td>
<td>4:1</td>
<td>-</td>
<td>82</td>
</tr>
<tr>
<td>15c</td>
<td>H</td>
<td>H</td>
<td>CO₂Et</td>
<td>3:1</td>
<td>-</td>
<td>84</td>
</tr>
<tr>
<td>15d</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>5:1</td>
<td>4:1</td>
<td>91</td>
</tr>
<tr>
<td>15e</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>2.5:1</td>
<td>3:1</td>
<td>87</td>
</tr>
<tr>
<td>15f</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>8:3</td>
<td>8:1</td>
<td>82</td>
</tr>
<tr>
<td>15g</td>
<td>H</td>
<td>Pr</td>
<td>H</td>
<td>5:1</td>
<td>3:1</td>
<td>89</td>
</tr>
</tbody>
</table>

Table 17: Yields and diastereomeric ratios of allylic amino acids 6a-g synthesised

Conditions: a) (S)-tBuSONH₂, OHCCO₂H, CH₂Cl₂, rt, 21 h; b) HCl, THF, 40 °C, 1 h, 82-97%.

a dr of major, syn-diastereomer to the minor, anti-diastereomer(s), combined if appropriate;
b isolated yield over two steps.
The observed diastereomeric ratios for compounds 16d-g were moderate. There are two possibilities for this result: high syn/anti selectivity with moderate stereocontrol at the α-position, or high stereocontrol at the α-position with moderate syn/anti selectivity. If there is high syn/anti control, deprotection of the compound 16, which would remove the stereocenter about the sulfur, would leave one major diastereomer (but in low enantiomeric excess) of 6. However, if there is high control at the α-position but only moderate syn/anti control, deprotection of the compound 16 would generate a mixture of two diastereomers (but both in high enantiomeric excess).

Upon deprotection, to yield compounds 6d-g, the diastereomeric ratios acquired remained moderate. Hence, a mixture of syn and anti diastereomers was presumably produced by the reactions in Table 17. The relative stereochemistry of compounds 6d-g was determined by comparing the 1H NMR data to the spectra
produced by Kobayashi and co-workers. The literature results showed that the internal vinylic proton was further downfield in the syn-isomer, compared with the anti-isomer. Here, the signal for the internal vinylic proton in the major isomer for compounds 6d-g (δ 5.94 ppm in 6d and 6e) was downfield of the minor isomer signal (δ 5.81 ppm in 6d and 6e), indicating that the compounds synthesised were all syn-isomers.

It can be seen from Table 17 that allyl boronates with hydrogen or methyl substituents (compounds 15a-b,d,e) gave diastereomeric ratios of approximately 3:1 or 4:1, whereas the boronic acid pinacol esters with larger steric bulk (compounds 15f-g) enforced higher selectivities. This is particularly noticeable for the phenyl derivative 15f, which gave a diastereomeric ratio of 8:1. In addition to the compounds in the table, allenyl boronic acid pinacol ester 22 was also applied to the Petasis reaction to give compound 23. This was then deprotected to give the alkynyl glycine 24 (Scheme 33) in an overall yield of 79% and a diastereomeric ratio of 5:1 for compound 23. This alkynyl amino acid could be used in further reactions (e.g. Sonogashira couplings) to create an expanded compound library.

![Scheme 33: Alkenyl boronic acid pinacol ester 22 in the Petasis reaction](image)

**Scheme 33: Alkenyl boronic acid pinacol ester 22 in the Petasis reaction**

**Conditions:** a) (S)-tBuSONH₂, OHCCO₂H, CH₂Cl₂, rt, 21 h; b) HCl, THF, 40 °C, 1 h, 79%.

Allenyl boronic acid pinacol ester 22 can act as either a vinylic or an allylic system. In the reaction above (Scheme 33), excellent selectivity was displayed and only the alkynyl amino acid 24 was observed. Hence, in this reaction allenyl boronate 22 acts only as an allyl-type system.

This finding is in accord with the recent report of Pyne and Thaima, who used allenyl boronic acid pinacol ester 22 in a series of Petasis reactions (Scheme 34). A one-pot
reaction between the primary amine benzylamine, allenyl boronate 22 and salicylaldehyde was regioselective for the alkyne product, Pathway A. However, in stark contrast a reaction with the secondary amine morpholine, allenyl boronate 22 and salicylaldehyde was completely regioselective for the allene product, Pathway B.

![Scheme 34: Reactions by Pyne and Thaima\textsuperscript{71}]

Hence, an analysis of the findings reported herein and those of Pyne and Thaima\textsuperscript{71} indicates that in Petasis reactions of allenyl boronate 22 (Scheme 33, Scheme 34) with primary amines, allenyl boronate 22 reacts as an allyl-type system. Conversely, in reactions with secondary amines, allenyl boronate 22 reacts as a vinyl-type system.\textsuperscript{71}

During the course of this work a paper was published by Sugiyama and co-workers\textsuperscript{72} documenting their recent research on the use of allyl boronic acid pinacol esters 15 in the Petasis reaction with glyoxylic acid 3 and tert-butyl sulfinamide 4. They found the reactions to be slow, with moderate to good yields but high stereoselectivity. Optimum conditions required three days reaction time in the presence of molecular sieves, and removal of the sulfinyl group was conducted in 6 M hydrochloric acid at 90 °C (Table 18).
Taking the most basic example, using unsubstituted allyl boronic acid pinacol ester 15a, the reported diastereomeric ratio was 94%, but the isolated yield was just 55% over two steps. This is in direct contrast to the results described in this chapter,
which report a diastereomeric ratio of 4:1, but an isolated yield of 97% for the same reaction. Due to this disparity the method reported by Sugiyama and co-workers\textsuperscript{72} was replicated in-house, but failed to yield the literature results. After several different attempts with a variety of allyl boronic acid pinacol esters\textsuperscript{15} the published results were unable to be reproduced. The diastereomeric ratios acquired in the laboratory were much lower than the reported values, although the overall yields were considerably better (Table 19).

<table>
<thead>
<tr>
<th>Compound</th>
<th>R\textsuperscript{1}</th>
<th>R\textsuperscript{2}</th>
<th>R\textsuperscript{3}</th>
<th>This work</th>
<th>Literature</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dr of 16\textsuperscript{a}</td>
<td>Yield of 6\textsuperscript{b}</td>
<td>dr of 6\textsuperscript{c}</td>
<td>Yield of 6\textsuperscript{b}</td>
<td></td>
</tr>
<tr>
<td>15a</td>
<td>H</td>
<td>H</td>
<td>H</td>
<td>4:1</td>
<td>97</td>
</tr>
<tr>
<td>15d</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>5:1</td>
<td>91</td>
</tr>
<tr>
<td>15e</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>2.5:1</td>
<td>87</td>
</tr>
<tr>
<td>15f</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>8:2:1</td>
<td>82</td>
</tr>
<tr>
<td>15g</td>
<td>H</td>
<td>Pr</td>
<td>H</td>
<td>5:1</td>
<td>89</td>
</tr>
</tbody>
</table>

Table 19: Comparison of results reported in this chapter with those of Sugiyama et al.\textsuperscript{72}

\textsuperscript{a} from crude \textsuperscript{1}H NMR spectrum; \textsuperscript{b} isolated yields over two steps; \textsuperscript{c} from HPLC trace.

After a further analysis of the reaction conditions it was noted that the stereoselectivity and yields reported were post purification by column chromatography, with no crude results given. It was rationalised that perhaps the high selectivity and low yield could both be accounted for by the purification process as it is highly likely that a mixture of isomers could be fractionated on the column; a yield of 97% with a 4:1 selectivity would provide approximately 80% of a single isomer, following purification and removal of the tert-butyl sulfinyl group.

The reaction was attempted again, using both the conditions reported by Sugiyama and co-workers\textsuperscript{72} and those reported earlier in this chapter. Compound 16a was synthesised in quantitative yield and a 4:1 diastereomeric ratio under both sets of reaction conditions. After purification by column chromatography the product was collected in 68% and 70% yields (using the literature method and the optimised
In both cases the observed diastereomeric ratio was 10:1, indicating that partial separation of the diastereomers by column chromatography was occurring, thereby affecting the diastereomeric ratios of the purified products. Compound 16d was also synthesised by this method and achieved similar results. No explanation was offered by Sugiyama and co-workers for the lack of reactivity of 15d and 15f, both of which were found to be successful Petasis partners in this work.

Although the allyl-Petasis reaction discussed in this work displayed moderate stereoselectivity, further work is required to achieve the same stereoselectivities observed by Kobayashi and co-workers\textsuperscript{34,35} and offered by the aryl- and vinyl-Petasis reactions conducted with tert-butyl sulfinamide 4 (section 1.3.2.1).

### 3.4. Use of Lewis acids

Literature reports have shown that by using a Lewis acid with tert-butyl sulfinamide 4 excellent stereocontrol of the Petasis reaction can be achieved.\textsuperscript{38} Therefore, several Lewis acids (Table 20) were chosen and applied to the Petasis reaction, using unsubstituted allyl boronic acid pinacol ester 15a under the previously optimised conditions (Table 20).
Table 20: Effect of Lewis acids on the allyl-Petasis reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>dr of 16a</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>-</td>
<td>4:1</td>
</tr>
<tr>
<td>B</td>
<td>FeCl₃</td>
<td>5:1</td>
</tr>
<tr>
<td>C</td>
<td>BF₃•OEt₂</td>
<td>3:1</td>
</tr>
<tr>
<td>D</td>
<td>Cu(OAc)₂</td>
<td>6:1</td>
</tr>
<tr>
<td>E</td>
<td>Ti(OEt)₄</td>
<td>No reaction</td>
</tr>
<tr>
<td>F</td>
<td>Sc(OTf)₃</td>
<td>20:1</td>
</tr>
<tr>
<td>G</td>
<td>Yb(OTf)₃</td>
<td>20:1</td>
</tr>
<tr>
<td>H</td>
<td>Hf(OTf)₄</td>
<td>20:1</td>
</tr>
</tbody>
</table>

Table 20: Effect of Lewis acids on the allyl-Petasis reaction

**Conditions:** a) Lewis acid, CH₂Cl₂, rt, 21 h.

Literature precedent supports the use of iron(III) chloride³⁸ and boron trifluoride,²⁸,⁴⁰ but in this system these additives provided no benefit. Previous work in-house found that 0.1 equivalents of copper(II) acetate enhanced the diastereomeric ratio of the Petasis products. However, here only a moderate diastereomeric ratio of 6:1 was attained.

Several transition metal catalysts were also applied to the reaction. Titanium(IV) tetraetherate prevented the reaction from occurring and it was hypothesised that, due to titanium’s high affinity for oxygen, the titanium was coordinating to the carboxylate oxygen and hindering oxygen-boron coordination. This would halt the reaction.

However, it was found that both scandium(III) and ytterbium(III) triflates were able to enforce a high level of stereocontrol, with scandium(III) triflate providing a cleaner reaction. Hafnium(IV) triflate also gave a high level of stereocontrol but the yield was compromised. On standing, crystals began to form in the reaction mixtures with scandium(III), ytterbium(III) and hafnium(IV) triflates (entries E, F and G, Table 20),
which were hoped to be enantiopure product. However, analysis by X-ray crystallography showed that the crystalline material was not the desired product, but instead was the sulfur containing by-product \( N\)-(tert-butylthio)-tert-butyl sulfonamide 25 (Figure 11).

\[
\begin{align*}
\text{t-Bu} & \quad \text{S} & \quad \text{N} & \quad \text{S} & \quad \text{t-Bu} \\
& \quad & \quad & \quad & 25
\end{align*}
\]

Figure 11: Disproportionated sulfur by-product \( N\)-(tert-butylthio)-tert-butyl sulfonamide 25

In 2011 Dubey and co-workers\(^7\) reported that tert-butyl sulfinamide 4 is unstable above room temperature and can undergo a thermal rearrangement (Scheme 35) to yield \( N\)-(tert-butylthio)-tert-butyl sulfonamide 25. This disproportionation can be catalysed by trace acid in chlorinated solvents or by Lewis acids.

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{S} & \quad \text{t-Bu} & \quad \text{Lewis acid} & \quad \text{H}_2\text{N} & \quad \text{S} & \quad \text{t-Bu} \\
& \quad & \quad & \quad & \quad & \quad & 25
\end{align*}
\]

Scheme 35: Rearrangement of tert-butyl sulfinamide 4
to give \( N\)-(tert-butylthio)-tert-butyl sulfonamide 25

To find conditions that gave a reduced amount of disproportionated by-product, a series of Petasis reactions with scandium(III) triflate were conducted (Table 21). Different amounts of catalyst were used and reaction temperature and the order of addition of components were varied.
An analysis of the results (Table 21) showed that scandium(III) triflate did promote the disproportionation of tert-butyl sulfinamide 4, with almost complete disproportionation observed if one equivalent of scandium(III) triflate was used (entry B, Table 21). If the catalyst was used in low amounts or if the reaction was conducted at low temperatures this disproportionation could be minimised, although the diastereoselectivity of the reaction was severely compromised.

In entries E and F (Table 21) scandium(III) triflate was added to the reaction at the same time as the boronic acid 15a. The presence of the boronic acid ensured that the imine was not available for disproportionation, but the Petasis reaction was still catalysed to enhance the stereoselectivity of the reaction.

Experimentally, adding 0.1 equivalents of the catalyst to the reaction mixture immediately after the boronic acid was added resulted in no observed disproportionation of the tert-butyl sulfinamide 4 and the diastereomeric ratio remained excellent, in excess of 20:1. The optimal conditions for the Lewis acid directed allyl-Petasis reaction were therefore to conduct the reaction at room temperature and to add 0.1 equivalents of scandium(III) triflate immediately after the addition of boronic acid pinacol ester 15a. These conditions were applied to the
reaction with the (Z)- and (E)-crotyl boronic acid pinacol esters 15d-e and cinnamyl boronic acid pinacol ester acid 15f (Table 22).

![Diagram of the reaction](image)

<table>
<thead>
<tr>
<th>Compound</th>
<th>R¹</th>
<th>R²</th>
<th>dr of 16ᵃ</th>
<th>dr of 6</th>
<th>Yield of 6ᵇ</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>H</td>
<td>H</td>
<td>20:1</td>
<td>-</td>
<td>95</td>
</tr>
<tr>
<td>d</td>
<td>Me</td>
<td>H</td>
<td>3:1</td>
<td>20:1</td>
<td>89</td>
</tr>
<tr>
<td>e</td>
<td>H</td>
<td>Me</td>
<td>2:1</td>
<td>20:1</td>
<td>86</td>
</tr>
<tr>
<td>f</td>
<td>H</td>
<td>Ph</td>
<td>3:1</td>
<td>20:1</td>
<td>82</td>
</tr>
</tbody>
</table>

Table 22: Effect of scandium(III) triflate on the allyl-Petasis reaction under optimised conditions

Conditions: a) 0.1 equivalents Sc(OTf)₃, CH₂Cl₂, rt, 21 h;

b) HCl, THF, 40 °C, 1 h, 82-95% over two steps.

ᵃ diastereomeric ratios of major, syn-diastereomer to the minor, anti-diastereomer(s);

ᵇ isolated yield over two steps.

It was found that scandium(III) triflate was unable to dictate stereoselectivity at the α-position, but did provide excellent control over the syn/anti configuration, as only two isomers were observed for both the tert-butyl sulfinyl protected 16 and deprotected products 6. Hence, from the Petasis reactions employing scandium(III) triflate, compounds 6d-f were synthesised with high diastereoselectivity, but low enantiomeric excess.

### 3.5. Determining the mechanism

Considering the excellent diastereomeric ratios achieved with tert-butyl sulfinamide 4 and vinyl boronic acids (section 1.3.2.1), and those acquired by Kobayashi and co-workers (section 3.3), an explanation for why the allyl system in this work yielded only moderate selectivities was needed. Hence, an analysis of the mechanism was
conducted. For the Petasis reaction with glyoxylic acid 3 the mechanism proceeds via an intermediate whereby either the carboxylate oxygen, or the imine nitrogen is coordinated to the boronic acid.\textsuperscript{7,12}

For the system used by Kobayashi and co-workers,\textsuperscript{34,35} using allyl boronates 15 with ammonia or ammonia substitutes, the mechanism could proceed via coordination to the nitrogen. The reaction would proceed through a 6-membered, Zimmerman-Traxler style transition state affording good stereocontrol (Figure 12). However, with tert-butyl sulfinamide 4 the nitrogen lone pair of the sulfinyl imine adduct is less available due to the presence of the electron withdrawing sulfinyl group, and thus would be unavailable to the boron. This would force the reaction to proceed via coordination to the oxygen, which would result in a 7-membered transition state (Figure 12). This would be unable to enforce much control over the stereochemical outcome of the reaction.

\textbf{Figure 12: 6- and 7-membered transition states for the allyl-Petasis reaction}

To investigate the proposed mechanism further, the Petasis reaction with tert-butyl sulfinamide 4, allyl boronic acid pinacol ester 15a and ethyl glyoxylate 26 (in place of glyoxylic acid 3) was performed (Scheme 36), such that coordination to the carboxylic acid was prevented. Analysis by TLC and \textsuperscript{1}H NMR spectroscopy showed that although the imine formed without hindrance the reaction was halted at this stage. In contrast, if the reaction was carried out with ethyl glyoxylate 26 but a simple amine in place of tert-butyl sulfinamide 4 (Scheme 36), the reaction proceeded to give compound 27b in high yield. The analogous reaction with glyoxylic acid 3 also proceeded with a comparable rate and yield. This is consistent with the reactions employing tert-butyl sulfinamide 4.
Scheme 36: Using ethyl glyoxalate 26 in the Petasis reaction

Conditions: a) CH₂Cl₂, rt, 21 h.

27a R¹ = S(O)₅Bu, no reaction; 27b R¹ = α-MeBn, 86%.

The reactions with ethyl glyoxalate 26 also highlighted an interesting difference in the stereoselectivities of the various Petasis reactions. A comparison of the reactions with (Z)- and (E)-crotyl boronic acid pinacol esters 15d-e as well as cinnamyl boronic acid pinacol ester 15f with ethyl glyoxalate 26 or glyoxylic acid 3 and different amine sources gave a mixture of diastereomeric ratios in the final products (Table 23).
Table 23: Varying stereochemistries for the Petasis reactions conducted in-house

<table>
<thead>
<tr>
<th>Entry</th>
<th>R¹</th>
<th>R²</th>
<th>R³</th>
<th>R⁴</th>
<th>Catalyst</th>
<th>dr of 28ᵃ</th>
<th>δ ppm of internal vinyl-H</th>
</tr>
</thead>
<tbody>
<tr>
<td>a</td>
<td>Bn</td>
<td>Me</td>
<td>H</td>
<td>Et</td>
<td>-</td>
<td>1:3</td>
<td>5.74 5.85</td>
</tr>
<tr>
<td>b</td>
<td>Bn</td>
<td>Me</td>
<td>H</td>
<td>Et</td>
<td>-</td>
<td>1:3</td>
<td>5.74 5.85</td>
</tr>
<tr>
<td>c</td>
<td>Bn</td>
<td>H</td>
<td>Me</td>
<td>Et</td>
<td>-</td>
<td>1:1.5</td>
<td>5.74 5.85</td>
</tr>
<tr>
<td>d</td>
<td>α-MeBn</td>
<td>Me</td>
<td>H</td>
<td>Et</td>
<td>-</td>
<td>5:1ᶜ</td>
<td>5.93 5.74</td>
</tr>
<tr>
<td>e</td>
<td>α-MeBn</td>
<td>H</td>
<td>Me</td>
<td>Et</td>
<td>-</td>
<td>4:1ᶜ</td>
<td>5.93 5.74</td>
</tr>
<tr>
<td>f</td>
<td>α-MeBn</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>-</td>
<td>2:1ᶜ</td>
<td>5.92 5.77</td>
</tr>
<tr>
<td>g</td>
<td>α-MeBn</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>-</td>
<td>2:1ᶜ</td>
<td>5.92 5.77</td>
</tr>
<tr>
<td>h</td>
<td>S(O)t-Bu</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>ScOTf₃</td>
<td>3:1ᵇ</td>
<td>5.89 5.80</td>
</tr>
<tr>
<td>i</td>
<td>S(O)t-Bu</td>
<td>Me</td>
<td>H</td>
<td>H</td>
<td>-</td>
<td>5:1ᶜ</td>
<td>5.89 5.80</td>
</tr>
<tr>
<td>j</td>
<td>S(O)t-Bu</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>ScOTf₃</td>
<td>2:1ᵇ</td>
<td>5.89 5.80</td>
</tr>
<tr>
<td>k</td>
<td>S(O)t-Bu</td>
<td>H</td>
<td>Me</td>
<td>H</td>
<td>-</td>
<td>2.5:1ᶜ</td>
<td>5.89 5.80</td>
</tr>
<tr>
<td>l</td>
<td>S(O)t-Bu</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>ScOTf₃</td>
<td>3:1ᵇ</td>
<td>6.70 6.65</td>
</tr>
<tr>
<td>m</td>
<td>S(O)t-Bu</td>
<td>H</td>
<td>Ph</td>
<td>H</td>
<td>-</td>
<td>8:3ᶜ</td>
<td>6.70 6.65</td>
</tr>
</tbody>
</table>

Conditions: a) CH₂Cl₂, rt, 21 h, 80-95%.

ᵃ diastereomeric ratios are of the major diastereomer to the minor diastereomer(s) combined; b two isomers present; c four isomers present.

In the reactions of Kobayashi and co-workers³⁴,³⁵ the (Z)-crotyl boronic acid pinacol ester 15d was seen to give almost exclusively the syn-product. The internal vinyl proton appeared at δ 5.84 ppm in the ¹H NMR spectrum for the major (syn) product and at δ 5.75 ppm for the minor (anti) product. The selectivity and ¹H NMR spectroscopy data for the reaction with (E)-crotyl boronic acid pinacol ester 15e was mirrored.
In this work the internal vinyl proton of the major isomer for most reactions (Table 23) came between $\delta$ 5.85 ppm and $\delta$ 5.93 ppm (or at $\delta$ 6.70 ppm for the reactions with cinnamyl boronic acid pinacol ester 15f, entries K and L, Table 23), and for the minor isomer it came between $\delta$ 5.74 ppm and $\delta$ 5.80 ppm (or at $\delta$ 6.65 ppm for the reactions with cinnamyl boronic acid pinacol ester 15f, entries K and L, Table 23). This suggests that the amino acids synthesised in this work are the syn-isomers as previously mentioned (section 3.3), regardless of whether (Z)- or (E)-allyl boronates 15 were employed. The only exceptions were those reactions using the non-chiral benzylamine (Entries A and B, Table 23).

These results showed that the allyl-Petasis reaction with tert-butyl sulfinamide 4 is transitioning through a different mechanism compared with those reactions that use ammonia as the nitrogen source, as has been discussed previously.

### 3.6. Conclusions

The Petasis reaction was used as a way to synthesise allylic amino acids 6 in a concise and efficient manner. Utilising tert-butyl sulfinamide 4, unsubstituted allyl boronic acid pinacol ester 15a and glyoxylic acid 3, optimal reaction conditions were determined. These were then applied to the synthesis of a variety of allyl amino acid derivatives 16a-g from their respective allyl boronic acid pinacol esters 15a-g. The allyl boronates 15a-g were synthesised from allyl alcohols through palladium catalysis. Isolated yields of the final amino acids were excellent, but the diastereoselective ratios achieved were low to moderate.

During the course of this work Sugiyama and co-workers\textsuperscript{72} published a report for the diastereoselective allyl-Petasis reaction. However, on repetition of the published reaction conditions the same level of diastereoselectivity could not be replicated and it was determined that fractionation was occurring during purification process in the reported method.

To improve the stereoselectivity of the allyl-Petasis reaction a variety of Lewis acids were scanned as potential catalysts for the reaction and scandium(III) triflate was
shown to effect excellent diastereocontrol on the unsubstituted system. A competing reaction, leading to the disproportionation of tert-butyl sulfinamide 4, was observed with the catalyst but could be effectively controlled by using 0.1 equivalents of catalyst and adding it to the reaction immediately after the boronic acid 15. Application of scandium(III) triflate to the Petasis reaction with other boronic acids 15 showed that the catalyst was unable to direct good stereoselectivity at the α-position, but did give excellent control over the syn/anti configuration of the product, resulting in a diastereomeric ratio in the order of >20:1, in favour of the syn-product.

It was proposed that the mechanism of the allyl-Petasis reaction with tert-butyl sulfinamide 4 and glyoxylic acid 3 proceeds via oxygen-boron coordination because the lone pair of the nitrogen is involved in conjugation with the sulfur-oxygen bond. To support this, the Petasis reaction was conducted with ethyl glyoxylate 26 in place of glyoxylic acid 3, as the ester would be unable to coordinate to the boron. As hypothesised, this system showed no reactivity beyond the initial amine-carbonyl condensation. A similar reaction using α-methyl benzylamine and ethyl glyoxylate 26 proceeded as normal.

This mechanism can be used to explain the poor stereoselectivities observed in the uncatalysed allyl-Petasis reaction. The necessity of oxygen-boron coordination in the sulfinyl system forces the Petasis reaction to proceed via a 7-membered ring, which is unable to dictate a strong stereochemical preference in the formation of the diastereomeric product.

The results of the allyl-Petasis reaction with scandium(III) triflate show great promise for the allyl-Petasis reaction as a tool for the organic chemist.
Chapter 4: 
*N*-Methylated systems

Exploring the Petasis reaction through amino acid synthesis
4. **N-Methylated systems**

*N*-methylation plays an important role in many biological systems and is a key feature of current epigenetic research. However, the synthetic methylation of a single nitrogen can be difficult. For nitrogen atoms that are sterically crowded, forcing conditions are frequently needed and the selective methylation of a compound with more than one potential methylation site can be problematic.

The use of *N*-methyl tert-butyl sulfinamide 29 in the Petasis reaction could provide an efficient method for the synthesis of *N*-methylated amino acids.

There are no reported uses of *N*-methyl tert-butyl sulfinamide 29 (or even methylamine) in the Petasis reaction, and the uses of *N*-methyl tert-butyl sulfinamide 29 as a reagent in other organic chemistry transformations are limited. However, tert-butyl sulfinamide 4 has been successful in the Petasis reaction (sections 1.3.2, 2, 3), and secondary amines tend to perform better than their primary counterparts (section 1.3.2). Therefore, it was anticipated that *N*-methyl tert-butyl sulfinamide 29 could be a successful Petasis reaction partner.

The synthesis of *N*-methyl tert-butyl sulfinamide 29 and its use in the Petasis reaction with different boronic acids was investigated to expand the scope of the Petasis reaction.

**4.1. Synthesis of *N*-methyl tert-butyl sulfinamide**

Initial attempts to synthesise *N*-methyl tert-butyl sulfinamide 29 focussed on methylation of the commercially available (S)-tert-butyl sulfinamide 4. Methyl iodide and methyl triflate were both used as potential methylating reagents. However, under a variety of conditions the desired product could not be prepared satisfactorily. The reaction did not proceed to completion if one equivalent of sodium hydride was used, even with an excess of methyl iodide or the application of heat. However, increasing the amount of sodium hydride led to a mixture of products, in which both singly and doubly methylated sulfinamides were observed, in addition to unmethylated...
sulfinamide. The use of methyl iodide with alternative bases and phase transfer catalysts, and the use of methyl triflate resulted in degradation or no reaction with the recovery of the starting material (Table 24).

![Chemical structure](image)

**Table 24: Attempted syntheses of (S)-N-methyl tert-butyl sulfinamide (S)-29**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Me source</th>
<th>Base</th>
<th>Catalyst</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>MeI, 2 eq.</td>
<td>NaH, 1 eq.</td>
<td>-</td>
<td>Low yield</td>
</tr>
<tr>
<td>B</td>
<td>MeI, 2 eq.</td>
<td>NaH, 2 eq.</td>
<td>-</td>
<td>Double methylation</td>
</tr>
<tr>
<td>C</td>
<td>MeI, 5 eq.</td>
<td>NaH, 1 eq.</td>
<td>-</td>
<td>Low yield</td>
</tr>
<tr>
<td>D</td>
<td>MeI, 5 eq.</td>
<td>K₂CO₃, KOH, Bu₄NI</td>
<td>-</td>
<td>No reaction</td>
</tr>
<tr>
<td>E</td>
<td>MeOTf, 2 eq.</td>
<td>Et₃N, 2 eq.</td>
<td>-</td>
<td>Degredation</td>
</tr>
</tbody>
</table>

Accordingly, an alternative method was investigated through the treatment of the racemic tert-butyl sulfinyl chloride 30 with methylamine. Use of methylamine in diethyl ether gave only partial conversion to the product and methylamine hydrochloride was also unsuccessful. However, the use of methylamine as a 2.0 M solution in THF gave the desired product in a yield of 98% after purification by column chromatography (Scheme 37).

![Chemical structure](image)

**Scheme 37: Synthesis of racemic N-methyl tert-butyl sulfinamide (R,S)-29**

Conditions: a) MeNH₂ (2.0 M in THF), rt, 5 h, 98%.
4.2. The Petasis reaction with N-methyl tert-butyl sulfinamide

With (R,S)-N-methyl tert-butyl sulfinamide (R,S)-29 in hand Petasis reactions were attempted with a variety of aryl and vinyl boron reagents. However, even after two days these failed to give any product, with starting materials recovered in all cases (Scheme 38).

![Scheme 38: Attempted Petasis reactions with (R,S)-N-methyl tert-butyl sulfinamide (R,S)-29](image)

Conditions: a) CH₂Cl₂, rt, 48 h.

To understand why these Petasis reactions were not proceeding, even with electron rich boronic acids, the reaction was broken down into stages. It was discovered that the condensation reaction between (R,S)-N-methyl tert-butyl sulfinamide (R,S)-29 and glyoxylic acid 3 to give the corresponding iminium ion intermediate was not proceeding. This was determined by the absence of the iminium proton in the ¹H NMR spectrum and only starting material peaks in the mass spectrum.

Due to the addition of the methyl group onto the nitrogen, the initial amine-aldehyde condensation with (R,S)-N-methyl tert-butyl sulfinamide (R,S)-29 must pass through an iminium ion, as opposed to an imine with tert-butyl sulfinamide 4. In these sulfinamides the nitrogen is less nucleophilic than in regular amines, because the lone pair is partially delocalised in the sulfinyl system. The formation of a positively charged iminium ion is therefore much more difficult than the formation of a neutral imine.

To facilitate iminium ion formation additives such as copper(II) sulfate, magnesium sulfate and molecular sieves were employed. In each case the iminium ion was synthesised, as confirmed by the appearance of the α-proton at δ 8.0 ppm in the
$^1$H NMR spectrum and a peak in the mass spectrum at an $m/z$ value of 192.06, which corresponds to $C_7H_{14}NO_3S^+$ ($M^+$).

With a method to the iminium intermediate in hand the Petasis reaction with ($R,S$)-$N$-methyl tert-butyl sulfinamide ($R,S$)-29 was then repeated, using styrenyl boronic acid 2.

![Chemical structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Temperature</th>
<th>Conversion</th>
<th>dr of 31$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Sieves</td>
<td>25</td>
<td>79</td>
<td>1.5:1</td>
</tr>
<tr>
<td>B</td>
<td>MgSO$_4$</td>
<td>25</td>
<td>33</td>
<td>1.8:1</td>
</tr>
<tr>
<td>C</td>
<td>CuSO$_4$</td>
<td>25</td>
<td>31</td>
<td>0.8:1</td>
</tr>
<tr>
<td>D</td>
<td>Sieves</td>
<td>60</td>
<td>71</td>
<td>1.4:1</td>
</tr>
<tr>
<td>E</td>
<td>MgSO$_4$</td>
<td>60</td>
<td>48</td>
<td>1.7:1</td>
</tr>
<tr>
<td>F</td>
<td>CuSO$_4$</td>
<td>60</td>
<td>54</td>
<td>1.3:1</td>
</tr>
</tbody>
</table>

Table 25: Petasis reaction with ($R,S$)-$N$-methyl tert-butyl sulfinamide ($R,S$)-29

Conditions: a) DCE, 21 h.

$^a$ % conversion and diastereomeric ratio determined by crude $^1$H NMR spectroscopy.

The styrenyl amino acid 31 was synthesised by each of the above methods (Table 25). The percentage conversion was determined by analysis of the $^1$H NMR spectra, through integration of the α-proton at approximately δ 4.40 ppm with the tert-butyl region between δ 1.38–1.28 ppm, set to nine protons, similar to the method used for the kinetics studies (section 2.2). The product 31 contains two chiral centres – one at the α-position and one at the sulfur – leading to two possible diastereomers.

From Table 25 it can be seen that all the conditions gave comparable diastereomeric ratios. However, by using powdered 3 Å molecular sieves (entry A, Table 25) at room
temperature a much higher conversion of 79% was achieved. Subsequently, these conditions were applied to the Petasis reaction with cinnamyl boronic acid pinacol ester 15f to give the analogous N-methyl cinnamyl glycine derivate 32 in 80% conversion (Scheme 39). The additional chiral centre at the β-position gives rise to four possible diastereomers, although only two isomers could be distinguished due to peak overlap (Figure 10, section 3.3).

\[
\begin{align*}
\text{(R,S)-29} & \quad 15f & \quad 3 & \quad \text{a} & \quad \text{(R,S)-32} \\
\text{MeHN-S-t-Bu} & \quad \text{Bpin} & \quad \text{H-CO}_2\text{H} & \quad \text{Ph} & \quad \text{MeN-S-t-Bu} & \quad \text{Ph-CO}_2\text{H}
\end{align*}
\]

Scheme 39: (R,S)-N-tert Butyl sulfinamide (R,S)-29 with cinnamyl boronic acid pinacol ester 15f in the Petasis reaction

Conditions: a) CH₂Cl₂, 3 Å molecular sieves, rt, 21 h, 80%, dr = 7:1.

Following on from the success of Lewis acids in the allyl-Petasis reaction (section 3.4), Petasis reactions with 3 Å molecular sieves were conducted and scandium(III) triflate was added at the same time as the organoboronate. This set of reaction conditions was used to generate the styrenyl 31 and cinnamyl 32 products stereoselectively. Both products were formed in good yields of approximately 80% and with excellent control of stereoselectivity, giving a diastereomeric ratio of 20:1 in both cases.

An analysis of the coupling constants was unable to indicate which isomer was the major product. However, comparing the chemical shifts of the vinyl protons in the N-methylated cinnamyl product 32, to the vinyl protons in the analogous unmethylated cinnamyl compound 16f (section 3.4) suggests that the major isomer is the syn-isomer.

4.3. Enantioselective synthesis of N-methyl tert-butyl sulfinamide

To synthesise N-methyl tert-butyl sulfinamide 29 stereoselectively a step-wise route was attempted, adapted from work developed by Ellman and co-workers.\(^\text{75}\)
To begin, an enantiopure chiral ligand 33 was synthesised from a substituted benzaldehyde 34 and cis-aminoinanol 35 (Scheme 40).

![Scheme 40: Synthesis of chiral ligand 33](image)

Conditions: a) EtOH, rt, 2 h, 98%.

This ligand 33 was then used to control the stereochemistry in the oxidation of di-tert-butyl-disulfide 36 with hydrogen peroxide and a vanadium catalyst (Scheme 41).

![Scheme 41: Synthesis of the oxidised sulfur compound 37](image)

Conditions: a) VO(acac)$_2$, ligand 33, 0 °C, 20 h, 71%.

To complete the synthesis of (R)-N-methyl tert-butyl sulfinamide (R)-29 a substitution on the oxidised sulfur compound 37 was required, using lithium methyl amide that was formed by the in situ reaction of methylamine with tert-butyl lithium. Unfortunately, several different attempts at this reaction all failed (Scheme 42).

![Scheme 42: Failed substitution of the sulfur compound 37](image)

Conditions: a) $t$-BuLi, THF, -78 °C→rt, 16 h.

To test the methodology, the reaction was attempted with benzylamine, according to the method of Ellman and co-workers.$^{75}$ Addition of the tert-butyl lithium to
benzylamine caused the reaction mixture to turn violet, whereas only a slight colour change had been observed with the methylamine. After reaction overnight the now magenta coloured reaction mixture was quenched with sodium chloride solution, immediately dissipating the colour and releasing the stench of a sulfide by-product. Analysis by $^1$H NMR spectroscopy showed that the desired (R)-N-benzyl tert-butyl sulfinamide 38 had been formed, due to the presence of the benzyl protons at δ 3.85 ppm. This was confirmed by mass spectrometry and the product was isolated by aqueous extraction.

Encouraged that the method (Scheme 42) was successful it was hypothesised that the methylamine solution may be of poor quality, because addition of the tert-butyl lithium to the initial reaction mixture gave little visible change. By using fresh reagent and taking rigorous care over reaction conditions and dryness a strong yellow colour was produced on addition of the tert-butyl lithium to the methylamine solution. As with the benzylamine reaction, quenching the completed reaction with sodium chloride solution released the stench of a sulfide by-product and the desired product (R)-29 was isolated following an aqueous extraction. Analysis of the resulting product by $^1$H NMR spectroscopy revealed methyl protons at δ 2.80 ppm and the presence of a peak at an $m/z$ value of 135.07, which corresponded to the protonated product, in the mass spectrum confirmed the formation of the desired product.

With (R)-N-methyl tert-butyl sulfinamide (R)-29 in hand the material was applied to the Petasis reaction, following the conditions previously used with molecular sieves (Scheme 43).
Scheme 43: Successful Petasis reactions with \((R)-N\)-methyl tert-butyl sulfinamide \((R)-29\)

Conditions: a) \(\text{OHCCO}_2\text{H}, \text{CH}_2\text{Cl}_2, 3 \text{ Å molecular sieves, styrenyl boronic acid, Sc(OTf)}_3, \text{rt}, 21 \text{ h}, 81\%, \text{dr} = 20:1\); b) \(\text{OHCCO}_2\text{H}, \text{CH}_2\text{Cl}_2, 3 \text{ Å molecular sieves, cinnamyl boronic acid pinacol ester, Sc(OTf)}_3, \text{rt}, 21 \text{ h}, 78\%, \text{dr} = 20:1\).

Styrenyl boronic acid 2 and cinnamyl boronic acid pinacol ester 15f were both used along with scandium(III) triflate. The resulting products were synthesised in an 81% conversion and 20:1 diastereomeric ratio for the styrenyl product 31, and a 78% conversion and 20:1 diastereomeric ratio for the cinnamyl product 32. Due to time constraints the absolute stereochemistry was not determined and full characterisation data was not acquired. However, stereochemistry has been proposed following a comparison of the \(^1\)H NMR data for products 31 and 32 to the \(^1\)H NMR data for the analogous unmethylated compounds 1 (section 2.2) and 16f (section 3.4). The data suggests that product 32 has been synthesised with complete syn-stereochemistry.

### 4.4. Conclusions

The use of \(N\)-methyl tert-butyl sulfinamide 29 in the Petasis reaction was envisaged as a way to synthesise \(N\)-methyl amino acids in a quick and efficient manner.

Methylation of \((S)\)-tert-butyl sulfinamide 4 was unsuccessful under a variety of conditions. However, \((R,S)\)-\(N\)-methyl tert-butyl sulfinamide \((R,S)-29\) was prepared in a pure yield of 98% by the addition of tert-butyl sulfinyl chloride 30 to a solution of methylamine in THF.

Petasis reactions with \((R,S)\)-\(N\)-methyl tert-butyl sulfinamide \((R,S)-29\) were initially unsuccessful. It was found that the initial aldehyde-amine condensation was hindered, because the addition of a methyl group to the nitrogen necessitated the formation of an iminium ion instead of an imine. By adding molecular sieves, magnesium sulfate or
copper(II) sulfate to the reaction, iminium ion formation was promoted and Petasis products were formed. The use of molecular sieves at room temperature gave the highest conversion. By using this simple additive both styrenyl 31 and cinnamyl 32 N-methylated amino acids were synthesised. The use of scandium(III) triflate gave increased stereocontrol.

The enantiopure (R)-N-methyl tert-butyl sulfinamide (R)-29 was synthesised in a step wise manner in an overall yield of 67%. This was applied to the Petasis reactions with styrenyl boronic acid 2 and cinnamyl boronic acid pinacol ester 15f and resulted in the synthesis of the Petasis products in excellent yields and stereoselectivities.
Overall conclusions
Exploring the Petasis reaction through amino acid synthesis
Chapter 5 | Conclusions

5. Overall conclusions

Previous work has shown the Petasis reaction to be a versatile and efficient method for the synthesis of nitrogen-containing compounds, including α-amino acids.

Although extensive Petasis reaction research had been conducted, several limitations still existed. These limitations included a robust asymmetric Petasis reaction, and the scope of boronic acids used in the reaction, past aryl and vinyl organoboronates.

By using tert-butyl sulfinamide 4 with vinyl boronic acids, particularly styrenyl boronic acid derivatives 2, good to excellent stereocontrol could be enforced. Additionally, the reaction with this amine equivalent 4 was found to possess interesting reaction kinetics, in which the boronic acid component acted as both a reagent and as a Lewis acid catalyst, promoting an exponential increase in the rate of reaction with increasing concentration. An analysis of the kinetics of this reaction was conducted and it was found that tert-butyl sulfinamide 4 and glyoxylic acid 3 had rate orders of one, whereas the boronic acid 2 had a rate order of two. A mechanism for this system has been proposed.

To explore the scope of the Petasis reaction with regards to the boronic acids that can be used, allyl boronic acid pinacol esters 15 were applied to the reaction. It was found that the method developed for use with vinyl boronic acids was applicable to this reaction, and this has been optimised to achieve allyl glycine derivatives 6 in excellent yields. Allyl boronic acid pinacol esters 15 can be synthesised in quantitative yields from allylic alcohols in the presence of palladium catalyst 21, and these can be carried through the Petasis reaction in their crude form. Unfortunately, allyl boronic acid pinacol esters 15 do not give the same high diastereoselectivity as the vinyl boronic acids. However, certain transition metal catalysts, in particular scandium(III) triflate, can allow the reaction to proceed with excellent syn/anti control. A method was developed to optimise this reaction. The mechanism of the allyl-Petasis reaction was investigated and was found to proceed via oxygen coordination and a 7-membered ring transition state if tert-butyl sulfinamide 4 was used as the amine component.
N-Methyl tert-butyl sulfinamide 29 has been shown to participate in the Petasis reaction. The use of this amine equivalent allows for the synthesis of N-methylated α-amino acids in a quick and efficient manner. Racemic N-methyl tert-butyl sulfinamide (R,S)-29 can be produced in an excellent yield in a single step, and a method for the synthesis of the enantiopure amine was also developed. The Petasis reaction with N-methyl tert-butyl sulfinamide 29 requires a mild dehydrating agent, such as molecular sieves, to aid in iminium ion formation. Scandium(III) triflate can also be used for enforcing good stereoccontrol. N-Methyl tert-butyl sulfinamide 29 has been shown to participate in vinyl and allyl Petasis reactions to give the corresponding glycine derivates in excellent yields and stereoselectivities.
Experimental details

Exploring the Petasis reaction through amino acid synthesis
6. Experimental

All solvents and reagents were used as obtained from commercial sources without purification unless otherwise stated. Reactions requiring anhydrous conditions were performed under nitrogen or argon in oven-dried apparatus. Dry solvents were obtained from an SPS system, solvent stills or through the use of molecular sieves. ‘Petroleum spirits’ refers to the fraction of petroleum ether boiling at 40-60 °C and hexanes refers to a mixture of hexane isomers. Solvents were evaporated on a Rotorvapor. All temperatures quoted are external.

$^1$H NMR spectra were recorded on Varian Unity 400 (400 MHz), 500 (500 MHz) or 600 (600 MHz) instruments, with deuterochloroform (or other indicated solvents) as reference for internal deuterium lock. The chemical shift data for each signal are given as $\delta$ in units of parts per million (ppm) relative to tetramethylsilane (TMS). The multiplicity of each signal is indicated by: s (singlet), br s (broad singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), dt (doublet of triplets), m (multiplet) and app (apparent). The number of protons (n) for a given resonance is indicated by nH. Coupling constants ($J$) are quoted in Hz and are recorded to the nearest 0.1 Hz.

$^{13}$C NMR spectra were recorded on Varian Unity 400 (100 MHz) or 500 (125 MHz) instruments, with the central resonance of the triplet of CDCl$_3$ at $\delta$ 77.00 ppm as an internal reference. The chemical shift data for each signal are given as $\delta$ ppm.

Flash chromatography was carried out on silica gel (Merck Kieselgel 60 [230–400 mesh]) under pressure, or by using a Reveleris® X2 Flash Chromatography System. Analytical thin layer chromatography (TLC) was done on pre-coated 0.2 mm thick Merck Kieselgel 60 F254 silica gel plates and visualised by absorption of UV light and ethanolic phosphomolybdic acid, aqueous potassium permanganate solution or alizarin solution.

Analytical infra-red spectra were recorded on a Perkin Elmer FT-IR spectrometer from a thin film of neat product. Absorption maxima are given in wavenumbers (cm$^{-1}$). Infra-red spectra for kinetics studies were collected on a Mettler Toledo ReactIR™ 4000
Reaction Analysis System. The K6 Conduit probe arm was purged with dry, compressed gas from a Parker Balston® FT-IR Purge Gas Generator 75-45, at a minimum rate of 14 Lmin⁻¹ and less than 1 ppm water, and used a 16 mm diameter probe with a 0.25 mm thick silicon wafer as the attenuated total reflection element. Analysis of the spectra was performed with iC IR™ Build 3.0.404.3. OriginPro 9.1® was used to analyse the initial rates of reactions.

Mass spectra were recorded by electron spray ionisation (ESI) time of flight, on a liquid chromatography mass spectrometry system composed of an Agilent 1100 HPLC connected to an Agilent 6220 esiTOF mass spectrometer fitted with a standard Agilent electro spray ion source.

**(E)-2-(1,1-Dimethylethylsulfinamido)-4-phenylbut-3-enoic acid 1**

(S)-2-Methylpropane-2-sulfinamide (61 mg, 0.5 mmol) and glyoxylic acid monohydrate (46 mg, 0.5 mmol) were stirred in dichloromethane (2 mL) for 30 minutes at room temperature. trans-2-Phenylvinyl boronic acid (89 mg, 0.6 mmol) was added and the reaction was stirred for 12 hours at room temperature. The solvent was removed in vacuo and the residue was triturated with toluene and filtered. The solid was washed with minimal amounts of cold toluene and cold acetone to afford the product as a white solid (136 mg, 95%) in a 10:1 mixture of isomers (determined by ¹H NMR spectroscopy).

Rf (1:9 methanol:dichloromethane) = 0.15; ¹H NMR (500 MHz, CDCl₃): δH = 7.36-7.23 (5H, m, Ph-H), 6.70 (1H, d, J = 15.9 Hz, CH=CH), 6.20 (1H, dd, J = 15.9, 6.4 Hz, CH=CH), 4.75-4.66 (1H, m, CH-N), 1.30 (9H, s, (CH₃)₃C); ¹³C NMR (125 MHz, CDCl₃): δC = 172.3, 136.0, 133.4, 128.6, 128.1, 126.7, 126.5, 124.7, 60.1, 56.8, 27.1; IR νmax/cm⁻¹ 3264 (OH), 1722 (CO), 1011 (SO); MS (ESI): m/z 282.1187, required 282.1164, C₁₄H₂₀NO₃S [M+H]⁺.
Distinct minor isomer peaks:

$^1$H NMR (500 MHz, CDCl$_3$): $\delta_H$ = 6.76 (1H, d, $J$ = 15.9 Hz, CH=CH), 6.33 (1H, dd, $J$ = 15.9, 6.8 Hz, CH=CH).

Analytical data is consistent with literature values.$^{29}$

**Kinetics reactions**

**Method A – kinetics reactions, monitored by FT-IR, in dichloromethane**

(S)-(−)-2-Methyl-2-propanesulfinamide and glyoxylic acid monohydrate were stirred in dichloromethane (2 mL) in a sealed 28 mL scintillation vial at room temperature for 30 minutes. The FT-IR probe was immersed in the reaction medium, the top sealed with Parafilm® and the data collection was started, taking one scan every 15 seconds. *trans*-2-Phenylvinylboronic acid was then added and the reaction was analysed continuously for an hour.

**Method B – kinetics reactions, monitored by FT-IR, in methanol**

Stock solutions were made up to a concentration of 1.25 M by dissolving each of the following reagents in spectroscopic grade methanol and making the solutions up to 5 mL: (S)-(−)-2-methyl-2-propanesulfinamide (756.6 mg, 6.25 mmol), glyoxylic acid monohydrate (575.1 mg, 6.25 mmol) and *trans*-2-phenylvinylboronic acid (925.4 mg, 6.25 mmol).

(S)-(−)-2-Methyl-2-propanesulfinamide and glyoxylic acid monohydrate were stirred in spectroscopic grade methanol (to give a final total volume of 1.4 mL) in a sealed 28 mL scintillation vial at room temperature for 30 minutes. The FT-IR probe was immersed in the reaction medium and the vial was closed with a lid, designed to fit the vial and probe. The data collection was started, taking one scan every 15 seconds. *trans*-2-Phenylvinylboronic acid was then added and the reaction analysed continuously until the initial reaction rate was deemed to be completed, usually less than 30 minutes.
Method C – kinetics reactions, monitored by $^1$H NMR spectroscopy

(S)-(-)-2-Methyl-2-propanesulfinamide (A) and glyoxylic acid monohydrate (B) were agitated by sonication in deuterated chloroform (1 mL) in a sealed NMR tube at room temperature for 30 minutes. trans-2-Phenylvinyl boronic acid (C) was added and the reaction mixture was immediately inserted into an NMR machine for continued analysis over the course of an hour. After removal from the NMR machine, agitation at room temperature was continued for a further 12 hours.

Reagent amounts used:

<table>
<thead>
<tr>
<th>Exp</th>
<th>A (mg, mmol)</th>
<th>B (mg, mmol)</th>
<th>C (mg, mmol)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6.1, 0.050</td>
<td>4.6, 0.050</td>
<td>7.4, 0.050</td>
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<tr>
<td>S1</td>
<td>3.0, 0.025</td>
<td>4.6, 0.050</td>
<td>7.4, 0.050</td>
</tr>
<tr>
<td>S2</td>
<td>9.1, 0.075</td>
<td>4.6, 0.050</td>
<td>7.4, 0.050</td>
</tr>
<tr>
<td>S3</td>
<td>12.1, 0.100</td>
<td>4.6, 0.050</td>
<td>7.4, 0.050</td>
</tr>
<tr>
<td>S4</td>
<td>15.1, 0.125</td>
<td>4.6, 0.050</td>
<td>7.4, 0.050</td>
</tr>
<tr>
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<td>2.3, 0.025</td>
<td>7.4, 0.050</td>
</tr>
<tr>
<td>B2</td>
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<td>6.9, 0.075</td>
<td>7.4, 0.050</td>
</tr>
<tr>
<td>B3</td>
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<td>9.2, 0.100</td>
<td>7.4, 0.050</td>
</tr>
<tr>
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</tr>
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<td>3.7, 0.025</td>
</tr>
<tr>
<td>G2</td>
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<td>4.6, 0.050</td>
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</tr>
<tr>
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<td>14.8, 0.100</td>
</tr>
<tr>
<td>G4</td>
<td>6.1, 0.050</td>
<td>4.6, 0.050</td>
<td>18.5, 0.125</td>
</tr>
</tbody>
</table>
Cinnamyl alcohol (1.00 g, 7.45 mmol) was dissolved in dichloromethane (1 mL) and cooled to 0 °C before thionyl chloride (6.0 mL, 8.27 mmol) was added. The reaction was stirred at 0 °C for two hours and then allowed to warm and was stirred at room temperature for one hour. The reaction was quenched by the slow addition of ice under a stream of nitrogen gas and then extracted with dichloromethane (10 mL). The solvent was removed in vacuo to leave the product as a viscous orange oil (1.00 g, 88%) in an 11:1 mixture of isomers (E:Z in alignment with literature values, determined by $^1$H NMR spectroscopy).

R$_f$ (1:3 ethyl acetate:petroleum spirits) = 0.81; $^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$ = 7.40-7.36 (2H, m, Ph-H), 7.34-7.29 (2H, m, Ph-H), 7.29-7.23 (1H, m, Ph-H), 6.65 (1H, d, $J$ = 15.7 Hz, CH=CH), 6.31 (1H, dt, $J$ = 15.7, 7.1 Hz, CH-CH$_2$), 4.24 (2H, d, $J$ = 7.1 Hz, CH$_2$-CH); MS (ESI): m/z 153.0430, required 153.0466, C$_9$H$_{10}$Cl [M+H]$^+$. Distinct minor isomer peaks:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$ = 6.64 (1H, d, $J$ = 15.7 Hz, CH=CH), 6.37 (1H, dt, $J$ = 10.6, 7.1 Hz, CH-CH$_2$).

Analytical data is consistent with literature values.  

\[ \text{(E)-(3-Chloroprop-1-enyl)benzene 19} \]
(E)-Cinnamyl acetate 20

Method A – synthesis using acid anhydride and TMS triflate

A solution of cinnamyl alcohol (67 mg, 0.5 mmol) dissolved in dichloromethane (1 mL) was treated with acetic anhydride (77 mg, 0.75 mmol), followed by a 1.0 M solution of TMS triflate in dichloromethane (10 μL, 0.01 mmol). The reaction was stirred at 0 °C for 24 hours then allowed to warm to room temperature and reacted for seven hours. The reaction was quenched with saturated sodium bicarbonate solution, extracted into ethyl acetate (3 x 5 mL) and washed with methanol (5 mL), sodium bicarbonate solution (5 mL) and water (5 mL). The organic layers were combined, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by column chromatography (1:3 ethyl acetate:petroleum spirits) to give the final product as a white solid (50 mg, 57%).

Method B – synthesis using acetic anhydride, DMAP and triethylamine

Cinnamyl alcohol (0.50 g, 3.73 mmol) was dissolved in dichloromethane (15 mL) and acetic anhydride (0.7 mL, 7.45 mmol), triethylamine (1.0 mL, 7.45 mmol) and DMAP (182 mg, 1.49 mmol) were added. The reaction was stirred at room temperature for five hours. The mixture was diluted with dichloromethane (15 mL) and washed with water, saturated sodium bicarbonate solution and 1.0 M hydrochloric acid. The organic layers were combined, dried over magnesium sulfate and concentrated in vacuo to yield the product as white solid (0.66 g, 100%).
Rf (1:3 ethyl acetate:petroleum spirits) = 0.66; ¹H NMR (400 MHz, CDCl₃): δH = 7.41-7.37 (2H, m, Ph-H), 7.35-7.30 (2H, m, Ph-H), 7.28-7.24 (1H, m, Ph-H), 6.66 (1H, d, J = 15.9 Hz, CH=CH), 6.29 (1H, dt, J = 15.9, 6.5 Hz, CH-CH₂), 4.73 (2H, d, J = 6.5 Hz, CH₂-CH), 2.10 (3H, s, CH₃-O); MS (ESI): m/z 177.0905, required 177.0916, C₁₁H₁₃O₂ [M+H]+.

Analytical data is consistent with literature values.²⁷

**General procedure 1 – synthesis of allylic boronic acid pinacol esters**

To oven dried glassware was added the allylic alcohol (5 mmol), DMSO dried over 4 Å molecular sieves (10 mL), methanol dried over 4 Å molecular sieves (10 mL), para-toluene sulfonic acid (45 mg, 0.5 mmol) and di-μ-chlorobis[2-[(dimethylamino)methyl]phenyl-C,N]dipalladium(II) (catalyst 21, 70 mg, 0.25 mmol). Bis(pinacolato) diborone (2.54 g, 10 mmol) was added and the reaction was stirred at 50 °C overnight. The reaction mixture was allowed to cool to room temperature, was diluted with water (50 mL) and extracted with diethyl ether (3 x 30 mL). The combined organic layers were washed with water (50 mL), dried over magnesium sulfate and then concentrated in vacuo. The material was used without further purification.

**2-ALLYL-4,4,5,5-TETRACTION 13,2-DIOXABOROLANE 15A**

![Bpin](image)

2-Alllyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was synthesised from allyl alcohol (340 µL, 5 mmol) according to general procedure 1. The product was collected as a colourless oil (0.84 g, 100%).

Rf (1:3 ethyl acetate:petroleum spirits) = 0.61; ¹H NMR (400 MHz, CDCl₃): δH = 5.86 (1H, ddt, J = 17.1, 10.0, 7.4 Hz, CH=CH₂), 5.03-4.98 (1H, dm, J = 17.1 Hz, CHH=CH), 4.95-4.91 (1H, dm, J = 10.0 Hz, CHH=CH), 1.73 (2H, d, J = 7.4 Hz, CH₂-B), 1.25 (12H, s, ((CH₃)₂C)₂); MS (ESI): m/z 169.1373, required 169.1394, C₉H₁₈BO₂ [M+H]+.

Analytical data is consistent with literature values.²⁸
4,4,5,5-Tetramethyl-2-(3-methylbut-2-enyl)-1,3,2-dioxaborolane 15b

4,4,5,5-Tetramethyl-2-(3-methylbut-2-enyl)-1,3,2-dioxaborolane was synthesised from 3-methylbut-2-en-1-ol (508 μL, 5 mmol) according to general procedure 1. The product was collected as a colourless oil (0.98 g, 100%).

Rf (1:3 ethyl acetate:petroleum spirits) = 0.87; 1H NMR (400 MHz, CDCl3): δH = 5.22 (1H, t, J = 6.4 Hz, CH=C), 1.69 (3H, s, CH3-C-CH3), 1.58 (3H, s, CH3-C-CH3), 1.27 (2H, d, J = 6.5 Hz, CH2-B), 1.24 (12H, s, ((CH3)2)2); MS (ESI): m/z 197.1715, required 197.1707, C11H22BO2 [M+H]+.

Analytical data is consistent with literature values.70

Ethyl 2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)acrylate 15c

Ethyl 2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)acrylate was synthesised from ethyl 2-(hydroxymethyl)acrylate (609 μL, 5 mmol) according to general procedure 1. The product was collected as an off-white solid (1.20 g, 100%).

Rf (1:3 ethyl acetate:petroleum spirits) = 0.72; 1H NMR (400 MHz, CDCl3): δH = 6.07 (1H, s, CHH=C), 5.52 (1H, s, CHH=C), 4.17 (2H, q, J = 7.1 Hz, CH2-CH3), 1.89 (2H, s, CH2-B), 1.27 (3H, t, J = 7.2 Hz, CH3-CH2), 1.23 (12H, s, ((CH3)2)2); MS (ESI): m/z 241.1615, required 241.1606, C12H22BO4 [M+H]+.

Analytical data is consistent with literature values.79
(Z)-2-But-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15d

(Z)-2-But-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was synthesised from (Z)-but-2-en-1-ol (609 μL, 5 mmol) according to general procedure 1. The product was collected as a colourless oil (0.91 mg, 100%).

Rf (1:3 ethyl acetate:petroleum spirits) = 0.83; ¹H NMR (400 MHz, CDCl₃): δ_H = 5.54-5.40 (2H, m, CH=CH), 1.66 (2H, d, J = 7.1 Hz, CH₂-B), 1.58 (3H, br d, J = 6.3 Hz, CH₃-CH), 1.23 (12H, s, ((CH₃)₂C)₂); MS (ESI): m/z 183.1544, required 183.1551, C₁₀H₂₀BO₂ [M+H]+.

Analytical data is consistent with literature values.⁷⁸

(E)-2-(But-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15e

(E)-2-(But-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was synthesised from (E)-but-2-en-1-ol (609 μL, 5 mmol) according to general procedure 1. The product was collected as a colourless oil (0.91 mg, 100%).

Rf (1:3 ethyl acetate:petroleum spirits) = 0.83; ¹H NMR (400 MHz, CDCl₃): δ_H = 5.50-5.35 (2H, m, CH=CH), 1.63 (2H app s, CH₂-B), 1.62 (3H, app s, CH₃-CH), 1.24 (12H, s, ((CH₃)₂C)₂); MS (ESI): m/z 183.1545, required 183.1551, C₁₀H₂₀BO₂ [M+H]+.

Analytical data is consistent with literature values.⁷⁸
2-Cinnamyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15f

2-Cinnamyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was synthesised from cinnamyl alcohol (670 mg, 5 mmol) according to general procedure 1. The product was collected as a white solid (1.22 g, 100%).

Rf (1:3 ethyl acetate:petroleum spirits) = 0.61; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta_H = 7.35-7.31\) (2H, app dm, J = 8.5 Hz, Ph-\(H\)), 7.29-7.24 (2H, app tm, J = 7.4 Hz, Ph-\(H\)), 7.28-7.13 (1H, app tt, J = 7.3, 1.4 Hz, Ph-\(H\)), 6.39 (1H, d, J = 15.8 Hz, CH-\(Ph\)), 6.29 (1H, dt, J = 15.7, 7.1 Hz, CH-CH\(_2\)), 1.87 (2H, d, J = 7.0 Hz, CH\(_2\)-CH), 1.26 (12H, s, ((CH\(_3\))\(_2\)C)); MS (ESI): m/z 245.1702, required 245.1707, C\(_{15}\)H\(_{22}\)BO\(_2\) [M+OH]\(^-\).

Analytical data is consistent with literature values.\(^{80}\)

(E)-2-(Hex-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15g

(E)-2-(Hex-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was synthesised from (E)-hex-2-en-1-ol (596 \(\mu\)L, 5 mmol) according to general procedure 1. The product was collected as a colourless oil (1.05 g, 100%).

Rf (1:3 ethyl acetate:petroleum spirits) = 0.74; \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta_H = 5.48-5.34\) (2H, m, CH=CH), 1.98-1.91 (2H, m, CH\(_2\)-CH), 1.63 (2H, d, J = 6.9 Hz, CH\(_2\)-B), 1.40-1.30 (2H, m, CH\(_2\)-CH\(_3\)), 1.24 (12H, s, ((CH\(_3\))\(_2\)C)); 0.86 (3H, t, J = 7.4 Hz, CH\(_3\)-CH\(_2\)); MS (ESI): m/z 211.1869, required 211.1864, C\(_{12}\)H\(_{24}\)BO\(_2\) [M+H]\(^+\).

The compound was carried forward without further purification.
**General procedure 2 – synthesis of tert-butyl sulfinyl protected allylic amino acids**

(S)-2-Methylpropane-2-sulfinamide (61 mg, 0.5 mmol) and glyoxylic acid monohydrate (46 mg, 0.5 mmol) were stirred in dichloromethane (2 mL) for 30 minutes at room temperature. The boronic acid (0.6 mmol) was added and the reaction was stirred for 21 hours at room temperature. The solvent was removed in vacuo to yield the product.

**General procedure 3 – synthesis of tert-butyl sulfinyl protected allylic amino acids for comparison with literature report**

(S)-2-Methylpropane-2-sulfinamide (121 mg, 1.0 mmol), glyoxylic acid monohydrate (92 mg, 1.0 mmol) and 3 Å powdered sieves were stirred in dry dichloromethane (9 mL) for 42 hours at room temperature. The boronic acid (1.0 mmol) was added and the reaction was stirred for 23 hours at room temperature. The reaction was filtered through Celite® and concentrated in vacuo to yield the product. The product was purified by column chromatography (9:1 dichloromethane:methanol).

**General procedure 4 – Lewis acid catalysed synthesis of amino acids**

(S)-2-Methylpropane-2-sulfinamide (61 mg, 0.5 mmol) and glyoxylic acid monohydrate (46 mg, 0.5 mmol) were stirred in dichloromethane (2 mL) for 30 minutes at room temperature. The boronic acid (0.6 mmol) and scandium(III) triflate (25 mg, 0.05 mmol) were added and the reaction was stirred for 21 hours at room temperature. The reaction mixture was filtered through Celite® and the solvent was removed in vacuo.
2-(1,1-Dimethylethylsulfinamido)pent-4-enoic acid 16a

2-(1,1-Dimethylethylsulfinamido)pent-4-enoic acid was synthesised from 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15a (101 mg, 0.6 mmol) according to general procedure 2 as a yellow oil (110 mg, 100%) in a 4:1 mixture of isomers (determined by $^1$H NMR spectroscopy).

2-(1,1-Dimethylethylsulfinamido)pent-4-enoic acid was synthesised from 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15a (168 mg, 1.0 mmol) according to general procedure 3 as a yellow oil (154 mg, 70%) in a 10:1 mixture of isomers (determined by $^1$H NMR spectroscopy).

2-(1,1-Dimethylethylsulfinamido)pent-4-enoic acid was synthesised from 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15a (101 mg, 0.6 mmol) according to general procedure 4 as a yellow oil (110 mg, 100%) in a 20:1 mixture of isomers (determined by $^1$H NMR spectroscopy).

$R_f$ (1:3 ethyl acetate:petroleum spirits) = 0.19; $^1$H NMR (400 MHz, CDCl$_3$): $\delta_H = 5.91$-$5.86$ (1H, m, CH=CH$_2$), 5.19 (1H, d, $J = 17.3$ Hz, CHH=CH), 5.16 (1H, d, $J = 10.3$ Hz, CHH=CH), 4.29 (1H, dd, $J = 6.1$, 4.6 Hz, CH-NH), 2.63-$2.53$ (1H, m, CHH-CH), 2.46-$2.39$ (1H, m, CHH-CH), 1.22 (9H, s, (CH$_3$)$_3$C); IR $\nu_{\max}$/cm$^{-1}$ 3264 (OH), 1722 (CO), 1011 (SO); MS (ESI): $m/z$ 220.1015, required 220.1002, C$_9$H$_{18}$NO$_3$S [M+H]$^+$.  

Distinct minor isomer peaks:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta_H = 5.83$-$5.77$ (1H, m, CH=CH$_2$).

Analytical data is consistent with literature values.$^{72}$
2-(1,1-Dimethylethylsulfinamido)-3,3-dimethylpent-4-enoic acid 16b

![Image](image1.png)

2-(1,1-Dimethylethylsulfinamido)-3,3-dimethylpent-4-enoic acid was synthesised from 4,4,5,5-tetramethyl-2-(3-methylbut-2-enyl)-1,3,2-dioxaborolane 15b (118 mg, 0.6 mmol) according to general procedure 2 as a yellow oil (124 mg, 100%) in a 4:1 mixture of isomers (determined by $^1$H NMR spectroscopy. Relative stereochemistry was determined to be analogous to 16a).

Rf (1:3 ethyl acetate:petroleum spirits) = 0.30; $^1$H NMR (400 MHz, CDCl$_3$): $\delta_H = 6.00$ (1H, dd, $J = 17.3, 10.6$ Hz, CH=CH$_2$), 5.04 (1H, d, $J = 17.3$ Hz, CH$_2$=CH), 5.03 (1H, d, $J = 10.5$ Hz, CH$_2$=CH), 4.02 (1H, s, CH-N), 1.42 (3H, s, CH$_3$-C(CH$_3$)$_2$), 1.31 (3H, s, CH$_3$-C-CH$_3$), 1.24 (9H, s, (CH$_3$)$_3$C); MS (ESI): m/z 248.1319, required 248.1315, C$_{11}$H$_{22}$NO$_3$S [M+H]$^+$.

Distinct minor isomer peaks:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta_H = 5.87$ (1H, dd, $J = 17.3, 10.6$ Hz, CH=CH$_2$), 5.12-5.08 (2H, m, CH$_2$=CH).

The compound was carried forward without further purification.

2-(1,1-Dimethylethylsulfinamido)-4-(ethoxycarbonyl)pent-4-enoic acid 16c

![Image](image2.png)

2-(1,1-Dimethylethylsulfinamido)-4-(ethoxycarbonyl)pent-4-enoic acid was synthesised from ethyl 2-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)acrylate 15c (144 mg, 0.6 mmol) according to general procedure 2 as a yellow oil (146 mg, 100%) in...
a 3:1 mixture of isomers (determined by $^1$H NMR spectroscopy. Relative stereochemistry was determined to be analogous to 16a).

$R_f$ (1:3 ethyl acetate:petroleum spirits) = 0.15; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$H = 6.29 (1H, app s, C\(\text{H} \text{H=C}\)), 5.78 (1H, app s, CH\(\text{H=C}\)), 4.37 (1H, dd, $J = 8.0$, 4.2 Hz, CH-NH), 4.22 (2H, q, $J = 7.1$ Hz, CH$_2$-CH$_3$), 2.91 (1H, dd, $J = 14.4$, 4.2 Hz, C\(\text{H}-\text{CH}\)), 2.64 (1H, dd, $J = 14.5$, 7.9 Hz, CHH-CH)), 1.31 (9H, s, (CH$_3$)$_3$C), 1.23 (3H, t, $J = 7.1$ Hz, CH$_3$-CH$_2$); MS (ESI): m/z 292.1216, required 292.1213, C$_{12}$H$_{22}$NO$_5$S [M+H]$^+$.

Distinct minor isomer peaks:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$H = 2.84 (1H, dd, $J = 14.2$, 4.5 Hz, CHH-CH).

The compound was carried forward without further purification.

**2-(1,1-Dimethylethylsulfinamido)-3-methylpent-4-enoic acid 16d and 16e**

2-(1,1-Dimethylethylsulfinamido)-3-methylpent-4-enoic acid was synthesised from 2-(but-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (109 mg, 0.6 mmol) according to general procedure 2. (Z)-2-(But-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15d gave the product as a yellow oil (117 mg, 100%) in a 5:1 mixture of isomers (major to minor isomers combined, determined by $^1$H NMR spectroscopy) and (E)-2-(but-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15e gave the product as a yellow oil (117 mg, 100%) in a 2.5:1 mixture of isomers (major to minor isomers combined, determined by $^1$H NMR spectroscopy).

2-(1,1-Dimethylethylsulfinamido)-3-methylpent-4-enoic acid was synthesised from (Z)-2-(but-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15d (182 mg, 1.0 mmol) according to general procedure 3 as a yellow oil (159 mg, 68%) in a 9:1 mixture of isomers (major to minor isomers combined, determined by $^1$H NMR spectroscopy).
2-(1,1-Dimethylethylsulfinamido)-3-methylpent-4-enoic acid was synthesised from 2-(but-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (109 mg, 0.6 mmol) according to general procedure 4. (Z)-2-(But-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15d gave the product as a yellow oil (117 mg, 100%) in a 3:1 mixture of isomers (determined by $^1$H NMR spectroscopy) and (E)-2-(but-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15e gave the product (117 mg, 100%) as a yellow oil in a 2:1 mixture of isomers (determined by $^1$H NMR spectroscopy).

$R_f$ (1:3 ethyl acetate:petroleum spirits) = 0.26; $^1$H NMR (400 MHz, CDCl$_3$): $\delta_H = 5.89$ (1H, ddd, $J = 17.2$, 10.3, 7.0 Hz, $CH=CH_2$), 5.10 (1H, d, $J = 17.3$ Hz, $CHH=CH$), 5.06 (1H, d, $J = 10.3$ Hz, $CHH=CH$), 4.27 (1H, d, $J = 3.3$ Hz, $CH=CH$), 2.79-2.71 (1H, m, $CH=CH_3$), 1.25 (9H, s, (CH$_3$)$_3$C), 1.06 (3H, d, $J = 6.9$ Hz, CH$_3$-CH); MS (ESI): $m/z$ 234.1169, required 234.1158, C$_{10}$H$_{20}$NO$_3$S [M+H]$^+$. 

Distinct minor isomer peaks:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta_H = 5.80$ (1H, ddd, $J = 17.0$, 10.8, 8.0 Hz, $CH=CH_2$), 4.17 (1H, d, $J = 3.4$ Hz, CH-N).

Analytical data is consistent with literature values.$^{72}$

**2-(1,1-Dimethylethylsulfinamido)-3-phenylpent-4-enoic acid 16f**

![Chemical Structure](image)

2-(1,1-Dimethylethylsulfinamido)-3-phenylpent-4-enoic acid was synthesised from 2-cinnamyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15f (146 mg, 0.6 mmol) according to general procedure 2 as a yellow oil (148 mg, 100%) in a 8:3 mixture of isomers (major to minor isomers combined, determined by $^1$H NMR spectroscopy).

2-(1,1-Dimethylethylsulfinamido)-3-phenylpent-4-enoic acid was synthesised from 2-cinnamyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15f (146 mg, 0.6 mmol) according
to general procedure 4 as a yellow oil (148 mg, 100%) in a 3:1 mixture of isomers
determined by $^1$H NMR spectroscopy. Relative stereochemistry was determined to be
analogous to 16a).

$$R_f$$ (1:3 ethyl acetate:petroleum spirits) = 0.23; $^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$
7.38-7.35 (2H, m, Ph-H), 7.33-7.30 (2H, m, Ph-H), 7.26-7.24 (1H, m, Ph-H), 6.70 (1H,
ddd, $J = 15.8, 10.4, 8.2$ Hz, $CH=CH$_2), 6.23 (1H, d, $J = 15.8$ Hz, $CHH=CH$), 6.22 (1H, d, $J =
10.4$ Hz, $CHH=CH$), 4.80-4.75 (1H, m, $CH$-Ph), 4.69-4.64 (1H, m, $CH$-NH), 1.30 (9H, s,
(CH$_3$)$_3$C); MS (ESI): $m/z$ 296.1325, required 296.1315, C$_{15}$H$_{22}$NO$_3$S [M+H]$^+$. 

Distinct minor isomer peaks:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$ = 6.68-6.63 (1H, m, $CH=CH$_2), 6.34 (1H, dd, $J = 15.8,$
7.2 Hz, $CHH=CH$), 6.33 (1H, dd, $J = 10.3, 7.2$ Hz, $CHH=CH$).

The compound was carried forward without further purification.

**2-(1,1-Dimethylethylsulfinamido)-3-vinylhexanoic acid 16g**

![Chemical structure](image)

2-(1,1-Dimethylethylsulfinamido)-3,3-dimethylpent-4-enoic acid was synthesised from
(Z)-2-(hex-2-ethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15g (126 mg, 0.6 mmol)
according to general procedure 2 as a yellow oil (131 mg, 100%) in a 5:1 mixture of
isomers (major to minor isomers combined, determined by $^1$H NMR spectroscopy).

$$R_f$$ (1:3 ethyl acetate:petroleum spirits) = 0.37; $^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$
5.77 (1H, ddd, $J = 16.9, 10.3, 7.6$ Hz, $CH=CH$_2), 5.09 (1H, d, $J = 10.3$ Hz, $CHH=CH$), 5.08 (1H, d, $J =
16.9$ Hz, $CHH=CH$), 4.22 (1H, d, $J = 3.0$ Hz, $CH$-N), 2.45-2.38 (2H, m, $CH$-CH$_2$), 1.94 (2H,
qt, $J = 7.3, 3.3$ Hz, $CH$_2-CH$_3$), 1.35 (2H, dt, $J = 6.1, 3.3$ Hz, $CH$_2-CH$_2$), 1.23 (9H, s, (CH$_3$)$_3$C),
0.86 (3H, t, $J = 7.3$ Hz, $CH$_3-CH$_2$); MS (ESI): $m/z$ 262.1459, required 262.1471,
C$_{12}$H$_{24}$NO$_3$S [M+H]$^+$. 

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Distinct minor isomer peaks:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$H = 5.59-5.55 (1H, m, CH=CH$_2$), 5.08-5.02 (2H, m, CH$_2$=CH), 4.19 (1H, d, $J$ = 3.9 Hz, CH-N).

Analytical data is consistent with literature values.$^{72}$

**2-(1,1-Dimethylethylsulfinamido)pent-4-ynoic acid 23**

![Chemical Structure](image)

2-(1,1-Dimethylethylsulfinamido)pent-4-ynoic acid was synthesised from 4,4,5,5-tetramethyl-2-propane-1,2-dienyl)-1,3,2-dioxaborolane 22 (100 mg, 0.6 mmol) according to general procedure 2 as a yellow oil (109 mg, 100%) in a 5:1 mixture of isomers (determined by $^1$H NMR spectroscopy. Relative stereochemistry was determined to be analogous to 16a).

$R_f$ (1:3 ethyl acetate:petroleum spirits) = 0.27; $^1$H NMR (400 MHz, CDCl$_3$): $\delta$H = 4.39 (1H, t, $J$ = 5.1 Hz, CH-CH$_2$), 2.75 (2H, dd, $J$ = 5.1, 2.9 Hz, CH$_2$-N), 2.10 (1H, t, $J$ = 2.9 Hz, CH≡C), 1.24 (9H, s, (CH$_3$)$_3$C); MS (ESI): $m/z$ 218.0838, required 218.0845, C$_9$H$_{16}$NO$_3$S [M+H]$^+$. 

Distinct minor isomer peaks:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$H = 4.20 (1H, t, $J$ = 4.9 Hz, CH-CH$_2$).

The compound was carried forward without further purification.
**Methyl 2-(1,1-dimethylethylsulfinamido)pent-4-enoate 17**

![Chemical structure of Methyl 2-(1,1-dimethylethylsulfinamido)pent-4-enoate 17]

**Method A – synthesis through the use of diazald**

A 125 mL conical flask (Flask A) was charged with a solution of methyl 2-(1,1-dimethylethyl-sulfinamido)pent-4-enoic acid 16a (110 mg, 0.5 mmol) in dichloromethane (20 mL) and was cooled in an ice bath. The volume of dichloromethane in Flask A was monitored over the course of the reaction and topped up if necessary.

A 40 mL side-arm flask (Flask B), free from scratches, was equipped with a stir bar and a rubber seal. Tygon tubing was attached to the side arm and set up to allow the produced diazomethane gas to bubble through the reaction mixture in Flask A.

Flask B was then charged with *para*-toluene sulfonyl methyl nitrosamide (Diazald®) (333 mg, 1.55 mmol) suspended in ethanol (2 mL) under nitrogen gas. A good flow of nitrogen gas was maintained throughout the reaction. Sodium hydroxide (6.0 M) was added dropwise into Flask B by syringe, producing a yellow colour in the solution. Addition of sodium hydroxide was continued until the yellow colour had been completely discharged. Flask A was then allowed to warm to room temperature and all glassware was purged with nitrogen gas for an additional hour before rinsing with acetic acid. The reaction mixture in Flask A was quenched with acetic acid (10 mL).

The reaction mixture was extracted into ethyl acetate (3 x 10 mL) and the solvent was removed in vacuo. The residue was purified by column chromatography (0-50% ethyl acetate in petroleum spirits) to afford the desired product as a white solid (10 mg, 9%) in 6:1 mixture of isomers (determined by $^1$H NMR spectroscopy. Relative stereochemistry was determined to be analogous to 16a).
Method B – synthesis through the use of trimethylsilyl diazomethane

Methyl 2-(1,1-dimethylethysulfamido)pent-4-enolic acid 16a (110 mg, 0.5 mmol, crude) was dissolved in dichloromethane (0.5 mL) and 2.0 M trimethylsilyl diazomethane in diethyl ether (0.5 mL, 1.0 mmol) was added dropwise. The reaction was stirred at room temperature for two hours before solvent and excess reagent was removed under a stream of nitrogen gas. The product was purified by column chromatography (0-50% ethyl acetate in petroleum spirits) to give the desired product as a white solid (9 mg, 8%) in a 6:1 mixture of isomers (determined by $^1$H NMR spectroscopy. Relative stereochemistry was determined to be analogous to 16a).

$RF (1:3$ ethyl acetate:petroleum spirits) = 0.27; $^1$H NMR (500 MHz, CDCl$_3$): $\delta_H$ = 6.07-5.94 (1H, m, CH=CH$_2$), 5.04 (1H, d, $J = 17.6$ Hz, CHH=CH), 5.03 (1H, d, $J = 10.5$ Hz, CHH=CH), 4.21 (1H, dd, $J = 6.1$, 5.0 Hz, CH-NH), 3.88 (3H, s, CO$_2$CH$_3$), 2.69-2.62 (1H, m, CHH-CH), 2.44-2.39 (1H, m, CHH-CH), 1.26 (9H, s, (CH$_3$)$_3$C); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta_C$ = 180.7, 173.0, 134.0, 117.7, 75.6, 42.0, 38.5, 23.7; IR $\nu_{max}/cm^{-1}$ 1725 (CO), 1012 (SO); MS (ESI): $m/z$ 234.1160, required 234.1158, C$_{10}$H$_{20}$NO$_3$S [M+H]$^+$. Distinct minor isomer peaks:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$ = 5.91-5.80 (1H, m, CH=CH$_2$), 5.10-5.06 (2H, m, CH$_2$=CH).

This compound was not characterised further.

General procedure 5 – deprotection of tert-butyl sulfinyl amino acids

The tert-butyl sulfinyl protected amino acid (0.5 mmol) was dissolved in THF (0.5 mL) and 6.0 M hydrochloric acid in water (0.5 mL, 3.0 mmol) and stirred for one hour at 40 °C. The reaction mixture was neutralised with anhydrous potassium carbonate, the resulting salts were filtered off and the solvent was removed under a stream of nitrogen. The residue was then taken up in minimal methanol and diethyl ether was added to cause the formation of a precipitate, which was collected by filtration.
General procedure 6 – deprotection of tert-butyl sulfinyl amino acids for comparison with literature report\(^{72}\)

The tert-butyl sulfinyl protected amino acid (1.0 mmol) was stirred in aqueous hydrochloric acid (6.0 M, 1.9 mL) at 90 °C for four hours. The reaction mixture was neutralised with anhydrous potassium carbonate and concentrated in vacuo. The product was purified by column chromatography (2.8% aqueous ammonia in 9:1 dichloromethane:methanol).

2-Aminopent-4-enoic acid 6a

![Structure of 2-Aminopent-4-enoic acid 6a](image)

2-Aminopent-4-enoic acid was synthesised from 2-(1,1-dimethylethylsulfinamido)pent-4-enoic acid 16a (110 mg, 0.5 mmol) according to general procedure 5. The product was isolated as a white solid (56 mg, 97%).

2-Aminopent-4-enoic acid was synthesised from 2-(1,1-dimethylethylsulfinamido)pent-4-enoic acid 16a (154 mg, 0.7 mmol, synthesised according to general procedure 3) according to general procedure 6. The product was isolated as a white solid (47 mg, 58%).

2-Aminopent-4-enoic acid was synthesised from 2-(1,1-dimethylethylsulfinamido)pent-4-enoic acid 16a (110 mg, 0.5 mmol, synthesised according to general procedure 4) according to general procedure 5. The product was isolated as a white solid (55 mg, 95%).

\( R_f \) (1:2:7 30% aqueous ammonia:methanol:dichloromethane) = 0.11; \(^1\)H NMR (500 MHz, D\(_2\)O): \( \delta_H = 5.83-5.75 \) (1H, m, CH=CH\(_2\)), 5.29-5.26 (2H, dm, \( J = 10.2 \) Hz, CH\(_2\)=CH), 3.82 (1H, dd, \( J = 4.8, 7.2 \) Hz, CH-NH\(_2\)), 2.72-2.59 (2H, m, CH\(_2\)-CH); MS (ESI): \( m/z \) 116.0731, required 116.0706, C\(_5\)H\(_9\)NO\(_2\) [M+H]\(^{+}\).

Analytical data is consistent with literature values.\(^{72}\)
**2-Amino-3,3-dimethylpent-4-enoic acid 6b**

![Chemical Structure]

2-Amino-3,3-dimethylpent-4-enoic acid was synthesised from 2-((1,1-dimethyl ethylsulfinamido)-3,3-dimethylpent-4-enoic acid **16b** (124 mg, 0.5 mmol) according to general procedure 5. The product was isolated as a white solid (59 mg, 82%).

R<sub>f</sub> (1:3 ethyl acetate:petroleum spirits) = 0.07; <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O): δ<sub>H</sub> = 5.95 (1H, dd, <i>J</i> = 17.3, 11.0 Hz, <i>CH</i>=<i>CH</i>), 5.12 (1H, d, <i>J</i> = 11.0 Hz, <i>CH</i>=<i>H</i>=<i>CH</i>), 5.07 (1H, d, <i>J</i> = 17.3 Hz, <i>CH</i>=<i>H</i>=<i>CH</i>), 3.75 (1H, s, <i>CH</i>=<i>H</i>-<i>N</i>), 1.34 (3H, s, <i>CH</i><sub>3</sub>-<i>CH</i><sub>3</sub>), 1.01 (3H, s, <i>CH</i><sub>3</sub>-<i>CH</i><sub>3</sub>); MS (ESI): <i>m/z</i> 144.1005, required 144.1019, C<sub>7</sub>H<sub>14</sub>N<sub>2</sub>[M+H]<sup>+</sup>.

Analytical data is consistent with literature values.<sup>35</sup>

**2-Amino-4-(ethoxycarbonyl)pent-4-enoic acid 6c**

![Chemical Structure]

2-Amino-4-(ethoxycarbonyl)pent-4-enoic acid was synthesised from 2-((1,1-dimethyl ethylsulfinamido)-4-(ethoxycarbonyl)pent-4-enoic acid **16c** (146 mg, 0.5 mmol) according to general procedure 5. The product was isolated as a white solid (79 mg, 84%). (Relative stereochemistry was determined to be analogous to **16a**.)

R<sub>f</sub> (1:2:7 30% aqueous ammonia:methanol:dichloromethane) = 0.13; <sup>1</sup>H NMR (400 MHz, D<sub>2</sub>O): δ<sub>H</sub> = 6.24 (1H, app s, <i>CH</i>=<i>NH</i>), 5.80 (1H, app s, <i>CHH</i>=<i>C</i>), 4.28 (1H, dd, <i>J</i> = 7.9, 4.3 Hz, <i>CH</i>-<i>NH</i>), 4.16 (2H, q, <i>J</i> = 7.4 Hz, <i>CH</i><sub>2</sub>-<i>CH</i><sub>3</sub>), 2.93 (1H, dd, <i>J</i> = 13.8, 4.3 Hz, <i>CHH</i>-<i>CH</i>), 2.65 (1H, dd, <i>J</i> = 13.9, 7.8 Hz, <i>CHH</i>-<i>CH</i>), 1.24 (3H, t, <i>J</i> = 7.4 Hz, <i>CH</i><sub>3</sub>-<i>CH</i><sub>2</sub>); MS (ESI): <i>m/z</i> 188.0909, required 188.0919, C<sub>8</sub>H<sub>14</sub>N<sub>4</sub>[M+H]<sup>+</sup>.

The compound was not characterised further.
2-Amino-3-methylpent-4-enoic acid 6d and 6e

2-Amino-3-methylpent-4-enoic acid was synthesised from 2-((1,1-dimethyl ethylsulfinamido))-3-methylpent-4-enoic acid (117 mg, 0.5 mmol) according to general procedure 5. 2-((1,1-Dimethylethylsulfinamido))-3-methylpent-4-enoic acid 16d (synthesised from (Z)-2-(but-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborole 15d) gave the product as a white solid (59 mg, 91%) in a 4:1 mixture of isomers (determined by $^1$H NMR spectroscopy) and 2-((1,1-dimethylethylsulfinamido))-3-methylpent-4-enoic acid 16e (synthesised from (E)-2-(but-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborole 15e) gave the product as a white solid (56 mg, 91%) in a 3:1 mixture of isomers (determined by $^1$H NMR spectroscopy).

2-Amino-3-methylpent-4-enoic acid was synthesised from 2-((1,1-dimethyl ethylsulfinamido))-3-methylpent-4-enoic acid 16d (159 mg, 0.68 mmol, synthesised according to general procedure 3) (from (Z)-2-(but-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborole 15d) according to general procedure 6. The product was isolated as a white solid (47 mg, 54%) in a 12:1 mixture of isomers (determined by $^1$H NMR spectroscopy).

2-Amino-3-methylpent-4-enoic acid was synthesised from 2-((1,1-dimethyl ethylsulfinamido))-3-methylpent-4-enoic acid (117 mg, 0.5 mmol) according to general procedure 4. 2-((1,1-Dimethylethylsulfinamido))-3-methylpent-4-enoic acid 16d (synthesised from (Z)-2-(but-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborole 15d according to general procedure 4) gave the product as a white solid (58 mg, 89%) in a 20:1 mixture of isomers (determined by $^1$H NMR spectroscopy) and 2-((1,1-dimethyl ethylsulfinamido))-3-methylpent-4-enoic acid 16e (synthesised from (E)-2-(but-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborole 15e according to general procedure 4) gave the product as a white solid (53 mg, 86%) in a 20:1 mixture of isomers (determined by $^1$H NMR spectroscopy).
Rf (1:3 ethyl acetate:petroleum spirits) = 0.11; 1H NMR (500 MHz, D2O): δH = 8.46 (1H, s, CO2H), 5.94 (1H, ddd, J = 17.3, 10.5, 6.5 Hz, CH=CH2), 5.17 (1H, d, J = 17.3 Hz, CHH=CH), 5.14 (1H, d, J = 10.9 Hz, CHH=CH), 4.02 (1H, d, J = 3.7 Hz, CH-N), 2.68-2.59 (1H, m, CH-CH3), 1.01 (3H, d, J = 6.9 Hz, CH3-CH); MS (ESI): m/z 130.0794, required 130.0863, C6H12NO2 [M+H]+.

Distinct minor isomer peaks:

1H NMR (500 MHz, D2O): δH = 5.81 (1H, ddd, J = 17.3, 10.4, 7.5 Hz, CH=CH2), 3.93 (1H, d, J = 4.0 Hz, CH-N).

Analytical data is consistent with literature values. 

2-Amino-3-phenylpent-4-enoic acid 6f

2-Amino-3-phenylpent-4-enoic acid was synthesised from 2-(1,1-dimethyl ethylsulfinamido)-3-phenylpent-4-enoic acid 16f (148 mg, 0.5 mmol) according to general procedure 5. The product was isolated as a white solid (78 mg, 82%) in an 8:1 mixture of isomers (determined by 1H NMR spectroscopy).

2-Amino-3-phenylpent-4-enoic acid was synthesised from 2-(1,1-dimethyl ethylsulfinamido)-3-phenylpent-4-enoic acid 16f (148 mg, 0.5 mmol, synthesised according to general procedure 4) according to general procedure 4. The product was isolated as a white solid (78 mg, 82%) in a 20:1 mixture of isomers (determined by 1H NMR spectroscopy).

Rf (1:2:7 30% aqueous ammonia:methanol:dichloromethane) = 0.30; 1H NMR (400 MHz, D2O): δH = 7.39-7.20 (5H, m, Ph-H), 6.23 (1H, ddd, J = 17.0, 10.3, 8.9 Hz, CH=CH2), 5.20 (2H, d, J = 17.0 Hz, CHH=CH), 5.19 (2H, d, J = 10.2 Hz, CHH=CH), 4.10 (1H, d, J = 3.1 Hz, CH-NH), 3.85 (1H, dd, J = 8.8, 3.1 Hz, CH-Ph); MS (ESI): m/z 192.1018, required 192.1019, C11H14NO2 [M+H]+.
Distinct minor isomer peaks:

$^1$H NMR (400 MHz, D$_2$O): $\delta_H = 6.18$ (1H, ddd, $J = 17.0, 9.8, 8.7$ Hz, $CH=CH_2$), 5.23 (2H, d, $J = 17.0$ Hz, $CHH=CH$), 5.22 (2H, d, $J = 9.8$ Hz, $CHH=CH$), 4.57 (1H, d, $J = 3.8$ Hz, $CH-NH$).

Analytical data is consistent with literature values.$^{35}$

2-Amino-3-vinylhexanoic acid 6g

2-Amino-3-vinylhexanoic acid was synthesised from 2-(1,1-dimethylethylsulfinamido)-3-vinylhexanoic acid 16g (131 mg, 0.5 mmol) according to general procedure 5. The product was isolated as a white solid (70 mg, 89%) in a 3:1 mixture of isomers (determined by $^1$H NMR spectroscopy).

$R_f$ (1:2:7 30% aqueous ammonia:methanol:dichloromethane) = 0.44; $^1$H NMR (400 MHz, D$_2$O): $\delta_H = 5.72$ (1H, ddd, $J = 17.0, 10.3, 6.7$ Hz, $CH=CH_2$), 5.11 (1H, d, $J = 10.3$ Hz, $CHH=CH$), 5.08 (1H, d, $J = 17.0$ Hz, $CHH=CH$), 4.02 (1H, d, $J = 3.5$ Hz, $CH-N$), 2.48-2.40 (1H, m, $CH-CH_2$), 1.97-1.90 (2H, m, $CH_2-CH_3$), 1.26 (2H, dt, $J = 7.2, 3.2$ Hz, $CH_2-CH_2$), 0.86 (3H, t, $J = 7.3$ Hz, $CH_3-CH_2$); MS (ESI): m/z 158.1165, required 158.1176, C$_8$H$_{16}$NO$_2$ [M+H]$^+$. 

Distinct minor isomer peaks:

$^1$H NMR (400 MHz, D$_2$O): $\delta_H = 5.60-5.56$ (1H, m, $CH=CH_2$), 5.21-5.13 (2H, m, $CH_2=CH$), 3.87 (1H, d, $J = 3.5$ Hz, $CH-N$).

Analytical data is consistent with literature values.$^{72}$
2-Aminopent-4-ynoic acid 24

2-Aminopent-4-ynoic acid was synthesised from 2-(1,1-dimethylethylsulfamidopent-4-ynoic acid 23 (109 mg, 0.5 mmol) according to general procedure 5. The product was isolated as a white solid (45 mg, 79%).

\[ R_f (1:2:7 \text{ 30\% aqueous ammonia:methanol:dichloromethane}) = 0.44; \]
\[ ^1H \text{ NMR (500 MHz, D}_2\text{O): } \delta H = 4.47 \text{ (1H, t, J = 5.3 Hz, CH}-CH_2\text{), 2.73 (2H, dd, J = 5.3, 2.6 Hz, CH}_2\text{-CH), 2.42 (1H, t, J = 2.6 Hz, CH≡C); MS (ESI): m/z 114.0557, required 114.0550, C}_5\text{H}_8\text{NO}_2 [M+H]^+.} \]

Analytical data is consistent with literature values.\textsuperscript{26}

\textbf{N-(tert-Butylthio)-2-methylpropane-2-sulfonamide 25}

2-Methylpropane-2-sulfonamide (31 mg, 0.25 mmol) was stirred with scandium(III) triflate (125 mg, 0.25 mmol) in dichloromethane for 30 minutes at room temperature. The reaction mixture was filtered through Celite\textsuperscript{®} and the solvent was removed in vacuo to yield the product as a white crystal (56 mg, 100%).

\[ ^1H \text{ NMR (400 MHz, CDCl}_3): \delta H = 1.31 \text{ (9H, s, (CH}_3\text)_3\text{CSO}_2\text{), 1.25 (9H, s, (CH}_3\text)_3\text{CS). The identity of the compound was also confirmed by X-ray diffraction.} \]

Analytical data is consistent with literature values.\textsuperscript{73}
General procedure 7 – amino acid synthesis for determining the mechanism of the allyl-Petasis reaction

The amine or amine equivalent (0.25 mmol) and aldehyde or aldehyde equivalent (0.25 mmol) were stirred in dichloromethane (1 mL) for 30 minutes at room temperature. The boronic acid pinacol ester 15 (0.3 mmol) was added and the reaction was stirred for 21 hours at room temperature. The solvent was removed in vacuo to afford the product.

(S)-Ethyl 2-(1-phenylethlamino)pent-4-enoate 27b

(S)-Ethyl 2-(1-phenylethlamino)pent-4-enoate was synthesised from (S)-1-phenyl ethanamine (32 μL, 0.25 mmol), ethyl glyoxylate (as a 50% solution in water, 51 μL, 0.25 mmol) and 2-allyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15a (51 mg, 0.30 mmol) according to general procedure 7. The product was isolated as a yellow oil (56 mg, 86%) as a 4:1 mixture of isomers (determined by $^1$H NMR spectroscopy).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$H = 7.39-7.23 (5H, m, Ph-H), 5.80 (1H, ddd, J = 17.2, 10.2, 7.1 Hz, CH=CH$_2$), 5.12 (1H, d, J = 10.1 Hz, CHH=CH), 5.09 (1H, d, J = 17.2 Hz, CHH=CH), 4.55 (1H, q, J = 6.7 Hz, CH-Ph), 4.31 (2H, q, J = 7.2 Hz, CH$_2$-CH$_3$), 4.19 (1H, dd, J = 7.2, 3.1 Hz, CH-NH), 2.62-2.53 (1H, m, CHH-CH), 2.48-2.40 (1H, m, CHH-CH), 1.43 (3H, d, J = 6.7 Hz, CH$_3$-CHPh), 1.26 (3H, t, J = 7.1 Hz, CH$_3$-CH$_2$).

Distinct minor isomer peaks:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$H = 5.72-5.62 (1H, m, CH=CH$_2$).

The compound was not characterised further.
(2R,3S)-Ethyl 2-(benzylamino)-3-methylpent-4-enoate 28a-b

(2R,3S)-Ethyl 2-(benzylamino)-3-methylpent-4-enoate was synthesised from benzylamine (27 μL, 0.25 mmol), ethyl glyoxylate (as a 50% solution in water, 51 μL, 0.25 mmol) and (Z)-2-(but-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15d (55 mg, 0.30 mmol) according to general procedure 7. The product was isolated as a yellow oil (54 mg, 87%) as a 1:3 mixture of isomers (determined by 1H NMR spectroscopy).

(2R,3S)-Ethyl 2-(benzylamino)-3-methylpent-4-enoate was synthesised from benzylamine (27 μL, 0.25 mmol), ethyl glyoxylate (as a 50% solution in water, 51 μL, 0.25 mmol) and (E)-2-(but-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15e (55 mg, 0.30 mmol) according to general procedure 7. The product was isolated as a yellow oil (52 mg, 84%) as a 1:1.5 mixture of isomers (determined by 1H NMR spectroscopy).

1H NMR (400 MHz, CDCl3): δH = 7.33-7.16 (5H, m, Ph-H), 5.74 (1H, ddd, J = 16.7, 10.7, 7.1 Hz, CH=CH2), 5.06 (1H, d, J = 16.7 Hz, CHH=CH), 5.05 (1H, d, J = 10.7 Hz, CHH=CH), 4.18 (2H, q, J = 7.0 Hz, CH2-CH3), 3.12 (1H, d, J = 7.1 Hz, CH-NH), 2.59-2.50 (1H, m, CH-CH3), 2.36 (2H, s, CH2-Ph), 1.26 (3H, t, J = 7.0 Hz, CH3-CH2), 1.06 (3H, d, J = 6.8 Hz, CH3-CH).

Distinct minor isomer peaks:

1H NMR (400 MHz, CDCl3): δH = 5.85 (1H, ddd, J = 17.7, 10.0, 7.8 Hz, CH=CH2).

The compound was not characterised further.
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**28c-d**

(2R,3R)-Ethyl 3-methyl-2-((S)-1-phenylethlamino)pent-4-enoate was synthesised from (S)-1-phenylethanalmine (32 μL, 0.25 mmol), ethyl glyoxylate (as a 50% solution in water, 51 μL, 0.25 mmol) and (Z)-2-(but-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxa borolane 15d (55 mg, 0.30 mmol) according to general procedure 7. The product was isolated as a yellow oil (58 mg, 89%) as a 5:1 mixture of isomers (determined by 1H NMR spectroscopy).

(2R,3R)-Ethyl 3-methyl-2-((S)-1-phenylethlamino)pent-4-enoate was synthesised from (S)-1-phenylethanalmine (32 μL, 0.25 mmol), ethyl glyoxylate (as a 50% solution in water, 51 μL, 0.25 mmol) and (E)-2-(but-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxa borolane 15e (55 mg, 0.30 mmol) according to general procedure 7. The product was isolated as a yellow oil (57 mg, 87%) as a 4:1 mixture of isomers (determined by 1H NMR spectroscopy).

1H NMR (400 MHz, CDCl₃): δH = 7.39-7.20 (5H, m, Ph-H), 5.93 (1H, ddd, J = 17.9, 9.9, 8.1 Hz, CH=CH₂), 5.11 (1H, d, J = 17.9 Hz, CHH=CH), 5.07 (1H, d, J = 9.9 Hz, CHH=CH), 4.61 (1H, q, J = 6.7 Hz, CH-Ph), 4.34 (2H, q, J = 7.1 Hz, CH₂-CH₃), 4.10 (1H, d, J = 3.4 Hz, CH-NH), 2.70-2.61 (1H, m, CH-CH), 1.47 (3H, d, J = 6.7 Hz, CH₃-CHPh), 1.26 (3H, t, J = 7.1 Hz, CH₃-CH₂), 1.12 (3H, d, J = 4.4 Hz, CH₃-CHNH).

Distinct minor isomer peaks:

1H NMR (400 MHz, CDCl₃): δH = 5.74 (1H, ddd, J = 16.4, 10.5, 5.6 Hz, CH=CH₂).

The compound was not characterised further.
(2R,3R)-3-Methyl-2-((S)-1-phenylethylamino)pent-4-enolic acid 28e-f

(2R,3R)-3-Methyl-2-((S)-1-phenylethylamino)pent-4-enolic acid was synthesised from (S)-1-phenylethanimine (32 μL, 0.25 mmol), glyoxylic acid monohydrate (23 mg, 0.25 mmol) and (Z)-2-(but-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15d (55 mg, 0.30 mmol) according to general procedure 7. The product was isolated as a yellow oil (51 mg, 88%) as a 2:1 mixture of isomers (determined by $^1$H NMR spectroscopy).

(2R,3R)-3-Methyl-2-((S)-1-phenylethylamino)pent-4-enolic acid was synthesised from (S)-1-phenylethanimine (32 μL, 0.25 mmol), glyoxylic acid monohydrate (23 mg, 0.30 mmol) and (E)-2-(but-2-enyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15e (55 mg, 0.30 mmol) according to general procedure 7. The product was isolated as a yellow oil (50 mg, 85%) as a 2:1 mixture of isomers (determined by $^1$H NMR spectroscopy).

$^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$ = 7.41-7.24 (5H, m, Ph-H), 5.92 (1H, ddd, $J$ = 16.9, 10.8, 6.9 Hz, CH=CH$_2$), 5.17 (1H, d, $J$ = 16.9 Hz, CHH=CH), 5.16 (1H, d, $J$ = 10.8 Hz, CHH=CH), 4.33 (1H, q, $J$ = 7.3 Hz, CH-Ph), 4.16 (1H, dd, $J$ = 6.3, 3.8 Hz, CH-NH), 2.75-2.65 (1H, m, CH-CH), 1.43 (3H, d, $J$ = 7.2 Hz, CH$_3$-CHPh), 1.06 (3H, d, $J$ = 7.0 Hz, CH$_3$-CH).

Distinct minor isomer peaks:

$^1$H NMR (400 MHz, CDCl$_3$): $\delta_H$ = 5.77 (1H, ddd, $J$ = 17.1, 10.4, 6.4 Hz, CH=CH$_2$).

The compound was not characterised further.
A mixture of 3.5-di-tert-butyl salicylaldehyde (0.30 g, 1.2 mmol) and (1S,2R)-(-)-cis-1-amino-2-indanol (0.18 g, 1.2 mmol) in dry ethanol (9 mL) was added to a dry round bottomed flask and stirred under nitrogen gas for two hours. The mixture was concentrated in vacuo to yield a yellow oil, which was dissolved in dichloromethane (9 mL) and concentrated in vacuo twice more before drying under high vacuum (caution: foaming) to afford the desired compound as a yellow powder (0.43 g 98%).

Rf (1:3 ethyl acetate:petroleum spirits) = 0.67; ¹H NMR (400 MHz, CDCl₃): δH = 13.09 (1H, s, OH), 8.63 (1H, s, CH=N), 7.43 (1H, d, J = 2.5 Hz, Ph-6H), 7.35-7.19 (4H, m, Ph-indene-H), 7.17 (1H, d, J = 2.5 Hz, Ph-4H), 4.80 (1H, d, J = 5.3 Hz, CH-N), 4.69 (1H, ddd, J = 5.8, 5.0, 5.4 Hz, CH-OH), 3.26 (1H, dd, J = 15.9, 5.0 Hz, CHH-CHOH), 3.13 (1H, dd, J = 15.9, 5.8 Hz, CHH-CHOH), 1.43 (3H, s, CH₃-C-PhOH), 1.42 (6H, s, (CH₃)₂C-PhOH), 1.33 (3H, s, CH₂-C), 1.32 (6H, s, (CH₃)₂C); IR νmax/cm⁻¹: 2957 (CH), 1625 (CN), 1468 (CC), 1439 (CH); MS (ESI): m/z 366.2432, required 366.2433, C₂₄H₃₂NO₂ [M+H]⁺.

This data aligns with literature data.⁸¹

**(S)-S-tert-Butyl 2-methylpropane-2-sulfinothioate 37**

Vanadyl bis-acetylacetonate (0.31 g, 1.16 mmol) and (1S,2R)-1-((E)-3,5-di-tert-butyl-2-hydroxybenzylideneamino)-2,3-dihydro-1H-inden-2-ol 33 (0.43 g, 1.18 mmol) were stirred in acetone for 30 minutes at room temperature in a vessel that was open to the air. di-tert-Butyl disulfide (40.94 g, 0.23 mol) was added and the reaction mixture was
cooled to 0 °C. The reaction was stirred vigorously and a 30% aqueous solution of hydrogen peroxide (12.65 mL, 0.25 mol) was added at 0 °C over 20 hours by using a syringe pump. The reaction was quenched with saturated aqueous sodium thiosulfate (23 mL) over 30 minutes and then allowed to warm to room temperature. The mixture was extracted into hexanes and washed with sodium chloride solution. The organic layer was dried over magnesium sulfate and concentrated in vacuo to yield a brown oil, which was purified by Kugelrohr distillation at 61.5 °C (100 mTorr) to give the title compound as a colourless liquid (31.69 g, 71%).

Rf (1:3 ethyl acetate:petroleum spirits) = 0.64; 1H NMR (400 MHz, CDCl3): δH = 1.56 (9H, s, (CH3)3C-S), 1.31 (9H, s, (CH3)3C-SO); 13C NMR (125 MHz, CDCl3): δC = 59.4, 46.1, 32.3, 24.2; MS (ESI): m/z 195.0904, required 195.0877, C8H19OS2 [M+H]+.

This data aligns with literature data.75

(R)-N-Benzyl-2-methylpropane-2-sulfinamide 38

A dry round bottomed flask at -78 °C under nitrogen gas was charged with benzylamine (803 mg, 819 μL, 7.5 mmol) and THF (15 mL). tert-Butyl lithium (0.97 M in pentane, 8.0 mL, 7.5 mmol) was added dropwise to give a violet solution. After 30 minutes (S)-S-tert-butyl 2-methylpropane-2-sulfinothioate 37 (300 mg, 1.5 mmol) was added slowly. The reaction was allowed to warm to room temperature and was stirred overnight. It was then quenched with saturated sodium chloride solution, which dissipated the colour and produced a stench of sulfur. The mixture was extracted with ethyl acetate (3 x 60 mL). The organic layers were combined, dried over magnesium sulfate and concentrated in vacuo. The resulting dark yellow liquid was purified by column chromatography (50:50 ethyl acetate:petroleum spirits) and recrystallised from hexanes to afford the title compound as a white solid (256 mg, 81%).
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Rf (1:3 ethyl acetate:petroleum spirits) = 0.29; $^1$H NMR (400 MHz, CDCl$_3$): $\delta_H = 7.35-7.23$ (5H, m, Ph-H), 3.90-3.80 (2H, m, CH$_2$-Ph), 2.05-1.95 (1H, m, NH), 1.30 (9H, s, (CH$_3$)$_3$C); MS (ESI): $m/z$ 212.1095, required 212.1104, C$_{11}$H$_{18}$NOS $[M+H]^+$. Analytical data is consistent with literature values.$^{75}$

$N,2$-Dimethylpropane-$2$-sulfinamide-29

\[
\begin{align*}
\text{MeHN} & \quad \text{S} \quad \text{t-Bu} \\
\end{align*}
\]

Method A – synthesis of (R)-$N,2$-dimethylpropane-$2$-sulfinamide (R)-29

A dry round bottomed flask at -78 °C under nitrogen gas was charged with a 2.0 M solution of methylamine in THF (4.5 mL, 8.96 mmol). tert-Butyl lithium (0.97 M in pentane, 7.7 mL, 7.46 mmol) was added dropwise to give a yellow solution. After 30 minutes (S)-S-tert-butyl 2-methylpropane-2-sulfinothioate 37 (299 mg, 1.54 mmol), as a solution in THF (3 mL), was added slowly. The reaction was allowed to warm to room temperature and was stirred overnight. It was then quenched with saturated sodium chloride solution, which dissipated the colour and produced a stench of sulfur. The mixture was extracted with ethyl acetate (3 x 60 mL). The organic layers were combined, dried over magnesium sulfate and concentrated in vacuo. The resulting dark yellow liquid was purified by column chromatography (50:50 ethyl acetate:petroleum spirits) and recrystallised from hexanes to yield the title compound as a pale yellow oil (196 mg, 94%).

Method B – synthesis of (S)-$N,2$-dimethylpropane-$2$-sulfinamide (S)-29

(S)-tert-Butyl sulfinamide (50 mg, 0.41 mmol) was dissolved in dry dichloromethane. Sodium hydride (10 mg, 0.41 mmol) and methyl iodide (52 μL, 0.83 mmol) were added and the reaction was stirred at room temperature for five hours. It was then quenched with ice cold water and extracted into dichloromethane. The organic layer was dried over magnesium sulfate and concentrated in vacuo. The resulting yellow oil was
purified by column chromatography (50:50 ethyl acetate:petroleum spirits) to yield the title compound as a pale yellow oil (13 mg, 23%).

**Method C – synthesis of N,2-dimethylpropane-2-sulfinamide (R,S)-29**

A 2.0 M solution of methylamine in THF (3.55 mL, 7.10 mmol) was stirred in a dry round bottomed flask equipped with a rubber seal. tert-Butyl sulfinyl chloride (176 μL, 1.42 mmol) was added dropwise, with the needle tip submerged, maintaining a temperature of below 30 °C. The reaction was stirred at room temperature for five hours. It was then quenched with water and extracted into dichloromethane. The organic layers were combined, dried over magnesium sulfate and concentrated in vacuo. The resulting dark yellow oil was purified by column chromatography (50:50 ethyl acetate: petroleum spirits) to yield the title compound as a pale yellow oil (188 mg, 98%).

Rf (1:3 ethyl acetate:petroleum spirits) = 0.18; 1H NMR (400 MHz, CDCl₃): δH = 3.06 (1H, br d, J = 5.4 Hz, NH), 2.84, (3H, d, J = 5.5 Hz, CH₃-N), 1.21, (9H, s, (CH₃)₃C); 13C NMR (125 MHz, CDCl₃): δC = 55.0, 31.4, 22.4; MS (ESI): m/z 136.0789, required 136.0796, C₅H₁₄NOS [M+H]^+.

**General procedure 8 – synthesis of N-methylated amino acids**

N,2-Dimethylpropane-2-sulfinamide (33 mg, 0.25 mmol), glyoxylic acid monohydrate (23 mg, 0.25 mmol) and powdered 3 Å molecular sieves (50 mg) were stirred in dichloromethane (1 mL) for 30 minutes at room temperature. The boronic acid (0.3 mmol) and scandium(III) triflate (12.5 mg, 0.025 mmol) were added and the reaction was stirred for 21 hours at room temperature. The reaction mixture was filtered through Celite® and the solvent was removed in vacuo to yield the product.
**(E)-2-(N,2-Dimethylpropan-2-ylsulfinamido)-4-phenylbut-3-enioic acid 31**

(E)-2-(N,2-Dimethylpropan-2-ylsulfinamido)-4-phenylbut-3-enioic acid was synthesised from styrenyl boronic acid 2 (44 mg, 0.3 mmol) according to general procedure 7 as a yellow oil (60 mg, 82%) in a greater than 20:1 mixture of isomers (determined by \(^1\)H NMR spectroscopy).

\[ R_f (1:3 \text{ ethyl acetate:petroleum spirits}) = 0.36; \ ^1\text{H NMR (400 MHz, CDCl}_3\text{)}: \delta_H = 7.41 (2H, d, J = 7.3 \text{ Hz, Ph-H}), 7.33 (2H, t, J = 7.2 \text{ Hz, Ph-H}), 7.23 (1H d, J = 7.4 \text{ Hz, Ph-H}), 6.77 (1H, d, J = 17.6 \text{ Hz, CH=CH}), 5.90 (1H, dd, J = 17.6, 8.4 \text{ Hz, CH=CH}), 4.27 (1H, d, J = 8.4 \text{ Hz, CH-N}), 2.67 (3H, s, CH\textsubscript{3}), 1.37 (9H, s, (CH\textsubscript{3})\textsubscript{3}C); \text{MS (ESI): m/z 296.1297, required 296.1315, C_{15}H_{22}NO_3S [M+H]^+}. \]

The compound was not characterised further.

**2-(N,2-Dimethylpropan-2-ylsulfinamido)-3-phenylpent-4-enioic acid 32**

2-(N,2-Dimethylpropan-2-ylsulfinamido)-3-phenylpent-4-enioic acid was synthesised from 2-cinnamyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane 15f (73 mg, 0.3 mmol) according to general procedure 7 as a yellow oil (63 mg, 81%) in a greater than 20:1 mixture of isomers (determined by \(^1\)H NMR spectroscopy).
Rf (1:3 ethyl acetate:petroleum spirits) = 0.45; $^1$H NMR (400 MHz, CDCl₃): $\delta_H = 7.39-7.28$ (5H, m, Ph-H), 6.19 (1H, ddd, $J = 17.1, 9.1, 8.7$ Hz, CH=CH₂), 5.23 (1H, d, $J = 17.1$ Hz, CH=CH), 5.22 (1H, d, $J = 9.1$ Hz, CHH=CH), 4.56 (1H, d, $J = 3.2$ Hz, CH-N), 3.87 (1H, dd, $J = 8.7, 3.1$ Hz, CH-Ph), 3.42 (3H, s, CH₃-N), 1.26 (9H, s, (CH₃)₃C); MS (ESI): m/z 310.1499, required 310.1471, C₁₆H₂₄NO₃S [M+H]+.

The compound was not characterised further.
7. References


Author/s:
Bradley, Lucie

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