AN INVESTIGATION INTO ORGANOCATALYTIC MICHAEL ADDITIONS

by

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

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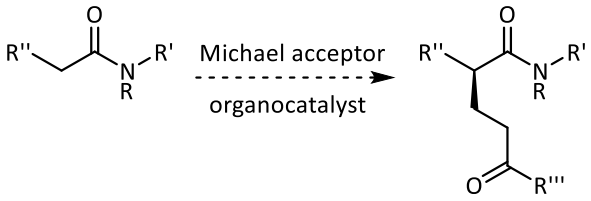
University of Birmingham

January 2015

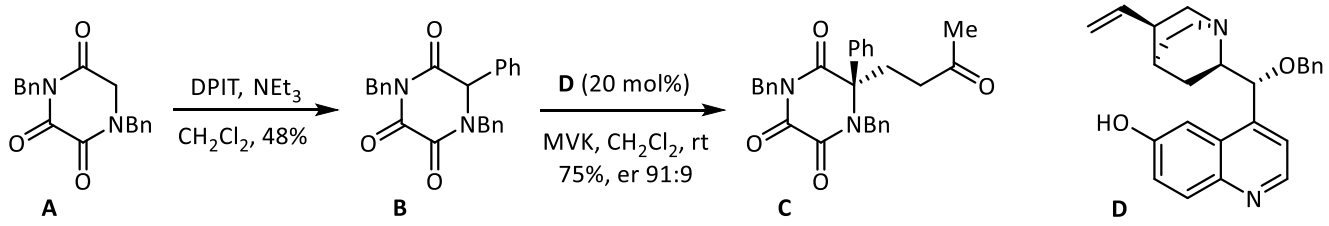
ABSTRACT

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.

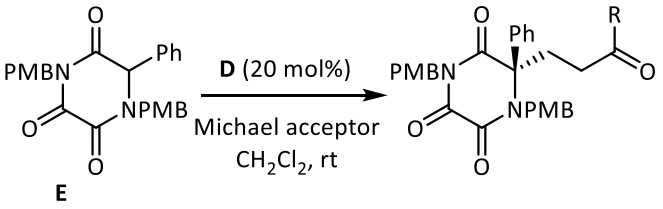


Cyclic substrates such as hydantoins and the drug thalidomide did not show any reactivity under the Michael addition conditions. Acyclic substrates were also tested and some limited success was achieved with an α-phenyl amide substrate. However, a strongly basic guanidine catalyst was required, so investigations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



E

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 in to 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

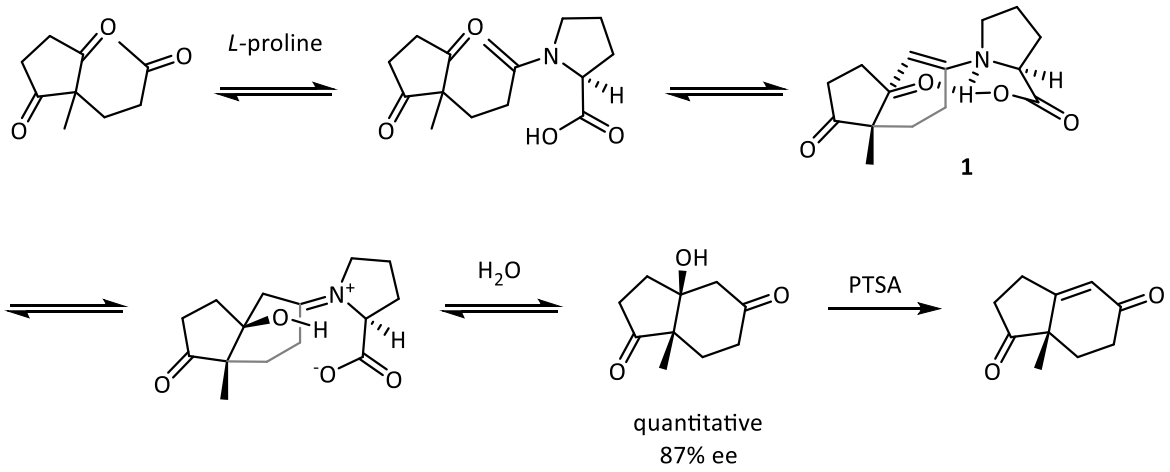
μW	microwave	IPA	isopropyl alcohol
Ac	acetyl	*i*Pr	isopropyl
Bn	benzyl	LDA	lithium diisopropylamide
Boc	*tert*-butyloxycarbonyl	LHMDS	lithium bis(trimethylsilyl)amide
Bzt	benzotriazole	LUMO	lowest unoccupied molecular orbital
CAN	ceric ammonium nitrate	m.p.	melting point
cf.	compare	mCPBA	*meta*-chloroperbenzoic acid
COSY	correlation spectroscopy	min	minute(s)
Cy	cyclohexyl	MVK	methyl vinyl ketone
DCC	dicyclohexyl carbodiimide	NMR	nuclear magnetic resonance
DDQ	2,3-dichloro-5,6-dicyano-*p*-benzoquinone	NOE	nuclear Overhauser effect
DEAD	diethyl azodicarboxylate	NR	no reaction
DIAD	diisopropyl azodicarboxylate	PMB	*p*-methoxybenzyl
DIPEA	diisopropylethylamine	PMP	*p*-methoxyphenyl
DKP	diketopiperazine	ppm	parts per million
DMAP	4-(dimethylamino)pyridine	PTSA	*p*-toluenesulfonic acid
DMF	dimethylformamide	Py	pyridine
DMSO	dimethyl sulfoxide	quant	quantitative yield
DPIT	diphenyliodonium triflate	rt	room temperature
DPPA	diphenylphosphoryl azide	SM	starting material
dr	diastereomeric ratio	*t*Bu	*tert*-butyl
ee	enatiomeric excess	TFA	trifluoroacetic acid
equiv	equivalents	TFAA	trifluoroacetic anhydride
er	enantiomeric ratio	TfO	trifluoromethanesulfonate
h	hour(s)	THF	tetrahydrofuran
HMBC	heteronuclear multiple bond correlation	TKP	triketopiperazine
HPLC	high performance liquid chromatography	tlc	thin later chromatography
HRMS	high resolution mass spectrometry	TMG	1,1,3,3-tetramethylguanidine
HSQC	heteronuclear single quantum correlation	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.

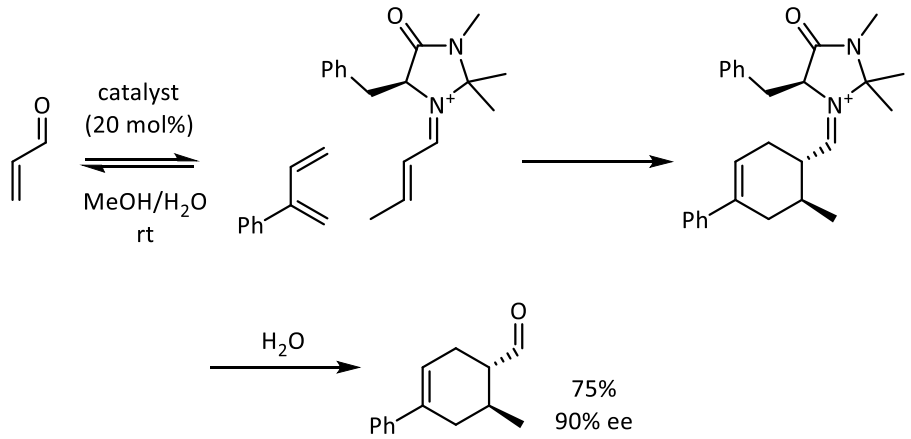
Early work in this area focused on the use of amines to give enamine or iminium intermediates which were then used in reactions such as the aldol reaction. The Hajos–Parrish–Eder–Sauer–Wiechert reaction uses proline as a readily available asymmetric organocatalyst and has been used in the synthesis of 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]



Scheme 1 - Hajos–Parrish–Eder–Sauer–Wiechert reaction

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

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).

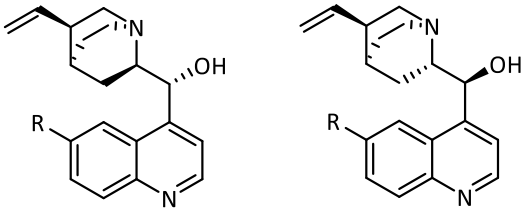
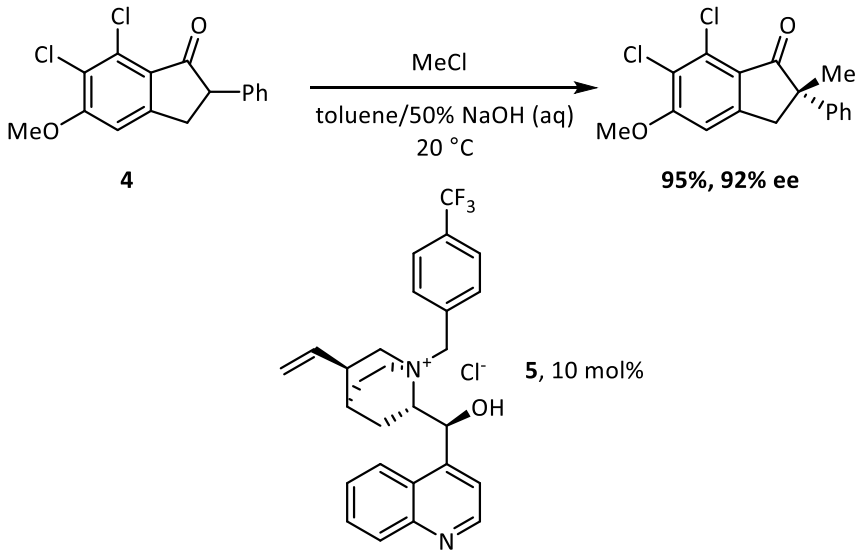


Figure 1 - cinchona alkaloids

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]

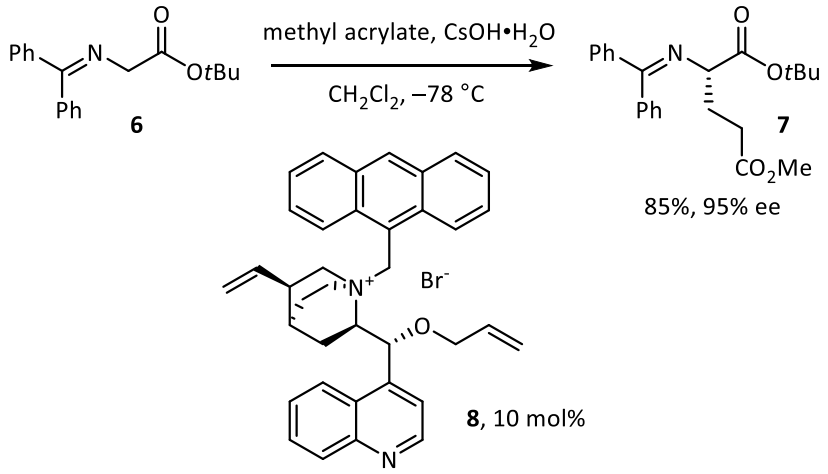


4 **95%, 92% ee**

Scheme 3 – Dolling and co-workers asymmetric alkylation

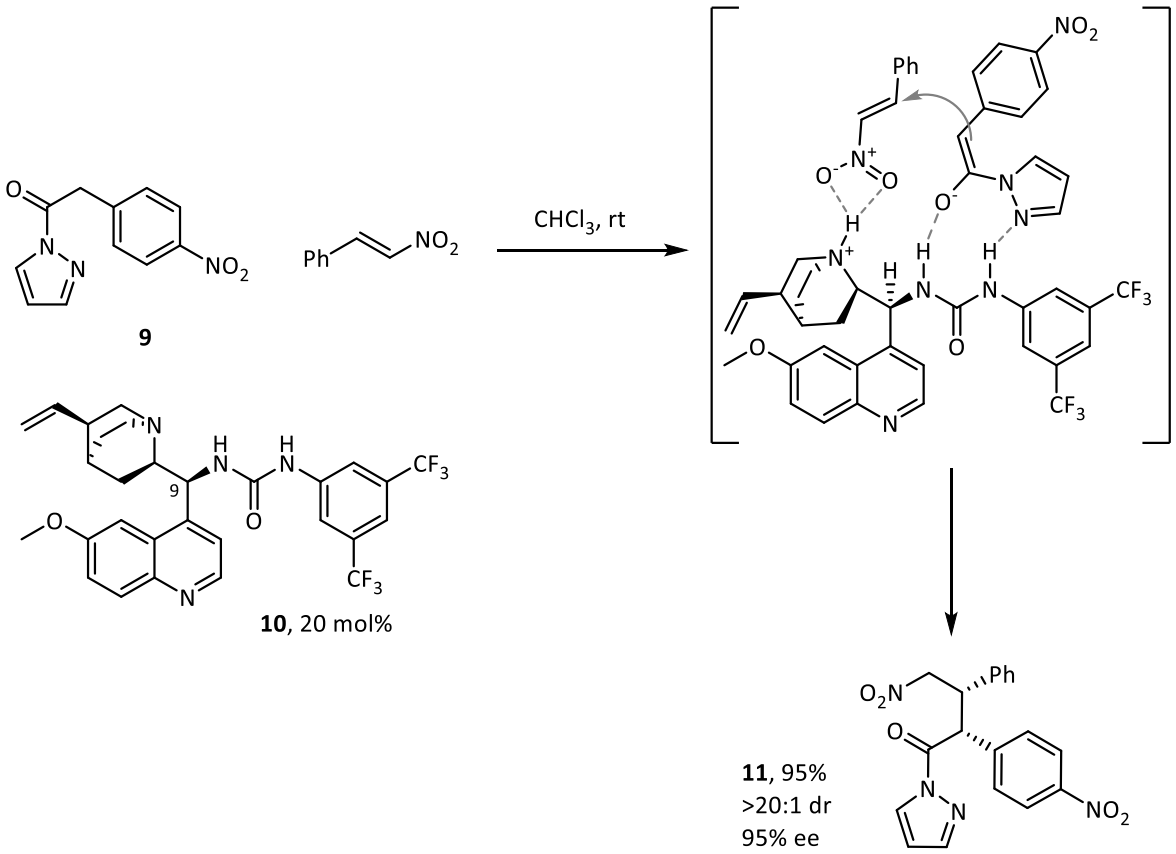
One well explored area of cinchona catalysis is the alkylation of glycine imino esters, such as **6** (scheme 4), under phase-transfer conditions to give natural and unnatural chiral α-amino acids. The free amine of the amino acid is converted to the imine by reacting with benzophenone imine and this 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

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 **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.[10]



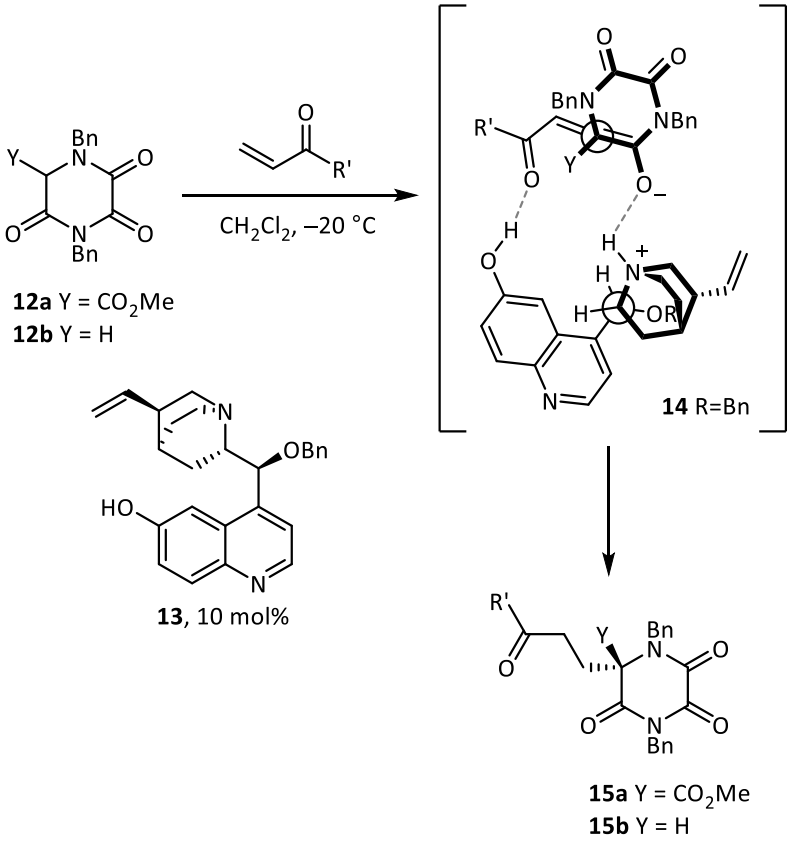
Scheme 5 - Barbas' Michael additions with pyrazoleamides

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 stephacidins.[11–16] 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 α-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).[17] 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, where as it is suspected that products **15b** do suffer erosion of their ee due to epimerisation occurring.



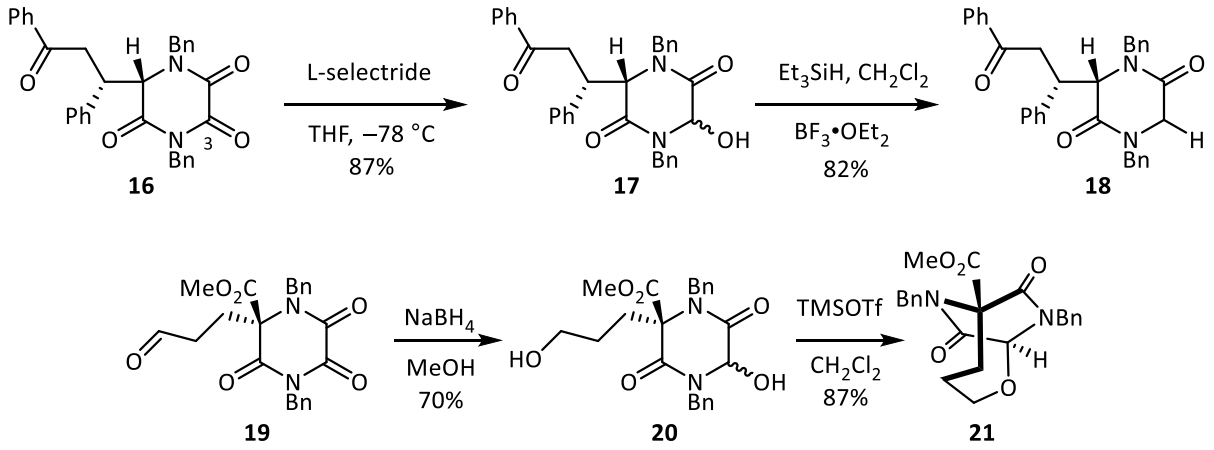
entry	TKP	R	yield (%)	ee (%)[a]
1	**12a**	Me	99	98
2	**12a**	H	99	99[b]
3	**12a**	*p*-C_6H_4Br	98	98
4	**12b**	Me	80	87
5	**12b**	H	74	37[b]
6	**12b**	*p*-C_6H_4Br	97	58

[a] determined by HPLC analysis
[b] 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).[17]



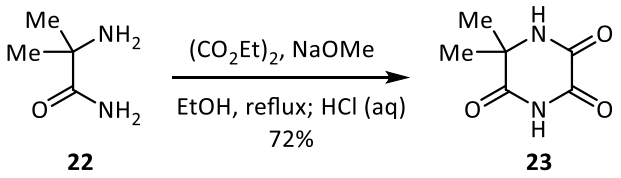
Scheme 6 - further transformations of TKPs

Alternatively, when acrolein is used as the Michael acceptor, the resultant alcohol **20** after reduction with $NaBH_4$ can undergo an *N*-acyliminium cyclisation under Lewis acidic conditions to give bicyclic product **21** (Scheme 6).[17]

1.4. Synthesis of TKPs

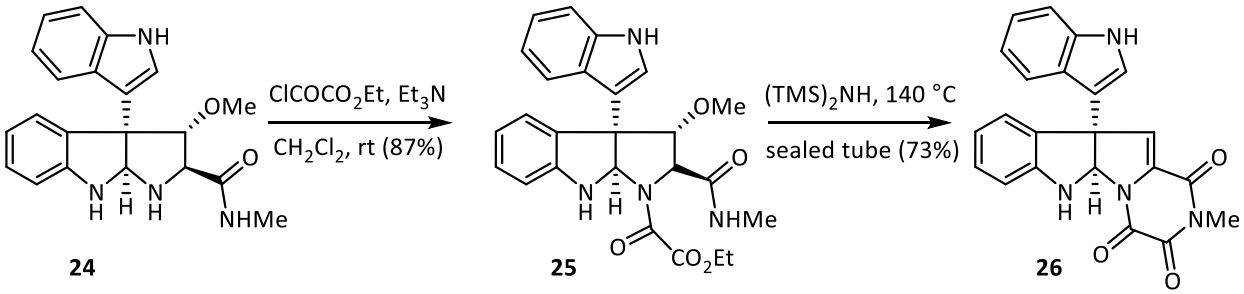
The synthesis of DKPs is relatively straightforward as they are the cyclic dimers of amino acids. TKPs have presented more of challenge, although several techniques have been developed especially as part of the synthesis of TKP containing natural products.

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**.[18]



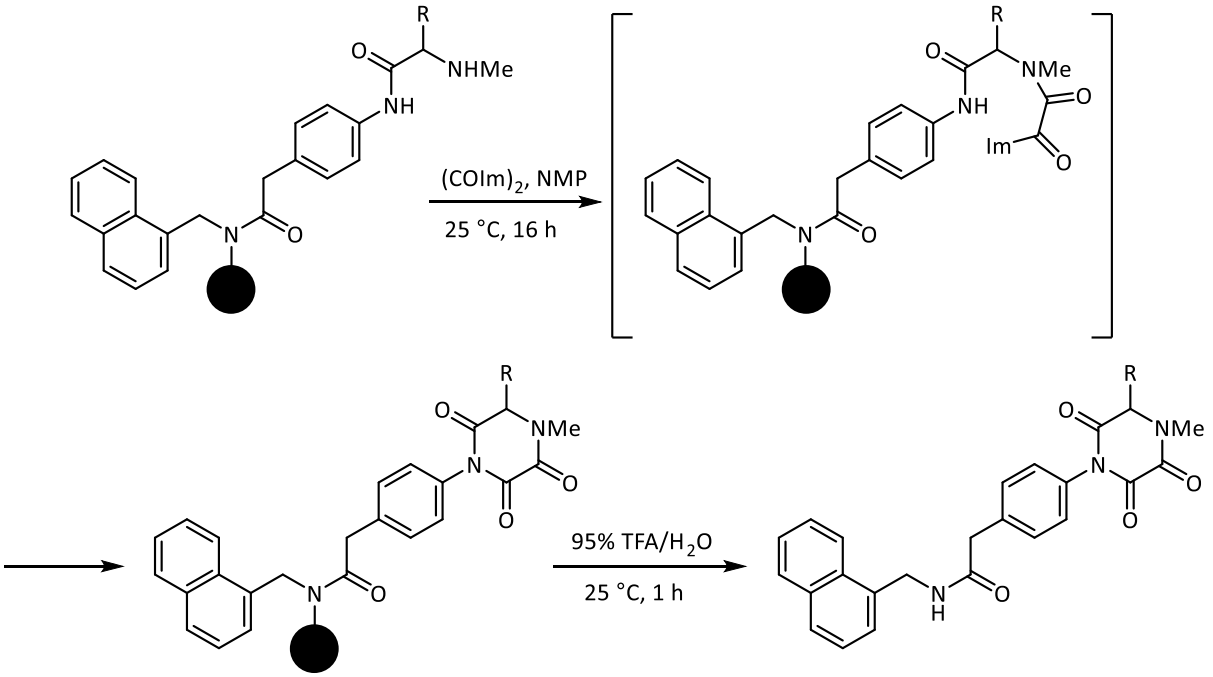
Scheme 7 - Safir's TKP synthesis

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]



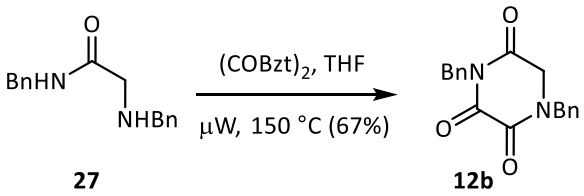
Scheme 8 - total synthesis of (+)-gliocladin C

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]



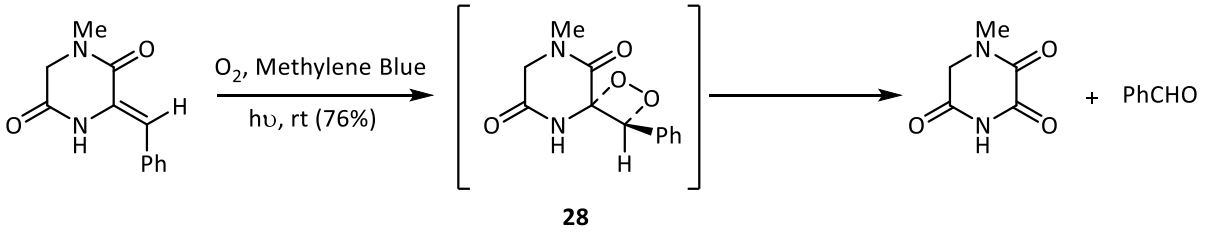
Scheme 9 - Makino's TKP synthesis

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]



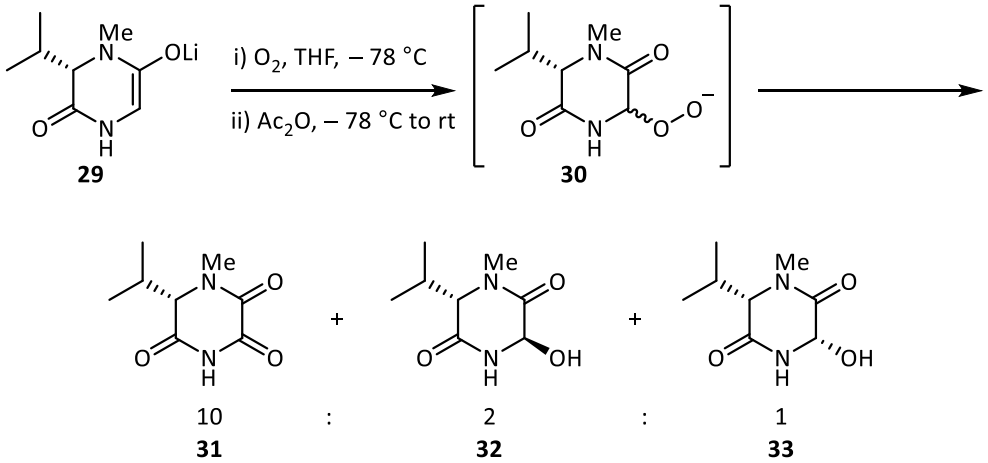
Scheme 10 - Simpkins' TKP synthesis

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 sensitiser and the reaction was thought to proceed through dioxetane intermediate **28** (Scheme 11).



Scheme 11 - Machin and Sammes' oxidative TKP synthesis

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.[23] 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.

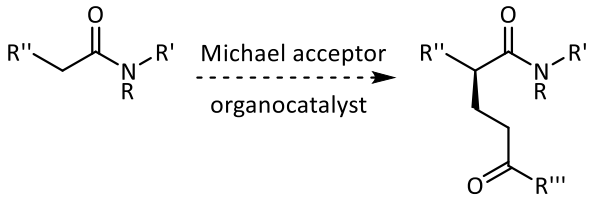


Scheme 12 - Davies' oxidative TKP synthesis

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

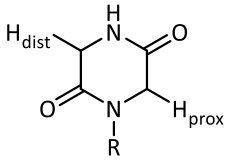
Having seen the potential for asymmetric organocatalytic Michael additions on amide-like systems (Scheme 5 and Table 1), this project began with asking whether other similar systems, including acyclic ones could show similar reactivity (Scheme 13).



Scheme 13 - target Michael addition

Given the comparatively low pK_as 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.[24] Calculations on the pK_a of TKP **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_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 **34**.[25,26]



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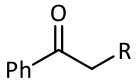
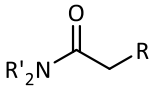
R	pK_a (H_{prox})	pK_a (H_{dist})
H	24.0	24.0
$COCH_3$	24.1	17.7
SO_2CH_3	22.8	16.8
$COCF_3$	23.7	15.3
SO_2CF_3	21.3	13.9

Table 2 - Easton's DKP pK_a values

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_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_a values of around 2000 acids.[27] This wealth of data proved very useful as we began looking for groups which could lower the pK_a of our substrates. The most relevant values are summarised in Table 3.





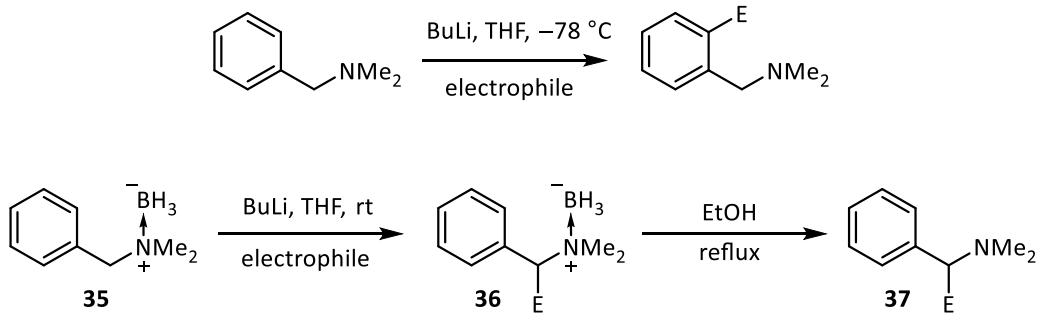
R	pK_a	R	R'	pK_a
H	24.7[28]	H	Et	35.0[28]
Ph	17.7[29]	Ph	Me	26.6[30]
NMe_2	23.6[31]	$NMe_3^+ Br^-$	Et	24.9[28]
$NMe_3^+ Br^-$	14.6[28]			
$Py^+ Br^-$	10.7[28]			

Table 3 - Bordwell's ketone and amide pK_a values

A phenyl group at the α position enhances the acidity by about seven or eight pK_a 'units' relative to no substituent at the α position. An amine group gives only a modest reduction in pK_a, 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 pK_a of carbon acids which uses ^1H NMR spectroscopy.[32] Equilibrium and rate constants for deuteration in D_2O allowed for determination of the pK_a 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 metalate benzylamine-type systems with lithium bases.[33,34] In the absence of borane there is exclusive *ortho* metalation of the aromatic ring; however, activation with a borane group **35** activates with α position to give regioselective α-metalation (Scheme 14).



Scheme 14 - Simpkin's metallation of benzylamines with and without borane

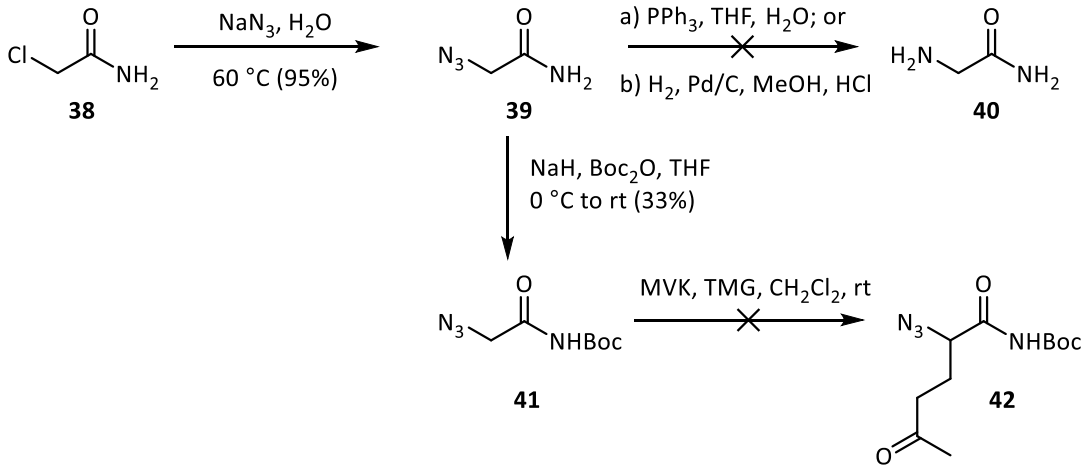
This work has been further extended to the diastereoselective and enantioselective alkylation of isoindoline-borane complexes.[35,36] It was reasoned that the borane group enhances the C-H acidity by withdrawing electron density away from the nitrogen. To the best of our knowledge, no work to date has been done to quantify the effect of boranes on amine pK_a values. There was potential for using amino boranes as a temporary group to lower the pK_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.

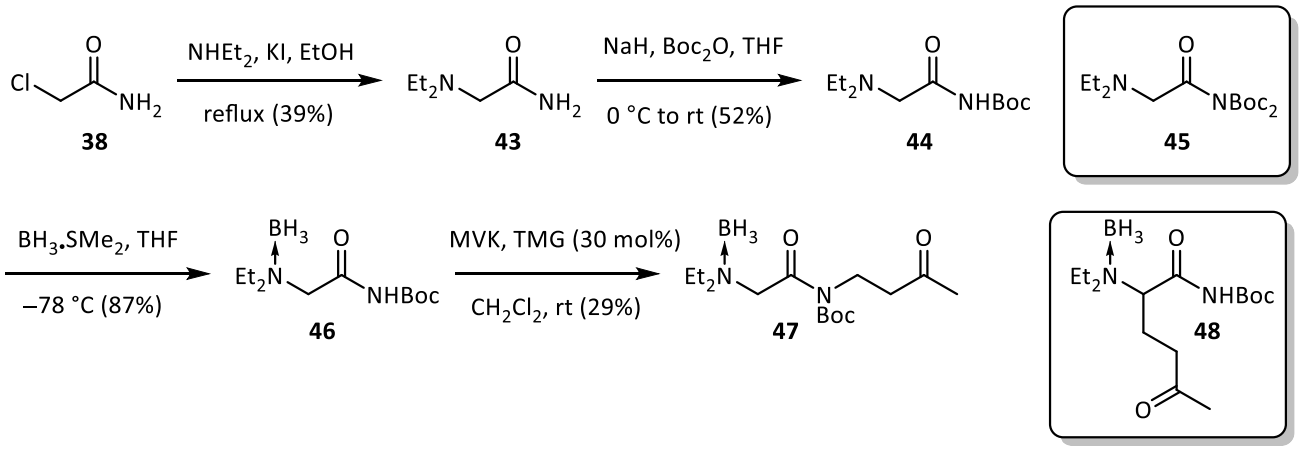


Scheme 15 - progress towards amino amide substrates

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 Boc_2O 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.

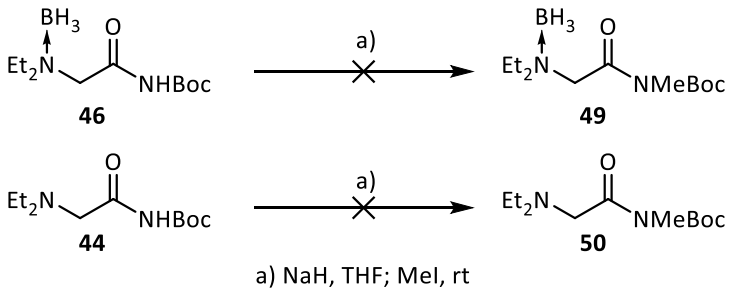
The use of sodium hydride did allow for singly Boc-protected amide **44** to be isolated but only in a modest 52% yield (Scheme 16). Further reflection on the mechanism of reaction with the cinchona catalysts revealed that generating an ammonium might not be very favourable. It was thought that the chiral 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 CH_2 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**.



Scheme 16 - synthesis and use of amino-borane substrates

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.

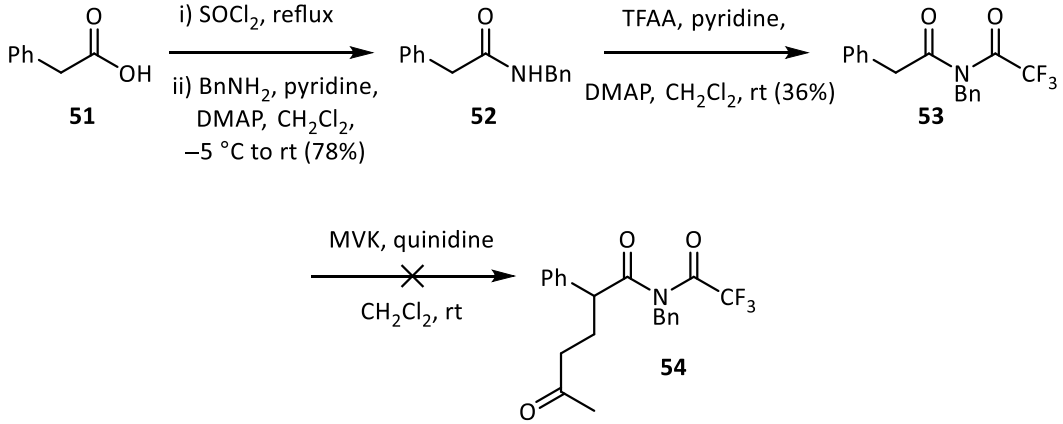


Scheme 17 - attempts to methylate the amino-amide substrates

2.2. α-Phenyl amide substrates

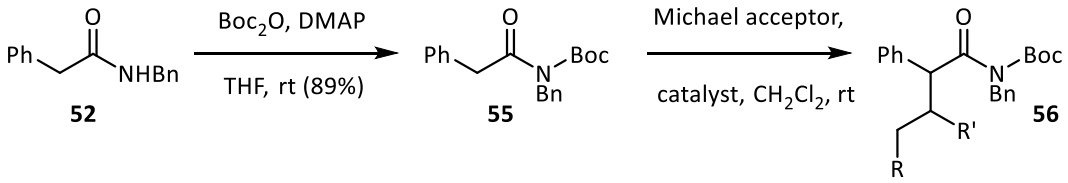
Attention turned next to the use of an aromatic group to lower the pK_a alongside an imide as before. Phenylacetic acid **51** was converted to secondary amide **52** in good yield via the acyl chloride (Scheme 18). This was then converted to the trifluoroacetyl imide **53**. The

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).



Scheme 18 - progress towards α-phenyl amide substrates

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.



entry	Michael acceptor (equiv)	catalyst (mol%)	result
1	MVK (2.5)	quinidine **3** (10)	NR
2	MVK (2.5)	TMG (20)	41%
3	MVK (10)	TMG (30)	78%
4	acrolein (2.5)	TMG (20)	NR
5	methyl acrylate (2.5)	TMG (20)	NR
6	nitro styrene (2.5)	TMG (20)	NR
7	chalcone (2)	TMG (30)	NR
8	MVK (10)	**57** (10)	NR
9	nitro styrene (1.2)	**57** (10)	NR
10	MVK (2.5)	**58** (10)	NR

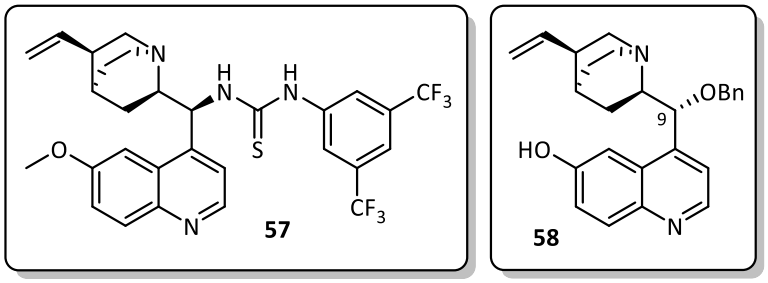
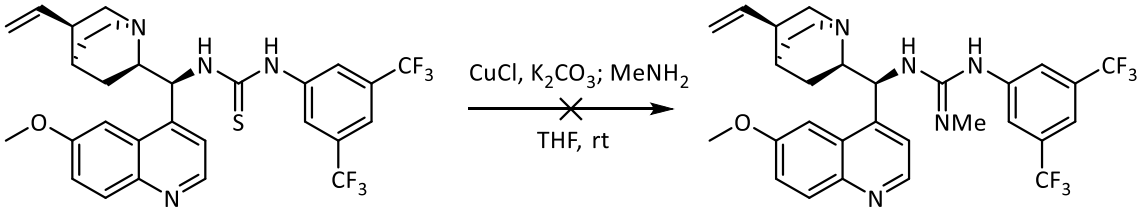


Table 4 - results from Michael additions on an α-phenyl amide substrate

The table shows that only TMG seemed to be basic enough to deprotonate substrate **55**. Guanidines have a pK_a of about 14 which is significantly different from the pK_a of the cinchona alkaloids (pK_a ~ 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

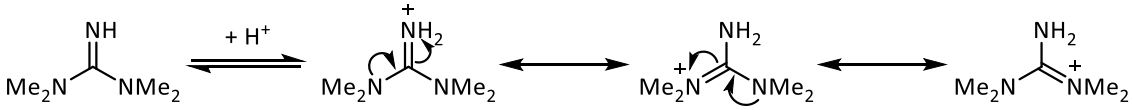
There are a number of ways of making guanidines and a common technique is to generate them from the corresponding thioureas.[37] Given the previous work done in the group using thioureas, this was chosen as the preferred route. The sulfur of the thiourea must be activated prior to its reaction with an 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]



57 **59**

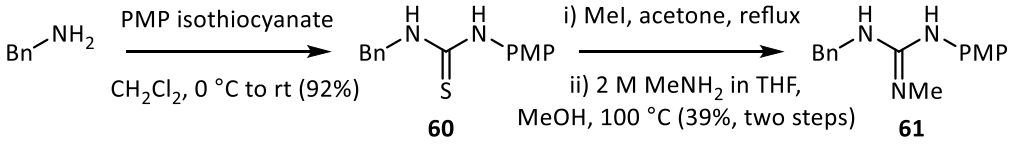
Scheme 19 - attempted guanidine formation with CuCl

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.



Scheme 20 – Resonance forms for the conjugate acid of TMG

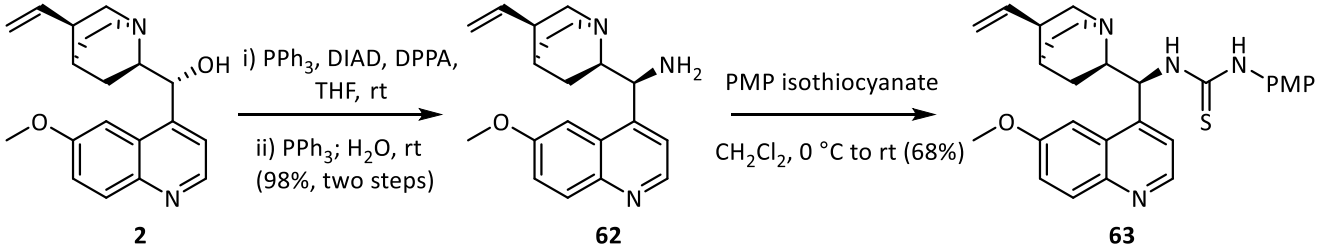
A model system was therefore conducted to test the formation of a PMP substituted guanidine. Benzylamine was converted to thiourea **60** (Scheme 21) in excellent yield using the appropriate isothiocyanate. Successful formation of guanidine **61** was achieved, albeit in low yield, with methyl iodide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



60 **61**

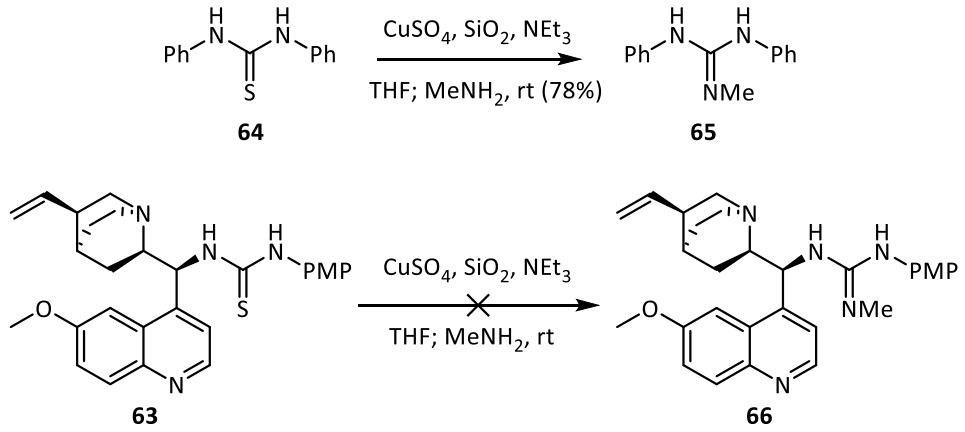
Scheme 21 - model system for guanidine formation

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.



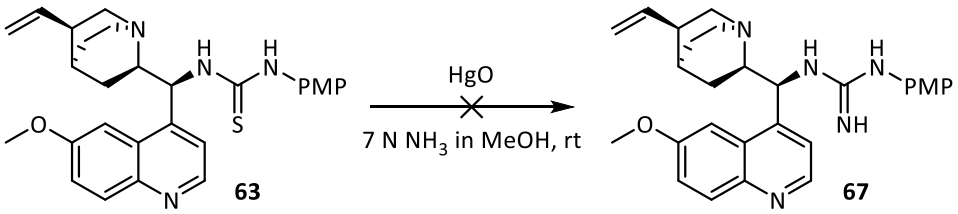
Scheme 22 - synthesis of PMP substituted thiourea

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).



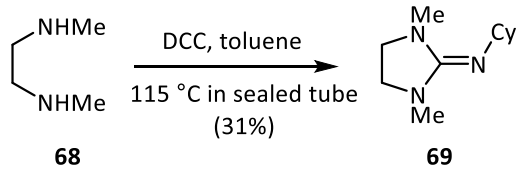
Scheme 23 - $CuSO_4$-mediated guanidine formation

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).



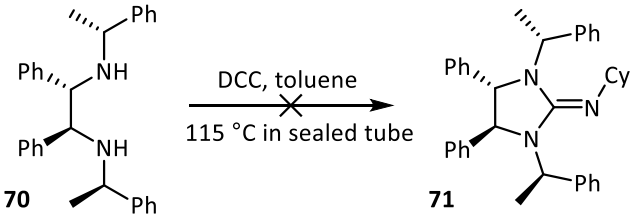
Scheme 24 - attempted guanidine formation with HgO

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.[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).



Scheme 25 - model system for guanidine formation with carbodiimide

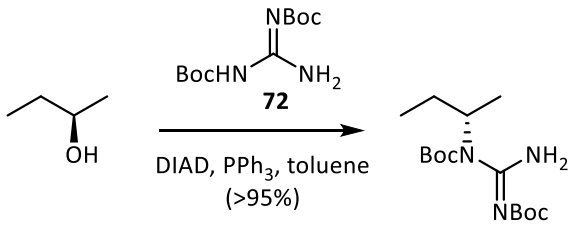
The same conditions were used on chiral diamine **70** (Scheme 26) and initially it was thought that reaction had occurred, however the diamine and DCC had just co-eluted from the column in a precisely 1:1 ratio. Despite harsh conditions and even with the addition of an iron(II) acetate Lewis acid, as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



Scheme 26 - attempted guanidine formation with carbodiimide

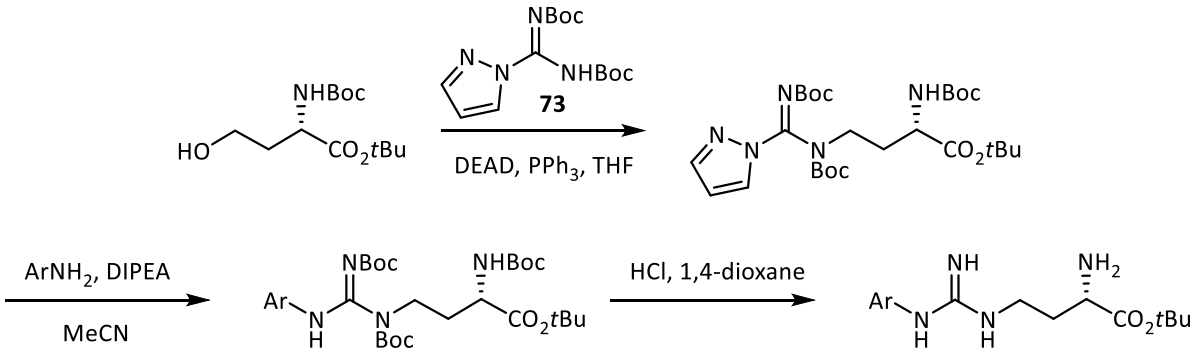
Alternative routes to the guanidine, not including the thiourea intermediate, were also explored. Mitsunobu reactions with guanidine equivalents have been reported, meaning that there was potential for catalysts to be made directly from the cinchona alkaloids. Kozikowski

and co-workers reported in 1994 that bis(Boc)-protected guanidine **72** can undergo a high yielding Mitsunobu reaction with alcohols. [43]



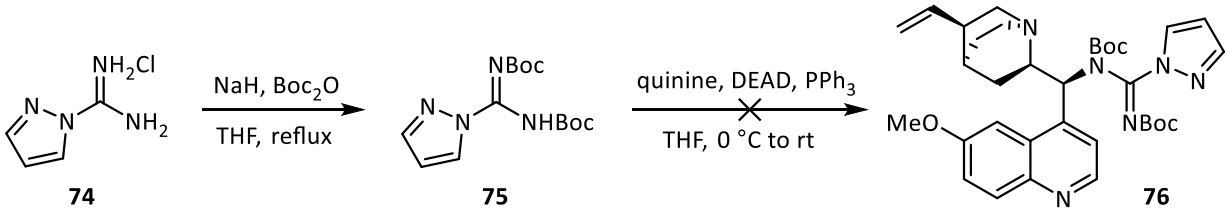
Scheme 27 - Kozikowski's method for guanidine formation

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).[44] This could allow for the generation of the PMP substituted guanidine which was our original target.



Scheme 28 - Rositer's synthesis of aryl guanidines

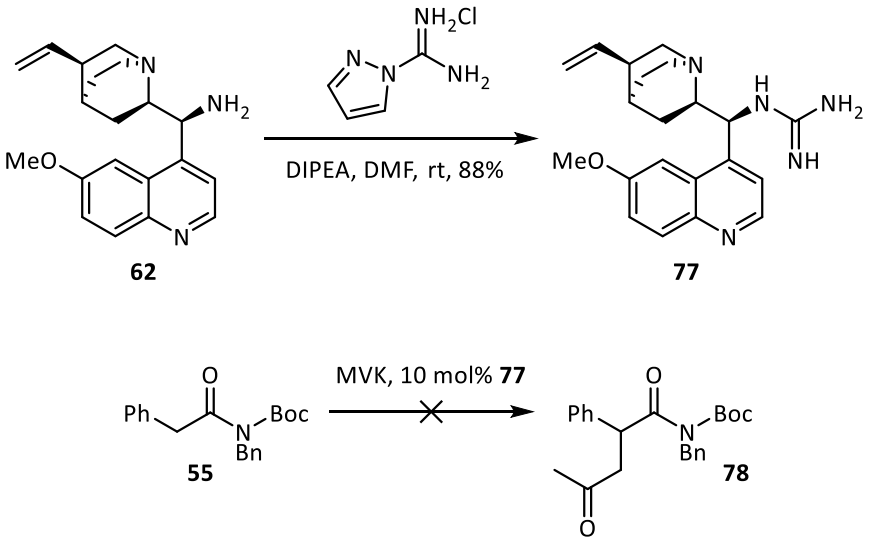
This technique first required the synthesis of **75** from 1*H*-pyrazole-1-carboxamidine hydrochloride **74**. This was carried out although the product was difficult to isolate cleanly and the subsequent Mitsunobu reaction with quinine gave a complex mixture with no product **76** isolated.



Scheme 29 - attempted synthesis of chiral guanidine

To overcome this challenge it was decided to do a direct substitution of amino-quinine **62** with 1*H*-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.



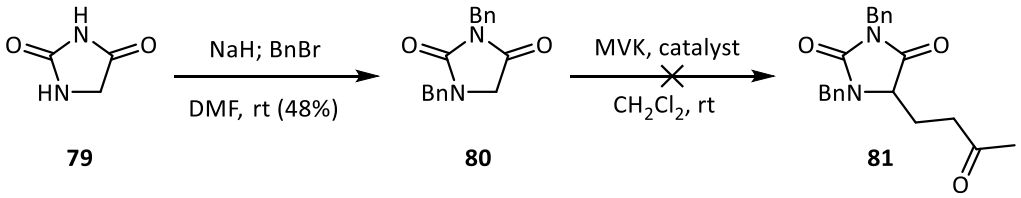
Scheme 30 - synthesis and use of a chiral guanidine catalyst

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

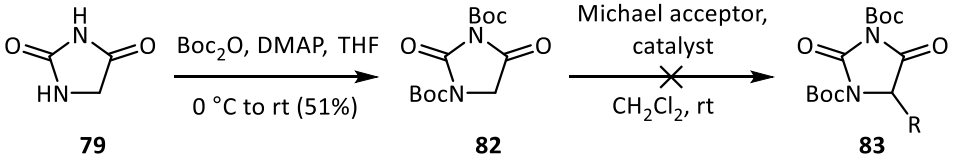
Hydantoins could be considered the five-membered analogue of the TKPs already in use in the research group. They contain one amide nitrogen and one imide nitrogen. There are no reported pK_a values for acidity of the C-H bond (the imide N-H bond has a pK_a value of 15.0 in unsubstituted hydantoin **79**[45]). 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.



Scheme 31 - synthesis and test of bis-benzyl hydantoin

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).



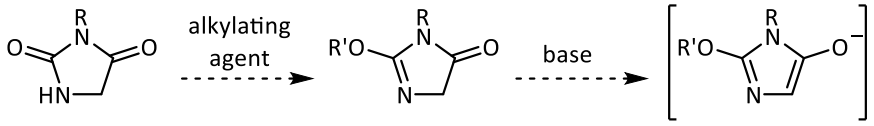
entry	Michael acceptor	catalyst	result
1	MVK	quinidine	NR
2	MVK	TMG	NR
3	acrolein	TMG	NR
4	nitro styrene	TMG	NR
5	MVK	**57**	NR
6	MVK	$MgBr_2$/DIPEA	NR

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 *i*Pr_2NEt could be used to promote soft-enolate formation.[46] 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.

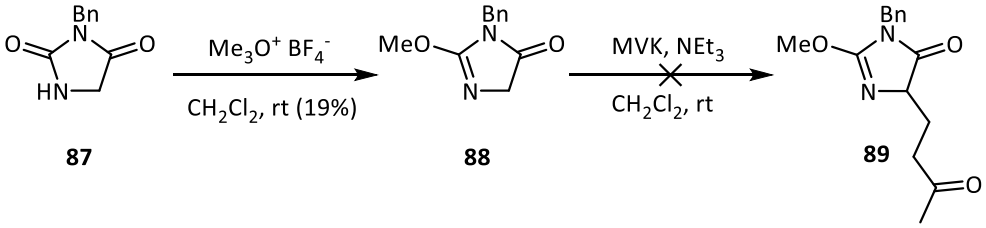
In order to enhance the acidity of the substrate it was hypothesised that it might be possible to make use of conjugate base aromaticity in the hydantoin. If the lactim ether **85** (Scheme 32) could be formed then the conjugate base **86** would resemble imidazole, presumably with some of the associated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



84 **85** **86**

Scheme 32 - proposed route to lactim ether substrate

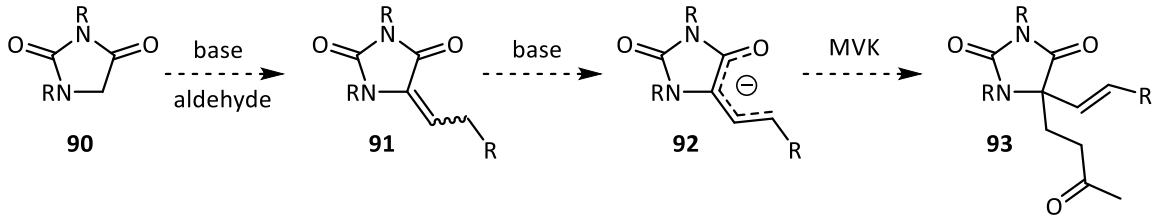
A large quantity of the mono protected hydantoin **87** had been recovered from the synthesis of bis-benzyl hydantoin **80** and this was successfully transformed into lactim ether **88** (Scheme 33). However when subjected to the Michael addition conditions using catalytic triethylamine, no reaction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



87 **88** **89**

Scheme 33 - synthesis and test of lactim ether substrate

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.



Scheme 34 - proposed route to unsaturated hydantoin substrates

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.

entry	hydantoin	conditions	aldehyde	result
1	**82**	*t*BuOK, *t*BuOH	acetaldehyde	complex mixture
2	**82**	AcONa, Ac_2O	benzaldehyde	complex mixture
3	**80**	AcONa, Ac_2O	benzaldehyde	SM
4	**80**	LHMDS, THF	acetaldehyde	SM and trace of product
5	**80**	LDA	acetaldehyde	SM and trace of product
6	**80**	LHMDS, THF	isobutyraldehyde	SM and trace of product

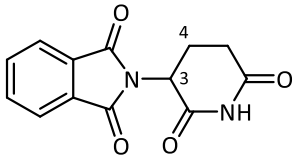
Table 6 - results from attempted synthesis of unsaturated hydantoins

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.

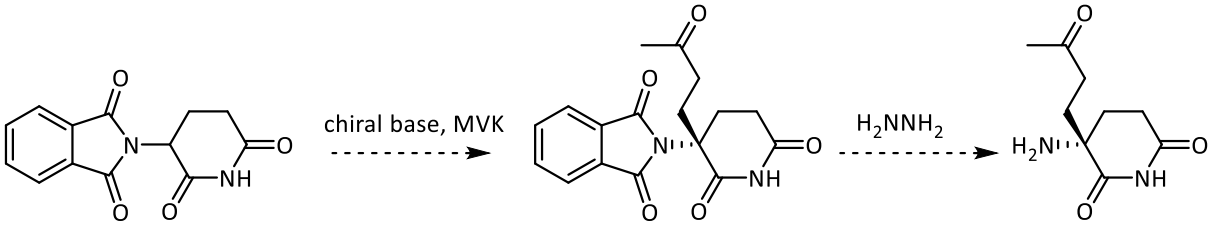


94

Figure 2 - thalidomide

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 pK_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).

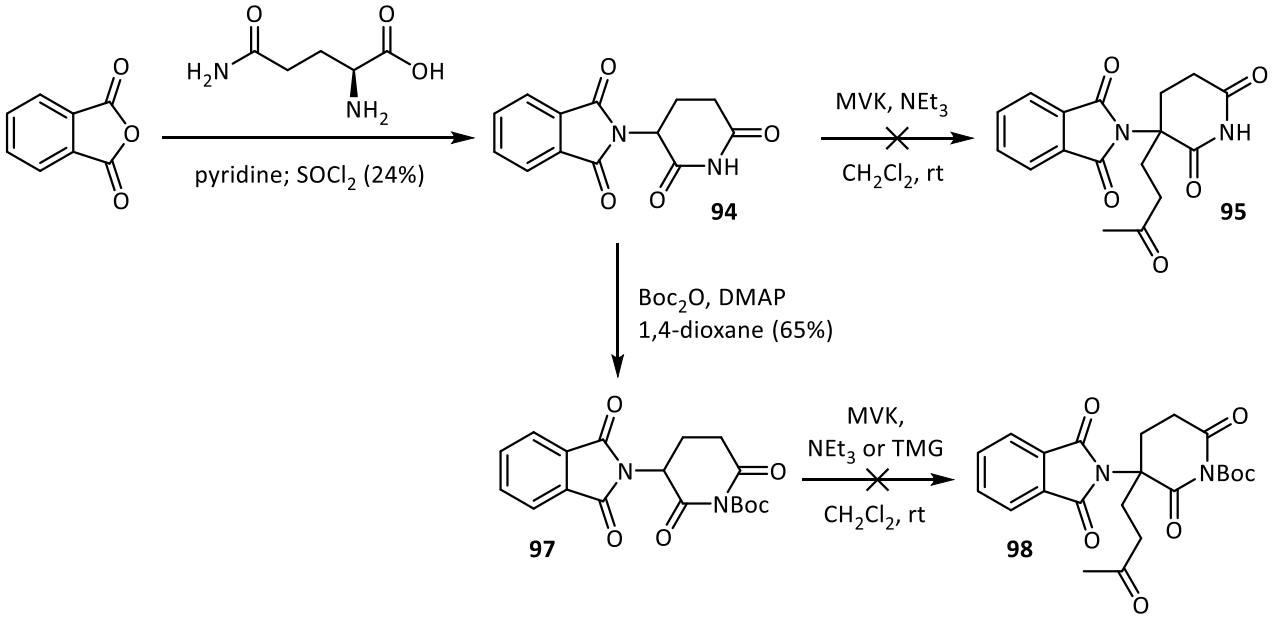


94 **95** **96**

Scheme 35 - proposed Michael addition with thalidomide

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.

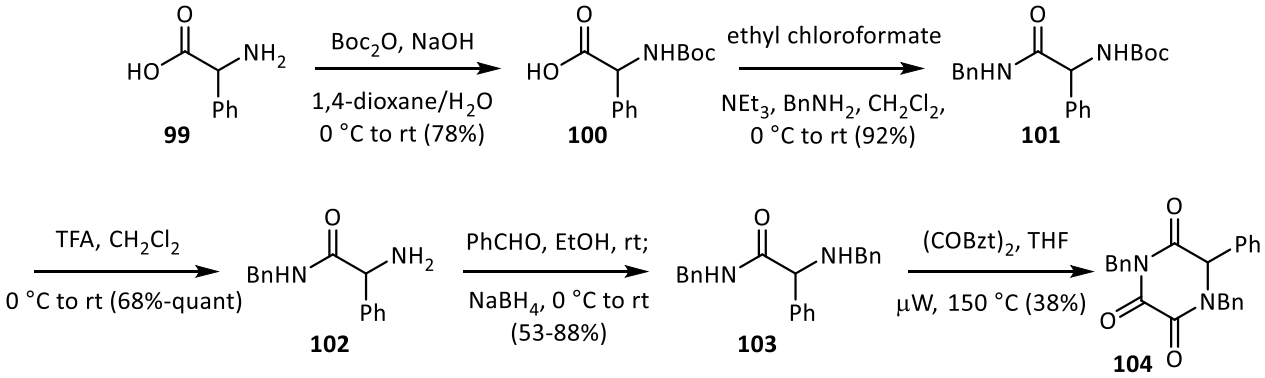


Scheme 36 - synthesis and test of thalidomide substrates

2.6. Phenyl-TKP substrates

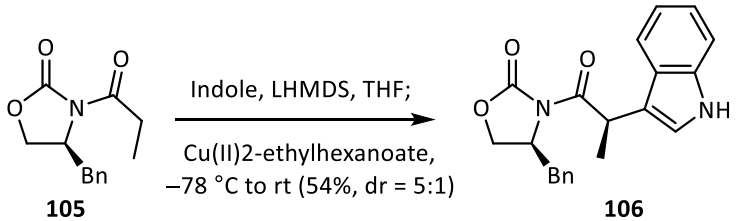
Following the limited success of the acyclic, hydantoin and thalidomide type systems for organocatalytic Michael additions, our attention returned to the TKP system which had previously worked so effectively in the group (Section 1.3). We had already explored the effect a phenyl group could have in lowering the pK_a 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.



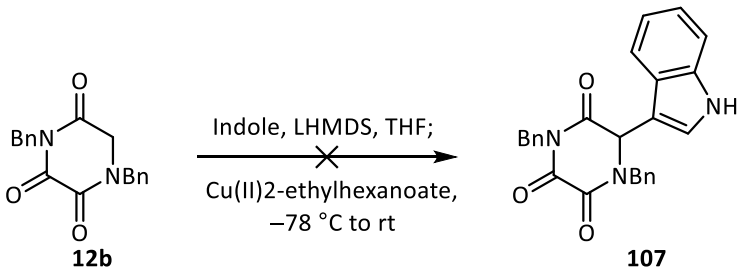
Scheme 37 - synthesis of phenyl-TKP

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.[53] Scheme 38 shows a further example with an oxazolidinone substrate **105**.



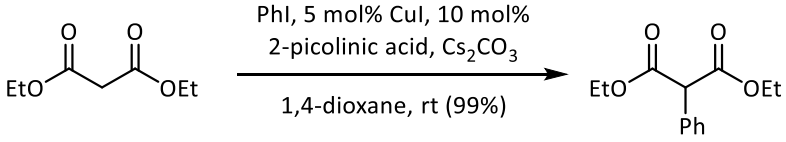
Scheme 38 - Baran's oxidative cross-coupling with indole

Application of this methodology to TKP **12b** was unsuccessful and a complex mixture was observed after the reaction (Scheme 39).



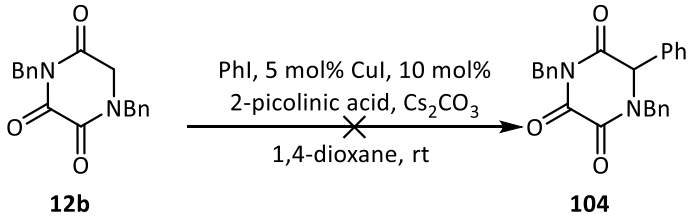
Scheme 39 - attempted cross-coupling with indole

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).[54]



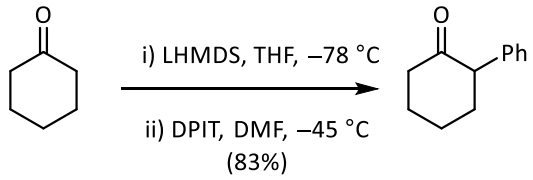
Scheme 40 - Kwong's CuI-catalysed arylation

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



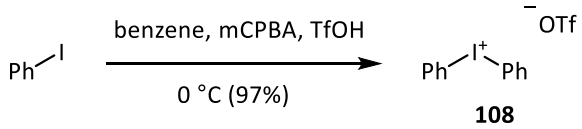
Scheme 41 - attempted arylation with CuI

A further idea for the phenylation of TKP **12b** was to use a hypervalent iodine species. Aggarwal and Olofsson reported in 2005 that they could perform an α-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).[55]



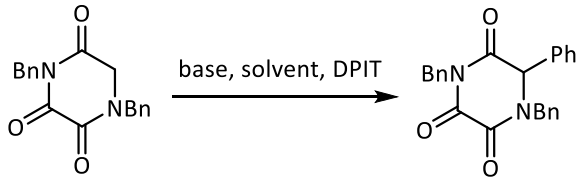
Scheme 42 - Aggarwal's phenylation with DPIT

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.[56]



Scheme 43 - synthesis of DPIT

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.



12b **104**

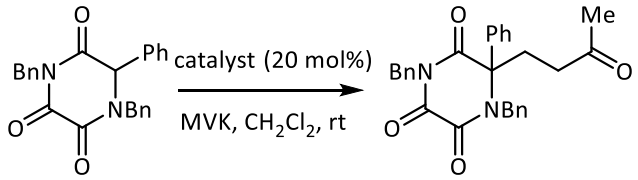
entry	base (equiv)	DPIT (equiv)	solvent	time (h)	temperature	yield (%)
1	LHMDS (2)	1.0	THF	3	−78 °C to −45 °C	decomposition
2	K_3PO_4 (2.5)	1.0	THF	18	rt	decomposition
3	NEt_3 (1.1)	1.3	CH_2Cl_2	16	0 °C to rt	26
4	NEt_3 (2.5)	1.2	CH_2Cl_2	18	0 °C to rt	17
5	NEt_3 (1.1)	1.1	CH_2Cl_2	6	0 °C to rt	33
6	NEt_3 (1.1)	1.1	CH_2Cl_2	72	0 °C to rt	41
7	NEt_3 (1.05)	1.05	CH_2Cl_2	19	0 °C to rt	48

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.



101 **109**

entry	catalyst	time (h)	yield (%)	er[a]
1	NEt_3	24	50	-
2	quinine **2**	19	42	72:38
3	quinidine **3**	27	77	30:70
4	**63**	27	63	50:50
5	**58**	6	75	9:91

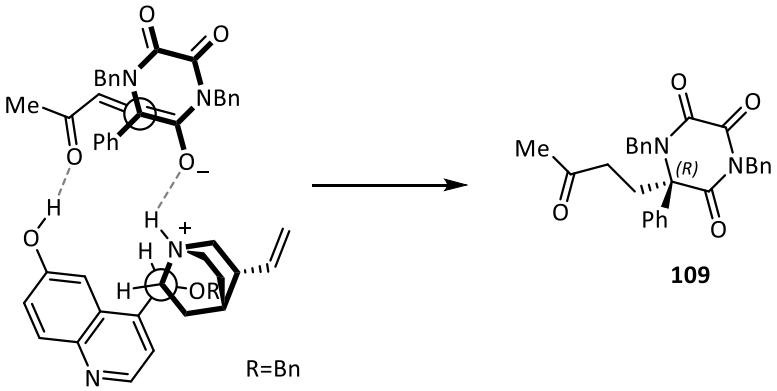
[a] determined by HPLC analysis

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.[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.



Scheme 44 - stereochemical model for cinchona-catalysed Michael addition

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.

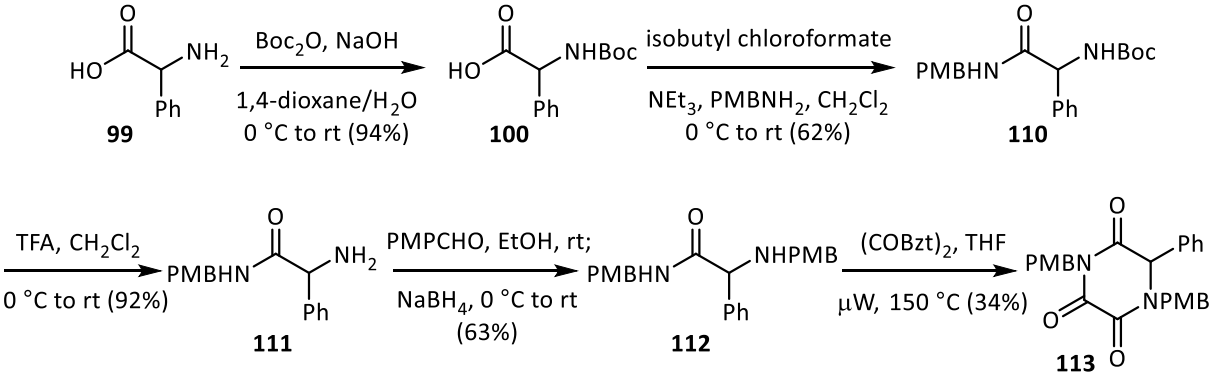
2.7. PMB-protected phenyl-TKP substrates

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.

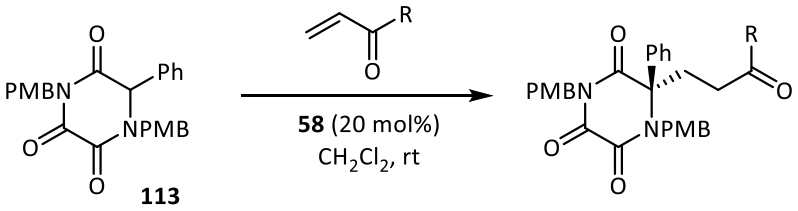
Benzyl groups can normally be removed under hydrogenolysis conditions, however, the phenyl group on TKP **104** is also 'benzylic' with respect to the amide nitrogen. *Para*-methoxybenzyl (PMB) groups were chosen as an alternative protecting group, as it was hoped that they could be removed selectively 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**.



Scheme 45 - synthesis of PMB-protected TKP

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.



113

entry	R	time (h)	yield (%)	er[a]
1	Me	72	quant	93:7
2	Ph	21	91	87:13
3	Cy	45	96	93:7
4	Et	20	quant	94:6
5	H	72	43	59:41[b]

[a] determined by HPLC analysis
[b] HPLC performed on an acetal derivative

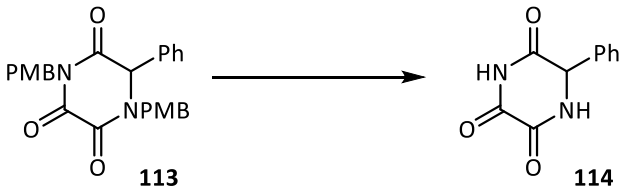
Table 9 - results from the Michael additions of PMB-protected TKP

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.[60] 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.[61] Jung and Lyster published a procedure using trimethylsilyl

iodide but again this was ineffective on our TKP and the starting material was fully recovered.[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.[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.[64]



entry	reagent	solvent	temperature (°C)	time (h)	yield
1	CAN	$MeCN/H_2O$	0 to rt	24	SM and some PMPCHO
2	TFA	-	rt	24	100% recovery of SM
3	TMSI	$CDCl_3$	rt-50	24	100% recovery of SM
4	$K_2S_2O_8$	$MeCN/H_2O$	75	4	decomposition
5	$K_2S_2O_8$	$MeCN/H_2O$	75	2	decomposition
6	DDQ	DCM	rt	25	94% recovery of SM

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.

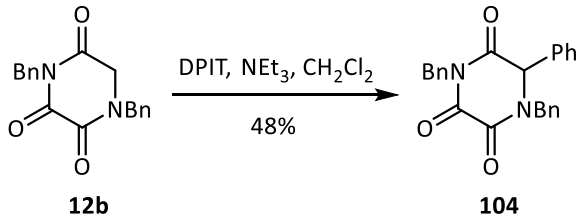
2.8. Conclusions and future work

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.

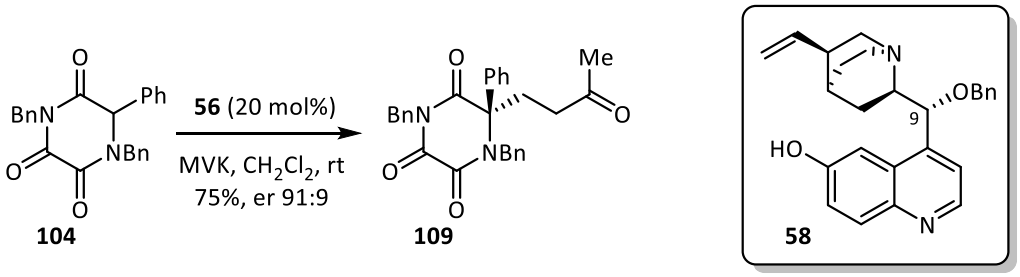
More success was achieved with the TKP substrates and the focus was on TKPs with a phenyl substituent at the reactive centre. A novel synthesis was devised which used a diphenyliodonium salt to arylate TKP **12b** (Scheme 46). This significantly shortened the synthesis of these substrates and would allow 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.



12b **104**

Scheme 46 - succesful phenylation of TKP

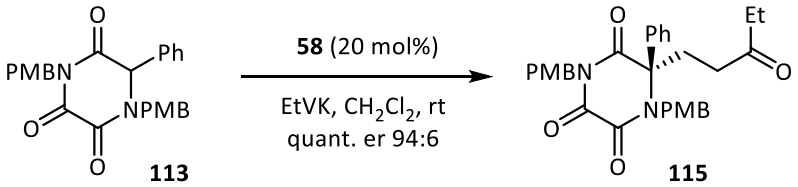
With the phenyl substituted TKP in hand, a range of Michael additions were tested and the optimal catalyst was found to be **58** with a free quinoline hydroxyl and the secondary alcohol protected. The reactions were relatively slow at rt and further work is needed to complete the optimisation of both 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.



104 **109** **58**

Scheme 47 - Michael addition with phenyl-TKP

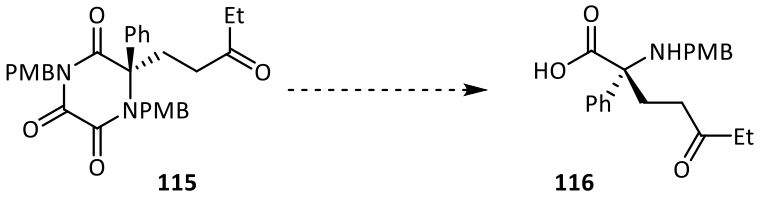
With a view to their subsequent removal, TKP **113** was synthesised with PMB protecting groups. This was found to perform better as a substrate and excellent yields and selectivities were achieved with unsaturated ketone acceptors (Scheme 48).



Scheme 48 - Michael addition with PMB-protected TKP

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.



Scheme 49 - proposed ring-opening of TKP

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_{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 (ν_{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 (^{1}H) (300 and 400 MHz) and carbon (^{13}C) (100 MHz) spectra were recorded on Bruker Avance III 300 MHz and Bruker Avance III 400 MHz spectrometers. Chemical shifts (δ_H or δ_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

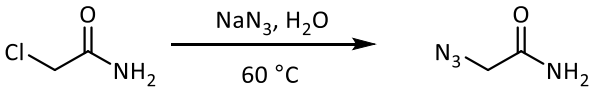
Novel compounds were analysed by means of the Synapt G2-S HDMS system (Waters, Manchester, UK). All experimental data was acquired with a resolution of 20,000 and samples were introduced into the mass spectrometer via the nanoAcquity system (Waters, Manchester, UK). Electrospray ionisation was performed 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

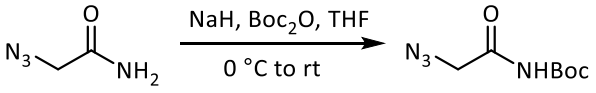
2-Azidoacetamide 39[65]



38 **39**

2-Chloroacetamide **38** (124 mg, 1.33 mmol) was added to a solution of sodium azide (259 mg, 3.98 mmol) in H_2O (2.5 mL). The reaction mixture was then stirred at 60 °C for 24 h before being cooled to rt, diluted with H_2O (40 mL) and extracted with EtOAc (3 x 30 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure. Purification by recrystallisation from CH_2Cl_2 afforded azide **39** as white crystals (126 mg, 95%). R_f 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, N*H*H'), 6.77 (1H, br s, NH*H'*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 52.2 (CH_2), 169.9 (CO); IR (neat) ν_{max}/cm^{-1} 3373m, 3184m, 2108s (azide), 1624s, 1412s, 1314s, 1270m, 1095m, 957w.

tert-Butyl (2-azidoacetyl)carbamate 41

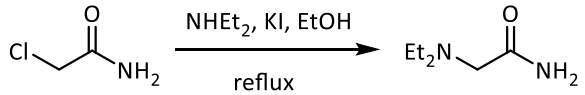


39 **41**

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 NH_4Cl (50 mL) and extracted with Et_2O (4 x 40 mL). The combined organic layers were washed with brine (100 mL), dried with Na_2SO_4 and concentrated under reduced pressure. Purification by flash column chromatography (6:1 petrol/Et_2O) afforded *Boc amide* **41** as a white solid (155 mg, 33%). R_f 0.58 (1:1 petrol/EtOAc); m.p. 70-72 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.49 (9H, s, $C(CH_3)_3$), 4.35 (2H, s, CH_2), 7.85 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.9 ($C(CH_3)_3$), 52.9 (CH_2), 83.6 ($C(CH_3)_3$), 150.1 ((NC(O)O), 169.5 ($NC(O)CH_2$); IR (neat) ν_{max}/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]$^+$, $C_7H_{12}N_4O_3Na$ requires 223.0807.

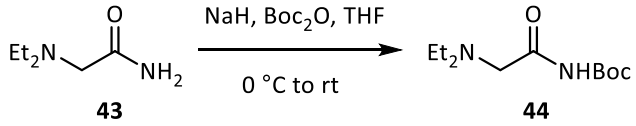
2-(Diethylamino)acetamide 43



38 **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 H_2O (500 mL) and extracted with Et_2O (3 x 400 mL). The combined organic layers were dried with Na_2SO_4 and concentrated under reduced pressure to afford *amino amide* **43** as an off-white powder (5.92 g, 39%). R_f 0.38 (3:1 EtOAc/MeOH); m.p. 72-74 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.99 (6H, t, *J* = 7.0 Hz, 2 x CH_3), 2.52 (4H, q, *J* = 7.0 Hz, 2 x CH_2), 2.96 (2H, s, $C(O)CH_2$), 6.65 (1H, br s, N*H*H'), 7.22 (1H, br s, NH*H'*); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.2 (2 x CH_3), 48.5 (2 x CH_2), 57.3 ($C(O)CH_2$), 175.7 ($C(O)NH_2$); IR (neat) ν_{max}/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]$^+$, $C_6H_{15}N_2O$ requires 131.1184.

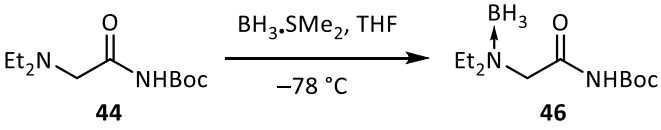
tert-Butyl (diethylglycyl)carbamate 44



43 **44**

Synthesised according to the literature procedure.[66] 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_4Cl (200 mL) and extracted with Et_2O (4 x 150 mL). The combined organic layers were washed with brine (400 mL), dried with Na_2SO_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, $CDCl_3$): δ 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, $CDCl_3$): δ 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) ν_{max}/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

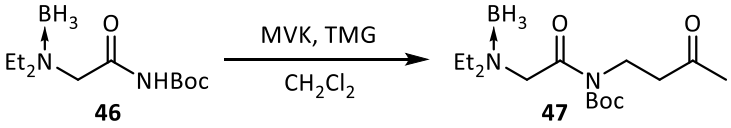


44 **46**

Synthesised according to the literature procedure.[33] $BH_3{\cdot}SMe_2$ (275 µL, 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_2O (1.5 mL) and warmed to rt. The mixture was then poured into a separating funnel with H_2O (150 mL) and Et_2O (150 mL) and separated. The aqueous phase was extracted with Et_2O (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 $MgSO_4$ and concentrated under reduced pressure to afford *amino borane* **46** (582 mg, 86%). R_f 0.72 (3:1 EtOAc/MeOH); m.p. 44-46 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.27 (6H, t, *J* = 7.0 Hz, 2 x CH_3), 1.51 (9H, s, $C(CH_3)_3$), 3.02-3.17 (2H, m, CH_2CH_3), 3.18-3.33 (2H, m, CH_2CH_3), 3.92 (2H, s, NCH_2), 7.54 (1H, br s, NH). BH_3 protons not observed; ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.4 (2 x CH_3), 27.9 ($C(CH_3)_3$), 54.8 (2 x CH_2CH_3), 57.2 (NCH_2), 83.6 ($C(CH_3)_3$), 149.5 (NC(O)O), 167.8 ($NC(O)CH_2$); IR (neat) ν_{max}/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-BH_3]$^+$, 100%); product unstable in gas phase so no molecular ion peak observed.

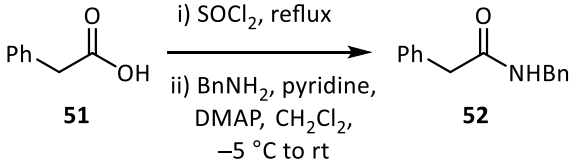
tert-Butyl (diethylglycyl)(3-oxobutyl)carbamate borane complex 47



46 **47**

Tetramethylguanidine (9 µL, 0.070 mmol) was added to a solution of amino borane **46** (60 mg, 0.246 mmol) in CH_2Cl_2 (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%). R_f 0.58 (3:1 EtOAc/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.23 (6H, t, *J* = 7.0 Hz, 2 x CH_2CH_3), 1.54 (9H, s, $C(CH_3)_3$), 2.16 (3H, s, $C(O)CH_3$), 2.68 (2H, t, *J* = 7.5 Hz, NCH_2CH_2), 3.03-3.15 (2H, m, CH_2CH_3), 3.21-3.33 (2H, m, CH_2CH_3), 3.92 (2H, t, *J* = 7.5 Hz, NCH_2CH_2), 4.07 (2H, s, $C(O)CH_2$), BH_3 protons not observed; ^{13}C NMR (100 MHz, $CDCl_3$): δ 9.5 (2 x CH_2CH_3), 27.9 ($C(CH_3)_3$), 30.1 ($C(O)CH_3$), 39.7 (NCH_2CH_2), 41.9 (NCH_2CH_2), 54.5 (2 x CH_2CH_3), 57.4 ($C(O)CH_2$), 84.8 ($C(CH_3)_3$), 152.1 (NC(O)O), 170.0 ($NC(O)CH_2$), 206.3 ($C(O)CH_3$); IR (neat) ν_{max}/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-BH_3]$^+$, 30%), product unstable in gas phase so no molecular ion peak observed.

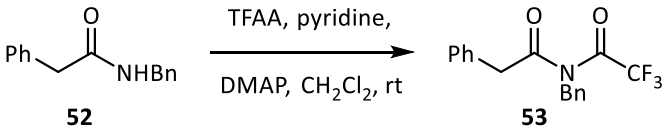
N-Benzyl-2-phenylacetamide 52[68]



Synthesised according to the literature procedure.[69] 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 CH_2Cl_2 (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 CH_2Cl_2 (350 mL) and washed with H_2O (200 mL), 1 N HCl (200 mL), 5% aqueous solution of $NaHCO_3$ (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%). R_f 0.60 (EtOAc); m.p. 112-113 °C (lit. 118-119 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.58 (2H, s, $CH_2C(O)$), 4.36 (1H, s, NC*H*H'), 4.38 (1H, s, NCH*H'*), 5.88 (1H, s br, NH), 7.12-7.36 (10H, m, 2 x Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.5 (*C*H_2CO), 43.7 (CH_2NH), 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) ν_{max}/cm^{-1} 3285m, 3032w, 1637s, 1548m, 1491w, 1453w, 1345w, 1027m.

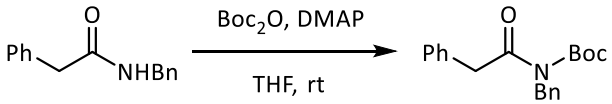
N-Benzyl-2,2,2-trifluoro-*N*-(2-phenylacetyl)acetamide 53



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 CH_2Cl_2 (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 $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (10:1 petrol/Et_2O) afforded *imide* **53** as an unstable dark brown oil (268 mg, 36%). R_f 0.40 (4:1 petrol/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.06 (2H, s, NCH_2), 4.94 (2H, s, $C(O)CH_2$), 7.08-7.34 (10H, m, 2 x Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.5 ($C(O)CH_2$), 47.9 (NCH_2), 115.8 (q, $J_{C\text{-}F}$ = 288 Hz, CF_3), 126.4 (2 x CH, Ph), 127.6 (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, $J_{C\text{-}F}$ = 39 Hz, $C(O)CF_3$), 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.

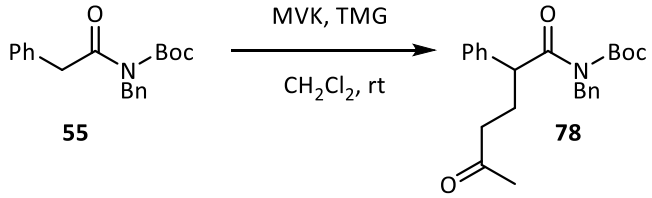
tert-Butyl benzyl(2-phenylacetyl)carbamate 55



52 **55**

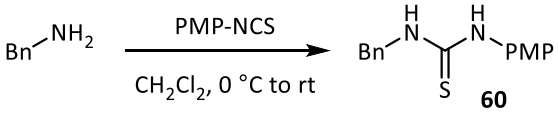
Di-*tert*-butyl dicarbonate (109 µL, 0.474 mmol) and DMAP (2 mg, 0.020 mmol) were added to a solution of amide **52** (89 mg, 0.395 mmol) in THF (2.4 mL) at 0 °C. The reaction mixture was warmed to rt and after 18 h the solvent was removed under reduced pressure. The residue was then taken up in CH_2Cl_2 (40 mL) and washed with 2 N HCl (30 mL), saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL). The organic layer was then dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (10:1 petrol/Et_2O) afforded *Boc amide* **55** as a yellow oil (114 mg, 89%). R_f 0.62 (1:1 petrol/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.48 (9H, s, $C(CH_3)_3$), 4.37 (2H, s, $C(O)CH_2$), 4.98 (2H, s, NCH_2), 7.28-7.44 (10H, m, 2 x Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.8 ($C(CH_3)_3$), 44.4 ($C(O)CH_2$), 47.7 (NCH_2), 83.3 ($C(CH_3)_3$), 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 ($NC(O)CH_2$); 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]$^+$, $C_{20}H_{23}NO_2Na$ requires 348.1576.

tert-Butyl benzyl(5-oxo-2-phenylhexanoyl)carbamate 78



Tetramethylguanidine (5 µL, 0.04 mmol) was added to a solution of Boc amide **55** (44 mg, 0.135 mmol) in CH_2Cl_2 (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/Et_2O) afforded *Michael adduct* **78** as a colourless oil (38 mg, 78%). R_f 0.38 (1:1 petrol/Et_2O); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.30 (9H, s, $C(CH_3)_3$), 1.99-2.09 (1H, m, NC(O)CHC*H*H'), 2.07 (3H, s, $C(O)CH_3$), 2.27-2.48 (3H, m, NC(O)CHCH*H*' and $CH_3C(O)CH_2$), 4.74 (1H, d, *J* = 15.0 Hz, NC*H*H'), 4.88 (1H, d, *J* = 15.0 Hz, NCH*H*'), 4.93-4.99 (1H, m, NC(O)CH), 7.07-7.30 (10H, m, 2 x Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 27.7 ($C(CH_3)_3$), 28.2 (NC(O)CHCH_2), 29.8 (CH_3), 41.4 ($CH_3C(O)CH_2$), 48.1 (NCH_2), 50.2 (NC(O)CH), 83.2 ($C(CH_3)_3$), 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) ν_{max}/cm^{-1} 2978w, 2934w, 1729s, 1716s, 1688m, 1367m, 1214m, 1142s; m/z (ES$^+$) 418.2 ([M+Na]$^+$, 100%); HRMS (ES$^+$) 418.1988 [M+Na]$^+$, $C_{24}H_{29}NO_4Na$ requires 418.1994.

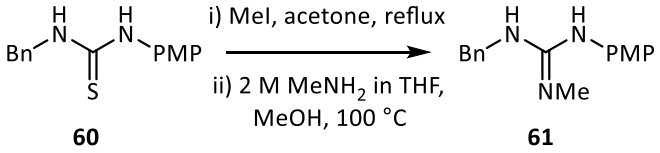
1-Benzyl-3-(4-methoxyphenyl)thiourea 60[70]



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 CH_2Cl_2 (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%). R_f 0.41 (1:1 petrol/EtOAc); m.p. 103-105 °C (lit. 113-114 °C); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.79 (3H, s, OCH_3), 4.85 (1H, s, C*H*H'Ph),

4.87 (1H, s, CH*H'*Ph), 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); ^{13}C NMR (100 MHz, $CDCl_3$): δ 49.3 (NCH_2Ph), 55.5 (OCH_3), 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 (*C*OCH_3, PMP), 181.5 (NHC(S)NH); IR (neat) ν_{max}/cm^{-1} 3384m, 3164m, 3014m, 1588m, 1542s, 1522s, 1504s, 1494s, 1311m, 1237s, 1227s, 1025s, 968m.

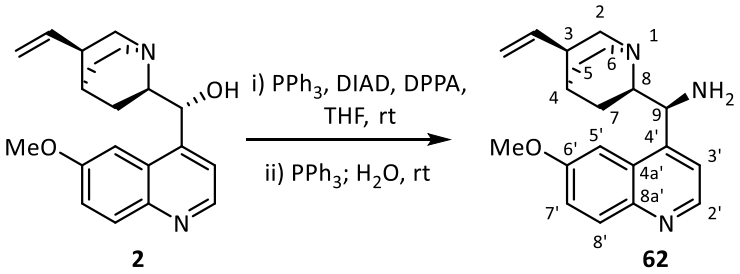
1-Benzyl-3-(4-methoxyphenyl)-2-methylguanidine 61



60 **61**

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 CH_2Cl_2 (30 mL) and washed with saturated aqueous $NaHCO_3$ (40 mL). The aqueous layer was then extracted with CH_2Cl_2 (30 mL) and the combined organic layers were washed with brine (50 mL), dried with Na_2SO_4 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%). R_f 0.28 (1:1 petrol/EtOAc); m.p. 141-143 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.26 (3H, s, NCH_3), 3.77 (3H, s, OCH_3), 4.38 (1H, s, NC*H*H'), 4.40 (1H, s, NCH*H'*), 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); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.7 (NCH_3), 44.2 (NCH_2), 55.5 (OCH_3), 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 (*C*OCH_3, PMP), 157.1 (C=N); IR (neat) ν_{max}/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]$^+$, $C_{16}H_{20}N_3O$ requires 270.1606.

9-Amino-(9-deoxy)-epi-quinine 62[72]

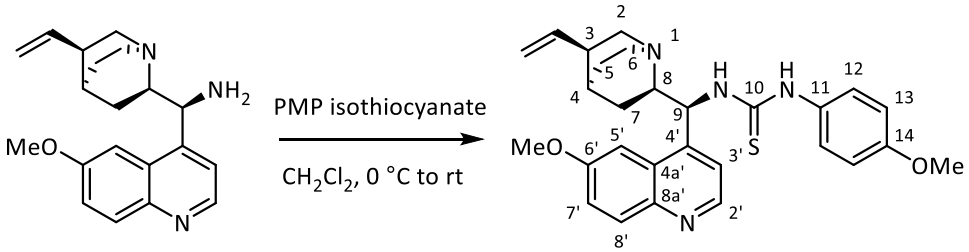


Quinine **2** (3.27 g, 10.1 mmol) was added to a solution of triphenylphosphine (3.18 g, 12.1 mmol) in THF (50 mL) at 0 °C. Diisopropyl azodicarboxylate (2.38 mL, 12.2 mmol) was added in one portion followed by a solution of diphenyl phosphoryl azide (2.61 mL, 12.1 mmol) in THF (20 mL). The reaction 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_2O (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_2Cl_2 (300 mL) and 10% HCl (300 mL). The aqueous layer was washed with CH_2Cl_2 (3 x 200 mL) and adjusted to pH 10 with concentrated NH_4OH. The aqueous layer was then extracted with CH_2Cl_2 (4 x 200 mL) and these combined organic layers were dried with Na_2SO_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_2Cl_2 (100 mL) and extracted into 2 N HCl (100 mL). The aqueous phase was then washed with CH_2Cl_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_2Cl_2 (4 x 100 mL). The combined organic layers were washed with brine, dried with Na_2SO_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, $CDCl_3$): δ 0.65-0.77 (1H, m, CH*H*^{7}), 1.30-1.41 (1H, m, C*H*H^7), 1.43-1.52 (2H, m, CH_2^5), 1.52-1.57

(1H, m, CH^4), 2.00-2.25 (3H, m, NH_2 overlays CH^3), 2.67-2.78 (2H, m, $CH\mathit{H}^6$ and $CH\mathit{H}^2$), 2.95-3.07 (1H, m, CH^8), 3.09-3.18 (1H, m, $C\mathit{H}H^6$), 3.20 (1H, dd, *J* = 14.0, 10.0, $C\mathit{H}H^2$), 3.88 (3H, s, OCH_3), 4.53 (1H, br d, *J* = 9.0 Hz, $C\mathit{H}^9NH_2$), 4.86-4.98 (2H, m, $CH=C\mathit{H}_2$), 5.73 (1H, ddd, *J* = 17.0, 10.0, 7.5 Hz, $C\mathit{H}=CH_2$), 7.31 (1H, dd, *J* = 9.0, 3.0 Hz, $CH^{7'}$), 7.34-7.42 (1H, m, $CH^{3'}$), 7.59 (1H, br s, $CH^{5'}$), 7.96 (1H, d, *J* = 9.0 Hz, $CH^{8'}$), 8.66 (1H, d, *J* = 4.5 Hz, $CH^{2'}$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.0 (C^7H_2), 27.5 (C^4H), 28.2 (C^5H_2), 39.8 (C^3H), 41.0 (C^6H_2), 52.5 (C^9H), 55.5 (OCH_3), 56.3 (C^2H_2), 61.8 (C^8H), 102.0 ($C^{5'}H$), 114.3 ($CH=\mathit{C}H_2$), 119.9 ($C^{3'}H$), 121.2 ($C^{7'}H$), 128.8 ($C^{4a'}$), 131.7 ($C^{8'}H$), 141.8 ($\mathit{C}H=CH_2$), 144.7 ($C^{4'}$), 147.0 ($C^{8a'}$), 147.8 ($C^{2'}H$), 157.6 ($C^{6'}OMe$); IR (neat) ν_{max}/cm^{-1} 3366w, 2933m, 2862m, 1620s, 1589m, 1506s, 1473m, 1431m, 1228s, 1029s, 912s; $[\alpha]_D$ +98 ° (*c* = 1.0, $CHCl_3$, 20 °C), (lit.[73] $[\alpha]_D$ +80 ° (*c* = 1.1, $CHCl_3$, 20 °C)).

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

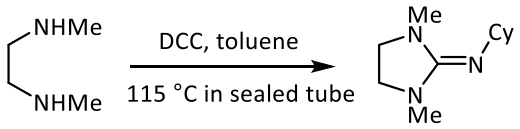


62 **63**

Synthesised according to the literature procedure.[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_2Cl_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_2Cl_2/MeOH/NEt_3) afforded *thiourea* **63** as a pale yellow powder (2.35 g, 68%). R_f 0.38 (3:1 EtOAc/MeOH); m.p. 110-113 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.92-1.00 (1H, m, $CH\mathit{H}^7$), 1.28-1.39 (1H, m, $C\mathit{H}H^7$), 1.55-1.74 (3H, m, CH^4 and CH_2^5), 2.22-2.32 (1H, m, CH^3), 2.62-2.74 (2H, m, $CH\mathit{H}^6$ and $CH\mathit{H}^2$), 3.13 (1H, dd, *J* = 13.5, 10.0 Hz, $C\mathit{H}H^2$), 3.12-3.22 (1H, m, CH^8), 3.30-3.41 (1H, m, $C\mathit{H}H^6$), 3.83 (3H, s, $C^{6'}OCH_3$), 3.95 (3H, s, $C^{14}OCH_3$), 4.90-4.98 (2H, m, $CH=C\mathit{H}_2$), 5.64 (1H, ddd, *J* = 17.0, 10.0, 7.5 Hz, $C\mathit{H}=CH_2$), 5.89 (1H, br s, CH^9), 6.89 (2H, d, *J* = 9.0 Hz, 2 x CH^{13}), 7.13 (2H, d, *J* = 9.0 Hz, 2 x CH^{12}), 7.16-7.23 (1H, m, $C^{3'}H$), 7.36 (1H, dd, *J* = 9.0, 2.5

Hz, $C^{7'}H$), 7.79 (1H, br s, $CH^{5'}$), 7.98 (1H, d, *J* = 9.0 Hz, $CH^{8'}$), 8.52 (1H, d, *J* = 4.0 Hz, $CH^{2'}$). NH protons not observed; ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.7 (C^7H_2), 27.2 (C^5H_2), 27.6 (C^4H), 39.2 (C^3H), 41.4 (C^6H_2), 55.2 (C^2H_2), 55.5 ($C^{6'}OCH_3$), 55.7 ($PhOCH_3$), 60.7 (C^8H, overlays C^9H), 102.4 ($C^{5'}H$), 114.6 (2 x $C^{13}H$), 114.8 ($CH=CH_2$), 119.8 ($C^{3'}H$), 121.8 ($C^{7'}H$), 127.3 (2 x $C^{12}H$, overlays $C^{8a'}$), 128.1 ($C^{4a'}$), 130.0 (C^{11}), 131.6 ($C^{8'}H$), 140.7 ($CH=CH_2$), 144.7 ($C^{4'}$), 147.5 ($C^{2'}H$), 157.8 ($C^{6'}OMe$), 158.3 (C^{14}), 181.0 ($C^{10}=S$); IR (neat) ν_{max}/cm^{-1} 3188w, 2935w, 1621w, 1506s, 1474m, 1238s, 1227s, 1028m; m/z (ES^+) 489.2 ($[M+H]^+$, 100%); HRMS (ES^+) 489.2329 $[M+H]^+$, $C_{28}H_{33}N_4O_2S$ requires 489.2324; $[\alpha]_D$ −142 ° (*c* = 1.0, $CHCl_3$, 20 °C).

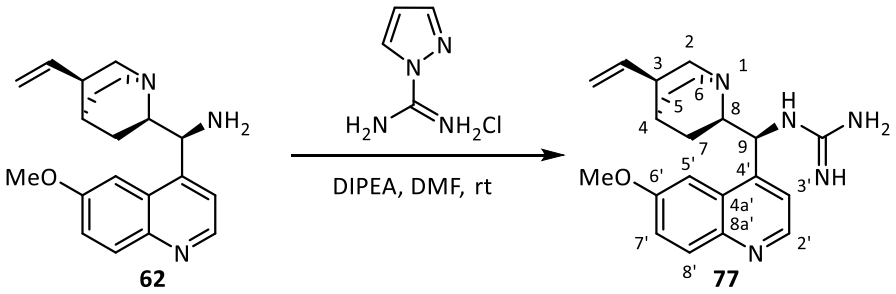
N-Cyclohexyl-1,3-dimethylimidazolidin-2-imine 69[74]



68 **69**

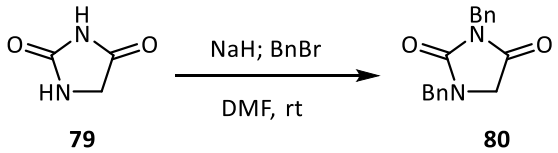
Synthesised according to the literature procedure.[75] Dicyclohexyl carbodiimide (240 mg, 1.16 mmol) was added to a solution of dimethyl ethylenediamine **68** (150 µL, 1.37 mmol) in toluene (7 mL) in a sealed tube. The sealed tube was then heated to 115 °C for 64 h. The reaction mixture was then concentrated under reduced pressure. The residue was treated with 30% aqueous NaOH (100 mL) and extracted with Et_2O (3 x 80 mL). The combined organic layers were dried with Na_2SO_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_f 0.05 (3:1 EtOAc/MeOH); ^1H NMR (400 MHz, $CDCl_3$): δ 1.03-1.32 (6H, m, Cy), 1.62-1.70 (4H, m, Cy), 2.70 (6H, br s, 2 x NCH_3), 3.06 (4H, s, NCH_2CH_2N), 3.31-3.41 (1H, m, NCH); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3 (3 x CH_2, Cy), 25.9 (2 x CH_2, Cy), 36.6 (2 x NCH_3), 49.4 (br, 2 x NCH_2), 54.2 (NCH), 155.7 (C=N); IR (neat) ν_{max}/cm^{-1} 2923m, 2849m, 1655s, 1479w, 1447m, 1378m, 1260m, 1226m, 1029m, 950m; m/z (ES^+) 196.2 ($[M+H]^+$, 90%); HRMS (ES^+) 196.1820 $[M+H]^+$, $C_{11}H_{22}N_3$ 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.[76] Amine **62** (136 mg, 0.420 mmol) was added to a stirring solution of NEt*i*Pr$_2$ (73 µL, 0.420 mmol) and 1*H*-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 Et$_2$O (3 mL) was added to precipitate the product. The product was then filtered and washed with more Et$_2$O (2 x 5 mL) before drying under reduced pressure to afford guanidine **77** as a white powder (136 mg, 88%). R_f 0.08 (1:1 EtOAc/MeOH); m.p. decomposed at 200 °C; ^{1}H NMR (400 MHz, CD$_3$OD): δ 0.97-1.08 (1H, m, CH*H*^{7}), 1.29-1.42 (1H, m, C*H*H^7), 1.59-1.81 (3H, m, CH$_2^5$ and CH^4), 2.40 (1H, br s, CH^3), 2.84-3.04 (2H, m, CH*H*^{6} and CH*H*^{2}), 3.25-3.52 (3H, m, C*H*H^6, CH^8 and C*H*H^2), 4.04 (3H, s, OCH$_3$), 4.95-5.10 (2H, m, CH=C*H*$_2$), 5.36 (1H, br s, C*H*^{9}NH), 5.81 (1H, ddd, *J* = 17.5, 10.5, 7.5 Hz, C*H*=CH$_2$), 7.51 (1H, dd, *J* = 9.0, 2.5 Hz, CH$^{7'}$), 7.64-7.70 (2H, m, CH$^{3'}$ and CH$^{5'}$), 8.02 (1H, d, *J* = 9.0 Hz, CH$^{8'}$), 8.73 (1H, d, *J* = 4.5 Hz, CH$^{2'}$), NH protons not observed; ^{13}C NMR (100 MHz, CD$_3$OD): δ 26.5 (C^{7}H$_2$), 28.4 (C^{4}H), 28.8 (C^{5}H$_2$), 40.6 (C^{3}H), 42.1 (C^{6}H$_2$), 56.2 (C^{2}H$_2$), 56.9 (OCH$_3$), 60.0 (C^{9}H overlays C^{8}H), 103.3 (C$^{5'}$H), 115.4 (CH=*C*H$_2$), 122.7 (C$^{3'}$H), 123.8 (C$^{7'}$H), 129.2 (C$^{4a'}$), 132.2 (C$^{8'}$H), 142.4 (*C*H=CH$_2$), 144.4 (C$^{4'}$), 145.6 (C$^{8a'}$), 148.6 (C$^{2'}$H), 159.1 (C$^{6'}$OMe), 160.3 (C=NH); IR (neat) ν_{max}/cm^{-1} 3130w (br), 2945w, 1660m, 1637s, 1622m, 1509w, 1478w, 1230m, 1026m; m/z (ES$^+$) 366.2 ([M+H]$^+$, 100%), 183.6 ([M+2H]$^{2+}$, 50%); HRMS (ES$^+$) 366.2300 [M+H]$^+$, C$_{21}$H$_{28}$N$_5$O requires 366.2294; $[\alpha]_D$ −44.4° (*c* = 1.0, MeOH, 23 °C).

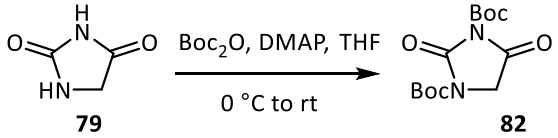
1,3-Dibenzylimidazolidine-2,4-dione 80[77]



79 **80**

Synthesised according to the literature procedure.[78] 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 H_2O (80 mL) and extracted with EtOAc (3 x 80 mL). The combined organic layers were washed with brine (150 mL), dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (4:1:0 to 1:0:0 to 98:0:2 CH_2Cl_2/petrol/MeOH) afforded protected hydantoin **80** as a pale yellow oil (298 mg, 48%). R_f 0.15 (1:1 petrol/Et_2O); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.65 (2H, s, CH_2CO), 4.47 (2H, s, NCH_2), 4.61 (2H, s, NCH_2), 7.13-7.39 (10H, m, 2 x Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 42.6 (*C*H_2CO), 46.7 (NCH_2), 49.1 (NCH_2), 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(O)N), 169.5 (NC(O)CH_2); IR (neat) ν_{max}/cm^{-1} 3032w, 2926w, 1768w, 1701s, 1451m, 1336m, 1235m, 1137m.

1,3-Di-(*tert*-butoxycarbonyl)hydantoin 82[79]

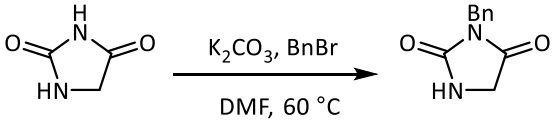


79 **82**

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 CH_2Cl_2 (400 mL) and washed with 2 N HCl (200 mL), saturated aqueous $NaHCO_3$ (200 mL) and brine (200 mL). The organic layer was then dried with $MgSO_4$ and concentrated under reduced pressure. Purification by flash column chromatography (1:1 petrol/Et_2O) afforded protected hydantoin **82** as a pale yellow powder (489 mg, 51%). R_f 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 (N*C*(O)CH_2); IR (neat) ν_{max}/cm^{-1} 3285m, 3063w, 3032w, 1771w, 1718w, 1635s, 1547s, 1490m, 1453m, 1364m, 1316m, 1259s, 1159m, 1027m.

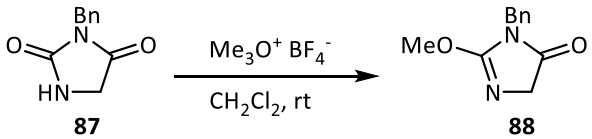
3-Benzylimidazolidine-2,4-dione 87[80]



79 **87**

Benzyl bromide (4.26 mL, 35.9 mmol) was added to a suspension of hydantoin **79** (1.20 g, 12.0 mmol) and K_2CO_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_2O (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_2SO_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, C*H*$_2$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_2NH), 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) ν_{max}/cm^{-1} 3222w, 3098w, 1768m, 1724s, 1706s, 1459s, 1450s, 1340m, 1141m.

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

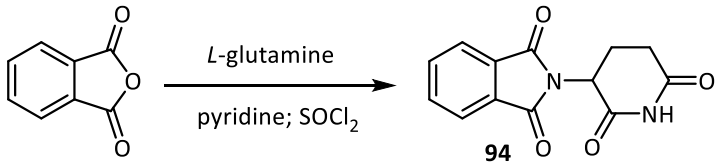


87 **88**

Synthesised according to the literature procedure.[81] Hydantoin **87** (106 mg, 0.558 mmol) as a solution in CH_2Cl_2 (1.5 mL) was added to trimethyloxonium tetrafluoroborate (99 mg, 0.669 mmol) in CH_2Cl_2 (1.5 mL). The reaction mixture was stirred at rt for 17 h. It was then diluted

with CH_2Cl_2 (20 mL), washed with ice cold saturated aqueous $NaHCO_3$ (20 mL), dried with $MgSO_4$ 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%). R_f 0.26 (EtOAc); m.p. 60-63 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.99 (3H, s, CH_3), 4.10 (2H, s, $CH_2C(O)$), 4.62 (2H, s, NCH_2) 7.26-7.38 (5H, m, Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.1 (NCH_2), 55.5 (OCH_3), 56.6 ($CH_2C(O)$), 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]$^+$, $C_{11}H_{13}N_2O_2$ requires 205.0977.

Thalidomide 94[82]

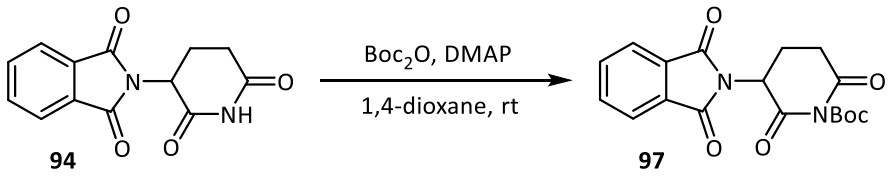


94

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%). R_f 0.26 (1:1 petrol/EtOAc); m.p. 221-224 °C (recrystallised from ethanol, lit. 274-276 °C); ^{1}H NMR (400 MHz, DMSO): δ 2.01-2.13 (1H, m, C(O)CH*H'*), 2.50-2.65 (2H, m, C(O)C*H*H'C*H*H'), 2.84-2.96 (1H, m, $C(O)CH_2CH$*H'*), 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); ^{13}C NMR (100 MHz, DMSO): δ 22.0 ($C(O)CHCH_2$), 30.9 ($C(O)CH_2$), 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 (CH_2C(O)NH); IR

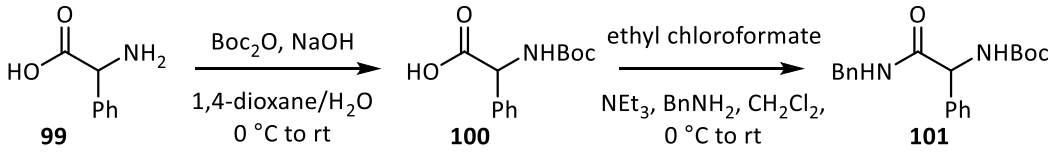
(neat) ν_{max}/cm^{-1} 3200w (br), 3097w, 1771w, 1697s, 1469w, 1383m, 1360m, 1324m, 1256m, 1196m, 1113m.

tert-Butyl 3-(1,3-dioxoisoindolin-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_2O (2 mL). The product was filtered, washed with Et_2O (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*H*'), 2.77-3.04 (3H, m, C(O)C*H*H'CH_2), 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*C*H_2), 27.4 (C(*C*H_3)$_3$), 31.6 (C(O)*C*H_2), 49.5 (C(O)*C*H), 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 (CH*C*(O)NH), 167.1 (*C*(O)N*C*(O)), 168.6 (CH_2*C*(O)NH); IR (neat) ν_{max}/cm^{-1} 3005w, 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]$^+$, $C_{18}H_{18}N_2O_6Na$ requires 381.1063.

tert-Butyl (2-(benzylamino)-2-oxo-1-phenylethyl)carbamate 101[83]

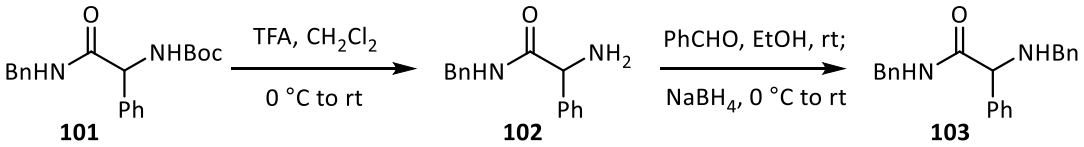


Boc protected amino acid **100** was synthesised according to the literature procedure.[84] Phenylglycine **99** (1.21 g, 7.99 mmol) was suspended in 1 N NaOH (16 mL) and 1,4-dioxane (5 mL) and cooled to 0 °C. Di-*tert*-butyl dicarbonate (2.02 mL, 8.79 mmol) in 1,4-dioxane (6 mL) was added to the reaction mixture and it was warmed to rt and stirred for 18 h. The reaction

mixture was then diluted with H_2O (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 H_2O (400 mL) and brine (400 mL), dried with $MgSO_4$ 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.[85] NEt_3 (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 CH_2Cl_2 (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 CH_2Cl_2 (300 mL) and washed with saturated aqueous $NaHCO_3$ (200 mL) and brine (200 mL). The organic layer was dried with $MgSO_4$, 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%). R_f 0.46 (1:1 petrol/EtOAc); m.p. 123-125 °C (lit. 118-119); ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.40 (9H, s, C(CH_3)$_3$), 4.42 (1H, s, C*H*H'), 4.44 (1H, s, CH*H'*), 5.21 (1H, br s, NH), 5.86 (1H, br s, C*H*NH), 6.15 (1H, br s, NH), 7.09-7.43 (10H, m, 2 x Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.3 (C(*C*H_3)$_3$), 43.6 (CH_2), 58.6 (CHNH), 80.1 (*C*(CH_3)$_3$), 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



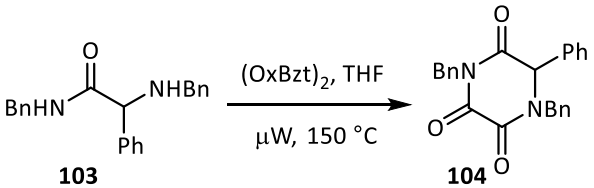
101 **102** **103**

Amine **102** was synthesised according to the literature procedure.[86] Trifluoroacetic acid (5.7 mL) was added carefully to a solution of Boc amide **101** (1.68 g, 4.94 mmol) in CH_2Cl_2 (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_2SO_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_2O (100 mL) and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were dried with Na_2SO_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, $CDCl_3$): δ 2.05 (1H, br s, CHN*H*), 3.78 (2H, s, CHNHC*H*$_2$), 4.31 (1H, s, C*H*NH), 4.46 (1H, s, C(O)NHC*H*H'), 4.48 (1H, s, C(O)NHCH*H*'), 7.20-7.54 (15H, m, 3 x Ph), C(O)NH proton not observed; ^{13}C NMR (100 MHz, $CDCl_3$): δ 43.2 (C(O)NH*C*H$_2$), 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) ν_{max}/cm^{-1} 3305w (br), 3029w, 1653s, 1515m, 1495m, 1453m, 1265w, 1028w; m/z (ES$^+$) 331.2 ([M+H]$^+$, 60%); HRMS (ES$^+$) 331.1800 [M+H]$^+$, $C_{22}H_{23}N_2O$ requires 331.1810.

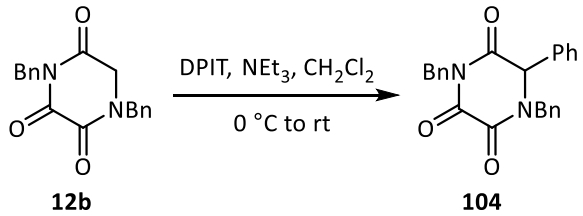
1,4-Dibenzyl-6-phenylpiperazine-2,3,5-trione 104



103 **104**

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%).

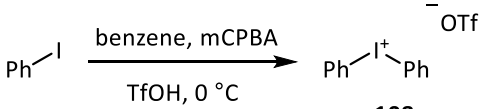


12b **104**

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 CH_2Cl_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 (CH_2Cl_2) afforded *TKP* **104** as a white powder (19 mg, 48%).

R_f 0.52 (1:1 petrol/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.59 (1H, d, *J* = 14.0 Hz, CHNC*H*H'), 4.85 (1H, d, *J* = 14.0 Hz, C(O)NC*H*H'), 5.04 (1H, d, *J* = 14.0 Hz, C(O)NCH*H'*), 5.12 (1H, s, CHPh), 5.54 (1H, d, *J* = 14.0 Hz, CHNCH*H'*), 7.13-7.48 (15H, m, 3 x Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 44.5 (C(O)N*C*H_2), 47.8 (CHN*C*H_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 (CHN*C*(O)), 156.3 (CHNC(O)*C*(O)), 166.6 (CH*C*(O)); IR (neat) ν_{max}/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[88]

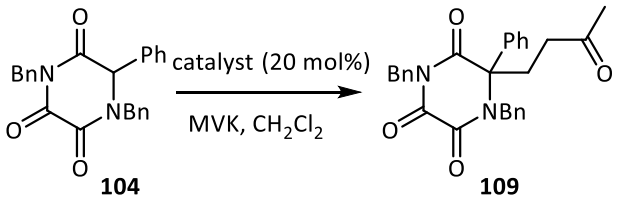


108

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 CH_2Cl_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 Et_2O (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 Et_2O (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 CH_2Cl_2/Et_2O, lit. 172-174 °C); ^{1}H NMR (300 MHz, $CDCl_3$): 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); ^{13}C NMR (100 MHz, $CDCl_3$): 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

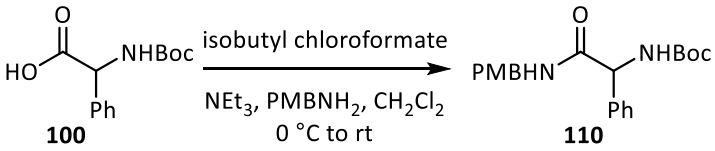


104 **109**

Methyl vinyl ketone (11 µL, 0.130 mmol) was added to a solution of TKP **104** (20 mg, 0.052 mmol) in CH_2Cl_2 (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). R_f 0.39 (1:1 petrol/EtOAc); m.p. 121-123 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.61 (3H, s, CH_3), 1.76-1.83 (2H, m, C(O)CH_2), 2.37-2.46 (1H, m, C(O)CH_2C*H*H'), 2.95-3.04 (1H, m, C(O)CH_2CH*H'*), 3.65 (1H, d, *J* = 15.0 Hz, PhCNC*H*H'), 4.94 (1H, d, *J* = 13.5 Hz, (C(O)NC*H*H'), 5.10 (1H, d, *J* = 13.5 Hz, C(O)NCH*H'*), 5.23 (1H, d, *J* = 15.0 Hz, PhCNCH*H'*), 7.20-7.44 (15H, m, 3 x Ph); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.3 (CH_3), 30.0 (C(O)CH_2*C*H_2), 37.0 (C(O)*C*H_2), 44.6 (C(O)N*C*H_2), 48.8 (PhCN*C*H_2), 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), 137.8 (C, Ph), 155.0 (PhCNC(O)*C*(O)), 155.7 (PhCN*C*(O), 169.0 (PhC*C*(O)), 205.0

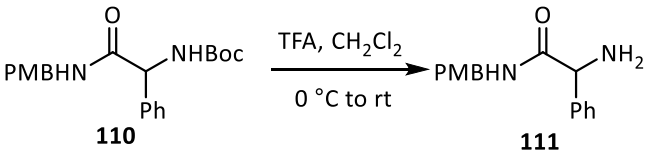
($CH_3C(O)$); IR (neat) ν_{max}/cm^{-1} 3064w, 2852w, 1744w, 1713w, 1681s, 1495w, 1420m, 1359m, 1266m, 1231m, 1144m, 1030w; m/z (ES^+) 477.2 ($[M+Na]^+$, 100%); HRMS (ES^+) 477.1788 $[M+Na]^+$, $C_{28}H_{26}N_2O_4Na$ requires 477.1790.

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



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_2Cl_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_2Cl_2 (200 mL) was added and the organic layer was washed with saturated aqueous $NaHCO_3$ (200 mL) and brine (200 mL). The organic later was then dried with Na_2SO_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; ^1H NMR (300 MHz, $CDCl_3$): δ 1.36 (9H, s, $C(CH_3)_3$), 3.76 (3H, s, OCH_3), 4.29 (1H, s, NHC*H*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, $CDCl_3$): δ 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 (*C*CH, Ph), 155.2 (NHC(O)O), 158.8 ($COCH_3$, PMP), 170.1 (NHC(O)); IR (neat) ν_{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 $[M+Na]^+$, $C_{21}H_{26}N_2O_4Na$ requires 393.1790.

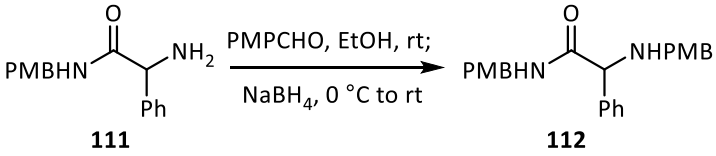
2-Amino-*N*-(4-methoxybenzyl)-2-phenylacetamide 111



110 **111**

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 CH_2Cl_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 $NaHCO_3$ (400 mL). The organic layer was then dried with Na_2SO_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}H NMR (300 MHz, $CDCl_3$): δ 1.97 (2H, br s, NH_2), 3.80 (3H, s, OCH_3), 4.37 (1H, s, NHC*H*H'), 4.39 (1H, s, NHCH*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}C NMR (100 MHz, $CDCl_3$): δ 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 (*C*CH_2, PMP), 140.9 (C, Ph), 158.9 (*C*OCH_3, PMP), 172.7 (NHC(O)); IR (neat) ν_{max}/cm^{-1} 3257w (br), 2936w, 1631m, 1612m, 1511s, 1454m, 1303m, 1245s, 1176m, 1026s; m/z (ES$^+$) 271.1 ([M+H]$^+$, 100%); HRMS (ES$^+$) 271.1444 [M+H]$^+$, $C_{16}H_{19}N_2O_2$ requires 271.1447.

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

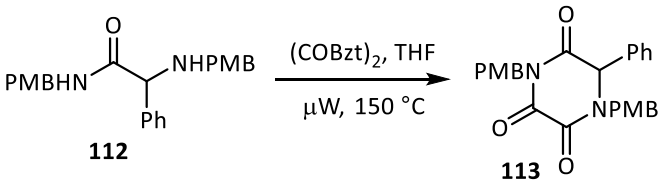


111 **112**

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_2O (100 mL) and extracted with CH_2Cl_2 (3 x 200 mL). The combined organic layers were dried

with Na_2SO_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, $CDCl_3$): δ 3.70 (2H, s, CHNHC*H*$_2$), 3.80 (6H, s, 2 x OCH_3), 4.31 (1H, s, CHPh), 4.38 (1H, s, C(O)NHC*H*H'), 4.40 (1H, s, C(O)NHCH*H'*), 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, $CDCl_3$): δ 42.6 (C(O)NH*C*H$_2$), 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 (CH, Ph), 128.8 (2 x CH, PMP), 129.0 (2 x CH, PMP), 129.4 (2 x CH, Ph), 130.4 (*C*CH$_2$, PMP), 131.2 (*C*CH$_2$, PMP), 139.2 (C, Ph), 158.8 (*C*OCH$_3$, PMP), 158.9 (*C*OCH$_3$, PMP), 171.8 (NHC(O)); IR (neat) ν_{max}/cm^{-1} 3308w (br), 2934w, 2835w, 1654m, 1611m, 1511s, 1454m, 1243s, 1175m, 1031m; m/z (ES$^+$) 391.2 ([M+H]$^+$, 100%); HRMS (ES$^+$) 391.2030 [M+H]$^+$, $C_{24}H_{27}N_2O_3$ requires 391.2022.

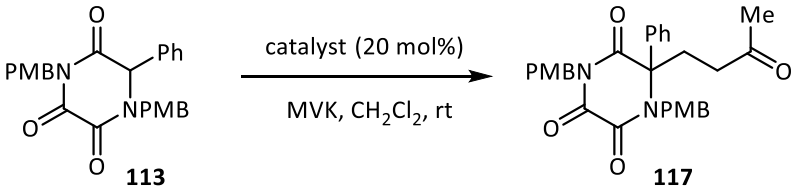
1,4-Bis(4-methoxybenzyl)-6-phenylpiperazine-2,3,5-trione 113



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_2Cl_2/Et_2O) 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, $CDCl_3$): δ 3.52 (1H, d, *J* = 14.5 Hz, CHNC*H*H'), 3.76 (3H, s, OCH_3), 3.81 (3H, s, OCH_3), 4.78 (1H, d, *J* = 13.5 Hz, C(O)NC*H*H'), 4.98 (1H, d, *J* = 13.5 Hz, C(O)NCH*H'*), 5.10 (1H, s, CHPh), 5.47 (1H, d, *J* = 14.5 Hz, CHNCH*H'*), 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, $CDCl_3$): δ 44.0 (C(O)N*C*H$_2$), 47.2 (CHN*C*H$_2$), 55.2 (OCH_3), 55.3 (OCH_3), 63.3 (CHPh), 113.8 (2 x CH, PMP), 114.4 (2 x CH, PMP), 125.7 (*C*CH$_2$, 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 (CHN*C*(O)), 156.3 (CHNC(O)*C*(O)), 159.3 (*C*OCH_3, PMP), 159.8 (*C*OCH_3, PMP), 166.7 (CH*C*(O)); IR (neat) ν_{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 $[M+Na]^+$, $C_{26}H_{24}N_2O_5Na$ requires 467.1583.

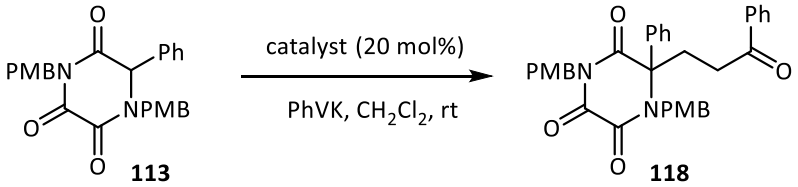
1,4-Bis(4-methoxybenzyl)-6-(3-oxobutyl)-6-phenylpiperazine-2,3,5-trione 117



Methyl vinyl ketone (13 µL, 0.155 mmol) was added to a solution of TKP **113** (28 mg, 0.062 mmol) in CH_2Cl_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, $CDCl_3$): δ 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_2C*H*H'), 3.00-3.15 (1H, m, C(O)CH_2CH*H'*), 3.68 (1H, d, *J* = 14.5 Hz, PhCNC*H*H'), 3.82 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 4.95 (1H, d, *J* = 13.5 Hz, C(O)NCH*H'*), 5.12 (1H, d, *J* = 13.5 Hz, C(O)NC*H*H'), 5.19 (1H, d, *J* = 14.5 Hz, PhCNCH*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, $CDCl_3$): δ 29.3 (CH_3), 30.1 (C(O)CH_2*C*H_2), 37.0 (C(O)*C*H_2), 44.1 (C(O)N*C*H_2), 48.2 (PhCN*C*H_2), 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 (*C*CH_2, PMP), 128.5 (*C*CH_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*C*(O)), 155.8 (PhCNC(O)*C*(O)), 159.3 (*C*OCH_3, PMP), 159.4 (*C*OCH_3, PMP), 169.1 (PhC*C*(O)), 205.2 (CH_3*C*(O)); IR (neat) ν_{max}/cm^{-1} 2958w, 1717w, 1681s, 1611w, 1512s, 1364m, 1247s, 1178m, 1031m; m/z

(ES$^+$) 537.2 ([M+Na]$^+$, 100%); HRMS (ES$^+$) 537.2005 [M+Na]$^+$, $C_{30}H_{30}N_3O_6Na$ requires 537.2002; $[\alpha]_D$ −15.1° (*c* = 1.0, $CHCl_3$, 23 °C).

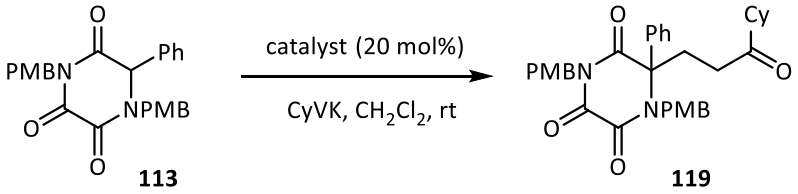
1,4-Bis(4-methoxybenzyl)-6-(3-oxo-3-phenylpropyl)-6-phenylpiperazine-2,3,5-trione 118



113 **118**

Phenyl vinyl ketone (13 µL, 0.101 mmol) was added to a solution of TKP **113** (18 mg, 0.040 mmol) in CH_2Cl_2 (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). R_f 0.42 (1:1 petrol/EtOAc); m.p. 174-175 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.22-2.37 (2H, m, C(O)CH_2), 2.55-2.75 (1H, m, C(O)CH_2C*H*H'), 3.09-3.28 (1H, m, C(O)CH_2CH*H'*), 3.44 (3H, s, OCH_3), 3.64 (1H, d, *J* = 14.5 Hz, PhCNC*H*H'), 3.67 (3H, s, OCH_3), 4.91 (1H, d, *J* = 13.5 Hz, C(O)NCH*H'*), 5.07 (1H, d, *J* = 13.5 Hz, C(O)NC*H*H'), 5.18 (1H, d, *J* = 14.5 Hz, PhCNCH*H'*), 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); ^{13}C NMR (100 MHz, $CDCl_3$): δ 30.5 (C(O)CH_2*C*H_2), 32.2 (C(O)*C*H_2), 44.0 (C(O)N*C*H_2), 48.3 (PhCN*C*H_2), 54.9 (OCH_3), 55.1 (OCH_3), 72.6 (CPh), 113.9 (2 x CH, PMP), 113.9 (2 x CH, PMP), 126.3 (2 x CH, Ph), 127.4 (*C*CH_2, PMP), 127.5 (2 x CH, Ph), 128.3 (2 x CH, Ph), 128.3 (*C*CH_2, PMP), 129.4 (CH, 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 (PhCN*C*(O)), 155.8 (PhCNC(O)*C*(O)), 159.0 (*C*OCH_3, PMP), 159.4 (*C*OCH_3, PMP), 169.2 (PhC*C*(O)), 196.8 (C(O)Ph); IR (neat) ν_{max}/cm^{-1} 2958w, 1678s, 1610m, 1512s, 1364m, 1302m, 1246s, 1177m; m/z (ES$^+$) 599.2 ([M+Na]$^+$, 100%); HRMS (ES$^+$) 599.2164 [M+Na]$^+$, $C_{35}H_{32}N_2O_6Na$ requires 599.2158; $[\alpha]_D$ −3.2° (*c* = 1.0, $CHCl_3$, 23 °C).

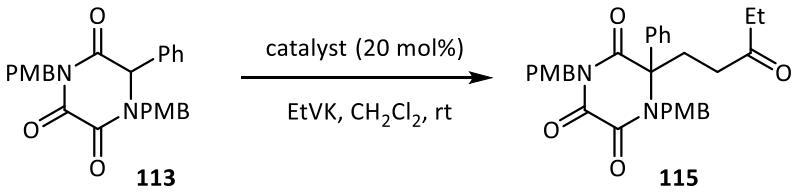
6-(3-Cyclohexyl-3-oxopropyl)-1,4-bis(4-methoxybenzyl)-6-phenylpiperazine-2,3,5-trione 119



113 **119**

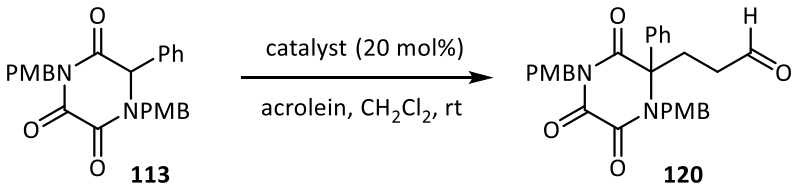
Cyclohexyl vinyl ketone (18 µL, 0.118 mmol) was added to a solution of TKP **113** (21 mg, 0.047 mmol) in CH_2Cl_2 (0.28 mL) at rt. Modified quinine catalyst **58** (4 mg, 9 µmol) was then added to the reaction mixture and stirred at rt for 45 h. Solvent was removed under reduced pressure and flash column 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). R_f 0.42 (1% MeOH in CH_2Cl_2); m.p. 64-67 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 0.80-1.45 (6H, m, 3 x CH_2, Cy), 1.50-1.77 (7H, m, 2 x CH_2, CH, Cy and C(O)CH_2), 2.35-2.51 (1H, m, C(O)CH_2C*H*H'), 2.87-3.03 (1H, m, C(O)CH_2CH*H'*), 3.55 (1H, d, *J* = 14.5 Hz, PhCNC*H*H'), 3.72 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 4.87 (1H, d, *J* = 13.0 Hz, C(O)NCH*H'*), 5.03-5.15 (2H, m, C(O)NC*H*H' 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); ^{13}C NMR (100 MHz, $CDCl_3$): δ 25.3 (CH_2, Cy), 25.5 (CH_2, Cy), 25.6 (CH_2, Cy), 28.0 (CH_2, Cy), 28.4 (CH_2, Cy), 30.3 (C(O)CH_2*C*H_2), 33.9 (C(O)*C*H_2), 44.0 (C(O)N*C*H_2), 48.3 (PhCN*C*H_2), 50.4 (C(O)*C*H), 55.1 (2 x OCH_3), 72.6 (CPh), 113.8 (2 x CH, PMP), 113.9 (2 x CH, PMP), 126.4 (2 x CH, Ph), 127.3 (*C*CH_2, PMP), 128.6 (*C*CH_2, 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*C*(O)), 155.8 (PhCNC(O)*C*(O)), 159.2 (*C*OCH_3, PMP), 159.4 (*C*OCH_3, PMP), 169.2 (PhC*C*(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]$^+$, $C_{35}H_{38}N_2O_6Na$ requires 605.2628; $[\alpha]_D$ −4.1° (*c* = 1.0, $CHCl_3$, 23 °C).

1,4-Bis(4-methoxybenzyl)-6-(3-oxopentyl)-6-phenylpiperazine-2,3,5-trione 115



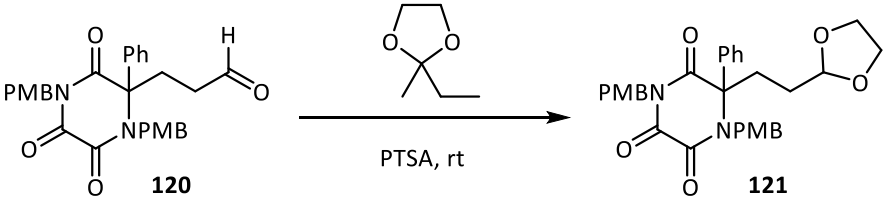
Ethyl vinyl ketone (11 µL, 0.112 mmol) was added to a solution of TKP **113** (20 mg, 0.045 mmol) in CH_2Cl_2 (0.27 mL) at rt. Modified quinine catalyst **58** (4 mg, 9 µmol) was then added to the reaction mixture and stirred at rt for 20 h. Solvent was removed under reduced pressure and flash column 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, $CH_2C(O)CH_2$), 2.39-2.53 (1H, m, $C(O)CH_2CHH'$), 2.93-3.09 (1H, m, $C(O)CH_2CHH'$), 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 ($C(O)CH_2CH_2$), 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 ($PhCNC(O)$), 155.8 ($PhCNC(O)C(O)$), 159.2 ($COCH_3$, PMP), 159.4 ($COCH_3$, PMP), 169.1 ($PhCC(O)$), 208.0 ($C(O)CH_2CH_3$); IR (neat) ν_{max}/cm^{-1} 1715w, 1682s, 1513s, 1365m, 1303m, 1247s, 1178m, 1032m; m/z (ES^+) 551.2 ($[M+H]^+$, 100%); HRMS (ES^+) 551.5156 $[M+H]^+$, $C_{31}H_{32}N_2O_6Na$ requires 551.2158; $[\alpha]_D$ −12.0° (*c* = 1.0, $CHCl_3$, 23 °C).

3-(1,4-Bis(4-methoxybenzyl)-3,5,6-trioxo-2-phenylpiperazin-2-yl)propanal 120



Acrolein (15 µL, 0.231 mmol) was added to a solution of TKP **113** (21 mg, 0.046 mmol) in CH_2Cl_2 (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%). R_f 0.39 (1:1 petrol/EtOAc); m.p. not obtainable; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.80-1.93 (2H, m, C(O)CH_2), 2.44-2.56 (1H, m, C(O)CH_2C*H*H'), 3.01-3.14 (1H, m, C(O)CH_2CH*H'*), 3.59 (1H, d, *J* = 14.5 Hz, PhCNC*H*H'), 3.74 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 4.87 (1H, d, *J* = 13.0 Hz, C(O)NCH*H'*), 5.01 (1H, d, *J* = 13.0 Hz, C(O)NC*H*H'), 5.18 (1H, d, *J* = 14.5 Hz, PhCNCH*H'*), 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); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.4 (C(O)CH_2*C*H_2), 38.0 (C(O)*C*H_2), 44.2 (C(O)N*C*H_2), 48.3 (PhCN*C*H_2), 55.2 (OCH_3), 55.3 (OCH_3), 72.5 (CPh), 113.9 (2 x CH, PMP), 114.0 (2 x CH, PMP), 126.1 (2 x CH, Ph), 127.2 (*C*CH_2, PMP), 128.4 (*C*CH_2, 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*C*(O)), 155.6 (PhCNC(O)*C*(O)), 159.3 (*C*OCH_3, PMP), 159.4 (*C*OCH_3, PMP), 168.9 (PhC*C*(O)), 198.3 (CHO); IR (neat) ν_{max}/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]$^+$, $C_{29}H_{29}N_2O_6$ 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 H_2O (5 mL) and extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were then dried with Na_2SO_4 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). R_f 0.29 (1:1 petrol/EtOAc); m.p. 157-159 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.07-1.23 (2H, m, $PhCCH_2CH_2$), 2.21-2.35 (1H, m, PhCC*H*H'), 2.80-2.92 (1H, m, PhCCH*H'*), 3.64-3.73 (4H, m, OCH_2CH_2O), 3.75 (3H, s, OCH_3), 3.76 (3H, s, OCH_3), 3.86 (1H, d, *J* = 14.5 Hz, PhCNC*H*H'), 4.39 (1H, t, *J* = 5.0 Hz, $PhCCH_2CH_2CH$), 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)NC*H*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); ^{13}C NMR (100 MHz, $CDCl_3$): δ 28.4 ($PhCCH_2$), 30.6 ($PhCCH_2CH_2$), 44.1 ($C(O)NCH_2$), 48.1 ($PhCNCH_2$), 55.2 (OCH_3), 55.3 (OCH_3), 64.7 (OCH_2CH_2O), 72.8 (CPh), 103.0 ($PhCCH_2CH_2CH$), 113.7 (2 x CH, PMP), 113.8 (2 x CH, PMP), 126.4 (2 x CH, Ph), 127.3 (CCH_2, PMP), 128.4 (CCH_2, 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 (PhCNC(O)C(O)), 159.1 ($COCH_3$, PMP), 159.3 ($COCH_3$, PMP), 169.5 (PhCC(O)); IR (neat) ν_{max}/cm^{-1} 2955w, 1686s, 1514s, 1367m, 1303m, 1248s, 1179m, 1032m; m/z (ES$^+$) 545.2 ([M+H]$^+$, 100%); HRMS (ES$^+$) 545.2292 [M+H]$^+$, $C_{31}H_{33}N_2O_7$ requires 545.2288.

4. LIST OF REFERENCES

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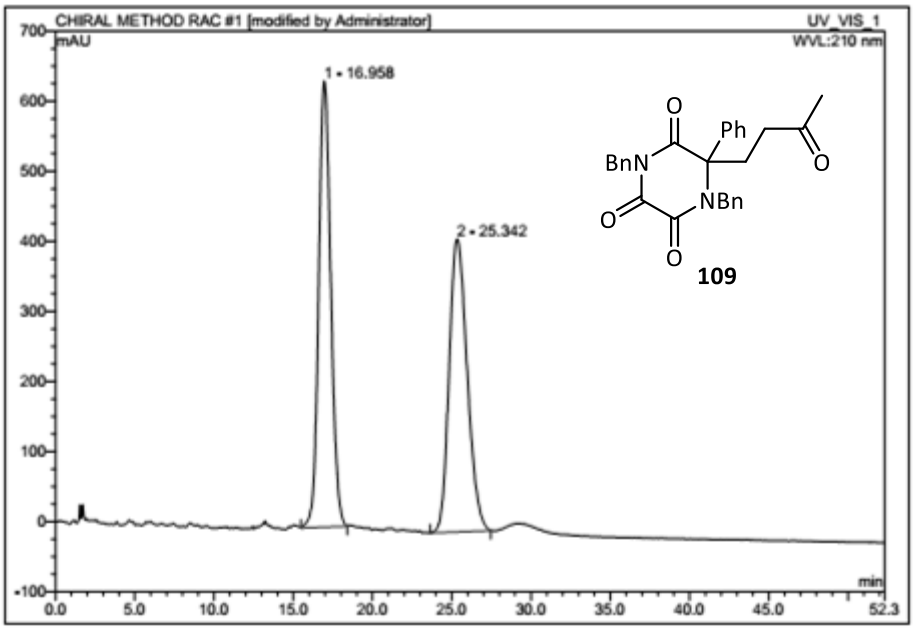
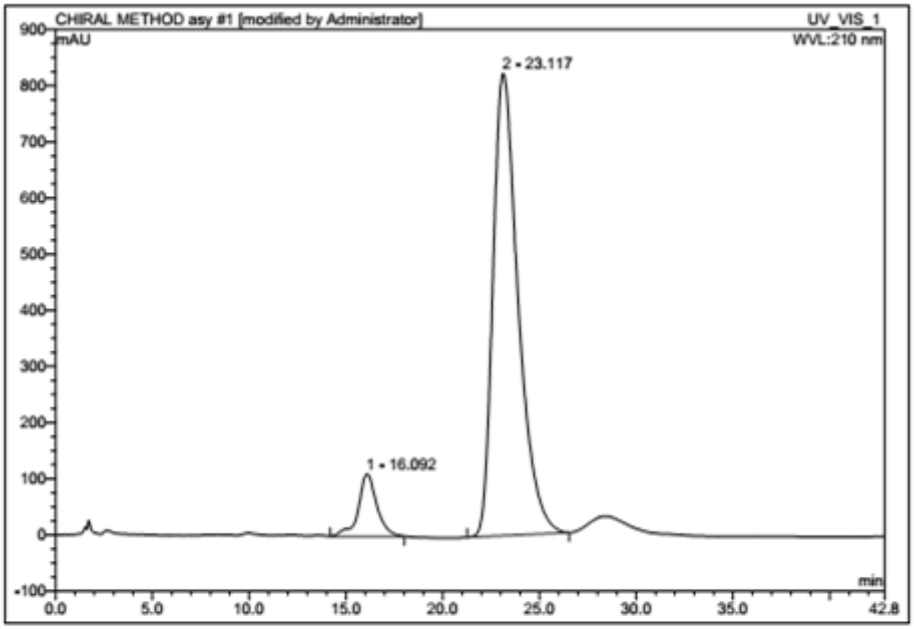
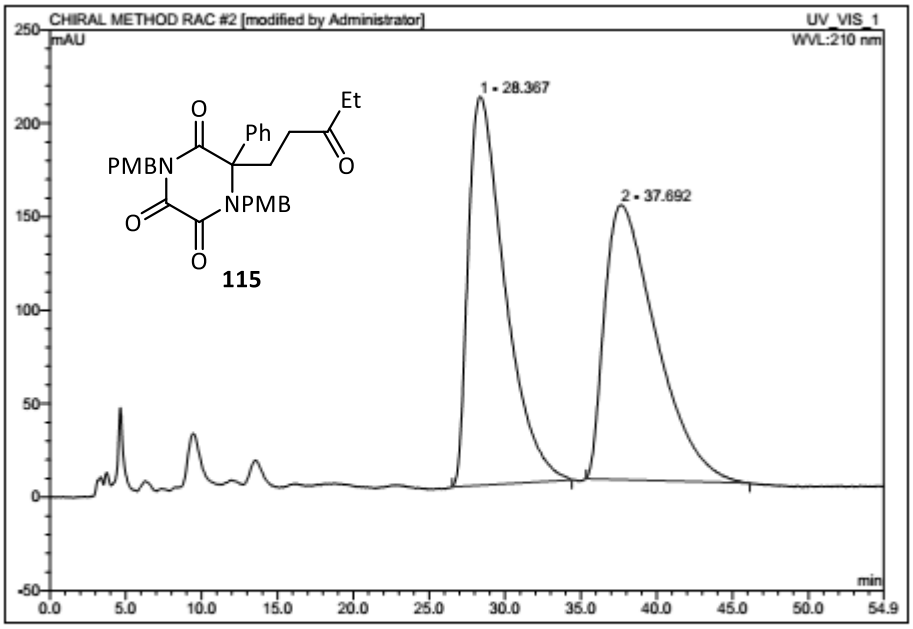
5. APPENDIX



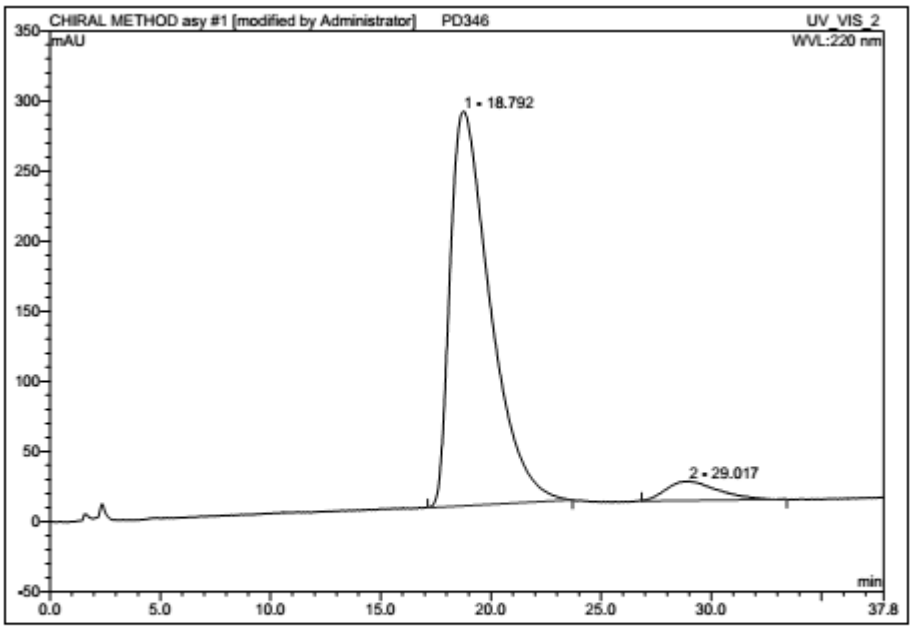
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	16.96	n.a.	636.401	563.819	50.58	n.a.	BMB
2	25.34	n.a.	418.226	550.780	49.42	n.a.	BMB
Total:			1054.627	1114.599	100.00	0.000	



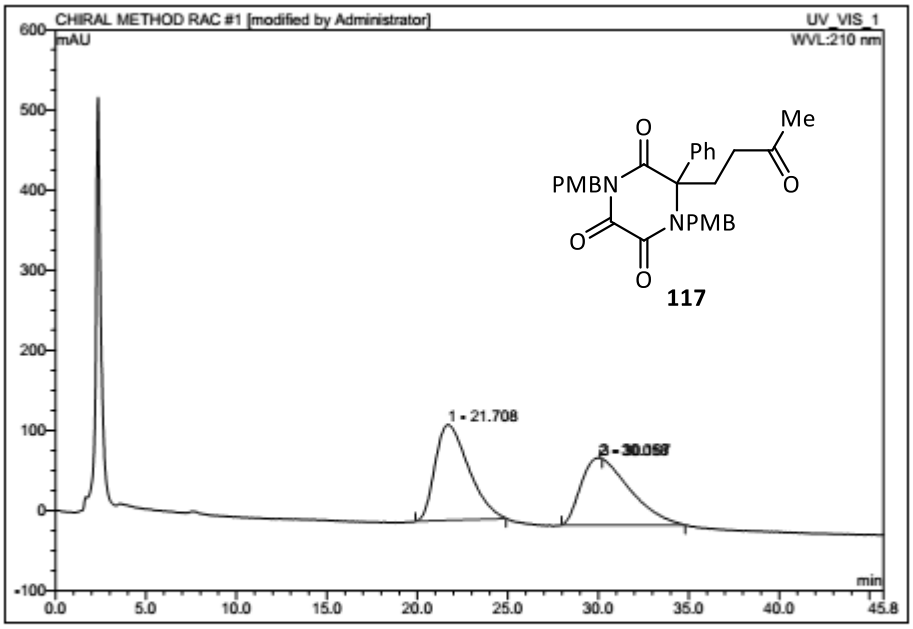
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	16.09	n.a.	111.253	123.174	9.03	n.a.	BMB
2	23.12	n.a.	823.869	1240.666	90.97	n.a.	BMB*
Total:			935.122	1363.840	100.00	0.000	



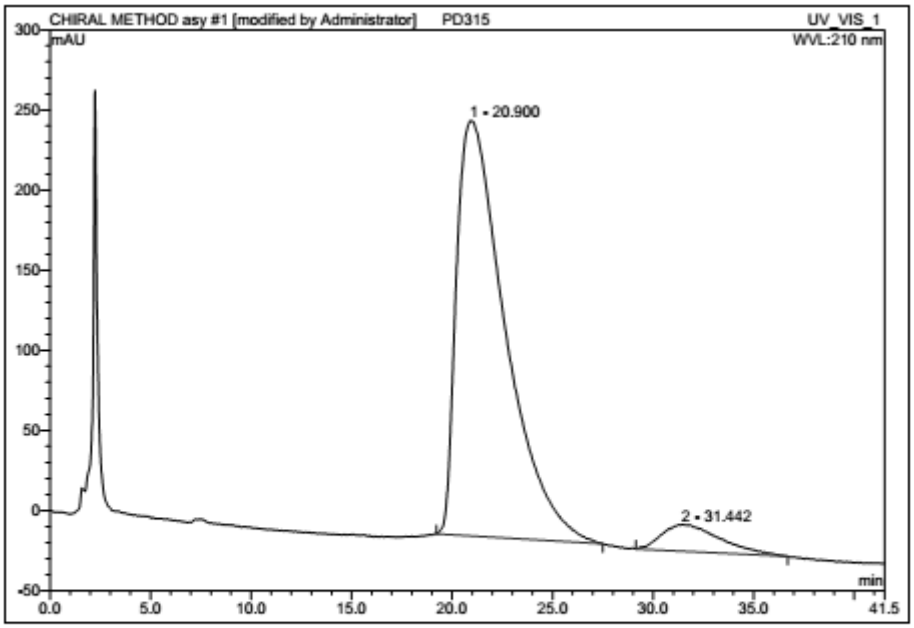
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	28.37	n.a.	207.994	583.685	50.08	n.a.	BMB*
2	37.69	n.a.	146.959	581.778	49.92	n.a.	BMB*
Total:			354.953	1165.463	100.00	0.000	



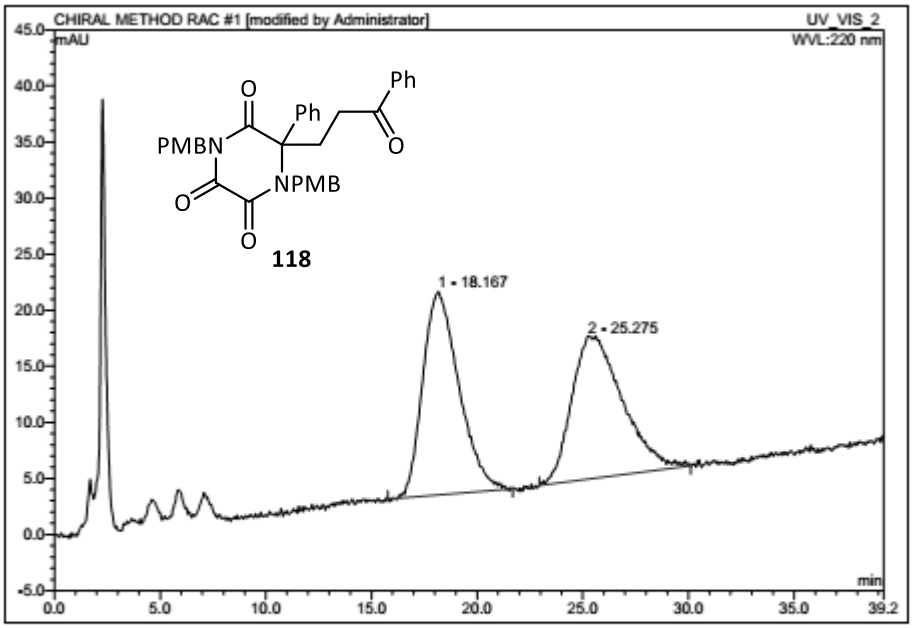
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	18.79	n.a.	281.165	591.314	94.09	n.a.	BMB*
2	29.02	n.a.	13.878	37.131	5.91	n.a.	BMB*
Total:			295.043	628.445	100.00	0.000	



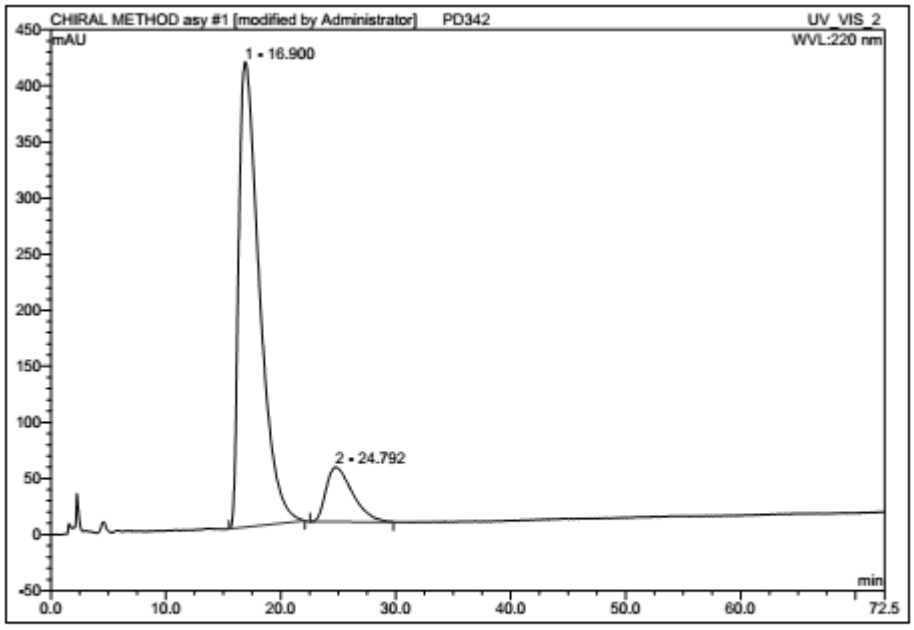
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	21.71	n.a.	119.091	256.608	49.84	n.a.	BMB
2	30.06	n.a.	83.728	258.246	50.16	n.a.	BMB*
3	30.17	n.a.	0.596	0.036	0.01	n.a.	Rd
Total:			203.415	514.891	100.00	0.000	



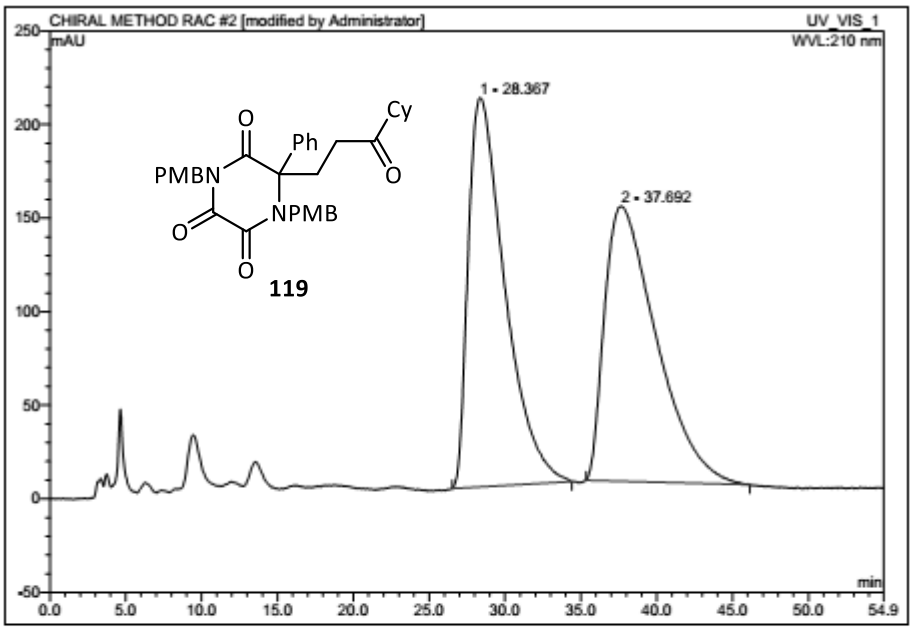
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	20.90	n.a.	258.955	728.238	92.83	n.a.	BMB*
2	31.44	n.a.	16.704	56.235	7.17	n.a.	BMB*
Total:			275.659	784.473	100.00	0.000	



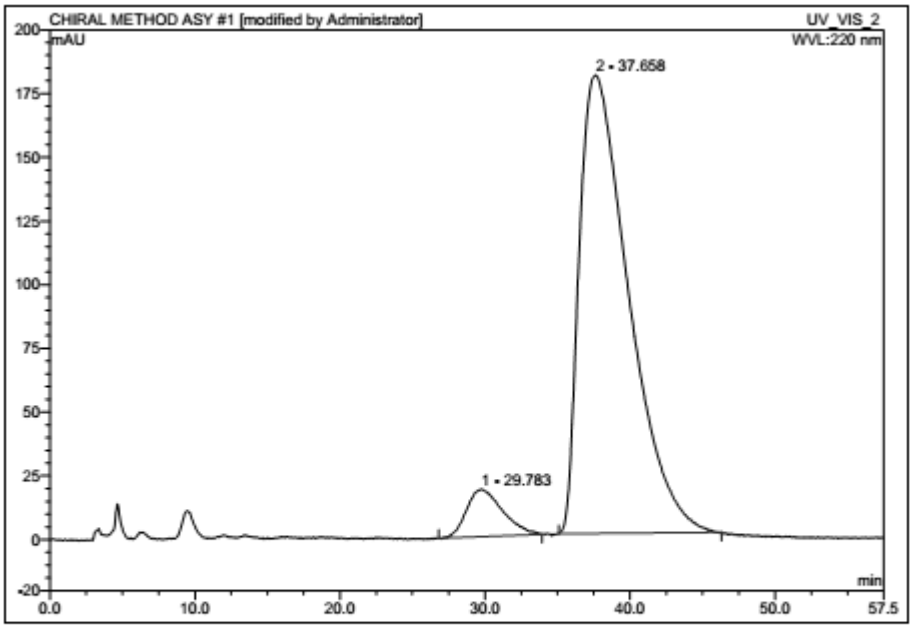
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	18.17	n.a.	18.182	35.833	50.41	n.a.	BMB*
2	25.28	n.a.	12.771	35.256	49.59	n.a.	BMB*
Total:			30.953	71.089	100.00	0.000	



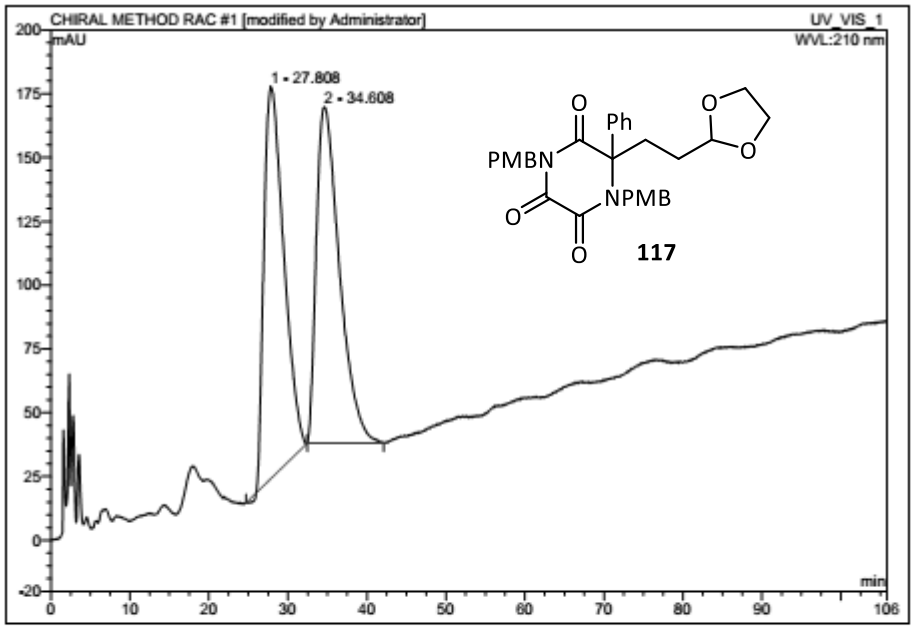
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	16.90	n.a.	415.117	866.099	86.99	n.a.	BMB*
2	24.79	n.a.	48.639	129.544	13.01	n.a.	BMB*
Total:			463.756	995.643	100.00	0.000	



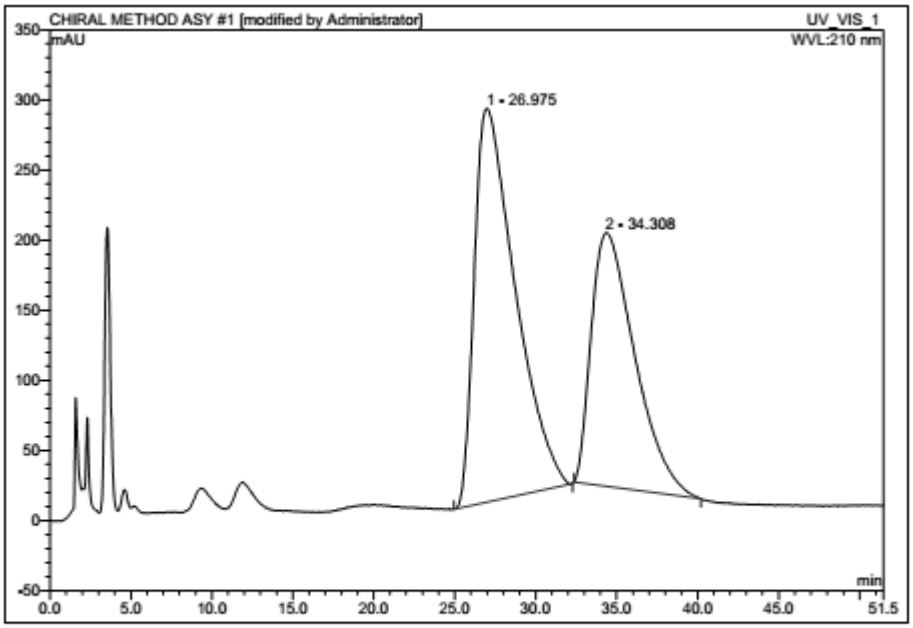
No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	28.37	n.a.	207.994	583.685	50.08	n.a.	BMB*
2	37.69	n.a.	146.959	581.778	49.92	n.a.	BMB*
Total:			354.953	1165.463	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	29.78	n.a.	18.578	53.225	7.00	n.a.	BMB*
2	37.66	n.a.	179.903	707.556	93.00	n.a.	BMB*
Total:			198.481	760.780	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	27.81	n.a.	153.837	443.875	49.84	n.a.	BMb*
2	34.61	n.a.	131.789	446.752	50.16	n.a.	bMB*
Total:			285.626	890.627	100.00	0.000	



No.	Ret.Time min	Peak Name	Height mAU	Area mAU*min	Rel.Area %	Amount	Type
1	26.98	n.a.	280.690	820.567	59.28	n.a.	BMB*
2	34.31	n.a.	180.742	563.728	40.72	n.a.	BMB*
Total:			461.432	1384.295	100.00	0.000	