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Synthetic Routes Towards Guanidines of Biological Interest



**A thesis presented to the University of Dublin
for the degree of Doctor of Philosophy**

by

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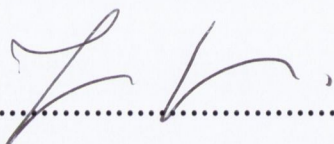
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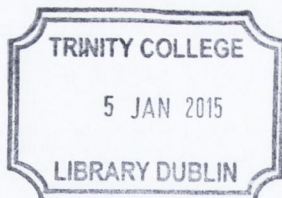


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August 2014

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Thesis 10430

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I would like to sincerely thank Prof. Isabel Rozas and Prof. David Grayson. I could not have asked for more supportive supervisors. You were both a source of constant encouragement throughout my 4 years.

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I would like to thank the Irish Fulbright Commission who gave me the most incredible experience in the Scripps Research Institute, U.S.A. I am grateful to Prof. Phil Baran for his guidance and support during my time in La Jolla, to Ming Yan, an incredibly talented graduate student who I worked on the araiosamine project with and to everyone in the Baran lab who taught me so much. I would like to also thank the Nicolaou, Yu, Boger, Sharpless/Fokin and Shenvi labs for the use of their chemicals and equipment.

Finally, I can't thank my parents and sister enough for always being there for me while I 'mucked' around in the lab for the past couple of years. Maybe someday I'll get a 'job' 😊.

Dedicated to my parents, Norman and Gladys.

Abstract.

The Rozas laboratory has been interested in the synthesis and biological evaluation of guanidine containing molecules for the past ten years. The application of guanidines as both minor groove binders (MGB) and α_2 -adrenoceptor (α_2 -AR) antagonists has been the focus of much of the research conducted. A number of promising results have been discovered in targeting the α_2 -AR, with a number of effective agonists and antagonists having been synthesised. α_2 -AR antagonists have proven to be a valid target for the alleviation of symptoms of Major Depressive Order. Historically these guanidines have been prepared by reacting the prerequisite anilines with *N,N*-bis-*tert*-butoxycarbonyl-thiourea in the presence of HgCl_2 to form the protected aryl guanidines. The use of mercury in such reactions is an obvious drawback and it was decided that its use should be eliminated from the synthesis of biologically active guanidines in Rozas group.

The overlying aim of this PhD project was therefore to design and implement the synthesis of guanidine containing compounds without the use of HgCl_2 . As previously described in the literature there are a myriad of synthetic procedures available for such a synthetic endeavour. However, many of these procedures involve the use of either toxic reagents, economically expensive precursors or lengthy procedures.

The aim of this project was therefore to design syntheses that are environmentally friendly, atom economical, cost effective, scalable and simple to purify. Gratifyingly this project has resulted in the development of three new synthetic methodologies for the formation of guanidine containing molecules all of which adhere to the above stipulations. A synthetic route for the formation of spiro guanidine containing compounds was also developed as this structural motif is prevalent in natural product chemistry and potentially useful in medicinal chemistry. It is intended that this motif will be used to explore chemical space in the α_2 -AR. The new synthetic methodologies developed have proven useful in the Rozas group for the synthesis of new α_2 -AR antagonists.

Investigations into the synthesis of guanidine containing natural products were also conducted at the Scripps Research Institute, USA under the direction of Prof. Baran.

Abbreviations.

α_2 -AR	α_2 -adrenoceptor
[O]	Oxidation
[Red.]	Reduction
BMS	Bristol Myers Squibb
Boc	<i>tert</i> -Butyloxycarbonyl
BRSM	Based on recovered starting material
Cbz	Carboxybenzyl
COSY	Correlation Spectroscopy
CSA	Camphor sulfonic acid
dba	dibenzylideneacetone
DCC	Dicyclohexyl carbodiimide
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethylazodicarboxylate
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMP	Dess-Martin Periodinane
DMSO	Dimethyl sulfoxide
DNA	Deoxyribonucleic acid
DtBPF	1,1'-Bis(di- <i>tert</i> -butylphosphino)ferrocene
EDCI	[1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ESI	Electrospray Ionisation
Fmoc	Fluoroenylmethoxycarbonyl
GPCR	G-Protein Coupled Receptor
Gua	Guanidylation
HB	Hydrogen Bond

HMBC	Heteronuclear Multiple Bond Correlation
HPLC	High Performance Liquid Chromatography
HSQC	Heteronuclear Single Quantum Coherence
HWE	Horner Wadsworth Emmons
IBX	Iodoxybenzoic acid
IR	Infrared
LDA	Lithium Diisopropylamine
LiHMDS	Lithium Hexamethyldisilazide
MBH	Morita Baylis Hillman
MDD	Major Depressive Disorder
MGB	Minor Groove Binder
mIBG	<i>meta</i> -Iodobenzylguanidine
MIT	Massachusetts Institute of Technology
MP	Melting Point
Mtr.	2,3,6-Trimethyl-4-methoxybenzenesulfonyl
MW	Microwave
NA	Noradrenaline
NAS	Nucleophilic Aromatic Substitution
NBS	<i>N</i> -Bromosuccinimide
NI	Neuraminidase Inhibitor
NIS	<i>N</i> -Iodosuccinimide
NMM	<i>N</i> -Methylmorpholine
NMR	Nuclear Magnetic Resonance
PET	Positron Emission Tomography
Ph	Phenyl
PhNO	Nitrosobenzene
Piv	Pivaloyl
PMB	<i>p</i> -Methoxybenzyl
Pmc.	2,2,5,7,8-Pentamethylchroman-6-sulfonyl
PTLC	Preparative Thin Layer Chromatography

Py.	Pyridine
PyHBr ₃	Pyridinium tribromide
RNA	Ribonucleic acid
RSM	Recovered Starting Material
SIOC	Shanghai Institute of Organic Chemistry
TBAB	<i>tetra</i> -Butylammonium Bromide
TBD	1,5,7-Triazabicyclo[4.4.0]dec-5-ene
Tces	2,2,2-Trichloroethoxysulfonyl
TCT	2,4,6-Trichloro-1,3,5-triazone
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic anhydride
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography
TMEDA	Tetramethylenediamine
TMG	1,1,3,3-Tetramethylguanidine
TON	Turnover number
Tosyl	4-Toluenesulfonyl
Trifyl	Trifluoromethylsulfonyl
Troc	2,2,2-Trichloroethoxycarbonyl
TsCl	4-Toluenesulfonyl chloride
TSRI	The Scripps Research Institute
UC	University of California
USA	United States of America
UV	Ultraviolet
Xantphos	4,5-Bis(diphenylphosphino)-9,9-dimethylxanthene

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1. Introduction.

1.1. Guanidine.

Guanidine **1**, with the molecular formula CN_3H_5 (Figure 1.1.1), is one of Nature's most simple building blocks and is essential to all life.¹ It forms the nitrogenous backbone of Guanine **2**, one of the four main nucleobases found in the nucleic acids DNA and RNA² and is also found in the ubiquitous amino acid arginine **3**.³

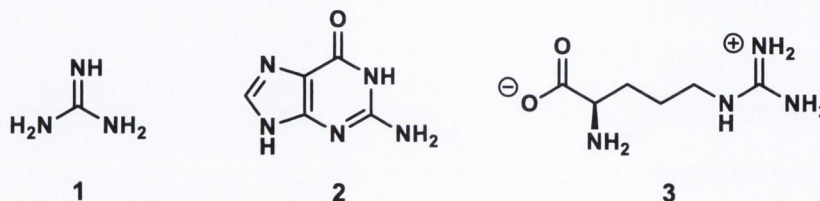


Figure 1.1.1. Guanidine (**1**), guanine (**2**) and arginine (**3**).

Guanidines ability to form hydrogen bonds (HBs) and its high basicity are two of its predominant characteristics. The high basicity of guanidine indicates that at physiological pH, guanidine will be protonated forming the guanidinium cation. The pK_{aH} of the guanidinium cation in water is 13.6.⁴ Due to the conjugation between the lone pair of the nitrogen atoms and the imine double bond, protonated guanidine has a number of resonance forms. These resonance forms delocalise the positive charge over the entire functional group leading to its high basicity (Figure 1.1.2). This feature of the guanidinium cation causes the nitrogenous backbone to be flat and this can often determine the conformation of substituted guanidinium species.^{5,6}

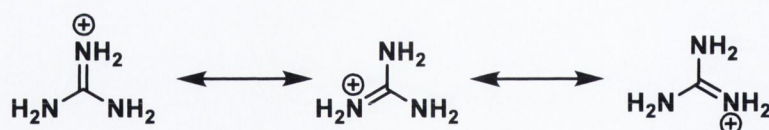


Figure 1.1.2. Guanidinium resonance forms.

In the guanidinium moiety there is six protons available for hydrogen bonding interactions, this allows the critical base pairing interactions possible for guanine (**2**) with cytosine in DNA⁶ and also facilitates numerous arginine (**3**) interactions throughout the mammalian body.^{3,7} Being protonated at physiological pH, the guanidine moiety in arginine (**3**) will be

cationic and planar. As well as being a HB donor, arginine is able to interact with other molecules through weaker interactions such as π cation interactions.⁸ The guanidinium cation has 6π electrons and all of them are in the bonding orbitals (Figure 1.1.3).⁹

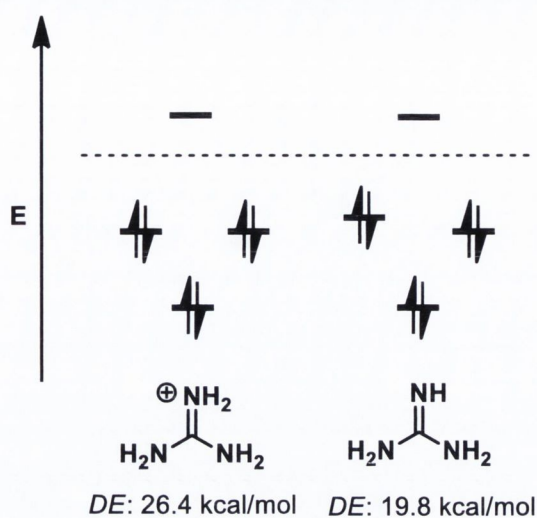


Figure 1.1.3. Electronic configuration (Hückel molecular orbitals) of guanidinium cation and guanidine. (DE: delocalisation energy).⁹

This gives guanidinium a type of Y aromaticity, allowing interactions with planar electron rich moieties such as phenyl rings.¹⁰ These properties of guanidine make it an important functional group in both the biological¹¹ and chemical¹² sciences.

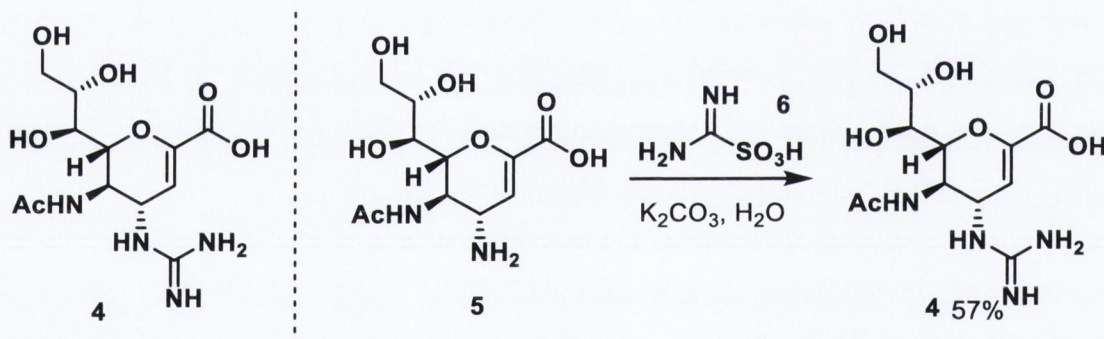
1.2. Pharmaceuticals containing guanidines.

The ever pressing need for novel pharmaceuticals drives chemical research forward, developing new ideas and strategies which ideally will find commercial application. One could therefore surmise that the level of importance of either a moiety or functionality in organic chemistry is related to its prevalence in the pharmaceutical industry. The abundant nature of the guanidine in pharmaceuticals therefore is an indicator of its status as a chemical entity.

1.2.1. Zanamivir.

Zanamivir (**4**, trade name Relenza) is a commercially available guanidine containing pharmaceutical used in the treatment of infection caused by the influenza A and influenza B virus.¹³ It is a neuraminidase inhibitor (NI) and was the first one to reach the market closely followed by oseltamivir. Neuraminidase enzymatic activity is essential for the release of recently formed virus particles from infected cells and is thus required for the influenza virus to spread in the body. Inhibition of this pathway is therefore a viable target for antiviral therapy. Global sales of zanamivir reached a high of €910 million in 2009 when governments stockpiled the drug due to the predicted outbreak of influenza virus A H1N1 (swine flu). Zanamivir was initially synthesised by a late stage guanidylation reaction. Primary amine **5** was reacted with formamidine sulfonic acid **6** to generate the desired guanidylated compound (Scheme 1.2.1.1).¹⁴

Scheme 1.2.1.1.

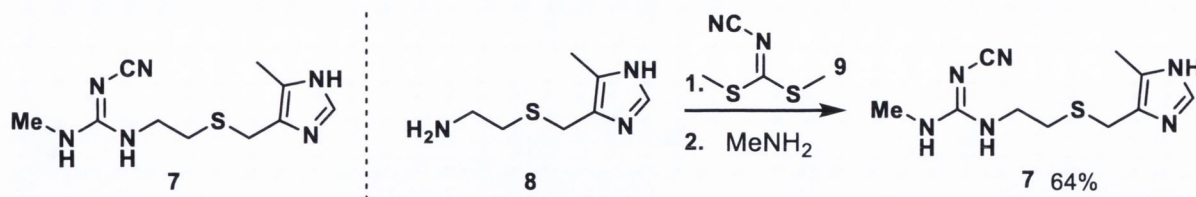


1.2.2. Cimetidine.

Cimetidine (**7**, trade name Tagamet) is a guanidine pharmaceutical of exceptional importance. Developed in 1976, it was one of the first drugs to be designed rationally as a histamine H₂ receptor competitive antagonist to inhibit stomach acid production. Its significance as a rationally designed drug is due to its stepwise development.¹⁵ Cimetidine was developed using histidine, the natural agonist, as a lead compound. Its primary uses are in the treatment of heartburn and peptic ulcers. It was also the first drug to break annual sales of \$1 billion in 1986, making it the first blockbuster drug. Cimetidine antagonism suppresses the normal secretion of acid from the parietal cells. The guanidine functionality is introduced in this compound by initial reaction of amine **8** with **9**, which is subsequently exposed to

methylamine to generate the substituted guanidine moiety found in cimetidine (Scheme 1.2.2.1).¹⁶

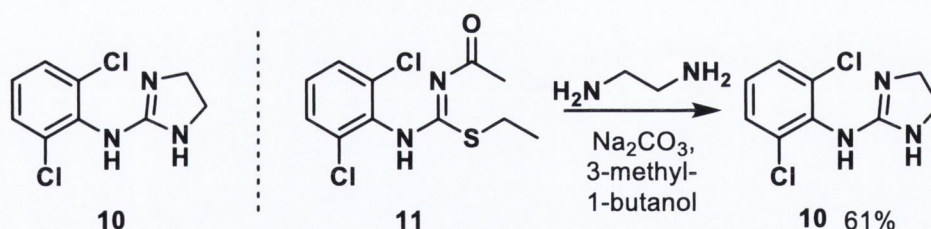
Scheme 1.2.2.1.



1.2.3. Clonidine.

Clonidine (**10**, trade name Catapres) is an α_2 -adrenoceptor agonist used in the treatment of high blood pressure, pain, anxiety and panic disorder.¹⁷ It agonises α_2 -adrenoceptors causing a decrease in the release of noradrenaline (NA) from presynaptic neurons. Clonidine is considered as a non-specific drug acting on a number of different pathways resulting in a number of undesired side effects. Such side effects can include dizziness, orthostatic hypotension (a drop in blood pressure that occurs upon standing) and anxiety. The cyclic guanidine moiety is formed through reaction of thiourea derivative **11** with ethylenediamine to yield the desired functionality (Scheme 1.2.3.1).¹⁸

Scheme 1.2.3.1.

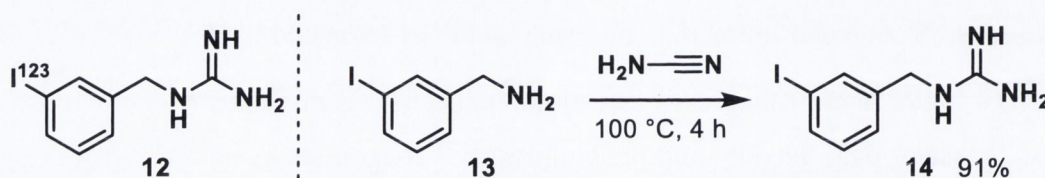


1.2.4. Iobenguane.

Iobenguane (**12**, trade name Adreview) also known as *meta*-iodobenzylguanidine (mIBG) is a radiopharmaceutical.¹⁹ There are two forms of **12**, one containing the radioisotope iodine-123 ($t_{1/2} = 8$ hr) and the other containing iodine-131 and both can be used in the imaging of cancerous tumours.²⁰ Due to the structural similarities of **12** to noradrenaline (NA) it localises in adrenergic tissue and is therefore very useful in the identification of tumours such as phaeochromocytomas (a neuroendocrine tumour of the medulla of the adrenal glands) and

neuroblastomas (a malignant tumour that develops from tissue).²¹ In order to prevent problems arising from the uptake of radiolabelled iodine in the thyroid potassium iodide is taken in conjunction with **12**.²² This inhibits the uptake of any radiolabelled iodine which could potentially cause thyroid carcinogenesis. Compound **12** is synthesised by reacting iodobenzylamine **13** with cyanamide to generate **14** which can then undergo substitution of iodine with radiolabelled ^{123}I (Scheme 1.2.4.1).²³

Scheme 1.2.4.1.



1.2.5. Desmopressin.

Desmopressin (**15**, trade name DDAVP, Figure 1.2.5.1) is an arginine containing pharmaceutical. It is a synthetic analogue of vasopressin which is a neurohypophyseal hormone associated with the reduction of urine production.²⁴ Desmopressin is most often used in the treatment of diabetes insipidus (a condition involving the excretion of severely diluted urine) and bedwetting.²⁵ Desmopressin exerts its mode of action by binding to V2 receptors in renal collecting ducts and increases the reabsorption of water,²⁶ controlling the amount of water that is being excreted as urine.

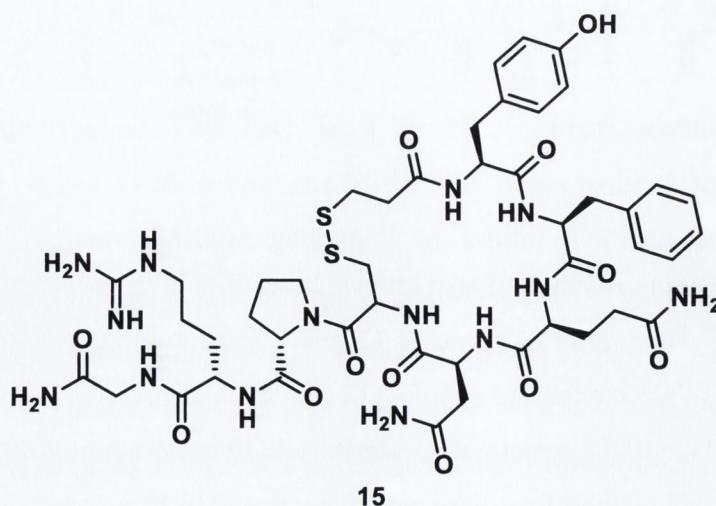


Figure 1.2.5.1. Structure of Desmopressin.

1.2.6. Gleevec.

Gleevec (**16**, trade name Imanitib, Figure 1.2.6.1) although not a guanidine containing pharmaceutical, is of particular interest for this thesis due to the presence of the 2-aminopyrimidine moiety which structurally is similar to guanidine. The aromaticity of the pyrimidine ring causes the typical characteristics of the guanidine portion to be lost. 2-Aminopyrimidine can therefore be thought of as a ‘masked’ guanidine. Gleevec is a tyrosine kinase inhibitor used as a chemotherapeutic against a wide variety of cancers that was rationally designed from *N*-phenyl-2-aminopyrimidine. Gleevec works by preventing a tyrosine kinase enzyme from phosphorylating subsequent proteins and initiating the signalling pathway that is necessary for cancer cell development. This interaction therefore prevents cancer cell growth leading to their death.²⁷⁻²⁹ Gleevec is a blockbuster drug with annual sales of \$4.7 billion. As a chemotherapeutic it is one of the most expensive options available to patients with a yearlong course in the USA costing €68,000 in 2012.³⁰

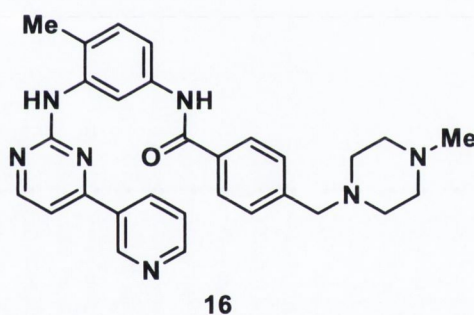


Figure 1.2.6.1. Structure of Gleevec.

1.3. Guanidine natural products.

The symbiotic nature of natural product chemistry and the pharmaceutical industry has been known for years.^{11,12} The earliest medicines were derived from substances found in nature and numerous new pharmaceuticals have stemmed from natural products. The renaissance in natural product chemistry is evident in the state of the art syntheses recently published by Baran and co-workers at the Scripps Research Institute, La Jolla, CA.^{31,32} Oubagenin³³ **17** and Ingenol³⁴ **18**, shown in Figure 1.3.1, are biologically active compounds of significant interest and previously were thought to be too complicated for efficient laboratory synthesis; now they have been prepared in ways which make them feasible for large scale production.

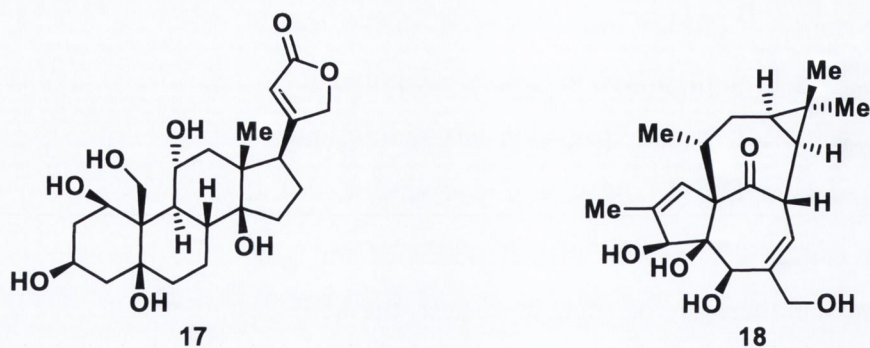


Figure 1.3.1. Biologically active natural products oubagenin **17** and ingenol **18**.

As in the synthetic pharmaceuticals, guanidines are prevalent in natural product chemistry and a number of these natural products have interesting biological activities.³⁵ Both in terrestrial and marine sources guanidine natural products are abundant. In particular, cyclic guanidines and aminoimidazole natural products are continuously being discovered often with interesting properties.³⁶

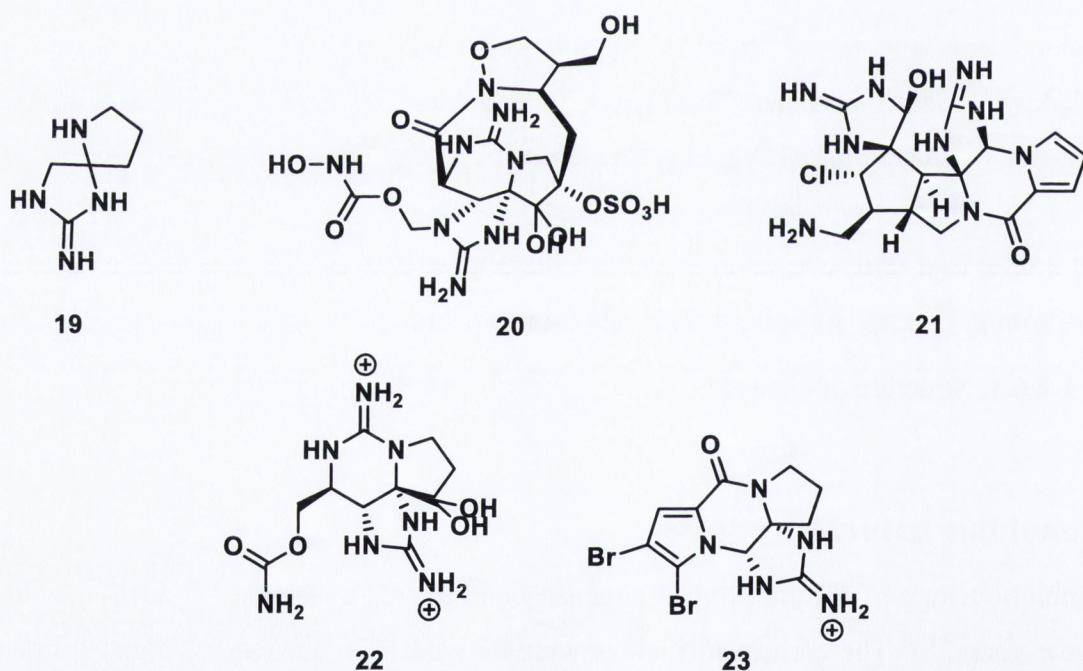


Figure 1.3.2. Natural products zetekitoxin **20**, palau'amine **21**, saxitoxin **22** and dibromophakellin **23** all contain the cyclic guanidine amination **19**.

A motif that appears in a wide variety of guanidine natural products is bicyclic guanidine amination **19** (Figure 1.3.2).³⁷ This cyclic structure is central to a number of natural products

such as zetekitoxin **20**,³⁸ palau'amine **21**,³⁹ saxitoxin **22**⁴⁰ and dibromophakellin **23**⁴¹ shown in Figure 1.3.2. Although many of these natural products have been extensively investigated in terms of their preparation, there has been no report of divergent syntheses stemming from the core **19**. The synthesis of this heterocyclic core as a means of exploring biological activity associated with a number of these compounds would be of great interest.

Saxitoxin **22**, a naturally occurring guanidinium toxin first isolated as a paralysing shellfish poison, is a potent, selective and reversible inhibitor of voltage gated sodium ion channels.⁴² In electrically excitable cells these channels are responsible for the rising phase of the action potential.⁴³ Molecules that interact specifically with these ion channels are sought after in a desire to further understand how these channels affect electrical signals in neuronal cells.⁴⁴ Aberrant behaviour of voltage gated sodium ion channels is thought to be associated with a number of diseases such as arrhythmia, epilepsy, neuropathic pain and congenital analgesia.⁴⁵

A number of natural products from the pyrrole-imidazole family have shown to have potent biological activity.⁴⁶ Of particular interest is dibromophakellin **23** which has been shown to act as an α_{2B} -adrenoceptor agonist. Non selective agonists of the α_2 -adrenoceptor GPCRs have been used clinically in antihypertensive treatment, pain control and as anaesthetic adjuncts.⁴⁷ However, these non-specific agents have a number of side effects which is thought could be prevented by means of selective agonism of specific α_2 -adrenoceptor subtypes. Facile access to the core **19** would allow its derivatives to be synthesised in a convergent manner allowing for investigations into which regions of **23** determine its specificity for α_{2B} -ARs.

Other biologically interesting guanidine natural products include the batzelladine family **24** (Figure 1.3.3), which have shown activity against specific human cancer cell lines and malaria protozoa⁴⁸ and the streptothricin family **25** of antibiotics which are known to have antibacterial activity against *Escherichia coli*, *Bacillus subtilis* and *Staphylococcus aureus* amongst many others.⁴⁹

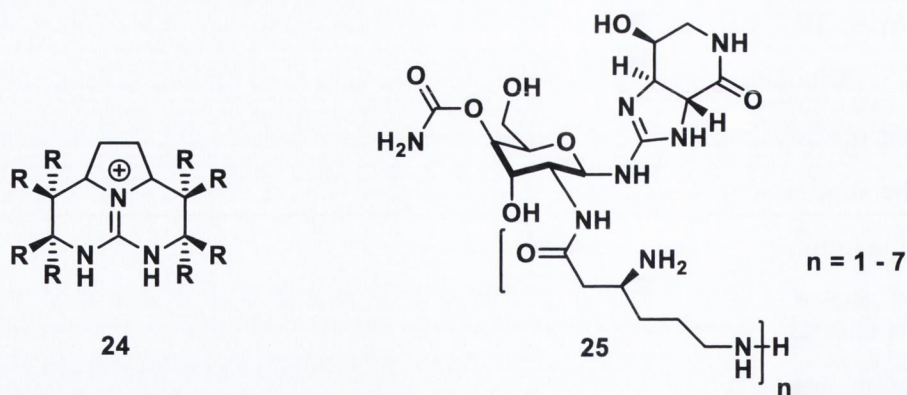


Figure 1.3.3. Structure of compounds **24** and **25** which are biologically active guanidine natural products.

1.4. Applications of guanidines in Organic Chemistry.

As alluded to previously the specific characteristics of guanidines determine their biological activity.⁵⁰ These characteristics, namely high basicity, planarity and hydrogen bonding ability, can be harnessed in organic chemistry to facilitate chemical transformations.⁵¹ A particular niche for guanidines has been uncovered particularly in the field of organocatalysis which has undergone a renaissance in recent times.⁵² The facile synthesis of guanidines would therefore facilitate their use in organic chemistry.

1.4.1. Guanidines as Brønsted Bases.

One of the most fundamental characteristic properties of guanidines is their high basicity.⁵³ This allows a myriad of organic transformations to be facilitated, often when the use of other inorganic bases of similar pK_a values is undesirable.⁵⁴ Often basic guanidine catalysts can have a dual method of activation. Firstly, neutral guanidines (such as **26**) can deprotonate a substrate **A-H** (Figure 1.4.1.1), forming a guanidinium cation **27**.

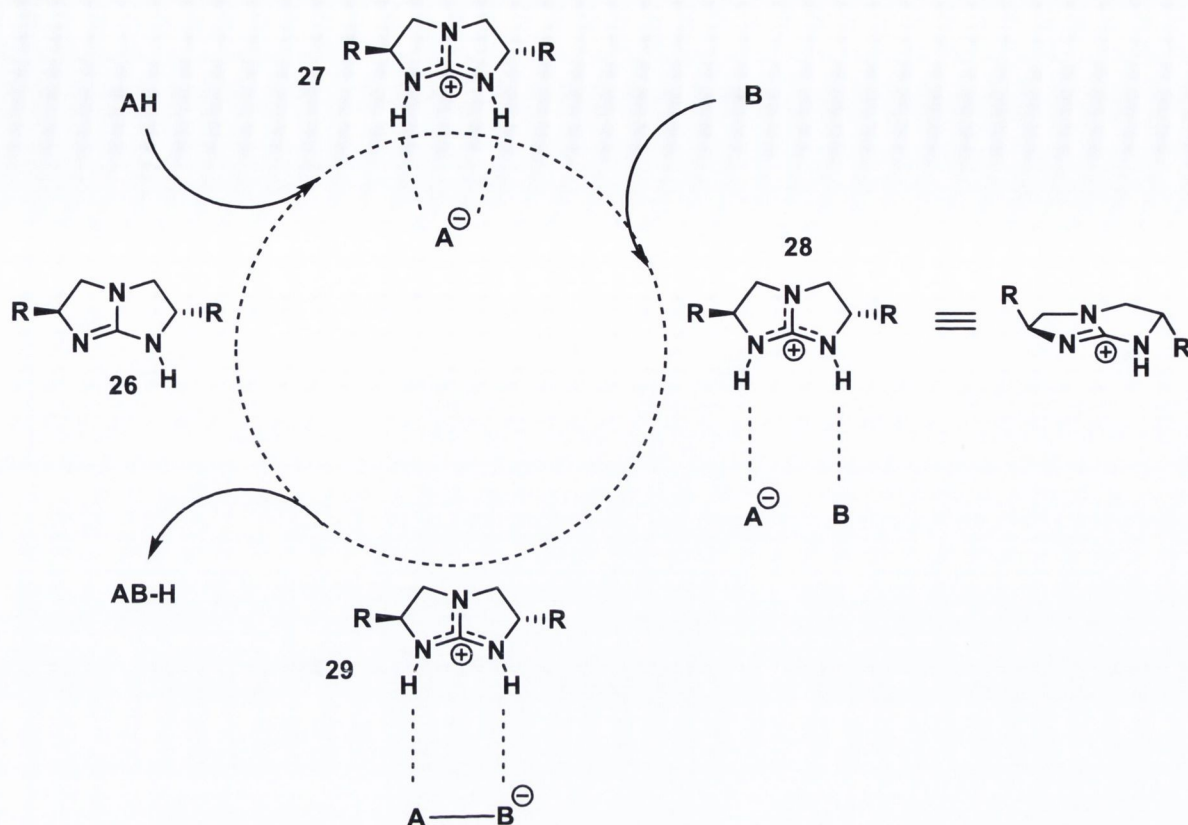


Figure 1.4.1.1. Dual mode of activation of guanidine catalyst **26**.

This species can then act as a HB donor to attract another molecule such as **B**. Structures **A** and **B** are now ideally positioned for an enantioselective interaction due to the chiral environment that they are locked into. Reaction and subsequent protonation results in regeneration of the guanidine catalyst **26** and formation of a new product, in this case **AB-H**.

1.4.1.1. Strecker Reaction.

One of the earliest examples of guanidine catalysed enantioselective reactions came from the laboratory of E. J. Corey at Harvard University with the use of catalyst **30** (Figure 1.4.1.1.1).^{55,56}

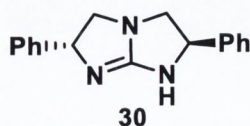
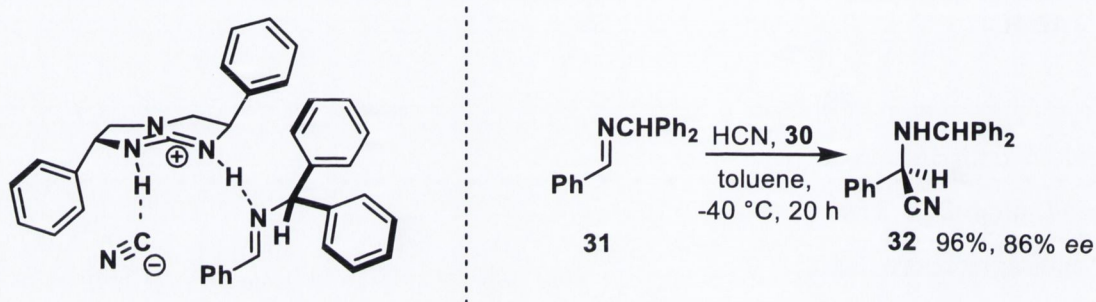


Figure 1.4.1.1.1. Structure of guanidine catalyst **30**.

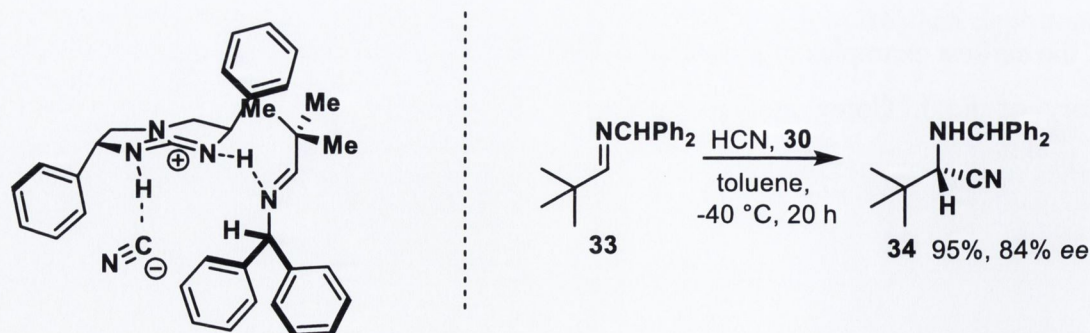
The guanidine catalyst **30** is able to facilitate an enantioselective reaction by firstly deprotonating HCN and holding the cyano anion in place while the guanidinium cation can now form a HB with the imine **31** and allow attack by cyanide from only one face leading to an enantioselective reaction (Scheme 1.4.1.1.1). The phenyl ring of the guanidine catalyst also would be perfectly positioned to assist in holding the imine molecule in the correct orientation through π -stacking interactions. This reaction between aromatic imines and hydrogen cyanide in the presence of this guanidine catalyst led to (*R*)- α -amino nitriles **32**.

Scheme 1.4.1.1.1.



Interestingly when aliphatic imine **33** was used instead of aromatic imine **31** an inversion of product configuration was observed with (*S*)- α -amino nitriles being the stereochemical outcome (Scheme 1.4.1.1.2). This observation is believed to stem from either steric repulsion for aliphatic substrates or attractive interactions for aromatic substrates.

Scheme 1.4.1.1.2.



An analogous racemic reaction with either aldehydes or ketones **35** replacing imine **33** has been investigated by Feng and coworkers.⁵⁷ The use of 1,1,3,3-tetramethylguanidine (TMG, $pK_a = 23.7$) to activate TMS-CN was employed under solvent free conditions. TMG could be converted to a reactive guanidinium cation (Figure 1.4.1.1.2, **36**) upon exposure to TMS-CN as proven by X-ray crystal structure analysis. This intermediate acts as a catalyst readily reacting with both aldehydes and ketones through a six membered transition state (Figure 1.4.1.1.2, **37**). Then, the corresponding cyanohydrins **38** are generated and the catalyst regenerated.

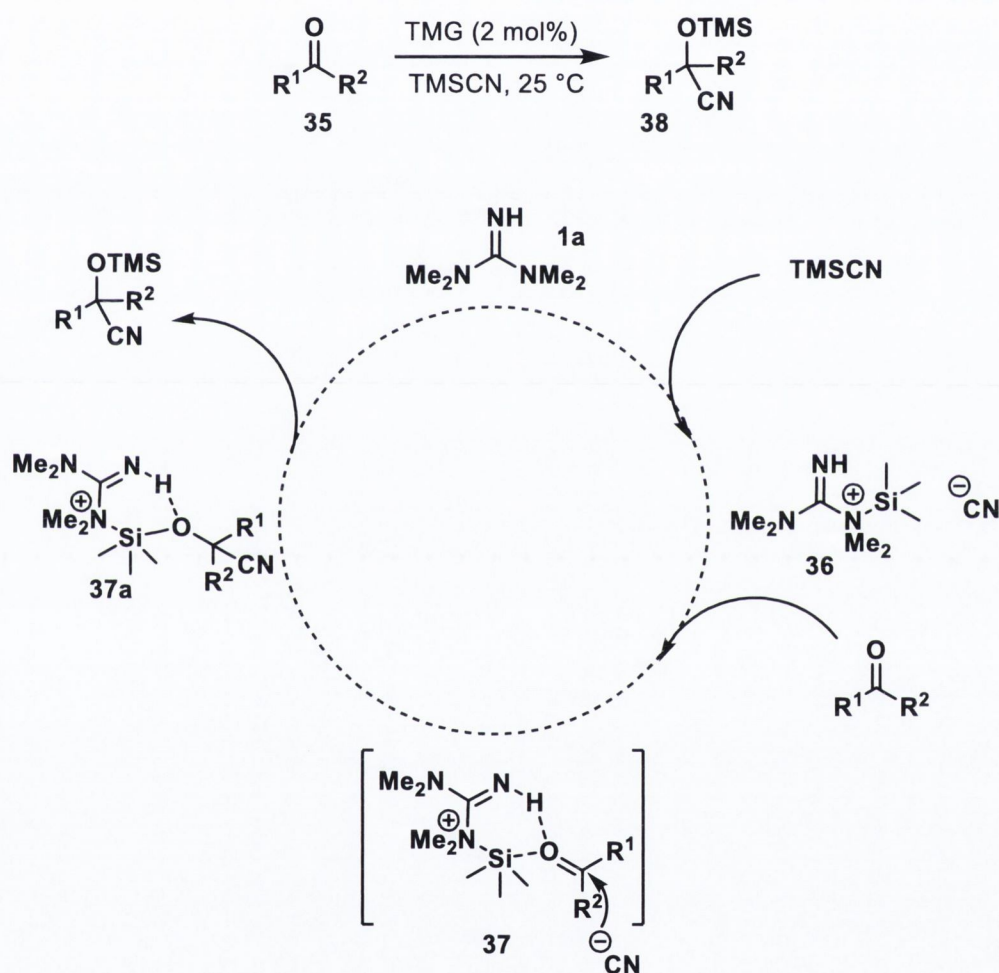


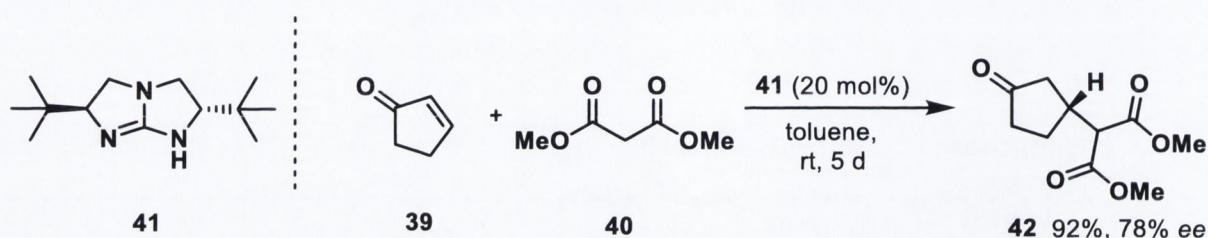
Figure 1.4.1.1.2. TMG catalysed Strecker reaction.

1.4.1.2. Michael Reaction.

The Michael reaction (1,4 conjugate addition) is one of the most utilised and important reactions in organic chemistry to generate either new C-C or C-X bonds.^{58,59,60} The need for

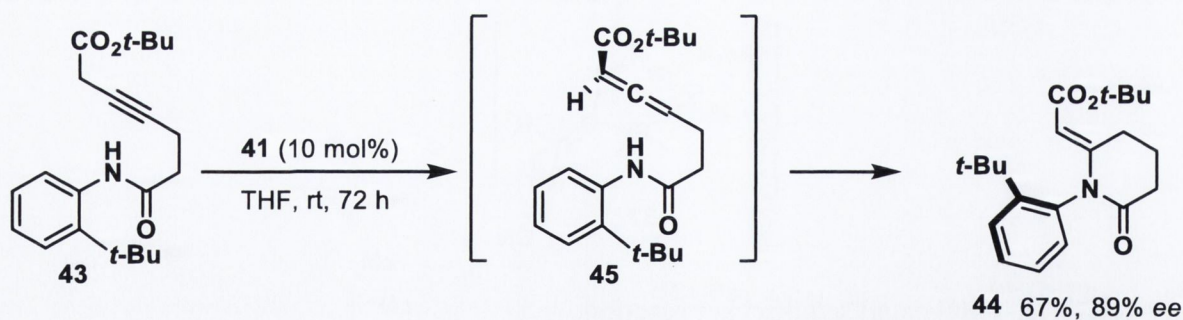
enantioselective variations is therefore essential. A plethora of examples using guanidine catalysed Michael reactions has arisen over the past years.⁶¹ In one of the earliest examples guanidine catalysts were shown to be effective in the Michael addition of either 1,3-diketones or malonates to cyclic enones in very good yields and stereoselectivities. In the example shown in Scheme 1.4.1.2.1, 2-cyclopenten-1-one **39** was reacted with dimethyl malonate **40** at room temperature for 5 days in the presence of catalyst **41** leading to 92% yield of the desired product **42** with 78% *ee*.⁶²

Scheme 1.4.1.2.1.



Another interesting example of the use of catalyst **41** in Michael additions is the enantioselective tandem alkyne-allene isomerization and resulting 1,4-addition of derivatised aniline amides **43** to form axially chiral lactams **44** (Scheme 1.4.1.2.2).⁶³

Scheme 1.4.1.2.2.

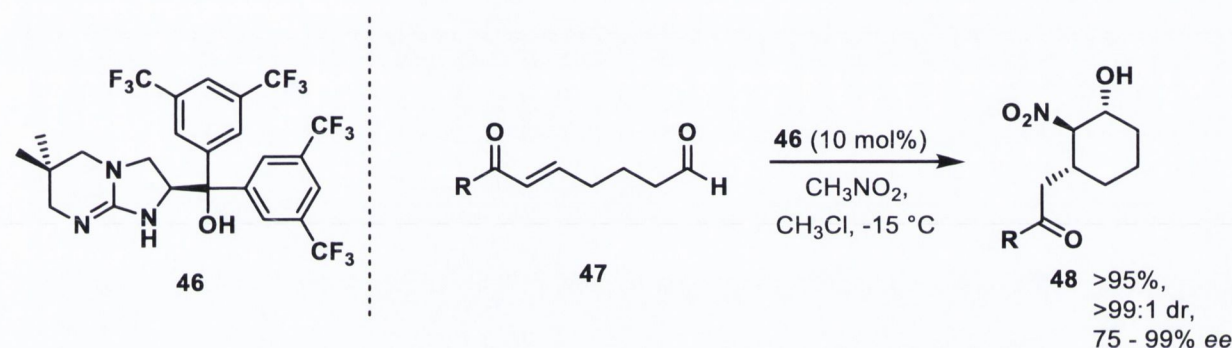


This reaction proceeds with good yield and very good enantioselectivity. Again the dual method of activation of the guanidine catalyst is shown with first deprotonation of the acidic proton α to the ester forming the allene **45** and subsequent ring closure arising from a 1,4-

addition by the nitrogen of the amide onto the electrophilic central conjugated carbon atom of the allene.

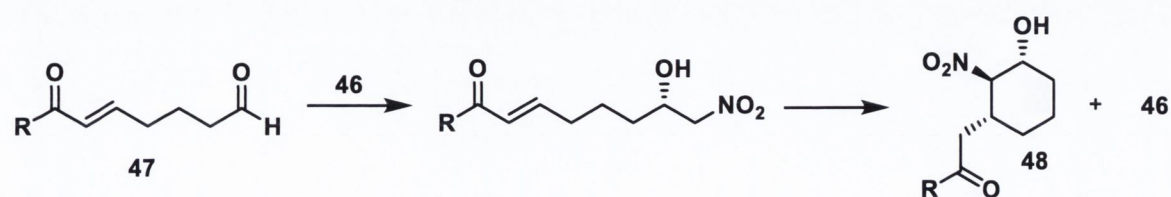
A wide variety of guanidine catalysts have shown to be effective for enantioselective Michael reactions. The cutting edge of this chemistry can be observed in a recent publication from the laboratory of Zhao at the University of Texas, San Antonio,⁶⁴ dealing with guanidine **46** catalysed tandem Henry-Michael reaction between 7-oxo-hept-5-enals **47** and nitromethane to generate trisubstituted cyclohexanols **48** in a highly enantioselective manner (Scheme 1.4.1.2.3).

Scheme 1.4.1.2.3.



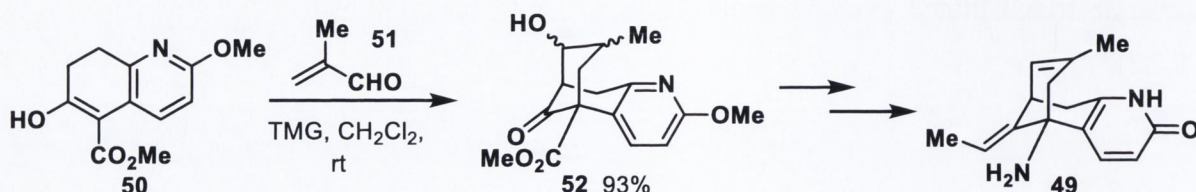
This reaction proceeds by guanidine catalysed addition of nitromethane to the aldehyde **47** as is well known in the chemical literature,⁶⁵ the resulting nitro alcohol then presumably undergoes deprotonation and subsequent 1,4-addition to the enone moiety in a stereospecific manner to generate the desired highly substituted cyclohexanol products **47** (Scheme 1.4.1.2.4).

Scheme 1.4.1.2.4.



An application of the guanidine catalysed Michael addition has been used in the synthesis of huperazine A **49**, a candidate drug for the treatment of Alzheimer's disease (Scheme 1.4.1.2.5).⁶⁶ Interestingly, the authors report that, while several other routes were examined for installation of the unsaturated carbon bridge, only TMG catalysed Michael addition between enol **50** and α,β unsaturated aldehyde **51** was successful to afford compound **52**.

Scheme 1.4.1.2.5.

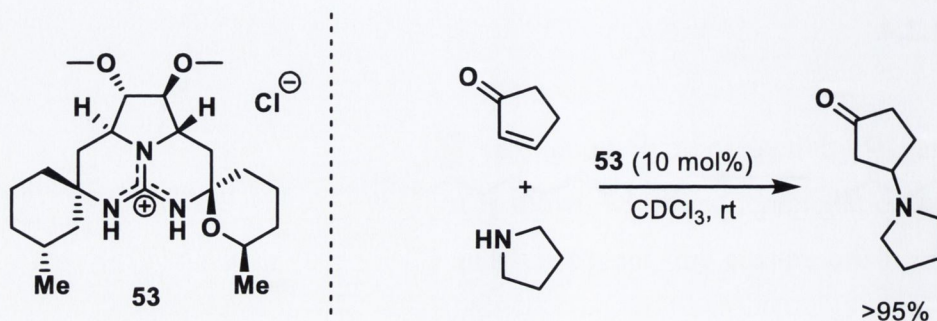


The mechanism of this reaction presumably follows a Robinson type annulation pathway to efficiently form the bicyclic system.⁶⁷

1.4.1.3. Aza-Michael Reaction.

The need for enantioselective carbon nitrogen bond forming reactions is evident from the ubiquitous nature of highly nitrogenated compounds throughout the pharmaceutical industry⁶⁸ and thus, aza-Michael reactions offer an appealing method for the generation of C-N bonds. A number of guanidine catalysed enantioselective aza-Michael reactions have been investigated recently in the literature.^{69,70} One example from Nagasawa and coworkers shows that guanidine catalyst **53** can effectively catalyse the addition of pyrrolidine to α,β -unsaturated lactones, however, no enantioselectivity was achieved (Scheme 1.4.1.3.1).⁷¹

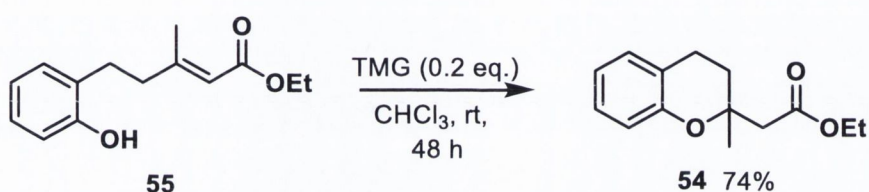
Scheme 1.4.1.3.1.



1.4.1.4. Oxa-Michael.

Oxa-Michael reactions have proven useful in the synthesis of C-O bonds when employing oxygen derivatives as a nucleophile. Ishikawa and co-workers have recently used such a method generating a highly substituted chromane skeleton **54** through a guanidine catalysed intramolecular oxa-Michael reaction.⁷² A number of bases were investigated to coax the ring closure of **55**, however, only TMG proved effective and could be used in catalytic quantities (Scheme 1.4.1.4.1).

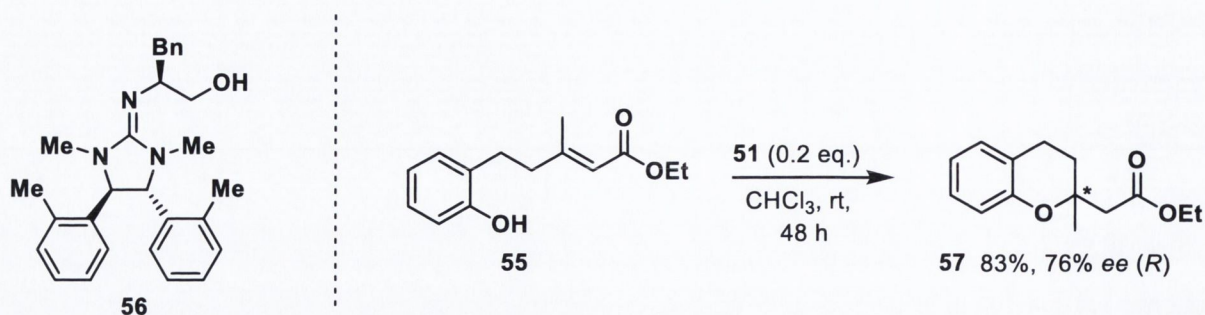
Scheme 1.4.1.4.1.



An enantioselective variation of this 6-*exo-trig*-type cyclisation was found to be useful for the synthesis of vitamin E and its derivatives.⁷² In a related ring closure, quinine had been employed as an organocatalyst to facilitate the reaction occurring enantioselectively,⁷⁴ however, in this instance quinine had no effect and it was realised that other amine bases would need to be examined.

After extensive investigation into varying guanidine organocatalysts it was discovered that the use of catalyst **56** was able to promote the ring closure with very good yield and moderate enantioselectivity (Scheme 1.4.1.4.2).

Scheme 1.4.1.4.2.



The geometry of the olefin also played a crucial role in the outcome of the reaction with significantly higher yields and *ee* values being obtained when the *E* isomer was used. The origin of the asymmetric induction in this reaction is shown in Figure 1.4.1.4.1. The presence of the hydroxyl moiety on the catalyst was shown to be crucial in the efficacy of the reaction.

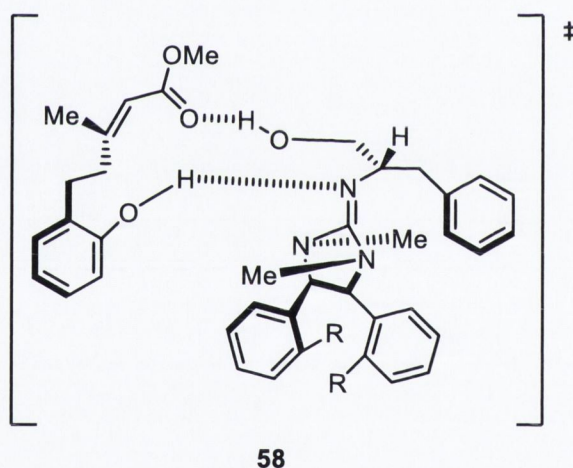


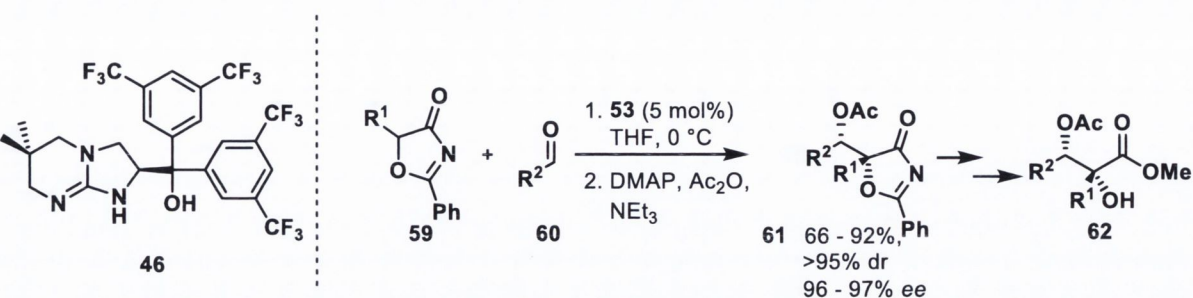
Figure 1.4.1.4.1. Pre-transition state **58** assembly of substrate **55** with catalyst **56**.⁷²

1.4.1.5. Aldol Reaction.

A guanidine **46** catalysed enantioselective example of the venerable aldol reaction has been published in the *Journal of the American Chemical Society* in 2010 by Misaki and co-workers.⁷³ This particular example involves the reaction of 5*H*-oxazol-4-ones **59** with a number of varying aldehydes **60** to generate chiral α,β -dihydroxycarboxylic acid precursors **61** and their derivatives **62** (Scheme 1.4.1.5.1). The introduction of quaternary chiral centres at the α -carbon atom of carboxylic derivatives results in important chiral precursors such as

compounds **62** and it is also useful in the preparation of many biologically active natural products.⁷⁴

Scheme 1.4.1.5.1.



The particular guanidine catalysts used in this study (for example compound **46**) were designed to carry a hydroxy group adjacent to the guanidine functionality. It was hoped that this would enable hydrogen bonding and subsequent activation on the aldehyde in a defined stereochemical environment. Additionally, it was assumed that the anionic enolates would have their geometry determined by the guanidinium cation, positioning them in a reactive location adjacent to the aldehyde as depicted in Figure 1.4.1.5.1.⁷³

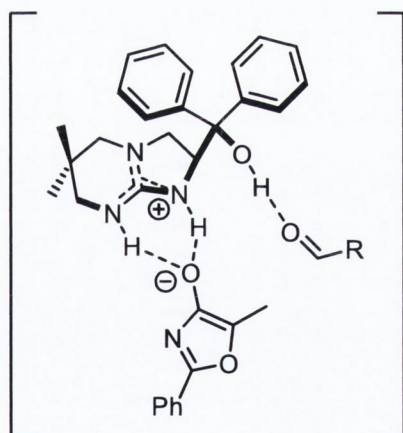


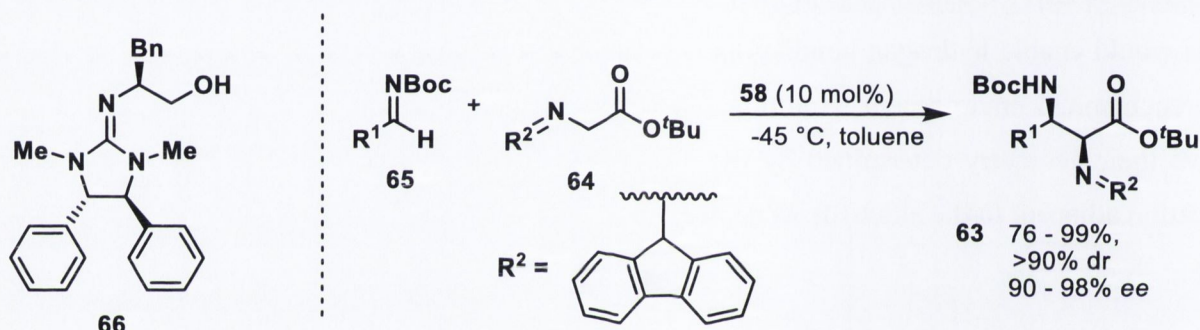
Figure 1.4.1.5.1. Proposed transition state in guanidine **46** catalysed aldol reaction.

The products of this reaction gave primarily *syn* diastereomers in excellent enantiomeric excess and in moderate to excellent yield. This is an inspiring example of the dual modes of activation of guanidine organocatalysts.

1.4.1.6. Mannich Reaction.

The enantioselective Mannich reaction is a powerful method in the synthesis of chiral β -aminocarbonyl compounds.⁷⁵ The ability of this C–C bond forming reaction to access α,β -diamino ester **63** was utilised by Kobayashi *et al.*⁷⁶ Fluorenone imines of glycinate **64** were found to be more reactive than benzophenone imine derivatives when reacted with *N*-Boc protected imines **65** under these guanidine **66** catalysed conditions (Scheme 1.4.1.6.1). This is thought to arise from the resonance stabilisation of the α -anion involving the 14 π -electrons of the aromatic anionic fluorene system. The diamino products were produced in excellent yield, enantioselectivity (*ee*) and good to excellent *syn:anti* selectivity.

Scheme 1.4.1.6.1.

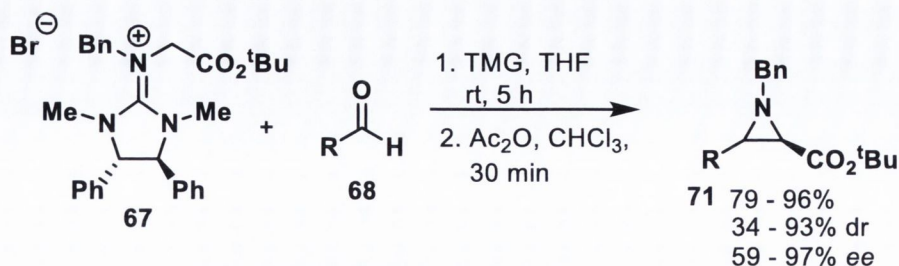


Nagasawa and co-workers have also developed guanidine catalysed enantioselective Mannich reaction between malonate derivatives and *N*-Boc protected imines.⁷⁷

1.4.1.7. Aziridination of aldehydes.

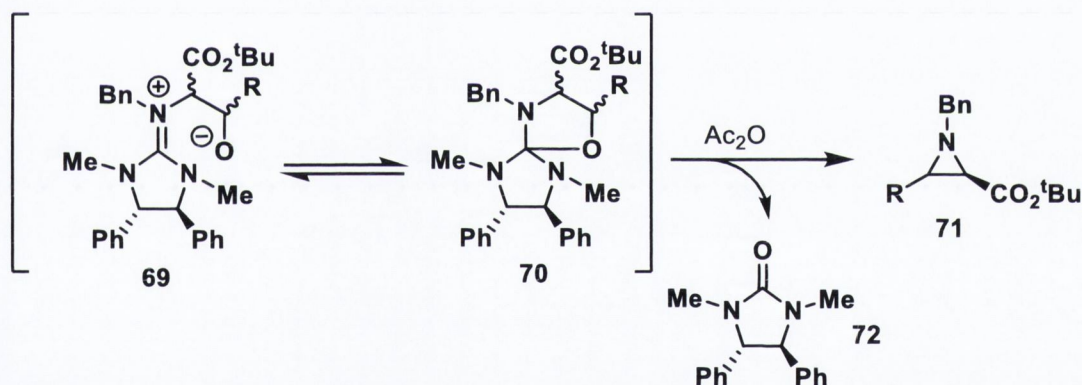
An interesting use of guanidine **67** is in the aziridination of aldehydes **68** facilitated by the use of TMG as a base (Scheme 1.4.1.7.1).⁷⁸

Scheme 1.4.1.7.1.



Formation of a guanidine ylide followed by addition to an aldehyde forms a mixture of open ring **69** and closed ring **70** products in equilibrium (Scheme 1.4.1.7.2). Subsequent exposure to Ac₂O facilitates the formation of the desired aziridine **71** in good to excellent yields with good stereochemical control. Urea **72** is formed as a side product.

Scheme 1.4.1.7.2.



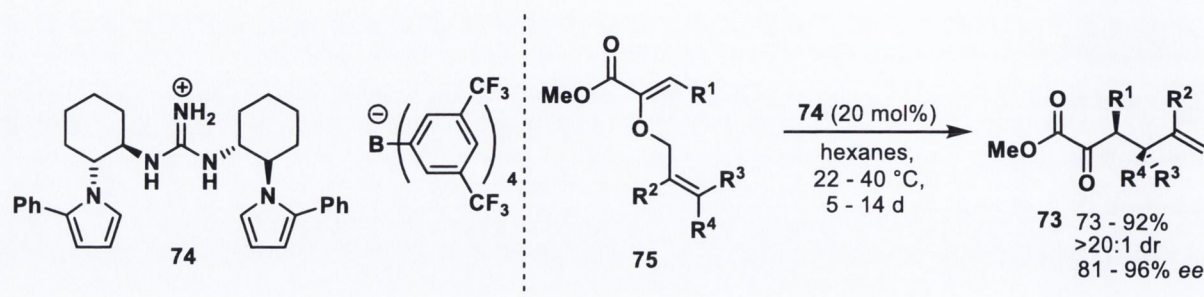
1.4.2. The uses of guanidines as weak Brønsted acids.

1.4.2.1. Claisen Rearrangement.

The [3+3]-sigmatropic rearrangement of allyl vinyl ethers (Claisen rearrangement) has effectively been used for over 100 years in the formation of C–C bonds.⁷⁹ Enantioselective variations have received extensive attention in recent years and Jacobsen *et al.* have utilised guanidine organocatalysis in their synthesis of β-keto ester Claisen products **73**.⁸⁰ Initial investigations into both urea and thiourea catalysed Claisen rearrangements indicated that neither induced a rate enhancement in the reaction. However, preliminary investigations into

guanidinium catalysis proved fruitful and, thus, chiral guanidinium catalyst **74** (Scheme 1.4.2.1.1) was designed to effect Claisen rearrangement of substrates **75**.

Scheme 1.4.2.1.1.



1.4.2.2. Henry Reaction.

The reaction between a nitroalkane and either an aldehyde or ketone in the presence of a base is a classic C–C bond forming process known as the Henry reaction (or nitro aldol reaction) and was discovered by L. Henry in 1895.⁸¹ The synthetic utility of this reaction stems from the plethora of transformations available to the β-nitro alcohol products formed (Figure 1.4.2.2.1).

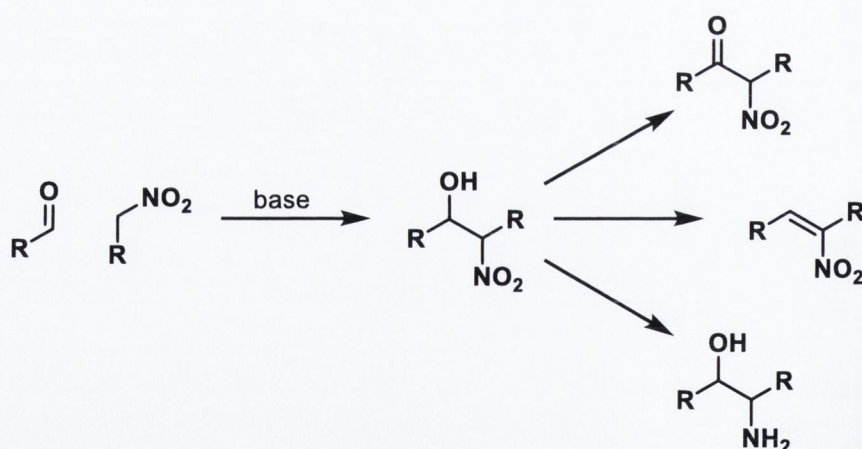
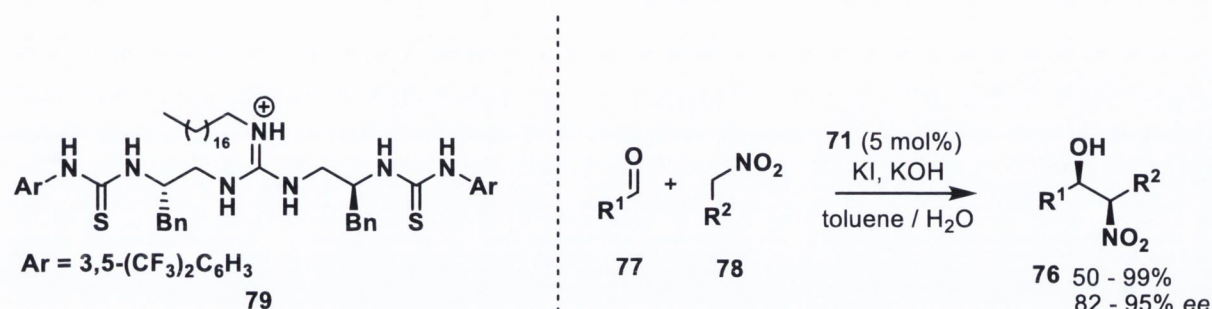


Figure 1.4.2.2.1. Synthetic versatility of the Henry reaction.

Therefore, the high basicity of guanidines and their hydrogen bonding abilities make them excellent candidates as catalysts of the Henry reaction. Pioneering work from the laboratory

of Nagasawa utilised guanidine catalysis to provide nitro aldol products **76** in a highly *syn* selective manner in high yield and *ee* (Scheme 1.4.2.2.1) from aldehydes **77** and nitroalkanes **78**.⁸²

Scheme 1.4.2.2.1.



Ensuing analogous studies using the opposite enantiomer of catalyst **79** with nitromethane as the nitroalkane source led to excellent *anti* selectivity proving the synthetic utility of this catalytic system. The hydrogen bonding abilities of this catalyst are essential as shown in the authors working model for conformational ordering (Figure 1.4.2.2.2).⁸²

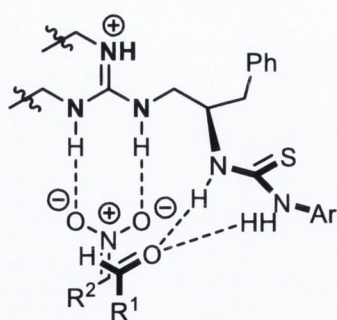


Figure 1.4.2.2.2. Hydrogen bonding interactions of catalyst **79** in enantioselective Henry reaction.⁸²

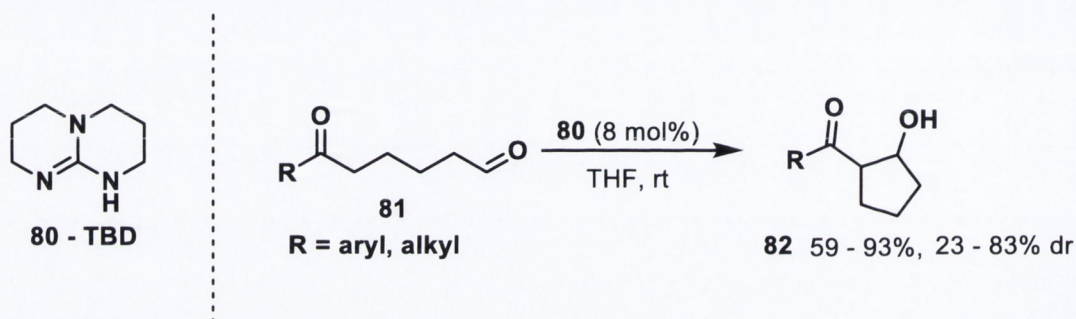
The use of guanidine catalysis has also shown to be of use in non enantioselective Henry reactions.⁸³

1.4.3. The use of guanidines in Lewis base catalysis.

1.4.3.1. Aldol Reaction.

The dual mode of activation of guanidine organocatalysts can be particularly effective in the case of intramolecular aldol reactions. Baati and co-workers have demonstrated how 1,5,7-triazabicyclo[4.4.0]dec-5-ene (TBD, **80**) can induce the formation of 2-ketocyclopentanols **81** from the corresponding ketoaldehydes **82** (Scheme 1.4.3.1.1).⁸⁴

Scheme 1.4.3.1.1.



Nucleophilic attack by TBD **80** on the aldehyde functionality results in the formation of intermediate **83** (Figure 1.4.3.1.1), which is stabilised through hydrogen bonding interactions. Subsequent proton transfer could form the necessary enolate **84**. Then, followed by regeneration of the aldehyde and expulsion of the guanidinium cation, ring closure can occur. The guanidinium species can also further activate the aldehyde through hydrogen bonding (Figure 1.4.3.1.1. **85**).

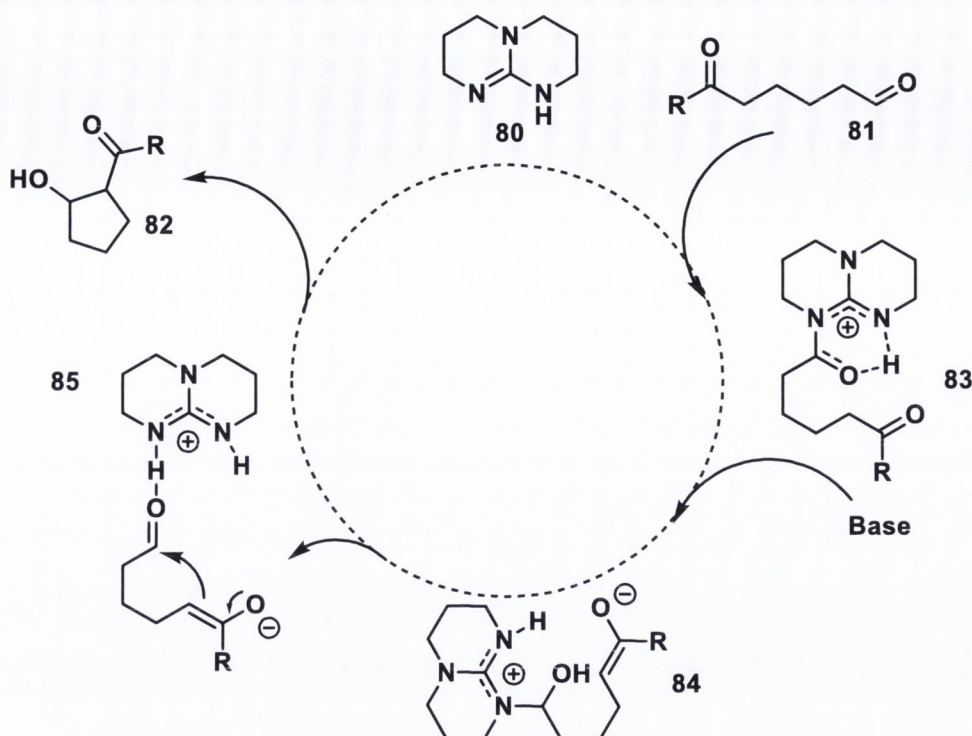
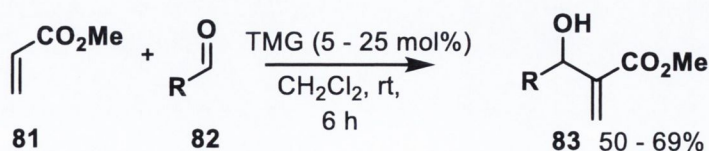


Figure 1.4.3.1.1. Role of TBD in intramolecular aldol reaction.

1.4.3.2. Morita-Baylis-Hillman reaction.

The ability of guanidines to catalyse Morita-Baylis-Hillman (MBH) reactions was discovered by Leadbeater *et al.* in their use of TMG to facilitate the reaction of methyl acrylate **81** and a variety of both aliphatic and aromatic aldehydes **82**.⁸⁵ Interestingly, the nucleophilicity of TMG dominated the reactivity of the reaction with no aldehyde aldol products being observed. Catalytic amounts of TMG gave rise to MBH products **83** in good yield with short reaction times (Scheme 1.4.3.2.1).

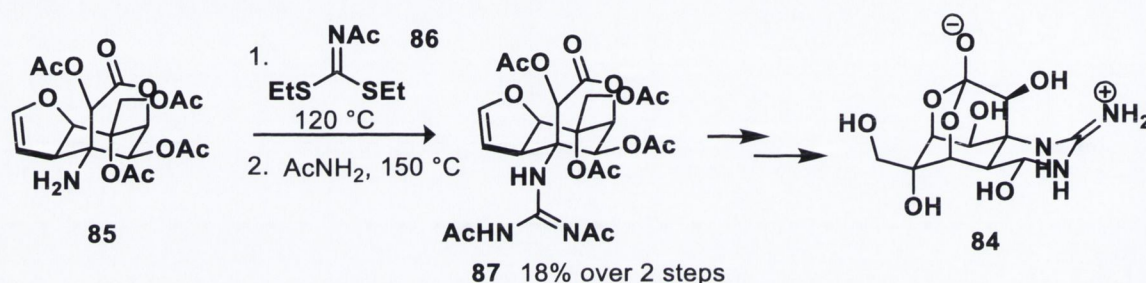
Scheme 1.4.3.2.1.



1.5. Synthetic methods for the construction of the guanidine functionality.

The synthesis of guanidines has come a long way from the landmark synthesis of tetrodotoxin **84** by Kishi in 1972⁸⁶ in which the guanidine functionality was introduced by exposing amine **85** to dithiocarbonimidate **86** at elevated temperature and, then, exposing the intermediate product to AcNH₂ to form the desired protected guanidine **87** in 18% yield over two steps (Scheme 1.5.0.1).

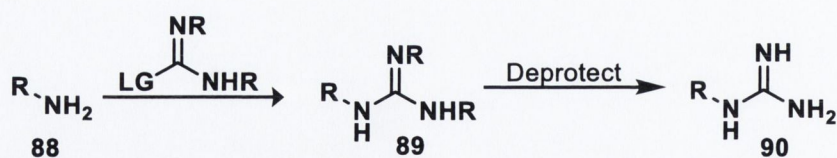
Scheme 1.5.0.1.



1.5.1. Synthesis of acyclic guanidines.

Advances in the field have led to a myriad of methods for the installation of the guanidine functional group.⁸⁷ In the past, the synthesis of guanidines involved the reaction of an amine **88** with an activated guanidine precursor followed by the deprotection of this moiety **89** to yield the corresponding free guanidine **90** (Scheme 1.5.1.1).

Scheme 1.5.1.1.



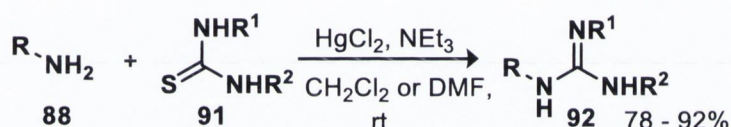
The choice of guanidine precursor usually has depended on the reactivity of the amine involved; in the case of anilines, Lewis acid promoted reactions have been the most successful while for aliphatic amines, there is a much wider scope of guanidine precursor

available due to their greater nucleophilicity. Herein, we will discuss the classical methods for guanidine synthesis followed by more recent developments in the area.

1.5.1.1. Thiourea derivatives as guanidylating agents.

Classical methods for guanidine synthesis have tended to make use of either substituted thiourea or urea moieties being reacted with an amine and promoted by a variety of reagents. The earliest examples of thiourea being utilised as a guanidylating agent made use of the thiophilic Lewis acid HgCl_2 as a stoichiometric promoter.⁸⁸ Mercury(II) chloride is believed to act as a desulfurising agent forming an electrophilic carbodiimide, which in turn will be rapidly attacked when in the presence of a nucleophilic amine (Scheme 1.5.1.1.1).

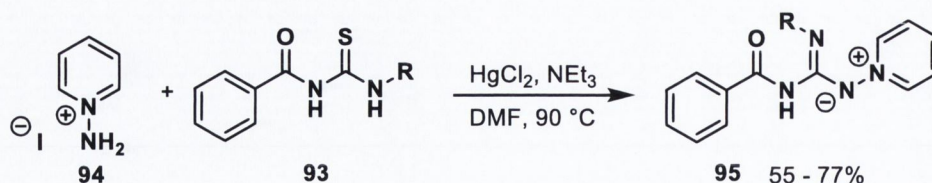
Scheme 1.5.1.1.1.



This methodology is incredibly robust and synthetically useful, the reaction of a number of varying amines both aromatic and aliphatic with *N,N*-bis-*tert*-butoxycarbonylthiourea in the presence of NEt_3 and HgCl_2 in CH_2Cl_2 afford the corresponding protected guanidines in good to excellent yields (Scheme 1.5.1.1.1. 78 – 92%). Acidic deprotection then yielded the corresponding guanidinium salts. The use of HgO as a replacement for HgCl_2 has been shown to be a viable alternative.⁸⁹

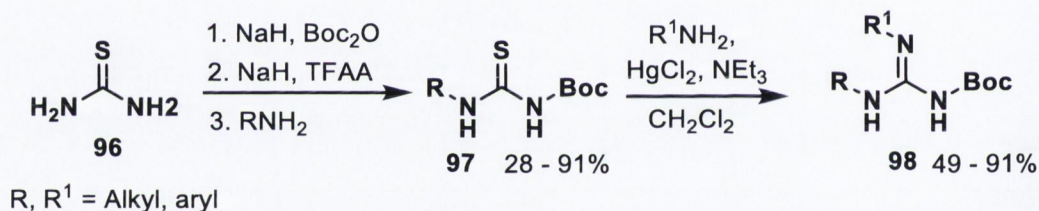
An interesting example of the synthetic utility of mercury-promoted guanidylation is the reaction between thiourea derivatives **93** (Scheme 1.5.1.1.2) and *N*-iminopyridinium ylide, generated from compound **94**, to form unusual *N*-pyridinium benzoylguanidines products **95**.⁹⁰ Bismuth salts were also shown to be effective in promoting this guanidylation reaction.

Scheme 1.5.1.1.2.

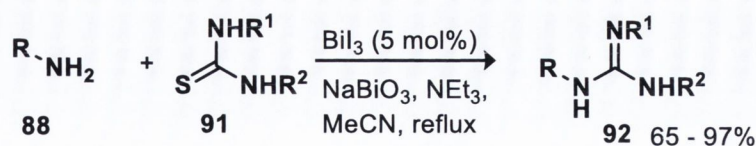


A useful method for the synthesis of *N,N'*-disubstituted aryl guanidines starts with Boc protection of thiourea **96** (Scheme 1.5.1.1.3) followed by exposure to trifluoroacetic anhydride (TFAA) which forms a highly reactive di-functionalised nitrogen atom.⁹¹ This substituent can in turn be displaced by addition of a nucleophile to form derivatised thiourea **97**. Exposure of **97** to HgCl_2 promoted guanidylating conditions resulting in the formation of *N,N'*-disubstituted *mono*-Boc protected guanidines **98** (Scheme 1.5.1.1.3).

Scheme 1.5.1.1.3.

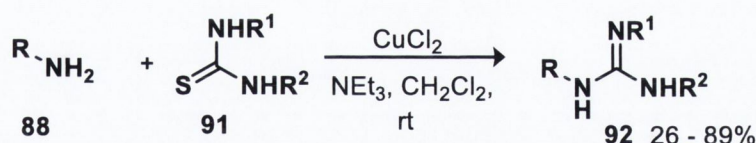


However, the use of mercury is an obvious drawback in the above methodologies and other methods have been invented to combat this problem. Thus, in 2006 Cunha *et al.* described the use of Bi(III) salts to promote the desulfurisation of protected thiourea **91** which is subsequently attacked by a nucleophilic amine species **88** constructing the appropriate protected guanidine **92** (Scheme 1.5.1.1.4) and expulsion of the Bi-S species.⁹²

Scheme 1.5.1.1.4.

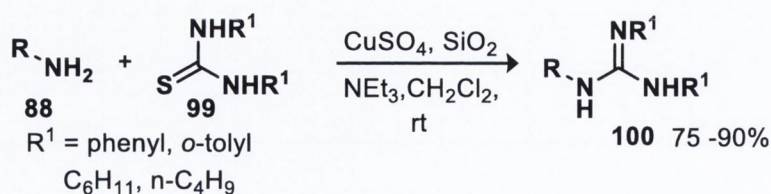
The authors found that BiI₃ could be used in catalytic quantities (5 mol%) when NaBiO₃ was used as an oxidant. This method proved to be comparable with the HgCl₂ promoted guanidylation reaction when either aliphatic amines or activated anilines were used. However, the substrate scope did not include deactivated amines.

The use of Cu(II) chloride salts has been reported to effect the conversion of protected thiourea **91** into the corresponding guanidine **92**. Initial reports from Kim⁸⁸ *et al.* describe CuCl₂ being an ineffective promoter of guanidylation; however, more recent findings⁹³ suggest that CuCl₂ can be used as a Lewis acid with yields similar to those of the benchmark HgCl₂ reaction being obtained (Scheme 1.5.1.1.5). As expected non nucleophilic amines required heating and gave poor to moderate yields.

Scheme 1.5.1.1.5.

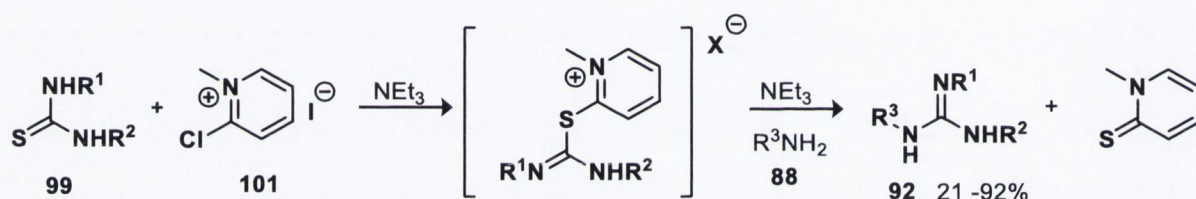
Copper(II) sulphate (CuSO₄) has also proven to be an active promoter in guanidylation reactions.⁹⁴ When used in conjunction with SiO₂ and NEt₃ in THF a number of aliphatic amines could be guanidylated with protected thiourea in adequate yields (Scheme 1.5.1.1.6). No aromatic amines were evaluated though indicating a lack of utility for the method with non-nucleophilic amines.

Scheme 1.5.1.1.6.



An attractive alternative to the utilisation of metal promoted guanidylation is the use of Mukaiyama's reagent **101** to assist in the desulfurisation of the thiourea. Mukaiyama's reagent works best when nucleophilic amines are used (Scheme 1.5.1.1.7).⁹⁵

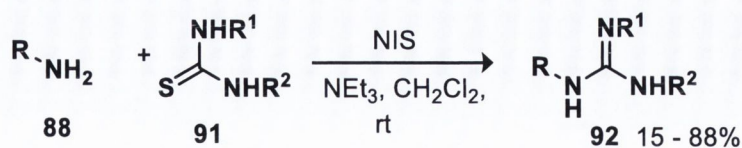
Scheme 1.5.1.1.7.



It has been shown that the choice of solvent can play a critical role in the reaction of the protected thiourea **91** with varying amines when using Mukaiyama's reagent **101**. The reaction of non-nucleophilic amines with thiourea **91** was shown to be much more effective in dichloromethane than dimethylformamide (as is the typical choice of solvent for this reaction), with yield increases of around 50% being achieved.

N-Iodosuccinimide (NIS) has also proven to be a viable choice in the guanidylation of an amine **88** with protected thiourea **91** (Scheme 1.5.1.1.8). In 2009 Smietana *et al.* reasoned that thiophilic NIS, acting as a soft Lewis acid, should coordinate to the sulfur of the protected thiourea and in the presence of an amine and a base form the desired guanidine **92**.⁹⁶

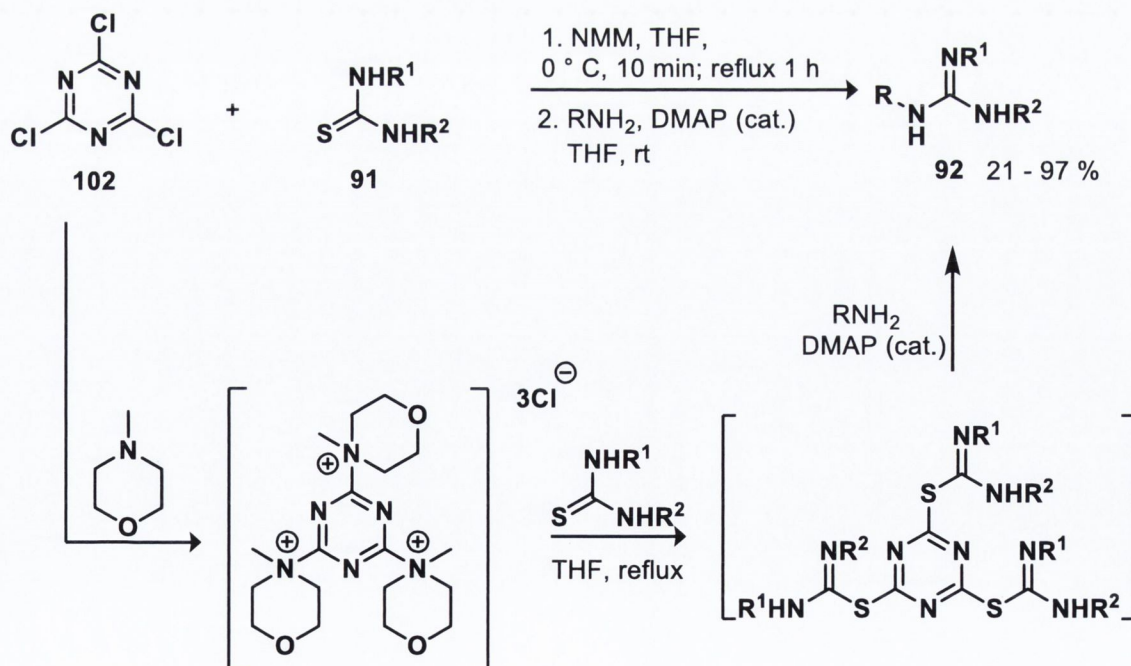
Scheme 1.5.1.1.8.



An array of amines was investigated with primary aliphatic amines giving excellent yields and hindered secondary amines giving moderate yields. When *bis*-Boc-*S*-methylisothiurea replaced *bis*-Boc-thiourea as the guanidylating agent higher yields were obtained for secondary amines.

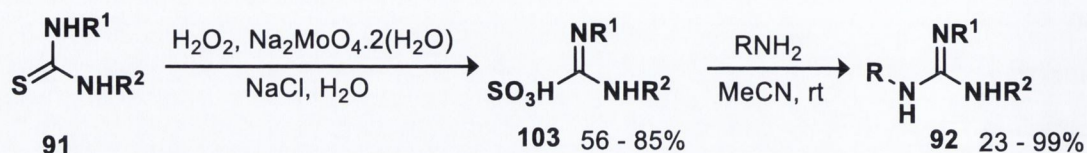
An interesting metal free guanidylation procedure makes use of 2,4,6-trichloro-1,3,5-triazone (TCT or cyanuric chloride **102**) as a promoter of desulfurisation of protected thiourea.⁹⁷ Compound **102** when used in conjunction with *N*-methylmorpholine (NMM) and catalytic DMAP in THF activates *bis*-Boc-thiourea leading to efficient guanidine formation. TCT can be used in 0.33 equivalents due to the three available sites for activation (Scheme 1.5.1.1.9).

Scheme 1.5.1.1.9.



Upon exposure to sodium molybdate dihydrate ($\text{Na}_2\text{MoO}_4 \cdot 2\text{H}_2\text{O}$) and hydrogen peroxide (H_2O_2 , 30% in water), thioureas **91** are known to be converted into sulfonic acids **103** (Scheme 1.5.1.1.10).

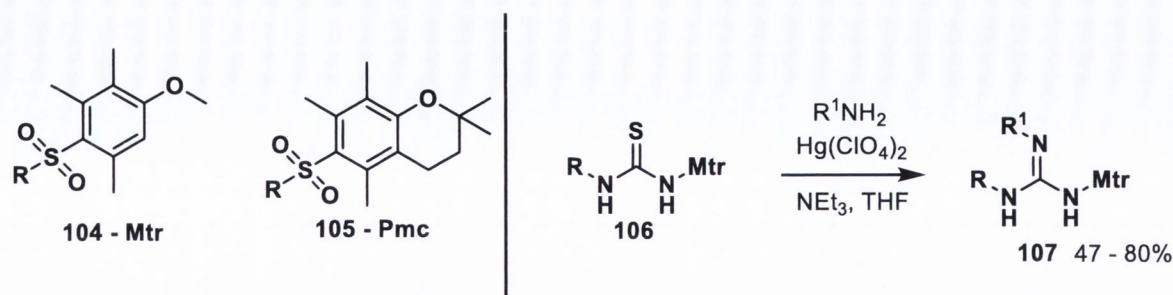
Scheme 1.5.1.1.10.



Maryanoff *et al.* discovered that these sulfonic acid substrates **103** are then viable options as guanidylating agents.⁹⁸ Upon exposure to nucleophilic amines the oxidised sulfur can be displaced to yield the desired guanidine **92** (Scheme 1.5.1.1.10). The reaction of several monosubstituted thioureas under these oxidising conditions was reported in good yields and these sulfonic acids **103** were shown to be thermally stable at room temperature. A range of amines were investigated for their efficacy in displacing the oxidised sulfur and good to excellent yields were reported. Elevated temperatures were required for either hindered or non-nucleophilic amines.

In the search for orthogonal protecting groups to those typically used in peptide synthesis and in particular peptides containing arginine residues two new functionalities have been discovered. 2,3,6-Trimethyl-4-methoxybenzenesulfonyl (**104**, Mtr) and 2,2,5,7,8-pentamethylchroman-6-sulfonyl (**105**, Pmc) groups have been designed to withstand cleavage conditions that would typically remove either Boc, Cbz or Fmoc protecting groups (Scheme 1.5.1.1.11).⁹⁹

Scheme 1.5.1.1.11.

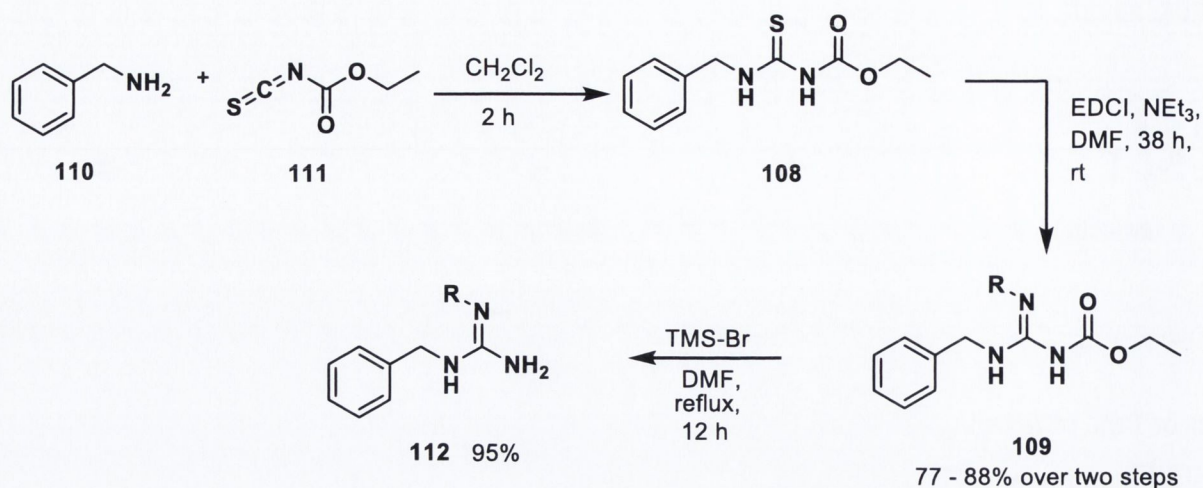


Mtr or Pmc protected thiourea (for example **106**) can be reacted with a range of amines under typical guanidylation conditions [Hg(ClO₄)₂ proved to be optimal] to form both Mtr or Pmc protected guanidines (for example **107**) respectively (Scheme 1.5.1.1.11). These groups, as previously alluded to, are particularly useful in peptide synthesis incorporating guanidine containing arginine residues. Deprotection occurs under strong acidic conditions.⁹⁹

1.5.1.2. Coupling reagents.

In a number of cases the coupling reagent EDCI [1-ethyl-3-(3-dimethylaminopropyl) carbodiimide] has been shown to be able to promote guanidylation between thiourea derivatives and nucleophilic amines. In an example published in 2002, EDCI was used to effectively facilitate the desulfurization of thiourea **108** and subsequent guanidine **109** formation (Scheme 1.5.1.2.1).¹⁰⁰ Compound **108** had been synthesised by reaction of benzylamine **110** and ethyl thiocyanatoformate **111** in CH₂Cl₂ affording the product in 2 h in a 98% yield.

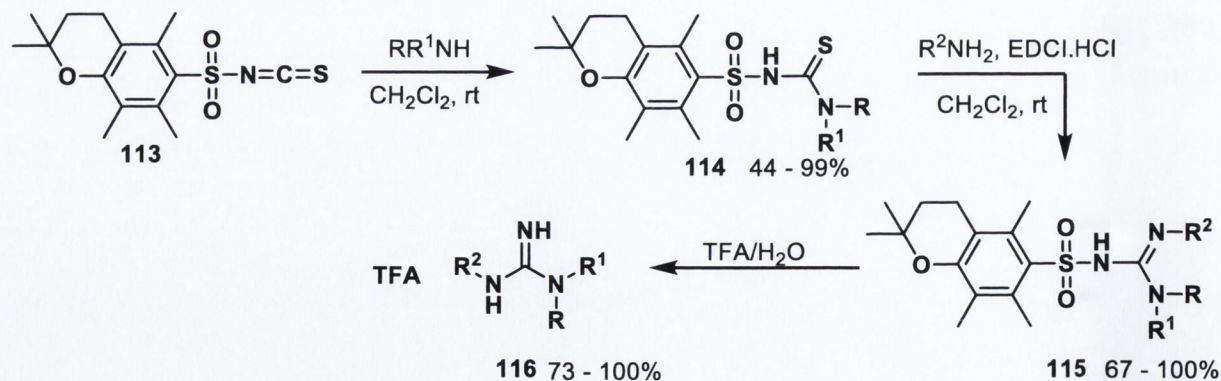
Scheme 1.5.1.2.1.



Most of the amines employed were aliphatic in nature with only one example of a non-nucleophilic amine, aniline, being used. To remove the ethyl carbamate group typical methodologies failed.¹⁰⁰ Interestingly, trimethylsilyl bromide under refluxing conditions in DMF turned out to be the conditions of choice in this deprotection. However, only a single yield of 95% **112** was reported for this deprotection step without a list of substrates being provided.

Another example found in the literature from 2007 also effectively uses EDCI to form substituted guanidines (Scheme 1.5.1.2.2).¹⁰¹

Scheme 1.5.1.2.2.



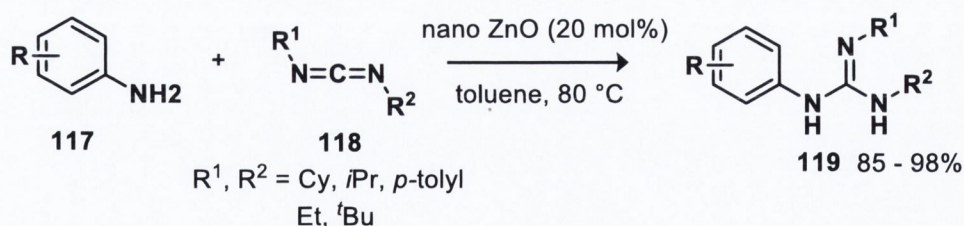
In the example in Scheme 1.5.1.2.2., *N*-Pmc-isothiocyanate **113** is reacted with a variety of both primary and secondary amines to form substituted thioureas **114** in good to excellent yields. Subsequently, other amines were reacted with the substrate **114** separately in the

presence of the coupling reagent EDCI to form compounds **115**. It is important to note the viability of forming derivatised guanidines in this manner. The relatively electrophilic isothiocyanate can react with a plethora of amines of varying nucleophilicities. However, the EDCI promoted step requires nucleophilic primary amines to obtain optimal results. By choosing the appropriate amines for each step the authors were able to synthesise a number of substituted guanidines which could then undergo deprotection of the Pmc group in acidic conditions to yield the guanidinium trifluoroacetate salts **116**.

1.5.1.3. Metal-catalysed carbodiimide guanidylation.

The reaction between an amine and a carbodiimide is one of the most atom economical methods of synthesising guanidines and has been a fruitful area of research in recent years.¹¹² Numerous examples of metal catalysed reactions between amines and carbodiimides have been published.¹⁰² In a 2012 publication it was reported that aniline **117** could be reacted with dicyclohexylcarbodiimide (DCC) and its derivatives **118** in the presence of a heterogeneous metal to form the corresponding guanidine **119**. Initial investigations (Scheme 1.5.1.3.1) showed that nanocrystalline zinc oxide (nano ZnO) catalysed this reaction effectively and after a quick solvent screen it was found that non-polar, non-coordinating solvents such as toluene gave optimal results (yield 98%).¹⁰³

Scheme 1.5.1.3.1.



Interestingly, the use of commercial ZnO as opposed to nano ZnO gave drastically inferior yields (~ 5%). The nano ZnO could be recycled up to 6 times giving similar yields on each occasion without dropping activity. A wide variety of anilines and a number of carbodiimides could be reacted under similar conditions generating the required trisubstituted guanidines. The drawback of this chemistry, however, is that only a select few carbodiimides are both

stable and/or commercially available allowing only very particular substrates to be synthesised in this way. Hindered amines required higher temperatures for reactivity to occur. The ZnO is thought to activate the carbodiimide facilitating the nucleophilic attack from the amine.

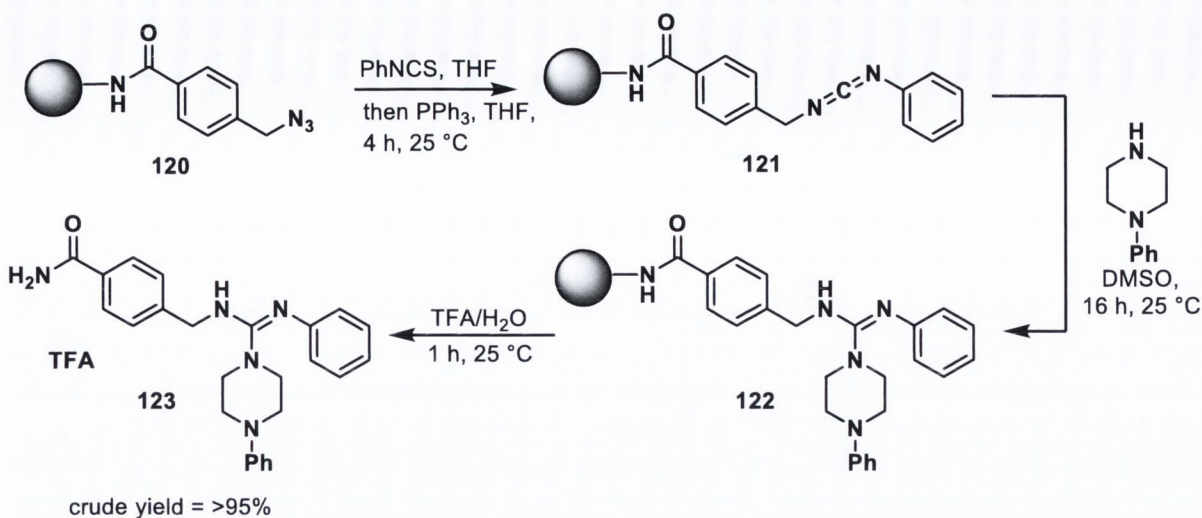
In another report in 2012, $\text{Fe}(\text{OAc})_2$ (2 mol%) was shown to catalyse this transformation between anilines **117** and carbodiimides **118** just as effectively as nano ZnO under similar conditions.¹⁰⁴ As in the previous report, both a wide range of aromatic amines and aliphatic amines were guanidylated in this manner. Similarly, the drawback is the lack of available carbodimides to obtain a truly diverse library of guanidines.

1.5.1.4. Polymer supported guanidylation.

A number of methods for the solid phase syntheses of guanidines have been reported. The use of polymer supported reagents have a number of advantages namely allowing the removal of excess reagent, unreacted starting materials and unwanted by-products from the reaction mixture.¹⁰⁵

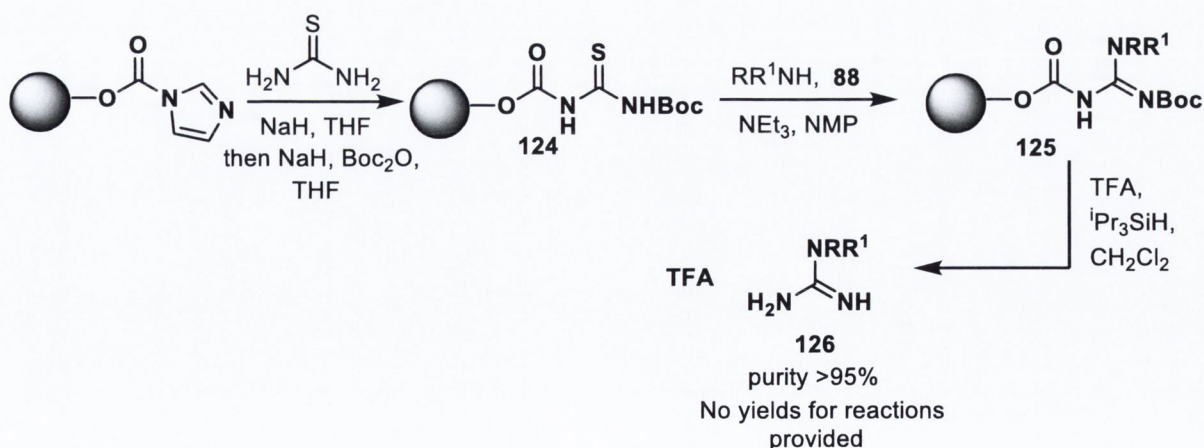
The utility of solid supported reagents in the preparation of guanidines has been demonstrated in the synthesis of *N,N',N''*-trisubstituted guanidines in a report by Drewry *et al.* in 1997 (Scheme 1.5.1.4.1).¹⁰⁶ The synthesis began with the preparation of solid phase supported reagent **120**. This azide is then exposed to PPh_3 to form an iminophosphorane which in the presence of PhNCS can undergo an aza-Wittig coupling forming the prerequisite carbodiimides **121** which are known to be stable in solid phase chemistry. Compound **121** can now be reacted with a variety of amines such as *N*-phenylpiperazine to form polymer bound guanidine **122**. Under acidic conditions the desired guanidine can be cleaved from the resin to yield the final compounds **123** in good yield.

Scheme 1.5.1.4.1.



The synthesis of mono-substituted aryl guanidines can also be achieved using solid support chemistry (Scheme 1.5.1.4.2). The preparation of solid supported Boc protected thiourea **124** can be thought of as a polymer bound guanidylating agent.¹⁰⁷ In the presence of a promoting agent such as Mukaiyama's reagent a range of amines could be reacted with the thiourea derivative to form polymer supported Boc protected guanidines **125**. Upon exposure to TFA the guanidines could then be cleaved from the resin yielding the desired mono substituted guanidines as their trifluoroacetic acid salts **126**.

Scheme 1.5.1.4.2.

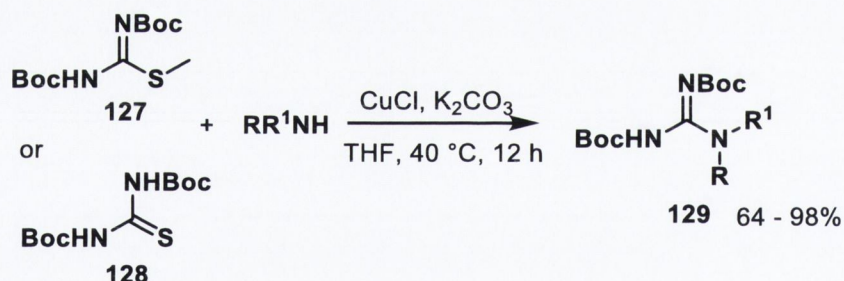


1.5.1.5. *S*-Methylisothiurea as guanidylating agent.

The use of *S*-methyl-*N,N'*-bis-Boc-isothiurea **127** as a guanidylating agent has found success in a number of literature examples. Its ability to replace *N,N'*-bis-Boc-thiourea **128** has proven to be advantageous in a number of circumstances. In a discovery by Rozas and co-workers⁹³ it was found that copper(II) salts could promote guanidylation of *N,N'*-bis-Boc-thiourea with a variety of amines but either gave either low or no yields for the analogous reaction with *S*-methyl-*N,N'*-bis-Boc-isothiurea.

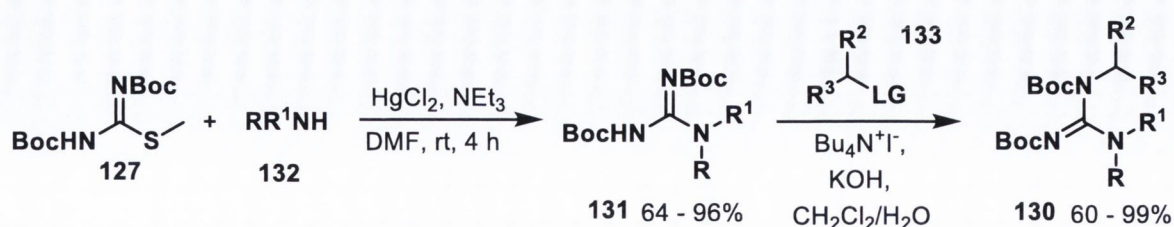
However, in another publication by Terada *et al.*¹⁰⁸ it was demonstrated that copper(I) salts could effectively promote guanidylation of both thiourea precursors (Scheme 1.5.1.5.1). In this work, a number of amines were exposed to both sets of conditions and in the two cases the protected guanidine products **129** were obtained in good to excellent yields (Scheme 1.5.1.5.1). This interestingly shows the specificity that promoters can sometimes have in guanidylation reactions and give an insight into why there is such a diverse literature for the synthesis of guanidines.

Scheme 1.5.1.5.1.



In an effort to efficiently synthesise a diverse variety of *N,N',N''*-trisubstituted guanidines **130**, an effective phase transfer catalysed alkylation of protected guanidines **131** was unveiled (Scheme 1.5.1.5.2).¹⁰⁹ A variety of amines **132** were reacted with *S*-methyl-*N,N'*-bis-Boc-isothiurea **127** in the presence of $HgCl_2$, as this is known in the literature to be very efficient in the preparation of protected guanidines.

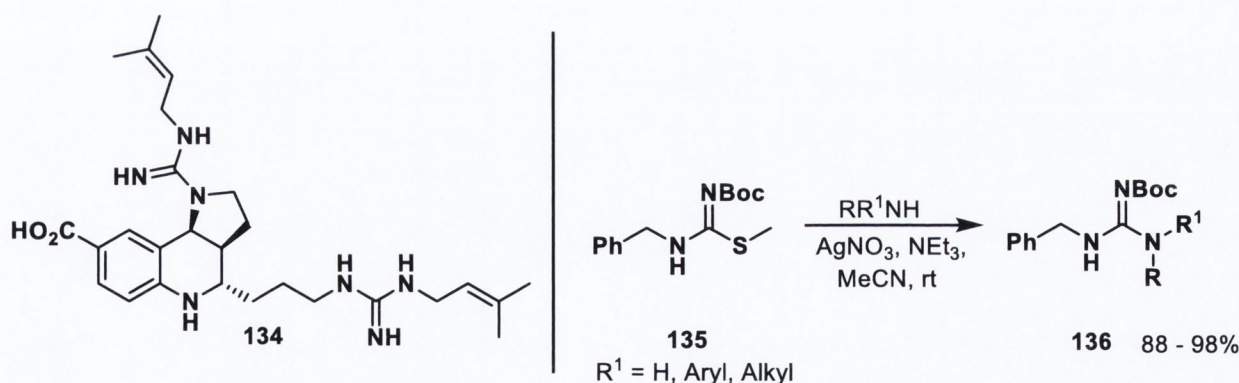
Scheme 1.5.1.5.2.



Then, in a biphasic system of CH_2Cl_2 and H_2O the compounds were reacted with KOH , a phase transfer catalyst (Bu_4NI , 0.1 eq) and a number of alkylating agents **133** (Scheme 1.5.1.5.2). This process allowed the rapid formation of highly diversified guanidines **130** in good to excellent yields. This reactivity, however, was only reliable when both R and R^1 were not equal to H , as this led to non-specific alkylation at either nitrogen or, in some cases, to *bis*-alkylation.

In Ma's synthesis of martinellie acid **134**, a novel method of guanidylation was devised.¹¹⁰ It was found that $AgNO_3$ is able to promote the guanidylation of *S*-methylisothiourea derivatives **135** with a variety of amines to form guanidine products **136** in excellent yield (Scheme 1.5.1.5.3).

Scheme 1.5.1.5.3

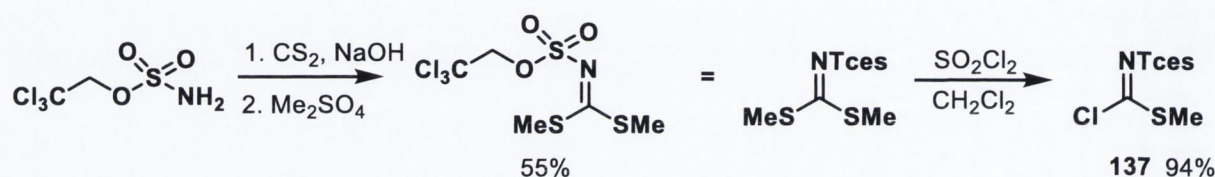


The reaction was shown to work well with aliphatic amines, sterically hindered secondary amines and also with aniline. This new method was formulated due to the fact that hindered secondary amines are often difficult to guanidylate and initial experiments using typical

guanidylation methodologies proved unfruitful. This method allowed the team to install the key guanidine functional groups with relative ease.

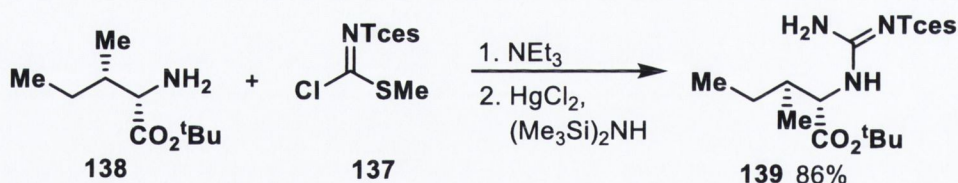
An interesting guanidylating agent designed by Du Bois and used in his synthesis of guanidine natural products is Tces (2,2,2-trichloroethoxysulfonyl) – protected imidochloride **137**.¹¹¹ This compound can be prepared as shown in Scheme 1.5.1.5.4.

Scheme 1.5.1.5.4.



This reagent **137**, although laborious to prepare, has shown to be an effective way of introducing guanidines (Scheme 1.5.1.5.5) which are to be used in C-H amination reactions.¹¹² Romo has also made use of this reagent in his synthesis of the natural product phakellin.¹¹³

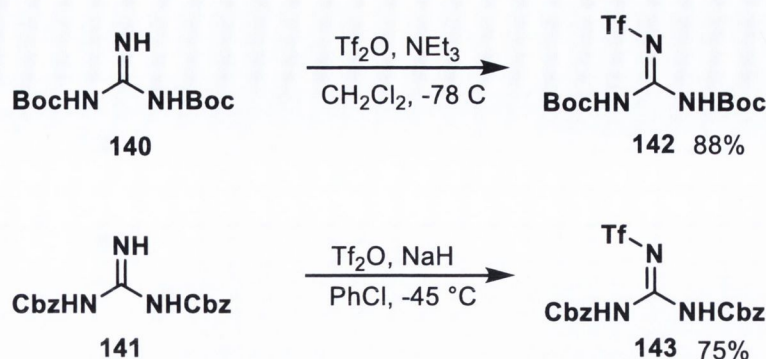
Scheme 1.5.1.5.5.



1.5.1.6. *N,N',N''*-Trisubstituted guanidines as guanidylating agents.

Since 1998 it has been known that guanidines can be synthesised from guanidine precursors by coaxing one of the nitrogens into being an effective leaving group. This can be done effectively as discovered by Goodman and co-workers by using triflate derivatised guanidines (Scheme 1.5.1.6.1).¹¹⁴

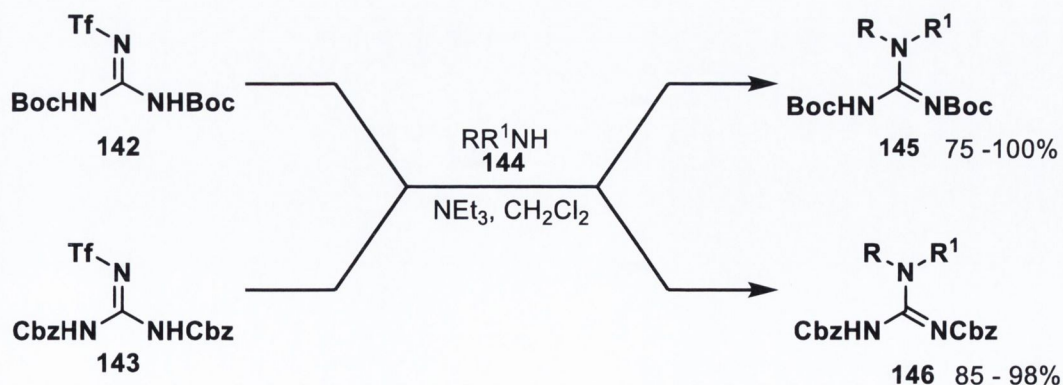
Scheme 1.5.1.6.1.



Firstly, either *N,N'*-bis-Boc-guanidine **140** or *N,N'*-bis-Cbz-guanidine **141** are synthesised. Subsequent exposure to triflic anhydride introduces a triflyl group to the remaining unsubstituted nitrogen atom of the guanidine moiety (Scheme 1.5.1.6.1. **142**, **143**).

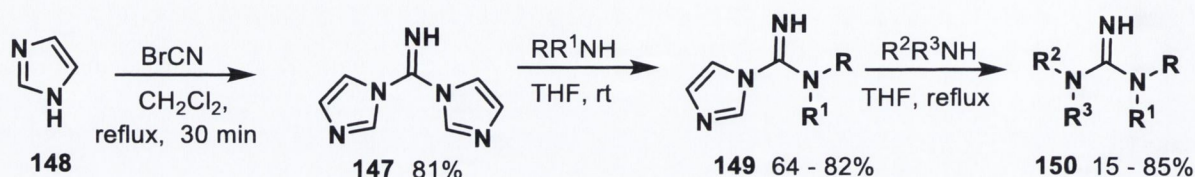
The two carbamate protecting groups (either Boc or Cbz) pull electron density away from the central carbon atom of the guanidine. Nucleophilic attack can follow and the triflated amine can act as a leaving group (Scheme 1.5.1.6.2). The relative stability (due to the delocalisation of the ensuing negative charge) of this expelled group is what drives this reaction forward and allows these reagents to be effective as guanidylating agents. Sterically hindered aliphatic amines and primary amines work particularly well under these conditions; however, limited studies have been conducted on the efficacy of these reagents with electron deficient anilines.¹¹⁵

Scheme 1.5.1.6.2.



The use of di(imidazol-1-yl)methanimine **147** as an effective guanidylating agent has also been shown to be synthetically useful in the preparation of derivatised guanidines.¹¹⁶ By exposing imidazole **148** (0.5 eq.) to cyanogen bromide (BrCN, 1.0 eq.), **147** can be synthesised in good yield (Scheme 1.5.1.6.3. **147** = 81%).

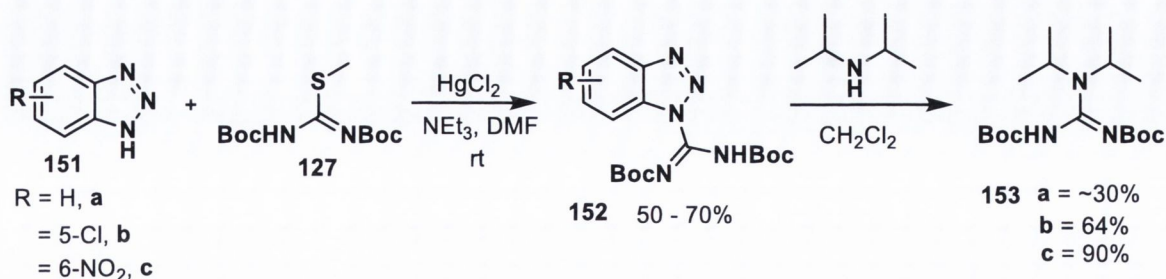
Scheme 1.5.1.6.3.



The presence of two imidazole leaving groups facilitates initial displacement of a single imidazole by an amine nucleophile. These compounds **149** can then be isolated and exposed to a further equivalent of another amine generating structurally diverse guanidines **150** in acceptable yields (Scheme 1.5.1.6.3). The success of these reactions is dependent on the nucleophilicity of the attacking amines; electron deficient anilines did not react in this case (4-nitroaniline, 0% yield).¹¹⁶ Similar pyrazole derivatives have also been designed and shown to be effective as guanidylating agents.¹¹⁷ A further study showed the effects of electron withdrawing substituents on the pyrazole ring in forming guanidines.¹¹⁸

Subsequent research in this area investigated the use of benzotriazoles **151a** as a leaving group in guanidylation reactions.¹¹⁹ A comparative investigation was conducted on the influence of decreasing the electron density of the benzotriazole group using chloro **151b** and nitro **151c** groups (Scheme 1.5.1.6.4). Increasing the leaving group ability of the benzotriazoles by allowing them to facilitate the resulting negative charge which would arise from expulsion increased their reactivity towards amine nucleophiles.

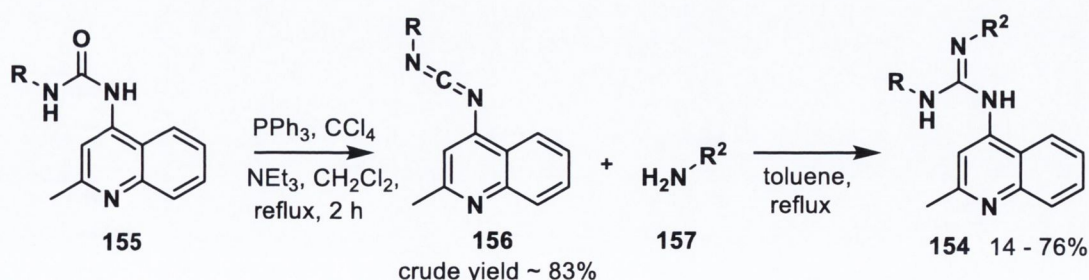
Scheme 1.5.1.6.4.



1.5.1.7. Urea derivatives in guanidine formation.

As an oxygen analogue of guanidine, urea would seem like an obvious precursor in the synthesis of guanidines. However, urea has received much less attention in comparison to its sulfur analogue, thiourea, presumably due to its stable nature. The literature examples are typically either low yielding or have a low substrate scope.¹²⁰ One such example is the synthesis of a library of quinoline guanidine derivatives **154** in the hope of discovering novel anti-inflammatory agents.¹²¹ Thiourea derivatised quinolines **155** were exposed to PPh₃, CCl₄ and NEt₃ under reflux in CH₂Cl₂ using Appel type conditions¹²² to form crude carbodiimides **156** which, without purification, were exposed to a number of amines **157** in different solvent yielding *N,N',N''*-trisubstituted guanidines **154** in varying yields (Scheme 1.5.1.7.1). The inability to purify the intermediate carbodiimide is an obvious drawback. This reaction has hugely varying yields with some substrates giving yields of just 14%.

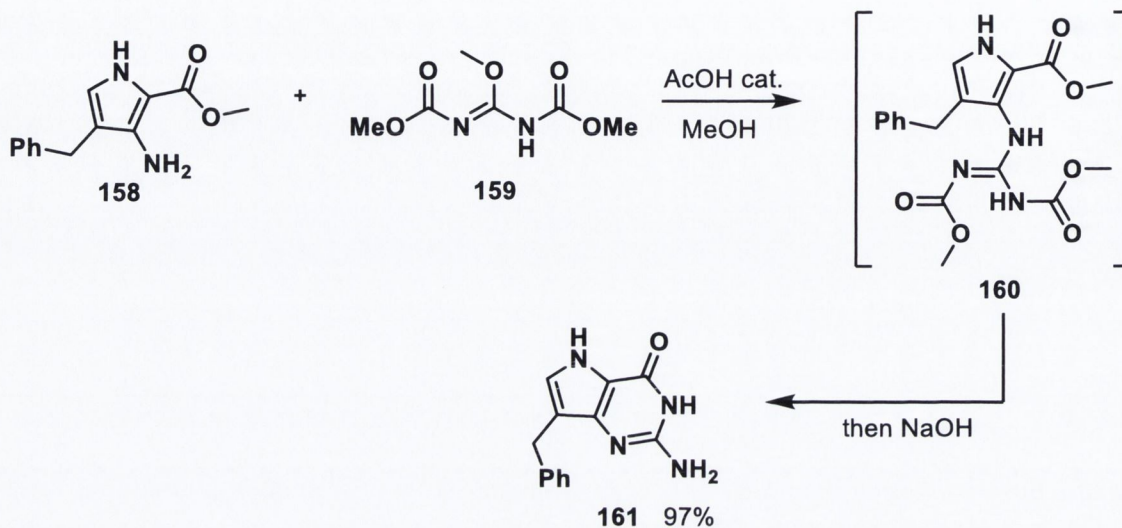
Scheme 1.5.1.7.1.



In an effort to synthesise 7-substituted pyrrolo[3,2-*d*]pyrimidines, 3-aminopyrrole derivative **158** was reacted with *bis*-protected pseudourea **159** in the presence of catalytic amounts of

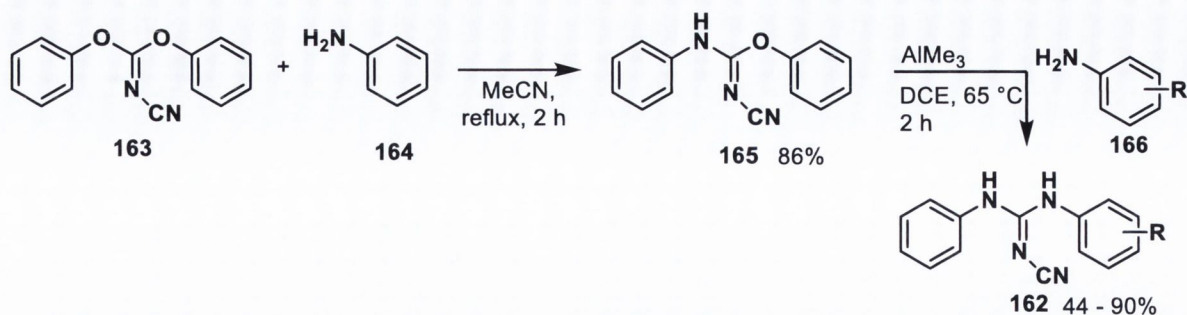
AcOH in MeOH (Scheme 1.5.1.7.2).¹²³ This led to guanidylated intermediate **160** which, upon exposure to NaOH, was deprotected and cyclised to form desired product **161**.

Scheme 1.5.1.7.2.



Initial attempts to guanidylate amine **158** using a thiourea analogue of **159** also led to the desired product. However, as is typical with the reaction of aromatic amines and thiourea derivatives, HgCl_2 was required to promote the reaction. The authors decided that, as the compounds were to be used in biological testing the presence of ppm amounts of mercury was unacceptable and that the use of urea precursor **159** was a much safer alternative.

In an effort to synthesise cyanoguanidine derivatives **162** a novel method of guanidylation was discovered by Atwal and co-workers at BMS, Princeton.¹²⁴ *N*-Cyano-*O*-phenylisourea **163** was found to react favourably with non-basic amines such as aniline **164** when AlMe_3 was used as a promoting agent (Scheme 1.5.1.7.3) to form derivatised ureas **165**.

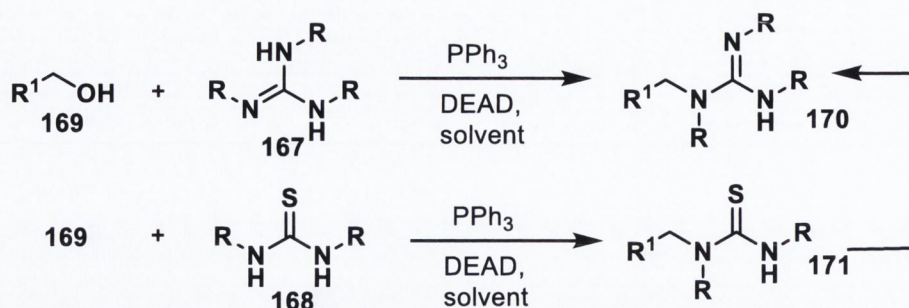
Scheme 1.5.1.7.3.

High yields were obtained when electron rich anilines **166** such as 4-methoxyaniline was used (90%), while electron deficient anilines such as 4-nitroaniline gave no reaction.

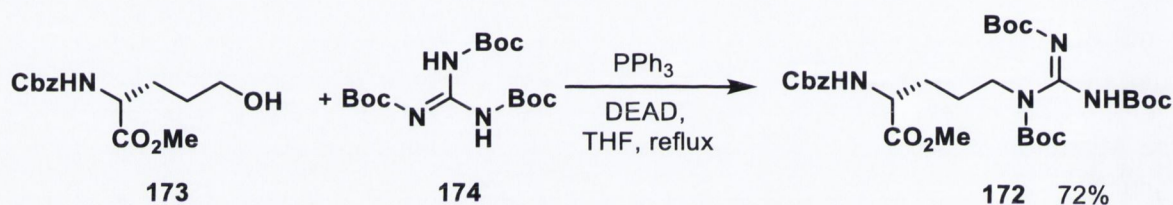
1.5.1.8. The Mitsunobu reaction to form guanidines.

The utility of hydroxyl groups as synthetic handles has been well established throughout chemical history. The ability to convert hydroxyl groups into varying substituents by means of the Mitsunobu reaction has proven to be ubiquitous in syntheses since its discovery in 1967¹²⁵ as is discussed in the numerous reviews on the topic.¹²⁶ As a means of guanidine introduction, the ability to replace primary hydroxy functionalities is particularly useful when it is advantageous to have hydroxy precursors as opposed to aliphatic amines.

Both thiourea guanidine precursors **167** and protected guanidines **168** can be reacted with primary alcohols **169** (Scheme 1.5.1.8.1) in the presence of triphenyl phosphine (PPh₃) and diethylazodicarboxylate (DEAD) to form alkylated derivatives (Scheme 1.5.1.8.1. **170**, **171**).¹²⁷

Scheme 1.5.1.8.1.

This methodology has been used to synthesise protected arginine derivatives¹²⁸ **172** (Scheme 1.5.1.8.2) and natural products¹²⁹ in acceptable yields.

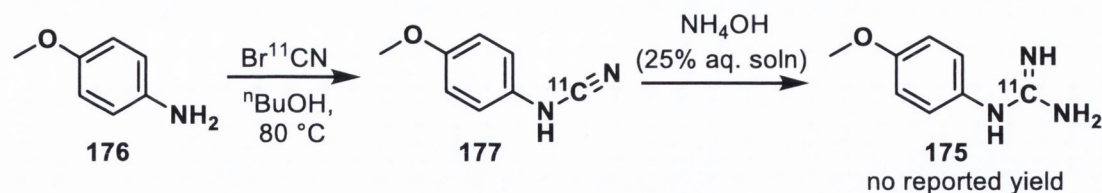
Scheme 1.5.1.8.2.**1.5.1.9. Cyanamides in guanidine synthesis.**

A rather dated method for the synthesis of guanidines makes use of the formation of cyanamides and subsequent reaction with derivatised amines. Both functionalised anilines can be reacted with cyanamide to form aryl guanidines¹³⁰ and, analogously, phenyl cyanamides can be synthesised and then further reacted with a variety of amines, also forming aryl guanidines.¹³¹

The synthesis of ^{11}C radiolabelled aryl guanidines **175** is of great importance as guanidines are involved in numerous biological activities and labelling them with short-lived positron emitters (^{11}C $t_{1/2} = 20.3$ min) such as ^{11}C would allow their use in both *in vivo* positron emission tomography (PET) studies and *in vitro* assays.¹³⁰ Thus, the preparation of ^{11}C labelled aryl guanidines was achieved using cyanamide chemistry (Scheme 1.5.1.9.1). Firstly, the appropriate aniline **176** was reacted with ^{11}C labelled cyanogen bromide and, then, this

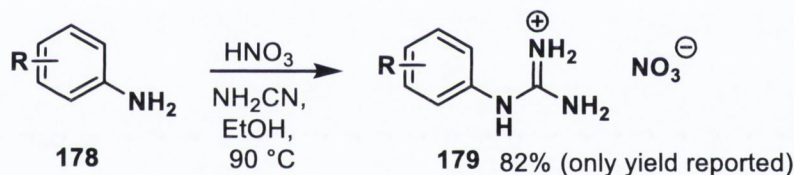
aryl cyanamide **177** was exposed to ammonia in different solvents to afford the desired products **175**.¹³⁰

Scheme 1.5.1.9.1.



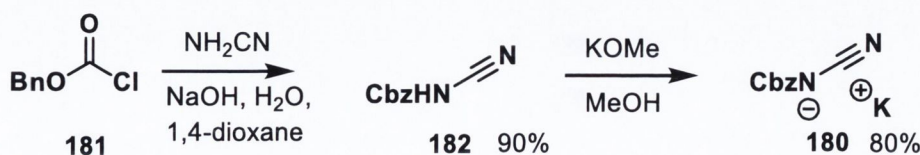
In a report from Kim *et al.*¹³¹ this reactivity was utilised in the synthesis of aryl guanidines which were required in their synthesis of inhibitors of the NF- κ B transcription regulation related to TNF- α cytokine release. A number of anilines **178** were reacted with conc. nitric acid in ethanol at 90°C to afford aryl guanidines **179** (Scheme 1.5.1.9.2).

Scheme 1.5.1.9.2.



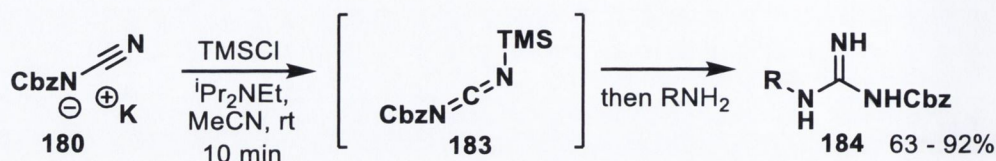
A more efficient method for the reaction of anilines and also aliphatic amines with cyanamides has recently been unveiled by Looper and co-workers at the University of Utah.¹³² Derivatised cyanamide **180** was first synthesised by reacting cyanamide with benzyl chloroformate **181** forming the Cbz protected cyanamide **182** (Scheme 1.5.1.9.3).

Scheme 1.5.1.9.3.



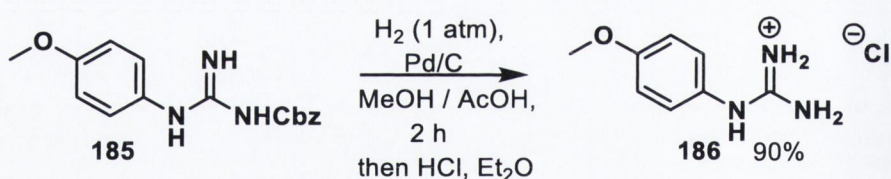
This was then converted into the potassium salt **180** by exposure to potassium methoxide in methanol. Compound **180** could then be activated in the presence of TMS-Cl and a base, forming a carbodiimide reactive intermediate **183** which can be nucleophilically attacked by a number of amines to form mono Cbz protected guanidines **184** (Scheme 1.5.1.9.4).

Scheme 1.5.1.9.4.



Aliphatic nucleophilic amines gave the highest yields with short reaction times (15 min) while both hindered and non-nucleophilic substrates such as anilines required longer reaction times and gave lower yields. The Cbz group could then potentially be removed by Pd catalysed hydrogenation (Scheme 1.5.1.9.5); however, only 1 example of deprotection was reported.

Scheme 1.5.1.9.5.



1.5.1.10. Copper catalysed cross coupling chemistry in guanidine synthesis.

Copper coupling chemistry has seen a renaissance in the past decade.¹³³ The harsh conditions historically required for Ullmann reactions have been discarded and replaced by mild, copper catalysed reactivity.¹³⁴ The ability to form C–N bonds in a facile manner is of clear importance in the synthesis of guanidines and copper coupling chemistry allows a type of *umpolung* reactivity in comparison to the typical methods of guanidine synthesis. As opposed to nucleophilic anilines reacting with a guanidine precursor, an aryl halide is exposed to a nucleophilic guanidine source. This reactivity allows for facile assembly of aryl guanidines.

As it is typical with copper coupling chemistry the exact mechanism of the catalytic cycle is still unclear. However, a possible catalytic cycle that would be in agreement with previous findings in copper chemistry has been suggested by Dawei Ma and co-workers at Shanghai Institute of Organic Chemistry (SIOC).¹³⁵ It is known that α -amino acids and CuI can form chelate complexes such as **187** (Figure 1.5.1.10.1). The formation of the Cu(I) – amino acid species makes it more reactive towards oxidative addition and may also stabilize the oxidative addition intermediates thereby promoting the coupling reaction.¹³⁶ Complex **187** may then coordinate to guanidine to give complex **188**, whose oxidative addition to an aryl halide could afford Cu(III) complex **189**. The presence of a base in the catalytic cycle could then result in the formation of **190** which upon reductive elimination could generate *mono*-arylated guanidines and regenerate the Cu(I) species **187**.

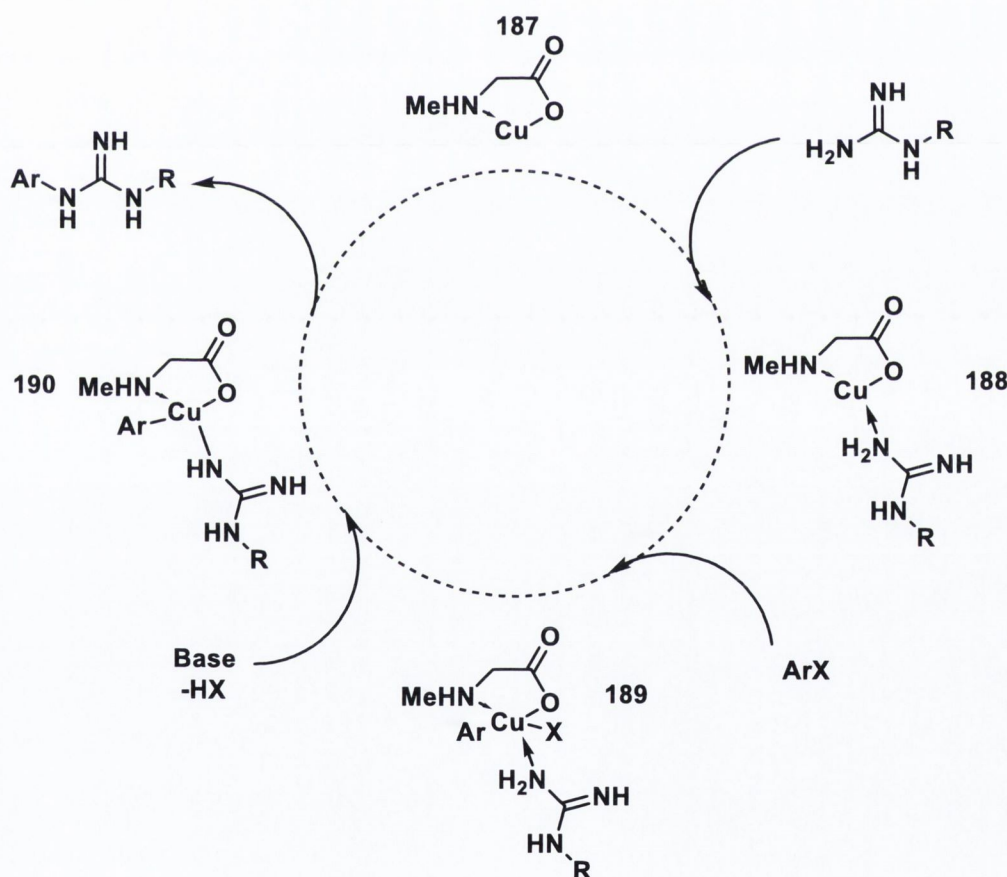


Figure 1.5.1.10.1. Proposed catalytic cycle for copper catalysed guanidylation.¹³⁵

Another plausible mechanism for copper catalysed coupling chemistry is depicted in Figure 1.5.1.3 and has been previously suggested.^{135,137} As occurs in the previous mechanism a Cu(I)

complex will be formed by coordination to the α -amino acid ligand. Chelated Cu(I) may possibly coordinate to an aryl halide forming the π -complex **191** which would be electron deficient and more susceptible to amine nucleophilic attack giving **192** (Figure 1.5.1.10.2). Subsequent expulsion of the halide leaving group to form **193** and dissociation of the copper complex regenerate the active Cu(I) species and yields the desired product. Although it is not known exactly which is the actual mechanism both have been often used to explain results arising from copper coupling chemistry.

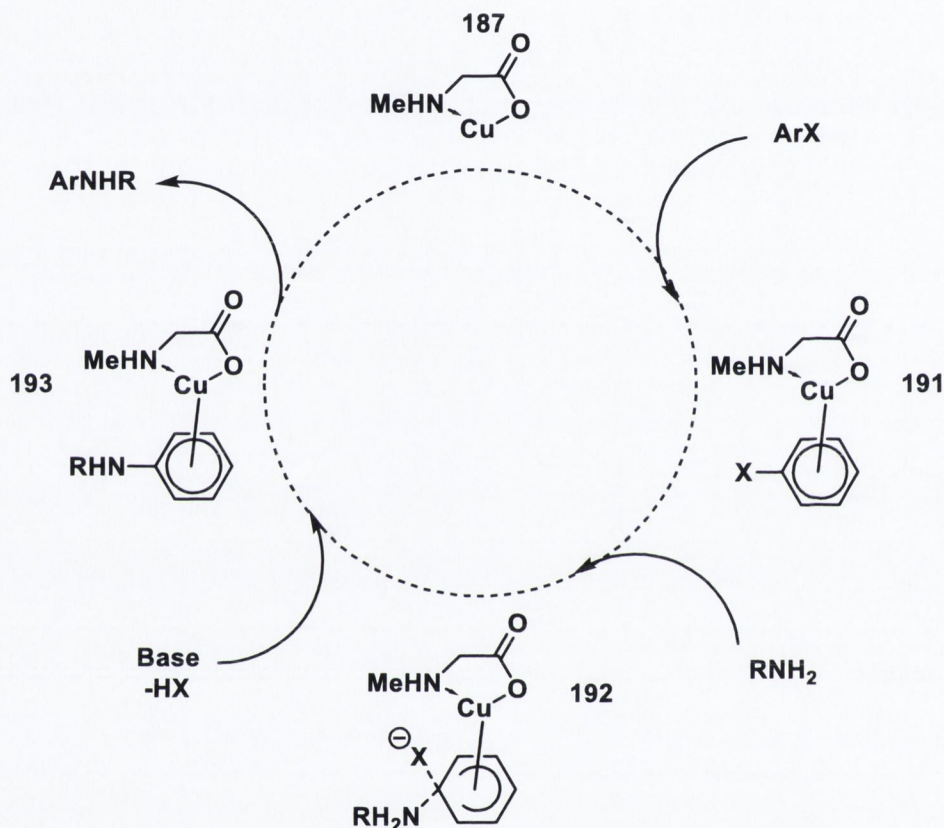
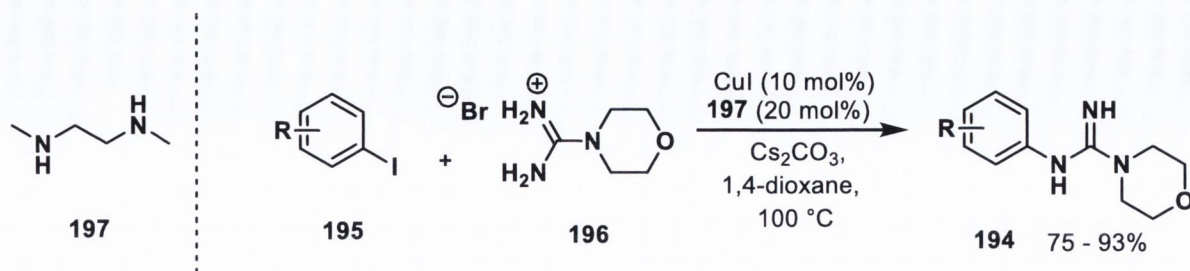


Figure 1.5.1.10.2. Alternative catalytic cycle for copper catalysed guanidylolation.¹³⁷

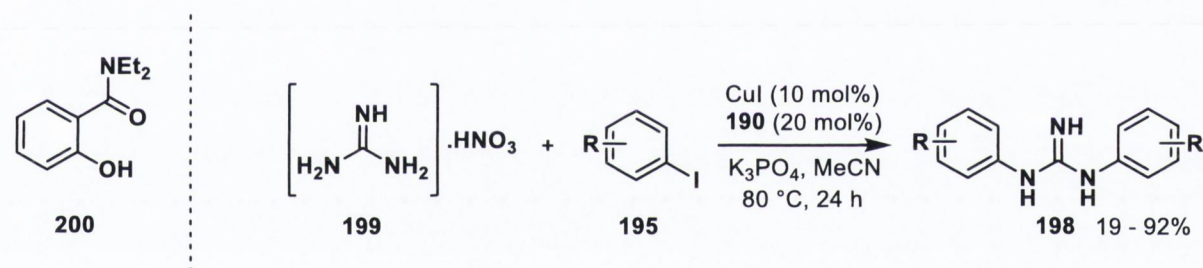
In an investigation into the synthesis of benzimidazoles, the formation of aryl guanidines **194** by means of copper catalysed cross coupling chemistry was discovered (Scheme 1.5.1.10.1).¹³⁸ Aryl iodides **195** and guanidines **196** could be coupled together in the presence of CuI and ligand **197** to yield arylguanidines **194**. This was the first report of its kind (with six examples) and was followed by investigations from other research groups developing further the result.

Scheme 1.5.1.10.1.



In 2010 a report from Antilla and co-workers at the University of South Florida described the formation of *N,N'*-disubstituted aryl guanidines **198**.¹³⁹ Guanidine nitrate **199** was chosen as the source of nucleophilic guanidine and a wide variety of aryl iodides **195** were selected as the coupling partners (scheme 1.5.1.10.2).

Scheme 1.5.1.10.2

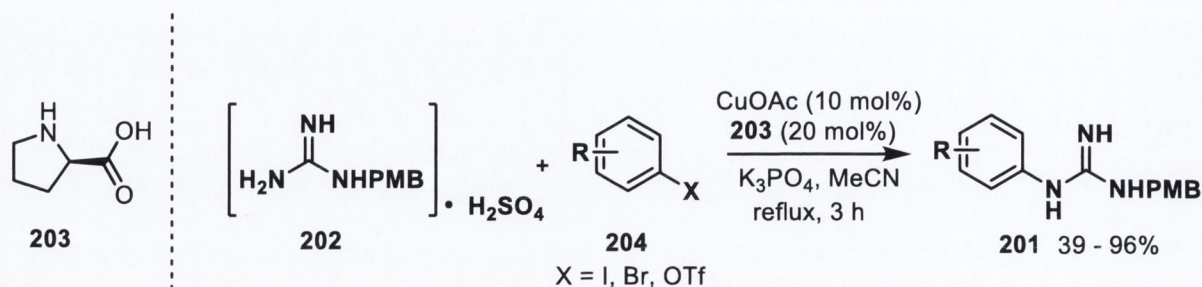


Thus, in the presence of catalytic amounts of CuI (10 mol%), ligand **200** (*N,N'*-diethylsalicylamide, 20 mol%) and K_3PO_4 in acetonitrile at 80°C for 24 h, successful couplings between the two substrates were achieved with varying yields. However, mono arylated products could not be obtained with diarylation being observed in all cases (Scheme 1.5.1.10.2).

A report in 2011 also investigated the feasibility of forming C–N bonds through copper catalysis with the aim of preparing *mono*-arylated guanidines **201** (Scheme 1.5.1.10.3).¹⁴⁰ A number of guanidine sources were investigated using both copper and palladium catalysts. Protected guanidines were chosen as the nucleophilic substrates due to their lower basicity and less reactive nature than guanidine itself. Palladium catalysis proved to be ineffective; however, initial experimentation with copper catalysts proved to be promising with a high

ratio of *mono*- arylated to diarylated products being observed. *p*-Methoxybenzyl (PMB) guanidine **202** was chosen as the most suitable form of protected guanidine. PMB protected guanidines were made from benzylamine and 2-methylthiopseudourea in 62–80% yields.

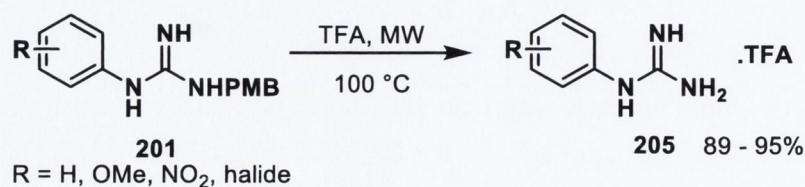
Scheme 1.5.1.10.3.



A range of α -amino acid ligands were investigated for their efficacy in this cross coupling reaction as were varying copper sources, bases, solvent, temperature and time. Optimal results were observed when $CuOAc$ (10 mol%), ligand **203** (20 mol%, proline) and K_3PO_4 in MeCN at 100 °C were employed for 3 hr. A wide variety of aryl halides **204** were coupled in good to excellent yields (Scheme 1.5.1.10.3). This is one of the few literature examples of C–N bond formation utilising copper coupling chemistry and an aryl triflate as a coupling partner.¹⁴¹

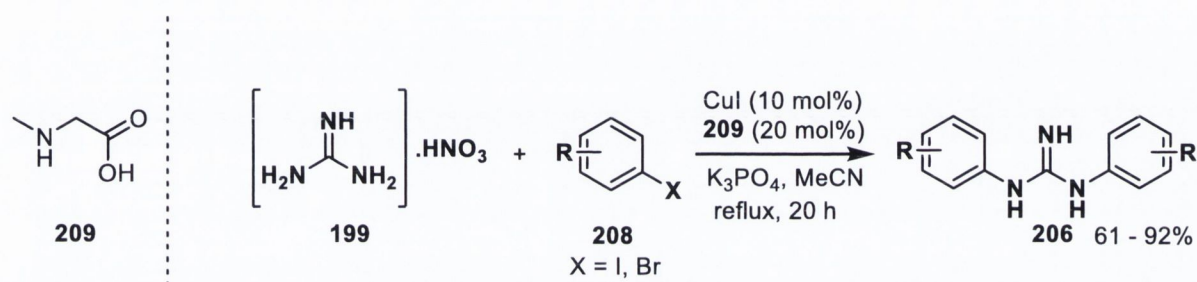
Deprotection of PMB protected guanidines **201** was then accomplished by microwave irradiation in TFA at 100 °C (Scheme 1.5.1.10.4). This afforded the corresponding guanidines as trifluoroacetate salts **205** in excellent yields (Scheme 1.5.1.10.4. 89 – 95%). Due to the harsh nature of these deprotection conditions not a wide variety of functional group as substituents on the aryl ring were investigated.

Scheme 1.5.1.10.4.



In an attempt to form both symmetrical and unsymmetrical *N,N'*-diaryl guanidines (**206** and **207** respectively) Ma *et al.* investigated the use of copper cross coupling chemistry.¹⁴² As with previous discoveries,^{139,140} initial investigations into the coupling of aryl halides with guanidines were concerned with optimising the reaction conditions to afford symmetrical *N,N'*-diaryl guanidines. Hence, aryl halides **208** and guanidine nitrate **199** were successfully coupled using a copper(I) source, an α -amino acid ligand **209**, base and solvent. The optimal reaction conditions are shown in Scheme 1.5.1.10.5.

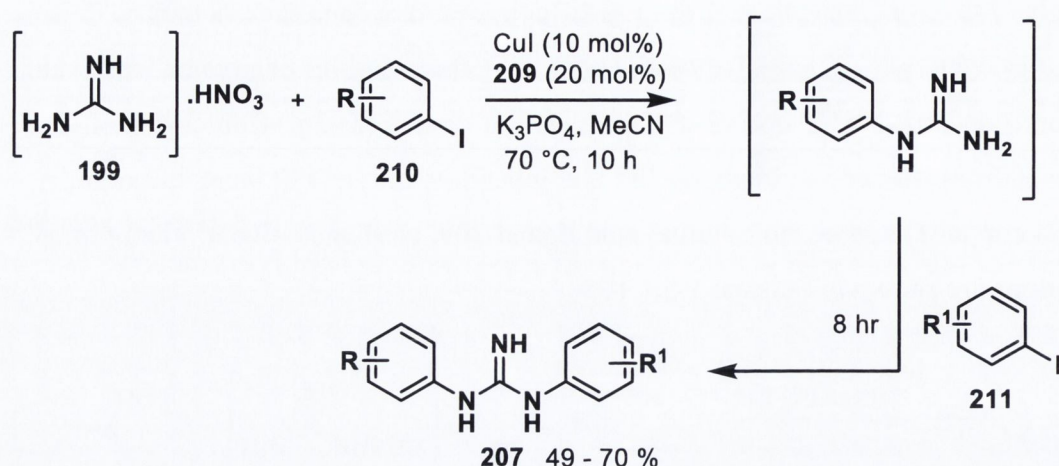
Scheme 1.5.1.10.5.



As has been previously reported, the use of CuI (10 mol%) and K_3PO_4 in MeCN was optimal, with *N*-methylglycine (ligand **209**, 20 mol%) being the ligand of choice. Under these conditions a number of aryl iodides could be diarylated in good yields and aryl bromides were also successfully coupled with guanidine nitrate in acceptable yields.

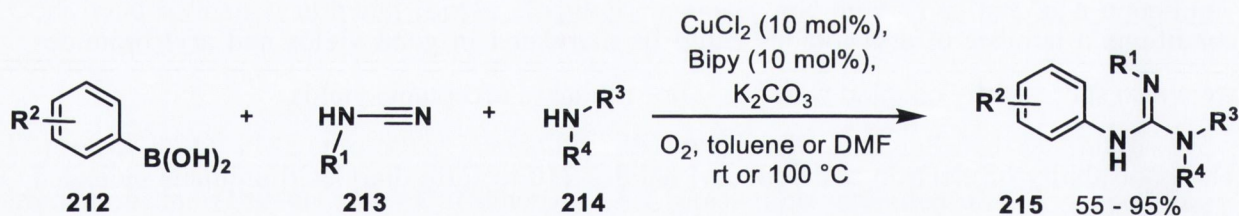
The poor ability of electron deficient aryl halides **210** to form diarylated products indicated the potential for forming unsymmetrical *N,N'*-diaryl guanidines in a sequential one pot process. Initial investigations coupled 4-nitroiodobenzene with guanidine nitrate **199** in conditions analogous to those reported for the previous diarylation.¹³⁹ After 10 h, an electron rich aryl halide **211** (for example 4-methoxyiodobenzene) was added to the reaction mixture and allowed to react for a further 8 h (Scheme 1.5.1.10.6). As desired, the reaction resulted in the formation of unsymmetrical *N,N'*-diaryl guanidines **207** in reasonable yields.

Scheme 1.5.1.10.6.



In 2013 a three component copper catalysed coupling reaction between arylboronic acids **212**, cyanamides **213** and amines **214** was reported.¹⁴³ This reaction allows access to trisubstituted aryl guanidines **215** with a high potential for introducing diversity (Scheme 1.5.1.10.7).

Scheme 1.5.1.10.7.



This reaction is thought to proceed through transmetalation of copper(II) species generated from the oxidation of the Cu(I) salt in the presence of O₂. Coordination of the cyanamide and deprotonation, followed by tautomerisation, would ensue the generation of the highly electrophilic carbodiimide. This could then be attacked by the amine and subsequent oxidation of the Cu(II) species to Cu(III) could enable reductive elimination generating the guanidine product and regenerating the Cu(I) species. This possible catalytic cycle, as described by the authors is presented in Figure 1.5.1.10.3.

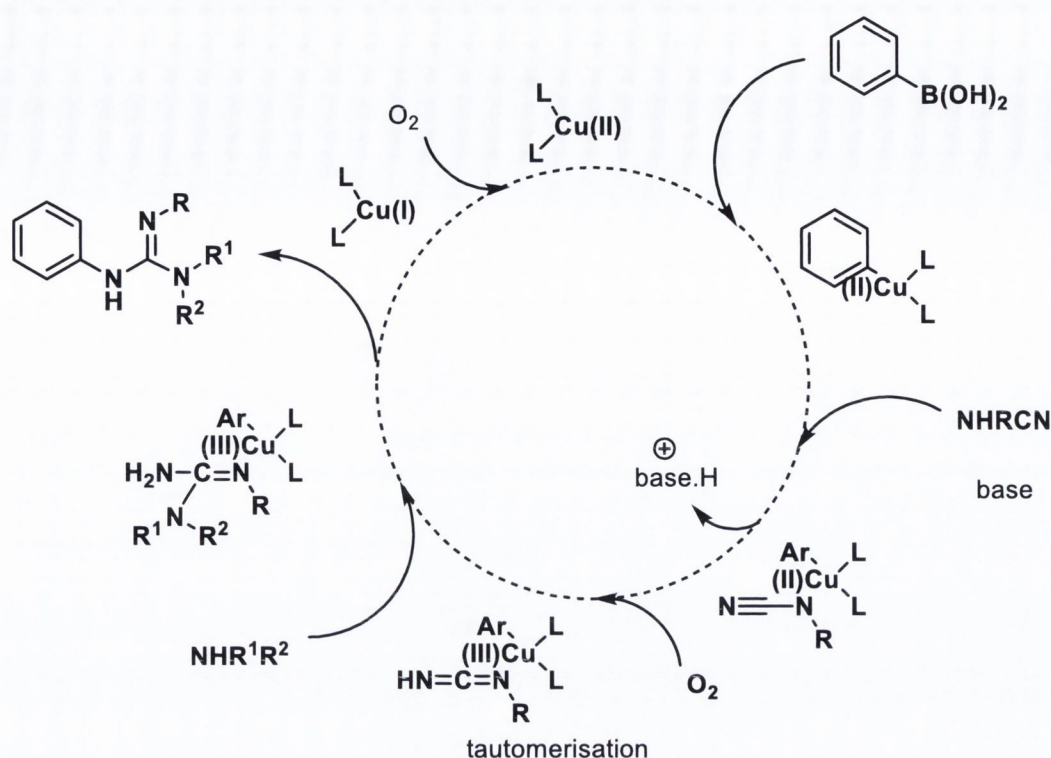
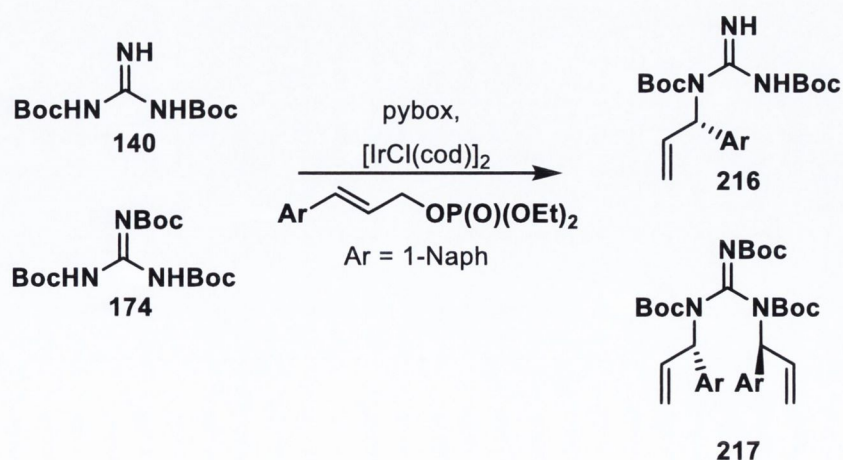


Figure 1.5.1.10.3. Proposed catalytic cycle for copper catalysed three component coupling.¹⁴³

In an effort to synthesise derivatised guanidines, transition metal catalysed allylic substitution of *N*-Boc protected guanidines was investigated (Scheme 1.5.1.10.8).¹⁴⁴ Miyabe and co-workers reported that both mono and double allylic substitution could occur. Guanidine bearing two electron withdrawing groups could act as a nucleophile in an allylation reaction to form the mono allylated product while tri-Boc-guanidine when exposed to similar conditions could afford the diallylated products.

Scheme 1.5.1.10.8.



The regiocontrol in the allylic substitution of unsymmetrical allylic substrates was investigated by using both Pd and Ir catalysis.

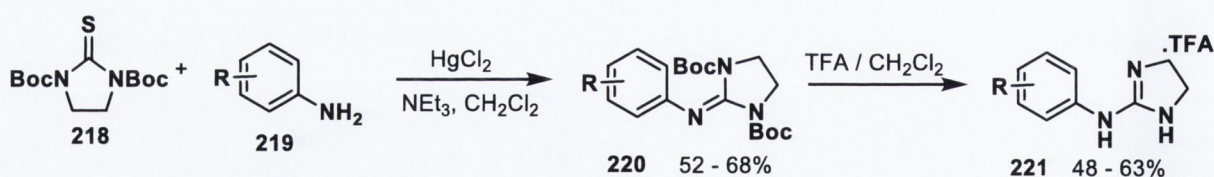
1.5.2. Synthesis of cyclic guanidines.

The ubiquitous nature of cyclic guanidine moieties throughout natural products¹² and compounds of medicinal interest¹¹ have ensured a wealth of methodologies designed for their facile synthesis. Herein we present some selected examples of literature methods for the formation of 5-, 6- and 7-membered rings incorporating the guanidine motif in their structure.

1.5.2.1. 5-Membered rings.

Among the most facile method for the synthesis of 5-membered rings containing guanidines is the use of *N,N'*-disubstituted-2-imidazolidinethione **218** as a 5-membered analogous derivative of thiourea. In this way **218** can be reacted with a variety of amines **219** in the presence of a Lewis acid promoter such as HgCl₂ (Scheme 1.5.2.1.1) to form protected guanidines **220**. Upon deprotection a wide variety of *N*-substituted-2-aminoimidazolines **221** can be generated as has been shown by Rozas and co-workers in their development of α_2 -adrenoceptor ligands.¹⁴⁵

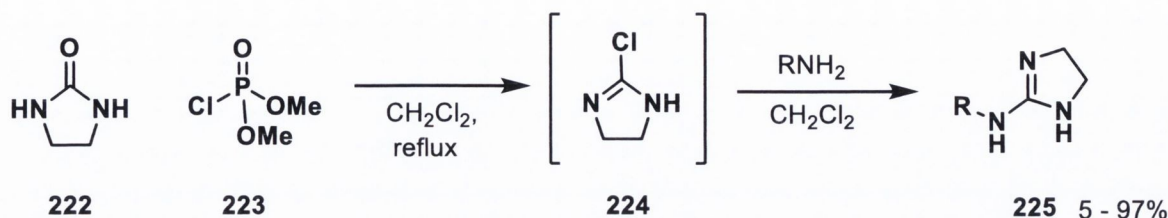
Scheme 1.5.2.1.1.



The oxygen analogue of **218** has also shown to be of some synthetic utility in this type of reactions and no intermediates are isolated in this one pot procedure.¹⁴⁶ Imidazolidin-2-one **222** is exposed to dimethyl chlorophosphate **223** forming intermediate **224** *in situ*, which in the presence of an amine will react to form the desired *N*-substituted imidazolines **225**, displacing the halide leaving group (Scheme 1.5.2.1.2). An extensive study has not been

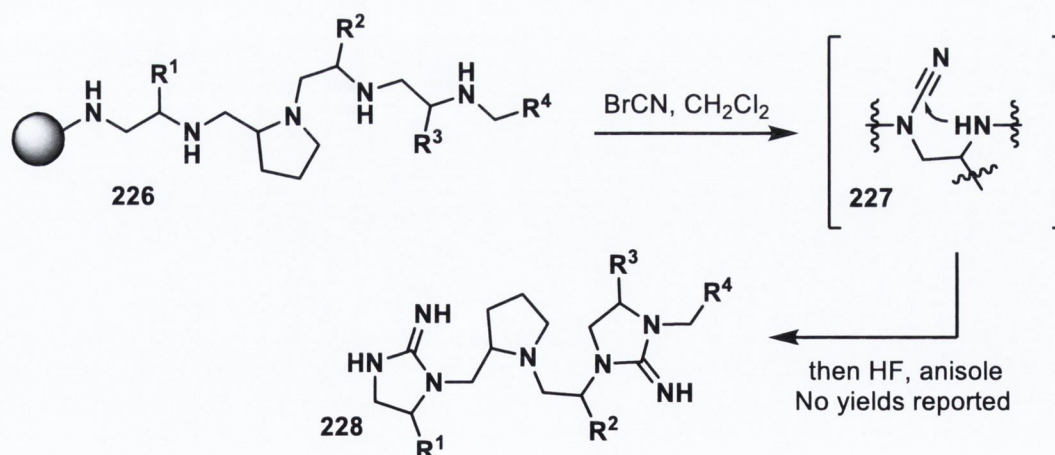
carried out on this type of reactivity with only few examples known. This methodology has also been applied to the synthesis of *N*-substituted-2-aminotetrahydropyrimidines.¹⁴⁶

Scheme 1.5.2.1.2.



Perhaps the most atom economical method for the generation of 5-membered cyclic guanidines is the exposure of 1,2-diamines to cyanogen bromide. Initial reaction of an amine such as compound **226** with cyanogen bromide will form compound **227**, in which the cyanamide functionality is now ideally located for a *5-exo-dig* cyclisation to form the desired product **228** as demonstrated in the polymer supported chemistry shown in Scheme 1.5.2.1.3. Using this very simple chemistry a vast library of compounds could be synthesised (R^1 (26) x R^2 (26) x R^3 (26) x R^4 (42) = 738,192 total number of compounds).¹⁴⁷

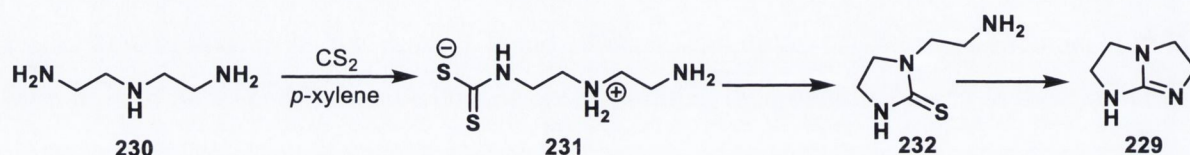
Scheme 1.5.2.1.3.



The synthesis of bicyclic guanidine containing compounds such as 2,3,5,6-tetrahydro-1*H*-imidazo[1,2-*a*]imidazole **229** has received considerable attention due to their unique

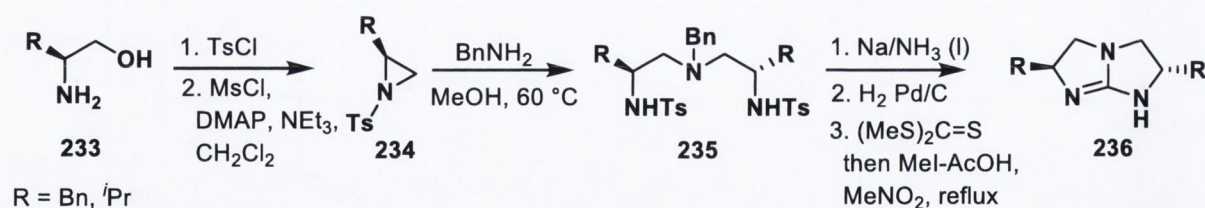
properties as superbases and application in organocatalysis as mentioned in Section 1.4.1. Initial investigations into their synthesis began with lengthy undesirable syntheses;¹⁴⁸ however, in 1990 an efficient synthesis was derived from linear tri-amines **230** being exposed to CS₂ in *p*-xylene (Scheme 1.5.2.1.4) to generate compound **231** which then cyclises to afford thiourea **232**.¹⁴⁹

Scheme 1.5.2.1.4.



A more elegant synthesis for derivatised bicyclic guanidines results in chirally substituted products.¹⁵⁰ Initial amine tosylation of a 1,2-aminoalcohol **233**, followed by mesylation of the hydroxyl group generates aziridine **234**. Exposure to benzylamine (0.5 eq.) stereospecifically opens aziridine **234** followed by opening of another equivalent of **234** to generate triamine **235**. Treatment of **235** with dimethyl trithiocarbonate, followed by methylation and heating, generates the desired bicyclic guanidines **236** in five steps (Scheme 1.5.2.1.5).

Scheme 1.5.2.1.5.

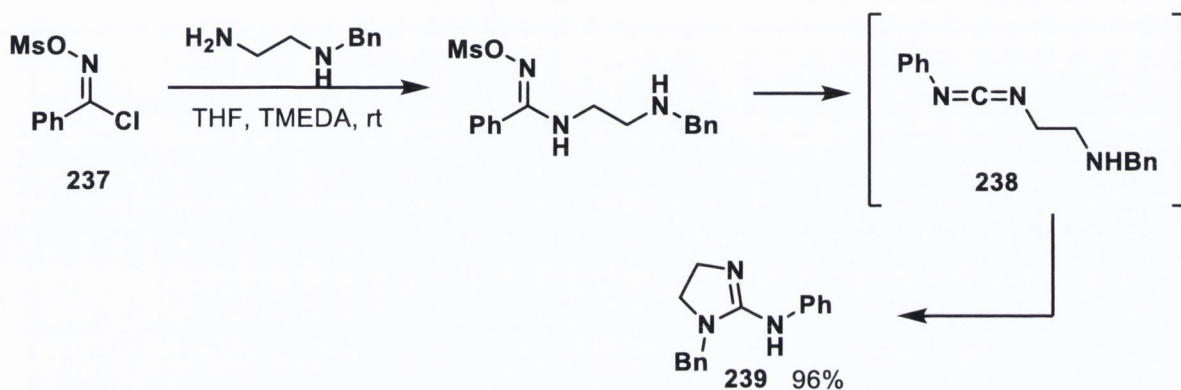


Corey initially designed a synthesis of bicyclic guanidine compounds while investigating the enantioselective Strecker reactions catalysed by chiral bicyclic guanidines (see Section 1.4.1.1); however, his synthetic route involved nine steps.⁵⁵

α -Chloroaldoxime-*O*-methanesulfonates, such as **237**, in the presence of nucleophilic amines are known to undergo Tiemann rearrangement¹⁵¹ (the aza analogue of the Lossen

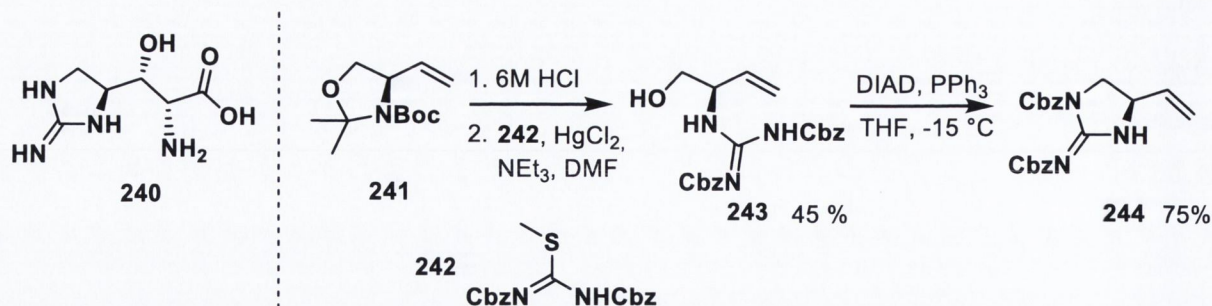
rearrangement¹⁵²). The resultant carbodiimide **238** is then available for nucleophilic attack by an external amine to generate both derivatised guanidines and imidazolines **239** (Scheme 1.5.2.1.6). This method was ingeniously used by Yamamoto *et al.* in their synthesis of a variety of guanidine containing compounds.¹⁵¹ A representative example is shown in Scheme 1.5.2.1.6.

Scheme 1.5.2.1.6.



As part of an ongoing programme into the synthesis of antibiotic mannopeptimycin β , van Nieuwenhze and co-workers applied a Mitsunobu reaction to their synthesis of cyclic guanidine intermediate **240**.¹²⁹ Synthesis began with deprotection of protected amino alcohol **241** followed by guanidylation using thiourea derivative **242** to afford compound **243**. Consequent Mitsunobu reactivity closed the 5-membered ring in good yield forming the desired cyclic guanidine **244** (Scheme 1.5.2.1.7).

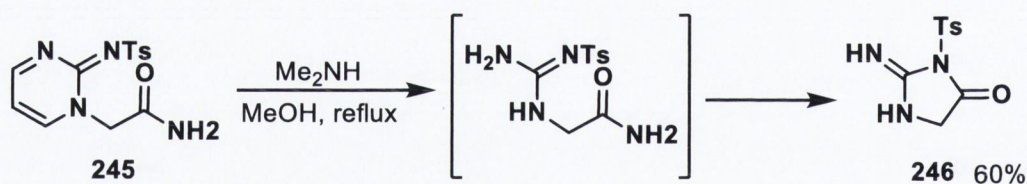
Scheme 1.5.2.1.7.



Interestingly, there was no aziridine side-product reported in the conversion of **243** into **244** even though the unprotected amine of the guanidine would presumably be more nucleophilic than the carbamate nitrogen. Presumably, the favourable formation of a 5-membered ring dominates the reactivity of this species.

In an interesting example of ring opening-ring closing reactions, a report in 2007 described the conversion of 2-aminopyrimidine derivatives **245** into cyclic guanidine moieties **246** as shown in Scheme 1.5.2.1.8.¹⁵²

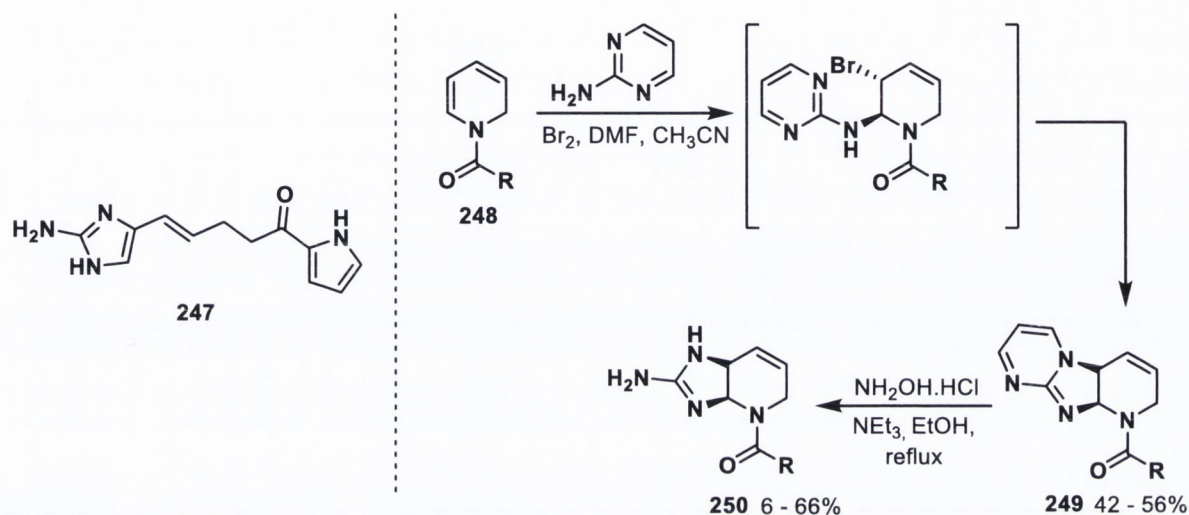
Scheme 1.5.2.1.8.



Ensuring tosyl protection of the exocyclic amine of 2-aminopyrimidine facilitates alkylation of a ring nitrogen of the pyrimidine affording **245**. Compounds of this sort are known to undergo ring opening and cleavage of the carbon framework connecting the two nitrogens of the pyrimidine.^{152,153} Exposure of **245** to MeNH₂ and heating results in ring cleavage and then condensation of the guanidine functionality onto the amide resulting in an unusual route to cyclic guanidines **246**.

Similar reactivity has been used effectively in Al-Mourabits synthesis of clathrodine **247** (Scheme 1.5.2.1.9).¹⁵³ Initial investigations into the addition of a protected guanidine to an alkene **248** exposed to bromine did not result in guanidine addition to the olefin.

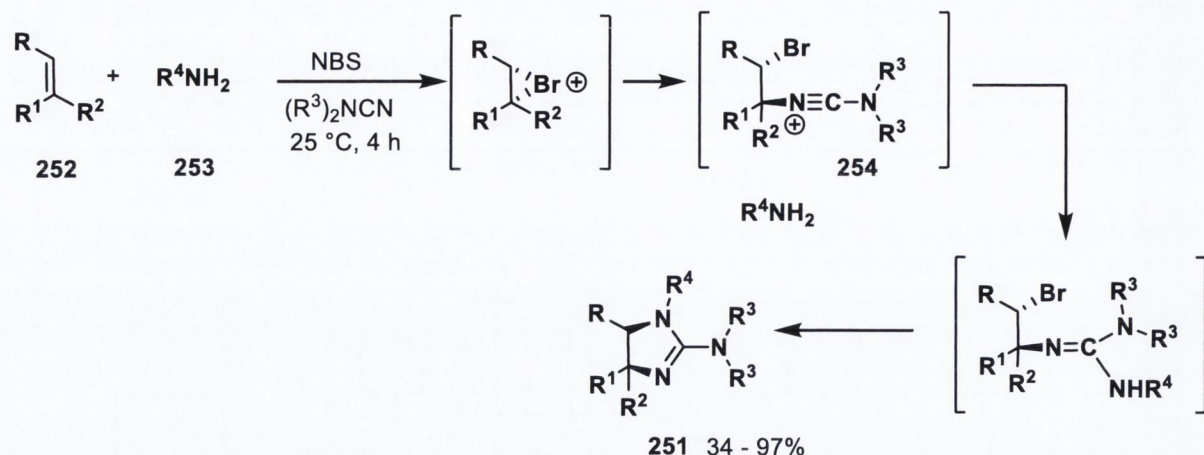
Scheme 1.5.2.1.9.



However, when the protected guanidine was replaced with 2-aminopyrimidine, initial displacement of a bromine atom and resulting ring closure to form **249** occurred. Treatment of **249** with $\text{NH}_2\text{OH} \cdot \text{HCl}$ in refluxing EtOH resulted in ring cleavage and cyclic guanidine **250** formation in good yield (Scheme 1.5.2.1.9).

In 2011 a novel one pot synthesis of cyclic guanidines was devised allowing for the formation of a diverse array of guanidine products **251**.¹⁵⁴ A variety of alkenes **252** were exposed to NBS, amines **253** and cyanamides resulting in the desired cyclic compounds (Scheme 1.5.2.1.10).

Scheme 1.5.2.1.10.



Initial activation of the olefin, followed by nucleophilic attack by the cyanamide would generate a highly electrophilic species **254**. This in turn could undergo attack from the amine present followed by ring closure and expulsion of bromine generating the desired 5-membered ring **251**.

One of the simplest approaches to the preparation of 5-membered guanidine containing molecules is a reaction pathway prevalent throughout nature, the biosynthesis of creatinine **255** (Figure 1.5.2.1.1).

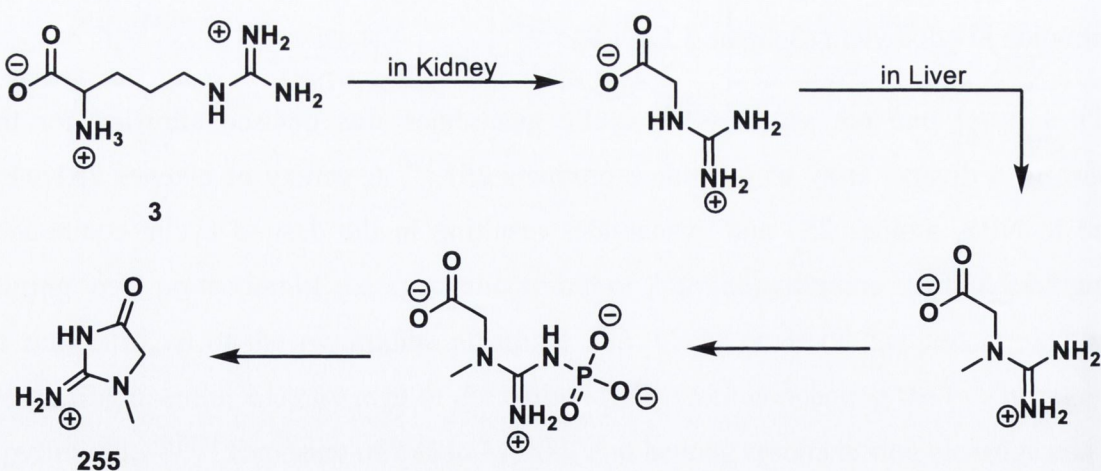
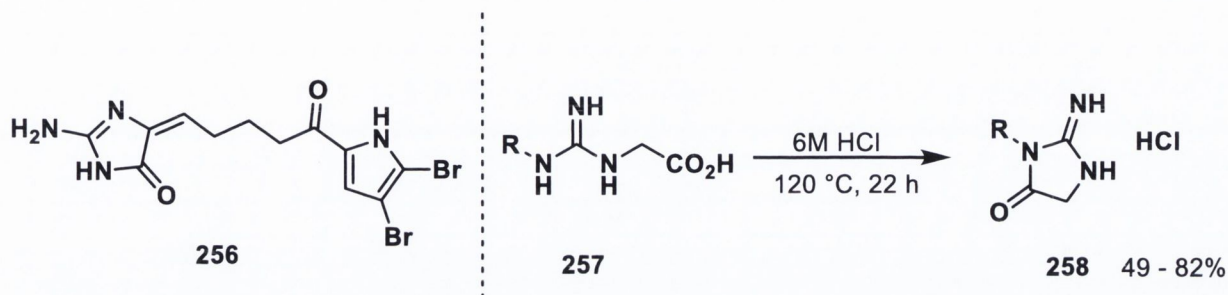


Figure 1.5.2.1.1. Biosynthesis of creatinine

This biosynthesis process involves the condensation of the nucleophilic guanidine functionality of arginine **3** onto a carboxylate to form a five membered ring as is present in

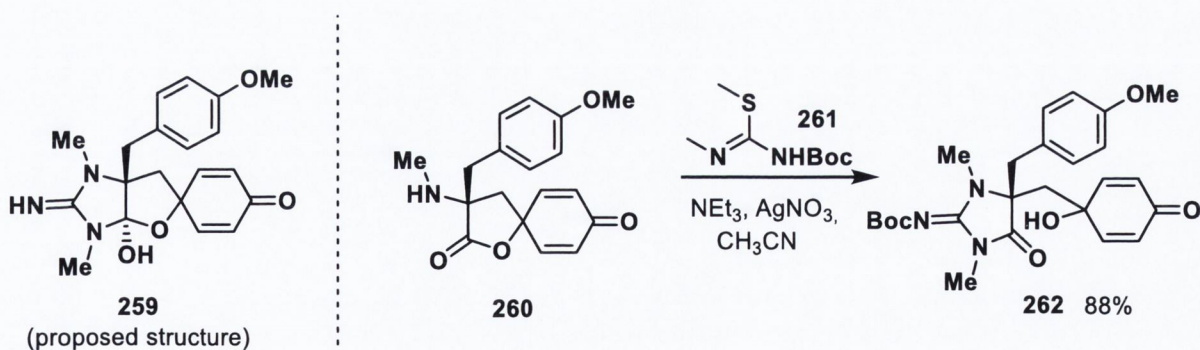
creatinine,¹⁵⁵ and this pathway can be easily replicated in the laboratory as displayed in Bazureau's dispacamide A **256** synthesis (Scheme 1.5.2.1.11).¹⁵⁶ Exposure of guanidine **257** to acidic conditions invoked ring closure to generate cyclic guanidine **258**.

Scheme 1.5.2.1.11.



In Danishefsky's efforts towards the total synthesis of spiroleucettadine **259** a similar type of reactivity was employed.¹⁵⁷ Initial guanidylation of **260** utilising compound **261** as a guanidylating agent, followed by ring opening of the lactone and then ring closing of the guanidine functionality resulted in a ring opened isomeric form **262** of the reported structure of **259** (Scheme 1.5.2.1.12).

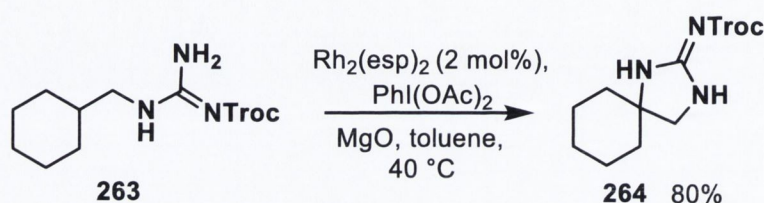
Scheme 1.5.2.1.12.



1.5.2.2. Metal-catalysed ring closure.

In Du Bois' seminal work in stereospecific C-H insertion chemistry, a novel route for the synthesis of cyclic guanidines was designed.¹¹¹ Oxidative C-H amination of *N*-Troc (Troc = 2,2,2-trichloroethoxycarbonyl) protected guanidines **263** to generate specifically 5-membered ring derivatives **264** over 6-membered rings was demonstrated (Scheme 1.5.2.2.1).¹⁵⁸

Scheme 1.5.2.2.1.

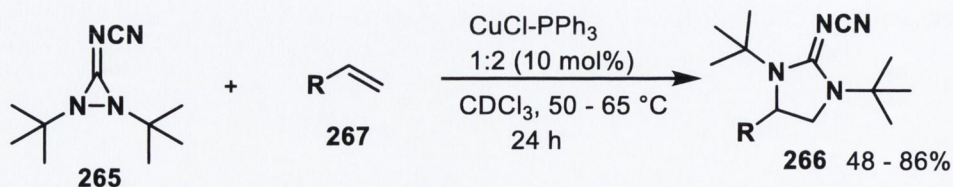


Troc = 2,2,2-trichloroethoxycarbonyl.

This chemistry has a wide range of applications and has found use in both natural product synthesis¹⁵⁹ and medicinal chemistry.⁴⁴ The use of Tces as a protecting group along with $\text{Rh}_2(\text{esp})_2$ in catalytic quantities proved essential for reactivity. This strategy was effectively employed in the synthesis of the guanidine natural product gonyautoxin.¹⁶⁰

The use of diaziridinimines **265** as precursors for guanidines is a facile and atom economical route towards 5-membered cyclic guanidines **266** (Scheme 1.5.2.2.2).¹⁶¹ Reacting **265** with a variety of olefins **267** in the presence of CuCl in catalytic quantities can afford the desired guanidine products as described by Shi *et al.* Reactivity was shown to proceed regioselectively at terminal alkenes preferentially in the case of either dienes or trienes.

Scheme 1.5.2.2.2.



The reaction mechanism although still unknown is thought to proceed *via* homolytic cleavage of the N–N bond of **265** by CuCl, followed by addition of the nitrogen centred radical **268** to olefin **267** and subsequent C–N bond formation (**269**) and regeneration of catalyst CuCl (Figure 1.5.2.2.1).

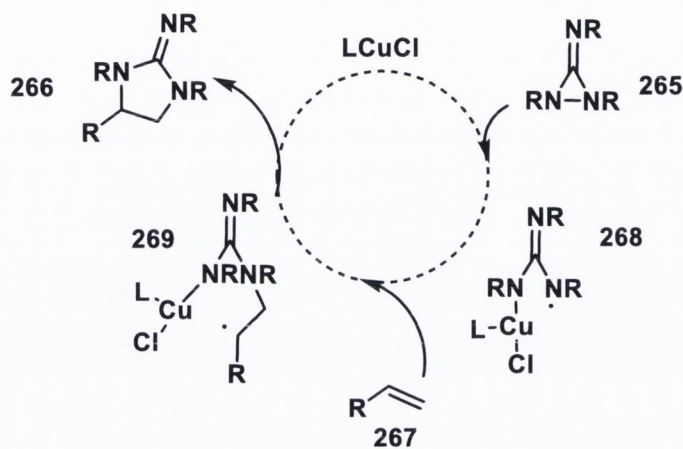
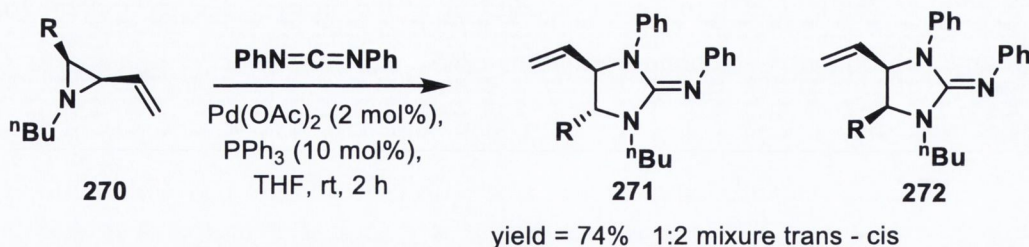


Figure 1.5.2.2.1. Proposed catalytic cycle of guanidylation.¹⁶¹

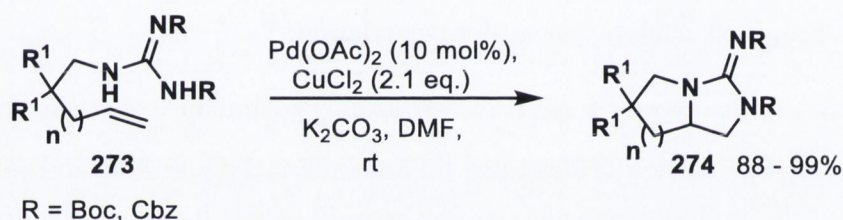
The exposure of vinyl aziridines **270** to catalytic amounts of Pd and PPh₃ in the presence of carbodiimides led to the generation of cycloaddition products **271** and **272** (Scheme 1.5.2.2.3).¹⁶² Initial Pd catalysed aziridine ring opening and subsequent π -allyl complex formation is presumably followed by guanidine formation and subsequent ring closure to yield the desired 5-membered rings. The mixture of stereoisomers obtained suggests that there is a η^3 - η^1 - η^3 interconversion of a π -allyl Pd complex.¹⁶³ A recent report from the Stoltz laboratory presented a Lewis acid mediated variation of this reaction in which aziridines, with no vinyl appendages, are exposed to a variety of carbodiimides to produce iminoimidazolidines.¹⁶⁴

Scheme 1.5.2.2.3.



In 2008, Muniz *et al.* described the direct synthesis of bicyclic guanidines through unprecedented palladium(II) catalysed diamination with copper chloride as an oxidant.¹⁶⁵ The synthesis of these bicycles occurs by means of a Pd catalysed intramolecular guanidine transfer to alkenes **273** affording product **274** (Scheme 1.5.2.2.4).

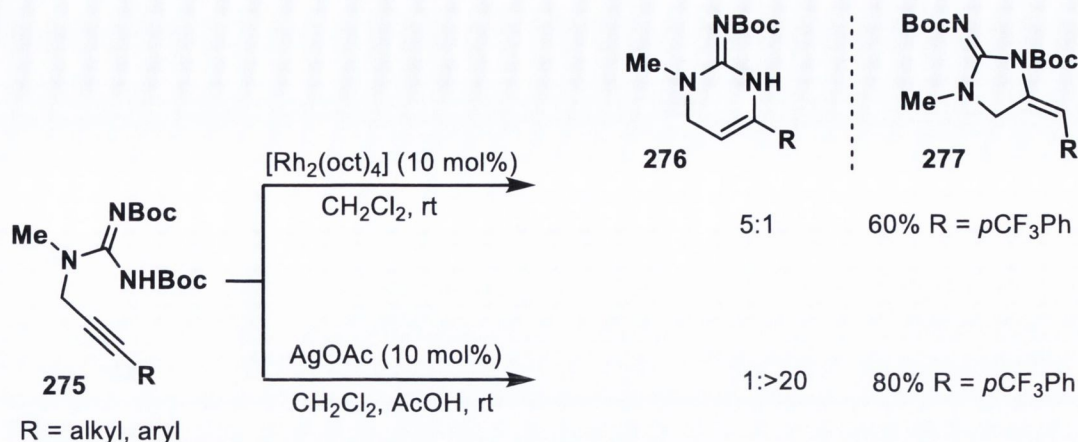
Scheme 1.5.2.2.4.



This method proves particularly effective in the formation of 5,5- and 5,6-bicyclic guanidines when guanidine is either Boc or Cbz protected.

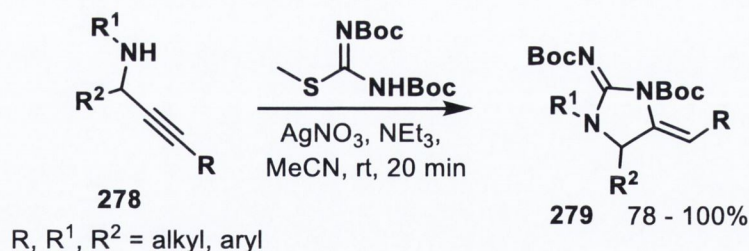
In 2011, a report by Looper and co-workers exploited the reactivity of propargylguanidines **275** in hydroamination reactions (Scheme 1.5.2.2.5).¹⁶⁶ Two possible cyclisation pathways of propargylguanidine **275** can be promoted leading to both 5- and 6-membered cyclic guanidines (**276** and **277**, respectively). The reactivity of these starting materials can be adapted into either product by choice of catalyst.

Scheme 1.5.2.2.5.



Metal catalysed cyclisations on alkynes typically favour 5-*exo*-dig pathways¹⁶⁷ and therefore the ability to also form 6-*endo*-dig products is of particular interest. Looper *et al.* have made use of this methodology in their synthesis of saxitoxin **22**.¹⁶⁸ During the preparation of the corresponding manuscript by Looper and co-workers, a similar type of reactivity was discovered by van der Eycken in an interesting set of reaction conditions to form cyclic guanidines.¹⁶⁹ In this approach, propargylamines **278** were exposed to guanidylating conditions using AgNO_3 as the promoting agent (Scheme 1.5.2.2.6).

Scheme 1.5.2.2.6.



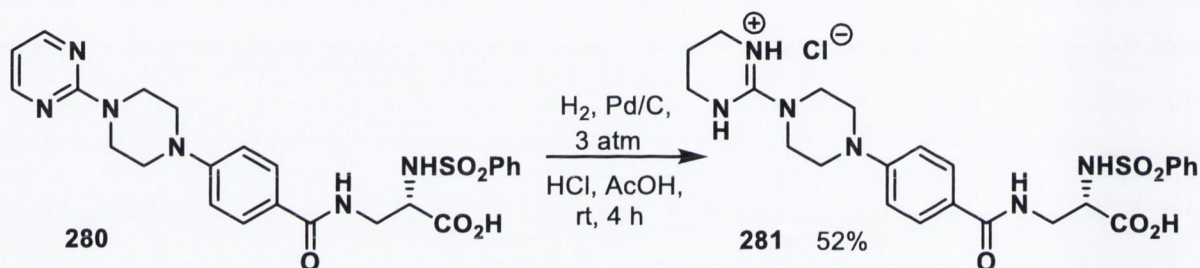
In the presence of silver (I) salts a 5-*exo*-dig was facilitated and, in one pot, the transformation of propargylamines **278** into cyclic guanidines **279** was effected. Sterically hindered propargylamines as well as *N*-aryl propargylamines were also interestingly able to undergo this cyclisation pathway.

1.5.2.3. 6-Membered cyclic guanidines.

Although not as widely researched as the formation of 5-membered guanidine containing cyclic structures, the formation of 6-membered rings has received attention in the synthesis of numerous natural products and biologically active compounds.

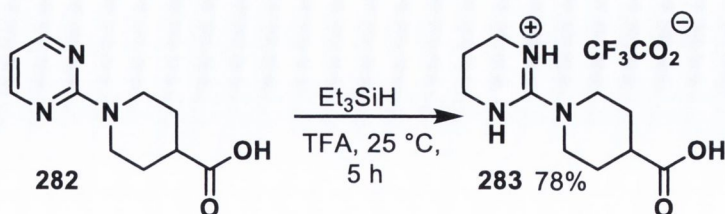
The synthesis of *N*-substituted-2-amino-1,4,5,6-tetrahydropyrimidines (6-membered cyclic guanidines) has been reported by means of hydrogenation of the 2-aminopyrimidine precursor **280**. In the search for integrin $\alpha_v\beta_3$ antagonists Ajito *et al.* employed hydrogenation in acidic conditions catalysed by Pd/C generating cyclic guanidine **281** in an acceptable yield (Scheme 1.5.2.3.1).¹⁷⁰

Scheme 1.5.2.3.1.



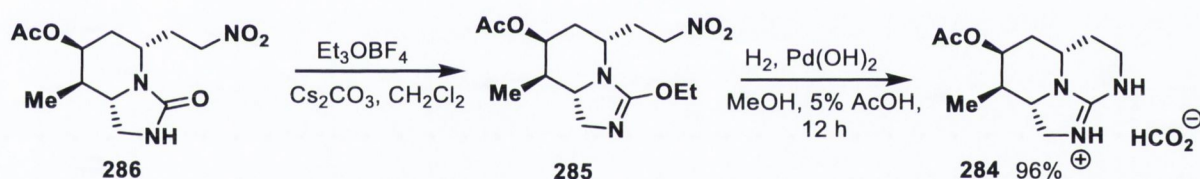
Another similar reductive method for the synthesis of *N*-substituted-2-amino-1,4,5,6-tetrahydropyrimidines from 2-aminopyrimidines is utilised by Shen and co-workers in their use of triethylsilane and TFA.¹⁷¹ Initial discoveries gave both dihydro- and tetrahydropyrimidine products; however, upon optimisation, tetrahydropyrimidines were generated in poor to excellent yields (25 – 90% yield). A representative example is shown in scheme 1.5.2.3.2. converting amino pyrimidine **282** into guanidine **283**.

Scheme 1.5.2.3.2.



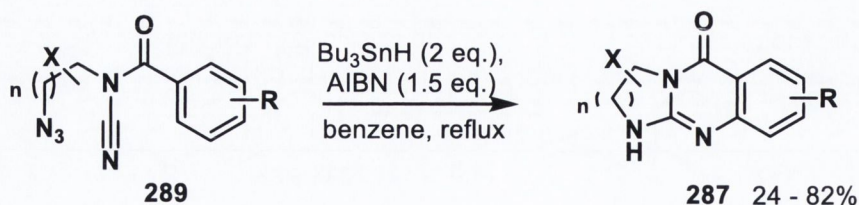
In an effort to synthesise tricyclic guanidine **284** a reductive guanidylation method was formulated by Williams and co-workers.¹⁷² Initial guanidine precursor **285** was synthesised from urea **286** using Meerwein's salt (triethyloxonium tetrafluoroborate). The alkyl nitro functionality was then reduced using palladium catalysed hydrogenation to form the prerequisite primary amine which is now ideally located to displace ethoxide in an addition-elimination reaction (Scheme 1.5.2.3.3).

Scheme 1.5.2.3.3.



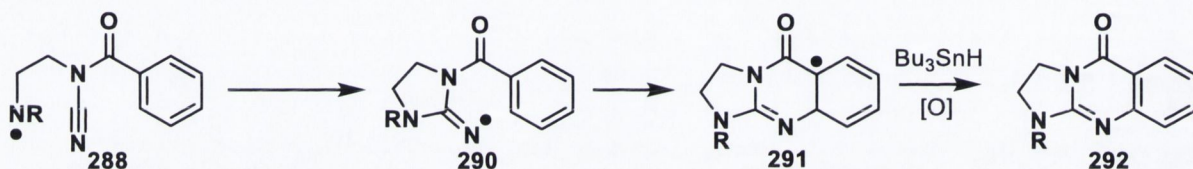
The facile synthesis of *N*-acyl cyanamides lends itself to an appealing method for the formation of tricyclic guanidines **287** by means of radical domino cycloaddition (Scheme 1.5.2.3.4).¹⁷³ This method by Lacôte and co-workers is a sole literature example of the utilisation of radical chemistry to form cyclic guanidines.

Scheme 1.5.2.3.4.



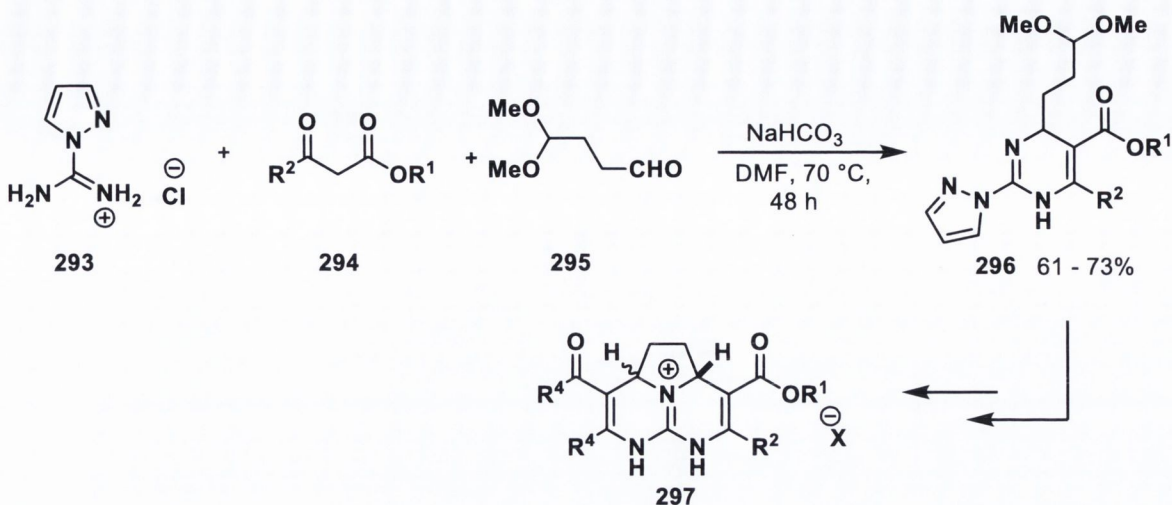
Initial formation of a nitrogen centred radical **288** from the prerequisite azide **289** may react with the adjacent cyanamide forming a guanidine type radical **290** (Scheme 1.5.2.3.5). Subsequent interaction with the π -system forms the final six membered ring **291**, while the presence of Bu_3SnH allows the re-aromatisation of the ring generating **292**.

Scheme 1.5.2.3.5.



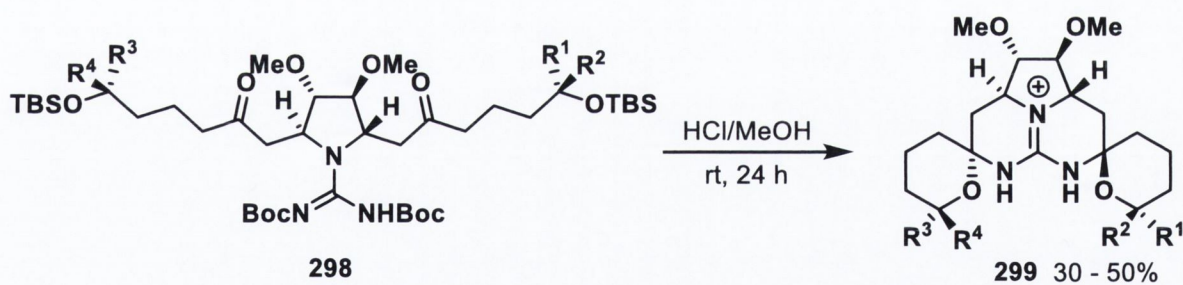
Overman and co-workers have effectively utilised the three component Biginelli reaction in their research towards the synthesis of 6-membered cyclic guanidines.¹⁷⁴ Utilising pyrazole guanidine **293**, β -keto-ester **294** and derivatised aldehyde **295**, in a three component Biginelli reaction, the desired cyclic guanidines **296** were formed in good yield (Scheme 1.5.2.3.6). These products, after further functionalisation, were converted into tricycle **297**, the precursor for numerous guanidine natural products.

Scheme 1.5.2.3.6.



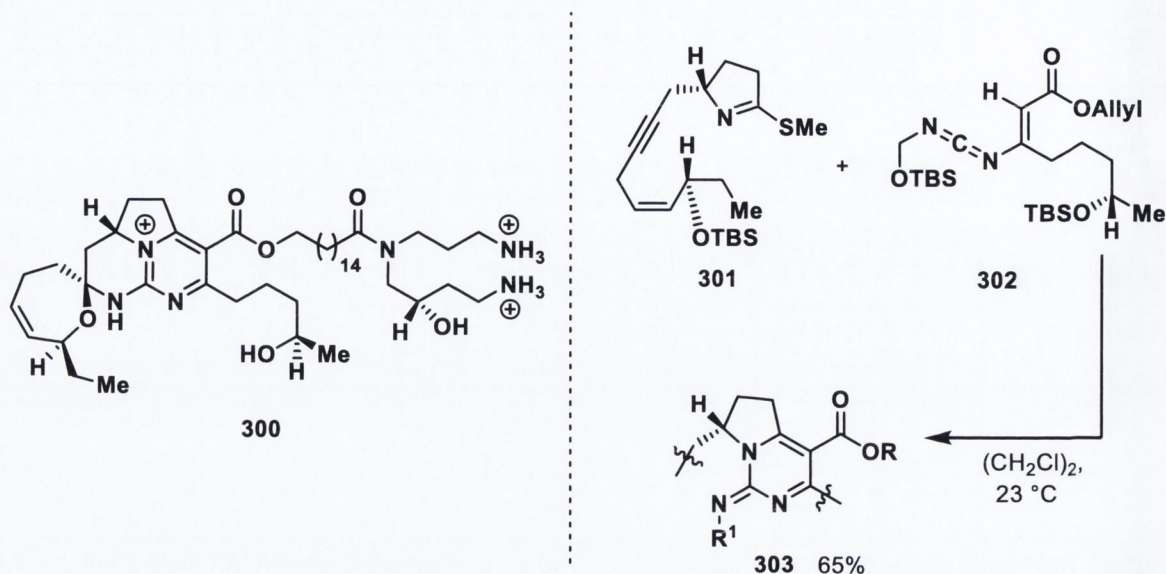
In an effort to synthesise similar tricyclic guanidine containing compounds, Nagasawa *et al.* designed a guanidine condensation type reaction leading to the generation of five rings in a single step.¹⁷⁵ This impressive reaction was facilitated by an acid mediated deprotection of **298** and concomitant condensation of the guanidine and hydroxy functionalities onto the available ketone moieties (Scheme 1.5.2.3.7) to afford compound **299**.

Scheme 1.5.2.3.7.



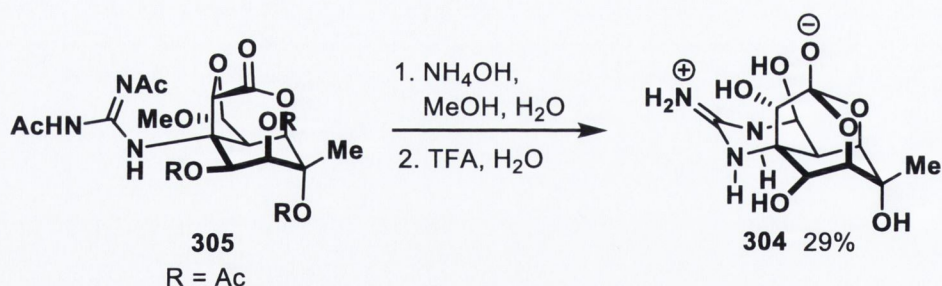
In Gin's exquisite synthesis of crambidine (**300**),¹⁷⁶ the construction of the central cyclic guanidine was achieved by means of a [4+2] annulation between thioimide **301** and vinyl carbodiimide **302** (Scheme 1.5.2.3.8). This route rapidly generated the core compound **303** which upon further functionalisation resulted in the completion of **300**. Another key step was the hydroamination of an alkyne moiety (present in substrate **301**) with derivatised 2-aminopyrimidine (present in substrate **303**) as the nucleophile.

Scheme 1.5.2.3.8.



In 2002, Isobe *et al.* described their synthesis of 11-deoxytetrodotoxin **304** incorporating an interesting method of cyclic guanidine formation (Scheme 1.5.2.3.9).¹⁷⁷ The acetate protected guanidine functionality present in precursor **305** had been installed using traditional methods.

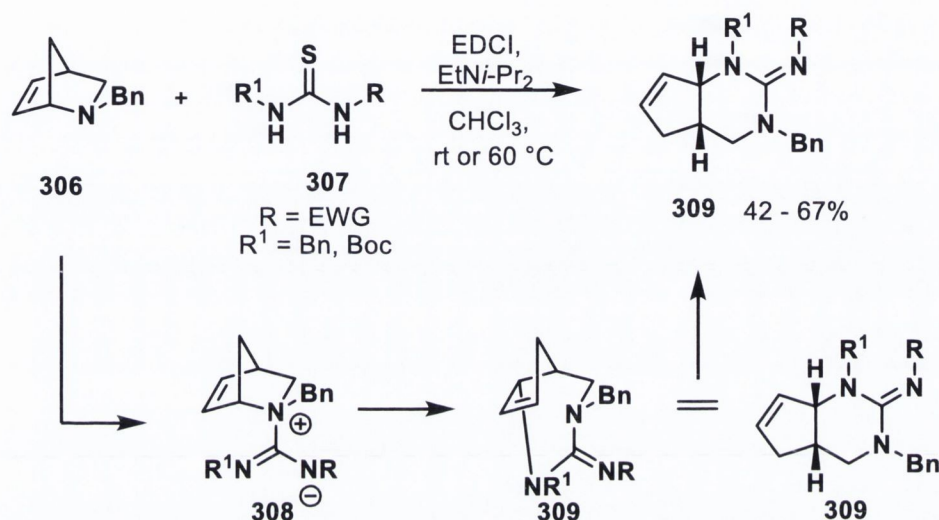
Scheme 1.5.2.3.9.



Deprotection of the acetate groups (NH_4OH , MeOH, H_2O) followed by exposure to acidic conditions (TFA, H_2O) resulted in orthoester formation and guanidine cyclisation, displacing a methoxy group and forming a hemi-aminal. This is an impressive transformation due to the molecular complexity of both starting material and product.

It has been shown that bridged bicyclic allylic tertiary amines such as aza-norbornene **306** can add to an *in situ* generated carbodiimide (formed from thiourea derivative **307**) to form a zwitterionic intermediate **308** (Scheme 1.5.2.3.10).¹⁷⁸

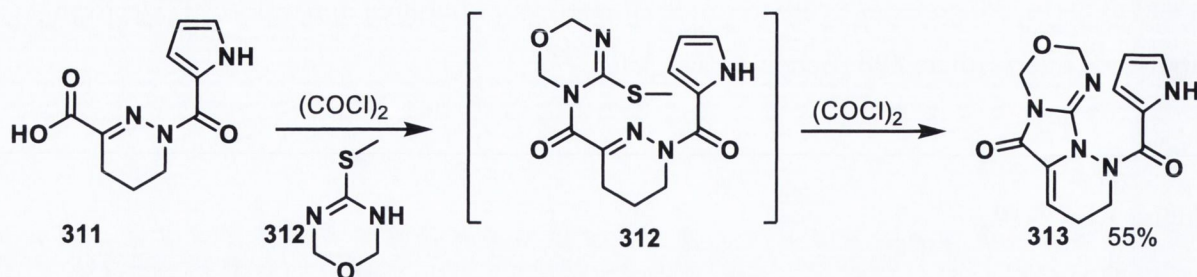
Scheme 1.5.2.3.10.



These strained systems are then ideally suited to undergo 1,3-diaza-Claisen rearrangement forming compound **309**. The presence of an electron withdrawing substituent on the intermediate carbodiimide not only make the species more reactive to nucleophilic attack, but also stabilise the developing negative charge present in the zwitterionic species **308** (Scheme 1.5.2.3.10). A number of varying thioureas **307** were shown to be reactive towards carbodiimide formation when EDCI was used as a promoting agent.

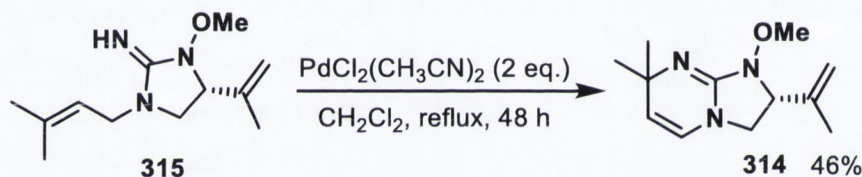
In Harran's study of the axinellamine natural products¹⁷⁹ a 6-membered thiourea analogue was used to introduce the guanidine functionality. Initially, compound **310** was reacted with carboxylic acid **311** to form intermediate **312** and, then, in the presence of oxalyl chloride cyclisation occurs to afford tricyclic compound **313** (Scheme 1.5.2.3.11). This presents an operationally simple and effective method for guanidine installation.

Scheme 1.5.2.3.11.



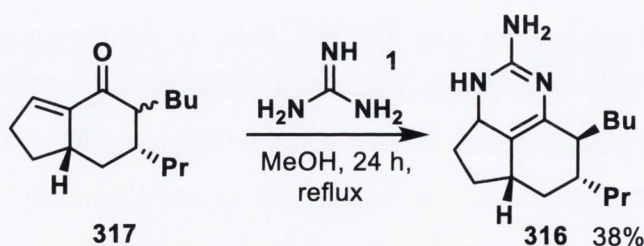
In the synthesis of the alkaloid alchorneine **314** a palladium mediated cyclisation of a prenyl functional group with cyclic guanidine **315** was developed (Scheme 1.5.2.3.12).¹⁸⁰ Although two equivalents of palladium were required for the cyclisation to occur this represents an interesting method for the formation of functionalised pyrimidines.

Scheme 1.5.2.3.12.



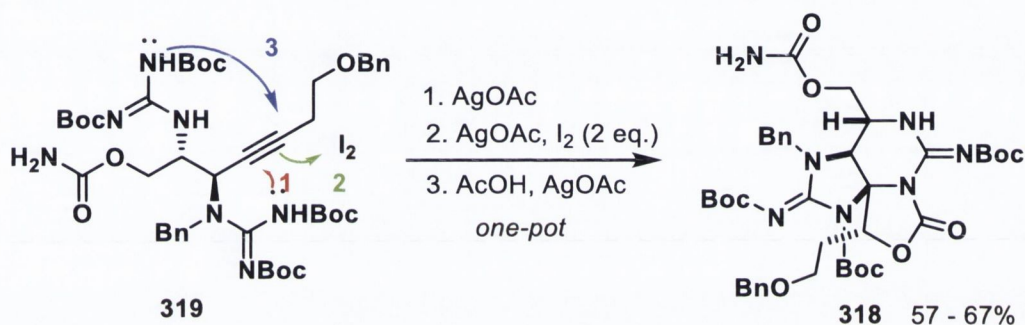
Snider and co-workers incorporated a Michael addition followed by a condensation reaction to form the tricyclic natural product netamine E **316**.¹⁸¹ This direct approach facilitated the synthesis of a number of natural products containing the same core. When Michael acceptor **317** in methanol under reflux was combined with guanidine, compound **316** was produced in 38% yield (Scheme 1.5.2.3.13).

Scheme 1.5.2.3.13.



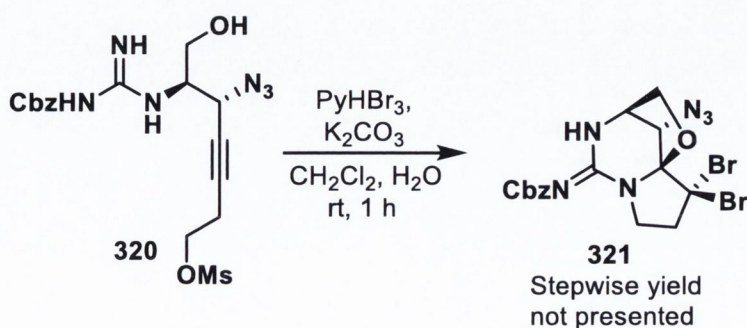
In an exceptionally elegant synthesis of saxitoxin **22** Looper *et al.* designed a highly elaborate cascade reaction to generate the key intermediate **318** starting from acyclic guanidine **319** (Scheme 1.5.2.3.14).¹⁶⁸ The cascade begins with Ag(I) promoted ring closure of the benzyl protected guanidine onto the alkyne generating a 5-membered ring with an exocyclic olefin (Scheme 1.5.2.3.14., **step 1**). This olefin, under iodine activation (**step 2**), is then prone to nucleophilic attack by the acyclic guanidine functionality forming the 6-membered ring (**step 3**). Ensuing expulsion of the resulting secondary alkyl iodide, facilitated by the use of Ag(I) and acetic acid, would then generate highly functionalised interemediate **318**.

Scheme 1.5.2.3.14.



In another approach towards saxitoxin **22** Nishikawa and co-workers have incorporated an ingenious cascade reaction in their synthetic route.¹⁸² This allows the rapid generation of complexity in their system. Exposure of alkyne **320** to pyridinium tribromide (PyHBr₃) facilitates a bromocyclisation reaction which allows *N*-alkylation of the guanidine to occur (Scheme 1.5.2.3.15). This remarkable reaction generated a tricyclic core **321** in a highly stereospecific manner.

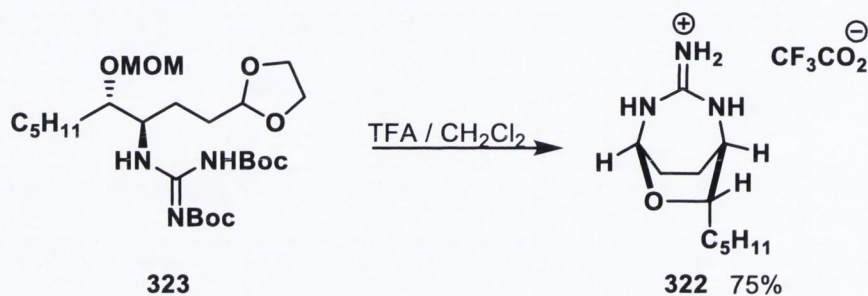
Scheme 1.5.2.3.15.



1.5.2.4. 7-membered rings.

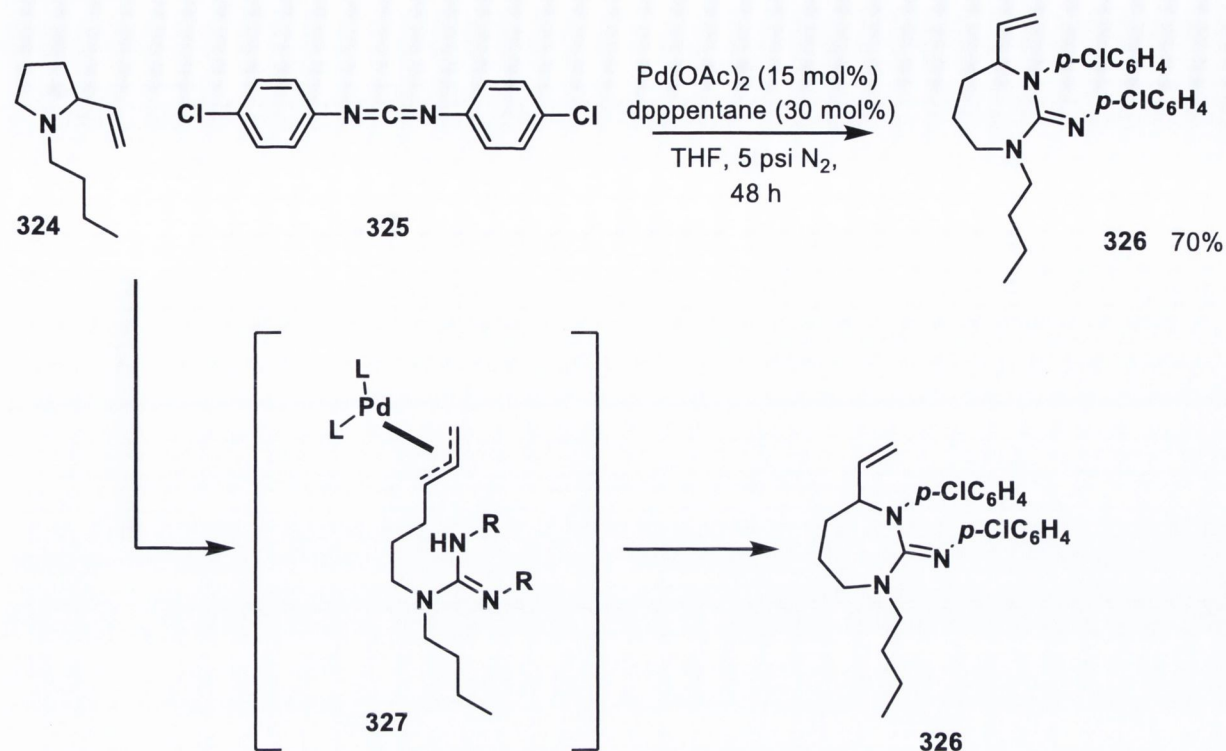
In their synthesis of bicyclic guanidine alkaloid (+)-monanchorin **322** Sutherland *et al.* reported a late stage deprotection-cyclisation cascade to form the desired guanidine hemiaminal product **322**.¹⁸³ Acid mediated deprotection of the aldehyde, hydroxy and guanidine functionalities of **323** in one pot allowed for an efficient cyclisation reaction pathway, forming an unusual 7-membered guanidine containing ring (Scheme 1.5.2.4.1).

Scheme 1.5.2.4.1



In an analogous reaction to the ring opening–ring closing reaction of aziridines with carbodiimides to form five membered cyclic guanidines (see Section 1.5.2.2), 2-vinylpyrrolidines **324** can react with carbodiimides **325** to form 7-membered cyclic guanidines **326** (Scheme 1.5.2.4.2).¹⁸⁴

Scheme 1.5.2.4.2.



The reaction was shown to be optimal under slightly longer and harsher conditions (48 h, 5 psi N_2) than those required for the aziridine ring opening presumably due to the inherent relief of ring strain associated with aziridine ring opening. Formation of the π -allyl Pd complex **327** followed by guanidine induced ring closure and β -hydride elimination generate the desired vinyl guanidines **326**.

2. Objectives

Rozas' laboratory has been interested in the synthesis and biological evaluation of guanidine containing molecules for the past ten years. The application of guanidines as both minor groove binders (MGB) and α_2 -adrenoceptor (α_2 -AR) antagonists has been the focus of much of the research conducted. A number of promising results have been discovered in targeting the α_2 -AR, with a number of effective agonists and antagonists having been synthesised. α_2 -AR antagonists have proven to be a valid target for the alleviation of symptoms of Major Depressive Disorder (MDD, Section 3.1.2). For many years, these guanidines have been prepared by reacting the required anilines with *N,N*-bis-*tert*-butoxycarbonylthiourea in the presence of HgCl_2 to form the protected arylguanidines (Section 1.5.1.1.).⁹¹ The use of mercury in such reactions is an obvious drawback and it was decided that its use should be eliminated from the synthesis of biologically active guanidines in Rozas' group.

2.1. Synthetic Chemistry.

i) An aim of this project is therefore to design and implement the synthesis of aryl guanidines without the use of HgCl_2 . As described in the Introduction section there are a myriad of synthetic procedures available for such a synthetic endeavour. However, many of these procedures involve the use of toxic reagents, economically expensive precursors, require nucleophilic amines or have lengthy procedures.⁸⁷ An aim of this project is therefore to design a synthesis for guanidine containing compounds that is:

1. Environmentally friendly.
2. Atom economical.
3. Cost Effective.
4. Scalable.
5. Simple to purify.

Once a suitable means of guanidylation is devised then it will be applied to the synthesis of biologically active guanidines such as α_2 -AR antagonists and MGBs. The synthesis of compounds which would be difficult to synthesise by mercury promoted guanidylation is also desirable. An ideal methodology is represented in Figure 2.1.1. An aryl halide **328** would be

reacted with a guanidine surrogate to form **329** which could easily then be transformed into the desired guanidine containing moiety **330**.

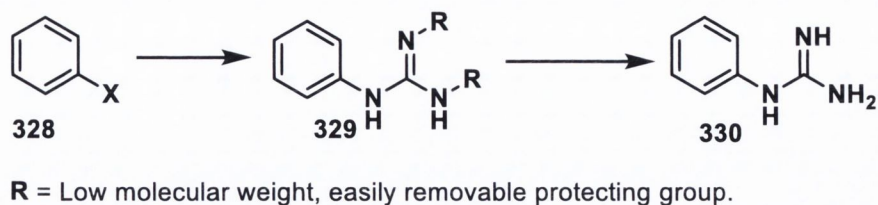


Figure 2.1.1. Desired guanidylation route.

It has been postulated in Rozas' group that 2-aminopyrimidine derivatives **331** may be suitable precursors for guanidine containing compounds **332** and it is hoped to discover a methodology which would enable this conversion (Figure 2.1.2.). Therefore, it is intended that 2-aminopyrimidine should be coupled with aryl halides and then a ring cleavage reaction is to be invented to afford the desired guanidine containing compounds **X**.

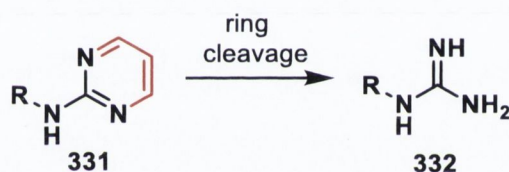


Figure 2.1.2. 2-Aminopyrimidine derivatives as guanidine precursor.

ii) Previously, the synthesis of 2-aminoimidazoline derivatives **333** has been investigated as cyclic guanidine derivatives by Rozas and co-workers with significant success.¹⁴⁵ The ethylene linker between the two guanidine nitrogen atoms adds a hydrophobic element to the guanidine functionality and also disrupts the typical hydrogen bonding interactions associated with guanidines. With our plans to investigate the cleavage of the 2-aminopyrimidine ring system **331** to yield guanidine a subsequent aim of this project is to investigate the synthesis of 2-aminotetrahydro-1,4,5,6-pyrimidines **334**. This would increase the hydrophobic interaction by increasing the size of the alkyl linker bridging the two nitrogen atoms (Figure 2.1.3.).

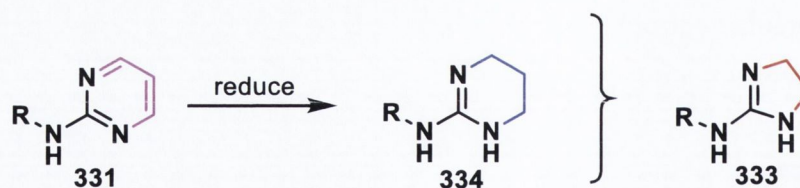


Figure 2.1.3. Increasing hydrophobic interactions by accessing 2-aminotetrahydro-1,4,5,6-pyrimidine derivatives **334**.

Importantly, the synthesis of 2-aminotetrahydro-1,4,5,6-pyrimidines **334** is to follow the same criteria as outlined for an ideal guanidine synthesis.

2.2. Guanidine Natural Product derivatives as biological targets.

A wide variety of guanidine natural products such as palau'amine **21**, saxitoxin **22** and dibromophakellin **23** contain the spirocyclic guanidine aminor backbone **19** (Figure 2.2.1). Another aim of this project is to design and implement a scalable, efficient and easily functionalised route to this core, centred on a cascade reaction designed in Rozas' group. In particular, dibromophakellin **23** is known to be an α_2 -AR agonist and it would be of considerable interest to design a synthesis of aminor **19** which could be easily derivatised to enable analogues of **23** to be synthesised.

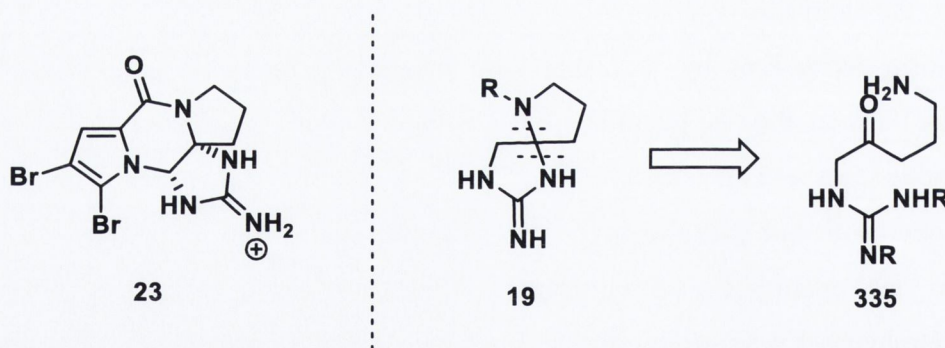


Figure 2.2.1. Cascade reaction to access spirocyclic guanidine aminor moiety

2.3. Pharmacology.

Novel guanidine containing compounds designed by new methodologies are then to be tested for biological activity as α_2 -AR antagonists. The α_2 -AR binding affinity (expressed as pK_i) for the synthesised compounds is to be determined firstly in human brain tissue. Next, those compounds with strong enough binding to the receptor ($pK_i > 6$).will undergo [^{35}S]GTP γ S assays (as discussed in Section 4.9), also in human brain tissue, to investigate the activity of the compounds as agonists, antagonists or inverse agonists. This work is to be conducted in collaboration with Dr. Luis F. Callado at the Department of Pharmacology of the School of Medicine of the Basque Country University (EHT, Leioa, Spain).

2.4. Araiosamine Natural Products.

As part of a Fulbright scholarship obtained, research into the synthesis of the araiosamine¹⁸⁵ family of guanidine – indole natural products will be conducted in the Baran laboratories at The Scripps Research Institute, USA.

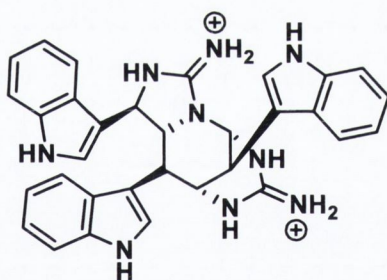


Figure 2.4.1. Araiosamine C

3. 2-(Arylamino)-tetrahydro-1,4,5,6-pyrimidines.

3.1. Introduction.

The search for biologically active guanidine containing molecules has been the foundation of research in Rozas' group for the past ten years. The vast possible interactions of guanidine in the mammalian body make it an exciting functional group to utilise. Two research areas in particular where promising results have been made are the utilisation of guanidine containing molecules as DNA minor groove binders and α_2 -adrenoceptor ligands. In the following section a brief introduction to both therapeutically relevant fields will be discussed and how this research project aims to synthesise new guanidine containing molecules to probe unexplored biological areas.

3.1.1. DNA minor groove binders.

DNA minor groove binders (MGBs) are compounds which can interact favourably with the minor groove of DNA (Figure 3.1.1.1).

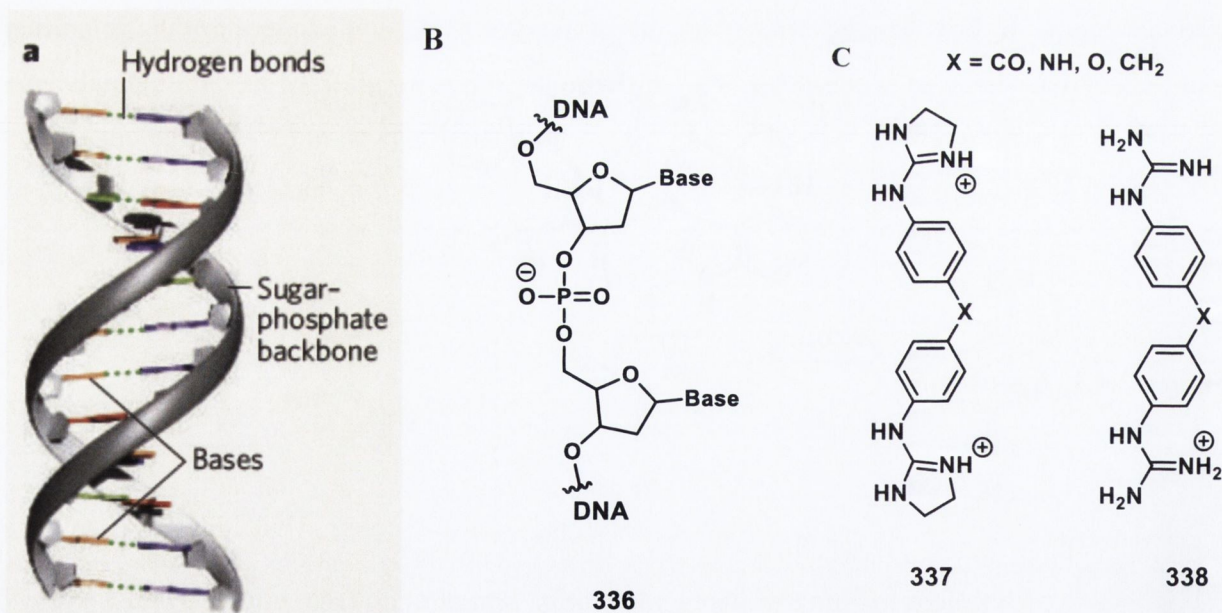


Figure 3.1.1.1. The helical structure of DNA (a),¹⁸⁶ the negatively charged phosphate backbone (b)¹⁸⁷ and selected examples of minor groove binders **337** and **338** developed in Rozas' laboratory (c).

The helical structure of DNA contains two grooves both the major and the minor forms,¹⁸⁶ and the walls of these grooves are lined up by a negatively charged phosphate backbone **336** (Figure 3.1.1.1).¹⁸⁷

The minor groove is the target for many transcription factors and it has been shown to exhibit a negative potential; hence, this is an appealing target for compounds aiming to interfere with the replication of cells such as anticancer or antiprotozoal agents.^{188,189} At physiological pH guanidine derivatives (pK_a values around 8 to 10) will be protonated with their positive charge being delocalised over the entire functionality. Previous research in Rozas' group has shown the efficacy of both di-aryl *bis*-guanidine and *bis*-2-aminoimidazolidine type of ligands as effective MGBs.¹⁹⁰

3.1.2. α_2 -Adrenoceptor ligands.

The α_2 -adrenoceptors (α_2 -ARs) are G-Protein Coupled Receptors (GPCR) associated with the heterotrimeric G_i protein. As is typical for a GPCR, α_2 -ARs are comprised of seven transmembrane α -helices, an intracellular domain and a ligand binding domain. There are three highly homologous subtypes comprising of the α_{2A} , α_{2B} and α_{2C} receptors. α_2 -ARs can be found both pre- and postsynaptically in the brain and, in particular, the prefrontal cortex has a high population of presynaptic α_2 -ARs. Activation of presynaptic α_2 -AR by its natural agonist noradrenaline (NA) leads to inhibition of NA release from the presynaptic neuron; hence, these receptors are modulators of the levels of NA in the synaptic cleft (Figure 3.1.2.1).¹⁹¹

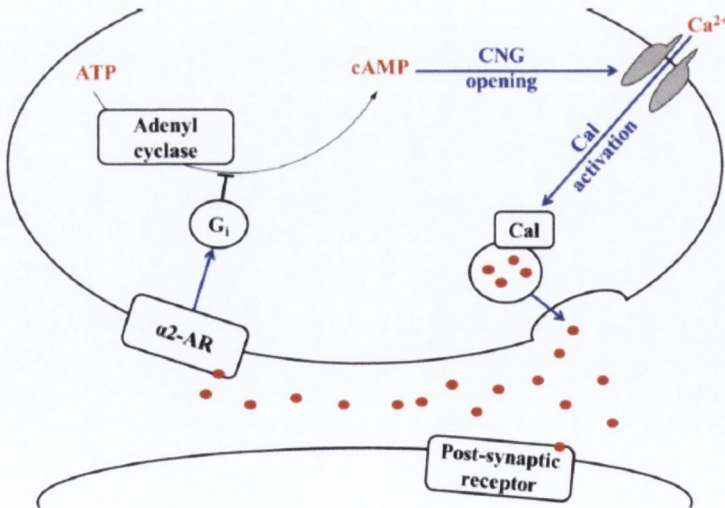


Figure 3.1.2.1. Schematic representation of the α_2 -AR and the effect of its activation by NA (represented by red circles).^{191,192}

Antagonism of the α_2 -ARs has been linked with treatment of a variety of medical conditions such as schizophrenia,¹⁹³ bi-polar disorder¹⁹⁴ and major depressive disorder.¹⁹⁵ The most basic description of depression states that reduced levels of monoamine in particular areas of the brain leads to symptoms of depression.¹⁹⁶ This is known as the Monoamine Theory and has been in existence since the 1960s. This analysis although hugely oversimplified has been the target of most of the therapeutics aiming to combat depression.¹⁹⁷ The majority of the commercially available antidepressants are selective serotonin reuptake inhibitors (SSRIs) which also act by elevating levels of monoamines in the brain. Examples include fluoxetine (Prozac ©) a blockbuster drug.

As α_2 -ARs are modulators of levels of NA in the synaptic cleft antagonism of this receptor can influence such levels, therefore potentially making it a viable target for antidepressants. In Rozas' group a number of both guanidine and 2-aminoimidazolidine containing compounds have shown to be effective antagonists of α_2 -ARs and these have potential as antidepressants.^{190,192} Examples of α_2 -AR antagonists with good pK_i values (a measure of the level of inhibition of the ligand for the GPCR receptor) are displayed in Figure 3.1.2.2. (compounds **339**, **340** and **341**). The larger the pK_i value, the greater the molecule's affinity for the receptor.

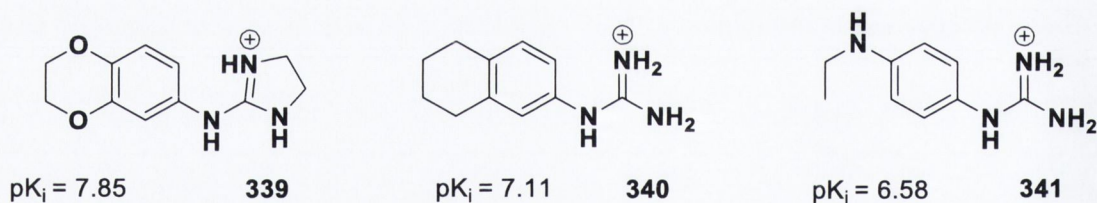


Figure 3.1.2.2. Selected examples of α_2 -AR antagonists.

This very brief description of the role that guanidine derivatives can play in medicinal chemistry tries to highlight the relevance of *designing and achieving new synthetic routes for the efficient, environmentally friendly and cost effective synthesis of aryl guanidines which may be used as MGBs or α_2 -AR antagonists*; and this is the fundamental aim of this project.

3.2. Extending the chain: the synthesis of derivatised 2-(arylamino)-tetrahydro-1,4,5,6-pyrimidines.

From the brief introduction above we have described how both guanidines and 2-aminoimidazolidines have proven to be useful functionalities in the context of medicinal chemistry research in Rozas' group. The idea to extend the alkyl chain linking the two nitrogen atoms of the imidazolidine heterocycles was an appealing one. The extra steric bulk and lipophilicity inferred by an extra methylene functionality could potentially alter the binding interactions in a favourable manner leading to more effective biologically active agents (Figure 3.2.1.1). This chemical space has previously never been explored for either MGBs or α_2 -AR antagonists.

3.2.1. Preparation of N-aryl-2-aminopyrimidines

Synthetically, 2-(arylamino)-tetrahydro-1,4,5,6-pyrimidines **342** could be accessed from their pyrimidine analogues **343** by a reductive procedure (Figure 3.2.1.1).

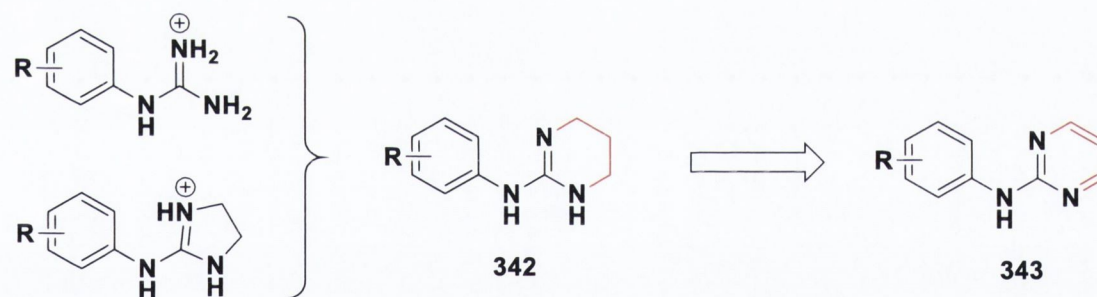


Figure 3.2.1.1. Design of tetrahydro-1,4,5,6-pyrimidine containing molecules.

From a retrosynthetic standpoint there are two possible disconnections to form these molecules; the combination of anilines **344** with 2-chloropyrimidine **345** (Figure 3.2.1.2, route **a**) or the palladium catalysed addition of 2-aminopyrimidine **346** to aryl halides **347** (Figure 3.2.1.2, route **b**). In order to achieve the most efficient method it was decided to undertake a comparative study between the two coupling approaches.

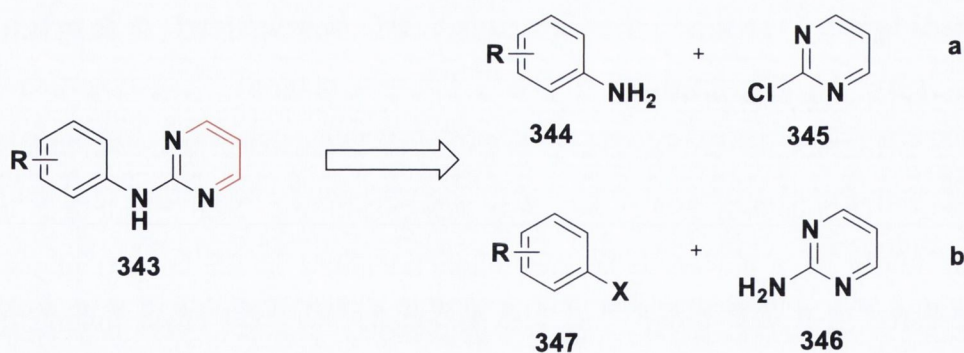


Figure 3.2.1.2. Retrosynthesis of *N*-aryl-2-aminopyrimidines.

Very few literature examples exist for the efficient uncatalysed addition of anilines to 2-chloropyrimidine and these examples suffer from poor yields typically obtaining the desired product in below 50% yield.¹⁹⁸ Therefore, the need for the use of Buchwald-Hartwig palladium catalysed amination chemistry seemed evident.

In 1995 both Buchwald¹⁹⁹ (MIT) and Hartwig²⁰⁰ (then Yale, now UC Berkley) published methods for the Pd catalysed coupling of aryl halides with amines to form aniline containing compounds. This was a major break through in the field of organic chemistry, allowing rapid formation of potentially one of the most important bonds in the pharmaceutical industry: the C–N bond.

The Pd catalysed coupling between an aryl halide and an amine begins with the formation of a Pd(0) species typically from a commercially available Pd precatalyst such as $Pd_2(dba)_3$. Dissociation of initial ligands to supply vacant coordination sites occurs followed by binding of phosphine ligands to the Pd centre.²⁰¹ The binding of these ligands increases the electron density of the metal which accelerates the oxidative addition step. This step involves the insertion of Pd into the C–halogen bond to form two new bonds. The coordination number of Pd is 4 and hence to form a stable $18\ e^-$ complex it requires four ligands donating $2\ e^-$ each and the use of the d^{10} ($4d^8$ and $5s^2$) electrons of Pd.²⁰¹

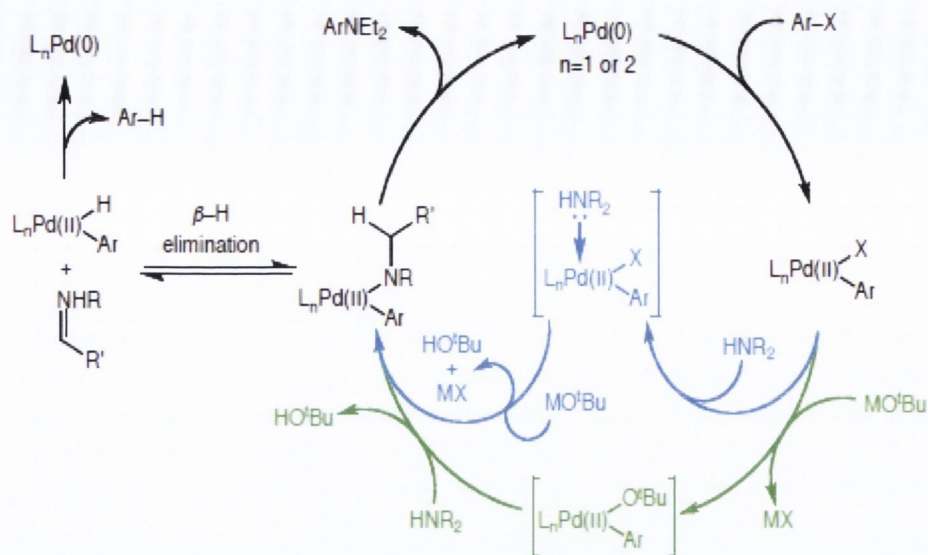


Figure 3.2.1.3. The proposed catalytic cycle of Pd catalysed amination of aryl halides.²⁰¹

Once this relatively stable complex has formed, coordination of the nucleophilic amine to the metal centre can occur, increasing the acidity of the amino protons, followed by deprotonation by a base (Figure 3.2.1.3, **blue cycle**). This is the most widely accepted interpretation of the catalytic cycle, but other suggestions propose initial binding of a nucleophilic base to the Pd centre before coordination of the amine, as is seen in other catalytic cycles (Figure 3.2.1.3, **green cycle**). These two interpretations still exist for the mechanism of this aspect of the catalytic cycle and there is experimental evidence for both routes.^{202,203} Small changes in reaction conditions have been proposed to have differing effects on this step. For example, when non nucleophilic bases such as Cs_2CO_3 or K_3PO_4 are utilised, the catalytic cycle is believed to follow the **blue cycle** in Figure 3.2.1.3.

Deprotonation of the amine and subsequent expulsion of the halogen leave a Pd(II) species bound to the incoming amine and the aryl functionality. Then, reduced electron density of the metal centre and the bulkiness of the ligand, facilitate reductive elimination to ensure regeneration of the L_nPd complex and expulsion of the new C–N bond containing compound. There are a number of factors affecting the efficacy of this highly effective synthetic transformation. The choice of ligand, base and solvent are all critical to the success of the reaction but each condition in turn also depend on the choice of substrates to be coupled.²⁰⁴

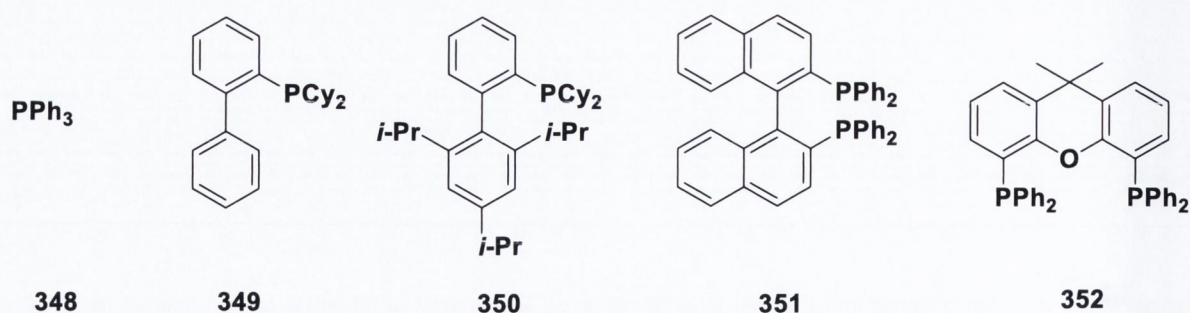
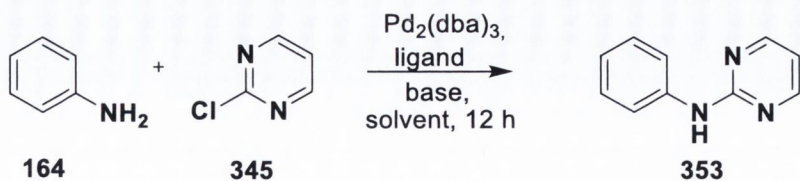


Figure 3.2.1.4. Selected examples of phosphine ligands typically utilised in Buchwald-Hartwig amination.

Our experimentation began with the coupling of aniline **164** with 2-chloropyrimidine **345**. Initially, the coupling of the two substrates was attempted without the use of Pd catalysis. As had been expected this generated the desired product **353** in poor yield (Table 3.2.1.1, entry 1). Systematically, each of the variables were changed and analysed including ligand choice (Table 3.2.1.1, entries 2 - 7), base (Table 3.2.1.1, entries 8 - 10), solvent (Table 3.2.1.1, entries 11 - 13) temperature (Table 3.2.1.1, entries 14 and 15). Catalyst and ligand loadings were also investigated (Table 3.2.1.1, entries 16 and 17). The reaction was also allowed run for an extended time period with little improvement in isolated yield being noted (Table 3.2.1.1, entries 18 and 19). The initial problem with reactivity was the poor level of conversion of starting material into product. After extensive optimisation for this reaction, as presented in Table 3.2.1.1, it was found that the ideal conditions for the coupling of our particular systems were: $\text{Pd}_2(\text{dba})_3$ (2 mol%), Xantphos **352** (3 mol%), NaOt-Bu in toluene at 95 °C for 12 h (Table 3.2.1.1, entry 16). A discussion on the role of each of the variables will be presented in a comparative manner at the end of this section.

Table 3.2.1.1. Optimisation of the Pd catalysed coupling of 2-chloropyrimidine **345** with aniline **164**.^a



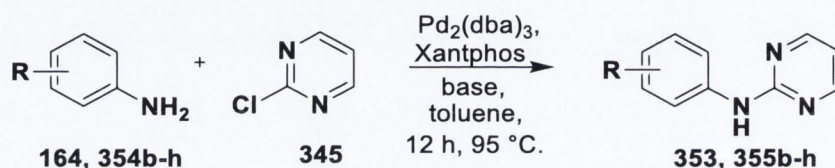
Entry	Pd (mol%)	Ligand (mol%)	Base	Solvent	Temp. (°C)	Yield (%)
1	-	-	NaOt-Bu	toluene	100	23
2	2	350 (2)	NaOt-Bu	toluene	90	56
3	2	349 (2)	NaOt-Bu	toluene	90	47
4	2	351 (2)	NaOt-Bu	toluene	90	<5
5	2	348 (2)	NaOt-Bu	toluene	100	<5
6	5	351 (5)	NaOt-Bu	toluene	100	55
7	2	352 (2)	NaOt-Bu	toluene	90	85
8	2	350 (2)	Cs ₂ CO ₃	toluene	90	29
9	2	350 (2)	K ₃ PO ₄	toluene	90	22
10	2	350 (2)	K ₂ CO ₃	<i>t</i> -BuOH	110	12
11	2	350 (2)	NaOt-Bu	toluene	100	56
12	2	350 (2)	NaOt-Bu	DME	75	<5
13	2	350 (2)	NaOt-Bu	1,4-dioxane	90	11
14	2	350 (3)	NaOt-Bu	toluene	90	55
15	3	350 (3)	NaOt-Bu	toluene	100	54
16	2	352 (3)	NaOt-Bu	toluene	95	88
17	4	350 (4)	NaOt-Bu	toluene	100	50
18	2	350 (2)	NaOt-Bu	toluene	100	64 ^b
19	2	350 (2)	NaOt-Bu	toluene	100	63 ^c

^a Aniline (1.5 mmol), base (1.5 mmol), 2-chloropyrimidine (1.0 mmol), Pd₂(dba)₃, ligand, solvent (1.5 mL), 12 h. ^b 24 h. ^c 48 h.

With our optimised conditions in hand, we decided to test the substrate scope of this reaction by choosing a variety of electronically (Table 3.1.1.2, entries 2-8) and sterically differing

anilines (Table 3.1.1.2, entries 1 and 8). The yields obtained were typically poor to good with electron deficient anilines noticeably underperforming as coupling partners (Table 3.1.1.2, entries 7 and 8). It was noted that in the case of electron deficient anilines, the use of K_3PO_4 as base was highly beneficial. An extensive screening of substrates was not undertaken in this step due to the initially poor results obtained and, hence, it was thought to be advantageous to turn our attention to the analogous couplings of 2-aminopyrimidine with aryl bromides (route b in Figure 3.2.3). This ‘inverse’ reactivity was hoped may lead to more satisfactory results.

Table 3.1.1.2. Anilines successfully coupled with 2-chloropyrimidine^a

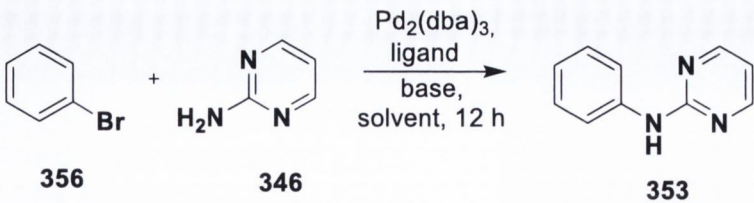


Entry	R	Products	Yield (%)
1	H	353	88
2	4-OCH ₃	355b	87
3	3-OCH ₃	355c	72
4	4-N(CH ₃) ₂	355d	72
5	4-F	355e	50
6	2-F	355f	49
7	3-CN	355g	55 ^b
8	4-NO ₂ -3-CH ₃	355h	54 ^b

^a Aniline (1.5 mmol), NaOt-Bu (1.5 mmol), 2-chloropyrimidine (1 mmol), $Pd_2(dba)_3$ (2 mol%), ligand (3 mol%), toluene (1.5 mL). ^b K_3PO_4 used as base.

The Pd-catalysed reaction between bromobenzene **356** and 2-aminopyrimidine **346** was optimised using the same optimisation process that we had employed in our first example by systematically changing all possible conditions including ligand (Table 3.2.1.3 entries 2 - 7), base (Table 3.2.1.3 entries 8 - 10), solvent (Table 3.2.1.3 entries 11 - 12), temperature (Table 3.2.1.3 entries 13 and 14), catalyst loadings (Table 3.2.1.3 entries 15 - 18) and time (Table 3.2.1.3 entries 19 and 20). Gratifyingly, it was immediately noticed that the yields were higher for this system than for our initial coupling reactions between aniline and 2-chloropyrimidine.

Table 3.2.1.3. Optimisation of the Pd catalysed coupling of 2-aminopyrimidine with bromobenzene.^a



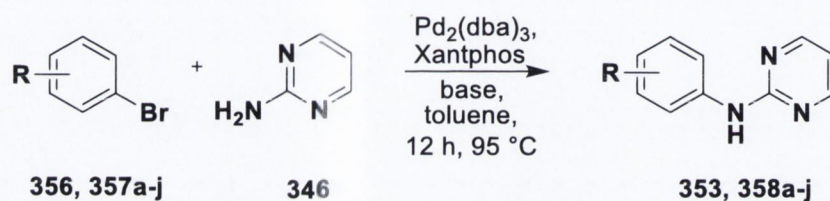
Entry	Pd (mol%)	Ligand (mol%)	Base	Solvent	Temp. (°C)	Yield (%)
1	-	-	NaOt-Bu	toluene	90	0
2	2	350 (2)	NaOt-Bu	toluene	90	45
3	2	349 (2)	NaOt-Bu	toluene	90	35
4	2	348 (2)	NaOt-Bu	toluene	100	<5
5	2	351 (2)	NaOt-Bu	toluene	90	9
6	2	352 (2)	NaOt-Bu	toluene	90	97
7	2	350 (2)	NaOt-Bu	toluene	100	50
8	2	350 (2)	CS ₂ CO ₃	toluene	90	23
9	2	350 (2)	K ₃ PO ₄	toluene	90	34
10	2	350 (2)	K ₂ CO ₃	<i>t</i> -BuOH	110	45
11	2	350 (2)	NaOt-Bu	DME	75	32
12	2	350 (2)	NaOt-Bu	1,4-dioxane	90	27
13	2	350 (2)	NaOt-Bu	toluene	90	52
14	2	350 (2)	NaOt-Bu	toluene	100	54
15	3	350 (3)	NaOt-Bu	toluene	100	55
16	4	350 (4)	NaOt-Bu	toluene	100	60
17	5	350 (5)	NaOt-Bu	toluene	100	59
18	2	352 (3)	NaOt-Bu	toluene	95	98
19	2	350 (2)	NaOt-Bu	toluene	100	58 ^b
20	2	350 (2)	NaOt-Bu	toluene	100	57 ^c

^a 2-Aminopyrimidine (1.5 mmol), base (1.5 mmol), aryl bromide (1.0 mmol), Pd₂(dba)₃, ligand, solvent (1.5 mL), 12 h. ^b 24 h. ^c 48 h.

The optimised conditions for the coupling of anilines with 2-chloropyrimidines also proved to be the preferred method to couple bromobenzene **356** with 2-aminopyrimidine **346** producing the desired *N*-phenyl-2-aminopyrimidine **353** in a highly satisfactory 98% yield (Table 3.2.1.3, entry 18).

Encouraged by this promising result a more extensive substrate scope was investigated for this coupling reaction. Electronically and sterically differing aryl bromides were exposed to these coupling conditions to afford a diverse library of *N*-aryl-2-aminopyrimidines (Table 3.2.1.4.).

Table 3.2.1.4. Aryl bromides **358 a-l** successfully coupled with 2-aminopyrimidine **346**.^a



Entry	R	Product	Yield (%)
1	H	353	98
2	4-OCH ₃	358a	90
3	3-OCH ₃	358b	95
4	2-OCH ₃	358c	90
5	4-F	358d	85
6	3-Br	358e	94
7	2-F	358f	92
8	4-CN	358g	78 ^b
9	3-CN	358h	66 ^b
10	2-CN	358i	82 ^b
11	2-Ph	358j	98
12	H	353	99 ^c

^a 2-Aminopyrimidine (2 mmol), NaOt-Bu (2 mmol), aryl halide (1 mmol), Pd₂(dba)₃ (2 mol%), Xantphos (3 mol%), toluene (1 mL mmol⁻¹ aryl halide). ^b K₃PO₄ used as base. ^c 2 g scale.

The substrate scope displayed in Table 3.2.1.4 portrays the utility of the coupling of aryl bromides **357** with 2-aminopyrimidine **346** under the optimised conditions. Electron

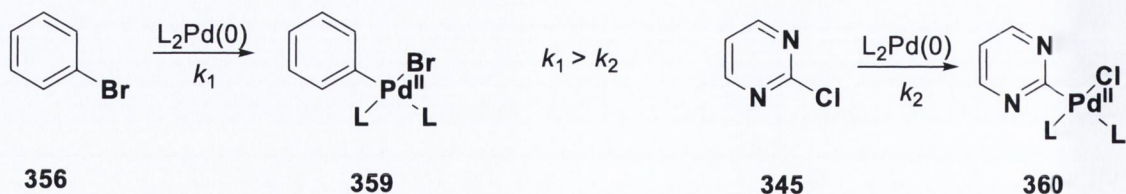
withdrawing (Table 3.2.1.4, entries 8-10), electron donating (Table 3.2.1.4, entries 2-4) and sterically differing (Table 3.2.1.4, entries 1 and 11) substituents on the aryl bromide were all well tolerated under these conditions. The reaction between bromobenzene **356** and 2-aminopyrimidine **346** was also replicable on a multi-gram scale (Table 3.2.1.4, entry 12) and afforded a single highly crystalline solid after simple recrystallisation techniques (Figure 3.2.1.5).



Figure 3.2.1.5. Highly crystalline *N*-phenyl-2-aminopyrimidine **357**.

The significant differences in the results obtained with these two coupling approaches can be explained by an analysis of the reaction mechanism in each case. Oxidative addition into a C–Cl bond of a heterocycle is known to be a slower process than that of their phenyl carbon bromine analogues (Scheme 3.2.1.1).²⁰⁵ There are a number of reasons for this such as the rate of insertion into C–halogen bonds is known to be faster for C–Br over C–Cl.²⁰¹ Moreover, the presence of a ring nitrogen on the pyrimidine scaffold have a deleterious effect on the oxidative addition step due to their ability to interact with the metal centre.²⁰⁵ The ability for pyrimidine systems to be used as ligands in Pd cross coupling reactions is testament to this fact.²⁰⁶ It was decided not to examine the use of 2-bromopyrimidine as a coupling partner with anilines because although it may be a better coupling partner than 2-chloropyrimidine **345** with anilines, it would most likely be of less synthetic utility than the coupling of aryl bromides with 2-aminopyrimidine **346**.

Scheme 3.2.1.1.



A number of factors proved essential for the reactivity of both systems. Interestingly, the use of Xantphos **352** was critical for the success of this reaction as has previously been demonstrated for the coupling chemistry of π -deficient heterocycles.²⁰⁷ The use of bidentate ligands such as Xantphos **352** have been widely studied for a variety of Pd catalysed transformations.²⁰⁸ Ligated Pd(0) species **361** has increased electron density on the metal centre due to the electron rich bidentate phosphine ligand. Xantphos' wide bite angle (the chelation angle between the ligand and the metal centre,²⁰⁹ see Figure 3.2.1.6) also aligns the appropriate molecular orbitals of Pd for facile oxidative insertion into an aryl halide bond (Figure 3.2.1.6, **362**).²⁰¹ This oxidative addition induces an increase in oxidation number for Pd from Pd(0) to Pd(II).²⁰¹ In our case, utilisation of a bulky bidentate ligand such as Xantphos **352** also could prevent interactions between the nitrogenous backbone of pyrimidine and the metal centre.

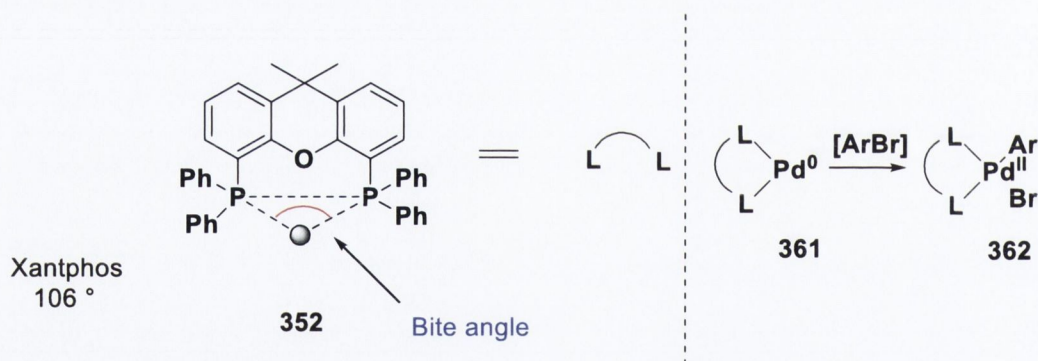


Figure 3.2.1.6. Oxidative addition of a bidentate ligand (Xantphos) to a Pd(0) species.

Additionally, the use of Xantphos **352** plays a critical role in reductive elimination. The oxidation number of the metal decreases by two, there is an increase in the d-electron count by two and a decrease in the overall number of valence electrons by two (Figure 3.2.1.7).

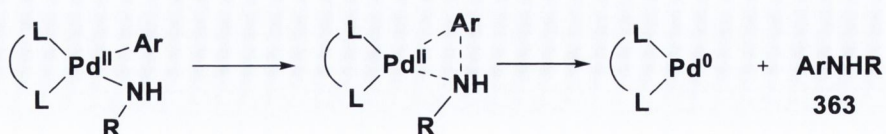


Figure 3.2.1.7. Schematic representation of reductive elimination from a tetra-coordinated Pd(II) complex to generate aniline **363**.

Bidentate Pd(II) Xantphos complexes are more unstable than their bi-coordinated Pd(0) counterparts due to the large bite angle which makes it a very strained, crowded tetra-coordinated system.²⁰⁹ This wide bite angle therefore facilitates reductive elimination of the aryl and amino groups *cis* one to each other as it pushes them together to regain its more stable Pd(0) form. There is a vast precedence in the chemical literature for the enhancement of the rate of reductive elimination by the utilisation of ligands with wide bite angles.²⁰⁸⁻²¹¹

In both Table 3.2.1.1 and Table 3.2.1.3., it was noted that NaOt-Bu ($pK_{aH} = 17$) was the optimal base to use. When electron withdrawing functionalities were present in the reaction mixture it was noted that K_3PO_4 ($pK_{aH} = 12$) gave better results than NaOt-Bu. It has been noted that the rate of Pd catalysed amination reactions is often dependent on both the concentration and the nature of bases utilised for electronically differing aryl halides.²¹²⁻²¹⁴ It would appear that subtle differences in the choice of base can play an important role in these reactions and that these small differences have not been fully explained to date.

As it has been previously reported in the literature^{215,216} we have observed that the use of an extra equivalent of ligand, relative to those of Pd, was beneficial (Table 3.2.1.3, entry 16) giving an increase in the isolated yield of product. It has been hypothesised that an extra equivalent of ligand is often necessary in order to stabilise the Pd catalyst in difficult cases in which long reaction times are required or when a high turnover number (TON) at the metal centre is desired.^{215,216}

In conclusion, the optimised Pd catalysed coupling of aryl bromides and 2-aminopyrimidine and the ‘inverse’ of this reaction, the coupling of anilines with 2-chloropyrimidine, has now been documented. The outcomes indicate that the first of these two reactions gives more favourable results affording higher overall isolatable yields of products. With this information in hand we then set our objectives on the development of a reductive methodology to

transform our *N*-aryl-2-aminopyrimidine library into their corresponding 2-(arylamino)-tetrahydro-1,4,5,6-pyrimidine analogues.

3.2.2 Reduction of the pyrimidine moiety to form 2-(arylamino)-tetrahydro-1,4,5,6-pyrimidines.

The transformation of *N*-alkyl-2-aminopyrimidine derivatives into their reduced guanidine counterparts is well catalogued.²¹⁷ To date no previous research for the transformation of *N*-aryl-2-aminopyrimidine exists in the chemical literature (Figure 3.2.2.1).

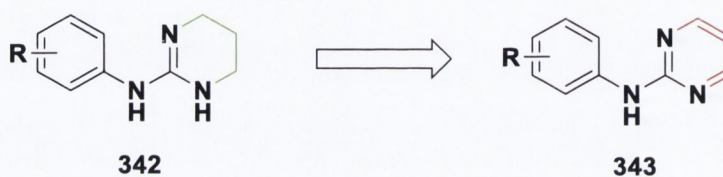
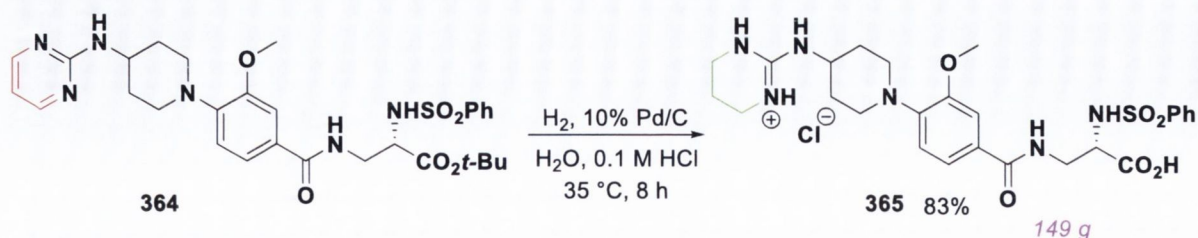


Figure 3.2.2.1. Retrosynthesis of *N*-aryl-2-amino-1,4,5,6-tetrahydropyrimidines.

The use of Pd catalysed hydrogenation to reduce the pyrimidine ring was an appealing idea and adhered to our plans for an atom economical, environmentally friendly and cost effective synthetic method.

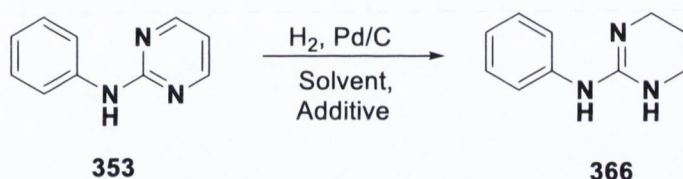
The reductive hydrogenation of *N*-alkyl-2-aminopyrimidine derivatives was described by Ajito *et al.* when synthesising antagonists of Integrins $\alpha_v\beta_3$ and $\alpha_{IIb}\beta_3$ for the treatment of coronary thrombosis (Scheme 3.2.2.1).¹⁷⁰

Scheme 3.2.2.1.



This reaction was performed under one atmosphere of hydrogen in what would appear to be non-forcing conditions. The desire to emulate such results in our system led us to begin our synthetic explorations with the exposure of *N*-phenyl-2-aminopyrimidine to Ajito's conditions.

Table 3.2.2.1. Optimisation of the reductive hydrogenation of *N*-phenyl-2-aminopyrimidine **357**.^a



Entry	Solvent	Pd/C (mg)	HCl (M)	Temp. (°C)	Yield (%)
1	H ₂ O	30	0.5	30	63
2	H ₂ O	30	0.5	rt	59
3	MeOH	30	0.5	rt	84
4	EtOH	30	0.5	rt	81
5	MeOH	50	0.5	rt	88
6	MeOH	50	1	rt	97
7	MeOH	50	-	rt	0

^a 0.25 mmol **353**, solvent (4 mL mmol⁻¹).

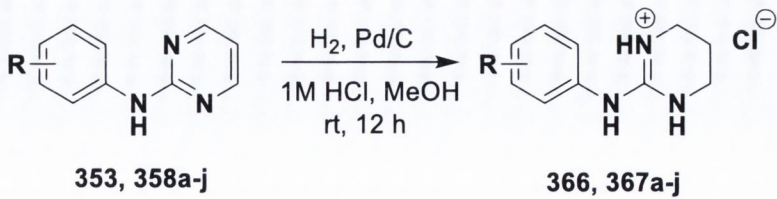
Utilisation of Ajito's conditions for our system gave initially promising results generating the desired product in 63% yield (Table 3.2.2.1. entry 1). Optimisation of these conditions indicated that the use of MeOH as a solvent proved highly beneficial most lightly due to the lack of solubility of protonated *N*-phenyl-2-aminopyrimidine in H₂O (Table 3.2.2.1. entries 1 – 5). Additionally, the pK_{aH} of *N*-phenyl-2-aminopyrimidine is approximately 3²¹⁸ and therefore this compound should be protonated when exposed to 1M HCl. This is obviously an

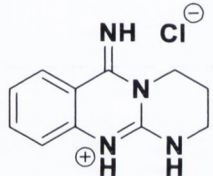
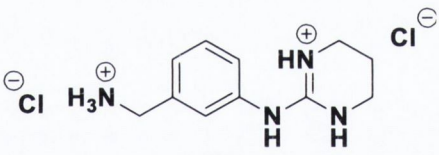
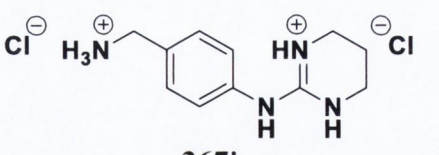
important driving force for this transformation since a control reaction displayed no reactivity when HCl was omitted from the reaction vessel (Table 3.2.2.1, entry 7). A slight increase in the molarity of HCl used and the Pd/C loading also proved advantageous leading to the optimal conditions (Table 3.2.2.1., entry 6).

These conditions were then applied to our library of *N*-aryl-2-aminopyrimidines. In each case the pyrimidine ring was reduced to its alkyl analogue (Table 3.2.2.2. entries 1 - 6, 11); however, a number of side reactions occurred under these hydrogenative conditions. When 2-(3-bromophenyl)aminopyrimidine **358f** was exposed to these reductive settings, unsurprisingly, the bromine atom was replaced with a hydrogen atom (Table 3.2.2.2. entry 7). This is expected as halides are known to be unstable in Pd catalysed hydrogenation due to the ability of Pd to insert into a C–halogen bond.²⁰¹

Other results of interest were the reduction of both the *meta* and *para* nitrile substituents on the phenyl ring of compounds **358h** and **358i** respectively (Table 3.2.2.2. entries 9 and 10). This type of reduction of nitriles is known;²¹⁹ however, the result obtained from the reduction of the *ortho* nitrile substituted compound **358g** was interesting. Although the *meta* and *para* nitrile substituents were easily reduced, the *ortho* nitrile functionality was attacked by the formed guanidine functionality to form the tricyclic compound **367g** (Table 3.2.2.2, entry 8).

Table 3.2.2.2. Hydrogenation of the 2-aminopyrimidine ring.^a



Entry	R	Product	Yield (%)
1	H	366	97
2	2-OCH ₃	367a	98
3	3-OCH ₃	367b	91
4	4-OCH ₃	367c	92
5	2-F	367d	95
6	4-F	367e	95
7	3-Br	366	90
8	2-CN	 367g	64
9	3-CN	 367h	71 ^b
10	4-CN	 367i	78 ^b
11	2-Ph	367j	92

^a *N*-phenyl-2-aminopyrimidine (1 mmol), Pd/C 10% (50 mg) MeOH (4 mL), aq. HCl (1M, 1 mL). ^b Concomitant reduction of the nitrile moiety.

In conclusion, a highly atom economical and efficient method for the synthesis of 2-(arylamino)-tetrahydro-1,4,5,6-pyrimidines has been developed.

4. 2-Aminopyrimidines as a guanidine precursor.

4.1. Introduction.

From the introduction of this thesis (Chapter 1) it is evident the multitude of synthetic procedures available to introduce the guanidine functional group. All of these methods have merit in different circumstances. For instance, if one requires the synthesis of *N,N,N'*-trisubstituted guanidines the use of Neuville's method (Scheme 1.5.1.10.7) would be advisable or if one would require the synthesis of *N*-alkylated guanidines it would be advantageous to use Mukaiyama's reagent **101** (Scheme 1.5.1.1.7).

However, in the context of synthesising aryl guanidines (Figure 4.1.1) for use as α_2 -AR antagonists or as MGBs then there is no particularly effective or atom economical method for their production.

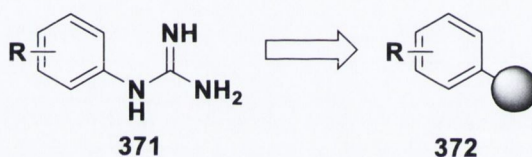


Figure 4.1.1. Retrosynthesis of aryl guanidines.

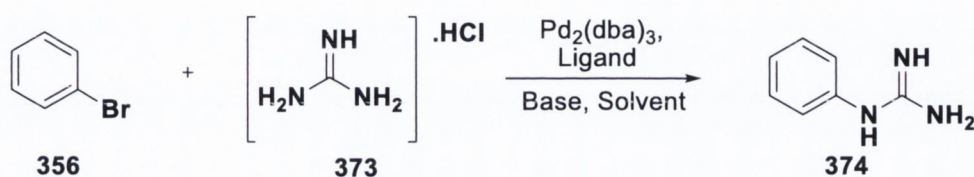
It was therefore intended to design and implement a synthetic procedure that would introduce such guanidine functionality in an expedient and robust manner.

4.2. Initial investigations into coupling chemistry.

The ability for an aryl halide to be directly transformed into the corresponding aryl guanidine is unknown in the chemical literature. Previous attempts to coax this reactivity utilising copper chemistry have resulted in diarylation of guanidine (Section 1.5.1.10).¹⁶⁰⁻¹⁶⁴ However, this reaction could potentially work if a Pd catalysed system is utilised considering that a more rigid metal ligand interaction may prevent the guanidine binding to the metal centre, as is known to occur.²²⁰ For instance, in certain metal catalysed coupling reactions guanidine derivatives are utilised as ligands.²⁰⁶

Preliminary attempts to couple bromobenzene **356** with guanidine hydrochloride **373** were unsuccessful with no observable product being formed (Table 4.2.1, entries 1 - 4). It was hoped that the use of bidentate Xantphos **352** might prove useful in preventing the binding of guanidine to the palladium metal allowing the desired reactivity to occur; however, no such result was obtained (Table 4.2.1, entries 5 - 8). It was therefore deemed logical to focus our attention on finding a guanidine surrogate which could be easily coupled with aryl halides and then deprotected as appropriate to yield the guanidine functionality.

Table 4.2.1. Attempts to couple bromobenzene and guanidine hydrochloride.^a



Entry	Ligand	Base	Solvent	Yield (%)
1	348	NaOt-Bu	toluene	0
2	349	NaOt-Bu	toluene	0
3	350	NaOt-Bu	toluene	0
4	351	NaOt-Bu	toluene	0
5	352	NaOt-Bu	toluene	0
6	352	K ₃ PO ₄	toluene	0
7	352	Cs ₂ CO ₃	toluene	0
8	352	NaOt-Bu	1,4-dioxane	0

^a **356** (1 mmol), Pd₂(dba)₃ (2 mol%), Ligand (3 mol%), NaOt-Bu (1.5 mmol), toluene (1.5 mL), 95 °C, 8-12 h.

4.3. The 2-aminopyrimidine scaffold as a guanidine surrogate.

As detailed in Section 1.5.2, Al-Mourabit has shown the potential for 2-aminopyrimidine derivatives to act as guanidine surrogates.^{153b} With our recently prepared library of *N*-aryl-2-

aminopyrimidines (see Chapter 3) we realised the possibility for cleavage of the aromatic pyrimidine ring (Figure 4.3.1).

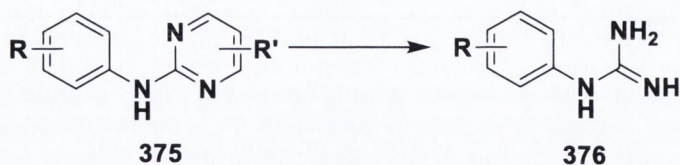
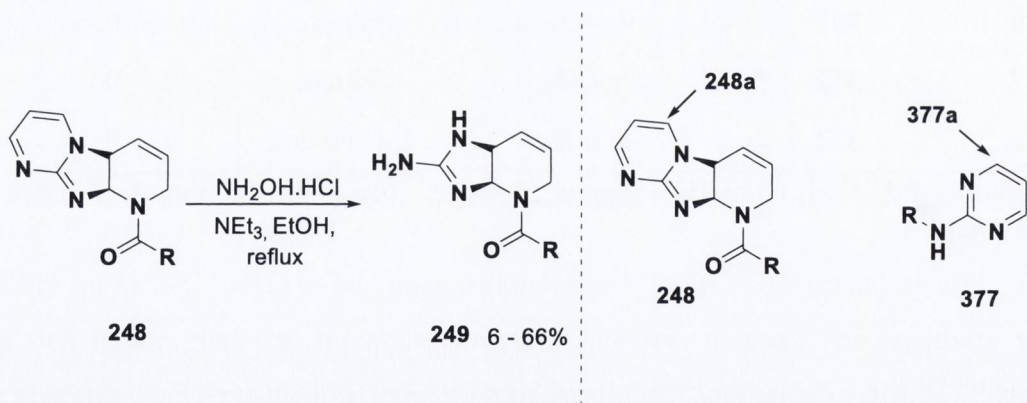


Figure 4.3.1. Potential for pyrimidines to act as a guanidine precursor.

The most challenging aspect of this proposed transformation would be the enhanced reactivity of compound **248** towards nucleophilic attack in comparison with **377** (Scheme 4.3.1). The reason for this enhanced reactivity is the extra substituent present on the nitrogen atom of **248** located in the pyrimidine ring. This alters the typical aromaticity associated with pyrimidine ring. The inability to form a cyclic six π electron species destabilises the system (Scheme 4.3.1).^{153b} Position **248a** has the potential to act as a conjugate addition acceptor while position **377a** does not have the same reactivity.

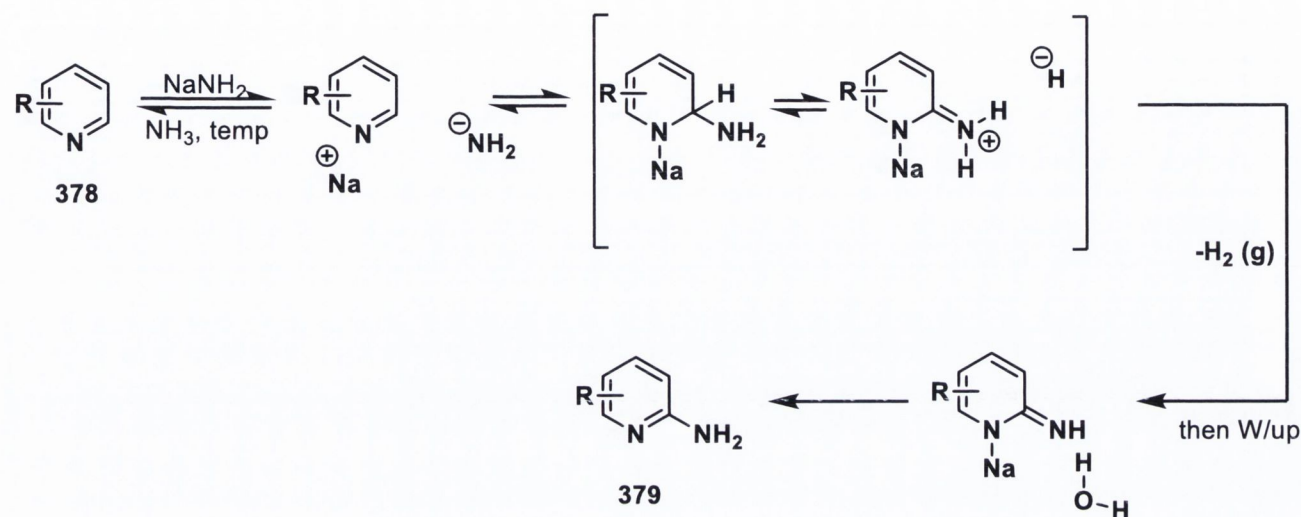
Scheme 4.3.1.



Another example of reactivity that inspired confidence in our synthetic plan to cleave the pyrimidine ring is the Chichibabin reaction (Scheme 4.3.2).²²¹ This reaction, although

typically used for the amination of pyridines **378**, has been applied to pyrimidines and related purines in a number of publications.²²²

Scheme 4.3.2.

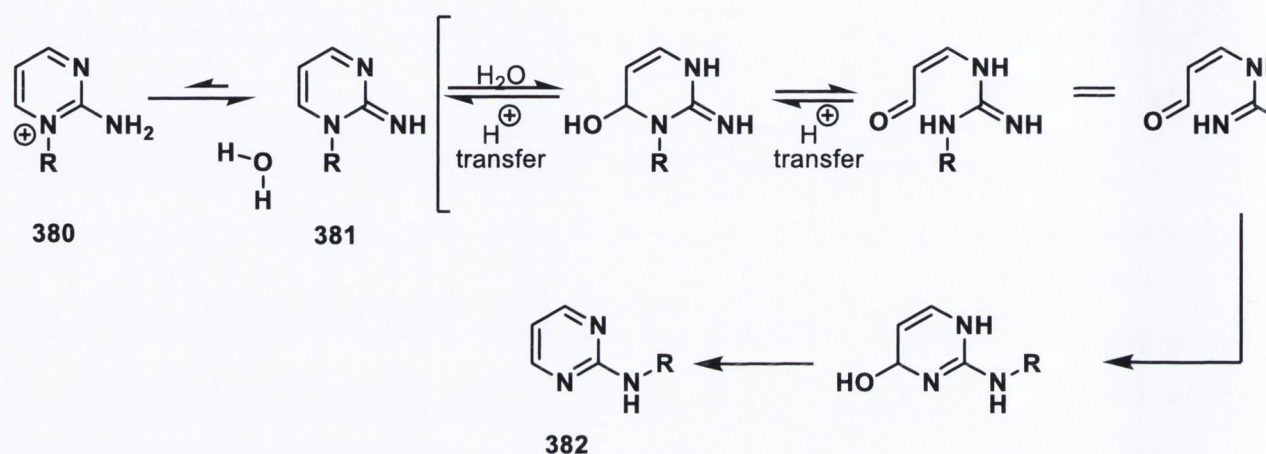


The Chichibabin reaction involves the use of sodium amide in an ammonia solution at elevated temperatures to facilitate the amination of nitrogen heterocycles **379**.²²¹ Although the Chichibabin reaction requires remarkably harsh conditions it should be noted the ability of a nitrogen nucleophile to break the aromaticity of pyridine forming a Meisenheimer complex. As pyrimidine has less aromatic stabilisation than pyridine due to the presence of an extra nitrogen atom in its ring, it was believed that more facile conditions than those used in the Chichibabin reaction could be used to break aromaticity.

An additional reaction that involves the ring opening of nitrogen heterocycles is the Dimroth reaction (Scheme 4.3.3).²²² When the ring nitrogen of 2-aminopyrimidine is substituted, there are two possible tautomeric forms, either an extracyclic amine **380** or an extracyclic imine **381**. The imino tautomer would be more stable due to the lack of a positive charge on the ring nitrogen (Scheme 4.3.3). When exposed to water this highly reactive species will undergo nucleophilic attack by the water on the aromatic ring. This has the ability to break the aromaticity of the pyrimidine ring and open it forming an aldehyde functionality along with a guanidine. The nucleophilic guanidine can reclose the ring but it will preferentially do this by the attack of the unsubstituted nitrogen to the aldehyde. In a forward sense, this will lead to

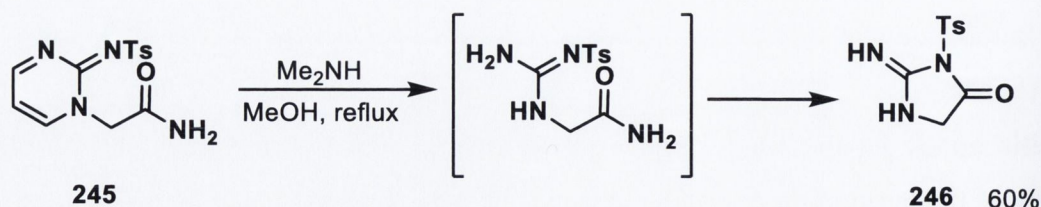
the extracyclic amino functionality being substituted and a highly stabilised, aromatic pyrimidine core **382**.

Scheme 4.3.3.



Coinciding with these findings a literature example that results in the ring opening of pyrimidine was discussed in Section 1.5.2. In this example, it was shown that the use of tosyl protected pyrimidines is critical for the success of a reaction to open the pyrimidine ring and result in subsequent rearrangement. The strongly electron withdrawing tosyl group facilitates the formation of an extracyclic imine **245**; then, the pyrimidine ring can be opened using the nucleophilic nitrogen of dimethylamine (Scheme 4.3.4.).

Scheme 4.3.4.

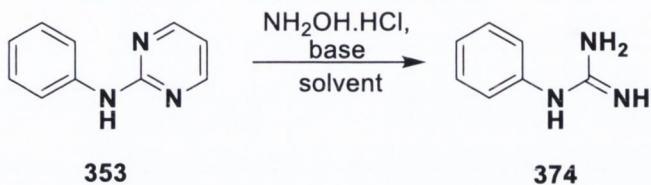


Each of the above examples encouraged us to attempt the cleavage of 2-aminopyrimidine derivatives. Unfortunately, the task was not as straightforward as had been expected.

4.4. Initial cleavage attempts.

N-Phenyl-2-aminopyrimidine **353** was chosen as a substrate to begin our initial cleavage experimentation. Choosing conditions which had proved useful for Al-Mourabit,^{153b} we began with the use of hydroxylamine hydrochloride as a nucleophile in combination with a variety of solvent, base and temperature choices (Table 4.4.1, entries 1-8).

Table 4.4.1. Initial attempts to cleave *N*-phenyl-2-aminopyrimidine **353**.^a

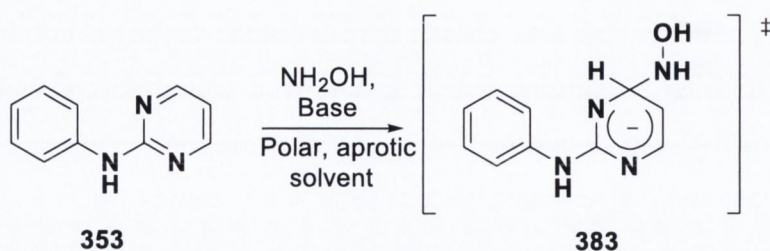


Entry	Base	Solvent	Temp (°C)	Yield (%)
1	NEt ₃	MeOH	60	0
2	DIPEA	MeOH	60	0
3	Pyridine	MeOH	60	0
4	Imidazole	MeOH	60	0
5	NEt ₃	EtOH	80	0
6	DIPEA	EtOH	80	0
7	Pyridine	EtOH	80	0
8	Imidazole	EtOH	80	0

^a **353** (1 mmol), NH₂OH.HCl (10 mmol), base (10 mmol), solvent (10 mL), 12 h.

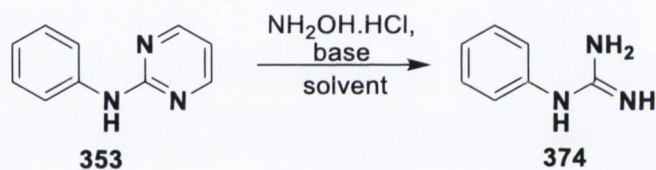
Discouragingly, no product was observed in any of the initial reaction conditions. As has previously been alluded to, the stability of our system was undoubtedly going to be our major hindrance in this reaction and it was thought to increase the temperature and choose a more polar solvent to try and facilitate reactivity (Scheme 4.4.1.).

Scheme 4.4.1.



Polar, aprotic solvents are known to often aid nucleophilic aromatic substitution (NAS) reactions and although this cleavage reaction does not adhere precisely to that type of reactivity it should have characteristics similar to NAS reactions. In particular, the formation of anionic Meisenheimer complexes (Scheme 4.4.1., **383**) is known to be favoured by the use of polar, aprotic solvents.²²³ Initial attempts to cleave compound **353** are presented in Table 4.4.2.

Table 4.4.2. Attempts to cleave *N*-phenyl-2-aminopyrimidine **353**.^a

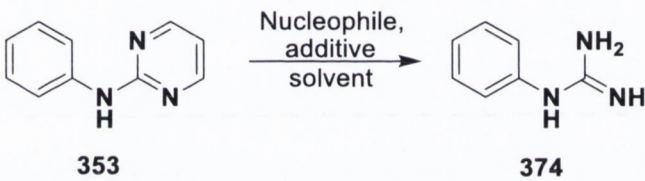


Entry	Base	Temp (°C)	Time (h)	Yield (%) ^b
1	NEt ₃	100	24	<5
2	DIPEA	100	24	<5
3	Pyridine	100	24	<5
4	Imidazole	100	24	12
5	NEt ₃	140	24	20
6	DIPEA	140	24	21
7	Pyridine	140	24	20
8	Imidazole	140	24	35
9	Imidazole	140	48	38
10	Imidazole	140	72	37

^a**353** (1 mmol), $\text{NH}_2\text{OH} \cdot \text{HCl}$ (10 mmol), base (10 mmol), DMF (10 mL). ^bBRSM.

It was with much delight that the first trace of product formation was detected using Mass spectroscopic analysis (Table 4.4.2, entries 1 – 3). Firstly a number of bases were investigated (Table 4.4.2, entries 4 – 7). However, even at a temperature of 140 °C, yields in excess of 40% could not be achieved (Table 4.4.2, entries 8 – 10). The polar nature of guanidines results in their arduous purification, therefore, yields were obtained by recovering the *N*-phenyl-2-aminopyrimidine **353** starting material. With these initial results we were unconvinced of the utility of this reaction due to the harsh conditions and the problems associated with the purification of the guanidine products. We therefore turned our attention to a number of other nucleophiles in the hope that the reaction conditions could be made more utilisable (Table 4.4.3).

Table 4.4.3. Attempts to cleave *N*-phenyl-2-aminopyrimidine.^a



Entry	Nucleophile	Additive	Solvent	Temp (°C)	Time (h)	Yield (%)
1	Propylamine	-	DMF	reflux	48	<5 ^b
2	NaS 	-	EtOH	reflux	24	0
3	-	NaH	DMSO	120	24	0
4	H ₂ O ₂ (34%)	NaOH	MeOH	rt	24	0
5	H ₂ O ₂ (34%)	H ₂ SO ₄ (10%)	MeOH	rt	24	0
6	H ₂ O ₂ (34%)	H ₂ SO ₄ (10%)	H ₂ O	rt	24	0

^a**353** (1 mmol), nucleophile (10 mmol), additive (10 mmol), solvent (10 mL). ^bBRSM.

The use of propylamine as a replacement for hydroxylamine was in no way advantageous giving similar results to those previously observed (Table 4.4.3.; entry 1). Attempted utilisation of a sulfur nucleophile such as sodium ethanethiolate (Table 4.4.3, entry 2) had no effect on the pyrimidine system. Utilisation of the dimsyl anion (methyl sulfinyl carbanion, formed from the deprotonation of DMSO using NaH) also had no effect on the system (Table

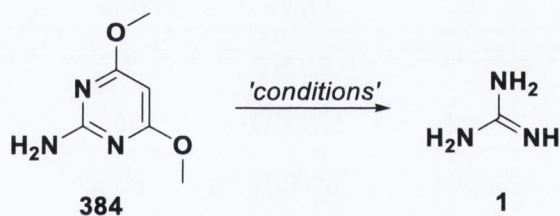
4.4.3, entry 3). A quick screening of hydrogen peroxide in a variety of conditions acting as a nucleophile also did not give the desired product (Table 4.4.3, entries 4 – 6).

From our initial findings it was therefore apparent that the stability of the pyrimidine ring was not going to be susceptible to facile cleavage conditions. Thus, it was decided to investigate alteration of the pyrimidine ring to make it more vulnerable to cleavage conditions since it is known that, for example, incorporation of a nitro derivative at the 5 position of pyrimidine makes the ring susceptible to basic hydrolysis.²²⁵

4.5. Functionalisation of the pyrimidine ring.

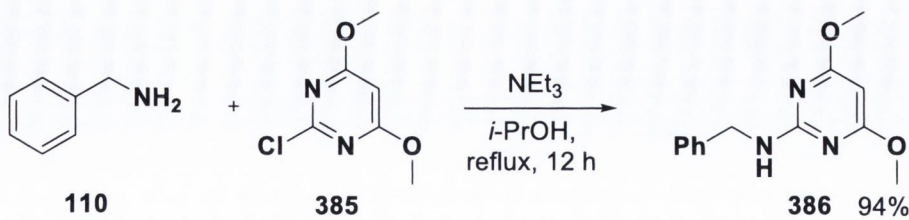
We proposed to change the electronic properties of the pyrimidine ring by introducing separately both electron withdrawing or electron donating groups. Our first choice was to use 2-amino-4,6-dimethoxypyrimidine **384** as a pyrimidine derivative with extra electron density in the ring due to the presence of the two electron donating methoxy groups. It was intended that these groups would make the pyrimidine a more susceptible target for either acid or base hydrolysis (Scheme 4.5.1).

Scheme 4.5.1.



The commercial availability of 2-chloro-4,6-dimethoxypyrimidine **385** and 2-amino-4,6-dimethoxypyrimidine **384** made this route particularly appealing. To quickly access a functionalised derivative of **385**, this was reacted with benzylamine **110** under basic conditions to generate **386** in high yield (Scheme 4.5.2). With *N*-benzyl-2-amino-4,6-dimethoxypyrimidine **386** synthesised we were then free to explore its potential to act as a guanidine precursor.

Scheme 4.5.2.



Before cleavage reactions were carried out in the laboratory, the ¹H and ¹³C NMR spectra corresponding to **386** were analysed (Figure 4.5.1).

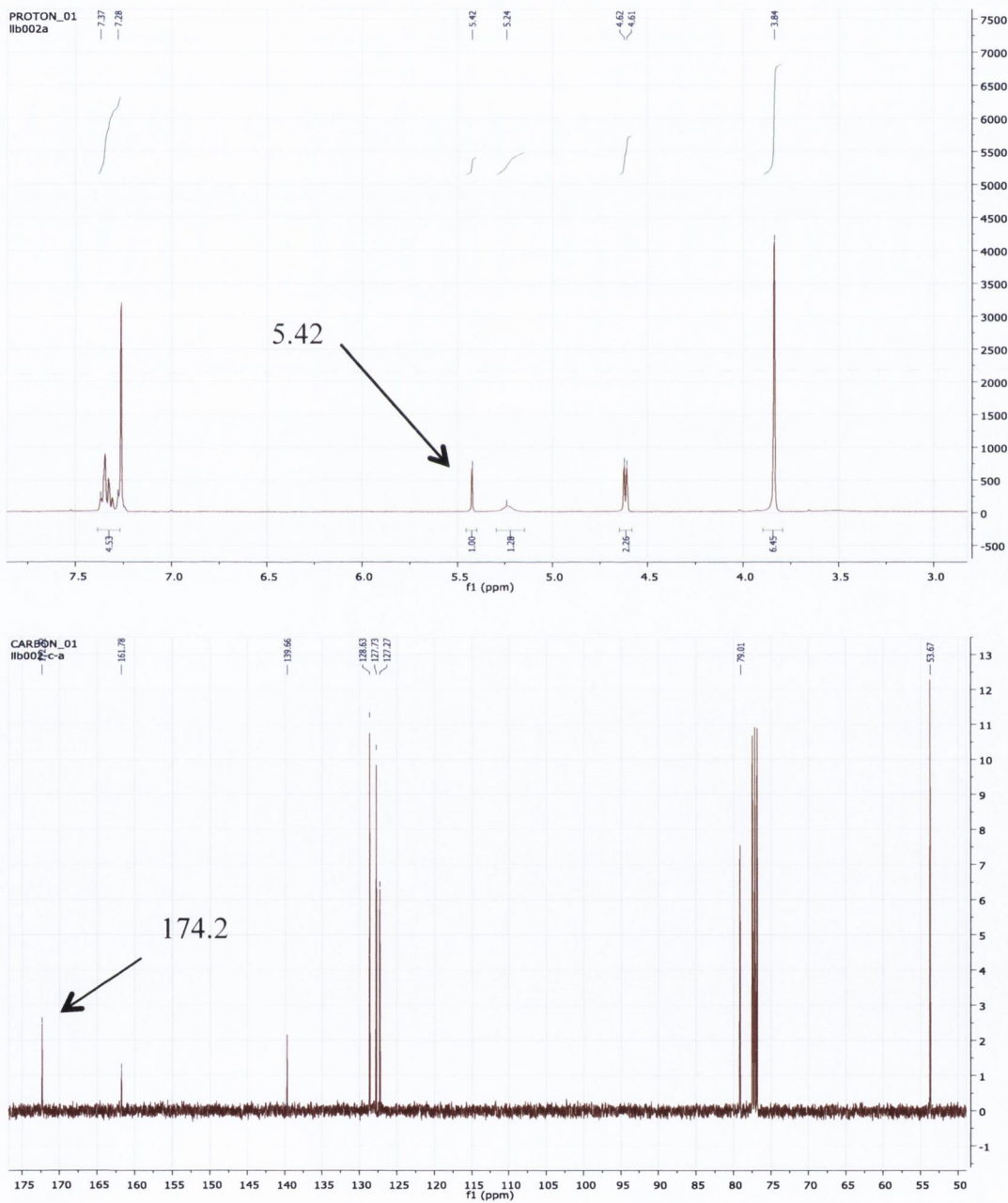
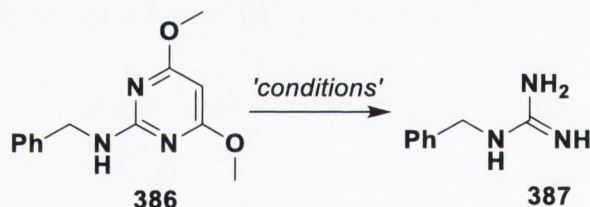


Figure 4.5.1. ¹H and ¹³C NMR spectra corresponding to compound **386**.

Scrutiny of the proton spectrum indicates the positioning of the single pyrimidine ring proton at 5.42 ppm. For an aromatic proton this is unusually far upfield and this would lead one to believe that the system does not have the same aromatic stabilisation seen in typical 2-aminopyrimidine derivatives. The analogous proton for an *N*-substituted 2-aminopyrimidine would be located typically at 6.70 – 6.80 ppm. Also of significant interest is the location of the methoxy substituted quaternary carbons of the pyrimidine ring. Their location at 174.2 ppm is more reminiscent of the carbonyl peak of an ester (ethyl acetate carbonyl peak 171.4 ppm) than that of a quaternary peak of an anisole (typically around 160.0 ppm).

These initial findings from our NMR spectroscopy analysis were encouraging. Thus, pyrimidine **386** was exposed to nucleophilic, acidic and basic conditions separately. The compound was unaffected by either base or nucleophile (Table 4.5.1. entries 1 and 2). However, in the presence of aqueous hydrochloric acid the pyrimidine backbone was cleaved resulting in guanidine hydrochloride salt formation (Table 4.5.1. entry 3). This was a most rewarding result after numerous, previously disheartening outcomes.

Table 4.5.1. Cleavage of *N*-benzyl-2-amino-4,6-dimethoxypyrimidine.^a



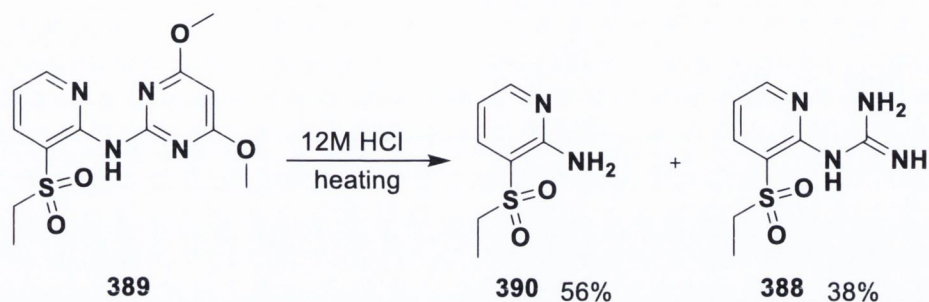
Entry	Additive	Solvent	Yield (%) ^b
1	NH ₂ OH .HCl	EtOH	0
2	1M NaOH	H ₂ O	0
3	2M HCl	H ₂ O	68

^a**386** (1 mmol), additive (10 eq.), solvent (1.5 mL), 80 °C. ^bIsolated yield as the HCl salt.

After several replications of this result it was decided that the synthesis of *N*-aryl-2-amino-4,6-dimethoxypyrimidines by means of Pd catalysed amination reaction was possible and that that the cleavage of compounds of this type would generate our desired aryl guanidines. During a literature search, a single example showed the instability of dimethoxypyrimidines

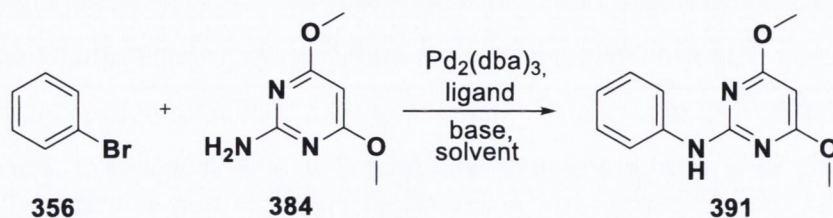
to acidic conditions. Moulard and coworkers reported the preparation of 1-(3-ethylsulfonylpyridin-2-yl)guanidine **388**, as a side-product, when treating *N*-(3-ethylsulfonylpyridin-2-yl)-2-amino-4,6-dimethoxypyrimidine **389** with concentrated HCl (Scheme 4.5.3).²²⁶ This publication further showed the potential for 2-amino-4,6-dimethoxypyrimidine derivatives to act as guanidine precursors.

Scheme 4.5.3.



4.6. Pd-catalysed coupling of aryl bromides with 2-amino-4,6-dimethoxypyrimidine and subsequent cleavage to afford aryl guanidines.

From our previous experience utilising Buchwald-Hartwig amination chemistry (see Chapter 3, Section 3.2.1), we realised that the most efficient method to synthesise *N*-aryl-2-amino-4,6-dimethoxypyrimidines would be to couple aryl bromides with 2-aminopyrimidine-4,6-dimethoxypyrimidine **384**. Optimisation of the coupling of bromobenzene **356** with **384** was therefore initially carried out. From our previous findings we decided it was necessary first to test each of the different ligands that we had examined in Section 3.2.1. as they had afforded the most dramatic change in yields (Table 4.6.1, entries 1 - 5). Different bases and solvents, known to be particularly effective in promoting this type of transformation, were also examined (Table 4.6.1, entries 6 & 7).²⁰⁴

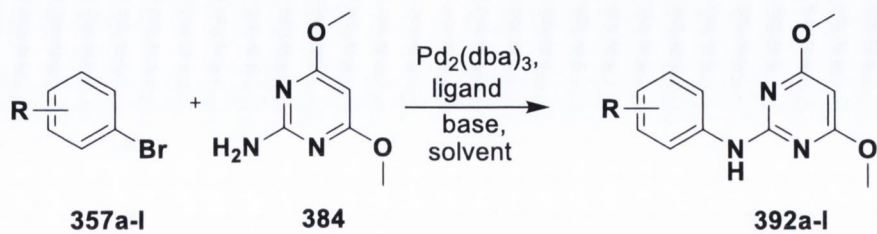
Table 4.6.1. Optimisation of Pd catalysed coupling of bromobenzene **356** with 2-amino-4,6-dimethoxypyrimidine **384**.^a

Entry	Ligand	Base	Solvent	Yield (%)
1	348	NaOt-Bu	toluene	51
2	349	NaOt-Bu	toluene	70
3	350	NaOt-Bu	toluene	70
4	351	NaOt-Bu	toluene	78
5	352	NaOt-Bu	toluene	96
6	352	K ₃ PO ₄	toluene	90
7	352	NaOt-Bu	1,4-dioxane	91
8	352	NaOt-Bu	toluene	97 ^b

^aPd₂(dba)₃ (2 mol%), ligand (3 mol%), NaOt-Bu (1.5 mmol), toluene (1.5 mL per mmol of aryl halide), 95 °C, 8-12 h. ^b2 g scale.

Compound **356** was readily coupled with pyrimidine **384** under Pd-catalysed conditions to afford the desired product **391** in 96% yield (Table 4.6.1, entry 5). This result was also replicable on a multi-gram scale (Table 4.6.1, entry 8). Then, we applied these optimised conditions to a wide range of aryl bromides incorporating electron donating (Table 4.6.2, entries 1 – 3), halogen (Table 4.6.2, entries 4 – 6), electron withdrawing (Table 4.6.2, entries 7 – 11) and sterically cumbersome (Table 4.6.2, entry 12) substituents.

Table 4.6.2. Aryl bromides successfully coupled with 2-aminopyrimidine^a



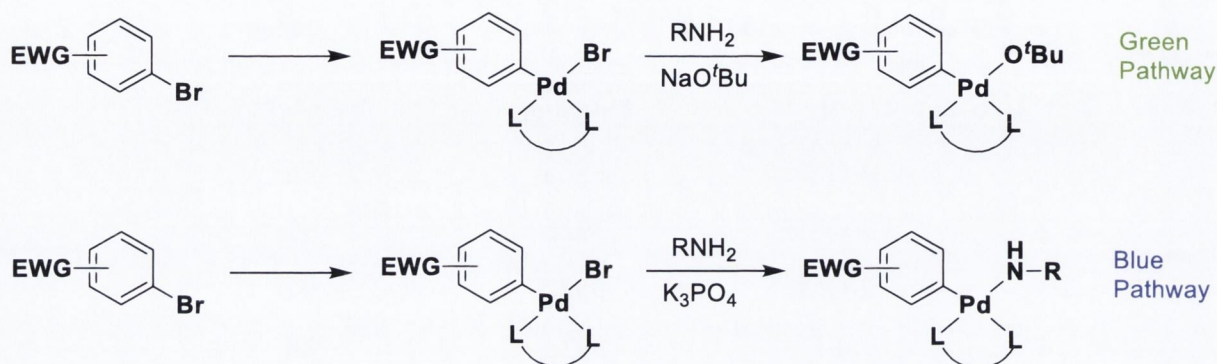
Entry	R	Product	Yield (%)
1	4-OMe	392a	86
2	3-OMe	392b	91
3	2-OMe	392c	97
4	4-F	392d	88
5	3-Br	392e	94
6	2-F	392f	84
7	4-CN	392g	73 ^b
8	3-CN	392h	66 ^b
9	2-CN	392i	68 ^b
10	4-NO ₂	392j	50 ^b
11	3-NO ₂	392k	51 ^b
12	2-Ph	392l	68

^a**384** (1.5 mmol), NaOt-Bu (1.5 mmol), aryl halide (1 mmol), Pd₂(dba)₃ (2 mol %), Xantphos (3 mol %), toluene (1.5 mL/mmol aryl halide), 12 h. 95 °C. ^bK₃PO₄ used as base.

The yields of isolated product range from 50 – 97%, but, in general, were very good to excellent. The slight downfall in yields appears for the aryl bromides with strongly electron withdrawing substituents (Table 4.6.2, entries 7-11). As previously discussed in Section 3.2.1. the use of NaOt-Bu is incompatible with electron withdrawing substituents located on the aryl bromide. We noted that K₃PO₄ was again the base of choice for this reaction. We have discussed the potential for two catalytic cycles through which the Buchwald-Hartwig reaction is thought to proceed (Figure 3.2.1.3, Chapter 3). Potentially, the presence of strongly electron withdrawing groups would favour the pathway involving initial interaction of NaOt-Bu with the Pd centre (Figure 3.2.1.3, **green pathway**), which may be unfavourable. Therefore, replacing the base with non-nucleophilic K₃PO₄ allows the reaction to continue to go through the **blue pathway** and prevents the deleterious effects seemingly associated with

the **green pathway** (for a linear representation of the beginning of the catalytic cycle see Scheme 4.6.1).

Scheme 4.6.1.

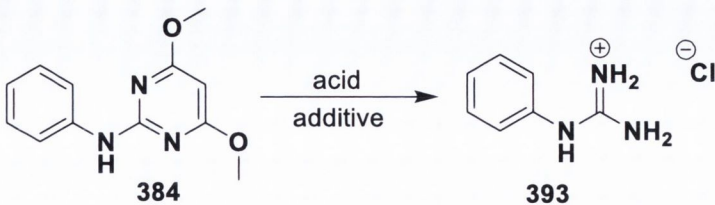


For a discussion on the merits of using Xantphos **352** as a ligand for the coupling of 2-aminopyrimidine and its derivatives please see Section 3.2.1.

4.7. Cleavage of *N*-aryl-2-amino-4,6-dimethoxypyrimidines to yield aryl guanidines.

With our selection of pyrimidines in hand we turned our attention to the optimisation of the cleavage reaction previously discovered in Section 4.5. *N*-phenyl-2-amino-4,6-dimethoxypyrimidine **391** was exposed to a variety of acidic conditions over a range of temperatures (Table 4.7.1).

Table 4.7.1. Optimisation of the acid mediated cleavage of 2-aminopyrimidine **384** to generate phenylguanidine hydrochloride **393**.^a



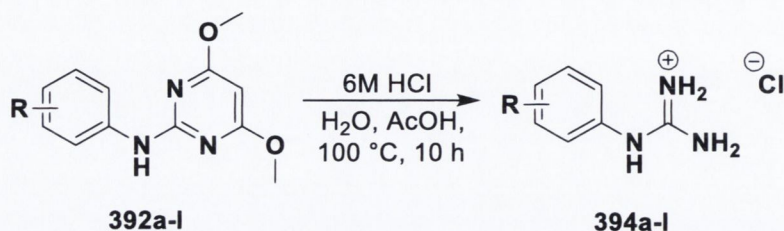
Entry	aq. Acid	Additive	Temp (°C)	Time (h)	Yield (%) ^d
1	2M HCl	-	80	24	0
2	4M HCl	-	80	24	56
3	6M HCl	-	80	24	66
4	8M HCl	-	80	24	66
5	6M HCl	-	100	24	78
6	6M HCl	MeOH	100	24	77
7	6M HCl	MeCN	100	24	80
8	6M HCl	EtOH	100	24	77
9	6M HCl	AcOH	100	24	91
10	6M HCl	AcOH	100	24	100 ^b
11	6M HCl	AcOH	100	12	100 ^b
12	6M HCl	AcOH	100	12	100 ^{b,c}

^a**384** (0.25 mmol), acid (5 mmol), additive (solution of acid prepared from 12N HCl with 1:1 additive/H₂O). ^bThe reaction vessel was wrapped in aluminium foil and the condenser was attached with vacuum grease. ^c2 g scale. ^d Isolated yield.

Preliminary cleavage experiments gave moderate yields and this was presumably due to the poor solubility of the pyrimidine in a number of solvent conditions (Table 4.7.1, entries 1 – 8). A significant improvement was noted when acetic acid was used as a co-solvent ensuring that the starting material was fully soluble (Table 4.7.1, entry 9). A further improvement was observed when the reaction vessel was coated with aluminium foil and the attached reflux condenser was fitted with vacuum grease (Table 4.7.1, entries 10 - 11).. Presumably, this acts to keep the reaction vessel temperature uniform throughout and ensures no change in the concentration of the reaction. Moreover, this reaction was gratifyingly replicable on a multi-gram scale (Table 4.7.1, entry 12).

The pyrimidine family previously synthesised was then exposed to the optimised cleavage conditions to afford a diverse family of aryl guanidines.

Table 4.7.2. Acid mediated cleavage of *N*-aryl-2-amino-4,6-dimethoxypyrimidines.



Entry	R	Product	Yield (%) ^a
1	4-OMe	394a	94
2	3-OMe	394b	84
3	2-OMe	394c	90
4	4-F	394d	74
5	3-Br	394e	87
6	2-F	394f	84
7	4-CN→4-CO ₂ H	394g	62
8	3-CN→3-CO ₂ H	394h	75
9	2-CN	394i	84
10	4-NO ₂	394j	46
11	3-NO ₂	394k	74
12	2-Ph	394l	65

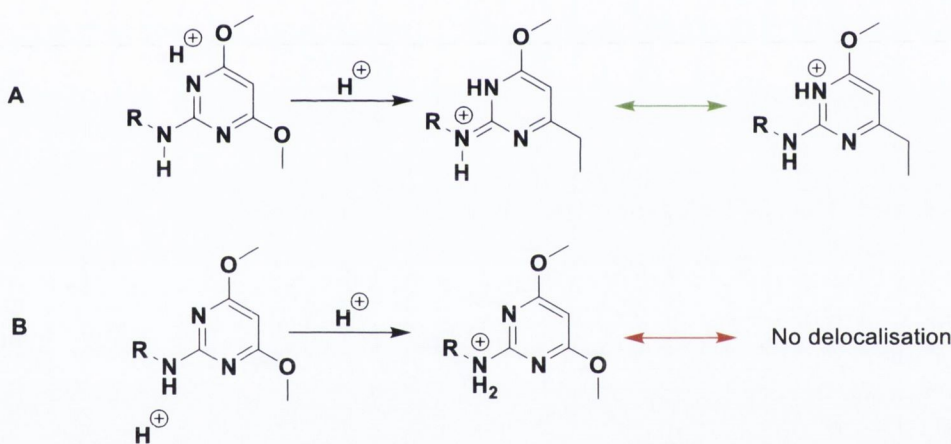
^a Isolated yields.

Yields for this reaction ranged from good to excellent with the exception of the *p*-nitro derivative which gave a meagre 46% yield. This result can be explained by the strong delocalisation of the anilino nitrogen atoms lone pair into the nitro derivatised phenyl ring which would impede the postulated mechanism for this reaction (Scheme 4.7.1). The hydrolysis of the nitrile groups located both *meta* and *para* on the phenyl ring to their

carboxylic acid counterparts was expected (Table 4.7.2, entries 7 & 8). When the hydrolysis of *ortho* nitrile compound **392i** was attempted initial guanidine formation resulted in attack of the guanidine group on the adjacent nitrile group resulting in ring closure to form compound **394i**. Similar reactivity has previously documented for the closure of guanidine on nitrile functionalities.²²⁶

A possible mechanistic explanation of this cleavage reaction is proposed in Scheme 4.7.2. The pK_{aH} of the pyrimidine ring nitrogen of *N*-phenyl-2-amino-4,6-dimethoxypyrimidine has been estimated to be $\sim 3^{218}$ and, therefore, will be protonated in strongly acidic conditions. Protonation will most likely occur on the ring nitrogen due to the ability for delocalisation of the positive charge (Scheme 4.7.1, **A**), addition of a proton to the exocyclic nitrogen would not benefit from this same stabilisation (Scheme 4.7.1, **B**).

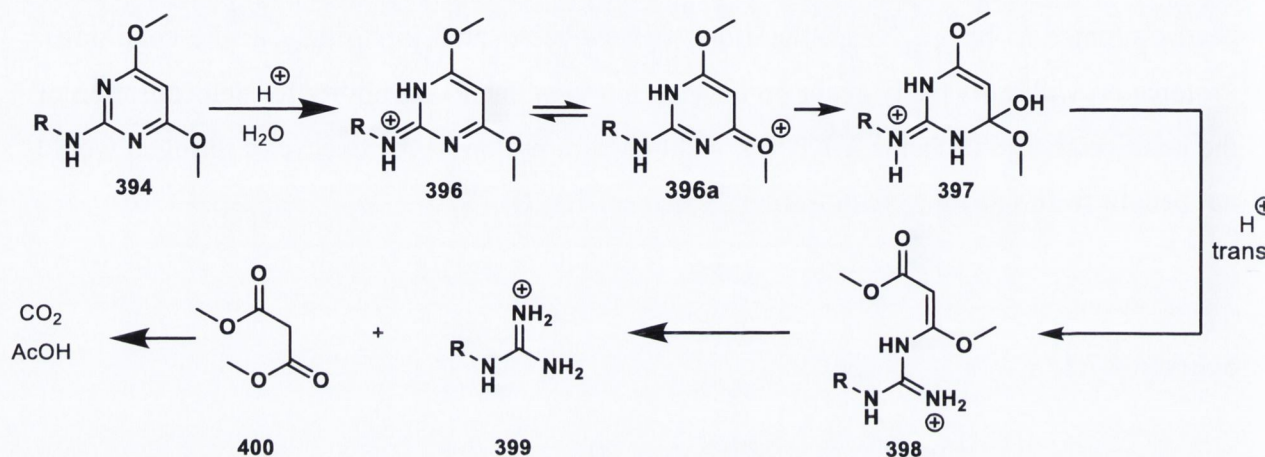
Scheme 4.7.1.



Protonation of the molecule **395** effectively lowers the aromaticity of the pyrimidine ring and makes **396** it more susceptible to nucleophilic attack from a water molecule. Delocalisation of the positive charge over the guanidine like moiety is also possible and this would further facilitate nucleophilic attack. After the attack of the water molecule (Scheme 4.7.2), proton transfer would afford intermediate **397**. Favourable expulsion of the protonated guanidine component from the formation of an ester would generate **398**. Enamine/imine tautomerisation of **398** would form an imine which, under these aqueous acidic conditions, would be hydrolysed to yield the desired guanidine containing compound **399** and dimethyl

malonate **400**. Compound **400** would then be hydrolysed to malonic acid which would decompose to give acetic acid and carbon dioxide²²⁸ thus ensuring no unwanted side products are formed.

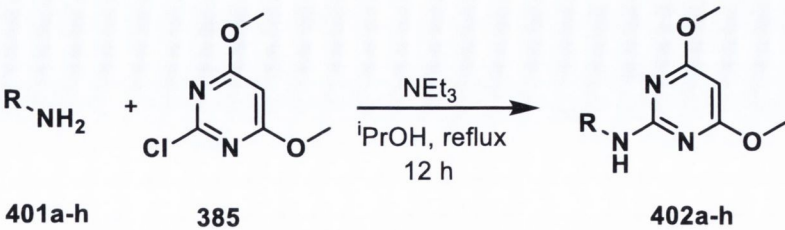
Scheme 4.7.2.



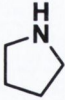
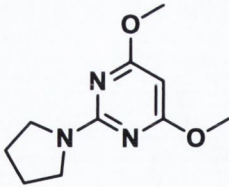
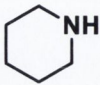
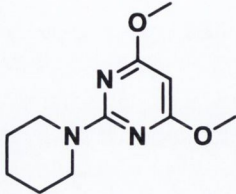
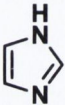
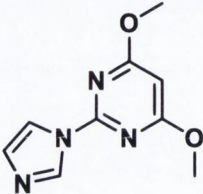
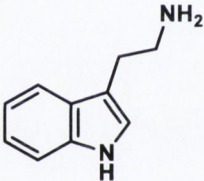
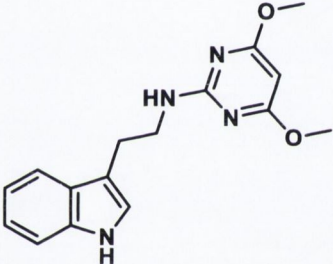
4.8. Synthesis of *N*-alkyl guanidines.

With our synthetic methodology successfully developed for the cleavage of the pyrimidine ring system it seemed logical to extend this reaction to the preparation of *N*-alkyl guanidines. The commercial availability of 2-chloro-4,6-dimethoxypyrimidine **385** enabled the facile synthesis of a number of varying *N*-substituted 2-aminopyrimidines. A selection of amines was reacted with **385** in the presence of a base (triethylamine) while heating to reflux in *i*PrOH to produce our desired products. The pyrimidine system readily underwent nucleophilic aromatic substitution with both primary (Table 4.8.1. entries 1, 2, 3, 9) and secondary amines (Table 4.8.1. entries 4 - 8)

Table 4.8.1. Synthesis of *N*-substituted 2-amino-4,6-dimethoxypyrimidines

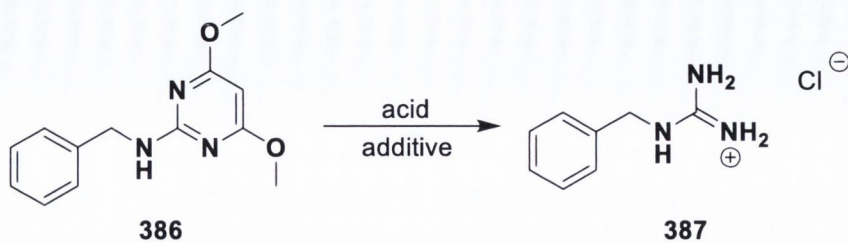


Entry	Substrate	Product	Yield (%) ^a
1		 402a	82
2		 402b	82
3		 402c	86
4		 402d	88
5		 402e	84

6		 402f	87
7		 402g	79
8		 402h	75
9		 402i	54

^a Isolated yields.

Our next challenge was to apply the cleavage reaction developed in Section 4.7 to the library of *N*-substituted 2-aminopyrimidines presented in Table 4.8.1. We began our investigations by utilising the conditions of 6M HCl in a combination of H₂O and AcOH to cleave the pyrimidine ring of compound **386**, which had previously proved to be very useful as a test (Table 4.8.2. entry 1). Full conversion of **386** into **387** was an encouraging result and we envisioned that more gentle conditions may be sufficient to hydrolyse this family of compounds and accordingly we optimised such conditions.

Table 4.8.2. Optimisation of the acid-mediated cleavage of **386** to generate benzyl guanidine hydrochloride **387**.

Entry	aq. Acid	Additive	Temp (°C)	Time (h)	Yield (%) ^a
1	6M HCl	AcOH	100	12	100
2	1M HCl	-	80	10	46
3	2M HCl	-	80	10	75
4	4M HCl	-	80	10	90

^a Isolated yield

Initial attempts at cleavage with weakly acidic conditions (Table 4.8.2, entry 2) gave poor results while increasing the concentration of hydrochloric acid led to the optimal conditions of 4M HCl at 80 °C being obtained (Table 4.8.2, entries 3 and 4) . It is thought that the use of milder conditions for the cleavage of alkyl derivatised aminopyrimidines in comparison with *N*-aryl 2-amino-4,6-dimethoxypyrimidines (4M HCl at 80 °C as opposed to 6M HCl at 100 °C) is due to the availability of the lone pair of the exocyclic nitrogen of compound **386**. This availability would most likely enable donation of the lone pair into the aromatic system of the pyrimidine enabling facile protonation of one of the ring nitrogens subsequently leading to hydrolysis. In comparison, the lone pair of the exocyclic nitrogen of **391** could be equally delocalised into the phenyl ring, preventing facile protonation of the pyrimidine. Examination of the calculated pK_{aH} values²¹⁸ of *N*-phenyl-2-amino-4,6-dimethoxypyrimidine **391** and of *N*-benzyl-2-amino-4,6-dimethoxy pyrimidine **386** indicate values of 3 and 4.2 respectively. This, although a calculated value, is a good indicator of the ease of protonation of the pyrimidine ring system in each of the two cases (Figure 4.8.1).

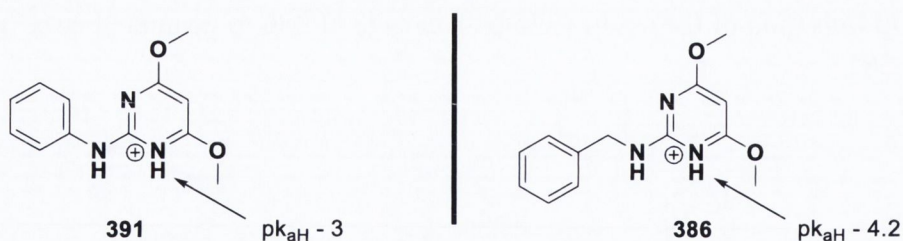
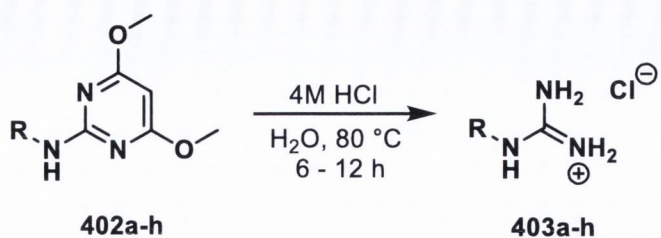
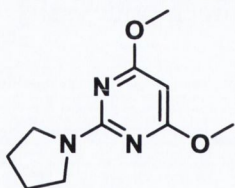
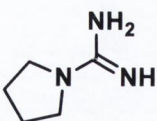
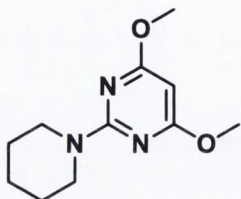
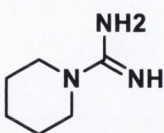
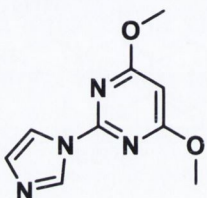
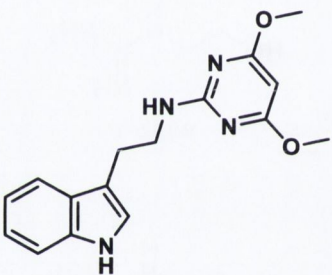


Figure 4.8.1. Comparison of calculated pK_{aH} values of **391** and **386**.

The optimised cleavage reaction was then applied to the synthesised pyrimidines shown in Table 4.9.1. Pleasingly, the conversion from pyrimidine into guanidine was afforded under these conditions in good to excellent yields (Table 4.8.3, entries 1, 3, 4, 5, 6, 7). The poor yields associated with entry 2 was due to the formation of exceptionally polar products which proved to be challenging in the purification step.

Table 4.8.3. Synthesis of *N*-alkyl guanidinium hydrochloride salts under ring cleavage conditions.

Entry	Substrate	Product (HCl salt)	Yield (%) ^a
1	402a	403a	82
2	402b	403b	45
3	402c	403c	78 ^b
4	402d	403d	84
5	402e	403e	66

6	 402f	 403f	91
7	 402g	 403g	88
8	 402h	 403h	>95
9	 402ih	Complex mixture	0

^a Isolated yield. ^b Dihydrochloride salt.

Unsurprisingly, exposure of 2-(1*H*-imidazol-1-yl)-4,6-dimethoxypyrimidine **402g** (Table 4.8.3, entry 7) to the acidic cleavage conditions resulted in favourable protonation of the imidazole moiety which subsequently led to carbon-nitrogen bond cleavage presumably through nucleophilic attack of water to the pyrimidine ring. The indole ring system of **402h** also proved susceptible to these conditions leading to the formation of a complex mixture of products which could not be characterised (Table 4.8.3, entry 9).

To further explore the synthetic utility of the developed cleavage reaction and for seeing a potential application of the 2-amino-4,6-dimethoxypyrimidine group as a precursor of guanidine groups in amino acid synthesis, it was decided to investigate the ability to utilise this guanidine precursor in conjunction with amino protecting groups such as Cbz-, Piv- and

Fmoc-. These groups were chosen as they are common in the preparation of amino acids and because they could potentially be used with 2-amino-4,6-dimethoxypyrimidine group in an 'orthogonal' manner. Thus, ethylenediamine (in excess) was reacted with compound **385** to form **402c**. This was in turn reacted with the requisite protecting group precursor to afford the desired compounds **404a-c** (for a more detailed account please see Chapter 8). Each of these protected substrates was then exposed to the optimised cleavage conditions with the hope of obtaining the corresponding guanidine and that the other protecting group would be retained. In the case of both the Cbz- protected analogue **404a** and the Piv- protected compound **404b**, the two protecting groups were both removed to afford deprotected guanidine **403c** (Table 4.8.4, entry 1 – 2). However, as was expected, Fmoc- protected **404c**, underwent ring cleavage but retained the Fmoc- protecting group which is known to be typically removed under basic conditions (Table 4.8.4, entry 3).²²⁹ This further shows the utility of this pyrimidine protecting group.

Table 4.8.4. Investigating protecting group orthogonality.

$\text{R} = \text{Fmoc, Piv, Cbz}$

404a-c **403c, 405a**

Entry	Substrate	Product	Yield (%) ^a
1	404a	403c	65
2	404b	403c	78
3	404c	405a	86

^a Isolated yield.

4.9. Application of the developed cleavage reaction to the synthesis of α_2 -adrenoceptor antagonists.

The role of guanidine containing compounds as α_2 -adrenoceptor antagonists was introduced in Section 3.1. From previous studies in the group, two compounds (Figure 4.9.1, **340** and **341**) had been discovered showing particularly good affinity and antagonism for the α_2 -adrenoceptor as well as antidepressant activity in animal models.^{145,230-232}

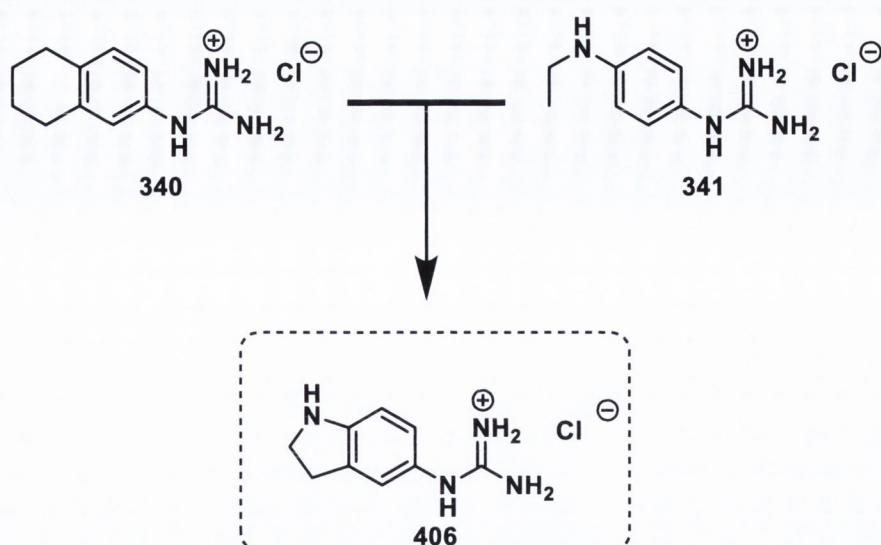
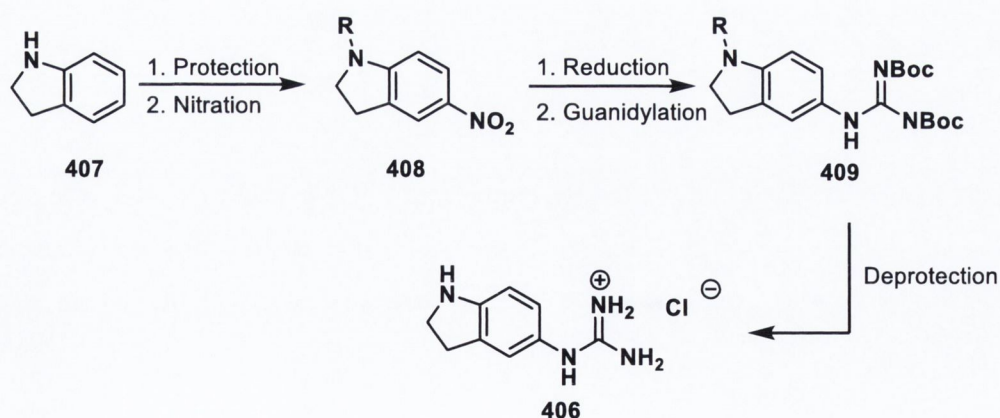


Figure 4.9.1. Development of new potential α_2 -adrenoceptor antagonist.

From these two structures a new compound was designed containing structural similarities to both. This indoline scaffold incorporates both the sterically demanding cyclohexyl ring of **340** along with the increased hydrogen bonding abilities of **341**. Previous synthetic studies in the group²³³ involved a cumbersome approach towards the preparation of **406** (Scheme 4.9.1).

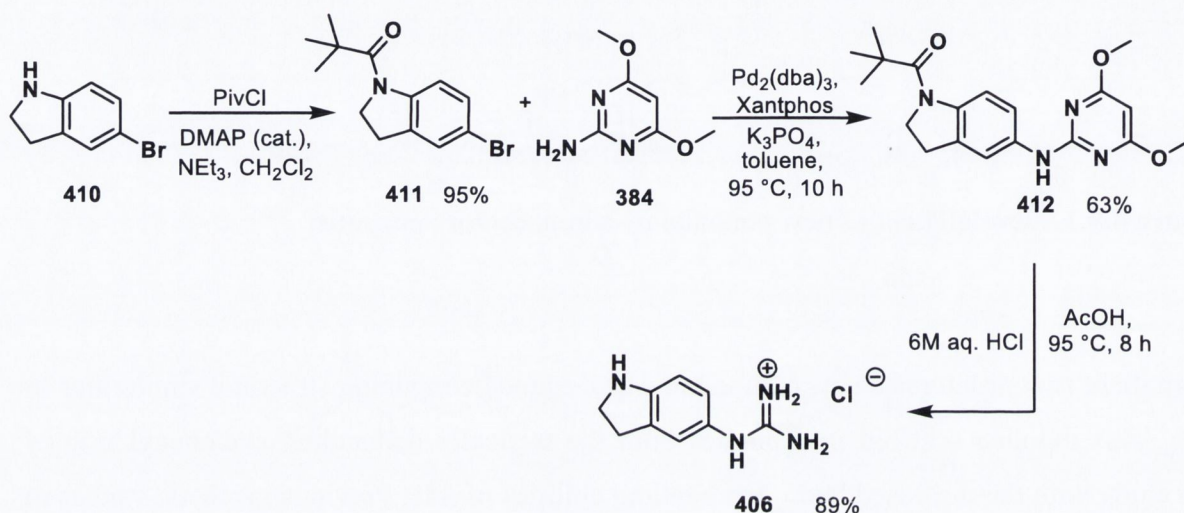
Scheme 4.9.1.



The ability of the newly developed cleavage reaction to access guanidine **406** quickly and efficiently was evident. The protection of 5-bromoindoline **410** with pivaloyl chloride generated **411**, which in turn was successfully coupled with 2-amino-4,6-

dimethoxypyrimidine **384** utilising the conditions shown in Table 4.6.1. to afford compound **412** in an adequate yield (63%). Then, the acid promoted deprotection of the pivaloyl group and concomitant cleavage of the pyrimidine ring yielded the corresponding target compound **406** in excellent yield (89%, Scheme 4.9.2).

Scheme 4.9.2.



Furthermore, compound **406** was evaluated for biological activity by measuring its affinity for the α_2 -adrenoceptor (pK_i value). The pK_i (the log of the binding constant for a particular drug) is a measure of how effectively a compound binds to a given receptor and this value is determined by the ability of the drug candidate to displace a compound with known high affinity for the receptor. The α_2 -adrenoceptor pK_i values of antagonists **340** and **341** are 7.11 and 6.58, respectively.

Unfortunately, in the case of compound **406** a relatively low pK_i value of 4.89 was obtained and such a result did not encourage further investigations into whether or not this compound acts as an α_2 -adrenoceptor antagonist as its binding affinity is too low for it ever to be an effective drug candidate (Figure 4.9.2).

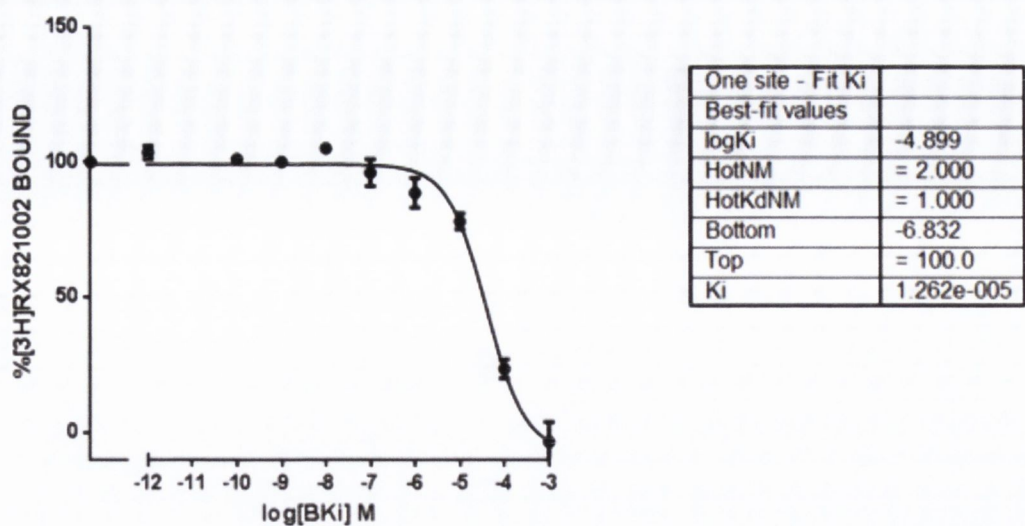


Figure 4.9.2. Determined pK_i value for compound **406** (Courtesy of Michela McMullan).

Despite the disappointing biological results obtained for compound **406** its facile synthetic route shows the utility of the developed cleavage reaction.

5. Spiro guanidine amins.

The prevalence of the guanidine group in natural products has been highlighted in the Introduction section of this thesis. In this Chapter, selected examples of the synthesis of spiro guanidine amins **19** are presented (Figure 5.1.).

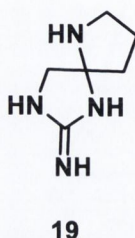


Figure 5.1. The spiro guanidine amins **19** functionality.

5.1. Spiro guanidine amins in natural products and selected syntheses of this motif.

The presence of a spiro guanidine amins moiety **19** is prevalent in natural product chemistry.³⁶ In particular, the pyrrole-2-aminoimidazole family of marine natural products often incorporate this interesting motif. These natural products predominantly originate from the *Agelasidae*, *Halichondridae* and *Axinellidae* families of marine sponges.³⁶ Looking at the proposed biosynthesis of such natural products, the origin of this molecular structure is evident. This molecular feature stems from central precursor clathrocin **413** and brominated analogue oridin **414** (Figure 5.1.1).

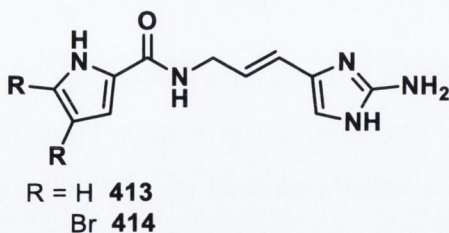


Figure 5.1.1. Structures of clathrocin (**413**, R=H) and oridin (**414**, R= Br).

Biosynthetic pathways proposed by Kitagawa²³⁴ and Braeckman²³⁵ propose the selective guanidylation of ornithine **415** to form intermediate **416** which upon cyclisation and

oxidation could generate the necessary imidazole precursor **417** (Figure 5.1.2). When combined with **418**, the oxidised pyrrole analogue of proline **203**, clathrocin **413** could be formed.

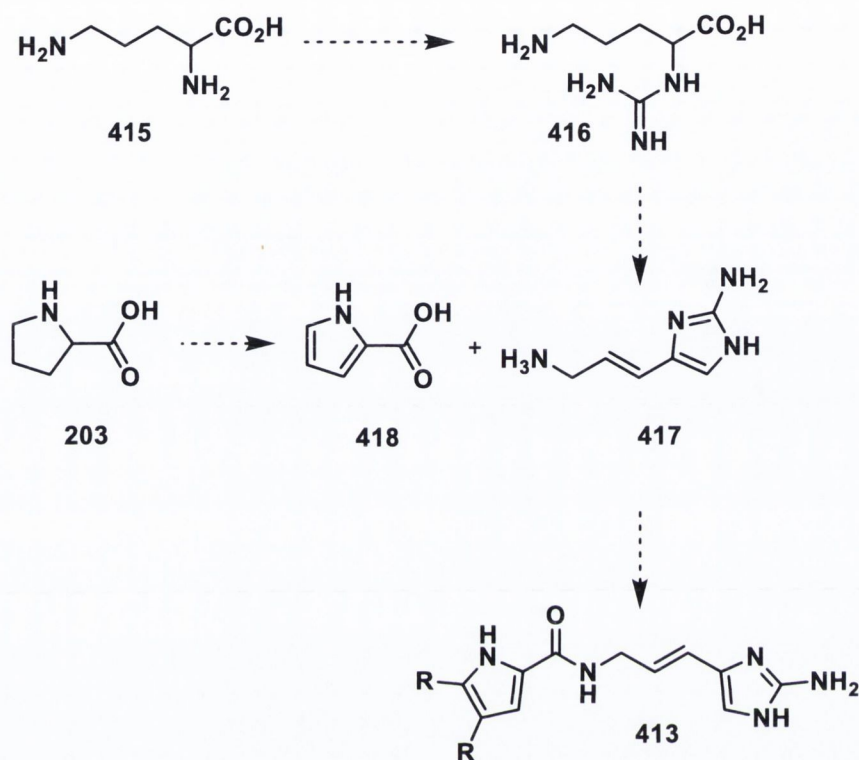


Figure 5.1.2. Proposed biosynthesis of clathrocin **413**.

The formation of the spiro guanidine aminal fragment is then proposed to occur via an oxidative polycyclisation reaction (Figure 5.1.3). This chemical behaviour of imidazoles is typically seen in the biosynthesis of spiro guanidine amins.

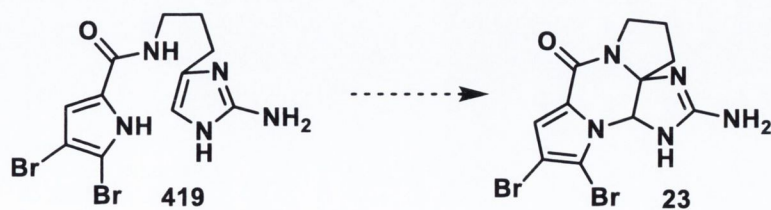
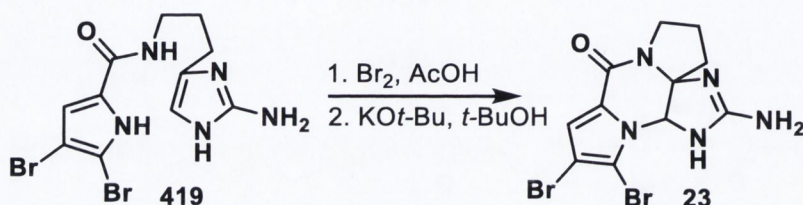


Figure 5.1.3. Oxidative cyclisation of dihydrooridin **419** to form dibromophakellin **23**.

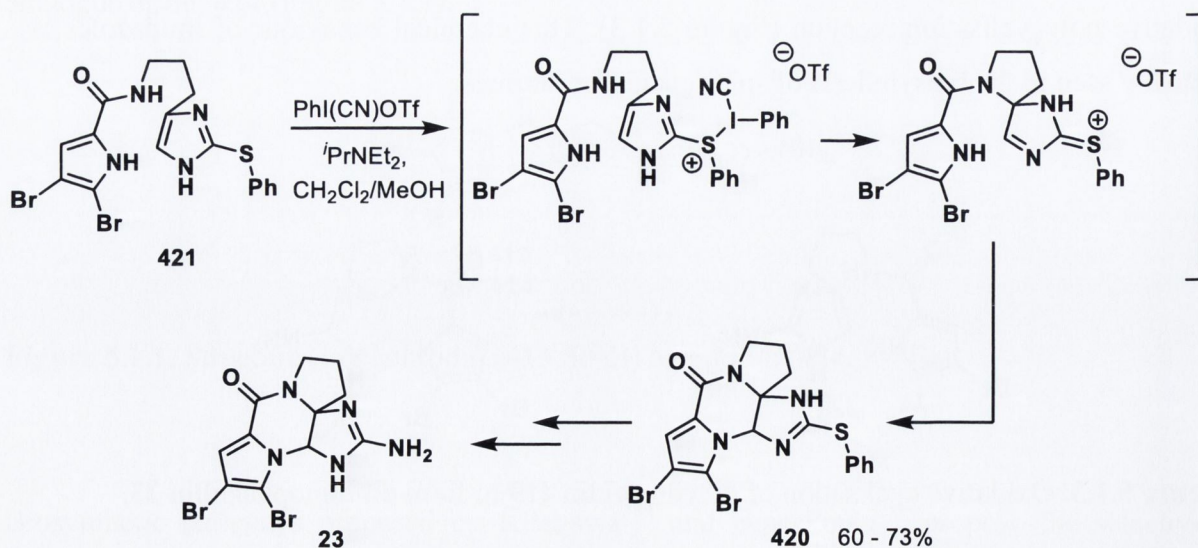
In an effort to investigate the mechanistic feasibility of this reaction Büchi and co-workers (1982) designed a laboratory experiment to mimic this reactivity (Scheme 5.1.1).²³⁶ As desired, exposure of **419** to bromine and, then, basic conditions, generated **23**. The reactivity displayed here reinforced the proposed biosynthetic pathway. This reactivity was again displayed in a synthesis of **23** by Horne in 2002.²³⁷

Scheme 5.1.1.



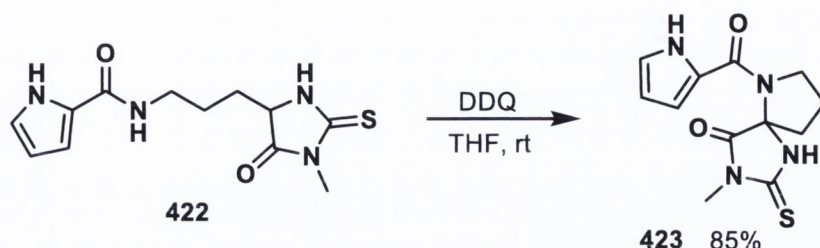
In an effort to mimic the oxidative polycyclic cyclisation that occurs in the biosynthesis of **23** (Figure 5.1.3), Feldman and co-workers (2007/2008) implemented a novel synthetic route to facilitate the formation of amination **420**. Oxidative cyclisation of phenylthiolated dihydrooridine derivative **421** triggered by a Pummerer reaction generated late stage intermediate **420** which could subsequently be converted into **23** (Scheme 5.1.2).²³⁸

Scheme 5.1.2.



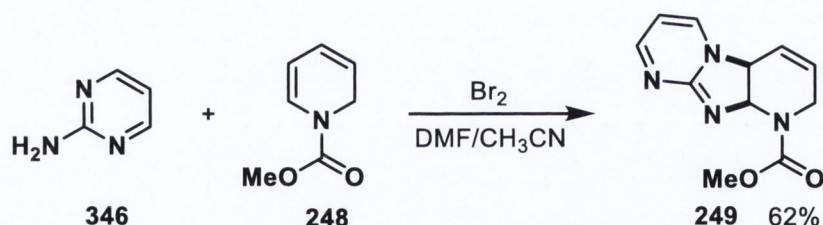
In another amination forming reaction, Molina *et al.*²³⁹ designed a highly effective oxidative spirocyclisation of thiohydantoin **422** to generate phakellin analogue **423** (Scheme 3.6.1.4.). This step is facilitated by the use of DDQ (DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone).

Scheme 5.1.3.



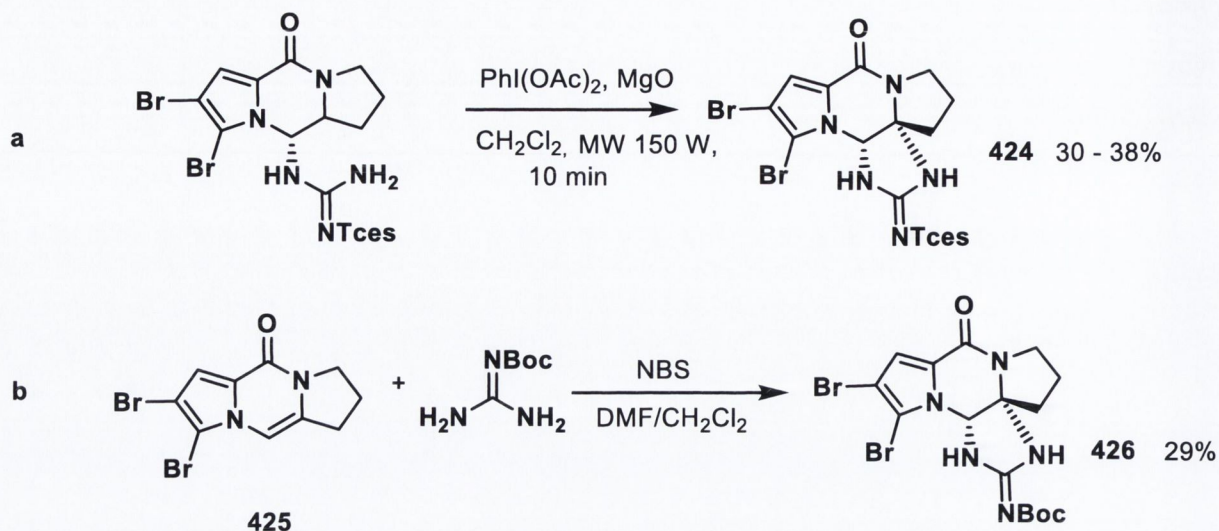
Al-Mourabit *et al.* have effectively synthesised numerous pyrrole imidazole alkaloids by a variety of intriguing methods.^{153b} Their use of 2-aminopyrimidine **346** as a guanidine surrogate is of particular interest. Addition of **346** to conjugated enecarbamate **248** facilitates the amination framework **249** in a concise and effective manner (Scheme 5.1.4).

Scheme 5.1.4.



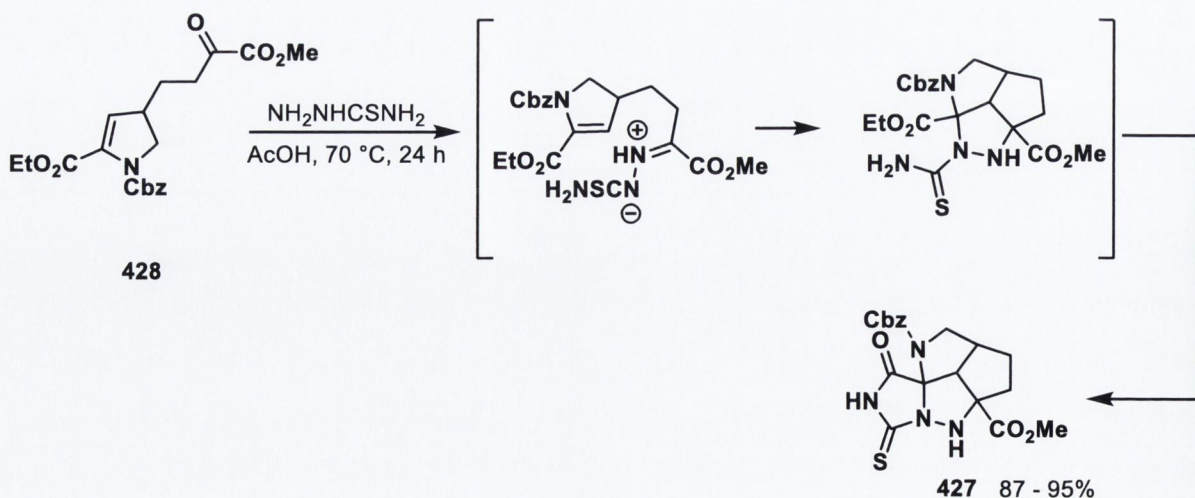
Since 2008 a number of reports detail late stage guanidine introduction and cyclisation during the synthesis of pyrrole–imidazole alkaloids. Of particular note are the publications from Romo²⁴⁰ and separately from Tepe.²⁴¹ Romo uses a potent C(sp³)-H activation reaction to furnish protected dibromophakellin **424** and form the desired amination moiety (Scheme 5.1.5, route **a**), while Tepe utilises NBS olefin activation to facilitate guanidine addition across the olefin **425** to form dibromophakellin precursor **426** (Scheme 5.1.5, route **b**).

Scheme 5.1.5.



In an elegant study towards another spirocyclic guanidine aminal natural product, palau'amine **21**, Overman and co-workers (1997) designed a cycloaddition reaction to form the carbon-nitrogen bonds of aminal **427**.²⁴² When exposed to acetic acid at 70 °C, compound **428** and thiosemicarbazide underwent [3+2] dipolar cycloaddition and subsequent acylation to deliver tetracycle **427** in excellent yield (Scheme 5.1.2). This method portrays an ingenious approach for the rapid generation of structural complexity.

Scheme 5.1.6.



5.2. α_2 -Adrenoceptor agonist dibromophakellin.

The discovery of dibromophakellin **23** as an agonist of the α_2 -adrenoceptor, stimulated the idea in Rozas' group that structural modifications to the spiro guanidine amina backbone may provoke an antagonistic effect. As part of the medicinal chemistry program in Rozas' group, new and effective structural motifs are constantly required to investigate agonism, antagonism and receptor affinity of new molecules at the α_2 -adrenoceptor. In an attempt to provide rapid access to this architecture, a novel cascade cyclisation reaction was envisaged (Figure 5.2.1).

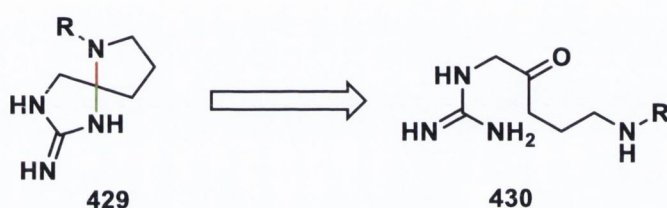


Figure 5.2.1. Retrosynthetic analysis of spiro guanidine amina derivative **429**.

The aim for this route was to devise a highly efficient synthesis which could afford large quantities of the required amina **19** that could be further derivatised to produce a library of guanidine containing compounds to be investigated for biological activity.

5.3. First generation synthetic route.

First, we planned to prepare an open ring variation of dibromophakellin **23** (Figure 5.3.1). This variation was thought to play a significant role in agonist/antagonist differentiation. Previous studies have showcased the substantial effects minute conformational changes can exhibit on the biological role of the ligand.^{145,190,230-232}

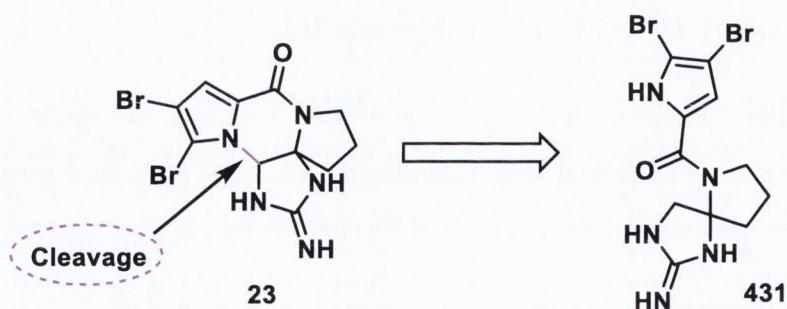


Figure 5.3.1. Desired structural change of **23**.

Retrosynthetic analysis of **431** led to the linear molecule **432** (Fig. 5.3.2), which was proposed to be rapidly generated through known synthetic procedures.

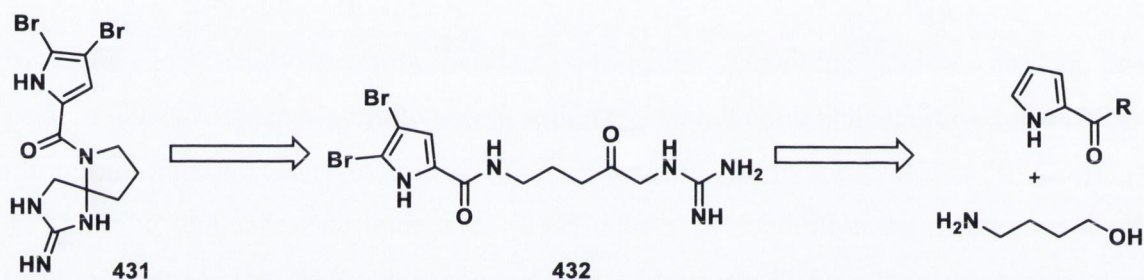
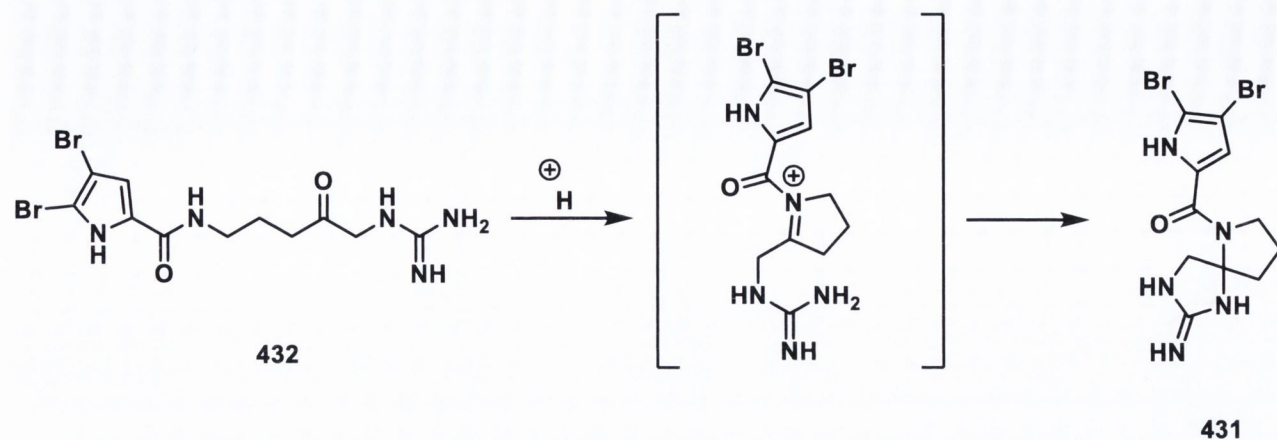


Figure 5.3.2. Retrosynthetic analysis of **431**.

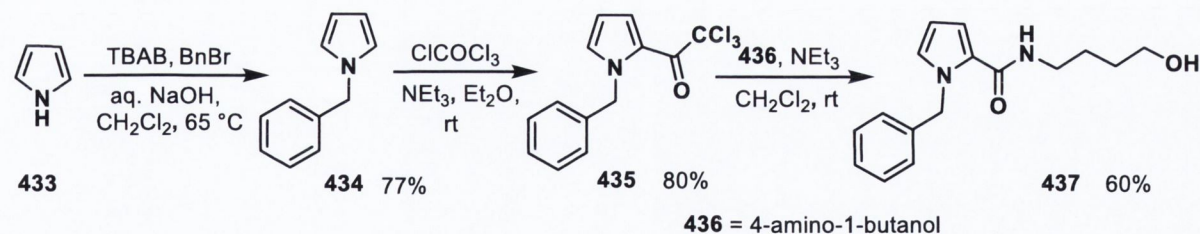
This retrosynthesis was centred on a late stage amide ketone condensation of compound **432** which should be directly followed by guanidine attack on the highly electrophilic carbon to form spiro compound **431**. Precedence for amide condensation has previously been observed utilising formic acid²⁴³ and it was expected that a range of both Brønsted and Lewis acids would be able to ameliorate this transformation. Under mildly acidic conditions it was imagined that iminium cation formation would coax guanidine attack (Scheme 5.3.1).

Scheme 5.3.1.



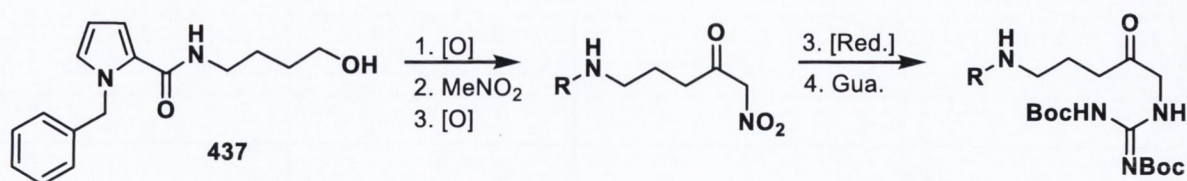
Our synthetic endeavour began with pyrrole **433** which was benzyl protected. Prior distillation of **433** was necessary to afford **434** in good yield which could advantageously be purified using vacuum distillation. Alkylation at the nitrogen was achieved by the use of sodium hydroxide to generate the sodium salt of pyrrole, an ionic species which favours reaction at nitrogen as opposed to ring substitution.²⁴⁴ Exposure of **434** to trichloroacetyl chloride furnished the trichloroacetate appendage at the nucleophilic 2-position of the pyrrole ring in good yield generating **435**. The use of 4-amino-1-butanol **436** to attack the trichloroacetate moiety began the formation of the linear aspect of the molecule, yielding alcohol **437** as a brown solid in acceptable yields (Scheme 5.3.2).

Scheme 5.3.2.



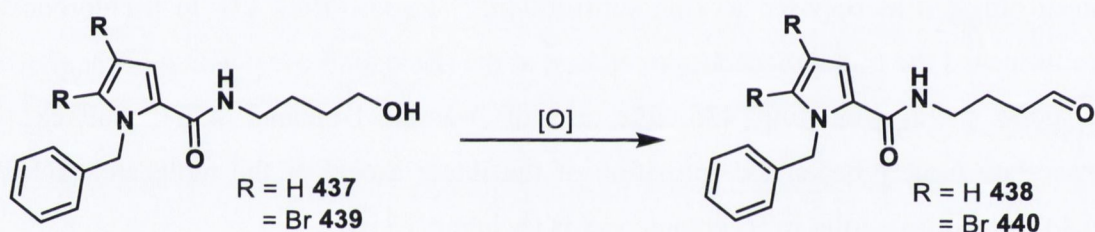
Generation of the α -guanidino ketone featured in **432** was planned through a series of known chemical transformations including oxidation of alcohol **437** to its aldehyde analogue. This would be followed by a Henry reaction, secondary alcohol oxidation, nitro reduction and guanidylation (Scheme 5.3.3).

Scheme 5.3.3.



With alcohol **437** in hand, a number of oxidising conditions were investigated (Table. 5.3.1. entries 1-5). Even though initial oxidation reactions proved to be problematic it was possible to generate the desired aldehyde as indicated by TLC (Figure 5.3.3, plate A). Attempts to purify aldehyde **438** by column chromatography led to a multitude of impurities. Replication of this reaction also led to a number of varying results.

Table 5.3.1. Conditions attempted for oxidation of primary alcohols **437** and **439**.^a



Entry	Substrate (R =)	Conditions	Yield (%)
1	H	IBX	61
2	H	DMP	50
3	H	DMP/NaHCO ₃	55
4	H	DMP/Pyridine	51
5	H	Swern	43
6	Br	IBX	47
7	Br	Swern	39

^a BRSM. For a full description of experimental conditions see Chapter 8.



A

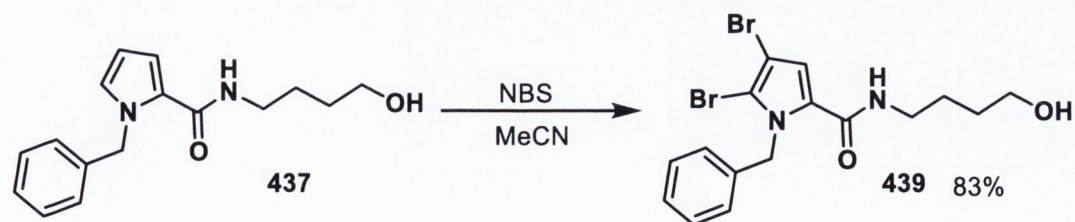


B

Figure 5.3.3. Typical TLC analysis of oxidation of alcohol **437** (A) and subsequent Henry reaction on crude aldehyde (B), (iodine stain, 1st TLC lane starting alcohol, 2nd TLC lane starting material and reaction mixture, 3rd TLC lane reaction mixture).

It was thought that the presence of the highly reactive pyrrole moiety might be responsible for the formation of side products as it is known to be sensitive to oxidising conditions.²⁴⁵ In an effort to harness the internal reactivity of this molecule the brominated analogue of alcohol **439** was synthesised (Scheme 5.3.4). Upon exposure to oxidative conditions (Table. 5.3.1. entries 6 and 7), this strategy had no effect on the uncontrollable nature of this reaction. After extensive attempts at purification involving differing column chromatography conditions it was decided that use of the crude aldehyde may be beneficial.

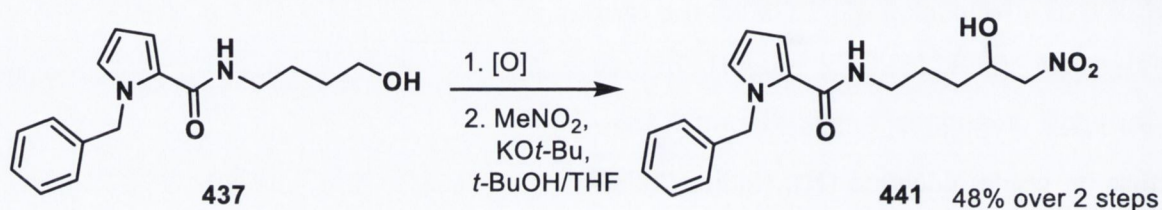
Scheme 5.3.4.



The next step in the synthesis required a Henry reaction to introduce the alkyl nitro moiety. Exposure of crude aldehyde to Henry conditions generated nitro product **441** along with a

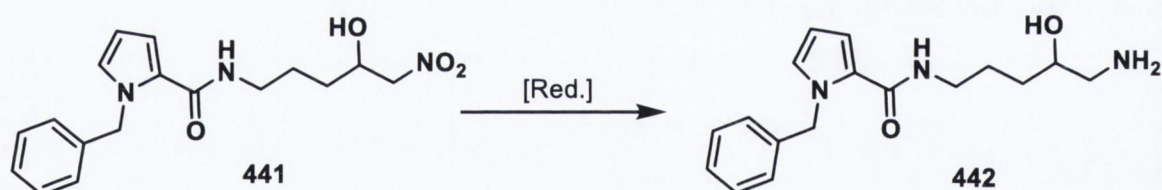
number of impurities (Fig 5.3.3, plate **B**). However, after purification **441** could be easily isolated as a yellow oil (Scheme 5.3.5) in an acceptable yield over the two steps (48%). This step became the initial bottleneck in our endeavour towards **432** as scale up complications were a major hindrance, and the realisation that another oxidising step was going to be required seemed daunting.

Scheme 5.3.5.



Therefore, attempts to reduce the nitro moiety to an aliphatic amine became the primary focus of our attention. A number of reducing metal conditions were all efficient in this synthetic step; however, the exceptional polarity of the amino alcohol **442** produced had not been anticipated (Table 5.3.2; entries 1-3) and led to purification issues.

Table 5.3.2. Conditions attempted for reduction of nitro compound **441**.^a



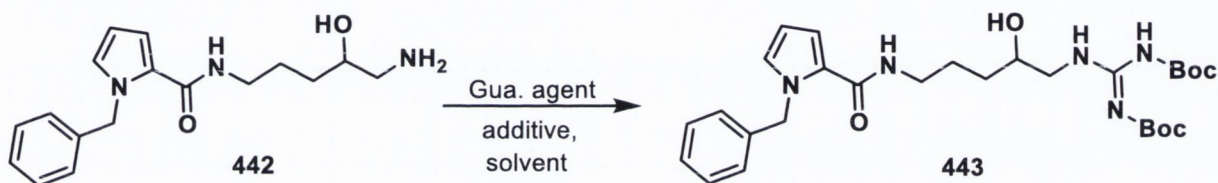
Entry	Conditions	Yield (%) ^b
1	SnCl ₄	39
3	Zn	30
4	H ₂ , Pd/C	74

^a For a full description of experimental conditions see Chapter 8. ^b Isolated yields.

The most efficient reduction process was found to be the use of hydrogenative conditions in the presence of catalytic Pd/C (Table 5.3.2, entry 4). Gratifyingly, this afforded amino alcohol **442** without the need for extensive purification.

Following this successful reduction our focus was guided towards the guanidylation of **442**. A number of guanidylating conditions were investigated for this transformation (Table 5.3.3, entries 1 - 7), with *N,N'*-bis-Boc-thiourea **128** proving to be the most effective (Table 5.3.3, entry 1).

Table 5.3.3. Conditions attempted for guanidylation of amine **442**.^a



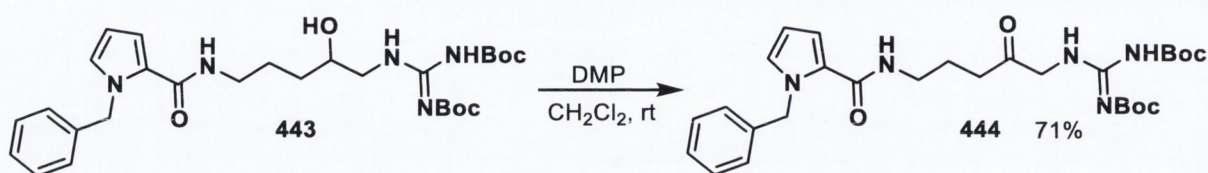
Entry	Gua. Agent	Conditions	Yield (%)
1	 128	HgCl ₂ , CH ₂ Cl ₂ , rt	65
2	128	HgCl ₂ , DMF, 50 °C	46
3	128	CH ₂ Cl ₂ , rt	32
4	128	DMF, 50 °C	37
5	 127	HgCl ₂ , CH ₂ Cl ₂ , rt	31
6	 443	HgCl ₂ , CH ₂ Cl ₂ , rt	0
7	443	CuCl ₂ , CH ₂ Cl ₂ , rt	0

^aFor a full description of experimental conditions see Chapter 8. ^b*N,N'*-Bis-Boc-thiourea **128** and *N,N'*-di-Cbz-thiourea **443** were prepared according to literature procedures.¹⁹²

This reaction worked efficiently when HgCl_2 was used as the Lewis acidic promoter to stimulate desulfurisation. Analogous experiments either without Lewis acid (Table 5.3.3, entries 3 and 4) or with CuCl_2 as an alternative Lewis acid (Table 5.3.3, entry 5) gave inferior results.

Oxidation of **443** to ketone **444** proved slightly less problematic than initially expected and gave additional insight into the problematic initial oxidation reaction (Scheme 5.3.6).

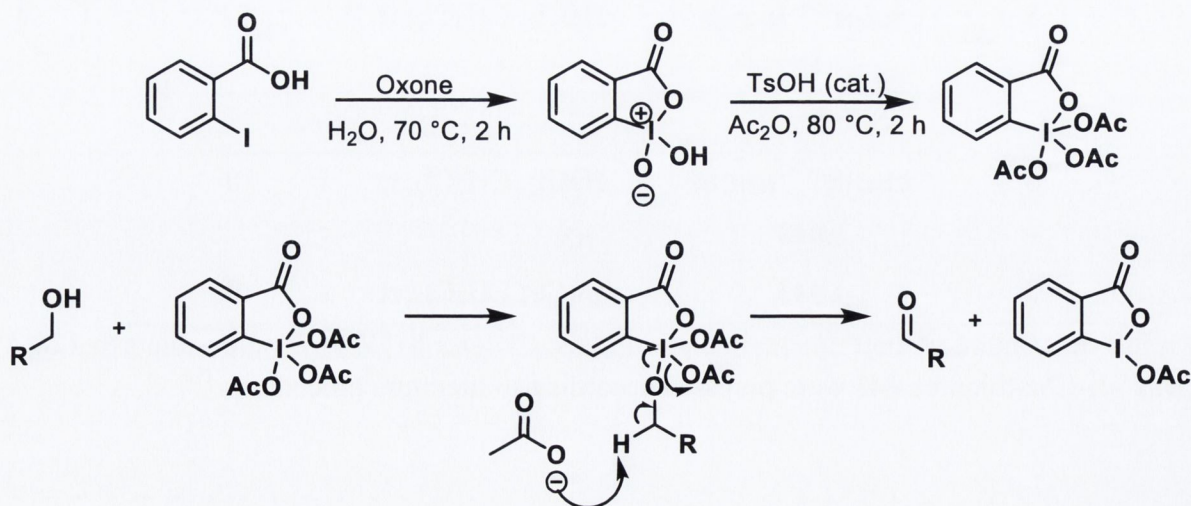
Scheme 5.3.6.



The relative ease of oxidation in this synthetic step suggests that the aldehyde present in product **438** (Table 5.3.1) was the source of problems in the first oxidation step. Potentially, the aldehyde was being attacked by the nucleophilic amide or pyrrole functionalities.

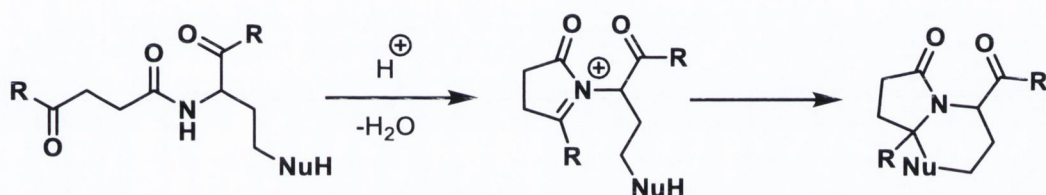
In this reaction, freshly prepared Dess-Martin periodinane (DMP, Scheme 5.3.7) proved to be an essential reagent for the oxidation of secondary alcohol **443** to α -guanidino ketone **444** (Scheme 5.3.6).

Scheme 5.3.7.



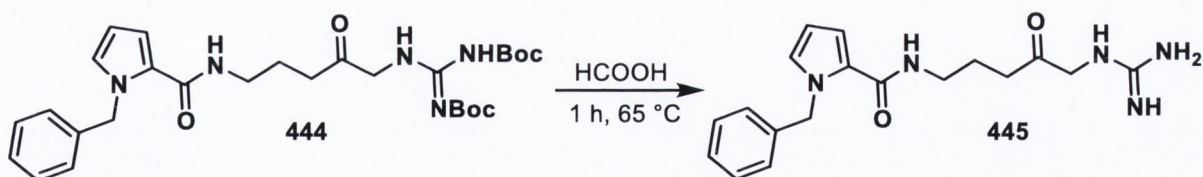
With our desired cyclisation precursor in hand we shifted our focus to transform **444** into the desired final compound **431**. With the hope that formic acid mediated condensation between an amide and a ketone could potentially induce our first ring closure, we attempted the conditions described by Nielsen and co-workers.²⁴³ In their paper, they describe the condensation of an amide onto a ketone to form an acyl iminium cation, which, when in the presence of a suitable nucleophile, can be captured (Scheme 5.3.8).

Scheme 5.3.8.



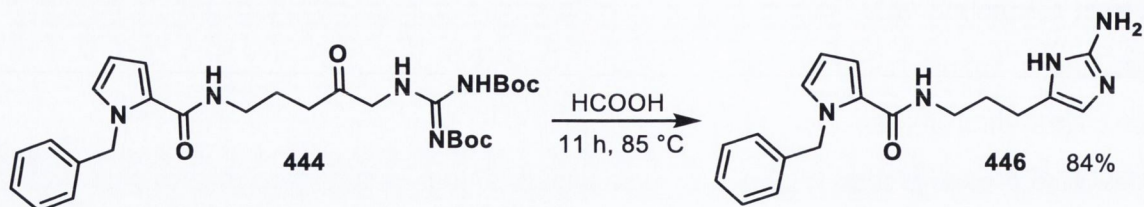
Initial experimentation using formic acid to achieve ring closure was unsuccessful. Upon exposure to formic acid at elevated temperatures Boc deprotection occurred leaving a highly polar guanidine product **445** (Scheme 5.3.8, as determined by TLC analysis).

Scheme 5.3.8.



Following this result, it was realised that the deprotected guanidine **445** should still be a suitable precursor for the cyclisation reaction to occur. Compound **444** was therefore exposed to formic acid at elevated temperatures of 80 °C for 11 h. However, this generated the undesired natural product dihydroclathrocin **446** in its benzyl protected form (Scheme 5.3.9). The guanidinium cation was proving to be more nucleophilic than the amide functionality and preferentially reacting with the ketone.

Scheme 5.3.9.



Although this compound is a precursor for dibromophakellin **23** it did not afford our desired aminal guanidine scaffold and, therefore, another synthetic route had to be devised.

5.4. Second generation synthetic route.

The condensation of a primary amine with a ketone is a ubiquitous reaction in chemistry and was therefore thought to be a more facile route towards our planned bicycle (Figure 5.4.1).

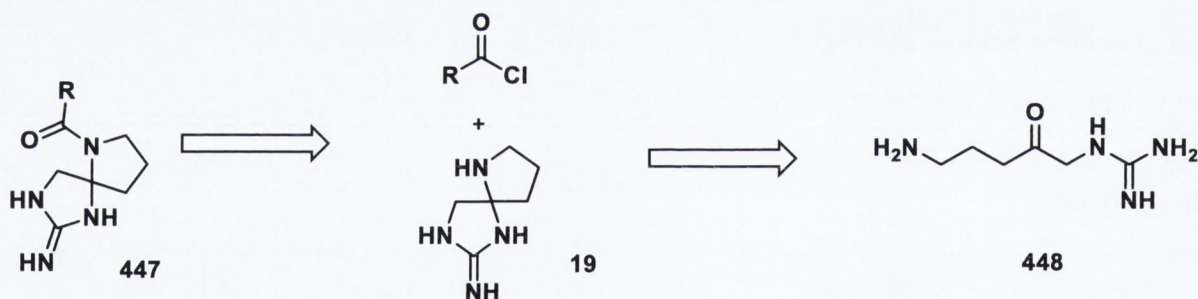


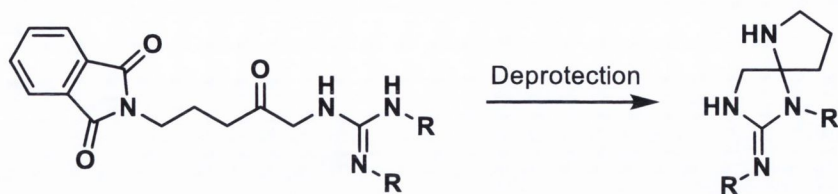
Figure 5.4.1. Second generation retrosynthesis of **447**.

This synthetic route would be mostly analogous to the first generation synthesis except for the late stage installation of the amide functionality. It was perceived that this would have the potential to be a more convergent route towards functionalised aminal-guanidines.

To synthesise guanidine **447** it was thought necessary to protect the primary amine of compound **448**, which upon subsequent deprotection would facilitate ring closure. Previous

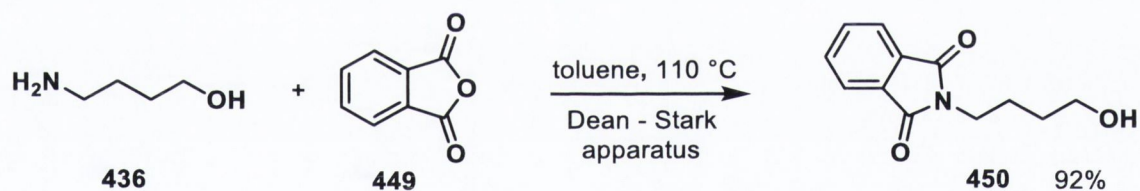
literature for phthalimide deprotection with ensuing ring closure supported the choice of phthalic anhydride **449** as a protecting group (Scheme 5.4.1).²⁴⁶

Scheme 5.4.1.

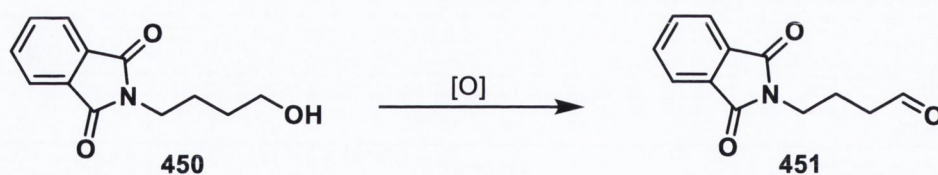


Hence, our forward synthetic route began with phthalimide protection of 4-aminobutan-1-ol **436** to afford primary alcohol **450**. This step gave high yields and required no column chromatography. Ensuring the use of a Dean-Stark apparatus was essential for obtaining satisfactory results (Scheme 5.4.2).

Scheme 5.4.2.



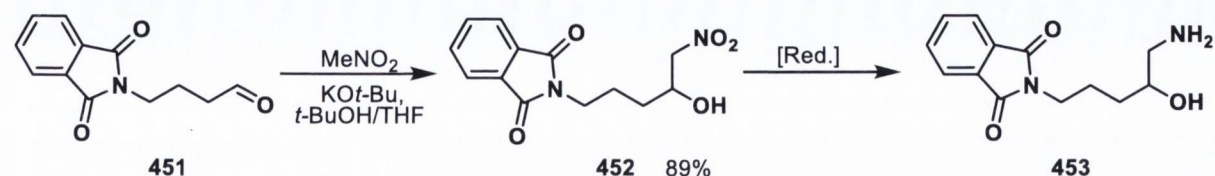
Without the presence of any other nucleophilic functionality on alcohol **450** oxidation was an unproblematic step. Upon exposure to IBX, DMP or Swern oxidising conditions aldehyde **451** could be generated in high yields (Table 5.4.1. entries 1 - 3). and on a multi-gram scale (Table 5.4.1. entries 4 and 5).

Table 5.4.1. Conditions attempted for oxidation of primary alcohol **450**.^a

Entry	Conditions	Yield (%)
1	IBX	96
2	DMP	94
3	Swern	87
4	IBX	92 ^b
5	Swern	84 ^b

^aFor a full description of experimental conditions see Chapter 8. ^bGram scale.

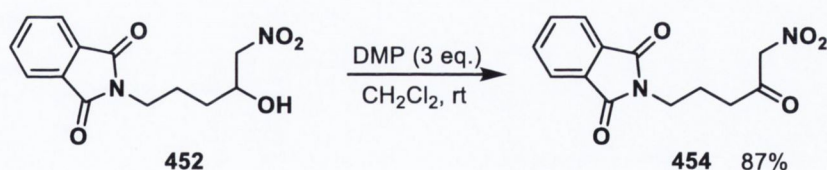
After obtaining aldehyde **451**, a Henry reaction was performed to generate nitro alcohol **452** in good yield (Table 5.4.2). Analogous reaction conditions were used to that in our first synthetic route which had always proven to be satisfactory. The decision to initially investigate the reduction of nitro **452** to generate amine **453** was made and a wide variety of conditions were analysed as outlined in Table 5.4.2. entries 1 – 3. It was found that Pd/C catalysed hydrogenation was the most effective reductive agent due to the facile work up required.

Table 5.4.2. Henry reaction and conditions for reduction of nitro derivative **452**.^a

Entry	Conditions	Yield (%) ^b
1	SnCl_4	68
2	Zn	64
3	H_2 , Pd/C	75

^a For a full description of experimental conditions see Chapter 8. ^bBRSM

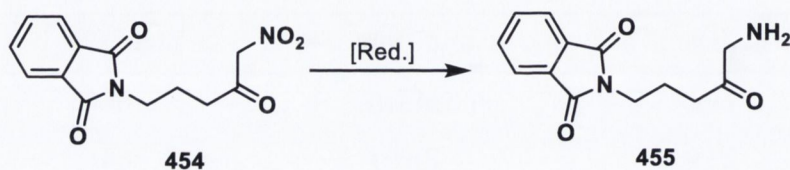
Contrary to our previous synthetic route, oxidation of nitro alcohol **452** was also attempted at this stage. The use of Dess-Martin periodinane was crucial in the effective oxidation of **452** to yield α -nitro ketone **454** in satisfactory yield with no column chromatography required (Scheme 5.4.3). Dichloromethane was essential as a TLC eluent for this reaction as combinations of typical solvents (ethyl acetate, hexane, diethyl ether) showed no polarity difference between starting alcohol **452** and ketone product **454**.

Scheme 5.4.3.

Reduction of the α -nitro ketone **454** proved somewhat problematic since it appeared to occur (as per TLC) using reducing metal conditions but no notable product was detectable. Hydrogenative conditions previously exploited in our reduction of nitro compounds proved completely unsuccessful for the reduction of **454**. After a number of dead-ends were encountered (Table 5.4.3. entries 1 - 3), hydrogenation in acidic conditions under 3 atm. of

hydrogen generated the required amine **455** as the hydrochloride salt (Table 5.4.3. entry 4). Much to our delight, amine **455** could be easily purified without the use of reverse phase column chromatography by simple trituration with diethyl ether.

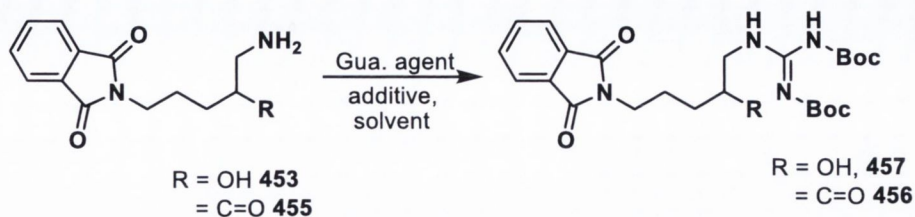
Table 5.4.3. Conditions for nitro **454** reduction.^a



Entry	Conditions	Yield (%)
1	SnCl ₄	43
2	Zn	47
3	H ₂ (1 atm.), Pd/C	54
4	H ₂ (3 atm.), Pd/C	85

^a For a full description of experimental conditions see Chapter 8.

Both α -amino ketone **455** (Table 5.4.4, entries 1 - 7) and amino alcohol **453** (Table 5.4.4, entries 8 - 14) were then individually exposed to guanidylating conditions (Table 5.4.4).

Table 5.4.4. Conditions attempted for guanidylation of amines **453** and **455**.^a

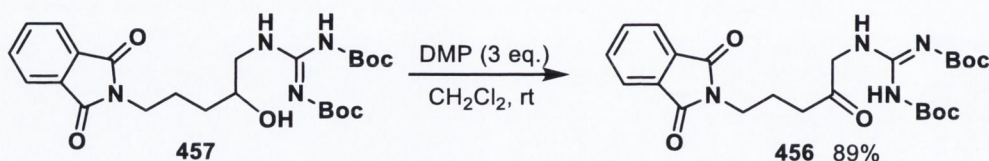
Entry	Substrate	Gua. Agent	Conditions	Yield (%)
1	455	$\text{BocHN}=\text{C}(\text{S})\text{NHBoc}$ 128	HgCl ₂ , CH ₂ Cl ₂ , rt	68
2	455	128	HgCl ₂ , DMF, 50 °C	36
3	455	128	CH ₂ Cl ₂ , rt	10
4	455	128	DMF, 50 °C	21
5	455	$\text{BocN}=\text{C}(\text{S})\text{NHBoc}$ 127	HgCl ₂ , CH ₂ Cl ₂ , rt	35
6	455	$\text{CbzHN}=\text{C}(\text{S})\text{NHCbz}$ 443	HgCl ₂ , CH ₂ Cl ₂ , rt	0
7	455	443	CuCl ₂ , CH ₂ Cl ₂ , rt	0
8	453	128	HgCl ₂ , CH ₂ Cl ₂ , rt	34
9	453	128	HgCl ₂ , DMF, 50 °C	21
10	453	128	CH ₂ Cl ₂ , rt	13
11	453	128	DMF, 50 °C	14
12	453	127	HgCl ₂ , CH ₂ Cl ₂ , rt	10
13	453	443	HgCl ₂ , CH ₂ Cl ₂ , rt	0
14	453	443	CuCl ₂ , CH ₂ Cl ₂ , rt	0

^aFor a full description of experimental conditions see Chapter 8.

In the case of α -amino ketone **455** the use of *N,N'*-bis-Boc-thiourea **128** proved to be the most efficient method of guanidylation furnishing the desired molecule **456** in 68% yield

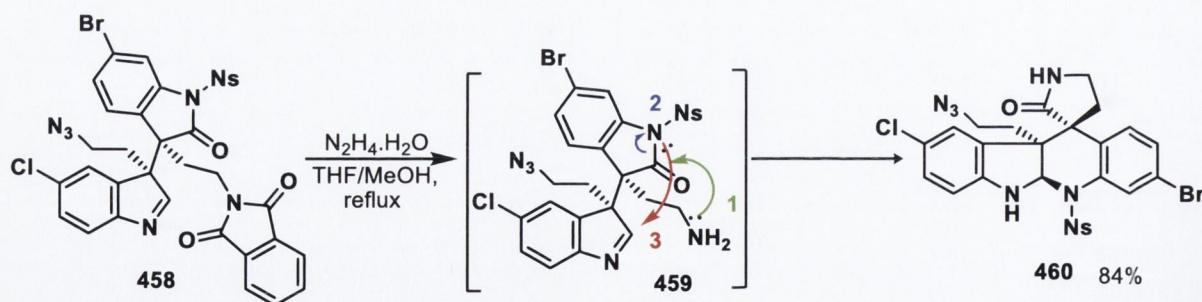
(Table 5.4.4, entry 1). Similarly, the guanidylation of amino alcohol **453** proved to be proficient utilising thiourea derivative **128** affording protected guanidine **457**. Oxidation of the secondary alcohol **457** could then be easily facilitated using DMP (Scheme 5.4.5)

Scheme 5.4.5.



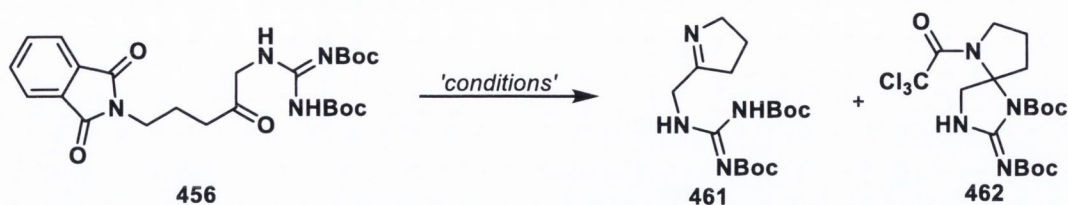
With cyclisation precursor **456** now in hand our attention moved to deprotection of the phthalimide group to attempt concurrent ring closures. A literature precedent utilises hydrazine as an effective means of deprotection.²⁴⁷ During the total synthesis of (+)-perophoramidine Wang and co-workers published a beautiful cascade reaction initiated by the hydrazine mediated deprotection of phthalimide.²⁴⁷ Initial deprotection of compound **458** generates a free amine **459** which attacks the oxindole amide in its immediate environment (Scheme 5.4.6, **step 1**) as opposed to the imine, preferentially forming a five membered ring. The expelled aniline (Scheme 5.4.6, **step 2**) can then attack the electrophilic imine (Scheme 5.4.6, **step 3**) forming the desired product **460**.

Scheme 5.4.6.



With this highly promising reactivity being found, we tried to replicate their cyclisation success on our molecule **456**. Cyclisation precursor **456** was exposed to a number of deprotecting conditions, initially with little success (Table 5.4.5. entries 1 and 2).

Table 5.4.5. Conditions attempted for ring closure of compound **456**.^a



Entry	Conditions	Temp. (°C)	Yield (%) ^b
1	N ₂ H ₄ /THF	reflux	-
2	N ₂ H ₄ /THF	50	-
3	N ₂ H ₄ /THF	rt	24
4	N ₂ H ₄ /THF	0	27
5	N ₂ H ₄ /THF	0	67 ^a
6	N ₂ H ₄ /THF	rt	68 ^a
7	N ₂ H ₄ /THF then TCACl, NEt ₃	rt	54 (462)

^a N₂H₄ (1M in THF solution). TCACl – Trichloroacetylchloride. ^b Yield of compound **461**.

The first breakthrough came when the temperature was lowered to room temperature and then to 0 °C (Table 5.4.5, entries 3 and 4) which resulted in the formation of imine **461** which was predicted as an intermediate in this reaction pathway. Further improvements were obtained upon the utilisation of dry N₂H₄ as a solution in THF (Table 5.4.5, entries 5 and 6). The absence of water in this reaction is of obvious benefit for imine formation with initial wet conditions affording poor results. This imine **461** was isolated and characterised. To facilitate the formation of the desired amination product **462** the reaction was carried out (Table 5.4.5, entry 6) and upon complete formation of the intermediate imine **461** (TLC analysis), trichloroacetylchloride and NEt₃ were added (Table 5.4.5, entry 7) to generate guanidine amination **462** in satisfactory yield (54%). This was a hugely rewarding result as a new cyclisation reaction for the formation of guanidine amins has been developed also incorporating the trichloroacetate group which can potentially undergo further synthetic

transformations to lead to a library of spirocyclic compounds. In conclusion, *N*-benzyl dihydroclathrocin **446** has been synthesised serendipitously and a method for the formation of spirocyclic guanidine amins has been discovered and its conditions optimised.

6. Investigations into the synthesis of araiosamines A-D.

Recently the araiosamine family of natural products have been isolated from a marine sponge of the family *Clathria Araiosa* (Figure 6.1).¹⁸⁵ The specimen was obtained from the island nation of Vanuatu in the South Pacific ocean. Initial investigations suggested a heavily nitorogenated and halogenated family of compounds, with detailed NMR spectroscopy analysis leading to the assignment of the araiosamines A-D as shown in Figure 6.2.¹⁸⁵ Indole functionalities and cyclic guanidines are ubiquitous in natural products isolated from marine sponges.³⁶ However, it is incredibly rare for a trimeric indole compound to be isolated even though there is quite a large precedence for dimeric indole natural products.^{12,37} The presence of this trimeric core along with the two cyclic guanidine functionalities makes this family an incredibly interesting target for total synthesis.

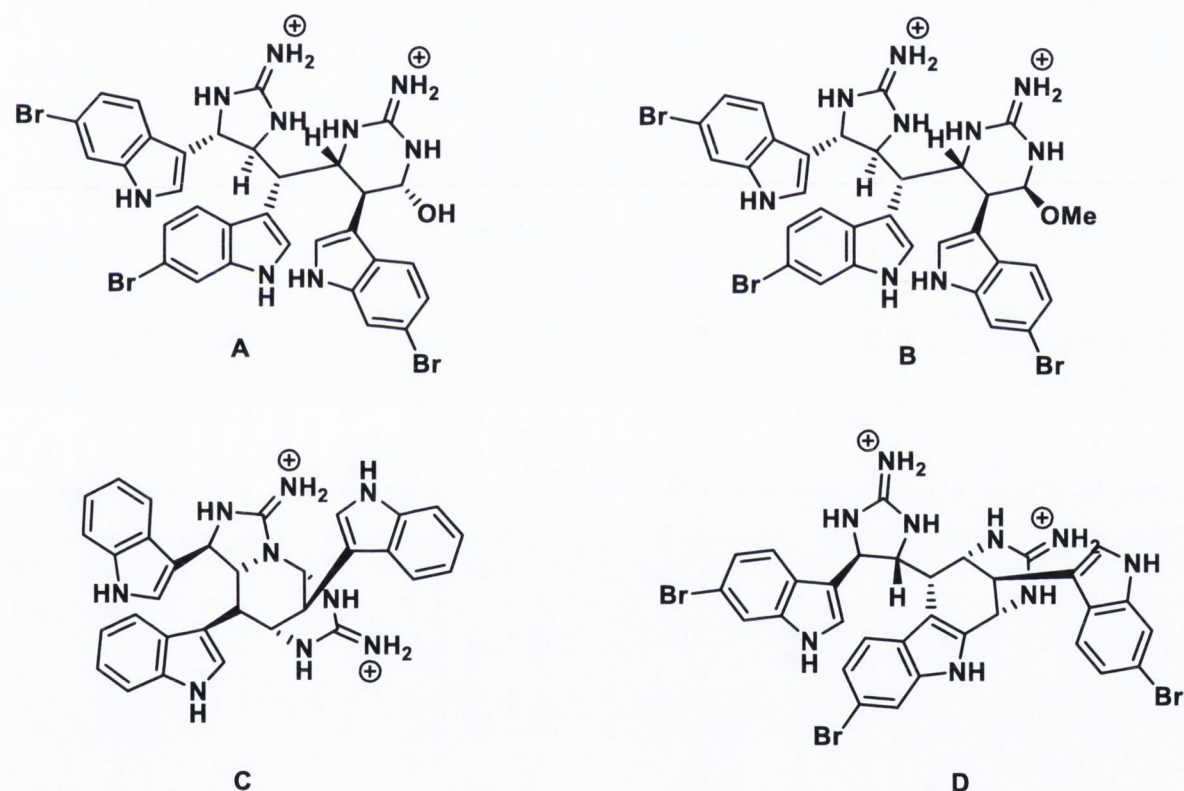


Figure 6.1. Araiosamines A-D.

The proposed biosynthesis of the araiosamines is shown in Figure 6.2. A trimerisation between three guanidine enamines **463** (step - a) is proposed to occur, generating intermediate **464**. This acyclic compound may then be able to undergo cyclisation from guanidine nitrogen **1** onto the imine functionality **2** forming the desired six membered moiety **465** present in araiosamine C (step - b). Subsequent expulsion of exocyclic guanidine **4** by

means of iminium formation from donation of electrons from the ring nitrogen **3** might facilitate a further cyclisation to occur from the other exocyclic guanidine **5** (step - c) forming intermediate **466**. This would relieve the highly electrophilic iminium of its positive charge. Intermediate **467** can also be formed from compound **465** by a similar pathway. Oxidation of the benzylic position **6** could then result in the final ring closure (step - d). From intermediate **467** a number of outcomes can also occur to yield the other members of the araiosamine family.

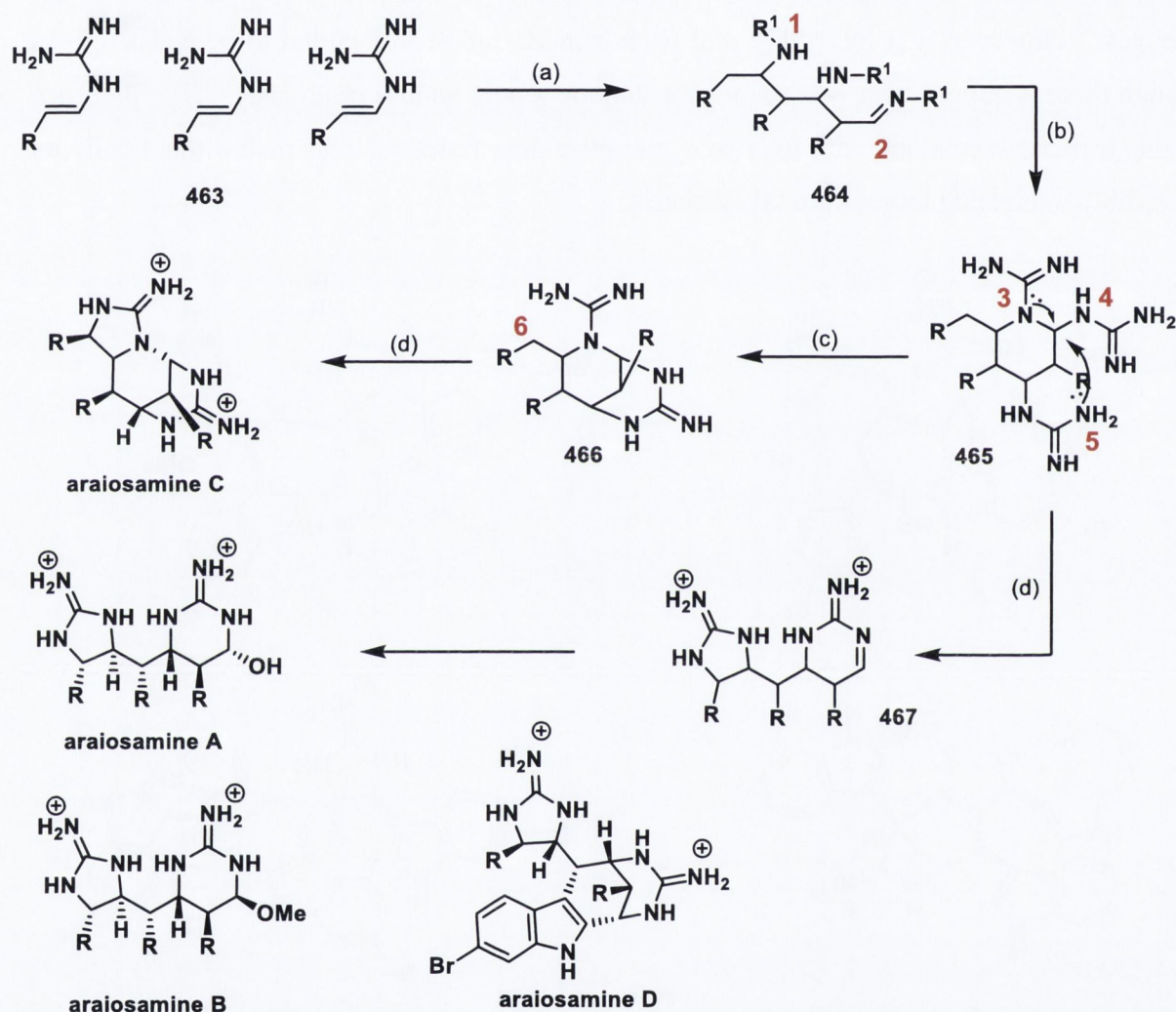


Figure 6.2. Proposed biosynthetic pathway of the araiosamine family. R = 6-Bromoindole, R¹ = amidine, omitted for clarity.

6.1. Biomimetic synthesis: Synthesis of indole guanidine **468**.

The initial synthetic plan focused on the idea that tautomeric forms of indole **468** would include guanidine enamine **469** under appropriate conditions (Figure 6.1.1) as has been proposed in the suggested biosynthetic pathway (Figure 6.2). In a biomimetic reaction, guanidine **469** would ideally be able to trimerise affording the desired natural products.

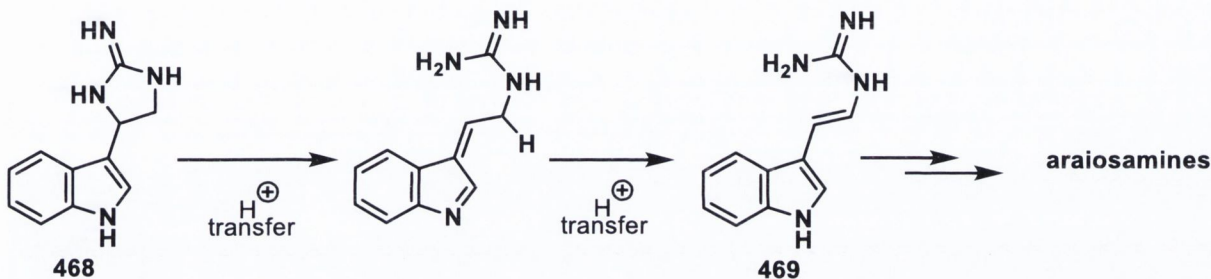
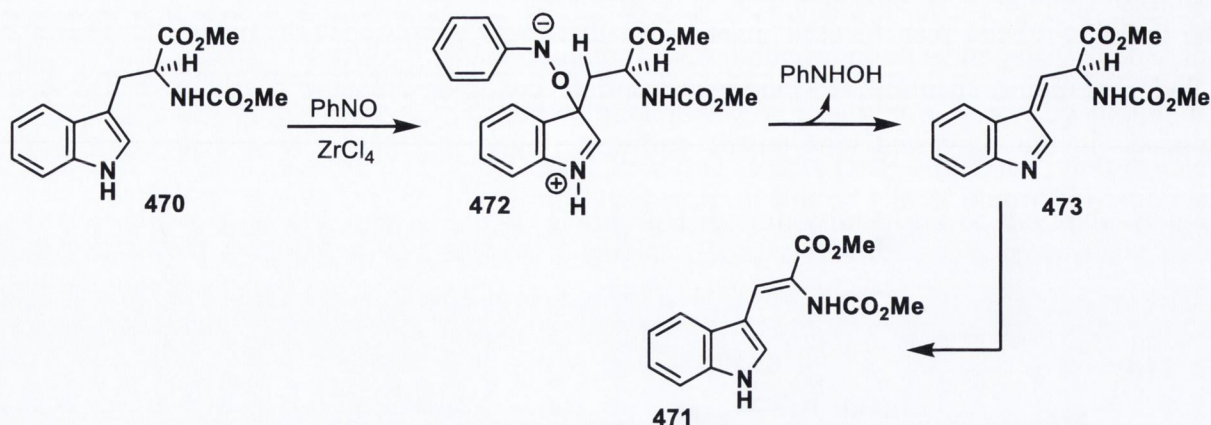


Figure. 6.1.1. Tautomeric forms of indole **468** and potential for trimerisation.

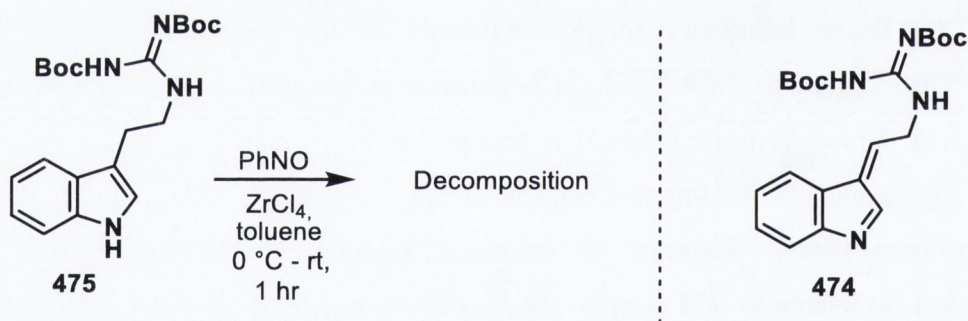
With this in mind, a synthesis of indole **468** was proposed using methodology previously utilised in the Baran laboratory for the synthesis of the stephacidins.²⁴⁸ Tryptophan derivatives **470** exposed to PhNO and $ZrCl_4$ generate tryptophan enamine derivatives **471** (Scheme 6.1.1). Nitrosobenzene (PhNO) is thought to be activated at the nitrogen in the presence of Lewis acids facilitating nucleophilic attack on oxygen. *O*-linked intermediate **472** might then immediately fragment to imine **473** and phenylhydroxylamine. Rapid interconversion to enamide **471** yields the desired compound. It was envisioned that intramolecular trapping of conjugated imine **474** by a guanidine nucleophile would result in the desired indole-guanidine structure.

Scheme 6.1.1.



Exposure of guanidine indole **475** to analogous conditions resulted in complete degradation of starting material (Scheme 6.1.2). Potentially, the Lewis acidic conditions were too harsh for the Boc- protecting groups as had been demonstrated previously.²⁴⁹ With such a poor result it was thought best to explore alternatives for the preparation of indole **468**.

Scheme 6.1.2.



Oxidative indole – enolate coupling is a proven method for the formation of C-C bonds between the 3 position of indole and an enolate.²⁵⁰ Exposure of both to base and an oxidising agent facilitates a radical type mechanism as outlined in Figure 6.1.2. Encouraged that this reactivity should facilitate rapid assembly of compound **468** it was decided to use commercially available creatinine **476** as a guanidine surrogate.

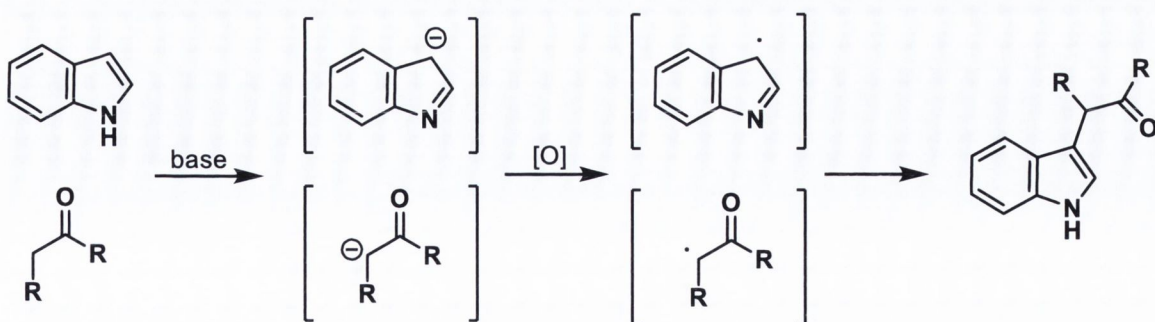
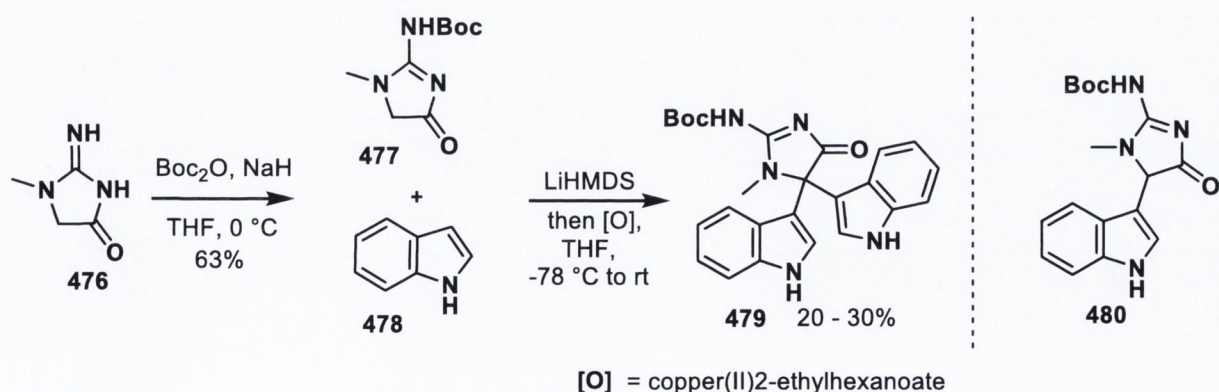


Figure 6.1.2. Schematic representation of oxidative indole – enolate coupling.

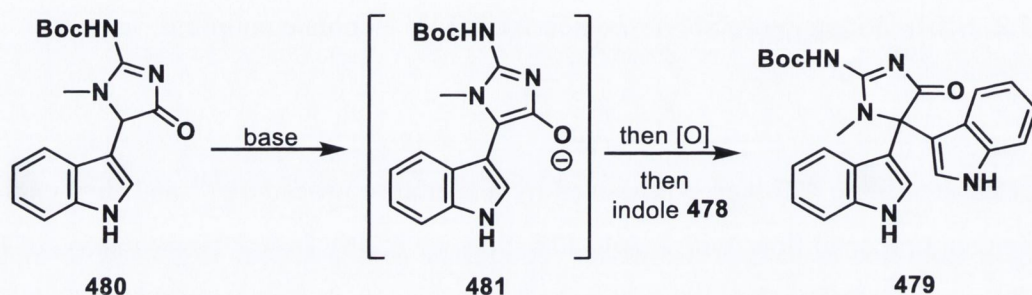
Boc-protected creatinine **477** was synthesised by a literature procedure²⁵¹ and then exposed to oxidative coupling conditions with indole **478** (Scheme 6.1.3). Initial deprotonation of both **477** and **478** using LiHMDS (3.5 eq.) generated the anionic equivalents at $-78\text{ }^{\circ}\text{C}$ which upon exposure to copper(II)2-ethylhexanoate as an oxidising agent initiated reactivity. After 2 hours two products (one major, one minor) appeared to be formed (as indicated by TLC). Purification of the reaction mixture and NMR spectroscopic analysis indicated the coupling of two equivalents of indole to protected creatinine **477** resulting in highly functionalised creatinine **479**. Efforts to synthesise desired mono-indole containing compound **480** were fruitless. The changing of equivalents of base, temperature or time individually either led to **479** or to no significant products.

Scheme 6.1.3.



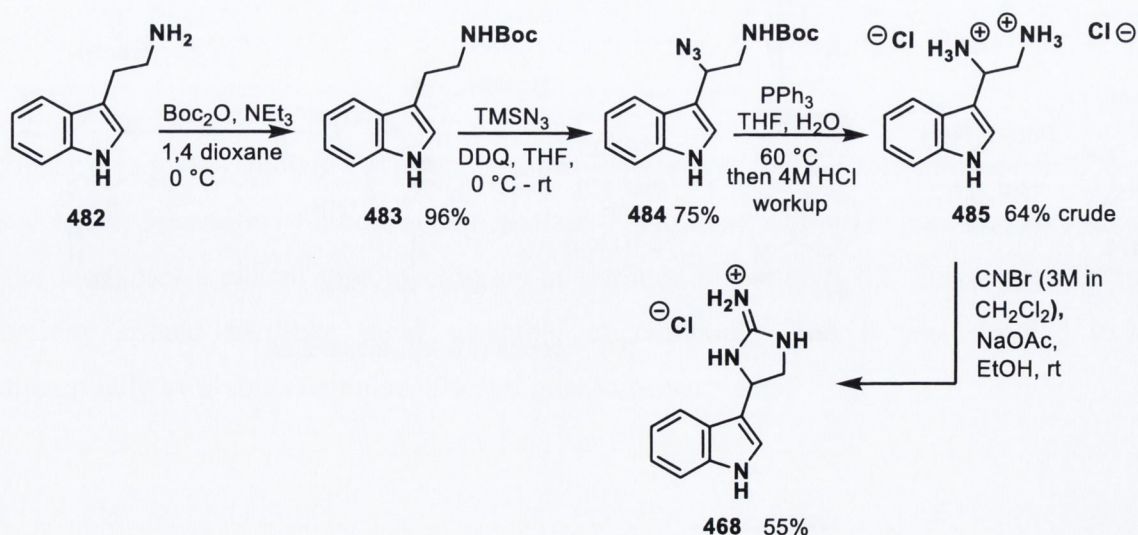
It is thought that the over-reactivity of this species is due to the aromatic nature of intermediate **481** which could be formed and would be highly susceptible to further reaction (Scheme 6.1.4).

Scheme 6.1.4.



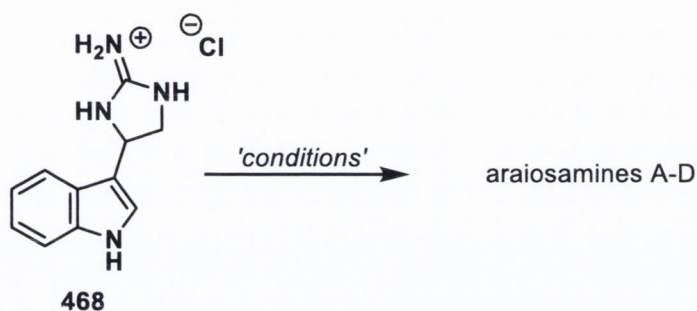
Following this dead-end, a more rewarding line of enquiry was investigated. Thus, tryptamine **482** was Boc-protected resulting in compound **483** and then exposed to DDQ to generate a benzylic carbocation as described by Feldman *et al.*²⁵² which can be captured by an azide nucleophile to afford azide **484**. Subsequent Staudinger reduction and acidic workup, generated diamine **485**.²⁵³ Gratifyingly, exposure of **485** to CNBr formed the target guanidine compound **468** (Scheme 6.1.5).

Scheme 6.1.5.



Then, a variety of conditions were investigated for the self – trimerisation of **468** (Table 6.1.1, entries 1 - 4); however, no experiments yielded any desired products. Decomposition of **468** or recovery of **468** were the only two outcomes for these reactions.

Table 6.1.1. Investigations into trimerisation reaction of indole monomer **468**.



Entry	Additive	Temp. (°C)	Time (h)	Yield (%)
1	TFA	rt	48	>95% SM
2	TFA	80	12	Decomposition
3	6M HCl	80	12	Decomposition
4	6M HCl	40	24	74% SM

6.2. Synthesis of indole **486**.

Further retrosynthetic analysis of the araiosamine family generated indole **486** as a desired target (Figure 6.2.1). It was envisioned that upon attainment of **486** further functionalisation would be possible. Michael addition onto the conjugated benzylic position (Figure 6.2.1, -a) of **487** by an appropriate nucleophile and functionalization of the imidazole moiety (Figure 6.2.1, -b) could lead to an advanced intermediate towards the synthesis of the araiosamines.

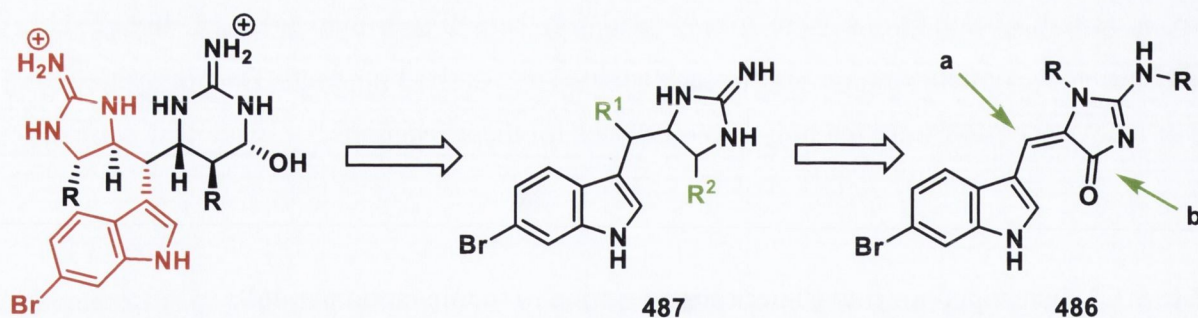
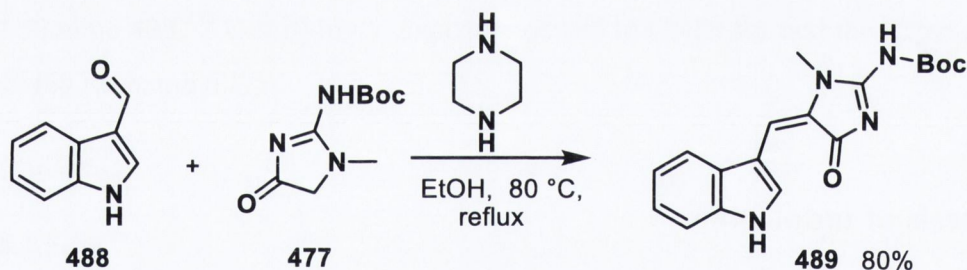


Figure 6.2.1. Retrosynthesis of araiosamine A.

To enable rapid production of **486**, Boc-protected creatinine **477** was used as a readily available guanidine containing heterocycle. After preliminary experimentation it was discovered that piperazine assisted Knoevenagel condensation between indole-3-carboxaldehyde **488** and creatinine **477** generated intermediate **489** as an intensely yellow solid in very good yield (Scheme 6.2.1, 80%).

Scheme 6.2.1.

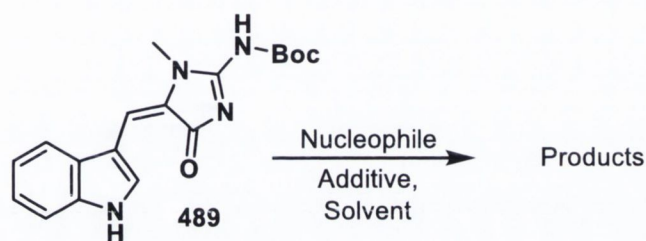


Initial experiments investigated the reactivity of the conjugated benzylic position of **489** (Figure 6.2.1, –a) towards nucleophilic attack. A variety of carbon nucleophiles were investigated for their potential to add to Michael acceptor **489**. Acetylacetone **490** is an example of a carbon nucleophile which have been proven to be effective in Michael addition reactions under a myriad of conditions.²⁵⁴ The use of **489** in conjunction with different additives (Table 6.2.1, entries 1-3) gave no desired product and **489** was recoverable in all instances. Meldrum's acid **491** was used as a more activated carbon nucleophile; however, as it was experienced with **490**, no reactivity was observed.

Accepting the lack of reactivity of the benzylic position towards nucleophilic attack it was decided to explore the creatinine ring as a moiety for further functionalisation. Reduction of

the conjugated amide could afford a hemi-aminal, a reactive synthetic handle which could hopefully be manipulated. Due to its conjugated nature, **489** was initially exposed to Luche reducing conditions²⁵⁵ (Table 6.2.1, entry 4); however, no reactivity was noted. Further exposure to a variety of reducing agents (Table 6.2.1, entries 5-8) proved unfruitful and in all cases no products were formed and starting material **489** was recovered.

Table 6.2.1. Reactivity of indole **489**.



Entry	Reagent	Additive	Yield (%) ^a
1	 490	NEt ₃ , toluene	RSM
2	490	FeCl ₃ , toluene	RSM
3	490	NaOH, EtOH	RSM
4	 491	NEt ₃ , toluene	RSM
5	NaBH ₄	CeCl ₃ , MeOH	RSM
6	LiAlH ₄	THF	RSM
7	NaCNBH ₃	AcOH, MeOH	RSM
8	LiEt ₃ BH	THF	RSM

^a RSM – recovered starting material, no desired products observed.

The lack of reactivity was due to the highly conjugated nature of **489** which prevented typical reactivity of this type of Michael acceptor to occur (Figure 6.2.2). Tautomerism between **489**, **492** and **493** leads to an unusual stability and even in harsh reducing conditions (Table 6.2.1, entry 8) no products are formed. Assuming tautomeric form **492**, sodium cyanoborohydride

was tested as a reducing agent (Table 6.2.1, entry 7). As expected from this incredibly stable molecule no reaction occurred.

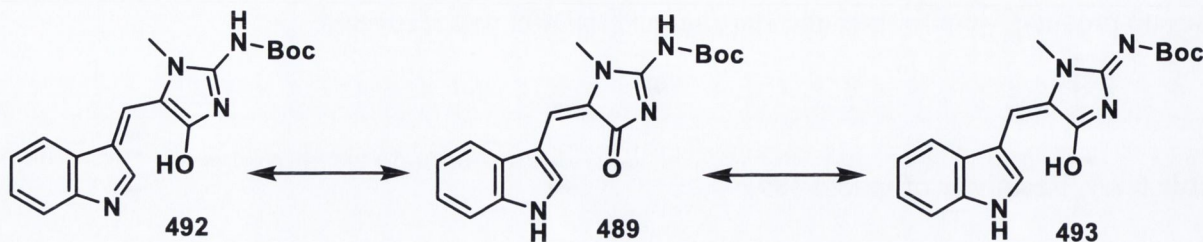


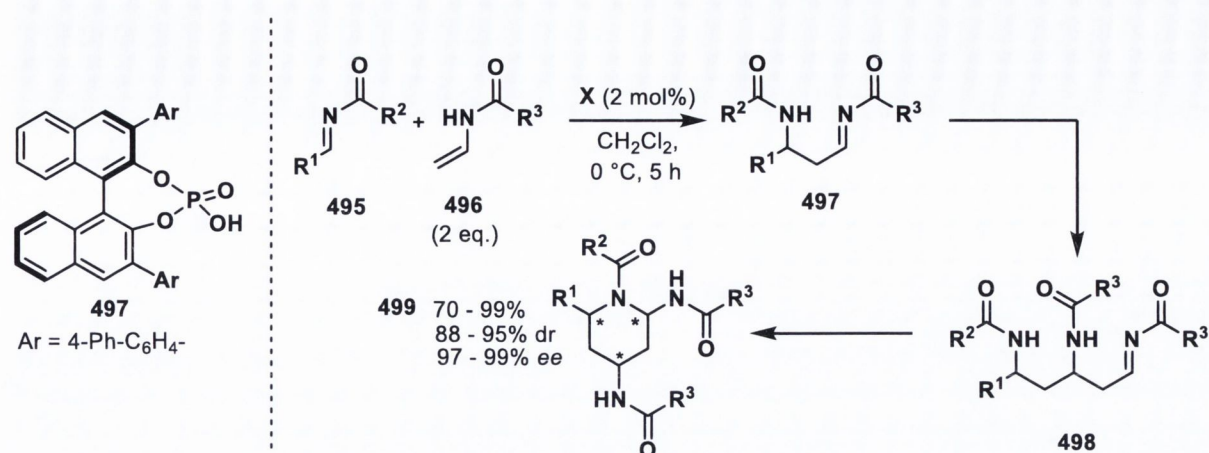
Figure 6.2.2. Conjugated nature of **489**.

Due to the inherent stability of indole **489** it was decided to abandon this line of investigation.

6.3. Enamide trimerisation.

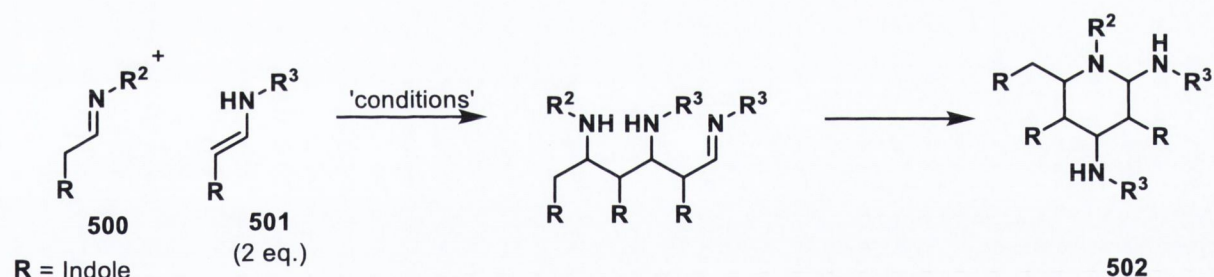
During initial investigations into trimerisation reactions a beautiful paper by Terada and co-workers caught our attention.²⁵⁶ This paper describes a chiral phosphoric acid catalysed azarene type reaction to generate highly functionalised piperidines. In this reaction, two equivalents of enamide **494** are reacted with imine **495** in the presence of a chiral phosphoric acid **496** to initiate enamide addition to the imine (Scheme 6.3.1). This is followed by another equivalent of enamide **494** adding to the newly formed imine **497**. This reactivity can then be terminated preventing polymerisation by an intramolecular attack of nitrogen on terminal imine **498** resulting in the formation of highly functionalised piperidine **499**.

Scheme 6.3.1.



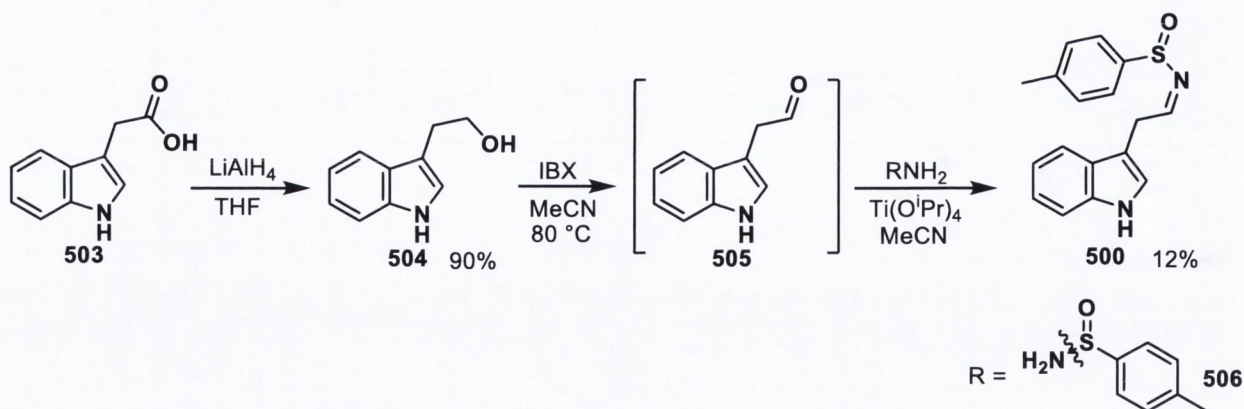
The synthetic utility of this procedure was obvious and appealing. It was thought that, by incorporating analogous indole-containing imine **500** and enamide functionalities **501**, a highly derivatised piperidine core **502** could be synthesised containing the requisite three indole moieties (Scheme 6.3.2).

Scheme 6.3.2.



The synthesis of indole imine **500** was investigated. Carboxylic acid **503** was exposed to reductive conditions (LiAlH_4 , THF) to generate alcohol **504** which it was hoped could be oxidised to furnish aldehyde **505**. The synthesis of intermediate **505** however proved to be a challenging task due to its characteristic reactivity (Figure 6.3.1).

Scheme 6.3.3.



Under oxidising conditions (iodoxybenzoic acid – IBX), **505** could cleanly and quantitatively be formed as indicated by TLC; however, upon attempted isolation polymerisation occurred as indicated by NMR spectroscopy. After exhaustive attempts to obtain aldehyde **505**, it could not be isolated or characterised and therefore it was decided to use **505** without purification.

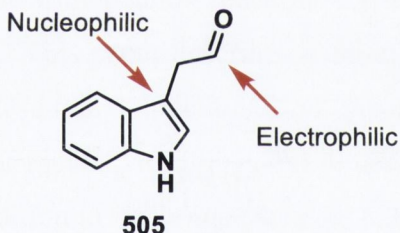


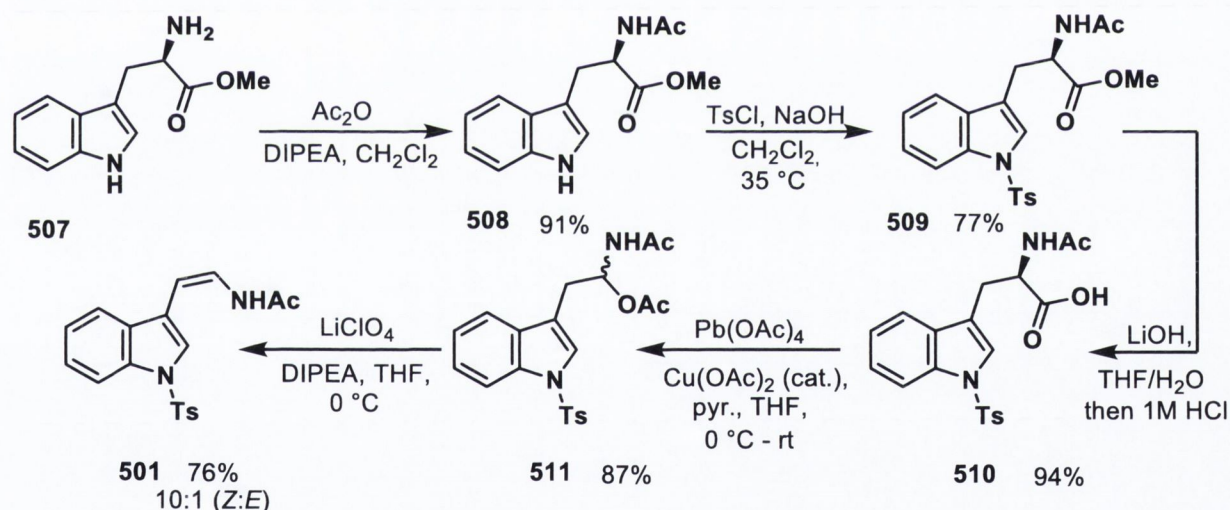
Figure 6.3.1. Inherent instability of aldehyde **505**.

Once the oxidation of alcohol **504** was deemed complete (TLC analysis) the reaction mixture was diluted with MeCN and filtered through a plug of Celite®. The resulting solution was then concentrated by rotary evaporation to give a roughly 1M solution of aldehyde **505** in MeCN. For instance, if the reaction scale was 1 mmol then the solution containing **505** was concentrated to ~1 mL of MeCN. The concentration dependence on the instability of **505** would indicate an intermolecular reactivity being the cause of our problems rather than an intramolecular problem (Figure 6.3.1). In order to form the imine it was decided to use sulfinamide **506** due to the extensive literature on the behaviour of sulfinimines.²⁵⁷ These

imines display unique reactivity and stereoselectivity due to the presence of the chiral electron withdrawing *N*-sulfinyl group.²⁵⁷ Condensation of sulfonamide **506** with aldehyde **505** was facilitated by $\text{Ti}(\text{O}i\text{-Pr})_4$ to yield imine **500**. Over the two steps, an optimal yield of 12% was obtained providing an unstable imine (Scheme 6.3.3). The imine was also unstable under an inert atmosphere at $-20\text{ }^\circ\text{C}$ if left for longer than 12 h.

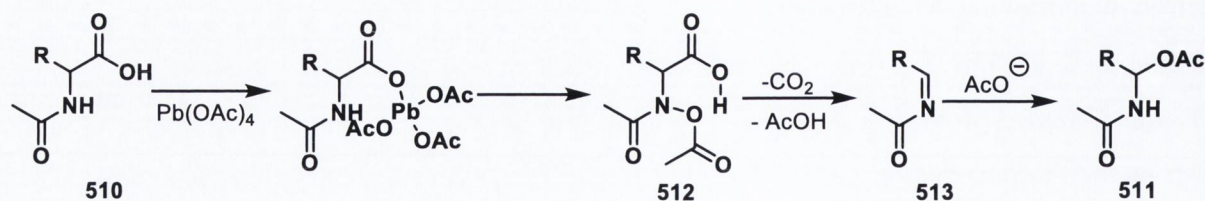
With the desired imine **500** tentatively in hand, we moved our attention to the formation of enamide **501**. This synthetic route started with the *N*-acetylation of tryptophan methyl ester **507** to afford **508** followed by protection of the indole nitrogen with a tosyl protecting group which resulted in intermediate **509**. Both steps proceeded efficiently and in good yield (Scheme 6.3.4). Hydrolysis of the ester afforded corresponding carboxylic acid **510** and, following this, a $\text{Pb}(\text{OAc})_4$ mediated oxidative decarboxylation was employed to yield hemi-aminal **511**.

Scheme 6.3.4.



This mechanistically interesting step is proposed to proceed as shown in Scheme 6.3.5.²⁵⁸ Interaction of the carboxylic acid **510** with $\text{Pb}(\text{OAc})_4$ facilitates the formation of *N*-acetoxo **512** which upon decarboxylation could generate imine **513**. In the presence of the OAc^- anion it would be feasible to imagine addition to the electrophilic imine.

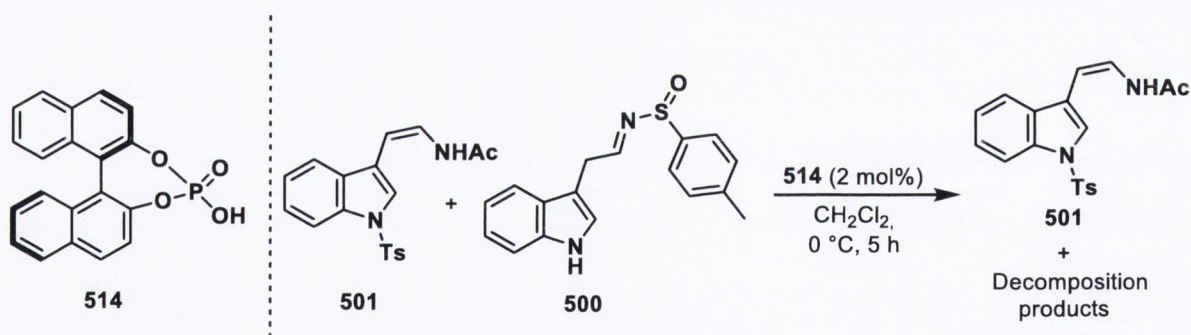
Scheme 6.3.5.



Hemi-aminal **511** was initially the focus of our attention since the prospect of nucleophilic attack and displacement of the acetoxy group by an appropriate substrate was appealing. However, we quickly learned that under basic conditions elimination of the acetoxy moiety ensued the formation of enamide **501** as primarily the *cis* isomer, which was presumably generated through a *syn* elimination pathway.

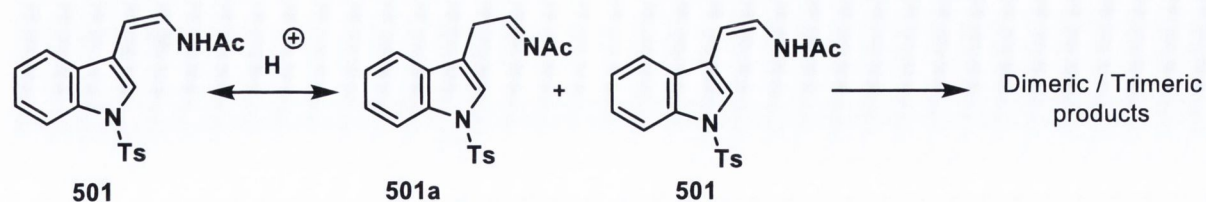
Now having access to both enamide **501** and imine **500** the trimerisation reaction conditions reported by Terada were investigated utilising phosphoric acid **514** as a catalyst. Upon exposure to this acidic environment only enamide **501** was recovered from the reaction (Scheme 6.3.6).

Scheme 6.3.6.



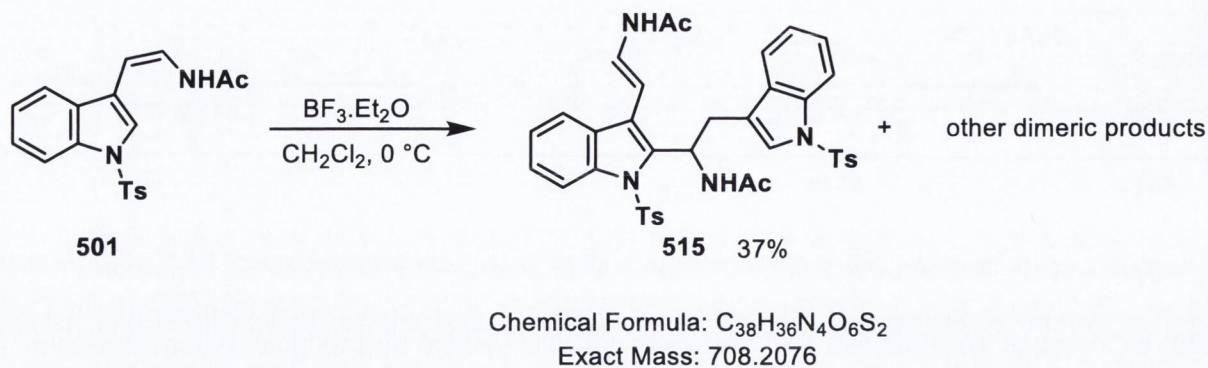
Realisation that trimerisation may be possible through the exposure of enamide **501** to suitably acidic conditions prompted further investigations in this area. Tautomerisation of **501** between its imine and enamide isomers may facilitate self-reactivity invoking the desired dimer- or trimerisation (Scheme 6.3.7).

Scheme 6.3.7.



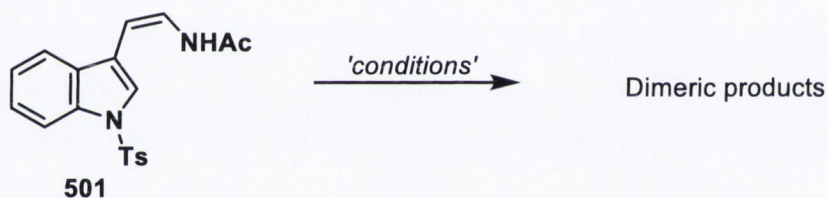
Initial exposure of enamide **501** to Terada's conditions yielded no products. After a suitable literature investigation it was decided to explore a number of both Lewis and Brønsted acids for promoting self-reactivity of **501** (Table 6.3.1, entries 1 - 4). Preliminary examination of $BF_3 \cdot OEt_2$ as a Lewis acid (Scheme 6.3.8) presented exciting results. Mass spectral analysis of the crude reaction mixture showed no starting material present and a mass peak corresponding to a dimeric product. TLC analysis confirmed the consumption of starting material **501**, but a number of new product spots had appeared, including one major spot. Preparative TLC was used to separate each of the products and the major one was assigned as dimeric compound **515** after extensive NMR spectroscopy experimentation (Chapter 8). As expected, isomerisation between the imine and enamide tautomers had occurred under acidic conditions. Interestingly, however, the most nucleophilic position of **501** had proven to be position two of the indole ring as opposed to the desired reactivity at the benzylic position of the indole.

Scheme 6.3.8.



Each of the products isolated from the reaction were also analysed by mass spectral analysis and all were confirmed to be dimeric products. However, as the major isomer was only isolated in 37% yield it was decided that detailed NMR spectroscopy of each of the remaining products would be futile.

Table 6.3.1. Investigations into dimerisation reaction of indole monomer **501**.

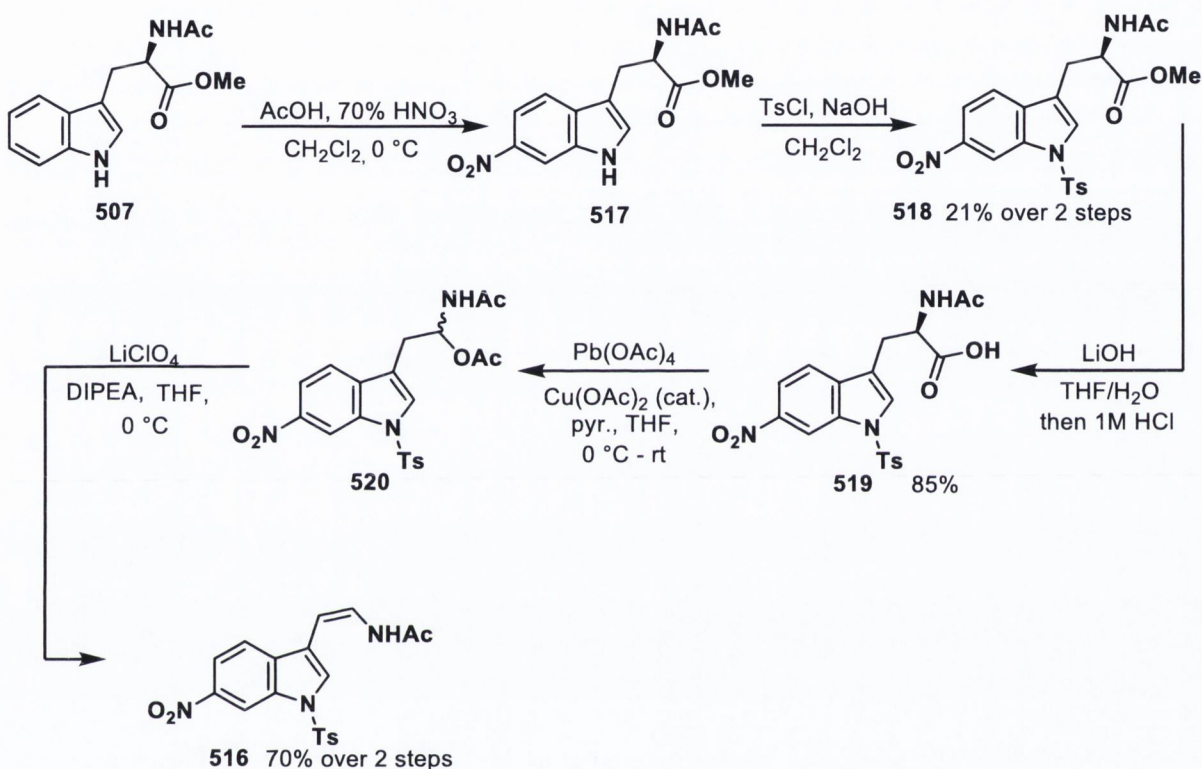


Entry	Additive	Temp. (°C)	Time (h)	Yield (%)
1	TFA	0	4	<5
2	CSA	0	8	<5
3	BF ₃ .OEt ₂	0	12	37
4	H ₂ SO ₄	0 - rt	12	0

In the presence of both camphor sulfonic acid (CSA) and TFA, dimerisation was also facilitated albeit producing the same undesired coupled product **515**. Sulfuric acid led to complete decomposition of starting material to yield unidentifiable potentially polymeric materials.

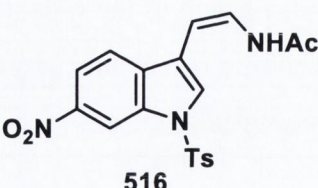
As the natural reactivity of this species **501** was not desirable, it was decided to try and tune the reactivity of the indole skeleton by introduction of a nitro group at the 6-position of the indole ring (Scheme 6.3.9). The idea that this may in fact mimic or enhance any effect that bromine may invoke in natural araiosamine biosynthesis was appealing.

Scheme 6.3.9.



It was thought that decreasing the reactivity of the indole ring could prevent reaction at the 2-position and allow preferential enamide dimerization. Synthesis of the 6-nitro analogue **516** of indole **501** is presented in Scheme 6.3.9. Unfortunately, incorporation of the nitro functionality prevented any dimerisation reactivity of the system as examined in Table 6.3.2, entries 1 - 4.

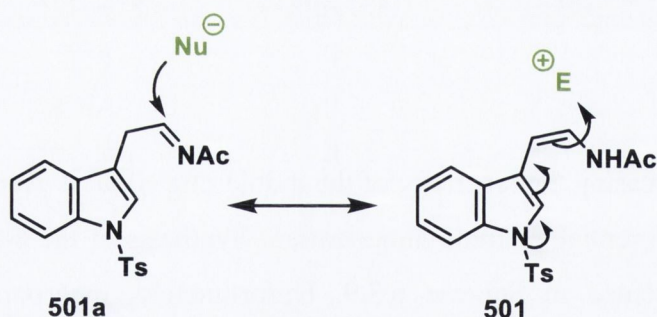
Table 6.3.2. Investigations into dimerization reaction of indole monomer **516**.


→ 'conditions' →
Dimeric products

Entry	Additive	Temp. (°C)	Time (h)	Yield (%)
1	TFA	rt	12	RSM
2	CSA	rt	12	RSM
3	BF ₃ .OEt ₂	0	2	RSM
4	H ₂ SO ₄	rt	24	RSM

6.4 Indoline trimerisation.

Unanticipated problems experienced in initial synthetic endeavours were obvious in hindsight. The highly conjugated nature of the enamide indole systems generated, ‘confused’ positions in the molecular architecture. For instance, the imino carbon (Figure 6.4.1) of imine **501a** would typically be electrophilic, however, tautomerisation to enamide **501** would facilitate electron donation from the indole ring and imply nucleophilic characteristics on the same imino carbon.

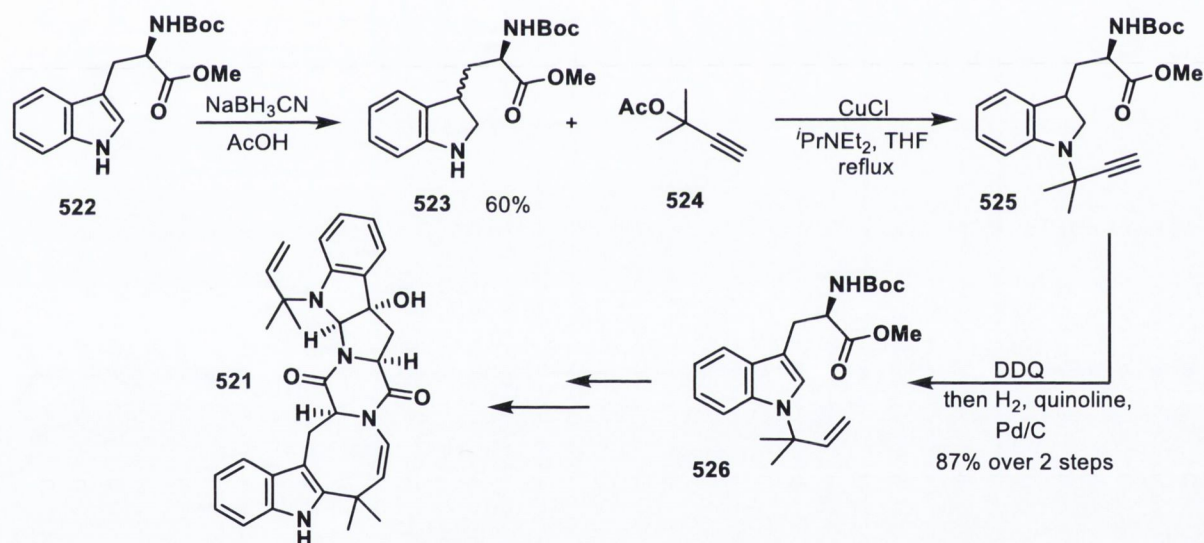
**Figure 6.4.1.** ‘Confused’ reactivity of the indole – enamide **501** system.

To circumvent this unwanted reactivity it was thought to negate the effects of the indole by reducing the ring system to an indoline moiety. This tactic has previously been successfully used in the laboratory of E.J. Corey in the total synthesis of okaramine N **521** (Scheme

6.4.1).²⁵⁹ The need to install a *tert*-prenyl functionality on the indole ring nitrogen required a reduction of the indole to facilitate known reactivity. Gribble reduction of tryptophan derivative **522** generated the desired indoline **523**, which upon exposure to copper catalysed alkylative conditions with 2-acetoxy-2-methyl-3-butyne **524**, yielded **525**. Rearomatisation of the indoline core was obtained utilising DDQ. Selective reduction of the ethynyl group to the desired vinyl functionality under Pd catalysed hydrogenation gave the desired okaramine N precursor **526**. Although a rather lengthy procedure to simply introduce a *tert*-prenyl moiety, it enabled the desired target to be synthesised and permitted the completion of okaramine N **521**.

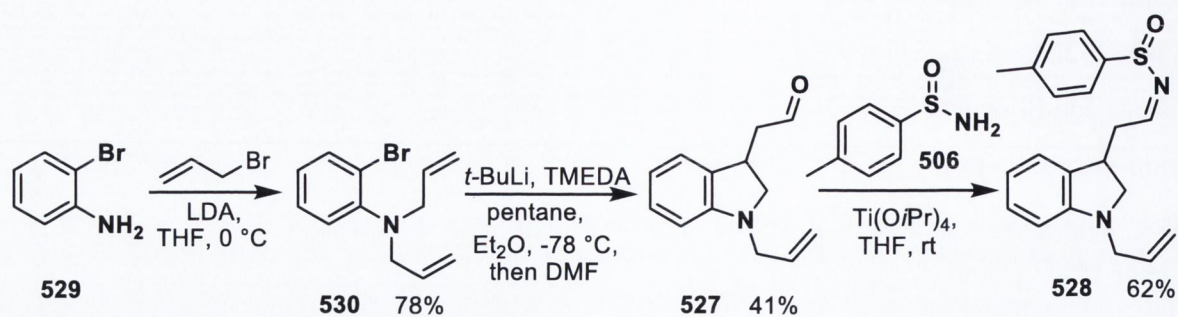
Since this publication the direct installation of *tert*-prenyl groups to indole nitrogens has been described by Baran and co-workers (Scheme 6.4.1).²⁶⁰

Scheme 6.4.1.



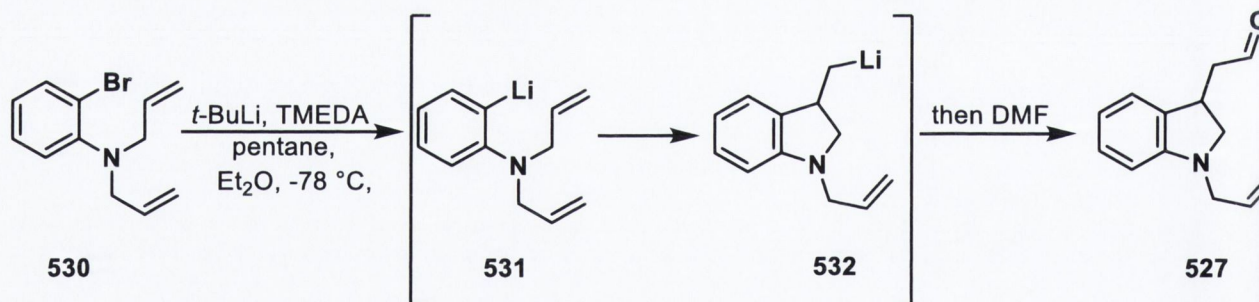
In the context of our araiosamines synthesis, the thought arose that harnessing the indole reactivity by negating the conjugative effects could be beneficial. This was to be employed by utilising indoline as an indole surrogate, as mentioned. With a desire to incorporate Terada's trimerisation conditions, we set about designing our indoline precursor. Previous work in the literature for the formation of aldehyde **527** (Scheme 6.4.2) was pivotal to our synthetic planning and in three steps enabled the synthesis of imine **528**. Bromoaniline **529** was *bis*-allylated successfully using LDA and allyl bromide to generate protected aniline **530**.

Scheme 6.4.2.



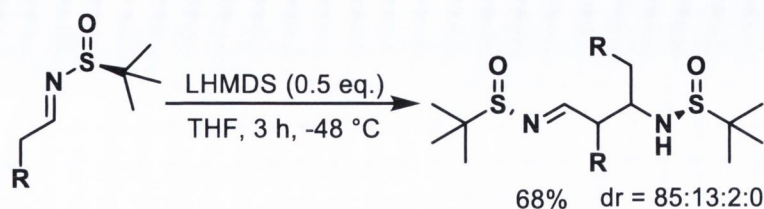
Next, the mechanistically interesting ring closing reaction was employed to quickly generate structural complexity. Allyl protected bromoaniline **530**, upon exposure to *t*-BuLi, undergoes lithium transmetalation (**531**). Subsequent 5-*exo* cyclisation generated intermediate **532** which can be exposed to a variety of electrophiles to produce highly derivatised indolines (Scheme 6.4.3). In our case, addition of DMF introduced the required aldehyde moiety. As previously employed, Ti(O*i*-Pr)₄ mediated condensation of Davis' sulfinamide **506** with aldehyde **527** proved fruitful and generated imine **528** in good yield (Scheme 6.4.2; 62%).

Scheme 6.4.3.



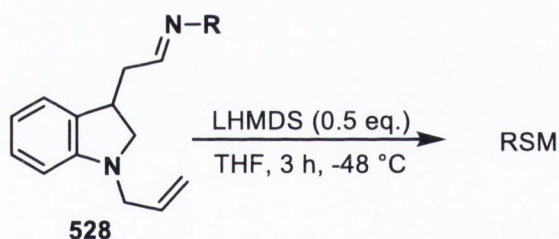
In a revealing report from the laboratory of Ellman and co-workers, an intermolecular self-condensation of sulfinimines utilising basic conditions was presented.²⁶¹ Under these conditions, enamide tautomerisation occurs and, assuming only half an equivalent of the appropriate base is used, the generated enamides should condense with the desired remaining imine. The presence of Ellman's chiral auxiliaries inferred good diastereomeric control over this reaction (Scheme 6.4.4).

Scheme 6.4.4.



An analogous reaction was thought to be feasible for imine **528** to produce the desired dimeric indoline containing compound. Exposure of **528** to identical reaction conditions failed to generate any corresponding product, but instead, afforded the starting material (Scheme 6.4.5). Disappointed by this preliminary result our attention turned to the addition of different nucleophiles to imine **528**.

Scheme 6.4.5.



A variety of different indole nucleophiles were prepared and their reactivity with imine **528** investigated. Further investigations in the Baran laboratories succeeded in coupling ester **533a** with imine **528** under basic conditions. Subsequent re-oxidation of the indoline core using chloranil proved effective in forming an indole dimeric core **534** of the araiosamine natural products (Figure 6.4.2). This synthetic route was abandoned due to the laborious chemistry involved and the unacceptable reaction step count.

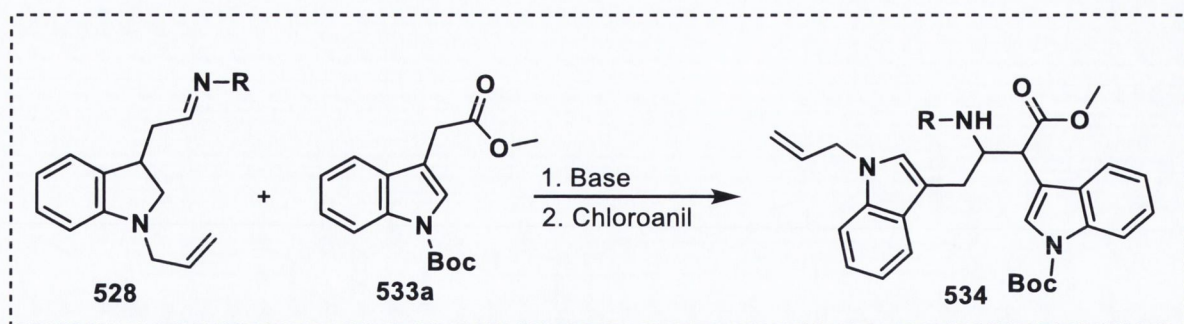
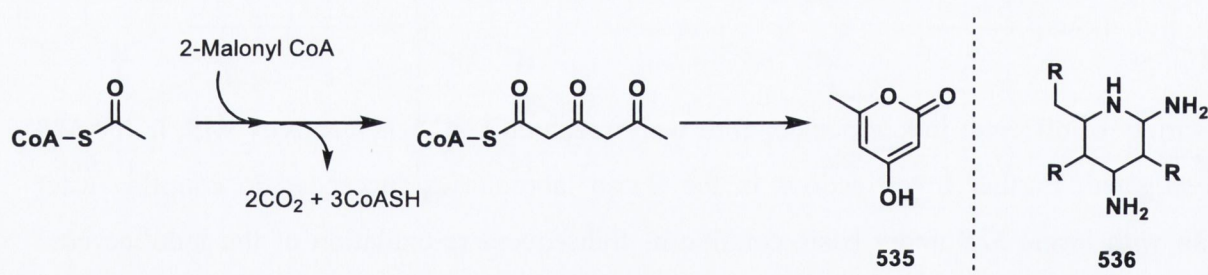


Figure 6.4.2. Work carried out in the Baran laboratory by Ming Yan.

6.5. Claisen Condensation.

The interesting biosynthesis of pyrone derivative **535** incorporates a Claisen condensation to quickly from a trimeric compound which can then undergo cyclisation (Scheme 6.5.1).²⁶² The similarities to our desired trimerisation and resulting cyclisation for the synthesis of araiosamines A-D generated an interest in utilising Claisen reactivity in our forward synthetic planning. An overall lowering of the oxidation state of the pyrone would provide an analogous oxygen containing heterocycle to our desired advanced intermediate **536**.

Scheme 6.5.1.

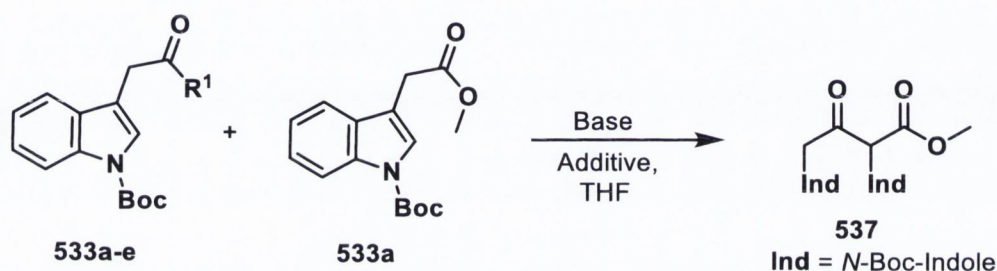


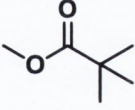
A number of suitable Claisen and cross Claisen condensation precursors were synthesised including ester **533a**, acid chloride **533b**, thioester **534c**, carboxylic acid **535d** and anhydride **535e**. Self Claisen condensation reactions were evaluated utilising ester **533a** with a variety of different bases (Table 6.5.1, entries 1-4); however, no condensation product was detected. The use of Ti(Oi-Pr)₄ has proven in the literature to be an effective additive for promoting

numerous Claisen condensation reactions. In our case however no notable effect was detected.

In an attempt to utilise the cross Claisen condensation reaction, ester **533a** was reacted with **533b**, **533c**, **533d** and **533e**, separately. Ester **533a** was exposed to basic conditions at -78 °C and subsequently each of the coupling partners were added respectively (Table 6.5.1; entries 5-8). As previously experienced with these substrates no reactivity was observed. The use of this type of reactivity was obviously incompatible with our indole substrates.

Table 6.5.1. Investigations into Claisen and cross Claisen reactivity.^a



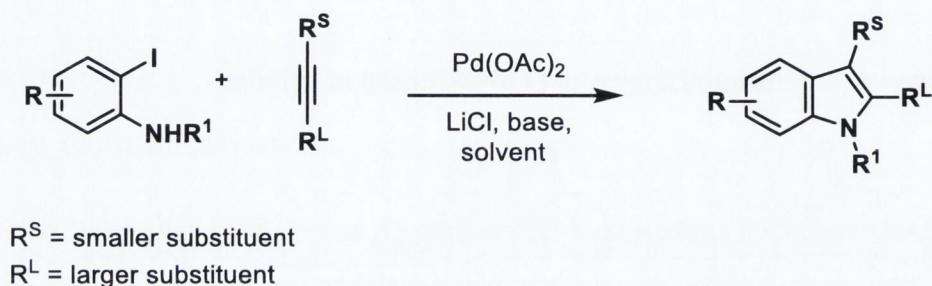
Entry	R ¹	R ²	Base	Additive	Yield (%)
1	OMe	OMe	LDA	-	0
2	OMe	OMe	LHMDS	-	0
3	OMe	OMe	KO <i>t</i> -Bu	-	0
4	OMe	OMe	NEt ₃	Ti(O <i>i</i> -Pr) ₄	0
5	533b - Cl	OMe	LHMDS	-	0
6	533c - SEt	OMe	LHMDS	-	0
7	533d - OH	OMe	LHMDS	-	0
8		OMe	LHMDS	-	0
533e					

^a **533a-e** (0.05 mmol), **533a** (0.05 mmol), base (0.05mmol), -78 °C to rt, THF (0.1 mL).

6.6. Alkyne trimerisation.

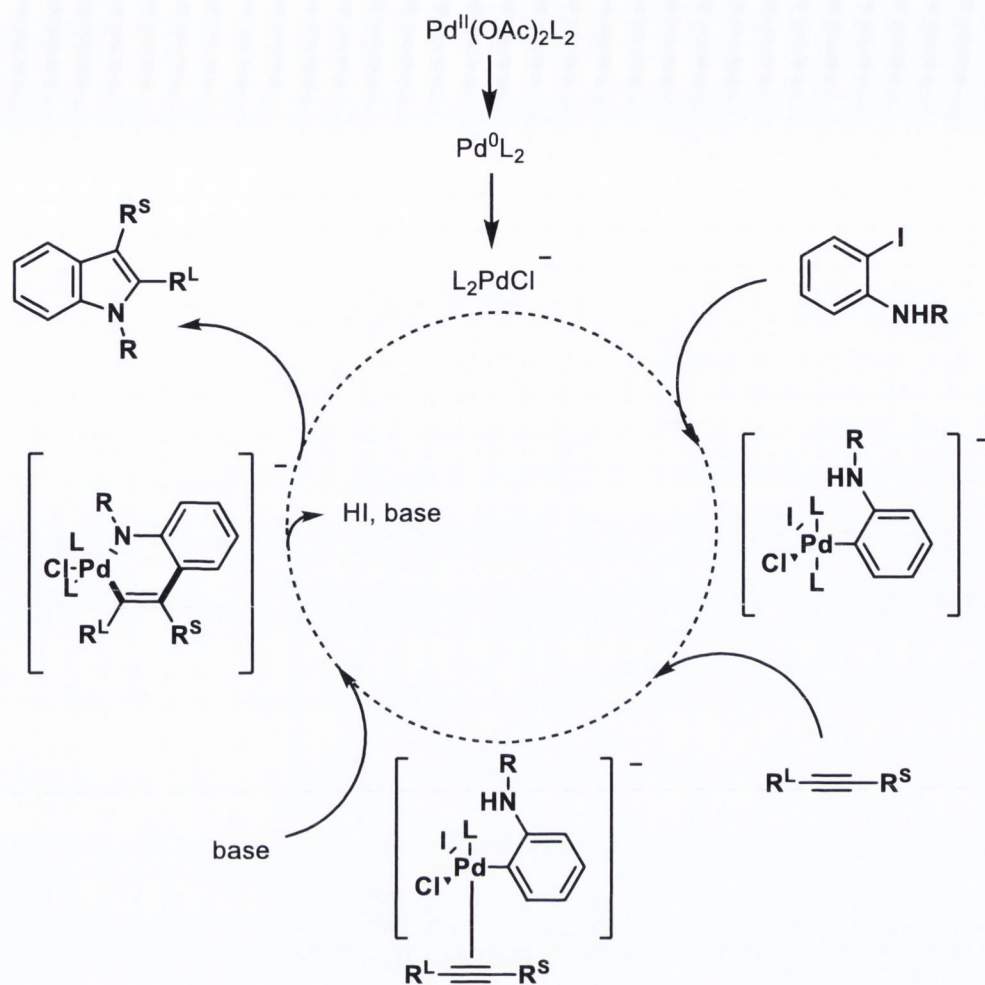
The Larock indole synthesis is a heteroannulation reaction between an iodoaniline and a disubstituted alkyne using catalytic amounts of palladium to generate highly functionalised indoles (Scheme 6.6.1).²⁶³

Scheme 6.6.1.



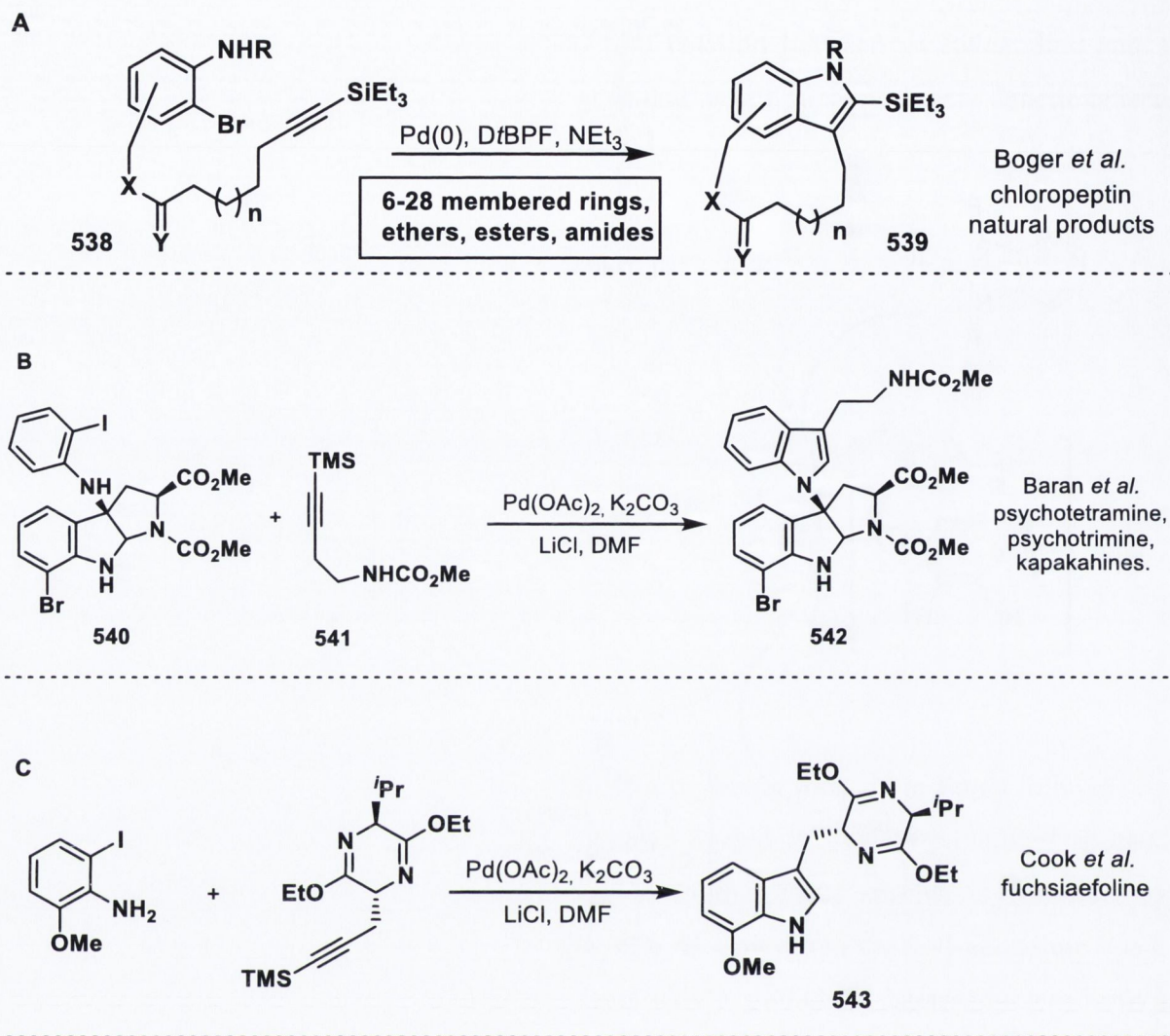
The catalytic cycle is proposed to start with Pd(II)OAc_2 being reduced to Pd(0) followed by coordination of a chloride anion to form a chloride ligated zerovalent palladium species. Subsequent oxidative addition of the aryl iodide to the Pd(0) species is followed by coordination of the alkyne moiety to the Pd atom. *Syn* insertion into the aryl-palladium bond, nitrogen displacement of the halide in the resulting vinylic palladium intermediate to form a six membered heteroatom containing palladacycle and reductive elimination form the desired indole. Pd(0) is also regenerated to continue the catalytic cycle (Scheme 6.6.2).

Scheme 6.6.2.



The synthetic utility of the Larock indole synthesis is surmised in its broad application throughout natural product chemistry. Due to the complicated reactivity of the indole system it is often beneficial to have indole precursors in place throughout a chemical synthesis and then perform a late stage indole forming reaction such as a Larock annulation. It is, therefore, possible to have either a disubstituted alkyne or an iodoaniline and transform them into the desired indole at the necessary stage in a synthesis. Selected examples of the ubiquitous nature of the Larock reaction in natural product chemistry are displayed in Scheme 6.6.3.

Scheme 6.6.3.

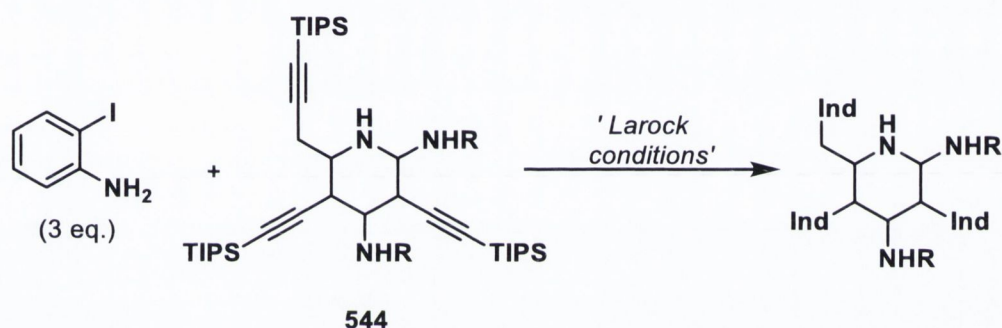


The possibility for forming typically challenging large rings (6 – 28 membered rings) was recognised by Boger and co-workers in 2013.²⁶⁴ Derivatised bromoanilines **538** containing an aliphatic linker moiety with a terminal protected alkyne were exposed to typical Larock conditions to generate the desired indole containing macrocycles **539** (Scheme 6.6.3, A). The Baran laboratory has a fond history of utilising the Larock indole synthesis en route to a number of architecturally complex natural products. The formation of a carbon nitrogen bond between the three position of an indole and the nitrogen atom of another indole molecule provided to be a daunting challenge. Initial attempts to introduce a leaving group at the three position of an indole, followed by nucleophilic displacement by a nucleophile proved ineffective. Eventually, the exposure of iodoaniline to NIS generated a haloamine, providing

a suitably electrophilic nitrogen source. Exposure to a nucleophilic indole constructed the required carbon nitrogen bond (Scheme 6.6.3, B). Now the molecule **540** was perfectly primed for a Larock reaction and in the presence of alkyne **541**, under suitable conditions, compound **542** was formed.²⁶⁵ Cook *et al.* have also effectively used the Larock reaction in their synthesis of tryptophan derivative **543** en route to the natural product fuchsiaefoline (Scheme 6.6.3, C).²⁶⁶

The idea to form a trimeric alkyne analogue **544** of the araiosamines and introduce the indoles in a late stage with a triple Larock reaction seemed a potential method for coping with the problematic indole reactivity encountered to date (Scheme 6.6.4).

Scheme 6.6.4.



Retrosynthetic analysis of trimeric alkyne **544** provided enamide **545**, which upon exposure to Terada's cyclising conditions could generate our desired compound **544** (Figure 6.6.1). It was hoped that, by incorporating such a sterically bulky protecting group as the triisopropylsilyl group at the terminal alkyne position, unwanted side reactivity could be avoided. The conjugated nature of the molecule however was an initial concern.

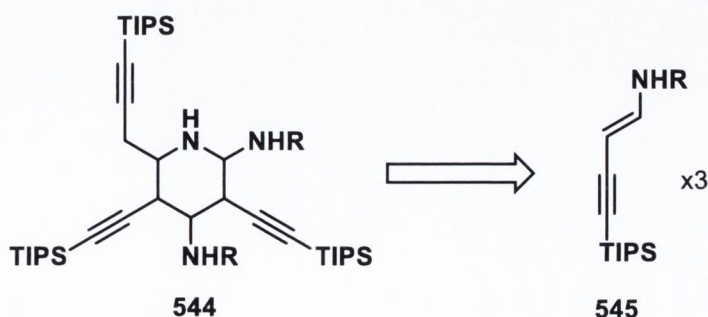
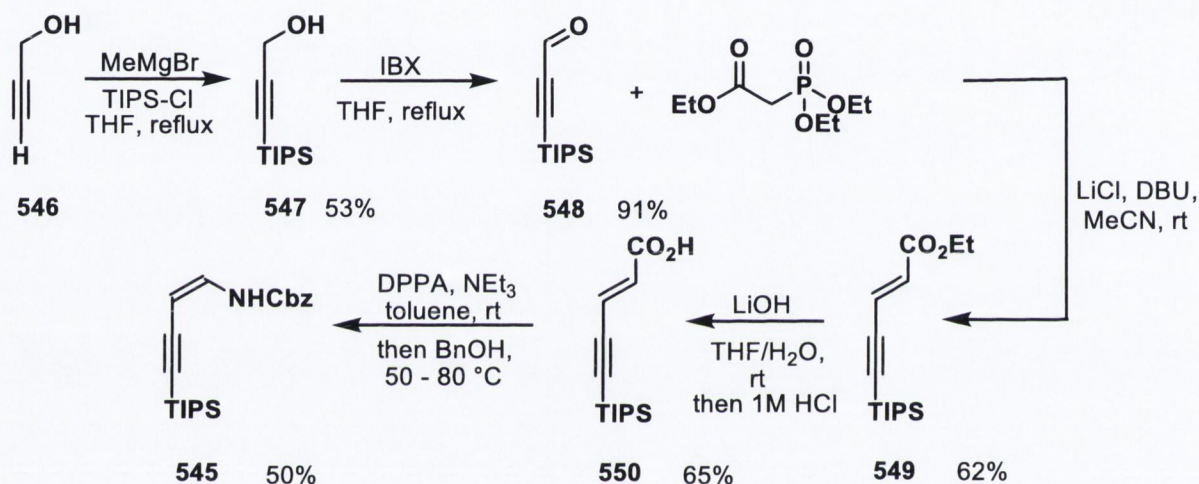


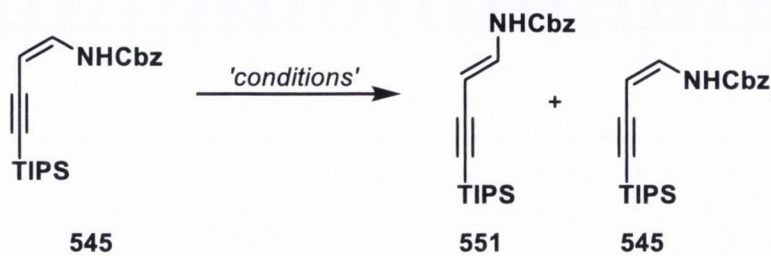
Figure 6.6.1. Retrosynthesis of Larock annulation precursor **544**.

Propargyl alcohol **546** was protected at the terminal alkyne position by exposure to TIPSCl to provide compound **547**.²⁶⁷ Oxidation of the primary alcohol **547** to aldehyde **548** was enabled using IBX. A mild modification of the Horner-Wadsworth-Emmons (HWE) reaction generated olefin **549** in primarily *trans* configuration, as it is typical for this type of reactivity.²⁶⁸ Basic hydrolysis of ester **549** formed carboxylic acid **550** which then underwent acyl azide formation and subsequent Curtius rearrangement²⁶⁹ to prepare enamide **545** (Scheme 6.6.5.).

Scheme 6.6.5.

With an unproblematic route to enamide **545** in hand, our attention turned to the elusive trimerisation reaction. Initial efforts attempted to replicate Terada's conditions with the use of chiral phosphoric acid **514**. Disappointingly, after a screening of acidic conditions the only observable product was *cis-trans* isomerization of the olefin (Table 6.6.1, entries 1 - 4).

Table 6.6.1. Investigations into trimerisation reaction of enamide monomer **545**.^a



Entry	Additive	Temp. (°C)	Product
1	514 (2 mol%)	0	>95% 545
2	514	rt	>90% 545 , trace 551
3	TFA	0	>90% 545 , trace 551
4	BF ₃ .OEt ₂	0	>90% 545 , trace 551

^a Additive (1 eq.), 12 h.

It was therefore concluded that trimerisation to afford advanced intermediates in the synthesis of the araiosamine natural products is unproductive and was terminated at this point. The substituted nature of the enamides used in these trimerisation studies has influenced the efficacy of this reaction and has proven unsuccessful for the formation of highly substituted piperidines (Figure 6.6.2).

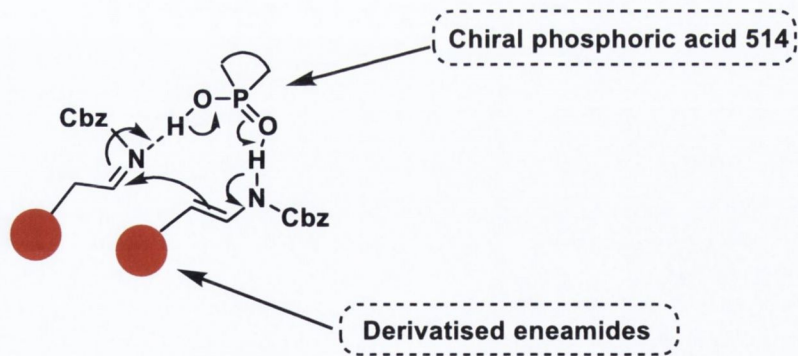


Figure 6.6.2. Proposed pre-transition state assembly of chiral phosphoric acid mediated addition of enamides to imines.

Further studies are ongoing into the synthesis of araiosamines A-D in the Baran laboratories.

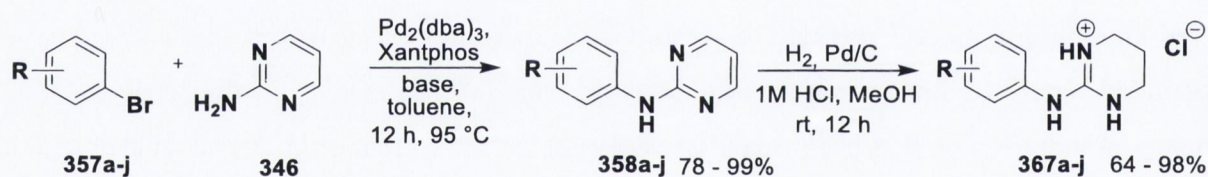
7. Conclusions and Future Work.

7.1. Conclusions.

This project has resulted in the development of three methodologies for the synthesis of biologically interesting guanidine containing compounds.

1) The first of these methods enables the rapid construction of 2-(arylamino)tetrahydro-1,4,5,6-pyrimidines **367**. This methodology incorporated a Pd mediated cross coupling reaction between aryl bromides **357** and 2-aminopyrimidine **346** followed by a Pd catalysed hydrogenation to afford the desired guanidine products in good to excellent yields (Scheme 7.1.1, 64 - 98%). In this way 11 guanidine containing compounds were prepared containing a variety of appendages on the arylamino moiety including electron withdrawing and electron donating substituents.

Scheme 7.1.1

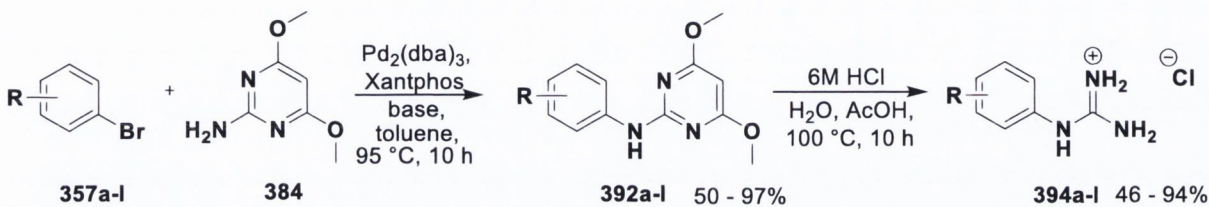


2) The next methodology developed introduced the use of 2-amino-4,6-dimethoxypyrimidine **384** as a guanidine precursor (Scheme 7.1.2). Thus, following the Buchwald-Hartwig approach (Scheme 7.1.2, A) the reaction of aryl bromides **357a-l** with 2-amino-4,6-dimethoxypyrimidine **384** in the presence of $\text{Pd}_2(\text{dba})_3$ as a Pd source, Xantphos **352** as a ligand and NaOt-Bu as a base, it was possible to achieve a library of 13 arylamino-4,6-dimethoxypyrimidine derivatives **392a-l** that by further treatment with HCl (6M) and acetic acid at $100\text{ }^\circ\text{C}$ were cleaved to render the corresponding 13 guanidine hydrochloride salts **394a-l**.

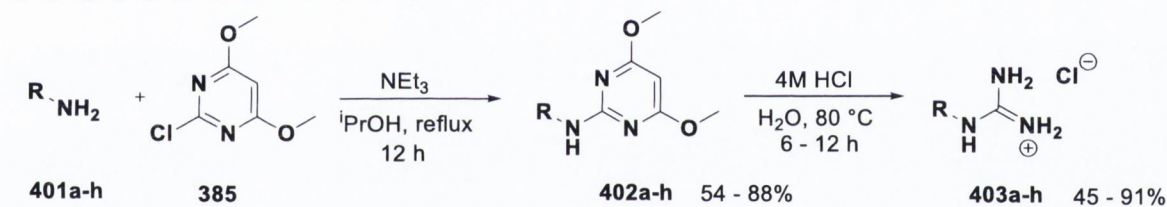
Alternatively, treatment of alkyl amines **401a-h** with 2-amino-4,6-dimethoxypyrimidine **385** in isopropanol, using NEt₃ as a base at reflux (Scheme 7.1.2, B) yielded the corresponding 8 alkylamino-4,6-dimethoxypyrimidines **402a-h** that were cleaved to the corresponding 8 guanidinium salts **403a-h** using HCl (4M) at 80 °C.

Scheme 7.1.2

A



B



This approach has shown to be very useful and versatile for the preparation of both aryl and alkyl guanidine derivatives allowing even for the use of orthogonal protective groups such as Fmoc.

This method of introducing a guanidine functional group has a number of characteristics which make it favourable to other known methods of guanidylation namely:

1. Environmentally friendly.
2. Atom economical in comparison with typical guanidine protecting groups.
3. Cost effective.
4. Typically no column chromatography required.

To surmise these points a comparison of typical guanidylating reagents with 2-amino-4,6-dimethoxypyrimidine **384** employed for the synthesis of aryl guanidines is presented in Figure 7.1.1.

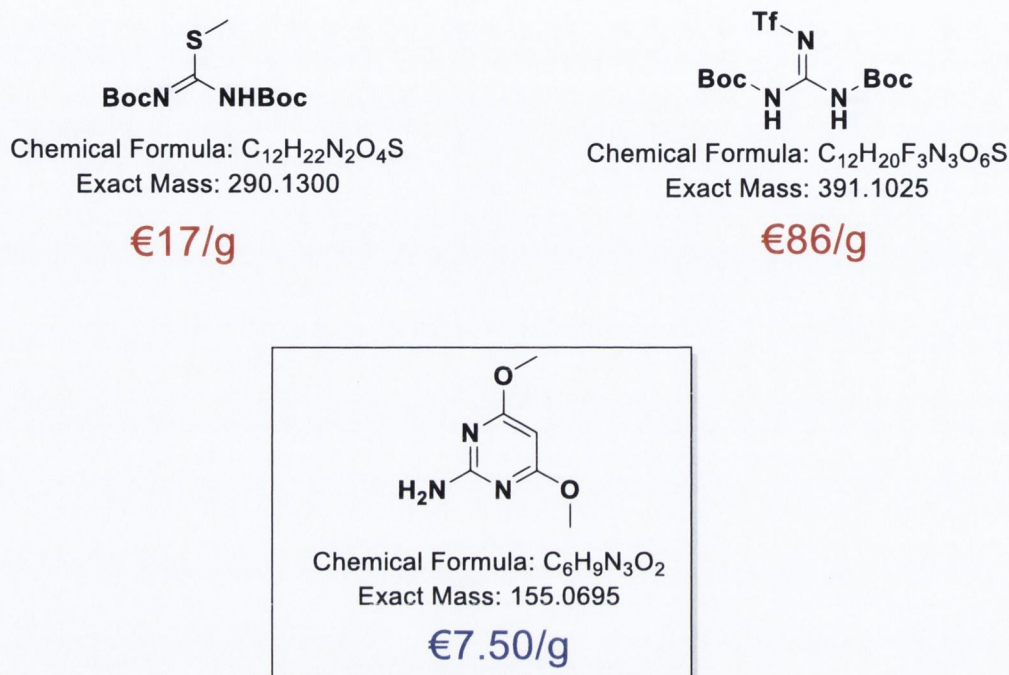


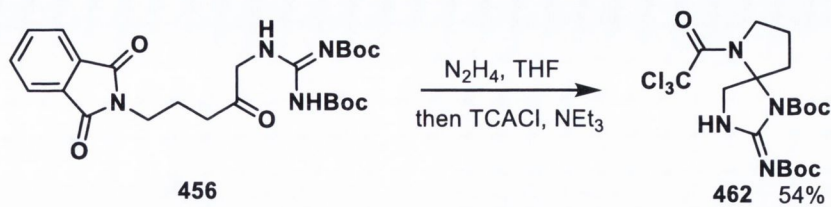
Figure 7.1.1. A comparison of typically employed guanidylating agents with 2-amino-4,6-dimethoxypyrimidine **384**.

3) The last method developed for preparing biologically interesting guanidine containing compounds, employed a cascade cyclisation reaction to form a spiro guanidine aminal structure (Scheme 7.1.3, **A**). Thus, unmasking of an amino group of **456** by the removal of the phthalimide protecting group facilitated an intramolecular cascade reaction forming an unprecedented spiro guanidine aminal **462**.

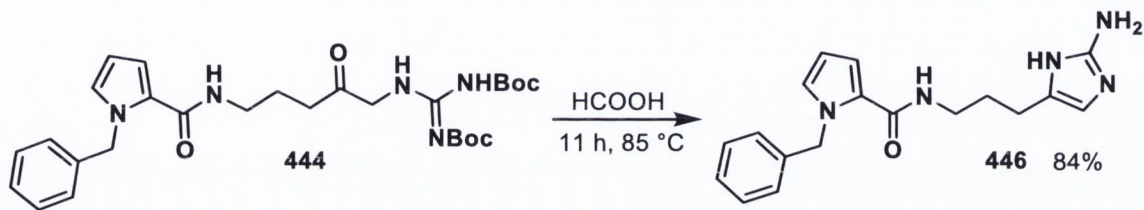
During this synthetic endeavour *N*-benzyl dihydroclathrocin **446** was synthesised (Scheme 7.1.3, **B**). The discovery that the guanidinium cation was more nucleophilic than the amide of compound **444** resulted in condensation of the guanidine onto the ketone forming the 2-aminoimidazole portion of dihydroclathrocin **446**.

Scheme 7.1.3.

A



B



Finally initial attempts to synthesis the araiosamine family of natural products (Figure 7.1.2) was conducted under the supervision of Prof. Baran at the Scripps Research Institute.

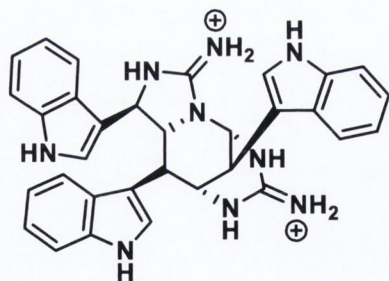


Figure 7.1.2. Araiosamine C.

The focus of our attention was to imitate the proposed biosynthesis of araiosamines A-D by means of an enamide trimerisation reaction (Figure 7.1.3).

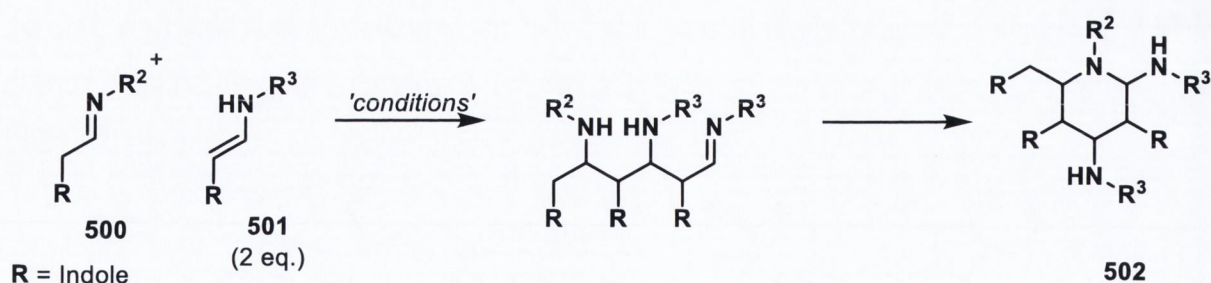


Figure 7.1.3. Desired trimerisation reaction for the formation of the araiosamine core.

7.2. Future Work.

After the success of our developed guanidylation reaction by means of cleavage of the 2-amino-4,6-dimethoxypyrimidine ring it is hoped that this procedure could be further investigated to find more facile methods for ring cleavage. A more gentle method of cleavage would enable this new guanidine precursor to find applications in peptide chemistry, an area which would greatly benefit from a new guanidine protecting group. Lewis acidic conditions may potentially facilitate the desired transformation (Scheme 7.2.1).

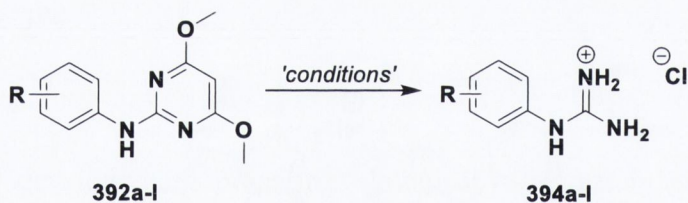


Figure 7.2.2. Desired facile cleavage of 2-amino-4,6-dimethoxypyrimidines **392a-l**.

As well as finding uses in peptide chemistry this methodology would be found exceptionally useful in the synthesis of guanidine natural products. Due to the stability of the pyrimidine system this protecting group would allow for the early stage installation of the guanidine functionality which is extremely rare. The system would then be untouched by the typical conditions known to deprotect guanidines.

The methods developed will be applied to the synthesis of potential α_2 -adrenoceptor (α_2 -AR) antagonists and minor groove binders (MGBs). It is intended that spiro guanidine amins will also be incorporated into new α_2 -ARs antagonists and MGBs.

The synthesis of aryl analogues of dibromophakellin **23** would enable the rapid construction of a vast library of guanidine containing compounds which could find uses as α_2 -AR antagonists (Figure 7.2.2).

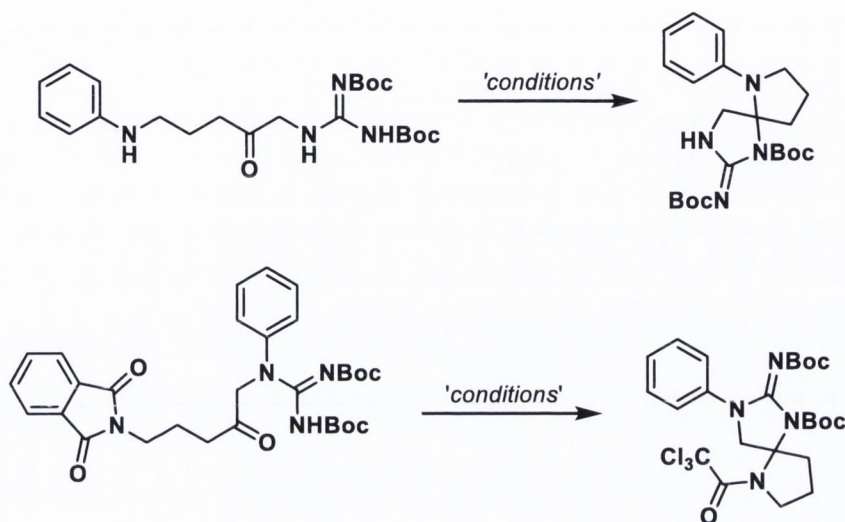
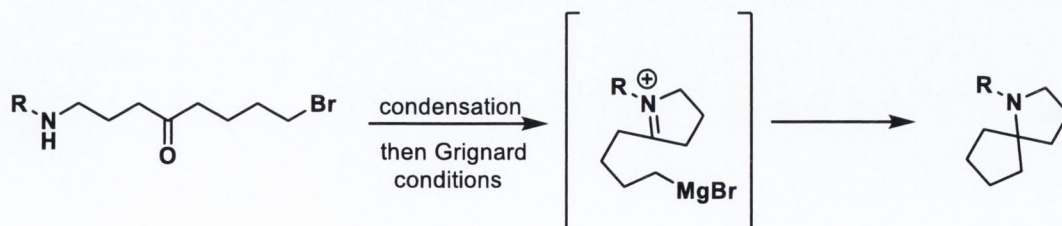


Figure 7.2.2. Generation of a diverse family of guanidine containing compounds.

This developed cyclisation reaction could also be applied to other cascade sequences such as the condensation of an amine onto a ketone followed by the formation of a carbon nucleophile by means of Grignard chemistry (Scheme 7.2.1). This would generate synthetically useful spirocyclic pyrrolidine derivatives.

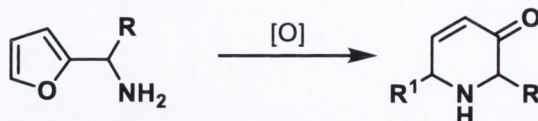
Scheme 7.2.1.



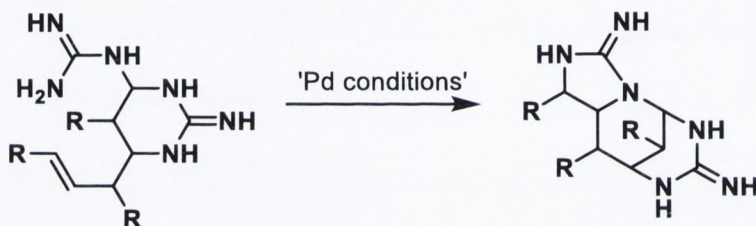
The araiosamine family of natural products is currently being synthesised at the Scripps Research Institute in Prof. Baran's laboratories by Ming Yan and co-workers. Routes developed include an aza-Achmatowicz reaction to form the piperidine core (Scheme 7.2.2, **A**) and also a Pd catalysed annulation reaction (Scheme 7.2.2, **B**).

Scheme 7.2.2.

A.



B.



8. Experimental procedures and data.

General Procedures.

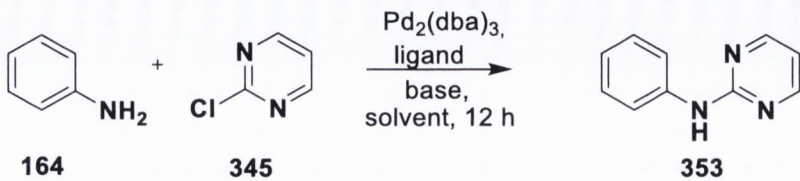
Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Dry diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), acetonitrile (CH_3CN), toluene, tetrahydrofuran (THF), methanol (MeOH), and triethylamine (Et_3N) were obtained by distillation (as described by Vogel)²⁷⁰ and stored over 4 Å molecular sieves. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using either UV light as the visualizing agent or an acidic mixture of anisaldehyde, phosphomolybdic acid, or ceric ammonium molybdate, or basic aqueous potassium permanganate (KMnO_4), or ninhydrin and heat as developing agents. E. Merck silica gel (60, particle size 0.0430–0.063 mm) was used for flash column chromatography. Preparative thin layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). Concentration of organic solvents was performed on a rotary evaporator under reduced pressure followed by further evacuation using a two-stage mechanical pump. NMR spectra were recorded on Bruker DPX-600 and Bruker DPX-400 instruments operating at 400.13 MHz and 600.1 MHz for ^1H NMR; 100.6 MHz and 150.9 MHz for ^{13}C -NMR and calibrated using residual undeuterated solvent as an internal reference (CHCl_3 @ δ 7.26 ppm ^1H NMR, δ 77.16 ^{13}C NMR; CH_2Cl_2 @ δ 5.32 ppm ^1H NMR, δ 53.84 ppm ^{13}C NMR). The following abbreviations (or combinations thereof) were used to explain ^1H NMR multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quin. = quintet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were measured on a Micromass LCT electrospray TOF instrument with a WATERS 2690 autosampler and methanol/acetonitrile as carrier solvent. Melting points were determined using a Stuart Scientific Melting Point SMP1 apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Spectrum One FT-IR Spectrometer equipped with a Universal ATR sampling accessory.

HPLC purity analysis was carried out using a Varian ProStar system equipped with a Varian Prostar 335 diode array detector and a manual injector (20 μ L). For purity assessment, UV detection was performed at 245 nm and peak purity was confirmed using a purity channel. The stationary phase consisted of an ACE 5 C18-AR column (150 $\times$ 4.6 mm), and the mobile phase used the following gradient system, eluting at 1 mL/min: aqueous formate buffer (30 mM, pH 3.0) for 10 minutes, linear ramp to 85% methanol buffered with the same system over 25 minutes, hold at 85% buffered methanol for 10 minutes. Minimum requirement for purity was set at 95.0%.

Compounds are assigned arbitrary numbers for assignment of the NMR spectrum and these numbers do not correspond to the naming of the compound.

8.1. 2-(Arylamino)-tetrahydro-1,4,5,6-pyrimidines.

Optimisation of the Pd catalysed coupling of 2-chloropyrimidine with aniline.^a

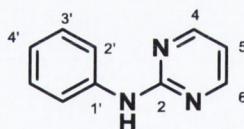


Entry	Pd (mol%)	Ligand (mol%)	Base	Solvent	Temp. (°C)	Yield (%)
1	-	-	NaOt-Bu	toluene	100	23
2	2	350 (2)	NaOt-Bu	toluene	90	56
3	2	350 (2)	NaOt-Bu	toluene	100	56
4	2	349 (2)	NaOt-Bu	toluene	90	47
5	2	350 (2)	Cs ₂ CO ₃	toluene	90	29
6	2	350 (2)	K ₃ PO ₄	toluene	90	22
7	2	350 (2)	NaOt-Bu	toluene	90	55
8	2	351 (2)	NaOt-Bu	toluene	90	<5
9	2	350 (2)	NaOt-Bu	DME	75	<5
10	2	350 (2)	NaOt-Bu	1,4-dioxane	90	11
11	2	348 (2)	NaOt-Bu	toluene	100	<5
12	3	350 (3)	NaOt-Bu	toluene	100	54
13	4	350 (4)	NaOt-Bu	toluene	100	50
14	5	351 (5)	NaOt-Bu	toluene	100	55
15	2	352 (2)	NaOt-Bu	toluene	90	85
16	2	352 (3)	NaOt-Bu	toluene	95	88
17	2	350 (2)	NaOt-Bu	toluene	100	64 ^b
18	2	350 (2)	NaOt-Bu	toluene	100	63 ^c
19	2	350 (2)	K ₂ CO ₃	<i>t</i> -BuOH	110	12

^a Aniline (1.5 mmol), base (1.5 mmol), 2-chloropyrimidine (1.0 mmol), Pd₂(dba)₃, ligand, solvent (1.5 mL/mmol 2-chloropyrimidine **345**), 12 h. ^b 24 h. ^c 48 h.

Method A: The coupling of anilines with 2-chloropyrimidine.

To an oven dried Schlenk tube charged with $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg) and Xantphos (3 mol%, 17 mg) was added 2-chloropyrimidine (114 mg, 1.0 mmol, 1.0 eq.), base (1.5 mmol, 1.5 eq.) and aniline (1.5 mmol, 1.5 eq.). The Schlenk tube was then put under vacuum and back filled with argon three times. To this was added freshly distilled toluene (1.5 mL). The Schlenk tube was then placed in an oil bath with vigorous stirring at 95 °C. The reaction was monitored by TLC and once deemed complete (typically 8 – 12 h, TLC analysis) was cooled to rt and diluted with EtOAc (10 mL). The reaction was then filtered through a pad of Celite® with any remaining residues in the Schlenk tube being further washed with another portion of EtOAc (5 mL). To the filtered solution was added H_2O (10 mL) and the layers separated. The aqueous phase was further extracted with EtOAc (3×10 mL) and the combined organic layers washed with brine (20 mL), dried over MgSO_4 and concentrated under reduced pressure to afford the crude product. This residue was then purified by column chromatography (silica gel, hexanes:EtOAc, 100:0 $\rightarrow$ 60:40) to yield the target compound.

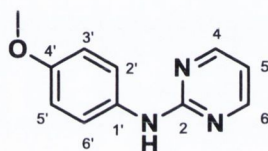
2-Anilinopyrimidine (353)

Following Method A aniline (91 μL , 1.5 mmol, 1.5 eq.) was added to an oven dried Schlenk tube charged with $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-chloropyrimidine (114 mg, 1.0 mmol, 1.0 eq.) and NaOt-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 °C for 12 h and then worked up according to Method A.

Yield:	88% (150 mg).
Physical State:	Colourless crystal.
Mp:	112-115 °C. (Lit. 115 - 116 °C) ²⁸⁶
R_f:	0.40 (hexanes:EtOAc, 80:20).
IR ν_{max} (film)/ cm^{-1} :	3254 (NH), 3054, 1609, 1576, 1444, 793, 746, 698.

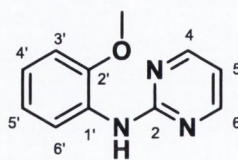
¹H NMR (400 MHz, CDCl ₃):	δ 6.75 (t, <i>J</i> = 5.0 Hz, 1H, H-5), 7.09 (t, <i>J</i> = 7.2 Hz, 1H, H-4'), 7.38 (app. t, 2H, H-3'), 7.43 (br s, NH) 7.64 (d, <i>J</i> = 7.2 Hz, 2H, H-2'), 8.45 (d, <i>J</i> = 5.0 Hz, 2H, H-4, 6).
¹³C NMR (100 MHz, CDCl ₃):	δ 112.1 (CH), 119.1 (2CH), 122.2 (CH), 128.5 (2CH), 138.9 (qC), 157.6 (2CH), 159.7 (qC).
HRMS (<i>m/z</i> ESI ⁺):	Found 172.0867 (M ⁺ + H. C ₁₀ H ₁₀ N ₃ Requires 172.0869).

2-(4-Methoxyanilino)pyrimidine (355b)



Following Method A *p*-anisidine (184 mg, 1.5 mmol, 1.5 eq.) was added to an oven dried Schlenk tube charged with Pd₂(dba)₃ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-chloropyrimidine (114 mg, 1.0 mmol, 1.0 eq.) and NaO*t*-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 100 °C for 10 h and then worked up according to Method A.

Yield:	87% (175 mg).
Physical State:	White solid.
Mp:	129-131 °C. (Lit. 125 - 126 °C) ²⁸⁷
R_f:	0.36 (hexanes:EtOAc, 80:20).
IR ν _{max} (film)/cm ⁻¹ :	3260 (NH), 2980, 1712, 1620, 1584, 1208, 1155, 852, 819, 777.
¹H NMR (400 MHz, CDCl ₃):	δ 3.82 (s, 3H, OCH ₃), 6.68 (t, <i>J</i> = 5.0 Hz, 1H, H-5), 6.91 (d, <i>J</i> = 9.0 Hz, 2H, H-3',5'), 7.34 (br s, NH), 7.49 (d, <i>J</i> = 9.0 Hz, 2H, H-2',6'), 8.39 (d, <i>J</i> = 5.0 Hz, 2H, H-4,6).
¹³C NMR (100 MHz, CDCl ₃):	δ 55.0 (CH ₃), 111.6 (CH), 113.8 (2CH), 119.8 (qC), 121.9 (2CH), 131.8 (qC), 157.6 (2CH), 160.2 (qC).
HRMS (<i>m/z</i> ESI ⁺):	Found 202.0982 (M ⁺ + H. C ₁₁ H ₁₂ N ₃ O Requires 202.0980).

2-(2-Methoxyanilino)pyrimidine (355c)

Following Method A *o*-anisidine (184 mg, 1.5 mmol, 1.5 eq.) was added to an oven dried Schlenk tube charged with Pd₂(dba)₃ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-chloropyrimidine (114 mg, 1.0 mmol, 1.0 eq.) and NaOt-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 100 °C for 10 h and then worked up according to Method A.

Yield: 72% (144 mg).

Physical State: Colourless crystal.

Mp: 121-124 °C.

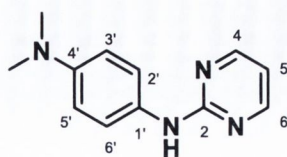
R_f: 0.39 (hexanes:EtOAc, 80:20).

IR ν_{max} (film)/cm⁻¹: 3255 (NH), 2972, 1608, 1576, 1444, 1251, 973, 793, 779, 693, 669.

¹H NMR (400 MHz, CDCl₃): δ 3.91 (s, 3H, OCH₃), 6.71 (t, *J* = 5.0 Hz, 1H, H-5), 6.92 (d, *J* = 7.0 Hz, 1H, H-3'), 7.02 (m, 2H, H-4',5'), 7.83 (br s, NH), 8.45 (d, *J* = 5.0 Hz, 1H, H-6'), 8.53 (d, *J* = 7.0 Hz, 2H, H-4,6).

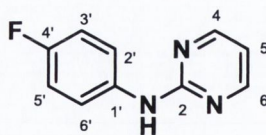
¹³C NMR (100 MHz, CDCl₃): δ 55.2 (CH₃), 109.5 (CH), 111.9 (CH), 118.1 (CH), 120.4 (CH), 121.4 (CH), 128.7 (qC), 147.5 (qC), 157.5 (2CH), 159.5 (qC).

HRMS (*m/z* ESI⁺): Found 202.0988 (M⁺ + H. C₁₁H₁₂N₃O Requires 202.0980).

2-[4-(*N,N*-Dimethylamino)anilino]pyrimidine (355d)

Following Method A *N,N*-dimethyl-*p*-phenylenediamine (204 mg, 1.5 mmol, 1.5 eq.) was added to an oven dried Schlenk tube charged with Pd₂(dba)₃ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-chloropyrimidine (114 mg, 1.0 mmol, 1.0 eq.) and NaOt-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 100 °C for 12 h and then worked up according to Method A.

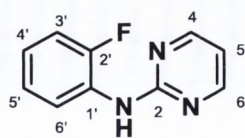
Yield:	72% (154 mg).
Physical State:	Dark red/black solid.
Mp:	137-140 °C.
R_f:	0.50 (hexanes:EtOAc, 80:20).
IR ν_{max} (film)/cm ⁻¹ :	3237 (NH), 3155, 2849, 1600, 1582, 1564, 1364, 991, 793, 704.
¹H NMR (400 MHz, CDCl ₃):	δ 2.92 (s, 6H), 6.60 (t, J = 4.8 Hz, 1H, H-5), 6.76 (d, J = 8.8 Hz, 2H, H-3',5'), 7.17 (br s, NH), 7.38 (d, J = 8.8 Hz, 2H, H-2',6'), 8.34(d, J = 4.8 Hz, 2H, H-4,6).
¹³C NMR (100 MHz, CDCl ₃):	δ 40.9 (2CH ₃), 111.6 (CH), 113.3 (2CH), 122.5 (2CH), 128.9 (qC), 147.6 (qC), 158.3 (2CH), 161.0 (qC).
HRMS (m/z ESI ⁺):	Found 215.1298. (M ⁺ + H. C ₁₂ H ₁₅ N ₄ Requires 215.1297).

2-(4-Fluoroanilino)pyrimidine (355e)

Following Method A 4-fluoroaniline (166 mg, 1.5 mmol, 1.5 eq.) was added to an oven dried Schlenk tube charged with $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-chloropyrimidine (114 mg, 1.0 mmol, 1.0 eq.) and NaOt-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 100 °C for 12 h and then worked up according to Method A.

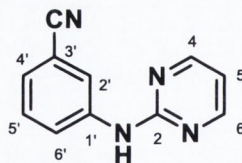
Yield:	50% (94 mg).
Physical State:	Pale yellow crystal.
Mp:	147-150 °C. (Lit. 148 - 149 °C) ²⁸⁷
R_f:	0.36 (hexanes:EtOAc, 80:20).
IR ν_{max} (film)/ cm^{-1} :	3259 (NH), 2972, 1713, 1619, 1584, 1506, 1416, 1280, 791, 709.
^1H NMR (400 MHz, CDCl_3):	δ 6.74 (t, $J = 5.0$ Hz, 1H, H-5), 7.06 - 7.07 (m, 2H, H-3',5'), 7.51 (br s, NH), 7.57 - 7.58 (m, 2H, H-2',6'), 8.43 (d, $J = 5.0$ Hz, 2H, H-4,6).
^{13}C NMR (100 MHz, CDCl_3):	δ 112.1 (CH), 114.9 (2CH, $J_{\text{CF}} = 23.0$ Hz), 121.1 (2CH, $J_{\text{CF}} = 15.0$ Hz), 134.8 (qC), 157.0 (qC), 157.6 (2CH), 159.4 (qC, $J_{\text{CF}} = 240.0$ Hz).
HRMS (m/z ESI ⁺):	Found 190.0789 ($\text{M}^+ + \text{H}$. $\text{C}_{10}\text{H}_9\text{FN}_3$ Requires 190.0780).

2-(2-Fluoroanilino)pyrimidine (355f)



Following Method A 2-fluoroaniline (166 mg, 1.5 mmol, 1.5 eq.) was added to an oven dried Schlenk tube charged with Pd₂(dba)₃ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-chloropyrimidine (114 mg, 1.0 mmol, 1.0 eq.) and NaO*t*-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 100 °C for 12 h and then worked up according to Method A.

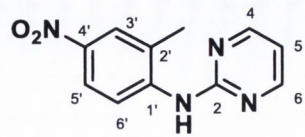
Yield:	49% (93 mg).
Physical State:	Yellow solid.
Mp:	110-114 °C. (Lit. 117 - 118 °C) ²⁸⁸
R_f:	0.38 (hexanes:EtOAc, 80:20).
IR ν _{max} (film)/cm ⁻¹ :	3249 (NH), 3014, 1576, 1489, 1439, 1252, 1106, 1030, 795, 753.
¹H NMR (400 MHz, CDCl ₃):	δ 6.73 (t, <i>J</i> = 5.0 Hz, 1H, H-5), 6.97 (m, 1H, H-3'), 7.09 (m, 2H, H-4',5'), 7.98 (br s, NH), 8.38 (d, <i>J</i> = 7.6 Hz, 1H, H-6'), 8.43 (d, <i>J</i> = 5.0 Hz, 2H, H-4,6).
¹³C NMR (100 MHz, CDCl ₃):	δ 112.5 (CH), 114.3 (CH, <i>J</i> _{CF} = 20.0 Hz), 114.5 (CH), 122.2 (CH, <i>J</i> _{CF} = 8.0 Hz), 123.7 (CH, <i>J</i> _{CF} = 8.0 Hz), 127.5 (qC, <i>J</i> _{CF} = 20.0 Hz), 151.3 (qC, <i>J</i> _{CF} = 260.0 Hz), 157.5 (2CH), 159.5 (qC).
HRMS (<i>m/z</i> ESI ⁺):	Found 190.0785 (M ⁺ + H. C ₁₀ H ₉ FN ₃ Requires 190.0780).

2-(3-Cyanoanilino)pyrimidine (355g)

Following Method A 3-aminobenzonitrile (177 mg, 1.5 mmol, 1.5 eq.) was added to an oven dried Schlenk tube charged with $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-chloropyrimidine (114 mg, 1.0 mmol, 1.0 eq.) and K_3PO_4 (318 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 100 °C for 12 h and then worked up according to Method A.

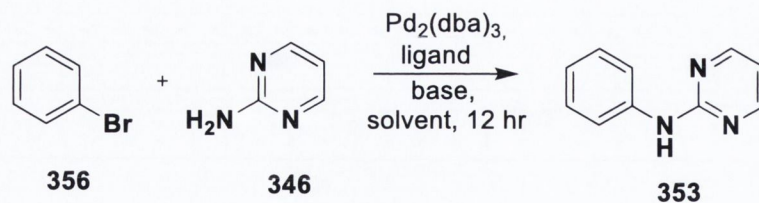
Yield:	55% (106 mg).
Physical State:	Colourless oil.
Mp:	-
R_f:	0.28 (hexanes:EtOAc, 80:20).
IR ν_{max} (film)/ cm^{-1} :	3265 (NH), 3087, 2227 (CN), 1603, 1577, 1493, 1308, 1179, 1094, 1004, 965, 856, 778, 705, 682.
^1H NMR (400 MHz, CDCl_3):	δ 6.88 (t, J = 4.4 Hz, 1H, H-5), 7.35 (d, J = 8.0 Hz, 1H, H-6'), 7.44 (app. t, 1H, H-5'), 7.63 (br s, NH), 7.69 (d, J = 8.0 Hz, 1H, H-4'), 8.31 (s, 1H, H-2'), 8.51 (d, J = 4.4 Hz, 2H, H-4,6).
^{13}C NMR (100 MHz, CDCl_3):	δ 112.5 (qC), 113.1 (CH), 118.5 (qCN), 121.4 (CH), 122.5 (CH), 125.2 (CH), 129.2 (CH), 139.7 (qC), 157.6 (2CH), 158.9 (qC).
HRMS (m/z ESI^+):	Found 197.0820 ($\text{M}^+ + \text{H}$. $\text{C}_{11}\text{H}_9\text{N}_4$ Requires 197.0827).

2-(4-Nitro-2-methylanilino)pyrimidine (355h)



Following Method A 4-nitro-2-methylaniline (228 mg, 1.5 mmol, 1.5 eq.) was added to an oven dried Schlenk tube charged with Pd₂(dba)₃ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-chloropyrimidine (114 mg, 1.0 mmol, 1.0 eq.) and K₃PO₄ (318 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 100 °C for 12 h and then worked up according to Method A.

Yield:	54% (85 mg).
Physical State:	Yellow fluffy solid.
Mp:	178-180 °C.
R_f:	0.30 (hexanes:EtOAc, 80:20).
IR ν_{max} (film)/cm ⁻¹ :	3260 (NH), 3060, 1712, 1620, 1538 (NO ₂), 1412, 1253 (NO ₂), 1155, 1081, 852, 818, 750, 703.
¹H NMR (400 MHz, CDCl ₃):	δ 2.46 (s, 3H, CH ₃), 6.92 (t, <i>J</i> = 5.0 Hz, 1H, H-5), 7.31 (br s, NH), 8.13 (s, 1H, H-3'), 8.16 (d, <i>J</i> = 8.8 Hz, 1H, H-6'), 8.55 (d, <i>J</i> = 5.0 Hz, 2H, H-4,6), 8.67 (d, <i>J</i> = 8.8 Hz, 1H, H-5').
¹³C NMR (100 MHz, CDCl ₃):	δ 17.6 (CH ₃), 113.9 (CH), 117.5 (CH), 122.7 (CH), 125.3 (CH), 139.9 (qC), 141.3 (qC), 143.4 (qC), 157.7 (2CH), 158.8 (qC).
HRMS (<i>m/z</i> ESI ⁺):	Found 231.0871 (M ⁺ + H. C ₁₁ H ₁₁ N ₄ O ₂ Requires 231.0882).

Optimisation of the Pd catalysed coupling of 2-aminopyrimidine with bromobenzene.^a

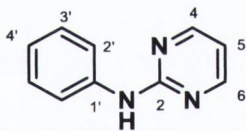
Entry	Pd (mol%)	Ligand (mol%)	Base	Solvent	Temp. (°C)	Yield (%)
1	-	-	NaOt-Bu	toluene	90	0
2	2	350 (2)	NaOt-Bu	toluene	90	45
3	2	350 (2)	NaOt-Bu	toluene	100	50
4	2	349 (2)	NaOt-Bu	toluene	90	35
5	2	350 (2)	Cs ₂ CO ₃	toluene	90	23
6	2	350 (2)	K ₃ PO ₄	toluene	90	34
7	2	350 (2)	NaOt-Bu	toluene	90	52
8	2	350 (2)	NaOt-Bu	toluene	100	54
9	2	351 (2)	NaOt-Bu	toluene	90	9
10	2	350 (2)	NaOt-Bu	DME	75	32
11	2	350 (2)	NaOt-Bu	1,4-dioxane	90	27
12	2	348 (2)	NaOt-Bu	toluene	100	<5
13	3	350 (3)	NaOt-Bu	toluene	100	55
14	4	350 (4)	NaOt-Bu	toluene	100	60
15	5	350 (5)	NaOt-Bu	toluene	100	59
16	2	352 (2)	NaOt-Bu	toluene	90	97
17	2	352 (3)	NaOt-Bu	toluene	95	98
18	2	350 (2)	NaOt-Bu	toluene	100	58 ^b
19	2	350 (2)	NaOt-Bu	toluene	100	57 ^c
20	2	350 (2)	K ₂ CO ₃	<i>t</i> -BuOH	110	45

^a 2-aminopyrimidine (1.5 mmol), base (1.5 mmol), aryl bromide (1.0 mmol), Pd₂(dba)₃, ligand, solvent (1.5 mL), 12 h. ^b 24 h. ^c 48 h.

Method B - The coupling of 2-aminopyrimidine with aryl bromides.

To an oven dried Schlenk tube charged with Pd₂(dba)₃ (2 mol%, 18 mg) and Xantphos **352** (3 mol%, 17 mg) was added 2-aminopyrimidine (142 mg, 1.5 mmol, 1.5 eq.), base (1.5 mmol, 1.5 eq.) and aryl bromide (1.0 mmol, 1.0 eq.). The Schlenk tube was then put under vacuum and back filled with argon three times. To this was added freshly distilled toluene (1.5 mL). The Schlenk tube was then placed in an oil bath with vigorous stirring at 95 °C. The reaction was monitored by TLC and once deemed complete (typically 8 – 12 h) was cooled to rt and diluted with EtOAc (10 mL). The reaction was then filtered through a pad of Celite© with any remaining residues in the Schlenk tube being further washed with another portion of EtOAc (5 mL). To the filtered solution was added H₂O (10 mL) and the layers separated. The aqueous phase was further extracted with EtOAc (3 × 10 mL) and the combined organic layers washed with brine (20 mL), dried over MgSO₄ and concentrated under reduced pressure to afford the crude product. This residue was then purified by column chromatography (silica gel, hexanes:EtOAc, 100:0 → 60:40) to yield the target compound.

2-Anilinopyrimidine (353)



Following Method B bromobenzene (1575 µL, 15.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with Pd₂(dba)₃ (2 mol%, 270 mg), Xantphos (3 mol%, 255 mg), 2-aminopyrimidine (2130 mg, 30.0 mmol, 1.5 eq.) and NaO*t*-Bu (2160 mg, 30.0 mmol, 1.5 eq.). After air extraction and backfilling with Ar, toluene (22.5 mL) was added. The reaction was stirred at 95 °C for 12 h and then worked up according to Method B.

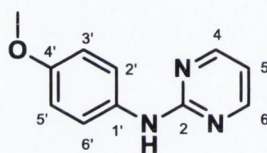
Spectral data for this compound were consistent with those of compound **353** prepared according to Method A.

Yield: 98% (2513 mg).

Physical State: Colourless crystal.

Mp:	112-113 °C.
R_f:	0.40 (hexanes:EtOAc, 80:20).
IR ν_{max} (film)/cm ⁻¹ :	3234 (NH), 3067, 2960, 1865, 1606, 1583, 1510, 1446, 1300, 1257, 1232, 1034, 1008, 885, 822, 787, 676, 660.
¹H NMR (400 MHz, CDCl ₃):	δ 6.75 (t, J = 5.0 Hz, 1H, H-5), 7.09 (t, J = 7.2 Hz, 1H, H-4'), 7.38 (app. t, 2H, H-3'), 7.43 (br s, NH) 7.64 (d, J = 7.2 Hz, 2H, H-2'), 8.45 (d, J = 5.0 Hz, 2H, H-4, 6).
HRMS (m/z ESI ⁺):	Found 172.0867 (M ⁺ + H. C ₁₀ H ₁₀ N ₃ Requires 172.0869).

2-(4-Methoxyanilino)pyrimidine (358a)

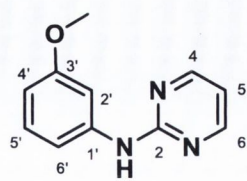


Following Method B 4-bromoanisole (125 μ L, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with Pd₂(dba)₃ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-aminopyrimidine (142 mg, 1.5 mmol, 1.5 eq.) and NaOt-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 °C for 12 h and then worked up according to Method B.

Spectral data for this compound were consistent with those of compound **355b** prepared according to Method A.

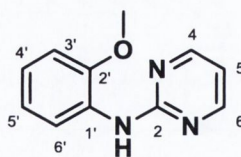
Yield:	90% (91 mg).
Physical State:	White crystal.
Mp:	130-131 °C.
R_f:	0.36 (hexanes:EtOAc, 80:20).
¹H NMR (400 MHz, CDCl ₃):	δ 3.82 (s, 3H, OCH ₃), 6.68 (t, J = 5.0 Hz, 1H, H-5), 6.91 (d, J = 9.0 Hz, 2H, H-3',5'), 7.34 (br s, NH), 7.49 (d, J = 9.0 Hz, 1H, H-2',6'), 8.39 (d, J = 5.0 Hz, 2H, H-4,6).
HRMS (m/z ESI ⁺):	Found 202.0982 (M ⁺ + H. C ₁₁ H ₁₂ N ₃ O Requires 202.0980).

2-(3-Methoxyanilino)pyrimidine (358b)



Following Method B 3-bromoanisoole (125 μ L, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with Pd₂(dba)₃ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-aminopyrimidine (142 mg, 1.5 mmol, 1.5 eq.) and NaOt-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 °C for 12 h and then worked up according to Method B.

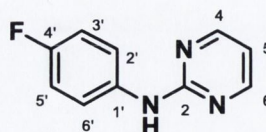
Yield:	95% (96 mg).
Physical State:	Colourless crystal.
Mp:	127-129 °C.
R_f:	0.37 (hexanes:EtOAc, 80:20).
IR ν_{max} (film)/cm ⁻¹ :	3259 (NH), 2971, 1712, 1620, 1584, 1507, 1412, 1155, 791, 777.
¹H NMR (400 MHz, CDCl ₃):	δ 3.86 (s, 3H, OCH ₃), 6.64 (d, J = 7.8 Hz, 1H, H-4'), 6.76 (t, J = 5.0 Hz, 1H, H-5), 7.12 (d, J = 7.8 Hz, 1H, H-6'), 7.26 (app. t, 1H, H-5'), 7.31 (br s, NH), 7.43 (s, 1H, H-2'), 8.45 (d, J = 5.0 Hz, 2H, H-4,6).
¹³C NMR (100 MHz, CDCl ₃):	δ 54.8 (CH ₃), 105.1 (CH), 107.4 (CH), 111.4 (CH), 112.2 (CH), 129.2 (CH), 140.1 (qC), 157.5 (2CH), 159.6 (qC), 159.8 (qC).
HRMS (m/z ESI ⁺):	Found 202.0982 (M ⁺ + H. C ₁₁ H ₁₂ N ₃ O Requires 202.0980).

2-(2-Methoxyanilino)pyrimidine (358c)

Following Method B 2-bromoanisole (125 μ L, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-aminopyrimidine (142 mg, 1.5 mmol, 1.5 eq.) and NaOt-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 $^\circ\text{C}$ for 12 h and then worked up according to Method B.

Spectral data for this compound were consistent with those of compound **355c** prepared according to Method A.

Yield:	90% (91 mg).
Physical State:	Colourless crystal.
Mp:	123-125 $^\circ\text{C}$.
R_f:	0.39 (hexanes:EtOAc, 80:20).
^1H NMR (400 MHz, CDCl_3):	δ 3.91 (s, 3H, OCH_3), 6.71 (t, $J = 5.0$ Hz, 1H, H-5), 6.92 (d, $J = 7.0$ Hz, 1H, H-3'), 7.02 – 7.03 (m, 2H, H-4',5'), 7.83 (br s, NH), 8.45 (d, $J = 5.0$ Hz, 2H, H-4,6), 8.53 (d, $J = 7.0$ Hz, 1H, H-6').
HRMS (m/z ESI^+):	Found 202.0982 ($\text{M}^+ + \text{H}$. $\text{C}_{11}\text{H}_{12}\text{N}_3\text{O}$ Requires 202.0980).

2-(4-Fluoroanilino)pyrimidine (358d)

Following Method B 1-bromo-4-fluorobenzene (110 μ L, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg), Xantphos (3 mol%, 17

mg), 2-aminopyrimidine (142 mg, 1.5 mmol, 1.5 eq.) and NaOt-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 °C for 12 h and then worked up according to Method B.

Spectral data for this compound were consistent with those of compound **355d** prepared according to Method A.

Yield: 66% (62 mg).

Physical State: Pale yellow crystal.

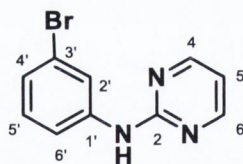
Mp: 148-150 °C.

R_f: 0.36 (hexanes:EtOAc, 80:20).

¹H NMR (400 MHz, CDCl₃): δ 6.74 (t, *J* = 5.0 Hz, 1H, H-5), 7.06 - 7.07 (m, 2H, H-3',5'), 7.51 (br s, NH), 7.57 - 7.58 (m, 2H, H-2',6'), 8.43 (d, *J* = 5.0 Hz, 2H, H-4,6).

HRMS (*m/z* ESI⁺): Found 190.0783 (M⁺ + H. C₁₀H₉FN₃ Requires 190.0780).

2-(3-Bromoanilino)pyrimidine (**358e**)



Following Method B 1,3-dibromobenzene (120 μL, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with Pd₂(dba)₃ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-aminopyrimidine (142 mg, 1.5 mmol, 1.5 eq.) and NaOt-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 °C for 12 h and then worked up according to Method B.

Yield: 94% (117 mg).

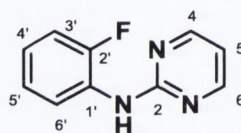
Physical State: Colourless crystal.

Mp: 93-94 °C.

R_f: 0.40 (hexanes:EtOAc, 80:20).

IR $\nu_{\max}$ (film)/ cm^{-1} :	3267 (NH), 3175, 1603, 1377, 1357, 1279, 1176, 1079, 889, 792, 769, 662.
^1H NMR (400 MHz, CDCl_3):	δ 6.80 (t, $J = 5.2$ Hz, 1H, H-5), 7.21 – 7.22 (m, 2H, H-4',5'), 7.42 (br s, NH), 7.48 (d, $J = 7.4$ Hz, 1H, H-6'), 8.02 (s, 1H, H-2'), 8.48 (d, $J = 5.2$ Hz, 2H, H-4,6).
^{13}C NMR (100 MHz, CDCl_3):	δ 112.7 (CH), 117.2 (CH), 121.4 (CH), 122.3 (qC), 124.9 (CH), 129.7 (CH), 140.3 (qC), 157.6 (2CH), 159.2 (qC).
HRMS (m/z ESI $^+$):	Found 249.9979 ($\text{M}^+ + \text{H}$, $\text{C}_{10}\text{H}_9^{79}\text{BrN}_3$ Requires 249.9980).

2-(2-Fluoroanilino)pyrimidine (358f)

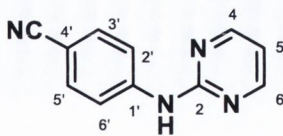


Following Method B 1-bromo-2-fluorobenzene (110 μL , 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-aminopyrimidine (142 mg, 1.5 mmol, 1.5 eq.) and NaOt-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 $^\circ\text{C}$ for 12 h and then worked up according to Method B.

Spectral data for this compound were consistent with those of compound **355e** prepared according to Method A.

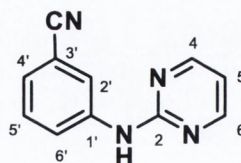
Yield:	92% (86 mg).
Physical State:	Off white crystal.
Mp:	113-115 $^\circ\text{C}$.
R_f:	0.38 (hexanes:EtOAc, 80:20).
^1H NMR (400 MHz, CDCl_3):	δ 6.73 (t, $J = 5.0$ Hz, 1H, H-5), 6.97 (m, 1H, H-3'), 7.09 (m, 2H, H-4',5'), 7.98 (br s, NH), 8.38 (d, $J = 7.6$ Hz, 1H, H-6'), 8.43 (d, $J = 5.0$ Hz, 2H, H-4,6).
HRMS (m/z ESI $^+$):	Found 190.0785 ($\text{M}^+ + \text{H}$, $\text{C}_{10}\text{H}_9\text{FN}_3$ Requires 190.0780).

2-(4-Cyanoanilino)pyrimidine (358g)



Following Method B 4-bromobenzonitrile (182 mg, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with Pd₂(dba)₃ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-aminopyrimidine (142 mg, 1.5 mmol, 1.5 eq.) and K₃PO₄ (318 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 °C for 12 h and then worked up according to Method B.

Yield:	78% (86 mg).
Physical State:	Yellow oil.
Mp:	-
R_f:	0.29 (hexanes:EtOAc, 80:20).
IR ν_{max} (film)/cm ⁻¹ :	3266 (NH), 3086, 2212 (CN), 1606, 1539, 1580, 1493, 1391, 1248, 1172, 1090, 1016, 914, 881, 832, 789, 710, 683.
¹H NMR (400 MHz, CDCl ₃):	δ 6.95 (t, J = 4.8 Hz, 1H, H-5), 7.69 (d, J = 8.0 Hz, 2H, H-2',6'), 7.95 (d, J = 8.0 Hz, 2H, H-3',5'), 8.55 (d, J = 4.8 Hz, 2H, H-4,6), 10.18 (br s, NH).
¹³C NMR (100 MHz, CDCl ₃):	δ 102.4 (qC), 114.3 (CH), 118.5 (2CH), 120.0 (qCN), 133.2 (2CH), 144.9 (qC), 158.4 (2CH), 159.8 (qC).
HRMS (m/z ESI ⁺):	Found 197.6790 (M ⁺ + H. C ₁₁ H ₉ N ₄ Requires 197.6795).

2-(3-Cyanoanilino)pyrimidine (358h)

Following Method B 3-bromobenzonitrile (182 mg, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-aminopyrimidine (142 mg, 1.5 mmol, 1.5 eq.) and K_3PO_4 (318 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 °C for 12 h and then worked up according to Method B.

Spectral data for this compound were consistent with those of compound **355g** prepared according to Method A.

Yield: 64% (76 mg).

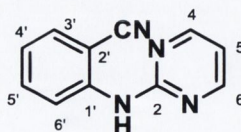
Physical State: Colourless oil.

Mp: -

R_f: 0.28 (hexanes:EtOAc, 80:20).

¹H NMR (400 MHz, CDCl_3): δ 6.88 (t, J = 4.4 Hz, 1H, H-5), 7.35 (d, J = 8.0 Hz, 1H, H-6'), 7.44 (app. t, 1H, H-5'), 7.63 (br s, NH), 7.69 (d, J = 8.0 Hz, 1H, H-4'), 8.31 (s, 1H, H-2'), 8.51 (d, J = 4.4 Hz, 2H, H-4,6).

HRMS (m/z ESI^+): Found 197.0827 ($\text{M}^+ + \text{H}$, $\text{C}_{11}\text{H}_9\text{N}_4$ Requires 197.0827).

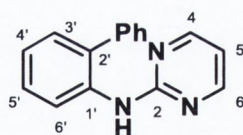
2-(Phenylamino)pyrimidine (358i)

Following Method B 2-bromobenzonitrile (182 mg, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-

aminopyrimidine (142 mg, 1.5 mmol, 1.5 eq.) and K_3PO_4 (318 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 °C for 12 h and then worked up according to Method B.

Yield:	82% (80 mg).
Physical State:	Yellow/orange gel.
Mp:	-
R_f:	0.33 (hexanes:EtOAc, 80:20).
IR ν_{max} (film)/ cm^{-1} :	3107 (NH), 2227 (CN), 1602, 1578, 1539, 1493, 1463, 1311, 1273, 1171, 1028, 1004, 965, 788, 753, 709, 682.
¹H NMR (400 MHz, $CDCl_3$):	δ 6.89 (t, J = 4.4 Hz, 1H, H-5), 7.10 (app. t, 1H, H-4'), 7.61 (m, 2H, H-5',6'), 7.69 (br s, NH), 8.53 (d, J = 4.4 Hz, 2H, H-4,6), 8.61 (d, J = 8.0 Hz, 1H, H-3').
¹³C NMR (100 MHz, $CDCl_3$):	δ 100.8 (qC), 113.8 (CH), 116.4 (qCN), 119.2 (CH), 121.7 (CH), 132.2 (CH), 133.3 (CH), 141.7 (qC), 157.6 (2CH), 158.9 (qC).
HRMS (m/z ESI ⁺):	Found 197.0822 ($M^+ + H$, $C_{11}H_9N_4$ Requires 197.0827).

2-(2-Phenylanilino)pyrimidine (358j)



Following Method B 2-bromobiphenyl (233 mg, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with $Pd_2(dba)_3$ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-aminopyrimidine (142 mg, 1.5 mmol, 1.5 eq.) and $NaOt-Bu$ (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 °C for 12 h and then worked up according to Method B.

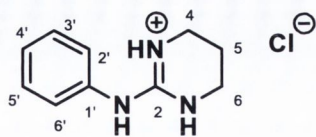
Yield:	98% (96 mg).
Physical State:	Off white solid.
Mp:	167-169 °C.

R_f:	0.47 (hexanes:EtOAc, 80:20).
IR $\nu_{\max}$ (film)/cm ⁻¹ :	3175 (NH), 2883, 2343, 2212, 1619, 1562, 1504, 1480, 1439, 1422, 1376, 1320, 1276, 1194, 1073, 952, 882, 831, 766, 743, 703.
¹H NMR (400 MHz, CDCl ₃):	δ 6.72 (t, J = 4.2 Hz, 1H, H-5), 7.20 – 7.21 (m, 2H, H-4',6'), 7.29 – 7.31 (m, 2H, H-3',5'), 7.30 (br s, NH), 7.39-7.51 (m, 5H, H-Ph), 8.41 (d, J = 4.2 Hz, 2H, H-4,6).
¹³C NMR (100 MHz, CDCl ₃):	δ 112.1 (CH), 120.1 (CH), 122.5 (CH), 127.3 (CH), 127.7 (CH), 128.6 (2CH), 129.0 (2CH), 129.9 (CH), 131.8 (CH), 136.7 (qC), 138.2 (qC), 157.5 (2CH), 159.6 (qC).
HRMS (m/z ESI ⁺):	Found 248.1176 (M ⁺ + H. C ₁₆ H ₁₄ N ₃ Requires 248.1188).

Method C - Hydrogenation of *N*-aryl-2-aminopyrimidines

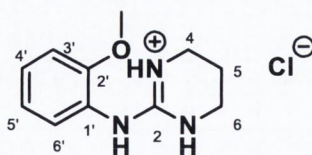
To *N*-aryl-2-aminopyrimidine (1.0 mmol) in MeOH (4.0 mL) was added 10% Pd/C (120 mg). To this was added aqueous HCl (1M, 1.0 mL). The mixture was then hydrogenated at atmospheric pressure for 10-12 hrs with vigorous stirring. It was then filtered through a pad of Celite® and concentrated. The residue was then purified by diluting the compound in the minimum amount of H₂O and passing through a reverse phase silica plug, using H₂O/MeCN (95:5) as the eluent. The solution was then concentrated under reduced pressure to yield the title compounds as the tetrahydropyrimidine hydrochloride salts.

2-Anilino-1,4,5,6-tetrahydropyrimidine hydrochloride (365)



Following Method C to 2-anilinopyrimidine **353** (85 mg, 0.50 mmol) in MeOH (2.0 mL) was added 10% Pd/C (60 mg). To this was added aqueous HCl (1M, 0.50 mL). The reaction was stirred at rt under 1 atm of hydrogen for 12 h and then worked up according to Method C.

Yield:	97% (102 mg).
Physical State:	Colourless gel.
Mp:	-
R_f:	Baseline (EtOAc).
IR ν_{max} (film)/ cm^{-1} :	3181 (NH), 2971, 2344, 1611, 1583, 1494, 1456, 1440, 1422, 1373, 1347, 1318, 1192, 1150, 1078, 1025, 1002, 967, 913, 881, 848, 763, 691.
^1H NMR (400 MHz, D_2O):	δ 1.80 (quin., $J = 5.0$ Hz, 2H, H-5), 3.19 (t, $J = 5.0$ Hz, 4H, H-4,6), 7.11 (d, $J = 8.2$ Hz, 2H, H-2',6'), 7.21 (t, $J = 8.2$ Hz, 1H, H-4'), 7.32 (app. t, 2H, H-3',5').
^{13}C NMR (100 MHz, D_2O):	δ 19.1 (CH_2), 38.0 (2CH_2), 125.3 (2CH), 127.3 (CH), 129.5 (2CH), 133.9 (qC), 152.3 (qC).
HRMS (m/z ESI^+):	Found 176.1168 ($\text{M}^+ + \text{H}$. $\text{C}_{10}\text{H}_{14}\text{N}_3$ Requires 176.1188).

2-(2-Methoxyanilino)-1,4,5,6-tetrahydropyrimidine hydrochloride (367a)

Following Method C to 2-(2-methoxyanilino)pyrimidine **358a** (101 mg, 0.50 mmol) in MeOH (2.0 mL) was added 10% Pd/C (60 mg). To this was added aqueous HCl (1M, 0.50 mL). The reaction was stirred at rt under 1 atm of hydrogen for 12 h and then worked up according to Method C.

Yield: 98% (118 mg).

Physical State: Pale yellow oil.

Mp: -

R_f: Baseline (EtOAc).

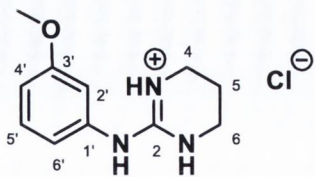
IR $\nu_{\max}$ (film)/cm⁻¹: 3183 (NH), 2970, 2883, 2382, 1619, 1568, 1502, 1463, 1438, 1376, 1320, 1277, 1244, 1219, 1043, 1020, 966, 933, 851, 755, 709, 685.

¹H NMR (400 MHz, D₂O): δ 1.80 (quin., J = 5.2 Hz, 2H, H-5), 3.18 (t, J = 5.2 Hz, 4H, H-4,6), 3.72 (s, 3H, OMe), 6.91 (app. t, 1H, H-4'), 7.01 (d, J = 8.0 Hz, 1H, H-3'), 7.10 (d, J = 8.0 Hz, 1H, H-6'), 7.25 (app. t, 1H, H-5').

¹³C NMR (100 MHz, D₂O): δ 19.3 (CH₂), 38.3 (CH₃), 55.8 (2CH₂), 112.9 (CH), 121.2 (CH), 122.0 (qC), 128.1 (CH), 129.6 (CH), 152.4 (qC), 154.2 (qC).

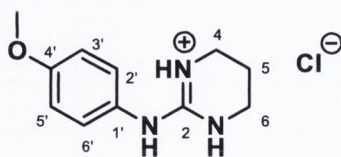
HRMS (m/z ESI⁺): Found 206.1297 (M⁺ + H. C₁₁H₁₆N₃O Requires 206.1293).

2-(3-Methoxyanilino)-1,4,5,6-tetrahydropyrimidine hydrochloride (367b)



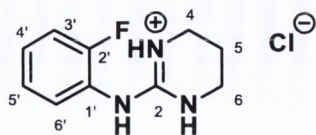
Following Method C to 2-(3-methoxyanilino)pyrimidine **358b** (101 mg, 0.50 mmol) in MeOH (2.0 mL) was added 10% Pd/C (60 mg). To this was added aqueous HCl (1M, 0.50 mL). The reaction was stirred at rt under 1 atm of hydrogen for 12 h and then worked up according to Method C.

Yield:	91% (109 mg).
Physical State:	Pale yellow oil.
Mp:	-
R_f:	Baseline (EtOAc).
IR ν_{max} (film)/cm ⁻¹ :	3188 (NH), 2961, 2345, 1624, 1583, 1561, 1491, 1455, 1441, 1374, 1322, 1209, 1191, 1141, 1032, 1002, 968, 880, 849, 780, 766, 705, 681.
¹H NMR (400 MHz, D ₂ O):	δ 1.85 (quin., J = 5.6 Hz, 2H, H-5), 3.23 (t, J = 5.6 Hz, 4H, H-4,6), 3.70 (s, 3H, OMe), 6.72 (s, 1H, H-2'), 6.75 (d, J = 7.8 Hz, 1H, H-4'), 6.83 (d, J = 7.8 Hz, 1H, H-6') 7.27 (app. t, 1H, H-5').
¹³C NMR (100 MHz, D ₂ O):	δ 19.5 (CH ₂), 38.0 (CH ₂), 55.2 (CH ₃), 111.0 (CH), 112.5 (CH), 117.8 (CH), 130.6 (CH), 135.3 (qC), 152.3 (qC), 159.8 (qC).
HRMS (m/z ESI ⁺):	Found 206.1295 (M ⁺ + H. C ₁₁ H ₁₆ N ₃ O Requires 206.1293).

2-(4-Methoxyanilino)-1,4,5,6-tetrahydropyrimidine hydrochloride (367c)

Following Method C to 2-(4-methoxyanilino)pyrimidine **358c** (101 mg, 0.50 mmol) in MeOH (2.0 mL) was added 10% Pd/C (60 mg). To this was added aqueous HCl (1M, 0.50 mL). The reaction was stirred at rt under 1 atm of hydrogen for 12 h and then worked up according to Method C.

Yield:	92% (110 mg).
Physical State:	Colourless gel.
Mp:	-
R_f:	Baseline (EtOAc).
IR $\nu_{\max}$ (film)/cm ⁻¹ :	3197 (NH), 2971, 2886, 2837, 1615, 1509, 1463, 1440, 1422, 1375, 1347, 1294, 1242, 1181, 1116, 1081, 1025, 967, 933, 884, 843, 823, 797, 766.
¹H NMR (400 MHz, D ₂ O):	δ 1.77 (quin., J = 6.0 Hz, 2H, H-5), 3.14 (t, J = 6.0 Hz, 4H, H-4,6), 3.65 (s, 3H, OMe), 6.85 (d, J = 8.2 Hz, 2H, H-3', 5'), 7.01 (d, J = 8.2 Hz, 2H, H-2',6').
¹³C NMR (100 MHz, D ₂ O):	18.9 (CH ₂), 38.2 (2CH ₂), 52.2 (CH ₃), 115.3 (2CH), 126.9 (qC), 127.8 (2CH), 153.0 (qC), 157.9 (qC).
HRMS (m/z ESI ⁺):	Found 206.1311 (M ⁺ + H. C ₁₁ H ₁₆ N ₃ O Requires 206.1293).

2-(2-Fluoroanilino)-1,4,5,6-tetrahydropyrimidine hydrochloride (367d)

Following Method C to 2-(2-fluoroanilino)pyrimidine **358d** (85 mg, 0.50 mmol) in MeOH (2.0 mL) was added 10% Pd/C (60 mg). To this was added aqueous HCl (1M, 0.50 mL). The reaction was stirred at rt under 1 atm of hydrogen for 12 h and then worked up according to Method C.

Yield: 95% (109 mg).

Physical State: Pale yellow gel.

Mp: -

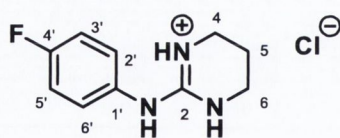
R_f: Baseline (EtOAc).

IR ν_{max} (film)/ cm^{-1} : 3184 (NH), 2971, 2887, 2359, 1621, 1601, 1567, 1501, 1459, 1441, 1424, 1377, 1289, 1265, 1237, 1151, 1101, 1027, 1022, 950, 878, 800, 750, 730, 706, 680.

¹H NMR (400 MHz, D₂O): δ 1.84 (quin., J = 5.6 Hz, 2H, H-5), 3.23 (t, J = 5.6 Hz, 4H, H-4,6), 7.16-7.17 (m, 2H, H-4',5'), 7.26-7.28 (m, 2H, H-3',6').

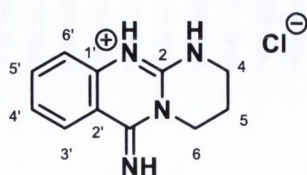
¹³C NMR (100 MHz, D₂O): δ 19.2 (CH₂), 38.2 (2CH₂), 116.6 (CH, J_{CF} = 6.0 Hz), 121.4 (d, CH, J_{CF} = 16.0 Hz), 125.3 (CH), 128.6 (CH), 129.7 (CH, J_{CF} = 6.0 Hz), 152.3 (q, C), 156.0 (qC, J_{CF} = 206.0 Hz).

HRMS (m/z ESI⁺): Found 194.1100 (M^+ + H. C₁₀H₁₃FN₃ Requires 194.1094).

2-(4-Fluoroanilino)-1,4,5,6-tetrahydropyrimidine (367e)

Following Method C to 2-(phenylamino)pyrimidine **358e** (85 mg, 0.50 mmol) in MeOH (2.0 mL) was added 10% Pd/C (60 mg). To this was added aqueous HCl (1M, 0.50 mL). The reaction was stirred at rt under 1 atm of hydrogen for 12 h and then worked up according to Method C.

Yield:	95% (109 mg).
Physical State:	Yellow solid, very hygroscopic.
Mp:	-
R_f:	Baseline (EtOAc).
IR $\nu_{\max}$ (film)/cm ⁻¹ :	3236 (NH), 2965, 2880, 2393, 2225, 2136, 1911, 1621, 1598, 1569, 1461, 1421, 1378, 1321, 1288, 1180, 1165, 1023, 1001, 966, 927, 843, 829, 819, 770, 708.
¹H NMR (400 MHz, D ₂ O):	δ 1.81 (quin., J = 4.2 Hz, 2H, H-5), 3.18 (t, J = 4.2 Hz, 4H, H-4,6), 7.04 – 7.05 (m, 2H, H-2',6'), 7.10 - 7.14 (m, 2H, H-3',5').
¹³C NMR (100 MHz, D ₂ O):	δ 18.9 (CH ₂), 38.0 (2CH ₂), 116.4 (2CH, J_{CF} = 9.0 Hz), 128.4 (2CH, J_{CF} = 9.0 Hz), 129.9 (qC, J_{CF} = 2.4 Hz), 152.8 (qC), 162.6 (qC, J_{CF} = 240.0 Hz).
HRMS (m/z ESI ⁺):	Found 194.1092 ($\text{M}^+ + \text{H}$. C ₁₀ H ₁₃ FN ₃ Requires 194.1094).

1,2,3,4-Tetrahydro-6*H*-pyrimido[2,1-*b*]quinazolin-6-imine hydrochloride (367g)

Following method B to 2-(2-cyanoanilino)pyrimidine **358g** (49 mg, 0.25 mmol) in MeOH (1.0 mL) was added 10% Pd/C (30 mg). To this was added aqueous HCl (1M, 0.250 mL). The reaction was stirred at rt under 1 atm of hydrogen for 12 h and then worked up according to Method C.

Yield: 64% (75 mg).

Physical State: Dark yellow viscous oil.

Mp: -

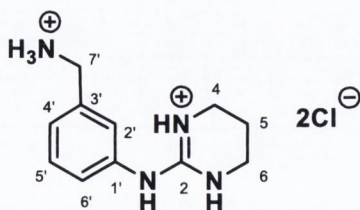
R_f: Baseline (EtOAc).

IR ν_{max} (film)/ cm^{-1} : 2971 (NH), 2332, 1682, 1633, 1603, 1553, 1489, 1380, 1340, 1291, 1265, 1121, 1108, 1080, 1001, 955, 893, 881, 752, 710, 681.

¹H NMR (400 MHz, D₂O): δ 1.94 (quin., $J = 4.2$ Hz, 2H, H-5), 3.22 (t, $J = 4.2$ Hz, 2H, H-4), 3.58 (t, $J = 4.2$ Hz, 2H, H-6), 7.03-7.04 (m, 2H, H-5',6'), 7.25 (d, $J = 8.0$ Hz, 1H, H-3'), 7.47 (app. t, 1H, H-4').

¹³C NMR (100 MHz, D₂O): δ 18.2 (CH₂), 37.3 (CH₂), 43.3 (CH₂), 109.2 (qC), 113.6 (CH), 123.9 (CH), 124.8 (CH), 135.3 (CH), 138.5 (qC), 151.4 (qC), 160.2 (qC).

HRMS (m/z ESI⁺): Found 201.1144 ($M^+ + H$. C₁₁H₁₃N₄ Requires 201.1140).

2-(3-Aminomethylanilino)-1,4,5,6-tetrahydropyrimidine dihydrochloride (367h)

Following method B to 2-(3-cyanoanilino)pyrimidine **358h** (49 mg, 0.25 mmol) in MeOH (1.0 mL) was added 10% Pd/C (30 mg). To this was added aqueous HCl (1M, 0.250 mL). The reaction was stirred at rt under 1 atm of hydrogen for 12 h and then worked up according to Method C.

Yield: 71% (49 mg).

Physical State: White gel.

Mp: -

R_f: Baseline (EtOAc).

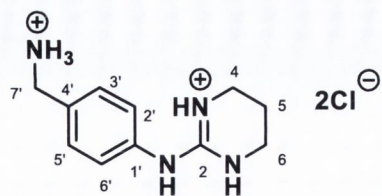
IR $\nu_{\max}$ (film)/cm⁻¹: 3260 (NH), 3060 (NH), 1712, 1620, 1538, 1412, 1253, 1155, 1081, 852, 818, 750, 703.

¹H NMR (400 MHz, D₂O): δ 1.86 (quin., J = 5.6 Hz, 2H, H-5), 3.24 (t, J = 5.6 Hz, 4H, H-4,6), 4.07 (s, 2H, H-7'), 7.20 – 7.22 (m, 2H, H-2',6'), 7.27 (d, J = 8.0 Hz, 1H, H-4'), 7.40 (app. t, 1H, H-5').

¹³C NMR (100 MHz, D₂O): δ 19.2 (CH₂), 38.4 (2CH₂), 42.4 (CH₂), 125.6 (CH), 125.9 (CH), 127.4 (CH), 130.7 (CH), 134.3 (qC), 135.0 (qC), 152.2 (qC).

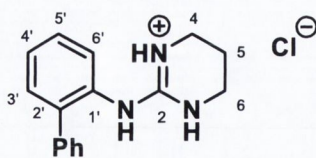
HRMS (m/z ESI⁺): Found 205.1461 (M⁺ + H. C₁₁H₁₇N₄ Requires 205.1453).

2-(4-Aminomethylanilino)-1,4,5,6-tetrahydropyrimidine dihydrochloride (367i)



Following method B to 2-(4-cyanoanilino)pyrimidine **358i** (49 mg, 0.25 mmol) in MeOH (1.0 mL) was added 10% Pd/C (30 mg). To this was added aqueous HCl (1M, 0.250 mL). The reaction was stirred at rt under 1 atm of hydrogen for 12 h and then worked up according to Method C.

Yield:	67% (46 mg).
Physical State:	Yellow gel.
Mp:	-
R_f:	Baseline (EtOAc).
IR ν_{max} (film)/cm ⁻¹ :	3383 (NH), 3235 (NH), 2968, 2855, 2394, 2210, 2134, 1621, 1568, 1505, 1482, 1462, 1439, 1372, 1205, 1146, 1081, 1028, 1001, 958, 913, 895, 808, 765, 709.
¹H NMR (400 MHz, D ₂ O):	δ 1.85 (quin., J = 4.0 Hz, 2H, H-5), 3.24 (t, J = 4.0 Hz, 4H, H-4,6), 4.07 (s, 2H, H-7'), 7.19 (d, J = 8.0 Hz, 2H, H-2',6'), 7.37 (d, J = 8.0 Hz, 2H, H-3',5').
¹³C NMR (100 MHz, D ₂ O):	18.9 (CH ₂), 38.3 (2CH ₂), 42.4 (CH ₂), 125.6 (2CH), 129.9 (2CH), 131.1 (qC), 136.1 (qC), 152.1 (qC).
HRMS (m/z ESI ⁺):	Found 205.1454 (M^+ + H. C ₁₁ H ₁₇ N ₄ Requires 205.1453).

2-(2-Phenylanilino)-1,4,5,6-tetrahydropyrimidine hydrochloride (367j)

Following method B to 2-(2-Phenylanilino)pyrimidine **358j** (124 mg, 0.5 mmol) in MeOH (2 mL) was added 10% Pd/C (60 mg). To this was added aqueous HCl (1M, 0.5 mL). The reaction was stirred at rt under 1 atm of hydrogen for 12 h and then worked up according to Method C.

Yield: 92% (132 mg).

Physical State: Colourless hygroscopic gel.

Mp: -

R_f: Baseline (EtOAc).

IR $\nu_{\max}$ (film)/cm⁻¹: 3175 (NH), 2883, 2343, 2212, 1619, 1562, 1504, 1480, 1439, 1422, 1376, 1320, 1276, 1194, 1073, 952, 882, 831, 766, 743, 703.

¹H NMR (400 MHz, D₂O): δ 1.31 (quin., J = 4.0 Hz, 2H, H-5), 2.86 (t, J = 4.0 Hz, 4H, H-4,6), 7.19 – 7.20 (m, 1H, H-6'), 7.28 – 7.30 (m, 3H, H-3',4',5'), 7.34 – 7.37 (m, 5H, H-Ph).

¹³C NMR (100 MHz, D₂O): 19.1 (CH₂), 37.9 (2CH₂), 122.7 (CH), 128.1 (CH), 128.5 (2CH), 128.6 (2CH), 128.6 (CH), 129.1 (CH), 131.0 (CH), 131.3 (qC), 138.2 (qC), 138.9 (qC), 151.8 (qC).

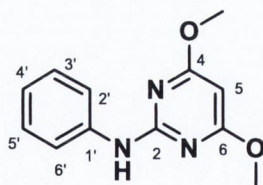
HRMS (m/z ESI⁺): Found 252.1501 (M⁺ + H. C₁₆H₁₈N₃ Requires 252.1501).

8.2. 2-Aminopyrimidines as a guanidine precursor.

Method D - General procedure for the coupling of aryl halides with 2-amino-4,6-dimethoxypyrimidine

To an oven dried Schlenk tube charged with a stir bar, $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg) and Xantphos **352** (3 mol%, 17 mg) was added 2-amino-4,6-dimethoxypyrimidine (1.5 mmol, 1.5 equiv, 232 mg), base (1.5 mmol, 1.5 equiv) and aryl halide (1.0 mmol, 1.0 equiv), if the aryl halide is a solid. The Schlenk tube was put under vacuum and back filled with argon three times. To this was added freshly distilled toluene (1.5 mL / mmol aryl halide). If the aryl halide was a liquid it was now added to the solution. The Schlenk tube was then placed in an oil bath with vigorous stirring at 95 °C. The reaction was monitored by TLC and once deemed complete (typically 6-12 h), was cooled to rt and diluted with EtOAc (10 mL). The reaction mixture was filtered through Celite© with any remaining residues in the Schlenk tube being washed out with a further amount of EtOAc (10 mL). The organic phase was then washed with water (20 mL). The aqueous phase was extracted with EtOAc (3 × 20 mL) and the combined organic layers washed with brine (30 mL), dried over MgSO_4 and concentrated under reduced pressure. The crude product was then purified by flash column chromatography (silica gel, hexanes:EtOAc, 100:0 → 60:40) to yield the target compound.

2-Anilino-4,6-dimethoxypyrimidine (**391**)



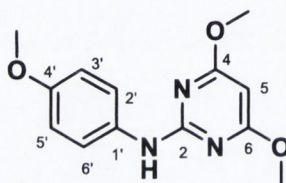
Following Method D bromobenzene (105 μL , 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-amino-4,6-dimethoxypyrimidine (232 mg, 1.5 mmol, 1.5 eq.) and NaOt-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 °C for 8 h and then worked up according to Method D.

Spectral data for this compound were consistent with those in the literature.²⁷¹

Yield: 96 % (221 mg).

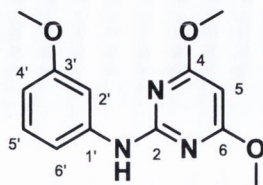
Physical State:	White solid.
Mp:	78-79 °C. (Lit. 78 °C)
R_f:	0.50 (hexanes:EtOAc, 80:20).
¹H NMR (400 MHz, CDCl₃):	δ 3.91 (s, 6H, OMe), 5.58 (s, 1H, H-5), 7.01 (t, <i>J</i> = 7.2 Hz, 1H, H-4'), 7.09 (br s, NH), 7.31 (app. t, 2H, H-3',5'), 7.62 (d, <i>J</i> = 7.2 Hz, 2H, H-2',6').

4,6-Dimethoxy-2-(4-methoxyanilino)pyrimidine (392a)



Following Method D 4-bromoanisole (125 μL, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with Pd₂(dba)₃ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-amino-4,6-dimethoxypyrimidine (232 mg, 1.5 mmol, 1.5 eq.) and NaOt-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 °C for 12 h and then worked up according to Method D.

Yield:	86% (224 mg).
Physical State:	Off white crystal.
Mp:	86-87 °C. (Lit. 90 - 91 °C) ²⁷¹
R_f:	0.46 (hexanes:EtOAc, 80:20).
IR ν_{max} (film)/cm⁻¹:	3234 (NH), 3067, 2960, 1865, 1606, 1583, 1510, 1446, 1300, 1257, 1232, 1034, 1008, 885, 822, 787, 676, 660.
¹H NMR (400 MHz, CDCl₃):	δ 3.79 (s, 3H, OMe), 3.89 (s, 6H, OMe), 5.54 (s, 1H, H-5), 6.85 (br s, NH), 6.87 (d, <i>J</i> = 9.2 Hz, 2H, H-3',5'), 7.51 (d, <i>J</i> = 9.2 Hz, 2H, H-2',6').
¹³C NMR (100 MHz, CDCl₃):	δ 53.8 (2CH ₃), 55.5 (CH ₃), 80.6 (CH), 114.0 (2CH), 121.0 (2CH), 132.9 (qC), 155.3 (qC), 159.1 (qC), 171.9 (2qC).
HRMS (<i>m/z</i> ESI⁺):	Found 262.1194 (M ⁺ + H. C ₁₃ H ₁₆ N ₃ O ₃ Requires 262.1186).

4,6-Dimethoxy-2-(3-methoxyanilino)pyrimidine (392b)

Following Method D 3-bromoanisole (125 μ L, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-amino-4,6-dimethoxypyrimidine (232 mg, 1.5 mmol, 1.5 eq.) and NaOt-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 $^\circ\text{C}$ for 12 h and then worked up according to Method D.

Yield: 91% (237 mg).

Physical State: Yellow oil.

Mp: -

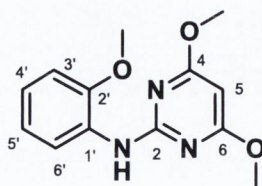
R_f : 0.49 (hexanes:EtOAc, 80:20).

IR ν_{max} (film)/ cm^{-1} : 3397 (NH), 2947, 2834, 2216, 1604, 1571, 1446, 1413, 1355, 1285, 1191, 1156, 1059, 965, 911, 851, 799, 768, 729, 685.

^1H NMR (400 MHz, CDCl_3): δ 3.80 (s, 3H, OMe), 3.92 (s, 6H, OMe), 5.59 (s, 1H, H-5), 6.59 (dd, $J = 2.8, 8.0$ Hz, 1H, H-4'), 7.05 (dd, $J = 2.8, 8.0$ Hz, 1H, H-6'), 7.11 (br s, NH), 7.20 (app. t, 1H, H-5'), 7.49 (app. s, 1H, H-2').

^{13}C NMR (100 MHz, CDCl_3): δ 53.9 (2CH₃), 55.1 (CH₃), 81.3 (CH), 104.7 (CH), 107.8 (CH), 111.2 (CH), 129.4 (CH), 141.1 (qC), 158.7 (qC), 160.1 (qC), 171.8 (2qC).

HRMS (m/z ESI⁺): Found 262.1195 ($\text{M}^+ + \text{H}$, $\text{C}_{13}\text{H}_{16}\text{N}_3\text{O}_3$ Requires 262.1186).

4,6-Dimethoxy-2-(2-methoxyanilino)pyrimidine (392c)

Following Method D 2-bromoanisoole (125 μ L, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-amino-4,6-dimethoxypyrimidine (232 mg, 1.5 mmol, 1.5 eq.) and NaOt-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 $^{\circ}\text{C}$ for 12 h and then worked up according to Method D.

Yield: 96% (252 mg).

Physical State: Off white solid.

Mp: 104 – 106 $^{\circ}\text{C}$.

R_f: 0.57 (hexanes:EtOAc, 80:20).

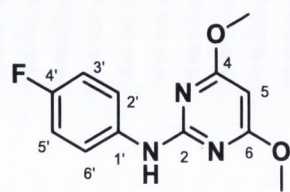
IR ν_{max} (film)/ cm^{-1} : 3430 (NH), 2938, 1576, 1481, 1437, 1416, 1382, 1294, 1247, 1192, 1160, 1028, 916, 768, 734, 690.

^1H NMR (400 MHz, CDCl_3): δ 3.92 (s, 3H, OMe), 3.94 (s, 6H, OMe), 5.57 (s, 1H, H-5), 6.88 – 6.99 (m, 3H, H-3',4',5'), 7.59 (br s, NH), 8.51 – 8.53 (m, 1H, H-Ar, 6').

^{13}C NMR (100 MHz, CDCl_3): δ 54.0 (2CH₃), 55.5 (CH₃), 81.3 (CH), 109.8 (CH), 118.4 (CH), 120.8 (CH), 121.4 (CH), 129.4 (qC), 147.6 (qC), 158.8 (qC), 171.9 (2qC).

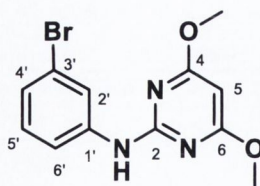
HRMS (m/z ESI⁺): Found 262.1194 ($\text{M}^+ + \text{H}$, $\text{C}_{13}\text{H}_{16}\text{N}_3\text{O}_3$ Requires 262.1192).

4,6-Dimethoxy-2-(4-fluoroanilino)pyrimidine (392d)



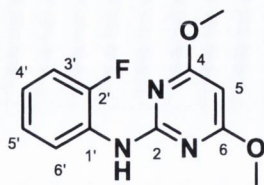
Following Method D 1-bromo-4-fluorobenzene (109 μ L, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-amino-4,6-dimethoxypyrimidine (232 mg, 1.5 mmol, 1.5 eq.) and NaOt-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 $^{\circ}\text{C}$ for 12 h and then worked up according to Method D.

Yield:	88% (220 mg).
Physical State:	White solid.
Mp:	92 – 94 $^{\circ}\text{C}$.
R_f:	0.42 (hexanes:EtOAc, 80:20).
IR ν_{max} (film)/ cm^{-1} :	3428 (NH), 2969, 1614, 1578, 1544, 1507, 1463, 1373, 1357, 1274, 1192, 1104, 1011, 858, 824, 781, 747, 713.
^1H NMR (400 MHz, CDCl_3):	δ 3.89 (s, 6H, OMe), 5.57 (s, 1H, H-5), 6.96 (br s, NH), 6.98 – 7.03 (m, 2H, H-3',5'), 7.53 – 7.57 (m, 2H, H-2',6').
^{13}C NMR (100 MHz, CDCl_3):	δ 53.9 (2CH ₃), 81.0 (CH), 115.2 (d, 2CH, $J_{\text{CF}} = 23.0$ Hz), 120.7 (d, 2CH, $J_{\text{CF}} = 15.0$ Hz), 136.6 (qC, $J_{\text{CF}} = 2.6$), 158.8 (q,C), 159.4 (d, CF, $J_{\text{CF}} = 240.0$ Hz), 172.0 (2qC).
HRMS (m/z ESI ⁺):	Found 250.0994 ($\text{M}^+ + \text{H}$, $\text{C}_{12}\text{H}_{13}\text{FN}_3\text{O}_2$ Requires 250.0992).

2-(3-Bromoanilino)-4,6-dimethoxypyrimidine (392e)

Following Method D 1,3-dibromofluorobenzene (120 μ L, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-amino-4,6-dimethoxypyrimidine (232 mg, 1.5 mmol, 1.5 eq.) and NaOt-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 $^\circ\text{C}$ for 12 h and then worked up according to Method D.

Yield:	94% (292 mg).
Physical State:	Off white solid.
Mp:	84-85 $^\circ\text{C}$.
R_f:	0.39 (hexanes:EtOAc, 80:20).
IR ν_{max} (film)/ cm^{-1} :	3423 (NH), 2945, 1604, 1578, 1481, 1420, 1360, 1301, 1230, 1214, 1195, 1160, 1060, 1008, 933, 872, 766, 734, 676.
^1H NMR (400 MHz, CDCl_3):	δ 3.93 (s, 6H, OMe), 5.61 (s, 1H, H-5), 6.93 (br s, NH), 7.15 (m, 2H, H-4',5'), 7.36 (d, J = 7.2 Hz, 1H, H-6'), 8.12 (s, 1H, H-2').
^{13}C NMR (100 MHz, CDCl_3):	δ 54.0 (2CH ₃), 81.9 (CH), 117.2 (CH), 121.9 (CH), 122.5 (qC), 124.8 (CH), 129.9 (CH), 141.0 (qC), 158.4 (qC), 171.4 (2qC).
HRMS (m/z ESI ⁺):	Found 310.0190 ($\text{M}^+ + \text{H}$, $\text{C}_{12}\text{H}_{13}^{79}\text{BrN}_3\text{O}_2$ Requires 310.0191).

4,6-Dimethoxy-2-(2-fluoroanilino)pyrimidine (392f)

Following Method D 1-bromo-2-fluorobenzene (109 μ L, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-amino-4,6-dimethoxypyrimidine (232 mg, 1.5 mmol, 1.5 eq.) and NaOt-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 $^\circ\text{C}$ for 12 h and then worked up according to Method D.

Yield: 84% (210 mg).

Physical State: Yellow oil.

Mp: -

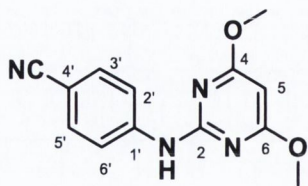
R_f: 0.54 (hexanes:EtOAc, 80:20).

IR ν_{max} (film)/ cm^{-1} : 3431 (NH), 3312, 2945, 1622, 1572, 1536, 1433, 1415, 1357, 1212, 1192, 1159, 1103, 1059, 981, 878, 849, 740, 690.

^1H NMR (400 MHz, CDCl_3): δ 3.93 (s, 6H, OMe), 5.61 (s, 1H, H-5), 6.94-6.95 (m, 1H, H-3'), 7.06 – 7.14 (m, 2H, H-5',6'), 7.16 (br s, NH), 8.50 (app. t, 1H, H-4') .

^{13}C NMR (100 MHz, CDCl_3): δ 54.0 (2 CH_3), 81.7 (CH), 114.6 (d, CH, $J_{\text{CF}} = 20.0$ Hz), 120.4 (CH), 121.9 (d, CH, $J_{\text{CF}} = 8.0$ Hz), 124.1 (d, CH, $J_{\text{CF}} = 3.0$ Hz), 128.1 (d, qC, $J_{\text{CF}} = 9.0$ Hz), 153.5 (d, CF, $J_{\text{CF}} = 260.0$ Hz), 158.4 (qC), 171.9 (2qC).

HRMS (m/z ESI $^+$): Found 250.0994 ($\text{M}^+ + \text{H}$. $\text{C}_{12}\text{H}_{13}\text{FN}_3\text{O}_3$ Requires 250.0992).

2-(4-Cyanoanilino)-4,6-dimethoxypyrimidine (392g)

Following Method D 4-bromobenzonitrile (182 mg, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-amino-4,6-dimethoxypyrimidine (232 mg, 1.5 mmol, 1.5 eq.) and K_3PO_4 (318 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 °C for 16 h and then worked up according to Method D.

Yield: 73% (167 mg).

Physical State: White powder.

Mp: 144-145 °C.

R_f: 0.31 (hexanes:EtOAc, 80:20).

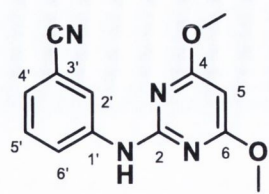
IR ν_{max} (film)/ cm^{-1} : 3423 (NH), 3397, 2947, 2220 (CN), 1601, 1576, 1510, 1480, 1455, 1359, 1305, 1281, 1193, 1161, 1060, 1008, 933, 872, 766, 707, 687.

^1H NMR (400 MHz, CDCl_3): δ 3.93 (s, 6H, OMe), 5.66 (s, 1H, H-5), 7.16 (br s, NH), 7.59 (d, $J = 8.0$ Hz, 2H, H-2',6'), 7.75 (d, $J = 8.0$ Hz, 2H, H-3',5').

^{13}C NMR (100 MHz, CDCl_3): δ 54.3 (2CH₃), 82.5 (CH), 104.6 (qC), 118.3 (2CH), 119.4 (qC), 133.2 (2CH), 143.7 (qC), 157.8 (qC), 171.9 (2qC).

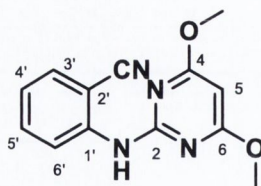
HRMS (m/z ESI⁺): Found 257.1038 ($\text{M}^+ + \text{H}$, $\text{C}_{13}\text{H}_{13}\text{N}_4\text{O}_2$ Requires 257.1041).

2-(3-Cyanoanilino)-4,6-dimethoxypyrimidine (392h)



Following Method D 3-bromobenzonitrile (182 mg, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with Pd₂(dba)₃ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-amino-4,6-dimethoxypyrimidine (232 mg, 1.5 mmol, 1.5 eq.) and K₃PO₄ (318 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 °C for 16 h and then worked up according to Method D.

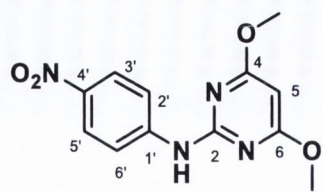
Yield:	66% (168 mg).
Physical State:	Yellow/white solid.
Mp:	141 – 143 °C
R_f:	0.30 (hexanes:EtOAc, 80:20).
IR ν_{max} (film)/cm ⁻¹ :	3327 (NH), 2950, 2230 (CN), 1607, 1572, 1543, 1463, 1432, 1363, 1286, 1244, 1194, 1163, 1113, 1060, 1005, 984, 847, 804, 787, 769, 699, 684.
¹H NMR (400 MHz, CDCl ₃):	δ 3.92 (s, 6H, OMe), 5.64 (s, 1H, H-5), 7.20 (br s, NH), 7.26 (d, J = 8.0 Hz, 1H, H-6'), 7.37 (app. t, 1H, H-5'), 7.65 (d, J = 8.0 Hz, 1H, H-4'), 8.22 (s, 1H, H-2').
¹³C NMR (100 MHz, CDCl ₃):	δ 54.1 (2CH ₃), 81.9 (CH), 112.7 (qC), 119.2 (qC), 121.9 (CH), 122.9 (CH), 125.4 (CH), 129.6 (CH), 140.4 (qC), 158.2 (qC), 171.9 (2qC).
HRMS (m/z ESI ⁺):	Found 257.1039 (M ⁺ + H. C ₁₃ H ₁₃ N ₄ O ₂ Requires 257.1039).

2-(2-Cyanoanilino)-4,6-dimethoxypyrimidine (392i)

Following Method D 2-bromobenzonitrile (182 mg, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-amino-4,6-dimethoxypyrimidine (232 mg, 1.5 mmol, 1.5 eq.) and K_3PO_4 (318 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 °C for 16 h and then worked up according to Method D.

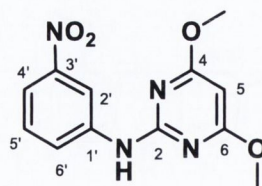
Yield:	70% (179 mg).
Physical State:	White powder.
Mp:	132 – 134 °C.
R_f:	0.39 (hexanes:EtOAc, 80:20).
IR ν_{max} (film)/ cm^{-1} :	3399 (NH), 3123, 3012, 2948, 2861, 2215 (CN), 1638, 1604, 1570, 1540, 1496, 1471, 1415, 1358, 1282, 1108, 1006, 948, 871, 803, 769, 689.
^1H NMR (400 MHz, CDCl_3):	δ 3.93 (s, 6H, OMe), 5.67 (s, 1H, H-5), 7.04 (app. t, 1H, H-5'), 7.43 (br s, NH), 7.53 – 7.58 (m, 2H, H-4',6'), 8.61 (d, J = 9.2 Hz, 1H, H-3').
^{13}C NMR (100 MHz, CDCl_3):	δ 54.2 (2 CH_3), 82.8 (CH), 100.9 (qC), 117.0 (qCN), 119.6 (CH), 121.8 (CH), 132.5 (CH), 133.7 (CH), 142.5 (qC), 157.7 (qC), 171.8 (2qC).
HRMS (m/z ESI $^+$):	Found 257.1038 ($\text{M}^+ + \text{H}$, $\text{C}_{13}\text{H}_{13}\text{N}_4\text{O}_2$ Requires 257.1033).

4,6-Dimethoxy-2-(4-nitroanilino)pyrimidine (392j)



Following Method D 1-bromo-4-nitrobenzene (202 mg, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with Pd₂(dba)₃ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-amino-4,6-dimethoxypyrimidine (232 mg, 1.5 mmol, 1.5 eq.) and K₃PO₄ (318 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 °C for 16 h and then worked up according to Method D.

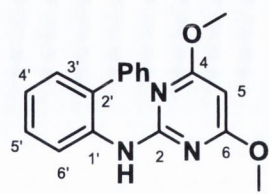
Yield:	50% (138 mg).
Physical State:	Yellow powder.
Mp:	198–200 °C.
R_f:	0.55 (hexanes:EtOAc, 50:50).
IR ν_{max} (film)/cm ⁻¹ :	3374 (NH), 2961, 2918, 2849, 2491, 1596, 1573, 1546 (NO ₂), 1488, 1389, 1318 (NO ₂), 1303, 1260, 1191, 1110, 1055, 929, 846, 795, 686.
¹H NMR (400 MHz, CDCl ₃):	δ 3.97 (s, 6H, OMe), 5.71 (s, 1H, H-5), 7.74 (br s, NH), 7.79 (d, J = 8.8 Hz, 2H, H-2',6'), 8.22 (d, J = 8.8 Hz, 2H, H-3',5').
¹³C NMR (100 MHz, CDCl ₃):	δ 52.3 (CH ₃), 80.2 (CH), 115.4 (2CH), 122.7 (2CH), 139.5 (qC), 142.6 (qC), 154.4 (qC), 169.0 (2qC).
HRMS (m/z ESI ⁺):	Found 277.0942 (M ⁺ + H. C ₁₂ H ₁₃ N ₄ O ₄ Requires 277.0937).

4,6-Dimethoxy-2-(3-nitroanilino)pyrimidine (392k)

Following Method D 1-bromo-3-nitrobenzene (202 mg, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-amino-4,6-dimethoxypyrimidine (232 mg, 1.5 mmol, 1.5 eq.) and K_3PO_4 (318 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 °C for 16 h and then worked up according to Method D.

Yield:	51% (139 mg).
Physical State:	Yellow powder.
Mp:	171 – 172 °C.
R_f:	0.56 (hexanes:EtOAc, 50:50).
IR ν_{max} (film)/ cm^{-1} :	3374 (NH), 2961, 2918, 2859, 2491, 1586, 1570, 1546 (NO_2), 1488, 1389, 1318 (NO_2), 1303, 1260, 1191, 1110, 1055.
^1H NMR (400 MHz, CDCl_3):	δ 3.99 (s, 6H, OMe), 5.67 (s, 1H, H-5), 7.44 (app. t, 1H, H-5'), 7.60 (dd, J = 8.0, 1.2 Hz, 1H, H-6'), 7.72 (br s, NH), 7.86 (dd, J = 8.0, 1.2 Hz, 1H, H-4'), 9.12 (app. t, 1H, H-2').
^{13}C NMR (100 MHz, CDCl_3):	δ 54.5 (CH_3), 81.6 (CH), 113.5 (CH), 117.0 (CH), 124.2 (CH), 129.4 (CH), 140.6 (qC), 148.9 (qC), 157.8 (qC), 171.8 (2qC).
HRMS (m/z ESI $^+$):	277.0940 ($\text{M}^+ + \text{H}$, $\text{C}_{12}\text{H}_{13}\text{N}_4\text{O}_4$ Requires 277.0942).

4,6-Dimethoxy-2-(2-phenylanilino)pyrimidine (392l)

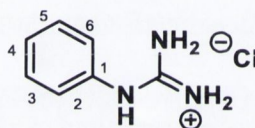


Following Method D 2-bromobiphenyl (233 mg, 1.0 mmol, 1.0 eq.) was added to an oven dried Schlenk tube charged with Pd₂(dba)₃ (2 mol%, 18 mg), Xantphos (3 mol%, 17 mg), 2-amino-4,6-dimethoxypyrimidine (232 mg, 1.5 mmol, 1.5 eq.) and NaOt-Bu (144 mg, 1.5 mmol, 1.5 eq.). The reaction was stirred at 95 °C for 16 h and then worked up according to Method D.

Yield:	68% (208 mg).
Physical State:	Fluffy white solid.
Mp:	82-83 °C.
R_f:	0.58 (hexanes:EtOAc, 80:20).
IR v _{max} (film)/cm ⁻¹ :	3423 (NH), 2942, 1602, 1578, 1537, 1481, 1359, 1283, 1195, 1060, 943, 857, 774, 759, 737, 688.
¹H NMR (400 MHz, CDCl ₃):	δ 3.87 (s, 6H, OMe), 5.56 (s, 1H, H-5), 6.92 (br s, NH), 7.09 (app. t, 1H, H-4'), 7.23 (m, 1H, H-6'), 7.34 – 7.50 (m, 6H, H-Ph, 5'), 8.49 (d, <i>J</i> = 8.0 Hz, 1H, H-3').
¹³C NMR (100 MHz, CDCl ₃):	δ 54.0 (2CH ₃), 80.9 (CH), 120.4 (CH), 122.3 (CH), 127.7 (CH), 128.0 (CH), 129.0 (2CH), 129.5 (2CH), 130.2 (CH), 131.7 (qC), 136.5 (qC), 138.6 (qC), 158.8 (qC), 171.9 (qC).
HRMS (<i>m/z</i> ESI ⁺):	Found 308.1393 (M ⁺ + H. C ₁₈ H ₁₈ N ₃ O ₃ Requires 308.1399).

General procedure for the cleavage of *N*-aryl-2-amino-4,6-dimethoxypyrimidine – Method E.

To an RBF (5 mL) containing *N*-aryl-2-amino-4,6-dimethoxypyrimidine (0.25 mmol, 1.0 equiv) in AcOH (0.210 mL) was added water (0.210 mL) and 12 M HCl (0.420 mL). To this was attached a reflux condenser making sure the joint was well greased. *The RBF was then covered with aluminium foil and fully submerged in an oil bath at 100 °C (essential).* The reaction was monitored by TLC, ensuring to basify all TLC samples using Et₃N, and once deemed complete was allowed cool to room temperature. The solution was washed with EtOAc (3 × 10 mL) and CH₂Cl₂/MeOH 80:20, 1 × 10 mL) to remove any unreacted starting materials and then the aqueous phase concentrated under reduced pressure to yield the target aryl guanidine as the hydrochloride salt.

Phenylguanidine hydrochloride (393)

Following Method E to 2-anilino-4,6-dimethoxypyrimidine **391** (58 mg, 0.25 mmol, 1.0 equiv) in AcOH (0.210 mL) was added water (0.210 mL) and 12 M HCl (0.420 mL). The reaction was stirred at 95 °C for 12 h and then worked up according to Method E.

Spectral data for this compound were consistent with those in the literature.¹⁴⁵

Yield: 98% (167 mg).

Physical State: Yellow/brown viscous oil.

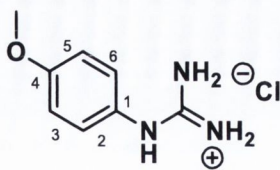
Mp: -

R_f: Baseline (EtOAc).

¹H NMR (400 MHz, D₂O): δ 7.06 (d, 2H, *J* = 7.6 Hz, H-2,6), 7.23 (t, 1H, *J* = 7.6 Hz, H-4), 7.31 (app. t, 2H, H-3,5).

HRMS (*m/z* ESI⁺): Found 136.0870 (M⁺ + H. C₇H₁₀N₃ Requires 136.0875).

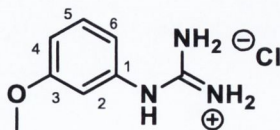
1-(4-Methoxyphenyl)guanidine hydrochloride (394a)



Following Method E to 4,6-dimethoxy-2-(4-methoxyanilino)pyrimidine **392a** (65 mg, 0.25 mmol, 1.0 equiv) in AcOH (0.210 mL) was added water (0.210 mL) and 12 M HCl (0.420 mL). The reaction was stirred at 95 °C for 8 h and then worked up according to Method E.

Yield:	94% (47 mg).
Physical State:	White crystal.
Mp:	145-148 °C. (Lit. 146 - 148 °C) ¹¹⁷
R_f:	Baseline (EtOAc).
IR ν_{max} (film)/cm ⁻¹ :	3398 (NH), 3131, 2978, 2497, 1671, 1630, 1293, 1176, 1015, 828, 682.
¹H NMR (400 MHz, D ₂ O):	δ 3.71 (s, 3H, OMe), 6.92 (d, J = 7.2 Hz, 2H, H-5,3), 7.14 (d, J = 7.2 Hz, 2H, H-2,6).
¹³C NMR (100 MHz, D ₂ O):	δ 58.0 (CH ₃), 117.8 (2CH), 129.4 (qC), 130.6 (2CH), 159.2 (qC), 161.2 (qCN)
HRMS (m/z ESI ⁺):	Found 166.0973 (M ⁺ + H. C ₈ H ₁₂ N ₃ O Requires 166.0980).

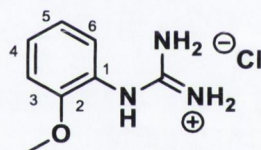
1-(3-Methoxyphenyl)guanidine hydrochloride (394b)



Following Method E to 4,6-dimethoxy-2-(3-methoxyanilino)pyrimidine **392b** (65 mg, 0.25 mmol, 1.0 equiv) in AcOH (0.210 mL) was added water (0.210 mL) and 12 M HCl (0.420 mL). The reaction was stirred at 95 °C for 12 h and then worked up according to Method E.

Yield:	84% (42 mg)
Physical State:	Yellow gel.
Mp:	-
R_f:	Baseline (EtOAc).
IR $\nu_{\max}$ (film)/cm ⁻¹ :	3147 (NH), 2430, 1660, 1579, 1457, 1205, 1040, 857, 690.
¹H NMR (400 MHz, D ₂ O):	δ 3.70 (s, 3H, OMe), 6.79 (m, 2H, H-2,4), 6.87 (d, J = 8.0 Hz, 1H, H-6), 7.29 (app. t, 1H, H-5).
¹³C NMR (100 MHz, D ₂ O):	δ 55.6 (CH ₃), 113.4 (CH), 113.5 (CH), 118.2 (CH), 136.3 (qC), 159.4 (qC), 160.1 (qCN).
HRMS (m/z ESI ⁺):	Found 166.0983 (M ⁺ + H. C ₈ H ₁₂ N ₃ O Requires 166.0975).

1-(2-Methoxyphenyl)guanidine hydrochloride (**394c**)



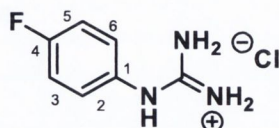
Following Method E to 4,6-dimethoxy-2-(2-methoxyanilino)pyrimidine **392c** (65 mg, 0.65 mmol, 1.0 equiv) in AcOH (0.210 mL) was added water (0.210 mL) and 12 M HCl (0.420 mL). The reaction was stirred at 95 °C for 12 h and then worked up according to Method E.

Yield:	90% (45 mg).
Physical State:	Green/yellow gel.
Mp:	-
R_f:	Baseline (EtOAc).
IR $\nu_{\max}$ (film)/cm ⁻¹ :	3312 (NH), 3155, 2972, 2462, 1667, 1455, 1287, 1161, 1045, 789.
¹H NMR (400 MHz, D ₂ O):	δ 3.75 (s, 3H, OMe), 6.95 (app. t, 1H, H-4), 7.05 (d, J = 8.0 Hz, 1H, H-3), 7.17 (d, J = 8.0 Hz, 1H, H-6), 7.31 (app. t, 1H, H-5).

^{13}C NMR (100 MHz, D_2O): δ 55.8 (CH_3), 113.0 (CH), 121.4 (CH), 122.0 (qC), 128.2 (CH), 130.1 (CH), 154.4 (qC), 156.6 (qC).

HRMS (m/z ESI^+): Found 166.0977 ($\text{M}^+ + \text{H}$. $\text{C}_8\text{H}_{12}\text{N}_3\text{O}$ Requires 166.0975).

1-(4-Fluorophenyl)guanidine hydrochloride (**394d**)



Following Method E to 4,6-dimethoxy-2-(4-fluoroanilino)pyrimidine **392d** (62 mg, 0.65 mmol, 1.0 equiv) in AcOH (0.210 mL) was added water (0.210 mL) and 12 M HCl (0.420 mL). The reaction was stirred at 95 °C for 12 h and then worked up according to Method E.

Yield: 74% (35 mg).

Physical State: Sticky yellow gel.

Mp: -

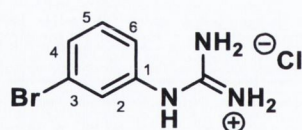
R_f : Baseline (EtOAc).

IR ν_{max} (film)/ cm^{-1} : 3311, 3139, 1665, 1590, 1507, 1215, 831, 793.

^1H NMR (400 MHz, D_2O): δ 7.20-7.24 (m, 2H, H-3,5), 7.28-7.41 (m, 2H, H-2,6).

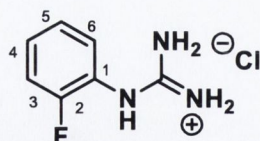
^{13}C NMR (100 MHz, D_2O): δ 119.2 (d, 2C, $J_{\text{CF}} = 9.0$ Hz), 131.1 (d, 2CH, $J_{\text{CF}} = 9.0$ Hz), 132.5 (d, qC, $J_{\text{CF}} = 2.3$ Hz), 159.1 (qCN), 163.1 (d, qC, $J_{\text{CF}} = 244.0$ Hz).

HRMS (m/z ESI^+): Found 154.0771 ($\text{M}^+ + \text{H}$. $\text{C}_7\text{H}_8\text{FN}_3$ Requires 154.0775).

1-(3-Bromophenyl)guanidine hydrochloride (394e)

Following Method E to 2-(3-bromoanilino)-4,6-dimethoxypyrimidine **392e** (77 mg, 0.65 mmol, 1.0 equiv) in AcOH (0.210 mL) was added water (0.210 mL) and 12 M HCl (0.420 mL). The reaction was stirred at 95 °C for 12 h and then worked up according to Method E.

Yield:	87% (53 mg).
Physical State:	Colourless viscous gel.
Mp:	-
R_f:	Baseline (EtOAc).
IR $\nu_{\max}$ (film)/cm ⁻¹ :	3319 (NH), 3133, 1668, 1568, 1476, 1301, 1069, 859, 671.
¹H NMR (600 MHz, D ₂ O):	δ 7.17 (d, J = 8.0 Hz, 1H, H-4), 7.27 (app. t, 1H, H-5), 7.42 (s, 1H, H-2), 7.45 (d, J = 8.0 Hz, 1H, H-6).
¹³C NMR (151 MHz, D ₂ O):	δ 122.2 (qC), 124.5 (CH), 128.6 (CH), 130.8 (CH), 131.2 (CH), 135.4 (qC), 156.1 (qCN).
HRMS (m/z ESI ⁺):	Found 213.9984 (M ⁺ + H. C ₇ H ₉ ⁷⁹ Br N ₃ Requires 213.9980).

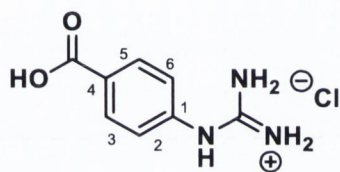
1-(4-Fluorophenyl)guanidine hydrochloride (394f)

Following Method E to 4,6-dimethoxy-2-(2-fluoroanilino)pyrimidine **392f** (62 mg, 0.65 mmol, 1.0 equiv) in AcOH (0.210 mL) was added water (0.210 mL) and 12 M HCl (0.420 mL). The reaction was stirred at 95 °C for 12 h and then worked up according to Method E.

Yield:	84% (39 mg).
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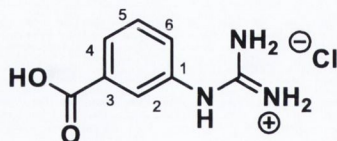
Physical State:	Colourless gel.
Mp:	-
R_f:	Baseline (EtOAc).
IR $\nu_{\max}$ (film)/cm ⁻¹ :	3323 (NH), 3146, 1672, 1621, 1501, 1423, 1264, 1106, 759.
¹H NMR (400 MHz, D ₂ O):	δ 7.17-7.27 (m, 4H, H-3,4,5,6).
¹³C NMR (100 MHz, D ₂ O):	δ 116.6 (d, J_{CF} = 16.0 Hz), 121.4 (d, J_{CF} = 16.0 Hz), 125.2 (CH), 128.7 (CH), 130.4 (d, J_{CF} = 6.0 Hz), 153.3 (qCN), 156.5 (d, CF, J_{CF} = 206.0 Hz).
HRMS (m/z ESI ⁺):	Found 154.0775 (M^+ + H. C ₇ H ₈ F N ₃ Requires 154.0775).

4-Guanidinobenzoic acid hydrochloride (394g)



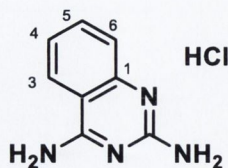
Following Method E to 2-(4-cyanoanilino)-4,6-dimethoxypyrimidine **392g** (64 mg, 0.65 mmol, 1.0 equiv) in AcOH (0.210 mL) was added water (0.210 mL) and 12 M HCl (0.420 mL). The reaction was stirred at 95 °C for 12 h and then worked up according to Method E.

Yield:	62% (33 mg).
Physical State:	White solid – hygroscopic.
Mp:	-
R_f:	Baseline (EtOAc).
IR $\nu_{\max}$ (film)/cm ⁻¹ :	3314 (NH), 3054, 2456, 2345, 2329, 2311, 1693, 1622, 1567, 1345, 1117, 1040, 827, 764.
¹H NMR (400 MHz, D ₂ O):	δ 7.39 (d, J = 8.0 Hz, 2H, H-2,6), 8.03 (d, J = 8.0 Hz, 2H, H-3,5).
¹³C NMR (100 MHz, D ₂ O):	δ 124.2 (2CH), 129.0 (qC), 131.2 (2CH), 139.0 (qC), 155.9 (q), 170.1 (qCO ₂ H).
HRMS (m/z ESI ⁺):	Found 180.0764 (M^+ + H. C ₈ H ₁₀ N ₃ O ₂ Requires 180.0773).

3-Guanidinobenzoic acid hydrochloride (394h)

Following Method E to 2-(3-cyanoanilino)-4,6-dimethoxypyrimidine **392h** (64 mg, 0.65 mmol, 1.0 equiv) in AcOH (0.210 mL) was added water (0.210 mL) and 12 M HCl (0.420 mL). The reaction was stirred at 95 °C for 12 h and then worked up according to Method E.

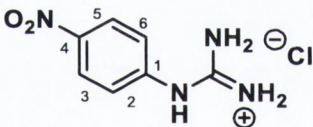
Yield:	75% (40 mg).
Physical State:	White solid – hygroscopic.
Mp:	-
R_f:	Baseline (EtOAc).
IR $\nu_{\max}$ (film)/cm ⁻¹ :	3369 (NH), 3171, 3069, 2871, 2345, 1699, 1654, 1577, 1346, 1215, 1082, 767.
¹H NMR (400 MHz, D ₂ O):	δ 7.57 (d, J = 8.0 Hz, 1H, H-6), 7.61 (app. t, 1H, H-5), 7.90 (s, 1H, H-2), 7.99 (d, J = 8.0 Hz, 1H, H-4).
¹³C NMR (100 MHz, D ₂ O):	δ 126.6 (CH), 128.7 (CH), 130.2 (CH), 130.4 (CH), 132.1 (qC), 134.5 (qC), 156.3 (qCN), 169.9 (qCO ₂ H).
HRMS (m/z ESI ⁺):	Found 180.0766 (M ⁺ + H. C ₈ H ₁₀ N ₃ O ₂ Requires 180.0773).

Quinazoline-2,4-diamine (394i)

Following Method E to 2-(2-cyanoanilino)-4,6-dimethoxypyrimidine **392i** (64 mg, 0.65 mmol, 1 equiv) in AcOH (0.210 mL) was added water (0.210 mL) and 12 M HCl (0.420 mL). The reaction was stirred at 95 °C for 12 h and then worked up according to Method E.

Yield:	84% (41 mg).
Physical State:	Off white gel.
Mp:	-
R_f:	Baseline (EtOAc).
IR ν_{max} (film)/ cm^{-1} :	3302 (NH), 3103, 3044, 2879, 2260 (CN), 1685, 1479, 1415, 1157, 751.
^1H NMR (400 MHz, D_2O):	δ 7.31 (d, J = 8.0 Hz, 1H, H-6), 7.45 (app. t, 1H, H-5), 7.81 (app. t, 1H, H-4), 7.98 (d, J = 8.0 Hz, 1H, H-3).
^{13}C NMR (100 MHz, D_2O):	δ 114.4 (qC), 116.7 (CH), 125.9 (CH), 126.9 (CH), 137.0 (CH), 137.6 (qC), 150.2 (qC), 161.4 (qC).
HRMS (m/z ESI^+):	Found 161.0638 ($\text{M}^+ + \text{H}$. $\text{C}_8\text{H}_9\text{N}_4$ Requires 161.0637).

1-(4-Nitrophenyl)guanidine hydrochloride (**394j**)



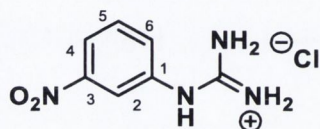
Following Method E to 4,6-dimethoxy-2-(4-nitroanilino)pyrimidine **392j** (69 mg, 0.65 mmol, 1.0 equiv) in AcOH (0.210 mL) was added water (0.210 mL) and 12 M HCl (0.420 mL). The reaction was stirred at 95 °C for 12 h and then worked up according to Method E.

Yield:	46% (28 mg).
Physical State:	Yellow paste.
Mp:	-
R_f:	Baseline (EtOAc).
IR ν_{max} (film)/ cm^{-1} :	3186 (NH), 1707, 1672, 1582 (NO_2), 1420, 1341 (NO_2), 1247, 1170, 853, 697.
^1H NMR (400 MHz, D_2O):	δ 7.38 (d, J = 8.8 Hz, 2H, H-2,6), 8.20 (d, J = 8.8 Hz, 2H, H-3,5).

^{13}C NMR (100 MHz, D_2O): δ 124.2 (2CH), 125.4 (2CH), 141.5 (qC), 145.3 (qC), 155.7 (qCN).

HRMS (m/z ESI^+): Found 181.1645 ($\text{M}^+ + \text{H}$. $\text{C}_7\text{H}_9\text{N}_4\text{O}_2$ Requires 181.1640).

1-(3-Nitrophenyl)guanidine hydrochloride (**394k**)



Following Method E to 4,6-dimethoxy-2-(3-nitroanilino)pyrimidine **392k** (69 mg, 0.65 mmol, 1.0 equiv) in AcOH (0.210 mL) was added water (0.210 mL) and 12 M HCl (0.420 mL). The reaction was stirred at 95 °C for 12 h and then worked up according to Method E.

Yield: 74% (40 mg).

Physical State: Yellow gel.

Mp: -

R_f : Baseline (EtOAc).

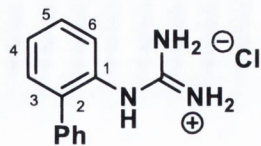
IR ν_{max} (film)/ cm^{-1} : 3313 (NH), 3115, 2582, 1671, 1631, 1525 (NO_2), 1416, 1349 (NO_2), 1249, 1093, 832, 805, 660.

^1H NMR (400 MHz, D_2O): δ 7.55 – 7.61 (m, 2H, H-5,6), 8.08 – 8.10 (m, 2H, H-2,4).

^{13}C NMR (100 MHz, D_2O): δ 119.9 (CH), 122.7 (CH), 131.1 (CH), 132.0 (CH), 136.0 (qC), 148.7 (qC), 169.1 (qCN).

HRMS (m/z ESI^+): Found 181.1642 ($\text{M}^+ + \text{H}$. $\text{C}_7\text{H}_9\text{N}_4\text{O}_2$ Requires 181.1640).

1-([1,1'-Biphenyl]-2-yl)guanidine hydrochloride (**394l**)



Following Method E to 4,6-dimethoxy-2-(2-phenylanilino)pyrimidine **392l** (76 mg, 0.25 mmol, 1.0 equiv) in AcOH (0.210 mL) was added water (0.210 mL) and 12 M HCl (0.420 mL). The reaction was stirred at 95 °C for 16 h and then worked up according to Method E.

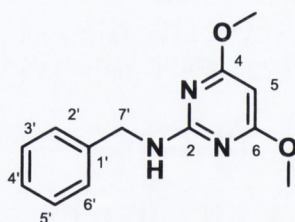
Yield:	65% (40 mg).
Physical State:	White crystal, very hygroscopic.
Mp:	-
R_f:	Baseline (EtOAc).
IR ν_{max} (film)/cm ⁻¹ :	3146, 2407, 1709, 1611, 1480, 1228, 763.
¹H NMR (400 MHz, D ₂ O):	δ 7.43 – 7.58 (m, 9H, H-Ar).
¹³C NMR (100 MHz, D ₂ O):	δ 127.8 (CH), 128.5 (CH), 128.6 (2CH), 128.6 (2CH), 129.1 (CH), 129.3 (CH), 131.1 (CH), 138.0 (qC), 139.8 (qC), 156.2 (qC), 171.3 (qCN).
HRMS (<i>m/z</i> ESI ⁺):	Found 212.1178 (M ⁺ + H. C ₁₃ H ₁₄ N ₃ Requires 212.1188).

***N*-Alkyl-2-amino-4,6-dimethoxypyrimidine Cleavage**

Method F - General procedure for formation of *N*-substituted 2-amino-4,6-dimethoxypyrimidines.

To amine (3.0 mmol, 3.0 eq.) in *i*-PrOH (2.0 mL) was added NEt₃ (416 μ L, 3.0 mmol, 3.0 eq.). To this was added 2-chloro-4,6-dimethoxypyrimidine (174 mg, 1.0 mmol, 1.0 eq.). A greased reflux condenser was attached and the mixture heated to reflux (120 °C). The reaction was left at this temperature until deemed complete by TLC analysis, typically 6 – 12 h. The reaction was then allowed cool to room temperature and then diluted with either EtOAc (10 mL, substrates **402b** and **402c**) or Et₂O (10 mL, all other substrates). This was then washed with water (5 mL). The aqueous phase was then extracted with the appropriate solvent as previously used (EtOAc or Et₂O, 3 $\times$ 10 mL). The combined organic layers were then washed with brine (10 mL), dried over MgSO₄ and then concentrated under reduced pressure to afford the title compound in its crude form. Purification by column chromatography (silica gel, hexanes:EtOAc, 100:0 $\rightarrow$ 60:40) afforded the title compound.

***N*-Benzyl-2-amino-4,6-dimethoxypyrimidine (386)**



Following Method F to benzylamine (327 μ L, 3.0 mmol, 3.0 eq.) in *i*-PrOH (2.0 mL) was added NEt₃ (416 μ L, 3.0 mmol, 3.0 eq.). To this was added 2-chloro-4,6-dimethoxypyrimidine (174 mg, 1.0 mmol, 1.0 eq.). The reaction was stirred at reflux (120 °C) for 12 h and then worked up according to Method F.

Yield: 90% (220 mg).

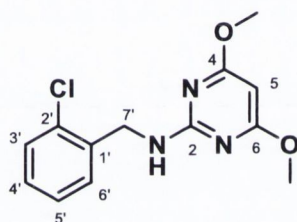
Physical State: White solid.

Mp: 64-65 °C.

R_f: 0.40 (hexanes:EtOAc, 90:10).

IR $\nu_{\max}$ (film)/ cm^{-1} :	3244 (NH), 3069, 3004, 2977, 2942, 1609, 1582, 1544, 1485, 1406, 1362, 1351, 1297, 1266, 1207, 1162, 1075, 1013, 952, 921, 895, 848, 795, 732.
^1H NMR (400 MHz, CDCl_3):	δ 3.84 (s, 6H, OMe), 4.61 (d, $J = 6.0$ Hz, 2H, H-7'), 5.23 (br s, NH), 5.43 (s, 1H, H-5), 7.26 – 7.37 (m, 5H, H-Bn).
^{13}C NMR (100 MHz, CDCl_3):	δ 45.7 (CH_2), 53.7 (2CH_3), 79.1 (CH), 127.3 (CH), 127.7 (2CH), 128.6 (2CH), 139.7 (qC), 161.8 (qC), 172.3 (2qC).
HRMS (m/z ESI^+):	Found 246.1237 ($\text{M}^+ + \text{H}$. $\text{C}_{13}\text{H}_{16}\text{N}_3\text{O}_2$ Requires 246.1243).

***N*-(2-Chlorobenzyl)-2-amino-4,6-dimethoxypyrimidine (402a)**



Following Method F to 2-chlorobenzylamine (360 μL , 3.0 mmol, 3.0 eq.) in *i*-PrOH (2.0 mL) was added NEt_3 (416 μL , 3.0 mmol, 3.0 eq.). To this was added 2-chloro-4,6-dimethoxypyrimidine (174 mg, 1.0 mmol, 1.0 eq.). The reaction was stirred at reflux (120 $^\circ\text{C}$) for 12 h and then worked up according to Method F.

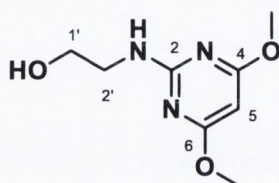
Yield:	82% (228 mg).
Physical State:	Yellow solid.
Mp:	68–70 $^\circ\text{C}$.
R_f:	0.32 (hexanes:EtOAc, 90:10).

IR $\nu_{\max}$ (film)/ cm^{-1} :	3242 (NH), 3071, 2949, 1609, 1583, 1546, 1458, 1442, 1345, 1302, 1274, 1212, 1200, 1150, 1078, 1049, 1037, 948, 790, 748.
^1H NMR (400 MHz, CDCl_3):	δ 3.83 (s, 6H, OMe), 4.70 (d, $J = 6.0$ Hz, 2H, H-7'), 5.40 (br s, NH), 5.42 (s, 1H, H-5), 7.17 – 7.19 (m, 2H, H-4',5'), 7.32 – 7.43 (m, 2H, H-3',6').

^{13}C NMR (100 MHz, CDCl_3): δ 43.2 (CH_2), 53.6 (2CH_3), 79.1 (CH), 126.7 (CH), 128.4 (CH), 129.4 (CH), 129.6 (CH), 133.5 (qC), 137.1 (qC), 161.5 (qC), 172.2 (2qC).

HRMS (m/z ESI^+): Found 280.0854 ($\text{M}^+ + \text{H}$, $\text{C}_{13}\text{H}_{15}^{35}\text{ClN}_3\text{O}_2$ Requires 280.0853).

***N*-(1-Ethanol-2-yl)-2-amino-4,6-dimethoxypyrimidine (402b)**



Following Method F to ethanolamine (180 μL , 3.0 mmol, 3.0 eq.) in *i*-PrOH (2.0 mL) was added NEt_3 (416 μL , 3.0 mmol, 3.0 eq.). To this was added 2-chloro-4,6-dimethoxypyrimidine (174 mg, 1.0 mmol, 1.0 eq.). The reaction was stirred at reflux (120 $^\circ\text{C}$) for 12 h and then worked up according to Method F.

Yield: 82% (163 mg).

Physical State: Yellow oil.

R_f : 0.32 (EtOAc).

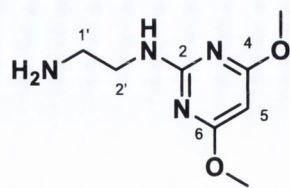
IR ν_{max} (film)/ cm^{-1} : 3244 (NH), 2949 (OH), 1580, 1546, 1444, 1344, 1211, 1192, 1158, 1038, 1011, 924, 862, 790.

^1H NMR (400 MHz, CDCl_3): δ 3.54 (app. q, 2H, H-2'), 3.78 (t, $J = 4.8$ Hz, 2H, H-1'), 3.81 (s, 6H, OMe), 3.95 (br s, OH), 5.39 (s, 1H, H-5), 5.58 (br s, NH).

^{13}C NMR (100 MHz, CDCl_3): δ 44.2 (CH_2), 53.5 (2CH_3), 63.2 (CH_2), 78.9 (CH), 161.9 (qC), 172.0 (2qC).

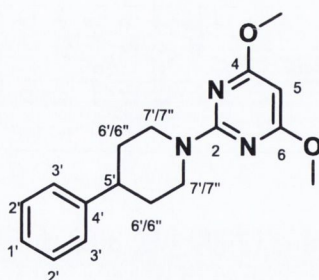
HRMS (m/z ESI^+): Found 200.1032 ($\text{M}^+ + \text{H}$, $\text{C}_8\text{H}_{14}\text{N}_3\text{O}_3$ Requires 200.1035).

N-(1-Aminoethen-2-yl)-2-amino-4,6-dimethoxypyrimidine (402c)



Following Method F to ethylenediamine (2000 μ L, 30.0 mmol, 3.0 eq.) in *i*-PrOH (20.0 mL) was added NEt₃ (4160 μ L, 30.0 mmol, 3.0 eq.). To this was added 2-chloro-4,6-dimethoxypyrimidine (1740 mg, 10.0 mmol, 1.0 eq.) in portions of 350 mg every hour over 5 h with only 340 mg being added on the 5th hour. The reaction was stirred at reflux (120 °C) for a further 12 h and then worked up according to Method F.

Yield:	86% (1700 mg -10 mmol scale).
Physical State:	Orange oil.
R_f:	0.08 (EtOAc).
IR ν_{max} (film)/cm ⁻¹ :	3293 (NH), 2947 (NH), 1575, 1542, 1456, 1420, 1363, 1348, 1210, 1192, 1156, 1010, 924, 793.
¹H NMR (400 MHz, D ₂ O):	δ 2.92 (t, <i>J</i> = 6.0 Hz, 2H, H-1'), 3.48 (app. q, 2H, H-2'), 3.84 (s, 6H, OMe), 5.40 (s, 1H, H-5).
¹³C NMR (100 MHz, D ₂ O):	δ 40.7 (CH ₂), 42.6 (CH ₂), 53.5 (2CH ₃), 78.2 (CH), 161.7 (qC), 172 (2qC).
HRMS (<i>m/z</i> ESI ⁺):	Found 199.1192 (M ⁺ + H. C ₈ H ₁₅ N ₄ O ₂ Requires 199.1195).

4,6-Dimethoxy-2-(4-phenylpiperidine-1-yl)pyrimidine (402d)

Following Method F to 4-phenylpiperidine (483 mg, 3.0 mmol, 3.0 eq.) in *i*-PrOH (2.0 mL) was added NEt_3 (416 μL , 3.0 mmol, 3.0 eq.). To this was added 2-chloro-4,6-dimethoxypyrimidine (174 mg, 1.0 mmol, 1.0 eq.). The reaction was stirred at reflux (120 $^{\circ}\text{C}$) for 12 h and then worked up according to Method F.

Yield: 88% (264 mg).

Physical State: White powder.

Mp: 103-106 $^{\circ}\text{C}$.

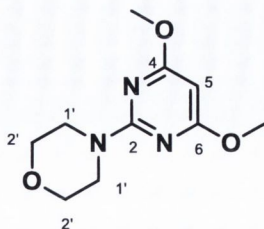
R_f : 0.52 (hexanes:EtOAc, 90:10).

IR ν_{max} (film)/ cm^{-1} : 3027, 2932, 2846, 1570, 1494, 1450, 1400, 1357, 1330, 1280, 1259, 1198, 1184, 1157, 1088, 1063, 1031, 987, 807, 788, 755.

^1H NMR (400 MHz, CDCl_3): δ 1.73 (app. ddd, 2H, H-6'), 1.94 (app. d, 2H, H-6''), 2.79 (app. tt, 1H, H-5'), 2.94 (app. td, 2H, H-7'), 3.90 (s, 6H, OMe), 4.94 (app. d, 2H, H-7''), 5.39 (s, 1H, H-5), 7.22 - 7.29 (m, 3H, H-Ar), 7.32 - 7.35 (m, 2H, H-Ar).

^{13}C NMR (100 MHz, CDCl_3): δ 33.2 (2CH_2), 43.2 (CH), 44.7 (2CH_2), 53.4 (2CH_3), 77.4 (CH), 126.2 (CH), 126.8 (2CH), 128.5 (2CH), 146.1 (qC), 160.8 (qC), 172.0 (2qC).

HRMS (m/z ESI $^+$): Found 300.1708 ($\text{M}^+ + \text{H}$. $\text{C}_{17}\text{H}_{22}\text{N}_3\text{O}_2$ Requires 300.1712).

4,6-Dimethoxy-2-(morpholin-4-yl)pyrimidine (402e)

Following Method F to morpholine (262 μL , 3.0 mmol, 3.0 eq.) in *i*-PrOH (2.0 mL) was added NEt_3 (416 μL , 3.0 mmol, 3.0 eq.). To this was added 2-chloro-4,6-dimethoxypyrimidine (174 mg, 1.0 mmol, 1.0 eq.). The reaction was stirred at reflux (120 $^\circ\text{C}$) for 12 h and then worked up according to Method F.

Yield: 84% (198 mg).

Physical State: Colourless crystal.

Mp: 99-102 $^\circ\text{C}$.

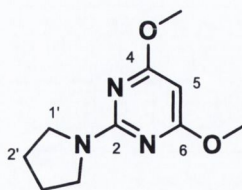
R_f : 0.32 (hexanes:EtOAc, 90:10).

IR ν_{max} (film)/ cm^{-1} : 3101, 2995, 2949, 2894, 2847, 1568, 1499, 1462, 1436, 1357, 1315, 1269, 1222, 1203, 1062, 1004, 990, 917, 809, 783.

^1H NMR (400 MHz, CDCl_3): δ 3.69 – 3.72 (m, 4H, H-2'), 3.73 – 3.76 (m, 4H, H-1'), 3.82 (s, 6H, OMe), 5.36 (s, 1H, H-5).

^{13}C NMR (100 MHz, CDCl_3): δ 44.3 (2CH_2), 53.4 (2CH_3), 66.8 (2CH_2), 78.3 (CH), 161.0 (qC), 172.0 (2qC).

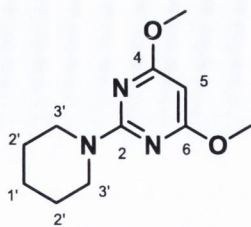
HRMS (m/z ESI $^+$): Found 226.1190 ($\text{M}^+ + \text{H}$, $\text{C}_{10}\text{H}_{16}\text{N}_3\text{O}_3$ Requires 226.1192).

4,6-Dimethoxy-2-(pyrrolidin-1-yl)pyrimidine (402f)

Following Method F to pyrrolidine (250 μ L, 3.0 mmol, 3.0 eq.) in *i*-PrOH (2.0 mL) was added NEt_3 (416 μ L, 3.0 mmol, 3.0 eq.). To this was added 2-chloro-4,6-dimethoxypyrimidine (174 mg, 1.0 mmol, 1.0 eq.). The reaction was stirred at reflux (120 $^{\circ}\text{C}$) for 12 h and then worked up according to Method F.

Yield:	87% (182 mg).
Physical State:	Off white solid.
Mp:	59-61 $^{\circ}\text{C}$. (Lit. 63.3 – 63.7 $^{\circ}\text{C}$) ²⁸⁹
R_f:	0.45 (hexanes:EtOAc, 90:10).
IR ν_{max} (film)/ cm^{-1} :	2972, 2943, 2873, 1563, 1529, 1475, 1451, 1396, 1364, 1277, 1251, 1208, 1188, 1151, 1056, 1013, 910, 891, 838, 794, 776, 702.
^1H NMR (400 MHz, CDCl_3):	δ 1.92 – 1.96 (m, 4H, H-2'), 3.54 – 3.57 (m, 4H, H-1'), 3.86 (s, 6H, OMe), 5.34 (s, 1H, H-5).
^{13}C NMR (100 MHz, CDCl_3):	δ 25.4 (2CH ₂), 46.7 (2CH ₂), 53.6 (2CH ₃), 76.6 (CH), 159.6 (qC), 171.7 (2qC).
HRMS (m/z ESI ⁺):	Found 210.1242 ($\text{M}^+ + \text{H}$. $\text{C}_{10}\text{H}_{16}\text{N}_3\text{O}_2$ Requires 210.1243).

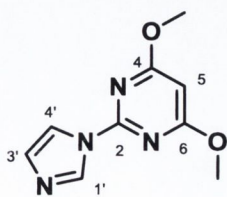
4,6-Dimethoxy-2-(piperidin-1-yl)pyrimidine (402g)



Following Method F to piperidine (295 μ L, 3.0 mmol, 3.0 eq.) in *i*-PrOH (2.0 mL) was added NEt_3 (416 μ L, 3.0 mmol, 3.0 eq.). To this was added 2-chloro-4,6-dimethoxypyrimidine (174 mg, 1.0 mmol, 1.0 eq.). The reaction was stirred at reflux (120 $^{\circ}\text{C}$) for 12 h and then worked up according to Method F.

Yield:	79% (353 mg).
Physical State:	White powder.
Mp:	48-49 $^{\circ}\text{C}$. (Lit. 58 – 60 $^{\circ}\text{C}$) ²⁸⁹
R_f:	0.73 (hexanes:EtOAc, 70:30).
IR ν_{max} (film)/cm^{-1}:	2943, 2853, 1562, 1441, 1399, 1276, 1257, 1189, 1154, 1092, 1033, 854, 796.
^1H NMR (400 MHz, CDCl_3):	δ 1.55-1.59 (m, 2H, H-1'), 1.63-1.67 (m, 4H, H-2'), 3.74-3.76 (m, 4H, H-3'), 3.85 (s, 6H, H-OMe), 5.32 (s, 1H, H-5).
^{13}C NMR (100 MHz, CDCl_3):	δ 25.1 (CH_2), 25.9 (2CH_2), 45.0 (2CH_2), 53.5 (2CH_3), 77.1 (CH), 161.0 (qC), 172.1 (2qC).
HRMS (m/z ESI^+):	Found 224.1402 ($\text{M}^+ + \text{H}$. $\text{C}_{11}\text{H}_{18}\text{N}_3\text{O}_2$ Requires 224.1394).

4,6-Dimethoxy-2-(1*H*-imidazol-1-yl)pyrimidine (402h)



Following Method F to imidazole (204 mg, 3.0 mmol, 3.0 eq.) in *i*-PrOH (2.0 mL) was added NEt_3 (416 μ L, 3.0 mmol, 3.0 eq.). To this was added 2-chloro-4,6-dimethoxypyrimidine (174

mg, 1.0 mmol, 1.0 eq.). The reaction was stirred at reflux (120 °C) for 12 h and then worked up according to Method F.

Yield: 75% (155 mg).

Physical State: White powder.

Mp: 110-113 °C.

R_f: 0.09 (hexanes:EtOAc, 90:10).

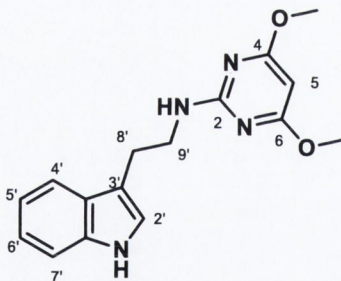
IR ν_{max} (film)/cm⁻¹: 3067, 1593, 1557, 1523, 1488, 1431, 1376, 1302, 1282, 1194, 1162, 1095, 1061, 1016, 919, 900, 862, 796, 776, 743.

¹H NMR (400 MHz, CDCl₃): δ 4.01 (s, 6H, OMe), 5.94 (s, 1H, H-5), 7.13 (app. s, 1H, H-3'), 7.84 (app. s, 1H, H-4'), 8.56 (s, 1H, H-1').

¹³C NMR (100 MHz, CDCl₃): δ 54.1 (2CH₃), 87.1 (CH), 116.3 (CH), 130.0 (CH), 136.8 (CH), 152.9 (qC), 171.8 (2qC).

HRMS (m/z ESI⁺): Found 207.0880 (M⁺ + H. C₉H₁₁N₄O₂ Requires 207.0882)

4,6-Dimethoxy-*N*-[2-(1*H*-indol-3-yl)ethyl]-2-aminopyrimidine (402i)



Following Method F to tryptamine (240 mg, 1.5 mmol, 3.0 eq.) in *i*-PrOH (2.0 mL) was added NEt₃ (213 μ L, 1.5 mmol, 3.0 eq.). To this was added 2-chloro-4,6-dimethoxypyrimidine (87 mg, 0.5 mmol, 1.0 eq.). The reaction was stirred at reflux (120 °C) for 12 h and then worked up according to Method F.

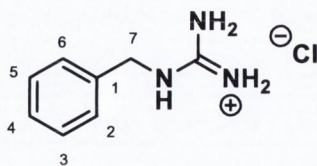
Yield: 54% (80 mg).

Physical State: Beige powder.

Mp:	85-86 °C.
R_f:	0.14 (hexanes:EtOAc, 80:20).
IR ν_{max} (film)/cm ⁻¹ :	3411 (NH), 3247, 3109, 2919, 1618, 1586, 1421, 1348, 1214, 1167, 926, 787, 737.
¹H NMR (400 MHz, CDCl ₃):	δ 3.07 (t, J = 7.2 Hz, 2H, H-8'), 3.75 (app. q, 2H, H-9'), 3.85 (s, 6H, OMe), 5.10 (br s, NH), 5.42 (s, 1H, H-5), 7.01 (br s, 1H), 7.13 (app. t, 1H, H-5'), 7.21 (app. t, 1H, H-6'), 7.36 (d, J = 8.0 Hz, 1H, H-7'), 7.65 (d, J = 8.0 Hz, 1H, H-4'), 8.19 (br s, 1H, H-2').
¹³C NMR (100 MHz, CDCl ₃):	δ 25.8 (CH ₂), 41.8 (CH ₂), 53.7 (2CH ₃), 78.5 (CH), 111.3 (CH), 113.5 (qC), 118.9 (CH), 119.4 (CH), 122.2 (CH), 122.2 (CH), 127.6 (qC), 136.5 (qC), 161.9 (qC), 172.5 (2qC).
HRMS (m/z ESI ⁺):	Found 299.1501 (M ⁺ + H. C ₁₆ H ₁₉ N ₄ O ₂ Requires 299.1502).

Method G - General procedure for pyrimidine ring cleavage

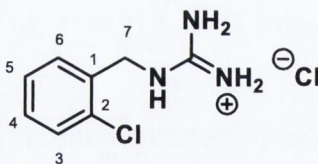
To *N*-substituted 2-amino-4,6-dimethoxypyrimidine (0.25 mmol) was added 4M aqueous HCl (5.0 mmol, 20.0 eq., 1.250 mL) at 80 °C in a sealed tube. The reaction was left to stir until deemed complete by TLC analysis (8 – 16 h). The reaction was cooled to room temperature and then diluted with EtOAc (4 mL). The phases were then separated and the aqueous phase was further washed with EtOAc (2 × 5 mL). The aqueous phase was then washed with CH₂Cl₂/MeOH (85:15, 5 mL). The aqueous phase containing the guanidine compound was then concentrated under reduced pressure. If further purification was required then the guanidine product was diluted in the minimum amount of water and passed through a plug of reverse phase silica (C₈) eluting with water to yield the title compound.

***N*-Benzylguanidine hydrochloride (387).**

Following Method G to *N*-benzyl-2-amino-4,6-dimethoxypyrimidine **386** (61 mg, 0.25 mmol, 1.0 eq.) was added 4M aqueous HCl (5.0 mmol, 20.0 eq., 1.250 mL) at 80 °C in a sealed tube. The reaction was stirred at 80 °C for 12 h and then worked up according to Method G.

Spectral data for this compound were consistent with those in the literature.²⁷²

Yield:	90% (135 mg).
Physical State:	Off white solid.
Mp:	175-177 °C (Lit. 173-174 °C)
R_f:	Baseline (EtOAc).
¹H NMR (400 MHz, D ₂ O):	δ 4.46 (s, 2H, H-7), 7.38 – 7.48 (m, 5H, H-2,3,4,5,6).
HRMS (<i>m/z</i> ESI ⁺):	Found 150.1026 (M ⁺ + H. C ₈ H ₁₂ N ₃ Requires 150.1031).

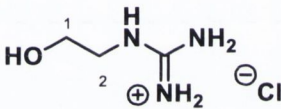
***N*-(2-Chlorobenzyl)guanidine hydrochloride (403a)**

Following Method G to *N*-(2-chlorobenzyl)-2-amino-4,6-dimethoxypyrimidine **402a** (70 mg, 0.25 mmol, 1.0 eq.) was added 4M aqueous HCl (5.0 mmol, 20.0 eq., 1.250 mL) at 80 °C in a sealed tube. The reaction was stirred at 80 °C for 12 h and then worked up according to Method G.

Yield:	82% (39 mg).
Physical State:	Beige solid.

Mp:	235-237 °C. (Lit. 188 - 189 °C) ²⁹⁰
R_f:	Baseline (EtOAc).
IR ν _{max} (film)/cm ⁻¹ :	3371 (NH), 2992, 2559, 1715, 1402, 1159, 1067, 797.
¹H NMR (400 MHz, D ₂ O):	δ 4.52 (s, 2H, H-7), 7.37-7.42 (m, 3H, H-4,5,6), 7.50-7.52 (m, 1H, H-3).
¹³C NMR (100 MHz, D ₂ O):	δ 42.8 (CH ₂), 127.3 (CH), 128.5 (CH), 129.5 (CH), 129.6 (CH), 132.7 (qC), 133.1 (qC), 156.8 (qC).
HRMS (<i>m/z</i> ESI ⁺):	Found 184.0643 (M ⁺ + H. C ₈ H ₁₁ ³⁵ ClN ₃ Requires 184.0636).

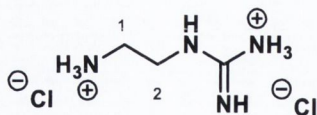
***N*-(2-Hydroxyethyl)guanidine hydrochloride (403b)**



Following Method G to *N*-(1-Ethanol-2-yl)-2-amino-4,6-dimethoxypyrimidine **402b** (50 mg, 0.25 mmol, 1.0 eq.) was added 4M aqueous HCl (5.0 mmol, 20.0 eq., 1.250 mL) at 80 °C in a sealed tube. The reaction was stirred at 80 °C for 12 h and then worked up according to Method G.

Spectral data for this compound were consistent with those in the literature.²⁷²

Yield:	45% (11 mg).
Physical State:	Colourless gel.
Mp:	-
R_f:	Baseline (EtOAc).
¹H NMR (400 MHz, D ₂ O):	δ 3.16 (t, <i>J</i> = 5.2 Hz, 2H, H-2), 3.83 (t, <i>J</i> = 5.2 Hz, 2H, H-1).

***N*-(2-Aminoethyl)guanidine dihydrochloride (403c)**

Following Method G to *N*-(1-Aminoethen-2-yl)-2-amino-4,6-dimethoxypyrimidine **402c** (49 mg, 0.25 mmol, 1.0 eq.) was added 4M aqueous HCl (5.0 mmol, 20.0 eq., 1.250 mL) at 80 °C in a sealed tube. The reaction was stirred at 80 °C for 12 h and then worked up according to Method G.

Spectral data for this compound were consistent with those in the literature.⁴²

Yield: 86% (37 mg).

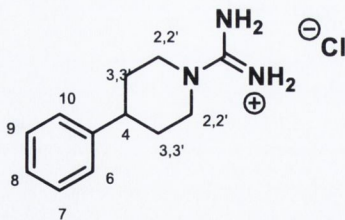
Physical State: Off white solid.

Mp: 198-202 °C. (No Lit. reported value).

R_f: Baseline (EtOAc).

IR (film) λ_{max}: 3366, 2491, 1612, 1425, 1199.

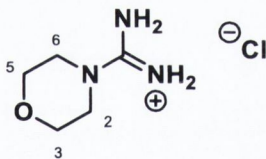
¹H NMR (400 MHz, D₂O): δ 3.25 (t, *J* = 6.0 Hz, 2H, H-1), 3.58 (t, *J* = 6.0 Hz, 2H, H-2).

4-Phenylpiperidine-1-carboxamidinium hydrochloride (403d)

Following Method G to 4,6-Dimethoxy-2-(4-phenylpiperidine-1-yl)pyrimidine **402d** (75 mg, 0.25 mmol, 1.0 eq.) was added 4M aqueous HCl (5.0 mmol, 20.0 eq., 1.250 mL) at 80 °C in a sealed tube. The reaction was stirred at 80 °C for 12 h and then worked up according to Method G.

Yield:	84% (50 mg).
Physical State:	Yellow solid.
Mp:	242-245 °C. (Lit. 283 - 284 °C) ²⁹¹
R_f:	Baseline (EtOAc).
IR ν_{max} (film)/cm ⁻¹ :	3316, 3148, 2942, 1659, 1613, 1494, 1165, 977, 766.
¹H NMR (400 MHz, D ₂ O):	δ 1.62 (app. ddd, 2H, 3), 1.81 (app. d, 2H, H-3'), 2.78 (app. tt, 1H, 4), 3.08 (app. td, 2H, H-2), 3.80 (app. dt, 2H, H-2'), 7.15 – 7.29 (m, 5H, H-6,7,8,9,10).
¹³C NMR (100 MHz, D ₂ O):	δ 31.8 (2CH ₂), 41.0 (CH), 46.3 (2CH ₂), 126.8 (CH), 126.8 (2CH), 128.6 (2CH), 145.3 (qC), 155.7 (qC).
HRMS (m/z ESI ⁺):	Found 204.1503 (M ⁺ + H. C ₁₂ H ₁₈ N ₃ Requires 204.1495).

Morpholine-4-carboxamidine hydrochloride (403e)



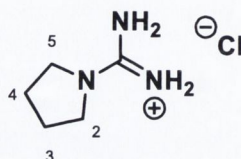
Following Method G to 4,6-Dimethoxy-2-(morpholin-4-yl)pyrimidine **402e** (56 mg, 0.25 mmol, 1.0 eq.) was added 4M aqueous HCl (5.0 mmol, 20.0 eq., 1.250 mL) at 80 °C in a sealed tube. The reaction was stirred at 80 °C for 12 h and then worked up according to Method G.

Spectral data for this compound were consistent with those in the literature.²⁷²

Yield:	66% (21 mg).
Physical State:	Reddish-beige solid.
Mp:	>250 °C (decompose, no Lit. value reported).
R_f:	Baseline (EtOAc).

¹H NMR (400 MHz, D₂O): δ 3.52 (t, *J* = 4.8 Hz, 2H, H-2,6), 3.83 (t, *J* = 4.8 Hz, 2H, H3,5).

Pyrrolidine-1-carboxamidine hydrochloride (403f)



Following Method G to 4,6-Dimethoxy-2-(pyrrolidin-1-yl)pyrimidine **402f** (53 mg, 0.25 mmol, 1.0 eq.) was added 4M aqueous HCl (5.0 mmol, 20.0 eq., 1.250 mL) at 80 °C in a sealed tube. The reaction was stirred at 80 °C for 12 h and then worked up according to Method G.

Spectral data for this compound were consistent with those in the literature.²⁷³

Yield: 87% (24 mg).

Physical State: Pale yellow viscous gel.

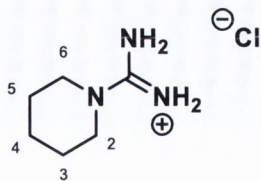
Mp: -

R_f: Baseline (EtOAc).

¹H NMR (400 MHz, D₂O): δ 2.09-2.11 (m, 4H, H-3,4), 3.61-3.75 (m, 4H, H-2,5).

HRMS (*m/z* ESI⁺): Found 114.1029 (M⁺ + H. C₅H₁₂N₃ Requires 114.1031).

Piperidine-1-carboxamidine hydrochloride (403g)

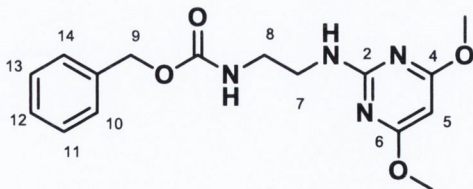


Following Method G to 4,6-Dimethoxy-2-(piperidin-1-yl)pyrimidine **402g** (56 mg, 0.25 mmol, 1.0 eq.) was added 4M aqueous HCl (5.0 mmol, 20.0 eq., 1.250 mL) at 80 °C in a sealed tube. The reaction was stirred at 80 °C for 12 h and then worked up according to Method G.

Spectral data for this compound were consistent with those in the literature.²⁷²

Yield:	88% (35 mg).
Physical State:	Yellowish solid.
Mp:	185-188 °C (Lit. 186-187 °C).
R_f:	Baseline (EtOAc).
¹H NMR (400 MHz, D₂O):	δ 1.72 – 1.75 (m, 6H, H-3,4,5), 3.59 – 3.75 (m, 4H, H-2,6).

2-[Benzyl(2-ethylamino)carbamate]-4,6-dimethoxypyrimidine (404a)

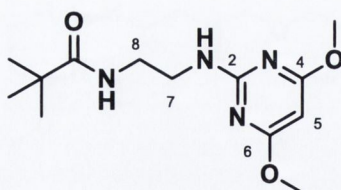


To *N*-(1-aminoethen-2-yl)-2-amino-4,6-dimethoxypyrimidine **402c** (199 mg, 1.0 mmol, 1.0 eq.) in CH₂Cl₂ (4.0 mL) was added NEt₃ (138 μL, 1.0 mmol, 1.0 eq.). To this was added benzyl chloroformate (156 μL, 1.1 mmol, 1.1 eq.) at 0 °C. This solution was allowed warm to rt over 1 h and stirred for 4 h or until deemed complete (TLC analysis). The reaction was then diluted with water (5 mL) and EtOAc (10 mL). The layers were separated and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic layers were then

washed with brine (15 mL), dried over MgSO_4 and concentrated under reduced pressure. The crude residue was then purified by column chromatography (silica gel, hexanes:EtOAc, 90:10 $\rightarrow$ 60:40) to yield the target compound.

Yield:	90% (222 mg).
Physical State:	White solid.
Mp:	60–61 °C.
R_f:	0.41 (hexanes:EtOAc, 60:40).
IR ν_{max} (film)/ cm^{-1} :	3340 (NH), 3245 (NH), 3111, 2927, 1685, 1611, 1584, 1535, 1484, 1453, 1432, 1351, 1260, 1163, 1152, 1067, 1016, 929, 790, 778.
^1H NMR (400 MHz, CDCl_3):	δ 3.39 (t, J = 5.2 Hz, 2H, H-8), 3.50 (t, J = 5.2 Hz, 2H, H-7), 3.80 (s, 6H, OMe), 5.06 (s, 2H, H-9), 5.93 (s, 1H, H-5), 5.42 (br s, NH), 5.62 (br s, NH), 7.26 – 7.34 (m, 5H, H-10,11,12,13,14).
^{13}C NMR (100 MHz, CDCl_3):	δ 41.4 (CH_2), 41.9 (CH_2), 53.7 (2CH_3), 66.7 (CH_2), 79.1 (CH), 128.1 (CH), 128.2 (2CH), 128.6 (2CH), 136.7 (qC), 156.7 (qC), 162.1 (qC), 172.7 (2qC).
HRMS (m/z ESI^+):	Found 333.1559 ($\text{M}^+ + \text{H}$. $\text{C}_{16}\text{H}_{21}\text{N}_4\text{O}_4$ Requires 333.1563).

2-[(Ethylamino)pivalamide]-4,6-dimethoxypyrimidine (**404b**)

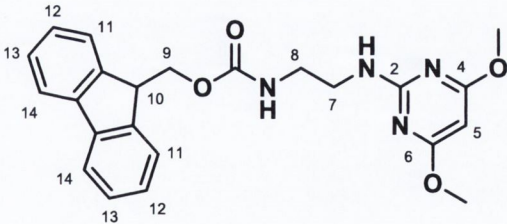


To *N*-(1-aminoethen-2-yl)-2-amino-4,6-dimethoxypyrimidine **402c** (199 mg, 1.0 mmol, 1.0 eq.) in CH_2Cl_2 (4.0 mL) was added NEt_3 (138 μL , 1.0 mmol, 1.0 eq.). To this was added pivaloyl chloride (135 μL , 1.1 mmol, 1.1 eq.) at 0 °C. This solution was allowed warm to rt over 1 h and stirred for 12 h or until deemed complete (TLC analysis). The reaction was then diluted with water (5 mL) and EtOAc (10 mL). The layers were separated and the aqueous

phase extracted with EtOAc (3 × 10 mL). The combined organic layers were then washed with brine (15 mL), dried over MgSO₄ and concentrated under reduced pressure. The crude residue was then purified by column chromatography (silica gel, hexanes:EtOAc, 90:10 → 60:40) to yield the target compound.

Yield:	69% (145 mg).
Physical State:	White solid.
Mp:	120–124 °C.
R_f:	0.18 (hexanes:EtOAc, 60:40).
IR ν _{max} (film)/cm ⁻¹ :	3371 (NH), 3244 (NH), 2984, 2923, 1635, 1607, 1584, 1526, 1485, 1452, 1417, 1352, 1293, 1252, 1207, 1171, 1161, 1110, 1073, 1006, 932, 856, 797, 772.
¹H NMR (400 MHz, CDCl ₃):	δ 1.11 (s, 9H, <i>t</i> -Bu), 3.43 (app. dd, 2H, H-7), 3.56 (app. dd, 2H, H-8), 3.82 (s, 6H, OMe), 5.35 (br s, NH), 5.39 (s, 1H, H-5), 6.32 (br s, NH).
¹³C NMR (100 MHz, CDCl ₃):	δ 27.6 (3CH ₃), 38.7 (qC), 40.8 (CH ₂), 40.9 (CH ₂), 53.8 (2CH ₃), 76.7 (CH), 162.3 (qC), 172.4 (2qC), 179.2 (qC).
HRMS (<i>m/z</i> ESI ⁺):	Found 283.1767 (M ⁺ + H. C ₁₃ H ₂₃ N ₄ O ₃ Requires 283.1770).

2-[9*H*-Fluoren-9-yl)methyl(2- ethylamino)carbamate]-4,6-dimethoxypyrimidine (**404c**)

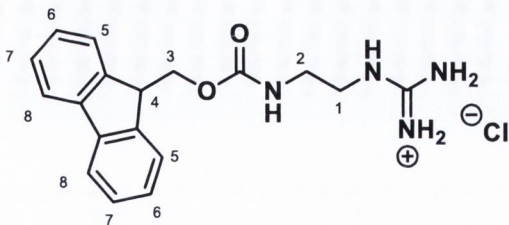


To *N*-(1-aminoethen-2-yl)-2-amino-4,6-dimethoxypyrimidine **402c** (400 mg, 2.0 mmol, 1.0 eq.), in EtOAc (3.0 mL) was added 9-fluorenylmethyl chloroformate (573 mg, 1.1 mmol, 1.1 eq.). To this was added a solution of sat. aq. NaHCO₃ (4.0 mL). The resultant mixture was stirred for 13 h after which time it was diluted with EtOAc (25 mL) and water (10 mL). The

layers were separated and the aqueous layer extracted with EtOAc (3×20 mL). The combined organic layers were then washed with brine (20 mL), dried over MgSO_4 and concentrated under reduced pressure. The crude residue was then dissolved in the minimum amount of EtOAc (~ 5 mL) and heated using a heat gun until the crude residue had fully dissolved in the EtOAc. Upon cooling the product crashed out of solution and was collected by vacuum filtration, yielding the desired product.

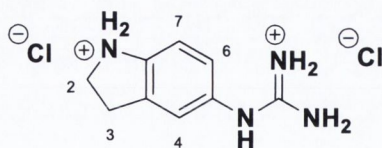
Yield:	75% (315 mg).
Physical State:	White fluffy solid.
Mp:	152–156 °C.
R_f:	0.40 (hexanes:EtOAc, 60:40).
IR ν_{max} (film)/ cm^{-1} :	3338 (NH), 3243 (NH), 3040, 2938, 1683, 1611, 1582, 1531, 1479, 1452, 1366, 1352, 1270, 1249, 1209, 1164, 1149, 1111, 1083, 1076, 1065, 1020, 957, 930, 881, 791, 781, 760, 735.
^1H NMR (400 MHz, CDCl_3):	δ 3.42 (app. dd, 2H, H-8), 3.55 (app. dd, 2H, H-7), 3.81(s, 6H, OMe), 4.19 (t, $J = 6.0$ Hz, 1H, H-10), 4.40 (d, $J = 6.0$ Hz, 2H, H-9), 5.20 (br s, NH), 5.43 (s, 1H, H-5), 5.61 (br s, NH), 7.29 (app. t, 2H, H-12), 7.39 (app. t, 2H, H-13), 7.55 (d, $J = 7.2$ Hz, 2H, H-11), 7.75 (d, $J = 7.2$ Hz, 2H, H-14).
^{13}C NMR (100 MHz, CDCl_3):	δ 41.3 (CH_2), 42.2 (qC), 47.4 (CH_2), 53.0 (2CH_3) 66.4 (CH_2), 79.3 (CH), 120.1 (2CH), 125.1 (2CH), 127.1 (2CH), 127.8 (2CH), 141.4 (2qC), 144.1 (2qC), 156.8 (qC), 162.2 (qC), 172.3 (2qC).
HRMS (m/z ESI $^+$):	Found 421.1876 ($\text{M}^+ + \text{H}$. $\text{C}_{23}\text{H}_{25}\text{N}_4\text{O}_4$ Requires 421.1870).

(9*H*-Fluoren-9-yl)methyl-(2-guanidinoethyl)carbamate (405a)



Following Method G to (9*H*-Fluoren-9-yl)methyl-(2-((4,6-dimethoxypyrimidin-2-yl)amino)ethyl)carbamate (105 mg, 0.25 mmol, 1.0 eq.) was added 4M aqueous HCl (5.0 mmol, 20 eq., 1.250 mL) at 80 °C in a sealed tube. The reaction was stirred at 80 °C for 12 h and then worked up according to Method G.

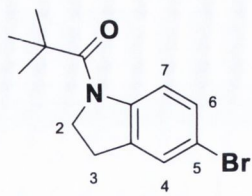
Yield:	86% (70 mg).
Physical State:	White solid.
Mp:	146-149 °C.
R_f:	Baseline (EtOAc).
IR ν_{max} (film)/cm ⁻¹ :	3332 (NH), 2971 (NH), 1683, 1581, 1367, 1266, 1077, 791, 736.
¹H NMR (400 MHz, DMSO):	δ 3.18 (t, J = 6.0 Hz, 2H, H-2), 3.31 (m, 2H, H-1), 3.78 (br s, 4NH), 4.21 (t, J = 6.0 Hz, 1H, H-4), 4.30 (d, J = 6.0 Hz, 2H, H-3), 7.05 (br s, NH), 7.33 (app. t, 2H, H-6), 7.42 (app. t, 2H, H-7), 7.68 (d, J = 7.2 Hz, 2H, H-5), 7.89 (d, J = 7.2 Hz, 2H, H-8).
¹³C NMR (100 MHz, DMSO):	δ 39.9 (CH ₂), 40.6 (CH ₂), 46.6 (CH ₂), 63.6 (CH), 119.8 (2CH), 125.1 (2CH), 127.1 (2CH), 127.5 (2CH), 140.6 (2qC), 143.8 (2qC), 161.4 (qC), 171.2 (qC).
HRMS (m/z ESI ⁺):	Found 325.1663 (M ⁺ + H. C ₁₈ H ₂₁ N ₄ O ₂ Requires 325.1659).

5-Guanidinoindoline dihydrochloride (406)

To an RBF (5 mL) containing 2-[(1-pivaloyl)indolinamino]-4,6-dimethoxypyrimidine **412** (89 mg, 0.25 mmol, 1.0 equiv) in AcOH (0.210 mL) was added water (0.210 mL) and 12 M HCl (0.420 mL). To this was attached a reflux condenser making sure the joint was well greased. *The RBF was then covered with aluminium foil and fully submerged in an oil bath at 100 °C (essential).* The reaction was monitored by TLC, ensuring to basify all TLC samples using NEt₃, and once deemed complete was allowed cool to room temperature. The solution was washed with EtOAc (3 × 10 mL) and CH₂Cl₂/MeOH (80:20, 1 × 10 mL) to remove any unreacted starting materials and then the aqueous phase concentrated under reduced pressure to yield the target aryl guanidine as the hydrochloride salt.

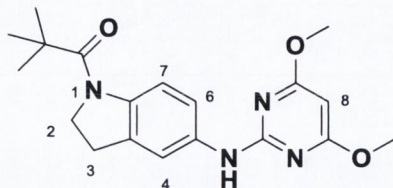
Yield:	89% (55 mg).
Physical State:	Off white solid.
Mp:	141-142 °C.
R_f:	Baseline (EtOAc).
IR $\nu_{\max}$ (film)/cm ⁻¹ :	3106 (NH), 2948, 2603, 2496, 1639, 1475, 1235, 1172, 1036, 827.
¹H NMR (400 MHz, D ₂ O):	δ 3.35 (t, J = 8.0 Hz, 2H, H-3), 3.94 (t, J = 8.0 Hz, 2H, H-2), 7.34 (dd, J = 8.0, 2.0 Hz, 1H, H-6), 7.45 (app. br s, 1H, H-4), 7.55 (d, J = 8.0 Hz, 1H, H-7).
¹³C NMR (100 MHz, D ₂ O):	δ 28.6 (CH ₂), 46.4 (CH ₂), 112.6 (CH), 123.0 (CH), 125.5 (CH), 127.0 (qC), 133.1 (qC), 147.7 (qC), 156.3 (qC).
HRMS (m/z ESI ⁺):	Found 177.1135 (M ⁺ + H. C ₉ H ₁₃ N ₄ Requires 177.1134).
Purity by HPLC:	99.3% (t _R 2.59 min).

N-Pivaloyl-5-bromoindoline (411)



To 5-bromoindoline (784 mg, 4.0 mmol, 1.0 eq.) in CH₂Cl₂ (6.0 mL) was added NEt₃ (583 μL, 4.2 mmol, 1.05 eq.) followed by pivaloyl chloride (514 μL, 4.2 mmol, 1.05 eq.) at 0 °C. To this was added DMAP (48 mg, 0.40 mmol, 0.10 eq.). The reaction was then allowed warm to rt over 1 h and stirred for 6 h. After this time the reaction was deemed complete by TLC analysis and the reaction was diluted with water (5 mL) and CH₂Cl₂ (10 mL). The layers were separated and the aqueous phase extracted with CH₂Cl₂ (3 × 15 mL). The combined organic layers were washed with brine (20 mL), dried over MgSO₄ and concentrated under reduced pressure. The crude residue was then purified by column chromatography (silica gel, hexanes:EtOAc, 80:20) to afford the pure title compound.

Yield:	95% (1067 mg).
Physical State:	Colourless crystal.
Mp:	55-56 °C.
R_f:	0.40 (Hex : EtOAc, 80:20).
IR ν _{max} (film)/cm ⁻¹ :	1645, 1545, 1322, 1197, 1009, 777.
¹H NMR (400 MHz, CDCl ₃):	δ 1.36 (s, 9H, <i>t</i> -Bu), 3.11 (t, <i>J</i> = 8.2 Hz, 2H, H-3), 4.22 (t, <i>J</i> = 8.2 Hz, 2H, H-2), 7.26 – 7.28 (m, 2H, H-4,7), 8.11 (d, <i>J</i> = 9.2 Hz, 1H, H-6).
¹³C NMR (100 MHz, CDCl ₃):	δ 27.6 (3CH ₃), 29.0 (CH ₂), 40.2 (qC), 49.5 (CH ₂), 115.8 (qC), 119.6 (CH), 127.1 (CH), 130.1 (CH), 133.2 (qC), 150.0 (qC), 176.6 (CH).
HRMS (<i>m/z</i> ESI ⁺):	Found 282.0488 (M ⁺ + H. C ₁₃ H ₁₇ ⁷⁹ BrNO Requires 282.0488).

2-[(1-pivaloyl)indolinamino]-4,6-dimethoxypyrimidine (**412**)

To an oven dried Schlenk tube charged with a stir bar, $\text{Pd}_2(\text{dba})_3$ (2 mol%, 18 mg) and Xantphos (3 mol%, 17 mg) was added 2-amino-4,6-dimethoxypyrimidine (1.5 mmol, 1.5 equiv, 232 mg), K_3PO_4 (1.5 mmol, 1.5 equiv) and *N*-pivaloyl-5-bromoindoline **411** (280 mg, 1.0 mmol, 1.0 equiv). The Schlenk tube was put under vacuum and back filled with argon three times. To this was added freshly distilled toluene (1.5 mL). The Schlenk tube was then placed in an oil bath with vigorous stirring at 95 °C. The reaction was monitored by TLC and once deemed complete (12 h), was cooled to rt and diluted with EtOAc (10 mL). The reaction mixture was filtered through Celite with any remaining residues in the Schlenk tube being washed out with a further amount of EtOAc (10 mL). The organic phase was then washed with water (50 mL). The aqueous phase was extracted with EtOAc (3 × 50 mL) and the combined organic layers washed with brine (50 mL), dried with MgSO_4 and concentrated under reduced pressure. The crude product was then purified by flash column chromatography (silica gel, hexanes:EtOAc, 100:0 → 60:40) to yield the target compound.

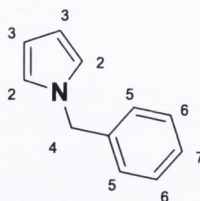
Yield:	63% (224 mg).
Physical State:	Off white solid.
Mp:	62-64 °C.
R_f:	0.50 (CH_2Cl_2 :EtOAc, 80:20).
IR ν_{max} (film)/cm^{-1}:	3257 (NH), 3109, 2957, 1603, 1451, 1350, 1206, 1079, 795.
^1H NMR (400 MHz, CDCl_3):	δ 1.08 (s, 9H, <i>t</i> -Bu), 2.83 (t, J = 8.0 Hz, 2H, H-3), 3.60 (s, 6H, OMe), 3.93 (t, J = 8.0 Hz, 2H, H-2), 5.26 (s, 1H, H-8), 6.82 (br s, NH), 7.05 (d, J = 8.0 Hz, 1H, H-7), 7.45 (s, 1H, H-4) 7.89 (d, J = 8.0 Hz, 1H, H-6).

¹³C NMR (100 MHz, CDCl₃): δ 27.8 (3CH₃), 29.6 (CH₂), 40.1 (qC), 49.6 (CH₂), 53.8 (2CH₃), 80.7 (CH), 115.6 (CH), 118.3 (CH), 118.4 (CH), 131.4 (qC), 136.6 (qC), 138.9 (qC), 158.9 (qC), 171.9 (2qC), 176.1 (qCO).

HRMS (*m/z* ESI⁺): Found 357.1914 (M⁺ + H. C₁₉H₂₅N₄O₃ Requires 357.1921).

8.3. Spiro guanidine amins.

N-Benzyl pyrrole (434)



To freshly distilled pyrrole (6937 μL , 100.0 mmol, 1.0 eq.) in CH_2Cl_2 (160.0 mL) was added benzyl bromide (13060 μL , 110.0 mmol, 1.1 eq.) and *tetra*-butyl ammonium bromide (37210 mg, 100.0 mmol, 1.0 eq.) at 0 $^\circ\text{C}$. To this was added NaOH (50.0 g in H_2O – 100.0 mL) slowly, ensuring the reaction mixture was kept at 0 $^\circ\text{C}$. Once the addition was complete a reflux condenser was attached and the solution heated to 65 $^\circ\text{C}$ for 24 h. After this time the reaction was cooled to room temperature and diluted with CH_2Cl_2 (100 mL) and H_2O (100 mL). The solution was vigorously stirred for 5 min and then allowed to settle. The organic layer was separated and the aqueous phase extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were then washed with 3M HCl (100 mL) followed by brine (100 mL). The organic layer was then dried over MgSO_4 , concentrated under reduced pressure and then purified by vacuum distillation to afford the title compound.

Spectral data for this compound were consistent with those in the literature.²⁷⁴

Yield: 77% (12089 mg).

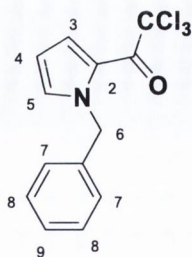
Physical State: Colourless oil.

Mp: -

R_f: 0.33 (hexanes:EtOAc, 90:10).

^1H NMR (400 MHz, CDCl_3): δ 5.10 (s, 2H, H-4), 6.20 (t, $J = 2.0$ Hz, 2H, H-3), 6.70 (d, $J = 2.0$ Hz, 2H, H-2), 7.20 (d, $J = 8.0$ Hz, 2H, H-5), 7.40 (m, 3H, H-6,7).

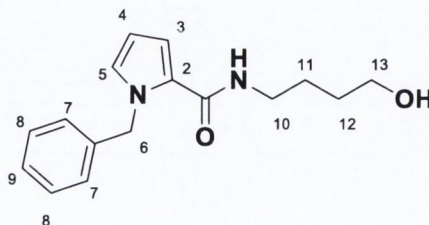
***N*-Benzyl-2-trichloroacetylpyrrole (435)**



To trichloroacetyl chloride (8086 μ L, 71.97 mmol, 1.0 eq.) in Et₂O (20.0 mL) at 0 °C was added *N*-benzyl pyrrole **434** (11300 mg, 71.97 mmol, 1.0 eq.) in Et₂O (60.0 mL). This reaction was then stirred for 12 h at rt. After this time the reaction was then very cautiously quenched with a solution of sat. aq. NaHCO₃ (80 mL). The aqueous phase was then extracted with Et₂O (3 $\times$ 50 mL). The combined organic layers were then washed with brine (50 mL), dried over MgSO₄ and then concentrated under reduced pressure. The crude product was then purified by column chromatography (silica gel, hexanes:EtOAc, 70:30) to afford the target compound as a colourless oil which solidified upon standing to give an off white solid.

Spectral data for this compound were consistent with those in the literature.²⁷⁵

Yield:	80% (17272 mg).
Physical State:	Colourless oil – off white solid.
MP:	47-49 °C (Lit. 49-50 °C).
R_f:	0.18 (hexanes:EtOAc, 60:40).
¹H NMR (400 MHz, CDCl₃):	δ 5.56 (s, 2H, H-6), 6.29 - 6.30 (m, 1H, H-4), 7.05 - 7.06 (m, 1H, H-3), 7.10 - 7.12 (m, 2H, H-7), 7.28 - 7.30 (m, 3H, H-8,9), 7.58 (dd, J = 4.0, 1.6 Hz, 1H, H-5)

1-Benzyl-*N*-(4-hydroxybutyl)-1*H*-pyrrole-2-carboxamide (437)

To *N*-benzyl-2-trichloroacetylpyrrole **435** (27000 mg, 90.0 mmol, 1.6 eq.) in CH_2Cl_2 (100.0 mL) was added NEt_3 (12.50 mL, 90.0 mmol, 1.6 eq.) at rt. To this was added 4-amino-1-butanol **436** (5000 mg, 56.0 mmol, 1.0 eq.). The reaction was left to stir at rt for 16 h after which time water (50 mL) was added and the solution stirred vigorously for 5 min. The layers were separated and the aqueous phase washed with CH_2Cl_2 (3×50 mL). The combined organic layers were washed with 1M HCl (40 mL), brine (50 mL), dried over MgSO_4 and then concentrated under reduced pressure to afford the crude product. This residue was then purified by column chromatography (silica gel, hexanes:EtOAc, 90:10 $\rightarrow$ 40:60) to afford the desired product.

Yield: 60% (9100 mg).

Physical State: Beige non-crystalline solid.

Mp: 69-70 °C.

R_f: 0.33 (EtOAc).

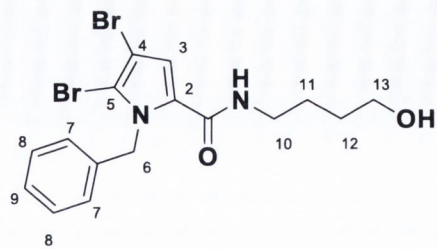
IR ν_{max} (film)/ cm^{-1} : 3342 (NH), 2982 (OH), 1705, 1333, 1122, 1070.

^1H NMR (400 MHz, CDCl_3): δ 1.50 – 1.63 (m, 4H, H-11,12), 2.47 (br s, OH), 3.34 (app. dd, 2H, H-10), 3.61 (t, $J = 6.0$ Hz, 2H, H-13), 5.58 (s, 2H, H-6), 6.09 – 6.11 (m, 1H, H-4), 6.31 (br s, NH), 6.56 – 6.58 (m, 1H, H-3), 6.77 – 6.78 (m, 1H, H-5), 7.10 (d, $J = 7.2$ Hz, 2H, H-7), 7.19 – 7.28 (m, 3H, H-8,9).

^{13}C NMR (100 MHz, CDCl_3): 26.2 (CH_2), 29.7 (CH_2), 39.0 (CH_2), 51.8 (CH_2), 62.2 (CH_2), 107.8 (CH), 112.1 (CH), 125.8 (qC), 127.1 (2CH), 127.1 (CH), 127.3 (CH), 128.6 (2CH), 138.8 (qC), 162.2 (qC).

HRMS (m/z ESI^+): Found 295.1429 ($\text{M}^+ + \text{Na}$. $\text{C}_{16}\text{H}_{20}\text{N}_2\text{O}_2\text{Na}$ Requires 295.1417).

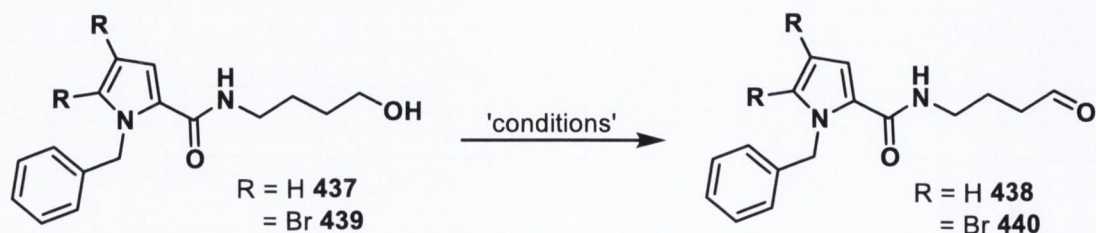
1-Benzyl-4,5-dibromo-*N*-(4-hydroxybutyl)-1*H*-pyrrole-2-carboxamide (439)



To 1-benzyl-*N*-(4-hydroxybutyl)-1*H*-pyrrole-2-carboxamide **437** (54 mg, 0.20 mmol, 1.0 eq.) in MeCN (5.0 mL) was added *N*-bromosuccinimide (71 mg, 0.40 mmol, 2.0 eq.) in one portion at rt. The reaction mixture was stirred for 4 h after which time the reaction was deemed complete by TLC analysis. The reaction was quenched with water (5 mL) and EtOAc (10 mL). The layers were separated and the aqueous phase extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO₄ and concentrated under reduced pressure. The crude product was then purified by column chromatography (silica gel, hexanes:EtOAc, 90:10 → 40:60) to afford the title compound.

Yield:	83% (70 mg).
Physical State:	Beige solid.
Mp:	104-105 °C.
R_f:	0.50 (EtOAc).
IR ν _{max} (film)/cm ⁻¹ :	3262 (NH), 3110, 2937 (OH), 2860, 1771, 1689, 1633, 1553, 1432, 1396, 1186, 1061, 1010, 881, 849, 820, 691 (Br).
¹H NMR (400 MHz, CDCl ₃):	δ 1.51 – 1.61 (m, 4H, H-11,12), 1.73 (br s, OH), 3.32 (app. dd, 2H, H-10), 3.63 (t, <i>J</i> = 6.4 Hz, 2H, H-13), 5.71 (s, 2H, H-6), 6.24 (br s, NH), 6.65 (s, 1H, H-3), 7.04 (d, <i>J</i> = 7.2 Hz, 2H, H-7), 7.20 – 7.26 (m, 3H, H-8,9).
¹³C NMR (100 MHz, CDCl ₃):	δ 26.4 (CH ₂), 29.8 (CH ₂), 39.4 (CH ₂), 50.9 (CH ₂), 62.6 (CH ₂), 98.9 (qC), 111.4 (qC), 114.1 (CH), 126.8 (2CH), 127.5 (CH), 128.1 (qC), 128.7 (2CH), 137.5 (qC), 160.5 (qC).
HRMS (<i>m/z</i> ESI ⁺):	Found 428.9815 (M ⁺ + H. C ₁₆ H ₁₉ ⁷⁹ Br ₂ N ₂ O ₂ Requires 428.9808).

Conditions attempted for oxidation of primary alcohols **437 and **439**.**



Entry	Substrate (R =)	Conditions	Yield (%) ^a
1	H	IBX	61
2	H	DMP	50
3	H	DMP/NaHCO ₃	55
4	H	DMP/Pyridine	51
5	H	Swern	43
6	Br	IBX	47
7	Br	Swern	39

^a BRSM.

Method H – IBX oxidation.

To pyrrole **437** (272 mg, 1.0 mmol, 1.0 eq.) in MeCN (10.0 mL) was added freshly prepared IBX (840 mg, 3.0 mmol, 3.0 eq.). The mixture was heated to 50 °C for 1.5 h or until complete consumption of starting alcohol as indicated by TLC. The reaction was cooled to rt and then diluted with MeCN (20 mL). The solution was then passed through a plug of Celite© and concentrated under reduced pressure to afford crude aldehyde **438** as a pale yellow oil.

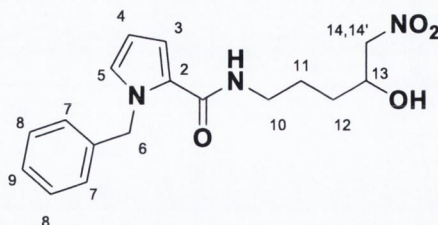
Method I – DMP oxidation.

To pyrrole **437** (272 mg, 1.0 mmol, 1.0 eq.) in CH₂Cl₂ (10.0 mL) was added freshly prepared DMP (1272 mg, 3.0 mmol, 3.0 eq.). The reaction was stirred for 1 h or until complete consumption of starting alcohol as indicated by TLC. The reaction was then quenched by the addition of a solution of sat. aq. NaHCO₃ (5 mL), a solution of sat. aq. Na₂S₂O₃ (5 mL) and then diluted with CH₂Cl₂ (10 mL). The layers were separated and the aqueous phase was

washed with CH_2Cl_2 (3×10 mL). The combined organic layers were then washed with a solution of sat. aq. NaHCO_3 (10 mL) mixed with sat. $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL). The combined organic layers were then washed with brine, dried with MgSO_4 and concentrated under reduced pressure to afford crude aldehyde **438** as a pale yellow oil.

Method J – Swern oxidation.

To oxalyl chloride (157 μL , 1.83 mmol, 1.83 eq.) in CH_2Cl_2 (5.0 mL) at -78°C was added DMSO (332 μL , 4.67 mmol, 4.67 eq.) in CH_2Cl_2 (1.50 mL) over 10 min. This solution was stirred for a further 5 min and then alcohol **437** (272 mg, 1.0 mmol, 1.0 eq.) in CH_2Cl_2 (1.50 mL) and DMSO (0.5 mL) was added dropwise over 10 min maintaining the temperature at -78°C . This mixture was then stirred for 1 h followed by the addition of NEt_3 (835 μL , 5 mL/6 mmol alcohol). The reaction was then allowed warm to rt over 1 h. After warming to rt the reaction was quenched by the addition of brine (10 mL). The layers were separated and the aqueous phase washed with CH_2Cl_2 (3×10 mL). The combined organic layers were then washed with brine (20 mL), dried over MgSO_4 and concentrated under reduced pressure to afford the crude aldehyde **438** as a yellow oil.

1-Benzyl-*N*-(4-hydroxy-5-nitropentyl)-1*H*-pyrrole-2-carboxamide (441)

To crude aldehyde **438** (1470 mg, 5.0 mmol, 1.0 eq.) in THF (5.0 mL) was added *t*-BuOH (5.0 mL) and MeNO₂ (2.5 mL) at rt. To this was added KO*t*-Bu (140 mg, 1.25 mmol, 0.25 eq.) in one portion. The reaction was stirred for 10 h and subsequently quenched by the addition of water (20 mL) and EtOAc (50 mL). The layers were separated and the organic layer washed with a solution of sat. aq. NaHCO₃ (20 mL), H₂O (20 mL) and brine (20 mL). The combined aqueous phase was then extracted with EtOAc (3 × 20 mL). The combined organic layers were then dried over MgSO₄, and concentrated under reduced pressure to afford the crude product as an orange gel. This was then purified by column chromatography (silica gel, hexanes:EtOAc, 90:10 → 40:60) to afford the pure product.

Yield: 86% (1428 mg).

Physical State: Pale orange gel.

Mp: -

R_f: 0.22 (hexanes:EtOAc, 50:50).

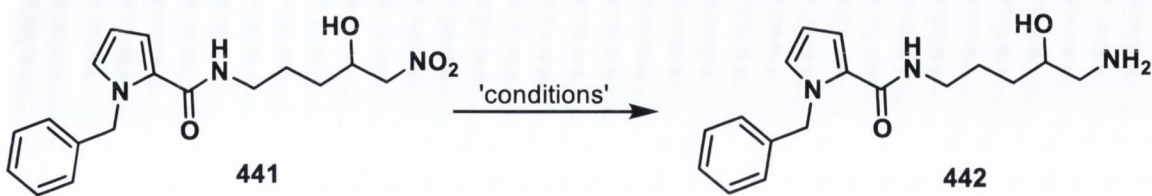
IR ν_{max} (film)/cm⁻¹: 3338 (NH), 2930 (OH), 1725, 1628, 1545 (NO₂), 1326 (NO₂), 1257, 1139, 1085, 882, 710.

¹H NMR (400 MHz, CDCl₃): δ 1.37 – 1.44 (m, 2H, H-11), 1.53 – 1.66 (m., 2H, H-12), 3.20 – 3.38 (m, 2H, H-10), 4.22 – 4.24 (m, 3H, H-13,14,14'), 5.54 (s, 2H, H-6), 6.11 (t, *J* = 4.0 Hz, 1H, H-4), 6.26 (br s, NH), 6.57 – 6.58 (m, 1H, H-3), 6.78 (app. br s, 1H, H-5), 7.04 (d, *J* = 7.6 Hz, 2H, H-7), 7.19 – 7.27 (m, 3H, H-8,9).

¹³C NMR (100 MHz, CDCl₃): δ 25.9 (CH₂), 30.4 (CH₂), 38.9 (CH₂), 51.9 (CH₂), 68.5 (CH), 80.9 (CH₂), 107.9 (CH), 112.4 (CH), 125.4 (qC), 126.9 (2CH), 127.0 (CH), 127.4 (CH), 128.6 (2CH), 138.8 (qC), 162.4 (qC).

HRMS (*m/z* ESI⁺): Found 354.1439 (M⁺ + Na. C₁₇H₂₁N₃O₄Na Requires 354.1424).

Reduction of Nitro **441**.



Entry	Conditions	Yield (%)
1	SnCl ₄	39
3	Zn	30
4	H ₂ , Pd/C	74

^x Isolated yield

Method K – SnCl₄ reduction.

To nitro **441** (241 mg, 0.73 mmol, 1.0 eq.) in EtOAc (7.30 mL, degassed) was added SnCl₂·2H₂O (1304 mg, 5.79 mmol, 8.0 eq.) at rt. The reaction mixture was heated to 80 °C with a reflux condenser attached. The reaction was stirred for 4.5 h after which time it was cooled to rt and diluted with EtOAc (10 mL). The solution was then filtered through a pad of Celite© and concentrated under reduced pressure. The resultant mixture was then dissolved in CH₂Cl₂ (~2 mL) and then HCl (4 M in Et₂O) was added dropwise until the desired amine crashed out as the HCl salt. This was then filtered and washed with Et₂O (5 mL) to afford the desired product as an off white solid (39%, 95 mg).

Method L – Zinc reduction

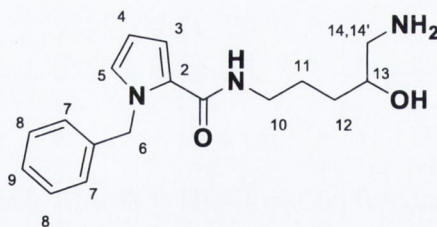
To nitro **441** (650 mg, 1.96 mmol, 1.0 eq.) in EtOH (6.8 mL) was added H₂O (1.6 mL) at rt. To this mixture was added Zn powder (642 mg, 9.82 mmol, 5 eq.) in one portion. Conc. HCl (1.2 mL, 12 M) was added dropwise to this vigorously stirred solution. The reaction was left to stir at rt for 5 h after which time the reaction was deemed complete by the full consumption of starting nitro **441** as indicated by TLC analysis. The reaction mixture was diluted with EtOAc and filtered through a double thickness of filter paper to remove the Zn residues. The mixture was concentrated under reduced pressure to afford the crude product. The resultant crude product was then dissolved in CH₂Cl₂ (~2 mL) and then HCl (4 M in

Et₂O) was added dropwise until the desired amine crashed out as the HCl salt. This was then filtered and washed with Et₂O (5 mL) to afford the desired product as an off white solid (30%, 198 mg).

Method M – H₂, Pd/C reduction

To nitro **441** (331 mg, 1.0 mmol, 1.0 eq.) in MeOH (3.0 mL) was added Pd / C (10 wt- %, 150 mg). The flask was then hydrogenated (3 atm.) over a period of 7 h. The flask was flushed with argon, the solution diluted with EtOH (5 mL) and then filtered through a double thickness of filter paper. The product was concentrated under reduced pressure. The solution was then filtered through a pad of Celite© and concentrated under reduced pressure. The resultant mixture was then dissolved in CH₂Cl₂ (~2 mL) and then HCl (4 M in Et₂O) was added dropwise until the desired amine crashed out as the HCl salt. This was then filtered and washed with Et₂O (5 mL) to afford the desired product (74%, 250 mg).

1-Benzyl-N-(4-hydroxy-5-aminopentyl)-1H-pyrrole-2-carboxamide (442)



Following Method M to nitro **441** (331 mg, 1.0 mmol, 1.0 eq.) in MeOH (3.0 mL) was added Pd / C (10 wt- %, 150 mg). The flask was then hydrogenated (3 atm.) over a period of 7 h. The compound was then worked up and purified according to Method M.

Yield: 74% (250 mg).

Physical State: Off white viscous gel.

Mp: -

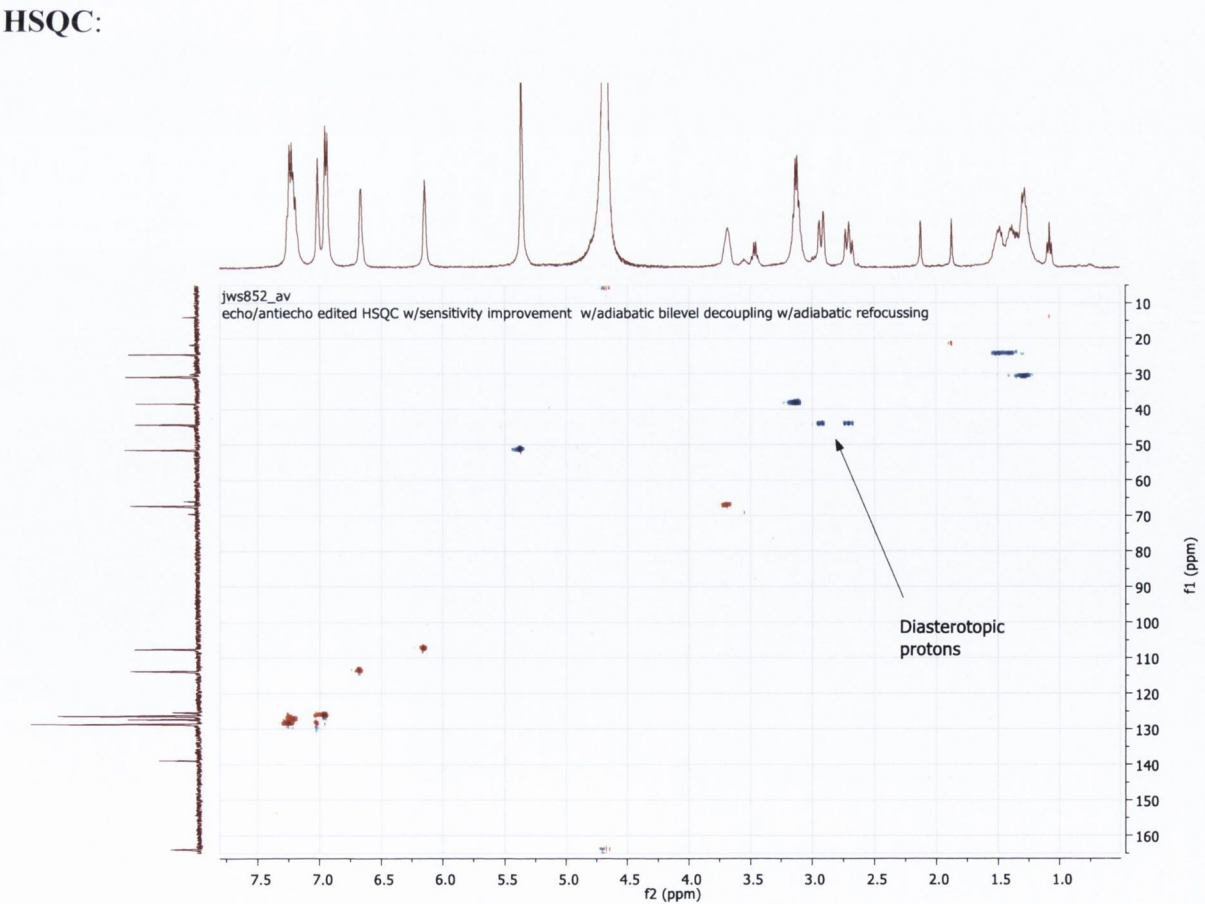
R_f: Baseline (EtOAc).

IR ν_{max} (film)/ cm^{-1} : 3305 (NH), 2928 (OH), 1624, 1542, 1496, 1359, 1326, 1258, 1139, 1326, 1258, 1139, 1028, 864, 827, 726.

^1H NMR (400 MHz, D_2O): δ 1.37 - 1.63 (m, 4H, H-11,12), 2.81 - 2.82 (m, 1H, H-14), 3.04 (app. d, 1H, H-14'), 3.20 - 3.28 (m, 2H, H-10), 3.76 - 3.83 (m, 1H, H-13), 5.48 (s, 2H, H-6), 6.25 - 6.26 (m, 1H, H-4), 6.75 - 6.78 (m, 1H, H-3), 7.05 (d, $J = 7.2$ Hz, 2H, H-7), 7.10 - 7.13 (m, 1H, H-5), 7.29 - 7.37 (m, 3H, H-8,9).

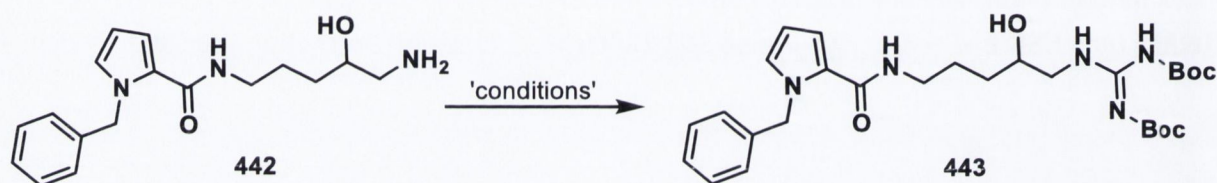
^{13}C NMR (100 MHz, D_2O): δ 24.6 (CH_2), 30.9 (CH_2), 38.5 (CH_2), 44.5 (CH_2), 51.5 (CH_2), 67.4 (CH), 107.7 (CH), 113.9 (CH), 125.4 (qC), 126.3 (2CH), 127.4 (CH), 128.7 (2CH), 128.8 (CH), 138.9 (qC), 164.1 (qC).

HRMS (m/z ESI $^+$): Found 302.1870 ($\text{M}^+ + \text{H}$. $\text{C}_{17}\text{H}_{24}\text{N}_3\text{O}_2$ Requires 302.1863).



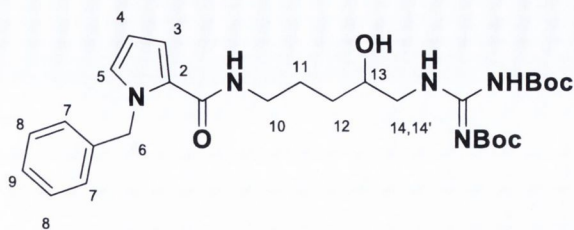
Method N for guanidylation.

To amine **442** (301 mg, 1.0 mmol, 1.0 eq.) in solvent (5.0 mL) was added NEt₃ (152 μ L, 1.1 mmol, 1.1 eq.) followed by thiourea guanidylating agent (1.2 mmol, 1.2 eq.). The mixture was then cooled to 0 °C and the Lewis acid promoter (1.1 mmol, 1.1 eq.) was added in one portion. The reaction was then stirred for 10 h at the said temperature or until the starting amine **442** was fully consumed as indicated by TLC analysis. At this point the reaction was diluted with EtOAc (20 mL) and then filtered through a plug of Celite®. The organic layer was then washed with water (20 mL). The layers were separated and the aqueous phase extracted with EtOAc (3 $\times$ 30 mL). The combined organic phases were then washed with brine (20 mL), dried over MgSO₄ and concentrated under reduced pressure to afford the crude product which was purified by column chromatography (silica gel, hexanes:EtOAc, 90:10 $\rightarrow$ 40:60) to afford the desired product.



Entry	Gua. Agent	Conditions	Yield (%)
1	 128	HgCl ₂ , CH ₂ Cl ₂ , rt	65
2	128	HgCl ₂ , DMF, 50 °C	46
3	128	CH ₂ Cl ₂ , rt	32
4	128	DMF, 50 °C	37
3	 127	HgCl ₂ , CH ₂ Cl ₂ , rt	31
4	 443	HgCl ₂ , CH ₂ Cl ₂ , rt	0
5	443	CuCl ₂ , CH ₂ Cl ₂ , rt	0

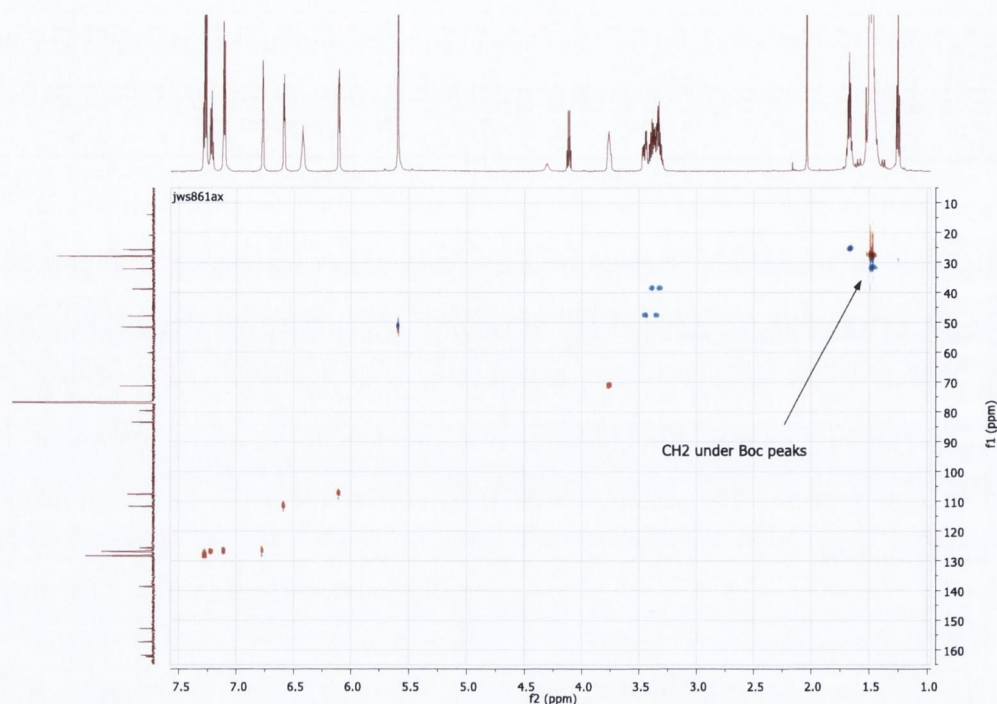
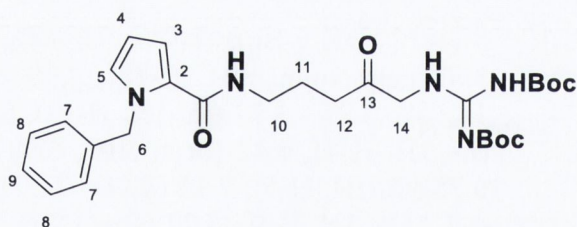
1-Benzyl-*N*-(4-hydroxy-5-(*N,N'*-bis-Boc-guanidine)pentyl)-1*H*-pyrrole-2-carboxamide (443)



Following Method M to amine **442** (62 mg, 0.1869 mmol, 1.0 eq.) in CH₂Cl₂ (3.0 mL) was added NEt₃ (29 μL, 0.205 mmol, 1.1 eq.) followed by *N,N'*-bis-Boc-thiourea (62 mg, 0.224 mmol, 1.2 eq.). The mixture was then cooled to 0 °C and HgCl₂ (55 mg, 0.205 mmol, 1.1 eq.) was added in one portion. The reaction was then stirred for 10 h and then worked up according to Method M.

Yield:	65% (66 mg)
Physical State:	Colourless bubbly foam.
Mp:	58-60 °C
R_f:	0.13 (hexanes:EtOAc, 50:50).
IR ν _{max} (film)/cm ⁻¹ :	3316 (NH), 2872 (OH), 1635, 1310, 1053.
¹H NMR (600 MHz, CDCl ₃):	δ 1.47 (s, 9H, <i>t</i> -Bu), 1.49 (s, 9H, <i>t</i> -Bu), 1.51 (m, 2H, H-11), 1.67 (app. quin., 2H, H-12), 3.29 - 3.43 (m, 4H, H-10, 14,14'), 3.75 - 3.77 (m, 1H, H-13), 5.59 (s, 2H, H-6), 6.11 (m, 1H, H-4), 6.42 (br s, NH), 6.58 (m, 1H, H-3), 6.77 – 6.78 (m, 1H, H-5), 7.16 (d, <i>J</i> = 7.2 Hz, 2H, H-7), 7.21 (t, <i>J</i> = 7.2 Hz, 1H, H-9), 7.27 (app. t, 2H, H-8), 8.66 (br s, NH), 11.43 (br s, NH). [OH proton not visible].
¹³C NMR (151 MHz, CDCl ₃):	δ 26.0 (CH ₂), 28.6 (3CH ₃), 28.3 (3CH ₃), 32.4 (CH ₂), 39.2 (CH ₂), 48.2 (CH ₂), 51.9 (CH ₂), 71.6 (CH), 79.9 (qC), 83.7 (qC), 107.9 (CH), 111.9 (CH), 125.9 (qC), 127.1 (CH), 127.2 (2CH), 127.4 (qC), 128.6 (2CH), 138.9 (qC), 153.1 (qC), 157.6 (qC), 162.2 (qC), 162.7 (qC).
HRMS (<i>m/z</i> ESI ⁺):	Found 544.3138 (M ⁺ + H. C ₂₈ H ₄₂ N ₅ O ₆ Requires 544.3135).

HSQC:

***N*-(5-(*N,N'*-Bis-Boc-guanidine)-4-oxopentyl)-1-benzyl-1H-pyrrole-2-carboxamide (444)**

To pyrrole **443** (500 mg, 0.92 mmol, 1.0 eq.) in CH_2Cl_2 (5.0 mL) was added freshly prepared DMP (1170 mg, 2.76 mmol, 3.0 eq.). The reaction was stirred for 1 h or until complete consumption of starting alcohol as indicated by TLC. The reaction was then quenched by the addition of a solution of sat. aq. NaHCO_3 (5 mL), a solution of sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (5 mL) and then diluted with CH_2Cl_2 (10 mL). The layers were separated and the aqueous phase was washed with CH_2Cl_2 (3×10 mL). The combined organic layers were then washed with solutions of sat. aq. NaHCO_3 (10 mL) and sat. aq. $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL). The combined organic layers were then washed with brine, dried over MgSO_4 and concentrated under reduced

pressure to afford crude ketone **444** as a pale yellow oil. This was purified by column chromatography (silica gel, hexanes:EtOAc, 90:10 → 40:60) to afford the desired product.

Yield: 71% (351 mg).

Physical State: White foam.

Mp: -

R_f: 0.49 (hexanes:EtOAc, 40:60).

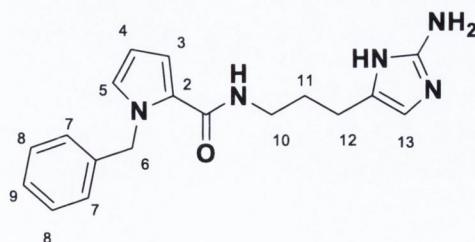
IR ν_{max} (film)/cm⁻¹: 3333 (NH), 2966, 1723 (CO), 1614, 1394, 1304, 1250, 1142, 1054, 800, 727.

¹H NMR (400 MHz, CDCl₃): δ 1.46 (s, 9H, *t*-Bu), 1.51 (s, 9H, *t*-Bu), 1.89 (app. quin., 2H, H-11), 2.42 (t, *J* = 6.8 Hz, 2H, H-12), 3.33 (app. dd, 2H, H-10), 4.22 (app. d, 2H, H-14), 5.59 (s, 2H, H-6), 6.12 – 6.13 (m, 1H, H-4), 6.19 (br s, NH), 6.59 – 6.60 (m, 1H, H-3), 6.79 (m, 1H, H-5), 7.10 (d, *J* = 8.0 Hz, 2H, H-7), 7.21 – 7.30 (m, 3H, H-8,9), 8.96 (br s, NH), 11.38 (br s, NH).

¹³C NMR (100 MHz, CDCl₃): δ 23.4 (CH₂), 27.9 (3CH₃), 28.1 (3CH₃), 36.7 (CH₂), 38.0 (CH₂), 50.7 (CH₂), 51.7 (CH₂), 79.3 (qC), 83.2 (qC), 107.6 (CH), 112.2 (CH), 125.4 (qC), 126.8 (2CH), 127.1 (CH), 127.1 (CH), 128.4 (2CH), 138.8 (qC), 152.7 (qC), 155.7 (qC), 162.0 (qC), 163.0 (qC), 204.3 (qCO).

HRMS (*m/z* ESI⁺): Found 542.2989 (M⁺ + H. C₂₈H₄₀N₅O₆ Requires 542.2973).

N-Benzyl-dihydroclathrodin (**446**)

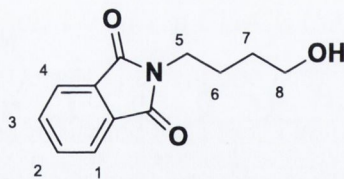


To *N*-(5-(*N,N'*-bis-Boc-guanidine)-4-oxopentyl)-1-benzyl-1*H*-pyrrole-2-carboxamide **444** (100 mg, 0.18 mmol, 1.0 eq.) was added formic acid (69 μ L, 1.80 mmol, 10.0 eq.) and the solution heated to 80 °C for 10.5 h. After this time the reaction was cooled to rt. The mixture was diluted with water (5 mL). The solution was washed with EtOAc (3 $\times$ 10 mL) and

$\text{CH}_2\text{Cl}_2/\text{MeOH}$ (80:20, 1×10 mL) and then the aqueous phase concentrated under reduced pressure to yield the target compound.

Yield:	84% (48 mg).
Physical State:	Colourless gel.
Mp:	-
R_f:	Baseline (EtOAc).
IR ν_{max} (film)/ cm^{-1} :	3117 (NH), 2974, 1631, 1550, 1520, 1465, 1389, 1310, 1211, 1025, 955.
^1H NMR (400 MHz, D_2O):	δ 1.64 (app. quin., 2H, H-11), 2.27 (t, $J = 7.2$ Hz, 2H, H-12), 3.19 (t, $J = 7.2$ Hz, 2H, H-10), 5.40 (s, 2H, H-6), 6.20 (app. br s, 1H, H-4), 6.31 (s, 1H, H-13), 6.72 (app. br s, 1H, H-3), 6.96 (d, $J = 7.2$ Hz, 2H, H-7), 7.03 (app. br s, 1H, H-5), 7.15 – 7.18 (m, 1H, H-9), 7.23 (app. t, 2H, H-8).
^{13}C NMR (100 MHz, D_2O):	δ 21.7 (CH_2), 27.8 (CH_2), 38.6 (CH_2), 52.1 (CH_2), 108.4 (CH), 108.9 (CH), 114.3 (CH), 125.6 (qC), 126.9 (2CH), 127.3 (CH), 127.8 (CH), 128.9 (qC), 129.0 (2CH), 139.4 (qC), 146.8 (qC), 164.0 (qC).
HRMS (m/z ESI^+):	Found 324.1821 ($\text{M}^+ + \text{H}$, $\text{C}_{18}\text{H}_{22}\text{N}_5\text{O}$ Requires 324.1818).

2-(4-Hydroxybutyl)isoindoline-1,3-dione (450)



To 4-amino-1-butanol (5584 mg, 62.74 mmol, 1.0 eq.) in toluene (220.0 mL) was added phthalic anhydride (9285 mg, 62.74 mmol, 1.0 eq.). This mixture was heated under Dean-Stark conditions to 120 °C for 15 h. After this time the reaction was allowed cool to rt and then diluted with EtOAc (100 mL) and water (100 mL). The layers were separated and the aqueous layer washed with EtOAc (3×50 mL). The combined organic layers were washed

with a solution of sat. aq. NaHCO₃ (50 mL), brine (50 mL), dried over MgSO₄ and concentrated under reduced pressure to afford the desired pure product as a pale oil which solidified upon standing.

Yield: 92% (12620 mg).

Physical State: White non-crystalline solid.

Mp: 76-78 °C.

R_f: 0.44 (EtOAc).

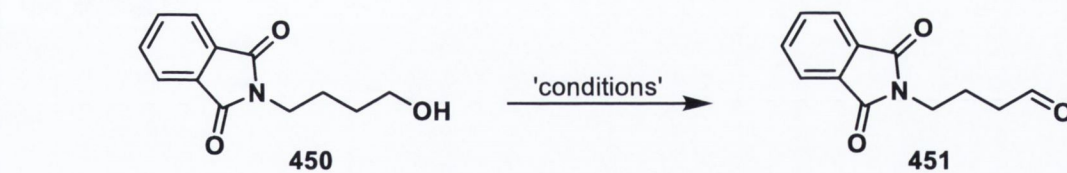
IR ν_{max} (film)/cm⁻¹: 3372, 3303, 3113, 3029, 2942, 1632, 1605, 1520, 1359, 1267, 1175, 1055, 830, 735.

¹H NMR (400 MHz, CDCl₃): δ 1.50 (app. quin., 2H, H-7) 1.66 (app. quin., 2H, H-6), 2.95 (br s, OH), 3.56 (t, *J* = 6.8 Hz, 2H, H-5), 3.59 (t, *J* = 6.8 Hz, 2H, H-8), 7.59 – 7.60 (m, 2H, H-2,3), 7.68 – 7.70 (m, 2H, H-1,4).

¹³C NMR (100 MHz, CDCl₃): δ 24.9 (CH₂), 29.7 (CH₂), 37.6 (CH₂), 61.8 (CH₂), 123.0 (2CH), 131.9 (2qC), 133.8 (2CH), 168.4 (2qC).

HRMS (*m/z* ESI⁺): Found 220.0969 (M⁺ + H. C₁₂H₁₄NO₃ Requires 220.0968).

Oxidation of alcohol 450



Entry	Conditions	Yield
1	IBX	92
2	DMP	94
3	Swern	87
4	IBX	96 ^a
5	Swern	84 ^a

^a Gram scale procedures.

Method H –IBX oxidation.

To alcohol **450** (100 mg, 0.456 mmol, 1.0 eq.) in MeCN (4.0 mL) was added freshly prepared IBX (383 mg, 1.36 mmol, 3.0 eq.). The mixture was heated to 50 °C for 1.5 h or until complete consumption of starting alcohol as indicated by TLC. The reaction was cooled to rt and then diluted with MeCN (5 mL). The solution was then passed through a plug of Celite® and concentrated under reduced pressure to afford crude aldehyde **451** as a colourless oil. The crude product was then purified by column chromatography (silica gel, hexanes:EtOAc, 70:30 → 40:60) to afford **451** as a colourless oil (92%, 98 mg).

Method I –DMP oxidation.

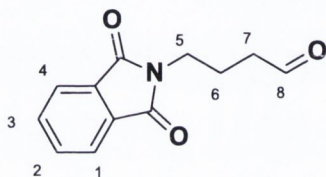
To alcohol **450** (219 mg, 1.0 mmol, 1.0 eq.) in CH₂Cl₂ (10.0 mL) was added freshly prepared DMP (1272 mg, 3.0 mmol, 3.0 eq.). The reaction was stirred for 1 h or until complete consumption of starting alcohol as indicated by TLC. The reaction was then quenched by the addition of a solution of sat. aq. NaHCO₃ (5 mL), a solution of sat. aq. Na₂S₂O₃ (5 mL) and then diluted with CH₂Cl₂ (10 mL). The layers were separated and the aqueous phase was washed with CH₂Cl₂ (3 × 10 mL). The combined organic layers were then washed with solutions of sat. NaHCO₃ (10 mL) and sat. Na₂S₂O₃ (10 mL). The combined organic layers were then washed with brine, dried over MgSO₄ and concentrated under reduced pressure to afford crude aldehyde **451** as a yellow oil. The crude product was then purified by column chromatography (silica gel, hexanes:EtOAc, 70:30 → 40:60) to afford **451** as a colourless oil (94%, 203 mg).

Method J –Swern oxidation.

To oxalyl chloride (4478 µL, 52.226 mmol, 1.83 eq.) in CH₂Cl₂ (142.0 mL) at -78 °C was added DMSO (9450 µL, 133.28 mmol, 4.67 eq.) in CH₂Cl₂ (42.80 mL) over 10 min. This solution was stirred for a further 5 min and then alcohol **450** (6250 mg, 28.54 mmol, 1.0 eq.) in CH₂Cl₂ (42.0 mL) and DMSO (9.45 mL) was added dropwise over 10 min maintaining the temperature at -78 °C. This mixture was then stirred for 1 h followed by the addition of NEt₃ (23780 µL, 833 µL/mmol alcohol). The reaction was then allowed warm to rt over 1 h. After reaching room temperature the reaction was quenched by the addition of brine (50 mL). The

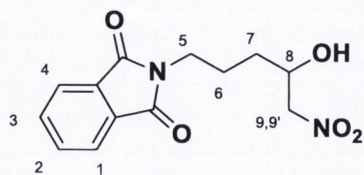
layers were separated and the aqueous phase washed with CH_2Cl_2 ($3 \times 10 \text{ mL}$). The combined organic layers were then washed with brine (20 mL), dried over MgSO_4 and concentrated under reduced pressure to afford the crude aldehyde **451** as a colourless oil. The crude product was then purified by column chromatography (silica gel, hexanes:EtOAc, 70:30 $\rightarrow$ 40:60) to afford **451** as a colourless oil (84%, 5197 mg).

4-(1,3-Dioxoisindolin-2-yl)butanal (451)



Following Method H to alcohol **450** (1000 mg, 4.566 mmol, 1.0 eq.) in MeCN (45.0 mL) was added freshly prepared IBX (3835 mg, 13.69 mmol, 3.0 eq.). The mixture was heated to 50 °C for 1.5 h and then worked up according to Method H.

Yield:	96% (4998 mg)
Physical State:	Colourless oil
Mp:	-
R_f:	0.31 (hexanes:EtOAc, 60:40).
IR ν_{max} (film)/ cm^{-1} :	1770 (CO), 1701, 1614, 1395, 1239, 1114, 1031, 717.
^1H NMR (400 MHz, CDCl_3):	δ 2.02 (app. quin., 2H, H-6), 2.54 (td, $J = 7.2, 0.8 \text{ Hz}$, 2H, H-7), 3.74 (t, $J = 7.2 \text{ Hz}$, 2H, H-5), 7.70 – 7.73 (m, 2H, H-2,3), 7.83 – 7.85 (m, 2H, H-1,4) 9.77 (app. br s, 1H, H-8).
^{13}C NMR (100 MHz, CDCl_3):	δ 23.4 (CH_2), 36.9 (CH_2), 40.8 (CH_2), 122.9 (2CH), 131.7 (2qC), 133.8 (2CH), 168.2 (2qC), 201.2 (qC).
HRMS (m/z ESI^+):	Found 218.0820 ($\text{M}^+ + \text{H}$. $\text{C}_{12}\text{H}_{12}\text{NO}_3$ Requires 218.0812).

2-(4-Hydroxy-5-nitropentyl)isoindoline-1,3-dione (452)

To aldehyde **451** (948 mg, 4.10 mmol, 1.0 eq.) in THF (4.10 mL) was added *t*-BuOH (4.10 mL) and MeNO₂ (2.05 mL) at rt. To this was added KO*t*-Bu (114 mg, 1.025 mmol, 0.25 eq.) in one portion. The reaction was stirred for 10 h and subsequently quenched by the addition of water (10 mL) and EtOAc (20 mL). The layers were separated and the organic layer washed with a solution of sat. aq. NaHCO₃ (10 mL), water (10 mL) and brine (10 mL). The combined aqueous phase was then extracted with EtOAc (3 × 10 mL). The combined organic layers were then dried over MgSO₄, and concentrated under reduced pressure to afford the crude product as an orange gel. This was then purified by column chromatography (silica gel, hexanes:EtOAc, 90:10 → 40:60) to afford the target compound.

Yield: 89% (1020 mg).

Physical State: Off white solid.

Mp: 88–89 °C.

R_f: 0.22 (hexanes:EtOAc, 60:40).

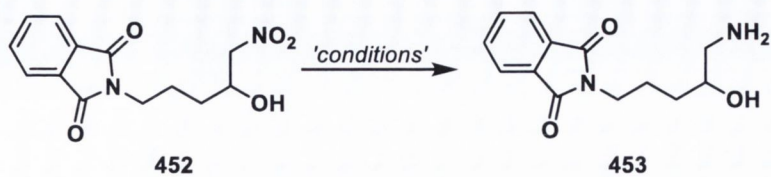
IR ν_{max} (film)/cm⁻¹: 3394, 2970, 2937, 1762, 1698, 1552, 1387, 1348, 1188, 1096, 1002, 879, 776.

¹H NMR (400 MHz, CDCl₃): δ 1.54 – 1.61 (m, 2H, H-7), 1.78 – 1.99 (m, 2H, H-6), 3.77 (t, *J* = 7.2 Hz, 2H, H-5), 4.36 – 4.44 (m, 3H, H-8,9,9'), 7.72 – 7.75 (m, 2H, H-2,3), 7.83 – 7.87 (m, 2H, H-1,4).

¹³C NMR (100 MHz, CDCl₃): δ 24.6 (CH₂), 30.8 (CH₂), 37.4 (CH₂), 68.2 (CH₂), 80.6 (CH₂), 123.4 (2CH), 131.9 (2qC), 134.2 (2CH), 168.7 (2qC).

HRMS (*m/z* ESI): Found 277.0833 (M⁻ - H. C₁₃H₁₃N₂O₅ Requires 277.0830).

Reduction of Compound X.



Entry	Conditions	Yield (%) ^a
1	SnCl ₄	68
2	Zn	64
3	H ₂ , Pd/C	75

^a BRSM.

Method K – SnCl₄ reduction.

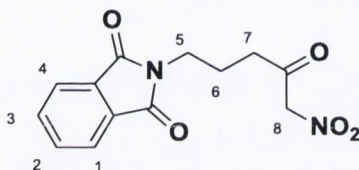
To nitro **452** (278 mg, 1.0 mmol, 1.0 eq.) in EtOAc (7.3 mL, degassed) was added SnCl₂·2H₂O (1800 mg, 8.0 mmol, 8.0 eq.) at rt. The reaction mixture was heated to 80 °C with a reflux condenser attached. The reaction was stirred for 4.5 h after which time it was cooled to rt and diluted with EtOAc (10 mL). The solution was then filtered through a pad of Celite© and concentrated under reduced pressure. The resulting product was then used without further purification.

Method L – Zinc reduction

To nitro **452** (278 mg, 1.0 mmol, 1.0 eq.) in EtOH (3.0 mL) was added H₂O (1.0 mL) at rt. To this mixture was added Zn powder (325 mg, 5.0 mmol, 5.0 eq.) in one portion. Conc. HCl (1.10 ml, 12 M) was added dropwise to this vigorously stirred solution. The reaction was left to stir at rt for 5 h after which time the reaction was deemed complete by the full consumption of starting nitro **452** as indicated by TLC analysis. The reaction mixture was diluted with EtOAc and filtered through a double thickness of filter paper to remove the Zn residues. The mixture was concentrated under reduced pressure to afford the crude product. The resulting product was then used without further purification.

Method M – H₂, Pd/C reduction

To nitro **452** (278 mg, 1.0 mmol, 1.0 eq.) in MeOH (3.0 mL) was added Pd / C (10 wt- %, 150 mg). The flask was then hydrogenated (3 atm.) over a period of 7 h. The flask was flushed with argon, the solution diluted with EtOH (5 mL) and then filtered through a double thickness of filter paper. The product was concentrated under reduced pressure. The solution was then filtered through a pad of Celite© and concentrated under reduced pressure. The resulting product was then used without further purification.

2-(5-Nitro-4-oxopentyl)isoindoline-1,3-dione (454)

To alcohol **452** (500 mg, 1.798 mmol, 1.0 eq.) in CH₂Cl₂ (9.0 mL) was added freshly prepared DMP (2287 mg, 3.0 mmol, 3.0 eq.). The reaction was stirred for 1 h or until complete consumption of starting alcohol as indicated by TLC. The reaction was then quenched by the addition of a solution of sat. aq. NaHCO₃ (5 mL), a solution of sat. aq. Na₂S₂O₃ (5 mL) and then diluted with CH₂Cl₂ (10 mL). The layers were separated and the aqueous phase was washed with CH₂Cl₂ (3 × 10 mL). The combined organic layers were then washed with solutions of sat. aq. NaHCO₃ (10 mL) and sat. aq. Na₂S₂O₃ (10 mL). The combined organic layers were then washed with brine (10 mL), dried over MgSO₄ and concentrated under reduced pressure to afford crude ketone **454** as a white solid. The product was the recrystallized from CH₂Cl₂/EtOAc (90:10, 15 mL) to afford the desired compound.

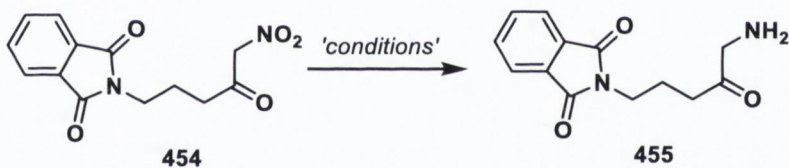
Yield: 87% (433 mg).

Physical State: White, free flowing powder.

Mp: 128-131 °C.

R_f:	0.68 (CH ₂ Cl ₂).
IR ν _{max} (film)/cm ⁻¹ :	2937, 1767, 1703 (CO), 1555 (NO ₂), 1402, 1375 (NO ₂), 1233, 1039, 722.
¹H NMR (400 MHz, CDCl ₃):	δ 2.06 (app. quin., 2H, H-6), 2.62 (t, <i>J</i> = 7.2 Hz, 2H, H-7), 3.74 (t, <i>J</i> = 7.2 Hz, 2H, H-5), 5.32 (s, 2H, H-8), 7.72 – 7.74 (m, 2H, H-2,3), 7.83 – 7.86 (m, 2H, H-1,4).
¹³C NMR (100 MHz, CDCl ₃):	δ 22.4 (CH ₂), 36.7 (CH ₂), 37.6 (CH ₂), 83.2 (CH ₂), 123.6 (2CH), 132.0 (2qC), 134.3 (2CH), 168.7 (2qC), 196.3 (qC).
HRMS (<i>m/z</i> ESI ⁺):	Found 275.0674 (M ⁺ - H. C ₁₃ H ₁₁ N ₂ O ₅ Requires 275.0673).

Reduction of Compound 454



Entry	Conditions	Yield (%)
1	SnCl ₄	43
2	Zn	47
3	H ₂ (1 atm.), Pd/C	74
4	H ₂ (3 atm.), Pd/C	85

Method K – SnCl₄ reduction.

To nitro **454** (276 mg, 1.0 mmol, 1.0 eq.) in EtOAc (5.0 mL, degassed) was added SnCl₂·2H₂O (1800 mg, 8.0 mmol, 8.0 eq.) at rt. The reaction mixture was heated to 80 °C with a reflux condenser attached. The reaction was stirred for 4.5 h after which time it was cooled to rt and diluted with EtOAc (10 mL). The solution was then filtered through a pad of

Celite© and concentrated under reduced pressure. The resultant mixture was then dissolved in CH_2Cl_2 (~2 mL) and then HCl (4 M in Et_2O) was added dropwise until the desired amine crashed out as the HCl salt. This was then filtered and washed with Et_2O (5 mL) to afford the desired product **455** (43%, 121 mg).

Method L – Zinc reduction

To nitro **454** (276 mg, 1.0 mmol, 1 eq.) in EtOH (5.0 mL) was added H_2O (0.8 mL) at rt. To this mixture was added Zn powder (325 mg, 5.0 mmol, 5.0 eq.) in one portion. Conc. HCl (0.8 mL, 12 M) was added dropwise to this vigorously stirred solution. The reaction was left to stir at rt for 5 h after which time the reaction was deemed complete by the full consumption of starting nitro **454** as indicated by TLC analysis. The reaction mixture was diluted with EtOAc and filtered through a double thickness of filter paper to remove the Zn residues. The mixture was concentrated under reduced pressure to afford the crude product. Et_2O (10 mL) was added and the resulting solid triturated. The solid was filtered, washed with a further Et_2O (10 mL) and collected to yield the desired amine as the hydrochloride salt **455** (47%, 132 mg).

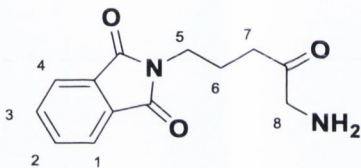
Method M – H_2 , Pd/C reduction

To nitro **454** (276 mg, 1.0 mmol, 1.0 eq.) in MeOH (3.0 mL) was added Pd / C (10 wt- %, 150 mg). The flask was then hydrogenated (1 atm.) over a period of 7 h. The flask was flushed with argon, the solution diluted with EtOH (5 mL) and then filtered through a double thickness of filter paper. The product was concentrated under reduced pressure. The solution was then filtered through a pad of Celite© and concentrated under reduced pressure. The resultant mixture was then dissolved in CH_2Cl_2 (~2 mL) and then HCl (4 M in Et_2O) was added dropwise until the desired amine crashed out as the HCl salt. This was then filtered and washed with Et_2O (5 mL) to afford the desired product **455** (74%, 208 mg).

Method O – H₂, Pd/C reduction (3 atm.)

To nitro **454** (276 mg, 1.0 mmol, 1.0 eq.) in MeOH (3.0 mL) was added Pd / C (10 wt- %, 150 mg). The flask was then hydrogenated (3 atm.) over a period of 7 h. The flask was flushed with argon, the solution diluted with EtOH (5 mL) and then filtered through a double thickness of filter paper. The product was concentrated under reduced pressure. The solution was then filtered through a pad of Celite© and concentrated under reduced pressure. The resultant mixture was then dissolved in CH₂Cl₂ (~2 mL) and then HCl (4 M in Et₂O) was added dropwise until the desired amine crashed out as the HCl salt. This was then filtered and washed with Et₂O (5 mL) to afford the desired product **455** (85%, 239 mg).

2-(5-Amino-4-oxopentyl)isoindoline-1,3-dione (455)



Following Method O to nitro **454** (276 mg, 1.0 mmol, 1.0 eq.) in MeOH (3.0 mL) was added Pd / C (10 wt- %, 150 mg). The flask was then hydrogenated (3 atm.) over a period of 12 h. The reaction was then worked up according to Method O.

Yield:	85% (239 mg).
Physical State:	Grey salt.
Mp:	146-149 °C.
R_f:	Baseline (EtOAc).
IR ν_{max} (film)/cm ⁻¹ :	3018 (NH), 2966, 1769, 1703, 1557, 1402, 1233, 1055, 722.
¹H NMR (400 MHz, D ₂ O):	δ 1.93 (app. quin., 2H, H-6), 2.68 (t, J = 7.2 Hz, 2H, H-7), 3.62 (t, J = 7.2 Hz, 2H, H-5), 4.05 (s, 2H, H-8), 7.72 – 7.73 (m, 4H, H-1,2,3,4).
¹³C NMR (100 MHz, D ₂ O):	δ 22.9 (CH ₂), 31.0 (CH ₂), 37.0 (CH ₂), 52.0 (CH ₂), 123.3 (2CH), 131.3 (2qC), 134.6 (2CH), 170.9 (2qC), 215.4 (qCO).

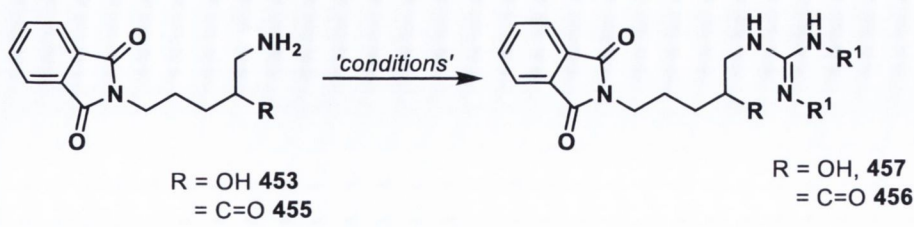
HRMS (m/z ESI⁺): Found 247.1079 ($M^+ + H$, C₁₃H₁₅N₂O₃ Requires 247.1077).

Guanidylation of Compounds **453** and **455**.

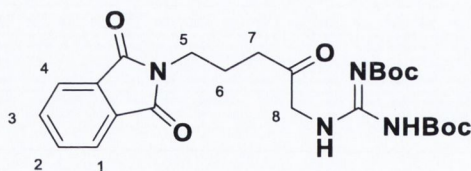
Method N - General method for guanidylation.

To amine **453** or **455** (1.0 mmol, 1.0 eq.) in solvent (5.0 mL) was added NEt₃ (152 μ L, 1.1 mmol, 1.1 eq.) followed by thiourea guanidylating agent (1.2 mmol, 1.2 eq.). The mixture was then cooled to 0 °C and the Lewis acid promoter (1.1 mmol, 1.1 eq.) was added in one portion. The reaction was then stirred for 10 h at the said temperature or until the starting amine was fully consumed as indicated by TLC analysis. At this point the reaction was diluted with EtOAc (20 mL) and then filtered through a plug of Celite®. The organic layer was then washed with H₂O (20 mL). The layers were separated and the aqueous phase extracted with EtOAc (3 $\times$ 30 mL). The combined organic phases were then washed with brine (20 mL), dried over MgSO₄ and concentrated under reduced pressure to afford the crude product which was purified by column chromatography (silica gel, hexanes:EtOAc, 90:10 $\rightarrow$ 40:60) to afford the desired product.

Guanidylation of Compounds 453 and 455.



Entry	Substrate	Gua. Agent	Conditions	Yield (%)
1	455	 128	HgCl ₂ , CH ₂ Cl ₂ , rt	68
2	455	128	HgCl ₂ , DMF, 50 °C	36
3	455	128	CH ₂ Cl ₂ , rt	10
4	455	128	DMF, 50 °C	21
5	455	 127	HgCl ₂ , CH ₂ Cl ₂ , rt	35
6	455	 443	HgCl ₂ , CH ₂ Cl ₂ , rt	0
7	455	443	CuCl ₂ , CH ₂ Cl ₂ , rt	0
8	453	128	HgCl ₂ , CH ₂ Cl ₂ , rt	34
9	453	128	HgCl ₂ , DMF, 50 °C	21
10	453	128	CH ₂ Cl ₂ , rt	13
11	453	128	DMF, 50 °C	14
12	453	127	HgCl ₂ , CH ₂ Cl ₂ , rt	10
13	453	443	HgCl ₂ , CH ₂ Cl ₂ , rt	0
14	453	443	CuCl ₂ , CH ₂ Cl ₂ , rt	0

2-[5-(*N,N'*-di-*tert*-butoxycarbonyl)guanidino-4-oxopentyl]isoindoline-1,3-dione (**456**)

Following Method M to amine **455** (292 mg, 1.04 mmol, 1.0 eq.) in CH_2Cl_2 (3.0 mL) was added NEt_3 (158 μL , 1.14 mmol, 1.1 eq.) followed by *N,N'*-Bis-Boc-thiourea (342 mg, 1.24 mmol, 1.2 eq.). The mixture was then cooled to 0 °C and HgCl_2 (308 mg, 1.139 mmol, 1.1 eq.) was added in one portion. The reaction was then stirred for 10 h and then worked up according to Method M.

Yield: 68% (343 mg).

Physical State: White foam.

Mp: -

R_f : 0.71 (EtOAc)

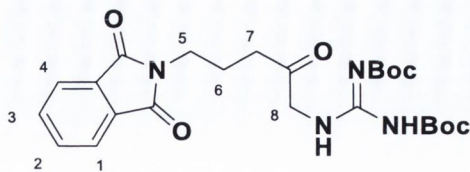
IR ν_{max} (film)/ cm^{-1} : 3288, 2979, 1791, 1773, 1708, 1637, 1612, 1394, 1367, 1134, 1111, 1027, 873, 775, 718.

^1H NMR (400 MHz, CDCl_3): δ 1.45 (s, 9H, *t*-Bu), 1.47 (s, 9H, *t*-Bu), 1.98 (app. quin., 2H, H-6), 2.47 (t, $J = 7.2$ Hz, 2H, H-7), 3.69 (t, $J = 7.2$ Hz, 2H, H-5), 4.29 (app. d, 2H, H-8), 7.66 – 7.71 (m, 2H, H-2,3), 7.79 – 7.82 (m, 2H, H-1,4), 8.99 (br s, NH), 11.36 (br s, NH).

^{13}C NMR (100 MHz, CDCl_3): δ 22.6 (CH_2), 28.1 (3CH_3), 28.4 (3CH_3), 37.0 (CH_2), 50.9 (CH_2), 79.6 (CH_2), 83.6 (2qC), 123.4 (2CH), 132.1 (2qC), 134.1 (2CH), 152.9 (qC), 155.9 (qC), 163.3 (qC), 168.6 (2qC), 203.2 (qCO).

HRMS (m/z ESI $^+$): Found 489.2350 ($\text{M}^+ + \text{H}$, $\text{C}_{24}\text{H}_{33}\text{N}_4\text{O}_7$ Requires 489.2349).

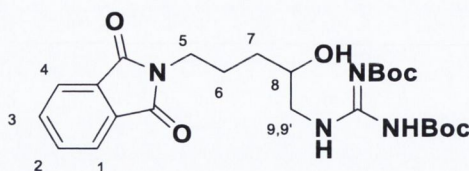
2-[5-(*N,N'*-di-*tert*-butoxycarbonyl)guanidino-4-oxopentyl]isoindoline-1,3-dione (**456**)



To alcohol **457** (49 mg, 0.10 mmol, 1.0 eq.) in CH₂Cl₂ (1.0 mL) was added freshly prepared DMP (127 mg, 0.30 mmol, 3.0 eq.). The reaction was stirred for 1 h or until complete consumption of starting alcohol as indicated by TLC. The reaction was then quenched by the addition of a solution of sat. aq. NaHCO₃ (1 mL), a solution of sat. aq. Na₂S₂O₃ (1 mL) and then diluted with CH₂Cl₂ (2 mL). The layers were separated and the aqueous phase was washed with CH₂Cl₂ (3 × 2 mL). The combined organic layers were then washed with solutions of sat. NaHCO₃ (5 mL) and sat. Na₂S₂O₃ (5 mL). The combined organic layers were then washed with brine (10 mL), dried with MgSO₄ and concentrated under reduced pressure to afford crude ketone **456** as a pale yellow oil. The crude product was purified by preparatory TLC eluting with hexanes:EtOAc, (50:50) to yield the desired product.

Yield:	89% (43 mg).
Physical State:	White foam.
Mp:	-
R_f:	0.71 (EtOAc).
IR ν_{max} (film)/cm ⁻¹ :	3288, 2979, 1791, 1773, 1708, 1637, 1612, 1394, 1367, 1134, 1111, 1027, 873, 775, 718.
¹H NMR (400 MHz, CDCl ₃):	δ 1.45 (s, 9H, <i>t</i> -Bu), 1.47 (s, 9H, <i>t</i> -Bu), 1.98 (app. quin., 2H, H-6), 2.47 (t, <i>J</i> = 7.2 Hz, 2H, H-7), 3.69 (t, <i>J</i> = 7.2 Hz, 2H, H-5), 4.29 (app. d, 2H, H-8), 7.66 – 7.71 (m, 2H, H-2,3), 7.79 – 7.82 (m, 2H, H-1,4), 8.99 (br s, NH), 11.36 (br s, NH).
¹³C NMR (100 MHz, CDCl ₃):	δ 22.6 (CH ₂), 28.1 (3CH ₃), 28.4 (3CH ₃), 37.0 (CH ₂), 50.9 (CH ₂), 79.6 (CH ₂), 83.6 (2qC), 123.4 (2CH), 132.1 (2qC), 134.1 (2CH), 152.9 (qC), 155.9 (qC), 163.3 (qC), 168.6 (2qC), 203.2 (CO).
HRMS (<i>m/z</i> ESI ⁺):	Found 489.2350 (M ⁺ + H. C ₂₄ H ₃₃ N ₄ O ₇ Requires 489.2349).

2-[5-(*N,N'*-di-*tert*-butoxycarbonyl)guanidino-4-hydroxypentyl]isoindoline-1,3-dione (457)



Following Method N to amine **453** (193 mg, 0.78 mmol, 1.0 eq.) in CH₂Cl₂ (5.0 mL) was added NEt₃ (433 μL, 3.12 mmol, 4.0 eq.) followed by *N,N'*-Bis-Boc-thiourea (236 mg, 0.856 mmol, 1.1 eq.). The mixture was then cooled to 0 °C and HgCl₂ (232 mg, 0.856 mmol, 1.1 eq.) was added in one portion. The reaction was then stirred for 10 h and then worked up according to Method N.

Yield: 34% (130 mg).

Physical State: Pale yellow foam.

Mp: -

R_f: 0.22 (EtOAc)

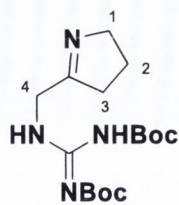
IR ν_{max} (film)/cm⁻¹: 3460, 3025, 2948, 1752, 1726, 1635, 1476, 1385, 1221, 1103, 746.

¹H NMR (400 MHz, CDCl₃): δ 1.46 (s, 9H, *t*-Bu), 1.49 (s, 9H, *t*-Bu), 1.64 – 1.93 (m, 4H, H-6,7), 3.25 – 3.41 (m, 2H, H-5), 3.49 – 3.56 (m, 1H, H-8), 3.78 – 3.88 (m, 2H, H-9,9'), 5.04 (br s, OH), 7.50 – 7.60 (m, 3H, H-2,3,4), 7.81 (d, *J* = 7.2 Hz, 1H, H-1), 8.68 (br s, NH), 11.43 (br s, NH).

¹³C NMR (100 MHz, CDCl₃): 24.5 (CH₂), 28.2 (3CH₃), 28.3 (3CH₃), 32.3 (CH₂), 39.4 (CH₂), 49.4 (CH₂), 71.6 (CH), 86.4 (2qC), 123.6 (CH), 123.6 (CH), 130.1 (CH), 132.0 (CH), 133.2 (qC), 141.0 (qC), 152.9 (qC), 157.5 (qC), 157.5 (qC), 168.1 (2qC).

HRMS (*m/z* ESI⁺): Found 491.2499 (M⁺ + H. C₂₄H₃₅N₄O₇ Requires 491.2500).

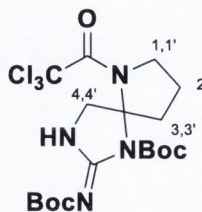
1-[(3,4-Dihydro-2*H*-pyrrol-5-yl)methane]-*N,N'*-(di-*tert*-butoxy)guanidine (**461**)



To guanidine **456** (30 mg, 0.06 mmol, 1.0 eq.) in an RBF at 0 °C was added N₂H₄ (1M in THF, 70 μL, 0.0737 mmol, 1.2 eq.) in strictly anhydrous conditions under Ar. The reaction was allowed warm to rt over 1 h and then left to stir for 3 h. After this time the reaction concentrated under reduced pressure and then purified using preparative TLC (EtOAc) to afford the desired imine **461**.

Yield:	68% (14 mg).
Physical State:	White solid.
Mp:	130-133 °C.
R_f:	0.50 (EtOAc).
IR ν _{max} (film)/cm ⁻¹ :	3333, 2976, 1725, 1633 (CN), 1545, 1362, 1310, 1151, 1122.
¹H NMR (400 MHz, CDCl ₃):	δ 1.50 (s, 18H, <i>t</i> -Bu), 1.94 (app. quin., 2H, H-2), 2.49 (t, <i>J</i> = 8.0 Hz, 2H, H-3), 3.89 (t, <i>J</i> = 8.0 Hz, 2H, H-2), 4.25 (br s, 2H, H-4), 9.20 (br s, NH), 11.45 (br s, NH).
¹³C NMR (100 MHz, CDCl ₃):	δ 22.6 (CH ₂), 28.1 (3CH ₃), 28.3 (3CH ₃), 36.9 (CH ₂), 43.7 (CH ₂), 60.7 (CH ₂), 79.3 (qC), 83.0 (qC), 152.8 (qC), 155.6 (qC), 163.4 (qC), 172.3 (qC).
HRMS (<i>m/z</i> ESI ⁺):	Found 341.2197 (M ⁺ + H. C ₁₆ H ₂₉ N ₄ O ₄ Requires 341.2183).

1-*tert*-Butoxycarbonyl-2-*tert*-butoxycarbonylimino-6-(trichloroacetyl)-1,3,6-triazaspiro[4,4]nonane (462)



To guanidine **456** (30 mg, 0.06 mmol, 1.0 eq.) in an RBF at 0 °C was added N₂H₄ (1M in THF, 70 μL, 0.0737 mmol, 1.2 eq.) in strictly anhydrous conditions under Ar. The reaction was allowed warm to rt over 1 h and then left to stir for 3 h. Once the starting material was fully consumed and imine **461** was present according to TLC, trichloroacetyl chloride (0.18 mmol, 3.0 eq.) and NEt₃ (0.18 mmol, 3.0 eq.) were added at 0 °C. The reaction was stirred at 0 °C for 1 h and then stirred at rt for a further 3 h. To this was added H₂O (1 mL) and CH₂Cl₂/MeOH (90:10, 3 mL). The layers were separated and the aqueous phase further extracted with CH₂Cl₂/MeOH (90:10, 3 × 3 mL). The combined organic layers were concentrated under reduced pressure and purified using Prep. TLC (EtOAc) to afford the desired compound.

Yield: 54% (15 mg).

Physical State: Yellow gel.

Mp: -

R_f: 0.12 (EtOAc).

IR ν_{max} (film)/cm⁻¹: 1810, 1725, 1645, 1452, 1300, 1101, 990.

¹H NMR (600 MHz, CDCl₃): δ 1.48 (s, 9H, *t*-Bu), 1.51 (s, 9H, *t*-Bu), 1.87 (app. quin., 2H, H-2), 2.05 – 2.10 (m, 1H, H-1), 2.56 – 2.57 (m, 1H, H-1'), 3.83 – 3.87 (m, 1H, H-3), 4.29 (app. t, 1H, H-3'), 3.44 (app. t, 1H, H-4'), 3.98 – 3.99 (m, 1H, H-4), 9.65 (br s, NH)

¹³C NMR (151 MHz, CDCl₃): δ 22.9 (CH₂), 27.2 (3CH₃), 28.4 (3CH₃), 37.4 (CH₂), 49.8 (CH₂), 65.6 (CH₂), 81.1 (qC), 84.2 (qC), 85.2 (qC), 93.7 (qCCl₃), 146.3 (qC), 153.2 (qC), 158.0 (qC), 172.2 (qCO).

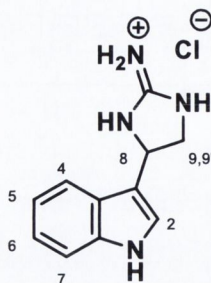
HRMS (*m/z* ESI⁺): Found 485.1113 (M⁺ + H. C₁₈H₂₈³⁵Cl₃N₄O₅ Requires 485.1120).

8.4. Investigations into the synthesis of araiosamines A-D.

General Procedures for experiments conducted in the Baran laboratories.

All reactions were carried out under an argon atmosphere with dry solvents using anhydrous conditions unless otherwise stated. Dry diethyl ether (Et_2O), dichloromethane (CH_2Cl_2), acetonitrile (CH_3CN), toluene (PhMe), tetrahydrofuran (THF), methanol (MeOH), and triethylamine (Et_3N) were obtained by passing these previously degassed solvents through activated alumina columns. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Yields refer to chromatographically and spectroscopically (^1H NMR) homogeneous materials, unless otherwise stated. Reactions were monitored by thin layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as the visualizing agent and an acidic mixture of anisaldehyde, phosphomolybdic acid, or ceric ammonium molybdate, or basic aqueous potassium permanganate (KMnO_4), and heat as developing agents. E. Merck silica gel (60, particle size 0.0430–0.063 mm) was used for flash column chromatography. Preparative thin layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). Concentration of organic solvents was performed on a rotary evaporator under reduced pressure followed by further evacuation using a two-stage mechanical pump. NMR spectra were recorded on Bruker DRX-600, DRX-500 and AMX-400 instruments and calibrated using residual undeuterated solvent as an internal reference (CHCl_3 @ δ 7.26 ppm ^1H NMR, δ 77.16 ^{13}C NMR; CH_2Cl_2 @ δ 5.32 ppm ^1H NMR, δ 53.84 ppm ^{13}C NMR). The following abbreviations (or combinations thereof) were used to explain ^1H NMR multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, quin. = quintet, m = multiplet, br = broad. High-resolution mass spectra (HRMS) were recorded on Agilent LC/MSD TOF mass spectrometer by electrospray ionization time of flight reflectron experiments. Melting points were recorded on a Fisher-Johns 12-144 melting point apparatus and are uncorrected.

Characterisation of the following compounds was deemed sufficiently thorough by Prof. Baran due to the short time frame of this project in the Scripps Research Institute, USA.

4-(1*H*-Indol-3-yl)imidazolidin-2-imine hydrochloride (468)

To azide **484** (500 mg, 1.66 mmol, 1.0 eq.) in THF (20.0 mL) was added PPh₃ (870.4 mg, 3.32 mmol, 2.0 eq.), H₂O (1.0 mL) and the mixture heated to 60 °C for 1 h. The solution was allowed cool to rt and EtOAc (20 mL) was added. This solution was then washed with 4 M HCl (10 mL) which deprotected the Boc group and protonated both amines. The acidified aqueous phase was then subsequently washed with CH₂Cl₂/MeOH (80:20, 2 × 10 mL) and the aqueous phase then concentrated under reduced pressure to afford the desired crude diamine **485** (262 mg, 64% crude).

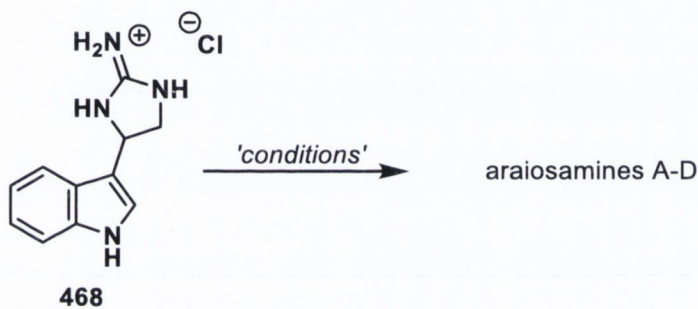
To the crude diamine **485** (230 mg, 0.93 mmol, 1.0 eq.) in EtOH (4.0 mL) was added NaOAc (152 mg, 1.86 mmol, 2.0 eq.) at rt. To this was added dropwise cyanogen bromide (3 M in CH₂Cl₂, 0.46 mL, 1.39 mmol, 1.5 eq.) and allowed to stir until deemed complete (TLC, 4 h). NaOH (1M solution, 10 mL) was added to the solution and the product extracted with IPA/Chloroform (20:80, 3 × 20 mL). The organic layer was then washed with 2 M HCl (25 mL). The aqueous layer was now washed a further time with EtOAc (3 × 20 mL). The aqueous layer was then concentrated under reduced pressure to yield crude product **468**. This crude oil was dissolved in the minimum amount of H₂O (~0.5 mL) and passed through a plug of reverse phase silica (C₈) to yield the desired guanidine.

Yield:	55% (120 mg).
Physical State:	Yellow viscous oil.
Mp:	-
R_f:	Baseline (EtOAc).

¹H NMR (400 MHz, D₂O): δ 3.74 (dd, *J* = 7.2, 2.8 Hz, 1H, H-9), 4.09 (t, *J* = 7.2 Hz, 1H, H-8), 5.43 (dd, *J* = 7.2, 2.8 Hz, 1H, H-9'), 7.24 (app. t, 1H, H-6), 7.35 (app. t, 1H, H-5), 7.44 (s, 1H, H-2), 7.61 (d, *J* = 8.0 Hz, 1H, H-7), 7.68 (d, *J* = 8.0 Hz, 1H, H-4).

HRMS (*m/z* ESI⁺): Found 201.1136 (M⁺ + H. C₁₁H₁₃N₄ Requires 201.1135).

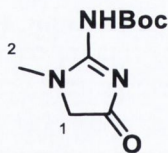
Attempted trimerization reaction conditions of **468**.



Entry	Additive	Temp. (°C)	Time (hr)	Yield (%)
1	TFA	rt	48	>95% SM
2	TFA	80	12	Decomposition
3	6M HCl	80	12	Decomposition
4	6M HCl	40	24	74% SM

To guanidine **468** (20 mg, 0.1 mmol, 1.0 eq.) in D₂O (0.1 mL) was added acid (TFA or 6 M HCl, 0.5 mmol, 5.0 eq.). This mixture was heated (rt, 40 °C or 80 °C) and was monitored by taking aliquots for ¹H NMR spectroscopy.

2-tert-Butoxycarbonylamino-1-methyl-1,5-dihydro-4H-imidazol-4-one (477)



To creatinine (1130 mg, 10.0 mmol, 1.0 eq.) in THF (50.0 mL) was added NaH (400 mg, 60% in mineral oil, 10.0 mmol, 1.0 eq.). This was followed by the addition of Boc₂O (2398 mg, 11.0 mmol, 1.1 eq.) in one portion. The reaction was stirred at room temperature for 12 h and subsequently quenched by the addition of water (10 mL). The resulting solution was extracted with IPA/Chloroform (80:20, 3 × 75 mL). The combined organic layers were then dried with MgSO₄, and concentrated to roughly 10 mL under reduced pressure. Hexanes (20 mL) were added until a white solid crashed out. This solid was filtered off and washed with cold hexanes (10 mL) to yield the title compound.

Spectral data for this compound were consistent with those in the literature.²⁷⁶

Yield: 38% (800 mg).

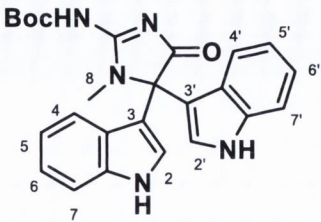
Physical State: White solid.

Mp: 35–36 °C (Lit. 33–34 °C).

R_f: 0.86 (hexanes:EtOAc, 70:30).

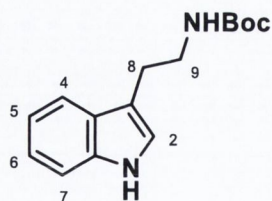
¹H NMR (400 MHz, CDCl₃): δ 1.51 (s, 9H, *t*-Bu), 3.10 (s, 3H, H-2), 3.90 (s, 2H, H-1), 10.45 (br s, NH).

2-*tert*-Butoxycarbonylamino(5,5-di(1*H*-indol-3-yl)-1-methyl-4,5-dihydro-1*H*-imidazol-4-one (479)



To a solution of Boc- creatinine **477** (79 mg, 0.37 mmol, 1.0 eq.) and indole **478** (86 mg, 0.742 mmol, 2.0 eq.) in THF (0.370 mL) at -78 °C was added LiHMDS (1 M in THF, 1.224 mmol, 3.3 eq.). This solution was allowed to stir for 30 min. To this was added copper (II) 2-ethylhexanoate (194 mg, 0.556 mmol, 1.5 eq.) by quickly removing the septa and adding the solid. The reaction was allowed warm to rt over 2 h. EtOAc (5 mL) and water (3 mL) were added to the reaction mixture. The aqueous phase was further extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with 0.5 M HCl (5 mL), brine (5 mL), dried over MgSO₄ and then concentrated under reduced pressure to afford the crude product. This was then purified by preparative TLC (hexanes:EtOAc, 50:50) to yield the title compound.

Yield:	25% (40 mg).
Physical State:	Yellow gel.
Mp:	-
R_f:	0.48 (hexanes:EtOAc, 50:50).
¹H NMR (400 MHz, CDCl₃):	δ1.59 (s, 9H, <i>t</i> -Bu), 2.89 (s, 3H, H-8), 7.09 (app. t, 2H, H-6,6'), 7.26 (app. t, 2H, H-5,5'), 7.36-7.38 (m, 4H, H-2,2',7,7'), 7.57 (d, <i>J</i> = 8.0 Hz, 2H, H-4,4'), 11.38 (br s, NHBoc), 11.48 (br s, 2NH).

***N*-tert-Butoxycarbonyltryptamine (483)**

To tryptamine HCl (3920 mg, 20.0 mmol, 1.0 eq.) in 1,4-dioxane (20.0 mL) was added NEt_3 (8.30 mL, 60.0 mmol, 3.0 eq.) at 0 °C. To this was added Boc_2O (5235 mg, 24.0 mmol, 1.2 eq.) in 1,4-dioxane (10.0 mL). The solution was left to stir for 1.5 h upon which time the reaction was deemed complete (TLC). The solution was concentrated under reduced pressure and purified by column chromatography (silica gel, hexanes: Et_2O , 66:34) to afford the desired product.

Spectral data for this compound were consistent with those in the literature.²⁷⁷

Yield: 96% (5012 mg).

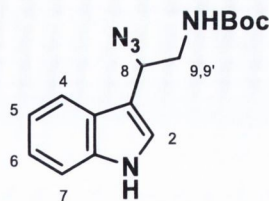
Physical State: Colourless oil.

Mp: -

R_f: 0.56 (hexanes: EtOAc , 60:40).

^1H NMR (400 MHz, CDCl_3): δ 1.47 (s, 9H, *t*-Bu), 2.97 (t, J = 6.2 Hz, 2H, H-8), 3.48 (m, 2H, H-9), 4.68 (br s, NH), 7.02 (s, 1H, H-2), 7.12-7.16 (m, 1H, H-6), 7.22-7.24 (m, 1H, H-5), 7.39 (d, J = 7.9 Hz, 1H, H-7), 7.62 (d, J = 7.9 Hz, 1H, H-4), 8.30 (br s, NH).

2-Azido-*tert*-butoxycarbonyltryptamine (484)

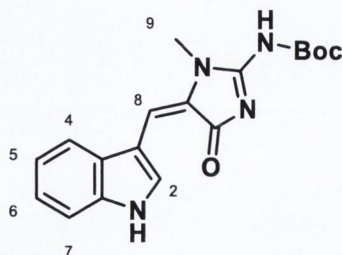


To compound **483** (1565 mg, 6.0 mmol, 1.0 eq.) in THF (30.0 mL) at 0 °C was added TMSN₃ (1.58 mL, 12.0 mmol, 2.0 eq.). Subsequently 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ, 1776 mg, 7.80 mmol, 1.3 eq.) in THF (30.0 mL) was added and allowed to warm to room temperature over 16 h. The reaction now deemed complete (TLC) was diluted with EtOAc (250 mL) and washed repeatedly with a solution of sat. aq. NaHCO₃ (10 × 50 mL) removing a large quantity of the deep red colour from the organic solution. The organic layer was further washed with brine (50 mL), dried with MgSO₄ and concentrated under reduced pressure to afford the crude product as a deep red gel. This was then purified by column chromatography (silica gel, hexanes:Et₂O, 67:33) to afford the title compound as a yellow solid.

Spectral data for this compound were consistent with those in the literature.²⁵²

Yield:	75% (1354 mg).
Physical State:	Yellow solid.
Mp:	65-66 °C (Lit. 64-66 °C).
R_f:	0.45 (hexanes:Et ₂ O, 70:30).
¹H NMR (400 MHz, CDCl₃):	δ1.47 (s, 9H, <i>t</i> -Bu), 3.46-3.53 (m, 1H, H-9), 3.62-3.68 (m, 1H, H-9'), 4.94-4.98 (m, 1H, H-8), 7.14-7.18 (m, 2H, H-2,6), 7.24 (app. t, 1H, H-5), 7.40 (d, <i>J</i> = 7.2 Hz, 1H, H-7), 7.72 (d, <i>J</i> = 7.2 Hz, 1H, H-4), 8.54 (br s, NH).

2-*tert*-Butoxycarbonylamino-5-[(*E*)-(1*H*-indol-3-yl)methylene]-1-methyl-4,5-dihydro-4*H*-imidazol-4-one (489)



To 3-indolecarboxaldehyde **488** (43 mg, 0.30 mmol, 1.2 eq.) and Boc-creatinine **477** (53 mg, 0.25 mmol, 1.0 eq.) in EtOH (0.5 mL) at rt was added piperazine (25 mg, 0.30 mmol, 1.2 eq.). The reaction mixture was then heated to 60 °C upon which the solution turned an intense yellow colour. After 4 h the reaction was deemed complete (TLC). The reaction was diluted with EtOAc (5 mL) and then washed with water (5 mL). The aqueous phase was then further extracted with EtOAc (3 × 5 mL). The combined organic layers were then washed with brine (5 mL), dried over MgSO₄ and concentrated under reduced pressure. The crude product was purified by column chromatography (silica gel, hexanes:EtOAc, 50:50) to yield an intensely yellow solid as the desired product.

Yield: 80% (67 mg).

Physical State: Bright yellow solid.

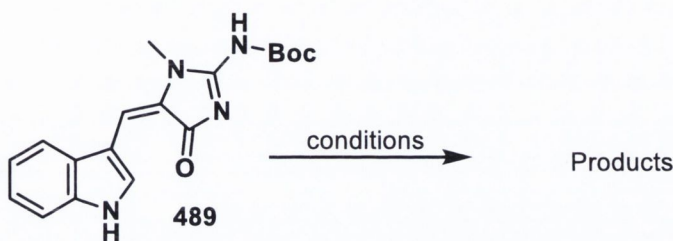
MP: 174-175 °C.

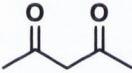
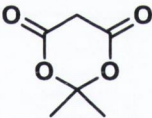
R_f: 0.30 (hexanes:EtOAc, 50:50).

¹H NMR (400 MHz, CDCl₃): δ 1.55 (s, 9H, *t*-Bu), 3.45 (s, 3H, H-9), 6.81 (s, 1H, H-8), 7.28 – 7.32 (m, 2H, H-5,6), 7.45 (d, *J* = 7.2 Hz, 1H, H-7), 7.75 (d, *J* = 7.2 Hz, 1H, H-4), 8.60 (br s, NH) 9.00 (s, 1H, H-2), 10.50 (br s, NHBoc).

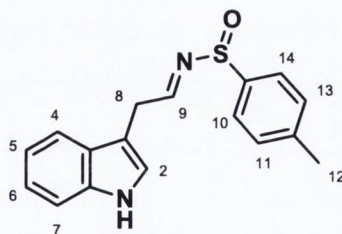
Typical condition for functionalisation of **489**.

To indole **489** (34 mg, 0.1 mmol, 1.0 eq.) in solvent (0.5 mL) was added the reagent (0.2 mmol, 2.0 eq.). If so required, a further additive (0.2 mmol, 2.0 eq.) was now added. Temperature was set as required. The reaction was monitored by TLC and each showed no progress in the forward direction with unchanged starting materials being isolable at the end of the reaction.



Entry	Reagent	Additive	Temp. (°C)	Yield (%) ^a
1	 490	NEt ₃ , toluene	rt	RSM
2	490	FeCl ₃ , toluene	rt	RSM
3	490	NaOH, EtOH	rt	RSM
4	 491	NEt ₃ , toluene	rt	RSM
5	NaBH ₄	CeCl ₃ , MeOH	0	RSM
6	LiAlH ₄	THF	0	RSM
7	NaCNBH ₃	AcOH, MeOH	0	RSM
8	LiEt ₃ BH	THF	-78	RSM

^a RSM – Recovered starting material.

(*E*)-*N*-(2-(1*H*-indol-3-yl)ethylidene)-4-methylbenzenesulfinamide (500)

To alcohol **504** (242 mg, 1.5 mmol, 1.0 eq.) in MeCN (6.0 mL) was added IBX (1260 mg, 4.5 mmol, 3.0 eq.). The solution was then heated to 80 °C for 3 h. This mixture was then cooled to rt and then filtered through a pad of Celite®. The resulting organic solution was then concentrated to roughly 3 mL and then continued on to the next step.

To crude aldehyde **505** (1.5 mmol, 1.0 eq.) in MeCN (~ 3.0 mL) was added sulfonamide **506** (232 mg, 1.5 mmol, 1 eq.). To this mixture was then added dropwise Ti(O*i*-Pr)₄ (898 µL, 3.0 mmol, 2.0 eq.) at rt and allowed to stir for 8 h. The reaction mixture was then evaporated under reduced pressure. The remaining residue was then diluted with hexanes (5 mL) and EtOAc (5 mL) and the solid impurities removed by filtration. The crude product was then purified by preparative TLC (hexanes:EtOAc, 50:50) to yield the desired imine in 12% yield over the two steps.

Yield: 12% (53 mg).

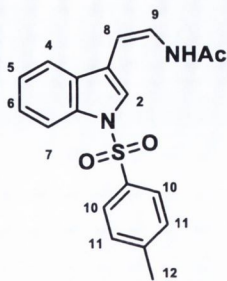
Physical State: Yellow/white solid

R_f: 0.61 (EtOAc).

¹H NMR (400 MHz, CDCl₃): δ 2.42 (s, 3H, H-12), 3.93 (d, *J* = 5.6 Hz, 2H, H-8), 7.05 – 7.07 (m, 2H, H-2,6), 7.20 (app. t, 1H, H-5), 7.30 (d, *J* = 8.0 Hz, 2H, H-11,13), 7.36 (d, *J* = 7.6 Hz, 1H, H-7), 7.45 (d, *J* = 7.6 Hz, 2H, H-4), 7.55 (d, *J* = 8.0 Hz, 2H, H-10,14), 8.19 (br s, NH), 9.70 (app. br s, 1H, H-9)

HRMS (*m/z* ESI⁺): Found 297.1060 (M⁺ + H. C₁₇H₁₇N₂OS Requires 297.1056).

(Z)-N-(2-(1-tosyl-1H-indol-3-yl)vinyl)acetamide (501)



(a) To carboxylic acid **510** (150 mg, 0.38 mmol, 1.0 eq.) in THF (1.5 mL) was added pyridine (0.060 mL, 0.75 mmol, 2.0 eq.) and Cu(OAc)₂ (20.4 mg, 0.11 mmol, 0.33 eq.) at 0 °C. An instant blue colour was observed. This mixture was stirred for 5 min followed by addition of Pb(OAc)₄ (182.7 mg, 0.41 mmol, 1.1 eq.) which immediately turned the reaction mixture a notable green colour. The reaction was stirred vigorously and allowed warm to rt over 2 h. The reaction was quenched by the addition of a solution of sat. aq. NaHCO₃ (3 mL) and the product extracted with EtOAc (3 × 5 mL). The combined organic phases were then washed with brine (5 mL), dried over MgSO₄ and concentrated under reduced pressure to afford the crude product as an off white solid (130 mg, 84%) which was used without further purification.

(b) The crude hemi-aminal **511** (125 mg, 0.30 mmol, 1.0 eq.) was dissolved in THF (1.0 mL) and to this was added LiClO₄ (192 mg, 1.81 mmol, 6.0 eq.) at 0 °C. This was stirred for 5 min after which time DIPEA (0.157 mL, 0.90 mmol, 1.0 eq.) was added dropwise. The reaction mixture was stirred for 10 min at 0 °C and then for 30 min (or until starting material was no longer detected, TLC) at rt. The reaction was quenched by the addition of a solution of sat. aq. NaHCO₃ (3 mL) and the product extracted with EtOAc (3 × 5 mL). The combined organic phases were then washed with brine (5 mL), dried over MgSO₄ and concentrated under reduced pressure to afford the crude enamide product **501** which was purified by column chromatography (silica gel, hexanes:EtOAc, 90:10 → 60:40, column pretreated with NEt₃, 1%). Enamide **501** was obtained in 76% yield over the two steps.

Yield: 76 % (81 mg).

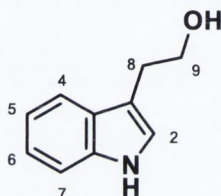
Physical State: Beige waxy solid.

R_f: 0.58 (hexanes:EtOAc, 20:80 - *p*-anisaldehyde stain).

^1H NMR (400 MHz, CDCl_3): δ 2.08 (s, 3H, H-Ac), 2.35 (s, 3H, H-12), 5.69 (d, J = 9.4 Hz, 1H, H-8), 7.09 (app. t, 1H, H-6), 7.23 – 7.31 (m, 3H, H-9,11), 7.37 (app. t, 1H, H-5), 7.47 (d, J = 8.0 Hz, 1H, H-7), 7.53 (s, 1H, H-2), 7.78 (d, J = 8.0 Hz, 2H, H-10), 8.01 (d, J = 8.4 Hz, 1H, H-4), 8.77 (br s, NH).

HRMS (m/z ESI^+): Found 355.1113 ($\text{M}^+ + \text{H}$, $\text{C}_{19}\text{H}_{19}\text{N}_2\text{O}_3\text{S}$ Requires 355.1111).

2-Hydroxyethylindol (504)



To lithium aluminium hydride (760 mg, 20.0 mmol, 2.0 eq.) in THF (30.0 mL) was added 2-(indol-3-yl)acetic acid **503** (1750 mg, 10.0 mmol, 1.0 eq.) in THF (20.0 mL) at 0 °C. This solution was stirred at 0 °C for 2 h and a further 10 h at rt. The reaction was now determined to be complete (TLC) and therefore quenched by the initial addition of water (1.75 mL), NaOH (10% aqueous solution, 3.5 mL) and then H_2O (6 mL). MgSO_4 was added and the resulting solids filtered through a pad of Celite®. The resulting mixture was extracted with EtOAc (3×50 mL). The combined organic layers were then washed with brine (50 mL), dried over MgSO_4 and concentrated under reduced pressure to afford alcohol **504** (1545 mg) which was used without further purification.

Spectral data for this compound were consistent with those in the literature.²⁷⁸

Yield: 96% (1545 mg).

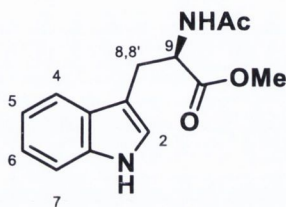
Physical State: Off white solid.

Mp: 54-57 °C (Lit. 54-55 °C)

R_f: 0.39 (EtOAc).

¹H NMR (400 MHz, CDCl₃): δ 1.54 (br s, OH), 3.04 (t, *J* = 6.2 Hz, 2H, H-8), 3.91 (m, 2H, H-9), 7.07 (s, 1H, H-2), 7.13 (app. t, 1H, H-6), 7.21 (app. t, 1H, H-5), 7.37 (d, *J* = 7.6 Hz, 1H, H-7), 7.63 (d, *J* = 7.6 Hz, 1H, H-4), 8.06 (br s, NH).

(S)-N-Acetyltryptohan methyl ester (508)

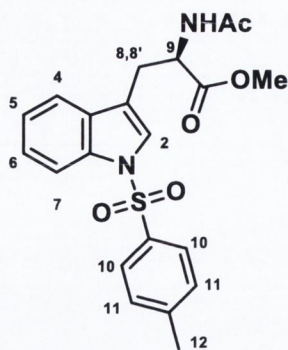


To tryptophan methyl ester **507** (7112 mg, 28.0 mmol, 1.0 eq.) in CH₂Cl₂ (56.0 mL) was added DIPEA (9.45 mL, 56.0 mmol, 2.0 eq.). Subsequently Ac₂O (2.66 mL, 28.0 mmol, 1.0 eq.) was added dropwise at rt. The reaction was stirred for 1 h. It was then diluted with CH₂Cl₂ (50 mL), washed with a solution of sat. aq. NaHCO₃ (25 mL), 1 M HCl (25 mL) and then brine (25 mL). The organic phase was dried over MgSO₄, concentrated under reduced pressure and then purified by column chromatography (silica gel, EtOAc) to afford the desired tryptophan derivative **508**.

Spectral data for this compound were consistent with those in the literature.²⁷⁹

Yield: 91% (6624 mg).
Physical State: White powder.
Mp: 150-153 °C (Lit. 152 °C).
R_f: 0.38 (EtOAc).

¹H NMR (400 MHz, CDCl₃): δ 1.96 (s, 3H, H-Ac), 3.33-3.35 (m, 2H, H-8, 8'), 3.70 (s, 3H, H-OMe), 4.95-4.96 (m, 1H, H-9), 6.01 (br s, NHAc), 6.97 (s, 1H, H-2), 7.12 (m, 1H, H-6), 7.20 (m, 1H, H-5), 7.36 (d, *J* = 8.0 Hz, 1H, H-7), 7.52 (d, *J* = 8.0 Hz, 1H, H-4), 8.19 (br s, NH).

(S)-N-Acetyl-1-tosyltryptohan methyl ester (509)

To indole **508** (258 mg, 0.98 mmol, 1.0 eq.) in CH_2Cl_2 (6.0 mL) was added TsCl (562 mg, 2.95 mmol, 3.0 eq.). To this was added NaOH (98 mg, 2.45 mmol, 2.5 eq) and the reaction heated to 35 °C. After 1 h, water (5 mL) was added along with CH_2Cl_2 (15 mL). The organic layer was washed water (5×5 mL) until the organic layer became nearly clear in appearance. The organic layer was then washed with brine (5 mL), dried over MgSO_4 and then concentrated under reduced pressure to afford the crude product. This was then purified by column chromatography (silica gel, hexanes:EtOAc, 60:40 $\rightarrow$ 0:100) to afford the desired product **509**.

Yield: 77% (313 mg).

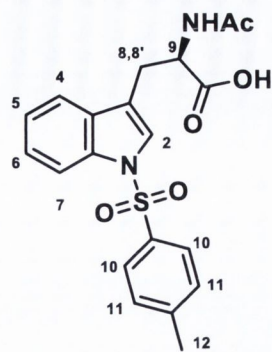
Physical State: Off beige solid.

Mp: 129-130 °C.

R_f: 0.46 (hexanes:EtOAc, 20:80).

^1H NMR (400 MHz, CDCl_3): δ 2.09 (s, 3H, H-Ac), 2.47 (s, 3H, H-12), 3.32 (dd, 1H, $J = 14.8, 16.0$ Hz, H-8), 3.40 (dd, $J = 14.8, 5.6$ Hz, 1H, H-8'), 3.80 (s, 3H, H-OMe), 5.05 (m, 1H, H-9), 6.18 (app. br s, NHAc), 7.35 (d, $J = 8.0$ Hz, 2H, H-11), 7.38 – 7.45 (m, 3H, H-2,5,6), 7.58 (d, $J = 8.0$ Hz, 1H, H-7), 7.85 (d, $J = 8.0$ Hz, 2H, H-10), 8.09 (d, $J = 8.0$ Hz, 1H, H-4).

(S)-N-Acetyl-1-tosyltryptohan (510)

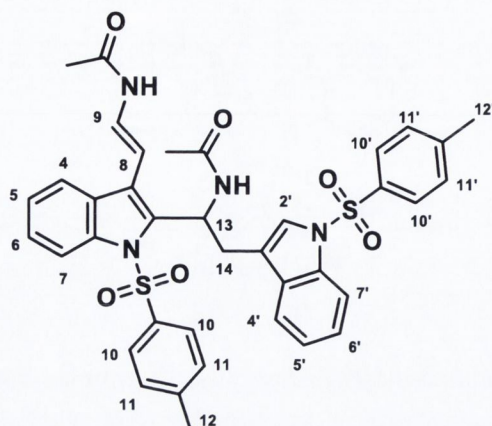


To tryptophan methyl ester derivative **509** (70 mg, 0.169 mmol, 1.0 eq.) in THF (1.0 mL) was added H₂O (0.5 mL) at rt. To this mixture was added LiOH (12 mg, 0.289 mmol, 1.7 eq.) in one portion while maintaining vigorous stirring. After 8 h the reaction was diluted with H₂O (5 mL) and the pH lowered to 2 using 1 M HCl (~ 15 mL). The product was then extracted from the reaction mixture with EtOAc (3 × 20 mL). The organic layer was then washed with brine (10 mL), dried over MgSO₄ and concentrated under reduced pressure to afford the title compound as a colourless gel which was used without further purification.

Yield:	94% (63 mg).
Physical State:	Colourless gel.
Mp:	-
R_f:	Baseline (EtOAc).

¹H NMR (400 MHz, CDCl₃): δ 1.94 (s, 3H, H-Ac), 2.31 (s, 3H, H-12), 3.22 (dd, *J* = 14.8, 5.4 Hz, 1H, H-8), 3.35 (dd, *J* = 14.8, 6.0 Hz, 1H, H-8'), 4.91 (m, 1H, H-9), 6.17 (app. br s, NHAc), 7.21 (d, *J* = 8.0 Hz, 2H, H-11), 7.22 (app. t, 1H, H-6), 7.29 (app. t, 1H, H-5), 7.42 (s, 1H, H-2), 7.48 (d, *J* = 8.0 Hz, 1H, H-7), 7.71 (d, *J* = 8.0 Hz, 2H, H-10), 7.98 (d, *J* = 8.0 Hz, 1H, H-4).

(*E*)-*N*-(2-(2-(1-acetamido-2-(1-tosyl-1*H*-indol-3-yl)ethyl)-1-tosyl-1*H*-indol-3-yl)vinyl)acetamide (515**)**



To enamide **501** (30 mg, 0.08 mmol, 1.0 eq.) in CH_2Cl_2 (0.80 mL) at 0 °C was added $\text{BF}_3 \cdot \text{OEt}_2$ (0.010 mL, 0.08 mmol, 1.0 eq.). The reaction was allowed to stir at 0 °C for 4 h and then at rt for a further 8 h. After this time solutions of sat. NaHCO_3 (2 mL) and sat. Na_2SO_3 (2 mL) were added and the product extracted with CH_2Cl_2 (3×10 mL). The combined organic layers were then washed with brine (10 mL), dried over MgSO_4 and concentrated under reduced pressure to afford crude dimeric indole **515**. The product was then purified using preparative TLC (EtOAc) to afford the dimeric product.

Yield: 37% (21 mg).

Physical State: Yellow gel.

Mp: -

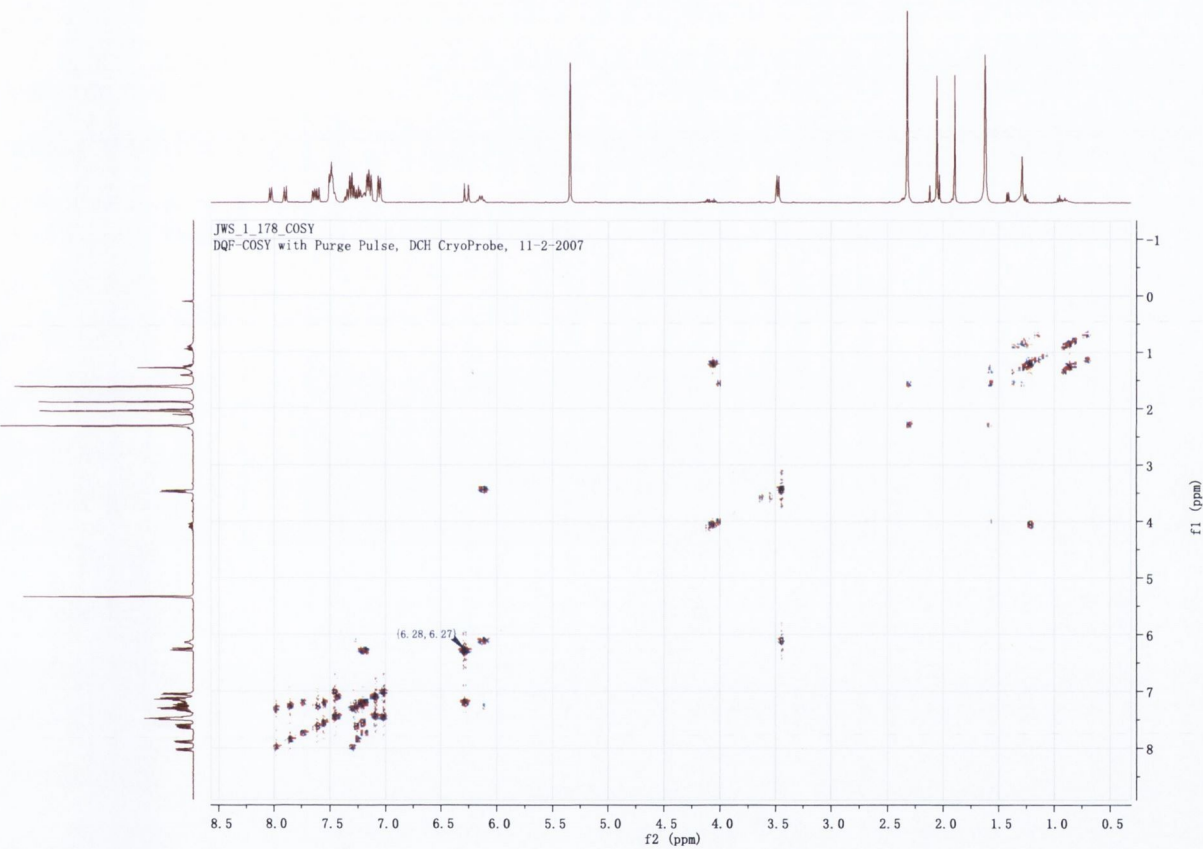
R_f: 0.29 (EtOAc).

^1H NMR (600 MHz, CD_2Cl_2): δ 1.89 (s, 3H, H-Ac), 2.05 (s, 3H, H-Ac), 2.23 (s, 6H, H-12,12'), 3.48 (app. d, 2H, H-14), 6.14 (dd, $J = 16.9, 8.0$ Hz, 1H, H-13), 6.27 (d, $J = 14.8$ Hz, 1H, H-8), 7.06 (d, $J = 8.0$ Hz, 2H, H-10), 7.13 – 7.20 (m, 3H, H-11',2'), 7.22 – 7.38 (m, 6H, H-5,5',6,6',11), 7.45 – 7.50 (m, 5H, H-7,7',9,10'), 7.63 – 7.64 (m, 2H, H-10), 7.90 (d, $J = 8.0$ Hz, 1H, H-4'), 8.03 (d, $J = 8.0$ Hz, 1H, H-4).

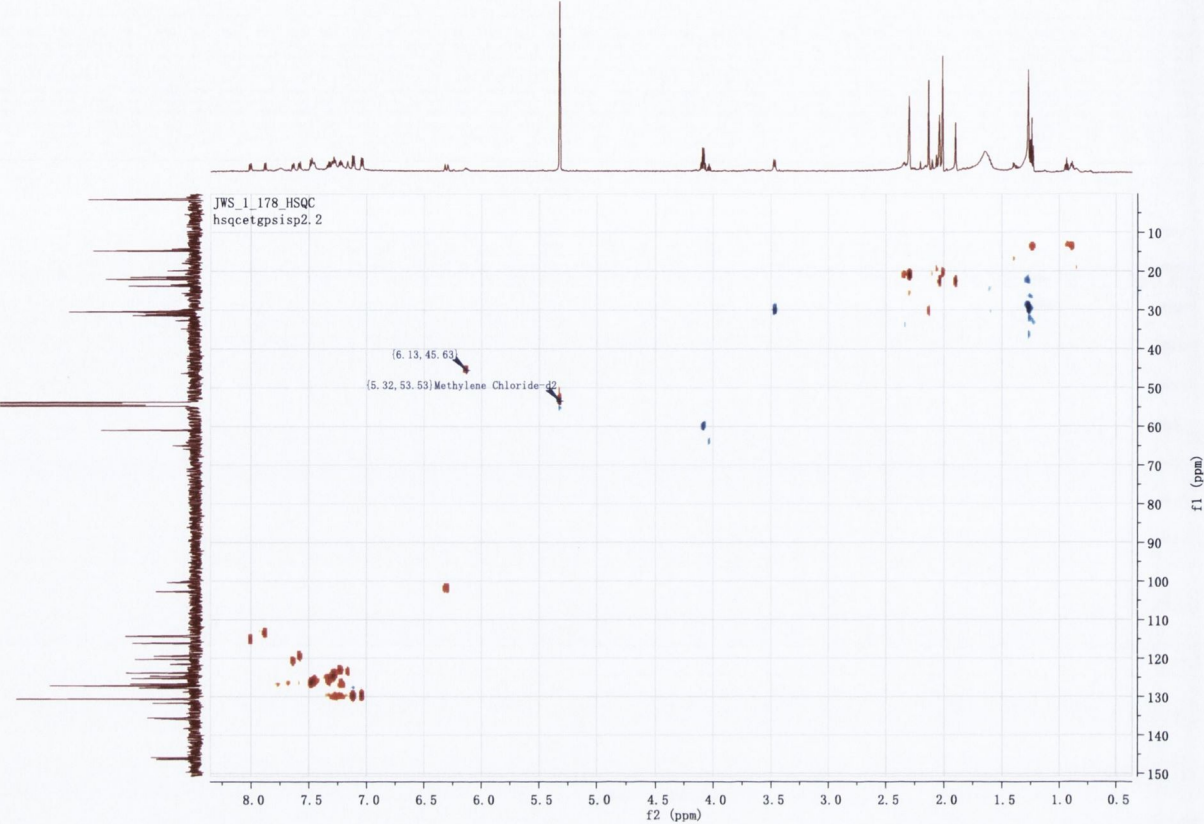
¹³C NMR (151 MHz,CD₂Cl₂): δ 23.5 (CH₃), 23.8 (CH₃), 30.2 (2CH₃), 31.1 (CH₂), 46.3 (CH), 99.9 (qC), 100.2 (qC), 102.5 (qC), 114.1 (CH), 115.9 (CH), 119.3 (CH), 120.1 (CH), 121.4 (CH), 123.6 (CH), 124.4 (CH), 125.0 (CH), 125.1 (CH), 126.3 (CH), 126.5 (CH), 126.9 (CH), 127.5 (2CH), 128.6 (qC), 130.4 (2CH), 130.4 (2CH), 131.5 (CH), 135.3 (qC), 135.4 (qC), 135.5 (qC), 135.7 (qC), 138.1 (qC), 145.8 (qC), 146.1 (qC), 167.7 (qC), 171.4 (qC).

HRMS (m/z ESI⁺): Found 709.2153 (M⁺ + H. C₃₈H₃₇N₄O₆S₂ Requires 709.2149).

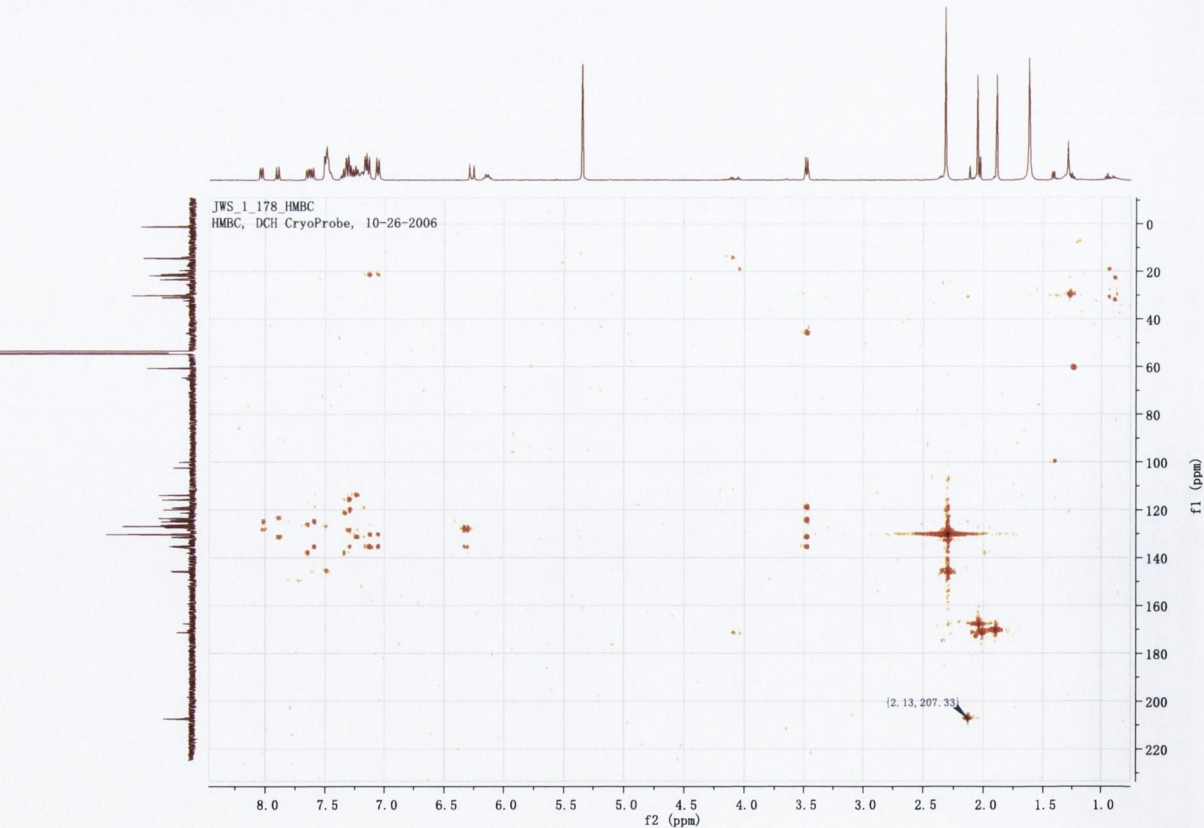
¹H-¹H COSY



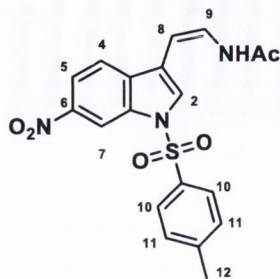
HSQC



HMBC



(Z)-N-(2-(6-nitro-1-tosyl-1H-indol-3-yl)vinyl)acetamide (516)



To tryptophan methyl ester derivative **518** (240 mg, 0.52 mmol, 1.0 eq.) in THF (1.0 mL) was added H₂O (0.5 mL) at rt. To this mixture was added LiOH (12 mg, 0.289 mmol, 1.7 eq.) in one portion while maintaining vigorous stirring. After 8 h the reaction was diluted with H₂O (5 mL) and the pH lowered to 2 using 1 M HCl (~ 15 mL). The product was then extracted from the reaction mixture with EtOAc (3 × 20 mL). The organic layer was then washed with brine (10 mL), dried over MgSO₄ and concentrated under reduced pressure to afford the title compound as a colourless gel which was used without further purification (99%, 230 mg).

(a) To carboxylic acid **519** (196 mg, 0.440 mmol, 1.0 eq.) in THF (4.0 mL) was added pyridine (70 µL, 0.880 mmol, 2.0 eq.) and Cu(OAc)₂ (23 mg, 0.132 mmol, 0.33 eq.) at 0 °C. An instant blue colour was observed. This mixture was stirred for 5 min followed by addition of Pb(OAc)₄ (214 mg, 0.485 mmol, 1.1 eq.) which immediately turned the reaction mixture a notable green-brown colour. The reaction was stirred vigorously and allowed warm to rt over 2 h. The reaction was quenched by the addition of a solution of sat. aq. NaHCO₃ (3 mL) and the product extracted with EtOAc (3 × 5 mL). The combined organic phases were then washed with brine (5 mL), dried over MgSO₄ and concentrated under reduced pressure to afford the crude product as an off white yellow solid which was used without further purification.

(b) The crude product **520** (0.440 mmol, 1.0 eq.) was dissolved in THF (2.0 mL) and to this was added LiClO₄ (279 mg, 2.64 mmol, 6.0 eq.) at 0 °C. This was stirred for 5 min after which time DIPEA (229 µL, 1.32 mmol, 1.0 eq.) was added dropwise. The reaction mixture was stirred for 10 min at 0 °C and then for 30 min (or until starting material was no longer detected, TLC) at rt. The reaction was quenched by the addition of a solution of sat. aq. NaHCO₃ (6 mL) and the product extracted with EtOAc (3 × 10 mL). The combined organic phases were then washed with brine (5 mL), dried over MgSO₄ and concentrated under reduced pressure to afford the crude enamide product **516** which was purified by column

chromatography (silica gel, hexanes:EtOAc, 90:10 → 60:40, column pretreated with NEt₃, 1%). Enamide **516** was obtained in 63% yield over the three steps (110 mg).

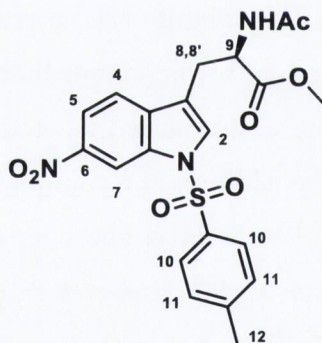
Yield: 63% (110 mg).

Physical State: Yellow gel

R_f: Baseline (EtOAc)

¹H NMR (400 MHz, CDCl₃): δ 2.10 (s, 3H, H-Ac), 2.38 (s, 3H, H-12), 5.65 (d, *J* = 9.2 Hz, 1H, H-8), 7.15 (m, 1H, H-9), 7.28 (br s, NH), 7.31 (d, *J* = 8.0 Hz, 2H, H-11), 7.58 (d, *J* = 8.0 Hz, 1H, H-4), 7.80 (s, 1H, H-2), 7.84 (d, *J* = 8.0 Hz, 2H, H-10), 8.16 (dd, *J* = 8.0, 2.0 Hz, 1H, H-5), 8.88 (d, *J* = 2.0 Hz, 1H, H-7).

(S)-N-Acetyl-6-nitro-1-tosyltryptohan methyl ester (518)



To (S)-N-acetyltryptohan methyl ester **507** (5410 mg, 20.8 mmol, 1.0 eq.) in CH₂Cl₂ (125.0 mL) at 0 °C was added AcOH (6.25 mL, 104.0 mmol, 5.0 eq) followed by HNO₃ (2015 μL, 35.4 mmol, 1.7 eq.) dropwise ensuring to keep the flask well cooled. After the addition the ice bath was removed and the reaction stirred at rt for a further 2 h. After this time, the mixture was cooled to 0 °C and a solution of sat. aq. NaHCO₃ (50 mL) was added. The layers were separated and the aqueous phase extracted with CH₂Cl₂ (3 × 50 mL), the combined organic layers washed with brine (10 mL), dried over MgSO₄ and concentrated under reduced pressure to yield the crude target compound as a mixture of regioisomers. This was then brought forward to the next step without further purification.

To crude nitro **517** (2050 mg, 6.72 mmol, 1.0 eq.) in CH₂Cl₂ (40.0 mL) was added TsCl (3830 mg, 20.16 mmol, 3.0 eq.) followed by NaOH (537 mg, 13.47 mmol, 2.0 eq.). This mixture was stirred at rt for 3 h after which time the reaction was diluted with water (25 mL) and CH₂Cl₂ (25 mL). The layers were separated and the aqueous phase extracted with CH₂Cl₂ (3 × 50 mL), the combined organic layers washed with brine (20 mL), dried over MgSO₄ and concentrated under reduced pressure to yield the crude target compound as a mixture of regioisomers. This was then purified by column chromatography (silica gel, hexanes:EtOAc, 60:40 → 0:100) to afford the desired product **518**.

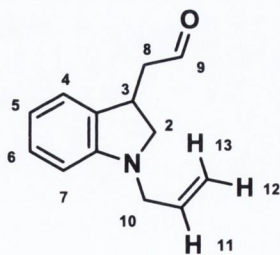
Yield: 21% (2004 mg, over 2 steps).

Physical State: Yellow solid.

R_f: 0.64 (EtOAc).

¹H NMR (400 MHz, CDCl₃): δ 1.99 (s, 3H, H-Ac), 2.37 (s, 3H, H-12), 3.22 (dd, *J* = 14.8, 5.0 Hz, 1H, H-8), 3.33 (dd, *J* = 14.8, 6.0 Hz, 1H, H-8'), 3.69 (s, 3H, H-OMe), 4.92 – 4.93 (m, 1H, H-9), 6.03 (br s, NH), 7.29 (d, *J* = 8.0 Hz, 2H, H-11), 7.58 – 7.60 (m, 2H, H-2,7), 7.80 (d, *J* = 8.0 Hz, 2H, H-10), 8.14 (dd, *J* = 8.0, 2.0 Hz, 1H, H-5), 8.85 (d, *J* = 2.0 Hz, 1H, H-4).

2-(1-Allyl-3-indoliny)acetaldehyde (**527**)



To 2-bromo-*N*-diallylaniline **530** (618 mg, 2.46 mmol, 1.0 eq.) in dry *n*-pentane (11.25 mL) and Et₂O (1.25 mL) was added *t*-BuLi (1.5 M in Hexanes, 4.1 mL, 6.16 mmol, 2.5 eq.) at -78 °C. The reaction mixture was stirred at this temperature for 10 min followed by TMEDA (degassed, 927 μL, 6.16 mmol, 2.5 eq.) dropwise. The reaction mixture was further stirred at

-78 °C for 7 min followed by stirring at 0 °C for 40 min. The reaction mixture was then recooled to -78 °C and DMF (2.0 mL) was added dropwise. This was stirred for 10 min after which time the reaction was allowed warm to rt over 1 h. The reaction was then quenched by the addition of a solution of sat. aq. NH₄Cl (4 mL). The organic layer was separated, dried over MgSO₄ and concentrated under reduced pressure to afford the crude aldehyde. This was then purified by column chromatography (hexanes:Et₂O, 80:20) to afford the pure aldehyde.

Spectral data for this compound were consistent with those in the literature.²⁸⁰

Yield: 41% (203 mg).

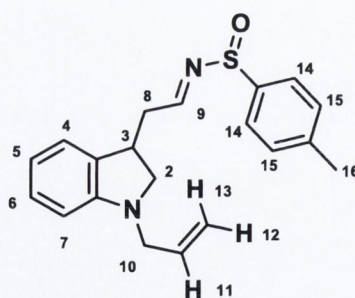
Physical State: Colourless oil.

Mp: -

R_f: 0.39 (hexanes:Et₂O - 80:20).

¹H NMR (400 MHz, CDCl₃): δ 2.75 – 3.00 (m, 3H, H-3,8), 3.58 – 3.72 (m, 4H, H-2,10), 5.17 – 5.30 (m, 2H, H-12,13), 5.83 – 5.89 (m, 1H, H-11), 6.51 (d, *J* = 7.8 Hz, 1H, H-7), 6.65 – 6.69 (m, 1H, H-5), 7.01 – 7.13 (m, 2H, H-4,6), 9.84 (t, *J* = 1.2 Hz, 1H, H-9).

N-(2-(1-Allylindolin-3-yl)ethylidene)-4-methylbenzenesulfinamide (**528**)



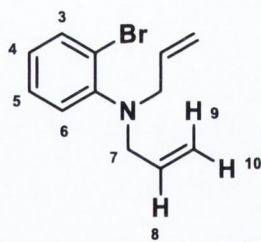
To aldehyde **527** (170 mg, 0.85 mmol, 1.0 eq.) and sulfonamide **506** (196 mg, 1.26 mmol, 1.5 eq.) in THF (4.0 mL) was added Ti(Oi-Pr)₄ (500 μL, 1.69 mmol, 2.0 eq.) at rt. This reaction was left to stir at rt for 6 h after which time it was quenched by the addition of brine (2 mL). The mixture was diluted with Et₂O (10 mL) and water (5 mL). The product was extracted with Et₂O (3 × 5 mL). The combined organic layers were washed with brine (10 mL), dried

over MgSO_4 and concentrated under reduced pressure. This crude residue was then purified by column chromatography (hexanes: Et_2O , 80:20) to afford the pure imine **528**.

Yield: 62% (171 mg).
Physical State: Pale yellow oil.
Mp: -
R_f: 0.51 (hexanes: Et_2O - 80:20).

^1H NMR (400 MHz, CDCl_3): δ 2.64 (s, 3H, H-16), 2.91 – 3.00 (m, 1H, H-3), 3.12 – 3.20 (m, 2H, H-8), 3.20 – 3.29 (m, 2H, H-2), 3.85 – 3.94 (m, 2H, H-10), 5.38 – 5.56 (m, 2H, H-12,13), 6.03 – 6.16 (m, 1H, H-11), 6.71 (d, $J = 7.2$ Hz, 1H, H-7), 7.16 – 7.27 (m, 3H, H-4,5,6), 7.56 (d, $J = 7.2$ Hz, 2H, H-15), 7.73 – 7.82 (m, 2H, H-14), 8.48 (app. br s, 1H, H-9).

Diallyl-(2-bromophenyl)-amine (530)



O-Bromoaniline (176 mg, 1.0 mmol, 1.0 eq.) was dissolved in THF (1.0 mL) at -10°C . To this was added freshly prepared LDA (1.25 M, 800 μL , 1.0 mmol, 1.0 eq.) and allowed to stir for 10 min. To this mixture was then added allyl bromide (87 μL , 1.0 mmol, 1.0 eq.) dropwise and the reaction allowed warm to rt. This solution was stirred for 20 min after which LDA (1.25 M, 800 μL , 1.0 mmol, 1.0 eq.) was added. This mixture was subsequently stirred for a further 10 min then allyl bromide (100 μL , 1.1 mmol, 1.1 eq.) was introduced dropwise. After 1 h the reaction mixture was quenched by the addition of a solution of sat. aq. NH_4Cl (1 mL) and the product extracted with Et_2O (3×5 mL). The combined organic layers were washed with brine (10 mL), dried over MgSO_4 and concentrated under reduced

pressure. The crude product was then dissolved in the minimum of hexanes:Et₂O (90:10, 0.5 mL) and passed through a plug of silica eluting with hexanes:Et₂O (90:10).

Spectral data for this compound were consistent with those in the literature.²⁸⁰

Yield: 78% (198 mg).

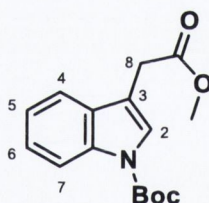
Physical State: Colourless oil.

Mp: -

R_f: ~0.10 (hexanes:EtOAc, 90:10).

¹H NMR (400 MHz, CDCl₃): δ 3.69 (d, *J* = 6.0 Hz, 4H, H-7), 5.12 (dd, *J* = 10.2, 1.6 Hz, 2H, H-10), 5.15 – 5.22 (m, 2H, H-9), 5.82 (ddt, *J* = 16.4, 10.2, 6.0 Hz, 2H, H-8), 6.89 (app. t, 1H, H-4), 7.04 (dd, *J* = 8.0, 1.5 Hz, 1H, H-6), 7.22 (app. t, 1H, H-5), 7.56 (dd, *J* = 8.0, 1.5 Hz, 1H, H-3).

1-*tert*-Butoxycarbonyl-3-(2-methoxy-2-oxoethyl)-1H-indole (533a)

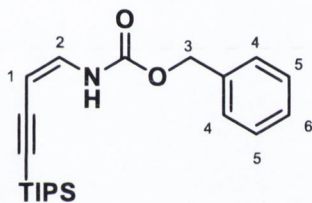


To a solution of 3-indole acetic acid methyl ester (1060 mg, 5.60 mmol 1.0 eq.) in acetonitrile (4.5 mL) was added DMAP (134 mg, 1.10 mmol 0.2 eq.) and di-*tert*-butyl dicarbonate (1830 mg, 8.40 mmol, 1.5 eq.) under an inert atmosphere at rt. The resulting reaction mixture was stirred for 8 h at rt. The reaction mixture was diluted with EtOAc (20 mL). Water (5 mL) was added to the reaction mixture. The organic layer was separated; the aqueous layer was extracted with EtOAc (2 × 10 mL). The combined extracts were washed with water (2 × 10 mL), brine (25 mL) and dried over MgSO₄. Solvent was filtered and evaporated under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexanes:EtOAc, 90:10) to afford **533a**.

Spectral data for this compound were consistent with those in the literature.²⁸¹

Yield:	86% (1400 mg).
Physical State:	Yellow oil.
Mp:	-
R_f:	0.53 (hexanes:EtOAc, 95:5).
¹H NMR (400 MHz, CDCl₃):	δ 1.66 (s, 9H, <i>t</i> -Bu), 3.71 (s, 3H, H-OMe), 3.72 (s, 2H, H-8), 7.26 (app. t, 1H, H-5), 7.33 (app. t, 1H, H-6), 7.52 (d, <i>J</i> = 8.0 Hz, 1H, H-7), 7.57 (d, <i>J</i> = 8.0 Hz, 1H, H-4), 8.22 (s, 1H, H-2).

Benzyl (Z)-(4-(tri-*iso*-propylsilyl)but-1-en-3-yn-1-yl)carbamate (545)



To (*E*)-5-(triisopropylsilyl)pent-2-en-4-ynoic acid **550** (40 mg, 0.158 mmol, 1.0 eq.) in toluene (5.0 mL) was added DPPA (136 μ L, 0.635 mmol, 4.0 eq.) followed by NEt₃ (103 μ L, 0.746 mmol, 4.7 eq.). The resulting mixture was stirred at rt after which time the reaction diluted with water (5 mL) and EtOAc (15 mL). The organic layer was separated; the aqueous layer was extracted with EtOAc (3 $\times$ 10 mL). The combined extracts were washed with brine (25 mL) and dried over MgSO₄. The solvent was evaporated under reduced pressure. The crude residue was purified by passing through a plug of silica, eluting with (hexanes:EtOAc, 90:10) and brought onto the next step without characterisation.

To the prepared azide (0.158 mmol, 1.0 eq.) in toluene (5 mL) was added BnOH (328 μ L, 3.174 mmol, 20.0 eq.) and the resulting mixture heated to 90 °C for 4 h. The reaction was allowed to cool to rt and then concentrated under reduced pressure. The residue was dissolved in MeOH (2 mL) and K₂CO₃ (20 mg) added. This mixture was allowed stir at rt for 1 h after which time the reaction was diluted with water (5 mL) and EtOAc (10 mL). The organic layer was separated; the aqueous layer was extracted with EtOAc (3 $\times$ 10 mL). The

combined extracts were washed with brine (20 mL) and dried over MgSO_4 . The solvent was evaporated under reduced pressure. The crude product was then purified by column chromatography (silica gel, hexanes:EtOAc, 90:10) to afford the title compound.

Yield: 50% (28 mg).

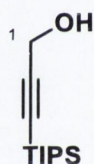
Physical State: Cloudy gel.

Mp: -

R_f: 0.69 (hexanes:EtOAc, 90:10)

^1H NMR (400 MHz, CDCl_3): δ 1.07 – 1.09 (m, 21H, H-TIPS), 4.81 (d, J = 8.0 Hz, 1H, H-1), 5.20 (s, 2H, H-3), 6.96 – 7.01 (m, 1H, H-2), 7.14 (br s, NH), 7.32 – 7.41 (m, 5H, H-4,5,6).

3-(Tri-*iso*-propylsilyl)prop-2-yn-1-ol (**547**)



To propargylic alcohol **546** (576 μL , 10.0 mmol, 1.0 eq.) in THF (20.0 mL) at rt was added MeMgBr (1.4 M in Et_2O , 15700 μL , 22.0 mmol, 2.2 eq.) dropwise. The resulting mixture was refluxed for 12 h and then cooled to rt. To this was added TIPS-Cl (1987 μL , 11.0 mmol, 1.1 eq.) and the reaction mixture was refluxed for a further 6 h. After this time period the mixture was cooled to rt and quenched by the addition of a solution of sat. aq. NH_4Cl (15 mL). The mixture was diluted with Et_2O (30 mL) and the layers separated. The organic layer was separated; the aqueous layer was extracted with Et_2O (2×15 mL). The combined extracts were washed with brine (25 mL) and dried over MgSO_4 . Solvent was filtered and evaporated under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexanes:EtOAc, 90:10) to afford **547**.

Spectral data for this compound were consistent with those in the literature.²⁸²

Yield: 53% (1123 mg).

Physical State:	Colourless oil.
Mp:	-
R _f :	0.83 (Hexanes : EtOAc - 95:5).
¹ H NMR (400 MHz, CDCl ₃):	δ 1.03 – 1.05 (m, 21H, H-TIPS), 4.27 (s, 2H, H-1).

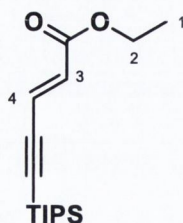
3-(tri-*iso*-propylsilyl)propiolaldehyde (**548**)



To alcohol **547** (1123 mg, 5.29 mmol, 1.0 eq.) in MeCN (6.5 mL) was added IBX (1779 mg, 6.3 mmol, 3.0 eq.). The solution was then heated to 80 °C for 2 h. This mixture was then cooled to rt, diluted with MeCN (10 mL) and then filtered through a pad of Celite©. The resulting organic solution was then concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexanes:EtOAc, 90:10) to afford **548**.

Spectral data for this compound were consistent with those in the literature.²⁸³

Yield:	91% (1010 mg).
Physical State:	Colourless oil.
Mp:	-
R _f :	0.72 (hexanes:EtOAc, 90:10)
¹ H NMR (400 MHz, CDCl ₃):	δ 1.07 – 1.09 (m, 21H, H-TIPS), 9.18 (s, 1H, H-1).

Ethyl (*E*)-5-(tri-*iso*-propylsilyl)pent-2-en-4-ynoate (549**)**

To LiCl (245 mg, 5.85 mmol, 1.2 eq.) in an RBF was added aldehyde **548** (1024 mg, 4.87 mmol, 1.0 eq.) in MeCN (50.0 mL) at rt. To this was added the triethylphosphonoacetate (1159 μ L, 5.85 mmol 1.2 eq.) dropwise followed by DBU (728 μ L 4.87 mmol, 1.0 eq.). The resulting mixture was stirred at rt for 10 h after which time the reaction was deemed complete by TLC analysis. The reaction was quenched by the addition of a solution of sat. aq. NH_4Cl (10 mL) and diluted with EtOAc (20 mL). The organic layer was separated; the aqueous layer was extracted with EtOAc (3×20 mL). The combined extracts were washed with brine (25 mL) and dried over MgSO_4 . Solvent was evaporated under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexanes:EtOAc, 90:10) to afford **549**.

Spectral data for this compound were consistent with those in the literature.²⁸⁴

Yield: 64% (851 mg)

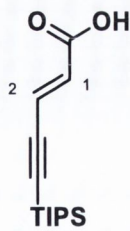
Physical State: Colourless viscous oil.

Mp: -

R_f: 0.53 (hexanes:EtOAc, 90:10).

^1H NMR (400 MHz, CDCl_3): δ 1.07 – 1.08 (m, 21H, H-TIPS), 1.29 (t, $J = 7.2$ Hz, 3H, H-1), 4.21 (q, $J = 7.2$ Hz, 2H, H-2), 6.26 (d, $J = 16.0$ Hz, 1H, H-3), 6.78 (d, $J = 16.0$ Hz, 1H, H-4).

(*E*)-5-(Tri-*iso*-propylsilyl)pent-2-en-4-ynoic acid (550)



To ester **549** (70 mg, 0.25 mmol, 1.0 eq.) in THF (0.5 mL) was added H₂O (0.25 mL) at rt. To this mixture was added LiOH (30 mg, 0.75 mmol, 3.0 eq.) in one portion while maintaining vigorous stirring. After 8 h the reaction was diluted with H₂O (5 mL) and the pH lowered to 2 using 1 M HCl (~ 7.5 mL). The product was then extracted from the reaction mixture with EtOAc (3 × 10 mL). The organic layer was then washed with brine (10 mL), dried over MgSO₄ and concentrated under reduced pressure to afford the title compound as a colourless gel which was used without further purification (65%, 41 mg).

Spectral data for this compound were consistent with those in the literature.²⁸⁵

Yield:	65% (41 mg)
Physical State:	Colourless gel.
Mp:	-
R_f:	Baseline (EtOAc).
¹H NMR (400 MHz, CDCl₃):	δ 1.05 – 1.08 (m, 21H, H-TIPS), 6.24 (d, <i>J</i> = 16.0 Hz, 1H, H-1), 6.76 (d, <i>J</i> = 16.0 Hz, 1H, H-2).

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