AN INVESTIGATION INTO
ORGANOCATALYTIC MICHAEL ADDITIONS

by

Peter Dale

A thesis submitted to the University of Birmingham for the degree
of MASTER OF SCIENCE

School of Chemistry
College of Engineering and Physical Sciences
University of Birmingham
January 2015
Previous work in the Simpkins group includes the Michael addition reactions of triketopiperazines (TKPs). These were performed asymmetrically using modified cinchona alkaloid catalysts. The aim of this project was to expand the range of substrates that could be used in similar organocatalytic reactions.

Cyclic substrates such as hydantoins and the drug thalidomide did not show any reactivity under the Michael addition conditions. Acyclic substrates were also tested and some limited success was achieved with an α-phenyl amide substrate. However, a strongly basic guanidine catalyst was required, so investigations were therefore carried out into developing chiral guanidine catalysts.

In the course of the project a new method for the arylation of TKP A was developed which used diphenyliodonium triflate (DPIT) as the electrophile. Phenyl-TKP B was subsequently used in asymmetric Michael additions. A range of catalysts were screened, with modified-quinine catalyst D performing the best.

The PMB-protected TKP E was also synthesised and this gave even better yields and selectivities when a range of unsaturated ketones were used.
In summary, a large number of substrates have been tested and a method for arylating TKPs has been developed. Furthermore, some excellent yields and selectivities have been achieved for organocatalytic Michael additions.
ACKNOWLEDGEMENTS

I owe my thanks and appreciation to Professor Nigel Simpkins for accepting me into his group and for both his ideas and support, especially when things weren’t going so smoothly.

Thanks also go to all of the staff in the School of Chemistry, especially Neil Spencer who helped me greatly with NMR experiments.

The Simpkins group have been a huge support to me through this project and I owe them all my thanks. Alejandro Cabanillas, you have been a huge help with your ideas, knowledge, catalysts and friendship. He Yang, you are one of the kindest and most considerate chemists I have had the pleasure to work with, thank you! François Saint-Dizier, I have really enjoyed working alongside you, and sharing the ups and downs of chemistry with you. Matt Rees, I’m really grateful for your friendship and generosity with help and catalysts. Thank you all for welcoming me so well and I wish you all the very best.

I also owe my thanks to my wife, Rachel, who has been so steadfast in listening to me and encouraging me.

Finally, my thanks to God for giving me this time in Birmingham to meet people, make molecules and discover more about his creation.

“To the only God our Saviour be glory, majesty, power and authority, through Jesus Christ our Lord, before all ages, now and for evermore! Amen.” Jude 25
# CONTENTS

Abbreviations........................................................................................................................................ vi

1. Introduction......................................................................................................................................... 1
   1.1. Organocatalysis ................................................................................................................................. 1
   1.2. Cinchona organocatalysis .................................................................................................................. 2
   1.3. Existing group methodology ............................................................................................................... 5
   1.4. Synthesis of TKPs ............................................................................................................................... 7
   1.5. Project aims ....................................................................................................................................... 10

2. Results and discussion............................................................................................................................ 14
   2.1. α-Amino amide substrates .................................................................................................................. 14
   2.2. α-Phenyl amide substrates ................................................................................................................ 16
   2.3. Synthesis of chiral guanidines ........................................................................................................... 18
   2.4. Hydantoin substrates ......................................................................................................................... 23
   2.5. Thalidomide substrates ....................................................................................................................... 27
   2.6. Phenyl-TKP substrates ....................................................................................................................... 28
   2.7. PMB-protected phenyl-TKP substrates .............................................................................................. 33
   2.8. Conclusions and future work ............................................................................................................ 36

3. Experimental ......................................................................................................................................... 39
   3.1. General experimental techniques ...................................................................................................... 39
   3.2. Compounds ....................................................................................................................................... 41

4. List of References .................................................................................................................................. 70

5. Appendix ............................................................................................................................................... 74
**ABBREVIATIONS**

μW microwave  
Ac acetyl  
Bn benzyl  
Boc tert-butyloxycarbonyl  
Bzt benzotriazole  
CAN ceric ammonium nitrate  
cf. compare  
COSY correlation spectroscopy  
Cy cyclohexyl  
DCC dicyclohexyl carbodiimide  
DDQ 2,3-dichloro-5,6-dicyano-p-benzoquinone  
DEAD diethyl azodicarboxylate  
DIAD diisopropyl azodicarboxylate  
DIPEA diisopropylethylamine  
DPPA diphenylphosphoryl azide  
dr diastereomeric ratio  
ee enatiomeric excess  
equiv equivalents  
er enantiomeric ratio  
h hour(s)  
HMBC heteronuclear multiple bond correlation  
HPLC high performance liquid chromatography  
HRMS high resolution mass spectrometry  
HSQC heteronuclear single quantum correlation  
IPA isopropyl alcohol  
iPr isopropyl  
LDA lithium diisopropylamide  
LHMDS lithium bis(trimethylsilyl)amide  
LUMO lowest unoccupied molecular orbital  
m.p. melting point  
mCPBA meta-chloroperbenzoic acid  
min minute(s)  
MVK methyl vinyl ketone  
NMR nuclear magnetic resonance  
NOE nuclear Overhauser effect  
NR no reaction  
PMB p-methoxybenzyl  
PMP p-methoxyphenyl  
ppm parts per million  
PTSA p-toluenesulfonic acid  
Py pyridine  
quant quantitative yield  
rt room temperature  
SM starting material  
tBu tert-butyl  
TFA trifluoroacetic acid  
TFAA trifluoroacetic anhydride  
TfO trifluoromethanesulfonate  
THF tetrahydrofuran  
TKP triketopiperazine  
tlc thin layer chromatography  
TMG 1,1,3,3-tetramethylguanidine  
TMS trimethylsilyl
1. INTRODUCTION

1.1. Organocatalysis

The field of organocatalysis has expanded rapidly since the beginning of the 21st century. The catalysis of reactions with small organic molecules which contain no inorganic element is appealing for many reasons; asymmetric organocatalysts can be made from chiral-pool molecules and no expensive or toxic metals are required.

Early work in this area focused on the use of amines to give enamine or iminium intermediates which were then used in reactions such as the aldol reaction. The Hajos–Parrish–Eder–Sauer–Wiechert reaction uses proline as a readily available asymmetric organocatalyst and has been used in the synthesis of steroid intermediates.\(^1,2\) List and co-workers suggest that the reaction proceeds via an enamine intermediate with a Zimmerman–Traxler type transition state 1 (Scheme 1).\(^3\)

An early example of iminium organocatalysis was published by MacMillan and co-workers in 2000. They disclosed the first Diels−Alder reaction using enantioselective iminium catalysis (Scheme 2).\(^4\) The MacMillan family of organocatalysts used for this purpose have an imidazolidinone core and are thought to function by lowering the LUMO of the dienophile for
the cycloaddition. The bulky benzyl group then provides the facial selectivity for the diene’s approach.

![Scheme 2 - MacMillan’s asymmetric Diels–Alder reaction](image)

These are both examples of Lewis base organocatalysis which has dominated the field to date. The three other classes of organocatalysis are: Lewis acid, Brønsted base and Brønsted acid.\(^5\)

The Brønsted acid and base forms of catalysis do not involve covalent bond formation with the substrate and typically work with much lower catalyst loadings (cf. up to 30 mol% for proline catalysis).

### 1.2. Cinchona organocatalysis

Examples of chiral Brønsted bases include the cinchona alkaloids which are isolated from the bark of cinchona trees found in the tropical forests of South America. Quinine 2 (Figure 1) is one of these alkaloids and it has found numerous medicinal applications, not least for treating malaria. It was isolated by Pelletier and Caventou in 1820\(^6\) and the other main alkaloids isolated from the bark were quinidine 3, cinchonine and cinchonidine (Figure 1).

![Figure 1 - cinchona alkaloids](image)
The quinoline unit, secondary alcohol and basic quinuclidine included in all of these alkaloids make them promising for use as Brønsted basic or bifunctional catalysts. Quinine 2 and quinidine 3 (likewise with cinchonidine and cinchonine) are pseudo-enantiomers and therefore allow for the possibility of generating enantiomeric products from the organocatalytic reaction. These properties have been extensively exploited and many modified catalysts have been used to great effect for a range of asymmetric reactions.⁷

In 1984, Dolling and co-workers published the first sub-stoichiometric catalytic enantioselective alkylation using a phase transfer catalyst. Their optimal catalyst was $N$-(p-(trifluoromethyl)benzyl)cinchoninium chloride 5 (Scheme 3) and they achieved 92% ee for the methylation of 6,7-dichloro-5-methoxy-2-phenyl-1-indanone 4.⁸

![Scheme 3](image)

Scheme 3 – Dolling and co-workers asymmetric alkylation

One well explored area of cinchona catalysis is the alkylation of glycine imino esters, such as 6 (scheme 4), under phase-transfer conditions to give natural and unnatural chiral α-amino acids. The free amine of the amino acid is converted to the imine by reacting with benzophenone imine and this dramatically lowers the $pK_a$ of the substrate. The cinchona-derived ammonium species 8 is able to solubilise some hydroxide in the organic phase allowing for the deprotonation of the glycine equivalent. The resultant ion pair then undergoes a conjugate addition with the Michael acceptor with the chiral ammonium
counterion providing the enantioinduction. Corey and co-workers published early examples of this in 1998 and they achieved enantiomeric excesses of 95% and above (Scheme 4).\(^9\)

![Scheme 4 - Corey’s asymmetric Michael additions](image)

In 2012 Barbas and co-workers reported the organocatalytic asymmetric Michael addition of pyrazoleamides \(^9\) (Scheme 5). The aromatic group was predicted to give an amide with a relatively low \(pK_a\) which would therefore make it amenable to deprotonation by cinchona derived catalysts. The best diastereoselectivity and enantioselectivity was achieved with urea groups at the C-9 carbon of the catalyst \(^\text{10}\). These bi-functional catalysts are thought to operate by the quinuclidine moiety acting as a Brønsted base and the urea unit acting as a hydrogen bond donor to activate the resulting enolate and pyrazole. The protonated quinuclidine is then thought to activate the nitro olefin. Excellent selectivities were achieved with a range of nitro olefins but no other Michael additions were reported. The substrate scope was limited to aromatic pyrazoleamides but a range of different aromatic substituents were used, and those with electron withdrawing groups gave the best yields and stereoselectivity.\(^\text{10}\)
1.3. Existing group methodology

Previous work done by the Simpkins group has included studies on the reactions of diketopiperazines (DKPs) and the synthesis of DKP-containing natural products such as the steptacidins. More recently, it was decided to investigate their use as potential substrates for cinchona-catalysed Michael additions. It is known that transforming an amide into an imide dramatically reduces the $pK_a$ of the $\alpha$-proton (vide infra) so the DKP structure was modified to incorporate an additional carbonyl group giving a triketopiperazine (TKP) $12b$ (Table 1).

These TKPs have proved to be very effective systems for Michael addition reactions with a wide range of Michael acceptors and with high enantioselectivity (Table 1). The reaction has been proposed to proceed by deprotonation of the TKP by the quinuclidine of the catalyst $13$ and a developing hydrogen bond between the quinoline hydroxyl and the Michael acceptor. The resultant complex $14$ allows for reaction on only one face of the TKP and this explains the
high levels of selectivity achieved. The products from the additionally activated substrates with an external ester group have a quaternary stereogenic centre 15a so do not suffer any loss of ee under acidic or basic conditions, whereas it is suspected that products 15b do suffer erosion of their ee due to epimerisation occurring.

![Chemical structure of 12a and 12b](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>TKP</th>
<th>R</th>
<th>yield (%)</th>
<th>ee (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12a</td>
<td>Me</td>
<td>99</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>12a</td>
<td>H</td>
<td>99</td>
<td>99&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3</td>
<td>12a</td>
<td>p-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;Br</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>12b</td>
<td>Me</td>
<td>80</td>
<td>87</td>
</tr>
<tr>
<td>5</td>
<td>12b</td>
<td>H</td>
<td>74</td>
<td>37&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>6</td>
<td>12b</td>
<td>p-C&lt;sub&gt;6&lt;/sub&gt;H&lt;sub&gt;4&lt;/sub&gt;Br</td>
<td>97</td>
<td>58</td>
</tr>
</tbody>
</table>

<sup>a</sup> determined by HPLC analysis
<sup>b</sup> HPLC performed on an acetal derivative

Table 1 - TKP Michael additions

Whilst interesting in themselves, TKPs should also be able to be manipulated into useful chiral building blocks such as DKPs, piperazines and unnatural amino acids. Preliminary work has
shown that the C-3 carbonyl can be selectively reduced due to its enhanced electrophilicity. This could then be further reduced to DKP 18 in good yield (Scheme 6).\textsuperscript{17}

Alternatively, when acrolein is used as the Michael acceptor, the resultant alcohol 20 after reduction with NaBH₄ can undergo an N-acyliminium cyclisation under Lewis acidic conditions to give bicyclic product 21 (Scheme 6).\textsuperscript{17}

### 1.4. Synthesis of TKPs

The synthesis of DKPs is relatively straightforward as they are the cyclic dimers of amino acids. TKPs have presented more of a challenge, although several techniques have been developed especially as part of the synthesis of TKP containing natural products.

The most common method has been to couple amino amides and an oxalyl equivalent. Oxalyl chloride is usually too reactive for this reaction but diethyl oxalate has been used. In 1953, Safir and co-workers reported heating aminoamides such as 22 (Scheme 7) with diethyl oxalate under basic conditions. This generated the sodium salt of the TKP which was quenched with an aqueous work up to give the desired TKP 23.\textsuperscript{18}
Overman and Shin used a stepwise process in their 2007 synthesis of (+)-gliocladin C 26 (Scheme 8). Pyrolidine 24 reacted with ethyl chlorooxoacetate to give oxalyl half-ester half-amide 25. Cyclisations with amine bases or sodium hydride were unsuccessful leading to decomposition of the starting material; however heating with HMDS at 140 °C in a sealed tube did afford the product in good yield. Elimination of the methoxy group occurred simultaneously to give the natural product 26.\(^{19}\)

In 2003, Makino and co-workers reported making a large number of TKPs using a solid support. A range of amino acids were coupled to solid supported anilines. The oxalyl equivalent they used was oxalyl diimidazole and the cyclisation was observed to occur at 25 °C when left overnight (Scheme 9). The solid support was then cleaved with TFA. For the phenylaniline derivative (R=Bn) the TKP was synthesised in high yield (86%) and high purity (89%).\(^{20}\) Oxalyl diimidazole was additionally used by Overman and co-workers in an improved synthesis of (+)-gliocladin C 26.\(^{21}\)
The relative high cost of oxalyl diimidazole led to the development of an alternative coupling partner within the Simpkins group. Oxalyl benzotriazole was easily synthesised from oxalyl chloride and was successfully used as an alternative (Scheme 10). However, microwave conditions were required due to its reduced reactivity.\(^{17}\)

A different route to the TKP motif is to oxidise the corresponding DKP. This can be achieved through treating methylene DKPs with singlet oxygen as reported by Machin and Sammes in 1976.\(^{22}\) Methylene Blue was used as a sensitisier and the reaction was thought to proceed through dioxetane intermediate 28 (Scheme 11).
If no methylene unit is in place then it is possible to oxygenate the lithium enolate of the DKP as reported by Davies and co-workers in 2002. They suggest that the mechanism proceeds through the peroxide anion 30 (Scheme 12) with the addition of acetic anhydride giving the three observed products. The diastereotopic alcohols 32 and 33 could be oxidised in high yield to the TKP with the use of IBX.

In summary, there are a number of ways of accessing the TKP motif with yields and strategies depending on the exact nature of the precursor. The predominant method used within the Simpkins group to date has been coupling with oxalyl benzotriazole but there is room for improvement as the yields have been low to moderate.

1.5. Project aims

Having seen the potential for asymmetric organocatalytic Michael additions on amide-like systems (Scheme 5 and Table 1), this project began with asking whether other similar systems, including acyclic ones could show similar reactivity (Scheme 13).
Given the comparatively low pK\textsubscript{a}s of quinine 2 and quinidine 3 at 7.73 and 7.95 respectively, the challenge of making an organic substrate acidic enough to be deprotonated by them was rather daunting.\textsuperscript{24} Calculations on the pK\textsubscript{a} of TKP \textbf{12b} are ongoing but we predict that they will be somewhat similar to that of a 1,3-dicarbonyl.

Clearly this project required the use of some electronic effects to help reduce the pK\textsubscript{a} of an amide from its normal value of about 35. Easton and co-workers have done computational and experimental work on the effect of electron-withdrawing groups on the proximal and distal protons of DKPs \textbf{34}.\textsuperscript{25,26}

Table 2 shows the calculated values and it is clear that there is a significant effect on the acidity of the distal proton when electron-withdrawing groups are used. Converting an amide to an imide therefore gives a pK\textsubscript{a} drop of over six ‘units’ and is one promising tool for getting in the right region for cinchona catalysis.

Bordwell devoted a large part of his career at Northwestern University to measuring the acidities of carbon acids. They used a range of indicators in DMSO to determine the pK\textsubscript{a} values of around 2000 acids.\textsuperscript{27} This wealth of data proved very useful as we began looking for groups which could lower the pK\textsubscript{a} of our substrates. The most relevant values are summarised in Table 3.
A phenyl group at the α position enhances the acidity by about seven or eight pKₐ ‘units’ relative to no substituent at the α position. An amine group gives only a modest reduction in pKₐ, whereas, an ammonium ion gives a reduction of about ten ‘units’. Pyridinium salts give an even greater drop of about 14 ‘units’.

Richard and co-workers have developed an alternative method for determining the pKₐ of carbon acids which uses ¹H NMR spectroscopy. Equilibrium and rate constants for deuteration in D₂O allowed for determination of the pKₐ values. Whilst they managed to determine accurate values, both this technique and Bordwell’s indicator method were initially considered beyond the scope of this project. However, it was noted that for a series of compounds, the chemical shift could be correlated with the acidity. For instance if a functional group was modified and the acidic proton chemical shift increases, then this strongly suggests that the compound has become more acidic. Whilst not quantitative or accurate this simple observation would allow for estimation of acidity through comparing chemical shift values.

Further to the functional groups already discussed, work had previously been done in the Simpkins group on forming amino-borane complexes. Initially, the focus of this work was using the borane group to regioselectively metalse the benzylamine-type systems with lithium bases. In the absence of borane there is exclusive ortho metalation of the aromatic ring; however, activation with a borane group activates with α position to give regioselective α-metalation (Scheme 14).
This work has been further extended to the diastereoselective and enantioselective alkylation of isoindoline-borane complexes.\textsuperscript{35,36} It was reasoned that the borane group enhances the C-H acidity by withdrawing electron density away from the nitrogen. To the best of our knowledge, no work to date has been done to quantify the effect of boranes on amine pK\textsubscript{a} values. There was potential for using amino boranes as a temporary group to lower the pK\textsubscript{a} of our substrates.
2. RESULTS AND DISCUSSION

2.1. α-Amino amide substrates

This investigation began by considering the combined effects of converting an amide to an imide as well as having an ammonium group in the α-position. It was hoped that these combined effects would give us substrates acidic enough to undergo cinchona-catalysed Michael additions. Chloroacetamide 38 (Scheme 15) was chosen as the starting material with due caution taken due to its toxic and sensitising properties. It was hoped that the chloride could be substituted by a nitrogen-containing species which could then be transformed to the quaternary ammonium salt.

Treating chloroacetamide with sodium azide in water cleanly gave the azido amide 39 (Scheme 15). Staudinger reduction to amine 40 proceeded cleanly by tlc but it proved very difficult to separate the product from triphenylphosphine oxide. Hydrogenation with a palladium on carbon catalyst also proved ineffective for yielding amino amide 40 possibly due to the very high polarity of the product. In order to try to decrease the polarity, Boc protection was first performed on the azido amide. Substrate 41 was then tested in a Michael addition reaction with tetramethylguanidine (TMG) used as the base. Unfortunately the crude NMR spectrum showed remaining starting material, decomposition products, and none of desired product. Reduction of Boc-protected azido amide 41 was not attempted due to success in parallel routes to amino amides.
Attempts to form the ammonium directly from chloroacetamide 38 involved heating under reflux with tribenzylamine and catalytic DMAP in ethanol. It was hoped that using benzyl groups would also allow for their subsequent removal to give a neutral species following the Michael addition. However, no reaction was observed so chloroacetamide 35 was instead treated with a secondary amine (Scheme 16) with an *in situ* Finkelstein reaction occurring. Amino amide 43 was then Boc protected to give imide 44. Gentle conditions using DMAP in THF surprisingly gave a mixture of bis-Boc amide 45 and the starting material regardless of how much Boc₂O was used in the reaction. Bis-Boc amide 45 was used in a Michael reaction with TMG catalyst and methyl vinyl ketone (MVK) but no product was formed. Attempts to remove one of the Boc groups by treating with mild acid and base were also unsuccessful and returned only the starting material.

The use of sodium hydride did allow for singly Boc-protected amide 44 to be isolated but only in a modest 52% yield (Scheme 16). Further reflection on the mechanism of reaction with the cinchona catalysts revealed that generating an ammonium might not be very favourable. It was thought that the chiral environment is sustained after the deprotonation of the substrate due to the ion pair that is generated between the catalyst and substrate. A cationic substrate would become an ylide after deprotonation and thus the ‘ion pair’ is unlikely to be tight, if they bind together at all. Attention therefore turned to the use of boranes to activate the
amine (Section 1.5) and 46 was formed in good yield with the CH₂ group having a chemical shift of 3.9 ppm (cf. 4.2 ppm for TKP 12b). To our surprise, the subsequent Michael addition gave Michael adduct 47 and none of the desired product 48.

To prevent this Michael addition happening, amino borane 46 was treated with sodium hydride, followed by methyl iodide. However, no methylation of the imide was observed, with only starting material recovered from the reaction (Scheme 17). Similar attempts to methylate precursor amino amide 44 were also unsuccessful. It looked like this route could progress no further without remaking the substrate with a secondary amide in place from an early stage.

2.2. α-Phenyl amide substrates

Attention turned next to the use of an aromatic group to lower the pKₐ alongside an imide as before. Phenylacetic acid 51 was converted to secondary amide 52 in good yield via the acyl chloride (Scheme 18). This was then converted to the trifluoroacetyl imide 53. The
trifluoroacetyl group is known to be highly electron-withdrawing (see Table 2) so it was hoped it would help bring the acidity of the CH$_2$ group into a workable range; the chemical shift for the α-CH$_2$ is 4.1 ppm which seemed promising when compared to TKP 12b (4.2 ppm).

However, when subjected to Michael addition conditions, the already slightly unstable imide decomposed with some benzylamide 52 visible in the crude NMR spectrum. Use of the Boc group gave a much more stable imide 55 and this was tested with a variety of bases and Michael acceptors as summarised in Table 4.

<table>
<thead>
<tr>
<th>entry</th>
<th>Michael acceptor (equiv)</th>
<th>catalyst (mol%)</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MVK (2.5)</td>
<td>quinidine 3 (10)</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>MVK (2.5)</td>
<td>TMG (20)</td>
<td>41%</td>
</tr>
<tr>
<td>3</td>
<td>MVK (10)</td>
<td>TMG (30)</td>
<td>78%</td>
</tr>
<tr>
<td>4</td>
<td>acrolein (2.5)</td>
<td>TMG (20)</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>methyl acrylate (2.5)</td>
<td>TMG (20)</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>nitro styrene (2.5)</td>
<td>TMG (20)</td>
<td>NR</td>
</tr>
<tr>
<td>7</td>
<td>chalcone (2)</td>
<td>TMG (30)</td>
<td>NR</td>
</tr>
<tr>
<td>8</td>
<td>MVK (10)</td>
<td>57 (10)</td>
<td>NR</td>
</tr>
<tr>
<td>9</td>
<td>nitro styrene (1.2)</td>
<td>57 (10)</td>
<td>NR</td>
</tr>
<tr>
<td>10</td>
<td>MVK (2.5)</td>
<td>58 (10)</td>
<td>NR</td>
</tr>
</tbody>
</table>
Table 4 - results from Michael additions on an α-phenyl amide substrate

The table shows that only TMG seemed to be basic enough to deprotonate substrate 55. Guanidines have a pKₐ of about 14 which is significantly different from the pKₐ of the cinchona alkaloids (pKₐ ~ 8). Increasing the amount of methyl vinyl ketone and the catalyst loading to 30 mol% gave a good yield of 78%. However, using this catalyst, the only Michael acceptor which reacted was MVK; even acrolein, with its comparable reactivity, gave no reaction. The quinine thiourea catalyst 57 and benzyl protected catalyst 58 was tested to see whether the bifunctional mode of action would encourage the reaction, but no product was observed. Attention was next turned to whether chiral guanidines based on the cinchona alkaloids could be made.

2.3. Synthesis of chiral guanidines

There are a number of ways of making guanidines and a common technique is to generate them from the corresponding thioureas.²⁷ Given the previous work done in the group using thioureas, this was chosen as the preferred route. The sulfur of the thiourea must be activated prior to its reaction with an amine and searching of the literature revealed a number of ways to do this. The first method attempted involved the use of copper(I) chloride to mediate the reaction. This method had the advantage of not requiring any highly toxic mercury salts. Terada and co-workers reported the reaction in 2007 and achieved some very high yields on thioureas with a binaphthyl backbone. Unfortunately, only decomposition was observed with thiourea 57 (Scheme 19).³⁸
The origin of the basicity of guanidines is the high electron density on the nitrogen atoms, due to mesomeric donation from the other nitrogen atoms, this means that the positive charge in the conjugate acid is also highly delocalised and therefore very stable (Scheme 20). It was therefore reasoned that if the electron density was increased further, then the basicity would be even more enhanced. This was especially appealing for us, because substrate 55 (Table 4) had proved to be at the threshold of reactivity with the simple TMG catalyst. 3,5-Bis(trifluoromethyl)phenyl thiourea 57 was very electron-deficient but a p-methoxyphenyl (PMP) group would be expected to give a much more electron rich system.

A model system was therefore conducted to test the formation of a PMP substituted guanidine. Benzylamine was converted to thiourea 60 (Scheme 21) in excellent yield using the appropriate isothiocyanate. Successful formation of guanidine 61 was achieved, albeit in low yield, with methyl iodide activation of the thiourea.

Returning to the cinchona alkaloids, epi-aminoquinine 62 (Scheme 22) was successfully synthesised using a Mitsunobu reaction and Staudinger reduction. This amine was then transformed into the thiourea using the same method as on the model system in good yield.
A number of methods were attempted to transform thiourea 63 into a guanidine. The methyl iodide activation method gave only a trace amount of product as well as some of the eliminated product, \( p \)-anisidine. Another procedure, using copper sulfate-silica gel reported by Ramadas and Srinivasan was attempted.\(^{39}\) They managed to form guanidine 65 in good to excellent yields but unfortunately only decomposition of the starting material was observed with thiourea 63 (Scheme 23).

Use of the copper(I) chloride method as attempted on 57 was similarly unsuccessful with the PMP substituted thiourea 63. The apparent sensitivity of these substrates was making the synthesis of the guanidine far from straightforward. Despite the toxicity, it was decided to investigate the use of mercury(II) oxide in mediating the reaction. This is a very common technique for the transformation and a one-step method was tried.\(^{40}\) Some starting material 63 was isolated from the reaction mixture, but no product 67 could be isolated from the remaining material (Scheme 24).
Parallel to this work we saw potential for using a completely different substrate for the synthesis of chiral guanidines. Previous work in the group had involved the use of a range of chiral lithium amide bases. Diamine 70 (Scheme 26) was used in the kinetic resolution of advanced bicyclic systems in the synthesis of polyprenylated natural product (+)-clusianone.\textsuperscript{41} It was hoped that this could be converted to a guanidine using a carbodiimide and this was successfully achieved on a very simple model system (Scheme 25).

The same conditions were used on chiral diamine 70 (Scheme 26) and initially it was thought that reaction had occurred, however the diamine and DCC had just co-eluted from the column in a precisely 1:1 ratio. Despite harsh conditions and even with the addition of an iron(II) acetate Lewis acid, as reported by Pottabathula and Royo in their synthesis of guanidines, no reaction occurred between diamine 70 and the carbodiimide.\textsuperscript{42}

Alternative routes to the guanidine, not including the thiourea intermediate, were also explored. Mitsunobu reactions with guanidine equivalents have been reported, meaning that there was potential for catalysts to be made directly from the cinchona alkaloids. Kozikowski
and co-workers reported in 1994 that bis(Boc)-protected guanidine 72 can undergo a high yielding Mitsunobu reaction with alcohols.  

![Scheme 27 - Kozikowski’s method for guanidine formation](attachment:image)

Even more promising is the report by Rossiter et al that N,N'-bis-tert-butoxycarbonylpyrazole-1-carboxamidine 73 can be used in a Mitsunobu reaction with the pyrazole group subsequently substituted by aryl amines (Scheme 28). This could allow for the generation of the PMP substituted guanidine which was our original target.

![Scheme 28 - Rositer’s synthesis of aryl guanidines](attachment:image)

This technique first required the synthesis of 75 from 1H-pyrazole-1-carboxamidine hydrochloride 74. This was carried out although the product was difficult to isolate cleanly and the subsequent Mitsunobu reaction with quinine gave a complex mixture with no product 76 isolated.

![Scheme 29 - attempted synthesis of chiral guanidine](attachment:image)

To overcome this challenge it was decided to do a direct substitution of amino-quinine 62 with 1H-pyrazole-1-carboxamidine hydrochloride, which was completed in excellent yield to finally
yield a chiral guanidine (Scheme 30). This guanidine was then used as a catalyst for a Michael addition on α-phenyl amide 55. Unfortunately no reaction occurred and the starting material was recovered after 24 h. This result indicates that the additional electron donating group of the PMP group may in fact be necessary to successfully catalyse this reaction.

Scheme 30 - synthesis and use of a chiral guanidine catalyst

In summary, extensive work has been done to access chiral guanidines. A number of reagents were tried in an attempt to convert a thiourea to a guanidine. The methyl iodide activation route was successful on a model system but gave no product on the actual system. The use of guanidine equivalents was not initially productive until one simple guanidine of quinine was synthesised, however it was not effective as a catalyst. Additional work was carried out on whether chiral diamine 70 (Scheme 26) could be transformed into a guanidine as had been achieved on a model system, but the diamine proved resistant to guanidine formation.

2.4. Hydantoin substrates

Hydantoins could be considered the five-membered analogue of the TKPs already in use in the research group. They contain one amide nitrogen and one imide nitrogen. There are no reported pKₐ values for acidity of the C-H bond (the imide N-H bond has a pKₐ value of 15.0 in unsubstituted hydantoin 79⁴⁵). Whilst we would not expect it to be as acidic a substrate as the
TKP, as there is no possibility for any aromaticity in the conjugate base, it looked like it had potential for use in organocatalytic Michael additions.

Hydantoin 79 (Scheme 31) was first protected as bis-benzyl hydantoin 80 and tested in a Michael addition reaction with MVK. No reaction was observed with either quinidine 3 or the more basic TMG suggesting that the substrate was not acidic enough to react with the catalysts. Using an electron-withdrawing protecting group, such as Boc, was the next obvious step to see if hydantoins could still be utilised in Michael additions. The chemical shift of the CH$_2$ group increased from 3.65 ppm to 4.24 ppm on switching from the benzyl groups to Boc groups, suggesting a noteworthy increase in acidity. This new hydantoin 82 was then tested with a number of bases and Michael acceptors (Table 5).

<table>
<thead>
<tr>
<th>entry</th>
<th>Michael acceptor</th>
<th>catalyst</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MVK</td>
<td>quinidine</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>MVK</td>
<td>TMG</td>
<td>NR</td>
</tr>
<tr>
<td>3</td>
<td>acrolein</td>
<td>TMG</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>nitro styrene</td>
<td>TMG</td>
<td>NR</td>
</tr>
<tr>
<td>5</td>
<td>MVK</td>
<td>57</td>
<td>NR</td>
</tr>
<tr>
<td>6</td>
<td>MVK</td>
<td>MgBr$_2$/DIEPA</td>
<td>NR</td>
</tr>
</tbody>
</table>

Table 5 - results from synthesis and tests of bis-Boc hydantoin

Similar to the benzyl system, no reaction was observed with either quinidine or TMG. Other Michael acceptors were tried but these gave the same result. Thiourea catalyst 57 did not give any product either. Coltart and co-workers reported in 2008 that magnesium bromide and iPr$_2$NEt could be used to promote soft-enolate formation. They formed the soft enolates of
ketones and then reacted them with acylating agents. Whilst no examples of Michael additions were reported, it was hoped that the same soft enolisation technique could be used on bis-Boc hydantoin 82. However when this reaction was tried on hydantoin 82 only some decomposition and unreacted starting material were observed.

In order to enhance the acidity of the substrate it was hypothesised that it might be possible to make use of conjugate base aromaticity in the hydantoin. If the lactim ether 85 (Scheme 32) could be formed then the conjugate base 86 would resemble imidazole, presumably with some of the associated aromatic stability.

A large quantity of the mono protected hydantoin 87 had been recovered from the synthesis of bis-benzyl hydantoin 80 and this was successfully transformed into lactim ether 88 (Scheme 33). However when subjected to the Michael addition conditions using catalytic triethylamine, no reaction was observed and the starting material was recovered.

Having had little success with these modified hydantoins (80, 82 and 88), it was next investigated whether the hydantoins would undergo an aldol condensation to give unsaturated compound 91 (Scheme 34). This, it was thought, would then give a more acidic compound as the negative charge would be more delocalised in the conjugate base 92. A further advantage was that a Michael addition would generate a quaternary stereogenic centre thus avoiding any potential for racemisation under the reaction conditions.
A range of conditions were attempted for the aldol condensation with both of the hydantoins previously synthesised. Successful aldol reaction of TKP 12b had proved elusive in the group for some time, likely due to the reversibility of the process and competitive retro-aldol reaction for such an acidic compound. The results are summarised in Table 6.

<table>
<thead>
<tr>
<th>entry</th>
<th>hydantoin</th>
<th>conditions</th>
<th>aldehyde</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>82</td>
<td>rBuOK, rBuOH</td>
<td>acetaldehyde</td>
<td>complex mixture</td>
</tr>
<tr>
<td>2</td>
<td>82</td>
<td>AcONa, Ac$_2$O</td>
<td>benzaldehyde</td>
<td>complex mixture</td>
</tr>
<tr>
<td>3</td>
<td>80</td>
<td>AcONa, Ac$_2$O</td>
<td>benzaldehyde</td>
<td>SM</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>LHMDS, THF</td>
<td>acetaldehyde</td>
<td>SM and trace of product</td>
</tr>
<tr>
<td>5</td>
<td>80</td>
<td>LDA</td>
<td>acetaldehyde</td>
<td>SM and trace of product</td>
</tr>
<tr>
<td>6</td>
<td>80</td>
<td>LHMDS, THF</td>
<td>isobutyraldehyde</td>
<td>SM and trace of product</td>
</tr>
</tbody>
</table>

Table 6 - results from attempted synthesis of unsaturated hydantoins

Milder alkoxide or acetate conditions gave a complex mixture with bis-Boc hydantoin 81 and no reaction with bis-benzyl hydantoin 80. Stronger bases were used with the benzyl substrate and the best results gave only trace amounts of the product. It was reported in 2013 by Britton and co-workers that aldol reactions of Boc-protected hydantoins can undergo a 1,3 migration of a Boc protecting group from the nitrogen to the oxygen; however there was no evidence of this having occurred in the above reactions.47

With these difficulties in accessing a successful substrate for the Michael additions of hydantoins this was proving a challenging system to work on, attention therefore turned to more promising substrates.
2.5. *Thalidomide substrates*

Thalidomide 94 (Figure 2) came to our attention because it is well documented that this drug racemises under physiological conditions.\(^48\) It was hoped that the acidic nature of the compound would allow for its use in cinchona organocatalysis.

![Figure 2 - thalidomide](image_url)

Work has been published on methylating\(^49\) and fluorinating\(^50\) at the 3-position of thalidomide which would prevent any racemisation. Further work has been reported on making configurationally stable thalidomides with methyl, phenyl\(^48\) or trifluoromethyl\(^51\) substituents in the 4-position. The phthalimide group is much more stable trans to these substituents, so a configurationally stable thalidomide derivative is formed.

To the best of our knowledge, organocatalytic Michael additions had not been done before on 94 and the reported p\(K_a\) of 12.5 means that it should be an amenable substrate for such reactions.\(^52\) Michael addition products could then be treated with hydrazine to remove the phthalimide group and yield chiral imide 96 (Scheme 35).

![Scheme 35 - proposed Michael addition with thalidomide](image_url)

The synthesis of thalidomide 94 was relatively straightforward as L-glutamine could be condensed with phthalic anhydride. The addition of thionyl chloride generates the acyl chloride which reacts with the amide to close the glutarimide ring (Scheme 36).
To our surprise no reaction was observed under the Michael addition conditions with triethylamine. In order to further enhance the acidity of the substrate and hopefully provoke a reaction, the glutarimide was protected with an electron withdrawing Boc group to give 97 (Scheme 36). However, no reaction was observed with methyl vinyl ketone in the presence of either triethylamine or TMG. The origin of this low reactivity was assumed to be the steric congestion at the reactive carbon. The glutarimide ring will prefer to be orientated out of the plane of the phthalimide and therefore will block approach of the Michael acceptor from either face.

Scheme 36 - synthesis and test of thalidomide substrates

2.6. Phenyl-TKP substrates

Following the limited success of the acyclic, hydantoin and thalidomide type systems for organocatalytic Michael additions, our attention returned to the TKP system which had previously worked so effectively in the group (Section 1.3). We had already explored the effect a phenyl group could have in lowering the pKₐ of substrates so we began to explore the possibility of having an aromatic group on the acidic carbon of the TKP.
The first generation synthesis of the desired TKP used phenylglycine 99 (Scheme 37) as the starting material. It was used in racemic form and is very cheap despite not being a naturally occurring amino acid. The carboxylic acid needed to be converted to an amide; to prevent self-condensation in this process, the amine group was first protected as the Boc derivative 100 in good yield. The carboxylic acid was then activated with ethyl chloroformate and benzylamine was added to generate the amide 101 in excellent yield. Deprotection of the amine with TFA was followed by reductive amination with benzaldehyde which gave the required amino amide 103. The group method for cyclisation was used and the amino amide was heated with oxalyl benzotriazole in the microwave at 150 °C for 1 h to give 104 in moderate yield.

Scheme 37 - synthesis of phenyl-TKP

Given the number of steps involved in making phenyl-TKP 104 the prospect of a direct coupling of an aryl group to the simple TKP 12b seemed appealing. Baran and co-workers have reported the oxidative coupling of indole and pyrrole with ketones, esters and amides. Scheme 38 shows a further example with an oxazolidinone substrate 105.

Scheme 38 - Baran's oxidative cross-coupling with indole

Application of this methodology to TKP 12b was unsuccessful and a complex mixture was observed after the reaction (Scheme 39).
Kwong and co-workers have used copper catalysis to couple aryl halides to simple malonates and this result was successfully replicated in our hands. The optimal ligand was reported to be 2-picolinic acid and the reaction proceeded at room temperature in high yield (Scheme 40).\(^\text{54}\)

These conditions were attempted on our TKP substrate 12\textit{b} but unfortunately only decomposition of the starting material was observed (Scheme 41). This was surprising because of the very mild conditions involved.

A further idea for the phenylation of TKP 12\textit{b} was to use a hypervalent iodine species. Aggarwal and Olofsson reported in 2005 that they could perform an \(\alpha\)-arylation of a ketone using diphenyliodonium triflate (DPIT) and a lithium base. They further report that this could be done asymmetrically when chiral bases were employed. For their simple cyclohexanone substrate yields of 83% were achieved with 2 equivalents of base required to allow for the second deprotonation after the arylation had occurred (Scheme 42).\(^\text{55}\)
The DPIT salt 108 was easily synthesised using a procedure published by Olofsson and co-workers which uses mCPBA as the oxidant (Scheme 43). This procedure allows for the synthesis of a wide range of diaryl iodonium salts so long as the aryl iodide is accessible.\textsuperscript{56}

With iodonium salt 108 in hand, the reported conditions were attempted on TKP 12b and were initially unsuccessful with decomposition occurring. Switching to an amine base at warmer temperatures did yield some of the desired product. Extensive optimisation was carried out to increase this yield as summarised in Table 7.

<table>
<thead>
<tr>
<th>entry</th>
<th>base (equiv)</th>
<th>DPIT (equiv)</th>
<th>solvent</th>
<th>time (h)</th>
<th>temperature</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LHMDS (2)</td>
<td>1.0</td>
<td>THF</td>
<td>3</td>
<td>−78 °C to −45 °C</td>
<td>decomposition</td>
</tr>
<tr>
<td>2</td>
<td>K$_3$PO$_4$ (2.5)</td>
<td>1.0</td>
<td>THF</td>
<td>18</td>
<td>rt</td>
<td>decomposition</td>
</tr>
<tr>
<td>3</td>
<td>NEt$_3$ (1.1)</td>
<td>1.3</td>
<td>CH$_2$Cl$_2$</td>
<td>16</td>
<td>0 °C to rt</td>
<td>26</td>
</tr>
<tr>
<td>4</td>
<td>NEt$_3$ (2.5)</td>
<td>1.2</td>
<td>CH$_2$Cl$_2$</td>
<td>18</td>
<td>0 °C to rt</td>
<td>17</td>
</tr>
<tr>
<td>5</td>
<td>NEt$_3$ (1.1)</td>
<td>1.1</td>
<td>CH$_2$Cl$_2$</td>
<td>6</td>
<td>0 °C to rt</td>
<td>33</td>
</tr>
<tr>
<td>6</td>
<td>NEt$_3$ (1.1)</td>
<td>1.1</td>
<td>CH$_2$Cl$_2$</td>
<td>72</td>
<td>0 °C to rt</td>
<td>41</td>
</tr>
<tr>
<td>7</td>
<td>NEt$_3$ (1.05)</td>
<td>1.05</td>
<td>CH$_2$Cl$_2$</td>
<td>19</td>
<td>0 °C to rt</td>
<td>48</td>
</tr>
</tbody>
</table>

Table 7 - results from DPIT phenylations

Increasing the amount of base and electrophile appeared to be detrimental to the yield and it was unclear whether there was any loss of product over long reaction times. Whilst no exceptional yields were achieved, this is a much more efficient route than the previous
synthesis outlined above (Scheme 37). Furthermore starting material could be recovered from this reaction to be used in successive arylations (for example, in entry 6, 23% of the starting material was recovered).

With promising substrate 104 now available, work began on the organocatalytic Michael additions. MVK was chosen as the test acceptor and a range of catalysts were used. Table 8 shows the results achieved.

![Catalysis Reaction Scheme](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>catalyst</th>
<th>time (h)</th>
<th>yield (%)</th>
<th>er&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NEt&lt;sub&gt;3&lt;/sub&gt;</td>
<td>24</td>
<td>50</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>quinine 2</td>
<td>19</td>
<td>42</td>
<td>72:38</td>
</tr>
<tr>
<td>3</td>
<td>quinidine 3</td>
<td>27</td>
<td>77</td>
<td>30:70</td>
</tr>
<tr>
<td>4</td>
<td>63</td>
<td>27</td>
<td>63</td>
<td>50:50</td>
</tr>
<tr>
<td>5</td>
<td>58</td>
<td>6</td>
<td>75</td>
<td>9:91</td>
</tr>
</tbody>
</table>

<sup>a</sup> determined by HPLC analysis

Table 8 - results from the Michael additions of phenyl-TKP

Pleasingly the Michael additions proceeded in good to moderate yield. The reaction was relatively slow with some starting material remaining after 24 h making chromatography difficult and contributing further to some of the lower yields. The natural cinchona catalysts (2 and 3) gave enantiomeric products, as would be predicted, with only a relatively low er. Interestingly the thiourea catalyst 63 (Scheme 22) gave a racemic mixture. The most successful catalyst 58 (Table 4) had the C-9 secondary alcohol protected with a benzyl group and a free quinoline hydroxyl. The reaction was much faster with this catalyst and respectable yields and selectivities were observed.

Interestingly, whilst catalyst 58 was a derivative of quinine, it gave the opposite selectivity to natural quinine 2 suggesting that the free hydroxyl might be fundamental to the catalyst reactivity. This is supported by the stereochemical model suggested by Deng and co-workers.
They suggest that the catalyst adopts a *gauche*-open conformation (Scheme 44) that allows for the simultaneous activation of the acceptor and substrate.\textsuperscript{57,58} As can be seen from the model, the quinuclidine acts as base to deprotonate the TKP with a hydrogen bond developing between them. The quinoline hydroxyl activates the Michael acceptor through a hydrogen bond and directs the acceptor to the lower face of the planar TKP. This model would therefore predict an absolute *R* stereochemistry for the product although this hypothesis needs to be confirmed by X-ray crystallography.

These exciting preliminary results have the potential for future optimisation of the reaction conditions, including the catalyst design, as well as opportunities to broaden the scope of the reaction.

\textbf{2.7. PMB-protected phenyl-TKP substrates}

In order to develop these asymmetric reactions, further transformations will need to be carried out on the TKP products. This could be reduction to the DKP which is a ‘privileged structure’ among natural products and in medicinal chemistry. Breaking apart the ring to unmask an α-amino acid would also be highly desirable.

Protecting groups are required on the TKP for the Michael additions to prevent reaction on the nitrogen atoms. However these groups quickly become redundant and may hinder attempts at further transformations. Having labile groups therefore became appealing to us.
Benzyl groups can normally be removed under hydrogenolysis conditions, however, the phenyl group on TKP 104 is also ‘benzylic’ with respect to the amide nitrogen. Para-methoxybenzyl (PMB) groups were chosen as an alternative protecting group, as it was hoped that they could be removed selectively due to their propensity to be oxidised. One example of this is in Mukaiyama and co-workers’ total synthesis of Taxol® where they report that a PMB ether could be cleaved in the presence of a benzyl ether with DDQ.\(^{59}\)

The synthesis of these PMB protected TKPs was conducted using the more lengthy technique shown previously for the benzyl TKP in Scheme 35. This was because investigations into the hypervalent iodine arylations reported above were still ongoing. Following Boc protection, the amino acid was converted to amide 110, this time using isobutyl chloroformate to form the mixed anhydride intermediate (Scheme 45). TFA was then used to cleave the Boc group in high yield and reductive amination with anisaldehyde gave amino amide 112. The cyclisation with oxalyl benzotriazole proceeded to give PMB protected TKP 113.

TKP 113 was then used in a number of Michael additions with ketones and an aldehyde. The most successful catalyst for the benzyl-protected TKP substrate 104 was the OBn modified quinine 58 and this was used again. The results of the asymmetric reactions are summarised in Table 9.
The four ketones tested gave excellent selectivities with ethyl vinyl ketone giving the highest; acrolein gave a much reduced selectivity. Acrolein needed to be converted to the acetal for HPLC analysis but it is not clear why the yield and selectivity were eroded with this acceptor. As would be predicted the more reactive phenyl vinyl ketone proceeded to completion faster than cyclohexyl vinyl ketone.

These results represent the successfully development of asymmetric organocatalytic Michael additions to phenyl substituted TKPs. High selectivities and yields have been achieved for a range of unsaturated ketones. Initial work on further transformations focussed on trying to remove the PMB group from the TKP.

Numerous methods of PMB group removal have been reported and a number were attempted with the results summarised in Table 10. Probably the most common method in the literature is to use ceric ammonium nitrate (CAN). A procedure published by Corey and co-workers was attempted on TKP 113, but no product was isolated from the reaction with starting material recovered and a small amount of anisaldehyde. Martin and co-workers report the use of neat TFA to remove a PMB group from an amide; however no reaction was observed for our system using this technique. Jung and Lyster published a procedure using trimethylsilyl...
iodide but again this was ineffective on our TKP and the starting material was fully recovered.\textsuperscript{62} Returning to the oxidative methods, a technique using potassium peroxydisulfate was attempted. Podlech and Linder had reported the removal of a PMB group from a lactam in moderate yield using these conditions but only decomposition could be observed on our TKP system along with some anisaldehyde by-product.\textsuperscript{63} The final technique tried was the use of DDQ as reported by Davies and co-workers, however no reaction was observed with this reagent.\textsuperscript{64}

\[
\begin{array}{cccccc}
\text{entry} & \text{reagent} & \text{solvent} & \text{temperature (°C)} & \text{time (h)} & \text{yield} \\
1 & \text{CAN} & \text{MeCN/H}_2\text{O} & 0 \text{ to rt} & 24 & \text{SM and some PMPCHO} \\
2 & \text{TFA} & - & \text{rt} & 24 & 100\% \text{ recovery of SM} \\
3 & \text{TMSI} & \text{CDCl}_3 & \text{rt-}50 & 24 & 100\% \text{ recovery of SM} \\
4 & \text{K}_2\text{S}_2\text{O}_8 & \text{MeCN/H}_2\text{O} & 75 & 4 & \text{decomposition} \\
5 & \text{K}_2\text{S}_2\text{O}_8 & \text{MeCN/H}_2\text{O} & 75 & 2 & \text{decomposition} \\
6 & \text{DDQ} & \text{DCM} & \text{rt} & 25 & 94\% \text{ recovery of SM} \\
\end{array}
\]

Table 10 - results from attempted PMB removal

These preliminary tests have not found a successful technique for the removal of the PMB group. Varying the temperature has yet to be explored and the use of other protecting groups such as allyl groups could also be investigated.

\textbf{2.8. Conclusions and future work}

Investigations have been carried out on organocatalytic Michael additions. Synthesising suitable substrates for this type of reaction proved more difficult than expected, and some substrates proved entirely unreactive including the hydantoins (Section 2.4) and thalidomide (Section 2.5). Other substrates reacted in unexpected ways (amino-borane 46, Section 2.1).

TMG showed limited success in catalysing the Michael additions of α-phenyl amide 55 (Section 2.2) but only with MVK as the Michael acceptor. This prompted further work on generating
highly-basic chiral organocatalysts. A number of methods were attempted to make a PMP-substituted guanidine attached to cinchona alkaloid. The use of thiourea intermediates was unsuccessful and the only chiral guanidine that could be generated was devoid of the extra electron-donating PMP group.

More success was achieved with the TKP substrates and the focus was on TKPs with a phenyl substituent at the reactive centre. A novel synthesis was devised which used a diphenyliodonium salt to arylate TKP 12b (Scheme 46). This significantly shortened the synthesis of these substrates and would allow for alternative aryl groups to be easily introduced. Further work will include optimisation of the yield for this reaction and also broadening the scope. It may also be possible to perform the arylation asymmetrically if a chiral base is used.

With the phenyl substituted TKP in hand, a range of Michael additions were tested and the optimal catalyst was found to be 58 with a free quinoline hydroxyl and the secondary alcohol protected. The reactions were relatively slow at rt and further work is needed to complete the optimisation of both yield and selectivity. Further work would also include crystallisation of Michael adduct 109 to allow for the absolute configuration to be determined by X-ray crystallography.
With a view to their subsequent removal, TKP 113 was synthesised with PMB protecting groups. This was found to perform better as a substrate and excellent yields and selectivities were achieved with unsaturated ketone acceptors (Scheme 48).

There is potential for the scope of this reaction to be increased to other classes of Michael acceptors. Work focussed on the removal of the PMB groups has so far not been fruitful, making this an area for future work or alternatively trying a different protecting group entirely.

Removal of the oxalyl component of the TKP would be appealing as it would reveal amino acid equivalents with unusual quaternary stereocenters (Scheme 49). These may find applications in making synthetic proteins with finely tuned properties.

In summary the project aims of investigating the scope of asymmetric organocatalytic Michael additions on amide-like systems have been achieved. The acyclic systems were largely not suitable substrates and the hydantoins and thalidomide were also not amenable to organocatalysis. However, excellent results have been reported for the synthesis of phenyl TKPs and the organocatalysed Michael additions with ketones with some quantitative yields and er values up to 94:6.
3. EXPERIMENTAL

3.1. General experimental techniques

Solvents and Reagents

All reaction solvents were acquired from the Innovative Technology solvent purification system except for acetone which was dried for a minimum of 3 h over 3 Å molecular sieves. Commercially available reagents were used as supplied except NEt$_3$ which was distilled from CaH$_2$ and stored over NaOH pellets and under nitrogen. Petrol refers to the fraction of petroleum ether boiling between 40 and 60 °C and was used interchangeably with hexane. All anhydrous reactions were carried out in oven-dried glassware and under an atmosphere of nitrogen.

Chromatographic Techniques

Thin layer chromatography was carried out using Merck aluminium-backed silica gel 60 F$_{254}$ plates. Spots were then visualised by quenching with ultraviolet light (λ$_{\text{max}}$ 254 nm) and then stained and heated with either anisaldehyde or potassium permanganate solutions as appropriate. Flash column chromatography was performed using Merck Geduran Silica (40-64 µm) unless otherwise stated and the solvent system is reported in brackets.

High Performance Liquid Chromatography

HPLC analysis was performed using a P580 Dionex pump and Chromeleon Client software. The columns used were the Chiralpak AD and OD columns (250 x 4.6 mm) from Daicel Chemical Industries Ltd. Detection was with a Waters 996 photodiode array detector using UV light (210 and 220 nm).
**Infrared Spectroscopy**

Infrared spectra were recorded using a Perkin Elmer Spectrum 100 FT-IR spectrometer. Absorption maxima ($v_{\text{max}}$) are reported in wavenumbers (cm$^{-1}$) and are described as strong (s), medium (m), weak (w) or broad (br).

**Nuclear Magnetic Resonance Spectroscopy**

Proton (1H) (300 and 400 MHz) and carbon (13C) (100 MHz) spectra were recorded on Bruker Avance III 300 MHz and Bruker Avance III 400 MHz spectrometers. Chemical shifts ($\delta_n$ or $\delta_c$) are reported in parts per million (ppm) downfield of tetramethylsilane using residual solvent as an internal reference. Assignments are made on the basis of chemical shifts, integrations and coupling constants, using COSY, HSQC, HMBC and NOE experiments where appropriate. Multiplicities are described as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), apparent (app) and broad (br) or combinations thereof. Coupling constants ($J$) are reported to the nearest 0.5 Hz.

**Melting Points**

Melting points were recorded on a Gallenkamp melting point apparatus used with a Hanna digital thermocouple thermometer and are uncorrected. Literature values for known compounds are from the overall reference given for the compound unless otherwise stated.

**Mass Spectrometry**

Novel compounds were analysed by means of the Synapt G2-S HDMS system (Waters, Manchester, UK). All experimental data was acquired with a resolution of 20,000 and samples were introduced into the mass spectrometer via the nanoAcquity system (Waters, Manchester, UK). Electrospray ionisation was performed with a capillary voltage of 3.2 kilovolts, and the sample cone was set at 40 volts. Mass to charge ratios (m/z) are reported in Daltons and the percentage abundance is given in brackets. High resolution mass spectrometry data is recorded to four decimal places.
Polarimetry

Asymmetric samples were analysed using PolAAr 2001 polarimeter (Optical Activity Ltd) and optical rotations are recorded in units of $10^{-1}$ deg cm$^2$ g$^{-1}$ with the concentration (g/100 mL), solvent and temperature.

3.2. Compounds

2-Azidoacetamide 39$^{65}$

![Chemical Structure]

2-Chloroacetamide 38 (124 mg, 1.33 mmol) was added to a solution of sodium azide (259 mg, 3.98 mmol) in H$_2$O (2.5 mL). The reaction mixture was then stirred at 60 °C for 24 h before being cooled to rt, diluted with H$_2$O (40 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried with Na$_2$SO$_4$ and concentrated under reduced pressure. Purification by recrystallisation from CH$_2$Cl$_2$ afforded azide 39 as white crystals (126 mg, 95%). Rf 0.56 (3:1 EtOAc/MeOH); m.p. 56-57 °C (lit. 55-56 °C); $^1$H NMR (300 MHz, CDCl$_3$): δ 3.96 (2H, s, CH$_2$), 6.44 (1H, br s, NHH'), 6.77 (1H, br s, NHH'); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 52.2 (CH$_2$), 169.9 (CO); IR (neat) $\nu_{\text{max}}$/cm$^{-1}$ 3373m, 3184m, 2108s (azide), 1624s, 1412s, 1314m, 1270m, 1095m, 957w.

tert-Butyl (2-azidoacetyl)carbamate 41

![Chemical Structure]

Synthesised according to the literature procedure.$^{66}$ A solution of azido amide 39 (224 mg, 2.24 mmol) in THF (6.5 mL) was added to a suspension of NaH (60% in mineral oil, 116 mg, 2.91 mmol) in THF (6.5 mL) at 0 °C. The reaction mixture was warmed to rt then cooled back to 0 °C and di-tert-butyl dicarbonate (1.0 M solution in THF, 3.13 mL, 3.13 mmol) was added. After 30 min the reaction mixture was warmed to rt and stirred for 24 h. It was then quenched
with saturated aqueous NH₄Cl (50 mL) and extracted with Et₂O (4 x 40 mL). The combined organic layers were washed with brine (100 mL), dried with Na₂SO₄ and concentrated under reduced pressure. Purification by flash column chromatography (6:1 petrol/Et₂O) afforded Boc amide 41 as a white solid (155 mg, 33%). Rf 0.58 (1:1 petrol/EtOAc); m.p. 70-72 °C; ¹H NMR (300 MHz, CDCl₃): δ 1.49 (9H, s, C(CH₃)₃), 4.35 (2H, s, CH₂), 7.85 (1H, s, NH); ¹³C NMR (100 MHz, CDCl₃): δ 27.9 (C(CH₃)₃), 52.9 (CH₂), 83.6 (C(CH₃)₃), 150.1 ((NC(O)O), 169.5 (NC(O)CH₂); IR (neat) νmax/cm⁻¹ 3216m, 2975m, 2117s (azide), 1750s, 1705s, 1691s, 1490s, 1368s, 1229s, 1148s, 1075s, 941m; m/z (ES⁺) 223.1 ([M+Na⁺], 100%), 167.0 ([CONHBoc+Na⁺], 40%); HRMS (ES⁺) 223.0811 [M+Na⁺], C₇H₁₂N₄O₃Na requires 223.0807.

2-(Diethylamino)acetamide 43

Synthesised according to the literature procedure.⁶⁷ A solution of diethylamine (26.7 mL, 258 mmol) in EtOH (50 mL) was added to a suspension of 2-chloroacetamide 38 (11.0 g, 117 mmol) and KI (21.4 g, 129 mmol) in EtOH (450 mL) and was then heated under reflux. After 3 h, the reaction mixture was cooled to rt and 90% of the solvent was removed under reduced pressure. The residue was diluted with H₂O (500 mL) and extracted with Et₂O (3 x 400 mL). The combined organic layers were dried with Na₂SO₄ and concentrated under reduced pressure to afford amino amide 43 as an off-white powder (5.92 g, 39%). Rf 0.38 (3:1 EtOAc/MeOH); m.p. 72-74 °C; ¹H NMR (300 MHz, CDCl₃): δ 0.99 (6H, t, J = 7.0 Hz, 2 x CH₃), 2.52 (4H, q, J = 7.0 Hz, 2 x CH₂), 2.96 (2H, s, C(O)CH₂), 6.65 (1H, br s, NH'), 7.22 (1H, br s, NH'); ¹³C NMR (100 MHz, CDCl₃): δ 12.2 (2 x CH₃), 48.5 (2 x CH₂), 57.3 (C(O)CH₂), 175.7 (C(O)NH₂); IR (neat) νmax/cm⁻¹ 3379s(br), 3173s(br), 2970s, 2932m, 2821m, 1649s, 1453m, 1399s, 1368s, 1340s, 1286m, 1257m, 1204m, 1064s; m/z (ES⁺) 131.1 ([M+H⁺], 65%); HRMS (ES⁺) 131.1183 [M+H⁺], C₆H₁₅N₂O requires 131.1184.
**tert-Butyl (diethylglycyl)carbamate 44**

![Chemical structure](image)

Synthesised according to the literature procedure.\(^6\) A solution of amino amide 43 (1.50 g, 11.5 mmol) in THF (50 mL) was added to a suspension of NaH (60% in mineral oil, 553 mg, 13.8 mmol) in THF (50 mL) at 0 °C. The reaction mixture was warmed to rt then cooled back to 0 °C and di-tert-butyl dicarbonate (1.0 M solution in THF, 12.7 mL, 12.7 mmol) was added. After 30 min the reaction mixture was warmed to rt and stirred for 1 h. It was then quenched with saturated aqueous NH\(_4\)Cl (200 mL) and extracted with Et\(_2\)O (4 x 150 mL). The combined organic layers were washed with brine (400 mL), dried with Na\(_2\)SO\(_4\) and concentrated under reduced pressure. Purification by flash column chromatography (6:1 petrol/EtOAc, 2% NEt\(_3\)) afforded Boc amide 44 as a white powder (1.37 g, 52%). R\(_f\) 0.59 (3:1 EtOAc/MeOH); m.p. 39–41 °C; \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 1.06 (6H, t, \(J = 7.0\) Hz, 2 x CH\(_3\)), 1.52 (9H, s, C(CH\(_3\))\(_3\)), 2.60 (4H, q, \(J = 7.0\) Hz, 2 x CH\(_2\)), 3.10 (C(O)CH\(_2\)), 9.35 (1H, br s, NH); \(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 12.1 (2 x CH\(_3\)), 28.0 (C(CH\(_3\))\(_3\)), 48.7 (2 x CH\(_2\)), 58.1 (NCH\(_2\)), 82.2 (C(CH\(_3\))\(_3\)), 149.4 (NHC(O)O), 170.9 (NHC(O)CH\(_2\)); IR (neat) \(\nu_{\text{max}}/\text{cm}^{-1}\) 3297w, 2972m, 2877w, 1786s, 1719s, 1478s, 1466s, 1368s, 1311m, 1246m, 1133s; m/z (ES\(^+\)) 231.2 ([M+H]\(^+\), 9%), 253.2 ([M+Na]\(^+\), 9%), 483.3 ([2M+Na]\(^+\), 100%); HRMS (ES\(^+\)) 231.1705 [M+H]\(^+\), \(C_{11}H_{23}N_2O_3\) requires 231.1709.

**tert-Butyl (diethylglycyl)carbamate borane complex 46**

![Chemical structure](image)

Synthesised according to the literature procedure.\(^3\) BH\(_3\)SMe\(_2\) (275 \(\mu\)L, 2.90 mmol) was added dropwise over 2 min to a solution of amino amide 44 (637 mg, 2.77 mmol) in THF (5.5 mL) at −78 °C. After 90 min the reaction was quenched with H\(_2\)O (1.5 mL) and warmed to rt. The mixture was then poured into a separating funnel with H\(_2\)O (150 mL) and Et\(_2\)O (150 mL) and separated. The aqueous phase was extracted with Et\(_2\)O (150 mL) and the combined organic layers were washed with 2 N HCl (200 mL) and brine (200 mL). The organic phase was then
dried with MgSO₄ and concentrated under reduced pressure to afford *amino borane 46* (582 mg, 86%). Rf 0.72 (3:1 EtOAc/MeOH); m.p. 44-46 °C; ¹H NMR (300 MHz, CDCl₃): δ 1.27 (6H, t, J = 7.0 Hz, 2 x CH₃), 1.51 (9H, s, C(CH₃)₃), 3.02-3.17 (2H, m, CH₂CH₃), 3.18-3.33 (2H, m, CH₂CH₃), 3.92 (2H, s, NCH₂), 7.54 (1H, br s, NH). BH₃ protons not observed; ¹³C NMR (100 MHz, CDCl₃): δ 9.4 (2 x CH₃), 27.9 (C(CH₃)₃), 54.8 (2 x CH₂CH₃), 57.2 (NCH₂), 83.6 (C(CH₃)₃), 149.5 (NC(O)O), 167.8 (NC(O)CH₂); IR (neat) νmax/cm⁻¹ 3275w, 2980w, 2382w (B-H), 2329w (B-H), 2284w (B-H), 1754m, 1510m, 1369m, 1254m, 1137s, 987m; m/z (ES⁺) 231.2 ([M+H-BH₃]⁺, 100%); product unstable in gas phase so no molecular ion peak observed.

**tert-Butyl (diethylglycyl)(3-oxobutyl)carbamate borane complex 47**

Tetramethylguanidine (9 µL, 0.070 mmol) was added to a solution of *amino borane 46* (60 mg, 0.246 mmol) in CH₂Cl₂ (0.75 mL). Next methyl vinyl ketone (50 µL, 0.614 mmol) was added dropwise over 1 min and the reaction mixture was stirred at rt for 18 h. Solvent was evaporated under reduced pressure and flash column chromatography (3:1 petrol/EtOAc) afforded *Michael adduct 47* as a colourless oil (22 mg, 29%). Rf 0.58 (3:1 EtOAc/MeOH); ¹H NMR (400 MHz, CDCl₃): δ 1.23 (6H, t, J = 7.0 Hz, 2 x CH₂CH₃), 1.54 (9H, s, C(CH₃)₃), 2.16 (3H, s, C(O)CH₃), 2.68 (2H, t, J = 7.5 Hz, NCH₂CH₂), 3.03-3.15 (2H, m, CH₂CH₃), 3.21-3.33 (2H, m, CH₂CH₃), 3.92 (2H, t, J = 7.5 Hz, NCH₂CH₂), 4.07 (2H, s, C(O)CH₂), BH₃ protons not observed; ¹³C NMR (100 MHz, CDCl₃): δ 9.5 (2 x CH₂CH₃), 27.9 (C(CH₃)₃), 30.1 (C(O)CH₃), 39.7 (NCH₂CH₂), 41.9 (NCH₂CH₂), 54.5 (2 x CH₂CH₃), 57.4 (C(O)CH₂), 84.8 (C(CH₃)₃), 152.1 (NC(O)O), 170.0 (NC(O)CH₂), 206.3 (C(O)CH₃); IR (neat) νmax/cm⁻¹ 2977w, 2378m (B-H), 2333w (B-H), 2284w (B-H), 1734m, 1713m, 1369s, 1350m, 1141s, 1054m; m/z (ES⁺) 301.2 ([M+H-BH₃]⁺, 30%), product unstable in gas phase so no molecular ion peak observed.
Synthesised according to the literature procedure. Phenylacetic acid 51 (2.04 g, 15.0 mmol) was added to thionyl chloride (45.0 mL) and heated under reflux for 3 h and then concentrated under reduced pressure to afford the acyl chloride as a brown oil in quantitative yield.

Benzylamine (708 µL, 6.48 mmol) and DMAP (158 mg, 1.23 mmol) were added to pyridine (550 µL, 6.81 mmol) in CH₂Cl₂ (11 mL) and cooled to −5 °C. The acyl chloride (1.05 g, 6.81 mmol) was then added and the reaction mixture was warmed to rt and stirred for 3 h. The reaction mixture was then diluted with CH₂Cl₂ (350 mL) and washed with H₂O (200 mL), 1 N HCl (200 mL), 5% aqueous solution of NaHCO₃ (200 mL) and brine (200 mL). The organic phase was then concentrated under reduced pressure to afford amide 52 as pale orange flakes (1.14 g, 78%). Rᵣ 0.60 (EtOAc); m.p. 112-113 °C (lit. 118-119 °C); ¹H NMR (300 MHz, CDCl₃): δ 3.58 (2H, s, CH₂C(O)), 4.36 (1H, s, NCHH'), 4.38 (1H, s, NCHH'), 5.88 (1H, s br, NH), 7.12-7.36 (10H, m, 2 x Ph); ¹³C NMR (100 MHz, CDCl₃): δ 43.5 (CH₂CO), 43.7 (CH₂NH), 127.3 (2 x CH, Ph), 127.4 (2 x CH, Ph), 128.6 (2 x CH, Ph), 129.0 (2 x CH, Ph), 129.4 (2 x CH, Ph), 134.8 (C, Ph), 138.0 (C, Ph), 170.8 (C(O)); IR (neat) νmax/cm⁻¹ 3285m, 3032w, 1637s, 1548m, 1491w, 1453w, 1345w, 1027m.

**N-Benzyl-2,2,2-trifluoro-N-(2-phenylacetyl)acetamide 53**

Trifluoroacetic anhydride (955 µL, 6.87 mmol) was added to a solution of amide 52 (515 mg, 2.29 mmol), DMAP (112 mg, 0.91 mmol) and pyridine (833 µL, 10.31 mmol) in CH₂Cl₂ (17 mL). The reaction mixture was then stirred at rt for 2 h before brine (30 mL) and petrol (100 mL) were added. The layers were separated and the organic layer was washed with brine (3 x 50
mL), dried with MgSO₄ and concentrated under reduced pressure. Purification by flash column chromatography (10:1 petrol/Et₂O) afforded imide 53 as an unstable dark brown oil (268 mg, 36%). Rf 0.40 (4:1 petrol/Et₂O); ¹H NMR (300 MHz, CDCl₃): δ 4.06 (2H, s, NCH₂), 4.94 (2H, s, C(O)CH₂), 7.07-7.34 (10H, m, 2 x Ph); ¹³C NMR (100 MHz, CDCl₃): δ 44.5 (C(O)CH₂), 47.9 (NCH₂), 115.8 (q, J_C-F = 288 Hz, CF₃), 126.4 (2 x CH, Ph), 127.9 (CH, Ph), 128.8 (2 x CH, Ph), 128.9 (2 x CH, Ph), 129.4 (2 x CH, Ph), 132.6 (C, Ph), 135.3 (C, Ph), 160.0 (q, J_C-F = 39 Hz, C(O)CF₃), 173.9 (NC(O)); IR (neat) ν_max/cm⁻¹ 3285m, 3063w, 3032w, 1636s, 1547s, 1491m, 1453m, 1432m, 1345m, 1160m, 1026m; product unstable in gas phase so no mass spectrum could be obtained.

**tert-Butyl benzyl(2-phenylacetyl)carbamate 55**

![Chemical structure]

Di-tert-butyl dicarbonate (109 µL, 0.474 mmol) and DMAP (2 mg, 0.020 mmol) were added to a solution of amide 52 (89 mg, 0.395 mmol) in THF (2.4 mL) at 0 °C. The reaction mixture was warmed to rt and after 18 h the solvent was removed under reduced pressure. The residue was then taken up in CH₂Cl₂ (40 mL) and washed with 2 N HCl (30 mL), saturated aqueous NaHCO₃ (30 mL) and brine (30 mL). The organic layer was then dried with MgSO₄ and concentrated under reduced pressure. Purification by flash column chromatography (10:1 petrol/Et₂O) afforded Boc amide 55 as a yellow oil (114 mg, 89%). Rf 0.62 (1:1 petrol/EtOAc); ¹H NMR (300 MHz, CDCl₃): δ 1.48 (9H, s, C(CH₃)₃), 4.37 (2H, s, C(O)CH₂), 4.98 (2H, s, NCH₂), 7.28-7.44 (10H, m, 2 x Ph); ¹³C NMR (100 MHz, CDCl₃): δ 27.8 (C(CH₃)₃), 44.4 (C(O)CH₂), 47.7 (NCH₂), 83.3 (C(CH₃)₃), 126.7 (CH, Ph), 127.1 (CH, Ph), 127.6 (2 x CH, Ph), 128.2 (2 x CH, Ph), 128.3 (2 x CH, Ph), 129.6 (2 x CH, Ph), 135.1 (C, Ph), 138.1 (C, Ph), 153.0 (NC(O)O), 174.2 (NC(O)CH₂); IR (neat) ν_max/cm⁻¹ 3032w, 2979w, 1731s, 1689m, 1455w, 1368m, 1355m, 1224m, 1143s, 1078m, 1031w, 1016w; m/z (ES⁺) 348.2 [(M+Na)⁺, 100%]; HRMS (ES⁺) 348.1581 [M+Na]⁺, C₂₀H₂₃NO₂Na requires 348.1576.
**tert-Butyl benzyl(5-oxo-2-phenylhexanoyl)carbamate 78**

![Chemical Structure](image)

Tetramethylguanidine (5 µL, 0.04 mmol) was added to a solution of Boc amide 55 (44 mg, 0.135 mmol) in CH₂Cl₂ (0.5 mL). Next methyl vinyl ketone (118 µL, 1.35 mmol) was added dropwise over 2 min and the reaction mixture was stirred at rt for 5 h. The solvent was evaporated under reduced pressure and flash column chromatography (15:1 to 5:1 petrol/Et₂O) afforded Michael adduct 78 as a colourless oil (38 mg, 78%). Rf 0.38 (1:1 petrol/Et₂O); ¹H NMR (400 MHz, CDCl₃): δ 1.30 (9H, s, C(CH₃)₃), 1.99-2.09 (1H, m, NC(O)CHC₆H₄), 2.10 (3H, s, C(O)CH₃), 2.27-2.48 (3H, m, NC(O)CHC₆H₄ and CH₃C(O)CH₂), 4.74 (1H, d, J = 15.0 Hz, NCH₂), 4.88 (1H, d, J = 15.0 Hz, NCH₂), 4.93-4.99 (1H, m, NC(O)), 7.07-7.30 (10H, m, 2 x Ph); ¹³C NMR (100 MHz, CDCl₃): δ 27.7 (C(CH₃)₃), 28.2 (NC(O)CHC₆H₄), 29.8 (CH₃), 41.4 (CH₃C(O)CH₂), 48.1 (NCH₂), 50.2 (NC(O)CH), 83.2 (C(CH₃)₃), 127.0 (CH, Ph), 127.1 (CH, Ph), 127.4 (2 x CH, Ph), 128.2 (2 x CH, Ph), 128.4 (2 x CH, Ph), 128.6 (2 x CH, Ph), 137.9 (C, Ph), 139.1 (C, Ph), 152.9 (NC(O)O), 176.4 (NC(O)), 208.2 (C(O)); IR (neat) νmax/cm⁻¹ 2978w, 2934w, 1729s, 1716s, 1688m, 1367m, 1214m, 1142s; m/z (ES⁺) 418.2 ([M+Na]⁺, 100%); HRMS (ES⁺) 418.1988 [M+Na]⁺, C₂₄H₂₉NO₄Na requires 418.1994.

**1-Benzyl-3-(4-methoxyphenyl)thiourea 60⁷⁰**

![Chemical Structure](image)

Synthesised according to the literature procedure.⁷¹ p-Methoxyphenyl isothiocyanate (375 µL, 2.71 mmol) was added to a solution of benzylamine (296 µL, 2.71 mmol) in CH₂Cl₂ (6.5 mL) at 0 °C. The reaction mixture was then warmed to rt, stirred for 16 h and then concentrated under reduced pressure. Purification by flash column chromatography (5:2 petrol/EtOAc) afforded thiourea 60 as a white powder (681 mg, 92%). Rf 0.41 (1:1 petrol/EtOAc); m.p. 103-105 °C (lit. 113-114 °C); ¹H NMR (300 MHz, CDCl₃): δ 3.79 (3H, s, OCH₃), 4.85 (1H, s, CHH'Ph),
4.87 (1H, s, CH'HPh), 6.08 (1H, br s, NH), 6.87-6.94 (2H, m, 2 x CH, PMP), 7.12-7.19 (2H, m, 2 x CH, PMP), 7.23-7.38 (5H, m, Ph), 7.89 (1H, br s, NH); 13C NMR (100 MHz, CDCl₃): δ 49.3 (NCH₃Ph), 55.5 (OCH₃), 115.3 (2 x CH, PMP), 127.5 (2 x CH, PMP), 127.6 (CH, Ph), 127.8 (2 x CH, Ph), 128.7 (2 x CH, Ph), 128.8 (CNH, PMP) 137.4 (C, Ph), 159.0 (COCH₃, PMP), 181.5 (NHC(S)NH); IR (neat) νmax/cm⁻¹ 3384m, 3164m, 3014m, 1588m, 1542s, 1522s, 1504s, 1494s, 1311m, 1237s, 1227s, 1025s, 968m.

1-Benzyl-3-(4-methoxyphenyl)-2-methylguanidine 61

![Reaction Scheme](attachment:reaction_scheme.png)

Methyl iodide (25 µL, 0.400 mmol) was added to a solution of thiourea 60 (99 mg, 0.363 mmol) in acetone (2 mL) and the reaction mixture was heated under reflux for 2.5 h. The solvent was then evaporated, the residue was dissolved in MeOH (0.7 mL) and methylamine (2.0 M in THF, 540 µL, 1.09 mmol) was added. The sealed tube was then heated to 100 °C for 17 h. The reaction mixture was cooled to rt, diluted with CH₂Cl₂ (30 mL) and washed with saturated aqueous NaHCO₃ (40 mL). The aqueous layer was then extracted with CH₂Cl₂ (30 mL) and the combined organic layers were washed with brine (50 mL), dried with Na₂SO₄ and concentrated under reduced pressure. Purification of a 23 mg portion of the crude product by flash column chromatography (neutral alumina, 4:1 to 0:1 petrol/EtOAc) afforded guanidine 61 as a white powder (9 mg, 39%). Rf 0.28 (1:1 petrol/EtOAc); m.p. 141-143 °C; 1H NMR (300 MHz, CDCl₃): δ 1.26 (3H, s, NCH₃), 3.77 (3H, s, OCH₃), 4.38 (1H, s, NCHH'), 4.40 (1H, s, NCHH'), 5.21 (1H, br s, NH), 6.51 (1H, br s, NH), 6.79-6.86 (2H, m, 2 x CH, PMP), 7.13-7.20 (2H, m, 2 x CH, PMP), 7.21-7.35 (5H, m, Ph); 13C NMR (100 MHz, CDCl₃): δ 29.7 (NCH₃), 44.2 (NCH₂), 55.5 (OCH₃), 114.6 (2 x CH, PMP), 124.9 (2 x CH, PMP), 127.3 (CH, Ph), 127.4 (2 x CH, Ph), 128.6 (2 x CH, Ph), 130.7 (CNH, PMP), 139.1 (C, Ph), 156.6 (COCH₃, PMP), 157.1 (C=N); IR (neat) νmax/cm⁻¹ 3305br, 2954w, 2922m, 2853w, 1630s, 1609s, 1562s, 1508s, 1455m, 1242s, 1033m; m/z (ES⁺) 270.2 ([M+H]+, 20%); HRMS (ES⁺) 270.1612 [M+H]+, C₁₆H₂₀N₃O requires 270.1606.
9-Amino-(9-deoxy)-epi-quinine 62

Quinine 2 (3.27 g, 10.1 mmol) was added to a solution of triphenylphosphine (3.18 g, 12.1 mmol) in THF (50 mL) at 0 °C. Diisopropyl azodicarboxylate (2.38 mL, 12.2 mmol) was added in one portion followed by a solution of diphenyl phosphoryl azide (2.61 mL, 12.1 mmol) in THF (20 mL). The reaction mixture was warmed to rt and stirred for 12 h, then warmed to 50 °C and stirred for 2 h. A second quantity of triphenylphosphine (3.44 g, 13.1 mmol) was then added and heating was maintained for a further 2 h. The reaction mixture was then cooled to rt, H$_2$O (1 mL) was added and stirring was continued for 18 h. The reaction mixture was concentrated under reduced pressure and the residue was dissolved in CH$_2$Cl$_2$ (300 mL) and 10% HCl (300 mL). The aqueous layer was washed with CH$_2$Cl$_2$ (3 x 200 mL) and adjusted to pH 10 with concentrated NH$_4$OH. The aqueous layer was then extracted with CH$_2$Cl$_2$ (4 x 200 mL) and these combined organic layers were dried with Na$_2$SO$_4$ and concentrated under reduced pressure to afford amine 62 as an orange semi-solid (3.18 g, 98%). Product was used crude but a small portion was recrystallized as the HCl salt.

Crude product (910 mg, 1.86 mmol) was dissolved in CH$_2$Cl$_2$ (100 mL) and extracted into 2 N HCl (100 mL). The aqueous phase was then washed with CH$_2$Cl$_2$ (2 x 100 mL) and concentrated under reduced pressure to give the 3HCl salt. This was recrystallized from MeOH and EtOAc and dried under reduced pressure. The product was basified with 1 N NaOH (100 mL) to achieve a pH of 10 and extracted with CH$_2$Cl$_2$ (4 x 100 mL). The combined organic layers were washed with brine, dried with Na$_2$SO$_4$ and concentrated under reduced pressure to afford the analytically pure amine 62 (507 mg, 56%). $R_f$ 0.07 (3:1 EtOAc/MeOH); $^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.65-0.77 (1H, m, CH$H^7$), 1.30-1.41 (1H, m, CH$H^7$), 1.43-1.52 (2H, m, CH$_2$), 1.52-1.57
(1H, m, CH\textsubscript{4}), 2.00-2.25 (3H, m, NH\textsubscript{2} overlays CH\textsuperscript{3}), 2.67-2.78 (2H, m, CH\textsubscript{H}\textsuperscript{6} and CH\textsubscript{H}\textsuperscript{2}), 2.95-3.07 (1H, m, CH\textsuperscript{8}), 3.09-3.18 (1H, m, CH\textsubscript{H}\textsuperscript{6}), 3.20 (1H, dd, J = 14.0, 10.0, CH\textsubscript{H}\textsuperscript{2}), 3.88 (3H, s, OCH\textsubscript{3}), 4.53 (1H, br d, J = 9.0 Hz, CH\textsubscript{H}NH\textsubscript{2}), 4.86-4.98 (2H, m, CH=CH\textsubscript{2}), 5.73 (1H, ddd, J = 17.0, 10.0, 7.5 Hz, CH=CH\textsubscript{2}), 7.31 (1H, dd, J = 9.0, 3.0 Hz, CH\textsuperscript{7}), 7.34-7.42 (1H, m, CH\textsuperscript{3}), 7.59 (1H, br s, CH\textsuperscript{5}), 7.96 (1H, d, J = 9.0 Hz, CH\textsuperscript{8}), 8.66 (1H, d, J = 4.5 Hz, CH\textsuperscript{2}); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 26.0 (C\textsuperscript{7}H\textsubscript{2}), 27.5 (C\textsuperscript{4}H), 28.2 (C\textsuperscript{5}H\textsubscript{2}), 39.8 (C\textsuperscript{3}H), 41.0 (C\textsuperscript{6}H\textsubscript{2}), 52.5 (C\textsuperscript{9}H), 55.5 (OCH\textsubscript{3}), 56.3 (C\textsuperscript{2}H\textsubscript{2}), 61.8 (C\textsuperscript{8}H), 102.0 (C\textsuperscript{5}H), 114.3 (CH=CH\textsubscript{2}), 119.9 (C\textsuperscript{3}H), 121.2 (C\textsuperscript{7}H), 128.8 (C\textsuperscript{4a}), 131.7 (C\textsuperscript{8}H), 141.8 (CH=CH\textsubscript{2}), 144.7 (C\textsuperscript{4}), 147.0 (C\textsuperscript{6a}), 147.8 (C\textsuperscript{2}H), 157.6 (C\textsuperscript{6}OMe); IR (neat) ν\textsubscript{max}/cm\textsuperscript{-1} 3366w, 2933m, 2862m, 1620s, 1589m, 1506s, 1473m, 1228s, 1029s, 912s; [α]\textsubscript{D} +98 ° (c = 1.0, CHCl\textsubscript{3}, 20 °C), (lit.\textsuperscript{73} [α]\textsubscript{D} +80 ° (c = 1.1, CHCl\textsubscript{3}, 20 °C)).

1-(4-Methoxyphenyl)-3-((S)-(6-methoxyquinolin-4-yl)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl)thiourea 63

Synthesised according to the literature procedure.\textsuperscript{71} p-Methoxyphenyl isothiocyanate (971 µL, 7.03 mmol) was added to a solution of amino quinine 62 (2.27 g, 7.03 mmol) in CH\textsubscript{2}Cl\textsubscript{2} (17.5 mL) at 0 °C. The reaction mixture was then warmed to rt, stirred for 16 h and then concentrated under reduced pressure. Purification by flash column chromatography (97:3:0 to 93:6:1 CH\textsubscript{2}Cl\textsubscript{2}/MeOH/NET\textsubscript{3}) afforded thiourea 63 as a pale yellow powder (2.35 g, 68%). Rf 0.38 (3:1 EtOAc/MeOH); m.p. 110-113 °C; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 0.92-1.00 (1H, m, CH\textsubscript{H}\textsuperscript{7}), 1.28-1.39 (1H, m, CHH\textsuperscript{7}), 1.55-1.74 (3H, m, CH\textsubscript{4} and CH\textsubscript{2}\textsuperscript{5}), 2.22-2.32 (1H, m, CH\textsuperscript{3}), 2.62-2.74 (2H, m, CH\textsubscript{H}\textsuperscript{6} and CH\textsubscript{H}\textsuperscript{2}), 3.13 (1H, dd, J = 13.5, 10.0 Hz, CHH\textsuperscript{2}), 3.12-3.22 (1H, m, CH\textsuperscript{8}), 3.30-3.41 (1H, m, CHH\textsuperscript{6}), 3.83 (3H, s, C\textsuperscript{6}OCH\textsubscript{3}), 3.95 (3H, s, C\textsuperscript{14}OCH\textsubscript{3}), 4.90-4.98 (2H, m, CH=CH\textsubscript{2}), 5.64 (1H, ddd, J = 17.0, 10.0, 7.5 Hz, CH=CH\textsubscript{2}), 5.89 (1H, br s, CH\textsuperscript{9}), 6.89 (2H, d, J = 9.0 Hz, 2 x CH\textsuperscript{13}), 7.13 (2H, d, J = 9.0 Hz, 2 x CH\textsuperscript{12}), 7.16-7.23 (1H, m, C\textsuperscript{3}H), 7.36 (1H, dd, J = 9.0, 2.5
Hz, C\textsuperscript{7}H), 7.79 (1H, br s, CH\textsuperscript{5'}), 7.98 (1H, d, J = 9.0 Hz, CH\textsuperscript{8'}), 8.52 (1H, d, J = 4.0 Hz, CH\textsuperscript{2'}). NH protons not observed; \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 25.7 (C\textsuperscript{7}H\textsubscript{2}), 27.2 (C\textsuperscript{5}H\textsubscript{2}), 27.6 (C\textsuperscript{4}H), 39.2 (C\textsuperscript{3}H), 41.4 (C\textsuperscript{6}H\textsubscript{2}), 55.2 (C\textsuperscript{2}H\textsubscript{2}), 55.5 (C\textsuperscript{6}OCH\textsubscript{3}), 55.7 (PhOCH\textsubscript{3}), 60.7 (C\textsuperscript{8}H, overlays C\textsuperscript{9}H), 102.4 (C\textsuperscript{5'}H), 114.6 (2 x C\textsuperscript{13}H), 114.8 (CH=CH\textsubscript{2}), 119.8 (C\textsuperscript{3}H), 121.8 (C\textsuperscript{7}H), 127.3 (2 x C\textsuperscript{12}H, overlays C\textsuperscript{8a'}), 128.1 (C\textsuperscript{4a'}), 130.0 (C\textsuperscript{11}), 131.6 (C\textsuperscript{8}H), 140.7 (CH=CH\textsubscript{2}), 144.7 (C\textsuperscript{4}), 147.5 (C\textsuperscript{2}H), 157.8 (C\textsuperscript{6}OMe), 158.3 (C\textsuperscript{14}), 181.0 (C\textsuperscript{10}=S); IR (neat) \(\nu\)\textsubscript{max}/cm\textsuperscript{-1} 3188w, 2935w, 1621w, 1506s, 1474m, 1238s, 1227s, 1028m; m/z (ES\textsuperscript{+}) 489.2 ([M+H]\textsuperscript{+}, 100%); HRMS (ES\textsuperscript{+}) 489.2329 [M+H]\textsuperscript{+}, C\textsubscript{28}H\textsubscript{33}N\textsubscript{4}O\textsubscript{2}S requires 489.2324; \([\alpha]_D\) −142 ° (c = 1.0, CHCl\textsubscript{3}, 20 °C).

\textbf{N-Cyclohexyl-1,3-dimethylimidazolidin-2-imine 69\textsuperscript{74}}

\[ \text{NHMe} \quad \begin{array}{c} \text{DCC, toluene} \\ 115 \degree \text{C in sealed tube} \end{array} \quad \text{NHMe} \quad \begin{array}{c} \text{Me} \\ \text{Me} \end{array} \quad \text{Cy} \quad \text{Cy} \quad \text{N} \quad \text{N} \]

Synthesised according to the literature procedure.\textsuperscript{75} Dicyclohexyl carbodiimide (240 mg, 1.16 mmol) was added to a solution of dimethyl ethylenediamine 68 (150 µL, 1.37 mmol) in toluene (7 mL) in a sealed tube. The sealed tube was then heated to 115 °C for 64 h. The reaction mixture was then concentrated under reduced pressure. The residue was treated with 30% aqueous NaOH (100 mL) and extracted with Et\textsubscript{2}O (3 x 80 mL). The combined organic layers were dried with Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure. Purification by flash column chromatography (neutral alumina, EtOAc with 3-30% MeOH) afforded guanidine 69 as a yellow oil (82 mg, 31%). R\textsubscript{o} 0.05 (3:1 EtOAc/MeOH); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 1.03-1.32 (6H, m, Cy), 1.62-1.70 (4H, m, Cy), 2.70 (6H, br s, 2 x NCH\textsubscript{3}), 3.06 (4H, s, NCH\textsubscript{2}CH\textsubscript{2}N), 3.31-3.41 (1H, m, NCH); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 25.3 (3 x CH\textsubscript{2}, Cy), 25.9 (2 x CH\textsubscript{2}, Cy), 36.6 (2 x NCH\textsubscript{3}), 49.4 (br, 2 x NCH\textsubscript{2}), 54.2 (NCH), 155.7 (C=N); IR (neat) \(\nu\)\textsubscript{max}/cm\textsuperscript{-1} 2923m, 2849m, 1655s, 1479w, 1447m, 1378m, 1260m, 1226m, 1029m, 950m; m/z (ES\textsuperscript{+}) 196.2 ([M+H]\textsuperscript{+}, 90%); HRMS (ES\textsuperscript{+}) 196.1820 [M+H]\textsuperscript{+}, C\textsubscript{11}H\textsubscript{22}N\textsubscript{3} requires 196.1814.
1-((S)-(6-Methoxyquinolin-4-yl)((1S,2R,4S,5R)-5-vinylquinuclidin-2-yl)methyl)guanidine 77

Synthesised according to the literature procedure. Amine 62 (136 mg, 0.420 mmol) was added to a stirring solution of NEt₂Pr₂ (73 µL, 0.420 mmol) and 1H-pyrazole-1-carboxamidine hydrochloride (62 mg, 0.420 mmol) in DMF (0.40 mL). The reaction mixture was stirred at rt for 23 h before Et₂O (3 mL) was added to precipitate the product. The product was then filtered and washed with more Et₂O (2 x 5 mL) before drying under reduced pressure to afford guanidine 77 as a white powder (136 mg, 88%).

Rf 0.08 (1:1 EtOAc/MeOH); m.p. decomposed at 200 °C; ¹H NMR (400 MHz, CD₃OD): δ 0.97-1.08 (1H, m, CH₇H), 1.29-1.42 (1H, m, CH₇H), 1.59-1.81 (3H, m, CH₅H and CH⁴H), 2.40 (1H, br s, CH₃), 2.84-3.04 (2H, m, CH₆H and CH₂H²), 3.25-3.52 (3H, m, CH⁵H, CH⁸H and CH₂H²), 4.04 (3H, s, OCH₃), 4.95-5.10 (2H, m, CH=CH₂), 5.36 (1H, br s, CH⁳NH), 5.81 (1H, ddd, J = 17.5, 10.5, 7.5 Hz, CH=CH₂), 7.51 (1H, dd, J = 9.0, 2.5 Hz, CH⁷H), 7.64-7.70 (2H, m, CH³H and CH⁴H), 8.02 (1H, d, J = 9.0 Hz, CH⁸H), 8.73 (1H, d, J = 4.5 Hz, CH²H), NH protons not observed; ¹³C NMR (100 MHz, CD₃OD): δ 26.5 (C⁷H₂), 28.4 (C⁴H), 28.8 (C⁵H₂), 40.6 (C³H), 42.1 (C⁶H₂), 56.2 (C²H₂), 56.9 (OCH₃), 60.0 (C⁵H overlays C⁶H), 103.3 (C⁵H), 115.4 (CH=CH₂), 122.7 (C³H), 123.8 (C⁷H), 129.2 (C⁴aH), 132.2 (C⁶H), 142.4 (CH=CH₂), 144.4 (C⁴), 145.6 (C⁵aH), 148.6 (C²H), 159.1 (C⁶OMe), 160.3 (C=NH); IR (neat) νmax/cm⁻¹ 3130w (br), 2945w, 1660m, 1637s, 1622m, 1590w, 1478w, 1230m, 1026m; m/z (ES⁺) 366.2 ([M+H]+, 100%), 183.6 ([M+2H]²⁺, 50%); HRMS (ES⁺) 366.2300 [M+H]+, C₂₁H₂₈N₅O requires 366.2294; [α]₀ = -44.4° (c = 1.0, MeOH, 23 °C).
1,3-Dibenzylimidazolidine-2,4-dione 80

Synthesised according to the literature procedure.⁷⁷ NaH (60% in mineral oil, 186 mg, 4.66 mmol) was added to a solution of hydantoin 79 (222 mg, 2.22 mmol) in DMF (6 mL). After 15 min at rt, benzyl bromide (554 µL, 4.66 mmol) as a solution in DMF (5 mL) was added dropwise over 10 min. The reaction mixture was stirred at rt for 18 h, poured into H₂O (80 mL) and extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine (150 mL), dried with MgSO₄ and concentrated under reduced pressure. Purification by flash column chromatography (4:1:0 to 1:0:0 to 98:0:2 CH₂Cl₂/petrol/MeOH) afforded protected hydantoin 80 as a pale yellow oil (298 mg, 48%). Rₜ 0.15 (1:1 petrol/Et₂O); ¹H NMR (300 MHz, CDCl₃): δ 3.65 (2H, s, CH₂CO), 4.47 (2H, s, NCH₂), 4.61 (2H, s, NCH₂), 7.13-7.39 (10H, m, 2 x Ph); ¹³C NMR (100 MHz, CDCl₃): δ 42.6 (CH₂CO), 46.7 (NCH₂), 49.1 (NCH₂), 127.9 (CH, Ph), 128.1 (2 x CH, Ph), 128.2 (CH, Ph), 128.6 (2 x CH, Ph), 128.7 (2 x CH, Ph), 129.0 (2 x CH, Ph), 135.3 (C, Ph), 136.0 (C, Ph), 156.5 (NC(ON)), 169.5 (NC(ON)CH₂); IR (neat) νmax/cm⁻¹ 3032w, 2926w, 1768w, 1701s, 1451m, 1336m, 1235m, 1137m.

1,3-Di-(tert-butoxycarbonyl)hydantoin 82

Di-tert-butyl dicarbonate (1.82 mL, 7.92 mmol) and DMAP (10 mg, 0.079) were added slowly to a solution of hydantoin 79 (317 mg, 3.17 mmol) in THF (20 mL) at 0 °C. The reaction mixture was then stirred at rt for 18 h and concentrated under reduced pressure. The residue was treated with CH₂Cl₂ (400 mL) and washed with 2 N HCl (200 mL), saturated aqueous NaHCO₃ (200 mL) and brine (200 mL). The organic layer was then dried with MgSO₄ and concentrated under reduced pressure. Purification by flash column chromatography (1:1 petrol/Et₂O) afforded protected hydantoin 82 as a pale yellow powder (489 mg, 51%). Rₜ 0.69 (EtOAc); m.p.
138-139 °C (lit. 141-143 °C); $^1$H NMR (300 MHz, CDCl$_3$): δ 1.56 (9H, s, C(CH$_3$)$_3$), 1.59 (9H, s, C(CH$_3$)$_3$), 4.24 (2H, s, CH$_2$); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 27.7 (C(CH$_3$)$_3$), 27.9 (C(CH$_3$)$_3$), 48.2 (NCH$_2$), 85.1 (C(CH$_3$)$_3$), 86.8 (C(CH$_3$)$_3$), 145.0 (NC(O)O), 147.3 (NC(O)O), 148.2 (NC(O)N), 163.9 (NC(O)CH$_2$); IR (neat) $\nu$$_{max}$/cm$^{-1}$ 3285m, 3063w, 3032w, 1771w, 1718w, 1635s, 1547s, 1490m, 1453m, 1364m, 1316m, 1259s, 1159m, 1027m.

### 3-Benzylimidazolidine-2,4-dione 87

![Chemical Structure of 3-Benzylimidazolidine-2,4-dione](image)

Benzyl bromide (4.26 mL, 35.9 mmol) was added to a suspension of hydantoin 79 (1.20 g, 12.0 mmol) and K$_2$CO$_3$ (4.96 g, 35.9 mmol) in DMF (38 mL). The reaction mixture was then heated to 60 °C for 18 h and then H$_2$O (300 mL) was added. The product was extracted with EtOAc (3 x 200 mL) and the combined organic layers were washed with brine (300 mL), dried with Na$_2$SO$_4$ and concentrated under reduced pressure. Purification by flash column chromatography (11:2 to 0:1 petrol/EtOAc) afforded mono-protected hydantoin 87 as a white solid (1.63 g, 72%). $R_f$ 0.46 (EtOAc); m.p. 130-132 °C (lit. 132-133 °C); $^1$H NMR (300 MHz, CDCl$_3$): δ 3.98 (2H, app d, $J = 1.0$ Hz, CH$_2$NH), 4.68 (2H, s, NCH$_2$), 6.41 (1H, br s, NH), 7.26-7.45 (5H, m, Ph); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 42.2 (CH$_2$NH), 46.5 (NCH$_2$), 128.0 (CH, Ph), 128.6 (2 x CH, Ph), 128.7 (2 x CH, Ph), 135.8 (C, Ph), 158.3 (HNC(O)), 171.0 (CH$_2$C(O)); IR (neat) $\nu$$_{max}$/cm$^{-1}$ 3222w, 3098w, 1768m, 1724w, 1706s, 1459s, 1450s, 1340m, 1141m.

### 3-Benzyl-2-methoxy-3,5-dihydro-4H-imidazol-4-one 88

![Chemical Structure of 3-Benzyl-2-methoxy-3,5-dihydro-4H-imidazol-4-one](image)

Synthesised according to the literature procedure.$^{81}$ Hydantoin 87 (106 mg, 0.558 mmol) as a solution in CH$_2$Cl$_2$ (1.5 mL) was added to trimethyloxonium tetrafluoroborate (99 mg, 0.669 mmol) in CH$_2$Cl$_2$ (1.5 mL). The reaction mixture was stirred at rt for 17 h. It was then diluted
with CH₂Cl₂ (20 mL), washed with ice cold saturated aqueous NaHCO₃ (20 mL), dried with MgSO₄ and concentrated under reduced pressure. Purification by flash column chromatography (2:1 to 1:0 EtOAc/petrol) afforded the lactim ether 88 as white powder (64 mg, 19%). Rf 0.26 (EtOAc); m.p. 60-63 °C; ¹H NMR (300 MHz, CDCl₃): δ 3.99 (3H, s, CH₃), 4.10 (2H, s, CH₂C(O)), 4.62 (2H, s, NCH₂), 7.26-7.38 (5H, m, Ph); ¹³C NMR (100 MHz, CDCl₃): δ 43.1 (NCH₂), 55.5 (OCH₃), 56.6 (CH₂C(O)), 127.8 (CH, Ph), 128.0 (2 x CH, Ph), 128.6 (2 x CH, Ph), 136.0 (C, Ph), 160.4 (NC=N), 178.8 (NC(O)); IR (neat) ν_max/cm⁻¹ 2949w, 1732s, 1655s, 1462s, 1454s, 1384s, 1355s, 1294m, 1234s, 1038s; m/z (ES⁺) 205.1 ([M+H]⁺, 100%); HRMS (ES⁺) 205.0980 [M+H]⁺, C₁₁H₁₃N₂O₂ requires 205.0977.

Thalidomide 94

Phthalic anhydride (2.60 g, 17.6 mmol) was added to L-glutamine (2.59 g, 17.7 mmol) in pyridine (13 mL) and stirred at 80 °C for 22 h then cooled to 5 °C. Thionyl chloride (1.32 mL, 18.2 mmol) was added slowly over 5 min. The reaction mixture was then stirred at rt for 3 h. The pyridine was then removed under reduced pressure until the volume of the reaction mixture was reduced by 80%. A 4:1 mixture of water/ethanol (50 mL) was added and the mixture was cooled to 10 °C in an ice bath before concentrated HCl solution was added to achieve a pH of 7.0 ± 0.5. After stirring at rt for 4 h, the precipitate was filtered by suction filtration, washed with water (100 mL) and dried under reduced pressure to afford thalidomide 94 as a pale brown powder (1.08 g, 24%). Rf 0.26 (1:1 petrol/EtOAc); m.p. 221-224 °C (recrystallised from ethanol, lit. 274-276 °C); ¹H NMR (400 MHz, DMSO): δ 2.01-2.13 (1H, m, C(O)CH₂), 2.50-2.65 (2H, m, C(O)CH₂CH'), 2.84-2.96 (1H, m, C(O)CH₂CHH'), 5.16 (1H, dd, J = 13.0, 5.5 Hz, C(O)CH), 7.87-7.96 (4H, m, 4 x CH, Ar), 11.14 (1H, br s, NH); ¹³C NMR (100 MHz, DMSO): δ 22.0 (C(O)CHCH₂), 30.9 (C(O)CH₂), 49.0 (C(O)CH), 123.4 (2 x CH, Ar), 131.2 (2 x C, Ar), 134.9 (2 x CH, Ar), 167.1 (C(O)NC(O)), 169.8 (CHC(O)NH), 172.7 (CH₂C(O)NH); IR
(neat) $\nu_{\text{max}}$/cm$^{-1}$: 3200 w (br), 3097 w, 1771 w, 1697 s, 1469 w, 1383 m, 1360 m, 1324 m, 1256 m, 1196 m, 1113 m.

tert-Butyl 3-(1,3-dioxoisindolin-2-yl)-2,6-dioxopiperidine-1-carboxylate 97

Di-tert-butyl dicarbonate (104 µL, 0.451 mmol) and DMAP (5 mg, 0.041 mmol) were added to thalidomide 94 (106 mg, 0.410 mmol) as a solution in 1,4-dioxane (1.2 mL). The reaction mixture was stirred at rt for 21 h and then diluted with Et$_2$O (2 mL). The product was filtered, washed with Et$_2$O (3 x 5 mL) and dried under reduced pressure to afford Boc protected thalidomide 97 as a pale brown solid (96 mg, 65%). R$_f$ 0.41 (1:1 petrol/EtOAc); m.p. decomposed above 223 °C. $^1$H NMR (400 MHz, CDCl$_3$): δ 1.56 (9H, s, C(CH$_3$)$_3$), 2.11-2.19 (1H, m, C(O)CH$_2$H'), 2.77-3.04 (3H, m, C(O)C'H$_2$H'), 5.05 (1H, dd, $J = 13.0, 5.5$ Hz, C(O)CH), 7.74-7.81 (2H, m, 2 x CH, Ar), 7.86-7.93 (2H, m, 2 x CH, Ar); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 21.8 (C(O)CH$_2$H$_2$), 27.4 (C(CH$_3$)$_3$), 31.6 (C(O)CH$_2$), 49.5 (C(O)CH), 86.8 (C(CH$_3$)$_3$), 123.8 (2 x CH, Ar), 131.7 (2 x C, Ar), 134.5 (2 x CH, Ar), 147.7 (NC(O)O), 166.1 (CHC(O)NH), 167.1 (C(O)NC(O)), 168.6 (CH$_2$C(O)NH); IR (neat) $\nu_{\text{max}}$/cm$^{-1}$: 3005 w, 1784m, 1713s, 1694s, 1388m, 1248s, 1140s; m/z (ES$^+$) 381.1 ([M+Na]$^+$, 10%), 739.2 ([2M+Na]$^+$, 100%); HRMS (ES$^+$) 381.1067 [M+Na]$^+$, C$_{18}$H$_{18}$N$_2$O$_6$Na requires 381.1063.

tert-Butyl (2-(benzylamino)-2-oxo-1-phenylethyl)carbamate 101

Boc protected amino acid 100 was synthesised according to the literature procedure. Phenylglycine 99 (1.21 g, 7.99 mmol) was suspended in 1 N NaOH (16 mL) and 1,4-dioxane (5 mL) and cooled to 0 °C. Di-tert-butyl dicarbonate (2.02 mL, 8.79 mmol) in 1,4-dioxane (6 mL) was added to the reaction mixture and it was warmed to rt and stirred for 18 h. The reaction
mixture was then diluted with H₂O (300 mL) and washed with petrol (3 x 200 mL). The aqueous layer was then carefully adjusted to pH 4 with citric acid and extracted with EtOAc (3 x 300 mL). The combined organic layers were washed with H₂O (400 mL) and brine (400 mL), dried with MgSO₄ and concentrated under reduced pressure. Purification by flash column chromatography (3:1 petrol/EtOAc) afforded Boc amine 100 (1.57 g, 78%).

Amide 101 was synthesised according to the literature procedure. NEt₃ (870 µL, 6.24 mmol) and ethyl chloroformate (597 µL, 6.24 mmol) were added slowly to a solution of Boc amine 100 (1.43 g, 5.67 mmol) in CH₂Cl₂ (23 mL) at 0 °C. The reaction mixture was warmed to rt and after 1 h, benzylamine (743 µL, 6.80 mmol) was added. After a further 2 h, the reaction mixture was diluted with CH₂Cl₂ (300 mL) and washed with saturated aqueous NaHCO₃ (200 mL) and brine (200 mL). The organic layer was dried with MgSO₄, concentrated under reduced pressure and purified by flash column chromatography (2:1 petrol/EtOAc) to afford amide 101 as white powder (1.77 g, 92%). Rf 0.46 (1:1 petrol/EtOAc); m.p. 123-125 °C (lit. 118-119); ¹H NMR (300 MHz, CDCl₃): δ 1.40 (9H, s, C(CH₃)₃), 4.42 (1H, s, CHH'), 4.44 (1H, s, CHH'), 5.21 (1H, br s, NH), 5.86 (1H, br s, CHNH), 6.15 (1H, br s, NH), 7.09-7.43 (10H, m, 2 x Ph); ¹³C NMR (100 MHz, CDCl₃): δ 28.3 (C(CH₃)₃), 43.6 (CH₂), 58.6 (CHNH), 80.1 (C(CH₃)₃), 127.2 (3 x CH, Ph), 127.5 (2 x CH, Ph), 128.4 (CH, Ph), 128.6 (2 x CH, Ph), 129.0 (2 x CH, Ph), 137.7 (C, Ph), 138.4 (C, Ph), 155.2 (C(O)O), 170.1 (C(O)NH); IR (neat) ν_max/cm⁻¹ 3278m, 2982w, 1689m, 1651s, 1561m, 1518s, 1495s, 1453m, 1364s, 1240s, 1156s, 1030m.

N-Benzyl-2-(benzylamino)-2-phenylacetamide 103

Amine 102 was synthesised according to the literature procedure. Trifluoroacetic acid (5.7 mL) was added carefully to a solution of Boc amide 101 (1.68 g, 4.94 mmol) in CH₂Cl₂ (17 mL) at 0 °C and the reaction mixture was warmed to rt and stirred for 2 h. The solvent was the evaporated under reduced pressure and the residue was taken up in EtOAc (500 mL) which
was washed with saturated aqueous NaHCO$_3$ (400 mL). The organic layer was then dried with Na$_2$SO$_4$ and concentrated under reduced pressure to afford amine 102 as a yellow oil (809 mg, 68%).

Amino amide 103 was synthesised according to the literature procedure.$^{87}$ Benzaldehyde (346 µL, 3.40 mmol) was added to a solution of amine 102 (779 mg, 3.24 mmol) in EtOH (29 mL) and stirred at rt for 2 h. The reaction mixture was then cooled to 0 °C, NaBH$_4$ (270 mg, 7.10 mmol) was added and stirring was continued at rt for 18 h. The reaction mixture was then carefully quenched with H$_2$O (100 mL) and extracted with CH$_2$Cl$_2$ (3 x 200 mL). The combined organic layers were dried with Na$_2$SO$_4$ and concentrated under reduced pressure. Flash column chromatography (5:1 to 3:1 petrol/EtOAc, 2% NEt$_3$) afforded amino amide 103 as colourless viscous oil (563 mg, 53%). R$_f$ 0.39 (1:1 petrol/EtOAc); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 2.05 (1H, br s, CHN$_\text{H}$), 3.78 (2H, s, CHNHCH$_2$), 4.31 (1H, s, CHNH), 4.46 (1H, s, C(O)NHCHH'), 4.48 (1H, s, C(O)NHCHH'), 7.20-7.54 (15H, m, 3 x Ph), C(O)NH proton not observed; $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 43.2 (C(O)NH$_\text{C}$H$\text{2}$), 52.5 (NHCH$_2$), 67.0 (NHCH), 127.1 (CH, Ph), 127.2 (2 x CH, Ph), 127.3 (CH, Ph), 127.4 (CH, Ph), 127.6 (2 x CH, Ph), 128.1 (2 x CH, Ph), 128.5 (2 x CH, Ph), 128.6 (2 x CH, Ph), 128.8 (2 x CH, Ph), 138.3 (C, Ph), 139.1 (2 x C, Ph), 171.9 (C(O)NH); IR (neat) $\nu_{\text{max}}$/cm$^{-1}$ 3305w (br), 3029w, 1653s, 1515m, 1495m, 1453m, 1265w, 1028w; m/z (ES$^+$) 331.2 ([M+H]$^+$+), HRMS (ES$^+$) 331.1800 [M+H]$^+$, C$_{22}$H$_{23}$N$_2$O requires 331.1810.

1,4-Dibenzyl-6-phenylpiperazine-2,3,5-trione 104

![1,4-Dibenzyl-6-phenylpiperazine-2,3,5-trione 104](image)

A solution of amino amide 103 (46 mg, 0.139 mmol) in THF (0.4 mL) was added to a suspension of oxalyl benzotriazole (47 mg, 0.160 mmol) in THF (1.4 mL) in a microwave vial. The vial was then heated at 150 °C with stirring for 1 h in the microwave. The reaction mixture was
concentrated under reduced pressure and then purified by flash column chromatography (4:1 petrol/EtOAc) to afford TKP 104 as a white powder (20 mg, 38%).

\[
\begin{align*}
\text{Bn} & \quad \text{DPIT, NEt}_3, \text{CH}_2\text{Cl}_2 \quad 0 ^\circ \text{C to rt} \\
12b & \quad \rightarrow \\
\text{Ph} & \quad \text{Bn} \quad \text{N} \\
104 & 
\end{align*}
\]

\(\text{NEt}_3\) (15 µL, 0.109 mmol) was added to a solution of TKP 12b (32 mg, 0.104 mmol) and diphenyliodonium triflate (47 mg, 0.109 mmol) in \(\text{CH}_2\text{Cl}_2\) (0.5 mL) at 0 °C. The reaction mixture was warmed to rt and after 19 h the reaction mixture was concentrated under reduced pressure. Purification by flash column chromatography (\(\text{CH}_2\text{Cl}_2\)) afforded TKP 104 as a white powder (19 mg, 48%).

\(R_f\) 0.52 (1:1 petrol/EtOAc); \(^1\)H NMR (300 MHz, CDCl\(_3\)): \(\delta\) 3.59 (1H, d, \(J = 14.0\) Hz, CHNCH\(_2\)H'), 4.85 (1H, d, \(J = 14.0\) Hz, C(O)NCH\(_2\)H'), 5.04 (1H, d, \(J = 14.0\) Hz, C(O)NCH\(_2\)H'), 5.12 (1H, s, CHPh), 5.54 (1H, d, \(J = 14.0\) Hz, CHNCH\(_2\)H'), 7.13-7.48 (15H, m, 3 x Ph); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 44.5 (C(O)NCH\(_2\)), 47.8 (CHNCH\(_2\)), 63.6 (CHPh), 126.8 (2 x CH, Ph), 128.1 (CH, Ph), 128.5 (2 x CH, Ph), 128.7 (CH, Ph), 129.0 (2 x CH, Ph), 129.1 (4 x CH, Ph), 129.7 (2 x CH, Ph), 129.8 (CH, Ph), 133.8 (C, Ph), 133.9 (C, Ph), 134.9 (C, Ph), 152.9 (CHNC(O)), 156.3 (CHNCO(O)(C)), 166.6 (CHC(O)); IR (neat) \(\nu_{\text{max}}/\text{cm}^{-1}\) 3033w, 1748w, 1691s, 1673s, 1493w, 1451m, 1437m, 1386m, 1370m, 1254m, 1188m; m/z (ES') 385.2 (([M+H]^+), 100%), 769.3 ([2M+H]^+, 30%); HRMS (ES') 385.1560 [M+H]^+, \(C_{24}H_{21}N_2O_3\) requires 385.1552.

**Diphenyliodonium triflate 108**

\[
\begin{align*}
\text{Ph} & \quad \text{I} \\
\text{Ph} & \quad \text{OTf} \quad \text{TFOH, 0 °C} \\
\text{Ph} & \quad \text{Ph} \quad \text{I}^{-} \\
108 & 
\end{align*}
\]

Synthesised according to the literature procedure.\(^{56}\) Iodobenzene (173 µL, 1.55 mmol) and benzene (155 µL, 1.75 mmol) were added to a solution of mCPBA (77% purity, 392 mg, 1.75 mmol) in \(\text{CH}_2\text{Cl}_2\) (6 mL). The solution was cooled to 0 °C and triflic acid (412 µL, 4.65 mmol)
was added dropwise over 5 min to give a suspension. After 10 min the reaction mixture was concentrated under reduced pressure and Et₂O (6 mL) was added. After a further 10 min of stirring the flask was put in the freezer at −20 °C for 30 min. The precipitate was filtered, washed with cold Et₂O (2 x 5 mL) and dried under reduced pressure to afford iodonium salt 108 as pale orange crystals (647 mg, 97%). M.p. 158-159 °C (recrystallised from CH₂Cl₂/Et₂O, lit. 172-174 °C); ¹H NMR (300 MHz, CDCl₃): δ 7.53 (4H, t, J = 7.5 Hz, 4 x CH, Ph), 7.67 (2H, t, J = 7.5 Hz, 2 x CH, Ph), 8.25 (4H, d, J = 7.5 Hz, 4 x CH, Ph); ¹³C NMR (100 MHz, CDCl₃): δ 116.5 (2 x C, Ph), 131.8 (4 x CH, Ph), 132.1 (2 x CH, Ph), 135.2 (4 x CH, Ph); IR (neat) ν max/cm⁻¹ 1472w, 1444w, 1268s, 1243s, 1220s, 1168s, 1024m, 987m.

1,4-Dibenzyl-6-(3-oxobutyl)-6-phenylpiperazine-2,3,5-trione 109

Methyl vinyl ketone (11 µL, 0.130 mmol) was added to a solution of TKP 104 (20 mg, 0.052 mmol) in CH₂Cl₂ (0.3 mL) at rt. Modified quinine catalyst 55 (4 mg, 9.4 µmol) was then added to the reaction mixture which was stirred at rt for 6 h. The solvent was removed under reduced pressure and flash column chromatography (5.5:1 to 4:1 petrol/EtOAc) afforded Michael adduct 109 as a white powder (18 mg, 75%). HPLC analysis was used to determine the er (see Table 8 for er values) (Daicel Chiralpak AD column, [9:1 hexane/IPA], retention times: 17.0 and 25.3 min). Rf 0.39 (1:1 petrol/EtOAc); m.p. 121-123 °C; ¹H NMR (400 MHz, CDCl₃): δ 1.61 (3H, s, CH₃), 1.76-1.83 (2H, m, C(O)CH₂), 2.37-2.46 (1H, m, C(O)CH₂CH'H), 2.95-3.04 (1H, m, C(O)CH₂CH'H), 3.65 (1H, d, J = 15.0 Hz, PhCNCH'H'), 4.94 (1H, d, J = 13.5 Hz, (C(O)NC(H)), 5.10 (1H, d, J = 13.5 Hz, (C(O)NC(H)), 5.23 (1H, d, J = 15.0 Hz, PhCNCH'H'), 7.20-7.44 (15H, m, 3 x Ph); ¹³C NMR (100 MHz, CDCl₃): δ 29.3 (CH₃), 30.0 (C(O)CH₂CH₂), 37.0 (C(O)CH₂), 44.6 (C(O)NCH₂), 48.8 (PhCNCH₂), 72.7 (CPh), 126.2 (2 x CH, Ph), 128.1 (CH, Ph), 128.2 (CH, Ph), 128.6 (2 x CH, Ph), 128.8 (2 x CH, Ph), 129.1 (4 x CH, Ph), 129.5 (CH, Ph), 129.6 (2 x CH, Ph), 135.0 (C, Ph), 136.5 (C, Ph), 157.5 (PhCN(C(O)C(O))), 155.7 (PhCN(C), 169.0 (PhCC(O)), 205.0
(CH$_3$C(O)); IR (neat) $\nu_{\text{max}}$/cm$^{-1}$ 3064w, 2852w, 1744w, 1713w, 1681s, 1495w, 1420m, 1359m, 1266m, 1231m, 1144m, 1030w; m/z (ES$^+$) 477.2 ([M+Na]$^+$, 100%); HRMS (ES$^+$) 477.1788 [M+Na]$^+$, C$_{28}$H$_{26}$N$_2$O$_4$Na requires 477.1790.

tert-Butyl (2-((4-methoxybenzyl)amino)-2-oxo-1-phenylethyl)carbamate 110

![Chemical structure](image)

Synthesised according to the literature procedure.$^{85}$ NEt$_3$ (4.65 mL, 33.3 mmol) and isobutyl chloroformate (4.34 mL, 33.3 mmol) were added slowly to protected phenylglycine 100 (7.61 g, 30.3 mmol) in CH$_2$Cl$_2$ (121 mL) at 0 °C. After stirring for 1 h, p-methoxybenzylamine (4.75 mL, 16.3 mmol) was added and the reaction mixture was stirred for a further 2 h. CH$_2$Cl$_2$ (200 mL) was added and the organic layer was washed with saturated aqueous NaHCO$_3$ (200 mL) and brine (200 mL). The organic layer was then dried with Na$_2$SO$_4$ and concentrated under reduced pressure. Purification by flash column chromatography (2:1 to 3:5 petrol/EtOAc) afforded amide 110 as a pale yellow solid (6.92 g, 62%). R$_f$ 0.50 (1:1 petrol/EtOAc); m.p. 121-122 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.36 (9H, s, C(CH$_3$)$_3$), 3.76 (3H, s, OCH$_3$), 4.29 (1H, s, NHCH'H'), 4.31 (1H, s, NHCH'H'), 5.31 (1H, br s, PhCH), 5.97 (1H, br s, NH), 6.62 (1H, br s, NH), 6.76 (2H, d, $J$ = 8.5 Hz, 2 x CH, PMP), 7.00 (2H, d, $J$ = 8.5 Hz, 2 x CH, PMP), 7.27-7.43 (5H, m, 5 x CH, Ph); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 28.2 (C(CH$_3$)$_3$), 43.0 (CH$_2$), 55.2 (OCH$_3$), 58.3 (CHPh), 80.0 (C(CH$_3$)$_3$), 113.9 (2 x CH, PMP), 127.1 (2 x CH, Ph), 128.2 (CH, Ph), 128.7 (2 x CH, PMP), 128.8 (2 x CH, Ph), 129.8 (CCH$_2$, PMP), 138.5 (CCH, Ph), 155.2 (NHC(O)O), 158.8 (COCH$_3$, PMP), 170.1 (NHC(O)); IR (neat) $\nu_{\text{max}}$/cm$^{-1}$ 3341m, 3306m, 1672s, 1652s, 1559m, 1512s, 1498m, 1365m, 1355m, 1247s, 1157s, 1034s; m/z (ES$^+$) 393.2 ([M+Na]$^+$, 100%); HRMS (ES$^+$) 393.1783 [M+Na]$^+$, C$_{21}$H$_{26}$N$_2$O$_4$Na requires 393.1790.
2-Amino-N-(4-methoxybenzyl)-2-phenylacetamide 111

![Chemical Structure](image)

Synthesised according to the literature procedure.\(^{86}\) Trifluoroacetic acid (21.3 mL) was added carefully to a solution of Boc amide 110 (6.85 g, 18.5 mmol) in \(\text{CH}_2\text{Cl}_2\) (65 mL) at 0 °C and the reaction mixture was warmed to rt and stirred for 2 h. The solvent was then evaporated under reduced pressure and the residue was taken up in EtOAc (500 mL) which was washed with saturated aqueous \(\text{NaHCO}_3\) (400 mL). The organic layer was then dried with \(\text{Na}_2\text{SO}_4\) and concentrated under reduced pressure to afford amine 111 as a yellow oil (4.54 g, 92%). \(R_f\) 0.47 (EtOAc); m.p. 64-67 °C; \(^1\text{H NMR}\) (300 MHz, \(\text{CDCl}_3\)): \(\delta\) 1.97 (2H, br s, NH\(_2\)), 3.80 (3H, s, OCH\(_3\)), 4.37 (1H, s, NHCH\(\text{H}'\)), 4.39 (1H, s, NHCH\(\text{H}'\)), 4.57 (1H, s, CHPh), 6.85 (2H, d, \(J = 7.0\) Hz, 2 x CH, PMP), 7.16 (2H, d, \(J = 7.0\) Hz, 2 x CH, PMP), 7.27-7.45 (5H, m, Ph). C(O)NH proton not observed; \(^{13}\text{C NMR}\) (100 MHz, \(\text{CDCl}_3\)): \(\delta\) 42.8 (CH\(_2\)), 55.3 (OCH\(_3\)), 59.8 (CHPh), 114.0 (2 x CH, PMP), 126.9 (2 x CH, Ph), 128.0 (CH, Ph), 128.8 (2 x CH, Ph), 129.0 (2 x CH, PMP), 130.4 (CCH\(_2\), PMP), 140.9 (C, Ph), 158.9 (C\(\text{OCH}_3\), PMP), 172.7 (NHC(O)); IR (neat) \(\nu_{\text{max}}/\text{cm}^{-1}\): 3257 (br), 2936, 1631, 1612, 1511, 1454, 1303, 1245, 1176, 1026; m/z (ES\(^+\)) 271.1 ([M+H\(^+\)], 100%); HRMS (ES\(^+\)) 271.1444 [M+H\(^+\)], \(\text{C}_{16}\text{H}_{19}\text{N}_2\text{O}_2\) requires 271.1447.

\(N\)-(4-Methoxybenzyl)-2-((4-methoxybenzyl)amino)-2-phenylacetamide 112

![Chemical Structure](image)

Synthesised according to the literature procedure.\(^{87}\) Anisaldehyde (569 µL, 4.67 mmol) was added to a solution of amine 111 (1.20 g, 4.45 mmol) in EtOH (40 mL) and stirred at rt for 21 h. The reaction mixture was then cooled to 0 °C, NaBH\(_4\) (370 mg, 9.79 mmol) was added and stirring was continued at rt for 23 h. The reaction mixture was then carefully quenched with H\(_2\)O (100 mL) and extracted with \(\text{CH}_2\text{Cl}_2\) (3 x 200 mL). The combined organic layers were dried
with Na$_2$SO$_4$ and concentrated under reduced pressure. Flash column chromatography (4:1 to 2:1 petrol/EtOAc, 2% NEt$_3$) afforded amino amide 112 as yellow oil (1.09 g, 63%). R$_f$ 0.21 (1:1 petrol/EtOAc); $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 3.70 (2H, s, CHNCH$_2$), 3.80 (6H, s, 2 x OCH$_3$), 4.31 (1H, s, CPh), 4.38 (1H, s, C(O)NHCH$_2$), 4.40 (1H, s, C(O)NHCHH'), 6.81-6.89 (4H, m, 4 x CH, PMP), 7.12-7.21 (4H, m, 4 x CH, PMP), 7.28-7.41 (5H, m, Ph); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 42.6 (C(O)NHCH$_2$), 51.8 (NHCH$_2$), 55.2 (2 x OCH$_3$, PMP), 66.8 (CHPh), 113.9 (2 x CH, PMP), 114.0 (2 x CH, PMP), 127.3 (2 x CH, Ph), 128.1 (2 x CH, Ph), 128.8 (2 x CH, PMP), 129.0 (2 x CH, PMP), 129.4 (2 x CH, Ph), 130.4 (CCH$_2$, PMP), 131.2 (CCH$_2$, PMP), 139.2 (C, Ph), 158.8 (COCH$_3$, PMP), 158.9 (COCH$_3$, PMP), 171.8 (NHC(O)); IR (neat) $\nu$$_{max}$/cm$^{-1}$ 3308 w (br), 2934w, 2835w, 1654m, 1611m, 1511s, 1454m, 1243s, 1175m, 1031m; m/z (ES$^+$) 391.2 ([M+H]$^+$, 100%); HRMS (ES$^+$) 391.2030 [M+H]$^+$, C$_{24}$H$_{27}$N$_2$O$_3$ requires 391.2022.

1,4-Bis(4-methoxybenzyl)-6-phenylpiperazine-2,3,5-trione 113

A solution of amino amide 112 (52 mg, 0.134 mmol) in THF (0.4 mL) was added to a suspension of oxalyl benzotriazole (45 mg, 0.154 mmol) in THF (1.3 mL) in a microwave vial. The vial was then heated at 150 °C with stirring for 1 h in the microwave. The reaction mixture was concentrated under reduced pressure and then purified by flash column chromatography (100:0 to 95:5 CH$_2$Cl$_2$/Et$_2$O) to afford TKP 113 as a white solid (17 mg, 28%). R$_f$ 0.39 (1:1 petrol/EtOAc); m.p. 150-152 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 3.52 (1H, d, $J$ = 14.5 Hz, CHNCHH'), 3.76 (3H, s, OCH$_3$), 3.81 (3H, s, OCH$_3$), 4.78 (1H, d, $J$ = 13.5 Hz, C(O)NCHH'), 4.98 (1H, d, $J$ = 13.5 Hz, C(O)NCHH'), 5.10 (1H, s, CPh), 5.47 (1H, d, $J$ = 14.5 Hz, CHNCHH'), 6.74 (2H, d, $J$ = 9.0 Hz, 2 x CH, PMP), 6.85 (2H, d, $J$ = 9.0 Hz, 2 x CH, PMP), 7.10 (2H, d, $J$ = 9.0 Hz, 2 x CH, PMP), 7.19-7.28 (4H, m, 2 x CH, PMP and 2 x CH, Ph), 7.37-7.47 (3H, m, 3 x CH, Ph); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 44.0 (C(O)NCH$_2$), 47.2 (CHNCH$_2$), 55.2 (OCH$_3$), 55.3 (OCH$_3$), 63.3 (CPh), 113.8 (2 x CH, PMP), 114.4 (2 x CH, PMP), 125.7 (CCH$_2$, PMP), 126.8 (2 x CH, Ph), 127.2
(CCH$_2$, PMP), 129.6 (2 x CH, PMP), 129.8 (2 x CH, PMP), 130.6 (CH, Ph), 130.7 (2 x CH, Ph), 134.0 (C, Ph), 152.8 (CHNC(O)), 156.3 (CHNC(O)C(O)), 159.3 (COCH$_3$, PMP), 159.8 (COCH$_3$, PMP), 166.7 (CHC(O)); IR (neat) $\nu_{\text{max}}$/cm$^{-1}$ 2959w, 2835w, 1750w, 1691s, 1673s, 1612m, 1513s, 1432m, 1305m, 1238s, 1210m, 1190m, 1173m, 1028m; m/z (ES$^+$) 467.2 ([M+Na]$^+$, 100%); HRMS (ES$^+$) 467.1599 [M+Na]$^+$, C$_{26}$H$_{24}$N$_2$O$_5$Na requires 467.1583.

1,4-Bis(4-methoxybenzyl)-6-(3-oxobutyl)-6-phenylpiperazine-2,3,5-trione 117

Methyl vinyl ketone (13 µL, 0.155 mmol) was added to a solution of TKP 113 (28 mg, 0.062 mmol) in CH$_2$Cl$_2$ (0.4 mL) at rt. Modified quinine catalyst 58 (5 mg, 12 µmol) was then added to the reaction mixture and stirred at rt for 72 h. Solvent was removed under reduced pressure and flash column chromatography (4:1 to 2:1 petrol/EtOAc) afforded Michael adduct 117 as a white solid (32 mg, quant). HPLC analysis was used to determine the er (see Table 9 for er values) (Daicel Chiralpak OD column, [4:1 hexane/IPA], retention times: 21.7 and 30.1 min). R$_f$ 0.47 (1:1 petrol/EtOAc); m.p. 145-147 °C; $^1$H NMR (300 MHz, CDCl$_3$): $\delta$ 1.74 (3H, s, C(O)CH$_3$), 1.82-1.92 (2H, m, C(O)CH$_2$), 2.46-2.59 (1H, m, C(O)CH$_2$CH$\cdot$H'), 3.00-3.15 (1H, m, C(O)CH$_2$CH$\cdot$H'), 3.68 (1H, d, $J = 14.5$ Hz, PhCNCH$\cdot$H'), 3.82 (3H, s, OCH$_3$), 3.83 (3H, s, OCH$_3$), 4.95 (1H, d, $J = 13.5$ Hz, C(O)NCH$\cdot$H'), 5.12 (1H, d, $J = 13.5$ Hz, C(O)NCH$\cdot$H'), 5.19 (1H, d, $J = 14.5$ Hz, PhCNCH$\cdot$H'), 6.76-6.87 (4H, m, 4 x CH, PMP), 7.25-7.36 (4H, m, 4 x CH, PMP), 7.38-7.52 (5H, m, Ph); $^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 29.3 (CH$_3$), 30.1 (C(O)CH$_2$CH$_2$), 37.0 (C(O)CH$_3$), 44.1 (C(O)NCH$_3$), 48.2 (PhCNCH$_3$), 55.2 (OCH$_3$), 55.3 (OCH$_3$), 72.5 (CPh), 113.8 (2 x CH, PMP), 114.0 (2 x CH, PMP), 126.2 (2 x CH, Ph), 127.2 (CCH$_2$, PMP), 128.5 (CCH$_2$, PMP), 129.4 (CH, Ph), 129.5 (2 x CH, Ph), 130.6 (2 x CH, PMP), 130.7 (2 x CH, PMP), 137.9 (C, Ph), 154.9 (PhCN(CO)), 155.8 (PhCN(CO)C(O)), 159.3 (COCH$_3$, PMP), 159.4 (COCH$_3$, PMP), 169.1 (PhCC(O)), 205.2 (CH$_3$C(O)); IR (neat) $\nu_{\text{max}}$/cm$^{-1}$ 2958w, 1717w, 1681s, 1611w, 1512s, 1364m, 1247s, 1178m, 1031m; m/z

**1,4-Bis(4-methoxybenzyl)-6-(3-oxo-3-phenylpropyl)-6-phenylpiperazine-2,3,5-trione 118**

Phenyl vinyl ketone (13 µL, 0.101 mmol) was added to a solution of TKP 113 (18 mg, 0.040 mmol) in CH₂Cl₂ (0.24 mL) at rt. Modified quinine catalyst 58 (3 mg, 8 µmol) was then added to the reaction mixture and stirred at rt for 21 h. Solvent was removed under reduced pressure and flash column chromatography (7:2 to 2:1 petrol/EtOAc) afforded Michael adduct 118 as a white powder (21 mg, 91%). HPLC analysis was used to determine the er (see Table 9 for er values) (Daicel Chiralpak OD column, [4:1 hexane/IPA], retention times: 18.2 and 25.3 min). Rf 0.42 (1:1 petrol/EtOAc); m.p. 174-175 ºC; ³H NMR (300 MHz, CDCl₃): δ 2.22-2.37 (2H, m, C(O)CH₂), 2.55-2.75 (1H, m, C(O)CH₂CHH'), 3.09-3.28 (1H, m, C(O)CH₂CHH'), 3.44 (3H, s, OCH₃), 3.64 (1H, d, J = 14.5 Hz, PhCNC₃H₃), 3.67 (3H, s, OCH₃), 4.91 (1H, d, J = 13.5 Hz, C(O)NCH₂H'), 5.07 (1H, d, J = 13.5 Hz, C(O)NCHH'), 5.18 (1H, d, J = 14.5 Hz, PhCNCH₃H'), 6.47-6.55 (2H, m, 2 x CH, PMP), 6.69-6.78 (2H, m, 2 x CH, PMP), 7.13-7.21 (2H, m, 2 x CH, PMP), 7.28-7.55 (12H, m, 2 x Ph, 2 x CH, PMP); ¹³C NMR (100 MHz, CDCl₃): δ 30.5 (C(O)CH₂CH₂), 32.2 (C(O)CH₂), 44.0 (C(O)NCH₂), 48.3 (PhCNCH₂), 54.9 (OCH₃), 55.1 (OCH₃), 72.6 (CPh), 113.9 (2 x CH, PMP), 113.9 (2 x CH, PMP), 126.3 (2 x CH, Ph), 127.4 (CCH₂, PMP), 127.5 (2 x CH, Ph), 128.3 (2 x CH, Ph), 128.3 (CCH₂, PMP), 129.4 (C, Ph), 129.5 (2 x CH, Ph), 130.3 (2 x CH, PMP), 130.8 (2 x CH, PMP), 133.1 (CH, Ph), 135.9 (C, Ph), 138.0 (C, Ph), 155.0 (PhCNC(O)), 155.8 (PhCNC(O)C(O)), 159.0 (COCH₃, PMP), 159.4 (COCH₃, PMP), 169.2 (PhCC(O)), 196.8 (C(O)Ph); IR (neat) νmax/cm⁻¹ 2958w, 1678s, 1610m, 1512s, 1364m, 1302m, 1246s, 1177m; m/z (ES') 599.2 ([M+Na]⁺, 100%); HRMS (ES') 599.2164 [M+Na]⁺, C₃₅H₃₂N₂O₆Na requires 599.2158; [α]₀ −3.2° (c = 1.0, CHCl₃, 23 ºC).
Cyclohexyl vinyl ketone (18 µL, 0.118 mmol) was added to a solution of TKP 113 (21 mg, 0.047 mmol) in CH₂Cl₂ (0.28 mL) at rt. Modified quinine catalyst 58 (4 mg, 9 µmol) was then added to the reaction mixture and stirred at rt for 45 h. Solvent was removed under reduced pressure and flash column chromatography (3:1 petrol/EtOAc) afforded Michael adduct 119 as a colourless solid (26 mg, 96%). HPLC analysis was used to determine the er (see Table 9 for er values) (Daicel Chiralpak OD column, [9:1 hexane/IPA], retention times: 28.4 and 37.7 min). Rf 0.42 (1% MeOH in CH₂Cl₂); m.p. 64-67 °C; ¹H NMR (300 MHz, CDCl₃): δ 0.80-1.45 (6H, m, 3 x CH₂, Cy), 1.50-1.77 (7H, m, 2 x CH₂, CH, Cy and C(O)CH₂), 2.35-2.51 (1H, m, C(O)CH₂C'H'), 2.87-3.03 (1H, m, C(O)CH₂CH'H'), 3.55 (1H, d, J = 14.5 Hz, PhCNCH'H'), 3.72 (3H, s, OCH₃), 3.75 (3H, s, OCH₃), 4.87 (1H, d, J = 13.0 Hz, C(O)NCH'H', 5.03-5.15 (2H, m, C(O)NCHH' and PhCNCH'H'), 6.66-6.79 (4H, m, 4 x CH, PMP), 7.18-7.48 (9H, m, 4 x CH, PMP and 5 x CH, Ph); ¹³C NMR (100 MHz, CDCl₃): δ 25.3 (CH₂, Cy), 25.5 (CH₂, Cy), 25.6 (CH₂, Cy), 28.0 (CH₂, Cy), 28.4 (CH₂, Cy), 30.3 (C(O)CH₂CH₂), 33.9 (C(O)CH₂), 44.0 (C(O)NCH₂), 48.3 (PhCNCH₂), 50.4 (C(O)CH), 55.1 (2 x OCH₃), 72.6 (CPh), 113.8 (2 x CH, PMP), 113.9 (2 x CH, PMP), 126.4 (2 x CH, Ph), 127.3 (CCH₂, PMP), 128.6 (CCH₂, PMP), 129.4 (CH, Ph), 129.5 (2 x CH, Ph), 130.6 (2 x CH, PMP), 130.8 (2 x CH, PMP), 138.1 (C, Ph), 154.8 (PhCN(CO)), 155.8 (PhCN(CO)C(O)), 159.2 (COCH₃, PMP), 159.4 (COCH₃, PMP), 169.2 (PhCC(O)), 210.5 (C(O)Cy); IR (neat) ν max/cm⁻¹ 2930m, 1681s, 1512s, 1365m, 1302m, 1246s, 1178m, 1032m; m/z (ES⁺) 605.3 ([M+Na]⁺, 100%); HRMS (ES⁺) 605.2625 [M+Na]⁺, C₃₅H₇₆N₂O₆Na requires 605.2628; [α]D ~4.1° (c = 1.0, CHCl₃, 23 °C).
1,4-Bis(4-methoxybenzyl)-6-(3-oxopentyl)-6-phenylpiperazine-2,3,5-trione 115

Ethyl vinyl ketone (11 µL, 0.112 mmol) was added to a solution of TKP 113 (20 mg, 0.045 mmol) in CH$_2$Cl$_2$ (0.27 mL) at rt. Modified quinine catalyst 58 (4 mg, 9 µmol) was then added to the reaction mixture and stirred at rt for 20 h. Solvent was removed under reduced pressure and flash column chromatography (7:2 petrol/EtOAc) afforded Michael adduct 115 as a colourless solid (26 mg, 96%). HPLC analysis was used to determine the er (see Table 9 for er values) (Daicel Chiralpak OD column, [9:1 hexane/IPA], retention times: 28.4 and 37.7 min). R$_f$ 0.41 (1:1 petrol/EtOAc); m.p. 120-122 °C; $^1$H NMR (300 MHz, CDCl$_3$): δ 0.79 (3H, t, $J = 7.5$ Hz, CH$_3$), 1.65-1.99 (4H, m, CH$_2$C(O)CH$_2$), 2.39-2.53 (1H, m, C(O)CH$_2$CHH$'$), 2.93-3.09 (1H, m, C(O)CH$_2$CHH$'$), 3.60 (1H, d, $J = 14.5$ Hz, PhCNCHH$'$), 3.73 (3H, s, OCH$_3$), 3.75 (3H, s, OCH$_3$), 4.87 (1H, d, $J = 13.5$ Hz, C(O)NCHH$'$), 5.03 (1H, d, $J = 13.5$ Hz, C(O)NCHH$'$), 5.12 (1H, d, $J = 14.5$ Hz, C(O)NCHH$'$), 6.67-6.78 (4H, m, 4 x CH, PMP), 7.17-7.27 (4H, m, 4 x CH, PMP), 7.30-7.45 (5H, m, Ph); $^{13}$C NMR (100 MHz, CDCl$_3$): δ 7.5 (CH$_3$), 30.1 (C(O)CH$_2$CH$_2$), 35.4 (C(O)CH$_2$), 35.6 (C(O)CH$_2$), 44.1 (C(O)NCH$_2$), 48.2 (PhCNCH$_2$), 55.2 (2 x OCH$_3$), 72.5 (CPh), 113.8 (2 x CH, PMP), 113.9 (2 x CH, PMP), 126.2 (2 x CH, Ph), 127.3 (CCH$_2$, PMP), 128.5 (CCH$_2$, PMP), 129.4 (CH, Ph), 129.5 (2 x CH, Ph), 130.6 (2 x CH, PMP), 130.7 (2 x CH, PMP), 138.0 (C, Ph), 154.9 (PhCN(CO)$_2$)), 155.8 (PhCN(CO)(C)(O)), 159.2 (COCH$_3$, PMP), 159.4 (COCH$_3$, PMP), 169.1 (PhCC(O)), 208.0 (C(O)CH$_2$CH$_3$); IR (neat) $\nu_{\text{max}}$/cm$^{-1}$ 1715 w, 1682 s, 1513 s, 1365 m, 1303 m, 1247 s, 1178 m, 1032 m; m/z (ES$^+$) 551.2 ([M+H]$^+$, 100%); HRMS (ES$^+$) 551.5156 [M+H]$^+$, C$_{31}$H$_{32}$N$_2$O$_6$Na requires 551.2158; [α]$^\text{D}$ −12.0° ($c = 1.0$, CHCl$_3$, 23 °C).
Acrolein (15 µL, 0.231 mmol) was added to a solution of TKP 113 (21 mg, 0.046 mmol) in CH₂Cl₂ (0.5 mL) at rt. Modified quinine catalyst 58 (4 mg, 9 µmol) was then added to the reaction mixture and stirred at rt for 72 h. Solvent was removed under reduced pressure and flash column chromatography (3:1 petrol/EtOAc) afforded Michael adduct 120 as a colourless solid (10 mg, 43%). Rf 0.39 (1:1 petrol/EtOAc); m.p. not obtainable; ¹H NMR (300 MHz, CDCl₃): δ 1.80-1.93 (2H, m, C(O)CH₂), 2.44-2.56 (1H, m, C(O)CH₂C₂H), 3.01-3.14 (1H, m, C(O)CH₂CH), 3.59 (1H, d, J = 14.5 Hz, PhCNC₂H), 3.74 (3H, s, OCH₃), 3.76 (3H, s, OCH₃), 4.87 (1H, d, J = 13.0 Hz, C(O)NCH₂), 5.01 (1H, d, J = 13.0 Hz, C(O)NC₂H), 5.18 (1H, d, J = 14.5 Hz, PhCNCH₂), 6.69-6.79 (4H, m, 4 x CH, PMP), 7.18-7.29 (4H, m, 4 x CH, PMP), 7.30-7.46 (5H, m, Ph), 9.17 (1H, s, CHO); ¹³C NMR (100 MHz, CDCl₃): δ 28.4 (C(O)CH₂CH₂), 38.0 (C(O)CH₂), 44.2 (C(O)NCH₂), 48.3 (PhCNCH₂), 55.2 (OCH₃), 55.3 (OCH₃), 72.5 (CPh), 113.9 (2 x CH, PMP), 114.0 (2 x CH, PMP), 126.1 (2 x CH, Ph), 127.2 (CCH₂, PMP), 128.4 (CCH₂, PMP), 129.5 (CH, Ph), 129.6 (2 x CH, Ph), 130.4 (2 x CH, PMP), 130.7 (2 x CH, PMP), 137.8 (C, Ph), 155.0 (PhCN(O)), 155.6 (PhCN(O)C(O)), 159.3 (COCH₃, PMP), 159.4 (COCH₃, PMP), 168.9 (PhCC(O)), 198.3 (CHO); IR (neat) νmax/cm⁻¹ 2937w, 1686s, 1514s, 1366w, 1303w, 1248s, 1179m, 1033m; m/z (ES⁺) 501.2 ([M+H]+, 10%), 1001.4 ([2M+H]⁺, 100%); HRMS (ES⁺) 501.2030 [M+H]+, C₂₉H₂₉N₂O₆ requires 501.2026.

6-(2-(1,3-Dioxolan-2-yl)ethyl)-1,4-bis(4-methoxybenzyl)-6-phenylpiperazine-2,3,5-trione 121
Acrolein Michael adduct 120 (10 mg, 0.020 mmol) was added to a solution of p-toluenesulfonic acid monohydrate (1 mg, 5 µmol) in 2-ethyl-2-methyl-1,3-dioxolane (100 µL). The reaction mixture was stirred at rt for 18 h, diluted with H₂O (5 mL) and extracted with CH₂Cl₂ (3 x 5 mL). The combined organic layers were then dried with Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography (5:2 to 5:3 petrol/EtOAc) afforded acetal 121 as a white solid (5 mg, 45%). HPLC analysis was used to determine the er (see Table 9 for er values) (Daicel Chiralpak OD column, [4:1 hexane/IPA], retention times: 27.0 and 34.3 min). 

Rf 0.29 (1:1 petrol/EtOAc); m.p. 157-159 °C; ¹H NMR (300 MHz, CDCl₃): δ 1.07-1.23 (2H, m, PhCCH₂CH₂), 2.21-2.35 (1H, m, PhCC₁H₂'), 2.80-2.92 (1H, m, PhCCH'H), 3.64-3.73 (4H, m, OCH₂CH₂O), 3.75 (3H, s, OCH₃), 3.76 (3H, s, OCH₃), 3.86 (1H, d, J = 14.5 Hz, PhCNCH'H), 4.39 (1H, t, J = 5.0 Hz, PhCCH₂CH₂CH), 4.85 (1H, d, J = 14.5 Hz, PhCNCH'H), 4.90 (1H, d, J = 13.5 Hz, C(O)NCH'H), 5.03 (1H, d, J = 13.5 Hz, C(O)NCH'H), 6.68-6.79 (4H, m, 4 x CH, PMP), 7.09-7.15 (2H, m, 2 x CH, PMP), 7.23-7.39 (7H, m, 2 x CH, PMP, 5 x CH, Ph); ¹³C NMR (100 MHz, CDCl₃): δ 28.4 (PhCCH₂), 30.6 (PhCCH₂CH₂), 44.1 (C(O)NCH₂), 48.1 (PhCNCH₂), 55.2 (OCH₃), 55.3 (OCH₃), 64.7 (OCH₂CH₂O), 72.8 (CPh), 103.0 (PhCCH₂CH₂CH), 113.7 (2 x CH, PMP), 113.8 (2 x CH, PMP), 126.4 (2 x CH, Ph), 127.3 (CCH₂, PMP), 128.4 (CCH₂, PMP), 129.2 (CH, Ph), 129.3 (2 x CH, Ph), 130.7 (2 x CH, PMP), 130.8 (2 x CH, PMP), 138.4 (C, Ph), 154.7 (PhCNC(O)), 155.9 (PhCN(C(O)C(O))), 159.1 (COCH₃, PMP), 159.3 (COCH₃, PMP), 169.5 (PhCC(O)); IR (neat) νmax/cm⁻¹ 2955w, 1686s, 1514s, 1367m, 1303m, 1248s, 1179m, 1032m; m/z (ES⁺) 545.2 ([M+H]⁺, 100%); HRMS (ES⁺) 545.2292 [M+H]⁺, C₃₁H₃₃N₂O₇ requires 545.2288.
4. **List of References**


(24) Braude, E. A.; Nachod, F. C. *Determination of organic structures by physical methods;*


5. APPENDIX

![Graph 1](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time (min)</th>
<th>Peak Name</th>
<th>Height (mAU)</th>
<th>Area (mAU*min)</th>
<th>Rel.Area (%)</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16.96</td>
<td>n.a.</td>
<td>636.401</td>
<td>553.819</td>
<td>50.56</td>
<td>n.a.</td>
<td>BMB</td>
</tr>
<tr>
<td>2</td>
<td>25.34</td>
<td>n.a.</td>
<td>418.726</td>
<td>550.780</td>
<td>49.42</td>
<td>n.a.</td>
<td>BMB</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>1064.627</td>
<td>1114.599</td>
<td>100.00</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

![Graph 2](image)

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time (min)</th>
<th>Peak Name</th>
<th>Height (mAU)</th>
<th>Area (mAU*min)</th>
<th>Rel.Area (%)</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16.09</td>
<td>n.a.</td>
<td>111.253</td>
<td>123.174</td>
<td>9.03</td>
<td>n.a.</td>
<td>BMB</td>
</tr>
<tr>
<td>2</td>
<td>23.12</td>
<td>n.a.</td>
<td>823.869</td>
<td>1240.666</td>
<td>90.97</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>935.122</td>
<td>1363.840</td>
<td>100.00</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>
### Table 1

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time (min)</th>
<th>Peak Name</th>
<th>Height (mAU)</th>
<th>Area (mAU)</th>
<th>Rel.Area (%)</th>
<th>Amount (%)</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28.37</td>
<td>n.a.</td>
<td>207.994</td>
<td>583.585</td>
<td>50.08</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
<td>2</td>
<td>37.69</td>
<td>n.a.</td>
<td>146.959</td>
<td>581.778</td>
<td>49.92</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>354.953</td>
<td>1165.463</td>
<td>100.00</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

### Table 2

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret.Time (min)</th>
<th>Peak Name</th>
<th>Height (mAU)</th>
<th>Area (mAU)</th>
<th>Rel.Area (%)</th>
<th>Amount (%)</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>18.79</td>
<td>n.a.</td>
<td>281.165</td>
<td>991.314</td>
<td>94.09</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
<td>2</td>
<td>29.02</td>
<td>n.a.</td>
<td>13.878</td>
<td>37.131</td>
<td>5.91</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>295.043</td>
<td>829.445</td>
<td>100.00</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>
### Chiral Method RAC #2 (modified by Administrator)

**UV VIS 1**

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret. Time (min)</th>
<th>Peak Name</th>
<th>Height (mAU)</th>
<th>Area (mAU*min)</th>
<th>Rel. Area (%)</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>28.37</td>
<td>n.a.</td>
<td>207.994</td>
<td>583.685</td>
<td>50.08</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
<td>2</td>
<td>37.89</td>
<td>n.a.</td>
<td>146.965</td>
<td>691.778</td>
<td>49.92</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>354.953</td>
<td>1155.463</td>
<td>100.00</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>

### Chiral Method ASY #1 (modified by Administrator)

**UV VIS 2**

<table>
<thead>
<tr>
<th>No.</th>
<th>Ret. Time (min)</th>
<th>Peak Name</th>
<th>Height (mAU)</th>
<th>Area (mAU*min)</th>
<th>Rel. Area (%)</th>
<th>Amount</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>29.78</td>
<td>n.a.</td>
<td>18.578</td>
<td>53.225</td>
<td>7.00</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
<td>2</td>
<td>37.66</td>
<td>n.a.</td>
<td>179.903</td>
<td>707.556</td>
<td>93.00</td>
<td>n.a.</td>
<td>BMB*</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td>198.481</td>
<td>760.780</td>
<td>100.00</td>
<td>0.000</td>
<td></td>
</tr>
</tbody>
</table>